Synthesis of Substituted Azepino[3,4-*b*]indole-1,5-diones

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Cyclic β-amino esters **4**, obtained from lactams, were condensed with indole-2-carbonyl chloride to afford the corresponding amides. Similarly, unusual conditions led to cyclisation at the 3-position of the indole moiety in the presence of *p*TSA and ethylene glycol to afford previously unknown pentacyclic derivatives **12** and **15**.
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Introduction

The benzodiazepine scaffold provides access to a large family of bioactive derivatives.[1] Of these the pyrrolo-[2,1-*c*][1,4]benzodiazepine (PDB) antitumor antibiotics are a well-known class of DNA-binding agents,[2,3] for example, anthramycin (Figure 1), which have shown significant in vitro cytotoxicity,[4,5] but have not progressed in clinical trials because of side effects. Recently, Erba and co-workers described the preparation of a similar indole analogue **A**, in which the pyrrolo[1,2-*c*][1,4]diazepine moiety was obtained from 2-amidinylindole-3-carboxaldehyde.[6] The seven-membered lactam moiety is also encountered in potent glycogen synthase kinase-3 (GSK3) and/or cyclin-dependant kinase inhibitors such as paullones,[7,8] hymenialdisine[9−15] and 5-(arylhydrazono)-3,4,5,10-tetrahydro-2*H*-azepino[3,4-*b*]indol-1-one.[16,17]

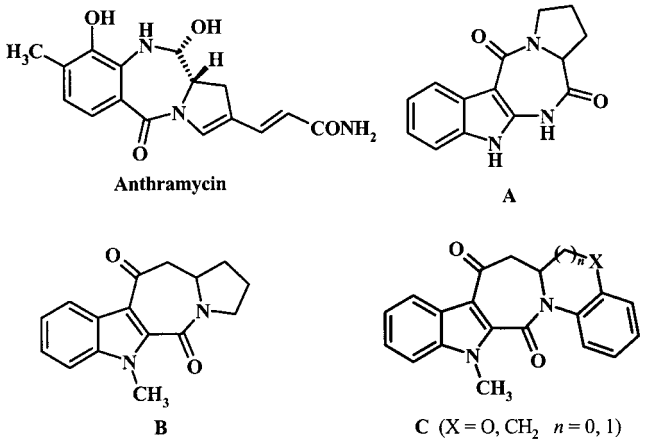

Figure 1. Anthramycin and selected azepinoindoles

For our part, we have reported the synthesis of the first pyrrolo[1,2:1′,2′]azepino[6,5-*b*]indole-1,5-dione framework **B** from indole-2-carboxylic acid and ethyl pyrrolidin-2-ylacetate through an unusual cyclisation reaction.[18−20] Given the versatility of this synthetic approach, we sought to extend it to the preparation of new pentacyclic compounds **C**. The two main aims of this work were (i) the development of a general preparation of N-heterocycle acetates from five- or six-membered aromatic and heteroaromatic lactams and (ii) the application of our original cyclisation reaction to various heterocycles.

First, the synthesis required the preparation of N-heterocycle acetates such as ethyl 2-(2,3-dihydro-1*H*-indol-2-yl)-acetate, ethyl 2-(1,2,3,4-tetrahydroquinolin-2-yl)acetate, ethyl 2-(3,4-dihydro-2*H*-benzo[1,4]benzoxazin-3-yl)acetate or ethyl 2-(1,2,3,4-tetrahydroquinoxalin-2-yl)acetate. Numerous preparations of these derivatives have been reported in the literature.[21−27] Some of them used nitroarenes as the starting materials and involved tandem sequences (reduction/reductive amination,[28,29] reduction/lactam formation[30−31] and reduction/Michael addition).[32,33] In our previous paper,[18] an effective synthesis of ethyl pyrrolidin-2-ylacetate from pyrrolidone was described using a closed method developed for the pyroglutamate series.[34] The three-step synthesis was based on the reduction of the pyrrolidinone followed by a Horner−Wadsworth−Emmons olefination and an intramolecular Michael addition (Scheme 1).

Results and Discussion

Preparation of β-Amino Esters

Neither the Wittig nor the Horner−Wadsworth−Emmons reaction is useful for the introduction of a two-

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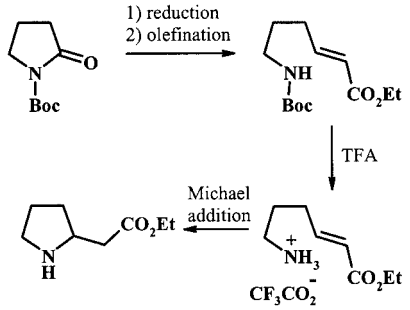


Scheme 1. Synthesis of ethyl (pyrolidin-2-yl)acetate

carbon unit onto a lactam derivative. To do this, it is necessary to increase the electrophilicity of the carbonyl group in order for the lactam to react with phosphorus ylides reagents. One way to achieve this, is to partially reduce the lactam function to a masked aldehyde such as an aminal (Scheme 2). Lactams **1a**, **1b** and **1d** are commercially available. Starting materials **1c** and **1e** were prepared according to reported procedures.[35,36] Compounds **1** were first *N*-protected with Boc_2O in the presence of a catalytic amount of DMAP to afford compounds **2**[37−40] in 72−99% yield. The formation of the aminals was achieved by using a super hydride®. These aminals were then immediately treated with the anion of triethyl phosphonoacetate. This olefination reaction was immediately followed by an intramolecular Michael addition to the acrylate chain by a favorable six-*exo-trig* process. The derivatives **3** were obtained in fair yields (see Table 1). Boc deprotection of **3** was carried out in TFA to afford derivatives **4**[21−23,32] in quantitative yield. Note that the spontaneous cyclisation reaction was not observed in the pyrrolidone series; instead the Horner−Wadsworth−Emmons adduct was isolated in good yield (Scheme 1). Deprotection of the nitrogen atom by TFA yielded the salt as an (*E*) isomer. The enhanced nucleophilicity of the nitrogen atom in the presence of triethylamine allowed the intramolecular Michael addition. In this way,

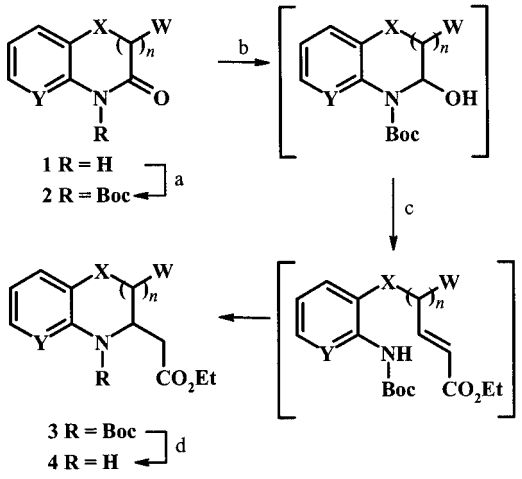
Table 1. Yields of **2** and **3** in the reduction/olefination/Michael addition reactions

	X	Y	W	n	Yield (%)		Yield (%)
2a[23]	CH_2	CH	H	0	72	**3a**	63
2b	CH_2	CH	H	1	83	**3b**	76
2c	O	N	H	1	99	**3c**	57
2d	O	CH	H	1	99	**3d**	91
2e	O	CH	Ph	1	75	**3e**	89

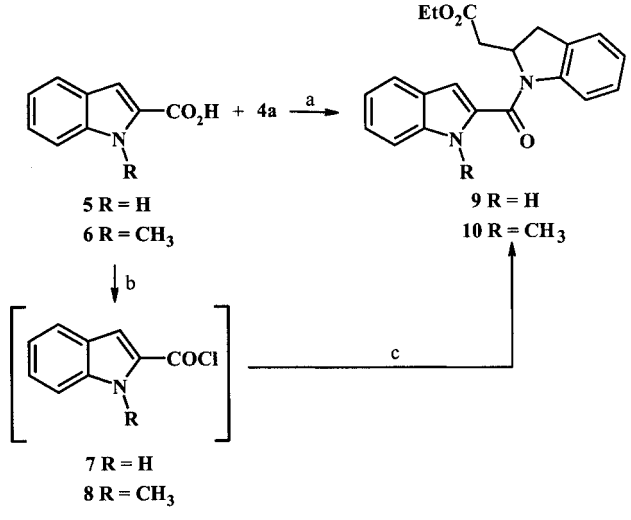
we developed an effective reduction/olefination/Michael addition reaction sequence for the preparation of N-heterocycle acetates.

