Synthesis of polyfluoroalkyl-containing 1-(4-acetoxybutyl)- and 1-(4-hydroxybutyl)pyrazoles and their tuberculostatic activity*

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Alkylation of polyfluoroalkyl-containing pyrazoles with 4-bromobutyl acetate in acetone in the presence of potassium carbonate leads to a mixture of isomeric 1-(4-acetoxybutyl)-3-fluoroalkyl- and 1-(4-acetoxybutyl)-5-fluoroalkylpyrazoles, which in a number of cases were successfully separated by HPLC. Deacylation in acidic medium with gaseous hydrogen chloride and in basic medium with gaseous ammonia leads to 1-(4-hydroxybutyl)pyrazoles, which manifest moderate tuberculostatic activity.

Key words: pyrazoles, alkylation, deacylation, tuberculostatic activity.

Pyrazoles are known for their various biological activity. They give rise to febrifugal and antiinflammatory drugs, such as analgin, antipyrin, butadion,[1] and celebrex,[2] which are widely used in practical medicine.

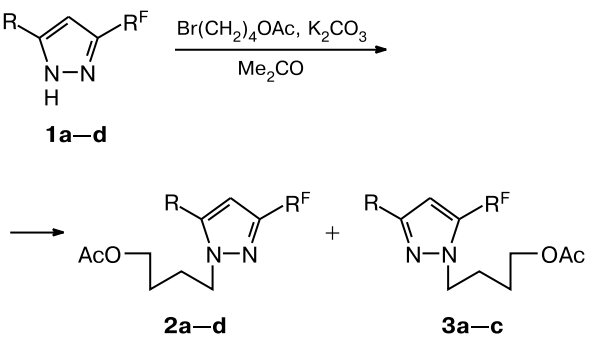
Recently, it has been found[3] that 4-nitroso-substituted fluoroalkylpyrazoles possess high tuberculostatic activity. In continuation of works on the search for tuberculostatics among fluoroalkyl-containing pyrazoles, in the present work we synthesized their N-alkylated derivatives.

4-Bromobutyl acetate has been chosen as the alkylating agent. The butyl acetate moiety incorporated into the heterocycle can be deacylated to 4-hydroxybutyl substituent. The presence of the hydroxyalkyl fragment in the heterocycle increases the lipophilicity of the molecule, and it can acquire new, including biological, properties, for example, antiviral activity.[4]

Heating in acetone in the presence of potassium carbonate has proved the most appropriate conditions for the alkylation of pyrazoles **1a—d** (Scheme 1). As a result, monofluoroalkyl-substituted pyrazoles **1a—c** were converted to the mixtures of isomeric pyrazoles **2a—c** and **3a—c**. Isomers **2c** and **3c** were successfully separated by HPLC. Alkylation of symmetric bis(tetrafluoroethyl) substituted pyrazole **1d** led to the only product **2d**. To assign isomers **2** and **3**, we used the NMR spectroscopic data.

Isomeric pyrazoles **2a** and **3a** differ in the position of the trifluoromethyl group with respect to the 4-acetoxybutyl substituent. Earlier,[5] it has been found that the CF_3 group at position 3 in 4-(het)arylazo-1-methyl-3,5-bis(trifluoromethyl)pyrazoles has more high-field chemical shift in the ^{19}F NMR spectrum (in the region δ 99.1—100.2) as compared to the CF_3 group at position 5, whose chemical shift is observed in the region δ 102.1—104.1. For the same reason, the signal for the fluorine nuclei observed in the ^{19}F NMR spectrum of the reaction products of pyrazole **1a** at δ 99.96 was assigned to 3-CF_3-pyrazole **2a**, whereas the signal at δ 102.46, to 5-CF_3-pyrazole **3a**. It is obvious that 3-CF_3-pyrazole **2a** was formed by the alkylation of pyrazole **1a** at the nitrogen atom neighboring to the phenyl substituent, whereas 5-CF_3-pyrazole **3a**, by the alkylation at the other nitrogen atom, adjacent to the CF_3 group.

Scheme 1



1—3: R = Ph, $R^F = CF_3$ (**a**); R = Me, $R^F = (CF_2)_2H$ (**b**); R = Ph, $R^F = (CF_2)_2H$ (**c**); $R = R^F = (CF_2)_2H$ (d)

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In the work,[6] the fluorine nuclei of the α-CF_2 group in the 3-polyfluoroalkyl substituent of pyrazoles were found to resonate in more high field with respect to the δ value of 53.9 (C_6F_6 internal standard). Therefore, the signals at δ 48 observed in the ^{19}F NMR spectra for the α-CF_2 group should correspond to 3-tetrafluoroethylpyrazoles **2b**,**c**, whereas more low-field signals at δ ~54, to 5-tetrafluoroethylpyrazoles **3b**,**c**. The fluorine nuclei signals in compounds **2a** and **3a** also confirm this assignment. Thus, the signal for the 3-CF_3 group is observed more up-field (δ 99.96) as compared to the signal for the 5-CF_3 substituent (δ 102.46).

