UDK 547.792 :616.921

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Synthesis and antiviral activity of 2-(4,6-dimorpholine-4-yl-1,3,5-triazine-2-yl)-N-arylhydrazinecarbothioamides for Flu A H1N1 virus

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Key words: antiviral activity, virus Flu A (H1N1) California / 07/2009, Ribavirin, Amizon, derivatives of 2-(4,6-dimorpholine-4-yl-1,3,5-triazine-2-yl)-N-arylhydrazinecarbothioamides

Nowadays the influenza A virus (subtype H1N1) has become epidemic and pandemic worldwide spread and is about 95% of all infectious diseases.

The most widespread virus strain was California/07/2009 IVA/H1N1/, which was formed as a result of the reassortment of human A virus (subtype H1N1) and several strains of the virus that was spread only in pigs (influenza swine). The newly formed strain of the influenza virus is characterized by specific epidemiological and clinical features of the disease, such as: a large contagious infection in the range of 22–33 % (the seasonal flu contagious is 5–15 %), a rapid deficiency of the respiratory tract, a predisposition to the incidence of all age groups [1].

According to the statistics of the World Health Organization (WHO), these annual epidemics result up to 5 million cases of severe illness and up to 500 000 deaths every year around the world. All these factors like high infectivity, constant mutation of the virus as a result of antigenic drift or gene reassortment lead to the existence of new virus subtypes and most people don't have immune defenses against them. As a result, there are pandemics causing high mortality [1, 2].

Bacterial infections during influenza can significantly affect the processes of the disease and lead even to lethality. Thus, severe acute respiratory syndrome (SARS) was diagnosed in more than 70 % of patients with H1N1, and mortality rates ranged from 17 % to 46 % [3].

Effective ways such as immune-regulating, pathogenetic, symptomatic therapy, virilidic and antiviral etiotropic drugs are used nowadays for the treatment of influenza. They are divided into several generations. Among the drugs of the first generation we can admit drugs of adamantane series: amantadine (the USA and Western Europe), rimantadine (the USA, Canada, the RF). The use of these drugs is limited by their lack of activity in relation to the B virus, side effects and the rapid onset of drug resistance [3]. Adamantane drugs are blockers of the M2 ion channels protein of the influenza A virus, but their constant use leads to the loss of antiviral properties. This fact is associated with a mutation in the transmembrane domain of the M2 protein of the influenza virus [3]. The second generation drugs (zenamivir, oseltamivir) are effective against influenza A and B viruses by inhibition of neurominidase. It should be mentioned that the use of neurominidase inhibitors is effective only at an early stage of infection [4]. An alternative way was the creation of drugs in which the active substance showed interferonogenic effect acting as an inducer of endogenous interferon [5].

Thus, the current mainstream view in medical chemistry is the development

and practical implementation of new high-performance pharmaceutical products for the treatment of influenza. One of the main solutions to this problem is the synthesis of derivatives of triazines that exhibit antioxidant [6, 7] and antiviral activity, which leads to a violation of the virus replication and, as a result, the ability to detect a therapeutic effect in the treatment of influenza caused by the H1N1 virus.

The aim of research is to synthesize the derivatives of 2-(4,6-dimorpholine-4-yl-1,3,5-triazine-2-yl)-N-arylhydrazine-carbothioamide and to study the antiviral activity of 2-(4,6-dimorpholine-4-yl-1,3,5-triazine-2-yl)-N-(4-ethoxyphenyl)-hydrazine-carbothioamide for Flu A H1N1 California/07/2009 at primary pharmacological screening stage.

