

Screening Search for Organic Fluorophores: Syntheses and Fluorescence Properties of 3-Azoly-7-diethylaminocoumarin Derivatives¹⁾

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In order to find a highly sensitive fluorophore, 3-azoly-7-diethylaminocoumarin derivatives were synthesized. Both the absorption and fluorescence maxima of the coumarin-thiazole compounds showed red shifts with increases of the molar absorptivities and fluorescence intensities, in comparison with those of the corresponding coumarin-oxazole compounds. Among them, 3-(5-ethoxycarbonyl-1,3-thiazol-2-yl)-7-diethylamino-2H-chromen-2-one (3e) was one of the most promising candidates as a fluorophore accessible for analytical purposes in the fields of analytical and biological chemistry.

Key words fluorophore; diethylaminocoumarin; thiazole; oxazole; molar absorptivity; fluorescence intensity

Since fluorescence is highly sensitive to physicochemical environments, a variety of organic fluorescent compounds (fluorophores) have been widely used in many scientific fields, for example, as analytical tools such as fluorescent labeling reagents,²⁾ fluorescence probes,³⁾ fluorescence sensors,⁴⁾ and laser dyes.⁵⁾ However, the development of more highly sensitive fluorophores is still required.

In previous papers, we have shown that the introduction of a phenyl group at the 3-position of the coumarin ring causes bathochromic shifts in absorption and fluorescence maxima with increases in the molar absorptivity and fluorescence intensity. We developed 7-diethylamino-3-[4-(bromomethyl)phenyl]-2H-chromen-2-one (MPAC-Br)^{2a)} and 4-(7-diethylaminocoumarin-3-yl)benzoyl cyanide (DACB-CN)¹⁾ which are among the most sensitive and practically useful fluorescent derivatization reagents for carboxylic acids and for alcohols, respectively. In order to develop more highly sensitive fluorophores, the introduction of an azole in the place of the phenyl group at the 3-position of a coumarin ring was considered.

There are a few examples of studies⁶⁾ on 3-(benzazol-2-yl)coumarin derivatives, but little is known about the systematic study of 3-azoly-substituted coumarins. This paper deals with the syntheses and spectroscopic properties of 3-azoly-7-diethylaminocoumarins as screening in our search for fluorophores.

Results and Discussion

Synthesis of Coumarin-oxazole Derivatives (2a—g, 4a—c, 5) Twenty-eight compounds, [F]-azole-R (2—8) were synthesized, in which [F] represented 7-diethylamino-2-oxo-2H-chromen-3-yl (*i.e.* 7-diethylaminocoumarin-3-yl) (Charts 1 and 2). 2-[F]-Oxazole-R, 2a and 2c—f were synthesized from 7-diethylaminocoumarin-3-carboxamide (9) and the corresponding α -halocarbonyl compounds, respectively, according to a modified method of Liu *et al.*⁷⁾ 2-[F]-Oxazole-R, 2b and 2g were prepared by cyclization of the corresponding aroylaminoethyl ketones (10a, 10b) with phosphorus oxychloride, respectively, according to Heinze's method.⁸⁾ 5-[F]-Oxazole-R 4a was obtained from 7-diethylaminocoumarin-3-carbaldehyde (11) and tosylmethyl isocyanide in the presence of potassium carbonate in poor yield. 5-[F]-Oxazole-R 4b and 4c were synthesized from 3-

azidomethylcarbonylcoumarin (13) and benzoyl chloride or ethyl (chlorocarbonyl)formate, respectively. 4-(Coumarin-3-yl)-oxazole derivative 5 was prepared by condensation of a 3-bromoacetylcoumarin derivative (12) with benzamide in the presence of boron trifluoride etherate.

Synthesis of Coumarin-thiazole Derivatives (3a—h, 6a—c) 2-[F]-Thiazole-R 3a, 3b, and 3d—g were synthesized from 7-diethylaminocoumarin-3-carbothioamide (14) and the corresponding α -halocarbonyl compounds according to the modified methods of the oxazole synthesis described above. 2-[F]-Thiazole-R, 3c and 3h were prepared by condensation of the corresponding aroylaminoethyl ketones (10a, 10b) with phosphorus pentasulfide. 4-[F]-Thiazole-R, 6a—c, were prepared by condensation of 3-bromoacetylcoumarin derivative (12) with thioacetamide, ethyl thioacetate, and thiobenzamide, respectively.

Synthesis of Coumarin-oxadiazole (7a—c) and Coumarin-thiadiazole Derivatives (8a—c) 2-[F]-Oxadiazole-R, 7a—c, were prepared by condensation of 7-diethylaminocoumarin-3-carbohydrazide (15) with ethyl orthoformate, trimethyl orthoacetate, and trimethyl orthobenzoate, respectively. Similarly, 2-[F]-thiadiazole-R, 8a—c, were obtained by condensation of coumarin-3-carbothiohydrazide (16) with ethyl orthoformate, trimethyl orthoacetate, and trimethyl orthobenzoate, respectively.

Absorption and Fluorescence Spectra Compound 1 was used as a standard sample for absorption and fluorescence spectra. The measurements of absorption and fluorescence spectra were carried out in ethanol solution at room temperature. Their spectroscopic properties, absorption maxima (λ_{\max}), molar absorptivities (ϵ), fluorescence maxima ($F\lambda_{\max}$), and the relative fluorescence intensities (RFI) are listed in Tables 1—3. The fluorescence sensitivity may be represented by the fluorescence intensity, that is, a peak-height at the fluorescence maximum. Unsubstituted [F]-azole-H, 2a, 3a, 4a, 7a, and 8a were defined as parent compounds (R=H) in 2-[F]-oxazole-R, 2-[F]-thiazole-R, 4-[F]-oxazole-R, 2-[F]-oxadiazole-R, and 2-[F]-thiadiazole-R series, respectively.

i) Influence of an Azole Introduction on the Spectroscopic Properties In comparison with the spectroscopic properties of the standard compound 1, both the absorption and fluorescence maxima (λ_{\max} and $F\lambda_{\max}$) of all the [F]-

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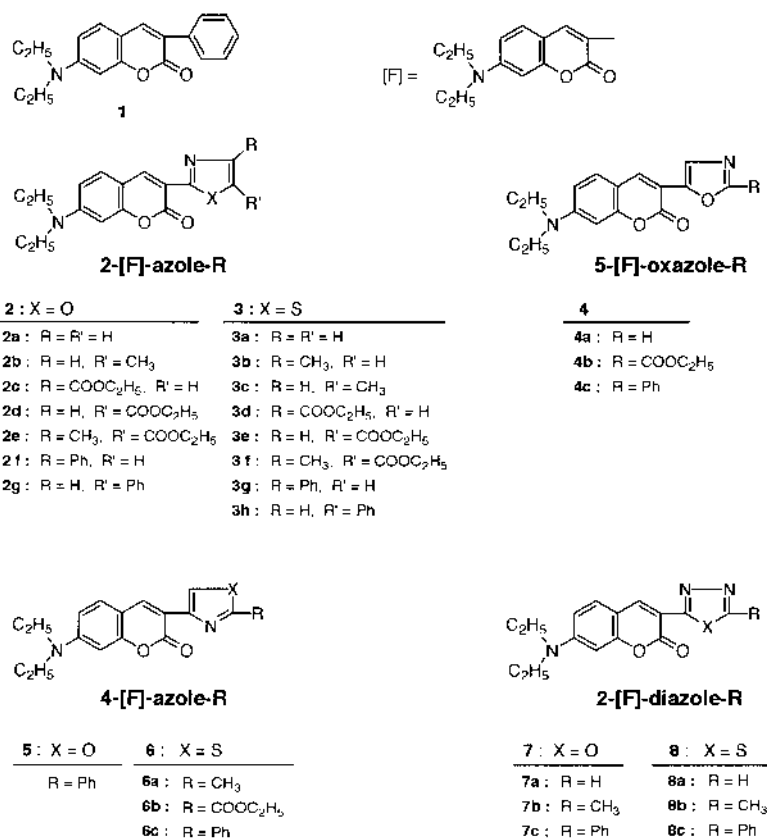


Chart 1

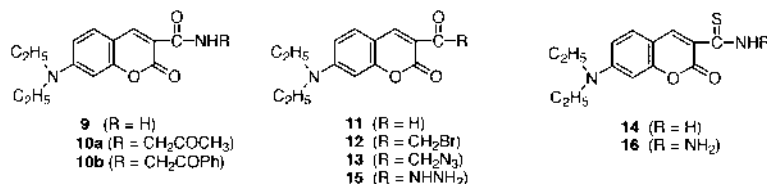


Chart 2

azole compounds (**2**—**8**) showed longer wavelength shifts, together with an increase in molar absorptivities (ϵ) (Tables 1—3). As for the relative fluorescence intensity (RFI), most of the azoles, except for 4-[F]-thiazoles (**6b**, **6c**) and 2-[F]-oxadiazoles (**7a**, **7b**), showed very similar or higher values than that of **1**.


