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Iodine-Promoted Synthesis of Pyrazoles from 1,3-Dicarbonyl Compounds and Oxamic Acid Thiohydrazides

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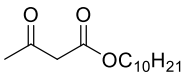
List of Contents

General Information

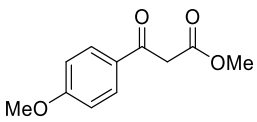
NMR spectra were acquired on Bruker Avance 600 and 300 spectrometers at room temperature; the chemical shifts δ were measured in ppm relative to the solvent (^{1}H: $CDCl_3$, δ = 7.27 ppm, DMSO-d_6, δ = 2.50 ppm; ^{13}C: $CDCl_3$, δ = 77.00 ppm, DMSO-d_6, δ = 39.50 ppm). Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, double doublet; ddd, double double doublet. The coupling constants (J) are in Hertz. The structures of all compounds were established using 1D NMR (^{1}H, ^{13}C, JMOD) and 2D NMR (^{1}H-^{1}H COSY, ^{13}C-^{1}H HMBC, ^{13}C-^{1}H HSQC) spectroscopy. High-resolution and accurate mass spectra were obtained on BrukermicrOTOF-QTM ESI-TOF (Electrospray Ionization/Time of Flight) and Thermo Scientific* LTQ Orbitrap mass spectrometers. Melting points (mp) are uncorrected and were measured on a Boetius capillary melting point apparatus. Analytical thin layer chromatography (TLC) was carried out on silica gel plates (silica gel 60 F254 aluminum supported plates); the visualization was accomplished with an UV lamp (365 nm). Column chromatography was performed on silica gel 60 (230-400 mesh, Merck). Ethyl acetoacetate, methyl acetoacetate, *n*-decanol, acetylacetone, 1-(4-methoxyphenyl)ethan-1-one, testosterone, diethyl 3-oxopentanedioate, 1,3-diphenylpropane-1,3-dione, 4,4,4-trifluoro-1-phenylbutane-1,3-dione, dimethyl carbonate, sodium hydride, *N*-halogen succinimides, chloroacetanilides, iodine, bromine, *p*-toluenesulfonic acid, hexamethylphosphoramide (HMPTA), *n*-butylamine, chloroacetanilides, and sodium methylate were commercially available and were used without additional purification. 4-Substituted 3-oxobutanoate esters were kindly provided by Prof. Valerii Shirinian from N. D. Zelinsky Institute of Organic Chemistry. All reactions were carried out using freshly distilled and dry solvents.[1]

Typical experimental procedures

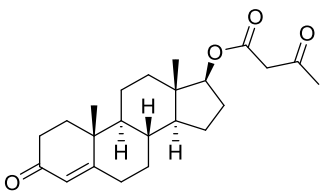
I. Synthesis of 1,3-dicarbonyl compounds



Decanoic 3-oxobutanoic anhydride (1b). A mixture of *n*-decanol (65 µL, 0.3 mmol) and ethyl acetoacetate (0.3 mL, 2.3 mmol) was heated to 100 °C for 10 h. After completion (TLC), the reaction mixture was cooled, and excess of ethyl acetoacetate was removed under reduced pressure. The residue was purified by column chromatography on silica gel (petr. ether/EtOAc, 50:1) to get 45 mg (yield 62%) of yellow oil. The spectral data matched that reported by Rezgui and coworkers.[2] ^{1}H NMR (300 MHz, $CDCl_3$, *keto form*): δ 0.86 (t, 3H, *J* = 6.60 Hz, CH_3), 1.18-1.40 (m, 14H, CH_2, CH_2, CH_2, CH_2, CH_2, CH_2, CH_2), 1.54-1.72 (m, 2H, CH_2), 2.20 (s, 3H, CH_3), 3.37 (s, 2H, CH_2), 4.06-4.17 (t, 2H, *J* = 6.60 Hz, CH_2). ^{1}H NMR (300 MHz, $CDCl_3$, *enol form*): δ 0.86 (t, 3H, *J* = 6.60 Hz, CH_3), 1.18-1.40 (m, 14H, CH_2, CH_2, CH_2, CH_2, CH_2, CH_2, CH_2), 1.54-1.72 (m, 2H, CH_2), 1.93 (s, 3H, CH_3), 4.06-4.17 (t, 2H, *J* = 6.60 Hz, CH_2), 4.99 (s, 1H, CH), 12.09 (s, 1H, CH).

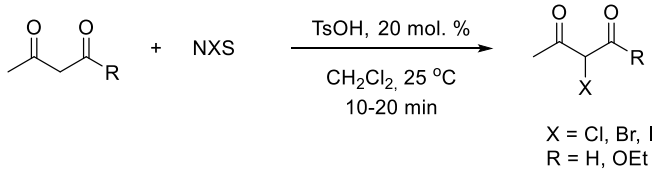


Methyl 3-(4-methoxyphenyl)-3-oxopropanoate (1g). Sodium hydride (80 mg, 60% dispersion in mineral oil, 2.0 mmol) was added in one portion at 25 ºC to a solution of 1-(4-methoxyphenyl)ethan-1-one (200 mg, 1.3 mmol) in dry THF. Mixture was cooled to 10 ºC (ice bath) and stirred for 20 min. Dimethyl carbonate (0.33 mL, 3.9 mmol) was added dropwise at 10 ºC and reaction mixture was stored 20 h at 25 ºC. Resulting mixture was poored into ice-water (30 mL), acidified with 2% HCl to pH 6 and extracted with CH_2Cl_2 (3 × 15 mL). Organic layer was dried with Na_2SO_4, solvent was removed under reduced pressure to get 254 mg (94% yield) of yellow oil. Product was used next step without additional purification (purity by ^{1}H NMR spectra is 90%). The spectral data matched that reported by Sun and coworkers.[3] ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.75 (s, 3H, CH_3), 3.88 (s, 3H, CH_3), 3.97 (s, 2H, CH_2), 6.95 (d, 2H, *J* = 8.77 Hz, Ar), 7.93 (d, 2H, *J* = 8.77 Hz, Ar).

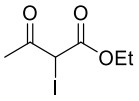


(8R,9S,10R,13S,14S,17S)-10,13-dimethyl-3-oxo-2,3,6,7,8,9,10,11, 12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[a]phenanthren-17-yl 3-oxobutanoate (1k). A mixture of testosterone (0.1 g, 0.35 mmol) and ethyl acetoacetate (2.7 mL, 20.8 mmol) was heated to 100 °C for 10 h. After completion (TLC), the reaction mixture was cooled, and excess of ethyl acetoacetate was removed under reduced pressure. The residue was purified by column chromatography on silica gel (petr. ether/EtOAc, 5:1) to get 75 mg (yield 75%) of colorless solid, mp 100 - 101 ºC. The spectral data matched that reported by Shapiro and coworkers.[4] ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.77 (s, 3H, 19-CH_3), 0.82-1.06 (m, 4H), 1.13 (s, 3H, 18-CH_3), 1.25-2.14 (m, 13H), 2.20 (s, 3H, CH_3), 2.26-2.40 (m, 2H, CH_2), 3.39 (s, 2H, CH_2), 4.46-4.54 (m, 1H, 17-CH), 5.65 (s, 1H, 4-CH).

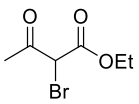
General procedure for the preparation of 2-halogen substituted 1,3-dicarbonyl compounds: Various 2-halogen substituted 1,3-dicarbonyl compounds as substrates were prepared from the corresponding 1,3-dicarbonyl compounds in high yields by the treatment with *N*-halogen succinimides according to the literature procedure.[5]



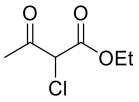
N-Halogen succinimide (1.2 mmol) and TsOH (34 mg, 0.2 mmol) were added to a solution of 1,3-dicarbonyl compound (1.0 mmol) in CH_2Cl_2 (10 mL). Resulting mixture was stored at 25 °C (Hal: I – 20 min, Br – 10 min, Cl – 20 min). After completion of the reaction (TLC monitoring), precipitate was removed by filtration and organic layer was washed with water (2 × 10 mL). Water layer was extracted with CH_2Cl_2 (3 × 10 mL). Combined organic layer was dried with Na_2SO_4 and solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (petr. ether/EtOAc, 10:1).



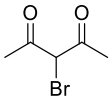
Ethyl 2-iodo-3-oxobutanoate (8a). Pale yellow oil (230 mg, 90%), R_f = 0.45 (petr. ether/EtOAc, 5:1). The spectral data matched that reported by Zhdankin and coworkers.[6] ^{1}H NMR (300 MHz, $CDCl_3$, *keto form*): δ 1.29 (t, 3H, *J* = 7.34 Hz, CH_3), 2.52 (s, 3H, CH_3), 4.25 (q, 2H, *J* = 7.34 Hz, CH_2), 5.00 (s, 1H, CH). ^{1}H NMR (300 MHz, $CDCl_3$, *enol form*): δ 1.29 (t, 3H, *J* = 7.34 Hz, CH_3), 2.76 (s, 3H, CH_3), 4.26 (q, 2H, *J* = 7.34 Hz, CH_2) (the signal of the OH group was not observed in ^{1}H NMR).



Ethyl 2-bromo-3-oxobutanoate (8b). Pale yellow oil (155 mg, 75%), R_f = 0.42 (petr. ether/EtOAc, 5:1). The spectral data matched that reported by Li and coworkers.[7] ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.33 (t, 3H, *J* = 7.34 Hz, CH_3), 2.46 (s, 3H, CH_3), 4.30 (q, 2H, *J* = 7.34 Hz, CH_2), 4.77 (s, 1H, CH).



Ethyl 2-chloro-3-oxobutanoate (8c). Pale yellow oil (105 mg, 64%), R_f = 0.55 (petr. ether/EtOAc, 5:1). The spectral data matched that reported by Dhakane and coworkers.[8] ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.35 (t, 3H, *J* = 7.34 Hz, CH_3), 2.39 (s, 3H, CH_3). 4.38 (q, 2H, *J* = 7.34 Hz, CH_2), 4.76 (s, 1H, CH).

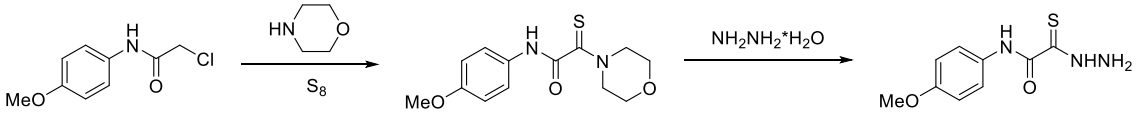


3-Bromopentane-2,4-dione. Colorless oil (154 mg, 87%), R_f = 0.67 (petr. ether/EtOAc, 5:1). The spectral data matched that reported by Dhar and coworkers.[9] ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.42 (s, 6H, 2 × CH_3), 4.69 (s, 1H, CH).

II. Synthesis of oxamic acids thiohydrazides

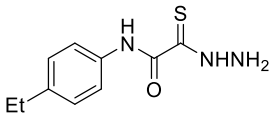
General procedure for the preparation of oxamic acids thiohydrazides: Various oxamic acid thiohydrazides as substrates were prepared from the corresponding chloroacetanilides in high yields by the treatment with hydrazine according to the literature procedure.[10]

Representative compound: **2-Hydrazinyl-*N*-(4-methoxyphenyl)-2-thioxoacetamide (2a)**.

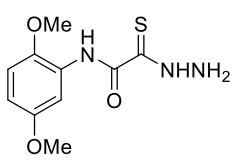


To a solution of sulfur (2.0 g, 62.5 mmol) in morpholine (7 mL) and DMF (7 mL), chloroacetanilide (2.0 g, 10.0 mmol)was added with stirring. The reaction mixture was kept overnight at room temperature (TLC monitoring). The mixture was poured into water (70 mL). The precipitate that formed was filtered off, dried, and dissolved in acetone to remove the sulfur excess. The organic fraction was separated, and the solvent was evaporated *in vacuo*. The solid residue was recrystallized from ethanol to give monothiooxamide as a white solid in 95% yield (2.7 g, 9.5 mmol).

To a solution of monothiooxamide (2.7 g, 9.5 mmol) in DMF (10 mL), hydrazine hydrate (2.7 mL, 50 mmol) was added, and the mixture was allowed to stand at room temperature for 10-12 h. After completion of the reaction (TLC monitoring), the reaction mixture was poured into water (40 mL) and the solution was acidified with hydrochloric acid to pH 6. The precipitate was filtered off and recrystallized from ethanol to give thiohydrazides in 62% yield (1.3 g, 5.9 mmol). mp 159 - 160^{o}C (mp_{lit} 161 - 163 ^{o}C).[10] ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.75 (s, 3H, OMe), 6.91 (d, 2H, *J* = 8.83 Hz, Ar), 7.70 (d, 2H, *J* = 8.83 Hz, Ar), 10.12 (br.s, 1H, NH).

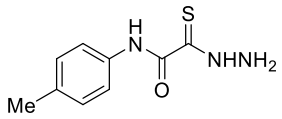


***N*-(4-Ethylphenyl)-2-hydrazinyl-2-thioxoacetamide (2b).** The general procedure was followed using 2-chloro-*N*-(4-ethylphenyl)acetamide (1.0 g, 5.1 mmol), sulfur (1.0 g, 31.3 mmol) in morpholine (1.3 mL) and DMF (10.0 mL). Workup afforded analytically pure compound as a pale pink solid (0.8 g, 70%), mp 145 - 147 ^{o}C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.16 (t, 3H, *J* = 7.32 Hz, CH_3), 3.56 (q, 2H, *J* = 7.32 Hz, CH_2), 7.20 (d, 2H, *J* = 8.41 Hz, Ar), 7.64 (d, 2H, *J* = 8.41 Hz, Ar), 10.13 (br.s, 1H, NH), (the signals of the $NHNH_2$ group was not observed in ^{1}H NMR). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 16.8 (CH_3), 28.9 (CH_2), 121.3 (2 × CH, Ar), 129.6 (2 × CH, Ar), 136.3 (C, Ar), 141.3 (C, Ar), 158.8 (C=O), 168.4 (C=S). IR (KBr): 3294 (NH), 2873 (CH), 1673 (CO), 1595, 1561, 1545, 1417, 1132, 1066, 915, 827, 662 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^{+}$ Calcd for $C_{10}H_{14}N_3OS$ 224.0847; Found 224.0852.

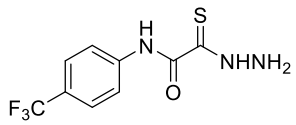


***N*-(2,5-Dimethoxyphenyl)-2-hydrazinyl-2-thioxoacetamide (2c).** The general procedure was followed using 2-chloro-*N*-(2,5-dimethoxyphenyl)acetamide (1.0 g, 4.4 mmol), sulfur (1.0 g, 31.3 mmol) in morpholine (1.3 mL) and DMF (10.0 mL). Workup afforded analytically pure compound as a yellow solid (0.9 g, 80%), mp 120 - 121 ^{o}C. The spectral data and melting

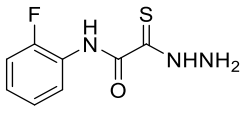
points matched that reported by Krayushkin and coworkers.[10, 11] ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.71 (s, 3H, OCH_3), 3.86 (s, 3H, CH_3),6.70 (dd, 1H, *J* = 2.93, 8.80 Hz, Ar),7.03 (d, 1H, *J* = 8.80 Hz, Ar), 7.86 (d, 1H, *J* = 2.93 Hz, Ar), 10.44 (br. s, 1H, NH), (the signals of the $NHNH_2$ group was not observed in ^{1}H NMR).



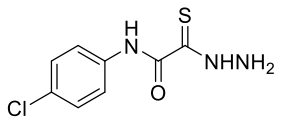
2-Hydrazinyl-2-thioxo-*N*-(p-tolyl)acetamide (2d). The general procedure was followed using 2-chloro-*N*-(*p*-tolyl)acetamide (1.0 g, 5.0 mmol), sulfur (1.0 g, 31.3 mmol) in morpholine (1.3 mL) and DMF (10.0 mL). Workup afforded analytically pure compound as a pale yellow solid (0.8 g, 77%), mp 155 - 157 ^{o}C. The spectral data and melting points matched that reported by Krasavin and coworkers.[12] ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.27 (s, 3H, CH_3), 7.16 (d, 2H, *J* = 8.03 Hz, Ar), 7.62 (d, 1H, *J* = 8.03 Hz, Ar), 10.11 (br.s, 1H, NH), (the signals of the $NHNH_2$ group was not observed in ^{1}H NMR).



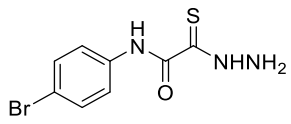
2-Hydrazinyl-2-thioxo-*N*-(4-(trifluoromethyl)phenyl)acetamide (2e). The general procedure was followed using 2-chloro-*N*-(4-(trifluoromethyl)phenyl)acetamide (2.4 g, 10.1 mmol), sulfur (2.0 g, 62.5 mmol) in morpholine (7.0 mL) and DMF (7.0 mL). Workup afforded analytically pure compound as a pale yellow solid (1.6 g, 60%), mp 169 - 170 ^{o}C. The spectral data matched that reported by Krayushkin and coworkers.[10] ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.72 (d, 2H, *J* = 8.07 Hz, Ar), 7.97 (d, 2H, *J* = 8.07 Hz, Ar), 10.52 (br.s, 1H, NH), (the signals of the $NHNH_2$ group was not observed in ^{1}H NMR).



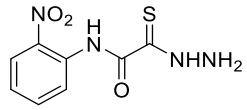
***N*-(2-Fluorophenyl)-2-hydrazinyl-2-thioxoacetamide (2f).** The general procedure was followed using 2-chloro-*N*-(2-fluorophenyl)acetamide (1.0 g, 5.3 mmol), sulfur (1.0 g, 31.3 mmol) in morpholine (1.3 mL) and DMF (10.0 mL). Workup afforded analytically pure compound as a pale yellow solid (0.8 g, 71%), mp 172 - 176 ^{o}C. The spectral data and melting point matched that reported by Krasavin and coworkers.[12] ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.21-7.30 (m, 2H, Ar), 7.31-7.41 (m, 1H, Ar), 8.03-8.15 (m, 1H, Ar), 10.28 (br.s, 1H, NH), (the signals of the $NHNH_2$ group was not observed in ^{1}H NMR). ^{13}C NMR (DMSO-d_6, 75 MHz):δ 115.5 (d, CH, *J* = 19.0 Hz, Ar), 122.2 (CH, Ar), 124.7 (d, CH, *J* = 3.6 Hz, Ar), 125.1 (d, C, *J* = 10.9 Hz, Ar), 125.9 (d, CH, *J* = 7.76 Hz, Ar), 153.4 (d, C, *J* = 244.84 Hz), 157.1 (C=O), 165.5 (C=S).



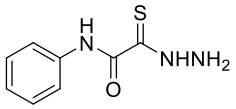
2-Hydrazinyl-*N*-(4-chlorophenyl)-2-thioxoacetamide (2g). The general procedure was followed using 2-chloro-*N*-(4-chlorophenyl)acetamide (2.0 g, 9.9 mmol), sulfur (2.0 g, 62.5 mmol) in morpholine (7.0 mL) and DMF (7.0 mL). Workup afforded analytically pure compound as a pale yellow solid (1.8 g, 79%), mp 172 - 174 ^{o}C. The spectral data matched that reported by Krayushkin and coworkers.[10] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.42 (d, 2H, *J* = 8.73 Hz, Ar), 7.86 (d, 2H, *J* = 8.72 Hz, Ar), 10.28 (br. s, 1H, NH), (the signals of the $NHNH_2$ group was not observed in ^{1}H NMR).



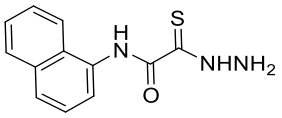
***N*-(4-Bromophenyl)-2-hydrazinyl-2-thioxoacetamide (2h).** The general procedure was followed using *N*-(4-bromophenyl)-2-chloroacetamide (0.5 g, 1.9 mmol), sulfur (0.5 g, 15.6 mmol) in morpholine (0.7 mL) and DMF (5.0 mL). Workup afforded analytically pure compound as a pale yellow solid (0.4 g, 77%), mp 164 - 166 ^{o}C. The spectral data and melting point matched that reported by Krasavin and coworkers.[10, 11] ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.55 (d, 2H, *J* = 8.80 Hz, Ar), 7.77 (d, 2H, *J* = 8.80 Hz, Ar), 10.34 (br.s, 1H, NH), (the signals of the $NHNH_2$ group was not observed in ^{1}H NMR). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 116.4 (C, Ar), 122.2 (2 × CH, Ar), 131.6 (2 × CH, Ar), 136.9 (C, Ar), 158.3 (C=O), 167.5 (C=S).



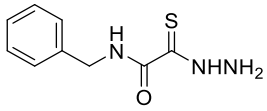
2-Hydrazinyl-*N*-(2-nitrophenyl)-2-thioxoacetamide (2i). The general procedure was followed using 2-chloro-*N*-(2-nitrophenyl)acetamide (1.0 g, 4.7 mmol), sulfur (1.0 g, 31.3 mmol) in morpholine (1.3 mL) and DMF (10.0 mL).Workup afforded analytically pure compound as a pale yellow solid (0.9 g, 78%), mp 190 - 192 ^{o}C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.41 (dd, 1H, *J* = 8.06 Hz, Ar), 7.84 (dd, 1H, *J* = 8.06 Hz, Ar), 8.23 (d, 1H, *J* = 8.06 Hz, Ar), 8.52 (d, 1H, *J* = 8.06 Hz, Ar), 11.92 (br.s, 1H, NH), (the signals of the $NHNH_2$ group was not observed in ^{1}H NMR). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 119.1 (C, Ar), 122.2 (CH, Ar), 124.6 (CH, Ar), 125.8 (CH, Ar), 132.3 (C, Ar), 135.5 (CH, Ar), 158.3 (C=O), 167.5 (C=S). IR (KBr): 3339, 3245 (NH), 3167 (CH), 1672 (C=O), 1605, 1549, 1509, 1453, 1340, 1282, 1136, 1064, 912, 816, 783, 742 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^{+}$ Calcd for $C_8H_9N_4O_3S$ 241.0390; Found 241.0390.



2-Hydrazinyl-*N*-phenyl-2-thioxoacetamide (2j). The general procedure was followed using 2-chloro-*N*-phenylacetamide (1.7 g, 10.0 mmol), sulfur (2.0 g, 62.5 mmol) in morpholine (7.0 mL) and DMF (7.0 mL). The spectral data matched that reported by Krayushkin and coworkers.[10] Workup afforded analytically pure compound as a white solid (1.5 g, 77%), mp 144-147 ^{o}C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.15-7.16 (m, 1H, Ph), 7.40-7.43 (m, 2H, Ph), 7.64 (d, 2H, *J* = 7.92 Hz, Ph), 10.20 (br. s, 1H, NH), (the signals of the $NHNH_2$ group was not observed in ^{1}H NMR).

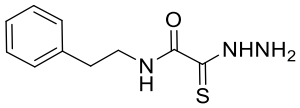


2-Hydrazinyl-*N*-(naphthalen-2-yl)-2-thioxoacetamide (2k). The general procedure was followed using 2-chloro-*N*-(naphthalen-2-yl)acetamide (1.0 g, 4.8 mmol), sulfur (1.0 g, 31.3 mmol) in morpholine (1.3 mL) and DMF (10.0 mL). Workup afforded analytically pure compound as a colorless solid (0.7 g, 60%), mp 187 - 189 ^{o}C. The spectral data and melting point matched that reported by Mayer and coworkers.[13] ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.50-7.72 (m, 3H, Ar), 7.80-8.05 (m, 4H, Ar), 10.73 (br.s, 1H, NH), (the signals of the $NHNH_2$ group was not observed in ^{1}H NMR).

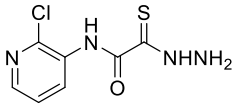


2-Hydrazinyl-*N*-benzyl-2-thioxoacetamide (2l). The general procedure was followed using *N*-benzyl-2-chloroacetamide (1.8 g, 10.0 mmol), sulfur (2.0 g, 62.5 mmol) in morpholine (7.0 mL) and DMF (7.0 mL). Workup afforded analytically pure compound as a pale yellow solid (1.3 g, 62%), mp 168 - 170

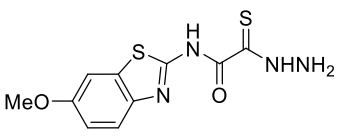
°C. The spectral data and melting point matched that reported by Volkova and coworkers.[14] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.41 (d, 2H, *J* = 5.86 Hz, CH_2), 6.34 (br.s, 2H, NH_2), 7.25-7.38 (m, 5H, Ph), 8.98-8.99 (t, 1H, *J* = 5.86 Hz, NH), 12.83 (br.s, 1H, NH).



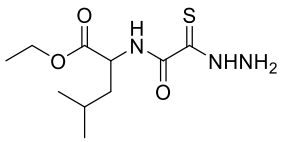
2-Hydrazinyl-*N*-phenethyl-2-thioxoacetamide (2m). The general procedure was followed using 2-chloro-*N*-phenethylacetamide (1.0 g, 4.7 mmol), sulfur (1.0 g, 31.3 mmol) in morpholine (1.3 mL) and DMF (10.0 mL). Workup afforded analytically pure compound as a yellow solid (0.5 g, 48%), mp 66 - 68 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.75-2.86 (m, 2H, CH_2), 3.40-3.49 (m, 2H, CH_2), 7.18-7.45 (m, 5H, Ph), 8.44-8.54 (m, 1H, NH), 12.83 (br.s, 1H, NH), (the signals of the NH_2 group was not observed in ^{1}H NMR). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 34.7 (CH_2), 40.9 (CH_2), 126.2 (CH, Ar), 128.4 (2 × CH, Ar), 128.6 (2 × CH, Ar), 139.1 (C, Ar), 157.6 (C=O), 168.4 (C=S). IR (KBr): 3325 (NH), 3028, 2936, 2866 (CH), 1662 (C=O), 1541, 1536, 1364, 1300, 1196, 1153, 1030, 907, 746, 697 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{10}H_{13}N_3OSNa$ 246.0675; Found 246.0672.



***N*-(2-Chloropyridin-3-yl)-2-hydrazinyl-2-thioxoacetamide (2n).** The general procedure was followed using 2-chloro-*N*-(2-chloropyridin-3-yl)acetamide (1.0 g, 4.9 mmol), sulfur (1.0 g, 31.3 mmol) in morpholine (1.3 mL) and DMF (10.0 mL). Workup afforded analytically pure compound as a yellow solid (0.9 g, 80%), mp 160 - 162 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.52 (dd, 1H, *J* = 5.03, 8.06 Hz, Ar), 8.23 (d, 1H, *J* = 5.03 Hz, Ar), 8.59 (d, 1H, *J* = 8.06 Hz, Ar), 10.56 (br.s, 1H, NH), (the signals of the $NHNH_2$ group was not observed in ^{1}H NMR). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 123.9 (CH, Ar), 129.3 (CH, Ar), 130.9 (C, Ar), 141.1 (C, Ar), 145.0 (CH, Ar), 157.3 (C=O), 164.7 (C=S). IR (KBr): 3424 (NH), 3227, 3138, 2909 (CH), 1698 (C=O), 1588, 1534, 1396, 1206, 1180, 1059, 992, 809, 733, 663 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_7H_8ClN_4OS$ 231.0106; Found 231.0102.

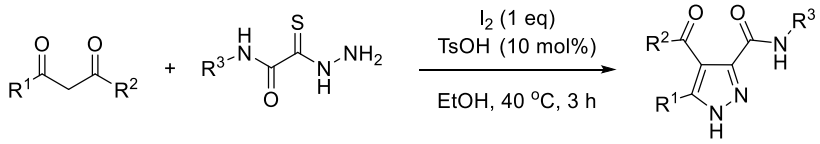


2-Hydrazinyl-*N*-(6-methoxybenzo[*d*]thiazol-2-yl)-2-thioxoacetamide (2o). The general procedure was followed using 2-chloro-*N*-(6-methoxybenzo[*d*]thiazol-2-yl)acetamide (1.0 g, 3.9 mmol), sulfur (1.0 g, 31.3 mmol) in morpholine (1.3 mL) and DMF (10.0 mL). Workup afforded analytically pure compound as a yellow solid (0.9 g, 81%), mp 170 - 172 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.82 (s, 3H, CH_3), 7.08 (dd, 1H, *J* = 2.44, 8.85 Hz, Ar), 7.63 (d, 1H, *J* = 2.44 Hz, Ar), 7.71 (d, 1H, *J* = 8.85 Hz, Ar), (the signals of the $NHNH_2$ and NHCO groups were not observed in ^{1}H NMR). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 55.7 (CH_3), 104.9 (CH, Ar), 109.6 (C, Ar), 115.3 (CH, Ar), 121.7 (CH, Ar), 142.6 (C, Ar), 154.7 (C, Ar), 156.5 (C=O), 159.2 (C), 166.4 (C=S). IR (KBr): 3333, 3251, 3219 (NH), 2963, 2931, 2827 (CH), 1667 (C=O), 1610, 1552, 1485, 1263, 1225, 1135, 1052, 1025, 832, 718 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{10}H_{10}N_4O_2S_2Na$ 305.0135; Found 305.0130.

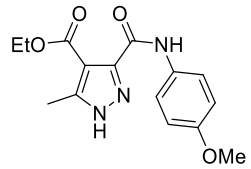


Ethyl (2-hydrazinyl-2-thioxoacetyl)leucinate (2p). The general procedure was followed using ethyl (2-chloroacetyl)leucinate (1.0 g, 4.2 mmol), sulfur (1.0 g, 31.3 mmol) in morpholine (1.3 mL) and DMF (10.0 mL). Workup afforded analytically pure compound as a yellow solid (0.4 g, 36%), mp 95 - 97 ^{o}C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.92 (d, 6H, J = 7.33 Hz, 2 × CH_3), 1.26 (t, 3H, J = 7.33 Hz, CH_3), 1.36-1.51 (m, 1H, CH), 4.04 (q, 2H, J = 7.33 Hz, CH_2), 4.50-4.57 (m, 2H, CH_2), 5.10-5.28 (m, 1H, CH), 8.45 (br.s, 1H, NH), (the signals of the $NHNH_2$ group was not observed in ^{1}H NMR). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 16.9 (CH_3), 22.9 (CH_3), 23.2 (CH_3), 29.6 (CH), 48.3 (CH_2), 50.5 (CH), 54.9 (CH_2), 167.8 (C=O), 173.3 (C=O), 199.3 (C=S). IR (KBr): 3261 (NH), 2958, 2871 (CH), 1663 (C=O), 1655 (C=O), 1523, 1437, 1368, 1203, 1166, 1055, 910, 821 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{10}H_{20}N_3O_3S$ 262.1219; Found 262.1212.

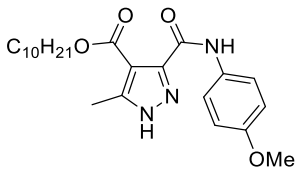
III. General procedure for the synthesis of pyrazoles



Oxamic acid thiohydrazide (1.0 mmol) was added to a solution of the 1,3-dicarbonyl compound (1.3 mmol) and *p*-toluenesulfonic acid monohydrate (22 mg, 0.1 mmol, 10 mol %) in ethanol (5 mL). The reaction mixture was stored at 25 °C for 30-60 min until the complete conversion of oxamic acid thiohydrazide. Next iodine (254 mg, 1.0 mmol) was added and reaction mixture was stored 3 h at 40 °C until the complete conversion of the hydrozone (TLC monitoring). The resulted mixture was cooled to room temperature, solvent was removed under reduced pressure and product was isolated by column chromatography using CH_2Cl_2 /MeOH.

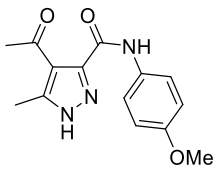


Ethyl 3-((4-methoxyphenyl)carbamoyl)-5-methyl-1*H*-pyrazole-4-carboxylate (3a). Pale yellow solid (282 mg, 83%); isolated by column chromatography (eluent CH_2Cl_2 / MeOH, 25:1), R_f = 0.15 (CH_2Cl_2 / MeOH, 50:1), mp 216 - 218 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.24 (t, 3H, *J* = 7.32 Hz, CH_3), 2.47 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 4.25 (q, 2H, *J* = 7.32 Hz, CH_2), 6.94 (d, 2H, *J* = 8.80 Hz, Ar), 7.64 (d, 2H, *J* = 8.80 Hz, Ar), 10.52 (br. s, 1H, NH) (a signal of the NH group was not observed in ^{1}H NMR spectra). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 11.9 (CH_3), 14.2 (CH_3), 55.4 (OCH_3), 60.3 (CH_2), 108.7 ($C_{Pyrazole}$), 114.2 (2 × CH, Ar), 121.3 (2 × CH, Ar), 132.1 (C, Ar), 143.0 ($C_{Pyrazole}$), 145.9 ($C_{Pyrazole}$), 155.8 (C, Ar), 159.9 (C=O), 163.9 (C=O). IR (KBr): 3141 (NH), 2854, 2836 (CH), 1676 (C=O), 1627 (C=O), 1569, 1511, 1300, 1246, 1140, 1040, 831 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{18}N_3O_4$ 304.1287; Found 304.1292.

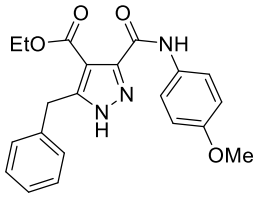


Decyl 3-((4-methoxyphenyl)carbamoyl)-5-methyl-1*H*-pyrazole-4-carboxylate (3b). Pale yellow solid (198 mg, 46%); isolated by column chromatography (eluent CH_2Cl_2 / MeOH, 75:1), R_f = 0.25 (CH_2Cl_2 / MeOH, 25:1), mp 147 - 149 °C. ^{1}H NMR (DMSO-d_6, 300 MHz, mixture of two isomers **A**/**B**, 90:10): isomer **A** δ 0.87 (t, 3H, *J* = 6.60 Hz, CH_3), 1.15-1.33 (m, 14H, CH_2 + CH_2 + CH_2 + CH_2 + CH_2 + CH_2 + CH_2), 1.45-1.56 (m, 2H, CH_2), 2.47 (s, 3H, CH_3), 3.75 (s, 3H, OCH_3), 4.10 (t, 2H, *J* = 6.60 Hz, CH_2), 6.91 (d, 2H, *J* = 8.80 Hz, Ar), 7.65 (d, 2H, *J* = 8.80 Hz, Ar), 10.31 (br. s, 1H, NH), 13.37 (br. s, 1H, NH); isomer **B** δ 0.87 (t, 3H, *J* = 6.60 Hz, CH_3), 1.15-1.33 (m, 14H, CH_2 + CH_2 + CH_2 + CH_2 + CH_2 + CH_2 + CH_2), 1.59-1.68 (m, 2H, *J* = 6.60 Hz, CH_2), 2.42 (s, 3H, CH_3), 3.75 (s, 3H, OCH_3), 4.25 (t, 2H, *J* = 6.60 Hz, CH_2), 6.98 (d, 2H, *J* = 8.80 Hz, Ar), 7.65 (d, 2H, *J* = 8.80 Hz, Ar), 11.43 (br. s, 1H, NH), 13.93 (br. s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 10.8 (CH_3), 14.0 (CH_3), 22.2 (CH_2), 25.7 (CH_2), 28.2 (CH_2), 28.8 (CH_2), 28.9 (CH_2), 29.0 (CH_2), 29.1 (CH_2). 31.4 (CH_2), 55.2 (OCH_3), 63.9 (CH_2), 108.3 ($C_{Pyrazole}$), 113.8 (2 × CH, Ar), 120.8 (2 × CH, Ar), 132.5 (C, Ar), 143.9 ($C_{Pyrazole}$), 149.2 ($C_{Pyrazole}$), 155.3 (C, Ar), 161.1 (C=O), 163.1 (C=O). IR (KBr): 3210 (NH), 2925, 2855 (CH), 1674 (C=O), 1629 (C=O), 1573, 1512, 1467, 1317, 1248, 1135, 1038,

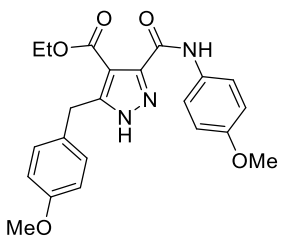
830, 758 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{34}N_3O_4$ 416.2544; Found 416.2538.



4-Acetyl-N-(4-methoxyphenyl)-5-methyl-1H-pyrazole-3-carboxamide (3c). The compound was obtained by a modified protocol: oxamic acid thiohydrazide (225 mg, 1 mmol) was added to a solution of the 3-bromopentane-2,4-dione (231 mg, 1.3 mmol) and *p*-toluenesulfonic acid monohydrate (22 mg, 0.1 mmol, 10 mol. %) in ethanol (5 mL). The reaction mixture was stored at 40 ºC for 3h until the complete conversion of the hydrozone (TLC monitoring). The resulted mixture was cooled to room temperature, solvent was removed under reduced pressure and residue was purified by column chromatography (eluent CH_2Cl_2 / MeOH, 75:1) to get 104 mg (34% yield) of pale yellow solid, R_f = 0.20 (CH_2Cl_2 / MeOH, 50:1), mp 207 - 209 ºC. ^{1}H NMR (DMSO-*d*$_6$, 300 MHz): δ 2.44 (s, 6H, CH_3 + CH_3) 3.76 (s, 3H, OCH_3), 6.93 (d, 2H, *J* = 8.80 Hz, Ar), 7.68 (d, 2H, *J* = 8.80 Hz, Ar), 10.43 (br. s, 1H, NH), 13.44 (br. s, 1H, NH). ^{13}C NMR (DMSO-*d*$_6$, 100 MHz): δ 11.1 (CH_3), 21.6 (CH_3), 46.5 (OCH_3), 105.2 (2 × CH, Ar), 107.7 ($C_{Pyrazole}$), 112.7 (2 × CH, Ar), 123.2 (C, Ar), 142.5 ($C_{Pyrazole}$), 146.9 ($C_{Pyrazole}$), 158.3 (C, Ar), 161.1 (C=O), 186.2 (C=O). IR (KBr): 3233 (NH), 3010, 2838 (CH), 1661 (C=O), 1624 (C=O), 1510, 1447, 1240, 1154, 1034, 829, 522 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{14}H_{15}N_3O_3Na$ 296.1006; Found 296.1011.

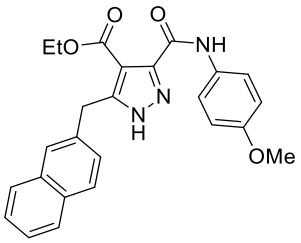


Ethyl 5-benzyl-3-((4-methoxyphenyl)carbamoyl)-1*H*-pyrazole-4-carboxylate (3d). Yellow solid (262 mg, 69%); isolated by column chromatography (eluent CH_2Cl_2 / MeOH, 100:1), R_f = 0.30 (CH_2Cl_2 / MeOH, 50:1), mp 172 - 174 ºC. ^{1}H NMR (DMSO-*d*$_6$, 300 MHz): δ 1.12 (t, 3H, *J* = 7.33 Hz, CH_3), 3.75 (s, 3H, OCH_3), 4.18 (q, 2H, *J* = 7.33 Hz, CH_2), 4.25 (s, 2H, CH_2), 6.94 (d, 2H, *J* = 8.80 Hz, Ar), 7.20-7.36 (m, 5H, Ph), 7.64 (d, 2H, *J* = 8.80 Hz, Ar), 10.30 (br. s, 1H, NH), 13.58 (br. s, 1H, NH). ^{13}C NMR (DMSO-*d*$_6$, 75 MHz): δ 13.9 (CH_3), 30.2 (CH_2), 55.2 (OCH_3), 59.8 (CH_2), 113.8 ($C_{Pyrazole}$), 113.9 ($C_{Pyrazole}$), 120.9 (2 × CH, Ar), 121.7 (CH, Ar), 126.5 (C, Ar), 128.3 (4 × CH, Ar), 128.5 (2 × CH, Ar), 132.3 (C, Ar), 145.9 ($C_{Pyrazole}$), 155.4 (C, Ar), 160.9 (C=O), 162.8 (C=O). IR (KBr): 3240 (NH), 2993, 2836 (CH), 1676 (C=O), 1630 (C=O), 1573, 1511, 1463, 1302, 1247, 1151, 1104, 1036, 1011, 834, 731 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{22}N_3O_4$ 380.1605; Found 380.1603.

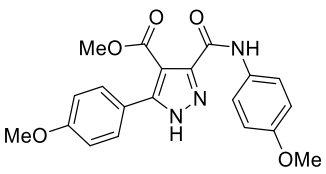


Ethyl 5-(4-methoxybenzyl)-3-((4-methoxyphenyl)carbamoyl)-1*H*-pyrazole-4-carboxylate (3e). Yellow solid (266 mg, 65%); isolated by column chromatography (eluent CH_2Cl_2 / MeOH, 75:1), R_f = 0.13 (CH_2Cl_2 / MeOH, 50:1), mp 153 - 155 ºC. ^{1}H NMR (DMSO-*d*$_6$, 300 MHz): δ 1.14 (t, 3H, *J* = 7.33 Hz, CH_3), 3.72 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 4.09-4.29 (m, 4H, CH_2 + CH_2), 6.88 (d, 2H, *J* = 8.80 Hz, Ar), 6.94 (d, 2H, *J* = 8.80 Hz, Ar), 7.20 (d, 2H, *J* = 8.80 Hz, Ar), 7.63 (d, 2H, *J* = 8.80 Hz, Ar), 10.29 (br. s, 1H, NH), 13.56 (br. s, 1H, NH). ^{13}C NMR (DMSO-*d*$_6$, 75 MHz): δ 13.9 (CH_3), 30.4 (CH_2), 55.1 (OCH_3), 55.2 (OCH_3), 60.0 (CH_2), 108.2 ($C_{Pyrazole}$), 113.7 ($C_{Pyrazole}$),

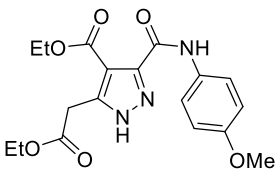
113.9 (4 × CH, Ar), 121.0 (2 × CH, Ar), 129.4 (2 × CH, Ar), 130.3 (C, Ar), 132.0 (C, Ar), 153.5 ($C_{Pyrazole}$), 155.5 (C, Ar), 157.9 (C, Ar), 161.6 (C=O), 163.4 (C=O). IR (KBr): 3219 (NH), 2996, 2835 (CH), 1685 (C=O), 1661 (C=O), 1573, 1511, 1465, 1303, 1243, 1177, 1106, 1034, 830, 755 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{24}N_3O_5$ 410.1710; Found 410.1705.



