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Synthesis of New 4-Amino-2,3,5,6,7,8-hexahydro-1*H*-10-thia-9-aza-pentaleno[1,2-*b*]naphthalen-5-ol Derivatives

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To date the representative therapeutic drugs most commonly used for treating Alzheimer's disease (AD) are acetylcholinesterase (AChE) inhibitors[1,2] such as tacrine (**1a**),[3] donepezil,[4] rivastigmine,[5] and galantamine.[6] Such inhibitors were indeed shown to improve the cognitive abilities of early-stage AD patients by inhibiting acetylcholine degradation in the central nervous system. The interest for AChE inhibitors has been greatly renewed due to the discoveries that AChE could play a key role in the development of the senile plaques, by accelerating β-amyloid peptide (Aβ) deposition in AD brain.[7,8] Moreover, AChE inhibitors were found to have another cholinergic effects such as the decrease and amelioration of the neuropsychiatric symptoms in AD, especially apathy and visual hallucinations.[9,10] Hepatotoxicity, gastrointestinal effects and poor selectivity of these drugs, however, have limited their use, and current research is focused on developing new AChE inhibitors with improved activity and reduced adverse side effects. Various analogues with modified structure of **1a** or **1b** have been synthesized and studied for this purpose.[11] For instance, compounds **2** and **3** as shown Figure 1 have been synthesized and investigated for the development of new AChE inhibitors.[12,13] Recently, we have also reported the synthesis of new thieno[2,3-*b*]quinolinol derivatives **4**[14] and thieno[3,2-*b*]quinolinol derivatives **5**[15] as potential AChE inhibitors.

As a continuation of our works for biologically active heterocyclic compounds[16] we now describe the synthesis of new 2,3,5,6,7,8-hexahydro-1*H*-10-thia-9-aza-pentaleno[1,2-*b*]naphthalen-4-ylamine derivatives (**6**) and 4-amino-2,3,5,6,7,8-hexahydro-1*H*-10-thia-9-aza-pentaleno[1,2-*b*]naphthalen-5-ol derivatives (**7**), which are structurally related to **2** and **4** as one of tetracyclic skeleton. Taking into account the concept of bioisosterism and the structural change to improve intrinsic pharmacological activity or selectivity, compounds **6** and **7** were prepared by incorporating cyclopentylthiophene and substituted cyclohexane or cyclohexanol ring instead of benzene and cyclohexane moiety present in **1**.

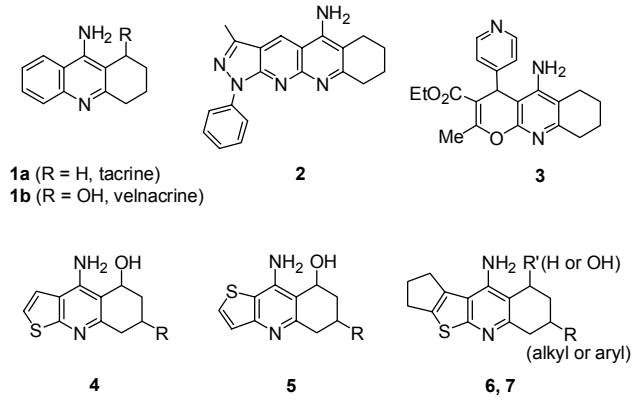
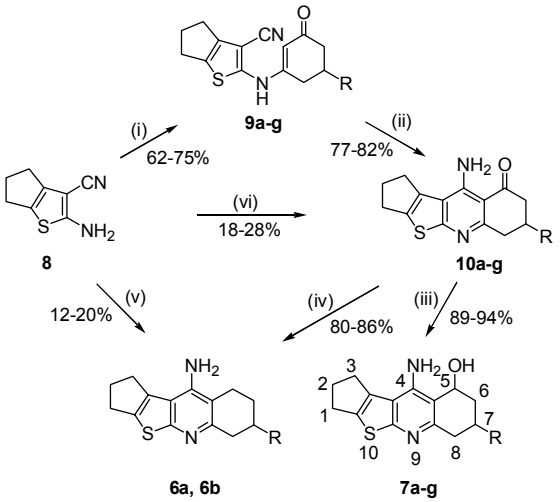


Figure 1. Tacrine (**1a**) and its analogs.

