Enamino esters in the synthesis of heterocyclic systems. Transformation of diethyl acetone-1,3-dicarboxylate into poly-substituted 1,2,7,8-tetrahydro-2,7-naphthyridine-4-carboxylates

Klemen Pirnat, Petr Šimunek,[a] Uroš Uršič, Jure Bezenšek, Uroš Grošelj, Amalija Golobič, Anton Meden, Jurij Svete, and Branko Stanovnik*

Faculty of Chemistry and Chemical Technology, University of Ljubljana, Aškerčeva 5, P. O. Box 537, 1000 Ljubljana, Slovenia

[a] *On leave from Department of Organic Chemistry and Technology, Faculty of Chemical Technology, University of Pardubice, 53210 Pardubice, Czech Republik*

E-mail: Branko.Stanovnik@fkkt.uni-lj.si

Dedicated to Professor Dr. Heinz Heimgartner, University of Zürich, Switzerland, on the occasion of his 70th anniversary

DOI: http://dx.doi.org/10.3998/ark.5550190.0012.610

Abstract

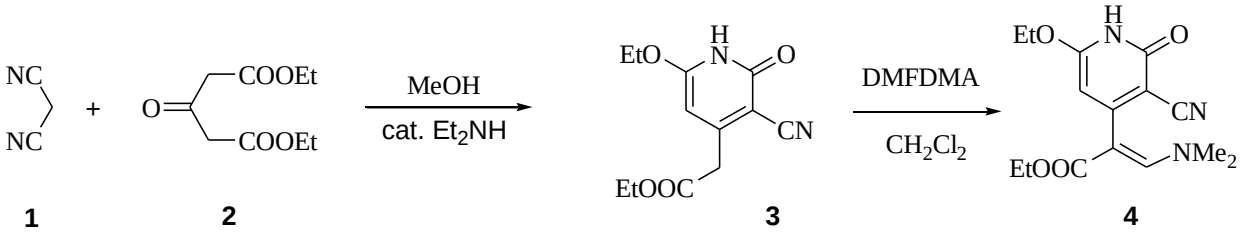
A simple three step synthesis of aminosubstituted 1,2,7,8-tetrahydro-2,7-naphthyridine-4-carboxylates is described. Ethyl (3-cyano-6-ethoxy-2-oxo-1,2-dihydropyridin-4-yl)acetate **3**, formed by the condensation of diethyl acetone-1,3-dicarboxylate with malononitrile, was transformed with *N*,*N*-dimethylformamide dimethylacetal (DMFDMA) into (*E*)-ethyl 2-(3-cyano-6-ethoxy-2-oxo-1,2-dihydropyridin-4-yl)-3-(dimethylamino)propenoate **4**. In further reaction the dimethylamino group was substituted with amino, hydroxy or substituted hydrazino group, followed by cyclisation to afford substituted 1-amino-7,8-dihydro-2,7-naphthyridine-4-carboxylate **6b**, 1-imino-7,8-dihydro-1*H*-pyrano[3,4-*c*]pyridine-4-carboxylate **8**, and 1-imino-2-aminosubstituted 1,2,7,8-tetrahydro-2,7-naphthyridine-4-carboxylates **13a-i**.

Keywords: Enaminoesters, ethyl (3-cyano-6-ethoxy-2-oxo-1,2-dihydropyridin-4-yl)acetate, (*E*)-ethyl 2-(3-cyano-6-ethoxy-2-oxo-1,2-dihydropyridin-4-yl)-3-(dimethylamino)propenoate, 1,2,7,8-tetrahydro-2,7-naphthyridine-4-carboxylates

Introduction

It has been reported that by the condensation of malononitrile **1** with diethyl acetone-1,3-dicarboxylate **2** ethyl (3-cyano-6-ethoxy-2-oxo-1,2-dihydropyridin-4-yl)acetate **3** is formed. This

has been transformed with *N*,*N*-dimethylformamide dimethylacetal (DMFDMA) into the corresponding (*E*)-ethyl 2-(3-cyano-6-ethoxy-2-oxo-1,2-dihydropyridin-4-yl)-3-(dimethylamino) -propenoate **4**[1] (Scheme 1).



