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SYNTHESIS OF 4-HETARYL-2-(DICHLOROMETHYL)PYRAZOLO[1,5-*a*][1,3,5]-TRIAZINES

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New pyrazolo[1,5-*a*][1,3,5]triazines with a heteroaromatic substituent in position 4 and dichloromethyl moiety in position 2 were obtained *via* a heterocyclization reaction of readily available reagents - *N*-(2,2-dichloro-1-cyanoethenyl)carboxamides and 3(5)-aminopyrazoles. The high efficiency of the proposed method for the synthesis of 2-(dichloromethyl)-pyrazolo[1,5-*a*][1,3,5]triazines with furan-2-yl, thien-2-yl, and pyridine-3-yl substituents was demonstrated.

K e y w o r d s: *N*-(2,2-Dichloro-1-cyanoethenyl)carboxamide, 1*H*-pyrazol-5-amine, pyrazolo-[1,5-*a*][1,3,5]triazine.

INTRODUCTION. The heterocyclic system of pyrazolo[1,5-*a*][1,3,5]triazine can be considered isosteric to the purine system, and for this reason pyrazolo[1,5-*a*]-[1,3,5]triazines are also sometimes called 5-aza-9-deazapurines [1]. Molecules with this ring in their structure demonstrate a wide spectrum of biological activity that is heavily dependent on the nature of substituents in the heterocycle.

A family of pyrazolo[1,5-*a*]-[1,3,5]triazines with an aminogroup in position 4 and an aryl moiety in position 8 has demonstrated CRF (Cotricotropin-releasing factor) inhibitory activity and was considered as potential medicine for curing depression and anxiety. DMP696 (1, Fig. 1) is the best studied derivative in this regard [2].

Introducing an arylmercapto group into the structure of 4-amino-8-arylpyrazolo-[1,5-*a*][1,3,5]triazine (2, Fig. 1) imbues these molecules with antibacterial properties [3].

Furthermore, the research of new xanthin-oxidase inhibitors (to treat gout) has established that the activity of 8-methyl-5-aza-9-deazahypo-xanthine (3a, Fig. 1) is roughly three orders of magnitude higher than that of the unsubstituted 5-aza-9-deazahypoxanthine (3b) [4]. Plenty of examples like the above exist, and when reviewing the literature it’s easy to notice that

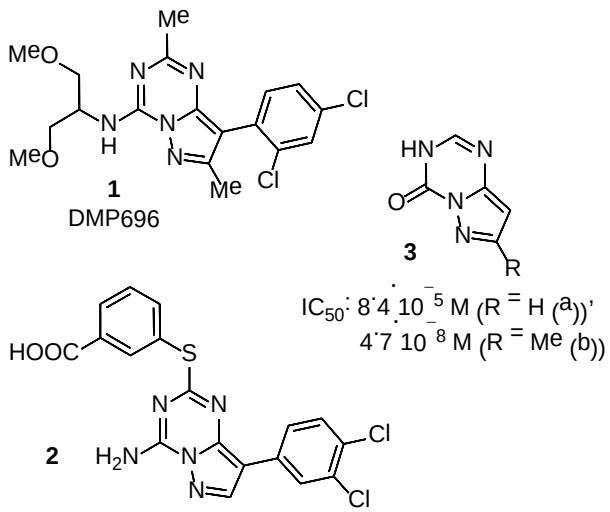


Fig. 1. Bioactive pyrazolo[1,5-*a*][1,3,5]triazines (literature data)

an important place among pyrazolo[1,5-*a*]-[1,3,5]triazines that have been synthesized and researched as bioactive compounds is occupied by 4-aminoderivatives [1]. Partly this is due to the peculiarities of the synthesis of these compound: the usual starting compounds for most pyrazolo[1,5-*a*][1,3,5]-triazines are 3(5)-aminopyrazoles [5] that, reacting as binucleophiles with *N*-cyanoamidines and their analogues, easily form various 4-aminopyrazolo[1,5-*a*][1,3,5]triazines. On the other side, in reactions with *N*-acylimidates 3(5)-aminopyrazoles give 4-alkyl- and 4-arylpyrazolo[1,5-*a*][1,3,5] triazines.

Therefore, varying electrophilic agents in 3(5)-aminopyrazole heterocyclization allows to obtain new functionalized pyrazolo-[1,5-*a*][1,3,5]triazines, and researching their biological activity is going to be the next task of interest.

The bielectrophile of our choosing became a derivative of ADAN – *N*-(2,2-dichloro-1-cyanoethenyl)carboxamide [6]. As the results of an interesting heterocyclization that was accompanied by the elimination of the CN group and formation of pyrazolo[1,5-*a*][1,3,5]triazines with a dichloromethyl group in position 2 [7]. Alternatively, previously we have synthesized 2,7-diaryl-4-(dichloro-methyl) pyrazolo-[1,5-*a*][1,3,5]triazines with yields up to 46% *via* interaction of 3-(5)-aminopyrazoles with 1-aryl-1,3,4,4-tetrachloro-2-azabuta-1,3-dienes [8].

