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A CONVENIENT PROCEDURE FOR THE SYNTHESIS OF SUBSTITUTED 4-METHYLAMINOCOUMARINS

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Abstract- 3-Bromo-7-methoxy-4-methylcoumarin and 3-bromo-4,7-dimethyl-coumarin give a mixture of the corresponding 3-aminocoumarins and 4-aminomethylcoumarins upon the reaction with a number of secondary amines. In addition, the reaction of 7-methoxy- and 7-methyl-4-bromomethylcoumarins with secondary diamines affords the corresponding *N*,*N*`-dicoumarinmethyldiamine.

INTRODUCTION

Coumarins and related derivatives have continued to attract attention for their interesting biological activities. Their anticoagulant and antithrombiotics activities are well known.[1] They display antibiotic and antifungal,[2] anti-inflammatory,[3] and antiviral activities including human immunodeficiency virus.[4] They have also been used as additives in food and cosmetics,[5] and in the preparation of optical brighteners, dispersed fluorescent, and laser dyes.[6]

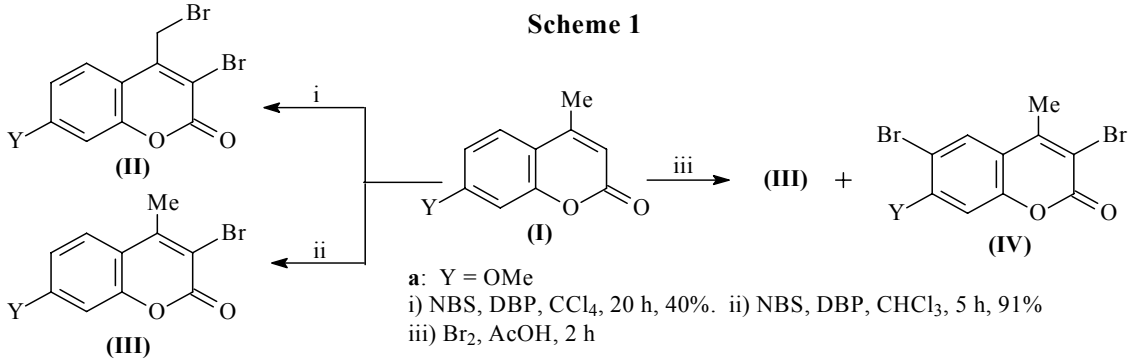
There have been relatively few previous reports concerning the synthesis of aminocoumarins; heating *o*-hydroxybenzaldehyde derivatives with glycine in acetic anhydride,[7] and nitration of coumarins followed by reduction[8] afforded the corresponding aminocoumarins. Joshi and Usgaonkar[9] and Desai and Mehta,[10] reported the synthesis of 4-aminomethyl-7-methoxycoumarin by condensation of 4-halomethyl-7-methoxycoumarin with amines. Kelkar *et al*,[11] reported that the reaction of 3-bromo-4-methylcoumarin with secondary amines gave 4-aminomethylcoumarin as a major product, and 3-amino-4-methylcoumarin as a minor product. On the other hand, 3-bromocoumarin reacted with amines to give substituted and rearranged product of benzofuran-2-carboxamides.[12] As part of our ongoing research on coumarin derivatives,[13] we report on the synthesis and spectral properties of a number of 3-amino-4-methylcoumarins and 4-aminomethyl-coumarins through the amination of 3-bromo-4-methylcoumarins and 4-bromomethylcoumarins.

RESULTS AND DISCUSSION

Bromination of coumarin derivatives has been achieved using different experimental conditions; Ghiya and Marathey[14] reported that bromination of 7-hydroxy-4-methylcoumarin using Br_2 gave the 3-bromo derivative, but in excess bromine, the 3,6-dibromo- and the 3,8-dibromo derivatives were obtained.[15] However, the 3-bromo derivative was obtained when bromine in acetic acid, chloroform, dioxane, and carbon tetrachloride at room temperature was used.[16]

The synthesis of 3-bromo-7-methoxy-4-methylcoumarin (**IIIa**) was achieved by treating 7-methoxy-4-methylcoumarin (**Ia**) with NBS in chloroform and few milligrams of dibenzoyl peroxide (DBP). However, the reaction of **Ia** with NBS in carbon tetrachloride with stepwise addition of DBP afforded 3-bromo-4-bromomethyl-7-methoxycoumarin (**IIa**). Additionally, compound **IIIa** was obtained, along with 3,6-dibromo-7-methoxy-4-methylcoumarin (**IVa**) as a side-product,[17] when **I** was treated with bromine in glacial acetic acid (Scheme 1).

Scheme 1



a: Y = OMe

i) NBS, DBP, CCl_4, 20 h, 40%. ii) NBS, DBP, $CHCl_3$, 5 h, 91%

iii) Br_2, AcOH, 2 h

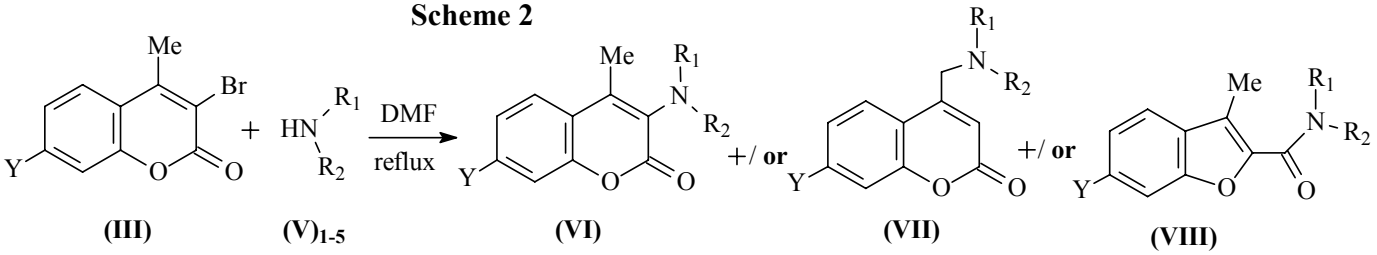
The NBS method, however, failed in the preparation of 4-bromomethylcoumarins as a monobromo derivative; we based our procedures for preparation of these compounds on a synthesis reported recently. This method involved bromination of ethyl acetoacetate with bromine to give ethyl 4-bromoacetoacetate in high yield.[18] Cyclization of the later with the desired phenol in the presence of Lewis acid afforded selectively the corresponding 4-bromomethylcoumarins.[19, 20]

Reaction of 3-bromo-4-methylcoumarins (**III**) with secondary amines (**V**) in dimethylformamide (DMF) gave the corresponding 3-aminocoumarins (**VI**) as the minor product and 4-aminomethylcoumarins (**VII**) as a major product (Scheme 2). The products were separated and their structures were confirmed by means of ^{1}H- and ^{13}C-NMR spectrometry. In the case of six-membered ring secondary amines, piperidine, morpholine and thiomorpholine ($\mathbf{V_{1\text{-}3}}$), the first spot (with higher R_f value), as shown by TLC analysis, was **VI**, while the second spot was **VII**. The ^{1}H-NMR spectra of compound **VI** revealed the absence of H-3 and the presence of methyl protons at C-4, while the presence of H-3, in the range 6.32-6.40 ppm confirms the identity of **VII**.

