

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-*b*]pyridines is described. The one-step transformation was carried out, *via Friedländer* reaction under microwave irradiation and classical heating methods. The use of microwave irradiation led to high conversion and shorter reaction times.

Keywords: Tacrine, *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.

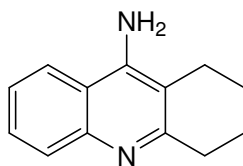
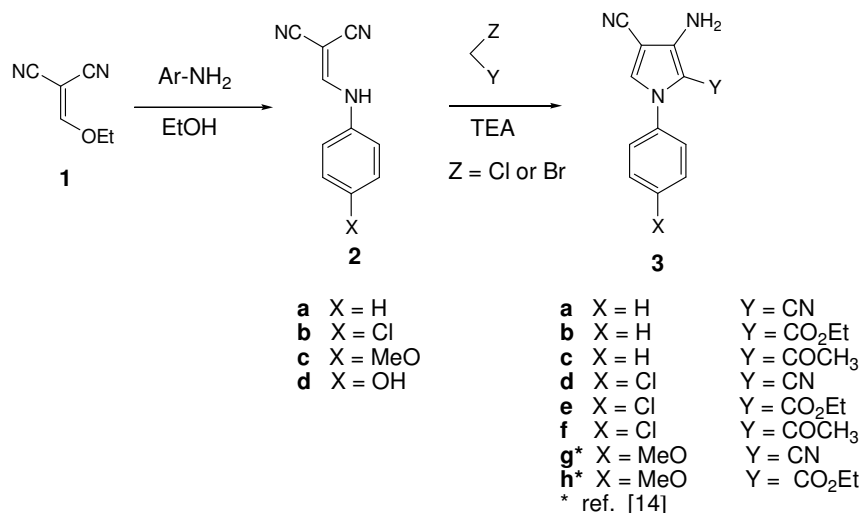


Fig. 1. *Structure of tacrine*

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 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 -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].



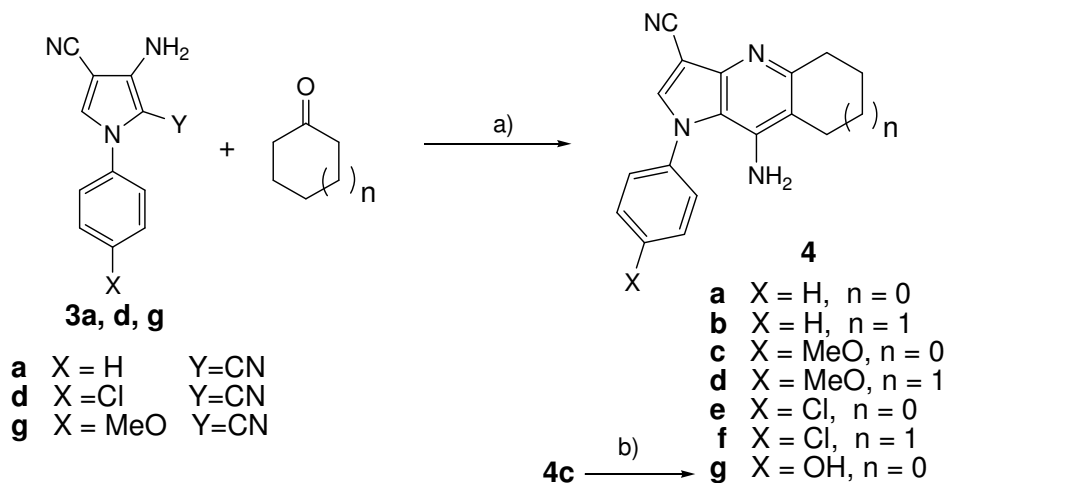
Scheme 1. Synthesis and structure of compounds **3**

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].

