TRANSFORMATIONS OF ETHYL 2-AMINO-4-(2-ETHOXY-2-OXO-ETHYL)THIAZOLE-5-CARBOXYLATE INTO 5-SUBSTITUTED 2-AMINO-4-OXO-4,5-DIHYDROTHIAZOLE[5,4-c]PYRIDINE-7-CARBOXYLATES

Alen Albreht, Uroš Uršič, Jurij Svete, and Branko Stanovnik*

Faculty of Chemistry and Chemical Technology, University of Ljubljana, Aškerčeva 5, P. O. Box 537, 1000 Ljubljana, Slovenia
E-mail: branko.stanovnik@fkkt.uni-lj.si

Dedicated to Professor Gerhard Maas, University of Ulm, on the occasion of his 60st birthday

Abstract – Ethyl 4-[1-(dimethylamino)-3-ethoxy-3-oxoprop-1-en-2-yl]-2-[(dimethylamino)methylideneamino]thiazole-5-carboxylate (2), prepared from ethyl 2-amino-4-(2-ethoxy-2-oxyethyl)thiazole-5-carboxylate (1) according to a known procedure, was transformed with aromatic amines 3a-d into 5-aryl substituted 2-aminothiazolo[5,4-c]pyridine-7-carboxylates 5a-d, while treatment of 2 with monosubstituted hydrazines 6a-h produced 5-N-amino substituted thiazolo[5,4-c]pyridine-7-carboxylates 8a-h.

In connection with our interest in enaminones and related compounds, as building blocks for the preparation of various heterocyclic systems,1 including also some natural products,2,3 dialkyl acetone-1,3-dicarboxylates have been recently employed for the synthesis of heteroaryl substituted pyrimidines,4 dialkyl 1-substituted 4-oxo-1,4-dihydropyridine-3,5-dicarboxylates,5 pyrazolo[4,3-d]-pyridine-7-carboxylates,6 pyrazolyl substituted pyridopyrimidines, pyranopyranediones, chromenediones,7 and pyrazolo[4,3-d][1,2]diazepines.8,9 Recently, we reported in this connection also the synthesis of substituted 2-amino-5-oxo-5,6-dihydropyrido[4,3-d]pyrimidine-8-carboxylates,10 and (4-oxo-4H-pyrido[1,2-a]pyrimidin-3-yl)thiazole-5-carboxylates.11 In this paper we describe the synthesis of 2-amino-4-oxo-4,5-dihydrothiazolo[5,4-c]pyridine-7-carboxylates from diethyl acetone-1,3-dicarboxylate. Derivatives of thiazolo[5,4-c]pyridine system have been previously prepared by cyclization of 2-aminobenzothiol with carboxylic anhydrides,12 by cyclization of...
S-(2-aminoheteroaryl)dithiocarbamates in the presence of a base,\textsuperscript{13} by cyclization of substituted 4-(2-isocyanatovinyl)thiazole,\textsuperscript{14} and by cyclization of \(o\)-disubstituted aminopyridines with diethoxymethyl acetate.\textsuperscript{15} A review on the methods for preparation of benzothiazoles and related thiazolazines has been published.\textsuperscript{16} They show various biological activities.\textsuperscript{17} Among others they have been reported to be potent inhibitors of factor Xa (fXa) blood coagulation cascade.\textsuperscript{18,19}

2-Amino-4-(2-ethoxy-2-oxoethyl)thiazole-5-carboxylate (1), prepared from diethyl acetone-1,3-dicarboxylate according to the procedure described in the literature,\textsuperscript{20} was transformed with excess \(N,N\)-dimethylformamide dimethyl acetal (DMFDMA) into ethyl 4-[1-(dimethylamino)-3-ethoxy-3-oxo-prop-1-en-2-yl]-2-[(dimethylamino)methylideneamino]thiazole-5-carboxylate (2). Compound 2 was treated with an excess of amines 3a-d in ethanol in the presence of catalytic amounts of hydrochloric acid under reflux for several hours. The initial substitution of the \(N,N\)-dimethylaminomethylene group from the amino group of the side chain is followed by cyclization taking place to the ester group at position 5 and elimination of the \(N,N\)-dimethylaminomethylene group from the \(N,N\)-dimethylaminomethyleneamino group at position 2 of the thiazole ring to give the corresponding 6-substituted 2-aminothiazolo[5,4-c]pyridine-4-carboxylates (5a-d). In the reaction of 2 with hydrazines 6a-h in ethanol in the presence of hydrochloric acid the corresponding 6-aminosubstituted 2-aminothiazolo[5,4-c]pyridine-4-carboxylates (8a-h) were isolated.

