Synthesis and antimicrobial activity of 5-oxo-1-thioxo-4,5-dihydro[1,3]thiazolo[3,4-a]quinazolines

Olexiy O. Parkhomenko[1]*, Sergiy M. Kovalenko[1], Valentyn P. Chernykh[1], and Tatyana P. Osolodchenko[2]

[1] National Pharmaceutical University 53 Poushkinska str., Kharkiv, 61002, Ukraine
[2] Institute microbiology and immunology n.I.I.Mechnikov 4 Poushkinska str., Kharkiv, 61002, Ukraine
E-mail: vegas00@ic.kharkov.ua

(received 16 Sep 05; accepted 11 Jan 06; published on the web 14 Feb 06)

Abstract

A three-component condensation of methyl-2-isothiocyanatobenzoate, sulfur and cyanoacetamides or cyanoacetic esters furnishes compounds containing the new heterocyclic system-1-thioxo[1,3]thiazolo[3,4-a]quinazolin-5(4H)-one. The antimicrobial and fungicidal activities of these synthesized compounds were tested.

Keywords: 2(3*H*)-Thioxo-1,3-thiazole, 4(3*H*)-quinazolinone, isothiocyanate, cyanoacetamide

Introduction

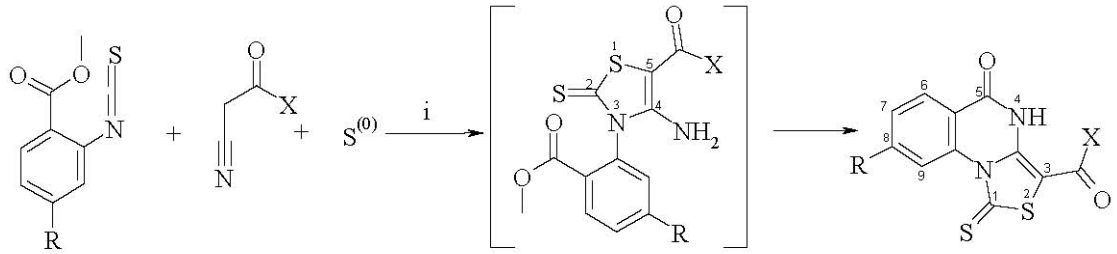
It is well known that the reaction of isothiocyanates, cyanoacetic acid esters or amides, and sulfur in the presence of weak organic bases results in the formation of proper 4-amino-2-thioxo-2,3-dihydro-1,3-thiazol-5-carboxamides or alkyl-4-amino-2-tioxo-2,3-dihydro-1,3-thiazol-5-carboxylates[1]. Compounds of these classes have been proved as potential bio-actives substances[2-5, 9-17]. Some of described compounds showed antimicrobial activity[13-17]. Continuing our research on the isothiocyanates' behaviour in multicomponent systems[6], we examined the specified three-component condensation, with methyl-2-isothiocyanatobenzoates as isothiocyanate component.

Results and Discussion

Chemistry

We established that the condensation of methyl-2-isothiocyanatobenzoates **(1)**, derivatives of cyanoacetic acid **(2)** and sulfur **(3)**, in the conditions of Gewald's reaction, does not stop at the stage of 2(3H)-thioxo-1,3-thiazoles **(4)** formation. It is proceeds to a subsequent intramolecular

reaction of carbmethoxy and aminogroups with formation 1- tioxo[1,3]thiazolo[3,4-a]quinazolin-5(4H)-ones **(5)**.



1 2 3 4 5 a-l

	R	X
5a	H	$N(CH_2)_5$,
5b	H	OMe
5c	COOMe	$N(CH_2)_4$
5d	H	NH-$CH(CH_3)$Ph
5e	H	NH(4-F)C_6H_4
5f	H	NH(2-F)C_6H_4
5g	H	$NHCH_2$(2-thienyl)
5h	H	NH-Tetrahydrofurfuryl
5i	H	OEt
5j	H	NHPh
5k	H	NH-n-C_5H_{11}
5l	COOMe	OMe

Scheme 1. Synthesis of 5-oxo-1-thioxo-4,5-dihydro[1,3]thiazolo[3,4-a]quinazolines. Reagents and reaction conditions. (i) DMF, TEA, 50°C, 1h.

