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

Egle M. Beccalli,*a Gianluigi Broggini,a Michela Martinelli,a Giuseppe Paladino,a Elisabetta Rossib

a Dipartimento di Scienze Chimiche e Ambientali, Università dell’Insubria, via Valleggio 11, 22100 Como, Italy
Fax +39(02)50314476; E-mail: egle.beccalli@unimi.it
b Istituto di Chimica Organica ‘A. Marchesini’, Facoltà di Farmacia, Università di Milano, via Venezian 21, 20133 Milano, Italy

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 eight-membered 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.1 General syntheses for larger ring heterocycles, indoloazocines and indoloazonines, are not available; only some synthetic paths to particular indoloazocines have been described.2 We describe here a novel sequence to obtain indolo-benzazepines, indolo-benzazocines, 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) inhibitors3 and as glycoyn synthase kinase-3β (GSK-3β) inhibitors4 and also their promising antitumoral properties (a representative example is compound A, Figure 1). Moreover, the pyrido-azepino-indoles (i.e., azakenpaullones) showed improved action as GSK-3β inhibitors.5 The indoloazocine derivatives, such as compound B (Figure 1), showed acetylcholinesterase (AChE) inhibitory activities6 which at present represents a major pharmacological approach to the treatment of Alzheimer’s disease.7 Indoloazocines have also been patented as a central nervous system depressant.8 Many indole alkaloid families (i.e., iboga, vinca, aspidosperma) include large, indolo-fused, heterocyclic rings.9 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 β- and γ-carbolinones.10

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.11 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 1H NMR spectra of the derivatives 4f, 4g, and 4k, in CDCl3 solution, display the existence of 1:1 ratio of rotational isomers caused by restricted rotation about the amide bond. Obtaining the 1H NMR spectrum of 4f in DMSO-d6, 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(tri-
phenylphosphine)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-benzazepines, indolo-benzazocines, indolo-benzazonines, 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. 1H NMR and 13C NMR spectra were obtained on a Bruker Avance 400. Chemical shifts are given in ppm downfield from TMS. 13C NMR spectra are 1H-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)Cl2 (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 CH2Cl2 (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 CH2Cl2 (3 × 20 mL). The organic layer was dried (Na2SO4) 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 CH2Cl2 (15 mL). A soln of the appropriate amine (2.2 mmol) and Et3N (8 mmol) in anhyd CH2Cl2 (5 mL) was added dropwise. The mixture was stirred for 18 h, then washed with 5% HCl (10 mL). The organic layer was dried (Na2SO4) 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-1H-indol-3-yl)acetamide (3a)**

**Method A:** stirring for 4 h; eluent: CH2Cl2–MeOH, 20:1; yield: 74%; mp 113–114 °C (cream powder from Et2O–hexane).

IR (Nujol): 1680, 3350 cm–1.

**Method B:** To a soln of 1 or 2 (1 mmol) in THF (10 mL), MeI (0.21 mL, 2.5 mmol) was added at 0 °C. After stirring at r.t. for 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 CH2Cl2 (3 × 20 mL). The organic layer was dried (Na2SO4) and evaporated under reduced pressure. The residue was chromatographed on a silica gel column (eluent indicated below) to give the amide 3.

**Scheme 1  Reagents and conditions:** (i) When n = 0: PhOP(O)Cl2, DMF, py, CH2Cl2, r.t.; When n = 1, 2: (COCl)2, THF, r.t.; (ii) NaH, MeI, THF, r.t.; (iii) Pd(OAc)2 (5 mol%), Ph3P (10 mol%), AcOK, TBACl, DMA, 110 °C.
Table 1 Compounds 4 and 5 Obtained from Indole-3-acetic Acid 1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>Amide 4</th>
<th>Cyclization time (h)</th>
<th>Product 5</th>
<th>Yield* of 5 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td><img src="image1" alt="Image" /></td>
<td><img src="image2" alt="Image" /></td>
<td>30</td>
<td><img src="image3" alt="Image" /></td>
<td>85</td>
</tr>
<tr>
<td>b</td>
<td><img src="image4" alt="Image" /></td>
<td><img src="image5" alt="Image" /></td>
<td>5</td>
<td><img src="image6" alt="Image" /></td>
<td>76</td>
</tr>
<tr>
<td>c</td>
<td><img src="image7" alt="Image" /></td>
<td><img src="image8" alt="Image" /></td>
<td>35 (2)</td>
<td><img src="image9" alt="Image" /></td>
<td>55 (70)</td>
</tr>
<tr>
<td>d</td>
<td><img src="image10" alt="Image" /></td>
<td><img src="image11" alt="Image" /></td>
<td>17</td>
<td><img src="image12" alt="Image" /></td>
<td>99</td>
</tr>
<tr>
<td>e</td>
<td><img src="image13" alt="Image" /></td>
<td><img src="image14" alt="Image" /></td>
<td>17</td>
<td><img src="image15" alt="Image" /></td>
<td>99</td>
</tr>
<tr>
<td>f</td>
<td><img src="image16" alt="Image" /></td>
<td><img src="image17" alt="Image" /></td>
<td>48 (1)</td>
<td><img src="image18" alt="Image" /></td>
<td>30 (45)</td>
</tr>
<tr>
<td>g</td>
<td><img src="image19" alt="Image" /></td>
<td><img src="image20" alt="Image" /></td>
<td>72 (2)</td>
<td><img src="image21" alt="Image" /></td>
<td>20 (51)</td>
</tr>
</tbody>
</table>