Also we have found that pyrazolo-[1,5-*a*][1,3,5]triazines exhibit moderate antiviral activity [7]; in contrast, anticancer activity of some compounds from the group was quite potent [9]. Of particular interest is the fact that 4-aryl-2-(dichloromethyl)pyrazolo[1,5-*a*][1,3,5]-triazines have demonstrated high activity, while that of corresponding 4-alkylderivatives was very weak, which prompted us to synthesize derivatives with heteroaromatic substituents in position 4 for further biological studies.

EXPERIMENT AND DISCUSSION OF THE RESULTS. Synthesis of new 4-aminopyrazolo[1,5-*a*][1,3,5]triazines with a $CHCl_2$ group in position 2 was performed in four stages, starting from amides 4-6 with chloral (7). To obtain such compounds with $CHCl_2$ group and heterocyclic moiety, we used the previously developed heterocyclization [10, 11].

Condensation of amides of corresponding heteroaromatic acids 4-6 with chloral (7) led to *N*-(2,2,2-trichloro-1-hydroxyethyl)-amides 8-10, which reacted with thionyl chloride to give *N*-(1,2,2,2-tetrachloroethyl)-amides 11-13, which can be used in the next step without purification. The subsequent

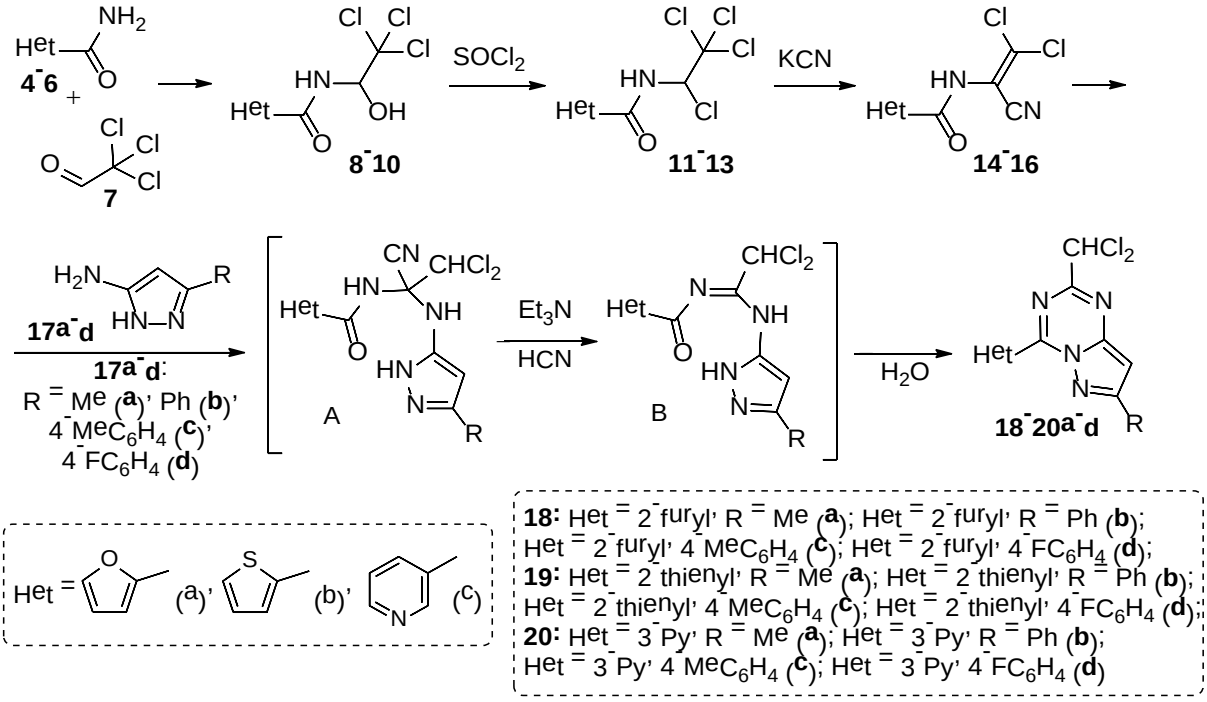
substitution of the chlorine atom in amides 11-13 with a cyano group gave access to *N*-(2,2-dichloro-1-cyanovinyl)-amides 14-16.
The final step was heterocyclization, which was based on the condensation of 1*H*-pyrazol-5-amines 17a-d with N-(2,2-dichloro-1-cyanovinyl) furan-2-carboxyamide 14, its thiophene analogue 15, and pyridine derivative 16 (Fig. 2). Key new compounds – 4-hetaryl-2-(dichloromethyl)-pyrazolo[1,5-*a*][1,3,5]triazines 18-20a-d were obtained in good yields (66-78%). This cyclocondensation occurs in several stages and involves the addition of an NH_2-group to the activated C-C double bond *via* form intermediate A with the subsequent triethylamine-promoted elimination of HCN, resulting in B that after the final intermolecular condensation gives products 18-20a-d. The developed procedure for the heterocyclization of the pyrazolo[1,5-*a*][1,3,5] triazine system provides high yields of target products 18-20a-d and is applicable to all three starting heterocyclic derivatives 14-16. The methods for the synthesis of the latter differed: for furan and thiophene derivatives – 14 and 15, it was possible to use the methodology developed and tested for *N*-(2,2-dichloro-1-cyanovinyl)carboxamides of aliphatic and aromatic acids [10, 11]; yet in the case of the basic pyridine cycle, it was necessary to adjust the method for processing the reaction mixture and isolating the product 16. We expect that this versatile protocol may be broadly applied to the synthesis of 2-(dichloromethyl)pyrazolo[1,5-*a*][1,3,5]-triazines.

