Synthesis of New Tacrine Analogues from 4-Aminopyrrole-3-carbonitrile

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Abstract: - An easy preparation of 4-aminopyrrole-3-carbonitrile derivatives and their transformation into new substituted pyrrolo[3,2-\textit{b}]pyridines is described. The one-step transformation was carried out, via \textit{Friedländer} reaction under microwave irradiation and classical heating methods. The use of microwave irradiation led to high conversion and shorter reaction times.

Keywords: Tacrine, \textit{Friedländer} reaction, Alzheimer disease, Thorpe-Ziegler cyclization, Microwave irradiation.

1. Introduction. – The Alzheimer’s disease (AD) is recognized as one of the most severe conditions affecting the aged and it is life-threatening for this group of people. The disease is characterized by neuronal loss, synaptic damage, vascular plaques and a deficit in neurotransmitter acetylcholine (ACh) that leads to a progressive impairment in memory, cognitive functions and behavioral disturbances. In order to increase the ACh level in the synapse, the inhibition of acetylcholinesterase (AChE) represents the currently employed
approach for the treatment of AD. Tacrine (Figure 1) was the first AChE inhibitor (AChEI) introduced in therapy, sold under the name Cognex® since 1993, but the poor selectivity of this drug for AChE resulted in side effects, especially hepatotoxicity. Currently, the AChEIs used to treat AD patients are donepezil, rivastigmine and galantamine but even those present some peripheral side effects [1-5]. Therefore, many efforts have been made by different research groups on the synthesis of several tacrine analogues.

Fig. 1. Structure of tacrine

Modifications on the tacrine structure have been performed, either by increasing the number of rings or changing their size or introducing heteroatoms [5-11]. During the course of this work, we found only one report on the synthesis of tacrine analogues of the pyrrolo-tetrahydroquinoline type [9], i.e., derivatives with a pyrrole ring instead of the benzene ring of tacrine.

2. Results and discussion. - In continuation of our interest in the chemistry of β,β-enaminonitriles, the results aimed at exploring the potential utility of 3-anilino-2-cyanoacrylonitrile in the synthesis of heterocycles, are reported here. The β,β-enaminonitriles 2, which were synthesized by known methods [12], are converted into the corresponding 3-aminopyrrole derivatives 3 by reaction with α-halogenated ketones, nitriles or esters under basic conditions, a Thorpe-Ziegler cyclization (Scheme 1) [13], [14].
Scheme 1. Synthesis and structure of compounds 3

The preparation of 2-substituted 3-aminopyrrole-4-carbonitrile 3 by using α-haloketones (or α-halo-nitriles or esters) in anhydrous DMF in the presence of K₂CO₃ as the base is well described in the literature [13]. Here, we prepared compounds 3 by a modification of the method used previously using Et₃N as the base [14]. When the reaction was carried out in an excess of Et₃N solution, the desired 3-aminopyrrole derivatives 3a-f were obtained in good yields (74-91%). Compounds 3g and 3h were already described by us [14].

The new tacrine analogues 4 could be obtained by applying the Friedländer reaction on pyrroles 3. As we have shown recently in the pyrazole series [11], the Friedländer reaction can be performed under classical heating for 5-7 h. Here we decided to compare the reaction time and the yields of 4 by using the classical heating under reflux and the microwave irradiation.

Pyrroles 3a,b, d, g were dissolved in CH₂Cl₂, cyclic ketones and AlCl₃ were added and the reaction mixture was refluxed for 7-10 h when compounds 4a-f were obtained in satisfactory yields (Scheme 2 and Table 1). Under microwave irradiation, the time of
reaction was reduced from 7-10 h to about 30 min, and compounds 4 were obtained in high yields (80-90%); only the regioisomers 4 are formed. When Y was an ester or ketone group (3c and 3h), the cyclization occurred exclusively towards the nitrile in position 4 of the pyrrole, thus forming regioisomers 5 and 6.

