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The synthesis and antitubercular activity of 4,5-dihydro-1*H*-pyrazole derivatives with a basic epoxybenzo[7,8]oxocine framework

Alena L. Stalinskaya[1], Natalia A. Dengis[2], Vasily S. Vlasenko[2], Ivan V. Kulakov[1]*

[1] *School of Natural Sciences, University of Tyumen, 15a Perekopskaya St., Tyumen 625003, Russia; e-mail: i.v.kulakov@utmn.ru*

[2] *Omsk Agricultural Scientific Center, 26 Koroleva Ave., Omsk 644012, Russia; e-mail: vvs-76@list.ru*

SUPPLEMENTARY INFORMATION

Table of contents

General information

^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX400 (400 and 100 MHz, respectively), Bruker AVANCE 500 (500 and 125 MHz, respectively) and Magritek spinsolve 80 carbon ultra (81 and 20 MHz, respectively) instruments using $CDCl_3$ the internal standard was residual solvent signals (7.26 and 77.0 ppm for ^{1}H and ^{13}C nuclei in $CDCl_3$).

Chromato-mass spectrometric studies were carried out on a chromatograph Chromatec Crystal 5000 with a mass-selective detector in electron ionization mode (70 eV) on a quartz capillary column, 30 m long, 0.25 mm inner diameter, with a film thickness of the stationary phase of 0.25 μm. Splitle input mode was used. Carrier gas discharge 20 ml / min. The velocity of the carrier gas (hydrogen) is 2 ml / min. Evaporator temperature 250 °C, transition chamber temperature 250 °C, ion source temperature 200 °C. The temperature of the column thermostat was changed according to the program: from 100 (5 min delay) to 250 °C (10 min delay) at a rate of 30 °C per minute, to 320 °C (15 min delay) at a rate of 30 °C per minute. The total analysis time was 37 min. The volume of the injected sample is 2 μl. Chromatograms were recorded in TIC mode. The range of mass scanning is 40 - 650 amu.

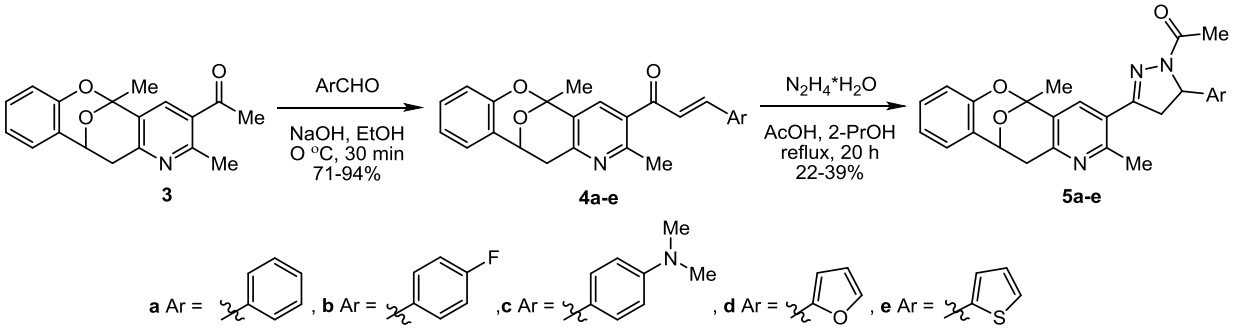
Elemental analysis was performed on a Carlo Erba 1106CHN instrument. Melting points were determined using a Koffler hot bench. Monitoring of the reaction course and the purity of the products was carried out by TLC on Sorbfil plates and visualized using iodine vapor or UV light. The mass spectra were recorded on DFS High Resolution double-focusing magnetic sector GC/MS and on Agilent Technologies 5977E (MSD), 7820A (GC System) GC-MS spectrometer (electron impact energy of 70 eV).

Synthesis of pyridylchalcones 4a–e (general method).

A solution of NaOH (163.0 mg, 4.0 mmol) in EtOH (10 ml) and H_2O (2 ml) was cooled to 5°C. Then (2,5-dimethyl-11,12-dihydro-5*H*-5,11-epoxybenzo[7,8]oxocino[4,3-*b*]pyridin-3-yl)ethan-1-one **3** (1.0 g, 3.0 mmol) was added, and the constantly stirred mixture was treated by dropwise addition of the appropriate aldehyde (4.0 mmol). A precipitate of bisazachalcone **4a–e** formed after 30 min. The mixture was stirred at room temperature for additional 3 hours. The precipitate was filtered, washed with EtOH-H_2O and dried in air. The crude product was purified by recrystallization from 2-PrOH.

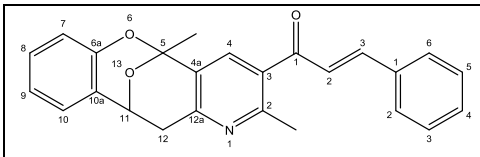
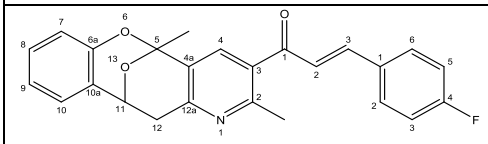
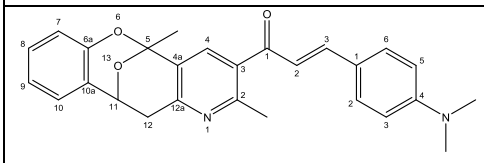
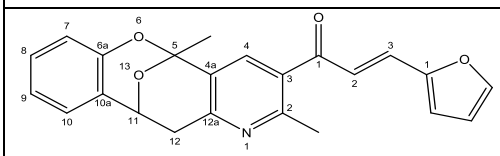
Synthesis of 4,5-dihydro-1*H*-pyrazoles 5a–e (general method).

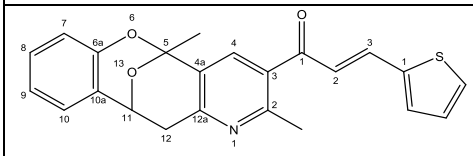
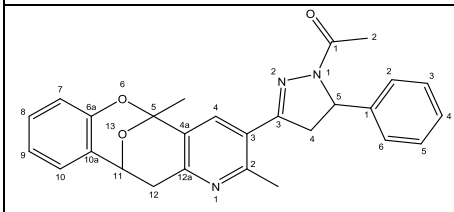
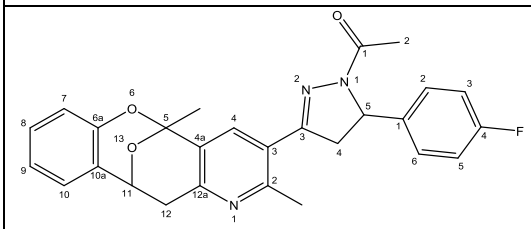
A solution of $N_2H_4 \cdot H_2O$ (0.5 ml, 10.0 mmol) in 2-PrOH was constantly stirred and treated by dropwise addition of a solution of pyridylchalcone **3a**–**e** (1.0 mmol) in AcOH. The mixture was refluxed for 20 hours, then it was cooled and poured onto ice. The obtained precipitate of 4,5-dihydro-1*H*-pyrazole **4a**–**c** was filtered off and washed with H_2O.

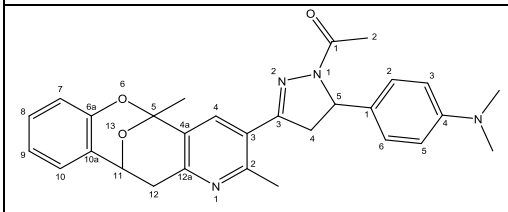
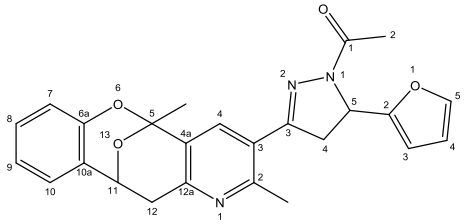
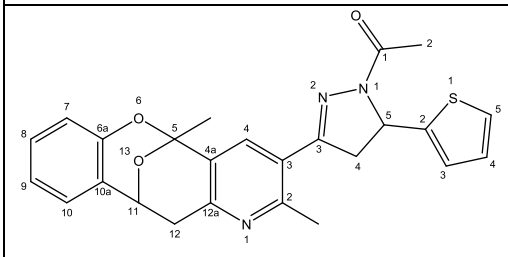