1 **2** **3** **4**

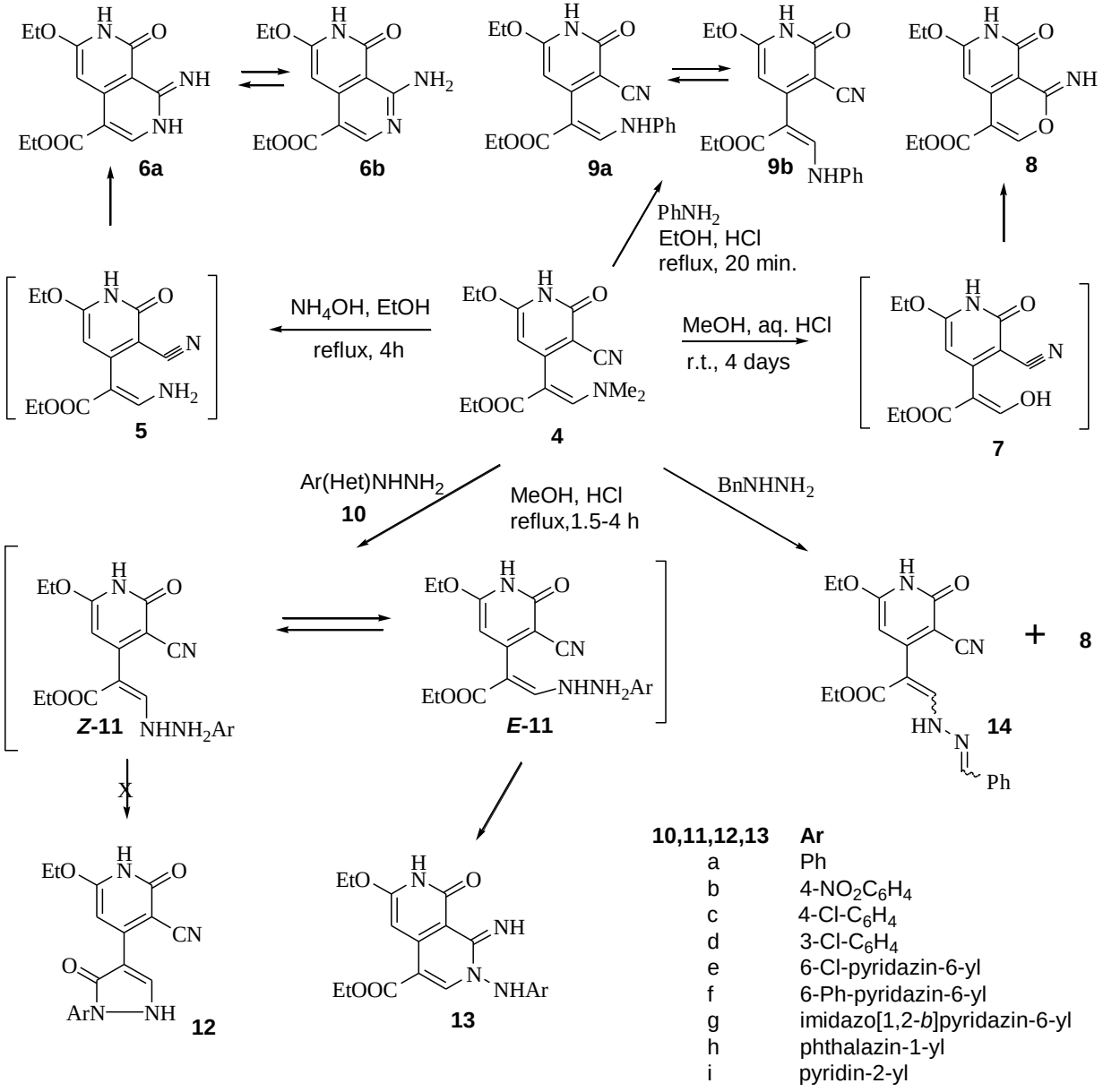
Scheme 1

In connection with our interest in the synthesis of various heterocyclic systems[2,3] and natural products[4] compound **4**, as a polyfunctional enamino ester, seems to be an excellent starting compound for the synthesis of 2,7-naphthyridine derivatives. The first preparation of 2,7-naphthyridines has been been reported in 1958.[5] There are several reviews dealing with the synthesis and application of 2,7-naphthyridines.[6] Only few synthetic methods have a wide scope and generality. The cyclization of *o*-cyano-pyridineacetonitriles or -acetaldehyde equivalent derivatives,[7,8] and a general synthesis of naphthyridines and their *N*-oxides starting from bromopyridines followed by electrophilic substitution with DMF, conventional palladium-catalyzed cross-coupling with acetylenes, and reaction with ammonia have been published, recently.[9,10] In this communication we extend the application of enamino esters to the synthesis of 1,2,7,8-tetrahydro-2,7-naphthyridine-4-carboxylates.

Results and Discussion

In the reaction of (*E*)-ethyl 2-(3-cyano-6-ethoxy-2-oxo-1,2-dihydropyridin-4-yl)-3-(dimethyl-amino)propenoate **4** with a mixture of aqueous ammonia and ethanol under reflux the dimethylamino group was substituted with an amino group to give intermediate **5**, which, without isolation cyclized into the 1-aminonaphthyridine derivative **6b.** Similarly, heating of **4** in a mixture of aqueous solution of hydrochloric acid in methanol substitution of dimethylamino group by hydroxy group took place to form the intermediate **7**, which was, without isolation, cyclized into 1*H*-pyrano[3,4-*c*]pyridine-4-carboxylate **8**. In the reaction with aniline only substitution of the dimethylamino group occurred to give the corresponding acrylate derivative, as a 1:1 mixture of (*E*)-**9a** and (*Z*)-**9b** isomers, which did not cyclize by further heating. In the reaction of **4** with aryl- and heteroarylhydrazines **10a-i** in methanol in the presence of catalytic amounts of hydrochloric acid substitution of the dimethylamino group took place to give intermediates **11**, which were, without isolation, further cyclized under reaction conditions. Two types of products could be formed. Cyclization could occur involving either the ester group to

form pyrazolidinone derivatives **12**, or involving the cyano group forming naphthyridine derivatives **13**, respectively. Since the ester group is present in the final product as shown by IR and ^{1}H NMR spectra, while the cyano group is absent in IR spectra, one can conclude that 2,7-naphthyridine derivatives **13** were formed. In these reactions always trace amounts of 1-amino derivative **6b** and pyrano[3,4-*c*]pyridine derivative **8** are formed as side products. In the reaction of **4** with benzylhydrazine in the presence of aqueous hydrochloric acid in methanol only a mixture of benzylidenehydrazinylacrylate **14** and **8** was formed (Scheme 2).



Scheme 2

The structures were confirmed by ^{1}H NMR and IR spectra, MS and elemental analyses for C, H, and N. ^{1}H NMR spectra of compounds **13a-i** exhibit besides typical signals for ethoxy group at position 6, ethyl ester group at position 4 and protons of aromatic or heteroaromatic groups attached at position 2, a singlet at δ = 7.90 – 8.19 ppm for H_3 and a singlet at δ = 6.69 – 7.14 ppm for H_5. For compound **6** the structure was confirmed also by X-ray analysis showing that this compound exists in the 1-amino form **6b** and not in 1-imino tautomeric form **6a** (Figure 1).

