

## SYNTHESIS OF COUMARIN-3-*O*-ACYLISOUREAS BY DIFFERENT CARBODIIMIDES

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**Abstract** - The synthesis and isolation of some *O*-acylisourea derivatives are described. The reaction between coumarin-3-carboxylic acids and diisopropyl- and di-*tert*-butyl-carbodiimides leads only to coumarin-isourea derivatives except for two reactions which lead, as by-products, also to coumarin-urea derivatives.

Carbodiimides are very important reagents used in peptide and nucleotide syntheses, heterocycle synthesis, oxidation, cycloaddition and alkylation reactions and so on.<sup>1</sup> Their use continues to provide a useful route to esters and the mechanism of their reaction with carboxylic acids has been extensively investigated.<sup>2</sup> In a previous work<sup>3</sup> we studied the reaction of some coumarin-3-carboxylic acids with dicyclohexylcarbodiimide, DCC (A), and we isolated coumarin derivatives of dicyclohexylisourea (I) and of dicyclohexylurea (II) (Figure 1).

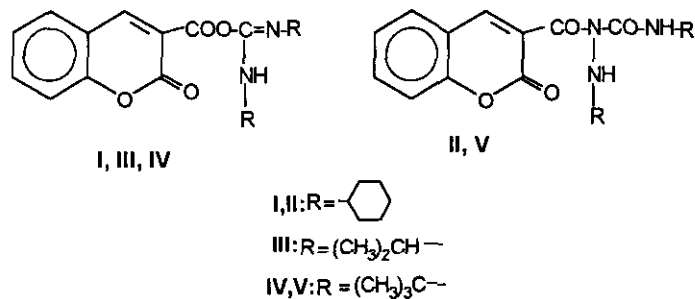


Figure 1

Moving from the consideration that coumarins constitute an important class of naturally occurring compounds with useful pharmacological activity<sup>4,7</sup> we carried on the previous research<sup>3</sup> completing the series of dicyclohexyl derivatives with two new coumarin compounds (**5a,b**) and performing the same reaction starting from the coumarin acids (**4c-l**) and using as reagents the diisopropylcarbodiimide, DISP (**B**), and the di-*tert*-butylcarbodiimide, DTB (**C**), also with the aim to confirm the reaction route. As attended the reaction led only to *O*-acylisourea derivatives III and IV except for two urea derivatives type V obtained using the di-*tert*-butylcarbodiimide as reagent. (Figure 1)

