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Synthesis of New Water-Soluble DNA-Binding Subunits for Analogues of the Cytotoxic Antibiotic CC-1065 and Their Prodrugs

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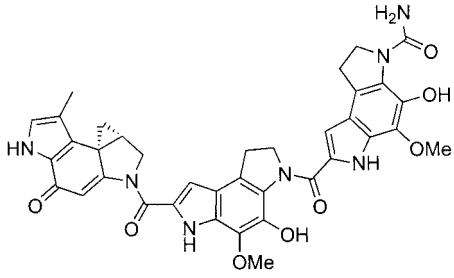
Novel water-soluble indole-2-carboxylic acid derivatives (**7**, **13**, **21** and **25**) bearing a substituent with a tertiary amino functionality at C-5 have been prepared. These new DNA-binding subunits can be used for the synthesis of new analogues of the cytotoxic antibiotic CC-1065 and their corresponding prodrugs for antibody-directed enzyme prodrug therapy (ADEPT) within a selective treatment of cancer.

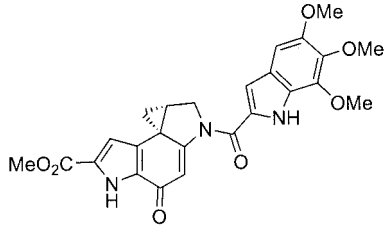
Introduction

Antibody-directed enzyme prodrug therapy (ADEPT)[1–10] is a promising concept for the selective treatment of cancer in which a non-toxic prodrug is enzymatically and selectively converted into a cytotoxic compound at the surface of malignant cells by employing an antibody–enzyme conjugate. A requirement in this approach is a relatively low cytotoxicity of the prodrug, whereas the corresponding drug that is formed enzymatically at the cancer cells should have a high cytotoxicity with an IC_{50} lower than about 10 nM[11] (IC_{50} is the drug concentration required for 50% inhibition of target cells.) A class of compounds which seem to be very appropriate for ADEPT, providing that they can be reversibly detoxified, are those characterised by the antibiotic CC-1065 (**1a**) and the duocarmycins such as **1b**, which are some of the most potent antitumour agents yet discovered.[12–17] CC-1065 (**1a**) and duocarmycin SA (**1b**) bind to double-stranded DNA within the minor groove and alkylate N-3 of adenine moieties.[18–20] However, CC-1065 (**1a**) cannot be used in the treatment of cancer due to a delayed lethal liver toxicity; other compounds of this type, such as **1b**, that have a similarly cytotoxicity do not show this effect.[21]

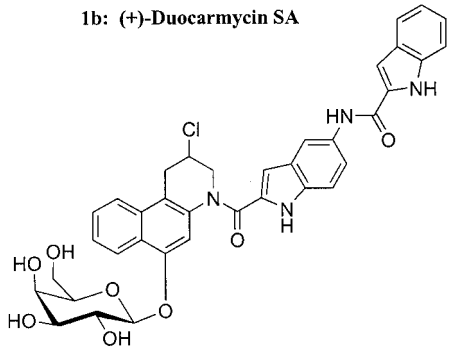
Some time ago we demonstrated that the formation of the spirocyclopropane moiety as the pharmacophoric group of CC-1065 from a corresponding *seco* compound can be halted by transforming its phenolic hydroxy group into a glycoside.[22] Such a derivative can be hydrolysed enzymatically with a glycohydrolase, which liberates the drug. Thus, the glycosidic *seco* compound **2** bearing a bisindolyl car-



1a: (+)-CC-1065



1b: (+)-Duocarmycin SA



2: Prodrug

Scheme 1. Structures of (+)-CC-1065 (**1a**), (+)-duocarmycin SA (**1b**) and glycosidic prodrug **2**.

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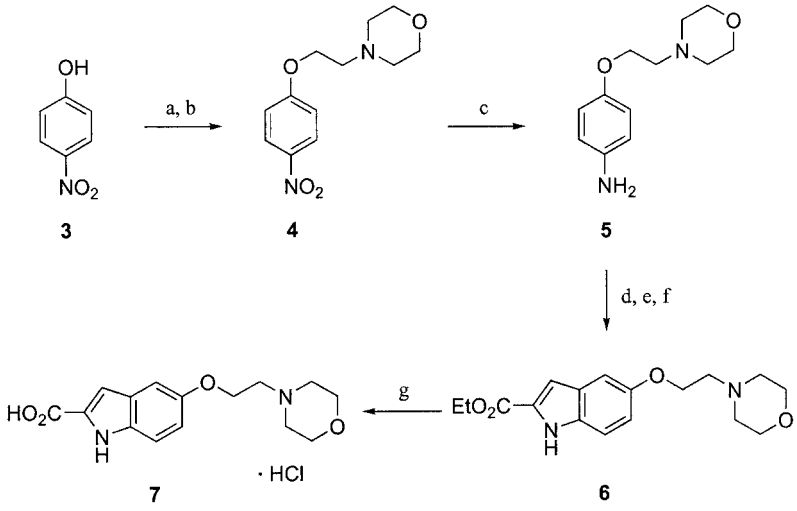
boxylic acid moiety as the DNA-binding subunit is a very suitable candidate for ADEPT.[23,24] However, a drawback in its application is its poor water solubility. Here we describe the synthesis of novel indole-2-carboxylic acid derivatives which have good water solubility and which could be used as DNA-binding units in novel analogues of CC-1065 and their corresponding prodrugs (Scheme 1).

Results and Discussion

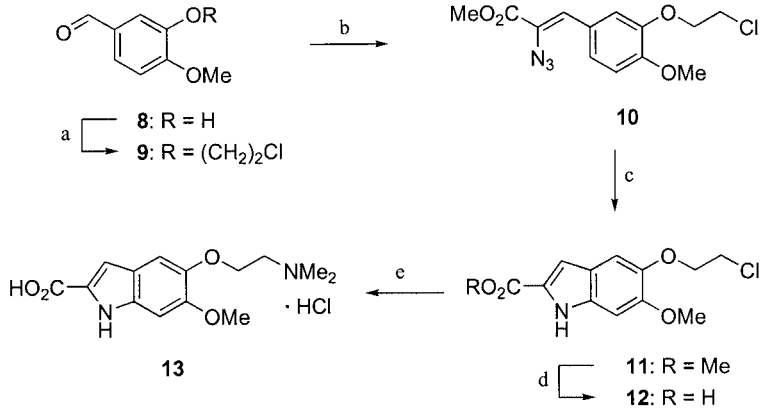
As reported previously by Boger et al., only the 5-methoxy substituent of the 5,6,7-trimethoxyindole-2-carboxylic acid unit (TMI) of duocarmycin SA (**1b**) is required for high potency.[25] Thus, substituents at C-5 of the DNA-binding subunit have been shown to have a pronounced effect on the rate and efficiency of DNA alkylation and the resulting biological potency of CC-1065 analogues.[26] Furthermore, Denny et al. have found that minor-groove-binding side chains of the TMI-type possessing a 5-alkoxy group and a solubilizing dimethylaminoethyl group, either as part of the 5-alkoxy substituent or at another position of the indole moiety, retain or enhance the cytotoxicity of the parent drug and provide an increased water solubility.[27] Based on these findings, we prepared the four new indole carboxylic acid derivatives **7**, **13**, **21** and **25** as DNA-binding subunits that carry a substituent at C-5 with a tertiary amino functionality. These new compounds show good water solubility as their hydrochlorides.