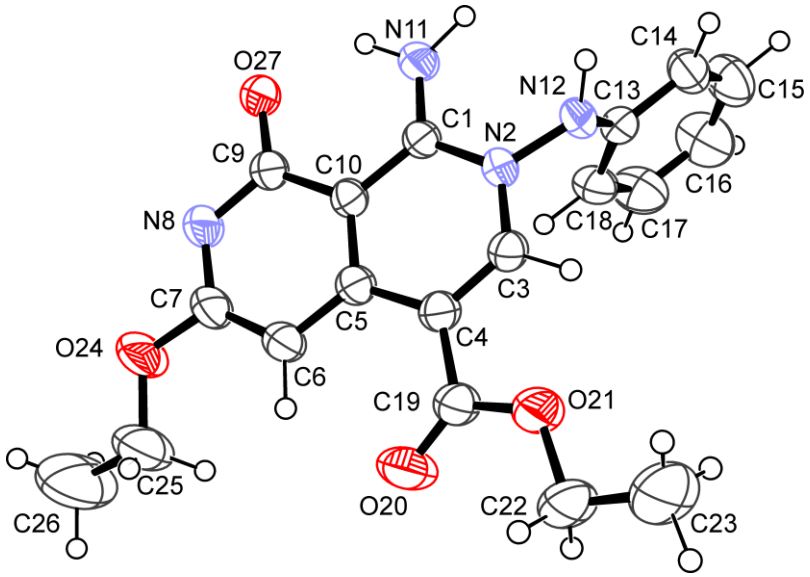


Figure 1. Ortep view of compound **6b** at the 50% probability level of ellipsoids. H atoms are drawn as small spheres of arbitrary radii.

Conclusions

A simple three step synthesis of substituted 1,2,7,8-tetrahydro-2,7-naphthyridine-4-carboxylates **6b** and **13a-i** by transformation of ethyl (3-cyano-6-ethoxy-2-oxo-1,2-dihydropyridin-4-yl)acetate **3**, formed by the condensation of diethyl acetone-1,3-dicarboxylate with malononitrile, with *N*,*N*-dimethylformamide dimethylacetal (DMFDMA) into (*E*)-ethyl 2-(3-cyano-6-ethoxy-2-oxo-1,2-dihydropyridin-4-yl)-3-(dimethylamino)propenoate **4** followed by treatment with ammonia or monosubstituted hydrazines was developed.

Experimental Section

General. Melting points were taken with a Kofler micro hot stage. The ^{1}H NMR (300 MHz) and ^{13}C (75MHz) spectra were obtained with a Bruker Avance DPX 300 (300 MHz) spectrometer with DMSO-d_6 as solvent and Me_4Si as internal standard. IR spectra were recorded with a

Perkin-Elmer Spectrum BX FTIR spectrophotometers (KBr discs). The microanalyses for C, H, and N were obtained with a Perkin-Elmer CHN Analyser 2400 II. Reactions were followed by TLC: Merck, Alufolien Kieselgel 60 F 254, 0.2 mm. (*E*)-ethyl 2-(3-cyano-6-ethoxy-2-oxo-1,2-dihydropyridin-4-yl)-3-(dimethylamino)propenoate **4** was prepared according to the literature procedure.[1]

Ethyl 6-ethoxy-1-amino-8-oxo-7,8-dihydro-2,7-naphthyridine-4-carboxylate (6b). Compound **4** (153 mg, 0.5 mmol) and ammonia (25% aqueous solution, 2 mL) in EtOH (4 mL) was heated under reflux for 4 h. The precipitate was after cooling collected by filtration, washed with hot EtOH. Yield 140 mg (72%), yellow crystals, m.p. 300-303 °C ($CHCl_3$/DMF). ^{1}H NMR (DMSO–d_6)**:** δ 1.31 (t, 3H, *J* = 6.9 Hz, OCH_2CH_3); 1.37 (t, 3H, *J* = 6.9 Hz, OCH_2CH_3); 4.22 (m, 4H, *J* = 6.9 Hz, 2 × OCH_2CH_3); 7.02 (s, 1H, =CH); 7.80 (br s, 1H, N*H*); 8.62 (s, 1H, =C*H*); 9.13 (br s, 1H, N*H*); 12.10 (s, 1H, N*H*). IR (KBr), cm^{-1}**:** 3338, 3157, 2983, 2673, 1687, 1619, 1571, 1509, 1464, 1368, 1304, 1269, 1183, 1131, 1074, 1027, 930, 895, 822, 725, 700, 669, 553, 457. ESI-HRMS: Calcd. for $C_{13}H_{15}N_3O_4$: *m/z* = 278,1141 (MH^+). Found: m/z = 278,1145. Anal. Calcd. for $C_{13}H_{15}N_3O_4$: C, 56.31; H, 5.45; N 15.15. Found: C, 56.21; H, 5.31; N, 15.13.