\[
\begin{align*}
3a, d, g & : X = H, Y = \text{CN} \\
3c, 3h & : X = \text{MeO}, Y = \text{CN} \\
4 & : \begin{array}{l}
a \quad X = H, n = 0 \\
b \quad X = H, n = 1 \\
c \quad X = \text{MeO}, n = 0 \\
d \quad X = \text{MeO}, n = 1 \\
e \quad X = \text{Cl}, n = 0 \\
f \quad X = \text{Cl}, n = 1 \\
g \quad X = \text{OH}, n = 0
\end{array}
\end{align*}
\]

\[a) \text{AlCl}_3 \text{ in DCM and reflux or MW. } b) \text{BBr}_3 \text{ in DCM}
\]

\[
\begin{align*}
c \quad X = H, Y = \text{COMe} \\
h \quad X = \text{MeO}, Y = \text{CO}_2\text{Et}
\end{align*}
\]

\[a)
\]

\[b)
\]

\[4c \text{ b) } g \text{ X = OH, n = 0}
\]

Scheme 2. Synthesis and structures of compounds 4a-g, 5 and 6
### Table 1. Friedländer cyclization reaction under classical heating and microwave irradiation

<table>
<thead>
<tr>
<th>Starting material</th>
<th>Product</th>
<th>Classical heating</th>
<th>MW irradiation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time (h)</td>
<td>Yield %</td>
<td>Time (min)</td>
</tr>
<tr>
<td>3a</td>
<td>8</td>
<td>67</td>
<td>2 x 15</td>
</tr>
<tr>
<td>3a</td>
<td>8</td>
<td>70</td>
<td>2 x 15</td>
</tr>
<tr>
<td>3g</td>
<td>7</td>
<td>74</td>
<td>2 x 12</td>
</tr>
<tr>
<td>3g</td>
<td>7</td>
<td>66</td>
<td>2 x 12</td>
</tr>
<tr>
<td>3d</td>
<td>10</td>
<td>55</td>
<td>2 x 16</td>
</tr>
<tr>
<td>3d</td>
<td>10</td>
<td>48</td>
<td>2 x 16</td>
</tr>
<tr>
<td>3h</td>
<td>5</td>
<td>69</td>
<td>2 x 15</td>
</tr>
<tr>
<td>3c</td>
<td>6</td>
<td>62</td>
<td>2 x 15</td>
</tr>
</tbody>
</table>

*Yield of pure compounds

The reaction of 3c with cyclohexanone and 3h with cyclopentanone under the classical heating and microwave irradiation afforded compounds 6 and 5, respectively. The structures of the new compounds were determined by mass spectrometry, $^1$H- and $^{13}$C-NMR spectroscopy. For example, the $^1$H-NMR spectrum of compound 5 showed the presence of a $t$ at 1.13 ppm and a $q$ at 4.21 ppm for the ester function and the absence of a CN absorption band in the IR spectrum. The $^{13}$C NMR and mass spectra of compound 5 are in agreement with the proposed structure.
Attempted cyclization of 2d to the corresponding pyrrole gave a complex mixture, probably due to N or/and O alkylation. The required p-hydroxy tacrine derivative 4g was obtained in 71% yield by demethylation of its precursor 4c.

3. Conclusion. - The 3-amino-4-cyanopyrrole derivatives reacted with cyclopentanone and cyclohexanone to afford the corresponding tacrine analogues through the Friedländer reaction under classical heating and microwave irradiation. Shorter reaction times and higher yields were obtained by the use of microwave irradiation.

Experimental Part

General. M. p. were determined on a Gallenkamp melting point apparatus and are uncorrected. IR spectra were registered on a Perkin Elmer FTIR-1600 using Nujol emulsions between NaCl plates and Cary 50 UV-Vis spectrophotometer. $^1$H-NMR (300 or 400 MHz) and $^{13}$C-NMR (75.4 or 100.62 MHz) spectra were recorded in (D$_6$)DMSO or CDCl$_3$ on a Varian Unity Plus or Bruker Avance II 400 Spectrometer using TMS as an internal reference, and results are expressed as $\delta$ values. Double resonance, HMQC and HMBC experiments were carried out for complete assignment of $^1$H and $^{13}$C in the NMR spectra, whenever possible. Mass spectra were performed on a Shimadzu GCMS-QP 1000 Ex mass spectrometer at 70 eV. Electrospray ionization mass spectra (ESI-MS) were recorded on a ThermoFinnigan LCQ Deca XP Plus quadrupole ion trap instrument on samples diluted in acetonitrile. Elemental analyses were obtained on a Leco CHNS-932 instrument. A CEM MARS oven was used for Friedländer’s reaction under microwave irradiation. Compounds 2 were prepared according to the literature [12], [14].
General procedure for preparation of 3-aminopyrrole derivatives (3a-f, see ref. [14]): To a sol. of the intermediate 2 (0.01 mol) the α-halo compound (chloroacetonitrile, chloroacetone and ethyl bromoacetate) (0.011 mol) and Et₃N (4 ml) were added with external cooling. The mixture was refluxed for 10-15 min after cooling, H₂O (50 ml) was added, the solid product was filtered off, washed thoroughly with cold H₂O and crystallized from EtOH. Compounds 3g, h, were previously reported by us [14].

