ALTERNATIVE SYNTHESIS OF TRYPTOPHAN PSEUDODIPEPTIDES

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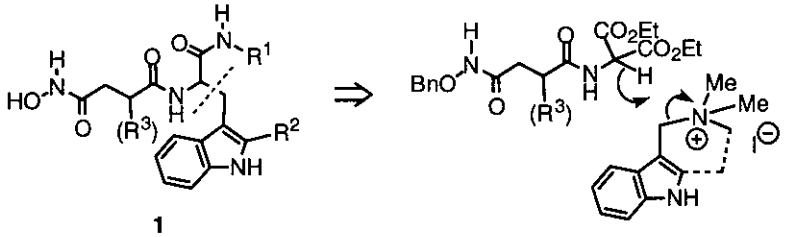
Abstract - The tryptophan pseudodipeptides (**8**) and (**13**) were synthesized *via* generation of the tryptophan backbone through the reaction of a succinylaminomalonate with a quaternarized gramine.

The amazing inhibition of matrix metalloproteinases by simple long chain fatty acids[1] asks the question of their site(s) of interaction with the enzymes, as compared with those of the known biologically active hydroxamate derivatives of *N*-succinyltryptophanamides.[2] To this purpose, it was of interest to develop a versatile synthesis of *N*-succinyltryptophanamides (**1**) that might allow introduction of various lipophilic substituents (Scheme 1).

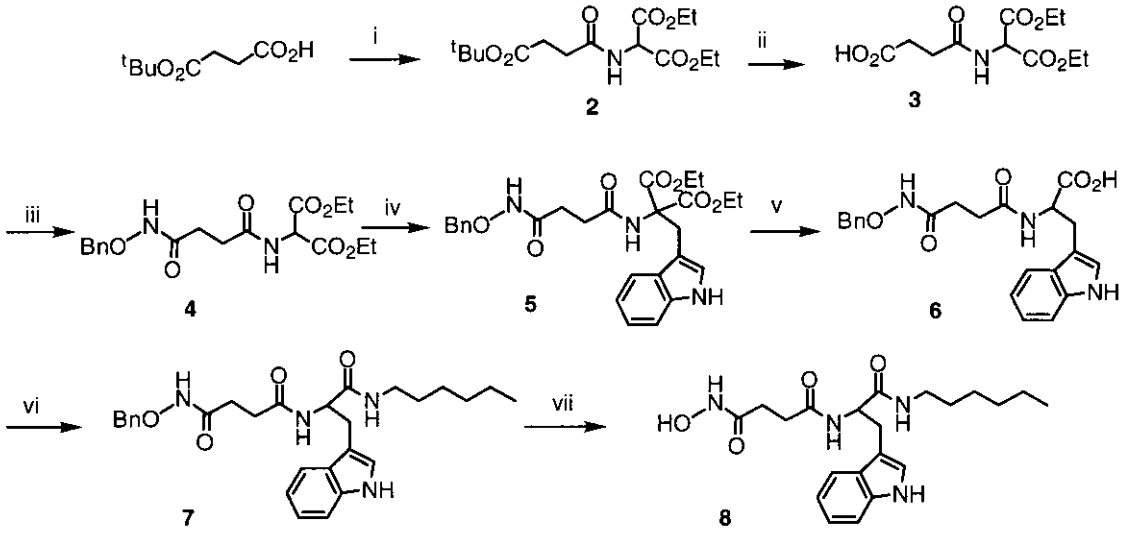


Scheme 1

While tryptophan dipeptides are most generally synthesized through classical peptide chemistry, application of the chemistry of gramines[3] seemed not to have been used to this purpose. As racemates were suitable for preliminary biological investigations, we then engaged ourselves in the construction of racemic compounds by reacting a quaternarized gramine with a suitably acylated aminomalonate. In particular, this approach makes it possible to introduce a dialkylaminoethyl R^2 substituent[4] and it should further open the way to combinatorial syntheses. The straightforward synthesis of model compounds (**1**) (R^1 = *n*-Hex, R^2 = H or $(CH_2)_2NMe_2$, R^3 = H) along such lines was performed in this preliminary work.

RESULTS

The protected diethyl succinylaminomalonate (**2**) (Scheme 2) obtained from *tert*-butyl succinate[5] was hydrolyzed (TFA) to the acid (**3**), which was reacted with *O*-benzylhydroxylamine (DCC, HOBt) to yield the protected hydroxamic acid (**4**). Reaction of **4** with gramine methiodide smoothly gave the diester (**5**), which was saponified and decarboxylated to the tryptophan derivative (**6**). Amidation of **6** with *n*-hexylamine (DCC) and further hydrogenolysis finally gave the hydroxamic acid (**8**).