Ethyl 6-ethoxy-1-imino-8-oxo-7,8-dihydro-1*H*-pyrano[3,4-*c*]pyridine-4-carboxylate (8). Compound **4** (153 mg, 0.5 mmol) and hydrochloric acid (37% aqueous solution, 0.5 mL) in MeOH (1.5 mL) was left at room temperature for 4 days. The precipitate was, after cooling, collected by filtration, washed with MeOH and recrystallized. Yield 47 mg (34%), m.p. 252-255 °C (AcOH). ^{1}H NMR (DMSO–d_6)**:** δ 1.32 (m, 6H, *J* = 7.2 Hz, 2 x OCH_2CH_3); 4.24 (m, 4H, *J* = 6.9 Hz, 2 x OCH_2CH_3); 7.31 (s, 1H, =C*H*); 8.11 (s, 1H, =C*H*); 12.39 (br s, 1H, N*H*); 13.63 (s, 1H, NH). IR (KBr), cm^{-1}**:** 3550, 3477, 3414, 3235, 2995, 2932, 1726, 1616, 1526, 1439, 1359, 1308, 1269, 1233, 1112, 1036, 934, 848, 760, 617, 474. EI-HRMS: Calcd. for $C_{13}H_{14}N_2O_5$: m/z = 278,0903 (M^+). Found: *m/z* = 278,0905. Anal Calcd for $C_{13}H_{14}N_2O_5$: C, 56,11; H, 5,07; N, 10,07. Found: C, 56.06; H, 5.10; N, 10.08.

Ethyl 2-(3-cyano-6-ethoxy-2-oxo-1,2-dihydropyridin-4-yl)-3-(2-phenylamino)acrylate (9). To a solution of compound **4** (153 mg, 0.5 mmol) and aniline (47 mg, 0.5 mmol) in EtOH (2 mL) hydrochloric acid (37% aqueous solution, 0.2 mL) was added and the mixture was heated under reflux for 20 min. The precipitate was, after cooling, collected by filtration and recrystallized. Yield 97 mg (55%), yellow solid, m.p. 191-193 °C (EtOH). ^{1}H NMR (DMSO-d_6): δ 1.21 (2 x t, 6H, *J* = 7.2 Hz, OCH_2CH_3); 1.33 (2 x t, 6H, *J* = 7.2 Hz, OCH_2CH_3); 4.08-4.35 (two overlapped q, 4H, OCH_2CH_3); 6.12 (br s, 1H, N*H*); 6.28 (br s, 1H, N*H*); 7.06 (m, 2H, Ph); 7.17 (d, 2H, *J* = 7.8 Hz, Ph); 7.34 (m, 6H, Ph); 7.89 (d, 1H, *J* = 13.2 Hz, =CH); 8.04 (d, 1H, *J* = 13.5 Hz, =CH); 8.95 (d, 1H, *J* = 13.8 Hz, NH); 10.40 (d, 1H, *J* = 13.2 Hz, NH); 12.34 (br s, 2H, NH). IR (KBr), cm^{-1}**:** 3548, 3478, 3416, 3234, 2202, 2170, 1680, 1649, 1617, 1595, 1577, 1474, 1374, 1354, 1229, 804, 760, 622, 482, 466, 412. EI-HRMS: Calcd. for $C_{19}H_{19}N_3O_4$: *m/z* = 353,1376 (M^+). Found: *m/z* = 353,1383. Anal Calcd. for: $C_{19}H_{19}N_3O_4$. Anal Calc. for $C_{19}H_{19}N_3O_4$: C, 64.58; H, 5.42; N, 11.89. Found: C, 64.55; H, 5.46; N, 11.77.

Ethyl 3-(2-benzylidenehydrazinyl)-2-(3-cyano-6-ethoxy-2-oxo-1,2-dihydropyridin-4yl)acrylate (14). A solution of compound **4** (153 mg, 0.5 mmol) and benzylhydrazine dihydrochloride (132 mg, 0.5 mmol) in water (0.5 mL) and MeOH (3 mL) was heated under reflux for 3.5 h. The precipitate was after cooling collected by filtration. The crude product, which is a mixture of **14** and **8** was heated with a boiling mixture of AcOH/toluene (4:1) in which **8** is solubile. The solid **14** was separated by filtration and recrystallized. Yellow solid, m.p. 185-188 ºC (MeCOOH/toluene): Yield: 17% (32 mg). **[1]**H NMR (DMSO–d_6)**:** δ 1.28 (t, 3H, *J* = 6.9 Hz, OCH_2CH_3); 1.34 (t, 3H, *J* = 7.2 Hz, OCH_2CH_3); 4.26 (q, 2H, *J* = 6.9 Hz, OCH_2CH_3); 4.32 (q, 2H, *J* = 6.9 Hz, OCH_2CH_3); 6.66 (s, 1H, =CH); 7.60 (m, 3H, Ph); 8.11 (dd, 2H, J_1 = 8.1, J_2 = 1.8 Hz, Ph); 8.65 (s + br s, 2H, =CH + N*H*); 9.00 (s, 1H, =CH); 12.53 (d, 1H, *J* = 3.9 Hz, NH). ^{13}C NMR (DMSO–d_6): δ 14.1; 14.6; 60.5; 60.8; 88.5; 96.0; 108.9; 128.8; 129.6; 132.1; 132.5; 141.7; 153.5; 159.3; 164.1; 168.0; 168.0; 172.1. IR (KBr), cm^{-1}**:** 3476, 3416, 3137, 2988, 2903, 2207, 1678, 1648, 1588, 1474, 1378, 1345, 1311, 1236, 1055, 1023, 980, 808, 784, 761, 698, 652, 513, 463. ESI-HRMS: Calcd. for $C_{20}H_{20}N_4O_4$: *m/z* = 381,1563 (MH^+). Found: *m/z* = 381,1567. Anal Calcd. for $C_{20}H_{20}N_4O_4$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.15; H, 5.30; N, 14.73.

