Synthesis of Coumarin-3-*O*-acylisoureas by Dicyclohexylcarbodiimide

Leonardo Bonsignore, Filippo Cottiglia, Anna M. Maccioni and Daniela Secci*

Dipartimento Farmaco Chimico Tecnologico, Università di Cagliari, I-09124 Cagliari, Italy

Silvio M. Lavagna

Dipartimento di Studi di Chimica e Tecnologia delle Sostanze, Biologicamente Attive, Università di Roma "La Sapienza", P.le Aldo Moro, 5, I-00185 Roma, Italy

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The synthesis and isolation of some *O*-acylisoureas are described. The reaction between dicyclohexylcarbodiimide and coumarin-3-carboxylic acids leads to coumarin-dicyclohexylisourea derivatives, isolated as the main products, and to coumarin-dicyclohexylurea derivatives as byproducts.

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Over the past twenty five years dicyclohexylcarbodiimide (DCC) has proved to be an exceptionally useful reagent [1-3] in different fields of synthetic organic chemistry, for example in peptide synthesis [3-7], enzimology [2,8,9] and polymer chemistry [3,10,11].

It is already used as a dehydrating agent in the condensation of carboxylic acids with nucleophiles [12].

The reaction of carboxylic acids with carbodiimides and the kinetics of this reaction have been extensively investigated [13,14]. The reaction involves an *O*-acylisourea as an intermediate but the evidence for its formation is scanty. In fact the *O*-acylisoureas have not been isolated in these kinds of reactions but only observed in solution [13] and in a peptide synthesis [15]. Therefore the reaction mechanism, proposed by Khorana *et al.* [1], was only supported on model intramolecular *O*-acylisoureas [16].

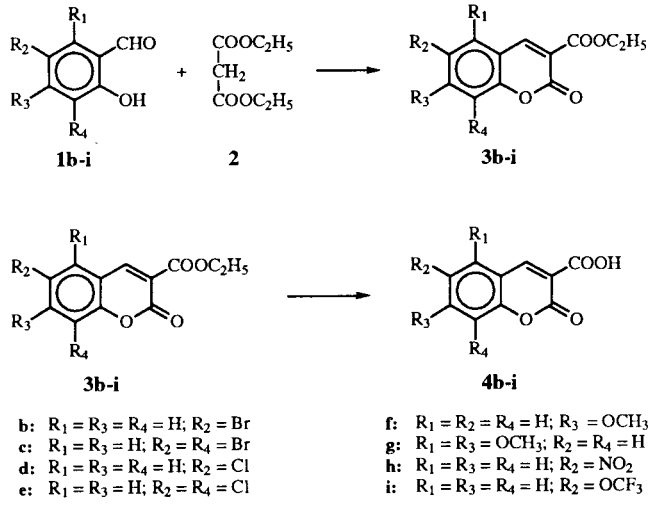
Moving from these considerations and bearing in mind that coumarins constitute an important class of naturally occurring compounds with useful pharmacological activity, such as anticoagulant [17], spasmolytic [18], anthelmintic [19] and diuretic [20] activity, we carried out a study on the reaction of coumarin-3-carboxylic acids **4a-i** with DCC (**5**) with the aim of preparing and isolating new coumarin derivatives of dicyclohexylisourea **7a-i**, with potential pharmacological activity.

Coumarin-3-carboxylic acids **4b-i**, not commercially available, were prepared according to the literature [21] (Scheme 1). Details about their synthesis, along with their analytical and spectroscopic data, are reported in the experimental and in Tables 1 and 2.

Subsequently, compounds **4 a-i** were reacted with DCC **5**. As reported in Scheme 2, *O*-acylisoureas **7a-i** were not the only compounds obtained during these reactions. In fact we also obtained *N*-acylureas **6a-f** as byproducts.

Compounds **7a-i** were obtained in high yields (*ca.* 80%) while dicyclohexylurea derivatives **6a-f** were obtained (not always) in very poor yields. In fact the reaction between coumarin acids **4g-i** and DCC **5** only leads to the derivatives **7g-i**.

