EXPERIMENTAL AND THEORETICAL STUDY OF THE ACYLATION REACTION OF AMINOPYRAZOLES WITH ARYL AND METHOXYMETHYL SUBSTITUENTS

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Abstract

As a result of the chain of transformations from 1,3-butanedione with aryl and methoxy substituents through nitrosation and cyclization with hydrazine, the corresponding nitrosopyrazoles and aminopyrazoles were synthesized. According to this scheme, eight new previously unknown compounds were obtained. Their structures were established by the methods of IR, UV, ^{1}H NMR, ^{13}C NMR spectroscopy and mass spectrometry. DFT method of quantum-chemical calculations showed that obtained aminopyrazoles can exist as two tautomers; it was also confirmed by NMR ^{1}H spectroscopy data. In the case of acylation, an isomer is formed, where aryl substituent takes place in the fifth, rather than in the third position of the pyrazole ring, as shown by the DFT calculations.

Keywords: nitrosopyrazoles, aminopyrazoles, acylation, tautomerism.

1. Introduction

It is known that many pyrazole derivatives exhibit different types of biological activity [1-10]. However, thousands of substances are synthesized or obtained from natural raw materials, but only some of them are ultimately effective in the creation of medicines [11]. The reasons of that are still unclear, because the strong theory, connecting the structure of mentioned compounds with their pharmaceutical properties, does not exist. Therefore, it seems important to obtain new previously unknown compounds, including new pyrazole derivatives, which can exhibit biological activity. We need more amount of experimental information to establish correlation between structure of these compounds and their potential properties and use.

In the present work we obtained aminopyrazoles with aryl and methoxymethyl substituents and investigated the reaction of their acylation. This direction of synthesis was chosen due to the fact that presence of pharmacophore amino or acetamide groups in the molecule provides the ap-

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pearance of any biological activity. Modification of molecule by a polar methoxymethyl group changes the polarity of the whole molecule, which leads to an increase in the activity [12].

There are also some results, presented early, indicating an importance of methoxy group presence for biological activity of molecules. For example, it ensures that the necessary conformations of (methoxypropyl)thiazole are adopted for successful binding to the 5-lipoxygenase enzyme [13]. A methoxy derivative of 2-hydroxymethyl estradiol (namely 2-methoxymethyl estradiol) is more effective, than its natural analog, as tubulin-binding substance killing cancerous cells by inhibiting microtubule dynamics [14]. 3-Methoxymethyl cephem derivatives showed good activity against a wide variety of bacteria including some β-lactamase producing species [15]. It was shown also that omitting of the (methoxymethyl)methinoxy moiety of the benzodioxanyl group considerably decreases haedoxan insecticidal activity [16].

At the same time, arylation is an interesting approach that can accomplish structural modifications of molecules with the goal of synthesizing new substances with biological activities [17]. For example, some of the combined molecules including the indole and 2-naphthol skeletons demonstrated strong antioxidant and antibacterial properties [18]. Arylation of quinolin-4-ylinidazoline leads to creation of compounds with a broad-spectrum antimicrobial activity, in particular, antiplasmodial and antimycobacterial [19]. Thereby both methoxymethyl and aryl groups are the substituents, which can vary or even enhance biological activity of other molecules, including pyrazole.

Earlier, we reported the synthesis of new derivatives of alkoxymethylnitrosopyrazoles [20], their reduction to aminopyrazoles [21] and their acylation [22]. The present work is devoted to the preparation of previously unknown 4-nitroso-1*H*-pyrazole derivative with methoxymethyl and 2-naphthyl substituents, its reduction to amine with further acylation by acetic anhydride or chloroacetyl chloride.

2. Experimental

2.1. Synthesis

*2.1.1. (**2a**) 4-Methoxy-1-(naphthalen-2-yl)butane-1,2,3-trione-2-oxime*

5 g (20.7 mmol) of diketone **1a** in acetic acid were dissolved and cooled to 12 °C. Sodium nitrite weighing 1.57 g (22.8 mmol) was added in portions over an hour so that $T \leq 15°$ C. The reaction mixture was diluted with water and extracted with ether. The extract was evaporated. As a result, white precipitate was formed. Yield 4.95 g (88.24%), white crystals, m.p. 169-170 °C. IR spectrum (thin layer), ν, cm^{-1}: 1672 ($CH_2C=O$), 1695 (naphthyl-C=O). Mass spectrum, m/z (I, %): 271 (13) $[M]^+$, 239 (12), 155 (100), 127 (75), 45 (54). NMR Spectrum (^1H, δ, ppm): 3.32 (3H, CH_3), 4.8 s (2H, CH_2O), 7.61-8.42 m (7H naphthyl), 13.29 s (1H, NH). NMR spectrum ^{13}C, δ, ppm: 58.96, 73.43, 122.84, 127.68, 128.16, 129.41, 129.92, 130.05, 131.87, 132.47, 132.55, 136.07,

153.84, 192.55, 194.07. Found, %: C, 67.01; H, 4.54; N, 4.99. *M* 271.27. C15H13NO4. Calculated, %: 66.41; H 4.83; N, 5.16.