As shown in Scheme 1, the synthetic route to **6a**, **6b** and **7a-g** is similar in many respects to the one used for the synthesis of compound **4**[14,15] except the starting material **8**. The synthesis started from 2-amino-5,6-dihydro-4*H*-cyclopenta[b]thiophene **8** which was prepared from the reaction of cyclopentanone, malonitrile and sulfur using modified Gewald reaction.[17] The thiophene compound **8** was condensed with cyclohexan-1,3-dione or 5-substituted cyclohexan-1,3-diones in refluxing toluene in the presence of *p*-toluenesulfonic acid to give the corresponding enamino ketones **9a-g** in moderate yield. These enamino ketones were then cyclized in refluxing THF in the presence of potassium carbonate and cuprous chloride to give thienoquinolinones **10a-g**. A stoichiometric cuprous chloride has to be used to run the reaction effectively and to get a higher yield. The reductive deoxygenation of **10a** and **10b** was efficiently accomplished with ^{t}BuNH$_2$-BH$_3$ and alu-



Scheme 1. Synthesis of **6a**, **6b** and **7a-g**. Reagent and conditions; (i) cyclohexan-1,3-diones, *p*-TsOH/toluene, reflux; (ii) K_2CO_3, CuCl/THF, reflux; (iii) $LiAlH_4$/THF, H^+, 30% NaOH, rt; (iv) ^{t}BuNH$_2$-BH$_3$, $AlCl_3$/methylene chloride, 0 °C; (v) cyclohexanone, $AlCl_3$, DCE, reflux; (vi) cyclohexan-1,3-dione, $AlCl_3$, DCE, reflux

minum trichloride in methylene chloride at 0 °C to afford **6a** and **6b**, respectively.[18] This procedure gave a higher product yield than that of modified Wolff-Kishner reduction[19] (hydrazine hydrate and KOH under hot ethylene glycol) we have previously used.[14,15] The compound **10a-g** were also reduced easily by lithium aluminum hydride in dry THF to give the target compounds **7a-g**, thiophene analogues of Velnacrine **1b** in good yield. The structure of compounds **7a-g** was characterized by their spectral data and elemental analysis. The compounds **7c-g** were formed with two diastereomers, and major ones were products with *cis* configuration between phenyl and hydroxyl group. The hydrogen of C-5 of **7c-g** that exists in a quasi-axial conformation on a half-chair ring appeared as a double doublet ($J_{5,6}$ = 6.0 and 11.0 Hz), not as a triplet, at δ 5.10 in ^{1}H NMR spectra, as it is shown in *cis*-3-phenyl-1-tetralin-1-ol. Since the protons on the alicyclic rings of **7c-g** were resolved at 300 MHz, it is possible to determine the coupling constants by first-order analysis and to assign the relative stereochemistry of two diastereomers.[20]

In another way, the direct synthesis of **6a**, **6b** or **10a**, **10b** from **8** was attempted by using Freidländer reaction[21] (under dry 1,2-dichloroethane as solvent and aluminum trichloride as promoter) of **8** with cyclohexanone or cyclohexan-1,3-dione derivatives. The expected compounds were obtained, but in low yield. For instance, the reaction of **8** with cyclohexanone or cyclohexan-1,3-dione by Freidländer's condensation gave **6a** or **10a** in 20% and 18% yield, respectively. The following reduction of **10a** with ^{t}BuNH$_2$-BH$_3$/aluminum trichloride or with lithium aluminum hydride provided **6a** or **7a**. Attempts to increase the yield of Freidländer's condensation by variation of the reaction time or the ratio of reagents were fruitless. But this synthetic way we report here might be useful and alternative direct synthetic route to compounds **6a**, **6b** and **7a-g** in spite of low yield when compared with the one we have previously used.[14,15]

In conclusion, we reported the synthesis of new 2,3,5,6,7,8-hexahydro-1*H*-10-thia-9-aza-pentaleno[1,2-*b*]naphthalen-4-ylamine derivatives (**6a**, **6b**) and 4-amino-2,3,5,6,7,8-hexahydro-1*H*-10-thia-9-aza-pentaleno[1,2-*b*]naphthalen-5-ol derivatives (**7a-g**) in two ways as potential AChE inhibitors. The AChE inhibition study of these compounds is underway and will be reported elsewhere.

