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Research Article

SYNTHESIS, STRUCTURAL ELUCIDATION, AND ANTIBACTERIAL EVALUATION OF SOME FLAVONES DERIVED FROM COUMARIN

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ABSTRACT

In the present study, substituted coumarin based flavones have been synthesized *via* chalcone. The additional benefit of this reaction is the chalcone synthesis. The structures of the compounds were elucidated by elemental and spectral (IR, ^{1}HNMR, and MS) analysis. The reactions are easy to conduct, under mild conditions, and form coumarin substituted flavones in moderate to good yields. The synthesized compounds have been evaluated against four strains of bacterial culture.

Keywords: Chalcone, Coumarin and Flavones.

1. INTRODUCTION

Coumarins and its derivatives have been proved as useful precursors for the synthesis of variety of medicinal agents[1]. The heterocycles derived from these have also been tested for their anti-HIV, anti-inflammatory, anti-convulsant, antioxidant, anti-bacterial, anti-fungal, anti-carcinogenic and anti-histaminic activities[2,3].

Flavones constitute one of the major classes of naturally occurring products. The basic flavanoid structure is a flavone nucleus, in nature; they are available as flavone, flavonol, flavanone, isoflavone, chalcone and their derivatives[4]. Natural and synthetic flavanoids and flavanones have attracted considerable attention because of their interesting biological activity including antimycobacterial[5], antimicrobial[6,7], anti-lung cancer[8], antibacterial[9], anti-proliferative[10], antituberculosis[11], antifungal[12], anti-arrhythmic[13], anti-viral [14], anti-hypertensive[15], antioxidant[15], anti-inflammatory[15].

Moreover, flavonoidal derivatives acquire a special place in natural chemistry and in heterocyclic chemistry because this system is a frequently encountered structural motif in many pharmacologically relevant compounds[16-19].

On the basis of our observation the present research work was carried out to synthesis some coumarin derivatives and further evaluate the antibacterial activity.

2. MATERIAL AND METHODS

Melting points were determined on a Veego melting point apparatus model no. VMP-DS with ± 0.5°C accuracy and are uncorrected. The ^{1}H NMR spectra were recorded on a BRUKER Spectrometer (400 MHz). Chemical shifts were reported in parts per million using tetramethylsilane as an internal standard and were given in δ units. The solvent for NMR spectra was DMSO. Infrared spectra were taken on SHIMADZU-FTIR-8400 Spectrophotometer instrument in the frequency range of 4000-400 cm^{-1} by KBr powder method. The mass spectra were recorded by MS-SHIMADZU-QP2010. All reactions were monitored by thin layer chromatography, carried out on 0.2 mm silica gel 60F254 (Merk) plates using UV light for detection. Common reagent grade chemicals are either commercially available and were used without further purification.

Preparation of 6-chloro-4-methyl-7-hydroxycoumarin (1)

1 gm of 4-chlororesorcinol was added to 1.18 ml ethyl acetoacetate and this mixture was cooled. 7 ml conc. H_2SO_4 was added with const. stirring for 12hr. reaction mixture was poured in crushed ice. The solid product obtained was dissolve in 5% NaOH and then acidified to obtained white solid of 6-chloro-4-methyl-7-hydroxycoumarin.

It is brownish crystalline solid; Yield 59%; mp. 220 °C; IR spectrum (KBr),υ (cm^{-1}): 1480.70 cm^{-1} (C=C str.); 1680.90 cm^{-1} (C=O str.); 3450.15 cm^{-1} (O-H str.); ^{1}HNMR spectrum (δ ppm): 2.52 (3H, d, CH_3); 4.82 (1H, s, OH); 6.24 (1H, d, CH); 7.1-7.69 (Ar-H)

Preparation of 6-chloro-4-methyl-2-oxo-2H chromen-7-yl acetate (2)

The mixture of 6-chloro-4-methyl-7-hydroxycoumarin 0.1M and 0.1M of acetyl chloride stirred for 1 hr. The reaction mixture was poured in crushed ice, to get the 4-methyl-2-oxo-2H-chromen-7yl acetate. It is crystallized from ethanol.

