Studies on Pyrrolidinones: Some Attempts to Improve the Anticancer Properties of Methyl *N*-(3,4,4',5-Tetramethoxybenzhydryl)pyroglutamate (HEI 81)

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The synthesis of esters, amides, pyrrolidinone and succinimide analogs of a new inhibitor of tubulin polymerization, methyl *N*-(3,4,4',5-tetramethoxybenzhydryl)pyroglutamate (HEI 81) was studied.

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Podophyllotoxin (**1**), etoposide (**2**) and azatoxin (**3**) are anticancer agents acting respectively by inhibition of tubulin polymerization [1] or inhibition of topoisomerase II [2]. We recently described the synthesis of analogs **4** of these compounds [3]. Methyl esters and acids **5** [4] which are the starting material for products **4** where also submitted for screening of their anticancer properties [5]. Methyl *N*-(3,4,4',5-tetramethoxybenzhydryl)pyroglutamate (HEI 81) (**6**) emerged from these tests (IC_{50} = 4.1 10^{-7} *M*) (MCF-7 cells) while all the other acids and esters **5** were devoid of antitumor activity. The structure of HEI 81 is atypical among the anticancer agents. Nevertheless it can be related to those of allocolchicine (**7**) [6], steganacin (**8**) [7], combretastatin A-4 (**9**) [8], phenstatin (**10**) [9] and other antitumor agents which interact with tubulin at the colchicine (**11**) binding site [10] (Scheme 1).

In this paper, we report some attempts to improve the biological properties of HEI 81. Because methyl esters and acids **5**, with different substitution pattern of the aromatic ring are inactive products, we attempted to modify the nature of the substituent on position 5 of the pyrrolidinone ring. This led us to synthesize some esters, amides, lactams and imides, which possess a diversity of lipophily and steric hindrance. In the beginning of this work the exact configuration of HEI 81 was not known, so the reactions described in this paper were realized starting from DL-pyroglutamic acid. It is known now that the biologically active compound HEI 81 is the *R,R* enantiomer [11].

In the published synthesis of HEI 81 (**6**), methyl *N*-trimethylsilylpyroglutamate **12** was reacted with *O*-trimethylsilyl 3,4,4',5-tetramethoxybenzhydrol (**13**) [4] (Scheme 2). In an improvement of this method, a mixture of esters **14-18** [12], tetramethoxybenzhydrol **19**, hexamethyldisilazane and a catalytic amount of saccharin was refluxed for 1-2 hours. After distillation of the hexamethyldisilazane excess, an acid catalyst (triflic acid) was added. Heating the mixture while distilling the hexamethyldisiloxane formed gave a very good yield of esters **20-24** formed as a mixture of diastereoisomers that cannot generally be separated by crystallization (Scheme 2). The lower yield of benzyl ester **24** mainly reflects purification difficulties. It must be noted that hexamethyldisilazane does not reacts with benzhydrols in the absence of catalyst [13].

Heating of amines with the mixture **6** of two racemics, in a melt or in methanol, at 50-80 °C, gave a good yield of amides **25-28** in the same ratio of diastereoisomers that

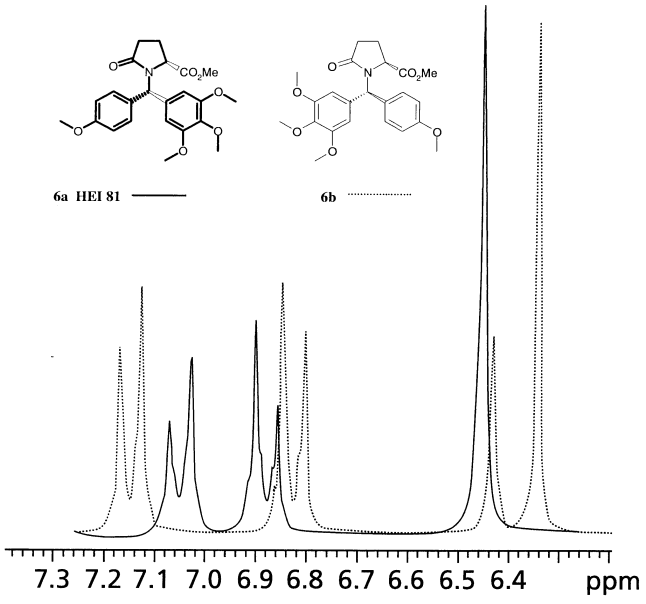
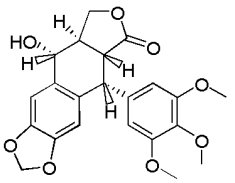
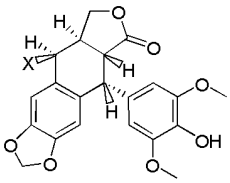


