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# **Graphical Abstract**

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# Synthesis of new fluorescent building blocks *via* the microwave-assisted annulation reaction of 1,1,2-trimethyl-1*H*-benzo[*e*]indole with acrylic acid and its derivatives

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#### ABSTRACT

The reaction of 1,1,2-trimethyl-1*H*-benzo[*e*]indole with acrylic acid and its derivatives was employed for the preparation of novel fluorescent building blocks. Treatment of 1,1,2-trimethyl-1*H*-benzo[*e*]indole with acrylic acid, acrylamide or *tert*-butyl acrylate in an autoclave or a microwave reactor at 180–200 °C afforded benzo[*e*]pyrido[1,2-*a*]indole derivatives. Various chemical transformations of the latter compounds have been performed to yield functionalized benzo[*e*]indole scaffolds. The structure assignments were based on data from <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy and single crystal X-ray analyses. The optical properties of the obtained benzo[*e*]indoline derivatives were studied by UV–Vis and fluorescence spectroscopy.

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#### 1. Introduction

During the last decade, there has been a significant increase in the use 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 and probes for high-contrast fluorescence imaging of biological tissues,<sup>1</sup> as well as novel fluorophores for multiple-mode molecular logic systems<sup>2</sup> or enzyme sensing in biological assays.<sup>3</sup> Furthermore, blue organic squaraine dyes containing the 1,1,2-trimethyl-1*H*-benzo[*e*]indole nucleus were used for dye-sensitized solar cell applications.<sup>4</sup> The preparation methods for these functional dyes traditionally include the alkylation of 1,1,2-trimethyl-1*H*-benzo[*e*]indole 1 to form the corresponding 3-substituted 1,1,2-trimethyl-1*H*-benzo[*e*]indolium salts.<sup>1-4</sup> For cyanine dye synthesis, the aforementioned salts were employed as nucleophilic substrates for stepwise condensation with polyene-chain precursors.<sup>5,6</sup> Recently, a significant number of alkylating agents, such as alkyl halides, <sup>la,e,2</sup> propargyl bromide, <sup>lc</sup> haloalkanoic acids, <sup>la,d,f,4,5a,b</sup> and 1,4-butane sultone<sup>56</sup> were employed for the alkylation of 1,1,2trimethyl-1*H*-benzo[e]indole 1. However, the potentially useful conjugate addition reactions of 1,1,2-trimethyl-1*H*benzo[e]indole 1 with 2,3-unsaturated carbonyl derivatives remain unexplored.

When reacted with acrylamide, the structurally similar 2,3,3trimethyl-3H-indole serves as a N-nucleophile and affords Michael addition adducts that can easily undergo intramolecular cyclisation to form pyrimido [1,2-a] indole derivatives,<sup>7</sup> which are useful precursors of basic cyanine dyes.<sup>8</sup> The corresponding 2methylidene bases, derived from 1-alkyl-2,3,3-trimethyl-3Hindolium salts, act as C-nucleophiles when reacted with acrylamide to yield spiro[indole-2,2'-piperidine] derivatives.9 Recently, the similar coupling of 2-methylidene-1Hbenzo[e]indole with acrylamide was utilized for the preparation of novel fluorescent scaffolds.<sup>10</sup> Finally, the condensation of 2,3,3-trimethyl-3H-indoles with 2,3-unsaturated aldehydes and ketones provides pyrido[1,2-a]indolium salts that have been applied to the synthesis of optical brighteners and dyes for synthetic fibers,<sup>11</sup> while their formylation afforded the corresponding dialdehydes, as synthons for the preparation of 2-(pyrazol-4-yl)-3*H*-indole derivatives.<sup>12</sup> The aim of the present work is the synthesis of fluorescent building blocks through the reaction of 1,1,2-trimethyl-1H-benzo[e]indole with acrylic acid and further chemical transformations of the obtained adducts.

#### 2. Results and discussion

The Michael addition of nucleophiles across active 2,3unsaturated carbonyl compounds are typically acid or base catalyzed.<sup>13</sup> A wide variety of acidic catalysts, mostly Lewis<sup>14</sup> and protic<sup>15</sup> acids, have been cited in the literature. Additionally, the aza-Michael addition of cyclic azomethines, such as 3*H*indoles and 3,4-dihydroisoquinolines, across acrylamide can be successfully carried out in acetic acid, which also acts as the solvent when used in excess.<sup>7,16</sup> However, when 1,1,2-trimethyl-1*H*-benzo[*e*]indole **1** was treated with acrylic acid in refluxing

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Investigation of the reaction conditions for the coupling of 1,1,2-trimethy
1 <i>H</i> -benzo[ <i>e</i> ]indole <b>1</b> with acrylic acid, acrylamide and <i>tert</i> -butyl acrylate

Entry	Reagents and reaction conditions ( <i>Method</i> )	Ratio of products <b>2</b> and <b>3</b> <sup>a</sup>	Total yield of products <b>2</b> and <b>3</b>
1	Acrylic acid, acetic acid, autoclave, 180 °C, 19 h; (A)	7/3	51%
2	Acrylic acid, <i>o</i> - xylene, autoclave, 200 °C, 12 h; ( <i>B</i> )	2/3	38%
3	Acrylamide, acetic acid, autoclave, 180 °C, 19 h; ( <i>C</i> )	1/2	21%
4	Acrylic acid, acetic acid, microwave (100 W), 180 °C, 1 h; (D)	7/2	51%
5	Acrylic acid, <i>o</i> - xylene, microwave (100 W), 180 °C, 1 h; ( <i>E</i> )	7/4	56%
6	Acrylic acid, <i>o</i> - xylene, microwave (120 W), 200 °C, 1 h; ( <i>F</i> )	1/1	67%
7	<i>tert</i> -Butyl acrylate, <i>o</i> - xylene, microwave (120 W), 200 °C, 1 h ( <i>G</i> )	1/4	14%
8	<i>tert</i> -Butyl acrylate, acetic acid, microwave (100 W), 180 °C, 1 h ( <i>H</i> )	4/1	56%

<sup>a</sup>Ratio determined for isolated products

glacial acetic acid or its mixture with hydrochloric acid, no desired addition products were obtained, and only the starting indole 1 was recovered. Heating the aforementioned reaction mixture in an autoclave at 180 °C for 19 h afforded isomeric pyrido[1,2-*a*]indolones 2 and 3 in isolated yields of 36% and 15%, respectively (Scheme 1 and Table 1, entry 1). When *o*-xylene was used as the solvent instead of acetic acid, the total yield of the reaction was only 38%, and compound 3 was the major product (Table 1, entry 2). A mixture of products 2 and 3 was also obtained when acrylamide was used instead of acrylic acid, but the total yield of the products decreased to 21% (Table 1, entry 3).

It is recognized that microwave irradiation efficiently promotes Michael addition of heteronucleophiles to 2,3-unsaturated carbonyl compounds.<sup>17</sup> The reaction of 1,1,2trimethyl-1*H*-benzo[*e*]indole 1 and acrylic acid under microwave irradiation in acetic acid and o-xylene gave a mixture of compounds 2 and 3 within a short period of time (1 h) (Table 1, entries 4, 5). The best total yield (67%) of products 2 and 3 was achieved when the reaction was performed in a closed reaction vessel at 200 °C using 120 W microwave irradiation power (Table 1, entry 6). However, when tert-butyl acrylate was used as the 2,3-unsaturated carbonyl substrate in similar reaction conditions and the reaction was performed in o-xylene, the total yield of the target products was miserable (Table 1, entry 7). The last experiment was designed to assess the importance of acid catalysis for this type of reaction. To this end, the aforementioned reaction was performed in acetic acid. The obtained result - fourfold increase of the total yield and change of the ratio between products 2 and 3 in favour of the first - confirmed that acid catalysis significantly stimulates aza-Michael addition of  $\alpha$ -C-



Scheme 1. Synthesis of benzo[e]pyrido[1,2-a]indolones 2 and 3

methylazomethines to 2,3-unsaturated carbonyl compounds (Table 1, entry 8).