Ethyl 3-((4-methoxyphenyl)carbamoyl)-5-(naphthalen-2-ylmethyl)-1*H*-pyrazole-4-carboxylate (3f). Yellow solid (193 mg, 45%); isolated by column chromatography (eluent CH_2Cl_2 / MeOH, 100:1), R_f = 0.35 (CH_2Cl_2 / MeOH, 25:1), mp 182 - 183 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 0.96 (t, 3H, *J* = 7.33 Hz, CH_3), 3.75 (s, 3H, OCH_3), 4.11 (q, 2H, *J* = 7.33 Hz, CH_2), 4.71 (s, 2H, CH_2), 6.94 (d, 2H, *J* = 8.80 Hz, Ar), 7.18 (d, 1H, *J* = 6.87 Hz, Ar), 7.44 (dd, 1H, *J* = 7.33, 7.82 Hz, Ar), 7.55 (ddd, 1H, *J* = 1.47, 6.87, 7.33 Hz, Ar), 7.59 (ddd, 1H, *J* = 1.47, 6.87, 7.33 Hz, Ar), 7.65 (d, 2H, *J* = 8.80 Hz, Ar), 7.83 (d, 1H, *J* = 8.32 Hz, CH), 7.96 (dd, 1H, *J* = 1.47, 7.82 Hz, Ar), 8.19 (dd, 1H, *J* = 1.47, 8.32 Hz, CH), 10.50 (br. s, 1H, NH), 13.46 (br. s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 13.7 (CH_3), 55.2 (OCH_3), 60.2 (CH_2), 108.9 ($C_{Pyrazole}$), 113.9 (2 × CH, Ar), 121.1 (2 × CH, Ar), 122.6 (C, Ar), 123.7 (CH, Ar), 125.6 (CH, Ar), 125.8 (CH, Ar), 125.9 (CH, Ar), 126.4 (CH, Ar), 127.1 (CH, Ar), 128.6 (CH, Ar), 131.4 (C, Ar), 133.4 (C, Ar), 139.8 (C, Ar), 155.6 (C, Ar), (some signals were not clearly observed in ^{13}C NMR).* IR (KBr): 3203 (NH), 2996, 2831 (CH), 1676 (C=O), 1630 (C=O), 1573, 1511, 1462, 1307, 1248, 1156, 1106, 1041, 1010, 831, 790 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{25}H_{24}N_3O_4$ 430.1761; Found 430.1758.



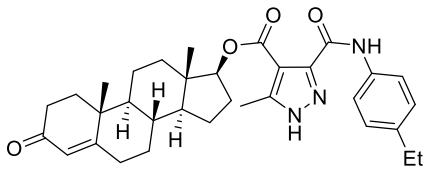
Methyl 5-(4-methoxyphenyl)-3-((4-methoxyphenyl)carbamoyl)-1*H*-pyrazole-4-carboxylate (3g). Pale yellow solid (190 mg, 50%); isolated by column chromatography (eluent CH_2Cl_2 / MeOH, 75:1), R_f = 0.18 (CH_2Cl_2 / MeOH, 25:1), mp 195 - 197 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.69 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 6.94 (d, 2H, *J* = 8.80 Hz, Ar), 7.08 (d, 2H, *J* = 8.80 Hz, Ar), 7.59 (d, 2H, *J* = 8.06 Hz, Ar), 7.68 (d, 2H, *J* = 8.06 Hz, Ar), 10.37 (br. s, 1H, NH) (a signal of the NH group was not observed in ^{1}H NMR spectra). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 51.8 (OCH_3), 55.3 (OCH_3), 55.4 (OCH_3), 109.1 ($C_{Pyrazole}$), 113.9 (2 × CH, Ar), 114.1 (2 × CH, Ar), 121.2 ($C_{Pyrazole}$), 121.4 (2 × CH, Ar), 122.7 (C, Ar), 129.8 (2 × CH, Ar), 131.9 (C, Ar), 155.4 ($C_{Pyrazole}$), 155.6 (C, Ar), 156.5 (C, Ar), 160.1 (C=O), 164.2 (C=O). IR (KBr): 3186 (NH), 3008, 2835 (CH), 1686 (C=O), 1649 (C=O), 1625, 1512, 1466, 1240, 1176, 1082, 1030, 976, 831, 756 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{20}H_{19}N_3O_5Na$ 404.1217; Found 404.1218.



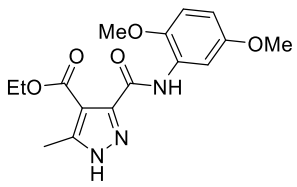
Ethyl 5-(2-ethoxy-2-oxoethyl)-3-((4-methoxyphenyl)carbamoyl)-1*H*-pyrazole-4-carboxylate (3j). Pale yellow solid (304 mg, 81%); isolated by column chromatography (eluent CH_2Cl_2 / MeOH, 50:1), R_f = 0.24 (CH_2Cl_2 / MeOH, 50:1), mp 170 - 172 °C. ^{1}H NMR (DMSO-d_6, 300

* Due to pyrazole isomerization for some signal peaks broadening in ^{13}C NMR spectra took place.

MHz): δ 1.21 (t, 6H, *J* = 6.60 Hz, CH_3 + CH_3), 3.76 (s, 3H, OCH_3), 3.94 (s, 2H, CH_2), 4.12 (q, 2H, *J* = 6.60 Hz, CH_2), 4.23 (q, 2H, *J* = 6.60 Hz, CH_2), 6.96 (d, 2H, *J* = 8.80 Hz, Ar), 7.64 (d, 2H, *J* = 8.80 Hz, Ar), 11.06 (br. s, 1H, NH), (a signal of the NH group was not observed in ^{1}H NMR spectra). ^{13}C NMR (DMSO-*d*$_6$, 75 MHz): δ 13.8 (CH_3), 14.0 (CH_3), 33.4 (CH_2), 55.2 (OCH_3), 60.6 (CH_2 + CH_2), 109.2 ($C_{Pyrazole}$), 114.1 (2 × CH, Ar), 121.1 (2 × CH, Ar), 131.6 (C, Ar), 147.9 ($C_{Pyrazole}$), 151.4 ($C_{Pyrazole}$), 155.7 (C, Ar), 160.0 (C=O), 163.8 (C=O), 169.3 (C=O). IR (KBr): 3196 (NH), 2982, 2936 (CH), 1743, 1681 (C=O), 1656 (C=O), 1568, 1510, 1461, 1301, 1246, 1183, 1106, 1030, 830 cm^{-1}. HRMS (ESI-TOF) m/z: [M + K]$^+$ Calcd for $C_{18}H_{21}N_3O_6K$ 414.1062; Found 414.1060.

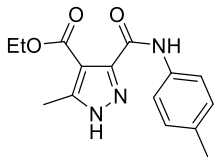


(10*R*,13*S*,17*S*)-10,13-Dimethyl-3-oxo-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[a]phenanthren-17-yl 3-((4-ethylphenyl)carbamoyl)-5-methyl-1*H*-pyrazole-4-carboxylate (3k). Colorless solid (435 mg, 80%); isolated by column chromatography (eluent CH_2Cl_2 / MeOH, 25:1), R_f = 0.15 (CH_2Cl_2 / MeOH, 50:1), mp 158 - 160 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.21 (t, 3H, *J* = 7.31 Hz, CH_3), 1.24 (s, 3H, 19-CH_3), 1.27 (s, 3H, 18-CH_3), 0.93-2.49 (m, 19H), 2.58 (s, 3H, CH_3), 2.64 (q, 2H, *J* = 7.31 Hz, CH_2), 4.83-5.01 (m, 1H, 17-CH), 5.76 (s, 1H, 4-H), 7.20 (d, 2H, *J* = 8.41 Hz, Ar), 7.66 (d, 2H, *J* = 8.41 Hz, Ar), 12.31 (br. s, 1H, NH), (a signal of the NH group was not observed in ^{1}H NMR spectra). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.6 (CH_3), 16.1 (18-CH_3), 16.4 (CH_3), 18.2 (19-CH_3), 21.3 (11-CH_2), 24.2 (15-CH_2), 28.4 (16-CH_2), 29.2 (CH_2), 32.2 (7-CH_2), 33.4 (6-CH_2), 34.7 (2-CH_2), 36.3 (8-CH), 36.5 (1-CH_2), 37.6 (12-CH_2), 39.4 (10-C), 43.5 (13-C), 50.9 (14-CH), 54.5 (9-CH), 85.4 (17-CH), 110.1 ($C_{Pyrazole}$), 121.3 (2 × CH, Ar), 124.8 (4-CH), 123.1 (2 × CH, Ar), 136.0 (C, Ar), 141.8 (C, Ar), 142.9 ($C_{Pyrazole}$), 152.3 ($C_{Pyrazole}$), 156.7 (C=O), 167.2 (C=O), 171.48 (5-C), 200.2 (3-C). IR (KBr): 3190 (NH), 2963, 2934 (CH), 1680 (C=O), 1677 (C=O), 1560, 1515, 1449, 1329, 1312, 1231, 1120, 1037, 834 cm^{-1}. HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{33}H_{41}N_3O_4Na$ 566.2989; Found 566.2986.

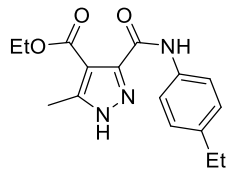


Ethyl 3-((2,5-dimethoxyphenyl)carbamoyl)-5-methyl-1*H*-pyrazole-4-carboxylate (3l). Yellow solid (43 mg, 13%); isolated by column chromatography (eluent CH_2Cl_2 / MeOH, 25:1), R_f = 0.14 (CH_2Cl_2 / MeOH, 25:1), mp 207 - 209 °C. ^{1}H NMR (DMSO-*d*$_6$, 300 MHz): δ 1.31 (t, 3H, *J* = 7.33 Hz, CH_3), 2.45 (s, 3H, CH_3), 3.73 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 4.31 (q, 2H, *J* = 7.33 Hz, CH_2), 6.68 (dd, 1H, *J* = 2.93, 8.80 Hz, Ar), 7.03 (d, 1H, *J* = 8.80 Hz, Ar), 8.00 (d, 1H, *J* = 2.93 Hz, Ar), 10.61 (br. s, 1H, NH), 13.50 (br. s, 1H, NH). ^{13}C NMR (DMSO-*d*$_6$, 75 MHz): δ 12.6 (CH_3), 13.9 (CH_3), 55.4 (OCH_3), 56.5 (OCH_3), 60.6 (CH_2), 107.4 (CH, Ar), 108.3 (CH, Ar), 112.0 (CH, Ar), 127.9 (C, Ar), 143.3 ($C_{Pyrazole}$), 153.0 (C, Ar), (some signals were not clearly observed in ^{13}C NMR).[†] IR (KBr): 3231 (NH), 2853, 2836 (CH), 1696 (C=O), 1652 (C=O), 1626, 1598, 1570, 1542, 1467, 1309, 1233, 1107, 1045, 869, 829 cm^{-1}. HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{16}H_{19}N_3O_5Na$ 356.1217; Found 356.1217.

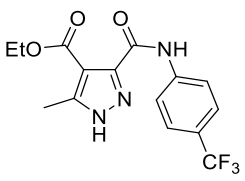
[†] Due to pyrazole isomerization for some signal peaks broadening in ^{13}C NMR spectra took place.



Ethyl 5-methyl-3-(*p*-tolylcarbamoyl)-1*H*-pyrazole-4-carboxylate (3m). Colorless solid (236 mg, 82%); isolated by column chromatography (eluent CH_2Cl_2 / MeOH, 25:1), R_f = 0.17 (CH_2Cl_2 / MeOH, 25:1), mp 280 - 281 °C. ^{1}H NMR (DMSO-d_6, 400 MHz, mixture of two isomers **A**/**B**, 80:20): isomer **A** δ 1.17 (t, 3H, *J* = 7.33 Hz, CH_3), 2.29 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 4.18 (q, 2H, *J* = 7.33 Hz, CH_2), 7.16 (d, 2H, *J* = 8.03 Hz, Ar), 7.60 (d, 2H, *J* = 8.03 Hz, Ar), 10.38 (br. s, 1H, NH), 13.40 (br. s, 1H, NH); isomer **B** δ 1.26 (t, 3H, *J* = 7.33 Hz, CH_3), 2.27 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 4.20 (q, 2H, *J* = 7.33 Hz, CH_2), 7.16 (d, 2H, *J* = 8.03 Hz, Ar), 7.60 (d, 2H, *J* = 8.03 Hz, Ar), 11.51 (br. s, 1H, NH), 13.95 (br. s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 10.8 (CH_3), 13.9 (CH_3), 20.5(CH_3), 59.7 (CH_2), 108.5 ($C_{Pyrazole}$), 119.5 (2 × CH, Ar), 129.1 (2 × CH, Ar), 132.3 (C, Ar), 136.6 (C, Ar) 143.9 ($C_{Pyrazole}$), 148.9 ($C_{Pyrazole}$), 161.3 (C=O), 163.1 (C=O). IR (KBr): 3139 (NH), 2870 (CH), 1673 (C=O), 1629 (C=O), 1562, 1515, 1486, 1340, 1141, 1039, 819, 767 cm^{-1}. HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{15}H_{17}N_3O_3Na$ 310.1162; Found 310.1162.

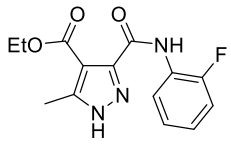


Ethyl 3-((4-ethylphenyl)carbamoyl)-5-methyl-1*H*-pyrazole-4-carboxylate (3n). Colorless solid (289 mg, 96%); isolated by column chromatography (eluent CH_2Cl_2 / MeOH, 25:1), R_f = 0.21 (CH_2Cl_2 / MeOH, 50:1), mp 232 - 233 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.04-1.36 (m, 6H, CH_3 + CH_3), 2.45 (s, 3H, CH_3), 2.54-2.68 (m, 2H, CH_2), 4.13-4.31 (m, 2H, CH_2), 7.18 (d, 2H, *J* = 7.30 Hz, Ar), 7.62 (d, 2H, *J* = 7.30 Hz, Ar), 10.67 (br. s, 1H, NH) (a signal of the NH group was not observed in ^{1}H NMR spectra). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 11.6 (CH_3), 13.9 (CH_3), 15.7 (CH_3), 27.6 (CH_2), 60.0 (CH_2), 108.5 ($C_{Pyrazole}$), 119.6 (2 × CH, Ar), 127.9 (2 × CH, Ar), 136.5 (C, Ar), 139.1 (C, Ar), (some signals were not clearly observed in ^{13}C NMR.‡ IR (KBr): 3152 (NH), 2966, 2873 (CH), 1678 (C=O), 1628 (C=O), 1561, 1514, 1487, 1339, 1140, 1038, 835 cm^{-1}. HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{16}H_{19}N_3O_3Na$ 324.1319; Found 324.1319.

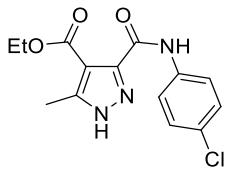


Ethyl 5-methyl-3-((4-(trifluoromethyl)phenyl)carbamoyl)-1*H*-pyrazole-4-carboxylate (3o). Yellow solid (259 mg, 76%); isolated by column chromatography (eluent CH_2Cl_2 / MeOH, 50:1), R_f = 0.13 (CH_2Cl_2 / MeOH, 50:1), mp 255 - 257 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.15 (t, 3H, *J* = 7.34 Hz, CH_3), 2.46 (s, 3H, CH_3), 4.18 (q, 2H, *J* = 7.34 Hz, CH_2), 7.72 (d, 2H, *J* = 8.80 Hz, Ar), 7.93 (d, 2H, *J* = 8.80 Hz, Ar), 10.96 (br. s, 1H, NH) (a signal of the NH group was not observed in ^{1}H NMR spectra). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 11.3 (CH_3), 13.9 (CH_3), 59.9 (CH_2), 108.7 ($C_{Pyrazole}$), 119.4 (2 × CH, Ar), 123.6 (q, CF_3, $J_{C,F}$ = 272.93 Hz), 125.7 (C, Ar), 126.6 (2 × CH, Ar), 128.5 (C, Ar), 142.5 ($C_{Pyrazole}$), 145.1 ($C_{Pyrazole}$), 161.2 (C=O), 163.2 (C=O). IR (KBr): 3150 (NH), 3052, 2988, 2956 (CH), 1682 (C=O), 1654 (C=O), 1633, 1611, 1566, 1330 (CF_3-Ar), 1218, 1159, 1112, 1068, 1038, 842 cm^{-1}. HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{15}H_{14}F_3N_3O_3Na$ 364.0871; Found 364.0871.

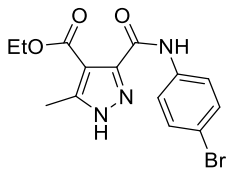
‡ Due to pyrazole isomerization for some signal peaks broadening in ^{13}C NMR spectra took place.



Ethyl 3-((2-fluorophenyl)carbamoyl)-5-methyl-1*H*-pyrazole-4-carboxylate (3p). Pale yellow solid (166 mg, 57%); isolated by column chromatography (eluent CH_2Cl_2 / MeOH, 50:1), R_f = 0.15 (CH_2Cl_2 / MeOH, 25:1), mp 255 - 256 ºC. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.31 (t, 3H, J = 7.34 Hz, CH_3), 2.48 (s, 3H, CH_3), 4.31 (q, 2H, J = 7.34 Hz, CH_2), 7.18-7.27 (m, 2H, Ar), 7.27-7.34 (m, 1H, Ar), 8.06-8.17 (m, 1H, Ar) (the signals of the NH groups were not observed in ^{1}H NMR spectra). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 11.0 (CH_3), 13.9 (CH_3), 60.1 (CH_2), 108.6 ($C_{Pyrazole}$), 115.4 (d, $J_{C,F}$ = 18.80 Hz, CH, Ar), 122.7 (CH, Ar), 124.3 (CH, Ar), 125.5 (d, $J_{C,F}$ = 7.74 Hz, CH, Ar), 125.8 (C, Ar), 144.3 ($C_{Pyrazole}$), 147.5 ($C_{Pyrazole}$), 153.8 (d, $J_{C,F}$ = 242.17 Hz, C-F, Ar), 160.5 (C=O), 163.6 (C=O). IR (KBr): 3145 (NH), 2958, 2870 (CH), 1683 (C=O), 1654 (C=O), 1622, 1561, 1491, 1457, 1341, 1226, 1140, 1038, 844, 751 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{14}H_{14}FN_3O_3Na$ 314.0911; Found 314.0914.

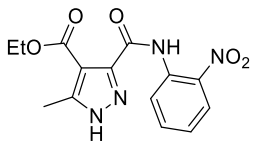


Ethyl 3-((4-chlorophenyl)carbamoyl)-5-methyl-1*H*-pyrazole-4-carboxylate (3q). Pale pink solid (283 mg, 92%); isolated by column chromatography (eluent CH_2Cl_2 / MeOH, 75:1), R_f = 0.10 (CH_2Cl_2 / MeOH, 50:1), mp 280 - 283 ºC. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.10-1.33 (m, 3H, CH_3), 2.47 (s, 3H, CH_3), 4.12-4.33 (m, 2H, CH_2), 7.40 (d, 2H, J = 7.32 Hz, Ar), 7.75 (d, 2H, J = 7.32 Hz, Ar), 10.70 (br. s, 1H, NH) (a signal of the NH group was not observed in ^{1}H NMR spectra). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 11.4 (CH_3), 13.9 (CH_3), 59.9 (CH_2), 108.6 ($C_{Pyrazole}$), 120.9 (2 × CH, Ar), 122.6 (C, Ar), 127.2 (C, Ar), 128.7 (2 × CH, Ar), 137.8 (C, Ar), (some signals were not clearly observed in ^{13}C NMR).[§] IR (KBr): 3144 (NH), 3038, 2984, 2952 (CH), 1677 (C=O), 1626 (C=O), 1561, 1494, 1340, 1141, 1039, 1013, 831 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{15}ClN_3O_3$ 308.0796; Found 308.0794.

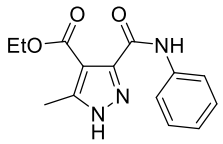


Ethyl 3-((4-bromophenyl)carbamoyl)-5-methyl-1*H*-pyrazole-4-carboxylate (3r). Colorless solid (292 mg, 83%); isolated by column chromatography (eluent CH_2Cl_2 / MeOH, 75:1), R_f = 0.11 (CH_2Cl_2 / MeOH, 50:1), mp 276 - 278 ºC. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.11-1.24 (m, 3H, CH_3), 2.47 (s, 3H, CH_3), 4.10-4.28 (m, 2H, CH_2), 7.54 (d, 2H, J = 8.80 Hz, Ar), 7.71 (d, 2H, J = 8.80 Hz, Ar), 10.58 (br. s, 1H, NH), 13.44 (br. s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 11.4 (CH_3), 13.9 (CH_3), 59.9 (CH_2), 108.7 ($C_{Pyrazole}$), 115.3 (C, Ar), 121.4 (2 × CH, Ar), 131.6 (2 × CH, Ar), 138.3 (C, Ar), 144.4 ($C_{Pyrazole}$), 147.9 ($C_{Pyrazole}$), 160.9 (C=O), 163.3 (C=O). IR (KBr): 3147 (NH), 3035, 2940, 2956 (CH), 1678 (CO), 1627 (CO), 1559, 1490, 1339, 1140, 1038, 1009, 828 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{15}BrN_3O_3$ 352.0291; Found 352.0291.

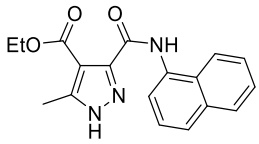
[§] Due to pyrazole isomerization for some signal peaks broadening in ^{13}C NMR spectra took place.



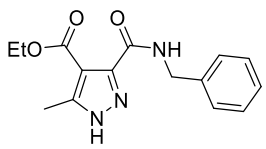
Ethyl 5-methyl-3-((2-nitrophenyl)carbamoyl)-1*H*-pyrazole-4-carboxylate (3s). Pale yellow solid (258 mg, 81%); isolated by column chromatography (eluent CH_2Cl_2 / MeOH, 75:1), R_f = 0.13 (CH_2Cl_2 / MeOH, 50:1), mp 188 - 190 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.33 (t, 3H, *J* = 7.33 Hz, CH_3), 2.45 (s, 3H, CH_3), 4.24 (q, 2H, *J* = 7.33 Hz, CH_2), 7.40 (dd, 1H, *J* = 7.33, 8.06 Hz, Ar), 7.79 (dd, 1H, *J* = 7.33, 8.06 Hz, Ar), 8.11 (d, 1H, *J* = 8.06 Hz, Ar), 8.11 (d, 1H, *J* = 8.06 Hz, Ar), 11.21 (br. s, 1H, NH) (a signal of the NH group was not observed in ^{1}H NMR spectra). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 11.1 (CH_3), 13.9 (CH_3), 60.2 (CH_2), 110.1 ($C_{Pyrazole}$), 123.9 (CH, Ar), 124.8 (CH, Ar), 125.3 (CH, Ar), 132.1 (C, Ar), 134.7 (CH, Ar), 140.3 (C, Ar), 145.1 ($C_{Pyrazole}$), 148.8 ($C_{Pyrazole}$), 159.7 (C=O), 163.2 (C=O). IR (KBr): 3312 (NH), 2980, 2939 (CH), 1728 (C=O), 1690 (C=O), 1506, 1341 (NO_2), 1290, 1103, 1035, 896, 745 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{15}N_4O_5$ 319.1037; Found 319.1038.



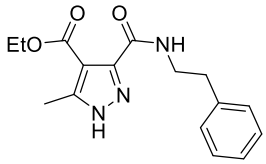
Ethyl 5-methyl-3-(phenylcarbamoyl)-1*H*-pyrazole-4-carboxylate (3t). Pale yellow solid (243 mg, 89%); isolated by column chromatography (eluent CH_2Cl_2 / MeOH, 100:1), R_f = 0.18 (CH_2Cl_2 / MeOH, 50:1), mp 252 - 253 °C. The spectral data and melting point matched that reported by Missio and coworkers.[15] ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.22 (t, 3H, *J* = 7.32 Hz, CH_3), 2.47 (s, 3H, CH_3), 4.24 (q, 2H, *J* = 7.32 Hz, CH_2), 7.11 (dd, 1H, *J* = 7.33 Hz, Ar), 7.36 (dd, 2H, *J* = 7.33 Hz, Ar), 7.72 (d, 2H, *J* = 7.33 Hz, Ar), 10.64 (br. s, 1H, NH) (a signal of the NH group was not observed in ^{1}H NMR spectra). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 11.6 (CH_3), 13.9 (CH_3), 59.9 (CH_2), 108.5 ($C_{Pyrazole}$), 119.4 (2 × CH, Ar), 121.0 (C, Ar), 123.6 (CH, Ar), 128.7 (2 × CH, Ar), 138.8 ($C_{Pyrazole}$), 145.4 ($C_{Pyrazole}$), 160.1 (C=O), 163.4 (C=O). IR (KBr): 3172 (NH), 3030, 2974 (CH), 1679 (C=O), 1654 (C=O), 1628, 1567, 1490, 1450, 1338, 1141, 1041, 768, 758 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + K]^+$ Calcd for $C_{14}H_{15}N_3O_3K$ 312.0745; Found 312.0748.



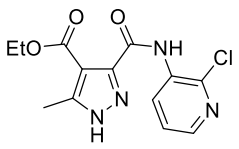
Ethyl 5-methyl-3-(naphthalen-1-ylcarbamoyl)-1*H*-pyrazole-4-carboxylate (3u). Colorless solid (307 mg, 95%); isolated by column chromatography (eluent CH_2Cl_2 / MeOH, 50:1), R_f = 0.18 (CH_2Cl_2 / MeOH, 50:1), mp 228 - 230 °C. ^{1}H NMR (DMSO-d_6, 300 MHz, mixture of two isomers **A**/**B**, 70:30): isomer **A** δ 1.25 (t, 3H, *J* = 7.33 Hz, CH_3), 2.48 (s, 3H, CH_3), 4.26 (q, 2H, *J* = 7.33 Hz, CH_2), 7.49-7.67 (m, 3H, Ar), 7.74-7.91 (m, 2H, Ar), 7.92-8.07 (m, 1H, Ar), 8.11-8.30 (m, 1H, Ar), 10.64 (br. s, 1H, NH), 13.47 (br. s, 1H, NH); isomer **B** δ 1.36 (t, 3H, *J* = 7.33 Hz, CH_3), 2.48 (s, 3H, CH_3), 4.40 (q, 2H, *J* = 7.33 Hz, CH_2), 7.49-7.67 (m, 3H, Ar), 7.74-7.91 (m, 2H, Ar), 7.92-8.07 (m, 1H, Ar), 8.11-8.30 (m, 1H, Ar), 11.93 (br. s, 1H, NH), 14.11 (br. s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 10.9 (CH_3), 14.1 (CH_3), 59.9 (CH_2), 108.7 ($C_{Pyrazole}$), 120.9 (C, Ar), 122.1 (CH, Ar), 123.0 (CH, Ar), 125.6 (2 × CH, Ar), 125.7 (CH, Ar), 125.9 (C, Ar), 126.1 (CH, Ar), 128.1 (CH, Ar), 133.8 (C, Ar), 144.1 ($C_{Pyrazole}$), 148.8 ($C_{Pyrazole}$), 161.9 (C=O), 163.5 (C=O). IR (KBr): 3156 (NH), 3041, 2942 (CH), 1680 (C=O), 1634 (C=O), 1561, 1491, 1327, 1257, 1140, 1119, 1035, 787, 764 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{17}N_3O_3Na$ 346.1162; Found 346.1165.



Ethyl 3-(benzylcarbamoyl)-5-methyl-1*H*-pyrazole-4-carboxylate (3v). Colorless solid (201 mg, 70%); isolated by column chromatography (eluent CH_2Cl_2 / MeOH, 50:1), R_f = 0.17 (CH_2Cl_2 / MeOH, 50:1), mp 158 - 160 °C. ^{1}H NMR (DMSO-d_6, 300 MHz, mixture of two isomers **A**/**B**, 70:30): isomer **A** δ 1.21 (t, 3H, *J* = 7.33 Hz, CH_3), 2.43 (s, 3H, CH_3), 4.16 (q, 2H, *J* = 7.33 Hz, CH_2), 4.44 (d, 2H, *J* = 5.86 Hz, CH_2), 7.22-7.41 (m, 5H, Ar), 8.95 (t, 1H, *J* = 5.86 Hz, NH), 13.31 (br. s, 1H, NH); isomer **B** δ 1.28 (t, 3H, *J* = 7.33 Hz, CH_3), 2.40 (s, 3H, CH_3), 4.26 (q, 2H, *J* = 7.33 Hz, CH_2), 4.56 (d, 2H, *J* = 5.86 Hz, CH_2), 7.22-7.41 (m, 5H, Ar), 8.95 (t, 1H, *J* = 5.86 Hz, NH), 10.05 (t, 1H, *J* = 5.86 Hz, NH), 13.89 (br. s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 10.8 (CH_3), 14.0 (CH_3), 42.2 (CH_2), 59.7 (CH_2), 108.6 ($C_{Pyrazole}$), 126.7 (CH, Ar), 127.2 (2 × CH, Ar), 128.2 (2 × CH, Ar), 139.4 (C, Ar), 143.7 ($C_{Pyrazole}$), 148.6 ($C_{Pyrazole}$), 162.6 (C=O) (some signals were not clearly observed in ^{13}C NMR).** IR (KBr): 3188 (NH), 2991, 2983 (CH), 1682 (C=O), 1649 (C=O), 1592, 1449, 1314, 1234, 1134, 1020, 981, 850, 737 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{18}N_3O_3$ 288.1343; Found 288.1342.



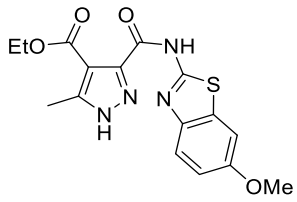
Ethyl 5-methyl-3-(phenethylcarbamoyl)-1*H*-pyrazole-4-carboxylate (3w). Pale yellow solid (214 mg, 71%); isolated by column chromatography (eluent CH_2Cl_2 / MeOH, 75:1), R_f = 0.20 (CH_2Cl_2 / MeOH, 50:1), mp 150 - 151 °C. ^{1}H NMR (DMSO-d_6, 300 MHz, mixture of two isomers **A**/**B**, 70:30): isomer **A** δ 1.25 (t, 3H, *J* = 7.33 Hz, CH_3), 2.42 (s, 3H, CH_3), 2.78-2.91 (m, 2H, CH_2), 3.43 (dt, 2H, *J* = 5.13, 7.96 Hz, CH_2), 4.18 (q, 2H, *J* = 7.33 Hz, CH_2), 7.18-7.36 (m, 5H, Ar), 8.53 (t, 1H, NH, *J* = 5.13 Hz), 13.27 (br. s, 1H, NH); isomer **B** δ 1.31 (t, 3H, *J* = 7.33 Hz, CH_3), 2.38 (s, 3H, CH_3), 2.78-2.91 (m, 2H, CH_2), 3.57 (dt, 2H, *J* = 5.13, 7.96 Hz, CH_2), 4.28 (q, 2H, *J* = 7.33 Hz, CH_2), 7.18-7.36 (m, 5H, Ar), 9.73 (t, 1H, NH, *J* = 5.13 Hz), 13.82 (br. s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 MHz, mixture of two isomers **A**/**B**): δ 10.8 (CH_3, isomers **A**,**B**), 14.1 (CH_3, isomer **A**), 14.8 (CH_3, isomer **B**), 34.8 (CH_2, isomer **B**), 34.9 (CH_2, isomer **A**), 40.5 (CH_2, isomers **A**,**B**), 59.7 (CH_2, isomer **A**), 60.9 (CH_2, isomer **B**), 108.6 ($C_{Pyrazole}$, isomer **A**), 112.2 ($C_{Pyrazole}$, isomer **B**), 126.1 (CH, Ar, isomers **A**,**B**), 128.4 (2 × CH, Ar, isomers **A**,**B**), 128.6 (2 × CH, Ar, isomers **A**,**B**), 139.1 (C, Ar, isomer **B**), 139.5 (C, Ar, isomer **A**), 143.7 ($C_{Pyrazole}$, isomers **A**,**B**), 148.6 ($C_{Pyrazole}$, isomer **A**), 151.1 ($C_{Pyrazole}$, isomer **B**), 157.7 (C=O, isomers **A**,**B**), 162.4 (C=O, isomer **A**), 163.3 (C=O, isomer **B**). IR (KBr): 3187 (NH), 3089, 2978 (CH), 1681 (C=O), 1646 (C=O), 1581, 1539, 1453, 1318, 1230, 1151, 1131, 1110, 1018, 853, 755, 703 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{19}N_3O_3Na$ 324.1319; Found 324.1318.



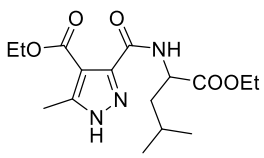
Ethyl 3-((2-chloropyridin-3-yl)carbamoyl)-5-methyl-1*H*-pyrazole-4-carboxylate (3x). Yellow solid (179 mg, 58%); isolated by column chromatography (eluent CH_2Cl_2 / MeOH, 100:1), R_f = 0.15 (CH_2Cl_2 / MeOH, 50:1), mp 145 - 146 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.29 (t, 3H, *J* = 7.33 Hz, CH_3), 2.47 (s, 3H, CH_3), 4.30 (q, 2H, *J* = 7.33 Hz, CH_2), 7.49 (dd, 1H, *J* = 6.81, 8.03 Hz, Ar), 8.23 (d, 1H, *J* = 6.81 Hz, Ar), 8.47 (d, 1H, *J* = 8.03 Hz, Ar), 10.54 (br. s, 1H, NH), 13.41 (br. s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 14.1 (CH_3), 60.7 (CH_2), 109.2

** Due to pyrazole isomerization for some signal peaks broadening in ^{13}C NMR spectra took place.

($C_{Pyrazole}$), 123.6 (CH, Ar), 131.8 (CH, Ar), 132.9 (C, Ar), 145.4 (CH, Ar), (some signals were not clearly observed in ^{13}C NMR).** IR (KBr): 3252 (NH), 2983, 2936 (CH), 1690 (C=O), 1654 (C=O), 1592, 1540, 1452, 1324, 1199, 1138, 1074, 1011, 795, 755 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{14}ClN_4O_3$ 309.0749; Found 309.0743.



Ethyl 3-((6-methoxybenzo[d]thiazol-2-yl)carbamoyl)-5-methyl-1*H*-pyrazole-4-carboxylate (3y). Yellow solid (162 mg, 45%); isolated by column chromatography (eluent CH_2Cl_2 / MeOH, 50:1), R_f = 0.17 (CH_2Cl_2 / MeOH, 50:1), mp 288 - 290 ºC. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.12-1.27 (m, 3H, CH_3), 2.47 (s, 3H, CH_3), 3.82 (s, 3H, OCH_3), 4.13-4.32 (m, 2H, CH_2), 7.05 (dd, 1H, *J* = 2.45, 8.81, Hz, Ar), 7.61 (d, 1H, *J* = 2.45 Hz, Ar), 7.68 (d, 1H, *J* = 8.81 Hz, Ar), 12.86 (br. s, 1H, NH), 13.67 (br. s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 13.8 (CH_3), 55.7 (OCH_3), 60.3 (CH_2), 104.8 (CH, Ar), 105.6 (C, Ar), 112.9 (C, Ar), 115.1 (CH, Ar), 117.9 (C, Ar), 121.4 (CH, Ar), 142.7 ($C_{Pyrazole}$), 155.9 (C=O), 156.4 (C=O), (some signals were not clearly observed in ^{13}C NMR).†† IR (KBr): 3386 (NH), 2934, 2934 (CH), 1685 (C=O), 1677 (C=O), 1606, 1546, 1469, 1320, 1264, 1225, 1120, 1028, 825, 807 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + K]^+$ Calcd for $C_{16}H_{16}N_4O_4SK$ 399.0524; Found 399.0529.

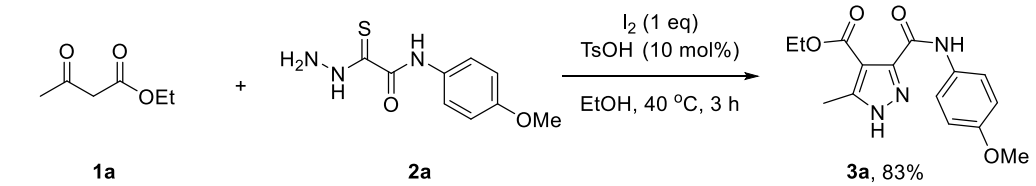


Ethyl 3-((1-ethoxy-4-methyl-1-oxopentan-2-yl)carbamoyl)-5-methyl-1*H*-pyrazole-4-carboxylate (3z). Yellow solid (85 mg, 25%); isolated by column chromatography (eluent CH_2Cl_2 / MeOH, 75:1), R_f = 0.11 (CH_2Cl_2 / MeOH, 50:1), mp 99 - 100 ºC. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.90 (d, 3H, *J* = 6.60 Hz, CH_3), 0.92 (d, 3H, *J* = 6.60 Hz, CH_3), 1.22 (t, 3H, *J* = 7.33 Hz, CH_3), 1.28 (t, 3H, *J* = 7.33 Hz, CH_3), 1.56-1.76 (m, 3H, CH + CH_2), 2.42 (s, 3H, CH_3), 4.13 (q, 2H, *J* = 7.33 Hz, CH_2), 4.24 (q, 2H, *J* = 7.33 Hz, CH_2), 4.44-4.53 (m, 1H, CH), 9.40 (br. s, 1H, NH) (a signal of the NH group was not observed in ^{1}H NMR spectra). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 12.4 (CH_3), 13.9 (CH_3), 14.0 (CH_3), 21.5 (CH_3), 22.7 (CH_3), 24.3 (CH), 43.8 (CH_2), 50.7 (CH), 60.4 (CH_2), 60.6 (CH_2), 108.6 ($C_{Pyrazole}$), 143.8 ($C_{Pyrazole}$), 149.5 ($C_{Pyrazole}$), 160.4 (C=O), 164.2 (C=O), 172.0 (C=O). IR (KBr): 3185 (NH), 2960, 2872 (CH), 1741 (C=O), 1685 (C=O), 1642 (C=O), 1578, 1492, 1323, 1247, 1137, 1040, 841, 774 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{26}N_3O_5$ 340.1867; Found 340.1865.

†† Due to pyrazole isomerization for some signal peaks broadening in ^{13}C NMR spectra took place.

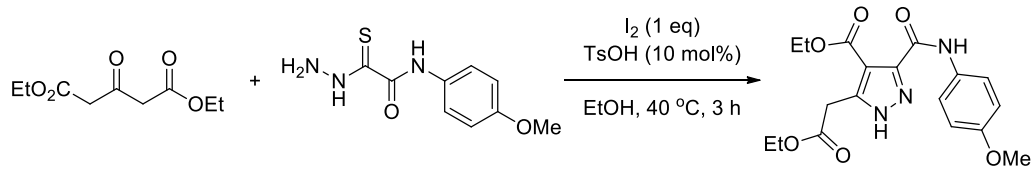
IV. Scaled-up experiments

Scaled-up synthesis of ethyl 3-((4-methoxyphenyl)carbamoyl)-5-methyl-1*H*-pyrazole-4-carboxylate (3a).



2-Hydrazinyl-*N*-(4-methoxyphenyl)-2-thioxoacetamide (**2a**) (1.0 g, 4.4 mmol) was added to a solution of ethyl acetoacetate (**1a**) (0.75 mL, 5.8 mmol) and *p*-toluenesulfonic acid monohydrate (84 mg, 0.44 mmol, 10 mol. %) in ethanol (22 mL). The reaction mixture was stored at 25 °C for 60 min until the complete conversion of oxamic acid thiohydrazide. Next iodine (1.1 g, 4.4 mmol) was added and reaction mixture was stored 3 h at 40 °C until the complete conversion of the hydrozone (TLC monitoring). The resulted mixture was cooled to room temperature, solvent was removed under reduced pressure and product was isolated by column chromatography (eluent CH_2Cl_2 / MeOH, 50:1) to get 1.1 g (83% yield) of pale yellow solid.

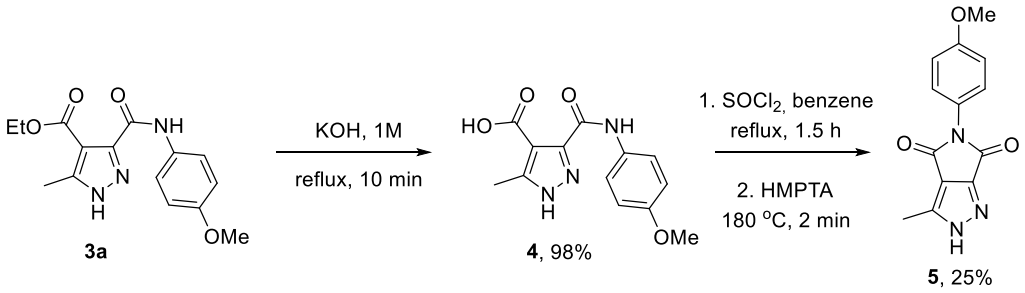
Scaled-up synthesis of ethyl 5-(2-ethoxy-2-oxoethyl)-3-((4-methoxyphenyl)carbamoyl)-1*H*-pyrazole-4-carboxylate (3j).



2-Hydrazinyl-*N*-(4-methoxyphenyl)-2-thioxoacetamide (**2a**) (0.50 g, 2.2 mmol) was added to a solution of diethyl 3-oxopentanedioate (**1j**) (0.48 mL, 2.7 mmol) and *p*-toluenesulfonic acid monohydrate (42 mg, 0.22 mmol, 10 mol. %) in ethanol (11 mL). The reaction mixture was stored at 25 °C for 60 min until the complete conversion of oxamic acid thiohydrazide. Next iodine (0.6 g, 2.2 mmol) was added and reaction mixture was stored 3 h at 40 °C until the complete conversion of the hydrozone (TLC monitoring). The resulted mixture was cooled to room temperature, solvent was removed under reduced pressure and product was isolated by column chromatography (eluent CH_2Cl_2 / MeOH, 50:1) to get 0.67 g (80% yield) of pale yellow solid.