The structure of the products were determined on the basis of elemental analysis for C, H, and N, and IR, \(^{1}\text{H}, \text{^{13}}\text{C} \) NMR, MS, and HRMS spectra. While in the reaction of compound 2 with primary amines 3a-d only one type of products could be formed, i.e. thiazolo[5,4-c]pyridines 5a-d, in the reaction of 2 with hydrazine and its derivatives 6a-h three types of products could be formed: thiazolo[5,4-c]pyridine derivatives 8a-h, thiazolo[5,4-d][1,2]diazepine derivatives 9a-h, and pyrazolylthiazole derivatives 10a-h. In order to differentiate among these three structures the comparison of \(^{1}\text{H} \) NMR spectral characteristics were taken into account. Namely, protons attached at position 6 in condensed pyridine ring appear at \(\delta = 8.06 - 8.10 \text{ ppm} \) for those derived from 2 and 3a-d, and at \(\delta = 8.2 - 8.31 \text{ ppm} \) for those derived from 2 and 6a-h. This observation is consistent with the structures 5a-d and 8a-h, since the chemical shifts for the protons in analogous environments in 5-oxo-5,6-dihydro-pyrido[4,3-d]pyrimidine-8-carboxylates are of the same order.\textsuperscript{21} This conclusion is also supported by \(^{1}\text{H} \) NMR spectrum of compound derived from hydrazine 6a. In the product 8a the CH\textsubscript{2} group of the CH\textsubscript{2}CF\textsubscript{3} group appears as a quartet of a doublet with \(J_{\text{NHCH2}} = 4.5 \text{ Hz} \) and \(J_{\text{CH2CF3}} = 9 \text{ Hz} \). This means that this group is coupled to NH group on one and to CF\textsubscript{3} group on the other side. This is consistent only with the structure 8a and not with the structures 9 and 10.
Scheme 1.

Table 1. Ethyl 2-amino-5-aryl-4-oxo-4.5-dihydrothiazolo[5,4-c]pyridine-7-carboxylates 5a-d.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Ar</th>
<th>Product 5 yield (%)</th>
<th>Reaction time (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a, 4a, 5a</td>
<td>C₆H₅-</td>
<td>20</td>
<td>6</td>
</tr>
<tr>
<td>3b, 4b, 5b</td>
<td>4-F- C₆H₄-</td>
<td>32</td>
<td>6</td>
</tr>
<tr>
<td>3c, 4c, 5c</td>
<td>4-Me- C₆H₄-</td>
<td>58</td>
<td>4.5</td>
</tr>
<tr>
<td>3d, 4d, 5d</td>
<td>4-MeO- C₆H₄-</td>
<td>24</td>
<td>5</td>
</tr>
</tbody>
</table>

Table 2. Ethyl 2-amino-5-aryl(or heteroaryl)amino-4-oxo-4.5-dihydrothiazolo[5,4-c]pyridine-7-carboxylates 8a-h.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>R</th>
<th>Product 8 yield (%)</th>
<th>Reaction time (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**EXPERIMENTAL**

Melting points were taken on a Kofler micro hot stage. The $^1$H NMR spectra were obtained on a Bruker Avance DPX 300 (300 MHz) spectrometer in DMSO-$d_6$ or CDCl$_3$ with TMS as the internal standard, MS spectra on an AutoSpecQ spectrometer, IR spectra on a Perkin-Elmer 1310 infrared spectrophotometer and elemental analyses for C, H and N on a Perkin-Elmer CHN Analyser 2400.