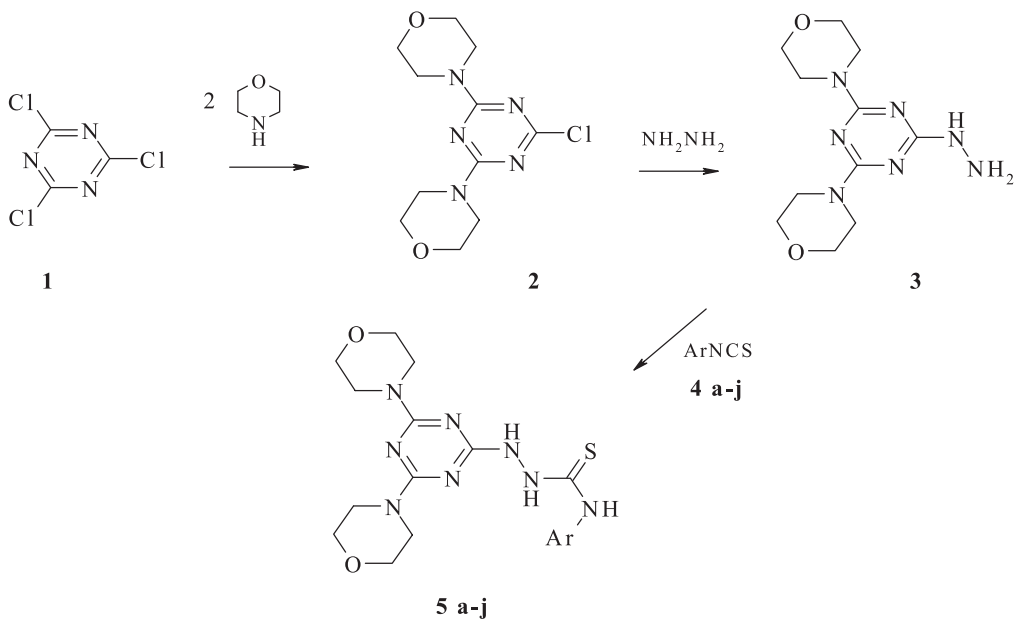
Materials and methods. Investigated compounds that are derivatives of 2-(4,6-dimorpholine-4-yl-1,3,5-triazine-2-yl)-N-arylhydrazine-carbothioamides and the substance of the drug «Amizon» were synthesized in the department of medical chemistry of State Institution «Institute of Pharmacology and Toxicology NMAS of Ukraine». We have synthesized compounds **(5a-j)** according to next scheme:

2-Chlor-4,6-dimorpholine-4-yl-[1,3,5] triazine **2** was obtained by the interaction of cyanuric chloride **1** with a double amount of morpholine in acetone solution according to the method [8].

It was found earlier [6, 7] that the derivatives of 2-R-(4,6-dimorpholine-4-yl-1,3,5-triazine-2-yl)-N-methylhydrazine-carbothioamide containing a substituent R in n-position possesse a more distinct biological activity than if it is in the *ortho-* or *meta-* position. Therefore, a substance **5 e** – 2-(4,6-dimorpholine-4-yl-1,3,5-triazine-2-yl)-N-4-ethoxyphenylhydrazine-carbothioamide was selected for the study of antiviral activity.

^{1}H-NMR spectra were recorded on the Varian Gemini 400 MHz (Germany) in DMSO-d6 using tetramethylsilane (TMS) as an internal standard. Chemical shifts are reported in ppm units with use of the δ scale.

*Synthesis of 2-(4,6-dimorpholine-4-yl-1,3,5-triazine-2-yl)-N-phenylhydrazine-carbothioamide **5 a***. 1.35 g (0.01 M) Phenylisothiocyanate was added to 2.81 g (0.01M) of 2-hydrazine-4,6-dimorpholinetriazine-1,3,5 **3** in 50 ml of ethanol. Stirred for one hour at a temperature of 75–78 °C, cooled to room temperature and left out overnight. The fallen-out



1 **2** **3**

5 a-j

where **4** and **5 Ar: a)** Ph, **b)** $2CH_3C_6H_4$, **c)** $2CH_3OC_6H_4$, **d)** $3ClC_6H_4$, **e)** $4CH_3CH_2OC_6H_4$, **f)** $2,3Me_2C_6H_3$, **g)** $2,4Me_2C_6H_3$, **h)** $2,5Me_2C_6H_4$, **i)** $2,6Me_2C_6H_4$, **j)** $3,4Me_2C_6H_4$.

precipitate was filtered off and recrystallized from ethanol. Yield – 3.54 g (85 %). Mp = 188–190 °C. Found %: N 27.1; S 7.61. $C_{18}H_{24}N_8O_2S$. Calculated, % N 26.9; S 7.68. The spectrum of NMR (DMSO-d_6, TMS): 3.56 (m, 8H, morpholine), 3.60 (m, 8H, morpholine), 7.10 – 7.46 (м, 5H, Ph), 8.85 (c, 1H, NH), 9.47 (c, 1H, NH), 9.61 (c, 1H, NH).