In the case of the five-membered ring secondary amine, pyrrolidine ($\mathbf{V_4}$), two products were also obtained; the first product was the expected **VI**, while the second was *N*-pyrrolidinyl-3-methylbenzofuran-2-carboxamide (**VIII**) (Scheme 2). The later compound may be formed by nucleophilic addition reaction of

less sterically hindered amine, i.e. five membered ring, followed by cyclization of phenolate to give benzofuran-3-carboxamide **(VIII)** (Scheme 3)

Scheme 2



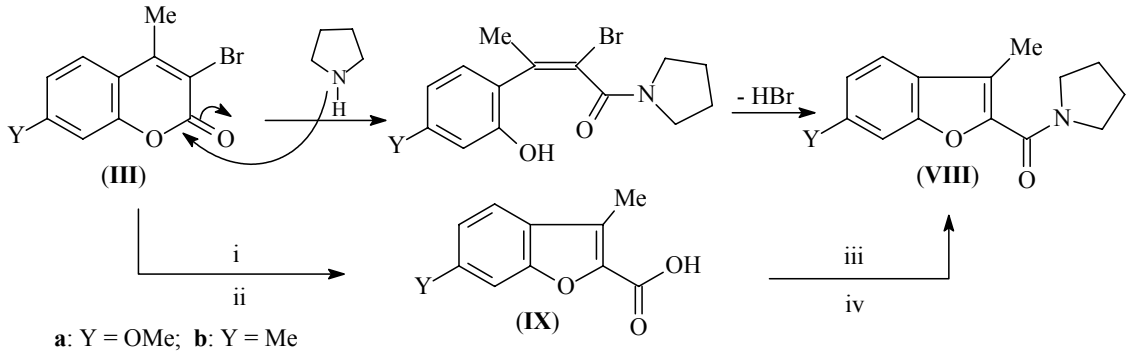
(III) **$(V)_{1-5}$** **(VI)** **(VII)** **(VIII)**

a: Y= OMe, **b**: Y= Me

Amine V	Products			Substituents
	VI (%)	**VII** (%)	**VIII** (%)	
1	**a** (19)	**a** (65)	-	$R_1, R_2 = (CH_2)_5$
2	**a** (13)	**a** (80)	-	$R_1, R_2 = [(CH_2)_2]_2O$
3	**b** (9)	**b** (83)	-	$R_1, R_2 = [(CH_2)_2]_2S$
4	**b** (23)	-	**a** (9.5)	$R_1, R_2 = (CH_2)_4$
4	**b** (22)	-	**b** (13)	$R_1, R_2 = (CH_2)_4$
5	-	**a** (25)	-	R_1 = benzyl, R_2 = 2-pyridyl
5	-	**b** (35)	-	R_1 = benzyl, R_2 = 2-pyridyl

The IR spectra of compounds (**VIII**) exhibited characteristic bands at ~ 1615 cm^{-1} due to the C=O stretching vibration of amide moiety in contrast to that of the coumarin which displays an absorption band in the 1750-1734 cm^{-1} region. The ^{1}H-NMR, ^{13}C-NMR, and MS spectra of these compounds are similar to those of authentic samples prepared through a modified procedure reported by Lele and S. Sethna[21] (Scheme 3).

Scheme 3

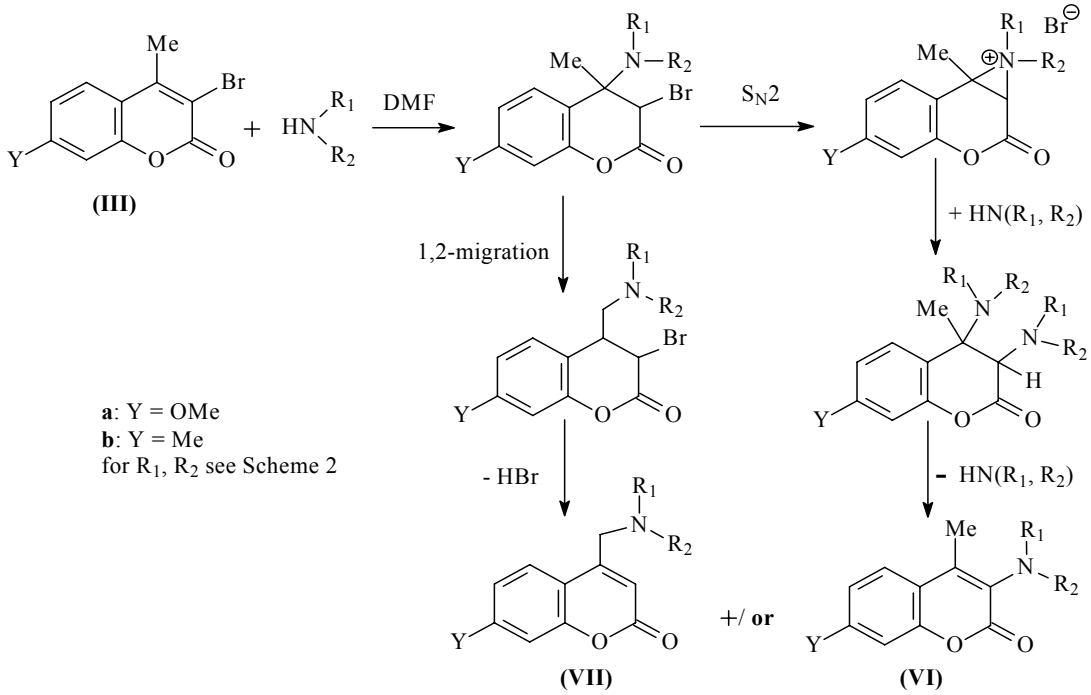


a: Y = OMe; **b**: Y = Me

i) KOH, EtOH, reflux 2 h, 85%. ii) HCl. iii) $SOCl_2$,. iv) Pyrrolidine, Py, 50%.