There is abundant evidence that cyclic  $\alpha$ -C-methyl azomethines exist in a tautomeric equilibrium with the corresponding enamine form.<sup>18</sup> Therefore, the formation of tetracyclic compound **2** can be explained as a result of the acid-catalysed aza-Michael addition reaction of **1** or its tautomer **A** across the acrylic double bond, leading to the formation of the intermediate adduct **B**, which undergoes further intramolecular cyclisation. However, when the corresponding carba-Michael addition reaction gives the intermediate adduct **C**, the cyclic enamide **3** results.

The structural assignment of compounds **2** and **3** was based on analysis of the spectral data. The <sup>1</sup>H NMR spectrum of **2** revealed two triplets of methylene protons at 4.07 and 4.55 ppm (J = 7.8Hz) and a singlet at 5.29 ppm for the isolated methine proton, which corresponded to the proton signals from the CH<sub>2</sub>CH<sub>2</sub>C(=O)CH moiety. The spectrum of **3** showed a set of signals attributable to the C(=O)CH<sub>2</sub>CH<sub>2</sub>CH moiety with multiplets at 2.43–2.50 ppm and 2.65–2.72 ppm for the two methylene groups and a triplet at 5.21 ppm (J = 4.2 Hz) for the methine proton. The <sup>13</sup>C NMR spectrum of **2** was characteristic of enaminones and contained signals at 93.4 (N–C=CH), 175.5 (N–C=CH) and 190.3 (C=O) ppm.<sup>19</sup> For enamide **3**, the corresponding carbon atom signals were present at 96.9, 151.3 and 168.2 ppm.<sup>20</sup>

Enaminones are versatile building blocks in organic synthesis<sup>21</sup> and are useful for the preparation of  $\gamma$ -aminoalcohols<sup>22</sup> and various heterocycles.<sup>23</sup> To test the synthetic



Scheme 2. The synthetic application of enaminone 2



Figure 1. ORTEP view of compound 4

potential of the enaminone **2**, the reduction of it with NaBH<sub>4</sub> and condensation reactions with hydroxylamine and 1-methyl-1phenylhydrazine were investigated (Scheme 2). The reduction of enaminones with NaBH<sub>4</sub> gives  $\gamma$ -aminoalcohols,<sup>22d,e</sup> while the condensation of enaminones with hydroxylamine forms isoxazole derivatives.<sup>23d</sup> Treatment of compound **2** with NaBH<sub>4</sub> in ethanol at 60 °C afforded alcohol **4** as a single diastereomer after recrystallisation from ethanol (Scheme 2).

The relative  $(10R^*, 11aS^*)$ -configuration of compound **4** was established by X-ray analysis (Figure 1).<sup>24</sup> The piperidine ring of the asymmetric, relatively rigid unit of **4** is in a chair conformation with the hydroxyl group in an equatorial position. The sum of the angles between the covalent bonds around the N(11) atom is 337.33°, which indicates that a pyramidal geometry exists at the sp<sup>3</sup>-hybridised nitrogen atom.<sup>25</sup> The length of the C(2)–N(11) bond is slightly longer [1.409(2) Å] than that in aniline (1.399; 1.385 Å)<sup>26</sup> and 2-(4-cyanophenylacylidene)-1,3,3-trimethyl-2,3-dihydro-1*H*-indole [1.402(4) Å].<sup>27</sup> This longer bond length may be explained by the disrupted conjugation of the nitrogen lone electron pair with the  $\pi$ -system of the aromatic ring.<sup>28</sup> The C(12)–N(11) and C(16)–N(11) bond lengths are 1.467(2) and 1.482(2) Å, respectively, and agree with the known bond lengths of piperidines.<sup>29</sup> The C(14)–O(18) bond length [1.428(2) Å] is similar to those found in related alcohols.<sup>30</sup>

Condensation of **2** with hydroxylamine hydrochloride in ethanol in the presence of pyridine afforded the oxime **5**. The <sup>1</sup>H NMR spectrum of **5**, acquired in DMSO- $d_6$  at 20 °C, revealed two sets of proton signals attributed to the presence of a mixture of the corresponding oxime Z- and E-isomers<sup>31</sup> (5/1 ratio of major/minor isomers) in solution. However, oxime **5** did not undergo any further cyclisation to form an isoxazole derivative.

Fluorescent functionalised heterocycles are suitable building blocks for the preparation of functional materials with various photonic, electronic and optoelectronic applications.<sup>32</sup> For example, the condensation of 9-alkyl-9*H*-carbazole and 10-alkyl-10*H*-phenothiazine derivatives, which possess a side-chain aldehyde moiety, with phenylhydrazines resulted in the formation of the corresponding hydrazones, which are efficient hole transport materials.<sup>33</sup> When compound **2** was heated with 1-methyl-1-phenylhydrazine in ethanol, the condensation of the enaminone carbonyl group with the hydrazine moiety occurred to afford a mixture of *Z*- and *E*-hydrazones **6a** and **6b**, respectively, in a ratio of 4/1. For the major isomer, the *Z*-configuration was assigned on the basis of the NOE effect in the NMR spectrum of the mixture of isomers.

Next, we investigated the chemical transformations of compound **3**, which possesses the cyclic enamide functionality (Scheme 3). Enamides have been shown to have ambident reactivity as they are simultaneously electrophilic at the  $\alpha$ -carbon and nucleophilic at the  $\beta$ -carbon. They are stable compounds under neutral or basic conditions, but in acidic media, protonation on the  $\beta$ -carbon atom occurs to form a reactive acyliminium intermediate, which might undergo hydrolysis.<sup>34</sup> Recently, alkylation,<sup>35</sup> arylation,<sup>36</sup> alkenylation<sup>37</sup> and fluorination<sup>38</sup> of enamides have been explored. Additionally, it is



Scheme 3. The chemical transformations of enamide 3

important to note that the enamide moiety is a frequently encountered structural motif in many medicinally valuable compounds.<sup>39</sup> When enamide **3** was treated with a methanolic solution of HCl, generated by the addition of acetyl choride to methanol, enaminone ring cleavage occurred to afford methyl 4-(1,1-dimethyl-1 H-benzo[e]indol-2-yl)butanoate **8a** in 86% yield. The corresponding ethyl butanoate **8b** was obtained in a similar manner. Unexpectedly, the formation of esters **8a,b** also occurred when enamide **3** was alkylated with methyl or ethyl iodide in DMF containing NaH, followed by a standard work-up of the reaction mixture with water. The treatment of benzo[e]indole derivative **8a** with 48% tetrafluoroboric acid afforded crystalline 1*H*-benzo[e]indolium tetrafluoroborate **9**, while alkylation with methyl iodide gave 2-(4-methoxy-4oxobutyl)-1,1,3-trimethyl-1*H*-benzo[e]indolium iodide **10**.