2-(4,6-Dimorpholine-4-yl-1,3,5-triazine-2-yl)-N-(2-methylphenyl)-hydrazine-carbothioamide ***5b*** was prepared analogously to the substituted hydrazine-carbothioamide 4a from 2.81 g (0.01 M) of 2-hydrazine-4,6-dimorpholinetriazine-1,3,5 **3** and 1.49 g (0.01M) of ortho-tolylisothiocyanate **4 b**. Yield 3.40 g (79 %). Mp = 200–201 °C. Found%: N 26.3; S 7.59. $C_{19}H_{26}N_8O_2S$. Calculated, % N 26.0; S 7.43. The spectrum of NMR (DMSO-d_6, TMS): 2.13 (c, 3H, CH_3), 3.57 (m, 8H, morpholine), 3.61 (m, 8H, morpholine), 7.01–7.17 (м, 4H, C_6H_4), 8.86 (s, 1H, NH), 9.39 (s, 1H, NH), 9.43 (s, 1H, NH).

2-(4,6-Dimorpholine-4-yl-1,3,5-triazine-2-yl)-N-(2-methoxyphenyl)hydrazine-carbothioamide ***5*** c was prepared in a similar manner to the substituted hydrazine carbothioamide **4 a** and from 2.81 g (0.01 M) of 2-hydrazine-4,6-dimorpholinetriazine-1,3,5 3 and 1.65 g (0.01 M) of 2-methoxyphenylisothiocyanate **4 c**. Yield 3.62 g (81 %). Mp = 209–211 °C. Found%: N 25.3; S 7.28. $C_{19}H_{26}N_8O_3S$. Calculated, % N 25.1; S 7.17. The spectrum of NMR ((DMSO-d_6, TMS): 3.55 (m, 8H, morpholine), 3.60 (m, 8H, morpholine), 3.75 (c, 3H, OCH_3), 6.86–7.12 (м, 4H, C_6H_4), 8.08 (s, 1H, NH), 8.94 (s, 1H, NH), 9.55 (s, 1H, NH).

2-(4,6-Dimorpholine-4-yl-1,3,5-triazine-2-yl)-N-(3-chlorphenyl)-hydrazine-carbothioamide ***5 d*** was prepared in a similar manner to the substituted hydrazine carbothioamide **4 a** and from 2.81 g (0.01 M) of 2-hydrazine-4,6-dimorpholinetriazine-1,3,5 **3** and 1.70 g (0.01 M) of 3-chlorophenylisothiocyanate **4 d**. Yield 3.97 g (88%). Mp = 186–188 °C. Found%: N 24.5; S 7.27. $C_{18}H_{23}ClN_8O_2S$. Calculated, % N 24.8; S 7.10. NMR spectrum (DMSO-d6, TMS): 3.60 (m, 8H, morpholine), 3.66 (m, 8H, morpholine), 7.14–7.59 (м, 4H, C_6H_4), 8.89 (s, 1H, NH), 9.65 (s, 1H, NH), 9.76 (s, 1H, NH).

2-(4,6-Dimorpholine-4-yl-1,3,5-triazine-2-yl)-N-(4-ethoxyphenyl)-hydrazine-carbothioamide ***5e*** was prepared analogously to the substituted hydrazine carbonylamide **4 a** and from 2.81 g (0.01 M) of 2-hydrazine-4,6-dimorpholinetriazine-1,3,5 **3** and 1.79g (0.01 M) of 4-ethoxyphenylisothiocyanate. Yield 4.24 g (92 %). Mp = 181–183 °C. Found %: N 24.3; S, 7.11 $C_{20}H_{28}N_8O_3S$ Calculated, % N 24.3; S 6.92. The spectrum of NMR (DMSO-d_6, TMS): 1.31 (т, 3H, CH_3), 3.56 (m, 8H, morpholine), 3.63 (m, 8H, morpholine), 4.00 (q, 2H, CH_2), 6.83 and 7.24 (d-d, 4H, C_6H_4), 8.82 (s, 1H, NH), 9.36 (s, 1H, NH), 9.49 (s, 1H, NH).