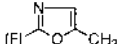
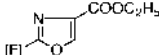
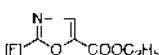
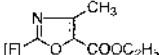
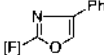
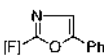

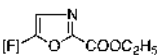
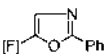
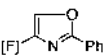

ii) Comparison of Spectroscopic Properties among [F]-Oxazoles, [F]-Thiazoles, and [F]-Diazoles Both the λ_{\max} 's and $F.\lambda_{\max}$'s of 2-[F]-thiazole-R **3** shifted to longer wavelengths, accompanied by increases of the ϵ values and enhanced RFI's, compared with those of the corresponding 2-[F]-oxazole-R **2** (Table 1 and Table 2). Also, in comparison with [F]-diazole themselves, the λ_{\max} 's and the $F.\lambda_{\max}$'s of **8** appeared at longer wavelengths, together with larger ϵ values and larger RFI's, compared with those of **7** (Table 3). In comparison among parent compounds themselves (2-[F]-azole-H; **2a**, **3a**, **7a**, and **8a**), the bathochromic and hypsochromic effects on the λ_{\max} and ϵ value in the absorption spectra decreased in the order of **8a** > **3a** > **7a** > **2a**, but the values of the $F.\lambda_{\max}$ and the RFI in the fluorescence spectra showed a tendency to decrease in the order of **3a** \cong **8a** > **2a** \cong **7a**. In the fluorescence spectra of diazoles, the values of the $F.\lambda_{\max}$ of **7a**

and **8a** were similar to those of **2a** and **3a**, respectively. Furthermore, as for the RFI of 2-[F]-diazole-H (**7a**, **8a**), marked decreases were observed in comparison with those of the corresponding 2-[F]-azole-H (**2a**, **3a**).

Thus, the influence on the spectroscopic properties (λ_{\max} , $F.\lambda_{\max}$, ϵ , RFI) of [F]-thiazoles was larger than those of [F]-oxazoles. This phenomenon may be explained in terms of the participation and delocalization of the lone pair of heteroatoms, predominantly *p* orbital electrons, on the basis of relative electronegativities of a sulfur and an oxygen atom. The extent of delocalization of the sulfur lone pair is larger than that of the oxygen one because of the higher nuclear charge of oxygen as compared with sulfur. Therefore, conjugation of the sulfur electrons with the four π electrons of the five-membered ring system is more complete than in the oxygen analogue. In addition, the low-lying *d* orbitals of sulfur play some role in the conjugation. As a result, thiazole compounds absorb at a longer wavelength than oxazole compounds. Such interpretation is put forward to explain the absorption spectra of five-membered heterocycles, in which thiophene absorbs at a longer wavelength than furan.⁹⁾

iii) Influence of the Positional Relation of [F] and a

Table 1. Spectral Properties of Coumarin-oxazole Derivatives (**2**, **4**, and **5**)

Compounds	Absorption ^{a)}		Fluorescence ^{b)}		
	λ_{\max} (nm)	ϵ	Ex (nm)	F. λ_{\max} (nm)	RFI ^{c)}
2a 	424	41100	424	481	1.02
2b 	425	42800	425	484	1.15
2c 	430	45200	430	483	0.96
2d 	443	48700	443	494	1.23
2e 	442	49700	442	493	1.49
2f 	428	43100	428	488	1.21
2g 	437	47300	437	498	1.32
4a 	422	40500	422	480	1.25
4b 	447	47900	447	504	1.45
4c 	433	46900	433	492	1.43
5 	411	38800	411	476	1.15
1 	398	34200	398	477	1.00


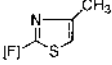
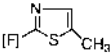
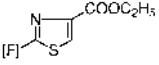
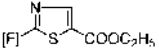
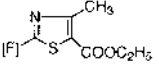


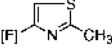
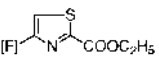


a) Concentration: 1.5×10^{-5} M. b) Concentration: 3.5×10^{-6} M. c) Relative fluorescence intensity: the fluorescence intensity of **1** is arbitrarily taken as 1.00.

Substituent (R) Connecting with an Azole Ring ([F]-azole-R) The influence of the connecting positions of two substituents ([F] and R) on an azole ring was investigated. The spectroscopic properties of four regioisomers of [F]-oxazole-Ph (positional isomers; **2f**, **2g**, **4c**, **5**) were compared (Table 4). The values of the λ_{\max} 's, the F. λ_{\max} 's, and the ϵ 's decreased in the order of 2-[F]-oxazole-5-Ph (**2g**) > 5-[F]-oxazole-2-Ph (**4c**) > 2-[F]-oxazole-4-Ph (**2f**) > 4-[F]-oxazole-2-Ph (**5**), but the order of the RFI's was **4c** > **2g** > **2f** > **5**. In [F]-thiazole-Ph, which is the sulfur analogue of the corresponding [F]-oxazole-Ph, a similar tendency was observed, in the order of **3h** > **3g** > **6c** for the λ_{\max} , the F. λ_{\max} , and the ϵ values, but in the order of **3g** = **3h** > **6c** for the RFI. Thus, in **2g**, **3h**, and **4c**, the presence of the conjugated system of a coumarin ring with a phenyl group through an azole ring was supported on the basis of their λ_{\max} 's appearing at longer wavelengths. However, both **5** and **6c** showed blue shifts in the λ_{\max} 's and F. λ_{\max} 's (**5**, λ_{\max} 411 nm, F. λ_{\max} 476 nm; **6c**, λ_{\max} 412 nm, F. λ_{\max} 477 nm), compared with compounds **2** and **3**. Also, in **6a**–**c** which contain the sulfur analogue of **5**, the λ_{\max} 's and F. λ_{\max} 's appeared at shorter wavelengths (λ_{\max} 408–418 nm, F. λ_{\max} 473–477 nm). Such blue shifts (hypsochromic effect) in the spectra of **5** and **6** seem to result from the conjugation of a coumarin ring with only a carbon–

carbon double bond moiety in an azole ring, not of the coumarin ring with a whole azole ring.


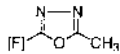
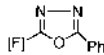

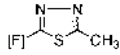
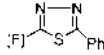

iv) Influence of Methyl, Ethoxycarbonyl, and Phenyl Substituents on an Azole Ring In order to determine the influence of each substituent, the spectroscopic properties of [F]-oxazole-R and [F]-thiazole-R (R = COOC₂H₅, Ph, CH₃) were compared with those of the corresponding parent compounds [F]-azole-H, respectively. In the substituent, the influence of 5-substituted compounds (2-[F]-thiazole-5-R; **3a**, **3c**, **3e**, **3h**), the values of the λ_{\max} 's and the ϵ 's decreased in the order of R = COOC₂H₅ > Ph > CH₃ > H, but on the F. λ_{\max} in the order of R = COOC₂H₅ \cong Ph > H \cong CH₃. In 4-substituted compounds (2-[F]-thiazole-4-R), a similar tendency was observed. Thus, the ethoxycarbonyl substituent had the largest influence on the absorption and fluorescence properties. As for the methyl substituent ([F]-azole-5-CH₃; **2b**, **3c**, **7b**, and **8b**), the spectral values were either the same or slightly larger than those of the parent compounds (**2a**, **3a**, **7a**, **8a**), respectively. In addition, a methyl group at the 4-position of a thiazole ring had little influence on spectral properties. Also, in the cases of **2e** and **3f**, which have both an ethoxycarbonyl group and a methyl group, the values of the λ_{\max} , the F. λ_{\max} , and the ϵ were similar to those of **2d** and **3e**, having only an ethoxycarbonyl group, respectively. Thus, the introduction of

Table 2. Spectral Properties of Coumarin-thiazole Derivatives (**3** and **6**)

Compounds	Absorption ^{a)}		Fluorescence ^{b)}		
	λ_{\max} (nm)	ϵ	Ex (nm)	F. λ_{\max} (nm)	RFI ^{c)}
3a 	437	45100	437	495	1.42
3b 	437	45500	437	496	1.40
3c 	439	45500	439	493	1.40
3d 	449	50200	449	494	1.52
3e 	463	60100	463	512	1.93
3f 	463	59000	463	508	1.93
3g 	441	46400	441	498	1.47
3h 	453	54100	453	511	1.47
6a 	408	38900	408	475	1.16
6b 	418	39900	418	473	0.05
6c 	412	40100	412	477	0.72
1 	398	34200	398	477	1.00

a) Concentration: 1.5×10^{-5} M. b) Concentration: 3.5×10^{-6} M. c) Relative fluorescence intensity: the fluorescence intensity of **1** is arbitrarily taken as 1.00.

Table 3. Spectral Properties of Coumarin-diazole Derivatives (**7** and **8**)

Compounds	Absorption ^{a)}		Fluorescence ^{b)}		
	λ_{\max} (nm)	ϵ	Ex (nm)	F. λ_{\max} (nm)	RFI ^{c)}
7a 	429	44300	429	480	0.35
7b 	428	44300	428	481	0.47
7c 	437	50800	437	488	1.02
8a 	446	48600	446	494	1.01
8b 	446	48600	446	493	1.23
8c 	458	58500	458	502	1.86
1 	398	34200	398	477	1.00

a) Concentration: 1.5×10^{-5} M. b) Concentration: 3.5×10^{-6} M. c) Relative fluorescence intensity: the fluorescence intensity of **1** is arbitrarily taken as 1.00.

