Indian Journal of Chemistry
Vol. 45B,January 2006, pp. 314-317

Note

Synthesis and antimicrobial screening of 5*H*,7*H*-*N*-(coumarin-6-yl)-2,8-diphenyl-5,7-dioxo-4,5,6,7-tetrahydrobenzimidazo[5,6-*c*]-furan and 5*H*,7*H*-*N*-(coumarin-6-yl)-2,8-diphenyl-5,7-dioxo-6-(7-methoxy-4-methylcoumarin-6-yl)-4,5,6,7-tetrahydro benzimidazo[5,6-*c*]pyrrole

B P Choudhari & V V Mulwad*

Department of Chemistry, The Institute of Science, 15, Madam Cama Road, Mumbai 400 032, India

E-mail: vinata_mulwad@hotmail.com

Received 19 May 2004; accepted (revised) 3 March 2005

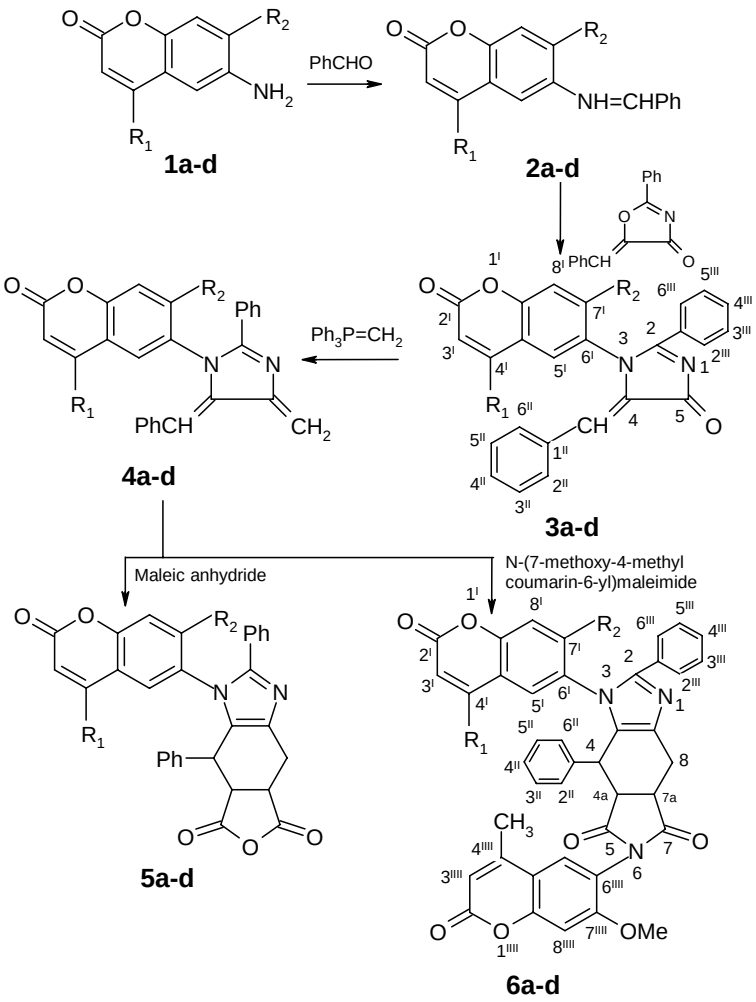
The Schiff bases **2a-d** of 6-aminocoumarins **1a-d** on reaction with 4-benzylidene-2-phenyloxazolin-5-one in DMF and catalytic amount of pyridine afford 4-benzylidene-3-(coumarin-6-yl)-2-phenylimidazolin-5-ones **3a-d** which on further Wittig reaction yield the corresponding 4-benzylidene-3-(coumarin-6-yl)-5-methylene-2-phenylimidazolines **4a-d**. Compounds **4a-d** on Diel's-Alder reaction with maleic anhydride and *N*-(7-methoxy-4-methylcoumarin-6-yl)maleimide separately give 5*H*,7*H*-*N*-(coumarin-6-yl)-2,8-diphenyl-5,7-dioxo-4,5,6,7-tetrahydrobenzimidazo(5,6-*c*)furans **5a-d** and 5*H*,7*H*-*N*-(coumarin-6-yl)-2,8-diphenyl-5,7-dioxo-6-(7-methoxy-4-methylcoumarin-6-yl)-4,5,6,7-tetrahydrobenzimidazo(5,6-*c*)pyrroles **6a-d** respectively. The structures of the compounds have been established on the basis of the spectral and analytical data. All the compounds **3-6a-d** have been screened for their antimicrobial activities and found to exhibit significant antibacterial and antifungal activities.

