Synthesis of Thiophene Analogues of the Tacrine Series

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Received 29 November 2006; revised 11 January 2007

Abstract: 3-Amino-2-cyanothiophenes condensed with cyclanones and afforded analogues of Velnacrine in two or three steps. Condensation under Friedländer's conditions gave tacrine analogues in one step.

Key words: Alzheimer's disease, tacrine analogues, Friedländer reaction, condensation, aminothiophene carbonitrile

Alzheimer's disease is a form of dementia of older people that looks set to be a major problem in the coming decade.[1] One possible treatment is to inhibit acetylcholinesterase, which plays a role in the formation of the β-amyloid plaque. The first acetylcholinesterase inhibitor used in this context was tacrine (**I**), sold under the name COGNEX® (Figure 1). The hydroxy 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 (**III**, **IV**) based on the thieno[2,3-*b*]quinoline moiety and 9-amino-5,6,7,8-tetrahydrothieno[3,2-*b*]quinoline have been described,[2] we chose to

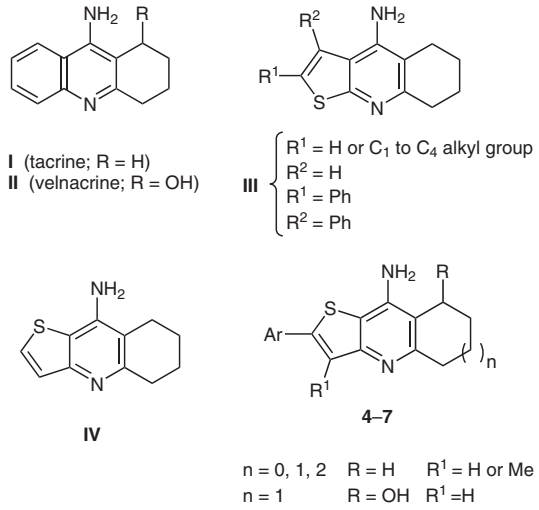

Figure 1 Strucure of tacrine (**I**), velnacrine (**II**), thiophene analogues (**III** and **IV**) and the target thiophene analogues **4**–**7**.

SYNTHESIS 2007, No. 7, pp 1027–1032
Advanced online publication: 20.02.2007
DOI: 10.1055/s-2007-965944; Art ID: Z24706SS
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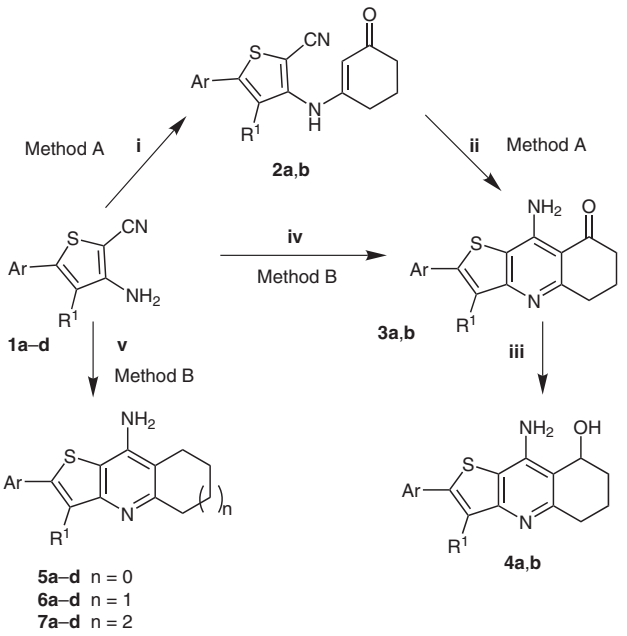
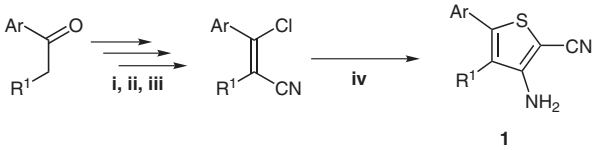


Scheme 1 *Reagents and conditions*: i) cyclohexan-1,3-dione, PTSA, toluene, reflux; ii) CuCl, base, DMF, reflux; iii) $LiAlH_4$, THF, reflux; iv) $AlCl_3$, cyclohexan-1,3-dione, DCE, reflux; v) $AlCl_3$, cyclic ketone, DCE, reflux.

prepare the hitherto unknown substituted thieno[3,2-*b*]quinoline series **4**–**7**. The proposed synthesis is shown in Scheme 1.

The synthesis started from 3-amino-2-cyano-5-arylthiophenes (**1**), which were prepared from the corresponding β-chloroacrylonitrile by a previously described method (Scheme 2).[4–10] The yields obtained in the preparation of a range of thiophenes **1** are shown in Table 1.

