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.

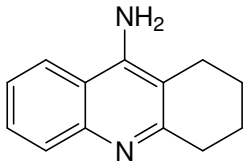
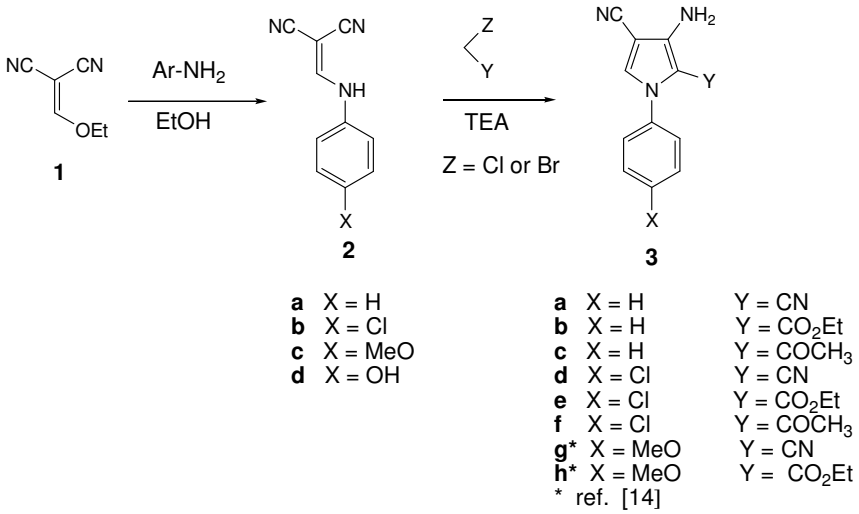


Fig. 1. *Structure of tacrine*

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].



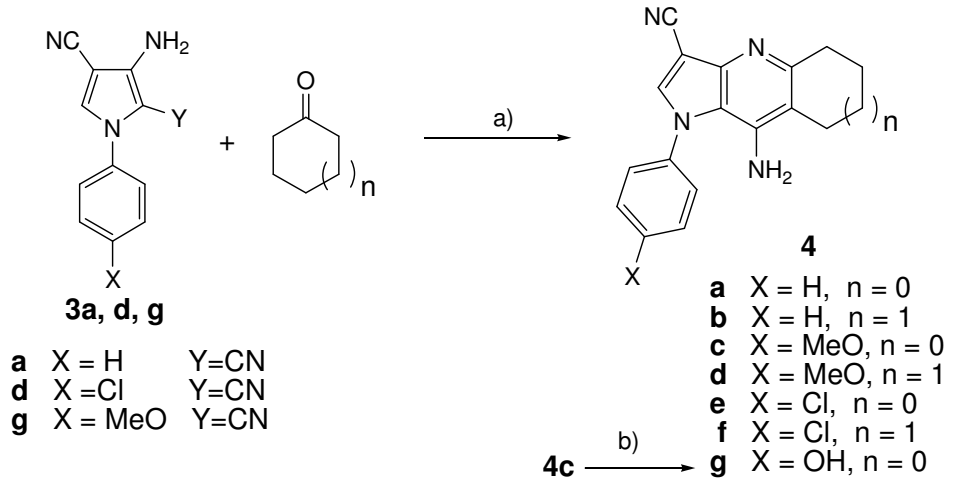
Scheme 1. *Synthesis and structure of compounds* **3**

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 K_2CO_3 as the base is well described in the literature [13]. Here, we prepared compounds **3** by a modification of the method used previously using Et_3N as the base [14]. When the reaction was carried out in an excess of Et_3N 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].

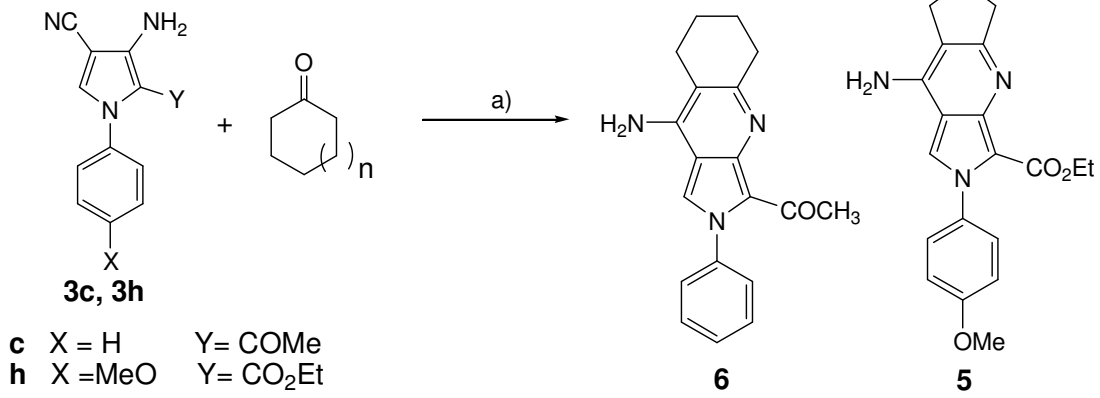
The new tacrine analogues **4** could be obtained by applying the *Friedländer* reaction on pyrroles **3**. As we have shown recently in the pyrazole series [11], the *Friedländer* reaction can be performed under classical heating for 5-7 h. Here we decided to compare the reaction time and the yields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

Pyrroles **3a,b, d, g** were dissolved in CH_2Cl_2, cyclic ketones and $AlCl_3$ 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 material	Product	Classical heating		MW irradiation	
		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

[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 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 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. Mass spectra were performed on a *Shimadzu GCMS-QP 1000 E*x 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 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, h**, were previously reported by us [14].