Reagents : (i) $H_2NCH(CO_2Et)_2$, DCC, CH_2Cl_2, rt, 16 h, 92% ; (ii) TFA, CH_2Cl_2, rt, 24 h, 93% ; (iii) $BnONH_2.HCl$, Et_3N, HOBt, DCC, CH_2Cl_2, rt, 16 h, 73%; (iv) a) NaH, THF, 0°C, 15 min, b) gramine methiodide, reflux, 16 h, 63% ; (v) a) NaOH, MeOH/H_2O 5:2, rt, 64 h, b) HCl, evaporation of MeOH, reflux, 3 h, 79% ; (vi) *n*-$HexNH_2$, DCC, CH_2Cl_2/DMF, rt, 15 h, 50% ; (vii) H_2/10% Pd•C, EtOH, rt, 2 h, 96%.

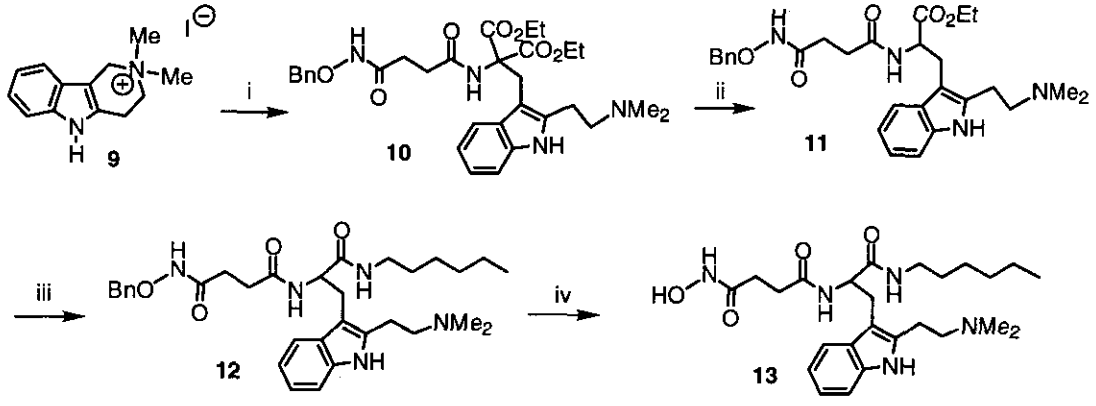
Scheme 2

The ^1H and ^{13}C NMR spectra and the MS spectra of the compounds were consistent with the structures. In particular, the MS spectra of compounds (**5**-**7**) exhibited a peak at $M^{+\cdot}$ - 106 due to the loss of PhCHO along a McLafferty's rearrangement; the hydroxamic acid (**8**) gave a characteristic violet spot on TLC after spraying with a $FeCl_3$ solution.[6]

Then, although the yields and the length of the synthesis compare disfavorably with those of a direct synthesis of **7** from a tryptophanamide, obtaining **8** nevertheless illustrates the feasibility of such an alternative way.

Application to the synthesis of **13** along similar lines (Scheme 3) further demonstrates the usefulness of the process. Thus, tetrahydro-γ-carboline methiodide (**9**) reacted with the amidomalonate (**4**) to yield the 2-substituted tryptophan derivative (**10**). Attempts to saponify and decarboxylate **10** as performed with **5** failed, and replacement of NaOH with LiOH, followed by acidic treatment unexpectedly gave ester (**11**), indicating that the saponification had affected only one ester group in **10**.[7] Ester (**11**) was transformed into

amide (**12**) in the presence of $AlMe_3$, and further submitted to hydrogenolysis to yield the hydroxamic acid (**13**). The structures of compounds (**10-13**) were ascertained by their spectroscopic data.



Reagents : (i) **4**, a) NaH, THF, 0°C, 15 min, b) add **9**, reflux, 16 h, 86% ; (ii) a) LiOH, THF/H_2O 3:1, rt, 24 h, b) 10% HCl, evaporation of THF, reflux 3 h, 39% ; (iii) *n*-HexNH_2, Me_3Al, CH_2Cl_2, 0°C, 30 min → **11**, CH_2Cl_2, 0°C, 30 min, then rt, 40 h, 63.5% ; (iv) H_2/10%Pd•C, EtOH, rt, 2 h, 96%.

Scheme 3

Not unexpectedly, compounds (**8**) and (**13**) were found to be inactive against 72 kDa gelatinase.

EXPERIMENTAL

Commercially available reagents purchased from Acros Organics were used without further purification. Melting points were measured with a Reichert microscope apparatus and were uncorrected. UV spectra (nm) were recorded on an UNICAM 8700 apparatus, IR spectra (cm^{-1}) on a BOMEM MB series spectrophotometer. ^1H (300 MHz) and ^{13}C NMR (75 MHz) spectra were measured on a Bruker AC 300 instrument with TMS as internal reference. MS spectra were determined on a VG Autospec apparatus. Elemental analyses were carried out by the microanalyses service of the Faculty of Sciences, University of Reims Champagne Ardenne. Preparative column chromatography was performed on Kieselgel 60 silica gel; for TLC control Kieselgel-60 PF_{254} plates were used.