The first approach to the tacrine derivatives **3** was made by applying a method developed by Tabarini et al. (Scheme 1; Method A).[11] In the first step, thiophenes **1** were condensed with cyclohexan-1,3-dione, in refluxing



Scheme 2 *Reagents and conditions*: i) $POCl_3$, DMF, 60 °C, 5 h; ii) hydroxylamine chloride, EtOH; iii) Ac_2O; iv) $Na_2S{\cdot}9H_2O$, DMF, $ClCH_2CN$, NaOEt.

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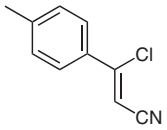
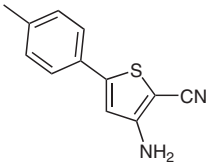
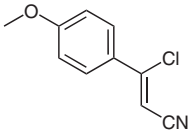
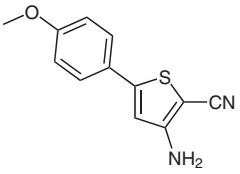
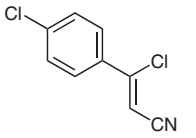
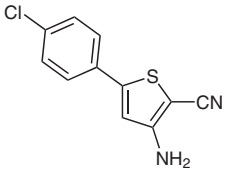
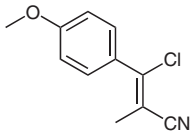
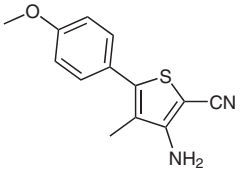
Table 1 Formation of Thiophenes **1**

Entry	β-Choroacrylonitrile	Thiophene **1**	Yield (%)[a]
a			93
b			95
c			95
d			95

[a] Crude product, analytically pure and used without further purification.

toluene in the presence of *p*-toluenesulfonic acid, to give the corresponding enamines **2** in various yields. Enamines **2** were cyclized in the presence of cuprous chloride and either sodium methanolate or potassium carbonate, in refluxing DMF, to give the ketones **3** (Table 2). The latter were easily reduced by lithium aluminum hydride to the thiophene analogues of velnacrine **4**.

In a second approach, using Friedländer's conditions,[11] it was found that ketone **3** could be obtained directly from **1** (Scheme 1; Method B), with better yields than the two-step procedure. These conditions also allowed us to conduct the direct condensation of cyclanones as well as 1,3-diones. In this way, the rapid preparation of tacrine analogues **5a**–**d** was possible and, furthermore, the introduction of a range of ring sizes could also be achieved (Table 3).

In conclusion, 3-amino-5-aryl-2-thiophenecarbonitriles have been synthesized in four steps. The Friedländer reaction allowed very rapid access to the target molecules with good yields. Biological evaluation of the synthesized compounds, using Ellman's tests on acetylcholinesterase inhibition,[13] are underway.

Melting points were determined on a Stuart SMP3 apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC 250 MHz spectrometer in $CDCl_3$ or DMSO-d_6. Elemental analyses were determined with a LECO CHNS 932 elemental analyzer. HRMS were determined on a Micromass Autospec 3F instrument.

Synthesis of 3-Amino-5-arylthiophenecarbonitriles 1a–d; General Procedure

A suspension of $Na_2S{\cdot}9H_2O$ (0.06 mol, 1 equiv) in DMF (80 mL) was heated at 40 °C for 30 min. β-Chloroacrylonitrile (0.06 mol, 1 equiv) dissolved in DMF (20 mL) was added and the solution was heated at 50 °C for 50 min. Chloroacetonitrile (0.06 mol, 1 equiv) in DMF (1 mL) was added and the solution was stirred at 50 °C for 90 min. A solution of NaOEt (0.06 mol, 1 equiv) in absolute EtOH (40 mL) was added and the solution was stirred at 50 °C for 30 min (the reaction was monitored by TLC). The reaction mixture was then cooled to r.t. and poured into ice-water (150 mL). The precipitate was filtered and washed with cold H_2O to give the product which was used directly in the next step. A sample was taken and purified either by recrystallization (isopropanol) or by column chromatography for analysis.

3-Amino-5-(4-methylphenyl)-2-thiophenecarbonitrile (1a)

Purified by column chromatography (CH_2Cl_2).

Yield: 93%; yellow solid; mp 195–197 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.40 (s, 3 H, CH_3), 4.91 (s, 2 H, NH_2), 6.75 (s, 1 H, CH), 7.18 (d, *J* = 7.5 Hz, 2 H, 2 × CH), 7.42 (d, *J* = 7.5 Hz, 2 H, 2 × CH).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 21.32, 74.79, 115.70, 116.37, 125.97, 129.88, 130.22, 139.71, 148.89, 158.44.

