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Synthesis and Antimicrobial Evaluation of Novel Coumarin derivatives Bearing Piperidinyl Substituent

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ABSTRACT

Novel 3-((E)-3-(aryl)-3-oxoprop-1-enyl)-4-(piperidin-1-yl)-2H-chromen-2-ones were synthesized by the reaction of 2-oxo-4-(piperidin-1-yl)-2H-chromene-3-carbaldehydewith different acetophenones in presence of piperidine. All the newly synthesized compoundswere characterized by different spectroscopic techniques and elemental analyses. All the compounds were evaluated for their antibacterial activity against S. aureus, E.coli and for their antifungal activity against C. albicans.

Keywords: Coumarins, Piperidinyl Substituent, Antibacterial activity, Antifungal activity

I. INTRODUCTION

Novobiocin and Chlorobiocin containing Coumarin nucleus are known antimicrobials. Literature survey revealed that number of Coumarin derivatives exhibited remarkable antimicrobial activity[1-8].

Various Coumarinylprop-2-en-1-one derivatives are reported to exhibitwide spectrum of pharmacological activities viz. Antibacterial[9], anti-inflammatory[10], anticancer[11], analgesic[12], antiviral[13]etc.

In view of above observations, we have synthesized novel 3-((E)-3-(aryl)-3-oxoprop-1-enyl)-4-(piperidin-1-yl)-2H-chromen-2-ones**(3a-e)** bearing piperidinyl substituent and evaluated their antimicrobial activity.

II. METHODS AND MATERIAL

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on SHIMADZU-FT-IR-8400 [Fourier transform–infrared (FT-IR)]. The IR spectra were taken using KBr pellets. 1H NMR were recorded on Bruker AMX spectrometer. All the chemicals were commercial products and were used without further purification.

Procedure for the Synthesis of 4-chloro-2-oxo-2H-chromene-3-carbaldehyde (1a)

The synthesis of 4-chloro-2-oxo-2H-chromene-3-carbaldehyde was accomplished using reported procedure[14].

Procedure for the Synthesis of 2-oxo-4-(piperidin-1-yl)-2H-chromene-3-carbaldehyde (2a)

To a solution of 4-chloro-2-oxo-2H-chromene-3-carbaldehyde **(1a)** (0.01 mol) in 15 mL of ethanol, piperidine (0.02 mol) was added. The resulting solution was refluxed. The reaction progress was monitored using TLC. After the completion of the reaction, the reaction mixture was allowed to cool, the resulting solid material was filtered and re-crystallized from ethanol.

General Procedure for the Synthesis of 3-((E)-3-(aryl)-3-oxoprop-1-enyl)-4-(piperidin-1-yl)-2H-chromen-2-ones (3a-e)

A mixture of 2-oxo-4-(piperidin-1-yl)-2H-chromene-3-carbaldehyde **(2a)** (0.01 mol) and appropriate acetophenone(0.01 mol) was dissolved in ethanol. To the resulting solution, few drops of piperidinewere added and the resulting mixture was refluxed. The reaction progress was monitored using TLC. After the

completion of the reaction, the reaction mixture was allowed to cool, the separated chalcone was filtered and re-crystallized from ethanol.

3-((E)-3-oxo-3-phenylprop-1-enyl)-4-(piperidin-1-yl)-2H-chromen-2-one (3a)

Yield 62%.mp 192-194 °C. ^{1}H NMR δ 1.57-1.61 (m, 2H, piperidine-CH_2), 1.69-1.74 (m, 2H, piperidine-CH_2), 1.81-1.87 (m, 2H, piperidine-CH_2), 3.79-3.82 (t, 2H, piperidine-CH_2), 3.93-3.96 (t, 2H, piperidine-CH_2), 7.21-7.80 (m, 9H, Ar-H), 7.99-8.04 (d, 1H, =CH), 8.31-8.34 (d, 1H, =CH). MS: m/z 359.

3-((E)-3-(4-methylphenyl)-3-oxoprop-1-enyl)-4-(piperidin-1-yl)-2H-chromen-2-one (3b)

Yield 68%.mp 186-188 °C. ^{1}H NMR δ 2.39 (s, 3H, CH_3), 1.57-1.65 (m, 4H, piperidine-CH_2), 1.72-1.81 (m, 2H, piperidine-CH_2), 3.75-3.78 (t, 2H, piperidine-CH_2), 3.88-3.91 (t, 2H, piperidine-CH_2), 7.31-7.38 (m, 4H, Ar-H), 7.65-7.71 (m, 4H, Ar-H), 8.03-8.07 (d, 1H, =CH), 8.40-8.45 (d, 1H, =CH). MS: m/z 373.

3-((E)-3-(3-chlorophenyl)-3-oxoprop-1-enyl)-4-(piperidin-1-yl)-2H-chromen-2-one (3c)

Yield 52%.mp 179-181 °C. ^{1}H NMR δ 1.61-1.66 (m, 4H, piperidine-CH_2), 1.75-1.80 (m, 2H, piperidine-CH_2), 3.66-3.71 (t, 2H, piperidine-CH_2), 3.84-3.88 (t, 2H, piperidine-CH_2), 7.33-7.85 (m, 8H, Ar-H), 8.08-8.12 (d, 1H, =CH), 8.33-8.37 (d, 1H, =CH). MS: m/z 393.