2-(4,6-Dimorpholine-4-yl-1,3,5-triazine-2-yl)-N-(2,3-dimethylphenyl)-hydrazine-carbothioamide ***5 f*** was prepared in a similar manner to the substituted hydrazine carbothioamide **4 a** and from 2.81 g (0.01 M) of 2-hydrazine-4,6-dimorpholinetriazine-1,3,5 **3** and 1.63 g (0.01 M) of 2,3-dimethylphenyl isothiocyanate **4 f**. Yield 3.25 g (73 %). Mp = 198–199 °C. Found %: N 25.5; S 7.31. $C_{20}H_{28}N_8O_2S$. Calculated, % N 25.2; S 7.20. NMR spectrum (DMSO-d_6, TMS): 2.00 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 3.59 (m, 8H, morpholine), 3.64 (m, 8H, morpholine), 6.84–7.06 (m, 3H, C_6H_3), 8.81 (s, 1H, NH), 9.33 (s, 2H, 2NH).

2-(4,6-Dimorpholine-4-yl-1,3,5-triazine-2-yl)-N-(2,4-dimethylphenyl)-hydrazine-carbothioamide ***5 g*** was prepared analogously to the substituted hydrazine carbonylamide **4 a** and from 2.81 g (0.01 M) of 2-hydrazine-4,6-dimorpholinetriazine-1,3,5 3 and 1.63 g (0.01 M) of 2,4-dimethylphenyl isothiocyanate 4 g. Yield 3.42 g (77 %). Mp = 214–215 °C. Found %: N 24.9; S 7.11. $C_{20}H_{28}N_8O_2S$. Calculated, % N 25.2; S 7.20. NMR spectrum (DMSO-d_6, TMS): 2.06 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 3.59 (m, 8H, morpholine), 3.68 (m, 8H, morpholine), 6.92–6.98 (m, 3H, C_6H_3), 8.82 (s, 1H, NH), 9.27 (s, 1H, NH), 9.35 (s, 1H, NH).

2-(4,6-Dimorpholine-4-yl-1,3,5-triazine-2-yl)-N-(2,5-dimethylphenyl)-hydrazine-carbothioamide for ***5 h*** was prepared in a similar manner to the substituted hydrazine carbothioamide **4 a** and from 2.81 g (0.01 M) of 2-hydrazine-4,6-dimorpholinetriazine-1,3,5 **3** and 1.63 g (0.01 M) of

2,5-dimethylphenyl isothiocyanate for 4 h. Yield 3.16 g (71%). Mp = 233–235 °C. Found %: N 25.4; S 7.33. $C_{20}H_{28}N_8O_2S$. Calculated, % N 25.2; S 7.20. NMR spectrum (DMSO-d_6, TMS): 2.06 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 3.59 (m, 8H, morpholine), 3.68 (m, 8H, morpholine), 6.83–7.07 (m, 3H, C_6H_3), 8.85 (s, 1H, NH), 9.32 (s, 1H, 1NH), 9.39 (s, 1H, 1NH).

2-(4,6-Dimorpholine-4-yl-1,3,5-triazine-2-yl)-N-(2,6-dimethylphenyl)-hydrazinecarbothioamide ***5i*** was prepared in a similar manner to the substituted hydrazine carbothioamide **4 a** and from 2.81 g (0.01M) of 2-hydrazino-4,6-dimorpholinotriazine-1,3,5 3 and 1.63 g (0.01 M) of 2,6-dimethylphenyl isothiocyanate **4 i**. Yield 2.85 g (64 %). Mp = 205–207 °C. Found %: N 25.0; S 7.15. $C_{20}H_{28}N_8O_2S$. Calculated, % N 25.2; S 7.20. The spectrum of NMR (DMSO-d_6, TMS): 2.10 (s, 6H, $2CH_3$), 3.56 (m, 8H, morpholine), 3.67 (m, 8H, morpholine), 6.95–7.04 (m, 3H, C_6H_3), 8.83 (s, 1H, NH), 9.21 (s, 1H, 1NH), 9.35 (s, 1H, 1NH).

2-(4,6-Dimorpholine-4-yl-1,3,5-triazine-2-yl)-N-(3,4-dimethylphenyl)-hydrazinecarbothioamide ***5 j*** was prepared in a similar manner to the substituted hydrazin carbothioamide **4 a** and from 2.81 g (0.01 M) of 2-hydrazine-4,6-dimorpholinetriazine-1,3,5 3 and 1.63 g (0.01 M) of 3,4-dimethylphenyl isothiocyanate **4 j**. Yield 2.85 g (64 %). Mp = 177–179 °C. Found %: N 25.4; S 7.33. $C_{20}H_{28}N_8O_2S$. Calculated, % N 25.2; S 7.20. The spectrum of NMR (DMSO-d_6, TMS): 2.14 (s, 6H, $2CH_3$), 3.57 (m, 8H, morpholine), 3.66 (m, 8H, morpholine), 7.05–7.14 (m, 3H, C_6H_3), 8.81 (s, 1H, NH), 9.37 (s, 1H, 1NH), 9.46 (s, 1H, 1NH).