Access to Pentacyclic Indole Derivatives

These β-amino esters are useful precursors in the synthesis of the pentacyclic derivatives **C**. We chose indolin-2-ylacetate **4a** as a model starting material for the synthesis of **C**. Our first attempt to couple **4a** and indole-2-carboxylic acid (**5**) in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) yielded **9** in only 35% yield owing to the low nucleophilicity of the amine **4a** (i.e. with pyrrolidine-2-acetate, the yield of amidification was 85%).[18] The use of other added activating agents also proved fruitless. Fortunately, when the crude indole-2-carbonyl chloride (**7**), obtained by classical treatment of **5** with thionyl chloride, was added in excess (3 equiv.) to the sodium salt of the amino ester **4a** (to enhance the nucleophilicity of the nitrogen atom) at room temperature, the desired amide **9** was obtained in 57% yield. Similarly, 1-methylindole-2-carbonyl chloride (**8**), prepared from **6**, was treated with **4a** to give amide **10** in excellent yield (96%). In this last reaction, only 1.5 equiv. of the crude acyl chloride was necessary (Scheme 3).



Scheme 2. a) Boc_2O (1 equiv.), DMAP (0.1 equiv.), MeCN, room temp., 48 h; b) $LiBEt_3H$ (1.2 equiv.), THF, −78 °C, 30 min; c) $(EtO)_2P(O)CH_2CO_2Et$ (2 equiv.), NaH (2 equiv.), THF, 30 min; d) CF_3CO_2H, CH_2Cl_2, room temp., 2 h, quantitative yield



Scheme 3. a) EDCI, DMAP, CH_2Cl_2, 0 °C to room temp., 24 h (35%); b) $SOCl_2$, Et_3N, THF, 0 °C, 45 min; c) **4a** (1 equiv.), NaH (2 equiv.), THF, room temp., 2 h followed by addition to **7** (3 equiv.) or **8** (1.5 equiv.), 2 h (**9** 57%; **10** 96%)

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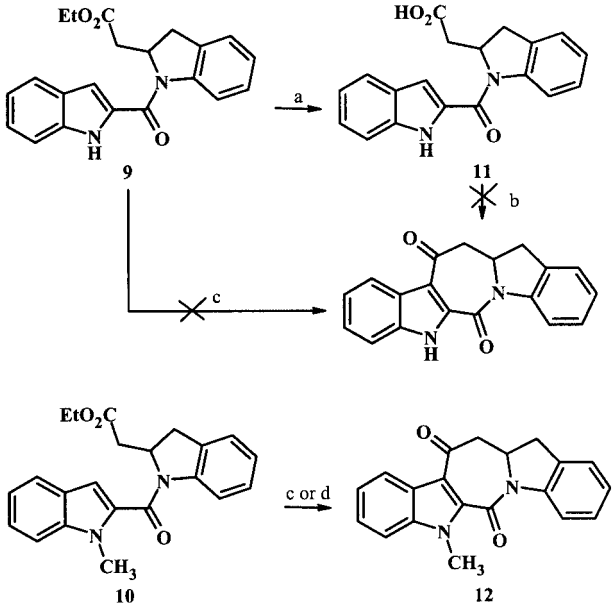
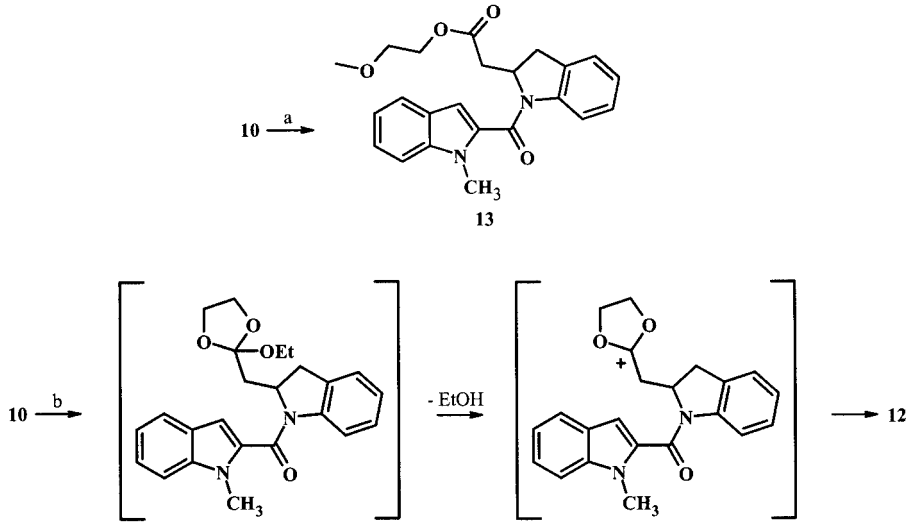
Saponification of **9** in the presence of lithium hydroxide in ethanol at room temperature led quantitatively to the acid **11**. But in contrast to the behavior of compounds of type **A**,[18] electrophilic cyclisation of the acid in polyphosphoric acid (PPA) was not successful and afforded by-products (Scheme 4). The same result was again observed when PPA cyclisation was applied to the acid obtained from **14d** (see below). Next, we refluxed **9** or **10** in toluene in the presence of 2 equiv. of *para*-toluenesulfonic acid (*p*TSA) for 24 h. In the first case, degradation of the starting material was again observed, but with **10** we isolated the azepino derivative **12** in 41% yield. This result and our previous work on the synthesis of pyrrolo[1,2:1′,2′]azepino[6,5-*b*]indole-1,5-dione[18] led us to investigate the electrophilic ring closure of ester derivative **10** in the presence of *p*TSA and ethylene glycol. Thus, this reaction was performed in toluene at reflux for 8 h to afford compound **12**. An optimal yield of 87% was obtained in the presence of 2 equiv. of *p*TSA monohydrate and 5 equiv.of ethylene glycol.



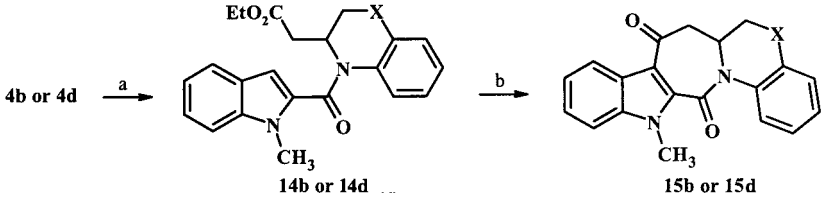
Scheme 4. a) LiOH (2 equiv.), EtOH, room temp., 20 h (**11** 100%); b) PPA, 120 °C, 2 h; c) *p*TSA monohydrate (2 equiv.), toluene, reflux, 24 h (**12** 41%); d) *p*TSA monohydrate (2 equiv.), ethylene glycol (5 equiv.), toluene, reflux, 8 h (**12** 87%)

In order to gain an insight into the role played by ethylene glycol, the latter was replaced by 2-methoxyethanol. After heating for 2 h, we observed only the formation of the 2-methoxyethoxy ester **13** in good yield from **10** with no trace of the azepino derivative (Scheme 5). A hypothetical mechanism for the cyclisation reaction involves the initial formation of an orthoester intermediate which then undergoes electrophilic cyclisation in acidic media. Water (from *p*TSA monohydrate) in the medium led to the final hydrolysis of the acetal into the carbonyl function.

