SYNTHESIS AND PHOTOBIOLOGICAL ACTIVITY OF N-SUBSTITUTED 2-OXO-2*H*-1-BENZOPYRAN-3-(THIO)CARBOXAMIDES.

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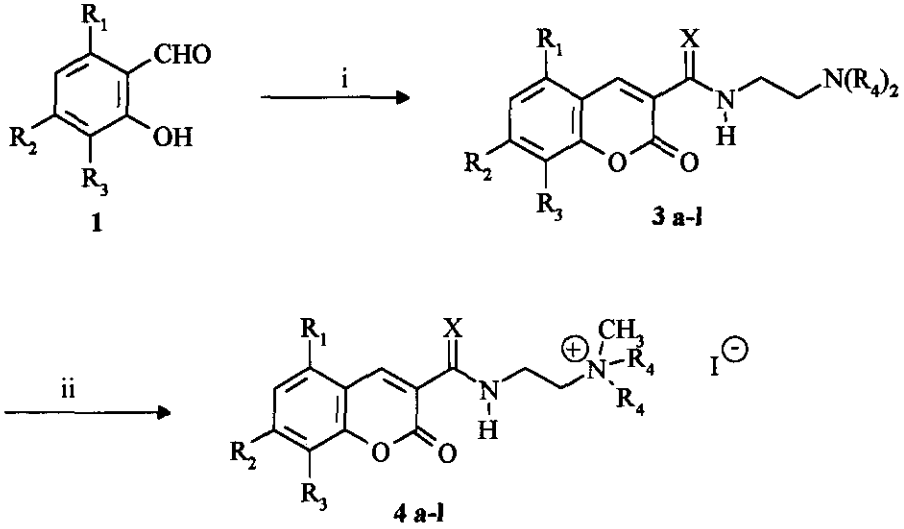
Abstract-Several polyfunctional coumarins and the corresponding quaternary ammoniums, associated with a coplanar structure have been synthesized in order to test the relationships between structure and photobiological activity. *In vitro* studies on their phototoxic effects in yeasts suggest that five of them are able to intercalate in DNA and to covalently photobind to DNA.

Furocoumarins such as 8-methoxypsoralen, are used as photoactive drugs for treatment of different skin diseases[1] in medicine, or as photoreactive probes of nucleic acid in biochemistry.[2] Photoactivable structural analogs are largely described in literature and capable of intercalating into double stranded DNA upon uvA irradiation. In order to appreciate if the affinity for DNA sequences is increased for molecules in which a positive center could counteract the negative charge of phosphate residues, we undertook synthesis of coumarins (**4a-l**) substituted with 2-alkylaminoalkyl chain which is described in this paper.

Scheme 1

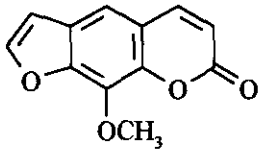


(i) $C_2H_5OC(O)CH_2C(X)NHCH_2CH_2N(R_4)_2$ (**2a-f**), piperidine (C_6H_6); (ii) CH_3I

2-Hydroxybenzaldehydes (**1**) were treated with malonic derivatives (**2a-f**) in a solvent (method A) or without a solvent (method B) and converted into coumarin-3-(thio)carboxamides (**3a-l**) (yield: 60-83%) or their hydrochlorides (for the biological assays). The quaternary ammonium synthesis was classically achieved using the corresponding alkyl halide in acetone (scheme 1).

	$N(R_4)_2$	X	R_1	R_2	R_3
a	$N(CH_3)_2$	O	H	H	OCH_3
b	$N(C_2H_5)_2$	O	H	H	OCH_3
c	morpholino	O	H	H	OCH_3
d	$N(CH_3)_2$	O	OCH_3	OCH_3	H
e	$N(C_2H_5)_2$	O	OCH_3	OCH_3	H
f	morpholino	O	OCH_3	OCH_3	H
g	$N(CH_3)_2$	S	H	H	OCH_3
h	$N(C_2H_5)_2$	S	H	H	OCH_3
i	morpholino	S	H	H	OCH_3
j	$N(CH_3)_2$	S	OCH_3	OCH_3	H
k	$N(C_2H_5)_2$	S	OCH_3	OCH_3	H
l	morpholino	S	OCH_3	OCH_3	H