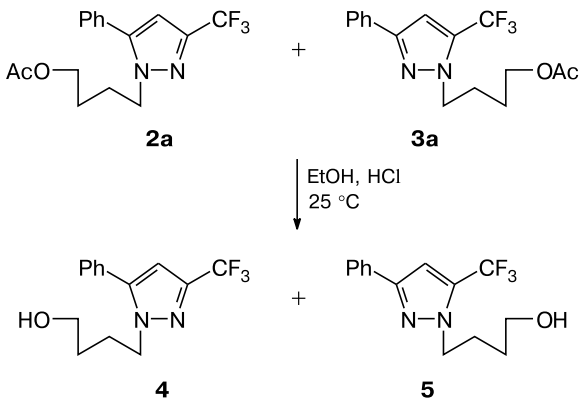
In the mixtures, isomers **2a**,**b** were found to be predominant over isomers **3a**,**b** (the ratio for regioisomers **2a** and **3a** is 62 : 38, for **2b** and **3b**, 9 : 1), whereas isomers **2c** and **3c** are present in the equal amounts. Comparison of the selectivity of alkylation of tetrafluoroethyl-substituted pyrazoles containing methyl (**1b**) and phenyl (**1c**) substituents led us to a conclusion that the presence of the methyl group increases regioselectivity of the alkylation, giving predominantly one of the isomers, which is formed at the nitrogen atom adjacent to the methyl substituent. When bulky phenyl substituent is present (pyrazoles **1a**,**c**), the alkylation can take both directions with almost equal probability, though an additive negative inductive effect of the CF_3 group leads to some predominance of isomer **2a** over isomer **3a**.

The position of 4-acetoxybutyl substituent affects chemical shifts of the adjacent phenyl and tetrafluoroethyl substituents in isomers **2** and **3**. Thus, the vicinal protons of the 4-acetoxybutyl fragment in compounds **2a**,**c** shield the *ortho*-protons of the phenyl substituent (δ 7.37—7.38) and deshield the proton in the $(CF_2)_2H$ fragment (δ 6.16). The situation is reverse for compounds **3a,c**: the *ortho*-protons are deshielded (δ 7.78), whereas the proton of the $(CF_2)_2H$ group, which is vicinal with respect to the 4-acetoxybutyl substituent, is shielded (δ 6.03).

The structures of compounds **2** and **3** were confirmed by GLC-MS. As it was expected, isomers **2a**,**c** and **3a**,**c** containing phenyl substituents have longer retention time (23.8—25.3 min) as compared to pyrazoles **2b**,**d** and **3b** containing alkyl and fluoroalkyl substituents (retention time of 18.8—20.7 min). The following pattern is observed in the mass spectra: the molecules of 3-R^F-isomers are cleaved with the formation of more stable fragment ions, since the intensities of the $[M - C_4H_7OC{=}OCH_3]^+$, $[M - C_4H_6OC{=}OCH_3]^+$, $[M - OC{=}OCH_3]^+$, and $[M - C{=}OCH_3]^+$ peaks in the spectra are higher than those for 5-R^F-isomers.

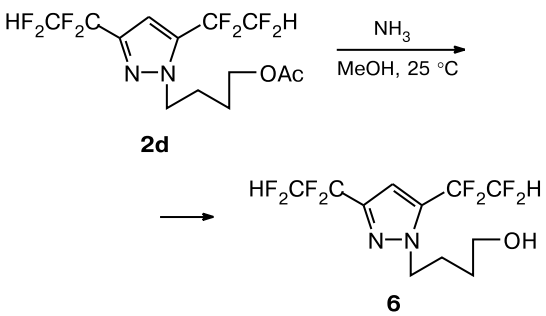
For the mixture of pyrazoles **2a** and **3a** taken as an example, it was shown that the 4-acetoxybutyl moiety can be deacylated under acidic conditions by bubbling gaseous hydrogen chloride through their solution in anhydrous ethanol to obtain a mixture of compounds **4** and **5** in quantitative yield (Scheme 2). Isomers **4** and **5** were separated by HPLC.

Scheme 2



Bubbling ammonia through the methanol solution of symmetric bis(1,1,2,2-tetrafluoroethyl)-substituted pyrazole **2d** has proved more efficient for the removal of the acetyl group from this compound (Scheme 3). The reaction takes place at room temperature in 99.8% yield (GLC data).

