

# Synthesis of Chalcones Derivatives and Their Biological Activities: A Review

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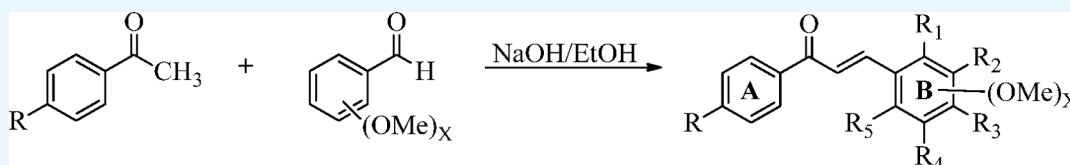


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**ABSTRACT:** Chalcone derivatives are considered valuable species because they possess a ketoethylenic moiety,  $\text{CO}-\text{CH}=\text{CH}-$ . Due to the presence of a reactive  $\alpha,\beta$ -unsaturated carbonyl group, chalcones and their derivatives possess a wide spectrum of antiproliferative, antifungal, antibacterial, antiviral, antileishmanial, and antimalarial pharmacological properties. Recent developments in heterocyclic chemistry have led to the synthesis of chalcone derivatives, which had been biologically investigated toward certain disease targets. The major aspect of this review is to present the most recent synthesis of chalcones bearing N, O, and/or S heterocycles, revealing their biological potential during the past decade (2010–2021). Based on a review of the literature, many chalcone–heterocycle hybrids appear to exhibit promise as future drug candidates owing to their similar or superior activities compared to those of the standards. Thus, this review may prove to be beneficial for the development and design of new potent therapeutic drugs based on previously developed strategies.

## 1. INTRODUCTION

The flavonoid family includes chalcones, which are secondary metabolites of an edible or medicinal plant. Chalcones, 1,3-diphenyl-2-propen-1-ones, are based on two aryl moieties bridged via an  $\alpha,\beta$ -unsaturated carbonyl group.<sup>1</sup> These molecules have a  $-\text{C}=\text{O}-\text{CH}=\text{CH}-$  ketoethylenic moiety in their structure. In their aromatic rings, they have a delocalized  $\pi$ -electron-containing order.<sup>2</sup> Chalcones mainly consist of polyphenolic compounds whose colors vary from yellow to orange and contribute significantly to the pigmentation of the corolla of some plants. Chalcones, which are naturally found in fruits, spices, teas, and soy-based foods, have gotten a lot of attention owing to their intriguing and potentially beneficial properties. Moreover, these molecules are found in natural products as pheromones, plant allelochemicals, and insect hormones.<sup>3,4</sup> Chalcones undergo many chemical reactions as well as being used to synthesize heterocyclic compounds. It is possible to synthesize a wide range of chalcone derivatives by treating aromatic aldehydes with aryl ketones in the presence of an appropriate amount of condensing agents.<sup>5</sup> By condensing aryl ketones with aromatic aldehydes and adding appropriate condensing agents, it is possible to synthesize a wide range of chalcone derivatives. Chalcones are used in several biosynthetic pathways as initial intermediate structures in the production of flavonoids, isoflavonoids, and aurones.<sup>6</sup> A significant part of medicinal chemistry research in the 21st century has been focused on both natural and synthetic chalcones because of their various

pharmacological potential including activities and characteristics such as antibacterial,<sup>7–9</sup> anti-inflammatory,<sup>10–12</sup> analgesic,<sup>13,14</sup> anticholinergic,<sup>15</sup> antiplatelet,<sup>16</sup> antiulcer,<sup>17</sup> antioxidant,<sup>18,19</sup> antimalarial,<sup>20</sup> anticancer,<sup>21,22</sup> antiviral,<sup>23–26</sup> antileishmanial,<sup>27</sup> antidiabetic,<sup>28,29</sup> immunomodulatory,<sup>30,31</sup> aldose reductase inhibition,<sup>32</sup> estrogenic,<sup>33</sup> acetylcholinesterase inhibition,<sup>34</sup> and as non-purine xanthine oxidase inhibitors.<sup>35</sup> Chalcones are highly attractive molecules because of their simple structure, ease of construction, and promising biological applications. Throughout this review, we present the various synthetic pathways used to synthesize chalcone derivatives over the past few years, including their chemistry and biological activities.

## 2. CHALCONE SYNTHESIS

**2.1. Synthesis of Chalcone Derivatives of 2-Acetyl Naphthalene.** Chalcones 1a–g were constructed by treating 2-acetyl naphthalene with benzaldehyde and/or substituted benzaldehyde in methanol and potassium hydroxide, and the

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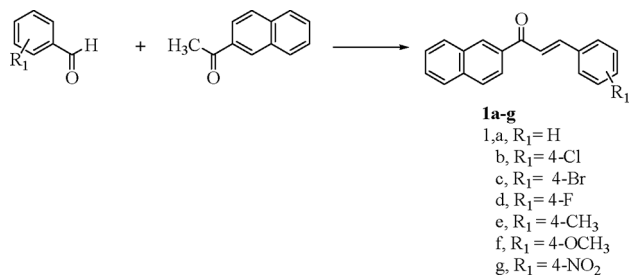
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Published: August 2, 2022



constructed derivatives exhibited antibacterial and antifungal activities (Scheme 1).<sup>36</sup>

**Scheme 1. Synthesis of Chalcones 1a–g**

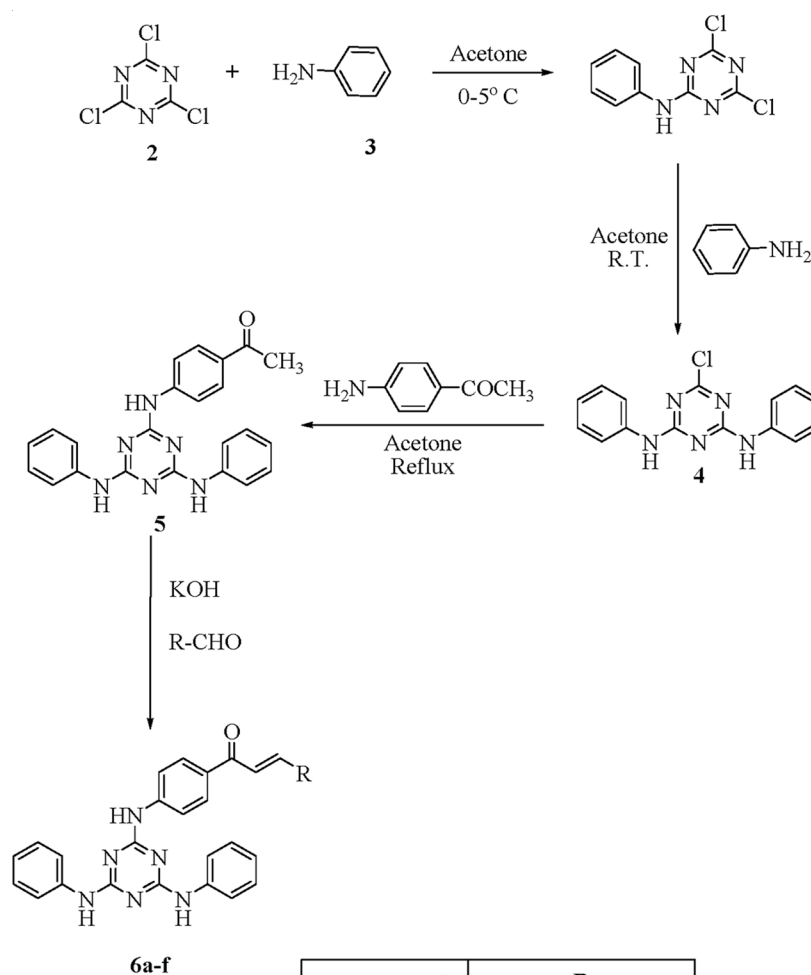


**2.2. Synthesis of Chalcone Derivatives Bearing Triazine.** The trisubstituted triazines **6a–f** were constructed by treating aniline with cyanuric acid at 0–5 °C to yield monosubstituted triazine, which was reacted with substituted amine at RT to produce disubstituted triazine **4**. Treating the latter **4** with 4-aminoacetophenone afforded the corresponding trisubstituted triazine **5**, which was reacted with different aldehydes to provide chalcone derivatives **6a–f** (Scheme 2).<sup>37</sup>

**2.3. Synthesis of Acetamido Chalcone Derivatives.** Treatment of 4-acetamidoacetophenone (**9**) with substituted aldehydes in potassium hydroxide as the base in ethanol and sonication for 10–15 min using a water bath of ultrasonic cleaner afforded chalcone derivatives **10a–f** (Scheme 3).<sup>37</sup>

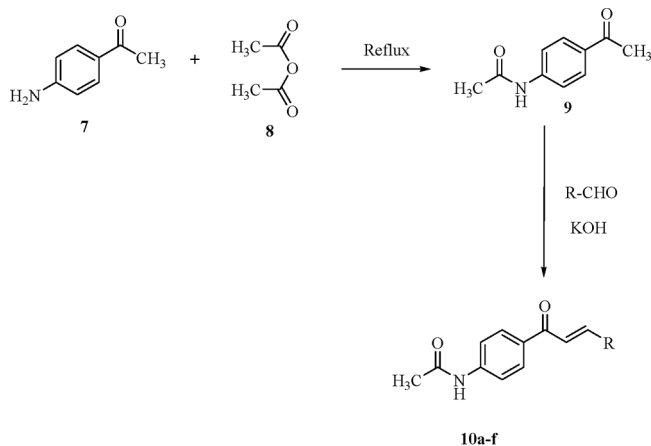
**2.4. Synthesis of Methoxyamino Chalcones.** The chalcone derivatives **13–29** were synthesized via treatment

**Scheme 2. Synthesis of Triazines 6a–f Containing Chalcone**



Compound No.	R
<b>6a</b>	5-methylfurfural
<b>6b</b>	3-nitrobenzaldehyde
<b>6c</b>	2-chlorobenzaldehyde
<b>6d</b>	2-bromobenzaldehyde
<b>6e</b>	3-bromobenzaldehyde
<b>6f</b>	4-bromobenzaldehyde

