Synthesis of Substituted Amino-Cycloalkyl[*b*]thieno-[3,2-*e*]Pyridines

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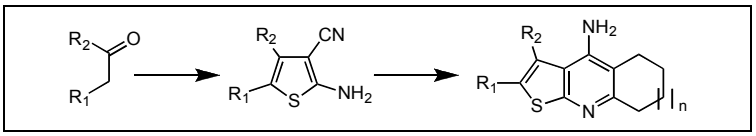

An efficient two respectively three steps procedure for the synthesis of cycloalkyl[*b*]thieno[3,2-*e*]-pyridine amines was developed and in general good to very good yields were obtained.

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INTRODUCTION

Alzheimer's disease is a form of dementia of older people that looks to become a major problem in the coming decade [1]. One possible treatment is to inhibit acetylcholinesterase to maintain as long as possible the neurotransmission by acetylcholine which is hindered by the formation of ß amyloïd plaques. The first acetyl-cholinesterase inhibitor used in this context was Tacrine (**I**) sold under the name of COGNEX® (Figure 1). The hydroxyl derivative of Tacrine is Velnacrine (**II**). In order to investigate the biological effects of structural modifications of Tacrine, we wanted to synthesize a series of thiophene analogues, since it is widely recognized that thiophene is a bioisostere of benzene. As few analogues based on the thieno[2,3-*b*]quinoline (**III**) and the thieno-[3,2-*b*]quinoline (**IV**) moieties have been described [2], we have chosen to prepare parallel to the synthesis of

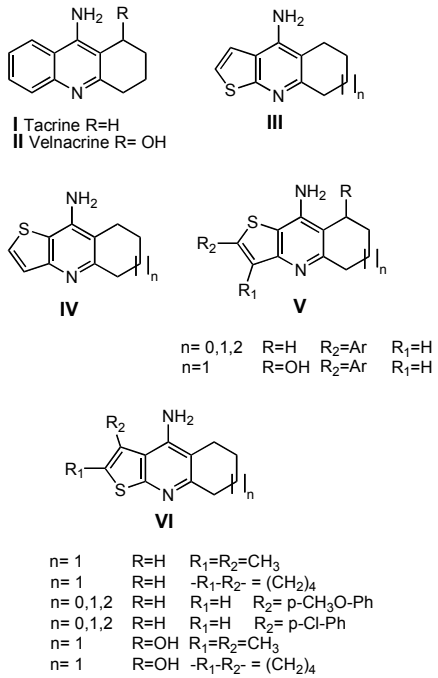
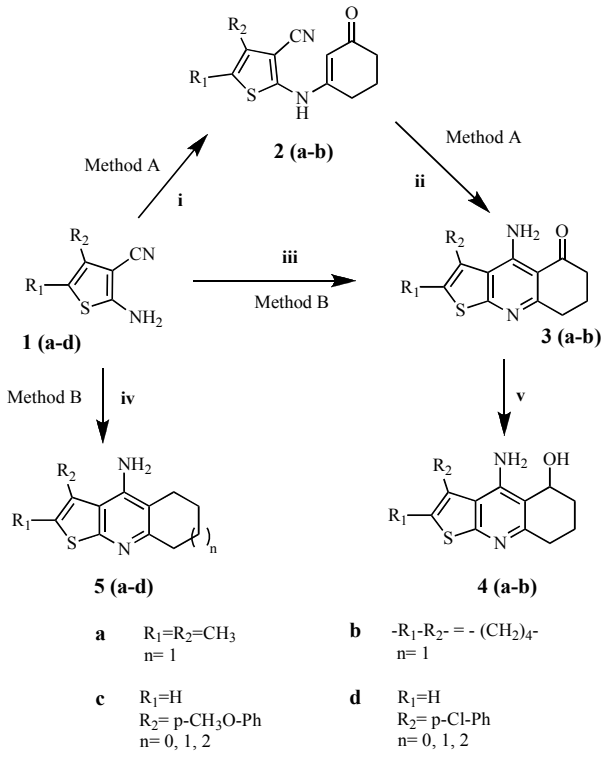


Figure 1

Scheme I



Reagents and conditions: **i** cyclohexane-1,3-dione, p-toluene-sulfonic acid, toluene, reflux, **ii** CuCl, base, DMF, reflux, **iii** $AlCl_3$, cyclohexane-1,3-dione, $(CH_2)_2Cl_2$, reflux, **iv** $AlCl_3$, cyclohexane-1,3-dione, $(CH_2)_2Cl_2$, reflux, **v** $LiAlH_4$, THF, reflux.

