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Regioselective Cyclocondensation of Ethyl 2-Ethoxymethylidene-3-oxo-3-polyfluoroalkylpropionates with Thiazolylhydrazines

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Abstract—Ethyl 2-ethoxymethylidene-3-oxo-3-polyfluoroalkylpropionates reacted in a regioselective fashion with thiazolylhydrazines to give the corresponding ethyl 1-thiazolyl-5-fluoroalkyl-1*H*-pyrazole-4-carboxylates. The product structure was determined on the basis of NMR and X-ray diffraction data.

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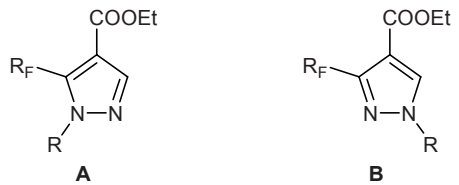
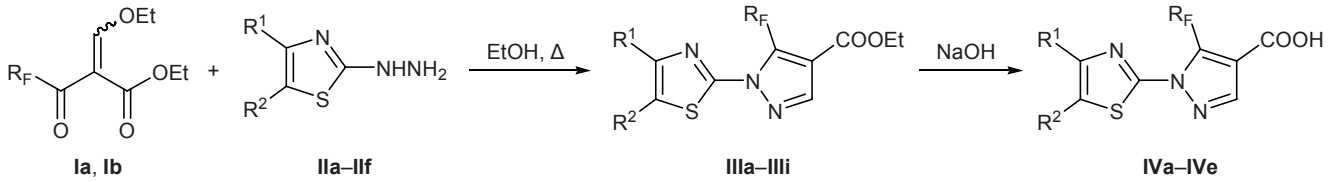
Pyrazole derivatives attract persistent attention due to their biological activity, in particular anesthetic [1]. A number of non-narcotic analgesics have been designed on the basis of pyrazolone derivatives, e.g., Phenazone, Aminophenazone, and Metamizole [1]. Fluoroalkyl-containing pyrazoles were covered by patents as substances possessing anti-inflammatory, analgesic, and antipyretic activity, highly efficient insecticides and herbicides, medical agents for the treatment of hyperglycemia, heat-resistant dyes, and surfactants [2]. A novel non-steroidal anti-inflammatory drug, Celecoxib {4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide} has found application in medicine. It is believed that this compound is a selective inhibitor of cyclooxygenase-2 which promotes synthesis of prostaglandins involved in the inflammation development [3]. There are published data on bactericidal [4], hypotensive [5], fungicidal, and herbicidal [6] activity of such pyrazole derivatives as thiazolylpyrazoles. Trifluoromethyl-substituted thiazol-2-ylpyrazoles were patented as blood platelet aggregation inhibitors and were recommended for the treatment of thromboses and concomitant vascular disorders [7].

The goal of the present study was to synthesize functionalized fluoroalkyl-containing thiazolylpyrazoles. A classical method for building up pyrazole ring is based on cyclocondensation of 1,3-dicarbonyl compounds and their derivatives with hydrazine and substituted hydrazines. Reactions with 1,3-dicarbonyl compounds having a functional group in the 2-position give rise to functionalized pyrazoles. Transformations of 2-ethoxymethylidene-substituted ethyl acetoacetate and ethyl trifluoroacetoacetate in reactions with arylhydrazines were reported [8] to produce ethyl 5-methyl-(trifluoromethyl)-1*H*-pyrazole-4-carboxylates.

We examined reactions of ethyl 2-ethoxymethylidene-3-fluoroalkyl-3-oxopropionates **Ia** and **Ib** with a number of thiazolyl-substituted hydrazines **IIa**–**IIf** (Scheme 1). Taking into account that both electrophiles **I** and nucleophiles **II** possess several nonequivalent reaction centers, formation of different products, including regioisomeric ones, may be expected as a result of concurrent processes. Esters **Ia** and **Ib** readily reacted with hydrazines **IIa**–**IIf** in boiling ethanol to give compounds **IIIa**–**IIIi** as the only products. According to the ^{1}H NMR and mass spectra, the products were ethyl pyrazolecarboxylates. However, these data did not allow us to distinguish between two possible regioisomers **A** (5-R_F) and **B** (3-R_F).



