Available online at www.sciencedirect.com

ScienceDirect

Mendeleev Commun., 2018, **28**, 52–54

Mendeleev Communications

β-D-Ribofuranosyl substituted polyfluoroalkylpyrazoles and their activity against the influenza virus

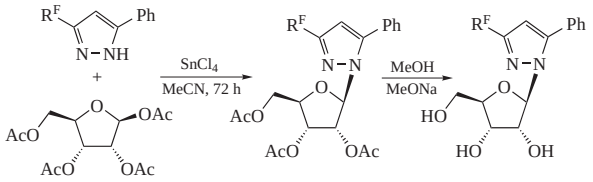
Anna E. Ivanova,*[a] Yanina V. Burgart,[a] Viktor I. Saloutin,[a] Yana R. Orshanskaya[b] and Vladimir V. Zarubaev[b]

[a] *I. Ya. Postovsky Institute of Organic Synthesis, Ural Branch of the Russian Academy of Sciences, 620990 Ekaterinburg, Russian Federation. Fax: +7 343 374 5954; e-mail: ivanova@ios.uran.ru*

[b] *Research Institute of Influenza, Ministry of Health of the Russian Federation, 197376 St. Petersburg, Russian Federation*

DOI: 10.1016/j.mencom.2018.01.017

Regiospecific ribosylation of 3-polyfluoroalkyl-5-phenylpyrazoles with 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose in the presence of tin(IV) chloride followed by deacetylation affords 1-(β-D-ribofuranosyl)-3-polyfluoroalkyl-5-phenyl-1*H*-pyrazoles. These derivatives as well as starting pyrazoles were tested for anti-influenza activity.



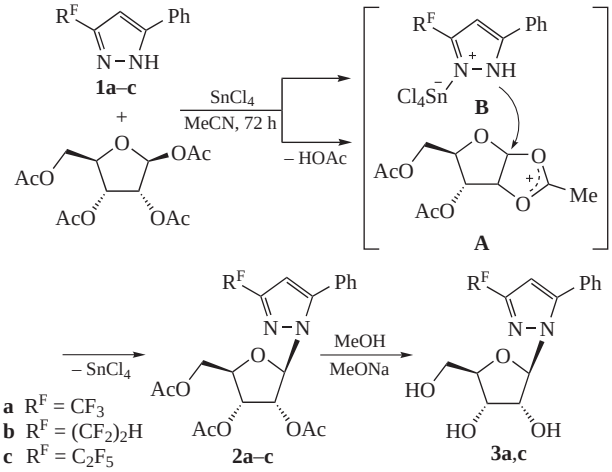
Development of new efficient anti-influenza drugs is among the most urgent tasks of medicinal chemistry since ~95% of infectious diseases are acute respiratory viral infections. Among these, the influenza virus is believed to be the most hazardous one as it is characterized by high genetic variability and long-term complications after the acute stage of the disease that result in 'hidden' or secondary mortality. The pharmaceutical market currently offers a limited set of internationally recognized anti-influenza drugs. These include the chemical compounds of two groups: adamantane derivatives (Amantadine and Remantadin) and polyfunctional compounds Oseltamivir (Tamiflu) and Zanamivir (Relenza) as inhibitors of viral neuraminidase.[1] Drugs not yet licensed in Russia, Peramivir and Laninamivir, are used in Western Europe, USA and South-East Asia.[2] The influenza virus can quickly develop resistance to both types of drugs,[3] which makes the search for and development of new antiviral drugs with a broad spectrum of activity a task of current interest.

Incorporation of a nucleoside moiety into various heterocyclic molecules is a promising direction in the search for new antiviral drugs.[4] In clinical practice, infections caused by virus hepatitis C and other viruses are treated with Ribavirin (1-β-D-ribofuranosyl-1*H*-[1,2,4]triazole-3-carboxamide).[5] Literature sources describe 5-phenyl- and 5-(4-trifluoromethylphenylethynyl)-substituted 1-ribofuranosyl-1*H*-1,2,4-triazole-3-carboxamides that inhibit the replication of hepatitis C virus.[6,7] 1-Ribofuranosyl-3-ethynyl[1,2,4]-triazole is efficient against flaviviruses.[8] Pyrazofurin, a nucleoside antibiotic, and its α-epimer are used in medicine for treatment of diseases induced by DNA-viruses.[9] 4-Fluoro-1-β-D-ribofuranosylpyrazole-3-carboxamide manifests activity against A and B influenza viruses.[10]

