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PREDICTION OF BIOLOGICAL ACTIVITY OF TRIAZOLES DERIVATIVES

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In silico forecasting methods are widely used to solve the current issues of pharmacology, which allow to establish new functional and structural relationships of virus metabolism and cells, to conduct preliminary screening of compounds for their biological activity. These methods play a key role in the discovery and development of new biologically active compounds and have both scientific and practical importance. At present, Herpesviridae have an important place in human infectious pathology but are poorly controlled. Therefore, new effective drugs screening is an urgent and important problem. ***Aim****. The aim of the study was to conduct a prediction of antiviral and antitumor biological action of 1,2,3-triazoles derivatives containing fluorine atoms.* ***Methods*** *The PASS (Prediction of Activity Spectra for Substances) program was used to predict biological effects of the studied compounds. The inhibitory effect of the compounds on the cell culture was determined using the MTT method.* ***Results****. It was established that perfluoropropyl-1,2,3-triazole, trifluoromethyl-1,2,3-triazole, and difluoromethyl-1,2,3-triazole may have antiviral effect with likelihood indicators of activity from 0.216 to 0.339. Correlation analysis of the potential antitumor effect for the compound of fluorinated 1,2,3-triazoles with different radicals was performed. The probability of antineoplastic action presence is slightly higher and ranged from 0.218 to 0.571. Correlation of results was found for compound G18 (2-(β-D-ribofuranosyl)-4-tosyl-5-(trifluoromethyl)-2H-1,2,3-triazole) in silico and in vitro with respect to the antitumor effect on cell B- human lymphoma. It should be noted that the ability to inhibit the enzymes of nucleic acid synthesis and activate proteins involved in the apoptotic cascades is predicted for many compounds.* ***Conclusion.*** *Potential biological action for novel synthesized fluorine-containing derivatives based on 1,2,3-triazole was predicted using the PASS program. Compounds are believed to be capable to realize high antiviral and antineoplastic properties. The data obtained indicate the feasibility of further in vitro research of triazole derivatives with the prospect of creating drugs on their basis.*

Keywords: antiviral activity, structure-activity relationship, nucleoside analogs, triazoles.

One of modern directions of promising antiviral substance investigation is a comparative analysis of practical and predictable results. To this purpose, *in silico* methods have been developed and actively used, which allow to establish new functional and structural interrelationships of virus metabolism and cells of an organism, as well as to conduct preliminary screening of chemical compounds in relation to their biological activity. These methods play a key role in the discovery and development of new biologically active compounds and have both scientific and practical importance. Drugs are essential for the prevention and treatment of diseases. Human life is constantly threatened by many diseases such as viral infections and cancer caused by herpesviruses [1, 2, 3]. Within the *Herpesviridae*, Kaposi's sarcoma-associated herpesvirus causes Kaposi's sarcoma, and Epstein-Barr virus causes Burkitt's lymphoma, Hodgkin's lymphoma, *B* lymphoproliferative disorder [4, 5, 6, 7]. Antiviral drugs are often presented by nucleoside analogs (as DNA building-blocks), viruses include them into genome during replication by mistake. Examples of nucleoside analogs are acyclovir for herpes simplex virus infections treatment and lamivudine for HIV and Hepatitis B virus infections treatment. Acyclovir is one of the oldest and most frequently prescribed antiviral drugs [8, 9]. Therefore, ideal drugs are always in great demand. To meet the challenges of ideal drugs, an efficient method of drug development is demanding. The process of drug development is challenging, time-consuming, expensive, and has other complicating aspects [10].

Over the past decades, the development of drugs has evolved into a new, large-scale, computer-aided technology that is called drug design. Drug design, often called rational drug design, is an inventive process of finding new medications based on the knowledge of biological target. Most commonly the drug is an organic small molecule that activates or inhibits the function of biomolecule such as protein, which in turn results in a therapeutic benefit to the patient. Thus, a new approach that relies on computer modeling techniques called the computer-aided drug design (CADD) has been developed to simplify the procedure of new drugs finding. Structure-based drug design (SBDD) and ligand-based drug design (LBDD) are the two general types of CADD approaches [10]. LBDD methods focus on known target ligands to establish a relationship between their physicochemical properties and activities, referred to as a quantitative structure-activity relationship (QSAR), this information can be used for optimization of known drugs or for design of new drugs with improved activity [10, 11]. The process of QSAR model development can be divided into three stages – data preparation, model development, and validation, representing a standard practice of any QSAR modeling. 3D-QSAR methodologies have been successfully used to generate models of various chemotherapeutic agents [12, 13].

Heterocyclic compounds particularly 1,2,3-triazole and their derivatives with specific activity compounds are used in the treatment of infectious disease. Biological activity of triazoles and their derivatives have been demonstrated by various studies [14, 15–18]. For instance, data came from previous investigations showed that 1,2,3-triazole nucleus possesses a wide range of pharmacological activities such as analgesic, antibacterial [14], antifungal [15–17], anti-inflammatory and antioxidant [18–22]. Thus, 1,2,3-triazoles are the promising class of heterocyclic compounds for antiviral activity studies. Extension of data on fluorine substances potential as antiviral agents, namely the study of possible targets for their action for abnormal fluorinated nucleosides involved in the reproduction of herpes viruses, is very important for the development of new antiviral agents, which can be applied in medical practice in the treatment of viral diseases in future.