V. Chemical transformations of 3,4-dicarbonyl-substituted pyrazoles

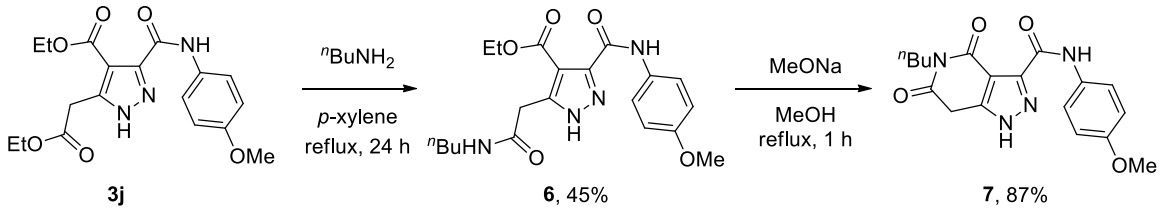
Synthesis of 5-(4-methoxyphenyl)-3-methylpyrrolo[3,4-c]pyrazole-4,6(2*H*,5*H*)-dione (5).



3-((4-Methoxyphenyl)carbamoyl)-5-methyl-1*H*-pyrazole-4-carboxylic acid (4). Potassium hydroxide (1M solution in water, 2 mL) was added with stirring to a solution of ethyl 3-((4-methoxyphenyl)carbamoyl)-5-methyl-1*H*-pyrazole-4-carboxylate (**3a**) (100 mg, 0.33 mmol) in methanol (2 mL). The reaction mixture was refluxed (oil bath) for 10 min and cooled to 25 °C. The mixture was acidified with HCl (2% water solution) to pH 1, diluted with water (10 mL) and extracted with EtOAc (3 × 10 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated to afford the 89 mg (98% yield) of pure product; colorless solid, R_f = 0.05 (petr. ether / EtOAc, 1:5), mp 228 - 230 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.36 (s, 3H, CH_3) 3.73 (s, 3H, OCH_3), 6.85 (d, 2H, *J* = 8.79 Hz, Ar), 7.69 (d, 2H, *J* = 8.79 Hz, Ar), 16.56 (br. s, 1H, OH) (the signals of the NH groups were not observed in ^{1}H NMR spectra). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 15.0 (CH_3), 55.1 (OCH_3), 113.7 (2 × CH, Ar), 116.3 ($C_{Pyrazole}$), 120.3 (2 × CH, Ar), 134.5 (C, Ar), 142.4 ($C_{Pyrazole}$), 149.5 ($C_{Pyrazole}$), 154.2 (C, Ar), 161.5 (C=O), 169.7 (C=O). IR (KBr): 3190 (NH), 2993, 2836 (CH), 1735 (CO), 1629 (CO), 1571, 1512, 1448, 1376, 1282, 1245, 1140, 1039, 882, 818 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + K]^+$ Calcd for $C_{13}H_{13}N_3O_4K$ 314.0538; Found 314.0538.

5-(4-Methoxyphenyl)-3-methylpyrrolo[3,4-c]pyrazole-4,6(2*H*,5*H*)-dione (5). Thionyl chloride (15 µL, 0.21 mmol) was added dropwise with stirring to a suspension of acid **4** (50 mg, 0.18 mmol) in benzene (1 mL) at 25 °C. The reaction mixture was refluxed for 1.5 h, cooled to 25 °C and solvent was removed under reduced pressure. The precipitate formed was redissolved in HMTPA (120 µL) and heated at 180 °C (oil bath) for 2 min. Resulting mixture was cooled to 25 °C and diluted with water (5 mL). The crude precipitate was filtered, washed with water (10 mL), and dried in air. The product was isolated by column chromatography (eluent CH_2Cl_2 / MeOH, 50:1) to get 12 mg (25% yield) of colorless solid, R_f = 0.25 (CH_2Cl_2 / MeOH, 25:1), mp 170 - 172 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.47 (s, 3H, CH_3), 3.82 (s, 3H, OCH_3), 7.05 (d, 2H, *J* = 8.06 Hz, Ar), 7.27 (d, 2H, *J* = 8.06 Hz, Ar), 10.49 (br. s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 11.4 (CH_3), 56.6 (OCH_3), 115.2 (2 × CH, Ar), 116.9 ($C_{Pyrazole}$), 126.4 (C, Ar), 130.3 (2 × CH, Ar), 148.7 ($C_{Pyrazole}$), 153.5 ($C_{Pyrazole}$), 159.9 (C, Ar), 162.7 (C=O), 163.0 (C=O). IR (KBr): 3432 (NH), 2889, 2839 (CH), 1735 (C=O), 1730 (C=O), 1617, 1509, 1439, 1361, 1302, 1252, 1164, 1045, 809 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{13}H_{11}N_3O_3Na$ 280.0693; Found 280.0694.

Synthesis of 5-butyl-*N*-(4-methoxyphenyl)-4,6-dioxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[4,3-c]pyridine-3-carboxamide (7).



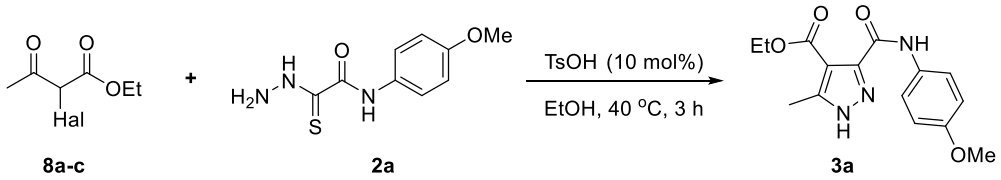
Ethyl 5-(2-(butylamino)-2-oxoethyl)-3-((4-methoxyphenyl)carbamoyl)-1*H*-pyrazole-4-carboxylate (6). A mixture of ethyl 5-(2-ethoxy-2-oxoethyl)-3-((4-methoxyphenyl)carbamoyl)-1*H*-pyrazole-4-carboxylate (**3j**) (158 mg, 0.42 mmol) and *n*-butylamine (1.0 ml, 10.1 mmol) in *p*-xylene (3.4 mL) was refluxed (silicon bath) for 12 h. Resulting mixture was stored at 25 °C for 12 h. The precipitate formed was filtered, washed with petr. ether (15 mL), and dried in air. The product was isolated by column chromatography (eluent CH_2Cl_2 / MeOH, 10:1) to get 76 mg (45% yield) of colorless solid, R_f = 0.24 (CH_2Cl_2 / MeOH, 25:1), mp 210 - 213 °C. ^{1}H NMR (DMSO-d_6, 300 MHz, mixture of two isomers **A**/**B**, 40:60): isomer **A** δ 0.91 (t, 3H, *J* = 7.33 Hz, CH_3), 1.16 (t, 3H, *J* = 6.60 Hz, CH_3), 1.21-1.36 (m, 2H, CH_2), 1.36-1.48 (m, 2H, CH_2), 3.00-3.15 (m, 2H, CH_2), 3.71 (s, 2H, CH_2), 3.79 (s, 3H, OCH_3), 4.26 (q, 2H, *J* = 6.60 Hz, CH_2), 6.99 (d, 2H, *J* = 8.06 Hz, Ar), 7.64 (d, 2H, *J* = 8.06 Hz, Ar), 7.81 (t, 1H, *J* = 4.40 Hz, NH), 11.52 (br. s, 1H, NH), 14.08 (br. s, 1H, NH); isomer **B**: δ 0.91 (t, 3H, *J* = 7.33 Hz, CH_3), 1.16 (t, 3H, *J* = 6.60 Hz, CH_3), 1.21-1.36 (m, 2H, CH_2), 1.36-1.48 (m, 2H, CH_2), 3.00-3.15 (m, 2H, CH_2), 3.71 (s, 2H, CH_2), 3.77 (s, 3H, OCH_3), 4.16 (q, 2H, *J* = 6.60 Hz, CH_2), 6.92 (d, 2H, *J* = 8.06 Hz, Ar), 7.64 (d, 2H, *J* = 8.06 Hz, Ar), 8.04 (t, 1H, *J* = 4.40 Hz, NH), 10.35 (br. s, 1H, NH), 13.45 (br. s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 13.7 (CH_3), 14.0 (CH_3), 19.4 (CH_2), 31.2 (CH_2), 32.7 (CH_2), 38.4 (CH_2), 55.2 (OCH_3), 113.8 (2 × CH, Ar), 115.2 ($C_{Pyrazole}$), 120.9 ($C_{Pyrazole}$), 122.6 (2 × CH, Ar), 132.0 (C, Ar), 142.5 ($C_{Pyrazole}$), 143.4 ($C_{Pyrazole}$), 155.8 (C, Ar), 162.0 (C=O), 162.2 (C=O), 167.6 (C=O). IR (KBr): 3435 (NH), 3297 (NH), 2959, 2931, 2862, 2837 (CH), 1677 (C=O), 1655 (C=O), 1649 (C=O), 1561, 1543, 1511, 1460, 1369, 1301, 1243, 1156, 1108, 1040, 844, 827 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{27}N_4O_5$ 403.1976; Found 403.1974.

5-Butyl-*N*-(4-methoxyphenyl)-4,6-dioxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[4,3-c]pyridine-3-carboxamide (7). A mixture of compound **6** (24 mg, 0.06 mmol) and sodium methylate (7 mg, 0.13 mmol) in MeOH (2 mL) was refluxed (oil bath) for 1 h. Resulting mixture was cooled to 25 °C and acidified with HCl (2% water solution) to pH 7. The precipitate formed was filtered, washed with MeOH (5 mL), and dried in air to get to get 19 mg (87% yield) of colorless solid, R_f = 0.18 (CH_2Cl_2 / MeOH, 25:1), mp 223 - 225 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.93 (t, 3H, *J* = 7.33 Hz, CH_3), 1.28-1.42 (m, 2H, CH_2), 1.47-1.62 (m, 2H, CH_2), 3.41 (s, 2H, CH_2), 3.78 (s, 3H, OCH_3), 3.88 (q, 2H, *J* = 7.06 Hz, CH_2), 7.01 (d, 2H, *J* = 8.79 Hz, Ar), 7.67 (d, 2H, *J* = 8.79 Hz, Ar), 12.09 (br. s, 1H, NH), 14.66 (br. s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 14.3 (CH_3), 20.1 (CH_2), 30.0 (CH_2), 30.1 (CH_2), 30.2 (CH_2), 55.7 (OCH_3), 114.9 (2 × CH, Ar), 122.0 (2 × CH, Ar), 131.2 (C, Ar), 156.8 (C, Ar), (some signals were not clearly observed in ^{13}C NMR).‡‡ IR (KBr): 3190 (NH), 2959, 2907, 2873, 2837 (CH), 1714 (CO), 1678 (CO), 1633 (CO), 1564, 1511, 1384, 1333, 1284, 1247, 1173, 1111, 1035, 943, 828 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{21}N_4O_4$ 357.1557; Found 357.1555.

‡‡ Due to pyrazole isomerization for some signal peaks broadening in ^{13}C NMR spectra took place.

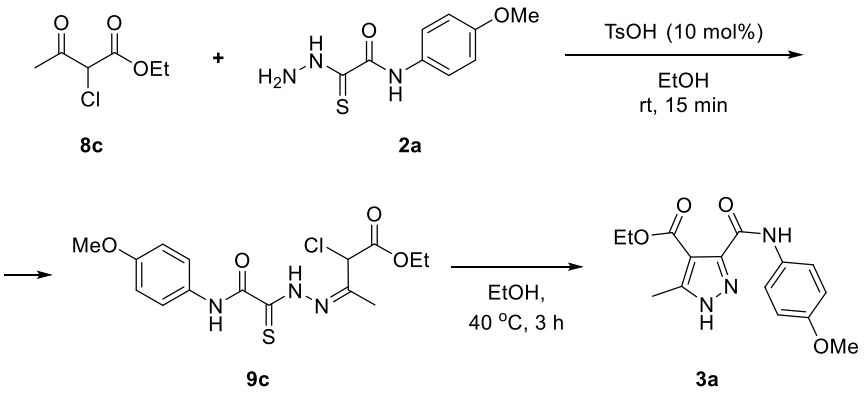
VI. Studies of the heterocyclization pathway

Reactions of 2-halo-3-oxobutanoates with 2-hydrazinyl-*N*-(4-methoxyphenyl)-2-thioxoacetamide.



A mixture of 2-hydrazinyl-*N*-(4-methoxyphenyl)-2-thioxoacetamide (**2a**) (68 mg, 0.30 mmol) and ethyl 2-halo-3-oxobutanoate **8** (0.30 mmol) and *p*-toluenesulfonic acid monohydrate (6 mg, 0.03 mmol, 10 mol. %) in ethanol (2 mL) was stored 3 h at 40 °C until the complete conversion of the hydrozone (TLC monitoring). The resulted mixture was cooled to room temperature, solvent was removed under reduced pressure and product was isolated by column chromatography (eluent CH_2Cl_2 / MeOH, 50:1) to get 75 mg (Hal = I, 83% yield), 59 mg (Hal = Br, 65% yield), 71 mg (Hal = Cl, 78% yield) of pale yellow solid.

Synthesis of ethyl 2-chloro-3-(2-(2-((4-methoxyphenyl)amino)-2-oxoethanethioyl)hydrazono)butanoate (9) and its reaction ability.



2-Hydrazinyl-*N*-(4-methoxyphenyl)-2-thioxoacetamide (**2a**) (68 mg, 0.30 mmol) was added to a solution of ethyl acetoacetate (**1a**) (50 mg, 0.30 mmol) and *p*-toluenesulfonic acid monohydrate (6 mg, 0.03 mmol, 10 mol. %) in ethanol (2 mL). The reaction mixture was stored at 25 °C for 15 min until the complete conversion of oxamic acid thiohydrazide. Solvent was removed under reduced pressure to get ^{1}H NMR and HRMS spectra (Figures S1,S2). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{19}ClN_3O_4S$ 372.0779; Found 372.0786.

Crude compound **9** was redissolved in ethanol (2 mL) and stored 3 h at 40 °C. The resulted mixture was cooled to room temperature, solvent was removed under reduced pressure and product **3a** was isolated by column chromatography (eluent CH_2Cl_2 / MeOH, 50:1) to get 65 mg (71% yield) of pale yellow solid.

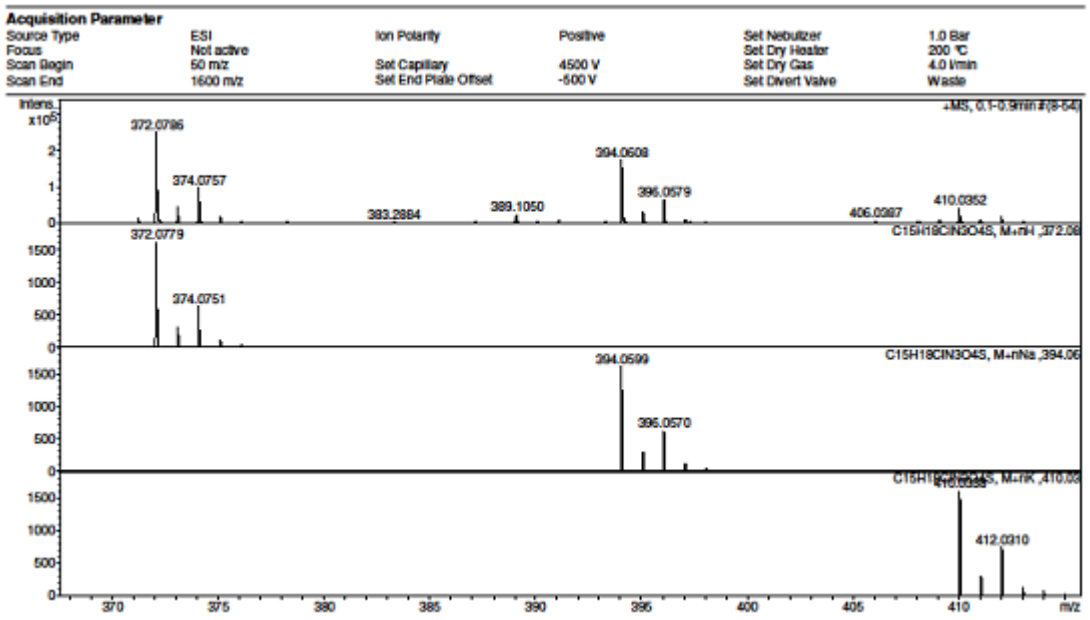


Figure S1. HRMS (ESI-TOF) spectrum of 2-chloro-3-(2-(2-((4-methoxyphenyl)amino)-2-oxoethanethioyl)hydrazono)butanoate (**9**)

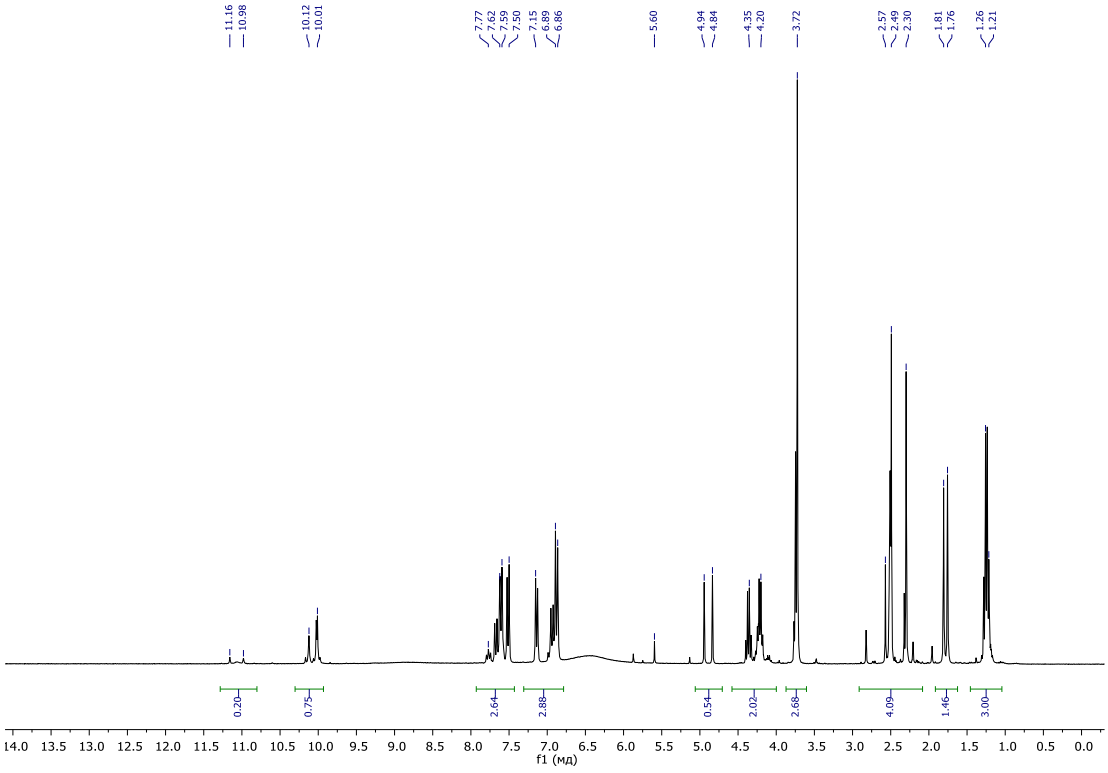


Figure S2. ^{1}H NMR (DMSO-d_6, 300 MHz) spectrum of 2-chloro-3-(2-(2-((4-methoxyphenyl)amino)-2-oxoethanethioyl)hydrazono)butanoate (**9**)

EI Mass spectrum of crude reaction mixture of **1** with hydrazide **2** contained moleqular ions peaks M^+ of product **4** (285 m/z) and S_8 (256 m/z) simultaneously (see below). Quantitative elimination of sulfur was proved by its isolation by column chromatography (petroleum ether-EtOAc, 10:1) as pale yellow solid well soluble in toluene, DCM and insoluble in acetone. Mass spectra (GC-MS) of isolated sample exhibited the S_8 characteristic fragmentation profile. Namely peaks 255.720 $(M)^+$, 223.780 $(M\text{-}S)^+$, 191.800 $(M\text{-}2S)^+$, 159.800 $(M\text{-}3S)^+$, 127.820 $(M\text{-}4S)^+$, 95.900 $(M\text{-}5S)^+$, 63.900 $(M\text{-}6S)^+$ were observed (Figure S3).

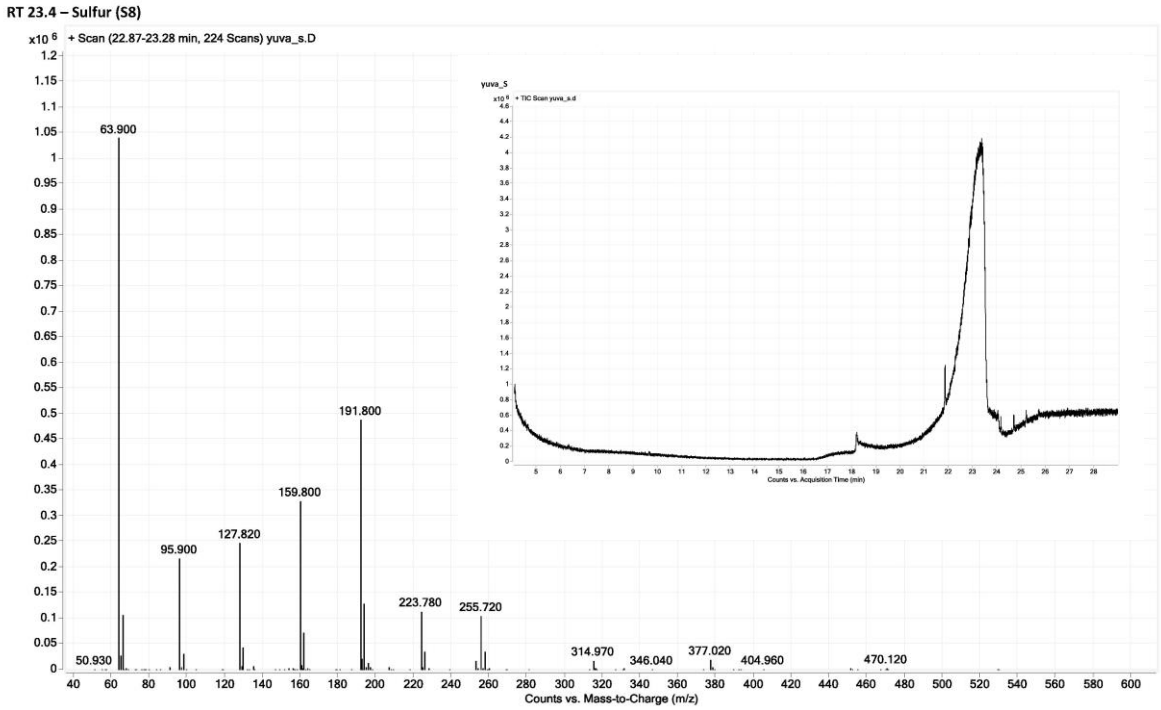


Figure S3. Representative GS-MS spectrum of sulfur isolated

Table S1. X-ray crystallographic data and refinement details for studied molecules

	3a	**3f**
CCDC number	1990863	1990862
Empirical formula	$C_{15}H_{17}N_3O_4$	$C_{25}H_{23}N_3O_4$
Formula weight	303.32	429.46
T, K	120	120
Crystal system	Monoclinic	Triclinic
Space group	$P2_1/n$	P-1
Z (Z')	4 (1)	2 (1)
a, Å	11.5210(8)	9.2276(6)
b, Å	7.7967(6)	10.5901(7)
c, Å	15.9176(11)	11.3733(7)
□, °	90	87.0120(10)
□, °	91.3708(14)	75.4310(10)
□, °	90	77.1710(10)
V, Å^3	1429.40(18)	1048.82(12)
d_{calc},gcm^{-3}	1.409	1.360
□, cm^{-1}	1.04	0.94
F(000)	640	452
2□$_{max}$, °	58	58
Reflections collected	16729	11114
Reflections unique (R_{int})	3809 (0.0213)	5579 (0.0210)
Reflections with I > 2σ(I)	3306	4459
Variables / restraints	211/0	299/0
R1	0.0369	0.0439
wR2	0.1011	0.1309
GOF	1.014	1.065
Largest difference in peak / hole (e/Å^3)	0.370/-0.215	0.423/-0.265

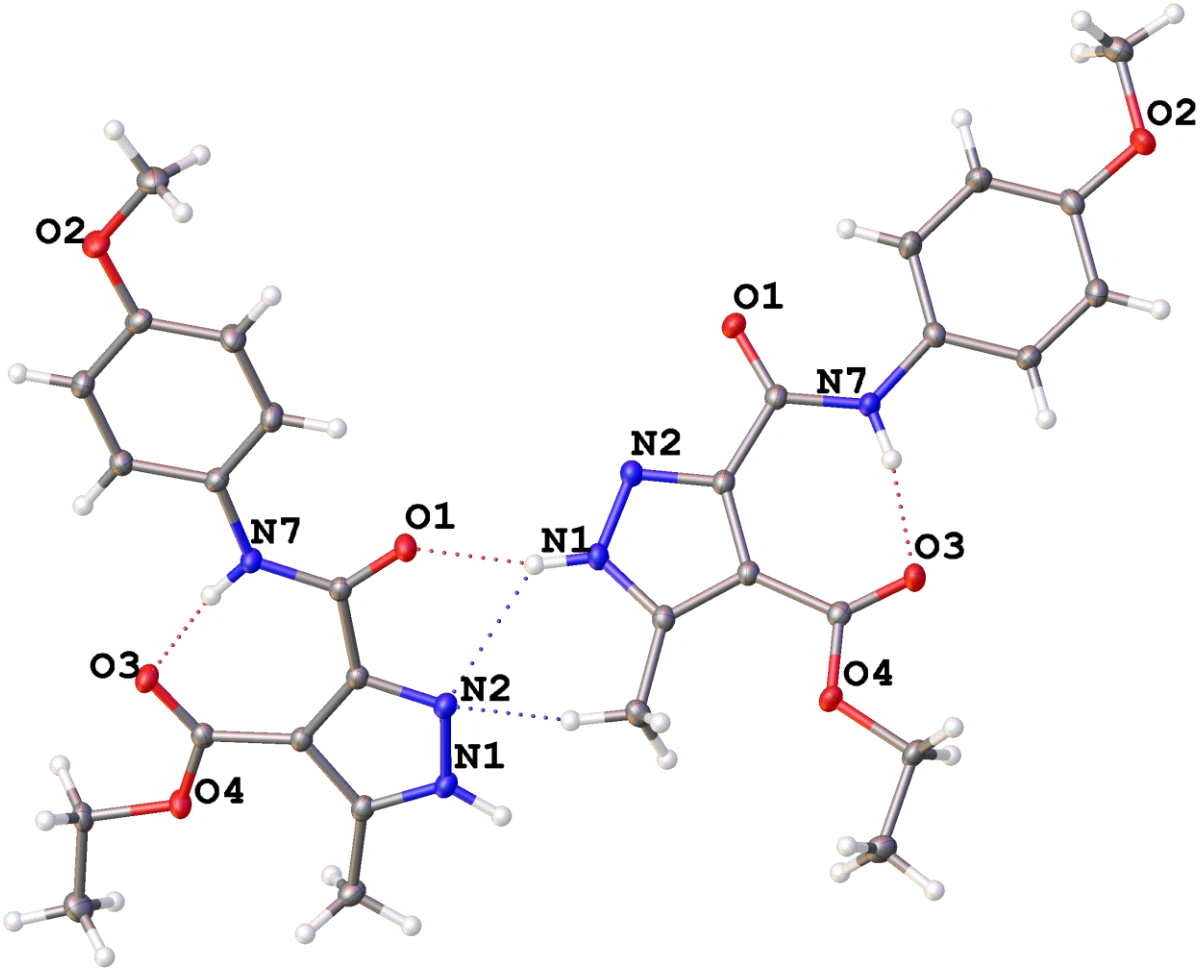


Figure S1. X-ray molecular structures of compound **3a** with displacement ellipsoids (p = 50%).

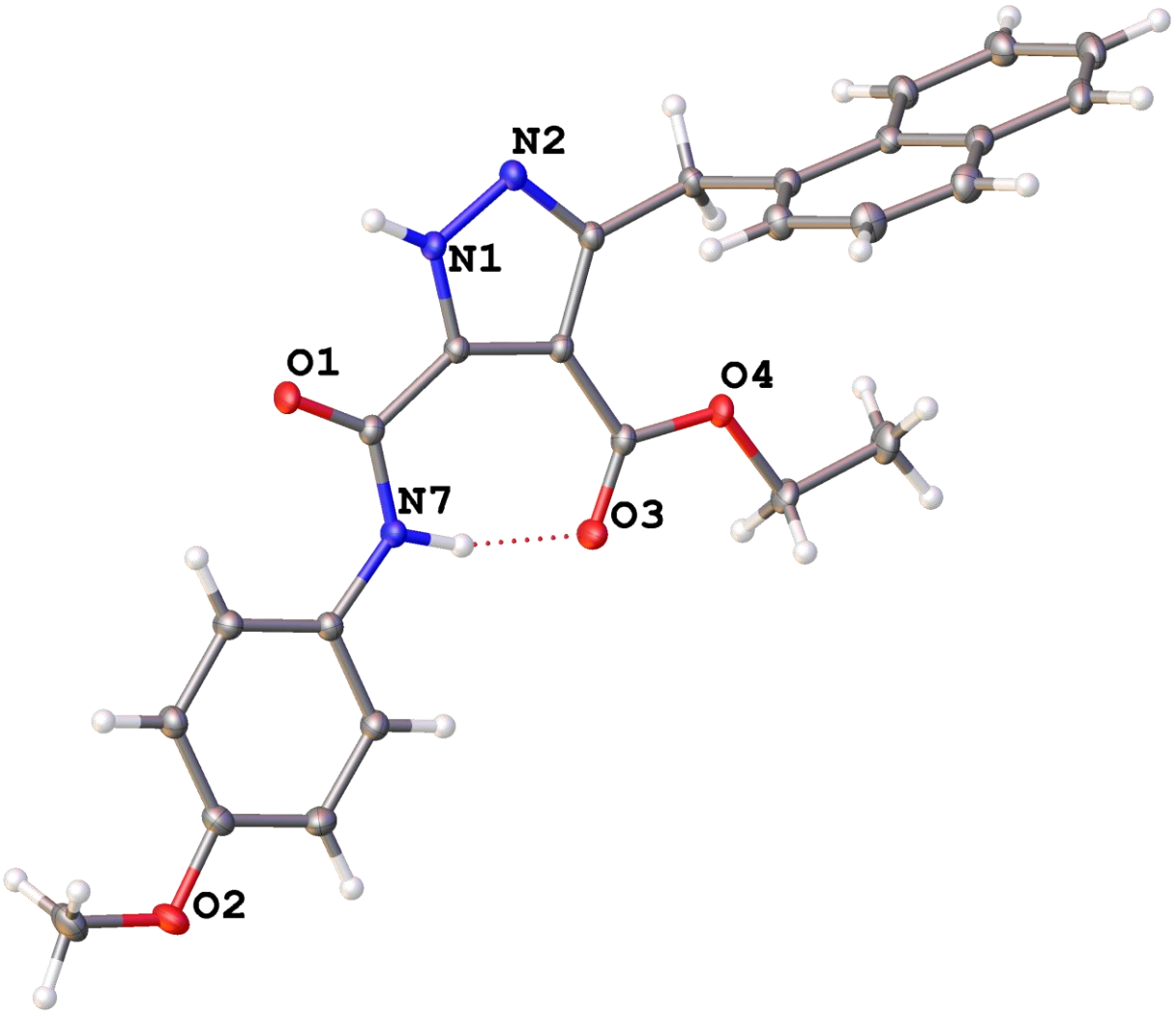


Figure S2. X-ray molecular structures of compound **3f** with displacement ellipsoids (p = 50%).

X-ray diffraction data for all studied compounds were collected using a SMART APEX II area-detector diffractometer (graphite monochromator, ω-scan technique) at the temperature of 120(2) K, using $Mo_{K\square}$ radiation (0.71073 Å). The intensity data were integrated by the SAINT program and corrected for absorption and decay by the multi-scan method (semi-empirical from equivalents) implemented in SADABS.[1] All structures were solved by direct methods using SHELXS[2] and were refined against F^2 using SHELXL-2017.[3] All non-hydrogen atoms were refined with anisotropic displacement parameters. All C-H hydrogen atoms were placed in ideal calculated positions and refined as riding atoms with relative isotropic displacement parameters taken as $U_{iso}(H)=1.5U_{eq}(C)$ for methyl H atoms and $U_{iso}(H)=1.2U_{eq}(C)$ otherwise. The hydrogen atoms of NH groups were located from the Fourier density synthesis. The SHELXTL program suite[4] was used for molecular graphics. Crystal data, data collection and structure refinement details are summarized in Table S1.

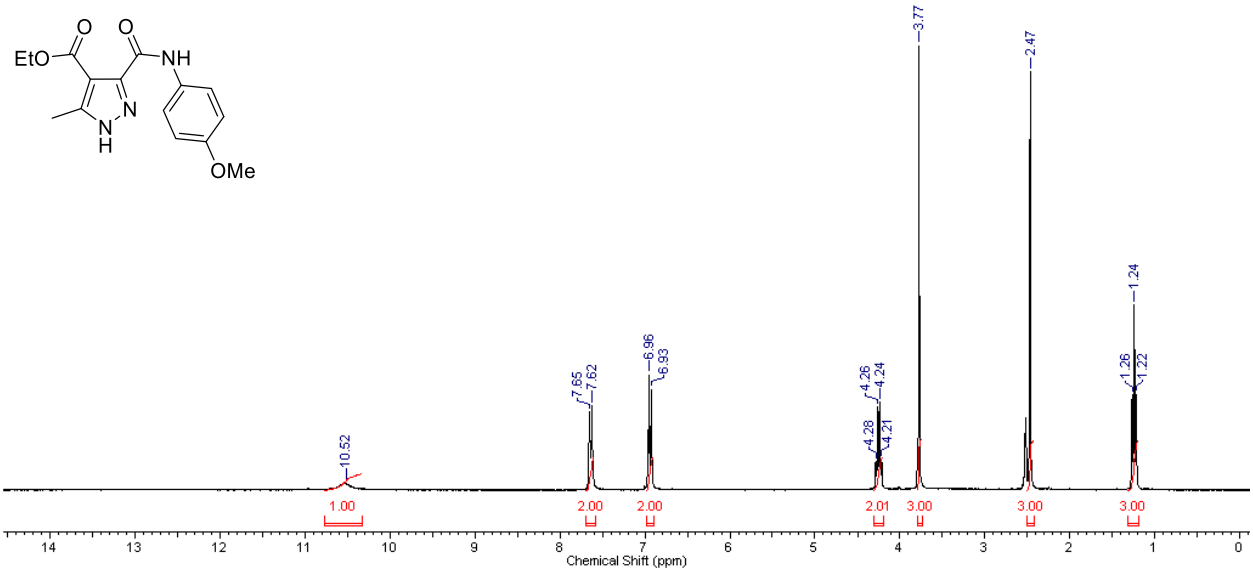
(1) *Bruker*. *APEXII*, Bruker AXS Inc.: Madison, Wisconsin, USA, 2008.

(2) Sheldrick, G. M. A short history of SHELX. *Acta Cryst., Sect. A* **2008**, *A64*, 112-122.

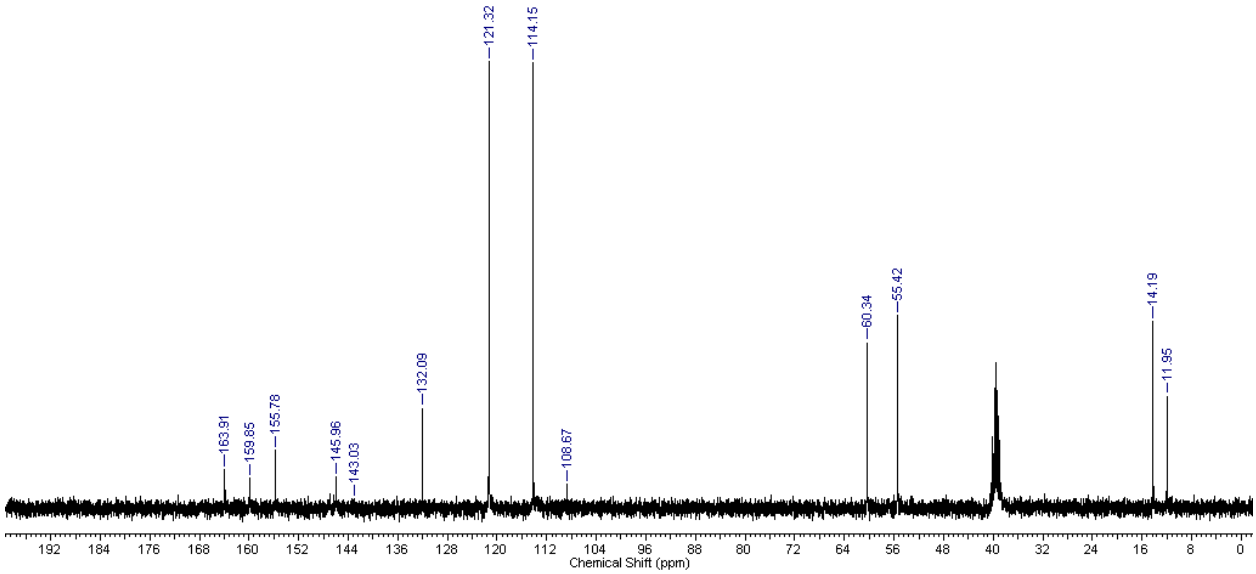
(3) Sheldrick, G. M. Crystal structure refinement with SHELXL. *Acta Cryst.* **2015**, *C71*, 3-8.

(4) Sheldrick, G. M. SHELXT - Integrated space-group and crystal-structure determination. *Acta Cryst.* **2015**, *A71*, 3-8.

