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Synthesis and evaluation of the antiviral activity of 2-(dichloromethyl)pyrazolo[1,5-*a*][1,3,5]triazines

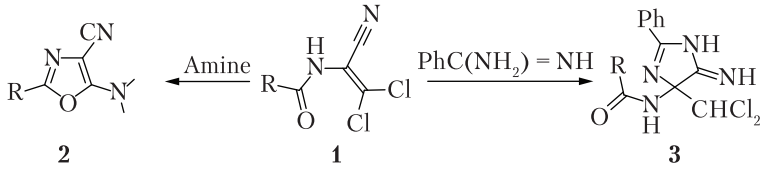
Presented by Corresponding Member of the NAS of Ukraine A.I. Vovk

It is found that N-(2,2-dichloro-1-cyanoethenyl)carboxamides react with 1H-pyrazol-5-amines in the presence of triethylamine to give 2-(dichloromethyl)pyrazolo[1,5-a][1,3,5]triazines. Apparently, this cyclocondensation consists of the following steps: a) the addition of an NH_2 group to the activated C=C bond to form the first amide intermediate, b) the elimination of HCN promoted by triethylamine to give the second amide intermediate, c) the intramolecular cyclization of the latter into the final product with H_2O elimination. 2 (Dichloromethyl)-4,7-diphenylpyrazolo[1,5-a][1,3,5]triazine was stable to boiling MeONa/MeOH, AcONa/AcOH, and Na_2S/H_2O/EtOH solutions, but cleaved with hydrochloric or sulfuric acid.

Five 2-(dichloromethyl)pyrazolo[1,5-a][1,3,5]triazines are 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), 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). The viral-induced cytopathic effect inhibition, as well as the compound toxicity in host cells, is evaluated. In primary assays (i-iii), the compounds have no sufficient antiviral activity that would exceed their cytotoxicity level at concentrations within 0.1-100 μg/mL, but assays (iv-vi) gave acceptable results. All compounds showed rather a low activity with the exception of 2-(dichloromethyl)-4,7-diphenylpyrazolo[1,5-a][1,3,5]triazine, which, however, had a comparatively high toxicity. In terms of selectivity, the interaction 2-(dichloromethyl)-4,7-bis(4-methylphenyl)pyrazolo[1,5-a][1,3,5]triazine—AD169—HFF (assay iv) with SI50 > 6 is noteworthy.

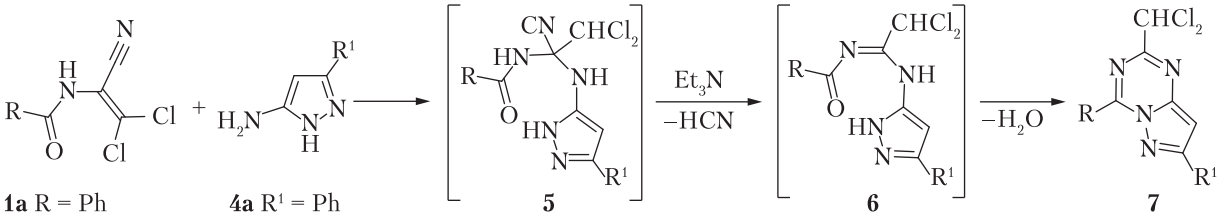
Keywords: *N-(2,2-dichloro-1-cyanoethenyl)carboxamide, 1H-pyrazol-5-amine, pyrazolo[1,5-a][1,3,5]triazine, antiviral activity.*

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



2 **1** **3**

Scheme 1. The known heterocyclizations of compounds **1** with N-nucleophiles



1a R = Ph
b R = 4-MeC_6H_4

4a R^1 = Ph
b R^1 = 4-MeC_6H_4
c R^1 = Me

5 **6** **7**

5—7: R = R^1 = Ph (**a**); R = Ph, R^1 = 4-MeC_6H_4 (**b**); R = 4-MeC_6H_4, R^1 = Ph (**c**); R = R^1 = 4-MeC_6H_4 (**d**); R = 4-MeC_6H_4, R^1 = Me (**e**)

Scheme 2. The new heterocyclization pathway resulting in pyrazolo[1,5-*a*][1,3,5]triazine derivatives **7**

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 1*H*-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** → **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. ^{1}H 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_2S/H_2O/EtOH solutions. But, in all cases, only the starting material was quantitatively recovered. On the other hand, the heating of **7a** with

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). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), 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). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), 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. $C_{18}H_{12}Cl_2N_4$. Calculated, %: C 60.86; H 3.41; Cl 19.96; N 15.77.

