Synthesis and antiviral activity of nonannulated tetrazolylpyrimidines

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Nonannulated tetrazolylpyrimidines in the structure of which the heterocyclic fragments are separated by hydrazinocarbonylmethyl, methylpyrazolyl groups or a sulfur atom were synthesized. Some of these compounds showed moderate in vitro activity against H1N1 subtype of influenza A virus. The selectivity index of the anti-influenza action of [5-[(4,6-dimethylpyrimidin-2-yl)sulfanyl]-1H-tetrazol-1-yl]acetic acid, which has very low cytotoxicity, was twice as high as the selectivity index of the reference drug rimantadine.

Keywords: pyrimidines, tetrazoles, biological activity, linkers, properties, structure, synthesis.

The relevance of the development of new antiviral drugs, as a rule, is determined by the presence or absence of prophylactic vaccines against newly emerging infections, as well as the ability of viruses to escape the host immune response and develop drug-resistant strains.1 The current situation has sharply exacerbated the problem of the availability of drugs against highly pathogenic variants of the influenza virus and the SARS2 coronavirus, the cause of COVID-19. The solution of this problem is determined by the effectiveness of the search for new drugs for the treatment of influenza and associated infectious diseases. Compounds of various structures are used in the treatment of this viral disease (Fig. 1). In this context, drugs that contain fragments of heterocyclic compounds, azoles and azines, in their active pharmaceutical ingredients (API) are of particular interest.

In 2014, riamilovir (Triazavirin) was registered as a drug for the treatment of influenza in the Russian Federation.2 Triazavirin has recently been proven effective in treating the new coronavirus infection and is well tolerated by patients with COVID-19.3 Triazavirin API, 7-(methylsulfanyl)-3-nitro[1,2,4]triazolo[5,1-c]triazin-4(1H)-one belongs to annulated azoloazines, which indirectly indicates the prospect of searching for new agents for influenza chemotherapy in the ranks of binuclear heterocyclic compounds based on azoles and azines. Derivatives of tetrazole and pyrimidine are among the most sought after scaffolds in modern medicinal chemistry.4,5 In particular, it was shown that some tetrazole derivatives exhibit pronounced activity against rhinoviruses6a and various strains of influenza A virus.6b In this regard, the synthesis and study of biological activity of binuclear...
heterocyclic compounds containing both tetrazolyl and pyrimidyl fragments in their structure are of interest. In the case of annulated tetrazolopyrimidines, the possibility of azidoazomethine-tetrazole isomerism should be considered.\textsuperscript{7,8} For some representatives of this series, the equilibrium can be shifted toward the open-chain azide form with significant cytotoxicity.

In this study, a series of nonannulated tetrazolopyrimidines was synthesized, and their structure and anti-influenza activity were investigated as well. Fragments of different nature were chosen as linker groups connecting the tetrazole and pyrimidine heterocycles – methylene, hydrazinocarbonylmethyl, pyrazolyl groups and a sulfur atom. This set of linkers would allow us to assess the prospects of given structural types in regards to biological activity.

At the first stage of our study, we attempted to synthesize 4,6-dimethyl-2-(5-phenyl-2\textsuperscript{H}-tetrazol-2-yl)pyrimidine (3) by direct hetarylation of the sodium salt of 5-phenyltetrazole (1) by 2-chloro-4,6-dimethylpyrimidine (2). However, it was not possible to isolate the target tetrazolopyrimidine 3 from the reaction mixture. Instead of nonannulated tetrazolopyrimidine 3, a compound was formed the properties of which were identical to those of 5,7-dimethyl-3-phenyl[1,2,4]triazolo[4,3-a]pyrimidine (4) described earlier.\textsuperscript{9} A possible reason for the discovered phenomenon is the thermolytic recyclization of intermediate 3 accompanied by the elimination of an N\textsubscript{2} molecule and the formation of annulated triazolopyrimidine 4 (Scheme 1).