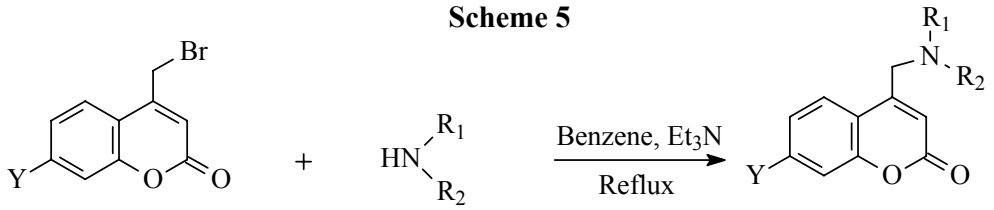
Moreover, *N*-(2-pyridyl)benzylamine (**V_5**), apparently a bulk amine, gave one product, 4-[2-(pyridyl)-benzylaminomethyl]coumarins (**VII_5**), when reacted with **III**. These observations may suggest that steric factors may play a role in this reaction. The formation of these products can be explained by Michael addition of one mole of the amine, followed by intramolecular nucleophilic attack of the formed tertiary amine on C-3 to displace the bromide through aziridinium intermediate. The addition of a second molecule of amine to the intermediate followed by deamination affords compound (**VI**). The mechanism for the formation of compound (**VII**) was not clear, but it may involve 1,2-migration of amino group followed by dehydrobromination as presented in Scheme 4.

Scheme 4



Compound (**VII**) could also be prepared from the amination of 4-bromomethylcoumarins **(X)**;[22, 23] condensastion of coumarin (**Xb**) with amines (**$V_{2,4,6}$**) afforded **VII** as shown in Scheme 5.

Scheme 5



a: Y = OMe
b: Y = Me

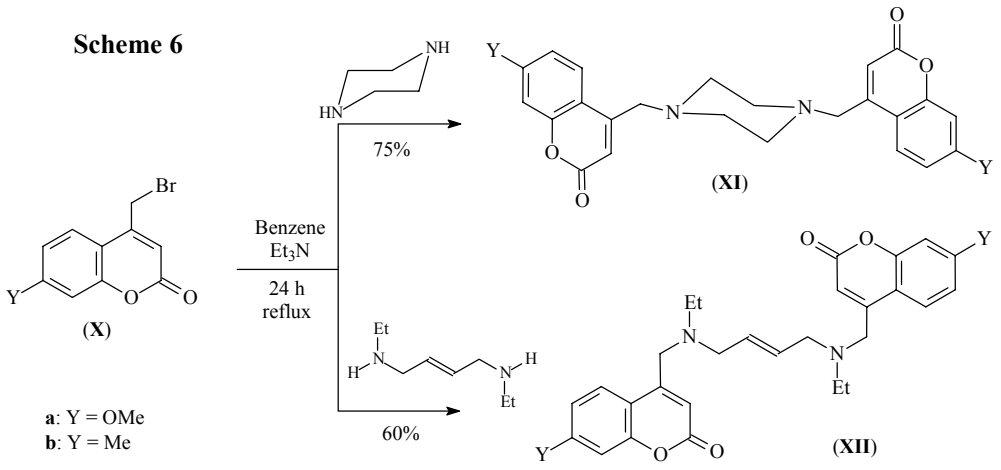
V_2: $R_1, R_2 = [(CH_2)_2]_2O$
V_4: $R_1, R_2 = (CH_2)_4$
V_6: R_1 = H, R_2 = piperonyl

$VIIb_2$: 83%
$VIIb_4$: 53%
$VIIb_6$: 71%

The antinocoplastic activity and inhibition of DNA-producing enzymes or proteins and nucleic acid synthesis, *in vivo,* shown by some known naturally occurring bis(coumarinyl)ethers; darphnoretin,[24, 25] attracted our attention towards the synthesis of dimeric compounds. Thus, compounds (**XI**) and (**XII**) were obtained when **X** was treated with the secondary diamines, piprazine and *N*,*N*`-diethyl-2-butene-1,4-diamine, respectively (Scheme 6).

^{1}H-NMR and ^{13}C-NMR spectra of all prepared compounds are in total agreement with the suggested structures; DEPT experiments were employed to differentiate secondary and quaternary carbons from primary and tertiary carbons. Additional support of the proposed structures comes from MS spectrum; MS spectrum of the prepared compounds show the correct molecular ions, $M^{+\cdot}$, as suggested by their molecular formulas. Analyses of the molecular ions and the fragmentation pattern are used in the identification and characterization of these compounds.

Scheme 6



EXPERIMENTAL

General consideration

Melting points were measured on an electrothermal melting point apparatus and are uncorrected. The IR spectra were recorded, as KBr discs, on a Thermo Nicolet Nexus 670 FT-IR instrument. The ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker DPX-300 and Bruker WM-400 spectrometers and are reported in ppm (δ) relative to tetramethylsilane as internal reference. EIMS spectra were obtained using a Finnegan MAT TSQ-70 spectrometer at 70 eV. Elemental analyses were acquired with the aid of Eurovector Euro EA3000, CHNS-O elemental analyzer.

7-Methoxy-4-methylcoumarin (Ia)

This compound was prepared according to literature procedure,[13] or by methylation of 7-hydroxy-4-methylcoumarin by refluxing, with stirring, a mixture of 26.4 g (0.15 mol) of 7-hydroxy-4-methylcoumarin, 28 mL (0.45 mol) of methyl iodide, and 23.9 g (0.225 mol) of anhydrous sodium carbonate in 150 mL of methanol for 12 h. Methanol was removed under vacuum and the solid product was treated with 300 mL of water and neutralized with 15% HCl, to remove the excess of sodium carbonate. The product was filtered and recrystallized from aqueous ethanol. Yield of **Ia** 95%, mp 159-160 ^{o}C (lit.,[13] 158-159 ^{o}C).

