

# SYNTHESIS OF TACRINE ANALOGUES DERIVED FROM N-ARYL-5-AMINO-4-CYANOPYRAZOLES

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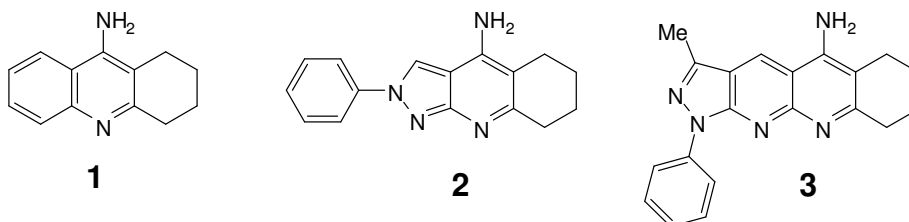
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**Abstract:** Synthesis of eleven tacrine analogues derived from *N*-aryl-5-amino-4-cyanopyrazoles, by a Friedländer type reaction, is described. Their structures were confirmed by  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopy, elemental analysis and/or mass spectrometry.

**Keywords:** Alzheimer's disease, tacrine analogues, Friedländer reaction, aminocyanopyrazole, nitrogen heterocycles.

## INTRODUCTION

The Alzheimer disease (AD) is very common nowadays in elderly individuals. The finding that in those patients there is acetylcholine deficiency, is the basis for research related to drugs that will inhibit acetylcholinesterase (AChE). The first of these inhibitors that received regulatory approval for AD treatment was tacrine (**1**).<sup>[1,2]</sup> Modifications have also been performed within the structure, either by increasing the number of rings or changing their size or introducing heteroatoms.



One group found out that compounds with four rings were less active than tacrine against AChE, however they were more selective and have shown potential against  $\beta$ -amyloid protein aggregation in the brain.<sup>[3]</sup>

Tacrine analogues containing a furan ring have been known for some time,<sup>[4]</sup> and recently, Kirsch et al. synthesized analogues of tacrine and velnacrine containing thiophene.<sup>[5]</sup> An

analogue of tacrine was also described, in which the primary amino group was replaced by the azetidine moiety.<sup>[6]</sup>

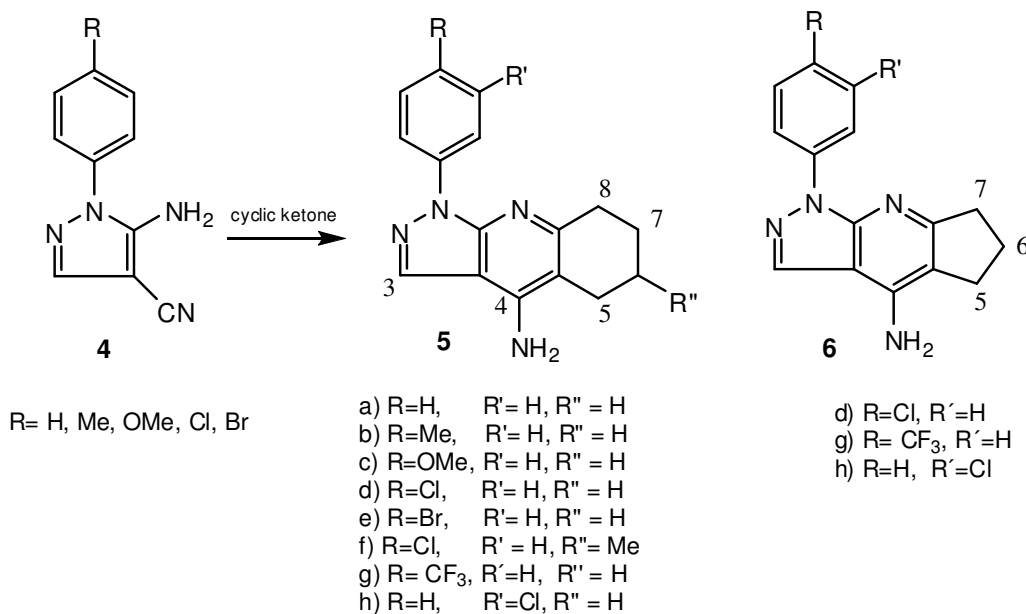
A Spanish-Portuguese group has described the synthesis of tacrine analogues containing heterocyclic rings, such as pyridine, pyran and oxazole, and their inhibitory effects on AChE and butyrylcholinesterase.<sup>[7]</sup>

