Synthesis and spectral investigation of some methyl-substituted 3-(2-pyridyl)-2-(2-thienyl)thiazolidin-4-one derivatives

İsmail Fidan[a], Cavit Kazaz[b]*, Ertan Şahin[b] and Şeniz Kaban[a]

[a]*Yildız Technical University, Faculty of Science and Arts, Department of Chemistry, 34220 Istanbul, Turkey*
[b]*Atatürk University, Faculty of Science, Department of Chemistry, 25240 Erzurum, Turkey*

Some heteroaryl-substituted thiazolidin-4-one derivatives have been synthesised starting from thiophenecarboxaldehydes, 2-amino-6-methylpyridine and 2-mercaptoacetic acid. However, the use of 2-mercaptopropanoic acid gave the thiazolidinone derivatives as a mixture of *cis*-and *trans*-isomers. The configuration of both the *cis*-and *trans*-isomers has been established by NOE-difference experiments. Furthermore, the stereochemistry of one of the *trans* isomers was established by X-ray crystallography.

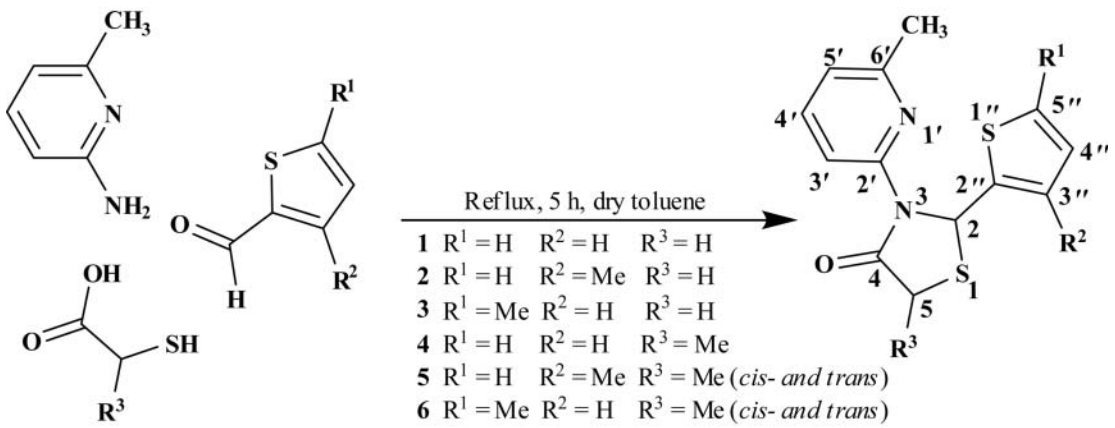
Keywords: heteroaryl-substituted thiazolidinone, configuration, diastereomer, NOE-difference, X-ray crystallography

Thiazolidinone derivatives are important compounds in medicinal and biological chemistry due to their pharmacological properties such as antibacterial,[1,2] antifungal,[3] anticonvulsant,[4,5] anticancer,[6] antileukaemic,[7] antimicrobial[8] and anti-HIV[9] activities. Synthetic combinatorial libraries made up of hundreds to millions of small organic molecules have been successfully developed and used to discover new antimicrobial leads.

Note that few examples of thiazolidin-4-ones having heteroaryl substituents at the 2- and 3- positions are known. We now report a series of heteroaryl-substituted thiazolidinone derivatives **1**–**6** (Scheme 1) obtained by slight modifications to a one-pot three-component condensation reaction[9,10] and unambiguous structural elucidation by analytical and spectroscopic data.

Results and discussion

While the compounds **1**–**3** were obtained from straightforwardly from mercaptoacetic acid, thiazolidinones **4**–**6** were generated from 2-mercaptopropionic acid as a mixture of *cis*- and *trans* diastereomers which could be separated by column chromatography on silica gel and elution with ethyl acetate: hexane (1:4). Although the *trans*-isomer of compound **4** and *cis*-*trans*-isomers of compounds **5**–**6** could be readily separated and characterised by using spectroscopic methods, *cis*-**4** could not be obtained because of its instability. The ratios of *cis*:*trans* isomers were determined to be 1:1 in each case by ^{1}H NMR spectroscopy. The ^{1}H NMR spectral data of compounds **1–6** are in agreement with the proposed structures in Scheme 1. The ^{1}H NMR spectra of compounds **1–3** show that the doublet signals at δ 4.10–3.78 and 4.11–3.82 ppm, with a coupling constant of J = 16.0 Hz can be ascribed to methylene protons (AB-system) attached to C-5. The chemical shifts, coupling constants and multiplicity of the remaining protons of **1**–**3** are similar to compounds **4**–**6**. For compounds **4**–**6**, the doublets observed at δ 1.62–1.77 and quartet signals at 4.08–4.37 ppm correspond to the C-5 methyl and H-5 methine protons (J = 7.0 Hz), respectively. The singlets between δ 2.27 and 2.40 ppm correspond to methyl groups on the thienyl and pyridyl substituents respectively. For compounds **1**–**6**, the doublet, double doublet, triplet and multiplet signals in the range δ 6.57–7.92 correspond to the pyridine and thiophene ring protons. It is noteworthy that in the whole series, the chemical shift of the methine protons (H-2) at C-2 was observed in the range δ 7.03–7.22. The downfield shift of this proton can be explained by deshielding which results from the inductive effect of the thiophene ring and the thiazolidine ring heteroatoms. The chemical shift values of H-2 are in agreement with the spectral data of similar compounds reported in the literature.[11] These spectral studies including ^{13}C NMR measurements allow us to determine the constitution of molecules **1**–**6**, but not the correct relative configuration of compounds **4**–**6**. For this purpose, NOE-difference experiments were performed to differentiate between the *cis*-and *trans*-isomers, based upon the orientation of the thienyl ring at C-2 and the C-5 methyl group in compounds **5** and **6**. The NOE-difference assignments of compound **5** are summarised in Fig. 1. While the irradiation of the H-5 signal at δ 4.08 caused an enhancement of both the methyl and H-2 signals, irradiation of the H-5 proton at δ 4.37 caused an enhancement only of the C-5 methyl signal. These



