N-(2,2-Dichloro-1-cyanoethenyl)carboxamides 1 are known to be highly reactive electrophilic reagents suitable for the synthesis of heterocyclic compounds. Two research groups headed by K. Matsumura and B. Drach began independently in the 1970s studying the cyclocondensation of these reagents with N-nucleophiles. It was found that the reaction of 1 with ammonia, high basicity amines, and hydrazine leads to the oxazole ring formation that has become a common method for the production of 5-amino-4-cyanooxazoles 2 (Scheme 1) [1–3]. A quite unusual cycloaddition of benzamidine to compounds 1 reported by Drach and co-workers was featured by the

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participation of a cyano group to provide imidazole derivatives 3 [4]. Surprisingly, both an acylamino and a dichloromethylene group do not react herein.

It would be of interest to examine other amidine-like species for such a cyclization. Aminoazoles seemed to be quite suitable for this purpose. Among all these, we chose aminopyrazoles, which are frequently used as building blocks for the syntheses of fused ring systems, especially in bioorganic and medicinal chemistry. They can be readily prepared by the condensation of 1,3-difunctional nitrile compounds with hydrazines [5-7].

The aim of this work was to study the interaction of $N$-(2,2-dichloro-1-cyanoethenyl)carboxamides 1 with some $1H$-pyrazol-5-amines 4 under various conditions. The most interesting result was achieved, when these reagents were heated in tetrahydrofuran in the presence of triethylamine (Scheme 2). New pyrazolo[1,5-$a$][1,3,5]triazine derivatives 7 were unexpectedly obtained therewith in good yield.

Apparently, cyclocondensation 1 $\rightarrow$ 7 consists of the following steps: i) the addition of an NH$_2$ group to the activated C=C bond to form intermediates 5; ii) the elimination of hydrogen cyanide promoted by triethylamine to give 6; iii) the intramolecular condensation of the latter into the final products 7.

Compounds 7 are tan solids, melting in the interval 150-190 °C. Their structure was established with the help of IR, NMR spectroscopy, and mass spectrometry. $^1H$ NMR of CHCl$_2$ and pyrazole CH group occurs in the region 6.7-7.8 ppm. In the spectrum of 7e, for example, there are two distinguished one-proton singlets at 6.75 and 7.33 ppm. For other samples, one or both of these signals are overlapped with those of ArH multiplets. X-ray crystal analysis of 7b was also performed to exclude the isomeric 4-(dichloromethyl)pyrazolo[1,5-$a$][1,3,5]triazine structure, which can be realized because of the initial pyrazole endocyclic NH addition to the C=C bond.

To judge the possibility of converting a CHCl$_2$ group into a CHO, product 7a was acted by boiling MeONa/MeOH, AcONa/AcOH, and Na$_2$S/H$_2$O/EtOH solutions. But, in all cases, only the starting material was quantitatively recovered. On the other hand, the heating of 7a with
Synthesis and evaluation of the antiviral activity of 2-(dichloromethyl)pyrazolo[1,5-a][1,3,5]triazines

Hydrochloric or sulfuric acid leads to the 1,3,5-triazine ring cleavage to yield a salt of 3-phenyl-1-H-pyrazol-5-amine 4a.

**General preparation procedure for pyrazolo[1,5-a][1,3,5]triazines 7.** To a solution of amide 1a [8] or 1b [9] (0.01 mol) in THF (10 mL), one of pyrazolamines 4a [10], 4b [11], 4c [12] (0.01 mol) followed by triethylamine (0.01 mol) were added. The mixture was stirred at room temperature during 24 h and then heated at 55–60 °C for 2 h. After evaporating the solvent in vacuum, the residue was triturated with water to give a crude product, which was separated and recrystallized for the analysis.

2-(Dichloromethyl)-4,7-diphenylpyrazolo[1,5-a][1,3,5]triazine (7a). Yield 2.66 g (75 %), light yellow solid, mp 154–156 °C (EtOH+MeCN, 2:1). 

1H NMR spectrum (400 MHz, DMSO- d6), δ, ppm (J, Hz): 7.47 (1H, s), 7.52–7.59 (4H, m), 7.72–7.82 (3H, m), 8.16 (2H, d, J = 7.2), 8.84 (2H, d, J = 7.2). 13C NMR spectrum (101 MHz, DMSO-d6), δ, ppm: 71.5, 95.4, 127.4, 129.1, 129.6, 130.0, 130.7, 131.7, 134.2, 151.2, 154.9, 157.0, 158.1, 158.9. Mass spectrum, m/z: 355 [M+H]+. Found, %: C 60.83; H 3.39; Cl 20.04; N 15.82. C18H12Cl2N4. Calculated, %: C 60.86; H 3.41; Cl 19.96; N 15.77.