*2.1.2. (***3a***) 3-methoxymethyl-5-(naphthalen-2-yl)-4-nitroso-1H-pyrazole*

Dissolve 0.5 g (1.85 mmol) of isonitrosodiketone **2a** in 40 ml of ethanol. Hydrazine hydrate 0.4 g (8 mmol) was added dropwise to the resulting mixture by continuously mixing. The progress of the reaction was monitored by TLC (thin layer chromatography) and the stirring was stopped when the starting compound was completely reacted. Diluted with water, filtered. Crystals of green color were obtained. Yield 0.15 g (30.36%), green crystals m.p. 125-126 °C. UV spectrum, λ_{max}, nm (ε): 686 (63.2). Mass spectrum, m/z (*I*, %): 267 (95.10) $[M]^+$, 153 (100), 127 (53), 45 (29). NMR Spectrum (^{1}H, δ, ppm): 3.4 s (3H, CH_3), 4.43 s (2H, CH_2O), 7.61-8.35 m (7H naphthyl), 8.89 s (1H, NH). NMR spectrum ^{13}C, δ, ppm: 48.88 57.97, 66.91, 125.93, 127.19, 128.02, 128.76, 129.00, 133.08, 133.79. Found, %: C 67.28; H 4.65; N 15.38. *M* 267.28. $C_{15}H_{13}N_3O_2$. Calculated, %: C 67.40; H 4.90; N 15.72.

*2.1.3. (***4a***) 4-Amino-3-methoxymethyl-5-(naphthalen-2-yl)-1H-pyrazole*

0.075 g (0.28 mmol) of nitrosopyrazole **3a** in methylene chloride (5 ml) was dissolved. Catalyst (Pd\C) (0.015 g) was added with vigorous stirring, 0.11 g (2.18 mmol) of hydrazine hydrate was added into the reaction mixture. The reaction was monitored by TLC. After 12 hours, the mixture was filtered off and evaporated. Colorless crystals were isolated. Yield 0.056 g (78.5%), m.p. 118-120 °C. UV spectrum, λ_{max}, nm (ε): 303 (8680). Mass spectrum, m/z (I_{rel}, %): 253 (100) $[M]^+$, 222 (19), 192 (75), 154 (37), 127 (29) 45 (17). ^{1}H NMR Spectrum (DMSO-d_6), δ, ppm: 3.29 s (3H, CH_3), 4.07 s (2H, CH_2O), 4.44 s (2H, NH_2), 7.48-8.31 m (7H naphthyl), 12.61 s (1H, NH). NMR spectrum ^{13}C, δ, ppm: 57.28, 123.23, 123.87, 125.14, 125.88, 126.80, 127.80, 128.15, 131.85, 133.53. Found, %: C 70.6; H 5.47; N 16.45. *M* 253.30. Calculated, %: $C_{15}H_{15}N_3O$. C 71.13; H 5.97; N 16.59.

*2.1.4. (***5a***) N-[1-Acetyl-3-(methoxymethyl)-5-(naphthalen-2-yl)-1H-pyrazol-4-yl]acetamide*

0.1 g (0.4 mmol) of aminopyrazole **4a** in toluene (60 ml) was dissolved. The mixture was heated with continuous stirring. After dissolving the substance, 1.04 g (10.2 mmol) of acetic anhydride was added. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was washed with water and a solution of diluted sodium carbonate. Colorless crystals were isolated. M.p.: 193-195 °C. Yield 0.153 g (35%). IR spectrum (thin layer), ν, cm^{-1}: 1654.48, 1740.30 (C=O). ^{1}H NMR Spectrum (DMSO-d_6), δ, ppm: 2.09 s (3H, NHCOC$\underline{H}_3$), 2.76 s (3H, NCOC$\underline{H}_3$), 3.27 s (3H, C$\underline{H}_3$OCH$_2$), 4.61 s (2H, CH$_3$OC$\underline{H}_2$), 7.58-8.31 m (7H naphthyl), 9.73 s

(1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 22.91, 23.10, 58.07, 62.95, 122.08, 124.82, 126.53, 126.95, 127.15, 127.92, 128.50, 128.63, 128.75, 133.02, 133.24, 149.27, 170.10, 170.80.