Anal. Calcd for $C_{12}H_{10}N_2S$: C, 67.26; H, 4.70; N, 11.07. Found: C, 67.35; H, 4.67; N, 10.99.

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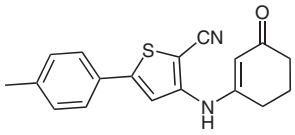
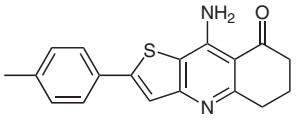
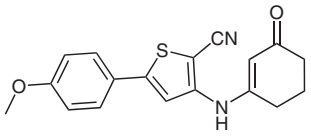
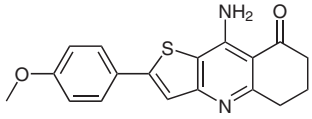
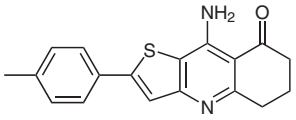
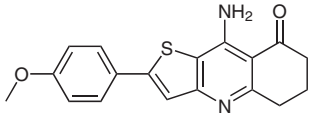
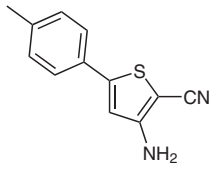
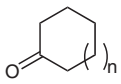
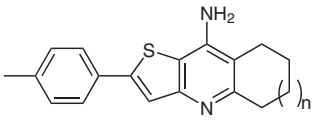
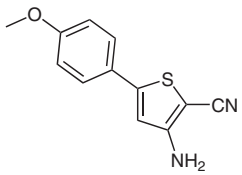
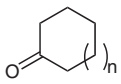
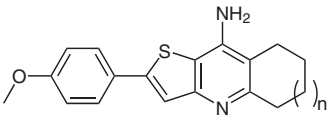
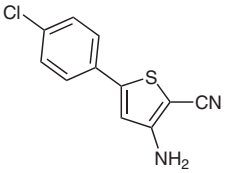
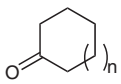
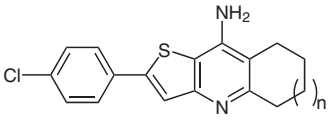
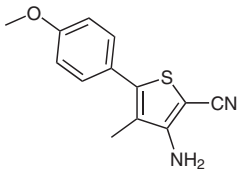
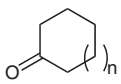
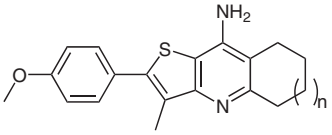
Table 2 Yields of Formation of **2** and **3** from Thiophenes **1**

	Entry	Enamine **2**	Yield (%)	Entry	Ketone **3**	Yield (%)	Overall yield (%) from **1**
Method A							
	a		11[c]	**a**		81[a]	9
	b		71	**b**		38[b]	27
Method B							
				a		80	80
				b		85	85

[a] CuCl, NaOMe, DMF, reflux.
[b] CuCl, K_2CO_3, DMF, reflux.

Table 3 Yields of the Friedländer Reaction

Thiophene	Cyclanones	Tacrine analogue	Product	Yield (%)
			n = 0; **5a** n = 1; **6a** n = 2; **7a**	87 88 80
			n = 0; **5b** n = 1; **6b** n = 2; **7b**	98 97 97
			n = 0; **5c** n = 1; **6c** n = 2; **7c**	88 89 85
			n = 0; **5d** n = 1; **6d** n = 2; **7d**	76 89 98

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3-Amino-5-(4-methoxyphenyl)-2-thiophenecarbonitrile (1b)
Yield: 95%; brown solid; mp 204–206 °C (isopropanol).

^{1}H NMR (250 MHz, DMSO-d_6): δ = 3.78 (s, 3 H, CH_3), 6.49 (s, 2 H, NH_2), 6.80 (s, 1 H, CH), 6.98 (d, *J* = 7.5 Hz, 2 H, 2 × CH), 7.52 (d, *J* = 7.5 Hz, 2 H, 2 × CH).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 55.85, 74.24, 115.04, 115.18, 116.43, 125.27, 127.61, 148.75, 158.50, 160.71.

Anal. Calcd for $C_{12}H_{10}N_2OS$: C, 62.59; H, 4.38; N, 12.16. Found: C, 62.32; H, 4.56; N, 12.47.

3-Amino-5-(4-chlorophenyl)-2-thiophenecarbonitrile (1c)
Yield: 95%; brown solid; mp 184–186 °C (isopropanol).