It has previously been shown that 2-ethyl-3,3-dimethyl-3*H*indole easily autooxidises to 2-acetyl-3,3-dimethyl-3*H*-indole.<sup>40</sup> We observed a similar tendency for oxidation of the 2-(3alkoxycarbonylpropyl) side-chain of compounds **8a,b**. Heating these compounds in DMSO, which is a weak oxidizer,<sup>41</sup> at 50 °C for 8 h afforded alkyl 4-(1,1-dimethyl-1*H*-benzo[*e*]indol-2-yl)-4oxobutanoates **11a,b** in 96% and 88% yields, respectively. The condensation of oxobutanoate **11a** with phenylhydrazine afforded phenylhydrazone **12** (Scheme 3).

The structure of compound **11a** was confirmed by the presence of the characteristic ketone carbonyl group absorption band at 1674 cm<sup>-1</sup> in the IR spectrum and a corresponding signal at 196.1 ppm (ketone carbon) in the <sup>13</sup>C NMR spectrum. Single crystal X-ray analysis of **11a** (Fig.2)<sup>42</sup> indicated that the molecule has a symmetry plane in which all skeletal atoms are positioned, with the exception of the methyl carbons C(22) and C(22<sup>i</sup>).The imino-carbonylic fragment [N(1)=C(2)–C(14)=O(15)] is in a *s*-trans conformation. The ethylenic bridge connecting the two carbonyl groups is in a staggered conformation, in which the carbonyls are oriented in an *anti*-position. The ester group possesses the *Z*-conformation.



Figure 2. ORTEP view of compound 11a

The optical properties of benzo[e] indoline derivatives 1-7, 11a and 12 in THF as well as 9 and 10 in MeOH were investigated by UV–Vis spectroscopy, and the compounds were subjected to fluorimetric measurements (Table 2). No significant difference was observed between the three main absorption bands of enaminone 2 and enamide 3.

However, the products of the condensation of enaminone 2 with hydroxylamine (5) and phenylhydrazine (6) showed a significant bathochromic shift (74 and 127 nm, respectively) compared to the starting compound; however, the bathochromic shift in the case of the hydroxylic compound 4 did not exceed 46 nm. The absorption maxima of salts 9 and 10 were similar to those of the 2,3,3-trimethyl-3H-indolium cations.<sup>43</sup>

The fluorescence spectra of products 2-7, 11a and 12 were measured in THF, while those of salts 9 and 10 were measured in methanol. The structurally similar benzo[e]indolo[1,2*a*]pyrimidine derivative exhibits a strong blue fluorescence with an emission maximum at approximately 435 nm (in ethanol).<sup>3</sup> The fluorescence spectra of products 2 and 3, measured in THF, displayed emission maxima at 402 and 382 nm (Stokes shifts of 141 and 131 nm), respectively. The emission maximum exhibited a marked displacement to longer wavelengths upon reduction of the enaminone moiety or condensation with hydroxylamine (Table 2, Entry 4 and 5, respectively). In contrast, hydrazone 6 exhibited a corresponding maximum at 377 nm with a 'negative' Stokes shift of 11 nm. The fluorescence spectra of the 3Hindolium salts 9,10 exhibited two distinct maxima, a strong emission band in the 440-470 nm region and a band of smaller intensity near 380 nm.

The fluorescence quantum yield  $(\Phi_f)$  of the solutions was estimated by the integrating sphere method. It appeared that the fluorescence quantum yield was sensitive to the structure of compounds. With enaminone **2**, which contains a tertiary aromatic amine nitrogen atom, the observed  $\Phi_f$  value was 30.7%. However, the fluorescence quantum yield of the enamide **3** was low and did not exceed 0.6%. The highest  $\Phi_f$  value (37.5%) was measured for hydroxyl-containing compound **4**, while hydrazones **6** and **12** emitted negligible fluorescence ( $\Phi_f = 0.1\%$ ).

#### 3. Conclusions

In conclusion, a new method for the preparation of new functionalised fluorescent building blocks possessing the benzo[e]indoline moiety has been developed. Treatment of 1,1,2-trimethyl-1*H*-benzo[e]indole with acrylic acid and its derivatives at elevated temperature afforded aza- or carba-Michael addition adducts, which underwent further cyclisation to form isomeric benzo[e]pyrido[1,2-a]indole derivatives possessing the reactive enaminone and enamide structural units, respectively. Microwave irradiation significantly expedited the aforementioned annulation reaction. Herein, it was demonstrated that the enaminone and enamide moieties annulated to the benzo[e]indoline nucleus may serve as reactive sites for various chemical transformations towards functionalised benzo[e]indoline derivatives possessing intense fluorescence and significant Stokes shifts.

Absorption ( $\lambda_{abs}$  and  $\epsilon$ ) and fluorescence ( $\lambda_{em}$  and quantum yield  $\Phi_f$ ) parameters for the benzo[*e*]indoline derivatives **1-7**, **11a**, **12** in THF and **9**,**10** in MeOH

Entry	Compound	$\lambda_{abs}$	$\epsilon \times 10^3$ (dm <sup>3</sup> mol <sup>-1</sup> cm <sup>-1</sup> )	${\lambda_{em}}^{*}$	$\Phi_f(\%)$
1	1	219 245 254	27.04 45.57 32.23	342 357	0.1
2	2	212 239 261	31.94 14.34 21.66	402	30.7
3	3	206 224 251	23.56 32.41 25.34	382	0.6
4	4	217 258 296 307	33.28 53.87 9.50 10.52	438	37.5
5	5	221 266 335	48.46 30.10 35.00	450	15.9
6	6	213 265 351 388	46.08 27.99 20.06 19.70	377	0.1
7	7	216 252 293 304	28.71 54.42 8.45 8.14	430	13.8
8	9	219 246 256 264	27.57 21.39 19.96 16.52	377 468	0.5
9	10	220 266 276	55.91 17.27 18.14	379 444	21.2
10	11a	222 274 283 335	37.87 25.27 28.33 12.88	376 442	0.1
11	12	218 248 294	31.68 23.73 16.63	365 434	0.1

 $\lambda_{ex} = 310 \text{ nm}$ 

#### 4. Experimental section

#### 4.1. General

Reagents and solvents were purchased from commercial suppliers and used without further purification unless indicated. High temperature reactions were carried out in a high pressure stainless steel laboratory autoclave Roth 1.4571 (Carl Roth GmbH) equipped with a magnetic stirrer. Microwave reactions were conducted using a CEM Discover Synthesis Unit (CEM Corp., Matthews, NC) and performed in glass vessels (capacity 10 mL) sealed with a septum. The pressure was controlled by a load cell connected to the vessel. The temperature of the contents of the vessel was monitored using a calibrated infrared temperature control mounted under the reaction vessel. All experiments were performed using the stirring option. 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  $F_{254}$ ) were used. Melting points were determined on a Büchi B-540 capillary melting point apparatus and are uncorrected. <sup>1</sup>H NMR spectra were recorded at 300 MHz on a

Varian Unity Inova spectrometer and at 400 MHz on a Bruker M Method A, to yield compounds 2 (842 mg, 32%) and 3 (921 mg, Avance III spectrometer. <sup>13</sup>C NMR spectra were collected using the same instruments at 75 and 100 MHz, respectively. The chemical shifts, expressed in ppm, were relative to tetramethylsilane (TMS). Infrared spectra were recorded on a Perkin Elmer Spectrum One spectrometer using potasium bromide pellets. UV-Vis spectra were recorded on a Perkin Elmer Lambda 35 UV/Vis spectrometer. Fluorescence spectra were recorded on a FL920 fluorescence spectrometer from Edinburgh Instruments. The PL quantum yields were measured from dilute THF or MeOH solutions by an absolute method using the Edinburgh Instruments integrating sphere excited with Xe lamp. Optical densities of the sample solutions were ensured to be below 0.1 to avoid reabsorption effects. All optical measurements were performed at room temperature under ambient conditions. Mass spectra were recorded on a Waters Micromass ZQ 2000 (APCI<sup>+</sup>, 20 V) instrument or on an Agilent 1100 series mass spectrometer using a direct inlet system (electron spray, 4000 V). High-resolution ESI-TOF mass spectra were measured on a Bruker maXis spectrometer. Diffraction data were collected on Bruker-Nonius KappaCCD diffractometer at room temperature and also at -100 °C. The crystal structures were solved using known programs.<sup>44</sup> 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.

