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Facile synthesis of spiro[benzo[*e*]indole-2,2′-piperidine] derivatives and their transformation to novel fluorescent scaffolds

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ABSTRACT

The reaction of azaheterocyclic enamines with acrylamide was employed for the preparation of novel fluorescent scaffolds possessing a benzo[*e*]indoline moiety. Reaction of 3-substituted 2-methylidene-1*H*-benzo[*e*]indole with acrylamide gave rise to spiro[benzo[*e*]indole-2,2′-piperidin]-6′-ones. Ring opening reactions of the latter spiro compounds were investigated. Benzo[*e*]indoline derivatives possessing 2-(3-carbamoylpropyl), 2-[3-(ethoxycarbonyl)propyl] and 2-(4-aminobutyl) side chains were synthesised. The optical properties of the benzo[*e*]indoline derivatives were studied by UV–vis and fluorescence spectroscopy.

1. Introduction

During the last decade, there has been a significant increase in the application of 1,1,2-trimethyl-1*H*-benzo[*e*]indole **1** as a precursor for the synthesis of fluorescent organic molecules that have wide biomedical and technical applications. In particular, this starting material was successfully used for the preparation of a number of near-infrared fluorescence emitting dyes. These dyes were used as labelling agents for biomolecules, probes for high-contrast fluorescence imaging of biological tissues,[1] novel fluorophores for multiple-mode molecular logic systems[2] and enzyme sensing in biological assays.[3] Furthermore, blue organic squaraine dyes, containing the 1,1,2-trimethyl-1*H*-benzo[*e*]indole nucleus, were used for dye-sensitised solar cell applications.[4]

The preparation protocols of these functional dyes usually include a step of *N*-alkylation of 1,1,2-trimethyl-1*H*-benzo[*e*]indole **1** with various alkylating agents, such as alkyl halides,[1a,e,2,5a] halocarboxylic acids,[1a,d,f,4,5b,c] and 1,4-butane sultone,[5c] to form the corresponding *N*-substituted 1,1,2-trimethyl-1*H*-benzo[*e*]indolium salts. For cyanine dye synthesis, the prepared salts were employed as nucleophilic substrates for stepwise condensation with polyene-chain precursors.[5]

The present work deals with functionalisation of the 2-methylidene-1*H*-benzo[*e*]indoles **3**, prepared in two steps from 1,1,2-trimethyl-1*H*-benzo[*e*]indole **1**, with acrylamide in order to obtain novel functionalised fluorescent heterocyclic derivatives that potentially can serve as fluorescent organic probes[6] for biomolecular labelling and scaffolds for the synthesis of optoelectronic materials.[7] It is known, that such 2-methylidene bases, derived from 1-alkyl-2,3,3-trimethyl-3*H*-indolium salts, act as C-nucleophiles in reactions with haloalkanes,[8] 2-haloalkanols or oxiranes[9] and acrylamide.[10] In the latter case, a carba-Michael addition of the enamine β-carbon atom across the α,β-unsaturated amide and subsequent cyclisation yielded spiro[indole[2,2′]piperidine] derivatives. It is important to note also that structurally similar spirocyclic ring systems, which possess a spiroannulated piperidine ring at the indole C-3 atom, are frequently encountered structural motifs in many medicinally valuable compounds.[11]

2. Results and discussion

The starting iodides **2a**[2] and **2b**[12] were prepared from 1,1,2-trimethyl-1*H*-benzo[*e*]indole **1** in accordance with the literature

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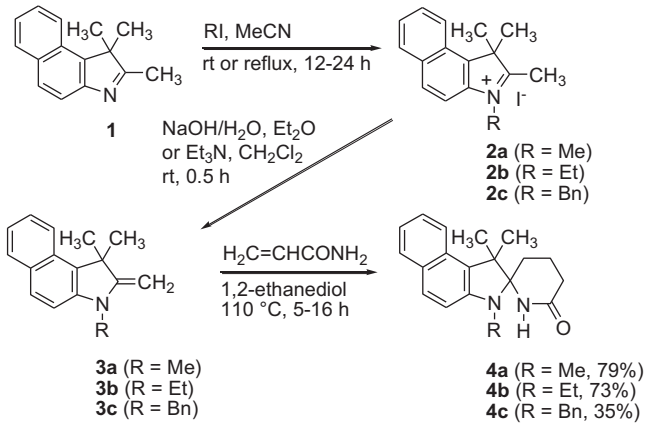
procedures. Treatment of iodides **2a**,**b** with sodium hydroxide afforded enamines **3a**,**b**, which were used in reactions without further purification (purity >95% by ^{1}H NMR/LCMS). For the preparation of enamine **3c**, benzo[*e*]indole **1** was alkylated with benzyl iodide and then the obtained intermediate iodide **2c** was treated with triethylamine in dichloromethane. Heating of enamines **3a**–**c** with acrylamide in 1,2-ethanediol at 110 °C resulted in the formation of spiro[benzo[*e*]indole-2,2′-piperidin]-6′-ones **4a**–**c** (Scheme 1).



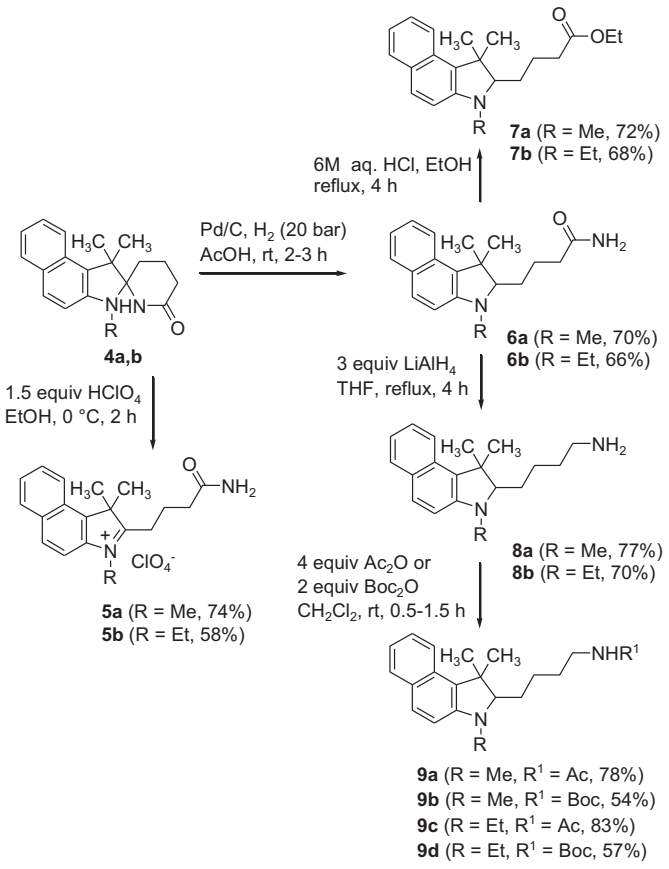
Scheme 1. Synthesis of spiro[benzo[*e*]indole-2,2′-piperidin]-6′-ones.

It can be assumed that the first stage of this reaction is the formation of the appropriate Michael adducts, which then undergo ring closure to the corresponding spiro compounds via the intramolecular addition of the amide nitrogen across the C-2 atom of the indole ring system. The 1,2-ethanediol participates in the reaction during proton transfer. In the ^{13}C NMR spectra of **4a**–**c**, the signal of the spiro-carbon atom resonates at ca. 87.0 ppm, and the signal of the carbonyl carbon atom is present at around 173.0 ppm.

