### Practical and Efficient Palladium-Promoted Synthesis of Indole Systems Containing Medium- and Large-Ring-Fused Heterocycles

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Received 1 March 2006; revised 10 March 2006

**Abstract:** The synthesis of indolo-benzazepine, indolo-benzazocine and indolo-benzazonine derivatives using a palladium-catalyzed coupling reaction is described. The polycyclic systems were obtained in a few steps directly from commercially available materials. The coupling of substrates containing aryl bromides was improved by microwave irradiation.

**Key words:** palladium catalyst, fused-ring systems, indoles, lactams, intramolecular cyclization

General syntheses of medium- and large-ring heterocycles have been difficult to develop. However, because of their occurrence, nitrogen-containing seven- and eightmembered ring systems, as well as larger fused-ring systems, are worthy of detailed investigation. In particular, the development of synthetic methods for the synthesis of seven-membered heterocycles fused to indole nucleus has received much attention.<sup>1</sup> General syntheses for largerring heterocycles, indoloazocines and indoloazonines, are not available; only some synthetic paths to particular indoloazocines have been described.<sup>2</sup> We describe here a novel sequence to obtain indolo-benzazepines, indolobenzazocines, and indolo-benzazonines in only three steps, which involves amide functionalization of indole derivatives and palladium-catalyzed intramolecular carbon-carbon bond formation. The formed heteropolycyclic systems constitute the skeleton of some important pharmaceutical building blocks. Their relevance is due to the activity of indolo-benzazepines as cyclin-dependant kinase (CDK) inhibitors<sup>3</sup> and as glycogen synthase kinase-3 $\beta$  (GSK-3 $\beta$ ) inhibitors<sup>4</sup> and also their promising antitumoral properties (a representative example is compound A, Figure 1). Moreover, the pyrido-azepino-



SYNTHESIS 2006, No. 14, pp 2404–2412 Advanced online publication: 16.05.2006 DOI: 10.1055/s-2006-942398; Art ID: Z04606SS © Georg Thieme Verlag Stuttgart · New York

indoles (i.e., azakenpaullones) showed improved action as GSK-3 $\beta$  inhibitors.<sup>5</sup> The indoloazocine derivatives, such as compound **B** (Figure 1), showed acetylcholinesterase (AChE) inhibitory activities<sup>6</sup> which at present represents a major pharmacological approach to the treatment of Alzheimer's disease.<sup>7</sup> Indoloazocines have also been patented as a central nervous system depressant.<sup>8</sup> Many indole alkaloid families (i.e., iboga, vinca, aspidosperma) include large, indolo-fused, heterocyclic rings.<sup>9</sup>

Following our studies on the wide applicability of palladium-catalyzed intramolecular coupling reactions, we reported previously the palladium-catalyzed ring cyclization of 2- and 3-carboxamide-substituted indoles resulting in the formation of  $\beta$ - and  $\gamma$ -carbolinones.<sup>10</sup>

To achieve larger heterocycles fused to the indole nucleus, we envisaged indole-3-acetic acid 1 and indole-3-propionic acid 2 as starting materials for the reaction sequence depicted in Scheme 1. The amides 4 obtained from indole-3-acetic acid and indole-3-propionic acid are collected in Tables 1 and 2, respectively, and are given with the cyclization times and yields of 5.

The synthesis of the intermediate amides **3** was dependent on the reactivity of the different starting amines. In the case of benzylamine or 2-phenylethylamine (Table 1, entries f, g and Table 2, entry k) the amidation was performed via the acyl chloride. In the case of anilines and aminopyridines (Table 1, entries a–e and Table 2, entries h-j) the coupling was achieved using a complex of phenyl dichlorophosphate and *N*,*N*-dimethylformamide.<sup>11</sup>

The subsequent N-methylation step, affording intermediates **4**, was necessary to avoid complexation of palladium to the amide nitrogen and was carried out with sodium hydride and iodomethane in tetrahydrofuran solution. It should be emphasized that the <sup>1</sup>H NMR spectra of the derivatives **4f**, **4g**, and **4k**, in CDCl<sub>3</sub> solution, display the existence of 1:1 ratio of rotational isomers caused by restricted rotation about the amide bond. Obtaining the <sup>1</sup>H NMR spectrum of **4f** in DMSO-*d*<sub>6</sub> at room temperature a 3:5 mixture of rotamers was revealed, while on raising the temperature to 110 °C the coalescence of the signals was observed.

Optimization studies for the intramolecular ring closure of the amides **4** with various palladium sources, bases, and solvents were undertaken. The use of palladium(II) acetate in the absence of a phosphine ligand or tetrakis(triphenylphosphine)palladium resulted in a low conversion, as did the use of potassium carbonate or cesium carbonate as bases. The investigation of the use of different solvents (MeCN and DMF) resulted in only moderate yields of **5**. The treatment of the amides **4** with palladium(II) acetate as catalyst, triphenylphosphine as ligand, potassium acetate as base, tetrabutylammonium chloride as additive, in *N*,*N*-dimethylacetamide (DMA) at 110 °C constitutes the best conditions for the synthesis of the target indolo-benzazopines, and aza-analogues thereof **5** in good to excellent yields.

The nature of the aryl halides was fundamental to evaluate the yields of the intramolecular cyclization step. Aryl iodides usually gave better results than aryl bromides (Table 1, entries a and b compared with entry c), but bromopyridine derivatives gave quantitative yields (Table 1, entries d and e).

In the case of the less reactive aryl bromides, microwave irradiation was tested to improve the cyclization step, since metal-catalyzed processes are ideal candidates for acceleration by microwaves. Heating the reacting molecules by means of absorption of microwave energy by a polar solvent effectively affords high temperatures in a short time and in uniform way. The reaction mixture was irradiated in a multimode oven equipped with temperature control at 600 W for the reported time and in this period the solution temperature reached 120 °C or 160 °C. The irradiation time for each experiment was determined by TLC control. This procedure gave better results compared with traditional heating as showed in Tables 1 and 2 (entries c, f, g, and k).

In conclusion, we have developed an efficient synthesis of unusual indolo-fused nitrogenated heterocycles of various sizes via palladium-catalyzed intramolecular cyclization of readily accessible amides **4**. Melting points were determined on a Büchi B-540 heating apparatus and are uncorrected. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were obtained on a Bruker Avance 400. Chemical shifts are given in ppm downfield from TMS. <sup>13</sup>C NMR spectra are <sup>1</sup>H-decoupled and the determination of the multiplicities was achieved by the APT pulse sequence. IR spectra were recorded on a Jasco FT–IR 5300 spectrophotometer.

### **Amides 3; General Procedure**

Method A: To DMF (0.15 mL, 1.95 mmol), PhOP(O)Cl<sub>2</sub> (0.18 mL, 1.2 mmol) was added at 0 °C. The mixture was stirred for 5 min, then **1** or **2** (1 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (15 mL) was added and the soln was stirred for 10 min. Pyridine (0.32 mL, 4 mmol) was added and, after 10 min, the appropriate amine (1.2 mmol) was added always at 0 °C. After stirring at r.t. for the reported time, the mixture was diluted with brine (15 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 20 mL). The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure. The residue was chromatographed on a silica gel column to give the amide **3**.