General procedure for the synthesis of compounds (13a-i)

A mixture of compound **4** (157 mg, 0.51 mmol) and aryl- or heteroarylhydrazine **10a-i** (0.54 mmol) dissolved in MeOH (1.5 to 4 mL) and hydrochloric acid (37%, 0.3 mL) was heated under reflux for 1.5 to 4 h. The yellow precipitate was, after cooling, collected by filtration and washed with MeOH to give analytically pure **13a-i.**

The following compounds were prepared accordingly:

Ethyl 6-ethoxy-1-imino-8-oxo-2-(phenylamino)-1,2,7,8-tetrahydro-2,7-naphthyridine-4-carboxylate (13a). This compound was prepared from **4** and phenylhydrazine hydrochloride **10** in MeOH (1.3 mL), reflux 2.5 h. Yield: 96 mg (51%), yellow microcrystals, m.p. 241-243 °C. ^{1}H NMR (DMSO–d_6): δ 1.26 (m, 6H, 2 × OCH_2CH_3), 4.24 (m, 4H, 2 × OCH_2CH_3), 6.69 (s, 1H, =CH), 6.71 (d, 2H, *J* = 7.5 Hz, Ph), 6.99 (t, 1H, *J* = 7.2 Hz, Ph), 7.31 (t, 2H, *J* = 7.8 Hz, Ph), 7.90 (s, 1H, =CH), 8.77 (d, 1H, *J* = 3.3 Hz, N*H*), 9.35 (s, 1H, N*H*), 12.41 (d, 1H, *J* = 3.3 Hz, N*H*). IR (KBr, cm^{-1}): 3434, 3142, 3105, 3064, 2982, 2903, 1723, 1651, 1606, 1586, 1541, 1527, 1445, 1384, 1275, 1194, 1136, 1107, 1026, 925, 829, 749. EI-HRMS: Calcd. for $C_{19}H_{20}N_4O_4$: *m/z* = 368.1485 (M^+). Found: *m/z* = 368.1493. Anal. Calcd. for $C_{19}H_{20}N_4O_4$: C, 61.95; H, 5.47; N, 15.21. Found: C, 62.12; H, 5.39; N, 15.31.

Ethyl 6-ethoxy-1-imino-8-oxo-2-(4-nitrophenylamino)-1,2,7,8-tetrahydro-2,7-naphthyridine-4-carboxylate (13b). This compound was prepared from **4** and 4-nitrophenylhydrazine **10b** in MeOH (4mL), reflux 4h. Yield: 130 mg (63%), yellow solid, m.p. 265-267 °C. ^{1}H NMR (DMSO–d_6): δ 12.6 (m, 6H, *J* = 7.8 Hz, 2 × OCH_2CH_3), 4.25 (m, 4H, *J* = 7.2 Hz, 2 × OCH_2CH_3), 6.70 (s, 1H, =CH), 6.85 (d, 2H, *J* = 9.0 Hz, Ph), 8.03 (s, 1H, =CH), 8.18 (d, 2H, *J* = 9.0 Hz, Ph), 8.87 (br s, 1H, N*H*), 10.37 (br s, 1H, N*H*), 12.50 (s, 1H, N*H*). IR (KBr cm^{-1}): 3418, 3077, 1715, 1666, 1593, 1528, 1440, 1336, 1296, 1269, 1191, 1109, 930, 851, 812, 756, 644,

472. ESI-HRMS: Calcd. for $C_{19}H_{19}N_5O_6$: *m/z* = 414.1414 (MH^+). Found: *m/z* = 414.1425. Anal. Calcd. for $C_{19}H_{19}N_5O_6$: C, 55.20; H, 4.63; N, 16.94. Found: C, 55.10; H, 4.48; N, 16.86.

Ethyl 6-ethoxy-1-imino-8-oxo-2-(4-chlorophenylamino)-1,2,7,8-tetrahydro-2,7-naphthyridine-4-carboxylate (13c). This compound was prepared from **4** and 4-chlorophenylhydrazine hydrochloride (**10c**) in MeOH (1.5 mL), reflux 1.5 h. Yield: 107 mg (53%), yellow microcrystals, m.p. 241-243 °C. ^{1}H NMR (DMSO–d_6): δ 1.27 (m, 6H, *J* = 7.2 Hz, 2 × OCH_2CH_3), 4.25 (m, 4H, *J* = 6.9 Hz, 2 × OCH_2CH_3), 6.69 (s, 1H, =CH), 6.74 (dt, 2H, J_1 = 8,7 Hz, J_2 = 1,8 Hz, Ph), 7.35 (dt, 2H, J_1 = 8.7 Hz, J_2 = 1.8 Hz, Ph), 7.92 (s, 1H, =CH), 8.78 (br s, 1H, N*H*), 9.50 (s, 1H, N*H*), 12.43 (br s, 1H, N*H*). IR (KBr, cm^{-1}): 3430, 3249, 3104, 2977, 1725, 1707, 1647, 1546, 1492, 1439, 1380, 1297, 1275, 1243, 1177, 1095, 1032, 925, 831, 816, 648, 509. EI-HRMS: Calcd. for $C_{19}H_{19}ClN_4O_4$: *m/z* = 402.1095. Found: *m/z* = 402.1103 (^{35}Cl, M^+). Anal. Calcd. for $C_{19}H_{19}ClN_4O_4$: C, 56.65; H, 4.75; N, 13.91. Found: C, 56.45; H, 4.74; N, 14.01.