#### 4.2. Procedures for the preparation of benzo[e]pyrido[1,2a]indolone derivatives (2 and 3).

*Method A*. To a solution of 1,1,2-trimethyl-1*H*-benzo[*e*]indole (1) (2.09 g, 10 mmol) in glacial acetic acid (10 mL), acrylic acid (1.01 g, 14 mmol) was added and the reaction mixture was heated in an autoclave at 180 °C for 19 h. Upon cooling to rt, the reaction mixture was diluted with toluene and the solvents were evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane/ethyl acetate, 8:1 $\rightarrow$ ethyl acetate, v/v) to yield compounds 2 (947 mg, 36%) and **3** (395 mg, 15%).

Method B. To a solution of compound 1 (2.09 mg, 10 mmol) in o-xylene (10 mL), acrylic acid (1.01 g, 14 mmol) was added and the reaction mixture was heated in an autoclave at 200 °C for 12 h. Upon cooling to rt, the solvent was removed under reduced pressure and the residue was refined according to the Method A to yield compounds 2 (368 mg, 14%) and 3 (631 mg, 24%).

Method C. To a solution of compound 1 (2.09 g, 10 mmol) in glacial acetic acid (10 mL), acrylamide (1.0 g, 14 mmol) was added and the reaction mixture was heated in an autoclave at 180 °C for 19 h. Standard workup and purification according to the Method A afforded compounds 2 (184 mg, 7%) and 3 (368 mg, 14%).

Method D. To a solution of compound 1 (2.09 g, 10 mmol) in glacial acetic acid (10 mL), acrylic acid (1.01 g, 14 mmol) was added and the reaction mixture was heated in a microwave reactor (100 W) at 180 °C for 1 h. Standard workup and purification according to the Method A yielded compounds 2 (1026 mg, 39%) and **3** (316 mg, 12%).

Method E. To a solution of compound 1 (2.09 g, 10 mmol) in oxylene (10 mL), acrylic acid (1.01 g, 14 mmol) was added and the reaction mixture was heated in a microwave reactor (100 W) at 180 °C for 1 h. Upon cooling to rt, the solvent was removed under reduced pressure and the residue was purified according to the Method A to yield compounds 2 (921 mg, 35%) and 3 (553 mg. 21%).

Method F. To a solution of compound 1 (2.09 g, 10 mmol) in oxylene (10 mL), acrylic acid (1.01 g, 14 mmol) was added and the mixture was heated in a microwave reactor (120 W) at 200 °C for 1 h. Upon cooling to rt, the solvent was removed under reduced pressure and the residue was refined according to the

# 35%)

Method G. To a solution of compound 1 (2.09 g, 10 mmol) in oxylene (10 mL), tert-butyl acrylate (1.79 g, 14 mmol) was added and the mixture was heated in a microwave reactor (120 W) at 200 °C for 1 h Upon cooling to rt, the solvent was removed under reduced pressure and the residue was purified according to the Method A, to yield compounds 2 (79 mg, 3%) and 3 (289 mg, 11%).

Method H. To a solution of compound 1 (2.09 g, 10 mmol) in glacial acetic acid (10 mL), tert-butyl acrylate (1.79 g, 14 mmol) was added and the mixture was heated in a microwave reactor (100 W) at 180 °C for 1 h. Standard workup and purification according to the Method A yielded compounds 2 (1159 mg, 44%) and 3 (316 mg, 12%).

#### 4.2.1. 12,12-Dimethyl-8,9-dihydrobenzo[e]pyrido[1,2-a]indol-

10(12H)-one (2). Brownish crystals, mp 127-128 °C (ethyl acetate). <sup>1</sup>H NMR (300 MHz, DMSO- $d_6$ ):  $\delta_H$  1.61 (s, 6H, 12-(CH<sub>3</sub>)<sub>2</sub>), 4.07 (t, J=7.8 Hz, 2H, CH<sub>2</sub>), 4.55 (t, J=7.8 Hz, 2H, CH<sub>2</sub>), 5.29 (s, 1H, CH), 7.33 (dd, J=8.0, 7.2 Hz, 1H, Ar-H), 7.42 (d, J=8.4 Hz, 1H, Ar-H), 7.51 (t, J=7.2 Hz, 1H, Ar-H), 7.92 (d, J=8.4 Hz, 2H, Ar-H), 8.05 (d, J=8.7 Hz, 1H, Ar-H); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>): δ<sub>C</sub> 26.6 (2×C, 12-(CH<sub>3</sub>)<sub>2</sub>), 34.7 (CH<sub>2</sub>), 40.7 (C=O); IR (KBr, v<sub>max</sub>, cm<sup>-1</sup>): 3064 (CH<sub>arom</sub>), 2960 (CH<sub>aliph</sub>), 1642 (C=O), 1600, 1564, 1204, 813; MS (APCI<sup>+</sup>), m/z (%): 286 (M+Na<sup>+</sup>, 100). Anal. Calcd for C<sub>18</sub>H<sub>17</sub>NO (%): C, 82.10; H, 6.51; N, 5.32. Found: C, 81.93; H, 6.57; N, 5.35.

4.2.2. 12,12-Dimethyl-10,12-dihydrobenzo[e]pyrido[1,2-a]indol-8(9H)-one (3). Light brown crystals, mp 100–101 °C (dichloromethane). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta_{\rm H}$  2.32 (s, 6H, 12-(CH<sub>3</sub>)<sub>2</sub>), 2.43–2.50 (m, 2H, CH<sub>2</sub>), 2.65–2.72 (m, 2H, CH<sub>2</sub>), 5.21 (t, J=4.2 Hz, 1H, CH), 7.37 (ddd, J=8.2, 6.8, 1.2 Hz, 1H, Ar-H), 7.47 (ddd, J=8.6, 6.8, 1.2 Hz, 1H, Ar-H), 7.78 (d, J=8.7 Hz, 1H, Ar-H), 7.83–7.88 (m, 1H, Ar-H), 8.04–8.09 (m, 1H, Ar-H), 8.56 (d, J=8.7 Hz, 1H, Ar-H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta_{\rm C}$ 20.1 (CH<sub>2</sub>), 29.4 (2×C, 12-(CH<sub>3</sub>)<sub>2</sub>), 32.2 (CH<sub>2</sub>), 44.7 (C-12), 96.9 (C-11), 116.1, 122.9, 123.9, 126.2, 129.0, 129.1, 129.5, 129.9, 131.7, 137.4, 151.3 (C-11a), 168.2 (C=O); IR (KBr,  $v_{max}$ , cm<sup>-1</sup>): 3060 (CH<sub>arom</sub>), 2955 (CH<sub>aliph</sub>), 1694, 1671 (C=O), 1394, 818; MS (APCI<sup>+</sup>), m/z (%): 286 (M+Na<sup>+</sup>, 100). Anal. Calcd for C<sub>18</sub>H<sub>17</sub>NO (%): C, 82.10; H, 6.51; N, 5.32. Found: C, 81.83; H, 6.62; N, 5.46.

