DOI 10.1007/s10593-015-1662-0

Chemistry of Heterocyclic Compounds **2015**, *51*(1), 73–79

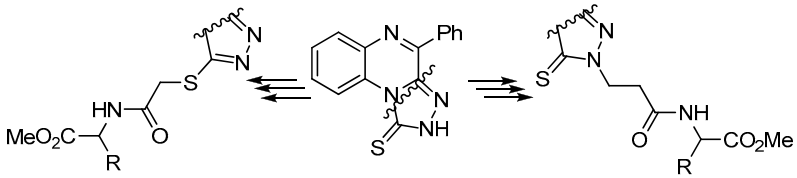
Synthesis of methyl 2-[2-(4-phenyl[1,2,4]triazolo-[4,3-*a*]quinoxalin-1-ylsulfanyl)acetamido]alkanoates and their *N*-regioisomeric analogs

Walid Fathalla[1]*

[1] *Department of Mathematics and Physics, Faculty of Engineering, Port-Said University, Port-Said, 41200, Egypt; e-mail: walid3369@yahoo.com*

Published in Khimiya Geterotsiklicheskikh Soedinenii, 2015, *51*(1), 73–79

Submitted October 15, 2014
Accepted November 28, 2014



Methyl 2-[2-(4-phenyl[1,2,4]triazolo[4,3-*a*]quinoxalin-1-ylsulfanyl)acetamido]alkanoates were formed by the reaction of 2-(4-phenyl-1,2-dihydro[1,2,4]triazolo[4,3-*a*]quinoxalin-1-ylsulfanyl)acetic acid with a variety of amino acid esters *via* DCC coupling method in the presence of *N*-hydroxybenzotriazole in good yields. These amino acid derivatives linked to triazoloquinoxaline moiety were also obtained by the reaction of 2-(4-phenyl[1,2,4]triazolo[4,3-*a*]quinoxalin-1-ylsulfanyl)acetohydrazide with amino acid ester derivatives *via* azide coupling method in poor yields due to the competing decomposition of the corresponding azide resulting in the starting 4-phenyl-[1,2,4]triazolo[4,3-*a*]quinoxaline-1(2*H*)-thione. The *N*-regioisomeric methyl 2-[3-(4-phenyl-1-thioxo[1,2,4]triazolo[4,3-*a*]quinoxalin-2(1*H*)-yl)propanamido]alkanoates were efficiently produced from the 3-(4-phenyl-1-thioxo[1,2,4]triazolo[4,3-*a*]quinoxalin-2(1*H*)-yl)-propanohydrazide and amino acid esters *via* azide coupling method in good to moderate yields.

Keywords: amino acids, *N*,*N*'-dicyclohexylcarbodiimide, azide coupling, chemoselective alkylation, Michael addition, tautomerism.

Quinoxaline and triazoloquinoxaline derivatives are important components of several pharmacologically active compounds.[1] Among [1,2,4]triazolo[4,3-*a*]quinoxalines, many compounds had been found with pronounced antimicrobial,[2] antiallergic,[3] antihypertensive,[4] antidepressant,[5] antiischemic activity,[6] excellent binding affinity at both the A_1 and A_2 adenosine receptor sites,[7] as well as compounds used in the treatment of indications caused by hyperactivity of the excitatory neurotransmitters.[8]

Non-proteinogenic amino acids are major components in a number of drugs including β-lactam antibiotics,[9] glutamate antagonists,[10] antiviral[11] and cytotoxic agents.[12] The attachment of a heterocyclic moiety to non-proteinogenic amino acid esters might provide structures with interesting conformation and biological activity.

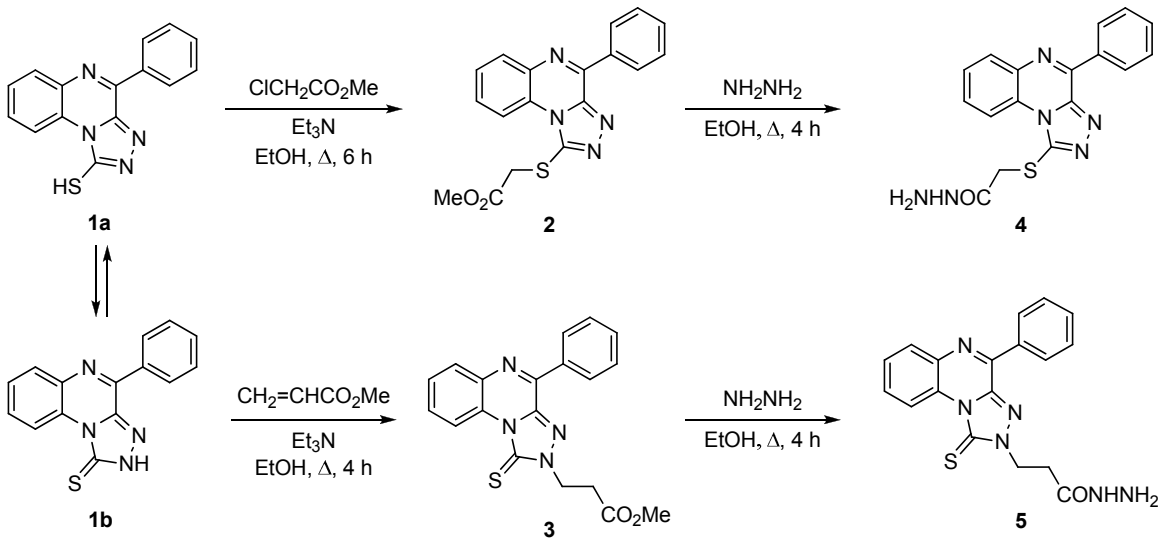
The chemoslective reactions of thioamides have always attracted the attention of our research group. Earlier we reported[13–15] the chemoselective *S*- and *N*-alkylation of the model compound 4-methyl-1-thioxo-1,2,4,5-tetrahydro[1,2,4]-triazolo[4,3-*a*]quinazolin-5-one with different electrophiles. These results were supported by quantum-chemical calculations.[13–15] We also applied these findings to the synthesis of interesting heterocycles *via* domino reactions,[16–18] rearrangement reactions,[19–20] and the preparation of heterocycle-coupled amino acid esters.[21,22]

These results motivated the development of a series of *N*- and *S*-substituted amino acid esters of biologically promising triazoloquinoxaline ring system. In the present article, we report the preparation of methyl 2-[2-(4-phenyl-[1,2,4]triazolo[4,3-a]quinoxalin-1-ylsulfanyl)acetamido] alkanoates and their isomers methyl 2-[3-(4-phenyl-1-thioxo[1,2,4]triazolo[4,3-*a*]quinoxalin-2(1*H*)-yl)propanamido]alkanoates. Triazoloquinoxaline **1** displays an interesting tautomeric equilibrium between thiol (structure **1a**) and thione (structure **1b**) forms.[23–26] Triazoloquinoxaline **1**, therefore, is amenable to structure modification by simple chemoselective alkylation reactions at the sulfur and nitrogen atoms. Thus, the reaction of triazoloquinoxaline **1** with methyl chloroacetate or methyl acrylate in the presence of a base afforded the *S*-alkylation product **2** and *N*-alkylation product **3**, respectively (Scheme 1).[25,26] The esters **2** and **3** were refluxed with hydrazine hydrate in ethyl alcohol to afford the corresponding hydrazides **4** and **5**, respectively. Hydrazides **4** and **5** are excellent precursors for the structure modification of triazoloquinoxaline with amino acids *via* azide coupling method at sulfur and nitrogen atoms, respectively.