Scheme 1

* Correspondent. E-mail: ckazaz@atauni.edu.tr

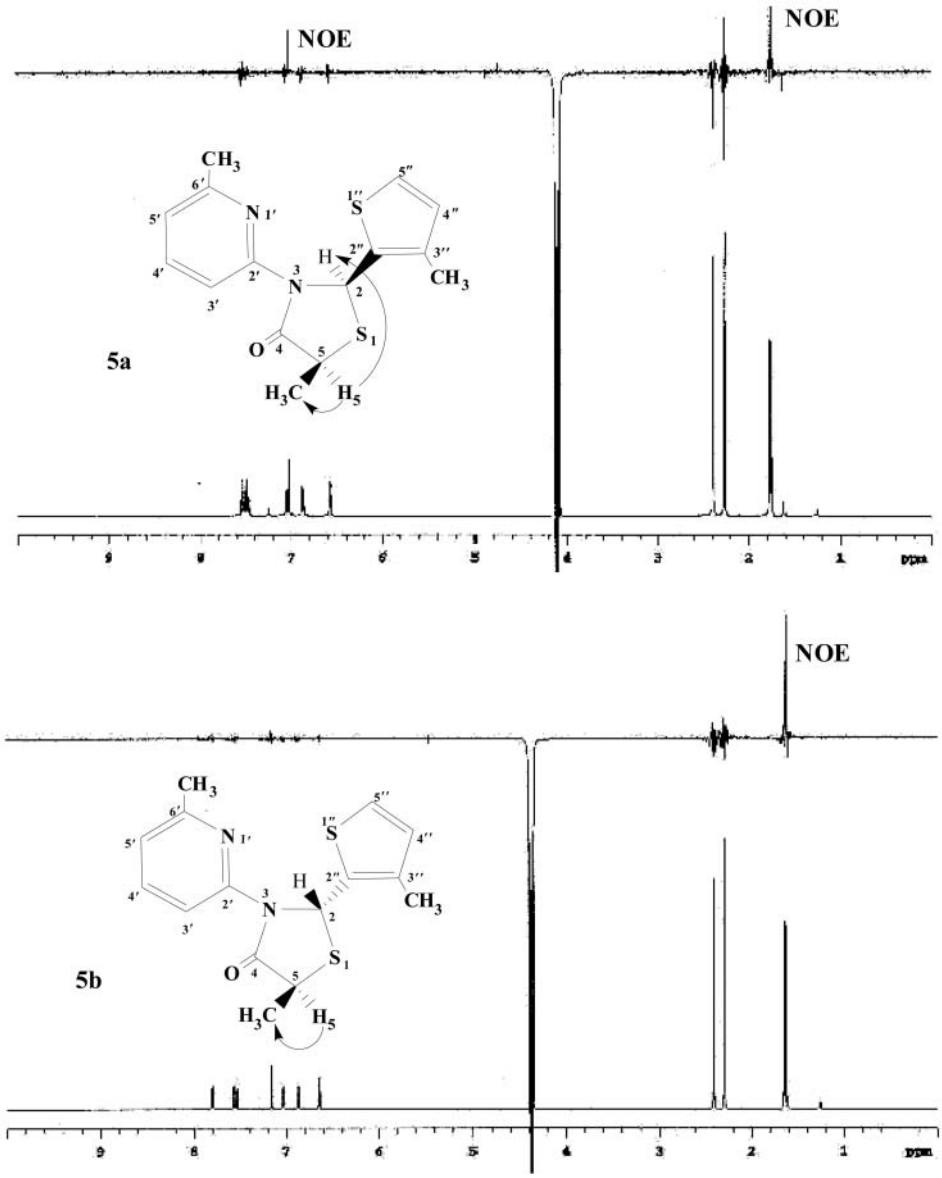


Fig. 1 The NOE-difference spectra of *cis*-and *trans*-isomers of compound **5**.

