DOI 10.1007/s10593-019-02418-4

Chemistry of Heterocyclic Compounds **2019**, *55*(1), 52–59

New one-pot synthesis of 4-hydroxyimino-5-polyfluoroalkylpyrazol-3-ones, their structure and biological activity

Yanina V. Burgart[1,2], Natalya A. Agafonova[1], Evgeny V. Shchegolkov[1,2], Vera V. Maslova[3], Galina A. Triandafilova[3], Sergey Yu. Solodnikov[3], Olga P. Krasnykh[3], Victor I. Saloutin[1,2]*

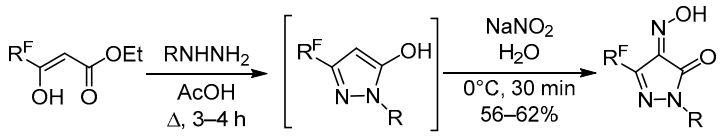
[1] *I. Ya. Postovsky Institute of Organic Synthesis, Ural Branch of the Russian Academy of Sciences, 22 S. Kovalevskoi / 20 Akademicheskaya St., Yekaterinburg 620990, Russia; e-mail: saloutin@ios.uran.ru*

[2] *Ural Federal University named after the first President of Russia B. N. Yeltsin, 19 Mira St., Yekaterinburg 620002, Russia*

[3] *Perm National Research Polytechnical University, 29 Komsomolsky Ave., Perm 614990, Russia; e-mail: ol.krasnykh@pstu.ru*

Translated from Khimiya Geterotsiklicheskikh Soedinenii, 2019, *55*(1), 52–59

Submitted November 14, 2018
Accepted December 21, 2018



R^F = CF_3, C_2F_5, C_3F_7, C_4F_9, CF_2CF_2H; R = H, Me, Ph

We propose different methods for the synthesis of 4-hydroxyimino-5-polyfluoroalkylpyrazol-3-ones. The simplest and most convenient procedure relies on sequential one-pot treatment of polyfluoroalkyl-3-oxoesters with hydrazine and sodium nitrite in acetic acid. It was established that 4-hydroxyimino-5-polyfluoroalkylpyrazol-3-ones exist in solid state and in solutions as mixtures of *Z*,*E*-isomers of the hydroxyimine tautomer. The synthesized compounds were characterized with respect to *in vivo* analgesic activity and acute toxicity.

Keywords: 2-hydroxyimino-3-polyfluoroalkylpyrazol-5-ones, analgesic activity, nitrosation, tautomerism.

The importance of pyrazole derivatives is obvious from the review articles published during the last 5 years, which consider the issues related to their synthesis,[1–3] ability of complex formation,[4–7] and biological properties.[8–10] The pyrazole moiety is found in many pharmaceutically relevant compounds (metamizole, celecoxib, phenylbutazone, edavarone).

The significant interest of researchers in compounds containing pyrazole ring is motivated by the broad possibilities for its modification. Of particular importance are 4-hydroxyiminopyrazol-5-ones, some of which have been characterized as pesticides[11] and bactericides,[12] as well as inhibitors of CDC25B phosphatases.[13] These compounds are important synthetic intermediates for the preparation of azo dyes,[14] heterocyclic products,[15–17] and 4-aminopyrazoles serving as important intermediates for the synthesis of biologically active compounds.[18] Besides that, 4-hydroxyiminopyrazolones are of interest to researchers as chelating ligands for the design of luminescent elements used in photovoltaic devices.[19,20]

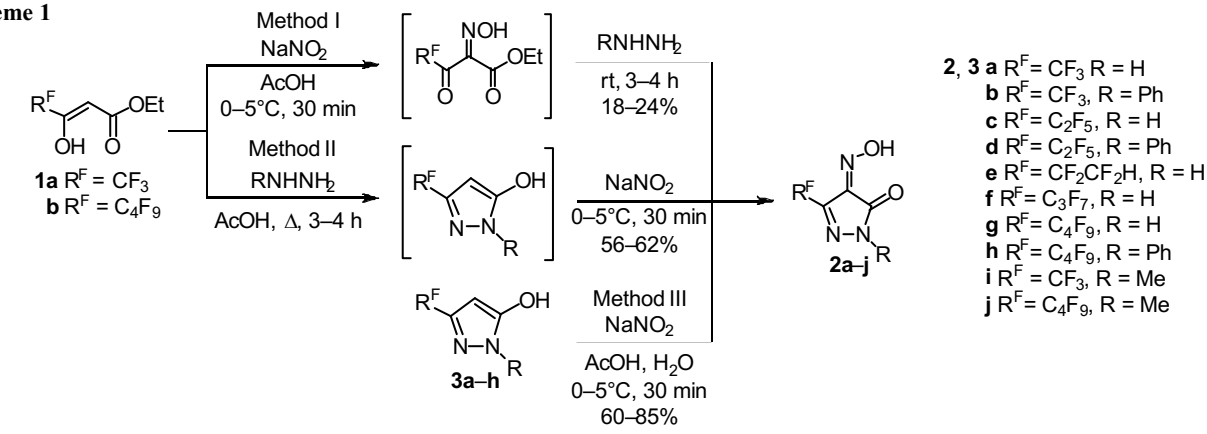
The synthesis of 4-nitrosopyrazol-5-ones has been achieved by nitrosation of existing pyrazolone nucleus with $NaNO_2$ in acetic[11,12,15,18,21] or hydrochloric acid.[14,22]

The data available on trifluoromethyl-substituted 3-hydroxyiminopyrazoles are limited to two publications,[20,23] even though fluorinated derivatives have been recognized as promising lead structures for the design of new medicinal compounds and crop protection agents, as well as other advanced materials of various nature. These possibilities are largely due to the unique nature of fluorine[24] that confers interesting physicochemical properties, reactivity, and biological effects to organofluorine compounds.[24–26]

The current work is devoted to the development of effective methods for the synthesis of polyfluoroalkyl-containing 4-hydroxyiminopyrazol-2-ones, characterization of their tautomeric structure, as well as the study of their biological properties.