We extended our synthesis to two other β-amino esters **4b** and **4d** (Scheme 6). Amidification of the indolecarbonyl



Scheme 5. a) *p*TSA (2 equiv.), 2-methoxyethanol (5 equiv.), toluene, reflux, 2 h (**13** 89%); b) *p*TSA monohydrate (2 equiv.), ethylene glycol (5 equiv.), toluene, reflux, 8 h



Scheme 6. a) NaH (2 equiv.), THF, room temp., 2 h followed by the addition of **8**, room temp., 2 h; b) *p*TSA (2 equiv.), ethylene glycol (5 equiv.), toluene, reflux, 3−5 h

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chloride **8** with the sodium salt of **4b** or **4d** afforded compounds **14b** and **14d** in 77 and 95% yields, respectively. Note that the coupling reaction between **7** and **4e** afforded the corresponding amide in low yield (15%, not described in the Expt. Sect.). Compounds **14b** and **14d** were subjected to the cyclization reaction to give **15b** and **15d** respectively, in good yields (Table 2). Note that the pyridinylamino ester **4c** did not react with **8** owing to the low nucleophilicity of the amine sodium salt.

Table 2. Yields of **14** and **15**

Amine	X		Yield (%)		Yield (%)
4b	CH_2	**14b**	77	**15b**	82
4d	O	**14d**	95	**15d**	76

Conclusions

An effective reduction/olefination/Michael addition reaction sequence has been developed for the preparation of N-heterocycle acetates **4**. Similarly, unusual conditions led to cyclisation at the 3-position of the indole moiety in the presence of *p*TSA and ethylene glycol to afford previously unknown pentacyclic derivatives **12** and **15**.

Experimental Section

General Remarks: Melting points were determined with a Büchi SMP-20 melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded with a Bruker Avance DPX-250 spectrometer (250.13 MHz for ^1H and 62.9 MHz for ^{13}C). The chemical shifts are reported in ppm (δ scale) and all J values are in Hz. The infrared spectra of the compounds were recorded with a Perkin−Elmer FTIR PARAGON 1000 PC spectrometer and values are reported in cm^{-1}. Mass spectra (ion spray) were recorded with a Perkin−Elmer Sciex PI 300 spectrometer. The reactions were monitored using silica gel TLC plates (silica Merck 60 F_{254}). Spots were visualised by UV light at 254 and 365 nm. Column chromatography was performed using silica gel 60 (0.063−0.200 mm, Merck). All solvents were purified by distillation or otherwise were analytical grade and used as received.

General Procedure for the Synthesis of Compounds 2: Di-*tert*-butyl dicarbonate (8.90 mmol) and 4-(dimethylamino)pyridine (0.89 mmol) were added to a solution of **1** (8.90 mmol) in MeCN (50 mL). The mixture was stirred at room temperature for 48 h. After concentration, the residue was diluted with ethyl acetate (40 mL) and water (40 mL) and the final solution was extracted ethyl acetate. The organic phase was washed with a solution of 2 M hydrochloric acid (2 × 20 mL). The organic phase was dried ($MgSO_4$) and the solvents were evaporated in vacuo. The residue was purified by column chromatography to afford *N*-Boc-substituted lactams **2**.

***tert*-Butyl 2-Oxo-2,3-dihydroindole-1-carboxylate (2a):** Compound **2a** was prepared in 72% yield from **1a** according to the procedure described above for the synthesis of **2**. The physical and analytical data of **2a** are identical in all respects to the data given in the literature.[37]

***tert*-Butyl 2-Oxo-1,2,3,4-tetrahydroquinoline-1-carboxylate (2b):** Compound **2b** was prepared in 83% yield from **1b** according to the procedure described above for the synthesis of **2**. The physical and analytical data of **2b** are identical in all respects to the data given in the literature.[38]

***tert*-Butyl 3-Oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-4-carboxylate (2c):** Compound **2c** was prepared in 99% yield from **1c** according to the procedure described above for the synthesis of **2**. The physical and analytical data of **2c** are identical in all respects to the data given in the literature.[39]

***tert*-Butyl 3-Oxo-3,4-dihydro-2*H*-1,4-benzoxazine-4-carboxylate (2d):** Compound **2d** was prepared in 99% yield from **1d** according to the procedure described above for the synthesis of **2**. The physical and analytical data of **2d** are identical in all respects to the data given in the literature.[40]

***tert*-Butyl 3-Oxo-2-phenyl-3,4-dihydro-2*H*-1,4-benzoxazine-4-carboxylate (2e):** Compound **2e** was prepared as a yellow oil in 75% yield from **1e** according to the procedure described above for the synthesis of **2**. IR (film): $\tilde{\nu}$ = 1748, 1734 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 1.64 (s, 9 H, 3 CH_3), 6.10 (s, 1 H, OCH), 6.89−7.07 (m, 3 H, H_{Ar}), 7.13−7.27 (m, 5 H, H_{Ar}), 7.79 (d, J = 7.9 Hz, 1 H, H_{Ar}) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ = 27.8 (3 CH_3), 76.9 (OCH), 84.3 (C), 116.0 (CH), 117.5 (CH), 118.4 (CH), 122.4 (CH), 125.1 (CH), 125.3 (CH), 125.7 (CH), 126.2 (C), 128.2 (CH), 128.7 (CH), 132.3 (C), 145.4 (C), 150.0 (C=O), 163.9 (C=O) ppm. ESI MS: m/z = 326 [M^+ + H]. $C_{19}H_{19}NO_4$ (325.4): calcd. C 70.14, H 5.89, N 4.30; found C 69.95, H 5.78; N 4.43.

***tert*-Butyl 2-(2-Ethoxy-2-oxoethyl)-2,3-dihydroindole-1-carboxylate (3a):** Under argon, 1 M $LiBEt_3H$ in THF (2.60 mL, 2.60 mmol) was added dropwise to a solution of **2a** (500 mg, 2.14 mmol) in anhydrous THF (10 mL) at −78 °C. After stirring at −78 °C for 30 min, the mixture was treated with a saturated Na_2CO_3 solution (3 mL); then a 35% H_2O_2 solution (3 mL) was slowly added at −15 °C. The mixture was stirred at room temperature for 30 min, then filtered. The filtrate was concentrated in vacuo and the residue was extracted with ethyl acetate (2 × 10 mL). The organic phase was washed with brine, dried with $MgSO_4$ and filtered. The filtrate was maintained under reduced pressure for 2 h. Then, the remaining residue was dissolved in THF (5 mL) and added dropwise at 0 °C to a freshly prepared solution of triethyl phosphonoacetate anion (4.30 mmol) in THF (5 mL). After stirring at room temperature for 30 min, the mixture was hydrolysed and extracted with ethyl acetate. The organic layer was dried with $MgSO_4$ and the solvents were evaporated in vacuo. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 95:5) to afford **3a** (410 mg, 63%) as a colorless oil. IR (film): $\tilde{\nu}$ = 1738, 1729 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 1.21 (t, J = 7.1 Hz, 3 H, CH_3), 1.57 (s, 9 H, CH_3), 2.50 (dd, J = 9.7, 15.8 Hz, 1 H, CH_2), 2.79−2.90 (m, 2 H, CH_2), 3.39 (dd, J = 9.7, 15.8 Hz, 1 H, CH_2), 4.09 (q, J = 7.1 Hz, 2 H, OCH_2), 4.72−4.80 (m, 1 H, NCH), 6.89−6.95 (m, 1 H, H_{Ar}), 7.10−7.17 (m, 2 H, H_{Ar}), 7.66 (br. s, 1 H, H_{Ar}) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ = 14.1 (CH_3), 28.4 (3 CH_3), 33.9 (CH_2), 39.2 (CH_2), 56.1 (CH), 60.3 (CH_2), 81.2 (C), 115.2 (CH), 122.6 (CH), 125.0 (CH), 127.4 (CH), 129.6 (C), 141.6 (C), 151.9 (C=O), 170.9 (C=O) ppm. ESI MS: m/z = 328 [M^+ + Na]. $C_{17}H_{23}NO_4$ (305.4): calcd. C 66.86, H 7.59, N 4.59; found C 66.54, H 7.77; N 4.48.