Scheme 3. Synthesis of Chalcones 10a–f



Compound No.	R
10a	5-methylfurfural
10b	3-nitrobenzaldehyde
10c	2-chlorobenzaldehyde
10d	2-bromobenzaldehyde
10e	3-bromobenzaldehyde
10f	2-methoxybenzaldehyde

of acetophenone derivative **11** and benzaldehyde derivative **12** in equal amounts using ethyl alcohol in 40% NaOH solution at 10 °C and stirred for 1 h and then at RT for 4 h; the reaction proceeded via Claisen–Schmidt reactions (Scheme 4).<sup>38</sup>

**2.5. Synthesis of Sappanchalcone.** Chalcone derivatives **32–44** were constructed via a Claisen–Schmidt reaction by treatment of benzaldehyde derivatives and acetophenone derivatives in methanol and potassium hydroxide and subject to ultrasonic irradiation for 8 h, utilizing a water bath at 80 °C, and exhibited XO inhibitory activity (Schemes 5–7).<sup>35</sup>

**2.6. Synthesis of Chalcone Derivatives from 1,3-Diacetylbenzene and 1,4-Diacetylbenzene.** Construction and biological potential of chalcone derivatives **45–47** were reported. These compounds were synthesized through acid-catalyzed one-step condensation of 1,3- and/or 1,4-diacetylbenzene and 1,3,5-triacetylbenzene with 4-hydroxy-3-methoxybenzaldehyde in the presence of acids as acetic acid, concentrated hydrochloric acid, phosphoric acid, and concentrated sulfuric acid. The best result was achieved in case using concentrated sulfuric acid in ethanol (Scheme 8).<sup>39</sup>

**2.7. Synthesis of Chalcone Derivatives from 1-(2',4'-Difluorobiphenyl-4-yl)ethanone.** The chalcone derivatives **50a–d** were prepared in good yield via solvent-free Claisen–Schmidt condensation reaction of equal amounts of 1-(2',4'-difluorobiphenyl-4-yl)ethanone with many aldehydes in 40% NaOH, leading to the formation of a sodium adduct which was neutralized by diluted HCl in cold water to afford the corresponding chalcone derivatives **50a–d** (Scheme 9).<sup>40</sup>

**2.8. Synthesis of Chalcone from Acetophenone Derivatives.** Treatment of hydroxyacetophenone **51** with benzaldehyde derivative **52** in 50% KOH provided the corresponding chalcones **53–56**, and the highest yield of chalcones ranged from 93 to 97%.<sup>41</sup> On the other hand, chalcone **53** was prepared in a low 32% yield in the presence of KOH as the catalyst,<sup>42</sup> whereas chalcone **B** was synthesized

with  $\text{BF}_3\text{-Et}_2\text{O}$  catalyst in a high yield 90%.<sup>43</sup> Reaction of veratraldehyde with 4-hydroxyacetophenone yielded chalcone **54** in a high 97% yield.<sup>41</sup> However, treatment of 2,4-dihydroxyacetophenone provided the corresponding chalcone **55** in 96% yield and **56** in 93% yield (Scheme 10).<sup>41</sup>

Chalcone derivatives **59–99** were constructed by treating aldehyde **57** with acetophenone **58** in ethanol containing NaOH 40% or few drops of hydrochloric acid (Scheme 11 and Table 1).<sup>44</sup>

Treatment of benzaldehyde and acetophenone derivatives in acid catalyst or alkaline conditions at 50–100 °C in presence of liquid solvent led to **100** (Scheme 12).<sup>45–47</sup>

**2.9. Synthesis of Chalcone from Phenyl Halide.** Chalcone **100** was prepared by reaction of phenyl halide and styrene in carbon monoxide and Pd catalyst (Scheme 13).<sup>48</sup>

Treatment of phenylacetylene with benzaldehyde in (BmimOTs) and HBr at 100 °C for 12 h provided the corresponding chalcone **99**. The reaction proceeds via a coupling reaction (Scheme 14).<sup>49</sup>

Chalcone derivative **101** was constructed from the reaction of propargyl alcohol and phenyl halide using microwave irradiation utilizing  $\text{PdCl}_2(\text{PPh}_3)_2$  in THF (Scheme 15).<sup>50,51</sup>

**2.10. Synthesis of Chalcone Derivatives from Benzoyl Chlorides.** Ynones were synthesized by reaction of benzoyl chlorides and phenylacetylenes using Sonogashira conditions described in a literature procedure. Ynones undergo deuteration using the H-Cube system using  $\text{D}_2\text{O}$  instead of water (Scheme 16).<sup>52,53</sup>

Chalcone **100** was synthesized by reaction of benzoyl chloride with styrylboronic acid **103** in anhydrous toluene and in presence of  $\text{Pd}(\text{PPh}_3)_4$  and  $\text{CsCO}_3$ . Also from the reaction of cinnamoyl chloride **104** and phenylboronic acid in anhydrous toluene and in the presence of  $\text{Pd}(\text{PPh}_3)_4$  and  $\text{CsCO}_3$ , the reaction proceeds via the Suzuki–Miyaura coupling reaction (Scheme 17).<sup>54</sup>

**2.11. Synthesis of Chalcone via One-Pot Synthesis.** Treatment of phenylmethanol **105** and acetophenone using  $\text{CrO}_3$  as the oxidizing agent provided chalcone derivative **100** (Scheme 18).<sup>45</sup>

Treatment of benzaldehyde and phenylacetylene under microwave irradiation using heterogeneous acid in a catalytic amount in 1,2-dichloroethane as solvent provided the corresponding chalcone **100** (Scheme 19).<sup>55</sup>

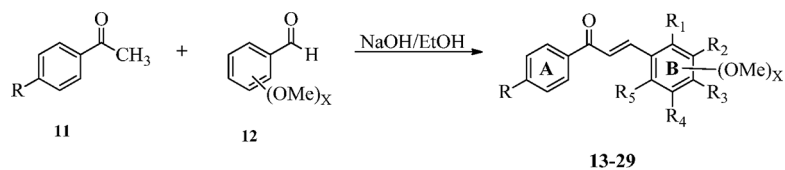
**2.12. Some Chalcones from Natural Product.** Chalcones occur in natural products derived from plant species, such as *Macaranga denticulata*, which contains compound **106**.<sup>56</sup> Also *Uvaria siamensis* roots contain compound **107**;<sup>57</sup> compound **108** is derived from *Stevia lucida*,<sup>58</sup> and compound **109** is found in *Pongamia pinnata* (L.).<sup>59</sup> Hydroxychalcone-based sugar functionalities **110–112** were separated from *Coreopsis lanceolata* flowers (Figure 1).<sup>60</sup>

### 3. BIOLOGICAL ACTIVITIES OF CHALCONE DERIVATIVES

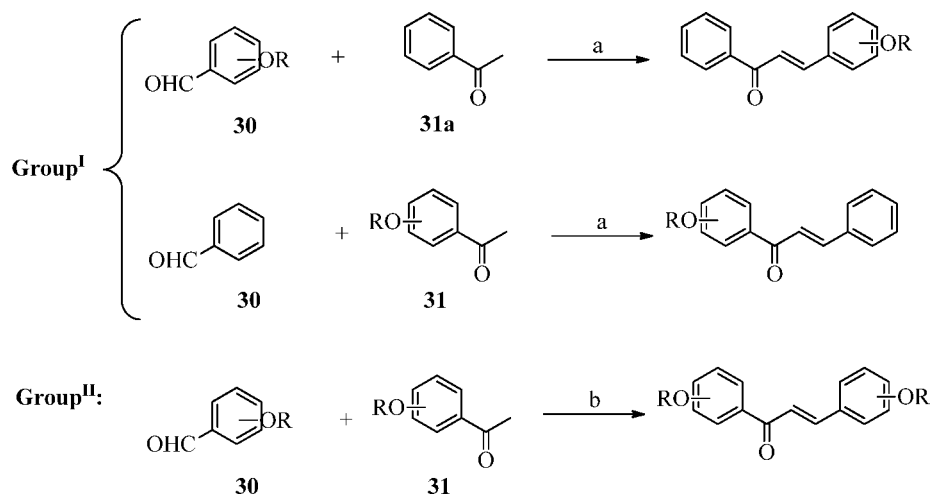
Some chalcones were investigated and were documented to exhibit many pharmacological activities, such as antioxidant activity,<sup>61–64</sup> such as yakuchinones A and curcumin-related enones, which inhibited the pro-survival transcription (Figure 2).

**3.1. Chalcone Derivatives Bearing Five-Membered N-Heterocycles.** As revealed in Figure 3, chalcone derivatives bearing benzimidazole and imidazole as five-membered N-heterocycle rings were synthesized. Synthesis and evaluation of

Scheme 4. Synthesis of Chalcones Derivatives 13–29



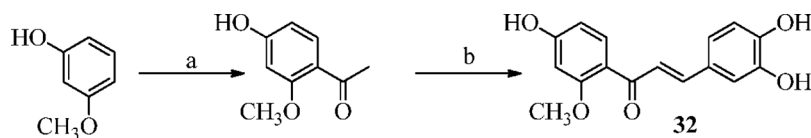
Compound	R	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>	R <sub>5</sub>
13	NH <sub>2</sub>	OCH <sub>3</sub>	H	H	H	H
14	NH <sub>2</sub>	H	OCH <sub>3</sub>	H	H	H
15	NH <sub>2</sub>	H	H	OCH <sub>3</sub>	H	H
16	NH <sub>2</sub>	OCH <sub>3</sub>	OCH <sub>3</sub>	H	H	H
17	NH <sub>2</sub>	OCH <sub>3</sub>	H	OCH <sub>3</sub>	H	H
18	NH <sub>2</sub>	OCH <sub>3</sub>	H	H	OCH <sub>3</sub>	H
19	NH <sub>2</sub>	H	H	H	H	H
20	H	OCH <sub>3</sub>	H	H	H	H
21	H	H	H	OCH <sub>3</sub>	H	H
22	H	H	H	OCH <sub>3</sub>	H	H
23	H	OCH <sub>3</sub>	OCH <sub>3</sub>	H	H	H
24	H	OCH <sub>3</sub>	H	OCH <sub>3</sub>	H	H
25	H	OCH <sub>3</sub>	H	H	OCH <sub>3</sub>	H
26	Br	H	H	OCH <sub>3</sub>	H	H
27	Br	OCH <sub>3</sub>	H	OCH <sub>3</sub>	H	H
28	Br	OCH <sub>3</sub>	H	H	OCH <sub>3</sub>	H
29	H	H	H	H	H	H

Scheme 5. Construction of Chalcone Derivatives<sup>a</sup>

<sup>a</sup>Reagents and conditions: (a) KOH<sub>aq</sub>, MeOH, ultrasound-assisted; (b) KOH<sub>aq</sub>, ultrasound-assisted.

