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Design and Synthesis of Chalcone and Chromone Derivatives as Antimicrobial Agents

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ABSTRACT

Coumarins are secondary plant metabolites that have significant pharmacological effects. Examples of their 3-substituted derivatives with antibacterial properties include numerobiocin, coumaromycin, and chartencin. In this study, coumarinyl chalcone was synthesized by combining three acetylcoumarins with an aromatic aldehyde using the Pachmann reaction. Compounds (Z2-Z4) were produced and then reacted with hydrazine hydrate to create compounds (Z5-Z7). The synthesized compounds were evaluated for various pharmacological activities, including anti-inflammatory and antibacterial activity using TLC, melting point, IR, and ^{1}H-NMR spectral studies. Compound (Z6) showed good antibacterial activities.

Keywords: *Chalcones, Chromones, Antimicrobial activity.*

INTRODUCTION

Chalcones, one of the main groups of flavonoids, are widely distributed in fruits, vegetables, tea, and soy [1, 2]. The use of plants and herbs in ancient medicinal applications to treat a variety of diseases has been linked to chalcones for many decades [3]. Recent research suggests that chalcones have a wide range of important pharmacological properties, including antiproliferative, antioxidant, anti-inflammatory, and anticancer effects [4, 5-7]. The Claisen-Schmidt condensation, which occurs when a base is used in a polar solvent, is commonly used to synthesize chalcones from acetophenones and benzaldehydes, and it plays a crucial role in the biosynthesis of flavones and flavanones [8-10]. Most flavonoids, including flavones, flavonols, and isoflavones, have the chromone ring structure, also known as 1-benzopyran-4-one [11]. The rigid bicyclic chromone fragment has been referred to as a preferred structure in drug discovery due to its use in a wide range of pharmacologically active compounds, including anticancer, anti-HIV, antibacterial, and anti-inflammatory medications that can supply ligands for various receptors [12-17]. Pyrazoles, five-membered heterocycles, are particularly helpful in the synthesis of organic compounds and are one of the azole family's most researched categories of chemical substances. Pyrazoles have a variety of uses in fields like technology, medicine, and agriculture, specifically as protein glycation inhibitors, antiviral, antibacterial, antifungal, anticancer, antidepressant, anti-inflammatory, and anti-tuberculosis medicines [18, 19]. Pyrazole systems have recently received more attention as biomolecules due to their intriguing pharmacological characteristics and can be found in a number of well-known medications from various categories with a variety of therapeutic activities [20-27]. The aim of this research article is to design and synthesize novel chalcone and chromone derivatives and evaluate their pharmacological activities, particularly their potential as anticancer agents.

