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Note

Synthesis and antimicrobial screening of *4H*-2-benzoyl-3-hydroxy-3-methyl-2-phenyl 2,3-dihydro-furo[3,2-*c*]benzopyran-4-one and *4H*-3-methyl-2-phenyl furo[3,2-*c*]benzopyran-4-one

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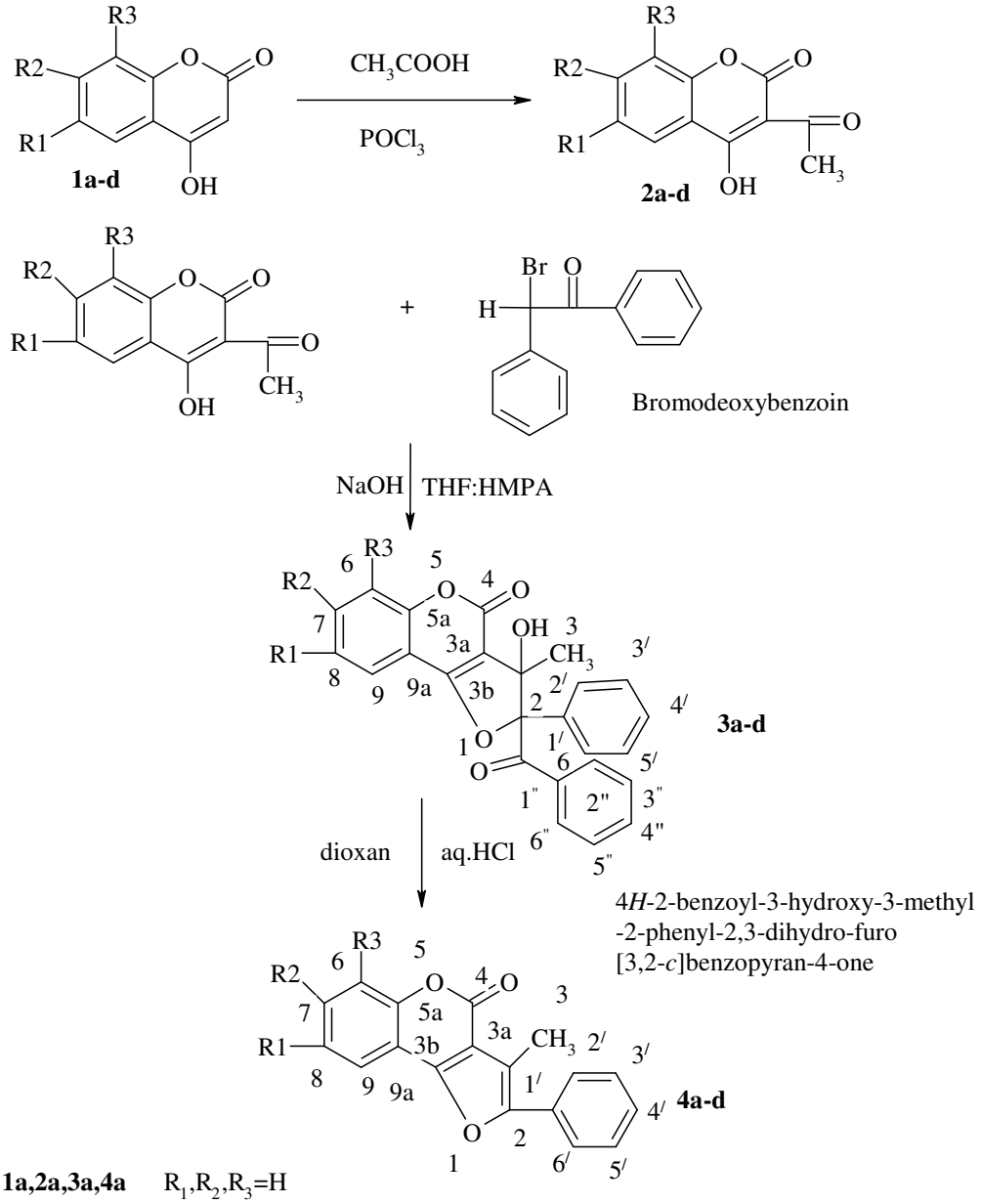
3-Acetyl-4-hydroxy-*2H*[1]benzopyran-2-one **2a-d** has been treated with bromodeoxybenzoin in NaOH, THF:HMPA to give *4H*-2-benzoyl-3-hydroxy-3-methyl-2-phenyl 2,3-dihydro-furo[3,2-*c*] benzopyran-4-one **3a-d**. This on treatment with aqueous HCl in presence of dioxane gives *4H*-3-methyl-2-phenyl furo[3,2-*c*] benzopyran-4-one **4a-d** through acid catalysed 1,2-elimination. All compounds have been screened for antimicrobial activity. They do not show significant activity.

