Synthesis of New Tacrine Analogues from 4-Amino-1*H*-pyrrole-3-carbonitrile

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An easy preparation of 4-amino-1*H*-pyrrole-3-carbonitrile derivatives and their transformation into new substituted pyrrolo[3,2-*b*]pyridines is described. The one-step transformation was carried out *via Friedländer* reaction under microwave irradiation and by classical heating methods. The use of microwave irradiation led to high conversion and shorter reaction times.

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. To increase the ACh level in the synapse, the inhibition of acetylcholinesterase (AChE) represents the currently employed approach for the treatment of AD. Tacrine (*Fig.*) 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.

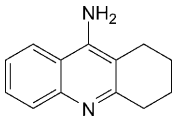


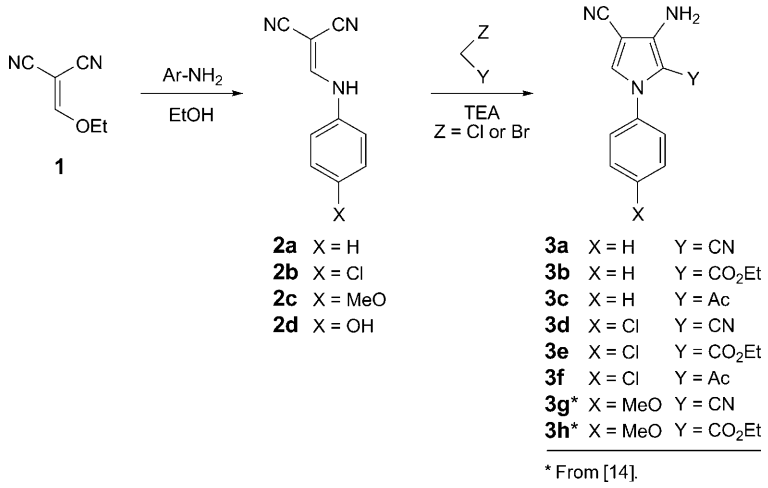
Figure. *Structure of tacrine*

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 'pyrrolotetrahydroquinoline' 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-enamino nitriles, the results aimed at exploring the potential utility of 3-anilino-2-cyanoacrylonitrile in the synthesis of heterocycles are reported here. The β,β-enamino nitriles **2**, which were synthesized by known methods [12], are converted into the corresponding 3-amino-1*H*-pyrrole 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**