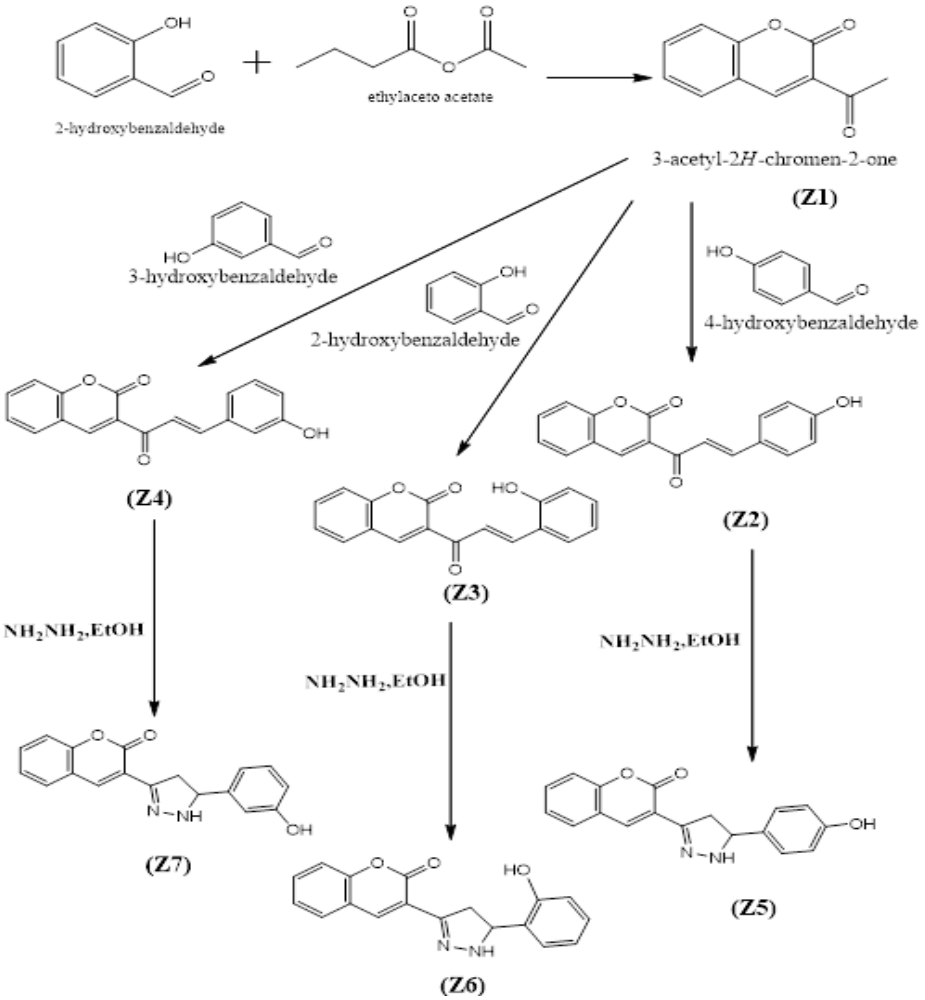

FIGURE 1: Reaction sequences of the synthesized compounds

EXPERIMENTAL DETAILS

Experimental method

Synthesis of the target compounds

a. Synthesis of 3-acetyl-2H-chromen-2-one (Z1): A solution of salicylaldehyde (1.2g, 0.01 mole) then, ethyl acetoacetate (1.3g. 0.01 mole) was added in ethanol (5 ml.) Added (4-5) drops of piperidine. For (3-6) hours were refluxing the reaction mixture and the product was then separated by filtration. The finished item was then recrystallized in EtOH [28].

b.Synthesis of (3-(3-(4-hydroxyphenyl)acryloyl)-2H-chromen-2-one (Z2), 3-(3-(2-hydroxyphenyl)acryloyl)-2H-chromen-2-one (Z3), (3-(3-(3-hydroxyphenyl)acryloyl)-2H-chromen-2-one (Z4): A combination of 3-acetylcoumarin (1 eq.) and 2-hydroxybenzaldehyde, 3-hydroxybenzaldehyde, and 4-hydroxybenzaldehyde (1.2 eq.) in EtOH was stirred for 2–12 hours while being refluxed with a few drops of piperidine. After cooling the combination, a solid was produced that was filtered and refined via re-crystallization in MeOH [29].

c. Synthesis 3-(5-(4-hydroxyphenyl)-4,5-dihydro-1H-pyrazol-3-yl)-2H-chromen-2-one (Z5), 3-(5-(2-hydroxyphenyl)-4,5-dihydro-1H-pyrazol-3-yl)-2H-chromen-2-one (Z6), 3-(5-(3-hydroxyphenyl)-4,5-dihydro-1H-pyrazol-3-yl)-2H-chromen-2-one (Z7): To a chalcone (1 mmol) in ethanol (5 ml), hydrazine hydrate (1 mmol) was added drop wise in a round bottom flask. The reaction mixture was heated at80 ^{0}C under reflux for 5 h. on oil bath. The reaction was monitored on TLC plates. After completion of reaction, the reaction mixture poured into ice cold water the precipitate was settle down at a bottom, precipitate filtered, dried and crystalized from ethanol [30].

Antimicrobial activity

The diffusion method [31, 32] was used to examine the antibacterial and antifungal

properties of two (G+) bacterial species, *Staphylococcus aureus* and *Staphylococcus epidermidits*, as well as the (G-) bacterial species *Klebsiella sp.*and *E. coli* and *Candida albicans*. Nutritional agar was used to estimate the antibacterial activity. Results were shown in millimeters along with inhibitory zones [33, 34]. The synthesized target compounds were dissolved in dimethyl sulfoxide to create stock solutions with a concentration of 1 mg/mL. The inhibitory zone was identified after 18-hour incubation at 37 °C in millimetres. The outcomes showed that none of the selected microorganisms were the target of any action.