We chose 3(5)-polyfluoroalkyl-containing pyrazoles for synthesizing new non-natural nucleosides. Trifluoromethylpyrazole derivatives are known to exhibit a broad spectrum of biological activity. For example, 1-methyl-3-trifluoromethyl-*N*-[4-(pyrrolidinylsulfonyl)phenyl]-1*H*-pyrazole-5-carboxamide is active against the measles virus with a selectivity index of 16500.[11] The anti-inflammatory agent Celebrex and the veterinary anti-arthritic agent Mavacoxib are widely used; the SC-560 anticancer agent and the Razaksaban coagulant are undergoing clinical trials.[12]

Previously, we have studied the ribosylation of 4-aryldiazenyl substituted pyrazoles, including polyfluoroalkylated ones.[13] The analysis of literature has shown the lack of data on the incorporation of a ribofuranosyl residue into 4-unsubstituted polyfluoroalkylpyrazoles. Therefore, the aim of this work was the synthesis of their *N*-ribofuranosinyl substituted derivatives and a study of the anti-influenza properties of the new and previously synthesized compounds.

Ribosylation of pyrazoles **1a**–**c** in the presence of $SnCl_4$ gave compounds **2a**–**c** in 40–53% yields (Scheme 1).† The insufficiently high yield of products **2a**–**c** is explained by incomplete conversion



Scheme 1

† NMR spectra were recorded using a Bruker Avance-500 spectrometer (^{1}H, 500.1 MHz; ^{13}C, 125.7 MHz relative to $SiMe_4$; ^{19}F, 470.5 MHz relative to C_6F_6). IR spectra were recorded on a Perkin Elmer Spectrum One Fourier IR spectrometer in the 4000–400 cm^{-1} range using an attenuated full total internal reflection (FTIR) device or a diffuse reflectance accessory (DRA). Melting points were measured in open capillaries in a Stuart SMP30 device. Column chromatography was carried out on silica gel 60 (0.063–0.2 mm). HPLC was performed in an Agilent 1200 Series preparative liquid chromatograph with a diode matrix detector, a preparative autosampler (900 μl) and a ZORBAX Eclipse XDB-C18 PrepHT 21.2×150 mm

of starting pyrazoles **1a–c** and difficulties of their preparative isolation using double column chromatography or HPLC.

We have found previously[13] that ribosylation of polyfluoroalkyl-containing 4-(aryldiazenyl)pyrazoles under similar conditions occurs regiospecifically at the nitrogen atom remote from the polyfluoroalkyl substituent to produce 3-R^F isomers. In this case, methyl substituted pyrazoles formed an α- and β-anomeric mixture, whereas phenyl-containing analogues gave only the β-anomers.

Ribosylation of pyrazoles **1a–c** proceeded nearly regio- and stereospecifically (according to GC-MS data, in cases of **1a**,**b** less than 2% of the second product was detected while nothing of this was observed in case of **1c**). Assignment of products **2a–c** to their 3-R^F-isomers was based on the ^{19}F NMR spectra,[14] where their CF_3- or α-CF_2 signals are located in the same region as those of the starting N-unsubstituted pyrazoles **1a–c**: δ_F 99.6 (**1a**) and 99.4 (**2a**); 48.9 (**1b**) and 47.6–49.3 (**2b**); 48.6 (**1c**) and 48.9–49.9 (**2c**).

To determine the anomeric structure of products **2a–c**, we used ^{1}H NMR spectroscopic data, taking into account that the signals of the H-1′ protons in β-ribofuranoses are observed at higher field and with smaller coupling constants [δ: 5.85–5.99 (H-1′, $J_{H1'H2'}$ 3.0–3.1 Hz)] in comparison with the similar signal of α-ribofuranoses [δ: 6.24–6.36 (H-1′, $J_{H1'H2'}$ 5.5–6.1 Hz)].[13] The H-1′ protons in compounds **2a–c** resonate in the region of δ 5.94–5.95 with J 2.6–3.9 Hz evidencing their β-configuration. The formation of only β-anomers **2a–c** from pyrazoles **1a–c** may be also due to steric hindrance created by the adjacent bulky phenyl substituent (*cf.* ref. 13), along with well-recognized mechanism including effect of $O^{2'}$-acyl group stabilizing carbocation **A** (see Scheme 1). Regiospecificity of these reactions is affected by the use of a Lewis acid coordinating at the N^2 imine nitrogen atom of pyrazole **1a–c** to give zwitter-ion complex **B**. The subsequent addition of carbocation **A** occurs at the N^1 nitrogen atom to eventually produce 3-R^F isomer **2a–c**.