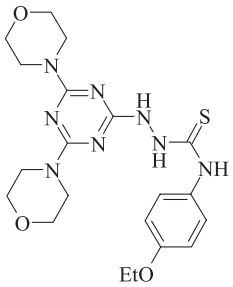
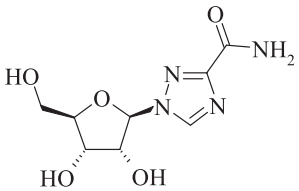
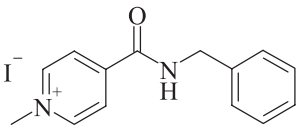
Antiviral activity research. Antiviral activity against the Flu A H1N1 California/ 07/2009 virus was conducted at the Southern Research Institute (SRI, Birmingham, Alabama, USA) within the framework of an international program to find new antiviral drugs and according to the agreement on cooperation with SI «Institute of Pharmacology and Toxicology of the National Academy of Medical Sciences of Ukraine». There were determined the antiviral activity of compound **5 e** – 2-(4,6-dimorpholine-4-yl-1,3,5-triazine-2-yl)-N-4-ethoxyphenylhydrazine-carbothioamide and the active substance of the drug Amizon - iodide 4-(N-benzyl)aminocarbonyl-1-methylpyridinium, an original development of the SI «Institute of Pharmacology and Toxicology of NAMS of Ukraine» [5, 9], which is widely used in Ukraine for the treatment of influenza [10].

The antiviral activity of the tested compounds was evaluated *in vitro* using a MDCK cell culture [11]. According to the procedure Ribavirin is always used at the stage of primary antiviral activity screening as positive control in this test. The cultural medium was grown in a 96-well microplate until the bottom of each well was covered with cells. The residual cultural medium was completely removed and each well was washed twice with phosphate buffer. A solution of Flu A H1N1 in dimethyl sulfoxide (DMSO) was added to each well, adjusted to the required concentration. Then, a compound **5 e** or Amizon, or Ribavirin (Sigma), dissolved in DMSO, was added to each well to a final concentration of 0.1 to 10 μg / ml. After 48 h cultivation the state of the culture of MSCK cell was observed in a microscope. Then 100 μl of 70% acetone was added and each well was kept at –20 °C for 1 h. After drying 100 μl of 0.4 % (w/v) solution of SRB (sulfodoamine B) dissolved in 1% (v/v) acetic acid was added. After 30 minutes of staining, the non-binding SRB was removed and each well was washed 4 times with 1% (v/v) acetic acid. After drying 100 μl 10 mM Tris solution (pH 10.5) was added to each well to dissolve the colored substance at the bottom of the well. Optical density was measured to evaluate antiviral activity. Cells treated with DMSO only and cells treated with DMSO and the Flu A H1N1 virus were used for control.

Results and discussion. Analysis of the results of antiviral activity against the Flu A H1N1 California/07/2009 virus indicates that compound **5 e** is effective at a concentration lower than 116 times than such of Ribavirin and 626.7 times that compared with Amizon. According to the selectivity index, the test compound (SI > 1300) significantly exceeds Ribavirin and Amizon (SI > 37 and SI > 2.1 respec-

Table

Antiviral activity of 2-(4,6-dimorpholine-4-yl-1,3,5-triazine-2-yl)-N-4-ethoxyphenylhydrazine-carbothioamide 5 e against the Flu A (H1N1) virus California / 07/2009

Compound	Structure	Type of virus	EC_{50}, μg /ml	IC_{50}, μg /ml	SI
5 e		Flu A (H1N1) California/07/2009	0.075	> 100	> 1300
Ribavirin		Flu A (H1N1) California/07/2009	8.7	> 320	> 37
Amizon		Flu A (H1N1) California/07/2009	47	> 100	> 2.1

Notes. 1) The EC_{50} represents the concentration of a compound where 50 % of the population exhibit a response, after a specified exposure duration. Expressed in μg/ml. 2) IC_{50} is the concentration of a drug that is required for 50% inhibition in vitro. Expressed in μg/ml. 3) SI is an index of selectivity, which is an indicator of the effectiveness of the drug, and is expressed by the ratio of IC_{50} to EC_{50}.

tively) at IC_{50} > 100 μg/ml [12]. Consequently, if the IC_{50} of the test substance and Ribavirin were the same, the selectivity index for compound 5e would be even three times higher.