Figure 1. ^{1}H nmr of isomers a and b: 6.2-7.4 ppm ^{1}H nmr spectra of **6a** and **6b**.

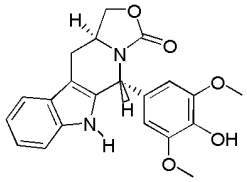
Scheme 1



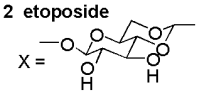
1 podophyllotoxin

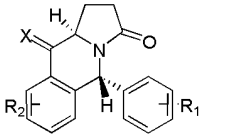


2 etoposide

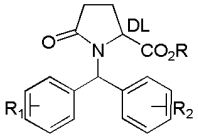


3 azatoxin

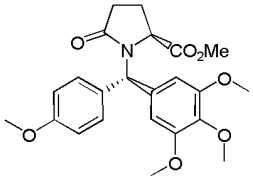




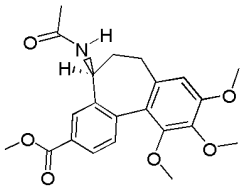
4 X = H, OH ; O
R1, R2 = H, $(OMe)_3$
Cl, F, OCH_2O



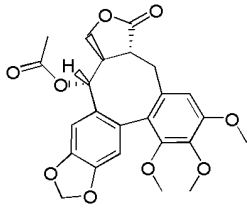
5 R = H, Me
R1, R2 = H, $(OMe)_3$
Cl, F, OCH_2O



