Tetrahedron 65 (2009) 9843–9849

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Naphthyridines. Part 3: First example of the polyfunctionally substituted 1,2,4-triazolo[1,5-*g*][1,6]naphthyridines ring system

Ramadan Ahmed Mekheimer [a,*], Yusria Rizk Ibrahim [a], Eltaib Ali Ahmed [a], Wolfgang Frey [b]

[a] *Department of Chemistry, Faculty of Science, El-Minia University, El-Minia 61519, Egypt*
[b] *Institute für Organische Chemie, Pfaffenwaldring 55, Universität Stuttgart, D-70569 Stuttgart, Germany*

ARTICLE INFO

Article history:
Received 13 May 2009
Received in revised form 30 August 2009
Accepted 17 September 2009
Available online 22 September 2009

ABSTRACT

Treatment of 1,2,4-triazoles (**1**) with diethylmalonate in bromobenzene gave 1,2,4-triazolo-[1,5-*a*]pyridines **2**. Chlorination of **2** using $POCl_3$/DMF (Vilsmeier reagent) led to the isolation of 7-chloro-6-formyl-1,2,4-triazolo[1,5-*a*]pyridine derivative **4**, which reacted with the stabilized ylid **5** to afford 6-ethoxycarbonylvinyl-1,2,4-triazolo[1,5-*a*]-pyridines **6**. Azidation of **6** yielded the corresponding azido compound **7**, (Scheme 2). Reduction of **7** with $Na_2S_2O_4$ gave the corresponding 7-amino compound **8**, which cyclized in boiling DMF to give the novel 1,2,4-triazolo[1,5-*g*][1,6]naphthyridines **9**. On the other hand, reacting **7** with one equivalent of PPh_3 (aza-Wittig reaction) in CH_2Cl_2 gave 7-imino-phosphorane derivative **10**, and subsequent cyclization in boiling DMF afforded the new 1,2,4-triazolo[1,5-*g*][1,6]naphthyridine derivative **11** (Scheme 3). However, treatment of **10** with phenyl isothiocyanate in 1,2-dichlorobenzene at reflux temperature gave the new 1,2,4-triazolo[1,5-*g*][1,6]naphthyridine derivative **14** (Scheme 4). Refluxing **6** with excess of a primary amines **15a**,**b** in absolute. EtOH yielded the corresponding 7-alkyl-amino-1,2,4-triazolo[1,5-*a*]pyridines **16a**,**b**. These obtained amines **16a**,**b** underwent intramolecular heterocyclization in boiling DMF to give the novel 9-alkyl-1,2,4-triazolo[1,5-*g*][1,6]-naphthyridines **17a**,**b**, in excellent yields (Scheme 5).

1. Introduction

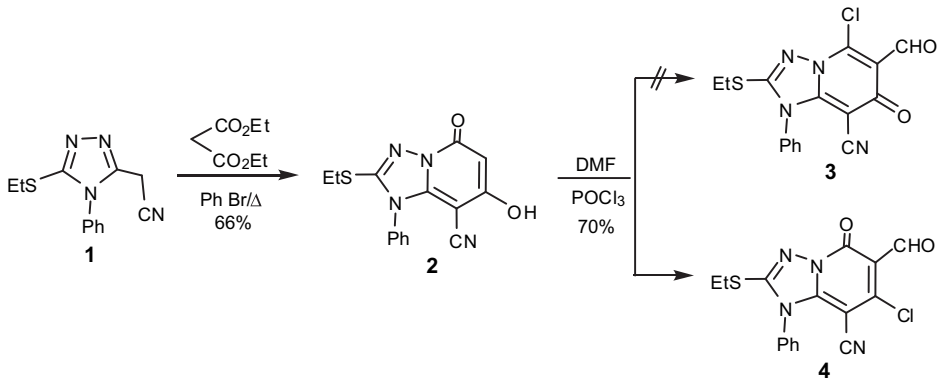
1,2,4-Triazoles and their derivatives are important constituents of pharmacologically active compounds, as these systems have demonstrated a broad spectrum of biological activities such as antifungal,[1–3] antiinflammatory,[4–6] antibacterial,[7–10] anticonvulsant,[11,12] and anticancer[13–16] activities. Several compounds containing 1,2,4-triazole rings are well known as drugs. For example, vorozole, letrozole, and anastrozole are non-steroidal drugs used for the treatment of cancer,[17] while loreclezole is used as anticonvulsant[18] and fluconazole is used as an antimicrobial drugs.[19] Furthermore, fused 1,2,4-triazoles have acquired considerable importance because of their CNS depressant, antiallergy, antiinflammatory, and antimicrobial properties.[20–23] 1,6-Naphthyridine derivatives constitute an important class of compounds possessing diverse types of biological properties. Recently, 1,4-dihydro-4-oxo-1,6-naphthyridine derivatives have been described as antibacterial agents.[24] 5-Substituted-8-hydroxy-1,6-naphthyridine-7-carboxamides are useful as HIV integrase inhibitors for the treatment of HIV infection (AIDS).[25] A series of novel 1,6-naphthyridine derivatives were prepared as potential inhibitors of human topoisomerase I,[26] anticonvulsive agents,[27] potential antimalarials,[28] p38 mitogen-activated protein kinase inhibitors,[29] and spleen tyrosine kinase inhibitors.[30] Considerable attention has recently been focused on procedures for the modification of 1,6-naphthyridine derivatives with the aim of searching for new biological active compounds. With the importance of these compounds in mind, we targeted the synthesis of a system that combines these two biolabile components together, *viz.* 1,2,4-triazole and 1,6-naphthyridine moieties, to give a compact structure like the title compounds with the expected significant biological activity.

Recently, we have been involved in the synthesis and chemistry of novel naphthyridine derivatives with a prospect to incorporate diverse bioactive heterocyclic nucleus intact for evaluating their biological significance and also as a reagent for effective functional group interconversion.[31,32] To the best of our knowledge, there are no reports on the synthesis of the title compounds.

As a continuation of our search for more potent naphthyridine derivatives, we now report the first members of a novel heterosystem, 1,2,4-triazolo[1,5-*g*][1,6]naphthyridine derivatives encompassing bioactive molecules, i.e., 1,2,4-triazole and 1,6-naphthyridine. The 7-azidotriazolopyridines **7** appear to serve as a good building block for these heterocycles.

* Corresponding author. Tel.: +02 0109309076.
E-mail address: rmekh@yahoo.com (R.A. Mekheimer).

0040-4020/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2009.09.082



Scheme 1.

