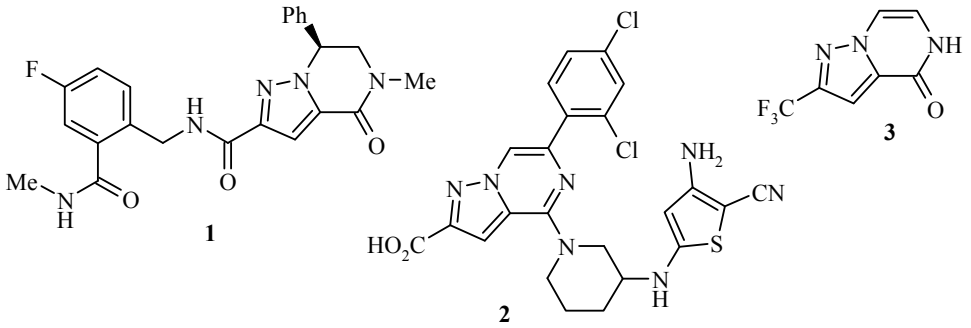
O. V. Zaremba[1], N. Yu. Gorobets[2], S. S. Kovalenko[1], O. G. Drushlyak[1]*, O. Yu. Grevtsov[1], S. M. Kovalenko[1]

FACILE ONE-POT SYNTHESIS OF PYRAZOLO[1,5-*a*]PYRAZINE SCAFFOLD

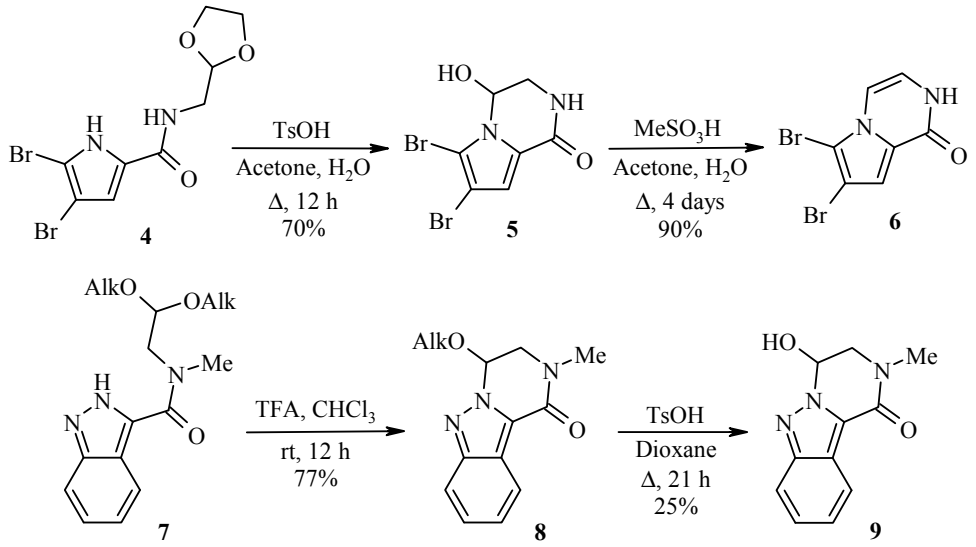
A series of novel pyrazolo[1,5-*a*]pyrazine derivatives has been synthesized using facile one-pot three-step protocol starting from pyrazole-3-carboxilic acids. The process occurs *via* amide formation with consequent pyrazine ring closure, hydrolysis, and dehydration. 7-Hydroxy-6,7-dihydropyrazolo[1,5-*a*]pyrazin-4(5*H*)-one and 7-methoxy-6,7-dihydropyrazolo[1,5-*a*]pyrazin-4(5*H*)-one have been isolated as intermediate compounds.

Keywords: azolocarboxamidoacetals, 6,7-dihydropyrazolo[1,5-*a*]pyrazin-4(5*H*)-one, 2,2-dimethoxyethanamine, pyrazole-3-carboxilic acid, pyrazolo[1,5-*a*]pyrazin-4(5*H*)-one, one-pot reaction.