Ethyl 6- ethoxy-1-imino-8-oxo-2-(3-chlorophenylamino)-1,2,7,8-tetrahydro-2,7-naphthyridine-4-carboxylate (13d). This compound was prepared from **4** and 3-chlorophenylhydrazine hydrochloride **10d** in MeOH (3.0 mL), reflux 1.5 h. Yield: 88 mg (44%), yellow microcrystals, m.p. 242-245 °C. ^{1}H NMR (DMSO–d_6): δ 1.26 (m, 6H, *J* = 6.9 Hz, 2 x OCH_2CH_3), 4.24 (m, 4H, *J* =6.9 Hz, 2 x OCH_2CH_3), 6.63 (dt, 1H, J_1 = 7.5 Hz, J_2 = 2.1 Hz, Ph), 6.69 (s, 1H, =CH), 6.78 (t, 1H, *J* = 2.1 Hz, Ph), 7.02 (dt, 1H, J_1 = 7.5 Hz, J_2 = 1.8 Hz, Ph), 7.31 (t, 1H, *J* = 8.1 Hz, Ph), 7.95 (s, 1H, =CH), 8.78 (br s, 1H, N*H*); 9.59 (s, 1H, N*H*), 12.44 (s, 1H, N*H*). IR (KBr, cm^{-1}): 3420, 2981, 1725, 1703, 1650, 1598, 1549, 1439, 1381, 1299, 1272, 1178, 1101, 1033, 929, 830, 768, 682. EI-HRMS: Calcd. for $C_{19}H_{19}ClN_4O_4$: *m/z* = 402.1095. Found: *m/z* = 402.1103 (^{35}Cl, M^+). Anal. Calcd. for $C_{19}H_{19}ClN_4O_4$: C, 56.65; H, 4.75; N, 13.91. Found: C, 56.53; H, 4.80; N, 13.93.

Ethyl 6-ethoxy-2-(6-chloropyridazin-3-ylamino)-1-imino-8-oxo-1,2,7,8-tetrahydro-2,7-naphthyridine-4-carboxylate (13e). This compound was prepared from **4** and 3-chloro-6-hydrazinopyridazine **10e** in MeOH (3.0 mL), reflux 2 h. Yield: 99 mg (49%), yellow microcrystals, m.p. > 350 °C. ^{1}H NMR (DMSO–d_6): δ 1.28 (m, 6H, J = 7.2 Hz, 2 × OCH_2CH_3), 4.25 (m, 4H, 2 × OCH_2CH_3), 6.73 (s, 1H, =CH), 7.29 (d, 1H, J = 9.3 Hz, Ar), 7.76 (d, 1H, J = 9.3 Hz, Ar), 8.19 (s, 1H, =CH), 8.89 (br s, 1H, N*H*), 10.74 (br s, 1H, N*H*), 12.34 (br s, 1H, N*H*). IR (KBr, cm^{-1}): 3407, 3231, 3079, 2985, 1713, 1668, 1655, 1598, 1553, 1425, 1385, 1283, 1210, 1177, 1140, 1097, 1034, 928, 834, 818, 770, 666. EI-HRMS: Calcd. for $C_{17}H_{17}ClN_6O_4$: *m/z* = 405,1078 (^{35}Cl,MH^+). Found: *m/z* = 405,1083. Anal. Calcd. for $C_{17}H_{17}ClN_6O_4$: C, 50.44; H, 4.23; N, 20.76. Found: C, 50.48; H, 4.06; N, 20.47.

Ethyl 6- ethoxy-2-(6-phenylpyridazin-3ylamino)-1-imino-8-oxo-1,2,7,8-tetrahydro-2,7-naphthyridine-4-carboxylate (13f). This compound was prepared from **4** and 3-hydrazino-6-phenylpyridazine **10f** in MeOH (1.5 mL), reflux 2.5 h. Yield: 128 mg (57%), yellow microcrystals, m.p. > 279-283 °C (decomp). ^{1}H NMR (DMSO–d_6): δ 1.32 (t, 3H, *J* = 7.2 Hz, OCH_2CH_3), 1.43 (t, 3H, *J* = 6.9 Hz, OCH_2CH_3), 4.35 (m, 4H, 2 × OCH_2CH_3), 7.14 (s, 1H, =CH), 7.54 (m, 3H, =CH and Ar), 8.02 (br s, 2H, Ar), 8.62 (br s, 1H, Ar), 9.06 (br s, 1H, Ar) , 9.74 (br s, 1H, Ar), 10.34 (br s, 1H, N*H*), 11.07 (br s, 1H, N*H*), 13.18 (br s, 1H, N*H*). IR (KBr, cm^{-1}): 3415, 3240, 3063, 2983, 2870, 1717, 1670, 1599, 1531, 1440, 1293, 1202, 1139, 1052, 1021,

816, 764, 692, 565. ESI-HRMS: Calcd. for $C_{23}H_{22}N_6O_4$: *m/z* = 447,1781 (MH^+). Found: *m/z* = 447,1790. Anal. Calcd. for $C_{23}H_{22}N_6O_4 \cdot HCl$: C, 57.20; H, 4.80; N, 17.40. Found: C, 56.94; H, 4.71; N, 17.13.

Ethyl 6-ethoxy-2-(imidazo[1,2-*b*]pyridazin-6-ylamino)-1-imino-8-oxo-1,2,7,8-tetrahydro 2,7-naphthyridine-4-carboxylate (13g). This compound was prepared from **4** and 6-hydrazinoimidazo[1,2-*b*]pyridazine **10g** in MeOH (2.0 mL), reflux 2.5 h. Yield: 120 mg (59 %), yellow microcrystals, m.p. > 250 °C (decomp). ^{1}H NMR (DMSO–d_6): δ 1.30 (t, 3H, *J* = 6.9 Hz, OCH_2CH_3), 1.42 (t, 3H, *J* = 6.9 Hz, OCH_2CH_3), 4.35 (m, 4H, 2 × OCH_2CH_3), 6.97 (d, 1H, *J* = 9.9 Hz, Ar), 7.11 (s, 1H, =CH), 7.58 (s, 1H, Ar), 7.97 (s, 1H, =CH), 8.09 (d, 1H, *J* = 9.9 Hz, Ar), 8.74 (s, 1H, Ar), 9.77 (br s, 1H, N*H*), 10.86 (br s, 1H, N*H*), 11.09 (br s, 1H, N*H*). IR (KBr, cm^{-1}): 3417, 3210, 3073, 2985, 1720, 1670, 1597, 1553, 1482, 1397, 1292, 1216, 1188, 1049, 1017, 815, 773, 725, 557. ESI-HRMS: Calcd. for $C_{19}H_{19}N_7O_4$: *m/z* = 410,1577 (MH^+). Found: *m/z* = 410,1591. Anal. Calcd. for $C_{19}H_{19}N_7O_4 \cdot HCl$: C, 51.18; H, 4.52; N, 21.99. Found: C, 51.00; H, 4.65; N, 21.79.

