Synthesis and Reactivity of 1,4-Oxazinoindole Derivatives

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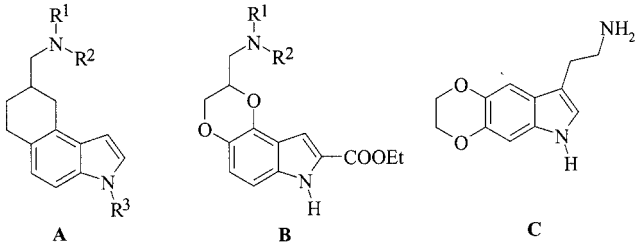
Application of the Hemetsberger reaction to ethyl 4-benzyl-7-formyl-2,3-dihydro-1,4-benzoxazine-2-carboxylate (**1**) or acetate (**2**) afforded a mixture of ethyl 2,3,4,6-tetrahydro-[1,4]oxazino[2,3-*f*]indole-7-carboxylate derivatives **3** or **4** and ethyl 2,3,4,9-tetrahydro[1,4]oxazino[3,2-*g*]indole-8-carboxylate derivatives **5** or **7**, with the "linear" derivatives predominant. Michael addition of *tert*-butyl acrylate to the indole nitrogen atom of **3**, **4** and subsequent electrophilic cyclisation gave access to tetracyclic compounds **24**, **25**.

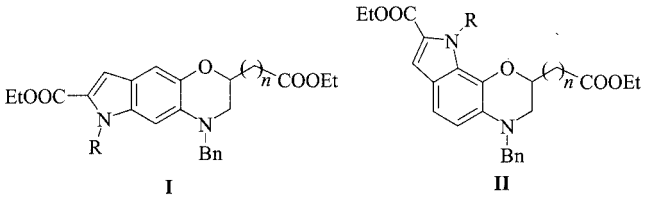
Introduction

Tricyclic derivatives containing an indole skeleton fused to another cyclic or heterocyclic moiety, such as a pyrano or a 1,4-dioxino nucleus, are well known and display various pharmacological properties. Illustrative examples such as compounds of type **A**,[1−3] **B**[4−6] and **C**[7] are shown in Scheme 1.



Scheme 1. Compounds A−C

Numerous methods for generating an indole ring have been reported,[8−10] and among them the Hemetsberger approach[11−18] is one of the most fruitful by which to obtain 2-carboxyindoles from aromatic or heterocyclic aldehydes. We have recently described[19] a synthetic route to 6- and 7-formyl-2,3-dihydro-1,4-benzoxazine derivatives. In this report, we have focused our efforts on the construction of 2,3,4,6-tetrahydro[1,4]oxazino[2,3-*f*]indole **I** and 2,3,4,9-tetrahydro[1,4]oxazino[3,2-*g*]indole **II** systems − promising scaffolds for pharmacologically active compounds such as anticancer or CNS agents − from 7-formyl derivatives **1**, **2** (Scheme 2).



Scheme 2. 2,3,4,6-Tetrahydro[1,4]oxazino[2,3-*f*]indole **I** and 2,3,4,9-tetrahydro[1,4]oxazino [3,2-*g*]indole **II**

Results and Discussion

Aldehyde **1** was treated with ethyl azidoacetate[20−23] in the presence of an excess of sodium ethoxide in ethanol at −18 °C for 20 h to give the ethyl azidocinnamate intermediate, which was immediately submitted to an intramolecular cyclisation according to the Hemetsberger methodology (Scheme 3). The aldolisation reaction proceeded slowly at −18 °C, but a slight increase in the temperature (−10 °C) resulted in degradation of the mixture. A mixture of the "linear" indole derivative **3** and the "curved" indole derivative **5** in a ratio of 85:15, together with the starting aldehyde **1**, was obtained. Addition of ethanol to the medium and subsequent stirring at 0 °C resulted in the crystallisation of **3** in 51% yield after filtration. Chromatographic separation of the filtrate (**1** and **5**) was problematic, so we first treated the mixture of **1** and **5** with di-*tert*-butyl dicarbonate to obtain the *N*-Boc compound **6**. This could then easily be isolated by column chromatography in 9% yield; starting material **1** was recovered in 10% yield. According to the procedure described below, aldehyde **2** afforded a mixture of indoles **4** and **7** in a ratio of 84:16. Compound **4** was obtained in 56% yield by crystallisation from ethanol. After column chromatographic separation, **7** was separated from residual **2** (7% yield) and obtained in 11% yield.

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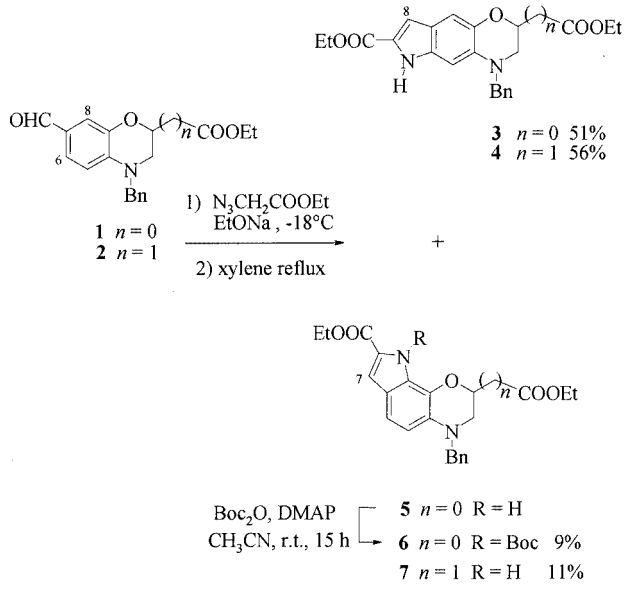
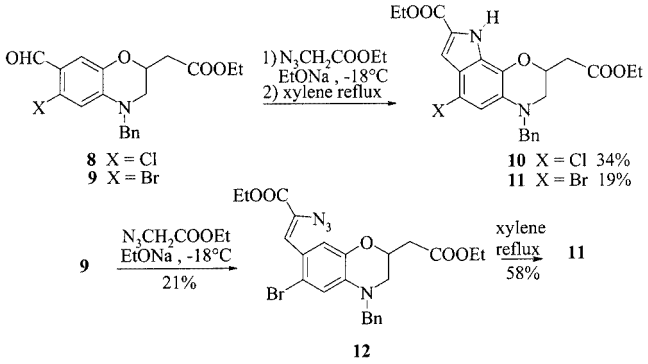


Scheme 3. Hemetsberger reaction of compounds **1**, **2**

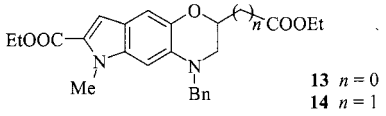
It should be noted that the regioselectivity of the formation of the pyrrolo ring in positions 6 or 8 was not temperature-dependent, with thermal cyclization of the azidocinnamate intermediate in diphenyl ether or xylene at reflux resulting in the same ratio of cyclized derivatives. This lack of selectivity is often observed in nitrene cyclizations of azides derived from 3,4-disubstituted benzaldehydes; the azide derivative obtained from 3-acetamido-4-methylbenzaldehyde, for example, gave an inseparable 1:1 mixture of the two possible indoles.[24] In our case, we observed one strongly predominant regioisomer, the "linear" structure.

The same conditions, when applied to the 6-chloro- or 6-bromo-7-formyl derivatives **8** and **9**, exclusively gave the "curved" indoles **10** and **11** in 34% and 19% yields, respectively. The low yields observed were the result of significant degradation in the aldolisation reaction step. In fact, purification of the intermediate provided the ethyl azidocinnamate **12** in only 21% yield, due to difficulties in chromatographic separation. Final thermal cyclisation of **12** afforded **11** in 58% yield (Scheme 4), which indicated that it was the aldolisation reaction that was yield-limiting.



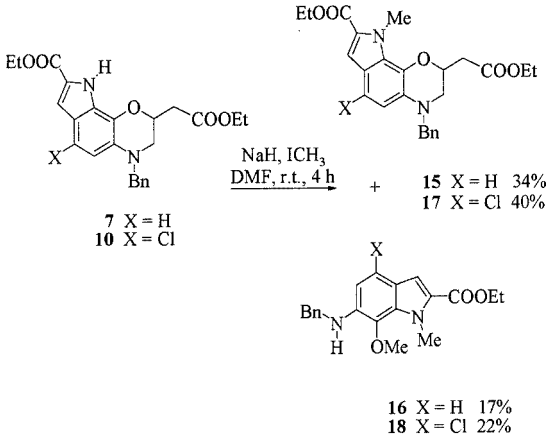
Scheme 4. Hemetsberger reaction of **8**, **9**

In order to increase the stability of the indole derivatives, the indole nitrogen atom was alkylated. Treatment of compounds **3**, **4** with iodomethane in the presence of sodium hydride in *N*,*N*-dimethylformamide at 0 °C afforded *N*-methyl derivatives **13**, **14** in 91−96% yields (Scheme 5). No methylation was observed in the position α to the ester group of compound **14**.