The indole carboxylic acid **7**, which contains a morpholinoethoxy substituent, was prepared by a Japp–Klingemann-type Fischer indole synthesis[28] from aniline **5**, followed by hydrolysis of the intermediate ester **6**, in 65% yield over four steps (Scheme 2). Aniline **5** was synthesised by alkylation of 4-nitrophenol (**3**) with 4-(2-chloroethyl)-morpholine and subsequent reduction of the obtained nitro compound **4** by hydrogen with palladium on charcoal as the catalyst in 57% yield based on **3**.

The indole carboxylic acid **13**, which contains a dimethylaminoethoxy group at C-5 and a methoxy group at C-6, was prepared following the Hemetsberger method[29] for the



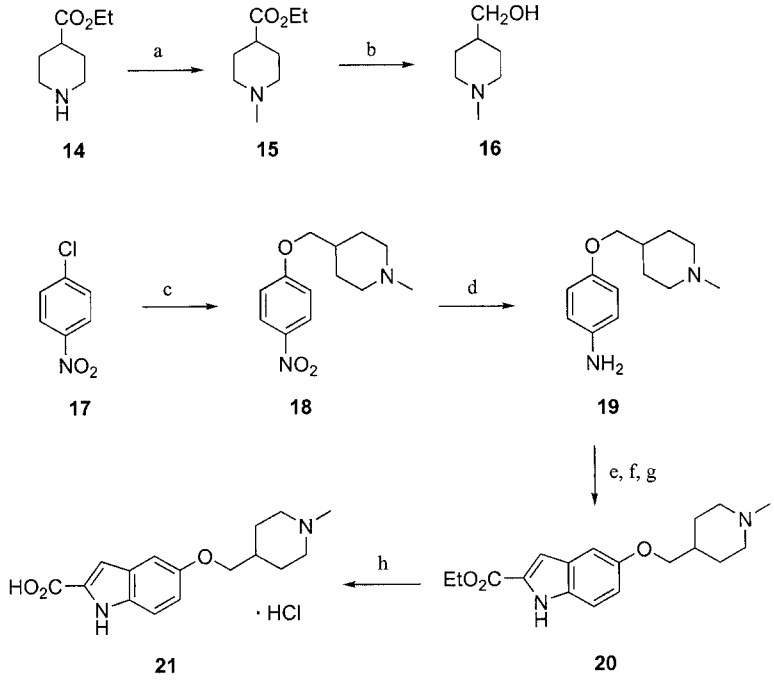
Scheme 2. (a) KOH, EtOH, room temp., 30 min; (b) 4-(2-chloroethyl)morpholine, toluene, reflux, 24 h, 57% from **3**; (c) Pd/C/H_2, EtOH/H_2O, room temp., 1 h, quant.; (d) $NaNO_2$, HCl/H_2O, 0 °C, 30 min; (e) ethyl 2-methylacetoacetate, NaOAc, EtOH, 0 °C to room temp., 3 h; (f) HCl/EtOH, reflux, 40 min, 71% from **5**; (g) NaOH, MeOH/H_2O, reflux, 3 h, then MeOH/HCl, 92%.



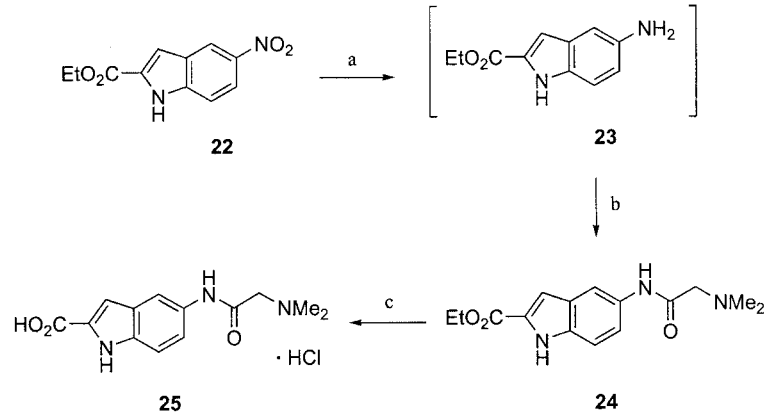
Scheme 3. (a) $(CH_2Cl)_2$, K_2CO_3, DMF, 70 °C, 16 h, 84%; (b) $N_3CH_2CO_2Me$, NaOMe/MeOH, MeOH, –30 °C to 0 °C, 16 h, 88%; (c) toluene, reflux, 4 h, 72%; (d) Cs_2CO_3, EtOH/H_2O, reflux, 8 h, 95%; (e) Me_2NH, Na_2CO_3, H_2O, 100 °C, 1.5 h, 98%.

formation of the indole moiety (Scheme 3). Thus, benzaldehyde **8** was O-alkylated with 1,2-dichloroethane in the presence of potassium carbonate to give **9**, which was subsequently condensed with methyl α-azidoacetate using sodium methoxide as base. The formed α-azido cinnamate **10** was heated at 115 °C for four hours to afford the indole carboxylic acid derivative **11** in 53% yield based on **8**. Hydrolysis of the methyl ester moiety in **11** followed by nucleophilic substitution of the chloro group with dimethylamine gave the desired indole carboxylic acid derivative in 93% yield over two steps.

For the synthesis of the indole carboxylic acid **21**, which contains an *N*-methylpiperidinylmethoxy side-chain, we again used a Japp–Klingemann-type Fischer indole synthesis (Scheme 4). The required aniline **19** was prepared in four steps starting from ethyl isonipecotate (**14**), which was *N*-methylated by a reductive methylation using a mixture of glacial acetic acid, formaldehyde and water over palladium on charcoal to give **15** in quantitative yield. In contrast, methylation of **14** with formic acid and formaldehyde was not successful. Subsequent reduction of **15** with $LiAlH_4$ provided alcohol **16** in 84% yield. This compound is an important building block in the preparation of pharmaceuticals in order to improve water solubility; this newly developed synthesis is superior to known procedures[30–33] and allows the synthesis of this compound from commercially available ethyl isonipecotate (**14**) in two steps with 84% overall yield. For the synthesis of **21**, alcohol **16** was treated with 1-chloro-4-nitrobenzene (**17**) in a nucleophilic aromatic substitution to give **18** in 83% yield. Finally, nitro



Scheme 4. (a) CH_2O, HOAc/H_2O, Pd/C/H_2, room temp., 3.5 h, quant.; (b) $LiAlH_4$, Et_2O, 0 °C to room temp., 4 h, 84%; (c) **16**, NaH, DMSO, 70 °C, 3 h, 83%; (d) Pd/C/H_2, MeOH/HCl, room temp., 1 h, 82%; (e) $NaNO_2$, HCl/H_2O, 0 °C, 50 min; (f) ethyl 2-methylacetoacetate, NaOAc, EtOH, 0 °C to room temp., 3 h; (g) HCl/EtOH, reflux, 50 min, 72% from **19**; (h) NaOH, MeOH/H_2O, reflux, 3.5 h, then MeOH/HCl, 91%.



Scheme 5. (a) Pd/C/H_2, EtOAc, room temp., 5 h; (b) *N*,*N*-dimethylglycine hydrochloride, EDC·HCl, DMF, room temp., 21 h, 68% from **22**; (c) LiOH·H_2O, THF/MeOH/H_2O, 60 °C, 4 h, then MeOH/HCl, quant.

compound **18** was hydrogenated over palladium on charcoal to yield aniline **19** in 82%. The concluding Fischer indole synthesis followed by hydrolysis of the primarily formed ester **20** provided the desired acid **21** in 66% yield over four steps.

