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Supplementary information

A novel strategy for the synthesis of thermally stable and apoptosis-inducing 2,3-dihydroazetes

Ilia A. Smetanin,[a] Mikhail S. Novikov,*[a] Anastasiya V. Agafonova,[a] Nikolai V. Rostovskii,[a] Alexander F. Khlebnikov,[a] Igor V. Kudryavtsev,[b] Maxim A. Terpilowski,[c] Maria K. Serebriakova,[b] Andrey S. Trulioff,[b] Nikolay V. Goncharov[c]

[a] St. Petersburg State University, Institute of Chemistry, 7/9 Universitetskaya nab., St. Petersburg, 199034 Russia.

[b] Institute of Experimental Medicine, Russian Academy of Sciences, ul. acad. Pavlov 12, St. Petersburg, 197376 Russia.

[c] Sechenov Institute of Evolutionary Physiology and Biochemistry, Russian Academy of Sciences, pr. Torez 44, St. Petersburg, 194223 Russia.

m.s.novikov@chem.spbu.ru

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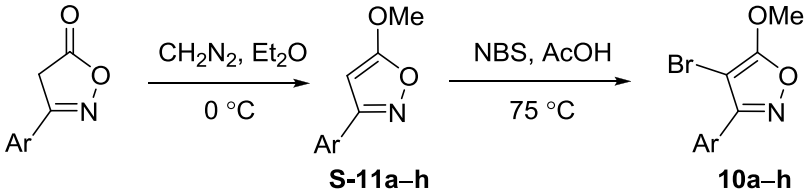
1. General experimental details

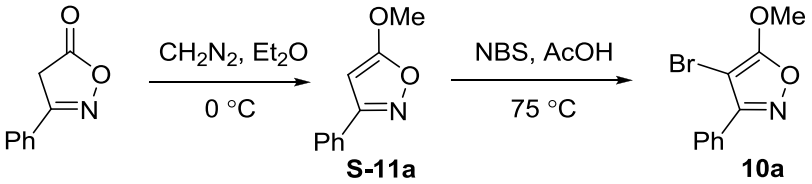
Melting points were determined on a hot stage microscope and are uncorrected. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a Bruker AVANCE 400 spectrometer in $CDCl_3$. Chemical shifts (δ) are reported in ppm downfield from tetramethylsilane. Electrospray ionization (ESI) mass spectra were measured on a Bruker MaXis mass spectrometer. Single crystal X-ray data were collected by means of Agilent Technologies «Supernova» and «Xcalibur» diffractometers. Crystallographic data for the structures **2a,h** have been deposited with the Cambridge Crystallographic Data Centre. Thin-layer chromatography (TLC) was conducted on aluminum sheets precoated with SiO_2 ALUGRAM SIL G/UV254. Toluene was distilled over sodium wire. 1,2-Dichloroethane was washed with concentrated H_2SO_4, water, then distilled from P_2O_5 and stored over anhydrous K_2CO_3. Commercially obtained *N*-bromosuccinimide and tributylstannane were used as received. 2*H*-Azirines **3b,**[1] **7a,**[2] **7b–d**[3] were prepared by the reported procedures.

2. Synthesis of isoxazoles 10a–h



3-Phenylisoxazol-5(4*H*)-one, 3-(4-methoxyphenyl)isoxazol-5(4*H*)-one, 3-(4-chlorophenyl)-isoxazol-5(4*H*)-one, 3-(4-bromophenyl)isoxazol-5(4*H*)-one, 3-(2,4-dimethylphenyl)isoxazol-5(4*H*)-one, 3-(*p*-tolyl)isoxazol-5(4*H*)-one, 3-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-isoxazol-5(4*H*)-one and 4-(5-oxo-4,5-dihydroisoxazol-3-yl)benzonitrile were obtained according the published procedure.[5] Methylation of 3-arylisoxazol-5(4*H*)-ones[6] as well as bromination of 3-aryl-5-methoxyisoxazoles (**S-11a–h**)[7] were carried out according to the known procedures.

4-Bromo-5-methoxy-3-phenylisoxazole (**10a**)

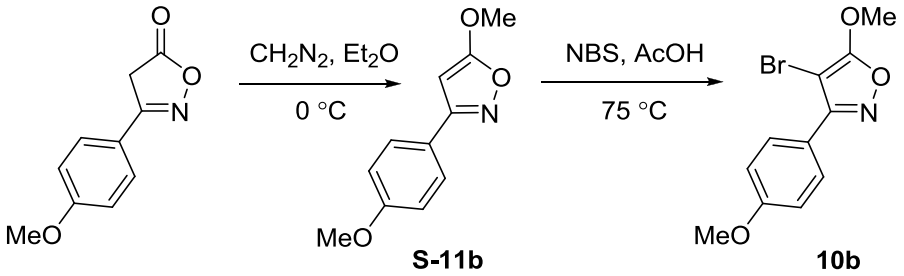


*5-Methoxy-3-phenylisoxazole (**S-11a**).* A solution of diazomethane (21 mmol) in Et_2O was added dropwise to a stirred suspension of 3-phenylisoxazol-5(4*H*)-one (1.69 g, 10.5 mmol) in dry Et_2O

(50 mL) at 0 °C. The resulting mixture was stirred at rt for 2h, and then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using gradient elution with hexane/EtOAc mixture to give isoxazole **S-11a** (1.40 g, 76%) as a colorless solid. M.p. 75–77 °C (Et_2O/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 4.06 (3 H, s), 5.55 (1 H, s), 7.41–7.51 (3 H, m), 7.72–7.82 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 58.8, 75.3, 126.4, 128.8, 129.5, 130.0, 164.2, 174.5; HRMS (ESI-TOF): $[M+H]^+$, found 176.0711; $C_{10}H_{10}NO_2^+$ requires 176.0706.

*4-Bromo-5-methoxy-3-phenylisoxazole **10a**.* A solution of isoxazole **S-11a** (350 mg, 2 mmol) and *N*-bromosuccinimide (392 mg, 2.2 mmol) in AcOH (20 mL) was heated at 75 °C under stirring for 40 min. The reaction mixture was cooled and diluted with cold water (60 mL) and extracted with dichloromethane (3×20 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column flash chromatography on silica gel using hexane/EtOAc (10:1) mixture to give **10a** (437 mg, 86%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 4.23 (3 H, s), 7.45–7.54 (3 H, m), 7.80–7.90 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 58.5, 66.8, 127.9, 128.3, 128.6, 130.3, 162.5, 169.3; HRMS (ESI-TOF): $[M+H]^+$, found 253.9818; $C_{10}H_9BrNO_2^+$ requires 253.9811.

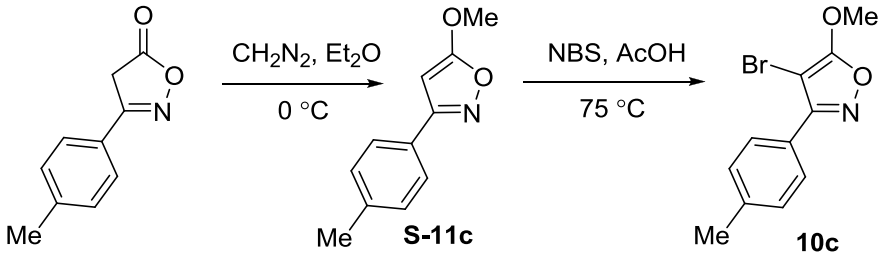
4-Bromo-5-methoxy-3-(4-methoxyphenyl)isoxazole (10b)



*5-Methoxy-3-(4-methoxyphenyl)isoxazole (**S-11b**).* To a stirred suspension of 3-(4-methoxyphenyl)isoxazol-5(4*H*)-one (2.01 g, 10.5 mmol) in dry Et_2O (50 mL) a solution of diazomethane (31.5 mmol) in Et_2O was added dropwise at 0 °C. The resulting mixture was stirred at rt for 2h and then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using gradient elution with hexane/EtOAc mixture to give isoxazole **S-11b** (1.83 g, 85%) as a colorless solid. M.p. 92–93 °C (Et_2O/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 3.86 (3 H, s), 4.04 (3 H, s), 5.49 (1 H, s), 6.93–7.01 (2 H, m), 7.66–7.75 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 55.3, 58.7, 75.1, 114.1, 122.1, 127.8, 161.0, 163.8, 174.3; HRMS (ESI-TOF): $[M+H]^+$, found 206.0819; $C_{11}H_{12}NO_3^+$ requires 206.0812.

*4-Bromo-5-methoxy-3-(4-methoxyphenyl)isoxazole **10b***. A solution of the isoxazole **S-11b** (410 mg, 2 mmol) and *N*-bromosuccinimide (392 mg, 2.2 mmol) in AcOH (20 mL) was heated at 75 °C under stirring for 40 min. The reaction mixture was cooled and diluted with cold water (60 mL) and the resulting precipitate was collected, washed with water and if necessary recrystallized from hexane/Et_2O mixture to give **10b** (500 mg, 88%) as a colorless solid. M.p. 106–107 °C (Et_2O/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 3.88 (3 H, s), 4.22 (3 H, s), 6.94–7.07 (2 H, m), 7.71–7.88 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 55.3, 58.4, 66.6, 114.1, 120.7, 129.3, 161.2, 162.1, 169.2; HRMS (ESI-TOF): $[M+H]^+$, found 283.9925; $C_{11}H_{11}BrNO_3^+$ requires 283.9917.

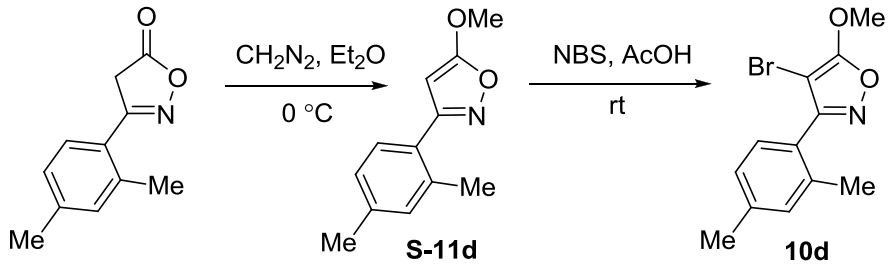
4-Bromo-5-methoxy-3-(*p*-tolyl)isoxazole (10c)



*5-Methoxy-3-(p-tolyl)isoxazole (**S-11c**).* To a stirred suspension of 3-(*p*-tolyl)isoxazol-5(4*H*)-one (1.84 g, 10.5 mmol) in dry Et_2O (50 mL) a solution of diazomethane (31.5 mmol) in Et_2O was added dropwise at 0 °C. The resulting mixture was stirred at rt for 2h, and then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using gradient elution with hexane/EtOAc mixture to give isoxazole **S-11c** (1.69 g, 85%) as a colorless solid. M.p. 74–76 °C (Et_2O/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.41 (3 H, s), 4.05 (3 H, s), 5.52 (1 H, s); 7.26 (2 H, d, J = 8.0 Hz), 7.67 (2 H, d, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 21.4, 58.7, 75.2, 126.3, 126.7, 129.4, 140.1, 164.1, 174.3; HRMS (ESI-TOF): $[M+H]^+$, found 190.0858; $C_{11}H_{12}NO_2^+$ requires 190.0863.

*4-Bromo-5-methoxy-3-(p-tolyl)isoxazole **10c***. A solution of isoxazole **S-11c** (378 mg, 2 mmol) and *N*-bromosuccinimide (392 mg, 2.2 mmol) in AcOH (20 mL) was heated at 75 °C under stirring for 40 min. The reaction mixture was cooled and diluted with cold water (60 mL) and the resulting precipitate was collected, washed with water and if necessary recrystallized from hexane/Et_2O mixture to give **10c** (499 mg, 93%) as a colorless solid. M.p. 58–60 °C (Et_2O/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.44 (3 H, s), 4.23 (3 H, s), 7.31 (2 H, d, J = 7.6 Hz), 7.75 (2 H, d, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 21.4, 58.7, 66.7, 125.4, 127.8, 129.3, 140.4, 162.5, 169.2; HRMS (ESI-TOF): $[M+H]^+$, found 267.9978; $C_{11}H_{11}BrNO_2^+$ requires 267.9968.

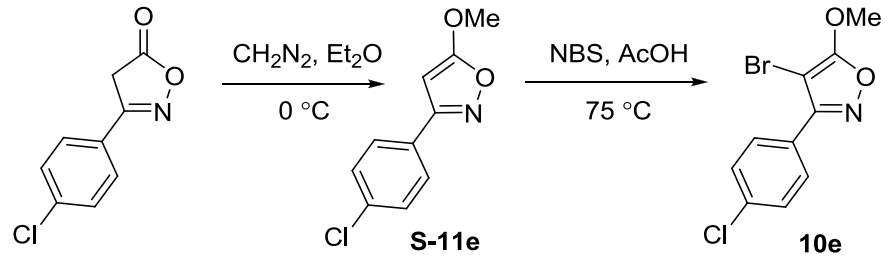
4-Bromo-3-(2,4-dimethylphenyl)-5-methoxyisoxazole (10d)



*3-(2,4-Dimethylphenyl)-5-methoxyisoxazole (**S-11d**).* To a stirred suspension of 3-(2,4-dimethylphenyl)isoxazol-5(4*H*)-one (1.98 g, 10.5 mmol) in dry Et_2O (50 mL) a solution of diazomethane (31.5 mmol) in Et_2O was added dropwise at 0 °C. The resulting mixture was stirred at rt for 2h and then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using gradient elution with hexane/EtOAc mixture to give isoxazole **S-11d** (1.74 g, 82%) as a colorless solid. M.p. 50–53 °C (from oil); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.38 (3 H, s), 2.48 (3 H, s), 4.05 (3 H, s), 5.40 (1 H, s); 7.05–7.16 (2 H, m), 7.39 (1 H, d, J = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 20.9, 21.1, 58.7, 77.9, 126.4, 126.6, 129.1, 131.7, 136.5, 139.4, 165.1, 173.7; HRMS (ESI-TOF): $[M+H]^+$, found 204.1011; $C_{12}H_{14}NO_2^+$ requires 204.1019.

*4-Bromo-3-(2,4-dimethylphenyl)-5-methoxyisoxazole **10d***. A solution of isoxazole **S-11d** (406 mg, 2 mmol) and *N*-bromosuccinimide (374 mg, 2.1 mmol) in AcOH (20 mL) was stirred at rt for 30 min. The reaction mixture was cooled and diluted with cold water (60 mL) and the resulting precipitate was collected, washed with water and if necessary recrystallized from hexane/Et_2O mixture to give **10d** (355 mg, 63%) as a colorless solid. M.p. 67–69 °C (Et_2O/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.35 (3 H, s), 2.40 (3 H, s), 4.24 (3 H, s), 7.08–7.18 (2 H, m), 7.26 (1 H, d, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 19.8, 21.3, 58.4, 68.6, 124.7, 126.4, 129.7, 131.3, 137.1, 140.0, 164.8, 168.8; HRMS (ESI-TOF): $[M+H]^+$, found 282.0131; $C_{12}H_{13}BrNO_2^+$ requires 282.0124.

4-Bromo-3-(4-chlorophenyl)-5-methoxyisoxazole (10e)

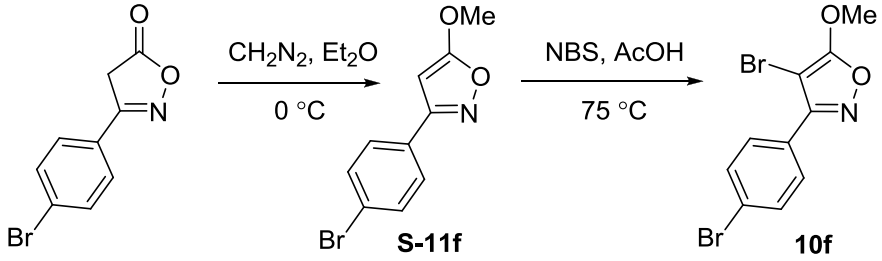


*3-(4-Chlorophenyl)-5-methoxyisoxazole (**S-11e**).* To a stirred suspension of 3-(4-chlorophenyl)isoxazol-5(4*H*)-one (2.05 g, 10.5 mmol) in dry Et_2O (50 mL) a solution of

diazomethane (31.5 mmol) in Et_2O was added dropwise at 0 °C. The resulting mixture was stirred at rt for 2h and then concentrated under under reduced pressure. The residue was purified by column chromatography on silica gel using gradient elution with hexane/EtOAc mixture to give isoxazole **S-11e** (1.74 g, 79%) as a colorless solid. M.p. 103–104 °C (Et_2O/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 4.06 (3 H, s), 5.52 (1 H, s), 7.37–7.48 (2 H, m), 7.65–7.75 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 58.9, 75.3, 127.7, 128.0, 129.0, 130.0, 163.2, 174.6; HRMS (ESI-TOF): $[M+Na]^+$, found 232.0143; $C_{10}H_8ClNaNO_2^+$ requires 232.0136.

4-Bromo-3-(4-chlorophenyl)-5-methoxyisoxazole **10e**. A solution of the isoxazole **S-11e** (419 mg, 2 mmol) and *N*-bromosuccinimide (392 mg, 2.2 mmol) in AcOH (20 mL) was heated at 75 °C under stirring for 40 min. The reaction mixture was cooled and diluted with cold water (60 mL) and the resulting precipitate was collected, washed with water and if necessary recrystallized from hexane/Et_2O mixture to give **10e** (421 mg, 73%) as a colorless solid. M.p. 64–66 °C (Et_2O/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 4.24 (3 H, s), 7.48 (2 H, d, J = 8.4 Hz), 7.81 (2 H, d, J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 58.5, 66.6, 126.8, 129.0, 129.2, 136.5, 161.5, 169.5; HRMS (ESI-TOF): $[M+Na]^+$, found 309.9256; $C_{10}H_7BrClNNaO_2^+$ requires 309.9241.

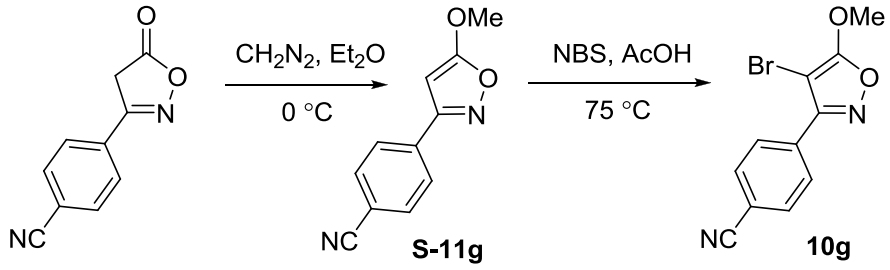
4-Bromo-3-(4-bromophenyl)-5-methoxyisoxazole (10f)



*3-(4-Bromophenyl)-5-methoxyisoxazole (**S-11f**).* To a stirred suspension of 3-(4-bromophenyl)isoxazol-5(4*H*)-one (2.52 g, 10.5 mmol) in dry Et_2O (50 mL) a solution of diazomethane (31.5 mmol) in ether was added dropwise at 0 °C. The resulting mixture was stirred at rt for 2h and then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using gradient elution with hexane/EtOAc mixture to give isoxazole **S-11f** (2.03 g, 76%) as a colorless solid. M.p. 122–124 °C (Et_2O/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 4.07 (3 H, s), 5.52 (1 H, s), 7.53–7.70 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 58.9, 75.3, 124.3, 127.9, 128.5, 132.0, 163.2, 174.6; HRMS (ESI-TOF): $[M+Na]^+$, found 275.9629; $C_{10}H_8BrNaNO_2^+$ requires 275.9631.

*4-Bromo-3-(4-bromophenyl)-5-methoxyisoxazole **10f***. A solution of the isoxazole **S-11f** (508 mg, 2 mmol) and *N*-bromosuccinimide (392 mg, 2.2 mmol) in AcOH (20 mL) was heated at 75 °C under stirring for 40 min. The reaction mixture was cooled and diluted with cold water (60 mL) and the resulting precipitate was collected, washed with water and if necessary recrystallized from hexane/Et_2O mixture to give **10f** (526 mg, 79%) as a colorless solid. M.p. 63–64 °C (Et_2O/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 4.24 (3 H, s), 7.57–7.68 (2 H, m), 7.69–7.78 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 58.6, 66.6, 124.9, 127.2, 129.4, 131.9, 161.6, 169.5; HRMS (ESI-TOF): $[M+Na]^+$, found 353.8741; $C_{10}H_7Br_2NNaO_2^+$ requires 353.8736.

4-(4-Bromo-5-methoxyisoxazol-3-yl)benzonitrile (10g)

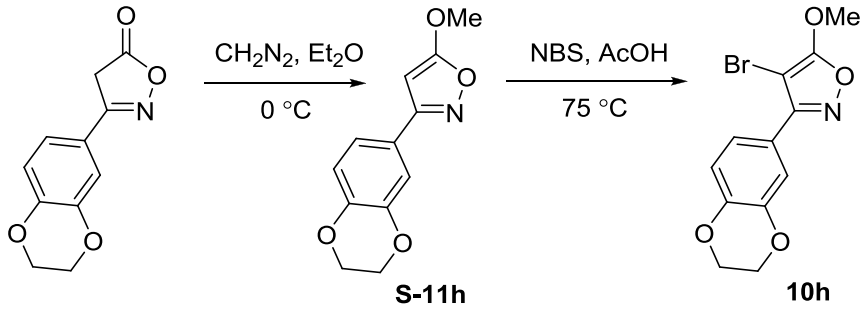


*4-(5-Methoxyisoxazol-3-yl)benzonitrile (**S-11g**)*. To a stirred suspension of 4-(5-oxo-4,5-dihydroisoxazol-3-yl)benzonitrile (1.95 g, 10.5 mmol) in dry Et_2O (50 mL) a solution of diazomethane (31.5 mmol) in Et_2O was added dropwise at 0 °C. The resulting mixture was stirred at rt for 2h and then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using gradient elution with hexane/EtOAc mixture to give isoxazole **S-11g** (1.68 g, 80%) as a colorless solid. M.p. 155–156 °C (Et_2O/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 4.09 (3 H, s), 5.59 (1 H, s), 7.75 (2 H, d, J = 8.3 Hz), 7.88 (2 H, d, J = 8.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 59.0, 75.5, 113.5, 118.3, 127.0, 132.6, 133.8, 162.5, 174.9; HRMS (ESI-TOF): $[M+Na]^+$, found 223.0485; $C_{11}H_8N_2NaO_2^+$ requires 223.0478.

*4-(4-Bromo-5-methoxyisoxazol-3-yl)benzonitrile **10g***. A solution of isoxazole **S-11g** (400 mg, 2 mmol) and *N*-bromosuccinimide (392 mg, 2.2 mmol) in AcOH (20 mL) was heated at 75 °C under stirring for 40 min. The reaction mixture was cooled and diluted with cold water (60 mL) and the resulting precipitate was collected, washed with water and if necessary recrystallized from hexane/Et_2O mixture to give **10g** (486 mg, 87%) as a colorless solid. M.p. 133–135 °C (Et_2O/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 4.26 (3 H, s), 7.79 (2 H, d, J = 8.0 Hz), 7.99 (2 H, d, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 58.7, 66.6, 114.0, 118.2, 128.5, 132.4, 132.7, 160.8, 169.8; HRMS (ESI-TOF): $[M+Na]^+$, found 300.9588;

$C_{11}H_7BrN_2NaO_2^+$ requires 300.9583.

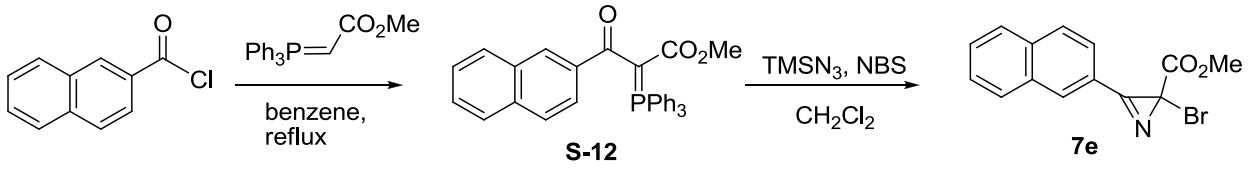
4-Bromo-3-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-5-methoxyisoxazole (10h)



*3-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)-5-methoxyisoxazole (**S-11h**).* To a stirred suspension of 3-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)isoxazol-5(4*H*)-one (2.30 g, 10.5 mmol) in dry Et_2O (50 mL) a solution of diazomethane (31.5 mmol) in Et_2O was added dropwise at 0 °C. The resulting mixture was stirred at rt for 2h and then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using gradient elution with hexane/EtOAc mixture to give isoxazole **S-11h** (2.01 g, 82%) as a colorless solid. M.p. 97–98 °C (Et_2O/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 4.04 (3 H, s), 4.26–4.35 (4 H, m), 5.46 (1 H, s); 6.93 (1 H, d, J = 8.4 Hz), 7.25 (1 H, dd, J = 8.4 Hz, 2.0 Hz), 7.29 (1 H, d, J = 2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 58.7, 64.2, 64.5, 75.2, 115.5, 117.6, 119.8, 122.9, 143.7, 145.2, 163.7, 174.3; HRMS (ESI-TOF): $[M+Na]^+$, found 256.0585; $C_{12}H_{11}NNaO_4^+$ requires 256.0580.

*4-Bromo-3-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-5-methoxyisoxazole **10h**.* A solution of isoxazole **S-11h** (466 mg, 2 mmol) and *N*-bromosuccinimide (392 mg, 2.2 mmol) in AcOH (20 mL) was heated at 75 °C under stirring for 40 min. The reaction mixture was cooled and diluted with cold water (60 mL) and the resulting precipitate was collected, washed with water and if necessary recrystallized from hexane/Et_2O mixture to give **10h** (512 mg, 82%) as a colorless solid. M.p. 85–87 °C (Et_2O/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 4.21 (3 H, s), 4.28–4.35 (4 H, m), 6.97 (1 H, d, J = 8.4 Hz), 7.36 (1 H, dd, J = 8.4 Hz, 2.0 Hz), 7.40 (1 H, d, J = 2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 58.4, 64.2, 64.5, 66.6, 117.0, 117.5, 121.3, 121.4, 143.5, 145.4, 161.8, 169.2; HRMS (ESI-TOF): $[M+Na]^+$, found 333.9696; $C_{12}H_{10}BrNNaO_4^+$ requires 333.9685.

3. Synthesis of methyl 2-bromo-3-(naphthalen-2-yl)-2*H*-azirine-2-carboxylate (7e)

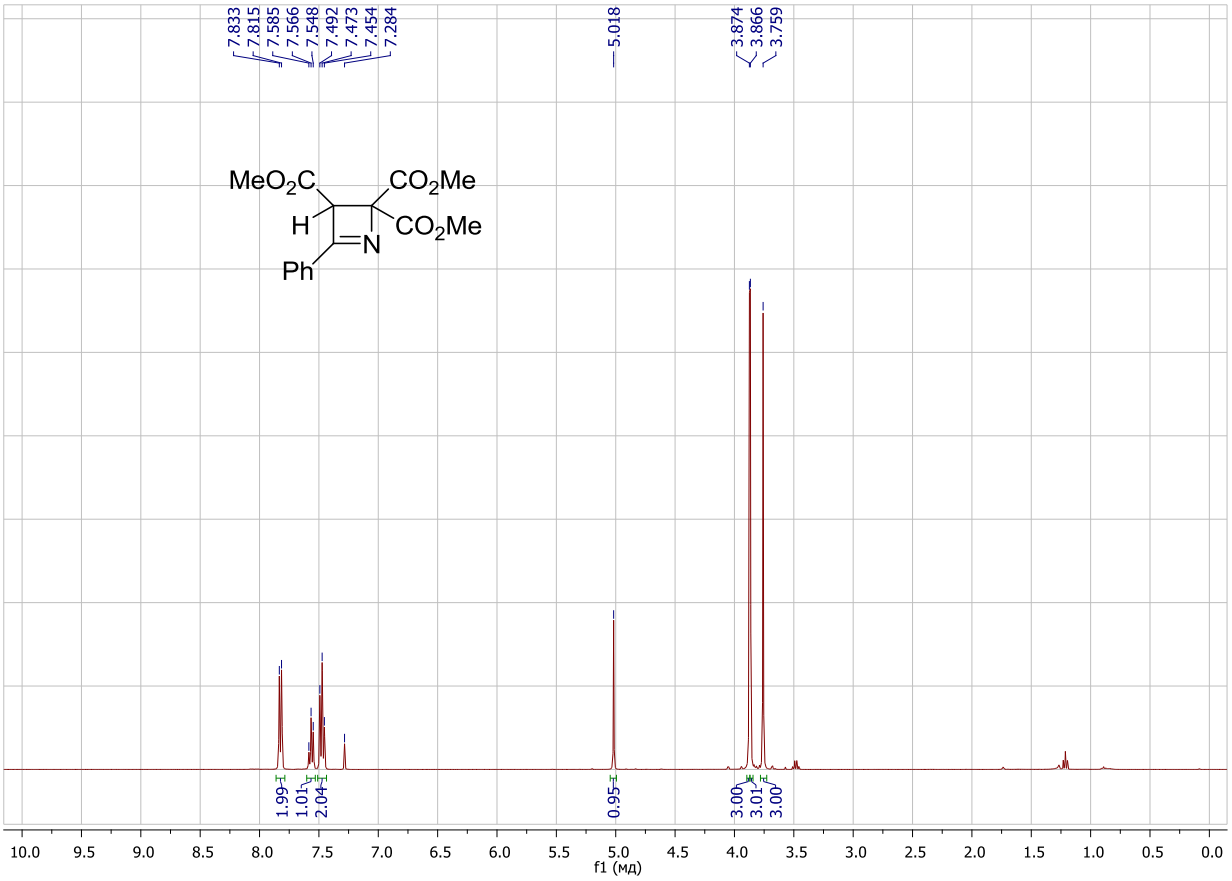


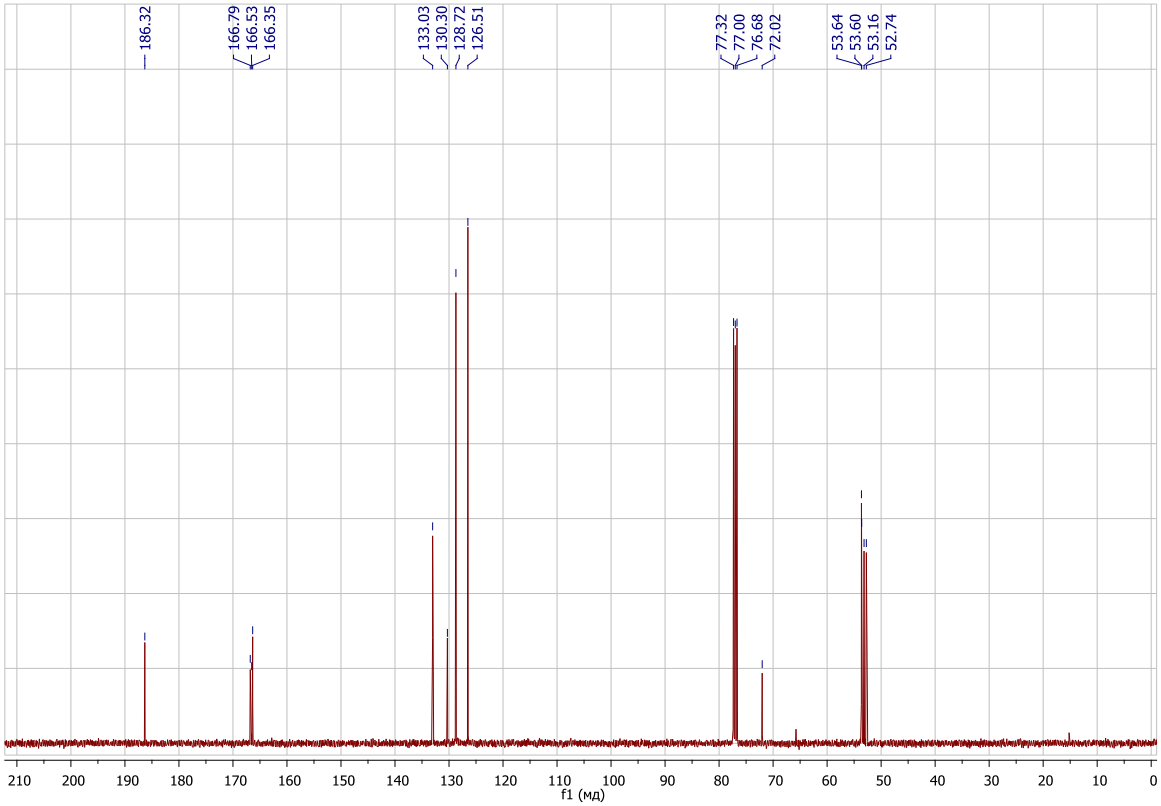
*3-(Naphthalen-2-yl)-3-oxo-2-(triphenyl-λ^5-phosphanylidene)propanoate (**S-12**).* The mixture of 2-naphthoyl chloride (2.86 g, 15 mmol) and methyl 2-(triphenyl-λ^5-phosphanylidene)acetate[4] (10.02 g, 30 mmol) in dry benzene (250 mL) was heated under reflux for 3 h. The resulting phosphonium salt was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by column flash chromatography on silica gel (hexane/EtOAc 1:1) to afford pure **S-12** (5.86 g, 80%). Colorless solid, m.p. 162–163 °C (EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 3.17 (3 H, s), 7.43–7.63 (11 H, m), 7.78–7.96 (10 H, m), 8.20–8.26 (1 H, br.s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 49.8, 69.3 (d, *J* = 112 Hz), 125.6, 126.1 (d, *J* = 94 Hz), 126.29, 126.3, 126.4, 127.5, 127.9, 128.6 (d, *J* = 12 Hz), 128.9, 131.85 (d, *J* = 3 Hz), 132.8, 133.4 (d, *J* = 10 Hz), 134.1, 140.4 (d, *J* = 9 Hz), 168.0 (d, *J* = 15 Hz), 193.0 (d, *J* 6 Hz).

*Methyl 2-bromo-3-(naphthalen-2-yl)-2H-azirine-2-carboxylate (**7e**).* To a stirred solution of ylide **S-12** (4.88 g, 10 mmol) in anhydrous dichloromethane (100 mL) a solution of trimethylsilyl azide (1.73 g, 15 mmol) and *N*-bromosuccinimide (2.67 g, 15 mmol) in anhydrous dichloromethane (250 mL) was added dropwise. The reaction mixture was stirred at room temperature for 24 h, and then the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/EtOAc, from 20:1 to 5:1) to afford after crystallization from Et_2O/hexane mixture pure **7e** (1.22 g, 40%). Colorless solid, m.p. 132–134 °C (Et_2O/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 3.86 (3 H, s), 7.63–7.77 (2 H, m), 7.94–8.11 (4 H, m), 8.42–8.48 (1 H, br. s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 44.1, 54.2, 116.8, 124.7, 127.7, 128.2, 129.4, 129.8, 129.9, 132.6, 133.8, 136.3, 166.4, 167.3; HRMS (ESI-TOF): $[M+Na]^+$, found 325.9792; $C_{14}H_{10}BrNaNO_2^+$ requires 325.9787.