*2.1.5. (***5b***) N-[1-Acetyl-3-(methoxymethyl)-5-phenyl-1H-pyrazol-4-yl]acetamide*

0.1 g (0.5 mmol) of aminopyrazole **4b** in toluene (70 ml) was dissolved. The mixture was heated with continuous stirring. After dissolving the substance, 1 g (2 mmol) of acetic anhydride was added. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was washed with water and solution of diluted sodium carbonate. Colorless crystals were isolated. M.p. 162-163 °C. Yield 0.055 g (38%). IR spectrum (thin layer), ν, cm^{-1}: 1690, 1750 (C=O). ^{1}H NMR Spectrum (DMSO-d_6), δ, ppm: 2.04 s (3H, NHCOC$\underline{H}_3$), 2.70 s (3H, NCOC$\underline{H}_3$), 3.24 s (3H, C$\underline{H}_3$OCH$_2$), 4.56 s (2H, CH$_3$OC$\underline{H}_2$), 7.45-7.77 m (5H phenyl), 9.64 s (1H, NH). NMR spectrum ^{13}C, δ, ppm: 22.85, 23.03, 58.07, 62.88, 121.80, 127.24, 128.98, 129.38, 131.20, 138.97, 149.55, 170.19, 170.81.

*2.1.6. (***6a***) N-[3-(methoxymethyl)-5-(naphthalen-2-yl)-1-chloroacetyl-1H-pyrazol-4-yl]-2-chloroacetamide*

0.1 g (0.4 mmol) of aminopyrazole **4a** was dissolved in minimum amount of toluene (70 ml), with heating and continuous stirring. After dissolving the amine, 0.113 g (1 mmol) of chloroacetyl chloride and 0.7 g (8.86 mmol) of pyridine were added. After filtering and washing the precipitate with water and soda solution, white crystals were obtained. M.p. 176-178 °C. The yield of the product was 0.035 g (22%). IR spectrum (thin layer), ν, cm^{-1}: 1679, 1756.64 (C=O). NMR Spectrum (^{1}H, δ, ppm).: 3.29 s (3H, CH$_3$), 4.36 s (2H, CH$_2$O), 4.65 s (2H, NHCOC$\underline{H}_2$Cl), 5.36 s (2H, NCOC$\underline{H}_2$Cl), 7.59-8.35 m (7H naphthyl), 10.23 s (1H, NH). NMR spectrum ^{13}C, δ, ppm: 42.93, 44.22, 58.20, 62.65, 121.52, 124.75, 126.78, 127.03, 127.35, 127.96, 128.07, 128.61, 128.63, 132.96, 133.41, 139.73, 149.71, 166.18, 166.77.

*2.1.7. (***6b***) N-[3-(methoxymethyl)-5-phenyl-1-(chloroacetyl)-1H-pyrazol-4-yl]-2-chloroacetamide*

0.128 g (0.63 mmol) of aminopyrazole **4b** in toluene (70 ml) was dissolved with heating. After complete dissolution, 0.09 g (0.7 mmol) of chloroacetyl chloride was added. 0.5 g (6.3 mmol) of pyridine was added for binding the liberated hydrogen chloride. The reaction was monitored by TLC. After completion of the reaction, the mixture was washed with water and 10% soda solution. It was extracted with ether. The ether layer was evaporated. As a result, white precipitate was formed. M.p. 144-145 °C. The yield of the product was 0.2 g (88%). IR spectrum (thin layer), ν, cm^{-1}: 1670.83, 1748.47 (C=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.27 s (3H, CH$_3$), 4.32 s

(2H, CH_2O), 4.61 s (2H, NHCOC$\underline{H}_2$Cl), 5.30 s (2H, NCOC$\underline{H}_2$Cl), 7.48-7.80 m (5H phenyl), 10.12 s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 42.83, 44.12, 58.20, 62.65, 121.33, 126.52, 127.40, 129.02, 129.74, 130.60, 139.65, 150.10, 166.15, 166.75.

2.2. Terms and conditions of ^{1}H NMR, IR, UV and mass spectra

All NMR data were collected in DMSO-d_6 on Bruker Avance III 600 spectrometer system (14.1 T, Bruker) at 295 K. For proton NMR experiments single p/2-pulse was applied. For proton NMR analyses the relaxation delay were 3 s, 90 p/2-pulses of 13.7 μs, spectral width is 5071 Hz.

Mass spectra were recorded on Finnigan MAT 8200 with double-focusing Nier-Johnson geometry and electron impact as ionization method. Range of recorded mass was set in the range of 5-2000 amu.

The reaction process and the purity of the compounds were monitored by TLC on Sorbfil plates of PTSX-AF-B (Russia) in ethyl acetate-toluene system (1:2), the spots were detected in ultraviolet light. UV spectra were recorded on HELIOS OMEGA spectrophotometer in ethanol. IR spectra were obtained on IR microscope SpecTRA TECH InspectIR based on the IR Fourier spectrophotometer Impact 400. Elemental analysis was performed on automatic CHNS analyzer EURO EA 3000 [23].

2.3. Quantum-chemical calculations

Molecular structures of **4a**, **4b**, **5a**, **5b**, **6a** and **6b** compounds were designed with help of DFT method, using BP86 exchange-correlation functional [24,25], def2-SVP basis set of atomic orbitals [26,27], Grimme dispersion correction [28,29] and ORCA software package [30]. RI approximation [31-37] was also additionally used in the case of calculations of their IR-spectra.