Other families of tacrine analogues, containing pyrazolopyridine (e.g. **2**) or pyrazolonaphthyridine (e.g. **3**) systems as isosteres of the quinoline ring of tacrine, has been described by Barreiro et al.<sup>[8]</sup> They concluded that compounds **2** and **3** were, in their class, the most potent inhibitors of AChE.

We report here the synthesis of new tacrine analogues from 5-amino-4-cyano-1-arylpyrazoles by reaction of an ortho-aminonitrile with a cyclic ketone in the presence of a Lewis acid.

## RESULTS AND DISCUSSION

We have been interested for some time on ortho-aminocyanopyrazoles, such as **4**, or their derivatives, as dye precursors<sup>[9]</sup> or xanthine oxidase inhibitors.<sup>[10]</sup> It was decided to prepare derivatives of the type **5** or similar, which would be positional isomers of tacrine analogue **2** (Scheme 1).



*Scheme 1*

Most published works build the system using the Friedländer synthesis of tetrahydroquinoline.<sup>[11]</sup>

In the first approach, we applied the conditions common to many authors<sup>[2,3]</sup> with dichloroethane, AlCl<sub>3</sub> and reflux for 6 h under argon (method A). One slight modification that we also applied includes heating for 6 h at 150 °C without solvent and AlCl<sub>3</sub> as the catalyst (method B). Finally conditions of heterogeneous or solid phase catalysis<sup>12</sup> were applied, with mixtures of ZnCl<sub>2</sub> and silica in proportions 2:1 and 4:1, heating for 4 h at 150°C (methods C and D).

The compounds were obtained in low yields, except for compound **5d** either with AlCl<sub>3</sub> (method B, 80%) or ZnCl<sub>2</sub> (method C, 60%). For this compound the yield dropped to 33% when method D (4:1 ZnCl<sub>2</sub> and silica) was used.

We observed that a less polar intermediate was quickly formed, possibly the Schiff's base, but the cyclization was difficult. If we think on the mechanism it is possible to assume that the acid will accelerate the formation of the imine. However the closing step may be easier when basic catalysis is applied.

One method reported by Kirsch,<sup>[5]</sup> obtained the imine, from the aminocyanothiophene and 1,3-dicyclohexanedione, in toluene and *p*-toluenesulphonic acid and cyclised it to the tacrine analogue in DMF solution with sodium methoxide and CuCl. Our attempt to obtain the imine from the aminocyanopyrazole and cyclohexanone by this method was not successful.

The newly synthesized compounds were identified by <sup>1</sup>H, <sup>13</sup>C NMR, mass spectra and/or elemental analysis (cf. Experimental).

## EXPERIMENTAL

**General.** Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. IR spectra were registered on a Perkin Elmer FTIR-1600. <sup>1</sup>H NMR (300 MHz) and <sup>13</sup>C NMR (75.4 MHz) spectra were recorded on a Varian Unity Plus Spectrometer. Double resonance, HMQC and HMBC experiments were carried out for complete assignment of proton and carbon signals in the NMR spectra, whenever

possible. Mass spectra were obtained on a AutoSpec E spectrometer. Elemental analyses were obtained on a Leco CHNS-932 instrument.

*Method A-* A solution of the *p*-chlorophenylpyrazole (**4d**) (0.7 mmol) in dichloroethane (25 mL), cyclohexanone (0.1 mL, 0.97 mmol) and AlCl<sub>3</sub> (0.1 g, 0.75 mmol) were added and the mixture was refluxed for 6 h, under argon. After cooling, a mixture of THF/H<sub>2</sub>O (1:1, 25 mL) was added, and then an aqueous solution of NaOH (10%) was added dropwise until the aqueous solution was basic. After stirring for 30 min the mixture was extracted with dichloromethane (3 x 20 mL) and the combined extracts were washed with brine (20 mL) and dried (MgSO<sub>4</sub>), filtered and the solvent was evaporated to give a solid which was purified by PLC (CH<sub>2</sub>Cl<sub>2</sub>-MeOH, 9:1) yield 32%.