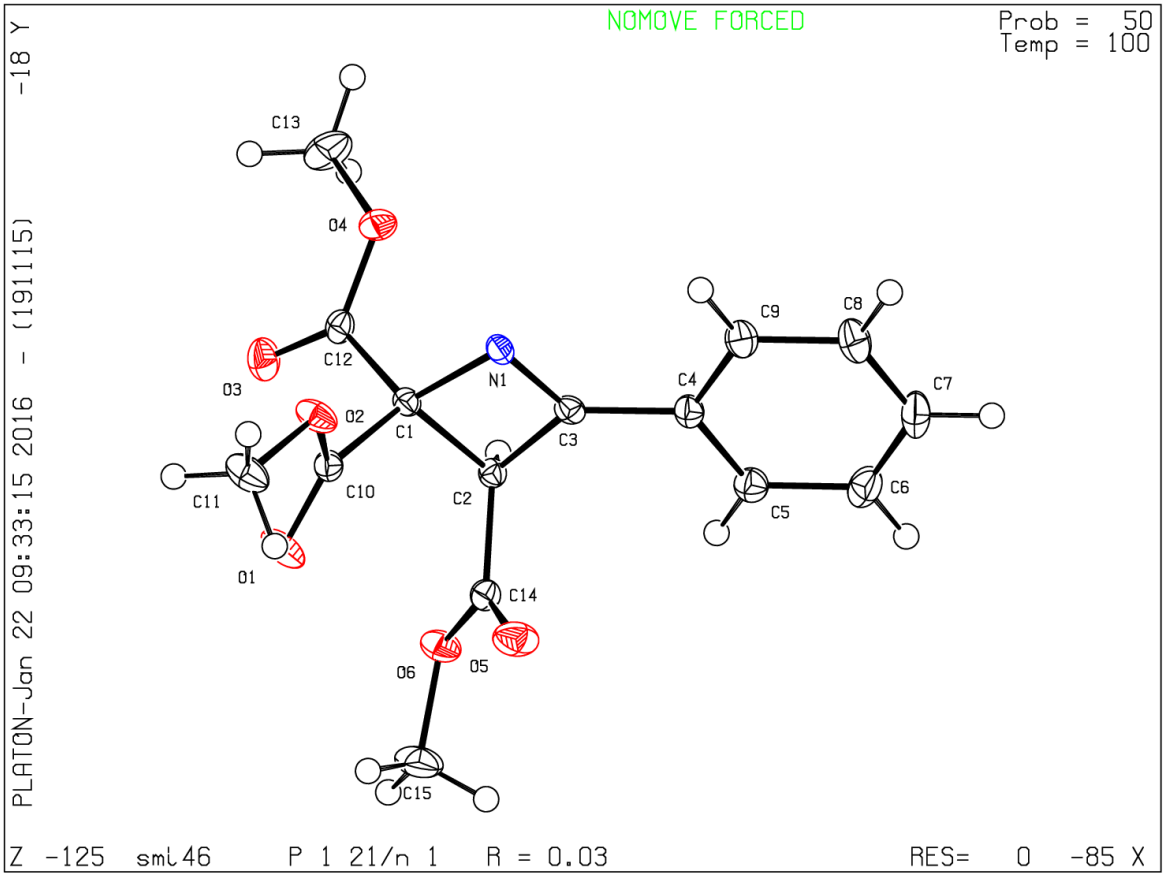
4. ^{1}H, ^{13}C NMR and 2D ^{1}H-^{19}F HOESY spectra and X-ray crystal structures

^{1}H and ^{13}C NMR spectra of compound **2a**

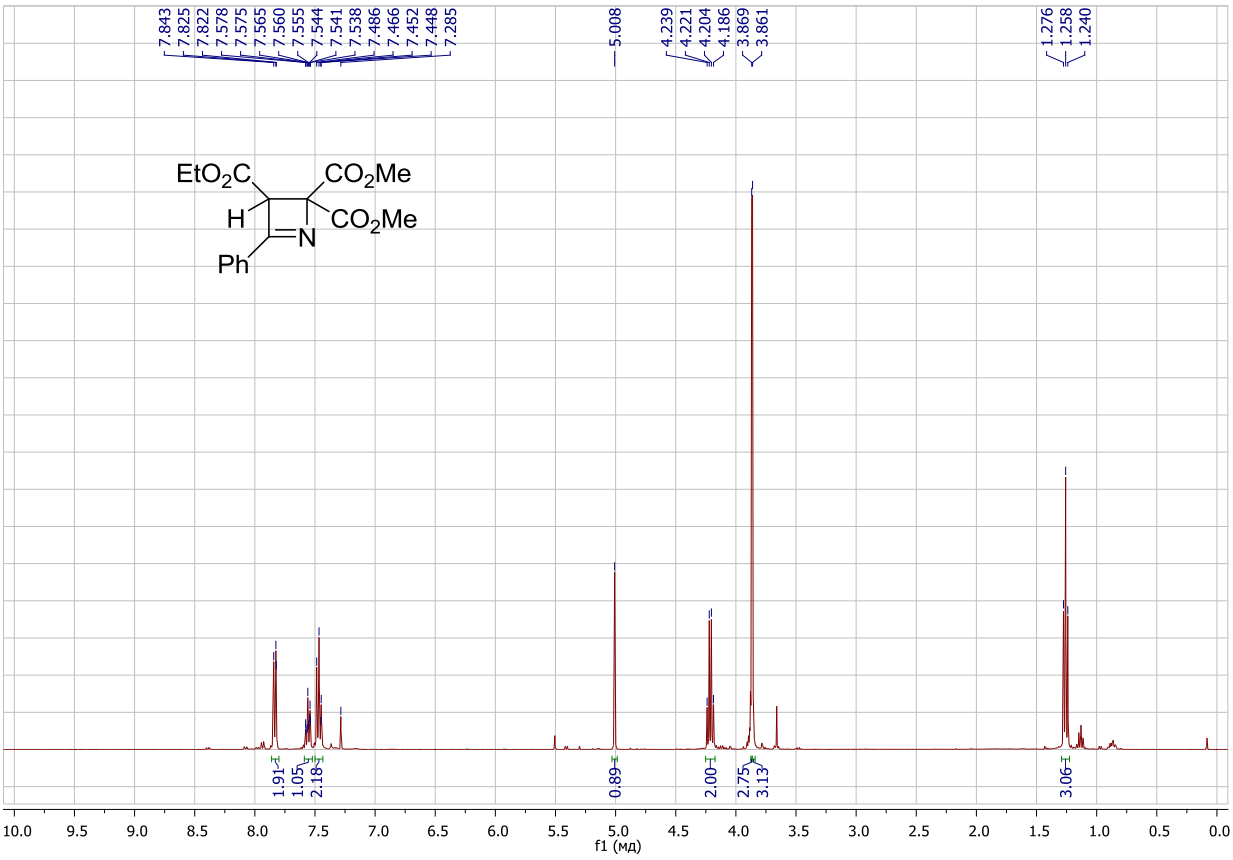


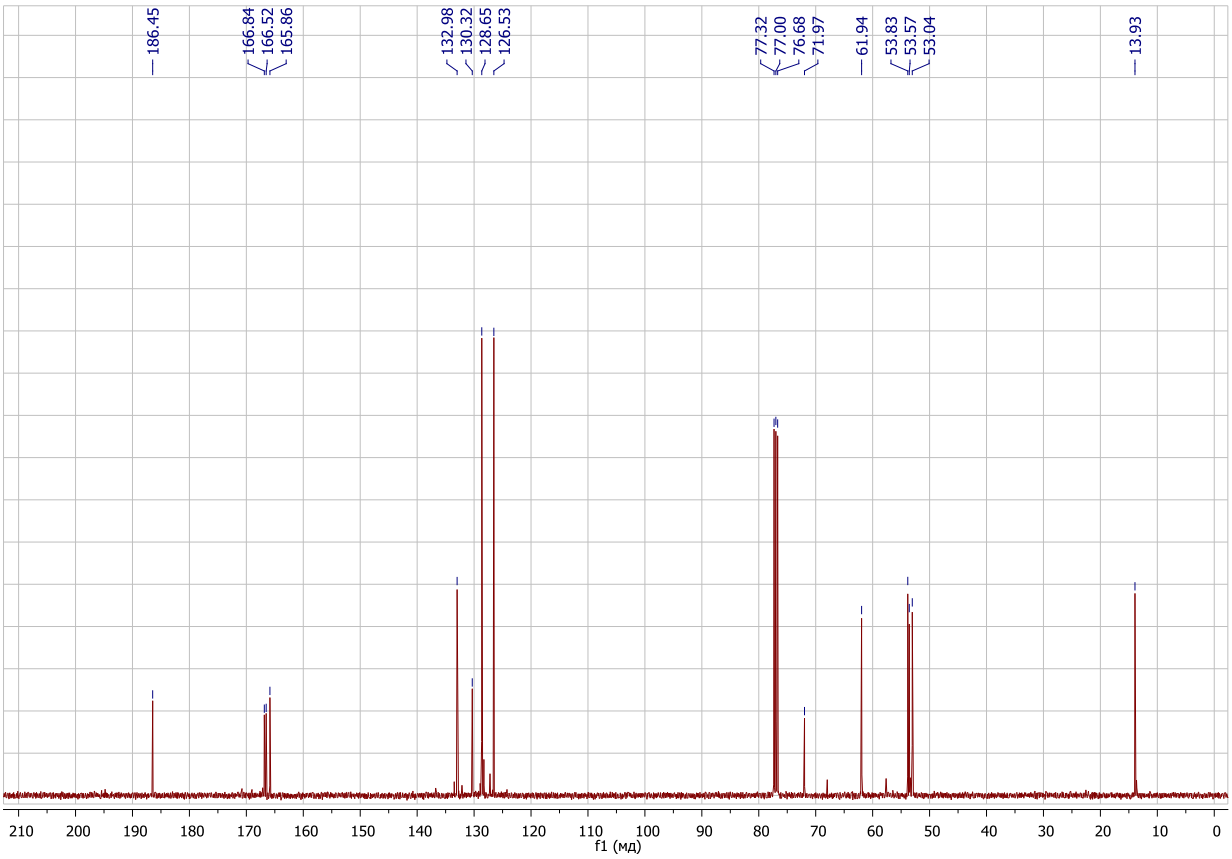


X-ray crystal structure of compound **2a**

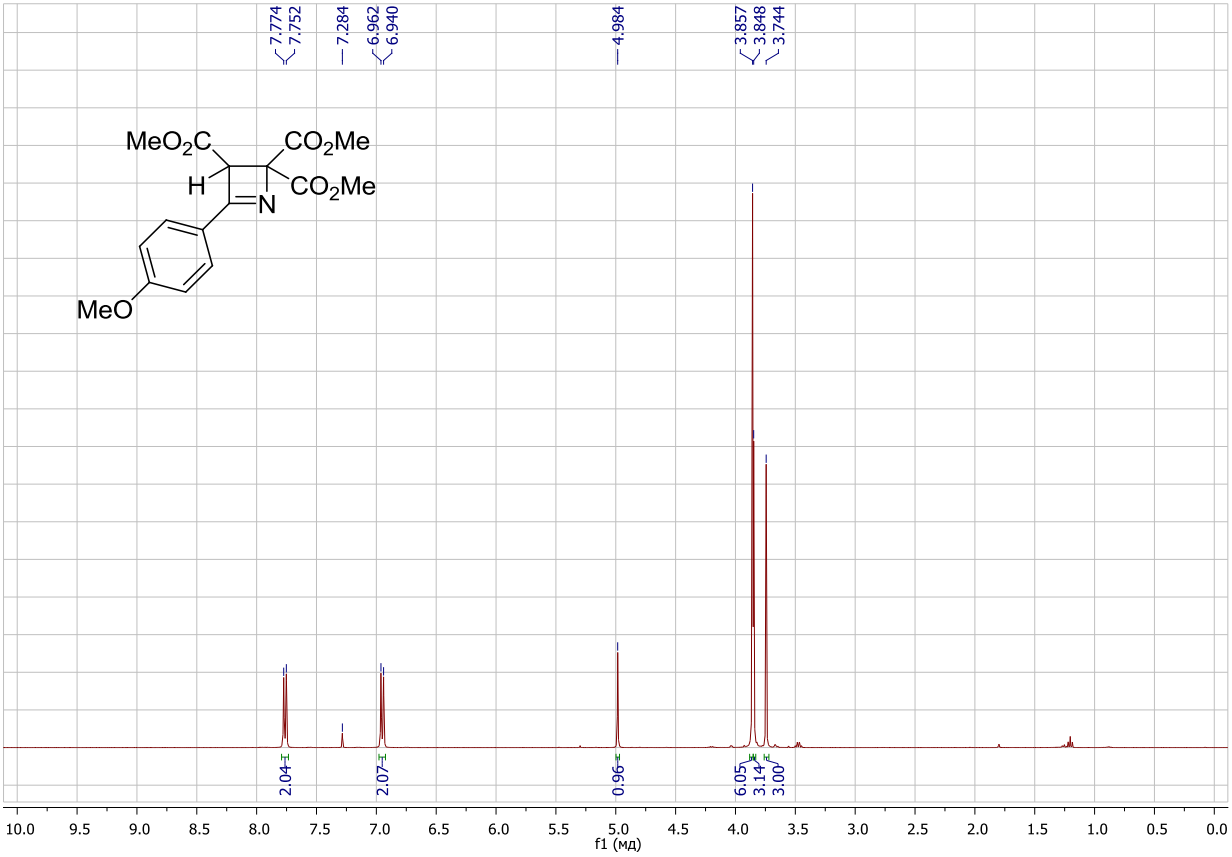


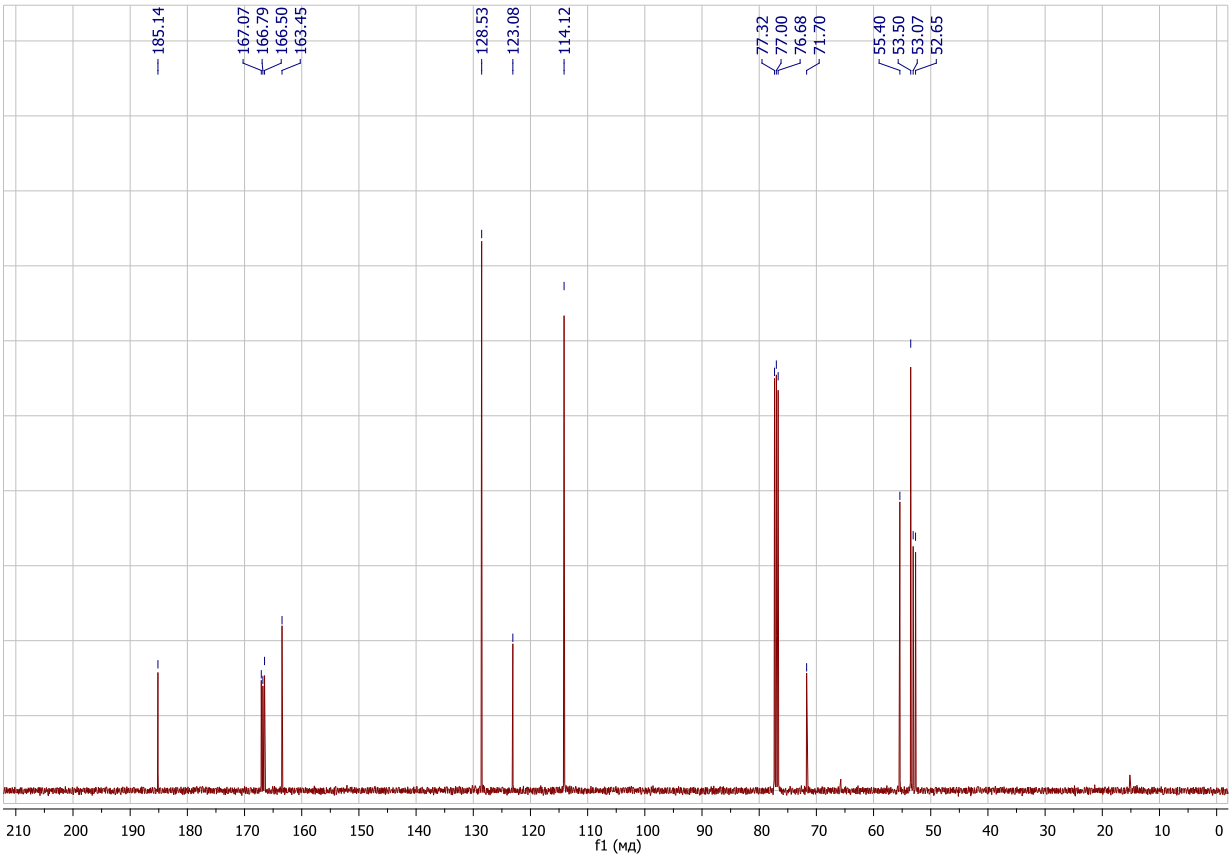
^{1}H and ^{13}C NMR spectra of compound **2a′**



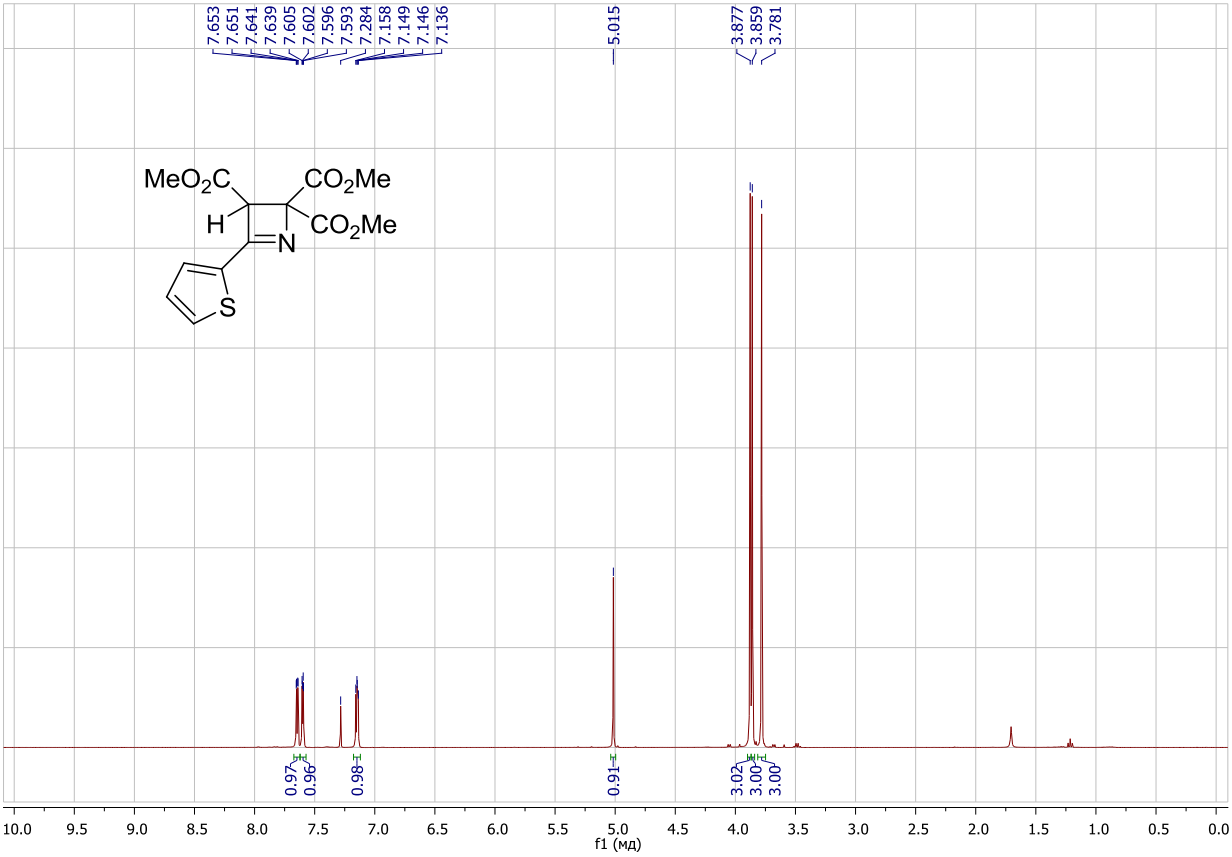


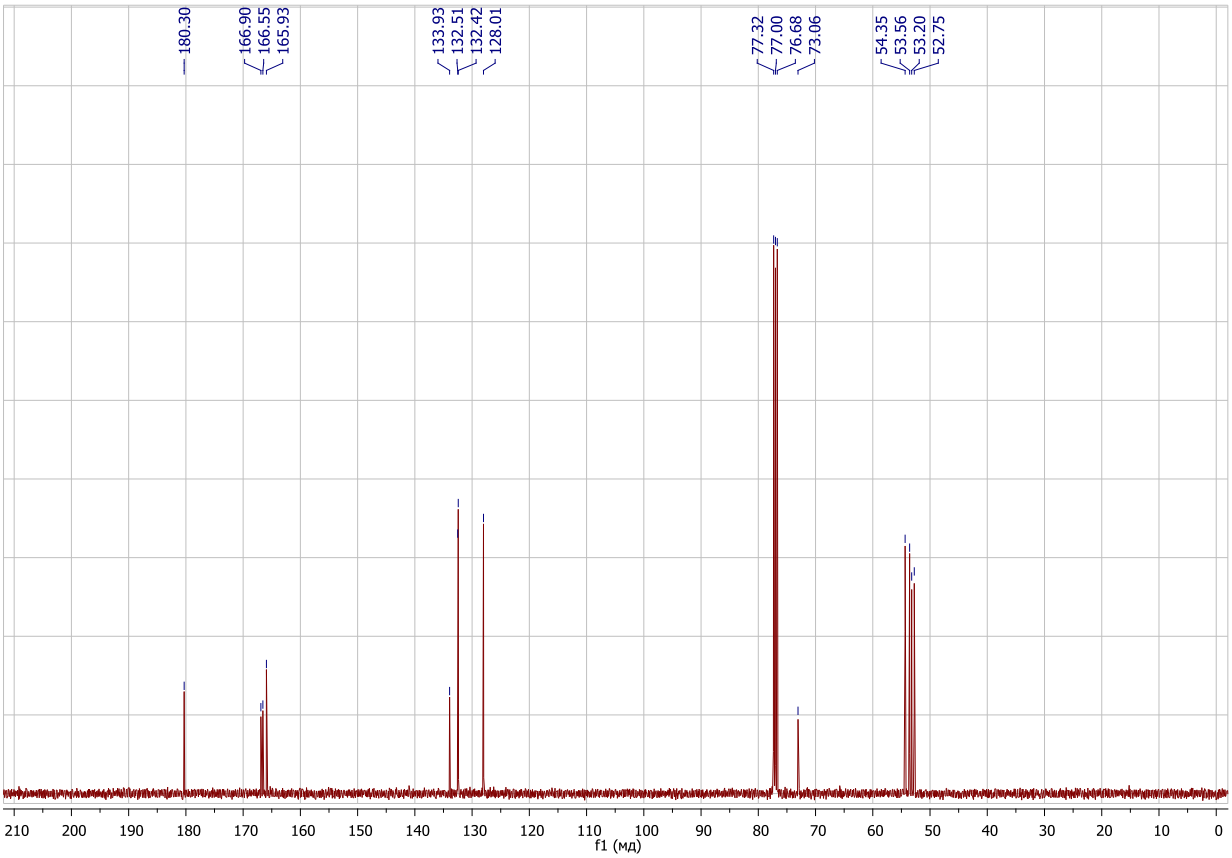
^{1}H and ^{13}C NMR spectra of compound **2b**



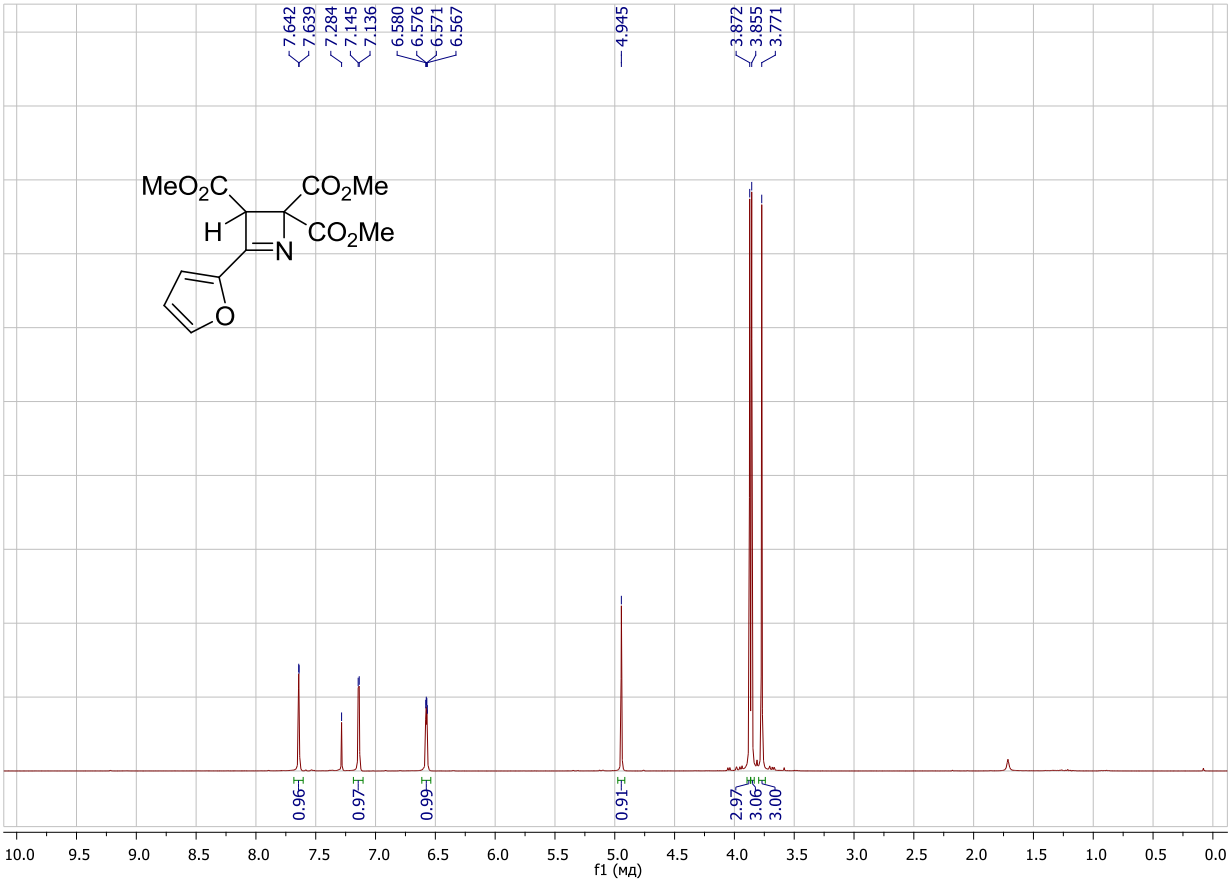


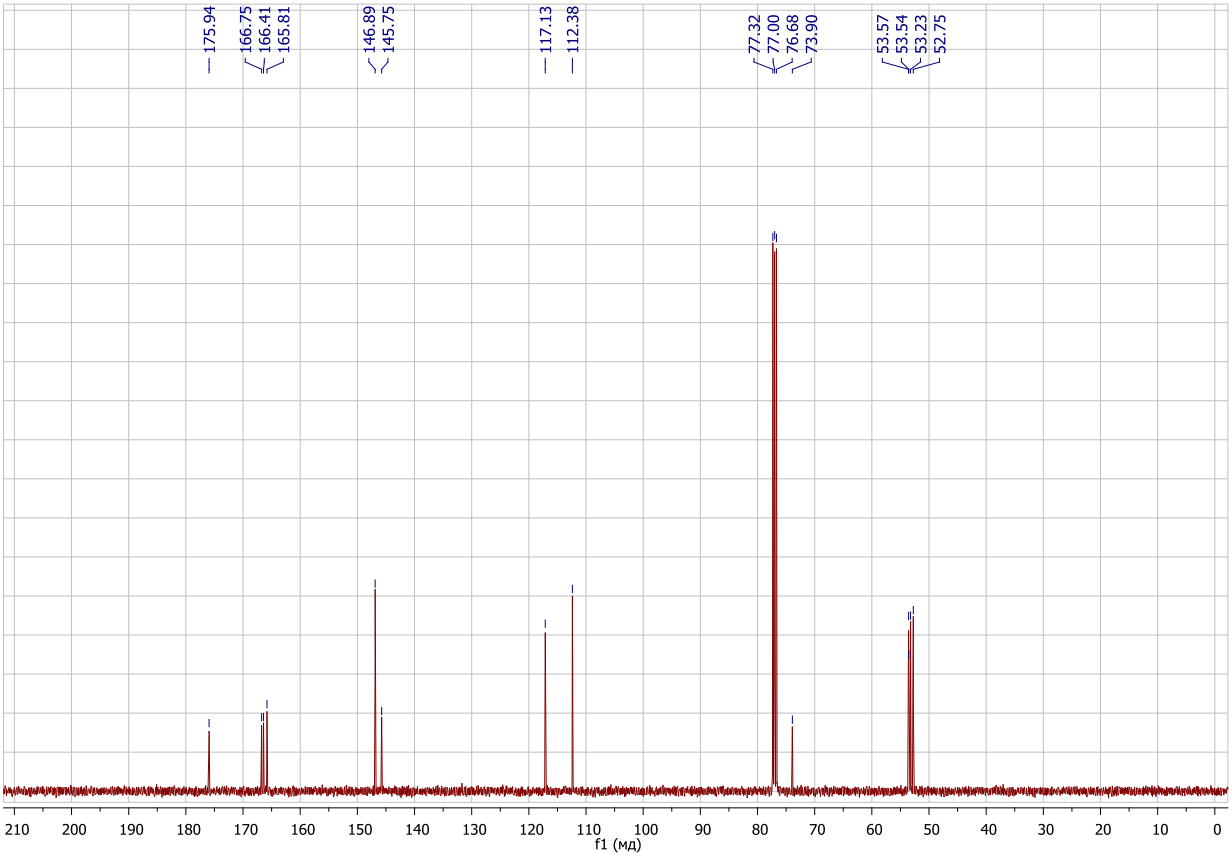
^{1}H and ^{13}C NMR spectra of compound **2c**



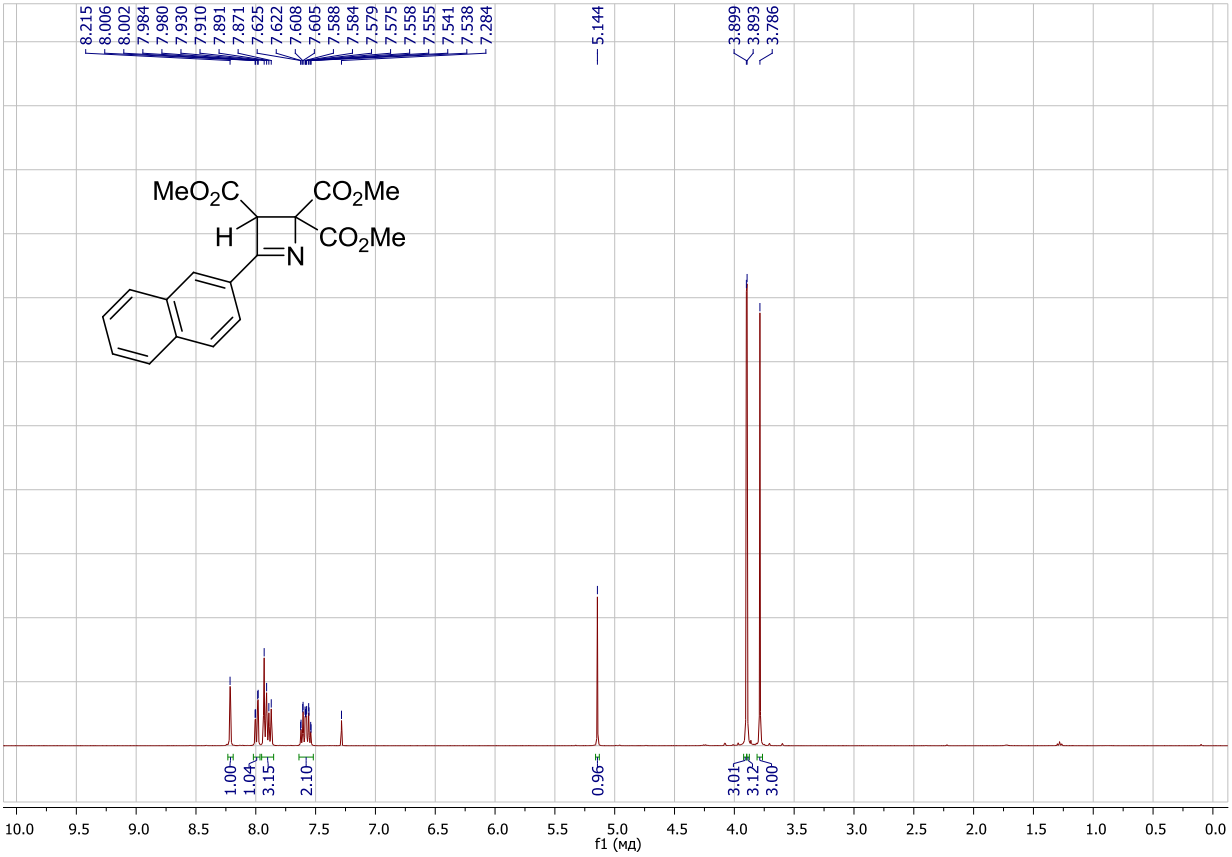


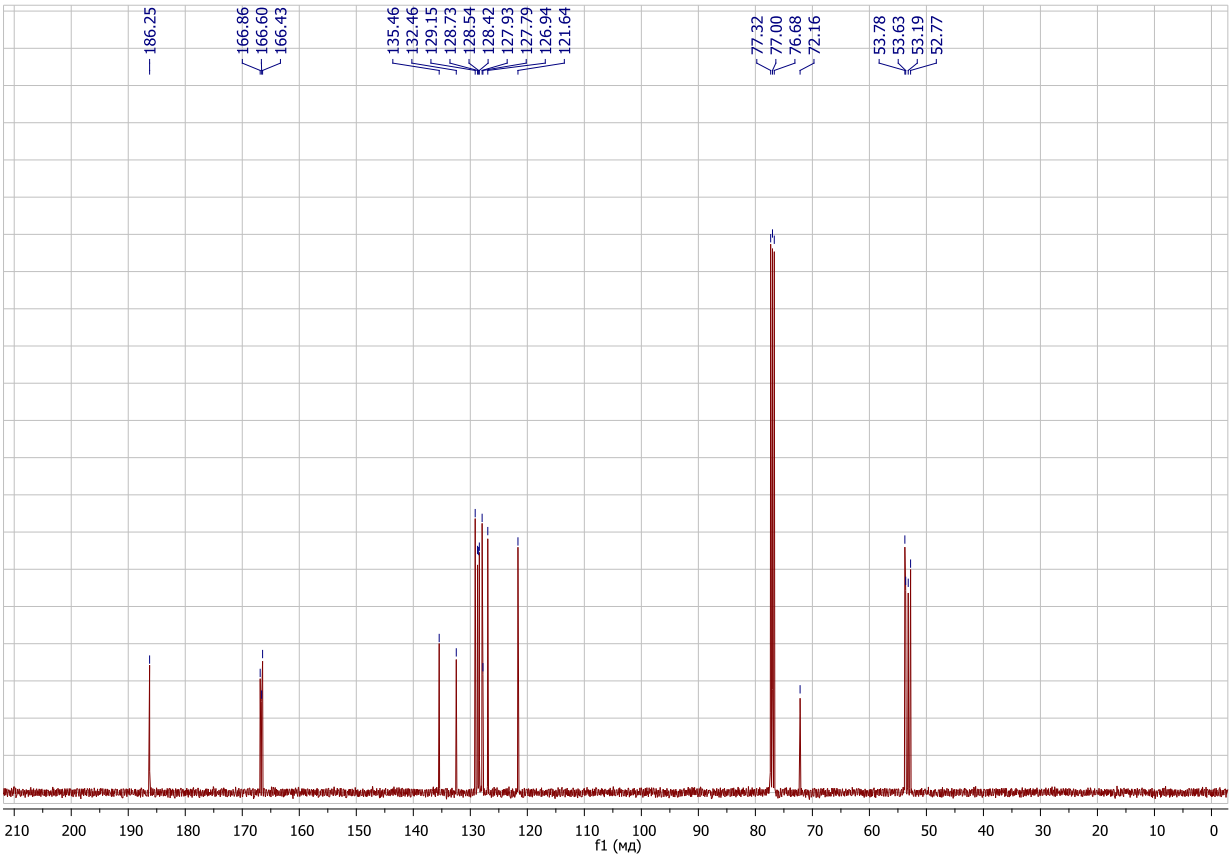
^{1}H and ^{13}C NMR spectra of compound **2d**



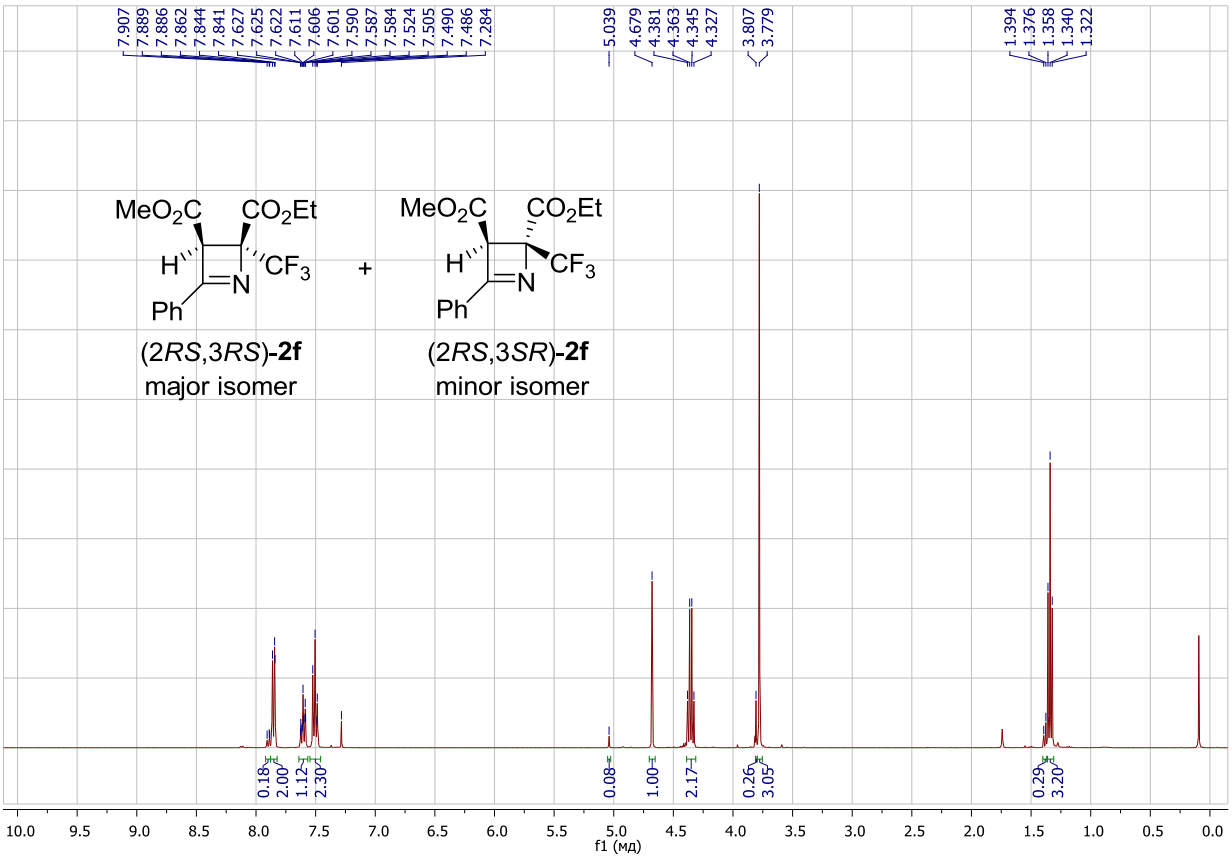


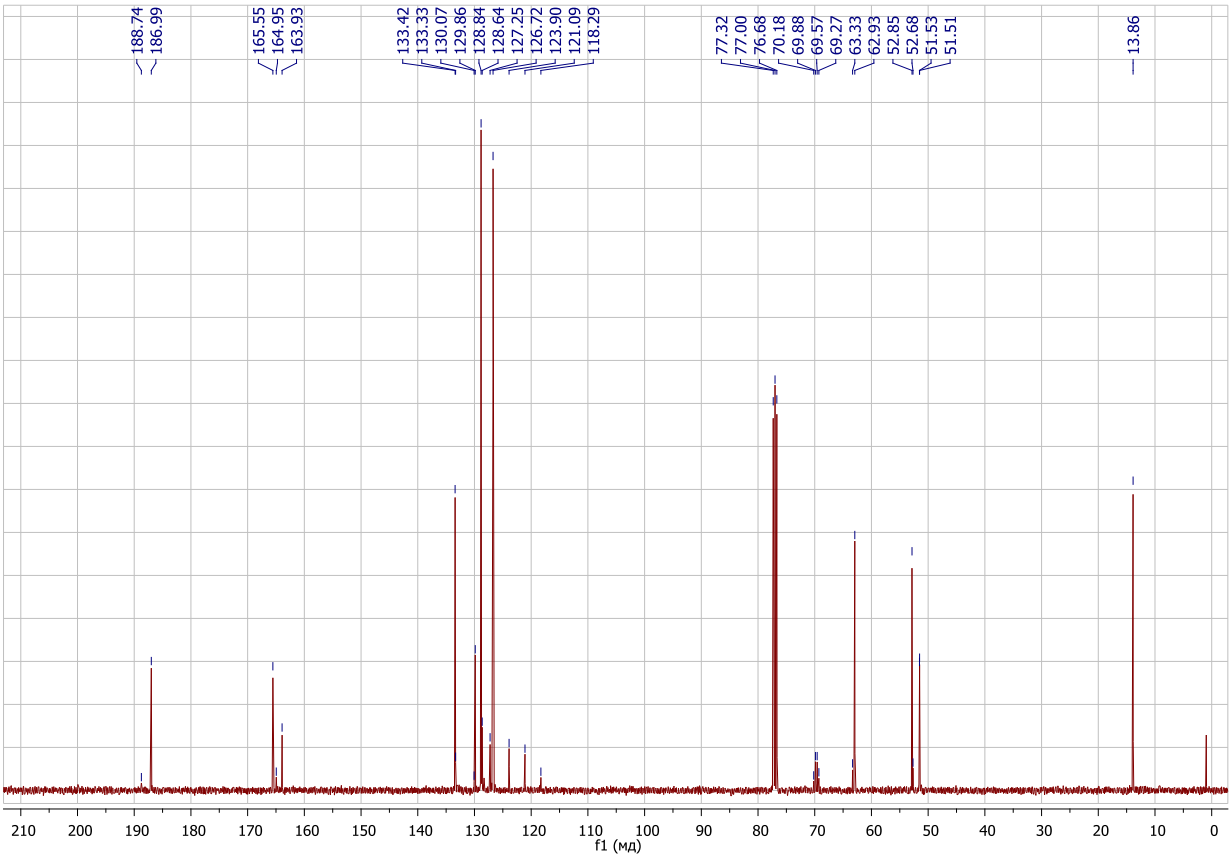
^{1}H and ^{13}C NMR spectra of compound **2e**