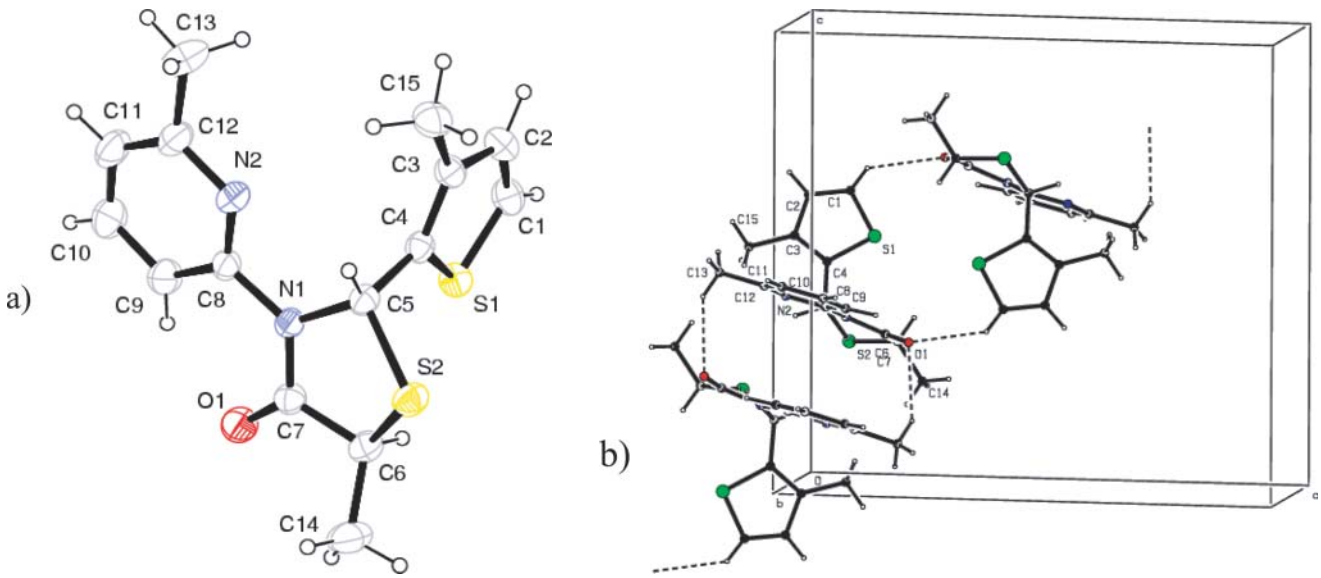


Fig. 2 (a) The molecular structure of **5b** showing the atom–labelling scheme. Displacement ellipsoids are drawn at the 50% probability level. (b) Crystal packing of **5b** with the *H*-bonding geometry.

Table 1 Selected bond lengths (Å) and angles (°), and hydrogen bonds for **5b**

Bond lengths			
N(2)–C(8)	1.329(3)	C(12)–C(13)	1.505(4)
O(1)–C(7)	1.209(3)	S(1)–C(4)	1.735(2)
S(1)–C(1)	1.708(3)	S(2)–C(6)	1.803(2)
N(1)–C(8)	1.424(3)	N(1)–C(5)	1.470(3)
N(1)–C(7)	1.378(3)	C(8)–C(9)	1.385(3)
C(5)–C(4)	1.496(3)	C(6)–C(14)	1.518(4)
C(3)–C(15)	1.500(3)	C(12)–C(11)	1.371(4)
Bond angles			
C(8)–N(2)–C(12)	118.2(2)	C(5)–N(1)–C(7)	116.0(2)
N(2)–C(8)–N(1)	114.3(2)	N(1)–C(5)–C(4)	113.2(2)
S(1)–C(4)–C(5)	121.4(2)	S(2)–C(6)–C(14)	112.5(2)
Hydrogen bonds			
D–H···A	d(*H···A*)	d(*D···A*)	<(*DHA*)
C(1)–H(1)···O(1)[a)]	2.53	3.238(3)	134
C(13)–H(13b)···O(1) [b)]	2.58	3.400(3)	144

Symmetry transformations used to generate equivalent atoms: [a] 1/2–*x*,1/2–*y*,1–*z*; [b] –*x*,*y*,1/2–*z*.

NOE experiments revealed compound **5a** to possess *cis*-stereochemistry whilst a *trans*-orientation was assigned to compound **5b**. Similar NOE experiments enabled the *cis*-and *trans*-isomers of compound **6** to be assigned. The H-5 protons of the *trans* isomers of compounds **5** and **6** resonate at δ 4.37 which is of comparable magnitude to that in the *trans* isomer of compound **4** (H-5 = δ 4.31).

The ^{13}C NMR chemical shifts are in agreement with the structure of compounds. In the whole series, the carbonyl carbons (C-4) and the carbons of pyridine and thiophene rings absorbed at δ 170–175 and 100–160, respectively. In the aliphatic region, the C-2 and C-5 carbons resonated at δ 54.96–58.94 and 34.77–43.46, respectively. While the methyl carbons attached to pyridine ring resonated at δ 24.22–24.34 those attached to a thiophene ring absorbed at δ 13.99–14.04. The methyl groups at C-5 on the thiazolidinone ring also resonated between 17.80 and 20.26 ppm. The *trans*-configuration of **5b** was also supported by X-ray diffraction analysis as shown in Fig. 2a.

