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

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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-oxoethyl)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**.

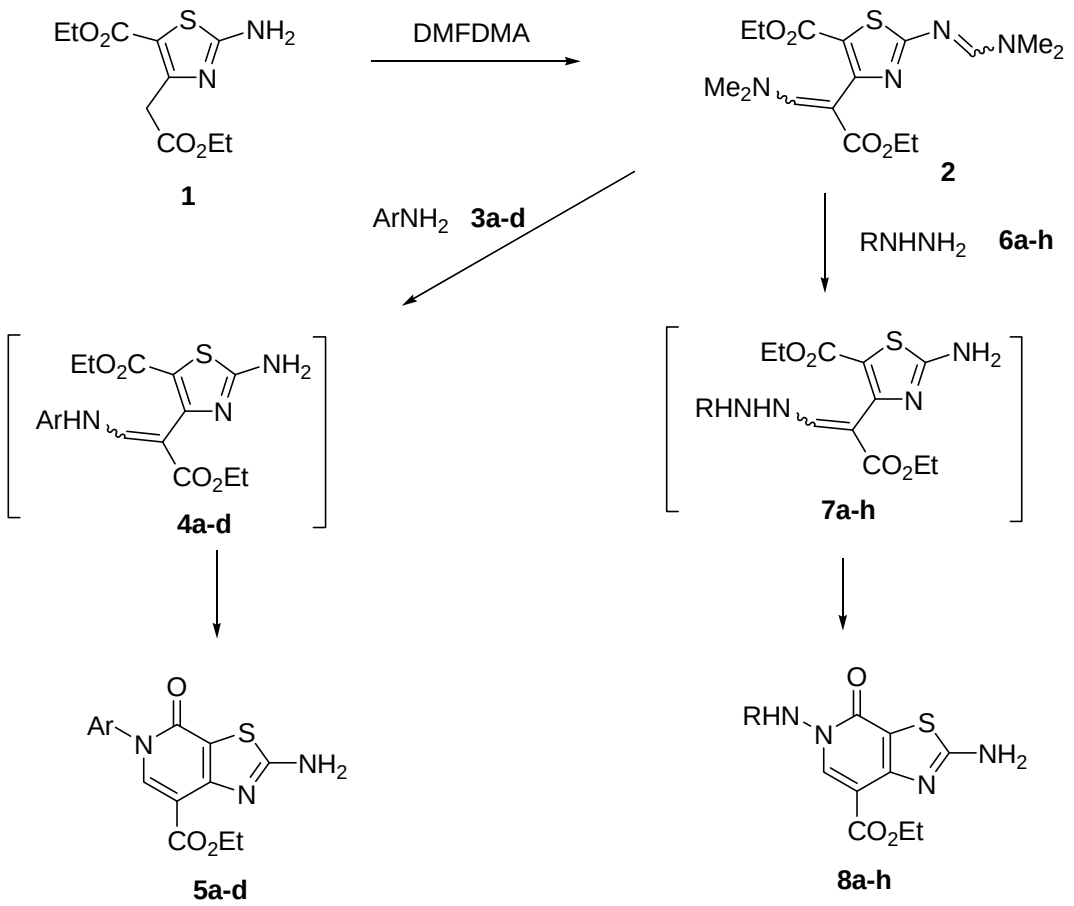
In connection with our interest in enaminones and related compounds, as building blocks for the preparation of various heterocyclic systems,[1] including also some natural products,[2,3] dialkyl acetone-1,3-dicarboxylates have been recently employed for the synthesis of heteroaryl substituted pyrimidines,[4] 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-4*H*-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,[13] by cyclization of substituted 4-(2-isocyanatovinyl)thiazole,[14] and by cyclization of *o*-disubstituted aminopyridines with diethoxymethyl acetate.[15] A review on the methods for preparation of benzothiazoles and related thiazolazines has been published.[16] They show various biological activities.[17] Among others they have been reported to be potent inhibitors of factor Xa(fXa) blood coagulation cascade.[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,[20] was transformed with excess *N,N*-dimethylformamide dimethyl acetal (DMFDMA) into ethyl 4-[1-(dimethylamino)-3-ethoxy-3-oxoprop-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}H, ^{13}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}H NMR spectral characteristics were taken into account. Namely, protons attached at position 6 in condensed pyridine ring appear at δ = 8.06 - 8.10 ppm for those derived from **2** and **3a-d,** and at δ = 8.2 - 8.31 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.[21] This conclusion is also supported by ^{1}H NMR spectrum of compound derived from hydrazine **6a**. In the product **8a** the CH_2 group of the CH_2CF_3 group appears as a quartet of a doublet with J_{NHCH2} = 4.5 Hz and J_{CH2CF3} =9 Hz. This means that this group is coupled to NH group on one and to CF_3 group on the other side. This is consistent only with the structure **8a** and not with the structures **9** and **10**.