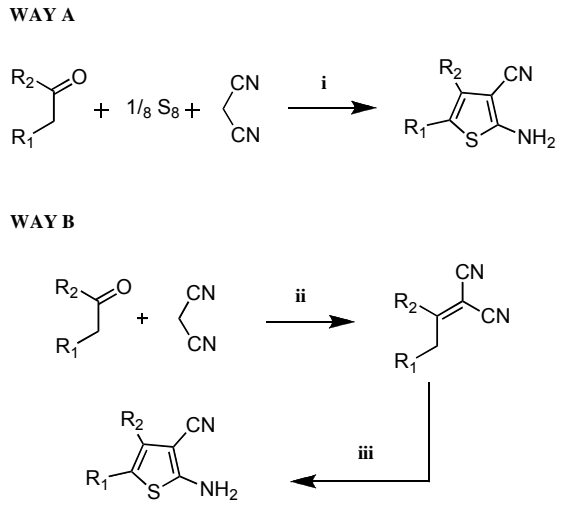
substituted cycloalkyl[*b*]thieno[2,3-*e*]pyridine amines (**V**) [3], the hitherto unknown substituted cycloalkyl[*b*]thieno-[3,2-*e*]pyridine amines (**VI**) (Figure 1) The proposed synthesis is shown in Scheme I.

RESULTS AND DISCUSSION

The synthesis started from substituted 2-amino-3-thiophenecarbonitriles **1** which were prepared in one or two steps from the corresponding ketones *via* a Gewald reaction [4] (Scheme II).

The first approach to the Tacrine derivatives **3** was made by applying a method developed by Tabarrini *et al* [5] (Scheme I/method A). In the first step, thiophenes **1** were condensed with cyclohexan-1,3-dione in refluxing toluene in the presence of *p*-toluenesulfonic acid to give the corresponding enamines **2** in various yields. These enamines were cyclized in the presence of cuprous chloride and either potassium carbonate or sodium methanolate in refluxing DMF to give the ketones **3**. The latter were easily reduced by lithium aluminium hydride to the thiophene analogues of Velnacrine **4**.

Scheme II



Reagents and conditions: **i** morpholine, ethanol, reflux, **ii** CH_3COOH / CH_3COONH_4, Bz, reflux, **iii** morpholine, DMF, RT or reflux.

In a second approach using Friedländer conditions [6] (Scheme I/method B), ketones **3** were obtained in comparable yields than by method A. These conditions allowed us to conduct the direct condensation of monocyclanones as well as 1,3-cyclanediones. In this way, the preparation of Tacrine analogues **5** was possible by only two or three steps and the introduction of a range of ring sizes could also be achieved.

In conclusion substituted 2-amino-3-thiopohenecarbonitriles have been synthesized in only one or two steps. The Friedländer reaction allowed by another single step the very rapid access to the target molecules with good yields. Biological evaluation of the synthesized compounds, using Ellman's tests on acetylcholinesterase inhibition [7] is underway.

EXPERIMENTAL

Melting points were determined on a Stuart SMP3 apparatus and are uncorrected. IR spectra were recorded neat from 4400 to 600 cm^{-1} on an Perkin Elmer FT-IR Baragon 1000PC equipped with a Graseby-Specac golden gate and treated with the Spectrum (Perkin-Elmer) software version 5.3.1. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC 250 MHz spectrometer in $CDCl_3$ if not stated otherwise. The coupling constants are in Hz. Ms spectra were recorded on an Agilent Technologies GC-MS instrument equipped with a 7683 injector, 6890N gas chromatograph and a 5973 mass selective detector. The mass spectrometer was operated in EI mode at 70 eV and ms spectra were recorded from m/z 50 to 650.

General procedure to obtain the substituted 2-Amino-3-thiophenecarbonitriles 1(a-d) (Fig. 2).