Diethyl 2-{[4-(*tert*-butoxy)-4-oxobutanoyl]amino}malonate (2). A solution of DCC (5.73 g, 27 mmol) in 30 mL of CH_2Cl_2 was added to a solution of diethyl aminomalonate (4.8 g, 27 mmol) and *tert*-butyl succinate (4.76 g, 27 mmol) in 70 mL of CH_2Cl_2. The reaction mixture was stirred at rt overnight. The urea was filtered off and washed with CH_2Cl_2. After evaporation of the solvent, the residue was taken up with AcOEt. Some urea precipitated again and was filtered off. The organic phase was washed successively with 5% citric acid, 5% $NaHCO_3$ and brine, dried (Na_2SO_4), filtered and evaporated. The residue was chromatographed on silica gel (CH_2Cl_2/0-2% MeOH) to yield **2** as an oil (8.31 g, 92%):

IR (CH_2Cl_2) 1682, 1738, 3350; ^1H NMR ($CDCl_3$) 1.30 (t, J=7.2, 6H, 2 CH_2CH_3), 1.45 (s, 9H, $C(CH_3)_3$), 2.58 (s, 4H, succinic H), 4.18-4.35 (m, 4H, 2 CH_2CH_3), 5.17 (d, J=7.2, 1H, CH), 6.91 (d, J=7.2, 1H, NH); ^{13}C NMR ($CDCl_3$) 13.8 (2 CH_2CH_3), 27.8 ($C(CH_3)_3$), 30.3, 30.4 (two succinic CH_2), 56.3 (CH), 62.3 (2 CH_2CH_3), 80.5 ($C(CH_3)_3$), 166.1 (CO_2Et), 171.4, 171.7 (CO_2tBu, CONH); EIMS 332 ($M^{+\cdot}$, 2), 258 (100); Anal. Calcd for $C_{15}H_{25}NO_7$ C 54.35, H 7.61, N 4.23. Found C 54.22, H 7.90, N 4.45.

Diethyl 2-(3-carboxypropionylamino)malonate (3). Trifluoroacetic acid (22 mL, 286 mmol) was added dropwise at rt to a solution of **2** (6.76 g, 9 mmol) in 110 mL of CH_2Cl_2. The reaction mixture was stirred at rt for 24 h and was then concentrated to give 6.80 g of a solid residue which was crystallized from acetone, affording **3** (5.21 g, 93%): mp = 119-120°C; IR (KBr) 1645, 1707, 1753, 3312; ^1H NMR ($CDCl_3$) 1.32 (t, J=7.2, 6H, 2 CH_2CH_3), 2.65, 2.74 (2t, J=6.7, 4H, succinic H), 4.26 (m, 4H, 2 CH_2CH_3), 5.16 (d, J=7.2, 1H, CH), 6.74 (d, J=7.2, 1H, NH); ^{13}C NMR ($CDCl_3$ + CD_3OD) 14.1 (2 CH_2CH_3), 29.4, 30.4 (two succinic CH_2), 56.9 (CH), 62.9 (2 CH_2CH_3), 166.6 (2 CO_2Et), 173.0 (CONH), 175.3 (CO_2H); EIMS 276 (MH^+, 10), 157 (100); Anal. Calcd for $C_{11}H_{17}NO_7$ C 47.98, H 6.23, N 5.09. Found C 48.32, H 6.02, N 5.33.

Diethyl 2-({4-[(benzyloxy)amino]-4-oxobutanoyl}amino)malonate (4). Triethylamine (1.3 mL, 9.3 mmol) was added to a suspension of *O*-benzylhydroxylamine hydrochloride (1.46 g, 9.1 mmol) in 100 mL of CH_2Cl_2. A solution of **3** (2.49 g, 9.1 mmol), 1-hydroxybenzotriazole (1.26 g, 9.1 mmol) and DCC (2.30 g, 11.0 mmol) in 30 mL of CH_2Cl_2 was then added. The mixture was stirred under nitrogen at rt overnight and then treated as for **2**. The resulting residue (3.48 g) was crystallized from ethanol to give **4** (2.52 g, 73%): mp = 104-106°C; UV (MeOH) 224, 276 (sh), 282, 291; IR (KBr) 1644, 1744, 3235, 3320; ^1H NMR ($CDCl_3$) 1.27 (t, J=7.2, 6H, 2 CH_2CH_3), 2.38, 2.63 (2m, 4H, succinic H), 4.23 (m, 4H, 2 CH_2CH_3), 4.85 (s, 2H, CH_2Ph), 5.02 (d, J=6.7, 1H, CH), 7.22 (br s, 1H, NHCO), 7.29-7.39 (m, 5H, phenyl H), 9.50 (br s, 1H, NHOBn); ^{13}C NMR ($CDCl_3$) 13.6 (2 CH_2CH_3), 28.0, 30.4 (two succinic CH_2), 56.4 (CH), 62.4 (2 CH_2CH_3), 77.8 (CH_2Ph), 128.3, 128.7, 129.0 (5 phenyl CH), 135.4 (phenyl C), 166.1 (2 CO_2Et), 169.8, 171.9 (CONH, CONHOBn); EIMS 380 ($M^{+\cdot}$, 8), 258 (100); HREIMS calcd for $C_{18}H_{24}N_2O_7$ 380.1583, found 380.1578.