Statistical analysis

The obtained data were statically analyzed using an unpaired t-test with GraphPad Prism [35]. The values were presented as the mean ± SD [36].

RESULTS AND DISCUSSION

Characterization of compound (Z1-Z7)

Using DMSO-d6 as the solvent and tetramethylsilane (TMS) as the internal standard, 1H-NMR spectra were recorded on a Varian 300 MHz spectrometer. The FT-IR spectra were obtained by noting KBr pellets on a Nicolet 380 FT-IR analyzer (Model Thermo Electron Corporation-Spectrum One). After processing, all organic extracts were dried over sodium sulfate. Unless otherwise stated, all solvents and reagents used were of commercial quality. Table (1) presents the physical characteristics and spectral data of the synthesized compounds.

Assay of Antimicrobial activity

Antimicrobial activity was evaluated based on the diameters of the clear inhibition zones surrounding the paper disks. Table 2 shows the results of the antimicrobial activity of compounds against Gram-negative (G (-)) and Gram-positive (G (+)) bacterial strains by disk diffusion method. In vitro antimicrobial tests showed that some of the prepared compounds in Scheme 1 exhibit a strong inhibitory effect. Compound 3-(2-(3-(2-hydroxyphenyl)-1H-pyrazol-5-yl)acetyl)-2H-chromen-2-one (Z6) showed more activity against Candida albicans with an inhibition zone of 22mm and more activity against Staphylococcus aureus, Staphylococcus epidermidis, Klebsiella sp., and E. coli than the standard drug Tetracycline due to the substitution of the (OH) group in their structures. Some of the derivatives (Z1, Z3, Z4, and Z7) were more active against S. aureus than the standard drug Tetracycline. Furthermore, Table 2 shows that the compounds (Z1, Z2, Z3, Z4, and Z7) were more active than Tetracycline against Staphylococcus epidermidis with inhibition zones of 18, 15, 20, 14, 16mm respectively, and the same compounds showed activity against Candida albicans with inhibition zones of 17, 18, 16, 14, 15mm respectively. Chalcone, a -unsaturated ketonic chemical, is made up of two benzenoid rings with a wide range of groups. It has three carbons between the aromatic groups and is a highly electrophilic compound with a linear structure [37, 38]. The results of this study suggest that the substitution of various functional groups in chalcone derivatives can significantly affect their antimicrobial activity. Some of the prepared compounds exhibited strong inhibitory effects against Gram-negative and Gram-positive bacterial strains, as well as against Candida albicans. In particular, compound Z6 showed the most potent activity against Candida albicans, while several other derivatives (Z1, Z3, Z4, and Z7) were more active against S. aureus than the standard drug Tetracycline. These findings highlight the potential of chalcone derivatives as promising antimicrobial agents for further development and optimization.

CONCLUSION

We have synthesized a series of coumarin-pyrazole derivatives, with the synthesized compounds (Z1-Z7) exhibiting significant antibacterial activities. The ring structure of coumarins has been studied for decades due to its extensive dispersion and diverse bioactivities. Coumarins have a wide range of biological effects. Several novel methods, such as the Pechmann, Claisen, Perkin, Knoevenagel, and Wittig reactions, can be used to synthesize coumarin and its derivatives. Compound (Z6) has been found to be highly effective as an antimicrobial activities.

COMPLIANCE WITH ETHICAL STANDARDS

The authors noted that none of the information used in this study had ever been published or offered for publication to another journal when they submitted their work. The corresponding author attests that all co-authors have given their consent for this work to be published.

Conflict of Interest: There are no conflicts of interest.