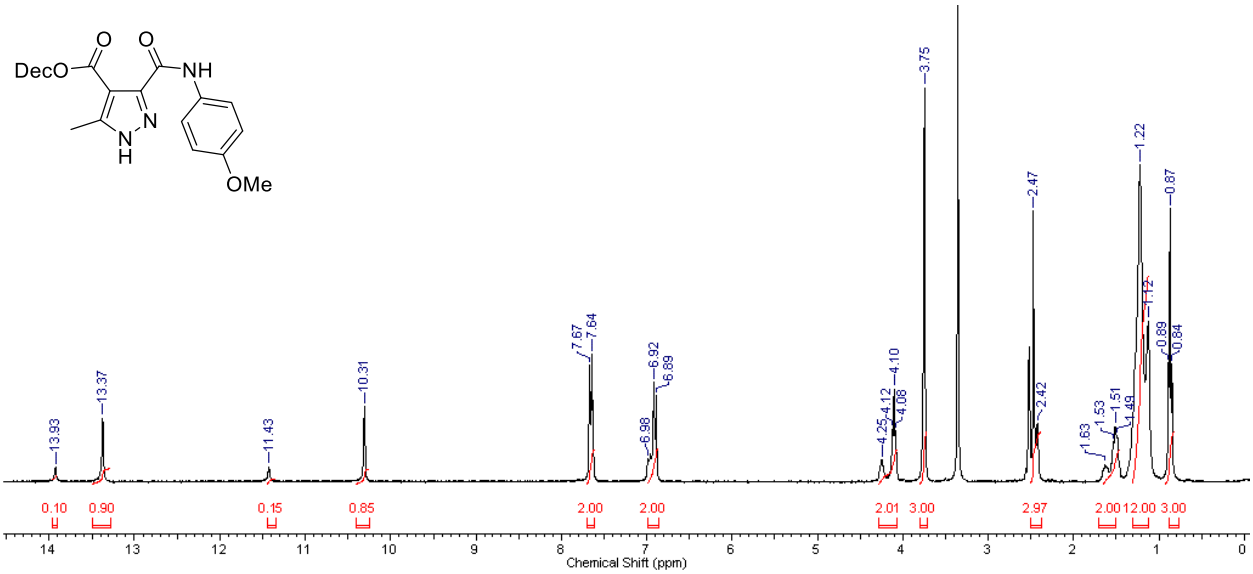
^{1}H NMR (DMSO-d_6, 300 MHz) spectrum of ethyl 3-((4-methoxyphenyl)carbamoyl)-5-methyl-1*H*-pyrazole-4-carboxylate (**3a**)



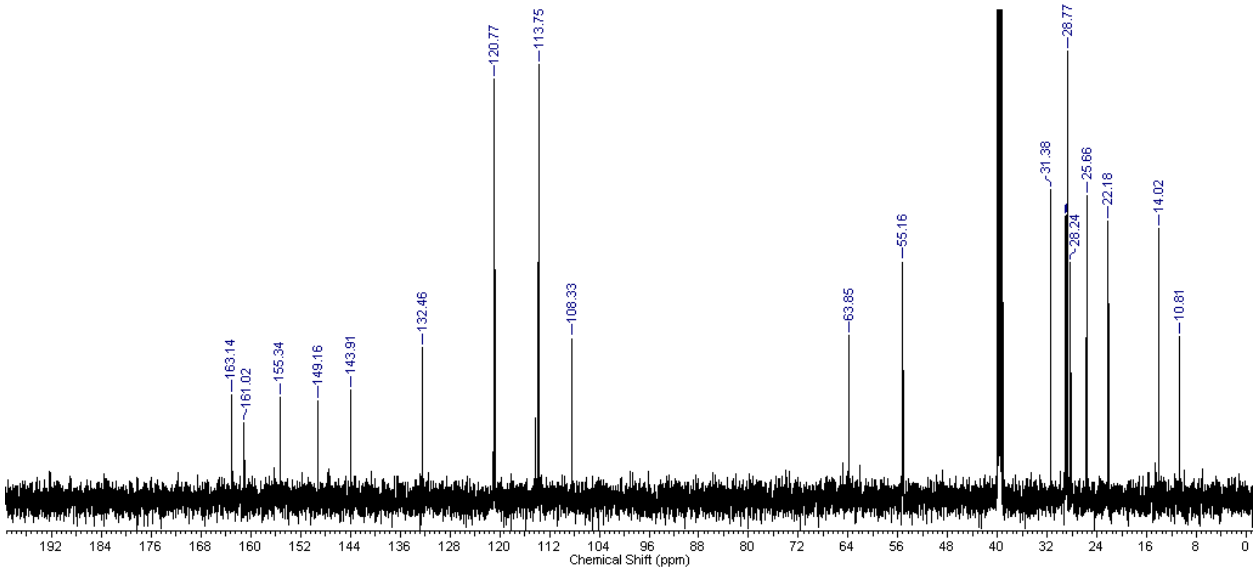
^{13}C NMR (DMSO-d_6, 75 MHz) spectrum of ethyl 3-((4-methoxyphenyl)carbamoyl)-5-methyl-1H-pyrazole-4-carboxylate (**3a**)



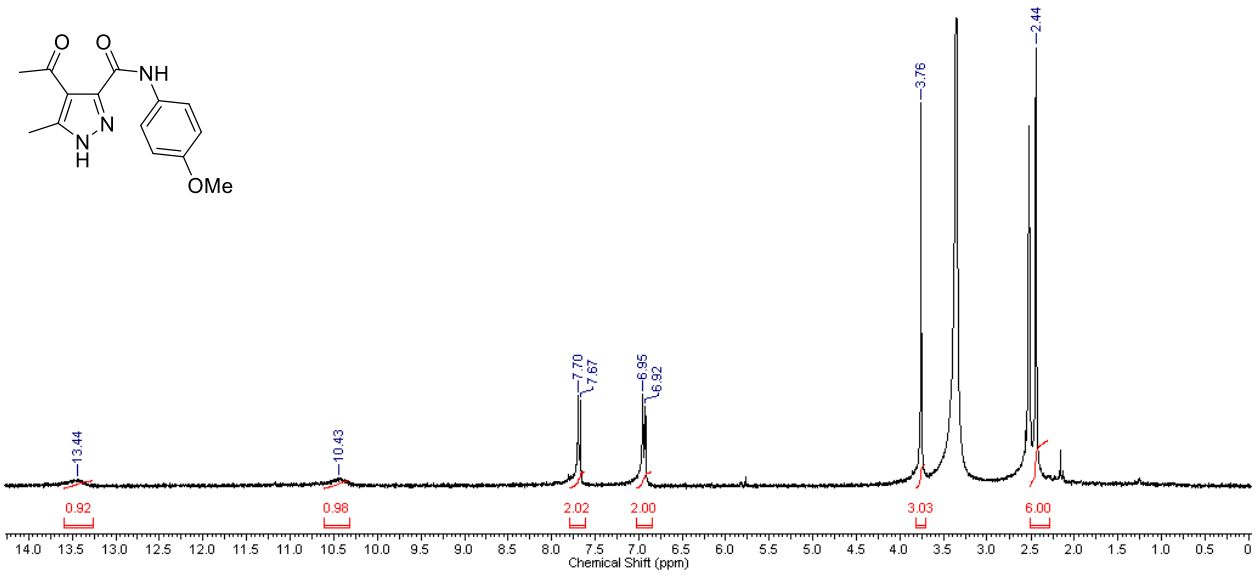
^{1}H NMR (DMSO-d_6, 300 MHz) spectrum of decyl 3-((4-methoxyphenyl)carbamoyl)-5-methyl-1*H*-pyrazole-4-carboxylate (**3b**)



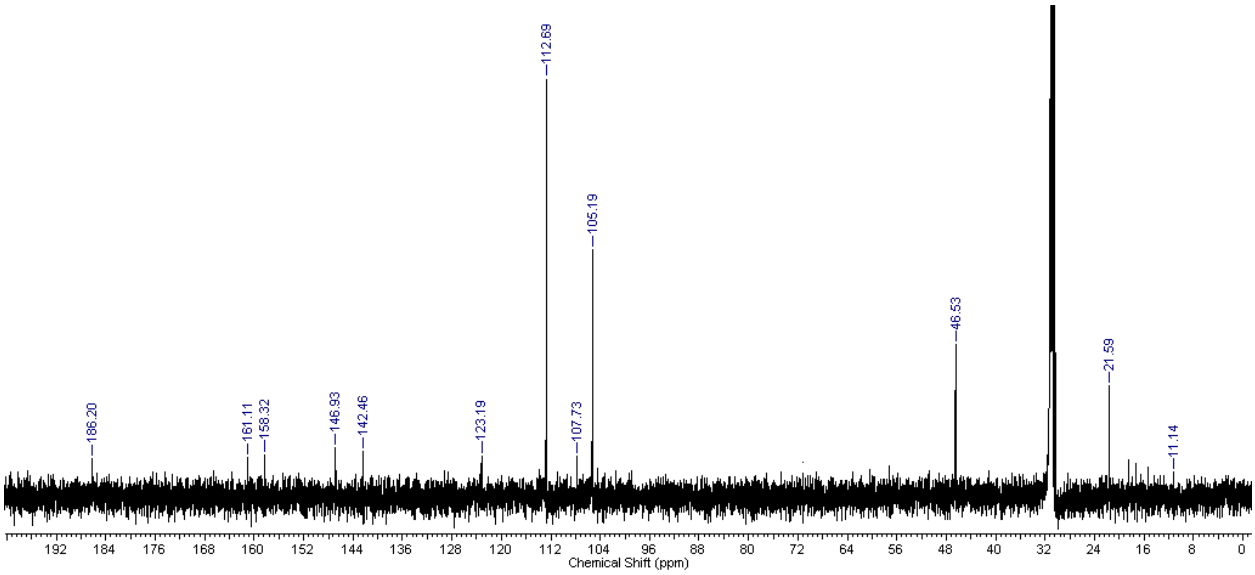
^{13}C NMR (DMSO-d_6, 75 MHz) spectrum of decyl 3-((4-methoxyphenyl)carbamoyl)-5-methyl-1*H*-pyrazole-4-carboxylate (**3b**)



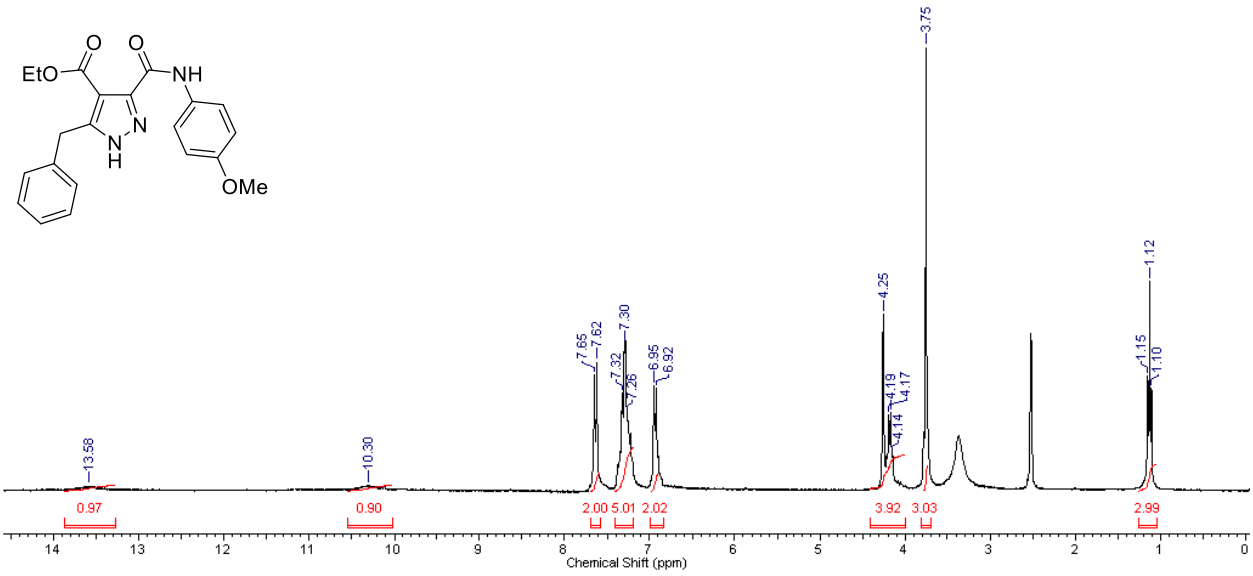
^{1}H NMR (DMSO-d_6, 300 MHz) spectrum of 4-acetyl-*N*-(4-methoxyphenyl)-5-methyl-1*H*-pyrazole-3-carboxamide (**3c**)



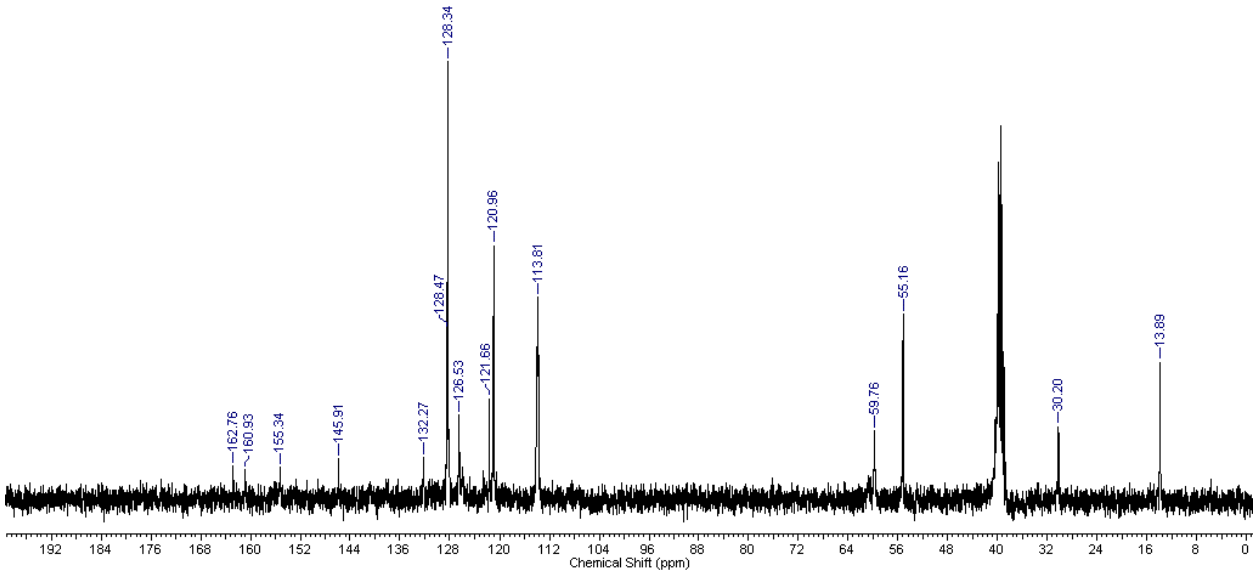
^{13}C NMR (DMSO-d_6, 75 MHz) spectrum of 4-acetyl-*N*-(4-methoxyphenyl)-5-methyl-1*H*-pyrazole-3-carboxamide (**3c**)



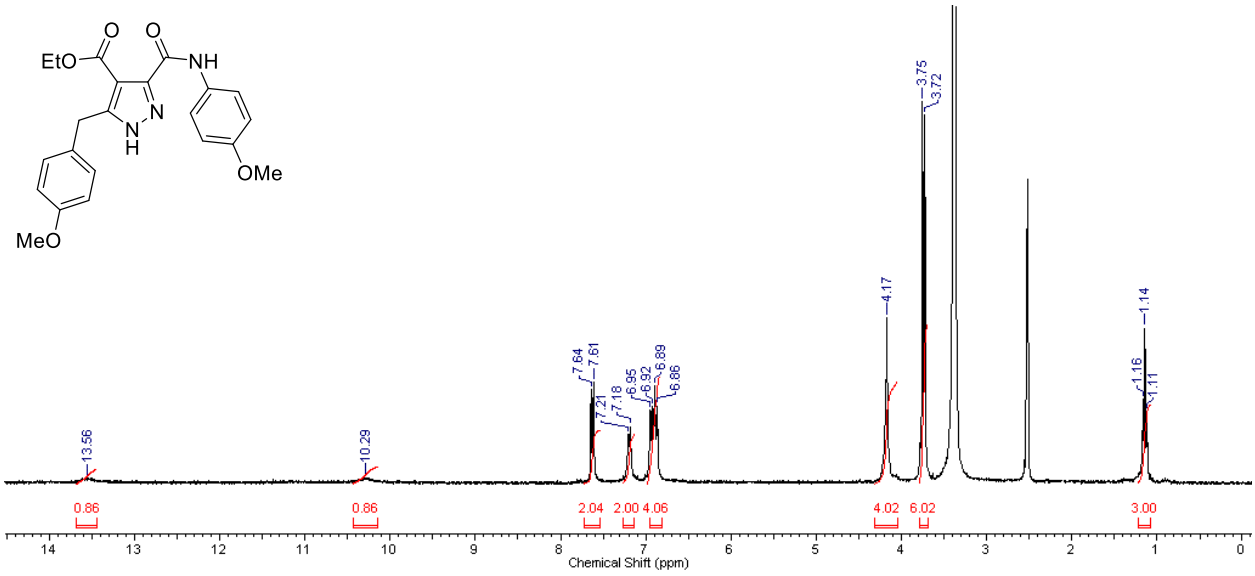
^{1}H NMR (DMSO-d_6, 300 MHz) spectrum of ethyl 5-benzyl-3-((4-methoxyphenyl)carbamoyl)-1*H*-pyrazole-4-carboxylate (**3d**)



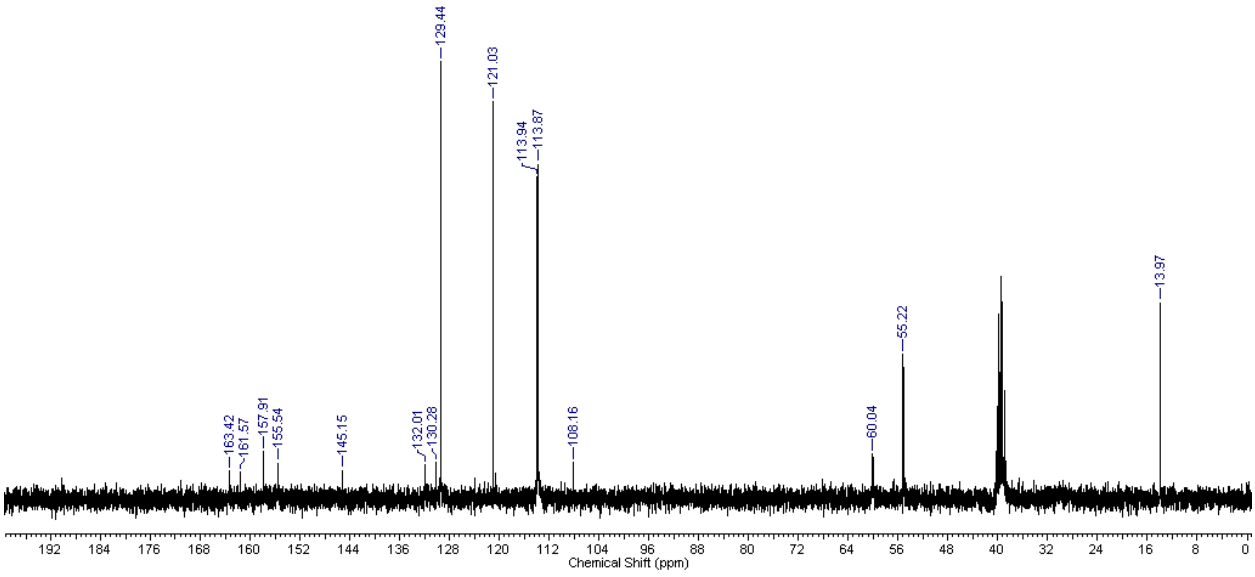
^{13}C NMR (DMSO-d_6, 75 MHz) spectrum of ethyl 5-benzyl-3-((4-methoxyphenyl)carbamoyl)-1H-pyrazole-4-carboxylate (**3d**)



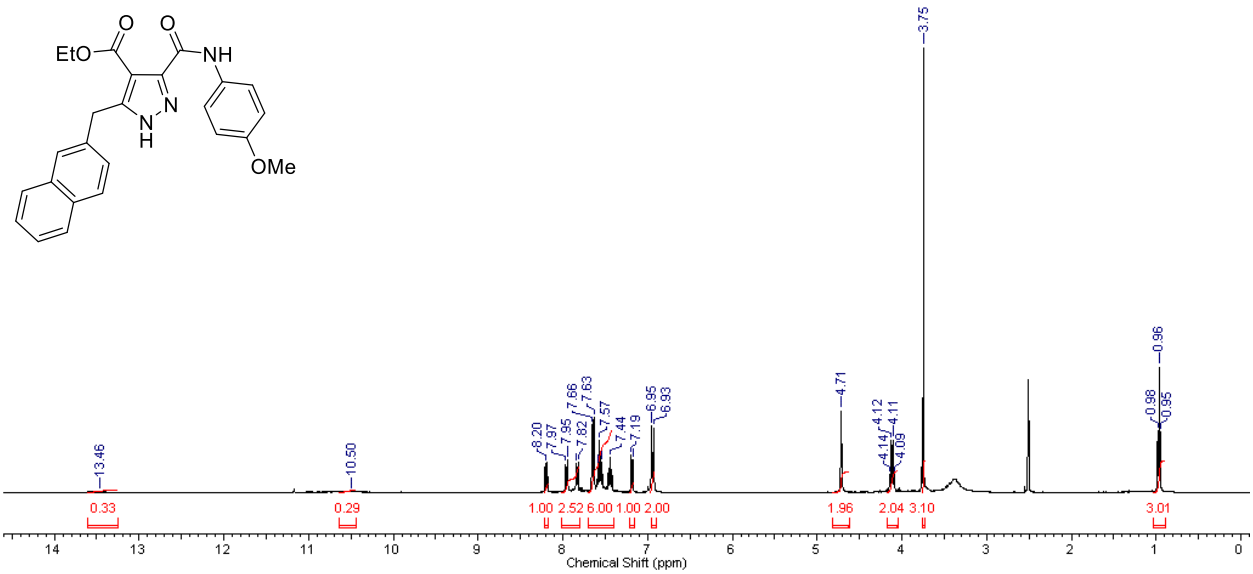
^{1}H NMR (DMSO-d_6, 300 MHz) spectrum of ethyl 5-(4-methoxybenzyl)-3-((4-methoxyphenyl)carbamoyl)-1*H*-pyrazole-4-carboxylate (**3e**)



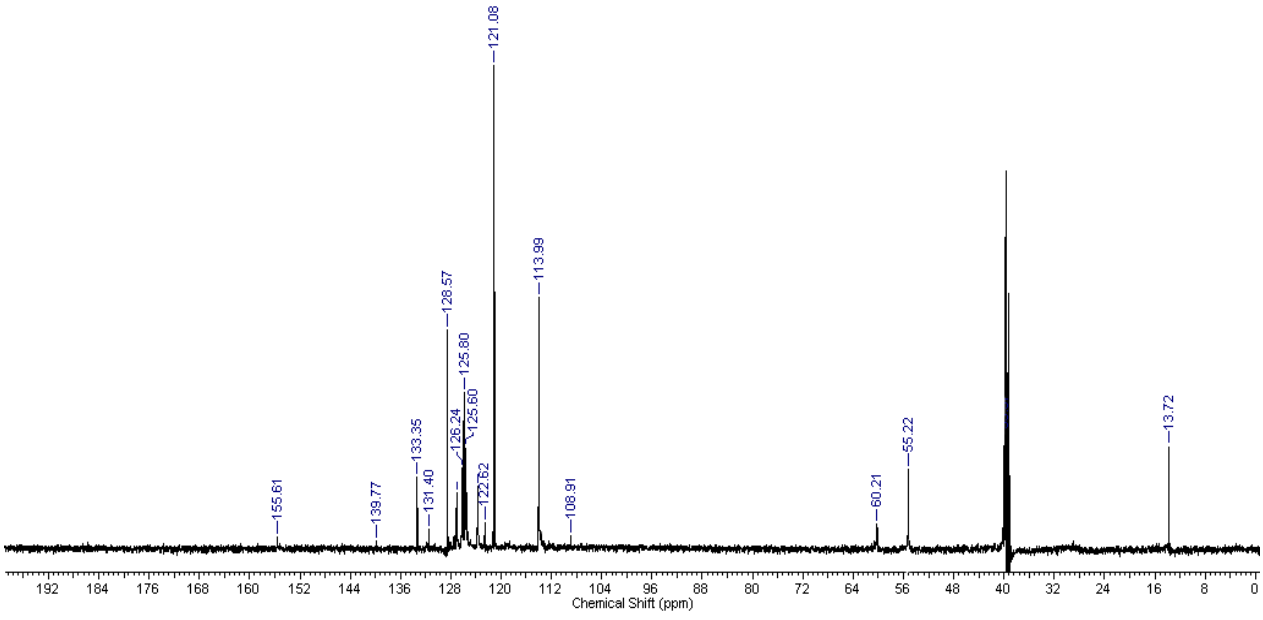
^{13}C NMR (DMSO-d_6, 75 MHz) spectrum of ethyl 5-(4-methoxybenzyl)-3-((4-methoxyphenyl)carbamoyl)-1*H*-pyrazole-4-carboxylate (**3e**)



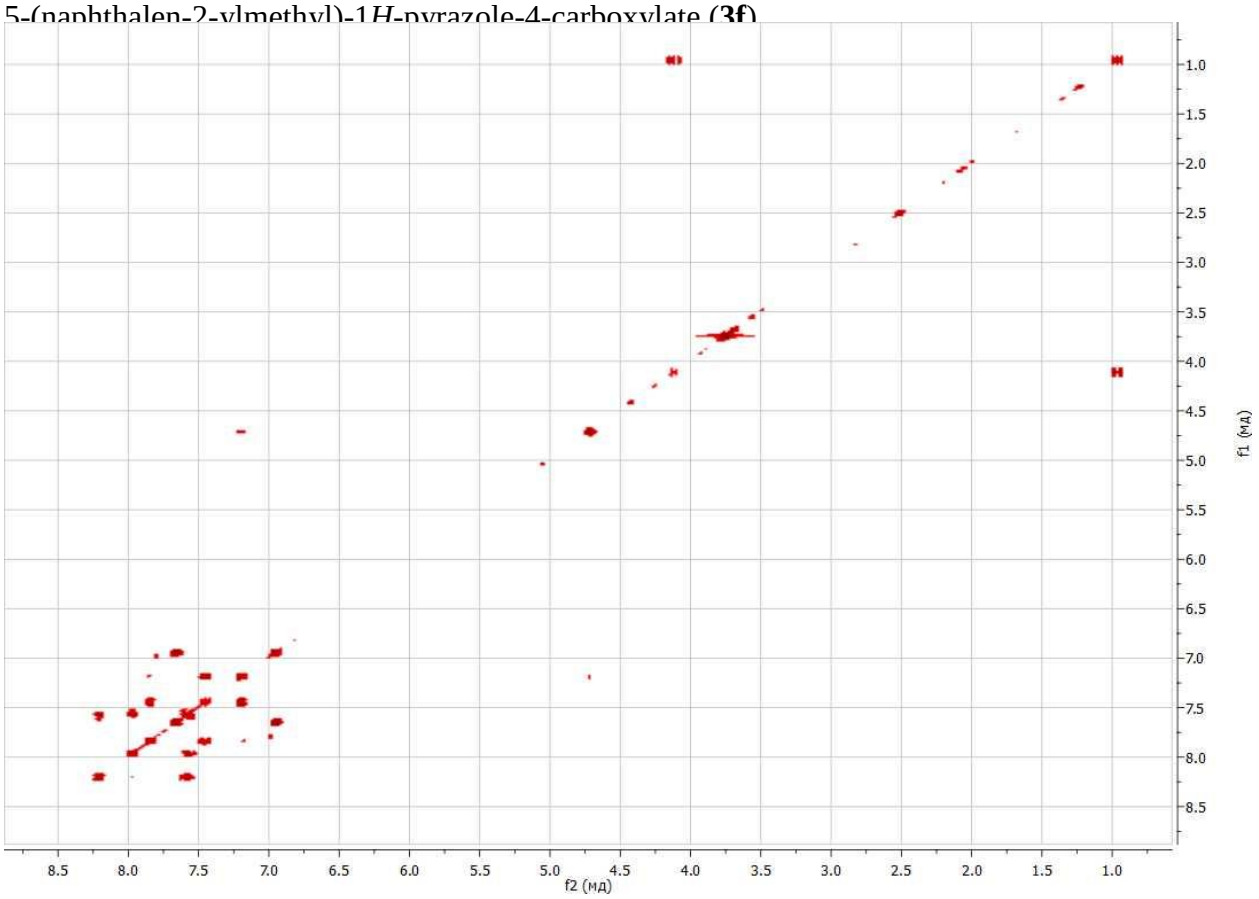
^{1}H NMR (DMSO-d_6, 500 MHz) spectrum of ethyl 3-((4-methoxyphenyl)carbamoyl)-5-(naphthalen-2-ylmethyl)-1*H*-pyrazole-4-carboxylate (**3f**)



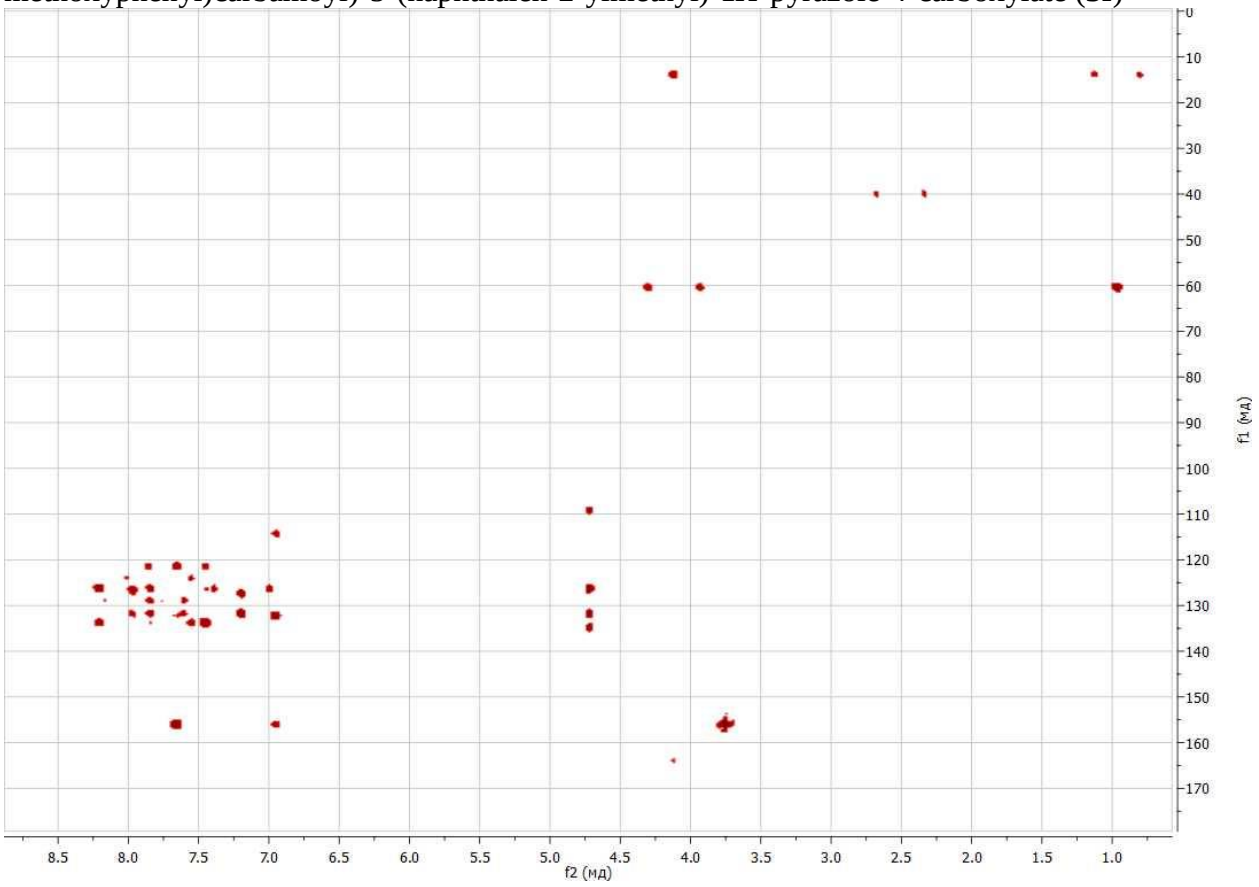
^{13}C NMR (DMSO-d_6, 100 MHz) spectrum of ethyl 3-((4-methoxyphenyl)carbamoyl)-5-(naphthalen-2-ylmethyl)-1*H*-pyrazole-4-carboxylate (**3f**)



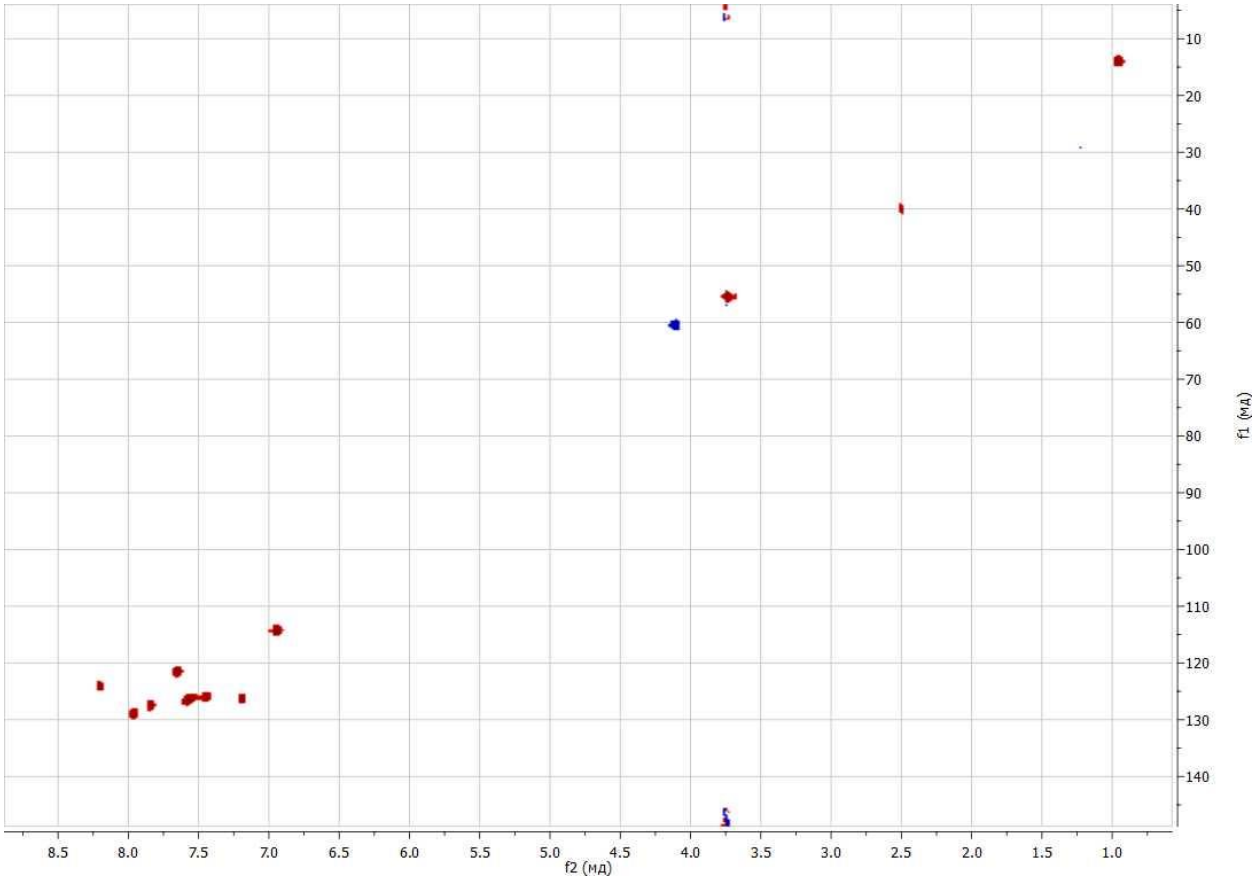
^{1}H-^{1}H COSY NMR (DMSO-d_6, 600 MHz) spectrum of ethyl 3-((4-methoxyphenyl)carbamoyl)-5-(naphthalen-2-ylmethyl)-1*H*-pyrazole-4-carboxylate (**3f**)



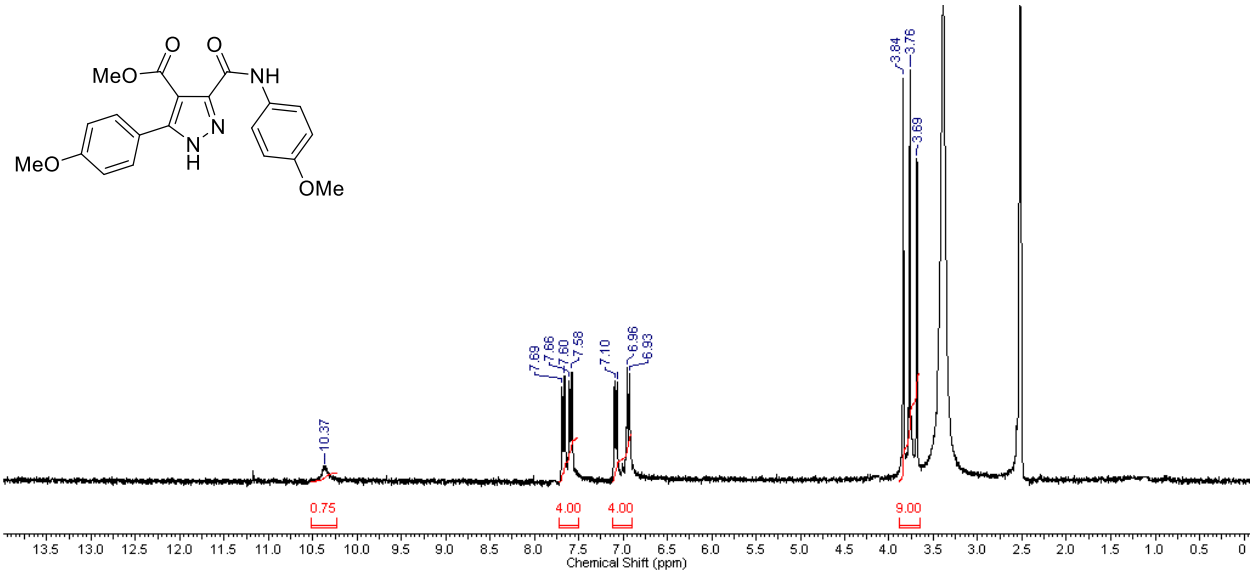
^{1}H-^{13}C HMBC NMR (DMSO-d_6, 600 MHz) spectrum of ethyl 3-((4-methoxyphenyl)carbamoyl)-5-(naphthalen-2-ylmethyl)-1*H*-pyrazole-4-carboxylate (**3f**)



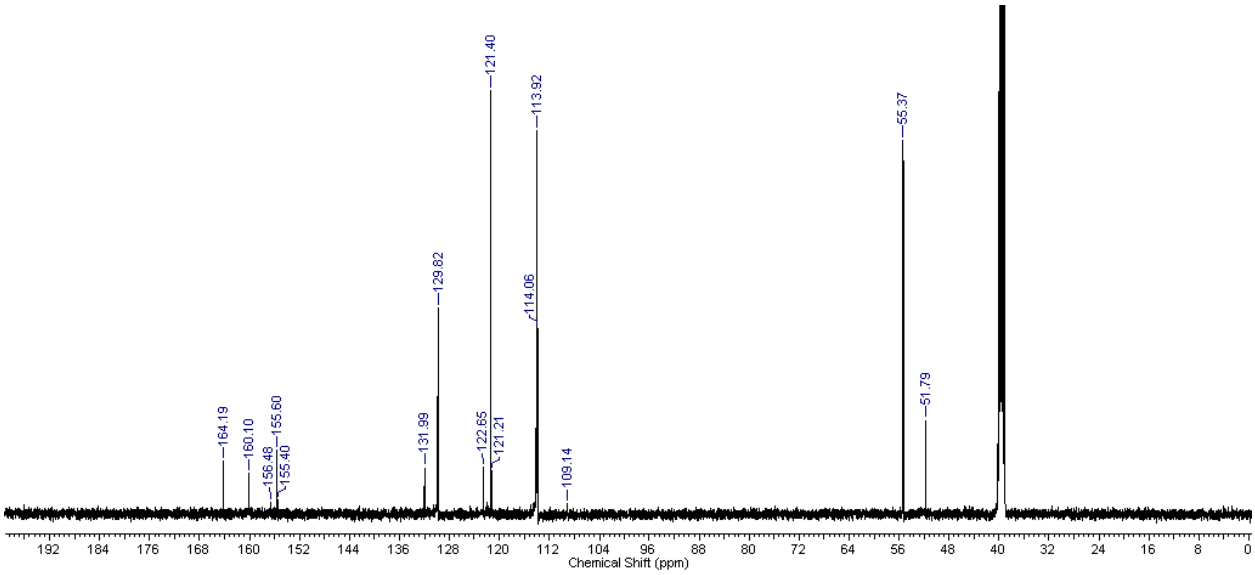
^{1}H-^{13}C HSQC NMR (DMSO-d_6, 600 MHz) spectrum of ethyl 3-((4-methoxyphenyl)carbamoyl)-5-(naphthalen-2-ylmethyl)-1*H*-pyrazole-4-carboxylate (**3f**)



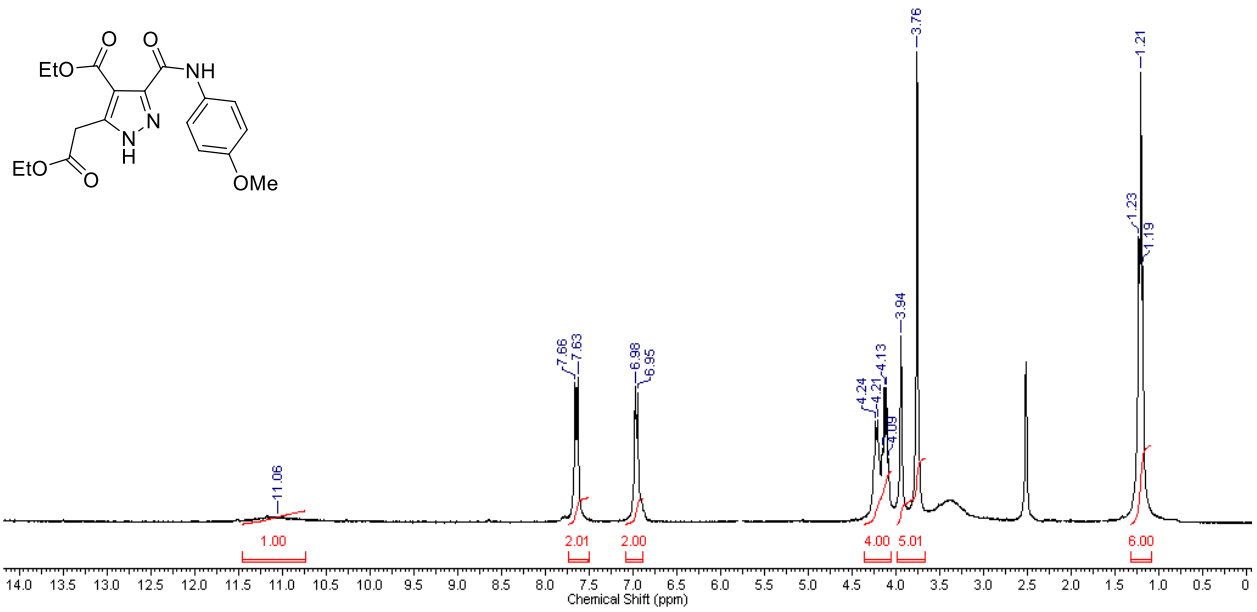
^{1}H NMR (DMSO-d_6, 300 MHz) spectrum of methyl 5-(4-methoxyphenyl)-3-((4-methoxyphenyl)carbamoyl)-1*H*-pyrazole-4-carboxylate (**3g**)



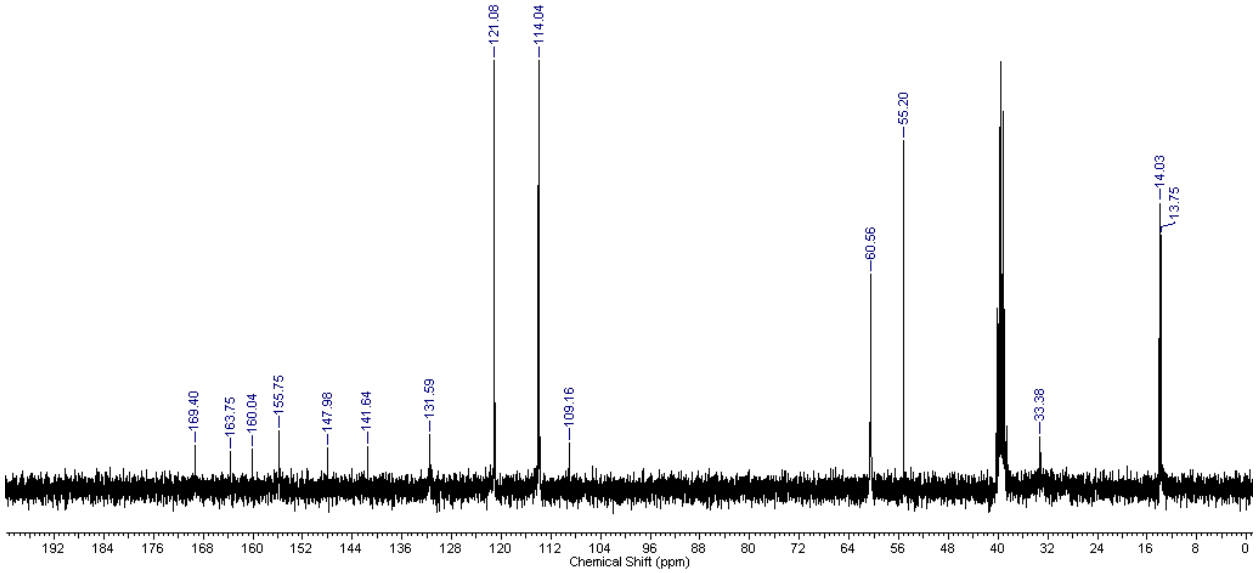
^{13}C NMR (DMSO-d_6, 75 MHz) spectrum of methyl 5-(4-methoxyphenyl)-3-((4-methoxyphenyl)carbamoyl)-1*H*-pyrazole-4-carboxylate (**3g**)