Recently,[14] we used quantum-chemical calculations in order to explain the regiospecificity of methylation of polyfluoroalkyl substituted pyrazoles **1**. According to the data obtained, the N^1 reaction centers in both possible tautomers of pyrazole **1a** are characterized by negative Δf values of the double descriptor of the Fukui function (Δf), which indicated their higher nucleophilicity as compared to the N^2 competitive centers. Moreover, 3-R^F isomers of N-methylated products were found to be thermodynamically more beneficial in comparison with 5-R^F isomers. Perhaps, these factors also determine the observed regiospecificity of our ribosylation reaction.

Deacylation in the sugar moiety in compounds **2a**,**c** performed by refluxing in methanol in the presence of MeONa afforded ribofuranosyl substituted pyrazoles **3a**,**c** in 70–80% yields (see Scheme 1).‡

Further, we studied the antiviral activities of pyrazole **1a** and its ribosylated derivative **3a**, as well as those of aryldiazenyl-

column, particle size 5 μm. The flow rate was 20 ml min^{-1}. The wavelength was 330 nm. Elemental analysis (C, H, N) was carried out with a Perkin Elmer PE 2400 series II analyzer. Optical rotations were determined at room temperature using a Perkin Elmer M 341 polarimeter. 1,2,3,5-Tetra-*O*-acetyl-β-D-ribofuranose was purchased from Alfa Aesar.

β-D-Triacetylribofuranosyl substituted pyrazoles **2a–c**. Pyrazole **1a–c** (2.8 mmol) and 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (2.9 mmol) were dissolved in anhydrous MeCN (20 ml), then anhydrous $SnCl_4$ (0.2 ml) was added and the mixture was kept for 72 h. Distilled water (2 ml) was added and the mixture was neutralized with $NaHCO_3$. The resulting suspension was filtered and the filtrate was concentrated. Product **2a** (colourless oil, yield 53%) was successively purified two times by column chromatography using chloroform as the eluent. Product **2b** (colourless oil, yield 40%) was purified by HPLC using acetonitrile–water (65 : 35) mixture as the eluent. Product **2c** (colourless oil, yield 48%) was successively purified two times by column chromatography using hexane–ethyl acetate (5 : 1) mixture as the eluent in the first purification and chloroform as the eluent in the second one.

1-(2,3,5-Tri-O-*acetyl-β-D-ribofuranosyl)-3-trifluoromethyl-5-phenyl-1*H*-pyrazole* **2a**. $[\alpha]_D$ –29 (*c* 1.35, MeOH). FTIR (ν/cm^{-1}): 1752 (C=O), 1225 (C–F). ^{1}H NMR ($CDCl_3$) δ: 2.06 (s, 3H, $MeCO_2$), 2.08 (s, 3H, $MeCO_2$), 2.09 (s, 3H, $MeCO_2$), 4.18 (dd, 1H, H-5′, $J_{H5'H5''}$ 12.2 Hz, $J_{H4'H5'}$ 4.6 Hz), 4.37–4.40 (m, 1H, H-4′), 4.50 (dd, 1H, H-5″, $J_{H5'H5''}$ 12.1 Hz, $J_{H4'H5''}$ 3.1 Hz), 5.83–5.86 (m, 2H, H-3′, H-2′), 5.95 (dd, 1H, H-1′, $J_{H1'H3'}$ 5.2 Hz, $J_{H1'H2'}$ 3.9 Hz), 6.58 (s, 1H, H-4), 7.50–7.52 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$) δ: 20.47, 20.52, 20.55 (3*Me*CO), 62.85 (C-5′), 71.22 (C-3′), 74.48 (C-2′), 80.51 (C-4′), 88.7 (C-1′), 104.95 (C-4), 120.92 (q, CF_3, $^1J_{CF}$ 269.0 Hz), 128.23 (C_p), 129.03 (C_m), 129.26 (C_o), 129.66 (C_{ipso}), 143.25 (q, C-3, $^2J_{C–F}$ 28.5 Hz), 146.62 (C-4), 169.31, 169.44, 170.74 (3C=O). ^{19}F NMR ($CDCl_3$) δ: 99.35 (s, CF_3). Found (%): C, 53.47; H, 4.45; N, 5.87. Calc. for $C_{21}H_{21}N_2O_7F_3$ (%): C, 53.62; H, 4.50; N, 5.96.