In this study, newly fluorinated derivatives of 1,2,3-triazoles were studied using PASS Online web-resource to predict their potential biological activity, especially antiviral, and possible mechanism of action. Also, the potential cytotoxic effect of new compounds was studied on the human cancer cell line.

Material and methods. *Tested substances*: Fluorinated derivatives of 1,2,3-triazoles: 2-(3-chlorotetrahydro-2*H*-pyran-2-yl)-4-tosyl-5-(trifluoromethyl)-2*H*-1,2,3-triazole (G6); 2-(3-chlorotetrahydro-2*H*-pyran-2-yl)-4-(perfluoropropyl)-5-tosyl-2*H*-1,2,3-triazole (G7); 2-(3-chlorotetrahydrofuran-2-yl)-4-tosyl-5-(trifluoromethyl)-2*H*-1,2,3-triazole (G8); 2-(3-chlorotetrahydrofuran-2-yl)-4-(perfluoropropyl)-5-tosyl-2*H*-1,2,3-triazole (G9); 2-(3,4-dihydro-2*H*-pyran-6-yl)-4-tosyl-5-(trifluoromethyl)-2*H*-1,2,3-triazole (G10); 2-(3,4-dihydro-2*H*-pyran-6-yl)-4-(perfluoropropyl)-5-tosyl-2*H*-1,2,3-triazole (G11); 2-(4,5-dihydrofuran-2-yl)-4-tosyl-5-(trifluoromethyl)-2*H*-1,2,3-triazole (G12); 2-(4,5-dihydrofuran-2-yl)-4-(perfluoropropyl)-5-tosyl-2*H*-1,2,3-triazole (G13); 2-(tetrahydro-2*H*-pyran-2-yl)-4-tosyl-5-(trifluoromethyl)-2H-1,2,3-triazole (G14); 2-(1-etoxyethyl)-4-tosyl-5-(trifluoromethyl)-2H-1,2,3-triazole (G15); 2-(2-deoxy-2-chloro-β-D-arabinofuranosyl)-4-tosyl-5-(perfluoropropyl)-2H-1,2,3-triazole (G16); 2-(2-deoxy-2-chloro-β-L-arabinopyranosyl)-4-tosyl-5-(perfluoropropyl)-2H-1,2,3-triazole (G17); 2-(β-D-ribofuranosyl)-4-tosyl-5-(trifluoromethyl)-2H-1,2,3-triazole (G18); 5-(difluoromethyl)-2-(β-D-ribofuranosyl)-4-tosyl-2H-1,2,3-triazole (G19); 2-(tetrahydrofuran-2-yl)-4-tosyl-5-(trifluoromethyl)-2H-1,2,3-triazole (G20); 5-(perfluoropropyl)-2-(tetrahydrofuran-2-yl)-4-tosyl-2H-1,2,3-triazole (G21); 2-(2-chloro-1-ethoxyethyl)-4-tosyl-5-(trifluoromethyl)-2H-1,2,3-triazole (G22); 2-(2-chloro-1-(2,2,2-trifluoroethoxy)ethyl)-4-tosyl-5-(trifluoromethyl)-2H-1,2,3-triazole (G23); 4-tosyl-2-(1-(2,2,2-trifluoroethoxy)vinyl)-5-(trifluoromethyl)-2*H*-1,2,3-triazole (G24); 2-(1-(4-tosyl-5-(trifluoromethyl)-2H-1,2,3-triazol-2-yl)ethoxy)ethan-1-ol (G25); 2-(3-clorotetrahydrofuran-2-yl)-4-tosyl-5-(perfluoropropyl)-1,2,3-triazole (G29), were studied in this research (table 1). All derivatives (G6 – 25, G29) were synthesized in Institute of Organic Chemistry of NAS of Ukraine [23].