Table 4. Comparison of Spectral Properties among Four [F]-Oxazole-Ph





				
λ_{\max} (nm)	437	433	428	411
ϵ	47300	46900	43100	38800
$F.\lambda_{\max}$ (nm)	498	492	488	476
RFI	1.32	1.43	1.21	1.15

Table 5. Relative Quantum Yields of Selected Coumarin-thiazoles and Coumarin-oxazoles

Compounds	Excitation wavelengths (nm)	Relative quantum yields ^{a)}
1	398	1.59
2a	424	1.03
2b	430	1.17
2d	443	0.80
2g	430	1.09
3a	437	1.15
3c	445	1.12
3e	465	1.04
3h	445	1.02

^{a)} The quantum yield of fluorescein in 0.1 N NaOH solution is arbitrarily taken as 1.00.

a methyl substituent on the azole ring had little influence on spectral properties in both the oxazole and thiazole series.

Next, the influence of the position of a substituent at the 4- or 5-position on an azole ring was examined. In 2-[F]-azole-COOC₂H₅, 5-substituted compounds (**2d**, **3e**) showed larger λ_{\max} values, $F.\lambda_{\max}$'s, and ϵ 's in comparison with 4-substituted compounds (**2c**, **3d**; 2-[F]-azole-4-COOC₂H₅). In comparisons between 4- and 5-substituted compounds themselves in the oxazole and thiazole series, the influence of an ethoxycarbonyl or a phenyl substituent in the 5-position was greater than that of the same substituent in the 4-position. Such influence of an ethoxycarbonyl group was also observed in the structure of **4b**, which is a positional isomer of **2d**.

In general, the introduction of an electron-withdrawing substituent at the 5-position on 2-[F]-azoles caused bathochromic shifts, with larger ϵ and enhanced RFI. This suggests the correlation of a push-pull system between a C7-electron donating group on a coumarin ring and a C5-electron-withdrawing group on an azole ring. Such a correlation may be explained analogously to that of a push-pull system between a C7-electron donating group and a C3-electron-withdrawing group on the coumarin ring.^{2a,10)}

v) Quantum Yields of Selected Coumarin-azoles

The quantum yields of selected coumarin-thiazoles and coumarin-oxazoles showed smaller values than that of **1** (Table 5). Compared with the parent compounds themselves, the quantum yield of **3a** showed a slightly larger value than that of **2a**. Other 2-[F]-thiazole-R (**3c**, **3e**, **3h**) also showed similar values to the corresponding 2-[F]-oxazole-R (**2b**, **2g**), except for **2d**. It was difficult to explain why the quantum yield of **2d** showed a lower value than those of the other 2-[F]-azole-R (**2b**, **2g** and **3c**, **3e**, **3h**).

In conclusion, among the coumarin-azoles synthesized in

this study, 2-[F]-thiazoles (**3**) were found to be most appropriate to fluorophore for fluorometric analysis, and the introduction of an electron-withdrawing substituent at the 5-position in this system would predominantly contribute to the enhancement of the relative fluorescence intensity of 7-diethylamino-3-thiazol-4-yl-chromen-2-one. Therefore, in the molecular design of strongly fluorescing coumarin-azoles, 2-[F]-thiazole-R **3** is one of the most promising candidates as a fluorophore from the viewpoint of larger molar absorptivity and stronger fluorescence intensity. Of these, **3e** showed the largest molar absorptivity and the highest fluorescence intensity. In addition, some of the coumarin-azoles synthesized in this study may serve as fluorophores for new application in various science fields, since they have excitation maxima at a longer wavelength region, being above 400 nm.

Experimental

All melting points were determined on a Yamato melting point apparatus (model MP-21) and are uncorrected. Infrared spectra (IR) were recorded on a JASCO FT/IR-300 spectrometer. Nuclear magnetic resonance spectra (NMR) were taken on JEOL JNM-LA-300 and JEOL JNM-EX-400 spectrometers. Mass spectra (MS) were measured with a Shimadzu GC MS-9100-MK gas chromatograph-mass spectrometer with a direct inlet system. Absorption and fluorescence spectra were measured with a Hitachi 288 dual-wavelength spectrophotometer, and a Hitachi F-4100 fluorescence spectrophotometer. Fluorescence quantum yields were measured with a Hitachi F-4500 fluorescence spectrometer equipped with an R928 photomultiplier (200–900 nm), and were determined according to the method of Parker and Rees,¹¹⁾ as reported previously,¹²⁾ in which fluorescein (uranine) in 0.1 N NaOH solution was used as a standard.¹³⁾

Materials and Methods Fluorescein sodium (uranine, JIS special grade reagent) and ethanol (for fluorometry, Uvasol) were purchased from Kanto Chemical Co., Inc.

7-Diethylamino-3-phenyl-2H-chromen-2-one (1) Compound **1** was synthesized according to the procedure described in a previous paper.^{2a)}

7-Diethylamino-2-oxo-2H-chromene-3-carboxamide (9) Compound **9** was obtained by ammonolysis of coumarin-3-carboxylic acid ester (ethyl 7-diethylamino-2-oxo-2H-chromene-3-carboxylate; 4.0 g, 13.8 mmol) with 25% NH₄OH (90 ml) in DMF (90 ml) at room temperature for 16 h. Yield, 82%, mp 218–219 °C (lit.,¹⁴⁾ mp 229–230 °C). ¹H-NMR (CDCl₃) δ : 1.24 (t, 6H, $J=7.2$ Hz, -N(CH₂CH₃)₂), 3.46 (q, 4H, $J=7.2$ Hz, -N(CH₂CH₃)₂), 5.76 (s, 1H, -NH₂), 6.50 (d, 1H, $J=2.4$ Hz, aromH), 6.64 (dd, 1H, $J=2.4$ Hz, 9.0 Hz, aromH), 7.42 (d, 1H, $J=9.0$ Hz, aromH), 8.55 (s, 1H, -NH₂), 8.71 (s, 1H, aromH). IR (Nujol) cm⁻¹: 1640, 1710. MS m/z : 260 (M⁺).

N-(2-Oxopropyl)-7-diethylamino-2-oxo-2H-chromene-3-carboxamide (10a) Isobutyl chloroformate (273 mg, 2.2 mmol) was added to a solution of coumarin-3-carboxylic acid (7-diethylamino-2-oxo-2H-chromene-3-carboxylic acid; 520 mg, 2.0 mmol) and triethylamine (404 mg, 4.0 mmol) in THF at room temperature, and stirred for several min. Powdered aminoacetone hydrochloride¹⁵⁾ was added to the mixture, and the reaction mixture was further stirred for 16 h. After evaporating THF *in vacuo*, the residue was chromatographed on silica gel using AcOEt as the eluent to give **10a**. Yellow needles (from EtOH), yield 56%, mp 186–188 °C. ¹H-NMR (CDCl₃) δ : 1.24 (t, 6H, $J=7.2$ Hz, -N(CH₂CH₃)₂), 2.24 (s, 3H, -CH₃), 3.45 (q, 4H, $J=7.2$ Hz, -N(CH₂CH₃)₂), 4.30 (d, 2H, $J=4.8$ Hz, -CH₂-), 6.50 (d, 1H, $J=2.4$ Hz, aromH), 6.64 (dd, 1H, $J=2.4$ Hz, 8.9 Hz, aromH), 7.42 (d, 1H, $J=8.9$ Hz, aromH), 8.67 (s, 1H, aromH). IR (Nujol) cm⁻¹: 1650, 1700, and 1730. MS m/z : 316 (M⁺).

N-(2-Oxo-2-phenylethyl)-7-diethylamino-2-oxo-2H-chromene-3-carboxamide (10b) Compound **10b** was prepared from coumarin-3-carboxylic acid (780 mg, 3.0 mmol) and aminoacetophenone hydrochloride (669 mg, 3.9 mmol) in a similar procedure (reaction temperature and time: room temperature, 16 h) to that carried out in the preparation of **10a**. Yellow prisms (from CHCl₃-hexane), yield 61%, mp 210–214 °C. ¹H-NMR (CDCl₃) δ : 1.25 (t, 6H, $J=7.2$ Hz, -N(CH₂CH₃)₂), 3.46 (q, 4H, $J=7.2$ Hz, -N(CH₂CH₃)₂), 4.96 (d, 2H, $J=4.7$ Hz, -CH₂-), 6.53 (d, 1H, $J=2.3$ Hz, aromH), 6.65 (dd, 1H, $J=2.3$ Hz, 8.9 Hz, aromH), 7.47 (d, 1H, $J=8.9$ Hz, aromH), 7.5 (m, 3H, aromH), 8.0 (m, 2H, aromH), 8.72 (s, 1H, aromH). IR (Nujol) cm⁻¹: 1680, 1700, and 1750. MS m/z : 378 (M⁺).