4-Hydroxyimino-5-trifluoromethylpyrazol-3-one has been previously prepared by our group using the cycli-

Scheme 1



zation of ethyl 2-hydroxyimino-4,4,4-trifluoro-3-oxobutanoate with hydrazine hydrate, including the intermediate isolation of 5-hydroxy-4-hydroxyimino-5-trifluoromethylpyrazolidin-3-one with the formation of hydrated hydrazide as a byproduct.[27] However, the synthesis of starting polyfluoroalkyl-containing 2-hydroxyimino-3-oxoesters was complicated due to their formation predominantly as hydrates at the polyfluoroacyl moiety.[23,27]

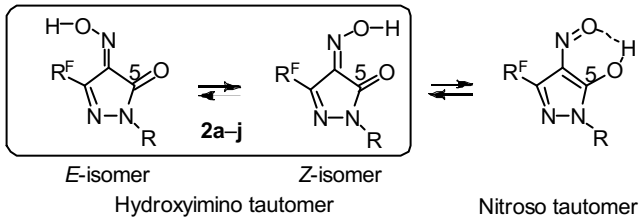
In order to prepare 4-hydroxyiminopyrazolones containing polyfluoroalkyl groups, in this work we explored the possibilities of a one-pot procedure that we had previously proposed for the synthesis of 4-nitroso-3-polyfluoroalkylpyrazoles from polyfluoroalkyl 1,3-diketones.[28,29] It was found that sequential treatment of 3-oxoesters **1a**,**b** with $NaNO_2$ in AcOH followed by heterocyclization of the hydroxyimine intermediate with hydrazines gave the target 4-hydroxyiminopyrazol-3-ones **2a**,**b**,**g**,**i** in mediocre yields (18–24%) (Scheme 1). The low productivity of this approach motivated us to use a more effective approach to the nitrosation of existing pyrazole rings. There is only a single literature source describing the nitrosation of 1-pentafluorophenyl-3-trifluoromethylpyrazol-5-ol using isoamyl nitrite in THF.[20] We demonstrated that the nitrosation of 3-polyfluoroalkylpyrazol-5-ols **3a**–**h** with $NaNO_2$ in AcOH enabled convenient access to 4-hydroxyimino-5-polyfluoroalkylpyrazol-3-ones **2a**–**h** in up to 85% yields.

In order to synthesize pyrazoles **2**, we further proposed an approach relying on *in situ* one-pot preparation of pyrazoles **3a**–**h** from 3-oxoesters **1a**,**b** and hydrazines in AcOH, followed by treatment of the reaction mixture with $NaNO_2$. It was found that the target pyrazoles **2a**,**b**,**g**,**i**,**j** were formed under such conditions in good yields (56–62%), therefore this method was recognized as the most preferred option for the synthesis of similar compounds, since it was possible to avoid the need for isolation of pyrazoles **3a**–**h**.

It should be noted that compounds **2a**,**c**,**e**,**f**,**g** were isolated as crystal hydrates containing one molecule of water for each molecule of pyrazole.

In the case of compounds **2a**–**j**, nitroso-oxime and keto-enol tautomerism can occur, therefore they can exist as nitroso form or *Z*,*E*-isomers of the hydroxyimine tautomer (Scheme 2).

Scheme 2



IR spectra of compounds **2a**–**j**, which were recorded for solid samples, featured a high frequency absorption band at 1704–1696 cm^{-1}, indicating the presence of a carbonyl group in the structure. According to the data of X-ray structural analysis, crystals of compound **2j** at room temperature contained a *Z*,*E*-isomer mixture of 4-hydroxyiminopyrazol-5-one tautomer (Fig. 1). This was observed from the characteristic doubling of hydroxyimine group atoms (N(3)(N(3A)), O(2)(O(2A)), H(2A)(H(2AA))).

The presence of hydroxyimine substituent was clearly established from the arrangement of well-defined double bonds in the pyrazole ring (one C=O bond and two C=N bonds). Remarkably, this molecule lacked intramolecular hydrogen bond between the hydrogen atom of hydroxyimine substituent and the oxygen atom of carbonyl group. Instead, one molecule of pyrazolone **2j** was linked by intermolecular hydrogen bonds (C=O···HON, bond length 2.474 Å) with two other molecules, forming chains of pyrazole molecules along the axis b (Fig. 2).

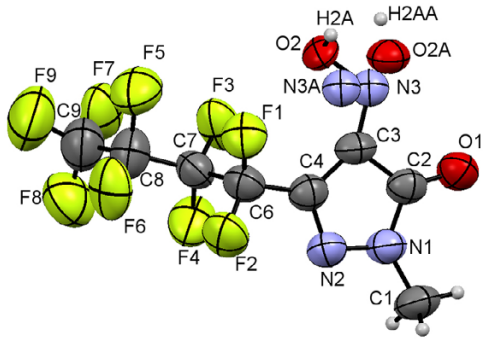


Figure 1. The molecular structure of compound **2j** with atoms represented by thermal vibration ellipsoids of 50% probability.

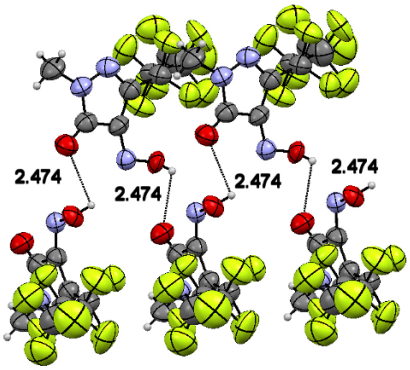


Figure 2. Interactions between the molecules of compound **2j**.

IR spectra of heterocycle **2b** in MeCN and $CHCl_3$ solutions still contained the high frequency absorption bands at 1735 and 1743 cm^{-1}, respectively, arising from carbonyl group vibrations. This indicated that the molecular structure in solid samples and in solution phase remained the same. According to the data of ^1H and ^{19}F NMR spectroscopy, pyrazoles **2a**–**j** existed in DMSO-d_6 solutions as mixtures of two isomers (Table 1). The analysis of NMR spectra of compounds **2b**,**d** in CD_3CN and $CDCl_3$ showed that the isomer ratio depended on the nature of solvent, with a tendency for one isomer to predominate when the less polar $CDCl_3$ was used as solvent.

The nitroso-hydroxyimine tautomerism of 5-alkylpyrazol-3-ones has been studied by many research groups.[22,30–32] Quantum-chemical calculations and experimental data were used to show the preferred existence of 5-alkyl(phenyl)pyrazol-3-ones in the form of hydroxyimine tautomer, with the *E*-form being predominant.[31] The energy characteristics of various isomers were calculated and ^{13}C NMR spectra were simulated using GIAO-ωb97xD/6-31G(d)//M06-2X/6-311++G(d,p) method. The predicted ^{13}C NMR chemical shifts for *Z*,*E*-isomers were δ_Z 153–150 and δ_E 159–150 ppm, which was also confirmed experimentally.[30]

Taking into account this trend, we assigned the isomers of compounds **2a**–**j** on the basis of ^{13}C NMR spectra (DMSO-d_6), in which the isomers differed by the chemical shifts of C-5 carbonyl carbon nucleus. Thus, the signal at 159–162 ppm was attributed to the carbonyl atom of *E*-isomer which predominated in DMSO-d_6, while the signal at 150–153 ppm belonged to the C-5 atom of *Z*-form (Scheme 2). The signals of α-CF_3 or α-CF_2 of polyfluoroalkyl substituents in *E*-isomers of pyrazoles **2a**–**j** were generally observed at upfield positions relative to the analogous signals of *Z*-form.