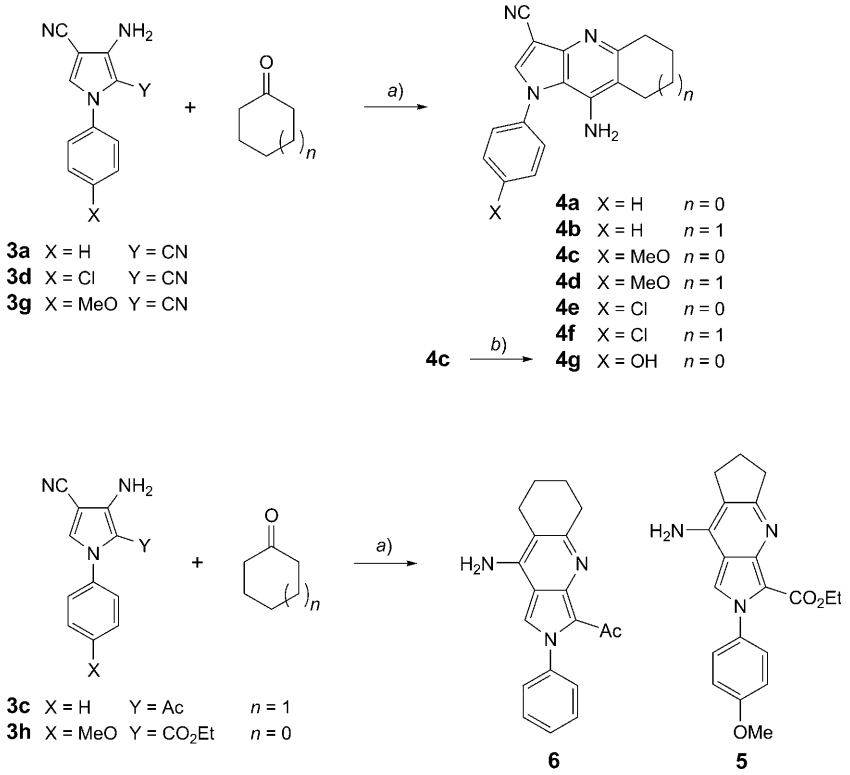


The preparation of 2-substituted 3-amino-1*H*-pyrrole-4-carbonitriles **3** by using α-halo ketones (or α-halo nitriles or esters) in anhydrous DMF in the presence of K_2CO_3 as the base has been well described in the literature [13]. Here, we report the preparation of compounds **3** by a modification of the method described previously using Et_3N (TEA) as the base [14]. When the reaction was carried out in a solution with an excess of Et_3N, the desired 3-amino-1*H*-pyrrole derivatives **3a**–**3f** were obtained in good yields (74–91%). Compounds **3g** and **3h** have already been described by us [14].

The new tacrine analogues **4** could be obtained by applying the *Friedländer* reaction on 1*H*-pyrroles **3**. As we have recently shown 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**, **3b**, **3d**, and **3g** were dissolved in CH_2Cl_2, cyclic ketones and $AlCl_3$ were added, and the mixture was refluxed for 7–10 h, whereupon compounds **4a**–**4f** were obtained in satisfactory yields (*Scheme 2* and *Table*). Under microwave irradiation, the time of reaction was reduced from 7–10 h to *ca.* 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, *i.e.*, **3c** and **3h**, the cyclization occurred exclusively with the CN group at C(4) of the pyrrole, thus affording regioisomers **6** and **5**, respectively.

Scheme 2. *Synthesis and Structures of Compounds* **4a**–**4g**, **5**, *and* **6**



a) $AlCl_3$ in CH_2Cl_2 and reflux, or microwave irradiation. *b*) BBr_3 in CH_2Cl_2.

Table. Friedländer *Cyclization Reaction under Classical Heating and Microwave* (MW) *Irradiation*

Starting material	Product	Classical heating		MW Irradiation	
		Time [h]	Yield [%]	Time [min]	Yield [%][a])
3a	**4a**	8	67	2 × 15	85
3a	**4b**	8	70	2 × 15	82
3g	**4c**	7	74	2 × 12	89
3g	**4d**	7	66	2 × 12	81
3d	**4e**	10	55	2 × 16	90
3d	**4f**	10	48	2 × 16	88
3h	**5**	8	69	2 × 15	84
3c	**6**	8	62	2 × 15	80

[a]) 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 ^{1}H- and ^{13}C-NMR spectroscopy, and mass spectrometry. 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 derivative **4g** was obtained in 71% yield by demethylation of its precursor **4c**.

3. Conclusions. – The 3-amino-4-cyano-1*H*-pyrrole 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 microwave irradiation.

Experimental Part

General. M.p.: *Gallenkamp* apparatus; uncorrected. IR Spectra: *Perkin-Elmer FTIR-1600*, with Nujol emulsions between NaCl plates. UV/VIS Spectra: *Cary 50* spectrophotometer. ^{1}H- (300 or 400 MHz) and ^{13}C-NMR (75.4 or 100.62 MHz) spectra: in (D_6)DMSO or $CDCl_3$ on a *Varian Unity Plus* or *Bruker Avance II 400 Spectrometer*, with TMS as an internal reference, results as δ 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. MS: *Shimadzu* GC/MS *QP 1000 Ex* mass spectrometer at 70 eV. Electrospray-ionization (ESI) MS: *ThermoFinnigan LCQ Deca XP Plus* quadrupole ion-trap instrument on samples diluted in MeCN. Elemental analyses: *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-Amino-1*H*-pyrrole Derivatives* **3a**–**3f** (see [14]). To a soln. of **2** (0.01 mol), the α-halo compound (chloroacetonitrile, chloroacetone, and ethyl bromoacetate; 0.011 mol) and Et_3N (4 ml) were added with external cooling. The mixture was refluxed for 10–15 min. After cooling, H_2O (50 ml) was added, the solid product was filtered off, washed thoroughly with cold H_2O, and crystallized from EtOH. Compounds **3g** and **3h** were previously reported by us [14].

