Synthesis of 4-Amino-5,6,7,8-tetrahydrothieno[2,3-*b*]quinolin-5-ol Derivatives

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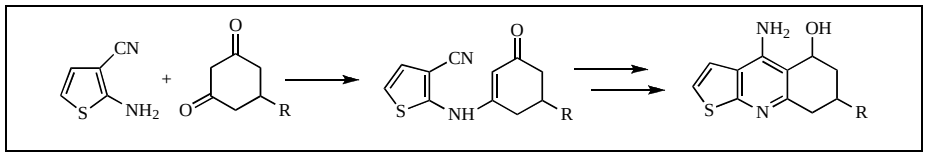
Received February 16, 2007



This paper describes the synthesis of 4-amino-5,6,7,8-tetrahydrothieno[2,3-*b*]quinolin-5-ol derivatives (**3a**-**h**) and 4-amino-5,6,7,8-tetrahydrothieno[2,3-*b*]quinoline (**8a**) in good yield by three-step procedures starting from 2-aminothiophene-3-carbonitrile and 5-substituted cyclohexane-1,3-dione.

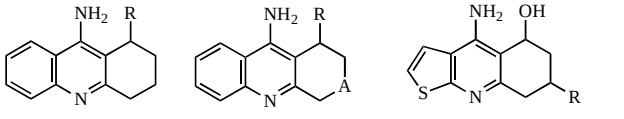
J. Heterocyclic Chem., **44**, 1439 (2007).

Alzheimer's disease (AD), the most common form of dementia among elderly people, is a progressive and degenerative 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]. One rationale therapeutic approach to amplify cholinergic neurotransmission is to inhibit acetyl- choline esterase (AChE). The AChE inhibitors currently on market for the symptomatic treatment of AD are Tacrine (THA, Cognex®) [4], Donepezil (Aricept®) [5], Rivastigmine (Exelon®) [6] and Galanthamine (Reminyl®) [7].

Various analogues and homologues of Tacrine (**1a**), the first AChE inhibitor approved by FDA for treatment of AD in 1993, have been synthesized and studied to enhance biological potency and to reduce serious side effects such as hepatotoxcity, which often forces patients to discontinue treatment. For instance, compounds **2a-b** [8,9] have been synthesized and investigated, which are structurally related to **1a** or Velnacrine (**1b**) [10], for the development of new AChE inhibitors.

Therefore, on the basis of the concept of bioisosterism as an approach for the improvement of biologically active drugs, it seemed to be suitable to prepare compounds **3a-h**, 4-amino-5,6,7,8-tetrahydrothieno[2,3-*b*]quinolin-5-ol derivatives, which have hitherto not been reported in the chemical literature. Only **3a** has ever been reported in a patent [11], but no spectroscopical data were represented. Compounds **3a-h** have the structure that was modified by replacement of a benzene ring by a thiophene in chemical mimic, and by changing the C-3 methylene unit of cylohexane ring in **1b**, known as a less toxic analogue of **1a**. This paper describes the facile synthesis of **3a-h** and **8a**, 4-amino-5,6,7,8-tetrahydrothieno[2,3-*b*]quinoline.

The synthetic routes to **3** are shown in Scheme 1. The starting material **4**, 2-aminothiophene-3-carbonitrile [12]