Scheme 1



b: $R_1 = R_3 = R_4 = H$; $R_2 = Br$
c: $R_1 = R_3 = H$; $R_2 = R_4 = Br$
d: $R_1 = R_3 = R_4 = H$; $R_2 = Cl$
e: $R_1 = R_3 = H$; $R_2 = R_4 = Cl$
f: $R_1 = R_2 = R_4 = H$; $R_3 = OCH_3$
g: $R_1 = R_3 = OCH_3$; $R_2 = R_4 = H$
h: $R_1 = R_3 = R_4 = H$; $R_2 = NO_2$
i: $R_1 = R_3 = R_4 = H$; $R_2 = OCF_3$

Compounds **6a-f** and **7a-i**, as well as the intermediates **3b-i** and **4b-i** were identified by analytical and spectroscopic methods. Particularly, by ir spectra we determined the band of amidic carbonyl in type-**6** derivatives and that of the ester carbonyl in type-**7** derivatives.

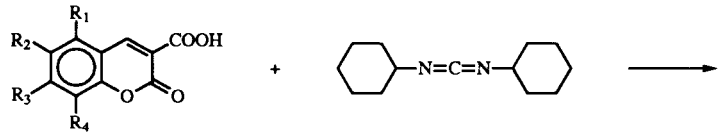
In the ^1H nmr spectra the only difference between **6** and **7** derivatives was the peak of the NH group measured at *ca.* 5.5 ppm and *ca.* 8.0 ppm respectively.

The interpretation of the mass spectra was very important in the differentiation of the two types of compounds. In fact although the molecular weight was the same for both compounds there was little difference in their spectra.

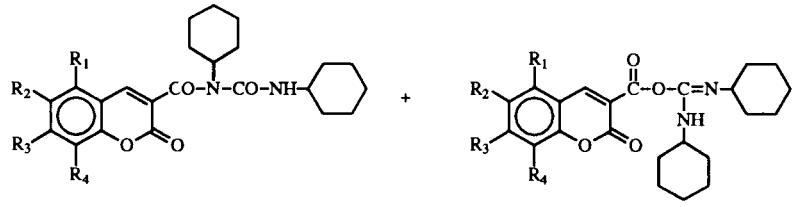
For example, in Scheme 3 we reported the main fragmentations of compounds **6a** and **7a**, which was similar in the mass spectra of all derivatives, while in Table 5 the relative abundances for compounds **6a-f** and **7a-i** are reported. With the aid of these routes of fragmentation it was possible to confirm the structure of derivates **6** and **7**.

Both compounds gave the acylio ion $[C_{10}H_5O_3]^+$, m/z 173 with high relative abundance. In both spectra we