The structures of synthesized compounds 18-20a-d were fully confirmed by spectral data and elemental analysis. The comparison of the reported ^{1}H NMR spectral data and spectra of compounds 18-20a-d revealed some abnormal chemical shifts for protons of heterocyclic moieties (furyl, thienyl and pyridyl) associated with electron-withdrawing triazine ring.

The furyl and thienyl proton signals of pyrazolo[1,5-*a*][1,3,5]triazines 18a-d and 19a-d in the NMR spectrum are deshielded (7.5–9.0 and 7.0–.6 ppm respectively) compared to unsubstituted furane and thiophene (about 6.0-7.5 and 6.5–7.5 ppm respectively). Proton chemical shifts of pyridine moiety for heterocycles 20a-d are also deshielded covered a range from 7.7 to 9.9 ppm. It should be noted that unsubstituted pyridine has corresponding shifts at about 7.0–8.5 ppm, therefore the chemical shifts in ^{1}H NMR of the heterocyclic moieties in compounds 18-20a-d differ by 1 ppm from those in the unsubstituted furane, thiophene and pyridine.

All reagents and solvents used in synthetic procedures were purchased from Aldrich and used as received. The reaction progress was monitored by the TLC method on Silica gel 60 F_{254} Merck. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra of obtained products were recorded at Varian Unityplus 400 spectrometer in DMSO-d_6 solution with TMS as the internal standard. IR spectra were recorded on a Vertex 70 spectrometer from KBr pellets. Melting points were measured on a Fisher-Johns instrument.

Chromatomass spectra were recorded on an Agilent 1100 Series high performance liquid chromatograph equipped with a diode matrix with an Agilent LC/MS mass selective detector allowing a fast switching of the



17a-d: R = Me (**a**), Ph (**b**), 4-MeC$_6$H$_4$ (**c**), 4-FC$_6$H$_4$ (**d**)

Het = 2-furyl (a), 2-thienyl (b), 3-Py (c)

18: Het = 2-furyl, R = Me (**a**); Het = 2-furyl, R = Ph (**b**); Het = 2-furyl, 4-MeC$_6$H$_4$ (**c**); Het = 2-furyl, 4-FC$_6$H$_4$ (**d**);
19: Het = 2-thienyl, R = Me (**a**); Het = 2-thienyl, R = Ph (**b**); Het = 2-thienyl, 4-MeC$_6$H$_4$ (**c**); Het = 2-thienyl, 4-FC$_6$H$_4$ (**d**);
20: Het = 3-Py, R = Me (**a**); Het = 3-Py, R = Ph (**b**); Het = 3-Py, 4-MeC$_6$H$_4$ (**c**); Het = 3-Py, 4-FC$_6$H$_4$ (**d**)

Fig. 2. Scheme of 4-(furan-2-yl/thien-2-yl/pyridin-3-yl)-2-(dichloromethyl)pyrazolo[1,5-*a*][1,3,5]-triazines 18-20a-d synthesis

positive/ negative ionization modes (chemical ionization).

Elemental analyses were performed at the Analytical Laboratory of the V.P. Kukhar Institute of Bioorganic Chemistry and Petrochemistry, NAS of Ukraine, their results were found to be in good agreement (±0.4%) with the calculated values.

General procedures of N-(2,2,2-trichloro-1-hydroxyethyl)amides 8-10 synthesis. The mixture of appropriate amide (1 mol), chloral hydrate (1.1 mol) and concentrated sulfuric acid (5 ml) was refluxed for 0.5 h. After cooling the water (300 ml) was added and the mixture was intensively stirred at room temperature. The precipitated crude product was filtered off and dried.

N-(2,2,2-Trichloro-1-hydroxyethyl)-2-furamide 8 was described in [12].

N-(2,2,2-Trichloro-1-hydroxyethyl) thiophene-2-carboxamide 9. Yield 250 g (91 %), white solid, mp 170–172 °C (benzene). IR, υ, cm^{-1}: 3311, 3179, 1632, 1537, 1416, 1103, 834, 719, 662. ^{1}H NMR, δ, ppm: 5.95–5.98 (1H, m, CH), 7.13–7.18 (1H, m, thienyl), 7.79-7.93 (2H, m, thienyl), 8.09 (1H, s, OH), 9.14 (1H, s, NH). ^{13}C NMR, δ, ppm: 81.8, 102.9, 128.6, 130.4, 132.7, 139.0, 161.7. MS, m/z 272 [M-H]$^-$. Found, %: C, 30.60; H, 2.19; Cl, 38.87; N, 5.27. $C_7H_6Cl_3NO_2S$. Calculated, %: C, 30.62; H, 2.20; Cl, 38.74; N, 5.10.