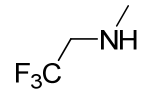
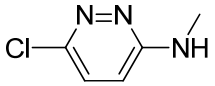
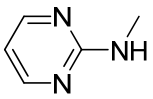
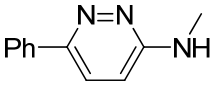
Scheme 1.

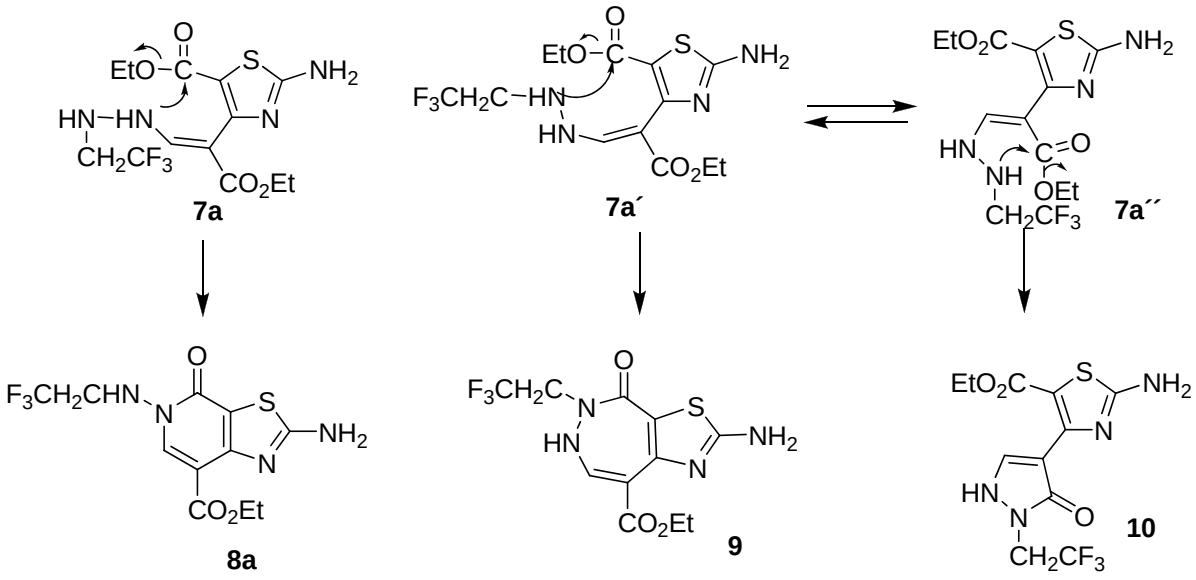
Table 1. Ethyl 2-amino-5-aryl-4-oxo-4,5-dihydrothiazolo[5,4-*c*]pyridine-7-carboxylates **5a-d**.

Compounds	Ar	Product **5** yield (%)	Reaction time (h)
3a, 4a, 5a	C_6H_5-	20	6
3b, 4b, 5b	4-F- C_6H_4-	32	6
3c, 4c, 5c	4-Me- C_6H_4-	58	4.5
3d, 4d, 5d	4-MeO- C_6H_4-	24	5

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

Compounds	R	Product **8** yield (%)	Rection time (h)

6a, 7a, 8a		82	2
6b, 7b, 8b	C_6H_5-NH-	37	2
6c, 7c, 8c	3-Cl- C_6H_4-NH-	30	2
6d, 7d, 8d	4-Me- C_6H_4-NH-	42	2
6e, 7e, 8e	4-NO_2- C_6H_4-NH-	83	3
6f, 7f, 8f		81	1
6g, 7g, 8g		73	4
6h, 7h, 8h		55	1



Scheme 2.