The synthesis of indole carboxylic acid **25**, which contains an *N*,*N*-dimethylglycine moiety, started from the commercially available ester **22** (Scheme 5). Reduction of the nitro group in **22** by hydrogenation over palladium on charcoal gave the sensitive amine **23**, which was subsequently coupled with *N*,*N*-dimethylglycine hydrochloride in the presence of *N*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide hydrochloride (EDC·HCl) to give amide **24** in 68% yield over two steps. Finally, the ester moiety in **24** was hydrolysed with LiOH in THF/methanol/water, a mild method that avoids cleavage of the amide functionality, to give the desired acid **25** in quantitative yield.

In the ^{1}H NMR spectra of **7**, **13**, **21** and **25** the resonance for 3-H, which is typical for indole-2-carboxylic acids, is found at δ = 6.97–7.13 ppm as a doublet (J = 1.3–2.1 Hz).

Conclusions

Four new water-soluble indole-2-carboxylic acid hydrochlorides (**7**, **13**, **21** and **25**) bearing a substituent with a tertiary amino functionality at C-5 have been prepared. These new DNA-binding subunits will be used for the synthesis of new prodrug analogues of the antibiotic CC-1065 to overcome the problem of poor water solubility during biological testing within the ADEPT approach. Furthermore, (1-methylpiperidin-4-yl)methanol (**16**), which is a valuable building block of pharmaceutical interest, has been prepared from ethyl isonipecotate (**14**) in 84% yield over two steps.

Experimental Section

General: All reactions were performed under argon in flame-dried flasks. All solvents were dried and distilled prior to use by usual laboratory methods. All reagents obtained from commercial sources were used without further purification. Thin-layer chromatography (TLC) was performed on precoated silica gel SIL G/UV$_{254}$ plates (Macherey–Nagel GmbH & Co. KG) and silica gel 60 (0.032–0.063 mm, Merck) was used for column chromatography. Phosphomolybdic acid in MeOH (PMA) or vanillin in methanolic sulfuric acid were used as staining reagents for TLC. UV spectra were taken in CH_3CN or MeOH with a Perkin–Elmer Lambda 2 spectrometer. IR spectra were recorded as KBr pellets or as films with a Bruker IFS 25 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded with Mercury-200, VXR-200, Unity 300, Inova 500, Unity Inova-600 (Varian) or AMX 300 (Bruker) spectrometers. Chemical shifts are reported in ppm with tetramethylsilane (TMS) as internal standard. Multiplicities of ^{13}C NMR peaks were determined with the APT pulse sequence. Mass spectra were measured with a Finnigan MAT 95, TSQ 7000 or LCQ instrument. Elemental analysis: Mikroanalytisches Labor, Institut für Organische und Biomolekulare Chemie, Georg-August-Universität Göttingen. PE = petroleum ether.

4-[2-(4-Nitrophenoxy)ethyl]morpholine (4): A solution of KOH (3.3 g, 58 mmol) in EtOH (15 mL) was added dropwise to a solution of 4-nitrophenol (**3**; 7.0 g, 50 mmol) in EtOH (10 mL). After stirring for 30 min at room temperature the resulting salt was collected by filtration, washed with cold EtOH and dried in vacuo to give the potassium salt of **3** as a yellow solid (7.1 g, 40 mmol). This salt (7.1 g, 40 mmol) was dissolved in toluene (100 mL), a solution of 4-(2-chloroethyl)morpholine (6.5 g, 43 mmol) in toluene (100 mL) was added, and the mixture was heated at reflux for 24 h. After cooling to room temperature the precipitate was separated by filtration, washed thoroughly with toluene, and the filtrate was concentrated in vacuo to give **4** as a pale-yellow solid (7.2 g, 57% overall yield), which was used in the next step without further purification. R_f = 0.67 (CH_2Cl_2/MeOH, 10:1). IR (KBr): $\tilde{\nu}$ = 2943, 2852, 1501, 1344 cm^{-1}. UV (CH_3CN): λ_{max} (logε) = 220.5 nm (3.873), 310.0 (4.072). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.54–2.64 (m, 4 H, 3-H$_2$, 5-H$_2$), 2.84 (t, J = 5.5 Hz, 2 H, 1′-H$_2$), 3.69–3.78 (m, 4 H, 2-H$_2$, 6-H$_2$), 4.20 (t, J = 5.5 Hz, 2 H, 2′-H$_2$), 6.92–7.01 (m, 2 H, 2′′-H, 6′′-H), 8.16–8.25 (m, 2 H, 3′′-H, 5′′-H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 54.1 (C-3, C-5), 57.3 (C-1′), 66.7 (C-2′), 66.9 (C-2, C-6), 114.5 (C-2′′, C-6′′), 125.9 (C-3′′, C-5′′), 141.6 (C-4′′), 163.7 (C-1′′) ppm. MS (70 eV, EI): m/z (%) = 252 (8) [M]$^+$, 100 (100) [M – $CH_2OC_6H_4$ – NO_2]$^+$. $C_{12}H_{16}N_2O_4$ (252.27).

4-[(2-Morpholin-4-yl)ethoxy]phenylamine (5): A solution of **4** (6.00 g, 23.8 mmol) in 95% EtOH (40 mL) was hydrogenated (Pd/C, 10%, 350 mg) at 58 psi H_2 for 1 h at room temperature. The solid formed was removed by filtration through celite, which was washed thoroughly with EtOH (100 mL) and MeOH (50 mL); the filtrate was concentrated in vacuo to give **5** (5.29 g, quant.) as a reddish brown oil, which was used for the next step without further purification. R_f = 0.54 (CH_2Cl_2/MeOH, 10:1). IR (KBr): $\tilde{\nu}$ = 3452, 3365, 2939 cm^{-1}. UV (CH_3CN): λ_{max} (logε) = 196.0 nm (4.520), 240.5 (3.996), 307.5 (3.358). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.57 (m$_c$, 4 H, 3′′-H$_2$, 5′′-H$_2$), 2.76 (t, J = 5.8 Hz, 2 H, 2′-H$_2$), 3.40 (br. s, 2 H, NH$_2$), 3.73 (m$_c$, 4 H, 2′′-H$_2$, 6′′-H$_2$), 4.03 (t, J = 5.8 Hz, 2 H, 1′-H$_2$), 6.59–6.66 (m, 2 H, 2-H, 6-H), 6.71–6.78 (m, 2 H, 3-H, 5-H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 54.0 (C-3′′, C-5′′), 57.7 (C-2′), 66.3 (C-1′), 66.8 (C-2′′, C-6′′), 115.7 (C-3, C-5), 116.2 (C-2, C-6), 140.2 (C-1), 151.7 (C-4) ppm. MS (70 eV, EI): m/z (%) = 222 (17) [M]$^+$, 100 (100) [M – $CH_2OC_6H_4$ – NH_2]$^+$. $C_{12}H_{18}N_2O_2$ (222.28).