Scheme 1.



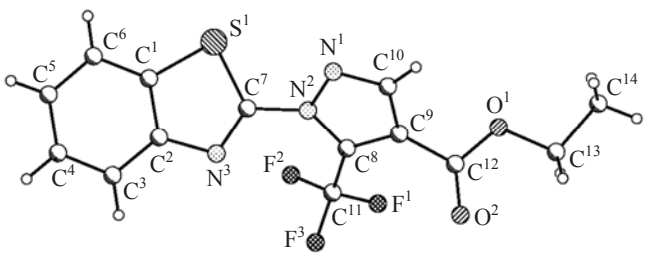
Ia, **Ib** **IIa–IIf** **IIIa–IIIi** **IVa–IVe**

I, R_F = CF_3 (**a**), $H(CF_2)_2$ (**b**); **II**, R^1R^2 = benzo (**a**); R^2 = H, R^1 = MeOCO (**b**), EtOCO (**c**), Ph (**d**), 4-BrC_6H_4 (**e**), 4-MeC_6H_4 (**f**); **III**, R_F = CF_3, R^1R^2 = benzo (**a**), R^2 = H, R^1 = MeOCO (**b**), 4-BrC_6H_4 (**c**), 4-MeC_6H_4 (**d**); R_F = $H(CF_2)_2$, R^1R^2 = benzo (**e**), R^2 = H, R^1 = MeOCO (**f**), EtOCO (**g**), Ph (**h**), 4-MeC_6H_4 (**i**); **IV**, R_F = CF_3, R^1 = HOCO, R^2 = H (**a**); R_F = $H(CF_2)_2$, R^1 = HOCO, R^2 = H (**b**); R^1R^2 = benzo (**c**); R^2 = H, R^1 = Ph (**d**), 4-MeC_6H_4 (**e**).

To elucidate the structure of compounds **IIIa**–**IIIi**, we have resorted to ^{19}F NMR spectroscopy. It is known that the chemical shift of fluorine atoms in the ^{19}F NMR spectra of trifluoromethyl-substituted pyrazoles is very characteristic. The CF_3 signal in the spectra of 4-fluoro [9] and 4-unsubstituted pyrazoles [10] appears in a stronger field (δ_F ~101 ppm relative to C_6F_6) for 3-CF_3 isomers as compared to the corresponding signals of 5-CF_3 isomers (δ_F ~105 ppm). In the ^{19}F NMR spectra of **IIIa**–**IIId** in DMSO-d_6, the CF_3 fluorine atoms resonated at δ_F ~106 ppm, which is better consistent with 5-CF_3 isomers.

The assumed structure was proved by the X-ray diffraction data for a single crystal of compound **IIIa** (see figure). Tetrafluoroethyl-substituted pyrazoles **IIIe**–**IIIi** were assigned structure **A** by comparing their ^{1}H NMR spectra with those of trifluoromethyl-substituted analogs **IIIa**–**IIId**. In this case, the most characteristic was the chemical shift of the CH proton (3-H) in the pyrazole ring (see table). It is seen that the position of its signal almost does not change in going from trifluoromethyl to tetrafluoroethyl derivatives.

Thus we have demonstrated that cyclocondensation of ethyl 2-ethoxymethylidene-3-fluoroalkyl-3-oxopropionates with thiazolylhydrazines regioselectively yields the corresponding ethyl 5-polyfluoroalkyl-1-(thiazol-2-yl)-1*H*-pyrazole-4-carboxylates. Presumably, condensation of the free amino group in hydrazine **II** at the ethoxymethylidene fragment of ester **I** occurs in the initial step, and next follows intramolecular ring closure with participation of the fluoroacyl fragment and secondary amino group, the ester moiety in **I** remaining intact.