Scheme S1

Spectroscopic and physical data

 Chemical Formula: $C_{25}H_{21}NO_3$ Molecular Weight: 383,4470	**(*E*)-1-(2,5-dimethyl-11,12-dihydro-5*H*-5,11-epoxybenzo[7,8]oxocino[4,3-*b*]pyridin-3-yl)-3-phenylprop-2-en-1-one 4a.** Yield 0.9 g (77%), white fine powder, mp 164-166 °C (2-PrOH). ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.95 (3H, s, 5-CH_3), 2.58 (3H, s, 2-CH_3 Py), 3.09 (1H, d, ^2J = 18.3, H-12a), 3.68 (1H, dd, ^2J = 16.8, ^3J = 6.1, H-12b), 5.43 (1H, d, ^3J = 4.6, H-11), 6.75 (1H, d, *J* = 7.6, H-7), 6.90 (1H, t, *J* = 7.6, H-9), 7.06 – 7.15 (3H, m, 2-CH=, H-8, H-4' Ph), 7.42 – 7.45 (4H, m, 3-CH=, H-10, H-3',5' Ph), 7.55 (2H, d, *J* = 7.6, H-2',6' Ph), 7.82 (1H, s, H-4 Py). ^{13}C NMR (101 MHz, $CDCl_3$), δ, ppm: 23.5 (CH_3), 26.2 (CH_3), 39.5 (CH_2), 69.7, 96.6, 116.9, 121.3, 123.2, 125.8, 125.9, 128.7 (2C), 129.0, 129.2 (3C), 131.3, 133.2, 133.6, 134.3, 146.9, 150.9, 154.2, 157.1, 194.5 (C=O). MS (EI) *m/z* (I_{rel}, %): $[M]^+$ 383.17 (94), 340.13 (68), 207.04 (52), 91.07 (36), 43.10 (100). Found, %: C, 78.54; H, 5.30; N, 3.82. $C_{25}H_{21}NO_3$. Calculated, %: C, 78.31; H, 5.52; N, 3.65.
 Chemical Formula: $C_{25}H_{20}FNO_3$ Molecular Weight: 401,4374	**(*E*)-1-(2,5-dimethyl-11,12-dihydro-5*H*-5,11-epoxybenzo[7,8]oxocino[4,3-*b*]pyridin-3-yl)-3-(4-fluorophenyl)prop-2-en-1-one 4b.** Yield 1.0 g (86%), white fine powder, mp 183-185 °C (2-PrOH). ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.95 (3H, s, 5-CH_3), 2.57 (3H, s, 2-CH_3 Py), 3.08 (1H, d, ^2J = 18.3, H-12a), 3.68 (1H, dd, ^2J = 16.8, ^3J = 6.1, H-12b), 5.43 (1H, d, ^3J = 6.1 Hz, H-11), 6.74 (1H, d, *J* = 7.6, H-7), 6.90 (1H, t, *J* = 6.9, H-9), 7.00 (1H, d, *J* = 16.8, 2-CH=), 7.06 – 7.13 (4H, m, H-8,10, H-3',5' Ar), 7.41 (1H, d, *J* = 15.3, 3-CH=), 7.54 (2H, m, H-2',6' Ar), 7.81 (1H, s, H-4 Py). ^{13}C NMR (101 MHz, $CDCl_3$), δ, ppm: 23.6 (CH_3), 26.3 (CH_3), 39.5 (CH_2), 69.7, 96.6, 116.5 (d, $^2J_{C\text{-}F}$ = 22,1 Hz), 116.9, 121.3, 123.2, 125.5, 125.8, 129.0, 129.3, 130.5 (2C), 130.6 (d, $^3J_{C\text{-}F}$ = 8.6 Hz), 130.7, 133.2, 133.6, 145.5, 150.9, 154.3, 157.1, 164.5 (d, $^1J_{C\text{-}F}$ = 253.1 Hz), 194.2 (C=O). MS (EI) *m/z* (I_{rel}, %): $[M]^+$ 401.09 (51), 358.09 (39), 206.99 (54), 43.04 (100). Found, %: C, 74.68; H, 5.24; N, 3.27. $C_{25}H_{20}FNO_3$. Calculated, %: C, 74.80; H, 5.02; N, 3.49.
 Chemical Formula: $C_{27}H_{26}N_2O_3$ Molecular Weight: 426,5160	**(*E*)-1-(2,5-dimethyl-11,12-dihydro-5*H*-5,11-epoxybenzo[7,8]oxocino[4,3-*b*]pyridin-3-yl)-3-(4-(dimethylamino)phenyl)prop-2-en-1-one 4c.** Yield 1.0 g (79%), bright-orange fine powder, mp 173-175 °C (2-PrOH). ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.94 (3H, s, 5-CH_3), 2.55 (s, 3H, 2-CH_3 Py), 3.04 (6H, s, 2 NCH_3), 3.10 (1H, d, *J* = 16.8, H-12a), 3.67 (1H, dd, ^2J = 16.8, ^3J = 4.6, H-12b), 5.42 (1H, d, *J* = 6.1, H-11), 6.67 (2H, d, *J* = 7.6, H-3',5' Ar), 6.74 (1H, d, *J* = 9.2, H-7), 6.84 (1H, d, *J* = 15.3, 2-CH=), 6.91 (1H, d, *J* = 7.6, H-9), 7.06 (1H, d, *J* = 7.6, H-10), 7.12 (1H, t, *J* = 7.6, H-8), 7.32 (1H, d, *J* = 16.7, 3-CH=), 7.42 (2H, d, *J* = 9.0, H-2',6' Ar), 7.76 (1H, s, H-4 Py). ^{13}C NMR (101 MHz, $CDCl_3$), δ, ppm: 23.3 (CH_3), 26.2 (CH_3), 39.5 (CH_2), 40.2 (2C, NCH_3), 69.7, 96.6, 111.9 (2C), 116.9, 120.9, 121.2, 121.7, 123.2, 125.8, 128.9, 129.0, 130.8 (2C), 133.4, 134.1, 148.4, 151.0, 152.5, 153.3, 156.7, 194.9 (C=O). MS (EI) *m/z* (I_{rel}, %): $[M]^+$ 426.27 (12), 281.02 (14), 206.98 (45), 73.02 (21), 43.06 (100). Found, %: C, 76.23; H, 6.30; N, 6.39. $C_{27}H_{26}N_2O_3$. Calculated, %: C, 76.03; H, 6.14; N, 6.57.
 Chemical Formula: $C_{23}H_{19}NO_4$ Molecular Weight: 373,4080	**(*E*)-1-(2,5-dimethyl-11,12-dihydro-5*H*-5,11-epoxybenzo[7,8]oxocino[4,3-*b*]pyridin-3-yl)-3-(furan-2-yl)prop-2-en-1-one 4d.** Yield 0.8 g (71%), bright-yellow needles, mp 145-147 °C (2-PrOH). ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.92 (3H, s, 5-CH_3), 2.55 (3H, s, 2-CH_3 Py), 3.04 (1H, d, *J* = 16.8, H-12a), 3.63 (dd, ^2J = 16.8, ^3J = 4.6, 1H, H-12b), 5.38 (1H, d, ^3J = 4.6, H-11), 6.48 (1H, br. s,

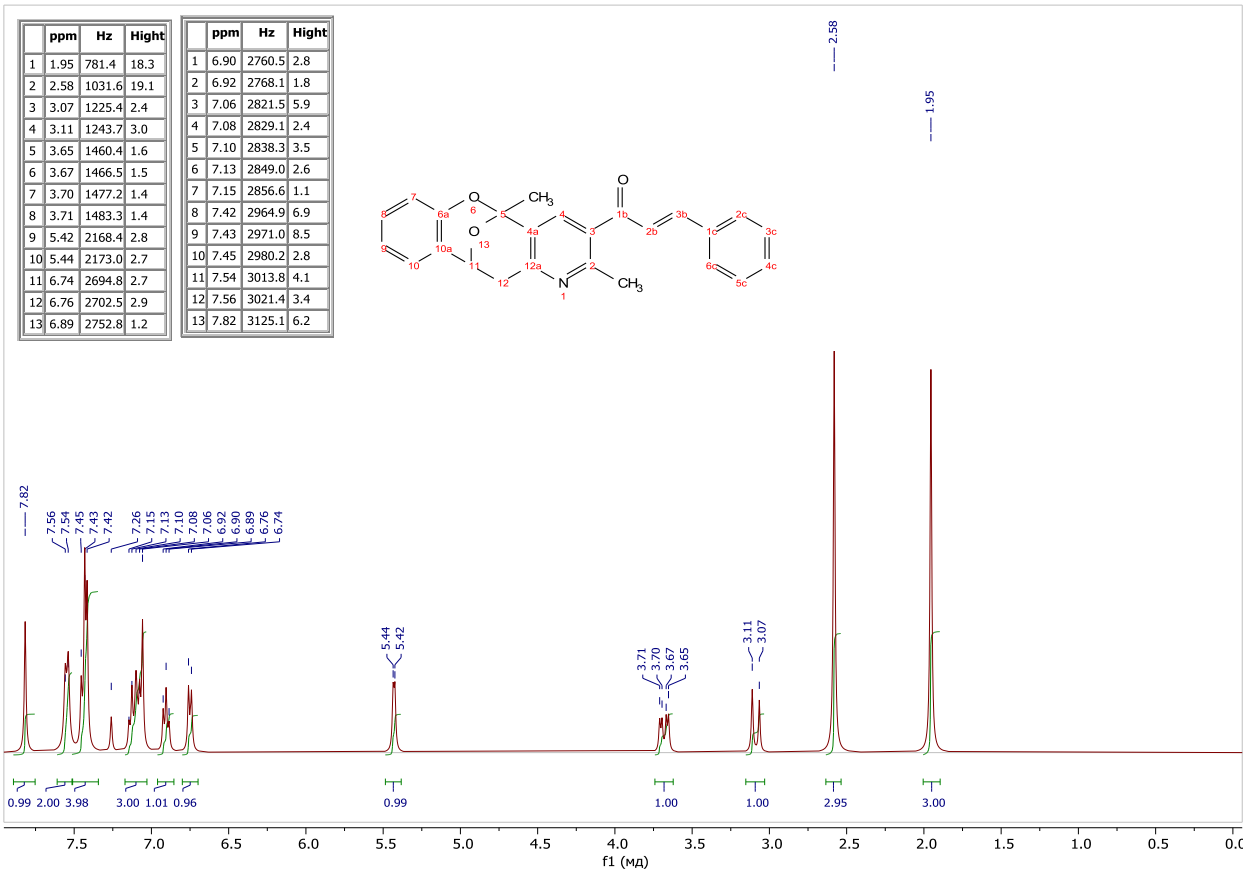
	H-4 furan), 6.67 (1H, d, *J* = 4.6, H-3 furan), 6.71 (1H, d, *J* = 7.6, H-7), 6.86 (1H, t, *J* = 7.6, H-9), 6.96 (d, *J* = 15.3, 1H, 2-CH=), 7.02 (1H, d, *J* = 9.2, H-10), 7.08 (1H, t, *J* = 7.6, H-8), 7.22 (1H, d, *J* = 15.2, 3-CH=), 7.51 (1H, br. s, H-5 furan), 7.80 (1H, s, H-4 Py). ^{13}C NMR (100 MHz, $CDCl_3$), δ, ppm: 23.6 (CH_3), 26.2 (CH_3), 39.5 (CH_2), 69.7, 96.6, 113.0, 116.9, 117.4, 121.3, 122.7, 123.1, 125.8, 128.9, 129.2, 132.1, 133.3, 133.6, 145.8, 150.9, 151.0, 154.1, 157.3, 193.4 (C=O). MS (EI) *m/z* (I_{rel}, %): $[M]^+$ 373.15 (100), 358.11 (12), 344.11 (23), 330.07 (67). Found, %: C, 73.74; H, 5.31; N, 3.90. $C_{23}H_{19}NO_4$. Calculated, %: C, 73.98; H, 5.13; N, 3.75.
 Chemical Formula: $C_{23}H_{19}NO_3S$ Molecular Weight: 389,4690	**(*E*)-1-(2,5-dimethyl-11,12-dihydro-5*H*-5,11-epoxybenzo[7,8]oxocino[4,3-*b*]pyridin-3-yl)-3-(thiophen-2-yl)prop-2-en-1-one 4e.** Yield 1.1 g (94%), light-yellow fine powder, mp 172-174 °C (2-PrOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ, ppm (*J*, Hz): 1.95 (3H, s, 5-CH_3), 2.57 (3H, s, 2-CH_3 Py), 3.08 (1H, d, ^2J = 17.1 Hz, H-12a), 3.67 (1H, dd, ^2J = 17.4, ^3J = 5.8, H-12b), 5.42 (1H, d, ^3J = 5.5, H-11), 6.75 (1H, d, *J* = 8.0, H-7), 6.86 (1H, d, *J* = 15.2, 2-CH=), 6.91 (1H, t, *J* = 8.0, H-9), 7.05 – 7.12 (3H, m, H-8,10, H-4 thiophene), 7.30 (1H, d, *J* = 3.7, H-3 thiophene), 7.47 (1H, d, *J* = 4.8, H-5 thiophene), 7.57 (1H, d, *J* = 15.6, 3-CH=), 7.80 (1H, s, H-4 Py). ^{13}C NMR (100 MHz, $CDCl_3$) δ, ppm: 23.5 (CH_3), 26.3 (CH_3), 39.5 (CH_2), 69.7, 96.6, 116.9, 121.3, 123.2, 124.6, 125.8, 128.7, 129.0, 129.3, 130.1, 132.8, 133.3, 133.5, 139.1, 139.7, 150.9, 154.2, 157.1, 193.8 (C=O). MS (EI) *m/z* (I_{rel}, %): $[M]^+$ 389.08 (100), 346.06 (59), 136.95 (18), 108.93 (20), 43.03 (33). Found, %: C, 70.77; H, 4.72; N, 3.45. $C_{23}H_{19}NO_3S$. Calculated, %: C, 70.93; H, 4.92; N, 3.60.
 Chemical Formula: $C_{27}H_{25}N_3O_3$ Molecular Weight: 439,5150	**1-(3-(2,5-dimethyl-11,12-dihydro-5*H*-5,11-epoxybenzo[7,8]oxocino[4,3-*b*]pyridin-3-yl)-5-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)ethan-1-one 5a.** Yield 145 mg (33%), light-yellow needles, mp 235-238 °C (2-PrOH). ^{1}H NMR (81 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.90 (3H, s, 5-CH_3), 2.38 (3H, s, 2-CH_3 Py), 2.81 (3H, s, $COCH_3$), 3.07 (1H, dd, ^2J = 17.5, ^3J = 4.7, H-4a pyrazole), 3.10 (1H, d, ^2J = 17.2, H-12a), 3.59 (1H, dd, ^2J = 16.8, ^3J = 5.3, H-12b), 3.86 (1H, dd, ^2J = 17.4, ^3J = 11.4, H-4b pyrazole), 5.39 (d, ^3J = 5.8, 1H, H-11), 5.55 (1H, dd, ^3J = 11.7, ^3J = 5.1, H-5 pyrazole), 6.53 – 7.29 (9H, m, H Ar), 7.61 (1H, s, H-4 Py). ^{13}C NMR (20 MHz, $CDCl_3$), δ, ppm: 22.1 (CH_3), 25.4 (CH_3), 26.2 (CH_3), 39.3 (CH_2), 44.3 (CH_2), 59.4, 69.6, 96.5, 116.8, 121.2, 123.1, 124.9, 125.5 (2C), 125.7, 127.9, 128.8, 129.1 (2C), 129.6, 133.5, 141.6, 150.8, 152.4 (2C), 158.0, 169.1 (C=O). MS (EI) *m/z* (I_{rel}, %): $[M]^+$ 439.25 (60), 396.24 (40), 354.21 (12), 207.11 (16), 91.07 (20), 43.10 (100). Found, %: C, 73.95; H, 5.91; N, 9.40. $C_{27}H_{25}N_3O_3$. Calculated, %: C, 73.79; H, 5.73; N, 9.56.
 Chemical Formula: $C_{27}H_{24}FN_3O_3$ Molecular Weight: 457,5054	**1-(3-(2,5-dimethyl-11,12-dihydro-5*H*-5,11-epoxybenzo[7,8]oxocino[4,3-*b*]pyridin-3-yl)-5-(4-fluorophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)ethan-1-one 5b.** Yield 178 mg (39%), white needles, mp 226-228 °C (2-PrOH). ^{1}H NMR (500 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.93 (3H, s, 5-CH_3), 2.38 (3H, s, 2-CH_3 Py), 2.87 (3H, s, $COCH_3$), 3.16 (1H, d, ^2J = 17.6, H-12a oxocine), 3.17 (1H, dd, ^2J = 17.6, ^3J = 4.6, H-4a pyrazole), 3.69 (1H, dd, ^2J = 17.5, ^3J = 5.6, H-12b oxocine), 3.83 (1H, dd, ^2J = 17.5, ^3J = 11.9, H-4b pyrazole), 5.41 (1H, d, ^3J = 5.5, H-11 oxocine), 5.55 (1H, dd, ^3J = 12.0, ^3J = 5.0, H-5 pyrazole), 6.71 (1H, t, *J* = 7.8, H Ar), 6.88 (1H, t, *J* = 7.5, H Ar), 6.99 – 7.10 (4H, m, H Ar), 7.14 – 7.23 (2H, m, H Ar), 7.66 (1H, s, H-4 Py). ^{13}C NMR (126 MHz, $CDCl_3$), δ, ppm: 22.0 (CH_3), 25.3 (CH_3), 26.1 (CH_3), 38.6 (CH_2), 44.0 (CH_2), 58.7, 69.2, 96.1, 115.9 (d, 2C, $^2J_{C-F}$ = 21.8 Hz), 116.7, 121.3, 122.8, 125.3, 125.7, 127.2 (d, 2C, $^3J_{C-F}$ = 8.2 Hz), 128.8,