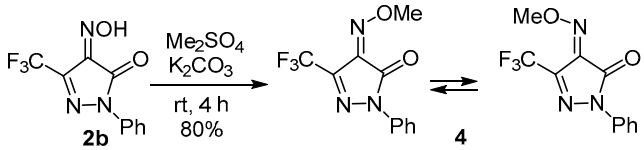
Methylation of pyrazole **2b** with dimethyl sulfate in the presence of K_2CO_3 in MeCN led to the formation of *O*-methylated product **4**, which also existed as a mixture of *Z*- and *E*-isomers (Scheme 3). The formation of a single product instead of two isomeric products due to methylation at two different oxygen atoms was confirmed by GC-MS analysis, as compound **4** gave only one chromatographic peak with the retention time of 18.38 min and *m*/*z* value of 271 [M^+]. It should be noted that the carbonyl carbon atoms of *Z*,*E*-isomers of compound **4** gave ^{13}C NMR signals in the same range (δ_E 158 and δ_Z 150 ppm) as the carbonyl carbon atoms in *Z*,*E*-isomers of the non-methylated starting pyrazole **2b** (Table 1). Furthermore, the isomer ratio did not depend on the solvent used (DMSO-d_6 or $CDCl_3$), which could be apparently explained by the lower possibility for intermolecular hydrogen bond formation in methoxy product **4** compared to the starting pyrazole **2b** containing a hydroxy group.

In a continuation of our study, the biological properties of the synthesized pyrazoles **2a**,**b**,**e**,**f**,**h**,**j** were tested. The possibilities for using functionalized pyrazoles as non-steroidal anti-inflammatory drugs are well known.[33] In addition, the obtained pyrazoles **2a**–**j** have a structural

Table 1. ^{19}F and ^{13}C NMR spectral data for compounds **2a**–**j**, **4**

Compound	R^F	R	*Z*:*E* isomer ratio (solvent)	Chemical shifts, δ, ppm			
				E-isomer		*Z*-isomer	
				α-CF_3 or α-CF_2	C=O	α-CF_3 or α-CF_2	C=O
2a	CF_3	H	1.5:1 (DMSO-d_6) 1:1 ($(CD_3)_2CO$)	97.1 97.2[23]	162.4	98.3 98.3[23]	153.8
2b	CF_3	Ph	1.3:1 (DMSO-d_6) 1.1:1 (CD_3CN) 0.3:1 ($CDCl_3$)	97.1 97.0 95.0	159.2	98.5 98.3 96.8	150.3
2c	C_2F_5	H	1.4:1 (DMSO-d_6)	49.0	162.1	51.9	153.6
2d	C_2F_5	Ph	1.6:1 (DMSO-d_6) 8.2:1 ($CDCl_3$)	49.0 46.8	158.9	51.6 49.3	150.2
2e	CF_2CF_2H	H	1:1 (DMSO-d_6)	46.1	162.2	46.7	153.6
2f	C_3F_7	H	2.2:1 (DMSO-d_6)	50.3	162.3	53.5	153.7
2g	C_4F_9	H	2.3:1 (DMSO-d_6) 2:1 ($(CD_3)_2CO$)	50.9 51.9	162.3	53.9 54.7	153.6
2h	C_4F_9	Ph	2.8:1 (DMSO-d_6)	51.1	158.9	53.9	150.2
2i	CF_3	Me	1.3:1 (DMSO-d_6)	97.3	160.5	98.6	151.8
2j	C_4F_9	Me	2.9:1 (DMSO-d_6) 13.2:1 ($CDCl_3$)	51.1 49.3	160.5	53.9 51.5	151.7
4	CF_3	Ph	1.6:1 (DMSO-d_6) 1.6:1 ($CDCl_3$)	98.4 96.6	158.9	96.9 94.9	150.5

Scheme 3



similarity with known analgesic drugs of antipyrine series, therefore the majority of the synthesized pyrazoles (compounds **2a**,**b**,**e**,**f**,**h**,**j**) were tested for acute toxicity and analgesic activity.

The acute toxicity was tested on CD-1 mice, using three mice in each group for one dose of compound. The compounds were introduced as single doses intra-abdominally as suspensions in 1% starch mucus, after which the animals were observed for 14 days.[34,35] The studied pyrazoles **2a**,**b**,**e**,**f**,**h**,**j** were generally less toxic than diclofenac, since the LD_{50} values for all of the tested compounds were estimated to be in the range of 150–300 or above 300 mg/kg (Table 2). A decrease in toxicity was observed upon lengthening of the carbon chain in the polyfluoroalkyl substituent, namely, replacement of trifluoromethyl group with a heptafluoropropyl group (compounds **2a**,**b**,**f**). An analogous trend was observed in the series of 4-unsubstituted analogs[36] where the replacement of trifluoromethyl substituent with pentafluoroethyl group also led to a slight decrease in toxicity. In the case of compound **2b**, it was shown that the toxicity of that compound was lower *via* the route of gastric administration.

The analgetic activity of pyrazoles **2a**,**b**,**e**,**h**,**j** was evaluated using *in vivo* experiments with SD rats at the dose level of 15 or 25 mg/kg (Table 2), according to the hot plate test. The compounds were introduced intra-abdominally as a suspension in 1% starch mucus. Except for compound **2h**, all of the studied compounds exhibited moderate analgesic activity, which in some cases approached the activity of diclofenac at the dose level of 10 mg/kg. When comparing compound **2h** with its *N*-methyl derivative **2j**, it can be expected that the introduction of substituent at the nitrogen atom of heterocycle should enhance the analgesic activity. Such a trend was to some extent confirmed by the results obtained from comparing compound **2a** with *N*-phenyl derivative **2b**.

Pyrazoles **2a**,**b** were tested for the presence of anti-inflammatory activity using the model of carrageenan-induced paw edema with Sprague Dawley rats.[34] Compound **2a** was found to be inactive at all experimental data points (1, 3, and 5 h after the introduction of carrageenan), while pyrazole **2b** showed slight inhibition of inflammation (17%, $p < 0.05$ compared to control) only in the data point at 3 h.

Thus, we have proposed alternative synthetic routes for the preparation of 4-hydroxyimino-5-polyfluoroalkylpyrazol-3-ones, among which the most effective method was based on a one-pot treatment of polyfluoroalkyl-3-oxoesters with hydrazine and sodium nitrite in acetic acid. It was established that 4-hydroxyimino-5-polyfluoroalkylpyrazol-3-ones in solid state and in solutions existed as mixtures of

Table 2. The analgesic activity and acute toxicity of compounds **2a**–**j**

Compound	Analgesic activity: increase in latency time after 1 h (after 2 h), %	Acute toxicity: dose, mg/kg (number of surviving animals)
2a	35.0* at 25 mg/kg dose	300 (1)
2b	62.4**	300 (0) 150 (2) 60 (3)*** 150 (3)***
2e	Inactive (89.5*[4])	150 (3)
2f	Not tested	300 (2)
2h	Inactive (Inactive)	150 (3)
2j	53.2* (69.1*[5])	150 (3)
Diclofenac	56.0 ±10.3[36] (83.4±18.1)[36] at 10 mg/kg dose	LD_{50} 74,[37] intra-abdominal administration

* $p < 0.05$.
** $p < 0.000001$.
*** Intragastric administration *via* gastric tube.
*[4] $p < 0.01$.
*[5] $p < 0.001$.