Under this test system Amizon substance showed much less antiviral activity against the Flu A H1N1 California/07/2009 virus compared with compound **5 e** and was lower than Ribavirin (Table).

Thus, new compound, 2-(4,6-dimorpholine-4-yl-1,3,5-triazine-2-yl)-N-4-ethoxyphenylhydrazine-carbothioamide, provides high antiviral activity against Flu A H1N1 California / 07/2009. The data obtained substantiate the expediency of further studies of 2-(4,6-dimorpholine-4-yl-1,3,5-triazine-2-yl)-N-4-arylhydrazine-carbothioamides as potential antiviral agents.

Acknowledgement. The authors express their appreciation to the Southern Research Institute (SRI, Birmingham, Alabama) for screening antiviral activity of compounds.

Conclusions

1. Under *in vitro* assay on MDCK cell culture 2-(4,6-dimorpholine-4-yl-1,3,5-triazine-2-yl)-N-4-ethoxyphenylhydrazine-carbothiomide exhibits high antiviral activity against the Flu A H1N1 California/07/2009, with an effective concentration (EC_{50}) of 0.075 μg / ml (116 times less than that of Ribavirin and 626.7 times that of Amizon) and selectivity index (SI) > 1300 that significantly exceeds such indicators for Ribavirin and Amizon (SI > 37 and SI > 2.1, respectively).
2. The data obtained indicate the expediency of further study of derivatives of 2-(4,6-dimorpholine-4-yl-1,3,5-triazine-2-yl)-N-arylhydrazine-carbothioamides as potential antiviral agents.

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Synthesis and antiviral activity of 2-(4,6-dimorpholine-4-yl-1,3,5-triazine-2-yl)-N-arylhydrazine-carbothioamides for FLU A H1N1 virus

The problem of acute respiratory viral infections (ARI) and influenza A (H1N1 subtype) has become very current with their epidemic and pandemic worldwide spread. Therefore, the current mainstream view of medical chemistry is the development and practical implementation of new high-performance pharmaceutical products for the treatment of influenza.

The aim of research is to synthesize the derivatives of 2-(4,6-dimorpholine-4-yl-1,3,5-triazine-2-yl)-N-arylhydrazine-carbothioamide and to study the antiviral activity of 2-(4,6-dimorpholine-4-yl-1,3,5-triazine-2-yl)-N-(4-ethoxyphenyl)-hydrazine-carbothioamide for Flu A H1N1 California/07/2009 at primary pharmacological screening stage.

The investigated compounds – derivatives of 2-(4,6-dimorpholine-4-yl-1,3,5-triazine-2-yl)-N-arylhydrazine-carbothioamides were synthesized by the interaction of 2-hydrazine-4,6-dimorpholinetriazine-1,3,5 with arylisothiocyanates.

The antiviral activity of 2-(4,6-dimorpholine-4-yl-1,3,5-triazine-2-yl)-N-4-ethoxyphenylhydrazine-carbothioamide against the virus Flu A H1N1 California/07/2009 was evaluated on MDCK cell culture test *in vitro*.

It has been shown that the test substance exhibits high antiviral activity against the influenza A virus H1N1 California/ 07/2009 with the effective concentration of EC_{50} 0,075 μg/ml and the selectivity index SI > 1300 (for Ribavirin SI > 37 and Amizona SI > 2,1).

The data obtained substantiate the expediency of further study of derivatives of 2-(4,6-dimorpholine-4-yl-1,3,5-triazine-2-yl)-N-arylhydrazine-carbothioamides as potential antiviral agents.