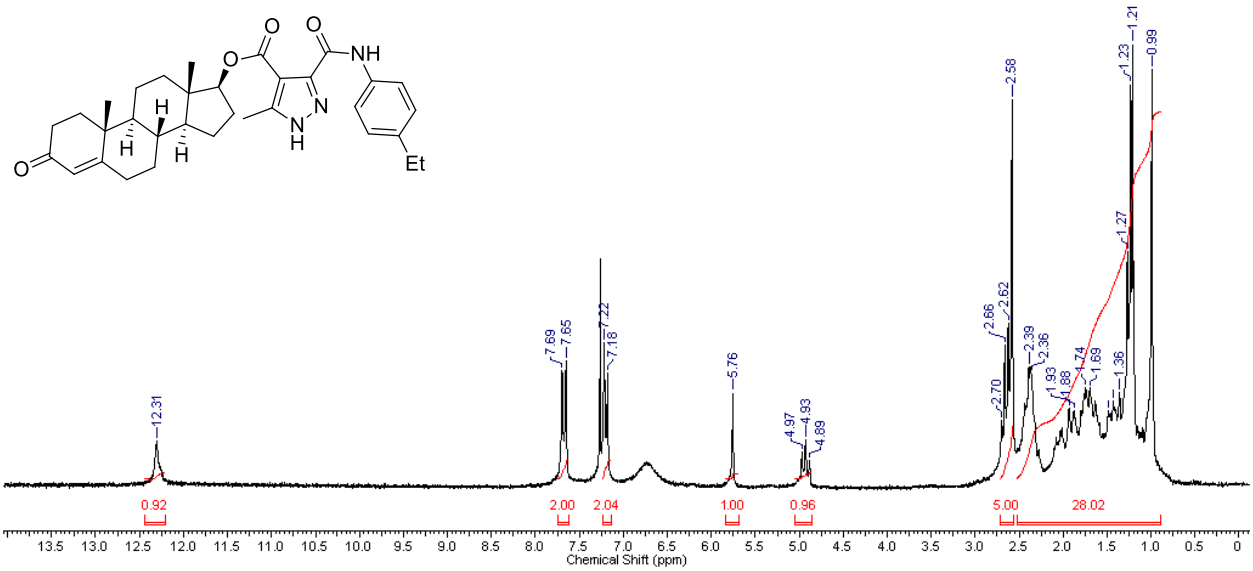
^{1}H NMR (DMSO-d_6, 300 MHz) spectrum of ethyl 5-(2-ethoxy-2-oxoethyl)-3-((4-methoxyphenyl)carbamoyl)-1*H*-pyrazole-4-carboxylate (**3j**)



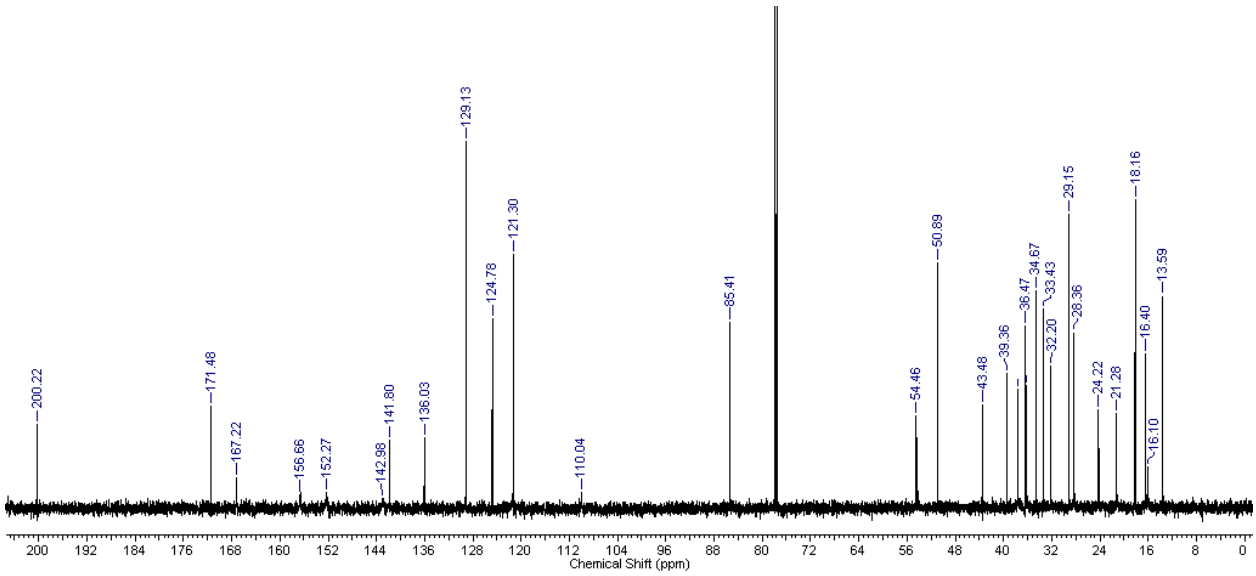
^{13}C NMR (DMSO-d_6, 75 MHz) spectrum of ethyl 5-(2-ethoxy-2-oxoethyl)-3-((4-methoxyphenyl)carbamoyl)-1*H*-pyrazole-4-carboxylate (**3j**)



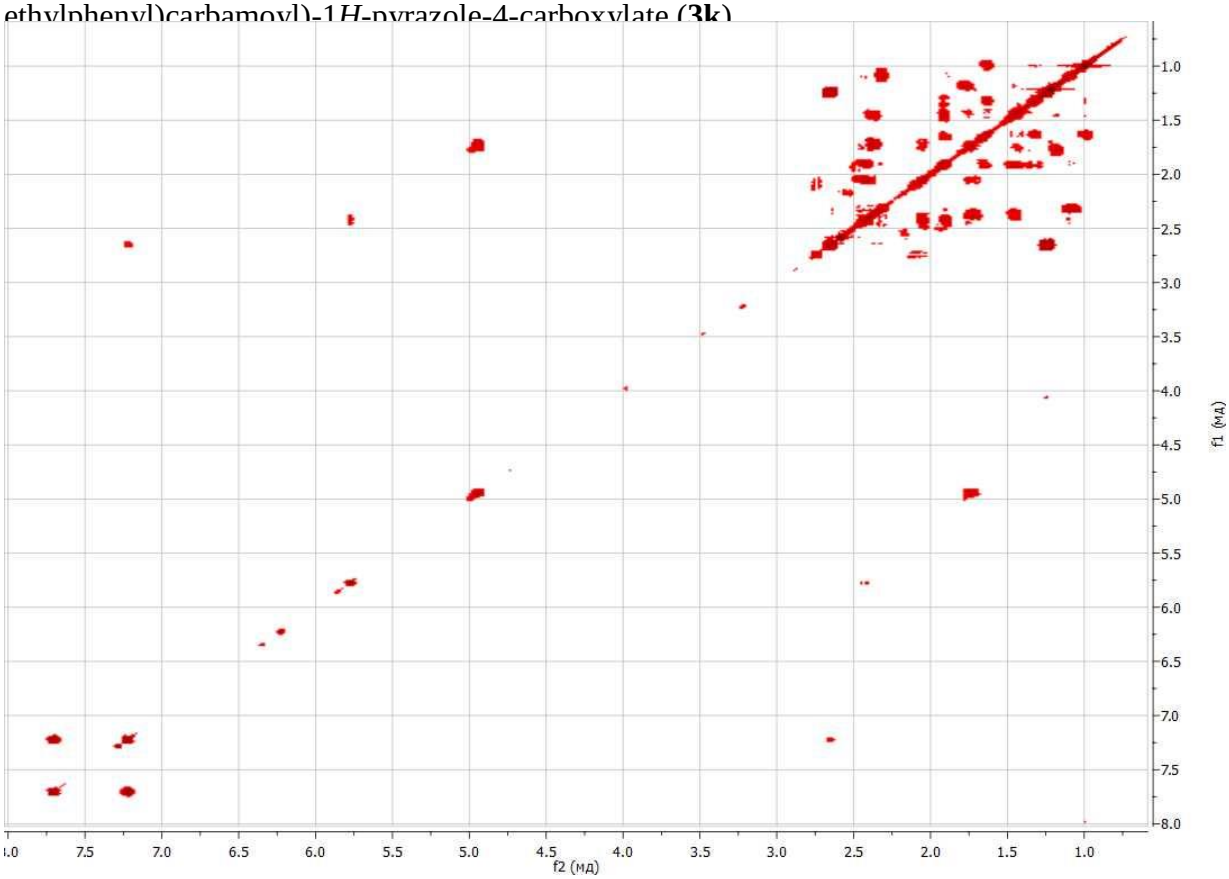
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of 10,13-dimethyl-3-oxo-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[a]phenanthren-17-yl 3-((4-ethylphenyl)carbamoyl)-1*H*-pyrazole-4-carboxylate (**3k**)



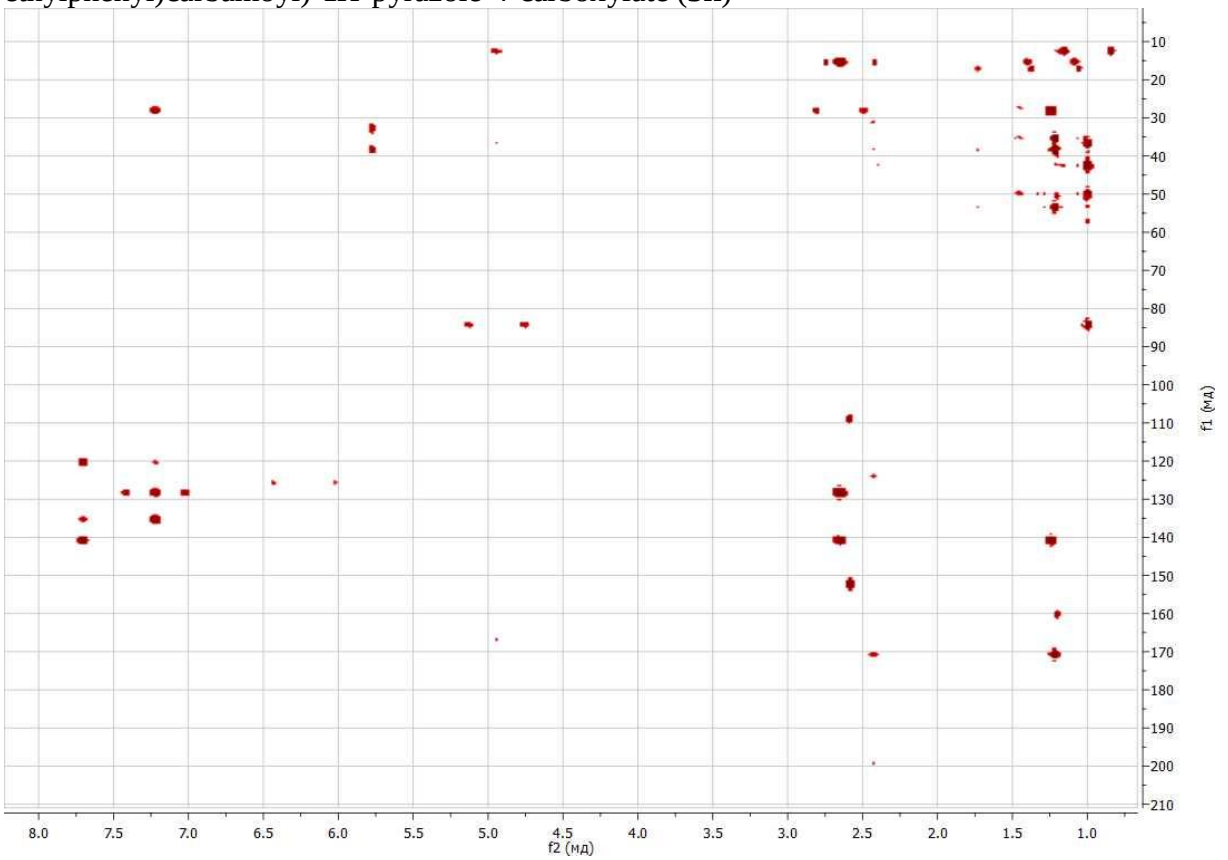
^{13}C NMR ($CDCl_3$, 100 MHz) spectrum of 10,13-dimethyl-3-oxo-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[a]phenanthren-17-yl 3-((4-ethylphenyl)carbamoyl)-1*H*-pyrazole-4-carboxylate (**3k**)



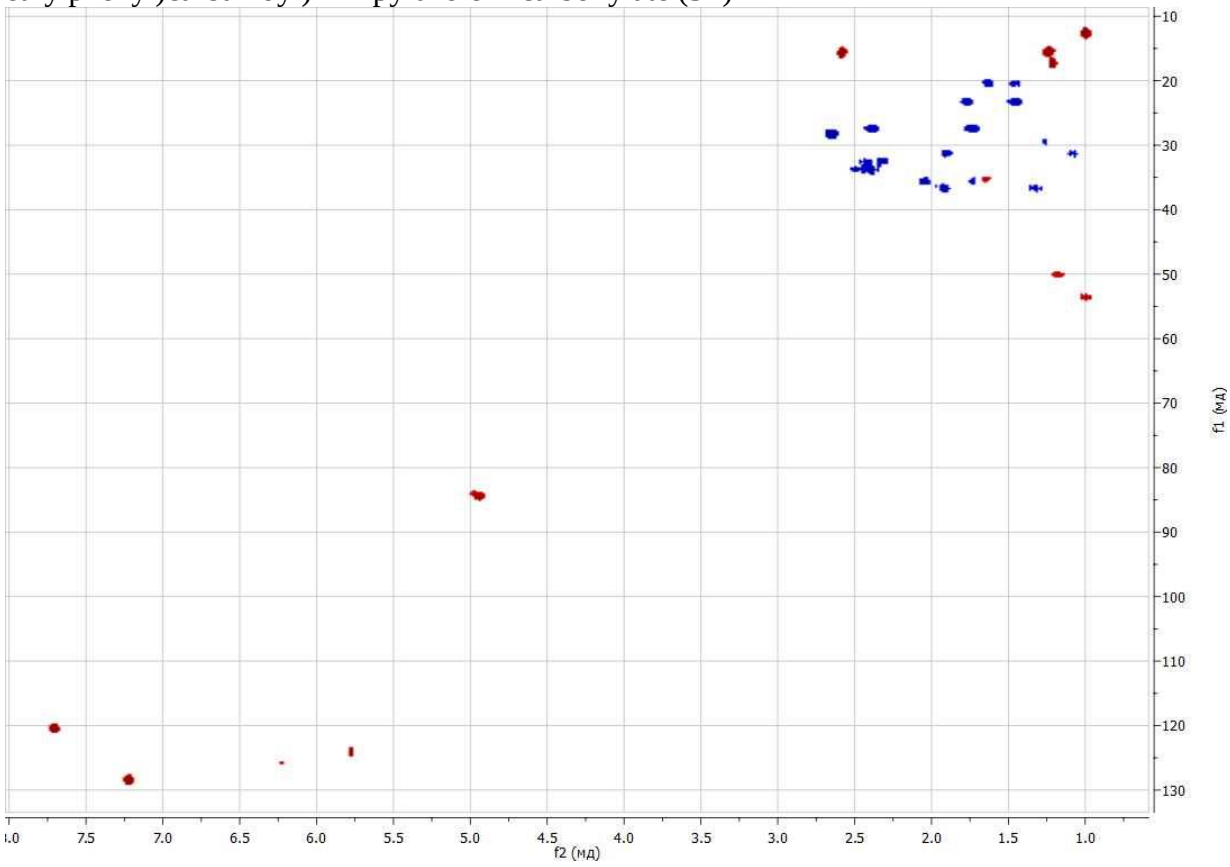
^{1}H-^{1}H COSY NMR ($CDCl_3$, 400 MHz) spectrum of 10,13-dimethyl-3-oxo-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[a]phenanthren-17-yl 3-((4-ethylphenyl)carbamoyl)-1*H*-pyrazole-4-carboxylate (**3k**)



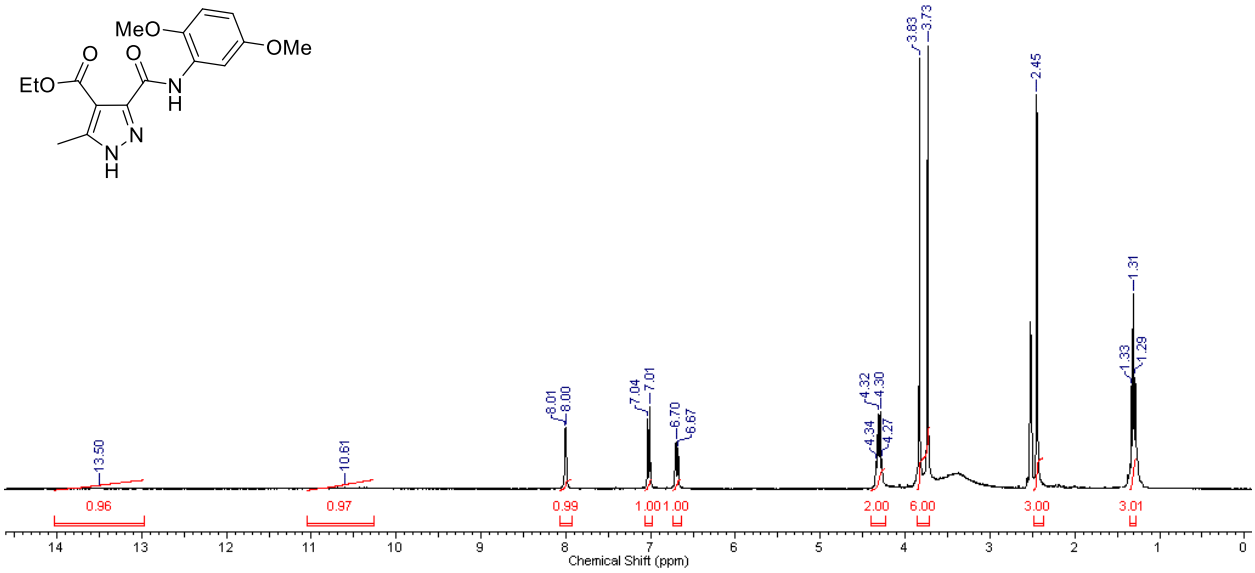
^{1}H-^{13}C HMBC NMR ($CDCl_3$, 400 MHz) spectrum of 10,13-dimethyl-3-oxo-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[a]phenanthren-17-yl 3-((4-ethylphenyl)carbamoyl)-1*H*-pyrazole-4-carboxylate (**3k**)



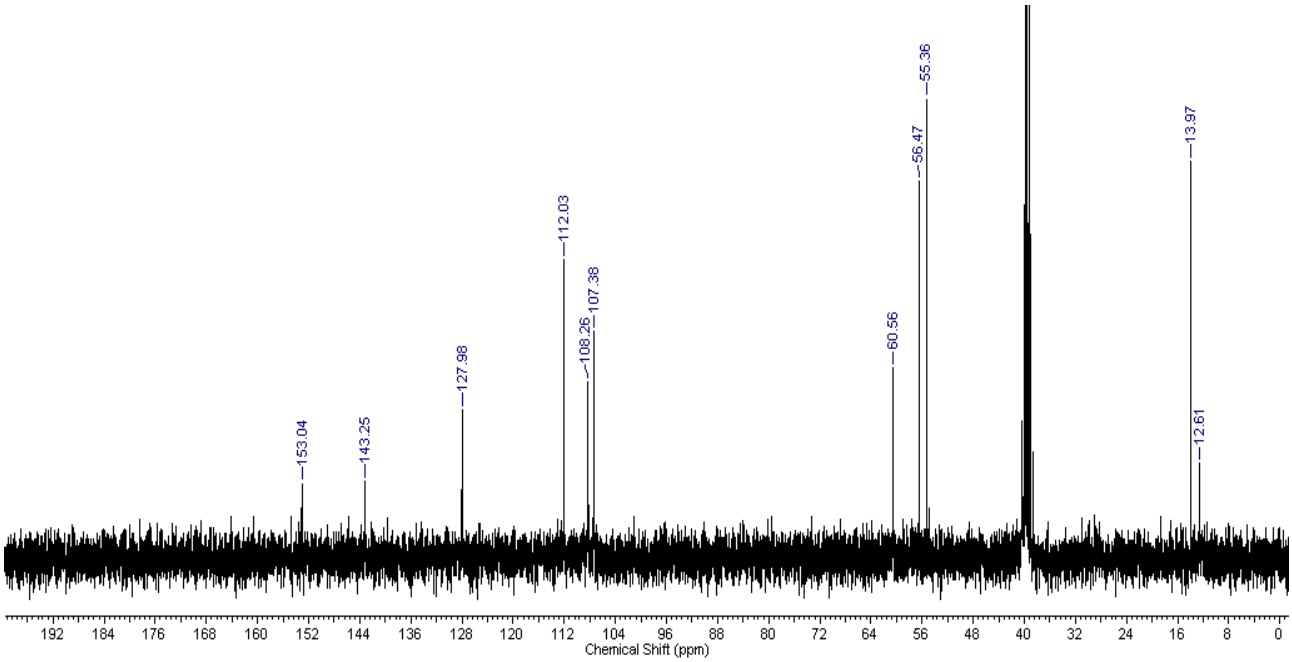
^{1}H-^{13}C HSQC NMR ($CDCl_3$, 400 MHz) spectrum of 10,13-dimethyl-3-oxo-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[a]phenanthren-17-yl 3-((4-ethylphenyl)carbamoyl)-1*H*-pyrazole-4-carboxylate (**3k**)



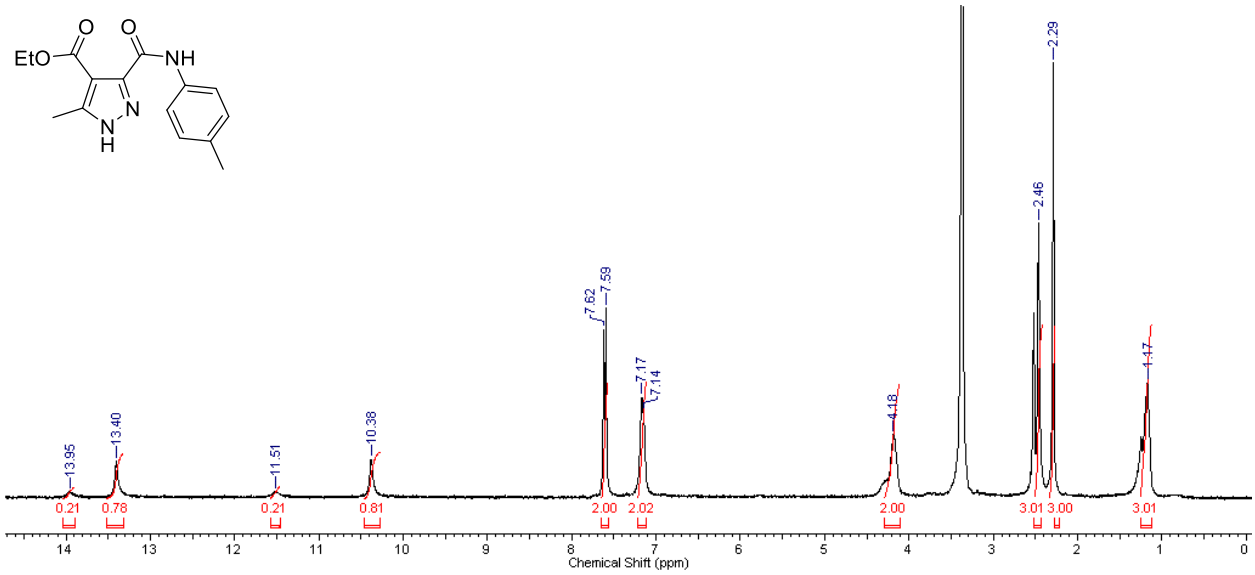
^{1}H NMR (DMSO-d_6, 300 MHz) spectrum of ethyl 3-((2,5-dimethoxyphenyl)carbamoyl)-5-methyl-1*H*-pyrazole-4-carboxylate (**3l**)



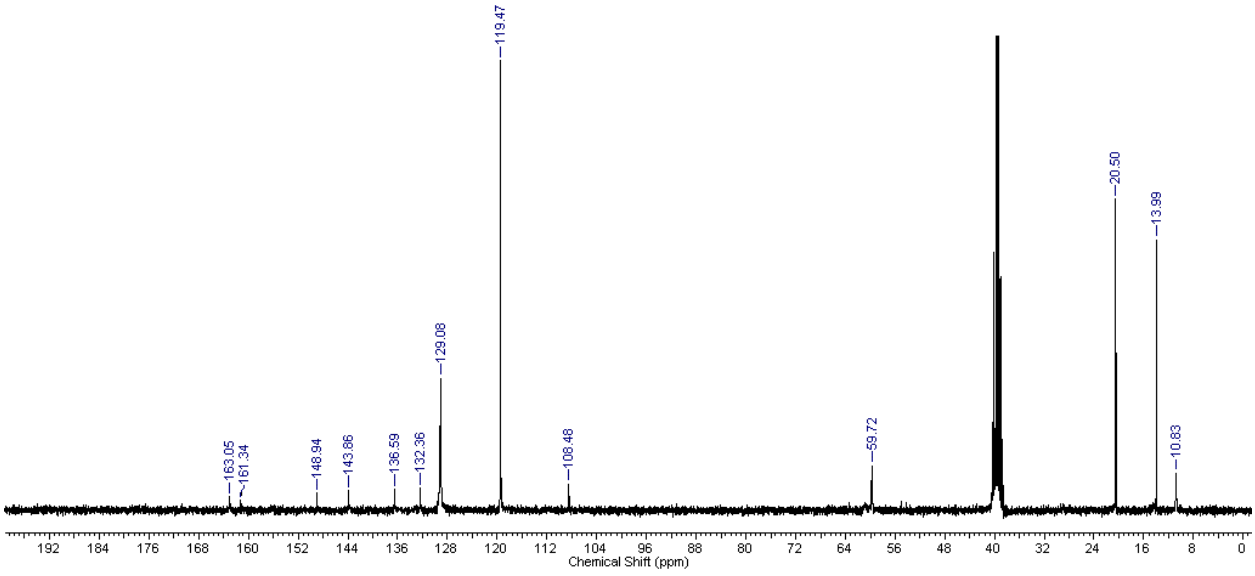
^{13}C NMR (DMSO-d_6, 75 MHz) spectrum of ethyl 3-((2,5-dimethoxyphenyl)carbamoyl)-5-methyl-1*H*-pyrazole-4-carboxylate (**3l**)



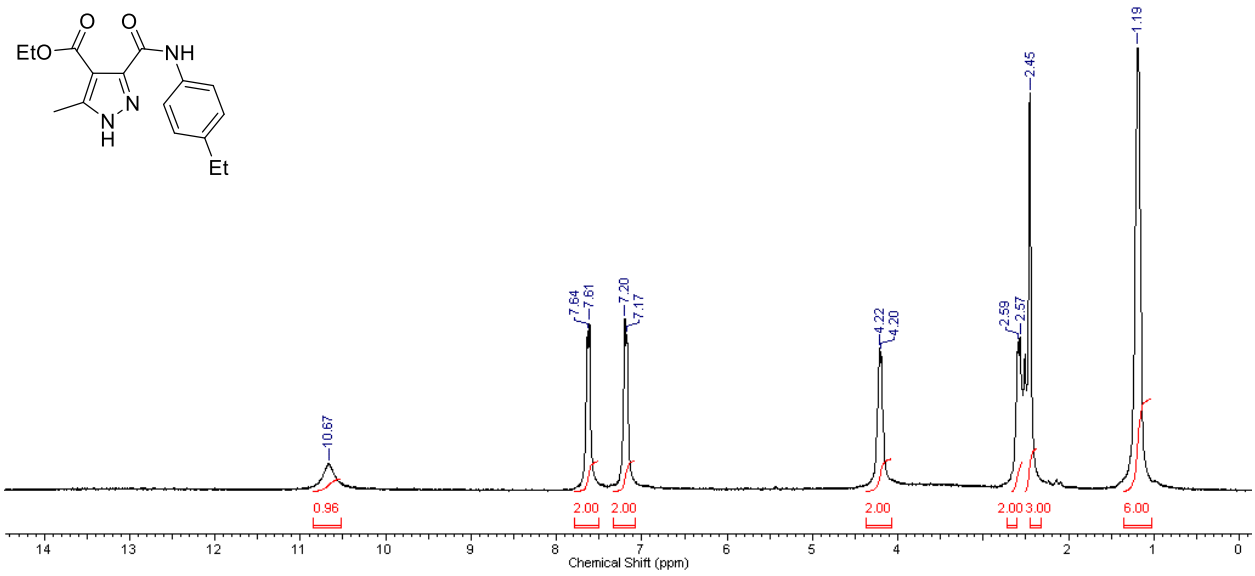
^{1}H NMR (DMSO-d_6, 300 MHz) spectrum of ethyl 5-methyl-3-(*p*-tolylcarbamoyl)-1*H*-pyrazole-4-carboxylate (**3m**)



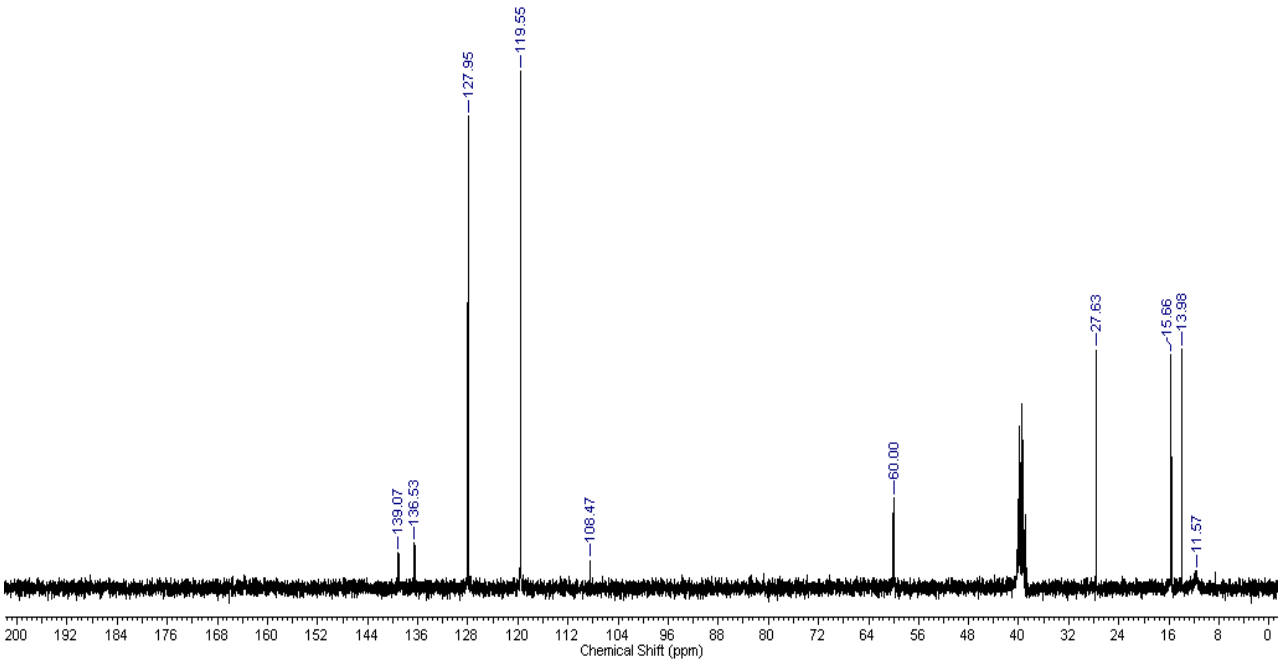
^{13}C NMR (DMSO-d_6, 75 MHz) spectrum of ethyl 5-methyl-3-(*p*-tolylcarbamoyl)-1*H*-pyrazole-4-carboxylate (**3m**)



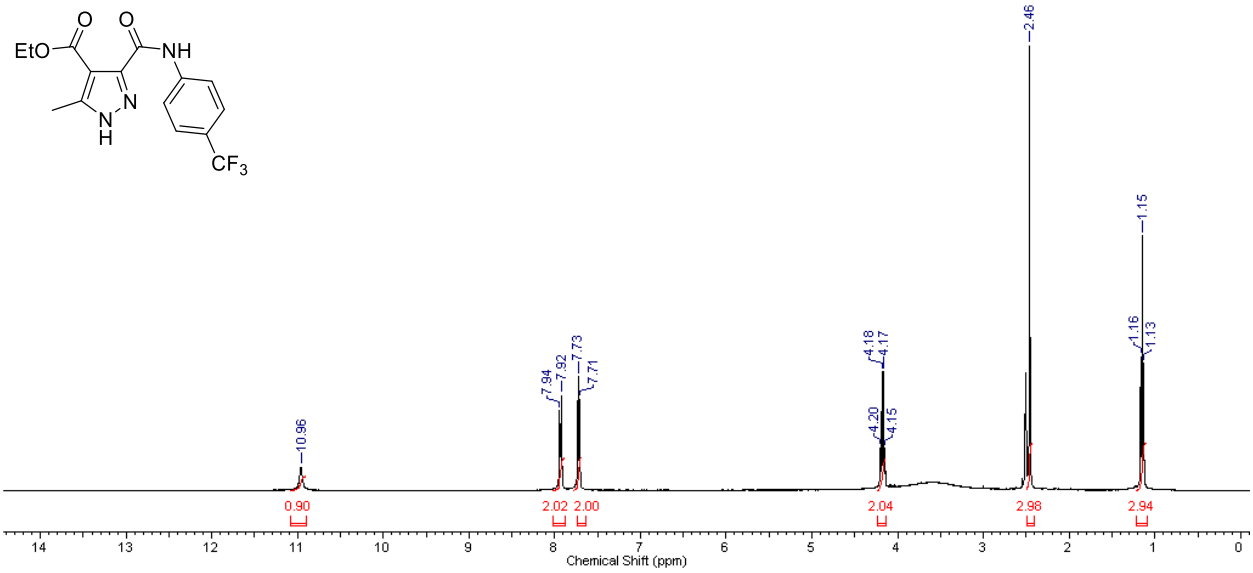
^{1}H NMR (DMSO-d_6, 300 MHz) spectrum of ethyl 3-((4-ethylphenyl)carbamoyl)-5-methyl-1*H*-pyrazole-4-carboxylate (**3n**)



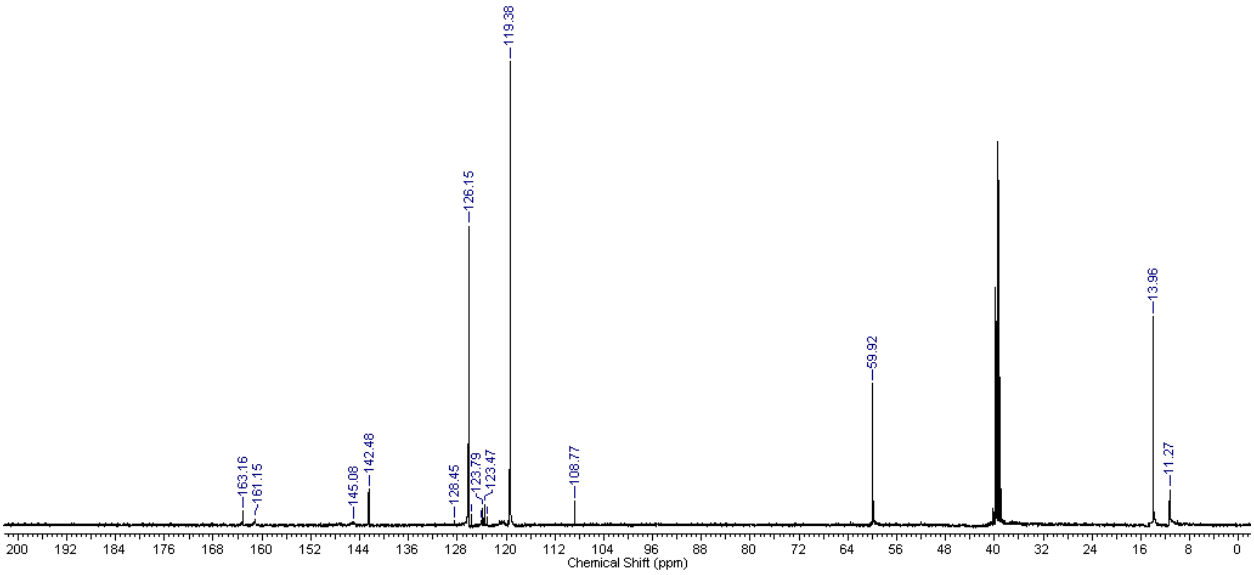
^{13}C NMR (DMSO-d_6, 75 MHz) spectrum of ethyl 3-((4-ethylphenyl)carbamoyl)-5-methyl-1*H*-pyrazole-4-carboxylate (**3n**)



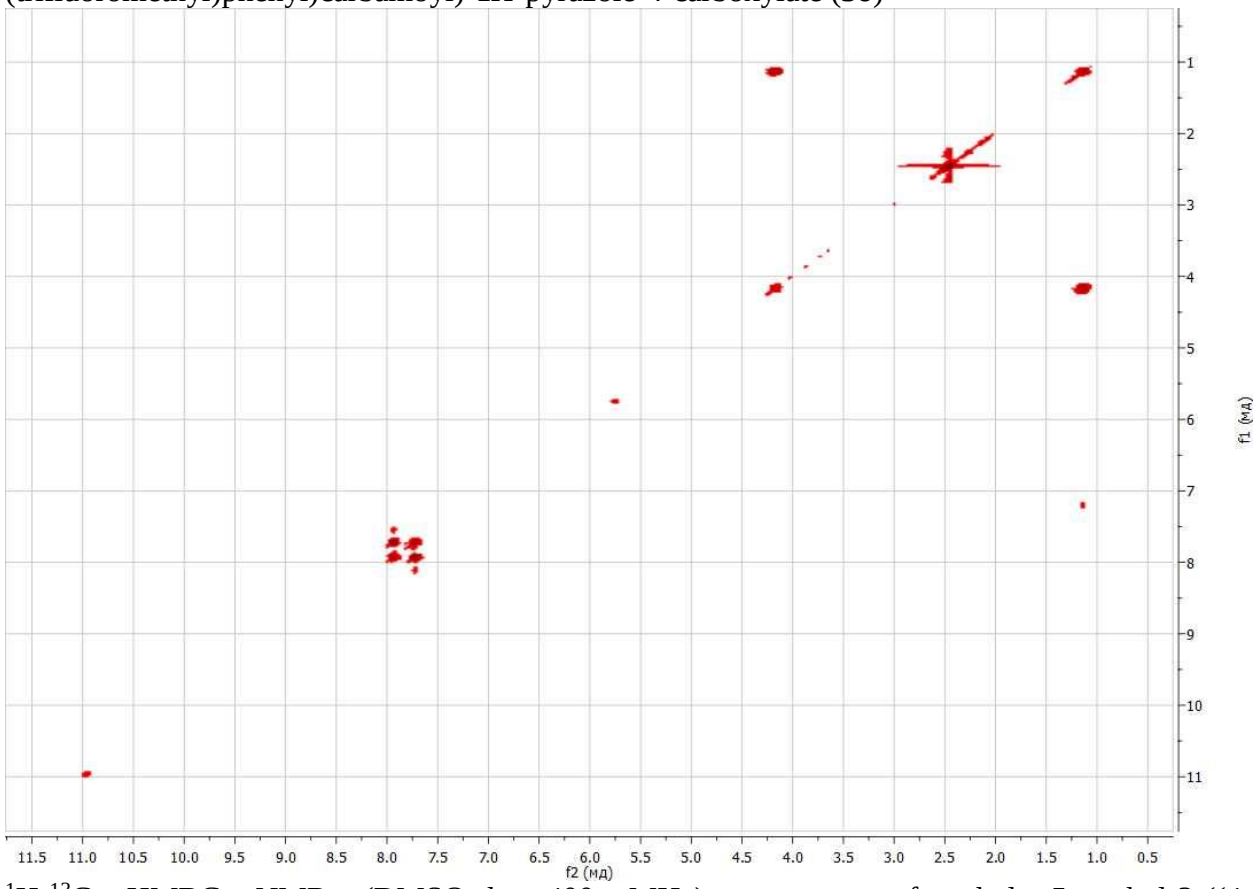
^{1}H NMR (DMSO-d_6, 400 MHz) spectrum of ethyl 5-methyl-3-((4-(trifluoromethyl)phenyl)carbamoyl)-1*H*-pyrazole-4-carboxylate (**3o**)