Z,*E*-isomers of the hydroxyimine tautomer. It was shown that the synthesized pyrazoles exhibited moderate to strong analgesic activity, which was comparable to the activity of diclofenac.

Experimental

IR spectra were recorded on a PerkinElmer Spectrum One FT-IR spectrometer over the wavenumber range of 4000–400 cm^{-1} using a diffuse reflectance accessory. ^1H and ^{19}F NMR spectra were acquired on Bruker DRX-400 (400 and 376 MHz, respectively, compounds **2a**,**b**,**e**,**g**,**i**) and Bruker Avance 500 (500 and 470 MHz, respectively, compounds **2c**,**d**,**f**,**h**,**j**,**4**) spectrometers. ^{13}C NMR spectra were recorded on a Bruker Avance-500 (125 MHz). Solvent was DMSO-d_6. TMS was used as internal standard for ^1H and ^{13}C NMR spectra, and C_6F_6 was used as the internal standard for ^{19}F NMR spectra (δ –162.9 ppm). Mass spectrum of compound **4** was recorded on an Agilent 7890A gas chromatograph coupled to Agilent 5975C Inert XL EI/CI quadrupole mass spectrometric detector, using an HP-5MS capillary fused silica column (polydimethylsiloxane, 5 mass % of phenyl groups, 30 m length, 0.25 mm diameter, 0.25 μm film thickness. Mass spectra were recorded in electron impact ionization mode (70 eV) while scanning the total ion current over the mass range of 20–1000 Da, carrier gas – helium. Injection volume was 1.0 μl, sample solutions with 3–5 mg/ml concentration were prepared in $CHCl_3$. Elemental analysis was performed using a PerkinElmer 2400 Series II CHN-O elemental analyzer. Melting points were determined in open capillaries on a Stuart SMP30 digital melting point apparatus. Column chromatography was performed on silica gel 60 (0.063–0.2 mm) from Alfa Aesar.

The starting polyfluoroalkyl-containing 3-oxoesters **1**[38] and pyrazolones **3**[39] were synthesized according to known procedures.

Synthesis of polyfluoroalkyl-containing 4-hydroxyiminopyrazol-5-ones 2a–j (General procedure). Method I. A solution of 3-oxoester **1a**,**b**,**g**,**i** (10 mmol) in AcOH (10 ml) was cooled to 0–5°C with stirring and treated by slow addition of $NaNO_2$ (0.86 g, 12.5 mmol) as solution in H_2O (10 ml). The mixture was maintained for 30 min at 5–10°C, treated with the appropriate hydrazine derivative (11 mmol), and stirred at room temperature for 3–4 h.

Method II. A mixture of the appropriate 3-oxoester **1a**,**b**,**g**,**i**,**j** (10 mmol) and the appropriate hydrazine derivative (11 mmol) was refluxed in AcOH (10 ml) for 3–4 h. The reaction mixture was then cooled to 0–5°C with stirring and treated by slow addition of $NaNO_2$ (1.72 g, 25 mmol) in H_2O (15 ml). The mixture was then maintained for 30 min at 5–10°C.

Method III. A solution of pyrazolone **3a–h** (10 mmol) in AcOH (10 ml) was cooled to 0–5°C with stirring and treated by slow addition of $NaNO_2$ (0.86 g, 12.5 mmol) in H_2O (10 ml). The mixture was maintained for 30 min at 5–10°C.

In all of the cases, the reaction mixture was extracted with Et_2O (2×20 ml), the organic layer was washed with saturated $NaHCO_3$ solution to neutral pH, dried over anhydrous Na_2SO_4, and evaporated at reduced pressure on a rotary evaporator. The obtained precipitate was washed with H_2O, hexane, and air-dried.

4-(Hydroxyimino)-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one hydrate (2a), a mixture of isomers, *E*:*Z* ratio 1.5:1. Yield 0.47 g (24%, method I), 1.23 g (62%, method II), 1.47 g (74%, method III), yellow powder, mp 113–114°C (sublim.) (mp 110°C[31]). ^{1}H NMR spectrum, δ, ppm: 12.50 (1H, s, OH *Z*-isomer); 12.60 (1H, s, OH *E*-isomer); 15.08 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 119.1 (q, *J* = 270.0, CF_3 *Z*-isomer); 119.2 (q, *J* = 268.5, CF_3 *E*-isomer); 129.5 (q, *J* = 40.3, $\underline{C}CF_3$ *E*-isomer); 136.1 (q, *J* = 38.3, $\underline{C}CF_3$ *Z*-isomer); 138.6 (*E*-isomer); 140.0 (*Z*-isomer); 153.8 (C=O *E*-isomer); 162.4 (C=O *Z*-isomer). ^{19}F NMR spectrum, δ, ppm: 97.1 (s, CF_3 *E*-isomer); 98.2 (s, CF_3 *Z*-isomer). Found, %: C 24.38; H 2.03; N 20.99. $C_4H_2F_3N_3O_2\cdot H_2O$. Calculated, %: C 24.13; H 2.03; N 21.11.

4-(Hydroxyimino)-5-(trifluoromethyl)-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (2b), a mixture of isomers, *E*:*Z* ratio 1.3:1. Yield 0.51 g (20%, method I), 1.52 g (59%, method II), 2.11 g (82%, method III), orange powder, mp 163–164°C. IR spectrum, ν, cm^{-1}: 3131, 3057, 3007 (OH), 1704 (C=O), 1678, 1614, 1596, 1563 (C=N, C=C), 1145–1066 (CF). ^{1}H NMR spectrum, δ, ppm: 7.30–7.35, 7.48–7.53, 7.71–7.75 (5H, m, H Ph); the signal of OH group was not observed due to deuterium exchange with solvent. ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 119.2 (2C, q, *J* = 269.5, CF_3); 119.6 (*E*-isomer); 119.7 (*Z*-isomer); 126.5 (*E*-isomer); 129.1 (*E*-isomer); 129.7 (2C, q, *J* = 40.9, $\underline{C}CF_3$); 136.8 (*E*-isomer); 126.4 (*Z*-isomer); 129.1 (*Z*-isomer); 136.8 (*Z*-isomer); 139.4 (*E*-isomer); 140.5 (*Z*-isomer); 150.3 (C=O *E*-isomer); 159.2 (C=O *Z*-isomer). ^{19}F NMR spectrum, δ, ppm: 97.1 (s, CF_3 *E*-isomer); 98.5 (s, CF_3 *Z*-isomer). Found, %: C 46.73; H 2.36; N 16.32. $C_{10}H_6F_3N_3O_2$. Calculated, %: C 46.70; H 2.35; N 16.34.

