Synthesis of Homocarbonyltopsentine Derivatives

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Received 14 July 2004; revised 2 September 2004

SYNTHESIS 2005, No. 1, pp 0136–0146
Advanced online publication: 02.11.2004
DOI: 10.1055/s-2004-834905; Art ID: T08504SS
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Abstract: Homocarbonyltopsentines I are known to exhibit interesting anti-inflammatory activity in vivo. In order to study the role of the heterocycles in the modulation of their activity, several analogues in which indoles were replaced either by substituted indoles or by bioisosteric heterocycles such as pyrrolo[2,3-b]pyridine, benzol[b]thiophene and pyridine were synthesised. The synthesis is based on selective halogen-metal exchange on triiodoimidazole 1 and subsequent addition to formylated heterocycles.

Key words: indoles, metalation, regioselectivity, addition reactions, palladium

Many naturally occurring bis-indole alkaloids such as topsentsins, dragmacidins, rhopaladins and hamacanthins, extracted from marine organisms and described to date, exhibit pharmacological properties.1 Among them, a closely related structure called homocarbonyltopsentine I was reported in the literature, which showed potent anti-inflammatory activity in vivo.2

In a previous paper, we have described a general approach to prepare this bis-indole skeleton via selective halogen–metal exchange reactions on triiodoimidazole followed by addition to formylated indoles.3 In our ongoing research work, we investigated the synthesis of compounds displaying the general structure II, in order to determine the importance of the nature of the substituent on the indole moiety and the nature of the heterocycle linked to the position 4 of the imidazole nucleus through a carbonyl function (Figure 1).

By this synthetic methodology, which allowed us to switch easily from one heterocycle to another, a wide range of homocarbonyltopsentine derivatives or analogues can be prepared in sufficient amount for biological assays (Scheme 1). Thus, selective halogen–metal exchange reactions were performed on triiodoimidazole 1 (EOM = ethoxymethyl) in order to prepare highly nucleophilic species which can then react with conveniently substituted and protected formylated heterocycles (Het-CHO and Het'-CHO). According to literature procedures, 3-formylindoles 2a,b and 2c3 were prepared in our laboratory (Scheme 1). Other aldehydes such as 3-formylpyridine (2d) and 3-formylbenzothiophene (2e) are commercially available.

The first step of the synthesis was realised by reaction of n-BuLi with triiodoimidazole 1 which produced selectively the carbanion at C-2.6 Addition of formylated heterocycles 2 to the carbanion intermediate afforded alcohols 3 in good yields (Scheme 2). Only in the case of 1-tert-butyloxycarbonyl-3-formylpyrrolo[2,3-b]pyridine, low reaction yield was observed (24%, not described). Alcohols 3 were then oxidised with MnO2 to produce the corresponding ketones 4 (Table 1). After the first part of the synthesis was achieved, the derivatives 4a–c were selected to reach the final compounds II.

Using the same conditions as for the first substitution, the alcohols 5 were obtained in good yields from 4a–c by selective iodine–lithium exchange at C-4 and reaction with aldehydes 2e–e (Scheme 3, Table 2).6 The alcohols were subsequently oxidised to produce the diketones 6 in fair yields (Table 2).

The last iodine on compounds 6 was then removed by hydrogenolysis in the presence of palladium on charcoal as
catalyst and potassium carbonate as proton scavenger (Scheme 3). Under these conditions, the benzyl group of \(6a\) was not affected. For \(6d\), we isolated \(7d\) in 55% yield along with the by-product \(7f\) (20%) in which the pyridine nucleus was reduced into 1,2,3,4-tetrahydropyridine (Scheme 3). Except this example, compounds 7 were isolated in 80–89% yields.

Final compounds 9 were obtained by successive deprotection of the tert-butyloxy carbonyl and the ethoxymethyl groups (Scheme 4). Thus, derivatives 7a–e were, first treated with aqueous 1 N NaOH in 1,4-dioxane at 70 °C for 30 minutes to afford compounds 8a–e in good yields (Table 3). The latter, when heated in the presence of aqueous 1 N HCl in 1,4-dioxane for 30 minutes gave 9a–e.

### Table 2 Yields of Compounds 5–7

<table>
<thead>
<tr>
<th>Het’</th>
<th>Y</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2c</td>
<td>OMe</td>
<td>61</td>
</tr>
<tr>
<td>2c</td>
<td>OMe</td>
<td>6b 99</td>
</tr>
<tr>
<td>2c</td>
<td>H</td>
<td>6c 84</td>
</tr>
<tr>
<td>2d</td>
<td>H</td>
<td>5d 70</td>
</tr>
<tr>
<td>2e</td>
<td>H</td>
<td>5e 65</td>
</tr>
</tbody>
</table>

Close derivatives of 9d have been reported as potent anticancer agents.\(^7\) Synthesis of homocarbonyltopsentine \(1a\) was finally achieved by hydrogenolysis (\(\text{HCO}_2\text{NH}_2\), 10% Pd/C, EtOH, reflux, 1 h) of the benzyl protecting group of \(9a\) in 91% yield.
Iodo derivative 10 was also prepared from 6c in 56% yield (Scheme 5). Taking advantage of iodine on the imidazole ring of compounds 6, introduction of a third substituent on the imidazole by palladium-mediated cross-coupling reaction can be done giving access to a wide variety of derivatives. From our part, only a Suzuki reaction was explored in our laboratory (Scheme 5). According to the classical method, commercially available boronic acids (phenylboronic acid, 2-thienylboronic acid, 2-furylboronic acid and 1-tert-butylxycarbonyl-2-pyrrolylboronic acid) were coupled to derivative 6c in the presence of tetrais(triphenylphosphine)palladium to afford 11a–d in good yields (Table 4). As a final example, two successive deprotection reactions were performed on 11a to afford 12 in 83% yield (Scheme 5). Surprisingly, we observed a complete degradation of 11d when submitted to the deprotection reactions.

In summary, we have prepared homocarbonyltopsentine Ia and several analogues or derivatives. These compounds are currently evaluated for anti-inflammatory activity and the results will be reported in due course.