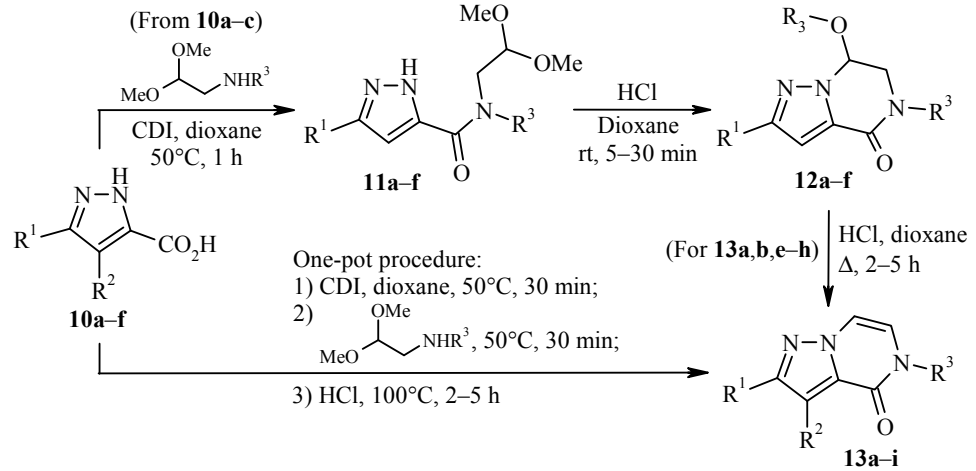
Pyrazolopyrazine scaffold is insufficiently known and only in recent years has attracted attention of organic and medicinal chemists. Among compounds containing this structural motif HIV-1 integrase inhibitor **1** was discovered [1, 2]. Several pyrazolopyrazinones are also potent for the treatment or prevention of hematological diseases [3] (e. g. compound **2**), the trifluoromethyl derivative **3** is useful for the treatment or prevention of diabetes as dipeptidyl peptidase-IV inhibitor [4].



Modern methods for the synthesis of this scaffold are limited to annulation of pyrazine ring to the pyrazole ring by application of pyrazole-3-carboxilic acid derivatives. In this way, a pyrazole-3-carboxilic derivative was alkylated with α-halo ketone followed by heterocyclization by the action of ammonium acetate in AcOH under prolonged reflux [1, 3, 5–8]. Recently, a base-mediated intramolecular hydroamination of aryl(prop-2-yn-1-yl)-1*H*-pyrazolyl-2-carboxamides was also proposed [9]. There are a few reports, where pyrazolo[1,5-*a*]pyrazines were synthesized by other synthetic methods [4, 10, 11]. However, these approaches apply multistep protocols and require laborious synthesis of starting materials. Therefore, the application of azolocarboxamidoacetals **4** [12] and **7** [13] seems to be more convenient for the synthesis of pyrazolo[1,5-*a*]pyrazine derivatives **5**, **6**, **8**, **9**.



In our first experiments, using the acid **10b** (R^1 = 4-ClC_6H_4) in the reaction with 2,2-dimethoxyethanamine (R^3 = H), we obtained amide **11c** (R^1 = 4-ClC_6H_4) in 95% yield under standard CDI-mediated amide coupling reaction conditions in dioxane at 50°C. The ring closure of the amide **11c** was performed by refluxing in different acidic media (in TFA, $MeSO_3H$ or TsOH in 1,4-dioxane) during 0.5–3.0 h (TLC control), which gave 2-(4-chlorophenyl)pyrazolo[1,5-*a*]pyrazin-4(5*H*)-one (**13e**) in 93% yield. However, application of these conditions to the synthesis of unsubstituted and *N*-methyl derivatives (**13a** and **13b**, respectively) resulted in significant decrease of their yields due to the formation of unidentified by-products. At the same time, the use of concentrated aqueous HCl in dioxane during reflux for 2.5 h gave the same yield for derivative **13e**; additionally, the yields of the derivatives **13a**,**b** were also improved (Table). Thus, aqueous HCl in dioxane was suitable for all the model cases and used in our final general procedures.



11a–f

12a–f

10a–f

13a–i

10 a $R^1 = R^2 = H$; **b** R^1 = 4-ClC_6H_4, $R^2 = H$; **c** R^1 = 4-MeC_6H_4, $R^2 = H$; **d** R^1 = Me, $R^2 = H$; **e** $R^1 + R^2 = (CH_2)_4$; **f** R^1 = 2-thienyl, $R^2 = H$; **11**,**12 a** $R^1 = R^3 = H$; **b** $R^1 = H$, R^3 = Me; **c** R^1 = 4-ClC_6H_4, $R^3 = H$; **d** R^1 = 4-ClC_6H_4, R^3 = Me; **e** R^1 = 4-MeC_6H_4, $R^3 = H$; **f** R^1 = 4-MeC_6H_4, R^3 = Me; **13 a** $R^1 = R^2 = R^3 = H$; **b** $R^1 = R^2 = H$, R^3 = Me; **c** R^1 = Me, $R^2 = R^3 = H$; **d** $R^1 + R^2 = (CH_2)_4$, $R^3 = H$; **e** R^1 = 4-ClC_6H_4, $R^2 = R^3 = H$; **f** R^1 = 4-ClC_6H_4, $R^2 = H$, R^3 = Me; **g** R^1 = 4-MeC_6H_4, $R^2 = R^3 = H$; **h** R^1 = 4-MeC_6H_4, $R^2 = H$, R^3 = Me; **i** R^1 = 2-thienyl, $R^2 = R^3 = H$