Diethyl 2-({4-[(benzyloxy)amino]-4-oxobutanoyl}amino)-2-(1*H*-indol-3-ylmethyl)malonate (5). 60% Sodium hydride (228 mg, 5.7 mmol) was added to a solution of **4** (1.95 g, 5.13 mmol) in dry THF at 0°C. After a 15 min stirring, the temperature was raised to 20°C and gramine methiodide (816 mg, 2.6 mmol) was added as a solid. The resulting mixture was refluxed overnight. After evaporation of the solvent, the residue was taken up in 100 mL of water. The aqueous phase was extracted once with CH_2Cl_2, acidified to pH 5-6 with 10% HCl and again extracted with CH_2Cl_2. The combined organic layers were dried on Na_2SO_4, filtered and evaporated. Purification by column chromatography on silica gel (CH_2Cl_2/0-3% MeOH) followed by centrifugal circular chromatography (CH_2Cl_2/0-3% MeOH) yielded **5** as a white foam (826 mg, 63%): UV (MeOH) 218, 276 (sh), 281, 290; IR (KBr) 1662, 1738, 3308, 3327; ^1H NMR ($CDCl_3$) 1.22 (t, J=7.2, 6H, 2 CH_2CH_3), 2.30, 2.45 (2m, 4H, succinic H), 3.82 (s, 2H,

$C\underline{H}_2$Ind), 4.14 (m, 4H, 2 $C\underline{H}_2CH_3$), 4.82 (s, 2H, $C\underline{H}_2$Ph), 6.90-7.13 (m, 4H, Ind H-2,5,6, N$\underline{H}$CO), 7.20-7.48 (m, 7H, phenyl H, Ind H-4,7), 8.79 (1H, s, Ind N$\underline{H}$), 9.37 (br s, 1H, N$\underline{H}$OBn); ^{13}C NMR ($CDCl_3$) 13.8 (2 $CH_2\underline{C}H_3$), 27.9, 28.0, 30.4 ($\underline{C}H_2$Ind, two succinic $\underline{C}H_2$), 62.5 (2 $\underline{C}H_2CH_3$), 67.2 (malonic C), 78.0 ($\underline{C}H_2$Ph), 108.0 (Ind C-3), 111.4 (Ind C-7), 118.2 (Ind C-4), 119.1 (Ind C-5), 121.6 (Ind C-6), 124.2 (Ind C-2), 127.7 (Ind C-3a), 128.4, 129.0 (5 phenyl $\underline{C}$H), 135.0 (phenyl C), 135.8 (Ind C-7a), 167.7 (2 $\underline{C}O_2$Et), 170.2, 171.0 ($\underline{C}$ONH, $\underline{C}$ONHOBn); EIMS 509 ($M^{+\cdot}$,3), 130 (100); HREIMS calcd for $C_{27}H_{31}N_3O_7$ 509.2162, found 509.2163.

