S. S. Kovalenko[1], K. Yu. Kulikovska[1], O. G. Drushlyak[1]*, I. O. Zhuravel[1], S. M. Kovalenko[1], V. P. Chernykh[1]

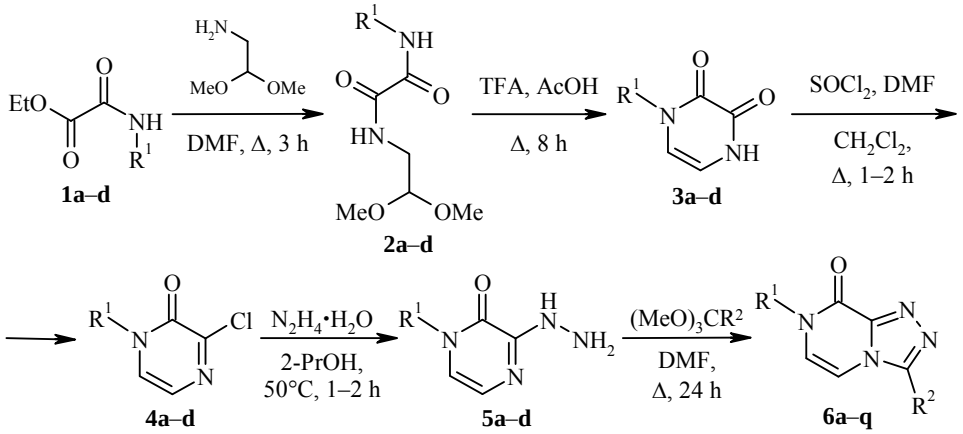
A SUITABLE SYNTHESIS OF [1,2,4]TRIAZOLO[4,3-*a*]PYRAZIN-8(7*H*)-ONE DERIVATIVES

A suitable approach to the synthesis of 3,7-disubstituted [1,2,4]triazolo[4,3-*a*]pyrazin-8(7*H*)-ones starting from esters of oxalic acid monoamides via cyclization of intermediate 3-hydrazinopyrazin-2-ones has been suggested.

Keywords: 3-hydrazinopyrazin-2(1*H*)-one, orthoester, pyrazine-2,3-dione, [1,2,4]triazolo-[4,3-*a*]pyrazin-8(7*H*)-one, cyclization.

Derivatives of [1,2,4]triazolo[4,3-*a*]pyrazin-8(7*H*)-one containing *N*-alkyl, alkylsulfanyl, alkylsulfinyl, or alkylsulfonyl substituents in position 3 were found as $P2X_7$ receptor antagonists and useful for treating pain or an inflammatory disease [1]. As their structure analogs, 3-alkyl[1,2,4]triazolo[4,3-*a*]pyrazin-8(7*H*)-ones could be reasonably expected to possess significant biological activity. A known scheme of [1,2,4]triazolo[4,3-*a*]pyrazin-8(7*H*)-one synthesis starts from 2,3-dichloropyrazine and consists of cyclization of the obtained 2-chloro-3-hydrazinopyrazine by the action of carbonic acid halo anhydrides followed by hydrolysis of the intermediate 8-chloro[1,2,4]triazolo[4,3-*a*]pyrazine and its consequent alkylation [2]. However, according to this approach only a limited set of substituents could be inserted at position 7 of triazolo[4,3-*a*]pyrazine, and the synthesis of 7-aryl derivatives presents a problem in our opinion.

We, therefore, suggest a suitable method of synthesis, which allows to obtain more diverse 7-substituted 3-alkyl[1,2,4]triazolo[4,3-*a*]pyrazin-8(7*H*)-ones.



1–**5 a**, **6b**,**f**,**j**,**n** R^1 = Ph; **1**–**5 b**, **6c**,**g**,**k**,**o** R^1 = 4-$MeOC_6H_4$; **1**–**5 c**, **6a**,**d**,**h**,**l**,**p** R^1 = 4-FC_6H_4;
1–**5 d**, **6e**,**i**,**m**,**q** R^1 = 4-$ClC_6H_4CH_2$; **6 a** R^2 = H, **b**–**e** R^2 = Me, **f**–**i** R^2 = Et, **j**–**m** R^2 = 1-Pr, **n**–**q** R^2 = 2-Pr

The reaction sequence starts from known oxalic acid monoamide esters **1a**–**d** [3, 4], already having the substituent, which shall occupy position 7 in the target [1,2,4]triazolo[4,3-*a*]pyrazin-8(7*H*)-ones. Monoamides **1a**–**d** are easily turned into asymmetric oxalic acid diamides **2a**–**d** by refluxing with 2,2-dimethoxyethylamine

in DMF. The subsequent cyclization of compounds **2a**–**d** by refluxing in trifluoroacetic acid or in mixture of acetic and trifluoroacetic acid results in 1-substituted pyrazine-2,3-diones **3a**–**d** [4].

The use of $POCl_3$ to obtain 3-chloropyrazin-2(1*H*)-ones **4a**–**d** was accompanied by the formation of considerable amount of tars, which required column chromatography for purification [4]. For the exchange of the oxygen atom to chlorine we suggested the use dimethylformamidinium chloride, which was produced *in situ* by the addition of DMF and $SOCl_2$ to the suspension of pyrazine-2,3-diones **3a**–**d** in dichloromethane. The mixture turned into a clear solution after reflux for 1–2 h, which upon the addition of hexane formed relatively pure precipitate of 3-chloropyrazin-2(1*H*)-one **4a**–**d**.