	130.2, 134.1, 137.2, 150.5, 151.5, 152.0, 157.5, 162.2 (d, $^{1}J_{C\text{-}F}$ = 246.6 Hz), 169.0 (C=O). MS (EI) *m/z* (I_{rel}, %): $[M]^+$ 457.18 (23), 414.11 (25), 281.07 (10), 207.03 (25), 73.03 (12), 43.05 (100). Found, %: C, 70.70; H, 5.43; N, 9.35. $C_{27}H_{24}FN_3O_3$. Calculated, %: C, 70.88; H, 5.29; N, 9.18.
 Chemical Formula: $C_{29}H_{30}N_4O_3$ Molecular Weight: 482,5840	**1-(3-(2,5-dimethyl-11,12-dihydro-5*H*-5,11-epoxybenzo-[7,8]oxocino[4,3-*b*]pyridin-3-yl)-5-(4-(dimethylamino)-phenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)ethan-1-one 5c.** Yield 140 mg (29%), bright-beige needles, mp 205-207 °C (SiO_2, EtOAc-hexane 1:3). ^{1}H NMR (81 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.91 (s, 3H, 5-CH_3), 2.36 (s, 3H, 2-CH_3 Py), 2.81 (s, 3H, $COCH_3$), 2.91 (s, 6H, 4-N(CH_3)$_2$), 2.99 – 3.37 (2H, m, H-12a oxocine, H-4a pyrazole), 3.67 (2H, dd, ^{2}J = 16.8, ^{3}J = 5.0, H-12b oxocine, H-4b pyrazole), 5.41 (1H, d, ^{3}J = 5.0, H-11 oxocine), 5.48 (1H, dd, ^{3}J = 11.8, ^{3}J = 5.5, H-5 pyrazole), 6.49 – 7.21 (8H, m, H Ar), 7.63 (1H, s, H-4 Py). ^{13}C NMR (20 MHz, $CDCl_3$), δ, ppm: 22.0 (CH_3), 25.3 (CH_3), 26.3 (CH_3), 39.2 (CH_2), 40.5 (2C, NCH_3), 44.1 (CH_2), 58.8, 69.6, 96.4, 112.7 (2C), 116.7, 121.1, 123.1, 124.9, 125.1, 125.6, 126.4 (2C), 128.7, 129.3, 133.3, 148.4, 150.1, 150.7, 152.2, 157.8, 168.8 (C=O). MS (EI) *m/z* (I_{rel}, %): $[M]^+$ 482.27, 207.02, 73.01, 43.03. Found, %: C, 72.34; H, 6.52; N, 11.38. $C_{29}H_{30}N_4O_3$. Calculated, %: C, 72.18; H, 6.27; N, 11.61.
 Chemical Formula: $C_{25}H_{23}N_3O_4$ Molecular Weight: 429,4760	**1-(3-(2,5-dimethyl-11,12-dihydro-5*H*-5,11-epoxybenzo[7,8]oxocino[4,3-*b*]pyridin-3-yl)-5-(furan-2-yl)-4,5-dihydro-1*H*-pyrazol-1-yl)ethan-1-one 5d.** Yield 94 mg (22%), light-yellow needles, mp 189-191 °C (SiO_2, EtOAc-hexane 1:3). ^{1}H NMR (81 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 2.03 (3H, s, 5-CH_3), 2.42 (3H, s, 2-CH_3 Py), 2.86 (3H, s, $COCH_3$), 3.12 (1H, d, ^{2}J = 17.0, H-12a oxocine), 3.53 – 3.90 (3H, dd, ^{2}J = 17.4, ^{3}J = 6.5, H-4a pyrazole, dd, ^{2}J = 17.4, ^{3}J = 11.5, H-4b pyrazole, dd, ^{2}J = 17.0, ^{3}J = 5.5, H-12b oxocine), 5.48 (1H, d, ^{3}J = 5.1, H-11 oxocine), 5.71 (1H, dd, ^{3}J = 10.3, ^{3}J = 6.3, H-5 pyrazole), 6.43 (2H, br. s, H-3,4 furan), 6.76-6.94 (2H, m, H-7,9 oxocine), 7.01-7.20 (2H,m, H-8,10 oxocine), 7.40 (1H, br. s, H-5 furan), 7.75 (1H, s, H-4 Py). ^{13}C NMR (20 MHz, $CDCl_3$), δ, ppm: 22.1 (CH_3), 26.2 (CH_3), 39.3 (CH_2), 40.1 (CH_2), 52.8, 60.4, 69.6, 96.5, 107.9, 110.7, 116.8, 121.2, 123.2, 124.9, 125.7, 128.8, 129.5, 133.5, 142.1, 150.8, 151.8, 152.5 (2C), 157.9, 169.1 (C=O). MS (EI) *m/z* (I_{rel}, %): $[M]^+$ 429.17 (100), 386.12 (79), 344.10 (14), 43.01 (79). Found, %: C, 69.77; H, 5.59; N, 9.91. $C_{25}H_{23}N_3O_4$. Calculated, %: C, 69.92; H, 5.40; N, 9.78.
 Chemical Formula: $C_{25}H_{23}N_3O_3S$ Molecular Weight: 445,5370	**1-(3-(2,5-dimethyl-11,12-dihydro-5*H*-5,11-epoxybenzo[7,8]oxocino[4,3-*b*]pyridin-3-yl)-5-(thiophen-2-yl)-4,5-dihydro-1*H*-pyrazol-1-yl)ethan-1-one 5e.** Yield 160 mg (36%), white needles, mp 190-192 °C (SiO_2, EtOAc-hexane 1:3). ^{1}H NMR (81 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.94 (3H, s, 5-CH_3), 2.37 (3H, s, 2-CH_3 Py), 2.79 (3H, s, $COCH_3$), 3.07 (1H, d, ^{2}J = 17.4, H-12a oxocine), 3.20 – 4.09 (3H, 2 dd, ^{2}J = 17.5, ^{3}J = 4.5, H-12b oxocine, H-4a pyrazole, dd, ^{2}J = 17.5, ^{2}J = 11.2, H-4b pyrazole), 5.41 (1H, d, ^{3}J = 4.3, H-11 oxocine), 5.88 (1H, dd, ^{3}J = 11.1, ^{3}J = 4.4, H-5 pyrazole), 6.72 (1H, dd, ^{3}J = 8.2, ^{4}J = 1.6, H-7 oxocine), 6.81 – 7.05 (4H, m, H-3,4 thiophene, H-8,9 oxocine), 7.09-7.26 (2H, H-5 thiophene, H-10 oxocine), 7.65 (1H, s, H-4 Py). ^{13}C NMR (20 MHz, $CDCl_3$), δ, ppm: 22.1 (CH_3), 26.3 (2C, CH_3), 39.4 (CH_2), 44.1 (CH_2), 54.9, 69.7, 96.5, 116.9, 121.3, 123.2, 124.9 (3C), 125.8, 127.0, 128.9, 129.6, 133.4, 144.1, 150.8, 152.3, 152.6, 158.0, 169.1 (C=O). MS (EI) *m/z* (I_{rel}, %): $[M]^+$ 445.23 (82), 402.19 (68), 360.18 (18), 43.05 (100). Found, %: C, 67.59; H, 5.42; N, 9.21. $C_{25}H_{23}N_3O_3S$. Calculated, %: C, 67.40; H, 5.20; N, 9.43.

