Note

Synthesis and antimicrobial screening of 2,4-diaryl-6-[2'H-[1']-4'-hydroxy-2'-oxo-benzopyran-3'-yl]pyridines and 2,6-diaryl-4-[2'H-[1']-4'-hydroxy-2'-oxo-benzopyran-3'-yl]pyridines

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The chalcones of 4-hydroxycoumarin such as 4-hydroxy-2-oxo-3-(1'-oxo-3'-phenylprop-2'-enyl)-2H-[1]-benzopyran 1 and 4-hydroxy-2-oxo-3-(3'-oxo-3'-phenylprop-1'-enyl)-2H-[1]-benzopyran 2 are separately refluxed with phenacyl pyridinium bromide and ammonium acetate in acetic acid to give 2,4-diaryl-6-[2'H-[1']-4'-hydroxy-2'-oxo-benzopyran-3'-yl]pyridines 3 and 2,6-diaryl-4-[2'H-[1']-4'-hydroxy-2'-oxo-benzopyran-3'-yl]pyridines 4 respectively. The structures of all the compounds have been confirmed on the basis of spectral and analytical data. All the above compounds have been screened for their antimicrobial activity and are found to possess significant antibacterial activities.

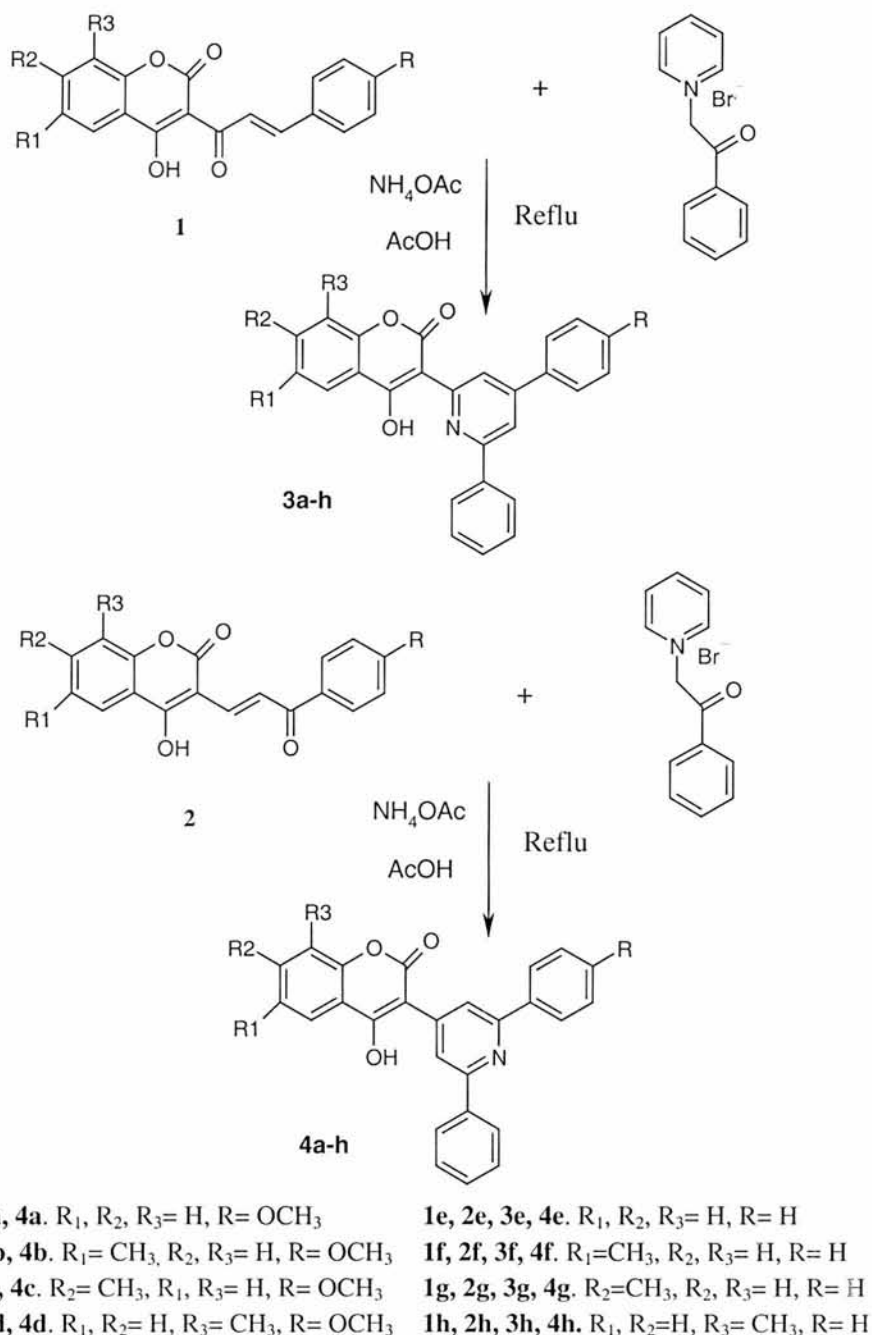**IPC: Int.Cl.[7] C 07 D 213/00 // A 61 P 31/04**