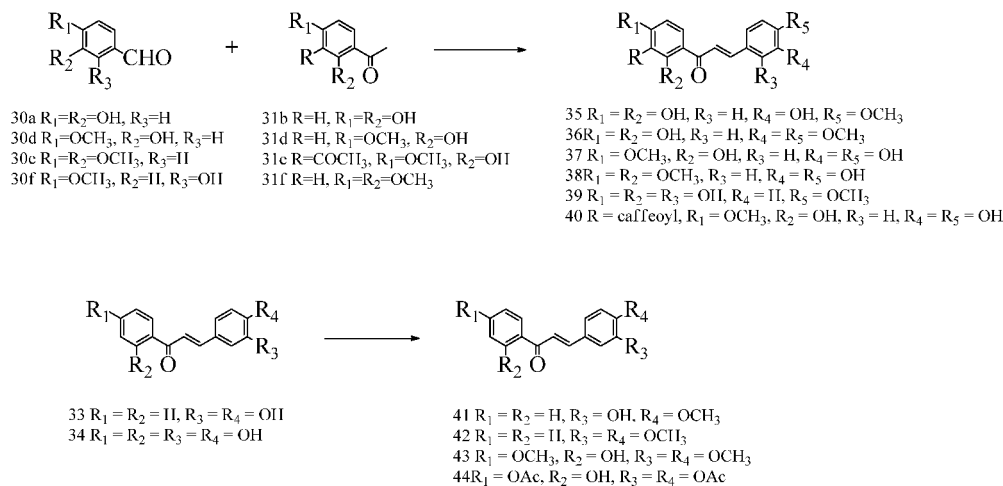
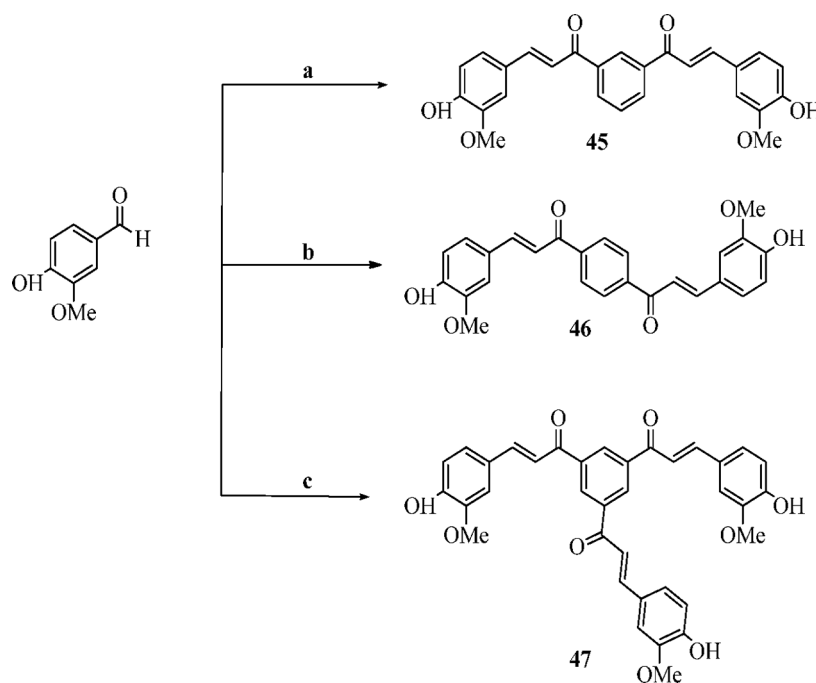
the imidazolylchalcones for their potential toward recombinant human monoamine oxidase (MAO) A and B inhibition were conducted. Compound 114 provided considerable activity as

an inhibitor, whereas derivative 113 was the most active. Compounds 113 (IC<sub>50</sub> = 1.6 ± 0.09 μM) showed inhibition activity on MAO-A suppression better than that recorded by

Scheme 6. Synthesis of Sappanchalcone 32<sup>a</sup>

<sup>a</sup>Reagents and conditions: (a) CH<sub>3</sub>COOH, polyphosphoric acid, 60 °C, 30 min; (b) 2',4'-dihydroxyacetophenone, 12 M KOH, ultrasound-assisted, 80 °C, 8 h.

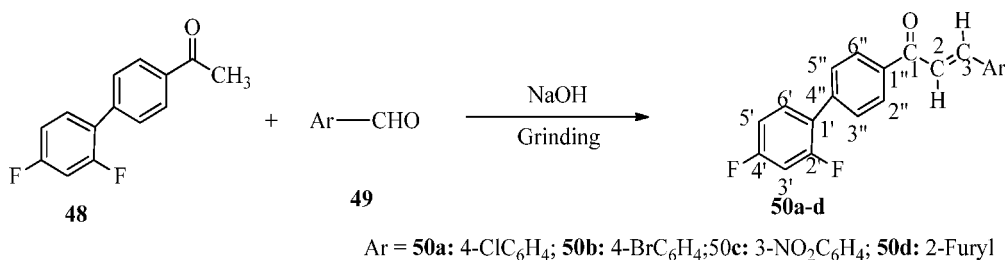
## Scheme 7. Synthesis of Chalcone Derivatives 35–44)

Scheme 8<sup>a</sup>

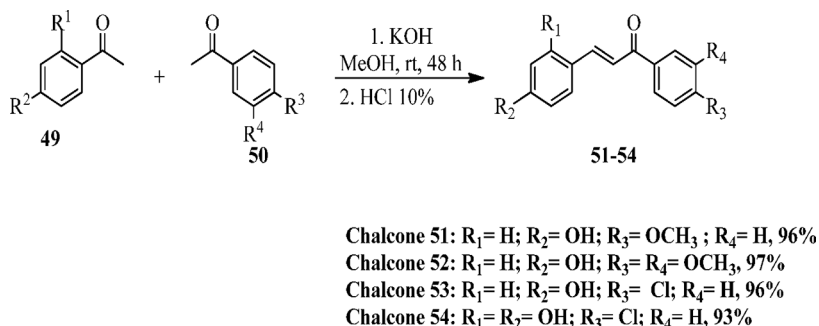
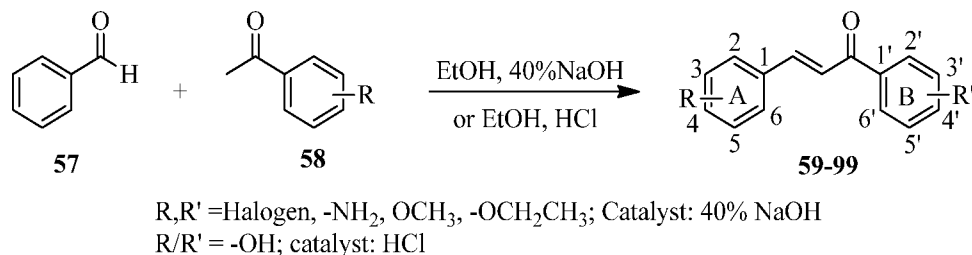
<sup>a</sup>Reagents and conditions: (a) H<sub>2</sub>SO<sub>4</sub>, 1,3-diacetylbenzene, ethyl alcohol, reflux, 3 h; (b) H<sub>2</sub>SO<sub>4</sub>, 1,4-diacetylbenzene, ethyl alcohol, reflux, 3 h; (c) H<sub>2</sub>SO<sub>4</sub>, 1,3,5-triacetylbenzene, reflux, 3 h.

Toloxatone (IC<sub>50</sub> = 1.10 ± 0.0085 μM) as a standard.<sup>65</sup> Moreover, compound 115 with a *p*-bromo-substituted phenyl ring exhibited insect antifeedant potential (Figure 3).<sup>66</sup> Alternatively, *N*-benzyl-substituted benzimidazole chalcones were prepared following multistep reaction sequences.<sup>67</sup> Antibacterial potential of the novel candidates was assessed

toward Gram-positive and Gram-negative bacteria. Benzimidazole-based chalcone 116 was effective against *Staphylococcus aureus* and *Bacillus subtilis*. Gram-negative bacteria, *Escherichia coli* and *Pseudomonas aeruginosa*, are less active against compound 116 (Figure 3).

Scheme 9. Synthesis of (*E*)-1-(2',4'-Difluorobiphenyl-4-yl)-3-arylprop-2-en-1-ones

## Scheme 10. Synthesis of Chalcones 53–56

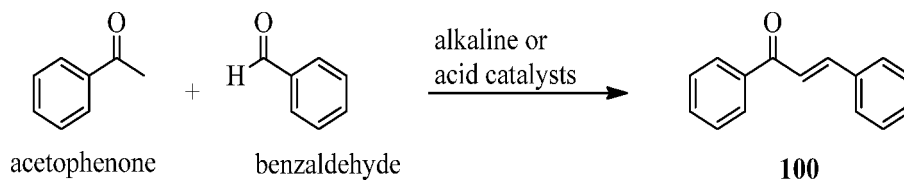
Scheme 11. Construction of Chalcones 59–99<sup>a</sup>

<sup>a</sup>Reagents and conditions: ethyl alcohol, 40% NaOH or HCl, room temperature, 12–24 h.

