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Synthesis of Tacrine Analogs Derived from N-Aryl-5-amino-4-cyanopyrazoles

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Synthesis of Tacrine Analogs Derived from *N*-Aryl-5-amino-4-cyanopyrazoles

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Abstract: Synthesis of 11 tacrine analogs derived from *N*-aryl-5-amino-4-cyanopyrazoles, by a Friedländer type reaction, is described. Their structures were confirmed by ^{1}H and ^{13}C NMR spectroscopy, elemental analysis, and/or mass spectrometry.

Keywords: Alzheimer's disease, aminocyanopyrazole, Friedländer reaction, nitrogen heterocycles, tacrine analogs

INTRODUCTION

Alzheimer's disease (AD) is very common nowadays in elderly individuals. The finding of acetylcholine deficiency in those patients 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**).[1,2] Modifications have also been performed within the structure, either by increasing the number of rings or changing their size or introducing heteroatoms

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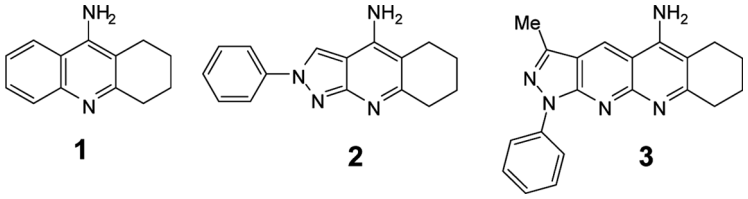

One group found out that compounds with four rings were less active than tacrine against AchE; however, they were more selective and have shown potential against β-amyloid protein aggregation in the brain.[3]

Tacrine analogs containing a furan ring have been known for some time,[4] and recently, Thomae et al. synthesized analogs of tacrine and velnacrine containing thiophene.[5] An analog of tacrine was also described, in which the primary amino group was replaced by the azetidine moiety.[6]

A Spanish–Portuguese group has described the synthesis of tacrine analogs containing heterocyclic rings, such as pyridine, pyran, and oxazole, and their inhibitory effects on AChE and butyrylcholinesterase.[7]

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

We report here the synthesis of new tacrine analogs 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 in ortho-aminocyanopyrazoles, such as **4**, or their derivatives, as dye precursors[9] or xanthine oxidase inhibitors.[10] We decided to prepare derivatives of the type **5** or similar, which would be positional isomers of tacrine analogs **2** (Scheme 1).

Most published works build the system using the Friedländer synthesis of tetrahydroquinoline.[11]

In the first approach, we applied the common conditions[2,3] with dichloroethane, $AlCl_3$, 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 $AlCl_3$ as the catalyst (method B). Finally conditions of heterogeneous or solid-phase catalysis[12] were applied with mixtures of $ZnCl_2$ and silica in proportions 2:1 and 4:1 and heating for 4 h at 150 °C (methods C and D).

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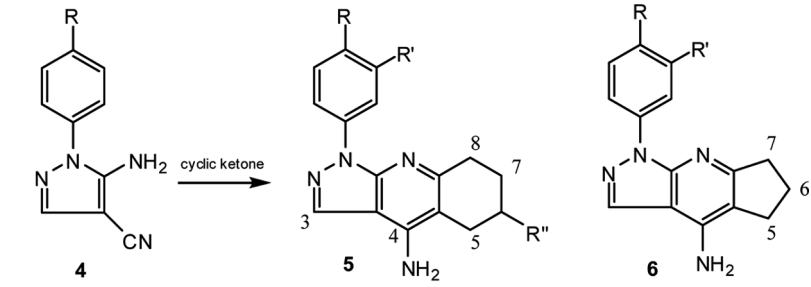

Scheme 1. Structures of compounds **4**, **5**, and **6**.

The compounds were obtained in low yields, except for compound **5d** either with $AlCl_3$ (method B, 80%) or $ZnCl_2$ (method C, 60%). For this compound, the yield dropped to 33% when method D (4:1 $ZnCl_2$ 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[5] obtained the imine, from the aminocyanothiophene and 1,3-dicyclohexanedione, in toluene and *p*-toluenesulphonic acid and cyclized it to the tacrine analog 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 ^{1}H NMR, ^{13}C NMR, mass spectra, and/or elemental analysis (cf. the Experimental section)

EXPERIMENTAL

General

Melting points were determined on a Gallenkamp melting-point apparatus and are uncorrected. IR spectra were registered on a Perkin-Elmer

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FTIR-1600. ^{1}H NMR (300-MHz) and ^{13}C NMR (75.4-MHz) spectra were recorded on a Varian Unity Plus spectrometer. Double-resonance heteronuclear multiple quantum coherence (HMQC) and heteronuclear multiple bond coherence (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.