The photoinduced cytotoxic activities were determined as previously[3] by measuring growth inhibition in the yeast *Saccharomyces cerevisiae*. The results obtained for 8-methoxypsoralen (8-MOP)[3-6] (**5**) and angelicin[3,6] (**6**) in clonogenic assays were taken as references. A haploid DNA repair deficient triple mutant *rad2rad6rad52* of *Saccharomyces cerevisiae*[5] was used in the phototoxicity test as described previously.[7] The data showed that only the 5,7-dimethoxycoumarin-3-thiocarboxamide (**3j**) (10^{-5} M upon 36 $kJ.m^{-2}$ irradiation with uvA light at 320-400 nm) exhibited photocytotoxic activity comparable to 8-MOP under the same experimental conditions. This phototoxicity may be explained by the close structural analogy with 5,7-dimethoxycoumarin (**7**) known for its photobiological activity.[4,8-10]



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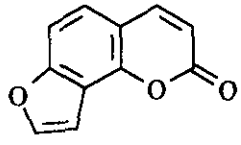

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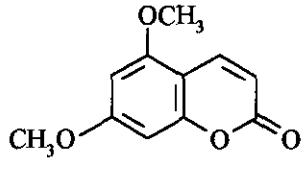

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The formation of an intramolecular hydrogen bond =O···H-N -as evidenced by ^1H nmr and radiocrystallography[11]- results in a coplanar pseudocyclic structure which favors its intercalating in DNA and subsequent photobinding.

The corresponding quaternary ammonium (**4j**) was less photoreactive than (**3j**). The activity was comparable to that of angelicin. On the other hand, the quaternary ammonium derivatives (**4g**, **4k**, **4l**) were approximately 5 times less active than compound (**4j**) whereas the corresponding amines (**3g**, **3k**) and (**3l**) were inactive. Based on the clonogenic survival responses of the triple mutant 8-MOP plus uvA treatments in comparison to the wild type strain[5,7] and the sensitivity of wild type cells to angelicin plus uvA treatments,[6] it can be shown that in a clonogenic survival assay in this mutant, approximately 1.35 $kJ.m^{-2}$, 4.05 $kJ.m^{-2}$ and 20.25 $kJ.m^{-2}$ of uvA are needed in the presence of compounds (**3j**), (**4j**), and (**4k**, **4l**) respectively to give 37% survivors. In other words, at the 37% survival level a 3 fold and 15 fold higher dose of uvA is needed with compounds (**4j**), (**4k**), and (**4l**) than with (**3j**).

This preliminary study pointed out the interest of thioamide compounds (the amides were inactive) and the importance of the 5,7-dimethoxy substitution on heterocyclic moiety and of the dimethylaminoethyl chain.

EXPERIMENTAL

Mp are measured by Buchi-Tottoli apparatus. Ir spectra are recorded with Perkin-Elmer apparatus in chloroform or in potassium bromide (1%). ^{1}H-Nmr spectra are recorded with Varian EM390 spectrometer in a solution ($CDCl_3$, DMSO-d_6, or CF_3COOD). The shifts are expressed in ppm from TMS (s, d, t, m, meaning singulet, doublet, triplet, multiplet respectively).

Ethyl *N*-(2-dialkylaminoethyl)carboxamidoacetates (2a-c)

A mixture of 2-dialkylaminoethylamine (0.1 mol) and diethyl malonate (32 g, 0.2 mol) was stirred at 40°C for 24 h. (**2a**) and (**2b**) were purified by distillation; (**2c**) was crystallized from petroleum ether.
Yield, ir and ^{1}H-nmr are listed in Table 1.

Ethyl *N*-(dialkylaminoethyl)thiocarboxamidoacetates (2d-f)

2-Dialkylaminoethylamine (0.11 mol) was added dropwise at room temperature to a solution of ethyl 3-methylthio-3-thioxopropionate[12] (17.8 g, 0.1 mol) in ether (80 ml). The mixture was stirred at room temperature for 5 h. The solvent removal afforded an oil.
Yield, ir and ^{1}H-nmr are listed in Table 1.