The obtained products are yellow crystals, easily soluble in DMSO and DMF and poorly soluble in ethanol and isopropanol. They are insoluble in water and chloroform. In the H^1-NMR-spectra of the synthesized compounds **5**, the peak of the aromatic proton in the 9th position of the heterocycle is shifted downfields (10,5-11,5) due to the influence of the spatially nearby sulphur atom in the thioxo-group in the first position. This fact, together with the methyl ester and amino group signals' disappearance in position 4 of compound **4,** is evidence of the proposed structure. The NH-proton in the 4th position of compound **5** was observed at 11,5-12,5 ppm, or found in an exchange with the solvent. The structures of obtained compounds were also confirmed by C^{13}-NMR spectroscopy, mass-spectrometry and elemental microanalysis. The condensation was performed in dimethylformamide, using an equimolar amount of triethylamine. After heating the reaction mixture for 1 hour and dissolving all of the components at 50°C, 1-thioxo[1,3]thiazolo[3,4-a]quinazolin-5(4H)-ones **(5)** were isolated as a solid.

Antimicrobial activity

The antibacterial activity of the synthesized compounds was studied by diffusion in agar and determination of diameters of growth delay areas. During the course of experiment, standard test cultures of different taxonomical groups of microorganisms recommended by Worldwide organization of health care were used. The diffusion in agar method was conducted on two layers of nourishing environments.

Table 1. The results of studies of antibacterial activity by the method of diffusion in agar

Compound	Diameters of growth delay areas, mm					
	Staphylococcus Aureus 25923 ATCC	*Escherichia Coli 25922* ATCC	*Proteus Vulgaris 4636* ATCC	*Bacillus Subtilis* 6633 ATCC	*Pseudomonas Aeruginosa* 27853 ATCC	*Candida albicans* 885-653 ATCC
5a	x	X	x	**14**	**16**	x
5l	x	x	x	**13**	**15**	x
5e	x	x	x	**19**	x	x
5g	**25**	x	x	**27**	**14**	**15**
5h	**20**	x	x	**27**	**14**	**15**
5i	x	x	x	x	x	**15**

x – No activity, 11-15 mm –low activity, 16-25 mm – medium activity, >25 mm – high activity.

It is evident from **Table 1** that all tested compounds showed antibacterial activity in one or more degrees. However, compounds **5g** and **5h** also showed a high level of activity on *S. Aureus*, and medium level on B. Subtilis, but not active on *E.Coli* and *Proteus Vulgaris*.

Experimental Section

General Procedures. Melting points (m.p.) were determined on a Koeffler model melting point apparatus and are uncorrected. ^{1}H NMR spectra were obtained at 500 MHz and ^{13}C NMR spectra were obtained at 125 MHz, in DMSO-d_6 on a Bruker model DRX-500 spectrometer; chemical shifts are reported in δ units (ppm) downfield from TMS as an internal standard. The microanalyses were carried out by the microanalyses service of the Institute of Organic Chemistry n. Zelinsky, Russian Academy of Sciences, Moskow. Analytical TLC was carried out on 5 cm x 10 cm glass plates precoated with a 0.25 mm layer of silica gel 60 F_{254} (Merck, Germany). The plates were illuminated with UV light at 254 nm. All solvents and reagents were obtained from commercial sources and were used without additional purification. Dimethyl 2-isothiocyanatotereftalate was synthesized by standard methods from dimethyl 2-aminotereftalate and thiofosgene[7,8].

