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Synthesis, characterization and *in vitro* antibacterial activity of new chalcones linked via coumarin ring

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ABSTRACT

In the present investigation, a novel series of chalcones 2a–2e were synthesized by the clasein-schmidt condensation of various aldehydes with 3-acetyl-7-dimethylaminocoumarin in the presence of pyridine in ethanol which lead to the formation of new chalcones. The structures of these compounds were elucidated by, IR, 1H-NMR spectral data. The in vitro antibacterial activity of these compounds was evaluated against two Gram positive and two Gram-negative bacteria Staphylococcus aureus, Streptococcus pyogenes, Escherichia coli and Pseudomonas aeruginosa by microdilution method and then the minimum inhibitory concentration (MIC) of these compounds was determined. The results showed that compounds 2d and 2e showed most promising antibacterial activity as compared to the antibiotics ciprofloxacin in (Tables 1).

Keywords: Chalcone; Antibacterial activity; coumarin, aminoacetophenone

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INTRODUCTION

Emerging pathogenous infections such as gastroenteritis, arthritis, listeriosis and pneumonia are caused by multidrug resistant Gram-positive and Gram-negative pathogens. These diseases are the world's most prevalent and fatal infectious dis- eases. Principal players among these problematic organisms are isolates of methonia resistant *Aeromonas hydrophila*, *Yersinia enterocolitica*, *Listeria monocytogenes*, *and Staphylococcus aureus* [1-4]. It is speculated that resistance to β- lactam antibiotics is due to the production of multiple inducible, chromosomally encoded b-lactames. Resistance to the third generation cephalosporins is known to be associated with the derepression of the chromosomal enzymes [5]. In rare cases, through direct inactivation of the antibiotic or by mutations in the 16S rRNA that prevent the binding of tetracycline to the ribosome. Amoxicillin, penicillin, ampicillin, norfloxacin, Ofloxacin and ciprofloxacin are the principal drugs of choice in the treatment of bacterial infection since they are effective against extraintestinal and intestinal wall infection [6], but these are associated with several side effects such as nausea, metallic taste, dizziness, hypertension, etc. as well as resistance have been reported [7,8]. The present strategy for new drug development is directed towards identifying the essential enzyme systems in the bacterial and developing molecules to inhibit them on our ongoing medicinal chemistry research activity. The study of chalcone derivatives has become of much interest in recent years on account of their antibacterial, antiviral, anti-cancer, anti-fungal, anti-hermitic and insecticidal [9-11] activities. Cyclization of chalcone such as pyrazolines dramatically increases the diversity of certain biological properties such as antibacterial, antiviral and anti-amoebic activities [12-14]. In view of these observations and in continuation of our group work on biologically active

heterocyclic compounds [15-18] and their increasing importance in pharmaceutical and biological field, it was considered of interest to synthesize some new chemical entities incorporating the molecular frame work and to evaluate their biological activities.

MATERIALS AND METHODS

2.1 Chemistry

To a cold mixture of salicylaldehyde (0.2 M) and ethylacetoacetate (0.2 M), 2 ml of piperidine was added by rapid stirring. After 20 min the yellowish solid 3-acetyl coumarin 1 separated was filtered off subsequently washed with ethanol and was recrystallised from water:ethanol (3:7). Chalcones **2(a-e)** were synthesized from the Claisen–Schmidt reaction of 3-acetyl coumarin with different aldehydes in the presence of piperidine as shown in Fig 1, which were crystallized from CH_3OH or C_2H_5OH to give pure crystalline solid compounds in moderate yields. All the compounds are insoluble in water but soluble in organic solvents. The structures of these compounds were analyzed by the rigorous analysis of their IR and ^{1}H- NMR spectral data.

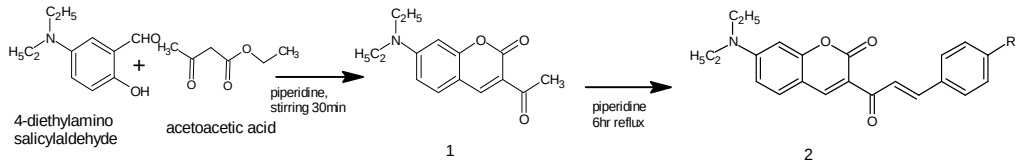

Fig.1. Schematic diagram indicating the synthesis of compound nos. 2a–2e. R = -H (2a), -OH (2b), -Cl (2c), -F (2d), -NO_2 (2e)