Structure of the molecule of ethyl 1-(benzothiazol-2-yl)-5-trifluoromethyl-1*H*-pyrazole-4-carboxylate (**IIIa**) according to the X-ray diffraction data.

The presence of an ethoxycarbonyl group in molecules **IIIa**–**IIIi** opens the way to their subsequent modification. Alkaline hydrolysis of pyrazolecarboxylates **IIIb**, **IIIe**, **IIIf**, **IIIh**, and **IIIi** gave the corresponding pyrazole-4-carboxylic acids **IVa**–**IVe** whose structure was confirmed by ^{1}H NMR spectroscopy, mass spectrometry, and elemental analysis. It should be noted that hydrolysis of compounds **IIIb** and **IIIf** involved both ester groups (in the pyrazole and thiazole rings).

EXPERIMENTAL

The IR diffuse reflectance spectra (400–4000 cm^{-1}) were recorded on a Perkin–Elmer Spectrum One spectrometer with Fourier transform. The NMR spectra were measured from solutions in DMSO-d_6 on Bruker DRX-400 (^{1}H, 400.13 MHz, Me_4Si; ^{19}F: 376.44 MHz, C_6F_6; **IIIa**–**IIIi**) and Bruker WM-250 spectrometers (^{1}H: 250.13 MHz, Me_4Si; **IVa**–**IVe**). Elemental analyses were obtained on a Perkin–Elmer PE 2400 Series II analyzer. The mass spectra (electron impact, 70 eV) were run on a Varian MAT-311A instrument.

The X-ray diffraction data for compound **IIIa** were acquired at 295(2) K on an XCalibur 3 diffractometer ($\omega/2\theta$ scanning, MoK_α irradiation, λ = 0.71073 Å, graphite monochromator, CCD detector); triclinic crystals, $C_{14}H_{10}F_3N_3O_2S$, M 341.31, space group $P\overline{1}$, unit cell parameters: a = 7.8490(7), b = 9.9010(15), c = 10.5404(11) Å; α = 108.387(11)°, β = 98.734(8)°, γ = 102.114(10)°; V = 738.71(15) Å^3; Z = 2; d_{calc} = 1.534 g/cm^3; μ(MoK_α) = 0.265 cm^{-1}; 216 parameters, $2\theta_{max}$ = 31.72°, $-11 \le h \le 11$, $-14 \le k \le 14$, $-15 \le l \le 15$. Total of 12619 reflections were measured, 4562 of which were independent (R_{int} = 0.0269); 2406 reflec-

tions with $F_o > 4\sigma(F_o)$. The structure was solved by the direct method and was refined by the least-squares procedure using SHELXL-97 software [11] to R = 0.0355, wR_2 = 0.0712; goodness of fit 1.001. The complete set of crystallographic data was deposited to the Cambridge crystallographic Data Center (entry no. CCDC 655617; http://www.ccdc.cam.ac.uk/deposit; CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (44)01223336033; e-mail: *deposit@ccdc.cam.ac.uk*].

Initial fluoroalkyl-containing esters **Ia** and **Ib** were synthesized as described in [12].

Thiazolylpyrazoles IIIa–IIIi (*general procedure*). A mixture of 0.001 mol of ester **Ia** or **Ib** and 0.001 mol of hydrazine **IIa–IIf** in 15 ml of ethanol was heated for 30–40 min under reflux. The mixture was cooled, and the precipitate was filtered off, recrystallized from ethanol, and dried.