Compound characterization

Syntheses of 5a-l. General procedure. To a solution of equimolar amounts of methyl-(2-isothiocyanato)benzoate **(1)** and cyanoaceto-derivative **(2)** (0,01 mol) in 10 ml DMF was added 0,32 g (0,01 mol) of sulfur **(3)**, and 2 ml triethylamine, and this was mixed with a magnetic stirrer at 50°C. After one hour, a cold reactionary mass was poured into water acidified with acetic acid (100 ml 3% solution), and the obtained solid was filtered off and crystallized from the mixture of ethanol-DMF(1:1).

3-(Piperidine-1-carbonyl)-5-oxo-1-thioxo-4,5-dihydro[1,3]thiazolo[3,4-a]quinazoline (5a). R = -H, X = -N(CH2)5, yield 74%, m.p. 194°C. ^{1}H-NMR: δ 11.94 (s, 1H, NH^4), 10.52 (d, *J* = 7.4 Hz, 1H, CH^9), 8.13 (d, *J* = 7.4 Hz, 1H, CH^6), 7.82 (t, *J* = 7.4 Hz, 1H, CH^7), 7.60 (t, *J* = 7.4 Hz, 1H, CH^8), 3.54-3.43 (m, 4H, N(CH$_2$)$_2$), 1.68-1.49 (m, 6H, (CH$_2$)$_3$); 8); ^{13}C NMR 182.55 (CS^1), 158.83 (CO^5), 157.18 (CO-amid), 138.45 (CH^9), 138.10 (CH^7), 133.6 (C^{5a}), 127.89 (C^{9a}), 127.75 (C^3), 118.07 (C^6), 117.38 (C^8), 117.35 (C^{3a}), 45.36 (C$^{2'}$ and C$^{6'}$), 25.61 (C$^{3'}$ and C$^{5'}$), 23.97 (C$^{4'}$). MS, (rel. intensity): 345 (40, Mz$^{+\cdot}$), 234 (15), 365 (17), 186 (22), 162 (32), 134 (19), 84(100). Anal. Calcd for C16H15N3O2S2: C, 55.64; H, 4.38; N, 12.17. Found: C, 54.91; H, 4.37; N, 11.87.

Methyl 5-oxo-1-thioxo-4,5-dihydro[1,3]thiazolo[3,4-*a*]quinazolin-3-carboxylate (5b). R = H, X = -OMe, yield 77%, m.p. 197°C. ^{1}H-NMR: δ 10.66 (s, 1H, NH^4), 10.49 (d, *J* = 7.4 Hz, 1H, CH^9), 8.21 (d, *J* = 7.4 Hz, 1H, CH^6), 7.89 (t, *J* = 7.4 Hz, 1H, CH^7), 7.66 (t, *J* = 7.4 Hz, 1H, CH^8), 3.83 (s, 3H, OCH$_3$); ^{13}C NMR 184.35 (CS^1), 160.48 (CO^5), 156.66 (CO-amid), 142.93 (CH^9), 138.28 (CH^7), 134.21 (C^{5a}), 128.33 (C^{9a}), 127.98 (C^3), 117.68 (C^6), 117.44 (C^8), 117.41 (C^{3a}), 52.72 (OCH$_3$). MS, (rel. intensity): 292 (100, Mz$^{+\cdot}$), 259 (9), 189 (13), 162 (76), 134 (28). Anal. Calcd for C12H8N2O3S2: C, 49.30; H, 2.76; N, 9.58. Found: C, 48.97; H, 2.85; N, 9.34.

