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6-THIO-SUBSTITUTED-*2H*-[1,2,4]TRIAZINO[2,3-*c*] QUINAZOLIN-2-ONES WITH THE DIALKYLAMINOETHYL MOIETY – A NEW CLASS OF ANTIVIRIAL AGENTS

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Key words: 6-[β-dialkylaminoethylthio]-3-R-2H-[1,2,4]triazino[2,3-c]quinazolin-2-ones; biodefence viruses; respiratory viruses; antiviral activity

*It has been found that 6-[(β-dialkylaminoethylthio]-3-R-2H-[1,2,4]triazino[2,3-c]quinazolin-2-ones exhibit the antiviral activity against respiratory and the biodefence virus panel (EC_{50} 3.2-36.0 mg/ml) and the influenza type A and B (EC_{50} 1.1-18.0 mg/ml) in the visual (viral CPE) and neutral red dye uptake increasing tests. The high inhibitory activity of compound 1.5 against the strain Flu B (EC_{50} 1.1-5.3 mg/ml) has been revealed. It has been suggested that the antiviral effect of compound **1.5** is comparable with Ribavirin. It has been shown that the planar [1,2,4]triazino[2,3-c]quinazoline system causes antiviral properties additionally determined by the b-dialkylaminoethylthiol fragment and depends on the nature of the substituent in position 3.*

The expansion of the mankind activity in the planet ecosystem causes the counter evolution of viruses specializing in exploiting the human organism resources. Today more than 1500 viral genotypes are known; they may strike human cells to cause different diseases, such as encephalitis, influenza, hepatitis, AIDS, etc. Moreover, virus diseases especially that often occur recently (Ebola virus disease, Marburg virus diseases) may cause menaces for the global safety, and this fact demands intensification of the search for new antiviral agents.

Drugs used for treating and preventing virus diseases are presented by different classes of compounds: vaccines, interferons, abnormal nucleosides, adamantan derivatives, thiosemicarbazones and other compounds with the virucidal action [2]. Among others, one of the most promising class is inductors of endogen interferon such as Amixin (Tilorone) (**1**), Cyclopheron (**2**), Neovir (**3**), Umifenovir (Arbidol) (**4**), etc. (Fig. 1) [5]. In most cases, the compounds mentioned above are planar polynuclear carbo- or heterecyclic systems with alkylamine, alkylcarboxyle and alkylcarboxamide fragments, and, as a rule, they are able to inhibit reproduction of the virus. The studies previously conducted showed reasonability of the strategy proposed for creating novel antiviral agents. It was shown that indoles (**5**), pyrrolo[3,2-*f*][1,3]benzoxazines (**6**), benzo[4,5]imidazo[1,2-*c*]quinazolines (**7**), chromeno[2',3':4,5]pyrimido[2,1-*b*][1,3]thiazines (**8**), benzo [*de*]isoquinolines (**9**), imidazo[2,1-*b*]thiazole, indolo[2,3-*b*] quinoxalines, benzo[4,5]indolo[2,3-*b*]quinoxaline, phenylbenzoimidazoles, benzoimidazo[1,2-*c*]quinazolines, naphto [1,2-*b*]furanes, phenanthroindolizidine, acridines, fluorenes and other planar polycyclic compounds were efficient inductors of interferon and antiviral agents (Fig. 1) [1, 3, 4, 6, 7, 9-11, 13, 14, 17-19, 21-24].

Our study describes the strategy for the synthesis of novel antiviral agents based on the "hybrid – pharmacophore" approach. According to the strategy mentioned above the planar [1,2,4]triazino[2,3-*c*]quinazoline system (**10**) was attached to the *N*,*N*-dialkylethylamine fragment. Compounds synthesized according to the pathway proposed already revealed a high antiviral activity against Flu A H_1N_1, Flu A H_3N_2, Flu A H_5N_1, Flu B (EC_{50} 3.1 – > 100 μg/ml) strains (Fig. 2) [16].

Thus, considering the latter fact that 6-thio-substituted-*2H*-[1,2,4]triazino[2,3-*c*]quinazolin-2-ones revealed the antiviral activity and were quite possibly capable for DNA-intercalation, their modification aimed to the synthesis of novel antiviral drugs was quite reasonable. Hence, it was decided to modify 6-thioxo-3-R-2*H*-[1,2,4] triazino[2,3-*c*]quinazoline-2-ones *via* introduction of *β*-dalkylaminoethyl moieties to evaluate their potential.