N-(2,2,2-Trichloro-1-hydroxyethyl)-nicotinamide 10 was described in [13].

General procedures of N-(2,2-dichloro-

1-cyanovinyl)amides 14 and 15 synthesis. The mixture of *N*-(2,2,2-trichloro-1-hydroxyethyl)amide 8, 9 (0.1 mol) in dry benzene (100 ml) and thionyl chloride (0.11 mol) was refluxed for 4 h. After cooling the mixture was evaporated to dryness. The crude product was washed by dry hexane to obtain the compound 11, 12.

Solution of appropriate *N*-(1,2,2,2-tetrachloroethyl)benzamide 11, 12 (0.1 mol) in dry dioxane (70 ml) was added dropwise to a stirred solution of KCN (0.2 mol) in water (30 ml) at -5–(-10) ºC. The solution was stirred for 4 h. The precipitated crude product was filtered off, washed with cold water, dried and recrystallized from toluene.

N-(2,2-Dichloro-1-cyanovinyl)-2-furamide 14. Yield 19 g (82 %), brown solid, mp 104–106 °C (benzene). IR, υ, cm^{-1}: 3287, 3138, 2240, 1694, 1593, 1491, 1464, 1305, 1179, 1108, 971, 948, 764, 594. ^{1}H NMR, δ, ppm: 6.67 (1H, s, furyl), 7.35 (1H, s, furyl), 7.94 (1H, s, furyl), 10.55 (1H, s, NH). ^{13}C NMR, δ, ppm: 110.6, 112.9, 113.2, 117.3, 135.7, 145.8, 147.4, 156.3. MS, m/z 233 $[M+H]^+$. Found, %: C, 41.57; H, 1.72; Cl, 30.83; N, 12.23. $C_8H_4Cl_2N_2O_2$. Calculated, %: C, 41.59; H, 1.75; Cl, 30.69; N, 12.12.

N-(2,2-Dichloro-1-cyanovinyl)thiophene-2-carboxamide 15. Yield 20 g (81 %), white solid, mp 131–133 °C (benzene). IR, υ, cm^{-1}: 3217, 2963, 2233, 1639, 1602, 1529, 1488, 1299, 1102, 964, 900, 854, 636. ^{1}H NMR, δ, ppm (*J*, Hz): 7.24 (1H, t, *J* = 4.4 Hz, thienyl), 7.96–7.98 (2H, m, thienyl), 10.69 (1H, s, NH). ^{13}C NMR, δ, ppm: 111.1, 113.4, 129.0, 131.6, 134.2, 135.4, 136.8, 160.3. MS, m/z 249 $[M+H]^+$. Found, %: C, 38.87; H, 1.60; Cl, 28.81; N, 11.44; S, 12.88. $C_8H_4Cl_2N_2OS$. Calculated, %: C, 38.89; H, 1.63; Cl, 28.69; N, 11.34; S, 12.98.

Procedures of *N*-(2,2-dichloro-1-cyanovinyl)nicotinamide 16 synthesis.

The mixture of *N*-(2,2,2-trichloro-1-hydroxyethyl)nicotinamide 10 (0.1 mol) in dry benzene (100 ml) and thionyl chloride (0.11 mol) was refluxed for 4 h. After cooling the mixture was evaporated to dryness. The crude product was washed by dry hexane to obtain compound 13.

Solution of *N*-(1,2,2,2-tetrachloroethyl)nicotinamide 13 (0.1 mol) in dry dioxane (70 ml) was added dropwise to a stirred solution of KCN (0.2 mol) in water (30 ml) at -5– (-10) ºC. The mixture was stirred for 4 h and evaporated until a precipitate appeared. The precipitated crude product was filtered off, washed with cold water, dried and recrystallized.

N-(2,2-Dichloro-1-cyanovinyl)nicotinamide 16. Yield 19 g (78 %), brown solid, mp 129–131 °C (benzene). IR, υ, cm^{-1}: 3229, 2963, 2233, 1662, 1593, 1491, 1422, 1302, 1199, 1122, 963, 890, 703, 636. ^{1}H NMR, δ, ppm: 7.54 (1H, s, pyridyl), 8.28 (1H, s, pyridyl), 8.76 (1H, s, pyridyl), 9.06 (1H, s, pyridyl), 11.02 (1H, s, NH). ^{13}C NMR, δ, ppm: 111.1, 113.2, 124.1, 128.0, 135.4, 136.3, 149.4, 153.6, 164.6. MS, m/z 243 $[M+H]^+$. Found, %: C, 44.64; H, 2.05; Cl, 29.38; N, 17.45. $C_9H_5Cl_2N_3O$. Calculated, %: C, 44.66; H, 2.08; Cl, 29.29; N, 17.36.

