Synthesis, NMR conformational analysis and pharmacological evaluation of 7,7a,13,14-tetrahydro-6*H*-cyclobuta[*b*]pyrimido[1,2-*a*:3,4-*a*′]diindole analogues as melatonin receptor ligands†

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A structure for the self-condensation product of 2-(1*H*-indol-2-yl)ethyl tosylate **2a**, previously proposed as 6,7,14,15-tetrahydro-15a*H*-azocino[1,2-*a*:6,5-*b*]diindole **3a**, was revised based on the ^{13}C-2D-INADEQUATE experiment, and proved to be 7,7a,13,14-tetrahydro-6*H*-cyclobuta[*b*]pyrimido[1,2-*a*:3,4-*a*′]diindole **4a**. A mechanism for the unexpected formation of this novel hexacyclic heterocycle was proposed and its NMR solution structure was elucidated. Five derivatives of the title ring skeleton **12–16** designed as melatonin receptor ligands were synthesized and their affinities for the human MT_1 and MT_2 receptors were determined. Both butyramides **13** and **15**, as well as the non-methoxy acetamide **12** exhibited micromolar binding affinities for both receptors being slightly MT_2 selective. The methoxy acetamide **14** showed the best pharmacological profile exhibiting a five times higher affinity for MT_1 (K_i = 49 nM) than for MT_2 (K_i = 246 nM) receptor.

Introduction

Melatonin **1** (Fig. 1) is a neurohormone exerting its diverse pharmacological actions mostly through activation of two G-protein-coupled receptors MT_1 and MT_2.[1]

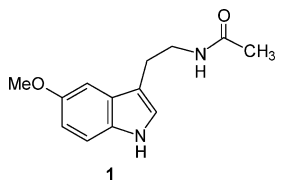

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Fig. 1 Structure of melatonin **1**.

Examination of the physiological roles of these receptors, which are not as yet clearly defined, requires MT_1 and MT_2 selective ligands. However, pronounced subtype selectivity is still a challenge, and only recently a limited number of selective compounds have been identified.[2] The majority of subtype selective agents behave as MT_2 receptor antagonists. A common structural feature in most of MT_2 selective antagonists is the presence of a lipophilic substituent located out of the plane of their core nucleus in a position corresponding to positions 1 and 2 of the indole in melatonin.[3] However, there are only limited studies concerning the steric tolerance of the hydrophobic binding pocket accommodating this lipophilic group.[4]

In the course of our studies on allosteric ligands of muscarinic M_2 receptors, we reported the self-condensation of **2a** to give the pentacyclic 6,7,14,15-tetrahydro-15a*H*-azocino[1,2-*a*:6,5-*b*]diindole **3a** using NaH in DMF.[5] The unusual formation of compound **3a** was explained by an ambident nucleophilic character of the indolyl anion, which can be alkylated either at N or at C-3. Based on this result, we became interested in the synthesis of a potential melatonergic ligand by applying the same procedure to the tosylate of 5-methoxyindol-2-yl ethanol **2b** to obtain **3b** and a subsequent introduction of the melatonin-like side chain. The desired compound is formally derived from melatonin by attaching the indole moiety to N-1 and C-2 *via* ethylene spacers, and therefore, it could be useful for probing the aforementioned pharmacophore for MT_2 antagonists with respect to location and size of the hydrophobic binding pocket. In order to determine the 3D structure of the ring system **3a**, we analysed the NOESY spectrum of **3a** finding several NOE interactions which were not consistent with our previously proposed structure. To our great surprise, analysis of the ^{13}C-2D-INADEQATE spectrum revealed that the condensation product of **2a** was not the previously reported pentacyclic ring system **3a**, but the isomeric hexacyclic ring skeleton **4a** (Scheme 1). In the first part of this paper, we describe the structure elucidation and NMR conformational analysis of this novel 7,7a,13,14-tetrahydro-6*H*-cyclobuta[*b*]pyrimido[1,2-*a*:3,4-*a*′]diindole ring system. The second part reports the synthesis of some analogues of the novel ring scaffold designed as melatonergic ligands and their pharmacological evaluation.

Results and discussion

Structure elucidation of compound 4a

The conclusions drawn from the NMR spectra which led to the previously assigned structure **3a** also apply to the novel ring **4a**.

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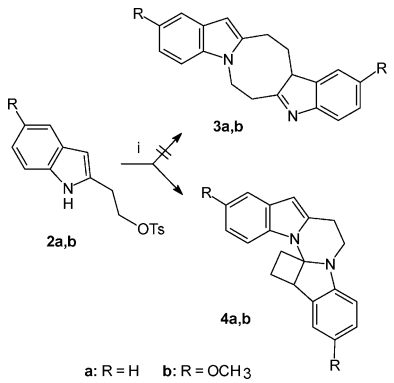
† Electronic supplementary information (ESI) available: NOESY spectrum of **4a** and the illustration of the observed NOEs in the 3D structure of **4a**. See DOI: 10.1039/b705550a



Scheme 1 *Reagents and conditions*: (i) NaH, DMF, 0 °C–rt.

Thus, analysis of the ^{1}H–^{1}H-COSY, and HMQC data established the presence of four independent spin systems including two indole moieties and two aliphatic chains identified as -CH-CH_2-CH_2- and -CH_2-CH_2-. The complete carbon sequence was now obtained by means of a ^{13}C-2D-INADEQATE spectrum displayed in Fig. 2. The most easily assignable resonance signal belonging to the indolic carbon C-15 (δ 98.4) was used as a starting point. This signal exhibited correlations with signals resonating at δ 128.9 (C-15a) and δ 135.3 (C-14a). From the latter, we could obtain the chemical shift of C-14 (δ 21.7), which in turn was correlated with C-13 (δ 36.6). Since C-13 shows no further cross peaks, the ethylene moiety 14-CH_2-13-CH_2- must be connected to a nitrogen atom. The second substructure can be deduced starting from the quaternary carbon C-5a. Its chemical shift (δ 83.3) indicates that C-5a is located between both nitrogen atoms. Further direct coupling partners of C-5a are the methine carbon C-7a (δ 48.1) and the methylene carbon C-6 (δ 34.2), which in turn are both connected with the same methylene carbon C-7 (δ 21.5) clearly indicating the presence of the cyclobutane ring incorporating the carbon atoms 5a, 6, 7, and 7a. The position of this four-membered ring could be identified by the correlation between C-7a (δ 48.1) and the aromatic carbon C-7b (δ 132.2). The assignment in both indole substructures was accomplished by following the coupling paths starting from the already assigned carbon atoms C-15a and C-7b.

Conformational analysis

The structure of the ring scaffold **4a** was first submitted to a conformational analysis using the Cartesian method of the steric energy minimization program GLOBAL-MMX implemented in PCModel 9.0 (Serena Software)[6] yielding two minimum geometries which were further optimized by means of semiempirical PM3 calculations of HyperChem 7.1 (Hypercube Inc.).[7] The resulting possible conformations A and B are depicted in Fig. 3. The central six-membered rings of A and B adopt different conformations leading to a slightly different relative position of the aromatic rings.

The 3D solution structure of the novel ring system was examined by means of a 600 MHz NOESY spectrum shown in the supplementary information†. Unfortunately, due to the