2-({4-[(benzyloxy)amino]-4-oxobutanoyl}amino)-3-(1*H*-indol-3-yl)propionic acid (6). A solution of **5** (200 mg, 0.39 mmol) in 10 mL of methanol was left with 4 mL (16 mmol) of 4N NaOH at rt for 64h. After cooling to 10°C the reaction mixture was acidified to pH 1 with conc HCl. After evaporating the methanol, the aqueous solution was refluxed for 3 h. The reaction mixture was then diluted with water, made basic by addition of solid Na_2CO_3 and washed once with CH_2Cl_2. The aqueous phase was acidified to pH 1 with conc HCl and extracted with EtOAc. The combined extracts were dried (Na_2SO_4), filtered and concentrated under vacuum to provide **6** (127mg 79%) as a pink foam. UV (MeOH) 224, 275 (sh), 281, 290; IR (KBr) 1653, 1724, 3187-3359; ^{1}H NMR (DMSO-d_6) 2.16, 2.39 (2m, 4H, succinic H), 3.10 (m, 2H, $C\underline{H}_2$Ind), 4.49 (m, 1H, C$\underline{H}$), 4.78 (s, 2H, $C\underline{H}_2$Ph), 7.00, 7.08 (2t, J=7.2, 2H, Ind H-5,6), 7.17 (d, J~2, 1H, H-2), 7.35 (d, J=7.6, 1H, Ind H-7), 7.36-7.44 (m, 5H, phenyl H), 7.55 (d, J=7.6, 1H, Ind H-4), 8.20 (d, J=8, 1H, N$\underline{H}$CO), 10.86 (s, 1H, Ind N$\underline{H}$), 11.00 (s, 1H, N$\underline{H}$OBn); ^{13}C NMR (DMSO-d_6) 27.4, 28.0, 30.4 ($\underline{C}H_2$Ind, two succinic $\underline{C}H_2$), 53.3 ($\underline{C}$H), 77.0 ($\underline{C}H_2$Ph), 110.1 (Ind C-3), 111.6 (Ind C-7), 118.4, 118.6 (Ind C-4, 5), 121.1 (Ind C-6), 123.8 (Ind C-2), 127.4 (Ind C-3a), 128.4, 128.5, 129.0 (5 phenyl $\underline{C}$H), 136.3 (Ind C-7a, phenyl C), 169.0, 171.3, 173.7 ($\underline{C}$ONH, $\underline{C}$ONHOBn, $\underline{C}O_2$H); CIMS 410 ($MH^{+\cdot}$, 8), 130 (100); Anal. Calcd for $C_{22}H_{23}N_3O_5$,0.3 H_2O C 63.68, H 5.74, N 10.13. Found C 63.78, H 5.31, N 10.13.

***N*'1-(benzyloxy)-*N*'4-[1-(hexylcarbamoyl)-2-(1*H*-indol-3-yl)ethyl]succinamide (7).** A solution of **6** (56 mg, 0.14 mmol) in a mixture of 4 mL of CH_2Cl_2 and a few drops of DMF was treated overnight with *n*-hexylamine (50 mL, 0.37 mmol) and DCC (41 mg, 2.2 mmol) under N_2 at rt. After treatment as for malonic synthon (**2**), purification by preparative TLC (CH_2Cl_2/4% MeOH) gave **7** (34 mg, 50%) as a white amorphous solid: UV (MeOH) 219, 275 (sh), 282, 290; IR (KBr) 1634, 1657, 3285 (br), 3478; ^{1}H NMR (DMSO-d_6) 0.87 (t, J=6.7, 3H, $C\underline{H}_3$), 1.13-1.41 (m, 8H, hexyl H), 2.12-2.47 (m, 4H, succinic H), 3.04 (m, 2H, $C\underline{H}_2$NH), 2.88-3.18 (m, 2H, $C\underline{H}_2$Ind), 4.47 (m, 1H, C$\underline{H}$), 4.79 (s, 2H, $C\underline{H}_2$Ph), 6.99, 7.07 (2t, J=7.2, 2H, Ind H-5,6), 7.15 (d, J~2, 1H, Ind H-2), 7.33 (d, J=8.0, 1H, Ind H-7), 7.36-7.43 (m, 5H, phenyl H), 7.60 (d, J=8.0, 1H, Ind H-4), 7.87 (t, J=5.4, 1H, N$\underline{H}$-Hex), 8.11 (d, J=8, 1H, CON$\underline{H}$), 10.79 (s, 1H, Ind N$\underline{H}$), 11.05 (s, 1H, N$\underline{H}$OBn); ^{13}C NMR (DMSO-d_6) 14.1 ($\underline{C}H_3$), 28.0, 28.1, 30.6 ($\underline{C}H_2$Ind, two succinic $\underline{C}H_2$), 22.3, 26.2, 29.1, 31.2, 38.7 (hexyl $\underline{C}H_2$), 54.0 ($\underline{C}$H), 77.1 ($\underline{C}H_2$Ph), 110.6 (Ind C-3), 111.5 (Ind C-7), 118.4, 118.6 (Ind C-4,5), 121.1 (Ind C-6), 123.7 (Ind C-2), 127.6 (Ind C-3a), 128.5, 129.0 (phenyl $\underline{C}$H), 136.3 (Ind C-7a, phenyl C), 169.2 ($\underline{C}$ONHOBn), 171.3 ($\underline{C}$ONH), 171.5 ($\underline{C}$ONH-Hex); EIMS 386 ($M^{+\cdot}$ - 106, 6), 130 (100); HREIMS calcd for $C_{21}H_{30}N_4O_3$ 386.2318, found 386.2224.

