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Recyclization of *N*-arylitaconimides with hydrazines as a new effective synthesis of 2-(3-oxopyrazolidin-4-yl)acetanilides

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Materials and Methods

^{1}H and ^{13}C NMR spectra were registered on Bruker DRX-500 (500 and 150.9 MHz, respectively) spectrometer in DMSO-d_6, internal standard was TMS. Melting points were determined on Stuart SMP 30. Control of reagent and products individuality, qualitative analysis of reaction mass was performed by TLC on Merck TLC Silica gel 60 F254 chromatographic plate; eluents: methanol, chloroform and their mixtures in various ratios. The chromatograms were visualized by UV or iodine vapor.

Product purity was monitored by high performance liquid chromatography with high resolution mass spectrometric electrospray ionization detection (HPLC-HRMS-ESI) in combination with UV detection. The analyzes were performed on Agilent 1260 Infinity chromatograph (Agilent Technologies, CA, USA) and Agilent 6230 TOF LC/MS high-resolution time-of-flight mass detector. The ionization block was double electrospray; the signals were recorded in positive polarity; nebulizer N_2 20 psig; desiccant gas N_2, 6 ml min^{-1}, 325 °C; mass detection range is 50-2000 Da. Capillary voltage 4.0 kV, fragmentator +191 V, skimmer +66 V, OctRF 750 V. Poroshell 120 EC-C18 column (4.6 x 50 mm; 2.7 μm) was used. Gradient elution: acetonitrile/water (0.1% formic acid); flow rate 0.4 ml min^{-1}. Software for processing research results - MassHunter Workstation/Data Acquisition V.06.00.

Table S1 Yield of 2-(2-oxopyrazolidin-4-yl)acetanilide **2a** in the reaction between *N*-phenylitaconimide **1a** and N_2H_4 at 20-40 °C

Solvent	Yield of **2a**, %	
	LC/MS	Isolated
MeOH	68	35
MeCN	70	30
Dioxane	78	65
$Pr^{i}OH$	55	15

Experimental.

Synthesis of 2-(3-oxopyrazolidin-4-yl)acetanilides 2a-f. Anhydrous hydrazine (0.32 g, 10 mmol) is added to a solution of *N*-arylitaconimide **1a-f** (5 mmol) in dioxane (50 ml), and this was stirred for 3-5 hours. The precipitate crystals are filtered and dried.

2-(3-Oxopyrazolidin-4-yl)-*N*-phenylacetamide 2a. Yield 55%, colorless powdery compound, m.p. 172-173 °C. ^{1}H NMR, ((δ, ppm., *J*/Hz): 10.00 (1H, s, CO-NH), 9.18 (1H, s, NH-2), 7.01-7.59 (5H, m, 5CH-Ar), 5.27 (1H, s, NH-1), 3.51 (1H, dd, *J* = 7.5, *J* = 10.9, CH_2-*endo*), 2.91 (1H, dd, *J* = 10.7, *J* = 21.5, CH_2-*endo*), 2.81-2.88 (1H, m, CH-4), 2.74 (1H. dd, *J* = 9.9, *J* = 15.6, CH_2-*exo*), 2.32 (1H, dd, *J* = 9.8, *J* = 15.6, CH_2-*exo*). ^{13}C NMR (δ, ppm): 176.54, 169.66, 139.12, 128.65, 123.06, 119.03, 52.24, 39.38, 35.81. HRMS: m/z calcd for $C_{11}H_{13}N_3O_2$, 220.1087; found, 220.1080.

2-(3-Oxopyrazolidin-4-yl)-*N*-(*p*-tolyl)acetamide 2b. Yield 60%, colorless powdery compound, m.p. 174-175 °C. ^{1}H NMR, ((δ, ppm., *J*/Hz): 9.88 (1H, s, CO-NH), 9.14 (1H, s, NH-2), 7.06-7.45 (4H, m, 5CH-Ar), 5.25 (1H, s, NH-1), 3.46 (1H, dd, *J* = 7.4, *J* = 10.7, CH_2-*endo*), 2.86 (1H, dd, *J* = 10.6, *J* = 21.3, CH_2-*endo*), 2.74-2.84 (1H, m, CH-4), 2.69 (1H. dd, *J* = 3.8, *J* = 15.6, CH_2-*exo*), 2.25 (1H, dd, *J* = 9.8, *J* = 15.6, CH_2-*exo*), 2.21 (3H, s, CH_3). ^{13}C NMR (δ, ppm): 176.98, 169.83, 137.09, 132.36, 129.47, 119.49, 52.73, 39.38, 36.21, 20.86. HRMS: m/z calcd for $C_{12}H_{15}N_3O_2$, 234.1243; found, 234.1237.

***N*-(4-Ethoxyphenyl)-2-(3-oxopyrazolidin-4-yl)acetamide 2c.** Yield 55%, colorless powdery compound, m.p. 170-172 °C. ^{1}H NMR, ((δ, ppm., *J*/Hz): 9.85 (1H, s, CO-NH), 9.17 (1H, s, NH-2), 6.83-7.47 (4H, m, 4CH-Ar), 5.28 (1H, s, NH-1), 3.96 (2H, q, *J* = 6.9, O-CH_2), 3.49 (1H, dd, *J* = 7.9, *J* = 10.3, CH_2-*endo*), 2.89 (1H, dd, *J* = 10.3, *J* = 21.1, CH_2-*endo*), 2.77-2.86 (1H, m, CH-4), 2.69 (1H. dd, *J* = 3.5, *J* = 15.5, CH_2-*exo*), 2.25 (1H, dd, *J* = 9.9, *J* = 15.4, CH_2-*exo*), 1.30 (3H, t, *J* = 6.9, CH_3). ^{13}C NMR (δ, ppm): 176.62, 169.16, 154.39, 132.29, 120.62, 114.37, 66.40, 63.10, 52.34, 35.72, 14.73. HRMS: m/z calcd for $C_{13}H_{17}N_3O_3$, 264.1349; found, 264.1345.

***N*-(4-Chlorophenyl)-2-(3-oxopyrazolidin-4-yl)acetamide 2d.** Yield 65%, colorless powdery compound, m.p. 183-184 °C. ^{1}H NMR, ((δ, ppm., *J*/Hz): 10.15 (1H, s, CO-NH), 9.18 (1H, s, NH-2), 7.34-7.62 (4H, m, 4CH-Ar), 5.28 (1H, s, NH-1), 3.49 (1H, dd, *J* = 7.9, J = 10.5, CH_2-*endo*), 2.80-2.95 (2H, m, CH-4 + CH_2-*endo*), 2.73 (1H. dd, *J* = 3.6, *J* = 15.8, CH_2-*exo*), 2.31 (1H, dd, *J* = 9.7, *J* = 15.6, CH_2-*exo*). ^{13}C NMR (δ, ppm): 176.50, 169.91, 138.14, 128.63, 126.64, 120.59, 66.40, 52.29, 35.84. HRMS: m/z calcd for $C_{13}H_{17}N_3O_3$, 254.0696; found, 254.0690.

***N*-(2,4-Dichlorophenyl)-2-(3-oxopyrazolidin-4-yl)acetamide 2e.** Yield 60%, colorless powdery compound, m.p. 207-208 °C. ^{1}H NMR, ((δ, ppm., *J*/Hz): 9.72 (1H, s, CO-NH), 9.18 (1H, s, NH-2), 7.36-7.73 (3H, m, 3CH-Ar), 5.27 (1H, s, NH-1), 3.50 (1H, dd, *J* = 7.0, *J* = 10.4, CH_2-*endo*), 2.85 (1H, dd, *J* = 10.7, *J* = 21.1, CH_2-*endo*), 2.72-2.87 (2H, m, CH-4 + CH_2-*exo*), 2.34 (1H, dd, *J* = 9.1, *J* = 15.2, CH_2-*exo*). ^{13}C NMR (δ, ppm): 176.86, 170.67, 134.54, 129.30, 127.93, 127.64, 52.59, 39.39, 35.75. HRMS: m/z calcd for $C_{11}H_{11}Cl_2N_3O_2$, 288.0307; found, 288.0303.

N-**(3-Chloro-4-methylphenyl)-2-(3-oxopyrazolidin-4-yl)acetamide 2f.** Yield 75%, colorless powdery compound, m.p. 177-178 °C. ^{1}H NMR, ((δ, ppm., *J*/Hz): 10.08 (1H, s, CO-NH), 9.15 (1H, s, NH-2), 7.15-7.85 (3H, m, 3CH-Ar), 5.29 (1H, s, NH-1), 3.48 (1H, dd, *J* = 7.3, *J* = 10.7, CH_2-*endo*), 2.87 (1H, dd, *J* = 10.5, *J* = 21.3, CH_2-*endo*), 2.72-2.85 (1H, m, CH-4), 2.69 (1H, dd. *J* = 3.8, *J* = 15.8 CH_2-*exo*), 2.29 (1H, dd, *J* = 13.2, *J* = 22.7, CH_2-*exo*), 2.24 (3H, s, CH_3). ^{13}C NMR (δ, ppm): 176.86, 170.28, 138.69, 133.37, 131.57, 130.06, 119.42, 118.06, 52.66, 39.38, 36.22, 19.34. HRMS: m/z calcd for $C_{12}H_{14}ClN_3O_2$, 268.0853; found: 268.0847.

Synthesis of 2-(3-oxo-1-phenyl-pyrazolidine-4-yl)acetanilides 7a-c and 2-(5-oxo-1-phenylpyrazolidine-4-yl)acetanilides 5a-c. A solution of *N*-arylitaconimide **1a,b,g** (5 mmol) and phenylhydrazine (0.55 g, 5 mmol) in methanol (10 ml) is boiled for 2-3 hours. The solvent is removed, the products are isolated by flash chromatography on silicon oxide, the eluent is chloroform.

2-(5-Oxo-1-phenylpyrazolidin-4-yl)-*N*-phenylacetamide 5a. Yield 15%, colorless powdery compound, m.p. 150-152 °C. ^{1}H NMR, ((δ, ppm., *J*/Hz): 10.05 (1H, s, CO-NH), 7.00-7.85 (10H, m, 10CH-Ar), 6.26 (1H, dd, *J* = 5.5, *J* = 11.2, NH-2), 3,60-3.66 (1H, m, CH_2-endo), 3.20- 3.28 (1H, м, CH-4), 3.07 (1H, dd, *J* = 11.1, *J* = 22.2, CH_2-endo), 2.86 (1H, dd, *J* = 3.9, *J* = 15.9, CH_2-exo), 2.48-2.55 (1H, m, CH_2-exo). ^{13}C NMR (δ, ppm): 172.88, 169.35, 139.26, 139.17, 128.75, 128.60, 123.50, 123.17, 119.10, 117.56, 49.07, 42.15, 35.77. HRMS: m/z calcd for $C_{17}H_{17}N_3O_2$, 296.1399; found, 296.1395.

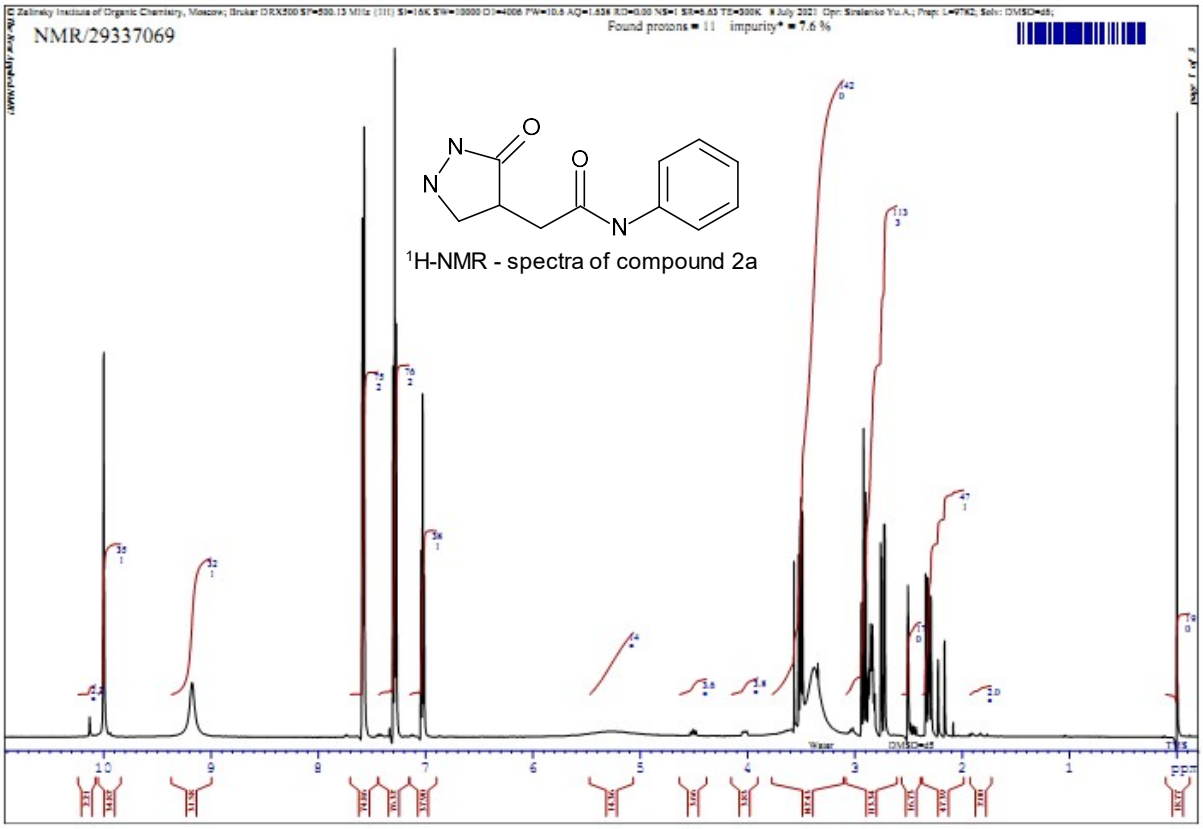
2-(3-Oxo-1-phenylpyrazolidin-4-yl)-*N*-phenylacetamide 7a. Yield 40%, colorless powdery compound, m.p. 152-154 °C. ^{1}H NMR, ((δ, ppm., *J*/Hz): 10.28 (1H, s, NH-2), 10.01 (1H, s, CO-NH), 6.90-7.65 (10H, m, 10CH-Ar), 4.15 (1H, dd, *J* = 8.3; *J* = 11.0; CH_2-*endo*), 3.60 (1H, t, *J* = 10.9, CH_2-*endo*), 2.94-3.04 (1H, m, CH-4), 2.80 (1H, dd, *J* = 4.0, *J* = 15.9, CH_2-*exo*), 2.39 (1H, dd, *J* = 9.9, *J* = 15.9, CH_2-*exo*). ^{13}C NMR (δ, ppm): 174.51, 169.17, 151.69, 139.12, 128.97, 128.72, 123.17, 121.36, 119.07, 115.69, 59.85, 36.87, 35.46. HRMS: m/z calcd for $C_{17}H_{17}N_3O_2$, 296.1399; found, 296.1392.