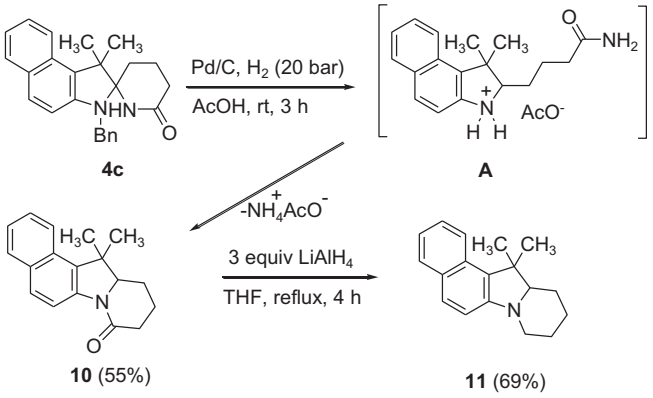
It is known that strong protic acids promote the cleavage of the spiroindole-2,2′-piperidinone ring system.[10] The action of perchloric acid on the 3-alkylspiro[benzo[*e*]indole-2,2′-piperidin]-6′-ones **4a**,**b** led to the opening of the piperidinone ring with formation of the 2-(3-carbamoylpropyl)-1*H*-benzo[*e*]indolium perchlorates **5a**,**b** (Scheme 2). The ^{13}C NMR spectra of perchlorates **5a** and **5b** contain signals at 196.5 and 196.7 ppm, respectively, which can be attributed to the sp^2-hybridised C-2 atom of the benzo[*e*]indolium nuclei. When the spiro compounds **4a**,**b** were dissolved in acetic acid and subjected to hydrogenolysis by treatment with hydrogen in the presence of catalytic palladium, ring opening of the spiropiperidine ring was accompanied by reduction of the iminium moiety to afford the novel benzo[*e*]indoline derivatives **6a**,**b**, which possess a 3-carbamoylpropyl side chain.

The ^{1}H NMR spectra of **6a** and **6b** showed a characteristic triplet for the H-2 proton at 2.34 and 2.31 ppm (^3J=7.1 Hz), respectively, which is due to the coupling with protons of the adjacent methylene group. The corresponding ^{13}C NMR spectra contained signals of the sp^3-hybridised C-2 atom of **6a** and **6b** at 77.4 and 71.9 ppm, respectively. Heating of the amides **6a**,**b** in ethanol under reflux in the presence of hydrochloric acid afforded the esters **7a**,**b**, while the reduction of the amides **6** with lithium aluminium hydride in THF gave the amines **8a**,**b**. Acylation of the latter with Ac_2O and Boc_2O yielded the amides **9a**,**c** and the carbamates **9b**,**d**, respectively.

However, when 3-benzylspiro[benzo[*e*]indole-2,2′-piperidinone] **4c** was subjected to hydrogenolysis under analogous conditions as compounds **4a**,**b**, the reaction afforded the tetracyclic 10,11,11a,12-tetrahydrobenzo[*e*]pyrido[1,2-*a*]indol-8(9*H*)-one **10** (Scheme 3).



Scheme 2. Ring transformations of 3-alkylspiro[benzo[*e*]indole-2,2′-piperidin]-6′-ones.



Scheme 3. Recyclization of 3-benzylspiro[benzo[*e*]indole-2,2′-piperidin]-6′-one.

The reaction outcome can be explained by the palladium-catalysed hydrogenolysis of the benzyl group,[13] leading to the formation of the intermediate product **A**, which underwent further intramolecular transamidation[14] to afford the condensed tetracyclic system **10**.

It is important to note that the reduction of the lactam ring of spiro compound **4a** with lithium aluminium hydride was unsuccessful, probably because of sterical hindrance, despite the presence of a large excess of the reducing agent and stirring under reflux in THF for 72 h. However, the lactam ring of compound **10** was cleanly reduced with lithium aluminium hydride by reaction in THF under reflux for 4 h to give the cyclic amine **11** in 69% isolated yield.

The single crystal X-ray structure of **11** (Fig. 1)[15] shows that the skeleton of the asymmetric unit contains the 8,9,10,11,11a,12-

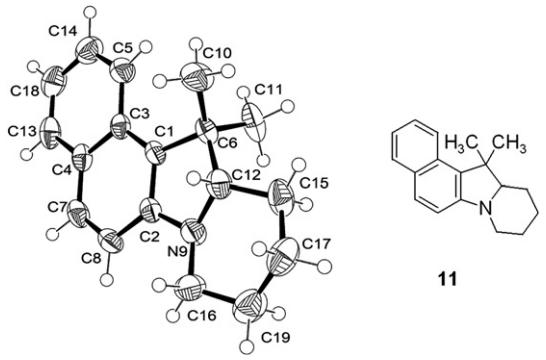


Fig. 1. ORTEP view of tetracyclic compound **11**.

hexahydrobenzo[*e*]pyrido[1,2-*a*]indole ring system. The pyrroline ring of compound **11** is in an envelope conformation with C(12) being out of the plane of the benzo[*e*]indole ring. The piperidine ring is in a chair conformation with the hydrogen atom at C(12) in the axial position. The sum of the valence bond angles around the N(9) atom of **11** is 348.46°, which indicates that a pyramidal geometry exists at the sp^3-hybridised nitrogen atom.[16]

The optical properties of 1,1,2-trimethyl-1*H*-benzo[*e*]indole **1** and the representative benzo[*e*]indoline derivatives **4a**, **7a**, **8a** and **11** were investigated by UV–vis spectroscopy, and the compounds were subjected to fluorimetric measurements (Table 1).

It is known that structurally similar benzo[*e*]indol[1,2-*a*]pyrimidine derivatives, possessing an annulated hexahydropyrimidine ring on the *a*-edge of the indoline ring, exhibit a strong blue fluorescence with an emission maximum around 435 nm (in ethanol).[3] First, the fluorescence spectra of the starting 1,1,2-trimethyl-1*H*-benzo[*e*]indole **1**, the spirobenzo[*e*]indole-2,2′-piperidinone **4a** and the products derived from its reductive ring opening **7a**, **8a** and **11** were measured in a low polarity solvent such as tetrahydrofuran (THF). Both the starting compound **1**, possessing an azomethine moiety, and the spiro compound **4a**, bearing the electron-withdrawing aminocarbonyl moiety attached to the C-2 atom of the indole ring, displayed emission maxima (λ_{em}) at 424 nm. However, the 2-substituted benzo[*e*]indolines **7a**, **8a** and **11** showed emission maxima (λ_{em}) varying between 440 and 445 nm in the same solvent. When fluorescence spectra of compounds **4a** and **8a** were measured in a polar solvent such as distilled water containing 1% (v/v) ethanol, the fluorescence of the latter compounds underwent a red shift, showing emission at λ_{em}=440 and 470 nm, respectively.

Table 1
Absorption (λ_{abs} and ε) and fluorescence (λ_{em} and quantum yield Φ_f) parameters for the benzo[*e*]indoline derivatives **1**, **4a**, **7a**, **8a**, **11** in THF

Compound	λ_{abs} (nm)	$\varepsilon\times10^3$ ($dm^3\,mol^{-1}\,cm^{-1}$)	λ_{em}[a] (nm)	Φ_f (%)
1	219	27.04	424	45
	245	45.57		
	254	32.23		
4a	217	33.63	424	32
	256	66.80		
	294	9.19		
7a	217	30.52	440	25
	257	45.63		
	307	7.93		
8a	217	30.93	441	32
	257	48.19		
	307	8.89		
11	217	32.79	445	22
	258	42.88		
	308	11.53		

[a] λ_{ex}=310 nm.

The fluorescence quantum yield (Φ_f) of the solutions in THF was estimated by comparing the wavelength-integrated PL intensity of the compound solution with that of the reference. Quinine sulfate in 0.1 M H_2SO_4 with Φ_f=53% at excitation wavelengths of 310–340 nm was used as a reference. Optical densities of the reference and the sample solutions were ensured to be below 0.05 to avoid reabsorption effects. Estimated quantum yields were verified by the integrating sphere method. In the case of benzoindolines **4a**, **7a**, **8a** and **11**, possessing the tertiary aromatic amine nitrogen atom, the Φ_f values observed were between 22% (for **11**) and 32% (for **4a** and **8a**).

Additional studies will be mostly directed to the investigation of the target properties of the synthesised compounds, with respect to their applications as molecular probes for biomolecular labelling and as fluorescent scaffolds for the synthesis of opto-electronic materials.

3. Conclusions

In conclusion, a new method for the preparation of functionalised fluorescent derivatives of benzo[*e*]indoline was developed. The reaction of 3-substituted 1,1-dimethyl-2-methylidene-2,3-dihydro-1*H*-benzo[*e*]indole with acrylamide afforded spiro[benzo[*e*]indole-2,2′-piperidin]-6′-ones via a carba-Michael addition of the enamine β-carbon atom across the α,β-unsaturated amide, and subsequent nucleophilic addition of the amide nitrogen to the enamine α-carbon atom. The reductive ring opening of 3-alkylspiro[benzo[*e*]indole-2,2′-piperidin]-6′-ones and further chemical transformations gave fluorescent benzo[*e*]indoline derivatives, possessing reactive 2-[3-(ethoxycarbonyl)propyl] and 2-(4-aminobutyl) side chains. 3-Benzyl[spirobenzo[*e*]indole-2,2′-piperidin]-6′-one underwent recyclisation to the benzo[*e*]pyrido[1,2-*a*]indole derivative under similar reaction conditions. The wavelengths of the absorption and emission maxima ($\lambda_{abs}/\lambda_{em}$) for benzo[*e*]indoline derivatives **7a** and **8a** were at about 307/440 nm; the fluorescence quantum yields were 25 and 32%, respectively.