Scheme 3



The IR spectra of compounds **4**—**6** exhibit an absorption band of the OH group at 3375—3380 cm^{-1}, while no absorption band of the acetate carbonyl group is observed. In the ^1H NMR spectra, the signal for the hydroxyl proton is observed in the high field at δ 1.94—2.45.

We studied the tuberculostatic activity of obtained (4-hydroxybutyl)pyrazoles **4**—**6** in the *in vitro* experiments toward a laboratory strain of tuberculosis mycobacteria (TMB) $H_{37}Rv$. Isoniazide was used as a comparison agent, whose minimum concentration necessary for the retardation of the TMB growth is 0.15 μg mL^{-1}.

Our studies showed that introduction of 4-hydroxybutyl substituent does not significantly affect antituberculosis properties. Thus, the starting 5-phenyl-3-trifluoromethylpyrazole (**1a**) possess moderate tuberculostatic activity (the minimum inhibition concentration (MIC) is 6.25 μg mL^{-1}). Introduction of 4-hydroxybutyl substituent at the position adjacent to the phenyl group does not affect tuberculostatic activity, since 1-(4-hydroxybutyl)-3-trifluoromethylpyrazole **4** manifests comparable activi-

ty. The presence of 4-hydroxybutyl substituent at the position adjacent to the CF_3 group in regioisomer **5** decreases tuberculostatic activity (the MIC is 12.5 μg mL^{-1}). Replacement of the phenyl substituent in pyrazole **4** with the fluoroalkyl fragment does not affect antituberculous properties either. Thus, the MIC for the N-alkylated 3,5-bis-(tetrafluoroethyl)-substituted pyrazole **6** is 6.25 μg mL^{-1}.

Further, we are planning to synthesize N-alkylated and N-glycosilated pyrazoles modified at position 4 with (het)arylhydrazone substituents, in particular, with antipyrinehydrazone fragment, which imposes antiinflammatory activity on compounds.

Experimental

^{1}H and ^{19}F NMR spectra were recorded on a Bruker DRX-400 spectrometer (400 (^{1}H) and 75 MHz (^{19}F)) in $CDCl_3$ relative to $SiMe_4$ and C_6F_6, respectively. IR spectra in the region of 4000—400 cm^{-1} were recorded on a Perkin—Elmer Spectrum One Fourier-transformed IR spectrometer equipped with a frustrated total internal reflection (FTIR) accessory. Melting points were measured in unsealed capillaries on a Stuart SMP30 apparatus. Column chromatography was performed on silica gel 60 (0.063—0.02 mm). Mass spectra were recorded on a Agilent GC 7890A MSD 5975C inert XL EI/CI GLC-MS spectrometer with an HP5-MS quartz capillary column (dimethylpolysiloxane with 5% of Ph groups, 30 m × 0.25 mm, 0.25 μm thick film) and a quadrupole mass spectrometric detector in the mode of electron ionization (70 eV); helium carrier gas, chloroform solvent. An Agilent 1200 Series preparative liquid chromatograph was used for HPLC, which was equipped with a diode-matrix detector, preparative autosampler (900 μL), ZORBAX Eclipse XDB-C18 PrepHT column (21.2×150 mm, 5 μm particle size). The acetonitrile—water mixtures in the ratios of 50 : 50 and 60 : 40 were used as eluents for the separation of (4-acetoxybutyl)pyrazoles **2c** and **3c** and (4-hydroxybutyl)pyrazoles **4** and **5**, respectively, at the rate of 20 mL min^{-1}, 254 nm wavelength. Elemental analysis was performed on a Perkin—Elmer PE 2400 series II analyzer.

Tuberculostatic activity of compounds **1a**, **4**—**6** was determined by the vertical diffusion using a Novaya solid culture medium. The $H_{37}Rv$ laboratory strain was prepared for the seeding. The culture strain was weighed on a torsional scale, a weighed amount (10 mg) was placed into a porcelain mortar, thoroughly mulled, and the culture suspension was prepared using a bacterial turbidity standard of 100 million of microbial bodies in 1 mL. A resulting suspension (0.2 mL) was seeded into the test-tubes with the culture medium and the compound under study of the corresponding dilution (5 mL). The agents of the following concentrations were prepared by a successive dilution: 100, 50, 12.5, 6.25, 3.5, 1.5, 0.7, 0.3, and 0.15 μg mL^{-1}. A test-tube was incubated for 7—10 days in a thermostat at 37 °C.[7] Activity of the compounds toward TMB was studied independently in three test-tubes for each concentration.