Azide coupling method is considered as one of the important methods to couple amino acid derivatives starting from hydrazides. It was also reported that this method

0009-3122/15/5101-0073©2015 Springer Science+Business Media New York

Scheme 1

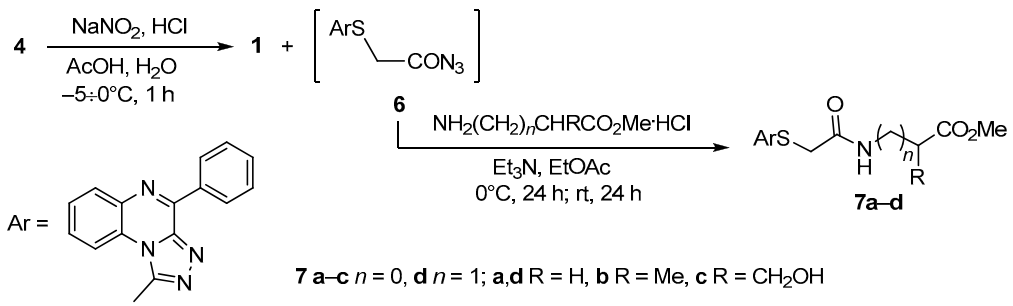


decreases the degree of racemization in the amino acid coupling.[27,28] Carbohydrazide **4** was converted to the corresponding carbonyl azide **6** by treatment with $NaNO_2$ and HCl mixture in an ice bath along with the precipitation of triazoloquinoxaline **1** as a side product. Azide **6** solution reacted with amino acid methyl ester hydrochlorides in the presence of triethylamine to afford a series of *S*-substituted [1,2,4]triazolo[4,3-*a*]quinoxaline derivatives **7a**–**d** in poor yields (Scheme 2, see Experimental, Method A).

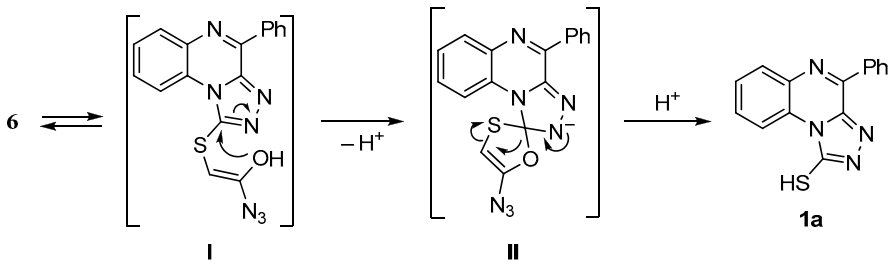
Proposed mechanistic rationalization for the formation of triazoloquinoxaline **1** from azide **6** through Smiles rearrangement[29] is shown in Scheme 3. The first step is acid-catalyzed tautomerization of the azide derivative **6** giving rise to enol **I**. The next step is nucleophilic substitution by oxygen at position 1 of the triazoloquinoxaline system to give the five-membered spiro intermediate **II** leaving a negative charge on the nitrogen atom. The final step is the regaining of the aromaticity at the triazoloquinoxaline ring with the subsequent cleavage of the $OC(N_3)CH$ fragment (its final molecular form was not established) to finally give tricycle **1**. Several examples were reported in literature showing similar results.[20,30] The earlier examples show the formation of amides from carbonyl azides with the elimination of thiirane ring residue[30]. A similar result was obtained by our group. Applying the azide coupling method to 2-(3-aryl-4-oxo-3,4-dihydroquinazolin-2-ylsulfanyl)-acetohydrazide gave an interesting rearrangement with the formation of 3-phenylarylquinazoline-2,4-dione, with the thiirane ring elimination[20]. This latter reaction appears to confirm the formation of intermediates **I** and **II**, but differs in the cleavage of the spiro system probably due to the differences in the properties of quinazoline and triazoloquinoxaline ring systems.

An alternative effort to introduce a peptide chain at the S atom connected to the triazoloquinoxaline tricycle was efficiently carried out with the key substrate carboxylic acid derivative **8** *via* *N*,*N*'-dicyclohexylcarbodiimide (DCC)

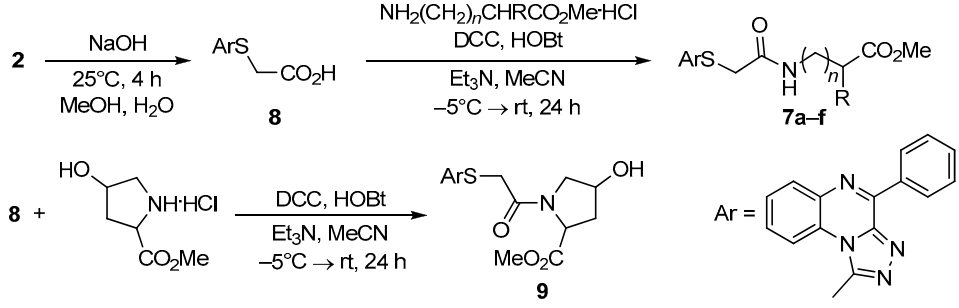
Scheme 2



Scheme 3



Scheme 4



7 a–c,e,f *n* = 0, **d** *n* = 1,
a,d R = H, **b** R = Me, **c** R = CH_2OH, **e** R = CH_2CHMe_2, **f** R = CMeOH