4. Experimental

4.1. General

Reagents and solvents were purchased from commercial suppliers and used without further purification unless indicated. Dichloromethane was distilled from calcium hydride before use. Tetrahydrofuran was dried over sodium. The purification of the reaction mixtures was performed by flash chromatography using a glass column with silica gel (0.035–0.070 nm, pore diameter ca. 6 nm). For thin layer chromatographic (TLC) analysis, Merck precoated TLC plates (Silica gel 60 F_{254}) were used. Melting points were determined on a Melt-Temp (Capillary Melting point Apparatus) and are uncorrected. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded at rt with a Varian Unity Inova spectrometer or with a Jeol Eclipse FT 300 NMR spectrometer. The chemical shifts, expressed in parts per million, were relative to tetramethylsilane (TMS). Infrared spectra were recorded on a Perkin Elmer Spectrum One spectrometer using potassium bromide pellets or on a Perkin–Elmer Spectrum BX FT-IR spectrometer in neat form with an attenuated total reflectance (ATR) accessory. UV–vis spectra were recorded on a Perkin Elmer Lambda 35 UV/Vis spectrometer. Fluorescence spectra were recorded on a Hitachi MPF-4 spectrometer. Estimated quantum yields were verified using an integrating sphere setup, which consisted of wavelength-tunable xenon light source with collimating optics serving as an excitation

source and the integrating sphere (Sphere Optics) coupled to the CCD spectrometer (Hamamatsu PMA-12) used for detection. Mass spectra were recorded on a Waters Micromass ZQ 2000 ($APCI^+$, 20 V) instrument or on an Agilent 1100 series mass spectrometer using a direct inlet system (electron spray, 4000 V). Elemental analyses (C, H, and N) were recorded with a CE-440 elemental analyser, Model 440 CHN/O/S at the Microanalytical Laboratory, Department of Organic Chemistry, Kaunas University of Technology, and were in good agreement (±0.4%) with the calculated values. Diffraction data were collected on Bruker-Nonius KappaCCD diffractometer at rt and also at −100 °C. The crystal structures were solved using known programs.[17]

4.2. Procedures for the preparation of 3-alkyl-1,1-dimethyl-2,3-dihydro-6′*H*-spiro[benzo[*e*]indole-2,2′-piperidin]-6′-ones (4)

*4.2.1. 1,1,3-Trimethyl-2,3-dihydro-6′H-spiro[benzo[e]indole-2,2′-piperidin]-6′-one (**4a**).* To a suspension of iodide **2a**[2] (3.51 g, 10 mmol) in diethyl ether (50 mL) was added aqueous 1 M NaOH solution (30 mL) and the reaction mixture stirred at rt for 0.5 h. The organic layer was separated and the water layer was additionally extracted with diethyl ether (2×25 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was dissolved in ethylene glycol (15 mL) and acrylamide (1.07 g, 15 mmol) was added to the solution. The mixture was stirred at 110 °C for 5 h. The reaction mixture was cooled to rt, water (50 mL) was added and the mixture was extracted with ethyl acetate (5×50 mL). The combined organic layers were washed with brine (3×50 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was recrystallised from ethyl acetate to give compound **4a** (yield 2.34 g, 79%) as grey crystals, mp 143–144.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.37 (s, 3H, 1-CH_3), 1.62 (s, 3H, 1-CH_3), 1.97–2.05 (m, 2H, 4′-CH_2), 2.13–2.17 (m, 2H, 3′-CH_2), 2.30 (dt, J=17.3, 7.5 Hz, 1H, 5′-H_a), 2.48 (dt, J=17.3, 5.4 Hz, 1H, 5′-H_b), 2.88 (s, 3H, NCH_3), 5.91 (br s, 1H, NH), 6.89 (d, J=8.7 Hz, 1H, 4-H), 7.19–7.26 (m, 1H, 7-H), 7.37–7.43 (m, 1H, 8-H), 7.69 (d, J=8.7 Hz, 1H, 5-H), 7.76 (d, J=8.2 Hz, 1H, 6-H), 7.90 (d, J=8.6 Hz, 1H, 9-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 18.7 (C-4′), 22.5 (1-CH_3), 23.4 (1-CH_3), 25.3 (C-3′), 29.3 (NCH_3), 31.4 (C-5′), 50.1 (C-1), 87.1 (C-2), 110.2 (C-4), 121.0 (C-9), 121.7 (C-7), 124.4 (C_{quat}), 126.5 (C-8), 129.2 (C_{quat}), 129.5 and 129.6 (C-5 and C-6), 130.3 (C_{quat}), 145.9 (C_{quat}), 173.0 (C=O); IR (KBr, ν_{max}, cm^{-1}): 3194 (N–H), 3052, 2973, 2959, 2894, 2874, 1655 (C=O), 1620, 1592, 1519, 1469, 1451, 1401, 1334, 1280, 1196, 1078, 1032, 953, 939, 811, 742; MS (API-ES, pos mode), m/z (%): 295 ($M+H^+$, 100). Anal. Calcd for $C_{19}H_{22}N_2O$ (%): C, 77.52; H, 7.53; N, 9.52. Found: C, 77.31; H, 7.67; N, 9.78.

*4.2.2. 3-Ethyl-1,1-dimethyl-2,3-dihydro-6′H-spiro[benzo[e]indole-2,2′-piperidin]-6′-one (**4b**).* Compound **4b** was obtained similarly to **4a** from iodide **2b**[12] (3.65 g, 10 mmol). Yield 2.23 g (73%), light brown crystals, mp 140.9–142.6 °C (ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.27 (t, J=7.3 Hz, 3H, CH_2CH_3), 1.37 (s, 3H, 1-CH_3), 1.63 (s, 3H, 1-CH_3), 1.93–2.10 (m, 3H, 4′-CH_2 and 3′-H_a), 2.16–2.25 (m, 1H, 3′-H_b), 2.34 (dt, J=17.8, 6.6 Hz, 1H, 5′-H_a), 2.46 (dt, J=17.8, 6.3 Hz, 1H, 5′-H_b), 3.23 (dq, J=14.8, 7.3 Hz, 1H, C(H)HCH_3), 3.35 (dq, J=14.8, 7.5 Hz, 1H, C(H)HCH_3), 5.95 (br s, 1H, NH), 6.87 (d, J=8.7 Hz, 1H, 4-H), 7.16–7.21 (m, 1H, 7-H), 7.35–7.41 (m, 1H, 8-H), 7.66 (d, J=8.7 Hz, 1H, 5-H), 7.74 (d, J=8.1 Hz, 1H, 6-H), 7.88 (d, J=8.5 Hz, 1H, 9-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 15.5 (CH_2CH_3), 18.2 (C-4′), 22.3 (1-CH_3), 23.6 (1-CH_3), 26.0 (C-3′), 31.1 (C-5′), 38.0 (CH_2CH_3), 50.2 (C-1), 87.0 (C-2), 109.7 (C-4), 120.9 (C-9), 121.3 (C-7), 123.6 (C_{quat}), 126.4 (C-8), 128.8 (C_{quat}), 129.4 and 129.5 (C-5 and C-6), 130.3 (C_{quat}), 145.3 (C_{quat}), 172.5 (C=O); IR (KBr, ν_{max}, cm^{-1}): 3192 (N–H), 3055, 2965, 2926, 2880, 1652 (C=O), 1618, 1592, 1516, 1466, 1368, 1340, 1189, 1048, 1033, 960, 932, 816, 745. MS (API-ES, pos mode), m/z (%): 309 ($M+H^+$, 100). Anal. Calcd for $C_{20}H_{24}N_2O$ (%): C, 77.89; H, 7.84; N, 9.08. Found: C, 78.12; H, 8.20; N, 9.09.