Scheme 2



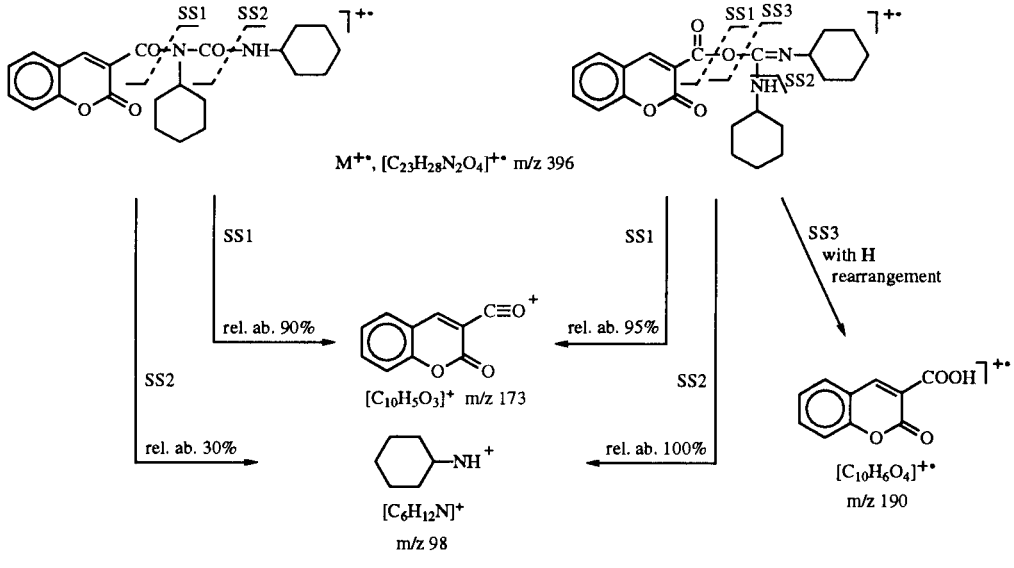
4a-i **5**



6a-f **7a-i**

a: $R_1 = R_2 = R_3 = R_4 = H$
b: $R_1 = R_3 = R_4 = H$; $R_2 = Br$
c: $R_1 = R_3 = H$; $R_2 = R_4 = Br$
d: $R_1 = R_3 = R_4 = H$; $R_2 = Cl$
e: $R_1 = R_3 = H$; $R_2 = R_4 = Cl$
f: $R_1 = R_2 = R_4 = H$; $R_3 = OCH_3$
g: $R_1 = R_3 = OCH_3$; $R_2 = R_4 = H$
h: $R_1 = R_3 = R_4 = H$; $R_2 = NO_2$
i: $R_1 = R_3 = R_4 = H$; $R_2 = OCF_3$

Scheme 3



found the peak corresponding to the cyclohexylaminic ion $[C_6H_{12}N]^+$, m/z 98, but with a different relative abundance. In fact, this peak was the base peak in **7** derivatives, while in **6** derivatives the relative abundance was *ca.* 30%.

In the mass spectra of compounds **7a-i** we observed a peak corresponding to the coumarin acid ion $[C_{10}H_6O_4]^{+\bullet}$, m/z 190, which was not present in the mass spectra of **6a-f**.

EXPERIMENTAL

Melting points were determined on a Köfler apparatus and are uncorrected. The ^1H nmr spectra were determined using a Varian Unity 300 spectrometer and the chemical shifts (δ) refer to tetramethylsilane. The ir spectra were recorded on a Perkin Elmer 1310 spectrophotometer on sodium chloride mulls. Elemental analyses were carried out on a Carlo Erba 1106 Elemental analyzer. Mass spectra were taken with a QMD 1000 instrument (Fisons Instruments) at 70 eV using a direct inlet system. All compounds were purchased from Aldrich Chemical Co. and the solvents were dried rigorously before use according to standard methods [22]. Coumarin-3-carboxylic esters **3b-i** and acids **4b-i** were prepared according to the literature [21]. Compound **4a** was commercially available.

General Procedure for the Preparation of Ethyl Coumarin-3-carboxylates **3b-i**.

Piperidine (0.5 ml) and acetic acid (0.01 ml) were added to solutions of salicylaldheydes **1b-i** (0.02 mole) in 150 ml of ethanol (95%). When the solution was clear, 0.026 mole of

diethyl malonate was added. The reaction solution was refluxed with stirring for 24 hours. The colourless substance which precipitated from the reaction mixture was filtered off and proved to be **3b-i** in almost quantitative yields. The analytical and spectral data of compounds **3b-i** are reported in Tables 1 and 2.

General Procedure for the Preparation of Coumarin-3-carboxylic Acids **4b-i**.

Suspensions of ethyl coumarin-3-carboxylates **3b-i** (0.015 mole) in 50 ml of 20% sodium hydroxide (20%) were refluxed with stirring for 2 hours. Hydrochloric acid (37%) was added at 0° to the clear solution until a *p*H of 1-2 was reached. The colourless precipitate was filtered off. The residue was washed with diethyl ether and dried. The analytical and spectral data for compounds **4b-i** are reported in Tables 1 and 2.

General Procedure for the Preparation of Urea Derivatives **6a-f** and Isourea Derivatives **7a-i**.