2. Results and discussion

The synthesis of this key intermediate **7** from the easily accessible 3-ethylthio-5-cyanomethyl-4-phenyl-1,2,4-triazole (**1**)[33] is summarized in Scheme 1. Beginning with the triazole **1**, treatment with diethylmalonate in bromobenzene at reflux temperature afforded 2-ethylthio-1,5-dihydro-7-hydroxy-5-oxo-1-phenyl-1,2,4-triazolo[1,5-*a*]pyridine-8-carbo-nitrile (**2**). Reacting **2** with the Vilsmeir–Haack reagent at 65–70 °C for 6 h led directly to 7-chloro-6-formyl-1,2,4-triazolo[1,5-*a*]pyridine derivative **4**. The structure of **4** was identified over the possible isomer **3** by the IR spectrum, which exhibited an absorption band at 1660 cm^{-1} due to the –C=O for an amide carbonyl group. Treatment of **4** with an equimolar amount of [(ethoxy-carbonyl)methylene]triphenyl-phosphorane (**5**) in $CHCl_3$ at room temperature gave 7-chloro-6-ethoxy-carbonylvinyl-2-ethylthio-1,5-dihydro-5-oxo-1-phenyl-1,2,4-triazolo[1,5-*a*]pyridine-8-carbonitrile (**6**) (Scheme 2). The ^1H NMR spectrum included a characteristic AB system (7.29 and 7.86 ppm, with a coupling constant J=16 Hz) that indicated a *trans*-configuration for the vinylic protons in this compound. The structure of **6** was unambiguously confirmed by X-ray crystallography.[34] Compound **6** (figures, bottom-with X-ray numbering) was crystallized with two independent molecules (Molecules A and B) in (Figs. 1 and 2) the asymmetric unit of the space group P-1. The molecules differ slightly in the orientation of their substituents, which are attached to the flat bicyclic system. The angles between the best plane through the atoms of the acrylicethylester side chain and the best plane through the atoms of the bicyclic core are 19.0(3)° (Mol. A) and 35.9(3)° (Mol. B), respectively. The phenyl moiety shows a nearly perpendicular orientation to the bicyclic system with angles of 77.1(2)° (Mol. A) and 69.5(2)° (Mol. B), respectively. In contrast to the expected results the positions of the oxygen O1A,B and the chlorine Cl1A,B are reversed, clearly indicated by the distances of C1A,*B*-O1A,B of 1.201(8) A and C3A,*B*-Cl1A,B of 1.728(7) A. The double bond C6A,*B*-N1A,B of the triazole moiety is identified by the distance of 1.299(9) A and the double bond C10A,*B*–C11A,B of the acrylic-ethylester side chain is verified by the distance of 1.31(1) A.

Azidation of **6** with sodium azide in DMF at room temperature gave the corresponding 7-azidotriazolopyridine derivatives **7** (Scheme 2). The structure of **7** was established and confirmed for

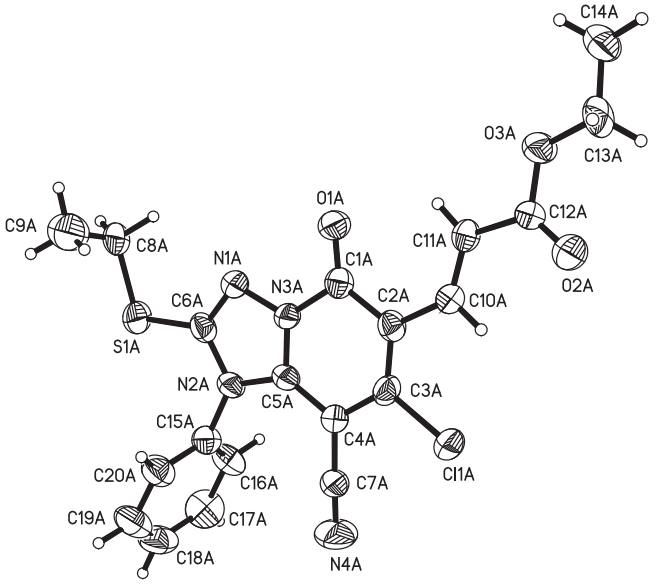
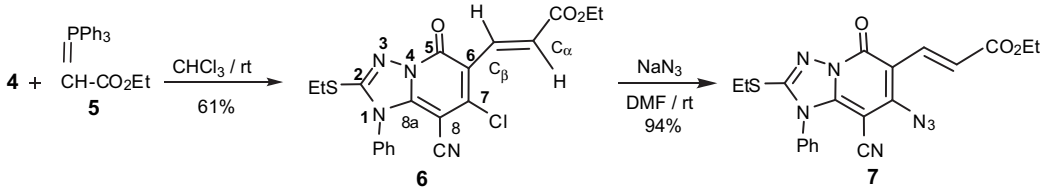


Figure 1. Molecule A of the asymmetric unit of the X-ray structure.

the reaction product on the basis of its elemental analysis and spectral data (MS, IR, ^1H and ^{13}C NMR) (see Experimental).

As the preparation of the novel tricyclic systems, *namely* 1,2,4-triazolo[1,5-*g*]-[1,6]naphthyridines, is the main target of this synthetic program, the 7-azido-1,2,4-triazolo-[1,5-*a*]pyridine derivatives **7** was selected as a model compound for studying all the reactions leading to the construction of novel tricyclic systems that incorporate a triazole nucleus in addition to naphthyridine moiety. As a model experiment, we first reacted **7** with $Na_2S_2O_4$. Thus, reduction of the azide moiety in **7** with $Na_2S_2O_4$ furnished the corresponding 7-amino-triazolopyridines **8** in 96% yield.



Scheme 2.