Considering this experience, we focused our efforts on the synthesis of nonannulated tetrazolopyrimidines in the structure of which heterocyclic fragments are linked by linker groups such as hydrazinocarbonylmethyl, pyrazolyl, as well as a sulfur atom. To form a linking bridge in the target compounds, we used classical methods such as acylation of the terminal nitrogen atom of the NH\textsubscript{2} group with carboxylic acid halides, hydrazinolysis of esters, and the substitution of the chlorine atom in the corresponding hetaryls for a sulfur atom by the action of hetarylthiones.\textsuperscript{10} Hydrazides 7a,b were obtained by acylation of 2-hydrazinylpyridines (5a) or 2-hydrazinyl-4,6-dimethylpyrimidine (5b) with 5-phenyltetrazol-2-yl-acetic acid chloride (6) (Scheme 2).

1-(4,6-Dimethylpyrimidin-2-yl)-3-[(5-phenyl-2H-tetrazol-2-yl)methyl]-1H-pyrazol-5-ol (9) was accessed by hydrazinolysis of ethyl 3-oxo-4-(5-phenyl-2H-tetrazol-2-yl)-

Scheme 1

\textbf{Scheme 2}
butanoate (8) by 2-hydrazinyl-4,6-dimethylpyrimidine (5b) (Scheme 3). According to X-ray structural analysis data, the pyrazole fragment of compound 9 exists in the aromatic form—a hydroxy group is present at position 5. The rendering of the structures of the molecules of compounds 7b and 9 according to X-ray structural analysis data is shown in Figure 2.

Scheme 3

![Scheme 3](image)

According to the results of X-ray structural analysis, compounds 7b and 9 are nonplanar systems. The torsion angle HN(5)N(4)H of the hydrazine fragment is 110°. The nitrogen atom in the pyrimidine ring has a trigonal pyramid configuration. The phenyl substituent lies practically in the same plane as the azole fragment, while the planes of the heterocycles intersect at a significant (81°) angle to each other. The peculiarities of molecular packing in the solid state are determined by the presence of intermolecular hydrogen bonds with the participation of protons of the hydrazine fragment. A feature of the structure of compound 9 is its existence in the 5-hydroxypyrazole form, rather than that of 2,3-dihydropyrazol-3-one. In this case, the conformation of the compound turned out to be locked by the intramolecular hydrogen bond O(1)–H(1)···N(6) with the distance O(1)···N(6) 2.599 Å. At the same time, the tetrazole and pyrazole fragments of the molecule at the tetrahedral carbon atom are turned in relation to each other at an angle of 88.4° which makes the conformation of this compound propeller-like. A solid-state structural feature is the packing of molecules in the form of stacks along the 0a axis in such a way that the pyrimidine fragments of neighboring molecules form interatomic π–π contacts at a distance that is 0.05 Å less than the sum of the van der Waals radii of the atoms of these fragments.

2-{[1-phenyl-1H-tetrazol-5-yl)sulfanyl]pyrimidine (12a) was obtained by hetarylation of 1-phenyl-5-sulfanyl-tetrazole (10a) with 2-chloropyrimidine (11). Likewise, 5-[(4,6-dimethylpyrimidin-2-yl)sulfanyl]-1H-tetrazol-1-yl]-acetic acid (12b) was synthesized from 1-carboxymethyl-5-sulfanyltetrazole (10b) and 2-chloro-4,6-dimethylpyrimidine (2) (Scheme 4).