Ethyl 5-[(2-Morpholin-4-yl)ethoxy]-1*H*-indole-2-carboxylate (6): A stirred solution of 4-[(2-morpholin-4-yl)ethoxy]phenylamine (**5**; 4.00 g, 18.0 mmol) in water (38 mL) and concentrated HCl (12 mL) was treated dropwise at 0 °C with a solution of $NaNO_2$ (1.36 g, 19.8 mmol) in water (3.8 mL) and the resulting mixture was stirred for 30 min at 0 °C (solution A). Ethyl 2-methylacetoacetate (2.75 mL, 18.9 mmol) was added dropwise to a suspension of NaOAc (15.3 g) in EtOH (29 mL) at 0 °C. After stirring for 30 min at this temperature ice (18 g) was added (solution B). Then, solution A was added to solution B by a transfer cannula at 0 °C, the mixture was warmed to room temperature and was stirred for a further 2.5 h. After that, the reaction mixture was basified by slow addition of a saturated aqueous solution of Na_2CO_3 at 0 °C and extracted with CH_2Cl_2 (3 × 200 mL). The combined organic layers were washed with water (300 mL), dried ($MgSO_4$) and the solvent was removed in vacuo. The residue was then dissolved in absolute EtOH (15 mL), treated with a freshly prepared saturated solution of HCl in absolute EtOH[34] (15 mL) and heated at reflux for 40 min. After cooling to room temperature the solvent was removed under reduced pressure and the residue was partitioned between water (50 mL) and CH_2Cl_2 (100 mL). The aqueous layer was basified with a saturated aqueous solution of Na_2CO_3 and ex-

tracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with brine (200 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification by crystallisation from iPr_2O and column chromatography (CH_2Cl_2/MeOH, 20:1) of the residue after evaporation of the mother liquor provided **6** (4.07 g, 71% overall yield) as a yellow solid. R_f = 0.45 (CH_2Cl_2/MeOH, 20:1). IR (KBr): $\tilde{\nu}$ = 3329, 2944, 2862, 1686 cm^{-1}. UV (CH_3CN): λ_{max} (log ε) = 215.0 nm (4.435), 293.5 (4.276), 322.5 (3.705). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.41 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 2.61 (m_c, 4 H, 3′′-H_2, 5′′-H_2), 2.84 (t, J = 5.7 Hz, 2 H, 2′-H_2), 3.76 (m_c, 4 H, 2′′-H_2, 6′′-H_2), 4.15 (t, J = 5.7 Hz, 2 H, 1′-H_2), 4.40 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 6.99 (dd, J = 9.0, 2.4 Hz, 1 H, 6-H), 7.08 (d, J = 2.4 Hz, 1 H, 4-H), 7.13 (d, J = 1.3 Hz, 1 H, 3-H), 7.30 (d, J = 9.0 Hz, 1 H, 7-H), 9.13 (br. s, 1 H, NH) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 14.4 (OCH_2CH_3), 54.1 (C-3′′, C-5′′), 57.7 (C-2′), 60.9 (OCH_2CH_3) 66.2 (C-1′), 66.9 (C-2′′, C-6′′), 103.7 (C-4), 108.1 (C-3), 112.7 (C-7), 117.3 (C-6), 127.7, 127.9 (C-2, C-3a), 132.3 (C-7a), 153.7 (C-5), 162.0 (C=O) ppm. MS (70 eV, EI): m/z (%) = 318 (14) $[M]^+$, 100 (100) $[CH_2N(CH_2)_4O]^+$. $C_{17}H_{22}N_2O_4$ (318.37): calcd. C 64.13, H 6.97; found 63.85, H 7.12.

5-[(2-Morpholin-4-yl)ethoxy]-1*H*-indole-2-carboxylic Acid Hydrochloride (7): A suspension of ester **6** (1.02 g, 3.20 mmol) in MeOH (8 mL) was treated with a solution of NaOH (150 mg, 3.75 mmol) in water (4 mL) and heated at reflux for 3 h. After cooling to room temperature, the solution was adjusted to pH 6 with 1 M HCl and the solvent was removed under reduced pressure. The residue was dissolved in MeOH, 1 M HCl was added dropwise, and the formed precipitate was collected by filtration to give **7** (727 mg, 70%) as a brown solid. Purification of the residue obtained by evaporation of the mother liquor by column filtration through silica gel (MeOH, 1% concd. HCl) provided a second batch of **7** (232 mg, 22%). R_f = 0.56 (MeOH, 1% concd. HCl). IR (KBr): $\tilde{\nu}$ = 3290, 2944, 2664, 1692 cm^{-1}. UV (CH_3CN): λ_{max} (log ε) = 196.5 nm (3.495), 285.0 (3.051), 293.0 (3.081). ^1H NMR (300 MHz, [D_6]DMSO): δ = 3.07–3.61 (m, 6 H, 2′-H_2, 3′′-H_2, 5′′-H_2), 3.76–4.06 (m, 4 H, 2′′-H_2, 6′′-H_2), 4.43 (t, J = 5.0 Hz, 2 H, 1′-H_2), 6.98 (dd, J = 8.9, 2.3 Hz, 1 H, 6-H), 7.01 (d, J = 1.8 Hz, 1 H, 3-H), 7.20 (d, J = 2.3 Hz, 1 H, 4-H), 7.37 (d, J = 8.9 Hz, 1 H, 7-H), 11.39 (br. s, 1 H, NH^+), 11.65 (s, 1 H, NH), 12.85 (br. s, 1 H, CO_2H) ppm. ^{13}C NMR (50.3 MHz, [D_6]DMSO): δ = 51.6 (C-3′′, C-5′′), 54.9 (C-2′), 62.8 (C-1′), 63.1 (C-2′′, C-6′′), 103.9 (C-4), 106.9 (C-3), 113.5 (C-7), 115.9 (C-6), 127.0 (C-2), 129.0 (C-3a), 133.0 (C-7a), 152.0 (C-5), 162.6 (C=O) ppm. MS (70 eV, EI): m/z (%) = 290 (6) $[M - Cl]^+$, 100 (100) $[CH_2N(CH_2)_4O]^+$. $C_{15}H_{19}ClN_2O_4$ (326.78): calcd. C 55.13, H 5.86; found C 54.96, H 5.81.

3-(2-Chloroethoxy)-4-methoxybenzaldehyde (9): A mixture of 3-hydroxy-4-methoxybenzaldehyde (**8**; 10.0 g, 65.7 mmol), K_2CO_3 (45.4 g, 329 mmol), 1,2-dichloroethane (104 mL, 1.31 mol) and DMF (300 mL) was stirred at 65–70 °C for 16 h. After cooling, 1,2-dichloroethane was removed under reduced pressure, the remaining slurry was poured onto ice and the mixture was extracted with Et_2O (3 × 250 mL) and EtOAc (4 × 250 mL). The combined organic layers were washed with water (4 × 400 mL) and brine (2 × 400 mL), dried ($MgSO_4$), and the solvent was removed in vacuo. Crystallisation from EtOAc/hexane provided **9** (11.9 g, 84%) as colourless needles. R_f = 0.63 (EtOAc/PE, 3:1). IR (KBr): $\tilde{\nu}$ = 3077, 2976, 2767, 1681 cm^{-1}. UV (CH_3CN): λ_{max} (log ε) = 202.5 nm (4.181), 228.0 (4.268), 272.5 (4.085), 302.0 (3.935). ^1H NMR (200 MHz, $CDCl_3$): δ = 3.88 (t, J = 6.1 Hz, 2 H, 2′-H_2), 3.97 (s, 3 H, OMe), 4.35 (t, J = 6.1 Hz, 2 H, 1′-H_2), 7.01 (d, J = 8.1 Hz, 1 H, 5-H), 7.43 (d, J = 1.8 Hz, 1 H, 2-H), 7.51 (dd, J = 8.1, 1.8 Hz, 1 H, 6-H), 9.86 (s, 1 H, CHO) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 41.5 (C-2′), 56.2 (OMe), 68.9 (C-1′), 111.0, 111.3 (C-2, C-5), 127.4 (C-6), 129.9 (C-1), 148.1 (C-3), 154.9 (C-4), 190.7 (CHO) ppm. MS (70 eV, EI): m/z (%) = 214 (100) $[M]^+$, 151 (57) $[M - (CH_2)_2Cl]^+$. $C_{10}H_{11}ClO_3$ (214.65): calcd. C 55.96, H 5.17; found 56.04, H 4.97.