An X-ray diffraction analysis of **5b** was undertaken. The molecular structure and packing diagram of the compound are shown in Figs 2a and 2b, respectively. Selected bond lengths and bond angles are given in Table 1. The results of this study confirmed unambiguously the proposed structure of **5b**. The compound crystallises in the monoclinic space group C2/c, with four molecules in the unit cell (Fig. 2b). In the crystal **5b** shows the (relative) *S,S* configuration (related to the stereogenic carbon atoms at C-5, C-6) and the thiazolidine ring has an envelope conformation (maximum deviation from mean plane is 0.206 Å for atom S-2). Thiophene and pyridine rings are planer (deviations from mean planes are less than 0.003 Å). The C–O_{ketone} bond length is 1.209(3) Å. Furthermore, the crystal structure of compound 5b consists of hydrogen bonded dimeric chains running along the diagonal axis in Fig.2b. The C—H···O are the detected intramolecular hydrogen bonds and the data are collated in Table 1.

In conclusion, in this study, we have achieved the synthesis and structural characterisation of some novel heteroaryl-substituted thiazolidinone derivatives starting from thiophenecarboxaldehyde, 2-amino-6-methylpyridine a 2-mercaptoalkanoic acid. The configurations of diastereomers were determined by X-ray diffraction and by NMR spectroscopy.

Experimental

Melting points were determined in open capillary tubes with a Gallenkamp melting point apparatus and are uncorrected. UV spectra were recorded on a UNICAM UV2-100 UV-visible spectrophotometer. FT-IR spectra were obtained on a Perkin-Elmer Spectrum One FT-IR spectrometer as KBr pellets. ^{1}H NMR, ^{13}C NMR and NOE-difference spectra were recorded in $CDCl_3$ on a Varian Mercury-Plus 400 MHz instrument equipped with a 5 mm ASW PFG probe at room temperature. The chemical shifts (δ) are expressed in parts per million (ppm) and coupling constants (*J*) in Hz relative to tetramethylsilane (TMS) as internal standard. The progress of the reaction and the purities of the obtained products were monitored by thin layer chromatography on silica gel sheets (Merck 5554) using ethyl acetate:hexane 1:4 as eluent and UV light was used for detection. Column chromatography was performed with silica gel 60 (70–230 mesh) purchased from Merck. 2-Amino-6-methylpyridine and 2-mercaptopropionic acid were purchased from Merck and Fluka respectively. Thiophene-2-carboxaldehyde and 5-methylthiophene-2-carboxaldehyde were obtained from Acros, 3-methylthiophene-2-carboxaldehyde was purchased from Aldrich. The aldehydes were vacuum distilled prior to use. Mass spectra were measured on a Shimadzu GC/MS QP 2000 A spectrometer with 70 eV electron impact ionisation. Elemental analyses were carried out on a Leco model CHNS-932 analyser.

*Synthesis of 1,3-thiazolidin-4-ones (***1–6***); general procedure*

A solution of the appropriate thiophenecarboxaldehyde (2.0 mmol), 2-amino-6-methylpyridine (2.0 mmol) and the appropriate 2-mercaptoalkanoic acid (1.3 mmol) in dry toluene (approx. 10 mL) was refluxed for 5 h in a flask equipped with a Dean–Stark trap and then allowed to cool to room temperature. The resulting brownish-orange solution was washed with 10% aqueous $NaHCO_3$ (2 × 25 mL) in order to remove traces of acid and then water (1 × 25 mL). The organic layer was dried over $CaCl_2$. Removal of toluene under reduced pressure gave a crude oily product which was dissolved in a minimum amount of EtOH-H_2O. After aging of this solution for 3 days at –20 °C, the product was obtained as crystals with sufficient purity.

3-(6-Methyl-2-pyridyl)-2-(2-thienyl)-1,3-thiazolidin-4-one (**1**): Yield 19%, pale yellow rods, m.p. 74–75 °C; R_f = 0.44 (ethyl acetate-hexane, 1:4); UV ($CHCl_3$): λ_{max} 245 and 279 nm; FT-IR (KBr): 3111 and 3066 (heteroaromatic, =C–H), 2983, 2919 and 2846 (aliphatic, C–H), 1698 (C=O), 1592, 1574, 1455, 1430 and 1416 (heteroaromatic, C=C and C=N), 1346, 1307, 1233, 785, 702 and 695 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, 1H, *J* = 8.4 Hz, H-3′), 7.57 (t, 1H, *J* = 7.8 Hz, H-4′), 7.22 (s, 1H, H-2), 7.17 (d, 1H, *J* = 4.8 Hz, H-5″), 7.07 (d, 1H, *J* = 3.2 Hz, H-3″), 6.91 (d, 1H, *J* = 7.6 Hz, H-5′), 6.83 (dd, 1H, $J_{4,5}$ = 4.8 Hz and $J_{4,3}$ = 3.2 Hz, H-4″), 4.10 (d, 1H, A part of AB-system, J_{ab} = 16.0 Hz, H-5_a), 3.78 (d, 1H, B part of AB-system, J_{ab} = 16.0 Hz, H-5_b), 2.45 (s, 3H, H_3C-6′); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.51 (C-4), 157.03, 149.89, 145.30, 138.37, 126.58, 126.50, 126.09, 120.55 and 114.45 (pyridine and thiophene ring carbons), 58.94 (C-2), 34.77 (C-5), 24.28 (H_3C-6′); GC-MS: *m/z* 276 (M^+, 100), 243 (27), 234 (65), 201 (67), 184 (31), 139 (50), 127 (12), 119 (11), 93 (79), 92 (50), 65 (18). Full details of the chromatographic and spectral characterisation data for this compound are given in the Electronic Supplementary Information.