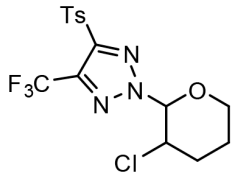
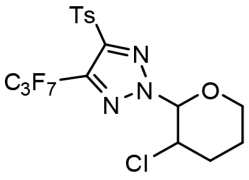
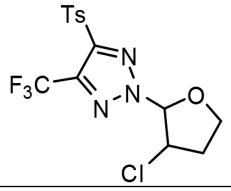
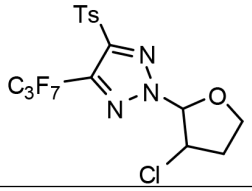
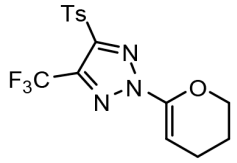
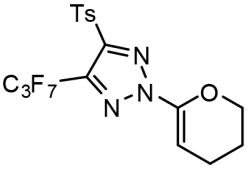
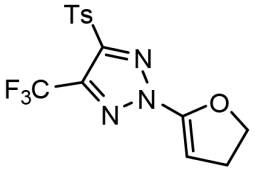
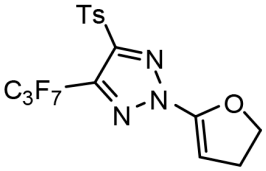
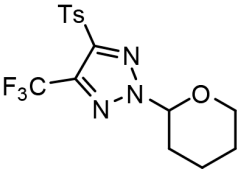
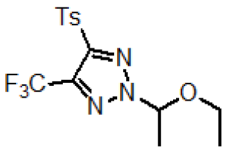
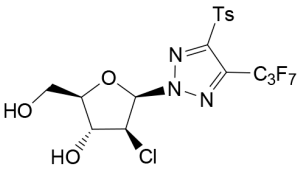
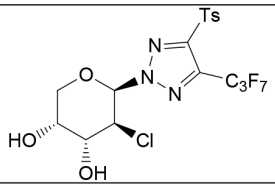
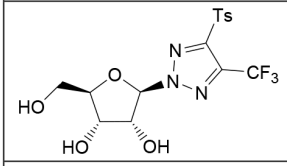
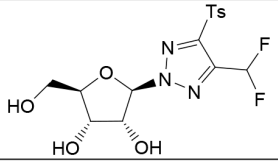
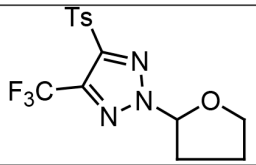
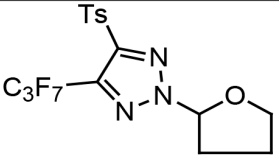
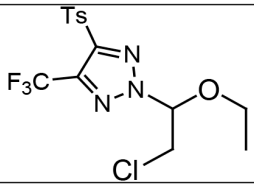
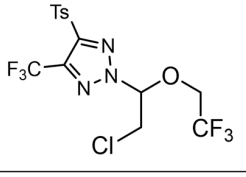
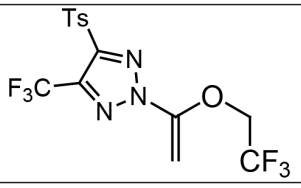
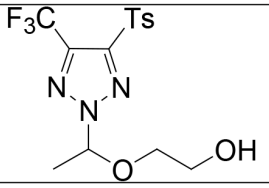
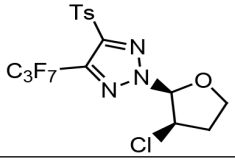
Prediction of biological activity. PASS (Prediction of Activity Spectra for Substances) was used in this study. This program provides simultaneous predictions for many types of biological activities (activity spectrum) based on the structure of drug-like compounds [18, 19, 20]. Biological activities are described qualitatively (active or inactive) in PASS. The algorithm of the

activity spectrum estimation is based on the naive Bayes approach with some significant enhancements [21]. Activity of the molecule is predicted by "comparing" the structure of the new compound with the structure of a well-known active substrate existing in the database. The PASS prediction tool predict Pa:Pi (active, inactive) ratio with Pa > 30%, Pa > 50%, and Pa > 70% prediction threshold. The average accuracy of prediction is about 95% according to leave-one-out cross-validation estimation. Accuracy of PASS prediction depends on comprehensive information about the biological activity spectrum for each compound available in the PASS training set, and therefore, the estimate of biological activity is more accurate [24–26].

Cell culture. B-lymphoblastoid Raji cell line (human B-lymphocyte isolated from Burkitt's lymphoma) was used as a model of EBV-infection *in vitro*. Cells were obtained from Culture Bank of D.I. Ivanovsky Institute of Virology of Russian Academy of Medical Sciences (Moscow, Russia). Cells were cultured in RPMI 1640 medium (Sigma, USA) containing 10% (v/v) fetal calf serum (Sigma, USA) and gentamicin (100 μg/mL) and incubated at 37 °C in 5% CO_2 atmosphere. Stock compound solutions were prepared in 50% dimethylsulphoxide (DMSO) and 50% serum-free media at 10 mg/ml. After using the stocks were kept at -20°C. The compounds were further diluted

Table 1

Chemical structure of studied fluorinated derivatives of 1,2,3-triazoles

G6	G7	G8	G9
			
G10	**G11**	**G12**	**G13**
			
G14	**G15**	**G16**	**G17**
			
G18	**G19**	**G20**	**G21**
			
G22	**G23**	**G24**	**G25**
			
G29			
			

for MTT-assays to the concentration in a range from 62.5 to 2000 μg/ml using complete medium and incubated for 48h.