4,7-Dimethylcoumarin (Ib)

This compound was prepared according to literature procedure.[26]

3-Bromo-4-bromomethyl-7-methoxycoumarin (IIa)

A mixture of 1.9 g (10 mmol) of 7-methoxy-4-methylcoumarin (**Ia**), 3.91 g (22 mmol) of NBS and 30 mg of dibenzoyl peroxide in carbon tetrachloride (100 mL) was refluxed for 24 h; additional amounts of 30 mg each of dibenzoyl peroxide were added every 2 h for four times (total amount of the initiator was 150 mg). The hot mixture was filtered and concentrated under vacuum and the precipitate was recrystallized from benzene. Yield of **IIa** 40%; mp 183-184 ^{o}C; IR (cm^{-1}): 1705 (C=O), 1615 (C=C); ^{1}H-NMR ($CDCl_3$) δ: 3.86 (s, 3H), 4.66 (s, 2H), 6.85 (d, 1H, *J* = 2.5 Hz), 6.92 (dd, 1H, *J* = 2.5, 8.9 Hz), 7.58 (d, 1H, *J* = 8.9 Hz); ^{13}C-NMR (DMSO-d_6) δ: 28.6, 56.6, 101.4, 110.4, 110.9, 113.5, 127.2, 149.8, 154.1, 157.0, 163.3; MS ($C_{11}H_8O_3Br_2$), *m*/*z* (% rel. int.): 350 (M^+, 27), 348 (M^+, 60), 346 (M^+, 30), 270 (100), 189 (20),

161 (29); Anal. Calcd for $C_{11}H_8O_3Br_2$: C, 37.97; H, 2.32; Br, 45.92. Found: C, 37.95; H, 2.30; Br, 45.93.

3-Bromo-7-methoxy-4-methylcoumarin (IIIa)

A mixture of 1.9 g (10 mmol) of 7-methoxy-4-methylcoumarin (**Ia**), 2.67 g (15 mmol) of NBS and 20 mg of DBP in 100 mL of $CHCl_3$ was refluxed for 5 h. The chloroform layer was concentrated under vacuum and the precipitate was stirred with 500 mL of warm water to remove the succinimide, filtered and recrystallized from aqueous ethanol. Yield of **IIIa** 91%; mp 148 ^oC (lit.,[17] 147); IR (cm^{-1}): 1705 (C=O), 1615 (C=C); ^1H-NMR ($CDCl_3$) δ: 2.38 (s, 3H), 3.95 (s, 3H), 6.75 (d, 1H, *J* = 2.3), 6.88 (dd, 1H, *J* = 8.5, 2.3), 7.53 (d, 1H, *J* = 8.5); ^{13}C-NMR ($CDCl_3$) δ: 19.2, 55.8, 99.5, 100.7, 113.0, 113.3, 126.1, 151.1, 153.7, 157.5, 163.1; MS ($C_{11}H_9O_3Br$), *m*/*z* (% rel. int.): 270 (M^+, 100), 268 (M^+, 97), 225 (32), 189 (26).

3-Bromo-4,7-dimethylcoumarin (IIIb)

This compound was prepared according to literature procedure.[11]

3-Amino- and 4-aminomethylcoumarins (VI-VII), general procedure

A mixture of (2 mmol) of 3-bromo-4-methylcoumarin (**IIIa,b**), 8 mmol of the appropriate secondary amine (**V_{1-5}**) and 5 mL of DMF was refluxed for 0.5-5 h. After cooling, the solution was poured onto 100 mL of saturated solution of sodium chloride. The precipitate was filtered, dried, and column chromotographed on silica gel column using ethyl acetate/hexane (1/4) as eluent. The earlier fractions afforded the 3-aminocoumarins (**VIa,b_{1-4}**) as the minor product, while the later fractions gave the 4-aminomethylcoumarins (**$VIIa,b_{1-3,5}$**) as the major product. The products were then recrystallized from aqueous ethanol. *N*-Pyrrolidinyl-3-methyl-6-(methoxy or methyl)benzofuran-2-carboxamide (**VIIIa,b**) was isolated from the reaction of (**IIIa,b**) with pyrrolidine. Presented below are the yields, melting points, and the spectral properties of the different 3-amino- and 4-aminomethylcoumarines prepared using this method.

7-Methoxy-4-methyl-3-(*N*-piperidino)coumarin (VIa_1)

Yield 19%, mp 90-91 ^oC; IR (cm^{-1}): 1705 (C=O), 1615 (C=C); ^1H-NMR ($CDCl_3$) δ: 1.54 (br, 2H), 1.63 (br, 4H), 2.44 (s, 3H), 2.99 (br, 4H), 3.82 (s, 3H), 6.75 (d, *J* = 2.4 Hz, 1H), 6.81 (dd, *J* = 2.4, 8.8 Hz, 1H); 7.44 (d, *J* = 8.8 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ: 13.3, 24.0, 26.2, 51.1, 55.6, 100.4, 112.0, 114.6, 126.1, 133.1, 146.0, 153.4, 159.2, 161.4; HRMS exact molar mass calculated for $C_{16}H_{19}NO_3$ (M^+) 273.1364, found: 273.1336. Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found: C, 70.36; H, 7.25; N, 5.29.

7-Methoxy-4-methyl-3-(*N*-morpholino)coumarin (VIa_2)

Yield 13%, mp 170-171 ^oC; IR (cm^{-1}): 1711 (C=O), 1608 (C=C); ^1H-NMR ($CDCl_3$) δ: 2.48 (s, 3H), 3.08 (t, *J* = 4.6 Hz, 4H), 3.79 (t, *J* = 4.6 Hz, 4H), 3.84 (s, 3H), 6.76 (d, *J* = 2.4 Hz, 1H), 6.83 (dd, *J* = 2.4, 8.8 Hz, 1H); 7.47 (d, *J* = 8.8 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ: 13.3, 50.0, 55.7, 67.5, 100.5, 112.2, 114.2, 126.2, 131.4, 147.1, 153.4, 158.9, 161.7; HRMS exact molar mass calculated for $C_{15}H_{17}NO_4$ (M^+) 275.1157, found: 275.1137. Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.21; H, 6.53; N, 5.22.

7-Methoxy-4-methyl-3-(*N*-pyrrolidino)coumarin (VIa_4)

Yield 23%, mp 90-91 ^oC; IR (cm^{-1}): 1724 (C=O), 1608 (C=C); ^1H-NMR ($CDCl_3$) δ: 1.92 (t, *J* = 12.0 Hz,

4H), 2.41 (s, 3H), 3.10 (br, 4H), 3.82 (s, 3H), 6.76 (d, *J* = 2.3 Hz, 1H), 6.81 (dd, *J* = 2.3, 8.7 Hz, 1H), 7.44 (d, *J* = 8.7 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ: 13.5, 26.0, 50.6, 55.7, 100.3, 112.0, 114.6, 125.9, 130.1, 147.3, 153.2, 159.0, 161.2; MS ($C_{15}H_{17}NO_3$), *m*/*z* (% rel. int.): 259 (M^+, 100), 231 (22), 190 (11), 174 (14), 162 (8); Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.34; H, 6.51; N, 5.62.