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 ($CDCl_3$): δ 1.16 (3H, t, J = 7.1 Hz, CH_2CH_3), 1.28 (3H, t, J = 7.1 Hz, CH_2CH_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_2CH_3), 4.23 (2H, q, J = 7.1 Hz, CH_2CH_3), 7.56 (1H, s, C*H*), 8.39 (1H, s, C*H*). *Anal.*Calcd for $C_{16}H_{24}N_4O_4S$: C, 52.16; H, 6.57; N, 15.21. Found: C, 52.20; H, 6.59; N, 15.19. IR (KBr) ν (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)methylene-amino)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): δ 1.26 (3H, t, J = 7.1 Hz, CH_2CH_3), 4.24 (2H, q, J = 7.1 Hz, CH_2CH_3), 7.45–7.56 (5H, m, 5H of *Ph*), 8.09 (1H, s, C*H*), 8.29 (2H, br s, NH_2). *Anal.* Calcd for $C_{15}H_{13}N_3O_3S$: C, 57.13; H, 4.16; N, 13.33. Found: C, 57.22; H, 3.81; N, 13.38. IR (KBr) ν (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): δ 1.26 (3H, t, J = 7.1 Hz, CH_2CH_3), 4.24 (2H, q, J = 7.1 Hz, CH_2CH_3), 7.32–7.41 (2H, m, 2H of *Ph*), 7.52–7.60 (2H, m, 2H of *Ph*), 8.10 (1H, s, C*H*), 8.29 (2H, br s, NH_2). *Anal.* Calcd for $C_{15}H_{12}FN_3O_3S$: 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^+); $C_{15}H_{13}FN_3O_3S$ requires: m/z = 334.0662. IR (KBr) . ν (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). ^{1}H NMR (DMSO-d_6): δ 1.26 (3H, t, J = 7.1 Hz, CH_2CH_3), 2.38 (3H, s, CH_3), 4.23 (2H, q, J = 7.1 Hz, CH_2CH_3), 7.30–7.38 (4H, m, 4H of *Ph*), 8.06 (1H, s, C*H*), 8.27 (2H, br s, NH_2). *Anal.* Calcd for $C_{16}H_{15}N_3O_3S$: 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). ^{1}H NMR (DMSO-d_6): δ 1.26 (3H, t, J = 7.1 Hz, CH_2CH_3), 3.82 (3H, s, OCH_3) 4.23 (2H, q, J = 7.1 Hz, CH_2CH_3), 7.03–7.09 (2H, m, 2H of *Ph*), 7.37–7.43 (2H, m, 2H of *Ph*), 8.06 (1H, s, C*H*), 8.26 (2H, br s, NH_2). *Anal.* Calcd for $C_{16}H_{15}N_3O_4S$: 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 amino)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^+). ^{1}H NMR (DMSO-d_6): δ 1.28 (3H, t, J = 7.1 Hz, CH_2CH_3), 3.82 (2H, dq, J = 9.9, 4.5 Hz, CH_2CF_3), 4.25 (2H, q, J = 7.1 Hz, CH_2CH_3), 7.44 (1H, t, J = 4.5 Hz, N*H*), 8.12 (1H, s, C*H*), 8.28 (2H, br s, NH_2). *Anal.* Calcd for $C_{11}H_{11}F_3N_4O_3S$: 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 Et_2O). EI-MS: *m*/*z* = 330 (M^+). ^{1}H NMR (DMSO-d_6): δ 1.28 (3H, t, *J* = 7.1 Hz, CH_2CH_3), 4.25 (2H, q, *J* = 7.1 Hz, CH_2CH_3), 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, C*H*), 8.31 (2H, br s, NH_2), 9,39 (1H, s, N*H*). *Anal.