Melting points were obtained on a Büchi capillary instrument and are uncorrected. IR spectra were recorded on a Perkin-Elmer 681 IR spectrophotometer. 1H and 13C NMR spectra were recorded on a Bruker Avance 300 spectrometer. Chemical shifts are expressed in parts per million (ppm) relative to TMS. Mass spectra were recorded on a Perkin-Elmer SCIEX API spectrometer. Elemental analyses were performed on a Thermoquest Flash 1112 series EA analyser. TLC was conducted on precoated silica gel plates (Merck 60F254).

Table 3 Yields of Compounds 8 and 9

<table>
<thead>
<tr>
<th></th>
<th>Yield (%)</th>
<th></th>
<th>Yield (%)</th>
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<tbody>
<tr>
<td>8a</td>
<td>85</td>
<td>9a</td>
<td>83</td>
</tr>
<tr>
<td>8b</td>
<td>89</td>
<td>9b</td>
<td>85</td>
</tr>
<tr>
<td>8c</td>
<td>89</td>
<td>9c</td>
<td>90</td>
</tr>
<tr>
<td>8d</td>
<td>97</td>
<td>9d</td>
<td>96</td>
</tr>
<tr>
<td>8e</td>
<td>80</td>
<td>9e</td>
<td>88</td>
</tr>
</tbody>
</table>

Table 4 Yields of Compounds 11

<table>
<thead>
<tr>
<th>Ar</th>
<th>11</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>11a</td>
<td>92</td>
</tr>
<tr>
<td>2-thienyl</td>
<td>11b</td>
<td>95</td>
</tr>
<tr>
<td>2-furyl</td>
<td>11c</td>
<td>96</td>
</tr>
<tr>
<td>2-(1-Boc)pyrrolyl</td>
<td>11d</td>
<td>89</td>
</tr>
</tbody>
</table>
and the spots were visualised under UV light. Flash chromatography was carried out on column using flash silica gel 60 Merck (40–63 µm) using the indicated solvents [petroleum ether (PE): bp 40–60 °C]. All reactions requiring anhydrous conditions were conducted in flame-dried apparatus. Boronic acids were purchased from Lancaster or Sigma-Aldrich.

tert-Butyl 6-Benzoxyl-3-formyl-1H-indole-1-carboxylate (2a); Typical Procedure
A solution of 6-benzoxylindole-3-carboxaldehyde \((1.1 \text{ mmol})\) in anhyd THF (10 mL) was added to a solution of \(n\)-BuLi in hexanes (321 mg, 99%; mp 111–112 °C (pentane)). The organic phases were combined, dried (MgSO\(_4\)), and evaporated in vacuo. The crude residue was purified by column chromatography to afford derivative 2a (321 mg, 99%); mp 118–119 °C (pentane).

IR (KBr): 3140, 2800, 2720, 1740, 1670 cm\(^{-1}\).

Found: C, 65.21; H, 6.12; N, 4.99.

\(1H\) NMR (CDCl\(_3\)):
- 5.13 (s, 2 H, CH\(_2\)O), 5.32 (AB system, 2 H, CH\(_2\)), 7.26 (d, 1 H, J = 8.7 Hz, H-2), 7.33–7.48 (m, 5 H, C\(_6\)H\(_5\)), 7.59 (s, 1 H, H-1), 7.83 (br s, 1 H, H-7).
- 3.82 (s, 9 H, 3 CH\(_3\)), 3.40–3.50 (m, 2 H, CH\(_2\)), 3.85 (s, 3 H, OCH\(_3\)), 3.86 (br s, 1 H, OH), 7.18 (t, 1 H, J = 7.0 Hz, CH\(_2\)), 3.24 (s, 3 H, OCH\(_3\)), 1.66 (t, 3 H, J = 7.0 Hz, CH\(_3\)), 3.24 (s, 3 H, OCH\(_3\)), 1.66 (t, 3 H, J = 7.0 Hz, CH\(_3\)), 3.24 (s, 3 H, OCH\(_3\)), 1.66 (t, 3 H, J = 7.0 Hz, CH\(_3\)).
1H NMR (300 MHz, CDCl3): δ = 1.18 (t, 3 H, J = 7.1 Hz, CH3), 1.70 (s, 9 H, 3 CH3), 3.60 (q, 2 H, J = 7.1 Hz, CH2), 5.15 (s, 2 H, CH2O), 6.00 (s, 2 H, CH2N), 7.08 (dd, 1 H, J = 2.2, 8.8 Hz, H-5), 7.30–7.49 (m, 5 H, C6H5), 7.87 (d, 1 H, J = 2.2 Hz, H-7), 8.32 (d, 1 H, J = 8.8 Hz, H-4), 9.01 (s, 1 H, H-2).

13C NMR (75 MHz, CDCl3): δ = 150.0 (CH), 28.1 (3 CH3), 64.6 (CH3), 70.3 (CH3), 87.7 (CH=N), 91.5 (C), 92.2 (C), 97.7 (C), 100.3 (CH), 114.1 (CH), 117.4 (C), 122.1 (C), 123.1 (C), 127.5 (2 CH), 127.9 (CH2), 128.5 (2 CH), 136.1 (C), 136.3 (CH), 136.9 (C), 148.2 (C), 149.8 (C), 157.5 (C=O). 176.3 (C=O).

MS (ESI): m/z = 728 (M+H+).


Chromatography eluent: PE-CH2Cl2 (5:1); yield: 91%; foam.

Oxidation of Alcohols to Ketones 4; General Procedure
A solution of 3 (0.65 mmol) in CH2Cl2 (18 mL) was stirred at r.t. for 4 h. MnO2 was removed by filtration on Celite and the filtrate was evaporated in vacuo. Product 4 was isolated either by crystallisation or by column chromatography.

tert-Butyl-3-(1-Ethoxymethyl-4,5-diido-1H-imidazol-2-yl)-6-benzyloxy-1H-indole-1-carboxylate (4a)
Chromatography eluent: PE-CH2Cl2 (1:2); yield: 91%; solid.