3-((E)-3-(4-chlorophenyl)-3-oxoprop-1-enyl)-4-(piperidin-1-yl)-2H-chromen-2-one (3d)

Yield 55%.mp 171-173 °C. ^{1}H NMR δ 1.64-1.69 (m, 4H, piperidine-CH_2), 1.78-1.82 (m, 2H, piperidine-CH_2), 3.72-3.76 (t, 2H, piperidine-CH_2), 3.81-3.86 (t, 2H, piperidine-CH_2), 8.11-8.15 (d, 1H, =CH), 8.40-8.44 (d, 1H, =CH). MS: m/z 393.

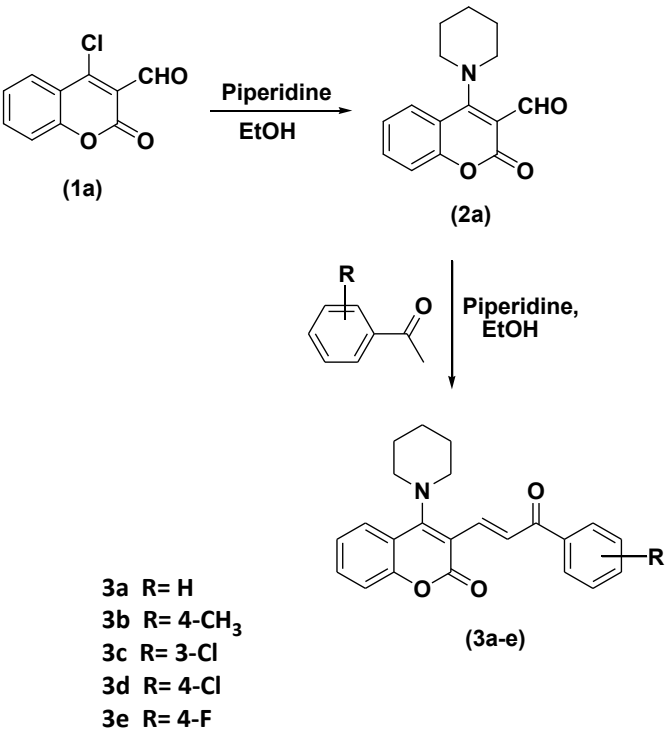
3-((E)-3-(4-Fluorophenyl)-3-oxoprop-1-enyl)-4-(piperidin-1-yl)-2H-chromen-2-one (3e)

Yield 59%.mp 223-225 °C. ^{1}H NMR δ 1.68-1.72 (m, 4H, piperidine-CH_2), 1.82-1.87 (m, 2H, piperidine-CH_2), 3.68-3.73 (t, 2H, piperidine-CH_2), 3.87-3.91 (t, 2H, piperidine-CH_2), 7.18-7.26 (m, 4H, Ar-H), 7.79-7.90 (m, 4H, Ar-H), 8.10-8.14 (d, 1H, =CH), 8.35-8.39 (d, 1H, =CH). MS: m/z 377.

III. RESULTS AND DISCUSSION

Chemistry

The synthesis of 2-oxo-4-(piperidin-1-yl)-2H-chromene-3-carbaldehyde **(2a)**was accomplished by the reaction of 4-chloro-2-oxo-2H-chromene-3-carbaldehyde **(1a)** withpiperidineusing ethanol as solvent, which was then reacted with different acetophenones in presence of catalytic amount of piperidine to furnish the title compounds **(3a-e)** (Scheme 1).



Scheme 1.Synthesis of Chalcones (3a-e)

All the newly synthesized compounds**(3a-e)**were characterized by different spectroscopic techniques.
The purity of the compounds was controlled by TLC. The spectral data of all the newly synthesized compounds were in full agreement with the proposed structures.

Biological screening

The compounds **(3a-e)**were evaluated for their antibacterial activity against Escherichia coli, Staphylococcus aureus and antifungal activity against Candida albicans using the broth-dilution method. After 24 h of incubation at 37 °C, the Minimum Inhibitory Concentration (MIC) was measured. The activities were

compared with those of some known drugs, viz. Ampicillin, Ciprofloxacin and Nystatin. The results are summarized in **Table 1**.

Table-1.Antimicrobial Evaluation of Chalcones (3a-e)

	Minimum inhibition concentration ($\mu g\ mL^{-1}$)		
Compound	**Antibacterial Activity**		**Antifungal Activity**
	E. coli	S. aureus	C. albicans
3a	1000	500	500
3b	500	250	500
3c	500	250	250
3d	125	125	250
3e	250	250	500
Ampicillin	100	250	-
Ciprofloxacin	25	50	-
Nystatin	-	-	100

IV.CONCLUSION

To summarize, a series of novel Coumarin derivatives bearing piperidinylsubstituentwas synthesized. The newly synthesized heterocycles exhibited moderate to promising antimicrobial activity against standard strains. These results make them interesting lead molecules for further synthesis of related heterocycles and their biological evaluation.

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