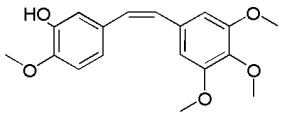
6 HEI 81



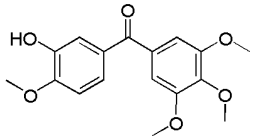
7 allocolchicine



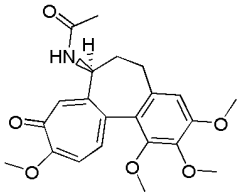
8 steganacin



9 combretastatin A-4

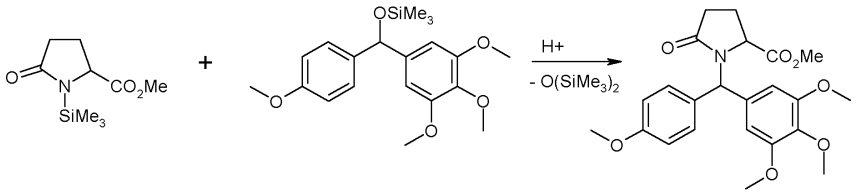


10 phenstatin

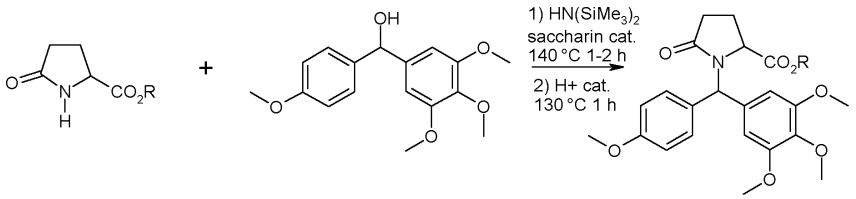


11 colchicine

Scheme 2



12 **13** **6** 95%



14 R = C_2H_5; **17** R = *n*-C_5H_{11}
15 R = *i*-C_3H_7; **18** R = CH_2Ph
16 R = *n*-C_4H_9

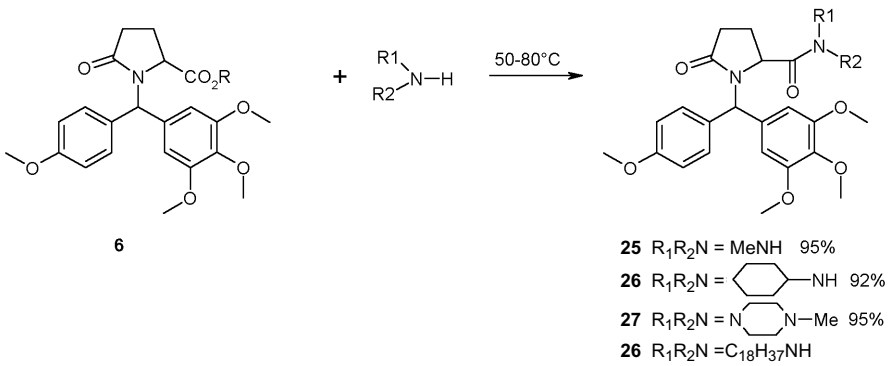
19

20 R = C_2H_5 89%; **23** R = *n*-C_5H_{11} 91%
21 R = *i*-C_3H_7 76%; **24** R = CH_2Ph 20%
22 R = *n*-C_4H_9 88%

generally cannot be separated by crystallization. Because these reactions were performed at low temperature the pyrrolidinone rings remained intact. The lower yield of **28** mainly reflects purification difficulties (Scheme 3).

reaction mixture. Electrochemical oxidation of acid **35** in methanol or in water [4] did not yield products **33** or **36**, probably because of an oxidative cleavage of the benzhydryl group [15] (Scheme 4).

Scheme 3



Structural assignment of each isomer was made easy because of the small but constant differences in the 6.3-7.3 ppm region of the ^{1}H nmr spectra, as it is illustrated in Figure 1 for **6a** (HEI 81) and **6b**.

In the same way as for esters **20-24** (Scheme 2), pyrrolidinone (**29**) and succinimide **30** were formed in a very good yield by reacting a mixture of the lactam **31** or **32** and benzhydrol **19** first with hexamethyldisilazane and saccharin then with a catalytic amount of triflic acid (Scheme 4). It was also attempted to obtain the N,O-acetal **33**. Not surprisingly, heating compound **34** with silyl ether **13** in the presence of triflic acid gave only decomposition of the

The 3,4,4',5-tetramethoxybenzhydrol (**19**) used in the described reactions was synthesized from 4-bromoanisole and trimethoxybenzaldehyde [16]. In that Grignard reaction, it was necessary to use an organolithium intermediate because 4-methoxyphenyl magnesium bromide led to the corresponding benzophenone [17].

The methods utilized lead to interesting new products but none of the synthesized compounds possess antitumor properties, so no more studies were performed in this field.

