Synthesis of 9-Amino-5,6,7,8-tetrahydrothieno[3,2-*b*]quinoline and 9-Amino-5,6,7,8-tetrahydrothieno[3,2-*b*]quinolin-8-ol Derivatives

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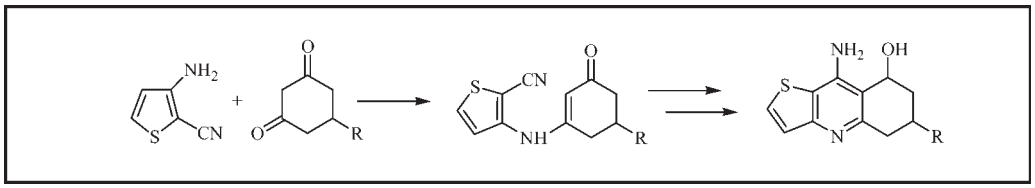

The synthesis of 9-amino-5,6,7,8-tetrahydrothieno[3,2-*b*]quinoline (**3**) and 9-amino-5,6,7,8-tetrahydrothieno[3,2-*b*]quinolin-5-ol derivatives (**4a–g**) in good yield by three-step procedures starting from 3-aminothiophene-2-carbonitrile and 5-substituted cyclohexane-1,3-dione is described.

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INTRODUCTION

Alzheimer's disease (AD) is characterized by the deficits in the cholinergic system [1,2] and presence of neurofibrillary tangles and amyloid plaques [3,4]. Since 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, cholinergic system became a target for the design of anti-Alzheimer drugs.

Acetylcholinesterase (AChE) inhibitors such as tacrine (**1a**) and donepezil by ''cholinergic hypothesis'' have been a useful and practical treatment for AD [5,6]. Moreover, the interest for AChE inhibitors has been greatly renewed due to the recent evidences that AChE might function to accelerate β-amyloid peptide (Aβ) formation and could play a role during amyloid deposition in AD brain [7,8].

We have recently reported the synthesis of new 4-amino-5,6,7,8-tetrahydrothieno[2,3-*b*]quinoline (**2a**) and 4-amino-5,6,7,8-tetrahydrothieno[2,3-*b*]quinolin-5-ol derivatives (**2b**) as potential AChE inhibitors as shown in Figure 1 [9]. Similar analogues based on the substituted thieno[3,2-*b*]quinoline and the thieno[2,3-*b*]quinoline moiety were also reported [10]. As a continuation of our previous works on thienopyridine and thienopyrimidine [9,11,12], we now report the synthesis of 9-amino-5,6,7,8-tetrahydrothieno[3,2-*b*]quinoline (**3**) and 9-amino-5,6,7,8-tetrahydrothieno[3,2-*b*]quinolin-8-ol (**4a–g**) derivatives, which have hitherto not reported.

For the synthesis of **3** and **4**, 3-aminothiophene-2-carbonitrile (**9**) as starting material was needed. However, the only synthetic method for **9** is associated with several drawbacks, such as use of toxic H_2S, low yield, and poor selectivity [13]. The reaction, in addition, was capricious, and further scale-up led reaction that would occasionally fail. Gronowitz et al. has prepared 3-bromothiophene-2-carbaldeyde (**6**) in low yield from 2,3-dibromothiophene through its successive treatment butyllithium and DMF [14]. As shown in Scheme 1, the aldehyde **6** could be obtained in high yield more conveniently and on a large scale by selective deprotonation at position-2 of 3-bromothiophene (**5**) with LDA followed by *N*-formylpiperidine quench [15]. The nucleophilic substitution of Br in **6** by sodium azide in DMPU afforded 3-azidothiophene-2-carbaldehyde (**7**) in good yield [16].

The conversion of aldehyde in **7** into nitrile was obtained in high yield by heating **7** with hydroxylamine-*O*-sulfonic acid in water. The use of hydroxylamine-*O*-sulfonic acid in water instead of hydroxylamine in dry alumina [17] could lead to a more efficient and clear route to 3-azidothiophene-2-carbonitrile (**8**). Finally, the reduction of azide in **8** to amine without affecting nitrile group could be achieved by hydrogenation over 10% Pd-carbon, not using toxic H_2S gas, to give **5** in high yield. Compounds **10a–g**, 5-substituted cyclohexane-1,3-dione, were prepared by previously known procedures [18,19] or purchased.