WAY A (GEWALD reaction). 0.10 mol (1 equiv.) of ketone and 0.10 mol of malonic acid dinitrile were dissolved in 150 mL absolute ethanol. 0.11 mol sulfur powder and 10 mL morpholine were added. The mixture was heated at reflux with good stirring. After approx. 2 hours, it was cooled to RT and poured into 300 mL ice-water. The precipitation was filtered of, washed with cold water and dried. It was purified either by recrystallization in isopropanol or by silica gel column chromatography using dichloromethane as eluent

WAY B. First step: 0.10 mol (1 equiv.) of ketone and 0.10 mol of malonic acid dinitrile were dissolved in 100 mL benzene. 0.10 mol ammonium acetate and 0.30 mol acetic acid were added and the reaction mixture was refluxed up to 6 hours in a Dean-Stark apparatus. After cooling to RT, the mixture was diluted with 100 mL water and the acetic acid was neutralized with a 10% solution of sodium bicarbonate. The organic layer was separated, dried on anhydrous sodium sulfite, filtered and the solvent was evaporated to give the product which was directly used in the next step.

Second step: (GEWALD reaction). 25 mmol of the product obtained by step 1 (substituted 1,1-dicyanoprop-1-ene) were dissolved in 60 mL DMF. 25 mmol of sulfur powder were added as well as some droplets of morpholine. After a very short heating (less than 10 minutes), up to 120ºC, the reaction mixture was cooled to RT then poured into ice-water. The precipitation was collected by filtration, washed with cold water, dried and purified either by recrystallization in isopropyl alcohol or by silica gel column chromatography using a mixture of dichloromethane/ethyl acetate (95:5) as eluent.

2-Amino-4,5-dimethyl-3-thiophencarbonitrile (1a). Yield: 72%; red-brownish needles; mp 138ºC (isopropanol); Lit: mp: 141-142°C [8]; ir: 3432 and 3217 (NH_2), 2188 (CN), 1606 (NH_2), 1377 (CH_3), 1305 (NH_2) cm^{-1}; ^1H nmr: δ 2.06 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 4.56 (s, 2H, NH_2); ^{13}C nmr: δ 12.39, 12.76, 90.56, 115.94, 117.17, 129.58, 159.17; ms: m/z $(M)^+$ = $(C_7H_8N_2S)^+$ = 152 (100%).

2-Amino-4,5,6,7-tetrahydrobenzo[*b*]-3-thiophenecarbonitrile (1b) Yield: 95%; ocher needles; mp: 144ºC

(isopropanol); Lit: mp: 147-148°C [4b] ; ir: 3443 and 3304 (NH_2), 2195 (CN), 1614 (NH_2), 1443 and 1431 (CH_2), 1330 (NH_2) cm^{-1}; ^1H nmr: δ 1.78 (t, 4H, 2×CH_2), 4.64 (s, 2H, NH_2), 2.49 (m, 4H, 2xCH_2); ^{13}C nmr: δ 22.10, 23.34, 23.72, 24.10, 88.45, 115.59, 120.50, 132.27, 160.15; ms : m/z $(M)^+$ = $(C_9H_{10}N_2S)^+$ = 178 (100%).

2-Amino-4-(4-methoxyphenyl)-3-thiophenecarbonitrile (1c). Yield: 89%; ocher needles; mp 161ºC (dichloromethane/ethylacetate 95:5); Lit: mp: 141-142 [9] ir: 3448 and 3207 (NH_2), 2193 (CN), 1607 (NH_2), 1248 and 1173 (OCH_3 on the phenyl), 736 (disubstituted phenyl); ^1H nmr: δ 3.86 (s, 3H, OCH_3), 4.90 (s, 2H, NH_2), 6.30 (s, 1H, CH), 7.00 (d, 2H, Ph-H, J=8.5), 7.58 (d, 2H, Ph-H, J=8.5); ^{13}C nmr: δ 55.34, 77.22, 104.80, 114.18, 115.90, 126.83, 128.38, 139.74, 159.61, 163.23; ms : m/z $(M)^+$ = $(C_{12}H_{1O}ON_2S)^+$ = 230 (100%).

2-Amino-4-(4-chlorophenyl)-3-thiophenecarbonitrile (1d). Yield: 90%; orange needles; mp 164ºC (dichloromethane/ethylacetate 95:5); ir: 3301 and 3201 (NH_2), 2216 (CN), 1642 (NH_2), 815 (disubstituted phenyl) cm^{-1}; ^1H nmr: δ 5.40 (s, 2H, NH_2), 6.90 (s, H, CH), 7.00 (d, Ph-H, J=8.5), 7.30 (d, 2H, Ph-H, J=8.5); ^{13}C nmr: δ 83.71, 104.07, 115.55, 127.80, 128.06, 132.19, 134.52, 136.89, 165.15; ms : m/z $(M)^+$ = $(C_{11}H_7N_2SCl)^+$ = 234 (100%). *Anal.* Calcd. for $C_{11}H_7ClN_2S$: C, 56.29; H, 3.01; N, 11.94. Found: C, 56.14; H, 3.09; N, 11.87.