1-(2,3,5-Tri-O-*acetyl-β-D-ribofuranosyl)-3-(1,1,2,2-tetrafluoroethyl)-5-phenyl-1*H*-pyrazole* **2b**. $[\alpha]_D$ –28 (*c* 0.995, MeOH). FTIR (ν/cm^{-1}): 1750 (C=O), 1231 (C–F). ^{1}H NMR ($CDCl_3$) δ: 2.05 (s, 3H, $MeCO_2$), 2.06 (s, 3H, $MeCO_2$), 2.09 (s, 3H, $MeCO_2$), 4.16 (dd, 1H, H-5′, $J_{H5'H5''}$ 12.1 Hz, $J_{H4'H5'}$ 5.1 Hz), 4.39 (ddd, 1H, H-4′, $J_{H3'H4'}$ 6.4 Hz, $J_{H4'H5'}$ 5.1 Hz, $J_{H4'H5''}$ 3.8 Hz), 4.47 (dd, 1H, H-5″, $J_{H5'H5''}$ 12.1 Hz, $J_{H4'H5''}$ 3.6 Hz), 5.84–5.87 (m, 2H, H-3′, H-2′), 5.95 (dd, 1H, H-1′, $J_{H1'H3'}$ 5.1 Hz, $J_{H1'H2'}$ 2.6 Hz), 6.21 [tt, 1H, H(CF_2)$_2$, $^2J_{H–F}$ 53.2 Hz, $^3J_{H–F}$ 4.5 Hz], 6.62 (s, 1H, H-4), 7.49–7.54 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$) δ: 20.46, 20.50, 20.53 (3MeCO), 63.01 (C-5′), 71.22 (C-3′), 74.49 (C-2′), 80.06 (C-4′), 88.70 (C-1′), 105.72 (C-4), 109.76, 112.18 [two tt, H(CF_2)$_2$, $J_{C–F}$ 250.9 and 30.6 Hz], 128.29 (C_p), 129.01 (C_m), 129.26 (C_o), 129.62 (C_{ipso}), 143.89 (t, C-3, $J_{C–F}$ 30.6 Hz), 146.67 (C-4), 169.32, 169.48, 170.68 (3C=O). ^{19}F NMR δ: 28.44 (tdd, 2F, HCF_2, $^2J_{F–H}$ 49.4 Hz, $^2J_{F–F}$ 33.4 Hz, $^3J_{F–F}$ 7.5 Hz), 47.61–49.33 (m, 2F, CF_2). Found (%): C, 52.47; H, 4.38; N, 5.47. Calc. for $C_{22}H_{22}F_4N_2O_7$ (%): C, 52.59; H, 4.41; N, 5.58.

1-(2,3,5-Tri-O-*acetyl-β-D-ribofuranosyl)-3-pentafluoroethyl-5-phenyl-1*H*-pyrazole* **2c**. $[\alpha]_D$ –29 (*c* 1.012, MeOH). IR (DRA, ν/cm^{-1}): 1756 (C=O), 1239 (C–F). ^{1}H NMR ($CDCl_3$) δ: 2.06 (s, 3H, $MeCO_2$), 2.07 (s, 3H, $MeCO_2$), 2.09 (s, 3H, $MeCO_2$), 4.18 (dd, 1H, H-5′, $J_{H5'H5''}$ 12.0 Hz, $J_{H4'H5'}$ 5.0 Hz), 4.39 (m, 1H, H-4′), 4.47 (dd, 1H, H-5″, $J_{H5'H5''}$ 12.0 Hz, $J_{H4'H5''}$ 3.4 Hz), 5.84–5.89 (m, 2H, H-3′, H-2′), 5.94 (dd, 1H, H-1', $J_{H1'H3'}$ 5.1 Hz, $J_{H1'H2'}$ 2.7 Hz), 6.61 (s, 1H, H-4), 7.49–7.53 (m, 5H, Ph). ^{19}F NMR δ: 48.29–49.95 (m, 2F, CF_2), 77.62 (t, 3F, CF_3, $J_{F–F}$ 2.3 Hz). Found (%): C, 50.89; H, 3.94; N, 5.41. Calc. for $C_{22}H_{21}F_5N_2O_7$ (%): C, 50.78; H, 4.07; N, 5.38.