^{1}H NMR (250 MHz, DMSO-d_6): δ = 6.58 (s, 2 H, NH_2), 6.94 (s, 1 H, CH), 7.48 (d, *J* = 7.5 Hz, 2 H, 2 × CH), 7.61 (d, *J* = 7.5 Hz, 2 H, 2 × CH).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 75.50, 116.04, 116.76, 127.82, 129.75, 131.42, 134.37, 147.06, 158.36.

Anal. Calcd for $C_{11}H_7ClN_2S$: C, 56.29; H, 3.01; N, 11.94. Found: C, 56.42; H, 3.15; N, 11.74.

3-Amino-5-(4-methoxyphenyl)-2-thiophenecarbonitrile (1d)
Purified by column chromatography (CH_2Cl_2).

Yield: 70%; yellow solid; mp 186–188 °C.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 1.73 (s, 3 H, CH_3), 3.01 (s, 3 H, CH_3O), 5.16 (s, 2 H, NH_2), 6.18 (d, *J* = 7.5 Hz, 2 H, 2 × CH), 6.56 (d, *J* = 7.5 Hz, 2 H, 2 × CH).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 12.38, 55.71, 114.66, 116.81, 123.54, 123.80, 125.42, 130.54, 143.19, 157.18, 160.14.

Anal. Calcd for $C_{13}H_{12}N_2OS$: C, 63.91; H, 4.95; N, 11.47. Found: C, 63.69; H, 4.56; N, 11.12.

Preparation of 5-Aryl-3-[(3-oxo-1-cyclohexen-1-yl)amino]-2-thiophenecarbonitriles 2a,b; General Procedure (Method A)
A suspension of **1** (0.02 mol), cyclohexan-1,3-dione (0.02 mol) and PTSA·H_2O (0.67 mmol) in anhyd toluene (20 mL), was refluxed for 4 h in a Dean–Stark apparatus. The reaction mixture was then chilled to 0 °C and the product was filtered off, washed with cold toluene followed by cold cyclohexane, dried and recrystallized (EtOH–Et_2O, 1:1).

5-(4-Methylphenyl)-3-[(3-oxo-1-cyclohexen-1-yl)amino]-2-thiophenecarbonitrile (2a)
Yield: 11%; orange solid; mp 232–234 °C.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 1.91 (m, 2 H, CH_2), 2.19 (m, 2 H, CH_2), 2.33 (s, 3 H, CH_3), 2.54 (m, 2 H, CH_2), 5.25 (s, 1 H, CHCO), 7.33 (d, *J* = 7.5 Hz, 2 H, CH), 7.56 (s, 1 H, CH), 7.61 (d, *J* = 7.5 Hz, 2 H, CH), 9.42 (s, 1 H, NH).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 21.38, 21.97, 28.23, 36.93, 94.85, 102.23, 113.93, 120.58, 126.39, 129.36, 130.47, 140.36, 148.36, 150.12, 161.77, 196.68.

Anal. Calcd for $C_{18}H_{16}N_2OS$: C, 70.10; H, 5.23; N, 9.08. Found: C, 69.89; H, 5.23; N, 9.21.

5-(4-Methoxyphenyl)-3-[(3-oxo-1-cyclohexen-1-yl)amino]-2-thiophenecarbonitrile (2b)
Yield: 71%; yellow solid; mp 224–226 °C.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 1.90 (m, 2 H, CH_2), 2.19 (m, 2 H, CH_2), 2.53 (m, 2 H, CH_2), 3.79 (s, 3 H, CH_3), 5.25 (s, 1 H, CHCO), 7.01 (d, *J* = 7.5 Hz, 2 H, CH), 7.49 (s, 1 H, CH), 7.61 (d, *J* = 7.5 Hz, 2 H, CH), 9.41 (s, 1 H, NH).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 21.97, 28.23, 36.91, 55.93, 94.25, 102.17, 114.01, 115.30, 119.86, 124.69, 128.06, 148.37 150.08, 161.12, 161.84, 196.75.

Anal. Calcd for $C_{18}H_{16}N_2O_2S$: C, 66.65; H, 4.97; N, 8.64. Found: C, 67.01; H, 5.14; N, 8.37.

Preparation of 9-Amino-2-(4-aryl)-6,7-dihydrothieno[3,2-*b*]quinolin-8(5*H*)-ones 3a,b; General Procedure (Method A)
NaOMe or K_2CO_3 (2.2 mmol) and CuCl (10.4 mmol) were added to a solution of **2** (10.4 mmol) in anhyd DMF (5 mL) and the mixture was heated at 80–90 °C for 4 h. After cooling, the reaction mixture was poured into ice-water containing sodium tartrate (15 mmol). The precipitate obtained was filtered and extracted several times with a mixture MeOH–EtOAc (1:1). The organic solution was dried (Na_2SO_4), filtered and the solvent was evaporated to give a solid which was purified by column chromatography (CH_2Cl_2–MeOH, 9:1).