Scheme 5. Derivatives **13**, **14**

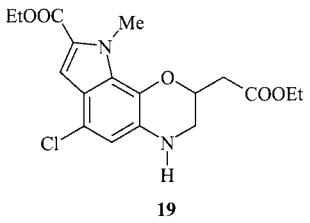
With the curved derivative **7**, the same conditions afforded a mixture of the expected *N*-methyl derivative **15** in 34% yield and the 6-aminoindole **16** in 17% yield (Scheme 6). Similarly, indole **10** afforded a mixture of **17** and **18** in 40% and 22% yields, respectively. The formation of compounds **16** and **18** results from the opening of the oxazino ring through a retro-Michael reaction followed by deconjugation of the double bond in the basic medium and hydrolysis of the generated enamine. This reaction provided access to 6,7-disubstituted indoles, which are not easily obtainable by substitution of indole derivatives. A lower reaction temperature (−15 °C) or the use of potassium carbonate as base in acetonitrile[25] afforded **15** and **17** in better yields (see Exp. Sect.).



Scheme 6. *N*-Alkylation of **7** and **10**

Hydrogenolysis of **17** in the presence of palladium catalyst under 3 atm of hydrogen for 1 h gave **19** in 88% yield (Scheme 7). An increased hydrogen pressure (35 atm) or reaction time did not modify the course of the reaction. In contrast, debenzylation of **17** in the presence of palladium in formic acid and triethylamine at reflux afforded a mixture of dechlorinated compound **15** and starting material **16** in a ratio of 1:1 (easily separable by column chromatography) in a 75% overall yield. The latter procedure, not totally satisfying in terms of yield, allowed us to obtain

pure unsubstituted "curved" indole **15** without tedious chromatographic separation.

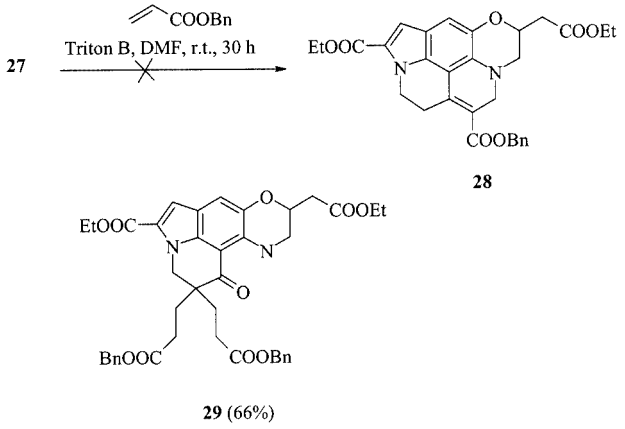


19

Scheme 7. Derivative **19**

The reactivity of the electron-rich heterocycles **3**, **4** towards electrophilic cyclisation was investigated, in order to generate new tetracyclic indole nuclei. Michael addition of *tert*-butyl acrylate to compounds **3**, **4** in the presence of a catalytic amount of Triton B in *N*,*N*-dimethylformamide[26] at 0 °C afforded the *N*-alkylated derivatives **20** and **21** in 76−94% yields. Acid hydrolysis of esters **20**, **21** was performed with trifluoroacetic acid in dichloromethane to give the corresponding acids **22**, **23** in 97−98% yields. Finally, electrophilic cyclisations were carried out in polyphosphoric acid trimethylsilyl ester (PPSE)[27] in refluxing dichloroethane to give the cyclic ketones **24**, **25** in 86−87% yields (Scheme 8). Hydrogenolysis of compounds **24**, **25** in the presence of palladium catalyst afforded the derivatives **26**, **27** in quantitative yields.

After these results, we briefly explored the preparation of a fifth ring between the oxo group and the nitrogen atom in position 4 (Scheme 9). We first planned the formation in situ of an enolate, resulting from a Michael-type addition, that might add to the carbonyl group of the ketone to generate compound **28**.[28] This reaction was attempted with compound **27** and benzyl acrylate in excess, in the presence of Triton B. Unfortunately, the *N*-alkylation reaction was not observed, due to the low reactivity of the nitrogen atom. In fact, dialkylation at the α-carbon atom of the ketone occurred, to afford **29** in 66% yield.



29 (66%)

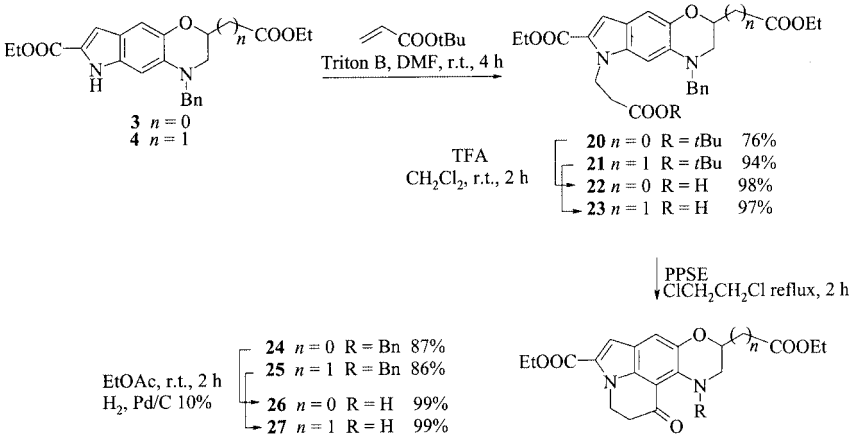
Scheme 9. Attempt to synthesise pentacyclic derivative **28**

Conclusion

We have developed new 1,4-oxazinoindole structures from 7-formyl-2,3-dihydro-1,4-benzoxazine derivatives by the Hemetsberger reaction. The reactivity of linear derivatives was investigated to give access to functionalised tetracyclic unknown derivatives with large synthetic and pharmacological potentials.

Experimental Section

General: Melting points were determined with a Büchi capillary instrument and are uncorrected. The infrared spectra of compounds were recorded with a Perkin−Elmer FTIR paragon 1000 spectrometer. NMR spectra were recorded in $CDCl_3$ or $[D_6]$DMSO (at 300 K if not specified) with a Bruker Avance DPX 250. Chemical shifts are given in ppm from tetramethylsilane (TMS) as internal standard. Mass spectra were recorded with a Perkin−Elmer SCIEX API 300 machine using ionspray methodology. Thin-layer chromatography (TLC) was run on precoated silica gel plates



Scheme 8. Synthesis of tetracyclic derivatives **24**−**27**

(Merck $60F_{254}$) and the spots were viewed by means of an ultraviolet lamp. Flash chromatography was carried out on columns with flash silica gel 60 Merck (40−63 μm) as the stationary phase. All reactions requiring anhydrous conditions were conducted in flame-dried apparatus. Compounds **1**, **2**, **8** and **9** were prepared according to a reported method.[19]

Diethyl 4-Benzyl-2,3,4,6-tetrahydro[1,4]oxazino[2,3-*f*]indole-2,7-dicarboxylate (3): A solution of aldehyde **1** (5.00 g, 15.41 mmol) and ethyl azidoacetate (9.15 g, 70.9 mmol) in EtOH (20 mL) was added dropwise at −18 °C to a solution of sodium ethoxide (1.4 N, 49 mL, 69.34 mmol). The mixture was stirred at −18 °C for 20 h, and a cooled saturated NH_4Cl solution was then added to the medium at −18 °C. The intermediate azidocinnamate was extracted with Et_2O. The organic phase was washed with water and dried with $MgSO_4$, and the solvents were evaporated in vacuo. The oil was dissolved in xylene (150 mL) and this solution was added dropwise to a refluxing xylene solution (130 mL). Compounds **3** and **5** were immediately formed. After cooling and evaporation of xylene, the residue was taken up in ethanol at 0 °C. The precipitate was filtered and recrystallised from EtOH to give **3** (3.21 g, 51%); m.p. 179−180 °C (EtOH). IR (KBr): $\tilde{\nu}$ = 3318, 1758, 1671 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.24 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.35 (t, *J* = 7.2 Hz, 3 H, CH_3), 3.63 (d, *J* = 4.2 Hz, 2 H, CH_2N), 4.15−4.29 (m, 2 H, CH_2O), 4.32 (q, *J* = 7.2 Hz, 2 H, CH_2O), 4.43 and 4.55, (d, *J* = 16.3 Hz, 1 H, NCH_2Ph), 4.86 (t, *J* = 4.2 Hz, 1 H, OCH), 6.51 (s, 1 H, H_{Ar}), 7.05 (d, *J* = 1.6 Hz, 1 H, H_8), 7.19 (s, 1 H, H_{Ar}), 7.25−7.37 (m, 5 H, H_{Ar}), 8.52 (br. s, 1 H, NH). ^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 14.3 (CH_3), 14.6 (CH_3), 49.2 (CH_2), 55.6 (CH_2), 60.7 (CH_2), 61.9 (CH_2), 72.6 (CH), 93.5 (CH), 108.0 (CH), 108.9 (CH), 120.0 (C), 125.8 (C), 127.1 (2 CH), 127.6 (CH), 129.0 (2 CH), 134.1 (C), 135.5 (C), 137.4 (C), 140.1 (C), 162.1 (C=O), 169.6 (C=O). MS (IS): *m*/*z* = 409 [M^+ + 1]. $C_{23}H_{24}N_2O_5$ (408.5): calcd. C 67.63, H 5.92, N 6.86; found C 67.99, H 5.77, N 7.02.