2-(Dichloromethyl)-7-(4-methylphenyl)-4-phenylpyrazolo[1,5-*a*][1,3,5]triazine (7b). Yield 2.58 g (70 %), dark yellow solid, mp 190—192 °C (MeCN). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), 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). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), 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. $C_{19}H_{14}Cl_2N_4$. Calculated, %: C 61.80; H 3.82; Cl 19.20; N 15.17.

2-(Dichloromethyl)-4-(4-methylphenyl)-7-phenylpyrazolo[1,5-*a*][1,3,5]triazine (7c). Yield 2.87 g (78 %), dark yellow solid, mp 163—165 °C (MeCN). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), 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). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), 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. $C_{19}H_{14}Cl_2N_4$. Calculated, %: C 61.80; H 3.82; Cl 19.20; N 15.17.

Antiviral activity and cytotoxicity of compounds 7a-e

Compd	EC_{50}	EC_{90}	CC_{50}	SI_{50}	SI_{90}
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. EC_{50} and EC_{90} — compound concentration (μM) that reduces the viral replication by 50 % and 90 %; CC_{50} — compound concentration (μM) that reduces the cell viability by 50 %; $SI_{50} = CC_{50}/EC_{50}$; $SI_{90} = CC_{50}/EC_{90}$.

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* = 8.0), 7.43 (1H, s), 7.45 (1H, s), 7.51 (2H, d, *J* = 8.2), 8.02 (2H, d, *J* = 8.0), 8.77 (2H, d, *J* = 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, 129.6, 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. $C_{20}H_{16}Cl_2N_4$. 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* = 7.8), 8.67 (2H, d, *J* = 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 23.16; N 18.16. $C_{14}H_{12}Cl_2N_4$. 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-cyanoethenyl)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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СИНТЕЗ І ПРОТИВІРУСНІ ВЛАСТИВОСТІ
2-(ДИХЛОРОМЕТИЛ)ПІРАЗОЛО[1,5-*a*][1,3,5]ТРИАЗИНІВ

Знайдено, що *N*-(2,2-дихлоро-1-ціаноетеніл)карбоксаміди реагують з 1*H*-піразол-5-амінами в присутності триетиламіну з утворенням 2-(дихлорометил)піразоло[1,5-*a*][1,3,5]триазинів. Циклоконденсація складається з таких ймовірних стадій: а) приєднання групи NH_2 до активованого зв'язку C=C, що зумовлює перший амідний інтермедіат; б) елімінування HCN під дією триетиламіну з утворенням другого амідного інтермедіату; в) внутрішньомолекулярна циклізація останнього в кінцевий продукт з відщепленням H_2O. 2-(Дихлорометил)-4,7-дифенілпіразоло[1,5-*a*][1,3,5]триазин виявився цілком стійким щодо киплячих розчинів MeONa/MeOH, AcONa/AcOH, а також Na_2S/H_2O/EtOH, однак розщеплювався під дією соляної або сірчаної кислот.

П'ять синтезованих 2-(дихлорометил)піразоло[1,5-*a*][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, спричиненого вірусами, а також токсичність сполук у клітинах хазяїна. У первинних випробуваннях (i—iii) сполуки не мали достатньої противірусної активності, яка перевищувала б 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-*a*][1,3,5]триа-

зину, який, однак, мав порівняно високу токсичність. Що стосується селективності, то заслуговує на увагу 2-(дихлорметил)-4,7-біс(4-метилфеніл)піразоло[1,5-*a*][1,3,5]триазин—AD169—HFF (випробування iv) з $SI_{50} > 6$.

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

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СИНТЕЗ И ПРОТИВОВИРУСНЫЕ СВОЙСТВА
2-(ДИХЛОРМЕТИЛ)ПИРАЗОЛО[1,5-*a*][1,3,5]ТРИАЗИНОВ

Найдено, что *N*-(2,2-дихлор-1-цианоэтенил)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, а также 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-цианоэтенил)карбоксамид, 1H-пиразол-5-амин, пиразоло[1,5-a][1,3,5]-триазин, противовирусная активность.*