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Synthesis and Antimicrobial Activity of Some Chalcones of 3-Acetyl Coumarin and 2-Hydroxy-1-acetonapthone

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Five chalcones were prepared by refluxing 3-acetyl coumarin with aldehydes in the presence of piperidine in ethanol and another five chalcones were synthesised by condensing 2-hydroxy-1-acetonaphthone with aldehyde derivatives in dilute ethanolic potassium hydroxide solution at room temperature according to Claisen-Schmidt condensation. All these compounds were characterised by means of their IR, ^{1}H NMR spectroscopic data and microanalyses. The antimicrobial activity of these compounds was evaluated by the cup plate method.

Key Words: Chalcones, Synthesis, Antimicrobial activity.

INTRODUCTION

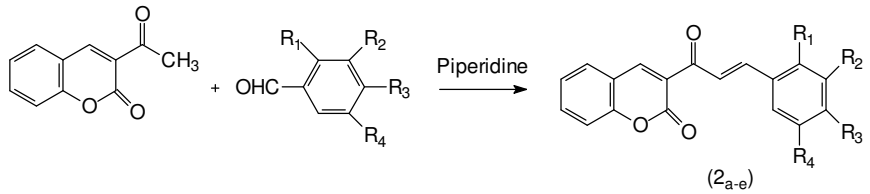
The compounds with the backbone of chalcones have been reported to exhibit a wide variety of pharmacological effects, including antioncogenic[1], antiinflammatory[2], antiulcerative[3], analgesic[4], antiviral[5], antimalarial[6] and antibacterial activities[7]. The presence of a reactive α,β-unsaturated keto function in chalcones is found to be responsible for their antimicrobial activity, which may be altered depending on the type and position of substituent on the aromatic rings. In the present communication we report the reaction of 2-hydroxy-1-acetonaphthone as well as 3-acetyl coumarin with different aromatic aldehydes to form chalcones ($\mathbf{2}_{a\text{-}e}$ and $\mathbf{3}_{a\text{-}e}$). The structures of the various synthesized compounds were assigned on the basis of elemental analysis, IR and ^{1}H NMR spectral data. The synthesized compounds were also screened for their antimicrobial activity.

EXPERIMENTAL

Melting points were determined on a capillary melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded in the indicated solvent on Bruker WM 400 MHz spectrometer with TMS as internal standard. Infrared spectra were recorded in KBr on Perkin-Elmer AC-1 spectrophotometer. Microanalyses were performed on Carlo Erba

EA-1108 element analyzer and were within the ± 0.4 % of the theoretical values. Column chromatography was performed on silica gel (Merck, 60-120 mesh).

General procedure for the preparation of 3-[1-oxo-3-(substituted phenyl)-2-propenyl]-2H-1-benzopyran-2-ones (2_{a-e}): To a mixture of 3-acetyl coumarin (0.011 mol) in ethanol (25 mL), piperidine (0.3 mL) in ethanol (5 mL) was added drop wise. The mixture was heated and refluxed for 1-7 h. After cooling, the product was separated and washed with ethanol (20 mL). The product was purified by column chromatography (**Scheme-I**).



2_a : R_2= H, R_1=R_3=R_4=OCH_3
2_b : R_1=R_4=H, R_2=R_2=OCH_3
2_c : R_1=R_3=R_4=H, R_2=NO_2
2_d : R_1=R_4=H, R_2=OCH_3, R_3=OH
2_e : R_1=R_3=R_4=H, R_2=Br

Scheme-I

3-[1-Oxo-3(2,4,5-trimethoxyphenyl)-2-propenyl]-2H-1-benzopyran-2-one (2_a): Yield 80 %; m.p. 192-194°C; IR (KBr, ν_{max}, cm^{-1}) 1720 (CO), 1640 (CH=CH), 1235 (C-O-C), 1184 (OCH_3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (1H, s, C_4-H), 8.21 (1H, d, =CH-Ar), 7.81 (1H, d, -CO-CH=), 7.32-7.66 (4H, m, Ar-H), 7.17 (1H, s, Ar-H), 6.49 (1H, s, Ar-H), 3.87-3.96 (9H, s, 3x OCH_3). Anal. Calcd for $C_{21}H_{18}O_6$: C, 68.91; H, 4.95. Found: C, 68.56; H, 4.76.