The synthetic routes to **3** and **4a–g** are shown in Scheme 1. The condensation of **9** with **10** in the presence of catalytic amounts of *p*-toluenesulfonic acid gave the corresponding enamines **11a–g**, 3-(3-oxo-cyclohex-1-enylamino)thiophene-2-carbonitrile derivatives in good yield. These enamins were then cyclized in refluxing THF in the presence of cuprous chloride and potassium carbonate to give thienoquinolinones **12a–g**, 9-amino-6,7-dihydro-5*H*-thieno[3,2-*b*]quinolin-8-one derivatives. It was noteworthy that a stoichiometric cuprous chloride has to be used to run the reaction effectively and to

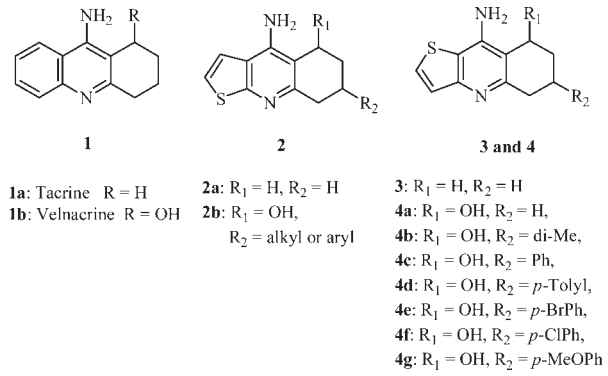


Figure 1. Tacrine and biosteric analogs.

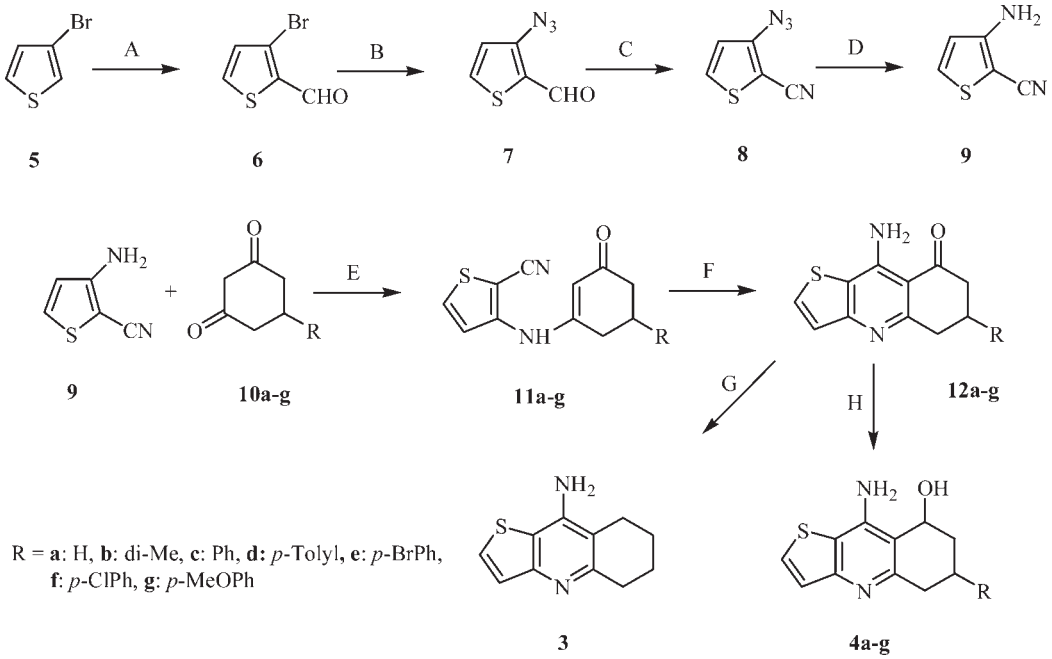
obtain a higher yield. The carbonyl of **12a** was transformed into methylene group by modified Wolff-Kishner reduction (hydrazine hydrate and KOH under hot ethylene glycol) [20] to give a new 9-amino-5,6,7,8-tetrahydrothieno[3,2-*b*]quinoline (**3**) in 57% yield. In another way, the reduction reaction of compounds **12a–g** 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 **4a–g**, 9-amino-5,6,7,8-tetrahydrothieno[3,2-*b*]quinolin-8-ol derivatives in quantitative yields. The compounds **4c–g** were formed with two diastereomers, and major products were *cis* compounds. Because the hydrogens on the alicyclic rings of **4c–g** 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 [21]. The product compounds **4a–g** were assayed on AChE inhibitory activity by the modified Ellman method [22]. None of these compounds showed an improved AChE inhibition ($IC_{50} \geq 100$ μ*M*) as compared with tacrine ($IC_{50} = 0.40$ μ*M*), with compound **4a** ($IC_{50} = 3.36$ μ*M*) being the most active. It showed that the introduction of alkyl or aryl group at the C-6 of cyclohexane ring resulted in marked decline in activity.