4,7-Dimethyl-3-(*N*-thiomorpholino)coumarin (VIb$_3$)

Yield 9%, mp 152-154 °C; IR (cm^{-1}): 1711 (C=O), 1615 (C=C); ^{1}H-NMR ($CDCl_3$) δ: 2.40 (s, 3H), 2.45 (s, 3H), 2.74 (br, 4H), 3.30 (br, 4H), 7.05 (br, 1H), 7.07 (s, 1H), 7.44 (d, *J* = 8.5 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ: 13.5, 21.5, 28.5, 52.3, 116.7, 118.3, 125.0, 125.3, 134.3, 141.5, 146.1, 151.8, 159.3; MS ($C_{15}H_{17}NO_2S$), *m*/*z* (% rel. int.): 275 (M^+, 100), 215 (24), 189 (16), 174 (48), 145 (18), 115 (16); Anal. Calcd for $C_{15}H_{17}NO_2S$: C, 65.43; H, 6.22; N, 5.09; S, 11.64. Found: C, 65.42; H, 6.22; N, 4.77; S, 11.72.

4,7-Dimethyl-3-(*N*-pyrrolidino)coumarin (VIb$_4$)

Yield 22%, mp 91-93 °C; IR (cm^{-1}): 1724 (C=O), 1608 (C=C); ^{1}H-NMR ($CDCl_3$) δ: 1.93 (quint, *J* = 3.2 Hz, 4H), 2.38 (s, 3H), 2.41 (s, 3H), 3.14 (t, *J* = 6.4 Hz, 4H), 7.02 (br, 1H), 7.04 (s, 1H), 7.40 (d, *J* = 8.6 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ: 13.6, 21.4, 26.0, 50.9, 116.5, 118.6, 124.7, 125.2, 131.3, 140.8, 146.5, 151.6, 158.8; MS ($C_{15}H_{17}NO_2$), *m*/*z* (% rel. int.): 243 (M^+, 100), 215 (55), 174 (37), 145 (13), 115 (15); Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 74.02; H, 7.06; N, 5.78.

7-Methoxy-4-(*N*-piperidinomethyl)coumarin (VIIa$_1$)

Yield 65%, mp 114-115 °C; IR (cm^{-1}): 1724 (C=O), 1608 (C=C); ^{1}H-NMR ($CDCl_3$) δ: 1.43 (br, 2H), 1.57 (br, 4H), 2.43 (br, 4H), 3.51 (s, 2H), 3.84 (s, 3H), 6.34 (s, 1H), 6.78 (d, *J* = 2.4 Hz, 1H), 6.81 (dd, *J* = 2.4, 8.8 Hz, 1H), 7.74 (d, *J* = 8.8 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ: 24.0, 25.9, 54.9, 55.7, 59.9, 100.8, 111.8, 112.1, 112.7, 125.9, 151.8, 155.7, 161.4, 162.5; HRMS exact molar mass calculated for $C_{16}H_{19}NO_3$ (M^+) 273.1364, found: 273.1397; Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found: C, 70.34; H, 7.33; N, 5.29.

7-Methoxy-4-(*N*-morpholinomethyl)coumarin(VIIa$_2$)

Yield 80%, mp 129-131 °C; IR (cm^{-1}): 1705 (C=O), 1615 (C=C); ^{1}H-NMR ($CDCl_3$) δ: 2.50 (t, *J* = 4.5 Hz, 4H), 3.55 (s, 2H), 3.68 (t, *J* = 4.5 Hz, 4H), 3.83 (s, 3H), 6.32 (s, 1H), 6.77 (d, *J* = 2.4 Hz, 1H), 6.80 (dd, *J* = 2.4, 8.8 Hz, 1H), 7.70 (d, *J* = 8.8 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ: 53.8, 55.7, 59.5, 66.9, 100.9, 112.0, 112.2, 112.4, 125.8, 151.5, 155.7, 161.2, 162.6; HRMS exact molar mass calculated for $C_{15}H_{17}NO_4$ (M^+) 275.1157, found: 275.1179; Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.21; H, 6.32; N, 5.21.

7-Methoxy-4-[2-(*N*-pyridyl)-*N*-benzylaminomethyl]coumarin (VIIa$_5$)

Yield 25%, mp 127-128 °C; IR (cm^{-1}): 1705 (C=O), 1615 (C=C); ^{1}H-NMR ($CDCl_3$) δ: 3.84 (s, 3H), 4.74 (s, 2H), 4.96 (d, *J* = 0.9 Hz, 2H), 6.08 (s, 1H), 6.79 (d, *J* = 2.5 Hz, 1H), 6.82 (br, 1H), 7.49 (d, *J* = 9.2 Hz, 1H), 6.49-8.15 (m, 9H); ^{13}C-NMR ($CDCl_3$) δ: 48.0, 51.6, 55.8, 101.0, 105.9, 109.4, 111.9, 112.4, 113.3, 124.7, 126.7, 127.4, 128.8, 137.3, 137.8, 148.1, 151.9, 155.6, 157.6, 161.5, 162.7; MS ($C_{23}H_{20}N_2O_3$), *m*/*z* (% rel. int.): 372 (M^+, 34), 330 (30), 253 (43), 239 (7), 183 (100), 149 (14), 105 (10), 91 (80); Anal. Calcd for $C_{23}H_{20}N_2O_3$: C, 74.18; H, 5.41; N, 7.52. Found: C, 74.32; H, 5.56; N, 7.63.