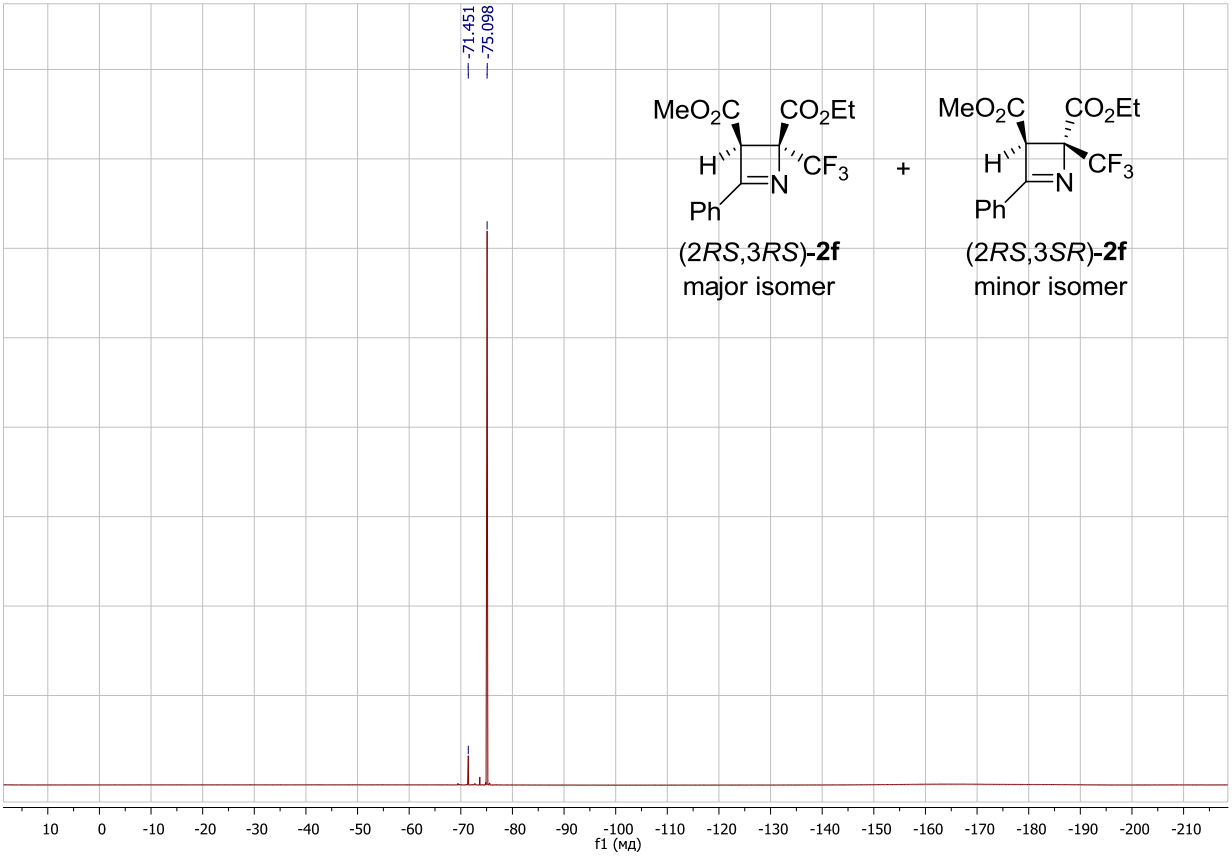


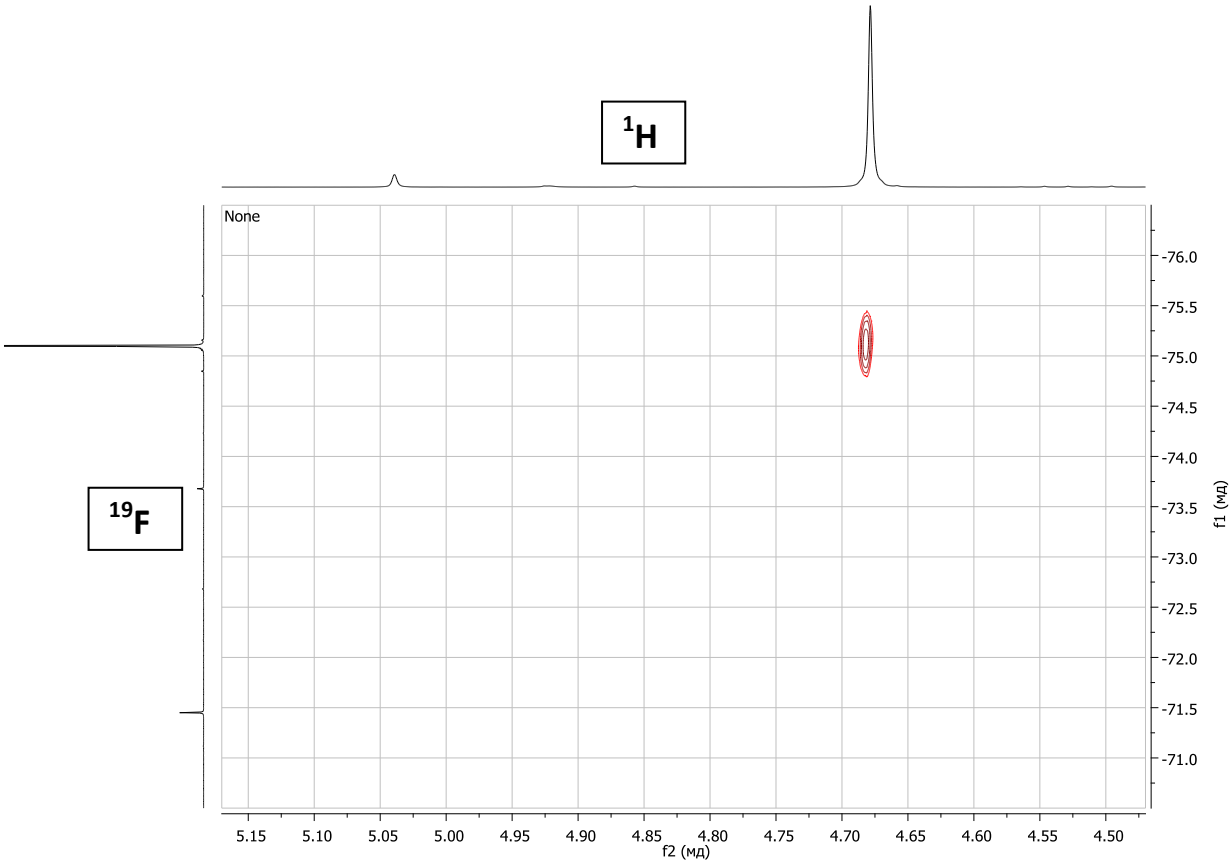
^{1}H and ^{13}C NMR spectra of compound **2f**



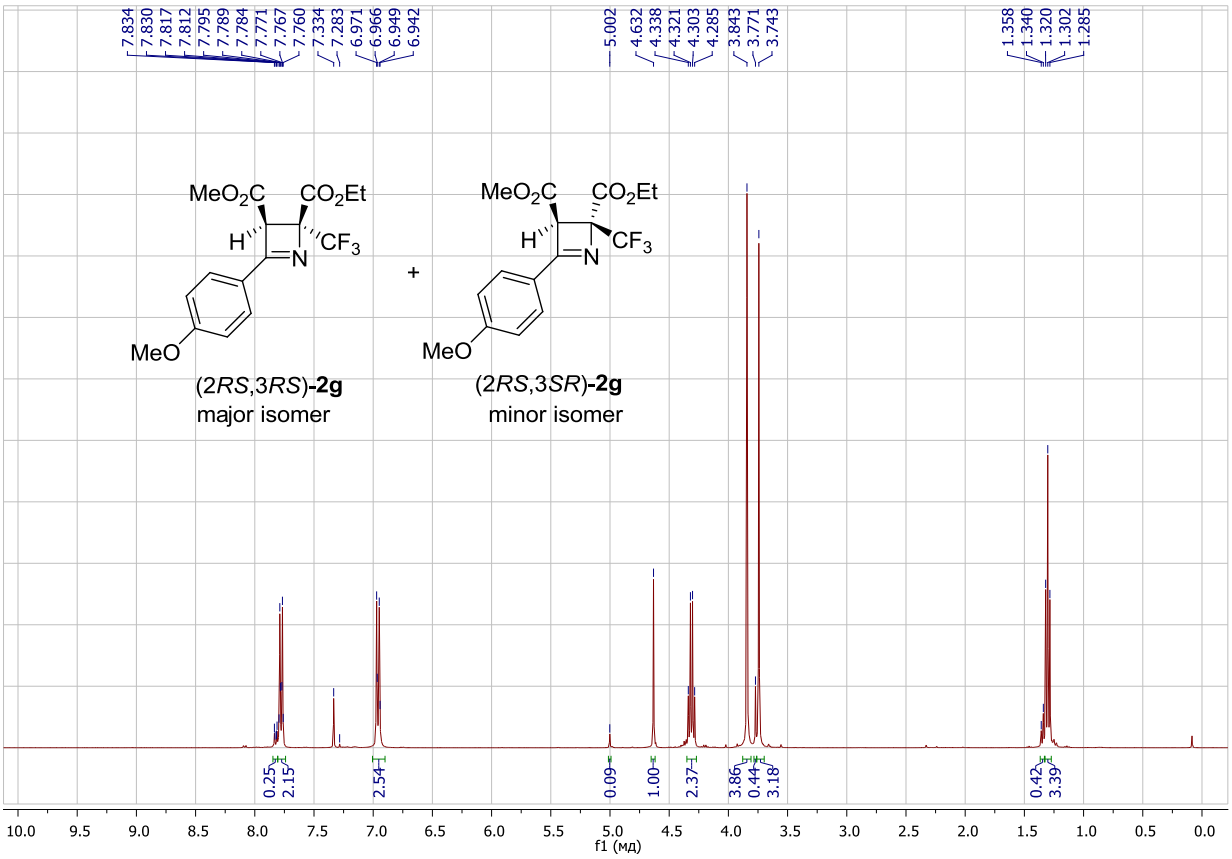


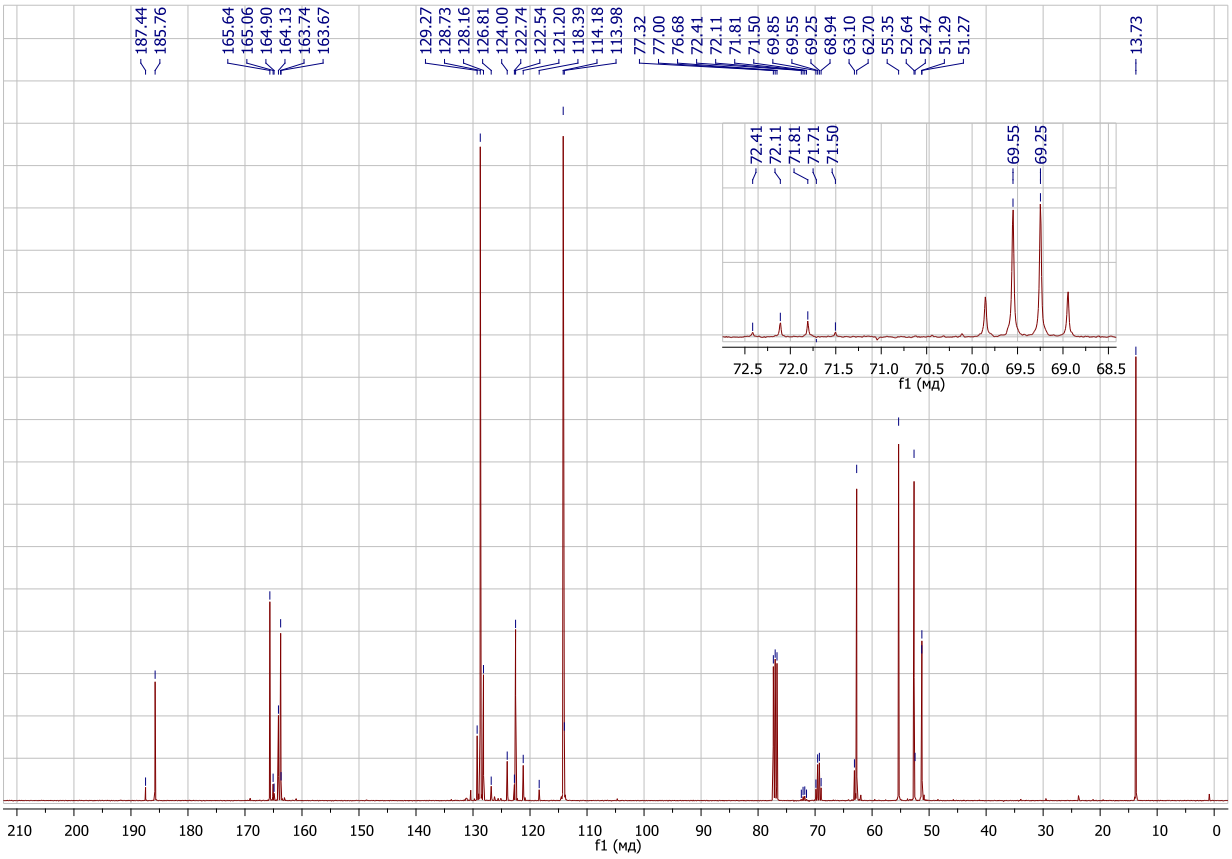
^{19}F NMR and 2D ^{1}H-^{19}F HOESY spectra of compound **2f**



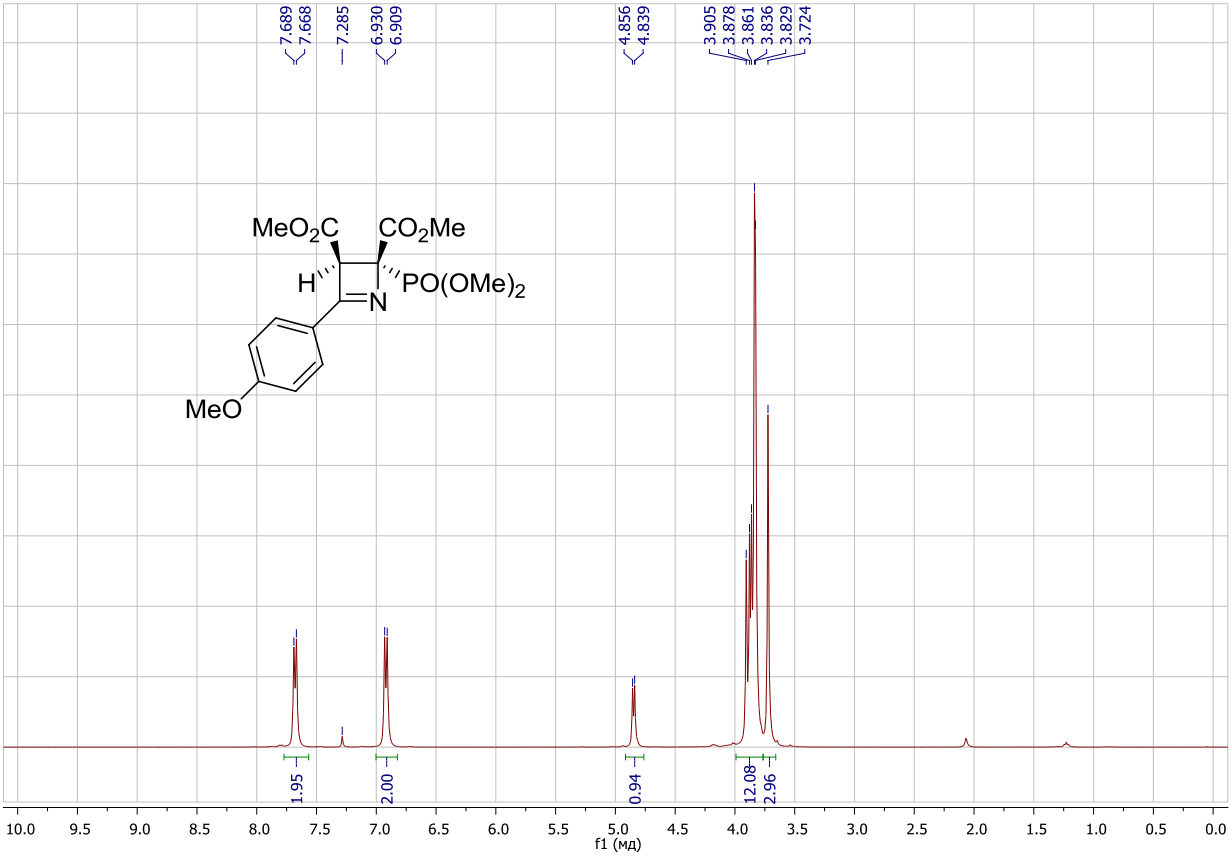


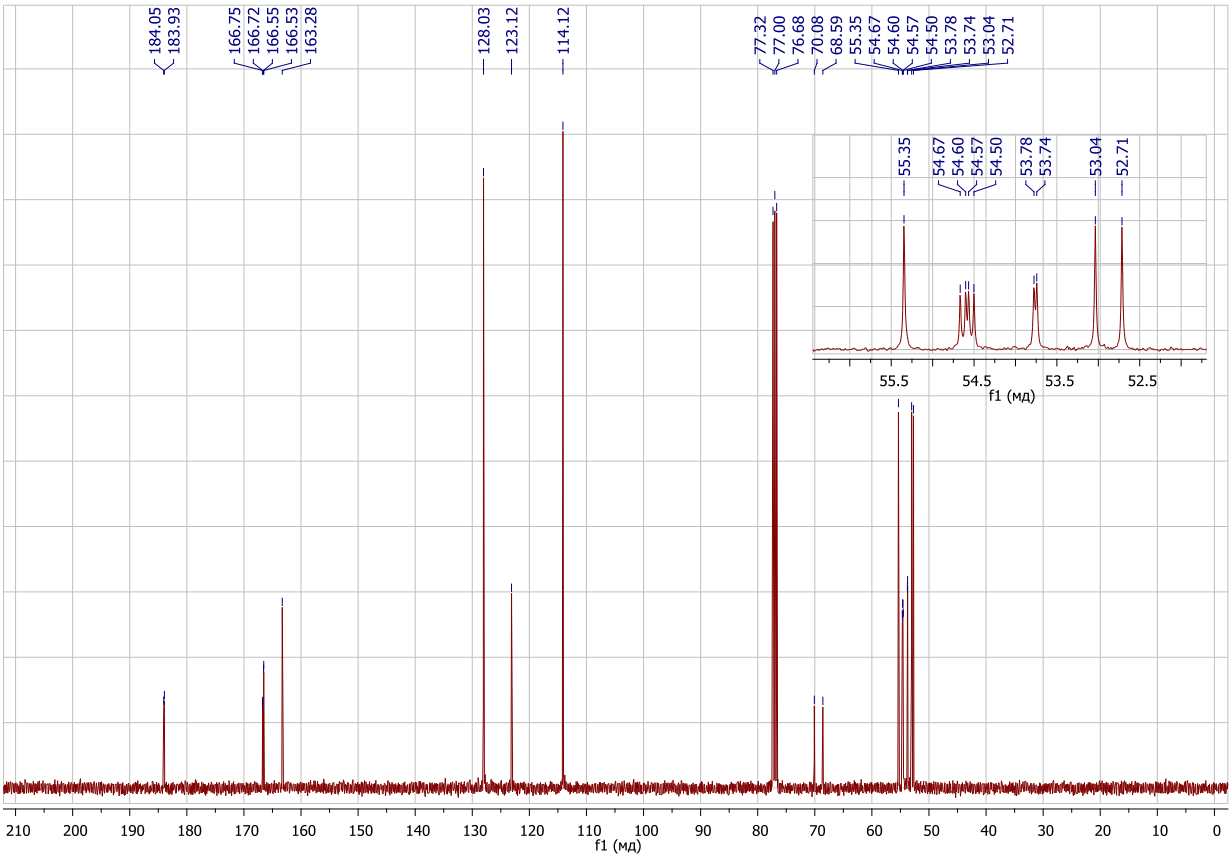
^{1}H and ^{13}C NMR spectra of compound **2g**



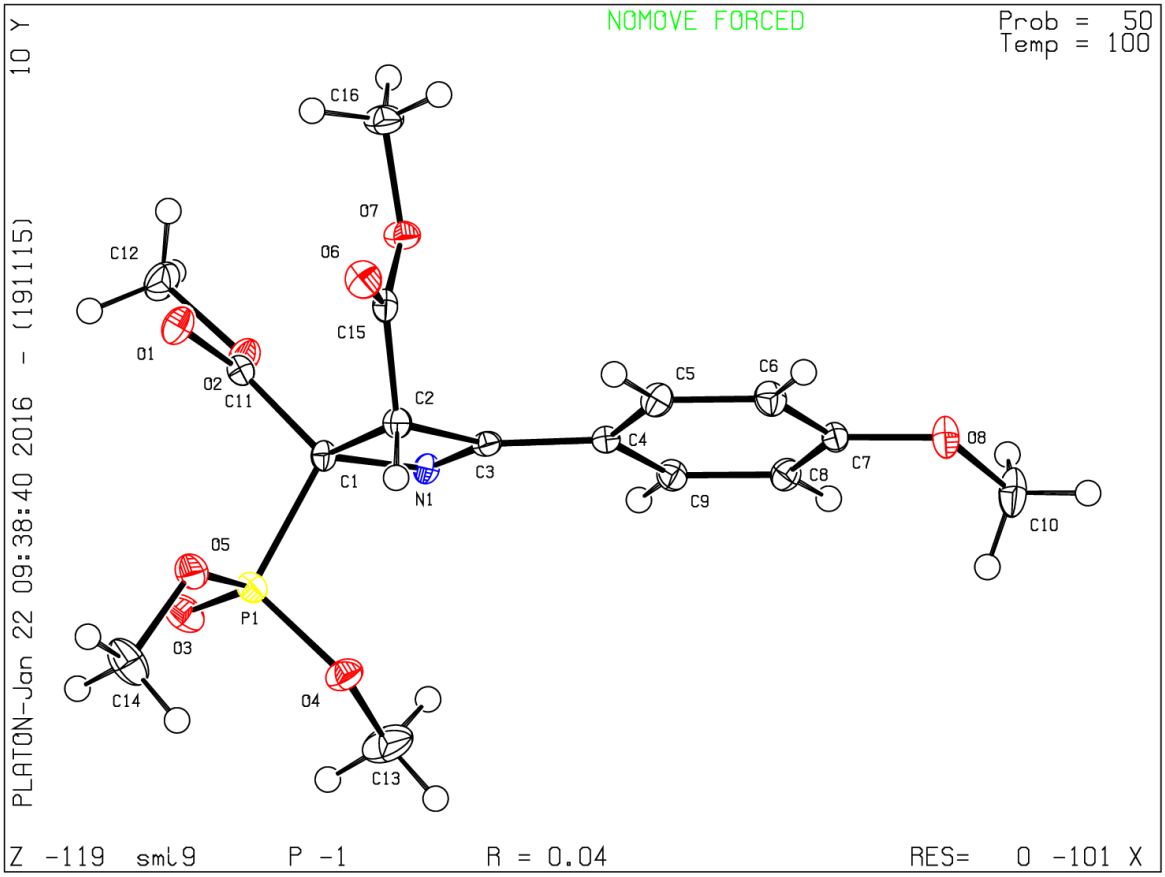


^{1}H and ^{13}C NMR spectra of compound **2h**

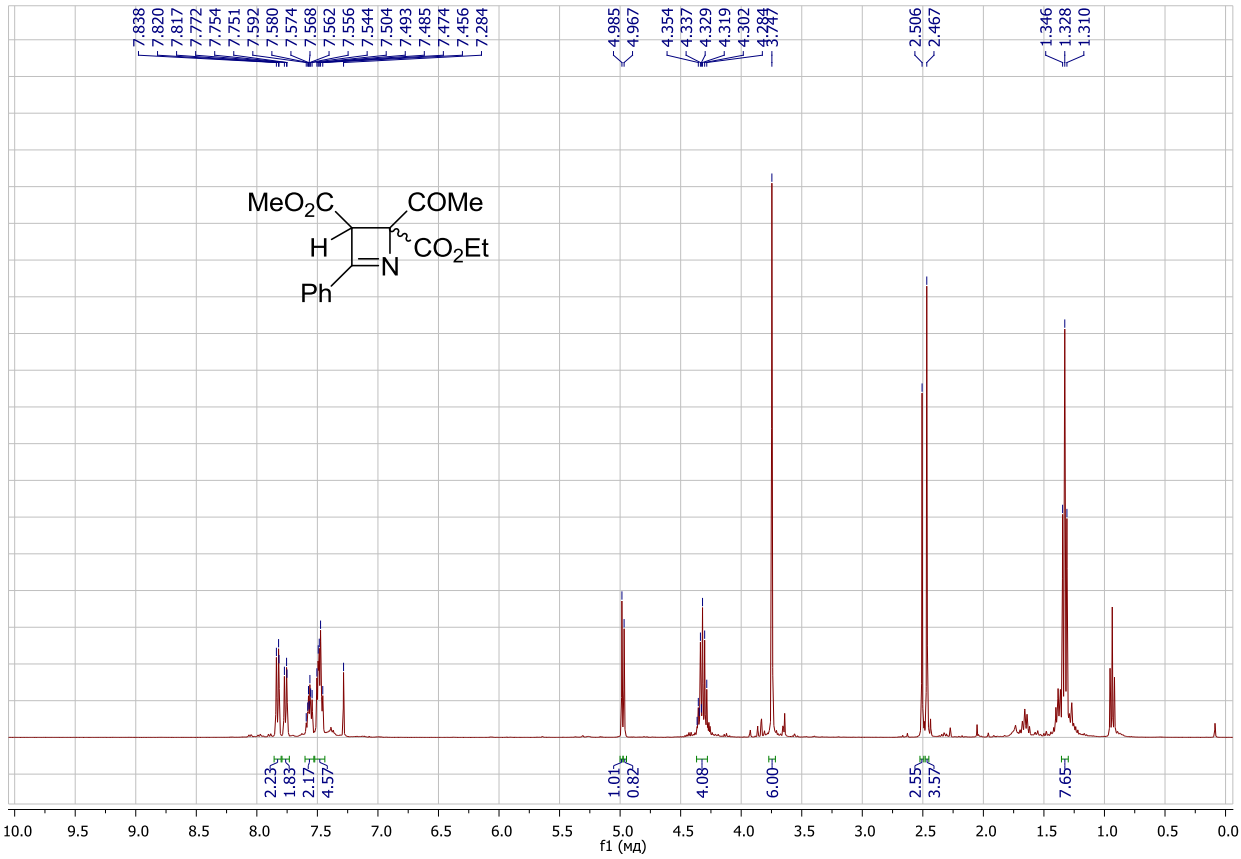


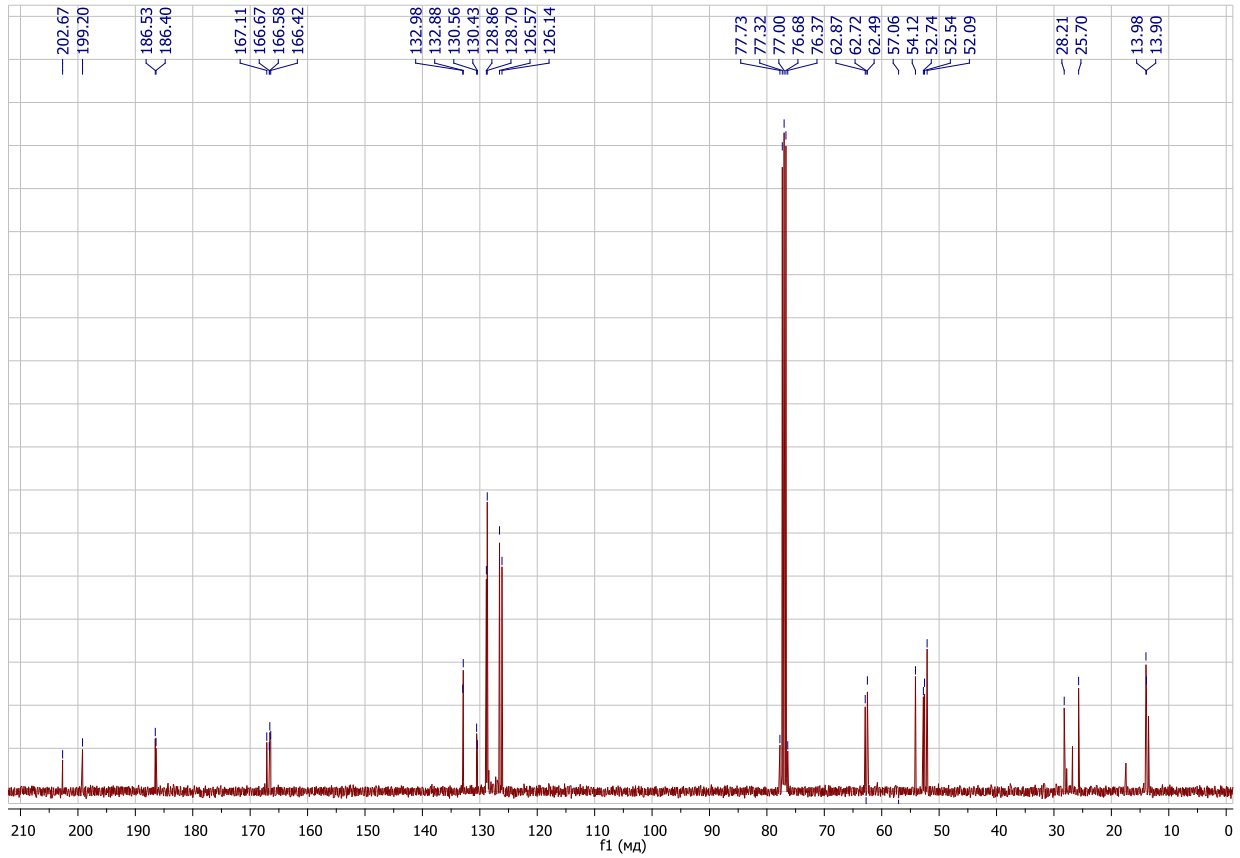


X-ray crystal structure of compound **2h**

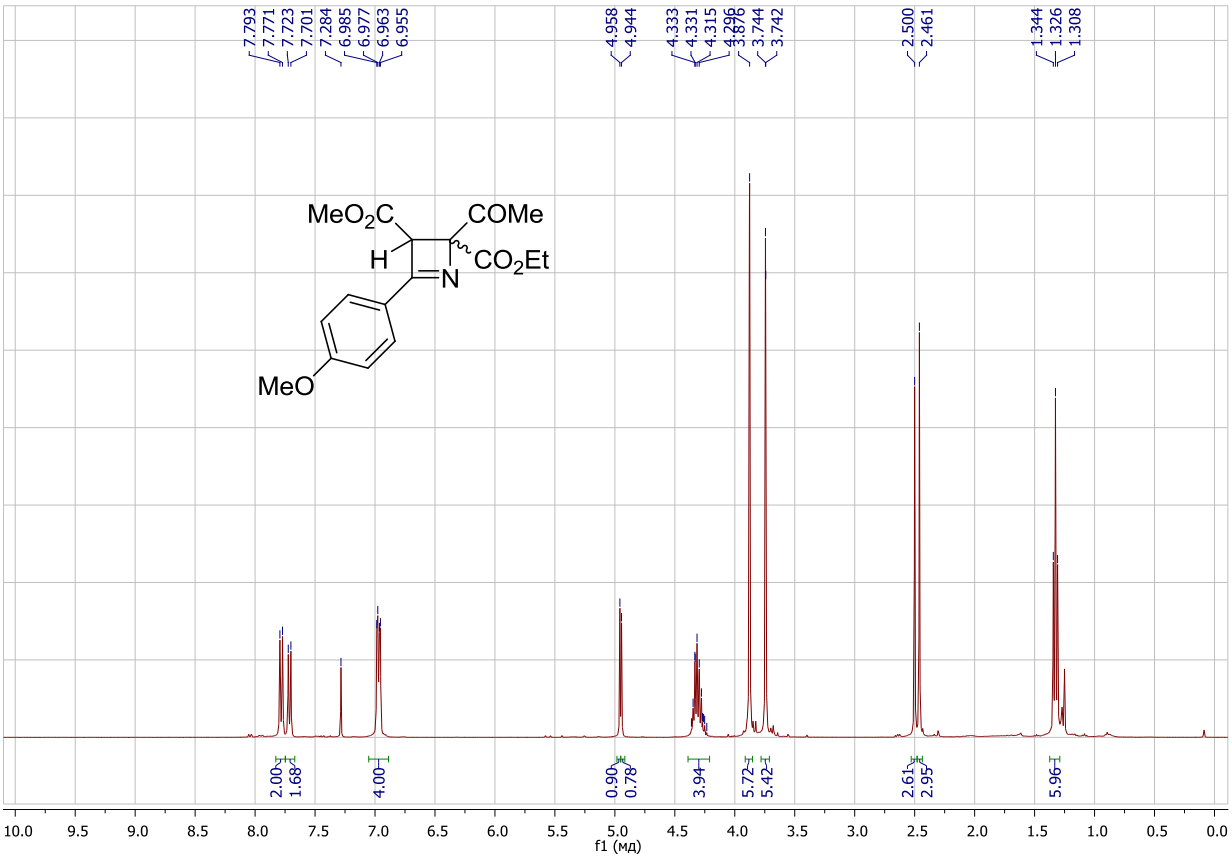


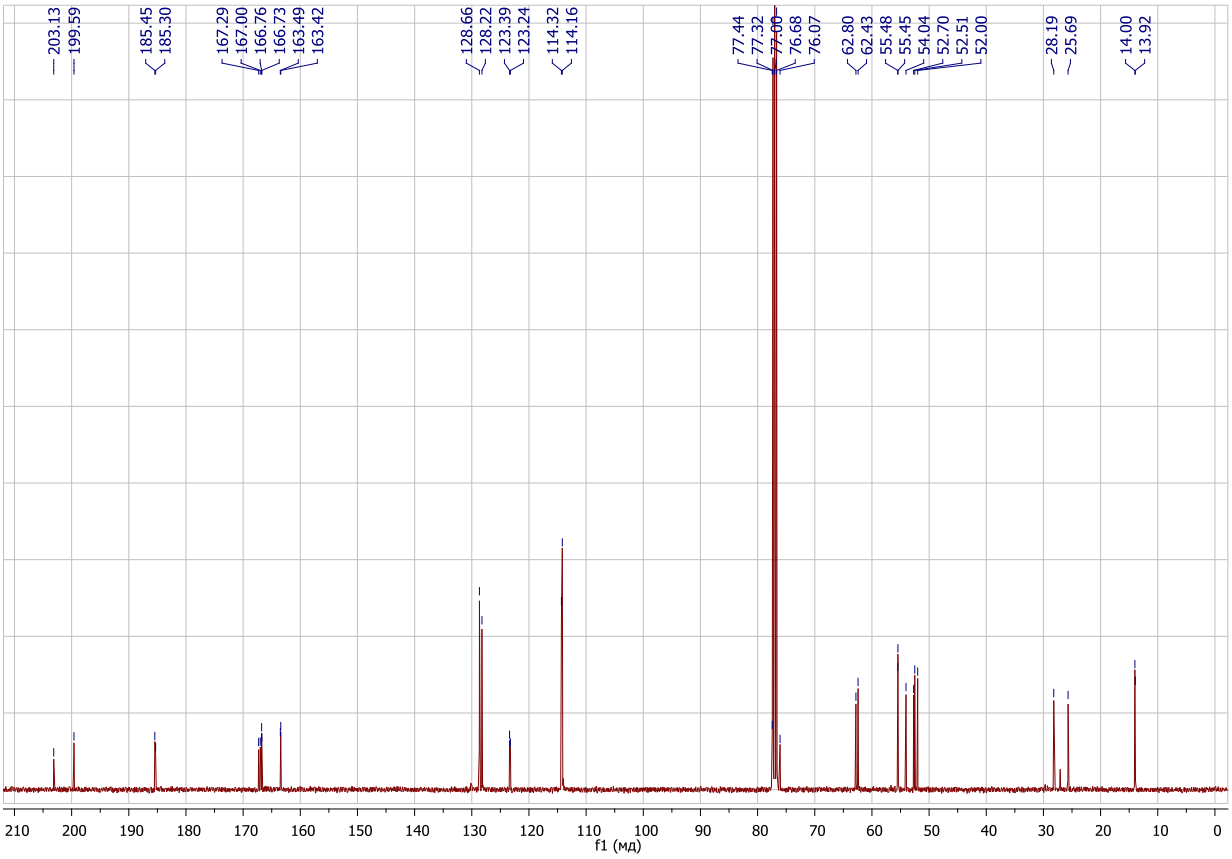
^{1}H and ^{13}C NMR spectra of compound **2i**