Scheme 4

![Scheme 4](image)

The prediction of the activity of nonannulated tetrazolylpyrimidines 7a,b, 9, and 12a,b, performed using the PASS computer system, indicates low (Pa 0.28–0.33) probability of antiviral activity for the compounds of this sample. However, low values of Pa factor are not always a verdict since they may indirectly indicate the novelty of the evaluated object. In this study, we investigated the in vitro antiviral activity of nonannulated tetrazolylpyrimidines 7a,b, 9, and 12a,b in the Laboratory of Experimental Virology of Saint Petersburg Pasteur Research Institute of Epidemiology and Microbiology. The study was carried out using the MDCK cell culture (ATCC CCL-34) against influenza virus strain A/Puerto Rico/8/34 (H1N1). Table 1 shows the values of 50% cytotoxic concentration (CC50), 50% inhibitory concentration (IC50), and selectivity index SI (the ratio of CC50 to IC50). Rimantadine was used as the reference drug. Compounds with a selectivity index of 10 and higher were considered promising.

The data in Table 1 illustrate that compounds 7a,b, 9, and 12a did not show activity against influenza virus strain A/Puerto Rico/8/34 (H1N1). The best results were obtained for compound 12b, the SI of which is twice that of the reference drug (rimantadine), but, in contrast to it, compound 12b has significantly lower cytotoxicity. This result indirectly indicates the promise of further study of compounds of this group and an expanded search for substances with pronounced antiviral activity among non-annulated tetrazolylpyrimidines the heterocyclic fragments.
of which are separated by a sulfur atom. The synthesis and study of the antiviral activity of analogs of compound 12b containing various functional groups at the nitrogen atom in position 1 of the tetrazole ring deserve further development. Importantly, the influenza virus used in the study is resistant to rimantadine (SI 5). The results of the study of tetrazolylpyrimidines indicate that this compound may have a different mechanism of interaction with the target as compared to adamantane derivatives. This makes the evaluated group of compounds promising as prototypes of anti-influenza drugs with an alternative mechanism of action in comparison with existing drugs for influenza therapy.

To conclude, nonannulated tetrazolylpyrimidines can be recommended for in vivo evaluation of antiviral activity.

**Experimental**

IR spectra were registered on a Shimadzu 8400-FTIR spectrometer in KBr pellets. 1H and 13C NMR spectra were acquired on a Bruker Avance III spectrometer (400 and 100 MHz, respectively) in DMSO-d6 (compounds 5a, 6b, 7a, b, 8, 9, 12a, b) and CDCl3 (compound 4) at 25°C with TMS as internal standard. Elemental analysis was performed on a Leco CHNS-932 elemental analyzer. Mass spectra were recorded on a Bruker maXis impact ultra-high resolution quadrupole time-of-flight mass spectrometer (electrospray ionization, MeOH solvent). Melting points were determined by the capillary method on a Büchi M-560 apparatus with a heating rate of 1°C/min in the melting range. Assessment of the purity of synthesized compounds was done by TLC on Macherey-Nagel Alugram Xtra SIL G plates, visualization in UV light (254 nm). The physiochemical properties of 1-phenyl-5-sulfanyl-tetrazole (10a) and other commercial reagents, solvents, and materials correspond to the data given in the catalogs of Sigma-Aldrich, Merck, Fluka. 5-Phenyltetrazole sodium salt (1, 13) 2-chloro-4,6-dimethylpyrimidine (2, 14) 1-carboxymethyl-5-sulfanyl tetrazole (10b), 15 and 2-chloropyrimidine (11) 16 were obtained following known or modified methods. The properties of compounds 1, 2, 10b, and 11 correspond to those described previously. 13–16

**Table 1.** Antiviral activity of nonannulated tetrazolylpyrimidines 7a, b, 9, and 12a, b against influenza A H1N1 virus in MDCK cell cultures

| Compound | IC50, μg/ml | SI  |
|----------|-------------|-----|
| 7a       | >300        | 1   |
| 7b       | >300        | 1   |
| 9        | 53.9        | 2   |
| 12a      | >300        | 2   |
| 12b      | >300        | 10  |
| Rimantadine | 60          | 12  |

| of which are separated by a sulfur atom. The synthesis and study of the antiviral activity of analogs of compound 12b containing various functional groups at the nitrogen atom in position 1 of the tetrazole ring deserve further development. Importantly, the influenza virus used in the study is resistant to rimantadine (SI 5). The results of the study of tetrazolylpyrimidines 12b indicate that this compound may have a different mechanism of interaction with the target as compared to adamantane derivatives. This makes the evaluated group of compounds promising as prototypes of anti-influenza drugs with an alternative mechanism of action in comparison with existing drugs for influenza therapy.