‡ *Deacylation of β-D-triacetylribofuranosyl substituted pyrazoles* **2a**,**c**. Compounds **2a**,**c** (0.5 mmol) were dissolved in methanol (5 ml), and this solution was added to MeONa/MeOH prepared from Na (0.03 g, 1.3 mmol) and MeOH (5 ml). The mixture was refluxed for 30 min, cooled, neutralized with glacial AcOH and concentrated. The products were extracted with CH_2Cl_2 (2 × 40 ml), washed with H_2O (300 ml) and dried with Na_2SO_4. The solution was concentrated. All the products were purified by column chromatography (eluent: chloroform, then chloroform–ethyl acetate, 3 : 1).

*1-(β-D-Ribofuranosyl)-3-trifluoromethyl-5-phenyl-1*H*-pyrazole* **3a**. Yellow oil, yield 80%, $[\alpha]_D$ –82 (*c* 1.065, MeOH). FTIR (ν/cm^{-1}): 3388 (O–H), 1134–1163 (C–F). ^{1}H NMR (DMSO-d_6) δ: 3.46 (td, 1H, H-5′, $J_{H5'H5''}$ 11.8 Hz, $J_{H4'H5'}$ 5.9 Hz), 3.59 (d, 1H, H-5″, $J_{H5'H5''}$ 10.7 Hz, $J_{H4'H5''}$ 5.2 Hz), 3.93 (dd, 1H, H-4′, $J_{H3'H4'}$ 9.9 Hz, $J_{H4'H5''}$ 5.1 Hz), 4.20 (dd, 1H, H-3′, $J_{H3'H4'}$ 9.5 Hz, $J_{H2'H3'}$ 4.9 Hz), 4.64 (dd, 1H, H-2′, $J_{H2'H3'}$ 5.1 Hz, $J_{H1'H2'}$ 10.7 Hz), 4.82 (t, 1H, H-1′, $J_{H1'H2'}$ 5.7 Hz), 5.21 (d, 1H, OH, *J* 5.4 Hz), 5.43 (d, 1H, OH, *J* 6.1 Hz), 5.62 (d, 1H, OH, *J* 4.7 Hz), 6.98 (s, 1H, H-4), 7.56–7.59 (m, 5H, Ph). ^{19}F NMR δ: 101.79 (s, CF_3). Found (%): C, 52.03; H, 4.35; N, 7.99. Calc. for $C_{15}H_{15}N_2F_3O_4$ (%): C, 52.33; H, 4.93; N, 8.14.

*1-(β-D-Ribofuranosyl)-3-pentafluoroethyl-5-phenyl-1*H*-pyrazole* **3c**. Colourless oil, yield 78%, $[\alpha]_D$ –84 (*c* 1.16, MeOH). IR (DRA, ν/cm^{-1}): 3396 (O–H), 1183–1216 (C–F). ^{1}H NMR ($CDCl_3$) δ: 3.73 (dd, 1H, H-5′, $J_{H5'H5''}$ 12.7 Hz, $J_{H4'H5'}$ 1.7 Hz), 3.97 (dd, 1H, H-5″, $J_{H5'H5''}$ 12.7 Hz, $J_{H4'H5''}$ 2.0 Hz), 4.22 (m, 1H, H-4′), 4.67 (t, 1H, H-3', *J* 4.4 Hz), 4.77 (m, 1H, H-2'), 5.91 (d, 1H, H-1', $J_{H1'H2'}$ 3.6 Hz), 6.59 (s, 1H, H-4), 7.47–7.51 (m, 5H, Ph). ^{19}F NMR δ: 48.33–49.01 (m, 2F, CF_2), 77.23 (t, 3F, CF_3, $J_{F–F}$ 2.3 Hz). Found (%): C, 50.13; H, 4.31; N, 7.04. Calc. for $C_{17}H_{17}N_2F_5O_4$ (%): C, 50.01; H, 4.20; N, 6.86.