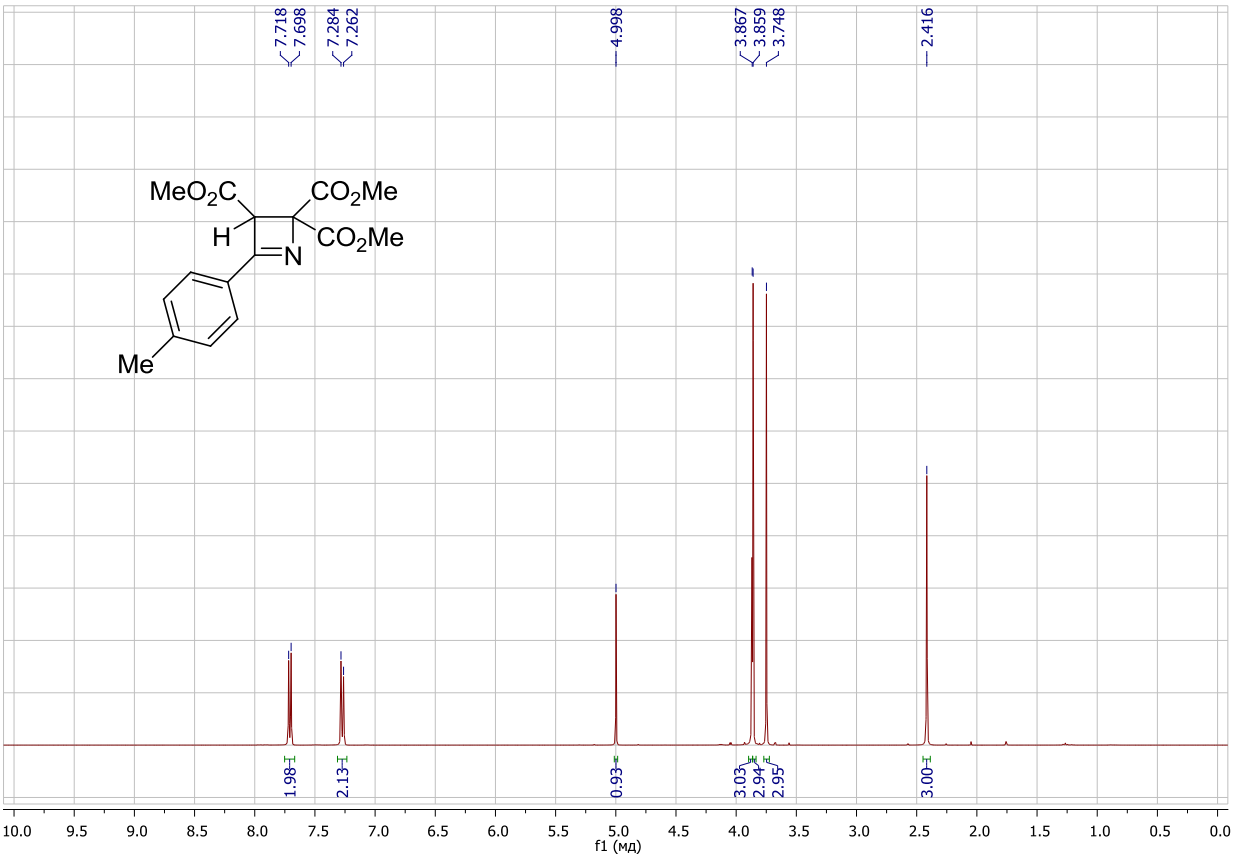


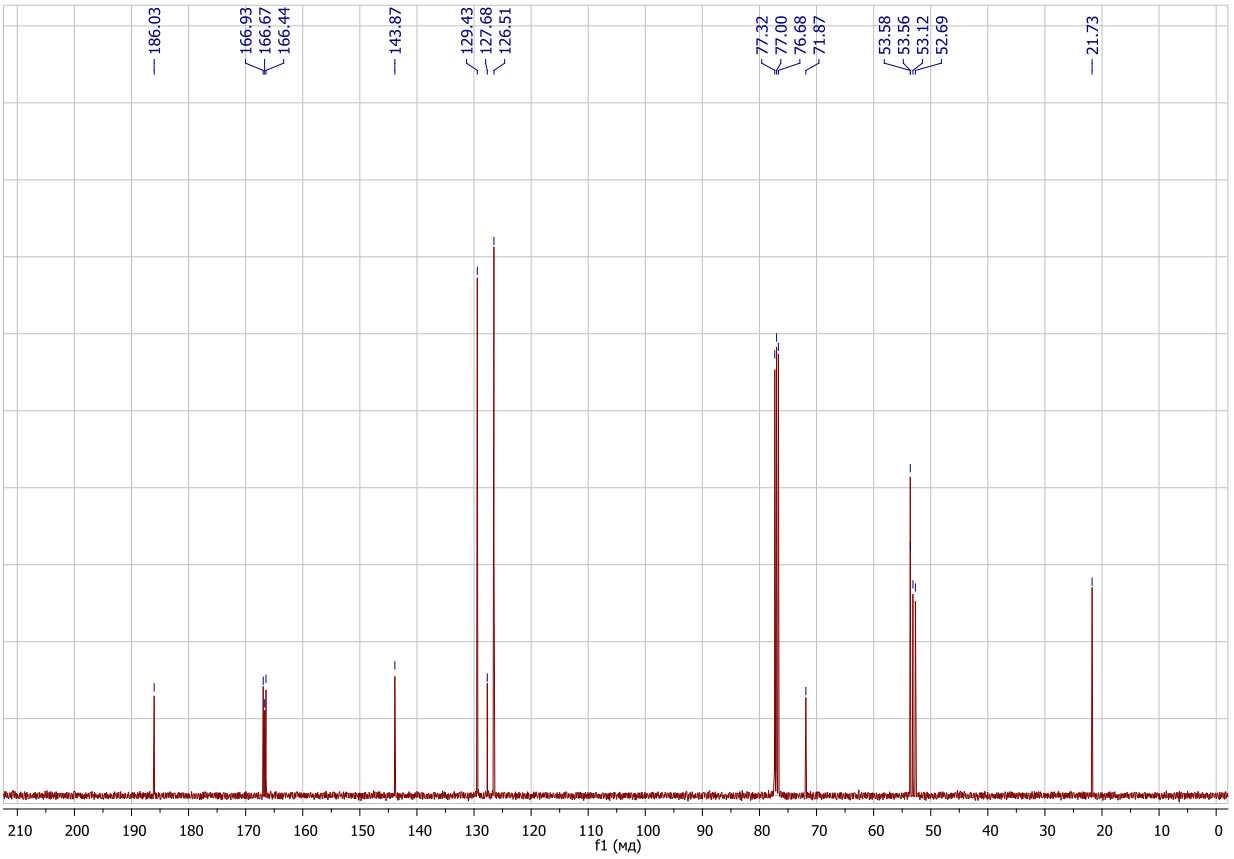
^{1}H and ^{13}C NMR spectra of compound **2j**



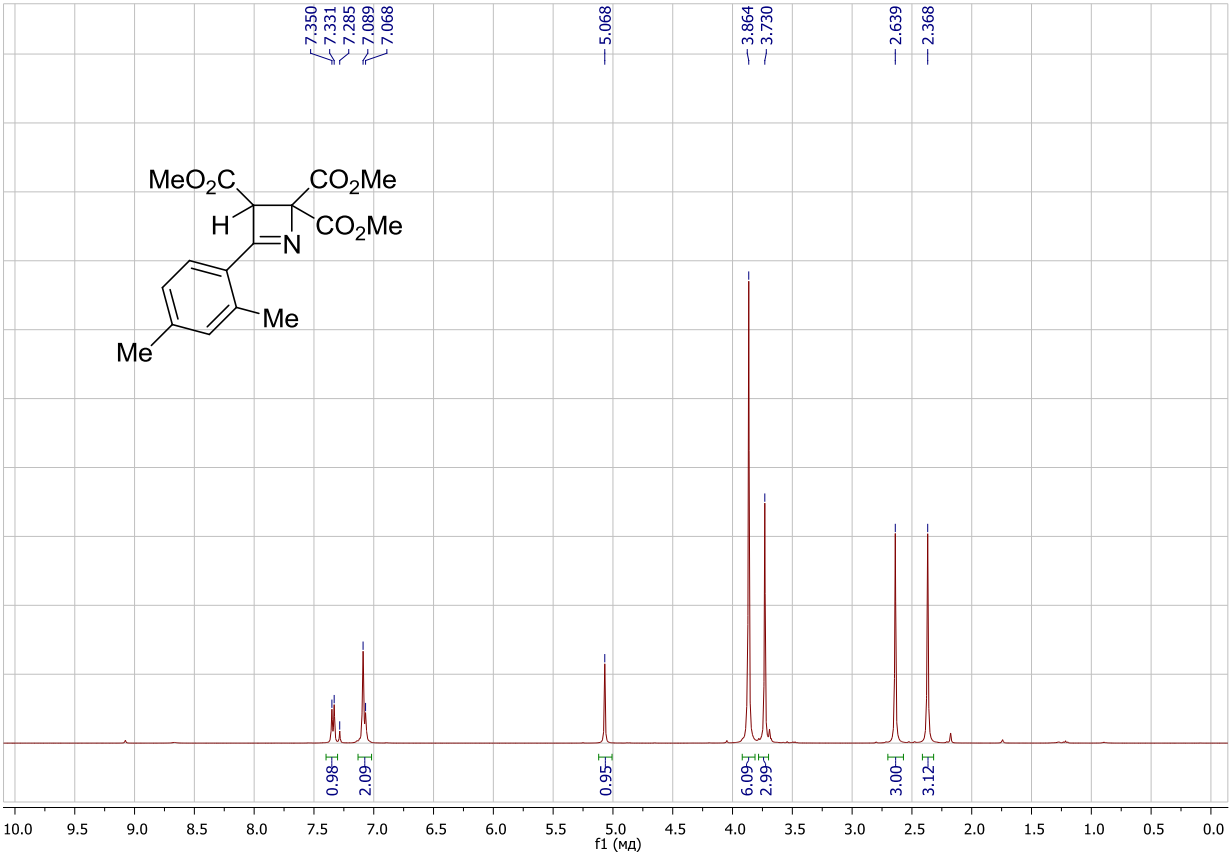


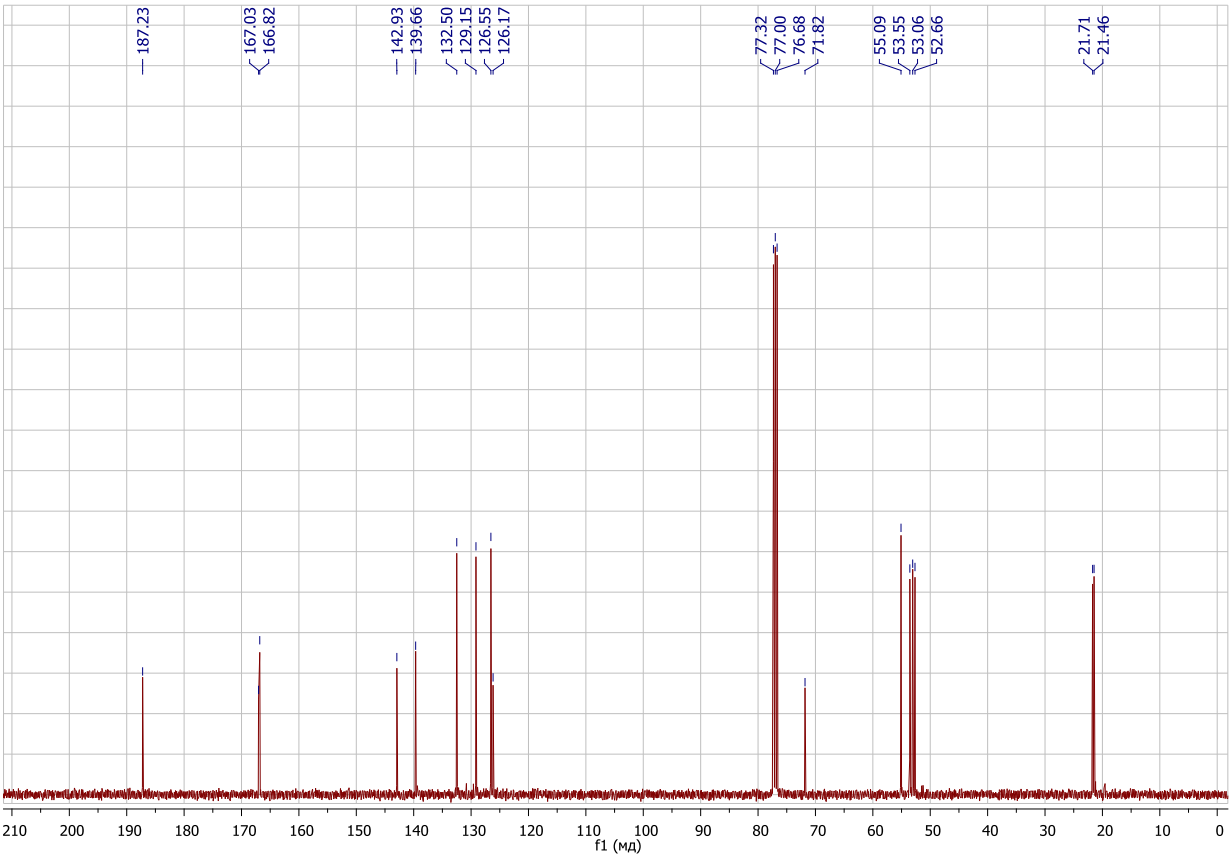
^{1}H and ^{13}C NMR spectra of compound **2k**



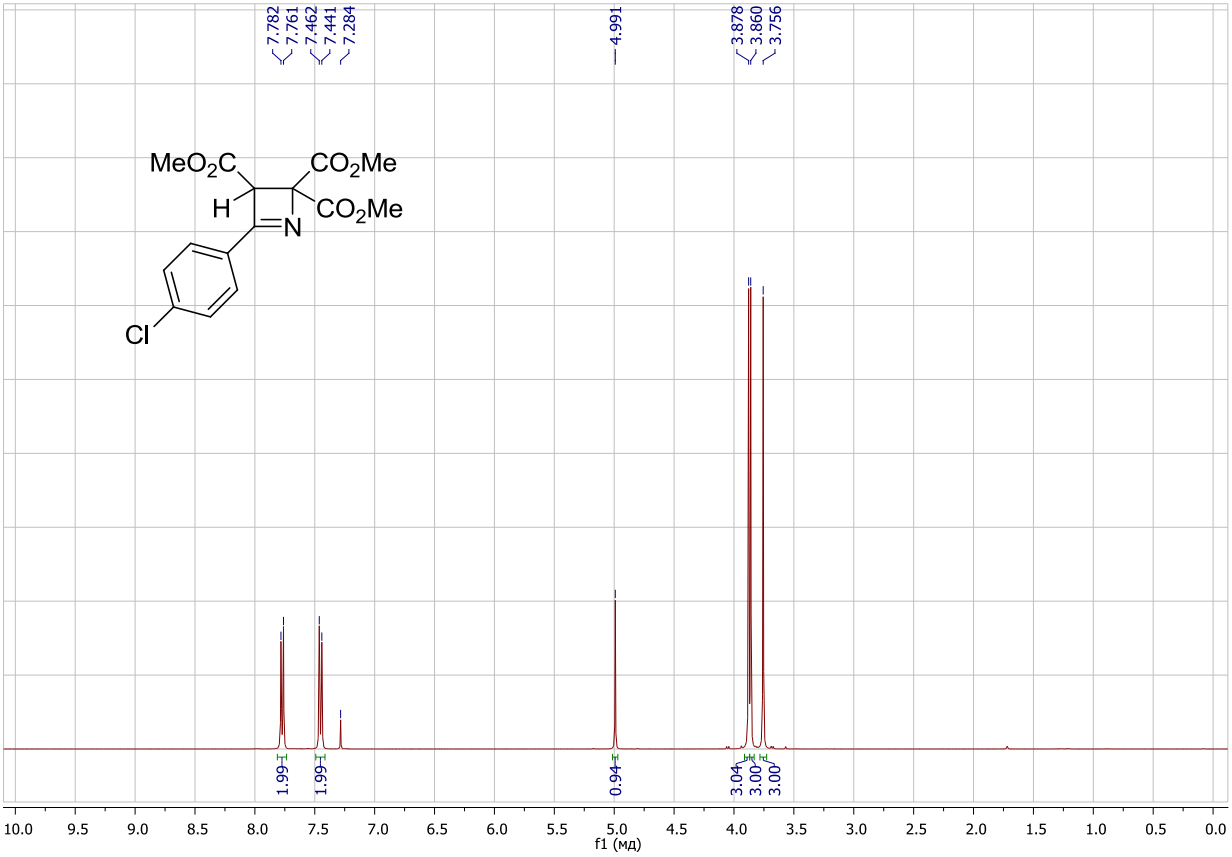


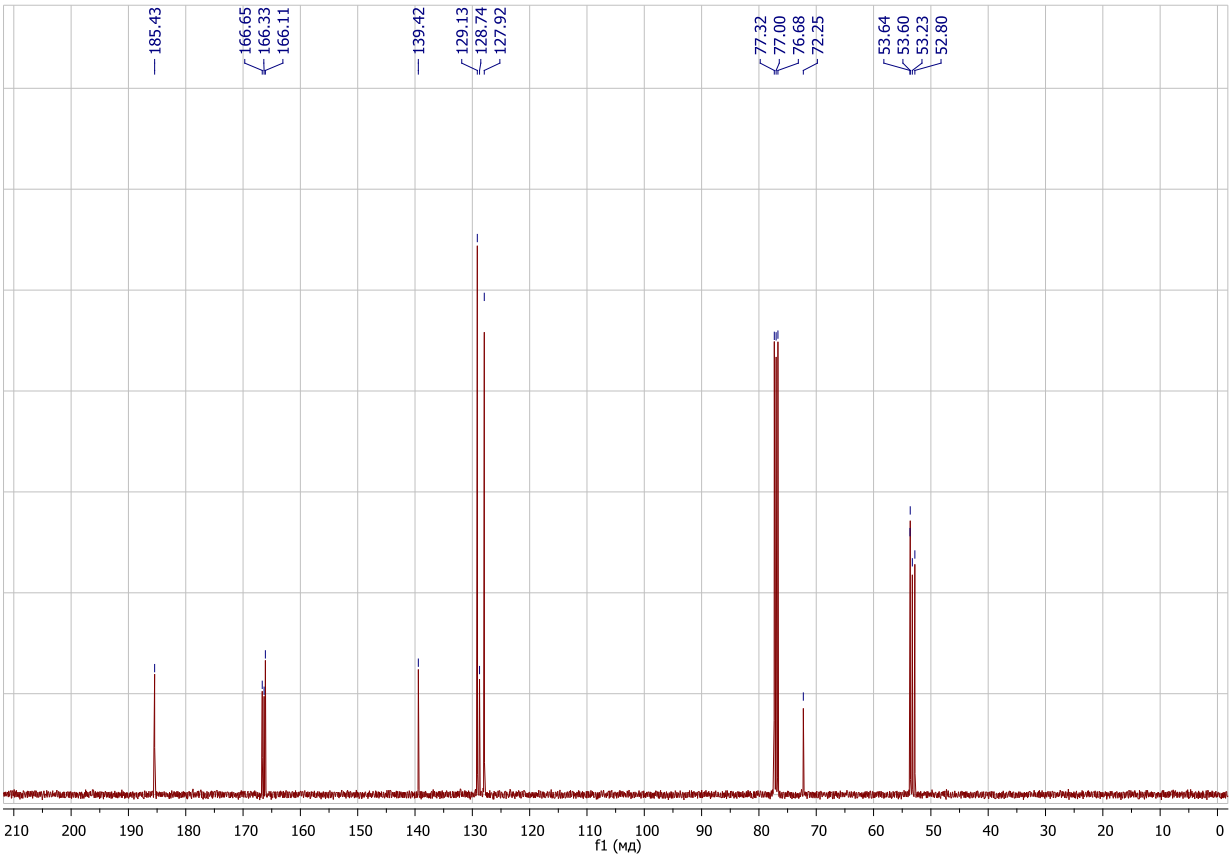
^{1}H and ^{13}C NMR spectra of compound **2l**



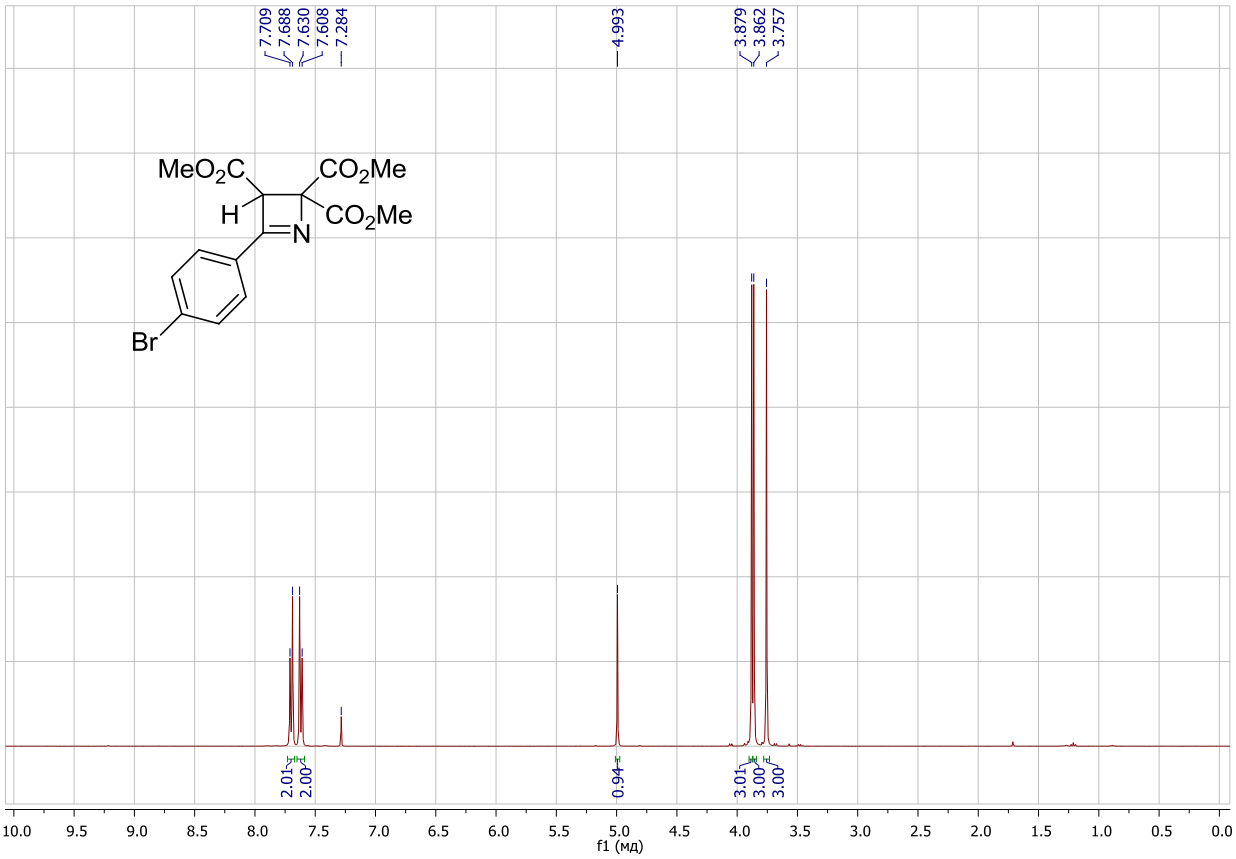


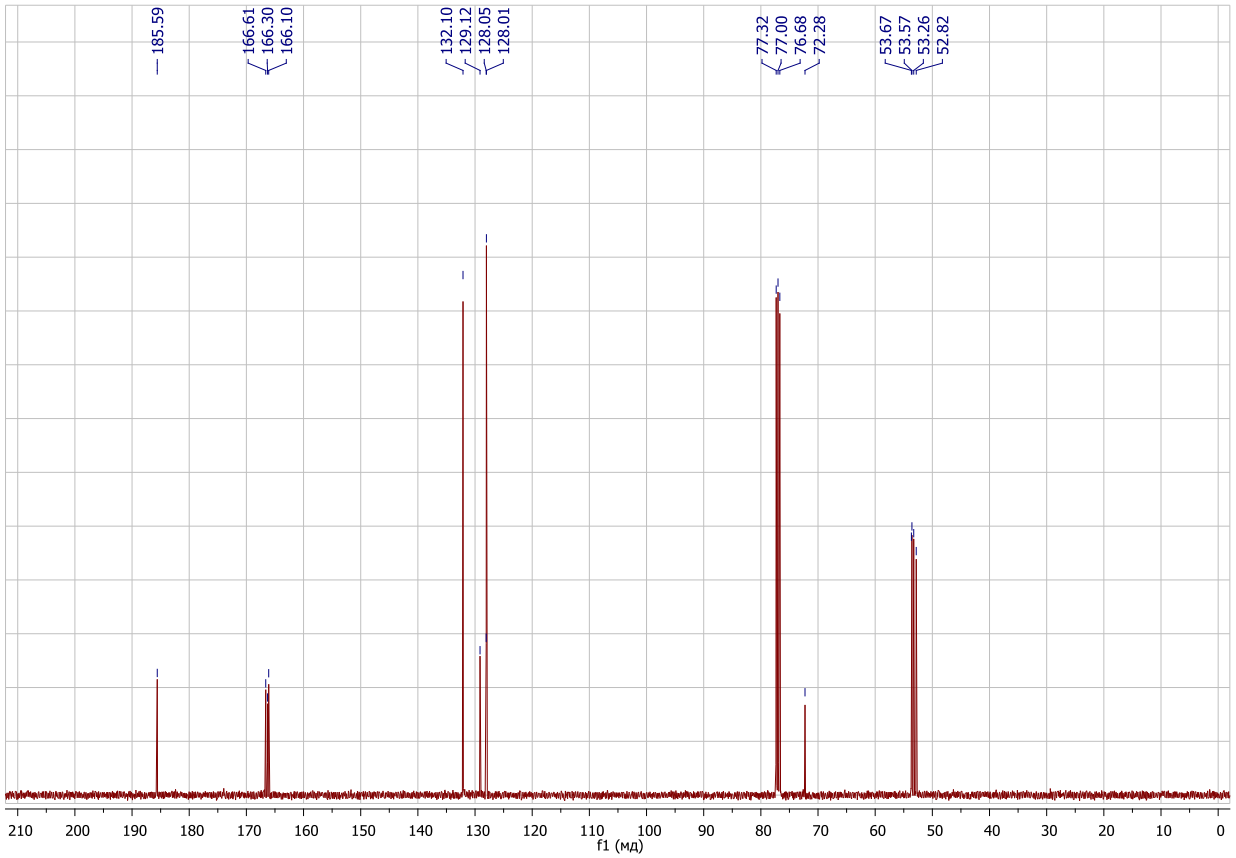
^{1}H and ^{13}C NMR spectra of compound **2m**



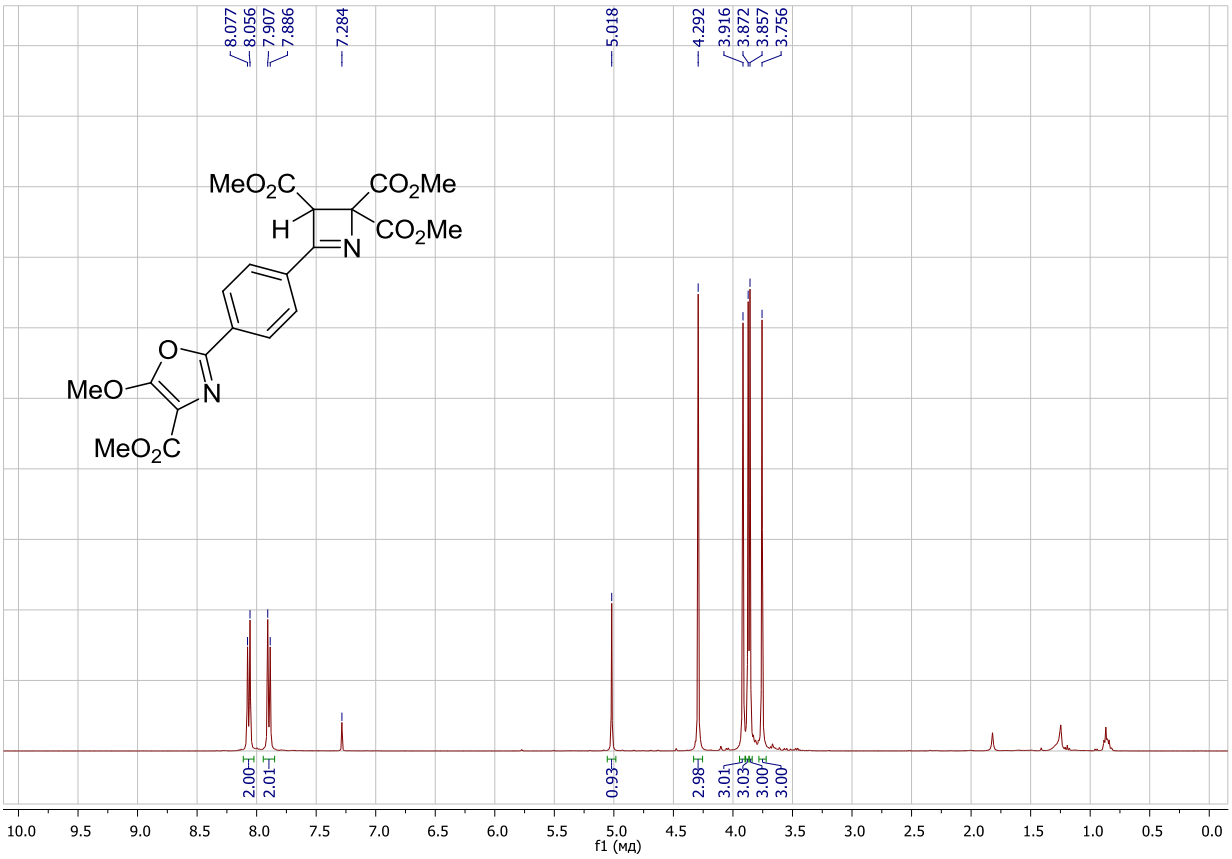


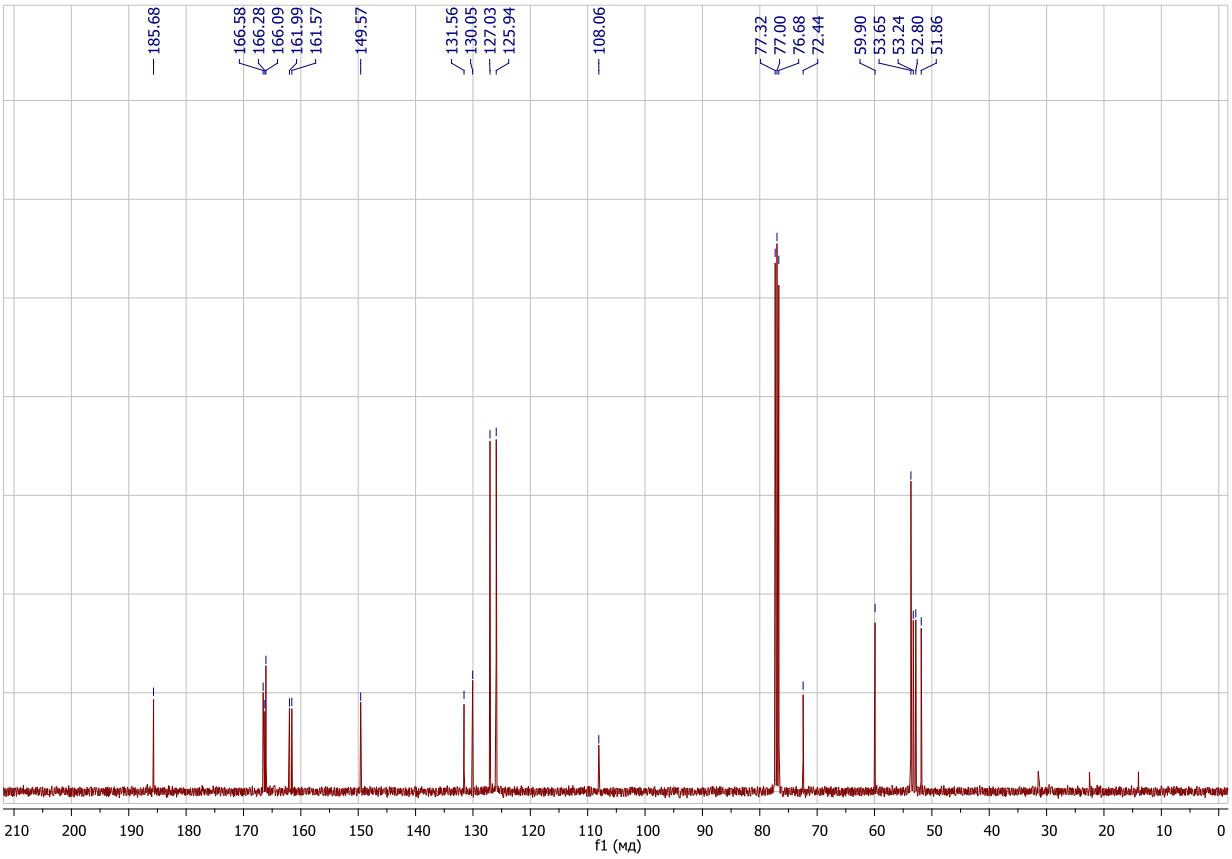
^{1}H and ^{13}C NMR spectra of compound **2n**