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| 12b      | >300        | 10  |
| Rimantadine | 60          | 12  |
104°C (hexane)\(^{10}\). IR spectrum, v, cm\(^{-1}\): 2985, 2945 (C–H), 1777 (C=O), 1450, 1278, 1148, 1073, 1039, 1022, 923 (C\(_2\)N)\(^{10}\), 729, 688 (C\(_6\)H\(_5\)). \(^1\)H NMR spectrum, \(\delta\), ppm: 5.84 (2H, s, CH\(_2\))\(^{10}\), 7.53–7.49 (3H, m, H Ph); 8.17–8.14 (2H, m, H Ph). \(^13\)C NMR spectrum, \(\delta\), ppm: 60.7 (CH\(_2\))\(^{10}\), 126.6 (C Ph); 127.2 (C Ph); 129.2 (C Ph); 131.0 (C Ph); 166.2 (C tetrozole); 166.5 (C=O). Found, %: C 48.31; H 3.20; N 25.60. C\(_{13}\)H\(_7\)C\(_4\)N\(_4\). Calculated, %: C 48.55; H 3.17; N 25.17.

\(\text{N'(Pyrimidin-2-yl)-2-(5-phenyl-2H-tetrazol-2-yl)acetoxydrazide (7a)}\), a mixture of isomers E/Z in a 3.6:1 ratio. Et\(_3\)N (0.97 g, 9.60 mmol) was added with stirring to a solution of 2-hydrazinopyrimidine (5a) (1.0 g, 9.08 mmol) in MeCN (20 ml). The reaction mixture was cooled to room temperature, and dried in a stream of air. Yield 1.1 g (78%), colorless crystals, mp 235–236°C. IR spectrum, v, cm\(^{-1}\): 3278 (N\(_2\)H\(_4\) def). Found, %: C 48.69; H 3.17; N 20.32.

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7.71 (2H, s, H pyrimidine); 7.65–7.67 (3H, m, H Ph); 7.69–7.71 (2H, m, H pyrimidine); 8.58–8.59 (2H, m, H Ph). 13C NMR spectrum, δ ppm: 2.31 (6H, s, 2CH3); 5.38 (2H, s, CH2); 7.15 (1H, s, H pyrimidine); 13.72 (1H, br. s, OH). 11B NMR spectrum, δ ppm: 23.7 (2CH3); 49.2 (CH2); 118.8 (C=5); 148.5 (C=2); 165.3 (C tetrazole); 167.5 (C=4,6); 169.1 (C=O). Found, %: C 40.97; H 4.03; N 31.35; S 12.05. C26H24N2O6S. Calculated, %: C 40.60; H 3.79; N 31.56; S 12.05.

