Synthesis of Novel 2-Thienylimino-1,3-thiazolidin-4-ones

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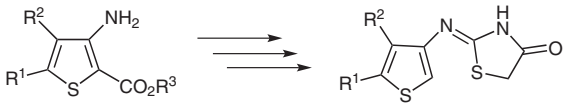
Dedicated to Professor Jan Bergman on the occasion of his retirement

Abstract: The preparation of new 2-thienylimino-1,3-thiazolidin-4-ones from 3-aminothiophene-2-carboxylate using an easy four-step procedure is described.

Key words: 3-aminothiophene-2-carboxylate, ammonium thiocyanate, 2-thienylimino-1,3-thiazolidin-4-ones

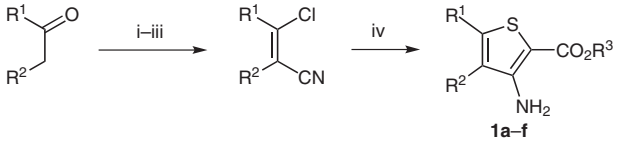
In continuation of our synthetic work with 3-amino-2-substituted thiophenes previously developed in our laboratory,[1] we propose here a new route to 2-thienylimino-1,3-thiazolidin-4-ones. The synthesis has been devised to use this kind of heterocycle as a scaffold for preparing new biologically active compounds.

2-Heteroarylimino-1,3-thiazolidin-4-ones, in particular thiazolimino- and benzothiazolimino-types, have previously been described in the literature and used as scaffolds for preparing a range of antifungal and antibacterial compounds,[2–4] however, derivatives bearing a substituted thiophene as the aromatic ring are not yet known. We describe here their preparation from ethyl or methyl 3-aminothiophene-2-carboxylate, as shown in Scheme 1.



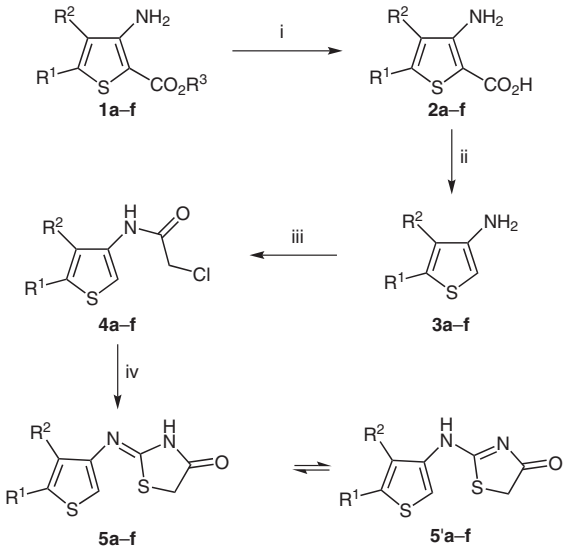
Scheme 1 Synthesis of 2-thienylimino-1,3-thiazolidin-4-ones

The aminothiophene esters (**1a–f**) were synthesized from β-chloropropenonitrile, which was obtained from β-chloropropenal as previously described (Scheme 2).[5–13]



Scheme 2 *Reagents and conditions*: (i) $POCl_3$, DMF, 60 °C, 5 h; (ii) hydroxylamine chloride, EtOH; (iii) Ac_2O; (iv) $HSCH_2CO_2Et$/Me, K_2CO_3, DMF.

The various aminothiophene carboxylates were first saponified by refluxing with a solution of potassium hydroxide for four hours, and the amino acids obtained were decarboxylated using anhydrous oxalic acid[14] with excellent yields. We also observed that the decarboxylation of these compounds may occur during the saponification, in particular with the 3-amino-5-(*tert*-butyl)-2-thiophenecarboxylic acid, which will therefore not be described here. The chloroacetamides were then synthesized by reaction between the thiophenamines and chloroacetyl chloride in *N*,*N*-dimethylformamide. The target thiazolidinones were finally reached by heating chloroacetamides and ammonium thiocyanate in ethanol at reflux for three hours (Scheme 3; Table 1). The cyclization mechanism has already been described by Vicini.[3]



Scheme 3 *Reagents and conditions*: (i) KOH, EtOH or MeOH, reflux, 4 h; (ii) Anhydrous oxalic acid, *i*-PrOH, 40 °C; (iii) $ClCOCH_2Cl$, anhydrous DMF, r.t., 2 h; (iv) NH_4SCN, EtOH, reflux, 3 h.