2-(5-Oxo-1-phenylpyrazolidin-4-yl)-*N*-(*p*-tolyl)acetamide 5b. Yield 25%, colorless powdery compound, m.p. 185-186 °C. ^{1}H NMR, ((δ, ppm., *J*/Hz): 9.96 (1H, s, CO-NH), 7.06-7.85 (9H, m, 9CH-Ar), 6.25 (1H, dd, *J* = 5.5, *J* = 11.2, NH-2), 3.59-3.66 (1H, m, CH_2-endo), 3.19-3.26 (1H, m, CH-4), 3.07 (1H, dd, *J* = 11.0, *J* = 22.1, CH_2-endo), 2.84 (1H, dd, *J* = 3.9, *J* = 15.8, CH_2-exo), 2.49 (1H, dd, *J* = 9.8, *J* = 16.0, CH_2-exo), 2.25 (3H, s; CH_3). ^{13}C NMR (δ, ppm): 172.90, 169.08, 139.28, 136.68, 132.05, 129.11, 128.58, 123.49, 119.16, 117.59, 49.10, 42.19, 35.74, 20.48. HRMS: m/z calcd for $C_{18}H_{19}N_3O_2$, 310.1556; found, 310.1558.

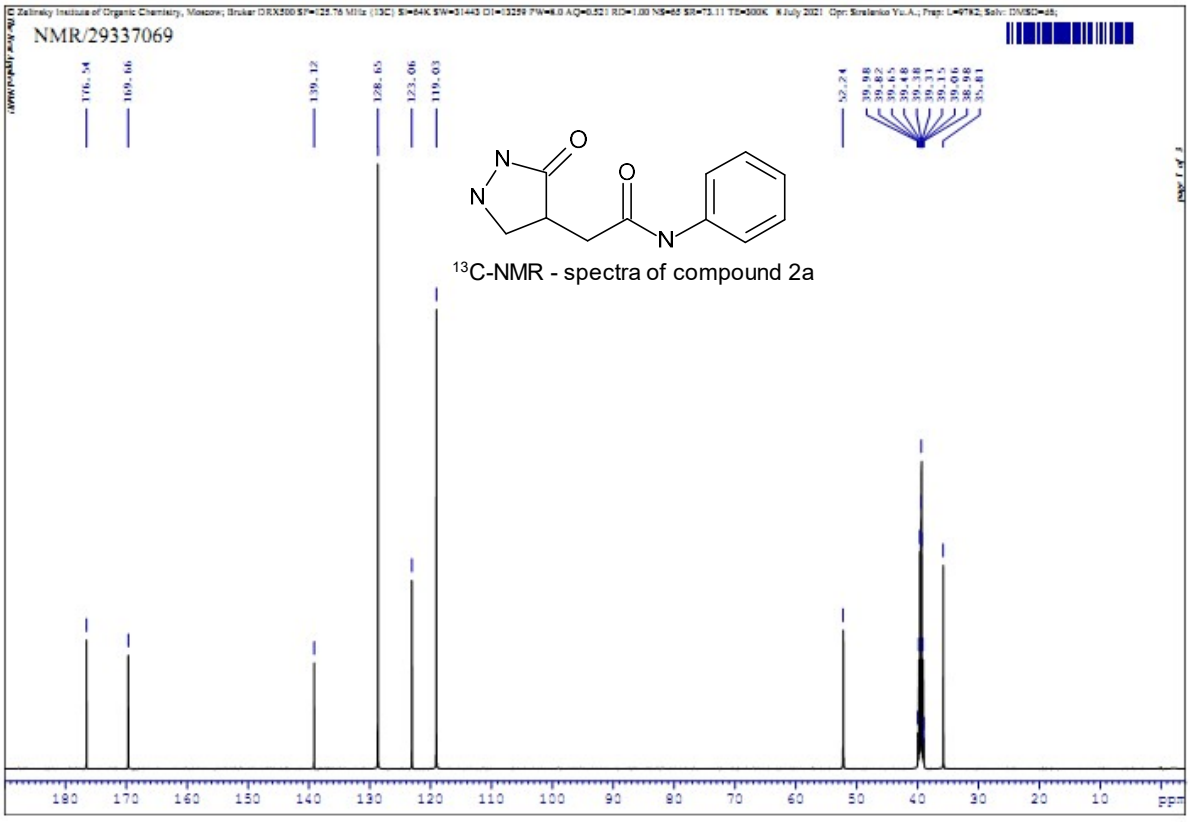
2-(3-Oxo-1-phenylpyrazolidin-4-yl)-*N*-(*p*-tolyl)acetamide 7b. Yield 45%, colorless powdery compound, m.p. 176-177 °C. ^{1}H NMR, ((δ, ppm., *J*/Hz): 10.26 (1H, c, NH-2), 9.91 (1H, s, CO-NH), 6.92-7.48 (9H, m, 9CH-Ar), 4.14 (1H, dd, *J* = 8.3, *J* = 11.0, CH_2-endo), 3.59 (1H, t, J=11.0, CH_2-endo), 2.93-3.01 (1H, m, CH-4), 2.77 (1H, dd, J = 3.9, J = 15.9, CH_2-exo), 2.37 (1H, dd, *J* = 9.9, *J* = 15.9, CH_2-exo), 2.23 (3H, s, CH_3). ^{13}C NMR (δ, ppm): 174.54, 168.90, 151.69, 136.62, 132.06, 129.08, 128.97, 121.35, 119.12, 115.70, 59.86, 36.91, 35.42, 20.46. HRMS: m/z calcd for $C_{18}H_{19}N_3O_2$, 310.1556; found, 310.1553.

***N*-(3-Chlorophenyl)-2-(5-oxo-1-phenylpyrazolidin-4-yl)acetamide 5c.** Yield 20%, colorless powdery compound, m.p. 154-155 °C. ^{1}H NMR, ((δ, ppm., *J*/Hz): 10.26 (1H, s, CO-NH), 7.07-7.85 (9H, m, 9CH-Ar), 6.27 (1H, dd, *J* = 5.5, *J* = 11.2, NH-2), 3,60-3.66 (1H, m, CH_2-*endo*), 3.20-3.29 (1H, m, CH-4), 3.07 (1H, dd, *J* = 11.2, *J* = 22.3, CH_2-*endo*), 2.86 (1H, dd, *J* = 4.1, *J* = 16.0, CH_2-*exo*), 2.53 (1H, dd, *J* = 9.6, *J* = 15.9, CH_2-*exo*). ^{13}C NMR (δ, ppm): 173.10, 170.13, 140.92, 139.58, 133.45, 130.79, 128.92, 123.85, 123.21, 118.92, 117.91, 117.79, 49.33, 42.38, 36.12. HRMS: m/z calcd for $C_{17}H_{16}ClN_3O_2$, 330.1010; found, 330.1014.

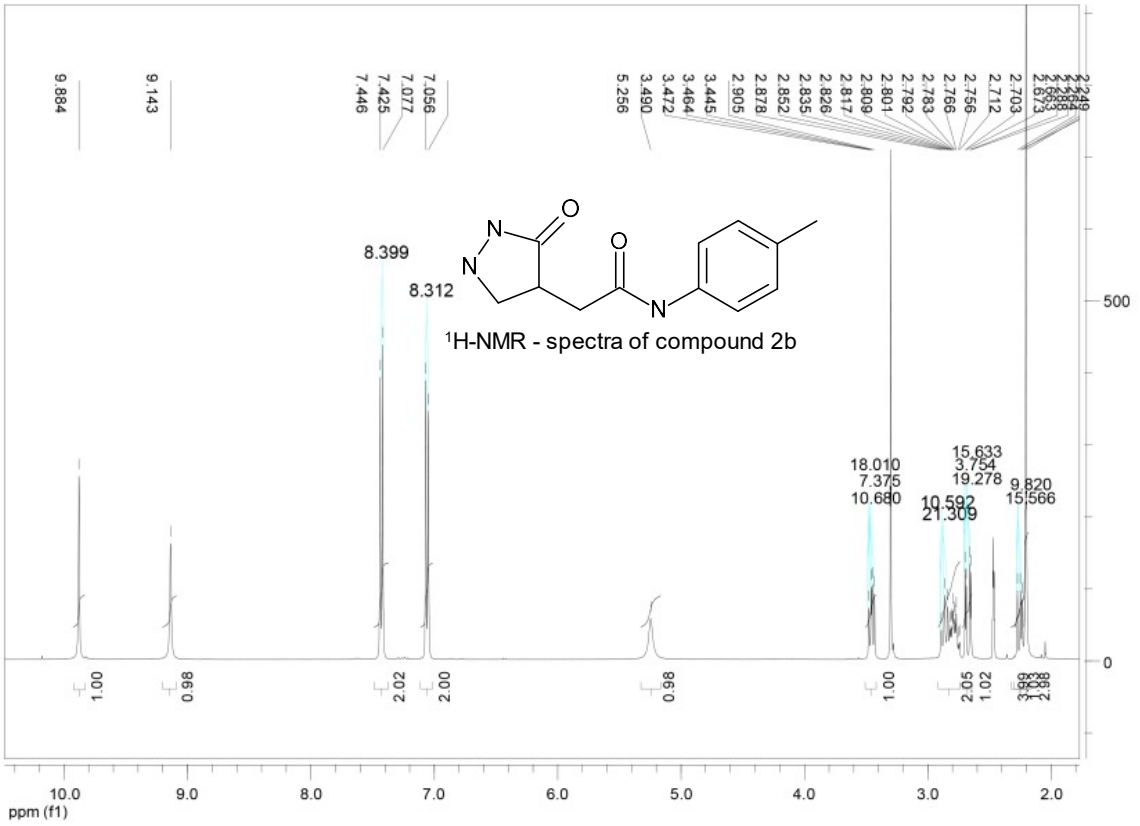
***N*-(3-Chlorophenyl)-2-(3-oxo-1-phenylpyrazolidin-4-yl)acetamide 7c.** Yield 30%, colorless powdery compound, m.p. 152-154 °C. ^{1}H NMR, ((δ, ppm., *J*/Hz): 10.28 (1H, s, NH-2), 10.21 (1H, s, CO-NH), 6.92-7.81 (9H, m, 9CH-Ar), 4.15 (1H, dd, *J* = 8.3, *J* = 11.0, CH_2-endo), 3.60 (1H, t, *J* = 11.1, CH_2-endo), 2.95- 3.03 (1H, m, CH-4), 2.80 (1H, dd, *J* = 4.1, *J* = 16.1, CH_2-exo), 2.41 (1H, dd, *J* = 9.7, *J* = 16.0, CH_2-exo). ^{13}C NMR (δ, ppm): 174.24, 169.47, 151.51, 140.37, 132.94, 130.27, 128.81, 122.72, 121.21, 118,42, 117.27, 115.54, 59.60, 36.63, 35.32. HRMS: m/z calcd for $C_{17}H_{16}ClN_3O_2$, 330.1010; found, 330.1015.