Ethyl 1-(benzothiazol-2-yl)-5-trifluoromethyl-1*H*-pyrazole-4-carboxylate (IIIa). Yield 0.249 g (73%), mp 120–122°C. IR spectrum, ν, cm^{-1}: 3100, 3067 (C–H); 1727 (C=O); 1577, 1529 (C=C, C=N); 1251–1101 (C–F). ^{1}H NMR spectrum, δ, ppm: 1.33 t (3H, $CH_2C\mathbf{H}_3$, J = 7.1 Hz), 4.36 q (2H, OCH_2, J = 7.1 Hz), 7.57 d.d.d (1H, 6′-H, J = 7.9, 7.8, 1.2 Hz), 7.62 d.d.d (1H, 5′-H, J = 8.0, 7.8, 1.3 Hz), 8.05 d.d.d (1H, 4′-H, J = 8.0.0, 1.2, 0.7 Hz), 8.22 d.d.d (1H, 7′-H, J = 7.9, 1.3, 0.7 Hz), 8.50 br.s (1H, 3-H). ^{19}F NMR spectrum: δ_F 106.46 ppm, d (CF_3, J = 0.7). Mass spectrum, m/z (I_{rel}, %): 341 (100) $[M]^+$, 313 (24.7), 296 (67.9) $[M - OEt]^+$, 201 (7.8), 148 (9.1), 134 (17) [benzothiazole]$^+$, 108 (6.5), 90 (6.2), 69 (7.2). Found, %: C 49.30; H 2.95; F 16.62; N 12.33. $C_{14}H_{10}F_3N_3O_2S$. Calculated, %: C 49.27; H 2.95; F 16.70; N 12.31.

Methyl 2-(4-ethoxycarbonyl-5-trifluoromethyl-1*H*-pyrazol-1-yl)thiazole-4-carboxylate (IIIb). Yield 0.293 g (84%), mp 135–137°C. IR spectrum, ν, cm^{-1}: 3134, 3111, 3031–2945 (C–H); 1735 (C=O); 1575, 1535 (C=C, C=N); 1245–1105 (C–F). ^{1}H NMR spectrum, δ, ppm: 1.31 t (3H, $CH_2C\mathbf{H}_3$, J = 7.1 Hz), 3.87 s (3H, OCH_3), 4.34 q (2H, OCH_2, J = 7.1 Hz), 8.46 br.s (1H, 3′-H), 8.67 s (1H, 5-H). ^{19}F NMR spectrum: δ_F 106.56 ppm, d (CF_3, J = 0.7 Hz). Mass spectrum, m/z (I_{rel}, %): 349 (98) $[M]^+$, 318 (35.5), 304 (100) $[M - OEt]^+$, 290 (24.5) $[M - CO_2Me]^+$, 263 (12.8), 137 (13.8), 83 (29.6), 59 (9.4). Found, %: C 41.30; H 2.88; F 16.28; N 12.10. $C_{12}H_{10}F_3N_3O_4S$. Calculated, %: C 41.26; H 2.89; F 16.32; N 12.03.

Ethyl 1-[4-(4-bromophenyl)thiazol-2-yl]-5-trifluoromethyl-1*H*-pyrazole-4-carboxylate (IIIc). Chemical shifts (δ, ppm) of CH protons in the heterorings of compounds **IIIa–IIIi**

Compound no.	3-H (pyrazole)	5-H (thiazole)
IIIa	8.50	–
IIIb	8.46	8.67
IIIc	8.45	8.34
IIId	8.44	8.20
IIIe	8.49	–
IIIf	8.45	8.64
IIIg	8.45	8.61
IIIh	8.45	8.27
IIIi	8.44	8.19