*3-Amino-1-phenyl-1*H*-pyrrole-2,4-dicarbonitrile* (**3a**). Yield 88%. White solid. M.p. 204–206° (EtOH) ([13]: 187–188°). IR (Nujol): 3456, 3360 (NH_2), 2205, 2227 (CN). ^{1}H-NMR ($CDCl_3$): 4.29 (*s*, NH_2); 7.22 (*s*, H–C(5)); 7.39–7.42 (*m*, 2 arom. H); 7.47–7.56 (*m*, 3 arom. H). Anal. calc. for $C_{12}H_8N_4$ (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-1*H*-pyrrole-2-carboxylate* (**3b**). Yield 74%. White solid. M.p. 154–155° (EtOH) ([13]: 153–154°). IR (Nujol): 3453, 3342 (NH_2), 2225 (CN), 1655 (CO). ^{1}H-NMR ($CDCl_3$): 1.04 (*t*, $J = 7.2$, Me); 4.09 (*q*, $J = 7.2$, CH_2); 5.05 (*s*, NH_2); 7.06 (*s*, H–C(5)); 7.23–7.27 (*m*, 2 arom. H); 7.41–7.44 (*m*, 3 arom. H). Anal. calc. for $C_{14}H_{13}N_3O_2$ (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-1*H*-pyrrole-3-carbonitrile* (**3c**). Yield 91%. White solid. M.p. 233–235° (EtOH). IR (Nujol): 3413, 3349 (NH_2), 2219 (CN), 1640 (CO). ^{1}H-NMR ($CDCl_3$): 1.74 (*s*, Me); 5.83 (*s*, NH_2); 7.06 (*s*, H–C(2)); 7.32–7.35 (*m*, H–C(2′), H–C(6′)); 7.50–7.52 (*m*, H–C(3′), H–C(4′), H–C(5′)). ^{13}C-NMR ($CDCl_3$): 28.72 (Me); 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 $C_{13}H_{11}N_4O$ (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)-1*H*-pyrrole-2,4-dicarbonitrile* (**3d**). Yield 84%. Pale yellow solid. M.p. 243–245° (EtOH). IR (Nujol): 3468, 3363 (NH_2), 2232, 2200 (CN). ^{1}H-NMR ($CDCl_3$): 4.30 (*s*, NH_2); 7.19 (*s*, H–C(5)); 7.35 (*d*, $J = 9.0$, H–C(2′), H–C(6′)); 7.51 (*d*, $J = 9.0$, H–C(3′), H–C(5′)). Anal. calc. for $C_{12}H_7ClN_4$ (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-1*H*-pyrrole-2-carboxylate* (**3e**). Yield 74%. White solid. M.p. 153–154° (EtOH) ([13]: 152–154°). IR (Nujol): 3445, 3343 (NH_2), 2216 (CN), 1661 (CO). ^{1}H-NMR ((D_6)DMSO): 1.00 (*t*, $J = 7.2$, Me); 4.02 (*q*, $J = 7.2$, CH_2); 6.00 (*s*, NH_2); 7.35 (*d*, $J = 9.0$,