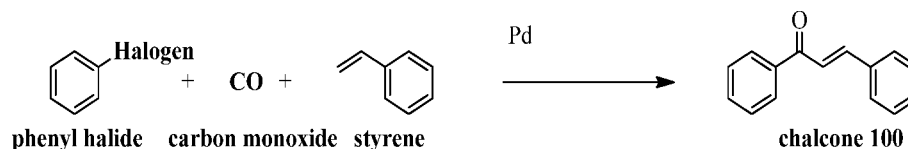
Table 1. Synthesis of Chalcone Derivatives 59–99

compound no.	R	R'	compound no.	R	R'
<b>59</b>	3,4-OH	3-OH	<b>80</b>	3,4-OCH <sub>3</sub>	3,5-F
<b>60</b>	3,4-OCH <sub>3</sub>	3-OH	<b>81</b>	4-OCH <sub>3</sub>	3,4-OH
<b>61</b>	3,4-OH	4-NH <sub>2</sub>	<b>82</b>	4-OCH <sub>3</sub>	,4-OCH <sub>3</sub>
<b>62</b>	3,4-OCH <sub>3</sub>	4-NH <sub>2</sub>	<b>83</b>	3-OH, 4-OCH <sub>3</sub>	3,4-OH
<b>63</b>	3,4-OH	4-OCH <sub>3</sub>	<b>84</b>	3-OH, 4-OCH <sub>3</sub>	3,4-OCH <sub>3</sub>
<b>64</b>	3,4-OCH <sub>3</sub>	4-OCH <sub>3</sub>	<b>85</b>	2,4-OCH <sub>3</sub>	3,4-OH
<b>65</b>	3,4-OH	4-OCH <sub>2</sub> CH <sub>3</sub>	<b>86</b>	2,4-OCH <sub>3</sub>	3,4-OCH <sub>3</sub>
<b>66</b>	3,4-OCH <sub>3</sub>	4-OCH <sub>2</sub> CH <sub>3</sub>	<b>87</b>	2-OCH <sub>3</sub>	3,4-OH
<b>67</b>	3,4-OH	4-Cl	<b>88</b>	2-OCH <sub>3</sub>	3,4-OCH <sub>3</sub>
<b>68</b>	3,4-OCH <sub>3</sub>	4-Cl	<b>89</b>	2,3-OCH <sub>3</sub>	3,4-OH
<b>69</b>	3,4-OH	2-F	<b>90</b>	2,3-OCH <sub>3</sub>	3,4-OCH <sub>3</sub>
<b>70</b>	3,4-OCH <sub>3</sub>	2-F	<b>91</b>	2,5-OCH <sub>3</sub>	3,4-OH
<b>71</b>	3,4-OH	2-Cl	<b>92</b>	2,5-OCH <sub>3</sub>	3,4-OCH <sub>3</sub>
<b>72</b>	3,4-OCH <sub>3</sub>	2-Cl	<b>93</b>	4-Cl	3,4-OH
<b>73</b>	3,4-OH	4-F	<b>94</b>	4-Cl	3,4-OCH <sub>3</sub>
<b>74</b>	3,4-OCH <sub>3</sub>	4-F	<b>95</b>	3,4-Cl	3,4-OH
<b>75</b>	3,4-OH	3,4-F	<b>96</b>	3,4-Cl	3,4-Cl
<b>76</b>	3,4-OCH <sub>3</sub>	3,4-F	<b>97</b>	3,4,5-OCH <sub>3</sub>	3,4,5-OCH <sub>3</sub>
<b>77</b>	3,4-OH	3,4-OCH <sub>3</sub>	<b>98</b>	3,4,5-OCH <sub>3</sub>	3,4,5-OCH <sub>3</sub>
<b>78</b>	3,4-OCH <sub>3</sub>	3,4-OCH <sub>3</sub>	<b>99</b>	3,4-OCH <sub>3</sub>	3,4-OCH <sub>3</sub>
<b>79</b>	3,4-OH	3,5-F			

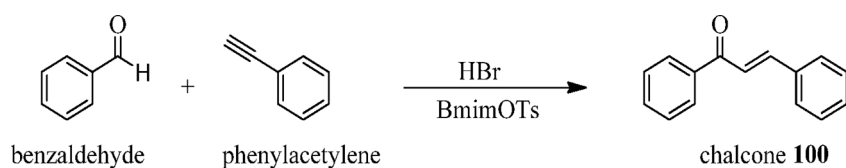
## Scheme 12. Claisen–Schmidt Condensation



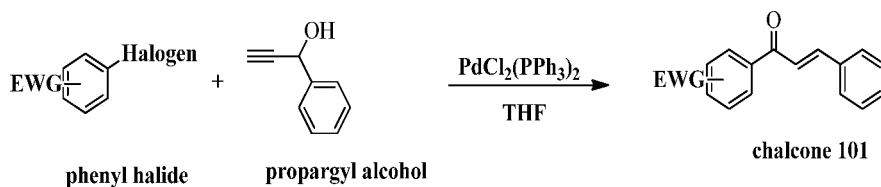
## Scheme 13. Construction of Chalcone Derivative 100



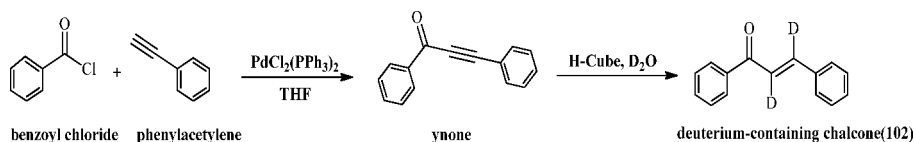
## Scheme 14. Synthesis of Chalcone 100 via a Coupling Reaction



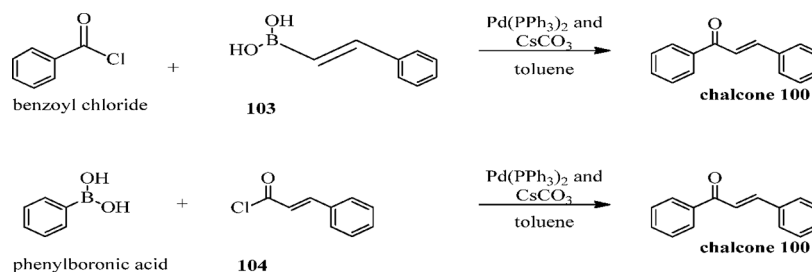
## Scheme 15. Synthesis of Chalcone 101



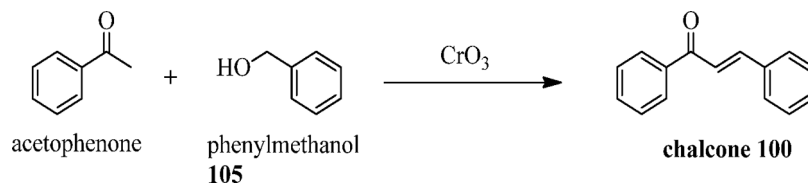
## Scheme 16. Synthesis of Chalcone 102 via Continuous-Flow Deuteration Reaction



## Scheme 17. Synthesis of Chalcone 100 through Suzuki–Miyaura Coupling Reaction



## Scheme 18. One-Pot Synthesis of Chalcone 100



The carbazole moiety of chalcone derivatives have been extensively tested as a nonintercalative inhibitor of topoisomer-

ase II and as an inducer of apoptosis.<sup>68</sup> The chalcone derivative 117 exhibited moderate topoisomerase II inhibitory activity



## Scheme 19. Synthesis of Chalcone Using Solid Acid Catalyst

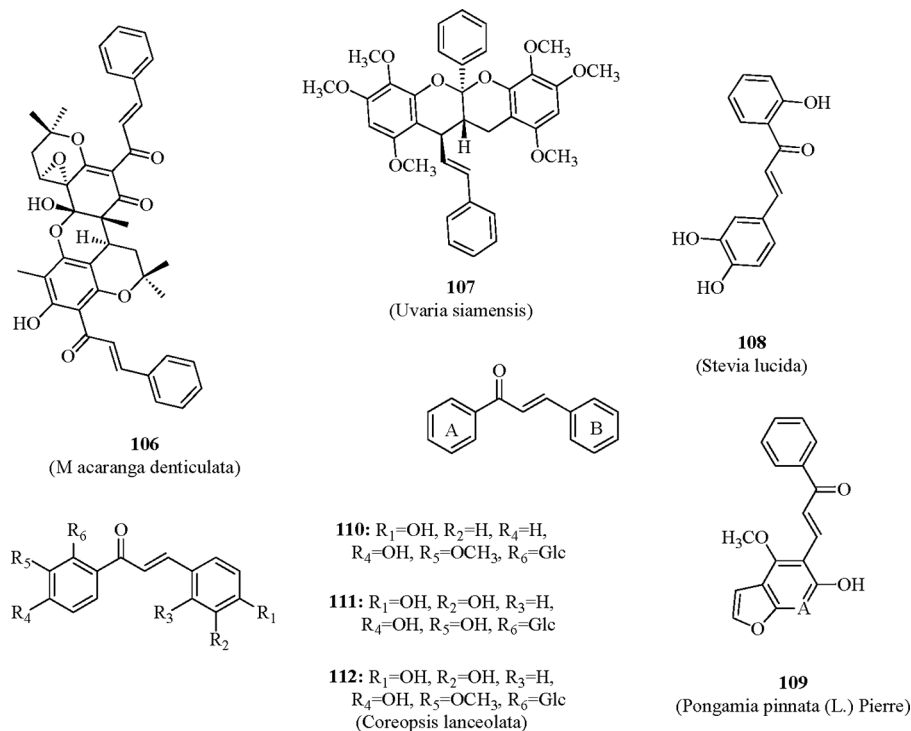
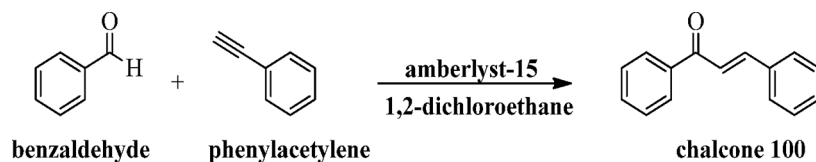


Figure 1. Some chalcones from natural products.