Scheme 4

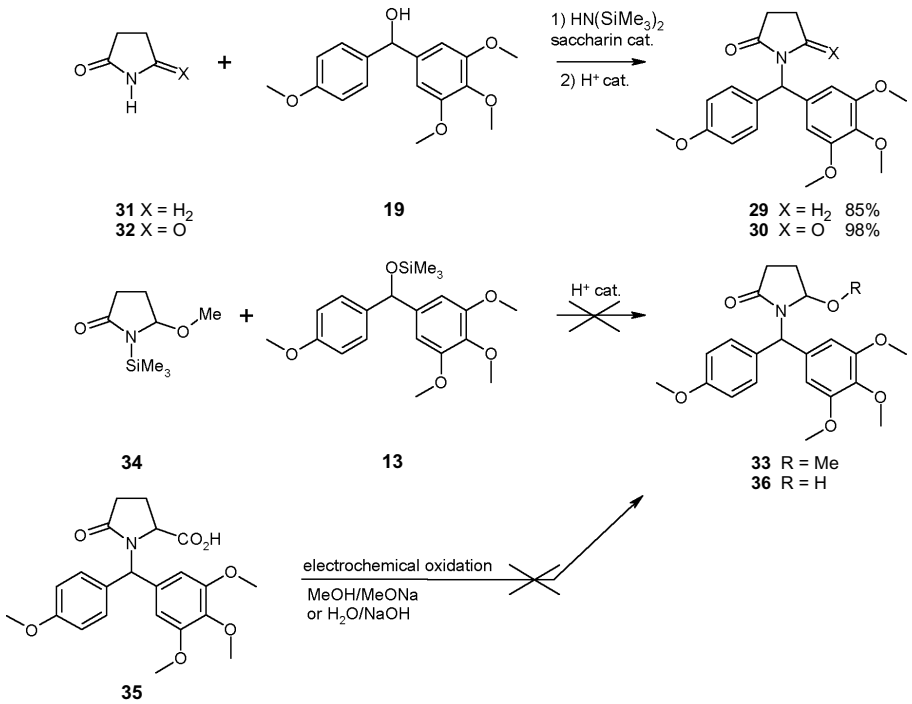


Table 1

Elemental Analysis of New Compounds (Calcd./Found)

N°	Formula	C	H	N	O
19	$C_{17}H_{20}O_5$	67.09	6.62		26.28
		66.91	6.59		26.48
20	$C_{24}H_{29}NO_7$	65.00	6.59	3.16	25.25
		65.22	6.47	2.76	25.91
21	$C_{25}H_{31}NO_7$	65.63	6.83	3.06	24.48
		65.77	6.88	2.80	24.33
22	$C_{26}H_{33}NO_7$	66.23	7.05	2.97	23.75
		66.54	7.12	2.83	23.62
23	$C_{27}H_{35}NO_7$	66.79	7.27	2.88	23.06
		66.41	7.16	2.85	22.66
24	$C_{29}H_{31}NO_7$	68.90	6.18	2.77	22.15
		69.25	6.51	2.78	21.75
25	$C_{23}H_{28}N_2O_6$	64.47	6.59	6.54	22.40
		64.19	6.67	6.49	22.78
26	$C_{28}H_{36}N_2O_6 \cdot H_2O$	65.35	7.44	5.44	21.76
		65.42	7.46	5.50	21.81
27	$C_{27}H_{35}N_3O_6$	65.17	7.09	8.44	19.29
		65.38	7.13	8.12	19.61
28	$C_{40}H_{62}N_2O_6$	72.04	9.37	4.20	14.39
		72.41	9.72	4.55	14.01
29	$C_{21}H_{25}NO_5 \cdot 0.5H_2O$	66.30	6.89	3.68	23.13
		65.92	7.17	3.37	23.51
30	$C_{21}H_{23}NO_6$	65.44	6.02	3.63	24.91
		65.53	6.00	3.91	24.82

Table 2

Yields and Physical Properties of New Compounds

N°	Yield %	MP °C (solvent)	IR (KBr, ν cm^{-1})
19	90	102-3 (AcOEt)	3490, 1590, 1510, 1435, 1130
20	89	125-7 (AcOEt)	1740, 1690, 1600, 1585, 1510, 1500, 1470, 1455, 1125
21	76	109 (AcOEt)	1730, 1690, 1595, 1510, 1465, 1450, 1130
22	88	112 (AcOEt)	1750, 1690, 1595, 1510, 1470, 1130
23	91	147-8 (AcOEt/ether)	1730, 1680, 1590, 1580, 1500, 1450, 1120
24	20	70 (AcOEt)	1750, 1700, 1615, 1585, 1510, 1500, 1470, 1455, 1125
25	95	120 (AcOEt)	3640, 1670, 1655, 1625, 1590, 1505, 1465, 1455, 1120
26	92	168-170 (AcOEt)	3325, 1680, 1620, 1585, 1510, 1465, 1450, 1120
27	95	164-166 (AcOEt)	1670, 1615, 1585, 1515, 1470, 1125
28	33	90-92 (AcOEt)	3325, 1670, 1650, 1580, 1500, 1460, 1120
29	85	oil	1700, 1615, 1580, 1510, 1130
30	98	138-9 (AcOEt)	1775, 1705, 1610, 1595, 1515, 1470, 1140