H–C(2′), H–C(6′)); 7.48 (*d*, *J* = 9.0, H–C(3′), H–C(5′)); 7.76 (*s*, H–C(5)). MS-EI: 289 (75, $[M, {}^{35}Cl]^+$), 291 (21, $[M, {}^{37}Cl]^+$). Anal. calc. for $C_{14}H_{12}ClN_3O_2$ (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)-1*H*-pyrrole-3-carbonitrile* (**3f**). Yield 91%. White solid. M.p. 233–235° (EtOH). IR (Nujol): 3443, 3337 (NH_2), 2222 (CN), 1612 (CO). ^{1}H-NMR ($CDCl_3$): 1.78 (*s*, Me); 5.83 (*s*, NH_2); 7.02 (*s*, H–C(2)); 7.28 (*d*, *J* = 9.0, H–C(2′), H–C(6′)); 7.50 (*d*, *J* = 9.0, H–C(3′), H–C(5′)). Anal. calc. for $C_{13}H_{10}ClN_3O$ (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**–**4f**, **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 $AlCl_3$ (anh., 3.1 mmol) in dist. $ClCH_2CH_2Cl$ (20 ml) was heated to reflux for 7–10 h (TLC control). After cooling to r.t., a mixture of THF/H_2O 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 CH_2Cl_2 (3 × 20 ml), and the combined extracts were washed with brine (20 ml), dried ($MgSO_4$), and filtered, and the solvent was evaporated to give a solid, which was purified by PLC (CH_2Cl_2/MeOH 9:1) or crystallized from EtOH.

b) *Under Microwave Irradiation.* In a 100-ml round-bottom flask equipped with a condenser, cyclohexanone or cyclopentanone (1.4 mmol) was added to a soln. of **3** (1 mmol) in 40 ml of dist. $ClCH_2CH_2Cl$. $AlCl_3$ (4 mmol) was added, and the mixture was heated at reflux during 30 and 32 min (*Table*) under microwave irradiation (at a constant power of 400 W). After cooling to r.t., a mixture of THF/H_2O 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 CH_2Cl_2 (3 × 20 ml), and the combined extracts were washed with brine (20 ml), dried ($MgSO_4$), and 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-1,5,6,7-tetrahydro-1-phenylcyclopenta[*e*]pyrrolo[3,2-*b*]pyridine-3-carbonitrile* (**4a**). Yield 75%. Yellow solid. M.p. 242–244°. IR (Nujol): 3465, 3360 (NH_2), 2224 (CN). ^{1}H-NMR ((D_6)DMSO): 2.16–2.26 (*m*, CH_2(6)), 2.71 (*t*, *J* = 7.7, CH_2(7)); 2.91 (*t*, *J* = 7.8, CH_2(5)); 4.85 (*s*, NH_2); 7.55–7.66 (*m*, 5 arom. H); 8.28 (*s*, H–C(2)). ^{13}C-NMR ((D_6)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.

*9-Amino-5,6,7,8-tetrahydro-1-phenyl-1*H*-pyrrolo[3,2-*b*]quinoline-3-carbonitrile* (**4b**). Yield 79%. Yellow solid. M.p. 222–224°. IR (Nujol): 3467, 3356 (NH_2), 2219 (CN). ^{1}H-NMR ((D_6)DMSO): 1.70–1.84 (*m*, CH_2(6), CH_2(7)); 2.40–2.52 (*m*, CH_2(8)); 2.74–2.86 (*m*, CH_2(5)); 4.74 (*s*, NH_2); 7.53–7.65 (*m*, 5 arom. H); 8.29 (*s*, 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-1,5,6,7-tetrahydro-1-(4-methoxyphenyl)cyclopenta[*e*]pyrrolo[3,2-*b*]pyridine-3-carbonitrile* (**4c**). Yield 81%. Yellow solid. M.p. 221–222°. IR (Nujol): 3393, 3299 (NH_2), 2218 (CN). ^{1}H-NMR ($CDCl_3$): 2.15–2.23 (*m*, CH_2(6)); 2.74 (*t*, *J* = 7.8, CH_2(7)); 3.01 (*t*, *J* = 7.8, CH_2(5)); 3.78 (*s*, NH_2); 3.90 (*s*, OMe); 7.07 (*d*, *J* = 9.2, H–C(3′), H–C(5′)); 7.38 (*d*, *J* = 9.2, H–C(2′), H–C(6′)); 7.55 (*s*, H–C(2)). ^{13}C-NMR ($CDCl_3$): 23.26 (C(6)); 26.97 (C(7)); 34.50 (C(5)); 55.71 (OMe); 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 $C_{18}H_{16}N_4O$ (304.35): C 71.04, H 5.30, N 18.41; found: C 71.15, H 4.94, N 18.20.