General procedure to obtain substituted 2-[(3-Oxo-1-cyclohexen-1yl) amino]-3-thiophenecarbonitriles 2 (a-b).

1st Step of method A/Scheme I. A suspension of a substituted 2-amino-3-thiophencarbonitrile **1** (0.02 mol), cyclohexane-1,3-dione (0.02 mol) and *p*-toluenesulfonic acid (0.67 mmol) in dry toluene (20 mL) were refluxed for 4 h in an Dean-Stark apparatus. The reaction mixture was then chilled to 0ºC and the crystallized product was collected by filtration, washed with cold toluene followed by cold cyclohexane, dried and recrystallized (ethanol/diethyl ether 1:1).

4,5-Dimethyl-2-[3-oxo-1-cyclohexen-1-yl)amino]-3-thiophenecarbonitrile (2a). Yield: 68%; yellow-greenish needles; mp 211ºC (ethanol/diethyl ether 1:1); ir: 3187 (NH), 2955 (CH_3), 2224 (CN), 1603 (CO), 1589 (NH), 1358 (CH_3), 1242 (NH) cm^{-1}; ^1H nmr: δ 2.05 (m, 2H, -CH_2-*CH_2*-CH_2-), 2.16 (s, 6H, 2xCH_3), 2.38 (m, 2H, =C-CH_2-), 2.54 (m, 2H, -CH_2-CO-), 5.70 (s, 1H, NH), 6.96 (s, 1H, =CH-CO-); ^{13}C nmr: δ 12.50, 12.86, 21.55, 28.75, 36.41, 103.34, 103.96, 114.10, 128.14, 130.93, 146.76, 160.67, 198.56; ms : m/z $(M)^+$= $(C_{13}H_{14}ON_2S)^+$ = 246 (100%). *Anal.* Calcd. for $C_{13}H_{14}N_2OS$: C, 63.39; H, 5.73; N, 11.37. Found: C, 63.54; H, 5.55; N, 11.38.

2-[3-Oxo-1-cyclohexen-1-yl)amino]-4,5,6,7-tetrahydro-1-benzo[b]thiophen-3-carbonitrile (2b). Yield: 62%; yellow needles; mp 200ºC (ethanol/diethyl ether 1:1); ir: 3188 (NH), 2924 $(CH_2)_4$, 2211 (CN), 1614 (CO), 1589 (NH), 1447 $(CH_2)_4$, 1247 (NH) cm^{-1}; ^1H nmr: δ 1.83 (m, 4H, 2×CH_2), 2.07 (m, 2H, -CH_2-*CH_2*-CH_2-), 2.38 (m, 2H, =C-CH_2-), 2.58 (m, 6H, -CH_2 -CH_2-CH_2-CO-), 5.70 (s, 1H, NH), 6,92 (s, 1H, =CH-CO-); ^{13}C nmr : δ 21.61, 21.92, 22.26, 22.54, 25.44, 26.57, 36.47, 102.49, 102.69, 113.81, 131.54, 133.37, 147.77, 161.63, 198.83; ms : m/z $(M)^+$ = $(C_{15}H_{16}ON_2S)^+$ = 272 (100%). *Anal.* Calcd. for $C_{15}H_{16}N_2OS$: C, 66.15; H, 5.92; N, 10.29. Found: C, 66.13; H, 5.87; N, 10.34.

General procedure to obtain the substituted amino-7,8-dihydrothieno [2,3-*b*] quinolinones 3 (a-b).

2nd Step of method A/Scheme I. Sodium methanolate or potassium carbonate (2.2 mmol) and cuprous chloride (10.4 mmol) were added to a solution of **2** (10.4 mmol) in dry DMF (20 mL) and the mixture was heated at 80-90ºC for 4 h. After cooling, the reaction mixture was poured into ice-water (150 mL) containing sodium tartrate (10%). The obtained precipitate was filtered off and extracted several times with a mixture of methanol/ethyl acetate (1:1). The organic extracts were dried on anhydrous sodium sulphate, filtered and the solvent was evaporated to give a solid which was purified by silica gel column chromatography using a mixture of dichloromethane/methanol (9:1) as eluent.