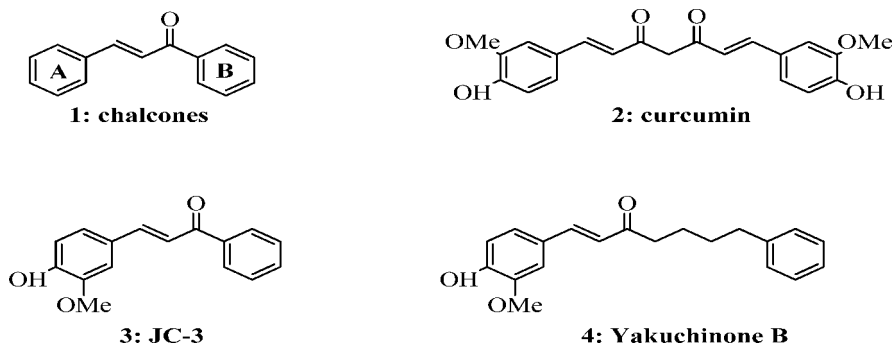


Figure 2. Some examples of chalcone (1), curcumin (2), JC-3 (3), and yakuchinones B (4).

and inhibited cell proliferation effectively against human cancer cell lines. Conversely, the chalcone derivative **118** exhibited high potential as a topoisomerase II suppressor but recorded less inhibitory potential toward cancerous cell lines. By inducing apoptosis, compounds **117** and **118** can arrest HL-60 cells in the sub-G1 phase, as shown in Figure 3 and Table 2.

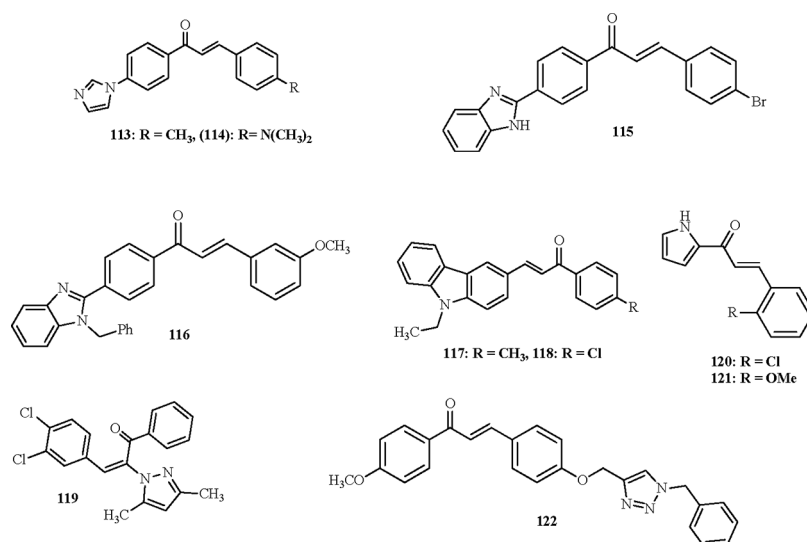
Kumari et al.<sup>69</sup> had also constructed chalcones containing a pyrazole moiety and tested them for their antioxidant and antimicrobial activity. The pyrazole–chalcone derivative **119** showed significant activity against *B. subtilis* (ZI =  $16 \pm 0.82$  mm), *P. aeruginosa* (ZI =  $14 \pm 1.24$  mm), *S. aureus* (ZI =  $13 \pm 0.60$  mm), and *E. coli* (ZI =  $14 \pm 0.83$  mm). Furthermore,

compound **119** revealed promising radical scavenging potential with an  $IC_{50}$  value equal to  $88.04 \mu\text{g/mL}$  (Figure 3).

The biological activity of chalcone derivatives bearing pyrrole was studied in relation to their inhibition of the CYP1 enzyme.<sup>70</sup> Chalcone derivative **120** displayed greater activity against the suppressed CYP1B1 isoform, revealing an  $IC_{50}$  of  $0.2 \mu\text{M}$ . In contrast, chalcone **121** inhibited both CYP1A1 and CYP1B1 isoforms with  $IC_{50}$  values of  $\sim 0.9 \mu\text{M}$  in similar conditions. Further, compound **121** inhibited the toxicity of benzo[a]pyrene in addition to resistance of reversed cisplatin in human cells (Figure 3).

Chalcone-based 1,2,3-triazoles were synthesized using catalytic copper nanoparticles supported on cellulose in an

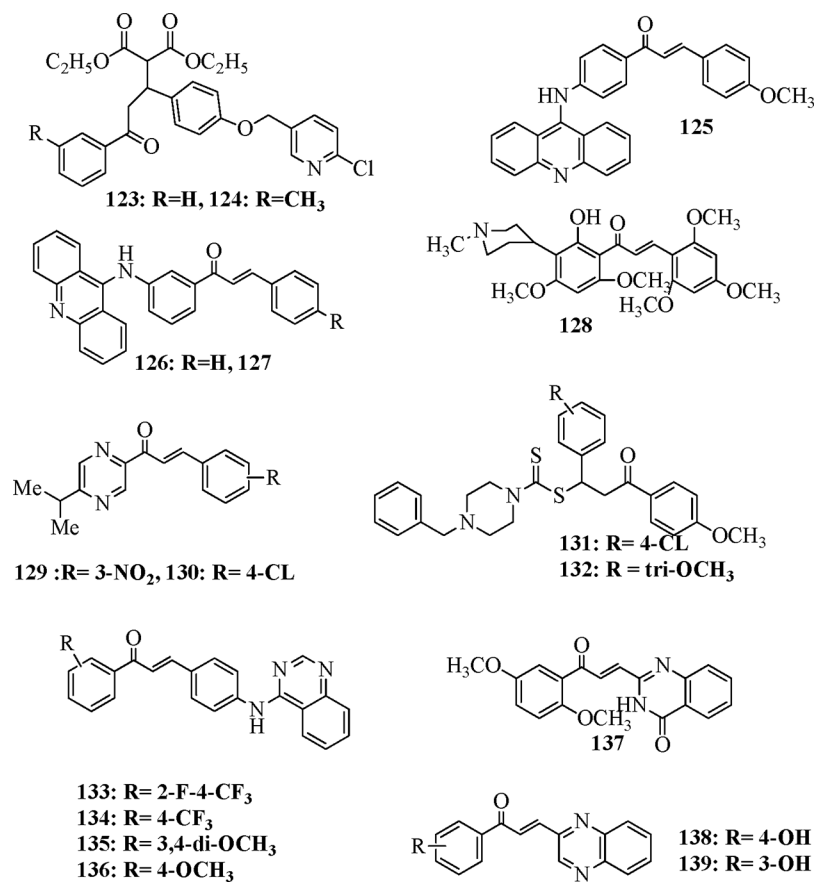




**Figure 3.** Chalcones bearing five-membered N-heterocycles.

**Table 2.** Anticancer Potential of Carbazole-Bearing Chalcones 117 and 118 and Triazole-Containing Chalcone 122

compound no.	IC <sub>50</sub> (μM)					
	HeLa	A549	PC-3	HL-60	MCF-7	HepG2
117	0.36	2.16	0.62	0.22		
118	5.48	9.57	7.12	2.85		
122		11			5	9
PI-103		8			3	4



**Figure 4.** Chalcone derivatives bearing six-membered N-heterocycles.

aqueous medium. From these compounds, compound **122** exhibited promising anticancer activity compared to the reference drug. Moreover, this triazolo chalcone derivative **122** was recorded to promote apoptosis and G2/S arrest, triggering loss of mitochondrial potential in pancreatic cells MIA-Pa-Ca-2,<sup>71</sup> as presented in Figure 3 and Table 2.

**3.2. Chalcone Derivatives Based on Six-Membered N-Heterocycles.** Pyridine-bearing chalcone derivatives were prepared and biologically screened for their antiviral potential. Antiviral properties were observed against cucumber mosaic virus (CMV) for the majority of the newly constructed compounds.<sup>72</sup> Most of the prepared compounds showed antiviral activity toward cucumber. The chalcone derivative **123** exhibited antiviral activity in terms of curative, inactivation, and protection properties. Furthermore, chalcone **124** demonstrated a high level of activity against CMV (Figure 4).

Chalcone derivatives based on acridine were constructed and examined toward *Plasmodium falciparum* to test their antimalarial effect. The tested compounds displayed 100% antimalarial potential, while chalcones **125–127** showed inhibition of >71% at 2 and 0.4  $\mu\text{g/mL}$ . Chalcone **125** demonstrated an inhibitory activity of 71.4% against the parasite (Figure 4).<sup>73</sup>

A chalcone derivative containing piperidine was constructed and evaluated as an inhibitor of anti-PI3K $\delta$  activity and normal basophil degranulation. Chalcone derivative **128** was found to inhibit normal basophil degranulation and revealed activity comparable to that of betamethasone as a drug reference (Figure 4).<sup>74</sup> A set of chalcone–pyrazine hybrids was constructed and biologically tested. Chalcones with nitro substituents **129** and **130** were effective against *Trychophyton mentagrophytes* fungi compared with fluconazole as a reference drug. Additionally, the synthesized chalcones were screened for their antimycobacterial potential. Compounds **129** and **130** were recorded to show activity against *Mycobacterium tuberculosis* H37Rv (ATCC 27294) (Figure 4).<sup>75</sup>

An investigation was conducted on the antibacterial activity of piperazine chalcone derivatives containing dithiocarbamate, morpholine, and piperazine moieties against multi-drug-resistant Gram-negative bacteria. The chalcone piperazine **131** inhibited *Klebsiella pneumonia* and *Pseudomonas aeruginosa* (Ps12). As a result, chalcone **132** exhibited a high level of antibacterial activity and a higher affinity for DNA binding than doxorubicin (Figure 4).<sup>76</sup>

There are many quinazoline moieties revealing anticancer activity reported in literature, such as Erlotinib and Gefitinib.<sup>77–79</sup> From 2-aminobenzoic acid, chalcone derivatives bearing a quinazoline moiety were prepared. Four human cancer cell lines MCF-7, A549, HT-29, and A375 tested with the derivatives **133–136** showed antiproliferative potential higher than that of Combretastatin-A4 as a reference compound,<sup>80</sup> as illustrated in Figure 4 and Table 3. Compounds **133–136** were demonstrated to possess higher or comparable anticancer potential with regard to A549, HT-29, MCF-7, and A375 human cancer cell lines when compared with the reference drug Combretastatin-A4. Compounds **134–136** inhibited MCF-7 human breast adenocarcinoma cells with IC<sub>50</sub> values of 0.17, 0.14, and 0.16  $\mu\text{M}$ , respectively, compared with the control drug with IC<sub>50</sub> = 0.18  $\mu\text{M}$  toward MCF-7 cancer cell line.