*Method B*: To a soln of **1** or **2** (1 mmol) in anhyd THF (10 mL), oxalyl chloride (0.21 mL, 2.5 mmol) was added at 0 °C. The mixture was stirred at r.t. for 2 h. The solvent was evaporated under reduced pressure and the residue was taken up with anhyd  $CH_2Cl_2$  (15 mL). A soln of the appropriate amine (2.2 mmol) and  $Et_3N$  (8 mmol) in anhyd  $CH_2Cl_2$  (5 mL) was added dropwise. The mixture was stirred for 18 h, then washed with 5% HCl (10 mL). The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure. The residue was chromatographed on a silica gel column (eluent indicated below) to give the amide **3**.

### N-(2-Iodophenyl)-2-(1-methyl-1*H*-indol-3-yl)acetamide (3a)

*Method A*; stirring for 4 h; eluent: CH<sub>2</sub>Cl<sub>2</sub>–MeOH, 20:1; yield: 74%; mp 113–114 °C (cream powder from Et<sub>2</sub>O–hexane).

### IR (Nujol): 1680, 3350 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 3.85 (s, 3 H), 3.95 (s, 2 H), 6.76 (t, *J* = 7.5 Hz, 1 H), 7.16–7.23 (m, 2 H), 7.30–7.40 (m, 3 H), 7.61–7.67 (m, 2 H), 7.85 (br s, 1 H, absent after deuteration), 8.32 (d, *J* = 8.0 Hz, 1 H).



Scheme 1 Reagents and conditions: (i) When n = 0: PhOP(O)Cl<sub>2</sub>, DMF, py, CH<sub>2</sub>Cl<sub>2</sub>, r.t.; When n = 1, 2: (COCl<sub>2</sub>, THF, r.t.; (ii) NaH, MeI, THF, r.t.; (iii) Pd(OAc)<sub>2</sub> (5 mol%), Ph<sub>3</sub>P (10 mol%), AcOK, TBACl, DMA, 110 °C.

Amine

Entry

a

b

c

d

e

f

g

	Amide 4	Cyclization time (h)	Product 5
	N-Me Me	30	N-Me Me
IH <sub>2</sub>	N-Me Me	5	N-Me N-Me
Br NH <sub>2</sub>	Cl N-Me Me Br	35 (2) <sup>b</sup>	CI N-Me Me
	Me N-Me	17	Me O N-Me

Table 1	Compounds 4	and 5 Obtained	from Indole-3-acet	ic Acid 1
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<sup>a</sup> Starting from 4.

<sup>b</sup> MW irradiation time.

<sup>c</sup> In brackets the yield obtained using MW irradiation.

<sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  = 33.3 (q), 34.9 (t), 89.5 (s), 107.2 (s), 109.9 (d), 119.5 (d), 120.3 (d), 121.6 (d), 122.9 (d), 126.1 (d), 128.1 (s), 129.2 (d), 129.5 (d), 137.9 (s), 138.6 (s), 139.2 (d), 170.5 (s).

Anal. Calcd for C<sub>17</sub>H<sub>15</sub>IN<sub>2</sub>O: C, 52.33; H, 3.87; N, 7.18. Found: C, 52.05; H, 4.08; N, 7.01.

#### N-(4-Chloro-2-iodophenyl)-2-(1-methyl-1H-indol-3-yl)acetamide (3b)

Method A; stirring for 4 h; eluent: from CH<sub>2</sub>Cl<sub>2</sub> to CH<sub>2</sub>Cl<sub>2</sub>-Et<sub>2</sub>O, 10:1; yield: 72%; mp 162-163 °C (white crystals from Et<sub>2</sub>O-hexane).

IR (Nujol): 1670, 3278 cm<sup>-1</sup>.

Yield<sup>a</sup> of 5 (%)

85

Table 2	Compounds 4 and 5	Obtained from	Indole-3-propionic Acid 2
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<sup>a</sup> Starting from **4**.

<sup>b</sup> MW irradiation time.

<sup>c</sup> In brackets the yield obtained using MW irradiation.

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 3.85 (s, 3 H), 3.94 (s, 2 H), 7.16 (s, 1 H), 7.19 (m, 1 H), 7.26–7.34 (m, 2 H), 7.37 (d, *J* = 8.2 Hz, 1 H), 7.59 (s, 1 H), 7.63 (d, *J* = 7.9 Hz, 1 H), 7.83 (br s, 1 H, absent after deuteration), 8.27 (d, *J* = 8.9 Hz, 1 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>): δ = 33.3 (q), 34.9 (t), 89.1 (s), 107.0 (s), 110.0 (d), 119.5 (d), 120.4 (d), 121.8 (d), 123.0 (d), 128.0 (s), 129.3 (d), 129.5 (d), 129.8 (s), 137.5 (s), 137.9 (s), 138.2 (d), 170.5 (s).

Anal. Calcd for  $C_{17}H_{14}CIIN_2O$ : C, 48.08; H, 3.32; N, 6.60. Found: C, 47.91; H, 3.57; N, 6.39.

#### *N*-(2-Bromo-4-methylphenyl)-2-(1-methyl-1*H*-indol-3-yl)acetamide (3c)

*Method A*; stirring for 24 h; eluent: from  $CH_2Cl_2$  to  $CH_2Cl_2-Et_2O$ , 10:1; yield: 68%; mp 101–102 °C (white powder from *i*-Pr<sub>2</sub>O).

#### IR (Nujol): 1680, 3350 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta = 2.26$  (s, 3 H), 3.84 (s, 3 H), 3.93 (s, 2 H), 7.09 (d, J = 8.4 Hz, 1 H), 7.14 (s, 1 H), 7.19 (dd, J = 7.2, 7.9 Hz, 1 H), 7.22 (s, 1 H), 7.31 (dd, J = 7.2, 8.2 Hz, 1 H), 7.37 (d, J = 8.2 Hz, 1 H), 7.65 (d, J = 7.9 Hz, 1 H), 7.94 (br s, 1 H, absent after deuteration), 8.23 (d, J = 8.4 Hz, 1 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta = 20.9$  (q), 33.3 (q), 34.9 (t), 107.3 (s), 109.9 (d), 113.6 (s), 119.4 (d), 120.2 (d), 121.8 (d), 122.8 (d), 127.9 (s), 129.0 (d), 129.2 (d), 132.8 (d), 133.5 (s), 135.4 (s), 137.7 (s), 170.2 (s).

Anal. Calcd for C<sub>18</sub>H<sub>17</sub>BrN<sub>2</sub>O: C, 60.52; H, 4.80; N, 7.84. Found: C, 60.75; H, 4.63; N, 7.99.

### *N*-(2-Bromopyridin-3-yl)-2-(1-methyl-1*H*-indol-3-yl)acetamide (3d)

*Method A*; stirring for 24 h; eluent: from  $CH_2Cl_2$  to  $CH_2Cl_2-Et_2O$ , 10:1; yield: 78%; mp 115–116 °C (white powder from *i*-Pr<sub>2</sub>O).

IR (Nujol): 1670, 3325 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 3.86 (s, 3 H), 3.96 (s, 2 H), 7.16 (s, 1 H), 7.20 (dd, *J* = 8.2, 7.3 Hz, 1 H), 7.23 (dd, *J* = 4.4, 8.1 Hz, 1 H), 7.31 (dd, *J* = 7.3, 7.9 Hz, 1 H), 7.39 (d, *J* = 8.2 Hz, 1 H), 7.62 (d, *J* = 7.9 Hz, 1 H), 8.02 (dd, *J* = 1.7, 4.4 Hz, 1 H), 8.09 (br s, 1 H, absent after deuteration), 8.71 (dd, *J* = 1.7, 8.1 Hz, 1 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>): δ = 33.3 (q), 35.0 (t), 106.7 (s), 110.1 (d), 119.2 (d), 120.4 (d), 123.0 (d), 123.8 (d), 127.7 (s), 128.6 (d), 129.0 (d), 133.3 (s), 133.9 (s), 137.8 (s), 144.7 (d), 170.9 (s).