4-Amino-2,3-dimethyl-7,8-dihydrothieno[2,3-*b*]quinolin-5(6*H*)-one (3a). Yield: 63%; brownish needles; mp 204ºC (dichloromethane/methanol 9:1); ir: 3410 and 3216 (NH_2), 2952 and 2864 (CH_3), 1636 (CO), 1589 (NH_2), 1423 and 1371 (CH_3), 1328 (NH_2) cm^{-1}; ^1H nmr: δ 1.65 (s, 1H of NH_2 linked by hydrogen-bonding to CO), 2.09 (m, 2H, -CH_2-*CH_2*-CH_2-); 2.39 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 2.67 (m, 2H, =C-CH_2-); 3.03 (m, 2H, -CH_2-CO-), 5.29 (s, 1H of NH_2 linked by hydrogen-bonding to CO); ^{13}C nmr: δ 13.30, 14.74, 21.41, 29.67, 39.91, 112.55, 122.20, 125.30, 129.55, 152.64, 161.17, 161.79, 202.36; ms: m/z $(M)^+$ = $(C_{13}H_{14}ON_2S)^+$ = 246 (100%). *Anal.* Calcd. for $C_{13}H_{14}N_2OS$: C, 63.39; H, 5.73; N, 11.37. Found: C, 63.41; H, 5.50; N, 11.38.

11-Amino-2,3,4,7,8,9-hexahydro[1]benzothieno[2,3-*b*]-quinolin-10(1*H*)-one (3b) Yield: 58%; brown needles; mp 223ºC (dichloromethane/methanol 9:1); ir: 3387 and 3217 (NH_2), 2941 (CH_2), 1636 (CO), 1587 (NH_2), 1426 (CH_2), 1311 (NH_2) cm^{-1}; ^1H nmr: δ 1.28 (s, 1H, NH_2 linked by hydrogen-bonding to CO), 1.89 (m, 4H, 2×CH_2), 2.07 (m, 2H, -CH_2-*CH_2*-CH_2-), 2.66 (m, 2H, =C-CH_2-), 2.77 (m, 2H, -CH_2-CO-), 3.02 (m, 6H, 3×CH_2), 5.01 (s, 1H, NH_2 linked by hydrogen-bonding to CO); ^{13}C nmr: 21.04, 21.66, 22.26, 22.54, 25.44, 26.57, 39.95, 107.88, 118.14, 127.37, 132.67, 152.74, 161.85, 162.62, 202.05; ms: m/z $(M)^+$ = $(C_{15}H_{16}ON_2S)^+$ = 272 (100%). *Anal.* Calcd. for $C_{15}H_{16}N_2OS$: C, 66.15; H, 5.92; N, 10.29. Found: C, 66.24; H, 5.83; N, 10.39.

General procedure to obtain the substituted amino-7,8-dihydrothieno [2,3-b] quinolinols 4 (a-b) (Scheme I). A solution of $LiAlH_4$ (1.6 mmol) in dry THF (20 mL) was added dropwise to a solution of 3 (1 mmol) under argon atmosphere. After the addition, the reaction mixture was refluxed for 1h, then quenched by 2 mL of HCl 10%. The mixture was then made basic with NaOH 30% and extracted with ethylacetate (3×20 mL). The combined organic layers were dried on anhydrous sodium sulfate, filtered and evaporated to give a solid, which was purified by silica gel column chromatography using a mixture of dichloromethane/methanol (9:1) as eluent.

4-Amino-2,3-dimethyl-5,6,7,8-tetrahydrothieno[2,3-*b*]-quinolin-5-ol (4a). Yield : 83% ; ocher crystalline powder; mp 182ºC (dichloromethane/methanol 9:1); ir: 3507 and 3383 (NH_2), 3118 (OH), 2937and 2864 (CH_3), 1589 (NH_2), 1438 and 1383 (CH_3), 1278 (NH_2), 1066 (OH) cm^{-1}; ^1H nmr: δ 1.20 (m, 4H, 2×CH_2), 1.60 (s, 3H, CH_3), 1.91 (m, 3H, CH_2+OH), 2.13 (s, 3H, CH_3), 4.14 (m, 1H, C*H*-OH), 4.96 (2H, NH_2); ^{13}C nmr: δ 13.09, 14.27, 17.74, 29.15, 32.83, 62.83, 113.24, 118.81, 124.67, 126.13, 149.34, 153.46, 158.67; ms: m/z $(M)^+$ = $(C_{13}H_{16}ON_2S)^+$ = 248 (100%). *Anal.* Calcd. for $C_{13}H_{16}N_2OS$: C, 62.87; H, 6.49; N, 11.28. Found: C, 63.02; H, 6.50; N, 11.18.