In conclusion, 9-amino-5,6,7,8-tetrahydrothieno[3,2-*b*]quinoline and 9-amino-5,6,7,8-tetrahydrothieno[3,2-*b*]quinolin-8-ol derivatives have been synthesized in good yield by three-step procedures.

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). Electron ionization mass spectra were recorded on a HP 59580 B spectrometer. Elemental analyses were performed on a Carlo Erba 1106 elemental analyzer.

Scheme 1. A: LDA/THF, *N*-formylpiperidne, 0°C; B: NaN_3/DMPU, 35°C; C: hydroxylamine-*O*-sulfonic acid/H_2O, 40–50°C; D: H_2, Pd-C/ EtOH, rt; E: *p*-TsOH/toluene, reflux; F: K_2CO_3, CuCl/THF, reflux; G: NH_2NH_2, KOH/ethylene glycol, reflux; H: $LiLH_4$/THF, H^+, 30% NaOH, rt.



Preparation of 3-aminothiophene-2-carbonitrile (9). 3-Bromothiophene (**5**) (0.3 mol) was added to a stirred solution of lithium diisopropylamide (0.3 mol) in dry THF (300 mL) at 0°C under nitrogen. After addition of *N*-formylpiperidine (0.3 mol), the reaction solution was stirred for 5 h. Then, it was poured into 30% aqueous ammonium chloride solution and extracted with ether. The combined extracts were dried over magnesium sulfate and evaporated to dryness to afford 3-bromothiophene-2-carbaldeyde (**6**) in 86% yield, bp 115–117°C at 10 mmHg (ref. 13, 113–115°C at 10 mmHg).

A suspension of **6** (0.2 mol) and sodium azide (0.8 mol) in DMPU (1,3-dimethyl-3,4,5,6-tetrahydro-2(*1H*)-pyrimidinone, 100 mL) was stirred at 50°C for 24 h. Then, it was poured into water and extracted with ether. The combined extracts were dried over magnesium sulfate and evaporated to dryness to give 3-azidothiophene-2-carbaldehyde (**7**) in 83% yield, mp 57–58°C (ref. 12, 56.6–57.2°C; ref. 15, 56–58°C).

A suspension of **7** (0.1 mol) and hydroxylamine-*O*-sulfonic acid (0.12 mol) in water (100 mL) was stirred at 50°C for 24 h. After cooling, the precipitate was filtered off and washed with water, giving 3-azidothiophene-2-carbonitrile (**8**) in 90% yield, mp 78–79°C (ref. 12, 77.5–79°C).

A suspension of **8** (0.05 mol) and 10% Pd-carbon (0.3 g) in ethanol (50 mL) was stirred under hydrogen at room temperature for 4 h. After completion of the reaction, the reaction mixture was filtered and evaporated to dryness to give 3-aminothiophene-2-carbonitrile (**9**) in 95% yield, mp 49–50°C (ref. 12, 47.5–50°C). ^{1}H NMR (deuteriochloroform): δ 7.28 (d, $J_{4,5}$ = 5.8 Hz, 1H, H-5), 6.54 (d, $J_{4,5}$ = 5.8 Hz, 1H, H-4), 4.48 (s, 2H, NH_2); ms: (*m*/*z*) 124 (M^+), 110. Anal. Calcd. for $C_5H_4N_2S$: C, 48.37; H, 3.25; N, 22.56. Found: C, 48.50; H, 3.40; N, 22.41.

General procedure for the preparation of 3-(3-oxocyclohex-1-enylamino)thiophene-2-carbonitrile derivatives (11a–g). A suspension of 3-aminothiophene-2-carbonitrile (0.03 mol), the appropriate 1,3-cyclohexanedione (0.03 mol) and *p*-toluene sulfonic acid monohydrate (0.10 g) in dry toluene (20 mL) was refluxed for 7–8 h, 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.