Friedländer Reaction; General Procedure (Method B)
$AlCl_3$ (3.4 mmol for cyclanones, 6.8 mmol for 1,3-cyclohexanedione) was suspended in anhyd DCE (10 mL/mmol of $AlCl_3$) at r.t. under argon. The corresponding thiophene **1** (2 mmol) and the ketone (1.7 mmol) were added and the reaction mixture was heated under reflux for 12 h. When the reaction was complete (monitored by TLC), a mixture of THF–H_2O (2:1) was added at r.t. and NaOH (10%) was added dropwise until the solution became basic. After stirring for 30 min, the mixture was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic layers were dried (Na_2SO_4), filtered and the solvent was evaporated to give a solid which was purified by column chromatography (CH_2Cl_2–MeOH, 9:1).

9-Amino-2-(4-methylphenyl)-6,7-dihydrothieno[3,2-*b*]quinolin-8(5*H*)-one (3a)
Column chromatography gave a brown solid; mp 220–222 °C.

Yield: 81% (Method A; NaOMe used as base).

Yield: 80% (Method B).

^{1}H NMR (250 MHz, DMSO-d_6): δ = 2.00 (m, 2 H, CH_2), 2.34 (s, 3 H, CH_3), 2.50 (m, 2 H, CH_2), 2.60 (m, 2 H, CH_2), 2.94 (s, 2 H, NH_2), 7.31 (d, *J* = 7.5 Hz, 2 H, 2 × CH), 7.64 (s, 1 H, CH), 7.69 (d, *J* = 7.5 Hz, 2 H, 2 × CH).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 21.38, 21.94, 22.33, 34.30, 115.46, 121.60, 126.42, 130.41, 130.76, 132.95, 139.72, 149.48, 151.72, 158.41, 164.55, 201.92.

Anal. Calcd for $C_{18}H_{16}N_2OS$: C, 70.10; H, 5.23; N, 9.08. Found: C, 70.26; H, 5.12; N, 8.77.

9-Amino-2-(4-methoxyphenyl)-6,7-dihydrothieno[3,2-*b*]quinolin-8(5*H*)-one (3b)
Column chromatography gave a brown solid; mp 228–230 °C.

Yield: 38% (Method A; K_2CO_3 used as base).

Yield: 85% (Method B).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.80 (s, 2 H, NH_2), 2.18 (m, 2 H, CH_2), 2.70 (m, 2 H, CH_2), 3.14 (m, 2 H, CH_2), 3.87 (s, 3 H, CH_3), 6.98 (d, *J* = 7.5 Hz, 2 H, 2 × CH), 7.58 (s, 1 H, CH), 7.64 (d, *J* = 7.5 Hz, 2 H, 2 × CH).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 21.38, 21.99, 34.07, 55.90, 106.63, 115.27, 116.86, 120.47, 126.08, 127.99, 149.23, 151.43, 158.41, 160.78, 164.23, 201.52.

HRMS: *m*/*z* calcd for $C_{18}H_{16}N_2O_2S$: 324.0932; found: 324.0930.

8-Amino-2-(4-methylphenyl)-6,7-dihydro-5*H*-cyclopenta[*b*]thieno[2,3-*e*]pyridine (5a)
Yield: 87% (Method B); mp 180–182 °C.

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^{1}H NMR (250 MHz, DMSO-d_6): δ = 2.04 (m, 2 H, CH_2), 2.33 (s, 3 H, CH_3), 2.77 (m, 2 H, CH_2), 2.85 (m, 2 H, CH_2), 6.26 (s, 2 H, NH_2), 7.27 (d, *J* = 7.5 Hz, 2 H, 2 × CH), 7.60 (s, 1 H, CH), 7.64 (d, *J* = 7.5 Hz, 2 H, 2 × CH).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 21.32, 23.06, 27.93, 34.37, 114.67, 116.36, 120.65, 126.04, 130.26, 131.54, 138.65, 144.22, 145.37, 157.08, 164.43.

Anal. Calcd for $C_{17}H_{16}N_2S$: C, 72.82; H, 5.75; N, 9.99. Found: C, 72.57; H, 5.59; N, 9.98.