11-Amino-1,2,3,4,7,8,9,10-octahydro[1]benzothieno[2,3-*b*]-quinolin-10-ol (4b). Yield: 43%; yellow-brown needles; mp 128ºC (dichloromethane/methanol 9:1); ir: 3503 and 3380 (NH_2), 3115 (OH), 2928 $(CH_2)_4$, 1611 (NH_2), 1444 $(CH_2)_4$, 1304

(NH_2), 1068 (OH) cm^{-1}; ^1H nmr: δ 1.72 (m, 4H, 2×CH_2), 2.27 (s, 1H, NH_2 linked by hydrogen-bonding to OH), 2.44 (m, 6H, 3×CH_2), 2.68 (m, 4H, 2×CH_2), 4.43 (m, 1H, C*H*-OH), 5.16 (s, 1H, NH_2 linked by hydrogen-bonding to OH); ^{13}C nmr: δ 17.78, 22.06, 22.17, 25.25, 25.89, 32.81, 33.22, 62.80, 113.25, 117.68, 129.39, 133.37, 149.28, 153.51, 159.23; ms: m/z $(M)^+$ = $(C_{15}H_{18}ON_2S)^+$ = 274 (100%). *Anal.* Calcd. for $C_{15}H_{18}N_2OS$: C, 65.66; H, 6.61; N, 10.21. Found: C, 65.83; H, 6.49; N, 10.36.

General procedure to obtain the substituted cycloalkyl[*b*]-thieno[3,2-*e*]pyridine amines 5 (a-d) by Friedländer reaction (method B /Scheme I). Aluminium chloride (3.4 mmol for monocyclanones and 6.8 mmol for cyclohexa-1,3-diones) was suspended in dry 1,2-dichloroethane (10 mL per mmol of $AlCl_3$) at RT under argon. The corresponding thiophene **1** (2 mmol) and the ketone (1.7 mmol) were added and the reaction mixture was heated under reflux up to 18 h for a monocyclanone and up to 36 h for a cyclohexa-1,3-dione. When the reaction was completed (monitoring by TLC) a mixture of THF/water (2:1) was added at RT and sodium hydroxide was added until the solution became basic. After stirring for at least 30 minutes, the mixture was extracted with dichloromethane (3×30 mL). The combined organic layers were dried on anhydrous sodium sulfate; the solvents are evaporated to give a brownish solid which was purified by silica gel column chromatography using dichloromethane/methanol (9:1) as eluant.

4-Amino-2,3-dimethyl-5,6,7,8-tetrahydrothieno[2,3-*b*]-quinoline (5a). Yield 95%; grey needles; mp 169ºC (dichloromethane/methanol 9:1); ir: 3506 and 3301 (NH_2), 2922 and 2857 (CH_3) and (CH_2), 1636 (NH_2), 1428 (CH_3), 1279 (NH_2) cm^{-1}; ^1H nmr: δ 1.89 (m, 6H, 3×CH_2), 2.39 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 2.88 (m, 2H, CH_2), 4.56 (s, 2H, NH_2); ^{13}C nmr: δ 13.48, 14.58, 23.06, 26.82, 32.92, 41.98, 110.93, 115.73, 123.36, 128.46, 146.77, 153.76, 157.97; ms: m/z $(M)^+$ = $(C_{13}H_{16}N_2S)^+$ = 232 (100%). *Anal.* Calcd. for $C_{13}H_{16}N_2S$: C, 67.20; H, 6.94; N, 12.06. Found: C, 67.20; H, 7.02; N, 12.35.

11-Amino-1,2,3,4,7,8,9,10-octahydro[1]benzothieno[2,3-*b*]-quinoline (5b). Yield 92%; brown needles; mp 218ºC (dichloromethane/methanol 9:1); ir: 3473 and 3361 (NH_2), 2924 and 2845 2(CH_2)$_4$, 1609 (NH_2), 1431 (CH_2), 1277 (NH_2) cm^{-1}; ^1H nmr: δ 1.90 (m, 8H, 4×CH_2), 2.45 (m, 4H, 2×CH_2), 2.75 (m, 2H, CH_2), 2.88 (m, 2H, CH_2), 4.56 (s, 2H, NH_2); ^{13}C nmr: δ 22.86, 22.97, 23.06, 25.65, 26.81, 33.10, 43.47, 110.89, 117.93, 125.73, 131.79, 132.57, 146.64, 153.92, 158.87; ms: m/z $(M)^+$ = $(C_{15}H_{18}N_2S)^+$ = 258 (100%). *Anal.* Calcd. for $C_{15}H_{18}N_2S$: C, 69.73; H, 7.02; N, 10.84. Found: C, 69.58; H, 7.06; N, 10.90.