Methyl 2-Azido-3-[3-(2-chloroethoxy)-4-methoxyphenyl]acrylate (10): NaN_3 (22.2 g, 341 mmol) was added slowly to a solution of methyl chloroacetate (20.0 mL, 227 mmol) in DMSO (100 mL). After stirring at room temperature for 24 h, water (150 mL) was added and the mixture was extracted with Et_2O (3 × 100 mL). The combined organic fractions were dried ($MgSO_4$) and concentrated in vacuo to 50 mL. Then, a solution of aldehyde **9** (5.37 g, 25.0 mmol) in MeOH (50 mL) was added and the mixture was cooled to –30 °C. After that, the reaction mixture was treated with 5.4 M NaOMe/MeOH (35.0 mL, 189 mmol) within 30 min at –30 °C, warmed to 0 °C and diluted with MeOH (50 mL). After stirring for 16 h at 0 °C, water (200 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 200 mL). The combined organic fractions were washed with brine (200 mL), dried ($MgSO_4$), and the solvent was removed in vacuo to give **10** (6.84 g, 88% from **9**) as a pale-yellow solid that was used for the next step without further purification. R_f = 0.44 (PE/EtOAc, 2:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 3.84 (t, J = 6.1 Hz, 2 H, 2′′-H_2), 3.87, 3.88 (2 × s, 6 H, OMe, CO_2Me), 4.29 (t, J = 6.1 Hz, 2 H, 1′′-H_2), 6.83 (s, 1 H, 1′-H), 6.87 (d, J = 8.5 Hz, 1 H, 5-H), 7.36 (dd, J = 8.5, 2.1 Hz, 1 H, 6-H), 7.53 (d, J = 2.1 Hz, 1 H, 2-H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 41.6 (C-2′′), 52.8 (CO_2Me), 56.0 (OMe), 69.3 (C-1′′), 111.5 (C-2), 116.2 (C-5), 123.4 (C-2′), 125.4, 126.0, 126.2 (C-1, C-1′, C-6), 147.1, 150.9 (C-3, C-4), 164.1 (C=O) ppm. $C_{13}H_{14}ClN_3O_4$ (311.72).

Methyl 5-(2-Chloroethoxy)-6-methoxy-1*H*-indole-2-carboxylate (11): A solution of **10** (6.81 g, 21.8 mmol) in toluene (200 mL) was heated at reflux for 4 h. After cooling to room temperature the reaction mixture was concentrated in vacuo and the formed precipitate was isolated by filtration and dried in vacuo to give **11** (4.48 g, 72%) as a pale-yellow solid. R_f = 0.24 (PE/EtOAc, 2:1). IR (KBr): $\tilde{\nu}$ = 3344, 2957, 1680 cm^{-1}. UV (CH_3CN): λ_{max} (log ε) = 208.5 nm (4.428), 318.0 (4.280). ^1H NMR (300 MHz, [D_6]DMSO): δ = 3.82, 3.84 (2 × s, 6 H, OMe, CO_2Me), 3.93 (t, J = 5.3 Hz, 2 H, 2′-H_2), 4.21 (t, J = 5.3 Hz, 2 H, 1′-H_2), 6.92 (s, 1 H, 7-H), 7.02 (d, J = 1.5 Hz, 1 H, 3-H), 7.15 (s, 1 H, 4-H), 11.62 (br. s, 1 H, NH) ppm. ^{13}C NMR (50.3 MHz, [D_6]DMSO): δ = 42.9 (C-2′), 51.3 (CO_2Me), 55.5 (OMe), 69.4 (C-1′), 94.8 (C-7), 105.6 (C-4), 107.9 (C-3), 119.7 (C-3a), 125.4 (C-2), 133.2 (C-7a), 144.1 (C-5), 149.8 (C-6), 161.4 (C=O) ppm. MS (70 eV, EI): m/z (%) = 283 (100) $[M]^+$, 220 (50) $[M - (CH_2)_2Cl]^+$. $C_{13}H_{14}ClNO_4$ (283.71): calcd. C 55.04, H 4.97; found C 54.86, H 5.06.

5-(2-Chloroethoxy)-6-methoxy-1*H*-indole-2-carboxylic Acid (12): A suspension of ester **11** (2.00 g, 7.05 mmol), Cs_2CO_3 (3.45 g, 10.6 mmol), 95% EtOH (40 mL) and water (20 mL) was heated at reflux for 8 h. After cooling to room temperature the solvent was removed in vacuo, the residue was treated with water (50 mL), and the resulting solution was acidified with 2 M HCl. The formed precipitate was isolated by filtration, washed with water (100 mL), and dried in vacuo to give **12** (1.80 g, 95%) as a beige solid. R_f = 0.30 (CH_2Cl_2/MeOH, 10:1, 1% concd. HCl). IR (KBr): $\tilde{\nu}$ = 3408, 3352, 2934, 1655 cm^{-1}. UV (CH_3CN): λ_{max} (log ε) = 209.0 nm (4.381), 316.5 (4.207). ^1H NMR (300 MHz, [D_6]DMSO): δ = 3.81 (s, 3 H, OMe), 3.93 (t, J = 5.3 Hz, 2 H, 2′-H_2), 4.21 (t, J = 5.3 Hz, 2 H, 1′-H_2), 6.91 (s, 1 H, 7-H), 6.96 (d, J = 2.1 Hz, 1 H, 3-H), 7.15 (s, 1 H, 4-H), 11.44 (br. s, 1 H, NH), 12.57 (br. s, 1 H, CO_2H) ppm. ^{13}C NMR (50.3 MHz, [D_6]DMSO): δ = 43.0 (C-2′), 55.6 (OMe), 69.5 (C-1′), 94.9 (C-7), 105.8 (C-4), 107.5 (C-3), 119.8 (C-3a), 126.8 (C-2), 133.0 (C-7a), 143.9 (C-5), 149.5 (C-6), 162.4 (C=O) ppm. MS (70 eV, EI): m/z (%) = 269 (100) $[M]^+$, 206 (58) $[M - (CH_2)_2Cl]^+$.

$C_{12}H_{12}ClNO_4$ (269.68): calcd. C 53.44, H 4.49; found C 53.54, H 4.29.