***tert*-Butyl 2-(2-Ethoxy-2-oxoethyl)-1,2,3,4-tetrahydroquinoline-1-carboxylate (3b):** Compound **3b** was prepared as an oil in 76% yield from **2b** according to the procedure described for the synthesis of

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3a; chromatography eluent: petroleum ether/ethyl acetate, 9:1. IR (film): $\tilde{\nu}$ = 1744, 1732 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 1.22 (t, J = 7.2 Hz, 3 H, CH_3), 1.50 (s, 9 H, 3 CH_3), 1.60−1.74 (m, 1 H, CH_2), 2.26−2.40 (m, 2 H, CH_2), 2.60−2.68 (m, 3 H, CH_2, CH_2), 4.09 (q, J = 7.1 Hz, 2 H, OCH_2), 4.83−4.94 (m, 1 H, NCH), 6.97−7.18 (m, 3 H, H_{Ar}), 7.48 (d, J = 8.1 Hz, 1 H, H_{Ar}) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ = 14.2 (CH_3), 24.9 (CH_2), 28.3 (3 CH_3), 29.1 (CH_2), 38.8 (CH_2), 50.2 (NCH), 60.4 (OCH_2), 80.9 (C), 124.0 (CH), 125.8 (CH), 125.9 (CH), 127.8 (CH), 131.3 (C), 136.8 (C), 153.6 (C=O), 171.1 (C=O) ppm. ESI MS: m/z = 320 [M^+ + H]. $C_{18}H_{25}NO_4$ (319.4): calcd. C 67.69, H 7.89, N 4.39; found C 67.40, H 7.98; N 4.22.

***tert*-Butyl 3-(2-Ethoxy-2-oxoethyl)-3,4-dihydro-2*H*-pyrido[3,2-*b*]-[1,4]oxazine-4-carboxylate (3c):** Compound **3c** was prepared as an oil in 57% yield from **2c** according to the procedure described for the synthesis of **3a**; chromatography eluent: petroleum ether/ethyl acetate, 6:4. IR (film): $\tilde{\nu}$ = 1740, 1732 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 1.26 (t, J = 7.1 Hz, 3 H, CH_3), 1.56 (s, 9 H, 3 CH_3), 2.57 (d, J = 7.3 Hz, 2 H, CH_2CO), 4.12 (dd, J = 11.3, 2.9 Hz, 1 H, OCH_2), 4.16 (q, J = 7.1 Hz, 2 H, OCH_2), 4.38 (dd, J = 11.3, 1.2 Hz, 1 H, OCH_2), 5.00−5.06 (m, 1 H, NCH), 6.94−6.99 (m, 1 H, H_{Ar}), 7.16−7.20 (m, 1 H, H_{Ar}), 8.09−8.11 (m, 1 H, H_{Ar}) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ = 14.1 (CH_3), 28.2 (3 CH_3), 34.5 (CH_2), 48.2 (NCH), 60.9 (OCH_2), 66.9 (OCH_2), 82.2 (C), 120.2 (CH), 124.1 (CH), 138.5 (C), 140.8 (CH), 141.2 (C), 151.1 (C=O), 170.6 (C=O) ppm. ESI MS: m/z = 323 [M^+ + H]. $C_{16}H_{22}N_2O_5$ (322.3): calcd. C 59.62, H 6.88, N 8.69; found C 60.00, H 6.74; N 8.53.

***tert*-Butyl 3-(2-Ethoxy-2-oxoethyl)-3,4-dihydro-2*H*-1,4-benzoxazine-4-carboxylate (3d):** Compound **3d** was prepared as an oil in 91% yield from **2d** according to the procedure described for the synthesis of **3a**; chromatography eluent: petroleum ether/ethyl acetate, 9:1. IR (film): $\tilde{\nu}$ = 1734, 1728 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 1.23 (t, J = 7.1 Hz, 3 H, CH_3), 1.54 (s, 9 H, 3 CH_3), 2.47 (dd, J = 15.9, 6.1 Hz, 1 H, CH_2), 2.59 (dd, J = 15.9, 8.1 Hz, 1 H, CH_2), 4.06−4.17 (m, 3 H, OCH_2CH_3, OCH_2), 4.32 (dd, J = 11.1, 1.6 Hz, 1 H, OCH_2), 4.96−5.02 (m, 1 H, NCH), 6.83−6.98 (m, 3 H, H_{Ar}), 7.86 (d, J = 7.9 Hz, 1 H, H_{Ar}) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ = 14.2 (CH_3), 28.3 (3 CH_3), 34.4 (CH_2), 47.3 (NCH), 60.7 (OCH_2), 67.0 (OCH_2), 81.9 (C), 116.9 (CH), 120.8 (CH), 123.7 (CH), 124.2 (C), 124.3 (CH), 144.9 (C), 152.0 (C=O), 170.8 (C=O) ppm. ESI MS: m/z = 322 [M + H]$^+$. $C_{17}H_{23}NO_5$ (321.4): calcd. C 63.54, H 7.21, N 4.36; found C 63.27, H 7.09; N 4.52.

***tert*-Butyl 3-(2-Ethoxy-2-oxoethyl)-2-phenyl-3,4-dihydro-2*H*-1,4-benzoxazine-4-carboxylate (3e):** Compound **3e** was prepared as a mixture of diastereomers (50:50 ratio), inseparable by column chromatography, as an oil in 89% yield from **2d** according to the procedure described for the synthesis of **3a**; chromatography eluent: petroleum ether/ethyl acetate, 95:5. IR (film): $\tilde{\nu}$ = 1755, 1735 cm^{-1}. **Diastereomer *1*:** ^1H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 1.11 (t, J = 7.1 Hz, 3 H, CH_3), 1.57 (s, 9 H, 3 CH_3), 2.21 (d, J = 6.5 Hz, 2 H, CH_2CO), 4.13 (q, J = 7.1 Hz, 2 H, OCH_2), 5.21−5.24 (m, 1 H, NCH), 6.64−6.78 (m, 2 H, OCH, H_{ar}), 6.89−7.05 (m, 2 H, H_{Ar}), 7.24−7.49 (m, 5 H, H_{Ar}), 7.78 (d, J = 8.1 Hz, 1 H, H_{Ar}) ppm. **Diastereomer *2*:** ^1H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 1.23 (t, J = 6.9 Hz, 3 H, CH_3), 1.56 (s, 9 H, 3 CH_3), 3.22 (d, J = 7.1 Hz, 2 H, CH_2CO), 3.92 (q, 2 H, OCH_2, J = 6.9 Hz), 5.26−5.33 (m, 1 H, NCH), 6.10 (t, J = 7.0 Hz, 1 H, OCH), 6.89−7.05 (m, 2 H, H_{Ar}), 7.24−7.49 (m, 6 H, H_{Ar}), 8.12 (d, J = 7.9 Hz, 1 H, H_{Ar}) ppm. **Diastereomers *1* + *2*:** ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ = 14.1 $(CH_3)^1$, 14.2 $(CH_3)^2$, 28.3 (3 $CH_3)^1$, 28.4 (3 $CH_3)^2$, 31.1 $(CH_2)^1$, 31.5 $(CH_2)^2$, 51.6 $(NCH)^{1+2}$, 60.5 $(OCH_2)^1$, 60.9 $(OCH_2)^2$, 77.4 $(OCH)^1$, 77.6 $(OCH)^2$, 80.6 $(C)^1$, 81.9 $(C)^2$, 109.8 (CH), 113.2 (CH), 116.8 (CH), 122.4 (2 CH), 123.4 (CH), 124.8 (CH), 125.0 (CH), 125.3 (CH), 125.7 (2 CH), 128.2 (CH), 128.4 (CH), 128.6 (4 CH), 128.8 (CH), 133.9 (C), 136.8 (C), 144.5 (C), 145.4 (C), 150.6 (2 C), 152.4 (C=O), 152.7 (C=O), 170.4 (C=O), 171.3 (C=O) ppm. ESI MS: m/z = 398 [M^+ + H]. $C_{23}H_{27}NO_5$ (397.5): calcd. C 69.50, H 6.85, N 3.52; found C 69.84, H 6.74; N 3.63.