The chlorine atom in 3-chloropyrazin-2(1*H*)-ones **4a**–**d** easily replaced by the action of nucleophilic reagents, even by H_2O contained in air. Therefore, compounds **4a**–**d** were used without additional purification. The formation of 3-hydrazinopyrazin-2(1*H*)-ones **5a**–**d** was carried out by heating the suspension of the intermediate products **4a**–**d** in 2-propanol with a hydrazine hydrate excess.

Synthesis of [1,2,4]triazolo[4,3-*a*]pyrazin-8(7*H*)-ones **6a**–**q** was performed following a typical procedure [5, 6] consisting of the addition of orthoesters to the solutions of 3-hydrazinopyrazin-2(1*H*)-ones **5a**–**d** in DMF with subsequent reflux for 24 h.

The purity and structures of the synthesized compounds were confirmed by ^{1}H NMR spectroscopy, as well as by ^{13}C NMR spectroscopy data for [1,2,4]triazolo[4,3-*a*]pyrazin-8(7*H*)-ones **6a**–**q**. The ^{1}H NMR spectra and the isolated yields are presented in Table.

Characteristic for the ^{1}H NMR spectra of pyrazine-2,3-diones **3a**–**d** are signals of protons H-5,6 appearing as triplets at 6.32–6.36 and doublets at 6.46–6.54 ppm, respectively. The position of the NH proton signals at 11.25–11.33 ppm is an evidence that pyrazine-2,3-diones **3a**–**d** exist in the amide form with sufficiently acidic nature of these protons. However, the signals of protons H-5,6 of 3-hydrazinopyrazin-2(1*H*)-ones **5a**–**d** all appear as doublets at 6.72–6.75 and 6.82–6.85 ppm, respectively. The signals of the NH_2 protons appear as broad singlets at 4.30–4.33 ppm and those of NH group – at 8.20–8.45 ppm. Such chemical shifts and the multiplicity of the H-5 signals confirm the hydrazino form of compounds **5a**–**d**. It should be noticed that the hydrazine protons are extremely sensitive to the presence of H_2O, their signals appear as broad singlets and, therefore, it is impossible to determine their multiplicity.

The ^{1}H NMR spectra of [1,2,4]triazolo[4,3-*a*]pyrazin-8(7*H*)-ones **6a**–**q** are characterized by the presence of the signals of protons H-5,6 as doublets at 7.13–7.26 and 7.52–7.63 ppm, respectively. The signals of *N*-methyl protons of compounds **6b–e** appear as singlets at 2.56–2.63 ppm. The chemical shifts of these signals are in good correlation with those of analogous compounds [2].

In summary, we have proposed a suitable approach to the synthesis of [1,2,4]triazolo[4,3-*a*]pyrazin-8(7*H*)-ones starting from esters of oxalic acid monoamides through the cyclization of the intermediate 3-hydrazinopyrazin-2-ones. The suggested method is suitable for the synthesis of highly diverse [1,2,4]triazolo[4,3-*a*]pyrazin-8(7*H*)-ones having various substituents at position 7 with the exception of aromatic or heterocyclic amine residues with lowered nucleophilicity of the amino group and residues possessing functional groups which could react with thionyl chloride, for example, hydroxyl group.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Varian WXR-400 (200 MHz) spectrometer. ^{13}C NMR spectra were recorded on a Bruker DRX-300 spectrometer (300 MHz). For all NMR spectra, DMSO-d_6 was used as solvent, internal standard – TMS. Elemental analysis was performed on an Euro EA-3000 apparatus. Melting points were determined on a Buchi B-520 melting point apparatus and were not corrected.

Ethyl phenylamino(oxo)acetates **1a**–**c** are commercially available.

Ethyl [2-(4-chlorobenzyl)amino]-2-oxoacetate (1d). A solution of 4-chlorobenzylamine (24.3 g, 0.2 mol) in diethyl oxalate (100 ml, 0.74 mol) was heated at 150ºC for 2 h. After cooling, the solution was diluted with ethanol (100 ml) and left overnight to form a precipitate of the diamide side product, which was separated by filtration. The filtrate was diluted with water (200 ml). On next day, the precipitate that formed was collected on filter, washed with ethanol (50 ml) and recrystallized from a mixture of DMF (20 ml) and ethanol (200 ml). Mp 97–99°C. Found, %: C 54.69; H 4.98; N 5.82. $C_{11}H_{12}ClNO_3$. Calculated, %: C 54.67; H 5.00; N 5.80.

Synthesis of *N*-R^1-*N*'-(2,2-dimethoxyethyl)ethanediamides 2a–d (General Method). 2,2-Dimethoxyethylamine (34.5 g, 0.33 mol) was added to an agitated solution of the corresponding ethyl amino(oxo)acetate **1a**–**d** (0.3 mol) in DMF (300 ml). The solution was refluxed for 3 h. After cooling, the solution was diluted with 2-propanol (500 ml) and left overnight to form the precipitate of the corresponding *N*-R^1-*N*'-(2,2-dimethoxyethyl)-ethanediamide **2a**–**d**. The precipitate was filtered off and washed with 2-propanol (300 ml) and recrystallized from a mixture of DMF (50 ml) and 2-PrOH (200 ml). The amides **2a**–**d** were obtained in the form of white solids.