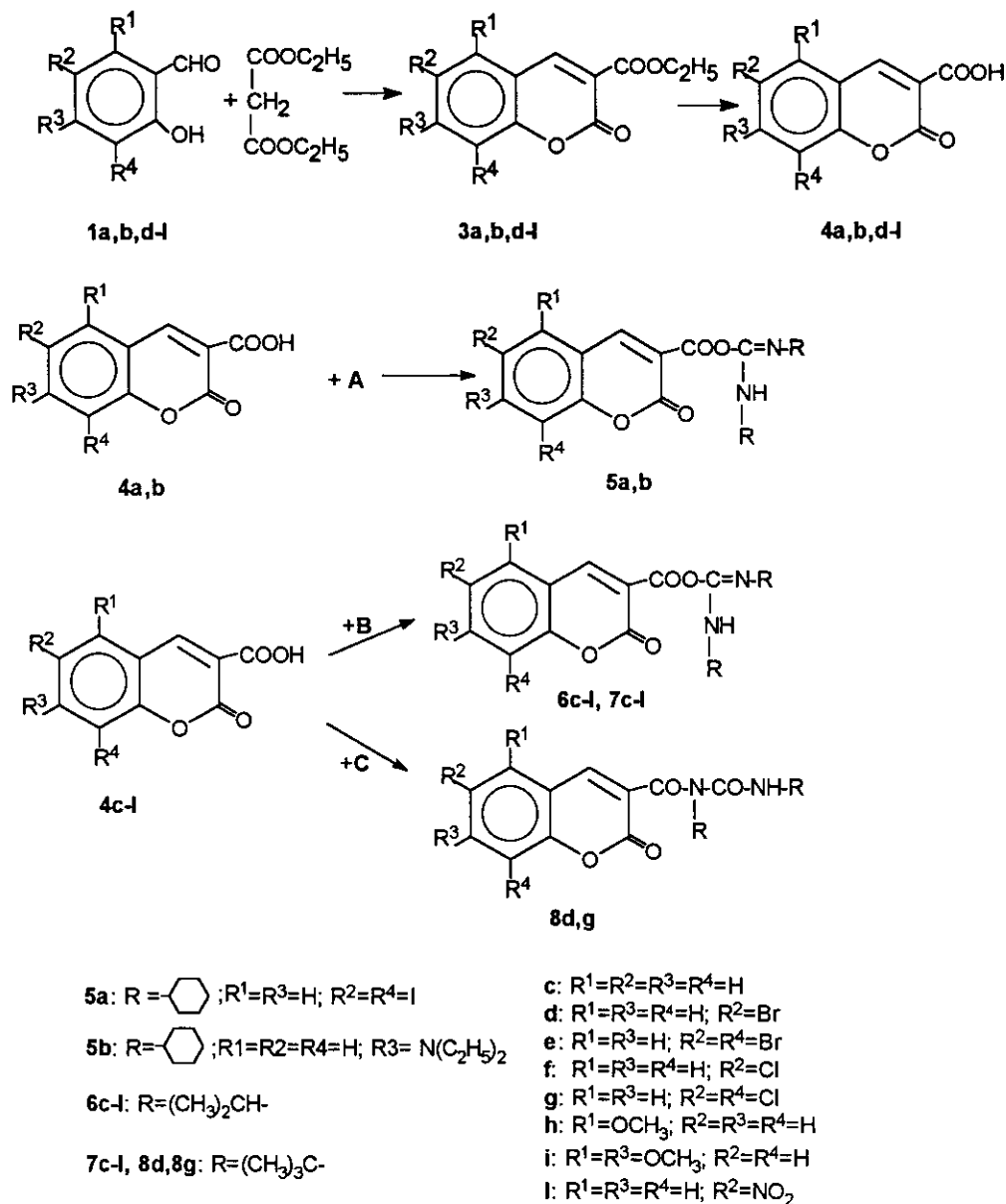
Coumarin-3-carboxylic acids (**4a,b,d-l**), were prepared according to the literature.<sup>3,8</sup> Details about the synthesis of **3a,b** and **4a,b**, along with their analytical and spectroscopic data are reported in the experimental section and in Table 1. For the other compounds the data were in accordance with literature.<sup>3</sup> Coumarin acids (**4a,b**) reacted with DCC (**A**) while acids (**4c-l**) reacted with DISP (**B**) and DTB (**C**) obtaining, in very good yields, *O*-acylisoureas (**6c-l**) and (**7c-l**), respectively. Only starting from coumarin acids (**4d**) and (**4g**) and DTB (**C**) we obtained, in very poor yields, urea derivatives (**8d**) and (**8g**) (Scheme I).

Isoureas (**5a,b**, **6c-l**, **7c-l**) and ureas (**8d,g**) were identified by analytical and spectroscopic methods. The difference between isoureas and ureas derivatives was evidenced by IR spectra (amidic carbonyl band in type -6 and -7 derivatives and ester carbonyl band in type-8 derivatives), <sup>1</sup>H NMR spectra (peak of the NH group measured at *ca.* 5.5 ppm for type-6 and -7 derivatives and measured at *ca.* 8.0 ppm for type-8 derivatives) and MS spectra (presence of the coumarin acid ion [C<sub>10</sub>H<sub>6</sub>O<sub>4</sub>]<sup>+•</sup>, *m/z* 190, only in the mass spectra of type-8 derivatives).

A preliminary antimicrobial screening performed against a *Bacillus subtilis* strain evidenced a good activity only for compounds (**6e**) and (**8g**) (Minimal Inhibitory Concentration 6.25 µg/mL and 12.5 µg/mL, respectively).

## EXPERIMENTAL

Melting points were determined using a Köfler apparatus and are uncorrected. The IR spectra were recorded with a Perkin Elmer 1310 spectrophotometer on sodium chloride mulls. The <sup>1</sup>H NMR spectra were recorded on a Varian Unity 300 instrument and the chemical shifts (δ) refer to tetramethylsilane. Elemental analyses (C, H, N) were performed on a Carlo Erba model 1106 Elemental Analyser. MS spectra were taken with a QMD 1000 instrument (Fisons Instruments) at 70 eV using a direct inlet system. Reagent-grade commercially available reagents and solvents were used. All compounds and solvents were rigorously dried before use according to standard methods.<sup>9</sup> Coumarin-3-carboxylic esters (**3a,b,d-l**) and acids (**4a,b,d-l**) were prepared according to the literature.<sup>3,8</sup> Compound (**4c**) was commercially available.