Yields and ^{1}H NMR spectral data of the obtained compounds

Com-pound	Yield, %	^{1}H NMR spectrum, δ, ppm (*J*, Hz)
11a	95	3.25 (6H, s, 2OCH$_3$); 3.38 (2H, t, *J* = 5.7, CH$_2$CH); 4.45 (1H, t, *J* = 5.7, CH$_2$CH); 6.60 (1H, d, *J* = 1.5, H-4); 7.77 (1H, d, *J* = 1.5, H-5); 7.98 (1H, br. s, 2-NH); 13.24 (1H, br. s, CONH)
11b	88	3.10 (3H, s, NCH$_3$); 3.25 (6H, s, 2OCH$_3$); 3.35 (2H, t, *J* = 5.7, CH$_2$CH); 4.45 (1H, t, *J* = 5.7, CH$_2$CH); 6.66 (1H, d, *J* = 1.5, H-4); 7.72 (1H, d, *J* = 1.5, H-5); 8.01 (1H, br. s, NH)
11c	95	3.22 (6H, s, 2OCH$_3$); 3.35 (2H, t, *J* = 5.8, CH$_2$CH); 4.45 (1H, t, *J* = 5.8, CH$_2$CH); 7.05 (1H, s, H-4); 7.45 (2H, d, *J* = 8.5, H-3,5 Ar); 7.95 (2H, d, *J* = 8.5, H-2,6 Ar); 8.10 (1H, br. s, 2-NH); 13.64 (1H, br. s, CONH)
11d	91	3.12 (3H, s, NCH$_3$); 3.22 (6H, s, 2OCH$_3$); 3.35 (2H, t, *J* = 5.8, CH$_2$CH); 4.48 (1H, t, *J* = 5.8, CH$_2$CH); 7.07 (1H, s, H-4); 7.49 (2H, d, *J* = 8.5, H-3,5 Ar); 7.97 (2H, d, *J* = 8.5, H-2,6 Ar); 8.10 (1H, br. s, NH)
11e	93	2.32 (3H, s, ArCH$_3$); 3.25 (6H, s, 2OCH$_3$); 3.35 (2H, t, *J* = 5.7, CH$_2$CH); 4.45 (1H, t, *J* = 5.7, CH$_2$CH); 7.00 (1H, s, H-4); 7.25 (2H, d, *J* = 7.8, H-3,5 Ar); 7.77 (2H, d, *J* = 7.8, H-2,6 Ar); 8.15 (1H, br. s, 2-NH); 13.60 (1H, br. s, CONH)
11f	87	2.33 (3H, s, ArCH$_3$); 3.12 (3H, s, NCH$_3$); 3.25 (6H, s, 2OCH$_3$); 3.35 (2H, t, *J* = 5.7, CH$_2$CH); 4.45 (1H, t, *J* = 5.7, CH$_2$CH); 7.05 (1H, s, H-4); 7.26 (2H, d, *J* = 7.8, H-3,5 Ar); 7.75 (2H, d, *J* = 7.8, H-2,6 Ar); 8.15 (1H, br. s, NH)
12a	97	3.43 (1H, dd, *J* = 13.7, *J* = 2.8) and 3.77 (1H, dd, *J* = 13.7, *J* = 2.8, 6-CH$_2$); 5.60–5.90 (1H, m, 7-CH); 6.73 (1H, d, *J* = 1.9, H-3); 7.18 (1H, br. s, OH); 7.62 (1H, d, *J* = 1.9, H-2); 8.14 (1H, br. s, NH)
12b	89	3.01 (3H, s, NCH$_3$); 3.32 (3H, s, OCH$_3$); 3.72 (1H, dd, *J* = 13.6, *J* = 2.9) and 4.07 (1H, dd, *J* = 13.6, *J* = 2.9, 6-CH$_2$); 5.58–5.90 (1H, m, 7-CH); 6.82 (1H, d, *J* = 1.7, H-3); 7.66 (1H, d, *J* = 1.7, H-2)
12c	92	3.46 (1H, dd, *J* = 13.8, *J* = 2.7) and 3.83 (1H, dd, *J* = 13.8, *J* = 2.7, 6-CH$_2$); 5.65–5.95 (1H, m, 7-CH); 7.27 (1H, s, H-3); 7.29 (1H, d, *J* = 6.0, OH); 7.49 (2H, d, *J* = 8.5, H-3,5 Ar); 7.92 (2H, d, *J* = 8.5, H-2,6 Ar); 8.21 (1H, br. s, NH)