3-(3-Oxocyclohex-1-enylamino)thiophene-3-carbonitrile (11a). This compound was obtained from 1,3-cyclohexanedione in 70% yield, mp 142–143°C; ^{1}H NMR (deuteriochloroform): δ 7.54 (d, $J_{4,5}$ = 5.8 Hz, 1H, thiophene proton), 7.21 (d, $J_{4,5}$ = 5.8 Hz, 1H, thiophene proton), 6.88 (s, 2H, NH_2), 5.61 (s, 1H, vinyl proton, H-2), 2.56 (t, 2H, H-6), 2.40 (t, 2H, H-4), 2.07 (quintet, 2H, H-5); ms: (*m*/*z*) 218 (M^+), 190, 162, 123, 68. Anal. Calcd. for $C_{11}H_{10}N_2OS$: C, 60.53; H, 4.62; N, 12.83. Found: C, 60.72; H, 4.49; N, 12.70.

3-(5,5-Dimethyl-3-oxocyclohex-1-enylamino)thiophene-2-carbonitrile (11b). This compound was obtained from 5,5-dimethylcyclohexane-1,3-dione in 68% yield, mp 152–153°C; ^{1}H NMR (deuteriochloroform): δ 7.54 (d, $J_{4,5}$ = 5.8 Hz, 1H, thiophene proton), 7.22 (d, $J_{4,5}$ = 5.8 Hz, 1H, thiophene proton), 6.23 (s, 2H, NH_2), 5.64 (s, 1H, vinyl proton, H-2), 2.40 (s, 1H, H-6), 2.26 (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. Found: C, 63.50; H, 5.50; N, 11.44.

3-(3-Oxo-5-phenylcyclohex-1-enylamino)thiophene-2-carbonitrile (11c). This compound was obtained from 5-phenylcyclohexane-1,3-dione in 70% yield, mp 189–190°C; ^{1}H NMR (deuteriochloroform): δ 7.56 (d, $J_{4,5}$ = 5.8 Hz, 1H, thiophene proton), 7.36–7.20 (m, 6H, thiophene and phenyl protons), 6.43 (s, 2H, NH_2), 5.70 (s, 1H, vinyl proton, H-2), 3.45 (m, 1H, H-5), 2.95(dd, 1H, H-6a), 2.68–2.58 (m, 3H, H-4 and H-6b); ms: (*m*/*z*) 294 (M^+), 265, 190, 159, 123. Anal. Calcd. for $C_{17}H_{14}N_2OS$: C, 69.36; H, 4.79; N, 9.52. Found: C, 69.47; H, 4.92; N, 9.38.

3-(3-Oxo-5-p-tolylcyclohex-1-enylamino)thiophene-2-carbonitrile (11d). This compound was obtained from 5-*p*-tolylcyclohexane-1,3-dione in 76% yield, mp 238–239°C; ^{1}H NMR (deuteriochloroform): δ 7.56 (d, $J_{4,5}$ = 5.8 Hz, 1H, thiophene proton), 7.22 (d, $J_{4,5}$ = 5.8 Hz, 1H, thiophene proton), 7.20 (s, 4H, phenyl protons), 6.60 (s, 2H, NH_2), 5.87 (s, 1H, vinyl proton, H-2), 3.42 (m, 1H, H-5), 2.89 (dd, 1H, H-6a), 2.66–2.59 (m, 3H, H-4 and H-6b), 2.35(s, 3H, CH_3); ms: (*m*/*z*) 308 (M^+), 279, 190, 162, 123, 67. Anal. Calcd. for $C_{18}H_{16}N_2OS$: C, 70.10; H, 5.23; N, 9.80. Found: C, 69.92; H, 5.10; N, 9.69.

3-(5-(4-Bromophenyl)-3-oxocyclohex-1-enylamino)thiophene-2-carbonitrile (11e). This compound was obtained from 5-(4-bromophenyl)-cyclohexane-1,3-dione in 70% yield, mp 238–239°C; ^{1}H NMR (deuteriochloroform): δ 7.60 (d, $J_{4,5}$ = 5.8 Hz, 1H, thiophene proton), 7.36 (d, $J_{2',3'}$ = 7.5 Hz, 2H, phenyl protons), 7.22 (d, $J_{4,5}$ = 5.8 Hz, 1H, thiophene proton), 7.18 (d, 2H, phenyl protons), 6.80 (s, 2H, NH_2), 5.71 (s, 1H, vinyl proton, H-2), 3.42 (m, 1H, H-5), 2.84 (dd, 1H, H-6a), 2.69–2.59 (m, 3H, H-4 and H-6b); ms: (*m*/*z*) 372 (M^+), 190, 123. Anal. Calcd. for $C_{17}H_{13}BrN_2OS$: C, 54.70; H, 3.51; N, 7.50. Found: C, 54.88; H, 3.70; N, 7.44.