2-(Dichloromethyl)-7-(4-methyl-phenyl)-4-phenylpyrazolo[1,5-a][1,3,5]triazine (7b). Yield 2.58 g (70 %), dark yellow solid, mp 190–192 °C (MeCN).

1H NMR spectrum (400 MHz, DMSO- d6), δ, ppm: 2.40 (3H, s), 7.39-7.52 (4H, m), 7.76-7.81 (3H, m), 8.07 (2H, s), 8.85 (2H, s). 13C NMR spectrum (101 MHz, DMSO-d6), δ, ppm: 21.5, 71.5, 95.1, 127.2, 128.9, 129.1, 130.0, 130.1, 131.7, 134.1, 140.5, 151.2, 154.7, 158.1, 159.0. Mass spectrum, m/z: 369 [M+H]+. Found, %: C 61.78; H 3.80; Cl 19.11; N 15.10. C19H14Cl2N4. Calculated, %: C 61.80; H 3.82; Cl 19.20; N 15.17.

2-(Dichloromethyl)-4-(4-methyl-phenyl)-7-phenylpyrazolo[1,5-a][1,3,5]triazine (7c). Yield 2.87 g (78 %), dark yellow solid, mp 163–165 °C (MeCN).

1H NMR spectrum (400 MHz, DMSO- d6), δ, ppm (J, Hz): 2.46 (3H, s), 7.43 (1H, s), 7.43-7.56 (6H, m), 8.13 (2H, d, J = 8.0), 8.77 (2H, d, J = 8.4). 13C NMR spectrum (101 MHz, DMSO-d6), δ, ppm: 21.9, 71.5, 95.2, 127.1, 127.3, 129.5, 129.7, 130.7, 131.7, 131.8, 144.9, 151.2, 154.6, 158.1, 158.8. Mass spectrum, m/z: 369 [M+H]+. Found, %: C 61.75; H 3.80; Cl 19.06; N 15.22. C19H14Cl2N4. Calculated, %: C 61.80; H 3.82; Cl 19.20; N 15.17.

**Antiviral activity and cytotoxicity of compounds 7a-e**

| Compd | EC50 | EC90 | CC50 | SI50 | SI90 |
|-------|------|------|------|------|------|
| Assay iv (Human cytomegalovirus) |
| 7a    | >1.20 | >1.20 | 3.86 | <3  | <3  |
| 7b    | >6.00 | >6.00 | 19.48 | <3  | <3  |
| 7c    | >6.00 | >6.00 | 14.69 | <2  | <2  |
| 7d    | 24.32 | >150.00 | >150.00 | >6  | 1   |
| 7e    | >30.00 | >30.00 | 70.63 | <2  | <2  |
| Ganciclovir | 4.65 | 15.80 | >100.00 | >21 | >6  |

| Assay v (Herpes simplex virus 1) |
| 7a    | >1.20 | >1.20 | 4.04 | <3  | <3  |
| 7b    | >30.00 | >30.00 | 31.37 | <1  | <1  |
| 7c    | >6.00 | >6.00 | 15.70 | <3  | <3  |
| 7d    | >150.00 | >150.00 | >150.00 | 1   | 1   |
| 7e    | >6.00 | >6.00 | 22.18 | <4  | <4  |
| Acyclovir | 0.78 | 13.55 | >150.00 | >192 | >11 |

| Assay vi (Varicella-Zoster virus) |
| 7a    | >1.20 | >1.20 | 4.15 | <3  | <3  |
| 7b    | >6.00 | >6.00 | 17.19 | <3  | <3  |
| 7c    | >6.00 | >6.00 | 15.88 | <3  | <3  |
| 7d    | >150.00 | >150.00 | >150.00 | 1   | 1   |
| 7e    | >6.00 | >6.00 | 19.24 | <3  | <3  |
| Acyclovir | 3.28 | 22.29 | >150.00 | >46 | >7  |