***N*-(2,2-Dimethoxyethyl)-*N*'-phenylethanediamide (2a)**. Mp >200°C (decomp.). Found, %: C 57.16; H 6.40; N 11.09. $C_{12}H_{16}N_2O_4$. Calculated, %: C 57.13; H 6.39; N 11.10.

***N*-(2,2-Dimethoxyethyl)-*N*'-(4-methoxyphenyl)ethanediamide (2b)**. Mp >200°C (decomp.). Found, %: C 55.35; H 6.43; N 9.90. $C_{13}H_{18}N_2O_5$. Calculated, %: C 55.31; H 6.43; N 9.92.

***N*'-(4-fluorophenyl)-*N*-(2,2-dimethoxyethyl)ethanediamide (2c)**. Mp >200°C (decomp.). Found, %: C 53.35; H 5.41; N 10.40. $C_{12}H_{15}FN_2O_4$. Calculated, %: C 53.33; H 5.59; N 10.37.

***N*-(4-Chlorobenzyl)-*N*'-(2,2-dimethoxyethyl)ethanediamide (2d)**. Mp >200°C (decomp.). Found, %: C 51.96; H 5.68; N 9.29. $C_{13}H_{17}ClN_2O_4$. Calculated, %: C 51.92; H 5.70; N 9.31.

Synthesis of 1,4-dihydropyrazine-2,3-diones 3a–d (General Method). A solution of the corresponding *N*-R^1-*N*'-(2,2-dimethoxyethyl)ethanediamide **2a**–**d** (0.2 mol) in a mixture of acetic acid (200 ml) and trifluoroacetic acid (20 ml) was refluxed for 8 h. After cooling, the solution was diluted with 2-propanol (500 ml) and left overnight to form the precipitate of corresponding 1,4-dihydropyrazine-2,3-dione **3a**–**d**. The precipitate was filtered off, washed with 2-propanol (200 ml), and recrystallized from a mixture of DMF (50 ml) and 2-propanol (200 ml). Compounds **3a**–**d** were obtained in a form of white solids.

1-Phenyl-1,4-dihydropyrazine-2,3-dione (3a). Mp >300°C. Found, %: C 63.86; H 4.29; N 14.86. $C_{10}H_8N_2O_2$. Calculated, %: C 63.82; H 4.28; N 14.89.

1-(4-Methoxyphenyl)-1,4-dihydropyrazine-2,3-dione (3b). Mp >300°C. Found, %: C 60.53; H 4.62; N 12.86. $C_{11}H_{10}N_2O_3$. Calculated, %: C 60.55; H 4.62; N 12.84.

1-(4-Fluorophenyl)-1,4-dihydropyrazine-2,3-dione (3c). Mp >300°C. Found, %: C 58.23; H 3.40; N 13.63. $C_{10}H_7FN_2O_2$. Calculated, %: C 58.26; H 3.42; N 13.59.

1-(4-Chlorobenzyl)-1,4-dihydropyrazine-2,3-dione (3d). Mp >300°C. Found, %: C 55.86; H 3.82; N 11.86. $C_{11}H_9ClN_2O_2$. Calculated, %: C 55.83; H 3.83; N 11.84.

Synthesis of 3-hydrazinopyrazin-2(1*H*)-ones 5a–d (General Method). Anhydrous DMF (8 ml, 0.1 mol) was added to a stirred suspension of the corresponding 1,4-dihydropyrazine-2,3-dione **3a**–**d** (0.1 mol) in dichloroethane (200 ml). Then $SOCl_2$ (8 ml, 0.11 mol) was added dropwise with vigorous stirring. The suspension was refluxed with stirring until the dissolution of the precipitate (1–2 h). After cooling, the reaction mixture was diluted with hexane (500 ml). The precipitate was filtered off and washed with hexane (200 ml). The obtained 3-chloropyrazin-2(1*H*)-one **4a**–**d** was used without additional purification and immediately added to a solution of hydrazine hydrate (65 ml, 1 mol) in 2-propanol (300 ml).