*a* Starting from 4.

*b* MW irradiation time.

*c* In brackets the yield obtained using MW irradiation.

1^1^C NMR (CDCl3): δ = 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_{17}H_{15}IN_{2}O: C, 52.33; H, 3.87; N, 7.18. Found: C, 52.05; H, 4.08; N, 7.01.

Method A: stirring for 4 h; eluent: from CH$_2$Cl$_2$ to CH$_2$Cl$_2$–Et$_2$O, 10:1; yield: 72%; mp 162–163 °C (white crystals from Et$_2$O–hexane).

IR (Nujol): 1670, 3278 cm$^{-1}$. 

1H NMR (CDCl3): \(\delta = 3.85 \text{ (s, 3 H)}, 3.94 \text{ (s, 2 H)}, 7.16 \text{ (s, 1 H)}, 7.19 \text{ (m, 1 H)}, 7.26-7.34 \text{ (m, 2 H)}, 7.37 \text{ (d, } J = 8.2 \text{ Hz, 1 H)}, 7.59 \text{ (s, 1 H)}, 7.63 \text{ (d, } J = 7.9 \text{ Hz, 1 H)}, 7.83 \text{ (br s, 1 H, absent after deuteration)}, 8.27 \text{ (d, } J = 8.9 \text{ Hz, 1 H)}.

13C NMR (CDCl3): \(\delta = 33.3 \text{ (q)}, 34.9 \text{ (t)}, 89.1 \text{ (s)}, 107.0 \text{ (s)}, 110.0 \text{ (d)}, 119.5 \text{ (d)}, 120.4 \text{ (d)}, 121.8 \text{ (d)}, 123.0 \text{ (d)}, 128.0 \text{ (s)}, 129.5 \text{ (d)}, 123.0 \text{ (s)}, 137.5 \text{ (s)}, 137.9 \text{ (s)}, 138.2 \text{ (d)}, 170.5 \text{ (s)}.

Anal. Calcd for C17H14ClIN2O: 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-1H-indol-3-yl)acetamide (3c)
Method A; stirring for 24 h; eluent: from CH2Cl2 to CH2Cl2–Et2O, 10:1; yield: 68%; mp 101–102 °C (white powder from i-Pr2O).

IR (Nujol): 1680, 3350 cm–1.

1H NMR (CDCl3): \(\delta = 2.26 \text{ (s, 3 H)}, 3.84 \text{ (s, 3 H)}, 3.93 \text{ (s, 2 H)}, 7.09 \text{ (d, } J = 8.4 \text{ Hz, 1 H)}, 7.14 \text{ (s, 1 H)}, 7.19 \text{ (dd, } J = 7.2, 7.9 \text{ Hz, 1 H)}, 7.22 \text{ (s)}, 7.31 \text{ (dd, } J = 7.2, 8.2 \text{ Hz, 1 H)}, 7.37 \text{ (d, } J = 8.2 \text{ Hz, 1 H)}, 7.65 \text{ (d, } J = 7.9 \text{ Hz, 1 H)}, 7.94 \text{ (br s, 1 H, absent after deuteration)}, 8.23 \text{ (d, } J = 8.4 \text{ Hz, 1 H)}.