Table 1 : Physicochemical and spectral data of compounds (2a-f)

Compound	X $N(R_4)_2$	Yield (%)	bp (torr)/mp (°C)	Molecular Formula	Microanalyses (%) C calcd found	 H calcd found	 N calcd found	1H-Nmr (DMSO-d_6) δ (ppm)	Ir (cm^{-1})
2a	O $N(CH_3)_2$	60	112 (0.15)	$C_9H_{18}N_2O_3$	53.44 53.29	8.97 8.70	13.85 13.61	1.30 (t, 3H, J = 7 Hz); 2.25 (s, 6H); 2.45 (t, 2H, J = 7 Hz); 3.30 (s, 2H); 3.35 (q, 2H, J = 7 Hz); 4.20 (q, 2H, J = 7 Hz); 7.30 (s, 1H, NH)	3600-3200 1735, 1655
2b	O $N(C_2H_5)_2$	56	160 (0.20)	$C_{11}H_{22}N_2O_3$	57.36 57.09	9.63 9.47	12.17 12.30	1.00 (t, 6H, J = 7 Hz); 1.30 (t, 3H, J = 7 Hz), 2.60 (m, 6H); 3.30 (s, 2H); 3.40 (q, 2H, J = 7 Hz); 4.25 (q, 2H, J = 7 Hz); 7.40 (s, 1H, NH)	3600-3200 1735, 1655
2c	O morpholino	52	109	$C_{11}H_{20}N_2O_4$	54.08 53.99	8.25 8.23	11.47 11.40	1.30 (t, 3H, J = 7 Hz); 2.60 (m, 6H); 3.30 (s, 2H); 3.40 (q, 2H, J = 7 Hz); 3.75 (m, 4H); 4.20 (q, 2H, J = 7 Hz); 7.40 (s, 1H, NH)	3600-3200 1730, 1655
2d	S $N(CH_3)_2$	91	-	$C_9H_{18}N_2O_2S$	49.54 49.51	8.25 8.16	12.84 12.71	1.30 (t, 3H, J = 7 Hz); 2.25 (s, 6H);2.55 (t, 2H, J = 7 Hz); 3.70 (q, 2H, J = 7 Hz); 3.80 (s, 2H); 4.25 (q, 2H, J = 7 Hz); 8.70 (s, 1H, NH)	3500-3200 1730
2e	S $N(C_2H_5)_2$	98	-	$C_{11}H_{22}N_2O_2S$	53.65 53.64	8.94 8.99	11.38 11.49	1.05 (t, 6H, J = 7 Hz); 1.30 (t, 3H, J = 7 Hz); 2.60 (m, 6H); 3.70 (q, 2H, J = 7 Hz); 3.80 (s, 2H); 4.20 (q, 2H, J = 7 Hz); 8.75 (s, 1H, NH)	3500-3200 1730
2f	S morpholino	97	-	$C_{11}H_{20}N_2O_3S$	50.77 50.65	7.69 7.80	10.77 10.60	1.30 (t, 3H, J = 7 Hz); 2.60 (m, 6H); 3.65 (m, 4H); 3.70 (q, 2H, J = 7 Hz); 3.75 (s, 2H); 4.20 (q, 2H, J = 7 Hz); 8.65 (s, 1H, NH)	3500-3200 1735

N-(2-Dialkylaminoethyl)-2-oxo-2*H*-1-benzopyran-3-(thio)carboxamides (3a-l)

Method A

Benzaldehyde (**1**) (0.05 mol) and (**2b,c,e,f**) (0.05 mol) were dissolved in benzene (300 ml) with few drops of piperidine and heated to reflux until the theoretical quantity of water (0.9 ml) in Dean-Stark apparatus was obtained. After cooling, the solvent was evaporated and the product was purified by recrystallization.

Method B

Benzaldehyde (1) (0.05 mol) was heated up to melting and **(2a,d,g-l)** (0.05 mol) was added with few drops of piperidine. The reaction was instantaneous and the reaction mixture crystallized. Operative conditions, yield, mp and spectral data are shown in Tables 2 and 3.