*4.2.3. 3-Benzyl-1,1-dimethyl-2,3-dihydro-6′H-spiro[benzo[e]indole-2,2′-piperidin]-6′-one (**4c**).* To a solution of 1,1,2-trimethyl-1*H*-benzo[*e*]indole **1** (2.09 g, 10 mmol) in acetonitrile (10 mL) was added benzyl iodide (2.39 g, 11 mmol) and the mixture was heated under reflux for 24 h. Upon cooling to rt, the solvent was removed under reduced pressure and the residue was kept under high vacuum for 20 min to yield iodide **2c** as a brown viscous substance, which was used in the following reaction without further purification. ^{1}H NMR of **2c** (300 MHz, $CDCl_3$): δ_H 1.93 (s, 6H, 1-$(CH_3)_2$), 3.20 (s, 3H, 2-CH_3), 6.05 (s, 2H, CH_2), 7.26–7.30 (m, 2H, 2×H_{benzyl}), 7.35–7.39 (m, 3H, 3×H_{benzyl}), 7.64–7.78 (m, 2H, 7-H and 8-H), 7.70 (d, J=8.9 Hz, 1H, 4-H), 8.02 (d, J=7.9 Hz, 1H, 6-H), 8.04 (d, J=8.9 Hz, 1H, 5-H), 8.12 (1H, d, J=8.4 Hz, 9-H). To the obtained iodide **2c** was added a solution of triethylamine (3.03 g, 30 mmol) in dichloromethane (40 mL) and the mixture was stirred at rt for 1 h. The organic solution was washed with water (2×50 mL), brine (1×50 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue (methylidene base **3c**) was dissolved in ethylene glycol (15 mL) and acrylamide (1.07 g, 15 mmol) was added to the solution. The reaction mixture was stirred at 110 °C for 16 h. Then the reaction mixture was cooled to rt, diluted with water (50 mL) and extracted with ethyl acetate (5×50 mL). The combined organic layers were washed with brine (3×50 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to flash chromatography on silica gel (dichloromethane/methanol, 100:0→25:1 v/v) to yield the title compound **4c** (1.28 g, 35%) as a light brown amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.52 (3H, s, 1-CH_3), 1.74 (s, 3H, 1-CH_3), 1.89–2.08 (m, 3H, 3′-H_a, 4′-CH_2), 2.24–2.53 (m, 3H, 3′-H_b, 5′-CH_2), 4.37 (d, J=17.4 Hz, 1H, NC(H)H), 4.55 (d, J=17.4 Hz, 1H, NC(H)H), 6.08 (br s, 1H, NH), 6.70 (d, J=8.7 Hz, 1H, 4-H), 7.22 (ddd, J=8.1, 6.9, 1.1 Hz, 1H, 7-H), 7.28–7.39 (m, 5H, 5×CH_{benzyl}), 7.43 (ddd, J=8.5, 6.9, 1.5 Hz, 1H, 8-H), 7.60 (d, J=8.7 Hz, 1H, 5-H), 7.73–7.76 (m, 1H, 6-H), 7.84–7.97 (m, 1H, 9-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 18.3 (C-4′), 23.3 (1-CH_3), 24.3 (1-CH_3), 26.0 (C-3′), 31.1 (C-5′), 47.7 (NCH_2), 50.4 (C-1), 87.4 (C-2), 110.5 (C-4), 121.1 (C-9), 121.7 (C-7), 124.2 (C_{quat}), 126.1 (2×C, CH_{benzyl}), 126.6 (C-8), 127.1, 128.7 (2×C, CH_{benzyl}), 129.3 (C_{quat}), 129.6 (2×C, C-5 and C-6), 130.2 (C_{quat}), 139.4 (C_{quat}), 145.7 (C_{quat}), 172.8 (C=O); IR (neat, ν_{max}, cm^{-1}): 3163 (N–H), 3050, 2963, 1654 (C=O), 1620, 1591, 1519, 1451, 1391, 1349, 816, 744, 723, 697; MS (API-ES, pos mode), m/z (%): 371 ($M+H^+$, 100). Anal. Calcd for $C_{25}H_{26}N_2O$ (%): C, 81.05; H, 7.07; N, 7.56. Found: C, 81.26; H, 6.82; N, 7.28.

4.3. Procedures for the preparation of 3-alkyl-2-(4-amino-4-oxobutyl)-1,1-dimethyl-1*H*-benzo[*e*]indolium perchlorates (5)

*4.3.1. 2-(4-Amino-4-oxobutyl)-1,1,3-trimethyl-1H-benzo[e]indolium perchlorate (**5a**).* To a solution of compound **4a** (294 mg, 1 mmol) in ethanol (10 mL), 74 wt% $HClO_4$ (0.13 mL, 1.5 mmol) was added dropwise and the solution was kept at 0 °C for 2 h. The precipitated crystalline material was filtered, washed with cold ethanol (1 mL) and recrystallised from ethanol to give perchlorate **5a** (291 mg, 74%) as white crystals, mp 171.3–172.2 °C (with decomposition). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 1.78 (s, 6H, 1-$(CH_3)_2$), 1.88–1.98 (m, 2H, $COCH_2CH_2$), 2.40 (t, J=6.6 Hz, 2H, $COCH_2$), 3.17–3.22 (m, 2H, 2-CH_2), 4.19 (s, 3H, NCH_3), 6.98 (br s, 1H, N(H)H), 7.47 (br s, 1H, N(H)H), 7.70–7.75 (m, 1H, 7-H), 7.76–7.82 (m, 1H, 8-H), 8.08 (d, J=8.9 Hz, 1H, 4-H), 8.20–8.23 (m, 1H, 6-H), 8.29 (d, J=8.9 Hz, 1H, 5-H), 8.36–8.38 (m, 9-H); ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 20.6 (2×C, 1-$(CH_3)_2$), 21.7 ($COCH_2CH_2$), 25.9 (2-CH_2), 33.7 ($COCH_2$), 35.2 (NCH_3), 55.6 (C-1), 113.2 (C-4), 123.3 (C-9), 126.9 and 127.1 (C-7 and C_{quat}), 128.3 (C-8), 129.7 (C-6), 130.5 (C-5), 133.1 (C_{quat}), 136.4 (C_{quat}), 139.5 (C_{quat}), 173.3 (C=O), 196.5 (C=N); IR (KBr, ν_{max}, cm^{-1}): 3423, 3305

(N–H), 3157, 3079, 2984, 2974, 2947, 2876, 1686 (C=O), 1640, 1623, 1584, 1481, 1442, 1392, 1094, 819, 754, 623; MS (API-ES, pos mode), *m*/*z* (%): 300 ($M-ClO_4^-$, 100). Anal. Calcd for $C_{19}H_{23}ClN_2O_5$ (%): C, 57.80; H, 5.87; N, 7.09. Found: C, 58.02; H, 6.10; N, 7.08.

*4.3.2. 2-(4-Amino-4-oxobutyl)-3-ethyl-1,1-dimethyl-1H-benzo[e]indolium perchlorate (**5b**).* Compound **5b** was obtained similarly to **5a** from compound **4b** (308 mg, 1 mmol). Yield 237 mg (58%), pink crystals, mp 183.5–184.4 °C (from ethanol, with decomposition). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 1.57 (t, *J*=7.2 Hz, 3H, CH_2CH_3), 1.80 (s, 6H, 1-$(CH_3)_2$), 1.90–2.01 (m, 2H, $COCH_2CH_2$), 2.42 (t, *J*=6.6 Hz, 2H, $COCH_2$), 3.17–3.23 (m, 2H, $NCCH_2$), 4.70 (q, *J*=7.2 Hz, 2H, NCH_2), 6.99 (br s, 1H, N(*H*)H), 7.50 (br s, 1H, N(H)*H*), 7.72–7.83 (m, 2H, 7-H and 8-H), 8.14 (d, *J*=8.9 Hz, 1H, 4-H), 8.22–8.24 (m, 1H, 6-H), 8.30 (d, *J*=8.9 Hz, 1H, 5-H), 8.37–8.40 (m, 9-H); ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 13.6 (CH_2CH_3), 20.9 (2×C, 1-$(CH_3)_2$), 22.6 ($COCH_2CH_2$), 25.9 (2-CH_2), 33.7 ($COCH_2$), 43.5 (NCH_2), 55.8 (C-1), 113.4 (C-4), 123.4 (C-9), 127.1 and 127.2 (C_{quat} and C-7), 128.3 (C-8), 129.7 (C-6), 130.6 (C-5), 133.1 (C_{quat}), 137.1 (C_{quat}), 138.0 (C_{quat}), 173.3 (C=O), 196.7 (C=N); IR (KBr, ν_{max}, cm^{-1}): 3423, 3319 (N–H), 3088, 2982, 2940, 2874, 1684 (C=O), 1652, 1583, 1479, 1465, 1393, 1100, 1089, 823, 755, 623; MS (API-ES, pos mode), *m*/*z* (%): 309 ($M-ClO_4^-$, 100). Anal. Calcd for $C_{20}H_{25}ClN_2O_5$ (%): C, 58.75; H, 6.16; N, 6.85. Found: C, 59.10; H, 6.30; N, 6.79.