*Method B-* To a sealed tube (screw cap) the pyrazole derivative (0.3 mmol), cyclohexanone (2.0 mmol) and AlCl<sub>3</sub> (0.1 g) were added. The mixture was heated for 6 h (external temperature 150°C), while a colour change occurs. After cooling, a mixture of THF/H<sub>2</sub>O (1:1, 5mL) was added, and then an aqueous solution of NaOH (10%) was added dropwise until the aqueous solution was basic. After stirring for 30 minutes the mixture was extracted with dichloromethane (4 x 10 mL) the combined extracts were washed with brine (20 mL) and dried (MgSO<sub>4</sub>). Concentration of the extract followed by chromatography yielded the target compound.

*Methods C and D*

#### Preparation of the catalyst ZnCl<sub>2</sub> / silica gel

A mixture of ZnCl<sub>2</sub> (8g), silica gel (4g, silica gel 60, 0.063 mm, Merck) and water (3 mL) was stirred for 15 min, left in the oven for 3 h at 80°C and then 15 h at 150°C. The catalyst (ZnCl<sub>2</sub> / silica gel (2:1)) was cooled and kept in the desiccator (method C).<sup>[12,13]</sup> The catalyst ZnCl<sub>2</sub> / silica gel (4:1) was prepared in a similar manner, using ZnCl<sub>2</sub> (8 g) and sílica (2 g) (method D).

#### Reaction with the catalyst ZnCl<sub>2</sub> / silica gel

In a screw cap tube was added the pyrazole (0.20 mmol), the catalyst 2:1 or 4:1 (0.55 g, and 0.31 g, respectively) and the cyclic ketone (cyclohexanone (0.1 mL, 0.97 mmol). The mixture was heated for 4 h at 150°C. After cooling ethyl acetate (50 mL) was added and the mixture was filtered. The filtrate was washed with saturated sodium bicarbonate

solution (2 x 20 mL), dried (MgSO<sub>4</sub>) and evaporated to give an oil that was submitted to chromatography.

### Data

1-Phenyl-5,6,7,8-tetrahydro-1H-pyrazolo[3,4-*b*]quinolin-4-amine (**5a**): The title compound was obtained by method A as a beige solid (32%); mp 195-197 °C;  $\delta_{\text{H}}$  (DMSO-*d*<sub>6</sub>): 8.33 (s, 3H, H-3), 8.40-8.29 (m, 2H, H-2' and 6'), 7.47 (t, 2H, *J* = 7.2 Hz, H-3' and 5'), 7.21 (t, 1H, *J* = 7.5 Hz, H-4'), 6.68 (br s, 2H, NH<sub>2</sub>), 2.85-2.74 (m, 2H, H-8), 2.52-2.40 (m, 2H, H-5), 1.85-1.71 (m, 4H, H-7 and H-6);  $\delta_{\text{C}}$  (DMSO-*d*<sub>6</sub>): 157.05 (C-8a), 150.07 (C-4), 146.99 (C-9a), 140.28 (C-1'), 132.94 (C-3), 128.84 (C-3' and 5'), 124.53 (C-4'), 119.45 (C-2' and 6'), 106.83 (C-4a), 105.05 (C-3a), 33.78 (C-8), 22.92 (C-5), 22.72 and 22.53 (C-7 and C-6). Anal. calcd for C<sub>16</sub>H<sub>16</sub>N<sub>4</sub>: C, 72.73; H, 6.06; N, 21.21. Found: C, 72.83; H, 6.16; N, 20.83.

