SYNTHESIS OF 6,7,8,9-TETRAHYDRO-5*H*-1-THIA-5,10-DIAZA-CYCLOHEPTA[*f*]INDEN-4-YLAMINE DERIVATIVES

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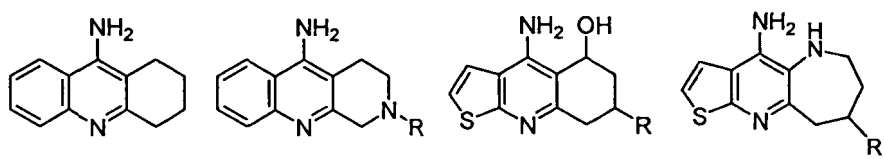
Abstract – This paper describes the synthesis of 6,7,8,9-tetrahydro-5*H*-1-thia-5,10-diazacyclohepta[*f*]inden-4-ylamine derivatives in good yield by four-step procedures starting from 2-aminothiophene-3-carbonitrile and 5-substituted cyclohexane-1,3-dione.

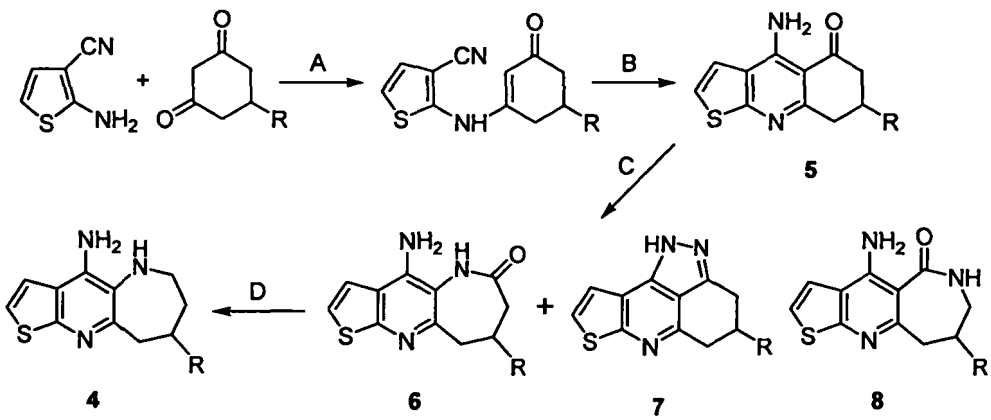
Alzheimer's disease (AD), the most common form of dementia among elderly persons, is a progressive and neurodegenerative disorder of the brain with a loss of memory and cognition.[1] The deficiency in cholinergic neurotransmission is believed to be one of the major causes of the decline in cognitive and mental functions associated with AD.[2,3] Therefore, the use of acetylcholinesterase (AChE) inhibitors, which amplify central cholinergic neurotransmission by inhibiting acetylcholine degradation in order to increase the level of brain acetylcholine, is currently practical therapy to alleviate symptoms of AD patients.[4] Moreover, the interest for AChE inhibitors has been greatly renewed due to the recent evidences that AChE might function to accelerate □-amyloid peptide (A□) formation and could play a role during amyloid deposition in AD brain.[5,6]



1 **2** **3** **4**

Tacrine **1**, the first AChE inhibitor approved by FDA, and various analogues (for instance, **2**) have been synthesized and studied to enhance biological activity and to reduce serious adverse effects such as hepatotoxicity, which often forces patients to discontinue treatment. Recently, we have reported the synthesis of new thienoquinolinol derivatives **3** as potential AChE inhibitors.[7] As a continuation of this and our previous works[8,9] we now describe the synthesis of 6,7,8,9-tetrahydro-5*H*-1-thia-5,10-diazacyclohepta[*f*]inden-4-ylamine derivatives (**4**). On the basis of the concept of bioisosterism as an approach for the improvement of biologically active drugs, our synthetic plan is the replacement of aromatic and cyclohexane moiety in tacrine **1** by thiophene and azepane scaffold.