Synthesis of 1-(4-acetoxybutyl)-substituted pyrazoles 2a—d and 3a—c (general procedure). A mixture of pyrazole **1a—d** (2.5 mmol), acetone (10 mL), 4-bromobutyl acetate (0.49 g, 2.5 mmol), and potassium carbonate (0.3 g, 3.0 mmol) was refluxed for 16—20 h. A precipitate was filtered off, the mother liquor was concentrated. The products were purified by column chromatography (the eluent was chloroform—ethyl acetate, 7 : 1 (**2b**,**d**, **3b**) or hexane—ethyl acetate, 1 : 1 (**2a**, **3a**)). Isomers **2a**,**b** and **3a,b** were not separated. Compounds **2a** and **3a** were obtained as a mixture in the ratio of 62 : 38 and in 52% yield, colorless oil; compounds **2b** and **3b** were obtained as a mixture in the ratio of 9 : 1 and in 54% yield, colorless oil. Isomers **2c** and **3c** were separated by HPLC.

1-(4-Acetoxybutyl)-5-phenyl-3-trifluoromethylpyrazole (2a). ^{1}H NMR, δ: 1.54 (m, 2 H, CH_2, ^3J = 6.5 Hz); 1.89 (m, 2 H, CH_2); 1.98 (s, 3 H, $MeCO_2$); 3.97 (t, 2 H, OCH_2, ^3J = 6.4 Hz); 4.17 (t, 2 H, NCH_2, ^3J = 7.3 Hz); 6.52 (s, 1 H, H(4)); 7.37 (dd, 2 H, *o*-H_{Ph}, ^3J = 6.9 Hz, ^4J = 2.4 Hz); 7.47—7.48 (m, 3 H, *m*-H_{Ph}, *p*-H_{Ph}). ^{19}F NMR, δ: 99.96 (s, CF_3). MS, *m*/*z* (*I*$_{rel}$ (%)): 43 $[C{=}OCH_3]^+$ (42.7), 55 $[C_4H_7]^+$ (22.8), 71 $[C_4H_7O]^+$ (37.4), 77 $[C_6H_5]^+$ (16.6), 164 $[M - C_6H_5 - C_4H_5O_2]^+$ (10.1), 193 $[M - C_4H_7OC{=}OCH_3 - F]^+$ (11.3), 205 $[M - C_6H_6 - C{=}OCH_3]^+$ (25.6), 212 $[M - C_4H_7OC{=}OCH_3]^+$ (88.8), 213 $[M - C_4H_6OC{=}OCH_3]^+$ (35.5), 225 $[M - C_3H_6OC{=}OCH_3]^+$ (99.9), 239 $[M - C_2H_4OC{=}OCH_3]^+$ (26.1), 265 $[M - C_2H_5O_2]^+$ (20.8), 266 $[M - CH_3COOH]^+$ (16.3), 267 $[M - OC{=}OCH_3]^+$ (87.9), 283 $[M - C{=}OCH_3]^+$ (49.9), 326 $[M]^+$ (15.0). Found (%): C, 59.02; H, 5.21; F, 17.66; N, 8.61. $C_{16}H_{17}F_3N_2O_2$. Calculated (%): C, 58.89; H, 5.25; F, 17.47; N, 8.58 (the elemental analysis data are given for the mixture of pyrazoles **2a** and **3a**).

1-(4-Acetoxybutyl)-5-methyl-3-(1,1,2,2-tetrafluoroethyl)-pyrazole (2b). ^{1}H NMR, δ: 1.64 (m, 2 H, CH_2, ^3J = 6.4 Hz); 1.90 (m, 2 H, CH_2, ^3J = 7.4 Hz); 2.04 (s, 3 H, $MeCO_2$); 2.28 (s, 3 H, Me); 4.06—4.11 (m, 4 H, OCH_2, NCH_2); 6.09 (tt, 1 H, $H(CF_2)_2$, $^2J_{H,F}$ = 53.6 Hz, $^3J_{H,F}$ = 4.3 Hz); 6.28 (s, 1 H, H(4)). ^{19}F NMR, δ: 25.34 (dt, 2 F, HCF_2, $^2J_{F,H}$ = 53.6 Hz, $^3J_{F,F}$ = 7.4 Hz); 48.52 (td, 2 F, CF_2, $^3J_{F,F}$ = 7.4 Hz, $^3J_{F,H}$ = 4.3 Hz). MS, *m*/*z* (*I*$_{rel}$ (%)): 43 $[C{=}OCH_3]^+$ (22.2), 55 $[C_4H_7]^+$ (13.0), 71 $[C_4H_7O]^+$ (17.4), 131 $[M - C_4H_7OC{=}OCH_3 - HCF_2]^+$ (24.0), 182 $[M - C_4H_7OC{=}OCH_3]^+$ (16.2), 183 $[M - C_4H_6OC{=}OCH_3]^+$ (23.1), 195 $[M - H(CF_2)_2]^+$ (99.9), 209 $[M - C_2H_4OC{=}OCH_3]^+$ (12.8), 235 $[M - C_2H_5O_2]^+$ (14.4), 236 $[M - CH_3COOH]^+$ (9.9), 237 $[M - OC{=}OCH_3]^+$ (52.4), 253 $[M - C{=}OCH_3]^+$ (40.8), 296 $[M]^+$ (14.6). Found (%): C, 48.8; H, 5.42; F, 25.51; N, 9.31. $C_{12}H_{16}F_4N_2O_2$. Calculated (%): C, 48.65; H, 5.44; F, 25.65; N, 9.46 (the elemental analysis data are given for the mixture of pyrazoles **2b** and **3b**).