Keywords: Aminocoumarin, Schiff bases, Wittig reaction, Diel's-Alder reaction, Antimicrobial activity

IPC: **Int.Cl.**[7] **C 07 D**

Coumarin derivatives have aroused considerable interest of chemists due their versatile practical applications as well as their wide range of biochemical properties[1]. Nitrogen mustards synthesized from 6-aminocoumarins exhibit carcinogenic activity[2]. They are also known to possess antiviral[3] activity and especially effective against HIV1(ref 4). The Schiff bases of 6-aminocoumarins are well-known for their wide range of pharmaceutical like antibacterial, and antifungal[5] activities. Moreover, many imidazoline derivatives have been reported to be topically effective in nasal congestion[6]. Also, the benzimidazoles and their derivatives constitute a class of biologically active antihelmintic compounds active against whipworm infestations[7]. Encouraged with the above reports, we planned to synthesize new heterocyclic compounds containing the benzimidazole moiety substituted at the 6-postion of the coumarin ring via the formation of the Schiff bases of the 6-aminocoumarin.

6-Aminocoumarins **1a-d** on treatment with benzaldehyde in ethanol in presence of catalytic amount of glacial acetic acid afforded the Schiff bases[5] **2a-d**, which on reaction with 4-benzylidene-2-phenyloxazoline-5-one[8] in DMF and catalytic amount of pyridine yielded 4-benzylidene-3-(coumarin-6-yl)-2-phenylimidazolin-5-one **3a-d**. The IR spectrum of **3b** in KBr suggested the absence of $-NH_2$ group due to absence of any significant band beyond 3056 cm^{-1} indicating the formation of product. Its ^{13}C NMR spectrum in DMSO-d_6 showed signals at δ 159.00 for the >C=N-, 173.20 for the carbonyl group at C_5, etc. Compounds **3a-d** on Wittig reaction in toluene afforded 4-benzylidene-3-(coumarin-6-yl)-5-methylene-2-phenylimidazoline **4a-d**. The ^{13}C NMR spectrum of **4b** in DMSO-d_6 did not show any signal at δ 173.20 indicating the absence of the carbonyl group at C_5 observed in the ^{13}C NMR spectrum of **3b**. Compounds **4a-d** on Diel's-Alder reaction with maleic anhydride and *N*-(7-methoxy-4-methylcoumarin-6-yl)maleimide separately in dichloromethane and anhy. $AlCl_3$ furnished the corresponding 5*H*,7*H*-*N*-(coumarin-6-yl)-2,8-diphenyl-5,7-dioxo-4,5,6,7-tetrahydrobenzimidazo[5,6-*c*]furan **5a-d** and 5*H*,7*H*-N-(coumarin-6-yl)-2,8-diphenyl-5,7-dioxo-6-(7-methoxy-4-methylcoumarin-6-yl)-4,5,6,7-tetrahydrobenzimidazo-[5,6-*c*]pyrrole (**6a-d, Scheme I**). The IR spectrum of **5b** in KBr showed band at 1792 cm^{-1} for the carbonyls at C_5 and C_7, etc. Its ^1H NMR spectrum in DMSO-d_6 showed a doublet at δ 2.23 for two protons of the methylene group at C_8, triplet at 2.42 for the proton at C_{4a}. A quartet was observed at 2.52 for the proton at C_{7a} and a doublet at 3.00 for the proton of C_4. The ^{13}C NMR spectrum in DMSO-d_6 showed signals at δ 25.75 for C_8, 35.25 for C_4, 82.25 for $C_{4a,}$ 82.50 for $C_{7a,}$ etc. Its mass spectrum showed molecular ion peak (m/z) M^+ 500 (35). The ^1H NMR spectrum of **6b** in



1a - 6a: R_1= H, R_2= H.
1b - 6b: R_1= H, R_2= CH_3.
1c - 6c: R_1= CH_3, R_2= CH_3.
1d - 6d: R_1= CH_3, R_2= OCH_3.