It is brownish crystalline solid; yield 63%; mp. 198°C; IR spectrum (KBr),υ (cm^{-1}): 1480.70 cm^{-1} (C=C str.); 1680.15 cm^{-1} (C=O str.); ^{1}HNMR spectrum (δ ppm): 2.92 (3H, s, CH_3); 3.05 (3H, d, CH_3); 6.23 (1H, d, CH); 6.8-7.4 (Ar-H)

Preparation of 8-acetyl-5-chloro-7-hydroxy-4-methyl-2H-chromen-2-one (3)

0.235gm of acetylated compound and 5gm of $AlCl_3$ was heated at 145-150˚C in oil bath for an hour, with $CaCl_2$ tube to prevent from moisture. HCl gas was continuously evolved. The reaction mixture was treated with ice and concentrate HCl. Thus the solid product obtained was collected washed with water and crystallized from ethanol.

It is brownish crystalline solid; yield 67%; mp. 195°C; IR spectrum (KBr),υ (cm^{-1}): 1445.78 cm^{-1} (C=C str.); 1671.91 cm^{-1} (C=O ketone str.); 3082.68 cm^{-1}(O-H str.); ^{1}HNMR spectrum (δ ppm): 2.92 (3H, s, CH_3); 3.05 (3H, d, CH_3); 6.23 (1H, d, CH); 6.8-7.4 (Ar-H).

Preparation of 6-chloro-8-[(2E)-3-(4-chlorophenyl)prop-2-enoyl]-7-hydroxy-4-methyl-2H-chromen-2-one (4a)

Compound (3) and 4-chlorobenzaldehyde was taken in 1:1 proportion, to this 50 ml of ethanol as a solvent, and 9ml of 40 % KOH was added, the reaction mixture was refluxed for 2 hrs to get the compound (4a). The product obtained was washed with water and crystallised from ethanol.

Similarly (4b) was synthesized by reaction of compound (3) with 4-hydroxybenzaldehyde.

6-chloro-8-[(2E)-3-(4-chlorophenyl)prop-2-enoyl]-7-hydroxy-4-methyl-2H-chromen-2-one (4a)

It is creamish crystalline solid; yield 67%; mp. 154°C; IR spectrum (KBr), υ (cm^{-1}) : 1491.77 cm^{-1} (Ar C=C str.); 1231.40 cm^{-1} (C-O-C str.); 1684.99 cm^{-1} (C=O ketone str.); 3368 cm^{-1}(O-H str.); 740.36 cm^{-1} (C-Cl str.); ^{1}HNMR spectrum (δ ppm): 2.35 (3H, s, CH_3); 4.67 (1H, s, OH); 6.09 (1H, d, CH); 6.97 (1H, d, CH); 7.51 (1H, d, CH); 7.2-7.5 (Ar-H).

6-chloro-8-[(2E)-3-(4-hydroxyphenyl)prop-2-enoyl]-7-hydroxy-4-methyl-2H-chromen-2-one (4b)

It is brownish crystalline solid; yield 65%; mp. 188°C ; IR spectrum (KBr),υ (cm^{-1}): 1450.48 cm^{-1} (Ar C=C str.); 1231.05 cm^{-1} (C-O-C str.); 1684.28 cm^{-1} (C=O ketone str.); 3375 cm^{-1}(O-H str.); 740.64 cm^{-1} (C-Cl str.); ^{1}HNMR spectrum (δ ppm): 2.36 (3H, s, CH_3); 4.74 (1H, s, OH); 6.11 (1H, d, CH); 6.98 (1H, d, CH); 7.52 (1H, d, CH); 7.2-7.5 (Ar-H).

Synthesis of 6-chloro-8-(4-chlorophenyl)-4-methyl-2H,10H-pyrano[2,3-f]chromene-2,10-dione (5a)

Few iodine crystals were added in the mixture of compound (4a) and DMSO, reaction mixture was refluxed for 1 hr. to get the final product (5a). Similarly compound (5b) was prepared.