Yield 0.308 g (69%), mp 102–103°C. IR spectrum, ν, cm^{-1}: 3100, 3067, 2984–2935 (C–H); 1727 (C=O); 1576, 1529 (C=C, C=N); 1282–1158 (C–F). ^{1}H NMR spectrum, δ, ppm: 1.32 t (3H, $CH_2C\mathbf{H}_3$, J = 7.1 Hz), 4.35 q (2H, OCH_2, J = 7.1 Hz), 7.70 d.m (2H, C_6H_4, J = 8.5 Hz), 7.90 d.m (2H, C_6H_4, J = 8.5 Hz), 8.34 s (1H, 5′-H), 8.45 s (1H, 3-H). ^{19}F NMR spectrum: δ_F 106.48 ppm, d (CF_3, J = 0.6 Hz). Mass spectrum, m/z (I_{rel}, %): 447 (100) $[M + H]^+$, 446 (19) $[M]^+$, 445 (96) $[M - H]^+$, 400 (20) $[M - HOEt]^+$, 133 (10.8), 89 (13.4). Found, %: C 43.02; H 2.46; F 12.78; N 9.40. $C_{16}H_{11}BrF_3N_3O_2S$. Calculated, %: C 43.07; H 2.48; F 12.77; N 9.42.

Ethyl 1-[4-(4-methylphenyl)thiazol-2-yl]-5-trifluoromethyl-1*H*-pyrazole-4-carboxylate (IIId). Yield 0.305 g (80%), yellow powder, mp 118–119°C. IR spectrum, ν, cm^{-1}: 3120, 2985–2916 (C–H); 1737 (C=O); 1572, 1527 (C=C, C=N); 1255–1053 (C–F). ^{1}H NMR spectrum, δ, ppm: 1.32 t (3H, $CH_2C\mathbf{H}_3$, J = 7.1 Hz), 2.35 s (3H, CH_3), 4.35 q (2H, OCH_2, J = 7.1 Hz), 7.30 d.m (2H, C_6H_4, J = 8.0 Hz), 7.84 d.m (2H, C_6H_4, J = 8.0 Hz), 8.20 s (1H, 5′-H), 8.44 s (1H, 3-H). ^{19}F NMR spectrum: δ_F 106.50 ppm, s (CF_3). Mass spectrum, m/z (I_{rel}, %): 381 (100) $[M]^+$, 353 (16.4), 336 (13.6) $[M - OEt]^+$, 205 (24.6), 147 (21.5), 115 (11.2), 91 (8.9). Found, %: C 53.24; H 3.56; F 14.80; N 10.97. $C_{17}H_{14}F_3N_3O_2S$. Calculated, %: C 53.54; H 3.70; F 14.94; N 11.02.

Ethyl 1-(benzothiazol-2-yl)-5-(1,1,2,2-tetrafluoroethyl)-1*H*-pyrazole-4-carboxylate (IIIe). Yield 0.326 g (88%), mp 110–112°C. IR spectrum, ν, cm^{-1}: 3110, 2985–2907 (C–H); 1714 (C=O); 1599, 1566, 1539 (C=C, C=N); 1251–1088 (C–F). ^{1}H NMR spectrum, δ, ppm: 1.31 t (3H, $CH_2C\mathbf{H}_3$, J = 7.1 Hz), 4.33 q (2H, OCH_2, J = 7.1 Hz), 7.42 t.t (1H, HCF_2, J = 52.5,

5.9 Hz), 7.56 d.d.d (1H, 5′-H, J = 7.9, 7.6, 1.3 Hz), 7.63 d.d.d (1H, 6′-H, J = 8.0, 7.6, 1.3 Hz), 8.05 d.d.d (1H, 4′-H, J = 7.9, 1.3, 0.7 Hz), 8.21 d.d.d (1H, 7′-H, J = 8.0, 1.3, 0.7 Hz), 8.49 s (1H, 3-H). ^{19}F NMR spectrum, δ_F, ppm: 26.85 d.t (2F, HCF_2, J = 52.5, 9.4 Hz), 53.39 m (2F, CF_2). Mass spectrum, m/z (I_{rel}, %): 373 (100) $[M]^+$, 328 (70.8) $[M - OEt]^+$, 300 (14.6), 281 (17.8), 201 (23.6), 185 (48.4), 161 (13.4), 141 (40.4), 108 (16.3), 90 (16.1), 69 (14.1) 51 (9.3). Found, %: C 48.17; N 2.69; F 20.27; N 11.29. $C_{15}H_{11}F_4N_3O_2S$. Calculated, %: C 48.26; N 2.97; F 20.36; N 11.26.

