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단 신

슈미트 반응을 이용한 10-amino-5,6,7,9-tetrahydro-1-thia-4,9-diazacyclohepta[*f*]inden-8-one 유도체의 합성

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Synthesis of 10-Amino-5,6,7,9-tetrahydro-1-thia-4,9-diazacyclohepta[*f*]inden-8-one Derivatives using Schmit Reaction

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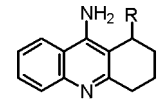
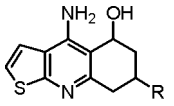
Keywords: Alzheimer's disease, Acetylcholinesterase inhibitor, Schmit reaction, Thienopyridine derivative

Alzheimer's disease (AD) is neurodegenerative disease characterized by a low concentration of acetylcholine (ACh) in the hippocampus and cortex.[1] The deficiency in cholinergic neurotransmission is also believed to be one of the major causes of the decline in cognitive and mental functions associated with AD.[2-4] Acetylcholinesterase (AChE) inhibitors, which inhibit the enzyme responsible for ACh hydrolysis in order to increase the level of brain ACh, have been used for years in treatment of AD.[5]



1a (R = H, tacrine)
1b (R = OH, velnacrine)



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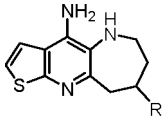

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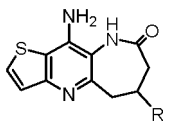

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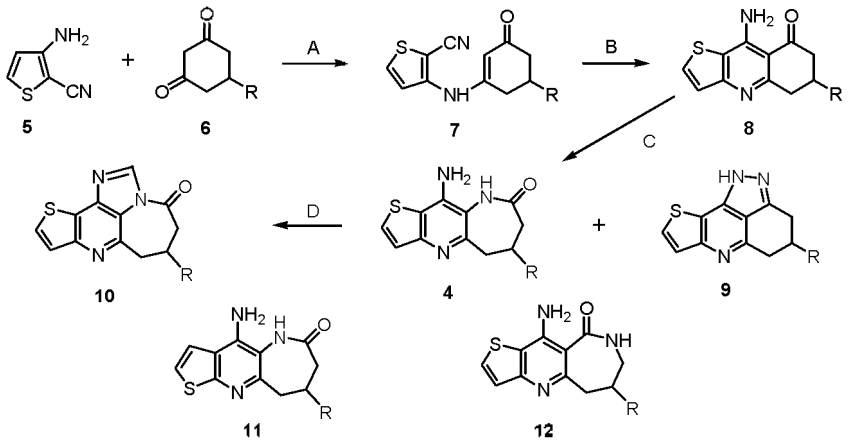
To date only tacrine (**1a**, the first AChE inhibitor), donepezil, rivastigmine, and galanthamine are available for AD treatment. However, the use of AChE inhibitors is sometimes limited mainly due to serious adverse effects such as hepatotoxicity and modest benefits to AD patients. Efforts to search for more potent and selective inhibitors of AChE without side effects still remain highly significant in AD treatment.

Recently, we have reported the synthesis of new thienopyridine derivatives **2** and **3** as potential AChE inhibitors.[6] In continuation of our works for biologically active heterocyclic compounds[7] we describe herein the synthesis of 10-amino-5,6,7,9-tetrahydro-1-thia-4,9-diazacyclohepta[*f*]inden-8-one derivatives (**4**). Since it is widely recognized that thiophene is a bioisoster of benzene, our synthetic plan is based on the replacement of benzene and cyclohexane moiety in tacrine **1** by thiophene and azepanone scaffold.

The synthetic route to **4** is, as shown in *Scheme* 1, similar in many respects to the one used for the synthesis of compound **11**[6b] except the starting material **5**. The condensation of 3-aminothiophene-2-carbonitrile **5** with 5-substituted cyclohexane-1,3-diones **6** in refluxing toluene in the



Scheme 1. Reagent and conditions; A: *p*-TsOH/toluene, reflux; B: K_2CO_3, CuCl/THF, reflux; C: NaN_3, $H_2SO_4/CHCl_3$, rt; D: $CH(OEt)_3$, reflux.

presence of *p*-TsOH, gave the corresponding enamino ketones **7**. The latter ones were then cyclized with potassium carbonate and cuprous chloride in refluxing THF to produce tricyclic ketones **8**.[7f] The ring expansion of **8** by Schmit reaction with sodium azide in a mixture of concentrated sulfuric acid and chloroform at room temperature for 5-6 h afforded one lactam, 6-substituted-10-amino-5,6,7,9-tetrahydro-1-thia-4,9-diazacyclohepta [*f*]inden-8-one **4** and 4-substituted-1,3,4,5-tetrahydro-9-thia-1,2,6-triazacyclopenta[*cd*] acenaphthylene **9** with the ratio of 4:1 in yield ranging from 44 to 65%. Another isomeric lactam **12** was not formed.