3-(6-Methyl-2-pyridyl)-2-(3-methyl-2-thienyl)-1,3-thiazolidin-4-one (**2**)**:** Yield 35%, pale yellow rods, m.p. 107–108°C; R_f = 0.42 (ethyl acetate-hexane, 1:4); UV ($CHCl_3$): λ_{max} 246 and 276 nm; FT-IR (KBr): 3094 (heteroaromatic, =C–H), 2923 (aliphatic, C–H), 1690 (C=O), 1592, 1571, 1457 and 1434 (heteroaromatic, C=C and C=N), 1365, 1319 and 796 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, 1H. *J* = 8.4 Hz, H-3′), 7.54 (t, 1H, *J* = 7.8 Hz, H-4′), 7.18 (s, 1H, H-2), 7.05 (d, 1H, *J* = 4.8 Hz, H-5″), 6.88 (d, 1H, *J* = 7.2 Hz, H-5′), 6.63 (d, 1H, *J* = 5.2 Hz, H-4″), 4.11 (d, 1H, A part of AB-system, J_{ab} = 16.0 Hz, H-5_a), 3.82 ((d, 1H, B part of AB-system, J_{ab} = 16.0 Hz, H-5_b), 2.40 (s, 3H, H_3C-6′), 2.28 (s, 3H, H_3C-3″); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.48 (C-4), 157.03, 149.91, 139.06, 138.19, 135.74, 129.96, 124.32, 120.77 and 115.44 (pyridine and thiophene ring carbons), 57.59 (C-2), 34.48 (C-5), 24.32 (H_3C-6′), 14.02 (H_3C-3″); Anal. Calcd for $C_{14}H_{14}N_2OS_2$: C, 57.90; H, 4.86; N, 9.65; S, 22.08. Found: C, 57.83; H, 4.85; N, 9.61; S, 22.09%; GC-MS: *m/z* 290 (M^+, 67), 275 (6), 257 (31), 248 (23), 216 (12), 215 (52), 198 (31), 141 (38), 139 (42), 135 (15), 119 (18), 108 (25), 93 (100), 92 (73), 65 (32).

3-(6-Methyl-2-pyridyl)-2-(5-methyl-2-thienyl)-1,3-thiazolidin-4-one (**3**)**:** Yield 9%, pale yellow rods, m.p. 104–105°C; R_f = 0.42 (ethyl acetate-hexane, 1:4); UV ($CHCl_3$): λ_{max} 246 and 276 nm; FT-IR (KBr): 3094 (heteroaromatic, =C–H), 2922 (aliphatic, C–H), 1690 (C=O), 1592, 1571, 1457 and 1424 (heteroaromatic, C=C and C=N), 1365, 1319 and 796 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, 1H, *J* = 8.1 Hz, H-3′), 7.55 (t, 1H, *J* = 7.8 Hz, H-4′), 7.18 (s, 1H, H-2), 7.05

(d, 1H, J = 5.0 Hz, H-3″), 6.88 (d, 1H, J = 7.4 Hz, 5′-H), 6.63 (d, 1H, J = 5.0 Hz, H-4″), 4.11 (d, 1H, A part of AB-system, J_{ab} = 15.9 Hz, H-5$_a$), 3.82 (d, 1H, B part of AB-system, J_{ab} = 15.9 Hz, H-5$_b$), 2.40 (s, 3H, H_3C-6′), 2.28 (s, 3H, H_3C-5″); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.46 (C-4), 157.00, 149.94, 139.10, 138.16, 135.70, 129.94, 124.26, 120.73 and 115.40 (pyridine and thiophene ring carbons), 57.59 (C-2), 34.46 (C-5), 24.28 (H_3C-6′), 13.99 (H_3C-5″); Anal. Calcd for $C_{14}H_{14}N_2OS_2$: C, 57.90; H, 4.86; N, 9.65; S, 22.08. Found: C, 57.81; H, 4.95; N, 9.48; S, 22.18%; GC-MS: *m/z* 290 (M^+, 100), 275 (8), 257 (42), 247 (31), 217 (22), 215 (59), 198 (31), 141 (30), 139 (35), 119 (15), 108 (18), 93 (67), 92 (52), 65 (24).

