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NOTE

Synthesis and Antimicrobial Activity of Some New Coumarin Derivatives

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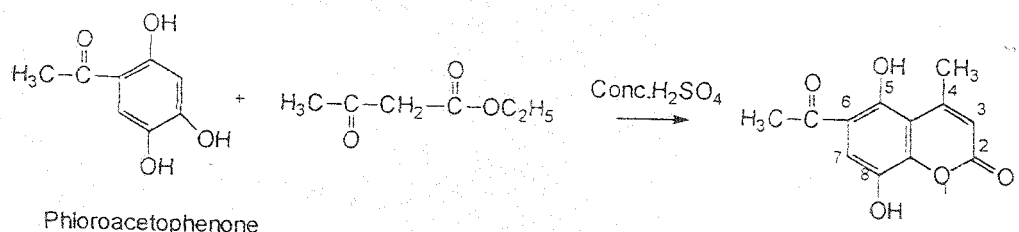
5,8-Dihydroxy-6-acetyl-4-methyl coumarin (1) was prepared by the reaction of phloroacetophenone with ethyl acetoacetate using Pechmann condensation. Different Schiff bases (2–5) were then synthesized by the reaction between this compound and various aromatic amines. The resulting Schiff bases were identified by chemical and spectral methods. Some of these compounds possessed significant antimicrobial activity.

Key Words: Phloroacetophenone, Coumarin derivatives, Synthesis, Antimicrobial activity.

Coumarins are known to possess antibacterial[1, 2], antifungal[3], antihelmentic[4] and anti-HIV[5] activities. A coumarin identified as 5,8-dihydroxy-6-acetyl-4-methyl coumarin (1) was prepared for the first time by the reaction of phloroacetophenone with ethylacetoacetate using Pechmann condensation[6]. The carbonyl group of the phloroaetophenone part now incorporated as acetyl moiety at position 6 of the compound 1 was involved in the reaction with various aromatic amines (A–D), but not the α-pyrone ring system, which remained intact as evidenced by IR spectra. Schiff bases thus obtained were characterized by chemical, chromatographic and spectral methods and screened for antimicrobial properties.

All the melting points were determined in an open capillary and are uncorrected. IR spectra were recorded on Perkin-Elmer 377 spectrophotometer and ^{1}H NMR spectra on AMX 400 MHz in DMSO-d_6 using TMS as an internal standard.

Preparation of Coumarin (I): Mix 5 g of phloroacetophenone (0.02 mol) and 6 mL of ethyl acetoacetate (0.04 mol) and then adding slowly this mixture with stirring to 20 mL of precooled conc. H_2SO_4. After the addition, stirring continued for about 30 min and the reaction mixture was poured into crushed ice, the product separated was filtered, washed, dried and crystallized from hot methanol as pale yellow needles, m.p. 271°C, showed a single spot on TLC (Scheme-1).

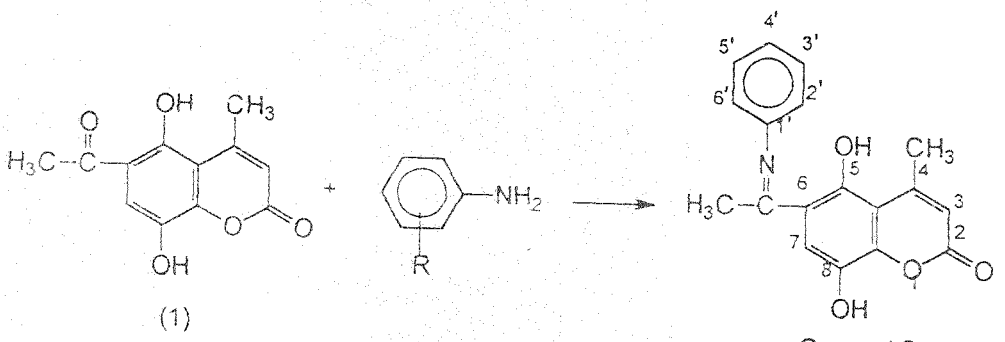


Phloroacetophenone (1)

Scheme-1

Synthesis of Schiff bases: 0.01 mol of compound **(1)** was dissolved in ethanol (3 mL) and then 0.06 mol of aromatic amine was added and refluxed for about 3 h. It was cooled and product separated was filtered, washed with cold water, dried and crystallized from appropriate solvent or solvent mixtures **(Scheme-2).**