The key intermediates **5** were prepared as shown in Scheme 1 by two-step reactions, starting from 2-aminothiophene-3-carbonitrile and 5-substituted cyclohexane-1,3-diones according to the procedure we have previously reported.[7] The ring expansion reaction (Schmit reaction) of **5** with NaN_3 in a mixture of concentrated H_2SO_4 and $CHCl_3$ at room temperature for 8-10 h resulted in the formation of the expected lactam, 8-substituted-4-amino-5,7,8,9-tetrahydro-1-



R = **a**: H, **b**: di-Me, **c**: Ph, **d**: *p*-Tolyl, **e**: 4-ClPh, **f**: 4-BrPh

Reagents: A: *p*-TsOH/toluene, reflux; B: K_2CO_3, CuCl/THF, reflux;
C: NaN_3, $H_2SO_4/CHCl_3$, rt; D: $LiAlH_4$/THF, reflux

Scheme-1

thia-5,10-diazacyclohepta[*f*]inden-6-one **6** and side product, 4-substituted-1,3,4,5-tetrahydro-7-thia-1,2,6-triazacyclopenta[*d*]acenaphthylene **7** with the ratio of 3:1 in yield ranging from 65 to 80%. Another isomeric lactam **8** could not be obtained. This result is different from what observed for hydropyrazoloquinolinone[8] and tetralone analogue[9] which gave a mixture of isomeric lactams, but is in agreement with the result from hydroacridinone analogue[10] which afforded a lactam and side product.

The structure of these compounds was characterized by their spectral data and elemental analysis (in Experimental). For instance, IR carbonyl absorption peak of **6a** was in agreement at 1670 cm^{-1} with the carbonyl value of amide but **7a** showed no carbonyl band. In the ^1H NMR spectrum of **6a** the NH appeared at □7.90 as a broad singlet while the broad NH signal in **7a** was shifted at lower field to □ 13.4. The chemical shift of C-3 methylene group in **6a**, next to carbonyl was □ 2.27 and the signal of C-3 methylene group in **7**, next to C=N shifted down field to □ 3.12. The structure of compound **6a** compared to **8a** was further supported by the imidazole cyclization product (not shown in Scheme 1) prepared from reaction of **6a** and triethylorthoformate, which showed a sharp singlet for 1H at □ 9.10 as a methinic proton.[10]

Finally, the reduction reaction of **6** with $LiAlH_4$ in dry THF, followed by work up of aqueous acidification, and by washing 30% NaOH solution in order to remove the aluminum salt from the product and to get free amine, provided the expected compounds **4** in high yield.

The AChE inhibition of these compounds was evaluated by a modified Ellman method.[11] Some of compound **4** showed strong inhibition comparable to tacrine. Further studies are underway and will be reported elsewhere.

Experimental

Melting points were determined in capillary tubes on Büchi apparatus and are uncorrected. Each compound of the reactions was checked on thin-layer chromatography of Merck Kieselgel $60F_{254}$ and purified by column chromatography using Merck silica gel (70-230 mesh). The ^{1}H NMR spectra were recorded on Bruker DRX-300 FT-NMR spectrometer (300 MHz) with Me_4Si as internal standard and chemical shifts are given in ppm (□). Electron ionization mass spectra were recorded on a HP 59580 B spectrometer. Elemental analyses were performed on a Carlo Erba 1106 elemental analyzer.

General procedure for the preparation of 4-amino-5,7,8,9-tetrahydro-1-thia-5,10-diaza- cyclohepta[*f*]inden-6-one (6) derivatives:

To a solution of **5** (0.01 mole) in concentrated H_2SO_4 (10 mL) and $CHCl_3$ (10 mL), sodium azide (0.03 mole) was slowly added over 1 h. The reaction mixture was stirred for 8-10 h at room temperature. The reaction mixture was basified with dilute NH_4OH and extracted with $CHCl_3$. After evaporation the precipitate was filtered and recrystallized from EtOH.