***N'*1-[1-(hexylcarbamoyl)-2-(1*H*-indol-3-yl)ethyl]-*N'*4-hydroxysuccinamide (8).** A solution of **7** (82 mg, 0.17 mmol) in a minimal volume of ethanol was subjected to hydrogenation over 10% Pd-C (21 mg) at rt for 2 h. The catalyst was filtered off and the filtrate evaporated. The resulting dark pink gum was purified by trituration with Et_2O/CH_2Cl_2 (2:1) to give **8** (64 mg, 96%) as a pink amorphous powder: UV (MeOH) 224, 275 (sh), 282, 290; IR (KBr) 1649, 3280 (br); ^{1}H NMR (DMSO-d$_6$) 0.87 (t, J=6.7, 3H, C$\underline{H}_3$), 1.12-1.38 (m, 8H, hexyl H), 2.10-2.45 (2m, 4H, succinic H), 3.04 (m, 2H, C$\underline{H}_2$NH), 2.87-3.16 (m, 2H, C$\underline{H}_2$Ind), 4.46 (m, 1H, C$\underline{H}$), 6.98, 7.07 (2t, J=7.8, 2H, Ind H-5,6), 7.15 (s, 1H, Ind H-2), 7.34 (d, J=7.8, H, Ind H-7), 7.59 (d, J=7.8, 1H, Ind H-4), 7.90 (t, J=5.6, 1H, N$\underline{H}$-Hex), 8.08 (d, J=8, 1H, CON$\underline{H}$), 10.03-10.63 (br s, 1H, N$\underline{H}$OH), 10.82 (s, 1H, Ind N$\underline{H}$); ^{13}C NMR (DMSO-d$_6$) 14.1 (C$\underline{H}_3$), 22.2, 26.2, 29.0, 31.1, 38.7 (hexyl C$\underline{H}_2$), 28.0, 28.1, 30.9 (C$\underline{H}_2$Ind, two succinic C$\underline{H}_2$), 53.9 (C$\underline{H}$), 110.5 (Ind C-3), 111.4 (Ind C-7), 118.3, 118.6 (Ind C-4,5), 121.0 (Ind C-6), 123.6 (Ind C-2), 127.5 (Ind C-3a), 136.2 (Ind C-7a), 168.6, 171.2, 171.5 (C$\underline{O}$NHOH, C$\underline{O}$NH, C$\underline{O}$NH-Hex); EIMS 402 ($M^{+\cdot}$, 0.5), 130 (100); HREIMS calcd for $C_{21}H_{30}N_4O_4$ 402.2322, found 402.2267.

Diethyl 2-{4-[(benzyloxy)amino]-4-oxobutanoyl}amino)-2-[2-(dimethylaminoethyl)-1*H*-indol-3-ylmethyl]}malonate (10). This product was prepared as reported above for **5** from **4** and tetrahydro-γ-carboline methiodide (**9**) (86%, white foam): UV (MeOH) 219, 275 (sh), 282, 291; IR (KBr) 1666, 1740, 3267, 3306; ^{1}H NMR ($CDCl_3$) 1.24 (t, J=7.2, 6H, 2 $CH_2C\underline{H}_3$), 2.34 (br s, 6H, N(C$\underline{H}_3$)$_2$), 2.34, 2.45 (2m, 4H, succinic H), 2.60, 2.73 (2m, 4H, C$\underline{H}_2$C$\underline{H}_2$NMe$_2$), 3.75 (s, 2H, C$\underline{H}_2$Ind), 4.06-4.27 (m, 4H, 2 C$\underline{H}_2$CH$_3$), 4.85 (s, 2H, C$\underline{H}_2$Ph), 6.83 (s, 1H, N$\underline{H}$CO), 6.98, 7.06 (t, J=7.8, 2H, Ind H-5,6), 7.25-7.38 (m, 7H, phenyl H, Ind H-4,7), 10.25 (1H, s, Ind N$\underline{H}$); ^{13}C NMR ($CDCl_3$) 13.7 (2 $CH_2\underline{C}H_3$), 22.3 (C$\underline{H}_2$CH$_2$NMe$_2$), 27.7, 28.0, 30.4 (C$\underline{H}_2$Ind, two succinic C$\underline{H}_2$), 44.8 (N(C$\underline{H}_3$)$_2$), 58.6 (CH$_2$C$\underline{H}_2$NMe$_2$), 62.4(2 C$\underline{H}_2$CH$_3$), 67.0 (malonic C), 77.9 (C$\underline{H}_2$Ph), 103.4 (Ind C-3), 110.8 (Ind C-7), 117.8, 118.8 (Ind C-4,5), 120.8 (Ind C-6), 128.4, 129.1 (5 phenyl C$\underline{H}$), 128.6 (Ind C-3a), 135.1 (phenyl C, Ind C-7a), 137.6 (Ind C-2), 167.8 (2 C$\underline{O}_2$Et), 169.0 (C$\underline{O}$NHOBn), 171.1 (C$\underline{O}$NH); EIMS 580 ($M^{+\cdot}$, 7), 144 (100); HREIMS calcd for $C_{31}H_{40}N_4O_7$ 580.2897, found 580.2892.