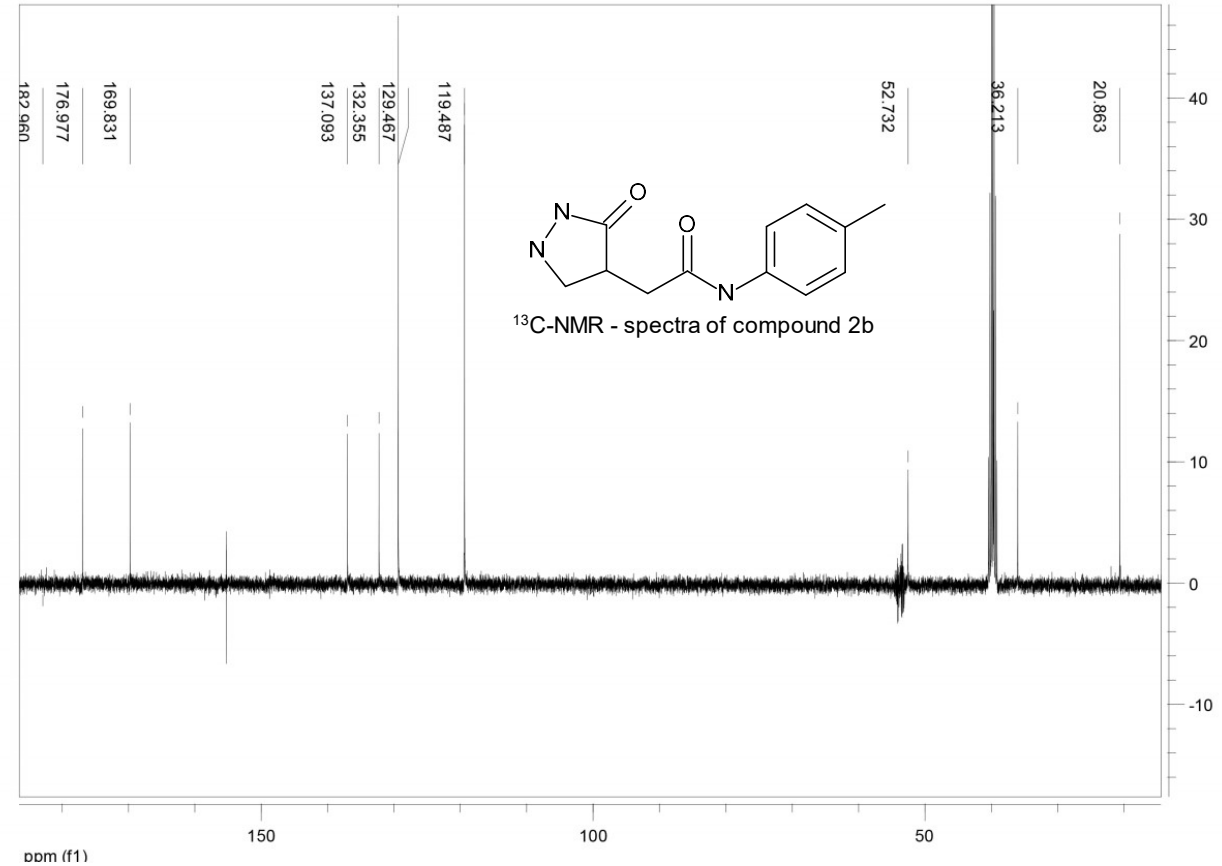
^{1}H-NMR - spectra of compound 2a



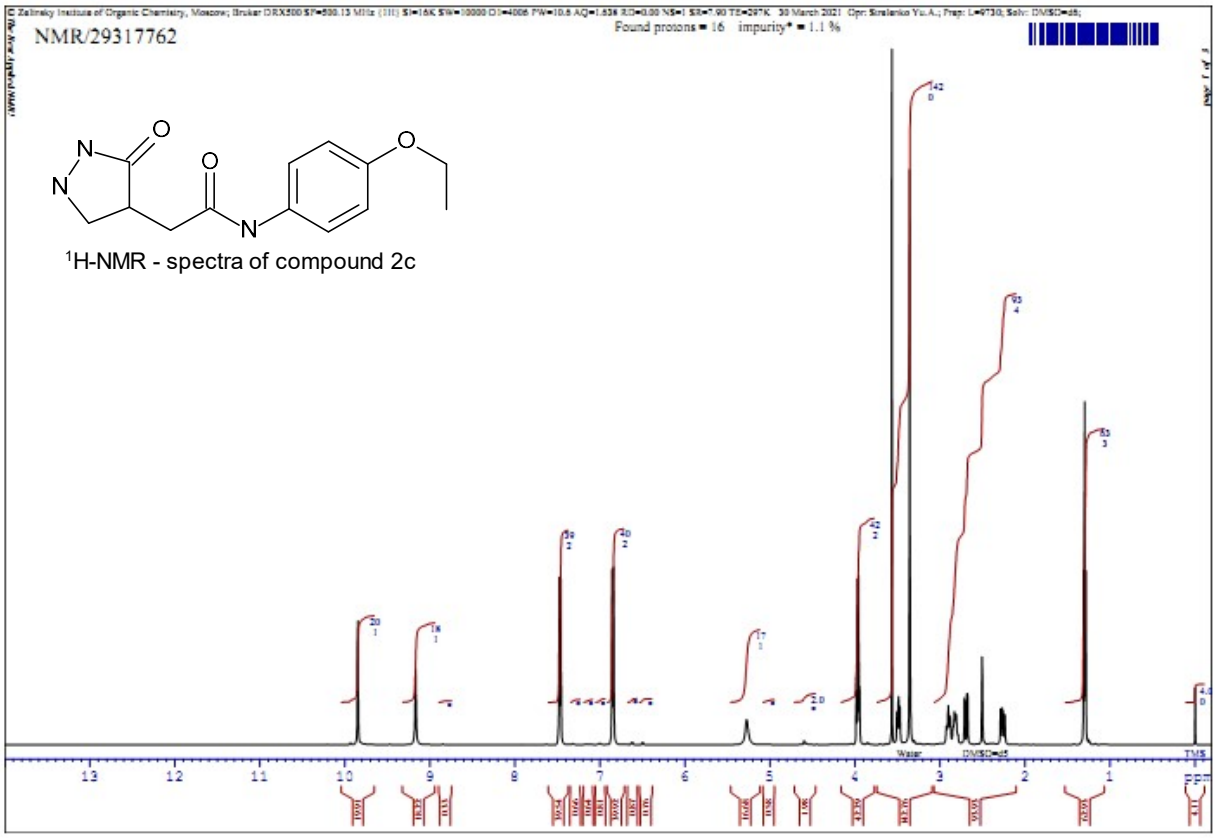
^{13}C-NMR - spectra of compound 2a



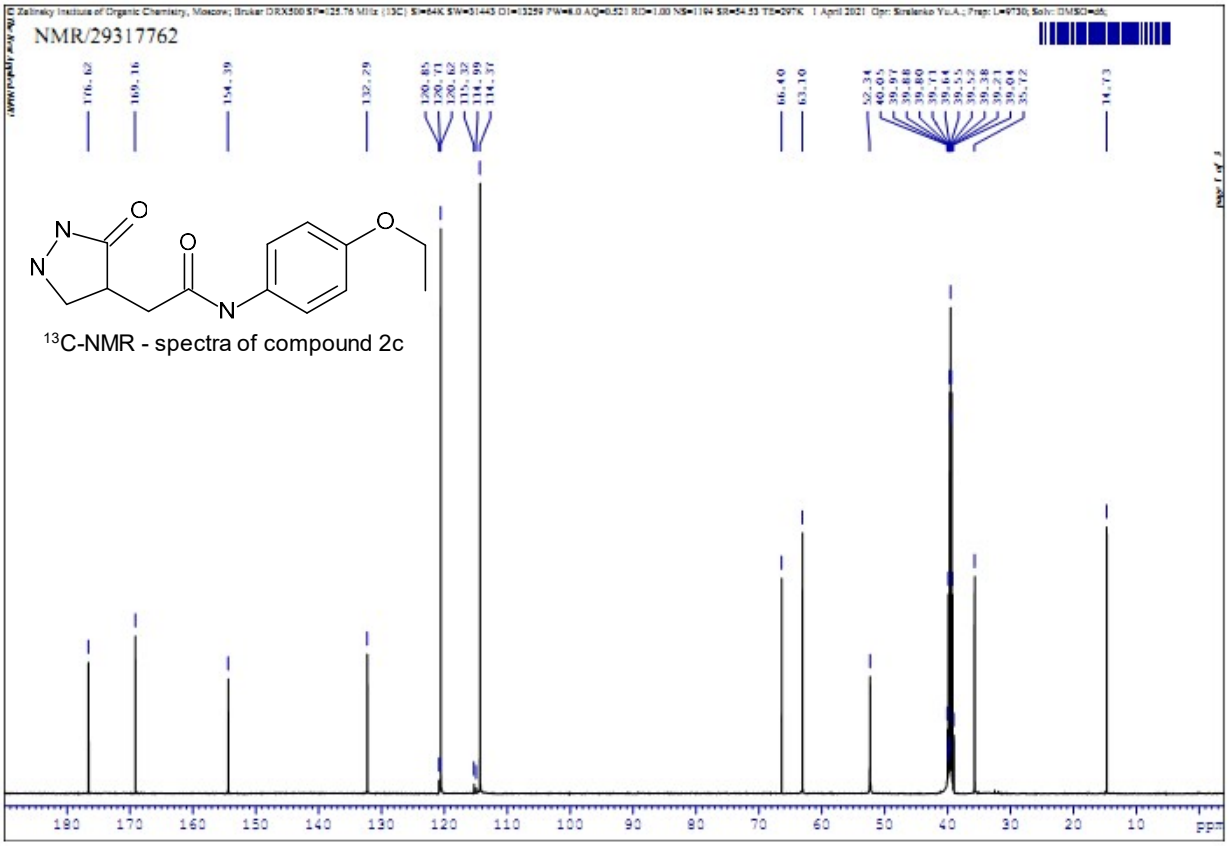
^{1}H-NMR - spectra of compound 2b



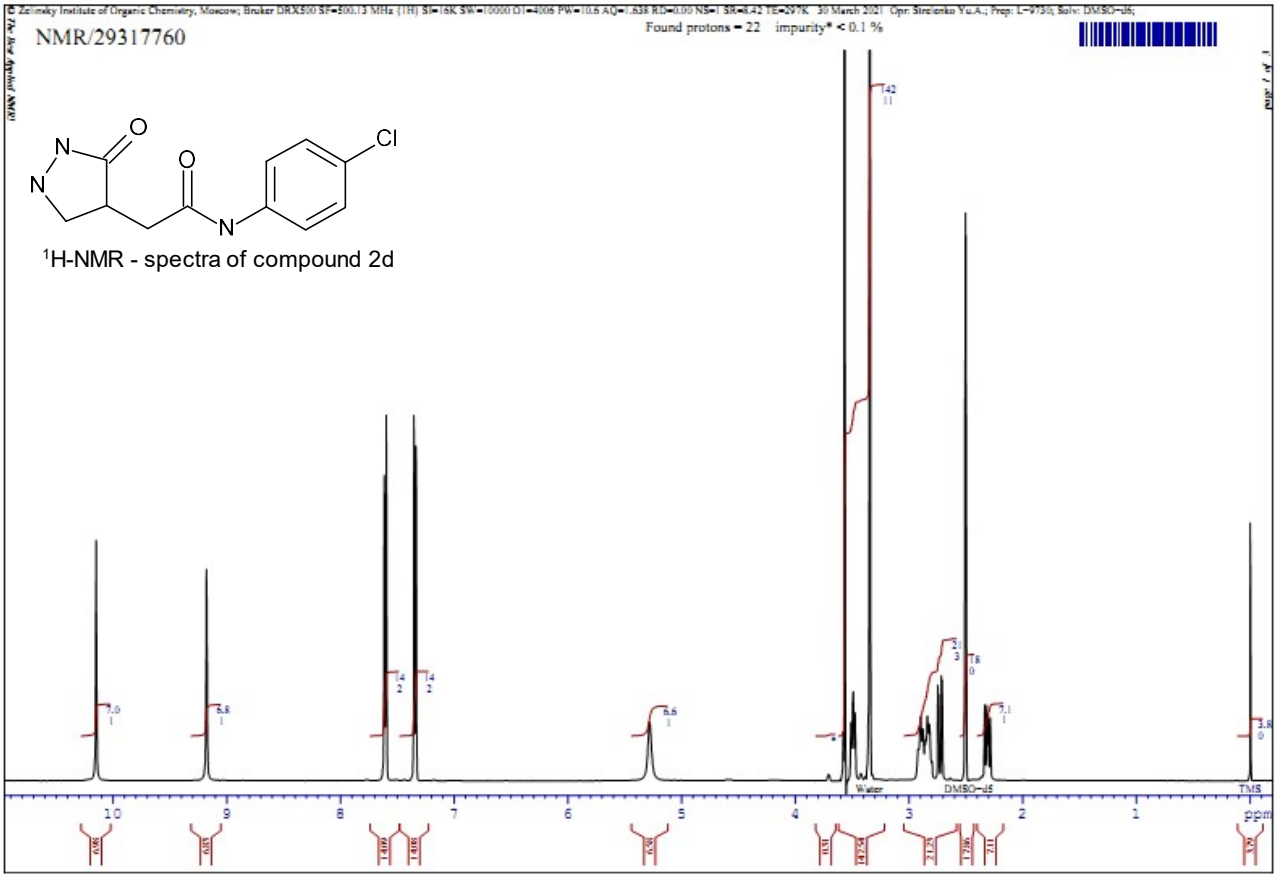
^{13}C-NMR - spectra of compound 2b



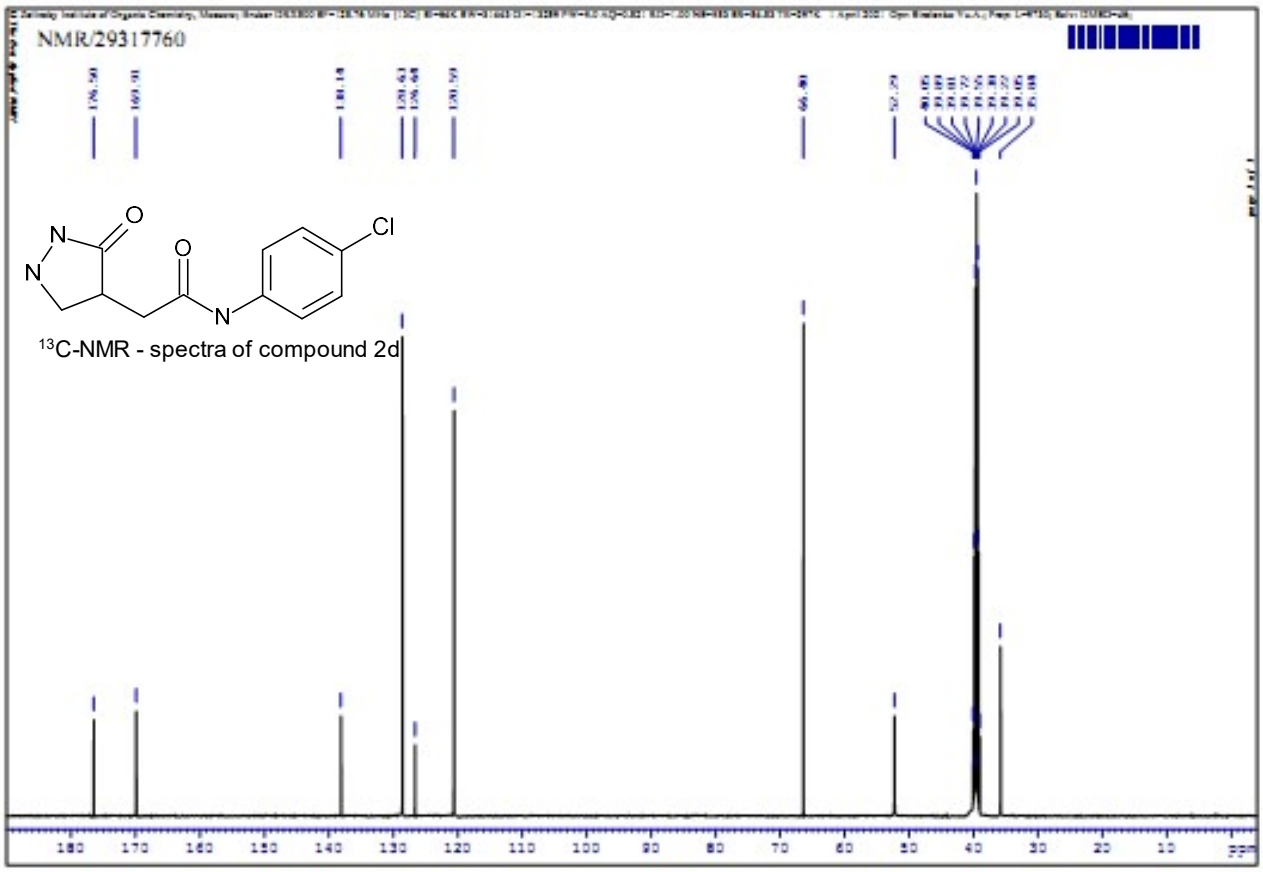
^{1}H-NMR - spectra of compound 2c