7-Diethylamino-2-oxo-2H-chromene-3-carbaldehyde (11) Vilsmeier reagent was prepared from DMF (5 ml) and POCl₃ (1.53 g, 10 mmol) under

Table 6. Physical and Spectral Data of Coumarin-azole Derivatives (2–8)

Compd.	mp (°C)	Appearance (Solvent)	IR (Nujol) (cm ⁻¹)	MS (<i>m/z</i>) (M ⁺)	Formula	Analysis (%)			
						Calcd	Found	C	H
2a	142.5–144.0	Orange needles (AcOEt–hexane)	1720	284	C ₁₆ H ₁₆ N ₂ O ₃	67.59 (67.36)	5.67 (5.69)	9.74 (9.85)	
2b	136–138	Orange prisms (Benzene–hexane)	1730	298	C ₁₇ H ₁₈ N ₂ O ₃	68.44 (68.61)	6.08 (6.16)	9.39 (9.39)	
2c	126–128	Yellow prisms (AcOEt–hexane)	1720	356	C ₁₉ H ₂₀ N ₂ O ₅	64.02 (63.98)	5.66 (5.67)	7.86 (7.83)	
2d	154–155	Orange needles (AcOEt–hexane)	1740	356	C ₁₉ H ₂₀ N ₂ O ₅	64.02 (63.84)	5.66 (5.77)	7.86 (7.76)	
2e	181–184	Orange prisms (AcOEt–hexane)	1720 1740	370	C ₂₀ H ₂₂ N ₂ O ₅	64.84 (64.91)	5.99 (6.05)	7.57 (7.58)	
2f	158.5–160.0	Reddish orange needles (AcOEt–hexane)	1700	360	C ₂₂ H ₂₀ N ₂ O ₃	73.32 (73.06)	5.59 (5.69)	7.77 (7.54)	
2g	163–165	Reddish orange needles (CHCl ₃ –hexane)	1720	360	C ₂₂ H ₂₀ N ₂ O ₃	73.32 (73.09)	5.59 (5.49)	7.77 (7.67)	
3a	95–98	Orange prisms (AcOEt–hexane)	1700	300	C ₁₆ H ₁₆ N ₂ O ₂ S	63.98 (63.83)	5.37 (5.43)	9.33 (9.19)	10.65 (10.65)
3b	162–163	Yellow needles (CHCl ₃ –hexane)	1700	314	C ₁₇ H ₁₈ N ₂ O ₂ S	64.95 (65.14)	5.78 (5.86)	8.92 (8.83)	10.18 (10.33)
3c	173–175	Yellow prisms (EtOH)	1710	314	C ₁₇ H ₁₈ N ₂ O ₂ S	64.95 (64.84)	5.78 (5.77)	8.92 (8.81)	10.18 (10.15)
3d	157–158	Reddish orange prisms (CHCl ₃ –hexane)	1700	372	C ₁₉ H ₂₀ N ₂ O ₄ S	61.27 (61.11)	5.42 (5.46)	7.53 (7.51)	8.59 (8.63)
3e	215–217	Reddish orange needles (CHCl ₃ –hexane)	1700	372	C ₁₉ H ₂₀ N ₂ O ₄ S	61.27 (61.21)	5.42 (5.54)	7.53 (7.36)	8.59 (8.66)
3f	210–211	Orange needles (CHCl ₃ –hexane)	1700	386	C ₂₀ H ₂₂ N ₂ O ₄ S	62.16 (61.95)	5.74 (5.75)	7.25 (7.08)	8.28 (8.30)
3g	126–128 ^{a)}	Orange needles (CHCl ₃ –hexane)	1710	376	C ₂₂ H ₂₀ N ₂ O ₂ S	70.19 (70.26)	5.35 (5.39)	7.44 (7.26)	8.52 (8.65)
3h	200–202	Yellow prisms (AcOEt–hexane)	1720	376	C ₂₂ H ₂₀ N ₂ O ₂ S	70.19 (69.86)	5.35 (5.43)	7.44 (7.25)	8.52 (8.59)
4a	181–182	Yellow orange prisms (AcOEt–hexane)	1720	284	C ₁₆ H ₁₆ N ₂ O ₃	67.59 (67.73)	5.67 (5.51)	9.74 (9.76)	
4b	145–146	Orange prisms (AcOEt–hexane)	1710 1730	356	C ₁₉ H ₂₀ N ₂ O ₅	64.02 (64.06)	5.66 (5.74)	7.86 (7.90)	
4c	191–193	Yellow prisms (AcOEt–hexane)	1720	360	C ₂₂ H ₂₀ N ₂ O ₃	73.32 (73.44)	5.59 (5.46)	7.77 (7.90)	
5	173–174	Orange prisms (AcOEt–hexane)	1700	360	C ₂₂ H ₂₀ N ₂ O ₃	73.32 (73.44)	5.59 (5.46)	7.77 (7.68)	
6a	141.0–142.5	Yellow needles (AcOEt–hexane)	1700	314	C ₁₇ H ₁₈ N ₂ O ₂ S	64.95 (65.06)	5.78 (5.83)	8.92 (8.84)	10.18 (10.25)
6b	141–142	Yellow needles (AcOEt–hexane)	1710	372	C ₁₉ H ₂₀ N ₂ O ₄ S	61.27 (61.28)	5.42 (5.47)	7.53 (7.46)	8.59 (8.65)
6c	127–129 ^{b)}	Yellow needles (AcOEt–hexane)	1710	376	C ₂₂ H ₂₀ N ₂ O ₄ S	70.19 (70.35)	5.35 (5.49)	7.44 (7.30)	8.52 (8.58)
7a	192–194	Yellow needles (CHCl ₃ –hexane)	1720	285	C ₁₅ H ₁₅ N ₃ O ₃	63.15 (62.98)	5.30 (5.35)	14.73 (14.70)	
7b	121–123	Orange prisms (AcOEt–hexane)	1740	299	C ₁₆ H ₁₇ N ₃ O ₃	64.20 (64.27)	5.72 (5.89)	14.04 (13.97)	
7c	201–203	Yellow needles (CHCl ₃ –hexane)	1720	361	C ₂₁ H ₁₉ N ₃ O ₃	64.95 (64.84)	5.78 (5.77)	11.63 (11.61)	
8a	242–245	Orange prisms (AcOEt–hexane)	1700	301	C ₁₅ H ₁₅ N ₃ O ₂ S	59.78 (59.53)	5.02 (5.10)	13.95 (14.06)	10.62 (10.49)
8b	201–203	Yellow needles (CHCl ₃ –hexane)	1710	315	C ₁₆ H ₁₇ N ₃ O ₂ S	60.93 (60.91)	5.44 (5.54)	13.33 (13.48)	10.15 (9.95)
8c	262–263	Yellow needles (CHCl ₃ –hexane)	1700	377	C ₂₁ H ₁₉ N ₃ O ₂ S	66.82 (66.58)	5.08 (5.20)	11.14 (11.25)	8.48 (8.32)

a) **3g**, lit.,¹⁸⁾ mp 130–133 °C. b) **6c**, lit.,²⁰⁾ mp 130–133 °C.

cooling. The resulting reagent was added dropwise to a solution of 7-diethylaminocoumarin [7-diethylamino-chromen-2-one] (432 mg, 2 mmol) in DMF (2 ml), and the mixture was stirred at room temperature for 16 h. The reaction mixture was poured into a saturated NaHCO₃ solution, then extracted with AcOEt. The AcOEt extraction was washed with brine and dried over MgSO₄. After evaporation, the residue was purified by column chromatography on silica gel (AcOEt: hexane=2:1, v/v). Orange needles (from

CHCl₃–hexane), yield 49%, mp 159–160 °C (lit.,¹⁶⁾ mp 160–162 °C). ¹H-NMR (CDCl₃) δ: 1.26 (t, 6H, *J*=7.2 Hz, –N(CH₂CH₃)₂), 3.47 (q, 4H, *J*=7.2 Hz, –N(CH₂CH₃)₂), 6.49 (d, 1H, *J*=2.5 Hz, aromH), 6.64 (dd, 1H, *J*=2.5 Hz, 8.9 Hz, aromH), 7.42 (d, 1H, *J*=8.9 Hz, aromH), 8.25 (s, 1H, aromH), 10.13 (s, 1H, –CHO). IR (Nujol) cm⁻¹: 1680, 1710. MS *m/z*: 245 (M⁺).

3-(2-Bromoacetyl)-7-diethylamino-2H-chromen-2-one (12) A solu-

Table 7. ¹H-NMR Data of Coumarin-azole Derivatives (2–8)