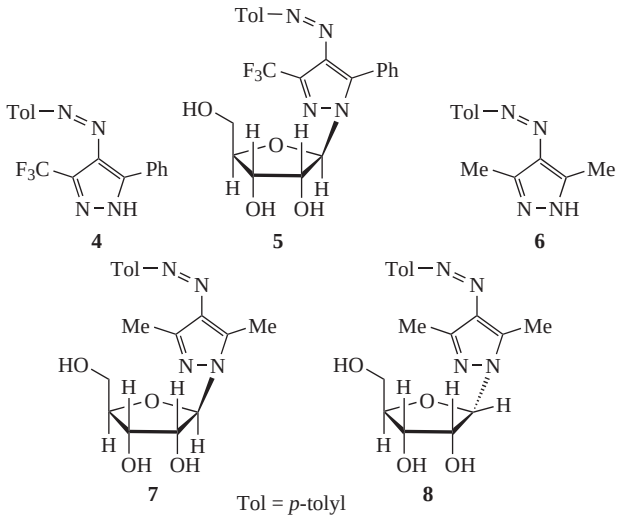


Table 1 Anti-influenza activity of polyfluoroalkylated pyrazole derivatives.

Compound	CC_{50}/μM[a]	IC_{50}/μM[b]	Selectivity index
1a	245 ± 11	> 141	2
3a	456 ± 30	25 ± 3	18
4	697 ± 41	> 303	2
5	12 ± 1	> 7	2
6	244 ± 16	> 140	2
7	37 ± 2	11 ± 3	3
8	506 ± 39	28 ± 4	18
Ribavirin	> 2130	36 ± 6	59

[a] CC_{50} is the 50% effective concentration causing the death of 50% cells. [b] IC_{50} is the 50% effective concentration decreasing the virus production by a factor of two.

containing analogues **4**–**8** previously obtained[13] (Table 1), against influenza strain A/Puerto Rico/8/34 (H1N1).§ Polyfluoroalkylpyrazoles **1a**, **4**, **6** by themselves were found to exhibit a comparatively low toxicity of about hundreds of micromols. Incorporation of a β-D-ribofuranosyl residue into 4-aryldiazenylpyrazoles **4** and **6** increased the toxicity by about an order (compounds **5** and **7**). On the other hand, incorporation of α-D-ribofuranosyl substituent into pyrazole **4** decreased its toxicity and the effective concentration by factors of two and five, respectively. As concerns 4-unsubstituted pyrazole **3a**, incorporation of β-D-ribofuranosyl substituent results in a decrease in cytotoxicity and effective concentration in comparison with the starting pyrazole **1a**. The NH-polyfluoroalkylpyrazoles **1a** and **6** showed no antiviral properties. However, their ribosylation increased the selectivity index, both due to a cytotoxicity decrease and to an increase in the target affinity for pyrazoles **3a** and **8**. In both cases, incorporation of a ribofuranosyl residue increased the selectivity index by a factor of 9.

In conclusion, we have obtained new β-D-ribofuranosylpyrazoles by regiospecific condensation of polyfluoroalkylpyrazoles with 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose under the action of $SnCl_4$. Deacylation in the sugar residue has been performed in good yields under basic conditions. Incorporation of a ribofuranosyl residue into pyrazoles **1a** and **6** increased their anti-influenza properties by a factor of nine.

This study was supported by the Russian Science Foundation (grant no. 16-13-10255).

