Synthesis of Thiophene Analogues of the Tacrine Series

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Abstract: 3-Amino-2-cyanothiophenes condensed with cyclonanes and afforded analogues of Velnacline 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 velnacline (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 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 1 Reagents and conditions: i) cyclohexan-1,3-dione, PTSA, toluene, reflux; ii) CuCl, base, DMF, reflux; iii) LiAlH4, THF, reflux; iv) AlCl3, cyclohexan-1,3-dione, DCE, reflux; v) AlCl3, cyclic ketone, DCE, reflux.

Scheme 2 Reagents and conditions: i) POCl3, DMF, 60 °C, 5 h; ii) hydroxylamine chloride, EtOH; iii) Ac2O; iv) Na2S·9H2O, DMF, ClCH2CN, NaOEt.
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, 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-arylthiophenecarbonitriles 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, are underway.

Melting points were determined on a Stuart SMP3 apparatus and are uncorrected. 1H and 13C NMR spectra were recorded on a Bruker AC 250 MHz spectrometer in CDCl3 or DMSO-d6. 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 Na2S·9H2O (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 H2O 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 (CH2Cl2).

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

1H NMR (250 MHz, CDCl3): δ = 2.40 (s, 3 H, CH3), 4.91 (s, 2 H, NH2), 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).

13C NMR (63 MHz, DMSO-d6): δ = 21.32, 74.79, 115.70, 116.37, 125.97, 129.88, 130.22, 139.71, 148.89, 158.44.

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Enamine 2</th>
<th>Yield (%)</th>
<th>Entry</th>
<th>Ketone 3</th>
<th>Yield (%)</th>
<th>Overall yield (%) from 1</th>
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<tbody>
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<td>Method A</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Method B</td>
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<td></td>
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<sup>a</sup> CuCl, NaOMe, DMF, reflux.
<sup>b</sup> CuCl, K₂CO₃, DMF, reflux.

Table 3  Yields of the Friedländer Reaction

<table>
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<tr>
<th>Thiophene</th>
<th>Cyclanones</th>
<th>Tacrine analogue</th>
<th>Product</th>
<th>Yield (%)</th>
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<td>n = 2; 7a</td>
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<td>n = 1; 6b</td>
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<td>n = 2; 7d</td>
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3-Amino-5-(4-methoxyphenyl)-2-thiophenecarbonitrile (1b)
Yield: 95%; brown solid; mp 204–206 °C (isopropanol).

1H NMR (250 MHz, DMSO-d6): δ = 3.78 (s, 3 H, CH2), 6.49 (s, 2 H, NH), 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).

13C NMR (63 MHz, DMSO-d6): δ = 75.50, 116.04, 116.76, 127.82, 129.29, 130.47, 139.72, 149.48, 151.72, 158.41, 164.55, 201.92.

Anal. Calcd for C18H16N2O2S: C, 69.42; H, 5.12; N, 8.77. Found: C, 69.89; H, 5.23; N, 9.08. (Method A; NaOMe used as base).

Preparation of 9-Amino-2-(4-aryl)-6,7-dihydrothieno[3,2-b]quinolin-8(5H)-ones 3a,b; General Procedure (Method A)
A suspension of 1 (0.02 mol), cyclohexan-1,3-dione (0.02 mol) and PTSA·H2O (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–Et2O, 1:1).

5-(4-Methylphenyl)-3-(5-oxo-1-cyclohexen-1-yl)amino-2-thiophenecarbonitriles 2a,b; General Procedure (Method A)
A suspension of 1 (Method A; NaOMe used as base).

Yield: 87% (Method B); mp 180–182 °C.

1H NMR (250 MHz, DMSO-d6): δ = 2.00 (m, 2 H, CH2), 2.34 (s, 3 H, CH3), 2.50 (m, 2 H, CH2), 2.60 (m, 2 H, CH2), 2.94 (s, 2 H, NH), 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).

13C NMR (63 MHz, DMSO-d6): δ = 23.18, 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.


HRMS: m/z calcld for C18H16N2O2S: 324.0932; found: 324.0930.

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

Friedländer Reaction; General Procedure (Method B)
AlCl3 (3.4 mmol for cyclonane, 6.8 mmol for 1,3-cyclohexanedione) was suspended in anhyd DCE (10 mL/mmol of AlCl3) at r.t. under argon. The corresponding thiophene (1 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–H2O (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 CH2Cl2 (3 × 30 mL) and the combined organic layers were dried (Na2SO4), filtered and the solvent was evaporated to give a solid which was purified by column chromatography (CH2Cl2–MeOH, 9:1).
1H NMR (250 MHz, DMSO-d6): δ = 2.04 (m, 2 H, CH2), 2.33 (s, 3 H, CH3), 2.77 (m, 2 H, CH2), 2.85 (m, 2 H, CH2), 6.26 (s, 2 H, NH2), 7.27 (d, J = 7.5 Hz, 2 H, 2 CH2), 7.60 (s, 1 H, CH), 7.64 (d, J = 7.5 Hz, 2 H, 2 CH2).

13C NMR (63 MHz, DMSO-d6): 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 C17H15ClN2S: C, 67.28; H, 4.64; N, 10.69. Found: C, 67.26; H, 4.70; N, 10.71.

Synthesis of Thiophene Analogues of the Tacrine Series

10-Amino-2-(4-methoxyphenyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]thieno[2,3-e]pyridine (7b)

Yield: 97% (Method B); mp 190–192 °C.