Scheme I

*General procedure for the preparation of ethyl coumarin-3-carboxylates (3a,b,d-l)*

Piperidine (0.5 mL) and acetic acid (0.01 mL) were added to a solution of salicyl aldehydes (**1 a,b,d-l**) (0.02 mol) in 150 mL of 95% ethanol. When the solution was clear 4.22 g (0.026 mol) of diethyl malonate was added. The reaction solution was refluxed with stirring for 24 h. The colourless substance which

precipitated from the reaction mixture was filtered off and proved to be **3a,b,d-l** in almost quantitative yields. The analytical and spectral data of compounds (**3a,b**) are reported in Table 1, while for compounds (**3d-l**) data were in accord with literature.<sup>3</sup> Compound (**4c**) was commercially available.

*General procedure for the preparation of coumarin-3-carboxylic acids (4a,b,d-l)*

Suspensions of ethyl coumarin-3-carboxylate (**3a,b,d-l**) (0.015 mol) in 50 mL of 20% sodium hydroxide were refluxed under stirring for 2 h. Hydrochloric acid (37%) was added at 0 °C to the clear solution until a pH of 1-2 was reached. The colourless precipitate was filtered off. The residue was washed with ether and dried. The analytical and spectral data for compounds (**4a,b**) are reported in Table 1 while for compounds (**4d-l**) data were in accord with literature.<sup>3</sup>

*General procedure for the preparation of isourea derivatives (5a,b, 6c-l, 7c-l) and urea derivatives (8d,g).*

A solution of DCC (**A**) (0.01 mol) in 50 mL of dry THF was added dropwise at rt to a stirred solution of coumarin-3-carboxylic acids (**4a,b**) (0.01 mol) in 50 mL of dry THF. The same procedure was performed starting from DISP (**B**) and DTP (**C**) and coumarin acids (**4c-l**). The reaction mixture was stirred overnight and the colourless precipitate was filtered off and crystallized from methanol to give **5a,b**, **6c-l** and **7c-l** respectively. When starting from **4d** and **4g** the filtrate, evaporated under reduced pressure gave **8d** and **8g**. The analytical and spectral data of compounds (**5a,b**, **6c-l**, **7c-l**, **8d** and **8g**) are reported in Table 1.

Table 1. Analytical and spectral data for compounds (**3a,b**, **4a,b**, **5a,b**, **6c-l**, **7c-l**, **8d** and **8g**).

Compd.	Yield %	mp (°C)	IR ( $\nu_{\max}$ $\text{cm}^{-1}$ ) nujol	<sup>1</sup> H NMR ( $\delta$ , ppm) DMSO-d <sub>6</sub>	Elemental Analysis Calcd (%) (Found)		
					C	H	N
<b>3a</b>	90	182-185	1765, 1700	1.26-1.30 (t, $J=5.35$ Hz, 3H, $\text{CH}_3\text{-CH}_2$ ), 4.22-4.30 (q, $J=5.35$ Hz, 2H, $\text{CH}_2\text{-CH}_3$ ), 8.24 (s, 1H Arom), 8.38 (s, 1H, Arom), 8.55 (s, 1H, CH=)	30.66 (30.59)	1.72 (1.72)	