3-[1-Oxo-3(3,4-dimethoxyphenyl)-2-propenyl]-2H-1-benzopyran-2-one (2_b): Yield 79 %; m.p. 204-206°C; IR (KBr, ν_{max}, cm^{-1}) 1718 (CO), 1638 (CH=CH), 1245 (C-O-C); 1180 (OCH_3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (1H, d, =CH-Ar), 8.66 (1H, s, C_4-H), 7.86 (1H, d, -CO-CH=), 7.35-8.06 (7H, m, Ar-H), 3.85-3.95 (6H, s, 3x OCH_3). Anal. Calcd for $C_{20}H_{16}O_5$: C, 71.42; H, 4.79. Found: C, 71.76; H, 4.53.

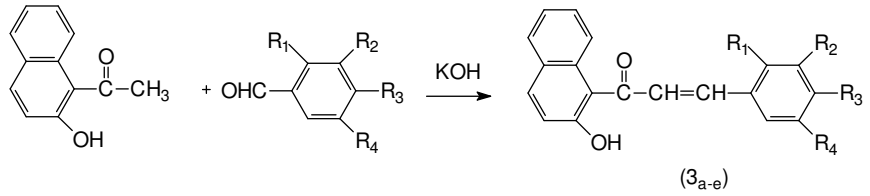
3-[1-Oxo-3(3-nitrophenyl)-2-propenyl]-2H-1-benzopyran-2-one (2_c): Yield 88 %; m.p. 206-208°C; IR (KBr, ν_{max}, cm^{-1}) 1725 (CO), 1644 (CH=CH), 1340 (C-N), 1238 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (1H, s, C_4-H), 7.88 (IH, d, =CH-Ar), 7.81 (1H, d, -CO-CH=), 7.42-7.77, 8.21-8.32 (8H, m, Ar-H). Anal. Calcd for $C_{18}H_{11}NO_5$: C, 67.35; H, 3.45; N, 4.36. Found: C, 67.08; H, 3.28; N, 4.28.

3-[1-Oxo-3(4-hydroxy-3-methoxyphenyl)-2-propenyl]-2H-1-benzopyran-2-one (2_d): Yield 75 %; m.p. 212-214°C; IR (KBr, ν_{max}, cm^{-1}) 3080

(OH), 1720 (CO), 1641 (CH=CH), 1250 (C-O-C), 1185 (OCH_3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (1H, s, C_4-H), 7.82 (1H, d, =CH-Ar), 7.78 (1H, d, -CO-CH=), 6.95-7.67 (7H, m, Ar-H), 5.97 (1H, s, -OH), 3.95 (3H, s, -OCH_3). Anal. Calcd for $C_{19}H_{14}O_5$: C, 70.80; H, 4.37. Found: C, 70.95; H, 4.18.

3-[1-Oxo-3(3-bromophenyl)-2-propenyl]-2H-1-benzopyran-2-one (2_e): Yield 81 %; m.p. 196-198°C; IR (KBr, ν_{max}, cm^{-1}) 1721 (CO), 1642 (CH=CH), 1260 (C-O-C), 850 (C-Br); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (1H, s, C_4-H), 7.94 (1H, d, =CH-Ar), 7.77 (1H, d, -CO-CH=), 7.26-7.73 (8H, m, Ar-H). Anal. Calcd for $C_{18}H_{11}O_3Br$: C, 60.90; H, 3.12; Br, 22.50. Found: C, 60.59; H, 3.35; Br, 22.46.

General procedure for the preparation of 1-(2'-hydroxy naphthyl)-3-phenyl-2-propene-1-ones (3_{a-e}): A mixture of 2-hydroxy-1-aceto naphthone (0.01 mol) and aryl aldehyde (0.01 mol) was stirred in ethanol (30 mL) and then an aqueous solution of KOH (40 %, 15 mL) added to it. The mixture was kept overnight at room temperature and then poured into crushed ice and acidified with HCl. The solid separated was filtered and recrystallized from ethanol (**Scheme-II**).