Scheme I

DMSO-d_6 showed a sharp singlet at δ 3.80 for the three protons of the methoxy group. Its ^{13}C NMR spectrum in DMSO-d_6 showed signals at δ 55.17 for the carbon of the methoxy group, etc.

Antimicrobial activity

The compounds **3-6a-d** were screened for their antibacterial activity against *S. aureus,* and *S typhi* and antifungal activity against *A. niger* and *C. albicans* **(Table I)**. The minimum inhibitory concentration (MIC) was determined using tube dilution method according to the standard procedure[9], DMF was used as a solvent and blank. Ciprofloxacin and miconazole were used as the antibacterial and antifungal standards respectively. An examination of result reveals that all the compounds showed antimicrobial activity ranging from 50 µg/mL to 200 µg/mL.

Experimental Section

General. Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a Perkin-Elmer 257 spectrophotometer using KBr, ^{1}H NMR and ^{13}C NMR were recorded on a Bruker AMX500 MHz using TMS as an internal standard; mass spectra on a Shimadzu GC-MS. The homogenity of the compounds was determined on the silica gel plates. The spots were developed in the

Table I — Antimicrobial activity data of compounds **3- 6a-d**. (MIC μg/mL)

Compd	Antibacterial activity		Antifungal activity	
	S. aureus	*S. typhi*	*A. niger*	*C. albicans*
3a	-	+	++	-
3b	+	++	++	-
3c	+	++	++	+
3d	++	+++	+++	++
4a	+	-	-	+
4b	+	-	+	+
4c	++	+	+	++
4d	++	++	++	+++
5a	+	++	-	+
5b	+	++	+	+
5c	++	++	+	++
5d	+++	+++	++	++
6a	++	+	+	-
6b	++	++	+	+
6c	++	+++	++	++
6d	+++	+++	++	++
Ciprofloxacin	*	*		
Miconazole			*	*

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

iodine chamber. All the compounds gave satisfactory elemental analysis.

4-Benzylidene-3-(7-methylcoumarin-6-yl)-2-phenylimidazolin-5-one 3b. A mixture of Schiff bases **2b** (0.01 mole) and 4-benzylidene-2-phenyloxazoline-5-one was refluxed in DMF in presence of catalytic amount of pyridine for 5 hr. The mixture was cooled and poured over crushed ice and water containing a little amount of conc. HCl. The product obtained was filtered, washed, dried and recrystallised from ethanol. Similarly **3a** and **3c-d** were also prepared.