3-(5-(4-Chlorophenyl)-3-oxocyclohex-1-enylamino)thiophene-2-carbonitrile (11f). This compound was obtained from 5-(4-chlorophenyl)cyclohexane-1,3-dione in 75% yield, mp 216–217°C; ^{1}H NMR (deuteriochloroform): δ 7.59 (d, $J_{4,5}$ = 5.8 Hz, 1H, thiophene proton), 7.37–7.24 (dd, $J_{2',3'}$ = 7.5 Hz, 4H, phenyl protons), 7.22 (d, $J_{4,5}$ = 5.8 Hz, 1H, thiophene proton), 6.32 (s, 2H, NH_2), 5.70 (s, 1H, vinyl proton, H-2), 3.43 (m, 1H, H-5), 2.83 (dd, 1H, H-6a), 2.70–2.60 (m, 3H, H-4 and H-6b); 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, 61.92; H, 3.88; N, 8.63.

3-(5-(4-Methoxyphenyl)-3-oxocyclohex-1-enylamino)thiophene-2-carbonitrile (11g). This compound was obtained from 5-(4-methoxyphenyl) cyclohexane-1,3-dione in 75% yield, mp 147–148°C; ^{1}H NMR (deuteriochloroform): δ 7.56 (d, $J_{4,5}$ = 5.8 Hz, 1H, thiophene proton), 7.36 (d, $J_{2',3'}$ = 7.5 Hz, 2H, phenyl protons), 7.21 (d, $J_{4,5}$ = 5.8 Hz, 1H, thiophene proton), 6.92 (d, 2H, phenyl protons), 6.40 (s, 2H, NH_2), 5.70 (s, 1H, vinyl proton, H-2), 3.46 (m, 1H, H-5), 2.84 (dd, 1H, H-6a), 2.70–2.63 (m, 3H, H-4 and H-6b); ms: (*m*/*z*) 324 (M^+), 190, 123, 67. Anal. Calcd. for $C_{18}H_{16}ClN_2OS$: C, 66.64; H, 4.97; N, 8.64. Found: C, 66.75; H, 5.13; N, 8.48.

General procedure for the preparation of 9-amino-6,7-dihydro-5*H*-thieno[3,2-*b*]quinolin-8-one derivatives (12a–g). A suspension of the appropriate 3-(3-oxocyclohex-1-enylamino)thiophene-2-carbonitrile (0.01 mol), K_2CO_3 (0.01 mol) and CuCl (0.01 mol) in dry THF (10 mL) was refluxed for 10 h. 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.

9-Amino-6,7-dihydro-5H-thieno[3,2-b]quinolin-8-one (12a). This compound was obtained from 3-(3-oxocyclohex-1-enyl-amino)-thiophene-2-carbonitrile in 55% yield, mp 199–200°C; ^{1}H NMR (deuteriochloroform): δ 7.70 and 7.40 (d and d, $J_{2,3}$ = 5.7 Hz, 2H, thiophene protons), 3.13 (t, 2H, H-5), 2.72 (t, 2H, H-7), 2.16 (quintet, 2H, H-6); ms: (*m*/*z*) 218 (M^+), 190, 71, 57. Anal. Calcd. for $C_{11}H_{10}N_2OS$: C, 60.53; H, 4.62; N, 12.83. Found: C, 60.66; H, 4.50; N, 12.94.

9-Amino-6,6-dimethyl-6,7-dihydro-5H-thieno[3,2-b]quinolin-8-one (12b). This compound was obtained from 3-(5,5-dimethyl-3-oxocyclohex-1-enylamino)thiophene-2-carbonitrile in 67% yield, mp 255–256°C; ^{1}H NMR (deuteriochloroform): δ 7.72 and 7.40 (d and d, $J_{2,3}$ = 5.7 Hz, 2H, thiophene protons), 3.01 (s, 2H, H-5), 2.57 (s, 2H, H-7), 1.01 [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, 63.23; H, 5.89; N, 11.48.

9-Amino-6-phenyl-6,7-dihydro-5H-thieno[3,2-b]quinolin-8-one (12c). This compound was obtained from 3-(3-oxo-5-phenylcyclohex-1-enylamino)thiophene-2-carbonitrile in 65% yield, mp 189–190°C; ^{1}H NMR (deuteriochloroform): δ 7.74 and 7.40 (d and d, $J_{2,3}$ = 5.7 Hz, 2H, thiophene protons), 7.38–7.25 (m, 5H, phenyl), 3.53 (m, 1H, H-6), 3.34–3.28 (m, 2H, H-5), 2.95–2.91 (m, 2H, H-7); ms: (*m*/*z*) 294 (M^+), 265, 238, 203, 190. Anal. Calcd. for $C_{17}H_{14}N_2OS$: C, 69.36; H, 4.79; N, 9.52. Found: C, 69.48; H, 4.63; N, 9.65.