Ethyl 6-ethoxy-1-imino-8-oxo-2-(phthalazin-1-ylamino)-1,2,7,8-tetrahydro-2,7-naphthyridine-4-carboxylate (13h). This compound was prepared from **4** and 1-hydrazinophthalazine (**10h**) in MeOH (4.0 mL), reflux 4 h. After addition of water (3 mL) white precipitate was collected by filtration and washed with water. Yield: 103 mg (49 %), white solid, m.p. 186-189 °C (decomp). ^{1}H NMR (DMSO–d_6): δ 1.29 (m, 6H, 2 × OCH_2CH_3), 4.26 (m, 4H, 2 × OCH_2CH_3), 6.79 (s, 1H, =CH), 7.94 (m, 3H, Ar), 8.13 (s, 1H, =CH), 8.28 (br s, 1H, N*H*), 8.47 (m, 2H, =CH and Ar), 11.96 (br s, 1H, N*H*), 12.59 (s, 1H, N*H*). ^{13}C NMR (DMSO–d_6): δ 13.9, 61.6, 66.4, 83.0, 101.2, 110.2, 116.0, 126.0, 129.2, 143.7 , 146.1, 147.9, 155.8, 160.9, 162.3, 162.7. IR (KBr, cm^{-1}): 3410, 2982, 1715, 1645, 1593, 1545, 1479, 1445, 1382, 1272, 1178, 1148, 1032, 926, 814, 762, 670, 597. ESI-HRMS: Calcd. for $C_{21}H_{20}N_6O_4$: *m/z* = 421.1624 (MH^+). Found: *m/z* = 421.1618. Anal. Calcd. for $C_{21}H_{20}N_6O_4$: C, 59.99; H, 4.79; N, 19.99. Found: C, 59.71; H, 4.77; N, 19.71.

Ethyl 6-ethoxy-1-imino-8-oxo-2-(pyridine-2-ylamino)-1,2,7,8-tetrahydro-2,7-naphthyridine-4-carboxylate (13i). This compound was prepared from **4** and 2-hydrazinopyridine (**10i**) in EtOH (1.5 mL), reflux 1 h. Yield: 59 mg (32 %), white solid, m.p. 246-248 °C (decomp). ^{1}H NMR (DMSO–d_6): δ 1.26 (m, 6H, 2 × OCH_2CH_3), 4.24 (m, 4H, 2 × OCH_2CH_3), 6.68 (s, 1H, =CH), 6.84 (d, 1H, *J* = 8.4 Hz, Ar), 6.97 (dd, 1H, J_1 = 6.9 Hz, J_2 = 5.1 Hz, Ar), 7.73 (ddd, 1H, J_1 = 8.1 Hz, J_2 = 6.6 Hz, J_3 = 1.8 Hz, Ar), 7.92 (s, 1H, =CH), 8.14 (br dd, 1H, *J* = 5.1 Hz, Ar), 8.68 (br s, 1H, N*H*), 10.04 (br s, 1H, N*H*), 12.41 (s, 1H, N*H*). IR (KBr, cm^{-1}): 2980, 1720, 1707, 1649, 1603, 1545, 1477, 1441, 1423, 1381, 1292, 1279, 1246, 1176, 1144, 1098, 1032, 927, 831, 774. EI-HRMS: Calcd. for $C_{18}H_{19}N_5O_4$: *m/z* = 369.1437 (M^+). Found: *m/z* = 369,1443. Anal. Calcd. for $C_{18}H_{19}N_5O_4$: C, 58.53; H, 5.18; N, 18.96. Found: C, 58.23; H, 5.01; N, 18,71.

X-Ray structure analysis for compound (6b)

Single crystal X-ray diffraction data of compound **6b** were collected at room temperature on a Nonius Kappa CCD diffractometer using the Nonius Collect Software.[11] DENZO and

SCALEPACK[12] were used for indexing and scaling of the data and the structures were solved by means of SIR97.[13] Refinement was done using Xtal3.6[14] program package and the crystallographic drawing was prepared by ORTEP-3.[15] Crystal structure was refined on *F* values using the full-matrix least-squares procedure. The non-hydrogen atoms were refined anisotropically, while the positions of hydrogen atoms were geometrically calculated and their positional and isotropic atomic displacement parameters were not refined. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary material with the deposition number CCDC 796256. Copies of the data can be obtained, free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html.