**Ethyl** 4-(1-(dimethylamino)-3-ethoxy-3-oxoprop-1-en-2-yl)-2-((dimethylamino)methyleneamino)-
thiazole-5-carboxylate (2)
A mixture of ethyl 2-amino-4-(2-ethoxy-2-oxoethyl)thiazole-5-carboxylate (1; 2.58 g, 10 mmol) and DMFDMA (8.5 mL, 100 mmol) was refluxed for 15 h. Volatile components were evaporated in vacuo and water (20-30 mL) was added to the residue. Precipitated product was separated by filtration and washed with water. Yield: 2.83 g (77%) of yellow orange crystals; mp 119–121 °C (from toluene and heptanes). \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 1.16 (3H, t, \(J = 7.1\) Hz, CH\(_2\)C\(_3\)H\(_3\)), 1.28 (3H, t, \(J = 7.1\) Hz, CH\(_2\)C\(_3\)H\(_3\)), 2.79 (6H, s, N-(CH\(_3\))\(_2\)), 3.09 (3H, s, N-CH\(_3\)), 3.11 (3H, s, N-CH\(_3\)), 4.00–4.17 (2H, m, CH\(_2\)CH\(_3\)), 4.23 (2H, q, \(J = 7.1\) Hz, CH\(_2\)CH\(_3\)), 7.56 (1H, s, N-CH\(_3\)), 8.39 (1H, s, CH). Anal. Calcd for C\(_{16}\)H\(_{24}\)N\(_4\)O\(_4\)S: C, 52.16; H, 6.57; N, 15.21. Found: C, 52.20; H, 6.59; N, 15.19. IR (KBr) \(\nu\) (cm\(^{-1}\)): 3546, 3474, 3414, 1704, 1677, 1621, 1594, 1460, 1374, 1298, 1248, 1218, 1085.

General Procedure for the Synthesis of 5a-d.
A mixture of ethyl 4-(1-(dimethylamino)-3-ethoxy-3-oxoprop-1-en-2-yl)-2-((dimethylamino)methyleneamino)thiazole-5-carboxylate (2) and aromatic amine or its hydrochloride (3a-d) and conc. aq. HCl in EtOH was refluxed. The reaction mixture was cooled overnight at 4 °C. The precipitated product was separated by filtration, washed with EtOH, and recrystallized from an appropriate solvent.

Ethyl 2-amino-4-oxo-5-phenyl-4,5-dihydrothiazolo[5,4-c]pyridine-7-carboxylate (5a)
This compound was prepared from (2; 0.368 g, 1 mmol), aniline (3a; 0.191 mL, 2.1 mmol) and conc. aq. HCl (6 drops) in EtOH (4 mL), 6 h. Yield: 0.062 g (20%) of white solid; mp 247–251 °C (from EtOH). \(^1\)H NMR (DMSO-\(d_6\)): \(\delta\) 1.26 (3H, t, \(J = 7.1\) Hz, CH\(_2\)C\(_3\)H\(_3\)), 4.24 (2H, q, \(J = 7.1\) Hz, CH\(_2\)CH\(_3\)), 7.45–7.56 (5H, m, 5H of Ph), 8.09 (1H, s, CH), 8.29 (2H, br s, NH\(_2\)). Anal. Calcd for C\(_{15}\)H\(_{13}\)N\(_3\)O\(_3\)S: C, 57.13; H, 4.16; N, 13.33. Found: C, 57.22; H, 3.81; N, 13.38. IR (KBr) \(\nu\) (cm\(^{-1}\)): 3440, 3137, 1724, 1667, 1645, 1541, 1488, 1402, 1295, 1269, 1124.