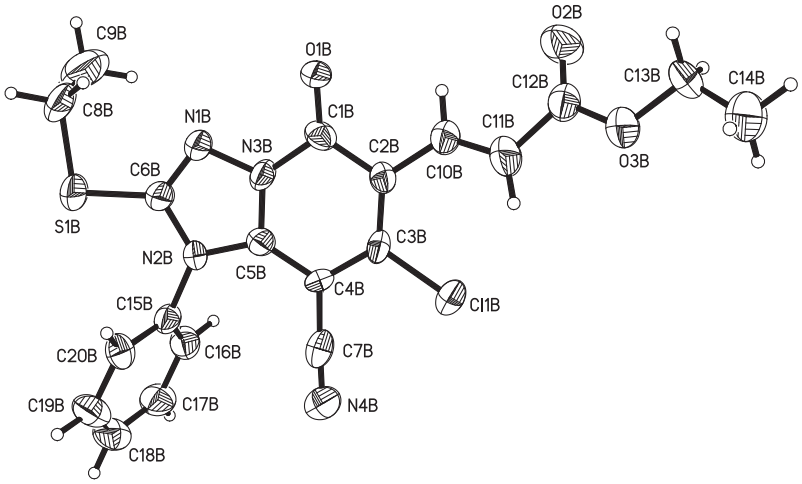
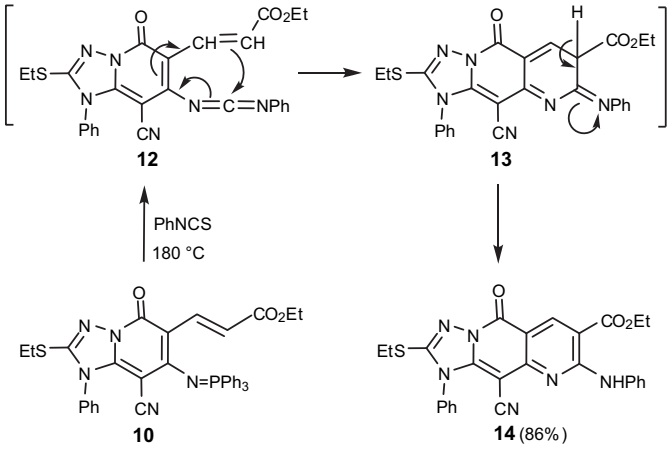


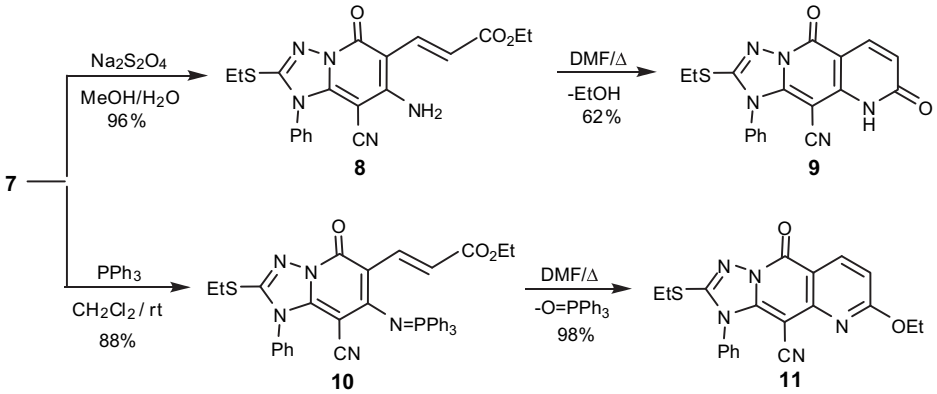
Figure 2. Molecule B of the asymmetric unit of the X-ray structure.

Attention was next turned to the cyclization of amino compound **8** to 1,2,4-triazolo-[1,5-*g*][1,6]naphthyridines **9**. Thus, when compound **8** was heated in DMF at reflux temperature, an intramolecular cyclization took place that led directly to the previously unknown ring system 2-ethylthio-1,5,8,9-tetrahydro-5,8-dioxo-1-phenyl-1,2,4-triazolo-[1,5-*g*][1,6]naphthyridine-10-carbonitrile (**9**) (Scheme 3), in fair yield (62%).

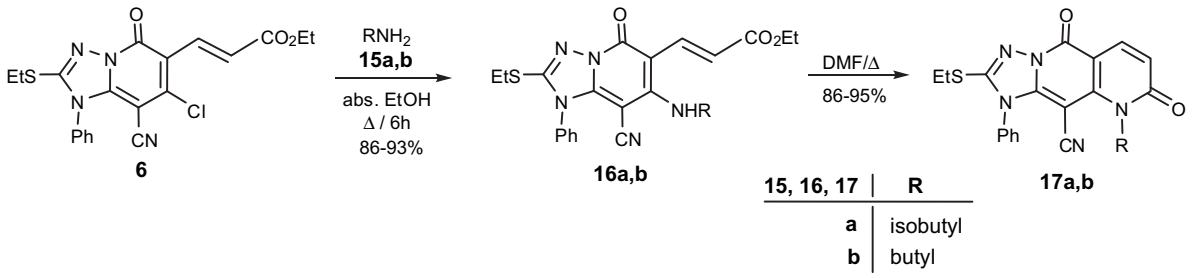
The iminophosphoranes of heterocyclic compounds have proved to be very versatile synthons for the construction of heterocondensed systems through an aza-Wittig reaction in very mild reaction conditions.[35] Encouraged by this result, and given our interest in developing synthetic approaches with a view to synthesize new derivatives of the interesting tricyclic system 1,2,4-triazolo[1,5-*g*][1,6]naphthyridines, we next examined the synthesis of iminophosphorane **10**. Staudinger reaction of azide **7** with triphenylphosphine in CH_2Cl_2 at room temperature provided at the desired key intermediate iminophosphorane **10**. When iminophosphorane **10** was heated to reflux in dry DMF for 40 h, an intramolecular aza-Wittig cyclization, involving an ester functionality occurred to afford triphenylphosphine oxide and the interesting heterocycle 1,2,4-triazolo[1,5-*g*][1,6]naphthyridine **11** (Scheme 3). The structure of **11** was established and confirmed for the reaction product on the basis of its elemental analysis and spectral data (see Experimental). On the other hand, treatment of iminophosphorane **10** with phenyl isothiocyanate in refluxing 1,2-dichlorobenzene for 4 h gave the novel ethyl 10-cyano-2-ethylthio-1,5-dihydro-5-oxo-1-phenyl-8-(phenylamino)-1,2,4-triazolo-[1,5-*g*][1,6]naphthyridine-7-carboxylate (**14**) in 86% yield (Scheme 4). The formation of tricyclic system **14** can be explained by an initial aza Wittig-type reaction between the iminophosphorane group directly linked to the heterocyclic ring and 1.25 equiv of the phenyl isothiocyanate to give carbodiimide **12**, as a highly reactive intermediate, which undergoes intramolecular cyclization by nucleophilic attack of the β-carbon atom of the vinyl moiety on the central carbon of



Scheme 4.



Scheme 3.



Scheme 5.

the carbodiimide moiety to yield a further intermediate **13**, which then undergoes a proton shift to afford the final product **14** (see Scheme 4).