Ethyl 4-Benzyl-2-[(ethoxycarbonyl)methyl]-2,3,4,6-tetrahydro[1,4]oxazino[2,3-*f*]indole-7-carboxylate (4): Compound **4** was prepared in 56% yield from aldehyde **2** according to the procedure for the synthesis of **3**; m.p. 172−173 °C (EtOH). IR (KBr): $\tilde{\nu}$ = 3313, 1741, 1674 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.27 (t, *J* = 7.1 Hz, 3 H, CH_3), 1.35 (t, *J* = 7.1 Hz, 3 H, CH_3), 2.61 (dd, *J* = 15.9, 6.6 Hz, 1 H, CH_2CO), 2.81 (dd, *J* = 15.9, 6.7 Hz, 1 H, CH_2CO), 3.32 (dd, *J* = 11.5, 7.5 Hz, 1 H, CH_2N), 3.49 (dd, *J* = 11.5, 2.7 Hz, 1 H, CH_2N), 4.18 (q, *J* = 7.1 Hz, 2 H, CH_2O), 4.32 (q, *J* = 7.1 Hz, 2 H, CH_2O), 4.47 and 4.56 (d, *J* = 16.5 Hz, 1 H, NCH_2Ph), 4.60−4.69 (m, 1 H, OCH), 6.49 (s, 1 H, H_{Ar}), 7.02 (d, *J* = 1.2 Hz, 1 H, H_8), 7.04 (s, 1 H, H_{Ar}), 7.25−7.33 (m, 5 H, H_{Ar}), 8.46 (br. s, 1 H, NH). ^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 14.4 (CH_3), 14.6 (CH_3), 38.2 (CH_2), 51.8 (CH_2), 55.5 (CH_2), 60.7 (CH_2), 61.0 (CH_2), 70.1 (CH), 92.7 (CH), 107.9 (CH), 108.8 (CH), 119.5 (C), 125.5 (C), 127.0 (2 CH), 127.5 (CH), 129.0 (2 CH), 134.3 (C), 135.7 (C), 137.6 (C), 140.6 (C), 162.1 (C=O), 170.5 (C=O). MS (IS): *m*/*z* = 423 [M^+ + 1]. $C_{24}H_{26}N_2O_5$ (422.5): calcd. C 68.23, H 6.20, N 6.63; found C 67.87, H 6.36, N 6.82.

9-*tert*-Butyl 2,8-Diethyl 4-Benzyl-2,3,4,9-tetrahydro[1,4]oxazino[3,2-*g*]indole-2,8,9-tricarboxylate (6): The filtrate remaining after the precipitation of compound **3** was concentrated in vacuo. The crude residue was chromatographed on a pad of silica gel (eluent petroleum ether/ethyl acetate, 7:3) to afford a mixture of **5** and starting aldehyde **1**. The two compounds were dissolved in acetonitrile (20 mL) and were added dropwise to a solution of di-*tert*-butyl dicarbonate (1.96 g, 9.0 mmol) and DMAP (305 mg, 2.5 mmol) in acetonitrile (20 mL). The final solution was stirred at room temperature for 15 h. After evaporation of the solvent, the obtained residue was partitioned between a saturated NH_4Cl solution and ethyl acetate and extracted. The organic phase was washed with H_2O and dried with $MgSO_4$, and the solvents were evaporated in vacuo. The crude residue was purified by column chromatography (petroleum ether/ethyl acetate, 75:25) to give **6** (705 mg, 9% from **1**) as a beige solid; m.p. 123−124 °C (ethyl acetate). IR (KBr): $\tilde{\nu}$ = 1771, 1759, 1732, 1713, 1706 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.17 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.37 (t, *J* = 7.1 Hz, 3 H, CH_3), 1.62 [s, 9 H, $C(CH_3)_3$], 3.57 (dd, *J* = 12.2, 3.3 Hz, 1 H, CH_2N), 3.65 (dd, *J* = 12.2, 3.8 Hz, 1 H, CH_2N), 4.08−4.27 (m, 2 H, CH_2O), 4.35 (q, *J* = 7.1 Hz, 2 H, CH_2O), 4.44 and 4.53 (d, *J* = 16.3 Hz, 1 H, NCH_2Ph), 4.88 (t, *J* = 3.1 Hz, 1 H, OCH), 6.68 (d, *J* = 8.8 Hz, 1 H, H_{Ar}), 7.06 (d, *J* = 8.8 Hz, 1 H, H_{Ar}), 7.11 (s, 1 H, 7-H), 7.25−7.36 (m, 5 H, H_{Ar}). ^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 14.3 (CH_3), 14.6 (CH_3), 27.6 [$(CH_3)_3$], 48.9 (CH_2), 56.1 (CH_2), 60.9 (CH_2), 61.7 (CH_2), 72.4 (CH), 84.4 (C), 110.8 (CH), 112.1 (CH), 115.5 (CH), 121.3 (C), 127.1(C), 127.3 (2 CH), 127.5 (CH), 128.0 (C), 128.9 (2 CH, C), 132.4 (C), 138.1 (C), 151.2 (C=O), 161.1 (C=O), 169.2 (C=O). MS (IS): *m*/*z* = 509 [M^+ + 1]. $C_{28}H_{32}N_2O_7$ (508.6): calcd. C 66.13, H 6.34, N 5.51; found C 65.71, H 6.50, N 5.67.

Ethyl 4-Benzyl-2-[(ethoxycarbonyl)methyl]-2,3,4,9-tetrahydro[1,4]-oxazino[3,2-*g*]indole-8-carboxylate (7): The filtrate remaining after the precipitation of compound **4** was concentrated in vacuo. The crude residue was purified by column chromatography (petroleum ether ether/ethyl acetate, 75:25) to give **7** (11% from **2**) as an oil. IR (film): $\tilde{\nu}$ = 3331, 1731, 1699 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 7.1 Hz, 3 H, CH_3), 1.38 (t, *J* = 7.1 Hz, 3 H, CH_3), 2.62 (dd, *J* = 15.9, 6.3 Hz, 1 H, CH_2CO), 2.83 (dd, *J* = 15.9, 6.8 Hz, 1 H, CH_2CO), 3.15 (dd, *J* = 12.2, 7.0 Hz, 1 H, CH_2N), 3.40 (dd, *J* = 12.2, 2.2 Hz, 1 H, CH_2N), 4.18 (q, *J* = 7.1 Hz, 2 H, CH_2O), 4.36 (q, *J* = 7.1 Hz, 2 H, CH_2O), 4.40 and 4.53 (d, *J* = 16.0 Hz, 1 H, NCH_2Ph), 4.63−4.75 (m, 1 H, OCH), 6.73 (d, *J* = 8.6 Hz, 1 H, H_{Ar}), 7.10 (d, *J* = 2.1 Hz, 1 H, 7-H), 7.11 (d, *J* = 8.6 Hz, 1 H, H_{Ar}), 7.24−7.32 (m, 5 H, H_{Ar}), 8.75 (br. s, 1 H, NH). ^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 14.3 (CH_3), 14.6 (CH_3), 38.1 (CH_2), 51.4 (CH_2), 56.2 (CH_2), 60.8 (CH_2), 61.0 (CH_2), 70.0 (CH), 109.5 (CH), 110.7 (CH), 115.2 (CH), 122.0 (C), 126.2 (C), 127.5 (2 CH), 128.4 (CH), 128.8 (2 CH), 131.0 (C), 135.6 (C), 137.6 (C), 138.3 (C), 162.0 (C=O), 170.5 (C=O). MS (IS): *m*/*z* = 423 [M^+ + 1]. $C_{24}H_{26}N_2O_5$ (422.5): calcd. C 68.23, H 6.20, N 6.63; found C 68.64, H 6.02, N 6.74.