Methyl 2-[4-ethoxycarbonyl-5-(1,1,2,2-tetrafluoroethyl)-1*H*-pyrazol-1-yl]thiazole-4-carboxylate (IIIf). Yield 0.290 g (76%), mp 125°C. ^{1}H NMR spectrum, δ, ppm: 1.31 t (3H, CH_2CH_3, J = 7.1 Hz), 3.88 s (3H, OCH_3), 4.32 q (2H, OCH_2, J = 7.1 Hz), 7.26 t.t (1H, HCF_2, J = 52.8, 5.8 Hz), 8.45 s (1H, 3′-H), 8.64 s (1H, 5-H). ^{19}F NMR spectrum, δ_F, ppm: 26.55 d.t (2F, HCF_2, J = 52.8, 9.4 Hz), 52.93 m (2F, CF_2). Mass spectrum, m/z (I_{rel}, %): 381 (86.0) $[M]^+$, 361 (16.0), 350 (31.4), 336 (100) $[M - OEt]^+$, 322 (18.7), 304 (57.2), 270 (13.6), 193 (30.5), 153 (16.8), 141 (37.5), 117 (19.6), 83 (39.7), 59 (18.2). Found, %: C 40.82; H 2.88; F 19.92; N 10.97. $C_{13}H_{11}F_4N_3O_4S$. Calculated, %: C 40.95; H 2.91; F 19.93; N 11.02.

Ethyl 2-[4-ethoxycarbonyl-5-(1,1,2,2-tetrafluoroethyl)-1*H*-pyrazol-1-yl]thiazole-4-carboxylate (IIIg). Yield 0.321 g (84%), mp 106–108°C. IR spectrum, ν, cm^{-1}: 3129, 1733 (C=O); 1572, 1529, 1459 (C=C, C=N); 1243–1076 (C–F). ^{1}H NMR spectrum, δ, ppm: 1.30 t (3H, CH_2CH_3, J = 7.1 Hz), 1.32 t (3H, CH_2CH_3, J = 7.2 Hz), 4.31 q (2H, OCH_2, J = 7.1 Hz), 4.33 q (2H, OCH_2, J = 7.2 Hz), 7.30 t.t (1H, HCF_2, J = 53.0, 5.6 Hz), 8.45 s (1H, 3′-H), 8.61 s (1H, 5-H). ^{19}F NMR spectrum, δ_F, ppm: 26.45 d.t (2F, HCF_2, J = 52.8, 9.5 Hz), 53.94 m (2F, CF_2). Found, %: C 42.96; H 3.32; F 15.67; N 11.57. $C_{13}H_{12}F_4N_3O_4S$. Calculated, %: C 42.98; H 3.33; F 15.69; N 11.57.

Ethyl 1-(4-phenylthiazol-2-yl)-5-(1,1,2,2-tetrafluoroethyl)-1*H*-pyrazole-4-carboxylate (IIIh). Yield 0.248 g (62%), mp 129–131°C. ^{1}H NMR spectrum, δ, ppm: 1.32 t (3H, CH_2CH_3, J = 7.1 Hz), 4.33 q (2H, OCH_2, J = 7.1 Hz), 7.25 t.t (1H, HCF_2, J = 52.4, 5.9 Hz), 7.41–7.52 m (3H, C_6H_5), 7.94 m (2H, C_6H_5), 8.27 s (1H, 5′-H), 8.45 s (1H, 3-H). ^{19}F NMR spectrum, δ_F, ppm: 26.54 d.t (2F, HCF_2, J = 52.4, 9.8 Hz), 52.83 m (2F, CF_2). Mass spectrum, m/z (I_{rel}, %): 399 (100) $[M]^+$, 354 (28) $[M - OEt]^+$, 210 (15.4), 177 (7.8), 134 (36.5), 102 (13.8), 89 (11.8), 77 (10.2). Found, %: C 51.06; H 3.12; F 19.00; N 10.43. $C_{17}H_{13}F_4N_3O_2S$. Calculated, %: C 51.13; H 3.28; F 19.03; N 10.52.