1-(4-Acetoxybutyl)-5-phenyl-3-(1,1,2,2-tetrafluoroethyl)-pyrazole (2c). The yield was 36%, yellow oil. ^{1}H NMR, δ: 1.53 (m, 2 H, CH_2, ^3J = 6.5 Hz); 1.88 (m, 2 H, CH_2, ^3J = 7.4 Hz); 1.99 (s, 3 H, $MeCO_2$); 3.97 (t, 2 H, OCH_2, ^3J = 6.4 Hz); 4.18 (t, 2 H, NCH_2, ^3J = 7.4 Hz); 6.16 (tt, 1 H, $H(CF_2)_2$, $^2J_{H,F}$ = = 53.5 Hz, $^3J_{H,F}$ = 4.3 Hz); 6.54 (s, 1 H, H(4)); 7.38 (dd, 2 H, *o*-H_{Ph}, ^3J = 7.2 Hz, ^4J = 2.2 Hz); 7.46—7.50 (m, 3 H, *m*-H_{Ph}, *p*-H_{Ph}). ^{19}F NMR, δ: 25.43 (dt, 2 F, HCF_2, $^2J_{F,H}$ = 53.5 Hz, $^3J_{F,F}$ = 7.4 Hz); 48.68 (td, 2 F, CF_2, ^3J = 7.4 Hz, ^3J = 4.3 Hz). MS, *m*/*z* (*I*$_{rel}$ (%)): 43 $[C{=}OCH_3]^+$ (30.1), 55 $[C_4H_7]^+$ (18.1), 71 $[C_4H_7O]^+$ (27.3), 77 $[C_6H_5]^+$ (9.5), 193 $[M - C_4H_7OC{=}OCH_3 - HCF_2]^+$ (25.5), 244 $[M - C_4H_7OC{=}OCH_3]^+$ (58.2), 245 $[M - C_4H_6OC{=}OCH_3]^+$ (36.7), 257 $[M - H(CF_2)_2]^+$ (99.9), 271 $[M - C_2H_4OC{=}OCH_3]^+$ (23.4), 297 $[M - C_2H_5O_2]^+$ (13.2), 299 $[M - OC{=}OCH_3]^+$ (97.6), 315 $[M - C{=}OCH_3]^+$ (45.8), 358 $[M]^+$ (13.0). Found (%): C, 57.19; H, 5.02; F, 21.50; N, 8.01. $C_{17}H_{18}F_4N_2O_2$. Calculated (%): C, 56.98; H, 5.06; F, 21.21; N, 7.82.