4.4. Procedures for the preparation of 4-(3-alkyl-1,1-dimethyl-2,3-dihydro-1*H*-benzo[*e*]indol-2-yl)butanamides (6)

*4.4.1. 4-(1,1,3-Trimethyl-2,3-dihydro-1H-benzo[e]indol-2-yl)butanamide (**6a**).* To a solution of compound **4a** (1.47 g, 5 mmol) in glacial acetic acid (5 mL) was added 10% Pd/C catalyst (74 mg, 5 wt% of starting compound) under argon. The solution was hydrogenated with H_2 at 20 bar and rt for 2 h. The mixture was filtered through a layer of Celite®, the filter cake was washed with ethyl acetate and the filtrate was concentrated under reduced pressure. The residue was dissolved in ethyl acetate and washed with saturated aqueous $NaHCO_3$ solution (3×30 mL). The organic extract was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was subjected to flash chromatography on silica gel (dichloromethane/methanol, 100:0→100:5 v/v) to afford the title compound **6a** (1.04 g, 70%) as white crystals, mp 118.0–119.6 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.32 (s, 3H, 1-CH_3), 1.70 (s, 3H, 1-CH_3), 1.79–1.98 (m, 4H, $COCH_2CH_2$, 2-CH_2), 2.34 (t, *J*=7.1 Hz, 2H, $COCH_2$), 2.84 (s, 3H, NCH_3), 2.90–2.94 (m, 1H, 2-H), 5.52 (br s, 2H, NH_2), 6.94 (d, *J*=8.7 Hz, 1H, 4-H), 7.16–7.21 (m, 1H, 7-H), 7.35–7.40 (m, 1H, 8-H), 7.64 (d, *J*=8.7 Hz, 1H, 5-H), 7.73–7.75 (m, 1H, 6-H), 7.94–7.97 (m, 1H, 9-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 21.2 (1-CH_3), 23.7 (CH_2), 28.1 and 28.2 (1-CH_3 and CH_2), 35.9 (NCH_3), 36.3 ($COCH_2$), 44.7 (C-1), 77.4 (C-2), 111.4 (C-4), 121.3 and 121.5 (C-7 and C-9), 126.0 (C-8), 128.1 (C_{quat}), 128.8 (C-5), 129.2 and 129.3 (C_{quat} and C-6), 130.1 (C_{quat}), 149.3 (C-3a), 175.1 (C=O); IR (KBr, ν_{max}, cm^{-1}): 3309, 3190 (N–H), 3048, 2961, 2866, 2794, 1686 (C=O), 1653, 1619, 1590, 1516, 1470, 1459, 1426, 1399, 1366, 1353, 1309, 1281, 1205, 1193, 1131, 977, 817, 750, 675; MS ($APCI^+$), *m*/*z* (%): 297 ($M+H^+$, 100). Anal. Calcd for $C_{19}H_{24}N_2O$ (%): C, 76.99; H, 8.16; N, 9.45. Found: C, 76.59; H, 8.05; N, 9.38.

*4.4.2. 4-(3-Ethyl-1,1-dimethyl-2,3-dihydro-1H-benzo[e]indol-2-yl)butanamide (**6b**).* Compound **6b** was obtained similarly to **6a** from compound **4b** (1.54 g, 5 mmol). Yield 1.023 g (66%), brown viscous substance. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.07 (t, *J*=7.2 Hz, 3H, CH_2CH_3), 1.32 (s, 3H, 1-CH_3), 1.68 (s, 3H, 1-CH_3), 1.74–1.96 (m, 4H, $COCH_2CH_2$ and 2-CH_2), 2.31 (t, *J*=7.1 Hz, 2H, $COCH_2$), 3.26 (dq, *J*=14.6, 7.2 Hz, 1H, C(*H*)HCH_3), 3.27–3.29 (m, 1H, 2-H), 3.50 (dq, *J*=14.6, 7.2 Hz, 1H, C(H)*H*CH_3), 5.54 (br s, 1H, N(*H*)H), 5.80 (br s, 1H, N(H)*H*), 6.89 (d, *J*=8.7 Hz, 1H, 4-H), 7.12–7.17 (m, 1H, 7-H), 7.32–7.38 (m, 1H, 8-H), 7.62 (d, *J*=8.7 Hz, 1H, 5-H), 7.71–7.73 (m, 1H, 6-H), 7.91–7.94 (m, 1H, 9-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 9.8 (CH_2CH_3), 21.1 (1-CH_3), 23.5 (CH_2), 28.3 (2×C, 1-CH_3 and CH_2), 36.3 ($COCH_2$), 39.8 (CH_2CH_3), 44.6 (C-1), 71.9 (C-2), 111.1 (C-4), 120.9 (C-7), 121.3 (C-9), 125.9 (C-8), 127.7 (C_{quat}), 128.7 (2×C, C-5 and C_{quat}), 129.3 (C-6), 130.3 (C_{quat}), 147.6 (C_{quat}), 175.2 (C=O); IR (neat, ν_{max}, cm^{-1}): 3331, 3185 (N–H), 3051, 2965, 2932, 2868, 2816, 1662 (C=O), 1619, 1591, 1518, 1462, 1439, 1366, 1350, 1322, 1274, 1209, 1186, 1145, 1132, 1069, 807, 735, 672; MS (API-ES, pos mode), *m*/*z* (%): 311 ($M+H^+$, 100). Anal. Calcd for $C_{20}H_{26}N_2O$ (%): C, 77.38; H, 8.44; N, 9.02. Found: C, 77.21; H, 8.51; N, 9.23.

4.5. Procedures for the preparation of ethyl 4-(3-alkyl-1,1-dimethyl-2,3-dihydro-1*H*-benzo[*e*]indol-2-yl)butanoates (7)

*4.5.1. Ethyl 4-(1,1,3-trimethyl-2,3-dihydro-1H-benzo[e]indol-2-yl) butanoate (**7a**).* To a solution of amide **6a** (148 mg, 0.5 mmol) in ethanol (2 mL) 6 M HCl (4 mL) was added and the mixture was stirred under reflux for 4 h. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in ethyl acetate, washed with saturated $NaHCO_3$ solution (2×10 mL). The organic layer was separated, dried over $MgSO_4$, filtered, concentrated under reduced pressure and purified by flash chromatography on silica gel (hexane/ethyl acetate, 3:1 v/v). Yield 117 mg (72%), a brown viscous substance. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.30 (t, *J*=7.1 Hz, 3H, CH_2CH_3), 1.34 (s, 3H, 1-CH_3), 1.71 (s, 3H, 1-CH_3), 1.79–1.96 (m, 4H, 2-CH_2CH_2), 2.44 (t, *J*=6.9 Hz, 2H, CH_2CO), 2.85 (s, 3H, NCH_3), 2.91 (t, *J*=5.4 Hz, 1H, 2-H), 4.18 (q, *J*=7.1 Hz, 2H, CH_2CH_3), 6.96 (d, *J*=8.7 Hz, 1H, 4-H), 7.20 (ddd, *J*=8.0, 6.9, 1.1 Hz, 1H, 7-H), 7.39 (ddd, *J*=8.5, 6.9, 1.5 Hz, 1H, 8-H), 7.66 (d, *J*=8.7 Hz, 1H, 5-H), 7.74–7.79 (m, 1H, 6-H), 7.96–7.99 (m, 1H, 9-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 14.3 (CH_2CH_3), 21.2 (1-CH_3), 23.3 (CH_2), 28.0 and 28.2 (1-CH_3 and CH_2), 34.9 (CH_2CO), 35.9 (NCH_3), 44.8 (C-1), 60.4 (CH_2CH_3), 77.4 (C-2), 111.5 (C-4), 121.4 (C-7), 121.6 (C-9), 126.0 (C-8), 128.2 (C_{quat}), 128.8 (C-5), 129.3 (C_{quat}), 129.4 (C-6), 130.1 (C_{quat}), 149.2 (C-3a), 173.4 (C=O); IR (KBr, ν_{max}, cm^{-1}): 3052, 2961, 2868, 2800, 1730 (C=O), 1621, 1592, 1518, 1459, 1363, 1292, 1191, 1121, 1025, 976, 806, 784, 744, 674; MS (API-ES, pos mode), *m*/*z* (%): 326 ($M+H^+$, 100). Anal. Calcd for $C_{21}H_{27}NO_2$ (%): C, 77.50; H, 8.36; N, 4.30. Found: C, 77.35; H, 8.44; N, 4.35.