trans-*5-Methyl-3-(6-methyl-2-pyridyl)-2-(2-thienyl)-1,3-thiazolidin-4-one* (**4):** Yield (17%), white microcrystals, m.p. 80–81°C; R_f = 0.56 (ethyl acetate-hexane, 1:4)**;** UV ($CHCl_3$): λ_{max} 246 and 280 nm; FT-IR (KBr): 3111, 3075 and 3055 (heteroaromatic, =C–H), 2966, 2926 and 2865 (aliphatic, C–H), 1692 (C=O), 1589, 1576, 1452 and 1415 (heteroaromatic, C=C and C=N), 1340, 1289, 1255, 1236, 790 and 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, 1H, J = 8.2 Hz, H-3′), 7.58 (t, 1H, J = 7.8 Hz, H-4′), 7.19 (s, 1H, H-2), 7.16 (dd, 1H, $J_{5,4}$ = 5.0 Hz and $J_{5,3}$ = 1.1 Hz, 5″-H), 7.06 (d, 1H, J = 3.4 Hz, H-3″), 6.91 (d, 1H, J = 7.4 Hz, H-5′), 6.83 (dd, 1H, $J_{4,5}$ = 5.0 and $J_{4,3}$ = 3.4 Hz, H-4″), 4.31 (q, 1H, J = 6.9 Hz, H-5), 2.45 (s, 3H, H_3C-6′), 1.62 (d, 3H, J = 6.9 Hz, H_3C-5); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.17 (C-4), 156.90, 150.02, 145.68, 138.36, 126.56, 126.10, 125.71, 120.22 and 113.64 (pyridine and thiophene ring carbons), 56.18 (C-2), 42.92 (C-5), 24.28 (H_3C-6′), 17.80 (H_3C-5); Anal. Calcd for $C_{14}H_{14}N_2OS_2$: C, 57.90; H, 4.86; N, 9.65; S, 22.08. Found: C, 57.66; H, 4.88; N, 9.65; S, 22.15%; GC-MS: *m/z* 290 (M^+, 84), 275 (2), 257 (76), 234 (28), 233(55), 202(23), 201 (67), 198 (28), 153 (28), 135 (38), 127 (13), 119 (8), 93 (100), 92 (43), 65 (20).

cis-*5-Methyl-3-(6-methyl-2-pyridyl)-2-(3-methyl-2-thienyl)-1,3-thiazolidin-4-one* (**5a):**Yield 17%, white microcrystals, m.p. 132–133°C; R_f = 0.42 (ethyl acetate-hexane, 1:4); UV ($CHCl_3$): λ_{max} 246 and 274 nm; FT-IR (KBr): 3113 (heteroaromatic, =C–H), 2979, 2925 and 2872 (aliphatic, C–H), 1692 (C=O), 1595, 1569 and 1455 (heteroaromatic, C=C and C=N), 1349, 1318, 790, 758 and 742 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55–7.47 (m, 2H, H-3′ and H-4′), 7.06 (d, 1H, J = 5.0 Hz, H-5″), 7.02 (s, 1H, H-2), 6.88 (d, 1H, J = 7.2 Hz, H-5′), 6.58 (d, 1H, J = 5.0 Hz, H-4″), 4.09 (q, 1H, J = 7.0 Hz, H-5), 2.39 (s, 3H, H_3C-6′), 2.27 (s, 3H, H_3C-3″), 1.77 (d, 3H, J = 7.0 Hz, H_3C-5); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.27 (C-4), 157.02, 150.35, 138.40, 137.99, 136.69, 129.71, 124.97, 120.92 and 116.86 (pyridine and thiophene ring carbons), 55.75 (C-2), 43.46 (C-5), 24.22 (H_3C-6′), 20.26 (H_3C-5), 14.04 (H_3C-3″); Anal. Calcd for $C_{15}H_{16}N_2OS_2$: C, 59.18; H, 5.30; N, 9.20; S, 21.07. Found: C, 59.17; H, 5.43; N, 9.14; S, 21.29%; GC-MS: *m/z* 304 (M^+, 90), 289 (10), 272 (20), 271 (100), 248 (15), 247 (17), 216 (25), 215 (74), 212 (55), 200 (21), 153 (28), 141 (36), 135 (34), 119 (12), 108 (26), 93 (100), 92 (38), 65 (28).

trans-*5-Methyl-3-(6-methyl-2-pyridyl)-2-(3-methyl-2-thienyl)-1,3-thiazolidin-4-one* (**5b):**Yield 17%, white microcrystals, m.p. 118–119°C; R_f = 0.54 (ethyl acetate-hexane, 1:4); UV ($CHCl_3$): λ_{max} 247 and 278 nm; FT-IR (KBr): 3108 and 3056 (heteroaromatic, =C–H), 2980, 2923 and 2879 (aliphatic, C–H), 1687 (C=O), 1593, 1576, 1450 and 1427 (heteroaromatic, C=C and C=N), 1353, 1290, 784, 756 and 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, 1H, J = 8.2 Hz, H-3′), 7.55 (t, 1H, J = 7.8 Hz, H-4′), 7.16 (s, 1H, H-2), 7.03 (d, 1H, J = 5.0 Hz, 5″-H), 6.87 (d, 1H, J = 7.4 Hz, H-5′), 6.65 (d, 1H, J = 5.0 Hz, H-4″), 4.37 (q, 1H, J = 6.9 Hz, H-5), 2.40 (s, 3H, H_3C-6′), 2.29 (s, 3H, H_3C-3″), 1.64 (d, 3H, J = 6.9 Hz, H_3C-5); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.22 (C-4), 156.89, 150.00, 139.65, 138.17, 135.14, 130.06, 123.66, 120.43 and 114.56 (pyridine and thiophene ring carbons), 54.96 (C-2), 42.63 (C-5), 24.34 (H_3C-6′), 18.42 (H_3C-5), 14.02 (H_3C-3″); Anal. Calcd for $C_{15}H_{16}N_2OS_2$: C, 59.18; H, 5.30; N, 9.20; S, 21.07. Found: C, 59.24; H, 5.51; N, 9.21; S, 21.02%; GC-MS: *m/z* 304 (M^+, 90), 289 (10), 272 (20), 271 (100), 248 (15), 247 (17), 216 (25), 215 (74), 212 (55), 200 (21), 153 (28), 141 (36), 135 (34), 119 (12), 108 (26), 93 (100), 92 (38), 65 (28).