9-Amino-6-p-tolyl-6,7-dihydro-5H-thieno[3,2-b]quinolin-8-one (12d). This compound was obtained from 3-(3-oxo-5-*p*-tolylcyclohex-1-enylamino)thiophene-2-carbonitrile in 62% yield, mp 262–263°C; ^{1}H NMR (deuteriochloroform): δ 7.74 and 7.41 (d and d, $J_{2,3}$ = 5.7 Hz, 2H, thiophene protons), 7.26–7.18 (m, 4H, phenyl), 3.55 (m, 1H, H-6), 3.33–3.29 (m, 2H, H-5), 2.95–2.92 (m, 2H, H-7), 2.35 (s, 3H, CH_3); ms: (*m*/*z*) 308 (M^+), 292, 201, 135. Anal. Calcd. for $C_{18}H_{16}N_2OS$: C, 70.10; H, 5.23; N, 9.08. Found: C, 70.28; H, 5.33; N, 9.19.

9-Amino-6-(4-bromophenyl)-6,7-dihydro-5H-thieno[3,2-b]quinolin-8-one (12e). This compound was obtained from 3-(5-(4-bromophenyl)-3-oxocyclohex-1-enylamino)thiophene-2-carbonitrile in 67% yield, mp 197–198°C; ^{1}H NMR (deuteriochloroform): δ 7.74 and 7.42 (d and d, $J_{2,3}$ = 5.7 Hz, 2H, thiophene protons), 7.45 and 7.19 (d and d, $J_{2',3'}$ = 7.5 Hz, 4H, phenyl H-3′and H-2′), 3.55 (m, 1H, H-6), 3.40–3.29 (m, 2H, H-5), 2.96–2.89 (m, 2H, H-7); ms: (*m*/*z*) 308 (M^+), 292, 203, 161. Anal. Calcd. for $C_{18}H_{16}N_2OS$: C, 70.10; H, 5.23; N, 9.08. Found: C, 70.21; H, 5.40; N, 9.22.

9-Amino-6-(4-chlorophenyl)-6,7-dihydro-5H-thieno[3,2-b]quinolin-8-one (12f). This compound was obtained from 3-(5-(4-chlorophenyl)-3-oxocyclohex-1-enylamino)thiophene-2-carbonitrile in 68% yield, mp 204–205°C; ^{1}H NMR (deuteriochloroform): δ 7.77 and 7.52 (d and d, $J_{2,3}$ = 5.7 Hz, 2H, thiophene protons), 7.35 and 7.24 (d and d, $J_{2',3'}$ = 7.5 Hz, 4H, phenyl), 3.57 (m, 1H, H-6), 3.38–3.30 (m, 2H, H-5), 2.97–2.90 (m, 2H, H-7); 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, 62.27; H, 4.14; N, 8.40.

9-Amino-6-(4-methoxyphenyl)-6,7-dihydro-5H-thieno[3,2-b]quinolin-8-one (12g). This compound was obtained from 3-(5-(4-methoxyphenyl)-3-oxocyclohex-1-enylamino)thiophene-2-carbonitrile in 70% yield, mp 244–245°C; ^{1}H NMR (deuteriochloroform): δ 7.74 and 7.29 (d and d, $J_{2,3}$ = 5.7 Hz, 2H, thiophene protons), 7.24 and 6.90 (d and d, $J_{2',3'}$ = 7.5 Hz, 4H, phenyl), 3.78 (s, 3H, OCH_3), 3.55 (m, 1H, H-6), 3.39–3.31 (m, 2H, H-5), 2.98–2.89 (m, 2H, H-7); ms: (*m*/*z*) 324 (M^+), 308, 201, 190. Anal. Calcd. for $C_{18}H_{16}N_2O_2S$: C, 66.64; H, 4.97; N, 8.64. Found: C, 66.79; H, 5.08; N, 8.53.

