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

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Abstract: Five novel 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 and another five novel chalcones were prepared by refluxing 3-acetyl coumarin with aldehydes in the presence of piperidine in ethanol. All these compounds were characterised by means of their IR, ^{1}H NMR spectroscopic data and microanalyses. The antimicrobial activity of these compounds were evaluated by the cup plate method.

Keywords: Chalcones, synthesis, antimicrobial activity

Introduction

Chalcones either natural or synthetic are known to exhibit various biological activities. They have been reported to possess antioxidant,[1-4] antimalarial,[5] antileishmanial,[6] antiinflammatory,[7] antitumor[8] and antibacterial activity[9].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 and heterocyclic

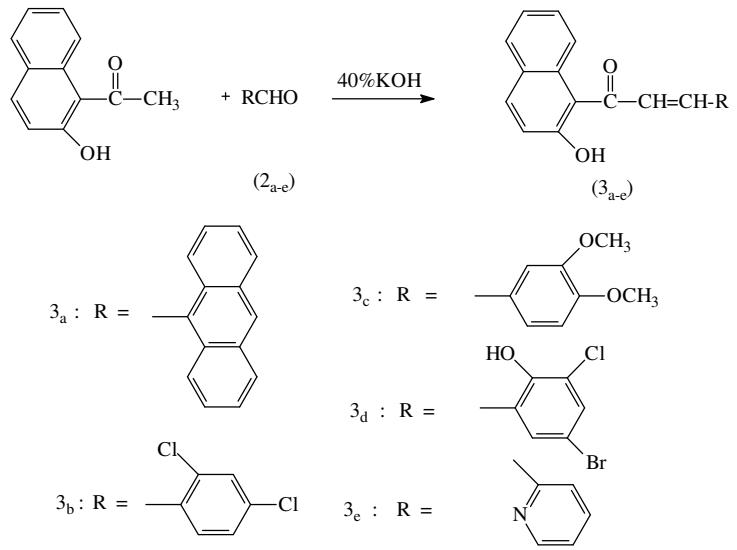
aldehydes (**2_{a-j}**) to form Chalcones (**3_{a-j}**). The structures of the various synthesized compounds were assigned on the basis of elemental analysis, IR and ^{1}H NMR spectral data. These compounds were also screened for their antimicrobial activity.

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 ± 0.5% of the theoretical values. Column chromatography was performed on silica gel (Merck, 60-120 mesh).

*General procedure for the preparation of 1-(2'-hydroxy naphthyl)-3-(phenyl/anthryl/pyridyl)-2-propene-1-ones (**3_{a-e}**):*

A mixture of 2-hydroxy-1-aceto naphthone (0.01mol) and aryl aldehyde (0.01 mol) was stirred in ethanol (30ml) and then an aqueous solution of KOH (40%, 15ml) added to it. The mixture was kept overnight at room temperature and then it was poured into crushed ice and acidified with HCl. The solid separated was filtered and crystallized from ethanol (Scheme 1).



Scheme 1. Synthesis of **1**-(2'-hydroxy naphthyl)-3-(phenyl/anthryl/pyridyl)-2- propene-1-ones (3_{a-e})

1-(2′-hydroxynaphthalene-1′-yl)-3-(9-anthryl)-2-propen-1-one (3_a):

Yield 90%; mp 184-186°C; IR (KBr) 3110 (OH), 1730 (CO), 1640 (CH=CH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.80 (1H, s, C-2′-OH), 8.98 (1H, d, J=9Hz, C-8′-H), 8.52 (1H, s, C-10-H), 8.33 (2H, d, J=9 Hz, C-4 and 5-H), 8.02-8.11 (3H, m, C-1, 8-H and 3′-H), 7.93 (1H, d, J=16Hz, =CH-Ar), 7.77 (1H, d, J=16Hz, -CO-CH=), 7.46-7.54 (6H, m, C-2, 3-H, 6-H, 7-H, 4′-H and 5′-H), 7.39 (1H, brt, J=12 Hz, C-6′-H), 7.33 (1H, brt, J=12 Hz, C-7′-H), 7.23 (1H, d, J=14 Hz, C-3-H) Anal. Calcd for $C_{27}H_{18}O_2$: C, 86.60; H, 4.84; O, 8.54. Found: C, 86.78; H, 4.56; O, 8.72.

1-(2´-hydroxynaphthalene-1´-yl)-3-(2,4-dichlorophenyl)-2-propen-1-one ***(3_b):***

Yield 81%; mp 154-156°C; IR (KBr) 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 (3H, m, C-6, C-6′ and 7′-H), 7.20 (1H, d, J=9 Hz, C-3′-H). Anal. Calcd for $C_{20}H_{15}O_3Cl_2$: C, 64.18; H, 4.03; O, 12.82. Found: C, 64.48; H, 3.92; O, 12.98.