IR (film): 1749, 1620, 1530 cm–1.

1H NMR (300 MHz, CDCl3): δ = 1.18 (t, 3 H, J = 7.1 Hz, CH3), 1.70 (s, 9 H, 3 CH3), 3.60 (q, 2 H, J = 7.1 Hz, CH2), 5.15 (s, 2 H, CH2O), 6.00 (s, 2 H, CH2N), 7.08 (dd, 1 H, J = 2.2, 8.8 Hz, H-5), 7.30–7.49 (m, 5 H, C6H5), 7.87 (d, 1 H, J = 2.2 Hz, H-7), 8.32 (d, 1 H, J = 8.8 Hz, H-4), 9.01 (s, 1 H, H-2).

13C NMR (75 MHz, CDCl3): δ = 150.0 (CH), 28.1 (3 CH3), 64.6 (CH3), 70.3 (CH3), 87.7 (CH=N), 91.5 (C), 92.2 (C), 97.7 (C), 100.3 (CH), 114.1 (CH), 117.4 (C), 122.1 (C), 123.1 (C), 127.5 (2 CH), 127.9 (CH2), 128.5 (2 CH), 136.1 (C), 136.3 (CH), 136.9 (C), 148.2 (C), 149.8 (C), 157.5 (C=O). 176.3 (C=O).

MS (ESI): m/z = 728 (M+H+).


Chromatography eluent: PE-CH2Cl2 (1:2); yield: 91%; solid.

At –78 °C and under argon, a solution of 2.3 M of n-BuLi in hexanes (0.64 mmol) was added dropwise to a solution of 4 (0.64 mmol) in anhyd THF (10 mL). After stirring for 5 min, compound 2 (0.70 mmol) in anhyd THF (5 mL) was added. The final solution...
was stirred at -78 °C for 45 min. The reaction was hydrolysed by addition of sat. aq NH₄Cl solution and the mixture was extracted with CH₂Cl₂ (2 × 10 mL). The combined organic phases were dried (MgSO₄) and evaporated in vacuo. The crude residue was purified by column chromatography to afford derivative 5.

tert-Butyl 3-{5-[1-tert-Butoxycarbonyl-1H-indol-3-yl]hydroyxymethyl}-1-ethoxymethyl-4-iodo-1H-imidazole-2-carbonyl-6-benzyloxy-1H-indole-1-carboxylate (5a)

Chromatography eluent: PE–EtOAc (85:15); yield: 61%; foam.

IR (KBr): 3440, 1735, 1630 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 1.20 (t, 3H, J = 7.0 Hz, CH₃), 1.75 (s, 9 H, 3 CH₃), 1.79 (s, 9 H, 3 CH₃), 3.65 (br q, 2 H, J = 7.0 Hz, CH₂), 4.73 (d, 1 H, J = 9.4 Hz, OH), 5.17 (s, 2 H, CH₂O), 5.42 (d, 1 H, J = 10.5 Hz, CH₃N), 6.33 (d, 1 H, J = 9.4 Hz, CHOH), 6.38 (d, 1 H, J = 10.5 Hz, CH₃N), 7.10 (dd, 1H, Jₕ₃ = 2.2, 8.8 Hz, 7.18–7.52 (m, 8 H, C₆H₅ + H₃, 7.83 (s, 1 H, H₃, 7.91 (d, 1 H, H₃, J = 2.2 Hz), 8.22 (d, 1 H, Jₕ₃ = 8.8 Hz), 8.33 (d, 1 H, Jₕ₃ = 8.8 Hz, 9.20 (s, 1 H, H₃, 9.20 (s, 1 H, H₃), 9.20 (s, 1 H, H₃), 9.20 (s, 1 H, H₃).

13C NMR (75 MHz, CDCl₃): δ = 14.7 (CH₃), 28.0 (3 CH₃), 28.2 (3 CH₃), 63.9 (CH), 64.9 (CH), 70.3 (CH₂), 73.7 (CH₃N), 84.0 (C), 85.1 (C), 88.2 (C), 100.3 (CH₃), 114.0 (CH₃), 115.4 (CH), 118.0 (CH), 119.7 (CH₃), 120.4 (C), 121.2 (C), 122.1 (CH), 123.0 (CH), 123.4 (CH₂), 124.8 (CH), 127.5 (2 CH₃), 127.6 (C), 127.9 (C), 128.5 (C), 136.0 (C), 136.2 (C), 136.6 (CH), 138.2 (C), 146.2 (C), 148.9 (C), 149.5 (C), 157.5 (C=O), 178.0 (C=O).

MS (ESI): m/z = 847 [(M + H)⁺].


3-{5-[1-tet-Butoxycarbonyl-1H-indol-3-yl]hydroyxymethyl}-1-ethoxymethyl-4-iodo-1H-imidazole-2-carbonyl-pyridine (5d)

Chromatography eluent: PE–EtOAc (6:4); yield: 70%; solid; mp 174–176 °C (dec.) (Et₂O).

IR (KBr): 3360, 1740, 1630 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 1.15 (t, 3H, J = 7.0 Hz, CH₃), 1.73 (s, 9 H, 3 CH₃), 3.62 (q, 2 H, J = 7.0 Hz, CH₂), 4.51 (d, 1 H, J = 9.4 Hz, OH), 5.07 (d, 1 H, J = 10.9 Hz, CH₃N), 6.20 (d, 1 H, J = 9.4 Hz, CHOH), 6.32 (d, 1 H, J = 10.9 Hz, CH₃), 7.32–7.41 (m, 3 H, Jₕ₃ = 10.7 Hz), 7.75 (bd, 1 H, Jₕ₃ = 7.9 Hz), 8.18–8.21 (m, 1 H, Jₕ₃ = 8.42 (m, 1 H, Jₕ₃ = 8.59 (brd, 1 H, Jₕ₃ = 4.1 Hz), 8.65 (s, 1 H, Jₕ₃ = 9.19 (s, 1 H, Jₕ₃ = 118.1 (C), 119.8 (CH₃), 119.8 (CH₃), 123.0 (CH), 123.1 (CH), 123.1 (CH), 123.4 (CH), 124.9 (CH₂), 127.5 (C), 127.5 (C), 136.0 (C), 136.0 (C), 136.3 (C), 136.6 (CH), 138.3 (C), 146.3 (C), 149.1 (C), 149.6 (C=O), 158.4 (C=O), 178.2 (C=O).