1 **2** **3**

a, Tacrine R = H
b, Velnacrine R = OH

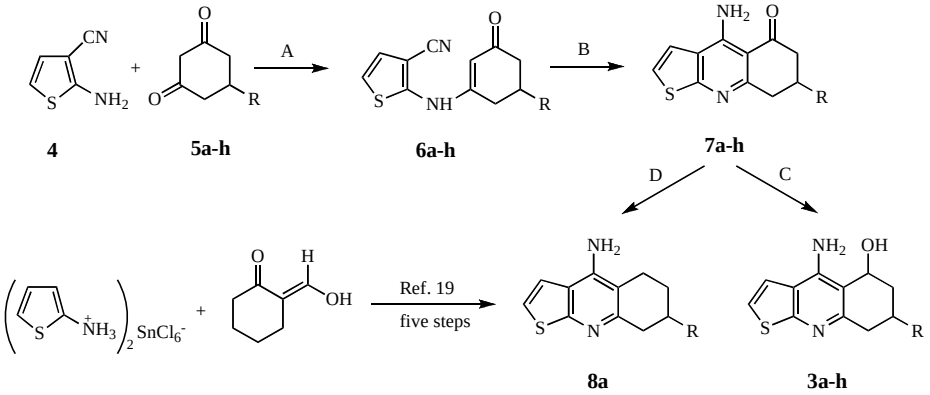
a, R = H, A = NR^1
b, R = OH, A = S

a: R = H, **b**: R= Me,
c: R = di-Me, **d**: R = *i*-Pr,
e: R = Ph, **f**: R = *p*-Tolyl,
g: R = *p*-ClPh, **h**: R = *p*-MeOPh

Figure 1

was obtained, according to modified Gewald reaction, by the reaction of 1,4-dithiane-2,5-diol and malononitrile with a catalytic amount of piperidine. Marked improvements in yield could be made when boiling acetonitrile as reaction solvent was used in place of DMF. Compound **5a-h**, 5-substituted cyclohexane-1,3-dione were prepared by previously known procedures [13,14] or purchased. The condensation of **4** with **5** under typical conditions for enamine formation (refluxing dry toluene in the presence of catalytic amounts of *p*-toluenesulfonic acid and following azeotropic removal of water by Dean-Stark trap) gave the enamino ketones **6a-h**, 2-(3-oxocyclohex-1-enylamino)thiophene-3-carbonitrile derivatives in good yield. The enamino ketones **6a-h** were then cyclized in refluxing THF in the presence of K_2CO_3 and CuCl to give thienoquinolinones **7a-h**, 4-amino-7,8-dihydrothieno[2,3-*b*]quinolin-5(6*H*)-one derivatives. It was noteworthy that a stoichiometric CuCl has to be used to run the reaction effectively and to obtain a higher yield, while, in the past, a catalytic amount of CuCl has been used as catalyst in this type of reaction [10,15-16]. The cyclization reaction of **6** moisten with small amounts of THF in the presence of K_2CO_3 and CuCl was also attempted by using the microwave assisted method [17], but it was found to yield instead an inseparable mixture of compounds.

Scheme 1



R = **a**: H, **b**: Me, **c** : di-Me, **d**: *i*-Pr,
e: Ph, **f**: *p*-Tolyl, **g**: *p*-ClPh,
h: *p*-MeOPh

Reagents: A: *p*-TsOH/toluene, reflux; B: K_2CO_3, CuCl/THF, reflux;
C: $LiALH_4$/THF, H^+, 30% NaOH, D: NH_2NH_2, KOH/ethylene glycol, reflux

The carbonyl of **7a** was transformed into methylene group by modified Wolff-Kishner reduction (hydrazine hydrate and KOH under hot ethylene glycol) [18] to give **8a** in 71% yield. Klemm *et al.* have first reported the preparation of compound **8a** in five steps [19], from the reaction of 2-hydroxymethylenecyclohexanone (which was stabilized by conversion to the methyl ether) with 2-aminothiophene salt, and successive *N*-oxidation, nitration and reduction reaction. However, the overall reaction pathway for **8a** was extremely poor (<1% overall yield) and not scaleable route. Thus, the synthetic way we report here might be very useful and new alternative synthetic route to **8a**.