Methyl 3-(pyrrolidine-1-carbonyl)-5-oxo-1-thioxo-4,5-dihydro[1,3]thiazolo[3,4-*a*]quinazoline-8-carboxylate (5c). R = -COOMe, X = -N(CH2)4, yield 77%, m.p. 280°C. ^{1}H-NMR: δ 12.43 (s, 1H, NH^4), 11.19 (s, 1H, CH^9), 8.27 (d, *J* = 7.4 Hz, 1H, CH^7), 8.13 (d, *J* = 7.4 Hz, 1H, CH^6), 3.92 (s, 3H, OCH$_3$), 3.54 (s, 4H, N(CH$_2$)$_2$), 1.89 (s, 4H, (CH$_2$)$_2$); ^{13}C NMR 182.99 (CS^1), 164.88 (CO^8), 159.76 (CO^5), 155.70 (CO^3-ester), 141.87 (CH^9), 138.15 (CH^7), 134.18 (C^{5a}), 128.22 (C^{9a}), 127.92 (C^3), 121.51 (C^6), 118.52 (C^8), 118.54 (C^{3a}), 52.60 (OCH$_3$), 46.84 (C$^{2'}$ and C$^{5'}$), 24.62 (C$^{3'}$ and C$^{4'}$). MS, (rel. intensity): 389 (47, Mz$^{+\cdot}$), 319 (13), 244 (17), 220 (43), 188 (12), 161 (11), 70(100). Anal. Calcd for C17H15N3O4S2: C, 52.43; H, 3.88; N, 10.79. Found: C, 52.41; H, 3.94; N, 10.70.

***N*-(1-Phenylethyl)-5-oxo-1-thioxo-4,5-dihydro[1,3]thiazolo[3,4-*a*]quinazolin-3-carboxamide (5d).** R = -H, X = -NH(1-Ph)Et, yield 69%, m.p. 221°C. ^{1}H-NMR: δ 10.53 (d, *J* = 7.4 Hz, 1H, CH^9), 8.68 (d, *J* = 6.4 Hz, 1H, NH-amid), 8.18 (d, *J* = 7.4 Hz, 1H, CH^6), 7.87 (t, *J* = 7.4 Hz, 1H, CH^7), 7.62 (t, *J* = 7.4 Hz, 1H, CH^8), 7.38-7.19 (m, 5H, Ph), 5.13 (q, *J* = 6.4 Hz, 1H, α-CH), 1.46 (d, *J* = 6.4 Hz, 3H, CH$_3$), NH^4 in exch.; ^{13}C NMR 182.88 (CS^1), 159.87 (CO^5), 156.44 (CO-amid), 143.99 (CH^9), 142.20 (C$^{1'}$), 138.43 (CH^7), 133.86 (C^{5a}), 128.36 (CH$^{4'}$), 128.01 (C^{9a}), 127.83 (C^3), 126.92 (CH$^{2'}$ and CH$^{6'}$), 126.19 (C^6), 117.92 (CH^8), 117.43 (C^{3a}), 48.56 (α-CH), 21.74 (CH$_3$). MS, (rel. intensity): 381 (5, Mz$^{+\cdot}$), 277 (7), 162 (6), 134 (7), 105 (100), 90 (14), 77

(33). Anal. Calcd for C19H15N3O2S2: C, 59.82; H, 3.96; N, 11.02. Found: C, 59.88; H, 4.10; N, 10.97.

***N*-(4-Fluorophenyl)-5-oxo-1-thioxo-4,5-dihydro[1,3]thiazolo[3,4-*a*]quinazolin-3-carboxamide (5e).** R = -H, X = -NH(4-F)C6H4 , yield 67%, m.p. >300°C. ^{1}H-NMR: δ 10.53 (d, *J* = 7.4 Hz, 1H, CH^9), 10.04 (s, 1H, NH-amid), 8.19 (d, *J* = 7.4 Hz, 1H, CH^6), 7.88 (t, *J* = 7.4 Hz, 1H, CH^7), 7.69-7.55 (m, 3H, arom.), 7.18 (t, *J* = 7.4 Hz, 2H, $C^{3,5}$ arylamide), NH^4 in exch.; ^{13}C NMR 183.10 (CS^1), 159.84 (CO^5), 159.12 (CO-amid), 157.92 ($CF^{4'}$), 156.89 ($CN^{1'}$), 142.76 (CH^9), 138.43 (CH^7), 134.12 ($CH^{3'}$ and $CH^{5'}$), 133.92 (C^{5a}), 128.09 (C^{9a}), 127.75 (C^3), 123.22 ($CH^{2'}$) 123.16 ($CH^{6'}$) 117.51(C^6), 115.38 (C^8), 115.20 (C^{3a}). MS, (rel. intensity): 371 (23, $Mz^{+\cdot}$), 261 (29), 189 (20), 162 (27), 134 (24), 111(100). Anal. Calcd for C17H10FN3O2S2: C, 54.98; H, 2.71; N, 11.31. Found: C, 54.66; H, 2.71; N, 10.92.