Keywords: Bromodeoxybenzoin, dioxane, furobenzopyran, herbicidal, antimicrobial activity

4-Hydroxycoumarin derivatives are of interest because of their anticoagulant[1-7], spasmolytic[8-10], rodenticidal[11-14] and estrongenic[15] activity. Some coumarin derivatives are known for their antifungal, antiinflammatory[16-18] and anti-HIV activity[19-21]. They are used as photosensitive drugs[22], potent and selective human dopamine D_4 antagonists[23] and antibiotic agent[24]. Furobenzopyran is found in a variety of natural products exhibiting various types of herbicidal[25] activity. They have excellent herbicidal activity on weeds and are completely selective to food crops such as paddy rice and soyabeans as well as cotton. Furan derivatives constitute their own class of important drug and drug intermediates. It was therefore thought of synthesizing furan ring at fourth position of benzopyran moiety which possess some of the above mentioned biological activities.

3-Acetyl-4-hydroxy *2H* [1] benzopyran-2-one[26] was treated with bromodeoxy- benzoin[27] using NaOH, THF:HMPA to give *4H*-2-benzoyl-3-hydroxy-3-methyl-2-phenyl 2,3-dihydro-furo[3,2-*c*]benzopyran-4-one **3a-d** in good yields[27] **(Scheme I)**. The IR spectra of **3b** showed peak at 3404 cm^{-1} for –OH stretching, 2924 cm^{-1} for CH stretching, 1700 cm^{-1} for carbonyl group of coumarin, 1694 cm^{-1} for C=O stretching. The ^{1}H NMR of **3b** in DMSO-d_6 showed singlet at δ 1.22 for three protons of methyl group at C_3, singlet at δ 2.25 for three protons of methyl group at C_8, doublet at δ 7.75 (J = 7.5Hz) for a proton at C_6, another doublet was observed at δ 8.0 (J = 7.5Hz) for a proton at C_7. The singlet at δ 8.25 was assigned to the proton at C_9. The hydroxyl proton appeared as a singlet at δ 5.25 which was D_2O exchangeable. The multiplets between δ 7.0-8.25 accounted for rest of the ten protons. The ^{13}C NMR spectra displayed signals at δ 17 for methyl carbon of C_3, δ 21 for methyl carbon of C_8, signal appeared at δ 95 for C_3, signal appeared at δ 101 for C_{3a}, signal appeared at δ 116 for C_{9a} and 120-140 for aromatic carbons, fused carbons at δ 152 for C_{5a}. Signal appeared at δ 154 for C_2, δ 167 for carbonyl carbon, signal appeared at δ 168 for C_{3b}, δ 179 for carbonyl carbon attached to phenyl ring. The mass spectra gave molecular ion peak *m/z* (M^+) at 412 (20%), 405, 393, 375, 281, 245, 203,134, 91, 77 (100%), 65 along with other peaks.

4H-2-benzoyl-3-hydroxy-3-methyl-2-phenyl-2, 3-dihydro-furo[3,2-*c*] benzopyran 4-one **3a-d** on treatment with aqueous HCl in dioxane gave *4H*-3-methyl-2-phenyl furo[3,2-*c*] benzopyran-4-one **4a-d** **(Table I)** through unusal acid catalysed 1,2-elimination[28] **(Scheme I**, **Scheme II)**. The IR spectra of **4b** did not show peak at 3404 cm^{-1} for -OH stretching. The IR spectra of **4b** showed peak at 2924 cm^{-1} for CH stretching and 1700 cm^{-1} for carbonyl group stretching. The ^{1}H NMR of **4b** in DMSO-d_6 showed singlet at δ 2.0 for three protons at C_3, singlet at δ 2.25 for three protons of methyl group at C_8, doublet at δ 7.76 (J = 7.5Hz) for a proton at C_6, another doublet at δ 8.1 (J = 7.5Hz) for a proton at C_7, singlet at δ 8.27 for proton at C_9 while rest of the five protons appeared as multiplets between δ 7.1-8.26. The ^{13}C NMR spectra displayed signals at δ 22 for methyl group at C_3, δ 21 for methyl carbon at C_8, δ 117 for C_{9a}, signal appeared at δ 119 for C_{3a}, δ 120-140 for aromatic carbons, fused carbons at δ 153 for C_{5a}, signal appeared at δ 154 for C_2, signal appeared at δ 159 for C_{3b}, δ 167 for carbonyl carbon. The mass spectra gave molecular ion peak *m/z* (M^+) at 290