#### 4.3. (10R\*,11aS\*)-12,12-Dimethyl-8,9,10,11,11a,12-

hexahydrobenzo[e]pyrido[1,2-a]indol-10-ol (4). To a solution of compound 2 (267 mg, 1 mmol) in ethanol (3 mL), sodium borohydride (114 mg, 3 mmol) was added and the reaction mixture was heated at 60 °C for 2 h. Upon cooling to rt, reaction mixture was quenched with water (10 mL) and extracted with ethyl acetate (3×30 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated under reduced pressure. The crude product was recrystallized from ethanol to give titled compound 4. Yield 134 mg (50%), white crystals, mp 175–176 °C (ethanol).  $^{1}$ H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta_{H}$  1.27 (s, 3H, 12-CH<sub>3</sub>), 1.59 (q, J=12.0 Hz, 1H, <sup>1</sup>/<sub>2</sub> CH<sub>2</sub>), 1.64 (s, 3H, 12-CH<sub>3</sub>), 1.68-1.78 (dq, J=12.0, 5.1 Hz, 1H, <sup>1</sup>/<sub>2</sub> CH<sub>2</sub>), 1.94 (s, 1H, OH), 2.04–2.15 (m, 2H, CH<sub>2</sub>), 2.64 (dt, J=12.0, 3.0 Hz, 1H, CHOH), 2.80 (dd, J=11.9, 2.3 Hz, 1H, <sup>1</sup>/<sub>2</sub> CH), 3.75–3.89 (m, 2H, CH<sub>2</sub>), 6.93 (d, J=8.4 Hz, 1H, Ar-H), 7.21 (ddd, J=8.0, 6.8, 1.1 Hz, 1H, Ar-H), 7.40 (ddd, J=8.4, 6.8, 1.4 Hz, 1H, Ar-H), 7.66 (d, J=8.6 Hz, 1H, Ar-H), 7.74–7.79 (m, 1H, Ar-H), 7.93–7.98 (m, 1H, Ar-H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ<sub>C</sub> 20.8 (12-CH<sub>3</sub>), 26.3 (12-CH<sub>3</sub>), 33.7 (CH<sub>2</sub>), 34.6 (CH<sub>2</sub>), 43.3 (C-12), 43.6 (CH<sub>2</sub>), 70.2 (CH), 73.2 (C-OH), 110.2, 121.4, 121.5, 126.1, 128.6, 128.7, 129.1, 129.4, 130.6, 147.4; IR (KBr,  $v_{max}$ , cm<sup>-1</sup>): 3396 (O-H), 3047 (CH<sub>arom</sub>) 2925 (CH<sub>aliph</sub>), 2814, 1519, 1298, 1074 (C-OH), 812; MS (APCI<sup>+</sup>), *m/z* 

# (%): 268 (M+H<sup>+</sup>, 100). Anal. Calcd for C<sub>18</sub>H<sub>21</sub>NO (%): C, 80.86; M 120–120.5 °C (acetonitrile). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): $\delta_{H}$ H, 7.92; N, 5.24. Found: C, 81.19; H, 8.18; N, 5.43. 1.27 (s, 3H, 1-CH<sub>3</sub>), 1.44–1.55 (m, 2H, CH<sub>2</sub>), 1.65 (s, 3H, 1-CH<sub>3</sub>), 1.44–1.55 (m, 2H, CH<sub>2</sub>), 1.44–

#### 4.4. 12,12-Dimethyl-8,9-dihydrobenzo[e]pyrido[1,2-a]indol-

10(12H)-hydroxyimine (5). To a solution of compound 2 (267 mg, 1 mmol) in ethanol (3 mL), pyridine (158 mg, 2 mmol) and hydroxylamine hydrochloride (145 mg, 2.1 mmol) were added and the reaction mixture was stirred at rt for 24 h. Then the reaction mixture was quenched with water (10 mL) and extracted with ethyl acetate (3×10 mL). The combined organic layers were dried over  $Na_2SO_4$ , concentrated under reduced pressure. The residues were refined by flash chromatography on silica gel (dichloromethane/ethyl acetate 5:1, v/v, saturated with gaseous NH<sub>3</sub>) to afford the title compound 5. Yield 235 mg (84%), yellowish crystals, mp 210-211 °C (ethanol). <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>): δ<sub>H</sub> 1.61 (s, 6H, 12-(CH<sub>3</sub>)<sub>2</sub>), 2.57–2.61 (m, 2H, CH<sub>2</sub>) (major isomer), 2.79 (t, J=7.0 Hz, 2H, CH<sub>2</sub>) (minor isomer), 3.69 (t, J=7.0 Hz, 2H, CH<sub>2</sub>) (minor isomer), 3.78-3.85 (m, 2H, CH<sub>2</sub>) (major isomer), 5.36 (s, 1H, CH) (minor isomer), 5.75 (s, 1H, CH) (major isomer), 7.22-7.30 (m, 2H, Ar-H), 7.44 (ddd, J=8.3, 6.8, 1.2 Hz, 1H, Ar-H), 7.84 (t, J=9.0 Hz, 2H, Ar-H), 7.97–8.00 (m, 1H, Ar-H), 10.03 (s, 1H, OH) (major isomer), 10.26 (s, 1H, OH) (minor isomer); <sup>13</sup>C NMR (75 MHz, DMSOd<sub>6</sub>): δ<sub>C</sub> 26.9, 27.8 (2×C, 12-(CH<sub>3</sub>)<sub>2</sub>), 28.0, 40.6, 45.5, 45.8, 82.6, 109.6, 109.8, 121.4, 122.6, 126.8, 127.0, 127.1, 129.1, 129.2, 129.3, 129.6, 141.8, 148.3, 151.2, 163.6; IR (KBr,  $v_{max}$ , cm<sup>-1</sup>): 3232 (O-H), 3086 (CH<sub>arom</sub>), 2953 (CH<sub>aliph</sub>), 1609 (C=N), 1518, 1352, 928, 812; MS (APCI<sup>+</sup>), m/z (%): 263 (M+H<sup>+</sup>, 100). Anal. Calcd for C<sub>18</sub>H<sub>18</sub>N<sub>2</sub>O (%): C, 77.67; H, 6.52; N, 10.06. Found: C, 77.37; H, 6.62; N, 9.83.