Coumarin chemistry has become more important since many years because of the discovery of the varied biochemical properties[1], industrial uses[2] and analytical applications[3] of these compounds. Coumarins are widely distributed in nature and are known to exhibit various physiological activities[4-5]. Coumarins have been found to be physiologically effective for animals as well as men[6]. Similarly, the chalcones and their derivatives have been reported to possess various biological activities such as antibacterial[7-9], antifungal[8], anti-inflammatory[10,11], antitumor[12], anticancer[13,14], prostaglandin binding[14]. Chalcones are detrimental to the growth of tubercle bacilli[15], acrus[16], Schistosoma and Intestinal worms[17]. In addition, several substituted pyridines have been reported to possess biological activities such as antihypertensive, antianginal and antibacterial activities[18], which created interest in the synthesis of heterocyclic substituted pyridines. The alkyl derivative of pyridines were used to reduce lipids and cholesterol levels in the blood[19]. There is large number of medicinal compounds based on the pyridine ring. In view of these observations and in continuation of our work on coumarin based heterocycles[20, 21], it was considered of interest to synthesize new chemical entities incorporating the three active pharmacophores namely, coumarin and pyridine in a single molecular framework using chalcones of 4-hydroxycoumarin as basic building block.

For this purpose, chalcones of 4-hydroxycoumarin i.e. 4-hydroxy-2-oxo-3-(1'-oxo-3'-phenylprop-2'-enyl)-2H-[1]-benzopyran 1 (ref. 22) and 4-hydroxy-2-oxo-3-(3'-oxo-3'-phenylprop-1'-enyl)-2H-[1]-benzopyran 2 (ref. 23) and phenacyl pyridinium bromide[24,25] were refluxed in acetic acid in presence of ammonium acetate to give 2,4-diaryl-6-[2'H-[1']-4'-hydroxy-2'-oxo-benzopyran-3'-yl]pyridines 3a-h and 2,6-diaryl-4-[2'H-[1']-4'-hydroxy-2'-oxo-benzopyran-3'-yl]pyridines 4a-h respectively (**Scheme I, Table I**). The IR spectrum of 3a in KBr showed peaks at 3440 cm^{-1} indicating the presence of OH group, at 1688 cm^{-1} for carbonyl group. The ^{1}H NMR of 3a in CDCl$_3$ showed singlet at δ 3.91 for the three protons of the methyl group of -OCH$_3$ and the hydroxy proton was observed as a singlet at δ 9.40 which is D$_2$O exchangeable. The ^{13}C NMR showed peak at δ 55.10 for the methyl group of −OCH$_3$ group and the carbonyl carbon was observed at δ 161.22. Mass spectrum showed molecular ion peak (M$^+$) at 421 (23%) along with other peaks at 390 (12%), 344(17%), 287(25%), 253(36%), 187(62%), 77(100%). The spectral and analytical data of compounds 4a-h showed similar observations and these were in agreement with the structure. All the above compounds were screened for their antimicrobial activity against various bacterial strains (**Table II**).