1-*p*-Tolyl-5,6,7,8-tetrahydro-1H-pyrazolo[3,4-*b*]quinolin-4-amine (**5b**): The compound was obtained by method B as an off-white solid in 40% yield mp 174-176 °C;  $\delta_{\text{H}}$  (DMSO-*d*<sub>6</sub>): 8.28 (s, 1H, H-3), 8.18 (d, 2H, *J* = 8.4 Hz, H-2' and 6' or H-3' and 5'), 7.28 (d, 2H, *J* = 8.7 Hz, H-3' and 5' or H-2' and 6'), 6.63 (br s 2H, NH<sub>2</sub>), 2.85-2.74 (m, 2H, H-8), 2.50-2.40 (m, 2H, H-5), 2.32 (s, 3H, Me), 1.85-1.70 (m, 4H, H-7 and H-6).  $\delta_{\text{C}}$  (DMSO-*d*<sub>6</sub>): 156.99 (C-8a), 149.89 (C-4), 146.93 (C-9a), 137.93 (C-1'), 133.67 (C-3), 132.51 (C-4'), 129.25 (C-3' and 5'), 119.56 (C-2' and 6'), 106.63 (C-4a), 104.95 (C-3a), 33.79 (C-8), 22.92 (C-5), 22.74 and 22.55 (C-7 and C-6), 20.53 (Me). Anal. calcd for C<sub>17</sub>H<sub>18</sub>N<sub>4</sub> ¼H<sub>2</sub>O: C, 72.18; H, 6.59; N, 19.80. Found: C, 72.19; H, 6.45; N, 19.58.

1-(4-Methoxyphenyl)-5,6,7,8-tetrahydro-1H-pyrazolo[3,4-*b*]quinolin-4-amine (**5c**): The compound was prepared by method B and obtained as an off-white solid (44%, m.p. 106-108 °C;  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>): 8.12 (d, 2H, *J* = 7.0 Hz, H-2' and 6'), 7.97 (s, 1H, H-3), 7.01 (d, 2H, *J* = 6.8 Hz, H-3' and 5'), 4.61 (br s, 2H, NH<sub>2</sub>), 2.98 (t, 2H, *J* = 6.0 Hz, H-8), 2.54 (t, 2H, *J* = 6.0 Hz, H-5), 2.0-1.80 (m, 4H, H-7 and H-6);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>): 158.51 (C-8a), 157.40 (C-4'), 149.76 (C-4), 144.85 (C-9a), 133.46 (C-1'), 129.78 (C-3), 122.72 (C-2' and 6'), 114.12 (C-3' and 5'), 107.40 (C-4a), 105.23 (C-3a), 55.51 (OMe), 34.16 (C-8), 22.93 (C-5), 22.88 and 22.87 (C-7 and C-6). The compound was left to crystallize from

the NMR solution and it was used for elemental analysis. HRMS calcd for C<sub>17</sub>H<sub>18</sub>N<sub>4</sub>O: 294.1481; found: (M)<sup>+</sup> 294.1482.

1-(4-Chlorophenyl)-5,6,7,8-tetrahydro-1H-pyrazolo[3,4-*b*]quinolin-4-amine (**5d**): The compound was obtained by methods B, C and D (80, 60 and 33%, respectively) as a beige solid, mp 150-152 °C; δ<sub>H</sub> (DMSO-*d*<sub>6</sub>): 8.41 (d, 2H, *J* = 7.0 Hz, H-2' and 6'), 8.34 (s, 1H, H-3), 7.52 (d, 2H, *J* = 7.0 Hz, H-3' and 5'), 6.72 (br s, 2H, NH<sub>2</sub>), 2.85-2.74 (m, 2H, H-8), 2.52-2.42 (m, 2H, H-5), 1.86-1.70 (m, 4H, H-7 and H-6). δ<sub>C</sub> (DMSO-*d*<sub>6</sub>): 157.15 (C-8a), 150.09 (C-4), 147.11 (C-9a), 139.12 (C-1'), 133.45 (C-3), 128.79 (C-3' and 5'), 128.34 (C-4'), 120.61 (C-2' and 6'), 107.08 (C-4a), 105.05 (C-3a), 33.73 (C-8), 22.89 (C-5), 22.65 and 22.45 (C-7 and C-6). *m/z* (EI/TOF): 297 (43), 300 (M<sup>+</sup>, <sup>37</sup>Cl, 22), 299 (16), 298 (M<sup>+</sup>, <sup>35</sup>Cl, 100). Anal. calcd for C<sub>16</sub>H<sub>15</sub>N<sub>4</sub>Cl: C, 64.32; H, 5.06; N, 18.75. Found: C, 63.92; H, 4.92; N, 18.36.