Another group of researchers<sup>81</sup> recently synthesized analogues of chalcones containing a 4-oxoquinazolinyl moiety

**Table 3. Anticancer Potential (IC<sub>50</sub>) of Chalcone Based on Quinazoline Heterocycles 133–136**

compound no.	A549	HT-29	MCF-7	A375
<b>133</b>	2.90	0.18		1.89
<b>134</b>	0.10	0.13	0.17	1.34
<b>135</b>	0.10	1.56	0.14	0.19
<b>136</b>	2.10	2.89	0.16	1.37
Combretastatin-A4	0.11	0.93	0.18	0.21

and screened these candidates for their antiproliferative potential. It was determined that out of 38 compounds synthesized, compound **137** recorded the greatest potency with anticancer potential toward HCT-116 (IC<sub>50</sub> = 3.56  $\mu\text{M}$ ) and MCF-7 cells (IC<sub>50</sub> = 4.08  $\mu\text{M}$ ). Compound **137** induced apoptosis in the sub-G1 phase and in the mitochondrial death pathway (Figure 4).

The antitubercular and antimicrobial properties of chalcone having a quinoxaline moiety were assessed. In comparison with the reference drugs ciprofloxacin and pyrazinamide, chalcone derivatives **138** and **139**, which contain a hydroxyl group in their rings, displayed significantly lower antitubercular activities. Compound **138** is not active against fungal strains, but it recorded an antibacterial potential against Gram-negative and Gram-positive bacteria. It is noteworthy that compound **139** exhibited both antifungal and antibacterial effects (Figure 4 and Table 4).<sup>82</sup>

**Table 4. Antimicrobial Potential of Chalcone Derivatives 138 and 139**

compound no.	<i>S. aureus</i>	<i>E. coli</i>	<i>C. albicans</i>
<b>138</b>	5	5	
<b>139</b>	10	5	10
ciprofloxacin	2	2	
fluconazole			16

**3.3. Chalcones Hybridized with Other Types of N-Heterocycles.** The antimalarial, antileishmanial, and anti-trypanosomal activity of chalcone derivatives bearing a caffeine moiety has been evaluated.<sup>83</sup> Chalcone derivatives **140** and **141** were reported to exhibit remarkable activity against *Leishmania panamensis* (Figure 4). In contrast, chalcone **142** containing a trimethoxy group showed activity against *Acrypanozoma cruzi* at very low concentrations. Despite the fact that compounds **140–142** did not exhibit significant antimalarial activity, several new tricyclic pyrido[3,4-*b*]indoles hybridized with chalcone derivatives were constructed and biologically evaluated for their anticancer activity and DNA binding affinity.<sup>84</sup> A majority of the synthesized derivatives were found to possess promising cytotoxic potential toward the lung adenocarcinoma cell line A549 with IC<sub>50</sub> below 10  $\mu\text{M}$ . Compound **143**, having a trimethoxy substituent on both the chalcone skeleton and the C-1 position of  $\beta$ -carboline, recorded significant anticancer potential toward lung adenocarcinoma A549 (IC<sub>50</sub> = 5.30  $\mu\text{M}$ ), B-16 melanoma (IC<sub>50</sub> = 6.37  $\mu\text{M}$ ), human prostate PC-3 cancer cells (IC<sub>50</sub> = 19.59  $\mu\text{M}$ ), human colorectal cancer cells (IC<sub>50</sub> = 23.08  $\mu\text{M}$ ), and HeLa cervical cancer cells (IC<sub>50</sub> = 44.26  $\mu\text{M}$ ). Despite this, compounds **144–151** showed significant elevation of  $\Delta T_m$  of DNA compared to Adriamycin, suggesting a significant interaction as well as DNA stabilization. A further series of chalcone derivatives derived from  $\beta$ -carboline via the C-1

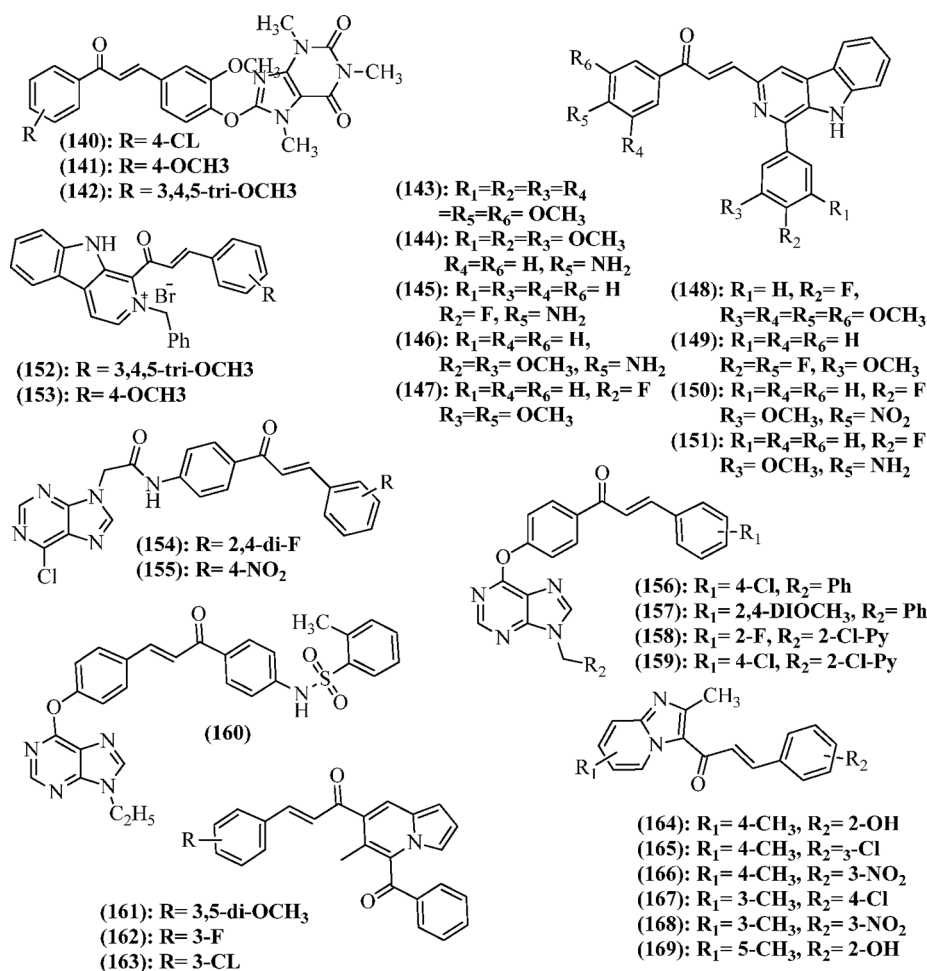


Figure 5. Chalcones bearing some other ring-type N-heterocycles.

position were synthesized and evaluated as potential anticancer and antibacterial agents.<sup>85</sup>

From the constructed  $\beta$ -carboline–chalcone conjugates, compound **152** containing a trimethoxy substituent and the molecule as a bromide salt was evaluated and determined to show the highest activity toward a panel of cancerous and noncancerous cell lines with IC<sub>50</sub> values of 20  $\pm$  2.1  $\mu$ M (BxPC-3), 22.1  $\pm$  3.23  $\mu$ M (HeLa), 22.02  $\pm$  3.25  $\mu$ M (PC-3), 17.18  $\pm$  2.98  $\mu$ M (HEK293T), 15.95  $\pm$  3.41  $\mu$ M (MDA-MB-231), and 55.23  $\pm$  5.8  $\mu$ M (NIH3T3). Meanwhile, compound **153** with a *p*-methoxy group was found to be the most effective analogue for inhibiting both Gram-positive and Gram-negative bacteria. The high antibacterial potential of this candidate was achieved when it inhibited *S. aureus* with a zone inhibition diameter of 15 mm and a MIC equal to 440  $\mu$ g/mL (Figure 5).

New chalcones hybridized with purines had been designed and constructed.<sup>86</sup> By means of an amide bridge, chalcones and purines were linked. Antiviral evaluations of the synthesized compounds had been performed against tobacco mosaic virus (TMV) and CMV. Among them, compounds **154** and **155** exhibited an inactivating potential toward TMV higher than that recorded by ribavirin, as recorded in Table 5. Furthermore, compound **154** recorded a moderate affinity for the coat protein of TMV, which is in accordance with its inactivating property (Figure 5). The same group of researchers constructed novel chalcone–purine hybrids that were evaluated in vivo for their antiviral properties.<sup>87</sup> It was

Table 5. EC<sub>50</sub> ( $\mu$ g/mL) of Chalcone Based on Purine Heterocycles **153** and **154** toward TMV

compound no.	curative	protective	inactivation
<b>154</b>	452.4 $\pm$ 3.7	416.2 $\pm$ 3.9	241.2 $\pm$ 4.9
<b>155</b>	438 $\pm$ 3.5	418.6 $\pm$ 3.3	261.7 $\pm$ 7.5
ribavirin	585.8 $\pm$ 4.1	436.0 $\pm$ 4.3	268.7 $\pm$ 5.1

found that among the compounds under study, compounds **156–159** displayed higher curative activity against CMV with EC<sub>50</sub> values of 301.1, 315.7, 282.3, and 230.5  $\mu$ g/mL, sequentially compared to that of ribavirin (726.3 ng/mL) and dufulin (373.7 ng/mL). In addition, a fluorescence spectroscopy study revealed that compound **156** had a strong affinity for the TMC coat protein. Zhou et al.<sup>88</sup> prepared a set of new chalcones linked with purine and benzenesulfonamide moieties. According to in vivo antiviral assays, some of the derivatives exhibited excellent anti-TMV and anti-CMV properties. Compound **160** demonstrated EC<sub>50</sub> = 51.65  $\mu$ g/mL and was identified as the most potent hybrid with significant inactivating activity against the TMV. This compound exhibited a strong affinity for the TMV coat protein.