13C NMR (CDCl3): \(\delta = 20.9 \text{ (q)}, 33.3 \text{ (q)}, 34.9 \text{ (t)}, 107.3 \text{ (s)}, 109.9 \text{ (d)}, 113.6 \text{ (s)}, 119.4 \text{ (d)}, 120.2 \text{ (d)}, 121.8 \text{ (d)}, 122.8 \text{ (d)}, 127.9 \text{ (s)}, 129.0 \text{ (d)}, 129.2 \text{ (d)}, 132.8 \text{ (d)}, 133.5 \text{ (s)}, 135.4 \text{ (s)}, 137.7 \text{ (s)}, 170.2 \text{ (s)}.

Anal. Calcd for C18H17BrN2O: 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-1H-indol-3-yl)acetamide (3d)
Method A; stirring for 24 h; eluent: from CH2Cl2 to CH2Cl2–Et2O, 10:1; yield: 78%; mp 115–116 °C (white powder from i-Pr2O).

IR (Nujol): 1670, 3325 cm–1.

1H NMR (CDCl3): \(\delta = 3.86 \text{ (s, 3 H)}, 3.96 \text{ (s, 2 H)}, 7.16 \text{ (s, 1 H)}, 7.20 \text{ (dd, } J = 8.2, 7.3 \text{ Hz, 1 H}), 7.23 \text{ (dd, } J = 4.4, 8.1 \text{ Hz, 1 H}), 7.31 \text{ (dd, } J = 7.3, 7.9 \text{ Hz, 1 H)}, 7.39 \text{ (d, } J = 8.2 \text{ Hz, 1 H)}, 7.62 \text{ (d, } J = 7.9 \text{ Hz, 1 H}), 8.02 \text{ (dd, } J = 1.7, 4.4 \text{ Hz, 1 H)}, 8.09 \text{ (br s, 1 H, absent after deuteration)}, 8.71 \text{ (dd, } J = 1.7, 8.1 \text{ Hz, 1 H)}.

13C NMR (CDCl3): \(\delta = 33.3 \text{ (q)}, 35.0 \text{ (t)}, 106.7 \text{ (s)}, 110.1 \text{ (d)}, 119.2 \text{ (d)}, 120.4 \text{ (d)}, 123.0 \text{ (d)}, 127.7 \text{ (s)}, 128.6 \text{ (s)}, 129.0 \text{ (s)}, 133.3 \text{ (s)}, 137.8 \text{ (s)}, 144.7 \text{ (d)}, 170.9 \text{ (s)}.


N-(3-Bromo-5-methylpyridin-2-yl)-2-(1-methyl-1H-indol-3-yl)acetamide (3e)
Method A; stirring for 4 h; eluent: CH2Cl2–MeOH, 20:1; yield: 71%; mp 159–160 °C (yellow crystals from CH2Cl2–hexane).

IR (Nujol): 1660, 3275 cm–1.

1H NMR (CDCl3): \(\delta = 2.25 \text{ (s, 3 H)}, 3.80 \text{ (s, 3 H)}, 3.98 \text{ (s, 2 H)}, 7.09 \text{ (d, } J = 8.2 \text{ Hz, 1 H)}, 7.17 \text{ (dd, } J = 7.3, 8.2 \text{ Hz, 1 H}), 7.28 \text{ (dd, } J = 7.3, 7.9 \text{ Hz, 1 H}), 7.34 \text{ (d, } J = 8.2 \text{ Hz, 1 H}), 7.65 \text{ (d, } J = 7.9 \text{ Hz, 1 H}), 8.09 \text{ (br s, 1 H, absent after deuteration)}, 8.10 \text{ (br s, 1 H, absent after deuteration)}, 8.15 \text{ (s, 1 H)}.

13C NMR (CDCl3): \(\delta = 17.8 \text{ (q)}, 33.2 \text{ (q)}, 34.6 \text{ (t)}, 107.2 \text{ (s)}, 109.9 \text{ (d)}, 112.7 \text{ (s)}, 119.5 \text{ (d)}, 120.1 \text{ (d)}, 122.7 \text{ (d)}, 128.0 \text{ (s)}, 129.1 \text{ (d)}, 131.9 \text{ (s)}, 137.7 \text{ (s)}, 142.0 \text{ (d)}, 146.5 \text{ (s)}, 147.8 \text{ (d)}, 170.1 \text{ (s)}.