We next considered the possibility that this design strategy could be extended to the preparation of new derivatives of the interesting triazolonaphthyridines of type **17**, that are alkylated at the heterocyclic nitrogen (i.e., at position 9). We attempted reaction of the chloro compound **6** with alkylamines. Heating to reflux compound **6** with an excess of alkylamines **15a**,**b** in absolute EtOH for 6 h gave in each case the corresponding 7-alkylamino-1,2,4-triazolo[1,5-*a*]-pyridines **16a**,**b**. Only the (*E*)-isomer was obtained for compounds **7**, **8**, **10**, and **16a**,**b** and in all cases, the ^{1}H NMR spectra included a characteristic AB system that indicated the *trans*-configuration of vinylic protons in these compounds (see Experimental). When compounds **16a**,**b** were heated in DMF at reflux temperature, an intramolecular heterocyclization across the electrophilic ester functionality was occurred to give the hitherto unknown fused tricyclic systems **17a**,**b**, *namely* 9-alkyl-2-ethylthio-1,5,8,9-tetrahydro-5,8-dioxo-1-phenyl-1,2,4-triazolo[1,5-*g*][1,6]naphthyridine-10-carbonitriles, as new model system for 1,2,4-triazolonaphthyridines (Scheme 5). Interestingly, a characteristic feature of the ^{1}H NMR spectra of compounds **17a**,**b** was the downfield shift by approx. 0.90 ppm of the *N*-CH_2 signals caused by the anisotropic effect of the ring nitrogen. From these results, we concluded that intramolecular cyclocondensation between the amino and ester groups in **16a**,**b** occurred with the formation of the first example of a linear, anellated 1,2,4-triazolo-[1,5-*g*][1,6]naphthyridines.

3. Conclusions

In summary, the results obtained in this third-generation version of our annulation strategy have demonstrated for the first time a new, simple and general methodology for the construction of a wide variety of biologically important novel 1,2,4-triazolo[1,5-*g*][1,6]-naphthyridines, obtainable only with difficulty otherwise. Currently, further studies in our laboratory aimed at the synthesis of new fused 1,2,4-triazolonaphthyridines are under investigation and will be published in due course.

4. Experimental

4.1. General

Melting points were taken on a Gallenkamp apparatus and are uncorrected. IR spectra were obtained with a Shimadzu 470 spectrophotometer as dispersions in KBr. Microanalyses were performed by the microanalytical Data Unit at Cairo University, and analytical values obtained were within ±0.4% of the calculated values. Mass spectra were registered on a Shimadzu GC–MS-QP 2010 instrument at 70 eV. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker-DPX-300 (300 MHz for ^{1}H and 75 MHz for ^{13}C) and Fa. Bruker ARX500 (500.1 MHz for ^{1}H NMR and 125.8 MHz for ^{13}C) spectrometers with DMSO as solvent and TMS as an internal standard. Chemical shifts are expressed in δ values (ppm).

4.2. Synthesis of 2-ethylthio-1,5-dihydro-7-hydroxy-5-oxo-1-phenyl-1,2,4-triazolo[1,5-*a*]-pyridine-8-carbonitrile (2)

A mixture of compound **1** (0.50 g, 2.046 mmol) and diethylmalonate (0.656 g, 4.095 mmol) in bromobenzene (5 mL) was heated to reflux for 20 h, during, which a colorless solid product separated out. After cooling to room temperature, the resulting solid product was filtered off, washed with MeOH, dried, and recrystallized from DMF to give compound **2** as colorless solid; 0.420 g (66%); mp 330–331 °C, dec; IR (KBr) 3450, 3100, 2900, 2200, 1660 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.68 (1H, s, OH); 7.58–7.69 (5H, m, Ar-H), 5.50 (1H, s, H-6), 3.22 (2H, q, J=7.2 Hz, CH_2), 1.36 (3H, t, J=7.2 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ 171.9 (C-7); 159.7 (C=O), 158.6 (C-8a), 151.8 (C-2), 137.5 136.7, 135.9, 135.7, 134.8, 134.0 (Ar-C), 117.0 (CN), 93.7 (C-6), 67.7 (C-8), 31.3 (CH_2), 19.4 (CH_3); MS *m*/*z* (%): 313 (M^++1, 17), 312 (M^+, 100), 283 (5), 268 (6), 242 (25), 216 (5), 194 (4), 185 (7), 161 (9), 142 (7), 118 (14), 105 (19), 91 (6), 77 (50), 69 (16), 51 (16), 44 (7). Anal. Calcd for $C_{15}H_{12}N_4O_2S$: C, 57.68; H, 3.87; N, 17.94; S, 10.27. Found: C, 57.78; H, 3.69; N, 18.07; S, 10.19.

4.3. Synthesis of 7-chloro-2-ethylthio-6-formyl-1,5-dihydro-5-oxo-1-phenyl-1,2,4-triazolo[1,5-*a*] pyridine-8-carbonitrile (4)

Phosphoryl chloride (0.69 g, 4.50 mmol) was added dropwise to cooled dimethyl-formamide (0.117 g, 1.603 mmol) at 0 °C, and the temperature of the reaction mixture was maintained at 0–5 °C. Compound **2** (0.20 g, 0.641 mmol) was added and the reaction mixture was stirred at 65–70 °C for 6 h. After cooling, the reaction mixture was poured into cold H_2O (20 mL). The obtained precipitate was filtered, washed with H_2O, dried and recrystallized from MeOH to give compound **4** as yellowish solid; 0.160 g (70%); mp 250–251 °C; IR (KBr) 3100, 2900, 2870, 2200, 1720, 1660 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.20 (1H, s, CHO), 7.70 (5H, m, Ar-H), 3.33 (2H, q, J=7 Hz, CH_2), 1.42 (3H, t, J=7 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ 185.8 (CHO); 156.5 (CO), 153.6 (C-7), 148.3 (C-8a), 147.2 (C-2), 132.2 129.9, 129.6, 128.6 (Ar-C), 110.8 (CN), 110.1 (C-6), 75.1 (C-8), 26.5 (CH_2), 14.1 (CH_3); MS *m*/*z* (%): 360 (M^+, 6), 358 (M^+, 15), 330 (84), 295 (26), 271 (20), 243 (19), 119 (20), 77 (100), 51 (41), 27 (34). Anal. Calcd for $C_{16}H_{11}ClN_4O_2S$: C, 53.56; H, 3.09; Cl, 9.88; N, 15.61; S, 8.94. Found: C, 53.47; H, 2.88; Cl, 10.14; N, 15.49; S, 8.73.