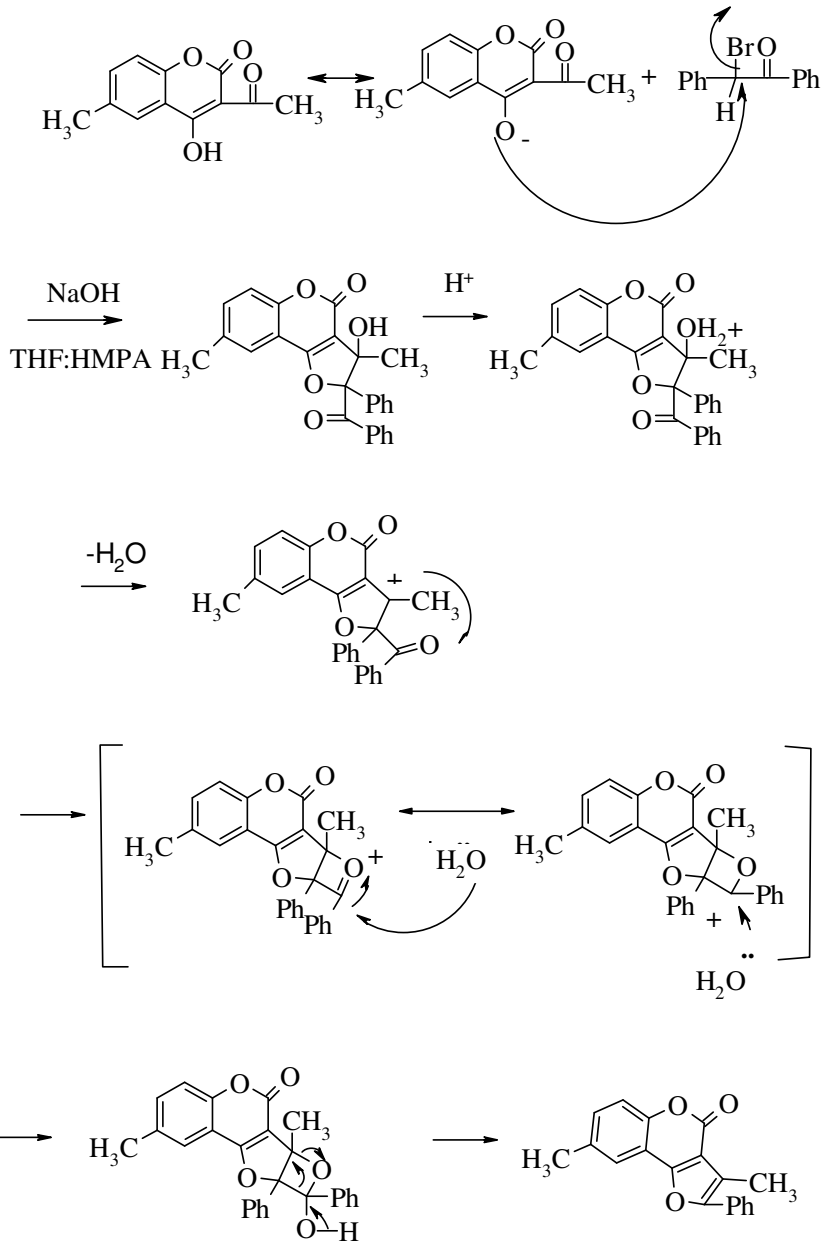


Scheme I

(45%), 279, 244, 228, 194, 133 (100%), 105, 104, 93, 78, 76 along with other peaks.

Antimicrobial activity

The above compounds **3a-d** and **4a-d** were screened for their antibacterial activity against *S. aureus*, *S. typhi* and *E. coli* and antifungal activity against *A. niger* and *C. albicans*. The minimum inhibitory concentration (MIC) was determined using tube dilution method according to the standard procedure[29]. DMSO was used as a blank and Ciprofloxacin (MIC: 5µg/mL) and Miconazole (MIC: 5 µg/mL) were used as antibacterial and antifungal standards respectively. An examination of the data



Scheme II

shows all the compounds had antibacterial activity ranging from 50 to 200 μg/mL **(Table II)**.