Table 1: Physical characteristics and spectral data of the synthesized compounds

NO. comp	M.P (ºC)	Yield (%)	Molecular formula (M.wt)	Spectral data	
				IR (cm^{-1})	^{1}H- NMR (δ, ppm)
Z1	120-122	89	$C_{11}H_8O_3$ 188	3029.59 (OH), 1738.64 (C=O), 1674.0 (C=O) carbonyl of lacton 1555.79, 1452.87 (C=C), 1264.24 (C-O)	8.65 (s,CH=C), 7.96 (d,1H,CH=C), 7.39–7.77 (m, 4H,aromatic), 2.58 (s, 3H,CH_3)
Z2	(213-215)	75	$C_{18}H_{12}O_4$ 292	3300.31 (OH) 1720.56 (C=O) 1680.50 (C=O) carbonyl of lacton 1566.25,1514.17 (C=C) 1278.85 (C-O)	9.78 (s,OH),8.65 (s,CH=C), , 7.62-7.80(m, 4H,aromatic), 6.81-6.98 (m, 4H,aromatic), 7.61 (d,1H) for CH=CH of α vinyl proton 7.93 (d, 1H) for CH=CH of β vinyl proton
Z3	(283-285)	60	$C_{18}H_{12}O_4$ 292	3433.41 (OH) 1722.49 (C=O) 1678.13 (C=O) carbonyl of lactone,1560.46,1454.38 (C=C) 1278.85 (C-O)	10.26 (s,OH),8.65 (s,CH=C), 7.30-7.70 (m, 4H,aromatic), 7.82 (d,1H) for CH=CH of α vinyl proton 8.38 (d, 1H) for CH=CH of β vinyl proton ,6.82-7.01 (m, 4H, Aromatic ring),
Z4	(273-275)	70	$C_{18}H_{12}O_4$ 292	3122.86 (OH) 1722.49 (C=O) 1678.13 (C=O) carbonyl of lactone 1564.32,1516.10 (C=C) 1278.85 (C-O)	9.69 (s,OH),8.67(s,CH=C), 7.25-7.35 (d1H) for CH=CH of α vinyl proton ,7.94 (d, 1H) for CH=CH of β vinyl proton 7.60-7.74 (m, 4H, Aromatic ring), 6.93- 7.22 (m, 4H, Aromatic ring)
Z5	(145-147)	54	$C_{18}H_{14}N_2O_3$ 306	2935.76 (C-H, Aromatic) 3203.87 (NH), 3061.13(OH) 1670.41 (C=O) carbonyl of lactone 1612.54 (C=N) 1508.38,1454.38(C=C) 1265.35 (C-O)	(s, OH), 8.23 7.95(s,CH=C), 7.21,7.32(m, 4H, Aromatic ring), 6.71-6.89 (m, 4H, Aromatic ring) , 7.0,(s, 1H,NH pyrazole), 1.85(t,1H, CH pyrazole), 2.93 (d, 2H,CH pyrazole) 3.6 (t,1H,CH pyrazol***e)***
Z6	300d	55	$C_{18}H_{14}N_2O_3$ 306	3026.41 (C-H, Aromatic) 3327.32(NH), 3248.23 (OH) 1681.98 (C=O) carbonyl of lactone 1627.97 (C=N) 1564.32,1535.39 (C=C) OR 1271.13 (C-O)	9.32(s,OH) , 8.22 (s,CH=C), 7.74,7.59(m, 4H, Aromatic ring), 7.42-7.57 (m, 4H, Aromatic ring) 7.0,(s, 1H,NH) pyrazole) , 3.34 (t,1H, CH pyrazole) 3.54 (d, 2H, CHpyrazole), 4.30 (t,1H,CH pyrazole)
Z7	(231-233)	45	$C_{18}H_{14}N_2O_3$ 306	3043.77 (C-H, Aromatic) 3325.39(NH), 3252.09 (OH) 1680.05 (C=O) carbonyl of lactone 1620.26 (C=N)	9.33 (s,OH), 7.93(s,CH=C), 7.44-7.72(m, 4H, Aromatic ring), 7.00,7.30 (m, 4H, Aromatic ring) , 7.0,(s, 1H,NH) pyrazole) ,2.28 (t,1H, CH pyrazole)

				1568.18, 1518 .03 (C=C) 1271.13 (C-O)	2.85 (d, 2H,CH pyrazole), 3.54 (t,1H,CH pyrazole)

TABLE 2: Antimicrobial activity of the prepared compounds in scheme (1), expressed as the inhibition zone (mm)

Microorganism	*Staphylococcus aureus*	*Staphylococcus epidermidits*	*Klebsiella sp.*	*E. coli*	*C. albicans*
Compound (1 mg/ml)	INHIBITION ZONES (mm)				
Z1	19	18	11	14	17
Z2	18	15	-	12	18
Z3	21	20	10	14	16
Z4	20	14	-	11	14
Z5	---	---	11	---	12
Z6	29	24	21	19	22
Z7	24	16	15	14	15
Tetracycline	19	11	12	21	---

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