<b>3b</b>	80	Oil	1760, 1700, 1610	1.10-1.13 (t, $J=5.85$ Hz, 6H, $2\text{CH}_3\text{-CH}_2$ ), 1.26- 1.31 (t, $J=5.37$ Hz, 3H, $\text{CH}_3\text{-CH}_2$ ), 3.30-3.37 (q, $J=5.85$ Hz, 4H, $2\text{CH}_2\text{-}$ $\text{CH}_3$ ), 4.22-4.30 (q, $J=5.37$ Hz, 2H, $\text{CH}_2\text{-}$ $\text{CH}_3$ ), 6.35 (s, 1H, Arom), 6.48-6.52 (d, $J=9.28$ Hz, 1H, Arom), 7.23-7.27 (d, $J=9.28$ Hz, 1H, Arom), 8.32(s, 1H, CH=)	66.42 (66.50)	6.62 6.64	4.84 4.83)
<b>4a</b>	95	273-274	1765, 1650, 1610	8.24 (s, 1H, Arom), 8.38 (s, 1H, Arom), 8.55 (s, 1H, CH=), 12.48 (s, 1H, COOH, D <sub>2</sub> O exch.)	27.17 (27.14)	0.91 0.91)	
<b>4b</b>	90	215-217	1760, 1645, 1610	1.07-1.12 (t, $J=6.84$ Hz, 6H, $2\text{CH}_3\text{-CH}_2$ ), 3.41- 3.48 (q, $J=6.84$ Hz, 4H, $2\text{CH}_2\text{-CH}_3$ ), 6.73-6.77 (d, $J=9.28$ Hz, 1H, Arom), 6.53 (s, 1H, Arom), 7.58-7.61 (d, $J=9.28$ Hz, 1H, Arom), 8.55(s, 1H, CH=), 12.48 (s, 1H, COOH, D <sub>2</sub> O exch.)	64.35 (64.33)	5.79 5.78	5.36 5.37)
<b>5a</b>	80	205-212	3350, 1750, 1710, 1610	0.79-1.74 (m, 22H, cyclohexyl-H), 7.88-7.90 (d, $J=7.81$ Hz, 1H, NH, D <sub>2</sub> O exch.), 7.98 (s, 1H, Arom), 8.16 (s, 1H, Arom), 8.35 (s, 1H, CH=)	42.61 (42.65)	4.04 4.05	4.32 4.32)
<b>5b</b>	70	180-182	3300, 1760, 1700, 1620	0.90-1.71 (m, 22H, cyclohexyl-H + $2\text{CH}_3\text{-}$ $\text{CH}_2$ ), 6.49 (s, 1H, Arom), 6.66-6.68 (d, $J=8.79$ Hz, 1H, Arom), 7.41-7.44 (d, $J=8.79$ Hz, 1H, Arom), 7.72-7.75 (d, $J=8.30$ Hz,	69.35 (69.34)	7.98 7.99	8.99 8.97)

				1H, NH, D <sub>2</sub> O exch.), 7.86 (s, 1H, CH=)			
<b>6c</b>	80	163-165	3350, 1770, 1710, 1620	0.77-0.79 (d, $J=6.35$ Hz, 6H, 2CH <sub>3</sub> ), 1.24-1.26 (d, $J=6.35$ Hz, 6H, 2CH <sub>3</sub> ), 3.48-3.54 (m, 1H, CH(CH <sub>3</sub> ) <sub>2</sub> ), 4.36-4.45 (m, 1H, CH(CH <sub>3</sub> ) <sub>2</sub> ), 7.33-7.85 (m, 5H, Arom + NH, D <sub>2</sub> O exch.), 8.13 (s, 1H, CH=)	64.54 (64.55	6.37 6.37	8.86 8.87)
<b>6d</b>	63	202-203	3300, 1765, 1700, 1610	0.78-0.81 (t, $J=6.35$ Hz, 6H, 2CH <sub>3</sub> ), 1.25-1.28 (t, $J=6.35$ Hz, 6H, 2CH <sub>3</sub> ), 3.49-3.55 (m, 1H, CH(CH <sub>3</sub> ) <sub>2</sub> ), 4.39-4.43 (m, 1H, CH(CH <sub>3</sub> ) <sub>2</sub> ), 7.38-7.41 (d, $J=8.79$ Hz, 1H, Arom), 7.76-7.86 (m, 2H, Arom), 8.05-8.10 (d, $J=12.21$ Hz, 2H, CH= + NH, D <sub>2</sub> O exch.)	51.65 (51.68	4.84 4.83	7.09 7.09)
<b>6e</b>	40	210-211	3310, 1760, 1690, 1620	0.79-0.81 (t, $J=6.35$ Hz, 6H, 2CH <sub>3</sub> ), 1.25-1.27 (t, $J=6.35$ Hz, 6H, 2CH <sub>3</sub> ), 3.36-3.54 (m, 1H, CH(CH <sub>3</sub> ) <sub>2</sub> ), 4.37-4.42 (m, 1H, CH(CH <sub>3</sub> ) <sub>2</sub> ), 7.85-7.88 (d, $J=7.81$ Hz, 1H, Arom), 8.08-8.17 (m, 3H, Arom + CH= + NH, D <sub>2</sub> O exch.)	43.06 (43.01	3.83 3.84	5.91 5.90)
<b>6f</b>	10	200-202	3320, 1760, 1700, 1610	0.78-0.81 (t, $J=6.35$ Hz, 6H, 2CH <sub>3</sub> ), 1.24-1.27 (t, $J=6.35$ Hz, 6H, 2CH <sub>3</sub> ), 3.50-3.53 (m, 1H, CH(CH <sub>3</sub> ) <sub>2</sub> ), 4.39-4.42 (m, 1H, CH(CH <sub>3</sub> ) <sub>2</sub> ), 7.44-7.93 (m, 4H, 3Arom + NH, D <sub>2</sub> O exch.), 8.10	58.20 (58.14	5.46 5.47	7.99 7.98)