MS (ESI): m/z = 603 [(M + H)⁺].


3-{5-[1-tet-Butoxycarbonyl-1H-indol-3-yl]hydroyxymethyl}-1-ethoxymethyl-4-iodo-1H-imidazole-2-carbonyl-benz[α]hiophene (5e)

Chromatography eluent: PE–EtOAc (9:1); yield: 65%; solid; mp 162–164 °C (dec.) (Et₂O).

IR (KBr): 3375, 1740, 1630 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 1.19 (t, 3H, J = 7.0 Hz, CH₃), 1.75 (s, 9 H, 3 CH₃), 3.57–3.66 (m, 2 H, CH₂), 4.62 (d, 1 H, J = 10.2 Hz, OH), 5.12 (d, 1 H, J = 10.7 Hz, CH₃N), 6.31 (d, 1 H, J = 10.2 Hz, CHOH), 6.29–6.35 (m, 1 H, J = 10.7 Hz, CH₃N), 7.28–7.42 (m, 4 H, Jₕ₃ = 6.8 Hz), 7.52 (dd, 1 H, Jₕ₃ = 2.0, 6.8 Hz), 7.65 (d, 1 H, Jₕ₃ = 1.5 Hz), 7.87 (dd, 1 H, Jₕ₃ = 2.0, 6.8 Hz), 8.18 (dd, 1 H, Jₕ₃ = 2.0, 6.8 Hz), 8.38 (d, 1 H, Jₕ₃ = 1.8, 6.8 Hz), 9.23 (s, 1 H, Jₕ₃ = 115.1 (C), 115.5 (CH), 118.1 (C), 122.5 (CH), 122.6 (CH₂), 123.2 (CH), 123.8 (CH), 125.6 (CH), 126.7 (C), 128.4 (C), 135.3 (C), 136.1 (C), 137.8 (CH), 138.5 (C), 146.4 (C), 149.1 (C=O), 149.7 (C=O), 178.3 (C=O).

MS (ESI): m/z = 658 [(M + H)⁺].


tert-Butyl 3-{5-[1-tet-Butoxycarbonyl-1H-indol-3-yl]hydroyxymethyl}-1-ethoxymethyl-4-iodo-1H-imidazole-2-carbonyl-6-benzyloxy-1H-indole-1-carboxylate (6a)

According to the procedure described for 4, compound 6a was prepared from 5a in 84% yield as a foam (chromatography eluent: PE–EtOAc, 85:15).
**tert-Butyl 3-[5-(1-Demethyl-1H-indole-3-carbonyl)-1-ethoxymethyl-4-iodo-1H-imidazol-2-carbonyl]indole-1-carboxylate (6b)**

According to the procedure described for 4, compound 6b was prepared from 5b in 99% yield as a solid; mp 157–158 °C (EtOAc–pentane).

IR (KBr): 1740, 1630, 1530 cm\(^{-1}\).

**tert-Butyl 3-[5-(1-Demethyl-1H-indole-3-carbonyl)-1-ethoxymethyl-4-iodo-1H-imidazol-2-carbonyl]indole-1-carboxylate (6c)**

According to the procedure described for 4, compound 6c was prepared from 5c in 84% yield as a solid; mp 162–164 °C (dec.) (EtOH).

IR (KBr): 1750, 1640, 1530 cm\(^{-1}\).

**tert-Butyl 3-[5-(1-Demethyl-1H-indole-3-carbonyl)-1-ethoxymethyl-4-iodo-1H-imidazol-2-carbonyl]indole-1-carboxylate (6a)**

According to the procedure described for 4, compound 6a was prepared from 5a in 84% yield as a solid; mp 157–158 °C (EtOAc–pentane).

IR (KBr): 1740, 1630, 1530 cm\(^{-1}\).

**tert-Butyl 3-[5-(1-Demethyl-1H-indole-3-carbonyl)-1-ethoxymethyl-4-iodo-1H-imidazol-2-carbonyl]indole-1-carboxylate (6e)**

According to the procedure described for 4, compound 6e was prepared from 5e in 65% yield as a solid (chromatography eluent: PE–EtOAc–EtOH; 9:1) mp 169–171 °C (dec.) (EtOAc).

IR (KBr): 1740, 1630 cm\(^{-1}\).

**tert-Butyl 3-[5-(1-Demethyl-1H-indole-3-carbonyl)-1-ethoxymethyl-4-iodo-1H-imidazol-2-carbonyl]indole-1-carboxylate (6d)**

According to the procedure described for 4, compound 6d was prepared from 5d in 82% yield as a solid; mp 168–169 °C (EtOH).

IR (KBr): 1745, 1657, 1628 cm\(^{-1}\).

**tert-Butyl 3-[1-Ethoxymethyl-4-iodo-5-(pyridine-3-carbonyl)-1H-imidazole-2-carbonyl]indole-1-carboxylate (6d)**

According to the procedure described for 4, compound 6d was prepared from 5d in 82% yield as a solid; mp 168–169 °C (EtOH).

IR (KBr): 1745, 1657, 1628 cm\(^{-1}\).

**tert-Butyl 3-[5-(Benzyl[2H]quinoline-3-carbonyl)-1-ethoxymethyl-4-iodo-1H-imidazol-2-carbonyl]indole-1-carboxylate (6e)**

According to the procedure described for 4, compound 6e was prepared from 5e in 65% yield as a solid (chromatography eluent: PE–EtOAc–EtOH; 9:1) mp 169–171 °C (dec.) (EtOAc).

IR (KBr): 1740, 1630 cm\(^{-1}\).