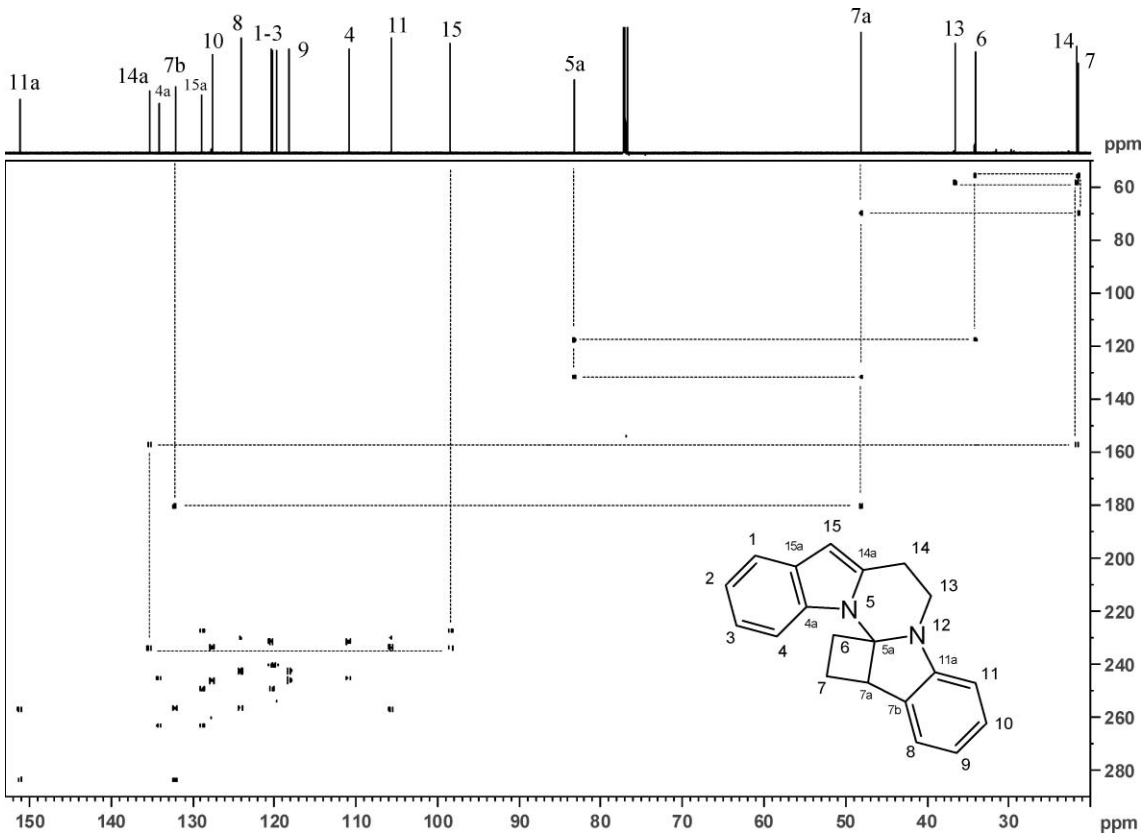


Fig. 2 ^{13}C NMR 2D-INADEQUATE (150.9 MHz) contour plot of **4a** (70 mg in 0.7 mL $CDCl_3$, ^{13}C optimized 5 mm DCH cryoprobe, total acquisition time 66 h).

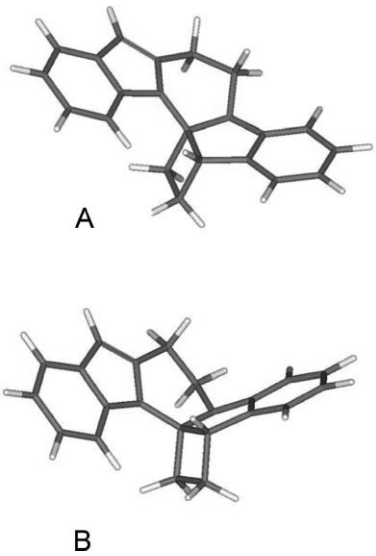
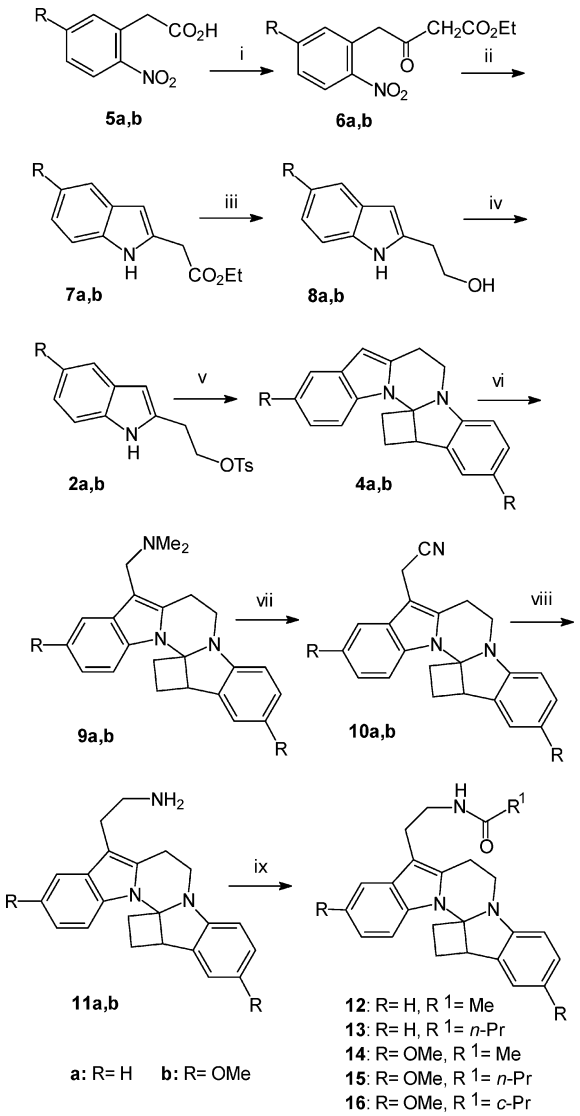


Fig. 3 Low energy conformations of compound **4a** (PM3 calculations of HyperChem 7.1).

very similar geometries of A and B the majority of the NOEs detected are consistent with both conformations. The only NOE signal clearly suggesting the presence of conformation B was the strong interaction between the aromatic proton H-4 and the methylene proton H^b-6 being in agreement with the H-4–H^b-6 distance of 2.27 Å (the corresponding distance in the conformer A is 3.34 Å). Furthermore, the equally strong H-7a–H-4 and H-7a–H-8 cross signals also indicate the presence of conformer B being consistent with the respective distances of 2.76 Å and 2.90 Å (the corresponding H-7a–H-4 and H-7a–H-8 distances in conformer A are 1.81 Å and 2.94 Å, respectively). The essential NOEs of compound **4a** are shown in the supplementary information. The preferred conformer B has, in fact, a slightly lower total energy than conformer A ($\Delta E = 0.47$ kcal mol^{-1}).

Chemistry

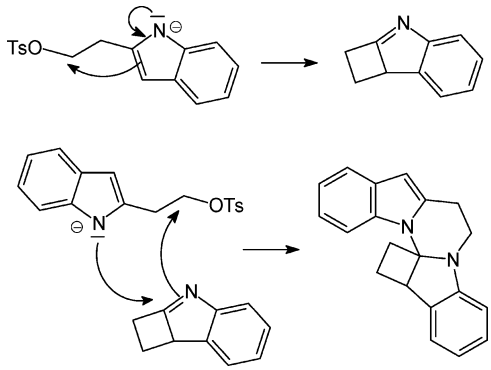
The synthetic route applied for the preparation of the desired melatonergic ligands derived from the novel ring system is shown in Scheme 2. Starting materials for the nine step synthesis were the commercially available 2-nitrophenyl acetic acid **5a** and the known 5-methoxy-2-nitrophenyl acetic acid **5b**.[8] The β-ketoesters **6a** and **6b** were prepared under conditions reported by Mai *et al.*[9] involving the reaction of potassium ethyl malonate with **5a** and **5b**-imidazolides in the presence of the magnesium dichloride–triethylamine system in 94% and 90% yield, respectively. Transfer hydrogenation of **6a** and **6b** using ammonium formate and a catalytic amount of 10% Pd/C in absolute ethanol and the subsequent spontaneous ring closure afforded the indole-2-acetates **7a** (90%) and **7b** (89%). Reduction of the ester groups using $LiAlH_4$ in THF provided the alcohols **8a** (79%) and **8b** (85%) which could be converted to the corresponding tosylates **2a** and **2b** in 70% and 64% yield, respectively. In the next crucial double-alkylation step, **2a** and **2b** were treated with an excess of NaH in DMF affording the hexacyclic heterocycles **4a** and **4b** as exclusive dimerisation products in 46% and 45% yield, respectively. From both reactions, small quantities of impure elimination by-products, 2-vinylindole and 5-methoxy-2-vinylindole could be



Scheme 2 *Reagents and conditions*: (i) 1. CDI, MeCN, rt, 2. potassium ethyl malonate, NEt_3, $MgCl_2$, MeCN, rt–reflux, 3. 13% HCl aq., rt; (ii) HCO_2NH_4, Pd/C 10%, EtOH, rt; (iii) $LiALH_4$, THF, 0 °C–rt; (iv) TsCl, NEt_3, CH_2Cl_2, rt; (v) NaH, DMF, 0 °C–rt; (vi) $(CH_2{=}NMe_2)^+Cl^-$, CH_2Cl_2, reflux; (vii) 1. MeI, CH_2Cl_2, rt, 2. KCN, dicyclohexyl-[18]-crown-[6], MeCN, reflux; (viii) $LiALH_4$, Et_2O, toluene, 40 °C; (ix) respective acylation agent, Et_3N, CH_2Cl_2, rt.

isolated. The unprecedented formation of the title ring system can be explained by the proposed mechanism displayed in Scheme 3. The ambident indolyl anion, built by *N*-deprotonation of **2a** with NaH, can be alkylated either at N or at C-3. In the first step, the four-membered ring was built in the intramolecular nucleophilic substitution with C-3 acting as a nucleophilic center. The so obtained imine was subsequently attacked by another indolyl anion yielding **4a** as a result of a double *N*-alkylation.