Experimental Section

Melting points were determined in capillary tubes on Büchi apparatus and are uncorrected. Each compound of the reactions was checked on thin-layer chromatograpohy of Merck Kieselgel 60F$_{254}$ and purified by column chromatograpohy Merck silica gel (70 - 230 mesh). The ^{1}H-NMR spectra were recorded on Bruker DRX-300 FT-NMR spectrometer (300 MHz) with Me$_4$Si 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 2-(3-Oxo-cyclohex-1-enylamino)-5,6-dihydro-4*H*-cyclopenta[*b*]thiophene-3-carbonitrile Derivatives (9a-g). A suspension of 2-amino-5,6-dihydro-4*H*-cyclopenta[*b*]thiophene-3-carbonitrile (0.03 mole), the appropriate 1,3-cyclohexanedione (0.03 mole) and *p*-toluenesulfonic acid monohydrate (0.10 g) in dry toluene (20 mL) was refluxed for 7 - 8 hours, and the water was collected in a Dean-Stark trap. After cooling, the reaction mixture was filtered off. The filtrate was evaporated to dryness, and the residue was chromatographed on a silica gel column by eluting with a 20:80 v/v ethyl acetate/chloroform mixture.

2-(3-Oxo-cyclohex-1-enylamino)-5,6-dihydro-4*H*-cyclopenta[*b*]thiophene-3-carbonitrile (9a): Yield 65%; mp 191 - 192 °C; ^{1}H NMR (CDCl$_3$) δ 6.56 (s, 1H, NH), 5.63 (s, 1H, vinyl proton), 2.90 (t, 2H), 2.82 (t, 2H), 2.54 (t, 2H), 2.48-2.37 (m, 4H), 2.07 (q, 2H). MS (*m*/*z*) 258 (M$^+$), 243, 229, 163. *Anal.* Calcd. for $C_{14}H_{14}N_2OS$: C, 65.09; H, 5.46; N, 10.84. Found: C, 65.24; H, 5.58; N, 10.64.

2-(5,5-Dimethyl-3-oxo-cyclohex-1-enylamino)-5,6-dihydro-4*H*-cyclopenta[*b*]thiophene-3-carbonitrile (9b): Yield 62%; mp 187 - 188 °C; ^{1}H NMR (CDCl$_3$) δ 6.54 (s, 1H, NH), 5.62 (s, 1H, vinyl proton), 2.90 (t, 2H), 2.84 (t, 2H), 2.46 (q, 2H), 2.38 (s, 2H), 2.25 (s, 2H), 1.12 (s, di-Me). MS (*m*/*z*) 286 (M$^+$), 271, 230, 201, 174. *Anal.* Calcd. for $C_{16}H_{18}N_2OS$: C, 67.10; H, 6.33; N, 9.78. Found: C, 67.28; H, 6.48; N, 9.60.

2-(3-Oxo-5-phenyl-cyclohex-1-enylamino)-5,6-dihydro-4*H*-cyclopenta[*b*]thiophene-3-carbonitrile (9c): Yield 70%; mp 187 - 188 °C; ^{1}H NMR (CDCl$_3$) δ 7.43 (m, 2H), 7.40 (m, 3H), 6.67 (s, 1H, NH), 5.69 (s, 1H, vinyl proton), 3.38 (m, 1H), 2.83-2.75 (m, 5H), 2.70-2.61 (m, 3H), 2.40-2.35 (m, 2H). MS (*m*/*z*) 334 (M$^+$), 305, 230, 204, 163. *Anal.* Calcd. for $C_{20}H_{18}N_2OS$: C, 71.83; H, 5.42; N, 8.38. Found: C, 71.69; H, 5.24; N, 8.52.