**tert-Butyl 3-[5-(1-Demethyl-1H-indole-3-carbonyl)-1-ethoxymethyl-4-iodo-1H-imidazol-2-carbonyl]indole-1-carboxylate (6c)**

According to the procedure described for 4, compound 6c was prepared from 5c in 84% yield as a solid; mp 162–164 °C (dec.) (EtOH).

IR (KBr): 1750, 1640, 1530 cm\(^{-1}\).

**Hydrogenolysis of Iodimidazoles 6; General Procedure**

A suspension of 6 (0.20 mmol), K₂CO₃ (1 mmol) and 10% Pd/C (15 mg) in CH₂Cl₂–MeOH (12 mL, 1:1) was stirred in a stainless steel reactor under 15 bar of H₂ overnight at rt. The catalyst was removed by filtration and the filtrate was evaporated in vacuo. The residue was purified by column chromatography to afford derivative 7.

**tert-Butyl 3-[5-(1-Demethyl-1H-indole-3-carbonyl)-1-ethoxymethyl-4-iodo-1H-imidazol-2-carbonyl]indole-1-carboxylate (7a)**

Chromatography eluent: PE–EtOAc (85:15); yield: 89%; mp 154–156 °C (dec.) (EtOAc–pentane).

IR (KBr): 1740, 1640 cm\(^{-1}\).

**tert-Butyl 3-[1-Ethoxymethyl-4-iodo-5-(pyridine-3-carbonyl)-1H-imidazole-2-carbonyl]indole-1-carboxylate (6d)**

According to the procedure described for 4, compound 6d was prepared from 5d in 82% yield as a solid; mp 168–169 °C (EtOH).

IR (KBr): 1745, 1657, 1628 cm\(^{-1}\).

**tert-Butyl 3-[5-(Benzyl[2H]quinoline-3-carbonyl)-1-ethoxymethyl-4-iodo-1H-imidazol-2-carbonyl]indole-1-carboxylate (6e)**

According to the procedure described for 4, compound 6e was prepared from 5e in 65% yield as a solid (chromatography eluent: PE–EtOAc–EtOH; 9:1) mp 169–171 °C (dec.) (EtOAc).

IR (KBr): 1740, 1630 cm\(^{-1}\).

**tert-Butyl 3-[5-(1-Demethyl-1H-indole-3-carbonyl)-1-ethoxymethyl-4-iodo-1H-imidazol-2-carbonyl]indole-1-carboxylate (6c)**

According to the procedure described for 4, compound 6c was prepared from 5c in 84% yield as a solid; mp 162–164 °C (dec.) (EtOH).

IR (KBr): 1750, 1640, 1530 cm\(^{-1}\).

**tert-Butyl 3-[5-(1-Demethyl-1H-indole-3-carbonyl)-1-ethoxymethyl-4-iodo-1H-imidazol-2-carbonyl]indole-1-carboxylate (6a)**

According to the procedure described for 4, compound 6a was prepared from 5a in 84% yield as a solid; mp 157–158 °C (EtOAc–pentane).

IR (KBr): 1740, 1640, 1530 cm\(^{-1}\).

**Hydrogenolysis of Iodimidazoles 6; General Procedure**

A suspension of 6 (0.20 mmol), K₂CO₃ (1 mmol) and 10% Pd/C (15 mg) in CH₂Cl₂–MeOH (12 mL, 1:1) was stirred in a stainless steel reactor under 15 bar of H₂ overnight at rt. The catalyst was removed by filtration and the filtrate was evaporated in vacuo. The residue was purified by column chromatography to afford derivative 7.

**tert-Butyl 3-[5-(1-Demethyl-1H-indole-3-carbonyl)-1-ethoxymethyl-4-iodo-1H-imidazol-2-carbonyl]indole-1-carboxylate (7a)**

Chromatography eluent: PE–EtOAc (85:15); yield: 89%; mp 154–156 °C (dec.) (EtOAc–pentane).

IR (KBr): 1740, 1640 cm\(^{-1}\).

**tert-Butyl 3-[5-(1-Demethyl-1H-indole-3-carbonyl)-1-ethoxymethyl-4-iodo-1H-imidazol-2-carbonyl]indole-1-carboxylate (6c)**

According to the procedure described for 4, compound 6c was prepared from 5c in 85% yield as a solid; mp 162–164 °C (dec.) (EtOH).

IR (KBr): 1750, 1640, 1530 cm\(^{-1}\).
**tert-Butyl 3-[[1-(tert-Butyloxy carbonyl)-1H-indole-3-carbonyl]-1-ethyl oxymethyl-5-(1H-imidazole-2-carbonyl)-6-methoxy-1H-indole-1-carboxylate (7b)](S)**

Chromatography eluent: PE–EtOAc (9:1); yield: 80%; solid; mp 162–163 °C (dec.) (EtOAc–pentane).

**tert-Butyl 3-[[1-Ethoxymethyl-5-(1,4,5,6-tetrahydropyridine-3-carbonyl)-1H-imidazol-2-ylidazole-2-carbonyl]indole-1-carboxylate (7e)](S)**

Chromatography eluent: PE–EtOAc (85:15); yield: 85%; solid; mp 173–175 °C (dec.) (EtOAc–pentane).

**tert-Butyl 3-[[1-Benzyl[b]thiophene-3-carbonyl]-1-ethyl oxymethyl-1H-imidazol-2-ylidazole-2-carbonyl]indole-1-carboxylate (7f)**

Chromatography eluent: PE–EtOAc (9:1); yield: 80%; solid; mp 213–215 °C (dec.) (EtOAc–pentane).

**Boc Deprotection of 7; General Procedure**

A solution of 7, 5% H2SO4 (0.17 mmol), and aq 1 N NaOH (2 mL) in 1,4-dioxane (4 mL) was stirred at 70 °C for 30 min. After cooling, the solution was neutralised by aq 1 N HCl (pH 6–7) and extracted with CH2Cl2 (2 × 5 mL). The combined organic phases were dried (MgSO4) and evaporated in vacuo. Product 8 was isolated either by crystallisation or by column chromatography.