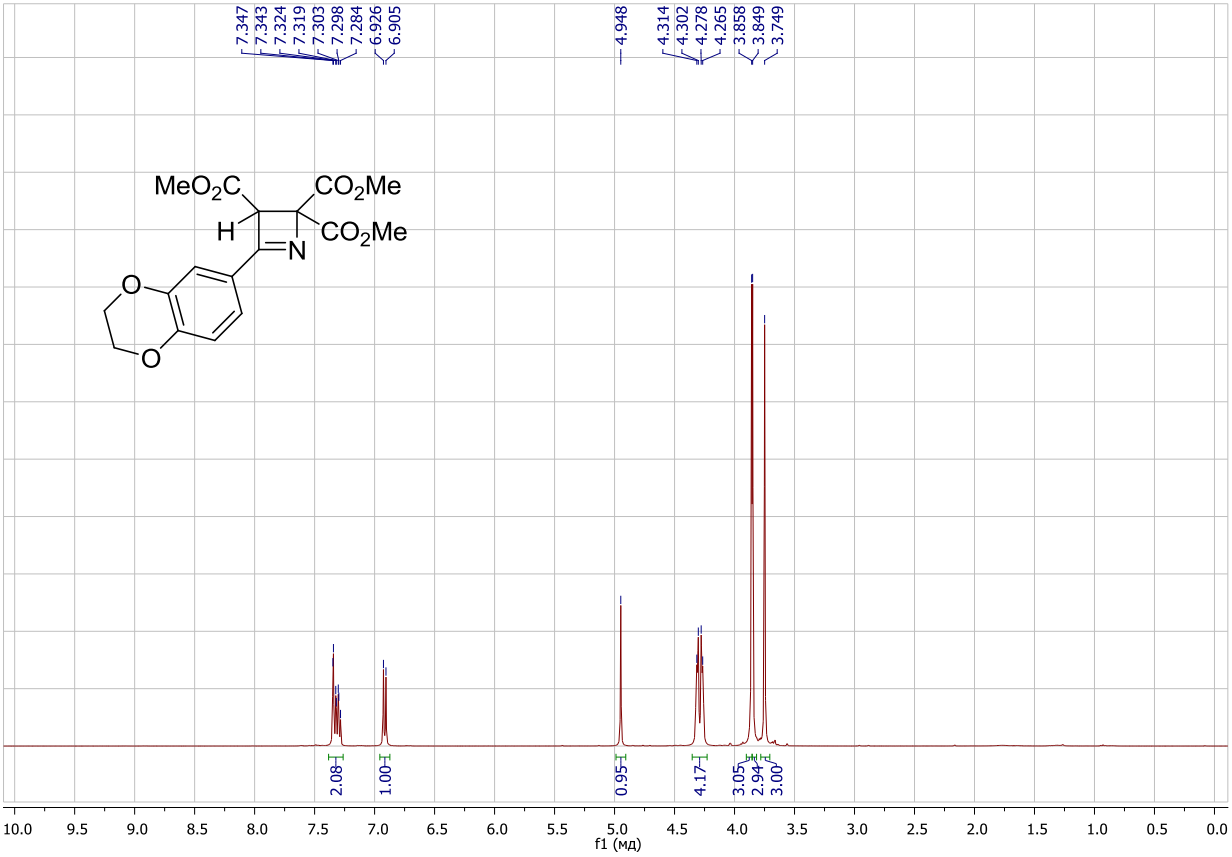


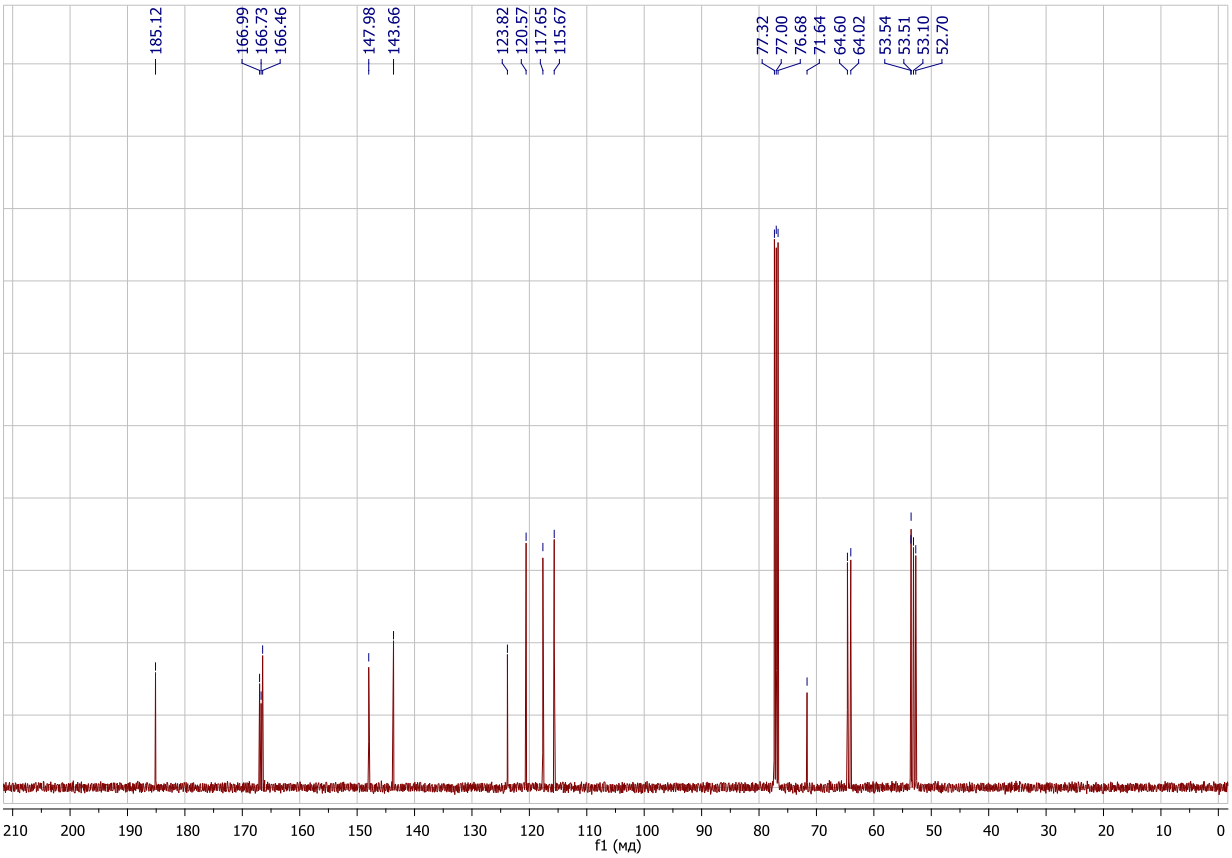
^{1}H and ^{13}C NMR spectra of compound **2o**



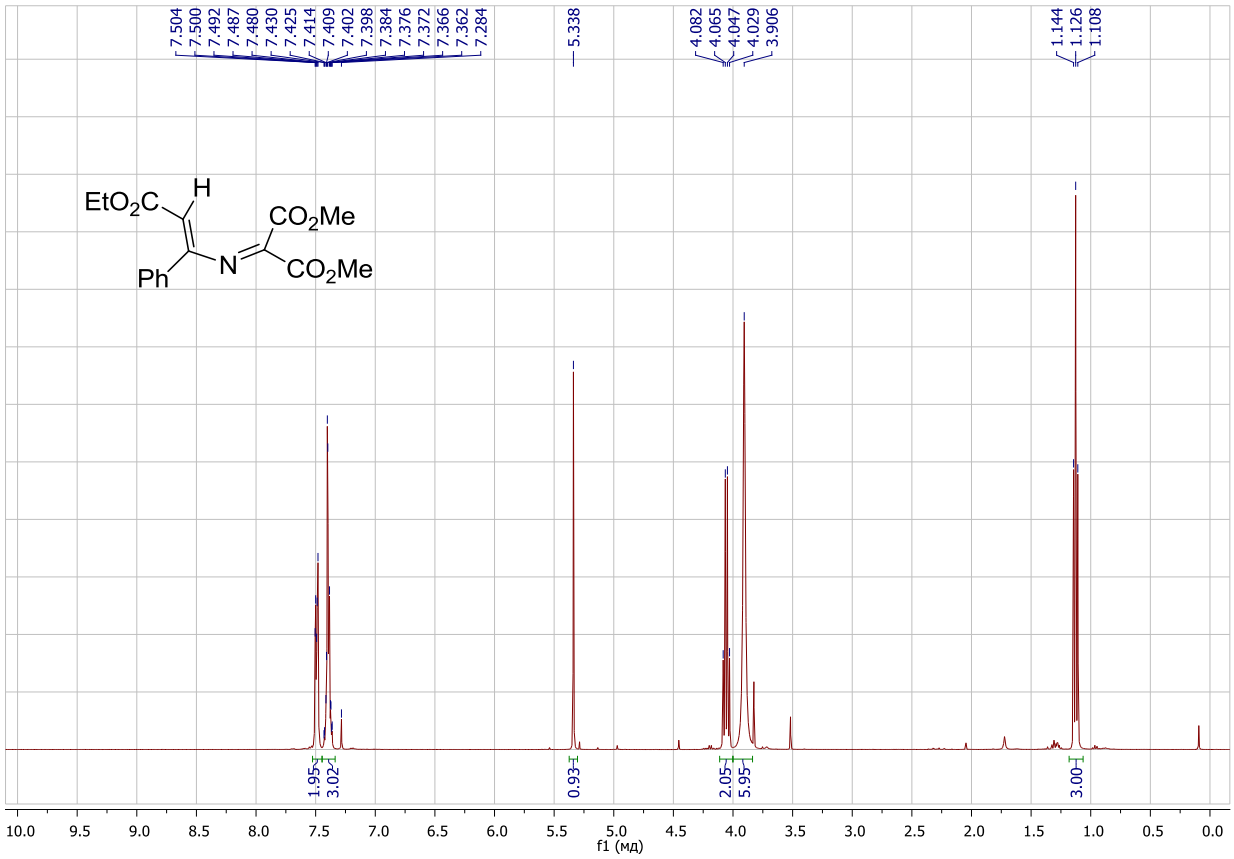


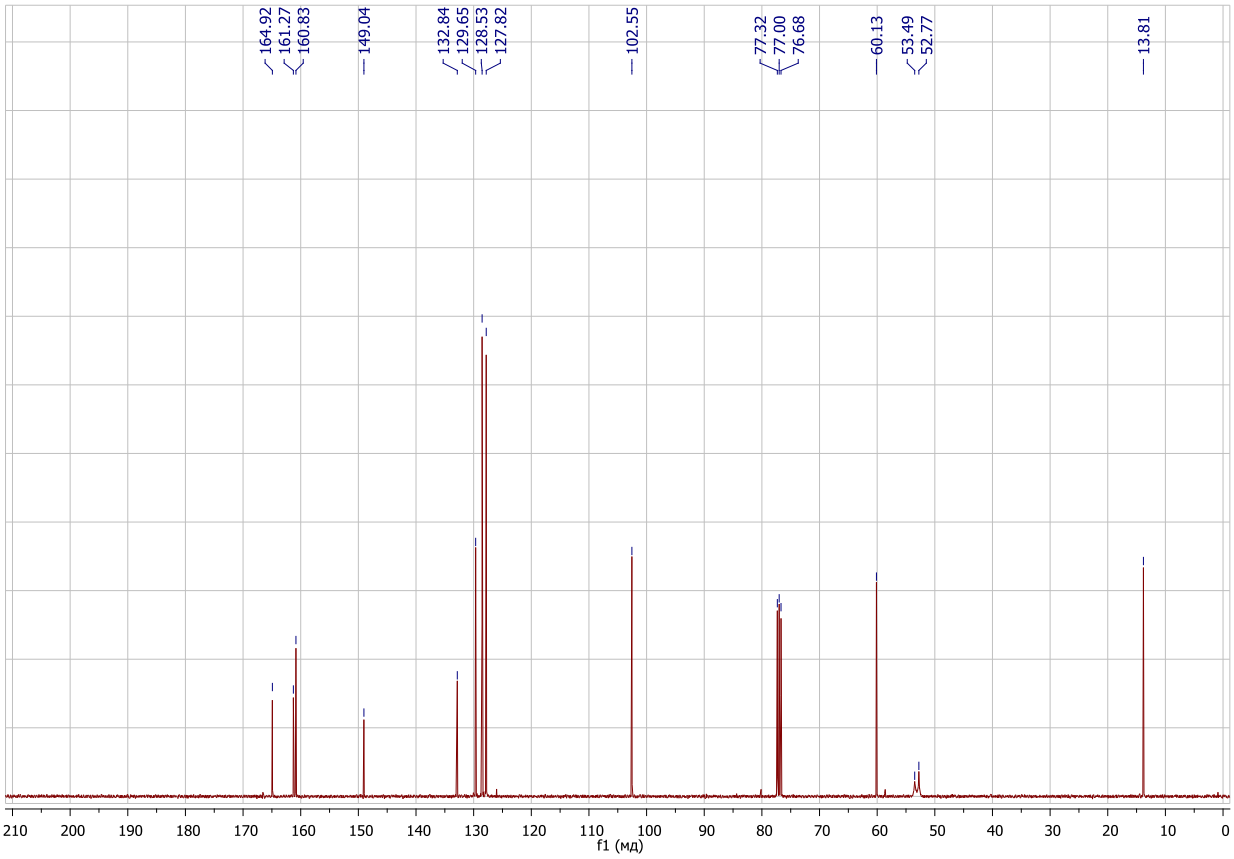
^{1}H and ^{13}C NMR spectra of compound **2p**



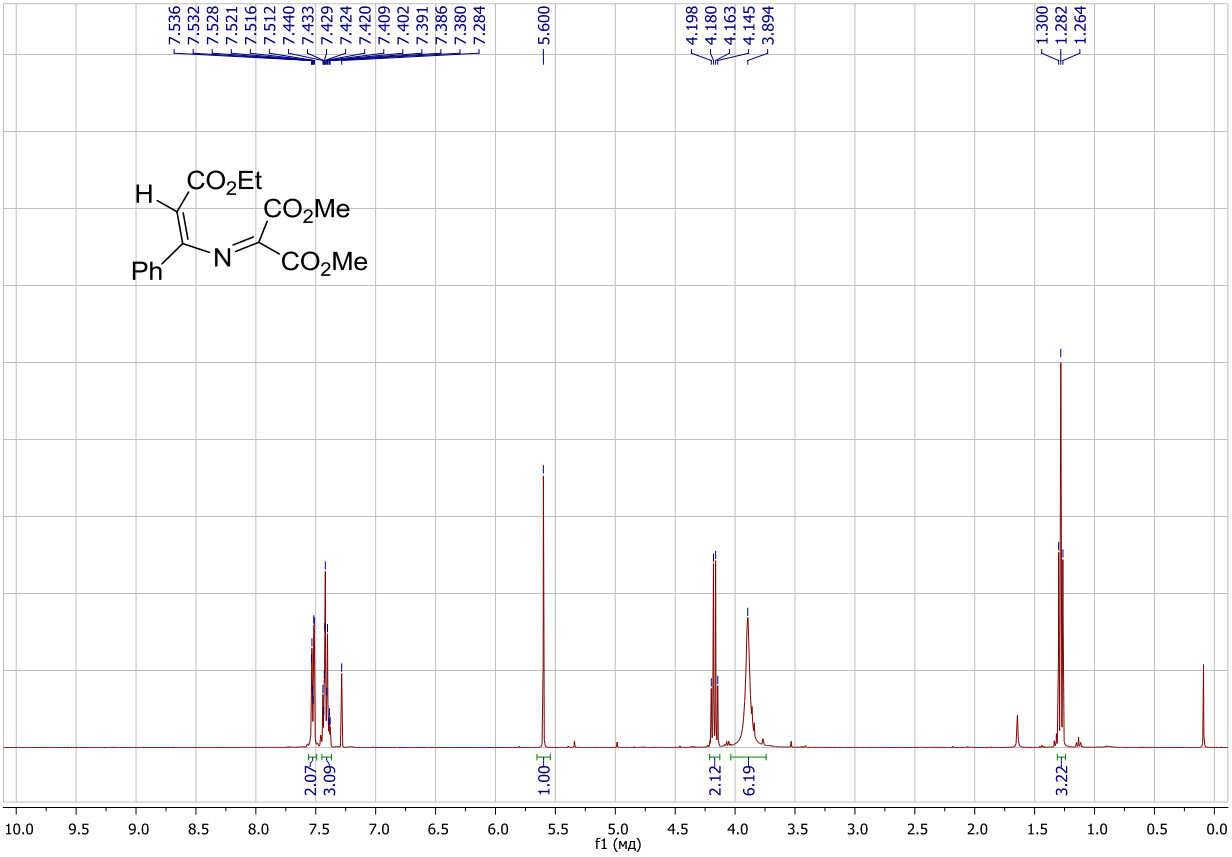


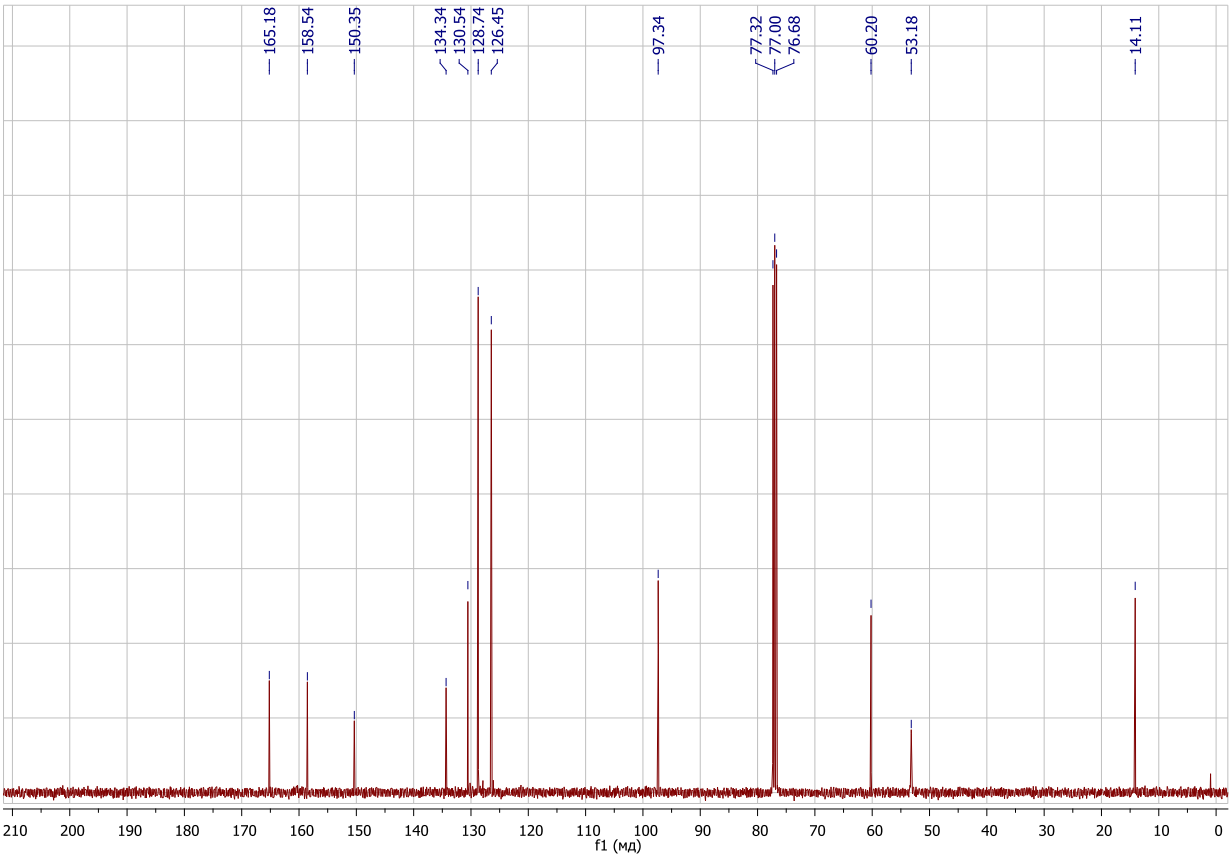
^{1}H and ^{13}C NMR spectra of compound *E*-**6**



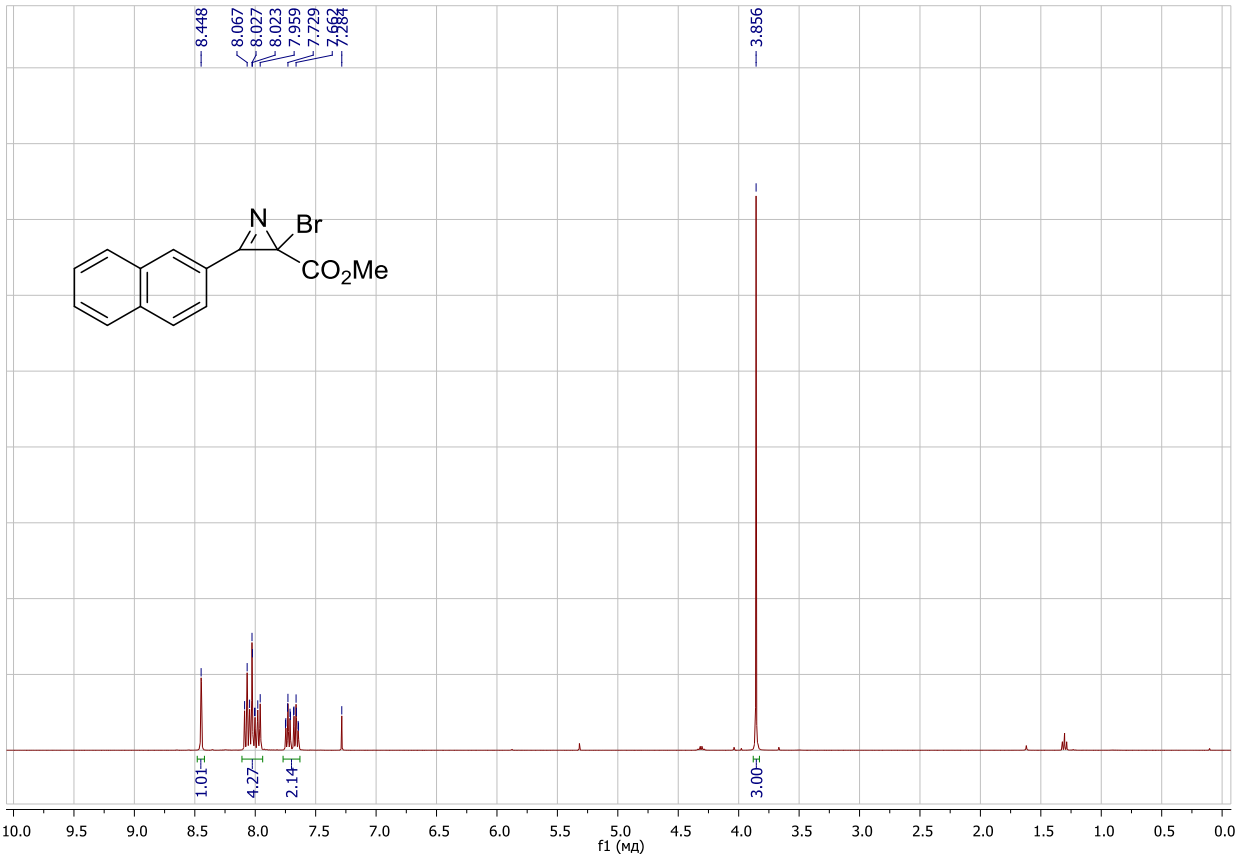


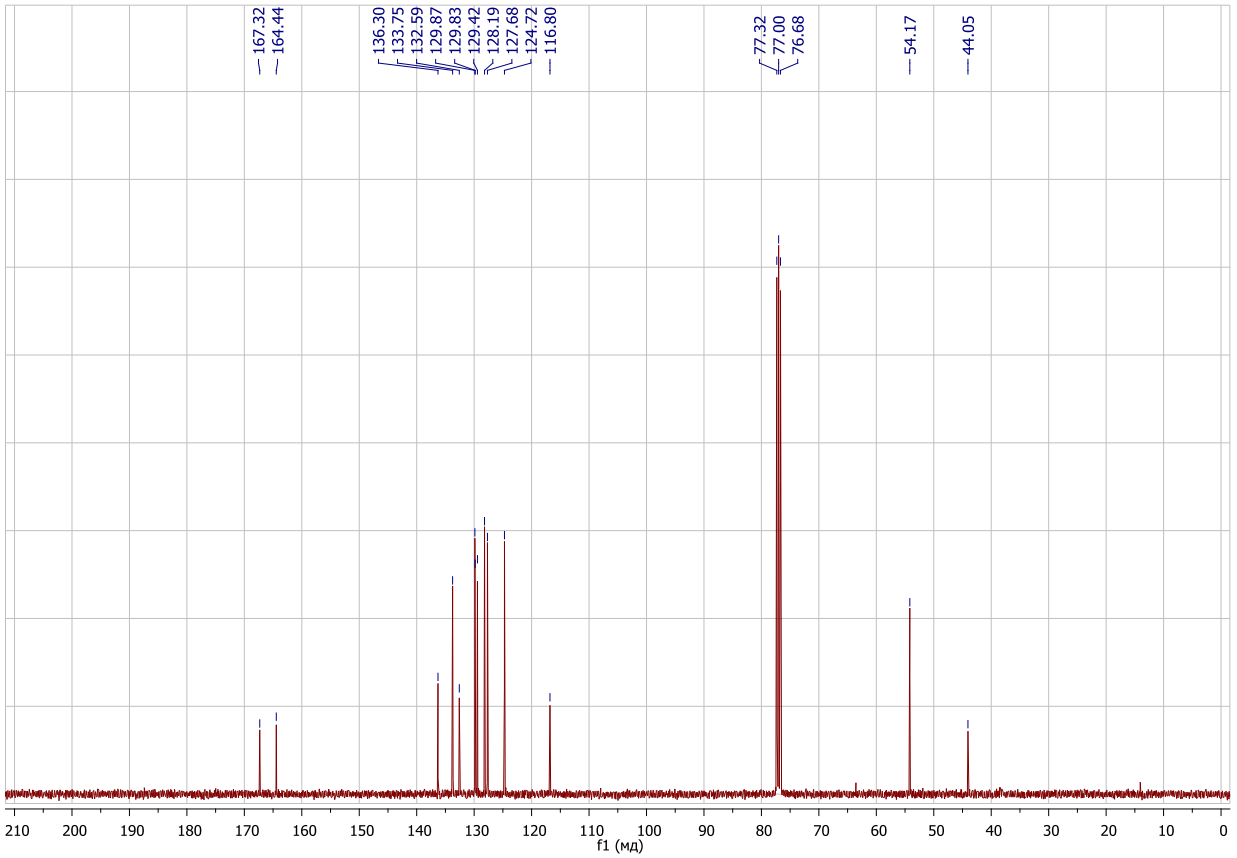
^{1}H and ^{13}C NMR spectra of compound *Z*-**6**



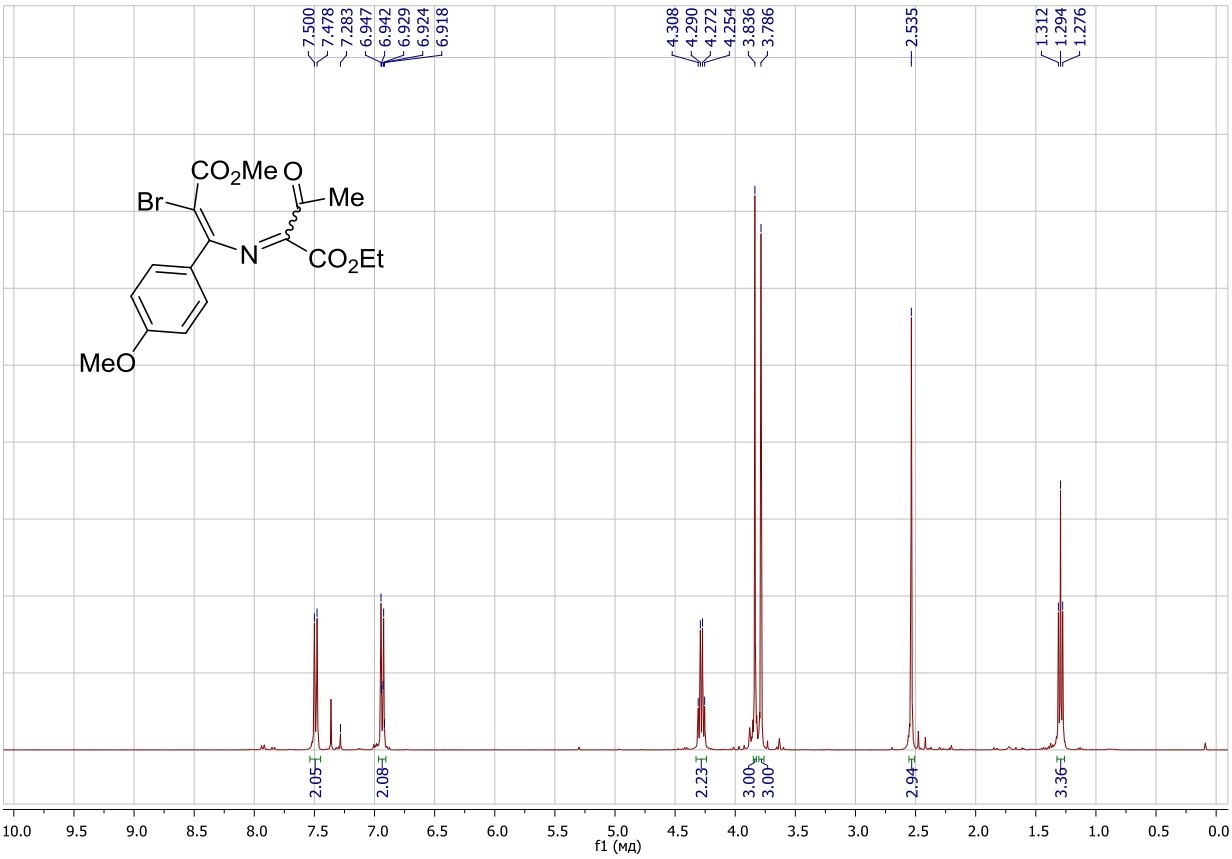


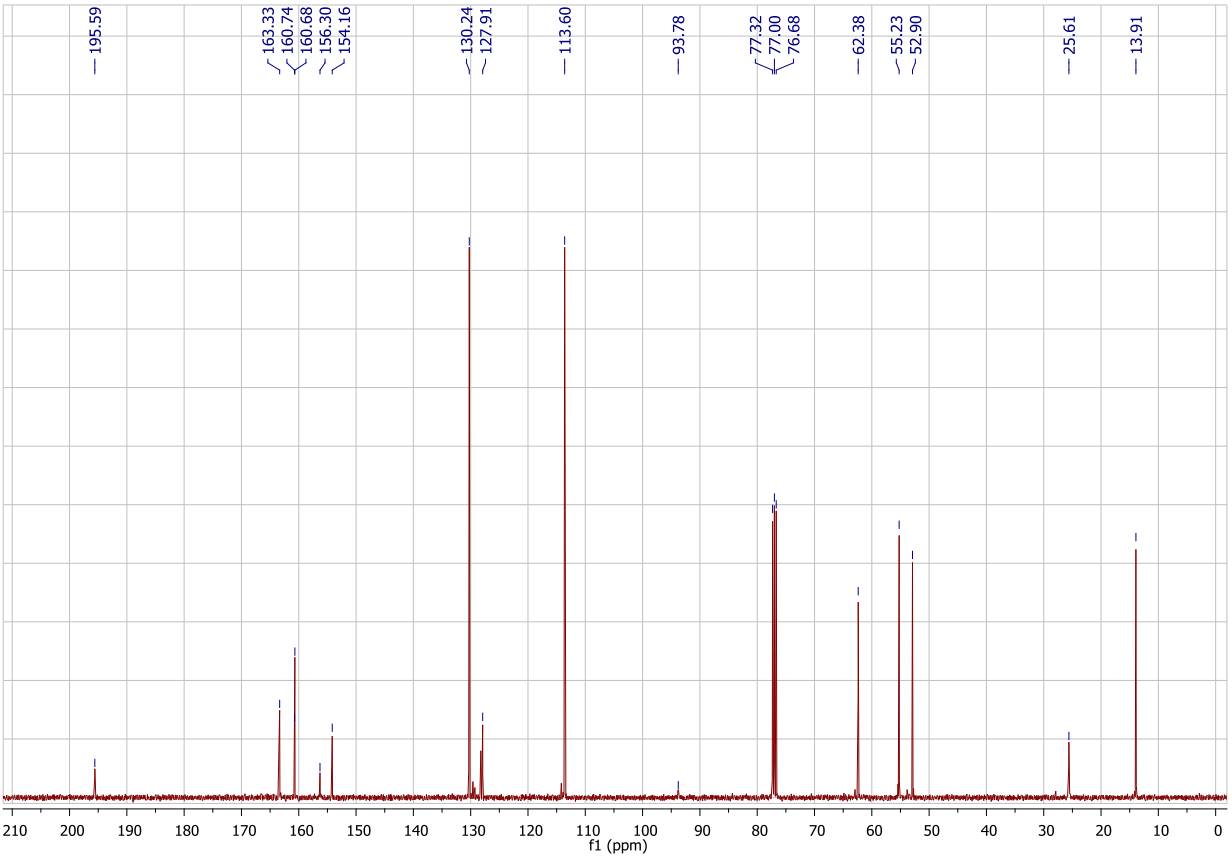
^{1}H and ^{13}C NMR spectra of azirine **7e**



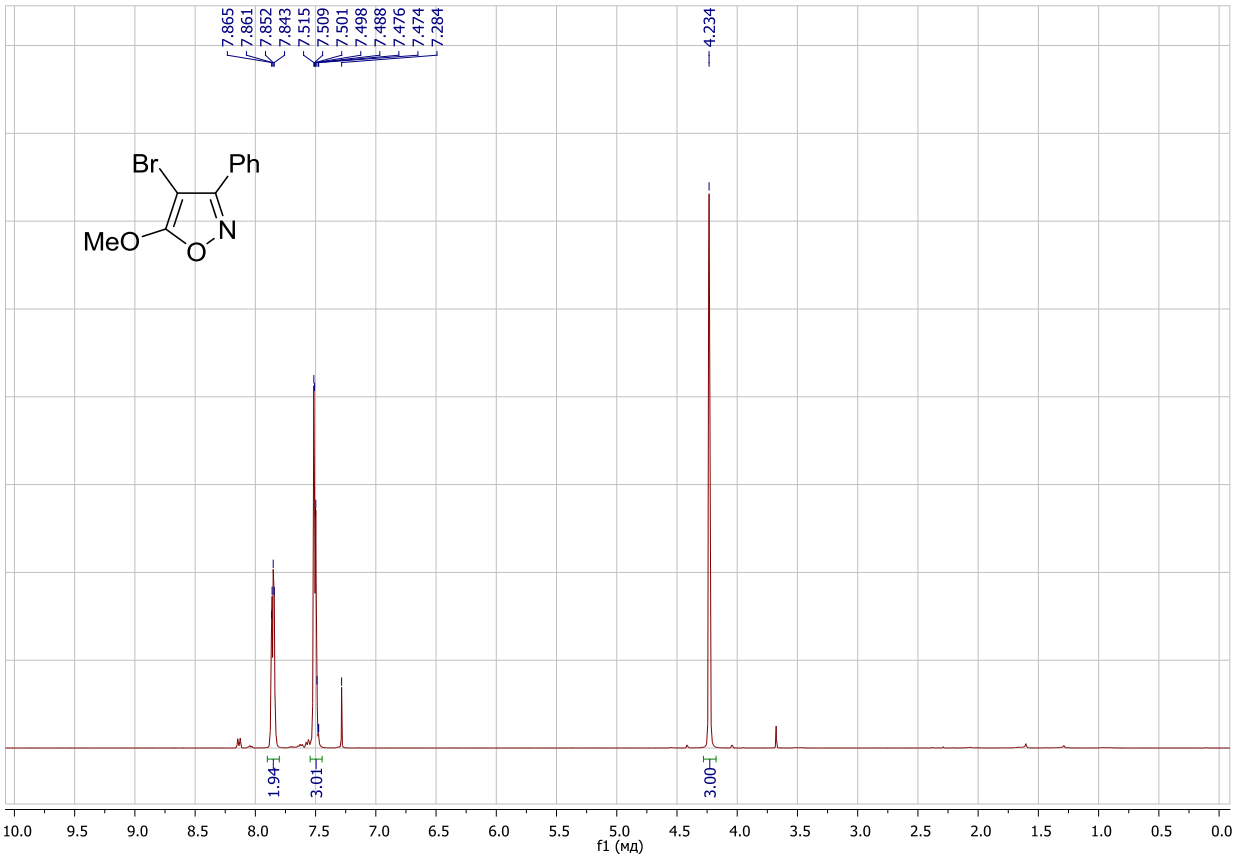


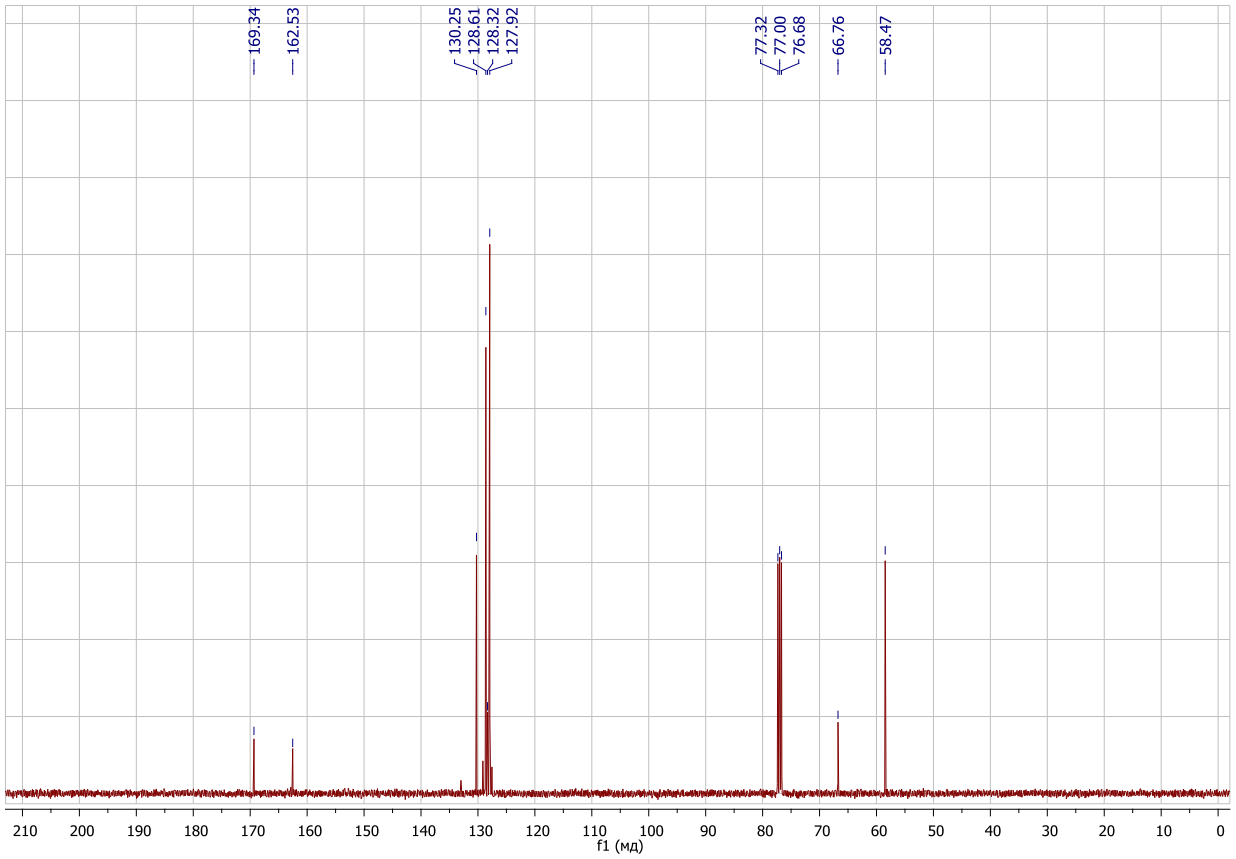
^{1}H and ^{13}C NMR spectra of compound **8j**