Ethyl 2-amino-5-(4-fluorophenyl)-4-oxo-4,5-dihydrothiazolo[5,4-c]pyridine-7-carboxylate (5b)
This compound was prepared from (2; 0.368 g, 1 mmol), 4-fluoroaniline (3b; 0.201 mL, 2.1 mmol) and conc. aq. HCl (6 drops) in EtOH (4 mL), 6 h. Yield: 0.106 g (32%) of white solid; mp 272–275 °C (from EtOH). EI-MS: \(m/z = 333\) (M\(^+\)). \(^1\)H NMR (DMSO-\(d_6\)): \(\delta\) 1.26 (3H, t, \(J = 7.1\) Hz, CH\(_2\)C\(_3\)H\(_3\)), 4.24 (2H, q, \(J = 7.1\) Hz, CH\(_2\)CH\(_3\)), 7.32–7.41 (2H, m, 2H of Ph), 7.52–7.60 (2H, m, 2H of Ph), 8.10 (1H, s, CH), 8.29 (2H, br s, NH\(_2\)). Anal. Calcd for C\(_{15}\)H\(_{12}\)FN\(_3\)O\(_3\)S: C, 54.05; H, 3.63; N, 12.61. Found: C, 53.89; H, 3.89; N, 12.53. ESI-HRMS: \(m/z = 334.0651\) (MH\(^+\)); C\(_{15}\)H\(_{13}\)FN\(_3\)O\(_3\)S requires: \(m/z = 334.0662\). IR (KBr) \(\nu\) (cm\(^{-1}\)): 3473, 3315, 3125, 1726, 1659, 1636, 1541, 1508, 1488, 1414, 1269, 1214, 1116, 846, 781.
Ethyl 2-amino-4-oxo-5-p-tolyl-4,5-dihydrothiazolo[5,4-c]pyridine-7-carboxylate (5c)
This compound was prepared from (2; 0.368 g, 1 mmol) and p-toluidine hydrochloride (3c; 0.201 mL, 2.1 mmol) in EtOH (2 mL), 4.5 h. Yield: 0.191 g (58%) of white solid; mp 248–254 °C (from EtOH). 1H NMR (DMSO-d6): δ 1.26 (3H, t, J = 7.1 Hz, CH2C6H3), 2.38 (3H, s, CH3), 4.23 (2H, q, J = 7.1 Hz, CH2CH3), 7.30–7.38 (4H, m, 4H of Ph), 8.06 (1H, s, CH), 8.27 (2H, br s, NH2). Anal. Calcd for C16H15N3O3S: C, 58.34; H, 4.59; N, 12.76. Found: C, 58.31; H, 4.50; N, 12.77. IR (KBr) ν(cm⁻¹): 3481, 3392, 3274, 3114, 1716, 1662, 1640, 1543, 1514, 1487, 1423, 1334, 1294, 1265, 1125, 823, 775.

Ethyl 2-amino-5-(4-methoxyphenyl)-4-oxo-4,5-dihydrothiazolo[5,4-c]pyridine-7-carboxylate (5d)
This compound was prepared from (2; 0.368 g, 1 mmol), 4-methoxyaniline (3d) (0.258 mL, 2.1 mmol) and conc. aq. HCl (6 drops) in EtOH (4 mL), 5 h. Yield: 0.084 g (24%) of white solid; mp 267–270 °C (from EtOH). 1H NMR (DMSO-d6): δ 1.26 (3H, t, J = 7.1 Hz, CH2C6H3), 3.82 (3H, s, OC6H3), 4.23 (2H, q, J = 7.1 Hz, CH2CH3), 7.03–7.09 (2H, m, 2H of Ph), 7.37–7.43 (2H, m, 2H of Ph), 8.06 (1H, s, CH), 8.26 (2H, br s, NH2). Anal. Calcd for C16H15N3O4S: C, 55.64; H, 4.38; N, 12.17. Found: C, 55.61; H, 4.29; N, 12.25. IR (KBr) ν(cm⁻¹): 3480, 3428, 3250, 3120, 2989, 1727, 1673, 1627, 1515, 1494, 1426, 1402, 1264, 1121, 834, 772.

General Procedure for the Synthesis of 8a-h
A mixture of ethyl 4-(1-(dimethylamino)-3-ethoxy-3-oxoprop-1-en-2-yl)-2-((dimethylamino)methylene)thiazole-5-carboxylate (2) and hydrazine or substituted hydrazine or its hydrochloride (6) and conc. aq. HCl in EtOH was refluxed. The reaction mixture was cooled over night at 4 °C. The precipitated product was filtrated under reduced pressure and washed with EtOH.