Finally, the reduction reaction of compounds **7a-h** with lithium aluminum hydride in dry THF, followed by work up of aqueous acidification, and by washing with 30% NaOH solution in order to remove the aluminum salt from the product and to get free amine, provided the expected compounds **3a-h**, 4-amino-5,6,7,8-tetrahydrothieno[2,3-*b*]quinolin-5-ol derivatives in quantitative yields. The compounds **3b** and **3d-h** were formed with two diastereomers, and major products were *cis* compounds. Since the hydrogens on the alicyclic rings of **3b** and **3d-h** were resolved at 300 MHz, it is possible to determine all the coupling constants by first-order analysis and to assign the relative stereochemistry of two diastereomers [20]. The investigation for the AChE inhibition of all compounds is under way and will be published 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 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 (δ). The ir spectra were taken on a Perkin Elmer Paragon 500 FT-IR spectrophotometer. 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-Oxocyclohex-1-enylamino)thiophene-3-carbonitrile Derivatives (6a-h). A suspension of 2-aminothiophene-3-carbonitrile (0.03 mole), the appropriate 1,3-cyclohexanedione (0.03 mole) and *p*-toluene sulfonic acid monohydrate (0.10 g) in dry toluene (20 ml) was refluxed for 5-6 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-Oxocyclohex-1-enylamino)thiophene-3-carbonitrile (**6a**). This compound was obtained from 1,3-cyclohexanedione in 72% yield, mp 157-158°; ^{1}H-nmr (deuteriochloroform): 7.02 (s, 2H, thiophene protons), 5.79 (s, 1H, vinyl proton, H-2), 2.59 (t, 2H, H-6), 2.42 (t, 2H, H-4), 2.21 (quintet, 2H, H-5); ms: (m/z) 218 (M^+), 190, 123. *Anal.* Calcd. for $C_{11}H_{10}N_2OS$: C, 60.53; H, 4.62, N, 12.83. Found: C, 60.80; H, 4.51; N, 12.69.

2-(5-Methyl-3-oxocyclohex-1-enylamino)thiophene-3-carbonitrile (**6b**). This compound was obtained from 5-methylcyclohexane-1,3-dione in 83% yield, mp 155-156°; ^{1}H-nmr (deuteriochloroform): 7.01 (s, 2H, thiophene protons), 5.76 (s, 1H, vinyl proton, H-2), 2.58-2.22 (m, 4H, H-4 and H-6), 2.20-2.02 (m, 1H, H-5), 1.13 (d, 3H, CH_3); ms: (m/z) 232 (M^+), 190, 123. *Anal.* Calcd. for $C_{12}H_{12}N_2OS$: C, 62.04; H, 5.21, N, 12.06. Found: C, 61.86; H, 5.10; N, 11.89.

2-(5,5-Dimethyl-3-oxocyclohex-1-enylamino)thiophene-3-carbonitrile (**6c**). This compound was obtained from 5,5-dimethylcyclohexane-1,3-dione in 85% yield, mp 173-174°; ^{1}H-

nmr (deuteriochloroform): 7.01 (dd, 2H, thiophene protons), 5.81 (s, 1H, vinyl proton, H-2), 2.42 (s, 1H, H-6), 2.27 (s, 1H, H-4), 1.13 (s, 6H, $(CH_3)_2$); ms: (m/z) 246 (M^+), 190, 123, 67. *Anal.* Calcd. for $C_{13}H_{14}N_2OS$: C, 63.39; H, 5.73, N, 11.37. (m, 1H, H-6), Found: C, 63.46; H, 5.57; N, 11.22.

2-(5-Isopropyl-3-oxocyclohex-1-enylamino)thiophene-3-carbonitrile (**6d**). This compound was obtained from 5-isopropylcyclohexane-1,3-dione in 70% yield, mp 138-139°; ^{1}H-nmr (deuteriochlo- roform): 7.01 (s, 2H, thiophene protons), 5.77 (s, 1H, vinyl proton, H-2), 2.45 2.10 (dd, 1H, H-4), 1.65 (m, 2H, H-5 and isopropyl CH) 1.13 (s, 6H, $(CH_3)_2$); ms: (m/z) 260 (M^+), 190, 123. *Anal.* Calcd. for $C_{14}H_{16}N_2OS$: C, 64.58; H, 6.19, N, 10.76. Found: C, 63.16; H, 5.97; N, 10.84.