3-Amino-1-phenyl-1H-pyrrole-2,4-dicarbonitrile (3a). Yield 88%. White solid. M.p. 204-206° (EtOH) ([13]: 187-188°). IR (Nujol): 3456, 3360 (NH₂), 2205, 2227 (CN). ¹H-NMR (CDCl₃): 4.29 (s, 2H, NH₂); 7.22 (s, 1H, H-C(5)); 7.39-7.42 (m, 2H, Ar-H); 7.47-7.56 (m, 3H, Ar-H). Anal. calc. for C₁₂H₈N₄ (208.22): C 69.22, H 3.87, N 26.91; found: C 69.12, H 4.07, N 26.81.

Ethyl 3-amino-4-cyano-1-phenyl-1H-pyrrole-2-carboxylate (3b). Yield (74%). White solid. M.p. 154-155° (EtOH) ([13]: 153-154°). IR (Nujol): 3453, 3342 (NH₂), 2225 (CN), 1655 (CO). ¹H-NMR (CDCl₃): 1.04 (t, 3H, J = 7.2, CH₃); 4.09 (q, 2H, J = 7.2, CH₂); 5.05 (s, 2H, NH₂); 7.06 (s, 1H, H-C(5)); 7.23-7.27 (m, 2H, Ar-H); 7.41-7.44 (m, 3H, Ar-H). Anal. calc. for C₁₄H₁₃N₃O₂ (255.27): C 65.87, H 5.13, N 16.46; found: C 65.82, H 5.32, N 16.50.

5-Acetyl-4-amino-1-phenyl-1H-pyrrole-3-carbonitrile (3c). Yield 91%. White solid. M.p. 233-235° (EtOH). IR (Nujol): 3413, 3349 (NH₂), 2219 (CN), 1640 (CO). ¹H- NMR (CDCl₃): 1.74 (s, 3H, CH₃); 5.83 (s, 2H, NH₂); 7.06 (s, 1H, H-C(2)); 7.32-7.35 (m, 2H, H-C(2'), H-C(6')); 7.50-7.52 (m, 3H, H-C(3'), H-C(4'), H-C(5')). ¹³C-NMR (CDCl₃): 28.72 (CH₃); 83.67 (C(3)); 113.84 (CN); 119.05 (C(5)); 126.27 (C(2')); C(6')); 129.35 (C(4'));
129.76 (C(3’), C(5’)); 132.80 (C(2)); 139.49 (C(1’)); 147.43 (C(4)); 187.61 (CO). Anal. calc. for C_{13}H_{11}N_{4}O (225.25): C 69.32, H 4.92, N 18.66; found: C 69.31, H 4.95, N 18.73.

3-Amino-1-(4-chlorophenyl)-1H-pyrrole-2,4-dicarbonitrile (3d). Yield 84%. Pale yellow solid. M.p. 243-245º (EtOH). IR (Nujol): 3468, 3363 (NH$_2$), 2232, 2200 (CN). $^1$H-NMR (CDCl$_3$): 4.30 (s, 2H, NH$_2$); 7.19 (s, 1H, H-C(5)); 7.35 (d, 2H, $J$ = 9.0, H-C(2’), H-C(6’)); 7.51 (d, 2H, $J$ = 9.0, H-C(3’), H-C(5’)). Anal. calc. for C$_{12}$H$_7$ClN$_4$ (242.66): C 59.39, H 2.91, N 23.09; found: C 59.32, H 2.88, N 23.10.