4-(Hydroxyimino)-5-(pentafluoroethyl)-2,4-dihydro-3*H*-pyrazol-3-one hydrate (2c), a mixture of isomers, *E*:*Z* ratio 1.4:1. Yield 1.61 g (65%, method III), yellow powder, mp 114–115°C. IR spectrum, ν, cm^{-1}: 3675, 3400, 3221 (OH, NH), 1735 (C=O), 1642, 1555, 1505 (C=N, C=C), 1135–1059 (CF). ^{1}H NMR spectrum, δ, ppm: 12.63 (1H, s, NH *E*-isomer); 12.73 (1H, s, NH *Z*-isomer); 15.19 (2H, br. s, OH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 109.4 (qt, *J* = 251.9, *J* = 39.4, CF_2); 118.1 (tq, *J* = 286.7, *J* = 36.8, CF_3); 153.6 (C=O *E*-isomer); 162.1 (C=O *Z*-isomer). ^{19}F NMR spectrum, δ, ppm (*J*, Hz): 49.0 (q, *J* = 2.5, CF_2 *E*-isomer); 51.9 (q, *J* = 1.8, CF_2 *Z*-isomer); 80.3 (t, *J* = 2.6, CF_3 *E*-isomer); 82.2 (unresolved t, CF_3 *Z*-isomer). Found, %: C 24.11; H 1.62; N 16.87. $C_5H_2F_5N_3O_2\cdot H_2O$. Calculated, %: C 24.03; H 1.57; N 18.69.

4-(Hydroxyimino)-5-(pentafluoroethyl)-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (2d), a mixture of isomers, *E*:*Z* ratio 1.6:1. Yield 1.93 g (63%, method III), yellow powder, mp 161–162°C. IR spectrum, ν, cm^{-1}: 3125, 3047, 3017 (OH), 1707 (C=O), 1675, 1610, 1592, 1560 (C=N, C=C), 1140–1060 (CF). ^{1}H NMR spectrum, δ, ppm: 7.31–7.34, 7.49–7.53, 7.71–7.73 (5H, m, H Ph); the signal of OH group was not observed due to deuterium exchange with solvent. ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 109.5 (2C, qt, *J* = 252.8, *J* = 39.6, CF_2); 118.1 (2C, tq, *J* = 287.1, *J* = 36.4, CF_3); 119.5 (*Z*-isomer); 119.7 (*E*-isomer); 126.4 (*E*-isomer); 126.5 (*Z*-isomer); 129.1 (2C); 135.7 (2C, t, *J* = 28.9, $\underline{C}CF_2$); 136.6 (*Z*-isomer); 136.7 (*E*-isomer); 139.2 (2C); 141.1; 150.2 (C=O *E*-isomer); 158.8 (C=O *Z*-isomer). ^{19}F NMR spectrum, δ, ppm (*J*, Hz): 49.0 (br. s, CF_2 *E*-isomer); 51.6 (br. s, CF_2 *Z*-isomer); 80.5 (t, *J* = 2.7, CF_3 *E*-isomer); 82.3 (unresolved t, CF_3 *Z*-isomer). Found, %: C 43.03; H 1.95; N 16.69. $C_{11}H_6F_5N_3O_2$. Calculated, %: C 43.01; H 1.97; N 13.68.

4-(Hydroxyimino)-5-(1,1,2,2-tetrafluoroethyl)-2,4-dihydro-3*H*-pyrazol-3-one hydrate (2e), a mixture of isomers, *E*:*Z* ratio 1:1. Yield 1.66 g (72%, method III), yellow powder, mp 50°C (sublim., PhMe). IR spectrum, ν, cm^{-1}: 3668, 3420, 3232, 1696 (OH, NH), 1746 (C=O), 1631, 1559, 1531 (C=N, C=C), 1102–1072 (CF). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 6.83 (1H, tt, *J* = 51.8, *J* = 5.1 $(CF_2)_2H$ *Z*-isomer); 6.85 (1H, tt, *J* = 51.8, *J* = 5.4, $(CF_2)_2H$ *E*-isomer); 12.48 (1H, s, OH *Z*-isomer); 12.60 (1H, s, OH *E*-isomer); 15.13 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 106.9–113.5 (m, $(CF_2)_2H$); 129.1 (t, *J* = 31.3, $\underline{C}CF_2$ *Z*-isomer); 135.1 (t, *J* = 29.6, $\underline{C}CF_2$ *E*-isomer); 138.1 (*Z*-isomer); 140.8 (*E*-isomer); 153.6 (*E*-isomer); (C=O *E*-isomer); 162.3 (C=O *Z*-isomer). ^{19}F NMR spectrum, δ, ppm (*J*, Hz): 25.1 (2F, dt, *J* = 51.8, *J* = 10.1, β-CF_2 *Z*-isomer); 25.2 (2F, dt, *J* = 51.8, *J* = 8.7, β-CF_2 *E*-isomer); 46.0–46.1 (2F, m, γ-CF_2 *Z*-isomer); 46.6–46.7 (2F, m, γ-CF_2 *E*-isomer). Found, %: C 26.05; H 2.41; N 18.05. $C_5H_3F_4N_3O_2\cdot H_2O$. Calculated, %: C 25.99; H 2.18; N 18.18.

5-(Heptafluoropropyl)-4-(hydroxyimino)-2,4-dihydro-3*H*-pyrazol-3-one hydrate (2f), a mixture of isomers, *E*:*Z*

ratio 2.2:1. Yield 1.79 g (60%, method III), yellow powder, mp 99–100°C (PhMe). IR spectrum, ν, cm^{-1}: 3680, 3416, 3234, 1698 (OH, NH), 1749 (C=O), 1631, 1547, 1494 (C=N, C=C), 1124–1065 (CF). ^{1}H NMR spectrum, δ, ppm: 12.69 (1H, s, OH *E*-isomer); 12.80 (1H, s, OH *Z*-isomer); 15.26 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 101.9–121.0 (C_3F_7); 131.4 (t, *J* = 31.7, $\underline{C}CF_2$ *Z*-isomer); 137.6 (t, *J* = 28.2, $\underline{C}CF_2$ *E*-isomer); 138.9 (*Z*-isomer); 140.6 (*E*-isomer); 153.7 (C=O *E*-isomer); 162.3 (C=O *Z*-isomer). ^{19}F NMR spectrum, δ, ppm (*J*, Hz): 36.6–36.7 (2F, m, γ-CF_2 *E*-isomer); 38.3–38.4 (2F, m, γ-CF_2 *Z*-isomer); 50.2–50.3 (2F, m, β-CF_2 *E*-isomer); 53.4–53.5 (2F, m, β-CF_2 *Z*-isomer); 82.8 (3F, t, *J* = 9.2, CF_3 *E*-isomer); 83.0 (3F, t, *J* = 9.6, CF_3 *Z*-isomer). Found, %: C 24.24; H 1.20; N 14.02. $C_6H_2F_7N_3O_2 \cdot H_2O$. Calculated, %: C 24.09; H 1.35; N 14.05.