Compounds	¹ H-NMR (CDCl ₃) δ (ppm)
2a	1.24 (t, 6H, <i>J</i> = 7.2 Hz, -N(CH ₂ CH ₃) ₂), 3.45 (q, 4H, <i>J</i> = 7.2 Hz, -N(CH ₂ CH ₃) ₂), 6.52 (d, 1H, <i>J</i> = 2.4 Hz, aromH), 6.63 (dd, 1H, <i>J</i> = 2.4 Hz, 9.0 Hz, aromH), 7.25 (d, 1H, <i>J</i> = 0.7 Hz, aromH), 7.74 (d, 1H, <i>J</i> = 9.0 Hz, aromH), 7.75 (d, 1H, <i>J</i> = 0.7 Hz, aromH), 8.39 (s, 1H, aromH)
2b	1.23 (t, 6H, <i>J</i> = 7.2 Hz, -N(CH ₂ CH ₃) ₂), 2.41 (d, 3H, <i>J</i> = 1.1 Hz, -CH ₃), 3.44 (q, 4H, <i>J</i> = 7.2 Hz, -N(CH ₂ CH ₃) ₂), 6.51 (d, 1H, <i>J</i> = 2.4 Hz, aromH), 6.62 (dd, 1H, <i>J</i> = 2.4 Hz, 8.9 Hz, aromH), 6.88 (q, 1H, <i>J</i> = 1.1 Hz, aromH), 7.37 (d, 1H, <i>J</i> = 8.9 Hz, aromH), 8.34 (s, 1H, aromH)
2c	1.24 (t, 6H, <i>J</i> = 7.2 Hz, -N(CH ₂ CH ₃) ₂), 1.41 (t, 3H, <i>J</i> = 7.2 Hz, -COOCH ₂ CH ₃), 3.46 (q, 4H, <i>J</i> = 7.2 Hz, -N(CH ₂ CH ₃) ₂), 4.43 (q, 2H, <i>J</i> = 7.2 Hz, -COOCH ₂ CH ₃), 6.52 (d, 1H, <i>J</i> = 2.4 Hz, aromH), 6.64 (dd, 1H, <i>J</i> = 2.4 Hz, 8.9 Hz, aromH), 7.38 (d, 1H, <i>J</i> = 8.9 Hz, aromH), 8.31 (s, 1H, aromH), 8.61 (s, 1H, aromH)
2d	1.25 (t, 6H, <i>J</i> = 7.2 Hz, -N(CH ₂ CH ₃) ₂), 1.41 (t, 3H, <i>J</i> = 7.2 Hz, -COOCH ₂ CH ₃), 3.46 (q, 4H, <i>J</i> = 7.2 Hz, -N(CH ₂ CH ₃) ₂), 4.42 (q, 2H, <i>J</i> = 7.2 Hz, -COOCH ₂ CH ₃), 6.52 (d, 1H, <i>J</i> = 2.4 Hz, aromH), 6.64 (dd, 1H, <i>J</i> = 2.4 Hz, 8.9 Hz, aromH), 7.40 (d, 1H, <i>J</i> = 8.9 Hz, aromH), 7.88 (s, 1H, aromH), 8.49 (s, 1H, aromH)
2e	1.24 (t, 6H, <i>J</i> = 7.2 Hz, -N(CH ₂ CH ₃) ₂), 1.42 (t, 3H, <i>J</i> = 7.2 Hz, -COOCH ₂ CH ₃), 2.56 (s, 3H, -CH ₃), 3.46 (q, 4H, <i>J</i> = 7.2 Hz, -N(CH ₂ CH ₃) ₂), 4.41 (q, 2H, <i>J</i> = 7.2 Hz, -COOCH ₂ CH ₃), 6.52 (d, 1H, <i>J</i> = 2.4 Hz, aromH), 6.64 (dd, 1H, <i>J</i> = 2.4 Hz, 8.9 Hz, aromH), 7.39 (d, 1H, <i>J</i> = 8.9 Hz, aromH), 8.47 (s, 1H, aromH)
2f	1.24 (t, 6H, <i>J</i> = 7.2 Hz, -N(CH ₂ CH ₃) ₂), 3.45 (q, 4H, <i>J</i> = 7.2 Hz, -N(CH ₂ CH ₃) ₂), 6.54 (d, 1H, <i>J</i> = 2.4 Hz, aromH), 6.62 (dd, 1H, <i>J</i> = 2.4 Hz, 9.1 Hz, aromH), 7.3 (m, 1H, aromH), 7.4 (m, 3H, aromH), 7.8 (m, 2H, aromH), 8.03 (s, 1H, aromH), 8.54 (s, 1H, aromH)
2g	1.24 (t, 6H, <i>J</i> = 7.2 Hz, -N(CH ₂ CH ₃) ₂), 3.45 (q, 4H, <i>J</i> = 7.2 Hz, -N(CH ₂ CH ₃) ₂), 6.53 (d, 1H, <i>J</i> = 2.4 Hz, aromH), 6.64 (dd, 1H, <i>J</i> = 2.4 Hz, 8.9 Hz, aromH), 7.3 (m, 3H, aromH), 7.40 (d, 1H, <i>J</i> = 8.9 Hz, aromH), 7.48 (s, 1H, aromH), 7.7 (m, 2H, aromH), 8.40 (s, 1H, aromH)
3a	1.25 (t, 6H, <i>J</i> = 7.2 Hz, -N(CH ₂ CH ₃) ₂), 3.46 (q, 4H, <i>J</i> = 7.2 Hz, -N(CH ₂ CH ₃) ₂), 6.57 (d, 1H, <i>J</i> = 2.4 Hz, aromH), 6.66 (dd, 1H, <i>J</i> = 2.4 Hz, 9.0 Hz, aromH), 7.40 (d, 1H, <i>J</i> = 3.3 Hz, aromH), 7.44 (d, 1H, <i>J</i> = 9.0 Hz, aromH), 7.89 (d, 1H, <i>J</i> = 3.3 Hz, aromH), 8.72 (s, 1H, aromH)
3b	1.24 (t, 6H, <i>J</i> = 7.2 Hz, -N(CH ₂ CH ₃) ₂), 2.52 (d, 3H, <i>J</i> = 0.9 Hz, -CH ₃), 3.45 (q, 4H, <i>J</i> = 7.2 Hz, -N(CH ₂ CH ₃) ₂), 6.56 (d, 1H, <i>J</i> = 2.6 Hz, aromH), 6.65 (dd, 1H, <i>J</i> = 2.6 Hz, 9.0 Hz, aromH), 6.96 (d, 1H, <i>J</i> = 0.9 Hz, aromH), 7.43 (d, 1H, <i>J</i> = 9.0 Hz, aromH), 8.69 (s, 1H, aromH)
3c	1.23 (t, 6H, <i>J</i> = 7.2 Hz, -N(CH ₂ CH ₃) ₂), 2.52 (d, 3H, <i>J</i> = 1.1 Hz, -CH ₃), 3.45 (q, 4H, <i>J</i> = 7.2 Hz, -N(CH ₂ CH ₃) ₂), 6.55 (d, 1H, <i>J</i> = 2.4 Hz, aromH), 6.64 (dd, 1H, <i>J</i> = 2.4 Hz, 9.0 Hz, aromH), 7.41 (d, 1H, <i>J</i> = 9.0 Hz, aromH), 7.53 (q, 1H, <i>J</i> = 1.1 Hz, aromH), 8.64 (s, 1H, aromH)
3d	1.25 (t, 6H, <i>J</i> = 7.3 Hz, -N(CH ₂ CH ₃) ₂), 1.44 (t, 3H, <i>J</i> = 7.3 Hz, -COOCH ₂ CH ₃), 3.46 (q, 4H, <i>J</i> = 7.3 Hz, -N(CH ₂ CH ₃) ₂), 4.45 (q, 2H, <i>J</i> = 7.3 Hz, -COOCH ₂ CH ₃), 6.56 (d, 1H, <i>J</i> = 2.4 Hz, aromH), 6.67 (dd, 1H, <i>J</i> = 2.4 Hz, 8.8 Hz, aromH), 7.46 (d, 1H, <i>J</i> = 8.8 Hz, aromH), 8.19 (s, 1H, aromH), 8.89 (s, 1H, aromH)
3e	1.26 (t, 6H, <i>J</i> = 7.2 Hz, -N(CH ₂ CH ₃) ₂), 1.39 (t, 3H, <i>J</i> = 7.2 Hz, -COOCH ₂ CH ₃), 3.47 (q, 4H, <i>J</i> = 7.2 Hz, -N(CH ₂ CH ₃) ₂), 4.38 (q, 2H, <i>J</i> = 7.2 Hz, -COOCH ₂ CH ₃), 6.56 (d, 1H, <i>J</i> = 2.4 Hz, aromH), 6.68 (dd, 1H, <i>J</i> = 2.4 Hz, 8.9 Hz, aromH), 7.45 (d, 1H, <i>J</i> = 8.9 Hz, aromH), 8.45 (s, 1H, aromH), 8.78 (s, 1H, aromH)
3f	1.25 (t, 6H, <i>J</i> = 7.2 Hz, -N(CH ₂ CH ₃) ₂), 1.38 (t, 3H, <i>J</i> = 7.2 Hz, -COOCH ₂ CH ₃), 2.78 (s, 3H, -CH ₃), 3.46 (q, 4H, <i>J</i> = 7.2 Hz, -N(CH ₂ CH ₃) ₂), 4.34 (q, 2H, <i>J</i> = 7.2 Hz, -COOCH ₂ CH ₃), 6.55 (d, 1H, <i>J</i> = 2.6 Hz, aromH), 6.67 (dd, 1H, <i>J</i> = 2.6 Hz, 9.0 Hz, aromH), 7.45 (d, 1H, <i>J</i> = 9.0 Hz, aromH), 8.76 (s, 1H, aromH)