4.4. Synthesis of 7-chloro-6-ethoxycarbonylvinyl-2-ethylthio-1,5-dihydro-5-oxo-1-phenyl-1,2,4-triazolo[1,5-*a*]pyridine-8-carbonitrile (6)

A mixture of **4** (0.50 g, 1.39 mmol) and **5** (0.485 g, 1.39 mmol) in $CHCl_3$ (10 mL) was stirred for 2 h at room temperature (25 °C). The

mixture was evaporated to dryness in vacuo. MeOH (3 mL) was added to the remaining oily residue with scratching. The precipitated solid product was collected by filtration, washed with cold MeOH, dried and recrystallized from MeOH to give compound **6** as yellowish solid; 0.366 g (61%); mp 184–185 °C; IR (KBr) 3100, 2970, 2930, 2220, 1710, 1680 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 7.86 (1H, d, J=16 Hz, =CH), 7.70 (5H, m, Ar-H), 7.29 (1H, d, J=16 Hz, CH=), 4.20 (2H, q, J=7 Hz, CH_2), 3.32 (2H, q, J=7 Hz, CH_2), 1.41 (3H, t, J=7 Hz, CH_3), 1.25 (3H, t, J=7 Hz, CH_3); ^{13}C NMR (125.8 MHz, DMSO-d_6) δ 166.9 (CO, ester), 156.0 (CO, amide), 151.9 (C-8a), 146.2 (C-2), 145.5 (C-7), 136.1 (C_α), 132.1, 129.9, 129.7, 128.6 (Ar-C), 119.7 (C-6), 111.5 (CN), 109.1 (C_β), 73.4 (C-8), 60.0 (CH_2), 26.3 (CH_2), 14.1 ($2CH_3$); MS m/z (%): 430 (M^+, 9), 428 (M^+, 13), 393 (12), 355 (100), 327 (41), 295 (22), 267 (16), 240 (11), 231 (12), 205 (21), 88 (17), 77 (81), 51 (62), 50 (29). Anal. Calcd for $C_{20}H_{17}ClN_4O_3S$: C, 56.01; H, 4.00; Cl, 8.27; N, 13.06; S, 7.48. Found: C, 56.19; H, 3.87; Cl, 8.38; N, 12.88; S, 7.67.

4.5. Synthesis of 7-azido-6-ethoxycarbonylvinyl-2-ethylthio-1,5-dihydro-5-oxo-1-phenyl-1,2,4-triazolo[1,5-*a*]pyridine-8-carbonitrile (7)

Sodium azide (0.060 g, 0.932 mmol) was added to a solution of **6** (0.20 g, 0.466 mmol) in DMF (5 mL) and the mixture was stirred for 3 h at room temperature (25 °C). Then, the reaction mixture was poured into H_2O (10 mL) and the precipitated solid product was collected by filtration, washed well with H_2O, dried, and recrystallized from $CHCl_3$ to give compound **7** as yellowish solid; 0.190 g (94%); mp 164–166 °C, dec; IR (KBr) 3100, 2950, 2220, 2130, 1710, 1680 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 7.82 (1H, d, J=16 Hz, =CH), 7.69 (5H, m, Ar-H), 7.15 (1H, d, J=16 Hz, CH=), 4.17 (2H, q, J=7 Hz, CH_2), 3.30 (2H, q, J=7.2 Hz, CH_2), 1.41 (3H, t, J=7.2 Hz, CH_3), 1.25 (3H, t, J=7.2 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.2 (CO, ester), 155.7 (CO, amide), 152.6 (C-8a), 147.9 (C-2), 145.8 (C-7), 134.8 (C_α), 132.0, 129.8, 129.6, 128.7 (Ar-C), 117.9 (C-6), 110.2 (CN), 103.4 (C_β), 67.0 (C-8), 60.0 (CH_2), 26.3 (CH_2), 14.1 ($2CH_3$); MS m/z (%): 407 (M^+-N_2, 92), 406 (10), 378 (5), 362 (26), 361 (100), 333 (18), 305 (13), 280 (3), 276 (14), 249 (2), 77 (31), 51 (16). Anal. Calcd for $C_{20}H_{17}N_7O_3S$: C, 55.16; H, 3.93; N, 22.52; S, 7.36. Found: C, 55.33; H, 4.12; N, 22.67; S, 7.19.

4.6. Synthesis of 7-amino-6-ethoxycarbonylvinyl-2-ethylthio-1,5-dihydro-5-oxo-1-phenyl-1,2,4-triazolo[1,5-*a*]pyridine-8-carbonitrile (8)

Sodium dithionite (0.40 g, 2.30 mmol) was added portion wise to a stirred suspension of **7** (0.20 g, 0.459 mmol) in a 2:1 MeOH/H_2O (30 mL) mixture. Stirring was maintained at room temperature for 2 h, during this period of time a yellow solid product was formed. Then, the reaction mixture was poured into H_2O (15 mL). The resulting solid product was collected by filtration, washed well with H_2O, dried, and recrystallized from $CHCl_3$ to give compound **8** as yellowish solid; 0.180 g (96%); mp 261–262 °C; IR (KBr) 3350, 3200, 3050, 2980, 2900, 2200, 1690, 1660 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 7.78 (1H, d, J=15 Hz, =CH), 7.65 (5H, m, 5Ar-H), 7.12 (1H, d, J=15 Hz, CH=), 6.97 (2H, s, NH_2), 4.14 (2H, q, J=7 Hz, CH_2), 3.24 (2H, q, J=7 Hz, CH_2), 1.34 (3H, t, J=7 Hz, CH_3), 1.25 (3H, t, J=7 Hz, CH_3); ^{13}C NMR (125.8 MHz, DMSO-d_6) δ 168.0 (CO, ester); 156.0 (CO, amide), 153.8 (C-7), 153.1 (C-8a), 146.0 (C-2), 136.7 (C_α), 131.6, 130.4, 129.6, 128.8 (Ar-C), 113.4 (C_β), 112.6 (CN), 93.0 (C-6), 60.2 (C-8), 59.1 (CH_2), 26.1 (CH_2), 14.3 (CH_3), 14.2 (CH_3); MS m/z (%): 410 (M^++1, 14), 409 (M^+, 29), 364 (12), 338 (14), 337 (70), 336 (100), 309 (11), 308 (15), 307 (19), 276 (7), 77 (27), 51 (12). Anal. Calcd for $C_{20}H_{19}N_5O_3S$: C, 58.67; H, 4.68; N, 17.10; S, 7.83. Found: C, 58.86; H, 4.51; N, 17.19; S, 8.04.