In order to obtain ligands binding at melatonin receptors, we first introduced the ethylamine side chain into **4a** and **4b** at the position corresponding to C-3 of melatonin using the procedure we previously applied for another ring system.[10] Our approach involved a sequence of a Mannich reaction, quaternization of the Mannich base, substitution of the trimethylamine moiety



Scheme 3 Proposed mechanism for the formation of compound **4a**.

by a cyanide, and a final reduction of the cyanomethyl group to the ethylamine moiety. Thus, aminomethylation of **4a** and **4b** using dimethylmethyleneammonium chloride in dichloromethane afforded the Mannich bases **9a** and **9b** in 78% and 95% yield, respectively. Treatment of **9a** and **9b** with methyl iodide in dichloromethane and heating of the resulting trimethylammonium iodides with potassium cyanide and dicyclohexyl-[18]-crown-[6] in acetonitrile provided the nitriles **10a** (92%) and **10b** (90%), respectively. Reduction of **10a** and **10b** using $LiAlH_4$ in diethyl ether and toluene afforded the ethylamines **11a** and **11b**, respectively, in a quantitative yield. Finally, both amines could be easily converted to the desired melatonergic ligands **12–16** by *N*-acylations using acetic anhydride (**12**, **14**), butyric anhydride (**13**, **15**), and cyclopropane carboxylic acid chloride (**16**) in good yields.

Pharmacology

The affinity of compounds **12–16** for human MT_1 or MT_2 melatonin receptors was measured by competition binding analysis using the radioligand 2-[^{125}I]-iodomelatonin as described.[11] Melatonin competition assays were run in parallel and the affinity of melatonin for the MT_1 (K_i = 457 pM) or MT_2 (K_i = 955 pM) melatonin receptors was in the range of the reported literature.[11]

As shown in Table 1, the non-methoxy acetamide **12** exhibits rather poor micromolar binding affinity for both melatonin receptors. Substitution of the *N*-acetyl group by a butyryl substituent yielding the butyramide **13** had no significant effect on binding affinity and selectivity. Melatonergic ligands bearing a methoxy substituent in a position equivalent to C-5 of melatonin display generally considerably higher binding affinities than the corresponding non-methoxy analogues.[2] However, this affinity trend could be confirmed only in the acetamide series. Thus, while the methoxy butyramide **15** exhibited nearly unchanged binding constants at both receptor subtypes when compared to the non-methoxy butyramide **13**, the methoxy acetamide **14** displayed 22-fold higher affinity for the MT_1 subtype and 3-fold higher affinity for the MT_2 subtype than the non-methoxy analogue **12**. Comparison of the binding constants at MT_1 (K_i = 49 nM) and MT_2 (K_i = 246 nM) receptors indicates that **14** is five times more selective for MT_1 than for MT_2 receptors. The MT_1-selectivity of **14** is rather surprising, taking into account that most compounds of this series seem to be slightly MT_2-selective. In a series of benzoxazole derivatives, the MT_1-selectivity could be improved by replacing the *N*-acetyl substituent with a cyclopropylcarbonyl moiety.[13] However, this did not occur in our series. In fact, the selectivity of the cyclopropanecarboxamide **16** for the melatonin receptors worsened from being five times more selective for MT_1 to only 1.4 times more selective for MT_1 (K_i = 385 nM) than MT_2 (K_i = 547 nM).

Table 1 Binding affinity[a] of compounds **12–16** for the human MT_1 and MT_2 receptors expressed in CHO cells obtained in competition radioligand binding assays using 2-[^{125}I]-iodomelatonin

	pK_i MT_1 ± SEM	pK_i MT_2 ± SEM
Melatonin	9.34 ± 0.10	9.02 ± 0.09
12	5.96 ± 0.14	6.15 ± 0.25
13	5.92 ± 0.03	6.36 ± 0.07
14	7.31 ± 0.07	6.61 ± 0.09
15	5.89 ± 0.12	6.20 ± 0.03
16	6.41 ± 0.10	6.26 ± 0.07

[a] pK_i values were calculated from IC_{50} values obtained from competitive curves according to the method of Cheng and Prusoff[12] and are the mean of at least three determinations.

Conclusions

In summary, in search for subtype selective ligands of melatonin receptors, we synthesized five derivatives of the novel 7,7a,13,14-tetrahydro-6*H*-cyclobuta[*b*]pyrimido[1,2-*a*:3,4-*a*′]diindole ring system. The non-methoxy and methoxy analogues **12**, **13** and **14–16**, respectively, were prepared in nine steps starting from the corresponding 2-nitrophenyl acetic acids. A mechanism for the unprecedented formation of the title ring system was proposed and its NMR solution structure was elucidated. Both butyramides **13** and **15**, as well as the non-methoxy acetamide **12** exhibited rather poor micromolar binding affinities for the human MT_1 and MT_2 receptors being slightly MT_2 selective. The findings indicate that the bulkiness and/or the spatial orientation of the cyclobutanoindole moiety is unfavourable for receptor binding at both subtypes. With respect to the MT_2 receptor, its hydrophobic pocket usually accommodating lipophilic substituents in positions corresponding to N-1 or C-2 of melatonin seems to be sterically restricted. The methoxy acetamide **14** showed the best pharmacological profile exhibiting surprisingly a five times higher affinity for MT_1 (K_i = 49 nM) than for MT_2 (K_i = 246 nM) receptors. Finally, the selectivity for the MT_1 receptor could not be improved by replacing the *N*-acetyl substituent with a cyclopropylcarbonyl moiety as occurred previously.[13]

Experimental

Melting points were determined using a capillary melting point apparatus (Gallenkamp, Sanyo) and are uncorrected. Column chromatography was carried out on silica gel 60 (0.063–0.200 mm) obtained from Merck. Bruker AV-400 and AV-600 spectrometers were used to obtain ^{1}H NMR and ^{13}C NMR spectra, respectively. Proton chemical shifts are referenced to $CHCl_3$ (7.24 ppm). *J* values are given in Hz. Carbon chemical shifts are referenced to $CDCl_3$ (77.00 ppm). The NMR resonances were assigned by means of HH-COSY, HMQC, and HMBC experiments. EI mass spectra were determined on Finnigan MAT 8200, Finnigan MAT 90, and on ESI-microTOF spectrometers. IR spectra, recorded as ATR, were obtained using a Biorad PharmalyzIR FT-IR instrument. Elemental analyses were performed by the microanalytical section

of the Institute of Inorganic Chemistry, University of Würzburg. All reactions were carried out under an argon atmosphere.

General procedure for the synthesis of 6a,b

Triethylamine (8.7 ml, 62.4 mmol) was added to a stirred suspension of potassium ethyl malonate (6.97 g, 40.95 mmol) and anhydrous magnesium chloride (4.64 g, 48.73 mmol) in dry acetonitrile (50 ml) and the reaction mixture was stirred for 2 h at room temperature. A solution of the appropriate imidazolide, prepared by stirring the respective phenylacetic acid **5a,b** (19.49 mmol) and *N*,*N*-carbonyldiimidazole (CDI; 3.47 g, 21.40 mmol) in dry acetonitrile (20 ml) for 15 min at room temperature, was added dropwise to the resulting reaction mixture. The reaction was allowed to stir for 18 h at room temperature and then heated at reflux for 2 h. 13% Hydrochloric acid (50 ml) was added dropwise while keeping the temperature below 25 °C. The resulting clear mixture was stirred at room temperature for 15 min and then the organic phase was separated and evaporated under reduced pressure. The residue was dissolved in ethyl acetate (50 ml). The aqueous phase was extracted with ethyl acetate (2 × 50 ml). The combined organic layers were washed with saturated $NaHCO_3$ solution (3 × 30 ml), saturated sodium chloride solution (2 × 30 ml), dried (Na_2SO_4) and evaporated under vacuum to afford **6a,b** as viscous oils that were solidified by cooling at −30 °C. Crude products were sufficiently pure to be used in the next step without further purification. Analytical samples were obtained by recrystallization from ethanol.