4-Amino-5,7,8,9-tetrahydro-1-thia-5,10-diazacyclohepta[*f*]inden-6-one (6a):

Yield 55%; mp 212-213 °C; ^{1}H NMR ($CDCl_3$): 7.90 (s, 1H,NH), 7.42 (d, J = 5.9 Hz, 1H, thiophene H-2), 7.38 (d, J = 5.9 Hz, 1H, H-3), 2.93 (t, 2H, H-9), 2.27-2.30 (m, 4H, H-7 and H-8); MS: (m/z) 233 (M^+), 204, 190, 109. *Anal.* Calcd. for $C_{11}H_{11}N_3OS$: C, 56.63; H, 3.14; N, 18.01. Found: C, 56.75; H, 3.25; N, 18.14.

4-Amino-8,8-dimethyl-5,7,8,9-tetrahydro-1-thia-5,10-diazacyclohepta[*f*]inden-6-one (6b):

Yield 60%; mp 254-256 °C; ^{1}H NMR ($CDCl_3$): 7.83 (s, 1H,NH), 7.40 (d, J = 5.9 Hz, 1H, thiophene H-2), 7.36 (d, J = 5.9 Hz, 1H, H-3), 2.66 (s, 2H, H-9), 2.00 (s, 2H, H-7) 1.07 (s, 6H, diMe); MS: (m/z) 262 (M^++H), 247, 219, 179. *Anal.* Calcd. for $C_{13}H_{15}N_3OS$: C, 59.75; H, 5.78; N, 16.08. Found: C, 59.82; H, 5.89; N, 16.26.

4-Amino-8-phenyl-5,7,8,9-tetrahydro-1-thia-5,10-diazacyclohepta[*f*]inden-6-one (6c):

Yield 62%; mp 259-260 °C; ^{1}H NMR ($CDCl_3$): 7.90 (s, 1H,NH), 7.48 (d, J = 6.0 Hz, 1H, thiophene H-2), 7.42 (d, J = 6.0 Hz, 1H, H-3), 7.39-7.27 (m, 5H, phenyl), 3.72 (q, 1H, H-8), 3.26 (m, 1H, H-9a), 3.10 (m, 1H, H-9b), 2.63 (m, 1H, H-7a), 2.55 (m, 1H, H-7b); MS: (m/z) 309 (M^+), 281, 266, 179, 131. *Anal.* Calcd. for $C_{17}H_{15}N_3OS$: C, 66.00; H, 4.89; N, 13.58. Found: C, 66.14; H, 4.98; N, 13.74.

4-Amino-8-*p*-tolyl-5,7,8,9-tetrahydro-1-thia-5,10-diazacyclohepta[*f*]inden-6-one (6d):

Yield 43%; mp 238-239 °C; ^{1}H NMR ($CDCl_3$): 7.94 (s, 1H,NH), 7.47 (d, J = 6.0 Hz, 1H, thiophene H-2), 7.44 (d, J = 6.0 Hz, 1H, H-3), 7.20 (d, 2H, phenyl H-2'and H-6'), 7.11 (d, 2H, phenyl H-3'and H-5'), 3.70 (q, 1H, H-8), 3.20 (m, 1H, H-9a), 3.08 (m, 1H, H-9b), 2.62 (m, 1H, H-7a), 2.52 (m, 1H, H-7b); MS: (m/z) 323 (M^+), 295, 280, 179, 145. *Anal.* Calcd. for $C_{18}H_{17}N_3OS$: C, 66.85; H, 5.30; N, 12.99. Found: C, 66.72; H, 5.47; N, 13.12.

4-Amino-8-(4-chlorophenyl)-5,7,8,9-tetrahydro-1-thia-5,10-diazacyclohepta[*f*]inden-6-one (6e):

Yield 57%; mp 259-260 °C; ^{1}H NMR ($CDCl_3$): 7.90 (s, 1H,NH), 7.47 (d, J = 6.0 Hz, 1H, thiophene H-2), 7.44 (d, J = 6.0 Hz, 1H, H-3), 7.35-7.28 (m, 4H, phenyl), 3.75 (q, 1H, H-8), 3.23 (m, 1H, H-9a), 3.07 (m, 1H, H-9b), 2.65 (m, 1H, H-7a), 2.49 (m, 1H, H-7b); MS: (m/z) 344 (M^+), 316, 300, 219, 191, 180, 165. *Anal.* Calcd. for $C_{17}H_{14}ClN_3OS$: C,

59.39; H, 4.10; N, 12.22. Found: C, 59.48; H, 4.23; N, 12.40.