4.7. 2-Ethylthio-1,5,8,9-tetrahydro-5,8-dioxo-1-phenyl-1,2,4-triazolo[1,5-*g*][1,6]naphthyridine-10-carbonitrile (9)

A solution of compound **8** (0.20 g, 0.488 mmol) in DMF (7 mL) was heated under reflux for 110 h. After concentration and cooling to room temperature, a small amount of EtOH (2 mL) was added. Then, the resulting solid product was collected by filtration, dried, and recrystallized from EtOH to give compound **9** as buff solid; 0.110 g (62%); mp 302–303 °C; IR (KBr) 3450, 3050, 2950, 2900, 2200, 1680, 1660 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 11.34 (1H, br s, NH), 8.14 (1H, d, J=9 Hz, H-6), 7.68 (5H, m, Ar-H), 6.37 (1H, d, J=9 Hz, H-7), 3.28 (2H, q, J=7 Hz, CH_2), 1.41 (3H, t, J=7.6 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.0 (CO), 156.6 (CO), 152.2 (C-10a), 148.5 (C-2), 147.3 (C-9a), 136.7 (C-6), 131.6, 130.5, 129.7, 128.9 (Ar-C), 122.7 (C-7), 115.2 (CN), 113.6 (C-5a), 61.3 (C-10), 26.3 (CH_2), 14.2 (CH_3); MS m/z (%): 364 (M^++1, 46), 363 (M^+, 100), 361 (16), 335 (22), 109 (6), 92 (4), 77 (28), 64 (10), 52 (8), 51 (22). Anal. Calcd for $C_{18}H_{13}N_5O_2S$: C, 59.49; H, 3.61; N, 19.27; S, 8.82. Found: C, 59.32; H, 3.52; N, 19.43; S, 9.05.

4.8. Synthesis of 6-ethoxycarbonylvinyl-2-ethylthio-1,5-dihydro-5-oxo-1-phenyl-7-[(triphenylphosphoranylidene)-amino]-1,2,4-triazolo[1,5-*a*]pyridine-8-carbonitrile (10)

A mixture of the azide **7** (0.130 g, 0.30 mmol) and triphenylphosphine (0.078 g, 0.30 mmol) in CH_2Cl_2 (5 mL) was stirred for 2 h at room temperature. After concentration, the resulting solid product was filtered off, washed with a small amount of EtOH, dried, and recrystallized from $CHCl_3$ to give **10** as yellow solid; 0.176 g (88%); mp 254–255 °C; IR (KBr) 3050, 2990, 2940, 2220, 1690, 1670 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 7.85 (1H, d, J=16 Hz, =CH), 7.49–7.67 (20H, m, Ar-H), 6.75 (1H, d, J=16 Hz, CH=), 3.95 (2H, q, J=7 Hz, CH_2), 3.22 (2H, q, J=7 Hz, CH_2), 1.37 (3H, t, J=7 Hz, CH_3), 1.07 (3H, t, J=7 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.7 (CO, ester); 161.7 (CO, amide), 153.6 (C-8a), 152.4 (C-7), 146.0 (C-2), 140.0 (C_α), 132.3, 132.2, 132.1, 131.2, 130.6, 130.1, 129.4, 128.8, 128.7, 128.6 (Ar-C), 114.6 (C_β), 112.3 (CN), 103.7 ($^3J_{cp}$=7.1 Hz, C-6), 70.8 ($^3J_{cp}$=10.6 Hz, C-8), 58.7 (CH_2), 26.1 (CH_2), 14.2 ($2CH_3$); MS m/z (%): 670 (M^++1, 4), 669 (M^+, 7), 596 (20), 569 (5), 391 (23), 376 (16), 363 (25), 336 (11), 334 (19), 277 (36), 262 (100), 261 (28), 201 (16), 183 (33), 171 (5), 152 (10), 109 (9), 108 (16), 107 (13), 103 (9), 77 (22), 61 (7), 51 (6). Anal. Calcd for $C_{38}H_{32}N_5O_3PS$: C, 68.15; H, 4.82; N, 10.46; S, 4.79. Found: C, 68.24; H, 4.64; N, 10.59; S, 4.95.

4.9. Synthesis of 8-ethoxy-2-ethylthio-1,5-dihydro-5-oxo-1-phenyl-1,2,4-triazolo[1,5-*g*]-[1,6]naphthyridine-10-carbonitrile (11)

A solution of compound **10** (0.20 g, 0.299 mmol) in dry DMF (7 mL) was heated to reflux for 40 h. After concentration and cooling to room temperature, MeOH (3 mL) was added. The precipitated solid product was collected by filtration, dried, and recrystallized from EtOH to give compound **11** as yellow solid; 0.115 g (98%), mp 230–232 °C; IR (KBr) 3070, 2975, 2910, 2210, 1667 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 8.43 (1H, d, J=9 Hz, H-6), 7.67–7.78 (5H, m, Ar-H), 6.80 (1H, d, J=9 Hz, H-7), 4.43 (2H, q, J=7 Hz, CH_2), 3.29 (2H, q, J=7 Hz, CH_2), 1.42 (3H, t, J=7 Hz, CH_3), 1.35 (3H, t, J=7 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.2 (C-8), 156.5 (CO), 151.5 (C-10a), 150.9 (C-9a), 148.3 (C-2), 137.4 (C-6), 131.6, 130.3, 129.6, 128.8 (Ar-C), 115.6 (CN), 107.2 (C-7), 104.6 (C-5a), 61.0 (C-10), 59.8 (CH_2), 26.2 (CH_2), 14.5 (CH_3), 14.1 (CH_3); MS m/z (%): 392 (M^++1, 36), 391 (M^+, 100), 390 (25), 378 (18), 377 (29), 376 (99), 375 (16), 365 (18), 364 (15), 363 (76), 362 (18), 350 (7), 348 (25), 347 (23), 346 (9), 334 (24), 316 (10), 290 (7), 278 (9), 260 (7), 246 (7), 206 (10), 109 (16), 77 (84), 64 (15), 51 (32). Anal. Calcd for $C_{20}H_{17}N_5O_2S$: C, 61.37; H, 4.38; N, 17.89; S, 8.19. Found: C, 61.19; H, 4.49; N, 18.01; S, 8.26.