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Method A

A solution of the *p*-chlorophenylpyrazole (**4d**) (0.7 mmol) in dichloroethane (25 mL), cyclohexanone (0.1 mL, 0.97 mmol), and $AlCl_3$ (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_2O (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 (3×20 mL), and the combined extracts were washed with brine (20 mL), dried ($MgSO_4$), and filtered. The solvent was evaporated to give a solid, which was purified by preparative layer chromatography (PLC) (CH_2Cl_2-MeOH, 9:1) yield 32%.

Method B

The pyrazole derivative (0.3 mmol), cyclohexanone (2.0 mmol), and $AlCl_3$ (0.1 g) were added to a sealed tube (screw cap). The mixture was heated for 6 h (external temperature 150 °C), while a color change occured. After cooling, a mixture of THF/H_2O (1:1, 5 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 (4×10 mL), and the combined extracts were washed with brine (20 mL) and dried ($MgSO_4$). Concentration of the extract followed by chromatography yielded the target compound.

Methods C and D

Preparation of the Catalyst $ZnCl_2$/Siliga Gel. A mixture of $ZnCl_2$ (8 g), siliga gel (4 g, silica gel 60, 0.063 mm, Merck), and water (3 mL) was stirred for 15 min and left in the oven for 3 h at 80 °C and then 15 h at 150 °C. The catalyst ($ZnCl_2$/siliga gel 2:1) was cooled and kept in the desiccator (method C).[12,13] The catalyst ($ZnCl_2$/siliga gel 4:1) was prepared in a similar manner, using $ZnCl_2$ (8 g) and silica (2 g) (method D).

Reaction with the Catalyst $ZnCl_2$/Siliga Gel. In a screw-cap tube, 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) were added. 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 (2×20 mL), dried ($MgSO_4$), and evaporated to give an oil that was submitted to chromatography.

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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; δ_H (DMSO-d6): 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_2), 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); δ_C (DMSO-d_6): 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 $C_{16}H_{16}N_4$: 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; δ_H (DMSO-d_6): 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, H3′ and 5′ or H-2′ and 6′), 6.63 (br s 2H, NH_2), 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). δ_C (DMSO-d_6): 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 $C_{17}H_{18}N_4 \cdot \frac{1}{4}H_2O$: 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% A), mp 106–108 °C; δ_H (400 MHz, $CDCl_3$): 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_2), 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); δ_C ($CDCl_3$): 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 mass analysis. HRMS calcd. for $C_{17}H_{18}N_4O$: 294.1481; found: $(M)^+$ 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_H (DMSO-d_6): 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_2), 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_C (DMSO-d_6): 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^+, ^{37}Cl, 22), 299 (16), 298 (M^+, ^{35}Cl, 100). Anal. calcd. for $C_{16}H_{15}N_4Cl$: 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_H (DMSO-d_6): 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_2), 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_C (DMSO-d_6): 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^+, ^{81}Br, 87), 343 (46), 342 (M^+, ^{79}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_H (DMSO-d_6): 8.41 (d, 2H, $J = 9.0$ Hz, H-2′ and 6′), 8.33 (s, 1H, H-3),

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7.53 (d, 2H, $J = 9.0$ Hz, H-3′ and 5′), 6.73 (br s, 2H, NH_2), 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_C (DMSO-d_6): 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}Cl, 22), 313 (18), 312 (M^+, ^{35}Cl, 100), 311 (17), 297 (12), 272 (15), 270 (79). HRMS: 312.1133 (M^+, $C_{17}H_{17}N_4{}^{35}Cl$; calc. 312.1142). 314.1114 (M^+, $C_{17}H_{17}N_4{}^{37}Cl$; 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; δ_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, 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); δ_C (DMSO-d_6): 157.35 (C-8a), 150.55 (C-4), 147.28 (C-9a), 143.30 (C1′), 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, 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; δ_H ($CDCl_3$): 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, 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); δ_C ($CDCl_3$): 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 $C_{16}H_{15}ClN_4$: 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}Cl, 22), 298 (M^+, ^{35}Cl, 100).

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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. δ_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, 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); δ_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}Cl, 22), 285.09 (14), 284.07 (M^+, ^{35}Cl, 100), 283.06 (64), 265.98 (95), 189.99 (92), 121 (80). Anal. calcd. for $C_{15}H_{13}ClN_4$: 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; δ_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, 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); δ_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, 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 $C_{16}H_{13}F_3N_4$: 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; δ_H (400 MHz, $CDCl_3$): 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, 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); δ_C ($CDCl_3$): 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

$C_{15}H_{13}ClN_4$: 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}Cl, 100), 286.08 (M^+, ^{37}Cl, 26).

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