**Synthesis of Homocarbonyltopsente Derivatives (1H)**

Yield: 85%; solid; mp > 210 °C (dec.) (EtOAc–pentane).
H, C₂H₄ + H₃N⁺), 7.44 (s, 1 H₂N⁺), 7.67 (s, 1 H₂N⁺), 8.42–8.45 (m, 3 H₃N⁺), 8.97 (s, 1 H, NH), 9.00 (s, 1 H NH).

1C NMR (75 MHz, DMSO-d₆): δ = 14.8 (CH₃), 63.6 (CH₃), 69.5 (CH₃O), 73.7 (CH₃N), 97.1 (CH₃), 112.4 (CH), 112.6 (CH), 115.2 (C), 116.5 (C), 120.5 (C), 121.4 (CH), 122.1 (CH), 122.2 (CH), 123.4 (CH), 126.0 (CH), 127.6 (2 CH), 127.7 (CH), 128.4 (2 CH), 133.2 (C), 134.5 (CH), 135.8 (CH), 136.9 (C), 137.2 (C), 137.3 (C), 137.7 (CH), 146.8 (C), 155.7 (C), 178.3 (C=O), 179.3 (C=O).

MS (ESI): m/z = 519 (M + H⁺).


[1-Ethoxymethyl-5-(1H-indole-3-carbonyl)-1H-imidazol-2-yl][1H-indol-3-yl]methanone (8b)

Yield: 89%; solid; mp 169–171 °C (dec.) (EtOAc).

IR (KBr): ν = 3340, 1615, 1510 cm⁻¹.

Yield: 89%; solid; mp >210 °C (EtOH).

1H NMR (300 MHz, CDCl₃): δ = 1.11 (t, 3 H, J = 7.0 Hz, CH₃), 3.63 (q, 2 H, J = 7.0 Hz, CH₂), 6.37 (s, 2 H, CH₂N), 7.32–7.56 (m, 5 H₃N⁺), 7.66 (s, 1 H₂N⁺), 7.94 (br d, 1 H₃N⁺, J = 7.4 Hz), 8.26 (s, 1 H₂N⁺), 8.57–8.61 (m, 2 H₂N⁺), 8.73 (s, 1 H NH), 8.78 (d, 1 H₂N⁺, J = 3.0 Hz).

13C NMR (75 MHz, DMSO-d₆): δ = 15.1 (CH₃), 65.1 (CH₄), 74.7 (CH₃N), 111.8 (CH), 116.7 (C), 122.6 (2 CH), 123.7 (CH), 124.1 (CH), 125.0 (CH), 126.0 (CH), 126.1 (CH), 126.6 (C), 133.0 (C), 133.8 (C), 134.6 (C), 134.7 (C), 137.4 (C), 137.6 (CH), 146.9 (C), 156.7 (C), 178.3 (C=O), 179.4 (C=O).

MS (ESI): m/z = 443 (M + H⁺).


[1-Ethoxymethyl-5-(1H-indole-3-carbonyl)-1H-imidazol-2-yl][1H-indol-3-yl]methanone (8c)

Yield: 89%; solid; mp 209–210 °C (EtOAc).

IR (KBr): 3375, 1630 cm⁻¹.

Chromatography eluent: PE–EtOAc (6:4); yield: 80%; foam.

1H NMR (300 MHz, CDCl₃): δ = 0.91 (t, 3 H, J = 7.0 Hz, CH₃), 3.40 (q, 2 H, J = 7.0 Hz, CH₂), 6.33 (s, 2 H, OCH₃), 6.07 (2 H, CH₂), 7.04 (d, 1 Harom, J = 7.0 Hz), 3.82 (s, 3 H, OCH₃), 6.15 (s, 2 H, CH₂N), 7.28–7.34 (m, 5 H₃N⁺), 8.01 (d, 1 Himid, J = 8.7 Hz), 8.25–8.29 (m, 2 H₂N⁺), 8.62 (s, 1 H₂N⁺), 12.05 (br s, 2 H, NH₂), 12.22 (br s, 2 H, NH₂).

13C NMR (75 MHz, CDCl₃): δ = 14.9 (CH₃), 55.3 (OCH₃), 63.7 (CH₃), 73.7 (CH₂N), 95.7 (CH), 112.0 (CH), 112.4 (CH), 115.3 (C), 116.5 (C), 120.3 (C), 121.4 (CH), 122.2 (2 CH), 123.5 (CH), 126.0 (CH), 133.2 (C), 134.5 (CH), 135.9 (CH), 136.9 (C), 137.4 (C), 137.6 (CH), 146.9 (C), 156.7 (C), 178.3 (C=O), 179.4 (C=O).

MS (ESI): m/z = 413 (M + H⁺).


[1-Ethoxymethyl-5-(1H-imidazol-2-yl)[1H-indol-3-yl]methanone (9a)

Yield: 83%; solid; mp >210 °C (EtOH).

IR (KBr): ν = 3375, 1630 cm⁻¹.

Chromatography eluent: PE–EtOAc (6:4); yield: 80%; foam.

1H NMR (300 MHz, CDCl₃): δ = 0.91 (t, 3 H, J = 7.0 Hz, CH₃), 3.40 (q, 2 H, J = 7.0 Hz, CH₂), 6.33 (s, 2 H, CH₂N), 7.04–7.32 (m, 2 H₂N⁺), 7.04–7.32 (m, 2 H₂N⁺), 7.04–7.32 (m, 2 H₂N⁺), 7.04–7.32 (m, 2 H₂N⁺), 7.04–7.32 (m, 2 H₂N⁺), 7.04–7.32 (m, 2 H₂N⁺).
121.8 (CH), 122.2 (CH), 122.9 (CH), 124.3 (CH), 126.7 (C), 135.7 (CH), 136.2 (CH), 137.3 (C), 143.3 (C), 145.5 (C), 156.6 (2 C), 176.4 (C=O), 181.6 (C=O).

MS (ESI): mz = 385 (M + H+).


Yield: 90%; solid; mp > 210 °C (purified by washing with hot MeOH).

IR (KBr): 3198, 1609, 1590, 1512 cm⁻¹.