Ethyl 2-(2,3-Dihydro-1*H*-indol-2-yl)acetate (4a):[27] A solution of compound **3a** (3.30 g, 10.8 mmol) in dichloromethane/trifluoroacetic acid (14 mL, 1:1, v/v) was stirred at 0 °C for 1 h 30 min. The solution was chilled with ice, treated with a saturated $NaHCO_3$ solution and extracted with dichloromethane (25 mL). The organic phase was dried with $MgSO_4$ and the solvents were evaporated in vacuo to give **4a** (2.2 g, 100%) as an oil. IR (film): $\tilde{\nu}$ = 3375 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 1.37 (t, J = 7.3 Hz, 3 H, CH_3), 2.68 (d, J = 6.6 Hz, 2 H, CH_2Ph), 2.76 (dd, J = 15.5, 8.4 Hz, 1 H, CH_2), 3.24 (dd, J = 15.5, 8.4 Hz, 1 H, CH_2), 4.22−4.30 (q, J = 7.3 Hz, 2 H, OCH_2), 4.22−4.30 (m, 1 H, CH), 4.57 (br. s, 1 H, NH); 6.66 (d, J = 7.5 Hz, 1 H, H_{Ar}), 6.75 (dd, J = 7.7, 7.5 Hz, 1 H, H_{Ar}), 7.08−7.17 (m, 2 H, H_{Ar}) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ = 14.0 (CH_3), 35.5 (CH_2), 40.6 (CH_2), 55.5 (NCH), 60.2 (OCH_2), 108.8 (CH), 118.2 (CH), 124.3 (CH), 127.1 (CH), 127.6 (C), 150.4 (C), 171.9 (C=O) ppm. ESI MS: m/z = 206 [M^+ + H]. $C_{12}H_{15}NO_2$ (205.3): calcd. C 70.22, H 7.37, N 6.82; found C 69.95, H 7.25; N 6.99.

Ethyl 2-(1,2,3,4-Tetrahydroquinolin-2-yl)acetate (4b): Compound **4b** was prepared in 99% yield from **3b** according to the procedure described for the synthesis of **4a**. The physical and analytical data of **4b** are identical in all respects to the data given in the literature.[32]

Ethyl 2-(3,4-Dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazin-3-yl)acetate (4c): Compound **4c** was prepared as an oil in 99% yield from **3c** according to the procedure described for the synthesis of **4a**. IR (film): $\tilde{\nu}$ = 3254, 1735 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 1.23 (t, J = 7.1 Hz, 3 H, CH_3), 2.56 (d, J = 7.3 Hz, 2 H, CH_2CO), 3.93−4.01 (m, 2 H, OCH_2), 4.11−4.20 (m, 3 H, OCH_2, NCH), 5.67 (br. s, 1 H, NH), 6.51−6.56 (m, 1 H, H_{Ar}), 6.93−6.97 (m, 1 H, H_{Ar}), 7.66 (d, 1 H, J = 4.4 Hz, H_{Ar}) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ 14.2 (CH_3), 37.2 (CH_2), 46.5 (NCH), 61.1 (OCH_2), 67.5 (OCH_2), 113.7 (CH), 122.7 (CH), 137.9 (CH), 139.4 (C), 146.4 (C), 170.7 (C=O) ppm. ESI MS: m/z = 223 [M^+ + H]. $C_{11}H_{14}N_2O_3$ (222.3): calcd. C 59.45, H 6.35, N 12.60; found C 59.11, H 6.50; N 12.43.

Ethyl 2-(3,4-Dihydro-2*H*-1,4-benzoxazin-3-yl)acetate (4d): Compound **4d** was prepared as an oil in 99% yield from **3d** according to the procedure described for the synthesis of **4a**. The physical and analytical data of **4d** are identical in all respects to the data given in the literature.[32,33]

Ethyl 2-(2-Phenyl-3,4-dihydro-2*H*-1,4-benzoxazin-3-yl)acetate (4e): Compound **4e** was prepared as an oil in 99% yield, as a mixture of two diastereomers (50:50 ratio), from **3e** according to the procedure described for the synthesis of **4a**. IR (film): $\tilde{\nu}$ = 3374, 1738 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 1.00 (t, J = 7.1 Hz, 3 H, CH_3), 1.10 (t, J = 7.1 Hz, 3 H, CH_3), 2.01 (dd, J = 17.3, 2.5 Hz, 1 H, CH_2CO), 2.34 (dd, J = 17.3, 11.0 Hz, 1 H, CH_2CO), 2.59 (t, J = 6.6 Hz, 1 H, CH_2CO), 3.12 (t, J = 6.6 Hz, 1 H, CH_2CO), 3.84−4.04 (m, 4 H, 2 OCH_2), 5.11 (s, 2 H, 2NH), 6.47−6.77 (m, 4 H, 2 OCH +2 NCH), 7.08−7.40 (m, 16 H, H_{Ar}), 7.78−7.86 (m, 2 H, H_{Ar}) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ = 14.1, 14.2 (CH_3), 32.5, 33.4 (CH_2), 51.1 (2 NCH), 60.7, 61.0 (OCH_2), 77.3, (2 OCH), 115.6, 115.7 (CH), 116.9 (2 CH), 118.7 (2 CH), 121.7,

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122.1 (CH), 125.9 (2 CH), 128.0, 128.1 (CH), 128.7, 128.8 (2 CH), 131.8 (2 C), 133.3 (2 CH), 138.0 (2 C), 143.4 (2 C), 172.6, 173.1 (C=O) ppm. ESI MS: *m*/*z* = 298 [M^+ + H]. $C_{18}H_{19}NO_3$ (297.4): calcd. C 72.71, H 6.44, N 4.71; found C 73.05, H 6.58; N 4.83.

Ethyl 2-[1-(1*H*-Indol-2-ylcarbonyl)-2,3-dihydro-1*H*-indol-2-yl]acetate (9): At 0 °C, compound **4a** (110 mg, 0.54 mmol), dissolved in THF (3 mL), was added dropwise to a suspension of sodium hydride (0.04 g, 1.07 mmol, 60% dispersed in oil) in anhydrous THF (2 mL). The final mixture was stirred at room temperature for 2 h. Thionyl chloride (0.09 mL, 1.23 mmol) was slowly added at 0 °C to a solution of indole-2-carboxylic acid (**5**) (0.13 g, 0.80 mmol) and triethylamine (0.15 mL, 1.07 mmol) in THF (15 mL). The solution was stirred at 0 °C for 50 min. The precipitate obtained was eliminated by filtration (washing with dichloromethane). The filtrate was concentrated to afford **7** as an oil which was kept under reduced pressure. Then, compound **7** was dissolved in anhydrous dichloromethane (5 mL) and added to the solution of the sodium salt of amine **4a** at 0 °C. The mixture was stirred at room temperature for 2 h. A saturated NH_4Cl solution was added to the medium and the resulting mixture was extracted with ethyl acetate (2 × 10 mL). The organic layer was dried ($MgSO_4$), and the solvents were evaporated in vacuo. The crude residue was purified by column chromatography (petroleum ether/ethyl acetate, 9:1) to give **9** (95 mg, 57%) as a solid; m.p. 135−137 °C (ethyl acetate/petroleum ether). IR (KBr): $\tilde{\nu}$ = 3381, 1731, 1623 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 1.30 (t, *J* = 7.1 Hz, 3 H, CH_3), 2.69 (dd, *J* = 15.9, 11.5 Hz, 1 H, CH_2), 2.97−3.05 (m, 2 H, CH_2Ph), 3.53 (dd, *J* = 15.9, 8.2 Hz, 1 H, CH_2), 4.21 (q, *J* = 7.1 Hz, 2 H, OCH_2), 5.48−5.54 (m, 1 H, NCH), 7.07−7.37 (m, 6 H, 5 H_{Ar}, =CH), 7.44 (d, *J* = 8.1 Hz, 1 H, H_{Ar}), 7.69 (d, *J* = 8.1 Hz, 1 H, H_{ar}), 8.20 (d, *J* = 7.7 Hz, 1 H, H_{Ar}), 10.02 (s, 1 H, NH) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ = 14.3 (CH_3), 35.2 (CH_2), 39.5 (CH_2), 57.5 (NCH), 61.1 (OCH_2), 105.8 (CH), 112.0 (CH), 118.6 (CH), 120.7 (CH), 122.5 (CH), 124.9 (CH), 125.1 (CH), 125.4 (CH), 127.7 (CH), 128.2 (C), 129.8 (C), 130.3 (C), 136.0 (C), 142.4 (C), 160.2 (C=O), 170.7 (C=O) ppm. ESI MS: *m*/*z* = 349 [M^+ + H]. $C_{21}H_{20}N_2O_3$ (348.4): calcd. C 72.40, H 5.79, N 8.04; found C 72.65, H 5.61; N 8.14.