Thiazolidinone **5** could exist in the tautomeric form **5′**, however, a ^1H NMR study led us to consider that **5** is the only form existing. First, the high value of the shift of the NH proton led us to assume that the proton is in the vicinity of the carbonyl. Furthermore, the signal corresponding to the CH_2 from the thiazolidinone ring appears as a doublet because of coupling with the NH, which is only possible in the first form. Finally, HMBC analysis showed that the hydrogen from the NH is only correlated with the

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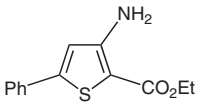
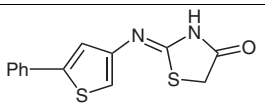
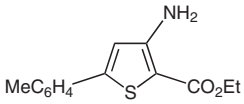
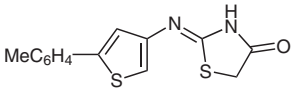
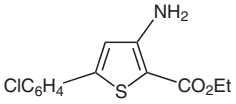
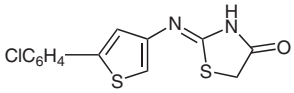
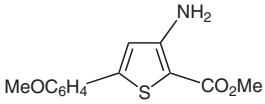
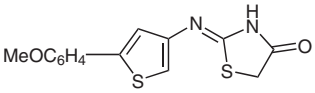
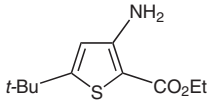
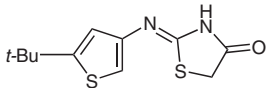
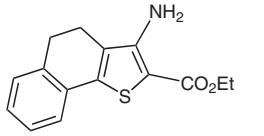
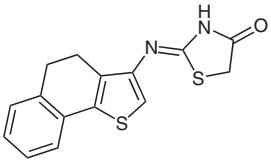
CH_2 carbon atom, and not with the aromatic carbon atoms from the thiophene ring, thus reinforcing the idea that the first form is favored.

Table 1 2-Thienylimino-1,3-tiazolidin-4-one Yields

Thiophene **1**	Thiazolidinone **5**	Yield (%)
	 **5a**	58
	 **5b**	48
	 **5c**	46
	 **5d**	90
	 **5e**	55
	 **5f**	77

The thiazolidinone scaffold will be used for structural modification on the nitrogen atom, and we intend to use the reactivity of the CH_2 group to introduce further diversity into the series.

Melting points were determined with a Stuart SMP3 apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AC 250 MHz spectrometer in either $CDCl_3$ or DMSO-d_6. Mass spectra were recorded with a MicroTof-Q 98. IR spectra were recorded with a Perkin–Elmer FTIR Baragon 1000PC instrument equipped with Spectrum (Perkin–Elmer) software version 5.3.1.

Synthesis of Aminothiophenecarboxylic Acids (2a–f); General Procedure

To a stirred solution of the appropriate thiophene (30 mmol) in EtOH or MeOH (30 mL) was added a solution of KOH (4 equiv) in H_2O (15 mL). The mixture was heated at reflux for 4 h and then the solvent was evaporated. The residue was poured into H_2O (45 mL) and acidified to neutral pH with orthophosphoric acid. The precipitate was filtered, washed with H_2O (2 × 10 mL) and petroleum ether (2 × 10 mL) and dried.

3-Amino-5-phenyl-2-thiophenecarboxylic Acid (2a)

Yield: 81%; pale-brown solid; mp 103 °C.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 6.78 (s, 1 H, CH), 7.39–7.41 (m, 3 H, 3 × CH), 7.59–7.61 (m, 2 H, 2 × CH).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 98.14, 116.20, 125.43, 128.90, 129.14, 132.92, 146.72, 155.04, 165.23.