4-Amino-8-(4-bromophenyl)-5,7,8,9-tetrahydro-1-thia-5,10-diazacyclohepta[*f*]inden-6-one (6f):

Yield 52%; mp 253-254 °C; ^{1}H NMR ($CDCl_3$): 7.87 (s, 1H,NH), 7.46 (d, J = 6.0 Hz, 1H, thiophene H-2), 7.44 (d, J = 6.0 Hz, 1H, H-3), 7.32-7.28 (m, 4H, phenyl), 3.72 (q, 1H, H-8), 3.24 (m, 1H, H-9a), 3.08 (m, 1H, H-9b), 2.66 (m, 1H, H-7a), 2.50 (m, 1H, H-7b); MS: (m/z) 389 (M^++H), 360, 346, 218, 190, 179, 133. *Anal.* Calcd. for $C_{17}H_{14}BrN_3OS$: C, 52.59; H, 3.63; N, 10.82. Found: C, 52.66; H, 3.81; N, 10.99.

1,3,4,5-Tetrahydro-7-thia-1,2,6-triazacyclopenta[*d*]acenaphthylene (7a):

Yield 17%; mp 220 °C (decompose); ^{1}H NMR ($CDCl_3$): 13.4 (s, 1H, NH), 7.48 (m, 2H, H-8 and H-9), 3.12-3.00 (m, 4H, H-3 and H-5), 2.31 (q, 2H, H-4); MS: (m/z) 215 (M^+), 186, 160. *Anal.* Calcd. for $C_{11}H_9N_3S$: C, 61.37; H, 4.21; N, 19.52. Found: C, 61.50; H, 4.34; N, 19.62.

General procedure for the preparation of 6,7,8,9-tetrahydro-5*H*-1-thia-5,10-diaza- cyclohepta[*f*]inden-4-ylamine (4) derivatives:

A solution of $LiAlH_4$ in Et_2O (5 mL of 1.0 M, 5 mmole) was added dropwise to a solution of the appropriate **6** (5 mmole) in dry THF (15 mL) maintained 0 °C under nitrogen. The resulting solution was allowed to reflux for 12 h. After cooling, the reaction solution was quenched by adding 10% HCl (0.5 mL) followed by washing the precipitate with 30% NaOH solution and extracted with EtOAc. The combined organic layers were evaporated to dryness, and the residue was purified by silica chromatography eluting with EtOAc and $CHCl_3$ mixture.

6,7,8,9-Tetrahydro-5*H*-1-thia-5,10-diazacyclohepta[*f*]inden-4-ylamine (4a):

Yield 89%; mp 168-169 °C; ^{1}H NMR ($CDCl_3$): 7.23 (d, J = 6.0 Hz, 1H, thiophene H-2), 7.08 (d, J = 6.0 Hz, 1H, H-3), 4.97 (br, 2H, NH_2), 3.03-2.97 (m, 4H, H-6 and H-9), 1.89-1.79 (m, 4H, H-7 and H-8); MS: (m/z) 219 (M^+), 204, 190, 164, 109. *Anal.* Calcd. for $C_{11}H_{13}N_3S$: C, 60.25; H, 5.97; N,19.16. Found: C, 60.40; H, 5.90; N,19.30.

8,8-Dimethyl-6,7,8,9-tetrahydro-5*H*-1-thia-5,10-diazacyclohepta[*f*]inden-4-ylamine (4b):

Yield 82%; mp 151-152 °C; ^{1}H NMR ($CDCl_3$): 7.21 (d, J = 6.0 Hz, 1H, thiophene H-2), 7.08 (d, J = 6.0 Hz, 1H, H-3), 4.97 (br, 2H, NH_2), 3.03 (t, 2H, H-6), 2.97 (s, 2H, H-9), 0.96 (s, 6H, diMe); MS: (m/z) 247 (M^+), 232, 204, 190, 179, 164. *Anal.* Calcd. for $C_{13}H_{17}N_3S$: C, 63.12; H, 6.93; N, 16.99. Found: C, 63.28; H, 6.79; N, 17.05.