9-Amino-2-(4-methylphenyl)-5,6,7,8-tetrahydrothieno[3,2-*b*]quinoline (6a)
Yield: 88% (Method B); mp 186–188 °C.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 1.78 (m, 2 H, CH_2), 1.80 (m, 2 H, CH_2), 2.33 (s, 3 H, CH_3), 2.55 (m, 2 H, CH_2), 2.77 (m, 2 H, CH_2), 6.20 (s, 2 H, NH_2), 7.27 (d, *J* = 7.5 Hz, 2 H, 2 × CH), 7.57 (s, 1 H, CH), 7.64 (d, *J* = 7.5 Hz, 2 H, 2 × CH).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 21.29, 22.91, 23.05, 23.75, 32.94, 110.17, 111.88, 120.13, 126.15, 130.28, 131.41, 138.85, 144.85, 147.44, 154.46, 154.80.

Anal. Calcd for $C_{18}H_{18}N_2S$: C, 73.43; H, 6.16; N, 9.51. Found: C, 73.41; H, 5.84; N, 9.66.

10-Amino-2-(4-methylphenyl)-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]thieno[2,3-*e*]pyridine (7a)
Yield: 80% (Method B); mp 188–190 °C.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 1.53 (m, 2 H, CH_2), 1.58 (m, 2 H, CH_2), 1.78 (m, 2 H, CH_2), 2.33 (s, 3 H, CH_3), 2.75 (t, 2 H, CH_2), 2.92 (m, 2 H, CH_2), 6.12 (s, 2 H, NH_2), 7.27 (d, *J* = 7.5 Hz, 2 H, 2 × CH), 7.58 (s, 1 H, CH), 7.64 (d, *J* = 7.5 Hz, 2 H, 2 × CH).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 21.25, 25.30, 26.93, 27.84, 32.17, 32.30, 115.41, 117.40, 120.56, 126.04, 130.21, 131.39, 138.68, 144.45, 146.30, 154.07, 162.10

Anal. Calcd for $C_{19}H_{20}N_2S$: C, 73.99; H, 6.54; N, 9.08. Found: C, 73.48; H, 6.84; N, 9.27.

8-Amino-2-(4-methoxyphenyl)-6,7-dihydro-5*H*-cyclopenta[*b*]thieno[2,3-*e*]pyridine (5b)
Yield: 98% (Method B); mp 180–182 °C.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 2.21 (m, 2 H, CH_2), 2.85 (m, 2 H, CH_2), 3.07 (m, 2 H, CH_2), 3.85 (s, 3 H, CH_3), 6.28 (s, 2 H, NH_2), 6.96 (d, *J* = 8.8 Hz, 2 H, 2 × CH), 7.50 (s, 1 H, CH), 7.64 (d, *J* = 8.8 Hz, 2 H, 2 × CH).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 23.05, 27.93, 34.35, 55.77, 114.58, 115.09, 116.12, 119.80, 126.87, 127.52, 144.21, 145.40, 157.14, 160.12, 164.25.

HRMS: *m*/*z* calcd for $C_{17}H_{16}N_2OS$: 296.0983; found: 296.0982.

9-Amino-2-(4-methoxyphenyl)-5,6,7,8-tetrahydrothieno[3,2-*b*]quinoline (6b)
Yield: 97% (Method B); mp 186–188 °C.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 1.79 (m, 2 H, CH_2), 1.80 (m, 2 H, CH_2), 2.25 (m, 2 H, CH_2), 2.78 (m, 2 H, CH_2), 3.82 (s, 3 H, CH_3), 6.16 (s, 2 H, NH_2), 7.06 (d, *J* = 8.8 Hz, 2 H, 2 × CH), 7.50 (s, 1 H, CH), 7.71 (d, *J* = 7.5 Hz, 2 H, 2 × CH).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 22.95, 23.15, 23.73, 33.30, 55.74, 109.94, 115.04, 115.53, 119.90, 126.84, 127.49, 144.11, 146.88, 155.13, 155.36, 160.07.

HRMS: *m*/*z* calcd for $C_{18}H_{18}N_2OS$: 310.1140; found: 310.1160.

10-Amino-2-(4-methoxyphenyl)-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]thieno[2,3-*e*]pyridine (7b)
Yield: 97% (Method B); mp 190–192 °C.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 1.73 (m, 2 H, CH_2), 1.75 (m, 2 H, CH_2), 2.48 (m, 2 H, CH_2), 2.74 (m, 2 H, CH_2), 3.08 (m, 2 H, CH_2), 3.85 (s, 3 H, CH_3), 4.14 (s, 2 H, NH_2), 6.96 (d, *J* = 9.0 Hz, 2 H, 2 × CH), 7.49 (s, 1 H, CH), 7.64 (d, *J* = 9.0 Hz, 2 H, 2 × CH).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 25.40, 27.09, 28.01, 32.31, 32.55, 55.82, 115.12, 115.31, 117.20, 120.28, 126.94, 127.54, 144.053, 146.04, 154.81, 162.39.