Ethyl 3-amino-1-(4-chlorophenyl)-4-cyano-1H-pyrrole-2-carboxylate (3e). Yield 74%. White solid. M.p. 153-154º (EtOH) ([13]: 152-154º). IR (Nujol): 3445, 3343 (NH$_2$), 2216 (CN), 1661 (CO). $^1$H-NMR ((D$_6$)DMSO): 1.00 (t, 3H, $J$ = 7.2, CH$_3$); 4.02 (q, 2H, $J$ = 7.2, CH$_2$); 6.00 (s, 2H, NH$_2$); 7.35 (d, 2H, $J$ = 9.0, H-C(2’), H-C(6’)); 7.48 (d, 2H, $J$ = 9.0, H-C(3’), H-C(5’)); 7.76 (s, 1H, H-C(5)). MS-El: 289 (75, [M$^+$, $^{35}$Cl]), 291 (21, [M$^+$, $^{37}$Cl]). Anal. calc. for C$_{14}$H$_{12}$ClN$_3$O$_2$ (289.72): C 58.04, H 4.17, N 14.50; found: C 57.92, H 4.45, N 14.43.

5-Acetyl-4-amino-1-(4-chlorophenyl)-1H-pyrrole-3-carbonitrile (3f). Yield 91%. White solid. M.p. 233-235º (EtOH). IR (Nujol): 3443, 3337 (NH$_2$), 2222 (CN), 1612 (CO). $^1$H-NMR (CDCl$_3$): 1.78 (s, 3H, CH$_3$); 5.83 (s, 2H, NH$_2$); 7.02 (s, 1H, H-C(2)); 7.28 (d, 2H, $J$ = 9.0, H-C(2’), H-C(6’)); 7.50 (d, 2H, $J$ = 9.0, H-C(3’), H-C(5’)). Anal. calc. for C$_{13}$H$_{10}$ClN$_3$O (259.69): C 60.12, H 3.88, N 16.18; found: C 60.13, H 3.96, N 16.17.

**Friedländer Reaction: General procedure for the preparation of tacrine analogues 4a-f, 5 and 6.**

a) By thermal heating. A mixture of 2-substituted-3-aminopyrrole-4-carbonitrile (3) (0.3 mmol), cyclohexanone or cyclopentanone (3.1 mmol) and AlCl$_3$ (anhyd. 3.1 mmol) in
distilled 1,2-dichloroethane (20 ml), was heated to reflux for 7-10 h (TLC control). After cooling to r.t., a mixture of THF/H₂O (1:1, 25 ml) was added, and then an aq. soln. of NaOH (10%) was added dropwise until basic. After stirring for 30 min, the mixture was extracted with CH₂Cl₂ (3 x 20 ml) and the combined extracts were washed with brine (20 ml) and dried (MgSO₄), filtered, and the solvent was evaporated to give a solid, which was purified by PLC (CH₂Cl₂/MeOH, 9:1) or crystallized from EtOH.

b) Under Microwave irradiation. In a round bottom flask of 100 ml equipped with a condenser, cyclohexanone or cyclopentanone (1.4 mmol) was added to a soln. of 2-substituted-3-aminopyrrole-4-carbonitrile 3 (1 mmol) in 40 ml of distilled 1,2-dichloroethane. AlCl₃ (4 mmol) was added and the mixture was heated at reflux during 30 and 32 min (Table 1) under microwave irradiation (at a constant power of 400 W). After cooling to r.t., a mixture of THF/H₂O (1:1, 25 ml) was added, and then an aq. soln. of NaOH (10%) was added dropwise until basic. After stirring for 30 min, the mixture was extracted with CH₂Cl₂ (3 x 20 ml) and the combined extracts were washed with brine (20 mL) and dried (MgSO₄), filtered, and the solvent was evaporated to give a solid, which was identical in all respects with that obtained from the above reaction (TLC, m.p., NMR).

8-Amino-1-phenyl-1,5,6,7-tetrahydrocyclopenta[e]pyrrolo[3,2-b]pyridine-3-carbonitrile (4a). Yield 75%. Yellow solid. M.p. 242-244°. IR (Nujol): 3465, 3360 (NH₂), 2224 (CN).

¹H-NMR ((D₆)DMSO): 2.16-2.26 (m, 2H, H-C(6)), 2.71 (t, 2H, J = 7.7, H-C(7)); 2.91 (t, 2H, J = 7.8, H-C(5)); 4.85 (s, 2H, NH₂); 7.55-7.66 (m, 5H, Ar-H); 8.28 (s, 1H, H-C(2)).

¹³C-NMR ((D₆)DMSO): 22.82 (C(6)); 27.30 (C(7)); 34.18 (C(5)); 86.75 (C(3)); 115.46 (CN); 116.15 (C(8a)); 119.23 (C(3a)); 124.54 (C(4')); 126.52 (C(2'); C(6')); 129.61 (C(3'), C(5')); 129.97 (C(7a)); 137.17 (C(2)); 138.21 (C(1')); 145.76 (C(8)); 162.19 (C(4a)). ESI⁺-
MS: 275.17 ([M+1]^+). Anal. calc. for C_{17}H_{14}N_{4} (274.32): C 74.43, H 5.14, N 20.42; found: C 74.34, H 4.96, N 20.54.