6g	57	190-192	3320, 1720, 1630, 1610	(s, 1H, CH=)	52.00	4.71	7.27
				0.80-1.34 (m, 14H, 2CH(CH <sub>3</sub> ) <sub>2</sub> ), 5.47 (s, 1H, NH, D <sub>2</sub> O exch.), 7.89-7.99 (m, 2H, Arom), 8.15 (s, 1H, CH=)			
6h	78	160-161	3310, 1750, 1700, 1600	0.78-0.80 (d, <i>J</i> =6.35 Hz, 6H, 2CH <sub>3</sub> ), 1.23-1.25 (d, <i>J</i> =6.35 Hz, 6H, 2CH <sub>3</sub> ), 3.48-3.55 (m, 1H, CH(CH <sub>3</sub> ) <sub>2</sub> ), 3.82 (s, 3H, OCH <sub>3</sub> ), 4.37-4.45 (m, 1H, CH(CH <sub>3</sub> ) <sub>2</sub> ), 6.93-6.96 (d, <i>J</i> =8.79 Hz, 1H, Arom), 7.01 (s, 1H, Arom), 7.66-7.69 (d, <i>J</i> =8.79 Hz, 1H, Arom), 7.77-7.80 (d, <i>J</i> =7.33 Hz, 1H, NH, D <sub>2</sub> O exch.), 8.06 (s, 1H, CH=)	62.41	6.40	8.09
				6H, 2CH <sub>3</sub> ), 1.23-1.25 (d, <i>J</i> =6.35 Hz, 6H, 2CH <sub>3</sub> ), 3.48-3.55 (m, 1H, CH(CH <sub>3</sub> ) <sub>2</sub> ), 3.82 (s, 3H, OCH <sub>3</sub> ), 4.37-4.45 (m, 1H, CH(CH <sub>3</sub> ) <sub>2</sub> ), 6.93-6.96 (d, <i>J</i> =8.79 Hz, 1H, Arom), 7.01 (s, 1H, Arom), 7.66-7.69 (d, <i>J</i> =8.79 Hz, 1H, Arom), 7.77-7.80 (d, <i>J</i> =7.33 Hz, 1H, NH, D <sub>2</sub> O exch.), 8.06 (s, 1H, CH=)	(62.45)	6.41	8.08)
6i	58	193-195	3300, 1760, 1700, 1610	0.79-0.81 (d, <i>J</i> =6.35 Hz, 6H, 2CH <sub>3</sub> ), 1.21-1.23 (d, <i>J</i> =6.35 Hz, 6H, 2CH <sub>3</sub> ), 3.26-3.43 (m, 1H, CH(CH <sub>3</sub> ) <sub>2</sub> ), 3.82 (s, 3H, OCH <sub>3</sub> ), 3.88 (s, 3H, OCH <sub>3</sub> ), 4.37-4.45 (m, 1H, CH(CH <sub>3</sub> ) <sub>2</sub> ), 6.50 (s, 1H, Arom), 6.60 (s, 1H, Arom), 7.78-7.80 (d, <i>J</i> =7.82 Hz, 1H, NH, D <sub>2</sub> O exch.), 8.08 (s, 1H, CH=)	60.62	5.89	7.44
				0.79-0.81 (d, <i>J</i> =6.35 Hz, 6H, 2CH <sub>3</sub> ), 1.21-1.23 (d, <i>J</i> =6.35 Hz, 6H, 2CH <sub>3</sub> ), 3.26-3.43 (m, 1H, CH(CH <sub>3</sub> ) <sub>2</sub> ), 3.82 (s, 3H, OCH <sub>3</sub> ), 3.88 (s, 3H, OCH <sub>3</sub> ), 4.37-4.45 (m, 1H, CH(CH <sub>3</sub> ) <sub>2</sub> ), 6.50 (s, 1H, Arom), 6.60 (s, 1H, Arom), 7.78-7.80 (d, <i>J</i> =7.82 Hz, 1H, NH, D <sub>2</sub> O exch.), 8.08 (s, 1H, CH=)	(60.62)	5.88	7.44)
6l	60	196-197	3340, 1750, 1640, 1610	0.80-0.82 (d, <i>J</i> =6.84 Hz, 6H, 2CH <sub>3</sub> ), 1.26-1.29 (d, <i>J</i> =6.84 Hz, 6H, 2CH <sub>3</sub> ), 3.53-3.58 (m, 1H, CH(CH <sub>3</sub> ) <sub>2</sub> ), 4.38-4.47 (m, 1H, CH(CH <sub>3</sub> ) <sub>2</sub> ), 7.63-7.67 (d, <i>J</i> =9.28 Hz, 1H, Arom), 7.86-7.89 (d,	56.50	5.30	11.63
				0.80-0.82 (d, <i>J</i> =6.84 Hz, 6H, 2CH <sub>3</sub> ), 1.26-1.29 (d, <i>J</i> =6.84 Hz, 6H, 2CH <sub>3</sub> ), 3.53-3.58 (m, 1H, CH(CH <sub>3</sub> ) <sub>2</sub> ), 4.38-4.47 (m, 1H, CH(CH <sub>3</sub> ) <sub>2</sub> ), 7.63-7.67 (d, <i>J</i> =9.28 Hz, 1H, Arom), 7.86-7.89 (d,	(56.47)	5.31	11.61)