Ethyl 2-({4-[(benzyloxy)amino]-4-oxobutanoyl}amino)-3-[2-(dimethylaminoethyl)-1*H*-indol-3-yl]propionate (11). A solution of **10** (244 mg, 0.42 mmol) and LiOH.H_2O (67 mg, 1.60 mmol) in THF/H_2O (3:1) (18 mL) was stirred at rt for 24 h. After acidification with 10% HCl (pH4) and evaporation of the THF, the remaining solution was refluxed for 3 h. After cooling to rt, the mixture was basified with 2N NaOH and extracted three times with AcOEt. The combined organic layers were dried on Na_2SO_4, filtered and evaporated. The residue was purified by preparative TLC (CH_2Cl_2/15% MeOH) to yield **11** (83 mg, 39%) as a foam : UV (MeOH) 222, 277 (sh), 283, 291; IR (KBr) 1655, 1736, 3266, 3299; ^{1}H NMR (DMSO-d$_6$) 1.04 (t, J=7.2, 3H, CH$_2$C$\underline{H}_3$), 2.25 (s, 6H, N(C$\underline{H}_3$)$_2$), 2.18, 2.39 (2m, 4H, succinic H), 2.59, 2.86 (2t, J=7.2, 4H, C$\underline{H}_2$C$\underline{H}_2$NMe$_2$), 2.96-3.18 (m, 2H, C$\underline{H}_2$Ind), 3.95 (q, J=7.2, 2H, C$\underline{H}_2$CH$_3$), 4.49 (m, 1H, C$\underline{H}$), 4.79 (s, 2H, C$\underline{H}_2$Ph), 6.95 (t, J=7.6, 1H, Ind H-5), 7.03 (t, J=7.6, 1H, Ind H-6), 7.28 (t, J=7.6, 1H, Ind H-7), 7.33-7.43 (m, 5H, phenyl H), 7.46 (d, J=7.6, 1H, Ind H-4), 8.46 (d, J=7.2, 1H, N$\underline{H}$CO), 10.85 (s, 1H, Ind NH), 11.07 (br s, 1H, N$\underline{H}$OBn); ^{13}C NMR (DMSO-d$_6$) 14.0 (CH$_2\underline{C}$H$_3$), 23.8 (C$\underline{H}_2$CH$_2$NMe$_2$), 26.8 (C$\underline{H}_2$Ind), 27.9, 30.3 (two succinic C$\underline{H}_2$),

45.2 (N($\underline{C}H_3)_2$), 53.6 ($\underline{C}H$), 59.0 ($CH_2\underline{C}H_2NMe_2$), 60.5 ($\underline{C}H_2CH_3$), 77.0 ($\underline{C}H_2Ph$), 106.0 (Ind C-3), 110.8 (Ind C-7), 117.7 (Ind C-4), 118.4 (Ind C-5), 120.4 (Ind C-6), 128.4, 128.5, 129.0 (5 phenyl $\underline{C}H$), 128.2 (Ind C-3a), 135.6, 135.8 (Ind C-7a, Ind C-2), 136.3 (phenyl C), 168.9 ($\underline{C}ONHOBn$), 171.3 ($\underline{C}ONH$), 172.3 ($\underline{C}O_2Et$); EIMS 508 ($M^{+\cdot}$,8), 201 (100); HREIMS calcd for $C_{28}H_{36}N_4O_5$ 508.2686, found 508.2690.