Novel chalcone–indolizines were constructed and tested toward lymphoma cells (U937, Raji, and JeKo-1) for their anticancer potential.<sup>89</sup> Among those compounds, candidate **161** was identified as the most potent agent, which resulted in below 60% cell viability at 1  $\mu$ M against U937 cells. The

provided results revealed the important role of the 3,5-dimethoxyphenyl moiety in regards to their anticancer properties. Compounds **162** and **163** with halogen substituents at the meta-position inhibited cell activity more effectively than those at the para-position. Moreover, compound **161** recorded apoptotic inducing potential higher than that of doxorubicin but not as high as that of cisplatin, as registered in Table 6.

**Table 6. Apoptotic Cell Percentage Induced by Compound 160, Doxorubicin, and Cisplatin**

compound no.	apoptotic cells percentage at 10 $\mu$ M		
	U937	Raji	Jeko-1
<b>161</b>	51.26	33.78	46.27
doxorubicin	74.66	95.35	87.92
cisplatin	8.58	23.05	44.26

Many imidazo[1,2-*a*]pyridine chalcone hybrids were constructed and tested as anticancer agents against the A549 cell line.<sup>90</sup> As determined by the MTT assay, compounds **164**–**169** showed significant inhibitory potential with  $IC_{50}$  values ranging from 7.0 to 42.2  $\mu$ g/mL. Chalcone derivative **166** was found to be the most active compound among the synthesized molecules, with  $IC_{50} = 7.0 \pm 2.1$   $\mu$ g/mL.

**3.4. Chalcone Derivatives Containing Five-Membered O-Heterocycles.** An investigation of the activity of the 36 novel constructed chalcones bearing quinoline, thiofuran, and furan systems against Gram-positive and Gram-negative bacteria was conducted.<sup>91</sup> Gram-positive bacteria, including multi-drug-resistant isolates, were selectively inhibited by some derivatives. *Streptococcus mutans* was significantly inhibited by the target compounds; in particular, 4-chlorophenylfuran derivative **170** (Figure 6) was the most active compound, with MIC = 2  $\mu$ g/mL. Candidate **170** recorded antibacterial potential similar to that of norfloxacin (MIC = 2  $\mu$ g/mL) and less activity than oxacillin (MIC = 1  $\mu$ g/mL).

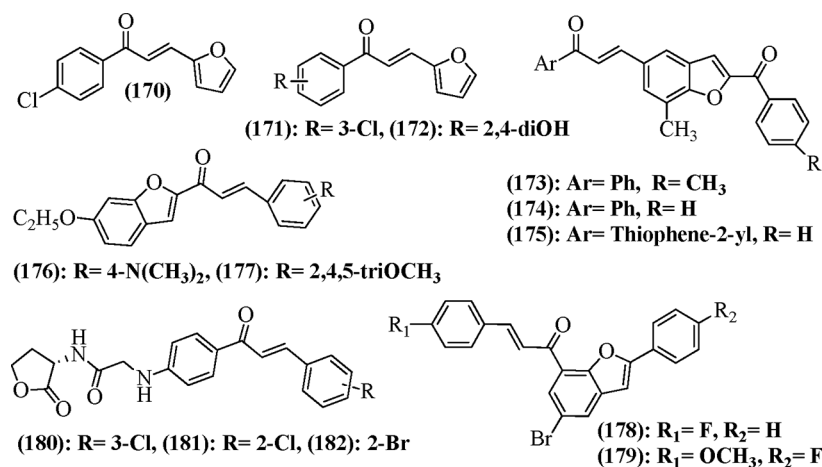
Chalcone–furan hybrids were designed and prepared to inhibit protein tyrosine phosphatases.<sup>92</sup> From these reported chalcones, compounds **171** ( $IC_{50} = 2.90 \pm 0.12$   $\mu$ M) and **172** ( $IC_{50} = 2.49 \pm 0.23$   $\mu$ M) inhibited protein tyrosine phosphatase 1B (PTP1B). Generally speaking, the findings indicated that compounds bearing dihydroxy or electron-

withdrawing groups had excellent activity against PTP1B (Figure 6).

Many benzofuran–chalcone hybrids have been constructed and studied in vivo with transgenic *Caenorhabditis elegans*.<sup>93</sup> Compounds **173**–**175** (Figure 6) decreased A $\beta$  aggregates, acetylcholinesterase (AChE) levels, and oxidative stress in the worms. It was demonstrated that these hybrids increased acetylcholine (ACh) levels and protected against chemically induced cholinergic neurodegeneration. Coskun et al.<sup>94</sup> constructed a set of 1-(7-ethoxy-1-benzofuran-2-yl)-substituted chalcone derivatives to develop an anticancer candidate by incorporating the chalcone–benzofuran system. A number of compounds containing dimethylamino or trimethoxy substituents have been shown to demonstrate promising effects against cancer cell lines. Compound **176** was identified as the most potent derivative against A549 ( $IC_{50} = 9$   $\mu$ M), MCF-7 ( $IC_{50} = 2$   $\mu$ M), and PC-3 ( $IC_{50} = 10$   $\mu$ M). Approximately 90% of the MCF-7 and A549 cells were in the late apoptotic stage at a concentration of 20  $\mu$ M, while in PC-3 cells, only 6.45 and 59.70% were in the early and late apoptotic stages, respectively. The sample concentration remains the same (Figure 6).

Compound **177** was the most effective at inhibiting the growth of PC-3 cells for 72 h. A series of benzofuran–chalcones were synthesized applying the Claisen–Schmidt reaction to yield chalcone, which was then cross-coupled to many aryl alkynes to afford the benzofuran moiety.<sup>95</sup> Moreover, these novel heterocycles had been assessed for their antiproliferative effects in vitro against the MCF-7 cancer cell line and for their inhibitory effect on EGFR phosphorylation and/or tubulin polymerization. In comparison with actinomycin D, almost all of the assessed chalcones recorded excellent antiproliferative effect on MCF-7; in particular, compounds **178** and **179** demonstrated significant inhibition toward the MCF-7 cell line (Figure 6 and Table 7).

An investigation of the antiproliferative activity of chalcone derivatives bearing homoserine lactone scaffolds was conducted recently against MCF-7, MGC-803, DU145, and PC-3 cell lines.<sup>96</sup> As a result of their in vitro assessment, many derivatives demonstrated selectivity and potency against PC-3 and DU145 prostate cell lines. It was found that compounds **180**–**182** showed the highest potential recording with  $IC_{50}$  less than 5  $\mu$ M. It was found that compound **181** inhibited migration and colony formation in DU145 cells to a dose-dependent extent.



**Figure 6.** Some biologically active chalcones bearing five-membered O-heterocycles.



**Table 7.** IC<sub>50</sub> of Compounds 178, 179, Actinomycin D, Colchicine, and Gefitinib toward MCF-7, Tubulin, and EGFR

compound no.	MCF (IC <sub>50</sub> , $\mu$ M)	tubulin (IC <sub>50</sub> , $\mu$ M)	EGFR (IC <sub>50</sub> , $\mu$ M)
178	0.55 $\pm$ 0.24	26.5	0.17 $\pm$ 0.03
179	3.55 $\times 10^{-4}$ $\pm$ 0.07	5.51 $\times 10^{-5}$	0.09 $\pm$ 0.03
actinomycin D	37.82 $\pm$ 1.30		0.04 $\pm$ 0.03
colchicine		9.88 $\times 10^{-2}$	
gefitinib			0.03 $\pm$ 0.02

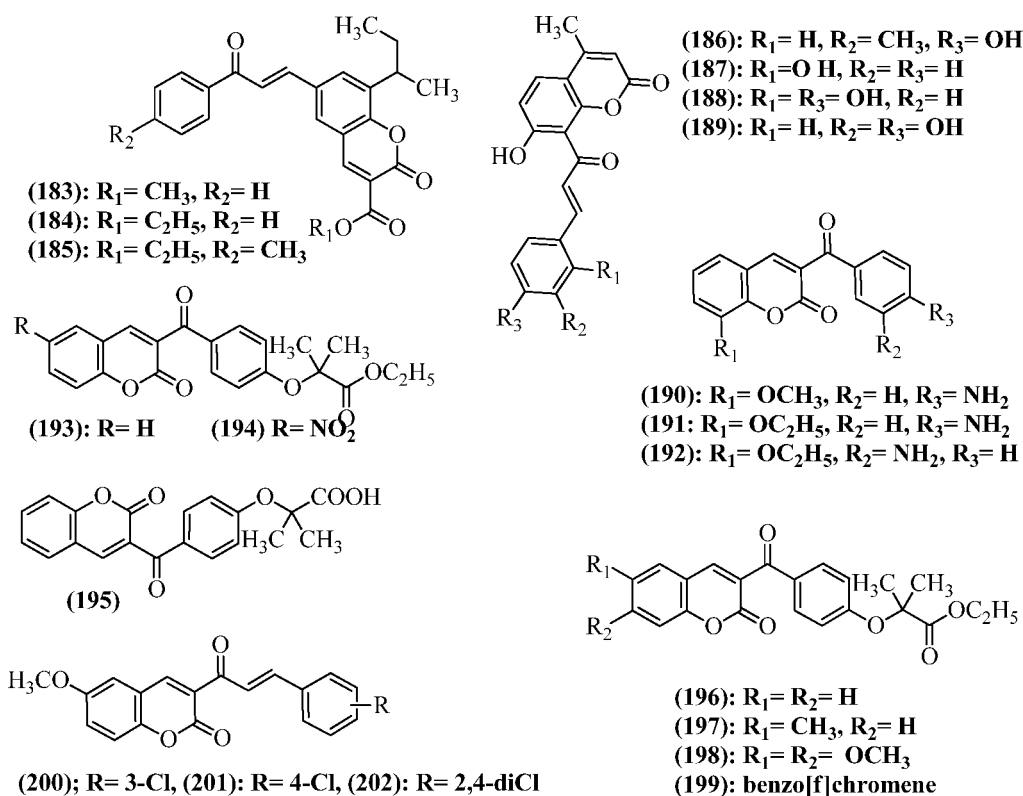
**3.5. Chalcone Derivatives Containing Six-Membered O-Heterocycles.** Coumarin derivatives have been reported to possess a variety of biological properties.<sup>97</sup> Therefore, the hybridization of chalcone with coumarin may generate new compounds with potential pharmacological activity. The synthesis of chalcone–coumarin hybrids was carried out, and their anticancer potential was tested in vitro.<sup>98</sup> It was reported that some of these derivatives exhibited excellent activities against KB (oral squamous carcinoma), C33A (cervical carcinoma), MCF-7 (breast adenocarcinoma), and A549 (lung carcinoma), as well as mouse embryo fibroblast (NIH3T3). Compounds 183–185 displayed significant performance, with IC<sub>50</sub> values ranging from 3.59 to 8.12  $\mu$ M. With an IC<sub>50</sub> of 3.59  $\mu$ M, compound 185 was the most potent candidate having selectivity against cervical carcinoma C33A 30-fold greater than that of the normal fibroblast NIH3T3 cell line.