2-(3-Oxo-5-phenylcyclohex-1-enylamino)thiophene-3-carbonitrile (**6e**). This compound was obtained from 5-phenylcyclohexane-1,3-dione in 66% yield, mp 180-181°; ^{1}H-nmr (deuteriochloroform): 7.34 (s, 5H, phenyl protons), 7.04 (d, 2H, thiophene protons), 6.63 (s, 1H, vinyl proton, H-2), 3.45 (m, 1H, H-5), 2.94-2.59 (m, 4H, H-4 and H-6); ms: (m/z) 294 (M^+), 190, 131, 123. *Anal.* Calcd. for $C_{17}H_{14}N_2OS$: C, 69.36; H, 4.79, N, 9.52, S, 10.89. Found: C, 69.19; H, 4.89; N, 9.33, S, 10.75.

2-(3-Oxo-5-*p*-tolylcyclohex-1-enylamino)thiophene-3-carbonitrile (6f). This compound was obtained from 5-*p*-tolylcyclohexane-1,3-dione in 65% yield, mp 209-210°; ^{1}H-nmr (deuteriochloroform): 7.26-7.09 (m, 6H, phenyl and thiophene protons), 5.87 (s, 1H, vinyl proton, H-2), 3.42-2.65 (m, 5H, H-4, H-5 and H-6), 2.35(s, 3H, CH_3); ms: (m/z) 308 (M^+), 190, 123, 67. *Anal.* Calcd. for $C_{18}H_{16}N_2OS$: C, 70.10; H, 5.23, N, 9.80, S, 10.40. Found: C, 69.88; H, 5.39; N, 9.73, S, 10.22.

2-(5-(4-Chlorophenyl)-3-oxocyclohex-1-enylamino)thioph- ene-3-carbonitrile (**6g**). This compound was obtained from 5-(4-chlorophenyl)cyclohexane-1,3-dione in 75% yield, mp 165-166°; ^{1}H-nmr (deuteriochloroform): 7.35-7.29 (dd, 4H, phenyl protons), 7.05(s, 2H, thiophene protons), 6.63 (s, 1H, vinyl proton, H-2), 3.45 (m, 1H, H-5), 2.94-2.59 (m, 4H, H-4 and H-6); ms: (m/z) 328 (M^+), 190, 123. *Anal.* Calcd. for $C_{17}H_{13}ClN_2OS$: C, 62.10; H, 3.98, N, 8.52. Found: C, 61.84; H, 3.86; N, 8.59.

2-(5-(4-Methoxyphenyl)-3-oxocyclohex-1-enylamino)thiophene-3-carbonitrile (**6h**). This compound was obtained from 5-(4-methoxyphenyl)cyclohexane-1,3-dione in 70% yield, mp 179-180°; ^{1}H-nmr (deuteriochloroform): 7.15-6.86 (dd, 4H, phenyl protons), 6.99 (s, 2H, thiophene protons), 5.84 (s, 1H, vinyl proton, H-2), 3.77 (s, 1H, OCH_3), 3.45 (m, 1H, H-5), 2.81-2.64 (m, 4H, H-4 and H-6); ms: (m/z) 324 (M^+), 190, 123, 67. *Anal.* Calcd. for $C_{18}H_{16}N_2OS$: C, 66.64; H, 4.97, N, 8.64. Found: C, 66.84; H, 4.92; N, 8.55.

General Procedure for the Preparation of 4-Amino-7,8-dihydrothieno[2,3-*b*]quinolin-5(6*H*)-one Derivatives (**7a-h**). A suspension of the appropriate 2-(3-oxocyclohex-1-enylamino)thiophene-3-carbonitrile (0.01 mole), K_2CO_3 (2.0 mmole) and CuCl (0.01 mole) in dry THF(10 ml) was refluxed for 5-6 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-7,8-dihydrothieno[2,3-*b*]quinolin-5(6*H*)-one (**7a**).

This compound was obtained from 2-(3-oxocyclohex-1-enylamino)thiophene-3-carbonitrile in 60% yield, mp 200-201°; ^{1}H-nmr (deuteriochloroform): 7.25 and 7.20 (d and d, 2H, thiophene protons), 3.10 (t, 2H, H-8), 2.70 (t, 2H, H-6), 2.13 (quintet, 2H, H-7); ms: (m/z) 218 (M^+), 202. *Anal.* Calcd. for $C_{11}H_{10}N_2OS$: C, 60.53; H, 4.62, N, 12.83. Found: C, 60.44; H, 4.43; N, 12.89.