1-(4-Acetoxybutyl)-3,5-bis(1,1,2,2-tetrafluoroethyl)pyrazole (2d). The yield was 54%, colorless oil. IR, ν/cm^{-1}: 1738 ($MeCO_2$); 1470, 1550 (C=C, C=N); 1110—1239 (C—F). ^{1}H NMR, δ: 1.68 (m, 2 H, CH_2, ^3J = 6.4 Hz); 2.02 (m, 2 H, CH_2); 2.05 (s, 3 H, $MeCO_2$); 4.09 (t, 2 H, OCH_2, ^3J = 6.4 Hz); 4.33 (t, 2 H, NCH_2, ^3J = 7.4 Hz); 6.05 (tt, 1 H, $H(CF_2)_2$, $^2J_{H,F}$ = 53.5 Hz, $^3J_{H,F}$ = = 2.4 Hz); 6.12 (tt, 1 H, $H(CF_2)_2$, $^2J_{H,F}$ = 53.4 Hz, $^3J_{H,F}$ = 4.1 Hz); 6.84 (s, 1 H, H(4)). ^{19}F NMR, δ: 25.67 (dt, 2 F, HCF_2, $^2J_{F,H}$ = = 53.4 Hz, $^3J_{F,F}$ = 6.7 Hz); 28.63 (dt, 2 F, HCF_2, $^2J_{F,H}$ = 53.5 Hz, $^3J_{F,F}$ = 4.7 Hz); 48.72 (td, 2 F, CF_2, ^3J = 6.7 Hz, ^3J = 4.1 Hz); 54.02 (m, 2 F, CF_2). MS, *m/z* (I_{rel} (%)): 43 $[C{=}OCH_3]^+$ (61.2), 54 $[C_4H_6]^+$ (22.2), 55 $[C_4H_7]^+$ (20.8), 71 $[C_4H_7O]^+$ (21.2), 209 $[M - H(CF_2)_2 - C_3H_4O_2]^+$ (9.5), 217 $[M - HCF_2 - C_4H_7OC{=}OCH_3]^+$ (15.6), 221 $[M - H(CF_2)_2 - CH_3COOH]^+$ (52.8), 243 $[M - HCF_2 - C_2H_5OC{=}OCH_3]^+$ (19.2), 269 $[M - C_4H_6OC{=}OCH_3]^+$ (10.9), 281 $[M - H(CF_2)_2]^+$ (99.9), 294 $[M - C_2H_5OC{=}OCH_3]^+$ (22.8), 321 $[M - C_2H_5O_2]^+$ (38.2), 322 $[M - CH_3COOH]^+$ (24.6), 382 $[M]^+$ (0.3). Found (%): C, 40.91; H, 3.59; F, 40.10; N, 7.48. $C_{13}H_{14}F_8N_2O_2$. Calculated (%): C, 40.85; H, 3.69; F, 39.76; N, 7.33.

1-(4-Acetoxybutyl)-3-phenyl-5-trifluoromethylpyrazole (3a). ^{1}H NMR, δ: 1.71 (m, 2 H, CH_2, ^3J = 6.5 Hz); 2.01—2.07 (m, 5 H, CH_2, $MeCO_2$); 4.10 (t, 2 H, OCH_2, ^3J = 6.4 Hz); 4.28 (t, 2 H, NCH_2, ^3J = 7.3 Hz); 6.88 (s, 1 H, H(4)); 7.33 (t, 1 H, *p*-H_{Ph}, ^3J = 7.3 Hz); 7.40 (t, 2 H, *m*-H_{Ph}, ^3J = 7.3 Hz); 7.78 (dd, 2 H, *o*-H_{Ph}, ^3J = 7.3 Hz, ^4J = 2.0 Hz). ^{19}F NMR, δ: 102.46 (s, CF_3). MS, *m/z* (I_{rel} (%)): 43 $[C{=}OCH_3]^+$ (27.2), 55 $[C_4H_7]^+$ (19.1), 71 $[C_4H_7O]^+$ (23.1), 77 $[C_6H_5]^+$ (16.3), 205 $[M - C_6H_6 - C{=}OCH_3]^+$ (9.6), 212 $[M - C_4H_7OC{=}OCH_3]^+$ (38.4), 225 $[M - C_3H_6OC{=}OCH_3]^+$ (99.9), 257 $[M - CF_3]^+$ (27.2), 265 $[M - C_2H_5O_2]^+$ (17.0), 267 $[M - OC{=}OCH_3]^+$ (42.8), 283 $[M - C{=}OCH_3]^+$ (11.4), 326 $[M]^+$ (15.2).

1-(4-Acetoxybutyl)-3-methyl-5-(1,1,2,2-tetrafluoroethyl)-pyrazole (3b). ^{1}H NMR, δ: 1.71, 1.97 (both m, 2 H each, 2 CH_2); 2.05 (s, 3 H, $MeCO_2$); 2.31 (s, 3 H, Me); 4.08 (t, 2 H, OCH_2, ^3J = 6.4 Hz); 4.19 (t, 2 H, NCH_2, ^3J = 7.4 Hz); 5.98 (tt, 1 H, $H(CF_2)_2$, $^2J_{H,F}$ = 53.7 Hz, $^3J_{H,F}$ = 2.8 Hz); 6.31 (s, 1 H, H(4)). ^{19}F NMR, δ: 28.25 (dt, 2 F, HCF_2, $^2J_{F,H}$ = 53.7 Hz, $^3J_{F,F}$ = 5.6 Hz); 54.01 (td, 2 F, CF_2, $^3J_{F,F}$ = 5.6 Hz, $^3J_{F,H}$ = 2.8 Hz). MS, *m/z* (I_{rel} (%)): 43 $[C{=}OCH_3]^+$ (14.5), 55 $[C_4H_7]^+$ (8.7), 71 $[C_4H_7O]^+$ (10.8), 131 $[M - C_4H_7OC{=}OCH_3 - HCF_2]^+$ (16.0), 182 $[M - C_4H_7OC{=}OCH_3]^+$ (7.2), 183 $[M - C_4H_6OC{=}OCH_3]^+$ (14.0), 195 $[M - H(CF_2)_2]^+$ (99.9), 237 $[M - OC{=}OCH_3]^+$ (18.8), 296 $[M]^+$ (3.0).