5-[2-(Dimethylamino)ethoxy]-6-methoxy-1*H*-indole-2-carboxylic Acid Hydrochloride (13): A mixture of acid **12** (300 mg, 1.11 mmol), 40% aqueous Me_2NH (2.81 mL, 22.2 mmol), Na_2CO_3 (295 mg, 2.78 mmol) and water (20 mL) was stirred at 100 °C for 1.5 h. After cooling to room temperature the solvent was removed in vacuo, the residue was dissolved in water (15 mL) and the resulting solution was acidified with 2 M HCl. Then, the solution was evaporated to dryness and the resulting crude product was purified by column chromatography on silica gel ($MeOH/CH_2Cl_2$, 10:1, 1% concd. HCl) to provide a green solid, which was dissolved in water. Silica gel was then removed by filtration, the water was removed under reduced pressure and the residue was dried in vacuo to give **13** (343 mg, 98%) as a grey-green solid. R_f = 0.30 (CH_2Cl_2/MeOH, 10:1, 1% concd. HCl). IR (KBr): $\tilde{\nu}$ = 3351, 3049, 2939, 1668 cm^{-1}. UV (CH_3CN): λ_{max} ($\log\varepsilon$) = 208.0 nm (4.384), 308.5 (4.160), 313.5 (4.158). ^1H NMR (300 MHz, [D$_6$]DMSO): δ = 2.87 (s, 6 H, NMe_2), 3.49 (t, J = 5.0 Hz, 2 H, 2′-H_2), 3.82 (s, 3 H, OMe), 4.34 (t, J = 5.0 Hz, 2 H, 1′-H_2), 6.94 (s, 1 H, 7-H), 6.97 (d, J = 1.8 Hz, 1 H, 3-H), 7.23 (s, 1 H, 4-H), 10.99 (br. s, 1 H, NH^+), 11.50 (br. s, 1 H, NH), 12.60 (br. s, 1 H, CO_2H) ppm. ^{13}C NMR (50.3 MHz, [D$_6$]-DMSO): δ = 42.7 (NMe_2), 55.2 (C-2′), 55.6 (OMe), 64.5 (C-1′), 94.8 (C-7), 106.2 (C-4), 107.5 (C-3), 119.7 (C-3a), 127.0 (C-2), 133.2 (C-7a), 143.4 (C-5), 149.4 (C-6), 162.4 (C=O) ppm. MS (70 eV, EI): m/z (%) = 278 (7) $[M - HCl]^+$, 58 (100) $[CH_2NMe_2]^+$. $C_{14}H_{19}ClN_2O_4$ (314.76): calcd. 278.1267 $[M - HCl]^+$; found 278.1267.

Ethyl 1-Methylpiperidine-4-carboxylate (15): Ethyl isonipecotate (**14**; 5.00 g, 31.8 mmol) was dissolved in an ice-cold mixture of glacial acetic acid (3.80 g, 63.6 mmol) and water (11 mL). Then, a 37% aqueous formaldehyde solution (2.85 mL, 38.2 mmol) was added and the reaction mixture was hydrogenated (Pd/C, 10%, 338 mg) at 58 psi H_2 for 3.5 h at room temperature. The solid was removed by filtration through celite, which was washed thoroughly with water (50 mL), and the filtrate was adjusted to pH 11 with 1 M NaOH under cooling. The resulting solution was extracted with Et_2O (5 × 100 mL), the combined organic fractions were dried ($MgSO_4$) and the solvent was removed under reduced pressure to provide **15** (5.44 g, quant.) as a colourless liquid that was used for the next step without further purification. R_f = 0.69 (CH_2Cl_2/MeOH, 10:1, 5% NEt_3; PMA: blue). IR (film): $\tilde{\nu}$ = 2940, 2845, 1733 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.25 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 1.69–2.06 (m, 6 H, 2-H_{ax}, 3-H_2, 5-H_2, 6-H_{ax}), 2.18–2.32 (m, 1 H, 4-H), 2.27 (s, 3 H, NMe), 2.75–2.87 (m, 2 H, 2-H_{eq}, 6-H_{eq}), 4.13 (q, J = 7.1 Hz, 2 H, OCH_2CH_3) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.1 (OCH_2CH_3), 28.2 (C-3, C-5), 40.5 (C-4), 46.3 (NMe), 54.9 (C-2, C-6), 60.2 (OCH_2CH_3), 175.0 (C=O) ppm. MS (70 eV, EI): m/z (%) = 171 (31) $[M]^+$, 142 (59) $[M - CH_2CH_3]^+$, 126 (40) $[M - OCH_2CH_3]^+$, 98 (56) $[M - CO_2Et]^+$. $C_9H_{17}NO_2$ (171.24).

(1-Methylpiperidin-4-yl)methanol (16): A solution of ester **15** (10.1 g, 59.0 mmol) in Et_2O (40 mL) was added dropwise to a suspension of $LiAlH_4$ (2.46 g, 64.9 mmol) in Et_2O (200 mL) at 0 °C. Then, the reaction mixture was warmed to room temperature and was stirred for 4 h at this temperature. Water (10 mL) was added slowly and stirring was continued for a further 30 min. The white precipitate formed was separated by filtration and washed thoroughly with Et_2O (250 mL). After removal of the solvent under reduced pressure the resulting oil was purified by distillation (b.p. 108 °C, 14 mbar) to give alcohol **16** (6.40 g, 84%) as a colourless oil. R_f = 0.53 (CH_2Cl_2/MeOH, 5:1, 5% NEt_3; PMA: dark blue). IR (film): $\tilde{\nu}$ = 3376, 2921, 1651 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.28 (dq, J = 12.2, 3.7 Hz, 2 H, 3-H_{ax}, 5-H_{ax}), 1.38–1.55 (m, 1 H, 4-H), 1.68–1.79 (m, 2 H, 3-H_{eq}, 5-H_{eq}), 1.93 (dt, J = 11.8, 2.3 Hz, 2 H, 2-H_{ax}, 6-H_{ax}), 2.26 (s, 3 H, NMe), 2.82–2.92 (m, 2 H, 2-H_{eq}, 6-H_{eq}), 3.12 (br. s, 1 H, OH), 3.46 (d, J = 6.4 Hz, 2 H, CH_2OH) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 28.8 (C-3, C-5), 37.9 (C-4), 46.3 (NMe), 55.5 (C-2, C-6), 67.4 (CH_2OH) ppm. MS (70 eV, EI): m/z (%) = 129 (55) $[M]^+$, 128 (100) $[M - H]^+$, 112 (10) $[M - OH]^+$, 98 (21) $[M - CH_2OH]^+$. $C_7H_{15}NO$ (129.20).

1-Methyl-4-[(4-nitrophenoxy)methyl]piperidine (18): A mixture of 1-chloro-4-nitrobenzene (**17**; 2.37 g, 15.0 mmol), alcohol **16** (1.94 g, 15.0 mmol) and DMSO (25 mL) was treated portionwise with NaH (60% in mineral oil, 660 mg, 16.5 mmol) at 40 °C. The mixture was stirred at 70 °C for 3 h, poured into water (150 mL) and extracted with Et_2O (5 × 100 mL). The combined organic fractions were washed with water (250 mL) and brine (250 mL), dried ($MgSO_4$) and the solvent was removed in vacuo. The resulting solid was recrystallised from Et_2O to give **18** (3.12 g, 83%) as yellow needles. R_f = 0.34 (CH_2Cl_2/MeOH, 10:1). IR (KBr): $\tilde{\nu}$ = 2982, 2856, 1503, 1338 cm^{-1}. UV (CH_3CN): λ_{max} ($\log\varepsilon$) = 220.5 nm (3.905), 311.0 (4.083). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.36–1.56 (m, 2 H, 3-H_{ax}, 5-H_{ax}), 1.75–1.91 (m, 3 H, 3-H_{eq}, 4-H, 5-H_{eq}), 1.98 (dt, J = 11.9, 1.9 Hz, 2 H, 2-H_{ax}, 6-H_{ax}), 2.30 (s, 3 H, NMe), 2.85–2.98 (m, 2 H, 2-H_{eq}, 6-H_{eq}), 3.90 (d, J = 5.8 Hz, 2 H, OCH_2), 6.94 (m_c, 2 H, 2′-H, 6′-H), 8.19 (m_c, 2 H, 3′-H, 5′-H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 28.9 (C-3, C-5), 35.1 (C-4), 46.4 (NMe), 55.3 (C-2, C-6), 73.3 (OCH_2), 114.3 (C-2′, C-6′), 125.8 (C-3′, C-5′), 141.3 (C-4′), 164.1 (C-1′) ppm. MS (70 eV, EI): m/z (%) = 250 (79) $[M]^+$, 249 (100) $[M - H]^+$. $C_{13}H_{18}N_2O_3$ (250.29): calcd. C 62.38, H 7.25; found C 62.25, H 7.40.