Ethyl 4-Benzyl-6-chloro-2-[(ethoxycarbonyl)methyl]-2,3,4,9-tetrahydro[1,4]oxazino[3,2-*g*]indole-8-carboxylate (10): A solution of aldehyde **8** (2.51 g, 6.70 mmol) and ethyl azidoacetate (3.98 g, 30.82 mmol) in EtOH (20 mL) was added dropwise at −18 °C to a solution of sodium ethoxide (1.4 N, 21.5 mL, 30.15 mmol). The mixture was stirred at −18 °C for 24 h. A cooled saturated NH_4Cl solution was added to the medium at −18 °C. The intermediate azidocinnamate was extracted with Et_2O. The organic phase was washed with water and dried with $MgSO_4$, and the solvents were evaporated in vacuo. The crude oil was dissolved in xylene (150 mL), and this solution was added dropwise to refluxing xylene (130 mL). Compound **10** was formed immediately. After cooling and evaporation of xylene, the crude residue was purified by column chromatography (petroleum ether/ethyl acetate, 75:25) to give **10** (1.04 g, 34%) as a beige solid; m.p. 103−104 °C (ethyl acetate). IR (KBr): $\tilde{\nu}$ = 3245, 1730, 1706 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.40 (t, *J* = 7.2 Hz, 3 H, CH_3), 2.60 (dd, *J* = 16.0, 6.3 Hz, 1 H, CH_2CO), 2.82 (dd, *J* = 16.0, 6.6 Hz, 1 H, CH_2CO), 3.14 (dd, *J* = 12.2, 6.9 Hz, 1 H, CH_2N), 3.39 (dd, *J* = 12.2, 2.5 Hz, 1 H, CH_2N), 4.18 (q, *J* = 7.2 Hz, 2 H, CH_2O), 4.38

(q, J = 7.2 Hz, 2 H, CH_2O), 4.39 and 4.51 (d, J = 16.0 Hz, 1 H, NCH_2Ph), 4.61−4.70 (m, 1 H, OCH), 6.76 (s, 1 H, H_{Ar}), 7.16 (d, J = 2.5 Hz, 1 H, 7-H), 7.25−7.37 (m, 5 H, H_{Ar}), 8.76 (br. s, 1 H, NH). ^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 14.4 (CH_3), 14.6 (CH_3), 38.0 (CH_2), 51.2 (CH_2), 56.2 (CH_2), 61.1 (2 CH_2), 70.1 (CH), 107.9 (CH), 109.9 (CH), 119.7 (C), 120.8 (C), 126.7 (C), 127.3 (C), 127.5 (2 CH), 127.7 (CH), 128.8 (C), 129.0 (2 CH), 131.6 (C), 137.8 (C), 161.8 (C=O), 170.3 (C=O). MS (IS): m/z = 457 [M^+ + 1, ^{35}Cl], 459 [M^+ + 1, ^{37}Cl]. $C_{24}H_{25}ClN_2O_5$: (456.9): calcd. C 63.09, H 5.51, N 6.13; found C 63.41, H 5.65, N 6.25.

Ethyl 4-Benzyl-6-bromo-2-[(ethoxycarbonyl)methyl]-2,3,4,9-tetrahydro[1,4]oxazino[3,2-*g*]indole-8-carboxylate (11). Method A: Compound **11** was prepared in 19% yield from aldehyde **9** according to the procedure for the synthesis of **10**. **Method B:** A solution of azide **12** (67 mg, 0.13 mmol) in xylene (1.5 mL) was added dropwise to xylene (5 mL) at reflux. Compound **11** was obtained in 5 min. After cooling and evaporation of xylene, the crude residue was purified by column chromatography (petroleum ether ether/ethyl acetate, 75:25) to give **11** (37 mg, 58%) as a beige solid; m.p. 89−90 °C (ethyl acetate). IR (KBr): $\tilde{\nu}$ = 3262, 1735, 1710 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.26 (t, J = 7.2 Hz, 3 H, CH_3), 1.40 (t, J = 7.1 Hz, 3 H, CH_3), 2.60 (dd, J = 15.9, 6.3 Hz, 1 H, CH_2CO), 2.81 (dd, J = 15.9, 6.8 Hz, 1 H, CH_2CO), 3.14 (dd, J = 12.2, 6.9 Hz, 1 H, CH_2N), 3.39 (dd, J = 12.2, 2.5 Hz, 1 H, CH_2N), 4.18 (q, J = 7.2 Hz, 2 H, CH_2O), 4.38 (q, J = 7.1 Hz, 2 H, CH_2O), 4.39 and 4.51 (d, J = 15.7 Hz, 1 H, NCH_2Ph), 4.61−4.70 (m, 1 H, OCH), 6.94 (s, 1 H, H_{Ar}), 7.10 (d, J = 2.5 Hz, 1 H, 7-H), 7.26−7.35 (m, 5 H, H_{Ar}), 8.84 (br. s, 1 H, NH). ^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 14.4 (CH_3), 14.6 (CH_3), 38.0 (CH_2), 51.1 (CH_2), 56.2 (CH_2), 61.1 (CH_2), 61.2 (CH_2), 70.1 (CH), 107.5 (C), 109.5 (CH), 113.0 (CH), 122.8 (C), 126.7 (C), 127.6 (2 CH), 127.7 (CH), 128.0 (C), 128.6 (C), 129.0 (2 CH), 131.9 (C), 137.7 (C), 161.9 (C=O), 170.3 (C=O). MS (IS): m/z = 501 [M^+ + 1, ^{79}Br], 503 [M^+ + 1, ^{81}Br]. $C_{24}H_{25}BrN_2O_5$ (501.4): calcd. C 57.49, H 5.03, N 5.59; found C 57.13, H 4.88, N 5.76.

Ethyl 2-Azido-3-{4-benzyl-6-bromo-2-[(ethoxycarbonyl)methyl]-3,4-dihydro-2*H*-1,4-benzoxazin-7-yl}prop-2-enoate (12): A solution of aldehyde **9** (250 mg, 0.60 mmol) and ethyl azidoacetate (361 mg, 2.76 mmol) in EtOH (20 mL) was added dropwise at −18 °C to a solution of sodium ethoxide (1.4 N, 1.93 mL, 2.70 mmol). The mixture was stirred at −18 °C for 20 h, and a cooled saturated NH_4Cl solution was then added to the medium at −18 °C. The intermediate azidocinnamate was extracted with Et_2O. The organic phase was washed with water and dried with $MgSO_4$, and the solvents were evaporated in vacuo. The crude residue was purified by column chromatography (petroleum ether/ethyl acetate, 75:25) to give the unstable compound **12** (67 mg, 21%), which was used in the next step without further characterisation. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.25 (t, J = 7.1 Hz, 3 H, CH_3), 1.38 (t, J = 7.1 Hz, 3 H, CH_3), 2.57 (dd, J = 6.7, 16.0 Hz, 1 H, CH_2CO), 2.80 (dd, J = 16.0, 6.5 Hz, 1 H, CH_2CO), 3.25 (dd, J = 11.7, 7.4 Hz, 1 H, CH_2N), 3.42 (dd, J = 11.7, 2.7 Hz, 1 H, CH_2N), 4.18 (q, J = 7.1 Hz, 2 H, CH_2O), 4.35 (q, J = 7.1 Hz, 2 H, CH_2O), 4.43 and 4.52 (d, J = 18.2 Hz, 1 H, NCH_2Ph), 4.53−4.62 (m, 1 H, OCH), 6.89 (s, 1 H, H_{Ar}), 7.22−7.39 (m, 6 H, H_{Ar}), 7.85 (s, 1 H, CH=).

Diethyl 4-Benzyl-6-methyl-2,3,4,6-tetrahydro[1,4]oxazino[2,3-*f*]indole-2,7-dicarboxylate (13): A solution of **3** (600 mg, 1.47 mmol) in dry DMF (6 mL) was added slowly at 0 °C, over 30 min, to a suspension of NaH (65 mg, 1.62 mmol, 60% oil dispersion) in dry DMF (2 mL) at 0 °C. After 20 min of stirring, a solution of iodomethane (120 μL, 1.91 mmol) in dry DMF (7 mL) was added. The final solution was stirred at room temperature for 4 h, hydrolysed with a saturated NH_4Cl solution and finally extracted with ethyl acetate. The organic phase was washed with water and dried with $MgSO_4$, and the solvents were evaporated in vacuo. The crude residue was purified by column chromatography (petroleum ether ether/ethyl acetate, 75:25) to give **13** (596 mg, 96%) as an oil. IR (film): $\tilde{\nu}$ = 1757, 1703 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.22 (t, J = 7.2 Hz, 3 H, CH_3), 1.36 (t, J = 7.2 Hz, 3 H, CH_3), 3.59 (d, J = 4.2 Hz, 2 H, CH_2N), 3.83 (s, 3 H, NCH_3), 4.09−4.33 (m, 2 H, CH_2O), 4.30 (q, J = 7.2 Hz, 2 H, CH_2O), 4.43 and 4.58 (d, J = 16.2 Hz, 1 H, NCH_2Ph), 4.83 (t, J = 4.2 Hz, 1 H, OCH), 6.44 (s, 1 H, H_{Ar}), 7.13 (s, 1 H, H_{Ar}), 7.17 (s, 1 H, H_{Ar}), 7.23−7.36 (m, 5 H, H_{Ar}). ^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 14.2 (CH_3), 14.5 (CH_3), 31.6 (CH_3), 48.9 (CH_2), 55.4 (CH_2), 60.1 (CH_2), 61.7 (CH_2), 72.6 (CH), 91.7 (CH), 107.9 (CH), 110.1 (CH), 118.0 (C), 126.1 (C), 127.2 (2 CH), 127.4 (CH), 128.9 (2 CH), 135.4 (C), 137.0 (C), 137.4 (C), 140.0 (C), 162.3 (C=O), 169.5 (C=O). MS (IS): m/z = 423 [M^+ + 1]. $C_{24}H_{26}N_2O_5$: (422.5): calcd. C 68.23, H 6.20, N 6.63; found C 67.85, H 6.37, N 6.75.