Table 3

NMR Spectra of New Compounds

N°	NMR ($CDCl_3$) δ ppm
19	^{1}H: 2.89 (s, 1H), 3.73 (s, 3H), 3.76 (s, 6H), 3.77 (s, 3H), 5.62 (s, 1H), 6.54 (s, 2H), 6.82 (d, J = 8.7 Hz, 2H), 7.24 (d, J = 8.7 Hz, 2H). ^{13}C: 55.3, 56.1, 60.9, 75.9, 103.4, 114, 128, 136.1, 137.2, 139.9, 153.3, 159.2
20a	^{1}H: 0.95 (t, J = 7 Hz, 3H), 1.80-2.16 (m, 1H), 2.20-2.54 (m, 2H), 2.54-2.82 (m, 1H), 3.52-3.70 (m, 2H), 3.78 (s, 6H), 3.75 (s, 3H), 3.76 (s, 3H), 4.12 (dd, J = 8.5, 1.1 Hz, 1H), 6.39 (s, 3H), 6.81 (d, J = 8.8 Hz, 2H), 6.98 (d, J = 8.8 Hz, 2H)
20b	^{1}H: 1.04 (t, J = 7.2 Hz, 3H), 1.96-2.19 (m, 1H), 2.19-2.60 (m, 2H), 2.60-2.88 (m, 1H), 3.66-3.75 (m, 2H), 3.78 (s, 6H), 3.79 (s, 3H), 3.84 (s, 3H), 4.21 (d, J = 8.4 Hz, 1H), 6.35 (s, 2H), 6.43 (s, 1H), 6.82 (d, J = 8.8 Hz, 2H), 7.15 (d, J = 8.8 Hz, 2H) ^{13}C: 13.8, 24.8, 29.8, 55.3, 56.2, 58.7, 58.9, 60.9, 61.2, 104.6, 113.7, 129.9, 131.7, 135.1, 136.9, 153.5, 159.5, 172.2, 175.6
21a	^{1}H: 0.97 (d, J = 5.6 Hz, 3H), 1.0 (d, J = 5.6 Hz, 3H), 1.95-2.10 (m, 1H), 2.30-2.60 (m, 2H), 2.60-2.80 (m, 1H), 3.78 (s, 9H), 3.82 (s, 3H), 4.16 (t, J = 8.3 Hz, 1H), 4.59 (m, 1H), 6.47 (s, 3H), 6.87 (d, J = 8.9 Hz, 2H), 7.04 (d, J = 8.9 Hz, 2H)
21b	^{1}H: 0.97 (d, J = 6.2 Hz, 3H), 1.04 (d, J = 6.2 Hz, 3H), 1.90-2.10 (m, 1H), 2.20-2.60 (m, 2H), 2.60-2.90 (m, 1H), 3.79 (s, 9H), 3.84 (s, 3H), 4.18 (t, J = 8.4 Hz, 1H), 4.57 (m, 1H), 6.34 (s, 2H), 6.42 (s, 1H), 6.81 (d, J = 8.8 Hz, 2H), 7.16 (d, J = 8.8 Hz, 2H)
22a	^{1}H: 0.87 (t, J = 7.2 Hz, 3H), 1.1-1.5 (m, 4H), 1.9-2.1 (m, 1H), 2.2-2.6 (m, 2H), 2.6-2.8 (m, 1H), 3.5-3.7 (m, 2H), 3.78 (s, 6H), 3.82 (s, 3H), 3.83 (s, 3H), 4.22 (d, J = 8.4 Hz, 1H), 6.46 (s, 3H), 6.87 (d, J = 8.7 Hz, 2H), 7.05 (d, J = 8.7 Hz, 2H)
22b	^{1}H: 0.88 (t, J = 7 Hz, 3H), 1.1-1.5 (m, 4H), 1.9-2.2 (m, 1H), 2.2-2.6 (m, 2H), 2.6-2.8 (m, 1H), 3.5-3.7 (m, 2H), 3.78 (s, 9H), 3.84 (s, 3H), 4.22 (d, J = 8.4 Hz, 1H), 6.34 (s, 2H), 6.43 (s, 1H), 6.81 (d, J = 8.8 Hz, 2H), 7.15 (d, J = 8.8 Hz, 2H)