4-Amino-7,8-dihydro-7-methylthieno[2,3-*b*]quinolin-5(6*H*)-one (**7b**). This compound was obtained from 2-(5-methyl-3-oxocyclohex-1-enylamino)thiophene-3-carbonitrile in 68% yield, mp 219-220°; ^{1}H-nmr (deuteriochloroform): 7.26 and 7.20 (d and d, 2H, thiophene protons), 3.09 (d, 2H, H-8), 2.79 (d, 2H, H-6), 2.40 (m, 1H, H-7), 1.14 (d, 3H, CH_3); ms: (m/z) 232 (M^+), 216, 201. *Anal.* Calcd. for $C_{12}H_{12}N_2OS$: C, 62.04; H, 5.21, N, 12.06. Found: C, 61.88; H, 5.16; N, 12.14.

4-Amino-7,8-dihydro-7,7-dimethylthieno[2,3-*b*]quinolin-5-(6*H*)-one (**7c**). This compound was obtained from 2-(5,5-dimethyl-3-oxocyclohex-1-enylamino)thiophene-3-carbonitrile in 80% yield, mp 221-222°; ^{1}H-nmr (deuteriochloroform): 7.26 (d, 2H, thiophene protons), 2.98 (s, 2H, H-8), 2.55 (s, 2H, H-6), 1.11 (s, 6H, $(CH_3)_2$); ms: (m/z) 246 (M^+), 230, 216. *Anal.* Calcd. for $C_{13}H_{14}N_2OS$: C, 63.39; H, 5.73, N, 11.37. Found: C, 63.12; H, 5.79; N, 11.34.

4-Amino-7,8-dihydro-7-isopropylthieno[2,3-*b*]quinolin-5-(6*H*)-one (**7d**). This compound was obtained from 2-(5-isopropyl-3-oxocyclohex-1-enylamino)thiophene-3-carbonitrile in 70% yield, mp 172-173°; ^{1}H-nmr (deuteriochloroform): 7.21 (d, 2H, thiophene protons), 3.24 (d, 2H, H-8), 2.78 (d, 2H, H-6), 2.43 (m, 1H, H-7), 1.65 (m, 1H, isopropyl CH), 1.00 (s, 6H, $(CH_3)_2$); ms: (m/z) 260 (M^+), 244, 217. *Anal.* Calcd. for $C_{14}H_{16}N_2OS$: C, 64.58; H, 6.19, N, 10.76. Found: C, 64.62; H, 6.25; N, 10.87.

4-Amino-7,8-dihydro-7-phenylthieno[2,3-*b*]quinolin-5(6*H*)-one (**7e**). This compound was obtained from 2-(3-oxo-5-phenylcyclohex-1-enylamino)thiophene-3-carbonitrile in 65% yield, mp 227-228°; ^{1}H-nmr (deuteriochloroform): 7.38-7.22 (m, 7H, phenyl and thiophene protons), 3.46 (m, 1H, H-7), 3.29 (m, 2H, H-8), 2.94 (m, 2H, H-6); ms: (m/z) 294 (M^+), 278, 201. *Anal.* Calcd. for $C_{17}H_{14}N_2OS$: C, 69.36; H, 4.79, N, 9.52. Found: C, 69.22; H, 4.76; N, 9.49.

4-Amino-7,8-dihydro-7-*p*-tolylthieno[2,3-*b*]quinolin-5(6*H*)-one (**7f**). This compound was obtained from 2-(3-oxo-5-*p*-tolylcyclohex-1-enylamino)thiophene-3-carbonitrile in 75% yield, mp 225-226°; ^{1}H-nmr (deuteriochloroform): 7.42-7.20 (m, 6H, phenyl and thiophene protons), 3.48 (m, 1H, H-7), 3.34 (m, 2H, H-8), 2.90 (m, 2H, H-6), 2.35 (s, 3H, CH_3); ms: (m/z) 308 (M^+), 292, 201. *Anal.* Calcd. for $C_{18}H_{16}N_2OS$: C, 70.10; H, 5.23, N, 9.08. Found: C, 70.04; H, 5.22; N, 9.14.