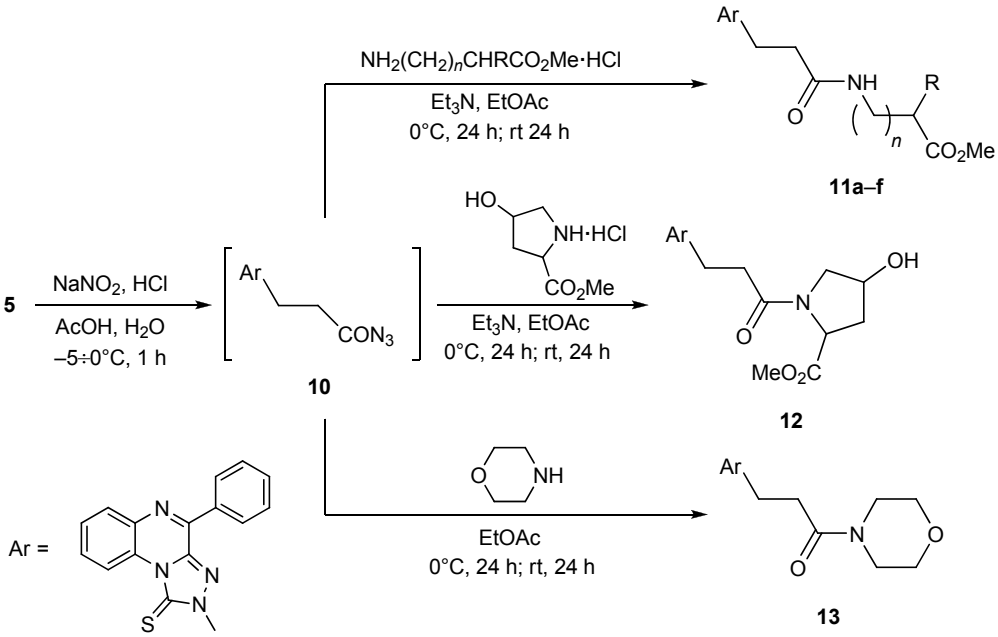
coupling method. The carboxylic acid **8** was formed by saponification of ester **2** in the presence of NaOH at room temperature for 4 h. The DCC coupling is one of the major tools employed to introduce peptide bonds by the reaction of carboxylic acid with amino acid methyl ester.[31] Hydroxybenzotriazole (HOBt) is widely used as an additive to decrease racemization in the carbodiimide peptide coupling.[32,33] Treatment of carboxylic acid **8** with amino acid ester hydrochlorides in the presence of coupling reagents DCC and HOBt afforded *S*-hetaryl acyclic amino acid esters **7a–f** and the analogous hydroxyproline derivative **9** in good yield (Scheme 4, see Experimental, Method B).

Our attempt to connect a peptide chain to position 2 of triazoloquinoxaline tricycle was carried out starting from hydrazide **5** obtained from *N*-alkylated triazoloquinoxaline derivative **3** (Scheme 1). Hydrazide **5** was converted into azide **10** by treatment with $NaNO_2$ and HCl. The obtained azide **10** dissolved in ethyl acetate reacted with amino acid methyl ester hydrochlorides in the presence of triethylamine to afford *N*-substituted acyclic amino acid derivatives **11a–f** and analogous hydroxyproline derivative **12** (Scheme 5). The azide **10** as ethyl acetate solution reacted also with morpholine to give *N*-substituted amide **13**.

The structure assignment of both the *S*-substituted amino acid derivatives and their *N*-regioisomeric analogs is based on ^1H, ^{13}C NMR spectroscopy, as well as physicochemical analysis (Fig. 1). The ^1H NMR clearly confirms the alkylation site for all the isolated *S*- and *N*-substituted derivatives. Thus the the ^1H NMR spectrum of compound **7a** exhibits two singlet signals at 3.88 and 3.73 ppm corresponding to NCH_2 and OCH_3 groups, respectively. The ^1H NMR spectrum also shows an interesting singlet signal at 4.28 ppm in the region typically associated with the SCH_2CO group,[13] which is common to all *S*-substituted amino acid derivatives **7a–f** and **9**. The ^{13}C NMR spectrum of compound **7a** shows also a signal at 37.66 ppm, i.e., in the region characteristic of SCH_2 group carbon signals, along with signals at 170.37, 167.44, 52.19, and 41.43 ppm assigned to ester C=O, amide C=O, OCH_3, and $NHCH_2$ groups, respectively.

On the other hand, the ^1H NMR spectrum of compound **11a** exhibits a triplet signal at 4.87 ppm typically associated with the $NC\underline{H_2}CH_2CO$ group,[14] which is common for all other

Scheme 5



11 a–c,e,f *n* = 0, **d** *n* = 1,
a,d R = H, **b** R = Me, **c** R = CH_2OH, **e** R = CH_2CHMe_2, **f** R = CMeOH

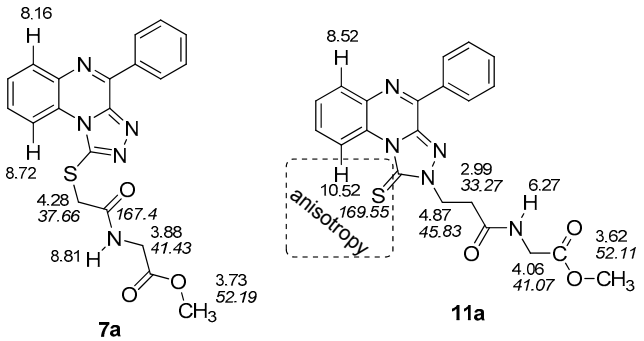


Figure 1. Selected ^{1}H and ^{13}C NMR chemical shifts of *S*- and *N*-substituted triazoloquinoxalines **7a** and **11a**.

N-substituted derivatives **11a**–**f**, **12**, and **13**. The ^{1}H NMR spectrum of compound **11a** shows also three signals at 4.06, 3.62 and 2.99 ppm assigned to NCH_2, OCH_3, and CH_2CO, respectively. The ^{1}H NMR spectrum also showed a very interesting doublet signal at 10.52 ppm corresponding to an aromatic proton. This strongly downfielded shift is likely due to an interesting anisotropy caused by the adjacent thiocarbonyl group (Fig. 1). This aromatic proton shift is common for all *N*-substituted derivatives **11a**–**f**, **12**, **13** and can be used as an indicator for *N*-substitution. Thus ^{13}C NMR spectrum can be used to discriminate between alternative chemoselective alkylation products coupled to amino acid chain. The ^{13}C NMR spectrum of compound **11a** also shows characteristic signals at 172.9, 169.5, 161.3, 52.1, and 41.0 ppm assigned to ester C=O, C=S, amide C=O, OCH_3, and $NHCH_2$ groups, respectively.

To conclude, a series of *S*- and *N*-substituted triazoloquinoxaline attached to amino acid esters by a spacer have been prepared *via* azide and DCC coupling methods. Although both methods were applied to the preparation of *S*-alkylated triazoloquinoxalines, due to instability of the intermediate 2-(hetarylsulfanyl)acetyl azide better yields were obtained with the DCC method. On the other hand, the azide coupling method gave excellent results for the *N*-substituted derivatives.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC 250 instrument (250 and 63 MHz, respectively) in DMSO-d_6 with TMS as internal standard. Elemental analyses were performed on a Flash EA-1112 instrument at the Microanalytical laboratory, Faculty of Science, Suez Canal University, Ismailia, Egypt. Melting points were determined on a Buchi 510 apparatus and are uncorrected. For TLC, silica gel 60 F_{254} plastic plates (E. Merck, layer thickness 0.2 mm) were used. Solvents were purified by standard procedures. Compounds **1**, **2**, and **3** were prepared as reported.[25]

Preparation of hydrazides 4 and 5 (General Method). Hydrazine hydrate (80%) (2.4 ml, 5 mmol) was added to a solution of ester **2** (0.35 g, 1.0 mmol) or **3** (0.36 g, 1.0 mmol) in absolute ethanol (30 ml). The reaction mixture was refluxed for 4 h and cooled. The resultant precipitate was filtered off, washed with ethanol and diethyl ether, then crystallized from aqueous ethanol to yield corresponding hydrazide.