Experimental Section

Melting points were recorded in open capillaries and are uncorrected. Homogenity of the compounds was checked on TLC. IR spectra (ν_{max} in cm^{-1}) were recorded on a Perkin-Elmer FT-IR instrument and ^{1}H and ^{13}C NMR on Jeol 300 MHz instrument using TMS as standard and mass spectra were recorded on a Shimadzu QP-2010 GC-MS. Biological testing were carried out at Padmaja Aerobiologicals (P) Ltd.

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

Compd	Mol. formula	m.p. °C	Yield (%)	Found (%) Calcd C	H	O
3a	$C_{25}H_{18}O_5$	142	50	75.35 (75.37	4.51 4.52	20.09 20.10)
3b	$C_{26}H_{20}O_5$	145	60	75.71 (75.72	4.84 4.85	19.40 19.41)
3c	$C_{26}H_{20}O_5$	110	50	75.70 (75.72	4.83 4.85	19.39 19.41)
3d	$C_{26}H_{20}O_5$	120	50	75.69 (75.72	4.82 4.85	19.38 19.41)
4a (Ref.30)	$C_{18}H_{12}O_3$	150	60	78.25. (78.26	4.33 4.34	17.38 17.39)
4b	$C_{19}H_{14}O_3$	122	65	78.61 (78.62	4.81 4.82	16.54 16.55)
4c	$C_{19}H_{14}O_3$	100	65	78.60 (78.62	4.80 4.82	16.53 16.55)
4d	$C_{19}H_{14}O_3$	117	60	78.59 (78.62	4.79 4.82	16.52 16.55)

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

Compd	Antibacterial activity µg/mL			Antifungal activity µg/mL	
	E. coli	*S. typhi*	*S. aureus*	*A. niger*	*C. albicans*
3a	160	200	80	50	60
3b	130	140	85	55	65
3c	150	150	90	80	90
3d	140	160	100	50	65
4a	160	200	110	90	100
4b	130	140	100	105	100
4c	150	150	115	95	100
4d	140	160	125	110	95
Ciprofloxacin(Std.)	5	5	5	-	-
Miconazole(Std.)	-	-	-	5	5

General procedure for the preparation of 4*H*-2-benzoyl-3-hydroxy-3-methyl-2-phenyl-2, 3-dihydro-furo[3,2-*c*]benzopyran-4-one, 3a-d

3-Acetyl-2*H*-[1]-4-hydroxy-2-oxo-benzopyran **2a-d** (0.122 g,1 mmol) was added to a stirred solution of NaOH (0.044 g, 1.1 mmol) and THF:HMPA(1:1, 4 mL) and the mixture was allowed to reflux for 30 min. To this, bromodeoxybenzoin (0.336 g, 1.1 mmole) in dry THF (2 mL) was added dropwise and the solution was refluxed for further 8 hr. On completion of the reaction, monitored by TLC, it was cooled and quenched with water. The reaction mixture was extracted with ether (3×50 mL) and washed with 5% KOH (3×10 mL), water (2×5mL) and dried over anhydrous Na_2SO_4. Excess of solvent was removed on a rotary evaporator. The residual oil was then triturated with ethyl acetate and cooled to give a crystalline solid. It was filtered, dried and purified by recrystallization from hexane to give pure **3a-d**.

General procedure for the preparation of 4*H*-3-methyl-2-phenyl-furo[3,2-*c*] benzopyran-4-one, 4a-d

To a solution of 4*H*-2-benzoyl-3-hydroxy-3-methyl-2-phenyl-furo[3,2-*c*]benzopyran-4-one, **3a-d** dissolved in dioxane (5 mL), aq. HCl (10%, 5 mL) was added and the mixture was refluxed for 10 hr.

The reaction mixture was quenched with water, extracted with ether, washed with water, dried over anhydrous Na_2SO_4 and after removal of the excess solvent on a rotary evaporator, the residue was purified by recrystallization from hexane to give pure **4a-d**.

3a: IR(KBr): 3403 (-OH), 2923,1710 (>C=O), 1694, 1404, 873 cm $^{-1}$; ^{1}H NMR (DMSO-d_6): δ 1.21 (s, 3H, C_3-CH_3), 5.24 (s, 1H,-OH, D_2O exchangeable), 7.1-8.25 (m, 14H, Ar-H).