HRMS: *m*/*z* calcd for $C_{19}H_{20}N_2OS$: 324.1296; found: 324.1308.

8-Amino-2-(4-chlorophenyl)-6,7-dihydro-5*H*-cyclopenta[*b*]thieno[2,3-*e*]pyridine (5c)
Yield: 88% (Method B); mp 189–191 °C.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 2.06 (m, 2 H, CH_2), 2.79 (t, 2 H, CH_2), 2.86 (m, 2 H, CH_2,), 6.27 (s, 2 H, NH_2), 7.52 (d, *J* = 7.5 Hz, 2 H, 2 × CH), 7.71 (s, 1 H, CH), 7.79 (d, *J* = 7.5 Hz, 2 H, 2 × CH).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 27.94, 31.20, 34.42, 114.93, 116.88, 122.16, 127.79, 129.71, 133.24, 133.48, 142.45, 145.31, 157.11, 164.87.

HRMS: *m*/*z* calcd for $C_{16}H_{13}ClN_2S$: 300.0487; found: 300.0497.

9-Amino-2-(4-chlorophenyl)-5,6,7,8-tetrahydrothieno[3,2-*b*]quinoline (6c)
Yield: 89% (Method B); mp 190–192 °C.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 1.77 (m, 4 H, CH_2), 2.50 (m, 2 H, CH_2), 2.78 (m, 2 H, CH_2), 6.15 (s, 2 H, NH_2), 7.54 (d, *J* = 7.5 Hz, 2 H, 2 × CH), 7.69 (s, 1 H, CH), 7.79 (d, *J* = 7.5 Hz, 2 H, 2 × CH).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 22.86, 23.05, 23.75, 33.19, 110.34, 116.26, 121.88, 127.78, 129.64, 133.08, 133.50, 142.73, 147.12, 154.81, 155.39.

HRMS: *m*/*z* calcd for $C_{17}H_{15}ClN_2S$: 314.0644; found: 314.0651.

10-Amino-2-(4-chlorophenyl)-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]thieno[2,3-*e*]pyridine (7c)
Yield: 85% (Method B); mp 191–193 °C.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 1.58 (m, 2 H, CH_2), 1.60 (m, 2 H, CH_2), 1.81 (m, 2 H, CH_2), 2.78 (m, 2 H, CH_2), 2.94 (m, 2 H, CH_2), 6.14 (s, 2 H, NH_2), 7.54 (d, *J* = 7.5 Hz, 2 H, 2 × CH), 7.71 (s, 1 H, CH), 7.79 (d, *J* = 7.5 Hz, 2 H, 2 × CH).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 25.36, 26.99, 27.90, 32.21, 32.84, 115.64, 117.92, 122.39, 127.44, 127.76, 129.64, 133.19, 142.43, 146.05, 154.48, 162.70.

HRMS: *m*/*z* calcd for $C_{18}H_{17}ClN_2S$: 328.0800; found: 328.0797.

8-Amino-2-(4-methoxyphenyl)-3-methyl-6,7-dihydro-5*H*-cyclopenta[*b*]thieno[2,3-*e*]pyridine (5d)
Yield: 76% (Method B); mp 207–209 °C.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 2.38 (s, 3 H, CH_3), 2.71 (m, 2 H, CH_2), 2.80 (m, 2 H, CH_2), 2.88 (m, 2 H, CH_2), 3.80 (s, 3 H, CH_3O), 6.21 (s, 1 H, NH_2), 7.09 (d, *J* = 7.5 Hz, 2 H, 2 × CH), 7.52 (d, *J* = 7.5 Hz, 2 H, 2 × CH).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 12.96, 23.05, 27.82, 34.30, 55.70, 114.85, 114.96, 115.73, 127.24, 127.95, 130.45, 130.55, 138.13, 145.41, 159.52, 163.48

HRMS: *m*/*z* calcd for $C_{18}H_{16}N_2OS$: 310.1139; found: 310.1146.

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9-Amino-2-(4-methoxyphenyl)-3-methyl-5,6,7,8-tetrahydrothieno[3,2-*b*]quinoline (6d)
Yield: 98% (Method B); mp 210–212 °C.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 1.68 (m, 2 H, CH_2), 1.81 (m, 2 H, CH_2), 2.37 (s, 3 H, CH_3), 2.65 (m, 2 H, CH_2), 2.83 (m, 2 H, CH_2), 3.83 (s, 3 H, CH_3O), 6.06 (s, 1 H, NH_2), 7.06 (d, *J* = 7.5 Hz, 2 H, 2 × CH), 7.71 (d, *J* = 7.5 Hz, 2 H, 2 × CH).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 12.86, 23.23, 23.71, 33.43, 36.45, 55.69, 110.30, 114.79, 115.24, 127.33, 128.07, 130.21, 130.42, 137.92, 146.94, 154.57, 159.50.