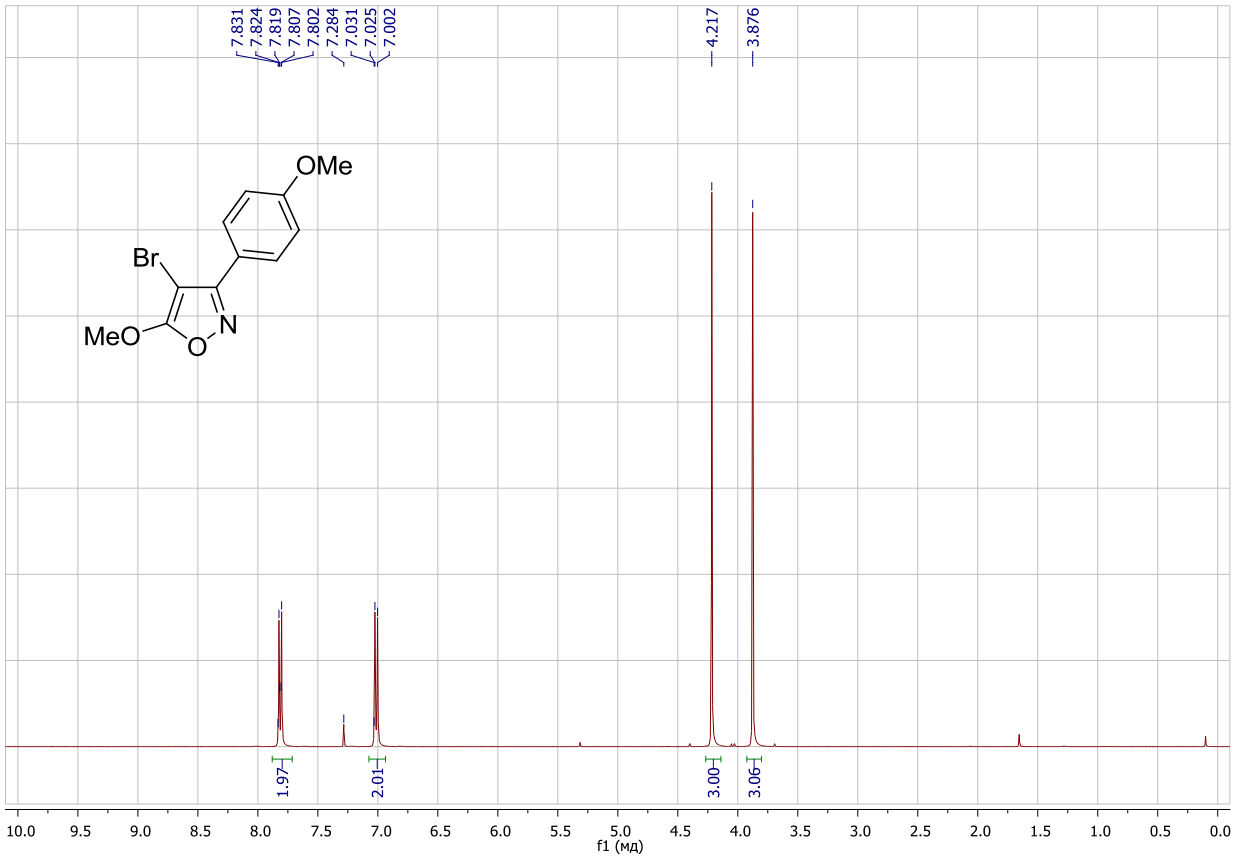


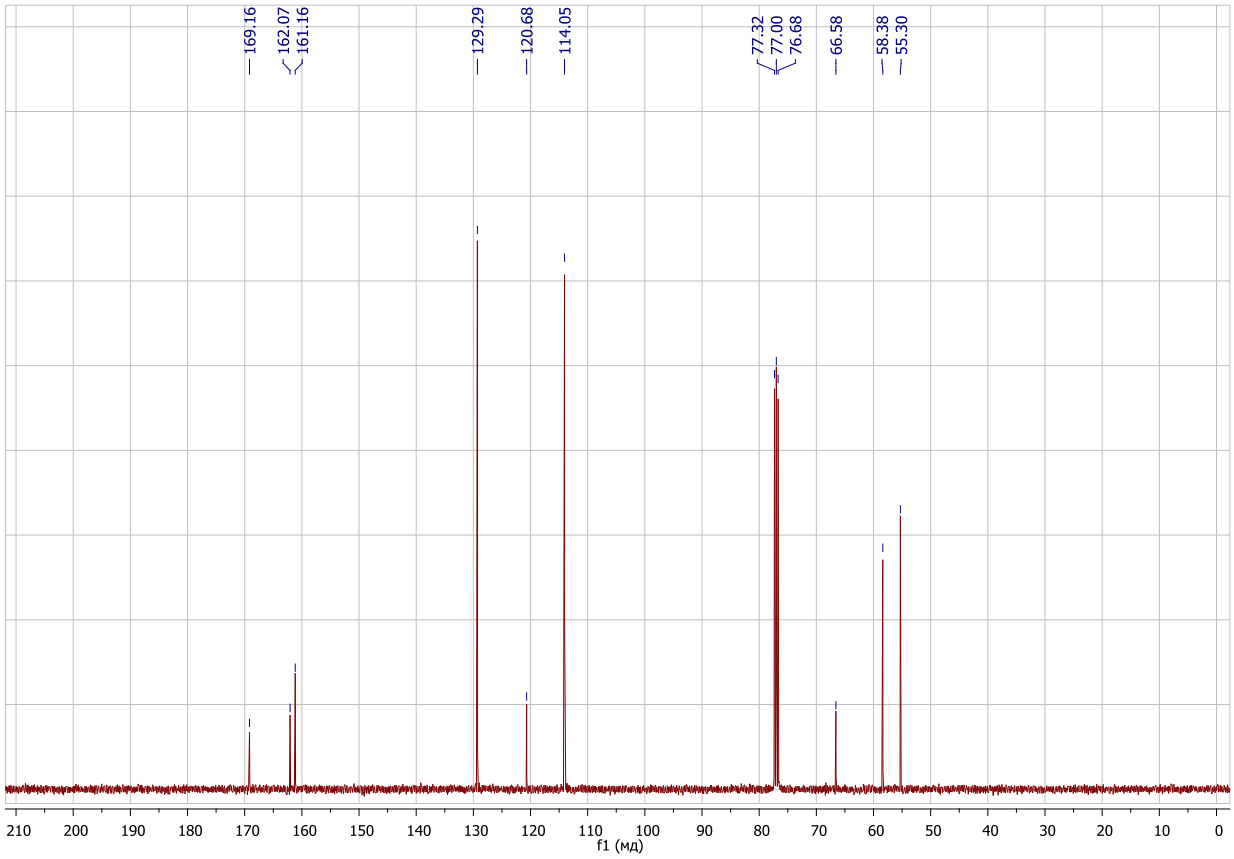
^{1}H and ^{13}C NMR spectra of compound **10a**



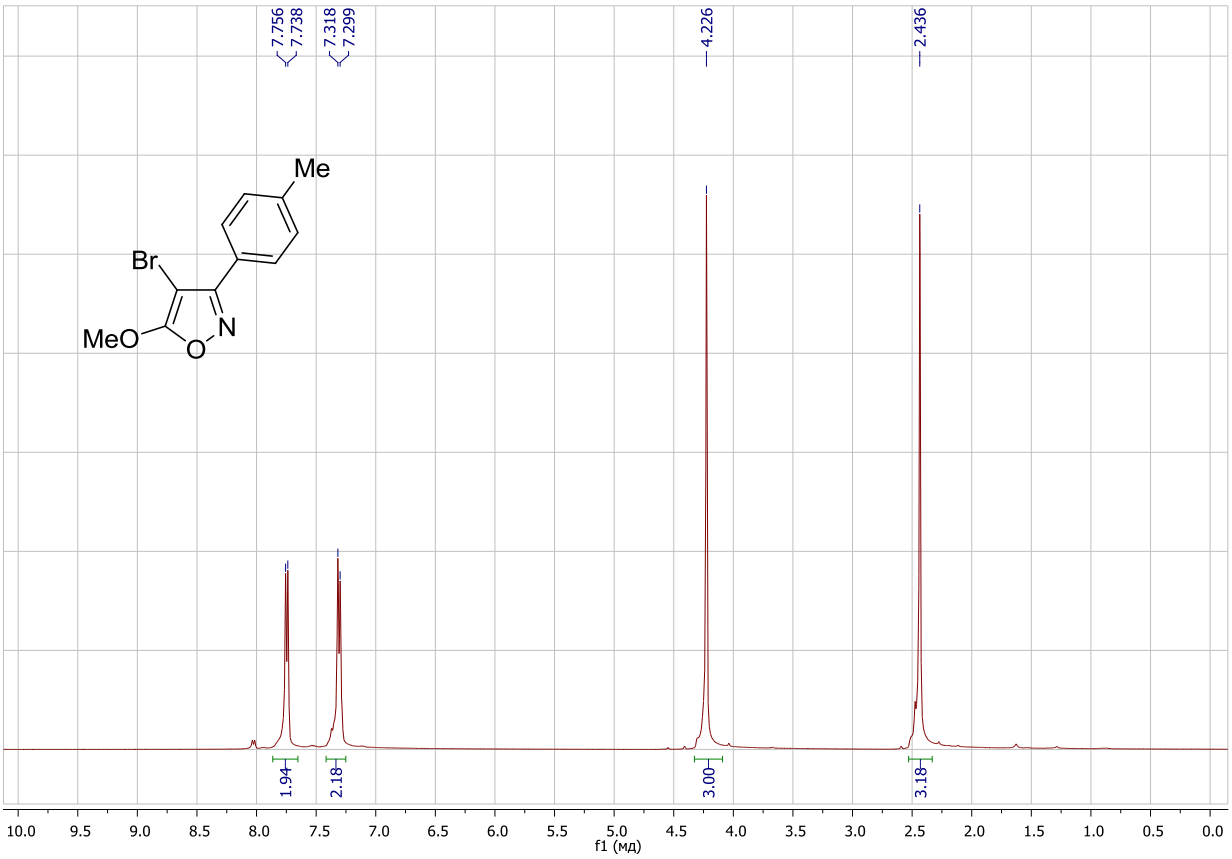


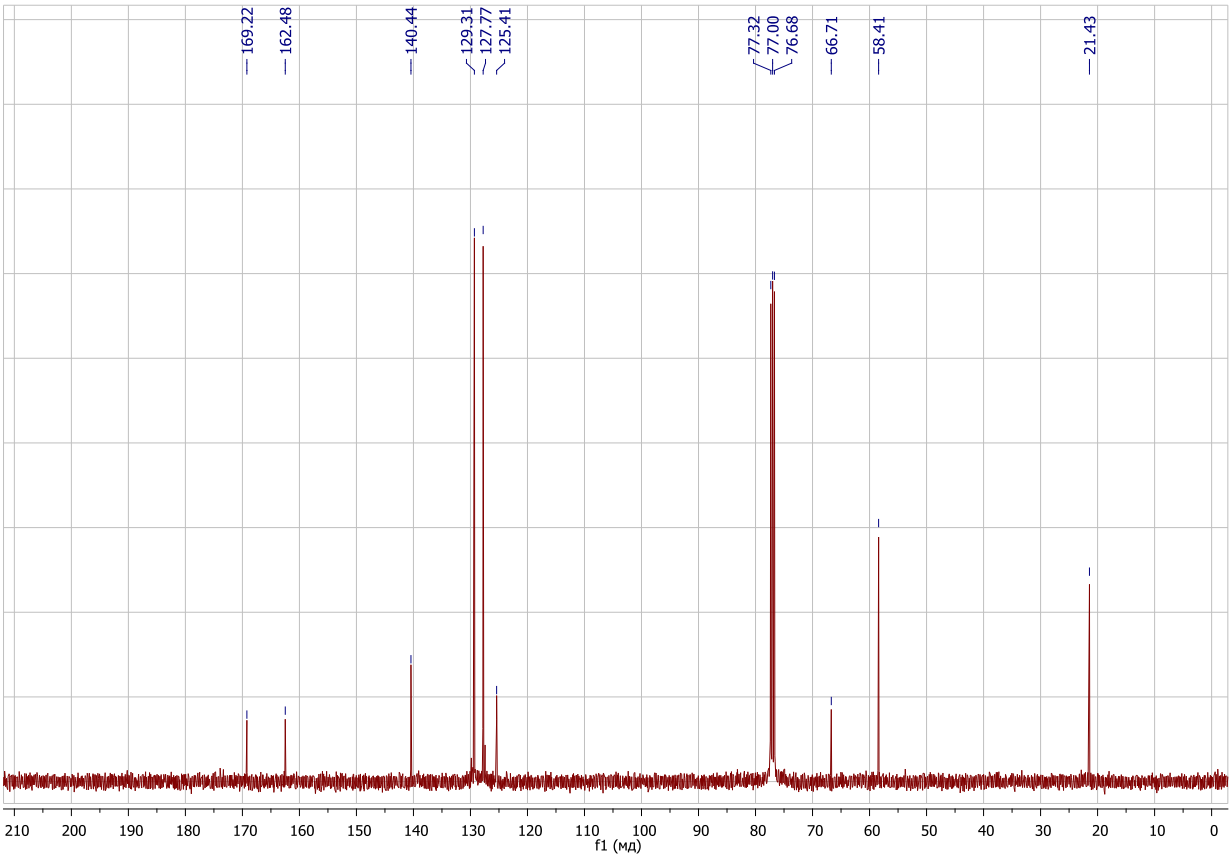
^{1}H and ^{13}C NMR spectra of compound **10b**



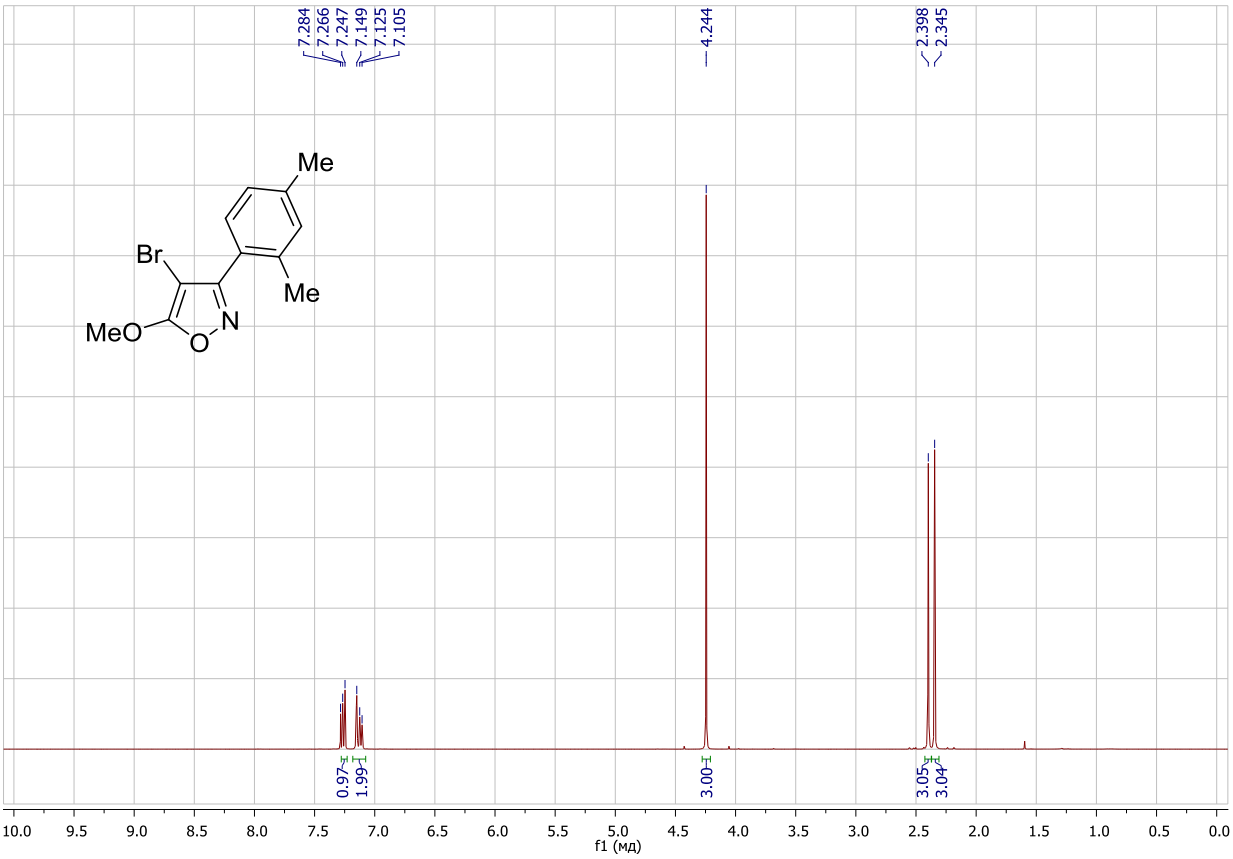


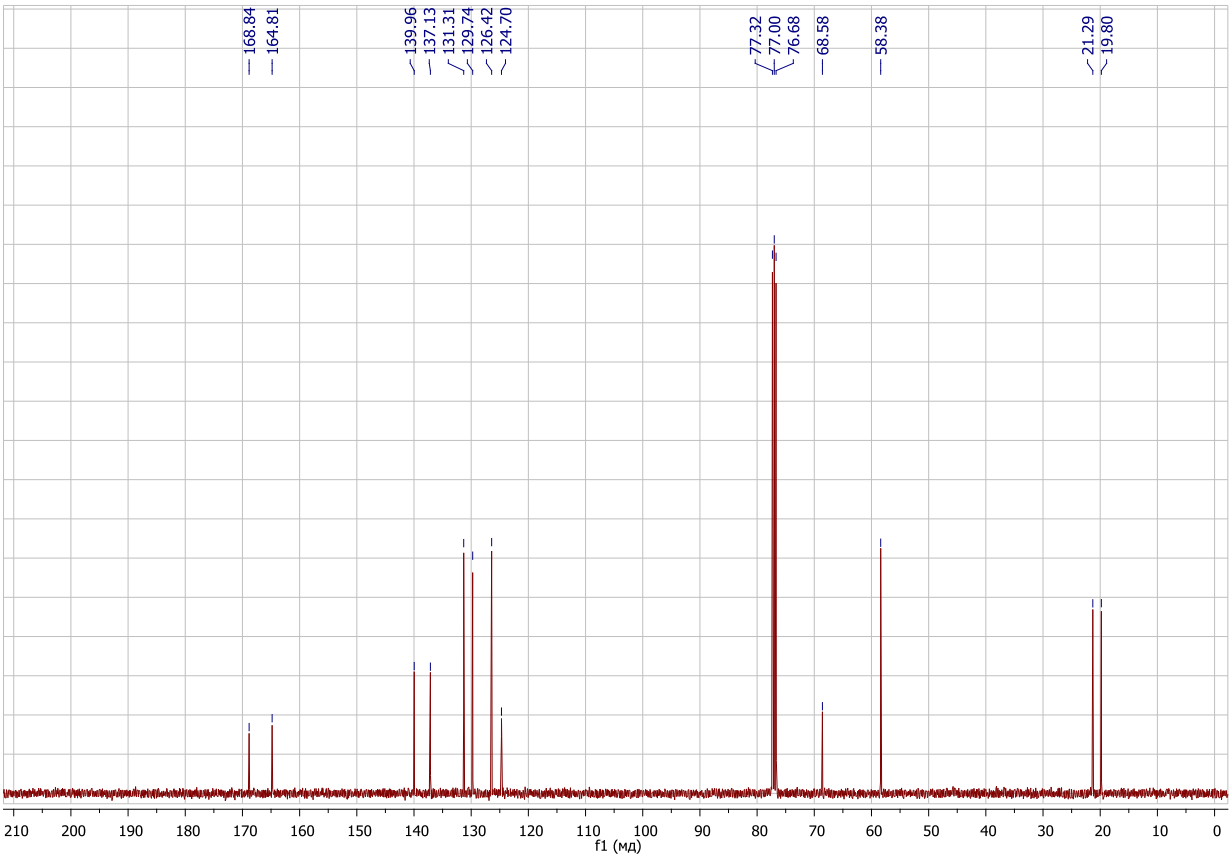
^{1}H and ^{13}C NMR spectra of compound **10c**



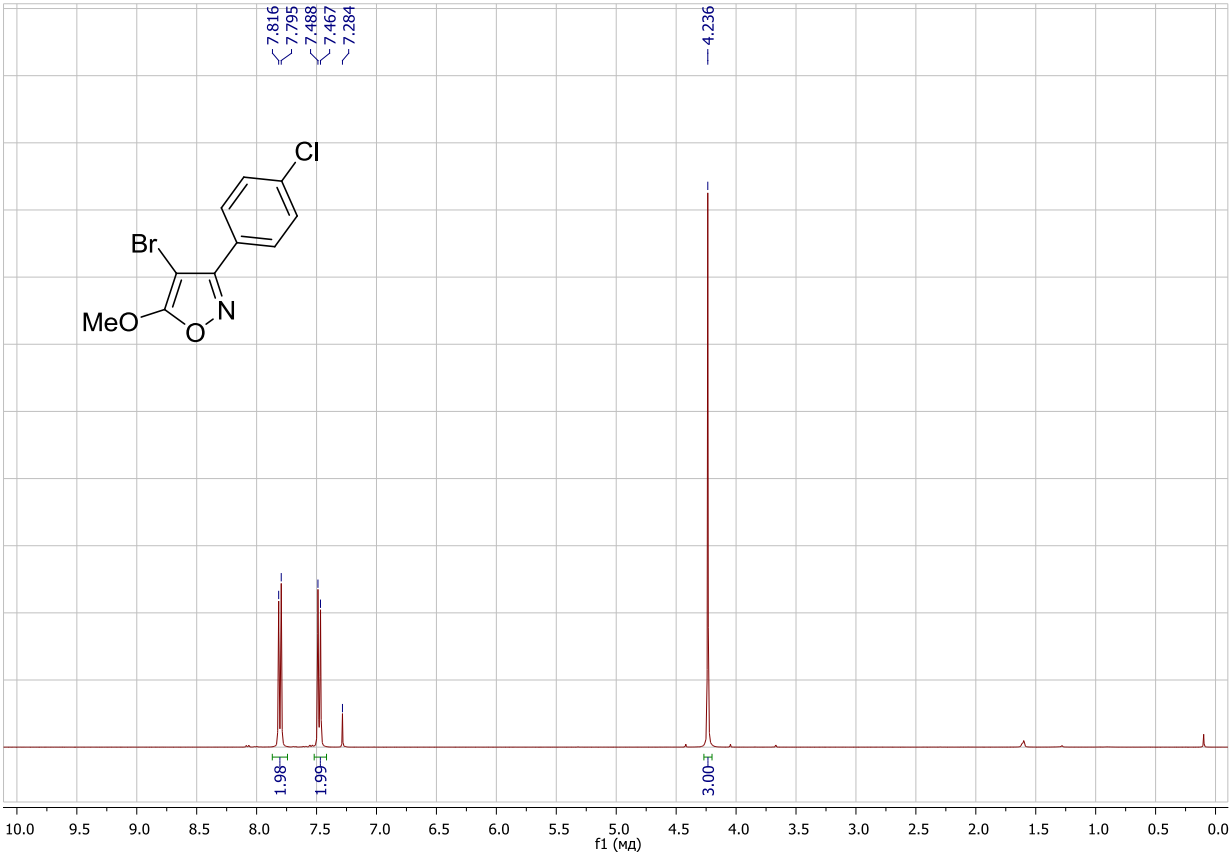


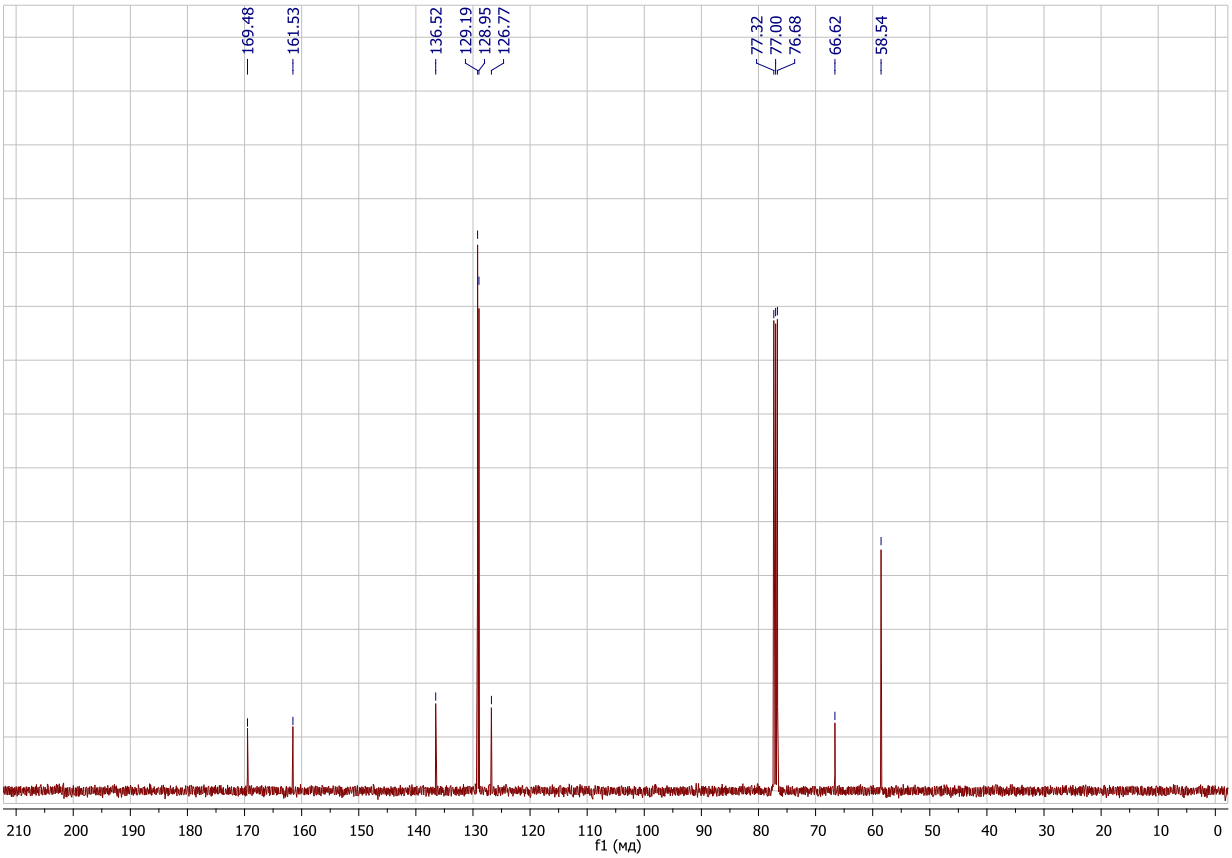
^{1}H and ^{13}C NMR spectra of compound **10d**



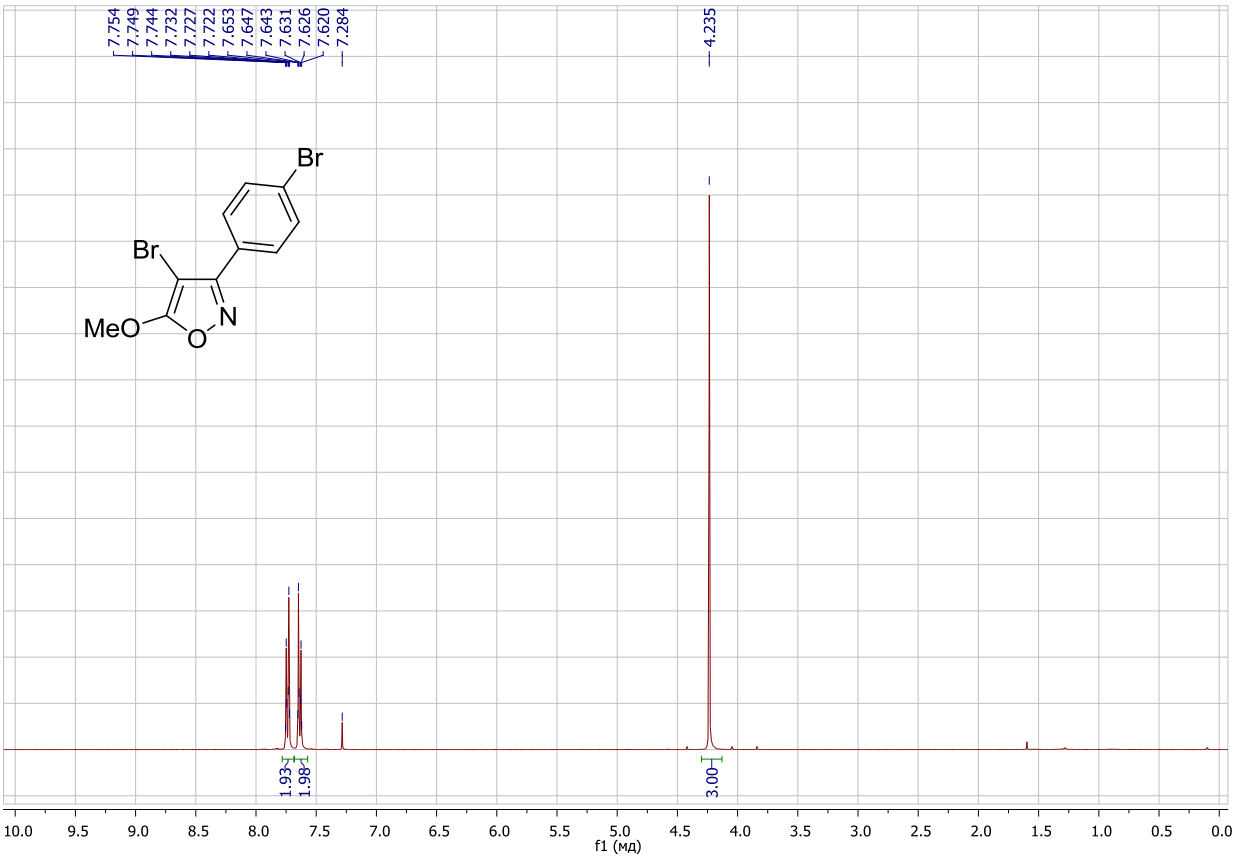


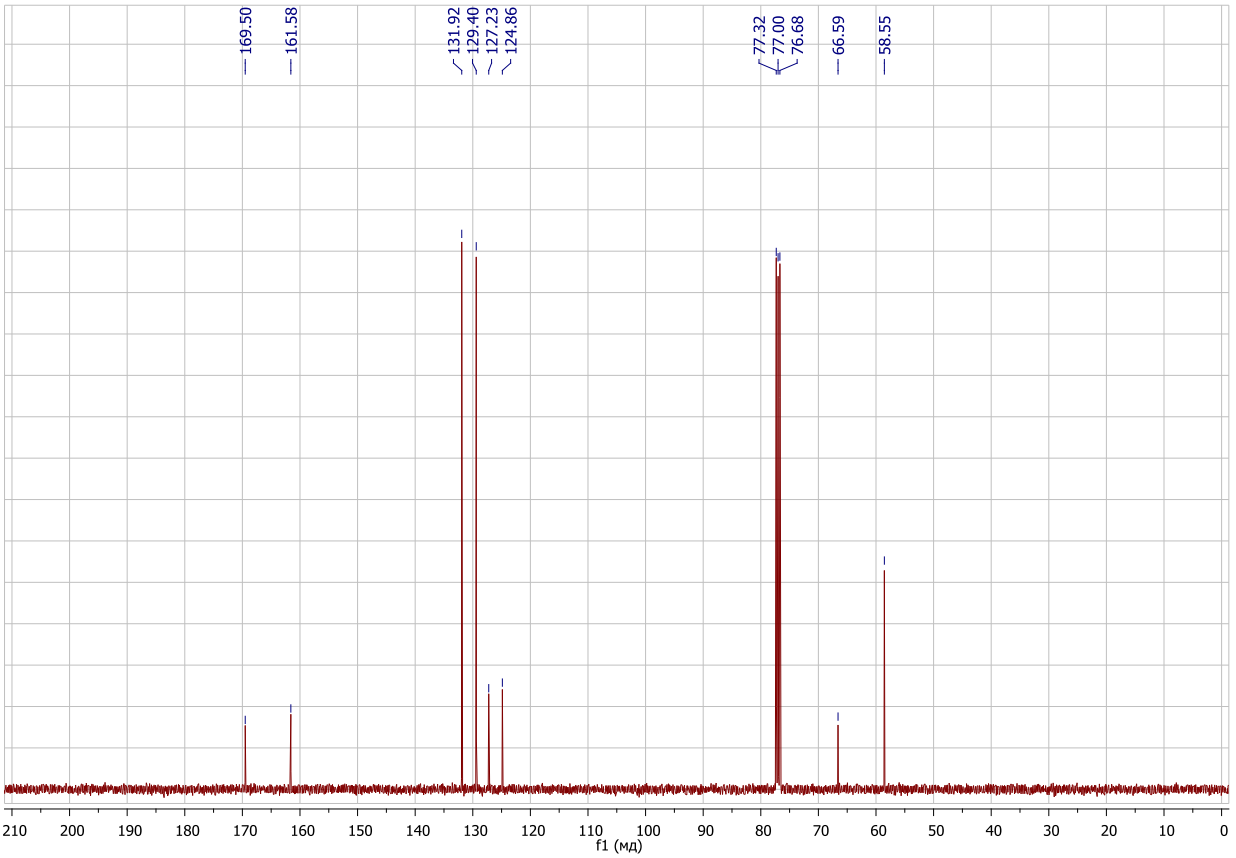
^{1}H and ^{13}C NMR spectra of compound **10e**