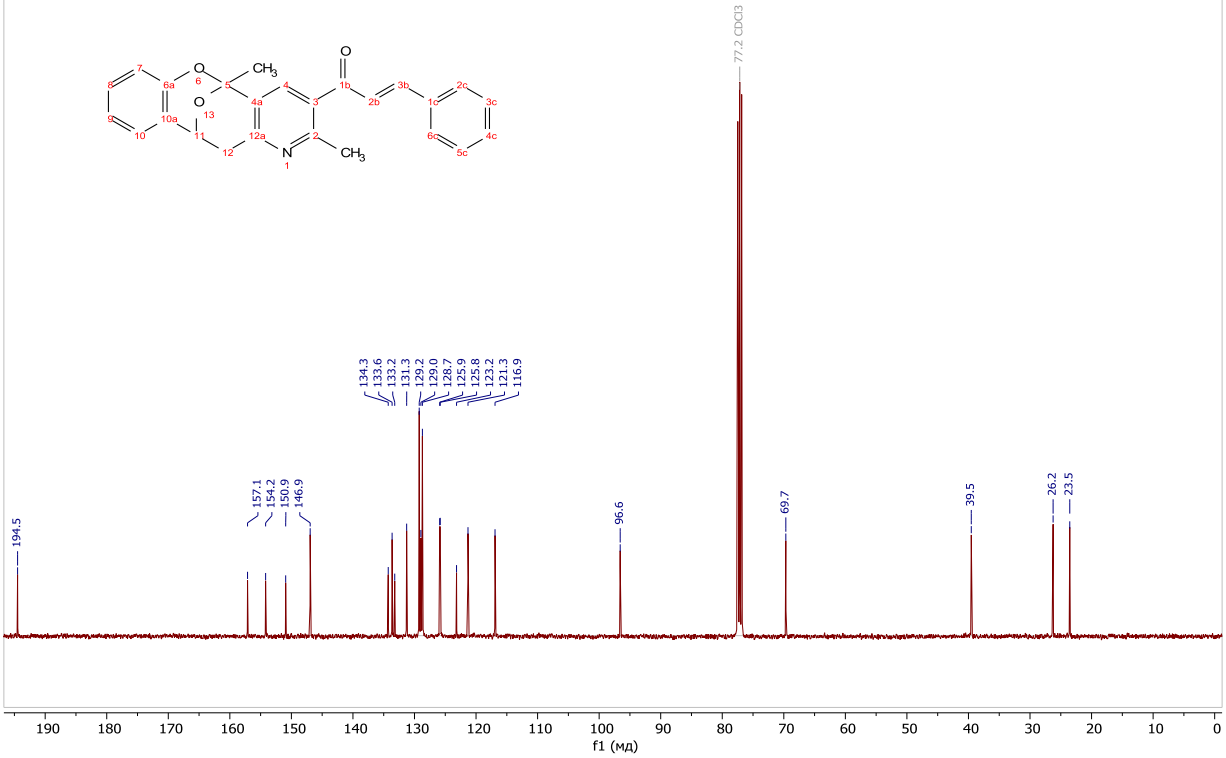
Copies of ^{1}H and ^{13}C NMR Spectra

	ppm	Hz	Hight
1	1.95	781.4	18.3
2	2.58	1031.6	19.1
3	3.07	1225.4	2.4
4	3.11	1243.7	3.0
5	3.65	1460.4	1.6
6	3.67	1466.5	1.5
7	3.70	1477.2	1.4
8	3.71	1483.3	1.4
9	5.42	2168.4	2.8
10	5.44	2173.0	2.7
11	6.74	2694.8	2.7
12	6.76	2702.5	2.9
13	6.89	2752.8	1.2

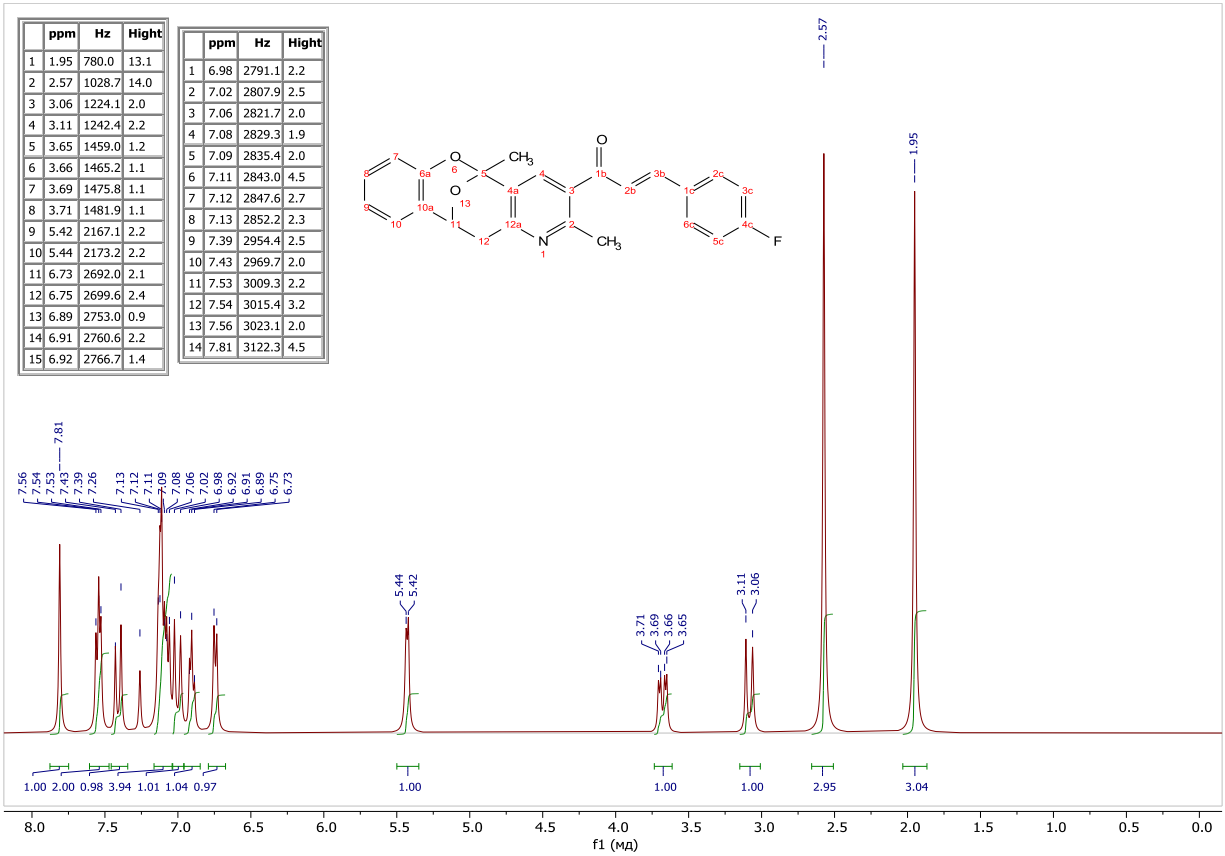
	ppm	Hz	Hight
1	6.90	2760.5	2.8
2	6.92	2768.1	1.8
3	7.06	2821.5	5.9
4	7.08	2829.1	2.4
5	7.10	2838.3	3.5
6	7.13	2849.0	2.6
7	7.15	2856.6	1.1
8	7.42	2964.9	6.9
9	7.43	2971.0	8.5
10	7.45	2980.2	2.8
11	7.54	3013.8	4.1
12	7.56	3021.4	3.4
13	7.82	3125.1	6.2



^{13}C NMR (101 MHz, $CDCl_3$) δ 194.5, 157.1, 154.2, 150.9, 146.9, 134.3, 133.6, 133.2, 131.3, 129.2, 129.0, 128.7, 125.9, 125.8, 123.2, 121.3, 116.9, 96.6, 69.7, 39.5, 26.2, 23.5.

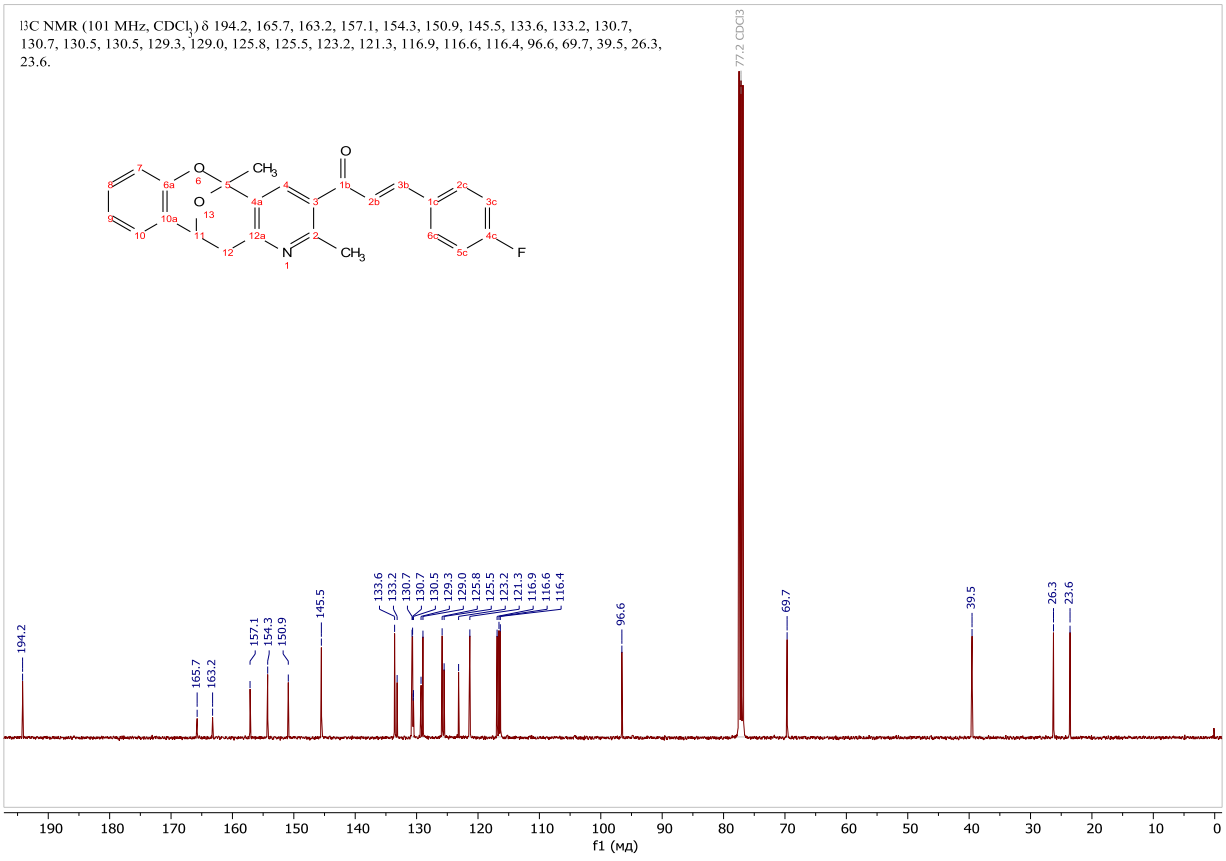


^{1}H (400 MHz, $CDCl_3$) and ^{13}C (100 MHz, $CDCl_3$) NMR Spectra of **4a**



	ppm	Hz	Hight
1	1.95	780.0	13.1
2	2.57	1028.7	14.0
3	3.06	1224.1	2.0
4	3.11	1242.4	2.2
5	3.65	1459.0	1.2
6	3.66	1465.2	1.1
7	3.69	1475.8	1.1
8	3.71	1481.9	1.1
9	5.42	2167.1	2.2
10	5.44	2173.2	2.2
11	6.73	2692.0	2.1
12	6.75	2699.6	2.4
13	6.89	2753.0	0.9
14	6.91	2760.6	2.2
15	6.92	2766.7	1.4

	ppm	Hz	Hight
1	6.98	2791.1	2.2
2	7.02	2807.9	2.5
3	7.06	2821.7	2.0
4	7.08	2829.3	1.9
5	7.09	2835.4	2.0
6	7.11	2843.0	4.5
7	7.12	2847.6	2.7
8	7.13	2852.2	2.3
9	7.39	2954.4	2.5
10	7.43	2969.7	2.0
11	7.53	3009.3	2.2
12	7.54	3015.4	3.2
13	7.56	3023.1	2.0
14	7.81	3122.3	4.5