MTT assay. The inhibitory concentration of tested substances, in which the viability of Raji cells population was reduced to 50% (IC_{50}) was studied by MTT-method. This method is based on the ability of mitochondrial dehydrogenase system of intact cells to convert the pale yellow artificial substrate MTT (Sigma, USA) to a blue formazan, which could be spectrophotometrically measured. After 48h incubation, the 96-well plates were spin at 1000xg, 4°C for 5 minutes in a microplate-compatible centrifuge, the media was carefully aspirated. MTT solution (25 μl; 5 mg/mL) and 100 μL of serum-free media were added in each well of a 96-well microtiter plate containing cells and incubated for 3h at 37 °C in 5% CO_2 atmosphere. After incubation period experimental material was centrifuged at 1500 rpm for 10 min, then supernatant from each well was collected and 200 μl of 96% ethanol was added to dissolve the dye. After 10 min gentle shaking at 37°C, the measurement of optical density (OD) at 540 nm was done using Multiskan FC universal microplate reader (Thermo Scientific, USA). The ratio of MTT into formazan conversion in each well was calculated by comparing their OD at 540 nm with the untreated sample control. Three wells were used for each concentration of the compounds with the calculation of the mean. The colonies formed by the control and test cells were counted to calculate the inhibitory concentration (IC_{50}) values at the appropriate dilution gradient [27].

Results. Current research was focused on a specific activity that may play an important role in the antiviral effect of 1,2,3-triazoles containing several atoms of fluorine. Quantitative structure-activity relationship (QSAR) model was used for biological activity prediction of the modified compounds. Studied derivatives of triazoles were divided into two groups by the number of fluorine atoms, namely, the first group was represented by G6, G8, G10, G12, G14, G15, G18-20, G22–25 compounds, which contained three fluorine atoms, while the second group compounds (G7, G9, G11, G13, G16, G17, G21, G29) contained seven fluorine atoms.

Analysis of the results obtained with the use of PASS allowed to establish general patterns between the two groups. G18 and G19 compounds may have antiviral activity as predicted (table 2). The probability of Pa/Pi was 0.339/0.043 for G18 and 0.310/0.054 for G19. Thus, both compounds contain a chlorinated substituent pyran (6-membered) ring, but G18 compound contains three fluorine residues, while G19 – only two. Also, 22–24 compounds could be promising molecules for the development of more potent and safe antiviral drugs, like 3C-like protease inhibitor of coronaviruses.

G6, G8, G10, G12, G14 compounds, based on chlorine substituted furan (5-membered) ring and G15 compound with acyclic substituent, did not have antiviral activity according to the results of forecasting (table 2). However, it should be noted that all of these compounds may be a substrate for cytochrome 450 (CYP2D15). The probability of the presence of activity/inactivity (Pa/Pi) ranged from 0.355/0.116 to 0.508/0.018. Cytochrome is one of the important components of mitochondrial system and plays an important role in metabolism of drugs. On the one hand, the cytochrome molecule is capable to deactivate drugs, either directly or by facilitating excretion from the body. On the other hand, many substances are activated by CYP to form their active forms. Also, cytochrome blocking and it's releasing from mitochondria is one of the apoptosis triggers. It should be noted that antitumor activity is among the list of probable activities for G6, G8, G14, and G15 compounds (table 2), the Pa/Pi index ranged from 0.262/0.024 to 0.268/0.017, which is relevant in the context of antitumor compounds search. The ability to stimulate caspase 3 is among the probable activities reported for G10 and G12 compounds, to inhibit DNA-dependent and RNA-dependent DNA polymerases – for G6, G8, G14, and G15 compounds. The Pa/Pi index was within the range of 0.228/0.029 – 0.285/0.158.

Another promising area of research is the predicted ability of G10, G12, G14, and G15 compounds to act as a chemosensitizer. According to the definition of the National Cancer Institute, chemosensitizers are a class of drugs that increase the sensitivity of tumor cells to chemotherapy. This potential activity was predicted for two compounds (G10 and G12), Pa/Pi was 0.373/0.073 and 0.501/0.020, respectively. Also, compounds of this group may effect on different systems of viruses and cells, such as inhibitor of transactivator transcription protein, phosphatase, dihydropyrimidine dehydrogenase, antagonist of sphingosine 1-phosphate receptor 1, and heat shock protein 27.

Table 2

The results of the biological activity prediction of fluorinated derivatives of 1,2,3-triazoles containing 3 atoms of fluorine