The aim of the research is to develop a new class of DNA oxidation inhibitors and radical scavengers.<sup>99</sup> In order to achieve that, chalcones containing coumarin frameworks were synthesized. Inhibitory activities were observed for compounds

186–189. It was observed that coumarin clubbed chalcone derivatives were more potent antioxidants in case of presence of incorporating phenolic hydroxy group in the structure. In addition, double OH groups at adjacent positions scavenged ABTS and DPPH radicals and inhibited Cu(II)/glutathione-induced DNA oxidation.<sup>100</sup>

It has been reported that chalcone–coumarin compounds had been constructed in a trial to act as selective antibacterial agents toward the pathogens causing tenacibaculosis in fish.<sup>101</sup> The hybrids 190–192 displayed significant activity against 14 strains of *Tenacibaculosis maritimus*. The coumarin derivative 192 was found to be the most active candidate with 20-fold MIC increase compared to that of enrofloxacin toward *Tenacibaculosis maritimus* strains LL01 8.3.1 and LL018.3.8. It should be noted that compounds containing an amino group at the para- or ortho-position to the benzoyl moiety revealed excellent antibacterial potential. An innovative set of chalcone–coumarin fibrates had been prepared and tested as PPAR $\alpha$ / $\gamma$  agonists showing good antioxidant potential.<sup>102</sup> Compounds 193–195 were potent dual PPAR $\alpha$  and  $\gamma$  agonists. As PPAR $\alpha$  agonists, they proved to be more effective than fenofibrate. Antioxidant studies recorded that 194 and 196–199 have antioxidant activity significantly greater than that of trolox, with the IC<sub>50</sub> ranging from 9.40 to 18.63  $\mu$ M.

A group of investigators<sup>101</sup> presented two sets of chalcones containing a chromene ring, which included 1-(6-methoxy-2H-chromen-3-yl)-3-phenylpropen-1-ones and 3-(6-methoxy-2H-chromen-3-yl)-1-phenylpropen-1-ones. In biological studies, chloro-substituted 1-(6-methoxy-2H-chromen-3-yl)-3-phenylpropen-1-ones displayed excellent antileishmanial effect toward *Leishmania major* in a nontoxic dose. Antileishmanial potential of compounds 200–202 with IC<sub>50</sub> values below 1  $\mu$ M was found to be the strongest (Figure 7).



**Figure 7.** Chalcones bearing six-membered O-heterocyclic moieties.

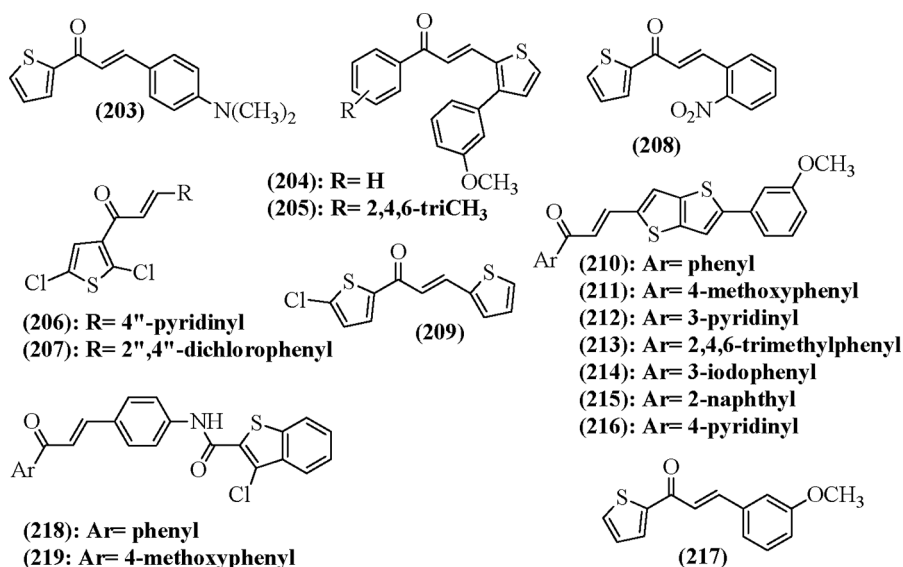


Figure 8. Chalcone derivatives containing five-membered S-heterocycles.

**3.6. Chalcones Bearing Five-Membered S-Heterocycles.** Chalcones containing thiophene were constructed from substituted aromatic aldehydes and 2-acetylthiophene.<sup>103</sup> A docking score of  $-8.46$  kcal/mol was achieved for compound **203** following ADME studies, in silico toxicity predictions, and explorations of molecular recognition. The calculated inhibitory constant toward the active site of MAO-B was approximately  $0.64$   $\mu$ M.<sup>104</sup> Aryl/heteroaryl chalcones derived from 3-arylthiophene-2-carbaldehydes were developed and studied for their anticancer properties. Among the compounds tested, compound **204** was identified as the most effective anticancer compound with an  $IC_{50}$  of  $21$   $\mu$ g/mL against the HCT-15 human colon cell line, slightly better than the doxorubicin control. In addition, compound **205** revealed significant potential showing  $IC_{50} = 22.8$   $\mu$ g/mL.<sup>105</sup> The anticancer effects of chalcone derivatives of 2-acetylthiophene were examined. A 48 h in vitro treatment of the human breast cancer cells MCF-7 and MDA-MB-231 with all chalcone derivatives resulting in significant reductions in cell viability in a dose-dependent manner. From the tested compounds, chalcone **205** was the most potent with  $IC_{50}$  values of  $11.76 \pm 4.87$  and  $5.52 \pm 4.26$   $\mu$ M against MCF-7 and MDA-MB-231 cells, respectively.

As reported in a previous work,<sup>106</sup> a set of 3-acetylthiophene chalcone hybrids was constructed, in vitro tested, and found to possess antitubercular, antifungal, and cytotoxic activity against the DU145 prostate cancer cell line. In terms of antifungal activity, compound **207** was comparable to fluconazole with a MIC value of  $4$   $\mu$ g/mL against *A. niger* and *C. tropicalis*. In addition, this candidate proved to be the most active toward DU145 ( $IC_{50} = 5 \pm 1$   $\mu$ g/mL), compared with methotrexate. Compared to pyrazinamide as a general tuberculosis drug, compound **208** recorded the best performance toward *M. tuberculosis* H37Rv with a MIC of  $3.12$   $\mu$ g/mL. Moreover, in the same year, chalcones incorporating a thiophene moiety were constructed and assessed as antifungal agents.<sup>107</sup> Among the tested compounds, compound **209** showed notable antifungal potential against *C. albicans* (MIC =  $128$   $\mu$ g/mL) and *A. niger* (MIC =  $64$   $\mu$ g/mL) (Figure 8).

An evaluation of the construction and biological potential of thieno[3,2-*b*]thiophene–chalcone, a chalcone derivative at-

tached to a thiophene scaffold, was reported. Compounds **210–213** recorded excellent antibacterial effect toward *S. aureus* (ZI = 24, 23, 22, and 22 mm, respectively), which was more active than ampicillin (ZI = 20 mm) as a reference antibacterial agent. Compounds **214–216** showed significant potential against A549 and SKNSH cancer cell lines, with  $IC_{50}$  values of 52.40, 51.00, and 47.17  $\mu$ M, respectively.<sup>108</sup> The synthesis and antimicrobial evaluation of thiophene–chalcone hybrids was reported. Among the prepared derivatives, compound **217** demonstrated activity against a wide range of bacteria with  $IC_{50}$  values of 219.1  $\mu$ g/mL (*S. aureus*), 441.9  $\mu$ g/mL (*P. aeruginosa*), 338.5  $\mu$ g/mL (*Enterococcus faecalis*). Nevertheless, none of these values is lower than that of reference drugs (Figure 8).

The antimicrobial activity of benzofused thiophene, also known as benzothiophene, was investigated in vitro for the chalcone structures linked by an amide bond.<sup>109</sup> Compounds **218** and **219** demonstrated moderate activity against bacterial strains and significant activity against fungal strains in this series (Figure 8).

## 4. CONCLUSION

Chemically, chalcones are easily modified and synthesized to create a variety of compounds with different structures. It is because of these properties that these compounds are very attractive as basic building blocks for the development of molecule-targeting agents. In this review, recent developments in the synthesis of chalcones have been summarized. In addition, it emphasizes how versatile these scaffolds can be in the development of various classes of compounds based on different moieties and synthetic methods. The present review describes the most important in vitro and in vivo biological activities of chalcone derivatives bearing various types of rings. A large number of preclinical studies have not completely established the mechanism of action of chalcone derivatives. Despite being relatively easy to synthesize, novel methods of synthesis must be developed in the future. This will enable the study of new biological properties, the study of molecular mechanisms of action, and, most importantly, the identification of their targets.

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### Notes

The authors declare no competing financial interest.

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