1-(4-Bromophenyl)-5,6,7,8-tetrahydro-1H-pyrazolo[3,4-*b*]quinolin-4-amine (**5e**): The compound was prepared by method B yielding a light brown solid (20%); mp 127-129 °C; δ<sub>H</sub> (DMSO-*d*<sub>6</sub>): 8.35 (d, 2H, *J* = 9.0 Hz, H-2' and 6'), 8.35 (s, 1H, H-3), 7.65 (d, 2H, *J* = 9.0 Hz, H-3' and 5'), 6.73 (br s, 2H, NH<sub>2</sub>), 2.87-2.74 (m, 2H, H-8), 2.50-2.40 (m, 2H, H-5), 1.90-1.70 (m, 4H, H-7 and H-6); δ<sub>C</sub> (DMSO-*d*<sub>6</sub>): 157.24 (C-8a), 150.17 (C-4), 147.19 (C-9a), 139.57 (C-1'), 133.61 (C-3), 131.78 (C-3' and 5'), 121.05 (C-2' and 6'), 116.59 (C-4'), 107.17 (C-4a), 105.12 (C-3a), 33.80 (C-8), 22.95 (C-5), 22.70 and 22.51 (C-7 and C-6). *m/z* (EI/TOF): 345 (7), 344 (M<sup>+</sup>, <sup>81</sup>Br, 87), 343 (46), 342 (M<sup>+</sup>, <sup>79</sup>Br, 100), 341 (37), 316 (17), 314 (17), 261 (9), 235 (7), 121 (11).

1-(4-Chlorophenyl)-6-methyl-5,6,7,8-tetrahydro-1H-pyrazolo[3,4-*b*]quinolin-4-amine (**5f**): The compound was prepared by method C (38%); mp 185-186 °C; δ<sub>H</sub> (DMSO-*d*<sub>6</sub>): 8.41 (d, 2H, *J* = 9.0 Hz, H-2' and 6'), 8.33 (s, 1H, H-3), 7.53 (d, 2H, *J* = 9.0 Hz, H-3' and 5'), 6.73 (br s, 2H, NH<sub>2</sub>), 2.84 (t, 2H, *J* = 4.2 Hz, H-8), 2.70-2.58 (m, 1H, H-5), 2.08-1.76 (m, 3H, H-5, H-6 and H-7), 1.50-1.30 (m, 1H, H-7), 1.09 (d, 3H, *J* = 6.3 Hz, Me). δ<sub>C</sub> (DMSO-*d*<sub>6</sub>): 156.97 (C-8a), 150.23 (C-4), 147.07 (C-9a), 139.14 (C-1'), 133.52 (C-3), 128.85 (C-3' and 5'), 128.38 (C-4'), 120.65 (C-2' and 6'), 106.81 (C-4a), 105.04 (C-3a),

33.46 (C-8), 31.52 (C-5), 30.87 (C-7), 28.77 (C-6), 21.98 (Me). *m/z* (EI/TOF): 315 (4), 314 ( $M^+$ ,  $^{37}\text{Cl}$ , 22), 313 (18), 312 ( $M^+$ ,  $^{35}\text{Cl}$ , 100), 311 (17), 297 (12), 272 (15), 270 (79). HRMS: 312.1133 ( $M^+$ ,  $\text{C}_{17}\text{H}_{17}\text{N}_4^{35}\text{Cl}$ ; calc. 312.1142). 314.1114 ( $M^+$ ,  $\text{C}_{17}\text{H}_{17}\text{N}_4^{37}\text{Cl}$ ; calc. 314.1112).