12d	91	3.03 (3H, s, NCH$_3$); 3.38 (3H, s, OCH$_3$); 3.75 (1H, dd, *J* = 14.0, *J* = 2.9) and 4.11 (1H, dd, *J* = 14.0, *J* = 2.9, 6-CH$_2$); 5.55–5.85 (1H, m, 7-CH); 7.37 (1H, s, H-3); 7.49 (2H, d, *J* = 8.4, H-3,5 Ar); 7.93 (2H, d, *J* = 8.4, H-2,6 Ar)
12e	93	2.31 (3H, s, ArCH$_3$); 3.42 (1H, dd, *J* = 14.0, *J* = 3.0) and 3.82 (1H, dd, *J* = 14.0, *J* = 3.0, 6-CH$_2$); 5.65–5.90 (1H, m, 7-CH); 7.17 (1H, s, H-3); 7.22 (1H, d, *J* = 6.0, OH); 7.26 (2H, d, *J* = 7.9, H-3,5 Ar); 7.75 (2H, d, *J* = 7.9, H-2,6 Ar); 8.17 (1H, br. s, NH)
12f	67	2.33 (3H, s, ArCH$_3$); 3.03 (3H, s, NCH$_3$); 3.38 (3H, s, OCH$_3$); 3.74 (1H, dd, *J* = 14.1, *J* = 3.0) and 4.10 (1H, dd, *J* = 14.1, *J* = 3.0, 6-CH$_2$); 5.58–5.81 (1H, m, 7-CH); 7.24 (2H, d, *J* = 8.1, H-3,5 Ar); 7.26 (1H, s, H-3); 7.78 (2H, d, *J* = 8.1, H-2,6 Ar)
13a	59	6.85 (1H, t, *J* = 5.5, H-6); 6.99 (1H, d, *J* = 1.5, H-3); 7.67 (1H, d, *J* = 5.5, H-7); 7.88 (1H, d, *J* = 1.5, H-2); 11.20 (1H, br. s, NH)
13b	61	3.40 (3H, s, NCH$_3$); 6.97 (1H, d, *J* = 2.1, H-3); 7.12 (1H, d, *J* = 6.0, H-6); 7.75 (1H, d, *J* = 6.0, H-7); 7.86 (1H, d, *J* = 2.1, H-2)
13c	75	2.32 (3H, s, CH$_3$); 6.75 (1H, s, H-3); 6.76 (1H, t, *J* = 5.6, H-6); 7.54 (1H, d, *J* = 5.6, H-7); 11.11 (1H, br. s, NH)
13d	79	1.55–1.95 (4H, m, 2CH$_2$); 2.52–2.70 (2H, m, CH$_2$); 2.72–2.85 (2H, m, CH$_2$); 6.65 (1H, t, *J* = 5.6, H-6); 7.44 (1H, d, *J* = 5.6, H-7); 10.90 (1H, br. s, NH)
13e	93	6.87 (1H, t, *J* = 5.4, H-6); 7.48 (1H, s, H-3); 7.49 (2H, d, *J* = 8.1, H-3,5 Ar); 7.65 (1H, d, *J* = 5.4, H-7); 7.97 (2H, d, *J* = 8.1, H-2,6 Ar); 11.16 (1H, br. s, NH)
13f	88	3.43 (3H, s, NCH$_3$); 7.16 (1H, d, *J* = 6.1, H-6); 7.49 (2H, d, *J* = 8.5, H-3,5 Ar); 7.55 (1H, s, H-3); 7.78 (1H, d, *J* = 6.1, H-7); 7.97 (2H, d, *J* = 8.5, H-2,6 Ar)
13g	89	2.32 (3H, s, ArCH$_3$); 6.86 (1H, t, *J* = 5.9, H-6); 7.25 (2H, d, *J* = 7.9, H-3,5 Ar); 7.43 (1H, s, H-3); 7.67 (1H, d, *J* = 5.9, H-7); 7.83 (2H, d, *J* = 7.9, H-2,6 Ar); 11.24 (1H, br. s, NH)
13h	93	2.30 (3H, s, ArCH$_3$); 3.42 (3H, s, NCH$_3$); 7.11 (1H, d, *J* = 6.0, H-6); 7.23 (2H, d, *J* = 8.1, H-3,5 Ar); 7.43 (1H, s, H-3); 7.75 (1H, d, *J* = 6.0, H-7); 7.82 (2H, d, *J* = 8.1, H-2,6 Ar)
13i	83	6.87 (1H, t, *J* = 5.3, H-6); 7.13 (1H, t, *J* = 4.3, H-4'); 7.39 (1H, s, H-3); 7.55 (1H, d, *J* = 4.3, H-5'); 7.64 (1H, d, *J* = 4.3, H-3'); 7.69 (1H, d, *J* = 5.3, H-7); 11.28 (1H, br. s, NH)