3. Results and discussion

Diketone **1a** was treated with sodium nitrite in acetic acid (Figure 1). As a result, isonitrosodiketone **2a** with methoxymethyl and 2-naphthyl substituents was first obtained. In the cyclization of isonitrosodiketone **2a** with hydrazine hydrate in alcohol, the previously unknown 3-methoxymethyl-5-(naphthalen-2-yl)-4-nitroso-1*H*-pyrazole **3a** was isolated as the only product. The reduction of compound **3a** was carried out in solution of methylene chloride with an excess of hydrazine hydrate in the presence of a catalyst of 0.5% Pd\C. At the end of the reaction, a new 4-amino-3-methoxymethyl-5-(naphthalen-2-yl)-1*H*-pyrazole **4a** was isolated. Dividing the signal of the proton of the pyrazole ring in the ^{1}H NMR spectrum of compound **4a** indicates that it exists as two tautomeric forms: 4-amino-3-methoxymethyl-5-(naphthalen-2-yl)-1*H*-pyrazole and 4-amino- 5-methoxymethyl-3-(naphthalen-2-yl)-1*H*-pyrazole.

The reaction of acylation of aminopyrazole **4a** and 4-amino-3-methoxymethyl-5-phenyl-1*H*-pyrazole **4b** [21] with acetic anhydride and chloroacetyl chloride was carried out. Aminopyrazoles **4a** and **4b** with acetic anhydride gave white crystals of diacetyl derivatives **5a** and **5b** (Figure 1). In reaction **4a** and **4b** with chloroacetyl chloride in toluene with addition of pyridine, *bis* chloroacetyl-derivatives in both the amine and the nitrogen of the pyrazole ring were isolated. We have previously shown that the acylation of these aminopyrazoles with chloroacetyl chloride in benzene takes place only at the nitrogen atom of the amine [38], but in the presence of pyridine **6a** and **6b** *bis* (chloroacetyl) derivatives were obtained.

It was expected that, because of the tautomerism of **4a** and **4b** compounds, their acylation would result in a mixture of products with different positions of the acyl group at the nitrogen atoms of the pyrazole ring. However, when analyzing ^{1}H NMR data, it was found that the product of the acylation reaction is only one of the possible isomers.

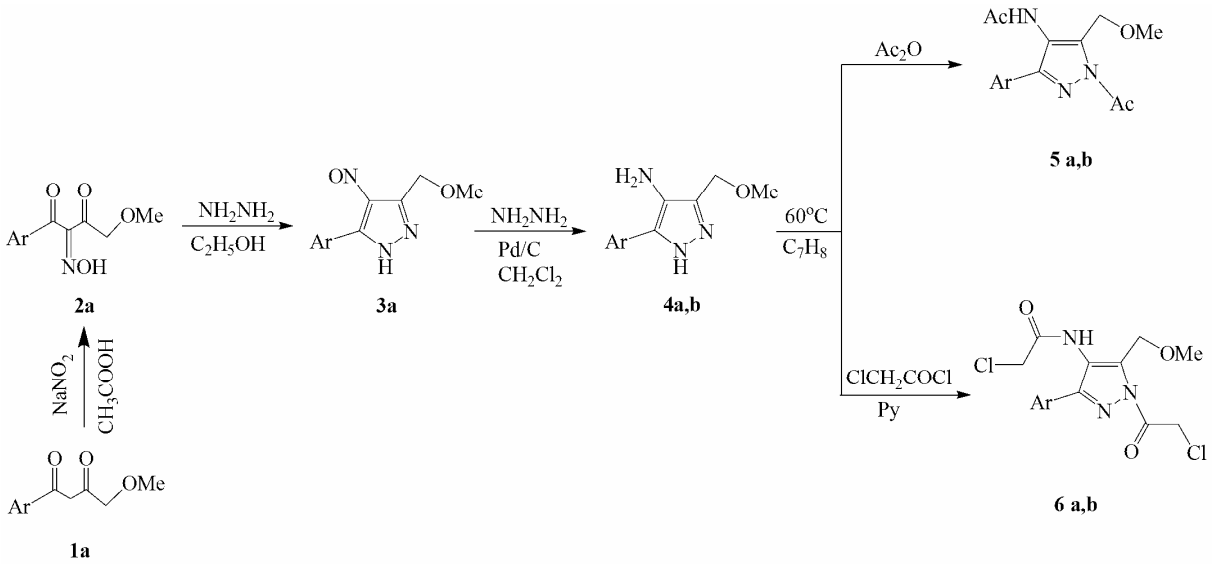

Figure 1. The synthesis of acylated substituted 4-aminopyrazoles

Quantum-chemical calculations of **4a** and **4b** tautomers were carried out for estimation of the synthesis results. It was shown, that their total energies difference is equal only to 0.004 eV. This value is essentially lower than energy of thermal oscillations at room temperature and can be explained by insignificant structural changes at transition from one form to another one, concerning generally the orientation of aromatic and methoxymethyl substituents (Figure 2, Table 1).