^{1}H NMR spectra and yields of compounds 2, 3, 5 a–d and 6a–q

Com-pound	^{1}H NMR spectrum, δ, ppm (*J*, Hz)	Yield, %
1d	1.23 (3H, t, *J* = 7.5, C<u>H</u>$_3$CH$_2$); 4.15–4.35 (4H, m, CH$_3$C<u>H</u>$_2$, NCH$_2$Ar); 7.26 (2H, d, *J* = 8.2, H-2,6 Ar); 7.37 (2H, d, *J* = 8.2, H-3,5 Ar); 9.44 (1H, t, *J* = 5.8, NH)	68
2a	3.22–3.35 (8H, m, NCH$_2$, 2OCH$_3$); 4.45 (1H, t, *J* = 5.0, CH); 7.12 (1H, t, *J* = 7.8, H-4 Ph); 7.33 (2H, t, *J* = 7.8, H-3,5 Ph); 7.72 (2H, d, *J* = 7.8, H-2,6 Ph); 8.65 (1H, t, *J* = 5.0, N<u>H</u>CH$_2$); 10.35 (1H, s, NH)	82
2b	3.25 (6H, s, 2OCH$_3$); 3.32 (2H, t, *J* = 5.4, NCH$_2$); 3.71 (3H, s, ArOCH$_3$); 4.50 (1H, t, *J* = 5.4, CH); 6.88 (2H, d, *J* = 7.8, H-3,5 Ar); 7.70 (2H, d, *J* = 7.8, H-2,6 Ar); 8.83 (1H, t, *J* = 5.4, N<u>H</u>CH$_2$); 10.53 (1H, s, NH)	85
2c	3.20 (6H, s, 2OCH$_3$); 3.30 (2H, t, *J* = 5.4, NC<u>H</u>$_2$); 4.50 (1H, t, *J* = 5.4, CH); 7.15 (2H, t, *J* = 8.3, H-3,5 Ar); 7.72–7.93 (2H, m, H-2,6 Ar); 8.84 (1H, t, *J* = 5.4, N<u>H</u>CH$_2$); 10.70 (1H, s, NH)	90
2d	3.20–3.35 (8H, m, NCH$_2$, 2OCH$_3$); 4.25 (2H, d, *J* = 5.8, NCH$_2$Ar); 4.45 (1H, t, *J* = 5.2, CH); 7.26 (2H, d, *J* = 8.3, H-2,6 Ar); 7.37 (2H, d, *J* = 8.3, H-3,5 Ar); 8.65 (1H, t, *J* = 5.2, N<u>H</u>CH$_2$); 9.37 (1H, t, *J* = 5.8, N<u>H</u>Bn)	81
3a	6.36 (1H, t, *J* = 4.9, H-5); 6.50 (1H, d, *J* = 4.9, H-6); 7.34–7.52 (5H, m, H Ph); 11.33 (1H, s, NH)	80
3b	3.75 (3H, s, 4-OCH$_3$); 6.36 (1H, t, *J* = 4.8, H-5); 6.46 (1H, d, *J* = 4.8, H-6); 7.01 (2H, d, *J* = 7.8, H-3,5 Ar); 7.31 (2H, d, *J* = 7.8, H-2,6 Ar); 11.27 (1H, s, NH)	82
3c	6.36 (1H, t, *J* = 4.8, H-5); 6.49 (1H, d, *J* = 4.8, H-6); 7.31 (2H, t, *J* = 8.0, H-3,5 Ar); 7.36–7.58 (2H, m, H-2,6 Ar); 11.30 (1H,s, NH)	85
3d	4.87 (2H, s, CH$_2$); 6.32 (1H, t, *J* = 5.0, H-5); 6.54 (1H, d, *J* = 5.0, H-6); 7.31 (2H, d, *J* = 8.2, H-2,6 Ar); 7.40 (2H, d, *J* = 8.2, H-3,5 Ar); 11.25 (1H, s, NH)	78
5a	4.30 (2H, br. s, NH$_2$); 6.72 (1H, d, *J* = 4.8, H-5); 6.82 (1H, d, *J* = 4.8, H-6); 7.34–7.53 (5H, m, H Ph); 8.30 (1H, br. s, NH)	62
5b	3.77 (3H, s, 4-OCH$_3$); 4.30 (2H, br. s, NH$_2$); 6.72 (1H, d, *J* = 4.7, H-5); 6.82 (1H, d, *J* = 4.7, H-6); 7.04 (2H, d, *J* = 7.8, H-3,5 Ar); 7.36 (2H, d, *J* = 7.8, H-2,6 Ar); 8.40 (1H, br. s, NH)	65
5c	4.33 (2H, br. s, NH$_2$); 6.75 (1H, d, *J* = 4.8, H-5); 6.85 (1H, d, *J* = 4.8, H-6); 7.35 (2H, t, *J* = 8.2, H-3,5 Ar); 7.48 (2H, dd, *J* = 8.2, *J* = 5.2, H-2,6 Ar); 8.45 (1H, br. s, NH)	70
5d	4.30 (2H, br. s, NH$_2$); 4.87 (2H, s, CH$_2$); 6.73 (1H, d, *J* = 5.0, H-5); 6.82 (1H, d, *J* = 5.0, H-6); 7.22–7.45 (4H, m, H Ar); 8.20 (1H, br. s, NH)	58
6a	7.15 (1H, d, *J* = 4.8, H-5); 7.35 (2H, t, *J* = 8.2, H-3,5 Ar); 7.44–7.58 (2H, m, H-2,6 Ar); 7.63 (1H, d, *J* = 4.8, H-6); 9.12 (1H, s, H-3)	57
6b	2.63 (3H, s, CH$_3$); 7.20 (1H, d, *J* = 4.6, H-5); 7.40–7.58 (6H, m, H Ph, H-6)	85