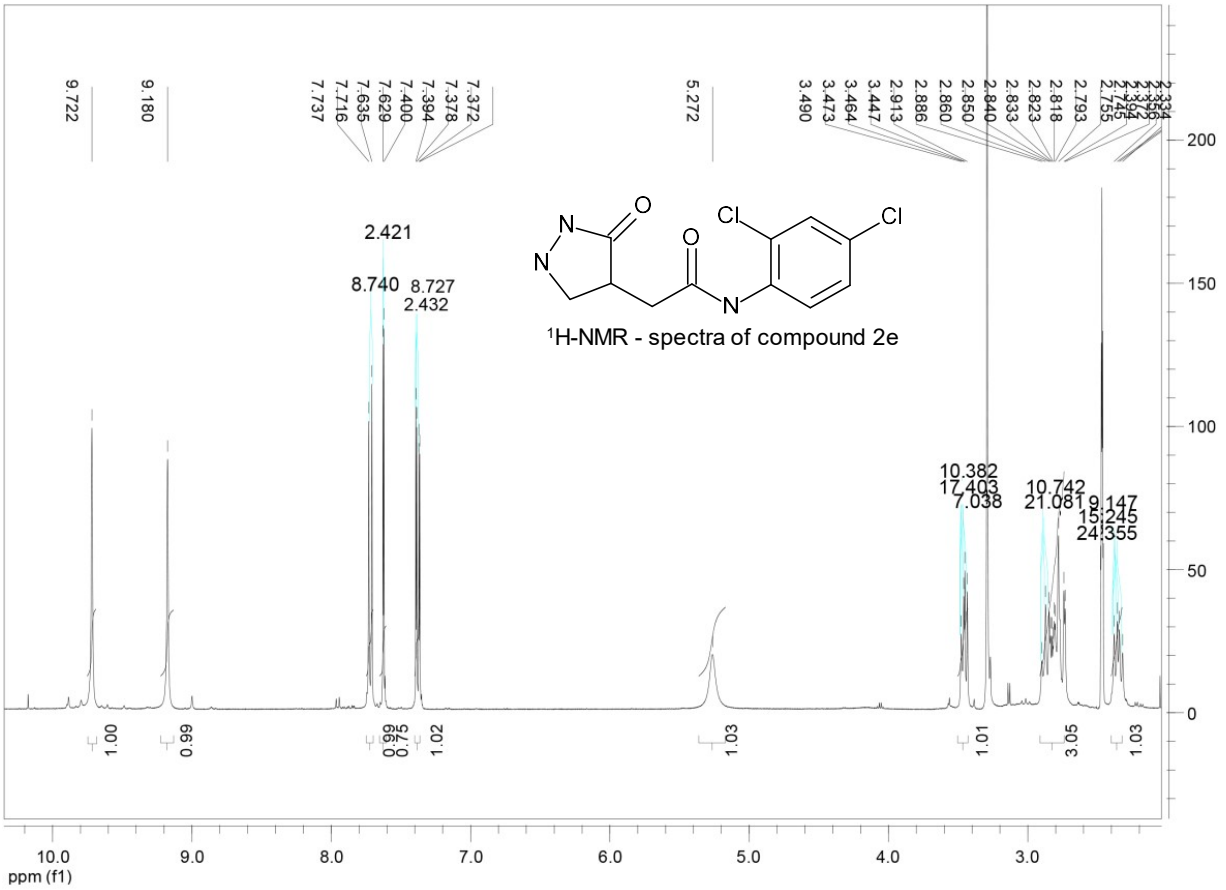
^{13}C-NMR - spectra of compound 2c



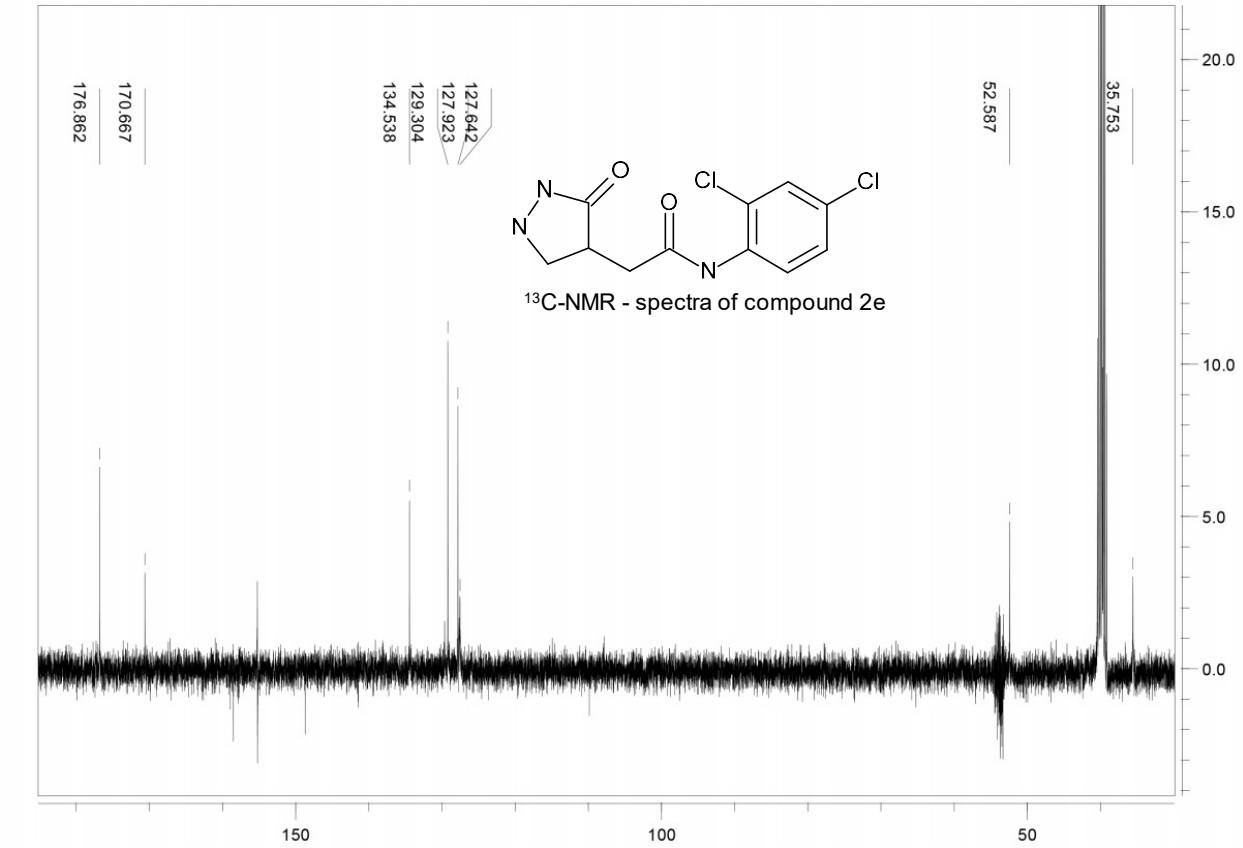
^{1}H-NMR - spectra of compound 2d



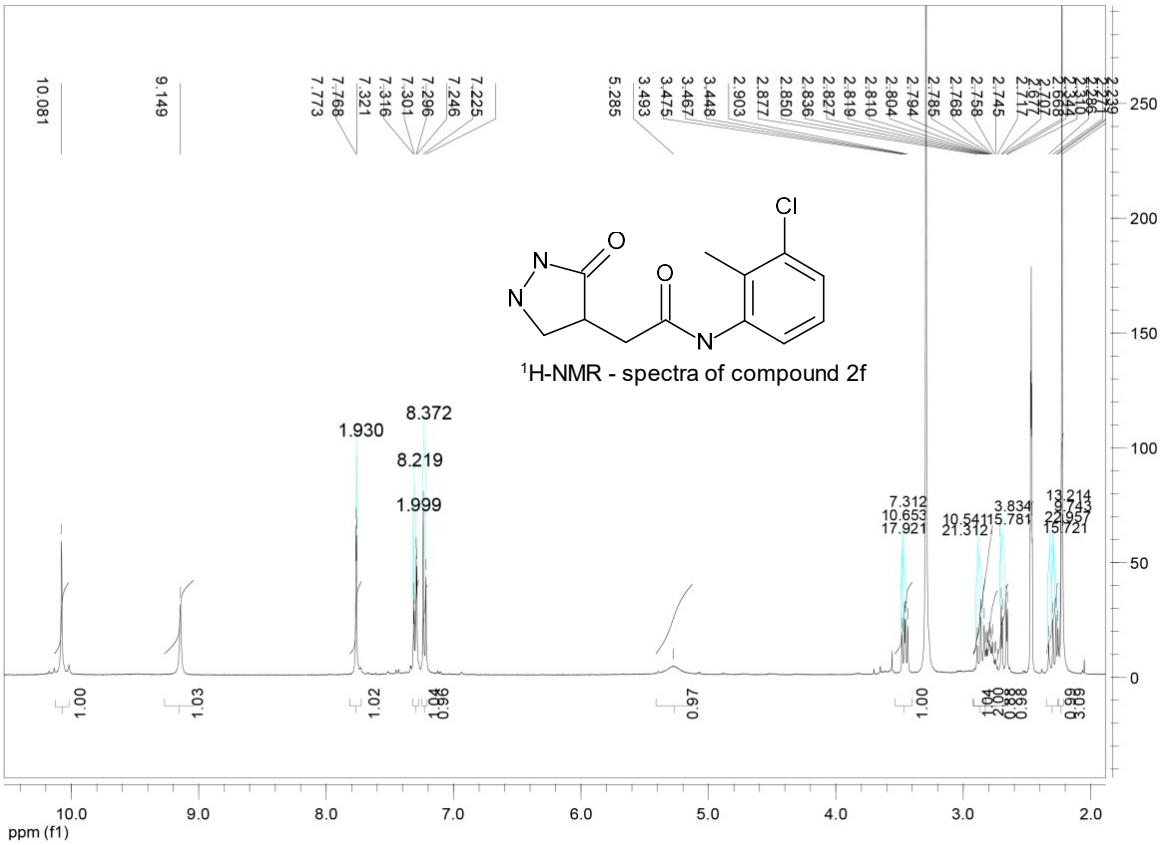
^{13}C-NMR - spectra of compound 2d



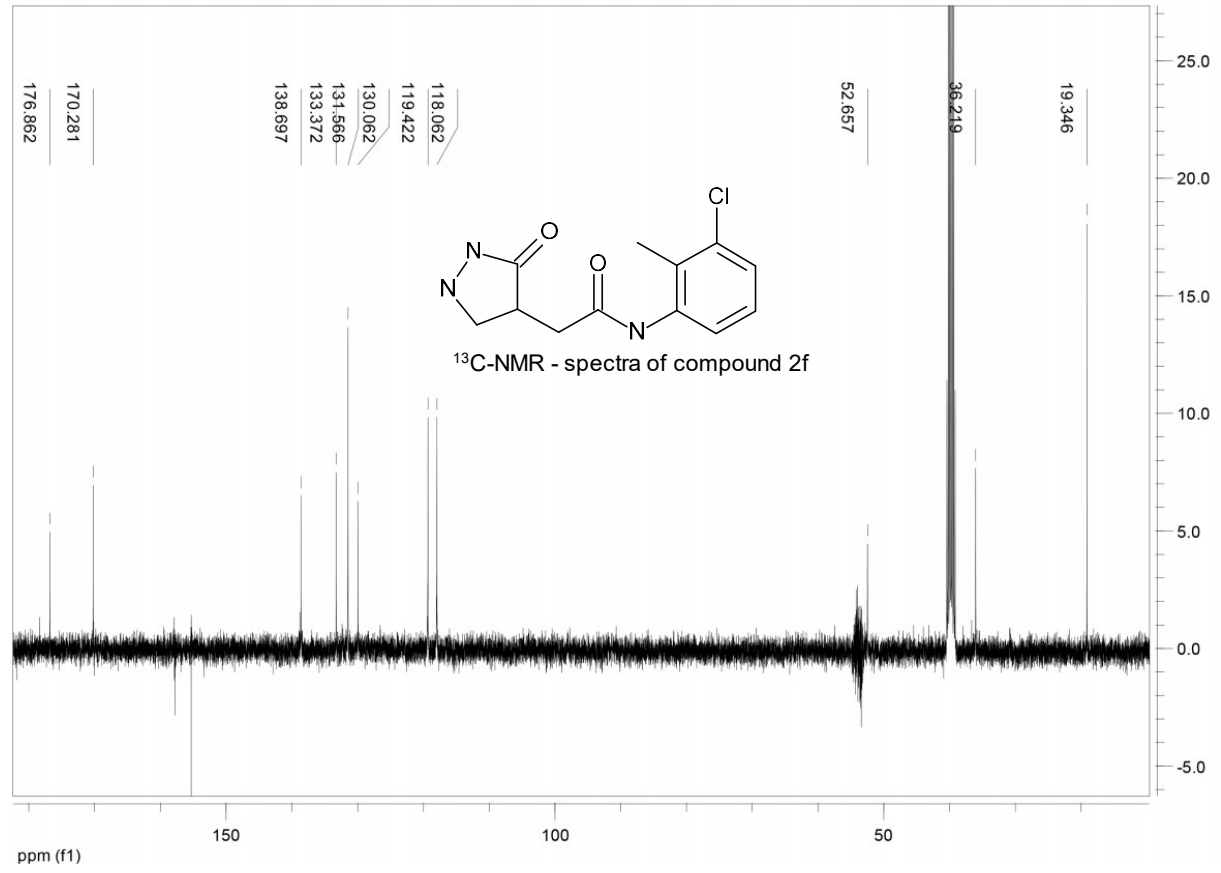
^{1}H-NMR - spectra of compound 2e



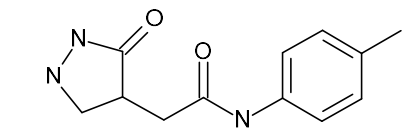
^{13}C-NMR - spectra of compound 2e