7-Methyl-4-(*N*-thiomorpholinomethyl)coumarin (VIIb$_3$)

Yield 83%, mp 136-138 °C; IR (cm^{-1}): 1711 (C=O), 1621 (C=C); ^{1}H-NMR ($CDCl_3$) δ: 2.39 (s, 3H), 2.64 (br, 4H), 2.74 (br, 4H), 3.57 (s, 2H), 6.40 (s, 1H), 7.04 (d, *J* = 8.0 Hz, 1H), 7.08 (s, 1H), 7.61 (d, *J* = 8.0 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ: 21.6, 28.0, 55.3, 59.5, 113.6, 116.3, 117.2, 124.3, 125.3, 142.9, 151.9, 153.8, 161.2; MS ($C_{15}H_{17}NO_2S$), *m*/*z* (% rel. int.): 275 (M^+, 65), 214 (15), 186 (18), 174 (100); Anal. Calcd for $C_{15}H_{17}NO_2S$: C, 65.43; H, 6.22; N, 5.09; S, 11.64. Found: C, 65.46; H, 6.20; N, 4.98; S, 11.71.

7-Methyl-4-[2-(*N*-pyridyl)-*N*-benzylaminomethyl]coumarin (VIIb$_5$)

Yield 35%, mp 155-156 °C; IR (cm^{-1}): 1705 (C=O), 1615 (C=C); ^{1}H-NMR ($CDCl_3$) δ: 2.42 (s, 3H), 4.76 (s, 2H), 4.99 (s, 2H), 6.16 (s, 1H), 7.06 (d, *J* = 8.0 Hz, 1H), 7.14 (s, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 6.49-8.15 (m, 9H); ^{13}C-NMR ($CDCl_3$) δ: 21.6, 48.4, 53.2, 101.0, 108.1, 108.6, 112.4, 116.1, 117.3, 121.3, 123.7, 125.3, 133.4, 142.8, 146.8, 147.8, 153.6, 153.8, 161.4; MS ($C_{23}H_{20}N_2O_2$), *m*/*z* (% rel. int.): 356 (M^+, 23), 315 (9), 265 (15), 236 (20), 183 (100)

4-Aminomethylcoumarins (VIIb$_{2,4,6}$), general procedure

A mixture of 0.51 g (2 mmol) of 4-bromomethyl-7-methylcoumarin (**Xb**), 5 mmol of the appropriate amine (**V**)$_{2,4,6}$ and 15 mL of dry benzene was refluxed for 4-10 h. The solvent was removed under vacuum and the residue was washed with water, to remove the ammonium salt, and recrystallized from ethanol.

7-Methyl-4-(*N*-morpholinomethyl)coumarin (VIIb$_2$)

Yield 87%, mp 138-139 °C (lit.,[11] 141); IR (cm^{-1}): 1711 (C=O), 1621 (C=C); ^{1}H-NMR ($CDCl_3$) δ: 2.41 (s, 3H), 2.51 (t, *J* = 4.5 Hz, 4H), 3.58 (s, 2H), 3.70 (t, *J* = 4.5 Hz, 4H), 6.45 (s, 1H), 7.05 (d, *J* = 8.0 Hz, 1H), 7.11 (s, 1H), 7.67 (d, *J* = 8.0 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ: 21.6, 53.8, 59.2, 66.9, 113.9, 116.3, 117.2, 124.4, 125.3, 142.9, 151.5, 153.9, 161.2; MS ($C_{15}H_{17}NO_3$), *m*/*z* (% rel. int.): 259 (M^+, 10), 214 (5), 186 (12), 174 (100); Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.62; H, 6.55; N, 5.34.

7-Methyl-4-(*N*-pyrrolidinomethyl)coumarin (VIIb$_4$)

Yield 53%, mp 74-75 °C; IR (cm^{-1}): 1706 (C=O), 1621 (C=C); ^{1}H-NMR ($CDCl_3$) δ: 2.41 (s, 3H), 1.81 (quint, *J* = 3.0 Hz, 4H), 2.61 (t, *J* = 15.0 Hz, 4H), 3.75 (s, 2H), 6.45 (s, 1H), 7.07 (d, *J* = 8.0 Hz, 1H), 7.12 (s, 1H), 7.67 (d, *J* = 8.0 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ: 21.6, 23.7, 54.5, 56.4, 113.6, 116.4, 117.2, 124.4, 125.3, 142.8, 153.8, 153.9, 161.4; MS ($C_{15}H_{17}NO_2$), *m*/*z* (% rel. int.): 243 (M^+, 47), 174 (100), 146 (55), 70 (48); Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 74.02; H, 7.06; N, 5.79.

7-Methyl-4-(*N*-piperonylinomethyl)coumarin (VIIb$_6$)

Yield 71%, mp 143-144 °C; IR (cm^{-1}): 3330 (N−H), 1711 (C=O), 1615 (C=C); ^{1}H-NMR ($CDCl_3$) δ: 2.39 (s, 3H), 3.77 (s, 2H), 3.88 (s, 2H), 5.91-6.83 (m, 3H), 6.49 (s, 1H), 7.04 (d, *J* = 8.0 Hz, 1H), 7.09 (s, 1H), 7.46 (d, *J* = 8.0 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ: 21.6, 48.4, 53.2, 101.1, 108.1, 108.6, 112.3, 116.1, 117.3, 121.3, 123.7, 125.3, 133.4, 142.8, 146.8, 147.8, 153.6, 153.8, 161.4; MS ($C_{19}H_{17}NO_4$), *m*/*z* (% rel. int.): 323 (M^+, 27), 149 (37), 135 (100); Anal. Calcd for $C_{19}H_{17}NO_4$: C, 70.58; H, 5.30; N, 4.33. Found: C, 70.28; H, 5.29; N, 3.91.

***N*-Pyrrolidinyl-6-methoxy-3-methylbenzofuran-2-carboxamide (VIIIa$_4$)**

Yield 9.5%, mp 126-127 ^{o}C; IR (cm^{-1}): 1615 (C=O), 1602 (C=C); ^{1}H-NMR ($CDCl_3$) δ: 1.91 (m, 4H), 2.51 (s, 3H), 3.63 (t, *J* = 6.5 Hz, 2H), 3.82 (s, 3H), 3.86 (t, *J* = 6.5 Hz, 2H), 6.88 (dd, *J* = 2.0, 8.5 Hz, 1H), 6.92 (d, *J* = 2.0 Hz, 1H), 7.42 (d, *J* = 8.5 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ: 9.4, 23.8, 26.6, 46.8, 47.9, 55.7, 95.4, 112.4, 120.9, 122.7, 122.8, 143.8, 154.5, 159.7, 160.3; MS ($C_{15}H_{17}NO_3$), *m*/*z* (% rel. int.): 259 (M^+, 100), 189 (75); Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.80; H, 7.68; N, 5.09.