Ethyl 2-amino-4-oxo-5-(2,2,2-trifluoroethylamino)-4,5-dihydrothiazolo[5,4-c]pyridine-7-carboxylate (8a)
This compound was prepared from (2; 0.184 g, 0.5 mmol), (2,2,2-trifluoroethyl)hydrazine (6a; 0.174 mL, 1.2 mmol) and conc. aq. HCl (3 drops) in EtOH (2 mL), 2 h. Yield: 0.138 g (82%) of white solid; mp 239–243 °C (from toluene and EtOH). EI-MS: m/z = 336 (M+). 1H NMR (DMSO-d6): δ 1.28 (3H, t, J = 7.1 Hz, CH2C6H3), 3.82 (2H, dq, J = 9.9, 4.5 Hz, CH2CF3), 4.25 (2H, q, J = 7.1 Hz, CH2CH3), 7.44 (1H, t, J = 4.5 Hz, NH), 8.12 (1H, s, CH), 8.28 (2H, br s, NH2). Anal. Calcd for C11H13F3N4O4S: C, 39.29; H, 3.30; N, 16.66. Found: C, 39.42; H, 3.34; N, 16.75. IR (KBr) ν(cm⁻¹): 3491, 3259, 3111, 1731, 1664, 1618, 1532, 1483, 1410, 1278, 1192, 1151, 1107.

Ethyl 2-amino-4-oxo-5-(phenylamino)-4,5-dihydrothiazolo[5,4-c]pyridine-7-carboxylate (8b)
This compound was prepared from (2; 0.736 g, 2 mmol) and phenylhydrazine hydrochloride (6b; 0.592 g, 4.1 mmol) in EtOH (7 mL), 2 h. Yield: 0.240 g (37%) of orange solid; mp 240–244 °C (from DMF and Et2O). EI-MS: m/z = 330 (M⁺). ¹H NMR (DMSO-d₆): δ 1.28 (3H, t, J = 7.1 Hz, CH₂CH₃), 4.25 (2H, q, J = 7.1 Hz, CH₂CH₃), 6.57–6.62 (2H, m, 2H of Ph), 6.82–6.89 (1H, m, 1H of Ph), 7.17–7.24 (2H, m, 2H of Ph), 8.22 (1H, s, CH), 8.31 (2H, br s, NH₂), 9.39 (1H, s, NH). Anal. Calcd for C₁₅H₁₄N₄O₃S: C, 54.53; H, 4.27; N, 16.96. Found: C, 54.27; H, 4.47; N, 16.78. EI-HRMS: m/z = 330.0795 (M⁺); C₁₅H₁₄N₄O₃S requires: m/z = 330.0787. IR (KBr) ν (cm⁻¹): 3458, 3237, 3128, 2977, 1733, 1651, 1625, 1574, 1546, 1525, 1484, 1406, 1269, 1108.

Ethyl 2-amino-5-(3-chlorophenylamino)-4-oxo-4,5-dihydrothiazolo[5,4-c]pyridine-7-carboxylate (8c)

This compound was prepared from (2; 0.184 g, 0.5 mmol) and (3-chlorophenyl)hydrazine hydrochloride (6c; 0.216 g, 1.2 mmol) in EtOH (2 mL), 2 h. Yield: 0.055 g (30%) of pale yellow solid; mp 272–276 °C (from DMF and diethyl ether). EI-MS: m/z = 364 (M⁺). ¹H NMR (DMSO-d₆): δ 1.29 (3H, t, J = 7.1 Hz, CH₂CH₃), 4.25 (2H, q, J = 7.1 Hz, CH₂CH₃), 6.53–6.58 (1H, m, 1H of Ph), 6.63 (1H, t, J = 2.0 Hz, 1H of Ph), 6.87–6.93 (1H, m, 1H of Ph), 7.22 (1H, t, J = 8.1 Hz, 1H of Ph), 8.23 (1H, s, CH), 8.34 (2H, br s, NH₂), 9.62 (1H, s, NH). Anal. Calcd for C₁₅H₁₃ClN₄O₃S: C, 49.39; H, 3.59; N, 15.36. Found: C, 49.36; H, 3.83; N, 15.53. EI-HRMS: m/z = 364.0407 (M⁺); C₁₅H₁₃ClN₄O₃S requires: m/z = 364.0396. IR (KBr) ν (cm⁻¹): 3471, 3416, 1738, 1649, 1620, 1479, 1404, 1273, 1115.