23a	^{1}H: 0.86 (t, J = 6.7 Hz, 3H), 1.12-1.29 (m, 4H), 1.29-1.48 (m, 2H), 1.95-2.10 (m, 1H), 2.22-2.57 (m, 2H), 2.60-2.85 (m, 1H), 3.54-3.75 (m, 2H), 3.78 (s, 6H), 3.82 (s, 3H), 3.83 (s, 3H), 4.18 (dd, J = 8.1, 1.2 Hz, 1H), 6.46 (s, 3H), 6.87 (d, J = 8.8 Hz, 2H), 7.05 (d, J = 8.8 Hz, 2H)
23b	^{1}H: 0.88 (t, J = 6.7 Hz, 3H), 1.12-1.29 (m, 4H), 1.29-1.47 (m, 2H), 1.99-2.11 (m, 1H), 2.24-2.54 (m, 2H), 2.63-2.83 (m, 1H), 3.52-3.73 (m, 2H), 3.78 (s, 6H), 3.79 (s, 3H), 3.84 (s, 3H), 4.22 (dd, J = 8.4, 1.0 Hz, 1H), 6.34 (s, 2H), 6.43 (s, 1H), 6.81 (d, J = 9.4 Hz, 2H), 7.15 (d, J = 9.4 Hz, 2H) ^{13}C: 13.9, 22.3, 24.9, 28.0, 29.7, 29.9, 55.3, 56.2, 58.7, 58.9, 60.9, 65.5, 104.6, 113.7, 129.9, 131.7, 135.1, 137.4, 153.5, 159.5, 172.3, 175.6
24a	^{1}H: 1.95-2.22 (m, 1H), 2.22-2.57 (m, 2H), 2.6-2.85 (m, 1H), 3.73 (s, 6H), 3.83 (s, 6H), 4.27 (d, J = 8.5 Hz, 1H), 4.62 (d, J = 12.1 Hz, 1H), 4.72 (d, J = 12.1 Hz, 1H), 6.48 (s, 3H), 6.85 (d, J = 8.7 Hz, 2H), 7.04 (d, J = 8.7 Hz, 2H), 7.1-7.2 (m, 2H), 7.25-7.35 (m, 3H)
24b	^{1}H: 1.95-2.22 (m, 1H), 2.22-2.57 (m, 2H), 2.6-2.85 (m, 1H), 3.74 (s, 6H), 3.75 (s, 3H), 3.78 (s, 3H), 4.23 (d, J = 8.4 Hz, 1H), 4.66 (s, 2H), 6.36 (s, 2H), 6.45 (s, 1H), 6.80 (d, J = 8.6 Hz, 2H), 7.15 (d, J = 8.6 Hz, 2H), 7.08-7.2 (m, 2H), 7.25-7.35 (m, 3H)
24a,b	^{13}C: 24.58, 24.63, 29.76, 29.82, 55.27, 55.30, 56.06, 58.38, 58.51, 58.98, 59.04, 60.79, 60.86, 104.63, 107.15, 113.74, 114.05, 128.07, 128.27, 128.54, 128.62, 128.71, 128.74, 129.84, 130.35, 131.58, 133.88, 134.94, 137.34, 137.49, 153.14, 153.44, 159.09, 159.47, 172, 172.14, 175.60, 175.71
25a	^{1}H: 2-2.26 (m, 1H), 2.26-2.58 (m, 2H), 2.40 (d, J = 4.9 Hz, 3H), 2.58-2.83 (m, 1H), 3.81 (s, 6H), 3.82 (s, 3H), 3.84 (s, 3H), 4.03 (dd, J = 8.4, 1.4 Hz, 1H), 4.96 (bq, J = 4.9 Hz, 1H), 6.47 (s, 1H), 6.51 (s, 2H), 6.88 (dt, J = 8.7, 2.4 Hz, 2H), 7.01 (dt, J = 8.7, 2.4 Hz, 2H)
25b	^{1}H: 2.07-2.25 (m, 1H), 2.27-2.58 (m, 2H), 2.34 (d, J = 4.9 Hz, 3H), 2.58-2.82 (m, 1H), 3.77 (s, 6H), 3.81 (s, 3H), 3.84 (s, 3H), 4.10 (dd, J = 8.5, 1.5 Hz, 1H), 4.90 (bq, J = 4.9 Hz, 1H), 6.29 (s, 2H), 6.46 (s, 1H), 6.87 (dt, J = 8.8, 2.6 Hz, 2H), 7.21 (dt, J = 8.8, 2.6 Hz, 2H)