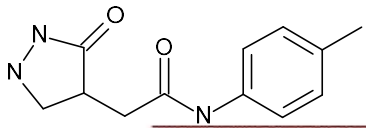
^{1}H-NMR - spectra of compound 2f



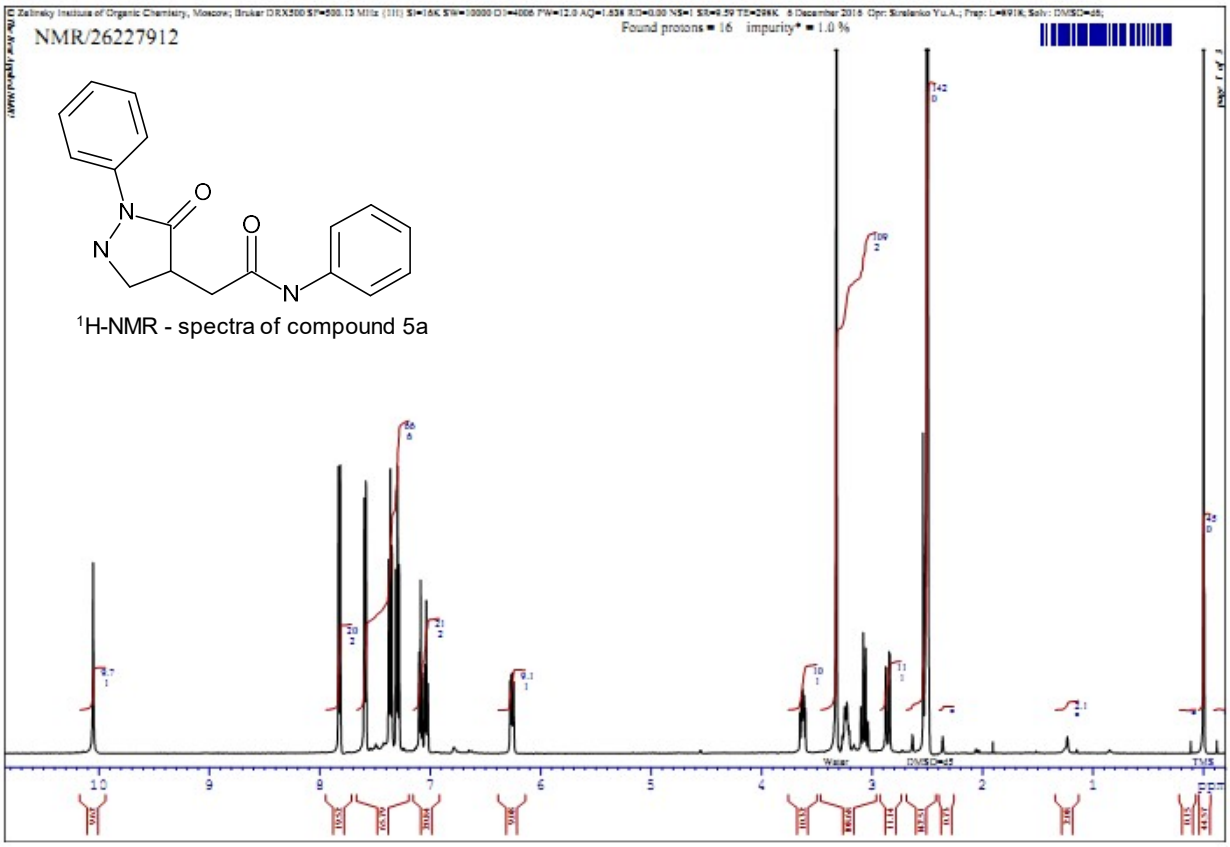
^{13}C-NMR - spectra of compound 2f



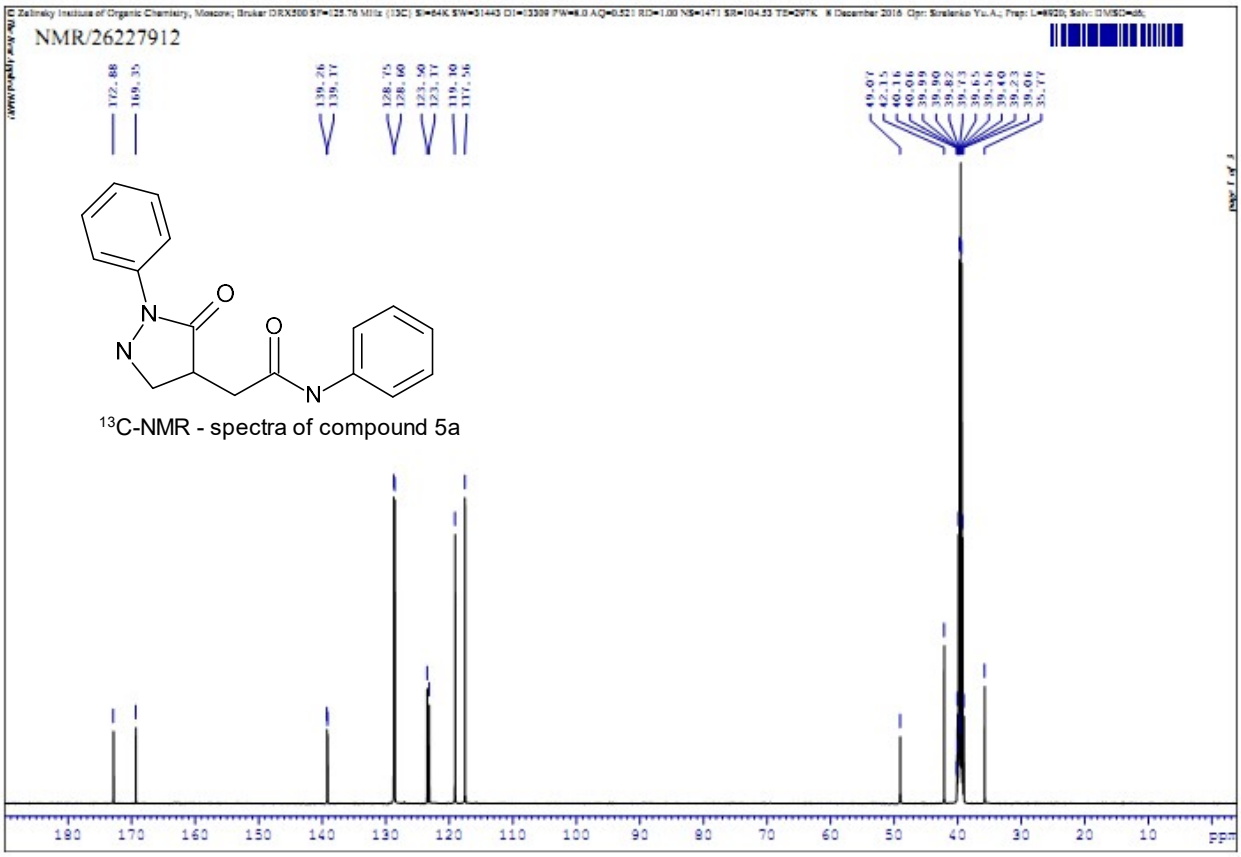
NOESY- spectra of compound 2b



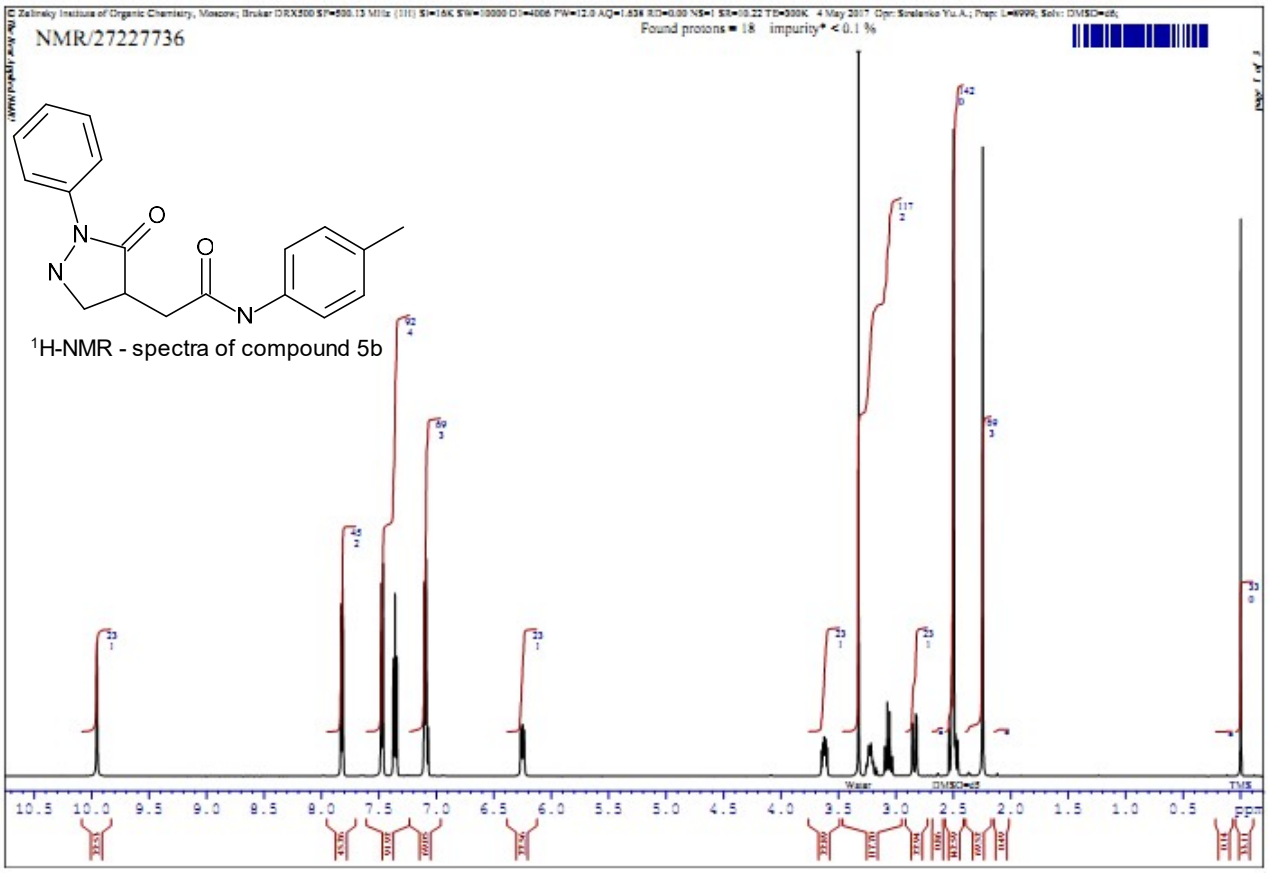
HMBC- spectra of compound 2b



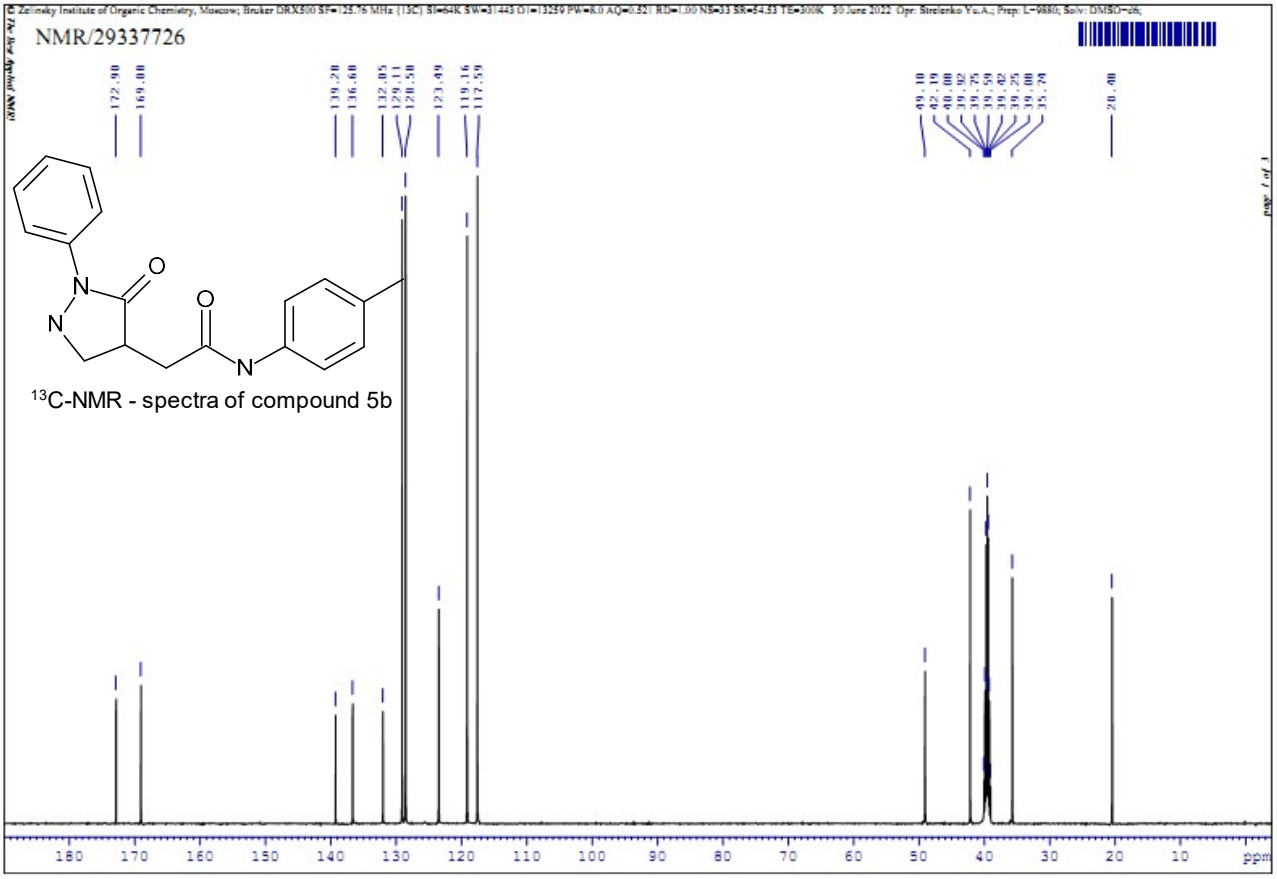
^{1}H-NMR - spectra of compound 5a



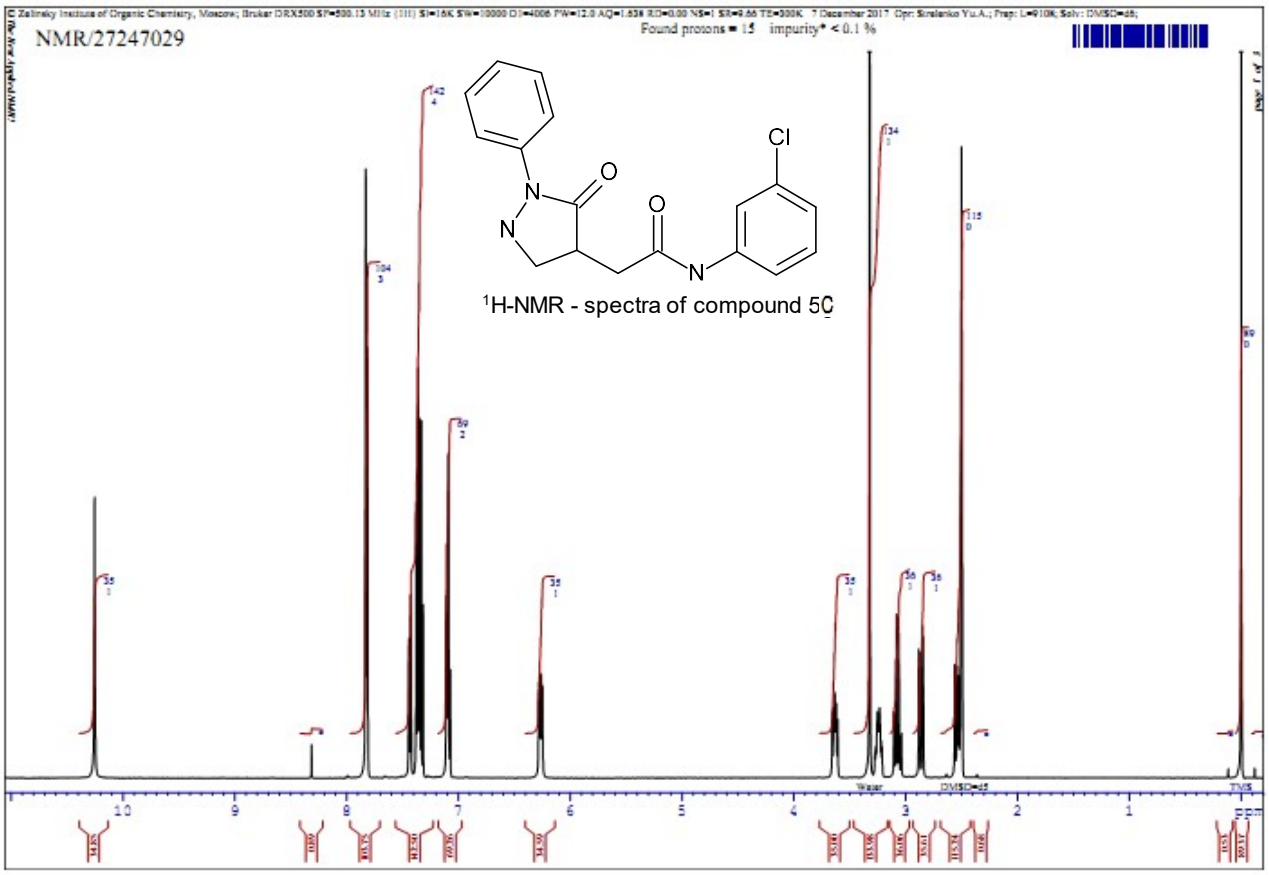