Table 2 Compounds 4 and 5 Obtained from Indole-3-propionic Acid 2

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>Amide 4</th>
<th>Cyclization time (h)</th>
<th>Product 5</th>
<th>Yielda of 5 (%)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>h</td>
<td></td>
<td></td>
<td>24</td>
<td></td>
<td>99</td>
</tr>
<tr>
<td>i</td>
<td></td>
<td></td>
<td>24</td>
<td></td>
<td>99</td>
</tr>
<tr>
<td>j</td>
<td></td>
<td></td>
<td>48</td>
<td></td>
<td>78</td>
</tr>
<tr>
<td>k</td>
<td></td>
<td></td>
<td>72 (2)b</td>
<td></td>
<td>26 (55)c</td>
</tr>
</tbody>
</table>

a Starting from 4.
b MW irradiation time.
c In brackets the yield obtained using MW irradiation.

N-(2-Bromo-4-methylphenyl)-2-(1-methyl-1H-indol-3-yl)acetamide (3c)
Method A; stirring for 24 h; eluent: from CH2Cl2 to CH2Cl2–Et2O, 10:1; yield: 78%; mp 115–116 °C (white powder from i-Pr2O).

N-(2-Bromopyridin-3-yl)-2-(1-methyl-1H-indol-3-yl)acetamide (3d)
Method A; stirring for 4 h; eluent: CH2Cl2–MeOH, 20:1; yield: 71%; mp 159–160 °C (yellow crystals from CH2Cl2–hexane).

N-(3-Bromo-5-methylpyridin-2-yl)-2-(1-methyl-1H-indol-3-yl)acetamide (3e)
Method A; stirring for 4 h; eluent: CH2Cl2–MeOH, 20:1; yield: 71%; mp 159–160 °C (yellow crystals from CH2Cl2–hexane).
Anal. Calcd for C$_{19}$H$_{19}$BrN$_2$O: C, 61.47; H, 5.16; N, 7.55. Found: C, 61.52; H, 4.91; N, 7.34.

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

Method B: eluent: CH$_2$Cl$_2$-Et$_2$O, 1:2; mp 151–152 °C (white powder from CH$_2$Cl$_2$–hexane).

NMR (Nujol): δ = 2.86 (t, 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 (ddd, J = 2.5, 6.7 Hz, 1 H), 7.00 (s, 1 H), 7.01–7.05 (m, 2 H), 7.15 (ddd, J = 7.3, 8.2 Hz, 1 H), 7.28 (dd, J = 7.3, 7.9 Hz, 1 H), 7.34 (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).

13C NMR (CDCl$_3$): δ = 129.1 (d), 130.0 (d), 130.1 (d), 137.6 (s), 137.7 (s), 143.2 (s), 147.2 (s).

Anal. Calcd for C$_{21}$H$_{21}$BrN$_3$O: C, 57.33; H, 4.32; N, 11.73. Found: C, 57.19; H, 5.33; N, 11.98.

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

Method B: eluent: CH$_2$Cl$_2$–MeOH, 20:1; yield: 51%; mp 121–122 °C (yellow crystals from CH$_2$Cl$_2$–hexane).

IR (Nujol): δ = 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).

13C NMR (CDCl$_3$): δ = 21.6 (t), 33.0 (q), 37.9 (t), 44.1 (t), 109.7 (d), 113.7 (s), 119.2 (d), 121.2 (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$_{20}$H$_{17}$IN$_2$O: 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$_2$ 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$_2$Cl$_2$ (2×20 mL). The organic layer was dried (Na$_2$SO$_4$), the solvent evaporated and the residue purified by chromatography (CH$_2$Cl$_2$–Et$_2$O, 5:1) or crystallization (entry h).

N-(2-Iodoophenyl)-N-methyl-2-(1-methyl-1H-indol-3-yl)acetamide (4a)

Pale yellow oil; yield: 76%.

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

1H NMR (CDCl$_3$): δ = 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).

13C NMR (CDCl$_3$): δ = 31.5 (t), 32.9 (q), 36.5 (q), 100.1 (s), 107.7 (s), 109.3 (d), 119.1 (d), 139.3 (d), 121.7 (d), 128.1 (d), 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$_{23}$H$_{20}$IN$_2$O: 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-vinyl-2-(1-methyl-1H-indol-3-yl)acetamide (4b)**

Yield: 72%; mp 77–80 °C (yellow crystals from Et₂O–hexane).

IR (Nujol): 1650 cm⁻¹.

1H NMR (CDCl₃): δ = 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).

13C NMR (CDCl₃): δ = 31.9 (t), 33.1 (q), 36.7 (q), 100.5 (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), 144.5 (s), 171.4 (s).