8-Phenyl-6,7,8,9-tetrahydro-5*H*-1-thia-5,10-diazacyclohepta[*f*]inden-4-ylamine (4c):

Yield 90%; mp 153-154 °C; ^{1}H NMR ($CDCl_3$): 7.48 (d, J = 6.0 Hz, 1H, thiophene H-2), 7.41 (d, J = 6.0 Hz, 1H, H-3), 7.24-7.15 (m, 5H, phenyl), 5.00 (br, 2H, NH_2), 3.58-3.44 (m, 2H, H-8 and H-9a), 3.21 (d, 1H, H-9b), 2.84 (t, 1H, H-6a), 2.67 (t, 1H, H-6b), 2.17-1.97 (m, 2H, H-7); MS: (m/z) 295 (M^+), 190. *Anal.* Calcd. for $C_{17}H_{17}N_3S$: C, 69.12; H, 5.80; N, 14.22. Found: C, 69.30; H, 5.92; N, 14.38.

8-(4-*p*-Tolyl)-6,7,8,9-tetrahydro-5*H*-1-thia-5,10-diazacyclohepta[*f*]inden-4-ylamine (4d):

Yield 92%; mp 134-135 °C; ^{1}H NMR ($CDCl_3$): 7.47 (d, J = 6.0 Hz, 1H, thiophene H-2), 7.40 (d, J = 6.0 Hz, 1H, H-3), 7.16-7.08 (m, 4H, phenyl), 5.05 (br, 2H, NH_2), 3.56-3.41 (m, 2H, H-8 and H-9a), 3.22 (d, 1H, H-9b), 2.85 (t, 1H, H-6a), 2.66 (t, 1H, H-6b), 2.32 (s, 3H, Me), 2.15-1.99 (m, 2H, H-7); MS: (m/z) 309 (M^+), 190, 149, 129. *Anal.* Calcd. for $C_{18}H_{19}N_3S$: C, 69.87; H, 6.19; N, 13.58. Found: C, 69.76; H, 6.26; N, 13.66.

8-(4-Chlorophenyl)-6,7,8,9-tetrahydro-5*H*-1-thia-5,10-diazacyclohepta[*f*]inden-4-yl- amine (4e):

Yield 85%; mp 103-105 °C; ^{1}H NMR ($CDCl_3$): 7.48 (d, J = 6.0 Hz, 1H, thiophene H-2), 7.41 (d, J = 6.0 Hz, 1H, H-3), 7.25-7.10 (m, 4H, phenyl), 5.01 (br, 2H, NH_2), 3.58-3.45 (m, 2H, H-8 and H-9a), 3.20 (d, 1H, H-9b), 2.84 (t, 1H, H-6a), 2.65 (t, 1H, H-6b), 2.12-2.02 (m, 2H, H-7); MS: (m/z) 329 (M^+), 203, 190, 178, 135. *Anal.* Calcd. for $C_{17}H_{16}ClN_3S$: C,

61.90; H, 4.89; N, 12.74. Found: C, 61.82; H, 4.96; N, 12.90.

8-(4-Bromophenyl)-6,7,8,9-tetrahydro-5*H*-1-thia-5,10-diazacyclohepta[*f*]inden-4-yl amine (4f):

Yield 88%; mp 163-164 °C; ^{1}H NMR ($CDCl_3$): 7.47 (d, J = 6.0 Hz, 1H, thiophene H-2), 7.42 (d, J = 6.0 Hz, 1H, H-3), 7.17-7.11 (m, 4H, phenyl), 5.10 (br, 2H, NH_2), 3.60-3.45 (m, 2H, H-8 and H-9a), 3.25 (d, 1H, H-9b), 2.86 (t, 1H, H-6a), 2.64 (t, 1H, H-6b), 2.11-1.99 (m, 2H, H-7); MS: (m/z) 374 (M^+), 190. *Anal.* Calcd. for $C_{17}H_{16}BrN_3S$: C, 54.55; H, 4.31; N, 11.23. Found: C, 54.70; H, 4.44; N, 11.10.

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