On the other hand, application of the same media (aqueous HCl in dioxane) at lower temperature (rt) and lower time (5–30 min) resulted in cyclization of amides **11a**–**f** to the compounds **12a**–**f**. In case of R^3 = H hydroxy derivatives **12a**,**c**,**e** were produced. If R^3 = Me, hydrolysis of methoxy group did not take place and methoxy derivatives **12b**,**d**,**f** were formed. Thus, the ring closure of the amides **11a**–**f** is accomplished in acidic medium at room temperature, whereas the evaluated temperature is required for the aromatization.

Based on our preliminary experiments, we have obtained the desired pyrazolo[1,5-*a*]pyrazin-4(5*H*)-ones **13a**–**i** using a one-pot protocol starting from acids **10a**–**f** without isolation of the amides **11a**–**f** and the hydroxy (or methoxy) derivatives **12a**–**f**. The isolated yields are presented in Table. The purity and structures of the products were determined by TLC, ^{1}H NMR spectra, and for several representatives – by ^{13}C NMR spectra and LC-MS; the purity of the obtained compounds exceeded 95% without any additional purification.

^{1}H NMR spectra of synthesized compounds are characterized by the presence of signals for the aromatic core protons at 6.7–8.1 ppm. The signal for proton H-3 of pyrazolopyrazine ring appears as a doublet at 6.73–6.99 ppm in the spectra of 2-unsubstituted compounds **12**, **13 a**,**b** or as a singlet at 7.17–7.55 ppm in the spectra of 2-arylsubstituted compounds **12c**–**f**, **13e**–**i**. Protons of CH_2 group in compounds **12a**–**f** are not chemically equivalent and appear as two doublet-doublets at 3.42–3.75 and 3.77–4.11 ppm. Also ^{1}H NMR spectra of compounds **12a**,**c**,**e** are characterized by the presence of OH and NH group protons signals at 7.18–7.29 and 8.14–8.21 ppm, respectively. Signals of protons H-6 and H-7 of pyrazolopyrazine ring in compounds **13a**–**i** appear at 6.65–7.12 and 7.44–7.78 ppm, respectively. Characteristic signal of NH group proton in compounds **13a**,**c**–**e**,**g**,**i** appears as broadened doublet at 11.11–11.28 ppm.

In summary, we have suggested a 3-component condensation reaction leading to a series of novel pyrazolo[1,5-*a*]pyrazine derivatives starting from simple and readily available precursors.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Varian WXR-400 spectrometer (200 MHz). ^{13}C NMR spectra were recorded on a Bruker DRX-300 spectrometer (200 MHz). For all NMR spectra DMSO-d_6 was used as solvent, internal standard TMS. LC-MS were recorded with PE SCIEX API 150EX liquid chromatograph equipped with a UV detector (λ_{max} 215 and 254 nm) and Phenomenex Luna-C_{18} column (100 × 4 mm). Elution started with H_2O and ended with MeCN–H_2O (95:5), linear gradient used at a flow rate 0.15 ml/min, analysis cycle time 25 min. Elemental analysis was performed on Euro EA-3000 apparatus. Melting points were measured with a Buchi B-520 melting point apparatus and were not corrected. Thin-layer chromatography was performed on Merck, Kieselgel 60 F-254 aluminum plates precoated with silica gel, eluent EtOAc–hexane (1:1). Starting pyrazole-3-carboxilic acids **10a**–**f** are commercially available.

Synthesis of *N*-(2,2-dimethoxyethyl)-2*H*-pyrazole-3-carboxamides 11a–f (General Method). A solution of the corresponding pyrazole-3-carboxilic acid **10a**–**c** (0.01 mol) in dry dioxane (10 ml) was mixed with CDI (1.78 g, 0.011 mol). The mixture was stirred at 50°C for 30 min (TLC control). 2,2-Dimethoxyethanamine (1.15 g, 0.011 mol) or 2,2-dimethoxy-*N*-methylethanamine (1.30 g, 0.011 mol) was added, and reaction mixture was stirred for additional 30 min (TLC control). Then H_2O (50 ml) was added, the precipitate was filtered, washed with H_2O, and recrystallized from DMF–H_2O (1:1). The amides **11a**–**f** obtained in a form of white solids; yields and ^{1}H NMR spectral data are given in Table.

***N*-(2,2-Dimethoxyethyl)-2*H*-pyrazole-3-carboxamide (11a)**. Mp >200°C (decomp.). Found, %: C 48.20; H 6.59; N 21.12. $C_8H_{13}N_3O_3$. Calculated, %: C 48.23; H 6.58; N 21.09.

***N*-(2,2-Dimethoxyethyl)-*N*-methyl-2*H*-pyrazole-3-carboxamide (11b)**. Mp >200°C (decomp.). Found, %: C 50.66; H 7.07; N 19.74. $C_9H_{15}N_3O_3$. Calculated, %: C 50.69; H 7.09; N 19.71.

5-(4-Chlorophenyl)-*N*-(2,2-dimethoxyethyl)-2*H*-pyrazole-3-carboxamide (11c). Mp >200°C (decomp.). Found, %: C 54.22; H 5.22; N 13.59. $C_{14}H_{16}ClN_3O_3$. Calculated, %: C 54.29; H 5.21; N 13.57.

5-(4-Chlorophenyl)-*N*-(2,2-dimethoxyethyl)-*N*-methyl-2*H*-pyrazole-3-carboxamide (11d). Mp >200°C (decomp.). Found, %: C 55.66; H 5.59; N 13.00. $C_{15}H_{18}ClN_3O_3$. Calculated, %: C 55.64; H 5.60; N 12.98.