Anal. Calcd for  $C_{16}H_{14}BrN_3O$ : C, 55.83; H, 4.10; N, 12.21. Found: C, 55.81; H, 3.88; N, 12.43.

## *N*-(3-Bromo-5-methylpyridin-2-yl)-2-(1-methyl-1*H*-indol-3-yl)acetamide (3e)

*Method A*; stirring for 4 h; eluent:  $CH_2Cl_2$ -MeOH, 20:1; yield: 71%; mp 159–160 °C (yellow crystals from  $CH_2Cl_2$ -hexane).

IR (Nujol): 1660, 3275 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta = 2.25$  (s, 3 H), 3.80 (s, 3 H), 3.98 (s, 2 H), 7.09 (s, 1 H), 7.17 (dd, J = 7.3, 8.2 Hz, 1 H), 7.28 (dd, J = 7.3, 7.9 Hz, 1 H), 7.34 (d, J = 8.2 Hz, 1 H), 7.60 (s, 1 H), 7.68 (d, J = 7.9 Hz, 1 H), 8.10 (br s, 1 H, absent after deuteration), 8.15 (s, 1 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>): δ = 17.8 (q), 33.2 (q), 34.6 (t), 107.2 (s), 109.9 (d), 112.7 (s), 119.5 (d), 120.1 (d), 122.7 (d), 128.0 (s), 129.1 (d), 131.9 (s), 137.7 (s), 142.0 (d), 146.5 (s), 147.8 (d), 170.1 (s).

Anal. Calcd for  $C_{17}H_{16}BrN_3O$ : C, 57.00; H, 4.50; N, 11.73. Found: C, 56.72; H, 4.73; N, 11.49.

### *N*-(2-Bromobenzyl)-2-(1-methyl-1*H*-indol-3-yl)acetamide (3f)

*Method B*; eluent:  $CH_2Cl_2-Et_2O$ , 5:1; yield: 85%; mp 128–129 °C (cream powder from  $CH_2Cl_2$ –hexane).

IR (Nujol): 1640, 3250 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 3.78 (s, 3 H), 3.80 (s, 2 H), 4.44 (d, *J* = 6.1 Hz, 2 H), 6.25 (br s, 1 H, absent after deuteration), 7.02 (s, 1 H), 7.10 (dd, *J* = 7.3, 8.2 Hz, 1 H), 7.14 (dd, *J* = 7.3, 7.9 Hz, 1 H), 7.19–7.32 (m, 2 H), 7.28 (dd, *J* = 7.4, 7.9 Hz, 1 H), 7.35 (d, *J* = 8.2 Hz, 1 H), 7.48 (d, *J* = 7.9 Hz, 1 H), 7.56 (d, *J* = 7.9 Hz, 1 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  = 33.2 (q), 33.7 (t), 44.1 (t), 107.7 (s), 109.9 (d), 119.3 (d), 120.0 (d), 122.6 (d), 123.8 (s), 127.9 (d), 128.7 (d), 129.3 (d), 130.1 (d), 131.9 (s), 133.1 (d), 137.6 (s), 145.7 (s), 172.0 (s).

Anal. Calcd for  $C_{18}H_{17}BrN_2O$ : C, 60.52; H, 4.80; N, 7.84. Found: C, 60.70; H, 4.72; N, 7.89.

#### *N*-[2-(2-Bromophenyl)ethyl]-2-(1-methyl-1*H*-indol-3-yl)acetamide (3g)

*Method B*; eluent:  $CH_2Cl_2-Et_2O$ , 5:1; yield: 59%; mp 100–101 °C (cream powder from  $Et_2O$ -hexane).

IR (Nujol): 1640, 3300 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta = 2.86$  (t, J = 6.8 Hz, 2 H), 3.47 (q, J = 6.8 Hz, 2 H), 3.71 (s, 2 H), 3.78 (s, 3 H), 5.76 (br s, 1 H, absent after deuteration), 6.90 (dd, J = 2.5, 6.7 Hz, 1 H), 7.00 (s, 1 H), 7.01–7.05 (m, 2 H), 7.15 (dd, J = 7.3, 8.2 Hz, 1 H), 7.28 (dd, J = 7.3, 7.9 Hz, 1 H), 7.34 (d, J = 8.2 Hz, 1 H), 7.45 (dd, J = 1.8, 7.4 Hz, 1 H), 7.51 (d, J = 7.9 Hz, 1 H).

 $^{13}\text{C}$  NMR (CDCl<sub>3</sub>):  $\delta$  = 33.1 (q), 33.7 (t), 36.0 (t), 39.5 (t), 107.8 (s), 109.8 (d), 119.2 (d), 120.0 (d), 122.6 (d), 124.8 (s), 127.8 (d), 127.9 (s), 128.5 (d), 128.7 (d), 131.3 (d), 133.2 (d), 137.6 (s), 138.6 (s), 172.0 (s).

Anal. Calcd for  $C_{19}H_{19}BrN_2O$ : C, 61.47; H, 5.16; N, 7.55. Found: C, 61.59; H, 5.01; N, 7.83.

## *N*-(2-Iodophenyl)-3-(1-methyl-1*H*-indol-3-yl)propionamide (3h)

*Method A*; stirring for 4 h; eluent: from  $CH_2Cl_2$  to  $CH_2Cl_2-Et_2O$ , 10:1; yield: 65%; mp 124–125 °C (cream needles from  $CH_2Cl_2$ –hexane).

IR (Nujol): 1640, 3250 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta = 2.86$  (t, J = 7.3 Hz, 2 H), 3.26 (t, J = 7.3 Hz, 2 H), 3.75 (s, 3 H), 6.84 (ddd, J = 1.2, 7.4, 8.0 Hz, 1 H), 6.95 (s, 1 H), 7.16 (dd, J = 7.1, 7.8 Hz, 1 H), 7.26 (dd, J = 6.9, 7.4 Hz, 1 H), 7.32 (d, J = 8.1 Hz, 1 H), 7.35 (m, 2 H, after deuteration dd, J = 7.1, 8.1 Hz, 1 H), 7.66 (d, J = 7.8 Hz, 1 H), 7.74 (dd, J = 1.0, 8.0 Hz, 1 H), 8.25 (dd, J = 1.2, 6.9 Hz, 1 H).

$$\label{eq:stars} \begin{split} ^{13}\text{C NMR} \ (\text{CDCl}_3) &: \delta = 21.6 \ (\text{t}), \ 30.0 \ (\text{q}), \ 39.1 \ (\text{t}), \ 90.2 \ (\text{s}), \ 109.7 \ (\text{d}), \\ 113.3 \ (\text{s}), \ 119.1 \ (\text{d}), \ 119.3 \ (\text{d}), \ 122.1 \ (\text{d}), \ 122.4 \ (\text{d}), \ 126.2 \ (\text{d}), \ 127.1 \\ (\text{d}), \ 127.9 \ (\text{s}), \ 129.5 \ (\text{d}), \ 137.6 \ (\text{s}), \ 138.6 \ (\text{s}), \ 139.1 \ (\text{d}), \ 171.4 \ (\text{s}). \end{split}$$

Anal. Calcd for  $C_{18}H_{17}IN_2O$ : C, 53.48; H, 4.24; N, 6.93. Found: C, 53.37; H, 4.17; N, 6.98.