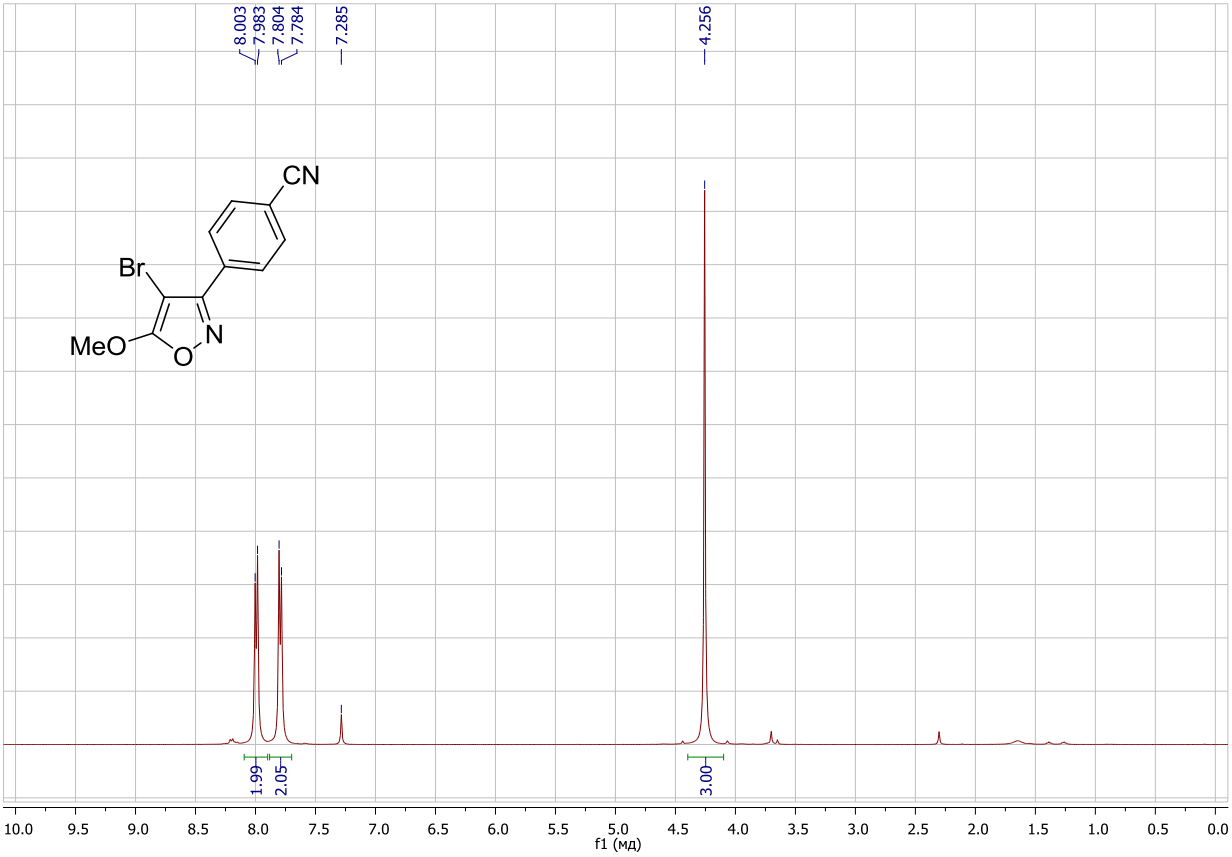


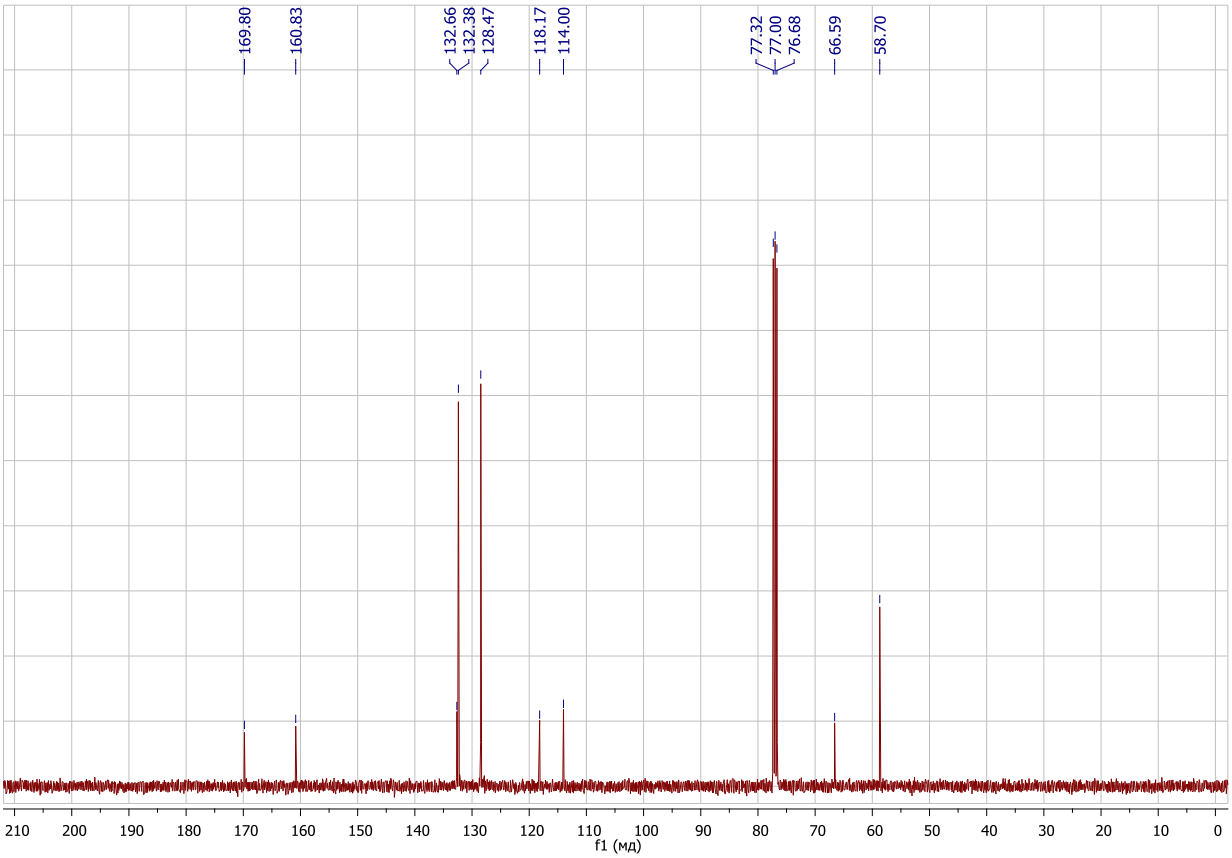
^{1}H and ^{13}C NMR spectra of compound **10f**



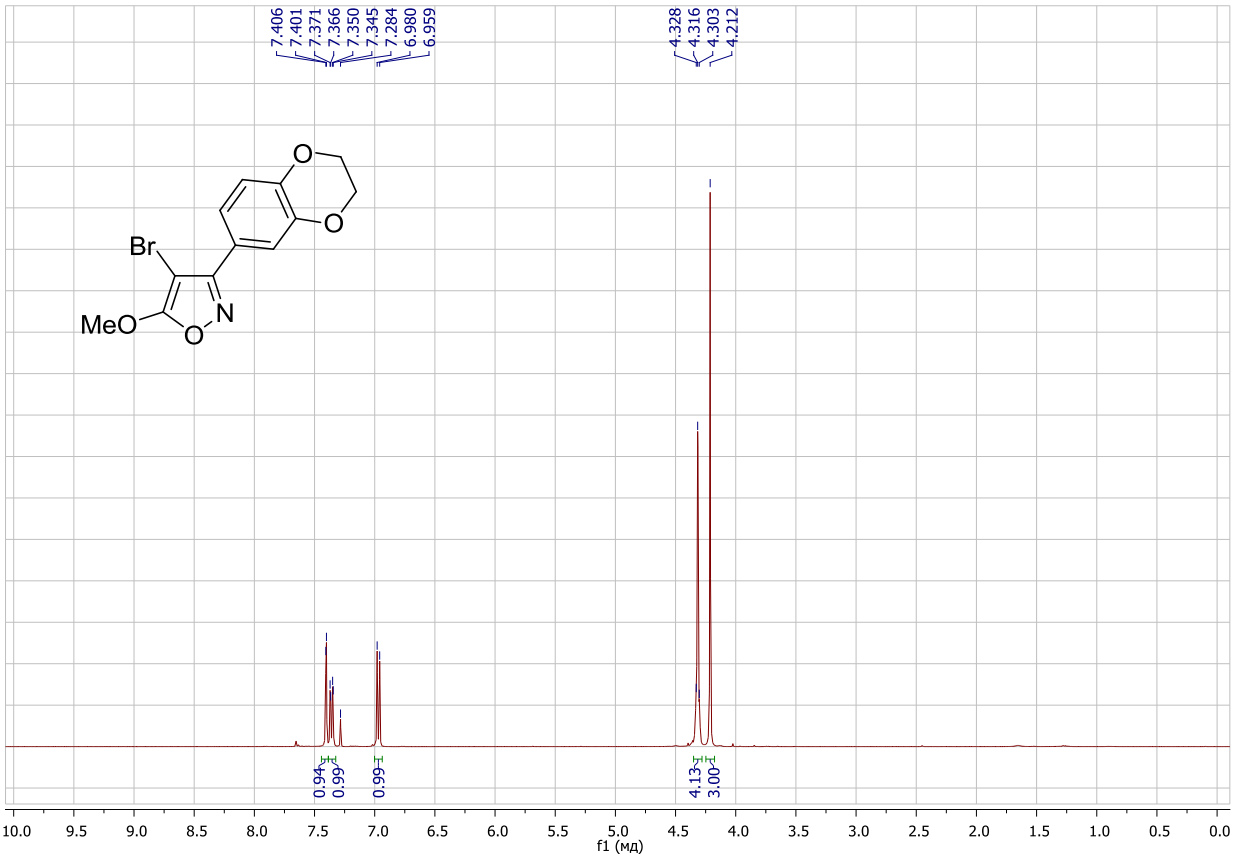


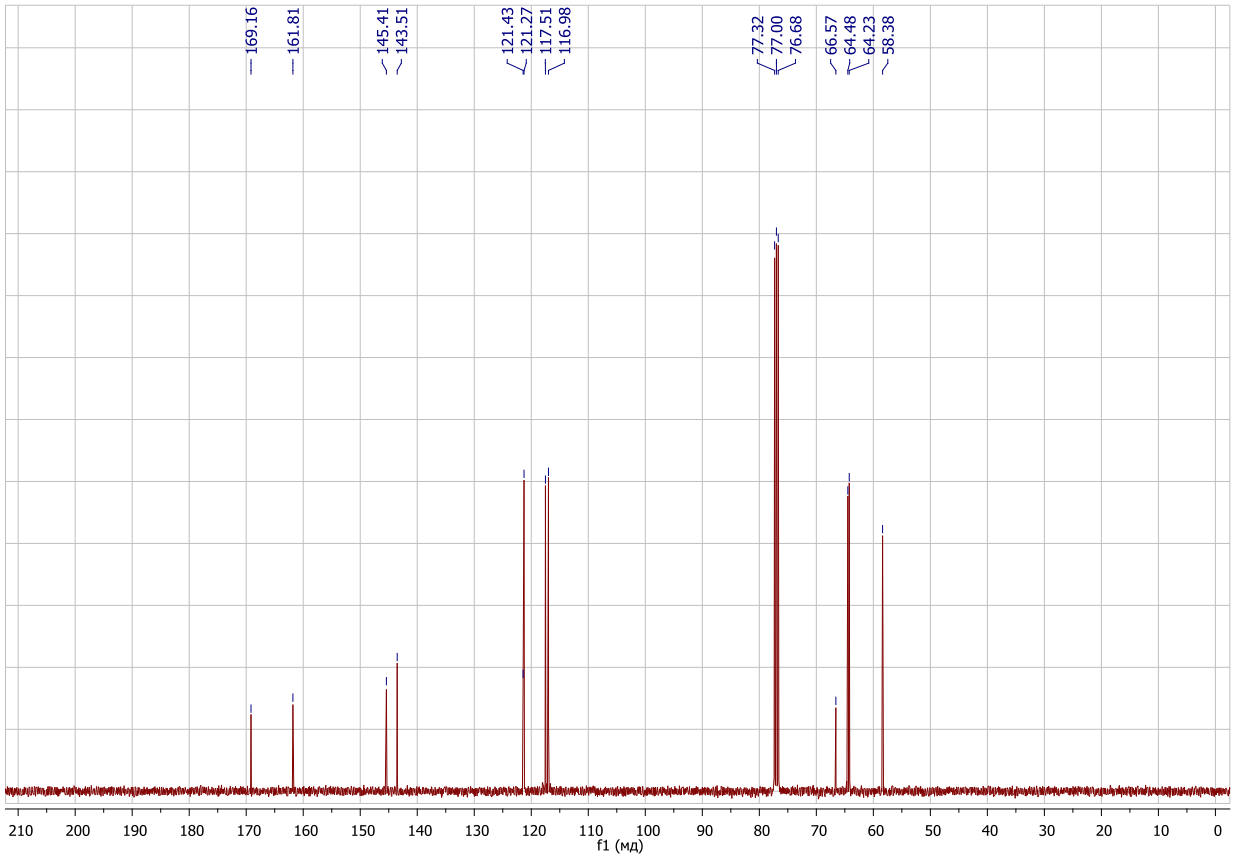
^{1}H and ^{13}C NMR spectra of compound **10g**



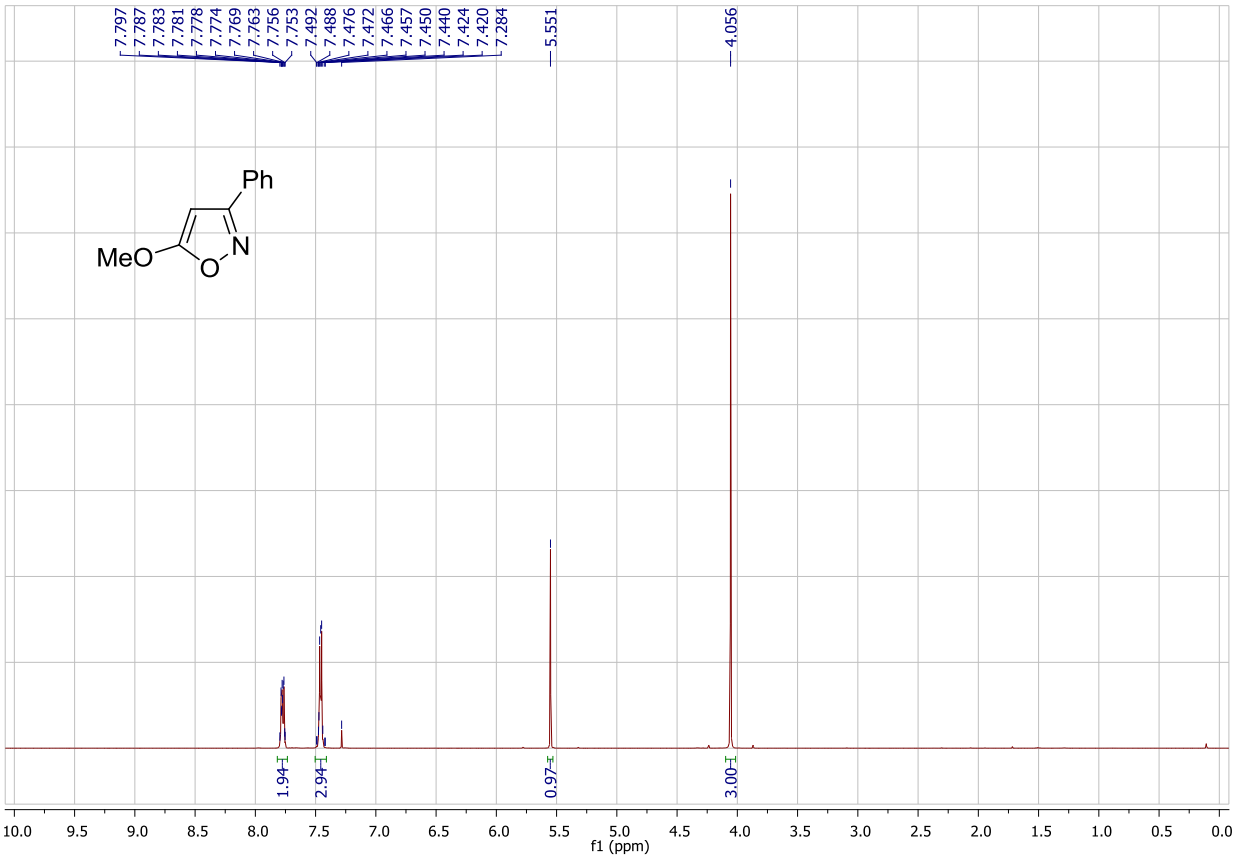


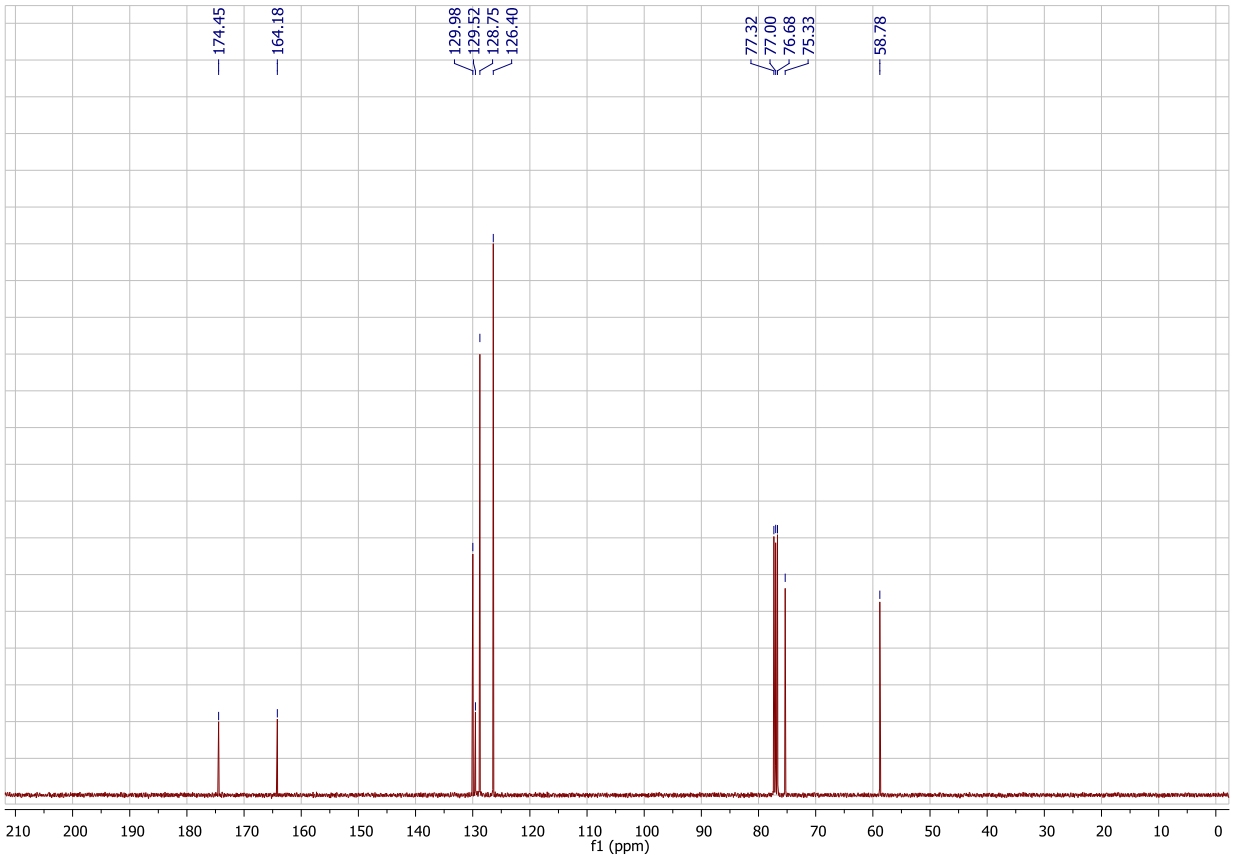
^{1}H and ^{13}C NMR spectra of compound **10h**



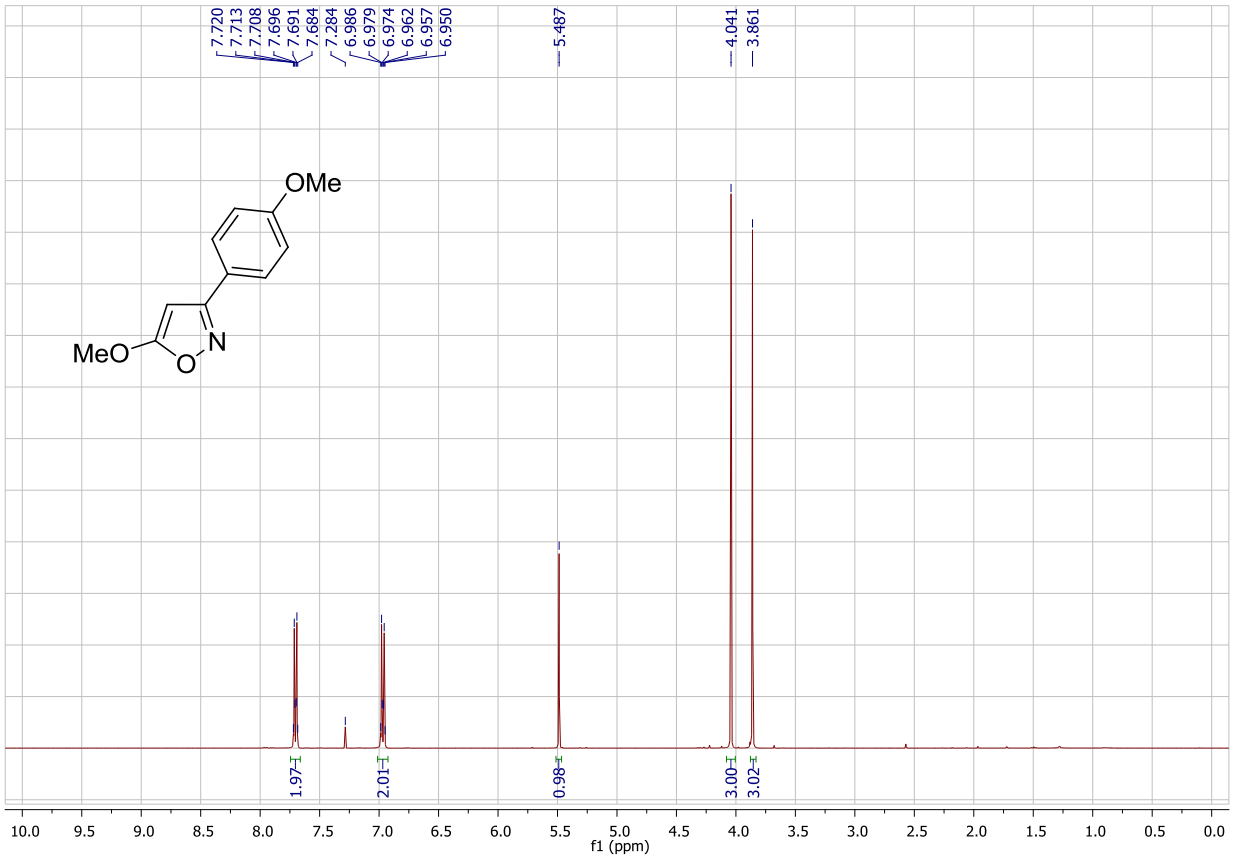


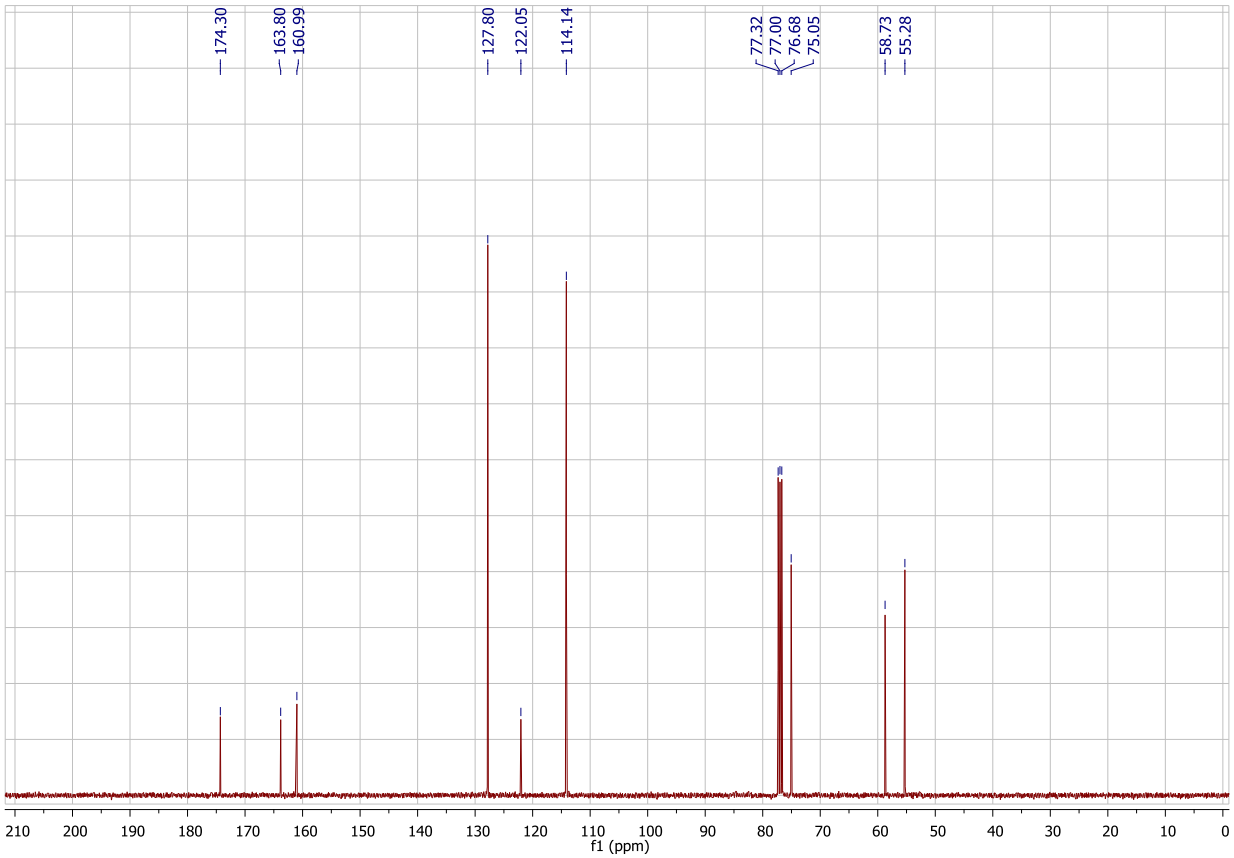
^{1}H and ^{13}C NMR spectra of compound (**S-11a**)



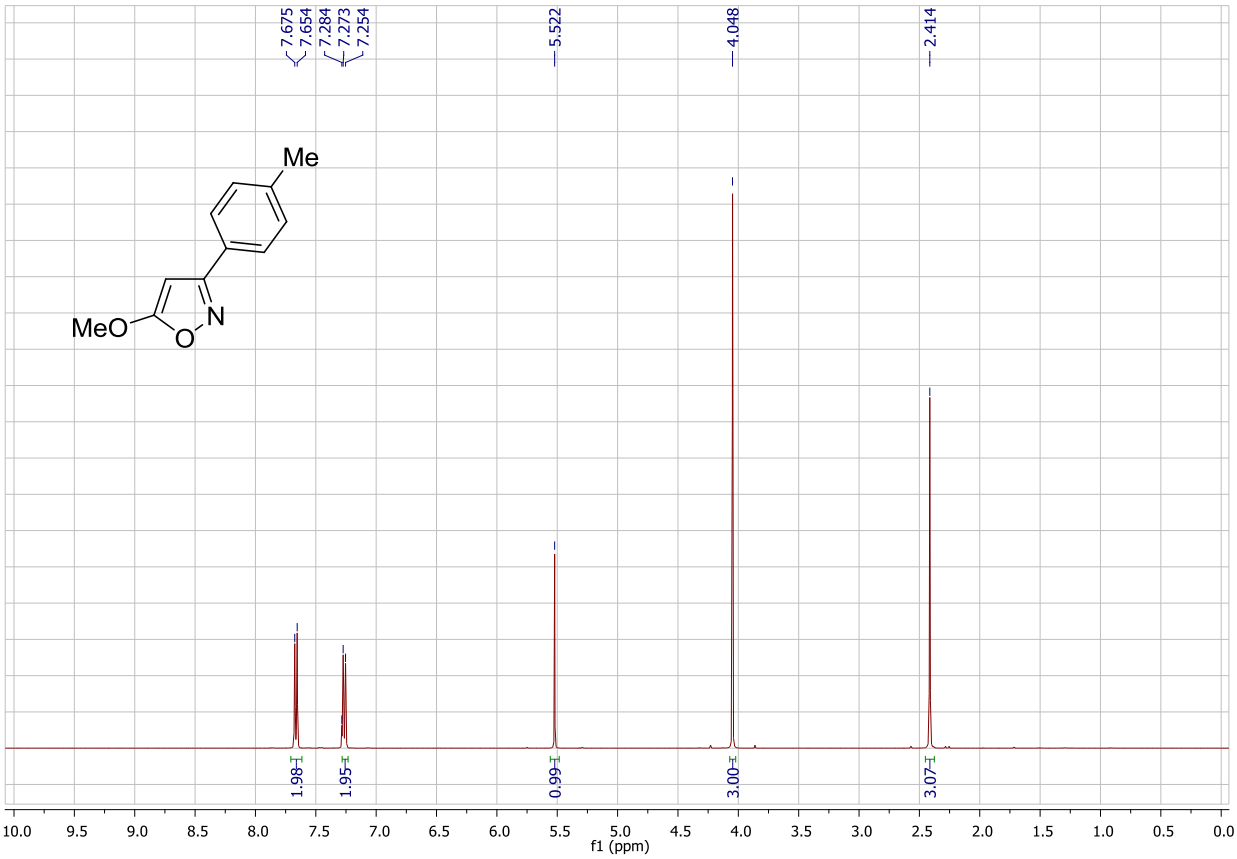


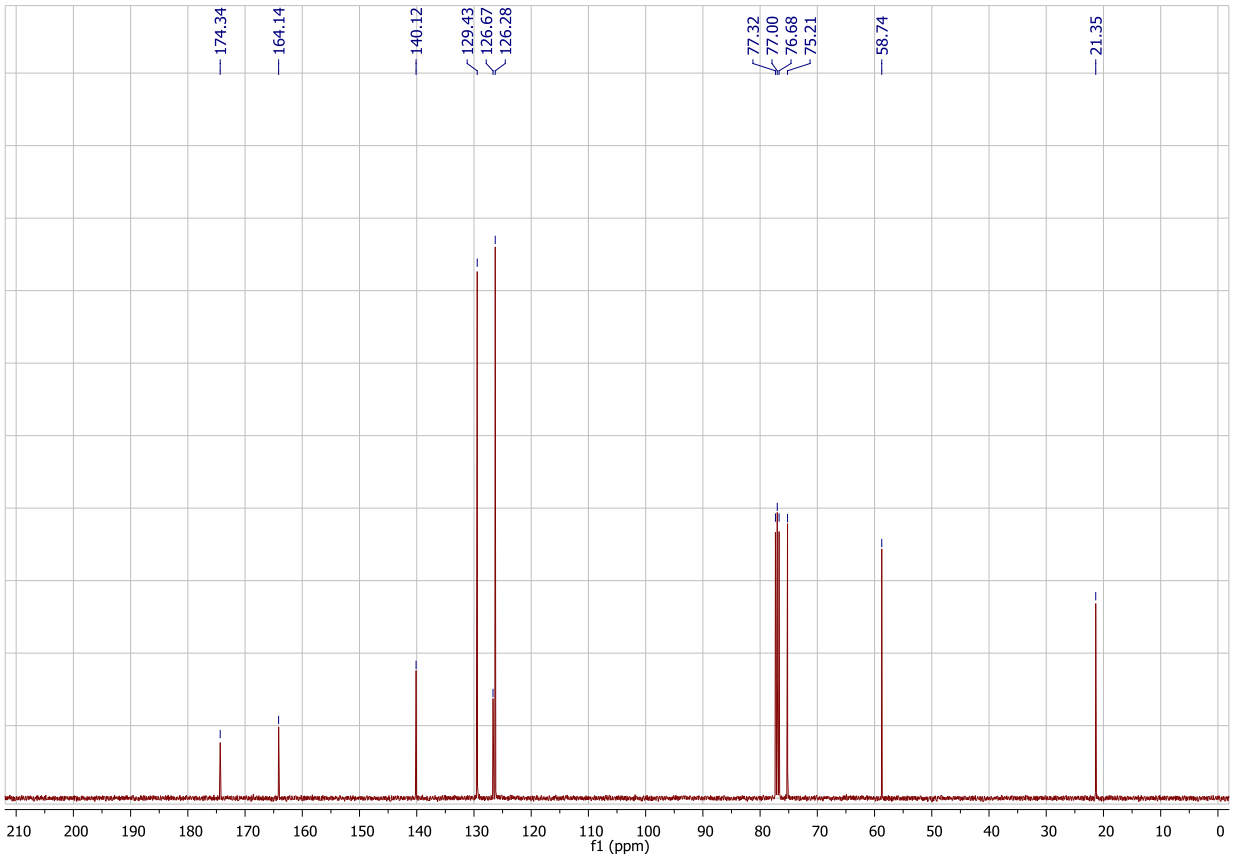
^{1}H and ^{13}C NMR spectra of compound (**S-11b**)





^{1}H and ^{13}C NMR spectra of compound (**S-11c**)





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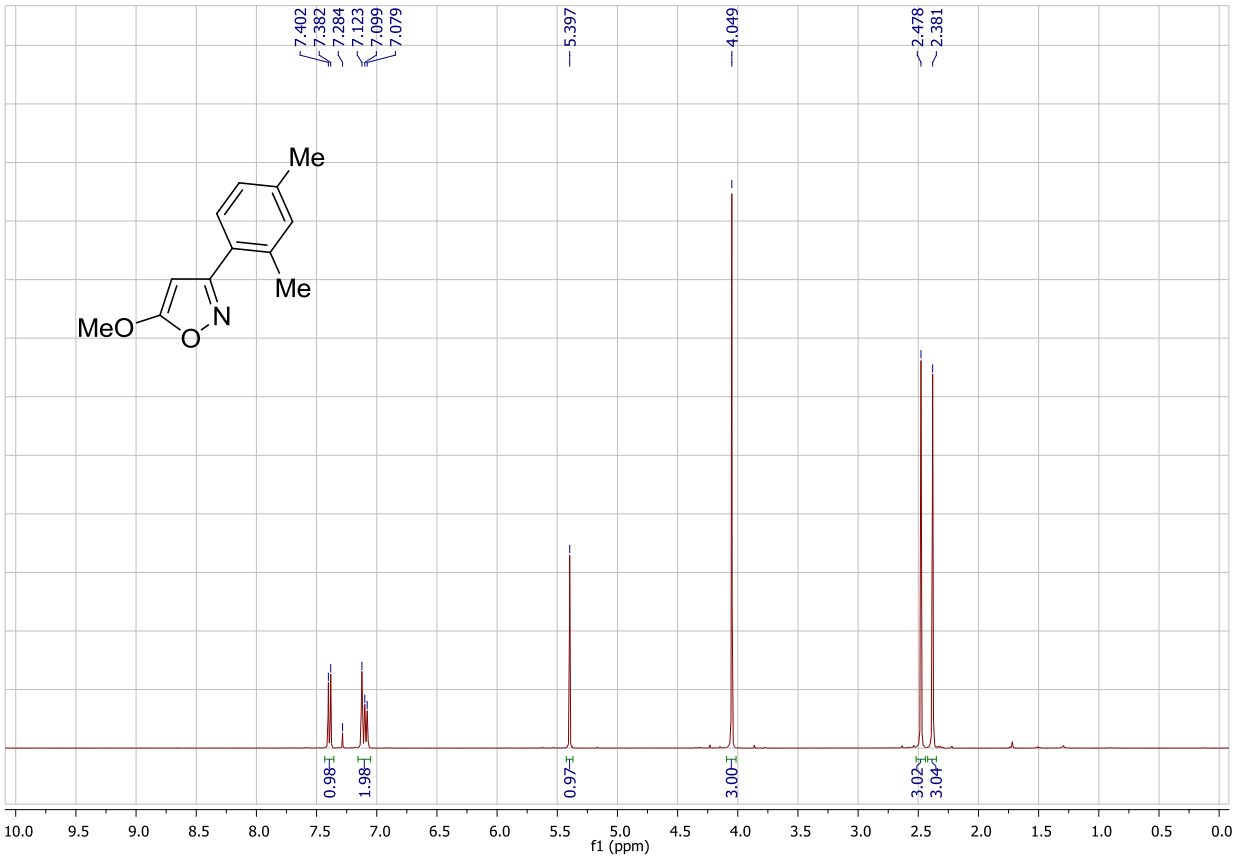
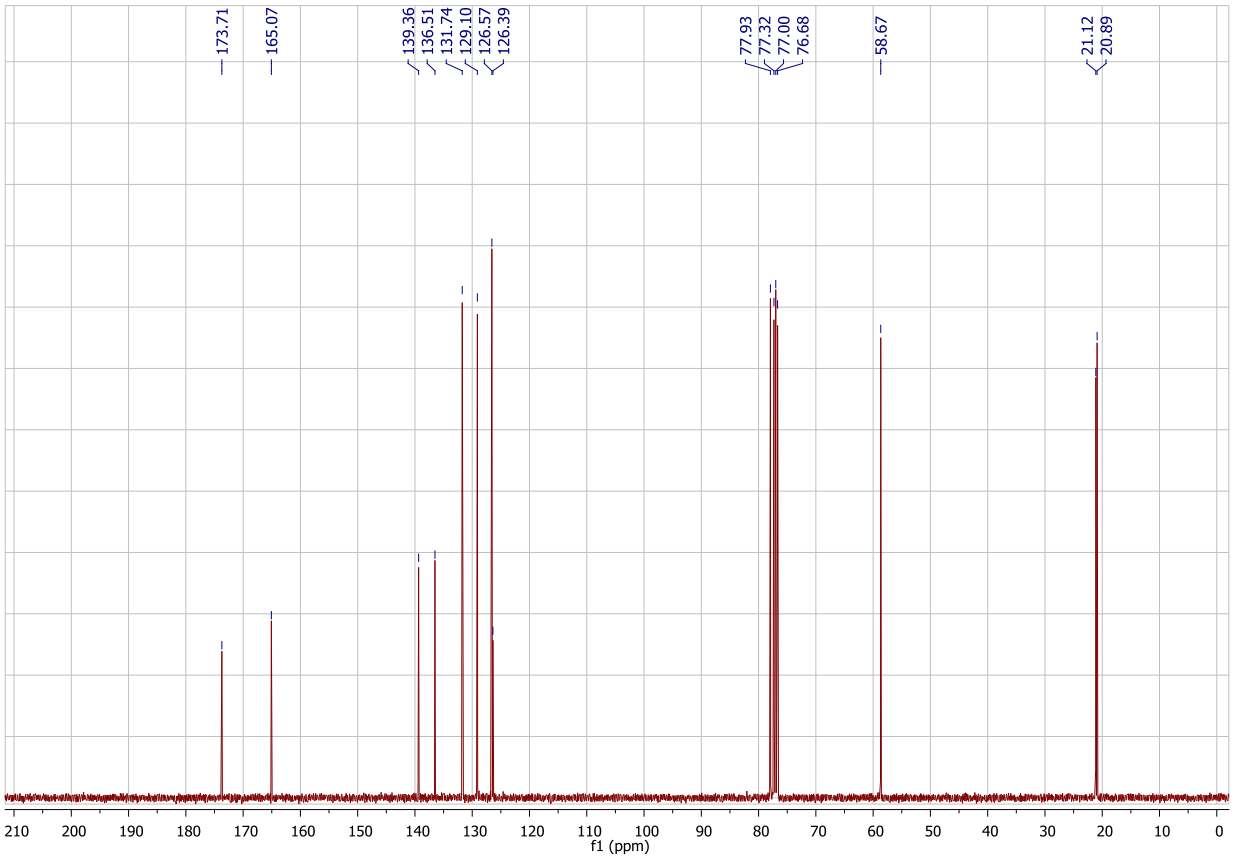
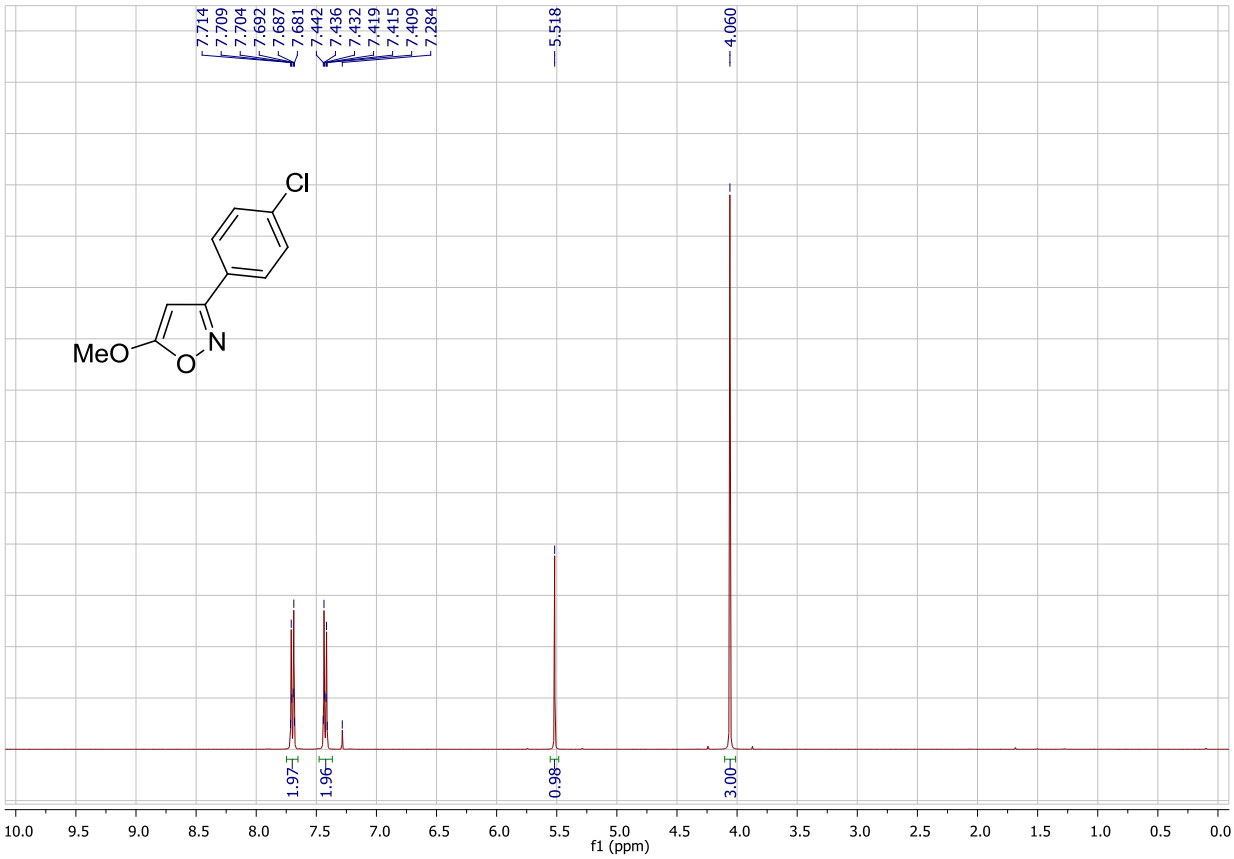
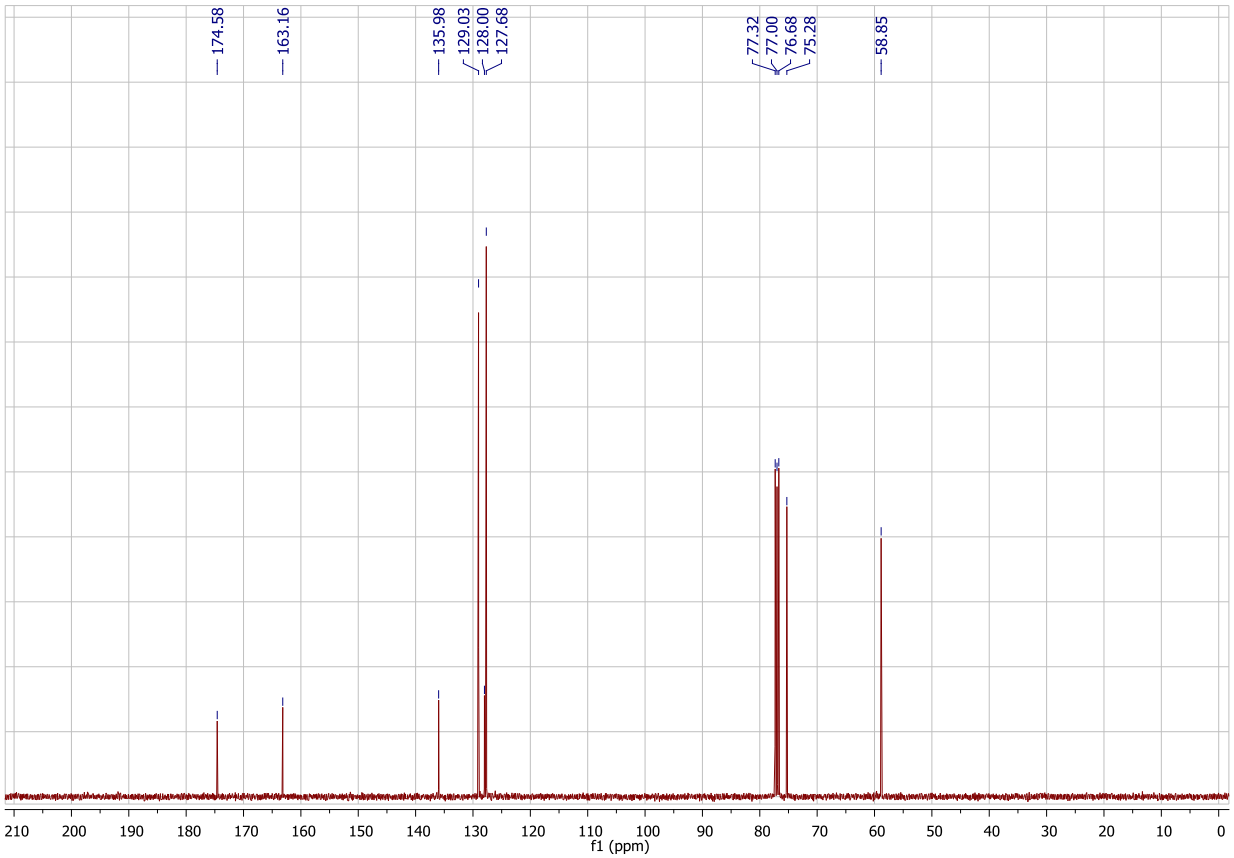