6c	2.60 (3H, s, CH_3); 3.80 (3H, s, 4-OCH_3); 7.06 (2H, d, *J* = 7.8, H-3,5 Ar); 7.16 (1H, d, *J* = 4.7, H-5); 7.38 (2H, d, *J* = 7.8, H-2,6 Ar); 7.53 (1H, d, *J* = 4.7, H-6)	85
6d	2.60 (3H, s, CH_3); 7.17 (1H, d, *J* = 4.6, H-5); 7.35 (2H, t, *J* = 8.2, H-3,5 Ar); 7.46–7.58 (3H, m, H-2,6 Ar, H-6)	88
6e	2.56 (3H, s, CH_3); 5.07 (2H, s, CH_2); 7.26 (1H, d, *J* = 4.8, H-5); 7.30–7.42 (4H, m, H Ar); 7.52 (1H, d, *J* = 4.8, H-6)	76
6f	1.30 (3H, t, *J* = 7.7, C$\underline{H}_3CH_2$); 3.00 (2H, q, *J* = 7.7, $CH_3C\underline{H}_2$; 7.21 (1H, d, *J* = 4.8, H-5); 7.42–7.62 (6H, m, H Ph, H-6)	71
6g	1.32 (3H, t, *J* = 7.8, C$\underline{H}_3CH_2$; 3.01 (2H, q, *J* = 7.8, $CH_3C\underline{H}_2$); 3.82 (3H, s, 4-OCH_3); 7.05 (2H, d, *J* = 7.9, H-3,5 Ar); 7.13 (1H, d, *J* = 4.6, H-5); 7.38 (2H, d, *J* = 7.9, H-2,6 Ar); 7.56 (1H, d, *J* = 4.6, H-6)	85
6h	1.30 (3H, t, *J* = 7.7, C$\underline{H}_3CH_2$); 3.00 (2H, q, *J* = 7.7, $CH_3C\underline{H}_2$); 7.16 (1H, d, *J* = 4.8, H-5); 7.35 (2H, t, *J* = 8.2, H-3,5 Ar); 7.46–7.60 (3H, m, H-2,6 Ar H-6)	87
6i	1.28 (3H, t, *J* = 7.7, C$\underline{H}_3CH_2$); 2.96 (2H, q, *J* = 7.7, $CH_3C\underline{H}_2$); 5.07 (2H, s, C$\underline{H}_2$Ar); 7.26 (1H, d, *J* = 4.8, H-5); 7.30–7.42 (4H, m, H Ar); 7.56 (1H, d, *J* = 4.8, H-6)	76
6j	0.94 (3H, t, *J* = 7.8, C$\underline{H}_3CH_2CH_2$); 1.75 (2H, sext, *J* = 7.8, $CH_3C\underline{H}_2CH_2$); 2.98 (2H, t, *J* = 7.8, $CH_3CH_2C\underline{H}_2$); 7.17 (1H, d, *J* = 4.8, H-5); 7.42–7.55 (5H, m, H Ph); 7.62 (1H, d, *J* = 4.8, H-6)	62
6k	0.92 (3H, t, *J* = 7.8, C$\underline{H}_3CH_2CH_2$); 1.72 (2H, sext, *J* = 7.8, $CH_3C\underline{H}_2CH_2$); 2.96 (2H, t, *J* = 7.8, $CH_3CH_2C\underline{H}_2$); 3.80 (3H, s, 4-OCH_3); 7.05 (2H, d, *J* = 7.9, H-3,5 Ar); 7.13 (1H, d, *J* = 4.6, H-5); 7.37 (2H, d, *J* = 7.9, H-2,6 Ar); 7.59 (1H, d, *J* = 4.6, H-6)	78
6l	0.92 (3H, t, *J* = 7.8, C$\underline{H}_3CH_2CH_2$); 1.73 (2H, sext, *J* = 7.8, $CH_3C\underline{H}_2CH_2$); 2.98 (2H, t, *J* = 7.8, $CH_3CH_2C\underline{H}_2$); 7.17 (1H, d, *J* = 4.8, H-5); 7.35 (2H, t, *J* = 8.2, H-3,5 Ar); 7.47–7.57 (2H, m, H-2,6 Ar); 7.61 (1H, d, *J* = 4.8, H-6)	82
6m	0.90 (3H, t, *J* = 7.8, C$\underline{H}_3CH_2CH_2$); 1.72 (2H, sext, *J* = 7.8, $CH_3C\underline{H}_2CH_2$); 2.96 (2H, t, *J* = 7.8, $CH_3CH_2C\underline{H}_2$); 5.03 (2H, s, C$\underline{H}_2$Ar); 7.23 (1H, d, *J* = 4.8, H-5); 7.32–7.42 (4H, m, H Ar); 7.57 (1H, d, *J* = 4.8, H-6)	77
6n	1.33 (6H, d, *J* = 7.2, $2CH_3$); 3.48 (1H, sept, *J* = 7.2, C$\underline{H}(CH_3)_2$); 7.19 (1H, d, *J* = 4.8, H-5); 7.44–7.55 (5H, m, H Ph); 7.62 (1H, d, *J* = 4.8, H-6)	67
6o	1.33 (6H, d, *J* = 7.2, $2CH_3$); 3.48 (1H, sept, *J* = 7.2, C$\underline{H}(CH_3)_2$); 3.78 (3H, s, 4-OCH_3); 7.05 (2H, d, *J* = 7.9, H-3,5 Ar); 7.14 (1H, d, *J* = 4.7, H-5); 7.37 (2H, d, *J* = 7.9, H-2,6 Ar); 7.61 (1H, d, *J* = 4.7, H-6)	70
6p	1.33 (6H, d, *J* = 7.2, $2CH_3$); 3.48 (1H, sept, *J* = 7.2, C$\underline{H}(CH_3)_2$); 7.18 (1H, d, *J* = 4.8, H-5); 7.35 (2H, t, *J* = 8.2, H-3,5 Ar); 7.47–7.56 (2H, m, H-2,6 Ar); 7.63 (1H, d, *J* = 4.8, H-6)	72
6q	1.31 (6H, d, *J* = 7.2, $2CH_3$); 3.40 (1H, sept, *J* = 7.2, C$\underline{H}(CH_3)_2$); 5.07 (2H, s, CH_2); 7.26 (1H, d, *J* = 4.8, H-5); 7.32–7.42 (4H, m, H Ar); 7.61 (1H, d, *J* = 4.8, H-6)	69