### *N*-(4-Chloro-2-iodophenyl)-3-(1-methyl-1*H*-indol-3-yl)propionamide (3i)

*Method A*; stirring for 4 h; eluent:  $CH_2Cl_2$ -MeOH 20:1. Yield: 48%; mp 151–152 °C (white powder from  $CH_2Cl_2$ -hexane).

IR (Nujol): 1650, 3250 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 2.85 (t, *J* = 7.2 Hz, 2 H), 3.24 (t, *J* = 7.2 Hz, 2 H), 3.75 (s, 3 H), 6.94 (s, 1 H), 7.15 (dd, *J* = 7.3, 7.8 Hz, 1 H),

7.22–7.35 (m, 4 H, after deuteration m, 3 H), 7.65 (d, J = 7.8 Hz, 1 H), 7.70 (d, J = 2.3 Hz, 1 H), 8.18 (d, J = 8.6 Hz, 1 H).

 $\label{eq:stars} \begin{array}{l} ^{13}\text{C NMR} \ (\text{CDCl}_3)\text{: } \delta = 21.6 \ (\text{t}), 33.1 \ (\text{q}), 39.1 \ (\text{t}), 89.7 \ (\text{s}), 109.8 \ (\text{d}), \\ 113.1 \ (\text{s}), 119.1 \ (\text{d}), 119.4 \ (\text{d}), 122.2 \ (\text{d}), 122.7 \ (\text{d}), 127.1 \ (\text{d}), 127.8 \\ (\text{s}), 129.6 \ (\text{d}), 130.1 \ (\text{s}), 137.4 \ (\text{s}), 137.7 \ (\text{s}), 138.2 \ (\text{d}), 171.5 \ (\text{s}). \end{array}$ 

Anal. Calcd for  $C_{18}H_{16}ClIN_2O$ : C, 49.28; H, 3.68; N, 6.39. Found: C, 49.02; H, 3.91; N, 6.26.

### *N*-(2-Bromopyridin-3-yl)-3-(1-methyl-1*H*-indol-3-yl)propionamide (3j)

*Method A*; eluent:  $CH_2Cl_2$ – $Et_2O$ , 5:1; light yellow oil; yield: 39%. IR (Nujol): 1645, 3300 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta = 1.86$  (t, J = 7.1 Hz, 2 H), 3.22 (t, J = 7.1 Hz, 2 H), 3.73 (s, 3 H), 6.92 (s, 1 H), 7.10–7.30 (m, 4 H), 7.53 (br s, 1 H, absent after deuteration), 7.62 (d, J = 7.6 Hz, 1 H), 8.04 (dd, J = 1.8, 4.8 Hz, 1 H), 8.66 (dd, J = 1.8, 8.4 Hz, 1 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>): δ = 21.5 (t), 33.1 (q), 39.2 (t), 109.8 (d), 112.9 (s), 119.1 (d), 119.4 (d), 122.3 (d), 123.9 (d), 127.1 (d), 127.7 (s), 129.2 (d), 133.2 (s), 133.9 (s), 137.7 (s), 144.7 (d), 171.9 (s).

Anal. Calcd for  $C_{17}H_{16}BrN_3O$ : C, 57.00; H, 4.50; N, 11.73. Found: C, 57.19; H, 5.33; N, 11.98.

# *N*-(2-Bromobenzyl)-3-(1-methyl-1*H*-indol-3-yl)propionamide (3k)

*Method B*; eluent:  $CH_2Cl_2$ -MeOH, 20:1; yield: 51%; mp 121-122 °C (yellow crystals from  $CH_2Cl_2$ -hexane).

IR (Nujol): 1640, 3300 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta = 2.62$  (t, J = 7.2 Hz, 2 H), 3.13 (t, J = 7.2 Hz, 2 H), 3.70 (s, 3 H), 4.45 (d, J = 6.0 Hz, 2 H), 5.90 (br s, 1 H, absent after deuteration), 6.81 (s, 1 H), 7.09–7.32 (m, 6 H), 7.51 (d, J = 7.9 Hz, 1 H), 7.60 (d, J = 7.9 Hz, 1 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>): δ = 21.6 (t), 33.0 (q), 37.9 (t), 44.1 (t), 109.7 (d), 113.7 (s), 119.2 (d), 119.3 (d), 122.0 (d), 124.0 (s), 127.0 (d), 127.9 (s), 128.0 (d), 129.4 (d), 130.6 (d), 133.1 (d), 137.5 (s), 137.7 (s), 173.0 (s).

Anal. Calcd for  $C_{19}H_{19}BrN_2O$ : C, 61.47; H, 5.16; N, 7.55. Found: C, 61.52; H, 4.91; N, 7.34.

#### **Amides 4; General Procedure**

To a soln of the amide **3** (1 mmol) in anhyd THF (10 mL), 60% NaH (60 mg, 1.5 mmol) was added portionwise under N<sub>2</sub> at 0 °C. After stirring for 15 min at r.t., MeI (0.5 mL, 8 mmol) was added. The mixture was stirred at 50 °C for 18 h (Tables 1 and 2, entries a, e, and g) or at r.t. (other entries), then the mixture was concentrated. The residue was diluted with 1 M HCl and extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 × 20 mL). The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>), the solvent evaporated and the residue purified by chromatography (CH<sub>2</sub>Cl<sub>2</sub>– Et<sub>2</sub>O, 5:1) or crystallization (entry h).

# *N*-(2-Iodophenyl)-*N*-methyl-2-(1-methyl-1*H*-indol-3-yl)acetamide (4a)

Pale yellow oil; yield: 76%.

IR (Nujol): 1660 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 3.20 (s, 3 H), 3.49 (d, *J* = 3.0 Hz, 2 H), 3.71 (s, 3 H), 6.85 (s, 1 H), 7.04 (m, 2 H), 7.10–7.38 (m, 5 H), 7.95 (dd, *J* = 1.4, 7.6 Hz, 1 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  = 31.5 (t), 32.9 (q), 36.5 (q), 100.1 (s), 107.7 (s), 109.3 (d), 119.1 (d), 193.3 (d), 121.7 (d), 128.1 (s), 128.2 (d), 129.6 (d), 130.0 (d), 130.1 (d), 137.0 (s), 140.4 (d), 146.5 (s), 171.4 (s).

Anal. Calcd for  $C_{18}H_{17}IN_2O$ : C, 53.48; H, 4.24; N, 6.93. Found: C, 53.66; H, 3.95; N, 7.19.

## *N*-(4-Chloro-2-iodophenyl)-*N*-methyl-2-(1-methyl-1*H*-indol-3-yl)acetamide (4b)

Yield: 72%; mp 77–80 °C (yellow crystals from  $Et_2O$ –hexane).