Biological activity	Probability of activity, Pa/Pi					
	G6	G8	G10	G12	G14	G15
CYP2D15 substrate	0.355*/ 0.116	0.397/ 0.074	0.482/ 0.025	0.503/ 0.018	0.448/ 0.040	0.448/ 0.040
Transactivator transcription protein inhibitor	0.277/ 0.021	0.285/ 0.015	-	-	-	-
Chemosensitizer	-	-	0.373/ 0.073	0.501/ 0.020	-	-
Dihydropyrimidine dehydrogenase inhibitor	0.274/ 0.009	0.247/ 0.012	-	-	0.410/ 0.003	0.410/ 0.033
Antineoplastic (bone cancer)	**0.258/ 0.021**	**0.268/ 0.017**	**-**	**-**	**0.226/ 0.024**	**0.226/ 0.024**
Phosphatase inhibitor	-		0.342/ 0.252	-	0.324/ 0.273	0.324/ 0.273
RNA directed DNA polymerase inhibitor	0.233/ 0.059	0.255/ 0.047	-	-	0.346/ 0.022	-
Sugar-phosphatase inhibitor	-	-	0.227/ 0.205	0.307/ 0.180	-	-
Heat shock protein 27 antagonist	-	-	-	-	0.307/ 0.205	0.307/ 0.205
Caspase 3 stimulant	-	-	0.285/ 0.158	0.274/ 0.180	-	-
DNA directed RNA polymerase inhibitor	-	-	-	-	0.228/ 0.029	0.228/ 0.029
Sphingosine 1-phosphate receptor 1 antagonist	-	-	-	-	0.223/ 0.033	0.223/ 0.033

Table 2. (Continued)

Biological activity	Probability of activity, Pa/Pi						
	G18	G19	G20	G22	G23	G24	G25
Sugar-phosphatase inhibitor	0.664/ 0.041	0.629/ 0.048	-	0.217/ 0.235	-	0.361/ 0.145	0.369/ 0.141
CYP2D15 substrate	-	-	0.439/ 0.044	-	-	0.517/ 0.015	0.502/ 0.018
CYP2C18 substrate	-	-	-	-	0.489/ 0.021	-	-
Adenosine regulator	0.626/ 0.009	0.616/ 0.009	-	-	-	-	-
Sphingosine 1-phosphate receptor antagonist	-	-	0.226/ 0.079	0.313/ 0.164	0.306/ 0.005	0.336/ 0.04	0.236/ 0.023
Antineoplastic	**0.572/ 0.051**	**0.520/ 0.005**	**0.235/ 0.012**	**0.218/ 0.214**	**-**	**-**	**0.224/ 0.176**
Heat shock protein 27 antagonist	0.538/ 0.010	0.529/ 0.011	0.302/ 0.215	-	-	-	-
RNA directed DNA polymerase inhibitor	0.356/ 0.021	0.331/ 0.024	0.356/ 0.021	-	-	-	-
3C-like protease (Human coronavirus) inhibitor	-	-	-	0.200/ 0.172	0.208/ 0.156	0.239/ 0.093	-
Caspase 3 stimulant	0.310/ 0.0320	-	-	-	-	0.282/ 0.164	0.252/ 0.235
CDK9/cyclin T1 inhibitor	0.443/ 0.029	0.435/ 0.031	-	-	-	-	0.261/ 0.197

Table 2. (Continued)

TP53 expression enhancer	0.509/ 0.086	0.390/ 0.147	-	0.265/ 0.243	-	-	-
Anti-inflammatory	-	0.420/ 0.085	-	-	-	-	-
Anti-metastatic	0.429/ 0.038	0.418/ 0.041	-	-	-	-	-
NF kappa B transcription factor stimulant	0.412/ 0.047	0.405/ 0.050	-	-	-	-	-
DNA synthesis inhibitor	-	0.365/ 0.034	-	-	-	-	-
Antiviral (*Poxvirus*)	**0.339/ 0.43**	**0.310/ 0.054**	-	-	-	-	-
Antiviral (*Herpesvirus*)	**0.322/ 0.076**	**0.293/ 0.023**	-	-	-	-	-
Antiviral (*Picornavirus*)	**0.305/ 0.219**	-	-	-	-	-	-

Annotation:*The range of Pa from 0.3 to 0.6 indicates potentially novel compounds and has a high likelihood of exhibiting the required biological activity in the in vitro system.

Another group of studied compounds that contain seven atoms of fluorine (G7, G9, G11, G13, G16, G21, and G29) was analyzed. Only G17 compound may have antiviral activity (Pa/Pi was 0.216/0.083), while other compounds do not have potential antiviral activity (table 3).

G7, G9, G16, G17, and G29 compounds may have antineoplastic activity, their Pa/Pi index ranged from 0.248/0.035 to 0.571/0.052. Our PASS analysis of 1,2,3-triazoles derivatives structure with seven atoms of fluorine shown that these compounds may possess their antineoplastic activities through

Table 3

The results of the biological activity prediction of fluorinated derivatives of 1,2,3-triazoles containing 7 atoms of fluorine