#### 4.5. 12,12-Dimethyl-10-(2-methyl-2-phenylhydrazinylidene)-

8,9,10,12-tetrahydrobenzo[e]pyrido[1,2-a]indole (6). To a solution of compound 2 (267 mg, 1 mmol) in toluene (3 mL) 1methyl-1-phenylhydrazine (257 mg, 2.1 mmol) and catalytic amount of glacial acetic acid were added and the reaction mixture was refluxed for 3 h. After cooling, toluene was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (dichloromethane/ethyl acetate 5:1, v/v, saturated with gaseous NH<sub>3</sub>) to give titled compound 6 as a mixture of Z- and E-isomers. Yield 290 mg (79%), yellow resin. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta_{\rm H}$  1.67 (s, 6H, 2×CH<sub>3</sub>) (major isomer), 1.75 (s, 6H, 2×CH<sub>3</sub>) (minor isomer), 2.92 (t, J=7.1 Hz, 2H, CH<sub>2</sub>) (minor isomer), 2.96-3.03 (m, 2H, CH<sub>2</sub>) (major isomer), 3.12 (s, 3H, N-CH<sub>3</sub>) (minor isomer), 3.13 (s, 3H, N-CH<sub>3</sub>) (major isomer), 3.73 (t, J=7.1 Hz, 2H, CH<sub>2</sub>) (minor isomer), 3.91-3.97 (m, 2H, CH<sub>2</sub>) (major isomer), 5.69 (s, 1H, CH) (minor isomer), 5.74 (s, 1H, CH) (major isomer), 6.80-6.98 (m, 3H, Ar-H), 7.03-7.13 (m, 1H, Ar-H), 7.22-7.34 (m, 3H, Ar-H), 7.43-7.51 (m, 1H, Ar-H), 7.74–7.86 (m, 2H, Ar-H), 7.93–8.00 (m, 1H, Ar-H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ<sub>C</sub> 24.8, 27.9 (2×C), 28.1 (2×C), 29.9, 40.5, 41.1, 41.2, 42.8, 46.8, 47.0, 85.3 (CH), 90.9 (CH), 109.0, 109.2, 114.8 (2×C), 115.2 (2×C), 119.1, 119.5, 121.81, 121.83, 122.7, 122.91, 126.96, 127.0, 128.4, 128.6, 128.8 (2×C), 128.95 (2×C), 129.58, 129.69, 129.71, 129.83, 129.84, 129.87, 129.9, 130.0, 141.3, 141.8, 151.59, 151.63, 162.9, 165.8, 166.9, 168.5; IR (KBr, v<sub>max</sub>, cm<sup>-1</sup>): 3053 (CH<sub>arom</sub>), 2962 (CH<sub>aliph</sub>), 1625, 1595 (C=N), 1570, 1207, 752; HRMS (ESI TOF): [M+H<sup>+</sup>], found 368.2125.  $[C_{25}H_{25}N_3+H^+]$  requires 368.2121.

#### 4.6. 4-(1,1-Dimethyl-2,3-dihydro-1H-benzo[e]indol-2-yl)butan-

*1-ol* (7). To a solution of compound **3** (267 mg, 1 mmol) in ethanol (3 mL), sodium borohydride (114 mg, 3 mmol) was added and the reaction mixture was heated at 60 °C for 5 h. Upon cooling to rt, water (10 mL) was added and reaction mixture was extracted with ethyl acetate (3×10 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was refined by flash chromatography on silica gel (hexane/ethyl acetate, 4:1→ethyl acetate, v/v) to yield the title compound **7**. Yield 243 mg (90%), grey crystals, mp

120–120.5 °C (acetonitrile). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta_{\rm H}$ 1.27 (s, 3H, 1-CH<sub>3</sub>), 1.44–1.55 (m, 2H, CH<sub>2</sub>), 1.65 (s, 3H, 1-CH<sub>3</sub>), 1.67–1.77 (m, 4H, CH<sub>2</sub>), 3.16 (brs, 2H, NH, OH), 3.44– 3.50 (m, 1H, CH), 3.69–3.75 (m, 2H, CH<sub>2</sub>), 7.01 (d, *J*=8.5 Hz, 1H, Ar-H), 7.22 (ddd, *J*=8.1, 6.8, 1.1 Hz, 1H, Ar-H), 7.40 (ddd, *J*=8.4, 6.8, 1.4 Hz, 1H, Ar-H), 7.59 (d, *J*=8.5 Hz, 1H, Ar-H), 7.74–7.78 (m, 1H, Ar-H), 7.94–7.99 (m, 1H, Ar-H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta_{\rm C}$  21.0 (CH<sub>2</sub>), 24.1 (1-CH<sub>3</sub>), 27.2 (1-CH<sub>3</sub>), 28.8 (CH<sub>2</sub>), 32.8 (CH<sub>2</sub>), 45.2 (C-1), 62.6 (C-OH), 70.4 (CH), 113.3, 121.7, 121.9, 126.1, 128.7, 128.8, 129.4, 129.9, 130.7, 146.2; IR (KBr, v<sub>max</sub>, cm<sup>-1</sup>): 3250 (O-H), 3071 (CH<sub>arom</sub>), 2940 (CH<sub>aliph</sub>), 2882, 1623, 1519, 810, 747; MS (ESI<sup>+</sup>), *m/z* (%): 270 (M+H<sup>+</sup>, 100). Anal. Calcd for C<sub>18</sub>H<sub>23</sub>NO (%): C, 80.26; H, 8.61; N, 5.20. Found: C, 80.35; H, 8.69; N, 5.14.

#### 4.7. Preparation of alkyl 4-(1,1-dimethyl-1H-benzo[e]indol-2yl)butanoate derivatives (8a,b)

Method A. To a solution of compound **3** (267 mg, 1 mmol) in dry alcohol (4 mL), acetyl chloride (157 mg, 2 mmol) was added dropwise and the reaction mixture was stirred under reflux under argon atmosphere for 1.5 h. After cooling, solvent was removed under reduced pressure, the reaction mixture quenched with water, neutralized with Na<sub>2</sub>CO<sub>3</sub> and extracted with diethyl ether ( $3\times15$  mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was refined by flash chromatography on silica gel (hexane/ethyl acetate 5:1, v/v) to afford compounds **8a,b**.

*Method B.* To a solution of compound **3** (267 mg, 1 mmol) in dry *N*,*N*-dimethylformamide (1 mL), sodium hydride (60% dispersion in mineral oil, 40 mg, 1 mmol) was added portion wise under argon atmosphere. The reaction mixture was stirred at 60 °C under argon atmosphere until complete dissolution of sodium hydride. Then, alkyl halide (2 mmol) was added dropwise to the reaction mixture and the mixture was stirred at rt for 2 h. Then the reaction mixture was quenched with water (10 mL) and extracted with diethyl ether (3×15 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was refined according to the *Method A* to yield compounds **8a**,**b**.