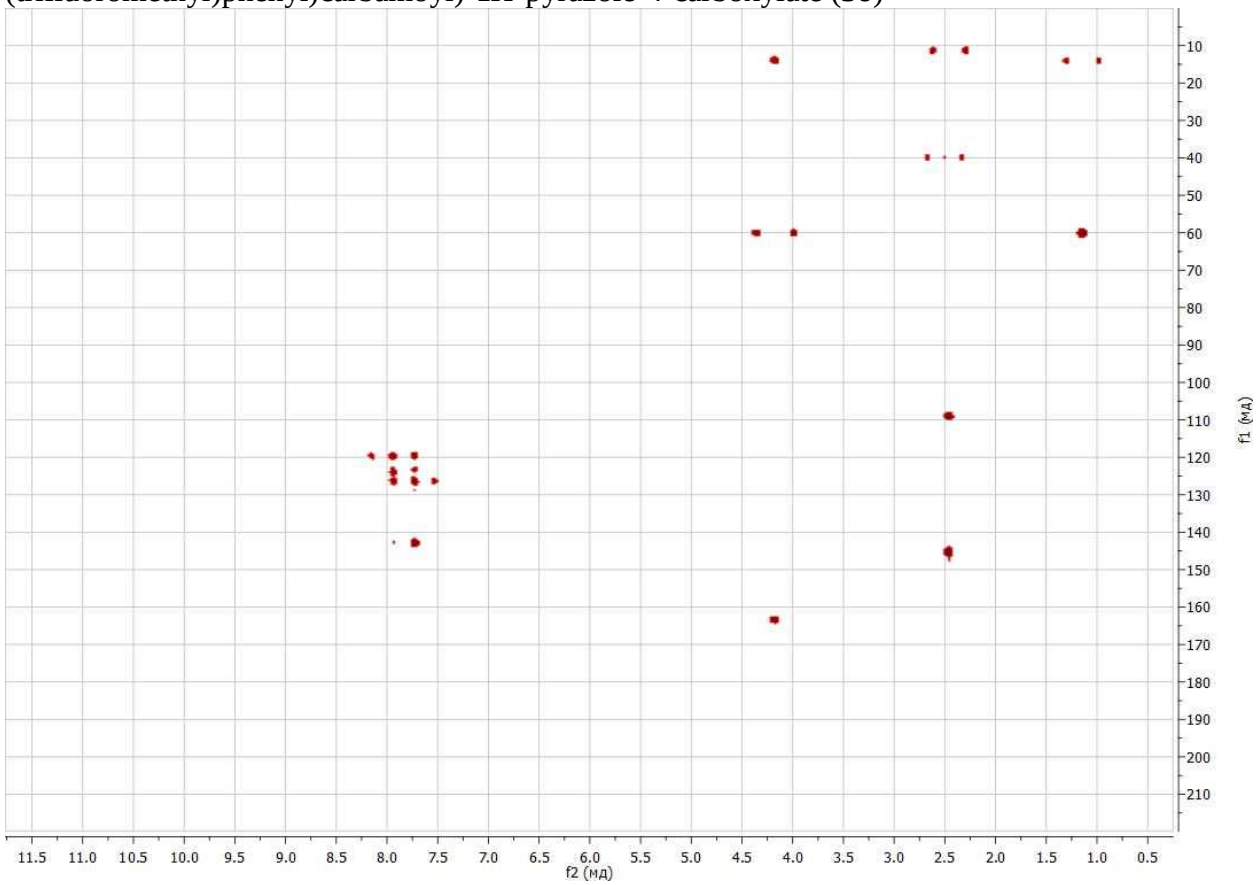
^{13}C NMR (DMSO-d_6, 100 MHz) spectrum of ethyl 5-methyl-3-((4-(trifluoromethyl)phenyl)carbamoyl)-1*H*-pyrazole-4-carboxylate (**3o**)



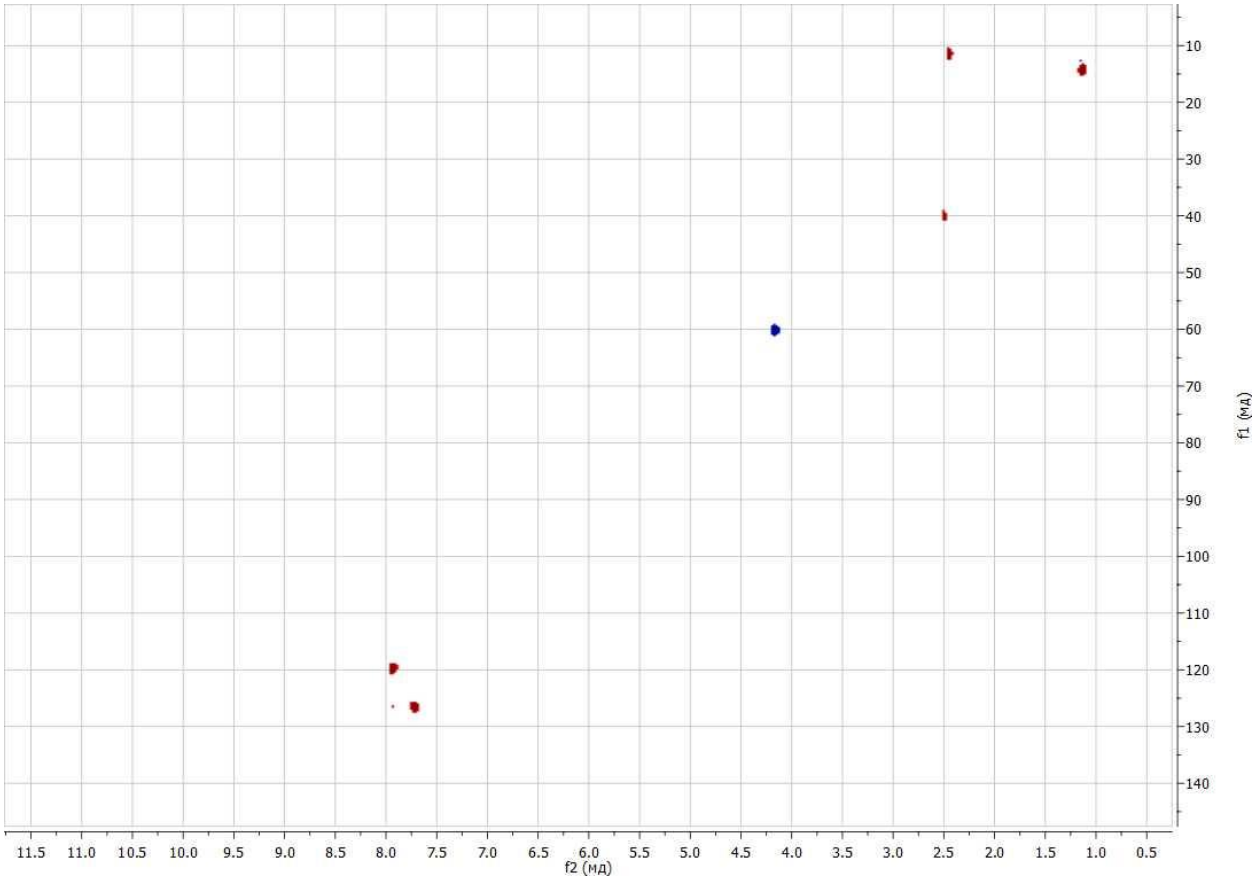
^{1}H-^{1}H COSY NMR (DMSO-d_6, 400 MHz) spectrum of ethyl 5-methyl-3-((4-(trifluoromethyl)phenyl)carbamoyl)-1*H*-pyrazole-4-carboxylate (**3o**)



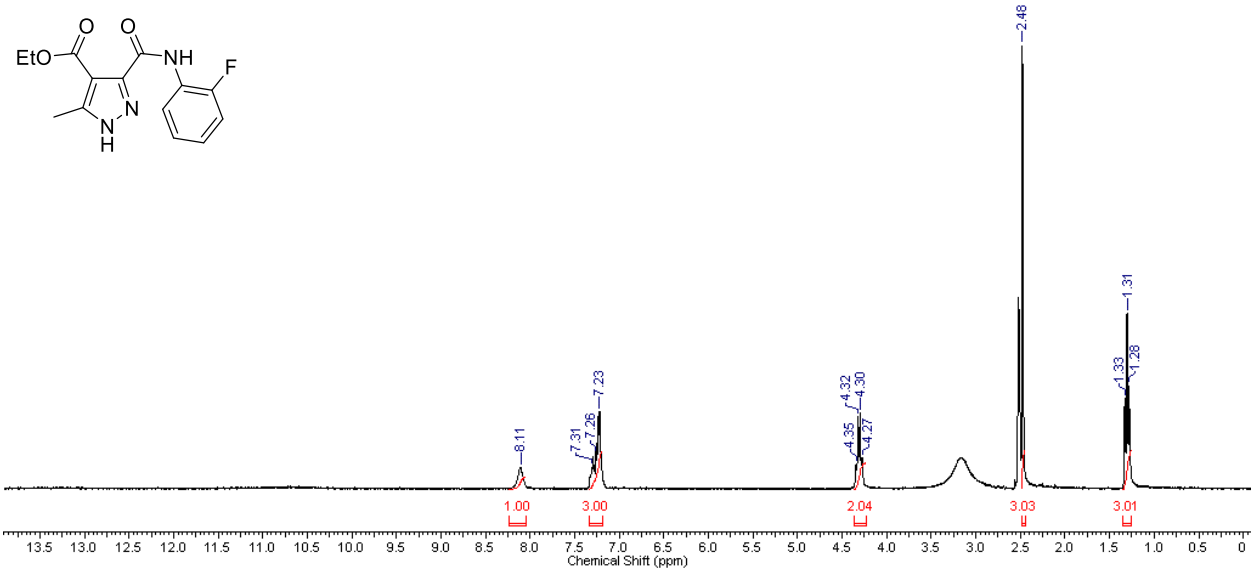
^{1}H-^{13}C HMBC NMR (DMSO-d_6, 400 MHz) spectrum of ethyl 5-methyl-3-((4-(trifluoromethyl)phenyl)carbamoyl)-1*H*-pyrazole-4-carboxylate (**3o**)



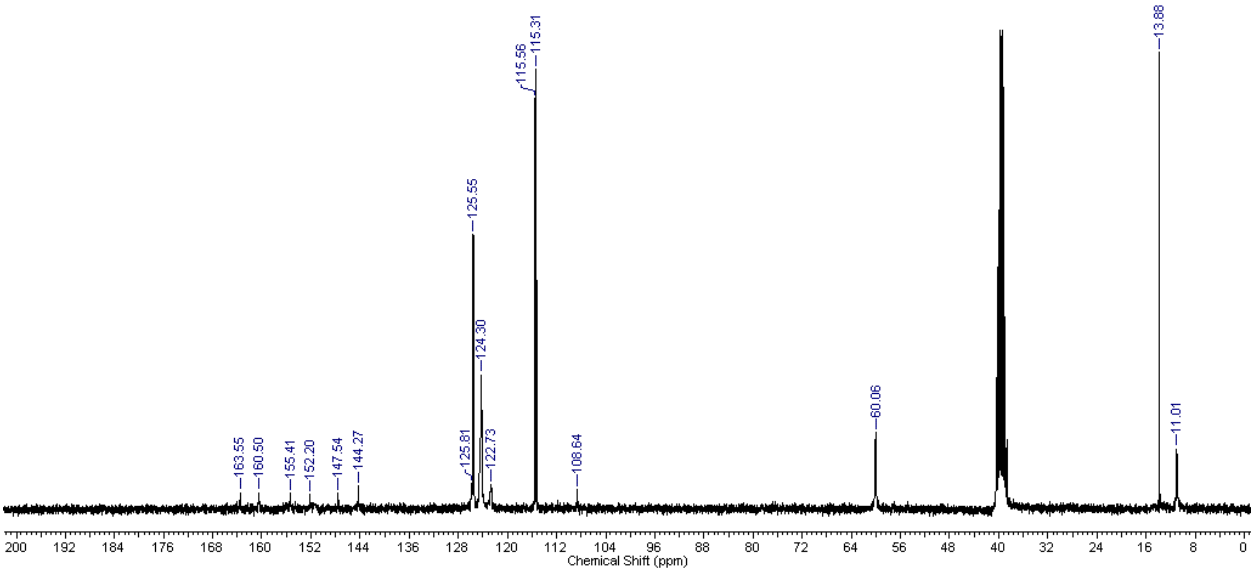
^{1}H-^{13}C HSQC NMR (DMSO-d_6, 400 MHz) spectrum of ethyl 5-methyl-3-((4-(trifluoromethyl)phenyl)carbamoyl)-1*H*-pyrazole-4-carboxylate (**3o**)



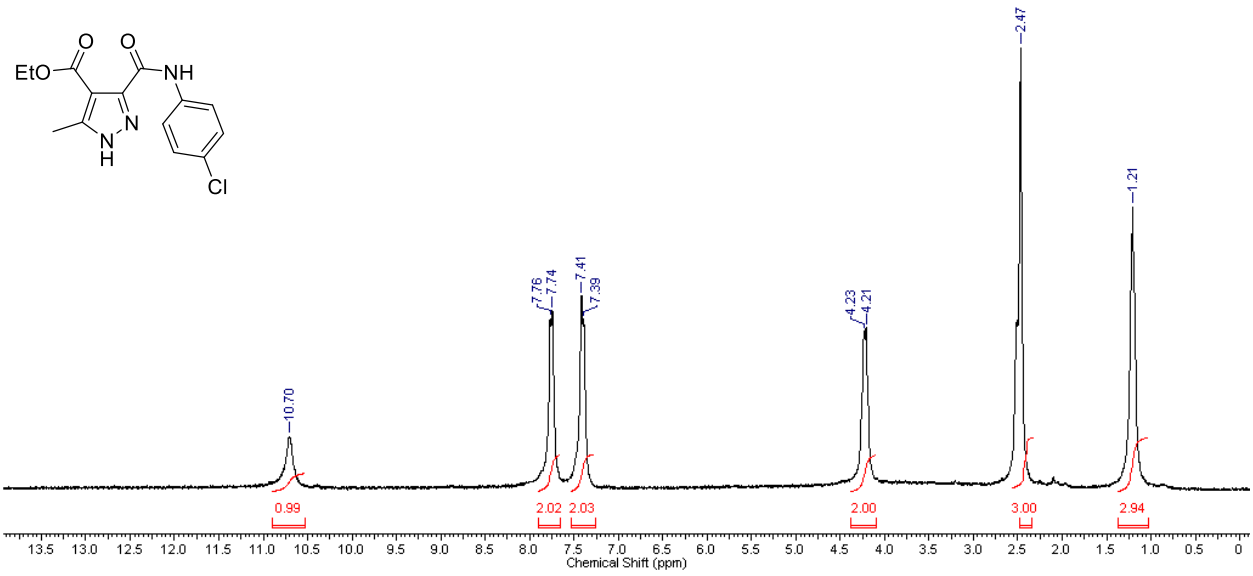
^{1}H NMR (DMSO-*d*$_6$, 300 MHz) spectrum of ethyl 3-((2-fluorophenyl)carbamoyl)-5-methyl-1*H*-pyrazole-4-carboxylate (**3p**)



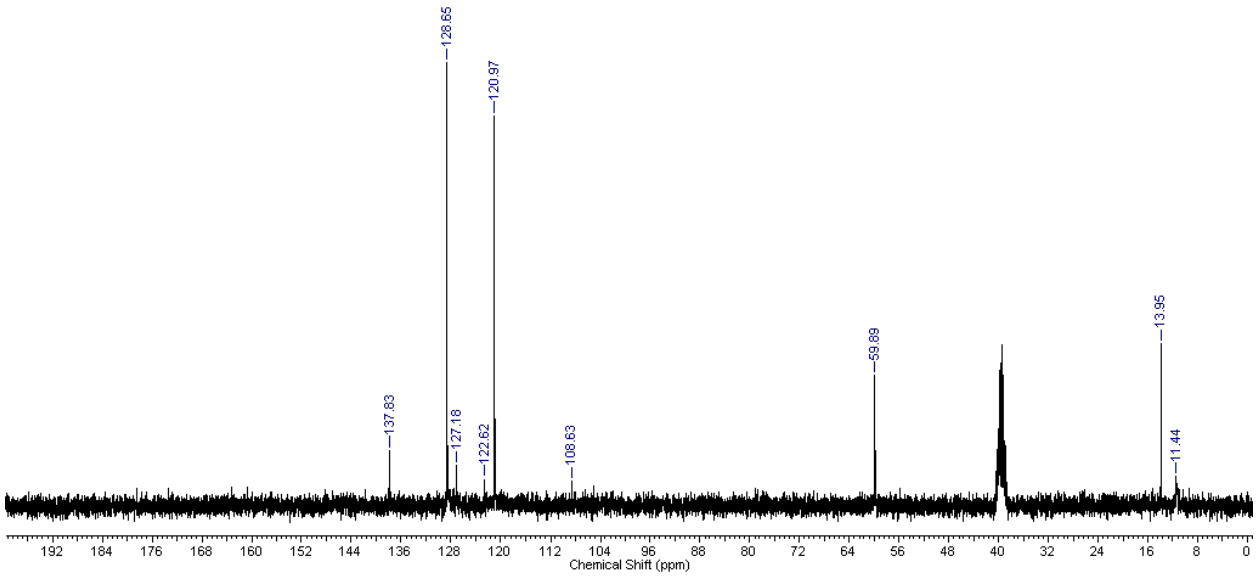
^{13}C NMR (DMSO-*d*$_6$, 75 MHz) spectrum of ethyl 3-((2-fluorophenyl)carbamoyl)-5-methyl-1*H*-pyrazole-4-carboxylate (**3p**)



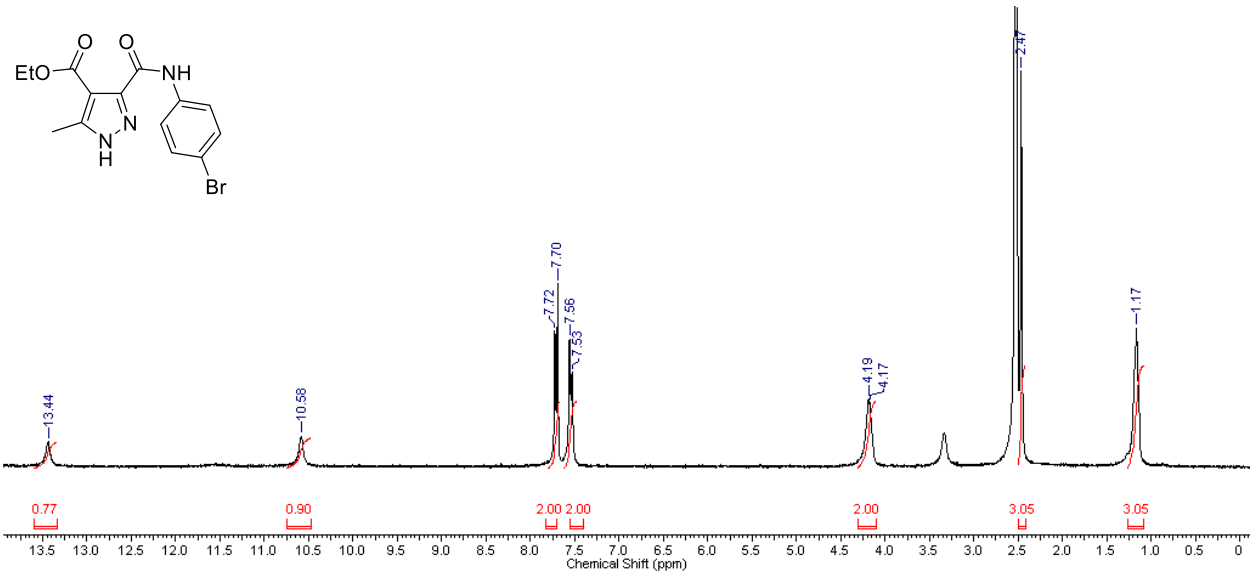
^{1}H NMR (DMSO-d_6, 300 MHz) spectrum of ethyl 3-((4-chlorophenyl)carbamoyl)-5-methyl-1*H*-pyrazole-4-carboxylate (**3q**)



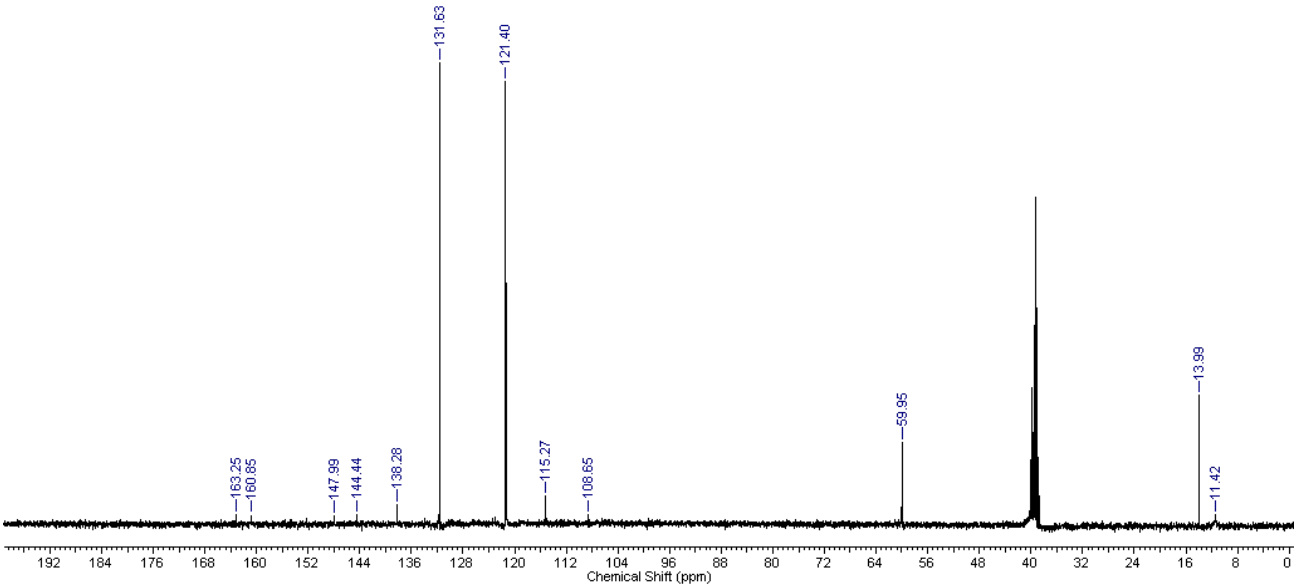
^{13}C NMR (DMSO-d_6, 75 MHz) spectrum of ethyl 3-((4-chlorophenyl)carbamoyl)-5-methyl-1*H*-pyrazole-4-carboxylate (**3q**)



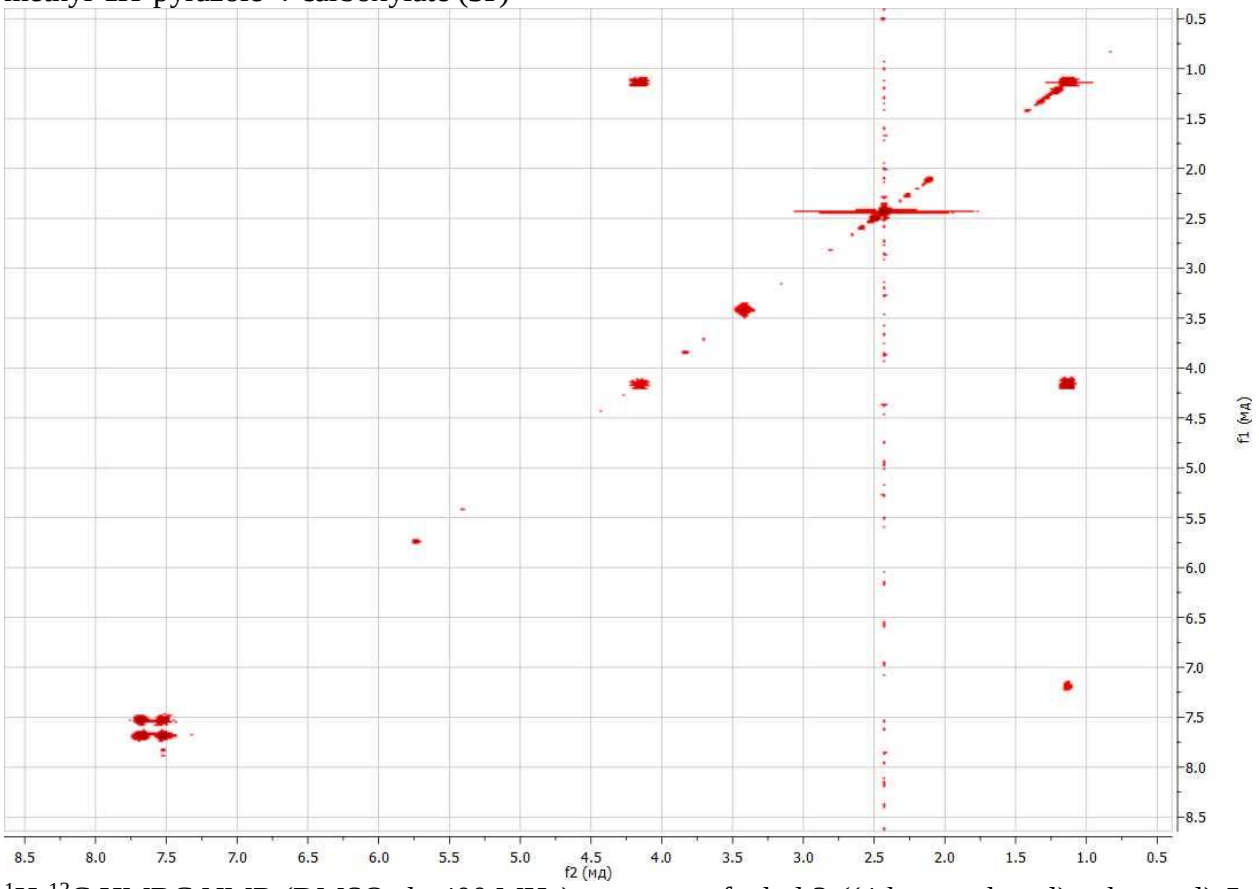
^{1}H NMR (DMSO-d_6, 300 MHz) spectrum of ethyl 3-((4-bromophenyl)carbamoyl)-5-methyl-1*H*-pyrazole-4-carboxylate (**3r**)



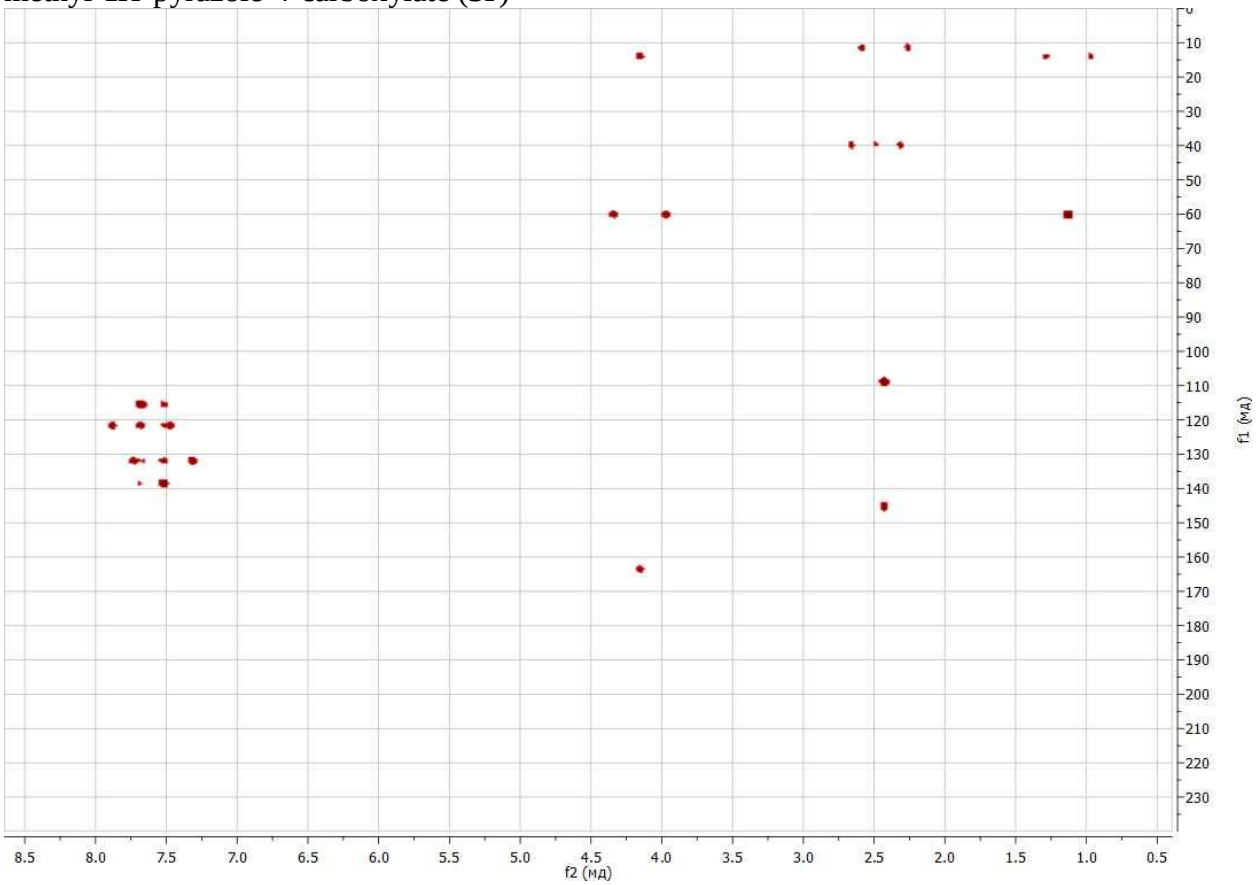
^{13}C NMR (DMSO-d_6, 100 MHz) spectrum of ethyl 3-((4-bromophenyl)carbamoyl)-5-methyl-1*H*-pyrazole-4-carboxylate (**3r**)



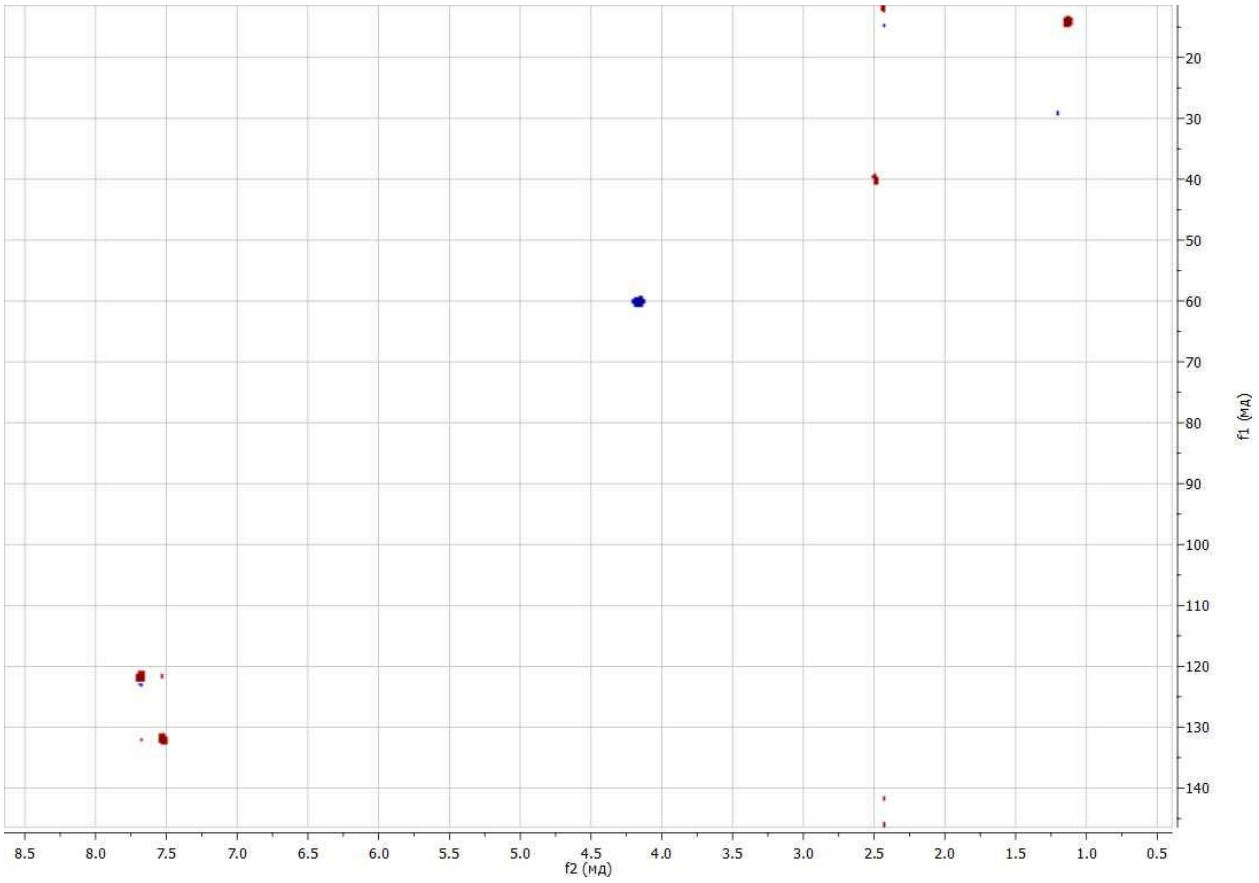
^{1}H-^{1}H COSY NMR (DMSO-d_6, 400 MHz) spectrum of ethyl 3-((4-bromophenyl)carbamoyl)-5-methyl-1*H*-pyrazole-4-carboxylate (**3r**)



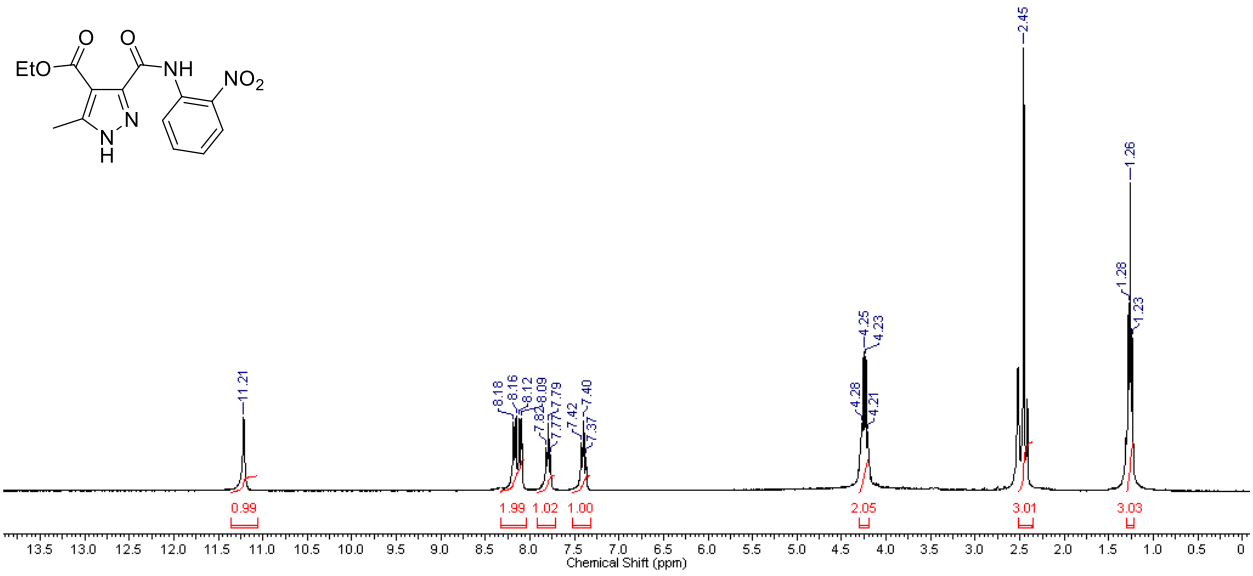
^{1}H-^{13}C HMBC NMR (DMSO-d_6, 400 MHz) spectrum of ethyl 3-((4-bromophenyl)carbamoyl)-5-methyl-1*H*-pyrazole-4-carboxylate (**3r**)



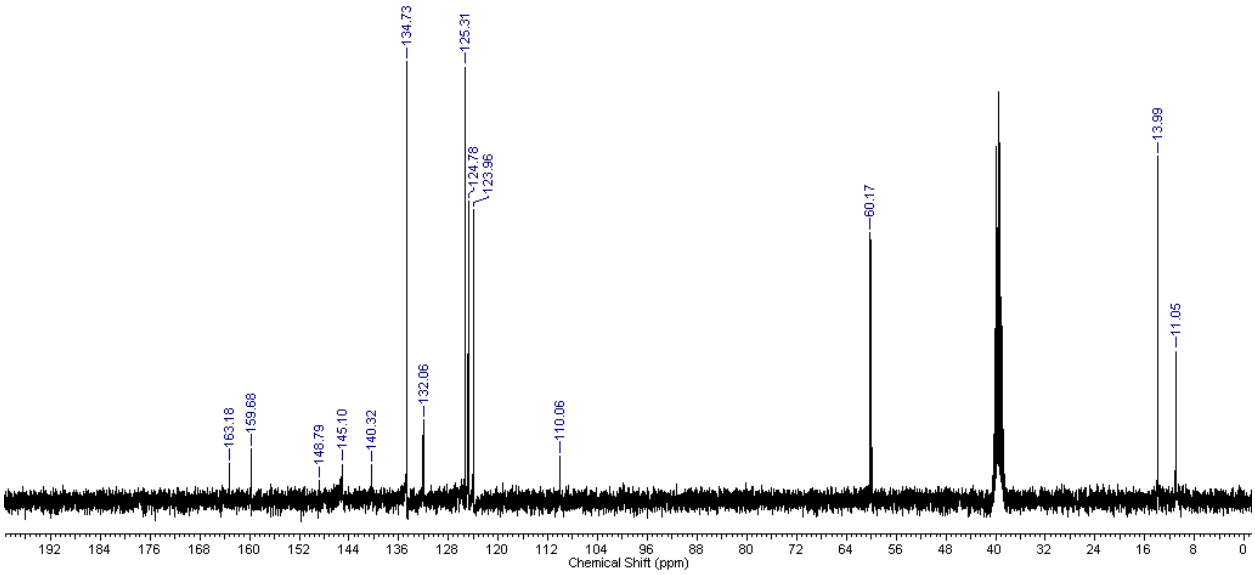
^{1}H-^{13}C HSQC NMR (DMSO-d_6, 400 MHz) spectrum of ethyl 3-((4-bromophenyl)carbamoyl)-5-methyl-1*H*-pyrazole-4-carboxylate (**3r**)



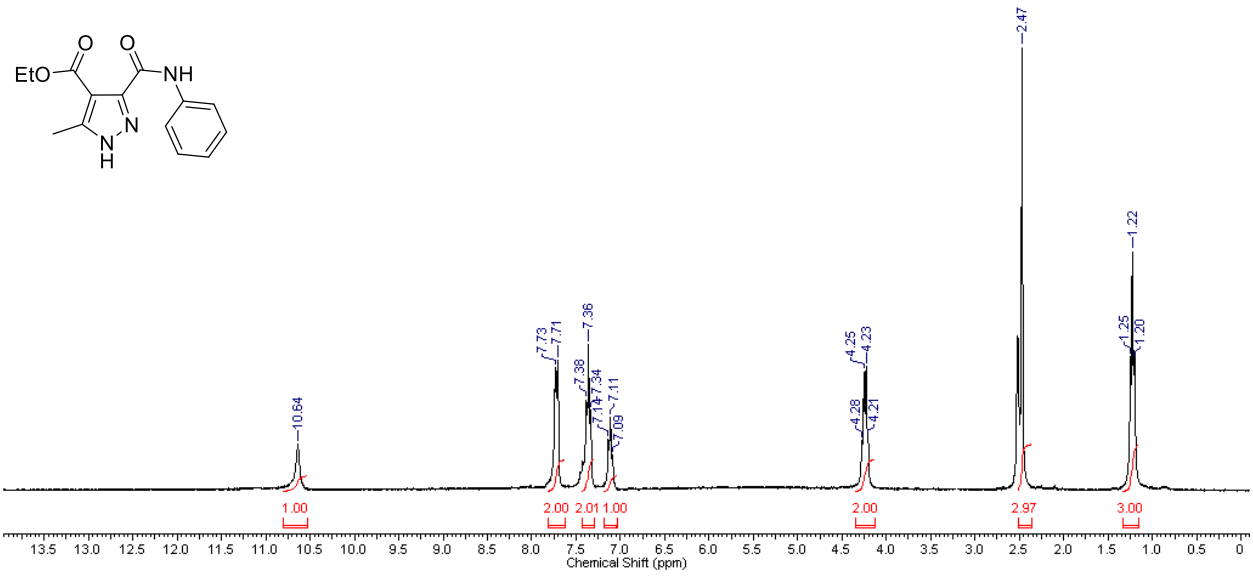
^{1}H NMR (DMSO-d_6, 300 MHz) spectrum of ethyl 5-methyl-3-((2-nitrophenyl)carbamoyl)-1*H*-pyrazole-4-carboxylate (**3s**)



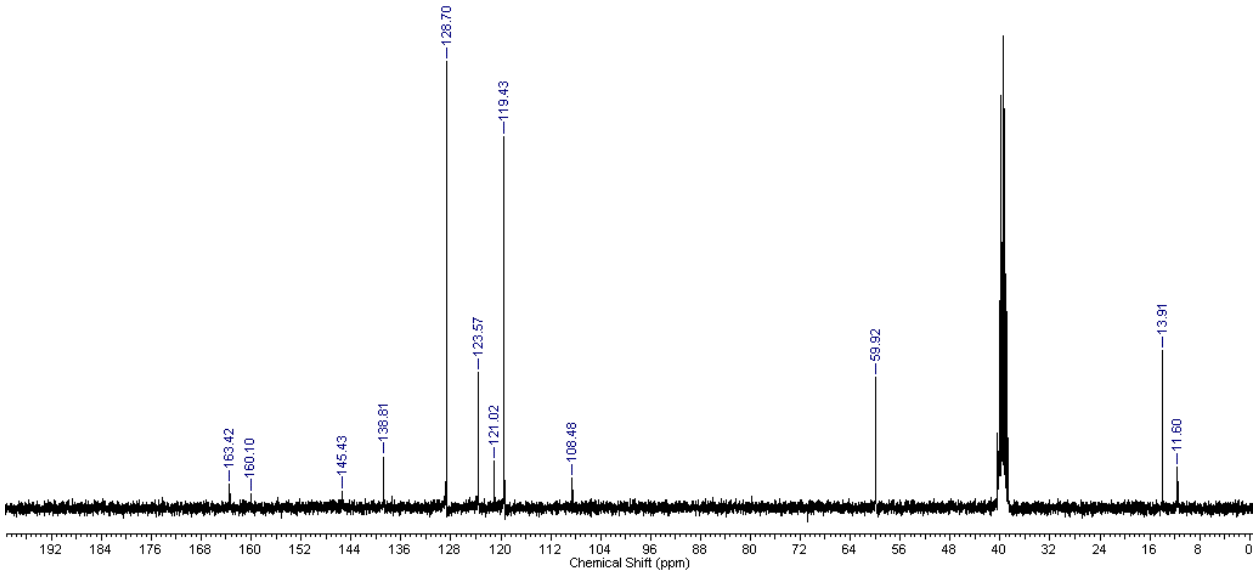
^{13}C NMR (DMSO-d_6, 75 MHz) spectrum of ethyl 5-methyl-3-((2-nitrophenyl)carbamoyl)-1*H*-pyrazole-4-carboxylate (**3s**)