4-Amino-7-(4-chlorophenyl)-7,8-dihydrolthieno[2,3-*b*]-quinolin-5(6*H*)-one (**7g**). This compound was obtained from 2-(5-(4-chlorophenyl)-3-oxo-cyclohex-1-enylamino)thiophene-3-carbonitrile in 70% yield, mp 222-223°; ^{1}H-nmr (deuteriochloroform): 7.34-7.23 (m, 6H, phenyl and thiophene protons), 3.48 (m, 1H, H-7), 3.36 (m, 2H, H-8), 2.91 (m, 2H, H-6); ms: (m/z) 328 (M^+), 312, 201. *Anal.* Calcd. for $C_{17}H_{13}ClN_2OS$: C, 62.10; H, 3.98, N, 8.52. Found: C, 61.88; H, 4.02; N, 8.44.

4-Amino-7,8-dihydro-7-(4-methoxyphenyl)thieno[2,3-*b*]-quinolin-5(6*H*)-one (**7h**). This compound was obtained from 2-(5-(4-methoxyphenyl)-3-oxo-cyclohex-1-enylamino)thio-phene-3-carbonitrile in 72% yield, mp 191-192°; ^{1}H-nmr (deuteriochloroform): 7.23 (d, 2H, thiophene protons), 6.90 (m, 4H, phenyl protons), 3.78 (s, 3H, OCH_3), 3.33 (s, 1H, H-7), 3.20 (d, 2H, H-8), 2.88 (d, 2H, H-6); ms: (m/z) 324 (M^+), 308 201. *Anal.* Calcd. for $C_{18}H_{16}N_2O_2S$: C, 66.64; H, 4.97, N, 8.64. Found: C, 66.57; H, 4.90; N, 8.47.

General Procedure for the Preparation of 4-Amino-5,6,7,8-tetrahydrothieno[2,3-*b*]quinolin-5-ol Derivatives (**3a-h**). A solution of $LiAlH_4$ in Et_2O (2.0 ml of 1.0 *M*, 2.0 mmole) was added dropwise to a solution of the appropriate 4-amino-7,8-dihydrothieno[2,3-*b*]quinolin-5(6*H*)-one (2.0 mmole) in dry THF (10 ml) maintained at 0° under nitrogen. After stirring at room temperature for 2-3 hours, the reaction solution was quenched by adding 10% HCl, followed by washing with 30% NaOH to make free base and extracted with ethyl acetate. The combined organic layers were evaporated to dryness, and the residue was purified by silica gel column chromatography eluting with a 40:60 v/v ethyl acetate/chloroform mixture.

4-Amino-5,6,7,8-tetrahydrothieno[2,3-*b*]quinolin-5-ol (**3a**). This compound was obtained from 4-amino-7,8-dihydro-thieno-[2,3-*b*]quinolin-5(6*H*)-one in 85% yield, mp 227-229° (dec) (lit [11] 226°); ^{1}H-nmr (dimethyl-d_6 sulfoxide): 7.49 (d, $J_{2,3}$ = 6 Hz, 1H, thiophene H-2), 7.30 (d, 1H, H-3), 4.96 (m, 1H, H-5), 4.72 (brs, 1H, exchanges with D_2O, OH), 2.62 (m, 2H, H-8), 2.04-1.74 (m, 4H, H-6 and H-7); ms: (m/z) 220 (M^+), 202, 201, 187. *Anal.* Calcd. for $C_{11}H_{12}N_2OS$: C, 59.97; H, 5.49, N, 12.72. Found: C, 60.28; H, 5.42; N, 12.84.