*4.5.2. Ethyl 4-(3-ethyl-1,1-dimethyl-2,3-dihydro-1H-benzo[e]indol-2-yl)butanoate (**7b**).* Compound **7b** was obtained similarly to **7a** from compound **6b** (155 mg, 0.5 mmol). Yield 115 mg (68%), a brown viscous substance. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.11 (t, *J*=7.1 Hz, 3H, NCH_2CH_3), 1.31 (t, *J*=7.1 Hz, 3H, OCH_2CH_3), 1.35 (s, 3H, 1-CH_3), 1.71 (s, 3H, 1-CH_3), 1.80–2.00 (m, 4H, 2-CH_2CH_2), 2.44 (t, *J*=7.1 Hz, 2H, CH_2CO), 3.29 (t, 1H, *J*=5.2 Hz, 2-H), 3.29 (dq, *J*=14.2, 7.1 Hz, 1H, NC(*H*)H), 3.53 (dq, *J*=14.2, 7.1 Hz, 1H, NC(H)*H*), 4.20 (q, *J*=7.1 Hz, 2H, OCH_2), 6.92 (d, *J*=8.7 Hz, 1H, 4-H), 7.17 (ddd, *J*=8.0, 6.8, 1.1 Hz, 1H, 7-H), 7.37 (ddd, *J*=8.5, 6.8, 1.4 Hz, 1H, 8-H), 7.64 (d, *J*=8.7 Hz, 1H, 5-H), 7.71–7.78 (m, 1H, 6-H), 7.95 (dd, *J*=8.5, 6.8 Hz, 1H, 9-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 10.0 (NCH_2CH_3), 14.4 (OCH_2CH_3), 21.2 (1-CH_3), 23.3 (CH_2), 28.4 (2×C, 1-CH_3 and CH_2), 35.1 (CH_2CO), 40.0 (NCH_2), 44.8 (C-1), 60.5 (OCH_2), 72.2 (C-2), 111.3 (C-4), 121.1 and 121.5 (C-7 and C-9), 126.0 (C-8), 127.9 (C_{quat}), 128.9 and 129.0 (C-5 and C_{quat}), 129.5 (C-6), 130.5 (C_{quat}), 147.8 (C-3a), 173.5 (C=O); IR (neat, ν_{max}, cm^{-1}): 3049, 2968, 2934, 2870, 2816, 1731 (C=O), 1620, 1591, 1518, 1465, 1439, 1369, 1349, 1274, 1184, 1069, 1025, 955, 806, 782, 742, 673; MS (API-ES, pos mode), *m*/*z* (%): 340 ($M+H^+$, 100). Anal. Calcd for $C_{22}H_{29}NO_2$ (%): C, 77.84; H, 8.61; N, 4.13. Found: C, 77.91; H, 8.56; N, 4.08.

4.6. Procedures for the preparation of 4-(3-alkyl-1,1-dimethyl-2,3-dihydro-1*H*-benzo[*e*]indol-2-yl)butan-1-amines (8)

*4.6.1. 4-(1,1,3-Trimethyl-2,3-dihydro-1H-benzo[e]indol-2-yl)butan-1-amine (**8a**).* A solution of the amide **6a** (296 mg, 1 mmol) in dry

tetrahydrofuran (2 mL) was added to a suspension of $LiAlH_4$ (114 mg, 3 mmol) in dry tetrahydrofuran (3 mL) under nitrogen atmosphere. The reaction mixture was stirred under reflux under nitrogen atmosphere for 4 h. After cooling to 0 °C, an aqueous 3 M NaOH solution (5 mL) was added and the mixture stirred at rt for 3 h. Then the reaction mixture was filtered over Celite®, the filter cake was washed with ethyl acetate and the filtrate was extracted with ethyl acetate (3×20 mL). The organic layers were combined, washed with brine (3×15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure and purified by flash chromatography on silica gel (dichloromethane/methanol, 10:1 v/v) to afford the title compound **8a** (yield 217 mg, 77%) as a yellow viscous substance. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.40 (s, 3H, 1-CH_3), 1.57–1.73 (m, 4H, $CH_2CH_2CH_2NH_2$), 1.76 (s, 3H, 1-CH_3), 1.81–1.95 (m, 2H, 2-CH_2), 2.56 (br s, 2H, NH_2), 2.77–2.84 (m, 2H, CH_2NH_2), 2.86 (s, 3H, NCH_3), 2.97 (t, J=5.8 Hz, 1H, 2-H), 7.00 (d, J=8.7 Hz, 1H, 4-H), 7.22–7.29 (m, 1H, 7-H), 7.42–7.47 (m, 1H, 8-H), 7.70 (d, J=8.7 Hz, 1H, 5-H), 7.81 (d, J=8.2 Hz, 1H, 6-H), 8.04 (d, J=8.7 Hz, 1H, 9-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 21.0 (1-CH_3), 25.0 (CH_2), 28.0 and 28.3 (1-CH_3 and 2-CH_2), 33.8 (CH_2), 35.6 (NCH_3), 41.6 (CH_2NH_2), 44.5 (C-1), 77.3 (C-2), 111.2 (C-4), 121.0 and 121.3 (C-7 and C-9), 125.7 (C-8), 127.9 (C_{quat}), 128.5 (C-5), 129.0 (C_{quat}), 129.2 (C-6), 130.0 (C_{quat}), 149.2 (C-3a); IR (neat, ν_{max}, cm^{-1}): 3301 (N–H), 3053, 2934, 2864, 2800, 1666, 1621, 1592, 1518, 1458, 1360, 1353, 1292, 1206, 1145, 1055, 907, 806, 729, 683, 672; MS (APCI$^+$, pos mode), m/z (%): 283 (M+H$^+$, 100). Anal. Calcd for $C_{19}H_{26}N_2 \cdot 0.7H_2O$ (%): C, 77.35; H, 9.36; N, 9.49. Found: C, 77.46; H, 9.13; N, 9.11.

*4.6.2. 4-(3-Ethyl-1,1-dimethyl-2,3-dihydro-1H-benzo[e]indol-2-yl) butan-1-amine (**8b**).* Compound **8b** was obtained similarly to **8a** from amide **6b** (310 mg, 1 mmol). Yield 207 mg (70%), a yellow oily substance. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.06 (t, J=7.2 Hz, 3H, CH_2CH_3), 1.30 (s, 3H, 1-CH_3), 1.57–1.64 (m, 4H, $CH_2CH_2CH_2NH_2$), 1.67 (s, 3H, 1-CH_3), 1.73–1.82 (m, 2H, 2-CH_2), 2.55 (br s, 2H, NH_2), 2.78–2.82 (2H, m, CH_2NH_2), 3.19–3.31 (2H, m, 2-H and $C(H)HCH_3$), 3.49 (dq, J=14.7, 7.2 Hz, 1H, C(H)HCH_3), 6.88 (d, J=8.7 Hz, 1H, 4-H), 7.14 (ddd, J=8.0, 6.9, 1.2 Hz, 1H, 7-H), 7.34 (ddd, J=8.5, 6.9, 1.5 Hz, 1H, 8-H), 7.61 (1H, d, J=8.7 Hz, 5-H), 7.70–7.73 (m, 1H, 6-H), 7.91–7.94 (m, 1H, 9-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 9.9 (CH_2CH_3), 21.1 (1-CH_3), 25.2 (CH_2), 28.4 and 28.7 (1-CH_3 and 2-CH_2), 34.0 (CH_2), 39.9 (CH_2CH_3), 41.9 (CH_2NH_2), 44.6 (C-1), 72.2 (C-2), 111.2 (C-4), 120.9 (C-7), 121.4 (C-9), 125.9 (C-8), 127.8 (C_{quat}), 128.8 (2×C, C-5 and C_{quat}), 129.4 (C-6), 130.4 (C_{quat}), 147.8 (C-3a); IR (neat, ν_{max}, cm^{-1}): 3363 (N–H), 3184 (N–H), 3049, 2965, 2932, 2866, 1620, 1591, 1518, 1471, 1439, 1366, 1349, 1324, 1274, 1209, 1186, 1145, 1133, 1067, 956, 806, 737, 672; MS (API-ES, pos mode), m/z (%): 297 (M+H$^+$, 100). Anal. Calcd for $C_{20}H_{28}N_2$ (%): C, 81.03; H, 9.52; N, 9.45. Found: C, 81.24; H, 9.38; N, 9.49.