3a: Mol. Formula $C_{25}H_{16}N_2O_3$, m.p. 150°C, yield: 69%. **3b**: Mol. formula $C_{26}H_{18}N_2O_3$, m.p. 179°C, yield: 65%; ^{1}H NMR (DMSO-d_6, δ): 2.43 (s, 3H, -CH_3), 6.10 (s, 1H, =C*H*-, =C*H*-C_6H_5), 6.44 (d, *J*=9.50Hz, 1H, C_3'-H), 6.60 (d, *J*=7.50Hz, 2H, $C_{2''}$H & $C_{6''}$-H), 6.80 (t, 2H, $C_{3''}$-H & $C_{5''}$-H), 6.95 (d, *J*=9.50Hz, 2H, $C_{2''}$-H & $C_{6''}$-H), 7.08 (t, 1H, $C_{4''}$-H), 7.25 (t, 2H, $C_{3'''}$-H& $C_{5'''}$-H), 7.32 (s, 1H, $C_{5'}$-H, coumarin), 7.60 (t, 1H, $C_{4'''}$-H, –Ph), 7.90 (s, 1H, $C_{7'}$-H), 8.11 (d, *J*=9.50Hz, 1H, $C_{4'}$-H). ^{13}C NMR (DMSO-d_6, δ): 17.00 (-CH_3), 112.00 (=*C*H-Ph), 116.00 ($C_{3'}$), 118.00 ($C_{4a'}$), 144.00 ($C_{4'}$), 148.18 ($C_{6'}$), 153.20 ($C_{7'}$), 154.00 ($C_{8a'}$), 159.00 (C_2), 161.10 ($C_{2'}$), 173.20 (C_5), 120.00–143.00 (16 C-atoms); **3c**: Mol. formula $C_{27}H_{20}N_2O_3$, m.p. 200°C, yield: 56%. **3d**: Mol. formula $C_{26}H_{18}N_2O_4$, m.p. 187°C, yield: 59%.

4-Benzylidene-3-(7-methylcoumarin-6-yl)-5-methylene-2-phenylimidazoline 4b. A mixture of **3b** (0.01 mole) and Wittig reagent ($Ph_3P=CH_2$), (0.01 mole) in toluene (20 mL) were refluxed for 3 hr. The mixture was cooled and quenched into saturated solution of ammonium chloride and later extracted with diethylether. The solvent on evaporation yielded the product, which was recrystallised from ethanol. Similarly **4a** and **4c-d** were also prepared.

4a: Mol. formula $C_{26}H_{18}N_2O_2$, m.p. 168°C, yield: 81%; **4b:** Mol. formula $C_{27}H_{20}N_2O_2$, m.p. 157°C, yield: 76%; ^{1}H NMR (DMSO-d_6, δ): 2.43 (s, 3H, -CH_3), 5.15 (s, 2H, =CH_2), 6.10 (s, 1H, =C*H*-, =C*H*-C_6H_5), 6.44 (d, *J*=9.50Hz, 1H, $C_{3'}$-H), 6.60 (d, *J*=7.50Hz, 2H, $C_{2''}$-H and $C_{6''}$-H), 6.80 (t, 2H, $C_{3''}$-H and $C_{5''}$-H, =CH-Ph), 6.95 (d, *J*=9.50Hz, 2H, $C_{2'''}$-H and $C_{6'''}$-H), 7.08 (t, 1H, $C_{4''}$-H), 7.25 (t, 2H, $C_{3'''}$-H and $C_{5'''}$-H), 7.32 (s, 1H, $C_{5'}$), 7.60 (t, 1H, $C_{4'''}$-H), 7.90 (s, 1H, $C_{7'}$-H), 8.11 (d, *J*=9.50Hz, 1H, $C_{4'}$-H); ^{13}C NMR (DMSO-d_6, δ): 17.00 (-CH_3), 110.00 (=*C*H_2), 112.00 (=*C*H-Ph), 116.00 ($C_{3'}$), 118.00 ($C_{4a'}$), 144.00 ($C_{4'}$), 148.18 ($C_{6'}$), 153.20 ($C_{7'}$), 154.00 ($C_{8a'}$), 159.00 (C_2), 161.10 ($C_{2'}$), 120.00 –143.00 (18 C-atoms); **4c**: Mol. formula $C_{28}H_{22}N_2O_2$, m.p. 177°C yield 72%; **4d**: Mol. formula $C_{28}H_{22}N_2O_3$, m.p. 197°C, yield 67%.

5*H*,7*H*-*N*-(7-methylcoumarin-6-yl)-2,8-diphenyl-5,7-dioxo-4,5,6,7-tetrahydrobenzimidazo[5,6-*c*]furan 5b. A mixture of **4a-d**, (0.001 mole) and maleic anhydride (0.001 mole) in dichloromethane (20 mL) were stirred at room temperature in presence of catalytic amount of anhy. $AlCl_3$ for 1 hr. It was then poured over crushed ice and water containing a little amount of conc. HCl and later extracted with dichloromethane. The solvent on evaporation afforded the product, which was recrystallised from ethanol. Similarly **5a** and **5c-d** were also prepared.