Ethyl 4-Benzyl-2-[(ethoxycarbonyl)methyl]-6-methyl-2,3,4,6-tetrahydro[1,4]oxazino[2,3-*f*]indole-7-carboxylate (14): Compound **14** was prepared in 91% yield from **4** according to the procedure for the synthesis of **13**; m.p. 102−103 °C (diisopropyl ether). IR (KBr): $\tilde{\nu}$ = 1715, 1695 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.25 (t, J = 7.1 Hz, 3 H, CH_3), 1.36 (t, J = 7.1 Hz, 3 H, CH_3), 2.59 (dd, J = 15.7, 6.3 Hz, 1 H, CH_2CO), 2.79 (dd, J = 15.7, 6.9 Hz, 1 H, CH_2CO), 3.28 (dd, J = 11.7, 7.4 Hz, 1 H, CH_2N), 3.46 (dd, J = 11.7, 2.5 Hz, 1 H, CH_2N), 3.83 (s, 3 H, NCH_3), 4.17 (q, J = 7.1 Hz, 2 H, CH_2O), 4.30 (q, J = 7.1 Hz, 2 H, CH_2), 4.49 and 4.57 (d, J = 16.3 Hz, 1 H, N CH_2Ph), 4.58−4.67 (m, 1 H, OCH), 6.42 (s, 1 H, H_{Ar}), 7.03 (s, 1 H, H_{Ar}), 7.10 (1s, 1 H, H_{Ar}), 7.23−7.37 (m, 5 H, H_{Ar}). ^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 14.3 (CH_3), 14.6 (CH_3), 31.6 (CH_3), 38.1 (CH_2), 51.6 (CH_2), 55.3 (CH_2), 60.1 (CH_2), 60.9 (CH_2), 70.0 (CH), 90.9 (CH), 107.8 (CH), 110.1 (CH), 117.6 (C), 125.8 (C), 127.1 (2 CH), 127.4 (CH), 128.9 (2 CH), 135.6 (C), 137.2 (C), 137.7 (C), 140.5 (C), 162.3 (C=O), 170.4 (C=O). MS (IS): m/z = 437 [M^+ + 1]. $C_{25}H_{28}N_2O_5$ (436.5): calcd. C 68.79, H 6.47, N 6.42; found C 68.35, H 6.64, N 6.59.

Ethyl 4-Benzyl-2-[(ethoxycarbonyl)methyl]-9-methyl-2,3,4,9-tetrahydro[1,4]oxazino[3,2-*g*]indole-8-carboxylate (15): Compounds **15** and **16** were prepared from **7** in 34% and 17% yields, respectively, according to the procedure for the synthesis of **13**. The same reaction performed at −15 °C for 4 h gave **15** in 78% yield as a beige solid; m.p. 90−92 °C (diisopropyl ether). IR (KBr): $\tilde{\nu}$ = 1723, 1702 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.26 (t, J = 7.2 Hz, 3 H, CH_3), 1.38 (t, J = 7.0 Hz, 3 H, CH_3), 2.62 (dd, J = 15.5, 5.0 Hz, 1 H, CH_2CO), 2.79 (dd, J = 15.5, 8.0 Hz, 1 H, CH_2CO), 3.17 (dd, J = 12.1, 7.7 Hz, 1 H, CH_2N), 3.38 (dd, J = 12.1, 2.4 Hz, 1 H, CH_2N), 4.18 (q, J = 7.2 Hz, 2 H, CH_2O), 4.26 (s, 3 H, NCH_3), 4.32 (q, J = 7.0 Hz, 2 H, CH_2O), 4.42 and 4.55 (d, J = 16.2 Hz, 1 H, NCH_2Ph), 4.58−4.68 (m, 1 H, OCH), 6.73 (d, J = 8.6 Hz, 1 H, H_{Ar}), 7.07 (d, J = 8.6 Hz, 1 H, H_{Ar}), 7.15 (s, 1 H, 7-H), 7.25−7.37 (m, 5 H, H_{Ar}). ^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 14.3 (CH_3), 14.5 (CH_3), 34.6 (CH_3), 38.3 (CH_2), 51.4 (CH_2), 56.9 (CH_2), 60.2 (CH_2), 61.0 (CH_2), 69.6 (OCH), 111.0 (CH), 111.4 (CH), 115.4 (CH), 121.3 (C), 127.3 (C), 127.4 (3 CH), 128.8 (2 CH), 130.1 (C), 130.7 (C), 131.2 (C), 138.4 (C), 162.2 (C=O), 170.5 (C=O). MS (IS): m/z = 437 [M^+ + 1]. $C_{25}H_{28}N_2O_5$ (436.5): calcd. C 68.79, H 6.47, N 6.42; found C 68.42, H 6.33, N 6.58.

Ethyl 6-(Benzylamino)-7-methoxy-1-methyl-1*H*-indole-2-carboxylate (16): Brown solid; m.p. 89−90 °C (ethyl acetate). IR (KBr): $\tilde{\nu}$ = 3396, 1693 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.38 (t, J = 7.2 Hz, 3 H, CH_3), 3.80 (s, 3 H, OCH_3), 4.28 (s, 3 H, NCH_3),

4.33 (q, J = 7.2 Hz, 2 H, CH_2O), 4.43 (s, 2 H, NCH_2Ph); 4.65 (br. s, 1 H, NH), 6.66 (d, J = 8.8 Hz, 1 H, H_{Ar}), 7.20 (s, 1 H, H_{Ar}), 7.24 (d, J = 8.8 Hz, 1 H, H_{Ar}), 7.27−7.42 (m, 5 H, H_{Ar}). ^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 14.6 (CH_3), 33.4 (CH_3), 48.7 (CH_2), 60.3 (CH_2), 61.0 (CH_3), 109.0 (CH), 112.1 (CH), 119.2 (CH), 121.1 (C), 127.3 (C), 127.4 (1 CH), 127.5 (2 CH), 128.8 (2 CH), 132.0 (C), 133.7 (C), 139.4 (C), 140.0 (C), 162.2 (C=O). MS (IS): m/z = 339 [M^+ + 1]. $C_{20}H_{22}N_2O_3$ (338.4): calcd. C 70.99, H 6.55, N 8.28; found C 70.62, H 6.69, N 8.37.

Ethyl 4-Benzyl-6-chloro-2-[(ethoxycarbonyl)methyl]-9-methyl-2,3,4,9-tetrahydro[1,4]oxazino[3,2-*g*]indole-8-carboxylate (17). Method A: Compounds **17** and **18** were prepared from **10** in 40% and 22% yields, respectively, according to the procedure for the synthesis of **13**. **Method B:** A solution of **7** (98 mg, 0.21 mmol), iodomethane (70 μL, 1.11 mmol) and K_2CO_3 (88 mg, 0.63 mmol) in acetonitrile (5 mL) was stirred at reflux for 16 h. After filtration, the solvent was evaporated. The crude residue was purified by column chromatography (petroleum ether ether/ethyl acetate, 75:25) to give **17** (64 mg, 64%) as a brown solid; m.p. 105−106 °C (ethyl acetate). IR (KBr): $\tilde{\nu}$ = 1721, 1697 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.26 (t, J = 7.1 Hz, 3 H, CH_3), 1.39 (t, J = 7.1 Hz, 3 H, CH_3), 2.61 (dd, J = 15.5, 5.3 Hz, 1 H, CH_2CO), 2.77 (dd, J = 15.5, 7.9 Hz, 1 H, CH_2CO), 3.15 (dd, J = 12.2, 7.6 Hz, 1 H, CH_2N), 3.37 (dd, J = 12.2, 2.4 Hz, 1 H, CH_2N), 4.17 (q, J = 7.1 Hz, 2 H, CH_2O), 4.24 (s, 3 H, NCH_3), 4.33 (q, J = 7.1 Hz, 2 H, CH_2O), 4.40 and 4.52 (d, J = 16.3 Hz, 1 H, NCH_2Ph), 4.56−4.65 (m, 1 H, OCH), 6.75 (s, 1 H, H_{Ar}), 7.22 (s, 1 H, H_{Ar}), 7.28−7.35 (m, 5 H, H_{Ar}). ^{13}C NMR (62.90 MHz, [D_6]DMSO): δ = 14.0 (CH_3), 14.1 (CH_3), 33.9 (CH_3), 37.2 (CH_2), 50.5 (CH_2), 54.9 (CH_2), 60.1 (CH_2), 60.3 (CH_2), 69.8 (CH), 108.4 (CH), 109.6 (CH), 113.0 (C), 118.0 (2 C), 127.0 (3 CH), 127.8 (C), 128.5 (2 CH), 130.0 (C), 131.6 (C), 138.1 (C), 160.7 (C=O), 169.9 (C=O). MS: m/z = 471 [M^+ + 1, ^{35}Cl], 473 [M^+ + 1, ^{37}Cl]. $C_{25}H_{27}ClN_2O_5$ (471.0): calcd. C 63.76, H 5.78, N 5.95; found C 64.06, H 5.64, N 6.09.