Table 2 : Physicochemical data of **3a-l**

Compound	Method	Yield (%)	mp (°C)	Molecular Formula	Microanalyses (%) C calcd found	H calcd found	N calcd found
3a	B	65	137[a]	$C_{15}H_{18}N_2O_4$	62.05 61.90	6.25 6.15	9.65 9.80
3b	A	60	76[b]	$C_{17}H_{22}N_2O_4$	64.13 63.91	6.96 6.86	8.80 8.63
3c	A	74	147[a]	$C_{17}H_{20}N_2O_5$	61.43 61.55	6.06 5.98	8.43 8.35
3d	B	61	162[a]	$C_{16}H_{20}N_2O_5$	59.98 59.82	6.29 6.15	8.74 8.60
3e	A	68	152[c]	$C_{18}H_{24}N_2O_5$	62.05 61.91	6.94 6.83	8.04 7.92
3f	A	72	200[a]	$C_{18}H_{22}N_2O_6$	59.65 59.80	6.12 6.20	7.73 7.53
3g	B	76	173[c]	$C_{15}H_{18}N_2O_3S$	58.80 58.63	5.92 5.92	9.14 9.22
3h	B	78	133[c]	$C_{17}H_{22}N_2O_3S$	61.05 60.90	6.63 6.55	8.38 8.23
3i	B	75	161[d]	$C_{17}H_{20}N_2O_4S$	58.60 58.61	5.78 5.81	8.04 8.07
3j	B	80	181[a]	$C_{16}H_{20}N_2O_4S$	57.12 56.95	5.99 5.94	8.33 8.22
3k	B	82	183[c]	$C_{18}H_{24}N_2O_4S$	59.31 59.23	6.63 6.53	7.69 7.55
3l	B	83	223[a,d]	$C_{18}H_{22}N_2O_5S$	57.12 57.11	5.86 5.87	7.40 7.37

Crystallization solvent : [a]ethyl acetate; [b]ether; [c]benzene; [d]ethanol

Table 3 : Spectral data of **3a-l**

Compound	Solvent	^{1}H-Nmr δ (ppm)	Ir (KBr) (cm^{-1})
3a	DMSO-d_6	2.35 (s, 6H); 2.60 (t, 2H, J = 7 Hz); 3.60 (q, 2H, J = 7 Hz); 4.05 (s, 3H); 7.30 (m, 3H); 8.85 (s, 1H, H_4); 8.90 (s, 1H, NH)	3350, 1705, 1655
3b	DMSO-d_6	1.05 (t, 6H, J = 7 Hz); 2.65 (m, 6H); 3.55 (q, 2H, J = 7 Hz); 4.00 (s, 3H); 7.25 (m, 3H); 8.80 (s, 1H, H_4); 8.95 (s, 1H, NH)	3330, 1715, 1650
3c	DMSO-d_6	2.60 (m, 6H); 3.60 (q, 2H, J = 7 Hz); 3.80 (m, 4H); 4.00 (s, 3H); 7.30 (m, 3H); 8.90 (s, 1H, H_4); 9.20 (s, 1H, NH)	3340, 1705, 1650
3d	DMSO-d_6	2.50 (s, 6H); 2.80 (t, 2H, J = 7 Hz); 3.55 (q, 2H, J = 7 Hz); 3.90 (s, 3H); 3.95 (s, 3H); 6.40 (d, 1H, H_8, J = 2Hz); 6.50 (d, 1H, H_6, J = 2 Hz); 8.70 (s, 1H, NH); 8.75 (s, 1H, H_4)	3350, 1705, 1650
3e	DMSO-d_6	1.05 (t, 6H, J = 7 Hz); 2.60 (m, 6H); 3.55 (q, 2H, J = 7 Hz); 3.90 (s, 3H); 3.95 (s, 3H); 6.30 (d, 1H, H_8, J = 2 Hz); 6.40 (d, 1H, H_6, J = 2 Hz); 8.80 (s, 1H, H_4); 8.85 (s, 1H, NH)	3350, 1700, 1650
3f	DMSO-d_6	2.60 (m, 6H); 3.55 (q, 2H, J = 7 Hz); 3.80 (m, 4H); 3.90 (s, 3H); 3.95 (s, 3H); 6.20 (t, 1H, H_8, J = 2 Hz); 6.35 (d, 1H, H_6, J = 2 Hz); 8.80 (s, 1H, H_4); 8.85 (s, 1H, NH)	3350, 1700, 1620
3g	$CDCl_3$	2.35 (s, 6H); 2.70 (t, 2H, J = 7 Hz); 3.95 (q, 2H, J = 7 Hz); 4.00 (s, 3H); 7.30 (m, 3H); 9.50 (s, 1H, H_4); 11.35 (s, 1H, NH)	3195, 1690
3h	$CDCl_3$	1.10 (t, 6H, J = 7 Hz); 2.65 (m, 4H); 2.80 (t, 2H, J = 7 Hz); 3.95 (q, 2H, J = 7 Hz); 4.00 (s, 3H); 7.30 (m, 3H); 9.50 (s, 1H, H_4); 11.45 (s, 1H, NH)	3220, 1690
3i	$CDCl_3$	2.60 (m, 4H); 2.80 (t, 2H, J = 7 Hz); 3.80 (m, 4H); 3.85 (q, 2H, J = 7 Hz); 4.00 (s, 3H); 7.35 (m, 3H); 9.50 (s, 1H, H_4); 11.50 (s, 1H, NH)	3190, 1690
3j	$CDCl_3$	2.35 (s, 6H); 2.70 (t, 2H, J = 7 Hz); 3.85 (q, 2H, J = 7 Hz); 3.90 (s, 3H); 4.00 (s, 3H); 6.30 (d, 1H, H_8, J = 2 Hz); 6.45 (d, 1H, H_6, J = 2 Hz); 9.70 (s, 1H, H_4); 11.35 (s, 1H, NH)	3260, 1695
3k	$CDCl_3$	1.10 (t, 6H, J = 7 Hz); 2.65 (m, 4H); 2.80 (t, 2H, J = 7 Hz); 3.90 (q, 2H, J = 7 Hz); 3.95 (s, 3H); 4.00 (s, 3H); 6.30 (d, 1H, H_8, J = 2 Hz); 6.40 (d, 1H, H_6, J = 2 Hz); 9.70 (s, 1H, H_4); 11.30 (s, 1H, NH)	3220, 1700
3l	$CDCl_3$	2.60 (m, 4H); 2.80 (t, 2H, J = 7 Hz); 3.80 (m, 4H); 3.85 (q, 2H, J = 7 Hz); 3.95 (s, 3H); 4.00 (s, 3H); 6.35 (d, 1H, H_8, J = 2 Hz); 6.50 (d, 1H, H_6, J = 2 Hz); 9.80 (s, 1H, H_4); 11.50 (s, 1H, NH)	3220, 1685