4-(Hydroxyimino)-5-(nonafluorobutyl)-2,4-dihydro-3*H*-pyrazol-3-one hydrate (2g), a mixture of isomers, *E*:*Z* ratio 2.3:1. Yield 0.63 g (18%, method I), 2.16 g (62%, method II), 2.97 g (85%, method III), yellow powder, mp 126–127°C. IR spectrum, ν, cm^{-1}: 3681, 3415, 3234, 2772 (OH, NH), 1745 (C=O), 1697, 1630, 1494 (C=N, C=C), 1231–1138 (CF). ^{1}H NMR spectrum, δ, ppm: 12.69 (1H, s, OH *E*-isomer); 12.80 (1H, s, OH *Z*-isomer); 15.25 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 106.0–120.4 (m, C_4F_9); 129.1 (t, *J* = 31.3, $\underline{C}CF_2$ *Z*-isomer); 135.1 (t, *J* = 28.1, $\underline{C}CF_2$ *E*-isomer); 138.1 (*Z*-isomer); 140.8 (*E*-isomer); 153.6 (C=O *E*-isomer); 162.3 (C=O *Z*-isomer). ^{19}F NMR spectrum, δ, ppm (*J*, Hz): 37.1–37.2 (2F, m, γ-CF_2 *E*-isomer); 37.5–37.6 (2F, m, γ-CF_2 *Z*-isomer); 40.2–40.3 (2F, m, β-CF_2 *E*-isomer); 41.8–41.9 (2F, m, β-CF_2 *Z*-isomer); 50.9 (2F, t, *J* =10.8, α-CF_2 *E*-isomer,); 53.9–54.0 (2F, m, α-CF_2 *Z*-isomer), 82.2 (6F, t, *J* = 9.4, CF_3). Found, %: C 24.15; H 1.12; N 11.95. $C_7H_2F_9N_3O_2 \cdot H_2O$. Calculated, %: C 24.08; H 1.15; N 12.04.

4-(Hydroxyimino)-5-(nonafluorobutyl)-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (2h), a mixture of isomers, *E*:*Z* ratio 2.8:1. Yield 3.34 g (82%, method III), yellow powder, mp 127–128°C. IR spectrum, ν, cm^{-1}: 3247, 3181 (NH), 1723 (C=O), 1704, 1616, 1595 (C=N, C=C), 1241–1129 (CF). ^{1}H NMR spectrum, δ, ppm: 7.20–7.25, 7.41–7.52, 7.83–7.93 (5H, m, H Ph). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 107.6–120.3 (C_4F_9); 119.4 (*Z*-isomer); 119.6 (*E*-isomer); 126.5 (*E*-isomer); 126.6 (*Z*-isomer); 129.1 (2C); 129.4 (t, *J* = 31.8, $\underline{C}CF_2$ *Z*-isomer); 135.8 (t, *J* = 28.4, $\underline{C}CF_2$ *E*-isomer); 136.6 (*Z*-isomer); 136.7 (*E*-isomer); 138.8 (*Z*-isomer); 141.2 (*E*-isomer); 150.2 (C=O *E*-isomer); 158.9 (C=O *Z*-isomer). ^{19}F NMR spectrum, δ, ppm (*J*, Hz): 37.3–37.4 (2F, m, γ-CF_2 *E*-isomer); 37.5–37.6 (2F, m, γ-CF_2 *Z*-isomer); 40.7–40.8 (2F, m, β-CF_2 *E*-isomer); 41.9–42.0 (2F, m, β-CF_2 *Z*-isomer); 51.0–51.1 (2F, m, α-CF_2 *E*-isomer); 53.9–54.0 (2F, m, α-CF_2 *Z*-isomer); 82.1 (3F, t, *J* = 9.4, CF_3 *E*-isomer); 82.2 (3F, t, *J* = 9.4, CF_3 *Z*-isomer). Found, %: C 38.30; H 1.42; N 10.43. $C_{13}H_6F_9N_3O_2$. Calculated, %: C 38.35; H 1.49; N 10.32.

4-(Hydroxyimino)-2-methyl-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one (2i), a mixture of isomers, *E*:*Z* ratio 1.3:1. Yield 0.43 g (22%, method I), 1.13 g (58%, method II), yellow powder, mp 99–100°C. IR spectrum, ν, cm^{-1}: 3510, 3446 (OH), 1705 (C=O), 1677, 1646, 1615 (C=N, C=C), 1213–1152 (CF). ^{1}H NMR spectrum, δ, ppm: 3.32 (3H, s, CH_3 *Z*-isomer); 3.34 (3H, s, CH_3 *E*-isomer); the signal of OH group was not observed due to deuterium exchange with solvent. ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 31.7 (CH_3 *E*-isomer); 31.9 (CH_3 *Z*-isomer); 119.0 (q, *J* = 269.8, CF_3 *E*-isomer); 119.1 (q, *J* = 268.4, CF_3 *Z*-isomer); 127.7 (q, *J* = 40.7, $\underline{C}CF_3$ *E*-isomer); 134.4 (q, *J* = 38.6, $\underline{C}CF_3$ *Z*-isomer); 138.7 (*Z*-isomer); 140.0 (*E*-isomer); 151.8 (C=O *E*-isomer); 160.5 (C=O *Z*-isomer). ^{19}F NMR spectrum, δ, ppm: 97.3 (s, CF_3 *E*-isomer); 98.6 (s, CF_3 *Z*-isomer). Found, %: C 30.70; H 2.09; N 21.62. $C_5H_4F_3N_3O_2$. Calculated, %: C 30.78; H 2.07; N 21.54.

4-(Hydroxyimino)-2-methyl-5-(nonafluorobutyl)-2,4-dihydro-3*H*-pyrazol-3-one (2j), a mixture of isomers, *E*:*Z* ratio 2.9:1. Yield 2.10 g (61%, method II), yellow crystals, mp 130–131°C. IR spectrum, ν, cm^{-1}: 3520, 3455 (OH), 1715 (C=O), 1670, 1645, 1605 (C=N, C=C), 1200–1105 (CF). ^{1}H NMR spectrum, δ, ppm: 3.36 (3H, s, CH_3 *E*-isomer); 3.37 (3H, s, CH_3 *Z*-isomer). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 31.8 (CH_3 *E*-isomer); 32.1 (CH_3 *Z*-isomer); 106.3–120.3 (m, C_4F_9); 127.1 (t, *J* = 31.3, $\underline{C}CF_2$ *Z*-isomer); 133.4 (t, *J* = 28.2, $\underline{C}CF_2$ *E*-isomer); 138.3 (*Z*-isomer); 140.9 (*E*-isomer); 151.7 (C=O *E*-isomer); 160.5 (C=O *Z*-isomer). ^{19}F NMR spectrum, δ, ppm: 37.2–37.3 (2F, m, γ-CF_2 *E*-isomer); 37.5–37.6 (2F, m, γ-CF_2 *Z*-isomer); 40.4–40.5 (2F, m, β-CF_2 *E*-isomer); 41.9–42.0 (2F, m, β-CF_2 *Z*-isomer); 51.0–51.1 (2F, m, α-CF_2 *E*-isomer); 53.9–54.0 (2F, m, α-CF_2 *Z*-isomer); 82.1 (3F, t, *J* = 9.5, CF_3 *E*-isomer); 82.2 (3F, t, *J* = 9.6, CF_3 *Z*-isomer). Found, %: C 27.84; H 1.17; N 12.18. $C_8H_4F_9N_3O_2$. Calculated, %: C 27.76; H 1.19; N 12.19.