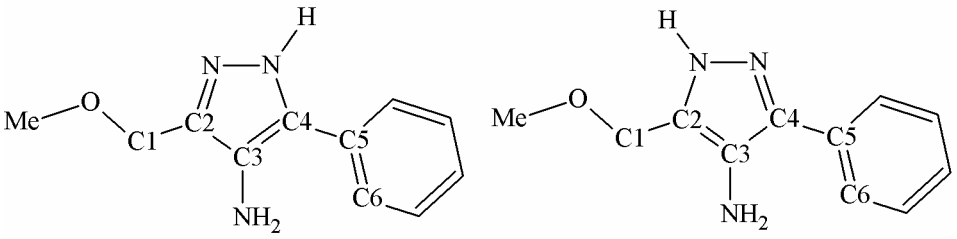

Figure 2. Structural formulae of both tautomer forms of 4-Amino-3-methoxymethyl-5-(naphthalen-2-yl)-1*H*-pyrazole

Table 1. The values of some dihedral angles of **4a** and **4b** structures

Compound	4a		4b	
Tautomer	1	2	1	2
OC1C2C3, degrees	-44.3	-47.4	-45.0	-47.7
C3C4C5C6, degrees	-26.8	-24.7	-26.6	-23.9

Therefore existence of **4a** and **4b** compounds in two forms simultaneously is expected. This fact is confirmed by bifurcation of proton signal of pyrazole cycle in NMR ^{1}H spectrums of these structures (Figure 3).

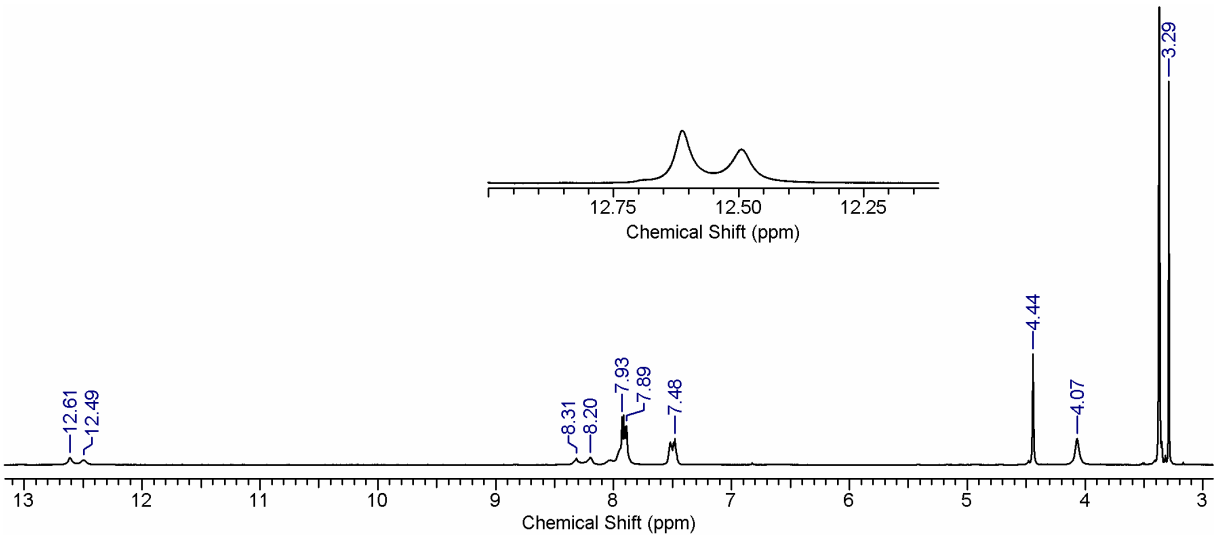

Figure 3. ^{1}H NMR spectrum (DMSO-d_6) of 4-amino-3-methoxymethyl-5-(2-naphthyl)-1*H*-pyrazole (**4a**)

From this point of view, acylation of **4a** and **4b** compounds at both nitrogen atoms of pyrazole seems equiprobable. However, it was mentioned above, reaction product in every specific case represents not a mix, and only one of two possible isomers. It is confirmed by NMR ^{1}H data (Figure 4), where spectrum of **5b** diacetyl derivative contains of singlets of one methylene group and three methyl groups, that indicates the absence of isomerism related to position of acetyl group.