3-Amino-5-(4-methylphenyl)-2-thiophenecarboxylic Acid (2b)

Yield: 88%; pale-brown solid; mp 184 °C.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 2.28 (s, 3 H, CH_3), 6.88 (s, 1 H, CH), 7.21 (d, J = 8 Hz, 2 H, 2 × CH), 7.47 (d, J = 8 Hz, 2 H, 2 × CH).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 20.64, 96.82, 117.08, 124.59, 129.59, 131.35, 137.08, 141.51, 146.82, 162.09.

3-Amino-5-(4-chlorophenyl)-2-thiophenecarboxylic Acid (2c)

Yield: 70%; pale-brown solid; mp 146 °C.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 6.96 (s, 1 H, CH), 7.48 (d, J = 8.5 Hz, 2 H, 2 × CH), 7.91 (d, J = 8.5 Hz, 2 H, 2 × CH).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 116.77, 127.17, 129.14, 131.83, 133.34, 145.06, 154.94, 165.21.

3-Amino-5-(4-methoxyphenyl)-2-thiophenecarboxylic Acid (2d)

Yield: 83%; pale-brown solid; mp 142 °C.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 3.77 (s, 3 H, OCH_3), 6.83 (s, 1 H, CH), 6.97 (d, J = 8.75 Hz, 2 H, 2 × CH), 7.53 (d, J = 8.75 Hz, 2 H, 2 × CH).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 55.23, 114.50, 125.61, 125.98, 126.96, 146.65, 154.96, 159.79, 165.40.

3-Amino-5,-6-dihydronaphtho[2′,1′,4,5]-2-thiophenecarboxylic Acid (2f)

Yield: 80%; green solid; mp 153 °C.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 2.60–2.63 (m, 2 H, CH_2), 2.85–2.91 (m, 2 H, CH_2), 7.18–7.20 (m, 3 H, 3 × CH), 7.27–7.32 (m, 1 H, CH).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 20.44, 28.12, 97.73, 123.03, 127.02, 127.72, 128.16, 128.35, 130.10, 135.45, 138.92, 152.50, 165.80.

Synthesis of Thiophenamines (3a–f); General Procedure

To a stirred solution of the appropriate aminothiophenecarboxylic acid (20 mmol) in *i*-PrOH (20 mL) was added anhydrous oxalic acid (1 equiv). The reaction was stirred at 40 °C until CO_2 evolution subsided. The mixture was cooled to r.t. and Et_2O (30 mL) was added. The precipitate was filtered, washed with petroleum ether (2 × 10 mL) and dried.

5-Phenyl-3-thiophenamine (3a)

Yield: 99%; pale-brown solid; mp 164 °C.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 6.05 (d, J = 1.5 Hz, 1 H, CH), 6.96 (d, J = 1.5 Hz, 1 H, CH), 7.26 (t, J = 7.25 Hz, 1 H, CH), 7.36 (t, J = 7.25 Hz, 2 H, 2 × CH), 7.51 (d, J = 7.25 Hz, 2 H, 2 × CH).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 97.19, 117.55, 124.66, 127.25, 128.97, 134.07, 141.33, 147.12, 161.25.

5-(4-Methylphenyl)-3-thiophenamine (3b)

Yield: 98%; pale-brown solid; mp 167 °C.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 2.27 (s, 3 H, CH_3), 6.01 (s, 1 H, CH), 6.90 (s, 1 H, CH), 7.17 (d, J = 8.2 Hz, 2 H, 2 × CH), 7.40 (d, J = 8.2 Hz, 2 H, 2 × CH).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 20.62, 95.55, 116.99, 124.14, 129.48, 131.40, 136.58, 141.33, 147.91.

5-(4-Chlorophenyl)-3-thiophenamine (3c)
Yield: 97%; pale-brown solid; mp 196 °C.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 6.03 (s, 1 H, CH), 6.96 (s, 1 H, CH), 7.41 (d, J = 8.5 Hz, 2 H, 2 × CH), 7.53 (d, J = 8.5 Hz, 2 H, 2 × CH).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 97.14, 118.03, 126.28, 128.93, 133.01, 139.77, 147.74, 162.