Biological activity	Probability of activity, Pa/Pi							
	G7	G9	G11	G13	G16	G17	G21	G29
Heat shock protein 27 antagonist	-	-	-	-	0.419/ 0.050	-	-	-
NF kappa B transcription factor stimulant	-	-	-	-	0.300/ 0.185	0.335/ 0.088	-	-
Transactivator transcription protein inhibitor	0.257/ 0.040	0.265/ 0.031	-	-	0.275/ 0.022	0.261/ 0.034	-	0.265/ 0.025
TP53 expression enhancer	-	0.291/ 0.218	-	-	0.573/ 0.058	0.272/ 0.236	-	0.291/ 0.218
RNA directed DNA polymerase inhibitor	-	-	-	-	0.319/ 0.027	-	0.289/ 0.034	-
Protein kinase (CK2) inhibitor	0.394/ 0.003	0.405/ 0.003	0.424/ 0.003	0.430/ 0.003	0.364/ 0.004	0.379/ 0.004	0.414/ 0.003	0.405/ 0.003
DNA synthesis inhibitor	-	-	-	-	0.263/ 0.073	-	-	-
DNA polymerase I inhibitor	-	-	-	-	0.329/ 0.101	-	-	-
Chemosensitizer	-	-	0.335/ 0.112	0.444/ 0.034	-	-	-	-
Antiviral	**-**	**-**	**-**	**-**	**-**	**0.216/ 0.083**	**-**	**-**
Antineoplastic (bone cancer)	**0.248/ 0.035**	**0.257/ 0.025**	**-**	**-**	**0.571/ 0.052**	**0.270/ 0.172**	**-**	**0.257/ 0.025**

multiple mechanisms including protein kinase (CDK2) inhibiting, enhancing of TP53 expression, stimulation of NF kappa B transcription factor and heat shock protein. Also G11 and G13 compound may act as a chemosensitizer.

G16 compound contains a chlorinated substituent furan (5-membered) ring, which may inhibit the activity of DNA polymerase I, RNA directed DNA polymerase, and DNA synthesis, respectively. Thus, the prediction of biological activity plays an important role in new active compounds screening.

Studies on the cytotoxic effects of compounds with detectable antitumor activity on the Raji cell culture model (human B-lymphoma) were conducted. The drug concentration that reduced the viability of cells by 50% (IC_{50}) was determined by using MTT-method. This test is widely used in the *in vitro* evaluation of the cytotoxic potency of drugs. *In vitro* cytotoxicity assays were used to evaluate anti-neoplastic effects of drugs on the target cell line.

In this paper, we used the MTT assay to evaluate the potential antineoplastic activity of new fluorinated compounds in comparison with the prediction by PASS. IC_{50} is the concentration of tested drug able to cause death of 50% of the cells and can be used for prediction of cytotoxic effect degree. The lower the value, the more cytotoxic is the substance. Figure 1 shows the comparison of the IC_{50} of fluorinated compounds against human cancer B-lymphoma cell lines. It was found that the G16 and G18 compounds, for which predicted activity level was the highest, had the most pronounced cytotoxic effect *in vitro* (figure 1).

Figure 1 shows that the relative potency of antineoplastic activity of tested compounds is almost the same as it was predicted by PASS. The range of the value of IC_{50} is comparable to Pa (predicted by PASS). According to the PASS prediction, G16 and G18 compounds have the highest probabilities of antineoplastic action, 0.571 and 0.572, respectively. At the same time, it should be noted that the IC_{50} of these compounds is quite little, for the G16 IC_{50} compound it was 250μg/ml, and for the G18 – 125μg/ml. The data obtained indicate a high toxic effect of the test compounds on the cancer cells by inhibiting the mitochondria metabolic activity. Mitochondrial dysfunction is one of the possible apoptosis triggering ways. Since one of the options for neoplastic disorders combating is the elimination of transformed cells from the body, it can be assumed that the antitumor effect of fluorinated derivatives (16 and 18) can be realized due to the high toxicity.

Discussion. 1,2,3-triazoles and their derivatives are important group of heterocyclic compounds characterized by a five-membered ring of two carbons and three nitrogen atoms. Triazole provides moderate dipole characteristics, hydrogen binding properties, stability and rigidity both under acidic and basic conditions. Triazoles constitute an important class of heterocycles because of their varied biological activities. Available 1,2,3-triazole drugs includes tazobactam, cefatrizine, and carboxyamidotriazole [28]. Several compounds with 1,2,3-triazole nucleus are registered as drugs, such as ribavirin (antiviral agent), terconazole and fluconazole (antifungal agents) [18, 19].

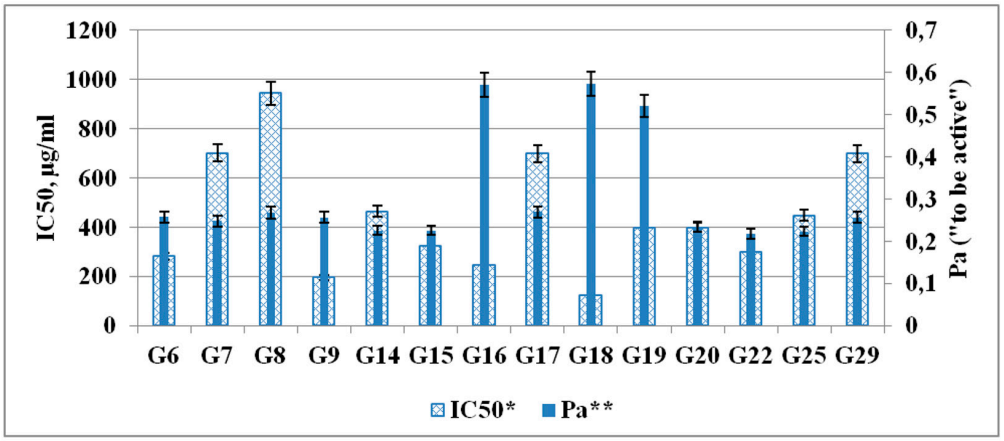


Fig.1 Comparison of the data of prediction of PASS and IC_{50}
***IC_{50} – The drug concentration, μg/ml, that reduced the viability of cells by 50%, (P>0.05);**
****Pa – "to be active".**