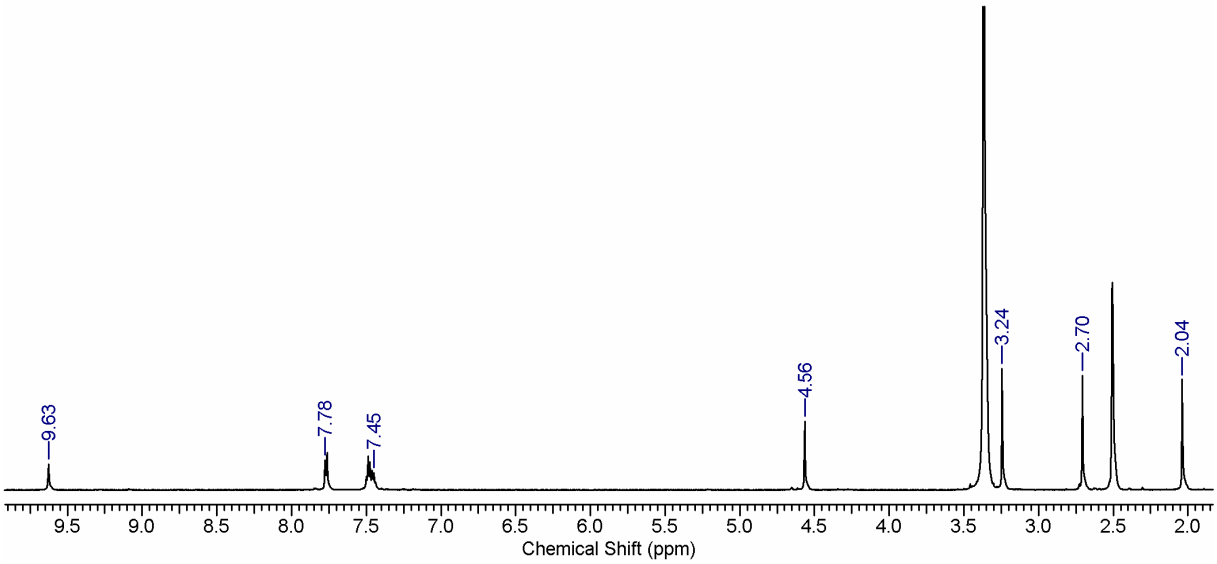

Figure 4. ^{1}H NMR spectrum (DMSO-d_6) of N-[1-Acetyl-3-(methoxymethyl)-5-phenyl-1*H*-pyrazol-4-yl]acetamide (**5b**)

For identification of these isomers the geometry optimization of **5a**, **5b**, **6a** and **6b** structures was performed for the cases when acetyl or, correspondingly, chloroacetyl groups were placed by the nitrogen atom, situated near to aromatic substituent (5a-1, 5b-1, 6a-1 and 6b-1), and the nitrogen atom, situated distantly (5a-2, 5b-2, 6a-2 and 6b-2). It was established that at least four possible conformers correspond to every compound (Figure 5). They differ by mutual orientation of substituents in pyrazole cycle (Figure 6, Table 2).

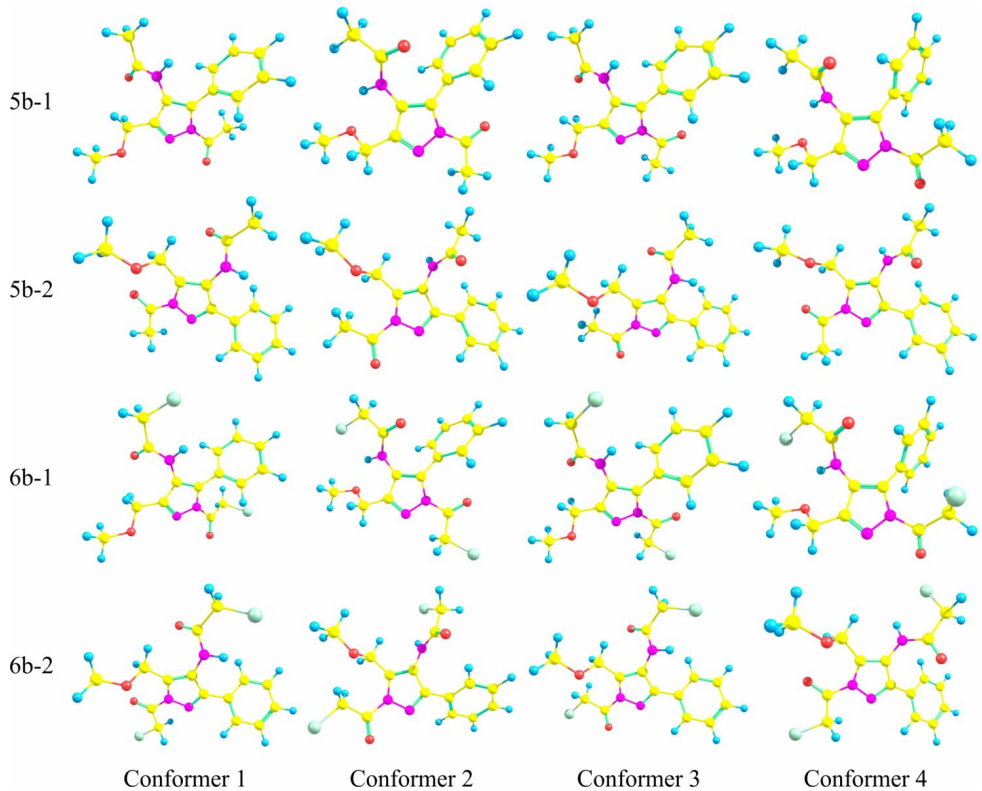

Figure 5. Molecular structure of isomers and conformers of **5b** and **6b** compounds