Key words: antiviral activity, Flu A virus (H1N1) California/07/2009, Ribavirin, Amizon, derivatives of 2-(4,6-dimorpholine-4-yl-1,3,5-triazine-2-yl)-N- arylhydrazine-carbothioamides

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Синтез і противірусна активність 2-(4,6-диморфолін-4-їл-1,3,5-триазин-2-їл)-N-арилгідразин-карботіоамідів відносно вірусу FLU A H1N1

Проблема гострих респіраторних вірусних інфекцій і грипу А (підтип H1N1) сьогодні зумовлена епідемічним розповсюдженням їх у світі. Тому актуальним напрямом медичної хімії є розробка та практичне впровадження нових високоефективних препаратів для лікування грипу.

Мета дослідження – синтез та вивчення противірусної активності похідних 2-(4,6-диморфолін-4-їл-1,3,5-триазин-2-їл)-N-арилгідразин-карботіоамідів відносно вірусу Flu A H1N1 California/07/2009 на етапі первинного фармакологічного скринінгу.

Досліджувані сполуки – похідні 2-(4,6-диморфолін-4-їл-1,3,5-триазин-2-їл)-N-арилгідразин-карботіоамідів було синтезовано шляхом взаємодії 2-гідразин-4,6-диморфолінтриазину-1,3,5 з арилізотіоціанатами. Оцінено противірусну активність 2-(4,6-диморфолін-4-їл-1,3,5-триазин-2-їл)-N-4-етоксифенілгідразинкарботіоаміду *in vitro* на культурі клітини MDCK з рибавірином як позитивним контролем у цьому тесті.

Показано, що досліджувана речовина виявляє високу противірусну активність відносно вірусу Flu A H1N1 California/07/2009 за показниками ефективної концентрації EC_{50} 0,075 мкг/мл та індексом селективності SI > 1300 (для Рибавірину SI > 37, Амізону SI > 2,1).

Отримані дані обґрунтовують доцільність подальшого вивчення похідних 2-(4,6-диморфолін-4-їл-1,3,5-триазин-2-їл)-N-арилгідразин-карботіоамідів як потенційних противірусних засобів.

Ключові слова: противірусна активність, вірус Flu A H1N1 California/07/2009, Рибавірин, Амізон, похідні 2-(4,6-диморфолін-4-їл-1,3,5-триазин-2-їл)-N-арилгідразинкарботіоамідів

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Синтез и противовирусная активность 2-(4,6-диморфолин-4-ил-1,3,5-триазин-2-ил)-N-арилгидразинкарботиоамидов по отношению к вирусу FLU A H1N1

Проблема острых респираторных вирусных инфекций и гриппа А (подтип H1N1) на сегодняшний день обусловлена эпидемическим распространением в мире. Поэтому актуальным направлением медицинской химии является разработка и практическое внедрение новых высокоэффективных лекарственных препаратов для лечения гриппа.

Цель исследования – синтез и изучение противовирусной активности производных 2-(4,6-диморфолин-4-ил-1,3,5-триазин-2-ил)-N-арилгидразинкарботиоамидов по отношению к вирусу Flu A H1N1 California/07/2009 на этапе первичного фармакологического скрининга.

Исследуемые соединения – производные 2-(4,6-диморфолин-4-ил-1,3,5-триазин-2-ил)-N-арилгидразинкарботиоамидов синтезированы путем взаимодействия 2-гидразин-4,6-диморфолинтриазина-1,3,5 с арилизотиоцианатами.

Оценена противовирусная активность 2-(4,6-диморфолин-4-ил-1,3,5-триазин-2-ил)-N-4-этоксифенилгидразинкарботиоамида *in vitro* на культуре клеток MDCK с рибавирином в качестве позитивного контроля в этом тесте.

Показано, что исследуемое вещество проявляет высокую антивирусную активность по отношению к вирусу Flu A H1N1 California/07/2009 по показателям эффективной концентрации EC_{50} – 0,075 мкг/мл и индексу селективности – SI > 1300 (для Рибавирина SI > 37, а Амизона SI > 2,1).

Полученные данные обосновывают целесообразность дальнейшего изучения производных 2-(4,6-диморфолин-4-ил-1,3,5-триазин-2-ил)-N-арилгидразинкарботиоамидов в качестве потенциальных противовирусных средств.

Ключевые слова: противовирусная активность, вирус Flu A H1N1 California/ 07/2009, Рибавирин, Амизон, производные 2-(4,6-диморфолин-4-ил-1,3,5-триазин-2-ил)-N-арилгидразинкарботиоамидов

Надійшла: 3 грудня 2018 р.

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