***N*-(2,2-Dimethoxyethyl)-5-(4-methylphenyl)-2*H*-pyrazole-3-carboxamide (11e)**. Mp >200°C (decomp.). Found, %: C 62.31; H 6.61; N 14.50. $C_{15}H_{19}N_3O_3$. Calculated, %: C 62.27; H 6.62; N 14.52.

***N*-(2,2-Dimethoxyethyl)-*N*-methyl-5-(4-methylphenyl)-2*H*-pyrazole-3-carboxamide (11f)**. Mp >200°C (decomp.). Found, %: C 63.32; H 6.97; N 13.88. $C_{16}H_{21}N_3O_3$. Calculated, %: C 63.35; H 6.98; N 13.85.

Synthesis of 7-hydroxy-6,7-dihydropyrazolo[1,5-*a*]pyrazin-4(5*H*)-ones 12a,c,e and 7-methoxy-5-methyl-6,7-dihydropyrazolo[1,5-*a*]pyrazin-4(5*H*)-ones 12b,d,f (General Method). To the solution of corresponding amide **11a–f** (0.01 mol) in dioxane (10 ml) some drops of conc. HCl were added. The mixture was stirred at room temperature for 5–30 min (TLC control). Then H_2O (50 ml) was added, precipitate was filtered and washed with H_2O. 7-Hydroxy derivatives **12a**,**c**,**e** were recrystallized from DMF–H_2O (1:1), 7-methoxy derivatives **12b**,**d**,**f** were purified by column chromatography on silica gel, eluent EtOAc–hexane (1:1). Compounds **12a–f** obtained in a form of white solids; yields and ^{1}H NMR spectral data are given in Table.

7-Hydroxy-6,7-dihydropyrazolo[1,5-*a*]pyrazin-4(5*H*)-one (12a). Mp 195–196°C. ^{13}C NMR spectrum, δ, ppm: 46.2 (C-6); 75.6 (C-7); 107.0 (C-3); 133.6 (C-3a); 139.4 (C-2); 157.8 (C-4). Found, %: C 47.11; H 4.60; N 27.44. $C_6H_7N_3O_2$. Calculated, %: C 47.06; H 4.61; N 27.44.

7-Methoxy-5-methyl-6,7-dihydropyrazolo[1,5-*a*]pyrazin-4(5*H*)-one (12b). Mp 156–158°C. Found, %: C 52.99; H 6.12; N 23.22. $C_8H_{11}N_3O_2$. Calculated, %: C 53.03; H 6.12; N 23.19.

2-(4-Chlorophenyl)-7-hydroxy-6,7-dihydropyrazolo[1,5-*a*]pyrazin-4(5*H*)-one (12c). Mp 225–226°C. ^{13}C NMR spectrum, δ, ppm: 46.1 (C-6); 75.9 (C-7); 104.2 (C-3); 127.1 (C-2,6 Ar); 128.9 (C-3,5 Ar); 131.4 (C-*i* Ar); 132.7 (C-3a); 135.4 (C-4 Ar); 149.6 (C-2); 157.5 (C-4). Mass-spectrum, *m/z* (I_{rel}, %): 264.0 $[M+H]^+$ (55). Found, %: C 54.62; H 3.83; N 15.95. $C_{12}H_{10}ClN_3O_2$. Calculated, %: C 54.66; H 3.82; N 15.94.

2-(4-Chlorophenyl)-7-methoxy-5-methyl-6,7-dihydropyrazolo[1,5-*a*]pyrazin-4(5*H*)-one (12d). Mp 184–185°C. ^{13}C NMR spectrum, δ, ppm: 33.5 (NCH_3); 52.0 (C-6); 56.3 (OCH_3); 82.8 (C-7); 105.0 (C-3); 127.3 (C-2,6 Ar); 128.9 (C-3,5 Ar); 131.1 (C-*i* Ar); 132.9 (C-3a); 135.4 (C-4 Ar); 150.1 (C-2); 156.1 (C-4). Mass-spectrum, *m/z* (I_{rel}, %): 292.1 $[M+H]^+$ (53). Found, %: C 57.60; H 4.84; N 14.42. $C_{14}H_{14}ClN_3O_2$. Calculated, %: C 57.64; H 4.84; N 14.40.

7-Hydroxy-2-(4-methylphenyl)-6,7-dihydropyrazolo[1,5-*a*]pyrazin-4(5*H*)-one (12e). Mp 209–210°C. Mass-spectrum, *m/z* (I_{rel}, %): 244.3 $[M+H]^+$ (38). Found, %: C 64.22; H 5.39; N 17.25. $C_{13}H_{13}N_3O_2$. Calculated, %: C 64.19; H 5.39; N 17.27.