^{13}C-NMR - spectra of compound 5a



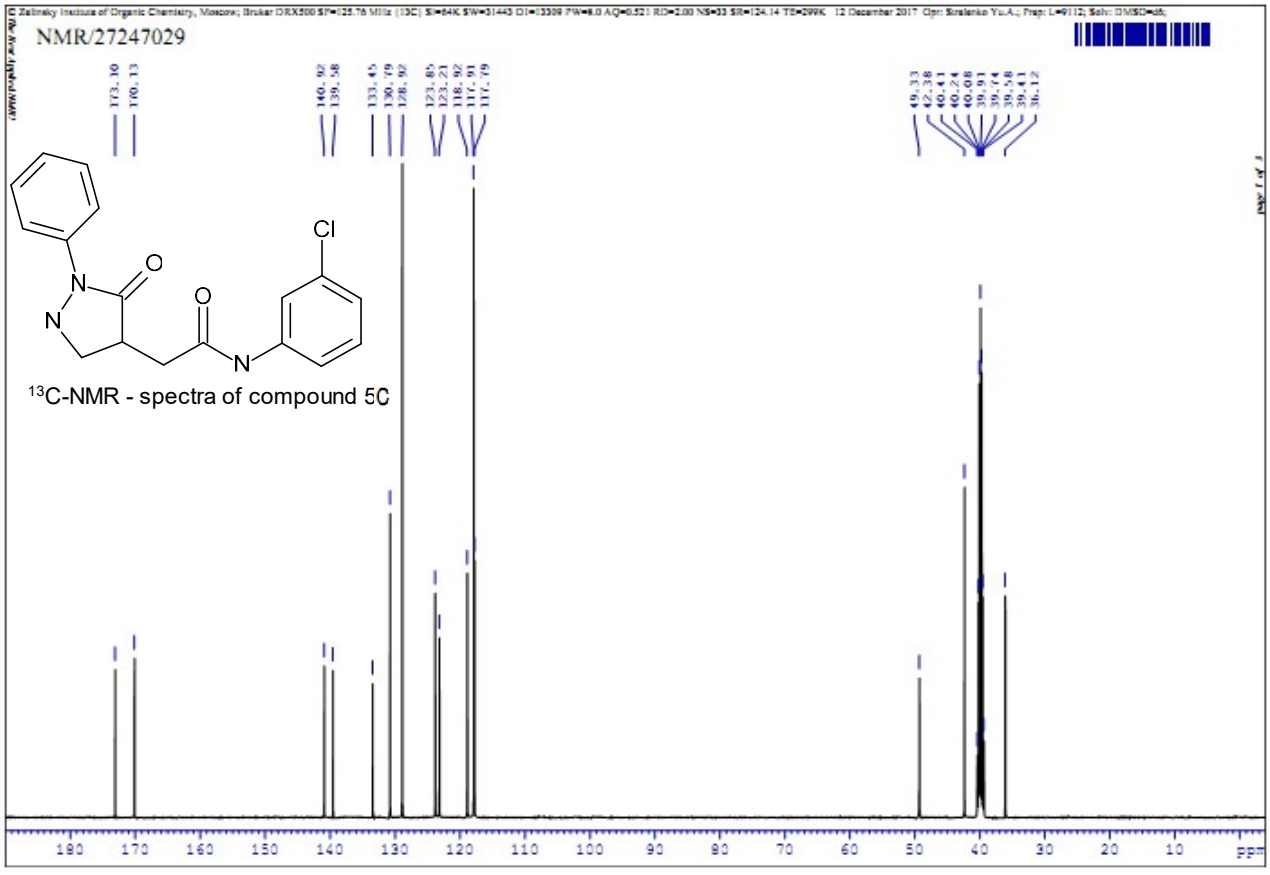
^{1}H-NMR - spectra of compound 5b



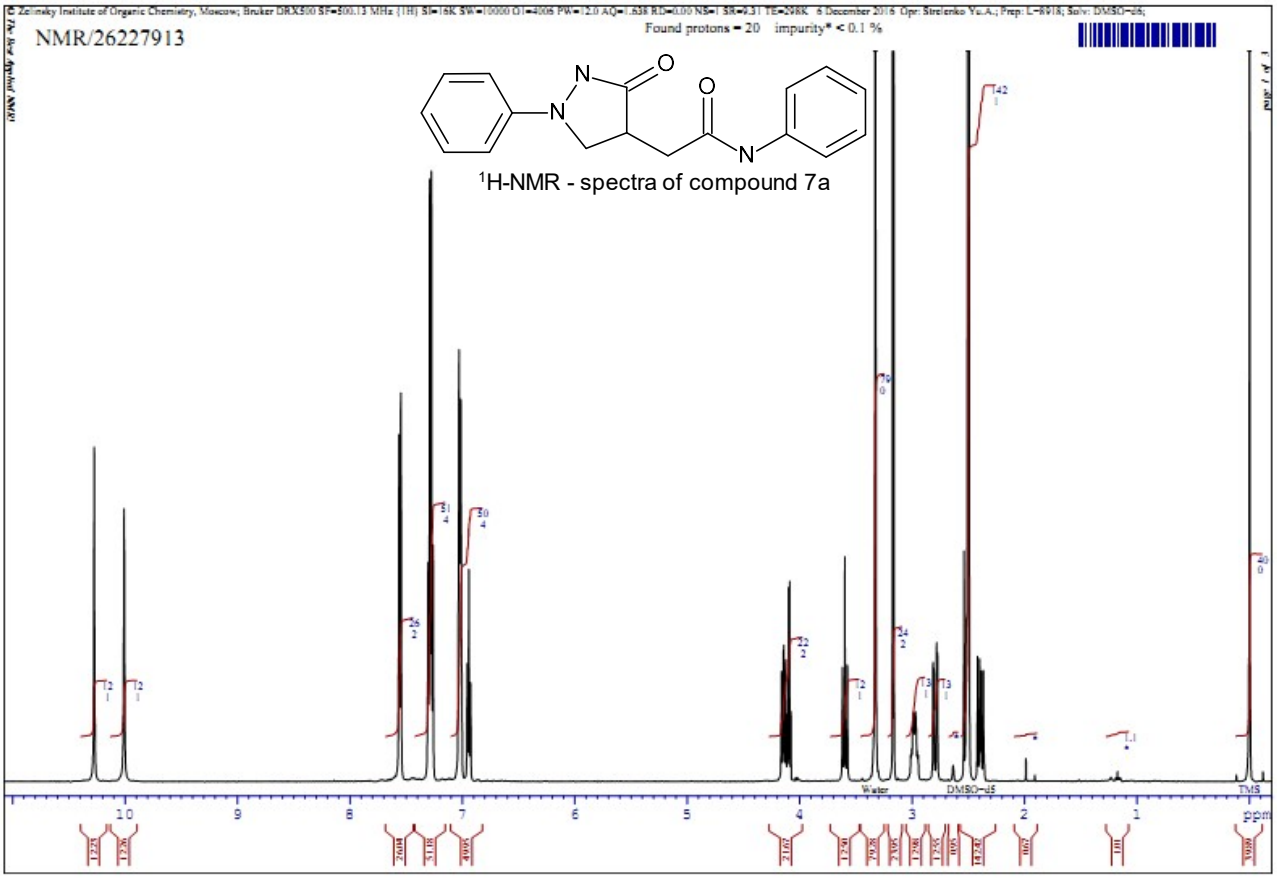
^{13}C-NMR - spectra of compound 5b



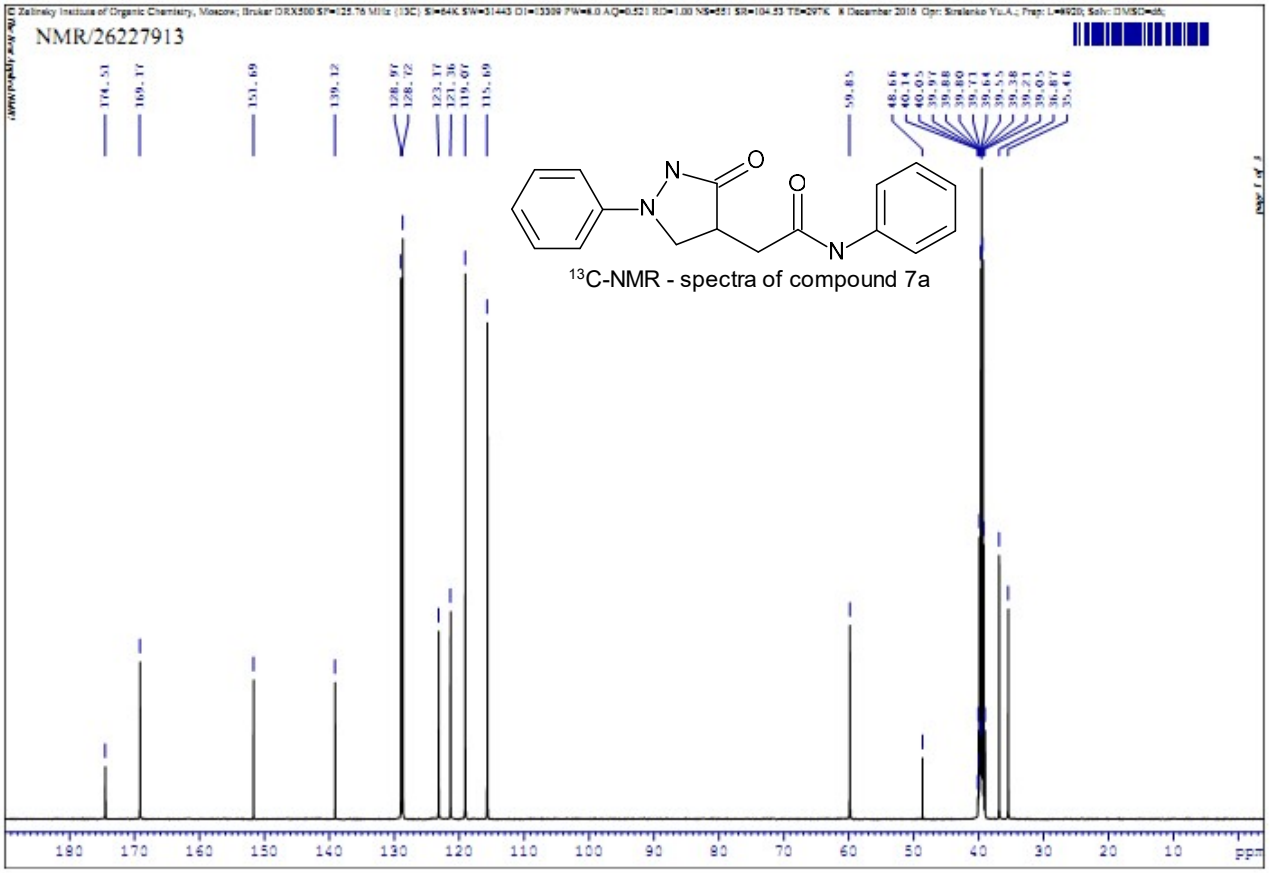
^{1}H-NMR - spectra of compound 5C



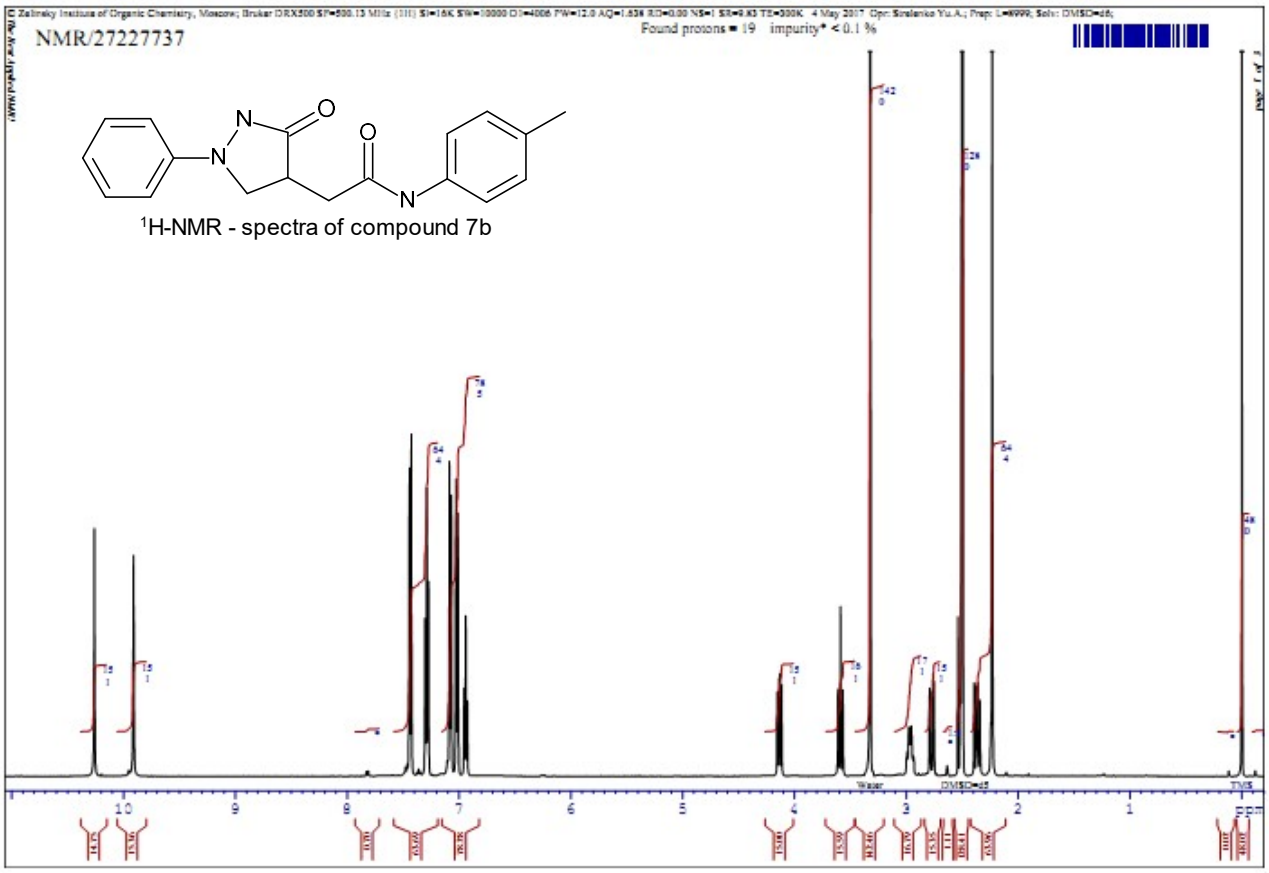
^{13}C-NMR - spectra of compound 5C



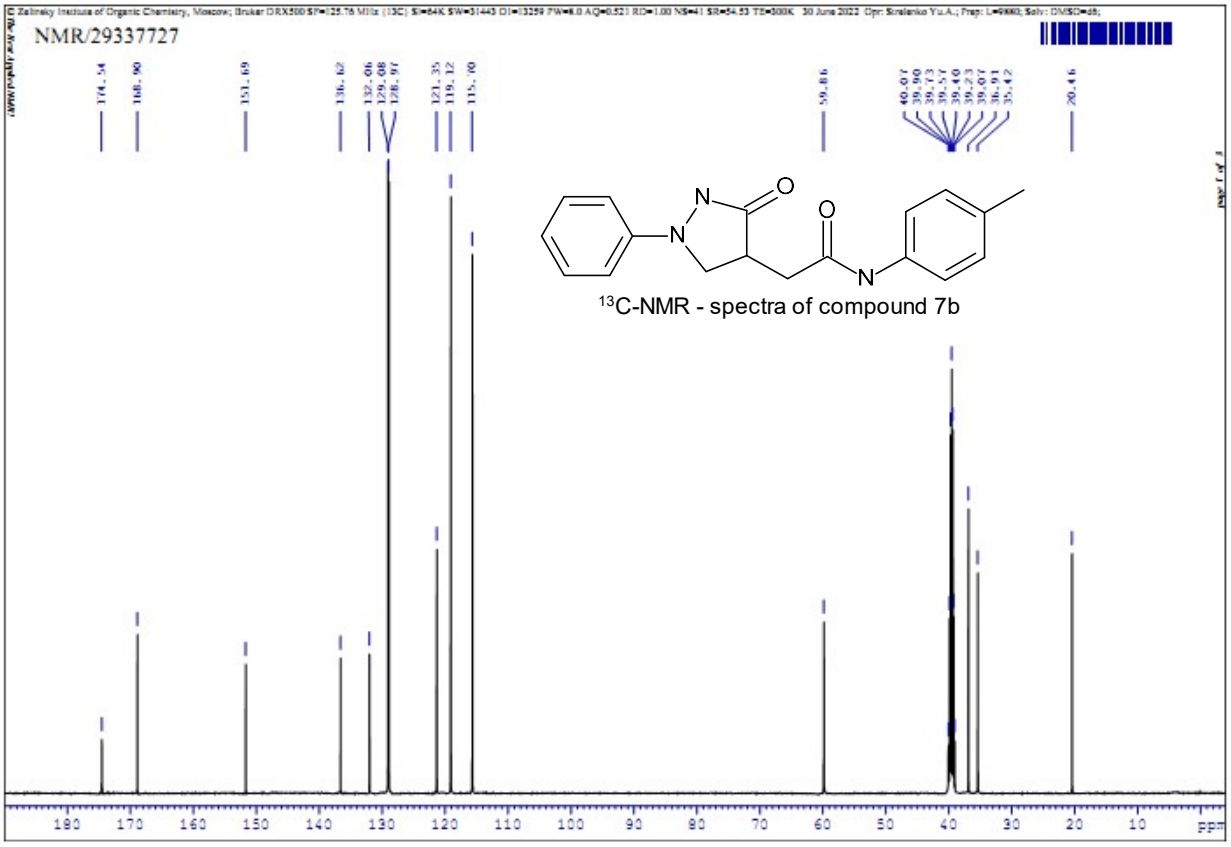