				<i>J</i> =7.33 Hz, 1H, Arom), 8.33 (s, 1H, NH, D <sub>2</sub> O exch.), 8.40-8.44 (d, <i>J</i> =9.28 Hz, 1H, Arom), 8.81 (s, 1H, CH=)				
7c	78	210-212	3340, 1720, 1650, 1610	0.89 (s, 9H, 3CH <sub>3</sub> ), 1.44 (s, 9H, 3CH <sub>3</sub> ), 7.32-7.72 (m, 4H, Arom), 7.94 (s, 1H, NH, D <sub>2</sub> O exch.), 8.01 (s, 1H, CH=)	65.04 (65.03)	7.28 7.30	8.43 8.43)	
7d	42	230-231	3335, 1715, 1640, 1610	0.90 (s, 9H, 3CH <sub>3</sub> ), 1.43 (s, 9H, 3CH <sub>3</sub> ), 7.37-7.40 (d, <i>J</i> =8.79 Hz, 1H, Arom), 7.75-7.77 (d, <i>J</i> =8.79 Hz, 1H, Arom), 7.95-7.99 (m, 3H, Arom + NH, D <sub>2</sub> O exch, + CH=)	52.56 (52.59)	5.64 5.64	6.81 6.82)	
7e	61	218-219	3320, 1800, 1720, 1610	0.92 (s, 9H, 3CH <sub>3</sub> ), 1.45 (s, 9H, 3CH <sub>3</sub> ), 8.03-8.16 (m, 4H, 2Arom + NH, D <sub>2</sub> O exch, + CH=)	44.10 (44.16)	4.52 4.51	5.72 5.73)	
7f	68	220-222	3370, 1750, 1680, 1610	0.92 (s, 9H, 3CH <sub>3</sub> ), 1.45 (s, 9H, 3CH <sub>3</sub> ), 7.45-7.48 (d, <i>J</i> =8.79 Hz, 1H, Arom), 7.64-7.68 (d, <i>J</i> =8.79 Hz, 1H, Arom), 7.87 (s, 1H, Arom), 7.98- 7.99 (d, <i>J</i> =4.88 Hz, 2H, NH, D <sub>2</sub> O exch, + CH=)	58.93 (58.90)	6.32 6.32	7.64 7.64)	
7g	60	190-192	3310, 1760, 1660, 1610	0.92 (s, 9H, 3CH <sub>3</sub> ), 1.44 (s, 9H, 3CH <sub>3</sub> ), 7.68-8.06 (m, 3H, 2H, Arom + NH, D <sub>2</sub> O exch,), 8.66 (s, 1H, CH=)	53.87 (53.86)	5.53 5.54	6.98 7.00)	
7h	77	191-193	3320, 1750, 1670, 1600	0.91 (s, 9H, 3CH <sub>3</sub> ), 1.44 (s, 9H, 3CH <sub>3</sub> ), 3.88 (s, 3H, OCH <sub>3</sub> ), 7.25-7.30 (m, 3H, Arom), 7.95-7.99 (d, <i>J</i> =12.70 Hz, 2H, NH, D <sub>2</sub> O exch, + CH=)	62.96 (62.96)	7.23 7.24	7.73 7.72)	