4-Amino-5,6,7,8-tetrahydro-7-methylthieno[2,3-*b*]quinolin-5-ol (**3b**). This compound was obtained from 4-amino-7,8-dihydro-7-methylthieno[2,3-*b*]quinolin-5(6*H*)-one in 92% yield, mp 158-159°; ^{1}H-nmr (dimethyl-d_6 sulfoxide): 7.51 (d, $J_{2,3}$ = 5.9 Hz, 1H, thiophene H-2), 7.30 (d, 1H, H-3), 4.96 (m, 1H, H-5), 2.81 (m, 2H, H-8), 2.40 (m, 1H, H-7), 1.45 (m, 2H, H-6), 1.08 (d, 3H, CH_3); ms: (m/z) 234 (M^+), 216, 201, 187. *Anal.* Calcd. for $C_{12}H_{14}N_2OS$: C, 61.51; H, 6.02, N, 11.96. Found: C, 61.33; H, 6.10; N, 12.20.

4-Amino-5,6,7,8-tetrahydro-7,7-dimethylthieno[2,3-*b*]-quinolin-5-ol (**3c**). This compound was obtained from 4-amino-7,8-dihydro-7,7-dimethylthieno[2,3-*b*]quinolin-5(6*H*)-one in 89% yield, mp 163-164°; ^{1}H-nmr (dimethyl-d_6 sulfoxide): 7.39 (d, $J_{2,3}$ = 5.9 Hz, 1H, thiophene H-2), 7.17 (d, 1H, H-3), 5.03 (m, 1H, H-5), 2.51 (d, 1H, AB system, H-8), 2.33 (d, 1H, AB system, H-8), 1.82 (dd, J = 6.0 and 13 Hz, 1H, H-6), 1.49 (dd, J = 5.5 and 13 Hz, 1H, H-6), 0.99 (s, 6H, $(CH_3)_2$); ms: (m/z) 248 (M^+), 230, 215. *Anal.* Calcd. for $C_{13}H_{16}N_2OS$: C, 62.87; H, 6.49, N, 11.28. Found: C, 62.72; H, 6.44; N, 11.40.

4-Amino-5,6,7,8-tetrahydro-7-isopropylthieno[2,3-*b*]quinolin-5-ol (**3d**). This compound was obtained from 4-amino-7,8-dihydro-7-isopropyllthieno[2,3-*b*]quinolin-5(6*H*)-one in 94% yield, mp 174-175°; ^{1}H-nmr (dimethyl-d_6 sulfoxide): 7.52 (d, $J_{2,3}$ = 5.9 Hz, 1H, thiophene H-2), 7.26 (d, 1H, H-3), 4.83 (m, 1H, H-5), 2.66 (d, 1H, AB system, H-8), 2.50 (d, 1H, AB system, H-8), 1.70-1.42 (m, 4H, H-6, H-7 and isopropyl CH), 0.99 (d, 6H, $(CH_3)_2$); ms: (m/z) 262 (M^+), 244, 229. *Anal.* Calcd. for $C_{14}H_{18}N_2OS$: C, 64.09; H, 6.91, N, 10.68. Found: C, 63.88; H, 6.94; N, 10.47.

4-Amino-5,6,7,8-tetrahydro-7-phenylthieno[2,3-*b*]quinolin-5-ol (**3e**). This compound was obtained from 4-amino-7,8-dihydro-7-phenylthieno[2,3-*b*]quinolin-5(6*H*)-one in 92% yield, mp 157-158°; ^{1}H-nmr (dimethyl-d_6 sulfoxide): 7.55 (d, $J_{2,3}$ = 5.9 Hz, 1H, thiophene H-2), 7.35-7.2 (m, 6H, H-3 and phenyl protons), 4.98 (m, 1H, H-5), 2.97 (m, 2H, H-8), 2.88 (d, 1H, H-7), 1.98 (m, 2H, H-6); ms: (m/z) 296 (M^+), 278, 263, 187. *Anal.* Calcd. for $C_{17}H_{16}N_2OS$: C, 68.89; H, 5.44, N, 9.45. Found: C, 69.02; H, 5.41; N, 9.60.