IR (Nujol): 1650 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 3.19 (s, 3 H), 3.48 and 3.55 (system AB, J = 15.7 Hz, 2 H), 3.74 (s, 3 H), 6.85 (s, 1 H), 7.03 (d, J = 8.2 Hz, 1 H), 7.06 (dd, J = 6.0, 7.5 Hz, 1 H), 7.20 (dd, J = 7.5, 7.8 Hz, 1 H), 7.24–7.35 (m, 3 H), 7.93 (d, J = 2.2 Hz, 1 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>): δ = 31.9 (t), 33.1 (q), 36.7 (q), 100.5 (s), 107.6 (s), 109.5 (d), 119.3 (d), 119.5 (d), 121.9 (d), 128.2 (d), 130.3 (d), 130.4 (d), 134.9 (s), 137.1 (s), 137.5 (s), 139.8 (d), 145.4 (s), 171.4 (s).

Anal. Calcd for  $C_{18}H_{16}CIIN_2O$ : C, 49.28; H, 3.68; N, 6.39. Found: C, 49.21; H, 3.91; N, 6.28.

# *N*-(2-Bromo-4-methylphenyl)-*N*-methyl-2-(1-methyl-1*H*-indol-3-yl)acetamide (4c)

Light yellow oil; yield: 78%.

IR (Nujol): 1660 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 2.41 (s, 3 H), 3.22 (s, 3 H), 3.52 (s, 2 H), 3.74 (s, 3 H), 6.91 (s, 1 H), 7.02–7.15 (m, 3 H), 7.19 (dd, *J* = 7.2, 7.9 Hz, 1 H), 7.26 (d, *J* = 8.7 Hz, 1 H), 7.34 (d, *J* = 7.9 Hz, 1 H), 7.53 (s, 1 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  = 21.2 (q), 31.1 (t), 33.1 (q), 36.6 (q), 108.0 (s), 109.4 (d), 113.4 (s), 119.1 (d), 119.3 (d), 121.8 (d), 123.5 (s), 128.3 (d), 129.6 (d), 129.9 (d), 134.6 (d), 135.0 (s), 137.1 (s), 140.6 (s), 171.9 (s).

Anal. Calcd for  $C_{19}H_{19}BrN_2O$ : C, 61.47; H, 5.16; N, 7.55. Found: C, 61.44; H, 5.04; N, 7.81.

# *N*-(2-Bromopyridin-3-yl)-*N*-methyl-2-(1-methyl-1*H*-indol-3-yl)acetamide (4d)

Light yellow oil; yield: 85%.

IR (Nujol): 1650 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 3.24 (s, 3 H), 3.51 and 3.60 (AB system, J = 15.7 Hz, 2 H), 3.72 (s, 3 H), 6.78 (s, 1 H), 7.05 (dd, J = 7.3, 7.9 Hz, 1 H), 7.16–7.23 (m, 2 H), 7.26 (d, J = 8.2 Hz, 1 H), 7.30 (d, J = 7.9 Hz, 1 H), 7.35 (dd, J = 1.8, 7.7 Hz, 1 H), 8.35 (dd, J = 1.8, 4.7 Hz, 1 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>): δ = 32.0 (t), 33.1 (q), 36.6 (q), 107.4 (s), 109.6 (d), 119.2 (d), 119.5 (d), 122.1 (d), 123.9 (d), 127.9 (s), 128.0 (d), 137.1 (s), 138.6 (d), 140.7 (s), 144.0 (s), 150.0 (d), 171.5 (s).

Anal. Calcd for  $C_{17}H_{16}BrN_3O$ : C, 57.00; H, 4.50; N, 11.73. Found: C, 56.86; H, 4.29; N, 11.47.

### *N*-(3-Bromo-5-methylpyridin-2-yl)-*N*-methyl-2-(1-methyl-1*H*indol-3-yl)acetamide (4e)

Yellow oil; yield: 89%.

IR (Nujol): 1660 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 2.35 (s, 3 H), 3.26 (s, 3 H), 3.58 (s, 2 H), 3.72 (s, 3 H), 6.90 (s, 1 H), 7.02 (dd, *J* = 7.3, 8.2 Hz, 1 H), 7.16 (dd, *J* = 7.3, 7.9 Hz, 1 H), 7.23 (d, *J* = 8.2 Hz, 1 H), 7.32 (d, *J* = 7.9 Hz, 1 H), 7.73 (s, 1 H), 8.28 (s, 1 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  = 17.9 (q), 31.5 (t), 33.0 (q), 35.1 (q), 107.6 (s), 109.3 (d), 119.0 (d), 119.1 (d), 119.5 (s), 121.7 (d), 128.1 (d), 128.2 (s), 135.5 (s), 137.0 (s), 143.1 (d), 149.1 (d), 152.4 (s), 171.8 (s).

Anal. Calcd for  $C_{18}H_{18}BrN_3O$ : C, 58.08; H, 4.87; N, 11.29. Found: C, 57.81; H, 5.10; N, 11.51.

# N-(2-Bromobenzyl)-N-methyl-2-(1-methyl-1H-indol-3-yl)acetamide (4f)

Yellow oil; yield: 64%.

IR (Nujol): 1644 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, mixture 1:1 of rotamers):  $\delta = 3.06$  (s, 6 H), 3.67 (s, 3 H), 3.72 (s, 5 H), 3.92 (s, 2 H), 4.60 (s, 2 H), 4.74 (s, 2 H), 6.91–7.79 (m, 18 H); (400 MHz, DMSO-*d*<sub>6</sub>, mixture 5:3 of rotamers): major rotamer  $\delta = 3.05$  (s, 3 H), 3.77 (s, 3 H), 3.89 (s, 2 H), 4.53 (s, 2 H), 6.91–7.79 (m, 9 H); minor rotamer  $\delta = 2.86$  (s, 3 H), 3.67 (s, 3 H), 3.71 (s, 2 H), 4.67 (s, 2 H), 6.91–7.79 (m, 9 H); (400 MHz, DMSO-*d*<sub>6</sub>, 110 °C):  $\delta = 2.95$  (s, 6 H), 3.74 (s, 2 H), 3.84 (s, 1 H), 4.65 (s, 1 H), 6.80–7.70 (m, 9 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, mixture 1:1 of rotamers): δ = 31.4 (t), 32.9 (q), 33.0 (q), 34.9 (q), 36.1 (q), 51.2 (t), 54.6 (t), 107.5 (s), 107.6 (s), 109.3 (d), 109.5 (d), 119.1 (d), 119.3 (d), 119.4 (d), 121.9 (d), 122.0 (d), 122.6 (s), 123.8 (s), 127.0 (d), 127.7 (d), 127.9 (d), 128.9 (d), 129.0 (d), 129.2 (d), 133.0 (d), 133.1 (d), 135.9 (s), 136.5 (s), 137.1 (s), 137.2 (s), 140.5 (s), 172.3 (s), 172.7 (s).

Anal. Calcd for  $C_{19}H_{19}BrN_2O$ : C, 61.47; H, 5.16; N, 7.55. Found: C, 61.39; H, 4.86; N, 7.32.

### *N*-[2-(2-Bromophenyl)ethyl]-*N*-methyl-2-(1-methyl-1*H*-indol-3-yl)acetamide (4g)

Yellow oil; yield: 68%.