1-(2´-hydroxynaphthalene-1´-yl)-3-(3,4-dimethoxyphenyl)-2-propen-1-one ***(3_c):***

Yield 78%; mp 218-220°C; IR (KBr) 3110 (OH), 1760 (CO), 1640 (CH=CH), 1190 (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 x OCH_3). Anal. Calcd for $C_{21}H_{18}O_4$: C, 75.43; H, 5.42; O, 19.13. Found: C, 75.75; H, 5.13; O, 19.58.

1-(2´-hydroxynaphthalene-1´-yl)-3-(5-bromo-3-chloro-2-hydroxyphenyl)-2-propen-1-one ***(3_d):***

Yield 88%; mp 204-206°C; IR (KBr) 3150 (OH), 1765 (CO), 1650 (CH=CH), 850 (C-Cl), 860 (C-Br); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.50 (1H, s, C-2′-H), 9.48 (1H, d, J=9Hz, C-8′-H), 7.98 (1H, d, J=16Hz, C-7-H), 7.67 (1H, d, J=16 Hz, C-8-H), 7.50-7.60 (2H, m, C-4′ and 5′-H), 7.40-7.49 (2H, m, C-6′ and 7′-H), 7.20 (1H, d, J=9 Hz, C-3′-H), 6.75 (2H, s,C-4 and 6-H). Anal. Calcd for $C_{19}H_{12}O_3ClBr$: C, 56.53; H, 2.99; O, 11.89. Found: C, 56.94; H, 2.63; O, 11.78.

1-(2´-hydroxynaphthalene-1´-yl)-3-(2-pyridyl)-2-propen-1-one ***(3_e):***

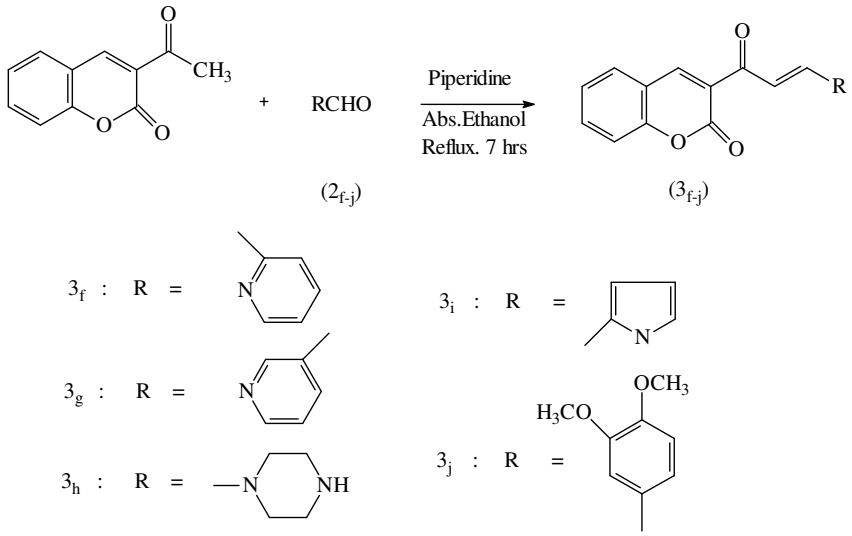
Yield 68%; mp 140-142°C; IR (KBr) 3120 (OH), 1730 (CO), 1650 (CH=CH), 1560 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.46 (1H, d, J=9Hz, C-8′-H), 7.94 (1H, d, J=16Hz, C-7-H), 7.18 (1H, d, J=16 Hz, C-8-H), 7.60-7.74 (3H, m, C-4′,5′ and 6′-H), 7.42 (1H, m, J=11Hz, C-7′-H), 7.40 (2H, d, J=13 Hz, C-2 and 6-H), 7.15 (1H, d, J= 9 Hz, C-3′-H), 6.78 (2H, d, J= 13 Hz, C-4 and 5-H). Anal. Calcd for $C_{18}H_{13}O_2N$: C, 78.53; H, 4.75; O, 11.62. Found: C, 78.98; H, 5.63; O, 10.56.

General procedure for the preparation of 3-[1-oxo-3-(substituted phenyl/heteroaryl)-2-propenyl]-2H-1-benzopyran-2-ones ***(3_{f-j})***

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 2).

3-[1-oxo-3(2-pyridyl)-2-propenyl]-2H-1-benzopyran-2-one ***(3_f).***

Yield 78%; mp 196-198 °C; IR (KBr) 1722 (CO), 1638 (CH=CH), 1610 (C=C), 1580 (C=N), 1225 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (1H, s, C_4-H), 8.26 (IH, d, =CH-Ar), 7.84 (1H, d, -CO-CH=), 7.25-7.77, (7H, m, Ar-H). Anal. Calcd for $C_{17}H_{11}O_5N$: C, 73.71; H, 4.02; O, 17.32; N, 5.05. Found: C, 73.85; H, 3.73; O, 17.56; N, 5.01.