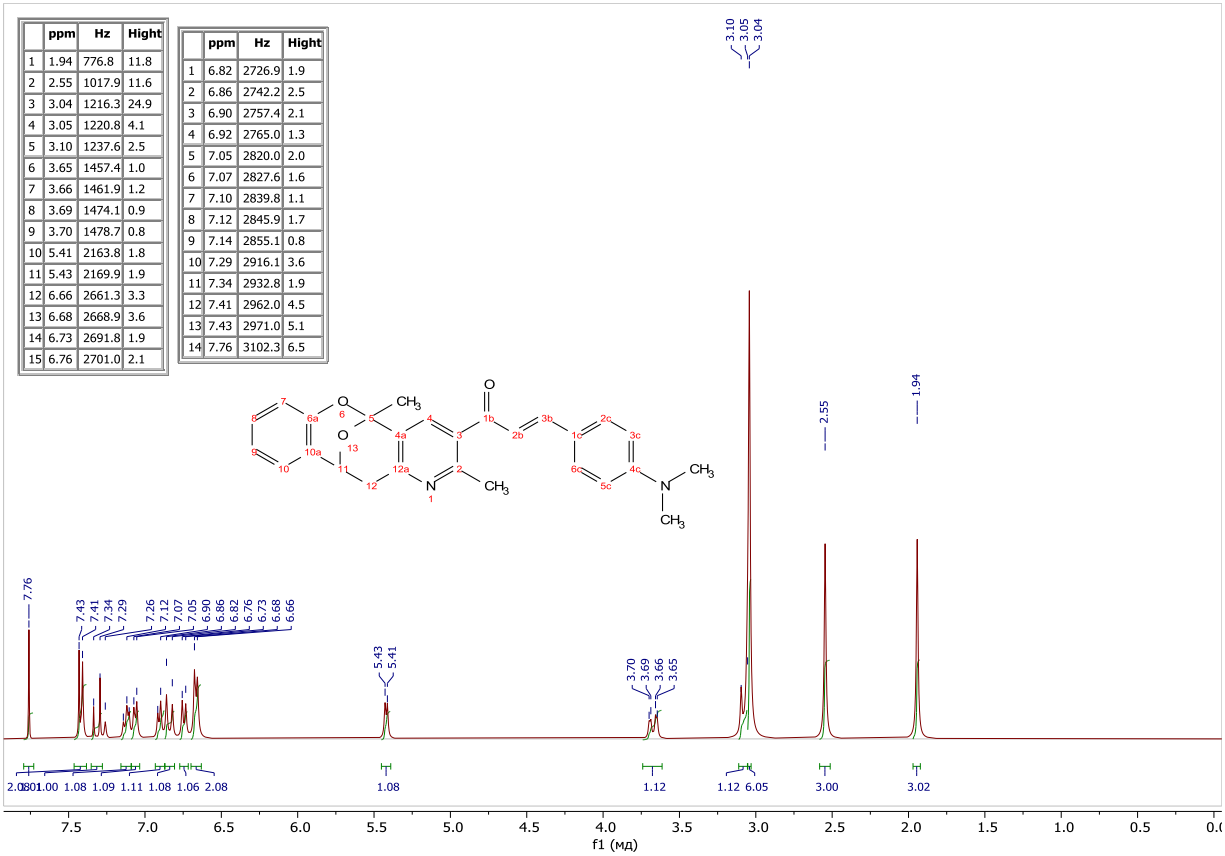


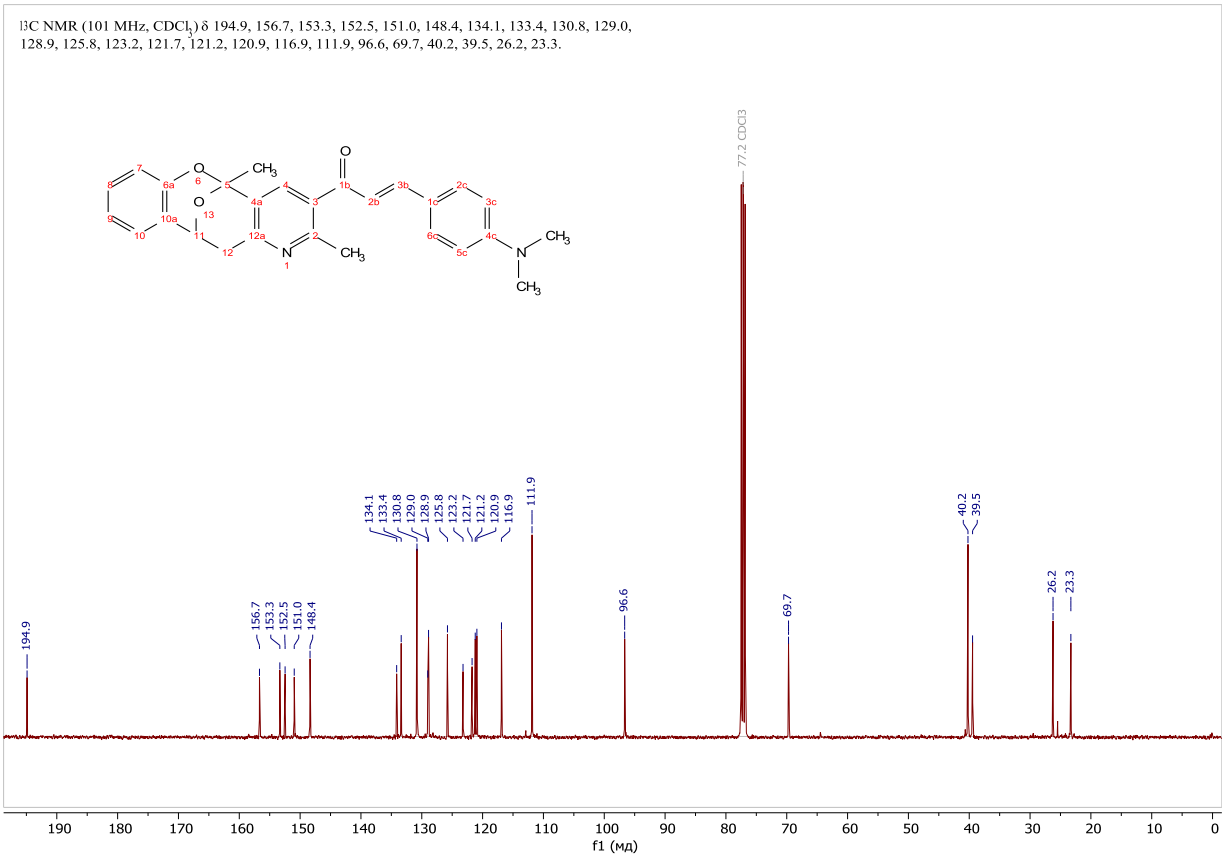
^{13}C NMR (101 MHz, $CDCl_3$) δ 194.2, 165.7, 163.2, 157.1, 154.3, 150.9, 145.5, 133.6, 133.2, 130.7, 130.7, 130.5, 130.5, 129.3, 129.0, 125.8, 125.5, 123.2, 121.3, 116.9, 116.6, 116.4, 96.6, 69.7, 39.5, 26.3, 23.6.

^{1}H (500 MHz, $CDCl_3$) and ^{13}C (126 MHz, $CDCl_3$) NMR Spectra of **4b**

	ppm	Hz	Hight
1	1.94	776.8	11.8
2	2.55	1017.9	11.6
3	3.04	1216.3	24.9
4	3.05	1220.8	4.1
5	3.10	1237.6	2.5
6	3.65	1457.4	1.0
7	3.66	1461.9	1.2
8	3.69	1474.1	0.9
9	3.70	1478.7	0.8
10	5.41	2163.8	1.8
11	5.43	2169.9	1.9
12	6.66	2661.3	3.3
13	6.68	2668.9	3.6
14	6.73	2691.8	1.9
15	6.76	2701.0	2.1

	ppm	Hz	Hight
1	6.82	2726.9	1.9
2	6.86	2742.2	2.5
3	6.90	2757.4	2.1
4	6.92	2765.0	1.3
5	7.05	2820.0	2.0
6	7.07	2827.6	1.6
7	7.10	2839.8	1.1
8	7.12	2845.9	1.7
9	7.14	2855.1	0.8
10	7.29	2916.1	3.6
11	7.34	2932.8	1.9
12	7.41	2962.0	4.5
13	7.43	2971.0	5.1
14	7.76	3102.3	6.5