***N'*1-(benzyloxy)-*N'*4-{2-[2-(dimethylaminoethyl)-1*H*-indol-3-yl]-1-(hexylcarbamoyl)-ethyl}succinamide (12).** A solution of *n*-hexylamine (100 mL, 0.75 mmol) in CH_2Cl_2 (2 mL) was cooled to 0°C and 2 M trimethylaluminium in hexane (0.4 mL, 0.8 mmol) was added under nitrogen. The mixture was stirred at 0°C for 30 min and was added *via* a syringe to a suspension of **11** (118 mg, 0.23 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was allowed to warm up to rt and stirred for 40 h. Then H_2O was added and the mixture was extracted three times with CH_2Cl_2. The combined organic phases were dried (Na_2SO_4), filtered, evaporated and the residue was purified by preparative TLC (CH_2Cl_2/5% MeOH: 2 migrations; CH_2Cl_2/7% MeOH: 1 migration). Compound (**12**) (65 mg, 50%) was obtained as an amorphous solid along with starting material (**11**) (29 mg, 25%): UV (MeOH) 222, 276 (sh), 283, 290; IR (KBr) 1645, 3287; ^{1}H NMR (DMSO-d_6) 0.85 (t, J=7.2, 3H, $C\underline{H}_3$), 1.04-1.31 (m, 8H, hexyl H), 2.28 (br s, 6H, N($C\underline{H}_3)_2$) 2.18, 2.38 (2m, 4H, succinic H), 2.60, 2.87 (2m, 4H, $C\underline{H}_2C\underline{H}_2NMe_2$), 2.95 (m, 2H, $C\underline{H}_2NH$), 2.80-3.14 (m, 2H, $C\underline{H}_2Ind$), 4.44 (m,1H, $C\underline{H}$), 4.78 (s, 2H, $C\underline{H}_2Ph$), 6.93 (t, J=7.6, 1H, Ind H-5), 7.00 (t, J=7.6, 1H, Ind H-6), 7.25 (d, J=7.6, 1H, Ind H-7), 7.30-7.44 (m, 5H, phenyl H), 7.54 (d, J=7.6, 1H, Ind H-4), 7.78 (t, J=5.2, 1H, $N\underline{H}$-Hex), 8.12 (d, J=8.0, 1H, $N\underline{H}CO$), 10.73 (1H, s, Ind NH), 11.06 (br s, 1H, $N\underline{H}OBn$); ^{13}C NMR (DMSO-d_6) 14.1 ($\underline{C}H_3$), 22.2, 26.1, 28.9, 31.1, 38.8 (hexyl $\underline{C}H_2$), 23.8 ($\underline{C}H_2CH_2NMe_2$), 27.5 ($\underline{C}H_2Ind$), 27.9, 30.5 (two succinic $\underline{C}H_2$), 45.2 (N($\underline{C}H_3)_2$), 54.3 ($\underline{C}H$), 59.0 ($CH_2\underline{C}H_2NMe_2$), 77.0 ($\underline{C}H_2Ph$), 106.8 (Ind C-3), 110.6 (Ind C-7), 118.2 (Ind C-4,5), 120.6 (Ind C-6), 128.4, 128.5, 128.9 (5 phenyl $\underline{C}H$), 135.5, 135.6 (Ind C-7a, Ind C-2), 136.2 (phenyl C), 169.1 ($\underline{C}ONHOBn$), 171.0, 171.2 ($\underline{C}ONH$), EIMS 563 ($M^{+\cdot}$, 1), 457 (18), 106 (100); HREIMS calcd for $C_{25}H_{39}N_5O_4$ 457.3053, found 457.3029.

***N'*1-{2-[2-(dimethylaminoethyl)-1*H*-indol-3-yl]-1-(hexylcarbamoyl)ethyl}-*N'*4-hydroxysuccinamide (13).** This compound was obtained from **12** as described above for **7** (96%, pale yellow solid) : UV (MeOH) 226, 275 (sh), 283, 291; IR (KBr) 1644, 3283; ^{1}H NMR (DMSO-d_6) 0.85 (t, J=7.2, 3H, $C\underline{H}_3$), 1.06-1.33 (m, 8H, hexyl H), 2.24 (s, 6H, N($C\underline{H}_3)_2$), 2.15, 2.35 (2m, 4H, succinic H), 2.52, 2.85 (m, 4H, $C\underline{H}_2C\underline{H}_2NMe_2$), 2.95 (m, 2H, $C\underline{H}_2NH$), 2.90-3.13 (m, 2H, $C\underline{H}_2Ind$), 4.42 (m,1H, $C\underline{H}$), 6.92 (t, J=7.2, 1H, Ind H-5), 6.98 (t, J=7.2, 1H, Ind H-6), 7.24 (d, J=7.6, 1H, Ind H-7), 7.52 (d, J=7.6, 1H, Ind H-4), 7.78 (t, J=5.2, 1H, $N\underline{H}$-Hex), 8.10 (d, J=8, 1H, $N\underline{H}CO$), 9.30-10.08 (br s, 1H, $N\underline{H}OH$), 10.71 (s, 1H, Ind NH); ^{13}C NMR (DMSO-d_6) 14.1 ($\underline{C}H_3$), 22.2, 26.1, 28.9, 31.2, 38.8 (hexyl $\underline{C}H_2$), 23.9 ($\underline{C}H_2CH_2NMe_2$), 27.6 ($\underline{C}H_2Ind$), 28.0, 30.8 (two succinic $\underline{C}H_2$), 45.3 (N($\underline{C}H_3)_2$), 54.3 ($\underline{C}H$), 59.3 ($CH_2\underline{C}H_2NMe_2$), 106.7 (Ind C-3), 110.6 (Ind C-7), 118.1 (Ind C-4, C-5), 120.2 (Ind C-6), 128.5 (Ind C-3a), 135.6, 135.8 (Ind C-7a,2), 168.7 ($\underline{C}ONHOH$), 171.1, 171.3 (2 $\underline{C}ONH$), EIMS 473 ($M^{+\cdot}$, 1), 457 (13), 156 (100); HREIMS calcd for $C_{25}H_{39}N_5O_4$ 473.3002, found 473.2997.

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