Also, the results of different studies describe the *N*-heterocyclic ring system as a core structure in many synthetic compounds exhibiting a broad range of biological activities. These include benzimidazole, benzothiazole, pyrazole, triazoles and other drugs containing pyridazine, pyridine and pyrimidines [28, 29].

The newly synthesized 1,2,3-triazole derivatives tested in this study may have significant antiviral activity against various types of viruses, such as herpesviruses, poxviruses, coronaviruses, and picornaviruses. The G18 and G19 compounds may be active against herpesviruses, poxviruses, and picornaviruses. The *Herpesviridae* and *Poxviridae* are large families of double-stranded DNA viruses responsible for many human and animal diseases. Viruses of both families have enveloped viruses that encode proteins for DNA replication and gene expression, but herpes viruses are replicated in the nucleus, while poxviruses – in the cytoplasm. Viruses encode in their genome a lot of necessary proteins, such as helicase-primase complex, DNA-polymerases, and other. However, many cellular proteins are involved in the reproduction of viruses that include proteins of DNA and RNA synthesis. According to the prediction of PASS, the 18 and 19 compounds can inhibit DNA polymerase and DNA synthesis in general. So, this may be one of the possible mechanisms of action of these compounds.

Also, our PASS analysis of the 1,2,3-triazoles structure shown that these compounds may possess their antitumor activities through multiple mechanisms including protein kinase inhibiting (CDK2, TP53 expression enhancer, CDK9/cyclin T1), caspase 3, heat shock protein stimulation. Obtained results are comparable to the literature data [9, 28–30]. Since many researchers describe a wide range of biological activity of triazoles, we anticipated the antiviral and antitumor activity of triazole derivatives, such as G6, G7, G8, G9, G14-20, G22, G25, and G29 compounds. There are only few 1,2,3-triazole-containing molecules on the market or in the last stage of clinical trials. Potential pharmaceuticals based on 1,2,3-triazoles include the anticancer compound carboxyamidotriazole (CAI), nucleoside derivative non-nucleoside reverse transcriptase inhibitor tert-butyldimethylsilylspiro-aminooxathioledioxide (known as TSAO), β-lactam Tazobactum antibiotic, Cefatrizine cephalosporin antibiotic, and so on.

It is known from literary sources, that medicinal chemists pay much attention to the selective introduction of a fluoro group into biologically active molecules [30]. Incorporating of fluorine atoms into a bioactive nucleoside as an isosteric replacement of hydrogen or as an isopolar mimic of hydroxyl group frequently leads to a dramatic change in biological activities and becomes an important strategy in the design and discovery of novel drug candidates [30]. It was established in our studies, that an increase in the number of fluorine atoms in the second group of compounds does not increase the probability of antiviral activity. But results analysis shown that 1,2,3-triazoles, which contains 7 atoms of fluorine, may inhibit RNA directed DNA polymerase, protein kinase, DNA polymerase, and other promising targets.

The MTT assay reported by Mosmann is a rapid and convenient colorimetric method of cells growth and survival *in vitro* investigation. In this paper, the MTT assay was used as a chemosensitivity test, and its potential was investigated. Our research shows the comparison of the IC_{50} of some chemotherapeutic drugs against human cancer cell line Raji. Thus, the fluorinated compounds with higher cytotoxic effect may possess antineoplastic potential.

Conclusion. Present research indicate the importance of 1,2,3-triazole and its fluorine containing derivatives studying. It is interesting that the fluorine substituent group also appeared to have a positive impact on the antiviral activity of these newly synthetic 1,2,3-triazole compounds. In this paper, we used the "Prediction of Activity Spectra for Substances" program for forecasting potential biological activity as the first step and fast way for screening promising compounds for further research. The results indicated that 17, 18, 19, 22, 23 and 24 compounds shown a potential activity against viruses, and 6–9, 14–17, 18–22, 25 and 29 compounds shown good antineoplastic activity against human cancer cell line Raji by inhibiting metabolic activity in MTT-assay. So, 1,2,3-triazoles are an important family of heterocyclic compounds that have a prominent place in medicinal chemistry.