3g	1.25 (t, 6H, <i>J</i> = 7.3 Hz, -N(CH ₂ CH ₃) ₂), 3.46 (q, 4H, <i>J</i> = 7.3 Hz, -N(CH ₂ CH ₃) ₂), 6.59 (d, 1H, <i>J</i> = 2.4 Hz, aromH), 6.66 (dd, 1H, <i>J</i> = 2.4 Hz, 8.8 Hz, aromH), 7.3 (m, 3H, aromH), 7.48 (d, 1H, <i>J</i> = 8.8 Hz, aromH), 7.57 (s, 1H, aromH), 8.0 (m, 2H, aromH), 8.85 (s, 1H, aromH)
3h	1.25 (t, 6H, <i>J</i> = 7.2 Hz, -N(CH ₂ CH ₃) ₂), 3.46 (q, 4H, <i>J</i> = 7.2 Hz, -N(CH ₂ CH ₃) ₂), 6.58 (d, 1H, <i>J</i> = 2.5 Hz, aromH), 6.67 (dd, 1H, <i>J</i> = 2.5 Hz, 8.9 Hz, aromH), 7.3 (m, 3H, aromH), 7.45 (d, 1H, <i>J</i> = 8.9 Hz, aromH), 7.6 (m, 2H, aromH), 8.06 (s, 1H, aromH), 8.72 (s, 1H, aromH)
4a	1.23 (t, 6H, <i>J</i> = 7.2 Hz, -N(CH ₂ CH ₃) ₂), 3.44 (q, 4H, <i>J</i> = 7.2 Hz, -N(CH ₂ CH ₃) ₂), 6.53 (d, 1H, <i>J</i> = 2.6 Hz, aromH), 6.63 (dd, 1H, <i>J</i> = 2.6 Hz, 8.8 Hz, aromH), 7.36 (d, 1H, <i>J</i> = 8.8 Hz, aromH), 7.77 (s, 1H, aromH), 7.89 (s, 1H, aromH), 7.98 (s, 1H, aromH)
4b	1.24 (t, 6H, <i>J</i> = 7.2 Hz, -N(CH ₂ CH ₃) ₂), 1.47 (t, 3H, <i>J</i> = 7.2 Hz, -COOCH ₂ CH ₃), 3.46 (q, 4H, <i>J</i> = 7.2 Hz, -N(CH ₂ CH ₃) ₂), 4.50 (q, 2H, <i>J</i> = 7.2 Hz, -COOCH ₂ CH ₃), 6.53 (d, 1H, <i>J</i> = 2.4 Hz, aromH), 6.65 (dd, 1H, <i>J</i> = 2.4 Hz, 8.9 Hz, aromH), 7.40 (d, 1H, <i>J</i> = 8.9 Hz, aromH), 7.93 (s, 1H, aromH), 8.20 (s, 1H, aromH)
4c	1.22 (t, 6H, <i>J</i> = 7.3 Hz, -N(CH ₂ CH ₃) ₂), 3.41 (q, 4H, <i>J</i> = 7.3 Hz, -N(CH ₂ CH ₃) ₂), 6.50 (d, 1H, <i>J</i> = 2.4 Hz, aromH), 6.62 (dd, 1H, <i>J</i> = 2.4 Hz, 9.1 Hz, aromH), 7.36 (d, 1H, <i>J</i> = 8.9 Hz, aromH), 7.5 (m, 3H, aromH), 7.85 (s, 1H, aromH), 7.99 (s, 1H, aromH), 8.0 (m, 2H, aromH)
5	1.23 (t, 6H, <i>J</i> = 7.3 Hz, -N(CH ₂ CH ₃) ₂), 3.43 (q, 4H, <i>J</i> = 7.3 Hz, -N(CH ₂ CH ₃) ₂), 6.55 (d, 1H, <i>J</i> = 2.4 Hz, aromH), 6.63 (dd, 1H, <i>J</i> = 2.4 Hz, 8.9 Hz, aromH), 7.41 (d, 1H, <i>J</i> = 8.9 Hz, aromH), 7.5 (m, 3H, aromH), 8.1 (m, 2H, aromH), 8.44 (s, 2H, aromH)
6a	1.22 (t, 6H, <i>J</i> = 7.2 Hz, -N(CH ₂ CH ₃) ₂), 2.76 (s, 3H, -CH ₃), 3.42 (q, 4H, <i>J</i> = 7.2 Hz, -N(CH ₂ CH ₃) ₂), 6.52 (d, 1H, <i>J</i> = 2.4 Hz, aromH), 6.61 (dd, 1H, <i>J</i> = 2.4 Hz, 8.9 Hz, aromH), 7.38 (d, 1H, <i>J</i> = 8.9 Hz, aromH), 8.12 (s, 1H, aromH), 8.56 (s, 1H, aromH)
6b	1.23 (t, 6H, <i>J</i> = 7.2 Hz, -N(CH ₂ CH ₃) ₂), 1.47 (t, 3H, <i>J</i> = 7.2 Hz, -COOCH ₂ CH ₃), 3.43 (q, 4H, <i>J</i> = 7.2 Hz, -N(CH ₂ CH ₃) ₂), 4.51 (q, 2H, <i>J</i> = 7.2 Hz, -COOCH ₂ CH ₃), 6.52 (d, 1H, <i>J</i> = 2.4 Hz, aromH), 6.63 (dd, 1H, <i>J</i> = 2.4 Hz, 9.0 Hz, aromH), 7.42 (d, 1H, <i>J</i> = 9.0 Hz, aromH), 8.57 (s, 1H, aromH), 8.74 (s, 1H, aromH)
6c	1.22 (t, 6H, <i>J</i> = 7.3 Hz, -N(CH ₂ CH ₃) ₂), 3.42 (q, 4H, <i>J</i> = 7.3 Hz, -N(CH ₂ CH ₃) ₂), 6.52 (d, 1H, <i>J</i> = 2.5 Hz, aromH), 6.62 (dd, 1H, <i>J</i> = 2.5 Hz, 8.8 Hz, aromH), 7.3 (m, 3H, aromH), 7.4 (m, 4H, aromH), 8.0 (m, 2H, aromH), 8.29 (s, 1H, aromH), 8.73 (s, 1H, aromH)
7a	1.26 (t, 6H, <i>J</i> = 7.3 Hz, -N(CH ₂ CH ₃) ₂), 3.47 (q, 4H, <i>J</i> = 7.3 Hz, -N(CH ₂ CH ₃) ₂), 6.53 (d, 1H, <i>J</i> = 2.5 Hz, aromH), 6.65 (dd, 1H, <i>J</i> = 2.5 Hz, 8.8 Hz, aromH), 7.41 (d, 1H, <i>J</i> = 8.8 Hz, aromH), 8.49 (s, 1H, aromH), 8.52 (s, 1H, aromH)
7b	1.25 (t, 6H, <i>J</i> = 7.3 Hz, -N(CH ₂ CH ₃) ₂), 2.63 (s, 3H, -CH ₃), 3.46 (q, 4H, <i>J</i> = 7.3 Hz, -N(CH ₂ CH ₃) ₂), 6.51 (d, 1H, <i>J</i> = 2.4 Hz, aromH), 6.65 (dd, 1H, <i>J</i> = 2.4 Hz, 8.8 Hz, aromH), 7.38 (d, 1H, <i>J</i> = 8.8 Hz, aromH), 8.43 (s, 1H, aromH)
7c	1.25 (t, 6H, <i>J</i> = 7.3 Hz, -N(CH ₂ CH ₃) ₂), 3.47 (q, 4H, <i>J</i> = 7.3 Hz, -N(CH ₂ CH ₃) ₂), 6.53 (d, 1H, <i>J</i> = 2.4 Hz, aromH), 6.65 (dd, 1H, <i>J</i> = 2.4 Hz, 8.8 Hz, aromH), 7.42 (d, 1H, <i>J</i> = 8.8 Hz, aromH), 7.5 (m, 3H, aromH), 8.2 (m, 2H, aromH), 8.52 (s, 1H, aromH)
8a	1.26 (t, 6H, <i>J</i> = 7.2 Hz, -N(CH ₂ CH ₃) ₂), 3.48 (q, 4H, <i>J</i> = 7.2 Hz, -N(CH ₂ CH ₃) ₂), 6.57 (d, 1H, <i>J</i> = 2.4 Hz, aromH), 6.69 (dd, 1H, <i>J</i> = 2.4 Hz, 8.9 Hz, aromH), 7.48 (d, 1H, <i>J</i> = 8.9 Hz, aromH), 8.92 (s, 1H, aromH), 9.14 (s, 1H, aromH)
8b	1.25 (t, 6H, <i>J</i> = 7.2 Hz, -N(CH ₂ CH ₃) ₂), 2.80 (s, 3H, -CH ₃), 3.47 (q, 4H, <i>J</i> = 7.2 Hz, -N(CH ₂ CH ₃) ₂), 6.55 (d, 1H, <i>J</i> = 2.4 Hz, aromH), 6.67 (dd, 1H, <i>J</i> = 2.4 Hz, 9.0 Hz, aromH), 7.45 (d, 1H, <i>J</i> = 9.0 Hz, aromH), 8.83 (s, 1H, aromH)
8c	1.27 (t, 6H, <i>J</i> = 7.2 Hz, -N(CH ₂ CH ₃) ₂), 3.48 (q, 4H, <i>J</i> = 7.2 Hz, -N(CH ₂ CH ₃) ₂), 6.58 (d, 1H, <i>J</i> = 2.4 Hz, aromH), 6.71 (dd, 1H, <i>J</i> = 2.4 Hz, 8.9 Hz, aromH), 7.5 (m, 4H, aromH), 8.0 (m, 2H, aromH), 8.97 (s, 1H, aromH)