^{1}H-NMR - spectra of compound 7a



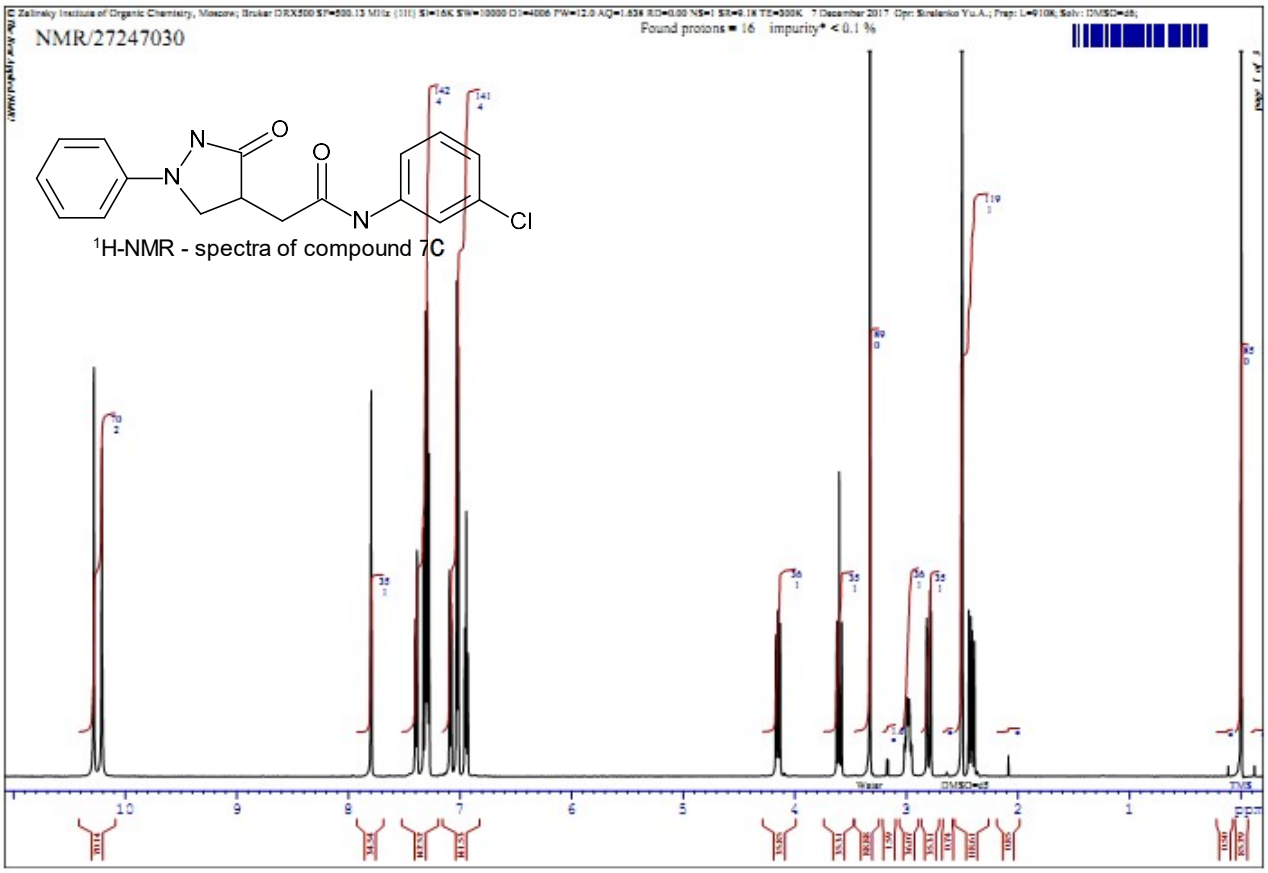
^{13}C-NMR - spectra of compound 7a



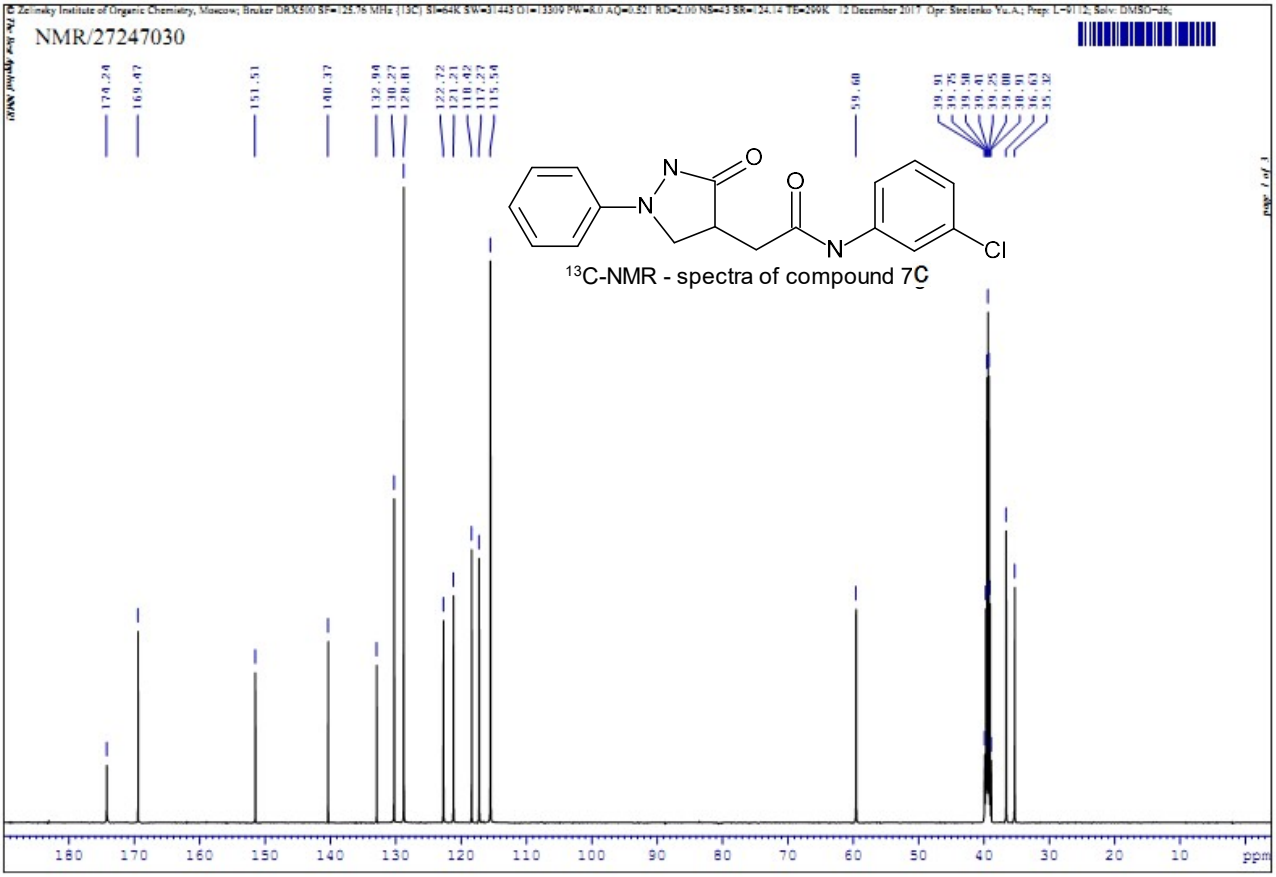
^{1}H-NMR - spectra of compound 7b



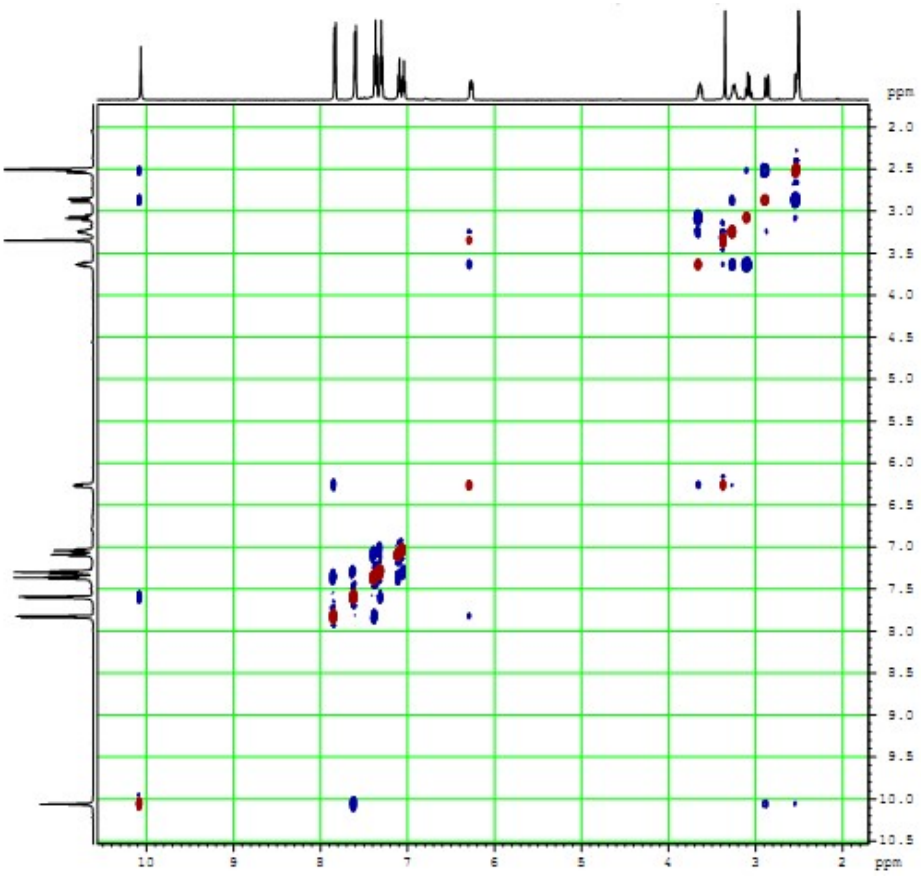
^{13}C-NMR - spectra of compound 7b

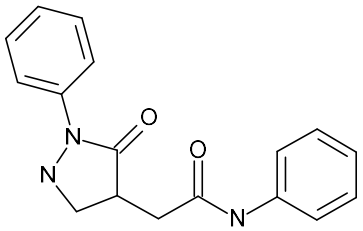


^{1}H-NMR - spectra of compound 7**C**

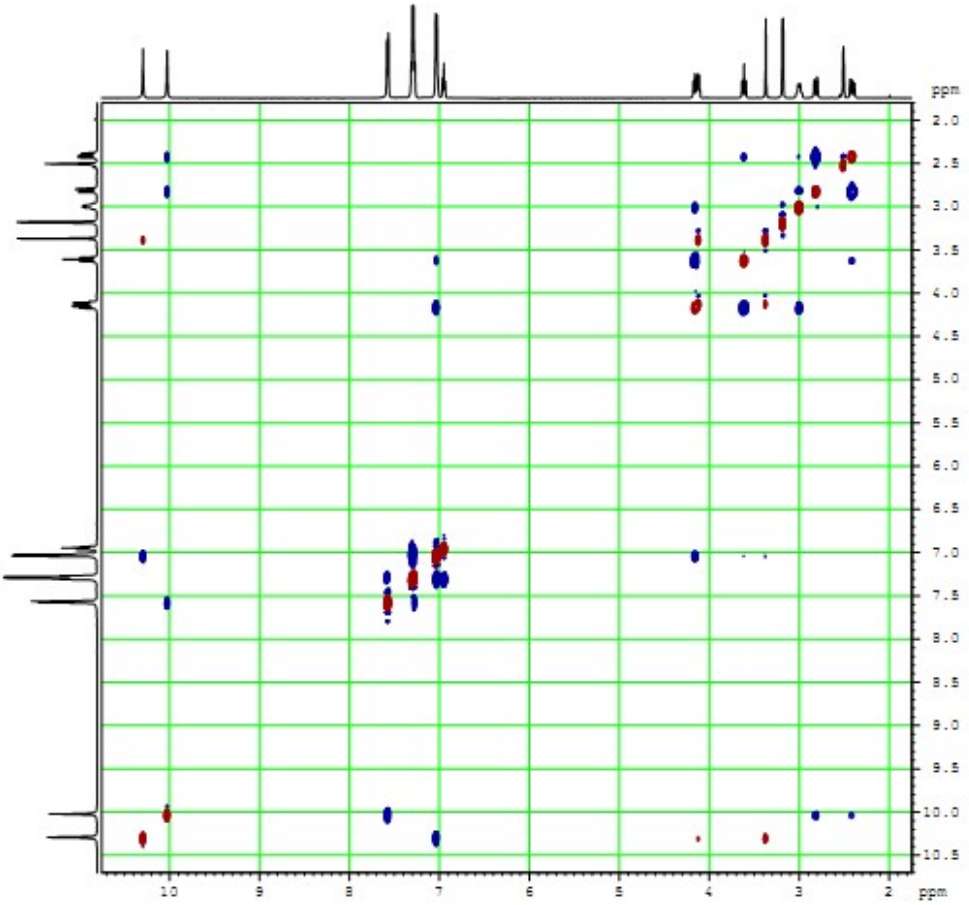