***N*-(2-Fluorophenyl)-5-oxo-1-thioxo-4,5-dihydro[1,3]thiazolo[3,4-*a*]quinazolin-3-carboxamide (5f).** R = -H, X = -NH(2-F)C6H4, yield 63%, m.p. 236°C. ^{1}H-NMR: δ 10.57 (d, *J* = 7.4 Hz, 1H, CH^9), 10.09 (s, 1H, NH-amid), 8.20 (d, *J* = 7.4 Hz, 1H, CH^6), 7.89 (t, *J* = 7.4 Hz, 1H, CH^7), 7.68 (t, *J* = 7.4 Hz, 1H, CH^8), 7.53 (t, *J* = 7.4 Hz, 1H, arylamide), 7.33-7.17 (m, 3H, arylamide), NH^4 in exch.; ^{13}C NMR 183.14 (CS^1), 159.52 (CO^5), 157.10 (CO-amid), 156.91 ($CF^{2'}$), 155.12 ($CN^{1'}$), 143.24 (CH^9), 138.45 (CH^7), 133.96 (C^{5a}), 128.12 (C^{9a}), 127.99 ($CH^{6'}$), 127.93 (C^3), 124.55 ($CH^{4'}$), 124.18 ($CH^{3'}$), 117.71 ($CH^{5'}$), 117.46(C^6), 116.12 (C^8), 115.96 (C^{3a}). MS, (rel. intensity): 371 (6, $Mz^{+\cdot}$), 261 (40), 189 (25), 162 (38), 134 (27), 130 (25), 111 (100). Anal. Calcd for C17H10FN3O2S2: C, 54.98; H, 2.71; N, 11.31. Found: C, 54.80; H, 2.92; N, 10.93.

***N*-(2-Thienylmethyl)-5-oxo-1-thioxo-4,5-dihydro[1,3]thiazolo[3,4-*a*]quinazolin-3-carboxamide (5g).** R = -H, X = -NHCH2(2-thienyl), yield 69%, m.p. 213°C. ^{1}H-NMR: δ 11.70 (s, 1H, NH^4), 10.52 (d, *J* = 7.4 Hz, 1H, CH^9), 8.97 (t, *J* = 6.2 Hz, 1H, NH-amid), 8.18 (d, *J* = 7.4 Hz, 1H, CH^6), 7.87 (t, *J* = 7.4 Hz, 1H, CH^7), 7.62 (t, *J* = 7.4 Hz, 1H, CH^8), 7.38 (d, *J* = 6.9 Hz, 1H, thiene), 7.03-6.93 (m, 2H, thiene), 4.58 (t, *J* = 6.2 Hz, 2H, CH_2) ; ^{13}C NMR 182.86 (CS^1), 160.44 (CO^5), 156.47 (CO-amid), 142.24 (CH^9), 141.41 ($C^{1'}$-thiene), 138.44 (CH^7), 133.92 (C^{5a}), 128.06 (C^{9a}), 127.87 (CH-thiene), 126.76 (CH-thiene), 126.15 (CH-thiene), 125.49 (C^3), 117.93 (C^6), 117.43 (C^{3a}), 117.41 (CH^8), 37.50 (CH_2). MS, (rel. intensity): 373 (6, $Mz^{+\cdot}$), 186 (5), 162 (13), 134 (13), 105 (10), 97 (100). Anal. Calcd for C16H11N3O2S3: C, 51.46; H, 2.97; N, 11.25. Found: C, 51.39; H, 3.23; N, 11.11.