Experimental Part

Chemistry

Previously 6-[(*β*-dialkylaminoethylthio]-3-R-*2H*-[1,2,4] triazino[2,3-*c*]quinazolin-2-ones (**1.1-1.9**) were discussed concerning their structure and anticancer activity (Fig. 2) [8].

Biological Activity

Rapid screening assay of the antiviral activity

The primary antiviral assay was performed using the respiratory viruses panel (Flu A H_1N_1 (California/07/2009/MDCK), Flu A H_3N_2 (Perth/16/2009/MDCK), Flu A H_5N_1 (Vietnam/1203/2004H/MDCK), Flu B (Florida/4/2006/MDCK), respiratory syncytial virus (A_2/MA_{104}), SARS coronavirus (Urbani/Vero 76), venezuelan equine encephalitis virus (TC-83/Vero)) and the biodefence viruses panel (Tacaribe virus (TRVL 11573/Vero), Rift Valley Fever virus (MP-12/Vero 76), Dengue virus type 2 (New Guinea C/Vero 76) with a protocol of the NIAID's antimicrobial acquisition and coordination [12, 15, 20]. The results for each compound tested were reported, the virus-inhibitory concentration, 50% endpoint (EC_{50} μg/ml),

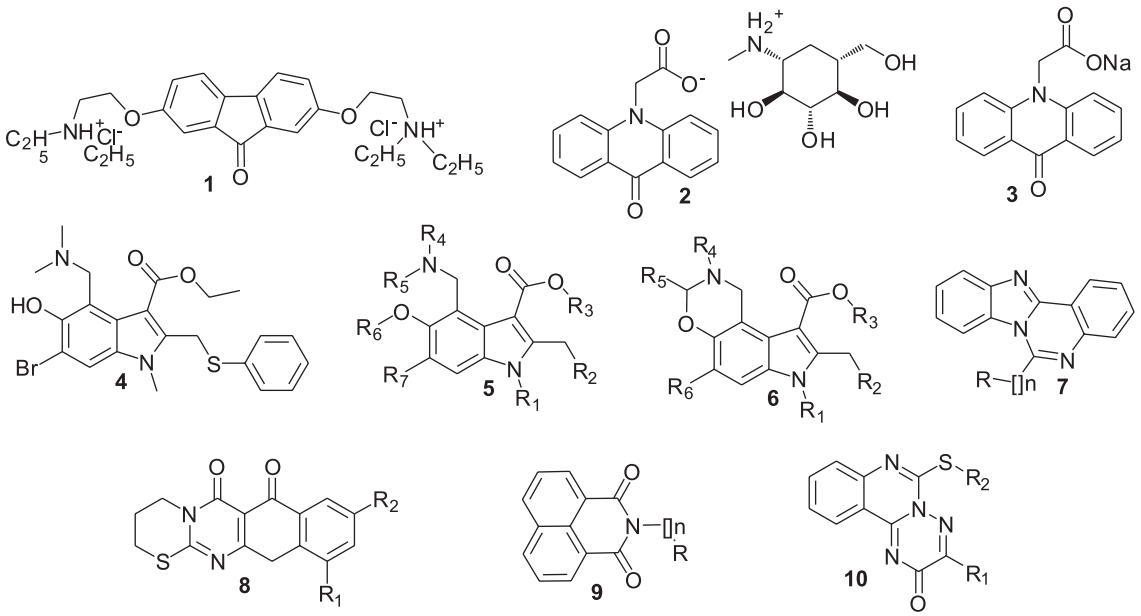


Fig. 1. Inductors of endogen interferons and promising polycyclic planar compounds with the antiviral activity.

or 90% effective concentration (EC_{90} μg/ml) and cell-inhibitory concentration, 50% endpoint (CC_{50} μg/ml) were determined. The general selectivity index (SI_{50}) was calculated as a ratio of (EC_{50})/(CC_{50}). The SI_{50} of 3 or greater indicates that confirmatory testing is needed.

Inhibition of the viral cytopathic effect (CPE)

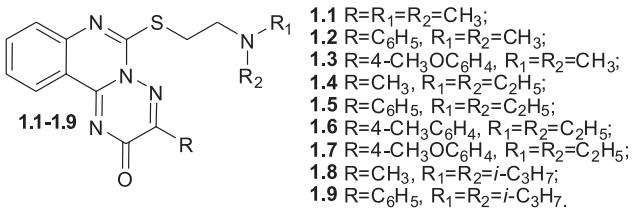
This test performed in 96 well flat-bottomed microplates was used for the initial antiviral evaluation of compounds. In this CPE inhibition test, four $\log_{10}$ dilutions of each test compound (e.g. 1000, 100, 10, 1 μg/ml) were added to 3 cups containing the cell monolayer within 5 min. Next the virus was added, and the plate was sealed and incubated at 37°C. The CPE was read microscopically when untreated infected controls developed 3 to 4+ CPE (approximately for 72 to 120 h). A known positive control drug was evaluated in parallel with test drugs in each test. This drug was Ribaverin for Rift Valley Fever, respiratory syncytial influenza type A and B and viruses Tacaribe; Infergen for viruses Dengue type 2, venezuelan equine encephalitis, "$M_{12}8_{533}$" – for SARS coronavirus virus. The data are expressed as 50% effective concentrations (EC_{50}).