Note: EC50 and EC90 — compound concentration (μM) that reduces the viral replication by 50 % and 90 %; CC50 — compound concentration (μM) that reduces the cell viability by 50 %; SI50 = CC50/EC50; SI90 = CC50/EC90.
2-(Dichloromethyl)-4,7-bis(4-methylphenyl)pyrazolo[1,5-a][1,3,5]triazine (7d). Yield 2.59 g (70 %), yellow solid, mp 188—190 °C (MeCN). $^1$H NMR spectrum (302 MHz, DMSO-$d_6$), δ, ppm (J, Hz): 2.38 (3H, s), 2.46 (3H, s), 7.34 (2H, d, $J_1=8.0$), 7.43 (1H, s), 7.45 (1H, s), 7.51 (2H, d, $J_2=8.2$), 8.02 (2H, d, $J_2=8.0$), 8.77 (2H, d, $J_2=8.3$). $^{13}$C NMR spectrum (101 MHz, DMSO-$d_6$), δ, ppm: 21.0, 21.4, 71.0, 94.4, 126.6, 126.7, 128.5, 129.2, 131.3, 139.9, 144.4, 150.7, 154.0, 157.6, 158.4. Mass spectrum, m/z: 383 [M+H]$^+$. Found, %: C 62.64; H 4.19; Cl 18.41; N 14.54. C$_{20}$H$_{16}$Cl$_2$N$_4$. Calculated, %: C 62.68; H 4.21; Cl 18.50; N 14.62.

2-(Dichloromethyl)-7-methyl-4-(4-methylphenyl)pyrazolo[1,5-a][1,3,5]triazine (7e). Yield 2.14 g (70 %), dark yellow solid, mp 155—157 °C (MeCN). $^1$H NMR spectrum (400 MHz, DMSO-$d_6$), δ, ppm (J, Hz): 2.43 (3H, s), 2.52 (3H, s), 6.75 (1H, s), 7.33 (1H, s), 7.44 (2H, d, $J_2=7.8$), 8.67 (2H, d, $J_2=7.9$). $^{13}$C NMR spectrum (101 MHz, DMSO-$d_6$), δ, ppm: 14.6, 21.4, 71.0, 97.4, 126.6, 129.0, 131.2, 144.3, 150.0, 153.7, 157.4, 158.6. Mass spectrum, m/z: 307 [M+H]$^+$. Found, %: C 54.71; H 3.93; Cl 18.41; N 14.54. C$_{14}$H$_{12}$Cl$_2$N$_4$. Calculated, %: C 54.74; H 3.94; Cl 23.08; N 18.24.

Being isosteres of purine, pyrazolo[1,5-a][1,3,5]triazines attract much attention of chemists and biologists, and their synthesis and bioactivity have been thoroughly reviewed [13, 14]. In this contribution, we would like to report the in vitro antiviral activity of compounds 7a-e, which were tested against: i) Dengue virus 2 (strain New Guinea C, cell line Huh7); ii) Tacaribe virus (strain TRVL 11573, cell line Vero); iii) Zika virus (strain MR766, cell line Vero 76) at Institute for Antiviral Research, Utah State University; iv) Human cytomegalovirus (strain AD169, cell line HFF); v) Herpes simplex virus 1 (strain E-377, cell line HFF); vi) Varicella-Zoster virus (strain Ellen, cell line HFF) at University of Alabama at Birmingham.

The viral-induced cytopathic effect inhibition, as well as compound toxicity in host cells, was evaluated. In primary assays i-iii, compounds 7 did not have a sufficient antiviral activity that exceeded their cytotoxicity level at concentrations within 0.1-100 μg/mL, but assays iv-vi gave acceptable results presented in the Table. As can be seen from it, the compounds activities are rather low with the exception of 7a, which, however, has comparatively high toxicity. In terms of selectivity, the interaction 7d – AD169 – HFF (assay iv) with SI$_{50} > 6$ is noteworthy.

It should be noted in conclusion that the N-(2,2-dichloro-1-cyanoethyl)carboxamides 1 with N-nucleophiles reaction mode is dictated by not only the nucleophile nature, but some other critical factors that will be considered in a further publication.

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СИНЕЗ І ПРОТИВІРУСНІ ВЛАСТИВОСТІ
2-(ДИХЛОРОМЕТИЛ)ПІРАЗОЛО[1,5-а][1,3,5]ТРИАЗИНОВ

Знайдено, що N-(2,2-дихлоро-1-ціаноетенил)карбоксаміди реагують з 1H-піразол-5-амінами в присутності триетиламіну з утворенням 2-(дихлорометил)піразоло[1,5-а][1,3,5]триазинів. Циклокоонденсація складається з таких ймовірних стадій: а) приєднання групи NH₂ до активованого зв'язку С=C, що зумовлює перший амідний інтермедіат; б) елімінування HCN під дією триетіламіну з утворенням другого амідного інтермедіату; в) внутрішньомолекулярна циклізація останнього в кінцевий продукт з відщепленням H₂O.