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

1. Šimunek, P.; Baškovč, J.; Grošelj, U.; Meden, A.; Svete, J.; Stanovnik, B. *Z. Naturforsch.* **2010**, *65b*, 807.
2. For reviews see: (a) Stanovnik, B. *J. Heterocycl Chem*. **1999**, *36*, 1581. (b) Stanovnik, B.; Svete, J. *Targets in Heterocycl. Syst*. **2000**, *4*, 105. (c) Stanovnik, B.; Svete, J. *Synlett* **2000**, 1077. (d) Stanovnik, B.; Svete, J. *Chem. Revs*. **2004**, *104*, 2433. (e) Stanovnik, B.; Svete, J. *Mini-Reviews in Organic Chemistry* **2005**, *2*, 211. (f) Svete, J.; *Monatsh. Chem*. **2004**, *135*, 629. (g) Bevk, D.; Svete, J.; Stanovnik, B. In *Modern Approaches to the Synthesis of* O- *and* N-*Heterocyles*, Vol. 3, Kaufmann, T. S.; Larghi, E. L., Eds., Research Signpost, Trivandrum (India), **2007**, Chapter 3, pp 73.
3. For recent publications see: (a) Stanovnik, B.; Smodiš, J. *Tetrahedron* **1998**, *54*, 9799. (b) Pirc, S.; Bevk, D.; Jakše, R.; Rečnik, S.; Golič, L.; Golobič, A.; Meden, A.; Stanovnik, B.; Svete, J. *Synthesis* **2005**, 2969. (c) Pirc, S.; Bevk, D.; Golobič, A.; Stanovnik, B.; Svete, J. *Helv. Chim. Acta* **2006**, *89*, 30. (d) Uršič, U.; Grošelj, U.; Meden, A.; Svete, J.; Stanovnik, B. *Tetrahedron Lett*. **2008**, *49*, 3775. (e) Uršič, U.; Svete, J.; Stanovnik, B. *Tetrahedron* **2008**, *64*, 9937. (f) Uršič, U.; Grošelj, U.; Meden, A.; Svete, J.; Stanovnik, B. *Helv. Chim. Acta* **2009**, *92*, 481. (g) Uršič, U.; Grošelj, U.; Meden, A.; Svete, J.; Stanovnik, *Synthesis* **2009**, 217.
4. (a) Strah, S.; Stanovnik, B.; Golič Grdadolnik, S. *J. Heterocycl. Chem*. **1997**, *34*, 263. (b) Selič, L.; Stanovnik, B. *Helv. Chim. Acta* **1998**, *81*, 1634. (c) Selič, S.; Jakše, R.; Lampič,

K.; Golič, L.; Golič Grdadolnik, S.; Stanovnik, B. *Helv. Chim Acta* **2000**, *83*, 2802. (d) Jakše, R.; Rečnik, S.; Svete, J.; Golobič, A.; Golič, L.; Stanovnik, B. *Tetrahedron* **2001**, *57*, 8395. (e) Grošelj, U.; Rečnik, S.; Svete, J.; Meden, A.; Stanovnik, B. *Tetrahedron: Asymmetry* **2002**, *13*, 821. (f) Čebašek, P.; Wagger, J.; Bevk, D.; Jakše, R.; Svete, J.; Stanovnik, B. *J. Comb. Chem.* **2004**, *6*, 356. (g) Jakše, R.; Bevk, D.; Golobič, A.; Svete, J.; Stanovnik, B. *Z. Naturforsch*. **2006**, *61b*, 413. (h) Časar, Z.; Bevk, D.; Svete, J.; Stanovnik, B. *Tetrahedron* **2005**, *61*, 7508. (i) Wagger, J.; Bevk, D.; Meden, A.; Svete, J.; Stanovnik, B. *Helv. Chim. Acta* **2006**, *89*, 240. (j) Jakše, R.; Grošelj, U.; Soršak, G.; Svete, J.; Stanovnik, B. *Heterocycles* **2007**, *73*, 743. (k) Jakše, R.; Golič, L.; Meden, A.; Grošelj, U.; Svete, J.; Stanovnik, B. *Heterocycles* **2007**, *74*, 293. (l) Wagger, J.; Grošelj, U.; Meden, A.; Svete, J.; Stanovnik, B. *Tetrahedron* **2008**, *64*, 2801. (m) Malavašič, Č.; Wagger, J.; Stanovnik, B.; Svete, J. *Tetrahedron: Asymmetry* **2008**, *19*, 1557. (n) Wagger, J.; Svete, J.; Stanovnik, B. *Synthesis* **2008**, 143.

5. Ikekawa, N. *Chem. Pharm. Bull.* **1958,** *6*, 263.
6. (a) Lowe, P. A. In *Comprehensive Heterocyclic Chemistry*: Vol. 2, 581. (b) Stanforth, S. P. In *Comprehensive Heterocyclic Chemistry* Vol 7, Pergamon **1996**, 527. (c) Dobbs, A. P. in *Comprehensive Heterocyclic Chemistry*, Vol 10, Amsterdam **2008**, 713. (d) Phuan, P.-W.; Kozlowski, M. C. In *Science of Synthesis*, Vol 15, Georg Thieme Verlag, Stuttgart, New York **2006**, 947. (e) Litvinov V. P. *Adv. Heterocycl. Chem.* **2006**, *91*, 11189.
7. Baldwin, J. J.; Mensler, K.; Ponticello, G. S. *J. Org. Chem.* **1978**, *43*, 4878.
8. Tan, R.; Taurins, A. *Tetrahedron Lett.* **1966,** *7*, 1233.
9. Numata, A.; Kondo, Y.; Sakamoto, T. *Synthesis* **1999**, 306.
10. van den Haak, H. J. W.; van der Plas, H. C.; Veldhuizen, B. *J. Heterocycl. Chem.* **1981**, *18*, 1349.
11. Collect Software. Nonius, BV, Delft, The Netherlands, 1998.
12. Otwinowski, Z.; Minor, W. *Methods Enzymol.* **1997**, *276*, 307.
13. Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, G. L.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A. G. G.; Polidori, G.; Spagna, R. *J. Appl. Crystallogr.* **1999**, *32*, 115.
14. Hall, S. R.; du Boulay, D. J.; Olthof-Hazekamp, R. Eds. Xtal3.6 System. 1999.
15. Farrugia, L. J. *J. Appl. Cryst.* **1997**, 30, 565.