Ethyl 2-amino-4-oxo-5-(p-tolylamino)-4,5-dihydrothiazolo[5,4-c]pyridine-7-carboxylate (8d)

This compound was prepared from (2; 0.736 g, 2 mmol) and 4-tolylhydrazine hydrochloride (6d; 0.666 g, 4.2 mmol) in EtOH (4 mL), 2 h. Yield: 0.290 g (42%) of pale yellow solid; mp 194–198 °C (from toluene, DMF and MeOH). EI-MS: m/z = 344 (M⁺). ¹H NMR (DMSO-d₆): δ 1.28 (3H, t, J = 7.1 Hz, CH₂CH₃), 2.19 (3H, s, CH₃Ph), 4.25 (2H, q, J = 7.1 Hz, CH₂CH₃), 6.48–6.54 (2H, m, 2H of Ph), 6.98–7.04 (2H, m, 2H of Ph), 8.21 (1H, s, CH), 8.30 (2H, br s, NH₂), 9.23 (1H, s, NH). ¹³C NMR (DMSO-d₆): δ 14.1, 20.0, 60.3, 104.6, 113.1, 115.9, 129.4, 129.5, 144.4, 145.2, 155.3, 156.2, 162.5, 173.2. Anal. Calcd for C₁₆H₁₆N₄O₃S: C, 55.80; H, 4.68; N, 16.17. Found: C, 55.95; H, 4.93; N, 16.27. EI-HRMS: m/z = 344.0951 (M⁺); C₁₆H₁₆N₄O₃S requires: m/z = 344.0943. IR (KBr) ν (cm⁻¹): 3420, 3268, 3124, 1708, 1667, 1663, 1531, 1483, 1404, 1272, 1105.

Ethyl 2-amino-5-(4-nitrophenylamino)-4-oxo-4,5-dihydrothiazolo[5,4-c]pyridine-7-carboxylate (8e)

This compound was prepared from (2; 0.736 g, 2 mmol), (4-nitrophenyl)hydrazine (6e; 0.627 g, 4.1 mmol) and conc. aq. HCl (12 drops) in EtOH (4 mL), 3 h. Yield: 0.627 g (83%) of brown solid; mp
257–261 °C (from toluene, DMF and EtOH). EI-MS: m/z = 375 (M+). ¹H NMR (DMSO-d₆): δ 1.28 (3H, t, J = 7.1 Hz, CH₂CH₃), 4.25 (2H, q, J = 7.1 Hz, CH₂CH₃), 6.71–6.78 (2H, m, 2H of Ph), 8.08–8.15 (2H, m, 2H of Ph), 8.27 (1H, s, CH), 8.38 (2H, br s, NH₂), 10.38 (1H, s, NH). ¹³C NMR (DMSO-d₆): δ 14.1, 60.4, 105.6, 112.0, 115.6, 125.7, 140.1, 143.9, 153.3, 154.8, 156.4, 162.4, 173.3. Anal. Calcd for C₁₅H₁₃N₅O₅S: C, 48.00; H, 3.49; N, 18.66. Found: C, 47.72; H, 3.63; N, 18.74. EI-HRMS: m/z = 375.0645 (M+); C₁₅H₁₃N₅O₅S requires: m/z = 375.0637. IR (KBr) ν (cm⁻¹): 3428, 3260, 3125, 1720, 1663, 1628, 1596, 1410, 1337, 1273, 1110, 845.