Ethyl 3-oxo-4-(2-nitrophenyl)butanoate (6a). **6a** (4.60 g, 94%) was obtained from **5a** (3.53 g) as a pale yellow solid. The analytical data of **6a** were identical to those previously reported.[14]

Ethyl 4-(5-methoxy-2-nitrophenyl)-3-oxobutanoate (6b). **6b** (4.9 g, 90%) was obtained from **5b** (4.12 g) as a pale yellow solid (Found: C, 55.14; H, 5.41; N, 4.98. $C_{13}H_{15}NO_6$ requires C, 55.51; H, 5.38; N, 4.98%); mp 67–68 °C; ν_{max}/cm^{-1}: 2990, 2910, 1740, 1720, 1607, 1588, 1505, 1329, 1261, 1211, 1132, 1211, 1072, 1020, 860, 841, 752; δ_H (400 MHz, $CDCl_3$) 1.27 (3H, t, *J* 7.1, CH_2-CH_3), 3.60 (2H, s, CH_2), 3.86 (3H, s, OCH_3), 4.19 (2H, q, *J* 7.1, CH_2-CH_3), 4.20 (2H, s, C_6H_3-CH_2), 6.72 (1H, d, *J* 2.8, 6-H), 6.88 (1H, dd, *J* 2.8, 9.2, 4-H), 8.16 (1H, d, *J* 9.2, 3-H); δ_C (100 MHz, $CDCl_3$) 14.07 (CH_2-CH_3), 48.41 (C_6H_3-CH_2), 49.36 (CH_2), 55.90 (OCH_3), 61.49 (CH_2-CH_3), 113.21 (C-4), 118.81 (C-6), 128.08 (C-3), 132.75 (C-1), 141.25 (C-5), 163.52 (C-2), 167.06 (ester), 198.19 (ketone); *m*/*z* (EI): 281.1 (2%, M^+), 194.1 (10), 167.2 (9), 150.2 (100), 122.2 (15), 87.1 (13).

General procedure for the synthesis of 7a,b

Ammonium formate (9.51 g, 142.2 mmol) was added to a stirred suspension of the appropriate β-ketoester **6a,b** (12.5 mmol) and 10% Pd/C (0.35 g) in absolute ethanol (80 ml). The resulting reaction mixture was stirred for 1 h at room temperature. The precipitates were removed by filtration and the solvent was evaporated under vacuum. The residue was dissolved in diethyl ether (40 ml) and washed with water (2 × 20 ml). The ether layer was dried (Na_2SO_4) and evaporated under reduced pressure to afford **7a,b** as viscous oils that were solidified by cooling at −30 °C. The crude products were used without further purification in the next step. Analytical samples were obtained by recrystallization from isopropanol.

Ethyl 1*H*-indol-2-ylacetate (7a). **7a** (2.30 g, 90%) was obtained from **6a** (3.14 g) as a light brown solid. The spectral data of **7a** were identical to those previously reported.[14]

Ethyl (5-methoxy-1*H*-indol-2-yl)acetate (7b). **7b** (2.60 g, 89%) was obtained from **6b** (3.52 g) as colourless crystals (Found: C, 66.76; H, 6.54; N, 5.92. $C_{13}H_{15}NO_3$ requires C, 66.94; H, 6.48; N, 6.00%); mp 57–59 °C; ν_{max}/cm^{-1}: 3404, 2990, 2911, 1722, 1624, 1591, 1487, 1319, 1026, 840, 800, 731; δ_H (400 MHz, $CDCl_3$) 1.29 (3H, t, *J* 7.1, CH_2-CH_3), 3.79 (2H, s, CH_2), 3.84 (3H, s, OCH_3), 4.20 (2H, q, *J* 7.1, CH_2-CH_3), 6.25 (1H, s, 3-H), 6.81 (1H, dd, *J* 2.6, 8.8, 6-H), 7.02 (1H, d, *J* 2.5, 4-H), 7.21 (1H, d, *J* 8.8, 7-H), 8.59 (1H, s, NH); δ_C (100 MHz, $CDCl_3$) 14.10 (CH_2-CH_3), 33.95 (CH_2), 55.81 (OCH_3), 61.31 (CH_2-CH_3), 101.58 (C-3), 102.05 (C-4), 111.43 (C-7), 111.70 (C-6), 128.62, 131.27, 131.45 (C-2, C-2a, C-7a), 154.14 (C-5), 170.57 (ester); *m*/*z* (EI): 233.1 (56%, M^+), 160.1 (100), 145.1 (13), 117.1 (14), 89.1 (5).

General procedure for the synthesis of 8a,b

A solution of the respective indolyl acetate **7a,b** (10 mmol) in dry THF (50 mL) was added dropwise to an ice-cooled and stirred suspension of $LiALH_4$ (2 g) in dry THF (50 mL). The reaction mixture was stirred at room temperature for 4 h and water (10 mL) was carefully added under ice-cooling. After vigorous stirring for 1 h at room temperature the precipitated solid was removed by filtration and washed with THF (2 × 30 mL). The combined THF solutions were dried (Na_2SO_4), evaporated under vacuum and the residual oil was purified by silica gel chromatography (ethyl acetate–n-hexane 1 : 1).

2-(1*H*-Indol-2-yl)ethanol (8a). **8a** (1.28 g, 79%) was obtained from **7a** (2.03 g) as a colourless oil showing the same analytical data as reported in the literature.[5]

2-(5-Methoxy-1*H*-indol-2-yl)ethanol (8b). **8b** (1.63 g, 85%) was obtained from **7b** (2.33 g) as a slightly yellow oil ($C_{11}H_{13}NO_2^+$ required 191.0941, found 191.0916); ν_{max}/cm^{-1}: 3395 br, 2941, 2831, 1624, 1588, 1483, 1451, 1222, 1199, 1166, 1026, 780; δ_H (400 MHz, $CDCl_3$) 2.90 (2H, t, *J* 5.8, CH_2-CH_2-OH), 3.82 (3H, s, -OCH_3), 3.86 (2H, t, *J* 5.8, CH_2-CH_2-OH), 6.18 (1H, br s, 3-H), 6.77 (1H, dd, *J* 8.8, 2.5, 6-H), 7.00 (1H, d, *J* 2.5, 4-H), 7.15 (1H, d, *J* 8.8, H-7), 8.40 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) 31.25 (CH_2-CH_2-OH), 55.89 (OCH_3), 62.13 (CH_2-CH_2-OH), 99.98 (C-3), 101.99 (C-4), 111.07 (C-6), 111.20 (C-7), 128.91 (C-3a), 131.23 (C-2), 137.82 (C-7a), 154.01 (C-5); *m*/*z* (EI) 191.1 (51%, M^+), 160.1 (100), 117.1 (29).

General procedure for the synthesis of 2a,b

A solution of *p*-toluensulfonyl chloride (1.8 g, 9.4 mmol) in dry dichloromethane (20 mL) was added dropwise to a solution of the respective alcohol **8a,b** (7.5 mmol) and triethylamine (2.5 mL) in dry dichloromethane (100 mL) under ice-cooling. The reaction mixture was stirred overnight at room temperature. The solvent was evaporated under reduced pressure and the residual oil was purified by silica gel chromatography (ethyl acetate–n-hexane 1 : 2).

2-(1*H*-Indol-2-yl)ethyl 4-methylbenzenesulfonate (2a). 2a (1.66 g, 70%) was obtained from **8a** (1.21 g) as a white solid showing the same analytical data as reported in the literature.[5]

2-(5-Methoxy-1*H*-indol-2-yl)ethyl 4-methylbenzenesulfonate (2b). 2b (1.65 g, 64%) was obtained from **8b** (1.43 g) as a grey solid (Found: C, 62.75; H, 5.56; N, 4.13; S, 9.35. $C_{18}H_{19}NO_4S$ requires C, 62.59; H, 5.54; N, 4.05; S, 9.28%); mp 106 °C; ν_{max}/cm^{-1}: 3430, 2992, 2955, 1622, 1591, 1485, 1449, 1352, 1196, 1170, 970, 899, 774, 660; δ_H (400 MHz, $CDCl_3$) 2.38 (3H, s, CH_3), 3.07 (2H, t, *J* 6.3, CH_2-CH_2-O), 3.82 (3H, s, OCH_3), 4.26 (2H, t, *J* 6.3, CH_2-CH_2-OH), 6.10 (1H, br s, 3-H), 6.79 (1H, dd, *J* 8.8, 2.5, 6-H), 6.95 (1H, d, *J* 2.5, 4-H), 7.14 (1H, d, *J* 8.8, H-7), 7.20 (2H, d, *J* 8.3), 7.67 (2H, d, *J* 8.3), 7.94 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) 21.59 (*C*H_3), 28.31 (*C*H_2-CH_2-OH), 55.85 (O*C*H_3), 69.60 (CH_2-*C*H_2-OH), 100.90 (C-3), 102.03 (C-4), 111.29 (C-7), 111.64 (C-6), 127.76 (2 × $C_{aromatic}$), 128.81 (C-3a), 129.82 (2 × $C_{aromatic}$), 132.59 (C-2), 134.64 (C-7a), 144.93 (-OSO_2C), 154.21 (C-5); *m*/*z* (EI): 345.1 (1%, M$^+$), 173.1 (100), 158.1 (56), 155.0 (26), 130.1 (38).