4-Amino-3-(4-methoxyphenyl)-6,7-dihydro-5*H*-cyclopenta-[*b*]thieno[3,2-*e*]pyridine (5c/n=0). Yield 83%; beige needles; mp 216° (dichloromethane/methanol 9:1); ir: 3477 and 3368 (NH_2), 2951 and 2832 (CH_2), 1610 (NH_2), 1455 (CH_2), 1175 (OCH_3), 755 (disubstituted phenyl); ^1H nmr: δ 2.20 (m, 2H, -CH_2-C*H*$_2$-CH_2-), 2.75 (m, 2H, =C-CH_2-), 3.1 (m, 2H, -N=C-CH_2-), 3.9 (s, 3H, OCH_3), 4.2 (s, 2H, NH_2), 6.9 (s, 1H, thiophene proton), 7.0 (d, 2H, 2×CH, J=8.5), 7.4 (d, 2H, 2×CH, J=8.5); ^{13}C nmr: δ 22.90, 26.75, 34.36, 55.35, 113.56, 113.93, 115.67, 116.20, 119.39, 129.67, 130.46, 134.37, 145.30, 159.45, 164.09; ms: m/z $(M)^+$ = $(C_{17}H_{16}ON_2S)^+$ = 296 (100%). *Anal.* Calcd. for $C_{17}H_{16}N_2OS$: C, 68.89; H, 5.44; N, 9.45. Found: C, 68.74; H, 5.88; N, 9.50.

4-Amino-3-(4-methoxyphenyl)-5,6,7,8-tetrahydro[2,3-*b*]-quinoline) (5c/n=1). Yield 85%; orange needles; mp 162ºC (dichloromethane/methanol 9:1); ir: 3474 and 3331 (NH_2), 2926 and 2863 (CH_2), 1630 (NH_2), 1441 (CH_2), 1176 (OCH_3), 769 (disubstituted phenyl); ^1H nmr: δ 1.9 (m, 4H, 2×CH_2), 2.45 (m, 2H, =C-CH_2-), 3.0 (m, 2H, -N=C-CH_2-), 3.86 (s, 3H, OCH_3), 4.3 (s, 2H, NH_2), 6.9 (s, 1H, thiophene proton), 7.0 (d, 2H, 2×CH, J=8.5), 7.4 (d, 2H, 2×CH, J=8.5); ^{13}C nmr: δ 22.78, 22.81, 22.95, 33.21, 55.38, 110.46, 113.99, 115.92, 120.15, 129.67, 130.50, 134.40, 147.18, 154.34, 155.34, 159.50; ms: m/z $(M)^+$ = $(C_{18}H_{18}ON_2S)^+$ = 310 (100%). *Anal.* Calcd. for $C_{18}H_{18}N_2OS$: C, 69.65; H, 5.84; N, 9.02. Found: C, 69.73; H, 5.87; N, 9.32.

4-Amino-3-(4-methoxyphenyl)-6,7,8,9-tetrahydro-5*H*-cyclo-hepta[*b*]thieno[3,2-*e*]pyridine (5c/n=2). Yield 95%; orange needles; mp 195ºC (dichloromethane/methanol 9:1); ir: 3462 and 3363 (NH_2), 2919 and 2842 (CH_2)$_5$, 1624 (NH_2), 1434 (CH_2)$_5$, 1170 (OCH_3), 775 (disubstituted phenyl); ^1H nmr: δ 1.85 (m, 6H, 3×CH_2), 2.6 (m, 2H, =C-CH_2-), 3.1 (m, 2H, -N=C-CH_2-), 3.9 (s, 3H, OCH_3), 4.4 (s, 2H, NH_2), 6.9 (s, 1H, thiophene proton), 7.0 (d, 2H, 2×CH, J=8.5), 7,4 (d, 2H, 2×CH, J=8.5); ^{13}C nmr: δ 25.24, 26.60, 27.12, 32.15, 39.04, 55.37, 113.91, 116.00, 120.12, 129.62, 130.62, 130.63, 134.70, 146.24, 153.99, 159.50, 161.88; ms: m/z $(M)^+$ = $(C_{19}H_{20}ON_2S)^+$ = 324 (100%). *Anal.* Calcd. for $C_{19}H_{20}N_2OS$: C, 70.34; H, 6.21; N, 8.63. Found: C, 70.25; H, 6.34; N, 8.79.