General procedures of 2-(dichloromethyl)pyrazolo[1,5-*a*][1,3,5]triazines 18-20a-d synthesis. To a solution of 2-acylamino-3,3-dichloroacrylonitrile 14-16 (0.01 mol) in 10 ml of THF, 5-aminopyrazole 17a-d (0.01 mol) and Et_3N

(1.39 ml, 0.01 mol) were added. The mixture was stirred at room temperature for 24 h, and then heated at 55–60 °C for 2 h. After solvent evaporation the residue was triturated with water to give a crude product which was dried and recrystallized to obtain yellow or brownish crystals.

2-Dichloromethyl-4-(furan-2-yl)-7-methylpyrazolo[1,5-*a*][1,3,5]triazine 18a. Yield 1.86 g (66 %), yellow solid, mp 187–189 °C (MeCN). IR, υ, cm^{-1}: 3118, 2996, 1606, 1577, 1502, 1459, 1361, 1262, 1143, 1031, 785, 712, 661, 533. ^{1}H NMR, δ, ppm (*J*, Hz): 2.55 (3H, s, CH_3), 6.79 (1H, s, C<u>H</u>Cl_2 or C-H pyrazole), 6.98–6.99 (1H, m, furan), 7.38 (1H, s, C<u>H</u>Cl_2 or C-H pyrazole), 8.33 (1H, s, C-H furan), 8.44 (1H, d, *J* = 2.9 Hz, C-H furan). ^{13}C NMR, δ, ppm: 15.2, 71.5, 98.1, 114.4, 125.9, 142.9, 144.8, 149.7, 150.4, 157.9, 159.2. MS, m/z 285 $[M+H]^+$. Found, %: C, 46.65; H, 2.82; Cl, 25.12; N, 19.70. $C_{11}H_8Cl_2N_4O$. Calculated (%): C, 46.67; H, 2.85; Cl, 25.04; N, 19.79.

2-Dichloromethyl-4-(furan-2-yl)-7-phenylpyrazolo[1,5-*a*][1,3,5]triazine 18b. Yield 2.58 g (75 %), brown solid, mp 203–205 °C (MeCN : DMF, 4 : 1). IR, υ, cm^{-1}: 3117, 3009, 2924, 1605, 1568, 1494, 1461, 1360, 1265, 1024, 766, 689, 654, 556. ^{1}H NMR, δ, ppm (*J*, Hz): 7.03 (1H, m, C<u>H</u>Cl_2 or C-H pyrazole), 7.41 (1H, d, *J* = 1.5 Hz, C-H furan), 7.50–7.57 (4H, m, C<u>H</u>Cl_2 or C-H pyrazole, H-3,4,5 Ph), 8.20 (2H, d, *J* = 7.8 Hz, H-2,6 Ph), 8.36 (1H, s, C-H furan), 8.63 (1H, d, *J* = 3.9 Hz, C-H furan). ^{13}C NMR, δ, ppm: 71.5, 95.3, 114.6, 126.4, 127.4, 129.5, 130.7, 131.7, 142.9, 145.2, 150.5, 150.6, 158.1, 159.0. MS, m/z 345 $[M+H]^+$. Found, %: C, 55.65; H, 2.88; Cl, 20.60; N, 16.30. $C_{16}H_{10}Cl_2N_4O$. Calculated (%): C, 55.67; H, 2.92; Cl, 20.54; N, 16.23.

2-Dichloromethyl-4-(furan-2-yl)-7-p-tolyl-pyrazolo[1,5-*a*][1,3,5]triazine 18c. Yield 2.61 g (73 %), brown solid, mp 209–211 °C (MeCN : DMF, 4 : 1). IR, υ, cm^{-1}: 3129, 2923, 1605, 1564, 1496, 1448, 1358, 1261, 1228, 1150, 1024, 790, 773, 741, 659. ^{1}H NMR, δ, ppm (*J*, Hz): 2.39 (3H, s, CH_3, Ar), 7.02–7.04 (1H, m, C-H furan), 7.35 (2H, d, *J* = 8.3 Hz, H-3,5 Ar), 7.41 (1H, s, C<u>H</u>Cl_2 or C-H, pyrazole), 7.45 (1H, s, C<u>H</u>Cl_2 or C-H pyrazole), 8.09 (2H, d, *J* = 8.3 Hz, H-2,6 Ar), 8.36 (1H, s, C-H furan), 8.63 (1H, d, *J* = 3.4 Hz, C-H furan). ^{13}C NMR, δ, ppm: 21.5, 71.5, 95.0, 114.6, 126.3, 127.3, 128.9, 130.1, 140.5, 142.9, 145.1, 150.5, 150.5, 158.1, 159.1. MS, m/z 359 $[M+H]^+$. Found, %: C, 56.80; H, 3.35; Cl, 19.80; N, 15.55. $C_{17}H_{12}Cl_2N_4O$. Calculated (%): C, 56.84; H, 3.37; Cl, 19.74; N, 15.60.