$^1$H-NMR ((D$_6$)DMSO): 1.70-1.84 (m, 4H, H-C(6), H-C(7)); 2.40-2.52 (m, 2H, H-C(8)); 2.74-2.86 (m, 2H, H-C(5)); 4.74 (s, 2H, NH$_2$); 7.53-7.65 (m, 5H, Ar-H); 8.29 (s, 1H, H-C(2)).

$^{13}$C-NMR ((D$_6$)DMSO): 22.40 (C(6)); 22.61 (C(7)); 23.28 (C(8)); 33.06 (C(5)); 86.52 (C(3)); 110.56 (C(9a)); 115.75 (CN); 118.48 (C(3a)); 124.49 (C(4')); 126.62 (C(2'), C(6')); 129.64 (C(3'), C(5')); 138.28 (C(2)); 138.69 (C(1')); 143.49 (C(8a)); 145.93 (C(9)); 153.41 (C(4a)). ESI$^+$-MS: 289.33 ([M+1]$^+$). Anal. calc. for C$_{18}$H$_{16}$N$_4$ (288.35): C 74.98, H 5.59, N 19.43; found: C 74.86, H 5.38, N 19.25.

8-Amino-1-(4-methoxyphenyl)-1,5,6,7-tetrahydrocyclopenta[e]pyrrolo[3,2-b]pyridine-3-carbonitrile (4c). Yield 81%. Yellow solid. M.p. 221-222º. IR (Nujol): 3393, 3299 (NH$_2$), 2218 (CN).

$^1$H-NMR (CDCl$_3$): 2.15-2.23 (m, 2H, H-C(6)); 2.74 (t, 2H, $J = 7.8$, H-C(7)); 3.01 (t, 2H, $J = 7.8$, H-C(5)); 3.78 (s, 2H, NH$_2$); 3.90 (s, 3H, OCH$_3$); 7.07 (d, 2H, $J = 9.2$, H-C(3'), H-C(5')); 7.38 (d, 2H, $J = 9.2$, H-C(2'), H-C(6')); 7.55 (s, 1H, H-C(2)).

$^{13}$C-NMR (CDCl$_3$): 23.26 (C(6)); 26.97 (C(7)); 34.50 (C(5)); 55.71 (OCH$_3$); 88.30 (C(3)); 114.70 (CN); 114.82 (C(3'), C(5')); 116.26 (C(7a)); 117.29 (C(8a)); 125.05 (C(3a)); 128.05 (C(2'), C(6')); 131.14 (C(1')); 136.15 (C(2)); 145.93 (C(8)); 160.32 (C(4')); 163.49 (C(4a)). ESI$^+$-MS: 305.17 ([M+1]$^+$). Anal. calc. for C$_{18}$H$_{16}$N$_4$O (304.35): C 71.04, H 5.30, N 18.41; found: C 71.15, H 4.94, N 18.20.


$^1$H-NMR ((D$_6$)DMSO): 1.85-1.88 (m, 4H, H-C(6), H-C(7)); 2.43-2.47 (m, 2H,
H-C(8)); 2.98-3.02 (m, 2H, H-C(5)); 6.34 (br s, 2H, NH₂); 7.03 (d, 2H, J = 8.8, H-C(3'), H-C(5')); 7.38 (d, 2H, J = 8.8, H-C(2'), H-C(6')); 7.53 (s, 1H, H-C(2)). ¹³C-NMR ((D₆)DMSO): 22.69 (C(6)); 22.80 (C(7)); 23.19 (C(8)); 33.48 (C(5)); 87.88 (C(3)); 110.97 (C(9a)); 114.78 (C(3'), C(5')); 114.84 (CN); 116.80 (C(3a)); 128.08 (C(2'), C(6')); 131.02 (C(1')); 136.76 (C(2)); 137.81 (C(7a)); 143.53 (C(9)); 154.70 (C(4a)); 160.27 (C(4')). ESI⁺-MS: 319.25 ([M+1]+). Anal. calc. for C₁₉H₁₈N₄O (318.37): C 71.68, H 5.70, N 17.60; found: C 71.62, H 5.79, N 17.41.