***N*-Tetrahydrofurfuryl-5-oxo-1-thioxo-4,5-dihydro[1,3]thiazolo[3,4-*a*]quinazolin-3-carboxamide (5h).** R = -H, X = -NH-Tetrahydrofurfuryl, yield 69%, m.p. 211°C. ^{1}H-NMR: δ 11.65 (s, 1H, NH^4), 10.52 (d, *J* = 7.4 Hz, 1H, CH^9), 8.43 (t, *J* = 6.4 Hz, 1H, NH-amid), 8.19 (d, *J* = 7.4 Hz, 1H, CH^6), 7.88 (t, *J* = 7.4 Hz, 1H, CH^7), 7.65 (t, *J* = 7.4 Hz, 1H, CH^8), 3.94 (q, *J* = 6.4 Hz, 1H, THF), 3.75 (q, *J* = 6.4 Hz, 1H, THF), 3.61 (q, *J* = 6.4 Hz, 1H, THF), 3.24 (t, *J* = 6.4 Hz, 2H, NCH_2), 1.94-1.73 (m, 3H, THF), 1.61-1.49 (m, 1H, THF); ^{13}C NMR 182.79 (CS^1), 160.67 (CO^5), 156.41 (CO-amid), 141.87 (CH^9), 138.41 (CH^7), 133.84 (C^{5a}), 128.00 (C^{9a}), 127.83 (C^3), 117.88 (C^6), 117.38 (C^8), 117.36 (C^{3a}), 76.80 ($OCH_2^{4'}$), 67.19 ($OCH^{1'}$), 43.24 (NCH_2), 28.68 ($CH_2^{3'}$), 25.13 ($CH_2^{2'}$). MS, (rel. intensity): 361 (22, $Mz^{+\cdot}$), 277(14), 261 (19), 190 (10), 162 (19),

134 (14), 97 (17), 71(100), 43 (88). Anal. Calcd for C16H15N3O3S2: C, 53.17; H, 4.18; N, 11.63. Found: C, 52.79; H, 4.15; N, 11.43.

Ethyl 5-oxo-1-thioxo-4,5-dihydro[1,3]thiazolo[3,4-*a*]quinazolin-3-carboxylate (5i). R = -H, X = -OEt, yield 77%, m.p. >300°C. ^{1}H-NMR: δ 10.62 (s, 1H, NH^4), 10.58 (d, *J* = 7.4 Hz, 1H, CH^9), 8.23 (d, *J* = 7.4 Hz, 1H, CH^6), 7.81 (t, *J* = 7.4 Hz, 1H, CH^7), 7.62 (t, *J* = 7.4 Hz, 1H, CH^8), 4.33(q, *J* = 6.4 Hz, 2H, OCH_2), 1.35(t, *J* = 6.4 Hz, 3H, CH_3); ^{13}C NMR 183.72 (CS^1), 160.94 (CO^5), 159.89 (CO-amid), 148.44 (CH^9), 138.54 (CH^7), 132.10 (C^{5a}), 127.57 (C^{9a}), 127.43 (C^3), 118.62 (C^6), 117.33 (C^8), 117.31 (C^{3a}), 60.34 (OCH_2), 14.43 (CH_3). Ms, (rel. intensity): 306 (100, $Mz^{+\cdot}$), 190 (43), 162 (76). Anal. Calcd for C13H10N2O3S2: C, 50.97; H, 3.29; N, 9.14. Found: C, 50.69; H, 3.17; N, 8.78.