Ethyl 2-{1-[(1-Methyl-1*H*-indol-2-yl)carbonyl]-2,3-dihydro-1*H*-indol-2-yl}acetate (10): Compound **10** was prepared as a foam in 96% yield from **4a** and 1-methylindole-2-carboxylic acid (**6**) according to the procedure described for the synthesis of **9**; chromatography eluent: petroleum ether/ethyl acetate, 9:1. IR (film): $\tilde{\nu}$ = 1740, 1621 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 1.12 (t, *J* = 6.9 Hz, 3 H, CH_3), 2.57 (dd, *J* = 15.6, 9.1 Hz, 1 H, CH_2), 2.80−2.94 (m, 2 H, CH_2Ph), 3.47 (dd, *J* = 15.6, 9.1 Hz, 1 H, CH_2), 3.79 (s, 3 H, NCH_3), 3.91−4.05 (m, 2 H, OCH_2), 5.20−5.25 (m, 1 H, NCH), 6.79 (s, 1 H, =CH), 6.93−7.35 (m, 7 H, H_{Ar}), 7.61 (d, *J* = 7.8 Hz, 1 H, H_{Ar}) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ = 13.9 (CH_3), 30.9 (NCH_3), 33.9 (CH_2), 38.7 (CH_2), 57.8 (NCH), 60.5 (OCH_2), 104.0 (=CH), 109.9 (CH), 116.0 (CH), 120.3 (CH), 121.9 (CH), 123.6 (CH), 124.1 (CH), 125.4 (CH), 126.4 (C), 127.2 (CH), 130.9 (C), 132.6 (C), 137.8 (C), 141.3 (C), 161.4 (C=O), 170.4 (C=O) ppm. ESI MS (IS): *m*/*z* = 363 [M^+ + H]. $C_{22}H_{22}N_2O_3$ (362.4): calcd. C 72.91, H 6.12, N 7.73; found C 72.67, H 5.94; N 7.86.

2[1-(1*H*-Indol-2-ylcarbonyl)-2,3-dihydro-1*H*-indol-2-yl]acetic Acid (11): Lithium hydroxide monohydrate (43 mg, 0.57 mmol) was added to a solution of compound **9** (100 mg, 0.29 mmol) in ethanol (5 mL). The mixture was stirred at room temperature for 20 h. After evaporation of the ethanol, the residue was dissolved in water and neutralised with a 1 N HCl solution. The mixture was extracted with ethyl acetate (2 × 10 mL). The organic phase was dried with $MgSO_4$ and the solvents were evaporated to give **11** (92 mg, 100%) as a colorless oil. IR (film): $\tilde{\nu}$ = 3363, 3205, 1728, 1627 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 2.51−2.56 (m, 1 H, CH_2), 2.69−2.87 (m, 2 H, CH_2Ph), 3.31−3.39 (m, 1 H, CH_2), 5.18−5.27 (m, 1 H, NCH), 6.84 (s, 1 H, =CH), 6.89−7.43 (m, 7 H, H_{Ar}), 7.59 (d, *J* = 7.9 Hz, 1 H, H_{Ar}), 11.51 (br. s, 1 H, NH) ppm. ^{13}C NMR (62.9 MHz, [D_6]DMSO, 80 °C): δ = 34.5 (CH_2), 39.4 (CH_2), 57.1 (NCH), 104.3 (CH), 112.3 (CH), 117.2 (CH), 120.1 (CH), 121.8 (CH), 124.0 (CH), 124.2 (CH), 125.5 (CH), 127.1 (CH), 127.3 (C), 130.4 (C), 130.8 (C), 136.2 (C), 142.3 (C), 160.2 (C=O), 171.8 (C=O) ppm. ESI MS: *m*/*z* = 321 [M^+ + H]. $C_{19}H_{16}N_2O_3$ (320.4): calcd. C 71.24, H 5.03, N 8.74; found C 70.97, H 5.16; N 8.88.

12-Methyl-5a,6-dihydroindolo[3′,2′:5,6]azepino[1,2-*a*]indoline-7,13(5*H*,12*H*)-dione (12): A solution of **10** (150 mg, 0.42 mmol), *p*TSA (157 mg, 0.83 mmol) and ethane-1,2-diol (0.11 mL, 2.07 mmol) in toluene (5 mL) was refluxed for 8 h. After cooling, water (10 mL) and ethyl acetate (10 mL) were added. The aqueous layer was extracted twice with ethyl acetate (2 × 10 mL). The organic layers were dried with $MgSO_4$ and the solvents evaporated in vacuo. The residue was purified by column chromatography (dichloromethane) to afford **12** (115 mg, 87%) as a solid; m.p. 280−282 °C (toluene). IR (KBr): $\tilde{\nu}$ = 1640 (CO) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 2.86−2.99 (m, 2 H, CH_2Ph), 3.31 (dd, *J* = 17.7, 11.7 Hz, 1 H, CH_2), 3.67 (dd, *J* = 17.7, 10.1 Hz, 1 H, CH_2), 4.12 (s, 3 H, NCH_3), 4.99−5.09 (m, 1 H, NCH), 7.12−7.18 (m, 1 H, H_{Ar}), 7.28−7.47 (m, 5 H, H_{Ar}), 8.38 (d, *J* = 8.1 Hz, 1 H, H_{Ar}), 8.44 (d, *J* = 8.1 Hz, 1 H, H_{Ar}) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ = 33.0 (NCH_3), 35.5 (CH_2), 51.4 (CH_2), 56.5 (NCH), 110.3 (CH), 116.2 (C), 117.7 (CH), 123.9 (CH), 124.0 (CH), 125.0 (CH), 125.3 (C), 125.4 (CH), 126.0 (CH), 128.2 (CH), 130.1 (C), 135.2 (C), 138.7 (C), 141.2 (C), 158.8 (C=O), 193.8 (C=O) ppm. ESI MS: *m*/*z* = 317 [M^+ + H]. $C_{20}H_{16}N_2O_2$ (316.4): calcd. C 75.93, H 5.10, N 8.85; found C 76.22, H 5.23; N 8.69.