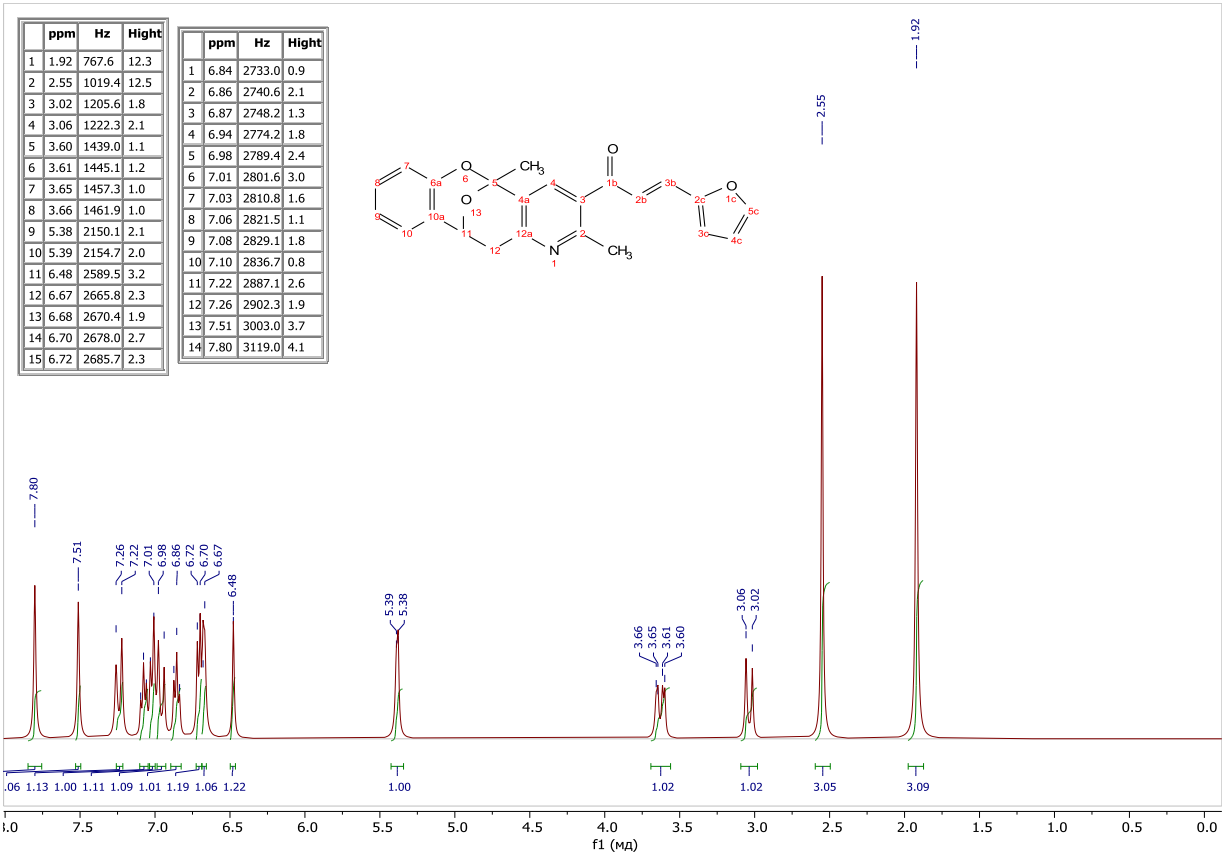


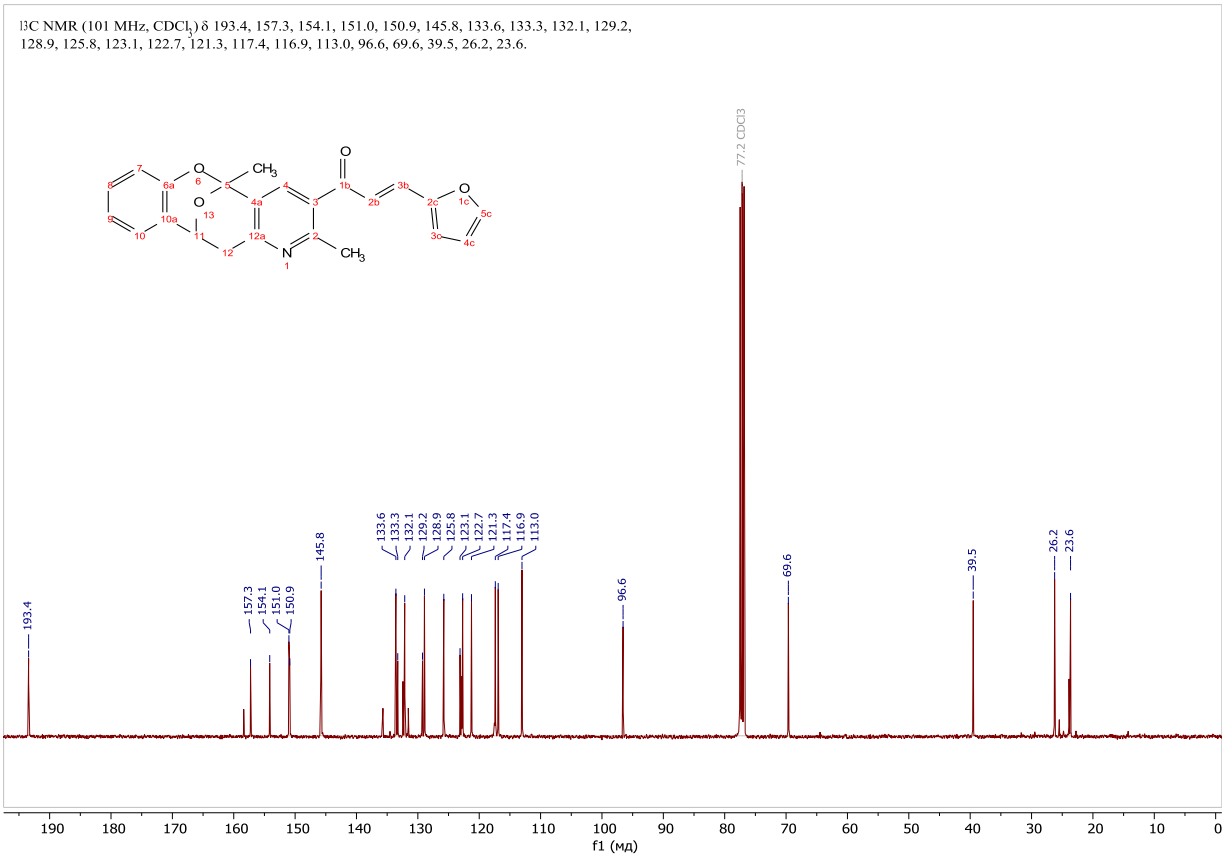


^{1}H (400 MHz, $CDCl_3$) and ^{13}C (100 MHz, $CDCl_3$) NMR Spectra of **4c**

	ppm	Hz	Hight
1	1.92	767.6	12.3
2	2.55	1019.4	12.5
3	3.02	1205.6	1.8
4	3.06	1222.3	2.1
5	3.60	1439.0	1.1
6	3.61	1445.1	1.2
7	3.65	1457.3	1.0
8	3.66	1461.9	1.0
9	5.38	2150.1	2.1
10	5.39	2154.7	2.0
11	6.48	2589.5	3.2
12	6.67	2665.8	2.3
13	6.68	2670.4	1.9
14	6.70	2678.0	2.7
15	6.72	2685.7	2.3

	ppm	Hz	Hight
1	6.84	2733.0	0.9
2	6.86	2740.6	2.1
3	6.87	2748.2	1.3
4	6.94	2774.2	1.8
5	6.98	2789.4	2.4
6	7.01	2801.6	3.0
7	7.03	2810.8	1.6
8	7.06	2821.5	1.1
9	7.08	2829.1	1.8
10	7.10	2836.7	0.8
11	7.22	2887.1	2.6
12	7.26	2902.3	1.9
13	7.51	3003.0	3.7
14	7.80	3119.0	4.1