***N*-Phenyl-5-oxo-1-thioxo-4,5-dihydro[1,3]thiazolo[3,4-*a*]quinazolin-3-carboxamide (5j).** R = -H, X = -NHPh, yield 70%, m.p. >300°C. ^{1}H-NMR: δ 10.56 (d, *J* = 7.4 Hz, 1H, CH^9), 9.98 (s, 1H, NH-amid), 8.21 (d, *J* = 7.4 Hz, 1H, CH^6), 7.87 (t, *J* = 7.4 Hz, 1H, CH^7), 7.71-7.62 (m, 3H, CH^8+$CH^{2,6}$Ph), 7.36 (t, *J* = 7.4 Hz, 2H, $CH^{3,5}$Ph), 7.12 (t, *J* = 7.4 Hz, 1H, CH^4Ph), NH^4 in exch.; ^{13}C NMR 183.35 (CS^1), 159.21 (CO^5), 156.89 (CO-amid), 142.47 (CH^9), 138.40 ($CN^{1'}$), 137.81 (CH^7), 133.66 (C^{5a}), 128.48 (C^{9a}), 127.90 ($CH^{1'}$ and $CH^{6'}$), 127.69 (C^3), 127.63 ($CH^{3'}$ and $CH^{5'}$), 124.44 ($CH^{4'}$), 121.55(C^6), 117.60 (C^8), 117.51 (C^{3a}). MS, (rel. intensity): 353 (55, $Mz^{+\cdot}$), 261 (24), 189 (19), 162 (33), 134 (23), 119 (8), 102 (11), 93 (100). Anal. Calcd for C17H11N3O2S2: C, 57.77; H, 3.25; N, 11.89. Found: C, 57.49; H, 3.14; N, 11.55.

***N*-pentyl-5-oxo-1-thioxo-4,5-dihydro[1,3]thiazolo[3,4-*a*]quinazolin-3-carboxamide (5k).** R = -H, X = -NH-n-C5H11, yield 77%, m.p. 168°C. ^{1}H-NMR: δ 11.89 (s, 1H, NH^4), 10.58 (d, *J* = 7.4 Hz, 1H, CH^9), 8.23 (d, *J* = 7.4 Hz, 1H, CH^6), 8.08 (t, *J* = 6.4 Hz, 1H, NH-amid), 7.77 (t, *J* = 7.4 Hz, 1H, CH^7), 7.58 (t, *J* = 7.4 Hz, 1H, CH^8), 3.21 (q, *J* = 6.4 Hz, 2H, NCH_2), 1.52 (q, *J* = 6.4 Hz, 2H, CH_2), 1.25-1.39 (m, 4H, $(CH_2)_2$), 0.92 (t, *J* = 6.4 Hz, 3H, CH_3); ^{13}C NMR 182.65 (CS^1), 160.39 (CO^5), 156.33 (CO-amid), 141.62 (CH^9), 138.40 (CH^7), 133.84 (C^{5a}), 127.99 (C^{9a}), 127.85 (C^3), 117.89 (C^6), 117.38 (C^8), 117.36 (C^{3a}), 39.09 (NCH_2), 28.63 (CH_2), 28.59 (CH_2), 21.87 (CH_2), 13.95 (CH_3). MS, (rel. intensity): 347 (58, $Mz^{+\cdot}$), 261 (33), 234 (16), 217 (27), 190 (61), 189 (27), 186 (17), 162 (100), 134 (50), 90 (35). Anal. Calcd for C16H17N3O2S2: C, 55.31; H, 4.93; N, 12.09. Found: C, 54.96; H, 5.00; N, 11.85.

Methyl 8-carbmethoxy-5-oxo-1-thioxo-4,5-dihydro[1,3]thiazolo[3,4-*a*]quinazolin-3-carboxylate (5l). R = -COOMe, X = -OMe, yield 67%, m.p. 232°C. ^{1}H-NMR: δ 11.18 (s, 1H, , CH^9), 8.31 (d, *J* = 7.4 Hz, 1H, CH^7), 8.15 (d, *J* = 7.4 Hz, 1H, CH^6), 3.94 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), NH^4 in exch.; ^{13}C NMR 184.57 (CS^1), 164.82 (CO^8), 160.39 (CO^5), 156.24 (CO^3), 142.77 (CH^9), 138.27 (CH^7), 134.00 (C^{5a}), 133.94 (C^{9a}), 128.50 (C^3), 128.23 (C^6), 121.16 (C^8), 118.22 (C^{3a}), 52.95 (OCH_3), 52.70 (OCH_3). MS, (rel. intensity): 350 (65, $Mz^{+\cdot}$), 335 (34), 303 (32), 220 (100), 161 (34), 75 (69), 59 (63). Anal. Calcd for C14H10N2O5S2: C, 47.99; H, 2.88; N, 8.00. Found: C, 47.62; H, 2.87; N, 7.67.