* Calcd for $C_{15}H_{14}N_4O_3S$: 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^+); $C_{15}H_{14}N_4O_3S$ requires: *m*/*z* = 330.0787 IR (KBr) *v* (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^+). ^{1}H NMR (DMSO-d_6): δ 1.29 (3H, t, *J* = 7.1 Hz, CH_2CH_3), 4.25 (2H, q, *J* = 7.1 Hz, CH_2CH_3), 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, C*H*), 8.34 (2H, br s, NH_2), 9.62 (1H, s, N*H*). *Anal.* Calcd for $C_{15}H_{13}ClN_4O_3S$: 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^+); $C_{15}H_{13}ClN_4O_3S$ requires: *m*/*z* = 364.0396. IR (KBr) *v* (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^+). ^{1}H NMR (DMSO-d_6): δ 1.28 (3H, t, *J* = 7.1 Hz, CH_2CH_3), 2.19 (3H, s, CH_3Ph), 4.25 (2H, q, *J* = 7.1 Hz, CH_2CH_3), 6.48–6.54 (2H, m, 2H of *Ph*), 6.98–7.04 (2H, m, 2H of *Ph*), 8,21 (1H, s, C*H*), 8,30 (2H, br s, NH_2), 9,23 (1H, s, N*H*). ^{13}C NMR (DMSO-d_6): *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 $C_{16}H_{16}N_4O_3S$: 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^+); $C_{16}H_{16}N_4O_3S$ requires: *m*/*z* = 344,0943. IR (KBr) *v* (cm^{-1}): 3420, 3268, 3124, 1708, 1667, 1663, 1531, 1483, 1409, 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^+). ^{1}H NMR (DMSO-d_6): δ 1.28 (3H, t, *J* = 7.1 Hz, CH_2CH_3), 4.25 (2H, q, *J* = 7.1 Hz, CH_2CH_3), 6.71–6.78 (2H, m, 2H of *Ph*), 8.08–8.15 (2H, m, 2H of *Ph*), 8.27 (1H, s, C*H*), 8.38 (2H, br s, NH_2), 10.38 (1H, s, N*H*). ^{13}C NMR (DMSO-d_6): 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 $C_{15}H_{13}N_5O_5S$: 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^+); $C_{15}H_{13}N_5O_5S$ 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). ^{1}H NMR (DMSO-d_6): δ 1.28 (3H, t, *J* = 7.1 Hz, CH_2CH_3), 4.25 (2H, q, *J* = 7.1 Hz, CH_2CH_3), 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, NH_2), 10.56 (1H, br s, N*H*). *Anal.* Calcd for $C_{13}H_{11}ClN_6O_3S$: 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 Et_2O). ^{1}H NMR (DMSO-d_6): δ 1.28 (3H, t, *J* = 7.1 Hz, CH_2CH_3), 4.24 (2H, q, *J* = 7.1 Hz, CH_2CH_3), 6.97 (1H, t, *J* = 4.8 Hz, 5'-*H*), 8.21 (1H, s, 6-*H*), 8.30 (2H, br s, NH_2), 8.46 (2H, d, *J* = 4.8 Hz, 4'-*H* and 6'-*H*), 10.39 (1H, s, N*H*). *Anal.* Calcd for $C_{13}H_{12}N_6O_3S$: 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). ^{1}H NMR (DMSO-d_6): δ 1.29 (3H, t, *J* = 7.1 Hz, CH_2CH_3), 4.26 (2H, q, *J* = 7.1 Hz, CH_2CH_3), 7.26 (1H, d, *J* = 9.3 Hz, 4'-*H*), 7.41–7.52 (3H, m, 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, NH_2), 10.45 (1H, s, N*H*). *Anal.* Calcd for $C_{19}H_{16}N_6O_3S$: C, 55.78; H, 3.95; N, 20.58). Found: C, 55.62; H, 3.89; N, 20.39. IR (KBr) ν (cm^{-1}): 3469, 3256, 3120, 2924, 1724, 1661, 1621, 1488, 1449, 1435, 1408, 1275, 1112.

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