4.10. Synthesis of ethyl 10-cyano-2-ethylthio-1,5-dihydro-5-oxo-1-phenyl-8-(phenyl-amino)-1,2,4-triazolo[1,5-*g*][1,6]naphthyridine-7-carboxylate (14)

A mixture of compound **10** (0.20 g, 0.299 mmol) and phenyl isothiocyanate (0.05 g, 0.370 mmol) in 1,2-dichlorobenzene (5 mL) was heated to reflux for 4 h. After concentration and cooling to room temperature, the resulting solid product was collected by filtration, washed with MeOH, dried, and recrystallized from MeOH to give compound **14** as greenish solid; 0.130 g (86%); mp 301–302 °C; IR (KBr) 3260, 3050, 2990, 2200, 1690, 1670 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 10.65 (1H, s, NH), 8.82 (1H, s, H-6), 7.94 (2H, d, J=8 Hz, Ar-H), 7.74 (5H, m, Ar-H), 7.25 (2H, t, J=8 Hz, Ar-H), 7.05 (1H, t, J=8 Hz, Ar-H), 4.31 (2H, q, J=7 Hz, CH_2), 3.28 (2H, q, J=7 Hz, CH_2), 1.41 (3H, t, J=7 Hz, CH_3), 1.37 (3H, t, J=7 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ 165.8 (CO, ester), 155.4 (CO, amide), 155.1 (C-9a), 154.9 (C-8), 152.8 (C-10a), 148.2 (C-2), 140.5 (C-6), 131.5, 130.3, 129.6, 128.7, 128.4, 123.0, 120.6 (Ar-C), 112.5 (CN), 105.6 (C-5a), 105.3 (C-7), 69.1 (C-10), 61.4 (CH_2), 26.2 (CH_2), 14.0 (CH_3), 13.8 (CH_3); MS m/z (%): 511 (M^++1, 28), 510 (M^+, 100), 509 (18), 466 (14), 465 (14), 464 (50), 438 (16), 437 (52), 436 (22), 350 (10), 92 (3), 77 (66), 61 (7), 51 (21); Anal. Calcd for $C_{27}H_{22}N_6O_3S$: C, 63.52; H, 4.34; N, 6.46; S, 6.28. Found: C, 63.69; H, 4.18; N, 16.35; S, 6.19.

4.11. General procedure for the synthesis of 7-alkylamino-6-ethoxycarbonylvinyl-2-ethylthio-1,5-dihydro-5-oxo-1-phenyl-1,2,4-triazolo[1,5-*a*]pyridine-8-carbonitrile 16a,b

A mixture of compound **6** (0.140 g, 0.33 mmol) and alkylamines **15a**,**b** (0.096 g, 1.31 mmol) in absolute EtOH (10 mL) was heated to reflux for 6 h, until TLC showed the disappearance of the starting compounds. After concentration and cooling to room temperature, the resulting solid product was collected by filtration, washed with EtOH, dried, and recrystallized from $CHCl_3$ to give compounds **16a**,**b**.

*4.11.1. 7-(Isobutylamino)-6-ethoxycarbonylvinyl-2-ethylthio-1,5-dihydro-5-oxo-1-phenyl-1,2,4-triazolo[1,5-a]pyridine-8-carbonitrile (**16a**).* Yellowish solid; 0.142 g (93%); mp 122–124 °C, dec; IR (KBr) 3350, 3050, 2950, 2900, 2850, 2200, 1680, 1660 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 7.84 (1H, d, J=15 Hz, =CH), 7.62 (5H, m, Ar-H), 7.05 (1H, d, J=15 Hz, CH=), 6.91 (1H, t, J=5 Hz, NH), 4.14 (2H, q, J=7 Hz, CH_2), 3.23 (4H, m, $2CH_2$), 1.89 (1H, m, aliph. CH), 1.38 (3H, t, J=7 Hz, CH_3), 1.24 (3H, t, J=7 Hz, CH_3), 0.84 (6H, d, J=6 Hz, $2CH_3$); ^{13}C NMR (75 MHz, DMSO-d_6) δ 168.1 (CO, ester), 156.9 (CO, amide), 153.6 (C-7), 152.9 (C-8a), 146.8 (C-2), 137.2 (C_α), 131.4, 130.7, 129.5, 128.8 (Ar-C), 114.0 (C_β), 113.7 (CN), 95.7 (C-6), 61.0 (C-8), 59.2 (CH_2), 53.6 (CH_2), 28.8 (aliph. CH), 26.3 (CH_2), 19.6 ($2CH_3$), 14.3 (CH_3), 14.2 (CH_3); MS m/z (%): 466 (M^++1, 12), 465 (M^+, 19), 422 (73), 394 (26), 393 (24), 392 (51), 380 (13), 379 (18), 378 (60), 377 (16), 364 (37), 363 (38), 350 (54), 349 (40), 348 (100), 336 (52), 335 (19), 334 (18), 321 (31), 320 (34), 311 (32), 309 (15), 307 (22), 302 (15), 295 (13), 290 (13), 288 (15), 275 (15), 262 (18), 232 (18), 193 (13), 179 (15), 168 (14), 145 (6), 136 (16), 118 (19), 105 (16), 104 (16), 100 (6), 92 (11), 91 (18), 77 (82), 73 (4), 66 (15), 64 (16), 61 (15), 57 (23), 56 (14), 55 (23), 51 (42), 50 (17). Anal. Calcd for $C_{24}H_{27}N_5O_3S$: C, 61.92; H, 5.85; N, 15.04; S, 6.89. Found: C, 62.11; H, 5.78; N, 14.88; S, 6.76.