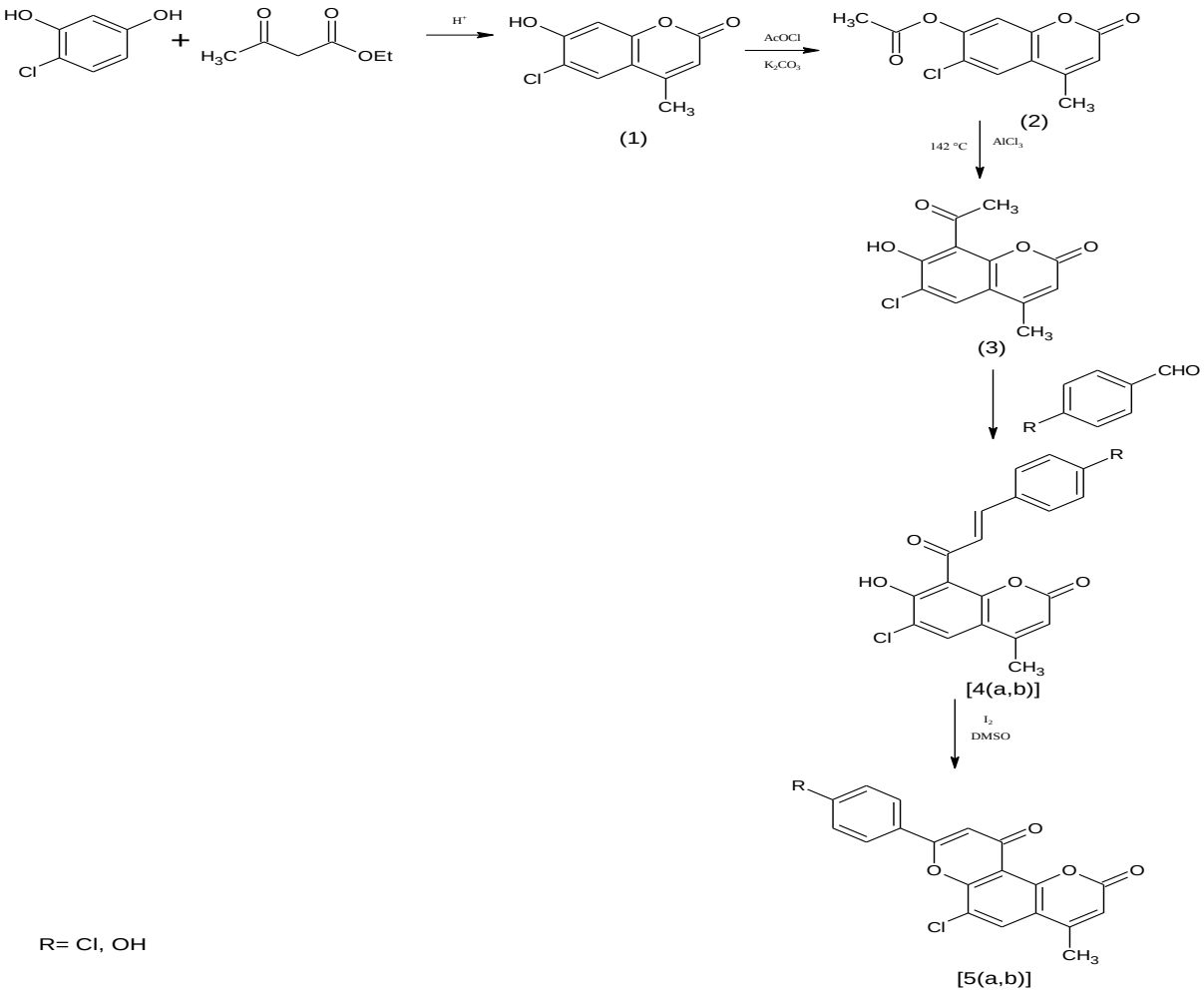
6-chloro-8-(4-chlorophenyl)-4-methyl-2H,10H-pyrano [2,3-f]chromene-2,10-dione (5a)