2-Dichloromethyl-7-(4-fluorophenyl)-4-(furan-2-yl)pyrazolo[1,5-*a*][1,3,5]triazine 18d. Yield 2.40 g (66 %), brown solid, mp 191–193 °C (MeCN : DMF, 4 : 1). IR, υ, cm^{-1}: 3121, 3000, 1609, 1570, 1494, 1449, 1358, 1267, 1234, 1155, 1026, 844, 783, 657, 523. ^{1}H NMR, δ, ppm (*J*, Hz): 7.02–7.03 (1H, m, furan), 7.36–7.42 (3H, m, C<u>H</u>Cl_2 or C-H pyrazole, H-3,5 Ar), 7.50 (1H, s, C<u>H</u>Cl_2 or C-H pyrazole), 8.24–8.28 (2H, m, H-2,6 Ar), 8.36 (1H, s, C-H, furan), 8.62 (1H, d, *J* = 3.4 Hz, furan). ^{13}C NMR, δ, ppm (*J*, Hz): 71.5, 95.3, 114.6, 116.6 (d, *J* = 21.4 Hz), 126.5, 128.3 (d, *J* = 3.0 Hz) 129.7 (*J* = 8.5 Hz), 142.8, 145.2, 150.5, 150.6, 158.0, 158.2, 163.8 (d, *J* = 247.3 Hz). MS, m/z 363 $[M+H]^+$. Found, %: C, 52.96; H, 2.53; Cl, 19.58; N, 15.50. $C_{16}H_9Cl_2FN_4O$. Calculated (%): C, 52.92; H, 2.50; Cl, 19.52;

N, 15.43.

2-Dichloromethyl-7-methyl-4-(thien-2-yl)pyrazolo[1,5-*a*][1,3,5]triazine 19a. Yield 2.03 g (68 %), light yellow solid, mp 168–170 °C (EtOH : MeCN, 4 : 1). IR, υ, cm^{-1}: 3107, 3029, 3107, 1595, 1527, 1475, 1247, 851, 771, 716, 652, 521. ^{1}H NMR, δ, ppm: 2.57 (3H, s, CH_3), 6.80 (1H, s, C<u>H</u>Cl_2 or C-H pyrazole), 7.38 (1H, s, C<u>H</u>Cl_2 or C-H pyrazole), 7.45–7.47 (1H, m, C-H thiophen), 8.28–8.30 (1H, m, C-H, thiophen), 8.92–8.93 (1H, m, C-H thiophen). ^{13}C NMR, δ, ppm: 15.2, 71.4, 97.9, 129.6, 131.9, 138.0, 138.5, 149.0, 150.0, 157.8, 159.3. MS, m/z 299 $[M+H]^+$. Found, %: C, 44.20; H, 2.68; Cl, 23.80; N, 18.77; S, 10.68. $C_{11}H_8Cl_2N_4S$. Calculated (%): C, 44.16; H, 2.70; Cl, 23.70; N, 18.73; S, 10.72.

2-Dichloromethyl-7-phenyl-4-(thien-2-yl)pyrazolo[1,5-*a*][1,3,5]triazine 19b. Yield 2.53 g (70 %), yellow solid, mp 189–191 °C (MeCN). IR, υ, cm^{-1}: 3102, 2924, 1598, 1524, 1463, 1253, 853, 766, 650, 554. ^{1}H NMR, δ, ppm (*J*, Hz): 7.40 (1H, s, C<u>H</u>Cl_2 or C-H pyrazole), 7.49–7.59 (5H, m, C<u>H</u>Cl_2 or C-H pyrazole, C-H thiophen, H-3,4,5 Ph), 8.21 (2H, d, *J* = 6.8 Hz, H-2,6 Ph), 8.34 (1H, d, *J* = 1.6 Hz, C-H thiophen), 8.99–9.00 (1H, m, C-H, thiophen). ^{13}C NMR, δ, ppm: 71.4, 95.2, 127.4, 129.6, 129.7, 130.8, 131.7, 131.8, 138.1, 139.0, 149.6, 150.8, 158.2, 159.0. MS, m/z 363 $[M+H]^+$. Found, %: C, 53.17; H, 2.80; Cl, 19.70; N, 15.56; S, 8.82. $C_{16}H_{10}Cl_2N_4S$. Calculated (%): C, 53.20; H, 2.79; Cl, 19.63; N, 15.51; S, 8.88.

2-Dichloromethyl-4-(thien-2-yl)-7-*p*-tolylpyrazolo[1,5-*a*][1,3,5]triazine 19c. Yield 2.81 g (75 %), yellow solid, mp 195–197 °C (MeCN). IR, υ, cm^{-1}: 3100, 2917, 1596, 1524, 1448, 1221, 854, 794, 726, 654. ^{1}H NMR, δ, ppm (*J*, Hz): 2.39 (3H, s, CH_3, Ar), 7.35–7.49 (5H, m, C<u>H</u>Cl_2, C-H pyrazole, C-H thiophen, H-3,5 Ar), 8.08 (2H, d, *J* = 7.2 Hz, H-2,6 Ar), 8.32–8.33 (1H, m, C-H thiophen), 8.97 (1H, s, C-H thiophen). ^{13}C NMR, δ, ppm (*J*, Hz): 21.6, 71.5, 94.9, 127.3, 128.9, 129.7, 130.2, 131.8, 138.1, 138.9, 140.6, 149.5, 150.8, 158.2, 159.1. MS, m/z 377 $[M+H]^+$. Found, %: C, 54.40; H, 3.24; Cl, 18.95; N, 15.00; S, 8.50. $C_{17}H_{12}Cl_2N_4S$. Calculated (%): C, 54.41; H, 3.22; Cl, 18.89; N, 14.93; S, 8.54.