4-Chloro-6-(benzylamino)-7-methoxy-1-methyl--1*H*-indole-2-carboxylate (18): Oil. IR (film): $\tilde{\nu}$ = 3391, 1707 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.39 (t, J = 7.2 Hz, 3 H, CH_3), 3.78 (s, 3 H, OCH_3), 4.26 (s, 3 H, NCH_3), 4.34 (q, J = 7.2 Hz, 2 H, CH_2O), 4.39 (s, 2 H, NCH_2Ph), 4.60 (br. s, 1 H, NH), 6.69 (s, 1 H, H_{Ar}), 7.25 (s, 1 H, H_{Ar}), 7.30−7.37 (m, 5 H, H_{Ar}). ^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 14.6 (CH_3), 33.5 (CH_3), 48.7 (CH_2), 61.2 (CH_3), 60.6 (CH_2), 108.6 (CH), 110.4 (CH), 119.7 (C), 123.8 (C), 127.6 (3 CH), 127.7 (C), 128.9 (2 CH), 131.0 (C), 133.7 (C), 139.3 (C), 139.7 (C), 162.0 (C=O). MS (IS): m/z = 373 [M^+ + 1, ^{35}Cl], 375[M^+ + 1, ^{37}Cl]. $C_{20}H_{21}ClN_2O_3$ (372.8): calcd. C 64.43 H 5.68 N 7.51; found C 64.77, H 5.83, N 7.68.

Ethyl 6-Chloro-2-[(ethoxycarbonyl)methyl]-9-methyl-2,3,4,9-tetrahydro[1,4]oxazino[3,2-*g*]indole-8-carboxylate (19): A suspension of **17** (182 mg, 0.39 mmol) and Pd/C 10% (20 mg) in ethyl acetate was shaken in a Parr apparatus under 3 atm of hydrogen at room temperature for 1 h. The catalyst was filtered off and the filtrate was concentrated in vacuo. The crude residue obtained was purified by column chromatography (petroleum ether/ethyl acetate, 7:3) to give **19** (130 mg, 88%) as a white solid; m.p. 145−146 °C (ethyl acetate). IR (KBr): $\tilde{\nu}$ = 3380, 1731, 1707 cm^{-1}. ^{1}H NMR (250 MHz, [D_6]DMSO at 80 °C): δ = 1.21 (t, J = 7.1 Hz, 3 H, CH_3), 1.32 (t, J = 7.1 Hz, 3 H, CH_3), 2.66 (dd, J = 15.5, 8.4 Hz, 1 H, CH_2CO), 2.79 (dd, J = 15.5, 4.5 Hz, 1 H, CH_2CO), 3.13 (dd, J = 12.2, 7.0 Hz, 1 H, CH_2N), 3.47 (dd, J = 12.2, 2.4 Hz, 1 H, CH_2N), 4.13 (s, 3 H, NCH_3), 4.14 (q, J = 7.1 Hz, 2 H, CH_2O), 4.28 (q, J = 7.1 Hz, 2 H, CH_2O), 4.41− 4.46 (m, 1 H, OCH), 6.62 (s, 1 H, H_{Ar}), 7.02 (1 s, 1 H, H_{Ar}). ^{13}C NMR (62.90 MHz, [D_6]DMSO at 80 °C): δ = 14.0 (CH_3), 14.1 (CH_3), 33.8 (CH_3), 37.2 (CH_2), 43.5 (CH_2), 60.0 (CH_2), 60.2 (CH_2), 70.3 (CH), 108.7 (CH), 111.1 (CH), 117.4 (C), 117.8 (C), 126.1 (C), 126.5 (C), 130.3 (C), 131.2 (C), 160.7 (C=O), 170.1 (C=O). MS (IS): m/z = 381 [M^+ + 1, ^{35}Cl], 383 [M^+ + 1, ^{37}Cl]. $C_{18}H_{21}ClN_2O_5$ (381.8): calcd. C 56.77, H 5.56, N 7.36; found C 57.03, H 5.43, N 7.19.

Diethyl 4-Benzyl-6-[2-(*tert*-butoxycarbonyl)ethyl]-2,3,4,6-tetrahydro[1,4]oxazino[2,3-*f*]indole-2,7-dicarboxylate (20): A solution of **3** (1.00 g, 2.37 mmol) in dry DMF (10 mL) was added at 0 °C to a solution of *tert*-butyl acrylate (1.4 mL, 9.56 mmol) and Triton B (70 μL, 40% in water) in dry DMF (10 mL). The final solution was stirred at room temperature for 4 h, and the solvent was then removed in vacuo. The crude residue was partitioned between water and ethyl acetate and extracted. The organic phase was washed with water, dried with $MgSO_4$ and concentrated in vacuo. The crude oil was stirred in EtOH at 0 °C, resulting in the precipitation of **20**. After filtration, washing with cold ethanol and drying, a beige solid was obtained (1.99 g, 76%); m.p. 103−104 °C (EtOH). IR (KBr): $\tilde{\nu}$ = 1757, 1724, 1701 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.24 (t, J = 7.2 Hz, 3 H, CH_3), 1.37 (t, J = 7.2 Hz, 3 H, CH_3), 1.37 (s, 9 H, $[CH_3)_3]$, 2.53−2.59 (m, 2 H, CH_2CO), 3.62 (d, J = 4.3 Hz, 2 H, CH_2N), 4.15−4.32 (m, 2 H, CH_2O), 4.31 (q, J = 7.2 Hz, 2 H, CH_2O), 4.45 and 4.60 (d, J = 15.7 Hz, 1 H, NCH_2Ph), 4.55−4.64 (m, 2 H, NCH_2), 4.84 (t, J = 4.3 Hz, 1 H, OCH), 6.58 (s, 1 H, H_{Ar}), 7.14 (s, 1 H, H_{Ar}), 7.16 (s, 1 H, H_{Ar}), 7.24−7.35 (m, 5 H, H_{Ar}). ^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 14.4 (CH_3), 14.6 (CH_3), 28.2 $[(CH_3)_3]$, 36.2 (CH_2), 40.7 (CH_2), 49.0 (CH_2), 55.6 (CH_2), 60.3 (CH_2), 61.9 (CH_2), 72.7 (CH), 80.8 (C), 92.3 (CH), 108.0 (CH), 111.0 (CH), 118.3 (C), 125.6 (C), 127.6 (3 CH), 129.0 (2 CH), 135.4 (C), 136.2 (C), 137.5 (C), 140.3 (C), 162.1 (C=O), 169.7 (C=O), 171.1 (C=O). MS: m/z = 537 [M^+ + 1]. $C_{30}H_{36}N_2O_7$ (536.6): calcd. C 67.15, H 6.76, N 5.22; found C 67.47, H 6.62, N 5.38.

Ethyl 4-Benzyl-6-[2-(*tert*-butoxycarbonyl)ethyl]-2-[(ethoxycarbonyl)methyl]-2,3,4,6-tetrahydro[1,4]oxazino[2,3-*f*]indole-7-carboxylate (21): Compound **21** was prepared as an oil in 94% yield from **4**, according to the procedure for the synthesis of **20**. IR (film): $\tilde{\nu}$ = 1734, 1694 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.26 (t, J = 7.2 Hz, 3 H, CH_3), 1.37 (t, J = 7.1 Hz, 3 H, CH_3), 1.37 (s, 9 H, $(CH_3)_3$], 2.56 (t, J = 7.5 Hz, 2 H, CH_2CO), 2.60 (d, J = 6.6 Hz, 1 H, CH_2CO), 2.80 (dd, J = 15.7, 6.6 Hz, 1 H, CH_2CO), 3.30 (dd, J = 11.7, 7.4 Hz, 1 H, CH_2N), 3.49 (dd, J = 11.7, 2.7 Hz, 1 H, CH_2N), 4.18 (q, J = 7.2 Hz, 2 H, CH_2O), 4.31 (q, J = 7.1 Hz, 2 H, CH_2O), 4.52 (d, J = 16.0 Hz, 1 H, NCH_2Ph), 4.58 (t, J = 7.5 Hz, 2 H, NCH_2), 4.60 (d, J = 16.0 Hz, 1 H, NCH_2Ph), 4.55 −4.68 (m, 1 H, OCH), 6.57 (s, 1 H, H_{Ar}), 7.01 (s, 1 H, H_{Ar}), 7.11 (s, 1 H, H_{Ar}), 7.26−7.35 (m, 5 H, H_{Ar}). ^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 14.4 (CH_3), 14.6 (CH_3), 28.2 $[(CH_3)_3]$, 36.2 (CH_2), 38.2 (CH_2), 40.7 (CH_2), 51.6 (CH_2), 55.7 (CH_2), 60.3 (CH_2), 61.0 (CH_2), 70.0 (OCH), 80.8 (C), 91.8 (CH), 107.9 (CH), 111.0 (CH), 118.0 (C), 125.4 (C), 127.6 (3 CH), 129.0 (2 CH), 135.3 (C), 136.3 (C), 137.7 (C), 140.7 (C), 161.3 (C=O), 170.2 (C=O), 171.1 (C=O). MS (IS): m/z = 551 [M^+ + 1]. $C_{31}H_{38}N_2O_7$ (550.7): calcd. C 67.62, H 6.96, N 5.09; found C 67.31, H 7.15, N 4.96.