A solution of dicyclohexylcarbodiimide (DCC) (**5**) (0.01 mole) in 50 ml of dry tetrahydrofuran was added dropwise at

Table 1

Analytical Data for Compounds **3b-i** and **4b-i**

Compound	Yield (%)	Formula Molecular weight	mp °C (Lit)	Elemental Analysis (%) Calcd./Found C	H	N
3b	73	$C_{12}H_9O_4Br$ (297.11)	162-164 (168-169) [21]	48.50 48.36	3.05 3.04	
3c	70	$C_{12}H_8O_4Br_2$ (376.02)	163-167	38.32 38.19	2.14 2.13	
3d	61	$C_{12}H_9O_4Cl$ (252.65)	145-147	57.04 56.99	3.59 3.60	
3e	80	$C_{12}H_8O_4Cl_2$ (287.09)	170-173	50.19 50.10	2.80 2.81	
3f	54	$C_{13}H_{12}O_5$ (248.23)	120-125	62.89 62.70	4.87 4.88	
3g	76	$C_{14}H_{14}O_6$ (278.26)	150-157	60.43 60.55	5.07 5.09	
3h	80	$C_{12}H_9O_6N$ (263.13)	188-192 (200-201) [21]	54.77 54.94	3.45 3.44	5.32 5.30
3i	75	$C_{13}H_9O_5F_3$ (302.20)	143-145	51.66 51.59	3.00 3.01	
4b	99	$C_{10}H_5O_4Br$	200-202 (199) [21]	44.63 44.75	1.87 1.87	
4c	89	$C_{10}H_4O_4Br_2$	275-280	34.51 34.40	1.15 1.16	
4d	94	$C_{10}H_5O_4Cl$	198-199	53.47 53.40	2.24 2.23	
4e	72	$C_{10}H_4O_4Cl_2$	198-202	46.36 46.48	1.55 1.54	
4f	84	$C_{11}H_8O_5$	175-179 (176-177) [21]	60.00 59.90	3.66 3.65	
4g	82	$C_{12}H_{10}O_6$	234-237	57.60 57.51	4.03 4.02	
4h	65	$C_{10}H_5O_6N$	237-238 (235-236) [21]	47.44 47.38	1.99 2.00	5.53 5.51
4i	91	$C_{11}H_5O_5F_3$	120-122	48.19 48.12	1.84 1.84	