2-Dichloromethyl-7-(4-fluorophenyl)-4-(thien-2-yl)pyrazolo[1,5-*a*][1,3,5]triazine 19d. Yield 2.65 g (70 %), yellow solid, mp 210–212 °C (MeCN : DMF, 3 : 1). IR, υ, cm^{-1}: 3100, 2924, 1606, 1584, 1525, 1478, 1451, 1228, 839, 793, 736, 667, 521. ^{1}H NMR, δ, ppm: 7.41–7.52 (5H, m, $CHCl_2$, C-H pyrazole, H thiophen, H-3,5 Ar), 8.26–8.35 (3H, m, H-2,6 Ar, C-H thiophen), 8.99–9.00 (1H, m, C-H, thiophen). ^{13}C NMR, δ, ppm (*J*, Hz): 70.4, 94.4, 116.1, 127.8, 128.6, 129.0, 131.6, 137.3, 137.7, 150.7, 158.3, 158.6, 162.1, 164.0. MS, m/z 379 $[M+H]^+$. Found, %: C, 50.70; H, 2.40; Cl, 18.75; N, 14.82; S, 8.50. $C_{16}H_9Cl_2FN_4S$. Calculated (%): C, 50.67; H, 2.39; Cl, 18.70; N, 14.77; S, 8.45.

2-(Dichloromethyl)-7-methyl-4-(pyridin-3-yl)pyrazolo[1,5-*a*][1,3,5]triazine 20a. Yield 2.3 g (78 %), brown solid, mp 119–121 °C (EtOH). IR, υ, cm^{-1}: 3085, 2995, 1600, 1505, 1469, 1371, 1219, 1126, 1018, 836, 777, 700, 530. ^{1}H NMR, δ, ppm: 2.53 (3H, s, CH_3), 6.85 (1H, s, C<u>H</u>Cl_2 or C-H pyrazolyl), 7.43 (1H, s, C<u>H</u>Cl_2 or C-H pyrazolyl), 7.69–7.75 (1H, m, pyridyl), 8.86–8.90 (1H, m, pyridyl), 8.95–9.00 (1H, m, pyridyl), 9.75 (1H, s, pyridyl). ^{13}C NMR,

δ, ppm: 71.3, 95.5, 124.0, 126.4, 127.2, 129.5, 130.7, 131.5, 139.0, 150.9, 151.8, 153.4, 153.9, 158.0, 159.0. MS, m/z 296 $[M+H]^+$. Found, %: C, 49.02; H, 3.05; Cl, 24.21; N, 23.91. $C_{12}H_9Cl_2N_5$. Calculated, %: C, 49.00; H, 3.08; Cl, 24.11; N, 23.81.

2-(Dichloromethyl)-7-phenyl-4-(pyridin-3-yl)pyrazolo[1,5-*a*][1,3,5]triazine 20b. Yield 2.6 g (73 %), brown solid, mp 165–167 °C (MeCN). IR, υ, cm^{-1}: 3087, 3003, 1604, 1581, 1517, 1460, 1389, 1228, 1192, 1023, 796, 767, 691, 557. ^{1}H NMR, δ, ppm (*J*, Hz): 7.41 (1H, s, Ph), 7.50–7.54 (4H, m, Ph), 7.76 (1H, t, *J* = 8.0 Hz, pyridyl), 8.12 (1H, s, C<u>H</u>Cl_2 or C-H pyrazolyl), 8.13 (1H, s, C<u>H</u>Cl_2 or C-H pyrazolyl), 8.91–8.92 (1H, m, pyridyl), 9.13 (1H, d, *J* = 7.2 Hz, pyridyl), 9.89 (1H, m, pyridyl). ^{13}C NMR, δ, ppm: 71.3, 95.5, 124.0, 126.4, 127.2, 129.5, 130.7, 131.5, 139.0, 150.9, 151.8, 153.4, 153.9, 158.0, 159.0. MS, m/z 358 $[M+H]^+$. Found, %: C, 57.29; H, 3.10; Cl, 19.99; N, 19.78. $C_{17}H_{11}Cl_2N_5$. Calculated, %: C, 57.32; H, 3.11; Cl, 19.91; N, 19.66.