***N*-Pyrrolidinyl-3,6-dimethylbenzofuran-2-carboxamide (VIIIb$_4$)**

Yield 13%, mp 127-129 ^{o}C; IR (cm^{-1}): 1615 (C=O), 1608 (C=C); ^{1}H-NMR ($CDCl_3$) δ: 1.93 (m, 4H), 2.45 (s, 3H), 2.52 (s, 3H), 3.86 (t, *J* = 6.5 Hz, 2H), 3.90 (t, *J* = 6.5 Hz, 2H), 7.08 (d, *J* = 8.0 Hz, 1H), 7.22 (s, 1H), 7.45 (d, *J* = 8.0 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ: 9.4, 21.8, 23.8, 26.5, 46.8, 48.0, 111.65, 120.1, 122.4, 124.4, 126.9, 136.9, 144.0, 153.8, 160.2; MS ($C_{15}H_{17}NO_2$), *m*/*z* (% rel. int.): 243 (M^+, 85), 200 (15), 187 (40); Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 74.02; H, 7.06; N, 5.79.

Coumarlic acids (IXa,b), general procedure

By a modified procedure,[21] 1 g of 7-substituted 3-bromo-4-methylcoumarin (**IIIa,b**) was refluxed with 50 mL of 10% ethanolic potassium hydroxide (100 mmol) for 2 h. The product was obtained on acidification of the diluted solution, filtered, washed with water, and recrystallized from ethanol.

6-Methoxy-3-methylcoumarlic acid (IXa)

Yield 85%, mp 190 ^{o}C. (lit.,[21] 186); IR (cm^{-1}): 1672 (C=O), 1615 (C=C); ^{1}H-NMR (DMSO-d_6) δ: 2.43 (s, 3H), 3.77 (s, 3H), 6.90 (d, *J* = 8.5 Hz, 1H), 7.16 (s, 1H), 7.56 (d, *J* = 8.5 Hz, 1H), 13.16 (s, 1H); ^{13}C-NMR (DMSO-d_6) δ: 9.6, 56.1, 96.1, 113.5, 122.2, 122.4, 125.4, 140.9, 155.5, 160.7, 161.5; MS ($C_{11}H_{10}O_4$), *m*/*z* (% rel. int.): 206 (M^+, 100), 190 (100), 163 (17), 132 (5), 88 (15).

6-Methyl-3-methylcoumarlic acid (IXb)

Yield 87%, mp 218-220 ^{o}C. (lit.,[27] 216-219); IR (cm^{-1}): 1672 (C=O), 1615 (C=C); ^{1}H-NMR (DMSO-d_6) δ: 2.38 (s, 3H), 2.43 (s, 3H), 7.09 (d, *J* = 8.0 Hz, 1H), 7.35 (s, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 13.29 (s, 1H); ^{13}C-NMR (DMSO-d_6) δ: 9.6, 21.8, 112.1, 121.3, 124.9, 125.2, 126.7, 138.5, 141.1, 154.4, 161.6; MS ($C_{11}H_{10}O_3$), *m*/*z* (% rel. int.): 190 (M^+, 100), 173 (12), 145 (77), 115 (44), 90 (27).

***N*-Pyrrolidinyl-6-(methoxy or methyl)benzofuran-2-carboxamide (VIIIa,b$_4$), general procedure**

To 5 mmol of dried acids (**IXa,b**), 5 mL (70 mmol) of thionyl chloride was added and the mixture was heated at gentle reflux for 30 min and excess thionyl chloride was removed under vacuum. To the residual acid chloride, 5 mL of pyridine followed by 0.85 g (12 mmol) of pyrrolidine was added and the mixture was stirred at rt for 3 h. The product was precipitated in water, filtered and then recrystallized from aqueous ethanol. Yields of **VIIIa$_4$** and **VIIIb$_4$** 54% and 48%, respectively.

4-Bromomethyl-7-methoxycoumarin (Xa) and 4-bromomethyl-7-methylcoumarin (Xb)

These compounds were prepared according to literature procedure.[20]

Di-[4-substitutedcoumarinomethyl]-1,4-diamines (XIa,b and XIIa,b), general procedure

A mixture of 2 mmol of 4-bromomethylcoumarins (**Xa,b**), 1 mmol with piperazine (86 mg) or with *N*,*N*`-diethyl-2-butene-1,4-diamine (142 mg) and 2 mL (14 mmol) of triethylamine was refluxed in 20 mL of dry benzene for 24 h. The solvent was removed under vacuum and the residue was washed with water and recrystallized from ethanol.

1,4-Di-(7-methoxy-4-coumarinmethyl)piperazine (XIa)

Yield 73%, mp 257-260 °C; IR (cm^{-1}): 1717 (C=O), 1615 (C=C); ^{1}H-NMR ($CDCl_3$) δ: 2.56 (s, 8H), 3.58 (s, 4H), 3.48 (s, 6H), 6.35 (s, 2H), 6.80 (dd, *J* = 2.5, 8.5 Hz, 2H), 6.84 (d, *J* = 2.5 Hz, 2H), 7.70 (d, *J* = 8.5 Hz, 2H); ^{13}C-NMR ($CDCl_3$) δ: 53.4, 55.7, 58.9, 100.8, 111.7, 112.3, 112.4, 125.8, 152.1, 155.6, 161.5, 162.6; MS ($C_{26}H_{26}N_2O_6$) *m/z* (% rel. int.): 462 (M^+, 100), 284 (55), 229 (22), 189 (72), 161 (20); Anal. Calcd for $C_{26}H_{26}N_2O_6$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.68; H, 5.32; N, 6.16.

1,4-Di-(7-methyl-4-coumarinmethyl)piperazine (XIb)

Yield 75%, mp 257-259 °C. IR (cm^{-1}): 1711 (C=O), 1615 (C=C); ^{1}H-NMR ($CDCl_3$) δ: 2.42 (s, 6H), 2.58 (s, 8H), 3.61 (s, 4H), 6.47 (s, 2H), 7.07 (d, *J* = 8.0 Hz, 2H), 7.13 (s, 2H), 7.65 (d, *J* = 8.0 Hz, 2H); ^{13}C-NMR ($CDCl_3$) δ: 21.6, 53.4, 58.6, 113.7, 116.4, 117.2, 124.3, 125.3, 142.9, 151.9, 153.9, 161.4; MS ($C_{26}H_{26}N_2O_4$) *m/z* (% rel. int.): 430 (M^+, 100), 269 (35), 228 (15), 174 (34), 145 (25), 115 (13); Anal. Calcd for $C_{26}H_{26}N_2O_4$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.38; H, 6.21; N, 6.72.