The reaction mixture was heated at 50ºC until the dissolution of the precipitate (1–2 h) and diluted with water (500 ml). At the next day, the precipitate formed was filtered, washed with 2-propanol (200 ml), and recrystallized from a mixture of DMF (50 ml) and 2-PrOH (200 ml). Compounds **5a**–**d** were obtained in a form of creamy solids.

3-Hydrazino-1-phenylpyrazin-2(1*H*)-one (5a). Mp >200°C (decomp.). Found, %: C 59.44; H 5.00; N 27.69. $C_{10}H_{10}N_4O$. Calculated, %:59.40; H 4.98; N 27.71.

3-Hydrazino-1-(4-methoxyphenyl)pyrazin-2(1*H*)-one (5b). Mp >200°C (decomp.). Found, %: C 56.91; H 5.20; N 24.09. $C_{11}H_{12}N_4O_2$. Calculated, %: C 56.89; H 5.21; N 24.12.

1-(4-Fluorophenyl)-3-hydrazinopyrazin-2(1*H*)-one (5c). Mp >200°C (decomp.). Found, %: C 54.51; H 4.12; N 25.39. $C_{10}H_9FN_4O$. Calculated, %: C 54.54; H 4.12; N 25.44.

1-(4-Chlorobenzyl)-3-hydrazinopyrazin-2(1*H*)-one (5d). Mp >200°C (decomp.). Found, %: C 52.71; H 4.40; N 22.33. $C_{11}H_{11}ClN_4O$. Calculated, %: C 52.70; H 4.42; N 22.35.

Synthesis of [1,2,4]triazolo[4,3-*a*]pyrazin-8(7*H*)-ones 6a–q (General Method). A methyl orthoester (0.015 mol) was added to a stirred solution of the corresponding 3-hydrazinopyrazin-2(1*H*)-one **5a**–**d** (0.01 mol) in anhydrous DMF (20 ml). The reaction mixture was refluxed for 24 h. After cooling, the reaction mixture was diluted with water (100 ml). On the next day the precipitate that formed was filtered off, washed with 2-propanol (200 ml), and recrystallized from a mixture of DMF (5 ml) and 2-propanol (20 ml). Compounds **6a**–**q** obtained in a form of creamy solids.

7-(4-Fluorophenyl)[1,2,4]triazolo[4,3-*a*]pyrazin-8(7*H*)-one (6a). Mp >300°C. ^{13}C NMR spectrum, δ, ppm: 104.7 (C-5); 122.0 (d, $J_{C–F}$ = 17.0, C-3,5 Ar); 122.8; 134.1 (C-2,6 Ar); 144.8; 148.9; 151.9; 152.4; 161.5 (d, $J_{C–F}$ = 257.0, C-4 Ar). Found, %: C 57.49; H 3.09; N 24.38. $C_{11}H_7FN_4O$. Calculated, %: C 57.39; H 3.07; N 24.34.

3-Methyl-7-phenyl[1,2,4]triazolo[4,3-*a*]pyrazin-8(7*H*)-one (6b). Mp >300°C. ^{13}C NMR spectrum, δ, ppm: 9.5 (CH_3); 103.8 (C-5); 122.2; 126.8 (C-2,6 Ar); 128.5; 129.1 (C-3,5 Ar); 139.2; 144.3; 150.3; 152.2. Found, %: C 63.66; H 4.46; N 24.76. $C_{12}H_{10}N_4O$. Calculated, %: C 63.71; H 4.46; N 24.76.

7-(4-Methoxyphenyl)-3-methyl[1,2,4]triazolo[4,3-*a*]pyrazin-8(7*H*)-one (6c). Mp >300°C. ^{13}C NMR spectrum, δ, ppm: 9.5 (CH_3); 55.7 (OCH_3); 103.9 (C-5); 114.7 (C-3,5 Ar); 122.1; 128.2 (C-2,6 Ar); 131.7; 144.3; 150.2; 152.2; 158.1. Found, %: C 60.92; H 4.71; N 21.84. $C_{13}H_{12}N_4O_2$. Calculated, %: C 60.93; H 4.72; N 21.86.

7-(4-Fluorophenyl)-3-methyl[1,2,4]triazolo[4,3-*a*]pyrazin-8(7*H*)-one (6d). Mp >300°C. ^{13}C NMR spectrum, δ, ppm: 9.6 (CH_3); 103.7 (C-5); 121.8 (d, $J_{C–F}$ = 17.6, C-3,5 Ar); 122.8; 134.3 (C-2,6 Ar); 144.5; 149.1; 151.3; 152.4; 161.5 (d, $J_{C–F}$ = 255.4, C-4 Ar). Found, %: C 58.95; H 3.71; N 22.98. $C_{12}H_9FN_4O$. Calculated, %: C 59.02; H 3.71; N 22.94.