4-Amino-5,6,7,8-tetrahydro-7-*p*-tolylthieno[2,3-*b*]quinolin-5-ol (**3f**). This compound was obtained from 4-amino-7,8-dihydro-7-p-tolylthieno[2,3-*b*]quinolin-5(6*H*)-one in 94% yield, mp 138-140°; ^{1}H-nmr (dimethyl-d_6 sulfoxide): 7.55 (d, $J_{2,3}$ = 5.9 Hz, 1H, thiophene H-2), 7.10 (d, 1H, thiophene H-3), 7.00 (d, $J_{2',3'}$ = 7.5 Hz, 2H, phenyl H-2'), 6.68 (d, 2H, phenyl H-3'), 5.19 (m, 1H, H-5), 3.20 (s, 3H, CH3), 2.85-2.62 (m, 3H, H-7 and H-8), 1.83 (m, 2H, H-6); ms: (m/z) 310 (M^+), 292, 277. *Anal.* Calcd. for $C_{18}H_{18}N_2OS$: C, 69.65; H, 5.84, N, 9.02. Found: C, 69.48; H, 5.88; N, 9.18.

4-Amino-7-(4-chlorophenyl)-5,6,7,8-tetrahydrothieno[2,3-*b*]-quinolin-5-ol (**3g**). This compound was obtained from 4-amino-7-(4-chlorophenyl)-7,8-dihydrothieno[2,3-*b*]quinolin-5(6*H*)-one in 93% yield, mp 133-134°; ^{1}H-nmr (dimethyl-d_6 sulfoxide): 7.57-7.10 (m, 6H, thiophene and phenyl protons), 5.09 (m, 1H, H-5), 3.12-2.65 (m, 3H, H-7 and H-8), 1.98 (m, 2H, H-6); ms: (m/z) 330 (M^+), 302, 287. *Anal.* Calcd. for $C_{17}H_{15}ClN_2OS$: C, 61.72; H, 4.57, N, 8.47. Found: C, 61.55; H, 4.50; N, 8.60.

4-Amino-5,6,7,8-tetrahydro-7-(4-methoxyphenyl)thieno-[2,3-*b*]quinolin-5-ol (**3h**). This compound was obtained from 4-amino-7,8-dihydro-7-(4-methoxyphenyl)-thieno[2,3-*b*]quinolin-5(6*H*)-one in 90% yield, mp 136-137°; ^{1}H-nmr (dimethyl-d_6 sulfoxide): 7.54 (d, $J_{2,3}$ = 6.0 Hz, 1H, thiophene H-2), 7.33 (d, 1H, thiophene H-3), 7.24 (d, $J_{2',3'}$ = 7.5 Hz, 2H, phenyl H-2'), 6.90 (d, 2H, phenyl H-3'), 5.39 (m, 1H, H-5), 3.73 (s, 3H, OCH_3), 2.92-2.65 (m, 3H, H-7 and H-8), 1.92 (m, 2H, H-6); ms: (m/z) 326 (M^+), 308, 293. *Anal.* Calcd. for $C_{18}H_{18}N_2O_2S$: C, 66.23; H, 5.56, N, 8.58. Found: C, 66.01; H, 5.45; N, 8.66.

Preparation of 4-Amino-5,6,7,8-tetrahydrothieno[2,3-*b*]-quinoline (**8a**). A mixture of 0.65 g (3.0 mmole) of 4-amino-7,8-dihydro- thieno[2,3-*b*]quinolin-5(6*H*)-one (**7a**), 0.60 g (12.0 mmole) of hydrazine hydrate, and 0.67 g (12.0 mmole) of potassium hydroxide in 30 ml of ethylene glycol was refluxed for 8 hours. After the starting material was consumed, the reaction mixture was concentrated by removing water and ethylene glycol by distillation. The concentrate was allowed to reach room temperature and extracted repeatedly with chloroform. The organic extract was dried with magnesium sulfate and evaporated. The residue was purified with silica gel column chromatography eluting with a 30:70 v/v ethyl acetate/ chloroform mixture to give 0.43 g (71%) of **8a**, mp 150-151° (lit [19] 150-152°). The spectroscopical data were identical with those reported previously [19].

Acknowledgement. The authors thank KBSI(Korea Basic Science Institute) for providing mass and elemental analysis data.

REFERENCES AND NOTES

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