2-(3-Oxo-5-*p*-tolyl-cyclohex-1-enylamino)-5,6-dihydro-4*H*-cyclopenta[*b*]thiophene-3-carbonitrile (9d): Yield 66%; mp 220 - 222 °C; ^{1}H NMR (CDCl$_3$) δ 7.25-7.15 (m, 4H), 6.47 (s, 1H, NH), 5.69 (s, 1H, vinyl proton), 3.40 (m, 1H), 2.90-2.86 (m, 2H), 2.83-2.79 (m, 3H), 2.70-2.65 (m, 3H), 2.42-2.38 (m, 2H). MS (*m*/*z*) 348 (M$^+$), 319, 305, 230, 204, 163. *Anal.* Calcd. for $C_{21}H_{20}N_2OS$: C, 72.38; H, 5.78; N, 8.04. Found: C, 72.55; H, 5.60; N, 8.12.

2-[5-(4-Bromophenyl)-3-oxo-cyclohex-1-enylamino]-5,6-dihydro-4*H*-cyclopenta[*b*]thiophene-3-carbonitrile (9e): Yield 73%; mp 260 - 262 °C; ^{1}H NMR (CDCl$_3$) δ 7.48 (d, 2H), 7.15 (d, 2H), 6.55 (s, 1H, NH), 5.68 (s, 1H, vinyl proton), 3.38 (m, 1H), 2.91-2.79 (m, 5H), 2.68-2.64 (m, 3H), 2.43-2.39 (m, 2H). MS (*m*/*z*) 413 (M$^+$), 412, 230, 211, 184, 163. *Anal.* Calcd. for $C_{20}H_{17}BrN_2OS$: C, 58.12; H, 4.15; N, 6.78. Found: C, 58.30; H, 4.01; N, 6.90.

2-[5-(4-Chlorophenyl)-3-oxo-cyclohex-1-enylamino]-5,6-dihydro-4*H*-cyclopenta[*b*]thiophene-3-carbonitrile (9f): Yield 75%; mp 241 - 243 °C; ^{1}H NMR (CDCl$_3$) δ 7.35 (d, 2H), 7.01 (d, 2H), 6.36 (s, 1H, NH), 5.65 (s, 1H, vinyl proton), 3.36 (m, 1H), 2.90-2.74 (m, 5H), 2.66-2.62 (m, 3H), 2.42-2.39 (m, 2H). MS (*m*/*z*) 368 (M$^+$), 368, 230, 204, 163. *Anal.* Calcd. for $C_{20}H_{17}ClN_2OS$: C, 65.12; H, 4.64; N, 7.59. Found: C, 64.98; H, 4.46; N, 7.66.

2-[5-(4-Methoxyphenyl)-3-oxo-cyclohex-1-enylamino]-5,6-dihydro-4*H*-cyclopenta[*b*]thiophene-3-carbonitrile (9g): Yield 70%; mp 228 - 230 °C; ^{1}H NMR (CDCl$_3$) δ 7.19 (d, 2H), 6.90 (d, 2H), 6.63 (s, 1H, NH), 5.68 (s, 1H, vinyl proton), 3.38 (m,

1H), 2.93-2.76 (m, 5H), 2.64-2.60 (m, 3H), 2.45-2.40 (m, 2H). MS (*m*/*z*) 364 (M^+), 230, 163, 134, 119, 91. *Anal.* Calcd. for $C_{21}H_{20}N_2O_2S$: C, 69.21; H, 5.53; N, 7.69. Found: C, 69.33; H, 5.60; N, 7.51.