1H NMR (300 MHz, DMSO-d₆): δ = 7.22–7.30 (m, 4 H arom), 7.53–7.59 (m, 2 H arom), 8.02 (s, 1 H imid), 8.37–8.40 (m, 2 H arom), 8.97 (s, 1 H arom), 9.14 (s, 1 H arom), 12.00 (s, 1 H, NH), 12.21 (s, 1 H, NH), 13.70 (s, 1 H, NH).

13C NMR (75 MHz, DMSO-d₆): δ = 112.2 (CH), 112.5 (CH), 113.4 (C), 114.9 (C), 121.6 (CH), 121.7 (2 CH), 122.3 (CH), 122.9 (CH), 123.2 (CH), 124.3 (CH), 126.5 (C), 126.7 (C), 135.7 (CH), 136.2 (C), 136.3 (C), 137.1 (CH), 143.3 (C), 145.5 (C), 176.5 (C=O), 181.6 (C=O).

MS (ESI): mz = 355 (M + H+).


Yield: 96%; solid; mp > 210 °C (dioxane-H₂O).

IR (KBr): 3280, 1610 cm⁻¹.

1H NMR (300 MHz, DMSO-d₆): δ = 7.24–7.26 (m, 2 H arom), 7.51–7.53 (m, 3 H arom), 7.57–7.61 (m, 4 H arom), 7.89 (br s, 1 H arom), 8.10 (s, 1 H imid), 8.42–8.46 (m, 1 H imid), 8.55 (d, 1 H imid), J = 7.5 Hz, 8.79 (br s, 1 H arom), 9.17 (s, 1 H pyr), 9.44 (br s, 1 H pyr), 12.13 (s, 1 H, NH), 14.10 (s, 1 H, NH).

13C NMR (75 MHz, DMSO-d₆): δ = 112.4 (CH), 113.6 (C), 121.7 (CH), 122.0 (CH), 123.0 (CH), 123.4 (CH + C), 126.7 (C), 134.2 (C), 136.2 (C), 137.1 (CH), 137.4 (CH), 149.1 (C), 150.6 (CH), 152.0 (CH), 185.6 (2 C=O).

MS (EI): mz = 316 (M⁺);


Found: C, 68.10; H, 3.90; N, 17.66.

[5-(1H-Indole-3-carbonyl)-1H-imidazol-2-yl][1H-indol-3-yl]methanone (9c)

Chromatography eluent: EtOAc; yield: 90%; solid; mp > 210 °C (purified by washing with hot EtOAc).

IR (KBr): 3380, 3200, 1592, 1572, 1525 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 6.78 (dd, 1 H arom, J = 1.7, 8.6 Hz), 6.92 (br s, 1 H arom), 7.20–7.28 (m, 2 H arom), 7.53–7.56 (m, 1 H arom), 8.01 (s, 1 H arom), 8.15 (d, 1 H arom, J = 8.6 Hz), 8.38–8.41 (m, 1 H arom), 8.96 (br s, 2 H arom), 9.33 (s, 1 H, OH), 11.84 (s, 1 H, NH), 11.99 (s, 1 H, NH), 13.63 (s, 1 H, NH).

13C NMR (75 MHz, CDCl₃): δ = 96.7 (CH), 112.2 (CH), 112.3 (CH), 113.6 (C), 114.9 (C), 121.7 (CH), 121.8 (CH), 122.1 (CH), 122.9 (CH), 124.2 (CH), 126.8 (C), 135.7 (CH), 135.9 (CH), 136.2 (C), 137.6 (C), 143.3 (C), 145.6 (C), 154.4 (C), 176.3 (C=O), 181.6 (C=O).

MS (ESI): mz = 371 (M + H+).

Anal. Calcd for C22H16N4O3 (384.40): C, 68.86; H, 4.02; N, 14.68.

[5-(1H-Indole-3-carbonyl)-1H-imidazol-2-yl][1H-indol-3-yl]methanone (10)

Compound 10 was prepared in 56% overall yield from 6c by two successive deprotection reactions; mp > 210 °C (purified with washing with MeOH).

IR (KBr): 3390, 3200, 1610, 1590, 1510 cm⁻¹.

1H NMR (300 MHz, acetone-d₆): δ = 7.25–7.31 (m, 4 H arom), 7.53–7.60 (m, 2 H arom), 8.45–8.55 (m, 2 H arom), 8.97 (s, 1 H arom), 9.27 (s, 1 H arom), 11.01 (s, 1 H, NH), 11.22 (s, 1 H, NH), 13.09 (s, 1 H, NH).

13C NMR (75 MHz, CDCl₃): δ = 90.2 (C), 112.2 (CH), 112.5 (CH), 113.1 (C), 115.1 (C), 121.5 (CH), 121.7 (CH), 121.8 (CH), 122.3 (CH), 122.9 (CH), 123.3 (CH), 126.5 (2 C), 126.7 (C), 136.1 (C), 136.4 (CH + C), 136.9 (CH), 142.5 (C), 175.7 (C=O), 181.6 (C=O).

HRMS (ESI): mz = 481 (M + H+).

Anal. Calcd for C22H18N3O2 (480.37): C, 52.52; H, 2.73; N, 11.67.

Found: C, 52.53; H, 2.85; N, 11.79.

**Suzuki Reaction of 6c with Arylboronic Acids; General Procedure**

To a stirred solution of 6c (131 mg, 0.18 mmol) in anhyd toluene (5 mL) was added freshly prepared Pd(PPh₃)₄ (12 mg, 6% mol). The solution was stirred for 30 min at r.t. The appropriate arylboronic acid (0.27 mmol) diluted with EtOH (2 mL) was then added, followed immediately by sat. aq NaHCO₃ solution (2 mL). The heterogeneous solution was stirred at 80 °C for 1 h. The Pd catalyst was removed by filtration. Brine was then added, the two layers were separated and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic extracts were dried (MgSO₄) and evaporated in vacuo. The crude residue was purified by column chromatography to give the desired compound 11.