3b: IR(KBr): 3404 (-OH), 2924,1700(>C=O), 1693, 1400, 870 cm $^{-1}$; ^{1}H NMR(DMSO-d_6): δ 1.22 (s, 3H, C_3-CH_3), 2.25 (s, 3H, C_8-CH_3), 5.25 (s, 1H,-OH, D_2O exchangeable), 7.75 (d,1H,C_6-H, *J*=7.5Hz), 8.0 (d,1H,C_7-H,*J*=7.5Hz), 8.25 (s, 1H, C_9-H), 7.0-8.25 (m, 10H, Ar-H); ^{13}C NMR(DMSO-d_6): δ 17 (C_3-CH_3), 21 (C_8-CH_3), 95 (C_3), 101 (C_{3a}), 116 (C_{9a}), 120-140 (aromatic carbons), 152 (C_{5a}), 154 (C_2), 167 (>C=O), 168 (C_{3b}), 179 (O=C-C_6H_6); MS: *m/z* (%) M^+ 412 (20), 405, 393, 375, 281, 245, 203,134, 91, 77 (100), 65.

3c: IR(KBr): 3402 (-OH), 2920,1720 (>C=O), 1690, 1401, 871 cm^{-1}; ^{1}H NMR(DMSO-d_6): δ 1.20 (s, 3H, C_3-CH_3), 2.24 (s, 3H, C_7-CH_3), 5.27 (s, 1H,-OH, D_2O exchangeable), 7.74 (d, 1H, C_8-H, *J*=7.5Hz), 8.0(d, 1H, C_9-H, *J*=7.5Hz), 8.25 (s, 1H, C_6-H), 7.1-8.24 (m, 10H, Ar-H).

3d: IR(KBr): 3409 (OH), 2937,1730 (C=O), 1690, 1457, 869 cm $^{-1}$; ^{1}H NMR(DMSO-d_6): δ 1.25 (s, 3H, C_3-CH_3), 2.28 (s, 3H, C_8-CH_3), 5.26 (s, 1H,-OH, D_2O exchangeable), 7.78 (d, 1H, C_7-H, *J*=7. 5), 8.3 (t, 1H, C_8-H), 8.26 (d, 1H, C_9-H), 7.0-8.30 (m, 10H, Ar-H).

4a: IR(KBr): 1702 (>C=O), 2925, 1403, 870 cm^{-1}; ^{1}HNMR(DMSO-d_6): δ 2.1 (s, 3H, C_3-CH_3), 7.1-7.90 (m, 9H, Ar-H).

4b: IR(KBr): 1700 (>C=O), 2924, 1401, 871 cm^{-1}; ^{1}H NMR(DMSO-d_6): δ 2.0 (s, 3H, C_3-CH_3), 2.25 (s, 3H, C_8-CH_3), 7.76 (d,1H,C_6-H, *J*=7.5Hz), 8.1 (d, 1H, C_7-H, *J*=7.5Hz), 8.27 (s, 1H, C_9-H), 7.1-8.26 (m,5H, Ar-H); ^{13}C NMR(DMSO-d_6): δ 22 (C_3- CH_3), 21 (C_8-CH_3), 117 (C_{9a}), 119 (C_{3a}), 120-140 (aromatic carbons), 153 (C_{5a}), 154 (C_2), 159 (C_{3b}), 167 (>C=O); MS: *m/z* (%) M^+ 290 (45), 279, 244, 228, 194, 133 (100), 105, 104, 93, 78, 76.

4c: IR(KBr): 1705 (>C=O), 2926, 1406, 875 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.2 (s, 3H, C_3-CH_3), 2.26 (s, 3H, C_7-CH_3), 7.78 (d, 1H, C_8-H, *J*=7.5Hz), 8.1(d, 1H, C_9-H, *J*=7.5Hz), 8.26 (s, 1H, C_6-H), 7.0-8.25 (m,5H, Ar-H).

4d: IR(KBr): 1708 (>C=O), 2924, 1408, 879 cm^{-1}; ^{1}H NMR(DMSO-d_6): δ 2.1 (s, 3H, C_3-CH_3), 2.29 (s, 3H, C_8-CH_3), 7.77 (d, 1H, C_7-H, *J*=7.5 Hz), 8.2 (t,1H, C_8-H), 8.25 (d,1H, C_9-H, *J*=7.5 Hz), 7.2-8.25 (m,5H, Ar-H).

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