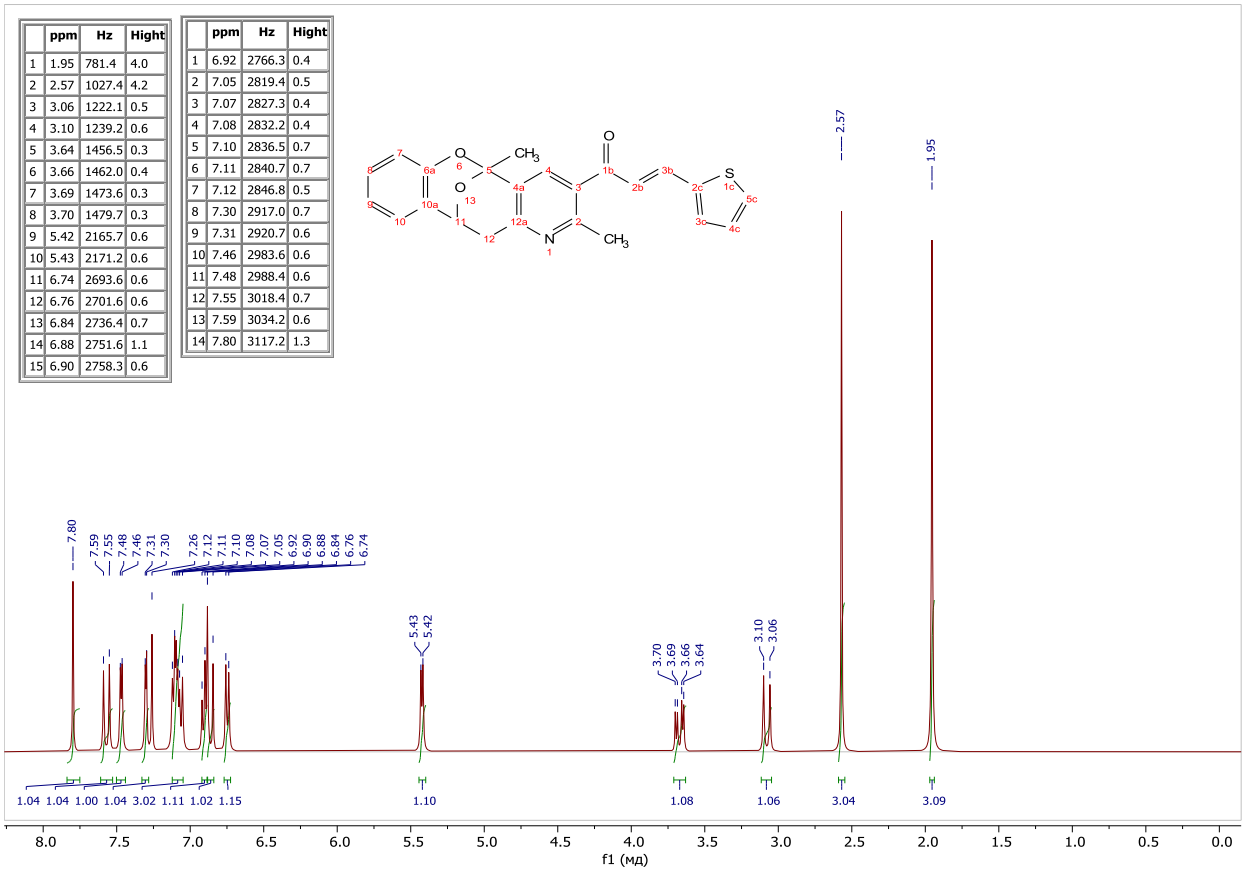


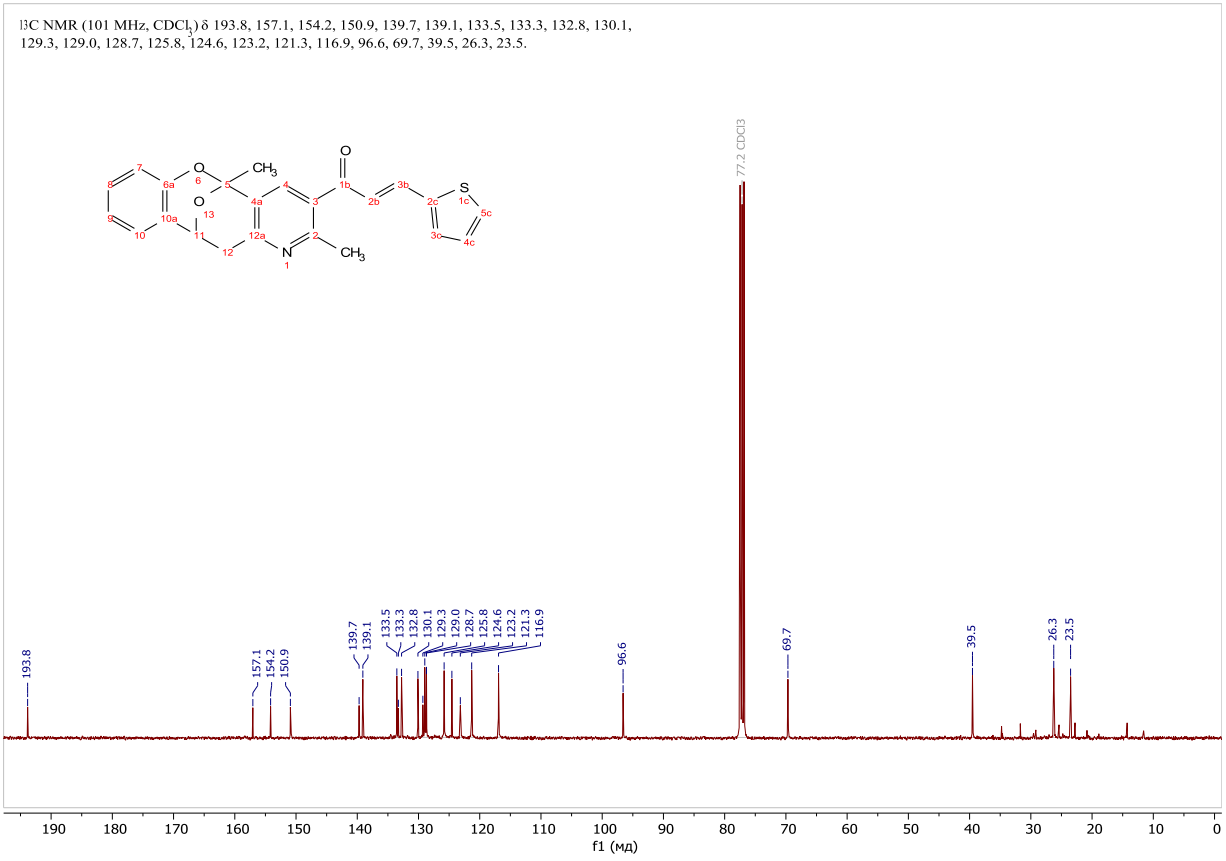


^{1}H (400 MHz, $CDCl_3$) and ^{13}C (100 MHz, $CDCl_3$) NMR Spectra of **4d**

	ppm	Hz	Hight
1	1.95	781.4	4.0
2	2.57	1027.4	4.2
3	3.06	1222.1	0.5
4	3.10	1239.2	0.6
5	3.64	1456.5	0.3
6	3.66	1462.0	0.4
7	3.69	1473.6	0.3
8	3.70	1479.7	0.3
9	5.42	2165.7	0.6
10	5.43	2171.2	0.6
11	6.74	2693.6	0.6
12	6.76	2701.6	0.6
13	6.84	2736.4	0.7
14	6.88	2751.6	1.1
15	6.90	2758.3	0.6

	ppm	Hz	Hight
1	6.92	2766.3	0.4
2	7.05	2819.4	0.5
3	7.07	2827.3	0.4
4	7.08	2832.2	0.4
5	7.10	2836.5	0.7
6	7.11	2840.7	0.7
7	7.12	2846.8	0.5
8	7.30	2917.0	0.7
9	7.31	2920.7	0.6
10	7.46	2983.6	0.6
11	7.48	2988.4	0.6
12	7.55	3018.4	0.7
13	7.59	3034.2	0.6
14	7.80	3117.2	1.3





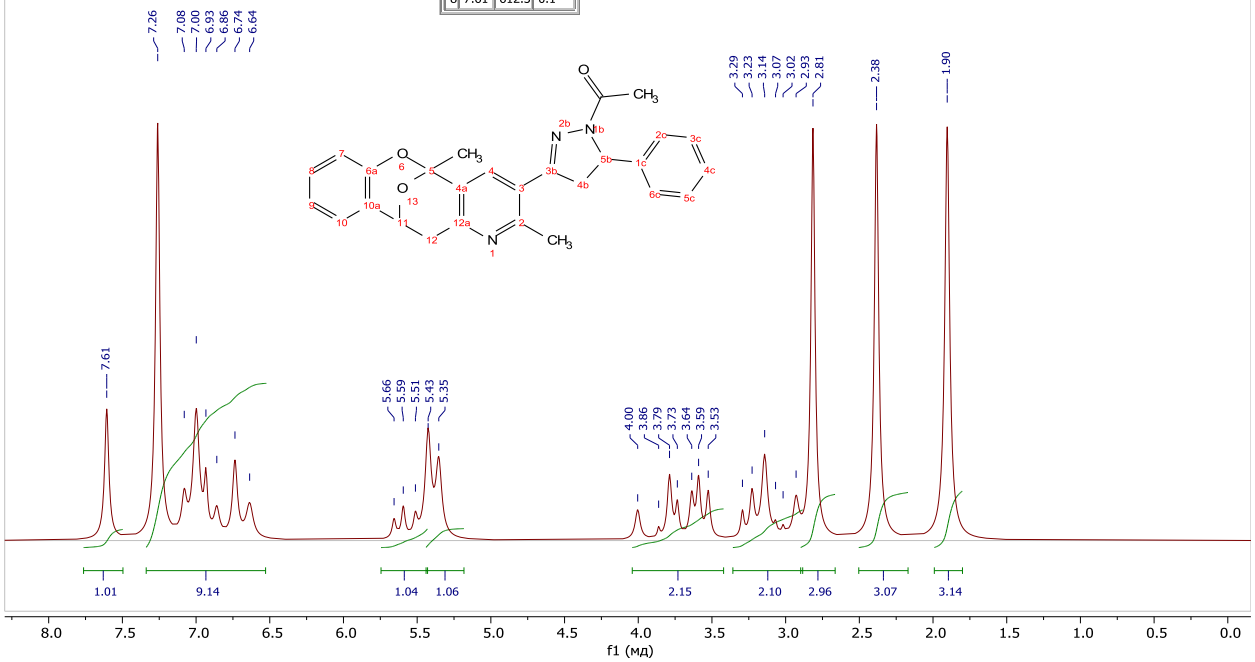
^{1}H (400 MHz, $CDCl_3$) and ^{13}C (100 MHz, $CDCl_3$) NMR Spectra of **4e**

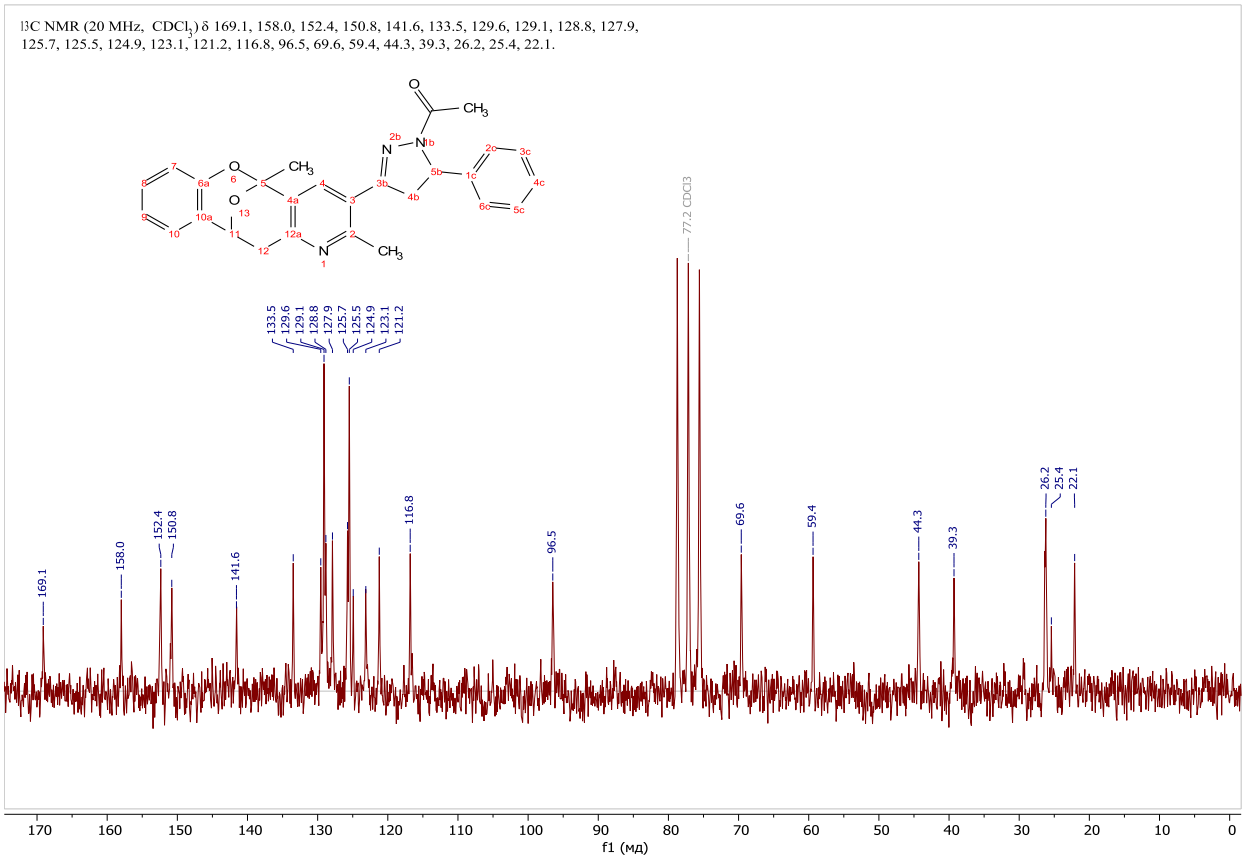
	ppm	Hz	Hight
1	1.90	153.2	0.4
2	2.38	191.9	0.4
3	2.81	226.6	0.4
4	2.93	235.8	0.0
5	3.02	242.9	0.0
6	3.07	247.0	0.0
7	3.14	253.0	0.1

	ppm	Hz	Hight
1	3.23	259.8	0.0
2	3.29	265.1	0.0
3	3.53	283.8	0.0
4	3.59	289.1	0.1
5	3.64	292.8	0.0
6	3.73	300.6	0.0
7	3.79	304.9	0.1

	ppm	Hz	Hight
1	3.86	310.9	0.0
2	4.00	322.3	0.0
3	5.35	431.0	0.1
4	5.43	436.8	0.1
5	5.51	443.7	0.0
6	5.59	450.3	0.0
7	5.66	455.4	0.0