4.7. Procedures for the preparation of *N*-[4-(1-alkyl-1,1-dimethyl-2,3-dihydro-1*H*-benzo[*e*]indol-2-yl)butyl]acetamides and the corresponding carbamates (9)

*4.7.1. N-[4-(1,1,3-Trimethyl-2,3-dihydro-1H-benzo[e]indol-2-yl)butyl]acetamide (**9a**).* A solution of acetic anhydride (204 mg, 2 mmol) and amine **8a** (141 mg, 0.5 mmol) in dry dichloromethane (5 mL) was stirred at rt for 1.5 h. The reaction mixture was diluted with dichloromethane (10 mL) and washed with saturated aqueous $NaHCO_3$ solution (2×10 mL), the organic layer was separated, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (dichloromethane/methanol, 100:3 v/v). Yield 126 mg (78%), yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.30 (s, 3H, 1-CH_3), 1.52–1.63 (m, 4H, $CH_2CH_2CH_2NH$), 1.67 (s, 3H, 1-CH_3), 1.76–1.82 (m, 2H, 2-CH_2), 1.98 (s, 3H, $COCH_3$), 2.81 (s, 3H, NCH_3), 2.88 (t, J=5.9 Hz, 1H, 2-H), 3.29 (q, J=6.2 Hz, 2H, CH_2NH), 5.69 (br s, 1H, NH), 6.93 (d, J=8.7 Hz, 1H, 4-H), 7.15–7.20 (m, 1H, 7-H), 7.34–7.40 (m, 1H, 8-H), 7.63 (d, J=8.7 Hz, 1H, 5-H), 7.72–7.75 (m, 1H, 6-H), 7.94–7.96 (m, 1H, 9-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 21.2 (1-CH_3), 23.3 ($COCH_3$), 25.2 (CH_2), 28.3 (2×C, 1-CH_3 and 2-CH_2), 30.5 (CH_2), 36.0 (NCH_3), 39.5 (CH_2NH), 44.8 (C-1), 77.5 (C-2), 111.5 (C-4), 121.3 (C-7), 121.6 (C-9), 126.0 (C-8), 128.2 (C_{quat}), 128.8 (C-5), 129.3 (C_{quat}), 129.4 (C-6), 130.2 (C_{quat}), 149.4 (C-3a), 170.2 (C=O); IR (neat, ν_{max}, cm^{-1}): 3288 (N–H), 3073, 3057, 2960, 2936, 2865, 2802, 1650 (C=O), 1621, 1592, 1519, 1458, 1363, 1292, 1206, 1122, 995, 908, 807, 727, 673, 684; MS (API-ES, pos mode), m/z (%): 325 (M+H$^+$, 100). Anal. Calcd for $C_{21}H_{28}N_2O$ (%): C, 77.74; H, 8.70; N, 8.63. Found: C, 77.59; H, 8.77; N, 8.71.

*4.7.2. tert-Butyl [4-(1,1,3-trimethyl-2,3-dihydro-1H-benzo[e]indol-2-yl)butyl]carbamate (**9b**).* To a solution of compound **4a** (141 mg, 0.5 mmol) in dry dichloromethane (5 mL), di-*tert*-butyl dicarbonate (218 mg, 1 mmol) was added and the mixture was stirred at rt for 30 min. Then the reaction mixture was diluted with dichloromethane (10 mL) and washed with saturated aqueous $NaHCO_3$ (2×10 mL). The organic extract was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether/diethyl ether, 4:1→2:1 v/v) to afford the title compound **9b** (103 mg, 54%) as a brown viscous substance. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.31 (s, 3H, 1-CH_3), 1.46 (s, 9H, $C(CH_3)_3$), 1.58–1.61 (m, 4H, $CH_2CH_2CH_2NH$), 1.68 (s, 3H, 1-CH_3), 1.77–1.81 (m, 2H, 2-CH_2), 2.83 (s, 3H, NCH_3), 2.89 (t, J=5.7 Hz, 1H, 2-H), 3.12–3.27 (m, 2H, CH_2NH), 4.58 (br s, 1H, NH), 6.95 (d, J=8.7 Hz, 1H, 4-H), 7.16–7.21 (m, 1H, 7-H), 7.35–7.40 (m, 1H, 8-H), 7.64 (d, J=8.7 Hz, 1H, 5-H), 7.72–7.75 (m, 1H, 6-H), 7.94–7.97 (m, 1H, 9-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 21.2 (1-CH_3), 25.1 (CH_2), 28.3 (2×C, 1-CH_3 and 2-CH_2), 28.4 (3×C, $C(CH_3)_3$), 31.0 (CH_2), 36.0 (NCH_3), 40.4 (CH_2NH), 44.8 (C-1), 77.6 (C-2), 79.2 ($C(CH_3)_3$), 111.6 (C-4), 121.4 and 121.6 (C-7 and C-9), 126.0 (C-8), 128.4 (C_{quat}), 128.8 (C-5), 129.4 (2×C, C_{quat} and C-6), 130.2 (C_{quat}), 149.4 (C-3a), 156.0 (C=O); IR (neat, ν_{max}, cm^{-1}): 3351 (N–H), 3057, 2971, 2933, 2865, 2798, 1691 (C=O), 1622, 1592, 1517, 1456, 1364, 1282, 1249, 1168, 909, 807, 730, 673; MS (API-ES, pos mode), m/z (%): 383 (M+H$^+$, 100). Anal. Calcd for $C_{24}H_{34}N_2O_2$ (%): C, 75.35; H, 8.96; N, 7.32. Found: C, 75.24; H, 9.01; N, 7.38.

*4.7.3. N-[4-(3-Ethyl-1,1-dimethyl-2,3-dihydro-1H-benzo[e]indol-2-yl)butyl]acetamide (**9c**).* Compound **9c** was obtained similarly to **9a** from compound **8b** (148 mg, 0.5 mmol). Yield 140 mg (83%), a brown viscous substance. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.07 (t, J=7.3 Hz, 3H, CH_2CH_3), 1.30 (s, 3H, 1-CH_3), 1.52–1.63 (m, 4H, $CH_2CH_2CH_2NH$), 1.67 (s, 3H, 1-CH_3), 1.73–1.80 (m, 2H, 2-CH_2), 1.99 (s, 3H, $COCH_3$), 3.18–3.33 (m, 4H, CH_2NH, 2-H and $C(H)HCH_3$), 3.49 (dq, J=14.7, 7.3 Hz, 1H, C(H)HCH_3), 5.61 (br s, 1H, NH), 6.89 (d, J=8.7 Hz, 1H, 4-H), 7.12–7.17 (m, 1H, 7-H), 7.35 (ddd, J=8.4, 6.9, 1.5 Hz, 1H, 8-H), 7.61 (d, J=8.7 Hz, 1H, 5-H), 7.70–7.73 (m, 1H, 6-H), 7.91–7.94 (m, 1H, 9-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 9.9 (CH_2CH_3), 21.1 (1-CH_3), 23.4 ($COCH_3$), 25.1 (CH_2), 28.4 and 28.5 (1-CH_3 and 2-CH_2), 30.6 (CH_2), 39.6 and 39.9 (CH_2CH_3 and CH_2NH), 44.6 (C-1), 72.1 (C-2), 111.2 (C-4), 120.9 (C-7), 121.3 (C-9), 125.9 (C-8), 127.8 (C_{quat}), 128.8 (C-5), 129.4 (2×C, C_{quat} and C-6), 130.4 (C_{quat}), 147.7 (C-3a), 170.1 (C=O); IR (neat, ν_{max}, cm^{-1}): 3278 (N–H), 3073, 2966, 2932, 2866, 1649 (C=O), 1621, 1591, 1555, 1518, 1473, 1462, 1438, 1366, 1275, 1209, 1186, 1146, 1133, 1066, 958, 909, 806, 782, 730, 684, 673; MS (API-ES, pos mode), m/z (%): 339 (M+H$^+$, 100). Anal. Calcd for $C_{22}H_{30}N_2O$ (%): C, 78.06; H, 8.93; N, 8.28. Found: C, 78.34; H, 9.08; N, 8.40.