(3_{a-e})

3_a : R_1=R_2=R_4=H, R_3=$N(CH_3)_2$
3_b : R_2=R_3=R_4=H, R_1=Cl
3_c : R_2=H, R_1=R_3=R_4=OCH_3
3_d : R_1=R_2=R_4=H, R_3=NO_2
3_e : R_1=R_2=R_4=H, R_3=CH_3

Scheme-II

1-(2′-Hydroxynaphthalene-1′-yl)-3-(4-dimethylaminophenyl)-2-propen-1-one (3_a): Yield 80 %; m.p. 130-132°C; IR (KBr, ν_{max}, cm^{-1}) 3115 (OH), 1725 (CO), 1643 (CH=CH), 1355 (C-N); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.48 (1H, d, *J* = 9Hz, C-8′-H), 7.93 (1H, d, *J* = 16Hz, C-7-H), 7.76 (1H, d, *J* = 16 Hz, C-8-H), 7.62-7.76 (3H, m, C-4′,5′ and 6′-H), 7.43 (1H, m, *J* = 11 Hz, C-7′-H), 7.39 (2H, d, *J* = 13 Hz, C-2 and 6-H), 7.15 (1H, d, *J* = 9 Hz, C-3′-H), 6.78 (2H, d, *J* = 13 Hz, C-3 and 5-H), 2.99 (6H, s, C-4-$N(CH_2)_1$). Anal. Calcd for $C_{21}H_{19}NO_2$: C, 79.47; H, 6.03. Found: C, 79.28; H, 5.88.

1-(2′-Hydroxynaphthalene-1′-yl)-3-(2-chlorophenyl)-2-propen-1-one (3_b): Yield 91 %; m.p. 134-136°C; IR (KBr, ν_{max}, cm^{-1}) 3100 (OH),

1722 (CO), 1645 (CH=CH), 855 (C-Cl); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.44 (1H, d, *J* = 9Hz, C-8′-H), 7.95 (1H, d, *J* = 16Hz, C-7-H), 7.75 (1H, d, *J* = 16 Hz, C-8-H), 7.60-7.70 (2H, m, C-4′ and 5′-H), 7.55-7.65 (2H, d, C-3 and C-5), 7.39-7.56 (4H, m, C-2 and C-6, C-6′ and 7′-H), 7.20 (1H, d, *J* = 9 Hz, C-3′-H). Anal. Calcd. for $C_{20}H_{16}O_3Cl$: C, 79.47; H, 6.03. Found: C, 78.67; H, 5.61.

1-(2′-Hydroxynaphthalene-1′-yl)-3-(2,4,5-trimethoxyphenyl)-2-propen-1-one (3_c): Yield 88 %; m.p. 208-210°C; IR (KBr, ν_{max}, cm^{-1}) 3106 (OH), 1765 (CO), 1642 (CH=CH), 1192 (OCH_3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.45 (1H, d, *J* = 9Hz, C-8′-H), 7.96 (1H, d, *J* = 16Hz, C-7-H), 7.77 (1H, d, *J* = 16 Hz, C-8-H), 7.60-7.70 (2H, m, C-4′ and 5′-H), 7.42-7.49 (2H, m, C-6′ and 7′-H), 7.20 (1H, d, *J* = 9 Hz, C-3′-H), 6.75 (2H, s, C-2 and 6-H), 3.91 (6H, s, 2 × OCH_3), 3.88 (3H, s, -OCH_3). Anal. Calcd. for $C_{22}H_{20}O_5$: C, 72.51; H, 5.53. Found: C, 72.30; H, 5.72.

1-(2′-Hydroxynaphthalene-1′-yl)-3-(4-nitrophenyl)-2-propen-1-one (3_d): Yield 90 %; m.p. 130-132°C; IR (KBr, ν_{max}, cm^{-1}) 3100 (OH), 1721 (CO), 1640 (CH=CH), 1345 (C-N); ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.5 (1H, s, C-2′-OH), 9.47 (1H, d, *J* = 9Hz, C-8′-H), 7.98 (1H, d, *J* = 16Hz, C-7-H), 7.77 (1H, d, *J* = 16 Hz, C-8-H), 7.71 (2H, s, C-2 and 4-H), 7.62-7.68 (2H, m, C-4′ and 5′-H), 7.28-7.55 (4H, m, C-5,6 and 6′, 7′-H), 7.17 (1H, d, *J* = 9 Hz, C-3′-H). Anal. Calcd. for $C_{19}H_{13}NO_4$: C, 71.46; H, 4.10. Found: C, 71.83; H, 4.05.