Table 2

Spectral Data for Compounds **3b-i** and **4b-i**

Compound	IR (ν) cm^{-1}	^1H NMR (δ) ppm
3b	1790 (C=O) 1770 (C=O) 1600 (CH=)	DMSO-d_6 1.30-1.35 (t, 3H, CH_3CH_2), 4.30-4.35 (m, 2H, CH_2CH_3), 7.35-8.13 (m, 3H, Arom-H), 8.65 (s, 1H, CH=)
3c	1790 (C=O) 1770 (C=O) 1620 (CH=)	DMSO-d_6 1.26-1.29 (t, 3H, CH_3CH_2), 4.24-4.29 (m, 2H, CH_2CH_3), 8.14-8.22 (m, 2H, Arom-H), 8.66 (s, 1H, CH=)
3d	1750 (C=O) 1700 (C=O) 1600 (CH=)	$CDCl_3$ 1.31-1.37 (t, 3H, CH_3CH_2), 4.32-4.39 (m, 2H, CH_2CH_3), 7.19-7.53 (m, 3H, Arom-H), 8.37 (s, 1H, CH=)
3e	1790 (C=O) 1765 (C=O) 1620 (CH=)	DMSO-d_6 1.23-1.30 (t, 3H, CH_3CH_2), 4.25-4.29 (m, 2H, CH_2CH_3), 8.00-8.04 (m, 2H, Arom-H), 8.67-8.68 (d, 1H, CH=)
3f	1760 (C=O) 1690 (C=O) 1600 (CH=)	$CDCl_3$ 1.30-1.36 (t, 3H, CH_3CH_2), 3.83 (s, 3H, OCH_3), 4.29-4.36 (m, 2H, CH_2CH_3) 6.75-7.45 (m , 3H, Arom-H), 8.44 (s, 1H, CH=)
3g	1755 (C=O) 1690 (C=O) 1600 (CH=)	DMSO-d_6 1.22-1.27 (t, 3H, CH_3CH_2), 3.84 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 4.17-4.24 (m, 2H, CH_2CH_3), 6.47-6.55 (d , 2H, Arom-H), 8.52 (s, 1H, CH=)
3h	1780 (C=O) 1710 (C=O) 1610 (CH=) 1560 (NO_2) 1340 (NO_2)	$CDCl_3$ 1.34-1.38 (t, 3H, CH_3CH_2), 4.34-4.40 (m, 2H, CH_2CH_3), 7.13-8.52 (m, 4H, 3 Arom-H + CH=)
3i	1760 (C=O) 1690 (C=O) 1615 (CH=)	DMSO-d_6 1.25-1.30 (t, 3H, CH_3CH_2), 4.23-4.30 (m, 2H, CH_2CH_3), 7.52-8.01 (m, 3H, Arom-H), 8.76 (s, 1H, CH=)
4b	1740 (C=O) 1710 (C=O) 1610 (CH=)	DMSO-d_6 8.10-8.18 (m, 3H, Arom-H), 8.48 (s, 1H, CH=), 13.80 (s, 1H, COOH exchange deuterium oxide)
4c	3600-3540 (OH) 1800-1760 (C=O) 1640 (CH=)	DMSO-d_6 8.09-8.15 (d, 2H, Arom-H), 8.45 (s, 1H, CH=), 13.73 (s, 1H, COOH exchange deuterium oxide)
4d	1760 (C=O) 1720 (C=O) 1600 (CH=)	DMSO-d_6 8.12-8.20 (m, 3H, Arom-H), 8.50 (s, 1H, CH=), 13.70 (s, 1H, COOH exchange deuterium oxide)
4e	3480 (OH) 1770 (C=O) 1750 (C=O) 1620 (CH=)	DMSO-d_6 7.97-7.99 (m, 2H, Arom-H), 8.60-8.63 (d, 1H, CH=), 13.19 (s, 1H, COOH exchange deuterium oxide)
4f	3660-3200 (OH) 1720 (C=O) 1680 (C=O) 1610 (CH=)	DMSO-d_6 3.85 (s, 3H, OCH_3), 6.96-7.81 (m, 3H, Arom-H), 8.69 (s, 1H, CH=), 12.98 (s, 1H, COOH exchange deuterium oxide)
4g	3600-3200 (OH) 1745 (C=O) 1680 (C=O) 1615 (CH=)	DMSO-d_6 3.84 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 6.45-6.53 (m, 2H, Arom-H) 8.54 (s, 1H, CH=), 12.93 (s, 1H, COOH exchange deuterium oxide)

Table 2 (continued)

Compound	IR (ν) cm^{-1}	^{1}H NMR (δ) ppm
4h	3600-3400 (OH) 1750 (C=O) 1700 (C=O) 1620 (CH=)	DMSO-d_6 7.59-8.87 (m, 4H, 3 Arom-H +CH=), 13.87 (s, 1H, COOH exchange deuterium oxide)
4i	1745 (C=O) 1680 (C=O) 1615 (CH=)	DMSO-d_6 7.52-7.98 (m, 3H, Arom-H), 8.72 (s, 1H, CH=), 13.76 (s, 1H. COOH exchange deuterium oxide)