2-(4-Phenyl[1,2,4]triazolo[4,3-*a*]quinoxalin-1-ylsulfanyl)-acetohydrazide (4). Yield 0.31 g (91%), white crystals, mp 235–236°C. ^{1}H NMR spectrum, δ, ppm: 1.84–1.97 (2H, m, NH_2); 4.21 (2H, s, SCH_2CO); 7.61–7.79 (5H, m, H Ar); 8.11–8.15 (1H, m, H Ar); 8.53–8.56 (1H, m, H Ar); 8.69–8.73 (2H, m, H Ar); 9.14 (1H, s, NH). Found, %: C 57.67; H 3.89; N 23.88. $C_{17}H_{14}N_6OS$. Calculated, %: C 58.27; H 4.03; N 23.98.

3-(4-Phenyl-1-thioxo[1,2,4]triazolo[4,3-*a*]quinoxalin-2(1*H*)-yl)propanohydrazide (5). Yield 0.3 g (82%), white crystals, mp 255–256°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.86–1.98 (2H, m, NH_2); 3.08 (2H, t, J = 7.1, CH_2); 4.83 (2H, t, J = 7.1, CH_2); 7.57–7.67 (5H, m, H Ar); 8.06–8.10 (1H, m, H Ar); 8.52–8.56 (2H, m, H Ar); 10.46–10.55 (1H, m, H Ar). Found, %: C 59.21; H 4.34; N 23.01. $C_{18}H_{16}N_6OS$. Calculated, %: C 59.32; H 4.43; N 23.06.

2-(4-Phenyl[1,2,4]triazolo[4,3-*a*]quinoxalin-1-ylsulfanyl)-acetic acid (8). A solution of sodium hydroxide (0.11 g, 2.8 mmol) in H_2O (10 ml) was added to a solution of ester **2** (0.35 g, 1.0 mmol) in methanol (30 ml). The reaction mixture was stirred for 4 h till complete consumption of the ester **2** (monitored by TLC). The reaction mixture was evaporated under reduced pressure, diluted with water, and acidified by 1 N HCl to pH 3. The yellowish precipitate formed was filtered off and washed several times with water, dried, and crystallized from DMF–H_2O, 7:3. Yield 0.27 g (80%), white crystals, mp 263–264°C (mp 260–261°C[26]). ^{1}H NMR spectrum, δ, ppm: 4.23 (2H, s, SCH_2CO); 7.61–7.68 (3H, m, H Ar); 7.69–7.81 (2H, m, H Ar); 8.17–8.22 (1H, m, H Ar); 8.48–8.57 (1H, m, H Ar); 8.72–8.78 (2H, m, H Ar). Found, %: C 60.63; H 3.59; N 16.64. $C_{17}H_{12}N_4O_2S$. Calculated, %: C 60.70; H 3.60; N 16.66.

Preparation of methyl 2-[2-(4-phenyl[1,2,4]triazolo-[4,3-*a*]quinoxalin-1-ylsulfanyl)acetamido]alkanoates 7a–f and 9 (General Method). A (for compounds **7a**–**d** only). A solution of $NaNO_2$ (0.34 g, 5.0 mmol) in cold water (3 ml) was added to a cold solution (–5°C) of hydrazide **4** (0.35 g, 1.0 mmol) in AcOH (6 ml), 1 N HCl (3 ml), and water (25 ml). After stirring at –5°C for 15 min, a thick precipitate started to form. The reaction mixture was stirred in ice bath for further 1 h. The reaction mixture was filtered, and the precipitate, identified as 4-phenyl[1,2,4]triazolo[4,3-*a*]-quinoxaline-1(2*H*)-thione (**1**), was washed several times with ethyl acetate and air-dried. The filtrate was extracted twice with ethyl acetate (30 ml). The combined organic layer was washed with 0.5 N HCl (30 ml), 3% $NaHCO_3$ (30 ml), H_2O (30 ml) and finally dried over Na_2SO_4 (10 g) to give an ethyl acetate solution of azide **6**. A solution of an appropriate amino acid ester hydrochloride (1.0 mmol) in ethyl acetate (20 ml) containing triethylamine (0.2 ml, 2 mmol) was added to the solution of azide **6**. The mixture was kept at –5°C for 24 h, then at 25°C for another 24 h, followed by washing with 0.5 N HCl (30 ml), 3% $NaHCO_3$ (30 ml), H_2O (30 ml) and finally dried over Na_2SO_4 (10 g). The solution was evaporated to dryness, and the residue was recrystallized from petroleum ether–ethyl acetate, 1:3, to give the desired *S*-coupled product **7a**–**d**.

B. 2-(4-Phenyl-1,2-dihydro[1,2,4]triazolo[4,3-*a*]quinoxalin-1-ylsulfanyl)acetic acid (**8**) (0.340 g, 1.0 mmol), *N*,*N*'-dicyclohexylcarbodiimide (0.207 g, 1.0 mmol), and *N*-hydroxybenzotriazole (0.135 g, 1.0 mmol) were successively added to a cold solution (–5°C) of the appropriate amino acid methyl ester hydrochloride (1.0 mmol) in acetonitrile (6 ml) containing triethylamine (0.14 ml, 1.0 mmol). The reaction mixture was stirred at 0°C for 1 h, then at 5°C for 1 h, then at room temperature for 8 h. The reaction mixture was set aside overnight. The precipitated *N*,*N*'-dicyclohexylurea was filtered off and the filtrate was evaporated under reduced pressure. The residue was dissolved in ethyl acetate, filtered, and the filtrate was washed with 0.5 N HCl (30 ml), 3% $NaHCO_3$ (30 ml), H_2O (30 ml) and finally dried over Na_2SO_4 (10 g). After evaporation of the solvent, the remaining oily residue was triturated with petroleum ether (bp 40–60°C) at 0°C, and the formed solid was filtered off and crystallized from petroleum ether–ethyl acetate, 1:3.

4-Phenyl[1,2,4]triazolo[4,3-*a*]quinoxaline-1(2*H*)-thione (1). Yield 0.17 g (63%) (Method A), white crystals, mp 265–266°C (DMF–H_2O, 7:3) (mp 272–274°C[25]). ^{1}H NMR spectrum, δ, ppm: 7.57–7.68 (5H, m, H Ar); 8.04–8.10 (1H, m, H Ar); 8.44–8.56 (2H, m, H Ar); 10.49–10.56 (1H, m, H Ar). Found, %: C 64.68; H 3.45; N 20.12. $C_{15}H_{10}N_4S$. Calculated, %: C 64.73; H 3.62; N 20.13.