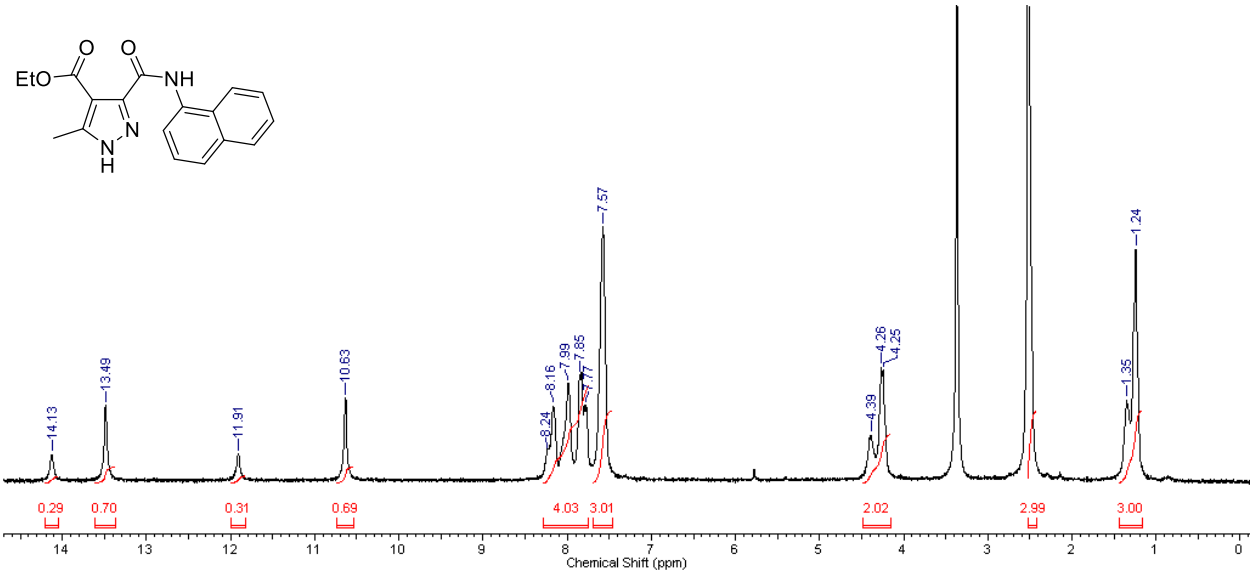
^{1}H NMR (DMSO-d_6, 300 MHz) spectrum of ethyl 5-methyl-3-(phenylcarbamoyl)-1*H*-pyrazole-4-carboxylate (**3t**)



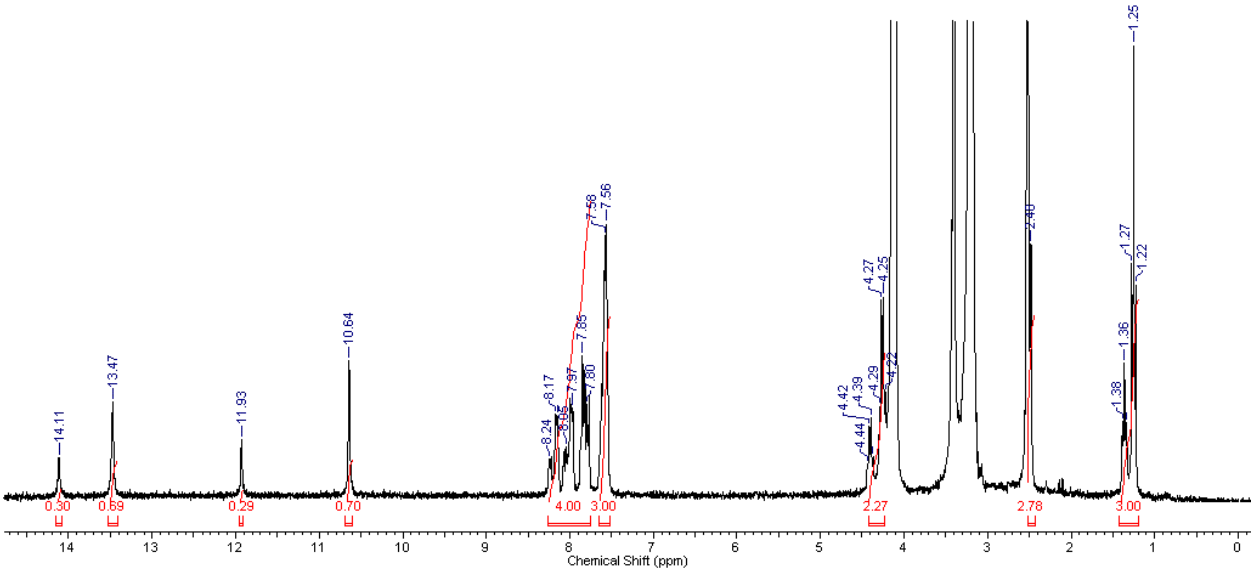
^{13}C NMR (DMSO-d_6, 75 MHz) spectrum of ethyl 5-methyl-3-(phenylcarbamoyl)-1*H*-pyrazole-4-carboxylate (**3t**)



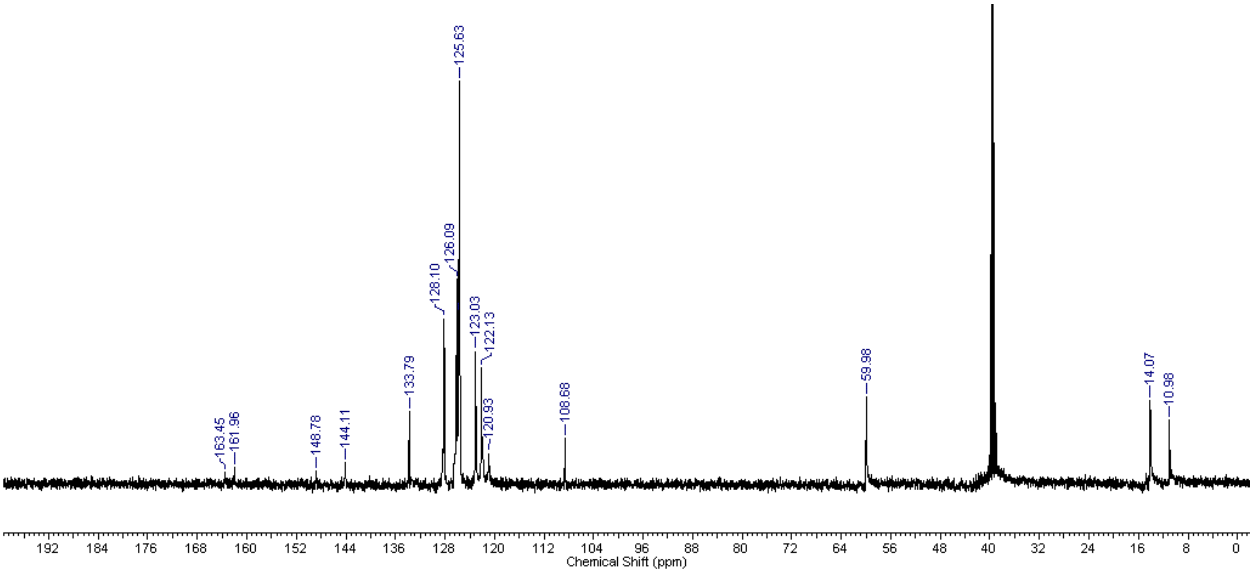
^{1}H NMR (DMSO-d_6, 300 MHz) spectrum of ethyl 5-methyl-3-(naphthalen-1-ylcarbamoyl)-1*H*-pyrazole-4-carboxylate (**3u**)



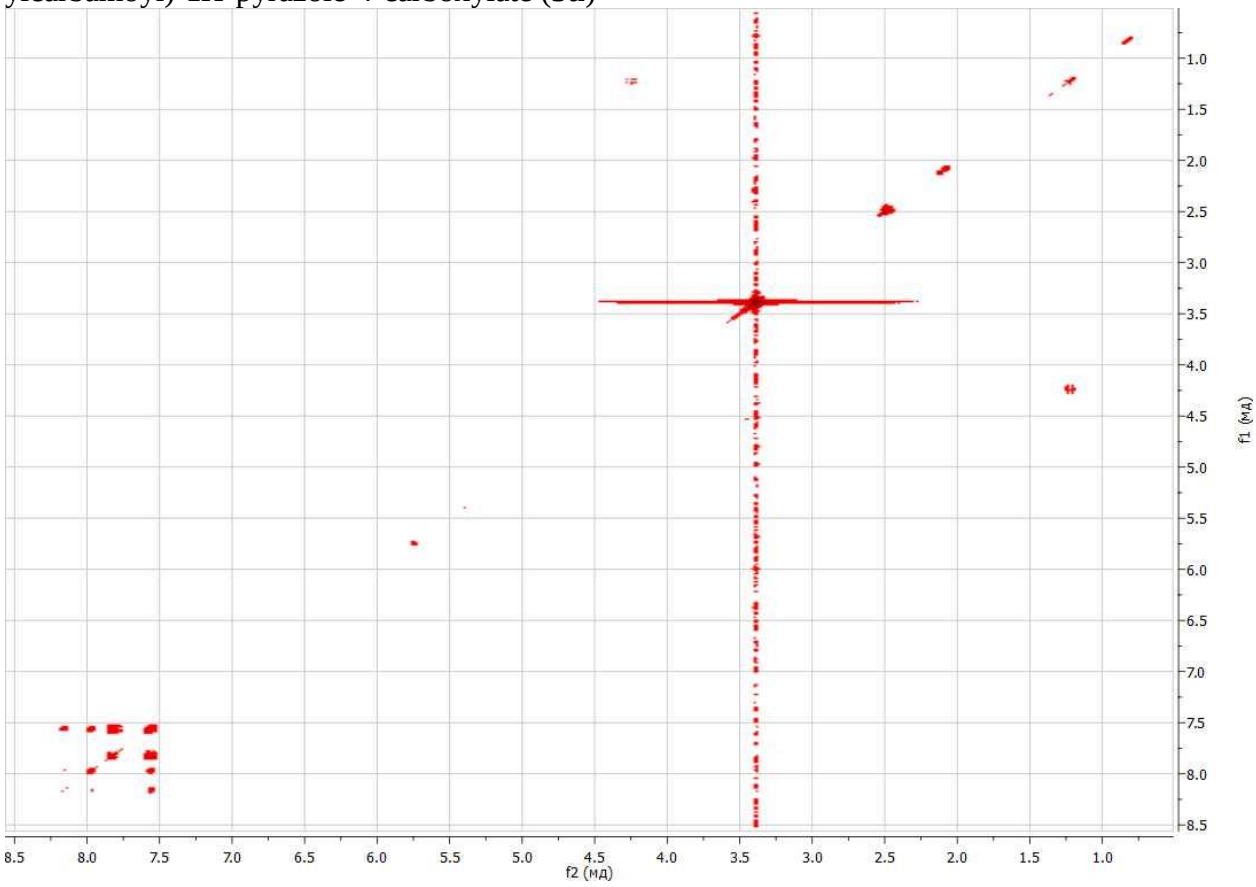
^{1}H NMR (DMSO-d_6, 400 MHz) spectrum of ethyl 5-methyl-3-(naphthalen-1-ylcarbamoyl)-1*H*-pyrazole-4-carboxylate after addition MeOH (**3u**)



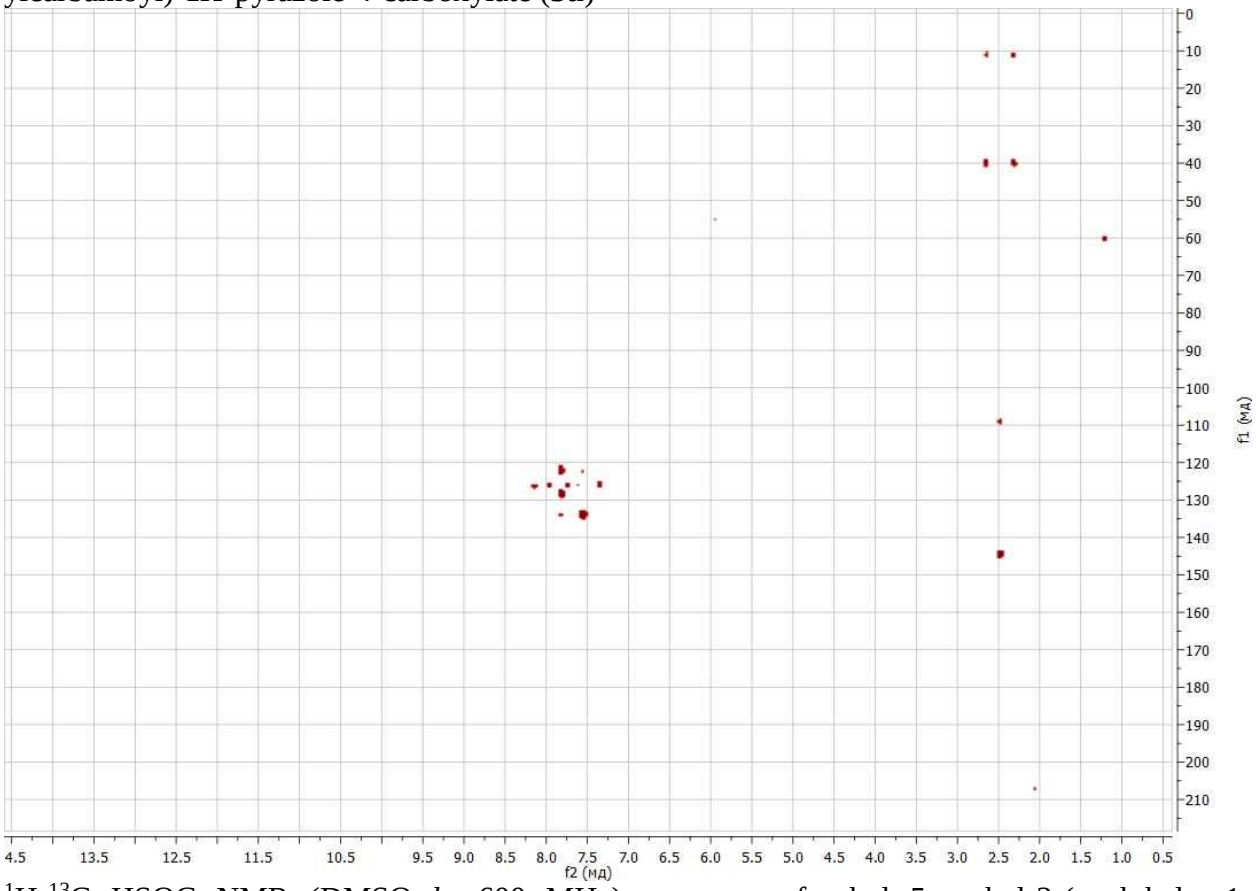
^{13}C NMR (DMSO-d_6, 75 MHz) spectrum of ethyl 5-methyl-3-(naphthalen-1-ylcarbamoyl)-1H-pyrazole-4-carboxylate (**3u**)



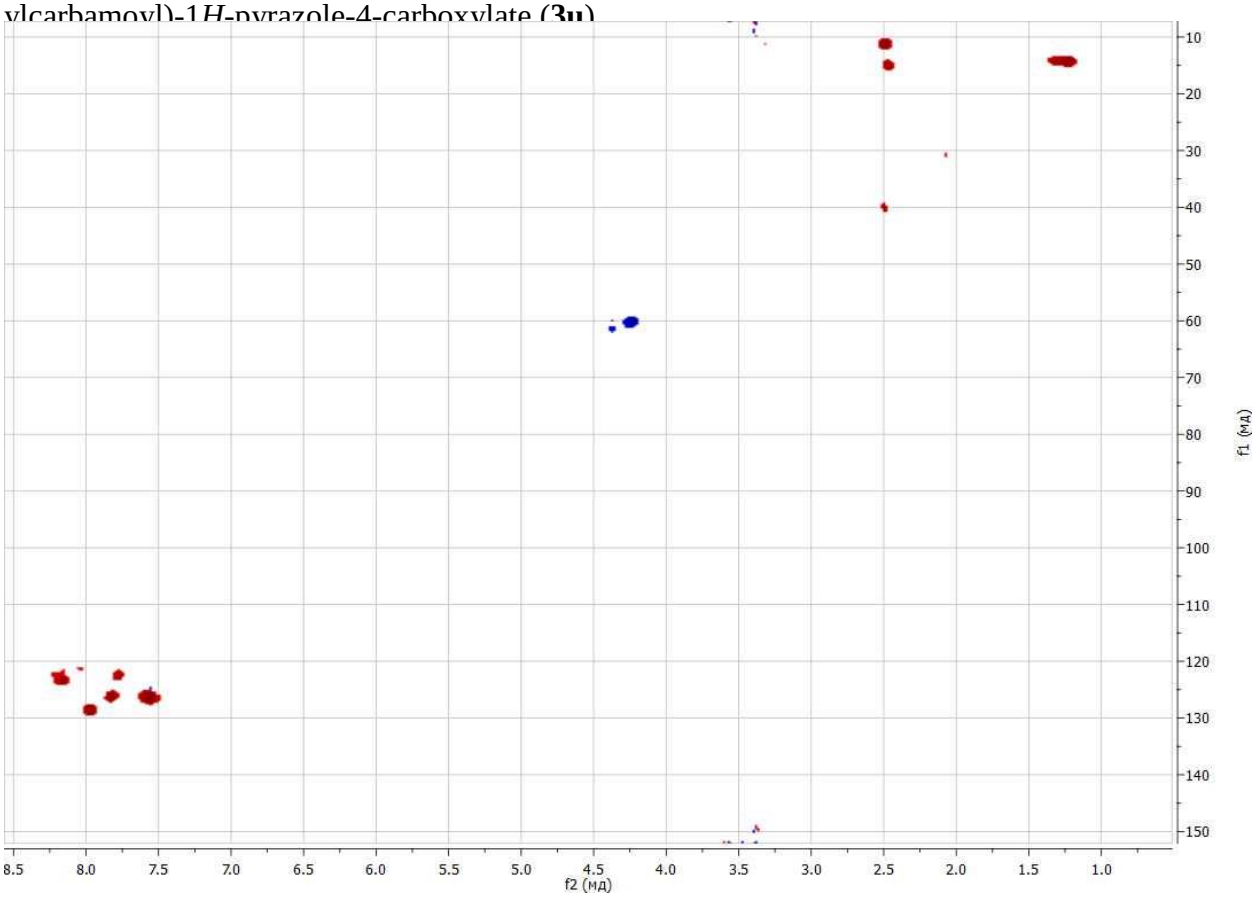
^{1}H-^{1}H COSY NMR (DMSO-d_6, 600 MHz) spectrum of ethyl 5-methyl-3-(naphthalen-1-ylcarbamoyl)-1*H*-pyrazole-4-carboxylate (**3u**)



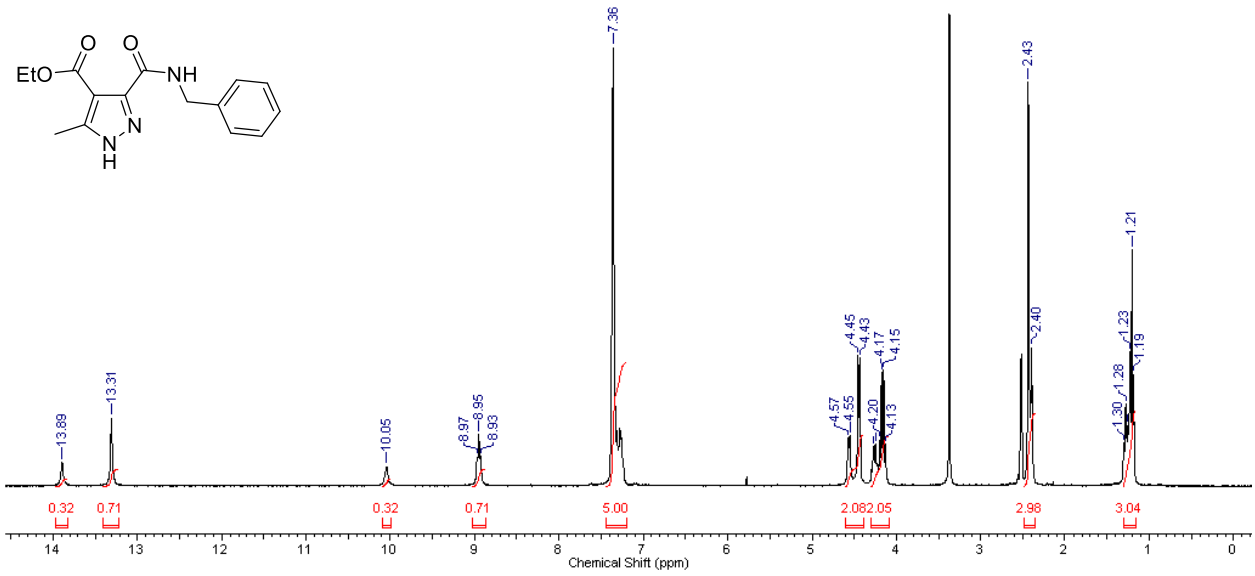
^{1}H-^{13}C HMBC NMR (DMSO-d_6, 600 MHz) spectrum of ethyl 5-methyl-3-(naphthalen-1-ylcarbamoyl)-1*H*-pyrazole-4-carboxylate (**3u**)



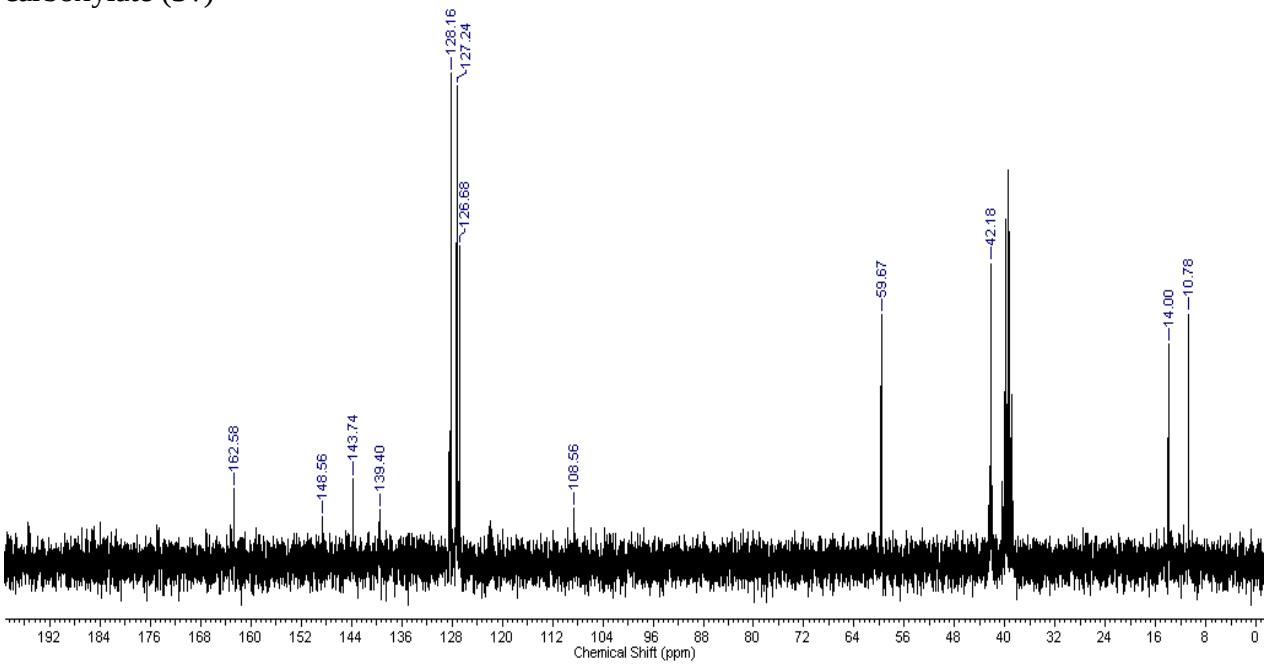
^{1}H-^{13}C HSQC NMR (DMSO-d_6, 600 MHz) spectrum of ethyl 5-methyl-3-(naphthalen-1-ylcarbamoyl)-1*H*-pyrazole-4-carboxylate (**3u**)



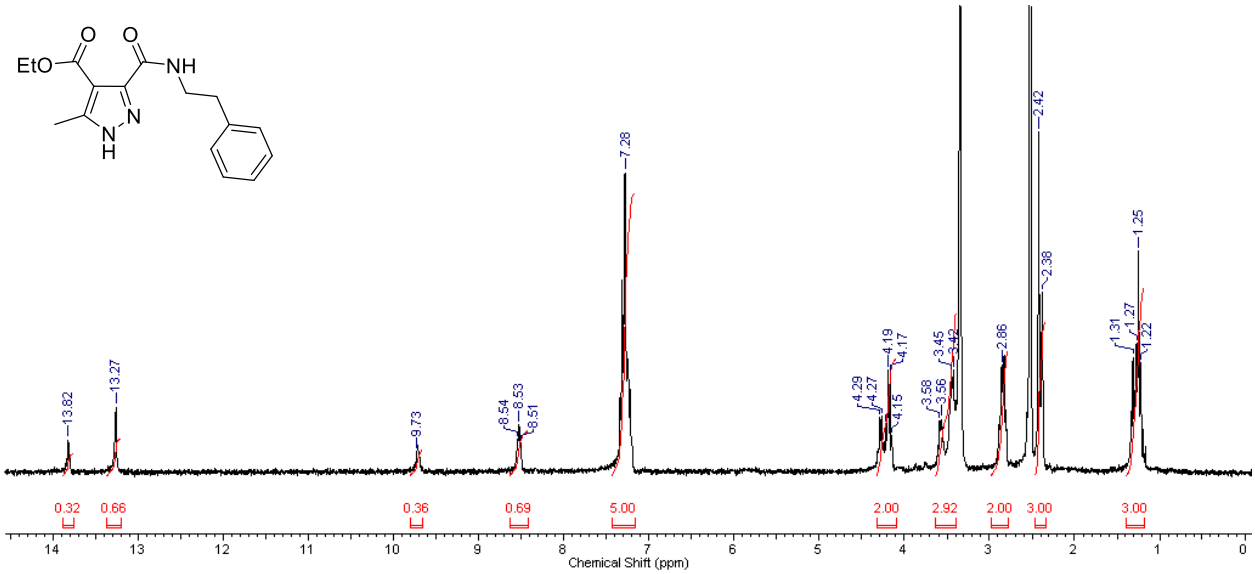
^{1}H NMR (DMSO-d_6, 300 MHz) spectrum of ethyl 3-(benzylcarbamoyl)-5-methyl-1*H*-pyrazole-4-carboxylate (**3v**)



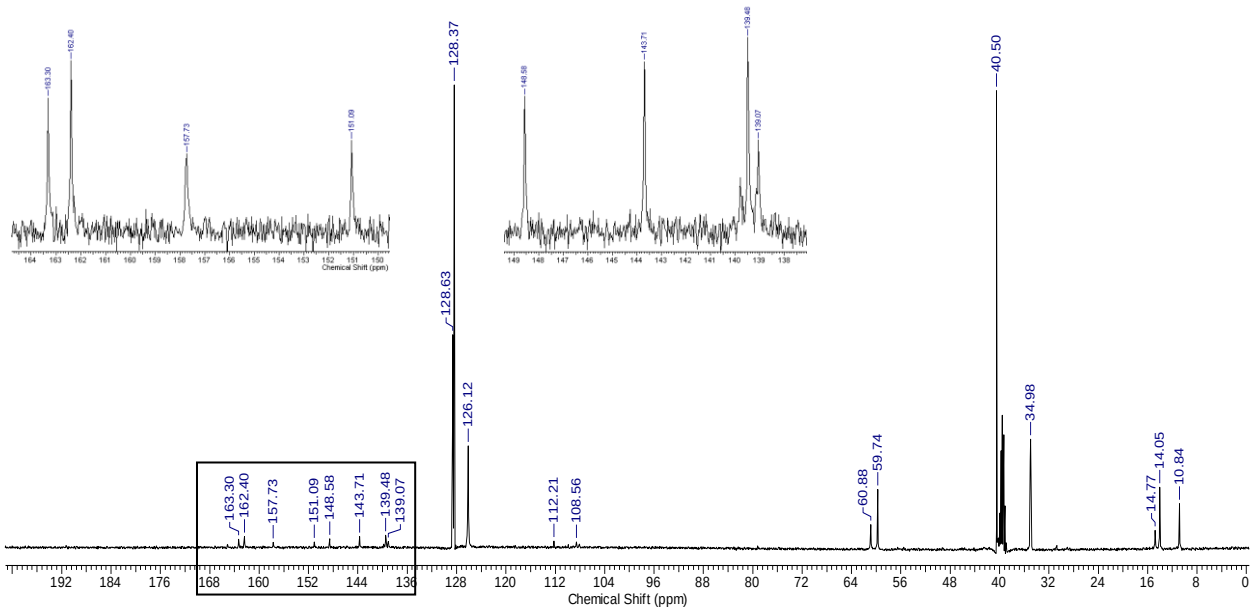
^{13}C NMR (DMSO-d_6, 75 MHz) spectrum of ethyl 3-(benzylcarbamoyl)-5-methyl-1*H*-pyrazole-4-carboxylate (**3v**)



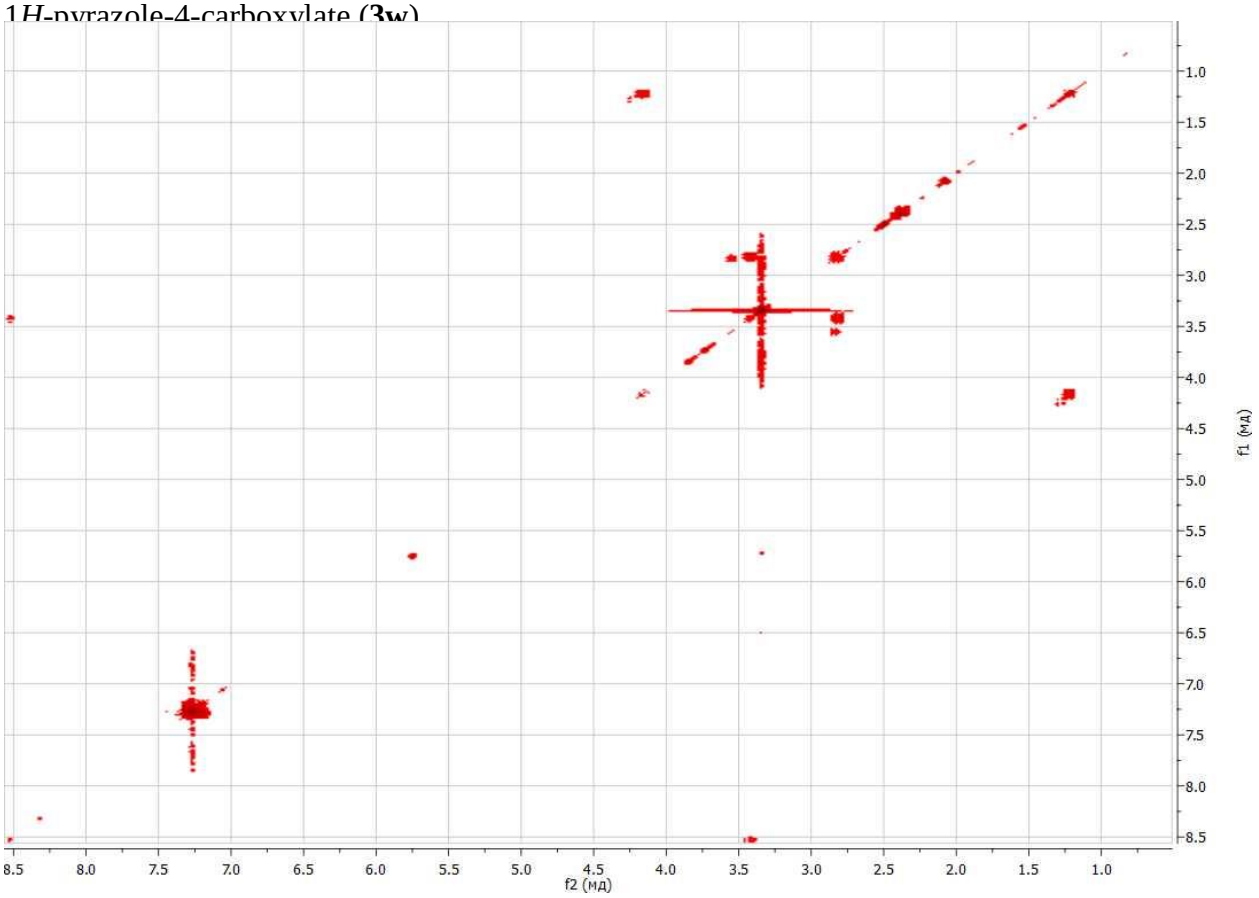
^{1}H NMR (DMSO-d_6, 300 MHz) spectrum of ethyl 5-methyl-3-(phenethylcarbamoyl)-1*H*-pyrazole-4-carboxylate (**3w**)



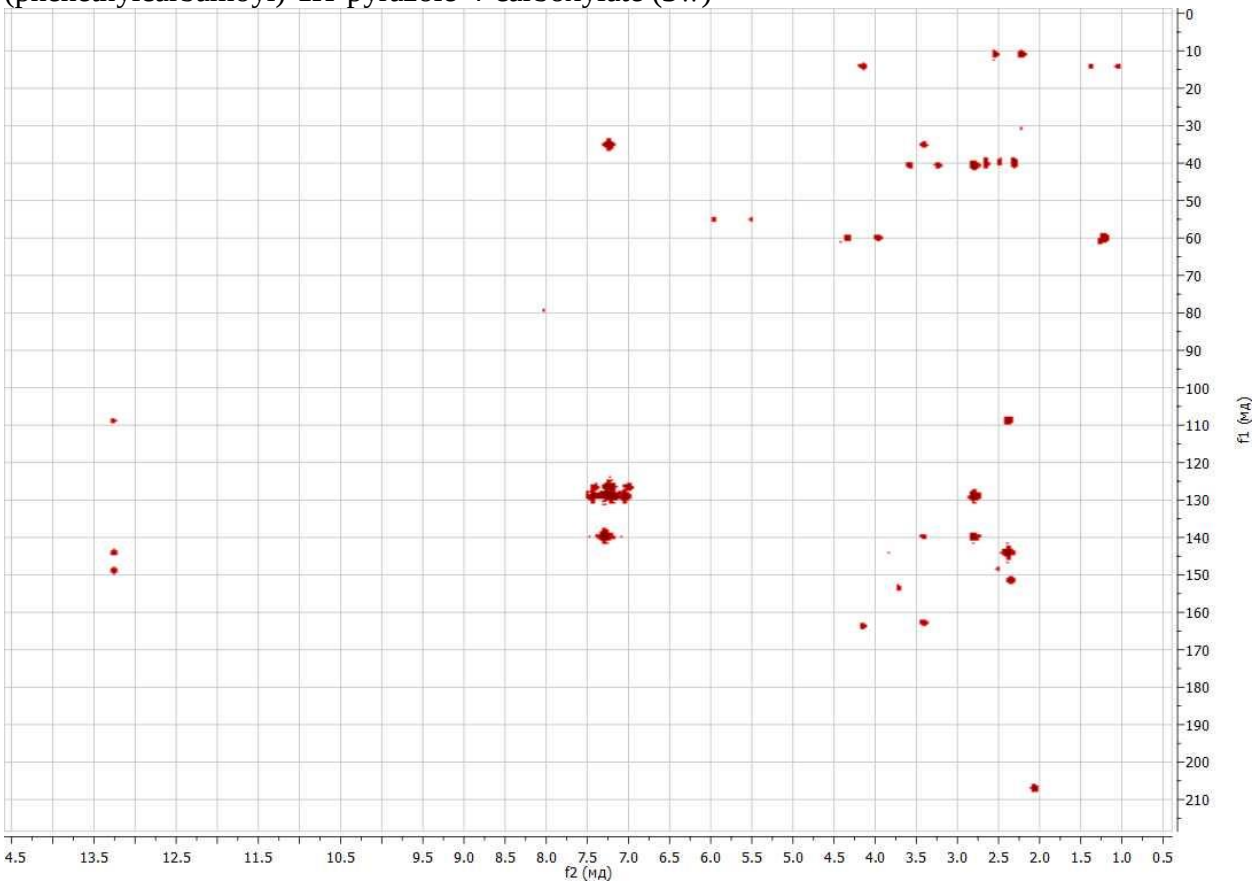
^{13}C NMR (DMSO-d_6, 100 MHz) spectrum of ethyl 5-methyl-3-(phenethylcarbamoyl)-1*H*-pyrazole-4-carboxylate (**3w**)



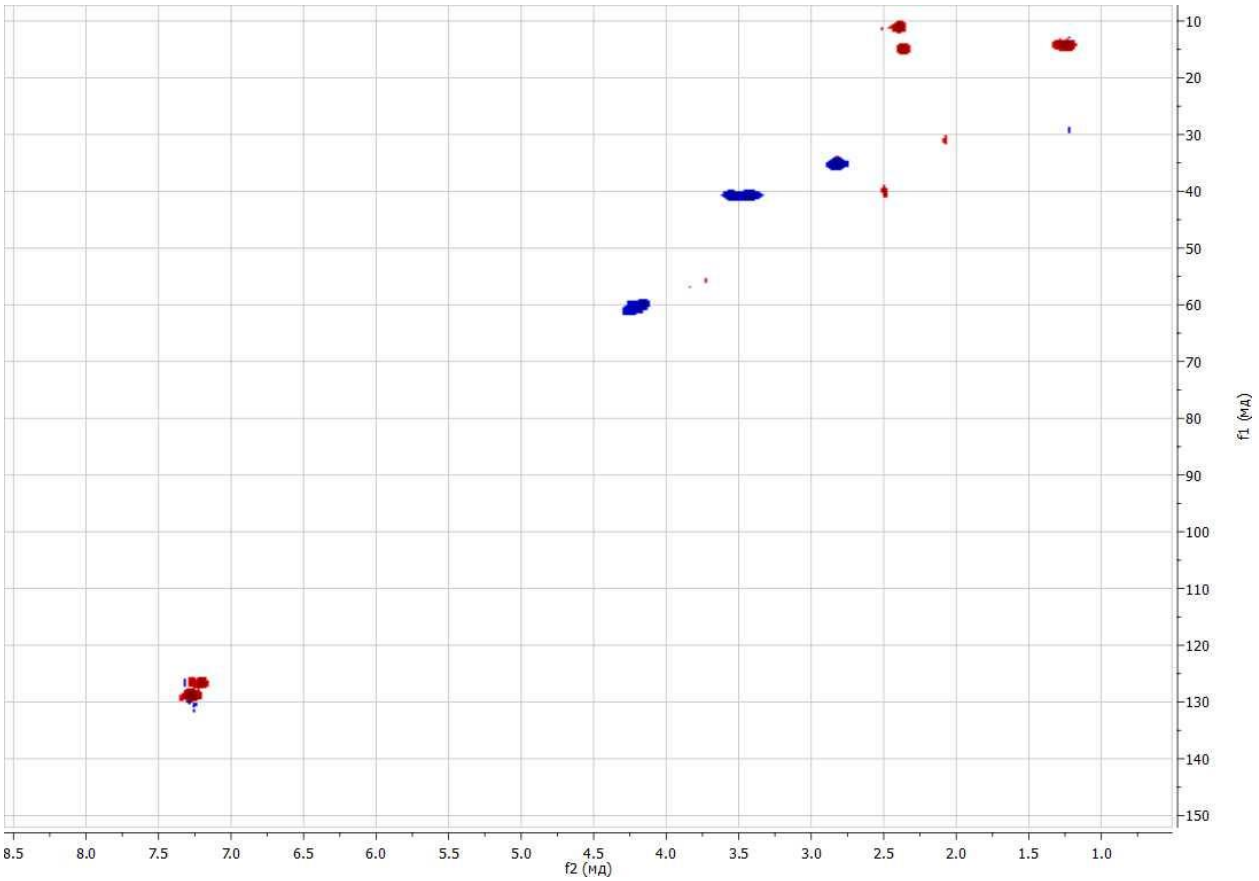
^{1}H-^{1}H COSY NMR (DMSO-d_6, 600 MHz) spectrum of ethyl 5-methyl-3-(phenethylcarbamoyl)-1*H*-pyrazole-4-carboxylate (**3w**)



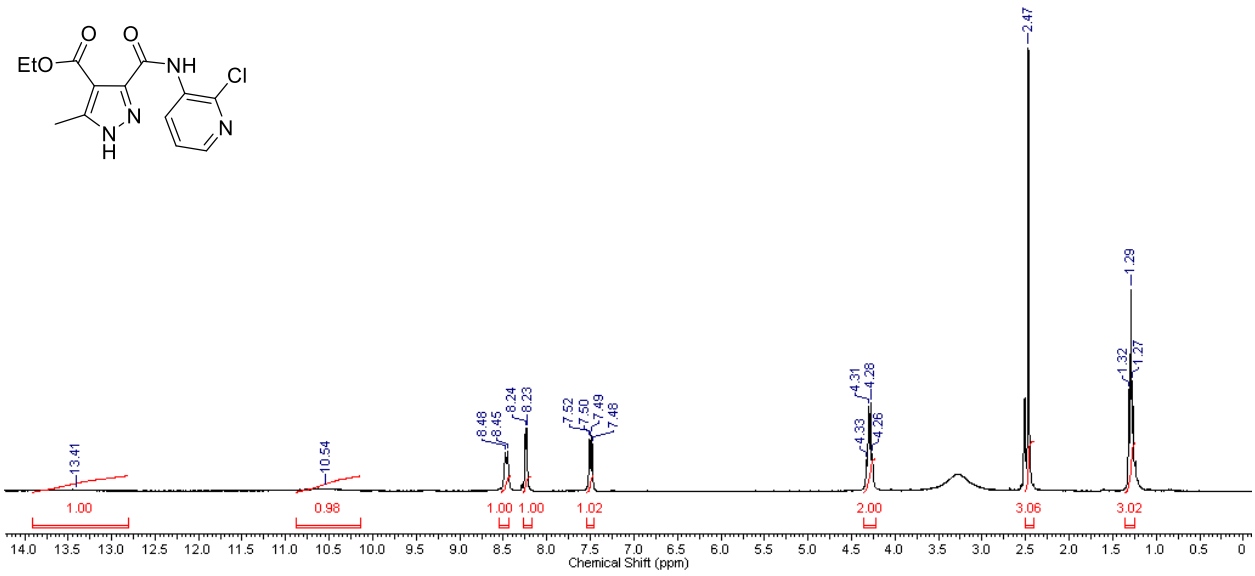
^{1}H-^{13}C HMBC NMR (DMSO-d_6, 600 MHz) spectrum of ethyl 5-methyl-3-(phenethylcarbamoyl)-1*H*-pyrazole-4-carboxylate (**3w**)