2-Methoxyethyl 2{1-[(1-Methyl-1*H*-indol-2-yl)carbonyl]-2,3-dihydro-1*H*-indol-2-yl}acetate (13): A solution of **10** (100 mg, 0.28 mmol), *p*TSA (110 mg, 0.55 mmol) and 2-methoxyethanol (0.08 mL, 1.38 mmol) in toluene (3 mL) was refluxed for 2 h. After cooling, water (10 mL) and ethyl acetate (10 mL) were added. The aqueous layer was extracted twice with ethyl acetate (2 × 10 mL). The organic layers were dried with $MgSO_4$ and the solvents evaporated in vacuo. The residue was purified by column chromatography (dichloromethane) to afford **13** (96 mg, 89%) as a foam. IR (film): $\tilde{\nu}$ = 1738, 1624 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 2.53 (dd, *J* = 15.9, 8.9 Hz, 1 H, CH_2), 2.79−2.90 (m, 2 H, CH_2Ph), 3.44 (dd, *J* = 15.9, 8.9 Hz, 1 H, CH_2), 3.81 (s, 3 H, NCH_3), 4.01 (s, 3 H, OCH_3), 4.09−4.16 (m, 4 H, 2 OCH_2), 5.21−5.24 (m, 1 H, NCH), 6.76 (s, 1 H, =CH), 6.95−7.39 (m, 7 H, H_{Ar}), 7.61 (d, *J* = 7.8 Hz, 1 H, H_{Ar}) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ = 30.9 (NCH_3), 34.1 (CH_2), 39.5 (CH_2), 56.4 (NCH), 58.8 (OCH_3), 63.8 (OCH_2), 67.5 (OCH_2), 104.1 (CH), 109.9 (CH), 116.6 (CH), 120.6 (CH), 121.1 (CH), 123.6 (CH), 123.7 (CH), 125.4 (CH), 127.0 (C), 127.3 (CH), 131.0 (C), 132.5 (C), 138.1 (C), 141.0 (C), 160.8 (C=O), 170.6 (C=O) ppm. ESI MS: *m*/*z* = 393 [M^+ + H]. $C_{23}H_{24}N_2O_4$ (392.5): calcd. C 70.39, H 6.16, N 7.14; found C 70.75, H 6.09; N 7.03.

Ethyl 2-{1-[(1-Methyl-1*H*-indol-2-yl)carbonyl]-1,2,3,4-tetrahydroquinolin-2-yl}acetate (14b): Compound **14b** was prepared as a foam in 77% yield from **4b** and 1-methylindole-2-carboxylic acid **6** according to the procedure described for the synthesis of **10**; chromatography eluent: petroleum ether/ethyl acetate, 8:2. IR (film): nu(tilde) = 1738, 1624 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$, 25 °C): δ =

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1.24 (t, J = 7.2 Hz, 3 H, CH_3), 1.65−1.76 (m, 1 H, CH_2), 2.40−2.61 (m, 2 H, CH_2, CH_2), 2.75−2.86 (m, 3 H, CH_2, CH_2), 3.85 (s, 3 H, NCH_3), 4.11 (q, J = 7.2 Hz, 2 H, OCH_2), 5.14−5.25 (m, 1 H, NCH), 6.13 (s, 1 H, =CH), 6.69−6.72 (m, 1 H, H_{Ar}), 6.83−6.89 (m, 1 H, H_{Ar}), 7.01−7.07 (m, 2 H, H_{Ar}), 7.17−7.44 (m, 4 H, H_{Ar}) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ = 14.3 (CH_3), 25.5 (CH_2), 30.4 (CH_2), 31.4 (NCH_3), 39.2 (CH_2), 50.4 (NCH), 60.7 (OCH_2), 106.2 (CH), 109.9 (CH), 120.1 (CH), 122.0 (CH), 123.6 (CH), 125.7 (CH), 126.2 (CH), 126.3 (C), 126.4 (CH), 127.7 (CH), 132.6 (CH), 133.6 (C), 137.9 (C), 138,0 (C), 163.2 (C=O), 170.9 (C=O) ppm. ESI MS: m/z = 377 [M^+ + H]. $C_{23}H_{24}N_2O_3$ (376.5): calcd. C 73.38, H 6.43, N 7.44; found C 73.06, H 6.60; N 7.58.

Ethyl 2-{4-[(1-Methyl-1*H*-indol-2-yl)carbonyl]-3,4-dihydro-2*H*-1,4-benzoxazin-3-yl}acetate (14d): Compound **14d** was prepared as a foam in 95% yield from **4c** and 1-methylindole-2-carboxylic acid **6** according to the procedure described for the synthesis of **10**; chromatography eluent: petroleum ether/ethyl acetate, 8:2. IR (film): $\tilde{\nu}$ = 1732, 1622 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 1.26 (t, J = 6.9 Hz, 3 H, CH_3), 2.67−2.71 (m, 2 H, CH_2), 3.87 (s, 3 H, NCH_3), 4.16 (q, J = 6.9 Hz, 2 H, OCH_2), 4.32 (dd, J = 11.3, 2.8 Hz, 1 H, OCH_2), 4.52 (dd, J = 11.3, 1.2 Hz, 1 H, OCH_2), 5.24−5.30 (m, 1 H, NCH), 6.63 (s, 1 H, =CH), 6.65−6.69 (m, 1 H, H_{Ar}), 6.91−7.05 (m, 3 H, H_{Ar}), 7.08−7.16 (m, 1 H, H_{Ar}), 7.31−7.38 (m, 2 H, H_{Ar}), 7.56 (d, J = 8.2 Hz, 1 H, H_{Ar}) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ = 14.3 (CH_3), 31.5 (NCH_3), 34.0 (CH_2), 47.4 (NCH), 61.0 (OCH_2), 68.1 (OCH_2), 106.6 (CH), 110.1 (CH), 117.2 (CH), 120.5 (CH), 120.6 (CH), 122.3 (CH), 123.9 (C), 124.2 (CH), 124.8 (CH), 126.0 (CH), 126.3 (C), 131.6 (C), 138.6 (C), 145.4 (C), 162.0 (C=O), 170.6 (C=O) ppm. ESI MS: m/z = 379 [M + H]$^+$. $C_{22}H_{22}N_2O_4$ (378.4): calcd. C 69.83, H 5.86, N 7.40; found C 70.12, H 5.69; N 7.53.

13-Methyl-6a,7-dihydro-5*H*-indolo[3′,2′:5,6]azepino[1,2-*a*]quinoline-8,14(6*H*,13*H*)-dione (15b): Compound **15b** was prepared as a solid in 82% yield from **14b** according to the procedure described for the synthesis of **12**; chromatography eluent: dichloromethane. M.p. 263−264 °C (toluene). IR (KBr): $\tilde{\nu}$ = 1640 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 1.54−1.70 (m, 1 H, CH_2), 2.38−2.49 (m, 1 H, CH_2), 2.64−2.68 (m, 2 H, CH_2), 2.83−3.08 (m, 2 H, CH_2), 4.06 (s, 3 H, NCH_3), 4.75−4.86 (m, 1 H, NCH), 7.13−7.46 (m, 6 H, H_{Ar}), 7.80 (d, J = 8.1 Hz, 1 H, H_{Ar}), 8.41 (d, J = 7.9 Hz, 1 H, H_{Ar}) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ = 21.1 (CH_2), 32.4 (CH_2), 33.2 (NCH_3), 50.9 (CH_2), 54.1 (NCH), 110.3 (CH), 116.8 (C), 123.6 (CH), 124.0 (CH), 125.1 (C), 125.7 (CH), 126.0 (CH), 126.2 (CH), 126.8 (CH), 127.6 (CH), 128.1 (C), 130.1 (C), 134.8 (C), 138.9 (C), 161.4 (C=O), 195.4 (C=O) ppm. ESI MS: m/z = 331 [M^+ + H]. $C_{21}H_{18}N_2O_2$ (330.4): calcd. C 76.34, H 5.49, N 8.48; found C 76.63, H 5.45; N 8.65.

13-Methyl-6a,7-dihydroindolo[3′,2′:5,6]azepino[2,1-*c*][1,4]benzoxazine-8,14(6*H*,13*H*)-dione (15d): Compound **15d** was prepared as a solid in 76% yield from **14d** according to the procedure described above for the synthesis of **12**; chromatography eluent: dichloromethane. M.p. 250−252 °C (toluene). IR (KBr): $\tilde{\nu}$ = 1640, 1607 cm^{-1}. ^{1}H NMR (250 MHz, [D$_6$]DMSO, 25 °C): δ = 2.88−3.04 (m, 2 H, CH_2), 4.06 (s, 3 H, NCH_3), 4.16 (dd, J = 11.2, 3.1 Hz, 1 H, OCH_2), 4.35 (dd, J = 11.2, 2.1 Hz, 1 H, OCH_2), 5.08−5.11 (m, 1 H, NCH), 6.98−7.12 (m, 3 H, H_{Ar}), 7.30−7.48 (m, 2 H, H_{Ar}), 7.72 (d, J = 7.5 Hz, 1 H, H_{Ar}), 8.18 (d, J = 8.3 Hz, 1 H, H_{Ar}), 8.79 (d, J = 8.1 Hz, 1 H, H_{Ar}) ppm. The ^{13}C NMR spectrum could not be recorded owing to the very poor solubility of **15d**. ESI MS: m/z = 333 [M^+ + H]. $C_{20}H_{16}N_2O_3$ (332.4): calcd. C 72.28, H 4.85, N 8.43; found C 72.57, H 4.98; N 8.32.