2.2 Pharmacology

B.1 In vitro antimicrobial activity

Antibacterial activities were evaluated by using agar well diffusion method. The nutrient agar medium (peptone, beef extract, NaCl and agar-agar) were used for antibacterial screening respectively. The inoculums of the different bacteria were spread over agar medium. After the media had cooled, wells of bore size (6 mm) were made in solid medium by using a sterile metallic borer and 25 mL test drug (2.0 mg/ml in DMSO) in 100µg/ml concentration was poured in each cavity of different plates. Standard drug, Ciprofloxacin (100µg/ml) was used against bacteria Staphylococcus aureus, Streptococcus pyogenes, Escherichia coli and Pseudomonas aeruginosa were placed aseptically in a separate petri dish. The plates were kept at room temperature for one hour to diffuse the drug in surrounding medium and then incubated at 37ºC for 24 h. The diameter of the zone of inhibition formed around the cavities and disc of standard drug after incubation was accurately measured in mm.

B.2 MIC of all active compounds

MIC measurements of all active compounds were carried out using the two fold serial dilution technique. Twofold serial dilutions of the selected compounds were prepared using proper nutrient broth. Compounds were prepared in the concentration range of 100, 50, 25, 12.5, 6.25, 3.125, 1.56 and 0.78 mg/mL. The microorganism suspensions (10^6 CFU/mL) were used to inoculate the test compounds in their suitable broth. The plates were incubated at 37ºC for 24 h for bacteria, respectively. At the end of experiment the growth of microorganisms was observed by turbidity measurements. The lowest concentrations showing no growth was taken as the minimum inhibitory concentration (MIC) which is presented in Table 1.

Table 1: Results of antibacterial screening of compounds (2a-h)

Entry	R	Minimum Inhibitory concentration for bacteria (µg/ml) ±SD			
		Gram negative		Gram positive	
		E coli	*P aeroginosa*	*S aureus*	*S pyogenes*
2a	-O	250 ± 1.60***	500 ±3.78*	500±2.64*	500±2.64**
2b	-OH	500±3.60	500 ±1.16*	500 ±2.50*	250 ±3.60*
2c	- Cl	250 ±1.20**	50 ±3.60*	100±2.04*	100 ± 1.92*
2d	- F	50±1.60**	100±2.04**	100 ±3.05*	25 ± 3.21*
2e	-NO_2	50 ±2.44*	25 ± 1.21*	250 ±4.16***	50 ±1.78
	Ciprofloxacin	100 ±2.05	100 ±1.0	250 ±1.52	100 ± 2.06

*±SD, standard deviation. All values are presented as mean of 6 experiments (n = 6). All significant differences are considered from control value 0.00.; * P < 0.05 significant.; ** P < 0.01 moderately significant.; *** P < 0.001 extremely significant.*

RESULTS AND DISCUSSION

7-dimethylamino coumarin chalcones which were synthesized in satisfactory yields (62–80%) as illustrated in Fig. 1 and their structures were characterized by spectral data. It may be concluded that this study describes the general method for the synthesis of some Chalcones linked through the coumarin ring under the normal conditions. All the five synthesized compounds 2a-2e were screened for their potential to inhibit emerging pathogens Staphylococcus aureus, Streptococcus pyogenes, Escherichia coli and Pseudomonas aeruginosa responsible for gastrointestinal diseases. The individual minimum inhibitory concentration (MIC, µg/mL) obtained for compounds 2a-e are presented in (Table 1). It was observed that compounds 2d (4-F) and 2e (4-NO_2) were most active compounds. On the basis of antibacterial screening, compounds 2d (4-F) and 2e (4-NO_2) were found to show very good activity against E. coli at MIC = 50 µg/mL. Compounds 2c (4-Cl) displayed very good activity at MIC = 50 µg/mL, whereas compounds 2e (4-NO_2) displayed excellent inhibitory activity against P. aeruginosa at MIC = 25 µg/mL as compared to ciprofloxacin (MIC = 100 µg/mL). Compounds 2c (4-Cl) and 2d (4-F) were found to exhibit activity at MIC = 100 µg/mL against S. aureus as compared to standard ciprofloxacin (MIC = 250 µg/mL). Compounds 2e (4-NO_2) showed very good activity (MIC = 50 µg/mL), while compounds 2d (4-F) have shown excellent activity against S. pyogenes as compared to ciprofloxacin (MIC = 100 µg/mL).

1. Experimental

The entire chemicals were purchased from Aldrich Chemical Company (USA) and were used without further purification. The reactions were monitored by percolated aluminium silica gel 60F 254 thin layer plates procured from Merck (Germany). All melting points were measured with a capillary apparatus.