Anal. Calcd for $C_{19}H_{20}N_2OS$: C, 70.34; H, 6.21; N, 8.63. Found: C, 70.22; H, 6.04; N, 8.87.

10-Amino-2-(4-chlorophenyl)-3-methyl-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]thieno[2,3-*e*]pyridine (7d)
Yield: 98% (Method B); mp 211–213 °C.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 1.68 (m, 2 H, CH_2), 1.74 (m, 2 H, CH_2), 1.81 (m, 2 H, CH_2), 2.37 (s, 3 H, CH_3), 2.65 (m, 2 H, CH_2), 2.83 (m, 2 H, CH_2), 3.83 (s, 3 H, CH_3O), 6.06 (s, 1 H, NH_2), 7.06 (d, *J* = 7.5 Hz, 2 H, 2 × CH), 7.71 (d, *J* = 7.5 Hz, 2 H, 2 × CH).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 12.62, 12.87, 27.00, 27.87, 30.49, 32.20, 55.77, 114.88, 115.79, 116.92, 130.57, 132.06, 132.18, 138.52, 146.56, 152.87, 159.64, 161.40.

HRMS: *m*/*z* calcd for $C_{20}H_{22}N_2S$: 338.1452; found: 338.1484.

Preparation of 9-Amino-2-aryl-5,6,7,8-tetrahydrothieno[3,2-*b*]quinolin-8-ols 4a,b; General Procedure
A solution of $LiAlH_4$ (1.6 mmol) in anhyd THF (20 mL) was added dropwise to a solution of **3** (1 mmol) in anhyd THF (20 mL) maintained at 0 °C under argon atmosphere. After the addition, the reaction mixture was refluxed for 1 h, then quenched by the addition of 10% HCl (2 mL). The mixture was made basic with 30% NaOH and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and evaporated to dryness to give a solid which was purified by column chromatography (CH_2Cl_2–MeOH, 9:1).

9-Amino-2-(4-methylphenyl)-5,6,7,8-tetrahydrothieno[3,2-*b*]quinolin-8-ol (4a)
Yield: 75%; brown solid; mp 225–227 °C.

^{1}H NMR (250 MHz, $CDCl_3$ + DMSO-d_6): δ = 1.47 (m, 2 H, CH_2), 1.88 (m, 2 H, CH_2), 2.05 (m, 2 H, CH_2), 2.71 (s, 3 H, CH_3), 4.38 (m, 1 H, CHO), 5.48 (s, 1 H, OH), 6.40 (s, 2 H, NH_2), 6.95 (s, 1 H, CH), 6.72 (d, *J* = 7.5 Hz, 2 H, 2 × CH), 7.06 (d, *J* = 7.5 Hz, 2 H, 2 × CH).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 18.33, 21.35, 32.93, 33.15, 63.11, 112.95, 116.58, 119.93, 126.232, 130.32, 131.18, 139.11, 146.04, 149.04, 154.95, 155.34.

Anal. Calcd for $C_{18}H_{18}N_2OS$: C, 69.65; H, 5.84; N, 9.02. Found: C, 69.70; H, 5.70; N, 8.79.

9-Amino-2-(4-methoxyphenyl)-5,6,7,8-tetrahydrothieno[3,2-*b*]quinolin-8-ol (4b)
Yield: 72%; brown solid; mp 225–228 °C.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 1.55 (m, 2 H, CH_2), 2.11 (m, 2 H, CH_2), 2.37 (m, 2 H, CH_2), 3.39 (s, 3 H, CH_3O), 4.23 (m, 1 H, CHO), 5.46 (s, 1 H, OH), 6.19 (s, 2 H, NH_2), 6.94 (s, 1 H, CH), 6.52 (d, *J* = 7.5 Hz, 2 H, 2 × CH), 7.18 (d, *J* = 7.5 Hz, 2 H, 2 × CH).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 18.54, 33.32, 33.52, 55.82, 63.37, 112.75, 115.13, 116.31, 119.85, 126.70, 127.65, 145.21, 148.53, 155.76, 156.40, 160.27.

HRMS: *m*/*z* calcd for $C_{18}H_{18}N_2O_2S$: 326.1089; found: 326.1089.

Acknowledgment

We thank the 'Ministère de l'Education Nationale, de l'Enseignement Supérieur et de la Recherche' for a PhD grant to D.T. We thank also the Université du Luxembourg for financial support to P.S.

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