*3-Amino-1-phenyl-1*H*-pyrrole-2,4-dicarbonitrile* **(3a).** Yield 88%. White solid. M.p. 204-206º (EtOH) ([13]: 187-188º). IR (Nujol): 3456, 3360 (NH_2), 2205, 2227 (CN). ^{1}H-NMR ($CDCl_3$): 4.29 (*s*, 2H, NH_2); 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 $C_{12}H_8N_4$ (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. 154-155º (EtOH) ([13]: 153-154º). IR (Nujol): 3453, 3342 (NH_2), 2225 (CN), 1655 (CO). ^{1}H-NMR ($CDCl_3$): 1.04 (*t*, 3H, J = 7.2, CH_3); 4.09 (*q*, 2H, J = 7.2, CH_2); 5.05 (*s*, 2H, NH_2); 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 $C_{14}H_{13}N_3O_2$ (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. 233-235º (EtOH). IR (Nujol): 3413, 3349 (NH_2), 2219 (CN), 1640 (CO). ^{1}H- NMR ($CDCl_3$): 1.74 (*s*, 3H, CH_3); 5.83 (*s*, 2H, NH_2); 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`)). $^{13}$C-NMR ($CDCl_3$): 28.72 ($CH_3$); 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. 243-245º (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 $C_{12}H_7ClN_4$ (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. 153-154º (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-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. 233-235º (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 $C_{13}H_{10}ClN_3O$ (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-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/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 x 20 ml) and the combined extracts were washed with brine (20 ml) and dried ($MgSO_4$), 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 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. $AlCl_3$ (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/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 x 20 ml) and the combined extracts were washed with brine (20 mL) and dried ($MgSO_4$), 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. 242-244º. IR (Nujol): 3465, 3360 (NH_2), 2224 (CN). ^{1}H-NMR ((D$_6$)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, NH_2); 7.55-7.66 (*m*, 5H, Ar-H); 8.28 (*s*, 1H, 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-1-phenyl-5,6,7,8-tetrahydro-1H-pyrrolo[3,2-*b*]quinoline-3-carbonitrile* **(4b).** Yield 79%. Yellow solid. M.p. 222-224º. IR (Nujol): 3467, 3356 (NH_2), 2219 (CN). ^{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 $C_{18}H_{16}N_4O$ (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-1*H*-pyrrolo[3,2-*b*]quinoline-3-carbonitrile* **(4d)**. Yield 72%. Yellow solid. M.p. 214-215º. IR (Nujol): 3485, 3360(NH_2), 2223 (CN). ^{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, NH_2); 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)). ^{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-(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 (NH_2), 2226 (CN). ^{1}H-NMR ((D_6)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, NH_2); 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 ($[M+1, {}^{35}Cl]^+$), 311.17 ($[M+1, {}^{37}Cl]^+$). Anal. calcd. 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-1-(4-chlorophenyl)-5,6,7,8-tetrahydro-1*H*-pyrrolo[3,2-*b*]quinoline-3-carbonitrile* **(4f).** Yield 62%. Pale yellow solid. M.p. 260-262º. IR (Nujol): 3412, 3335 (NH_2), 2229 (CN). ^{1}H-NMR ($CDCl_3$): 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, NH_2); 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)). ^{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-(4-methoxyphenyl)-2,5,6,7-tetrahydrocyclopenta[*e*]pyrrolo[3,4-*b*]pyridine -3-carboxylate* **(5).** Yield 75%. Yellow solid. M.p. 208-210º. IR (Nujol): 3478, 3339 (NH_2), 1710 (CO). ^{1}H-NMR ($CDCl_3$): 1.13 (*t*, 3H, *J* = 7.5, CH_3); 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, CH_2); 6.31 (*s*, 2H, NH_2); 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)). ^{13}C-NMR ($CDCl_3$): 14.24 (CH_3); 22.73 (C(6)); 26.93 (C(7)); 34.31 (C(5)); 55.48 (OCH_3); 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-2-phenyl-5,6,7,8-tetrahydro-2*H*-pyrrolo[3,4-*b*]quinolin-3-yl)ethanone* **(6).** Yield 75%. Yellow solid. M.p. 292-294º. IR (Nujol): 3458, 3342 (NH_2), 1657 (CO). ^{1}H-NMR ((D$_6$)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, CH_3); 2.76-2.85 (*m*, 2H, H-C(5)); 6.42 (*s*, 2H, NH_2); 7.31-7.35 (*m*, 2H, Ar-H); 7.41-7.46 (*m*, 3H, Ar-H); 7.85 (*s*, 1H, H-C(1)). ^{13}C-NMR ((D$_6$)DMSO): 22.67 (C(7)); 22.91 (C(6)); 26.17 (C(8)); 28.94 (CH_3); 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-(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 CH_2Cl_2 (15 ml) at -80^o and under Arg, a soln. of BBr_3 (1.0 M 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 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 $C_{17}H_{14}N_4O$ (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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