§ Cytotoxic properties of compounds were studied using the methyltetrazolium test (MTT).[15] A series of threefold dilutions on the MEM medium was prepared from the compounds. MDCK cells were incubated for 48 h at 36 °C in 5% CO_2 atmosphere in the presence of compounds in various concentrations. The cells were washed twice with physiological phosphate buffer and a solution of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (ICN Biochemicals) (0.5 mg ml^{-1} in phosphate buffer) was added to the wells. After 1 h of incubation at 36 °C in 5% CO_2 atmosphere, the wells were washed and the formazan deposit was dissolved in DMSO (0.1 ml per well). The optical density in the wells was measured in a Perkin Elmer Victor2 1440 multifunctional reader at a wavelength of 535 nm. Tests with each concentration of compounds were performed in triplicate. The 50% cytotoxic concentration (CC_{50}) was determined from the data obtained.

Virus titration. Compounds were dissolved in DMSO, and the working solutions were prepared in MEM medium with addition of trypsin (1 μg ml^{-1}). Compounds were incubated for 1 h at 36°C with MDCK cells in 5% CO_2 atmosphere and infected for 1 h with A/Puerto Rico/8/34 influenza virus (H1N1) (moi 0.01). The unbound virus was washed out. The cells were incubated for 24 h at 36 °C in 5% CO_2 atmosphere, then the infective activity of the virus in the culture medium was determined by titration on cells in the hemagglutination reaction. Based on the data obtained, the 50% inhibitive concentration (IC_{50}) and the selectivity index, *i.e.*, CC_{50} : IC_{50} ratios, were determined.

References

1 V. V. Zarubaev, P. M. Anfimov, A. A. Shtro, A. V. Garshinina, I. A. Melekshina, L. A. Karpinskaya, K. N. Kozeletskaya and O. I. Kiselev, *Voprosy Virusologii* (*Problems of Virology*), 2012, **57** (6), 30 (in Russian).
2 M. G. Ison, *Clin. Chest Med*., 2017, **38**, 139.
3 L. Naesens, A. Stevaert and E. Vanderlinden, *Curr. Opin. Pharmacol.*, 2016, **30**,106.
4 C. Simons, *Nucleoside Mimetics: Their Chemistry and Biological Properties*, Gordon and Breach Science Publishers, Amsterdam, 2001.
5 R. W. Sidwell, J. H. Huffman, G. P. Khare, L. B. Allen, J. T. Witkowski and R. K. Robins, *Science*, 1972, **177**, 705.
6 J. Wan, Y. Xia, Y. Liu, M. Wang, P. Rocchi, J. Yao, F. Qu, J. Neyts, J. L. Iovanna and L. Peng, *J. Med. Chem*., 2009, **52**, 1144.
7 M. V. Chudinov, A. V. Matveev, A. N. Prutkov, I. D. Konstantinova, I. V. Fateev, V. S. Prasolov, O. A. Smirnova, A. V. Ivanov, G. A. Galegov and P. G. Deryabin, *Mendeleev Commun*., 2016, **26**, 214.
8 M. McDowell, S. R. Gonzales, S. C. Kumarapperuma, M. Jeselnik, J. B. Arterburn and K. A. Hanley, *Antiviral Res*., 2010, **87**, 78.
9 G. H. Elgemeie, W. A. Zaghary, K. M. Amin and T. M. Nasr, *Nucleosides Nucleotides Nucleic Acids*, 2005, **24**, 1227.
10 R. Storer, C. J. Aston, A. D. Baxter, M. M. Hann, C. L. P. Marr, A. M. Mason, C.-L. Mo, P. L. Myers, S. A. Noble, C. R. Penn, N. G. Weir, J. M. Woods and P. L. Coe, *Nucleosides Nucleotides Nucleic Acids*, 1999, **18**, 203.
11 A. Sun, N. Chandrakumar, J.-J. Yoon, R. K. Plemper and J. P. Snyder, *Bioorg. Med. Chem. Lett*., 2007, **17**, 5199.
12 F. Li, J. Nie, L. Sun, Y. Zheng and J.-A. Ma, *Angew. Chem. Int. Ed*., 2013, **52**, 6255.
13 A. E. Ivanova, Ya. V. Burgart and V. I. Saloutin, *Mendeleev Commun*., 2016, **26**, 106.
14 A. E. Ivanova, Y. V. Burgart, V. I. Saloutin, P. A. Slepukhin, S. S. Borisevich and S. L. Khursan, *J. Fluorine Chem*., 2017, **195**, 47.
15 T. Mosmann, *J. Immunol. Methods*, 1983, **65**, 55.

Received: 11th April 2017; Com. 17/5220