Increase in the neutral red (NR) dye uptake

This test was performed to validate the CPE inhibition observed in the initial test, and it used the same 96-well microplates after the CPE was read. When neutral red was added to the medium cells that were not damaged by virus, a greater amount of dye was placed on a computerized microplate autoreader. The EC_{50} was determined from this dye uptake.

Decrease in the virus yield assay (VYR-test)

Compounds considered to be active by the CPE inhibition and by the NR dye uptake were re-tested on reduction of the virus yield by assaying frozen and thawed eluates from each cup for the virus titre by serial dilution onto monolayers of susceptible cells. Development of the CPE in these cells was the indication of the presence of the infectious virus. The same as in the initial tests, a known active drug was used in parallel as a positive control. The 90% effective concentration (EC_{90}), being the drug concentration inhibiting the virus yield by 1 $\log_{10}$, was determined from these data.



1.1 R=R_1=R_2=CH_3;
1.2 R=C_6H_5, R_1=R_2=CH_3;
1.3 R=4-$CH_3OC_6H_4$, R_1=R_2=CH_3;
1.4 R=CH_3, R_1=R_2=C_2H_5;
1.5 R=C_6H_5, R_1=R_2=C_2H_5;
1.6 R=4-$CH_3C_6H_4$, R_1=R_2=C_2H_5;
1.7 R=4-$CH_3OC_6H_4$, R_1=R_2=C_2H_5;
1.8 R=CH_3, R_1=R_2=*i*-C_3H_7;
1.9 R=C_6H_5, R_1=R_2=*i*-C_3H_7.

Fig. 2. The general structure of 6-[(*β*-dialkylaminoethylthio]-3-R-2H-[1,2,4]triazino[2,3-*c*]quinazolin-2-ones (**1.1-1.9**).

Methods for cytotoxicity determination

In the CPE inhibition tests, two wells of uninfected cells treated with each concentration of the test compounds were run in parallel with the infected treated wells. At the time the CPE was determined microscopically. The toxicity control cells were also examined microscopically for any changes in the cell appearance compared to normal control cells in the same plate. These changes may be enlargement, granularity, cells with ragged edges, filmy appearance, rounding, detachment from the surface of the well, or other changes. The changes were given the designation of T (100% toxic), PVH (partially toxic-very heavy – 80%), PH (partially toxic-heavy – 60%), P (partially toxic – 40%), Ps (partially toxic-slight – 20%), or 0 (no toxicity – 0%), conforming to the degree of cytotoxicity observed. The 50% cell inhibitory (cytotoxic) concentration (IC_{50}) was determined by regression analysis of these data.

Results and Discussion

The mean values of the antiviral activity basic parameters, namely EC_{50}, μg/ml, CC_{50}, μg/ml and SI_{50} are presented in Tab. 1.

It was found that compounds **1.5** and **1.6** (EC_{50} 3.2-5.6 μg/ml, SI 2.7-4.7) were the most active against SARS virus according to the viral CPE and increase in the neutral red dye uptake increasing tests. At the same time,

Table 1

The antiviral activity of the compounds synthesized against respiratory viruses and biodefence viruses

Compound*	Virus	Assay	EC_{50}, mg/ml	CC_{50}, mg/ml	SI_{50}
1.1	Tacaribe	neutral red	36	>100	>2.8
1.2			13	21	1.6
	venezuelan equine encephalitis		9.7	17	1.8
1.5	SARS	viral CPE	3.2	15	4.7
		neutral red	3.2	15	4.7
1.6		viral CPE	5.6	15	2.7
	venezuelan equine encephalitis	neutral red	21	34	1.6
1.7		viral CPE	10	32	3.2
1.8		neutral red	10	43	4.3
$M_{12}8_{533}$	SARS	viral CPE	<0.1	>100	>1000
		neutral red	<0.13	>100	>770
Ribavirin	Tacaribe	viral CPE	5.6	>1000	>180
		neutral red	6.7	>1000	>150
	respiratoty syncytial	viral CPE	10	>320	>32
		neutral red	9.3	>320	>34
	Rift Valley Fever	viral CPE	8.2	>1000	>120
		neutral red	7.2	>1000	>140
Infergen	venezuelan equine encephalitis	viral CPE	0.00002	>0.01	>500
		neutral red	0.00002	>0.01	>500
	Dengue	viral CPE	0.00005	>0.01	>200
		neutral red	0.00004	>0.01	>250

* – The table presents the results of the antiviral activity against strains for which the selectivity index > 1.5.