7-Methoxy-5-methyl-2-(4-methylphenyl)-6,7-dihydropyrazolo[1,5-*a*]pyrazin-4(5*H*)-one (12f). Mp 170–171°C. ^{13}C NMR spectrum, δ, ppm: 20.9 ($Ar\underline{C}H_3$); 33.5 (NCH_3); 52.1 (C-6); 56.2 (OCH_3); 82.7 (C-7); 104.5 (C-3); 125.5 (C-2,6 Ar); 129.4 (C-3,5 Ar); 132.9 (C-3a); 135.2 (C-*i* Ar); 137.7 (C-4 Ar); 151.3 (C-2); 156.1 (C-4). Found, %: C 66.37; H 6.33; N 15.52. $C_{15}H_{17}N_3O_2$. Calculated, %: C 66.40; H 6.32; N 15.49.

Synthesis of pyrazolo[1,5-*a*]pyrazin-4(5*H*)-ones 13a,b,e–h (General Method). To the solution of the corresponding compound **12a–f** (0.01 mol) in dioxane (10 ml) some drops

of conc. HCl were added. The mixture was stirred at 100°C for 2–5 h (TLC control). Then H_2O (50 ml) was added, the precipitate was filtered and washed with H_2O.

One-pot synthesis of substituted pyrazolo[1,5-*a*]pyrazin-4(5*H*)-ones 13a–i (General Method). A solution of the corresponding pyrazole-3-carboxilic acid **10a**–**f** (0.01 mol) in dry dioxane (10 ml) was mixed with CDI (1.78 g, 0.011 mol). The mixture was stirred at 50°C for 30 min (TLC control). Then 2,2-dimethoxyethanamine (1.15 g, 0.011 mol) or 2,2-dimethoxy-*N*-methylethanamine (1.30 g, 0.011 mol) was added, and the reaction mixture was stirred for additional 30 min (TLC control). After that, some drops of conc. HCl were added and mixture was stirred at 100°C for 2–5 h (TLC control). Then H_2O (50 ml) was added, precipitate was filtered and washed with H_2O.

Compounds **13b**,**f**,**h** were purified by column chromatography on silica gel, eluent EtOAc–hexane (1:1), the remaining compounds were recrystallized from DMF–H_2O (1:1). Compounds **13a–i** were obtained in a form of white solids; yields and ^{1}H NMR spectral data are given in Table.

Pyrazolo[1,5-*a*]pyrazin-4(5*H*)-one (13a). Mp 257–256°C. ^{13}C NMR spectrum, δ, ppm: 104.5 (C-3); 110.2 (C-7); 116.2 (C-6); 133.5 (C-3a); 140.4 (C-2); 155.6 (C-4). Mass-spectrum, *m/z* (I_{rel}, %): 271.2 $[2M+H]^+$ (55). Found, %: C 53.29; H 3.74; N 31.13. $C_6H_5N_3O$. Calculated, %: C 53.33; H 3.73; N 31.10.

5-Methylpyrazolo[1,5-*a*]pyrazin-4(5*H*)-one (13b). Mp 196–198°C. Found, %: C 56.40; H 4.74; N 28.15. $C_7H_7N_3O$. Calculated, %: C 56.37; H 4.73; N 28.17.

2-Methylpyrazolo[1,5-*a*]pyrazin-4(5*H*)-one (13c). Mp 233–234°C. ^{13}C NMR spectrum, δ, ppm: 13.3 (CH_3); 103.5 (C-3); 109.9 (C-7); 115.3 (C-6); 134.2 (C-3a); 149.4 (C-2); 155.3 (C-4). Found, %: C 56.36; H 4.73; N 28.20. $C_7H_7N_3O$. Calculated, %: C 56.37; H 4.73; N 28.17.

7,8,9,10-Tetrahydropyrazino[1,2-*b*]indazol-1(2*H*)-one (13d). Mp 277–279°C. Found, %: C 63.53; H 5.88; N 22.18. $C_{10}H_{11}N_3O$. Calculated, %: C 63.48; H 5.86; N 22.21.

2-(4-Chlorophenyl)pyrazolo[1,5-*a*]pyrazin-4(5*H*)-one (13e). Mp 292–295°C. ^{13}C NMR spectrum, δ, ppm: 101.6 (C-3); 110.1 (C-7); 116.7 (C-6); 127.5 (C-2,6 Ar); 128.9 (C-3,5 Ar); 130.9 (C-*i* Ar); 133.1 (C-3a); 135.2 (C-4 Ar); 150.2 (C-2); 155.4 (C-4). Mass-spectrum, *m/z* (I_{rel}, %): 246.1 $[M+H]^+$ (67). Found, %: C 58.71; H 3.27; N 17.11. $C_{12}H_8ClN_3O$. Calculated, %: C 58.67; H 3.28; N 17.10.