5-(4-Methoxyphenyl)-3-thiophenamine (3d)
Yield: 98%; pale-green solid; mp 216 °C.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 3.77 (s, 3 H, CH_3), 5.92 (d, J = 1.5 Hz, 1 H, CH), 6.81 (d, J = 1.5 Hz, 1 H, CH), 6.93 (d, J = 7.25 Hz, 2 H, 2 × CH), 7.44 (d, J = 7.25 Hz, 2 H, 2 × CH).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 55.12, 95.46, 114.33, 116.5, 126, 126.9, 141.28, 147.38, 158.59, 161.94.

5-*tert*-Butyl-3-thiophenamine (3e)
Yield: 52%; green solid; mp 145 °C.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 1.25 (s, 9 H, 3 × CH_3), 5.93 (s, 1 H, CH), 6.41 (s, 1 H, CH).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 31.6, 33.9, 95.2, 116.2, 141.4, 154.7.

5,6-Dihydronaphtho[2′,1′,4,5]-3-thiophenamine (3f)
Yield: 90%; green solid; mp 168 °C.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 2.55 (t, J = 7.5 Hz, 2 H, CH_2), 2.84 (t, J = 7.5 Hz, 2 H, CH_2), 6.02 (s, 1 H, CH), 7.08–7.21 (m, 4 H, 4 × CH).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 21, 28.1, 96.1, 121.8, 126.5, 126.8, 127.9, 129.4, 131.4, 134.1, 144.5, 161.6.

Synthesis of 2-Chloro-*N*-thienylacetamides (4a–f); General Procedure
To a stirred solution of the appropriate aminothiophene (10 mmol) in anhydrous DMF (15 mL) was added dropwise using a syringe, chloroacetyl chloride (1.1 equiv). The mixture was stirred at 25 °C for 2 h and then poured into H_2O. The precipitate was filtered, washed with H_2O (2 × 10 mL) and petroleum ether (2 × 10 mL) and dried.

2-Chloro-*N*-(5-phenyl-3-thienyl)acetamide (4a)
Yield: 71%; pale-brown solid; mp 128 °C.

IR (KBr): 3271 (NH), 1651 (C=O) cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 4.24 (s, 2 H, CH_2), 7.31 (t, J = 7.5 Hz, 1 H, CH), 7.41 (t, J = 7.5 Hz, 3 H, 3 × CH), 7.57 (t, J = 7.5 Hz, 3 H, 3 × CH), 10.71 (s, 1 H, NH).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 43.01, 109.40, 117.34, 125.07, 127.91, 129.17, 133.27, 136.61, 141.65, 163.97.

HRMS (APCI): m/z [$C_{12}H_{10}ClNOS$ + H]$^+$ calcd: 252.0244; found: 252.0254.

2-Chloro-*N*-[5-(4-methylphenyl)-3-thienyl]acetamide (4b)
Yield: 56%; green solid; mp 121 °C.

IR (KBr): 3285 (NH), 1653 (C=O) cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 2.37 (s, 3 H, CH_3), 4.21 (s, 2 H, CH_2), 7.17–7.20 (m, 2 H, 2 × CH), 7.24–7.26 (m, 1 H, CH), 7.45–7.48 (m, 2 H, 2 × CH), 8.49 (s, 1 H, NH).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 20.7, 43, 108.8, 116.8, 125, 129.7, 130.7, 136.4, 136.5, 141.8, 163.9.

HRMS (APCI): m/z [$C_{13}H_{12}ClNOS$ + H]$^+$ calcd: 266.0401; found: 266.0400.

2-Chloro-*N*-[5-(4-chlorophenyl)-3-thienyl]acetamide (4c)
Yield: 88%; brown solid; mp 135 °C.

IR (KBr): 3255 (NH), 1647 (C=O) cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 4.24 (s, 2 H, CH_2), 7.43–7.48 (m, 3 H, 3 × CH), 7.55–7.63 (m, 3 H, 3 × CH), 10.73 (s, 1 H, NH).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 43.33, 109.95, 117.92, 126.62, 129.13, 132.18, 132.31, 136.7, 140.22, 164.02.

HRMS (APCI): m/z [$C_{12}H_9Cl_2NOS$ + H]$^+$ calcd: 285.9855; found: 285.9862.

2-Chloro-*N*-[5-(4-methoxyphenyl)-3-thienyl]acetamide (4d)
Yield: 62%; pale-brown solid; mp 138 °C.