***N*,*N*`-Diethyl-*N*,*N*`-di-(7-methoxy-4-coumarinmethyl)-2-butene-1,4-diamine (XIIa)**

Yield 60%, mp 125-127 °C; IR (cm^{-1}): 1705 (C=O), 1602 (C=C); ^{1}H-NMR ($CDCl_3$) δ: 1.00 (t, *J* = 7.0 Hz, 6H), 2.49 (q, *J* = 7.0 Hz, 4H), 3.09 (d, *J* = 4.7 Hz, 4H), 3.54 (s, 4H), 3.48 (s, 6H), 5.65 (s, 2H), 6.40 (s, 2H), 6.42 (dd, *J* = 2.5, 9.5 Hz, 2H), 6.74 (d, *J* = 2.5 Hz, 2H), 7.56 (d, *J* = 9.5 Hz, 2H); ^{13}C-NMR ($CDCl_3$) δ: 12.0, 48.4, 54.1, 55.7, 55.9, 100.8, 111.3, 111.9, 112.3, 125.2, 130.8, 154.0, 155.3, 161.7, 162.4; MS ($C_{30}H_{34}N_2O_6$) *m/z* (% rel. int.): 518 (M^+, 7), 328 (94), 284 (100), 231 (25), 189 (96), 161 (21), 140 (59); Anal. Calcd for $C_{30}H_{34}N_2O_6$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.23; H, 6.57; N, 5.63.

***N*,*N*`-Diethyl-*N*,*N*`-di-(7-methyl-4-coumarinmethyl)-2-butene-1,4-diamine (XIIb)**

Yield 54%, mp 136-137 °C; IR (cm^{-1}): 1711 (C=O), 1621 (C=C); ^{1}H-NMR ($CDCl_3$) δ: 0.98 (t, *J* = 7.0 Hz, 3H), 2.38 (s, 3H), 2.48 (q, *J* = 7.0 Hz, 2H), 3.09 (d, *J* = 4.0 Hz, 2H), 3.65 (s, 2H), 5.65 (s, 1H), 6.49 (s, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 7.01 (s, 1H), 7.51 (d, *J* = 8.0 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ: 12.0, 21.6, 48.4, 53.8, 55.9, 113.2, 116.2, 117.1, 123.8, 125.2, 130.8, 142.6, 153.6, 153.9, 161.5; MS ($C_{30}H_{34}N_2O_4$) *m/z* (% rel. int.): 486 (M^+, 14), 313 (80), 269 (100), 230 (20), 216 (25), 174 (50), 146 (23), 140 (55); Anal. Calcd for $C_{30}H_{34}N_2O_4$: C, 74.05; H, 7.04; N, 5.76. Found: C, 74.05; H, 7.05; N, 5.75.

REFERENCES

1. R. D. H. Murray, J. Mendenz, and S. A. Bouwn, *The Natural Coumarins*, Wiley, New York, 1982.
2. S. Sardari, Y, Mori, K. Horita, R. G. Micetich, S. Nishibe, and M. Daneshtalab, *Bioorg. Med. Chem.*, 1999, **7**, 1933.

3. M. S. Y. Khan and P. Sharma, *Indian J. Chem.*, 1993, **32**, 817.
4. L. Xie, Y. Takeuchi, L. M. Cosentino, A. T. MacPhail, and H. K. Lee, *J. Med. Chem.*, 2001, **44**, 664.
5. R. O'Kennedy and R. D. Thornes, *Coumarins*: *Biology, Application and Mode of Action*, Wiley & Sons, Chichester, 1997.
6. M. Zahradnik, *The Production and Application of Florescent Brightening Agents*, Wiley & Sons, 1992.
7. C. Antonello, F. Carlassare, P. Malfer, and P. Siliprandi, *Farmaco. Ed. Sci.*, 1974, **29**, 697.
8. S. A. Essawy, M. Y. El-Kady, S. G. Donia, and A. I. El-Shenawy, *Egyptian J. Chem.*, 1994, **37**, 381.
9. S. D Joshi and R. N. Usgaonkar, *Indian J. Chem.*, 1982, **21**, 399.
10. D. Desai and R. H. Mehta, *Indian J. Heterocycl. Chem.*, 2004, **13**, 355.
11. R. M. Kelkar, U. K. Joshi, and M. V. Paradkar, *Synthesis*, 1986, **3**, 214.
12. I. E. El-Kholy, M. M. Mishrikey, and H. M. Feid-Allah, *J. Heterocycl. Chem.*, 1981, **18**, 105.
13. K. S. M. Salih, K. H. Al-Zghoul, M. S. Mubarak, and M. T. Ayoub, *J. Saudi Chem. Soc.*, in press.
14. B. J. Ghiya and M. G. Marathey, *J. Indian Chem. Soc.*, 1965, **42**, 229.
15. J. V. Dalvi and S. Sethana, *J. Indian Chem. Soc.*, 1949, **26**, 360.
16. S. R. Ghantwal and S. D. Samant, *Indian J. Chem.*, 1999, **38**, 1242.
17. D. B. Limaye and N. V. Bhide, *Rasayanam*, 1938, **1**, 136 (*Chem. Abstr.*, 1939, **33**, 1699).
18. H. Y. Choi and D. Y. Chi, *Org. Lett.*, 2003, **5**, 411.
19. B. B. Dey and Y. Sankaranarayanan, *J. Indian Chem. Soc.*, 1934, **11**, 687.
20. H. Kimura, H. Sato, C. Tsuchiya, T. Chiba, and T. Kato, *Chem. Pharm. Bull.*, 1982, **30**, 552.
21. S. S. Lele and S. Sethna, *J. Org. Chem.*, 1958, **23**, 1731.
22. M. Ghate, D. Manohar, V. Kulkarani, R. Shobha, and S. Y. Kattimani, *Europ. J. Med. Chem.*, 2003, **38**, 297.
23. N-H. Nam, Y. Kim, Y-J. You, D-H. Hong, H-M. Kim, and B-Z. Ahn, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 2345.
24. S. J. Torrance, J. J. Hoffmann, and J. R. Cole, *J. Pharm. Soc.*, 1979, **68**, 664.
25. G. A. Cordell, *J. Nat. Prod.*, 1984, **47**, 84.
26. A. G. Osborne, *Tetrahedron*, 1981, **37**, 2021.
27. B. Sila, *Roczniki Chemii*, 1967, **41**, 399.