7-(4-Chlorobenzyl)-3-methyl[1,2,4]triazolo[4,3-*a*]pyrazin-8(7*H*)-one (6e). Mp >300°C. ^{13}C NMR spectrum, δ, ppm: 9.6 (CH_3); 49.1 (CH_2); 104.2 (C-5); 121.3; 128.6 (C-3,5 Ar); 129.7 (C-2,6 Ar); 132.4; 135.7 (C-1 Ar); 144.0; 147.4; 152.3. Found, %: C 56.86; H 4.02; N 20.36. $C_{13}H_{11}ClN_4O$. Calculated, %: C 56.84; H 4.04; N 20.39.

3-Ethyl-7-phenyl[1,2,4]triazolo[4,3-*a*]pyrazin-8(7*H*)-one (6f). Mp >300°C. ^{13}C NMR spectrum, δ, ppm: 11.2 (CH_3); 17.2 (CH_2); 103.4 (C-5); 122.4; 126.8 (C-2,6 Ar); 128.5; 129.3 (C-3,5 Ar); 139.4; 144.3; 151.0; 152.3. Found, %: C 65.01; H 5.01; N 23.35. $C_{13}H_{12}N_4O$. Calculated, %: C 64.99; H 5.03; N 23.32.

3-Ethyl-7-(4-methoxyphenyl)[1,2,4]triazolo[4,3-*a*]pyrazin-8(7*H*)-one (6g). Mp >300°C. ^{13}C NMR spectrum, δ, ppm: 11.3 (CH_3); 17.2 (CH_2); 55.5 (OCH_3); 103.4 (C-5); 114.4 (C-3,5 Ar); 122.6; 128.1 (C-2,6 Ar); 131.9; 144.4; 151.7; 152.2; 159.0. Found, %: C 62.19; H 5.21; N 20.75. $C_{14}H_{14}N_4O_2$. Calculated, %: C 62.21; H 5.22; N 20.73.

3-Ethyl-7-(4-fluorophenyl)[1,2,4]triazolo[4,3-*a*]pyrazin-8(7*H*)-one (6h). Mp >300°C. ^{13}C NMR spectrum, δ, ppm: 11.6 (CH_3); 17.3 (CH_2); 104.0 (C-5); 122.0 (d, $J_{C–F}$ = 17.3, C-3,5 Ar); 122.4; 133.7 (C-2,6 Ar); 144.4; 149.1; 151.8; 152.2; 161.5 (d, $J_{C–F}$ = 257.4, C-4 Ar). Found, %: C 60.49; H 4.30; N 21.71. $C_{13}H_{11}FN_4O$. Calculated, %: C 60.46; H 4.29; N 21.69.

7-(4-Chlorobenzyl)-3-ethyl[1,2,4]triazolo[4,3-*a*]pyrazin-8(7*H*)-one (6i). Mp >300°C. ^{13}C NMR spectrum, δ, ppm: 11.35 (CH_3); 17.1 (CH_2); 49.3 (CH_2); 103.8 (C-5); 122.2; 128.8 (C-3,5 Ar); 129.5 (C-2,6 Ar); 133.0; 136.0; 144.5; 149.0; 152.3. Found, %: C 58.26; H 4.52; N 19.43. $C_{14}H_{13}ClN_4O$. Calculated, %: C 58.24; H 4.54; N 19.40.

7-Phenyl-3-propyl[1,2,4]triazolo[4,3-*a*]pyrazin-8(7*H*)-one (6j). Mp 256–258°C. ^{13}C NMR spectrum, δ, ppm: 13.4 (CH_3); 20.2 ($CH_3\underline{C}H_2CH_2$); 25.2 ($CH_3CH_2\underline{C}H_2$); 103.6

(C-5); 122.2; 126.9 (C-2,6 Ar); 128.3; 129.2 (C-3,5 Ar); 139.1; 144.2; 150.5; 151.9. Found, %: C 66.16; H 5.54; N 22.02. $C_{14}H_{14}N_4O$. Calculated, %: C 66.13; H 5.55; N 22.03.

7-(4-Methoxyphenyl)-3-propyl[1,2,4]triazolo[4,3-*a*]pyrazin-8(7*H*)-one (6k). Mp 264–267°C. ^{13}C NMR spectrum, δ, ppm: 13.3 (CH_3); 20.1 ($CH_3\underline{C}H_2CH_2$); 25.1 ($CH_3CH_2\underline{C}H_2$); 55.4 (OCH_3); 103.5 (C-5); 114.7 (C-3,5 Ar); 122.6; 128.5 (C-2,6 Ar); 132.3; 144.3; 151.1; 152.1; 158.2. Found, %: C 63.40; H 5.68; N 19.68. $C_{15}H_{16}N_4O_2$. Calculated, %: C 63.37; H 5.67; N 19.71.

7-(4-Fluorophenyl)-3-propyl[1,2,4]triazolo[4,3-*a*]pyrazin-8(7*H*)-one (6l). Mp 270–273°C. ^{13}C NMR spectrum, δ, ppm: 13.3(CH_3); 20.2 ($CH_3\underline{C}H_2CH_2$); 25.0 ($CH_3CH_2\underline{C}H_2$); 104.2 (C-5); 121.9 (d, $J_{C–F}$ = 16.6, C-3,5 Ar); 122.1; 134.3 (C-2,6 Ar); 144.2; 149.2; 151.0 (C-8); 152.2 (C-3); 161.2 (d, $J_{C–F}$ = 256.0, C-4 Ar). Found, %: C 61.72; H 4.83; N 20.54. $C_{14}H_{13}FN_4O$. Calculated, %: C 61.76; H 4.81; N 20.58.