4.7.1. Methyl 4-(1,1-dimethyl-1H-benzo[e]indol-2-yl)butanoate (8a). Method A: treatment of 3 with a mixture of acetyl chloride and absolute methanol; yield 254 mg (86%). Method B: treatment of 3 with methyl iodide (284 mg, 2 mmol); yield 268 mg (91%). Yellow resin. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta_{\rm H}$  1.53 (s, 6H, 1-(CH<sub>3</sub>)<sub>2</sub>), 2.27 (p, J=7.4 Hz, 2H, CH<sub>2</sub>), 2.55 (t, J=7.2 Hz, 2H, CH<sub>2</sub>), 2.71 (t, J=7.5 Hz, 2H, CH<sub>2</sub>), 3.69 (s, 3H, OCH<sub>3</sub>), 7.44 (ddd, J=8.1, 6.9, 1.1 Hz, 1H, Ar-H), 7.54 (ddd, J=8.3, 6.8, 1.3 Hz, 1H, Ar-H), 7.83 (q, J=8.5 Hz, 2H, Ar-H), 7.94 (d, J=7.8 Hz, 1H, Ar-H), 8.01 (d, J=8.4 Hz, 1H, Ar-H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta_C$  21.7, 22.7 (2×C, 1-(CH<sub>3</sub>)<sub>2</sub>), 27.7, 33.6, 51.7, 55.6, 120.1, 122.7, 124.5, 126.4, 128.7, 128.9, 129.7, 132.4, 138.6, 150.8, 173.9 (C=O), 191.6 (C=N); IR (KBr,  $v_{max}$ , cm<sup>-1</sup>): 3060  $(CH_{arom})$ , 2964  $(CH_{aliph})$ , 1745, 1728 (C=0), 1567, 1169 (C-0), (ESI TOF):  $[M+H^+]$ , found 296.1650. 752. HRMS  $[C_{19}H_{21}NO_2+H^+]$  requires 296.1645. Anal. Calcd for  $C_{19}H_{21}NO_2$ (%): C, 77.26; H, 7.17; N, 4.74. Found: C, 77.16; H, 7.34; N, 5.04.

4.7.2. *Ethyl* 4-(1,1-dimethyl-1H-benzo[e]indol-2-yl)butanoate (**8b**). *Method* A: treatment of **3** with a mixture of acetyl chloride and absolute ethanol; yield 232 mg (75%). *Method* B: treatment of **3** with ethyl iodide (312 mg, 2 mmol); yield 124 mg (40%). Yellow resin. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta_{\rm H}$  1.26 (t, *J*=7.2 Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>), 1.52 (s, 6H, 1-(CH<sub>3</sub>)<sub>2</sub>), 2.23–2.31 (m, 2H, CH<sub>2</sub>), 2.53 (t, *J*=7.2 Hz, 2H, CH<sub>2</sub>), 2.71 (t, *J*=7.5 Hz, 2H, CH<sub>2</sub>), 4.15 (q, *J*=7.1 Hz, 2H, CH<sub>2</sub>CH<sub>3</sub>), 7.43 (ddd, 1H, *J*=8.1, 6.9, 1.2 Hz, 1H, Ar-H), 7.53 (ddd, *J*=8.3, 6.8, 1.3 Hz, 1H, Ar-H), 7.83 (q, *J*=8.5 Hz, 2H, Ar-H), 7.93 (d, *J*=6.3 Hz, 1H, Ar-H), 7.99 (d, *J*=8.2 Hz, 1H, Ar-H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta_{C}$  [4.3, 21.7, 22.6 M (2×C, 1-(CH<sub>3</sub>)<sub>2</sub>), 27.7, 33.9, 55.6, 60.4, 120.1, 122.7, 124.5, 126.3, 128.7, 128.9, 129.7, 132.4, 138.6, 150.7, 173.4 (C=O), 191.6 (C=N); IR (KBr,  $v_{max}$ , cm<sup>-1</sup>): 3045 (CH<sub>arom</sub>), 2973 (CH<sub>aliph</sub>), 1676 (C=O), 1333, 1163 (C-O), 822, 752; MS (ESI<sup>+</sup>), m/z (%): 310 (M+H<sup>+</sup>, 100). Anal. Calcd for C<sub>20</sub>H<sub>23</sub>NO<sub>2</sub> (%): C, 77.64; H, 7.49; N, 4.53. Found: C, 77.85; H, 7.54; N, 4.50.

#### 4.8. 2-(4-Methoxy-4-oxobutyl)-1,1-dimethyl-1H-

benzo[e]indolium tetrafluoroborate (9). To a solution of compound 8a (295 mg, 1 mmol) in diethyl ether (5 mL) 48% solution of tetrafluoroboric acid was added dropwise and the reaction mixture was kept at +5 °C for 1 h. The formed salt was filtered and recrystallized from ethanol to give the title compound 9. Yield 156 mg (41%), brownish crystals, mp 114-115 °C (ethanol). <sup>1</sup>H NMR (400 MHz, DMSO- $d_6$ ):  $\delta_H$  1.64 (s, 6H, 1-(CH<sub>3</sub>)<sub>2</sub>), 2.14 (p, J=7.5 Hz, 2H, CH<sub>2</sub>), 2.57 (t, J=7.5 Hz, 2H, CH<sub>2</sub>), 3.05 (t, J=7.5 Hz, 2H, CH<sub>2</sub>), 3.64 (s, 3H, OCH<sub>3</sub>), 6.97 (br.s., 1H, NH), 7.61 (t, J=7.2 Hz, 1H, Ar-H), 7.69 (dd, J=11.7, 4.5 Hz, 1H, Ar-H), 7.81 (d, J=8.6 Hz, 1H, Ar-H), 8.08-8.15 (m, 2H, Ar-H), 8.25 (d, J=8.4 Hz, 1H, Ar-H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ<sub>C</sub> 20.6, 21.8 (2×C, 1-(CH<sub>3</sub>)<sub>2</sub>), 27.2, 32.5, 51.4, 55.6, 116.3, 116.4, 123.0, 126.1, 127.7, 127.8, 129.7, 129.9, 132.5, 137.8, 172.9, 197.0; IR (KBr,  $v_{max}$ , cm<sup>-1</sup>): 3574, 3506 (N-H), 3114 (CH<sub>aron</sub>), 2953 (CH<sub>aliph</sub>), 1739, 1197, 1059, 822; MS (ESI<sup>+</sup>) m/z (%): 296 (M-BF<sub>4</sub>)<sup>+</sup>, 100). Anal. Calcd for C<sub>19</sub>H<sub>22</sub>BF<sub>4</sub>NO<sub>2</sub> (%): C, 59.55; H, 5.79; N, 3.66. Found: C, 59.37; H, 5.81; N, 3.64.

#### 4.9. 2-(4-Methoxy-4-oxobutyl)-1,1,3-trimethyl-1H-

benzo[e]indolium iodide (10). A solution of compound 8a (295 mg, 1 mmol) in methyl iodide (6,84 g, 48 mmol, 3 mL) was stirred at rt for 4 h. After termination, the reaction mixture was kept at +5 °C for another 2 h. The formed salt was filtered and recrystallized from acetonitrile to give the title compound 10. Yield 220 mg (50%), grey crystals, 181–182 °C (acetonitrile). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta_H$  1.79 (s, 6H, 1-(CH<sub>3</sub>)<sub>2</sub>), 1.92–2.01 (m, 2H, CH<sub>2</sub>), 2.69 (t, J=7.0 Hz, 2H, CH<sub>2</sub>), 3.21-3.30 (m, 2H, CH<sub>2</sub>), 3.66 (s, 3H, CH<sub>3</sub>), 4.18 (s, 3H, CH<sub>3</sub>), 7.70-7.76 (m, 1H, Ar-H), 7.76–7.82 (m, 1H, Ar-H), 8.09 (d, J=8.9 Hz, 1H, Ar-H), 8.22 (d, J=7.8 Hz, 1H, Ar-H), 8.30 (d, J=8.9 Hz, 1H, Ar-H), 8.38 (d, J=8.4 Hz, 1H, Ar-H);  ${}^{13}$ C NMR (100 MHz, DMSO- $d_6$ ):  $\delta_C$ 20.7 (2×C, 1-(CH<sub>3</sub>)<sub>2</sub>), 21.4, 25.7, 32.7, 35.5, 51.6, 55.7, 113.4, 123.5, 127.0, 127.2, 128.4, 129.8, 130.5, 133.2, 136.5, 139.6, 172.9 (C=O), 196.1 (N<sup>+</sup>=C); IR (KBr,  $v_{max}$ , cm<sup>-1</sup>): 3057 (CH<sub>arom</sub>), 2950 (CH<sub>aliph</sub>), 1723 (C=O), 1428, 1192 (C-O), 821; MS (ESI<sup>+</sup>), m/z (%): 310 (M-I)<sup>+</sup>, 100). Anal. Calcd for C<sub>20</sub>H<sub>24</sub>INO<sub>2</sub> (%): C, 54.93; H, 5.53; N, 3.20. Found: C, 54.78; H, 5.34; N, 3.42.