**tetr-Butyl 3-[5-(1-tert-Butyloxy carbonyl-1H-indole-3-carbonyl)-1-ethoxymethyl-4-phenyl-1H-imidazole-2-carbonyl]indole-1-carboxylate (11a)**

* t = 1.5 h; chromatography eluent: PE–EtOAc (9:1); yield: 92%; amorphous solid.

[1H NMR (300 MHz, CDCl₃): δ = 1.00 (t, 3 H, J = 7.0 Hz, CH₃), 1.56 (s, 9 H, 3 CH₃), 1.74 (s, 9 H, 3 CH₃), 3.54 (q, 2 H, J = 7.0 Hz, CH₂), 6.16 (s, 2 H, CH₂N), 7.20–23 (m, 3 H, C₆H₅), 7.40–7.43 (m, 4 H, C₆H₅).]
**tert-Butyl 3-[5-(1-tert-Butylocarbonyl-1H-indole-3-carbonyl)-1-ethoxymethyl-4-(2-thienyl)-1H-imidazole-2-carbonyl]indole-1-carboxylate (11b)**

*1H NMR* (300 MHz, CDCl₃): δ = 1.01 (t, 3 H, CH₃), 1.61 (s, 9 H, 3 CH₃), 1.75 (s, 9 H, 3 CH₃), 3.54 (q, 2 H, J = 7.0 Hz, CH₂), 6.10 (s, 2 H, CH₂N), 6.85 (dd, 1 H furyl, J = 3.6, 5.1 Hz), 7.04 (dd, 1 H furyl, J = 1.0, 5.0 Hz), 7.40–7.45 (m, 4 H arom), 7.96 (s, 1 H arom), 8.13–8.17 (m, 1 H arom), 8.25–8.28 (m, 1 H arom), 8.40–8.43 (m, 1 H arom), 8.53–8.56 (m, 1 H arom), 9.50 (s, 1 H arom).

**13C NMR** (75 MHz, CDCl₃): δ = 14.9 (CH₃), 28.1 (3 CH₃), 28.2 (3 CH₃), 64.9 (CH₂), 75.2 (CH₂N), 85.3 (C), 85.8 (C), 115.2 (C), 115.3 (CH), 118.5 (C), 120.2 (C), 122.5 (CH), 122.7 (CH), 124.7 (CH₂), 124.9 (CH), 125.7 (CH), 125.9 (CH₂), 126.1 (CH), 126.5 (CH₂), 127.2 (CH), 127.8 (CH₂), 128.5 (C), 129.1 (C), 135.5 (C), 135.9 (C+CH), 136.0 (C), 137.0 (C), 138.1 (CH), 143.3 (C), 148.7 (C), 149.1 (C), 178.8 (C=O), 182.7 (C=O).

**MS (ESI):** m/z = 695 (M + H⁺).

**tert-Butyl 3-[5-(1-tert-Butylocarbonyl-1H-indole-3-carbonyl)-1-ethoxymethyl-4-(2-furyl)-1H-imidazole-2-carbonyl]indole-1-carboxylate (11c)**

*1H NMR* (300 MHz, CDCl₃): δ = 1.00 (t, 3 H, CH₃), 1.62 (s, 9 H, 3 CH₃), 1.74 (s, 9 H, 3 CH₃), 3.53 (q, 2 H, J = 7.0 Hz, CH₂), 6.09 (s, 2 H, CH₂N), 6.35 (dd, 1 H furyl, J = 1.7, 3.2 Hz), 6.66 (d, 1 H furyl, J = 3.2 Hz), 7.21 (br s, 1 H furyl), 7.39–7.44 (m, 4 H aromatic), 7.92 (s, 1 H aromatic), 8.14–8.17 (m, 1 H aromatic), 8.22–8.25 (m, 1 H aromatic), 8.41–8.44 (m, 1 H aromatic), 8.51–8.54 (m, 1 H aromatic), 9.42 (s, 1 H aromatic).

**MS (ESI):** m/z = 679 (M + H⁺).

**tert-Butyl 3-[5-(1-tert-Butylocarbonyl-1H-indole-3-carbonyl)-1-ethoxymethyl-4-(1H-imidazol-2-yl)-1H-imidazole-2-carbonyl]indole-1-carboxylate (11d)**

*1H NMR* (300 MHz, CDCl₃): δ = 1.05 (t, 3 H, J = 7.0 Hz, CH₃), 1.33 (s, 9 H, 3 CH₃), 1.66 (s, 9 H, 3 CH₃), 1.70 (s, 9 H, 3 CH₃), 3.56 (q, 2 H, J = 7.0 Hz, CH₂), 6.10–6.12 (m, 1 H aromatic), 6.29 (s, 2 H, CH₂N), 6.45–6.47 (m, 1 H aromatic), 7.10–7.11 (m, 1 H aromatic), 7.35–7.42 (m, 4 H aromatic), 7.91 (s, 1 H aromatic), 8.05–8.08 (m, 1 H aromatic), 8.18–8.21 (m, 1 H aromatic), 8.36–8.39 (m, 1 H aromatic), 8.54–8.57 (m, 1 H aromatic), 9.36 (s, 1 H aromatic).

**13C NMR** (75 MHz, CDCl₃): δ = 14.9 (CH₃), 27.0 (3 CH₂), 27.4 (6 CH₂), 63.7 (CH₃), 73.9 (CH₃N), 83.3 (C), 84.4 (C), 84.6 (C), 110.1 (CH), 114.5 (2 CH), 116.2 (CH), 117.6 (C), 118.8 (C), 121.9 (CH), 122.2 (CH), 122.3 (CH), 123.8 (CH), 124.9 (CH), 125.1 (CH), 126.1 (CH), 126.9 (C), 127.9 (C), 130.5 (C), 134.2 (CH), 134.5 (C), 136.3 (C), 137.3 (CH), 142.9 (C), 147.6 (C), 147.8 (C), 148.1 (C), 177.9 (C=O), 180.2 (C=O).

**MS (ESI):** m/z = 778 (M + H⁺).

**Acknowledgement**

This research work was supported by a grant from the Ministère de la Jeunesse, de l’Éducation Nationale et de la Recherche to C.M.

**References**