IR (Nujol): 1640 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, mixture 1:1 of rotamers):  $\delta = 2.92$  (t, J = 7.6 Hz, 2 H), 2.96 (s, 3 H) 3.02 (t, J = 7.6 Hz, 2 H), 3.04 (s, 3 H), 3.58 (t, J = 7.6 Hz, 2 H), 3.65 (t, J = 7.6 Hz, 2 H), 3.69 (s, 2 H), 3.75 (s, 3 H), 3.78 (s, 3 H), 3.84 (s, 2 H), 6.94 (d, J = 7.9 Hz, 2 H), 6.99 (s, 2 H), 7.02–7.58 (m, 11 H), 7.55 (m, 1 H) 7.60 (d, J = 7.9 Hz, 1 H), 7.65 (d, J = 7.9 Hz, 1 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, mixture 1:1 of rotamers): δ = 31.0 (t), 31.7 (t), 31.1 (q), 34.1 (q), 34.3 (t), 35.6 (t), 37.1 (q), 48.8 (t), 50.5 (t), 107.9 (s), 108.3 (s), 109.6 (d), 119.2 (d), 119.3 (d), 119.4 (d), 119.5 (d), 122.1 (d), 124.7 (s), 124.8 (s), 124.7 (s) 124.8 (s) 126.6 (d), 126.7 (d), 128.0 (d), 128.2 (d), 128.5 (d), 129.0 (d), 131.6 (d), 131.7 (d), 133.1 (d), 133.4 (d), 137.3 (s), 137.9 (s), 138.9 (s), 171.2 (s), 172.1 (s).

Anal. Calcd for  $C_{20}H_{21}BrN_2O$ : C, 62.35; H, 5.49; N, 7.27. Found: C, 62.09; H, 5.72; N, 7.11.

# *N*-(2-Iodophenyl)-*N*-methyl-3-(1-methyl-1*H*-indol-3-yl)propionamide (4h)

Yield: 99%; mp 95 °C (light yellow crystals from  $Et_2O$ -hexane). IP (Nuich): 1650 cm<sup>-1</sup>

IR (Nujol): 1650 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta = 2.36$  (m, 2 H), 3.10 (m, 2 H), 3.21 (s, 3 H), 3.71 (s, 3 H), 6.81 (s, 1 H), 6.98–7.07 (m, 3 H), 7.20 (ddd, J = 1.3, 7.2, 7.8 Hz, 1 H), 7.26 (d, J = 8.1 Hz, 1 H), 7.28 (ddd, J = 1.4, 7.6, 8.1 Hz, 1 H), 7.37 (d, J = 7.8 Hz, 1 H), 7.90 (dd, J = 1.3; 7.8 Hz, 1 H).

 $^{13}\text{C}$  NMR (CDCl<sub>3</sub>):  $\delta$  = 21.4 (t), 32.9 (q), 35.9 (t), 36.3 (q), 100.1 (s), 109.4 (d), 114.2 (s), 119.0 (d), 119.3 (d), 121.8 (d), 126.8 (d), 128.0 (s), 129.4 (d), 130.0 (d), 130.2 (d), 137.3 (s), 140.5 (d), 146.4 (s), 172.8. (s).

Anal. Calcd for  $C_{19}H_{19}IN_2O$ : C, 54.56; H, 4.58; N, 6.70. Found: C, 54.50; H, 4.66; N, 6.47.

# N-(4-Chloro-2-iodophenyl)-N-methyl-3-(1-methyl-1H-indol-3-yl)propionamide (4i)

Yellow oil; yield: 89%.

IR (Nujol): 1660 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 2.34 (t, *J* = 7.9 Hz, 2 H), 3.03–3.14 (m, 2 H), 3.16 (s, 3 H), 3.73 (s, 3 H), 6.78 (d, *J* = 8.4 Hz, 1 H), 6.81 (s, 1 H), 7.06 (dd, *J* = 7.3, 7.9 Hz, 1 H), 7.16–7.22 (m, 2 H), 7.27 (d, *J* = 6.9 Hz, 1 H), 7.37 (d, *J* = 7.9 Hz, 1 H), 7.87 (d, *J* = 2.1 Hz, 1 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>): δ = 21.5 (t), 32.9 (q), 35.9 (t), 36.3 (q), 100.4 (s), 109.5 (d), 114.1 (s), 119.1 (d), 119.2 (d), 121.9 (d), 126.9 (d), 128.0 (s), 129.9 (d), 130.4 (d), 134.9 (s), 137.3 (s), 139.7 (d), 145.2 (s), 172.8 (s).

Anal. Calcd for  $C_{19}H_{18}ClIN_2O$ : C, 50.41; H, 4.01; N, 6.19. Found: C, 50.66; H, 3.72; N, 6.36.

### *N*-(2-Bromopyridin-3-yl)-*N*-methyl-3-(1-methyl-1*H*-indol-3-yl)propionamide (4j)

Yield: 96%; mp 197–198 °C (cream crystals from  $Et_2O$ -hexane).

IR (Nujol):  $1660 \text{ cm}^{-1}$ .

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta = 2.37$  (m, 2 H), 3.09 (m, 2 H), 3.20 (s, 3 H), 3.72 (s, 3 H), 6.81 (s, 1 H), 7.01–7.09 (m, 3 H), 7.21 (ddd, J = 0.8, 7.1, 8.1 Hz, 1 H), 7.28 (d, J = 8.1 Hz, 1 H), 7.36 (d, J = 7.9 Hz, 1 H), 8.30 (dd, J = 2.0, 4.6 Hz, 1 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>): δ = 21.5 (t), 32.9 (q), 35.7 (t), 36.2 (q), 109.5 (d), 109.6 (d), 113.8 (s), 119.2 (d), 122.0 (d), 124.1 (d), 126.9 (d), 127.9 (s), 137.3 (s), 138.4 (d), 140.5 (s), 143.9 (s), 149.6 (d), 172.8 (s).

Anal. Calcd for  $C_{18}H_{18}BrN_3O$ : C, 58.08; H, 4.87; N, 11.29. Found: C, 58.02; H, 5.08; N, 11.13.

# $N\mbox{-}(2\mbox{-Bromobenzyl})\mbox{-}N\mbox{-methyl-}3\mbox{-}(1\mbox{-methyl-}1\mbox{H}\mbox{-indol-}3\mbox{-}yl)\mbox{propionamide}\ (4k)$

Brownish oil; yield: 99%.

IR (Nujol): 1660 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, mixture 1:1 of rotamers):  $\delta = 2.65$  (t, J = 8.1 Hz, 2 H), 2.80 (t, J = 8.1 Hz, 2 H), 2.89 (s, 3 H), 3.00 (s, 3 H), 3.02–3.20 (m, 4 H), 3.71 (s, 3 H), 3.74 (s, 3 H), 4.46 (s, 2 H), 4.72 (s, 2 H), 6.85 (s, 1 H), 6.92 (s, 1 H), 6.96–7.35 (m, 12 H), 7.44–7.64 (m, 4 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, mixture 1:1 of rotamers): δ = 20.9 (t), 21.2 (t), 32.8 (q), 34.3 (t), 34.5 (q), 34.6 (t), 35.5 (q), 51.1 (t), 54.0 (t), 109.4 (d), 109.5 (d), 114.0 (s), 114.1 (s), 118.9 (d), 119.0 (d), 121.7 (d), 121.8 (d), 122.8 (s) 123.8 (s), 126.7 (d), 126.9 (d), 127.0 (d), 127.8 (d), 128.1 (d), 128.9 (d), 129.0 (d), 129.2 (d), 133.0 (d), 133.3 (d), 135.8 (s), 136.5 (s), 137.2 (s), 137.3 (s), 173.8 (s).

Anal. Calcd for  $C_{20}H_{21}BrN_2O$ : C, 62.35; H, 5.49; N, 7.27. Found: C, 62.08; H, 5.70; N, 7.12.