3-[4-Benzyl-2,7-bis(ethoxycarbonyl)-2,3,4,6-tetrahydro[1,4]-oxazino[2,3-*f*]indol-6-yl]propanoic Acid (22): Trifluoroacetic acid (0.50 mL, 6.42 mmol) was slowly added to a solution of **20** (175 mg, 0.32 mmol) in dry CH_2Cl_2 (1 mL). The solution was stirred at room temperature for 2 h. The medium was diluted with CH_2Cl_2, hydrolysed with a saturated $NaHCO_3$ solution and extracted. The organic phase was washed with H_2O and dried with $MgSO_4$. After concentration, the acid **22** (1.27 g, 98%) was ob-

tained without further purification as a beige solid; m.p. 139−140 °C (CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 3600−2800, 1767, 1710, 1694 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$ + D_2O): δ = 1.24 (t, *J* = 7.1 Hz, 3 H, CH_3), 1.36 (t, *J* = 7.1 Hz, 3 H, CH_3), 2.71 (t, *J* = 7.1 Hz, 2 H, CH_2), 3.63 (d, *J* = 4.1 Hz, 2 H, CH_2N), 4.18−4.32 (m, 2 H, CH_2O), 4.30 (q, *J* = 7.1 Hz, 2 H, CH_2O), 4.43 and 4.57 (d, *J* = 16.0 Hz, 1 H, NCH_2Ph), 4.60 (t, *J* = 7.1 Hz, 2 H, NCH_2), 4.85 (t, *J* = 4.1 Hz, 1 H, OCH), 6.53 (s, 1 H, H_{Ar}), 7.15 (s, 1 H, H_{Ar}), 7.16 (s, 1 H, H_{Ar}), 7.21−7.35 (m, 5 H, H_{Ar}). ^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 14.4 (CH_3), 14.6 (CH_3), 34.8 (CH_2), 40.3 (CH_2), 49.1 (CH_2), 55.7 (CH_2), 60.4 (CH_2), 61.9 (CH_2), 72.7 (OCH), 92.1 (CH), 108.3 (CH), 111.3 (CH), 118.3 (C), 125.4 (C), 127.4 (2 CH), 127.7 (CH), 129.0 (2 CH), 135.6 (C), 136.1 (C), 137.5 (C), 140.3 (C), 162.1 (C=O), 169.7 (C=O), 180.2 (C=O). MS (IS): *m*/*z* = 481 [M^+ + 1]. $C_{26}H_{28}N_2O_7$ (480.5): calcd. C 64.99, H 5.87, N 5.83; found C 64.60, H 6.04, N 6.00.

3-{2-[(Ethoxycarbonyl)methyl]-4-benzyl-7-(ethoxycarbonyl)-2,3,4,6-tetrahydro[1,4]oxazino[2,3-*f*]indol-6-yl}propanoic Acid (23): Compound **23** was prepared in 97% yield from **21** according to the procedure for the synthesis of **22**; m.p. 139−140 °C (CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 3500−2500, 1739, 1694 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$ + D_2O): δ = 1.27 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.36 (t, *J* = 7.1 Hz, 3 H, CH_3), 2.62 (dd, *J* = 15.8, 6.6 Hz, 1 H, CH_2CO), 2.71 (t, *J* = 7.3 Hz, 2 H, CH_2), 2.81 (dd, *J* = 15.8, 6.7 Hz, 1 H, CH_2CO), 3.32 (dd, *J* = 11.6, 7.2 Hz, 1 H, CH_2N), 3.50 (dd, *J* = 11.6, 2.5 Hz, 1 H, CH_2N), 4.18 (q, *J* = 7.2 Hz, 2 H, CH_2O), 4.30 (q, *J* = 7.1 Hz, 2 H, CH_2O), 4.49 and 4.57 (d, *J* = 16.3 Hz, 1 H, NCH_2Ph), 4.61 (t, *J* = 7.3 Hz, 2 H, NCH_2), 4.58−4.68 (m, 1 H, OCH), 6.50 (s, 1 H, H_{Ar}), 7.02 (s, 1 H, H_{Ar}), 7.12 (s, 1 H, H_{Ar}), 7.22−7.36 (m, 5 H, H_{Ar}). ^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 14.4 (CH_3), 14.6 (CH_3), 34.7 (CH_2), 38.2 (CH_2), 40.3 (CH_2), 51.8 (CH_2), 55.6 (CH_2), 60.4 (CH_2), 61.1 (CH_2), 70.1 (CH), 91.3 (CH), 108.0 (CH), 111.2 (CH), 117.8 (C), 125.1 (C), 127.3 (2 CH), 127.6 (CH), 129.0 (2 CH), 135.7 (C), 136.3 (C), 137.7 (C), 140.7 (C), 162.1 (C=O), 170.5 (C=O), 176.6 (C=O). MS (IS): *m*/*z* = 495 [M^+ + 1]. $C_{27}H_{30}N_2O_7$ (494.5): calcd. C 65.58, H 6.11, N 5.66; found C 65.27, H 6.29, N 5.83.

Diethyl 11-Benzyl-1-oxo-1,2,3,9,10,11-hexahydro[1,4]oxazino[3,2-*f*]pyrrolo[3,2,1-*ij*]quinoline-5,9-dicarboxylate (24): A freshly prepared solution of PPSE (2.67 g of phosphorus pentoxide and 16 mL of hexamethyldisiloxane in 1,2-dichloroethane, stirred at 90 °C until complete dissolution of P_2O_5 with subsequent evaporation of solvent) was added to a solution of acid **22** (1.10 g, 2.30 mmol) in 1,2-dichloroethane (10 mL). The reaction mixture was stirred at reflux for 2 h. After cooling and evaporation of the solvent, the residue was dissolved in DMF (5 mL) and H_2O (5 mL). Neutralisation of the medium with a saturated $NaHCO_3$ solution afforded a yellow precipitate, which was filtered, washed with H_2O and dried over P_2O_5 to provide **24** (925 mg, 87%); m.p. 159−160 °C (H_2O). IR (KBr): $\tilde{\nu}$ = 1740, 1699, 1665 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.27 (t, *J* = 7.1 Hz, 3 H, CH_3), 1.39 (t, *J* = 7.2 Hz, 3 H, CH_3), 2.91−2.98 (m, 2 H, CH_2CO), 3.32 (dd, *J* = 13.5, 8.3 Hz, 1 H, CH_2N), 3.56 (dd, *J* = 13.5, 2.9 Hz, 1 H, CH_2N), 4.15−4.30 (m, 2 H, CH_2O), 4.35 (q, *J* = 7.2 Hz, 2 H, CH_2O), 4.42 (d, *J* = 15.3 Hz, 1 H, NCH_2Ph), 4.49 (dd, *J* = 8.3, 2.9 Hz, 1 H, OCH), 4.67 (d, *J* = 15.3 Hz, 1 H, NCH_2Ph), 4.63−4.74 (m, 1 H, NCH_2), 4.78−4.88 (m, 1 H, NCH_2), 7.18 (s, 1 H, H_{Ar}), 7.46 (s, 1 H, H_{Ar}), 7.27−7.44 (m, 5 H, H_{Ar}). ^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 14.2 (CH_3), 14.5 (CH_3), 39.4 (CH_2), 42.4 (CH_2), 48.6 (CH_2), 60.6 (CH_2), 61.7 (CH_2), 61.8 (CH_2), 69.7 (CH), 107.7 (C), 110.4 (CH), 115.5 (CH), 118.2 (C), 126.8 (C), 127.6 (CH), 128.6 (4 CH), 135.9 (C), 137.1 (C), 138.6 (C), 142.6 (C), 161.7 (C=O), 168.7 (C=O), 189.9 (C=O). MS (IS): *m*/*z* = 463 [M^+ + 1]. $C_{26}H_{26}N_2O_6$ (462.5): calcd. C 67.52, H 5.67, N 6.06; found C 67.15, H 5.49, N 5.92.