Preparation of 9-amino-5,6,7,8-tetrahydrothieno[3,2-*b*]quinoline (3). A mixture of 0.65 g (3.0 mmol) of 9-amino-6,7-dihydro-5*H*-thieno[3,2-*b*]quinolin-8-one (12a), 0.60 g (12.0 mmol) of hydrazine hydrate, and 0.67 g (12.0 mmol) of potassium hydroxide in 30 mL of ethylene glycol was refluxed for 8 h. After the starting material was disappeared, the reaction mixture was concentrated by distillating off water and ethylene glycol. 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 0.35 g (57%) of **3**, mp 137–138°C; ^{1}H NMR (deuteriochloroform): δ 7.21 and 7.10 (d and d, 2H, thiophene protons), 4.47 (s, 2H, NH_2), 2.99 (m, 2H, H-5), 2.54 (m, 2H, H-8), 1.99–1.84 (m, 4H, H-6 and H-7); ms: (*m*/*z*) 204 (M^+), 190, 161, 135. Anal. Calcd. for $C_{11}H_{12}N_2S$: C, 64.67; H, 5.92; N, 13.71. Found: C, 64.88; H, 6.09; N, 13.60.

General procedure for the preparation of 9-amino-5,6,7,8-tetrahydrothieno[3,2-*b*]quinolin-8-ol derivatives (4a–g). A solution of $LiAlH_4$ in Et_2O (2.0 mL of 1.0*M*, 2.0 mmol) was added dropwise to a solution of the appropriate 9-amino-6,7-dihydro-5*H*-thieno[3,2-*b*]quinolin-8-one (2.0 mmol) in dry THF (10 mL) maintained at 0°C under nitrogen. After stirring at room temperature for 5 h, 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.

9-Amino-5,6,7,8-tetrahydrothieno[3,2-b]quinolin-8-ol (4a). This compound was obtained from 9-amino-6,7-dihydro-5*H*-thieno[3,2-*b*]quinolin-8-one in 80% yield, mp 218–219°C; ^{1}H NMR (dimethyl sulfoxide-d_6): δ 7.78 and 7.22 (d and d, $J_{2,3}$ = 5.8 Hz, 2H, thiophene protons), 6.16 (s, 2H, NH_2), 5.06 (m, 1H, H-8), 2.78–2.66 (m, 2H, H-5), 1.93–1.70 (m, 4H, H-6 and H-7); ms: (*m*/*z*) 220 (M^+), 202, 201, 187, 175, 164. Anal. Calcd. for $C_{11}H_{12}N_2OS$: C, 59.97; H, 5.49; N, 12.72. Found: C, 60.18; H, 5.33; N, 12.88.

9-Amino-6,6-dimethyl-5,6,7,8-tetrahydrothieno[3,2-b]quinolin-8-ol (4b). This compound was obtained from 9-amino-6,6-dimethyl-6,7-dihydro-5*H*-thieno[3,2-b]quinolin-8-one in 84% yield, mp 176–177°C; ^{1}H NMR (dimethyl sulfoxide-d_6): δ 7.74 and 7.24 (d and d, $J_{2,3}$ = 5.8 Hz, 2H, thiophene protons), 5.06 (m, 1H, H-8), 2.80 and 2.58 (d and d, $J_{5a,5b}$ = 13 Hz, 2H, H-5), 2.10 (dd, *J* = 5.5 and 13 Hz, 1H, H-7a), 1.74 (dd, *J* = 6.0 and 13 Hz, 1H, H-7b), 1.13 (s, 3H, CH_3), 0.99 (s, 3H, CH_3); ms: (*m*/*z*) 248 (M^+), 230, 215, 203, 188. Anal. Calcd. for $C_{13}H_{16}N_2OS$: C, 62.87; H, 6.49; N, 11.28. Found: C, 62.94; H, 6.40; N, 11.39.

9-Amino-6-phenyl-5,6,7,8-tetrahydrothieno[3,2-b]quinolin 8-ol (4c). This compound was obtained from 9-amino-6-phenyl-6,7-dihydro-5*H*-thieno[3,2-b]quinolin-8-one in 89% yield, mp 193–194°C; ^{1}H NMR (dimethyl sulfoxide-d_6): δ 7.57 (d, $J_{2,3}$ = 5.8 Hz, 1H, thiophene proton), 7.41–7.29 (m, 6H, thiophene and phenyl protons), 5.20 (m, 1H, H-8), 3.19–3.09 (m, 3H, H-5 and H-6), 2.68–2.62 (m, 1H, H-7a), 2.06–2.02 (m, 1H, H-7b); ms: (*m*/*z*) 296 (M^+), 278, 263, 251, 201, 187.

Anal. Calcd. for $C_{17}H_{16}N_2OS$: C, 68.89; H, 5.44; N, 9.45. Found: C, 69.98; H, 5.53; N, 9.57.