General Procedure for the Preparation of 4-Amino-1,2,3,6,7,8-hexahydro-10-thia-9-aza-pentaleno[1,2-*b*]naphthalen-5-one Derivatives (10a-g). A suspension of the appropriate 2-(3-oxo-cyclohex-1-enylamino)-5,6-dihydro-4*H*-cyclopenta-[*b*]thiophene-3-carbonitrile (0.01 mole), K_2CO_3 (0.01 mole) and CuCl (0.01 mole) in dry THF (20 mL) was refluxed for 12 hours. After completion of reaction, the warm reaction solution was filtered off. The filtrate was evaporated to dryness, and the residue was chromatographed on a silica gel column by eluting with a 30:70 v/v ethyl acetate/chloroform mixture.

4-Amino-1,2,3,6,7,8-hexahydro-10-thia-9-aza-pentaleno-[1,2-*b*]naphthalen-5-one (10a): Yield 79%; mp 199 °C (dec); ^{1}H NMR ($CDCl_3$) δ 3.31 (t, 2H), 3.11 (t, 2H), 2.98 (t, 2H), 2.67 (t, 2H), 2.56 (q, 2H), 2.19 (q, 2H). MS (*m*/*z*) 258 (M^+), 243, 57. *Anal.* Calcd. for $C_{14}H_{14}N_2OS$: C, 65.09; H, 5.46; N, 10.84. Found: C, 65.18; H, 5.60; N, 10.69.

4-Amino-7,7-dimethyl-1,2,3,6,7,8-hexahydro-10-thia-9-aza-pentaleno[1,2-*b*]naphthalen-5-one (10b): Yield 77%; mp 213 - 214 °C; ^{1}H NMR ($CDCl_3$) δ 3.09-3.02 (m, 6H), 2.60-2.51 (m, 4H), 1.12 (s, 6H). MS (*m*/*z*) 286 (M^+), 271, 230, 201. *Anal.* Calcd. for $C_{16}H_{18}N_2OS$: C, 67.10; H, 6.33; N, 9.78. Found: C, 67.24; H, 6.39; N, 9.60.

4-Amino-7-phenyl-1,2,3,6,7,8-hexahydro-10-thia-9-aza-pentaleno[1,2-*b*]naphthalen-5-one (10c): Yield 80%; mp 219 - 220 °C; ^{1}H NMR ($CDCl_3$) δ 7.39-7.24 (m, 5H), 3.46 (m, 1H), 3.37-3.22 (m, 2H), 3.13 (t, 2H), 3.00 (t, 2H), 2.94-2.81 (m, 2H), 2.62-2.54 (q, 2H). MS (*m*/*z*) 334 (M^+), 271, 201, 57. *Anal.* Calcd. for $C_{20}H_{18}N_2OS$: C, 71.83; H, 5.42; N, 8.38. Found: C, 71.99; H, 5.30; N, 8.26.

4-Amino-7-*p*-tolyl-1,2,3,6,7,8-hexahydro-10-thia-9-aza-pentaleno[1,2-*b*]naphthalen-5-one (10d): Yield 78%; mp 254 - 256 °C; ^{1}H NMR ($CDCl_3$) δ 7.26-7.18 (m, 4H), 3.48 (m, 1H), 3.35-3.20 (m, 2H), 3.11 (t, 2H), 2.99 (t, 2H), 2.92-2.80 (m, 2H), 2.60-2.52 (q, 2H). MS (*m*/*z*) 348 (M^+), 320, 230, 201. *Anal.* Calcd. for $C_{21}H_{20}N_2OS$: C, 72.38; H, 5.78; N, 8.04. Found: C, 72.49; H, 5.64; N, 8.15.

4-Amino-7-(4-bromophenyl)-1,2,3,6,7,8-hexahydro-10-thia-9-aza-pentaleno[1,2-*b*]naphthalen-5-one (10e): Yield 80%; mp 222 - 224 °C; ^{1}H NMR ($CDCl_3$) δ 7.50 (d, 2H), 7.16 (d, 2H), 3.46 (m, 1H), 3.34-3.22 (m, 2H), 3.10 (t, 2H), 2.97 (t, 2H), 2.90-2.80 (m, 2H), 2.58-2.49 (q, 2H). MS (*m*/*z*) 413 (M^+), 412, 257, 243, 230, 201. *Anal.* Calcd. for $C_{20}H_{17}BrN_2OS$: C, 58.12 ; H, 4.15; N, 6.78. Found: C, 58.29; H, 4.00; N, 6.70.