Ethyl 11-Benzyl-9-[(ethoxycarbonyl)methyl]-1-oxo-1,2,3,9,10,11-hexahydro[1,4]oxazino[3,2-*f*]pyrrolo[3,2,1-*ij*]quinoline-5-carboxylate (25): Compound **25** was prepared in 86% yield from **23** according to the procedure for the synthesis of **24**; m.p. 151−152 °C (H_2O). IR (KBr): $\tilde{\nu}$ = 1733, 1705, 1673 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.25 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.39 (t, *J* = 7.1 Hz, 3 H, CH_3), 2.51 (dd, *J* = 15.9, 6.1 Hz, 1 H, CH_2CO); 2.71 (dd, *J* = 15.9, 7.1 Hz, 1 H, CH_2CO), 2.93 (m, 2 H, CH_2CO), 3.10 (dd, *J* = 12.9, 9.6 Hz, 1 H, CH_2N), 3.42 (dd, *J* = 12.9, 2.5 Hz, 1 H, CH_2N), 4.16 (q, *J* = 7.2 Hz, 2 H, CH_2O), 4.35 (q, *J* = 7.1 Hz, 2 H, CH_2O), 4.30−4.42 (m, 1 H, OCH), 4.43 (d, *J* = 15.1 Hz, 1 H, NCH_2Ph), 4.70 (dd, *J* = 13.5, 7.2 Hz, 1 H, NCH_2), 4.76 (d, *J* = 15.1 Hz, 1 H, NCH_2Ph), 4.81 (dd, *J* = 13.5, 6.9 Hz, 1 H, NCH_2), 7.15 (s, 1 H, H_{Ar}), 7.28 (s, 1 H, H_{Ar}), 7.25−7.39 (m, 5 H, H_{Ar}). ^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 14.4 (CH_3), 14.6 (CH_3), 38.3 (CH_2), 39.5 (CH_2), 42.6 (CH_2), 51.9 (CH_2), 60.6 (CH_2), 61.1 (CH_2), 61.6 (CH_2), 68.5 (OCH), 107.1 (C), 110.6 (CH), 114.8 (CH), 117.4 (C), 126.3 (C), 127.6 (CH), 128.7 (4 CH), 137.2 (C), 137.5 (C), 138.8 (C), 143.9 (C), 161.9 (CO), 170.0 (CO), 189.9 (CO). MS (IS): *m*/*z* = 477 [M^+ + 1]. $C_{27}H_{28}N_2O_6$ (476.5): calcd. C 68.05, H 5.92, N 5.88; found C 67.74, H 6.03, N 5.71.

Diethyl 1-Oxo-1,2,3,9,10,11-hexahydro[1,4]oxazino[3,2-*f*]pyrrolo-[3,2,1-*ij*]quinoline-5,9-dicarboxylate (26): A suspension of **24** (500 mg, 1.08 mmol) and Pd/C (10%, 50 mg) in ethyl acetate (15 mL) was shaken in a Parr apparatus under 3 atm of hydrogen at room temperature for 2 h. The catalyst was filtered off and the filtrate was concentrated in vacuo to give **26** (399 mg, 100%) as a yellow solid; m.p. 209−210 °C (ethyl acetate). IR (KBr): $\tilde{\nu}$ = 3332, 1745, 1689, 1638 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.29 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.38 (t, *J* = 7.1 Hz, 3 H, CH_3), 2.97 (t, *J* = 7.1 Hz, 2 H, CH_2CO), 3.72 (ddd, *J* = 12.6, 5.7, 2.5 Hz, 1 H, CH_2N), 3.81 (ddd, *J* = 12.6, 3.6, 2.7 Hz, 1 H, CH_2N), 4.26 (q, *J* = 7.2 Hz, 2 H, CH_2O), 4.33 (q, *J* = 7.1 Hz, 2 H, CH_2O), 4.66−4.81 (m, 3 H, NCH_2 + OCH), 7.13 (s, 1 H, H_{Ar}), 7.29 (s, 1 H, H_{Ar}), 8.36 (br. s, 1 H, NH). ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 14.3 (CH_3), 14.6 (CH_3), 37.9 (CH_2), 41.6 (CH_2), 43.2 (CH_2), 60.4 (CH_2), 62.0 (CH_2), 71.3 (CH), 100.4 (C), 112.0 (CH), 114.0 (C), 115.3 (CH), 125.4 (C), 137.0 (C), 137.9 (C), 138.5 (C), 162.0 (C=O), 168.8 (C=O), 193.4 (C=O). MS (IS): *m*/*z* = 373 [M^+ + 1]. $C_{19}H_{20}N_2O_6$ (372.4): calcd. C 61.28, H 5.41, N 7.52; found C 61.62, H 5.35, N 7.48.

Ethyl 9-[(Ethoxycarbonyl)methyl]-1-oxo-1,2,3,9,10,11-hexahydro-[1,4]oxazino[3,2-*f*]pyrrolo[3,2,1-*ij*]quinoline-5-carboxylate (27): Compound **27** was prepared in quantitative yield from **25** according to the procedure for the synthesis of **26**; m.p. 157−158 °C (ethyl acetate). IR (KBr): $\tilde{\nu}$ = 3330, 1736, 1700, 1645 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.29 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.38 (t, *J* = 7.1 Hz, 3 H, CH_3), 2.63 (dd, *J* = 15.9, 6.3 Hz, 1 H, CH_2CO), 2.79 (dd, *J* = 15.9, 6.8 Hz, 1 H, CH_2CO), 2.97 (t, *J* = 7.1 Hz, 2 H, CH_2CO), 3.39 (ddd, *J* = 12.4, 7.8, 1.3 Hz, 1 H, CH_2N), 3.68 (ddd, *J* = 12.4, 3.9, 3.8 Hz, 1 H, CH_2N), 4.21 (q, *J* = 7.2 Hz, 2 H, CH_2O), 4.33 (q, *J* = 7.1 Hz, 2 H, CH_2O), 4.45−4.54 (m, 1 H, OCH), 4.72 (t, *J* = 7.1 Hz, 2 H, NCH_2) 7.11 (s, 1 H, H_{Ar}), 7.14 (1s, 1 H, H_{Ar}), 8.41 (br. s, 1 H, NH). ^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 14.4 (CH_3), 14.6 (CH_3), 38.0 (CH_2), 38.0 (CH_2), 43.4 (CH_2), 44.0 (CH_2), 60.4 (CH_2), 61.2 (CH_2), 69.4 (CH), 100.2 (C), 112.1 (CH), 113.2 (C), 115.1 (CH), 125.2 (C), 137.2 (C), 138.0 (C), 139.2 (C), 162.0 (C=O), 170.2 (C=O), 193.3 (C=O). MS (IS): *m*/*z* = 387 [M^+ + 1]. $C_{20}H_{22}N_2O_6$ (386.41): calcd. C 62.17, H 5.74, N 7.25; found C 61.76, H 5.60, N 7.42.

Ethyl 2,2-Bis[2-(benzyloxycarbonyl)ethyl]-9-[(ethoxycarbonyl)methyl]-1-oxo-1,2,3,9,10,11-hexahydro[1,4]oxazino[3,2-*f*]pyrrolo[3,2,1-

***ij*]quinoline-5-carboxylate (29):** A solution of benzyl acrylate (508 mg, 3.04 mmol) and Triton B (45 μL, 40% in water) in dry DMF (10 mL) was added at 0 °C to a solution of **27** (151 mg, 0.39 mmol) in dry DMF (3 mL). The final solution was stirred at room temperature for 30 h, and the solvent was removed in vacuo. The crude residue was partitioned between H_2O and ethyl acetate and extracted. The organic layer was washed with H_2O, dried with $MgSO_4$ and concentrated in vacuo. The crude residue was purified by column chromatography (petroleum ether ether/ethyl acetate, 7:3) to give **29** (183 mg, 66%) as an oil. IR (film): $\tilde{\nu}$ = 3329, 1738, 1698, 1641 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.28 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.37 (t, *J* = 7.1 Hz, 3 H, CH_3), 1.91−2.19 (m, 4 H, CH_2), 2.28−2.53 (m, 4 H, CH_2), 2.61 (dd, *J* = 16.0, 6.6 Hz, 1 H, CH_2CO), 2.78 (dd, *J* = 16.0, 6.9 Hz, 1 H, CH_2CO), 3.36 (dd, *J* = 8.5, 12.2 Hz, 1 H, CH_2N), 3.68 (dt, *J* = 12.2, 3.2, 3.2 Hz, 1 H, CH_2N), 4.20 (q, *J* = 7.2 Hz, 2 H, CH_2O), 4.32 (q, *J* = 7.1 Hz, 2 H, CH_2O), 4.43−4.52 (m, 1 H, OCH), 4.54 (s, 2 H, NCH_2), 5.06 [s, 4 H, $(OCH_2)_2$], 7.10 (s, 1 H, H_{Ar}), 7.14 (s, 1 H, H_{Ar}), 7.24−7.36 (m, 10 H, H_{Ar}), 8.55 (br. s, 1 H, NH). ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 14.4 (CH_3), 14.6 (CH_3), 29.3 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 29.9 (CH_2), 38.0 (CH_2), 44.0 (CH_2), 48.2 (C), 51.1 (CH_2), 60.4 (CH_2), 61.1 (CH_2), 66.6 (2 CH_2), 69.2 (CH), 99.0 (C), 112.1 (CH), 113.4 (C), 115.4 (CH), 125.4 (C), 128.3 (4 CH), 128.4 (2 CH), 128.7 (4 CH), 136.0 (2 C), 136.8 (C), 138.5 (C), 139.5 (C), 161.9 (CO), 170.1 (CO), 173.0 (2 CO), 190.0 (CO). MS (IS): *m*/*z* = 711 [M^+ + 1]. $C_{40}H_{42}N_2O_{10}$ (710.8): calcd. C 67.59, H 5.96, N 3.94; found C 67.97, H 6.14, N 3.81.

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