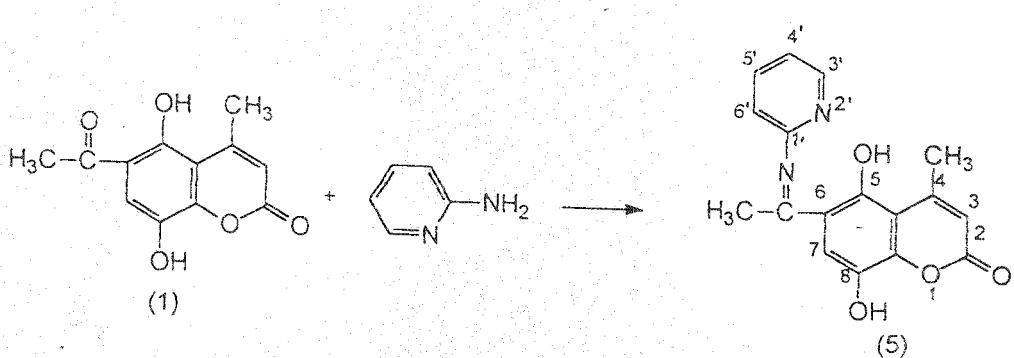
(i)



(1) General Structure

Compopund	R
2	4-Fluoro, 5-Chloro
3	3-nitro
4	4-SO_2NH_2

(ii)



(1) (5)

Scheme-2

The spectral data of the Schiff bases **(2–5)** are given in the Tables-2 and 3.

TABLE-1
CHARACTERISATION DATA OF THE COMPOUNDS

Compound	m.p. (°C)	Yield (%)	m.f.
1	271	82	$C_{12}H_{10}O_5$
2	284	88	$C_{18}H_{13}O_4NFCl$
3	252	87	$C_{18}H_{14}O_6N_2$
4	281	88	$C_{18}H_{16}O_6N_2S$
5	248	78	$C_{17}H_{14}O_4N_2$

TABLE-2
IR and ^1H NMR SPECTRAL DATA OF COMPOUNDS

Compound	^1H NMR (ppm)	IR (KBr, cm^{-1})
1	δ2.6 and 2.8 (2s, 6H, 2 × CH_3)	1720 ν(α-pyrone)
	δ6.5 (s, 1H, 3-H)	1700 ν(C═O)
	δ6.0 (s, 1H, 7-H)	
	δ6.3 (s, 1H, D_2O exchangeable, 8-OH)	3340 ν(O—H)
	δ11.5 (s, 1H, D_2O exchangeable, 5-OH)	
2	δ7.5 (dd, J = 9, 2Hz, 1H, 2′-H)	1720 ν(α-pyrone)
	δ7.9 (d, J = 9Hz, 3′-H)	1630 ν(C═N)
	δ7.7 (d, J = 2Hz, 6′-H)	1230 ν(Ar-F)
		1090 ν(Ar-Cl)
3	δ7.9 (dd, J = 9, 2Hz, 2H, 2′-H and 4′-H)	Asymmetric and symmetric ν(N═O_2) stretchings at 1490 and 1326 respectively
	δ7.4 (m, 2H, 2′-H and 6′-H)	
4	δ7.7 (dd, J = 9, 2Hz, 2H, 2′-H and 6′-H)	Asymmetric and symmetric ν(S═O_2) stretchings at 1394 and 1177 respectively
	δ6.9 (dd, J = 9, 2Hz, 2H, 3′-H and 5′-H)	
	δ3.4 (s (br), 2H—SO_2NH_2)	3400 ν(NH_2 stretching)
5	δ6.6 (m, 2H, 4′-H and 5′-H)	1433 ν(C···C)
	δ7.4 (dd, J = 9, 2 Hz, 1H, 3′-H)	1480 ν(C···C)
	δ7.9 (dd, J = 9, 2 Hz, 1H, 6′-H)	

Antimicrobial screening

Antibacterial activity of the compounds was evaluated by cup-plate method against B*acillus subtilis* and *Escherichia coli* using neomycin sulphate as standard at 100 μg/mL concentration. Similarly, antifungal activity of title compounds was evaluated against *Candida albicans, Aspergillus niger* using nystatin as standard at 100 μg/mL concentration. The results are given in Table-3.

TABLE-3
ZONE OF INHIBITION OF COMPOUNDS

Compound	Inhibition zone diameter (mm)			
	B. subtitis	*E. coli*	*A. niger*	*C. albicans*
1	12	13	12	12
2	16	17	17	17
3	15	15	16	16
4	16	16	17	17
5	13	14	14	13
A	8	10	10	9
B	7	8	9	9
C	8	8	10	10
D	6	8	9	8
Neomycin	18	20	—	—
Nystatin	—	—	19	20

The compound **2, 3** and **4** have shown significant activity against the bacteria *Bacillus subtilis, Escherichia coli* and the fungi *Aspergillus niger* and *Candida albicans*. Compounds **1** and **5** shown moderate zones of inhibition against all the above mentioned microbes. This proved that the anti-microbial spectrum of coumarins earlier reported could be improved by the resulting Schiff bases, when the carbonyl of the coumarin reacted with aromatic amines like 4-fluoro-5-chloro aniline (**A**), *m*-nitro aniline (**B**) and sulfanilamide (**C**) and 2-amino pyridine (**D**). This may be due to the presence of pharmacophores like halogens, nitro and sulfonamido groups present in these amines. Even though these amines by themselves are moderately active, but when incorporated these pharmacophores, the resulting Schiff bases were found to be more active.

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