tion of 3-acetyl-7-diethylamino-2*H*-chromen-2-one¹⁴) (5.2 g, 20 mmol) and tetra-*n*-butyl ammonium tribromide (19.3 g, 40 mmol) in CH₂Cl₂ (100 ml) was stirred at room temperature for 2 d. The resulting precipitates were

collected on a filter funnel and washed with AcOEt. Yellow prisms, yield 81%, mp 211–214 °C. IR (Nujol) cm⁻¹: 1710. MS *m/z*: 338 (M⁺). Product **12** was used in the next step without further purification.

3-(2-Azidoacetyl)-7-diethylamino-2H-chromen-2-one (13) One milliliter of an aqueous NaN_3 (488 mg, 7.5 mmol) and AcOH (0.43 ml, 7.5 mmol) were added to a solution of **12** (1.01 g, 3.0 mmol) in DMF (15 ml), and the reaction mixture was allowed to stand for 2 d at room temperature. The resulting precipitates were collected on a filter funnel. Orange needles, yield 62%, mp 172–175 °C. $^1\text{H-NMR}$ (CDCl_3) δ : 1.26 (t, 6H, $J=7.2$ Hz, $-\text{N}(\text{CH}_2\text{CH}_3)_2$), 4.96 (s, 2H, $-\text{COCH}_2\text{N}_3$), 5.22 (q, 4H, $J=7.2$ Hz, $-\text{N}(\text{CH}_2\text{CH}_3)_2$), 6.49 (d, 1H, $J=2.6$ Hz, aromH), 6.65 (dd, 1H, $J=2.6$ Hz, 8.8 Hz, aromH), 7.36 (d, 1H, $J=8.8$ Hz, aromH), 8.56 (s, 1H, aromH). IR (Nujol) cm^{-1} : 1670, 1710. MS m/z : 300 (M^+). Product **13** was used in the next step without further purification.

7-Diethylamino-2-oxo-2H-chromene-3-carbothioamide (14) A mixture of **9** (7.8 g, 30 mmol) and Lawesson's reagent (6.5 g, 16 mmol) in dioxane (170 ml) was refluxed for 18 h. After removing dioxane *in vacuo*, the residue was chromatographed on a silica gel column (eluent, CHCl_3) to give **14**. Yellow needles (from CHCl_3 -hexane), yield 71%, mp 216–218 °C. $^1\text{H-NMR}$ (CDCl_3) δ : 1.26 (t, 6H, $J=7.2$ Hz, $-\text{N}(\text{CH}_2\text{CH}_3)_2$), 3.48 (q, 4H, $J=7.2$ Hz, $-\text{N}(\text{CH}_2\text{CH}_3)_2$), 6.48 (d, 1H, $J=2.4$ Hz, aromH), 6.67 (dd, 1H, $J=2.4$ Hz, 9.0 Hz, aromH), 7.50 (d, 1H, $J=9.0$ Hz, aromH), 7.77 (s, 1H, $-\text{NH}_2$), 9.34 (s, 1H, aromH), 10.38 (s, 1H, $-\text{NH}_2$). IR (Nujol) cm^{-1} : 1690. MS m/z : 276 (M^+).

7-Diethylamino-2-oxo-2H-chromene-3-carbohydrazide (15) Compound **15** was prepared from ethyl 7-diethylaminocoumarin-3-carboxylate and hydrazine according to the modified procedure in the literature.¹⁷ Hydrazine monohydrate (3.0 ml, 60 mmol) was added to a solution of ethyl 7-diethylaminocoumarin-3-carboxylate (4.3 g, 15 mmol) in EtOH (40 ml), and the reaction mixture was stirred at room temperature for 12 min. After cooling in an ice bath for 15 min, the precipitates were collected on a filter funnel. Orange needles (from CHCl_3 -hexane), yield 50%, mp 160–165 °C. $^1\text{H-NMR}$ (CDCl_3) δ : 1.24 (t, 6H, $J=7.2$ Hz, $-\text{N}(\text{CH}_2\text{CH}_3)_2$), 3.46 (q, 4H, $J=7.2$ Hz, $-\text{N}(\text{CH}_2\text{CH}_3)_2$), 4.14 (s, 2H, $-\text{NHNH}_2$), 6.50 (d, 1H, $J=2.4$ Hz, aromH), 6.65 (dd, 1H, $J=2.4$ Hz, 9.0 Hz, aromH), 7.51 (d, 1H, $J=9.0$ Hz, aromH), 9.23 (s, 1H, aromH), 10.38 (s, 1H, $-\text{NHNH}_2$). IR (Nujol) cm^{-1} : 1700. MS m/z : 275 (M^+).

7-Diethylamino-2-oxo-2H-chromene-3-carbothiohydrazide (16) A solution of **15** (825 mg, 3.0 mmol) and Lawesson's reagent (606 mg, 1.5 mmol) in dioxane (170 ml) was refluxed for 23 h. After removing dioxane *in vacuo*, the residue was chromatographed on a silica gel column (eluent, hexane: $\text{AcOEt}=2:1$, v/v) to give **16**. Brownish needles (from CHCl_3 -hexane), yield 18%, mp 209–212 °C. $^1\text{H-NMR}$ (CDCl_3) δ : 1.25 (t, 6H, $J=7.2$ Hz, $-\text{N}(\text{CH}_2\text{CH}_3)_2$), 3.47 (q, 4H, $J=7.2$ Hz, $-\text{N}(\text{CH}_2\text{CH}_3)_2$), 5.57 (s, 2H, $-\text{NHNH}_2$), 6.49 (d, 1H, $J=2.4$ Hz, aromH), 6.69 (dd, 1H, $J=2.4$ Hz, 9.0 Hz, aromH), 7.51 (d, 1H, $J=9.0$ Hz, aromH), 9.23 (s, 1H, aromH), 12.33 (s, 1H, $-\text{NHNH}_2$). IR (Nujol) cm^{-1} : 1680. MS m/z : 291 (M^+).

Preparation of 2a and 2c–2f: 7-Diethylamino-3-(1,3-oxazol-2-yl)-2H-chromen-2-one (2a) A solution of **9** (364 mg, 1.4 mmol) and bromoacetaldehyde (467 mg, 3.8 mmol) in DMF (10 ml) was refluxed for 2.5 h. After removing the solvent *in vacuo*, the residue was purified by column chromatography (hexane: $\text{AcOEt}=1:1$, v/v). Yield 23%. Similarly, **2c**, **2d**, **2e**, and **2f** were prepared from **9** and the corresponding ethyl bromopyruvate, ethyl 2-chloro-3-oxopropanoate, ethyl 2-chloroacetoacetate, and bromoacetophenone in 14, 15, 49, and 9% yields, respectively.

Preparation of 2b and 2g: 7-Diethylamino-3-(5-methyl-1,3-oxazol-2-yl)-2H-chromen-2-one (2b) A mixture of **10a** (316 mg, 1 mmol) and POCl_3 (1.5 g, 10 mmol) was refluxed for 1 h. The reaction mixture was neutralized with a saturated aqueous NaHCO_3 solution, then extracted with CHCl_3 . The extract was washed with brine, dried over MgSO_4 , concentrated to dryness and the residue was purified by column chromatography using AcOEt-MeOH (9:1, v/v) as an eluent to give **2b**. Yield 72%. Similarly, **2g** was obtained from **10b**, in almost quantitative yield.

Preparation of 3a, 3b, and 3d–3g: 7-Diethylamino-3-(1,3-thiazol-2-yl)-2H-chromen-2-one (3a) A solution of coumarin-3-thioamide **14** (300 mg, 1.1 mmol) and bromoacetaldehyde (262 mg, 2.1 mmol) in DMF (10 ml) was stirred in the presence of K_2CO_3 (965 mg, 7.0 mmol) at room temperature for 7.5 h under an argon atmosphere. The reaction mixture was poured into brine, then extracted with AcOEt . The organic layer was washed with brine and dried over MgSO_4 . After evaporating the solvent, the residue was diluted with CHCl_3 (12 ml). To the resulting solution was added pyridium *p*-toluenesulfonate (30 mg, 0.1 mmol), and the mixture was refluxed for 4.5 h. After removing the solvent *in vacuo*, the residue was purified by column chromatography (hexane: $\text{AcOEt}=2:1$, v/v). Yield 58%. Similarly, **3b**, **3d**, **3e**, **3f**, and **3g**¹⁸ were prepared from **14** and the corresponding bromoacetone, ethyl bromopyruvate, ethyl 2-chloro-3-oxopropanoate, ethyl 2-chloroacetoacetate, and bromoacetophenone in 39, 68, 87, 14, and 93%

yields, respectively.

Preparation of 3c and 3h: 7-Diethylamino-3-(5-methyl-1,3-thiazol-2-yl)-2H-chromen-2-one (3c) A mixture of **10a** (95 mg, 0.3 mmol) and P_2S_5 (200 mg, 0.5 mmol) in CHCl_3 (6 ml) was refluxed for 2.5 h. After cooling, the reaction mixture was washed with brine and dried over MgSO_4 . After removing the solvent *in vacuo*, the residue was purified by recrystallization from EtOH to give yellow prisms. Yield 53%. Similarly, **3h** was obtained by cyclization of **10b** with P_2S_5 in 42% yield.

Preparation of 7-Diethylamino-3-(1,3-oxazol-5-yl)-2H-chromen-2-one (4a) Compound **4a** was prepared according to the modified method in the literature.¹⁹ A solution of 7-diethylaminocoumarin-3-carbaldehyde **11** (735 mg, 3 mmol) and [(4-methylphenyl)sulfonyl]-methaneisocyanide (585 mg, 3 mmol) in MeOH (50 ml) was refluxed in the presence of K_2CO_3 (414 mg, 3 mmol) for 5 h. After removing the solvent *in vacuo*, the residue was dissolved in AcOEt . The solution was washed brine and dried over MgSO_4 . After removing the solvent, the residue was purified by column chromatography (hexane: $\text{AcOEt}=3:1$, v/v). Yield 5%.