*4.11.2. 7-(Butylamino)-6-ethoxycarbonylvinyl-2-ethylthio-1,5-dihydro-5-oxo-1-phenyl-1,2,4-triazolo[1,5-a]pyridine-8-carbonitrile (**16b**).* Yellowish solid; 0.130 g (86%); mp 226–228 °C; IR (KBr) 3350, 3050, 2950, 2900, 2850, 2200, 1680, 1660 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 7.68 (1H, d, J=16 Hz, =CH); 7.62 (5H, m, Ar-H), 7.04 (1H, d, J=16 Hz, CH=), 6.88 (1H, t, J=5 Hz, NH), 4.15 (2H, q, J=7 Hz, CH_2), 3.42 (2H, q, J=7 Hz, CH_2), 3.23 (2H, q, J=7 Hz, CH_2), 1.54 (2H, m, CH_2), 1.37 (3H, t, J=7 Hz, CH_3), 1.26 (3H, t, J=7 Hz, CH_3), 1.24 (2H, m, CH_2), 0.84 (3H, t, J=7 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ 168.0 (CO, ester), 156.9 (CO, amide), 153.5 (C-7), 152.8 (C-8a), 146.8 (C-2), 137.2 (C_α), 131.3, 130.8, 129.4, 128.8 (Ar-C), 114.0 (C_β), 113.6 (CN), 95.7 (C-6), 60.9 (C-8), 59.3 (CH_2), 43.8 (CH_2), 30.7 (CH_2), 26.3 (CH_2), 18.4 (CH_2), 14.3 (CH_3), 14.2 (CH_3), 13.4 (CH_3); MS m/z (%): 466 (M^++1, 13), 465 (M+, 14), 424 (17), 423 (40), 422 (67), 421 (10), 420 (18), 419 (18), 403 (18), 393 (51), 392 (67), 391 (8), 380 (18), 379 (30), 378 (100), 377 (18), 376 (17), 375 (13), 364 (41), 363 (71), 362 (10), 350 (21), 349 (26), 348 (87), 337 (13), 336 (22), 335 (24), 334 (17), 320 (25), 308 (11), 288 (16), 77 (47), 55 (15), 51 (17). Anal. Calcd for $C_{24}H_{27}N_5O_3S$: C, 61.92; H, 5.85; N, 15.04; S, 6.89. Found: C, 62.07; H, 5.66; N, 15.25; S, 7.09.

4.12. General procedure for the synthesis of 9-alkyl-2-ethylthio-1,5,8,9-tetrahydro-5,8-dioxo-1-phenyl-1,2,4-triazolo[1,5-*g*][1,6]naphthyridine-10-carbonitriles 17a,b

A solution of compounds **16a**,**b** (0.20 g, 0.430 mmol) in DMF (10 mL) was heated to reflux for 40 h. After concentration and cooling to room temperature, H_2O (10 mL) was added and the resulting solid product was collected by filtration, washed with H_2O and dried to give compound **17a**. In the case of **17b**, the reaction mixture was refluxed for 125 h and then it was worked up as described for **17a**.

*4.12.1. 9-Isobutyl-2-ethylthio-1,5,8,9-tetrahydro-5,8-dioxo-1-phenyl-1,2,4-triazolo[1,5-g]-[1,6]naphthyridine-10-carbonitrile (**17a**).* Yellowish solid; 0.155 g (86%); mp 126–127 °C, dec (from $CHCl_3$); IR (KBr) 3050, 2950, 2850, 2200, 1660 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 8.07 (1H, d, J=10 Hz, H-6), 7.61–7.68 (5H, m, Ar-H), 6.30 (1H, d, J=10 Hz, H-7), 4.13 (2H, br, CH_2), 3.20 (2H, q, J=7 Hz, CH_2), 1.89 (1H, m, aliph. CH), 1.37 (3H, t, J=7 Hz, CH_3), 0.87 (6H, d, J=6 Hz, $2CH_3$); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.1 (CO), 156.3 (CO), 152.1 (C-10a), 148.4 (C-2), 147.2 (C-9a), 136.6 (C-6), 131.4, 130.9, 129.6, 128.8 (Ar-C), 115.0 (CN), 113.5 (C-5a), 101.8 (C-7), 60.9 (C-10), 54.7 (CH_2), 28.9 (aliph. CH), 26.3 (CH_2), 19.7 ($2CH_3$), 14.1 (CH_3); MS m/z (%): 420 (M^++1, 24), 419 (M^+, 21), 367 (18), 364 (25), 363 (62), 347 (28), 336 (14), 335 (31), 334 (22), 324 (18), 318 (23), 311 (75), 310 (25), 283 (17), 282 (22), 266 (15), 262 (16), 235 (13), 181 (11), 179 (14), 142 (11), 120 (14), 118 (16), 109 (18), 105 (12), 96 (15), 91 (18), 77 (100), 64 (17), 63 (13), 61 (11), 57 (14), 55 (8), 53 (20), 52 (18), 51 (41), 50 (24). Anal. Calcd for $C_{22}H_{21}N_5O_2S$: C, 62.99; H, 5.05; N, 16.69; S, 7.64. Found: C, 62.78; H, 5.19; N, 16.82; S, 7.47.

*4.12.2. 9-Butyl-2-ethylthio-1,5,8,9-tetrahydro-5,8-dioxo-1-phenyl-1,2,4-triazolo[1,5-g][1,6]-naphthyridine-10-carbonitrile (**17b**).* Yellowish solid; 0.171 g (95%); mp 130–132 °C (from MeOH); IR (KBr) 3050, 2960, 2850, 2200, 1660 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 8.13 (1H, d, J=10 Hz, H-6), 7.66 (5H, m, Ar-H), 6.40 (1H, d, J=10 Hz, H-7), 4.29 (2H, t, J=7.6 Hz, CH_2), 3.30 (2H, q, J=7 Hz, CH_2), 1.58 (2H, m, CH_2), 1.40 (3H, t, J=7 Hz, CH_3), 1.24 (2H, m, CH_2), 0.83 (3H, t, J=7 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.1 (CO), 156.4 (CO), 152.1 (C-10a), 148.4 (C-2), 147.2 (C-9a), 136.6 (C-6), 131.5, 130.9, 129.6, 128.9 (Ar-C), 115.1 (CN), 113.5 (C-5a), 101.8 (C-7), 60.9 (C-10), 44.0 (CH_2), 30.8 (CH_2), 26.3 (CH_2), 18.6 (CH_2), 14.1 (CH_3), 13.5 (CH_3); MS m/z (%): 420 (M^++1, 16), 419 (M^+, 33), 403 (15), 402 (45), 390 (14), 377 (18), 376 (12), 364 (42), 363 (100), 348 (12), 336 (10), 335 (14), 313 (9), 290 (8), 278 (11), 277 (10), 262 (7), 149 (10), 83 (4), 77 (37), 71 (7), 61 (6), 57 (10), 56 (8), 55 (15), 51 (17). Anal. Calcd for $C_{22}H_{21}N_5O_2S$: C, 62.99; H, 5.05; N, 16.69; S, 7.64. Found: C, 63.13; H, 5.16; N, 16.50; S, 7.85.

Acknowledgements

We are thankful to prof. Dr. Volker Jäger and Dr. Peter Fischer, Institute für Organische Chemie, Pfaffenwaldring 55, Universität

Stuttgart, D-70569 Stuttgart, Germany, for recording NMR spectra (^{1}H and ^{13}C NMR).

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