3-acetyl-7-(diethylamino)-2H-chromen-2-one (1). The yellow solid was recrystallized in EtOH: yield 89%; mp 280-285 °C; 1H NMR (CDCl3, 300 MHz) δ 8.57 (s, 1H, ArH), 7.43 (d, 1H, ArH), 6.63 (d, 1H, ArH), 6.56 (s, 1H, ArH), 3.29 (q, 4H, -CH_2), 1.23 (t, 6H, -CH_3); IR ν (KBr) 1710, 1596, 1422, 815 cm^{-1}

1-[7-(diethylamino)-2H-chromen-2on]-3-phenyl-2-propen-1-one (2a). The solid was recrystallized in EtOH: yield 68%; mp 223-225 °C; 1H NMR (CDCl3, 300 MHz) δ 8.25 (d, 1H, -CH), 8.01 (d, 1H, -CH), 8.52(s, 1H, ArH), 7.41 (d, 1H, ArH), 6.69 (d, 1H, ArH), 7.40 (d, 2H, ArH), 6.62 (dd, 1H, ArH), 6.52 (s, 1H, ArH), 3.41 (q, 4H, -CH_2), 1.15 (t, 6H, -CH_3); IR ν (KBr) 3430, 1703, 1588,1419 cm^{-1}

1-[7-(diethylamino)-2H-chromen-2on]-3-(p-hydroxyphenyl)-2-propen-1-one (2b). The brown solid was recrystallized in EtOH: yield 72%; mp 233-237 °C; 1H NMR (CDCl3, 300 MHz) δ 5.35 (s, 1H, OH), 7.82 (d, 1H, -CH), 7.01 (d, 1H, -CH), 8.51(s, 1H, ArH), 7.45 (d, 1H, ArH), 6.67 (d, 1H, ArH), 7.56 (d, 2H, ArH), 6.65 (d, 1H, ArH), 6.53 (s, 1H, ArH), 3.42 (q, 4H, -CH_2), 1.10 (t, 6H, -CH_3); IR ν (KBr) 1705, 1589,1420, 816 cm^{-1}

1-[7-(diethylamino)-2H-chromen-2on]-3-(p-chlorophenyl)-2-propen-1-one one (2c). The orange solid was recrystallized in EtOH: yield 66%; mp 246-248 °C; 1H NMR (CDCl3, 300 MHz) δ 7.86 (d, 1H, -CH), 7.03 (d, 1H, -CH), 8.51 (s, 1H, ArH), 7.42 (d, 1H, ArH), 6.68 (d, 1H, ArH), 7.68 (d, 2H, ArH), 7.44 (d, 2H, ArH), 6.56 (s, 1H, ArH), 3.42 (q, 4H, -CH_2), 1.17 (t, 6H, -CH_3); IR ν (KBr) 1708, 1577,1423, 810 cm^{-1}

1-[7-(diethylamino)-2H-chromen-2on]-3-(p-fluorophenyl)-2-propen-1-one (2d). The orange solid was recrystallized in EtOH: yield 74%; mp 260-262 °C; 1H NMR (CDCl3, 300 MHz) δ 8.03 (d, 1H, -CH), 7.75 (d, 1H, -CH), 8.57 (s, 1H, ArH), 7.46 (d, 1H, ArH), 6.69 (d, 1H, ArH), 7.72 (d, 2H, ArH), 7.19 (d, 2H, ArH), 6.51 (s, 1H, ArH), 3.45 (q, 4H, -CH_2), 1.21 (t, 6H, -CH_3); IR ν (KBr) 1723, 1585,1420, 821 cm^{-1}

1-[7-(diethylamino)-2H-chromen-2on]-3-(p-nitrophenyl)-2-propen-1-one (2e). The red solid was recrystallized in EtOH: yield 89%; mp 229-232 °C; 1H NMR (CDCl3, 300 MHz) δ 7.96 (d, 1H, -CH), 7.32 (d, 1H, -CH), 8.57 (s, 1H, ArH), 7.49 (d, 1H, ArH), 6.62 (d, 1H, ArH), 8.21 (d, 2H, ArH), 8.03 (d, 2H, ArH), 6.59 (s, 1H, ArH), 3.38 (q, 4H, -CH_2), 1.11 (t, 6H, -CH_3); IR ν (KBr) 1710, 1581, 1550,1390 cm^{-1}

CONCLUSION

The novel chalcones derivatives were synthesized by the reaction of 3-acetyl coumarin with different aldehydes and were studied for their antibacterial activity. This research involves the synthesis of chalcone derivatives 2a-2e and antibacterial activity of these chalcone compounds were examined using culture S. aureus, S. pyogenes, E. coli and

P. aeruginosa. The results of antibacterial screening reveal that among all the compounds screened, compound 2c showed moderate antibacterial activity while compounds 2d displayed good antibacterial activity when compared with Ciprofloxacin used as the standard drugs. Particularly, compound 2e which carries the nitro substituent appears to exhibit the highest antibacterial activity against all bacteria.

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