1-(4-Trifluoromethylphenyl)-5,6,7,8-tetrahydro-1H-pyrazolo[3,4-*b*]quinolin-4-amine

**(5g)**: The compound was obtained by methods A (16%), mp 115-118 °C;  $\delta_{\text{H}}$  (DMSO- $d_6$ ): 8.65 (d, 2H,  $J = 8.4$  Hz, H-2' and 6'), 8.40 (s, 3H, H-3), 7.85 (d, 2H,  $J = 8.7$  Hz, H-3' and 5'), 6.78 (br s, 2H,  $\text{NH}_2$ ), 2.88-2.78 (m, 2H, H-8), 2.52-2.42 (m, 2H, H-5), 1.86-1.74 (m, 4H, H-7 and H-6);  $\delta_{\text{C}}$  (DMSO- $d_6$ ): 157.35 (C-8a), 150.55 (C-4), 147.28 (C-9a), 143.30 (C-1'), 134.45 (C-3), 126.21 (C-3' and 5'), 122.61, 126.17, 129.80 (the other peak of the q is hidden under C-2' and C-6',  $^1J = 272.9$  Hz,  $\text{CF}_3$ ), 124.32 (q,  $^2J = 31.9$  Hz, C-4'), 118.92 (C-2' and 6'), 107.59 (C-4a), 105.21 (C-3a), 33.75 (C-8), 22.91 (C-6 or C-7), 22.63 (C-5), 22.43 (C-6 or C-7). ESI: 333.25 ( $M+1$ ) $^+$ ; EI/TOF: 333.13 (15, ( $M+1$ ) $^+$ ), 332.13 (100, ( $M$ ) $^+$ ), 331.13 (64), 304 (32), 303 (16).

1-(3-Chlorophenyl)-5,6,7,8-tetrahydro-1H-pyrazolo[3,4-*b*]quinolin-4-amine **(5h)**: The compound was obtained in 15% yield by method A as a beige solid; mp 199-201 °C;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ): 8.45 (t, 1H,  $J = 2.6$  Hz, H-2'), 8.34 (ddd, 1H,  $J = 1.2, 2.5, 10.9$  Hz, H-4'), 7.99 (s, 1H, H-3), 7.20 (ddd, 1H,  $J = 1.2, 2.4, 10.4$  Hz, H-6'), 7.41 (t, 1H,  $J = 10.4$  Hz, H-5'), 4.62 (br s, 2H,  $\text{NH}_2$ ), 2.30 (t, 2H,  $J = 8.0$  Hz, H-8), 2.53 (t, 2H,  $J = 7.6$  Hz, H-5), 1.90-2.00 (m, 4H, H-6 and H-7);  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ ): 158.77 (C-8a), 150.22 (C-9a), 144.94 (C-4), 141.21 (C-3'), 134.50 (C-1'), 130.99 (C-3), 129.90 (C-5'), 124.98 (C-6'), 120.43 (C-2'), 118.35 (C-4'), 108.05 (C-4a), 105.54 (C-3a), 34.15 (C-8), 22.85 (C-6 and C-7), 22.79 (C-5). Anal. calcd for  $\text{C}_{16}\text{H}_{15}\text{ClN}_4$ : C, 64.32; H, 5.06; N, 18.75. Found: C, 63.94; H, 5.00; N, 18.37. *m/z* (EI/TOF): 300 ( $M^+$ ,  $^{37}\text{Cl}$ , 22), 298 ( $M^+$ ,  $^{35}\text{Cl}$ , 100).

1-(4-Chlorophenyl)-1,5,6,7-tetrahydrocyclopenta[*e*]pyrazolo[3,4-*b*]pyridin-4-amine **(6d)**:

The compound was prepared by methods A (15%) and B (27%), mp 289-290 °C.  $\delta_{\text{H}}$  (DMSO- $d_6$ ): 8.37 (d, 2H,  $J = 9.0$  Hz, H-2' and 6'), 8.30 (s, 1H, H-3), 7.54 (d, 2H,  $J = 9.0$  Hz, H-3' and 5'), 6.80 (br s, 2H,  $\text{NH}_2$ ), 2.88 (t, 2H,  $J = 7.8$  Hz, H-7), 2.71 (t, 2H,  $J = 7.5$

Hz, H-5), 2.03 (quintet, 2H,  $J = 7.5$  Hz, H-6);  $\delta_C$  (DMSO- $d_6$ ): 166.57 (C-7a), 152.47 (C-4), 144.91 (C-8a), 139.05 (C-1'), 133.50 (C-3), 128.87 (C-3' and 5'), 128.61 (C-4'), 120.96 (C-2' and 6'), 111.62 (C-4a), 105.66 (C-3a), 34.57 (C-7), 26.71 (C-5), 22.57 (C-6).  $m/z$  -EI/TOF: 286.06 ( $M^+$ ,  $^{37}\text{Cl}$ , 22), 285.09 (14), 284.07 ( $M^+$ ,  $^{35}\text{Cl}$ , 100), 283.06 (64), 265.98 (95), 189.99 (92), 121 (80). Anal. calcd for  $\text{C}_{15}\text{H}_{13}\text{ClN}_4$ : C, 63.27; H, 4.60; N, 19.68. Found: C, 63.09; H, 4.79; N, 19.10.