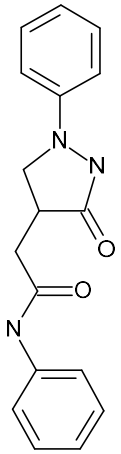
^{13}C-NMR - spectra of compound 7**C**



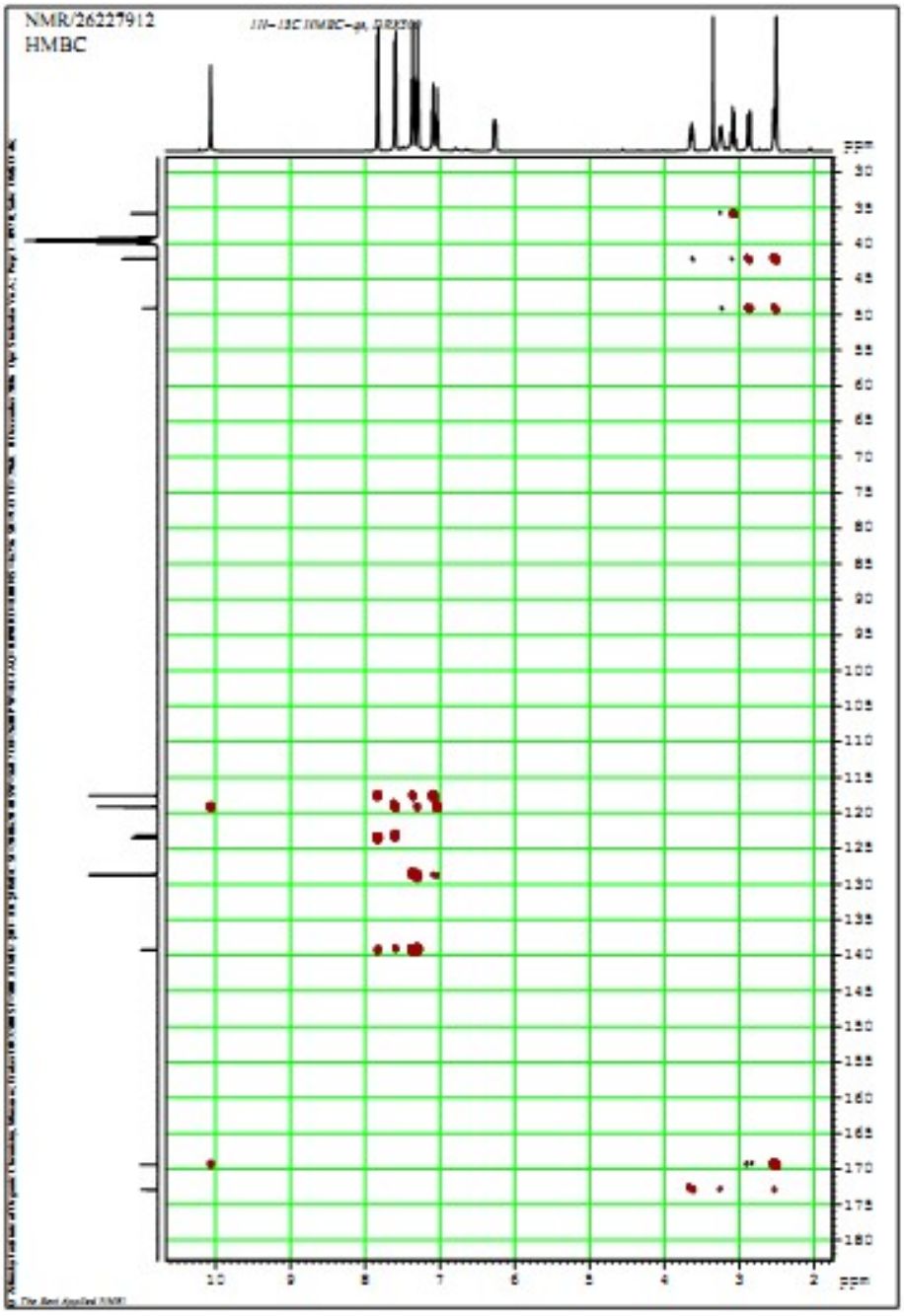


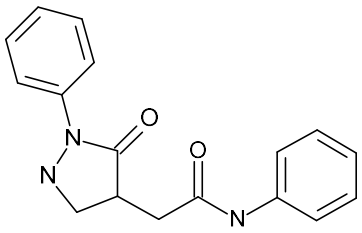
NOESY - spectra of compound 5a



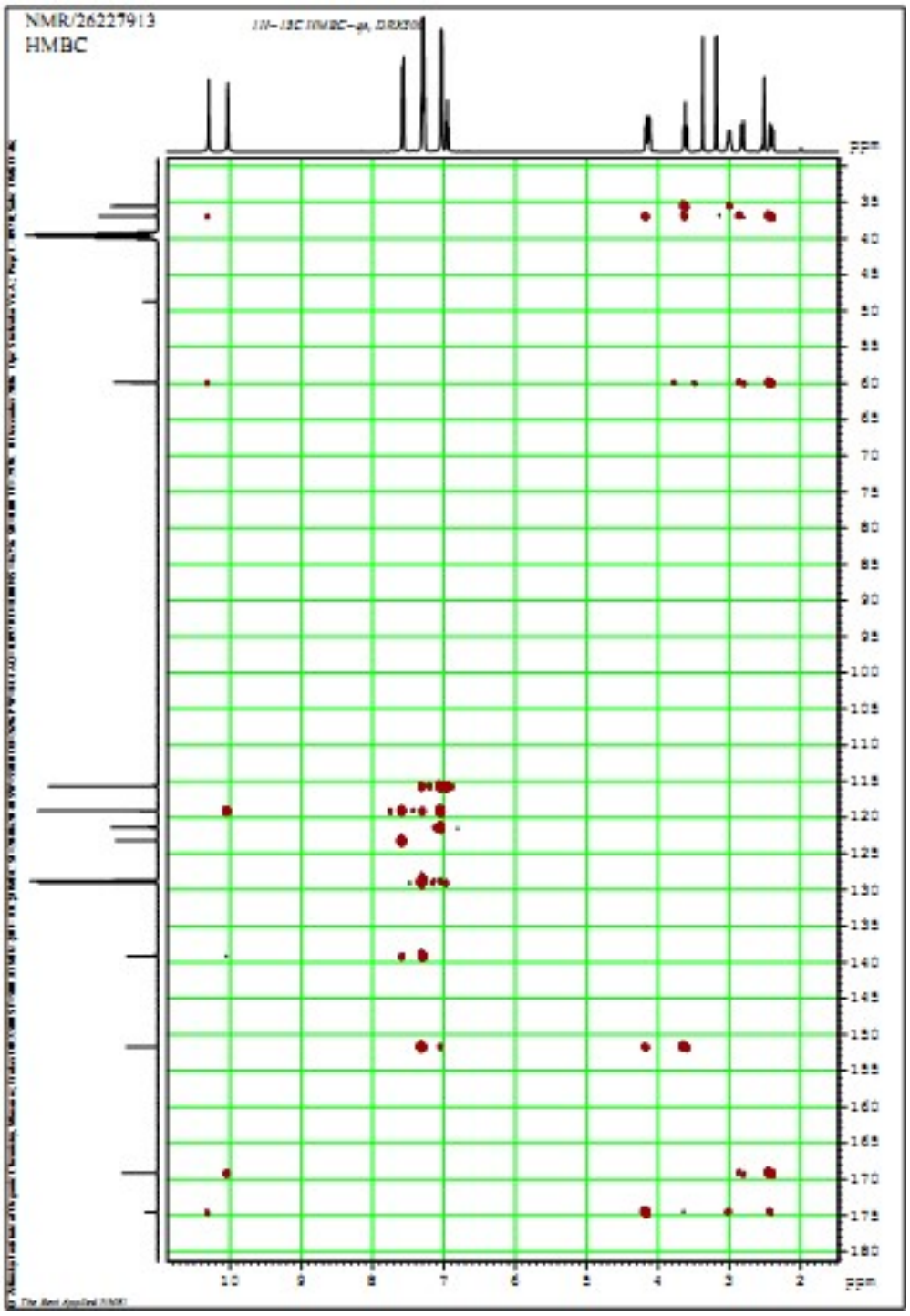


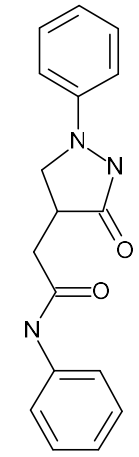
NOESY- spectra
of compound 7a





HMBC - spectra of compound 5a





HMBC- spectra of compound 7a