Antimicrobial activity

All the above compounds 3a-h and 4a-h were screened for their antibacterial activity against *S. aureus*, *S. typhi* and *E. coli* (**Table II**). The minimum inhibitory concentration (MIC) was determined using tube dilution method according to the standard procedure[26]. DMF was used as a blank and Cipro-

1a, 2a, 3a, 4a. R_1, R_2, R_3= H, R= OCH_3

1b, 2b, 3b, 4b. R_1= CH_3, R_2, R_3= H, R= OCH_3

1c, 2c, 3c, 4c. R_2= CH_3, R_1, R_3= H, R= OCH_3

1d, 2d, 3d, 4d. R_1, R_2= H, R_3= CH_3, R= OCH_3

1e, 2e, 3e, 4e. R_1, R_2, R_3= H, R= H

1f, 2f, 3f, 4f. R_1=CH_3, R_2, R_3= H, R= H

1g, 2g, 3g, 4g. R_2=CH_3, R_2, R_3= H, R= H

1h, 2h, 3h, 4h. R_1, R_2=H, R_3= CH_3, R= H

Scheme I

floxacin was used as antibacterial standard. An examination of the data reveals that all the compounds showed antibacterial activity ranging from 50 µg/mL to 200 µg/mL.

From the antimicrobial screening of the compounds **3a-h** and **4a-h** it is observed that the presence of methyl group in coumarin ring increases the antibacterial activity. The activity is found to be maximum when methyl group is at position-7 of coumarin ring. The chalcone **1** has been screened for

antibacterial activity and shows activity at 100µg/mL and product **3** synthesized from **1** also shows same activity. The chalcone **2** shows antibacterial activity at 10µg/mL and product **4** obtained from **2** shows activity at 50µg/mL.

Experimental Section

General. Melting points were taken in open capillaries and are uncorrected. Purity of the

Table I — Characterization data of compounds **3a-h** and **4a-h**

Compd	Mol. formula	m.p. °C	Yield (%)
3a	$C_{27}H_{19}NO_4$	223	68
3b	$C_{28}H_{21}NO_4$	218	59
3c	$C_{28}H_{21}NO_4$	215	67
3d	$C_{28}H_{21}NO_4$	208	66
3e	$C_{26}H_{17}NO_3$	178	70
3f	$C_{27}H_{19}NO_3$	163	68
3g	$C_{27}H_{19}NO_3$	195	65
3h	$C_{27}H_{19}NO_3$	183	67
4a	$C_{27}H_{19}NO_4$	238	56
4b	$C_{28}H_{19}NO_4$	213	72
4c	$C_{28}H_{19}NO_4$	198	68
4d	$C_{28}H_{19}NO_4$	182	71
4e	$C_{26}H_{19}NO_3$	213	58
4f	$C_{27}H_{19}NO_3$	230	62
4g	$C_{27}H_{19}NO_3$	180	55
4h	$C_{27}H_{19}NO_3$	167	68

Table II — Antibacterial activity of compounds **3a-h** and **4a-h**

Compd	Antibacterial activity µg/mL		
	S. aureus	S. typhi	E. coli
3a	-	+	++
3b	+++	++	+++
3c	++++	++++	+++
3d	+++	++	++++
3e	-	+	+
3f	++	++	+++
3g	+++	++++	+++
3h	+++	+++	++
4a	++	-	+
4b	-	++	+++
4c	++++	+++	++++
4d	+++	+++	+++
4e	-	++	+
4f	++	+	+
4g	++++	++++	+++
4h	+++	+++	+
Ciprofloxacin	*	*	*

Note: 200 µg/ mL = +, 150 µg/ mL = ++, 100 µg/ mL = +++, 50 µg/ mL = ++++, - = Not active up to 200µg/ mL, * = 5 µg/ mL.