Ethyl 2-amino-5-(6-chloropyridazin-3-ylamino)-4-oxo-4,5-dihydrothiazolo[5,4-c]pyridine-7-carboxylate (8f)

This compound was prepared from (2; 0.184 g, 0.5 mmol), 3-chloro-6-hydrazinylpyridazine (6f; 0.173 g, 1.2 mmol) and conc. aq. HCl (3 drops) in EtOH (2 mL), 1 h. Yield: 0.148 g (81%) of pale brown solid; mp 246–250 °C (from toluene, DMF and MeOH). ¹H NMR (DMSO-d₆): δ 1.28 (3H, t, J = 7.1 Hz, CH₂CH₃), 4.25 (2H, q, J = 7.1 Hz, CH₂CH₃), 7.27 (1H, d, J = 9.3 Hz, 4'-H), 7.70 (1H, d, J = 9.3 Hz, 5'-H), 8.27 (1H, s, 6-H), 8.34 (2H, br s, NH₂), 10.56 (1H, br s, NH). Anal. Calcd for C₁₃H₁₁ClN₆O₃S: C, 42.57; H, 3.02; N, 22.91. Found: C, 42.48; H, 3.11; N, 22.65. IR (KBr) ν (cm⁻¹): 3416, 3265, 3127, 2989, 1718, 1662, 1627, 1533, 1486, 1427, 1370, 1274, 1113, 778.

Ethyl 2-amino-4-oxo-5-(pyrimidin-2-ylamino)-4,5-dihydrothiazolo[5,4-c]pyridine-7-carboxylate (8g)

This compound was prepared from (2; 0.184 g, 0.5 mmol), 2-hydrazinylpyrimidine (6g; 0.133 g, 1.2 mmol) and conc. aq. HCl (3 drops) in EtOH (2 mL), 4 h. Yield: 0.122 g (73%) of white solid; mp 283–287 °C (from DMF and Et₂O). ¹H NMR (DMSO-d₆): δ 1.28 (3H, t, J = 7.1 Hz, CH₂CH₃), 4.24 (2H, q, J = 7.1 Hz, CH₂CH₃), 6.97 (1H, t, J = 4.8 Hz, 5'-H), 8.21 (1H, s, 6-H), 8.30 (2H, br s, NH₂), 8.46 (2H, d, J = 4.8 Hz, 4'-H and 6'-H), 10.39 (1H, s, NH). Anal. Calcd for C₁₃H₁₁ClN₆O₃S: C, 46.98; H, 3.64; N, 25.29. Found: C, 46.91; H, 3.70; N, 25.12. IR (KBr) ν (cm⁻¹): 3487, 3256, 3106, 2983, 1723, 1677, 1645, 1621, 1598, 1487, 1447, 1417, 1286, 1263, 1108, 772.

Ethyl 2-amino-4-oxo-5-(6-phenylpyridazin-3-ylamino)-4,5-dihydrothiazolo[5,4-c]pyridine-7-carboxylate (8h)

This compound was prepared from (2; 0.368 g, 1 mmol), 3-hydrazinyl-6-phenylpyridazine (6h; 0.409 g, 2.2 mmol) conc. aq. HCl (6 drops) in EtOH (4 mL), 1 h. Yield: 0.224 g (55%) of pale yellow solid; mp 259–261 °C (from toluene, DMF and MeOH). ¹H NMR (DMSO-d₆): δ 1.29 (3H, t, J = 7.1 Hz, CH₂CH₃), 4.26 (2H, q, J = 7.1 Hz, CH₂CH₃), 7.26 (1H, d, J = 9.3 Hz, 4'-H), 7.41–7.52 (3H of Ph), 7.98–8.04
(2H, m, 2H of Ph), 8.09 (1H, d, \( J = 9.3 \) Hz, 5'-H), 8.31 (1H, s, 6-H), 8.33 (2H, br s, NH2), 10.45 (1H, s, NH). Anal. Calcd for C19H16N6O3S: C, 55.78; H, 3.95; N, 20.58. Found: C, 55.62; H, 3.89; N, 20.39. IR (KBr) \( \nu (\text{cm}^{-1}) \): 3469, 3256, 3120, 2924, 1724, 1661, 1621, 1488, 1449, 1435, 1408, 1275, 1112.

ACKNOWLEDGEMENTS

The financial support from the Slovenian Research Agency, Slovenia through grants P0-0502-0103, P1-0179, and J1-6689-0103-04 is gratefully acknowledged. Financial support by the pharmaceutical companies LEK-SANDOZ, Ljubljana, and KRKA, Novo mesto, is fully appreciated.

REFERENCES