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[1] G. A. Archer, L. H. Sternbach, *Chem. Rev.* **1968**, *68*, 747−784.
[2] D. E. Thurston, D. S. Bose, P. W. Howard, T. C. Jenkins, A. Leoni, P. G. Baraldi, A. Guiotto, B. Cacciari, L. R. Kelland, M.-P. Foloppe, S. Rault, *J. Med. Chem.* **1999**, *42*, 1951−1964.
[3] D. E. Thurston, D. S. Bose, A. S. Thompson, P.W. Howard, A. Leoni, S. J. Croker, T. C. Jenkins, S. Neidle, J. A. Hartley, L. H. Hurley, *J. Org. Chem.* **1996**, *61*, 8141−8147.
[4] S. J. Gregson, P. W. Howard, K. E. Corcoran, S. Barcella, M. M. Yasin, A. A. Hurst, T. C. Jenkins, L. R. Kelland, D. E. Thurston, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1845−1847; S. J. Gregson, P. W. Howard, K. E. Corcoran, S. Barcella, M. M. Yasin, A. A. Hurst, T. C. Jenkins, L. R. Kelland, D. E. Thurston, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1849−1851.
[5] A. Kamal, G. Suresh Kumar Reddy, K. Laxma Reddy, S. Raghavan, *Tetrahedron Lett.* **2002**, *43*, 2103−2106.
[6] F. Clerici, E. Erba, D. Pocar, *Tetrahedron* **2003**, *59*, 1667−1671.
[7] C. Kunick, K. Lauenroth, M. Leost, L. Meijer, T. Lemcke, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 413−416.
[8] C. Kunick, K. Lauenroth, K. Wieking, X. Xie, C. Schultz, R. Gussio, D. Zaharevitz, M. Leost, L. Meijer, A. Weber, F. S. Jorgensen, T. Lemcke, *J. Med. Chem.* **2004**, *47*, 22−36.
[9] L. Meijer, A.-M. W. H. Thunnissen, A. W. White, M. Garnier, M. Nikolic, L.-H. Tsai, J. Walter, K. E. Cleverley, P. C. Salinas, Y.-Z. Wu, J. Biernat, E.-M. Mandelkow, S.-H. Kim, G. R. Pettit, *Chem. Biol.* **2000**, *7*, 51−63.
[10] R. G. Kerr, S. S. Kerr, *Expert Opin. Ther. Pat.* **1999**, *9*, 1207−1222.
[11] E. Winterfeldt, *Pure Appl. Chem.* **1999**, *71*, 1095−1099.
[12] D. J. Faulkner, *Nat. Prod. Rep.* **1999**, *16*, 155−198 and earlier reports in this series.
[13] S. Forenza, L. Minale, R. Riccio, E. Fattorusso, *J. Chem. Soc., Chem. Commun.* **1971**, 1129−1130.
[14] E. Garcia, L. E. Benjamin, R. I. Fryer, *J. Chem. Soc., Chem. Commun.* **1973**, 78−79.
[15] M. Knockaert, P. Greengard, L. Meijer, *Trends Pharm. Sci.* **2002**, *23*, 417−425.
[16] M. A. Lago, WO Patent **2001**, 0164680 (*Chem. Abstr.* **2001**, *135*, 211033).
[17] Y. Wan, W. Hur, C. Y. Cho, Y. Liu, F. J. Adrian, O. Lozach, S. Bach, T. Mayer, D. Fabbro, L. Meijer, N. S. Gray, *Chem. Biol.* **2004**, *11*, 247−259.
[18] J. Perron, B. Joseph, J.-Y. Mérour, *Tetrahedron Lett.* **2003**, *44*, 6553−6556.
[19] L. Chacun-Lefèvre, B. Joseph, J.-Y. Mérour, *Synlett* **2001**, 848−850.
[20] L. Chacun-Lefèvre, B. Joseph, J.-Y. Mérour, *Tetrahedron* **2000**, *56*, 4491−4499.
[21] R. Nagata, N. Tanno, T. Kodo, N. Ae, H. Yamaguchi, T. Nishimura, F. Antoku, T. Tatsuno, T. Kato, Y. Tanaka, M. Nakamura, *J. Med. Chem.* **1994**, *37*, 3956−3968.
[22] T. L. Gilchrist, A. Rahman, *J. Chem. Soc., Perkin Trans. 1* **1998**, 1203−1208.
[23] S. Coulton, T. L. Gilchrist, K. Graham, *J. Chem. Soc., Perkin Trans. 1* **1998**, 1193−1202.
[24] M. D. Ennis, R. L. Hoffman, N. B. Ghazal, R. M. Olson, C. S. Knauer, C. L. Chio, D. K. Hyslop, J. E. Campbell, L. W. Fitzgerald, N. F. Nichols, K. A. Svensson, R. B. McCall, C. L. Haber, M. L. Kagey, D. M. Dinh, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2369−2372.
[25] H. J. C. Deboves, C. Hunter, R. F. W. Jackson, *J. Chem. Soc., Perkin Trans. 1* **2002**, 733−736.
[26] K. Narasaka, Y. Kohno, *Bull. Chem. Soc. Jpn.* **1993**, *66*, 3456−3463.

 © 2004 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

[27] H. G. Chen, C. Hoechstetter, P. Knochel, *Tetrahedron Lett.* **1989**, *30*, 4795−4798.
[28] P. N. Rylander, in *Hydrogenation Methods*, Academic Press, New York, **1985**, pp. 82−93.
[29] M. Artico, G. DeMartino, G. Filacchione, R. Giuliano, *Farmaco* **1969**, *24*, 276−284.
[30] D. M. Floyd, R. V. Moquin, K. S. Atwal, S. Z. Ahmed, S. H. Spergel, J. Z. Gougoutas, M. F. Malley, *J. Org. Chem.* **1990**, *55*, 5572−5579.
[31] R. Tapia, C. R. Centella, J. A. Valderrama, *Synth. Commun.* **1999**, *29*, 2163−2168.
[32] R. A. Bunce, D. M. Herron, M. L. Ackerman, *J. Org. Chem.* **2000**, *65*, 2847−2850.
[33] B. K. Banik, I. Banik, L. Hackfeld, F. F. Becker, *Heterocycles* **2002**, *56*, 467−470.
[34] I. Collado, J. Ezquerra, J. J. Vaquero, C. Pedregal, *Tetrahedron Lett.* **1994**, *35*, 8037−8040.
[35] M. Ogata, H. Matsumoto, *Chem. Pharm. Bull.* **1972**, *20*, 2264−2268.
[36] T. O. Olagbemiro, C. A. Nyakutse, L. Laijide, M. O. Agho, C. E. Chukwu, *Bull. Soc. Chim. Belg.* **1987**, *96*, 473−480.
[37] S. Akai, T. Tsujino, T. Naka, K. Tanimoto, Y. Kita, *Tetrahedron Lett.* **2001**, *42*, 7315−7317.
[38] A. Guarna, F. Machetti, E. G. Occhiato, D. Scarpi, A. Comerci, G. Danza, R. Mancina, M. Serio, K. Hardy, *J. Med. Chem.* **2000**, *43*, 3718−3735.
[39] F. Lepifre, C. Buon, R. Rabot, P. Bouyssou, G. Coudert, *Tetrahedron Lett.* **1999**, *40*, 6373−6376.
[40] C. Buon, L. Chacun-Lefèvre, R. Rabot, P. Bouyssou, G. Coudert, *Tetrahedron* **2000**, *56*, 605−614.

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