IR (KBr): 3287 (NH), 1658 (C=O) cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 3.76 (s, 3 H, CH_3), 4.21 (s, 2 H, CH_2), 6.97 (d, J = 8.75 Hz, 2 H, 2 × CH), 7.27 (s, 1 H, CH), 7.43 (s, 1 H, CH), 7.50 (d, J = 8.75 Hz, 2 H, 2 × CH), 10.70 (s, 1 H, NH).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 42.97, 61.56, 108.24, 114.52, 116.2, 125.96, 126.58, 136.67, 141.68, 159.06, 170.31.

HRMS (APCI): m/z [$C_{13}H_{12}ClNO_2S$ + H]$^+$ calcd: 282.0350; found: 282.0356.

2-Chloro-*N*-(5-*tert*-butyl-3-thienyl)acetamide (4e)
Yield: 77%; pale-brown solid; mp 136 °C.

IR (KBr): 3278 (NH), 1648 (C=O) cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 1.28 (s, 9 H, 3 × CH_3), 4.16 (s, 2 H, CH_2), 6.84 (s, 1 H, CH), 7.28 (s, 1 H, CH), 10.53 (s, 1 H, NH).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 33.9, 38.7, 43, 106.5, 116.1, 134.9, 155.2, 163.7.

HRMS (APCI): m/z [$C_{10}H_{14}ClNOS$ + H]$^+$ calcd: 232.0557; found: 232.0564.

2-Chloro-*N*-(5,6-dihydronaphtho[2′,1′,4,5]-3-thienyl)acetamide (4f)
Yield: 73%; green solid; mp 146 °C.

IR (KBr): 3276 (NH), 1653 (C=O) cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 2.73 (d, J = 7.5 Hz, 2 H, CH_2), 2.88 (d, J = 7.5 Hz, 2 H, CH_2), 4.34 (s, 2 H, CH_2), 7.18–7.31 (m, 4 H, 4 × CH), 7.60 (s, 1 H, CH), 9.96 (s, 1 H, NH).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 21.4, 27.9, 43, 110.7, 122.2, 127, 127.2, 128, 130.6, 133.7, 133.8, 133.9, 134.3, 164.6.

HRMS (APCI): m/z [$C_{14}H_{12}ClNOS$ + H]$^+$ calcd: 278.0401; found: 278.0414.

Synthesis of Thiazolidinones (5a–f): General Procedure
To a stirred solution of the appropriate acetamide (5 mmol) in EtOH (20 mL) was added ammonium thiocyanate (1 equiv). The mixture was heated at reflux for 3 h and allowed to stand overnight. The precipitate was filtered, washed with H_2O (2 × 10 mL) and petroleum ether (2 × 10 mL) and dried.

2-[(5-Phenyl-3-thienyl)imino]-1,3-thiazolidin-4-one (5a)
Yield: 58%; pale-brown solid; mp 197 °C.

IR (KBr): 3060 (NH), 1602 (C=O) cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 4.01 (d, J = 9.5 Hz, 2 H, CH_2), 7.01 (s, 1 H, CH), 7.27–7.46 (m, 4 H, 4 × CH), 7.58–7.63 (m, 2 H, 2 × CH), 11.55 (s, 1 H, NH).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 34.95, 111.29, 117.49, 120.29, 124.99, 129.11, 133.06, 136.98, 142.26, 177.54, 187.96.

HRMS (APCI): *m/z* $[C_{13}H_{10}N_2OS_2 + H]^+$ calcd: 275.0307; found: 275.0312.

2-{[5-(4-Methylphenyl)-3-thienyl]imino}-1,3-thiazolidin-4-one (5b)
Yield: 48%; green solid; mp 250 °C.

IR (KBr): 2919 (NH), 1614 (C=O) cm^{-1}.

^1H NMR (250 MHz, DMSO-d_6): δ = 2.30 (s, 3 H, CH_3), 4.01 (d, *J* = 9.5 Hz, 2 H, CH_2), 6.96 (s, 1 H, CH), 7.19–7.24 (m, 2 H, 2 × CH), 7.41–7.55 (m, 3 H, 3 × CH), 11.53 (s, 1 H, NH).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 20.7, 34.92, 110.7, 117, 119.7, 125, 129.7, 130.5, 137.5, 142.4. 177.4, 187.8.