Scheme 2. Synthesis of 3-[1-oxo-3-(substituted phenyl/heteroaryl)-2-propenyl]-2*H*-1-benzopyran-2-ones (3_{f-j})

3-[1-oxo-3(3-pyridyl)-2-propenyl]-2H-1-benzopyran-2-one ***(3_g).***

Yield 72%; mp 210-212 °C; IR (KBr) 1720 (CO), 1640 (CH=CH), 1605 (C=C), 1575 (C=N), 1230 (C-O-C); ^{1}H NMR (400 MHz, DMSO) δ 8.92 (1H, s, C_4-H), 8.19 (IH, d, =CH-Ar), 7.78 (1H, d, -CO-CH=), 7.01-8.69 (7H, m, Ar-H). Anal. Calcd for $C_{17}H_{11}O_5N$: C, 73.71; H, 4.02; O, 17.32; N, 5.05. Found: C, 73.49; H, 3.62; O, 17.10; N, 4.96.

3-[1-oxo-3(N-piperazinyl)-2-propenyl]-2H-1-benzopyran-2-one ***(3_h).***

Yield 76%; mp 214-216 °C; IR (KBr) 3320 (NH), 1718 (CO), 1639 (CH=CH), 1263 (C-O-C); ^{1}H NMR (400 MHz, DMSO) δ 8.59 (1H, s, C_4-H), 8.41 (IH, d, =CH-Ar), 8.23 (1H, s, -NH), 7.46 (1H, d, -CO-CH=), 7.42-7.85, (8H, m, Ar-H). Anal. Calcd for $C_{16}H_{16}O_5N_2$: C, 67.66; H, 5.67; O, 16.90; N, 9.86. Found: C, 67.32; H, 5.56; O, 16.53; N, 9.43.

3-[1-oxo-3(2-pyrrolyl)-2-propenyl]-2H-1-benzopyran-2-one ***(3_i).***

Yield 72%; mp 204-206 °C; IR (KBr) 3460 (-NH), 1720 (CO), 1642 (CH=CH), 1225 (C-O-C); ^{1}H NMR (400 MHz, DMSO) δ 9.18 (1H, s, -NH)8.62 (1H, s, C_4-H), 7.83 (IH, d, =CH-Ar), 7.57 (1H, d, -CO-CH=), 7.02--7.79 (7H, m, Ar-H). Anal. Calcd for $C_{16}H_{11}O_5N$: C, 72.52; H, 4.18; O, 18.11; N, 5.28. Found: C, 72.28; H, 4.32; O, 18.22; N, 5.32.

3-[1-oxo-3(3,4-dimethoxy phenyl)-2-propenyl]-2H-1-benzopyran-2-one ***(3_j).***

Yield 80%; mp 190-192 °C; IR (KBr) 1730 (CO), 1632 (CH=CH), 1225 (C-O-C); 1186 (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), 3.90-3.96 (6H, s, 2x OCH_3). Anal. Calcd for $C_{20}H_{16}O_5$: C, 71.42; H, 4.79; O, 23.78. Found: C, 71.68; H, 4.93; O, 23.42.

Antimicrobial activity

Cup plate method[10,11] using Mueller-Hinton agar medium was employed to study the preliminary antibacterial activity of **3**$_{(a-j)}$ against *B. pumilis B. substilis 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 mL 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 3$_{(a-j)}$ 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 dimethyl sulfoxide (1000 µg/mL). Volumes of 0.05 mL, and 0.1 mL of each compound were used for testing.

The cups each of 9mm diameter were made by scooping out medium with a sterilized cork borer in a Petri dish which were 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 & 1000 µg/ml respectively) and Dimethyl Sulphoxide 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 **[3$_{a-j}$]**

Compound No	*B. pumilis*		*B. subtilis*		*E. coli*		*A.niger*		*R.oriza*	
	0.05 mL	0.1 mL	0.05 mL	0.1 mL	0.05 mL	0.1 mL	0.05 mL	0.1 mL	0.05 mL	0.1 mL
3$_a$	8	9	8	9	8	10	9	13	10	12
3$_b$	10	12	7	10	8	9	8	12	8	13
3$_c$	9	12	8	10	7	10	10	14	9	12
3$_d$	11	15	11	13	11	12	13	18	12	16
3$_e$	8	10	9	11	8	10	8	13	8	11
3$_f$	10	11	9	11	10	11	10	11	11	12
3$_g$	10	12	9	10	10	11	11	13	9	10
3$_h$	10	11	10	11	9	9	12	13	9	10
3$_i$	10	12	8	9	9	10	10	11	8	9
3$_j$	11	14	10	14	11	13	13	16	10	14
Chloram	-	-	16	-*	14	-*				
Fluconazole							25	-*	-	-

(-) indicates no zone of inhibition (-*) indicates activity not done

Conclusion

The screening results revealed that the compounds 3_{a-j} showed significant antimicrobial activity. In particular compounds 3_d and 3_j 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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