2-(Дихлорометил)-4,7-дифенілпіразоло[1,5-а][1,3,5]триазин виявився цілком стійким щодо киплячих розчинів MeONa/MeOH, AcONa/AcOH, а також Na₂S/H₂O/EtOH, однак розщеплювався під дією соляної або сірчаної кислот.

П'ять синтезованих 2-(дихлорометил)піразоло[1,5-а][1,3,5]триазинів були протестовані проти: i) Dengue virus 2 (штам New Guinea C, клітинна лінія Huh7); ii) Tacaribe virus (штам TRVL 11573, клітинна лінія Vero); iii) Zika virus (штам MR766, клітинна лінія Vero 76); iv) Human cytomegalovirus (штам AD169, клітинна лінія HFF); v) Herpes simplex virus 1 (штам E-377, клітинна лінія HFF); vi) Varicella-Zoster virus (штам Ellen, клітинна лінія HFF). Визначено ступінь інгібування цитопатичного ефекту, спричиненої вірусами, а також токсичність сполук у клітинах хазяїна. У первинних випробуваннях (i—iii) сполуки не мали достатньої противірусної активності, яка перевищувала їх рівень цитотоксичності при концентрації в межах 0,1—100 мкг/мл, але випробування iv—vi дали прийнятні результати. Всі сполуки показали досить низьку активність, за винятком 2-(дихлорометил)-4,7-дифенілпіразоло[1,5-а][1,3,5]триа-
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СИНТЕЗ И ПРОТИВОВИРУСНЫЕ СВОЙСТВА 2-(ДИХЛОРЕТИЛ)ПИРАЗОЛО[1,5-a][1,3,5]ТРИАЗИНОВ

Найдено, что \(N-(2,2-дихлор-1-цианоэтил)карбоксамиды\) реагируют с 1\(H\)-пиразол-5-аминами в присутствии триэтиламина с образованием 2-(дихлорметил)пиразоло[1,5-a][1,3,5]триазинов. Циклоконденсация состоит из следующих вероятных стадий: а) присоединение группы \(NH_2\) к активированной связи \(C=C\), что приводит к первому амидному интермедиату; б) элиминирование \(HCN\) под действием триэтиламина с образованием второго амидного интермедиата; в) внутримолекулярная циклизация последнего в конечный продукт с отщеплением \(H_2O\). 2-(Дихлорметил)-4,7-дифенилпиразоло[1,5-a][1,3,5]триазин оказался вполне устойчивым по отношению к кипящим растворам \(MeONa/MeOH\), \(AcONa/AcOH\), \(Na_2S/H_2O/EtOH\), однако расщеплялся при действии соляной или серной кислот.

Пять синтезированных 2-(дихлорметил)пиразоло[1,5-a][1,3,5]триазинов были протестированы против:
i) Dengue virus 2 (штамм New Guinea C, клеточная линия Huh7); ii) Tacaribe virus (штамм TRVL 11573, клеточная линия Vero); iii) Zika virus (штамм MR766, клеточная линия Vero 76); iv) Human cytomegalovirus (штамм AD169, клеточная линия HFF); v) Herpes simplex virus 1 (штамм E-377, клеточная линия HFF); vi) Varicella-Zoster virus (штамм Ellen, клеточная линия HFF). Определена степень ингибирования цитопатического эффекта, вызванного вирусами, а также токсичность соединений в клетках хозяина. В первичных испытаниях (i—iii) соединения не проявили достаточной противовирусной активности, которая превышала бы их уровень цитотоксичности при концентрации в пределах 0,1—100 мкг/мл, но испытания iv—vi дали приемлемые результаты. Все соединения показали довольно низкую активность, за исключением 2-(дихлорметил)-4,7-дифенилпиразоло[1,5-a][1,3,5]триазина, который, однако, имел сравнительно высокую токсичность. Что касается селективности, то заслуживает внимания 2-(дихлорметил)-4,7-бис(4-метилфенил)пиразоло[1,5-a][1,3,5]триазин—AD169—HFF (испытание iv) с \(SI_{50} > 6\).

Ключевые слова: \(N-(2,2-дихлор-1-цианоэтил)карбоксамид, 1H-пиразол-5-амин, пиразоло[1,5-a][1,3,5]-триазин, противовирусная активность.\