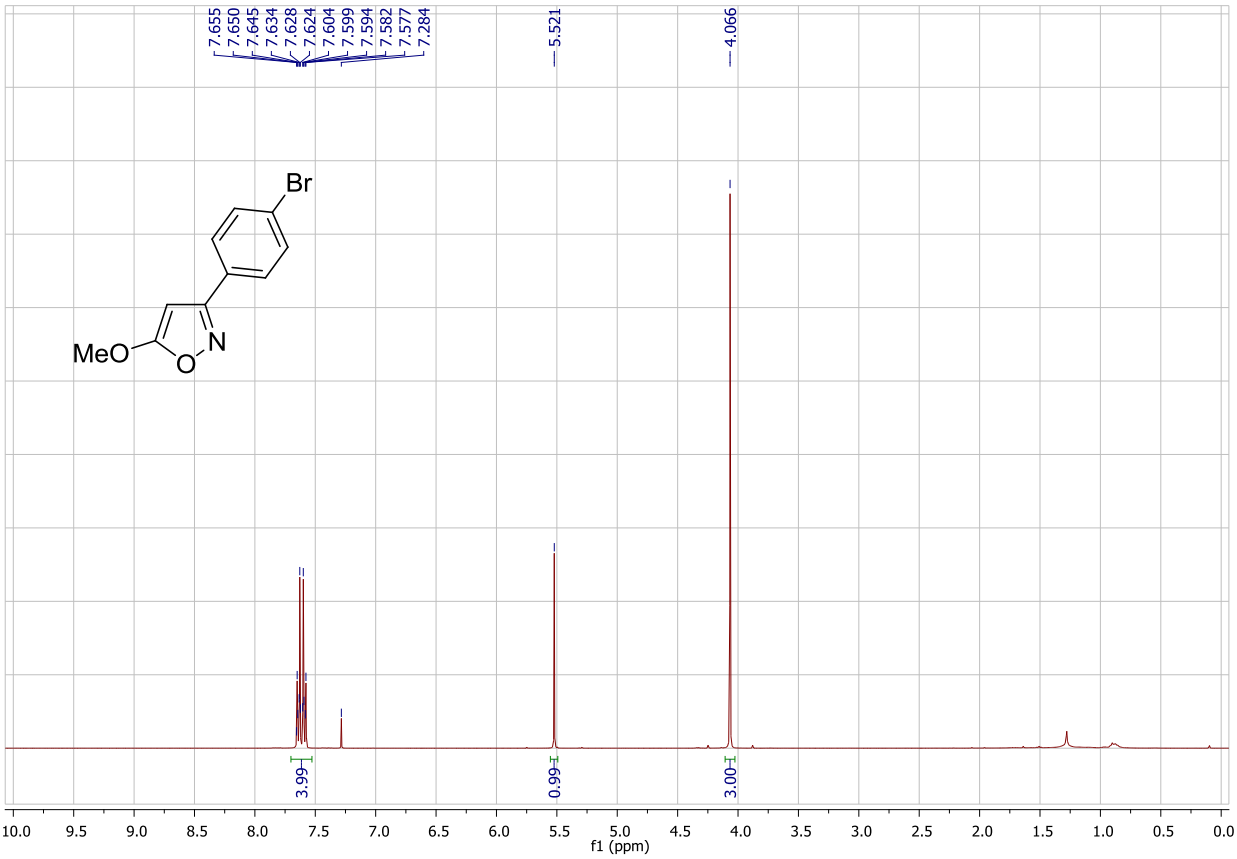


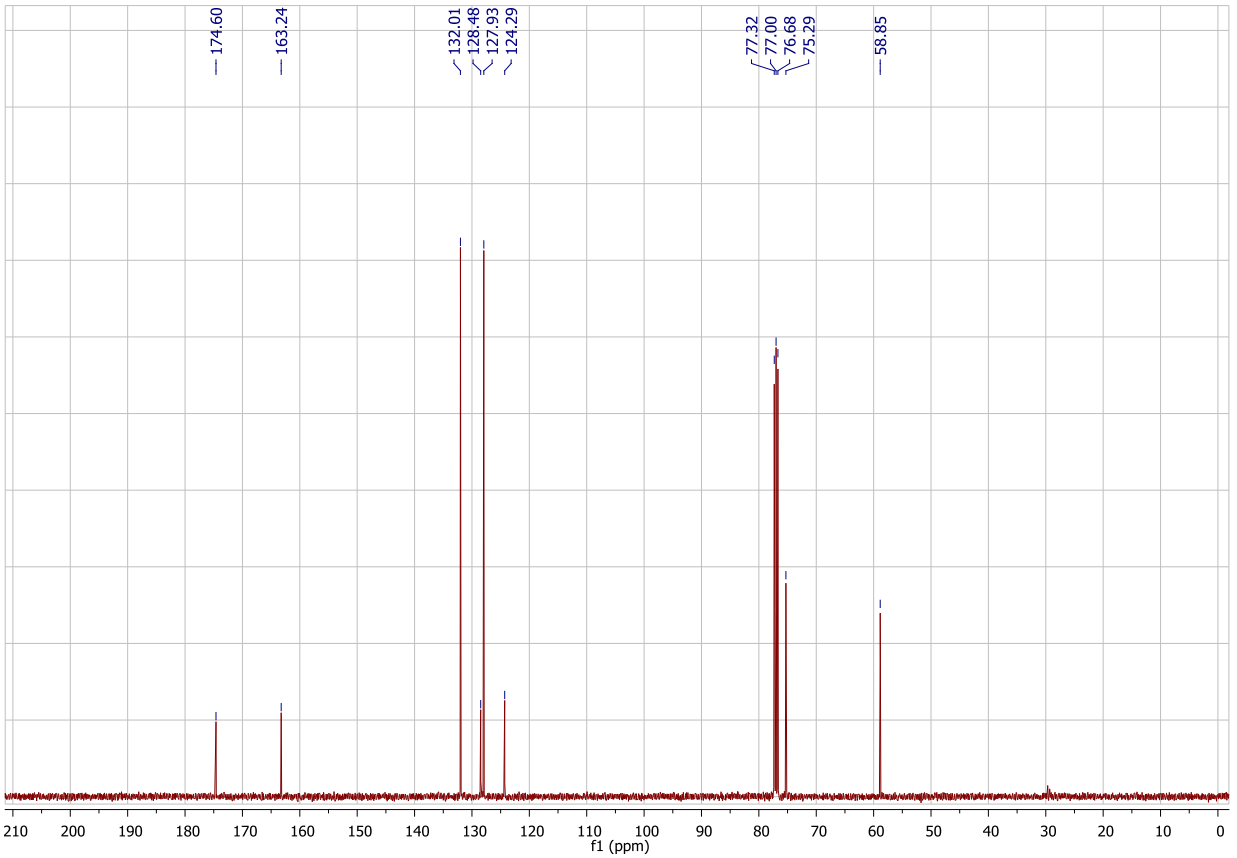
^{1}H and ^{13}C NMR spectra of compound (**S-11e**)



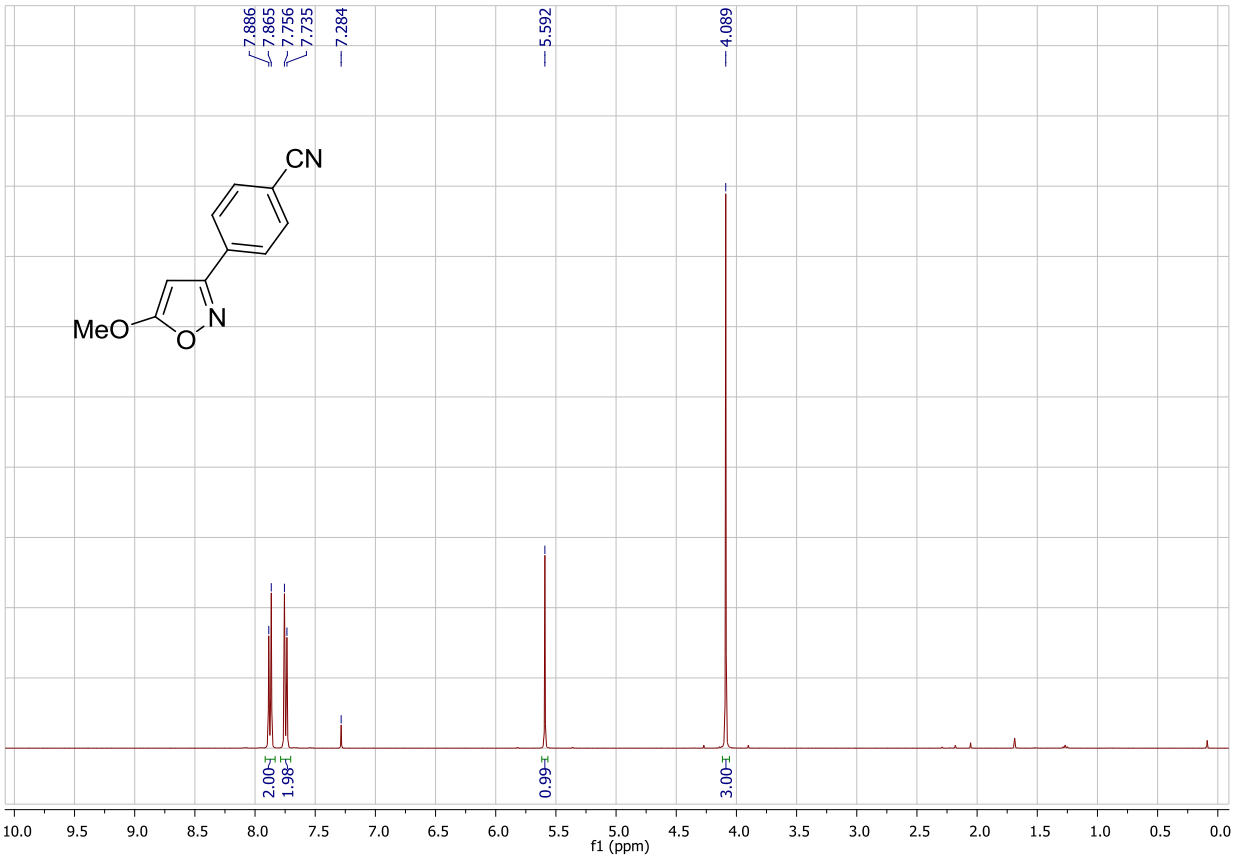


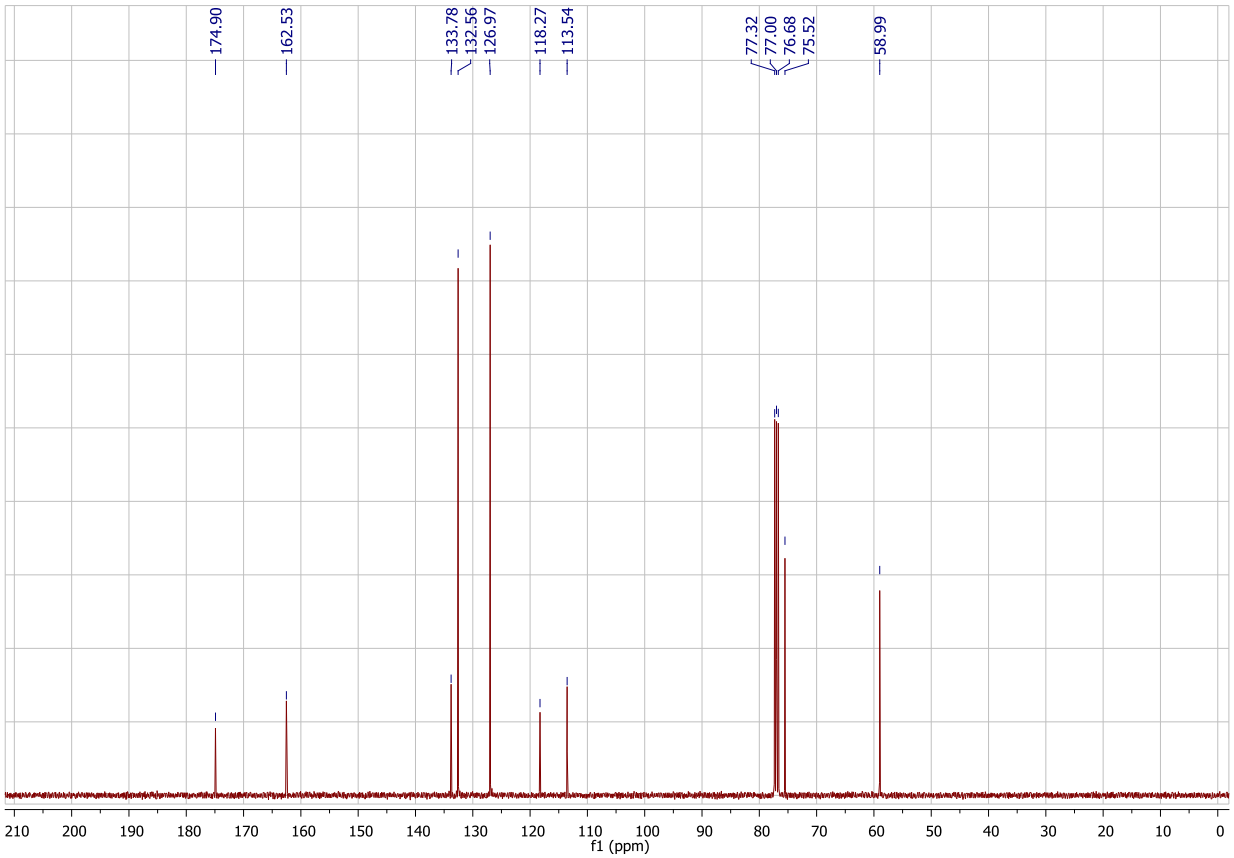
^{1}H and ^{13}C NMR spectra of compound (**S-11f**)



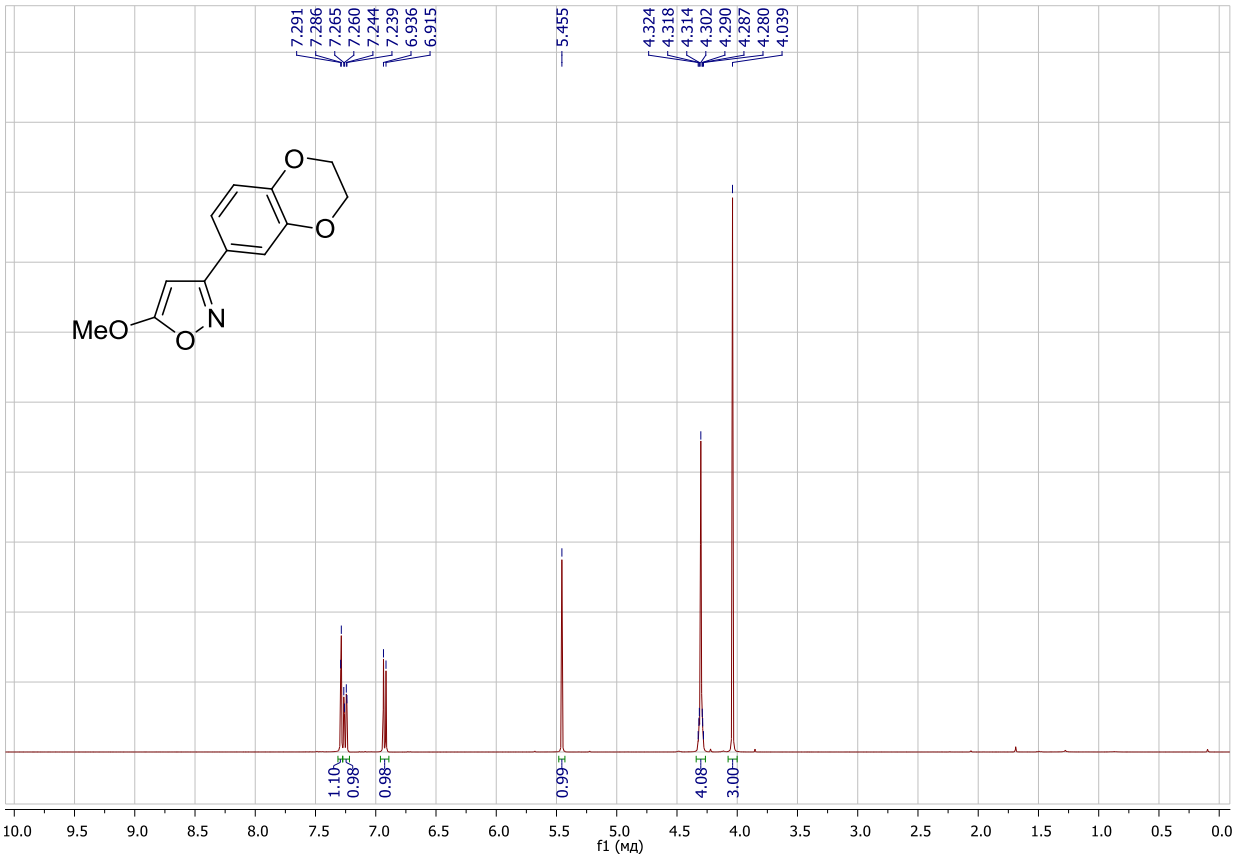


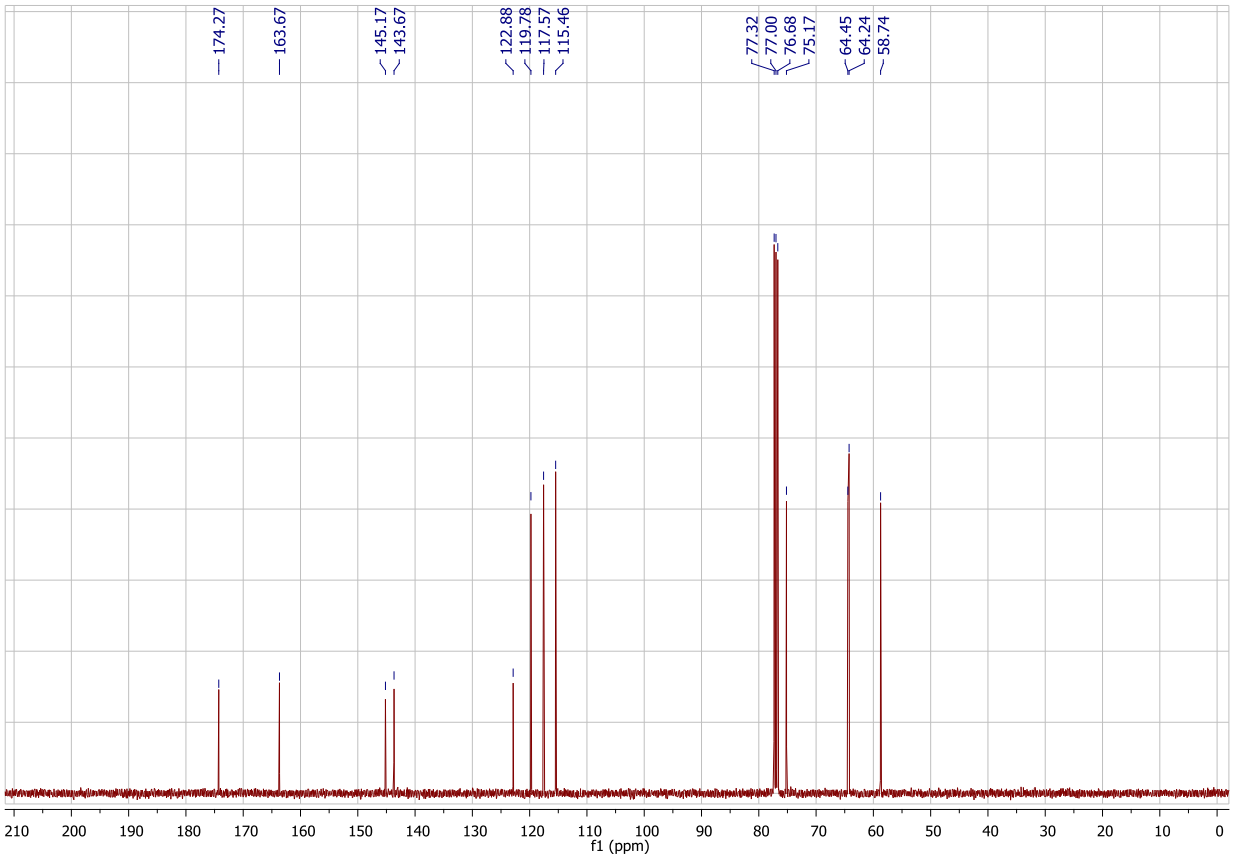
^{1}H and ^{13}C NMR spectra of compound (**S-11g**)



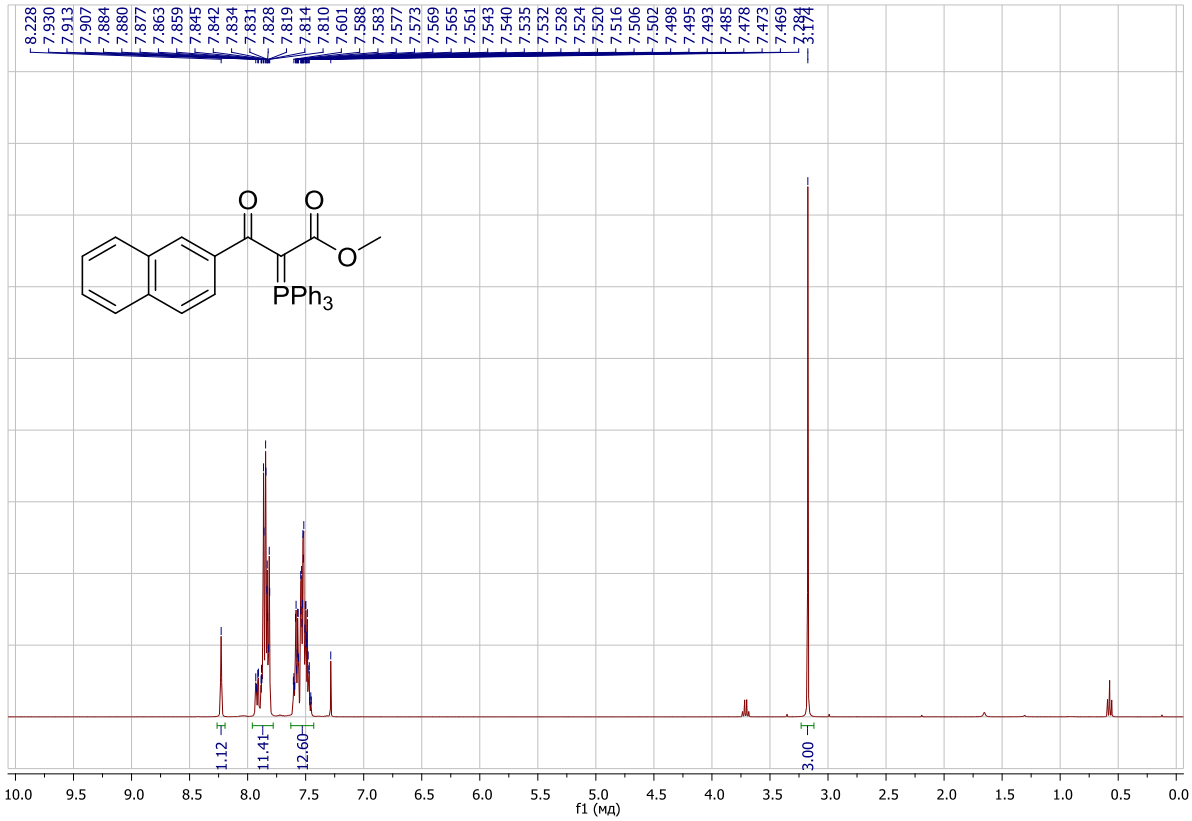


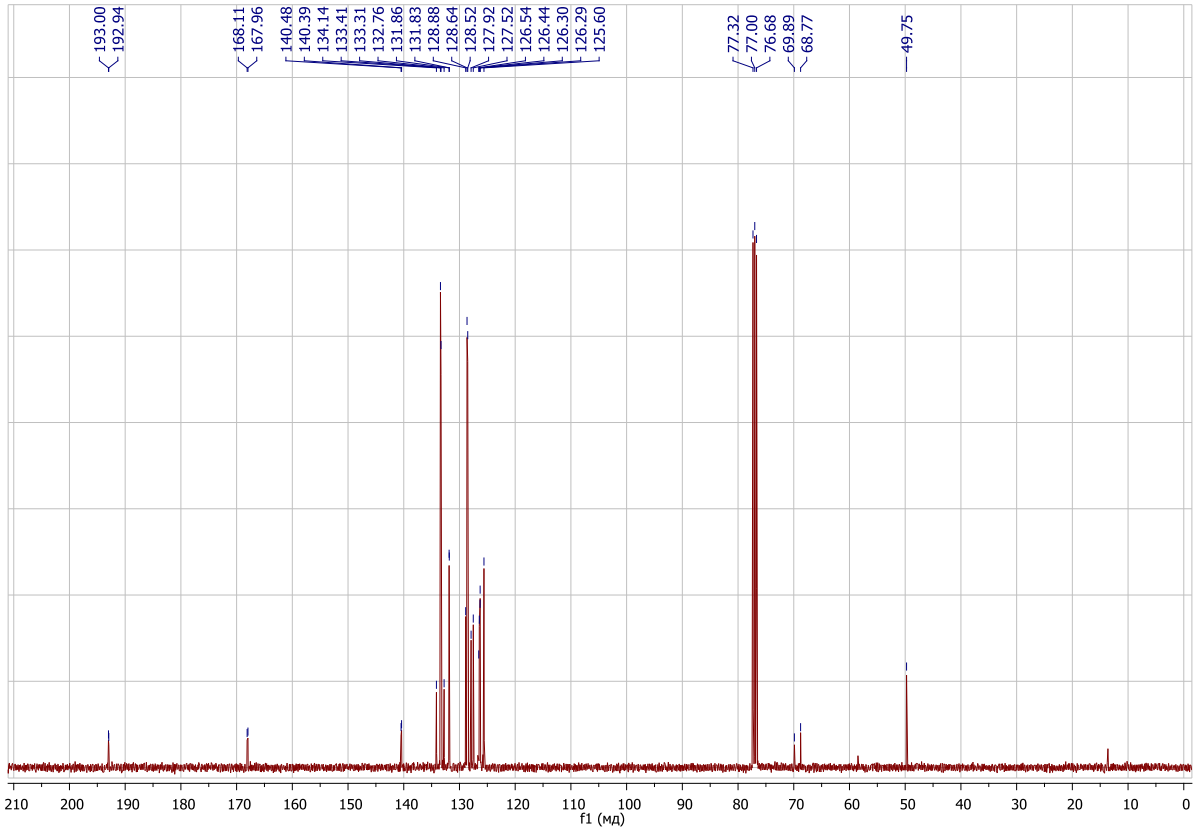
^{1}H and ^{13}C NMR spectra of compound (**S-11h**)





^{1}H and ^{13}C NMR spectra of compound **S-12**





5. Bioassay details

Methods. Cell suspension culture of THP-1 (human monocytic leukemia cells) was selected as the object of biological studies. Cultivation of the THP-1 cell line was carried out with RPMI-1640 medium with addition of 10% heat-inactivated fetal bovine serum (FBS), 50 μg/mL gentamicin and 2 mM L-glutamine (all culture reagents mentioned were purchased from "Biolot", St. Petersburg). The cells were subcultured (passaged) every 2–3 days. To maintain the cells in culture we used plastic bottles of 50 ml («Sarstedt», Germany), in which they were incubated at 37 °C under 5% CO_2. For the experiments, 200 μL of cell suspension (2×10^6 cells per ml) in complete culture medium was added to each well of 96-well flat-bottomed plate («Sarstedt», Germany). Dimethyl sulfoxide used for dilution of substances was also used as the negative control. As a positive control we used camptothecin in final concentrations of 1 and 0.2 μM, the proapoptotic effect of which is based on inhibition of the DNA topoisomerase I.

Assessment of cell viability using DNA binding dyes - YO-PRO-1 and propidium iodide (PI).[9] YO-PRO-1 is a DNA-binding probe, which is used together with PI to stoichiometrically bind to nucleic acids, i.e. RNA in the cytoplasm and DNA in the nucleus. Being excited at 488 nm, YO-PRO-1 emits fluorescence in the green region (near 509 nm) and PI - in the red region (near 617 nm) of the spectrum. But the principal difference between them is the way of penetration into the cells. YO-PRO-1 enters cells through purinergic receptors, P2RX7, which are ligand-dependent ionic channels.[10] In the living cells, YO-PRO-1 would not accumulate because of almost inactive channels and very low transporting ability of the membrane. The channels become activated at early stages of apoptosis development, together with disturbance of plasma membrane asymmetry. To reveal the later stages, cells should be stained with DNA-binding PI, which does not need special transporters and is able to penetrate into cells and nuclei only via damaged/fragmented membranes, the process taking place at late stages of apoptosis or necrotic cell death. Thus, the living cells would not be stained at all, the cells at early stages of apoptosis would be onlyYO-PRO-1 positive, and the cells at later stages would be effectively stained by both probes.

The cell staining procedure. Staining of the cells was carried out in cytometric test tubes 12×75 mm («Beckman Coulter», USA). 5 μL of concentrated (20×) solution of YO-PRO-1 («Invitrogen», USA) was added to 100 μL of the cell suspension ($2–3\times10^6$ cells/mL) to give a final dye concentration of 250 nM. The working solution was prepared ex tempore of stock solution (100 mM in DMSO, 10 μL aliquoted and stored at -20 °C). After that, 10 μL of PI solution («Sigma-Aldrich», USA) were loaded to the samples to give a final concentration of 1 μg/mL. The staining was carried out at room temperature for 15 min in a dark place. Upon completion of incubation, 200 μL of phospate buffered saline (PBS) was added to the samples,

which were then analyzed with a flow cytometer Navios ™ («Beckman Coulter», USA). Not less than 20000 single cells were analyzed in each of the samples.

Analysis of the primary data was performed using the software Kaluza™ («Beckman Coulter», USA). In order to distinguish single cells from aggregates and remove aggregates from the analysis, the following combinations of signals for forward (FS, a quantity proportional to the size of the cells) and side (SS, a quantity characterizing the structure of cells) light scattering were used: the intensity of the peak versus the intensity of the integrated FS or SS signals, as well as the time of flight against the intensity of the integral FS or SS signals.

All assays were performed at least 3 times. Statistical analysis and curve fitting was done with GraphPad Prism 6 (GraphPad Software, La Jolla, CA) using one-way or two-way analysis of variance (ANOVA) where appropriate. Regression analysis was done using four-parameter logistic (sigmoidal) equation, log (concentration) vs response (variable slope). Apoptotic/necrotic difference was calculated using integration (as area between curves) with baseline correction (values are given in percent). $P<0.05$ was considered as significant. Data are expressed as means ± SEM. Error bars illustrate SEM.

Table S-1. The apoptotic/necrotic difference (AND) of the dihydroazetes **2a,b,e,h,k,m,n** and **9a,c,g** exhibited with the THP-1 cell line

Compound	AND	Compound	AND
2a	19.9 ± 1	**2m**	16.1 ± 2.3
2b	9.5 ± 0.5	**2n**	13.5 ± 2.6
2e	8.3 ± 2.4	**9a**	7.7 ± 1.5
2h	2.7 ± 0.9	**9c**	-28.5 ± 2
2k	13.0 ± 2.1	**9g**	-15.1 ± 0.9

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