Table 3
NMR Spectra of New Compounds

N°	NMR ($CDCl_3$) δ ppm
26a	^{1}H: 0.8-2.05 (m, 10H), 2.07-2.2 (m, 1H), 2.2-2.55 (m, 2H), 2.55-2.81 (m, 1H), 2.81-3.03 (m, 1H), 3.70-3.90 (m, 1H), 3.74 (s, 6H), 3.80 (s, 3H), 3.81 (s, 3H), 4.17 (d, J = 8.1 Hz, 1H), 6.43 (s, 3H), 6.87 (d, J = 8.8 Hz, 2H), 7.03 (d, J = 8.8 Hz, 2H)
26b	^{1}H: 0.8-2.5 (m, 10H), 2.05-2.2 (m, 1H), 2.2-2.55 (m, 2H), 2.55-2.80 (m, 1H), 2.80-3.05 (m, 1H), 3.70-3.90 (m, 1H), 3.79 (s, 9H), 3.85 (s, 3H), 4.14 (d, J = 7.8 Hz, 1H), 6.35 (s, 1H), 6.37 (s, 2H), 6.80 (d, J = 8.8 Hz, 2H), 7.20 (d, J = 8.8 Hz, 2H)
28b	^{1}H: 0.89 (t, J = 6.1 Hz, 3H), 1-1.5 (m, 32H), 2-2.2 (m, 1H), 2.2-2.6 (m, 2H), 2.6-2.9 (m, 1H), 2.9-3.2 (m, 2H), 3.77 (s, 6H), 3.80 (s, 3H), 3.84 (s, 3H), 4.09 (d, J = 8.1 Hz, 1H), 4.85-5.05 (m, 1H), 6.30 (s, 2H), 6.43 (s, 1H), 6.85 (d, J = 8.7 Hz, 2H), 7.20 (d, J = 8.7 Hz, 2H) ^{13}C: 14.2, 22.7, 26.1, 26.9, 29.1, 29.3, 29.4, 29.5, 29.7, 32, 39.7, 55.3, 56.2, 59.5, 60.7, 61, 104.6, 114.2, 130.2, 131.3, 134.7, 137.5, 153.5, 159.7, 171.7, 176.4
29	^{1}H: 2.04 (m, J = 7.4 Hz, 2H), 2.50 (t, J = 8.1 Hz, 2H), 3.22 (bt, J = 7 Hz, 2H), 3.78 (s, 6H), 3.82 (s, 3H), 3.85 (s, 3H), 6.39 (s, 2H), 6.49 (s, 1H), 6.88 (d, J = 8.8 Hz, 2H), 7.12 (d, J = 8.8 Hz, 2H) ^{13}C: 18.3, 31.3, 44.4, 55.3, 56.2, 58.2, 60.9, 105.7, 114, 129.8, 130.6, 134.8, 137.4, 153.4, 159.2, 175.2
30	^{1}H: 2.75 (s, 4H), 3.80 (s, 6H), 3.81 (s, 3H), 3.85 (s, 3H), 6.43 (s, 1H), 6.64 (s, 2H), 6.86 (dt, J = 6.9, 2.7 Hz, 2H), 7.21 (dt, J = 6.9, 2.6 Hz, 2H) ^{13}C: 28.2, 55.3, 56.2, 58.3, 60.9, 106.4, 113.8, 129.6, 129.7 (2C), 133.8, 137.8, 153.3, 159.2, 177