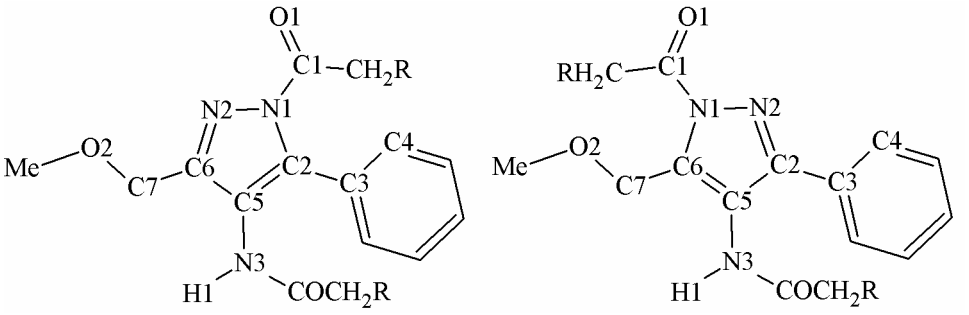

Figure 6. Structural formulae of isomers of **5b** (R = H) and **6b** (R = Cl) compounds

Table 2. The values of dihedral angles of **6a** and **6b** structures and their total energies (ΔE) relative to the lowest energy state

Compound	5a-1				5a-2			
Conformer	1	2	3	4	1	2	3	4
O1C1N1N2, degrees	-21.6	-178.9	179.0	24.0	-172.1	5.4	9.3	-172.2
C4C3C2C5, degrees	118.1	130.7	127.2	-117.6	148.3	158.3	149.9	155.0
C2C5N3H1, degrees	-29.4	152.7	-26.4	140.0	-33.0	114.0	-33.0	136.0
C5C6C7O2, degrees	-156.6	43.1	-157.1	45.9	-109.9	-111.9	-113.0	-109.8
ΔE, eV	0.017	0.002	0.006	0.007	0.000	0.014	0.009	0.003
Compound	5b-1				5b-2			
Conformer	1	2	3	4	1	2	3	4
O1C1N1N2, degrees	-20.3	178.9	177.3	23.7	-172.2	5.3	8.7	-172.2
C4C3C2C5, degrees	115.0	125.4	124.6	-115.7	148.4	159.8	150.4	155.7
C2C5N3H1, degrees	-27.3	152.3	-25.0	140.8	-32.2	110.3	-31.8	134.1
C5C6C7O2, degrees	-154.8	43.2	-157.1	45.5	-110.2	-112.1	-112.9	-109.7
ΔE, eV	0.017	0.002	0.006	0.008	0.000	0.014	0.009	0.004
Compound	6a-1				6a-2			
Conformer	1	2	3	4	1	2	3	4
O1C1N1N2, degrees	-29.2	-179.9	178.5	-33.0	-172.3	5.1	11.3	-172.1
C4C3C2C5, degrees	128.6	132.9	129.6	129.0	150.7	157.1	152.7	154.1
C2C5N3H1, degrees	-27.2	153.2	-24.2	170.4	-30.9	96.7	-32.6	131.8
C5C6C7O2, degrees	-156.9	42.8	-158.3	-20.7	-110.0	-113.4	-116.6	-110.3
ΔE, eV	0.015	0.002	0.006	0.010	0.000	0.015	0.010	0.004
Compound	6b-1				6b-2			
Conformer	1	2	3	4	1	2	3	4
O1C1N1N2, degrees	-27.6	179.1	178.0	29.2	-172.2	1.3	10.8	-172.2
C4C3C2C5, degrees	126.3	127.8	127.2	-114.9	151.9	-141.8	157.9	155.4
C2C5N3H1, degrees	-25.6	152.8	-22.6	140.7	-30.5	103.5	-34.6	130.7
C5C6C7O2, degrees	-159.5	43.1	-159.4	47.5	-110.0	-110.7	-116.7	-110.5
ΔE, eV	0.017	0.002	0.006	0.006	0.000	0.016	0.010	0.004