General procedure for the synthesis of 4a,b

NaH (300 mg of 60% suspension in mineral oil, 7.5 mmol) was added in small portions to the stirred solution of the respective tosylate **2a,b** (3 mmol) in dry DMF (30 mL) under ice-cooling. The ice bath was removed after 20 min and stirring was continued for further 40 min. Water (20 mL) was added carefully and the reaction mixture was extracted with diethyl ether (3 × 50 mL). The combined ether extracts were washed with water (2 × 10 mL) and dried (Na_2SO_4). The solvent was evaporated *in vacuo* and the residues were purified by silica gel chromatography ($CHCl_3$–n-hexane 1 : 1).

7,7a,13,14-Tetrahydro-6*H*-cyclobuta[*b*]pyrimido[1,2-*a*:3,4-*a*′]diindole (4a). 4a (198 mg, 46%) was obtained from **2a** (950 mg) as a white solid (Found: C, 83.54; H, 6.27; N, 9.44. $C_{20}H_{18}N_2$ requires C, 83.88; H, 6.34; N, 9.78%; $C_{20}H_{17}N_2$ requires 285.1392, found 285.1393; mp 150 °C; ν_{max}/cm^{-1}: 2992, 2967, 1607, 1480, 1454, 1387, 1351, 1320, 1199, 1018, 739; δ_H (600 MHz, $CDCl_3$) 2.00–2.07 (1H, m, 7-H^a), 2.59–2.67 (2H, m, 6-H^a, 7-H^b), 2.87 (1H, br d, *J* 15.8, 14-H^a), 3.11 (1H, dddd, *J* 15.8, 13.0, 5.4, 1.4, 14-H^b), 3.41 (1H, m, 6-H^b), 3.51 (1H, ddd, *J* 14.3, 13.0, 3.2, 13-H^a), 3.91 (1H, ddd, *J* 14.3, 5.4, 1.0, 13-H^b), 4.71 (1H, t, *J* 8.2, 7a-H), 6.14 (1H, br s, H-15), 6.60–6.65 (2H, m, H-9, H-11), 6.99 (1H, d, *J* 7.1, H-8), 7.07–7.11 (2H, m, H-2, H-10), 7.18 (1H, m, H-3), 7.52 (1H, d, *J* 7.8, H-1), 7.66, 1H, d, *J* 8.2, H-1); δ_C (150 MHz, $CDCl_3$) 21.48 (C-7), 21.56 (C-14), 34.15 (C-6), 36.58 (C-13), 48.07 (C-7a), 83.30 (C-5a), 98.41 (C-15), 105.70 (C-11), 110.91 (C-4), 118.19 (C-9), 119.76 (C-2), 120.31 (C-1), 120.43 (C-3), 124.13 (C-8), 127.65 (C-10), 128.88 (C-15a), 132.15 (C-7b), 134.10 (C-4a), 135.29 (C-14a), 151.14 (C-11a); *m*/*z* (EI): 286 (3%, M$^+$), 258 (100), 257 (26), 129 (15), 128 (16).

2,9-Dimethoxy-7,7a,13,14-tetrahydro-6*H*-cyclobuta[*b*]pyrimido-[1,2-*a*:3,4-*a*′]diindole (4b). 4b (250 mg, 45%) was obtained from **2b** (1.036 g) as a white solid (Found: C, 75.89; H, 6.19; N, 7.94. $C_{22}H_{22}N_2O_2$ requires C, 76.26; H, 6.41; N, 8.09%); mp 73 °C; ν_{max}/cm^{-1}: 2944, 2830, 1615, 1579, 1475, 1450, 1352, 1292, 1157, 1031, 794; δ_H (400 MHz, $CDCl_3$) 1.99–2.09 (1H, m, 7-H^a), 2.53–2.65 (2H, m, 6-H^a, 7-H^b), 2.80 (1H, br d, *J* 15.9, 14-H^a), 3.01–3.11 (1H, m, 14-H^b), 3.31–3.39 (1H, m, 6-H^b), 3.45 (1H, ddd, *J* 14.4, 13.0, 3.3, 13-H^a), 3.69 (3H, s, C-9-OCH_3), 3.83 (1H, ddd, *J* 14.4, 5.3, 1.0, 13-H^b), 3.83 (3H, s, C-2-OCH_3), 4.59 (1H, t, *J* 8.2, 7a-H), 6.06 (1H, br s, H-15), 6.50 (1H, d, *J* 9.1, H-11), 6.62–6.65 (2H, m, H-8, H-10), 6.83 (1H, dd, *J* 8.8, 2.5 H-3), 6.99 (1H, d, *J* 2.5, H-1), 7.51 (1H, d, *J* 8.8, H-4); δ_C (100 MHz, $CDCl_3$) 21.31 (C-7), 21.43 (C-14), 34.19 (C-6), 37.03 (C-13), 48.43 (C-7a), 55.84 (C-9-O*C*H_3), 56.04 (C-2-O*C*H_3), 83.62 (C-5a), 98.12 (C-15), 102.41 (C-1), 105.82 (C-11), 110.26 (C-3), 111.49 (C-4), 111.94, 111.97 (C-8, C-10), 129.43 (C-4a), 129.57 (C-15a), 133.45 (C-7b), 136.12 (C-14a), 145.49 (C-11a), 153.02 (C-9), 154.20 (C-2); *m*/*z* (EI): 346.2 (2%, M$^+$), 319.2 (24), 318.2 (100), 303.2 (9), 275.2 (19)

General procedure for the synthesis of 9a,b

N,*N*-Dimethylmethyleneiminium chloride (187 mg, 2 mmol) was added to a solution of the respective hexacyclic compound **4a,b** (0.6 mmol) in dry CH_2Cl_2 (100 mL). After heating for 1 h at reflux, the reaction mixture was made basic with 25% ammonia. The organic layer was separated, washed with water and dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue was purified by silica gel chromatography ($CHCl_3$–methanol–25% ammonia, 100 : 10 : 1).

1-(7,7a,13,14-Tetrahydro-6*H*-cyclobuta[*b*]pyrimido[1,2-*a*:3,4-*a*′]-diindol-15-yl)-*N*,*N*-dimethylmethanamine (9a). 9a (160 mg, 0.47 mmol, 78%) was obtained from **4a** (172 mg) as a white solid ($C_{23}H_{25}N_3H^+$ required 344.2127, found 344.2121); mp 89 °C; ν_{max}/cm^{-1}: 2942, 2807, 2760, 1605, 1477, 1456, 1321, 1196, 1012, 733; δ_H (400 MHz, $CDCl_3$) 1.98–2.04 (1H, m, 7-H^a), 2.20 (6H, s, 2 × CH_3), 2.58–2.69 (2H, m, 6-H^a, 7-H^b), 2.92–3.05 (2H, m, CH_2-14), 3.37–3.54 (2H, m, H-6^b, 13-H^a), 3.40 (1H, d, *J* 13.1, *H*CH-NMe_2), 3.49 (1H, d, *J* 13.1, HC*H*-NMe_2), 3.94 (1H, ddd, *J* 14.4, 4.9, 1.8, 13-H^b), 4.71 (1H, t, *J* 8.2, H-7a), 6.60–6.66 (2H, m, H-9, H-11), 6.98 (1H, d, *J* 7.0, H-8), 7.06–7.10 (2H, m, H-2, H-10), 7.19 (1H, m, H-3), 7.62–7.66 (2H, m, H-1, H-8); δ_C (100 MHz, $CDCl_3$) 20.17 (C-14), 21.54 (C-7), 34.32 (C-6), 36.46 (C-13), 45.51 (2 × *C*H_3), 48.20 (C-7a), 52.95 (*C*H_2-NMe_2), 83.29 (C-5a), 105.71 (C-11), 110.73 (C-4), 118.20 (C-9), 119.02 (C-1), 119.63 (C-2), 120.56 (C-3), 124.15 (C-8), 127.66 (C-10), 129.58 (C-15a), 132.22 (C-7b), 133.70 (C-4a), 133.97 (C-14a), 151.14 (C-11a).