4.10. Procedure for preparation of alkyl 4-(1,1-dimethyl-1Hbenzo[e]indol-2-yl)-4-oxobutanoate derivatives (11a,b). A solution of compound 8a,b (1 mmol) in dimethyl sulfoxide (2 mL) was stirred at 50 °C for 8 h. Then the reaction mixture was diluted with ethyl acetate (10 mL) and washed with brine (3×10 mL), the organic layer was separated, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was recrystallized from ethanol to give the title compounds 11a,b.

4.10.1. Methyl 4-(1,1-dimethyl-1H-benzo[e]indol-2-yl)-4oxobutanoate (11a). Compound 8a (295 mg, 1 mmol) was used to prepare 11a according to the general procedure. Yield 298 mg (96%), yellow crystals, mp 133.5–134.5 °C (ethanol). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta_{\rm H}$  1.72 (s, 6H, 1-(CH<sub>3</sub>)<sub>2</sub>), 2.77 (t, J=6.6 Hz, 2H, CH<sub>2</sub>), 3.52 (t, J=6.6 Hz, 2H, CH<sub>2</sub>), 3.71 (s, 3H, OCH<sub>3</sub>), 7.55 (ddd, J=8.1, 6.9, 1.3 Hz, 1H, Ar-H), 7.61 (ddd, J=8.4, 6.9, 1.5 Hz, 1H, Ar-H), 7.91–7.96 (m, 2H, Ar-H), 7.97–8.01 (m, 1H, Ar-H), 8.11 (d, J=8.3 Hz, 1H, Ar-H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta_{\rm C}$  22.6 (2×C, 1-(CH<sub>3</sub>)<sub>2</sub>), 28.1, 34.1, 52.0, 55.5, 121.7, 123.8, 126.3, 126.9, 128.4, 129.7, 129.9, 134.2, 143.2, 149.6, 173.3, 180.7 (C=O), 196.1 (C=O); IR (KBr, v<sub>max</sub>, cm<sup>-1</sup>): 3070 (CH<sub>arom</sub>),

4.10.2. Ethyl 4-(1,1-dimethyl-1H-benzo[e]indol-2-yl)-4oxobutanoate (11b). Compound 8b (0.31 g, 1 mmol) was used to prepare 11b according to the general procedure. Yield 282 mg (88%), yellow crystals, mp 126–127 °C (ethanol). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ<sub>H</sub> 1.27 (t, J=7.1 Hz, 3H, CH<sub>3</sub>), 1.72 (s, 6H, 1-(CH<sub>3</sub>)<sub>2</sub>), 2.76 (t, J=6.6 Hz, 2H, CH<sub>2</sub>), 3.51 (t, J=6.6 Hz, 2H, CH<sub>2</sub>), 4.17 (q, J=7.1 Hz, 2H, CH<sub>2</sub>), 7.53-7.58 (m, 1H, Ar-H), 7.60 (ddd, J=8.4, 6.9, 1.5 Hz, 1H, Ar-H), 7.91-7.97 (m, 2H, Ar-H), 7.97–8.00 (m, 1H, Ar-H), 8.11 (d, J=7.8 Hz, 1H, Ar-H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ<sub>C</sub> 14.2, 22.4 (2×C, 1-(CH<sub>3</sub>)<sub>2</sub>), 28.2, 33.9, 55.4, 60.6, 121.6, 123.6, 126.1, 126.7, 128.2, 129.5, 129.7, 133.9, 143.1, 149.4, 172.7, 180.5 (C=O), 195.9 (C=O); IR (KBr,  $\nu_{max},\ cm^{-1}):\ 3068\ (CH_{arom}),\ 2930\ (CH_{aliph}),\ 1747\ (C=O),\ 1677\ (C=O),\ 1333,\ 1163,\ 1119,\ 822,\ 754;\ MS\ (ESI^+),\ m/z\ (\%):\ 324$ (M+H<sup>+</sup>, 100). Anal. Calcd for C<sub>20</sub>H<sub>21</sub>NO<sub>3</sub> (%): C, 74.28; H, 6.55; N, 4.33. Found: C, 74.06; H, 6.85; N, 4.42.

4.11. Methyl 4-(1,1-dimethyl-1H-benzo[e]indol-2-yl)-4-(2phenylhydrazinylidene)butanoate (12). To a solution of compound 11a (0.31 g, 1 mmol) in ethanol (4 mL) phenyl hydrazine (0.22 g, 2 mmol) was added and the reaction mixture was refluxed for 3 h. Upon cooling to rt, water (10 mL) was added and the reaction mixture was extracted with diethyl ether (3×15 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was refined by flash chromatography on silica gel (hexane/ethyl acetate, 6:1, v/v) to afford compound 12. Yield 328 mg (82%), brown resin, <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta_H$  1.89 (s, 6H, 1-(CH<sub>3</sub>)<sub>2</sub>), 2.84–2.90 (m, 2H, CH<sub>2</sub>), 3.22–3.29 (m, 2H, CH<sub>2</sub>), 3.72 (s, 3H, CH<sub>3</sub>), 6.94–7.04 (m, 1H, Ar-H), 7.29–7.34 (m, 2H, Ar-H), 7.36-7.41 (m, 2H, Ar-H), 7.46 (ddd, J=8.0, 6.9, 1.1 Hz, 1H, Ar-H), 7.56 (ddd, J=8.3, 6.8, 1.3 Hz, 1H, Ar-H), 7.87 (s, 2H, Ar-H), 7.95 (dd, J=8.2, 0.5 Hz, 1H, Ar-H), 8.18 (d, J=8.4 Hz, 1H, Ar-H), 9.70 (s, 1H, NH); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta_{C}$  19.8, 25.5 (2×C, 1-(CH<sub>3</sub>)<sub>2</sub>), 31.8, 52.5, 55.4, 113.8 (2×C), 120.2 (2×C), 121.5 (2×C), 123.0, 124.8, 126.4, 128.5, 129.1, 129.6 (2×C), 129.9, 132.8, 141.4, 144.4, 176.2, 183.3 (C=O); IR (KBr, v<sub>max</sub>, cm<sup>-1</sup>): 3273 (NH), 3059 (CH<sub>arom</sub>), 2934 (CH<sub>aliph</sub>), 1716 (C=O), 1602, 1496, 1246, 1167 (C-O), 820, 751; MS (ESI<sup>+</sup>), m/z (%): 400 (M+H<sup>+</sup>, 100). Anal. Calcd for C<sub>25</sub>H<sub>25</sub>N<sub>3</sub>O<sub>2</sub> (%): C, 75.16; H, 6.31; N, 10.52. Found: C, 74.93; H, 6.45; N, 10.63.

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