Ethyl 1-[4-(4-methylphenyl)thiazol-2-yl]-5-(1,1,2,2-tetrafluoroethyl)-1*H*-pyrazole-4-carboxylate (IIIi). Yield 0.310 g (75%), mp 139–141°C. IR spectrum, ν, cm^{-1}: 3129, 3030–2910 (C–H); 1731 (C=O); 1562, 1524 (C=C, C=N); 1218–1054 (C–F). ^{1}H NMR spectrum, δ, ppm: 1.32 t (3H, CH_2CH_3, J = 7.1 Hz), 2.35 s (3H, CH_3), 4.33 q (2H, OCH_2, J = 7.1 Hz), 7.24 t.t (1H, HCF_2, J = 52.4, 5.8 Hz), 7.30 d.m (2H, C_6H_4, J = 8.0 Hz), 7.82 d.m (2H, C_6H_4, J = 8.0 Hz), 8.19 s (1H, 5′-H), 8.44 s (1H, 3-H). ^{19}F NMR spectrum, δ_F, ppm: 26.52 d.t (2F, HCF_2, J = 52.4, 9.7 Hz), 52.81 m (2F, CF_2). Mass spectrum, m/z (I_{rel}, %): 413 (100) $[M]^+$, 385 (10.6), 368 (14.9) $[M - OEt]^+$, 224 (11.6), 147 (22.3), 115 (11.6), 91 (10.0), 77 (3.3). Found, %: C 52.18; H 3.71; F 18.20; N 10.19. $C_{18}H_{15}F_4N_3O_2S$. Calculated, %: C 52.30; H 3.66; F 18.38; N 10.16.

2-[4-Carboxy-5-(trifluoromethyl)-1*H*-pyrazol-1-yl]thiazole-4-carboxylic acid (IVa). A mixture of 0.175 g (0.5 mmol) of compound **IIIb** and 0.040 g (1 mmol) of sodium hydroxide in ethanol was heated for 5–15 min under reflux. The solvent was distilled off, the residue was dissolved in water, and the solution was acidified to pH ~5–6 with concentrated hydrochloric acid. The precipitate was filtered off, washed with ethanol, and dried. Yield 0.124 g (81%), mp 215°C. ^{1}H NMR spectrum, δ, ppm: 8.19 s (1H, 3′-H), 8.45 s (1H, 5-H), 13.25 br.s (2H, COOH). Mass spectrum, m/z (I_{rel}, %): 307 (100) $[M]^+$, 290 (10.1), 263 (17.2), 187 (27.3), 163 (10.9), 127 (13.6), 99 (28.3), 83 (86.4), 69 (21.7), 58 (25.2). Found, %: C 35.09; H 1.27; F 18.40; N 13.59. $C_9H_4F_3N_3O_4S$. Calculated, %: C 35.19; H 1.31; F 18.55; N 13.68.

Compounds **IVb–IVe** were synthesized in a similar way.

2-[4-Carboxy-5-(1,1,2,2-tetrafluoroethyl)-1*H*-pyrazol-1-yl]thiazole-4-carboxylic acid (IVb) was obtained from 0.191 g (0.5 mmol) of compound **IIIf**. Yield 0.122 g (72%), mp 210–212°C. ^{1}H NMR spectrum, δ, ppm: 7.29 t.t (1H, HCF_2, J = 53.4, 5.8 Hz), 8.18 s (1H, 3′-H), 8.42 s (1H, 5-H). Mass spectrum, m/z (I_{rel}, %): 339 (100) $[M]^+$, 319 (61.9), 270 (46.2), 219 (23.4), 177 (33.2), 161 (35.2), 141 (67.6), 117 (100), 101 (23.6), 83 (90.9), 71 (23.0), 58 (40.5), 51 (46.1). Found, %: C 35.29; H 1.38; F 22.25; N 12.30. $C_{10}H_5F_4N_3O_4S$. Calculated, %: C 35.41; H 1.49; F 22.40; N 12.39.