### Cyclization of the Amides 4; General Procedure

*Thermal heating.* A soln of **4** (1 mmol),  $Pd(OAc)_2$  (12 mg, 0.05 mmol),  $Ph_3P$  (26 mg, 0.1 mmol), AcOK (196 mg, 2 mmol), and TBACl (278 mg, 1 mmol) in DMA (5 mL) was stirred at 110 °C for the time reported in Tables 1 and 2. After cooling to r.t., the mixture was diluted with brine (15 mL) and extracted with  $Et_2O$ . The organic layer was dried ( $Na_2SO_4$ ) and evaporated under reduced pressure. The residue was chromatographed on a silica gel column (light petroleum ether– $Et_2O$ , 1:1) to give compound **5**.

*Microwave irradiation.* A soln of the amide **4c**, **4f**, **4g**, or **4k** (1 mmol),  $Pd(OAc)_2$  (12 mg, 0.05 mmol),  $Ph_3P$  (26 mg, 0.1 mmol), AcOK (196 mg, 2 mmol), and TBACl (278 mg, 1 mmol) in DMA (5 mL) was heated in a microwave oven (600 W) at 160 °C for 2 h for **4c** and **4g** and at 120 °C for the time reported in Tables 1 and 2 for **4f** and **4k**. The mixture was elaborated as indicated above.

### 5,12-Dimethyl-7,12-dihydroindolo[3,2-d][1]benzazepin-6(5H)-

**one (5a)** Yield: 85%.<sup>1f</sup>

### 2-Chloro-5,12-dimethyl-7,12-dihydroindolo[3,2-*d*][1]benzazepin-6(5*H*)-one (5b)

Yield: 76%; mp 171–172 °C (light yellow crystals from  $Et_2O$ –hexane).

IR (Nujol): 1660 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 3.07 and 3.99 (AB system, *J* = 14.1 Hz, 2 H), 3.35 (s, 3 H), 3.92 (s, 3 H), 7.23 (dd, *J* = 7.2, 7.5 Hz, 1 H), 7.35 (dd, *J* = 7.2, 7.9 Hz, 1 H), 7.40–7.44 (m, 3 H), 7.53 (s, 1 H), 7.75 (d, *J* = 7.9 Hz, 1 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  = 32.2 (q), 32.6 (t), 38.1 (q), 110.2 (d), 113.5 (s), 119.3 (d), 120.6 (d), 123.7 (d), 125.9 (s), 126.0 (d), 126.9 (s), 128.3 (d), 128.4 (d), 130.4 (s), 132.8 (s), 139.8 (s), 140.5 (s), 172.8 (s).

Anal. Calcd for  $C_{18}H_{15}ClN_2O$ : C, 69.57; H, 4.86; N, 9.01. Found: C, 69.74; H, 5.11; N, 8.72.

# 2,5,12-Trimethyl-7,12-dihydroindolo[3,2-*d*][1]benzazepin-6(5*H*)-one (5c)

Pale yellow oil; yield: 55%; 70% using MW irradiation.

IR (Nujol): 1635 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta = 2.49$  (s, 3 H), 3.08 and 3.97 (AB system, J = 14.0 Hz, 2 H), 3.35 (s, 3 H), 3.92 (s, 3 H), 7.22 (dd, J = 7.2, 7.9 Hz, 1 H), 7.27 (d, J = 8.1 Hz, 1 H), 7.32 (dd, J = 7.2, 8.0 Hz, 1 H), 7.35–7.42 (m, 3 H), 7.75 (d, J = 8.1 Hz, 1 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  = 21.5 (q), 32.2 (q), 32.7 (t), 38.0 (q), 110.1 (d), 112.6 (s), 119.1 (d), 120.3 (d), 123.1 (d), 124.5 (d), 125.2 (s), 126.1 (s), 129.1 (d), 129.3 (d), 134.2 (s), 134.8 (s), 139.6 (s), 139.8 (s), 173.2 (s).

Anal. Calcd for  $C_{19}H_{18}N_2O$ : C, 78.59; H, 6.25; N, 9.65. Found: C, 78.87; H, 6.01; N, 9.40.

# 5,12-Dimethyl-7,12-dihydropyrido[3',2':2,3]azepino[4,5-*b*]in-dol-6(5*H*)-one (5d)

Yield: 99%; mp 150–152 °C (red crystals from  $CH_2Cl_2$ –hexane).

IR (Nujol):  $1660 \text{ cm}^{-1}$ .

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 3.11 and 4.08 (AB system, *J* = 14.0 Hz, 2 H), 3.36 (s, 3 H), 4.13 (s, 3 H), 7.21 (dd, *J* = 7.2, 7.7 Hz, 1 H), 7.33–7.38 (m, 2 H), 7.45 (d, *J* = 8.3 Hz, 1 H), 7.74–7.78 (m, 2 H), 8.61 (d, *J* = 4.5 Hz, 1 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>): δ = 32.0 (q), 32.7 (t), 37.7 (q), 110.3 (d), 114.6 (s), 119.4 (d), 120.3 (d), 122.0 (d), 124.0 (d), 125.7 (s), 131.8 (d), 132.6 (s), 138.5 (s), 139.9 (s), 144.6 (s), 145.7 (d), 172.4 (s).

Anal. Calcd for  $C_{17}H_{15}N_3O$ : C, 73.63; H, 5.45; N, 15.15. Found: C, 73.58; H, 5.22; N, 14.99.

#### 2,5,12-Trimethyl-7,12-dihydropyrido[2',3':2,3]azepino[4,5*b*]indol-6(5*H*)-one (5e)

Yield: 99%; mp 163–164  $^{\circ}\text{C}$  (light yellow crystals from  $\text{CH}_{2}\text{Cl}_{2}\text{-}$  hexane).

IR (Nujol): 1675 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 2.49 (s, 3 H), 3.12 and 4.04 (AB system, J = 14.2 Hz, 2 H), 3.46 (s, 3 H), 3.87 (s, 3 H), 7.22 (dd, J = 7.2, 7.8 Hz, 1 H), 7.34 (dd, J = 7.2, 8.1 Hz, 1 H), 7.40 (d, J = 8.1 Hz, 1 H), 7.70 (s, 1 H), 7.75 (d, J = 7.8 Hz, 1 H), 8.40 (s, 1 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  = 18.4 (q), 32.1 (q), 32.8 (t), 35.6 (q), 110.2 (d), 112.9 (s), 119.3 (d), 119.7 (s), 120.6 (d), 123.6 (d), 125.9 (s), 129.5 (s), 132.2 (s), 137.3 (d), 140.1 (s) 148.3 (d), 151.0 (s), 172.8 (s).

Anal. Calcd for  $C_{18}H_{17}N_3O$ : C, 74.21; H, 5.88; N, 14.42. Found: C, 74.33; H, 6.10; N, 14.19.

# 6,13-Dimethyl-5,6,8,13-tetrahydroindolo[3,2-*e*][2]benzazocin-7-one (5f)

Brownish oil; yield: 30%; 45% using MW irradiation.

IR (Nujol): 1620 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 2.97–4.65 (m, 4 H), 3.18 (s, 3 H), 3.77 (s, 3 H), 7.15 (m, 1 H), 7.23 (dd, *J* = 7.1, 7.4 Hz, 1 H), 7.33 (dd, *J* = 7.1, 7.6 Hz, 1 H), 7.41 (d, *J* = 8.1 Hz, 1 H), 7.47–7.52 (m, 2 H), 7.58 (d, *J* = 6.4 Hz, 1 H), 7.73 (d, *J* = 7.6 Hz, 1 H).