4-[(1-Methylpiperidin-4-yl)methoxy]phenylamine (19): A solution of 1-methyl-4-[(4-nitrophenoxy)methyl]piperidine (**18**; 1.0 g, 4.0 mmol), MeOH (20 mL) and concentrated HCl (1 mL) was hydrogenated (Pd/C, 10%, 100 mg) at 58 psi H_2 for 1 h at room temperature. Then, the solid was removed by filtration through celite, which was washed thoroughly with MeOH (200 mL), and the filtrate was concentrated in vacuo. The residue was dissolved in water (50 mL) and the resulting solution was adjusted to pH 10 with a saturated aqueous solution of $NaHCO_3$ and 2 M NaOH. The mixture was extracted with CH_2Cl_2 (3 × 100 mL), dried ($MgSO_4$) and the solvent was removed in vacuo. Purification by column chromatography (CH_2Cl_2/MeOH, 10:1, 2% NEt_3) gave **19** (0.72 g, 82%) as a reddish brown solid. R_f = 0.42 (CH_2Cl_2/MeOH, 10:1, 2% NEt_3). IR (KBr): $\tilde{\nu}$ = 3425, 3300, 3160, 2978 cm^{-1}. UV (CH_3CN): λ_{max} ($\log\varepsilon$) = 196.0 nm (4.538), 240.0 (4.016), 307.5 (3.393). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.31–1.48 (m, 2 H, 3′-H_{ax}, 5′-H_{ax}), 1.66–1.89 (m, 3 H, 3′-H_{eq}, 4′-H, 5′-H_{eq}), 1.96 (dt, J = 11.9, 2.3 Hz, 2 H, 2′-H_{ax}, 6′-H_{ax}), 2.28 (s, 3 H, NMe), 2.84–2.93 (m, 2 H, 2′-H_{eq}, 6′-H_{eq}), 3.41 (br. s, 2 H, NH_2), 3.73 (d, J = 6.4 Hz, 2 H, OCH_2), 6.60–6.67 (m, 2 H, 3-H, 5-H), 6.70–6.76 (m, 2 H, 2-H, 6-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 29.1 (C-3′, C-5′), 35.3 (C-4′), 46.4 (NMe), 55.4 (C-2′, C-6′), 73.2 (OCH_2), 115.4 (C-3, C-5), 116.3 (C-2, C-6), 139.8 (C-1), 152.2 (C-4) ppm. MS (70 eV, EI): m/z (%) = 220 (3) $[M]^+$, 112 (100) $[C_7H_{14}N]^+$. $C_{13}H_{20}N_2O$ (220.31): calcd. C 70.87, H 9.15; found C 70.50, H 8.94.

Ethyl 5-[(1-Methylpiperidin-4-yl)methoxy]-1*H*-indole-2-carboxylate (20): A solution of $NaNO_2$ (689 mg, 9.99 mmol) in water (2 mL) was added dropwise to a stirred solution of 4-[(1-methylpiperidin-4-yl)methoxy]phenylamine (**19**; 2.00 g, 9.08 mmol) in water (19 mL) and concentrated HCl (6 mL) at 0 °C and stirring was continued for 50 min at 0 °C (solution A). Ethyl 2-methylacetoacetate (1.39 mL, 9.53 mmol) was added dropwise to a stirred suspension

of NaOAc (7.8 g) in EtOH (15 mL) at 0 °C and stirring was continued for 30 min at this temperature; then ice (9 g) was added (solution B). Solution A was added to solution B by a transfer cannula at 0 °C and the mixture was warmed to room temperature. After 2.5 h the reaction mixture was basified by slow addition of a saturated aqueous solution of Na_2CO_3 at 0 °C and extracted with CH_2Cl_2 (3×100 mL). The combined organic layers were washed with water (200 mL), dried ($MgSO_4$), and the solvent was removed in vacuo. The residue was then dissolved in absolute EtOH (10 mL), treated with a freshly prepared saturated solution of HCl in absolute EtOH[34] (10 mL), and heated at reflux for 50 min. After cooling to room temperature the solvent was removed under reduced pressure and the residue was partitioned between water (50 mL) and CH_2Cl_2 (100 mL). The aqueous layer was basified with a saturated aqueous solution of Na_2CO_3 and extracted with CH_2Cl_2 (3×100 mL). The combined organic layers were washed with brine (200 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification by crystallisation from iPr_2O and column chromatography (CH_2Cl_2/MeOH, 30:1, 2% NEt_3) of the residue obtained after evaporation of the mother liquor provided **20** (2.06 g, 72% overall yield) as a yellow solid. R_f = 0.34 (CH_2Cl_2/MeOH, 10:1). IR (KBr): $\tilde{\nu}$ = 3312, 2965, 2926, 1689 cm^{-1}. UV (CH_3CN): λ_{max} ($\log\varepsilon$) = 215.0 nm (4.476), 294.0 (4.310), 324.5 (3.729). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.36–1.54 (m, 5 H, OCH_2CH_3, 3′-H_{ax}, 5′-H_{ax}), 1.73–2.06 (m, 5 H, 2′-H_{ax}, 3′-H_{eq}, 4′-H, 5′-H_{eq}, 6′-H_{ax}), 2.30 (s, 3 H, NMe), 2.87–2.97 (m, 2 H, 2′-H_{eq}, 6′-H_{eq}), 3.83 (d, J = 6.2 Hz, 2 H, ArOCH_2), 4.40 (q, J = 7.2 Hz, 2 H, OCH_2CH_3), 6.98 (dd, J = 8.9, 2.4 Hz, 1 H, 6-H), 7.05 (d, J = 2.0 Hz, 1 H, 3-H), 7.12 (m_c, 1 H, 4-H), 7.30 (d, J = 8.9 Hz, 1 H, 7-H), 9.11 (br. s, 1 H, NH) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 14.4 (OCH_2CH_3), 29.2 (C-3′, C-5′), 35.3 (C-4′), 46.4 (NMe), 55.5 (C-2′, C-6′), 60.9 (OCH_2CH_3), 73.2 (ArOCH_2), 103.4 (C-4), 108.1 (C-3), 112.7 (C-7), 117.2 (C-6), 127.8 (C-2, C-3a), 132.2 (C-7a), 154.1 (C-5), 162.0 (C=O) ppm. MS (70 eV, EI): m/z (%) = 316 (6) $[M]^+$, 112 (100) $[C_7H_{14}N]^+$. $C_{18}H_{24}N_2O_3$ (316.39): calcd. C 68.33, H 7.65; found C 68.03, H 7.84.