Table 3

Chemical and Physical Data for Compounds **6a-f** and **7a-i**

Compound	Yield (%)	Molecular Formula MS (Mz/M+)	mp (°C)	Elemental Analysis Calcd./Found (%) C	H	N
6a	24	$C_{23}H_{28}N_2O_4$ (396)	198-203	69.67 69.65	7.10 7.11	7.07 7.06
6b	17	$C_{23}H_{27}N_2O_4Br$ (475)	205-210	58.11 58.09	5.73 5.72	5.89 5.90
6c	20	$C_{23}H_{26}N_2O_4Br_2$ (554)	210-214	49.84 49.87	4.73 4.72	5.05 5.04
6d	5	$C_{23}H_{27}N_2O_4Cl$ (430)	195-202	64.01 63.99	6.32 6.33	6.50 6.50
6e	11	$C_{23}H_{26}N_2O_4Cl_2$ (465)	205-210	59.36 59.35	5.63 5.65	6.02 6.01
6f	26	$C_{24}H_{30}N_2O_5$ (426)	175-180	67.59 67.61	7.09 7.07	6.57 6.58
7a	72	$C_{23}H_{28}N_2O_4$ (396)	200	69.67 69.64	7.10 7.08	7.07 7.08
7b	75	$C_{23}H_{27}N_2O_4Br$ (475)	220-225	58.11 58.10	5.73 5.75	5.89 5.90
7c	75	$C_{23}H_{26}N_2O_4Br_2$ (554)	225-227	49.84 49.87	4.73 4.73	5.05 5.03
7d	86	$C_{23}H_{27}N_2O_4Cl$ (431)	219-222	64.10 64.11	6.32 6.30	6.50 6.49
7e	87	$C_{23}H_{26}N_2O_4Cl_2$ (465)	210-214	59.36 59.35	5.63 5.64	6.02 6.05
7f	67	$C_{24}H_{30}N_2O_5$ (426)	167-170	67.59 67.62	7.09 7.08	6.57 6.57
7g	78	$C_{25}H_{32}N_2O_6$ (456)	148-155	70.07 70.05	7.53 7.54	6.53 6.52
7h	89	$C_{23}H_{27}N_3O_6$ (441)	205-207	62.57 62.58	6.16 6.15	9.52 9.54
7i	91	$C_{24}H_{27}N_2O_5F_3$ (480)	193-195	59.99 59.02	5.66 5.65	5.83 5.81

Table 4

Spectroscopic Data for Compounds **6a-f** and **7a-i**

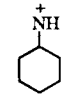
Compound	ir (ν) cm^{-1}	^{1}H nmr (δ) ppm, dmso-d_6
6a	3305 (NH) 1720 -1625 (C=O) 1610 (CH=)	0.85-1.80 (m, 22H, Cyclohexyl-H), 5.51-5.54 (d, 1H, NH exchange deuterium oxide), 7.32-7.93 (m, 4H, Arom-H), 8.09 (s, 1H, CH=)
6b	3310 (NH) 1730-1625 (C=O) 1610 (CH=)	0.85-1.74 (m, 22H, Cyclohexyl-H), 5.52-5.54 (d, 1H, NH exchange deuterium oxide), 7.36-8.05 (m, 4H, Arom-H + CH=)
6c	3310 (NH) 1735-1630 (C=O) 1610 (CH=)	0.87-1.75 (m, 22H, Cyclohexyl-H), 5.50-5.53 (d, 1H, NH exchange deuterium oxide) 7.89-8.27 (m, 3H, Arom-H + CH=)

Table 4 (continued)