Antimicrobial activity were determined by diffusion in agar method on two layers of nourishing environments. The lower one was "hungry" environment containing agar-agar 15-20 g, Na_2HPO_4 3 g, H_2O 1000 ml. The higher one contained meat-peptone clear soup 1:2 1000 ml,

agar-agar 15 g, Na_2HPO_4 3 g. The higher layer was sowed by 1 ml with 10^9 of proper micro-organism cells. After 30 minutes 5-6 discs with explored compounds placed on the surface of nourishing environment, maintained 30 minutes at room temperature and 18-24 hours at 37°C. The results fixed by measuring of diameters of growth delay areas including the diameters of disks.

Conclusions

Offered here is a simple high-yield method for synthesizing the new class of heterocyclic system derivatives, 1-thioxo[1,3]thiazolo[3,4-a]quinazolin-5(4H)ones. Synthesized compounds showed antibacterial activity and this class can be recommended for the searching of new antibacterial drugs.

References and Footnotes

1. Gewald, V. K. *J. prakt. Chem.* **1966**, *32*, 26.
2. Devani, M. B.; Shishoo, C. J.; Pathak, U. S.; Parikh, S. H.; Radhakrishnan, A. V.; Padhya, A. C. *Arzneim.-Forsch.* **1977**, *27*, 1652.
3. Habib, N. S.; Rida, S. M.; Badawey, E.A. M.; Fahmy, H. T. *Monatsh. Chem*. **1996**, *127*, 1209.
4. El-Sherbeny, M. A.; Badria, F. A.; Kheira, S. *Med. Chem. Res.* **1996**, *6*, 28.
5. El-Bendary, E. R.; El-Sherbeny, M. A.; Badria, F. A. *Boll. Chim. Farm*. **1998**, *137*, 115.
6. Ivachtchenko, A.; Kovalenko, S.; Parkhomenko, O.; Chernykh, V. *Het. Comm*. **2002**,*8*, 329.
7. Glazer, E. A.; McFariand, J. W. U.S. Patent *4725599* 1988.
8. Chenard, B. L.; Elliot, M. L.; Welch, W. M.Jr. U.S. Patent 5962457, 1999.
9. El-Ablack F. Z. *Boll. Chim. Farm*. **2003**, *142(9)*, 406.
10. Balkan, A.; Goren, Z.; Urgun, H.; Calis, U.; Cakar, A. N.; Atilla, P.; Uzbay, T. *Arzneim.-Forsch.* **2002**, *52*, 462.
11. Bekhit, A. A.; Fahmy, H. T. Y.; Rostom, S. A. F.; Baraka, A. M. *Eur. J. Med. Chem.* **2003,** *38,* 27.
12. Fahmy, H. T. Y.; Rostom, S. A. F.; Bekhit, A. A. *Archiv Pharm.* **2002**, *335,* 213.
13. Balkan, A.; Urgun, H.; Ozalp, M. *Arzneim.-Forsch.* **2001**, *51*, 839.
14. Urgun H.; Balkan A.; Ozalp M. *Arzneim.-Forsch.* **2000**, *50,* 1115.
15. Badawey, E. S. A. M.; Rida, S. M.; Hazza, A. A.; Fahmy, H. T. Y.; Gohar, Y. M. *European J. Med. Chem*. **1993,** *28,* 91.
16. Fahmy H. T. Y. *Pharmazie.* **1997**, *52*, 750.
17. Habib, N. S.; Rida, S. M.; Badawey, E. A. M.; Fahmy, H. T. Y.; Ghozlan, H. A. *Eur. J. Med. Chem.* **1997**, *32*, 759.