cis-*5-Methyl-3-(6-methyl-2-pyridyl)-2-(5-methyl-2-thienyl)-1,3-thiazolidin-4-one* (**6a):**Yield 9%, greenish rods, m.p. 133–134°C; R_f = 0.43 (ethyl acetate-hexane, 1:4); UV ($CHCl_3$): λ_{max} 247 and 272 nm; FT-IR (KBr): 3113 (heteroaromatic, =C–H), 2979, 2926 and 2872 (aliphatic, C–H), 1690 (C=O), 1595, 1569 and 1455 (heteroaromatic, C=C and C=N), 1349, 1318, 790, 758 and 742 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55-7.47 (m, 2H, H-3′ and H-4′), 7.06 (d, 1H, J = 5.08 Hz, H-3″), 7.03 (s, 1H, H-2), 6.88 (d, 1H, J = 7.28 Hz, H-5′), 6.58 (d, 1H, J = 5.0 Hz, H-4″), 4.09 (q, 1H, J = 7.0 Hz, H-5), 2.39 (s, 3H, H_3C-6′), 2.27 (s, 3H, H_3C-5″), 1.77 (d, 3H, J = 7.0 Hz, 5-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.27 (C-4), 157.02, 150.34, 138.40, 137.00, 136.70, 129.71, 124.98, 120.94 and 116.86 (pyridine and thiophene ring carbons), 55.75 (C-2), 43.46 (C-5), 24.22 (H_3C-6′), 20.26 (H_3C-5), 14.04 (H_3C-5″); Anal. Calcd for $C_{15}H_{16}N_2OS_2$: C, 59.18; H, 5.30; N, 9.20; S, 21.07. Found: C, 59.06; H, 5.27; N, 9.20; S, 21.02%; GC-MS: *m/z* 304 (M^+, 90), 289(10), 272(20), 271(100), 248(15), 247(17), 216(25), 215(74), 212(55), 200(21), 153(28), 141(36), 135(34), 108(26), 93(100), 92(38), 65(27).

trans-*5-Methyl-3-(6-methyl-2-pyridyl)-2-(5-methyl-2-thienyl)-1,3-thiazolidin-4-one* (**6b):**Yield 9%, greenish rods, m.p. 115–116 °C; R_f = 0.53 (ethyl acetate-hexane, 1:4); UV ($CHCl_3$): λ_{max} 247 and 278 nm; FT-IR (KBr): 3107 (heteroaromatic, =C–H), 2980, 2924 and 2879 (aliphatic, C–H), 1690 (C=O), 1593, 1576, 1450 and 1427 (heteroaromatic, C=C and C=N), 1358, 1305, 1290, 784, 756 and 734 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, 1H, $J_{3,4}$ = 8.2 Hz, H-3′), 7.55 (t, 1H, J = 7.86 Hz, H-4′), 7.16 (s, 1H, H-2), 7.03 (d, 1H, $J_{3,4}$ = 5.05 Hz, H-3″), 6.87 (d, 1H, J = 7.49 Hz, H-5′), 6.65 (d, 1H, J = 5.07 Hz, H-4″), 4.37 (q, 1H, J = 6.95 Hz, H-5), 2.40 (s, 3H, H_3C-6′), 2.29 (s, 3H, H_3C-5″), 1.64 (d, 3H, J = 6.96 Hz, H_3C-5); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.22 (C-4), 156.89, 150.00, 139.66, 138.18, 135.14, 130.06, 123.66, 120.43 and 114.56 (pyridine and thiophene ring carbons), 54.95 (C-2), 42.63 (C-5), 24.34 (H_3C-6′), 18.42 (H_3C-5), 14.02 (H_3C-5″); Anal. Calcd for $C_{15}H_{16}N_2OS_2$: C, 59.18; H, 5.30; N, 9.20; S, 21.07. Found: C, 59.04; H, 5.25; N, 9.17; S, 21.04%; GC-MS: *m/z* 304 (M^+, 90), 289 (10), 272 (20), 271 (100), 248 (15), 247 (17), 216 (25), 215 (74), 212 (55), 200 (21), 153 (28), 141 (36), 135 (34), 119 (12), 108 (26), 93 (100), 92 (38), 65 (28).