2-(4-Chlorophenyl)-5-methylpyrazolo[1,5-*a*]pyrazin-4(5*H*)-one (13f). Mp 231–233°C. Mass-spectrum, *m/z* (I_{rel}, %): 260.2 $[M+H]^+$ (63.4). Found, %: C 60.09; H 3.88; N 16.16. $C_{13}H_{10}ClN_3O$. Calculated, %: C 60.13; H 3.88; N 16.18.

2-(4-Methylphenyl)pyrazolo[1,5-*a*]pyrazin-4(5*H*)-one (13g). Mp 284–286°C. ^{13}C NMR spectrum, δ, ppm: 21.4 (CH_3); 101.6 (C-3); 110.7 (C-7); 116.8 (C-6); 126.5 (C-2,6 Ar); 130.0 (C-*i*,3,5 Ar); 133.0 (C-3a); 138.5 (C-4 Ar); 150.4 (C-2); 156.0 (C-4). Mass-spectrum, *m/z* (I_{rel}, %): 226.1 $[M+H]^+$ (37). Found, %: C 69.29; H 4.93; N 18.66. $C_{13}H_{11}N_3O$. Calculated, %: C 69.32; H 4.92; N 18.65.

5-Methyl-2-(4-methylphenyl)pyrazolo[1,5-*a*]pyrazin-4(5*H*)-one (13h). Mp 226–227°C. Mass-spectrum, *m/z* (I_{rel}, %): 240.0 $[M+H]^+$ (64). Found, %: C 70.33; H 5.50; N 17.55. $C_{14}H_{13}N_3O$. Calculated, %: C 70.28; H 5.48; N 17.56.

2-(2-Thienyl)pyrazolo[1,5-*a*]pyrazin-4(5*H*)-one (13i). Mp 279–281°C. Mass-spectrum, *m/z* (I_{rel}, %): 218.2 $[M+H]^+$ (21). Found, %: C 55.33; H 3.25; N 19.34. $C_{10}H_7N_3OS$. Calculated, %: C 55.29; H 3.25; N 19.34.

REFERENCES

1. H. M. Langford, P. D. Williams, C. F. Homnick, J. P. Vacca, P. J. Felock, K. A. Stillmock, M. V. Witmer, D. J. Hazuda, L. J. Gabryelski, W. A. Schleif, *Bioorg. Med. Chem. Lett.*, **18**, 721 (2008).
2. J. S. Wai, P. D. Williams, H. M. Langford, Pat. WO Appl. 2005120516.
3. S. Siegel, A. Wilmen, S. Roehrig, N. Svenstrup, M. J. Gnoth, S. Heitmeier, U. Rester, A. Tersteegen, M. Gerisch, Pat. WO Appl. 2009007029.

4. A. E. Weber, W. T. Ashton, Pat. WO Appl. 2006023750.
5. F. J. Pastor Fernandez, S. Martinez Gonzales, R. M. Alvarez Escobar, A. Rodriguez Hergueta, J. I. Martin Hernando, F. J. Ramos Lima, Pat. WO Appl. 2011089400.
6. J. Pastor Fernandez, S. Martinez Gonzales, A. Rodriguez Hergueta, F. J. Ramos Lima, R. M. Alvarez Escobar, A. I. Higueras Hernandes, Pat. WO Appl. 2011141713.
7. P. J. Conn, C. W. Lindsley, S. R. Stauffer, J. M. Bartolome-Nebreda, S. Conde-Ceide, G. J. Macdonald, H. M. Tong, C. K. Jones, M. J. Alcazar-Vaca, J. I. Andres-Gil, C. Malosh, Pat. WO Appl. 2012083224.
8. L.-W. Zheng, Z.-L. Gong, W.-L. Liu, Y.-R. Liu, B.-X. Zhao, *Spectrochim. Acta*, *Part A*, **81**, 372 (2011).
9. L. Llauger, C. Bergami, O. D. Kinzel, S. Lillini, G. Pescatore, C. Torrisi, P. Jones, *Tetrahedron Lett*., **50**, 172 (2009).
10. K. Kasuga, M. Hirobe, T. Okamoto, *Chem. Pharm. Bull*, **22**, 1814 (1974).
11. A. M. Zvonok, N. M. Kuz'menok, L. S. Stanishevskii, *Khim. Geterotsikl. Soedin.*, 1391 (1989). [*Chem. Heterocycl. Compd.*, **25**, 1164 (1989).]
12. A. C. Barrios Sosa, K. Yakushijin, D. A. Horne, *Tetrahedron Lett.*, **41**, 4295 (2000).
13. H. Jakobi, H. Helmke, T. Auler, M. Hills, H. Kehne, D. Feucht, K. Kather, Pat. DE Appl. 102004054665.

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

Received 4.03.2013

[2] *Institute for Single Crystals*
National Academy of Science of Ukraine,
60 Lenin Ave., Kharkiv 61001, *Ukraine*
e-mail: gorobets@isc.kharkov.com