Methyl 2-[2-(4-phenyl[1,2,4]triazolo[4,3-*a*]quinoxalin-1-ylsulfanyl)acetamido]acetate (7a). Yield 16% (Method A), 71% (Method B), white crystals, mp 164–165°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.73 (3H, s, OCH_3); 3.88 (2H, d, *J* = 5.7, NCH_2); 4.28 (2H, s, SCH_2); 7.55–7.64 (3H, m, H Ar); 7.78–7.85 (3H, m, H Ar); 8.14–8.17 (1H, m, H Ar); 8.68–8.79 (2H, m, H Ar); 8.81 (1H, t, *J* = 5.7, NH). ^{13}C NMR spectrum, δ, ppm: 37.6 (SCH_2); 41.4 (NCH_2); 52.2 (OCH_3); 116.3 (C Ar); 125.9 (C Ar); 128.1 (C Ar); 128.8 (C Ar); 129.6 (C Ar); 129.8 (C Ar); 131.7 (C Ar); 134.9 (C Ar); 136.1 (C Ar); 145.1 (C Ar); 146.2 (C Ar); 148.7 (C Ar); 167.4 (C=O amide); 170.3 (C=O ester). Found, %: C 58.84; H 4.18; N 17.11.$C_{20}H_{17}N_5O_3S$. Calculated, %: C 58.96; H 4.21; N 17.19.

Methyl 2-[2-(4-phenyl[1,2,4]triazolo[4,3-*a*]quinoxalin-1-ylsulfanyl)acetamido]propanoate (7b). Yield 22% (Method A), 56% (Method B), white crystals, mp 133–134°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.42 (3H, d, *J* = 7.2, CH_3); 3.69 (3H, s, OCH_3); 4.04 (1H, d, *J* = 14.4) and 4.12 (1H, d, *J* = 14.4, SCH_2); 4.48–4.63 (1H, m, CH); 7.58–7.61 (3H, m, H Ar); 7.68–7.71 (2H, m, H Ar); 7.93 (1H, d, *J* = 8.1, NH); 8.27–8.18 (1H, m, H Ar); 8.43–8.59 (1H, m, H Ar); 8.77–8.80 (2H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 18.4 (CH_3); 37.8 (SCH_2); 51.6 (CH); 52.6 (OCH_3); 116.4 (C Ar); 126.1 (C Ar); 128.1 (C Ar); 128.8 (C Ar); 129.4 (C Ar); 129.9 (C Ar); 130.5 (C Ar); 131.7 (C Ar); 135.0 (C Ar); 136.1 (C Ar); 145.2 (C Ar); 146.4 (C Ar); 148.6 (C Ar); 166.4 (C=O amide); 172.3 (C=O ester). Found , %: C 59.76; H 4.51; N 16.60. $C_{21}H_{19}N_5O_3S$. Calculated, %: C 59.84; H 4.54; N 16.62.

Methyl 3-hydroxy-2-[2-(4-phenyl[1,2,4]triazolo[4,3-*a*]-quinoxalin-1-ylsulfanyl)acetamido]propanoate (7c). Yield 25% (Method A), 48% (Method B), white crystals, mp 148–149°C. ^{1}H NMR spectrum, δ, ppm: 3.61 (3H, s, OCH_3); 3.65–3.73 (2H, m, OCH_2); 4.24–4.29 (1H, m, CH); 4.34 (2H, s, SCH_2); 5.08 (1H, br. s, OH, D_2O exchangeable); 7.62–7.65 (3H, m, H Ar); 7.73–7.83 (2H, m, H Ar); 7.94 (1H, br. s, NH); 8.43–8.59 (1H, m, H Ar); 8.71–8.81 (2H, m, H Ar); 8.85–8.94 (1H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 37.9 (SCH_2); 52.3 (OCH_3); 57.6 (CH); 61.6 (OCH_2); 116.4 (C Ar); 126.1 (C Ar); 128.2 (C Ar); 128.8 (C Ar); 129.7 (C Ar); 129.8 (C Ar); 130.5 (C Ar); 131.7 (C Ar); 134.9 (C Ar); 136.2 (C Ar); 145.2 (C Ar); 146.4 (C Ar); 148.8 (C Ar); 167.1 (C=O amide); 171.1 (C=O ester). Found, %: C 57.45; H 4.21; N 15.72. $C_{21}H_{19}N_5O_4S$. Calculated, %: C 57.66; H 4.38; N 16.01.

Methyl 3-[2-(4-phenyl[1,2,4]triazolo[4,3-*a*]quinoxalin-1-ylsulfanyl)acetamido]propanoate (7d). Yield 16% (Method A), 64% (Method B), white crystals, mp 111–112°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.54 (2H, t, *J* = 6.4, CH_2); 3.54 (2H, q, *J* = 6.6, NCH_2); 3.59 (3H, s, OCH_3); 4.22 (2H, s, SCH_2); 7.59–7.68 (3H, m, H Ar); 7.69–7.71 (3H, m, H Ar); 7.84 (1H, br. s, NH); 8.17–8.23 (1H, m, H Ar); 8.48–8.55 (1H, m, H Ar); 8.77–8.79 (1H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 33.8 ($\underline{C}H_2CO$); 35.6 ($NHCH_2$); 37.9 (SCH_2); 51.8 (OCH_3); 116.4 (C Ar); 126.1 (C Ar); 128.2 (C Ar); 128.8 (C Ar); 129.7 (C Ar); 129.8 (C Ar); 130.5 (C Ar); 131.7 (C Ar); 135.0 (C Ar); 136.1 (C Ar); 145.2 (C Ar); 146.4 (C Ar); 148.9 (C Ar); 166.8 (C=O amide); 172.0 (C=O ester). Found, %: C 59.80; H 4.55; N 16.58. $C_{21}H_{19}N_5O_3S$. Calculated, %: C 59.84; H 4.54; N 16.62.