4-Amino-3-(4-chlorophenyl)-6,7-dihydro-5*H*-cyclopenta[*b*]-thieno[3,2-*e*]pyridine (5d/n=0). Yield 95%; orange needles; mp 176ºC (dichloromethane/methanol 9:1); ir: 3473 and 3308 (NH_2), 2946 and 2840 (CH_2)$_3$, 1635 (NH_2), 1455 (CH_2)$_3$, 818 (Cl), 761 (disubstituted phenyl); ^1H nmr: δ 2.28 (m, 2H, -CH_2-C*H*$_2$-CH_2-), 2.75 (m, 2H, =C-CH_2-), 3.1 (m, 2H, -N=C-CH_2-), 4.15 (s, 2H, NH_2), 6.9 (s, 1H, thiophene proton), 7.4 (m, 4H, 4×CH); ^{13}C nmr: δ 22.87, 26.79, 34.39, 115.73, 115.91, 120.25, 128.72, 130.57, 133.42, 134.15, 135.88, 145.04, 164.42, 166.31; ms: m/z $(M)^+$ = $(C_{16}H_{13}N_2SCl)^+$ = 300 (100%). *Anal.* Calcd. for $C_{16}H_{13}ClN_2S$: C, 63.89; H, 4.36; N, 9.31. Found: C, 63.87; H, 4.56; N, 9.52.

4-Amino-3-(4-chlorophenyl)-5,6,7,8-tetrahydrothieno[2,3-*b*]-quinoline (5d/n=1). Yield 83%; orange needles; mp 179ºC (dichloromethane/methanol 9:1); ir: 3488 and 3340 (NH_2), 2935 and 2859 (CH_2), 1627 (NH_2), 1447 (CH_2)$_4$, 831 (Cl), 766 (disubstituted phenyl); ^1H nmr: δ 1.9 (m, 4H, 2×CH_2), 2.45 (m, 2H, =C-CH_2-), 3.0 (m, 2H, -N=C-CH_2-), 4.2 (s, 2H, NH_2), 6.9 (s, 1H, thiophene proton), 7.4 (m, 4H, 4×CH); ^{13}C nmr: δ 22.56, 22.72, 22.93, 33.18, 110.64, 115.43, 120.39, 128.74, 130.59, 133.40, 134.17, 135.86, 146.91, 155.58, 158.41; ms: m/z $(M)^+$ = $(C_{17}H_{15}N_2SCl)^+$ = 314 (100%). *Anal.* Calcd. for $C_{17}H_{15}ClN_2S$: C, 64.85; H, 4.80; N, 8.90. Found: C, 64.81; H, 4.76; N, 9.02.

4-Amino-3-(4-chlorophenyl)-6,7,8,9-tetrahydro-5*H*-cyclo-hepta[*b*]thieno[3,2-*e*]pyridine (5d/n=2). Yield 86%; orange needles; mp 175ºC (dichloromethane/methanol 9:1); ir: 3489 and 3382 (NH_2), 2913 and 2846 (CH_2)$_5$, 1622 (NH_2), 1455 (CH_2)$_5$, 824 (Cl), 755 (disubstituted phenyl). ^1H nmr: δ 1.8 (m, 6H, 3×CH_2), 2.65 (m, 2H, =C-CH_2-), 3.1 (m, 2H, -N=C-CH_2-), 4.3 (s, 2H, NH_2), 6.95 (s, 1H, thiophene proton), 7.4 (m, 4H, 4×CH); ^{13}C nmr: δ 25.18, 26.48, 26.99, 32.05, 39.05, 116.13, 116.23, 120.78, 128.61, 130.65, 133.69, 134.11, 135.76, 145.91, 159.77, 162.09; ms: m/z $(M)^+$ = $(C_{18}H_{17}N_2SCl)^+$ = 328 (100%). *Anal.* Calcd. for $C_{18}H_{17}ClN_2S$: C, 65.74; H, 5.21; N, 10.78. Found: C, 65.81; H, 5.32; N, 10.65.

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