The similar conclusion, in toto, can be done at comparative analysis of absorption vibration spectra, received by experimentally and as a result of DFT simulations (Figure 7). Here the Lorentzian broadening of spectral lines was used for visualization of calculated spectra, where the spectral width on 1/2 height was equal to 15 cm^{-1}. The shift of calculated spectral lines along frequencies axis was performed relative to intensive maximum in the region of 1800 cm^{-1} of experimental spectrum by multiplication onto correction factor, which was equal to 0.979, 0.980, 0.975, 0.977, 0.975, 0.978, 0.973 and 0.976 in the set of 5a-1, 5a-2, 5b-1, 5b-2, 6a-1, 6a-2, 6b-1 и 6b-2 structures, correspondingly. It was shown, that in all cases the results received with help of DFT calculations repeats well the experimental values. However, the best agreement is observed in the case of 5a-2, 5b-2, 6a-2 and 6b-2 compounds. This fact is also additional confirmation that acylation of **4a** and **4b** structures at the nitrogen atom, situated further from aromatic substituent, is more probable than at the second one of pyrazole cycle.

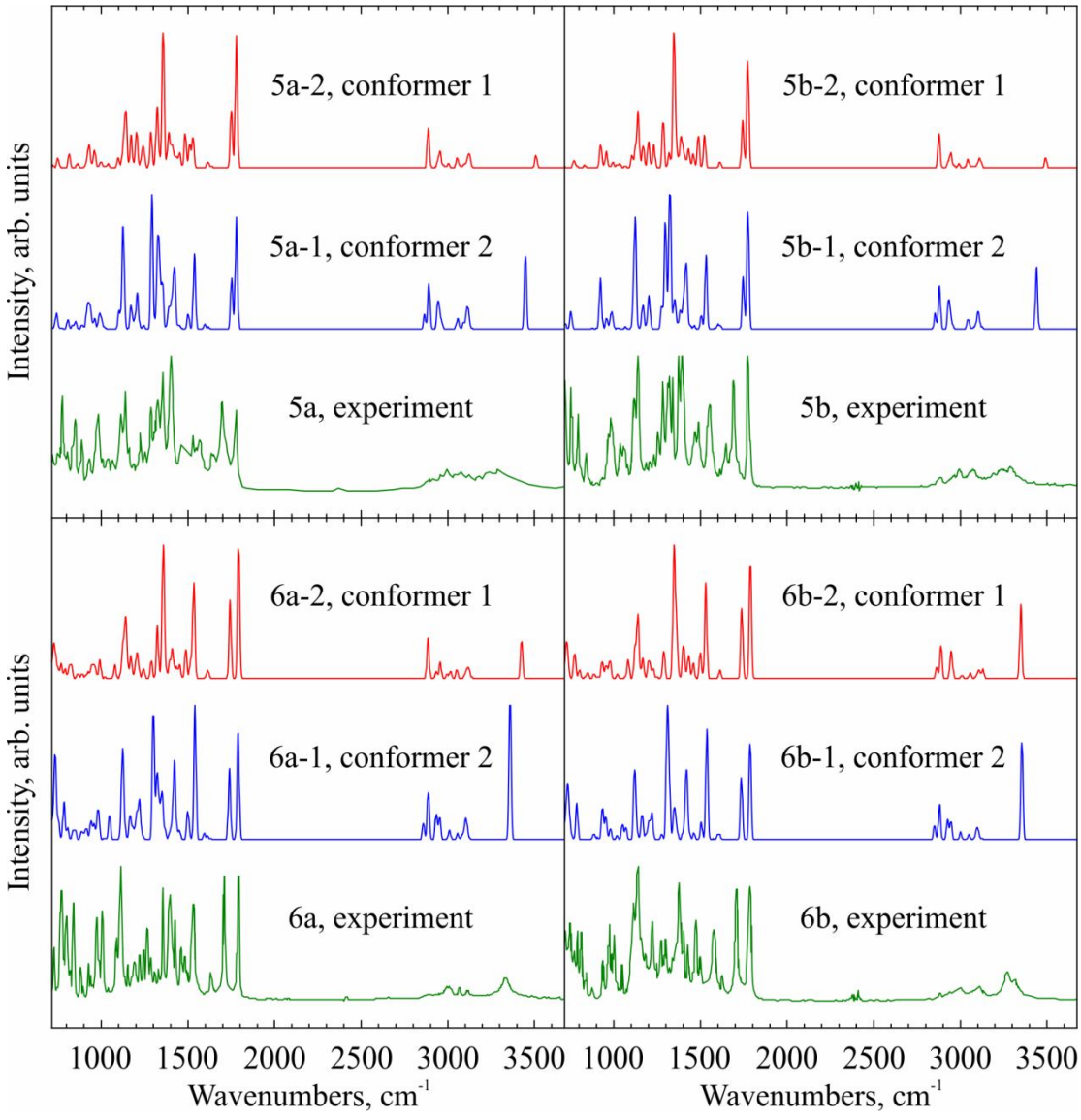

Figure 7. Experimental and DFT calculated IR-spectrums of **5a**, **5b**, **6a** and **6b** compounds

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