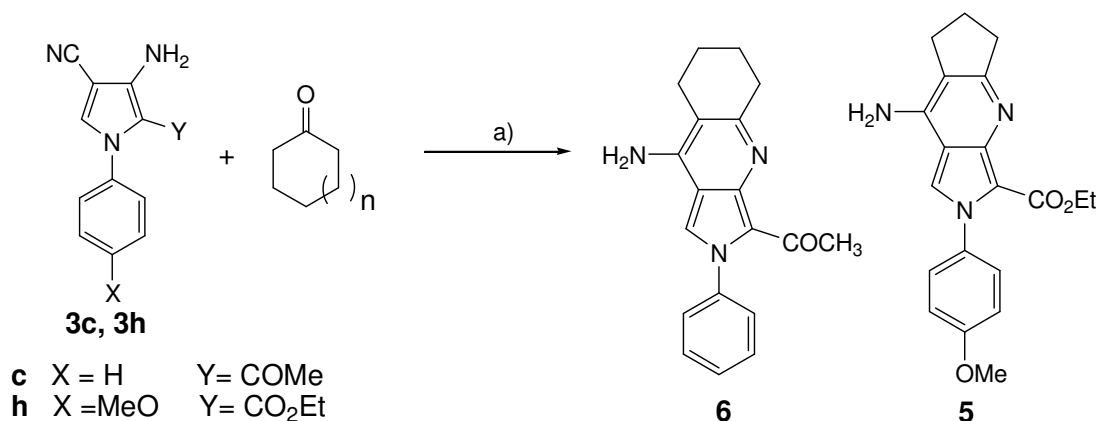
The new tacrine analogues **4** could be obtained by applying the *Friedländer* reaction on pyrroles **3**. As we have shown recently in the pyrazole series [11], the *Friedländer* reaction can be performed under classical heating for 5-7 h. Here we decided to compare the reaction time and the yields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



a) AlCl_3 in DCM and reflux or MW. b) BBr_3 in DCM



Scheme 2. Synthesis and structures of compounds **4a-g**, **5** and **6**

Table 1. Friedländer cyclization reaction under classical heating and microwave irradiation

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

^aYield 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, ¹H- and ¹³C-NMR spectroscopy. For example, the ¹H-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 ¹³C 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*. ¹H-NMR (300 or 400 MHz) and ¹³C-NMR (75.4 or 100.62 MHz) spectra were recorded in (D₆)DMSO or CDCl₃ on a *Varian Unity Plus* or *Bruker Avance II 400 Spectrometer* using TMS as an internal reference, and results are expressed as δ values. Double resonance, HMQC and HMBC experiments were carried out for complete assignment of ¹H and ¹³C 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 C₁₃H₁₁N₄O (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. 243-245° (EtOH). IR (Nujol): 3468, 3363 (NH₂), 2232, 2200 (CN). ¹H-NMR (CDCl₃): 4.30 (s, 2H, NH₂); 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 C₁₂H₇ClN₄ (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. 153-154° (EtOH) ([13]: 152-154°). IR (Nujol): 3445, 3343 (NH₂), 2216 (CN), 1661 (CO). ¹H-NMR ((D₆)DMSO): 1.00 (t, 3H, J = 7.2, CH₃); 4.02 (q, 2H, J = 7.2, CH₂); 6.00 (s, 2H, NH₂); 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-EI: 289 (75, [M⁺, ³⁵Cl]), 291 (21, [M⁺, ³⁷Cl]). Anal. calc. for C₁₄H₁₂ClN₃O₂ (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. 233-235° (EtOH). IR (Nujol): 3443, 3337 (NH₂), 2222 (CN), 1612 (CO). ¹H-NMR (CDCl₃): 1.78 (s, 3H, CH₃); 5.83 (s, 2H, NH₂); 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 C₁₃H₁₀ClN₃O (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 AlCl₃ (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.

9-Amino-1-phenyl-5,6,7,8-tetrahydro-1H-pyrrolo[3,2-b]quinoline-3-carbonitrile (**4b**).

Yield 79%. Yellow solid. M.p. 222-224°. IR (Nujol): 3467, 3356 (NH_2), 2219 (CN). 1H -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. 221-222°. IR (Nujol): 3393, 3299 (NH_2), 2218 (CN). 1H -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 $C_{18}H_{16}N_4O$ (304.35): C 71.04, H 5.30, N 18.41; found: C 71.15, H 4.94, N 18.20.

9-Amino-1-(4-methoxyphenyl)-5,6,7,8-tetrahydro-1H-pyrrolo[3,2-b]quinoline-3-carbonitrile (**4d**). Yield 72%. Yellow solid. M.p. 214-215°. IR (Nujol): 3485, 3360(NH_2), 2223 (CN). 1H -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. 304-306°. 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. 260-262°. 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. calc. for C₁₈H₁₅ClN₄ (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 CH₂Cl₂ (3 x 20 ml) and the combined extracts were washed with brine (20 ml), dried (MgSO₄), filtered, and the solvent was evaporated to give a solid. Yield 71%. Greenish solid. M.p. 320-322°. IR (Nujol): 3486 (OH), 3387 (NH₂), 2219 (CN). ¹H-NMR ((D₆)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, NH₂); 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). ¹³C-NMR ((D₆)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 C₁₇H₁₄N₄O (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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