4-Amino-7-(4-chlorophenyl)-1,2,3,6,7,8-hexahydro-10-thia-9-aza-pentaleno[1,2-*b*]naphthalen-5-one (10f): Yield 82%; mp 233 - 235 °C; ^{1}H NMR ($CDCl_3$) δ 7.35 (d, 2H), 7.18 (d, 2H), 3.45 (m, 1H), 3.36-3.24 (m, 2H), 3.12 (t, 2H), 2.98 (t, 2H), 2.93-2.83 (m, 2H), 2.58-2.51 (q, 2H). MS (*m*/*z*) 368 (M^+), 353, 339, 243, 230, 201. *Anal.* Calcd. for $C_{20}H_{17}ClN_2OS$: C, 65.12; H, 4.64; N, 7.59. Found: C, 65.05; H, 4.50; N, 7.72.

4-Amino-7-(4-methoxyphenyl)-1,2,3,6,7,8-hexahydro-10-thia-9-aza-pentaleno[1,2-*b*]naphthalen-5-one (10g): Yield 79%; mp 200 - 201 °C; ^{1}H NMR ($CDCl_3$) δ 7.22 (d, 2H), 6.90 (d, 2H), 3.46 (m, 1H), 3.37-3.20 (m, 2H), 3.12 (t, 2H), 2.99 (t, 2H), 2.92-2.80 (m, 2H), 2.63-2.53 (q, 2H). MS (*m*/*z*) 364 (M^+), 349, 335, 230, 201, 174. *Anal.* Calcd. for $C_{21}H_{20}N_2O_2S$: C, 69.21; H, 5.53; N, 7.69. Found: C, 69.29; H, 5.70; N, 7.55.

General Procedure for the Preparation of 4-Amino-2,3,5,6,7,8-hexahydro-1*H*-10-thia-9-aza-pentaleno[1,2-*b*]naphthalen-5-ol Derivatives (7a-g). A solution of $LiAlH_4$ in Et_2O (3.0 mL of 1.0 M, 3.0 mmole) was added dropwise to a solution of the appropriate 4-amino-1,2,3,6,7,8-hexahydro-10-thia-9-aza-pentaleno[1,2-*b*]naphthalen-5-one (2.0 mmole) in dry THF (10 mL) maintained at 0 °C under nitrogen. After stirring at room temperature for 5 hours, the reaction solution was quenched by adding 10% HCl, followed by washing with 30% NaOH to make free base and extracted with chloroform. The combined organic layers were evaporated to dryness, and the residue was purified by silica gel column chromatography eluting with a 50:50 v/v ethyl acetate/chloroform mixture.

4-Amino-2,3,5,6,7,8-hexahydro-1*H*-10-thia-9-aza-pentaleno[1,2-*b*]naphthalen-5-ol (7a): Yield 89%; mp 186 - 187 °C; ^{1}H NMR ($CDCl_3$) δ 5.18 (s, 2H, NH_2), 4.98 (m, 1H), 3.11 (t, 2H), 3.07 (t, 2H), 2.76-2.55 (m, 2H), 2.49 (q, 2H), 2.10-1.93 (m, 4H). MS (*m*/*z*) 260 (M^+), 242, 227. *Anal.* Calcd. for $C_{14}H_{16}N_2OS$: C, 64.59; H, 6.19; N, 10.76. Found: C, 64.66; H, 6.02; N, 10.88.