1H NMR (250 MHz, DMSO-d6): δ = 1.73 (m, 2 H, CH2), 1.75 (m, 2 H, CH2), 2.48 (m, 2 H, CH2), 2.74 (m, 2 H, CH2), 3.08 (m, 2 H, CH2), 3.85 (s, 3 H, CH3), 4.14 (s, 2 H, NH2), 6.96 (d, J = 9.0 Hz, 2 H, 2 CH2), 7.49 (s, 1 H, CH), 7.64 (d, J = 9.0 Hz, 2 H, 2 CH2).

13C NMR (63 MHz, DMSO-d6): 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 C19H20N2O3S: 324.1296; found: 324.1308.

8-Amino-2-(4-chlorophenyl)-6,7-dihydro-5H-cyclohepta[b]thieno[2,3-e]pyridine (7c)

Yield: 88% (Method B); mp 191–193 °C.

1H NMR (250 MHz, DMSO-d6): δ = 2.06 (m, 2 H, CH2), 2.79 (t, 2 H, CH2), 2.86 (m, 2 H, CH2), 6.27 (s, 2 H, NH2), 7.52 (d, J = 7.5 Hz, 2 H, 2 CH2), 7.71 (s, 1 H, CH), 7.79 (d, J = 7.5 Hz, 2 H, 2 CH2).

13C NMR (63 MHz, DMSO-d6): 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 C19H19ClN2O3S: 300.0487; found: 300.0497.

8-Amino-2-(4-methylphenyl)-6,7,8-tetrahydrothieno[3,2-b]quinoline (6a)

Yield: 88% (Method B); mp 186–188 °C.

1H NMR (250 MHz, DMSO-d6): δ = 1.78 (m, 2 H, CH2), 1.80 (m, 2 H, CH2), 2.33 (s, 3 H, CH3), 2.75 (t, 2 H, CH2), 2.92 (m, 2 H, CH2), 6.12 (s, 2 H, NH2), 7.27 (d, J = 7.5 Hz, 2 H, 2 CH2), 7.58 (s, 1 H, CH), 7.64 (d, J = 7.5 Hz, 2 H, 2 CH2).

13C NMR (63 MHz, DMSO-d6): δ = 21.25, 25.30, 26.93, 27.84, 32.17, 32.30, 115.41, 114.70, 120.56, 126.04, 130.21, 131.39, 138.68, 144.45, 146.30, 154.07, 162.10.


9-Amino-2-(4-methylphenyl)-5,6,7,8-tetrahydrothieno[3,2-b]quinoline (6a)

Yield: 88% (Method B); mp 186–188 °C.

1H NMR (250 MHz, DMSO-d6): δ = 1.78 (m, 2 H, CH2), 1.80 (m, 2 H, CH2), 2.33 (s, 3 H, CH3), 2.75 (t, 2 H, CH2), 2.92 (m, 2 H, CH2), 6.12 (s, 2 H, NH2), 7.27 (d, J = 7.5 Hz, 2 H, 2 CH2), 7.58 (s, 1 H, CH), 7.64 (d, J = 7.5 Hz, 2 H, 2 CH2).

13C NMR (63 MHz, DMSO-d6): δ = 21.25, 25.30, 26.93, 27.84, 32.17, 32.30, 115.41, 114.70, 120.56, 126.04, 130.21, 131.39, 138.68, 144.45, 146.30, 154.07, 162.10.


9-Amino-2-(4-methoxyphenyl)-3-methyl-5,6,7,8-tetrahydrothieno[2,3-b]quinoline (6d)
Yield: 98% (Method B); mp 210–212 °C.
\[\begin{align*}
\text{1H NMR (250 MHz, DMSO-}d_6\text{)}: \delta = 1.68 (m, 2 \text{ H, CH}_2), 1.81 (m, 2 \text{ H, CH}_2), 2.37 (s, 3 \text{ H, CH}_3), 2.65 (m, 2 \text{ H, CH}_2), 3.83 (s, 3 \text{ H, CH}_3O), 6.06 (s, 1 \text{ H, NH}), 7.06 (d, J = 7.5 Hz, 2 \text{ H, 2 CH}).
\end{align*}\]

Preparation of 9-Amino-2-aryl-5,6,7,8-tetrahydrothieno[3,2-b]quinolin-8-ol (4a,b; General Procedure
A solution of LiAlH₄ (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 layer was dried (Na₂SO₄) and evaporated to dryness to give a solid and the residue was dried (Na₂SO₄) and evaporated to dryness to give a solid.

13C NMR (63 MHz, DMSO-\(d_6\)): \(\delta = 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.

Yield: 72%; brown solid; mp 225–228 °C.
\[\text{1H NMR (250 MHz, DMSO-}d_6\text{): } \delta = 1.55 (m, 2 \text{ H, CH}_2), 2.11 (m, 2 \text{ H, CH}_2), 2.37 (s, 3 \text{ H, CH}_3), 3.39 (s, 3 \text{ H, CH}_2O), 4.23 (m, 1 \text{ H, CHO}), 5.46 (s, 1 \text{ H, OH}), 6.19 (s, 2 \text{ H, NH}), 6.94 (s, 1 \text{ H, CH}), 6.52 (d, J = 7.5 Hz, 2 \text{ H, 2 CH}), 7.18 (d, J = 7.5 Hz, 2 \text{ H, 2 CH}).\]

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