Quaternary ammoniums (4a-l)

Methyl iodide (0.5 ml, 8 mmol) was added to a solution of (**3a-f**) (3.5 mmol) in a mixture of benzene-DMSO (1/1) (20 ml), (or to (**3g-l**) (3.5 mmol) dissolved in chloroform (25 ml)). The ammonium salt crystallized immediately. (**4a-f**) were purified by crystallization in water, or for (**4g-l**) in chloroform. Yield and spectral data are listed in Tables 4 and 5.

Table 4 : Physicochemical data of **4a-l**

Compound	Yield (%)	mp (°C)	Molecular Formula	Microanalyses (%) C calcd found	H calcd found	N calcd found
4a	91	275[a]	$C_{16}H_{21}N_2O_4I$	44.54 44.52	4.90 4.99	6.48 6.41
4b	58	213[a]	$C_{18}H_{25}N_2O_4I$	46.96 46.78	5.47 5.64	6.09 6.16
4c	77	253[a]	$C_{18}H_{23}N_2O_5I$	46.58 46.72	4.89 5.07	5.91 6.03
4d	95	258[a]	$C_{17}H_{23}N_2O_5I$	44.16 43.98	5.01 5.24	6.06 5.94
4e	86	249[a]	$C_{19}H_{27}N_2O_5I$	46.54 46.71	5.55 5.41	5.71 5.88
4f	75	230[a]	$C_{19}H_{25}N_2O_6I$	45.25 45.06	5.00 4.95	5.55 5.74
4g	91	223[b]	$C_{16}H_{21}N_2O_3IS$	42.86 42.73	4.72 4.80	6.25 6.29
4h	90	193[b]	$C_{18}H_{25}N_2O_3IS$	45.38 45.32	5.29 5.40	5.88 5.92
4i	87	191[b]	$C_{18}H_{23}N_2O_4IS$	44.08 43.83	4.73 4.80	5.71 5.89
4j	92	208[b]	$C_{17}H_{23}N_2O_4IS$	42.68 42.62	4.85 4.91	5.85 5.80
4k	80	212[b]	$C_{19}H_{27}N_2O_4IS$	44.06 44.24	5.37 5.40	5.53 5.64
4l	75	187[b]	$C_{19}H_{25}N_2O_5IS$	43.85 43.69	4.84 5.04	5.38 5.46