4-Amino-7,7-dimethyl-2,3,5,6,7,8-hexahydro-1*H*-10-thia-9-aza-pentaleno[1,2-*b*]naphthalen-5-ol (7b): Yield 90%; mp 226 - 227 °C; ^{1}H NMR ($CDCl_3$) δ 5.37 (s, 2H, NH_2), 5.11 (dd, 1H), 3.13 (t, 2H), 3.06 (t, 2H), 2.78-2.58 (m, 2H), 2.50 (q, 2H), 2.12 (m, 1H), 1.67 (m, 1H), 1.12 (s, 3H), 0.95 (s, 3H). MS (*m*/*z*) 288 (M^+), 270, 255, 240, 227. *Anal.* Calcd. for $C_{16}H_{20}N_2OS$: C, 66.63; H, 6.99; N, 9.71. Found: C, 66.75; H, 7.10; N, 9.58.

4-Amino-7-phenyl-2,3,5,6,7,8-hexahydro-1*H*-10-thia-9-aza-pentaleno[1,2-*b*]naphthalen-5-ol (7c): Yield 94%; mp 198 - 200 °C; ^{1}H NMR ($CDCl_3$) δ 7.35-7.24 (m, 5H), 5.35 (s, 2H, NH_2), 5.10 (dd, 1H), 3.14-3.07 (m, 5H), 3.01-2.95 (t, 2H), 2.65-2.50 (m, 3H), 2.08-2.04 (m, 1H). MS (*m*/*z*) 336 (M^+), 306, 238, 111, 71, 64. *Anal.* Calcd. for $C_{20}H_{20}N_2OS$: C, 71.40; H, 5.99; N, 8.33. Found: C, 71.52; H, 6.10; N, 8.15.

4-Amino-7-*p*-tolyl-2,3,5,6,7,8-hexahydro-1*H*-10-thia-9-aza-pentaleno[1,2-*b*]naphthalen-5-ol (7d): Yield 89%; mp 210 - 212 °C; ^{1}H NMR ($CDCl_3$) δ 7.23 (d, 2H), 7.15 (d, 2H), 5.40 (s, 2H, NH_2), 5.11 (dd, 1H), 3.15-3.08 (m, 5H), 3.00-2.91 (t, 2H), 2.62-2.47 (m, 3H), 2.32 (s, 3H), 2.06-1.98 (m, 1H). MS (*m*/*z*) 350 (M^+), 332, 230. *Anal.* Calcd. for $C_{21}H_{22}N_2OS$: C, 71.97; H, 6.33; N, 7.99. Found: C, 71.85; H, 6.44; N, 8.10.

4-Amino-7-(4-bromophenyl)-2,3,5,6,7,8-hexahydro-1*H*-10-thia-9-aza-pentaleno[1,2-*b*]naphthalen-5-ol (7e): Yield 92%; mp 207 - 209 °C; ^{1}H NMR ($CDCl_3$) δ 7.48 (d, 2H), 7.13 (d, 2H), 5.49 (s, 2H, NH_2), 5.09 (dd, 1H), 3.14-3.09 (m, 5H), 3.01-2.94 (t, 2H), 2.62-2.48 (m, 3H), 2.08-2.00 (m, 1H). MS (*m*/*z*) 415 (M^+), 398, 396, 316, 227. *Anal.* Calcd. for $C_{20}H_{19}Br\,N_2OS$: C, 57.84; H, 4.61; N, 6.74. Found: C, 57.92; H, 4.44; N, 6.88.

4-Amino-7-(4-chlorophenyl)-2,3,5,6,7,8-hexahydro-1*H*-10-thia-9-aza-pentaleno[1,2-*b*]naphthalen-5-ol (7f): Yield 87%; mp 202 - 203 °C; ^{1}H NMR ($CDCl_3$) δ 7.49 (d, 2H), 7.16 (d, 2H), 5.40 (s, 2H, NH_2), 5.11 (dd, 1H), 3.15-3.06 (m, 5H), 3.01-2.96 (t, 2H), 2.63-2.48 (m, 3H), 2.10-2.02 (m, 1H). MS (*m*/*z*) 370 (M^+), 227. *Anal.* Calcd. for $C_{20}H_{19}ClN_2OS$: C, 64.77; H, 5.16; N, 7.55. Found: C, 64.59; H, 4.88; N, 7.70.