1-(Benzothiazol-2-yl)-5-(1,1,2,2-tetrafluoroethyl)-1*H*-pyrazole-4-carboxylic acid (IVc) was ob-

tained from 0.171 g (0.5 mmol) of compound **IIIe**. Yield 0.135 g (78%), mp 177–179°C. ^{1}H NMR spectrum, δ, ppm: 7.28 t.t (1H, HCF_2, J = 54.3, 5.8 Hz), 7.47–7.60 m (2H, H_{arom}), 8.02–8.09 m (2H, H_{arom}), 8.26 s (1H, 3-H). Mass spectrum, m/z (I_{rel}, %): 345 (100) $[M]^+$, 328 (35.6), 281 (22.5), 201 (46.1), 184 (78.3), 161 (14.1), 134 (42.1), 108 (25.0), 90 (25.9), 69 (26.3), 51 (17.9). Found, %: C 45.19; H 1.97; F 21.95; N 12.06. $C_{13}H_7F_4N_3O_2S$. Calculated, %: C 45.22; H 2.04; F 22.01; N 12.17.

1-(4-Phenylthiazol-2-yl)-5-(1,1,2,2-tetrafluoroethyl)-1*H*-pyrazole-4-carboxylic acid (IVd) was obtained from 0.199 g (0.5 mmol) of compound **IIIh**. Yield 0.158 g (85%), mp 168–170°C. ^{1}H NMR spectrum, δ, ppm: 7.11 t.t (1H, HCF_2, J = 53.1, 6.0 Hz), 7.29–7.46 m (3H, C_6H_5), 7.84 m (2H, C_6H_5), 8.09 s (1H, 5′-H), 8.22 s (1H, 3-H). Mass spectrum, m/z (I_{rel}, %): 371 (100) $[M]^+$, 300 (5.6), 227 (15.3), 210 (28.2), 134 (61.6), 102 (20.7), 89 (21.8), 77 (22.0), 69 (7.3), 51 (15.2). Found, %: C 48.39; H 2.37; F 20.29; N 11.20. $C_{15}H_9F_4N_3O_2S$. Calculated, %: C 48.52; H 2.44; F 20.47; N 11.32.

1-[4-(4-Methylphenyl)thiazol-2-yl]-5-(1,1,2,2-tetrafluoroethyl)-1*H*-pyrazole-4-carboxylic acid (IVe) was obtained from 0.207 g (0.5 mmol) of compound **IIIi**. Yield 0.154 g (68%), mp 186–188°C. ^{1}H NMR spectrum, δ, ppm: 2.38 s (1H, CH_3), 7.10 t.t (1H, HCF_2, J = 53.0, 6.0 Hz), 7.23 d.m (2H, C_6H_4, J = 7.9 Hz), 7.76 d.m (2H, C_6H_4, J = 7.9 Hz), 7.99 s (1H, 5′-H), 8.18 s (1H, 3-H). Mass spectrum, m/z (I_{rel}, %): 385 (100) $[M]^+$, 340 (7.3), 326 (7.1), 224 (18.9), 159 (8.4), 150 (6.4), 147 (27.2), 115 (16.6), 91 (16.4), 77 (7.3), 65 (6.7). Found, %: C 49.80; H 2.79; F 19.67; N 10.81. $C_{16}H_{11}F_4N_3O_2S$. Calculated, %: C 49.87; H 2.88; F 19.72; N 10.90.

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