7-(4-Chlorobenzyl)-3-propyl[1,2,4]triazolo[4,3-*a*]pyrazin-8(7*H*)-one (6m). Mp 267–270°C. ^{13}C NMR spectrum, δ, ppm: 13.36 (CH_3); 20.0 ($CH_3\underline{C}H_2CH_2$); 25.0 ($CH_3CH_2\underline{C}H_2$); 49.2 (CH_2); 104.2 (C-5); 121.3; 128.6 (C-3,5 Ar); 129.7 (C-2,6 Ar); 132.4; 135.7; 144.0; 147.4; 152.3. Found, %: C 59.56; H 5.00; N 18.53. $C_{15}H_{15}ClN_4O$. Calculated, %: C 59.51; H 4.99; N 18.50.

3-Isopropyl-7-phenyl[1,2,4]triazolo[4,3-*a*]pyrazin-8(7*H*)-one (6n). Mp 264–266°C. ^{13}C NMR spectrum, δ, ppm: 20.6 ($2CH_3$); 24.2 ($\underline{C}H(CH_3)_2$); 103.6 (C-5); 122.2; 127.0 (C-2,6 Ar); 128.4; 129.2 (C-3,5 Ar); 139.2; 144.4; 152.1; 155.0. Found, %: C 66.11; H 5.56; N 22.05. $C_{14}H_{14}N_4O$. Calculated, %: C 66.13; H 5.55; N 22.03.

3-Isopropyl-7-(4-methoxyphenyl)[1,2,4]triazolo[4,3-*a*]pyrazin-8(7*H*)-one (6o). Mp 276–278°C. ^{13}C NMR spectrum, δ, ppm: 20.5 ($2CH_3$); 24.1 ($\underline{C}H(CH_3)_2$); 55.6 (OCH_3); 103.5 (C-5); 114.5 (C-3,5 Ar); 122.3; 128.2 (C-2,6 Ar); 132.3; 144.4; 151.7; 154.2; 158.8. Found, %: C 63.39; H 5.66; N 19.73. $C_{15}H_{16}N_4O_2$. Calculated, %: C 63.37; H 5.67; N 19.71.

7-(4-Fluorophenyl)-3-isopropyl[1,2,4]triazolo[4,3-*a*]pyrazin-8(7*H*)-one (6p). Mp 290–293°C. ^{13}C NMR spectrum, δ, ppm: 20.5 ($2CH_3$); 24.2 ($\underline{C}H(CH_3)_2$); 103.8 (C-5); 121.6 (d, $J_{C–F}$ = 17.0, C-3,5 Ar); 122.1; 134.4 (C-2,6 Ar); 144.5; 149.0; 152.0; 152.4; 161.6 (d, $J_{C–F}$ = 257.0, C-4 Ar). Found, %: C 61.79; H 4.80; N 20.55. $C_{14}H_{13}FN_4O$. Calculated, %: C 61.76; H 4.81; N 20.58.

7-(4-Chlorobenzyl)-3-isopropyl[1,2,4]triazolo[4,3-*a*]pyrazin-8(7*H*)-one (6q). Mp 287–289°C. ^{13}C NMR spectrum, δ, ppm: 20.7 ($2CH_3$); 24.5 ($\underline{C}H(CH_3)_2$); 49.2 (CH_2); 103.4 (C-5); 121.8; 128.6 (C-3,5 Ar); 129.8 (C-2,6 Ar); 132.3; 135.5; 144.2; 147.8; 154.2. Found, %: C 59.48; H 5.00; N 18.48. $C_{15}H_{15}ClN_4O$. Calculated, %: C 59.51; H 4.99; N 18.50.

R E F E R E N C E S

1. M. Labroli, M. F. Czarniecki, C. S. Poker, Pat. WO Appl. 2012040048.
2. S. W. Schneller, J. L. May, *J. Heterocycl. Chem*., **15**, 987 (1978).
3. A. P. Krapcho, M. J. Maresch, C. E. Gallagher, M. P. Hacker, E. Menta, A. Oliva, R. Di Domenico, G. Da Re, S. Spinelli, *J. Heterocycl. Chem.*, **32**, 1693 (1995).
4. F. J. Fleitz, T. A. Lyle, N. Zheng, J. D. Armstrong, R. P. Volante, *Synth. Commun.*, **30**, 3171 (2000).
5. C. Temple, in *The Chemistry of Heterocyclic Compounds*, J. A. Montgomery (Ed.), John Wiley & Sons, New York, 2009, vol. 37, p. 6.
6. P. V. Savitsky, R. I. Vas'kevich, V. I. Staninets, M. V. Vovk, *Zh. Org. Farm. Khim.*, **11**, № 2, 3 (2013).

[1] *National University of Pharmacy*,
53 Pushkinska St., *Kharkiv 61002*, *Ukraine*
e-mail: aldry18@hotmail.com

Received 8.12.2013
In revised version 4.05.2014