7i	75	195-197	3320, 1750, 1660, 1600	0.91 (s, 9H, 3CH <sub>3</sub> ), 1.44 (s, 9H, CH <sub>3</sub> ), 3.84 (s, 3H, OCH <sub>3</sub> ), 3.88 (s, 3H, OCH <sub>3</sub> ), 6.45-6.53 (m, 2H, Arom), 8.15 (s, 1H, NH, D <sub>2</sub> O exch), 8.54 (s, 1H, CH=)	61.21 (61.19)	7.19 7.21	7.14 7.13)
7l	74	220-222	3300, 1730, 1650, 1600	0.92 (s, 9H, 3CH <sub>3</sub> ), 1.46 (s, 9H, 3CH <sub>3</sub> ), 7.65-7.67 (d, J=9.28 Hz, 1H, Arom), 8.05 (s, 1H, CH=), 8.20 (s, 1H, NH, D <sub>2</sub> O exch), 8.40-8.43 (d, J=8.79 Hz, 1H, Arom), 8.73 (s, 1H, Arom)	57.28 (57.33)	6.14 6.14	11.13 11.13)
8d	10	185-186	3460, 1700, 1670, 1600	0.89-1.44 (m, 18H, 6CH <sub>3</sub> ), 5.39 (s, 1H, NH, D <sub>2</sub> O exch), 7.34-8.65 (m, 4H, 3Arom + CH=)	57.73 (57.72)	5.86 5.87)	
8g	53	185-187	3450, 1760, 1680, 1610	0.90-1.44 (m, 18H, 6CH <sub>3</sub> ), 5.39 (s, 1H, NH, D <sub>2</sub> O exch), 7.98 (s, 1H, Arom), 8.00 (s, 1H, Arom), 8.65 (s, 1H, CH=)	59.23 (59.27)	5.76 5.76)	

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## REFERENCES AND NOTES

1. A. Williams and I.T. Ibrahim, *Chem.Rev.*, 1981, **81**, 589 and references cited therein.
2. I.T. Ibrahim and A. Williams, *J.Am.Chem.Soc.*, 1978, **100**, 7420; I.T. Ibrahim and A. Williams, *J.Chem.Soc., Chem.Commun.*, 1980, 25; A. Arendt and A.M. Kolodziejczyk, *Tetrahedron Lett.*, 1978, 3867; G. Doleschall and K. Lempert, *Tetrahedron Lett.*, 1963, 1195; H.G. Khorana, *Chem.Rev.*, 1953, **53**, 145.
3. L. Bonsignore, F. Cottiglia, S.M. Lavagna, A.M. Maccioni and D. Secci, *J.Heterocycl. Chem.*, 1995, **32**,

573.

4. W.O.Foye, "Principi di Chimica Farmaceutica" ed. by Piccin Nuova Libreria S.p.A., Padova, Italy, 1991, p. 416.
5. L.Lazzeri Andreani and E.Lapi, *Boll.Chim.Farm.*, 1960, **99**, 583.
6. Z.Y.Lang, C.Baozhen, Z.Keqin, X.Mouli, Z.Lizhu and L.Xinghan, *Yaoxue Xuebao*, 1982, **17**, 17 (*Chem.Abstr.*, 1982, **96**, 135383e).
7. L.Bonsignore, G.Loy, D.Secci and A.Calignano, *Eur.J.Med.Chem.*, 1993, **28**, 517
8. R.O.Clinton and S.C.Laskowski, *J.Am.Chem.Soc.*, 1949, **71**, 3602.
9. "Vogel's Textbook of Practical Organic Chemistry", ed. by Longman Scientific & Technical, Essex, England, 1989, p. 395.

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