5-[(1-Methylpiperidin-4-yl)methoxy]-1*H*-indole-2-carboxylic Acid Hydrochloride (21): A suspension of ester **20** (1.00 g, 3.16 mmol) in MeOH (8 mL) was treated with a solution of NaOH (155 mg, 3.88 mmol) in water (4 mL) and heated at reflux for 3.5 h. After cooling to room temperature, the solution was adjusted to pH 6 with 2 M HCl and the solvent was removed under reduced pressure. The residue was dissolved in MeOH, 2 M HCl was added dropwise, and the formed precipitate was collected by filtration to give **21** (712 mg, 69%) as a brown solid. The residue obtained after evaporation of the mother liquor was purified by column chromatography (CH_2Cl_2/MeOH, 6:1, 1% concd. HCl) to provide a second batch of **21** (226 mg, 22%). R_f = 0.23 (CH_2Cl_2/MeOH, 6:1, 1% concd. HCl). IR (KBr): $\tilde{\nu}$ = 3251, 3077, 2735, 1728 cm^{-1}. UV (MeOH): λ_{max} ($\log\varepsilon$) = 216.0 nm (4.447), 290.5 (4.215). ^1H NMR (300 MHz, [D_6]DMSO): δ = 1.56–1.77 (m, 2 H, 3′-H_{ax}, 5′-H_{ax}), 1.89–2.09 (m, 3 H, 3′-H_{eq}, 4′-H, 5′-H_{eq}), 2.69 (s, 3 H, NMe), 2.87–3.05 (m, 2 H, 2′-H_{ax}, 6′-H_{ax}) 3.24–3.48 (m, 2 H, 2′-H_{eq}, 6′-H_{eq}), 3.79–3.92 (m, 2 H, ArOCH_2), 6.90 (dd, J = 9.0, 2.2 Hz, 1 H, 6-H), 6.98 (d, J = 1.7 Hz, 1 H, 3-H), 7.12 (d, J = 2.2 Hz, 1 H, 4-H), 7.34 (d, J = 9.0 Hz, 1 H, 7-H), 10.84 (br. s, 1 H, NH^+), 11.59 (s, 1 H, NH), 12.74 (br. s, 1 H, CO_2H) ppm. ^{13}C NMR (75.5 MHz, [D_6]-DMSO): δ = 25.8 (C-3′, C-5′), 32.8 (C-4′), 42.5 (NMe), 52.8 (C-2′, C-6′), 71.6 (OCH_2), 103.4 (C-4), 106.8 (C-3), 113.3 (C-7), 116.0 (C-6), 127.1 (C-2), 128.7 (C-3a), 132.6 (C-7a), 152.9 (C-5), 162.5 (C=O) ppm. MS (70 eV, EI): m/z (%) = 288 (14) $[M - HCl]^+$, 112 (100) $[C_7H_{14}N]^+$. $C_{16}H_{21}ClN_2O_3$ (324.80): calcd. 288.1474 $[M - HCl]^+$; found 288.1474.

Ethyl 5-[2-(Dimethylamino)acetylamino]-1*H*-indole-2-carboxylate (24): A solution of 5-nitro-1*H*-indole-2-carboxylic acid ethyl ester (**22**; 750 mg, 3.20 mmol) in EtOAc (125 mL) was hydrogenated (Pd/C, 10%, 300 mg) at 60 psi H_2 for 5 h at room temperature. Then, the solid was removed by filtration through celite, which was washed thoroughly with CH_2Cl_2 (400 mL) and MeOH (400 mL), and the filtrate was concentrated in vacuo. The residue was dissolved in DMF (30 mL) and the solution was cooled to 0 °C. EDC·HCl (1.84 g, 9.60 mmol) and *N*,*N*-dimethylglycine hydrochloride (670 mg, 4.80 mmol) were added and the reaction mixture was warmed to room temperature. After stirring for 21 h at this temperature, the solution was diluted with EtOAc (100 mL) and water (100 mL). The mixture was adjusted to pH 9 with a saturated aqueous solution of $NaHCO_3$ and extracted with EtOAc (4×150 mL). The combined organic fractions were washed with water (4×200 mL) and brine (300 mL), dried ($MgSO_4$), and the solvent was removed in vacuo. Purification by column chromatography (CH_2Cl_2/MeOH, 10:1) gave **24** (626 mg, 68% overall yield) as a pale-brown solid. R_f = 0.46 (CH_2Cl_2/MeOH, 10:1). IR (KBr): $\tilde{\nu}$ = 3315, 2981, 1696, 1667 cm^{-1}. UV (CH_3CN): λ_{max} ($\log\varepsilon$) = 248.0 nm (4.503), 295.5 (4.262). ^1H NMR (200 MHz, $CDCl_3$): δ = 1.42 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 2.40 (s, 6 H, NMe_2), 3.11 (s, 2 H, 1′-H_2), 4.41 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 7.18 (d, J = 1.8 Hz, 1 H, 3-H), 7.36 (d, J = 8.8 Hz, 1 H, 7-H), 7.43 (dd, J = 8.8, 1.8 Hz, 1 H, 6-H), 8.04 (br. s, 1 H, 4-H), 9.04 (br. s, 1 H, NH), 9.13 (br. s, 1 H, NH) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 14.3 (OCH_2CH_3), 46.0 (NMe_2), 61.0 (OCH_2CH_3), 63.6 (C-1′), 108.5 (C-3), 112.2, 112.8 (C-4, C-7), 119.2 (C-6), 127.5, 128.2 (C-2, C-3a), 131.1 (C-5), 134.1 (C-7a), 162.0 (NHCO), 168.6 (CO_2Et) ppm. MS (70 eV, EI): m/z (%) = 289 (25) $[M]^+$, 58 (100) $[CH_2NMe_2]^+$. $C_{15}H_{19}N_3O_3$ (289.33): calcd. 289.1426; found 289.1426.

5-[2-(Dimethylamino)acetylamino]-1*H*-indole-2-carboxylic Acid Hydrochloride (25): A mixture of ester **24** (0.200 g, 0.691 mmol), THF (6 mL), MeOH (2 mL) and water (2 mL) was treated with $LiOH·H_2O$ (0.035 g, 0.830 mmol) and stirred at 60 °C for 4 h. After that, the solvent was removed in vacuo and the residue dissolved in water. The resulting solution was acidified with 2 M HCl, water was then evaporated under reduced pressure and the residue was taken up in acetone/EtOH (1:1). The remaining precipitate (LiCl) was separated by filtration and the filtrate was concentrated under reduced pressure. Purification of the crude product by column chromatography (CH_2Cl_2/MeOH, 5:1, 0.5% concd. HCl) provided acid **25** (0.205 g, quant.) as a pale-yellow solid. R_f = 0.19 (CH_2Cl_2/MeOH, 5:1, 0.5% concd. HCl). IR (KBr): $\tilde{\nu}$ = 3324, 3086, 1671, 1601 cm^{-1}. UV (MeOH): λ_{max} ($\log\varepsilon$) = 201.5 nm (4.215), 249.0 (4.426), 294.0 (4.107). ^1H NMR (300 MHz, [D_6]DMSO): δ = 2.89 (s, 6 H, NMe_2), 4.16 (s, 2 H, 1′-H_2), 7.07 (d, J = 2.1 Hz, 1 H, 3-H), 7.38–7.46 (m, 2 H, 6-H, 7-H), 8.01 (br. s, 1 H, 4-H), 10.11 (br. s, 1 H, NH^+), 10.80 (br. s, 1 H, NH), 11.74 (br. s, 1 H, NH), 12.90 (br. s, 1 H, CO_2H) ppm. ^{13}C NMR (50.3 MHz, [D_6]DMSO): δ = 43.1 (NMe_2), 57.8 (C-1′), 107.3 (C-3), 112.1, 112.6 (C-4, C-7), 118.4 (C-6), 126.6, 129.2 (C-2, C-3a), 130.9 (C-5), 134.4 (C-7a), 162.4, 162.5 (2×C=O) ppm. MS (70 eV, EI): m/z (%) = 261 (7) $[M - HCl]^+$, 58 (100) $[C_3H_8N]^+$. $C_{13}H_{16}ClN_3O_3$ (297.74): calcd. 261.1113 $[M - HCl]^+$; found 261.1113.

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