Anal. Calcd for C₁₈H₁₈BrN₃O: C, 58.08; H, 4.87; N, 11.29. Found: C, 57.81; H, 5.10; N, 11.51.

---

**N-(2-Bromophenyl)-N-vinyl-2-(1-methyl-1H-indol-3-yl)acetamide (4f)**

Yellow oil; yield: 64%.

IR (Nujol): 1644 cm⁻¹.

1H NMR (CDCl₃, mixture 1:1 of rotamers): δ = 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-d₆, mixture 5:3 of rotamers): major rotamer δ = 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 δ = 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-d₆, 110 °C): δ = 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).

13C NMR (CDCl₃, 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).


---

**N-(2-Bromomethyl)-N-vinyl-2-(1-methyl-1H-indol-3-yl)acetamide (4g)**

Yellow oil; yield: 68%.

IR (Nujol): 1640 cm⁻¹.

1H NMR (CDCl₃, mixture 1:1 of rotamers): δ = 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).

13C NMR (CDCl₃, mixture 1:1 of rotamers): δ = 31.0 (t), 31.7 (t), 31.1 (q), 34.1 (q), 34.3 (t), 35.6 (s), 37.1 (q), 48.8 (t), 50.5 (s), 108.3 (s), 109.6 (d), 119.2 (d), 119.3 (d), 119.4 (d), 119.5 (s), 122.1 (d), 124.7 (s), 124.8 (s), 124.7 (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 C₂₁H₁₉BrN₃O: C, 62.35; H, 5.49; N, 7.27. Found: C, 62.09; H, 5.72; N, 7.11.

---

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

Yield: 99%; mp 95 °C (light yellow crystals from Et₂O–hexane).

IR (Nujol): 1650 cm⁻¹.

1H NMR (CDCl₃): δ = 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).

13C NMR (CDCl₃): δ = 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 (d), 129.4 (d), 130.0 (d), 137.3 (s), 140.5 (d), 174.6 (s).

Anal. Calcd for C₂₁H₁₉BrN₃O: 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-vinyl-2-(1-methyl-1H-indol-3-yl)propionamide (4i)**

Yellow oil; yield: 89%.

IR (Nujol): 1660 cm⁻¹.
Yield: 96%; mp 197–198 °C (cream crystals from Et₂O-hexane).

IR (Nujol): 1660 cm⁻¹.

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

Yield: 76%; mp 171–172 °C (light yellow crystals from Et₂O-hexane).

IR (Nujol): 1660 cm⁻¹.

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

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

IR (Nujol): 1635 cm⁻¹.

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

Yield: 99%; mp 150–152 °C (red crystals from CH₂Cl₂–hexane).

IR (Nujol): 1660 cm⁻¹.

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

Yield: 99%; mp 163–164 °C (light yellow crystals from CH₂Cl₂–hexane).

IR (Nujol): 1675 cm⁻¹.

Cyclization of the Amides 4: General Procedure

**Thermal heating.** A solution of 4 (1 mmol), Pd(OAc)₂ (12 mg, 0.05 mmol), Ph₃P (26 mg, 0.1 mmol), AcOK (196 mg, 2 mmol), and TBACI (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 Et₂O. The organic layer was dried (Na₂SO₄) and evaporated under reduced pressure. The residue was chromatographed on a silica gel column (light petroleum ether–Et₂O, 1:1 to give 5f.

**Microwave irradiation.** A solution of the amide 4c, 4f, 4g, or 4k (1 mmol), Pd(OAc)₂ (12 mg, 0.05 mmol), Ph₃P (26 mg, 0.1 mmol), AcOK (196 mg, 2 mmol), and TBACI (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%."
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): 1630 cm⁻¹.

1H NMR (CDCl₃): δ = 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), 7.56 (d, J = 6.4 Hz, 1 H), 7.73 (d, J = 7.6 Hz, 1 H).

13C NMR (CDCl₃): δ = 31.4 (q), 34.8 (t), 39.2 (t), 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).


7,14-Dimethyl-6,7,9,14-tetrahydroindolo[3,2-f][3]benzazoin-8(SH)-one (5g)
Yellow oil; yield: 20%; 51% using MW irradiation.
IR (Nujol): 1650 cm⁻¹.

1H NMR (CDCl₃): δ = 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).

13C NMR (CDCl₃): 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 C₁₉H₁₇ClN₂O: C, 70.26; H, 5.28; N, 8.62. Found: C, 78.78; H, 5.54; N, 8.39.

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

References