9-Amino-6-p-tolyl-5,6,7,8-tetrahydrothieno[3,2-b]quinolin-8-ol (4d). This compound was obtained from 9-amino-6-*p*-tolyl-6,7-dihydro-5*H*-thieno[3,2-b]quinolin-8-one in 78% yield, mp 131–132°C; ^{1}H NMR (dimethyl sulfoxide-d_6): δ 7.84 and 7.25 (d and d, $J_{2,3} = 5.7$ Hz, 2H, thiophene protons), 7.22 (d, $J_{2',3'} = 7.5$ Hz, 2H, phenyl H-2′), 7.16 (d, 2H, phenyl H-3′), 5.18 (m, 1H, H-5), 3.15–2.98 (m, 3H, H-5 and H-6), 2.60–2.52 (m, 1H, H-7a), 2.32 (s, 3H, CH_3), 2.06–2.00 (m, 1H, H-7b); ms: (*m*/*z*) 310 (M^+), 292, 277, 265, 201. Anal. Calcd. for $C_{18}H_{18}N_2OS$: C, 69.65; H, 5.84; N, 9.02. Found: C, 69.77; H, 5.70; N, 9.10.

9-Amino-6-(4-bromophenyl)-5,6,7,8-tetrahydrothieno[3,2-b]quinolin-8-ol (4e). This compound was obtained from 9-amino-6-(4-bromo-phenyl)-6,7-dihydro-5*H*-thieno[3,2-b]quinolin-8-one in 85% yield, mp 116.5–117.5°C; ^{1}H NMR (dimethyl sulfoxide-d_6): δ 7.75 (d, $J_{2,3} = 5.7$ Hz, 1H, thiophene proton), 7.50 (d, $J_{2',3'} = 7.5$ Hz, 2H, phenyl H-3′), 7.34 (d, 1H, thiophene proton), 7.25 (d, 2H, phenyl H-2′), 5.13 (m, 1H, H-5), 3.14–3.02 (m, 3H, H-5 and H-6), 2.54–2.49 (m, 1H, H-7a), 2.10–2.03 (m, 1H, H-7b); ms: (*m*/*z*) 374 (M^+), 356, 277, 201. Anal. Calcd. for $C_{17}H_{15}BrN_2OS$: C, 54.41; H, 4.03; N, 7.46. Found: C, 54.57; H, 4.13; N, 7.34.

9-Amino-6-(4-chlorophenyl)-5,6,7,8-tetrahydrothieno[3,2-b]quinolin-8-ol (4f). This compound was obtained from 9-amino-6-(4-chloro-phenyl)-6,7-dihydro-5*H*-thieno[3,2-b]quinolin-8-one in 88% yield, mp 117–118°C; ^{1}H NMR (dimethyl sulfoxide-d_6): δ 7.75 (d, $J_{2,3} = 5.7$ Hz, 1H, thiophene proton), 7.35 (s, 4H, phenyl protons), 7.24 (d, 1H, thiophene proton), 5.16 (m, 1H, H-5), 3.13–3.03 (m, 3H, H-5 and H-6), 2.53–2.48 (m, 1H, H-7a), 2.10–2.03 (m, 1H, H-7b); ms: (*m*/*z*) 330 (M^+), 312, 277, 187, 201, 126. Anal. Calcd. for $C_{17}H_{15}ClN_2OS$: C, 61.72; H, 4.57; N, 8.47. Found: C, 61.83; H, 4.64; N, 8.58.

9-Amino-6-(4-methoxyphenyl)-5,6,7,8-tetrahydrothieno[3,2-b]quinolin-8-ol (4g). This compound was obtained from 9-amino-6-(4-methoxy-phenyl)-6,7-dihydro-5*H*-thieno[3,2-b]quinolin-8-one in 86% yield, mp 170–171°C; ^{1}H NMR (dimethyl sulfoxide-d_6): δ 7.74 (d, $J_{2,3} = 6.0$ Hz, 1H, thiophene H-2), 7.28–7.23 (m, 3H, thiophene H-3 proton and phenyl H-3′), 6.90 (d, $J_{2',3'} = 7.5$ Hz, 2H, phenyl H-2′), 5.12 (m, 1H, H-5), 3.77 (s, 3H, OCH_3), 3.07–2.99 (m, 3H, H-5 and H-6), 2.53–2.48 (m, 1H, H-7a), 2.09–2.00 (m, 1H, H-7b); ms: (*m*/*z*) 326 (M^+), 308, 293, 201. Anal. Calcd. for $C_{18}H_{18}N_2O_2S$: C, 66.23; H, 5.56; N, 8.58. Found: C, 66.34; H, 5.64; N, 8.47.

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