*9-Amino-5,6,7,8-tetrahydro-1-(4-methoxyphenyl)-1*H*-pyrrolo[3,2-*b*]quinoline-3-carbonitrile* (**4d**). Yield 72%. Yellow solid. M.p. 214–215°. IR (Nujol): 3485, 3360 (NH_2), 2223 (CN). ^{1}H-NMR ((D_6)DMSO): 1.85–1.88 (*m*, CH_2(6), CH_2(7)); 2.43–2.47 (*m*, CH_2(8)); 2.98–3.02 (*m*, CH_2(5)); 6.34 (br. *s*, NH_2); 7.03 (*d*, *J* = 8.8, H–C(3′), H–C(5′)); 7.38 (*d*, *J* = 8.8, H–C(2′), H–C(6′)); 7.53 (*s*, H–C(2)). ^{13}C-NMR ((D_6)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 $C_{19}H_{18}N_4O$ (318.37): C 71.68, H 5.70, N 17.60; found: C 71.62, H 5.79, N 17.41.

*8-Amino-1,5,6,7-tetrahydro-1-(4-chlorophenyl)cyclopenta[*e*]pyrrolo[3,2-*b*]pyridine-3-carbonitrile* (**4e**). Yield 68%. Yellow solid. M.p. 304–306°. IR (Nujol): 3446, 3325 (NH_2), 2226 (CN). ^{1}H-NMR ((D_6)DMSO): 2.14–2.24 (*m*, CH_2(6)); 2.81 (*t*, *J* = 7.7, CH_2(7)); 3.11 (*t*, *J* = 7.7, CH_2(5)); 6.75 (br. *s*, NH_2); 7.59 (*d*, *J* = 9.0, H–C(2′), H–C(6′)); 7.71 (*d*, *J* = 9.0, H–C(3′), H–C(5′)); 8.64 (*s*, H–C(2)). ESI-MS: 309.17 ($[M+1, {}^{35}Cl]^+$), 311.17 ($[M+1, {}^{37}Cl]^+$). Anal. calc. for $C_{17}H_{13}ClN_4$ (308.76): C 66.13, H 4.24, N 18.15; found: C 66.09, H 4.20, N 17.95.

*9-Amino-5,6,7,8-tetrahydro-1-(4-chlorophenyl)-1*H*-pyrrolo[3,2-*b*]quinoline-3-carbonitrile* (**4f**). Yield 62%. Pale yellow solid. M.p. 260–262°. IR (Nujol): 3412, 3335 (NH_2), 2229 (CN). ^{1}H-NMR ($CDCl_3$): 1.85–1.92 (*m*, CH_2(6), CH_2(7)); 2.40–2.60 (*m*, CH_2(8)); 3.01–3.06 (*m*, CH_2(5)); 3.86 (*s*, NH_2); 7.42 (*d*, *J* = 9.0, H–C(2′), H–C(6′)); 7.57 (*d*, *J* = 9.0, H–C(3′), H–C(5′)); 7.54 (*s*, H–C(2)). ^{13}C-NMR ($CDCl_3$): 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 ($[M+1, {}^{35}Cl]^+$); 325.25 ($[M+1, {}^{37}Cl]^+$). Anal. calc. for $C_{18}H_{15}ClN_4$ (322.79): C 66.98, H 4.68, N 17.36; found: C 66.94, H 4.72, N 17.12.