Spectral Data: 3a: ^1H NMR: 3.91 (s, 3H, OCH_3), 7.07(d, J=8.5Hz, 2H, $C_3'''\&C_5'''$-H), 7.3(d, J=8Hz, 1H, C_5'-H), 7.36(s, 1H, C_3-H), 7.55-7.65(m, 5H, C_6', C_7', C_3'', C_4'', & C_5''-H), 7.74(s, 1H, C_5-H), 7.83(d, J=8Hz, 2H, $C_2''\&C_6''$-H), 8.00(d, J=8.5Hz, 2H, $C_2'''\&C_6'''$-H), 8.17(d, J=8Hz, 1H, C_8'-H), 9.4(s, 1H, OH, D_2O exchangeable); ^{13}C NMR: 55.0 (OCH_3), 91.8 (C_3'), 113.7 (C_{4a}'), 114.5 ($C_3'''\&C_5'''$), 114.8 (C_4''), 115.9 (C_4), 117.8 (C_8'), 119.8 (C_5), 122.5 (C_5'), 122.8 (C_1'''), 125.0 (C_6'), 126.0 ($C_3''\&C_5''$), 128.6 ($C_2''\&C_6''$), 129.3 (C_3), 130.0 (C_1''), 130.7 ($C_2'''\&C_6'''$), 132.5 (C_7'), 146.8 (C_4'''), 152.9 (C_6, -C=N), 153.1 (C_{8a}'), 154.0(C_2, -C=N), 161.2(C_2', C_4', >C=O, >C-OH); Mass: M^+ 421(23) (m/z %) 390(12), 344(17), 287(25), 187(62), 77(100) etc.

4a: ^1H NMR: 3.89 (s, 3H, OCH_3), 7.07(d, J=8.5Hz, 2H, $C_3'''\&C_5'''$-H), 7.3(d, J=8Hz, 1H, C_5'-H), 7.36(s, 1H, C_3-H), 7.55-7.65(m, 5H, C_6', C_7', C_3'', C_4'', & C_5''-H), 7.70(s, 1H, C_5-H), 7.80(d, J=8Hz, 2H, $C_2''\&C_6''$-H), 7.98(d, J=8.5Hz, 2H, $C_2'''\&C_6'''$-H), 8.21(d, J=8Hz, 1H, C_8'-H), 9.6(s, 1H, OH, D_2O exchangeable); ^{13}C NMR: 54.99 (OCH_3), 92.3 (C_3'), 112.5 (C_{4a}'), 114.2 ($C_3'''\&C_5'''$), 114.8 (C_4''), 116.4 (C_4), 117.3 (C_8'), 119.2 (C_5), 122.0 (C_5'), 122.6 (C_1'''), 125.0 (C_6'), 126.0 ($C_3''\&C_5''$), 128.0 ($C_2''\&C_6''$), 128.8 (C_3), 130.0 (C_1''), 130.8 ($C_2'''\&C_6'''$), 132.5 (C_7'), 146.4 (C_4'''), 152.5 (C_6, -C=N), 153.2 (C_{8a}'), 154.8(C_2, -C=N), 161.2(C_2', C_4', >C=O, >C-OH); Mass: M^+ 421(31) (m/z %) 390(5.6), 305(4.8), 253(31), 235(25), 187(46), 1334(31), 105(61), 91(100), 77(67) etc.

compounds was checked on TLC. IR spectra (ν_{max} in cm^{-1}) were recorded on a Perkin-Elmer FTIR; NMR (^1H and ^{13}C) on Bruker AMX 500MHz using TMS as standard; and mass spectra on a Shimadzu GC-MS.

2, 4-Diaryl-6-[2′H-[1′]-4′-hydroxy-2′-oxo-benzo-pyran-3′-yl]pyridines 3a-h. General procedure.

A mixture of 4-hydroxy-2-oxo-3-(1′-oxo-3′-phenyl prop-2′-enyl)-2H-[1]-benzopyran **1** (0.002 mole), phenacyl pyridinium bromide (0.002 mole) and ammonium acetate (0.012 mole) was refluxed in acetic acid (15 mL) for 20 hr. The reaction was cooled and poured into crushed ice. The solid obtained was filtered, dried and recrystallised from chloroform to give **3a-h.**

2, 6-Diaryl-4-[2′H-[1′]-4′-hydroxy-2′-oxo-benzo-pyran-3′-yl]pyridines 4a-h. General Procedure. A mixture of 4-hydroxy-2-oxo-3-(3′-oxo-3′-phenyl prop-1′-enyl)-2H-[1]-benzopyran **2** (0.002 mole), phenacyl pyridinium bromide (0.002 mole) and ammonium acetate (0.012 mole) was refluxed in acetic acid (15 mL) for 20 hr. The reaction mixture was cooled and poured in to crushed ice. The solid obtained was filtered, dried and recrystallised from chloroform to give **4a-h.**

Acknowledgement

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