Table 2 Crystallographic data and structure refinement parameters for compound **5b**

Empirical formula	$C_{15}H_{16}N_2OS_2$
Formula weight	304.4
Crystal colour	White
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	C2/c
Unit cell dimensions	a = 16.0249(4) Å, b = 12.6099(3) Å, c = 14.8161(3) Å β = 90.984(2)°
Volume	2993.5(2) Å^3
Z, Calculated density	8, 1.35 Mg m^{-3}
Absorption coefficient	0.352 mm^{-1}
F(000)	1280
Theta range for data collection	2.1 to 30.5 deg.
Limiting indices	$-22\leq h\leq 22$, $-18\leq k\leq 18$, $-21\leq l\leq 21$
Reflections collected / unique	44616/4583 [R(int) = 0.063]
Max. and min. transmission	0.992 and 0.982
Refinement method	Full-matrix least-squares on F^2
Data/ parameters	3478/ 213
Goodness-of-fit on F^2	1.059
Final R indices [I>2sigma(I)]	R^1 = 0.049, wR^2 = 0.116
R indices (all data)	R^1 = 0.069, wR^2 = 0.128
Largest diff. peak and hole	0.259 and –0.254 e. Å^{-3}

Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre CCDC: 740884. Copies of this information may be obtained free of charge from The Director, 12 Union Road, Cambridge, CB2 1EZ, UK (Fax: +44 1223 336033; E-mail: deposit@ccdc.cam.ac.uk or www:http://www.ccdc.cam.ac.uk).

Crystallography

For the crystal structure determination, a single-crystal of compound **5b** was used for data collection on a four-circle Rigaku R-AXIS RAPID-S diffractometer (equipped with a two-dimensional area IP detector). The graphite-monochromatised Mo K_α radiation (λ = 0.71073 Å) and oscillation scans technique with Δω = 5° for one image were used for data collection. The lattice parameters were determined by the least-squares methods on the basis of all reflections with $F^2 > 2\sigma(F^2)$. Integration of the intensities, correction for Lorentz and polarisation effects and cell refinement was performed using Crystal Clear (Rigaku/MSC Inc., 2005) software.[12] The structures

were solved by direct methods using SHELXS-97[13] and refined by a full-matrix least-squares procedure using the program SHELXL-97.[13] The positional and isotropic atomic displacement parameters of hydrogen atoms were refined together with other structural parameters by the full-matrix least-squares procedure based on the squared value of the structure factors. Hydrogen atomic positions were calculated from assumed geometries except the thiophene, pyridine and thiazolidinone hydrogen atoms that were located in difference map. Hydrogen atoms were included in structure factor calculations but they were not refined. The isotropic displacement parameters of the hydrogen atoms were approximated from the *U*(equiv.) value of the atom to which they are bonded. The final difference Fourier maps showed no peaks of chemical significance. The details of the data collection and final refinement parameters are listed in Table 2.

We thank Prof. Dr Hasan Seçen for his helpful discussion. We also thank for Dr Ebru Mete for elemental analysis.

Received 16 February 2010; accepted 29 April 2010
Paper 101006 *doi: 10.3184/030823410X12746350585058*
Published online: 8 June 2010

References

1 B.K. Garnaik and R.K. Behera, *Indian J. Chem., Sect. B*, 1988, **27**, 1157.
2 E. V. Vladzimirskaya, O. T. Novikevich and O. G. Demchuk, *Farm. Zh*., 1991, 67.
3 R. Lakhan and R. L. Singh, *J. Agric. Food Chem*., 1991, **39**, 580.
4 S. A. H. El-Feky and Z. K.Abd El-Samii, *Arch. Pharm. (Weinheim)*, 1991, **324**, 381.
5 S. A. H. El-Feky, *Pharmazie*, 1993, **48**, 894.
6 S. Grasso, A. Chimirri, P. Monforte, G. Fenech and M. Zappalà, *Farmaco*, 1986, **41**, 713.
7 S. Grasso, A. Chimirri, P. Monforte, G. Fenech, M. Zappalà and A.M. Monforte, *Farmaco*, 1988, **43**, 851.
8 M. M. Dutta, B. N. Goswami and J. C. S. Kataky, *J. Indian Chem. Soc*., 1990, **67**, 332.
9 M. L. Barreca, A. Chimirri, L. De Luca, A. M. Monforte, P. Monforte, A. Rao, M. Zappalà, J. Balzarini, E. De Clercq, C. Pannecouque and M. Witvrouw, *Bioorg. Med. Chem. Lett*., 2001, **11**, 1793.
10 I. Fidan, MSc thesis, Yildiz Technical University, Istanbul, Turkey, 2006.
11 R. K. Rawal, R. Tripathi, S. B. Katti, C, Pannecouque and E. De Clercq, *Eur. J. Med. Chem*., 2008, **43**, 2800.
12 Rigaku/MSC, Inc., 9009 New Trails Drive, The Woodlands, TX 77381, USA.
13 G. M. Sheldrick, SHELXS97 and SHELXL97, University of Göttingen, Germany, 1997.