HRMS (APCI): *m/z* $[C_{14}H_{12}N_2OS_2 + H]^+$ calcd: 289.0464; found: 289.0474.

2-{[5-(4-Chlorophenyl)-3-thienyl]imino}-1,3-thiazolidin-4-one (5c)
Yield: 46%; pale-brown solid; mp 280 °C.

IR (KBr): 3119 (NH), 1619 (C=O) cm^{-1}.

^1H NMR (250 MHz, DMSO-d_6): δ = 4.02 (d, *J* = 9.5 Hz, 2 H, CH_2), 7.03 (s, 1 H, CH), 7.30 (s, 1 H, CH), 7.43–7.49 (m, 2 H, 2 × CH), 7.61–7.65 (m, 2 H, 2 × CH), 11.67 (s, 1 H, NH).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 39.63, 111.83, 120.97, 126.84, 129.16, 131.98, 132.50, 137.06, 141.30, 177.77, 187.92.

HRMS (APCI): *m/z* $[C_{13}H_9ClN_2OS_2 + H]^+$ calcd: 308.9918; found: 308.9925.

2-{[5-(4-Methoxyphenyl)-3-thienyl]imino}-1,3-thiazolidin-4-one (5d)
Yield: 90%; orange solid; mp 219 °C.

IR (KBr): 3102 (NH), 1610 (C=O) cm^{-1}.

^1H NMR (250 MHz, DMSO-d_6): δ = 3.76 (s, 3 H, CH_3), 4.02 (d, *J* = 9.5 Hz, 2 H, CH_2), 6.92–7.00 (m, 2 H, 2 × CH), 7.14 (s, 1 H, CH), 7.33 (s, 1 H, CH), 7.51–7.56 (m, 2 H, 2 × CH), 11.75 (s, 1 H, NH).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 18.45, 55.18, 110.12, 114.47, 119.07, 126.07, 126.53, 136.77, 142.31, 159.06, 177.47, 187.98.

HRMS (ESI): *m/z* $[C_{14}H_{12}N_2O_2S_2 + Na]^+$ calcd: 327.0232; found: 327.0247.

2-[(5-*tert*-Butyl-3-thienyl)imino]-1,3-thiazolidin-4-one (5e)
Yield: 55%; green solid; mp 167 °C.

IR (KBr): 2955 (NH), 1603 (C=O) cm^{-1}.

^1H NMR (250 MHz, DMSO-d_6): δ = 1.30 (s, 9 H, 3 × CH_3), 4.00 (d, *J* = 9.5 Hz, 2 H, CH_2), 6.96 (s, 1 H, CH), 7.42 (s, 1 H, CH), 11.35 (s, 1 H, NH).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 32.09, 34.1, 108.5, 116.2, 118.8, 135.4, 156, 171, 187.86.

HRMS (ESI): *m/z* $[C_{11}H_{14}N_2OS_2 + Na]^+$ calcd: 277.0440; found: 277.0440.

2-{(5,6-Dihydronaphtho[2′,1′,4,5]-3-thienyl)imino}-1,3-thiazolidin-4-one (5f)
Yield: 74%; green solid; mp 100 °C.

IR (KBr): 2970 (NH), 1633 (C=O) cm^{-1}.

^1H NMR (250 MHz, DMSO-d_6): δ = 2.57 (t, *J* = 7.5 Hz, 2 H, CH_2), 2.87 (t, *J* = 7.5 Hz, 2 H, CH_2), 3.98 (d, *J* = 9.5 Hz, 2 H, CH_2), 6.93 (s, 1 H, CH), 7.13–7.35 (m, 4 H, 4 × CH), 11.76 (s, 1 H, NH).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 21.56, 28.04, 34.71, 121.99, 122.15, 127.02, 127.19, 128.12, 130.77, 132.82, 134.24, 134.43, 134.86, 175.74.

HRMS (ESI): *m/z* $[C_{15}H_{12}N_2OS_2 + Na]^+$ calcd: 323.0283; found: 323.0281.

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