1-(2,9-Dimethoxy-7,7a,13,14-tetrahydro-6*H*-cyclobuta[*b*]pyrimido[1,2-*a*:3,4-*a*′]diindol-15-yl)-*N*,*N*-dimethylmethanamine (9b). 9b (230 mg, 0.51 mmol, 95%) was obtained from **4b** (242 mg) as a white solid ($C_{25}H_{29}N_3O_2Na^+$ required 426.2157, found 426.2152); mp 71 °C; ν_{max}/cm^{-1}: 2940, 2760, 1616, 1584, 1477, 1455, 1296, 1244, 1225, 1165, 1031, 794; δ_H (400 MHz, $CDCl_3$) 1.99–2.09 (1H, m, 7-H^a), 2.22 (6H, s, 2 × CH_3), 2.54–2.64 (2H, m, 6-H^a, 7-H^b), 2.87–3.01 (2H, m, CH_2-14), 3.30–3.51 (2H, m, H-6^b,13-H^a), 3.39 (1H, d, *J* 13.0, *H*CH-NMe_2), 3.49 (1H, d, *J* 13.0, HC*H*-NMe_2), 3.69 (3H, s, C-9-OCH_3), 3.82–3.89 (1H, m, *J* 13-H^b), 3.86 (3H, s, C-2-OCH_3), 4.59 (1H, t, *J* 8.1, H-7a), 6.51 (1H, d, *J* 9.3, H-11), 6.61–6.65 (2H, m, H-8, H-10), 6.84 (1H, dd, *J* 8.8, 2.5 H-3), 7.08 (1H, d, *J* 2.5, H-1), 7.51 (1H, d, *J* 8.8, H-4); δ_C (100 MHz, $CDCl_3$) 19.74 (C-7), 21.40 (C-14), 34.28 (C-6), 36.80 (C-13), 45.51 (2 × *C*H_3), 48.46 (C-7a), 52.89 (*C*H_2-NMe_2), 55.90 (C-9-O*C*H_3), 55.98

(C-2-O*C*H$_3$), 83.52 (C-5a), 101.33 (C-1), 105.80 (C-11), 110.13 (C-3), 111.34 (C-4), 111.90, 111.92 (C-8, C-10), 129.22 (C-4a), 130.15 (C-15a), 133.41 (C-7b), 134.76 (C-14a), 145.41 (C-11a), 152.98 (C-9), 154.15 (C-2).

General procedure for the synthesis of 10a,b

Methyl iodide (0.4 ml) was added to a solution of the respective Mannich base **9a,b** (0.45 mmol) in dry CH_2Cl_2 (50 ml). The reaction mixture was stirred at room temperature for one hour. The volatiles were removed under vacuum and the residual ammonium salt was dissolved in dry acetonitrile (100 ml). Dicyclohexyl-[18]-crown-[6] (200 mg) and potassium cyanide (400 mg) were added and the resulting reaction mixture was heated at reflux for 2 h. The solvent was evaporated under reduced pressure and the residue was subjected to silica gel chromatography ($CHCl_3$).

7,7a,13,14-Tetrahydro-6*H*-cyclobuta[*b*]pyrimido[1,2-*a*:3,4-*a*′]diindole-15-carbonitrile (10a). **10a** (135 mg, 92%) was obtained from **9a** (155 mg) as a white solid (Found: C, 79.85; H, 5.81; N, 12.84. $C_{22}H_{19}N_3$ requires C, 81.20; H, 5.89; N, 12.91%); mp 95 °C; ν_{max}/cm^{-1}: 2948, 2120, 1605, 1479, 1457, 1353, 1323, 1197, 743; δ_H (400 MHz, $CDCl_3$) 2.01–2.11 (1H, m, 7-H^a), 2.60–2.70 (2H, m, 6-H^a, 7-H^b), 2.89 (1H, dd, *J* 15.9, 3.5, 14-H^a), 3.05 (1H, ddd, *J* 15.9, 12.8, 5.4, 14-H^b), 3.38 (1H, ddd, *J* 20.0, 11.3, 2.3, H-6^b), 3.53 (1H, ddd, *J* 14.3, 12.6, 3.5, 13-H^a), 3.66 (2H, s, C*H*$_2$-CN), 3.99 (1H, dd, *J* 14.5, 5.3, 13-H^b), 4.69 (1H, t, *J* 7.9, H-7a), 6.61–6.67 (2H, m, H-9, H-11), 6.99 (1H, d, *J* 7.0, H-8), 7.10 (1H, m, H-2), 7.18 (1H, t, *J* 7.8, H-10), 7.25 (1H, m, H-3), 7.55 (1H, d, *J* 7.8, H-1), 7.68 (1H, d, *J* 8.3, H-4); δ_C (100 MHz, $CDCl_3$) 12.36 (*C*H$_2$-CN), 19.79 (C-14), 21.50 (C-7), 34.25 (C-6), 36.00 (C-13), 48.19 (C-7a), 83.27 (C-5a), 98.41 (*C*N), 105.82 (C-11), 111.20 (C-4), 117.70 (C-15), 117.79 (C-9), 118.59 (C-1), 120.30 (C-2), 121.47 (C-3), 124.26 (C-8), 127.43 (C-10), 127.82 (C-15a), 131.91 (C-7b), 132.95 (C-4a), 133.93 (C-14a), 150.85 (C-11a); *m*/*z* (EI): 325.2 (2%, M$^+$), 324.2 (3), 298.2 (23), 297.2 (100), 257.2 (36).

2,9-Dimethoxy-7,7a,13,14-tetrahydro-6*H*-cyclobuta[*b*]pyrimido-[1,2-*a*:3,4-*a*′]diindole-15-carbonitrile (10b). **10b** (156 mg, 90%) was obtained from **9b** (180 mg) as a white solid (Found: C, 74.35; H, 6.07; N, 10.57. $C_{24}H_{23}N_3O_2$ requires C, 74.78; H, 6.01; N, 10.90%); mp 77 °C; ν_{max}/cm^{-1}: 2945, 2830, 1616, 1590, 1480, 1457, 1245, 1227, 1159, 1031, 798; δ_H (400 MHz, $CDCl_3$) 2.01–2.11 (1H, m, 7-H^a), 2.56–2.66 (2H, m, 6-H^a, 7-H^b), 2.82 (1H, ddd, *J* 15.9, 3.3, 1.2, 14-H^a), 3.01 (1H, ddd, *J* 15.9, 12.8, 5.3, 14-H^b), 3.33 (1H, ddd, *J* 20.0, 11.3, 2.2, H-6^b), 3.48 (1H, ddd, *J* 15.9, 12.6, 3.5, 13-H^a), 3.62 (2H, s, C*H*$_2$-CN), 3.69 (3H, s, C-9-OC*H*$_3$), 3.86 (3H, s, C-2-OC*H*$_3$), 3.89 (1H, dd, *J* 14.4, 5.3, 13-H^b), 4.57 (1H, t, *J* 8.1, H-7a), 6.52 (1H, d, *J* 9.3, H-11), 6.63–6.67 (2H, m, H-8, H-10), 6.89 (1H, dd, *J* 9.0, 2.5 H-3), 6.98 (1H, d, *J* 2.5, H-1), 7.54 (1H, d, *J* 9.0, H-4); δ_C (100 MHz, $CDCl_3$) 12.38 (*C*H$_2$-CN), 19.34 (C-14), 21.61 (C-7), 34.22 (C-6), 36.36 (C-13), 48.47 (C-7a), 55.85 (C-9-O*C*H$_3$), 56.01 (C-2-O*C*H$_3$), 83.50 (C-5a), 97.96 (*C*N), 99.81 (C-1), 105.92 (C-11), 111.28 (C-3), 111.92 (C-4), 112.02, 112.05 (C-8, C-10), 117.76 (C-15), 128.05 (C-4a), 129.04 (C-15a), 133.16 (C-7b), 133.61 (C-14a), 145.08 (C-11a), 153.21 (C-9), 154.54 (C-2); *m*/*z* (EI): 385.2 (3%, M$^+$), 384.2 (2), 358.2 (24), 357.2 (100), 317.2 (25), 314.2 (14), 274.2 (8).

General procedure for the synthesis of 11a,b

A solution of the respective cyanide **10a,b** (0.35 mmol) in dry toluene (30 ml) was added to a stirred suspension of $LiAlH_4$ (0.30 g) in dry diethyl ether (30 ml) at 0–5 °C. The reaction mixture was heated at 40 °C for 2 h. Water (3 ml) was added dropwise under ice-cooling and the reaction mixture was stirred for 1 h at room temperature. The precipitate was filtered off and washed with diethyl ether. The combined filtrates and washings were dried (Na_2SO_4), filtered and evaporated under vacuum to afford the respective ethylamine **11a,b** that was used in the next step without further purification.

2-(7,7a,13,14-Tetrahydro-6*H*-cyclobuta[*b*]pyrimido[1,2-*a*:3,4-*a*′]-diindole-15-yl)ethanamine (11a). **11a** (115 mg, 100%) was obtained from **10a** (114 mg) as a colourless oil. δ_H (400 MHz, $CDCl_3$) 2.00–2.10 (1H, m, 7-H^a), 2.59–2.69 (2H, m, 6-H^a, 7-H^b), 2.70–2.93 (5H, m, C*H*$_2$-C*H*$_2$-NH$_2$, H-14^a), 2.96–3.06 (1H, m, H-14^b), 3.37–3.46 (1H, m, H-6^b), 3.50 (1H, ddd, *J* 14.4, 12.5, 3.5, 13-H^a), 3.96 (1H, ddd, *J* 14.4, 5.1, 1.2, 13-H^b), 4.72 (1H, t, *J* 8.2, H-7a), 6.61–6.67 (2H, m, H-9, H-11), 7.00 (1H, d, *J* 7.1, H-8), 7.08–7.29 (3H, m, H-2, H-10, H-3), 7.55 (1H, d, *J* 7.8, H-1), 7.67 (1H, d, *J* 8.3, H-4); δ_C (100 MHz, $CDCl_3$) 20.09 (C-14), 21.41 (C-7), 27.76 (*C*H$_2$-CH$_2$-NH$_2$), 34.25 (C-6), 36.51 (C-13), 42.49 (CH$_2$-*C*H$_2$-NH$_2$), 48.19 (C-7a), 83.24 (C-5a), 105.67 (C-11), 107.72 (C-15), 110.82 (C-4), 118.19 (C-9), 118.52 (C-1), 119.33 (C-2), 120.57 (C-3), 124.13 (C-8), 125.26 (C-10), 127.65 (C-15a), 128.99 (C-7b), 132.20 (C-4a), 134.40 (C-14a), 151.11 (C-11a).