The structure of **4** was characterized by their spectral data and chemical evidence. For instance, IR carbonyl absorption peak of **4a** appeared at 1670 cm^{-1} as carbonyl value of amide but **9a** showed no carbonyl band. The ^1H NMR spectrum of **4a** showed NH_2 and NH at δ 8.71 and 6.18, respectively, while the broad NH signal in **9a** was shifted at lower field to δ 13.30. The mass and elemental analysis data for **4a** and **9a** also matched the proposed structures and formulas, respectively (in Experimental). And, the chemical shift of C-7 methylene group, next to carbonyl in **4a** was δ 2.13. Its value is in agreement with the fact that a methylene of **4a** absorbs at higher field when compared to a methylene next to NH group of **12a**. The structure of compound **4a** compared to **12a** was further supported by the result that cyclization of **4a** with triethylorthoformate gave imidazo derivative **10a**, whose NMR spectrum showed a sharp singlet for one proton at δ 9.13 as a imine proton.[8]

In conclusion, we reported the synthesis of new 10-amino-5,6,7,9-tetrahydro-1-thia-4,9-diazacycl ohepta[*f*]inden-8-one derivatives (**4**), as potential AChE inhibitors, from **8** using Schmit reaction.

EXPERIMENTAL

All products were characterized by IR, ^1H NMR, MS and elemental analysis. Melting points were measured by using the 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). IR spectra were recorded on the FT-IR Brucker Tensor 27. The ^1H 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 (δ). 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 10-amino-5,6,7,9-tetrahydro-1-thia-4,9-diazacyclohepta[*f*]inden-8-one derivatives (4):

To a solution of **8** (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 solution was stirred for 5 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.

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

Yield 58%; mp 231 °C (dec); IR (KBr): 1670 cm^{-1}; ^1H NMR (DMSO-d_6): δ 8.71 (s, 1H, NH), 7.78 (d, J = 5.9 Hz, 1H, thiophene H-2), 7.24 (d, J = 5.9 Hz, 1H, H-3), 6.18 (s, 2H, NH_2), 2.78 (m, 2H, H-5), 2.13-2.07 (m, 4H, H-6 and H-7); MS: (m/z) 233 (M^+), 204, 190. *Anal.* Calcd. for $C_{11}H_{11}N_3OS$: C, 56.63; H, 3.14; N, 18.01. Found: C, 56.50; H, 3.30; N, 18.22.

1,3,4,5-Tetrahydro-9-thia-1,2,6-triazacyclopenta[*d*]acenaphthylene (9a):

Yield 14%; mp 283-284 °C; ^1H NMR (DMSO-d_6): δ13.30 (s, 1H, NH), 7.91 (d, J = 5.9 Hz, 1H, thiophene H-8), 7.59 (d, J = 5.9 Hz, 1H, H-9), 3.00-2.94 (m, 4H, H-3 and H-5), 2.19 (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, 61.49; H, 4.10; N, 19.70.

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

Yield 52%; mp 227 °C (dec); ^1H NMR (DMSO-d_6): δ8.77 (s, 1H,NH), 7.76 (d, J = 5.9 Hz, 1H, thiophene H-2), 7.29 (d, J = 5.9 Hz, 1H, H-3), 6.18 (s, 2H, NH_2), 2.90 (s, 2H, H-5), 2.58 (s, 2H, H-7), 1.00 (s, 6H, diMe); MS: (m/z) 261 (M^+), 246, 218, 178, 135. *Anal.* Calcd. for $C_{13}H_{15}N_3OS$: C, 59.75; H, 5.78; N, 16.08. Found: C, 59.90; H, 5.59; N, 16.20.