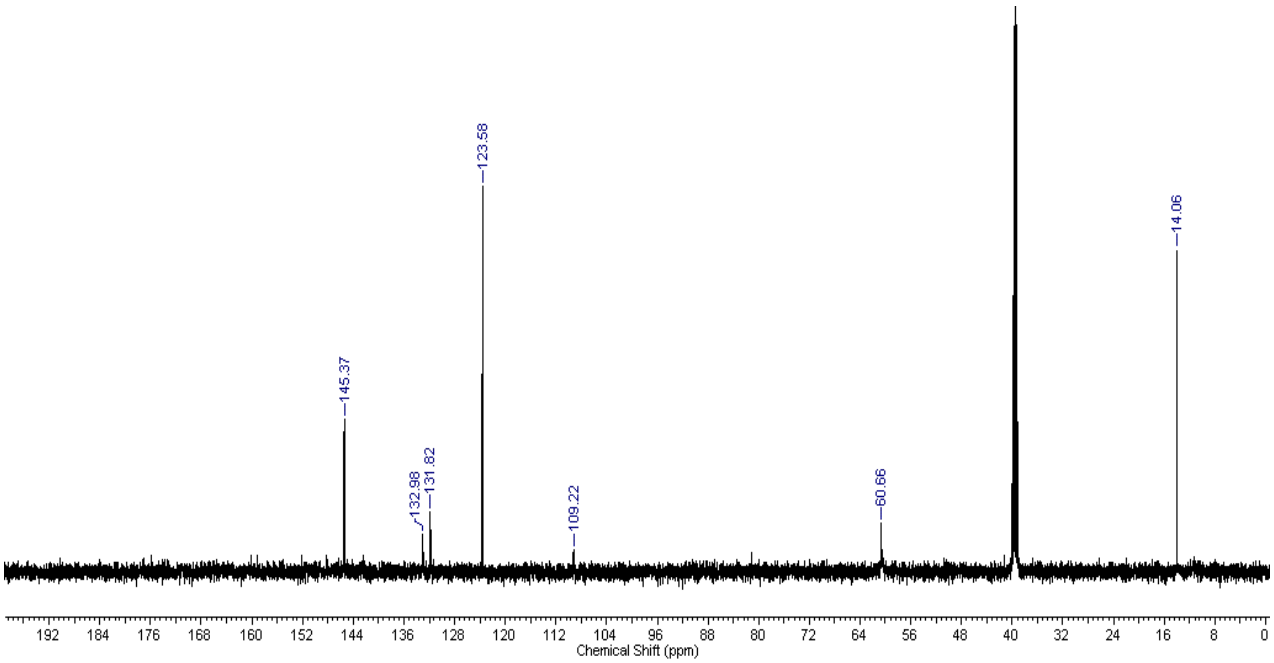
^{1}H-^{13}C HSQC NMR (DMSO-d_6, 600 MHz) spectrum of ethyl 5-methyl-3-(phenethylcarbamoyl)-1*H*-pyrazole-4-carboxylate (**3w**)



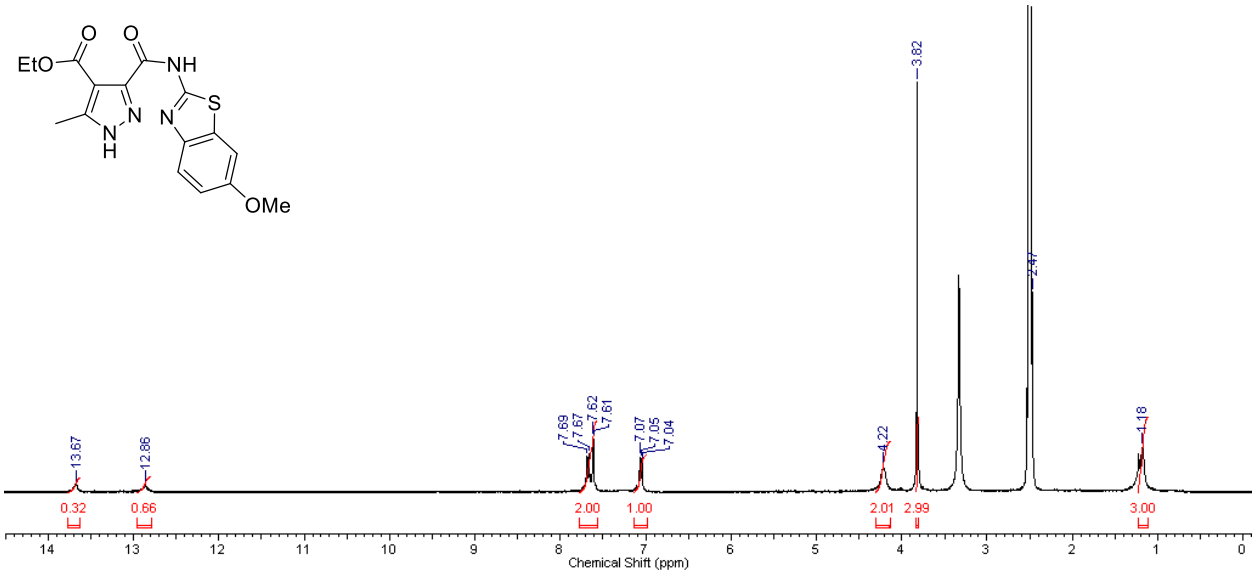
^{1}H NMR (DMSO-d_6, 300 MHz) spectrum of ethyl 3-((2-chloropyridin-3-yl)carbamoyl)-5-methyl-1*H*-pyrazole-4-carboxylate (**3x**)



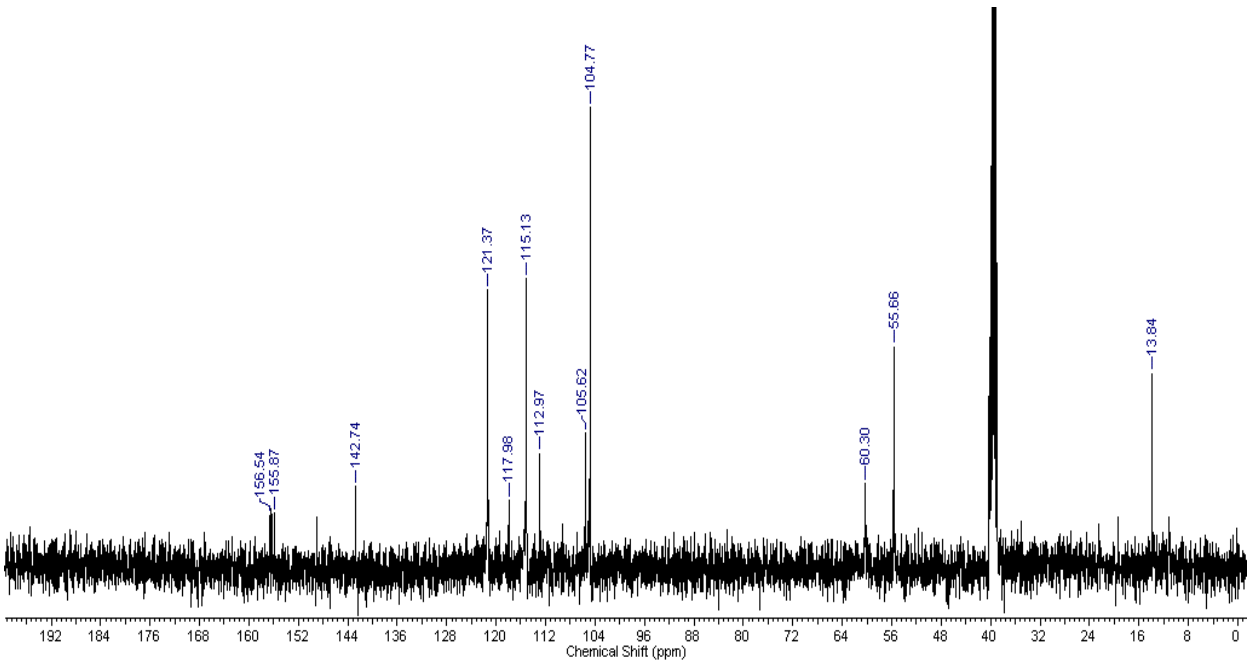
^{13}C NMR (DMSO-d_6, 75 MHz) spectrum of ethyl 3-((2-chloropyridin-3-yl)carbamoyl)-5-methyl-1*H*-pyrazole-4-carboxylate (**3x**)



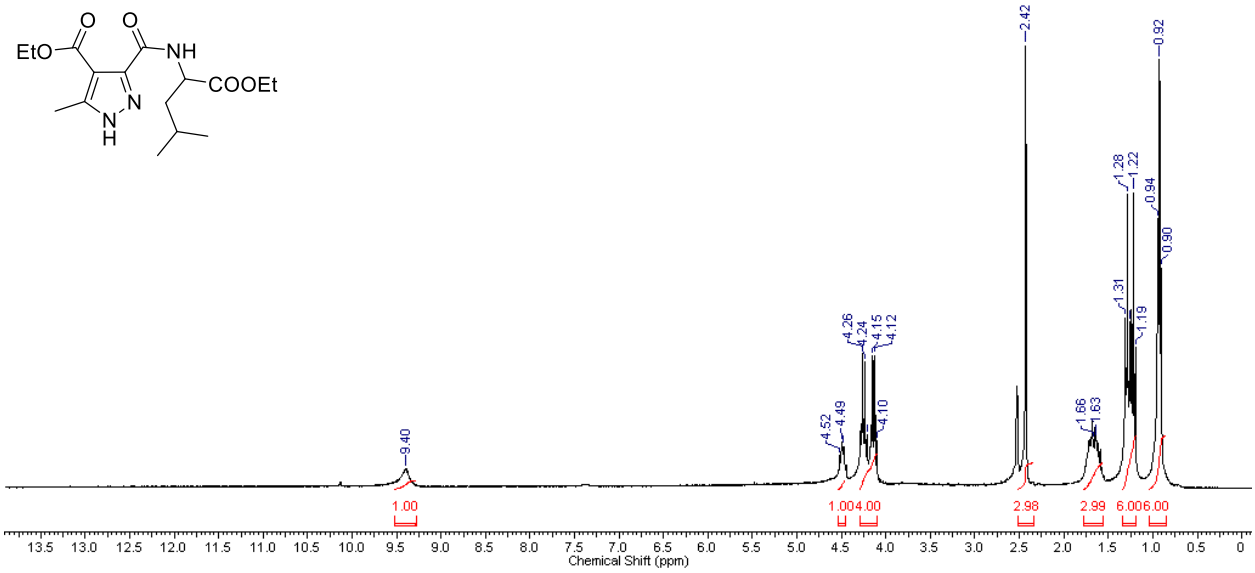
^{1}H NMR (DMSO-d_6, 300 MHz) spectrum of ethyl 3-((6-methoxybenzo[d]thiazol-2-yl)carbamoyl)-5-methyl-1*H*-pyrazole-4-carboxylate (**3y**)



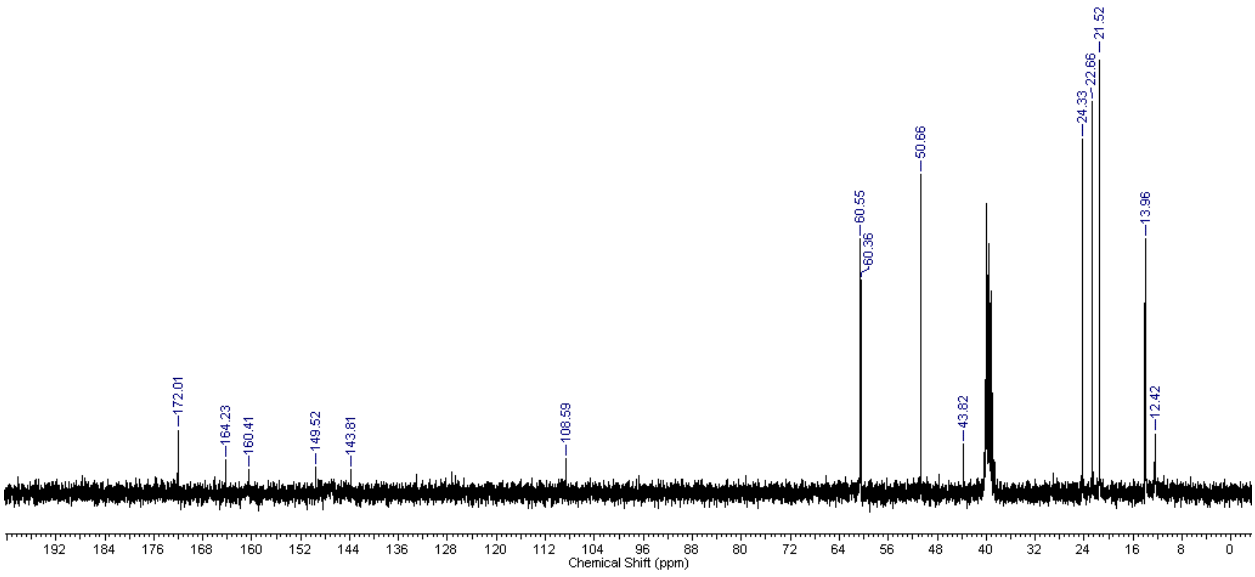
^{13}C NMR (DMSO-d_6, 75 MHz) spectrum of ethyl 3-((6-methoxybenzo[d]thiazol-2-yl)carbamoyl)-5-methyl-1*H*-pyrazole-4-carboxylate (**3y**)



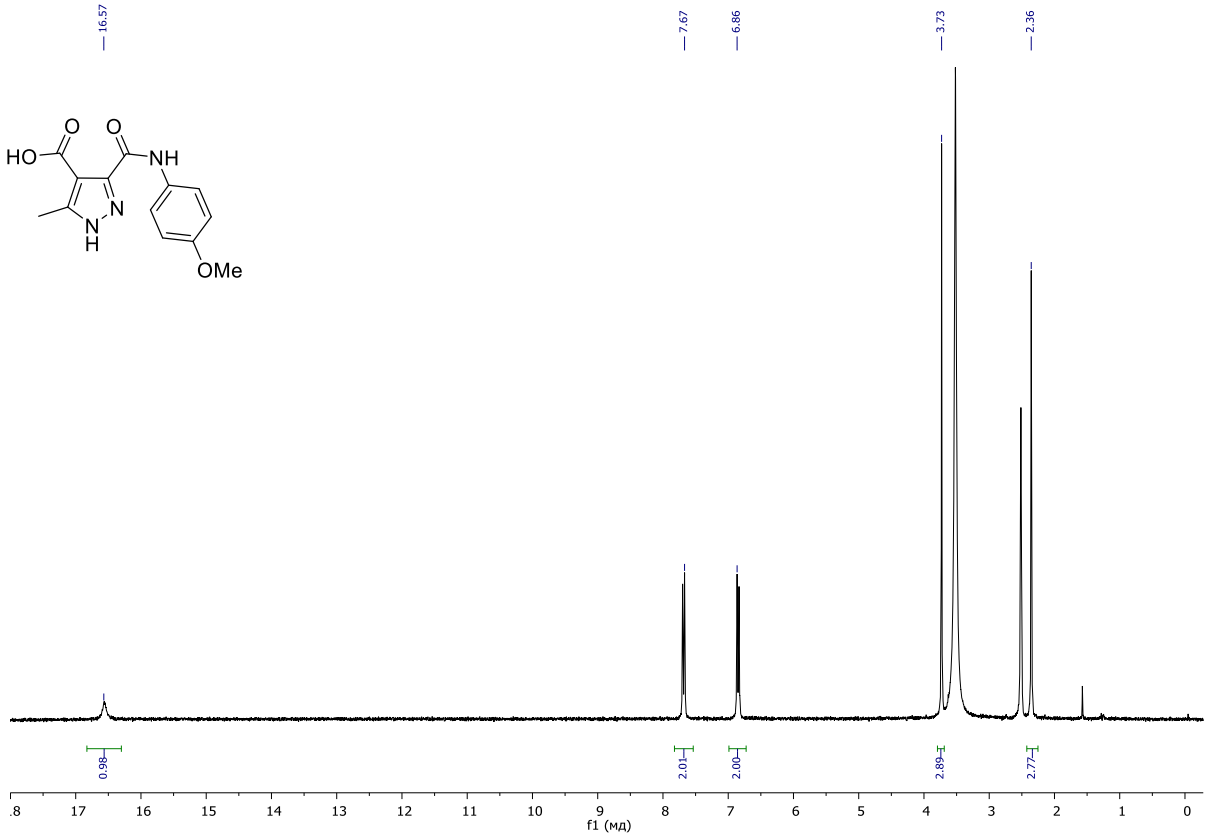
^{1}H NMR (DMSO-d_6, 300 MHz) spectrum of ethyl 3-((1-ethoxy-4-methyl-1-oxopentan-2-yl)carbamoyl)-5-methyl-1*H*-pyrazole-4-carboxylate (**3z**)



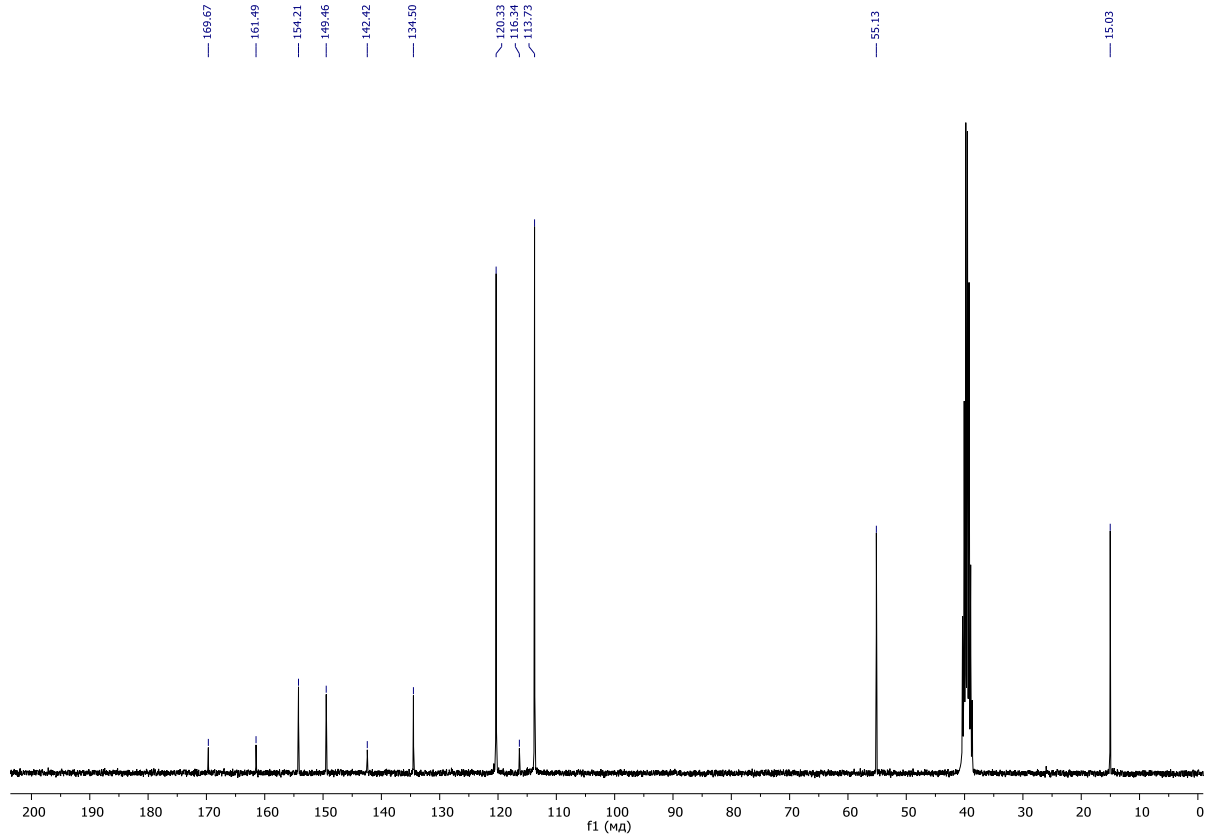
^{13}C NMR (DMSO-d_6, 75 MHz) spectrum of ethyl 3-((1-ethoxy-4-methyl-1-oxopentan-2-yl)carbamoyl)-5-methyl-1*H*-pyrazole-4-carboxylate (**3z**)



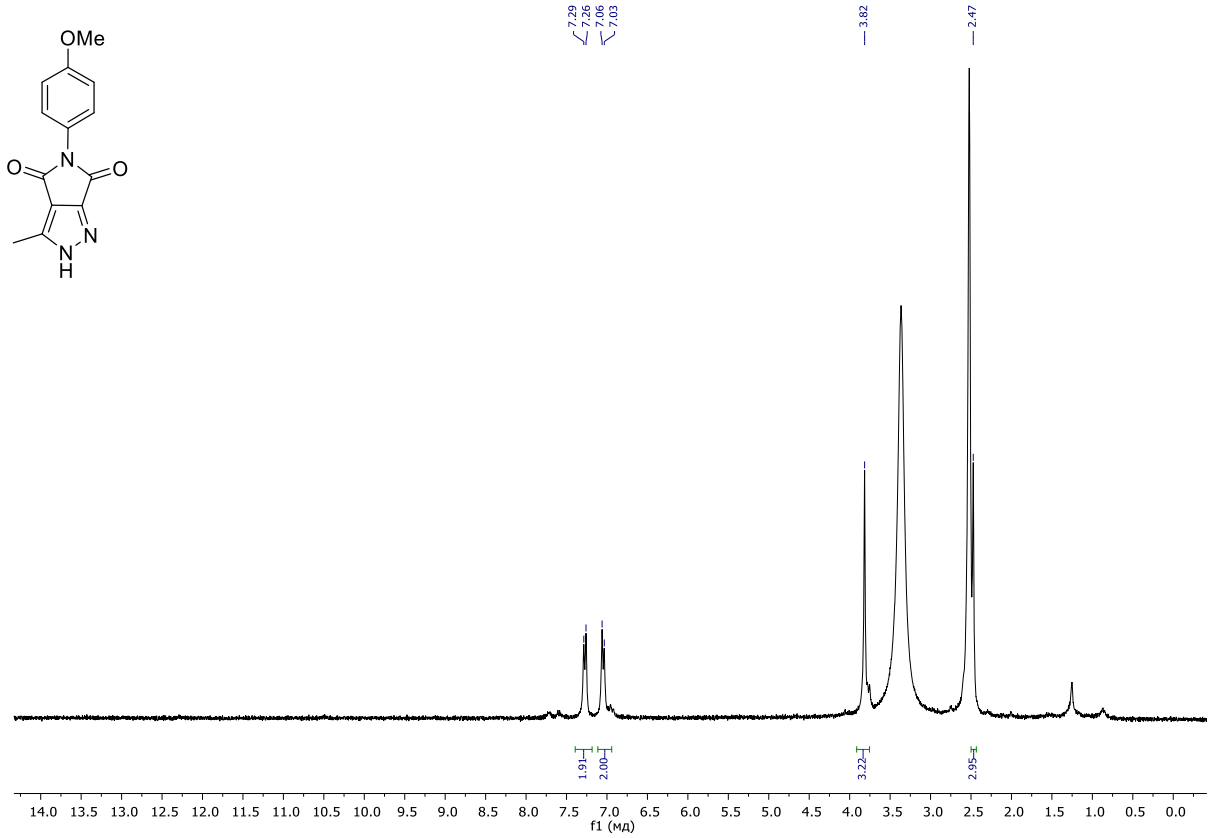
^{1}H NMR (DMSO-d_6, 300 MHz) spectrum of 3-((4-methoxyphenyl)carbamoyl)-5-methyl-1*H*-pyrazole-4-carboxylic acid (**4**)



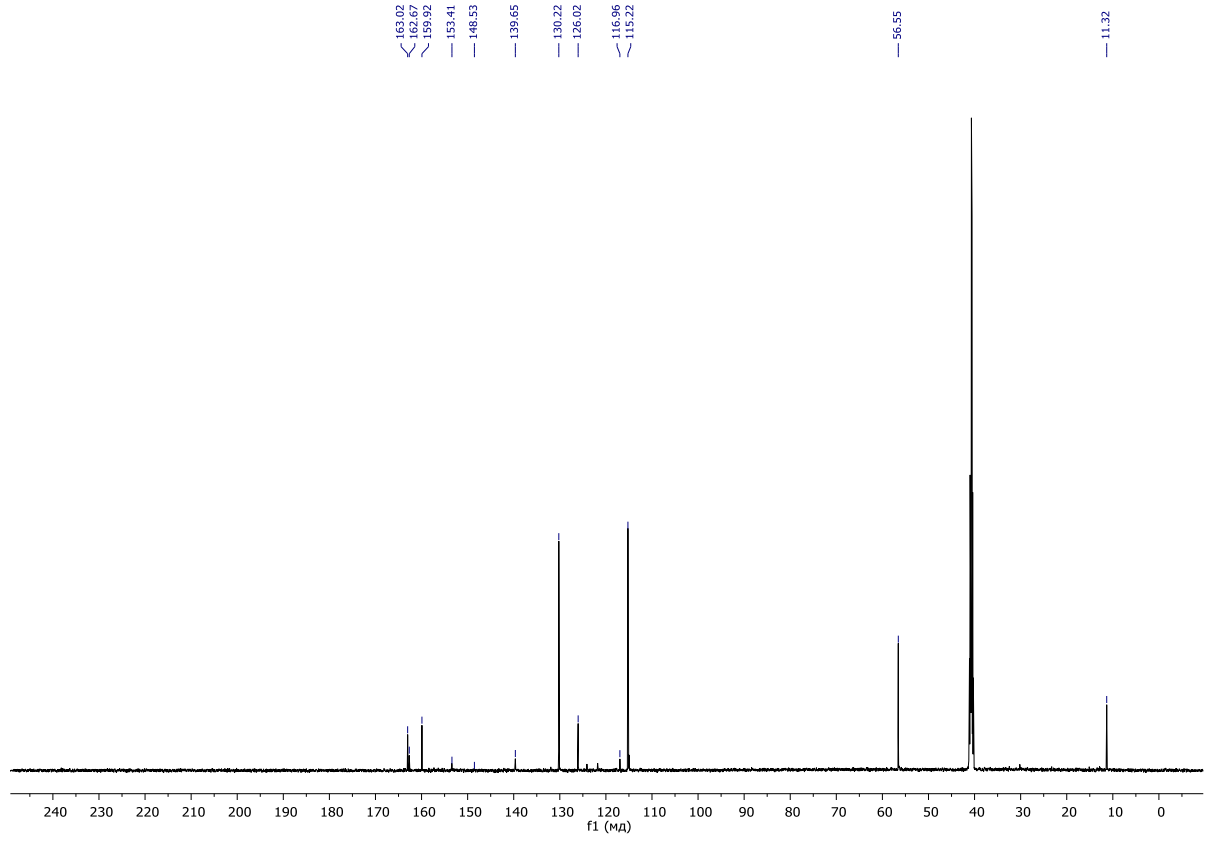
^{13}C NMR (DMSO-d_6, 75 MHz) spectrum of 3-((4-methoxyphenyl)carbamoyl)-5-methyl-1*H*-pyrazole-4-carboxylic acid (**4**)



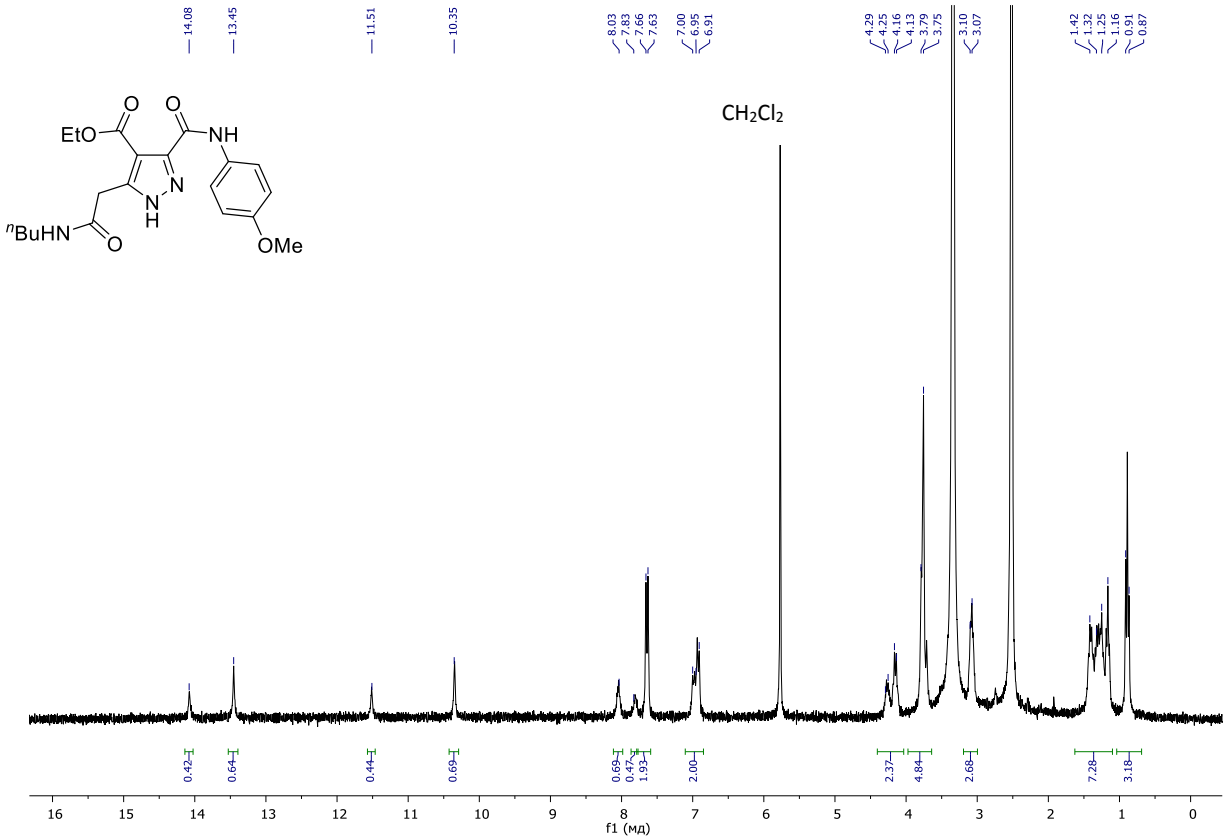
^{1}H NMR (DMSO-d_6, 300 MHz) spectrum of 5-(4-methoxyphenyl)-3-methylpyrrolo[3,4-c]pyrazole-4,6(2*H*,5*H*)-dione (**5**)



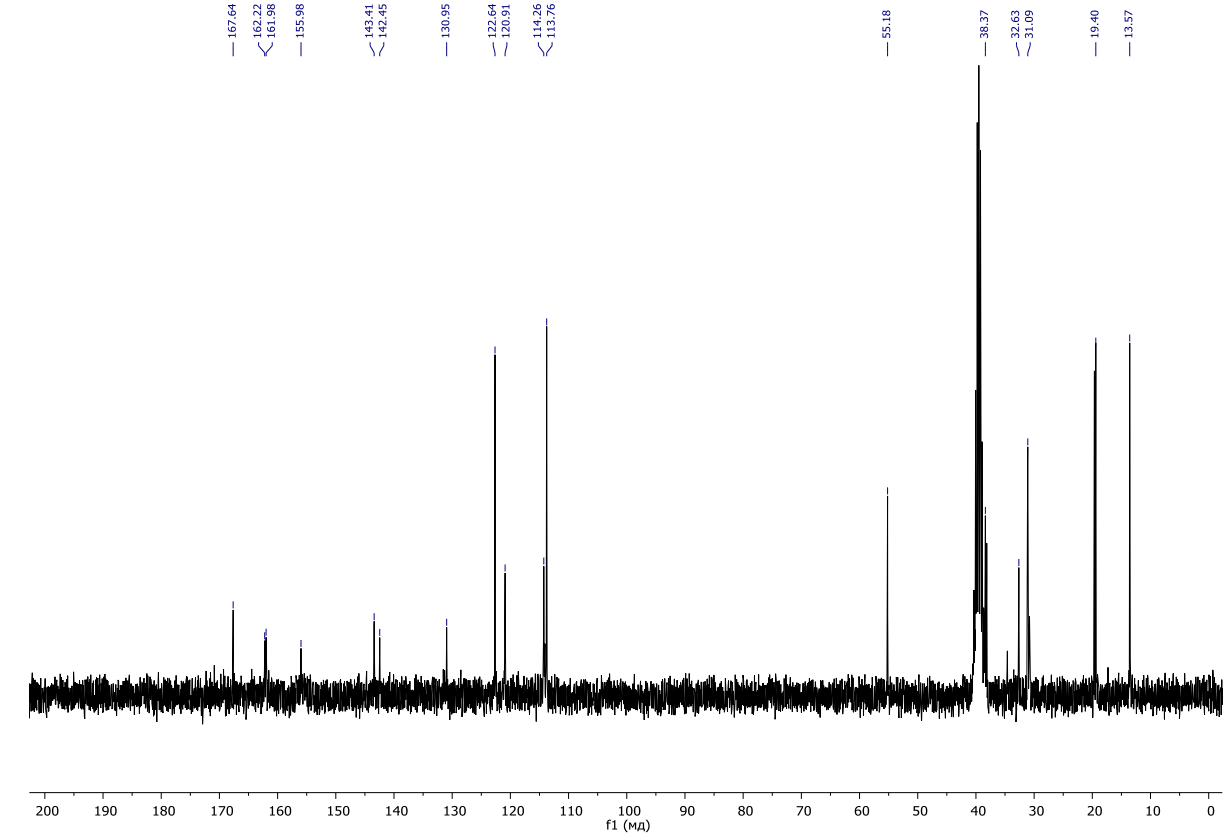
^{13}C NMR (DMSO-d_6, 75 MHz) spectrum of 5-(4-methoxyphenyl)-3-methylpyrrolo[3,4-c]pyrazole-4,6(2*H*,5*H*)-dione (**5**)



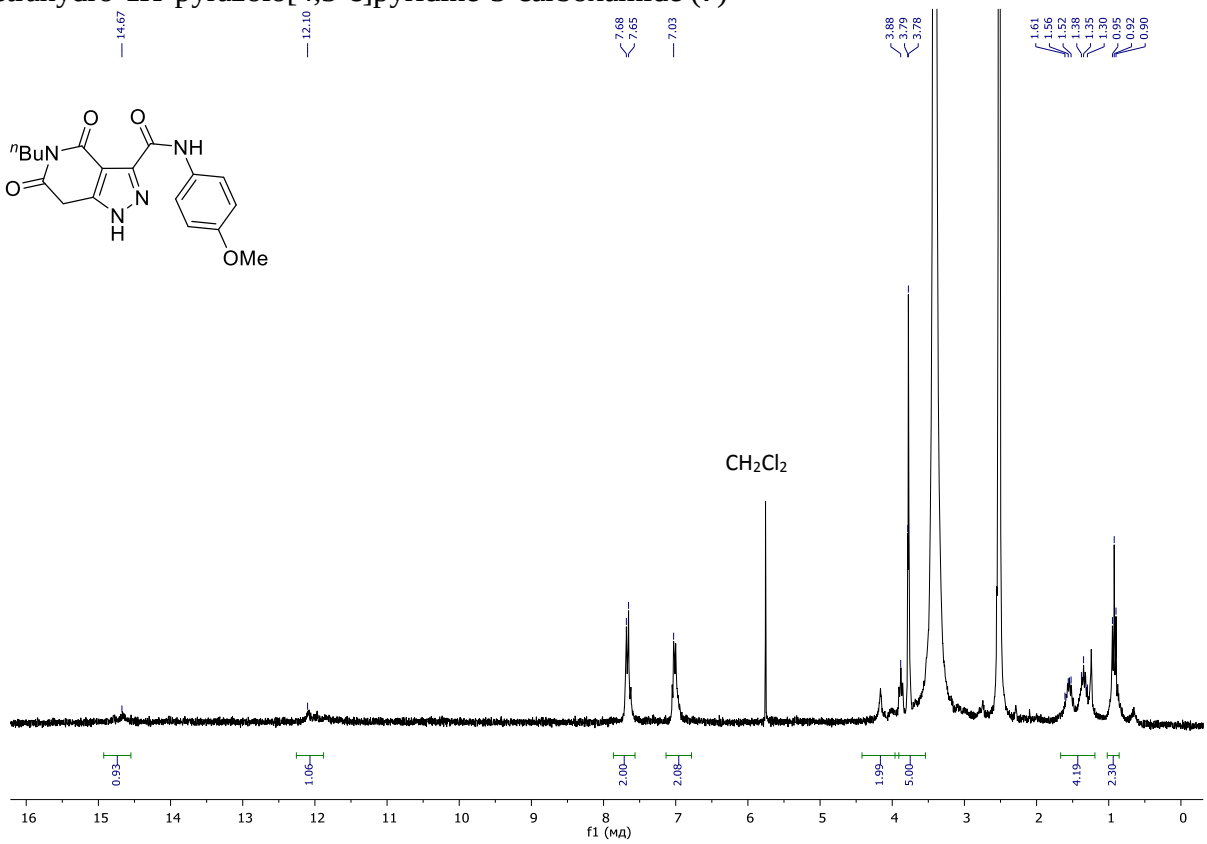
^{1}H NMR (DMSO-d_6, 300 MHz) spectrum of ethyl 5-(2-(butylamino)-2-oxoethyl)-3-((4-methoxyphenyl)carbamoyl)-1*H*-pyrazole-4-carboxylate (**6**)



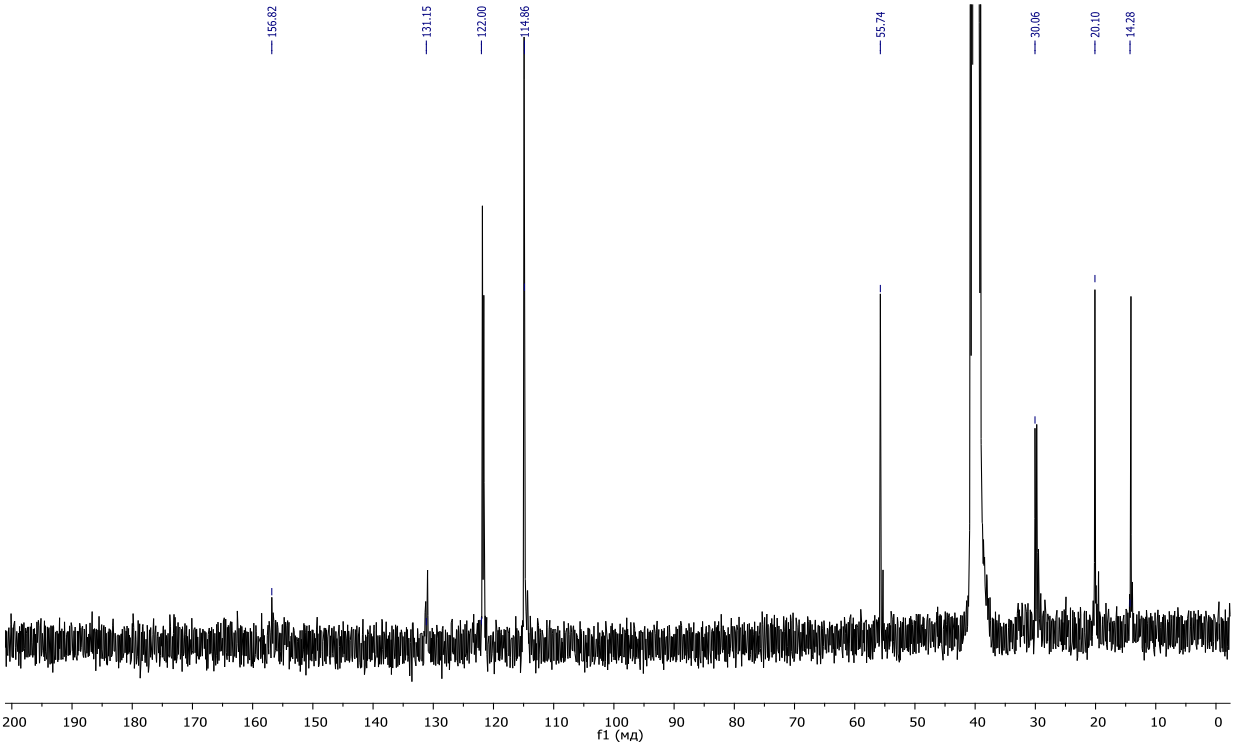
^{13}C NMR (DMSO-d_6, 75 MHz) spectrum of ethyl 5-(2-(butylamino)-2-oxoethyl)-3-((4-methoxyphenyl)carbamoyl)-1*H*-pyrazole-4-carboxylate (**6**)



^{1}H NMR (DMSO-d_6, 300 MHz) spectrum of 5-butyl-*N*-(4-methoxyphenyl)-4,6-dioxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[4,3-c]pyridine-3-carboxamide (**7**)



^{13}C NMR (DMSO-d_6, 75 MHz) spectrum of 5-butyl-*N*-(4-methoxyphenyl)-4,6-dioxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[4,3-c]pyridine-3-carboxamide (**7**)



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