EXPERIMENTAL

Melting points are uncorrected. The ir spectra were recorded on a 'Perkin-Elmer' 700 spectrometer and the nmr spectra on a Varian 'Gemini 2000' at 200 MHz for ^{1}H and 50 MHz for ^{13}C, using tetramethylsilane as an internal reference. Elemental analyses were performed by the «Service Central de Microanalyses» (CNRS, Vernaison, France). Melting points, ir spectra and elemental analyses were not determined for moisture sensitive compounds. Pyroglutamic acid was a gift of UCIB, Ivry-la-Bataille, France, which can provide this chemical in bulk quantities.

Pentyl *N*-[(4-Methoxyphenyl)-(3,4,5-trimethoxyphenyl)-methyl]pyroglutamate (**23**).

A stirred mixture of pentyl pyroglutamate (**17**) (3.3 g, 0.016 mol), 3,4,4',5-tetramethoxybenzhydrol (**19**) (5 g, 0.016 mol), saccharin (10 mg) and hexamethyldisilazane (7 ml, 5.4 g, 0.033 mol) was refluxed for 2 hours giving a mixture of **13** and *N*-silylated ester **19** as very water sensitive compounds. Hexamethyldisilazane excess was distilled under vacuum (water aspirator). Triflic acid (0.05 ml, 0.1 g, 0.6 mmol) was added and the mixture was stirred at 130 °C for 1 hour. Methylene dichloride was added and the solution was washed with water, dried, then chromatographed (Silica gel, ethyl acetate/heptane (70/30)), giving a diastereomeric mixture of esters **23a** and **23b** (50/50).

Esters **20**, **21**, **22** and **24** were obtained by using the same procedure.

N-[(4-Methoxyphenyl)-(3,4,5-trimethoxyphenyl)-methyl]pyroglutamic acid methylamide (**25**).

A methanol (60 ml) solution of ester **6a,b** (2.5 g, 5.8 mmol) was saturated with methyl amine, then the solution was heated at 50 °C for 12 hours in a closed vessel. After evaporation amide **25** crystallized from a mixture ethyl acetate/methanol (90/10).

N-[(4-Methoxyphenyl)-(3,4,5-trimethoxyphenyl)-methyl]pyroglutamic acid cyclohexylamide (**26**).

A stirred solution of ester **6a,b** (2g, 4.7 mmol) in cyclohexylamine (2 ml, 1.7 g, 17.5 mmol) was heated at 135 °C for 12 hours. Methylene dichloride was added and the solution was washed with a dilute hydrochloric acid solution then with water. The solution was dried (sodium sulfate) then evaporated, giving an oil which crystallized from ethyl acetate/methanol (95/5).

1-[(4-Methoxyphenyl)-(3,4,5-trimethoxyphenyl)-methyl]-5-(4-methylpiperazine-1-carbonyl)-pyrrolidin-2-one (**27**).

A stirred solution of ester **6a,b** (2 g, 4.7 mmol) and *N*-methylpiperazine (2 ml, 1.7 g, 17.3 mmol) in methanol (10 ml) was refluxed for 3 days. Solvents were evaporated, methylene dichloride was added and the solution was washed with water. The solution was dried (sodium sulfate) then evaporated, giving an oil which crystallized from ethyl acetate/methanol (95/5).

N-[(4-Methoxyphenyl)-(3,4,5-trimethoxyphenyl)-methyl]pyroglutamic acid octadecylamide (**28**).

This product was obtained in the same way as for compound **26**.

N-[(4-Methoxyphenyl)-(3,4,5-trimethoxyphenyl)-methyl]pyrrolidin-2-one (**29**).

This product was obtained in the same way as for compound **23**, starting from pyrrolidinone **31** (chromatography : ethyl acetate/heptane 70/30).

N-[(4-Methoxyphenyl)-(3,4,5-trimethoxyphenyl)-methyl]-pyrrolidine-2,5-dione (**30**).

This product was synthesized in the same way as for compound **23**, starting from succinimide **32**. The oil obtained crystallized from ethyl acetate.

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