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 phenacetyl 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 3a-h and 2,6-diaryl-4-[2'H-[1']-4'-hydroxy-2'-oxo-benzopyran-3'-yl]pyridines 4a-h 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.

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Coumarin chemistry has become more important since many years because of the discovery of the varied biochemical properties1, industrial uses2 and analytical applications3 of these compounds. Coumarins are widely distributed in nature and are known to exhibit various physiological activities4,5. Coumarins have been found to be physiologically effective for animals as well as men6. Similarly, the chalcones and their derivatives have been reported to possess various biological activities such as antibacterial7-9, antifungal8, anti-inflammatory9,10, antitumor11, anticancer12,13, prostaglandin binding14. Chalcones are detrimental to the growth of tubercle bacilli15, acarus16, Schistosoma and Intestinal worms17. In addition, several substituted pyridines have been reported to possess biological activities such as antihypertensive, antiangi and antibacterial activities18, 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 blood19. 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 heterocycles20,21, 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 phenacetyl 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 ¹H NMR of 3a in CDCl₃ showed singlet at δ 3.91 for the three protons of the methyl group of -OCH₃ and the hydroxy proton was observed as a singlet at δ 9.40 which is D₂O exchangeable. The ¹³C NMR showed peak at δ 55.10 for the methyl group of -OCH₃ 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 procedure26. DMF was used as a blank and Cipro-
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
Spectral Data: 3a: ¹H NMR: 3.91 (s, 3H, OCH₃), 7.07 (d, J=8.5 Hz, 2H, C₅ ' & C₆ ' -H), 7.3 (d, J=8 Hz, 1H, C₅ ' -H), 7.55-7.65 (m, 5H, C₅ ', C₆ ' , C₇ ' , C₈ ' , & C₉ ' -H), 7.7 (s, 1H, C₈ ' -H), 7.83 (d, J=8.5 Hz, 2H, C₉ ' & C₆ ' -H). 8.0 (d, J=8 Hz, 2H, C₇ ' & C₆ ' -H), 8.17 (d, J=8 Hz, 1H, C₇ ' -H), 9.4 (s, 1H, OH, D₂O exchangeable); ¹³C NMR: 55.0 (OCH₃), 91.8 (C₅ ' ), 113.7 (C₆ ' ), 114.5 (C₇ ' & C₈ ' ), 114.8 (C₉ ' ), 115.9 (C₈ ' ), 117.8 (C₆ ' ), 119.8 (C₅ ' ), 122.5 (C₇ ' ), 122.8 (C₈ ' ), 125.0 (C₉ ' ), 126.0 (C₇ ' & C₈ ' ), 128.6 (C₆ ' & C₇ ' ), 129.3 (C₅ ' ), 130.0 (C₆ ' ), 130.7 (C₇ ' & C₈ ' ), 132.5 (C₉ ' ), 146.8 (C₅ ' ), 152.9 (C₈ ' - C₉ ' - C₅ ' - C₆ ' = C=N), 153.1 (C₆ ' ), 154.0 (C₅ ' - C=N), 161.2 (C₇ ' , C₈ ' , > C=O, > C=OH), Mass: M⁺ 421 (31) (m/z %) 390 (12), 344 (17), 287 (25), 187 (62), 156 (100) etc.

4a: ¹H NMR: 3.89 (s, 3H, OCH₃), 7.07 (d, J=8.5 Hz, 2H, C₅ ' & C₆ ' -H), 7.3 (d, J=8 Hz, 1H, C₅ ' -H), 7.55-7.65 (m, 5H, C₅ ', C₆ ', C₇ ', C₈ ', & C₉ ' -H), 7.7 (s, 1H, C₈ ' -H), 7.83 (d, J=8.5 Hz, 2H, C₉ ' & C₆ ' -H). 8.0 (d, J=8 Hz, 2H, C₇ ' & C₆ ' -H), 8.17 (d, J=8 Hz, 1H, C₇ ' -H), 9.4 (s, 1H, OH, D₂O exchangeable); ¹³C NMR: 54.99 (OCH₃), 92.3 (C₅ ' ), 112.5 (C₆ ' ), 114.2 (C₇ ' & C₈ ' ), 114.8 (C₉ ' ), 116.4 (C₈ ' ), 117.3 (C₇ ' ), 119.2 (C₆ ' ), 122.0 (C₅ ' ), 122.6 (C₇ ' ), 125.0 (C₈ ' ), 126.0 (C₇ ' & C₈ ' ), 128.0 (C₆ ' & C₇ ' ), 128.8 (C₅ ' ), 130.0 (C₆ ' ), 130.8 (C₇ ' & C₈ ' ), 132.5 (C₉ ' ), 146.4 (C₅ ' ), 152.5 (C₈ ' - C₉ ' - C₅ ' - C₆ ' = C=N), 153.2 (C₆ ' ), 154.8 (C₅ ' - C=N), 161.2 (C₇ ' , C₈ ' , > C=O, > C=OH), Mass: M⁺ 421 (31) (m/z %) 390 (5.6), 305 (4.8), 253 (31), 235 (25), 187 (46), 133 (31), 185 (61), 91 (100), 77 (67) etc.

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

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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-Diary-4-[2'H-[1']-4'-hydroxy-2'-oxo-benzopyran-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 mixture was cooled and poured into crushed ice. The solid obtained was filtered, dried and recrystallised from chloroform to give 4a-h.

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References