2-(Dichloromethyl)-7-(4-methylphenyl)-4-(pyridin-3-yl)pyrazolo[1,5-*a*][1,3,5]-triazine 20c. Yield 2.9 g (78 %), brown solid, mp 184–186 °C (MeCN). IR, υ, cm^{-1}: 3009, 2957, 1598, 1583, 1521, 1477, 1386, 1227, 1185, 1023, 838, 787, 692, 555. ^{1}H NMR, δ, ppm (*J*, Hz): 2.39 (3H, s, CH_3), 7.39–7.46 (4H, m, Ph), 7.76 (1H, t, *J* = 5.4 Hz, pyridyl), 8.01 (1H, s, C<u>H</u>Cl_2 or C-H pyrazolyl), 8.02 (1H, s, C<u>H</u>Cl_2 or C-H pyrazolyl), 8.91–8.92 (1H, m, pyridyl), 9.11-9.13 (1H, m, pyridyl), 9.88 (1H, s, pyridyl). ^{13}C NMR, δ, ppm: 21.5, 71.3, 95.2, 124.1, 124.3, 127.2, 129.8, 130.1, 130.7, 139.1, 150.9, 151.8, 153.3, 153.9, 159.2, 159.3. MS, m/z 372 $[M+H]^+$. Found, %: C, 58.35; H, 3.55; Cl, 19.36; N, 18.99. $C_{18}H_{13}Cl_2N_5$. Calculated, %: C, 58.39; H, 3.54; Cl, 19.15; N, 18.92.

2-(Dichloromethyl)-7-(4-fluorophenyl)-4-(pyridin-3-yl)pyrazolo[1,5-*a*][1,3,5]-triazine 20d. Yield 2.9 g (78 %), brown solid, mp 185–187 °C (MeCN). IR, υ, cm^{-1}: 3079, 3016, 1609, 1589, 1503, 1471, 1369, 1230, 1197, 1027, 841, 746, 562. ^{1}H NMR, δ, ppm (*J*, Hz): 2.39 (3H, s, CH_3), 7.32–7.40 (3H, m, Ph), 7.47–7.48 (1H, m, Ph), 7.74 (1H, t, *J* = 5.6 Hz, pyridyl), 8.16 (1H, s, C<u>H</u>Cl_2 or C-H pyrazolyl), 8.18 (1H, s, C<u>H</u>Cl_2 or C-H pyrazolyl), 8.90–8.91 (1H, m, pyridyl), 9.10–9.12 (1H, m, pyridyl), 9.87 (1H, s, pyridyl). ^{13}C NMR, δ, ppm: 71.3, 95.4, 116.4, 116.6, 124.0, 126.3, 128.0, 129.5, 129.6, 139.0, 150.9, 151.8, 153.4, 153.9, 158.0. MS, m/z 374 $[M+H]^+$. Found, %: C, 54.59; H, 2.66, Cl, 18.88; N, 18.79. $C_{17}H_{10}Cl_2FN_5$. Calculated, %: C, 54.57; H, 2.69, Cl, 18.95; N, 18.72.

CONCLUSIONS. A series of new pyrazolo[1,5-*a*][1,3,5]triazines with a heteroaromatic substituent in position 4 and dichloromethyl moiety in position 2 was obtained *via* a heterocyclization accompanied by hydrogen cyanide elimination. The reaction involved readily available reagents – *N*-(2,2-dichloro-1-cyanoethenyl)carboxamides and 3(5)-aminopyrazoles. The heterocyclic moiety has little effect on the efficiency of the method and the yields of 2-(dichloromethyl)pyrazolo[1,5-*a*][1,3,5]triazines with furan-2-yl, thien-2-yl, and pyridine-3-yl moieties, which makes the method suitable for the synthesis of other 4-hetaryl-2-(dichloromethyl)pyrazolo[1,5-*a*][1,3,5]-triazines.

СИНТЕЗ 4-ГЕТАРИЛ-2-(ДИХЛОРОМЕТИЛ)-ПІРАЗОЛО[1,5-*a*][1,3,5]ТРИАЗИНІВ

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Шляхом гетероциклізації легкодоступних реагентів – *N*-(2,2-дихлор-1-ціаноетеніл)карбоксамідів та 3(5)-амінопіразолів – синтезовано нові піразоло[1,5-*a*][1,3,5]-триазини з гетероароматичним замісником в положенні 4 та дихлорометильним фрагментом в положенні 2. Продемонстровано високу ефективність запропонованого способу синтезу 2-(дихлорометил)-піразоло[1,5-*a*]-[1,3,5]триазинів з фуран-2-ільним, тієн-2-ільним і піридин-3-ільним замісниками.

Ключові слова: *N*-(2,2-Дихлоро-1-ціаноетеніл)карбоксамід, 1*H*-піразол-5-амін, піразоло[1,5-*a*][1,3,5]триазин.

СИНТЕЗ 4-ГЕТАРИЛ-2-(ДИХЛОРМЕТИЛ)-ПИРАЗОЛО[1,5-*a*][1,3,5]ТРИАЗИНОВ

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Путем гетероциклизации легкодоступных реагентов – *N*-(2,2-дихлор-1-цианоэтенил)карбоксамидов и 3(5)-аминопиразолов – получены новые пиразоло-[1,5-*a*][1,3,5]триазины с гетероароматическим заместителем в положении 4 и дихлорометильной группой в положении 2. Продемонстрирована высокая эффективность предлагаемого способа синтеза 2-(дихлорметил)пиразоло[1,5-*a*][1,3,5]триазинов с фуран-2-ильным, тиен-2-ильным и пиридин-3-ильным заместителями.

Ключевые слова: *N*-(2,2-Дихлор-1-цианоэтенил)карбоксамид, 1*H*-пиразол-5-амин, пиразоло-[1,5-*a*][1,3,5]триазин.

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