Methyl 4-methyl-2-[2-(4-phenyl[1,2,4]triazolo[4,3-*a*]-quinoxalin-1-ylsulfanyl)acetamido]pentanoate (7e). Yield 51% (Method B), white crystals, mp 145–146°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.87 (6H, d, *J* = 6.0, $2CH_3$) 0.95–0.97 (1H, m, CH); 1.45–1.63 (2H, m, CH_2); 3.81 (3H, s, OCH_3); 4.28 (2H, d, *J* = 5.1, SCH_2); 4.48–4.61 (1H, m, CH); 7.60–7.67 (3H, m, H Ar); 7.68–7.85 (2H, m, H Ar); 7.95 (1H, d, *J* = 8.1, NH); 8.20–8.24 (1H, m, H Ar); 8.50–8.54 (1H, m, H Ar); 8.71–8.86 (2H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 10.1 (CH_3); 22.7 (CH); 25.1 (CH_2); 37.7 (SCH_2); 52.7 (OCH_3); 55.4 (CH); 116.4 (C Ar); 126.1 (C Ar); 128.2 (C Ar); 128.8 (C Ar); 129.6 (C Ar); 129.7 (C Ar); 130.5 (C Ar); 131.7 (C Ar); 135.1 (C Ar); 136.1 (C Ar); 145.2 (C Ar); 146.2 (C Ar); 148.4 (C Ar); 166.4 (C=O amide); 172.3 (C=O ester). Found, %: C 62.14; H 5.42; N 15.03. $C_{24}H_{25}N_5O_3S$. Calculated, %: C 62.18; H 5.44; N 15.11.

Methyl 3-hydroxy-2-[2-(4-phenyl[1,2,4]triazolo[4,3-*a*]-quinoxalin-1-ylsulfanyl)acetamido]butanoate (7f). Yield 75% (Method B), white crystals, mp 134–135°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.42 (3H, d, *J* = 7.2, CH_3); 3.71 (3H, s, OCH_3); 4.13–4.34 (3H, m, SCH_2, CH); 4.65 (1H, d, *J* = 6.0, CH); 7.55–7.58 (3H, m, H Ar); 7.59–7.69 (2H, m, H Ar); 7.94 (1H, d, *J* = 6.0, NH); 8.16–8.20 (1H, m, H Ar); 8.42–8.60 (2H, m, H Ar, OH); 8.71–8.74 (2H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 22.1 (CH_3); 37.8 (SCH_2); 52.6 (OCH_3); 58.4 (CH); 65.3 (OCH); 116.4 (C Ar); 126.1 (C Ar); 128.2 (C Ar); 128.8 (C Ar); 129.6 (C Ar); 130.5 (C Ar); 131.7 (C Ar); 135.1 (C Ar); 136.2 (C Ar); 145.2 (C Ar); 146.3 (C Ar); 148.7 (C Ar); 166.8 (C=O amide);

172.4 (C=O ester). Found, %: C 58.36; H 4.52; N 15.34. $C_{22}H_{21}N_5O_4S$. Calculated, %: C 58.52; H 4.69; N 15.51.

Methyl 4-hydroxy-1-[2-(4-phenyl[1,2,4]triazolo[4,3-*a*]-quinoxalin-1-ylsulfanyl)acetyl]pyrrolidine-2-carboxylate (9). Yield 63% (Method B), white crystals, mp 103–104°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.95–2.18 (2H, m, CH_2); 3.58 (3H, s, OCH_3); 3.73–3.83 (2H, m, CH_2); 4.29 (1H, d, *J* = 6.0, CH); 4.35 (1H, br. s, OH, D_2O-exchangeable); 4.44 (1H, d, *J* = 14.6) and 4.63 (1H, d, *J* = 14.4, SCH_2); 5.26 (1H, d, *J* = 6.0, CH); 7.63–7.64 (3H, m, H Ar); 7.65–7.87 (2H, m, H Ar); 8.16–8.23 (1H, m, H Ar): 8.71–8.79 (3H, m, H Ar). Found, %: C 59.60; H 4.32; N 14.59. $C_{23}H_{21}N_5O_4S$. Calculated, %: C 59.60; H 4.57; N 15.11.

Preparation of 2-[3-(4-phenyl-1-thioxo[1,2,4]triazolo-[4,3-*a*]quinoxalin-2(1*H*)-yl)propanamido]alkanoates 11a–f, 12, and 13 (General Method). A solution of $NaNO_2$ (0.340 g, 5.0 mmol) in cold water (3 ml) was added to a cold solution (–5°C) of hydrazide **5** (0.300 g, 1.0 mmol) in a mixture of AcOH (6 ml), 1 N HCl (3 ml), and water (25 ml). After stirring at –5°C for 15 min, a thick precipitate started to form. The reaction mixture was stirred for further 1 h and extracted by cold ethyl acetate (30 ml). The organic layer was washed with 3% $NaHCO_3$ (30 ml), H_2O (30 ml) and finally dried over Na_2SO_4 (10 g) to give an ethyl acetate solution of the azide **10**. A solution of the appropriate amino acid ester hydrochloride (1.0 mmol) or morpholine (0.174 g, 2.0 mmol) in ethyl acetate (20 ml), containing, in the case of amino acid ester hydrochlorides, triethylamine (0.2 ml), was added to the azide **10** solution. The mixture was kept at –5°C for 24 h, then at 25°C for another 24 h. The reaction mixture was washed with 0.5 N HCl, water, 3% solution of $NaHCO_3$ and finally dried over Na_2SO_4. The solution was evaporated to dryness and the residue was recrystallized from petroleum ether–ethyl acetate, 3:1, to give the desired *N*-coupled product **11a**–**f**, **12**, or **13**.

Methyl 2-[3-(4-phenyl-1-thioxo[1,2,4]triazolo[4,3-*a*]-quinoxalin-2(1*H*)-yl]propanamido]acetate (11a). Yield 66%, yellow crystals, mp 191–192°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.99 (2H, t, *J* = 7.1, CH_2); 3.62 (3H, s, OCH_3); 4.06 (2H, d, *J* = 6.4, $NHC\underline{H}_2$); 4.87 (2H, t, *J* = 7.1, NCH_2); 6.27 (1H, br. s, NH); 7.54–7.62 (3H, m, H Ar); 7.64–7.69 (2H, m, H Ar); 8.07–8.10 (1H, m, H Ar); 8.49–8.53 (2H, m, H Ar); 10.50–10.53 (1H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 33.2 (CH_2CO); 41.0 ($NHCH_2$); 45.8 (NCH_2); 52.1 (OCH_3); 115.7 (C Ar); 127.4 (C Ar); 128.2 (C Ar); 128.9 (C Ar); 129.1 (C Ar); 129.5 (C Ar); 130.2 (C Ar); 131.9 (C Ar); 134.4 (C Ar); 135.8 (C Ar); 138.1 (C Ar); 148.7 (C Ar); 161.3 (C=O amide); 169.5 (C=S); 172.9 (C=O ester). Found, %: C 59.82; H 4.45; N 16.57. $C_{21}H_{19}N_5O_3S$. Calculated, %: C 59.84; H 4.54; N 16.62.