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

Yield 62%; mp 196-197 °C; ^1H NMR (DMSO-d_6): δ8.94 (s, 1H,NH), 7.81 (d, J = 6.0 Hz, 1H, thiophene H-2), 7.29-7.22 (m, 6H, H-3 and phenyl), 6.27 (s, 2H, NH_2), 3.65 (m, 1H, H-6), 3.15 (m, 1H, H-5a), 2.98 (m, 1H, H-5b), 2.49 (m, 1H, H-7a), 2.29 (m, 1H, H-7b); MS: (m/z) 309 (M^+), 284, 179. *Anal.* Calcd. for $C_{17}H_{15}N_3OS$: C, 66.00; H, 4.89; N, 13.58. Found: C, 65.84; H, 4.73; N, 13.70.

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

Yield 44%; mp 169-171 °C; ^1H NMR (DMSO-d_6): δ 8.92 (s, 1H,NH), 7.81 (d, J = 6.0 Hz, 1H, thiophene H-2), 7.29 (d, J = 5.9 Hz, 1H, H-3), 7.25 (d, 2H, phenyl H-2'and H-6'), 7.09 (d, 2H, phenyl H-3'and H-5'), 6.26 (s, 2H, NH_2), 3.57 (m, 1H, H-6), 3.12 (m, 1H, H-5a), 2.96 (m, 1H, H-5b), 2.50 (m, 1H, H-7a), 2.27-2.20 (m, 4H, H-7b and Me); 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, 66.99; H, 5.48; N, 13.19.

4-*p*-Tolyl-1,3,4,5-tetrahydro-9-thia-1,2,6-triazacyclopenta[*d*]acenaphthylene (9d):

Yield 10%; mp 246-247 °C; ^1H NMR (DMSO-d_6): δ 13.60 (s, 1H, NH), 7.95 (d, J = 5.9 Hz, 1H, thiophene H-8), 7.34 (d, J = 5.9 Hz, 1H, H-9), 7.24 (d, 2H, phenyl H-2'and H-6'), 7.07 (d, 2H, phenyl H-3'and H-5'), 3.40 (m, 1H, H-4), 3.11-2.95 (m, 4H, H-3 and H-5), 2.22(s, 3H, Me); MS: (m/z) 305 (M^-), 299, 286. *Anal.* Calcd. for $C_{18}H_{15}N_3S$: C,70.79; H, 4.95; N, 13.76. Found: C, 70.62; H, 4.76; N, 13.90.

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

Yield 65%; mp 189-190 °C; ^1H NMR (DMSO-d_6): δ 8.97 (s, 1H,NH), 7.83 (d, J = 5.9 Hz, 1H, thiophene H-2), 7.48 (d, 2H, phenyl H-3'and H-5'), 7.31 (d, 2H, phenyl H-2'and H-6'), 7.28 (d, J = 5.9 Hz, 1H, H-3), 6.35 (s, 2H, NH_2), 3.67 (m, 1H, H-6), 3.16 (m, 1H, H-5a), 2.98 (m, 1H, H-5b), 2.49 (m, 1H, H-7a), 2.28 (m, 1H, H-7b); MS: (m/z) 344 (M^+), 316, 300, 219, 180, 165. *Anal.* Calcd. for $C_{17}H_{14}ClN_3OS$: C, 59.39; H, 4.10; N, 12.22. Found: C, 59.22; H, 4.28; N, 12.10.

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

Yield 56%; mp 252-254 °C; ^1H NMR (DMSO-d_6): δ 8.96 (s, 1H,NH), 7.82 (d, J = 5.9 Hz, 1H,

thiophene H-2). 7.47 (d, 2H, phenyl H-3`and H-5`). 7.31 (d, 2H, phenyl H-2`and H-6`). 7.27 (d, J = 5.9 Hz, 1H, H-3). 6.30 (s, 2H, NH_2), 3.66 (m, 1H, H-6), 3.15 (m, 1H, H-5a). 2.96 (m, 1H, H-5b). 2.49 (m, 1H, H-7a). 2.26 (m, 1H, H-7b); MS: (m/z) 388 (M^+). 360, 218, 190, 179. *Anal.* Calcd. for $C_{17}H_{14}BrN_3OS$: C, 52.59; H, 3.63; N, 10.82. Found: C, 52.75; H, 3.48; N, 11.01.

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