Table 2

The antiviral activity of the compounds synthesized against type A and B influenza

Compound*	Virus	Assay	EC_{50}, mg/ml	CC_{50}, mg/ml	SI_{50}
1.2	Flu A H_3N_2	viral CPE	10	32	3.2
		neutral red	4.2	17	4
Ribavirin		viral CPE	12	>100	>8.3
		neutral red	11	>100	>9.1
1.9	Flu A H_5N_1	viral CPE	7.9	28	3.5
		neutral red	6.3	37	5.9
Ribavirin		viral CPE	3.6	>100	>28
		neutral red	3.2	>100	>31
1.4	Flu A H_1N_1	neutral red	18	33	1.8
1.6		neutral red	3.3	5.5	1.7
Ribavirin		viral CPE	5.7	>100	>18
		neutral red	5.9	>100	>17
1.5	Flu B	viral CPE	1.1	24	22
		neutral red	1.4	34	24
		Secondary viral CPE	5.2	14	2.7
		Secondary neutral red	5.3	16	3
Ribavirin		viral CPE	3.6	>100	>28
		neutral red	3.1	>100	>32
		Secondary viral CPE	0.19	100	530
		Secondary neutral red	1	100	100

* – The table presents the results of the antiviral activity against strains for which the selectivity index > 1.5.

compounds **1.2**, **1.6-1.8** revealed the high antiviral activity against venezuelan equine encephalitis virus (EC_{50} 9.7-21 μg/ml, SI 1.8-4.3) according to increase in the neutral red dye uptake increasing test. Compounds **1.1** and **1.2** were also active against Tacaribe (EC_{50} 13-36 μg/ml, SI 1.6-2.8).

However, inhibitory properties of compounds **1.1-1.9** against other biodefence viruses were not significant (SI 0-4.7), and were less comparing to the reference drugs Ribavirin (SI>32), Infergen (SI>250) and $M_{12}8_{533}$ (SI>770). Thus, they could not be considered as promising antiviral agents.

The results of the study of 6-[(*β*-dialkylaminoethyl) thio]-3-R-*2H*-[1,2,4]triazino[2,3-*c*]quinazolin-2-ones (**1.1-1.9**) for their effect on respiratory viruses were more interesting. Thus, compound **1.2** in the viral CPE and the neutral red dye uptake increasing tests showed EC_{50} 4.2-10 μg/ml and the cell-inhibitory concentration (CC_{50} 17-32 μg/ml). Besides the fact that the antiviral activity of **1.2** was comparable with Ribavirin (EC_{50} 11-12 μg/ml, CC_{50}> 100 μg/ml), the last one had a higher selectivity index (Tab. 2).

The results obtained for compound **1.9** were similar and competed with the virus-inhibiting concentration of Ribavirin, and the cell-inhibitory concentration against Flu *A* H_5N_1 was inferior by the selectivity index. Substances **1.4** and **1.6** were the most active against Flu *A* H_1N_1 virus. Thus, according to the neutral red dye uptake increasing test their virus-inhibiting concentration EC_{50} were 18 and 3.3 μg/ml, respectively. However, the values of selectivity indexes for the compounds mentioned were in the range of 1.7-1.8; therefore, they were too low to be the promising antiviral agents. The high antiviral activity against Flu *B* was found for 6-[(*β*-diethylaminoethyl)thio]-3-phenyl-*2H*-[1,2,4]triazino [2,3-*c*]quinazoline-2-one (**1.5**). Its EC_{50} was 1.1 μg/ml in the viral CPE test and 1.4 μg/ml in the increase and neutral red dye uptake increasing test (SI_{50} 22-24). The advanced tests conducted demonstrated higher effectiveness of Ribavirin (SI_{50} 100-530).