5a: Mol. formula $C_{30}H_{18}N_2O_5$, m.p. 185°C, yield: 77%; **5b**: Mol. formula $C_{31}H_{20}N_2O_5$, m.p. 206°C, yield: 73%, ^{1}H NMR (DMSO-d_6, δ): 2.23 (d, 2H, C_8), 2.33 (s, 3H, -CH_3), 2.42 (t, 1H, C_{4a}-H), 2.52 (q, *J*=6.50Hz, 1H, C_{7a}-H), 3.00 (d, 1H, C_4), 6.44 (d, *J*=9.50Hz, 1H, $C_{3'}$-H), 6.60 (d, *J*=7.50Hz, 2H, $C_{2''}$-H & $C_{6''}$-H), 6.80 (t, 2H, $C_{3''}$-H and $C_{5''}$-H), 6.95 (d, *J*=9.50Hz, 2H, $C_{2'''}$-H and $C_{6''}$-H), 7.08 (t, 1H, $C_{4''}$-H),

7.25 (t, 2H, $C_{3'''}$-H and $C_{5'''}$-H), 7.32 (s, 1H, $C_{5'}$-H), 7.60 (t, 1H, $C_{4'''}$-H), 7.90 (s, 1H, $C_{8'}$-H), 8.11 (d, *J*=9.50Hz, 1H, $C_{4'}$-H); ^{13}C NMR (DMSO-d_6, δ): 17.00 (-CH_3), 25.75 (C_8), 35.25 (C_4), 82.25 (C_{4a}), 82.50 (C_{7a}), 116.00 ($C_{3'}$), 118.00 ($C_{4a'}$), 144.00 ($C_{4'}$), 148.18 ($C_{6'}$), 153.20 ($C_{7'}$), 154.00 ($C_{8a'}$), 159.00 (C_2), 161.10 ($C_{2'}$), 173.20 (C_5), 174.10 (C_7), 120.00 –143.00 (16 C-atoms); Mass (m/z) (%): M^+ 500 (35), 423 (39), 346 (52), 187 (30), 161 (12), 159 (10), 135 (40), 131 (20), 130 (10), 102 (03), 91 (44), 77 (100), 76 (10), 63 (23), **5c**: Mol. formula $C_{32}H_{22}N_2O_5$, m.p. 196°C, yield: 67%, **5d**: Mol. formula $C_{32}H_{22}N_2O_6$, m.p. 182°C, yield: 81%.

5*H*,7*H*-*N*-(7-methylcoumarin-6-yl)-2,8-diphenyl-5,7-dioxo-6-(7-methoxy-4-methylcoumarin-6-yl]-4,5,6,7-tetrahydrobenzimidazo(5,6-*c*)pyrrole 6b. A mixture of **4a-d** (0.01 mole) and *N*-(7-methoxy-4-methylcoumarin-6-yl)maleimide (0.01 mole) in dichloromethane (20 mL) were stirred at room temperature in presence of catalytic amount of anhy. $AlCl_3$ for 1 hr. It was then poured over crushed ice and water containing a little amount of conc. HCl and later extracted with dichloromethane. The solvent on evaporation afforded product, which was recrystallised from ethanol. Similarly **6a** and **6c-d** were also prepared.