1-(4-Trifluoromethylphenyl)-1,5,6,7-tetrahydrocyclopenta[e]pyrazolo[3,4-*b*]pyridin-4-amine (**6g**): The compound was prepared by method A (31%) as a light brown solid, mp 265-268 °C;  $\delta_H$  (DMSO- $d_6$ ): 8.62 (d, 2H,  $J = 8.7$  Hz, H-2' and 6'), 8.37 (s, 1H, H-3), 7.85 (d, 2H,  $J = 8.4$  Hz, H-3' and 5'), 6.84 (br s, 2H,  $\text{NH}_2$ ), 2.90 (t, 2H,  $J = 7.5$  Hz, H-7), 2.73 (t, 2H,  $J = 7.5$  Hz, H-5), 2.07 (quintet, 2H,  $J = 7.5$  Hz, H-6);  $\delta_C$  (DMSO- $d_6$ ): 166.33 (C-7a), 152.89 (C-8a), 145.01 (C-4), 143.21 (C-1'), 134.41 (C-3), 126.18 (C-3' and 5'), 124.50 (q,  $^2J = 31.8$  Hz, C-4'), 122.58, 126.18, 129.89 (the other peak of the q is hidden under C2' and C-6',  $^1J = 274.5$  Hz,  $\text{CF}_3$ ), 119.19 (C-2' and 6'), 112.05 (C-4a), 105.82 (C-3a), 34.57 (C-7), 26.70 (C-5), 22.52 (C-6). HRMS calcd for  $\text{C}_{16}\text{H}_{13}\text{F}_3\text{N}_4$ : 318.1092; found: ( $M$ ) $^+$  318.1096.

1-(3-Chlorophenyl)-1,5,6,7-tetrahydrocyclopenta[e]pyrazolo[3,4-*b*]pyridin-4-amine (**6h**): The compound was prepared by method A (15%) as a light brown solid; mp 233.5-235 °C;  $\delta_H$  (400 MHz,  $\text{CDCl}_3$ ): 8.38 (t, 1H,  $J = 2.4$  Hz, H-2'), 8.29 (ddd, 1H,  $J = 1.2, 1.8, 8.3$  Hz, H-4'), 8.01 (s, 1H, H-3), 7.22 (ddd, 1H,  $J = 0.8, 2.2, 8.1$  Hz, H-6'), 7.41 (t, 1H,  $J = 8.0$  Hz, H-5'), 4.54 (br s, 2H,  $\text{NH}_2$ ), 3.08 (t, 2H,  $J = 7.6$  Hz, H-7), 2.80 (t, 2H,  $J = 7.6$  Hz, H-5), 2.23 (quintet, 2H,  $J = 7.6$  Hz, H-6);  $\delta_C$  ( $\text{CDCl}_3$ ): 168.11 (C-7a), 152.65 (C-8a), 142.71 (C-4), 141.10 (C-1'), 134.58 (C-3'), 131.03 (C-3), 129.96 (C-6'), 125.32 (C-5'), 120.93 (C-2'), 118.83 (C-4'), 112.93 (C-4a), 106.07 (C-3a), 35.00 (C-7), 26.37 (C-5), 23.14 (C-6). Anal. calcd for  $\text{C}_{15}\text{H}_{13}\text{ClN}_4$ : C, 63.27; H, 4.60; N, 19.68. Found: C, 63.22; H, 4.62; N, 18.29. EI/TOF: 284.08 ( $M^+$ ,  $^{35}\text{Cl}$ , 100), 286.08 ( $M^+$ ,  $^{37}\text{Cl}$ , 26).

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