4-(Methoxyimino)-2-phenyl-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one (4), a mixture of isomers, *E*:*Z* ratio 1.6:1. A mixture of oxime **2b** (0.5 g, 1.9 mmol), dimethyl sulfate (0.24 g, 1.9 mmol), and K_2CO_3 (0.39 g, 3 mmol) in MeCN (5 ml) was stirred at room temperature for 4 h. The reaction mixture was then cooled, quenched with H_2O (5 ml), extracted with $CHCl_3$ (2×10 ml), evaporated at reduced pressure, and purified by column chromatography, eluent $CHCl_3$–hexane, 4:1. Yield 2.17 g (80%), orange powder, mp 82–83°C. ^{1}H NMR spectrum, δ, ppm: 4.35 (3H, s, OCH_3 *Z*-isomer); 4.36 (3H, s, OCH_3 *E*-isomer); 7.32–7.36, 7.49–7.53, 7.68–7.72 (5H, m, H Ph). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 66.6 (*Z*-isomer); 67.0 (*E*-isomer); 118.7 (q, *J* = 270.8, CF_3 *E*-isomer); 118.9 (q, *J* = 269.3, CF_3 *Z*-isomer); 119.6 (*Z*-isomer); 119.7 (*E*-isomer); 126.5 (*E*-isomer); 126.7 (*Z*-isomer); 129.1 (2C); 129.8 (q, *J* = 41.0, $\underline{C}CF_3$ *Z*-isomer); 135.7 (q, *J* = 39.0, $\underline{C}CF_3$ *E*-isomer); 136.5 (2C); 138.2 (*Z*-isomer); 140.0 (*E*-isomer); 150.6 (C=O *E*-isomer); 158.1 (C=O *Z*-isomer). ^{19}F NMR spectrum, δ, ppm: 98.4 (s, CF_3 *E*-isomer); 96.9 (s, CF_3 *Z*-isomer). Mass spectrum, *m*/*z* (I_{rel}, %): 271 $[M]^+$ (20). Calculated, %: C 48.72; H 2.97; N 15.49. $C_{11}H_8F_3N_3O_2$. Found, %: C 48.65; H 2.84; N 15.55.

X-ray structural analysis of compound 2j was performed on an Xcalibur 3 automatic diffractometer equipped with a CCD detector (graphite monochromator, λ(MoKα) = 0.71073 Å, ω-scanning, temperature 295(2) K).

Absorption was taken into account analytically according to the multifaceted crystal model using the CrysAlis RED 1.171.39.38a program.[40] The crystal structure was solved by direct method and refined with full-matrix method of least squares by F^2 using the SHELXTL software suite.[41] Refinement for non-hydrogen atoms was performed in anisotropic approximation, hydrogen atoms were placed in geometrically calculated positions and included in the refinement according to the riding model in isotropic approximation with temperature parameters dependent on the "parent" atoms. The crystallographic data for compound **2j** (crystals grown from CH_2Cl_2 solution): $C_8H_4F_9N_3O_2$, *M* 345.14; space group $P2_1/c$; monoclinic crystals; *a* 17.558(4), *b* 5.4462(7), *c* 13.617(3) Å; β 105.40(2)°; *V* 1255.3(4) Å; *Z* 4; d_{calc} 1.826 g/cm^{-3}; μ 0.217 mm^{-1}. A total of 7779 reflections were collected, of which 3087 were independent, *R* factor 0.086, the number of refined parameters were 257. The complete crystallographic dataset for compound **2j** was deposited at the Cambridge Crystallographic Data Center (deposit CCDC 1878730).

The study of analgesic activity and acute toxicity of compounds 2a,**b**,**e**,**f**,**h**,**j**. Laboratory animals (Sprague Dawley rats and CD-1 mice) were obtained from the Branch of the Institute of Biochemistry, Russian Academy of Sciences, nursery "Pushchino". The second generation of animals was used for the described experiments. The animals were kept under natural light cycle in polypropylene rodent housing (Bioscape, Germany) on standard animal bedding (RehoFix MK 2000, J. Rettenmaier & Söhne, Germany), with the standard Chara chow for conventional laboratory rodents (Assortiment-Agro, Russia and BioPro, Russia) according to schedule and water *ad libitum*. The work with laboratory animals was performed by a professional veterinary doctor, pharmacologist, and trained specialists according to bioethics regulations and guidelines for human treatment of laboratory animals.[34,42,43]

The determination of acute toxicity was performed on outbred albino mice of CD-1 line according to the standard recommendations.[34,35] The study compounds were administered one time intra-abdominally as suspensions in 1% starch mucus, with each sample given to three animals. The survival of mice in groups after the administration of compounds was determined by close observation for 24 h and subsequent general observation for 14 days.

The analgesic activity was evaluated using hot plate test that was performed with outbred Sprague Dawley rats (3 females and 3 males in each group) according to the standard procedure.[34] The compounds were administered intra-abdominally as suspensions in 1% starch mucus. The latent period was determined using a 60200 series Hotplate (TSE Systems, Germany), the measurements were performed after 1 h, for compounds **2e**,**i**,**j** – also after 2 h. The longest time that an animal could be placed on the hot plate at 50°C was set at 30 s in order to prevent unintended damage to the skin of the experimental animals.[34] The reference medication was diclofenac (Hemofarm, Serbia) at the dose of 10 mg/kg (close to ED_{50}).

The anti-inflammatory activity was evaluated on outbred Sprague Dawley rats (3 females and 3 males in each group) using the carrageenan-induced paw edema model according to the standard procedure.[34] The study compounds were administered intra-abdominally as suspensions in 1% starch mucus (15 mg/kg) 30 min prior to the administration of carrageenan. The volume of rat paws was measured oncometrically across four time points: before the administration of carrageenan, then 1, 3, and 5 h after its administration using a TSE Volume Meter plethysmometer (TSE Systems, Germany).

The obtained experimental data were processed by Multiplet tests method using the GraphPad Prism 6 program. The results were interpreted as sufficiently different at $p < 0.05$.

This work was performed with financial support from the Russian Science Foundation (grant 16-13-10255).

The equipment used was kindly provided by the Collective Use Center "Spectroscopy and Analysis of Organic Compounds", I. Ya. Postovsky Institute of Organic Synthesis, Ural Branch of the Russian Academy of Sciences.