Methyl 2-[3-(4-phenyl-1-thioxo[1,2,4]triazolo[4,3-*a*]-quinoxalin-2(1*H*)-yl)propanamido]propanoate (11b). Yield 48%, yellow crystals, mp 173–174°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.17 (3H, d, *J* = 7.2, CH_3); 2.83 (2H, t, *J* = 7.1, CH_2); 3.57 (3H, s, OCH_3); 4.21–4.33 (1H, m, CH), 4.61 (2H, t, *J* = 7.1, NCH_2); 7.01 (1H, br. s, NH); 7.52–7.71 (3H, m, H Ar); 7.73–7.77 (2H, m, H Ar); 8.04–8.07 (1H, m, H Ar); 8.45–8.51 (2H, m, H Ar); 10.42–10.46 (1H, m, H Ar). Found, %: C 60.63; H 4.85; N 16.02. $C_{22}H_{21}N_5O_3S$. Calculated, %: C 60.67; H 4.86; N 16.08.

Methyl 3-hydroxy-2-[3-(4-phenyl-1-thioxo[1,2,4]triazolo-[4,3-*a*]quinoxalin-2(1*H*)-yl)propanamido]propanoate (11c). Yield 68%, yellow crystals, mp 154–155°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.89 (2H, t, *J* = 7.1, CH_2); 3.18 (1H, br. s, OH, D_2O-exchangeable); 3.58–3.85 (5H, m, OCH_2, OCH_3); 4.19–4.26 (1H, m, CH); 4.61 (2H, t, *J* = 7.1, NCH_2); 7.03 (1H, br. s, NH); 7.60–7.69 (3H, m, H Ar); 7.70–7.73 (2H, m, H Ar); 8.02–8.06 (1H, m, H Ar); 8.44–8.49 (2H, m, H Ar); 10.41–10.45 (1H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 33.2 ($\underline{C}H_2CO$); 45.9 (NCH_2); 52.2 (OCH_3); 55.2 (CH); 61.6 (OCH_2); 115.6 (C Ar); 127.6 (C Ar); 128.1 (C Ar); 128.8 (C Ar); 129.1 (C Ar); 129.4 (C Ar); 130.1 (C Ar); 131.8 (C Ar); 134.3 (C Ar); 135.9 (C Ar); 138.3 (C Ar); 148.6 (C Ar); 161.1 (C=O amide); 169.7 (C=S); 172.4 (C=O ester). Found, %: C 58.48; H 4.64; N 15.36. $C_{22}H_{21}N_5O_4S$ (451.5). Calculated, %: C 58.52; H 4.69; N 15.51.

Methyl 3-[3-(4-phenyl-1-thioxo[1,2,4]triazolo[4,3-*a*]-quinoxalin-2(1*H*)-yl)propanamido]propanoate (11d). Yield 74%, yellow crystals, mp 191–192°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.51 (2H, t, *J* = 7.1, $C\underline{H}_2CO_2CH_3$); 2.92 (2H, t, *J* = 7.1, CH_2); 3.50 (2H, q, *J* = 7.1, $NHCH_2$); 3.61 (3H, s, OCH_3); 4.84 (2H, t, *J* = 7.1, NCH_2); 6.34 (1H, br. s, NH), 7.57–7.64 (3H, m, H Ar); 7.66–7.68 (2H, m, H Ar); 8.07–8.15 (1H, m, H Ar), 8.50–8.53 (2H, m, H Ar), 10.43–10.51 (1H, m, H Ar). Found, %: C 60.49; H 4.74; N 16.03. $C_{22}H_{21}N_5O_3S$. Calculated, %: C 60.67; H 4.86; N 16.08.

Methyl 4-methyl-2-[(3-(4-phenyl-1-thioxo[1,2,4]triazolo-[4,3-*a*]quinoxalin-2(1*H*)-yl)propanamido]pentanoate (11e). Yield 59%, yellow crystals, mp 174–175°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.83–0.88 (6H, m, $2CH_3$); 0.95–0.97 (1H, m, CH); 1.48–1.68 (2H, m, $CHC\underline{H}_2CH$); 2.92 (2H, t, *J* = 7.1, CH_2); 3.62 (3H, s, OCH_3); 4.59–4.68 (1H, m, CH); 4.64 (2H, t, *J* = 7.1, NCH_2); 6.18 (1H, d, *J* = 7.2, NH), 7.58–7.63 (3H, m, H Ar), 7.64–7.67 (2H, m, H Ar), 8.06–8.11 (1H, m, H Ar), 8.49–8.54 (2H, m, H Ar), 10.52–10.56 (1H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 8.9 (CH_3); 23.0 (CH); 24.6 (CH_2); 33.2 ($\underline{C}H_2CO$); 45.8 (NCH_2); 50.7 (CH); 52.2 (OCH_3); 115.6 (C Ar); 127.6 (C Ar); 128.2 (C Ar); 128.9 (C Ar); 129.1 (C Ar); 129.4 (C Ar); 130.1 (C Ar); 131.9 (C Ar); 134.3 (C Ar); 135.9 (C Ar); 138.2 (C Ar); 148.6 (C Ar); 161.2 (C=O amide); 169.5 (C=S); 173.3 (C=O ester). Found, %: C 62.78; H 5.69; N 14.56. $C_{25}H_{27}N_5O_3S$. Calculated, %: C 62.87; H 5.70; N 14.66.

Methyl 3-hydroxy-2-[3-(4-phenyl-1-thioxo[1,2,4]triazolo-[4,3-*a*]quinoxalin-2(1*H*)-yl)propanamido]butanoate (11f). Yield 47%, yellow crystals, mp 161–162°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.03 (3H, d, *J* = 7.2, CH_3); 2.89 (2H, t, *J* = 7.1, CH_2); 3.57 (3H, s, OCH_3); 4.02–4.09 (1H, m, CH); 4.32 (1H, d, *J* = 6.0, CH); 4.63 (2H, t, *J* = 7.1, NCH_2); 7.60–7.75 (5H, m, H Ar); 8.04–8.08 (1H, m, H Ar); 8.26 (1H, d, *J* = 8.1, NH); 8.45–8.50 (2H, m, H Ar); 10.43–10.47 (1H, m, H Ar). ^{13}C NMR spectrum, δ, ppm.: 20.5 (CH_3); 33.2 ($\underline{C}H_2CO$); 45.9 (NCH_2); 52.2 (OCH_3); 58.4 (CH); 66.7 (OCH); 115.6 (C Ar); 127.5 (C Ar); 128.1 (C Ar); 128.8 (C Ar); 129.0 (C Ar); 129.4 (C Ar); 130.0

(C Ar); 131.8 (C Ar); 134.2 (C Ar); 135.9 (C Ar); 138.2 (C Ar); 148.5 (C Ar); 161.1 (C=O amide); 170.1 (C=S); 172.4 (C=O ester). Found, %: C 59.22; H 4.87; N 15.02. $C_{23}H_{23}N_5O_4S$. Calculated, %: C 59.34; H 4.98; N 15.04.