ПРОГНОЗУВАННЯ БІОЛОГІЧНОЇ АКТИВНОСТІ ПОХІДНИХ ТРИАЗОЛІВ

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Резюме

З метою вирішення нагальних питань фармакології широко застосовуються методи прогнозування *in silico*, які дозволяють встановити нові структурно-функціональні взаємозв'язки метаболізму вірусу та клітини, проводити попередній скринінг сполук щодо їх біологічної активності та займають ключове місце у відкритті та розробці нових біологічно активних сполук як на науковому, так і на практичному рівнях. На сьогодні віруси родини *Herpesviridae* займають важливе місце в інфекційній патології людини, але погано контролюються. Тому скринінг нових ефективних препаратів є актуальною і важливою проблемою. **Мета**. Провести прогнозування біологічної активності похідних 1,2,3-триазолів, що містять атом фтору за напрямками "антивірусна" та "протипухлинна" активність. **Методи.** Для прогнозування біологічних ефектів досліджуваних сполук застосовували програму PASS (Prediction of Activity Spectra for Substances). Інгібуючий вплив сполук на культуру клітин визначали за допомогою МТТ-тесту. **Результати**. Встановлено, що антивірусну дію можуть мати перфторпропіл-1,2,3-триазол, трифторметил-1,2,3-триазол та дифторметил-1,2,3-триазол з показниками ймовірності наявності активності від 0,216 до 0,339. Проведено кореляційний аналіз потенційної протипухлинної дії для сполуки фторованих похідних 1,2,3-триазолів з різними радикалами. Ймовірність наявності антинеопластичної активності дещо вища і склала від 0,218 до 0,571. Виявлено кореляцію результатів для сполуки G18 (2- (β-D-рибофуранозил) -4-тозил-5- (трифторметил) -2H-1,2,3-триазол) *in silico* та *in vitro* щодо протипухлинної дії на моделі клітин В-лімфоми людини. Слід відмітити, що для багатьох сполук спрогнозована здатність інгібувати ферменти синтезу нуклеїнових кислот та активувати залучені в апоптотичні каскади білки. **Висновки**. Із застосуванням програми PASS зпрогнозовано потенційну біологічну активність для новосинтезованих фторовмісних похідних на основі 1,2,3-триазолу. Передбачено, що сполуки здатні реалізувати високу антивірусну, антинеопластичну активність. Отримані дані свідчать про доцільність подальших досліджень *in vitro* похідних триазолу з перспективою створення на їх основі лікарських засобів.

Ключові слова: антивірусна активність, залежність "структура-активність", нуклеозидні аналоги, триазоли.

ПРОГНОЗИРОВАНИЕ БИОЛОГИЧЕСКОЙ АКТИВНОСТИ ПРОИЗВОДНЫХ ТРИАЗОЛА

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Резюме

С целью решения неотложных вопросов фармакологии широко применяются методы прогнозирования *in silico*, которые позволяют установить новые функционально-структурные взаимосвязи метаболизма вируса и клетки, проводить предварительный скрининг соединений по их биологической активности и занимают ключевое место в открытии и разработке новых биологически активных соединений как на научном, так и практическом уровнях. На сегодня вирусы семейства *Herpesviridae* занимают важное место в инфекционной патологии человека, но плохо контролируются. Поэтому скрининг новых эффективных препаратов является актуальной и важной проблемой. **Цель**. Провести прогнозирование биологической активности производных 1,2,3-триазолов, содержащих атом фтора, по направлениям "антивирусная" и "противоопухолевая" активность. **Методы**. Для прогнозирования биологических эффектов исследуемых соединений применяли программу PASS (Prediction of Activity Spectra for Substances). Ингибирующее влияние соединений на культуру клеток определяли с помощью МТТ-теста. **Результаты**. Установлено, что антивирусное действие могут иметь перфторпропил-1,2,3-триазол, трифторметил-1,2,3-триазол и дифторметил-1,2,3-триазол с показателями вероятности наличия активности от 0,216 до 0,339. Проведен корреляционный анализ потенциального противоопухо-

левого действия для соединений фторированных производных 1,2,3-триазолов с различными радикалами. Вероятность наличия антинеопластической активности несколько выше и составила от 0,218 до 0,571. Выявлена корреляция результатов для соединения G18 (2- (β-D-рибофуранозил)-4-тозил-5 (трифторметил)-2H-1,2,3-триазол) *in silico* и *in vitro* по противоопухолевого действия на модели клеток В- лимфомы человека. Следует отметить, что для многих соединений спрогнозирована способность ингибировать ферменты синтеза нуклеиновых кислот и активировать белки, вовлеченные в апоптотические каскады. **Выводы**. С применением программы PASS спрогнозировано потенциальную биологическую активность для новосинтезированных фторсодержащих производных на основе 1,2,3-триазола. Предполагается, что соединения способны реализовать высокую антивирусную, антинеопластическую активность. Полученные данные свидетельствуют о целесообразности дальнейших исследований *in vitro* производных триазола с перспективой создания на их основе лекарственных средств.

Ключевые слова: противовирусная активность, зависимость “структура-активность”, нуклеозидные аналоги, триазолы.

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