1-(2′-Hydroxynaphthalene-1′-yl)-3-(4-methylphenyl)-2-propen-1-one (3_e): Yield 85 %; m.p. 180-182°C; IR (KBr, ν_{max}, cm^{-1}) 3060 (OH), 1722 (CO), 1642 (CH=CH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (1H, d, *J* = 9Hz, C-8′-H), 7.92 (1H, d, *J* = 16Hz, C-7-H), 7.77 (1H, d, *J* = 16 Hz, C-8-H), 7.55 (2H, d, C-2 and 6-H), 7.51 (1H, brt, C-6′-H) 7.39 (1H, brt, 7′-H), 7.34 (2H, d, *J* = 14 Hz, C-3 and 5-H), 2.41 (3H, s, -CH_3). Anal. Calcd. for $C_{20}H_{16}O_2$: C, 83.30; H, 5.59. Found: C, 83.16; H, 5.38.

Antimicrobial activity:

Cup plate method[8,9] using Mueller-Hinton agar medium was employed to study the preliminary antibacterial activity of $\mathbf{2}_{a-e}$ and $\mathbf{3}_{a-e}$ against *B. pumilis*, *B. subtilis* and *E. coli*. The agar medium was purchased from HI media Laboratories Ltd., Mumbai, India. Preparation of nutrient broth, subsculture, base layer medium, agar medium and peptone water was done as per the standard procedure. Each test compound (5 mg) was dissolved in 5 mL of dimethyl sulfoxide (1000 µg/mL). Volumes of 0.05 and 0.1 mL of each compound were used for testing.

Same cup plate method using PDA medium was employed to study the preliminary antifungal activity of $\mathbf{2}_{a-e}$ and $\mathbf{3}_{a-e}$ against *A.niger* and *R.oriza*. The PDA medium was purchased from HI media Laboratories Ltd.,

Mumbai, India. Preparation of nutrient broth, subculture, base layer medium and PDA medium was done as per the standard procedure. Each test compound (5 mg) was dissolved in 5 mL of DMSO (1000 μg/mL). Volumes of 0.05 and 0.1 mL of each compound were used for testing.

The cups each of 9 mm diameter were made by scooping out medium with a sterilized cork borer in a petri dish which was streaked with the organisms. The solutions of each test compound (0.05 and 0.1 mL) were added separately in the cups and petri dishes were subsequently incubated. Chloramphenicol and fluconazole were used as standard reference drugs (200 and 1000 μg/mL respectively) and DMSO as a control which did not reveal any inhibition. Zone of inhibition produced by each compound was measured in mm and the results are presented in Table-1.

TABLE-1
ZONE OF INHIBITION OF COMPOUNDS [$\mathbf{2}_{a-e}$ AND $\mathbf{3}_{a-e}$]

Compd. no.	(in mL)									
	BP		BS		EC		AN		RO	
	0.05	0.10	0.05	0.10	0.05	0.10	0.05	0.10	0.05	0.10
2_a	12	15	12	13	11	12	14	18	13	16
2_b	10	13	9	11	10	11	11	14	9	12
2_c	10	12	7	10	8	9	8	12	8	13
2_d	11	14	10	14	11	13	13	16	11	14
2_e	9	12	8	10	7	10	10	14	9	12
3_a	10	11	9	11	10	11	10	11	11	12
3_b	8	10	9	11	8	10	8	13	8	11
3_c	10	12	10	11	9	10	12	13	9	11
3_d	8	9	8	9	8	10	9	13	10	12
3_e	10	12	8	9	9	10	10	11	8	9
Chloram-phenicol	-	-	16	18	14	16				
Fluconazole							20	24	-	-

BP = *B. pumilis*, BS = *B. subtilis*, EC = *E. coli*, AN = *A. niger*, RO = *R. oriza*
(-)Indicates no zone of inhibition

RESULTS AND DISCUSSION

The screening results revealed that the compounds $\mathbf{2}_{a-e}$ and $\mathbf{3}_{a-e}$ showed significant antimicrobial activity. In particular compounds $\mathbf{2}_a$, $\mathbf{2}_d$, $\mathbf{2}_b$, $\mathbf{3}_c$ and $\mathbf{3}_a$ showed moderate to considerable antibacterial and antifungal activities against all the organisms employed at a conc. of 1000 μg/mL (0.1 mL dose level) and are comparable to that of standard drugs chloramphenicol and fluconazole, respectively.

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