Compound	ir (ν) cm^{-1}	1Hnmr (6) ppm, dmso-d_6
6d	3305 (NH) 1730-1635 (C=O) 1610 (CH=)	0.88-1.80 (m, 22H, Cyclohexyl-H), 5.52-5.54 (d, 1H, NH exchange deuterium oxide) 7.43-8.07 (m, 3H, Arom-H), 8.27 (s, 1H, CH=)
6e	3310 (NH) 1735-1630 (C=O) 1610 (CH=)	0.85-1.75 (m, 22H, Cyclohexyl-H), 5.50-5.53 (d, 1H, NH exchange deuterium oxide) 7.92-7.98 (m, 2H, Arom-H), 8.09 (s, 1H, CH=)
6f	3305 (NH) 1720-1630 (C=O) 1610 (CH=)	0.88-1.73 (m, 22H, Cyclohexyl-H) 3.82 (s, 3H, OCH_3), 5.56-5.58 (d, 1H, NH exchange deuterium oxide), 6.92-7.66 (m, 3H, Arom-H), 8.03 (s, 1H, CH=)
7a	3300 (NH) 1790 -1620 (C=O) 1600 (CH=)	0.82-1.80 (m, 22H, Cyclohexyl-H), 7.32-7.91 (m, 5H, Arom-H + NH exchange deuterium oxide), 8.09 (s, 1H, CH=)
7b	3300 (NH) 1750-1630 (C=O) 1610 (CH=)	0.90-1.75 (m, 22H, Cyclohexyl-H) 7.35-8.10 (m, 5H, Arom-H + NH exchange deuterium oxide + CH=)
7c	3310 (NH) 1760 -1630 (C=O) 1610 (CH=)	0.87-1.75 (m, 22H, Cyclohexyl-H) 7.91-8.17 (m, 4H, Arom-H + NH exchange deuterium oxide + CH=)
7d	3305 (NH) 1750-1635 (C=O) 1610 (CH=)	0.88-1.80 (m, 22H, Cyclohexyl-H) 7.43-8.06 (m, 4H, Arom-H + NH exchange deuterium oxide), 8.26 (s, 1H, CH=)
7e	3310 (NH) 1780 -1630 (C=O) 1610 (CH=)	0.85-1.75 (m, 22H, Cyclohexyl-H) 7.92-7.98 (m, 3H, Arom-H + NH exchange deuterium oxide), 8.09 (s, 1H, CH=)
7f	3305 (NH) 1760-1630 (C=O) 1610 (CH=)	0.88-1.75 (m, 22H, Cyclohexyl-H), 3.82 (s, 3H, OCH_3), 6.93-7.77 (m, 3H, Arom-H) 7.85-7.87 (d, 1H, NH exchange deuterium oxide), 8.02 (s, 1H, CH=)
7g	3300 (NH) 1740-1635 (C=O) 1610 (CH=)	0.88-1.72 (m, 22H, Cyclohexyl-H), 3.81 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 6.50-6.59 (d, 2H, Arom-H), 7.85-7.88 (d, 1H, NH exchange deuterium oxide), 8.07 (s, 1H, CH=)
7h	3315 (NH) 1760-1630 (C=O) 1610 (CH=)	0.80-1.70 (m, 22H, Cyclohexyl-H), 7.63-8.44 (m, 5H, Arom-H + NH exchange deuterium oxide + CH=)
7i	3305 (NH) 1720-1630 (C=O) 1615 (CH=)	0.86-1.79 (m, 22H, Cyclohexyl-H) 7.53-7.96 (m, 4H, Arom-H + NH exchange deuterium oxide), 8.14 (s, 1H, CH=)

Table 5

Ionic Species m/z with Relative Abundances in Parentheses

Compound	$M^{+\cdot}$	$[M-C_{13}H_{22}N_2]^{+\cdot}$	$[M-C_{13}H_{22}N_2O]^+$	
6a	396 (8%)	-----	173 (90%)	98 (100%)
6b	475 (2%)	-----	252 (50%)	98 (100%)
6c	554 (2%)	-----	331 (69%)	98 (100%)
6d	431 (2%)	-----	207 (100%)	98 (92%)
6e	465 (3%)	-----	242 (72%)	98 (100%)
6f	426 (3%)	-----	203 (72%)	98 (100%)
7a	396 (6%)	190 (38%)	173 (95%)	98 (30%)
7b	475 (3%)	269 (44%)	252 (97%)	98 (23%)
7c	554 (1%)	348 (27%)	331 (75%)	98 (33%)
7d	431 (2%)	225 (57%)	207 (100%)	98 (35%)
7e	465 (3%)	259 (40%)	242 (100%)	98 (23%)
7f	426 (2%)	220 (59%)	203 (100%)	98 (35%)
7g	456 (2%)	250 (58%)	233 (100%)	98 (29%)
7m	441 (3%)	235 (74%)	218 (88%)	98 (45%)
7i	480 (1%)	274 (42%)	257 (90%)	98 (26%)

room temperature to a stirred solution of coumarin-3-carboxylic acids **4b-i** (0.01 mole) in 50 ml of dry tetrahydrofuran. The reaction mixture was stirred overnight and the colourless precipitate was filtered off. The precipitate, when crystallized from methanol gave **7a-i**. When starting from **4a-f**, the filtrate was evaporated under reduced pressure to give **6a-f**. The analytical and spectral data of compounds **7a-i** and **6a-f** are reported in Tables 3 and 4.

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