4-Amino-7-(4-methoxyphenyl)-2,3,5,6,7,8-hexahydro-1*H*-

10-thia-9-aza-pentaleno[1,2-*b*]naphthalen-5-ol (7g): Yield 90 %; mp 206 - 207 °C; ^{1}H NMR ($CDCl_3$) δ 7.19 (d, 2H), 6.87 (d, 2H), 5.38 (s, 2H, NH_2), 5.10 (dd, 1H), 3.14-3.04 (m, 5H), 3.01-2.95 (t, 2H), 2.62-2.50 (m, 3H), 2.10-2.05 (m, 1H). MS (*m*/*z*) 366 (M^+), 348, 227, 121. *Anal.* Calcd. for $C_{21}H_{22}N_2O_2S$: C, 68.83; H, 6.05; N, 7.64. Found: C, 68.98; H, 6.19; N, 7.50.

General Procedure for the Preparation of 2,3,5,6,7,8-Hexahydro-1*H*-10-thia-9-aza-pentaleno[1,2-*b*]naphthalen-4-ylamine Derivatives (6a, 6b). To a solution of aluminum trichloride (10 mmole) in dry methylene chloride (20 mL) was added in one portion borane-*tert*-butylamine complex (20 mmole) at 0 °C under nitrogen. The mixture was stirred for 1 hour at 0 °C, and then a solution of **10a** or **10b** (5 mmole) in methylene chloride (10 mL) was added dropwise to the reaction solution. After stirring at room temperature for 12 hours, it quenched with dropwise addition of ice-cold water, basified and extracted with chloroform. The solvent was evaporated to dryness and the residue was then purified by silica gel column chromatography eluting with a 30:70 v/v ethyl acetate/chloroform mixture.

2,3,5,6,7,8-Hexahydro-1*H*-10-thia-9-aza-pentaleno[1,2-*b*]naphthalen-4-ylamine (6a): Yield 80%; mp 233 - 234 °C; ^{1}H NMR ($CDCl_3$) δ 4.41 (s, 2H, NH_2), 3.15-2.92 (m, 6H), 2.60-2.42 (m, 4H), 1.97-1.84 (m, 4H). MS (*m*/*z*) 244 (M^+), 243, 229, 216, 58. *Anal.* Calcd. for $C_{14}H_{16}N_2S$: C, 68.82; H, 6.60; N, 11.46. Found: C, 68.96; H, 6.49; N, 11.56.

7,7-Dimethyl-2,3,5,6,7,8-hexahydro-1*H*-10-thia-9-aza-pentaleno[1,2-*b*]naphthalen-4-ylamine (6b): Yield 86%; mp 238 - 240 °C; ^{1}H NMR ($CDCl_3$) δ 4.36 (s, 2H, NH_2), 3.08 (t, 2H), 2.96 (t, 2H), 2.70 (s, 2H), 2.54-2.47 (m, 4H), 1.66 (t, 2H), 1.01 (s, 6H). MS (*m*/*z*) 272 (M^+), 257, 216, 201. *Anal.* Calcd. for $C_{16}H_{20}N_2S$: C, 70.55; H, 7.40; N, 10.28. Found: C, 70.60; H, 7.27; N, 10.41.

General Procedure for the Preparation of Compounds (6a, 6b) and (10a, 10b) Using Freidländer Reaction. To a solution of aluminum trichloride (3.5 mmole for cyclohexanone, 7 mmole for cyclohexan-1,3-dione) in dry 1,2-dichloroethane (20 mL) was added compound **8** (2 mmole) and cyclic ketone (2 mmole) at room temperature under nitrogen. After refluxing for 24 hours, it quenched with dropwise addition of ice-cold water, basified with 10% NaOH and extracted with chloroform. The solvent was evaporated to dryness and the residue was then purified by silica gel column chromatography eluting with a 30:70 v/v ethyl acetate/chloroform mixture.

Yield **6a**: 20%, **6b**: 12%, **10a**: 18%, **10b**: 28%. The spectroscopical data of products were identical with those reported above.

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