8-Amino-1-(4-chlorophenyl)-1,5,6,7-tetrahydrocyclopenta[e]pyrrolo[3,2-b]pyridine-3-carbonitrile (4e). Yield 68%. Yellow solid. M.p. 304-306º. IR (Nujol): 3446, 3325 (NH₂), 2226 (CN). ¹H-NMR ((D₆)DMSO): 2.14-2.24 (m, 2H, H-C(6)); 2.81 (t, 2H, J = 7.7, H-C(7)); 3.11 (t, 2H, J = 7.7, H-C(5)); 6.75 (br s, 2H, NH₂); 7.59 (d, 2H, J = 9.0, H-C(2'), H-C(6')); 7.71 (d, 2H, J = 9.0, H-C(3'), H-C(5')); 8.64 (s, 1H, H-C(2)). ESI⁺-MS: 309.17 ([M+1, ³⁵Cl]+), 311.17 ([M+1, ³⁷Cl]+). Anal. calcd. for C₁₇H₁₃ClN₄ (308.76): C 66.13, H 4.24, N 18.15; found: C 66.09, H 4.20, N 17.95.

9-Amino-1-(4-chlorophenyl)-5,6,7,8-tetrahydro-1H-pyrrolo[3,2-b]quinoline-3-carbonitrile (4f). Yield 62%. Pale yellow solid. M.p. 260-262º. IR (Nujol): 3412, 3335 (NH₂), 2229 (CN). ¹H-NMR (CDCl₃): 1.85-1.92 (m, 4H, H-C(6), H-C(7)); 2.40-2.60 (m, 2H, H-C(8)); 3.01-3.06 (m, 2H, H-C(5)); 3.86 (s, 2H, NH₂); 7.42 (d, 2H, J = 9.0, H-C(2'), H-C(6')); 7.57 (d, 2H, J = 9.0, H-C(3'), H-C(5')); 7.54 (s, 1H, H-C(2)). ¹³C-NMR (CDCl₃): 22.70 (C(7)); 23.29 (C(6)); 26.81 (C(8)); 33.59 (C(5)); 89.41 (C(3)); 111.45 (C(8a)); 114.42 (CN); 116.39 (C(9a)); 127.79 (C(2'), C(6')); 130.02 (C(3'), C(5')); 135.49 (C(4')); 136.46 (C(3a)); 136.92 (C(2)); 137.49 (C(1')); 143.93 (C(9)); 155.19 (C(4a)). ESI⁺-MS: 323.25 ([M+1, ³⁵Cl]+), 325.25 ([M+1, ³⁷Cl]+). Anal. calcd. for C₁₉H₁₅ClN₄ (322.79): C 66.98, H 4.68, N 17.36; found: C 66.94, H 4.72, N 17.12.
Ethyl 8-amino-2-(4-methoxyphenyl)-2,5,6,7-tetrahydrocyclopenta[e]pyrrolo[3,4-b]pyridine-3-carboxylate (5). Yield 75%. Yellow solid. M.p. 208-210°. IR (Nujol): 3478, 3339 (NH₂), 1710 (CO). ¹H-NMR (CDCl₃): 1.13 (t, 3H, J = 7.5, CH₃); 2.04-2.14 (m, 2H, H-C(6)); 2.78 (t, 2H, J = 8.0, H-C(7)); 3.03 (t, 2H, J = 8.1, H-C(5)); 4.21 (q, 2H, J = 7.5, CH₂); 6.31 (s, 2H, NH₂); 6.89 (d, 2H, J = 9.0, H-C(3’), H-C(5’)); 7.20 (d, 2H, J = 9.0, H-C(2’), H-C(6’)); 7.93 (s, 1H, H-C(1)). ¹³C-NMR (CDCl₃): 14.24 (CH₃); 22.73 (C(6)); 26.93 (C(7)); 34.31 (C(5)); 55.48 (OCH₃); 60.09 (CH₂); 109.59 (C(8a)); 110.04 (C(3a)); 111.48 (C(7a)); 113.61 (C(3’), C(5’)); 121.47 (C(1)); 127.15 (C(2’), C(6’)); 133.39 (C(1’)); 141.39 (C(3)); 145.94 (C(8)); 159.44 (C(4’)); 160.48 (CO); 165.68 (C(4a)). ESI⁺-MS: 352.25 ([M+1]⁺). Anal. calc. for C₂₀H₂₁N₃O₃ (351.40): C 68.36, H 6.02, N 11.96; found: C 68.53, H 5.87, N 11.91.