 $^{13}\text{C}$  NMR (CDCl<sub>3</sub>):  $\delta$  = 31.4 (q), 34.8 (t), 39.2 (q), 54.6 (t), 108.5 (s), 110.0 (d), 119.3 (d), 120.4 (d), 122.8 (d), 127.8 (s), 128.6 (d), 129.3 (d), 129.6 (d), 131.3 (d), 131.7 (s), 137.5 (s), 137.6 (s), 138.1 (s), 170.3 (s).

Anal. Calcd for  $C_{19}H_{18}N_2O;\,C,\,78.59;\,H,\,6.25;\,N,\,9.65.$  Found: C, 78.78; H, 6.56; N, 9.41.

# 7,14-Dimethyl-6,7,9,14-tetrahydroindolo[3,2-f][3]benzazonin-8(5H)-one (5g)

Yellow oil; yield: 20%; 51% using MW irradiation.

IR (Nujol): 1630 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 2.51–2.57 (m, 2 H), 2.86–3.03 (m, 3 H), 3.25 (m, 1 H), 3.41 (m, 1 H), 3.56–3.89 (m, 5 H), 7.13–7.45 (m, 7 H), 8.21 (d, *J* = 7.6 Hz, 1 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>): δ = 30.1 (t), 30.7 (q), 35.2 (t), 36.2 (q), 53.2 (t), 108.0 (s), 109.4 (d), 120.0 (d), 123.0 (d), 123.4 (d), 126.6 (d), 129.4 (d), 130.0 (d), 130.1 (s), 132.3 (d), 136.5 (s), 137.3 (s), 137.9 (s), 142.8 (s), 172.0 (s).

Anal. Calcd for  $C_{20}H_{20}N_2O$ : C, 78.92; H, 6.62; N, 9.20. Found: C, 79.25; H, 6.39; N, 9.02.

# 5,13-Dimethyl-5,7,8,13-tetrahydroindolo[3,2-*e*][1]benzazocin-6-one (5h)

Yield: 99%; mp 188–189 °C (red crystals from  $CH_2Cl_2$ -hexane).

IR (Nujol): 1650 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta = 2.45$  (m, 1 H), 2.91 (m, 1 H), 3.10 (m, 1 H), 3.23 (s, 3 H), 3.52 (m, 1 H), 3.53 (s, 3 H), 7.19 (ddd, J = 1.4, 6.7, 7.9 Hz, 1 H), 7.29–7.34 (m, 2 H), 7.36–7.53 (m, 4 H), 7.61 (d, J = 7.9 Hz, 1 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  = 22.9 (t), 31.2 (q), 31.6 (t), 36.6 (q), 109.7 (d), 113.6 (s), 119.3 (d), 119.8 (d), 123.0 (d), 126.8 (d), 127.4 (d), 128.2 (s), 129.7 (d), 130.4 (s), 132.6 (s), 132.9 (d), 138.2 (s), 143.8 (s), 173.8 (s).

Anal. Calcd for  $C_{19}H_{18}N_2O$ : C, 78.59; H, 6.25; N, 9.65. Found: C, 78.61; H, 6.07; N, 9.82.

### 2-Chloro-5,13-dimethyl-5,7,8,13-tetrahydroindolo[3,2e][1]benzazocin-6-one (5i)

Yield: 99%; mp 198–199 °C (ochre powder from  $Et_2O$ –hexane).

IR (Nujol): 1660 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 2.45 (m, 1 H), 2.92 (m, 1 H), 3.07 (m, 1 H), 3.19 (s, 3 H), 3.50 (m, 1 H), 3.54 (s, 3 H), 7.19 (t, *J* = 6.3 Hz, 1 H), 7.28–7.37 (m, 4 H), 7.47 (d, *J* = 8.3 Hz, 1 H), 7.59 (d, *J* = 7.7 Hz, 1 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  = 22.9 (t), 31.4 (q), 31.5 (t), 36.7 (q), 109.8 (d), 114.4 (s), 119.5 (d), 120.1 (d), 123.5 (d), 127.0 (s), 128.1 (d), 129.8 (d), 131.2 (s), 132.2 (s), 132.6 (d), 133.0 (s), 138.5 (s), 142.4 (s), 173.7 (s).

Anal. Calcd for  $C_{19}H_{17}ClN_2O$ : C, 70.26; H, 5.28; N, 8.62. Found: C, 70.33; H, 5.54; N, 8.39.

### 5,13-Dimethyl-5,7,8,13-tetrahydropyrido[3',2':2,3]azocino[4,5*b*]indol-6-one (5j)

Yield: 78%; mp 199–201 °C (cream powder from  $Et_2O$ ).

IR (Nujol): 1660 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 2.47 (m, 1 H), 2.81 (m, 1 H), 3.10 (m, 1 H), 3.21 (s, 3 H), 3.56 (m, 1 H), 3.59 (s, 3 H), 7.16 (m, 1 H), 7.30–7.33 (m, 2 H), 7.42 (m, 1 H), 7.58 (d, *J* = 7.7 Hz, 1 H), 7.74 (d, *J* = 8.1 Hz, 1 H), 8.75 (d, *J* = 4.0 Hz, 1 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  = 23.2 (t), 31.3 (q), 31.3 (t), 36.6 (q), 109.7 (d), 114.7 (s), 119.5 (d), 119.6 (d), 123.5 (d), 127.6 (s), 128.3 (d), 132.2 (d), 133.7 (s), 138.4 (s), 140.4 (s), 148.4 (d), 149.4 (s), 173.3 (s).

Anal. Calcd for  $C_{18}H_{17}N_3O$ : C, 74.21; H, 5.88; N, 14.42. Found: C, 74.02; H, 6.11; N, 14.16.

# 6,14-Dimethyl-6,8,9,14-tetrahydroindolo[3,2-f][2]benzazonin-7(6H)-one (5k)

Yield: 26%; 55% using MW irradiation; mp 209–210  $^{\circ}\text{C}$  (ochre powder from Et\_2O).

IR (Nujol): 1630 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta = 2.27$  (m, 1 H), 2.60 (m, 1 H), 3.12 (m, 1 H), 3.30 (s, 3 H), 3.39 (m, 1 H), 3.57 (s, 3 H), 4.10 and 4.71 (AB system, J = 15.1 Hz, 2 H), 7.23 (t, J = 7.2 Hz, 1 H), 7.30–7.40 (m, 3 H), 7.43–7.53 (m, 2 H), 7.63 (d, J = 7.8 Hz, 1 H), 7.73 (d, J = 7.2 Hz, 1 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>): δ = 14.5 (q), 23.1 (t), 31.7 (q), 32.3 (t), 52.4 (t), 109.9 (d), 115.5 (s), 117.0 (s), 119.0 (d), 120.1 (d), 122.7 (d), 127.0 (s), 128.0 (d), 129.2 (d), 130.5 (d), 132.0 (d), 135.6 (s), 137.4 (s), 138.2 (s), 175.0 (s).

Anal. Calcd for  $C_{20}H_{20}N_2O$ : C, 78.92; H, 6.62; N, 9.20. Found: C, 78.80; H, 6.85; N, 9.13.

### Acknowledgment

The authors gratefully acknowledge the MIUR (Cofin 2003) for financial support.

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