*Ethyl 8-Amino-2,5,6,7-tetrahydro-2-(4-methoxyphenyl)cyclopenta[*e*]pyrrolo[3,4-*b*]pyridine-3-carboxylate* (**5**). Yield 75%. Yellow solid. M.p. 208–210°. IR (Nujol): 3478, 3339 (NH_2), 1710 (CO). ^{1}H-NMR ($CDCl_3$): 1.13 (*t*, *J* = 7.5, Me); 2.04–2.14 (*m*, CH_2(6)); 2.78 (*t*, *J* = 8.0, CH_2(7)); 3.03 (*t*, *J* = 8.1, CH_2(5)); 4.21 (*q*, *J* = 7.5, CH_2); 6.31 (*s*, NH_2); 6.89 (*d*, *J* = 9.0, H–C(3′), H–C(5′)); 7.20 (*d*, *J* = 9.0, H–C(2′), H–C(6′)); 7.93 (*s*, H–C(1)). ^{13}C-NMR ($CDCl_3$): 14.24 (Me); 22.73 (C(6)); 26.93 (C(7)); 34.31 (C(5)); 55.48 (OMe); 60.09 (CH_2); 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 $C_{20}H_{21}N_3O_3$ (351.40): C 68.36, H 6.02, N 11.96; found: C 68.53, H 5.87, N 11.91.

*1-(9-Amino-5,6,7,8-tetrahydro-2-phenyl-2*H*-pyrrolo[3,4-*b*]quinolin-3-yl)ethanone* (**6**). Yield 75%. Yellow solid. M.p. 292–294°. IR (Nujol): 3458, 3342 (NH_2), 1657 (CO). ^{1}H-NMR ((D_6)DMSO): 1.78–1.82 (*m*, CH_2(6), CH_2(7)); 2.40–2.52 (*m*, CH_2(8)); 2.73 (*s*, Me); 2.76–2.85 (*m*, CH_2(5)); 6.42 (*s*, NH_2); 7.31–7.35 (*m*, 2 arom. H); 7.41–7.46 (*m*, 3 arom. H); 7.85 (*s*, H–C(1)). ^{13}C-NMR ((D_6)DMSO): 22.67 (C(7)); 22.91 (C(6)); 26.17 (C(8)); 28.94 (Me); 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 $C_{19}H_{19}N_3O$ (305.37): C 74.73, H 6.27, N 13.76; found: C 74.62, H 6.31, N 13.65.

*8-Amino-1,5,6,7-tetrahydro-1-(4-hydroxyphenyl)cyclopenta[*e*]pyrrolo[3,2-*b*]pyridine-3-carbonitrile* (**4g**). To a stirred cold soln. of **4c** (1.0 mmol) in dry CH_2Cl_2 (15 ml) at −80° and under Ar, a soln. of BBr_3 (1.0M in CH_2Cl_2; 3 ml) was added dropwise. The mixture was left stirring overnight at r.t., and then H_2O (20 ml) was added. After stirring for 30 min, the mixture was extracted with CH_2Cl_2 (3 × 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. 320–322°. IR (Nujol): 3486 (OH), 3387 (NH_2), 2219 (CN). ^{1}H-NMR ((D_6)DMSO): 2.02–2.07 (*m*, CH_2(6)); 2.69 (*t*, *J* = 7.8, CH_2(7)); 2.88 (*t*, *J* = 7.8, CH_2(5)); 4.81 (*s*, NH_2); 6.92 (*d*, *J* = 8.7, H–C(3′), H–C(5′)); 7.36 (*d*, *J* = 8.7, H–C(2′), H–C(6′)); 8.16 (*s*, H–C(2)); 10.07 (*s*, 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 $C_{17}H_{14}N_4O$ (290.32): C 70.33, H 4.86, N 19.30; found: C 70.17, H 4.60, N 19.07.

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