Crystallization solvent : [a]H_2O; [b]$CHCl_3$

Table 5 : Spectral data of **4a-l**

Compound	Solvent	1H-Nmr δ(ppm)	Ir(KBr) (cm^{-1})
4a	DMSO-d_6	3.25 (s, 9H); 3.70 (m, 4H); 3.95 (s, 3H); 7.40 (m, 3H); 8.80 (s, 1H, H_4); 9.00 (s, 1H, NH)	3360, 1710, 1650
4b	DMSO-d_6	1.35 (t, 6H, J = 7 Hz); 3.15 (s, 3H); 3.5 (m, 6H); 3.75 (q, 2H, J = 7 Hz); 4.00 (s, 3H); 7.45 (m, 3H); 8.83 (s, 1H, H_4); 9.05 (s, 1H, NH)	3350, 1705, 1655
4c	TFA	3.55 (s, 3H); 3.80 (m, 6H); 4.10 (s, 3H); 4.20 (m, 6H); 7.50 (m, 3H); 9.00 (s, 1H, H_4); *NH exchanged with solvent deuterium*	3350, 1705, 1650
4d	DMSO-d_6	3.25 (s, 9H); 3.70 (m, 4H); 3.95 (s, 3H); 4.00 (s, 3H); 6.55 (d, 1H, H_8, J = 2 Hz); 6.65 (d, 1H, H_6, J = 2 Hz); 8.87 (s, 1H, H_4); 9.00 (s, 1H, NH);	3355, 1700, 1660
4e	TFA	1.5 (t, 6H, J = 7 Hz); 3.15 (s, 3H); 3.50 (m, 6H); 3.90 (t, 2H, J = 7 Hz) 4.00 (s, 6H); 9.07 (s, 1H, H_4); *H_6 ,H_8 and NH exchanged with solvent deuterium*	3350, 1700, 1655
4f	TFA	3.50 (s, 3H) 3.80 (m, 6H); 4.00 (s, 6H); 4.20 (m, 6H); 9.00 (s, 1H, H_4) *H_6 ,H_8 and NH exchanged with solvent deuterium*	3360, 1705, 1650
4g	DMSO-d_6	3.25 (s, 9H); 3.70 (t, 2H, J = 7 Hz); 4.00 (s, 3H) 4.3 (q, 2H, J = 7 Hz) 7.45 (m, 3H); 8.90 (s, 1H,H_4); 10.85 (s, 1H, NH);	3246, 1685
4h	DMSO-d_6	1.35 (t, 6H, J = 7 Hz); 3.15 (s, 3H); 3.6 (m, 6H); 4.00 (s, 3H); 4.30 (q, 2H, J = 7 Hz); 7.40 (m, 3H); 9.00 (s, 1H, H_4); 10.90 (s, 1H, NH);	3260, 1690
4i	DMSO-d_6	3.40 (s, 3H); 3.65 (m, 6H); 3.95 (m, 4H); 4.00 (s, 3H); 4.30 (q, 2H, J = 7 Hz); 7.40 (m, 3H); 8.95 (s, 1H, H_4); 10.85 (s, 1H, NH);	3225, 1690
4j	DMSO-d_6	3.25 (s, 9H); 3.75 (t, 2H, J = 7 Hz); 3.90 (s, 3H); 3.95 (s, 3H); 4.35 (q, 2H, J = 7 Hz); 6.50 (d, 1H, H_8, J = 2Hz); 6.60 (d, 1H, H_6, J = 2 Hz); 9.30 (s, 1H, H_4); 11.00 (s, 1H, NH);	3290, 1703
4k	TFA	1.55 (t, 6H, J = 7 Hz); 3.20 (s, 3H); 3.60 (m, 6H); 3.95 (s, 3H); 4.00 (s, 3H); 4.50 (t, 2H, J = 7 Hz); 9.65 (s, 1H, H_4); *H_6 ,H_8 and NH exchanged with solvent deuterium*	3270, 1700
4l	TFA	3.50 (s, 3H); 3.80 (m, 6H); 3.95 (s, 3H); 4.00 (s, 3H); 4.25 (m, 4H); 4.5 (t, 2H, J = 7 Hz); 9.60 (s, 1H, H_4); *H_6 ,H_8 and NH exchanged with solvent deuterium*	3260, 1690

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Received, 3rd June, 1996