The study of the biological activity of compounds 7a,b, 9, 12a,b. A series of threefold dilutions (300–3.7 µg/ml) were prepared from the studied compounds. The dilutions were introduced into the wells of plates with a monolayer of MDCK cells. The plates were incubated for 72 h at 36°C in 5% CO2. The analysis of cell survival was carried out using the methyl tetrazolium (MTT) assay: MTT solution was added to the wells, wherein by the action of mitochondrial enzymes it transforms into an insoluble violet formazan derivative. The formed precipitate was filtered off and dried in a stream of air. Yield 1.0 g (46%), beige crystals, mp 76°C (PhMe–EtOH, 1:1). Rf 0.17 (CCl4–i-PrOH, 4:1, 25°C). IR spectrum, ν, cm−1: 1554 (C=H3), 1444, 1045 (CN4), 765 (C4N2H def). 1H NMR spectrum, δ, ppm: 7.30–7.32 (1H, m, H pyrimidine); 7.56–7.57 (3H, m, H Ph); 7.69–7.71 (2H, m, H pyrimidine); 8.58–8.59 (2H, m, H Ph). 13C NMR spectrum, δ ppm: 119.8 (C=5); 125.7 (C Ph); 130.0 (C Ph); 131.2 (C Ph); 133.9 (C Ph); 148.3 (C=4,6); 159.3 (C=2); 167.1 (C tetrazole). Found, m/z: 257.0616 [M+H]+. C19H16N6S. Calculated, m/z: 257.0604. Found, %: C 51.59; H 3.28; N 32.44; S 12.62.

5-[(4,6-Dimethylpyrimidin-2-yl)sulfonyl]-1H-tetrazol-1-yl)acetic acid (12b). Et3N (0.85 g, 8.42 mmol) and 2-chloropyrimidine (1.1 g, 9.60 mmol) were added with stirring to a solution of 1-[phenyl-1-yl]acetic acid (12b) (1.1 g, 9.60 mmol) in MeCN (10 ml). The reaction mixture was heated under reflux for 4 h. The mixture was concentrated to half the original volume by evaporation under reduced pressure, the remaining reaction mixture was cooled, and H2O (50 ml) was added. The formed precipitate was filtered off and dried in a stream of air. Yield 1.0 g (46%), beige crystals, mp 76°C (PhMe–EtOH, 1:1). Rf 0.17 (CCl4–i-PrOH, 4:1, 25°C). IR spectrum, ν, cm−1: 1554 (C=H3), 1444, 1045 (CN4), 765 (C4N2H def). 1H NMR spectrum, δ, ppm: 7.30–7.32 (1H, m, H pyrimidine); 7.56–7.57 (3H, m, H Ph); 7.69–7.71 (2H, m, H pyrimidine); 8.58–8.59 (2H, m, H Ph). 13C NMR spectrum, δ ppm: 119.8 (C=5); 125.7 (C Ph); 130.0 (C Ph); 131.2 (C Ph); 133.9 (C Ph); 148.3 (C=4,6); 159.3 (C=2); 167.1 (C tetrazole). Found, m/z: 257.0616 [M+H]+. C19H16N6S. Calculated, m/z: 257.0604. Found, %: C 51.59; H 3.28; N 32.44; S 12.62.

The study of the antiviral activity of compounds 7a,b, 9, 12a,b was carried by determining the reduction of the degree of cytopathic effect. The experiments used influenza virus strains A/Puerto Rico/8/34 (H1N1) and B/Florida/4/2006. The studied compounds in various concentrations were added to the cells in the wells of the plate, incubated for 1 h at 36°C in 5% CO2, then the cells were infected with the virus at a dose of 0.01 TCID50 per cell. The cells were incubated for 72 h at 36°C in 5% CO2, after which the cell viability assay was performed using the methyl tetrazolium assay as described above. Based on the obtained data, a 50% inhibitory concentration was calculated for each compound, that is, the concentration that reduces the degree of viral cell destruction by 50%.

X-ray structural analysis of compounds 7b and 9 was carried out on an Xcalibur 3 automatic 4-circle diffractometer equipped with a CCD detector. All calculations were carried out in the Olex software shell using the SHELX software package.17 The full set of X-ray structural data for compounds 7b and 9 was deposited at the Cambridge Crystallographic Data Center (deposits CCDC 1818619 and CCDC 2047135, respectively).

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X-ray structural analysis for compounds 7b and 9 was carried out on the equipment of the Center for Collective Use "Spectroscopy and Analysis of Organic Compounds" of Postovsky Institute of Organic Synthesis of the Ural Branch of the Russian Academy of Sciences.

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