1-(4-Acetoxybutyl)-3-phenyl-5-(1,1,2,2-tetrafluoroethyl-pyrazole (3c). The yield was 36%, yellow oil. ^{1}H NMR, δ: 1.71 (m, 2 H, CH_2, ^3J = 6.5 Hz); 2.00—2.08 (m, 5 H, CH_2, $MeCO_2$); 4.10 (t, 2 H, OCH_2, ^3J = 6.5 Hz); 4.30 (t, 2 H, NCH_2, ^3J = 7.3 Hz); 6.03 (tt, 1 H, $H(CF_2)_2$, $^2J_{H,F}$ = 53.7 Hz, $^3J_{H,F}$ = 2.6 Hz); 6.82 (s, 1 H, H(4)); 7.33 (t, 1 H, *p*-H_{Ph}, ^3J = 7.4 Hz); 7.41 (t, 2 H, *m*-H_{Ph}, ^3J = 7.4 Hz); 7.78 (dd, 2 H, *o*-H_{Ph}, ^3J = 7.4 Hz, ^4J = 1.5 Hz). ^{19}F NMR, δ: 28.44 (dt, 2 F, HCF_2, $^2J_{F,H}$ = 53.7 Hz, $^3J_{F,F}$ = = 5.5 Hz); 54.0 (td, 2 F, CF_2, $^3J_{F,F}$ = 5.5 Hz, $^3J_{F,H}$ = 2.6 Hz). MS, *m/z* (I_{rel} (%)): 43 $[C{=}OCH_3]^+$ (17.2), 55 $[C_4H_7]^+$ (13.6), 71 $[C_4H_7O]^+$ (15.9), 77 $[C_6H_5]^+$ (8.3), 193 $[M - C_4H_7OC{=}OCH_3 - HCF_2]^+$ (21.1), 244 $[M - C_4H_7OC{=}OCH_3]^+$ (17.2), 245 $[M - C_4H_6OC{=}OCH_3]^+$ (17.4), 257 $[M - H(CF_2)_2]^+$ (99.9), 297 $[M - C_2H_5O_2]^+$ (10.8), 299 $[M - OC{=}OCH_3]^+$ (46), 315 $[M - C{=}OCH_3]^+$ (9.9), 358 $[M]^+$ (10.1). Found (%): C, 56.76; H, 4.98; F, 21.57; N, 7.63. $C_{17}H_{18}F_4N_2O_2$. Calculated (%): C, 56.98; H, 5.06; F, 21.21; N, 7.82.

Deacylation of the mixture of compounds 2a and 3a. A mixture of (4-acetoxybutyl)-substituted pyrazoles **2a** and **3a** (0.16 g, 0.5 mmol) was dissolved in ethanol (5 mL), then gaseous hydrogen chloride was bubbled through the solution for 1 h. The reaction mixture was stirred for 30 min at room temperature and neutralized with $NaHCO_3$. The product was extracted with chloroform and dried with Na_2SO_4. The solvent was evaporated. Isomers **4** and **5** were separated by HPLC.

1-(4-Hydroxybutyl)-5-phenyl-3-trifluoromethylpyrazole (4). The yield was 82%, yellow oil. IR, ν/cm^{-1}: 3375 (OH); 1475, 1505 (C=C, C=N); 1130—1210 (C—F). ^{1}H NMR, δ: 1.48 (m, 2 H, CH_2, ^3J = 6.3 Hz); 1.91 (m, 2 H, CH_2, ^3J = 7.4 Hz); 2.45 (br.s, 1 H, OH); 3.57 (t, 2 H, OCH_2, ^3J = 6.3 Hz); 4.18 (t, 2 H, NCH_2, ^3J = 7.4 Hz); 6.51 (s, 1 H, H(4)); 7.38 (dd, 2 H, *o*-H_{Ph}, ^3J = 7.2 Hz, ^4J = 2.5 Hz); 7.46—7.50 (m, 3 H, *m*-H_{Ph}, *p*-H_{Ph}). ^{19}F NMR, δ: 99.81 (s, CF_3). Found (%): C, 59.37; H, 5.29; F, 20.34; N, 9.77. $C_{14}H_{15}F_3N_2O$. Calculated (%): C, 59.15; H, 5.32; F, 20.05; N, 9.85.