Methyl 4-hydroxy-1-[3-(4-phenyl-1-thioxo[1,2,4]triazolo[4,3-*a*]quinoxalin-2(1*H*)-yl)propanoyl]pyrrolidine-2-carboxylate (12). Yield 38%, yellow crystals, mp 142–143°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.94–2.13 (2H, m, CH_2); 3.00 (2H, t, *J* = 7.1, CH_2); 3.63 (3H, s, OCH_3); 3.64–3.76 (2H, m, CH_2); 4.10 (1H, br. s, OH, D_2O-exchangeable); 4.34 (1H, t, *J* = 7.1, CH); 4.60 (2H, t, *J* = 7.1, NCH_2); 5.11 (1H, d, *J* = 6.0, CH); 7.58–7.63 (3H, m, H Ar); 7.69–7.73 (2H, m, H Ar); 8.02–8.05 (1H, m, H Ar); 8.44–8.47 (2H, m, H Ar); 10.40–10.43 (1H, m, H Ar). Found, %: C 60.24; H 4.81; N 14.55. $C_{24}H_{23}N_5O_4S$. Calculated, %: C 60.36; H 4.85; N 14.67.

1-Morpholino-3-(4-phenyl-1-thioxo[1,2,4]triazolo-[4,3-*a*]quinoxalin-2(1*H*)-yl)propan-1-one (13). Yield 72%, yellow crystals, mp 220–221°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.99 (2H, t, *J* = 7.1, CH_2); 3.45 (4H, t, *J* = 7.1, $2NCH_2$); 3.65 (4H, t, *J* = 7.1, $2OCH_2$); 4.62 (2H, t, *J* = 7.1, NCH_2); 7.63–7.70 (3H, m, H Ar); 7.72–7.76 (2H, m, H Ar); 8.04–8.08 (1H, m, H Ar); 8.42–8.46 (2H, m, H Ar); 10.41–10.45 (1H, m, H Ar). Found, %: C 62.74; H 5.01; N 16.53. $C_{22}H_{21}N_5O_2S$. Calculated, %: C 62.99; H 5.05; N 16.69.

The author would like to thank Faculty of Engineering, Port-Said University, Egypt for financial support, Assoc. Professor Pavel Pazdera, Head of the Centre for the Syntheses at Sustainable Conditions and their Management, Faculty of Science of Masaryk University for technical support, and, finally, Ministry of Higher Education, Arab Republic of Egypt, for financial support.

References

1. Brown, D. J. In *Quinoxalines*, Taylor, E. C.; Wipf, P.; Weissberger, A., Eds.; John Wiley & Sons, Inc.: Hoboken, 2004, suppl. II, vol. 61, p. 1.
2. Badran, M. M.; Abouzid, K. A. M.; Hussein, M. H. M. *Arch. Pharm. Res.* **2003**, *26*, 107.
3. Loev, B.; Musser, J. H.; Brown, R. E.; Jones, H.; Robert, K. R.; Huang, F-C.; Khandwala, A.; Sonnino-Goldman, P.; Leibowitz, M. J. *J. Med. Chem.* **1985**, *28*, 363.
4. Loev, B.; Suh, J. T.; Williams, B. E.; Georgiev, V. US Patent 4354027.
5. Saul, B.; Sarges, K. R. US Patent 4623725.
6. Sakamoto, S.; Ohmori, J.-Y.; Sasamata, M.; Okada, M.; Hidaka, K. WO Patent 1993020077.
7. Trivedi, B. K. US Patent 4780464.
8. Jacobsen, P.; Nielsen, F. E. US Patent 5504085.
9. Townsend, C. A.; Brown, A. M. *J. Am. Chem. Soc.* **1983**, *105*, 913.
10. Maloney, M. G. *Nat. Prod. Rep.* **1999**, *16*, 485.
11. Bhide, R.; Mortezaei, R.; Scilimati, A.; Sih, C. J. *Tetrahedron Lett.* **1990**, *31*, 4827.
12. Kawasaki, T.; Enoki, H.; Matsumura, K.; Ohyama, M.; Inagawa, M.; Sakamoto, M. *Org. Lett.* **2000**, *2*, 3027.
13. Fathalla, W.; Čajan, M.; Pazdera, P. *Molecules* **2001**, *6*, 557.
14. Fathalla, W.; Čajan, M.; Pazdera, P. *Molecules* **2000**, *5*, 1210.
15. Fathalla, W.; Pazdera, P.; Čajan, M.; Marek, J. *J. Heterocycl. Chem.* 2002, *39*, 1145.
16. Fathalla, W.; Pazdera, P.; Marek, J. *J. Heterocycl. Chem.* **2002**, *39*, 1139.
17. Fathalla, W.; Marek, J.; Pazdera, P. *Heterocycl. Commun.* **2002**, *8*, 157.
18. Fathalla, W.; Marek, J.; Pazdera, P. *J. Sulfur Chem.* **2008**, *29*, 31.
19. Fathalla, W.; Ali, I. A. I.; Marek, J.; Pazdera, P. *J. Sulfur Chem*. **2012**, *33*, 49.
20. Elfekki, I.; Fathalla, W.; Abd El Hamid, H.; Ali, I. A. I.; Eltamany, S. *Chem. Pharm. Bull*. **2014**, *62*, 675.
21. Fathalla, W.; Ali, I. A. I. *Heteroat. Chem.* **2007**, *18*, 637.
22. Fathalla, W.; El Rayes, S. M.; Ali, I. A. I. *ARKIVOC* **2007**, (xvi), 173.
23. El-Hawash, S. A. M.; Habib, N. S.; Kassem, M. A. *Arch Pharm*. (*Weinheim*) **2006**, *339*, 564.
24. Stöesser, R.; Siegmund, M.; Westphal, G. *Tetrahedron* **1978**, *34*, 2701.
25. Westphal, G.; Wasicki, H.; Esser, A.; Zielinski, U.; Weber, F. G.; Tonew, M.; Tonew, E. *Pharmazie* **1977**, *32*, 687.
26. Westphal, G.; Zielinski, U.; Esser, A.; Wasicki, H.; Tonev, E.; Tonev, M. DD Patent 126390.
27. Han, S.-Y.; Kim, Y.-A. *Tetrahedron* **2004**, *60*, 2447.
28. Ali, I. A. I.; Al-Masoudi, I. A.; Saeed, B.; Al-Masoudi, N. A.; La Colla P. *Heteroat. Chem.* **2005**, *16*, 148.
29. Warren, L. A.; Smiles, S. *J. Chem. Soc.* **1930**, 956.
30. Plesniak, K.; Zarecki, A.; Wicha, J. In *Sulfur-Mediated Rearrangements II*, Schaumann, E., Ed.; Springer: Berlin, 2007, p. 163.
31. Davis, J. S.; Mohammed, A. K. *J. Chem. Soc*., *Perkin Trans. 1* **1981**, 2982.
32. König, W.; Geiger, R. *Chem. Ber.* **1970**, *103*, 788.
33. Pennington, R. M.; Fischer, R. R. *J. Biol. Chem.* **1981**, 256, 8963.