2-(2,9-Dimethoxy-7,7a,13,14-tetrahydro-6*H*-cyclobuta[*b*]pyrimido[1,2-*a*:3,4-*a*′]diindole-15-yl)ethanamine (11b). **11b** (135 mg, 100%) was obtained from **10b** (135 mg) as a colourless oil. δ_H (400 MHz, $CDCl_3$) 1.98–2.09 (1H, m, 7-H^a), 2.53–2.63 (2H, m, 6-H^a, 7-H^b), 2.66–3.00 (6H, m, C*H*$_2$-C*H*$_2$-NH$_2$, 14-C*H*$_2$), 3.29–3.38 (1H, m, H-6^b), 3.44 (1H, ddd, *J* 14.4, 12.6, 3.5, 13-H^a), 3.69 (3H, s, C-9-OC*H*$_3$), 3.84 (3H, s, C-2-OC*H*$_3$), 3.83–3.89 (1H, m, 13-H^b), 4.57 (1H, t, *J* 8.1, H-7a), 6.51 (1H, d, *J* 9.3, H-11), 6.61–6.65 (2H, m, H-8, H-10), 6.83 (1H, dd, *J* 8.9, 2.5 H-3), 6.98 (1H, d, *J* 2.5, H-1), 7.51 (1H, d, *J* 8.9, H-4); δ_C (100 MHz, $CDCl_3$) 19.70 (C-14), 21.40 (C-7), 27.75 (*C*H$_2$-CH$_2$-NH$_2$), 34.27 (C-6), 36.92 (C-13), 42.34 (CH$_2$-*C*H$_2$-NH$_2$), 48.52 (C-7a), 55.98 (C-9-O*C*H$_3$), 56.02 (C-2-O*C*H$_3$), 83.54 (C-5a), 100.86 (C-1), 105.79 (C-11), 107.24 (C-15), 110.18 (C-3), 111.47 (C-4), 111.92, 111.97 (C-8, C-10), 129.35 (C-4a), 129.60 (C-15a), 133.06 (C-7b), 133.48 (C-14a), 145.44 (C-11a), 153.01 (C-9), 154.00 (C-2).

General procedure for the synthesis of 12–16

A stirred solution of the respective ethylamine **11a,b** (0.35 mmol) in dry CH_2Cl_2 (10 ml) was treated with triethylamine (0.30 mL) and the respective acylation agent (0.20 mL) at 0–5 °C. The reaction mixture was stirred at ambient temperature for 2 h. The solvent was evaporated and the residue was purified by silica gel chromatography ($CHCl_3$, MeOH, 25% NH_3 100 : 10 : 1 for **12–15**; $CHCl_3$ for **16**).

***N*-[2-(7,7a,13,14-Tetrahydro-6*H*-cyclobuta[*b*]pyrimido[1,2-*a*:3,4-*a*′]diindole-15-yl)ethyl]acetamide (12).** **12** (105 mg, 81%) was obtained from **11a** (115 mg) and acetic anhydride (0.2 mL) as a white solid (Found: C, 77.64; H, 6.96; N, 10.98. $C_{24}H_{25}N_3O$ requires C, 77.60; H, 6.78; N, 11.31%); mp 97 °C; ν_{max}/cm^{-1}: 3281,

2940, 1649, 1606, 1549, 1479, 1458, 1321, 1196, 741; δ_H (400 MHz, $CDCl_3$) 1.82 (3H, s, CH_3), 1.99–2.09 (1H, m, 7-H^a), 2.58–2.69 (2H, m, 6-H^a, 7-H^b), 2.75–3.02 (4H, m, CH_2-CH$_2$-NH$_2$,CH_2-14), 3.32–3.52 (4H, m, CH$_2$-CH_2-NH$_2$, 6-H^b, 13-H^a), 3.95 (1H, ddd, *J* 14.3,5.1, 1.2, 13-H^b), 4.69 (1H, t, *J* 8.2, H-7a), 5.39 (1H, br, NH), 6.60–6.65 (2H, m, H-9, H-11), 6.98 (1H, d, *J* 7.1, H-8), 7.07–7.14 (2H, m, H-2, H-10), 7.20 (1H, m, H-3), 7.51 (1H, d, *J* 7.6, H-1), 7.65 (1H, d, *J* 8.1, H-4); δ_C (100 MHz, $CDCl_3$) 19.95 (C-14), 21.49 (C-7), 23.35 (*C*H$_3$), 23.56 (*C*H$_2$-CH$_2$-NH), 34.23 (C-6), 36.45 (C-13), 39.85 (CH$_2$-*C*H$_2$-NH$_2$), 48.21 (C-7a), 83.35 (C-5a), 105.77 (C-11), 107.08 (C-15), 110.97 (C-4), 118.27 (C-9), 118.31 (C-1), 119.63 (C-2), 120.79 (C-3), 124.17, (C-8), 127.76 (C-10), 128.90 (C-7b), 132.14 (C-15a), 132.35 (C-4a), 134.05 (C-14a), 151.10 (C-11a), 169.99 (C=O); *m*/*z* (EI): 371.2 (2%, M$^+$), 370.2 (3), 344.2 (13), 343.3 (54), 284.2 (30), 272.2 (21), 271.2 (100), 256.1 (8).

***N*-[2-(7,7a,13,14-Tetrahydro-6*H*-cyclobuta[*b*]pyrimido[1,2-*a*:3,4-*a*′]diindole-15-yl)ethyl]butanamide (13). 13** (109 mg, 78%) was obtained from **11a** (115 mg) and butyric anhydride (0.2 mL) as a white solid (Found: C, 77.85; H, 7.54; N, 10.40%. $C_{26}H_{29}N_3O$ requires C, 78.16; H, 7.32; N, 10.52%); mp 96 °C; ν_{max}/cm^{-1}: 3280, 2930, 2940, 2872, 1642, 1606, 1543, 1479, 1456, 1321, 1196, 1163, 739; δ_H (400 MHz, $CDCl_3$) 0.85 (3H, t, *J* 7.3, CH$_2$-CH$_2$-CH_3), 1.53 (2H, quint., *J* 7.3, CH$_2$-CH_2-CH$_3$), 1.97 (2H, t, *J* 7.3, CH_2-CH$_2$-CH$_3$), 1.99–2.09 (1H, m, 7-H^a), 2.58–2.68 (2H, m, 6-H^a, 7-H^b), 2.73–3.02 (4H, m, CH_2-CH$_2$-NH$_2$,CH_2-14), 3.34–3.52 (4H, m, CH$_2$-CH_2-NH$_2$, 6-H^b, 13-H^a), 3.94 (1H, ddd, *J* 14.3,5.1, 1.2, 13-H^b), 4.69 (1H, t, *J* 8.2, H-7a), 5.38 (1H, br, NH), 6.59–6.65 (2H, m, H-9, H-11), 6.98 (1H, d, *J* 7.3, H-8), 7.06–7.14 (2H, m, H-2, H-10), 7.20 (1H, m, H-3), 7.51 (1H, d, *J* 7.8, H-1), 7.66 (1H, d, *J* 8.1, H-4); δ_C (100 MHz, $CDCl_3$) 13.74 (*C*H$_3$), 18.98 (CH$_2$-*C*H$_2$-CH$_3$), 19.96 (C-14), 21.48 (C-7), 23.68 (*C*H$_2$-CH$_2$-NH), 34.22 (C-6), 36.44 (C-13), 38.72 (*C*H$_2$-CH$_2$-CH$_3$), 39.62 (CH$_2$-*C*H$_2$-NH$_2$), 48.20 (C-7a), 83.34 (C-5a), 105.76 (C-11), 107.11 (C-15), 110.94 (C-4), 118.31 (C-9), 118.34 (C-1), 119.58 (C-2), 120.77 (C-3), 124.16 (C-8), 127.76 (C-10), 128.86 (C-7b), 132.13 (C-15a), 132.36 (C-4a), 134.06 (C-14a), 151.10 (C-11a), 172.83 (C=O); *m*/*z* (EI): 399.2 (2%, M$^+$), 398.2 (4), 372.2 (15), 371.2 (56), 284.2 (55), 272.2 (23), 271.2 (100), 256.1 (8).