1-(9-Amino-2-phenyl-5,6,7,8-tetrahydro-2H-pyrrolo[3,4-b]quinolin-3-yl)ethanone (6). Yield 75%. Yellow solid. M.p. 292-294°. IR (Nujol): 3458, 3342 (NH₂), 1657 (CO). ¹H-NMR ((D₆)DMSO): 1.78-1.82 (m, 4H, H-C(6), H-C(7)); 2.40-2.52 (m, 2H, H-C(8)); 2.73 (s, 3H, CH₃); 2.76-2.85 (m, 2H, H-C(5)); 6.42 (s, 2H, NH₂); 7.31-7.35 (m, 2H, Ar-H); 7.41-7.46 (m, 3H, Ar-H); 7.85 (s, 1H, H-C(1)). ¹³C-NMR ((D₆)DMSO): 22.67 (C(7)); 22.91 (C(6)); 26.17 (C(8)); 28.94 (CH₃); 34.59 (C(5)); 104.63 (C(8a)); 109.97 (C(9a)); 119.47 (C(3)); 122.37 (C(1)); 125.78 (C(2’), C(6’)); 127.60 (C(4’)), 128.53 (C(3’), C(5’)), 131.42 (C(3a)), 141.66 (C(1’)), 145.81 (C(9)), 159.41 (C(9a)); 184.56 (CO). ESI⁺-MS: 306.25 ([M+1]⁺). Anal. calc. for C₁₉H₁₉N₃O (305.37): C 74.73, H 6.27, N 13.76; found: C 74.62, H 6.31, N 13.65.

8-Amino-1-(4-hydroxyphenyl)-1,5,6,7-tetrahydrocyclopenta[e]pyrrolo[3,2-b]pyridine-3-carbonitrile (4g). To a stirred cold sol. of 4c (1.0 mmol) in dry CH₂Cl₂ (15 ml) at -80° and under Arg, a soln. of BBr₃ (1.0 M in CH₂Cl₂; 3 ml) was added dropwise. The mixture was left stirring overnight at r.t. and then H₂O (20 ml) was added. After stirring for 30 min, the
mixture was extracted with CH$_2$Cl$_2$ (3 x 20 ml) and the combined extracts were washed with brine (20 ml), dried (MgSO$_4$), filtered, and the solvent was evaporated to give a solid. Yield 71%. Greenish solid., M.p. 320-322º. IR (Nujol): 3486 (OH), 3387 (NH$_2$), 2219 (CN).

$^1$H-NMR ((D$_6$)DMSO): 2.02-2.07 (m, 2H, H-C(6)); 2.69 (t, 2H, $J = 7.8$, H-C(7)); 2.88 (t, 2H, $J = 7.8$, H-C(5)); 4.81 ($s$, 2H, NH$_2$); 6.92 ($d$, 2H, $J = 8.7$, H-C(3'), H-C(5')); 7.36 ($d$, 2H, $J = 8.7$, H-C(2'), H-C(6')); 8.16 ($s$, 1H, H-C(2)); 10.07 ($s$, 1H, OH). $^{13}$C-NMR ((D$_6$)DMSO): 22.86 (C(6)); 27.23 (C(7)); 33.80 (C(5)); 85.85 (C(3)); 115.19 (C(3a)); 115.61 (CN); 115.85 (C(3'), C(5')); 116.64 (C(8a)); 128.21 (C(2'), C(6')); 129.46 (C(1')); 137.25 (C(7a)); 137.69 (C(2)); 145.31 (C(8)); 158.22 (C(4')); 162.04 (C(4a)). ESI$^+$-MS: 291.33 ([M+1]$^+$). Anal. calc. for C$_{17}$H$_{14}$N$_4$O (290.32): C 70.33, H 4.86, N 19.30; found: C 70.17, H 4.60, N 19.07.

Acknowledgements: We acknowledge the financial support from FCT (Fundação para a Ciência e Tecnologia) and FEDER, for National NMR Network (Bruker Avance II 400) and REEQ/ 630/QUI/2005 (LCMS instrument), and also post-Doctoral grant for A. M. Salaheldin (SFRH/BPD/31490/2006). We thank Ms. E. Pinto for obtaining NMR spectra and elemental analyses and Ms. N. Nunes for LCMS determinations.

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