*4.7.4. tert-Butyl [4-(3-ethyl-1,1-dimethyl-2,3-dihydro-1H-benzo[e]indol-2-yl)butyl]carbamate (**9d**).* Compound **9d** was obtained similarly to **9b** from amine **8b** (148 mg, 0.5 mmol). Yield 113 mg (57%), brown viscous substance. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.06 (t,

J=7.2 Hz, 3H, CH_2CH_3), 1.30 (s, 3H, 1-CH_3), 1.46 (s, 9H, $C(CH_3)_3$), 1.51–1.62 (m, 4H, $CH_2CH_2CH_2NH$), 1.67 (s, 3H, 1-CH_3), 1.72–1.79 (m, 2H, 2-CH_2), 3.06–3.30 (m, 4H, CH_2NH, 2-H and $C(H)HCH_3$), 3.49 (dq, J=14.7, 7.2 Hz, 1H, $C(H)HCH_3$), 4.61 (br s, 1H, NH), 6.88 (d, J=8.7 Hz, 1H, 4-H), 7.11–7.16 (m, 1H, 7-H), 7.34 (ddd, J=8.4, 6.9, 1.2 Hz, 1H, 8-H), 7.61 (d, J=8.7 Hz, 1H, 5-H), 7.70–7.73 (m, 1H, 6-H), 7.91–7.94 (m, 1H, 9-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 9.8 (CH_2CH_3), 21.0 (1-CH_3), 24.9 (CH_2), 28.2 (2×C, 1-CH_3 and 2-CH_2), 28.4 (3×C, $C(CH_3)_3$), 31.0 (CH_2), 39.7 (CH_2CH_3), 40.3 (CH_2NH), 44.5 (C-1), 72.0 (C-2), 79.2 ($C(CH_3)_3$), 111.1 (C-4), 120.8 (C-7), 121.3 (C-9), 125.8 (C-8), 127.7 (C_{quat}), 128.7 (2×C, C-5 and C_{quat}), 129.3 (C-6), 130.3 (C_{quat}), 147.7 (C-3a), 155.9 (C=O); IR (neat, ν_{max}, cm^{-1}): 3346 (N–H), 3057, 2969, 2933, 2866, 1691 (C=O), 1621, 1591, 1518, 1474, 1439, 1364, 1274, 1249, 1169, 908, 806, 781, 740, 672; MS (API-ES, pos mode), m/z (%): 397 ($M+H^+$, 100). Anal. Calcd for $C_{25}H_{36}N_2O_2$ (%): C, 75.72; H, 9.15; N, 7.06. Found: C, 75.53; H, 9.28; N, 7.14.

4.8. Procedure for the preparation of 12,12-dimethyl-10, 11,11a,12-tetrahydrobenzo[*e*]pyrido[1,2-*a*]indol-8(9*H*)-one (10)

To a solution of compound **4c** (740 mg, 2 mmol) in glacial acetic acid (2 mL) was added 10% Pd/C catalyst (37 mg, 5 wt % of starting compound) under argon. The solution was hydrogenated with H_2 at 20 bar and rt for 3 h. The mixture was filtered through a layer of Celite®, the filter cake was washed with ethyl acetate and the filtrate was concentrated under reduced pressure. The residue was dissolved in ethyl acetate and washed with saturated aqueous $NaHCO_3$ solution (3×30 mL). The organic extract was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The product was purified by flash chromatography on silica gel (dichloromethane/methanol, 100:0→100:1 v/v) to afford the title compound **10** (291 mg, 55%) as brown crystals, mp 123–125 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.28 (s, 3H, 12-CH_3), 1.73 (s, 3H, 12-CH_3), 1.66–1.90 (m, 2H, 10-H_a and 11-H_a), 2.05–2.18 (m, 2H, 10-H_b and 11-H_b), 2.47–2.59 (m, 1H, 9-H_a), 2.65–2.74 (m, 1H, 9-H_b), 3.85 (dd, J=3.3, 11.5 Hz, 1H, 11a-H), 7.38 (ddd, J=8.1, 6.9, 1.3 Hz, 1H, 3-H), 7.47 (ddd, J=8.5, 6.9, 1.5 Hz, 1H, 2-H), 7.75 (d, J=8.8 Hz, 1H, 5-H), 7.84–7.87 (m, 1H, 4-H), 8.07–8.11 (m, 1H, 1-H), 8.50 (d, J=8.8 Hz, 1H, 6-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 20.7 (C-10), 22.4 (2×C, C-11-CH_2 and 1-CH_3), 26.1 (1-CH_3), 32.8 (C-9), 44.4 (C-12), 71.1 (C-11a), 117.6 (C-6), 122.9 (C-1), 123.9 (C-3), 126.1 (C-2), 128.6 (C-5), 129.4 (2×C, C-4 and C_{quat}), 131.9 (C_{quat}), 132.4 (C_{quat}), 139.2 (C_{quat}), 168.5 (C=O); IR (KBr, ν_{max}, cm^{-1}): 3057, 2982, 2962, 2934, 2869, 1643 (C=O), 1590, 1471, 1462, 1425, 1407, 1336, 1310, 1220, 1178, 1149, 820, 741; MS (API-ES, pos mode), m/z (%): 266 ($M+H^+$, 100). Anal. Calcd for $C_{18}H_{19}NO$ (%): C, 81.47; H, 7.22; N, 5.28. Found: C, 81.62; H, 7.16; N, 5.26.

4.9. Procedure for the preparation of 12,12-dimethyl-8,9,10,11,11a,12-hexahydrobenzo[*e*]pyrido[1,2-*a*]indole (11)

To a suspension of $LiAlH_4$ (114 mg, 3 mmol) in dry tetrahydrofuran (3 mL), a solution of compound **10** (265 mg, 1 mmol) in dry tetrahydrofuran (2 mL) was added and the reaction mixture was stirred under nitrogen at reflux temperature for 4 h. After the reaction mixture was cooled to rt, 3 M NaOH (1 mL) was added dropwise to the reaction mixture. A finely suspended solid was filtered off using a fritted glass Buchner funnel and the filter cake was washed with ethyl acetate. The filtrate was extracted with ethyl acetate (3×20 mL), the combined organic layers were washed with brine (3×15 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to flash chromatography on silica gel (dichloromethane) to afford the title compound **11** (173 mg, 69%), as grey crystals, mp 142.5–144.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.21 (s, 3H, 12-CH_3), 1.30–1.45 (m, 1H, 10-H_a), 1.50–1.59 (m, 1H, 11-H_a), 1.62 (3H, s, 12-CH_3), 1.64–1.83 (m, 3H, 11-CH_b and 9-CH_2), 2.00 (dp, J=12.7, 2.9 Hz, 1H, 10-H_b), 2.56 (dt, J=3.1, 11.5 Hz, 1H, 8-H_a), 2.71 (dd, J=2.5, 11.5 Hz, 1H, 11a-H), 3.76–3.80 (m, 1H, 8-H_b), 6.92 (d, J=8.6 Hz, 1H, 6-H), 7.14–7.19 (m, 1H, 3-H), 7.33–7.39 (m, 1H, 2-H), 7.62 (d, J=8.6 Hz, 1H, 5-H), 7.72–7.75 (m, 1H, 4-H), 7.92–7.95 (m, 1H, 1-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 20.8 (12-CH_3), 24.1 (C-11), 24.6 (C-10), 25.3 (C-9), 26.5 (12-CH_3), 43.6 (C-12), 46.5 (C-8), 75.5 (C-11a), 110.2 (C-6), 121.1 (C-1), 121.6 (C-3), 125.9 (C-2), 128.3 (C_{quat}), 128.5 (C-5), 129.1 (C_{quat}), 129.4 (C-4), 130.6 (C_{quat}); IR (KBr, ν_{max}, cm^{-1}): 3076, 3050, 2968, 2928, 2852, 2798, 1619, 1589, 1519, 1473, 1440, 1373, 1341, 1299, 1252, 1205, 1143, 1078, 986, 832, 806, 737, 680; MS (API-ES, pos mode), m/z (%): 252 ($M+H^+$, 100). Anal. Calcd for $C_{18}H_{21}N\cdot 0.8H_2O$ (%): C, 81.34; H, 8.57; N, 5.27. Found: C, 81.13; H, 8.17; N, 5.44.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2012.08.073. These data include MOL files and InChiKeys of the most important compounds described in this article.

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