6a: Mol. formula $C_{41}H_{27}N_3O_7$, m.p. 187°C, yield: 76%, **6b**: Mol. formula $C_{42}H_{29}N_3O_7$, m.p. 195°C, yield: 66%; ^{1}H NMR (DMSO-d_6, δ): 2.23 (d, *J*=6.50Hz, 2H, C_8), 2.33 (s, 2 x 3H, 2 x–CH_3), 2.42 (t, 1H, C_{4a}-H), 2.52 (q, *J*=6.50Hz, 1H, C_{7a}-H), 3.00 (d, *J*=6.50Hz, 1H, C_4), 3.80 (s, 3H, –OCH_3), 6.30 (s, 1H, $C_{2''''}$–H), 6.44 (d, *J*=9.50Hz, 1H, $C_{3'}$-H), 6.60 (d, *J*=7.50Hz, 2H, $C_{2''}$-H and $C_{6''}$-H), 6.80 (t, 2H, $C_{3''}$-H and $C_{5''}$-H), 6.95 (d, *J*=9.50Hz, 2H, $C_{2'''}$-H and $C_{6'''}$-H), 7.08 (t, 1H, $C_{4''}$-H), 7.25 (t, 2H, $C_{3'''}$-H and $C_{5'''}$-H), 7.32 (s, 1H, $C_{5'}$-H), 7.45 (s, 1H, $C_{5''''}$H), 7.60 (t, 1H, $C_{4'''}$-H), 7.75 (s, 1H, $C_{8'}$-H), 7.90 (s, 1H, $C_{8''''}$-H), 8.11 (d, *J*=9.50Hz, 1H, C4'-H). ^{13}C NMR (DMSO-d_6, δ): 17.00 ($C_{7'}$–CH_3), 17.50 ($C_{4''''}$–CH_3), 25.75 (C_8), 35.25 (C_4), 55.17 (–OCH_3), 82.25 (C_{4a}), 82.50 (C_{7a}), 116.00 ($C_{3'}$& $C_{3''''}$), 118.00 ($C_{4a'}$ and $C_{4a'}$), 144.00 ($C_{4'}$ 148.18 ($C_{6'}$ $C_{6''''}$), 153.20 ($C_{7'}$ and $C_{7''''}$), 154.00 ($C_{8a'}$ and $C_{8a''''}$), 159.00 (C_2), 161.10 ($C_{2'}$), 162.10 ($C_{2''''}$), 173.20 (C_5), 174.10 (C_7), 110.00– 143.00 (19 C-atoms). **6c**: Mol. formula $C_{44}H_{31}N_3O_7$, m.p. 213°C, yield: 69%, **6d**: Mol. formula $C_{44}H_{31}N_3O_8$, m.p. 193°C, yield: 57%.

Acknowledgement

Authors thank S V Chiplunkar, MUICT for elemental analysis, TIFR Mumbai for ^{1}H and ^{13}C NMR spectral analysis, Prof Vaidya, Head of Microbiology Department, Institute of Science, Mumbai and Haffkine Institute, Parel for biological testing. Authors also thank the Government of Maharashtra for scholarship, Women Graduates Union for awarding 'The Amy Rustomjee International Scholarship' and the University of Mumbai for the 'Sir Currimbhoy Ebrahim and Bai Khanoobai Noormohamed Jairazbhoy Peefbhoy Scholarship'.

References

1 Ghoto T & Yamamura S, *Pyran Compounds*, In *Methodicum Chimicum*, Part 3, Vol 11, edited by Korte F & Ghoto M, (Academic Press, New York), **1978**.

2 Schuda P F, *Top Org Chem*, 91, **1980**, 75.

3 Kun E & Aurelian L, *US Pat* 412 783, **1991**; *Chem Abstr*, 115, **1991**, 92071t.

4 Kun E (*Octamer Inc USA*) *PCT Int App*, WO9851, 307.

5 Mulwad V V & Shirodkar J M, *Indian J Heterocyclic Chem*, 11, **2002**, 199.

6 *AMA Drug Evaluation*, 3rd edition, (PSG Publishing Company Inc), **1977**, 649- 653.

7 Rao R S, Chawate V & Shah S J, *An introduction to synthetic drugs and dyes*, 2nd edn, (Himalaya Publishing House), **1955**, 53.

8 Vogel A I, *Textbook of Practical Organic Chemistry*, 5th edn., **1996**, 1155.

9 Frankel S, Reitman S & Sonnenwirth A C,*Clinical Laboratory Methods and Diagonosis*, 7th edn,. (C V Mosby Company, Germany), Vol. 2, **1970**, 1406.