It is interesting to note that according to the viral CPE and the increase and neutral red dye uptake increasing tests the activity of other compounds (**1.1**, **1.3**, **1.7** and **1.8**) against Flu *A* H_3N_2, Flu *A* H_5N_1, Flu *A* H_1N_1 and Flu *B* was not significant, and the selectivity indexes SI_{50} were in the range of 0-1.5. Meanwhile, the reference drug Ribavirin under the same conditions had much higher selectivity indexes in the range of 8.3-32.

CONCLUSIONS

Summing up the results presented allows to suggest that the presence of the planar 3-R-*2H*-[1,2,4]triazino [2,3-*c*]quinazoline-2-one system has determined the antiviral activity against biodefence and respiratory viruses. The *SAR*-analysis conducted has shown that it is also influenced by the presence of the lipophilic *β*-dialkylaminoethantiol fragment and the nature of substituents in position 3. The most active were compounds which contained aryl moieties in the following series: Me<Ph< 4-$MeOC_6H_4$<4-MeC_6H_4. In our opinion, the promising approaches for further modification of the planar *as*-triasino[2,3-*c*]quinazoline system and for purposeful synthesis of novel antiviral agents are functionalization of the substituent in position 3, including introduction of benzene cycles with different substituents (alkyl-, alkoxy-, halogen-, trifluormethyl-), functionalization of position 6 of the thioalkyl fragment change to oxo, alkyl, aryl, heteryl, or amino groups and introduction of halogens, trifluoromethyl and alkoxy groups to positions 8-11 aimed to increase the lipophilicity.

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6-ТІОЗАМІЩЕНІ 2*H*-[1,2,4]ТРИАЗИНО[2,3-*c*]ХІНАЗОЛІН-2-ОНИ З ДІАЛКІЛАМІНОЕТИЛЬНИМ ФРАГМЕНТОМ – НОВИЙ КЛАС ПРОТИВІРУСНИХ АГЕНТІВ

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***Ключові слова**: 6-[β-діалкіламіноетилтіо]-3-R-2H-[1,2,4]триазино[2,3-c]хіназолін-2-они; особливо небезпечні віруси; респіраторні віруси; противірусна активність*

*Встановлено, що 6-[(β-діалкіламіноалкілтіо]-3-R-2H-[1,2,4]триазино[2,3-c]хіназолін-2-они проявляють противірусну активність у візуальному тесті (viral CPE) і тесті підвищення захвату барвника нейтрального червоного (neutral red) щодо респіраторних і особливо небезпечних вірусів (EC_{50} 3.2-36.0 mg/ml) та вірусу грипу A&B (EC_{50} 1.1-18.0 mg/ml). Виявлена висока інгібуюча концентрація у сполуки **1.5** щодо штаму вірусу грипу B (EC_{50} 1.1-5.3 mg/ml), яка конкурує з препаратом порівняння Рибавірином (EC_{50} 0.19-1.0 mg/ml). Показано, що планарна [1,2,4]триазино[2,3-c]хіназолінова система є носієм противірусної активності, яка додатково визначається ліпофільним b-діалкіламіноетилтіольним фрагментом і залежить від будови арильного замісника у третьому положенні.*

6-ТИОЗАМЕЩЕННЫЕ 2*H*-[1,2,4]ТРИАЗИНО[2,3-*c*]ХИНАЗОЛИН-2-ОНЫ С ДИАЛКИЛАМИНОЭТИЛЬНЫМ ФРАГМЕНТОМ – НОВЫЙ КЛАСС ПРОТИВОВИРУСНЫХ АГЕНТОВ

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***Ключевые слова**: 6-[β-диалкиламиноэтилтио]-3-R-2H-[1,2,4]триазино[2,3-c]хиназолин-2-оны; особенно опасные вирусы; респираторные вирусы; противовирусная активность*

*Установлено, что 6-[(β-диалкиламиноалкилтио]-3-R-2H-[1,2,4]триазино[2,3-c]хиназолин-2-оны проявляют противовирусную активность в визуальном тесте (viral CPE) и тесте увеличения захвата красителя нейтрального красного (neutral red) к респираторным, особенно опасным вирусам (EC_{50} 3.2-36.0 mg/ml) и вирусам гриппа A&B (EC_{50} 1.1-18.0 mg/ml). Выявлена высокая ингибирующая концентрация вещества **1.5** к штамму вируса гриппа B (EC_{50} 1.1-5.3 mg/ml), конкурирующая с препаратом сравнения Рибавирином (EC_{50} 0.19-1.0 mg/ml). Показано, что планарная [1,2,4]триазино[2,3-c]хиназолиновая система является носителем противовирусной активности, которая дополнительно определяется липофильным b-диалкиламиноэтилтиольным фрагментом и зависит от строения арильного заместителя в третьем положении.*