***N*-[2-(2,9-Dimethoxy-7,7a,13,14-tetrahydro-6*H*-cyclobuta[*b*]-pyrimido[1,2-*a*:3,4-*a*′]diindole-15-yl)ethyl]acetamide (14). 14** (113 mg, 75%) was obtained from **11b** (135 mg) and acetic anhydride (0.2 mL) as a white solid (Found: C, 71.98; H, 6.89; N, 9.57. $C_{26}H_{29}N_3O_3$ requires C, 72.37; H, 6.77; N, 9.74%); mp 85 °C; ν_{max}/cm^{-1}: 3320, 2937, 1649, 1586, 1543, 1477, 1294, 1244, 1225, 1030, 796; δ_H (400 MHz, $CDCl_3$) 1.84 (3H, s, CH_3), 1.99–2.09 (1H, m, 7-H^a), 2.54–2.64 (2H, m, 6-H^a, 7-H^b), 2.71–2.98 (4H, m, CH_2-CH$_2$-NH$_2$,CH_2-14), 3.29–3.47 (4H, m, CH$_2$-CH_2-NH$_2$, 6-H^b, 13-H^a), 3.69 (3H, s, C-9-OCH_3), 3.84 (3H, s, C-2-OCH_3), 3.83–3.89 (1H, m, 13-H^b), 4.57 (1H, t, *J* 8.1, H-7a), 5.41 (1H, br, NH), 6.51 (1H, d, *J* 9.3, H-11), 6.62–6.65 (2H, m, H-8, H-10), 6.84 (1H, dd, *J* 8.8, 2.5 H-3), 6.96 (1H, d, *J* 2.3, H-1), 7.51 (1H, d, *J* 8.8, H-4); δ_C (100 MHz, $CDCl_3$) 19.53 (C-14), 21.39 (C-7), 23.40 (*C*H$_3$), 23.59 (*C*H$_2$-CH$_2$-NH), 34.23 (C-6), 36.82 (C-13), 39.78 (CH$_2$-*C*H$_2$-NH$_2$), 48.50 (C-7a), 55.93 (C-9-O*C*H$_3$), 56.02 (C-2-O*C*H$_3$), 83.59 (C-5a), 100.40 (C-1), 105.84 (C-11), 106.68 (C-15), 110.48 (C-3), 111.61 (C-4), 111.92, 111.98 (C-8, C-10), 129.26 (C-4a), 129.50 (C-15a), 133.19 (C-7b), 133.40 (C-14a), 145.37 (C-11a), 153.06 (C-9), 154.19 (C-2), 169.94 (C=O); *m*/*z* (EI): 431.3 (2%, M$^+$), 404.2 (15), 403.2 (55), 344.2 (23), 332.2 (25), 331.2 (100).

***N*-[2-(2,9-Dimethoxy-7,7a,13,14-tetrahydro-6*H*-cyclobuta[*b*]-pyrimido[1,2-*a*:3,4-*a*′]diindole-15-yl)ethyl]butanamide (15). 15** (105 mg, 65%) was obtained from **11b** (135 mg) and butyric anhydride (0.2 mL) as a white solid (Found: C, 72.84; H, 7.15; N, 9.00 $C_{28}H_{33}N_3O_3$ requires C, 73.18; H, 7.24; N, 9.14%); mp 87 °C; ν_{max}/cm^{-1}: 3295, 2957, 2926, 2854, 1643, 1589, 1539, 1477, 1434, 1256, 1244, 1225, 1160, 1604, 1028, 796; δ_H (400 MHz, $CDCl_3$) 0.85 (3H, t, *J* 7.3, CH$_2$-CH$_2$-CH_3), 1.53 (2H, quint., *J* 7.3, CH$_2$-CH_2-CH$_3$), 1.98 (2H, t, *J* 7.3, CH_2-CH$_2$-CH$_3$), 1.99–2.09 (1H, m, 7-H^a), 2.53–2.64 (2H, m, 6-H^a, 7-H^b), 2.72–2.98 (4H, m, CH_2-CH$_2$-NH$_2$, CH_2-14), 3.28–3.48 (4H, m, CH$_2$-CH_2-NH$_2$,6-H^b, 13-H^a), 3.69 (3H, s, C-9-OCH_3), 3.84 (3H, s, C-2-OCH_3), 3.83–3.89 (1H, m, 13-H^b), 4.57 (1H, t, *J* 8.1, H-7a), 5.41 (1H, br, NH), 6.51 (1H, d, *J* 9.1, H-11), 6.61–6.65 (2H, m, H-8, H-10), 6.84 (1H, dd, *J* 9.1, 2.5 H-3), 6.96 (1H, d, *J* 2.3, H-1), 7.51 (1H, d, *J* 8.8, H-4); δ_C (100 MHz, $CDCl_3$) 13.75 (*C*H$_3$), 19.02 (CH$_2$-*C*H$_2$-CH$_3$), 19.55 (C-14), 21.38 (C-7), 23.69 (*C*H$_2$-CH$_2$-NH), 34.21 (C-6), 36.81 (C-13), 38.76 (*C*H$_2$-CH$_2$-CH$_3$), 39.51 (CH$_2$-*C*H$_2$-NH$_2$), 48.50 (C-7a), 55.94 (C-9-O*C*H$_3$), 56.01 (C-2-O*C*H$_3$), 83.59 (C-5a), 100.51 (C-1), 105.84 (C-11), 106.68 (C-15), 110.42 (C-3), 111.59 (C-4), 111.91, 111.98 (C-8, C-10), 129.28 (C-4a), 129.45 (C-15a), 133.23 (C-7b), 133.40 (C-14a), 145.38 (C-11a), 153.06 (C-9), 154.16 (C-2), 172.85 (C=O); *m*/*z* (EI): 459.2 (3%, M$^+$), 458.2 (5), 432.2 (22), 431.2 (72), 344.2 (34), 331.1 (100).

***N*-[2-(2,9-Dimethoxy-7,7a,13,14-tetrahydro-6*H*-cyclobuta[*b*]-pyrimido[1,2-*a*:3,4-*a*′]diindole-15-yl)ethyl]cyclopropanecarboxamide (16). 16** (88 mg, 55%) was obtained from **11b** (135 mg) and cyclopropanecarboxylic acid chloride (0.2 mL) as a white solid ($C_{28}H_{31}N_3O_3Na^+$ required 480.2263, found 480.2258); mp 94 °C; ν_{max}/cm^{-1}: 3298, 2936, 1643, 1589, 1534, 1478, 1434, 1245, 1227, 1157, 1064, 1030; 795; δ_H (400 MHz, $CDCl_3$) 0.64 (2H, m, *c*Pr-C*H*H), 0.91 (2H, m, *c*Pr-CH*H*), 1.10 (1H, m, *c*Pr-C*H*), 1.99–2.09 (1H, m, 7-H^a), 2.53–2.64 (2H, m, 6-H^a, 7-H^b), 2.72–3.00 (4H, m, CH_2-CH$_2$-NH$_2$,CH_2-14), 3.28–3.48 (4H, m, CH$_2$-CH_2-NH$_2$, 6-H^b, 13-H^a), 3.69 (3H, s, C-9-OCH_3), 3.85 (3H, s, C-2-OCH_3), 3.81–3.89 (1H, m, 13-H^b), 4.57 (1H, t, *J* 8.1, H-7a), 5.60 (1H, br, NH), 6.51 (1H, d, *J* 9.1, H-11), 6.61–6.64 (2H, m, H-8, H-10), 6.85 (1H, dd, *J* 8.8, 2.5 H-3), 6.97 (1H, d, *J* 2.3, H-1), 7.52 (1H, d, *J* 8.8, H-4); δ_C (100 MHz, $CDCl_3$) 6.89, 6.93 (2 × *c*Pr-*C*H$_2$), 14.73 (*c*Pr-*C*H), 19.53 (C-14), 21.38 (C-7), 23.66 (*C*H$_2$-CH$_2$-NH), 34.23 (C-6), 36.84 (C-13), 39.88 (CH$_2$-*C*H$_2$-NH$_2$), 48.50 (C-7a), 55.92 (C-9-O*C*H$_3$), 56.01 (C-2-O*C*H$_3$), 83.59 (C-5a), 100.48 (C-1), 105.84 (C-11), 106.76 (C-15), 110.43 (C-3), 111.57 (C-4), 111.89, 111.94 (C-8, C-10), 129.26 (C-4a), 129.48 (C-15a), 133.33 (C-7b), 133.39 (C-14a), 145.40 (C-11a), 153.03 (C-9), 154.16 (C-2), 172.35 (C=O).

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