1-(4-Hydroxybutyl)-3-phenyl-5-trifluoromethylpyrazole (5). The yield was 16%, yellow oil. IR, ν/cm^{-1}: 3375 (OH); 1475, 1515, 1555 (C=C, C=N); 1125—1200 (C—F). ^{1}H NMR, δ: 1.62 (m, 2 H, CH_2, ^3J = 6.4 Hz); 2.02 (m, 2 H, CH_2, ^3J = 7.4 Hz); 2.37 (br.s, 1 H, OH); 3.66 (t, 2 H, OCH_2, ^3J = 6.4 Hz); 4.28 (t, 2 H, NCH_2, ^3J = 7.4 Hz); 6.86 (s, 1 H, H(4)); 7.33 (tt, 1 H, *p*-H_{Ph}, ^3J = 7.3 Hz, ^4J = 1.3 Hz); 7.40 (m, 2 H, *m*-H_{Ph}); 7.76 (dd, 2 H, *o*-H_{Ph}, ^3J = 8.3 Hz, ^4J = 1.3 Hz). ^{19}F NMR, δ: 102.27 (s, CF_3). Found (%): C, 59.01; H, 5.33; F, 20.37; N, 9.98. $C_{14}H_{15}F_3N_2O$. Calculated (%): C, 59.15; H, 5.32; F, 20.05; N, 9.85.

Deacylation of 1-(4-acetoxybutyl)pyrazole 2d. Compound **2d** (0.19 g, 0.5 mmol) was dissolved in methanol (5 mL), then gaseous ammonia was bubbled through the solution for 1 h. The reaction mixture was stirred for 30 min at room temperature and neutralized with dilute HCl to pH 7. The product was extracted with chloroform and dried with Na_2SO_4. The solvent was evaporated to obtain **1-(4-hydroxybutyl)-3,5-bis(1,1,2,2-tetrafluoroethyl)pyrazole (6)**, the yield was 100%, yellow oil. IR, ν/cm^{-1}: 3380 (OH); 1475, 1550 (C=C, C=N); 1110—1225 (C—F). ^{1}H NMR, δ: 1.60 (m, 2 H, CH_2, ^3J = 6.3 Hz); 1.94 (s, 1 H, OH); 2.02 (m, 2 H, CH_2, ^3J = 7.5 Hz); 3.67 (t, 2 H, OCH_2, ^3J = 6.3 Hz); 4.34 (t, 2 H, NCH_2, ^3J = 7.5 Hz); 6.05 (tt, 1 H, $H(CF_2)_2$, $^2J_{H,F}$ = = 53.5 Hz, $^3J_{H,F}$ = 2.4 Hz); 6.11 (tt, 1 H, $H(CF_2)_2$, $^2J_{H,F}$ = 53.4 Hz, $^3J_{H,F}$ = 4.0 Hz); 6.82 (s, 1 H, H(4)). ^{19}F NMR, δ: 25.68 (dt, 2 F, HCF_2, $^2J_{F,H}$ = 53.4 Hz, $^3J_{F,F}$ = 6.5 Hz); 28.57 (dt, 2 F, HCF_2, $^2J_{F,H}$ = 53.5 Hz, $^3J_{F,F}$ = 4.6 Hz); 48.69 (td, 2 F, CF_2, ^3J = 6.5 Hz, ^3J = 4.0 Hz); 53.9 (m, 2 F, CF_2). MS, *m/z* (I_{rel} (%)): 55 $[C_4H_7]^+$ (9.6), 199 $[M - HCF_2 - F - C_4H_6OH]^+$ (10.3), 209 $[M - H(CF_2)_2 - CH_2O]^+$ (19.6), 217 $[M - HCF_2 - C_4H_7OH]^+$ (42.8), 239 $[M - H(CF_2)_2]^+$ (52.6), 249 $[M - F - C_4H_7OH]^+$ (10.5), 269 $[M - C_4H_6OH]^+$ (14.9), 281 $[M - C_3F_6OH]^+$ (99.9), 295 $[M - C_2H_4OH]^+$ (10.9), 340 $[M]^+$ (1.4). Found (%): C, 38.67; H, 3.61; F, 44.43; N, 7.97. $C_{11}H_{12}F_8N_2O$. Calculated (%): C, 38.83; H, 3.56; F, 44.67; N, 8.23.

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