Preparation of 4b and 4c: Ethyl 5-(7-Diethylamino-2-oxo-2H-chromen-3-yl)-1,3-oxazole-2-carboxylate (4b) A mixture of azidoacetyl compound **13** (200 mg, 0.75 mmol), Ph_3P (263 mg, 1.0 mmol) and ethyl (chlorocarbonyl)formate (102 mg, 0.7 mmol) in THF (6 ml) was refluxed for 4 h. After removing the solvent, the residue was dissolved in CHCl_3 , washed with a saturated aqueous NaHCO_3 , brine, and dried over MgSO_4 . After evaporation, the residue was purified by column chromatography using CHCl_3 - EtOH (5:1, v/v) as an eluent to give **4b**. Yield 15%. Similarly, **4c** was prepared from azidoacetyl compound **13** and benzoyl chloride in 56% yield.

Preparation of 7-Diethylamino-3-(2-phenyl-1,3-oxazol-4-yl)-2H-chromen-2-one (5) A mixture of bromoacetyl compound **12** (838 mg, 2.0 mmol), benzamide (726 mg, 6.0 mmol), and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (0.04 ml, 0.3 mmol) in DMF (8 ml) was heated at 130 °C for 24 h. After cooling, the reaction mixture was poured into a saturated aqueous NaHCO_3 solution, and was extracted with AcOEt . The organic layer was washed with brine, dried over Na_2SO_4 , and evaporated to dryness. The residue was purified by column chromatography using CHCl_3 - EtOH (5:1, v/v) as an eluent to give **5**. Yield 10%.

Preparation of 7-Diethylamino-3-(2-methyl-1,3-thiazol-4-yl)-2H-chromen-2-one (6a) To a solution of **12** (210 mg, 0.6 mmol) and thioacetamide (150 mg, 2.0 mmol) in DMF (3 ml) was added K_2CO_3 (138 mg, 1.0 mmol), and the mixture was stirred at room temperature for 3 d. After the reaction, the reaction mixture was poured into brine and extracted with AcOEt . The organic layer was washed with brine and dried over MgSO_4 . After evaporation, the residue was purified by column chromatography using hexane- AcOEt (3:1, v/v) as an eluent to give **6a**. Yield 58%.

Preparation of Ethyl 4-(7-Diethylamino-2-oxo-2H-chromen-3-yl)-1,3-thiazole-2-carboxylate (6b) A solution of **12** (36 mg, 0.3 mmol) and ethyl thioacetamide (ethyl 2-amino-2-thioacetate) (36 mg, 0.1 mmol) in DMF (1 ml) was heated at 120 °C for 2 h. After the reaction, the reaction mixture was poured into brine and extracted with AcOEt . The organic layer was washed with brine and dried over MgSO_4 . After evaporation, the residue was purified by column chromatography using hexane- AcOEt (3:1, v/v) as an eluent to give **6b**. Yield 71%.

Preparation of 7-Diethylamino-3-(2-phenyl-1,3-thiazol-4-yl)-2H-chromen-2-one (6c) Compound **6c** was prepared from **12** (328 mg, 1 mmol) and thiobenzamide (274 mg, 2 mmol) using the same procedure as above (reaction conditions: DMF 6 ml, 120 °C, 4 d). Yield 29% (lit.,²⁰ mp 130–133 °C).

Preparation of 7a, 7b and 7c: 7-Diethylamino-3-(1,3,4-oxadiazol-2-yl)-2H-chromen-2-one (7a) A mixture of 7-diethylaminocoumarin-3-carbohydrazide **15** (550 mg, 2 mmol) and $\text{HC}(\text{OC}_2\text{H}_5)_3$ (3.0 g, 20 mmol) was heated at 180 °C for 40 min. After removing excess $\text{HC}(\text{OC}_2\text{H}_5)_3$ *in vacuo*, the residue was dissolved in CHCl_3 (12 ml), then $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (0.02 ml, 0.16 mmol) was added to the solution, which was refluxed for 2 d. After cooling, the reaction mixture was treated with aqueous NaHCO_3 solution. The organic layer was dried over Na_2SO_4 and evaporated to dryness. The residue was purified by column chromatography (AcOEt). Yield 39%. Similarly, **7b** and **7c** were obtained from **15** and the corresponding $\text{CH}_3\text{C}(\text{OCH}_3)_3$ and $\text{PhC}(\text{OCH}_3)_3$ in 92 and 41% yields, respectively. In the case of **7b**, pyridinium *p*-toluenesulfonate in place of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ was used (refluxed for 24 h).

Preparation of 8a–8c: 7-Diethylamino-3-(1,3,4-thiadiazol-2-yl)-2H-chromen-2-one (8a) A mixture of coumarin-3-carbothiohydrazide **16** (52 mg, 0.18 mmol) and $\text{HC}(\text{OC}_2\text{H}_5)_3$ (891 mg, 6.0 mmol) was heated at 160 °C for 2 h. After removing excess $\text{HC}(\text{OC}_2\text{H}_5)_3$ *in vacuo*, the residue was

purified by column chromatography (CHCl₃). Yield 79%. Similarly, **8b** and **8c** were prepared from **16** and the corresponding CH₃C(OCH₃)₃ and PhC(OCH₃)₃, in 55 and 41% yields, respectively.

The physical and analytical data of coumarin-azole compounds (**2—8**) are listed in Tables 6 and 7.

Fluorescence Quantum Yields of Selected Compounds Absorbances of the sample solution were kept below 0.2 at the excitation wavelength. Since the quantum yield of fluorescein is dependent on changes in excitation wavelengths,¹³ the relative quantum yields were taken as the ratio of [F]-azoles quantum yields to that of the fluorescein at each different excitation wavelength.

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References

- 1) Fluorescent Labeling Reagents. Part 3. Part 2: Takechi H., Goto Y., Machida M., *Chem. Pharm. Bull.*, **46**, 159—162 (1998).
- 2) a) Takechi H., Kamada S., Machida M., *Chem. Pharm. Bull.*, **44**, 793—799 (1996); b) Machida M., Machida M. I., Sekine T., Kanaoka Y., *ibid.*, **15**, 1678—1684 (1977).
- 3) a) Minta A., Kao J. P. Y., Tsien R. Y., *J. Biol. Chem.*, **264**, 8171—8178 (1989) and references cited therein; b) Gryniewicz G., Poenie M., Tsien R. Y., *ibid.*, **260**, 3440—3450 (1985); c) Wang X., Krebs L. J., Al-Nuri M., Pudavar H. E., Ghosal S., Liebow C., Nagy A. A., Schally A. V., Prasad P. N., *Proc. Natl. Acad. Sci. U.S.A.*, **96**, 11081—11084 (1999).
- 4) de Silva A. P., Gunaratne H. Q. N., Gunnlaugsson T., Huxley A. J. M., McCoy C. P., Rademacher J. T., Rice T. E., *Chem. Rev.*, **97**, 1515—1566 (1997).
- 5) Rettig W., *Angew. Chem. Int. Ed. Engl.*, **25**, 971—988 (1986).
- 6) a) Jones G. II, Jimenez J. A. C., *Tetrahedron Lett.*, **40**, 8551—8555 (1999); b) Jones G. II, Jackson W. R., Choi C.-Y., Bergmark W. R., *J. Phys. Chem.*, **89**, 294—300 (1985); c) Jones G. II, Griffin S. F., Choi C.-Y., Bergmark W. R., *J. Org. Chem.*, **49**, 2705—2708 (1984); d) Reynolds G. A., Drexhage K. H., *Opt. Commun.*, **13**, 222—225 (1975).
- 7) Liu P., Celatka C. A., Panek J. S., *Tetrahedron Lett.*, **38**, 5445—5448 (1997).
- 8) Heinze J., Baumgärtel H., *Chem. Ber.*, **103**, 1572—1577 (1970).
- 9) Jaffe H. H., Orchin M., "Theory and Applications of Ultraviolet Spectroscopy," John Wiley and Sons, Inc., New York, 1964, pp. 345—361.
- 10) Takadate A., Masuda T., Murata C., Shibuya M., Isobe A., *Chem. Pharm. Bull.*, **48**, 256—260 (2000) and references cited therein.
- 11) Parker C. A., Rees W. T., *Analyst*, **85**, 587—600 (1960).
- 12) Kanaoka Y., Machida M., Kokubun H., Sekine T., *Chem. Pharm. Bull.*, **16**, 1747—1753 (1968).
- 13) Dawson W. R., Windsor M. W., *J. Phys. Chem.*, **72**, 3251—3260 (1968).
- 14) Czerney P., Hartmann H., *J. Prakt. Chem.*, **324**, 21—28 (1982).
- 15) Hepworth J. D., "Organic Syntheses," Coll. Vol. 5, ed. by Baumgarten H. E., John Wiley and Sons, Inc., New York, 1973, pp. 27—29.
- 16) Komlev I. V., Tavrizova M. A., Khrolova O. R., Mikhailova T. A., *Zh. Obshch. Khim.*, **55**, 888—892 (1985) [*Chem. Abstr.*, **103**, 72603s (1985)].
- 17) Fujino H., Eguchi M., Goya S., *Yakugaku Zasshi*, **110**, 155—158 (1990).
- 18) Vamvakaris C., Patsch M., Mach W., Ger. Patent 2807761 (1979) [*Chem. Abstr.*, **92**, 41931x (1980)].
- 19) Anderson B. A., Becke L. M., Booher R. N., Flaugh M. E., Harn N. K., Kress T. J., Varie D. L., Wepsiec J. P., *J. Org. Chem.*, **62**, 8634—8639 (1997).
- 20) Hartmann H., Czerney P., Liebscher J., East Ger. Patent DD 204094 (1983) [*Chem. Abstr.*, **101**, 7145p (1984)].