References

1. Sloop, J. C.; Holder, C.; Henary, M. *Eur. J. Org. Chem.* **2015**, *2015*, 3405.
2. Janin, Y. L. *Chem. Rev.* **2012**, *112*, 3924.
3. Chauhan, P.; Mahajan, S.; Enders, D. *Chem. Commun.* **2015**, *51*, 12890.
4. Omae, I. *Coord. Chem. Rev.* **2016**, *310*, 154.
5. Pettinari, C.; Tăbăcaru, A.; Galli, S. *Coord. Chem. Rev.* **2016**, *307*, 1.
6. Castro, I.; Barros, W. P.; Calatayud, M. L.; Lloret, F.; Marino, N.; De Munno, G.; Stumpf, H. O.; Ruiz-García, R.; Julve, M. *Coord. Chem. Rev.* **2016**, *315*, 135.
7. Adach, A. *J. Coord. Chem.* **2017**, *70*, 757.
8. Havrylyuk, D.; Roman, O.; Lesyk, R. *Eur. J. Med. Chem.* **2016**, *113*, 145.
9. Moreau, P.; Anizon, F.; Giraud, F.; J. Esvan, Y. *Recent Pat. Anti-Cancer Drug Discovery* **2016**, *11*, 309.
10. Akhtar, J.; Khan, A. A.; Ali, Z.; Haider, R.; Shahar Yar, M. *Eur. J. Med. Chem.* **2017**, *125*, 143.
11. El-Telbani, E. M.; El Shehry, M. F.; Nawwar, G. A. M. *Monatsh. Chem.* **2008**, *139*, 685.
12. Abd El Salam, H. A.; Shaker, N. O.; El-Telbani, E. M.; Nawwar, G. A. M. *J. Chem. Res.* **2009**, *2009*, 400.
13. Seo, M.-J.; Kim, J.-K.; Son, B.-S.; Song, B.-G.; No, Z.-S.; Cheon, H.-G.; Kim, K.-R.; Sohn, Y.-S.; Kim, H.-R. N. *Bull. Korean Chem. Soc.* **2004**, *25*, 1121.
14. Hussain, G.; Ather, M.; Khan, M. U. A.; Saeed, A.; Saleem, R.; Shabir, G.; Channar, P. A. *Dyes Pigm.* **2016**, *130*, 90.
15. El-Shehry, M. F.; El-Telbani, E. M.; Swellem, R. H. *J. Chem. Res.* **2009**, *2009*, 625.
16. Okonnishnikova, G. P.; Kostyuchenko, I. V.; Shulishov, E. V.; Tomilov, Y. V. *Russ. Chem. Bull., Int. Ed.* **2006**, *55*, 2233. [*Izv. Akad. Nauk*, *Ser. Khim.* **2006**, 2151.]
17. El-Rady, E. A. *J. Chin. Chem. Soc.* **2004**, *51*, 859.
18. Bao, X.; Wei, S.; Qian, X.; Qu, J.; Wang, B.; Zou, L.; Ge, G. *Org. Lett.* **2018**, *20*, 3394.
19. Sanguineti, A.; Monguzzi, A.; Vaccaro, G.; Meinardi, F.; Ronchi, E.; Moret, M.; Cosentino, U.; Moro, G.; Simonutti, R.; Mauri, M.; Tubino, R.; Beverina, L. *Phys. Chem. Chem. Phys.* **2012**, *14*, 6452.
20. Beverina, L.; Crippa, M.; Sassi, M.; Monguzzi, A.; Meinardi, F.; Tubino, R.; Pagani, G. A. *Chem. Commun.* **2009**, *34*, 5103.

21. Yassin, F. A. *Chem. Heterocycl. Compd.* **2009**, *45*, 997. [*Khim. Geterotsikl. Soedin.* **2009**, 1253.]
22. Belmar, J.; Quezada, J.; Jiménez, C. A.; Díaz-Gallifa, P.; Pasán, J.; Ruiz-Pérez, C. *New J. Chem.* **2013**, *37*, 2002.
23. Saloutin, V. I.; Burgart, Ya. V.; Skryabina, Z. E.; Kuzueva, O. G. *J. Fluorine Chem.* **1997**, *84*, 107.
24. Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432.
25. O'Hagan, D. *J. Fluorine Chem.* **2010**, *131*, 1071.
26. Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320.
27. Bazhin, D. N.; Kudyakova, Y. S.; Nemytova, N. A.; Burgart, Ya. V.; Saloutin, V. I. *J. Fluorine Chem.* **2016**, *186*, 28.
28. Khudina, O. G.; Burgart, Ya. V.; Saloutin, V. I.; Kravchenko, M. A. *Russ. Chem. Bull., Int. Ed.* **2010**, *59*, 1967. [*Izv. Akad. Nauk, Ser. Khim.* **2010**, 1917.]
29. Khudina, O. G.; Burgart, Ya. V.; Saloutin, V. I.; Kravchenko, M. A. *Russ. J. Org. Chem.* **2011**, *47*, 904. [*Zh. Org. Khim.* **2011**, *47*, 887.]
30. Koch, R.; Wollweber, H.-J.; Wentrup, C. *Aust. J. Chem.* **2015**, *68*, 1329.
31. Enchev, V.; Angelova, S. *J. Mol. Struct.: THEOCHEM* **2009**, *897*, 55.
32. Belmar, J.; Jiménez, C.; Ortiz, L.; Garland, M. T.; Baggio, R. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **2006**, *62*, o76.
33. Liu, J.-J.; Zhao, M.-Y.; Zhang, X.; Zhao, X.; Zhu, H.-L. *Mini-Rev. Med. Chem.* **2013**, *13*, 1957.
34. *Guidelines for preclinical studies of drugs. Part I* [in Russian]; Mironov, A. N., Ed.; Grif i K: Moscow, 2012.
35. *OECD Guideline for Testing of Chemicals*; *423: Acute Oral Toxicity – Acute Toxic Class Method*; Paris, 2001.
36. Agafonova, N.; Shchegolkov, E.; Burgart, Ya.; Saloutin, V.; Trefilova, A.; Triandafilova, G.; Solodnikov, S.; Maslova, V.; Borisevich, S.; Krasnykh, O.; Khusan, S. *Med. Chem.* **2018**. DOI: 10.2174/1573406414666181106145435.
37. Gein, V. L.; Popov, A. V.; Kolla, V. E.; Popova, N. A.; Potemkin, K. D. *Pharm. Chem. J.* **1993**, *27*, 343. [*Khim.-Farm. Zh.* **1993**, *27*, 42.]
38. Pashkevich, K. I.; Saloutin, V. I. *Russ. Chem. Rev.* **1985**, *54*, 1185. [*Usp. Khim.* **1985**, *54*, 1997.]
39. Saloutin, V. I.; Fomin, A. N.; Pashkevich, K. I. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1985**, *34*, 135. [*Izv. Akad. Nauk SSSR, Ser. Khim.* **1985**, 144.]
40. *CrysAlis RED, Version 1.171.35.11*; Oxford Diffraction Ltd., 2011.
41. Sheldrick, G. M. *Acta Crystallogr., Sect. A: Found Crystallogr.* **2008**, *A64*, 112.
42. *European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes*; ETC 123; Strasbourg, 1986.
43. *Russian Federal Law of April 12, 2010 No. 61-FZ "On Circulation of Medicines".*