It is brownish crystalline solid; yield 69%; mp.160°C ; IR spectrum (KBr),υ (cm^{-1}): 1491.65 cm^{-1} (ArC=C str.); cm^{-1} 1700.60 cm^{-1} (C=O ketone str.); 1267.11 cm^{-1}(C-O-C str.); 749.03 cm^{-1} (C-Cl str.); ^{1}HNMR spectrum (δ ppm): 2. 41 (3H, s, CH_3); 7.02 (1H, d, CH); 7.28 (1H, d, CH); 7.68-7.72 (Ar-H)

6-chloro-8-(4-hydroxyphenyl)-4-methyl-2H,10H-pyrano[2,3-f]chromene-2,10-dione (5b)

It is brownish crystalline solid; yield 68%; mp.173°C ; IR spectrum (KBr),υ (cm^{-1}): 1472.61 cm^{-1} (Ar C=C str.); 1697.81 cm^{-1} (C=O ketone str.); 1266.55 cm^{-1}(C-O-C str.); 748.55 cm^{-1} (C-Cl str.); 3235.53 cm^{-1} (Ar O-H str.); ^{1}HNMR spectrum (δ ppm): 2. 45 (3H, s, CH_3); 7.12 (1H, d, CH); 7.41 (1H, d, CH); 7.71-7.97 (Ar-H).

REACTION SCHEME



R= Cl, OH

3. RESULTS AND DISCUSSION

The structures of compounds (4a,b) and (5a,b) were confirmed on the basis of spectral analysis. The IR spectrum of chalcones (4a,b) showed a band due to C-O-C str. (1231.05-1231.40 cm^{-1}); C=C str. (1450-1491cm^{-1}); C=O str. (1684.28-1684.99 cm^{-1}); O-H str. (3368-3375 cm^{-1}); vibration band indicates formation of chalcone. ^{1}H-NMR ($CDCl_3$) spectrum of chalcone showed a signal at δ 6.09-6.11 (*d*, 1H, CH); 6.97-6.98 (*d*, 1H, CH); 7.51-7.52 (*d*, 1H, CH) and δ 4.67-4.74 (*s*, 1H, OH) confirms presence of chalcone.

The IR spectrum of (5a,b) exhibited a band due to C=O str. (1697–1700 cm^{-1}); C=C str. (1472–1491 cm^{-1}); and C-O-C ring str. (1266-1267 cm^{-1}) and OH str. (3235.53 cm^{-1}) in 5b; stretching vibration band which indicates the presence of the flavone ring. Further, in their ^{1}H-NMR (DMSO) spectrum, the appearance of a signal at δ 7.02-7.12 (*d*, 1H, CH flavone) and δ 7.28-7.41 (*d*, 1H, CH, flavone) confirms the presence of flavone ring.

3.1 Antibacterial activity

The target molecules were tested for antibacterial activity against the variety of test organisms *Escherichia coli*, *Pseudomonas* (gram-negative bacteria) and *Staphylococcus aureus, Salmonella typhi* (gram-positive bacteria) by disc diffusion method with concentration 0.1 mg/ml. The screening results indicate that compound **5b** shows high activity against *Pseudomonas* and *S. typhi*. Compound **5a** shows good activity against *S. typhi*, *Pseudomonas* and low activity against *S. aureus.* Compounds **5a** and **5b** shows poor activity against *E. coli* and *S. aureus.*

Table 1: Antibacterial activity of the compounds 5a and 5b

Compound	Antibacterial activity Diameter of zone of inhibition (in mm)			
	S. aureus	*S. paratyphi*	*E. coli*	*Pseudomonas*
5a	7	8	5	10
5b	6	11	5	14
Oxacillin (standard)	15	14	12	16

The zones of inhibition of the reference compound oxacillin are also given in Table 1. The result indicates that the presence of chloro-, and hydroxyl groups enhanced the antibacterial activity. However, no specific structure–activity relationship could be established.

4. CONCLUSION

The successful synthesis of chalcone and flavone compounds follows a mild, efficient route with a good to moderate yield. In present work we synthesized flavones by reacting chalcones with iodine crystals in DMSO medium. The synthesized compounds exhibited good antimicrobial activity.

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