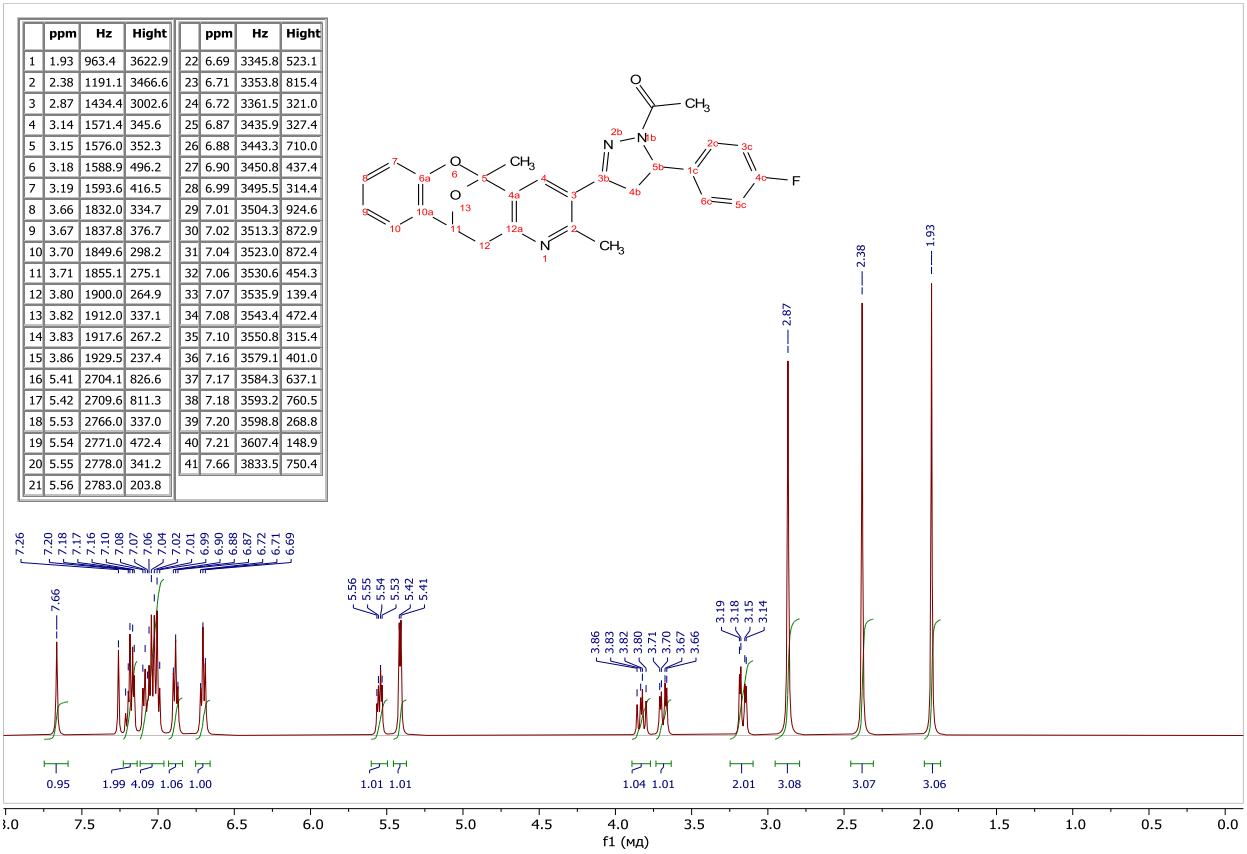
	ppm	Hz	Hight
1	6.64	534.3	0.0
2	6.74	542.3	0.1
3	6.86	552.2	0.0
4	6.93	558.1	0.0
5	7.00	563.4	0.1
6	7.08	570.0	0.0
7	7.26	584.5	0.4
8	7.61	612.3	0.1



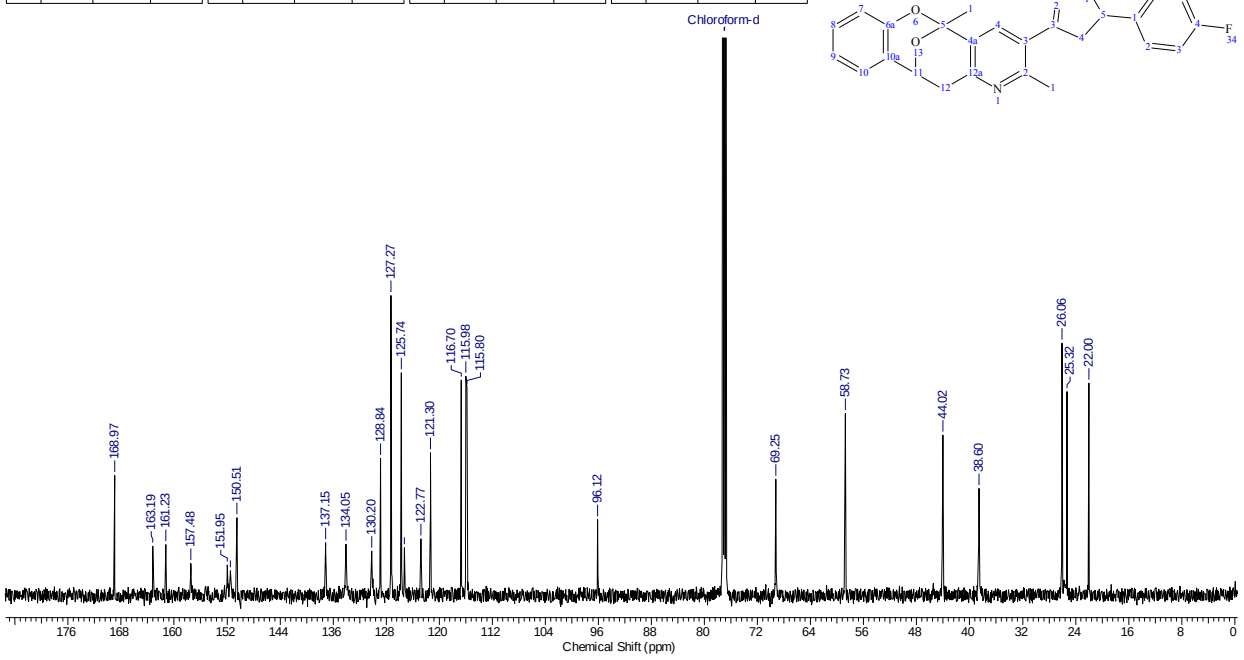


^{1}H (81 MHz, $CDCl_3$) and ^{13}C (20 MHz, $CDCl_3$) NMR Spectra of **5a**

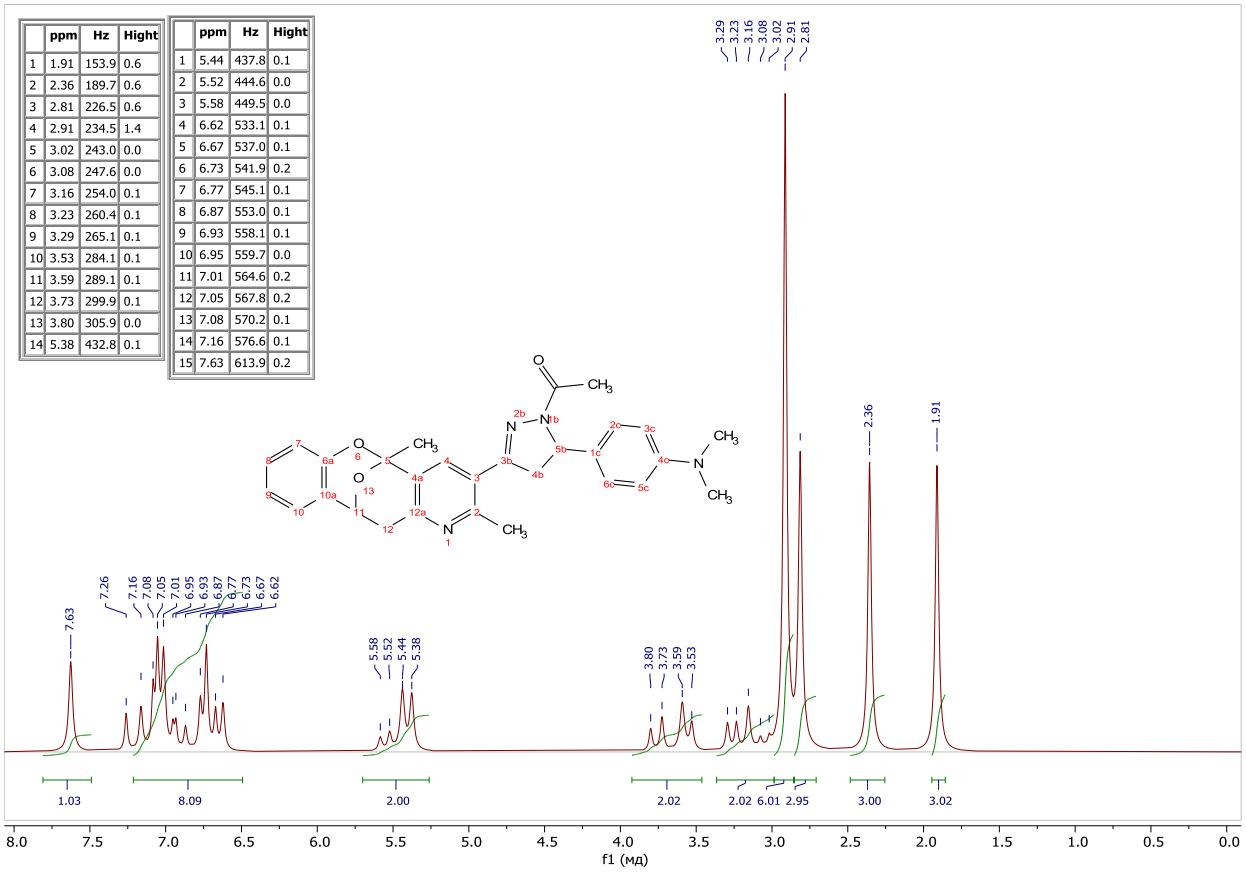
	ppm	Hz	Hight		ppm	Hz	Hight
1	1.93	963.4	3622.9	22	6.69	3345.8	523.1
2	2.38	1191.1	3466.6	23	6.71	3353.8	815.4
3	2.87	1434.4	3002.6	24	6.72	3361.5	321.0
4	3.14	1571.4	345.6	25	6.87	3435.9	327.4
5	3.15	1576.0	352.3	26	6.88	3443.3	710.0
6	3.18	1588.9	496.2	27	6.90	3450.8	437.4
7	3.19	1593.6	416.5	28	6.99	3495.5	314.4
8	3.66	1832.0	334.7	29	7.01	3504.3	924.6
9	3.67	1837.8	376.7	30	7.02	3513.3	872.9
10	3.70	1849.6	298.2	31	7.04	3523.0	872.4
11	3.71	1855.1	275.1	32	7.06	3530.6	454.3
12	3.80	1900.0	264.9	33	7.07	3535.9	139.4
13	3.82	1912.0	337.1	34	7.08	3543.4	472.4
14	3.83	1917.6	267.2	35	7.10	3550.8	315.4
15	3.86	1929.5	237.4	36	7.16	3579.1	401.0
16	5.41	2704.1	826.6	37	7.17	3584.3	637.1
17	5.42	2709.6	811.3	38	7.18	3593.2	760.5
18	5.53	2766.0	337.0	39	7.20	3598.8	268.8
19	5.54	2771.0	472.4	40	7.21	3607.4	148.9
20	5.55	2778.0	341.2	41	7.66	3833.5	750.4
21	5.56	2783.0	203.8				



No.	(ppm)	(Hz)	Height	No.	(ppm)	(Hz)	Height	No.	(ppm)	(Hz)	Height	No.	(ppm)	(Hz)	Height
1	22.00	2766.2	0.1832	8	96.12	12087.5	0.0653	15	125.74	15812.9	0.1919	22	150.51	18927.3	0.0670
2	25.32	3184.4	0.1758	9	115.80	14563.2	0.1793	16	127.21	15998.0	0.2463	23	151.48	19050.1	0.0212
3	26.06	3277.8	0.2174	10	115.98	14585.1	0.1890	17	127.27	16005.6	0.2585	24	151.95	19109.0	0.0263
4	38.60	4854.8	0.0921	11	116.70	14676.0	0.1856	18	128.84	16202.5	0.1181	25	157.48	19804.1	0.0273
5	44.02	5535.6	0.1381	12	121.30	15254.9	0.1229	19	130.20	16373.3	0.0379	26	161.23	20276.2	0.0438
6	58.73	7385.2	0.1569	13	122.77	15439.2	0.0486	20	134.05	16858.0	0.0439	27	163.19	20522.8	0.0424
7	69.25	8708.9	0.1001	14	125.27	15753.1	0.0412	21	137.15	17247.6	0.0452	28	168.97	21249.8	0.1034

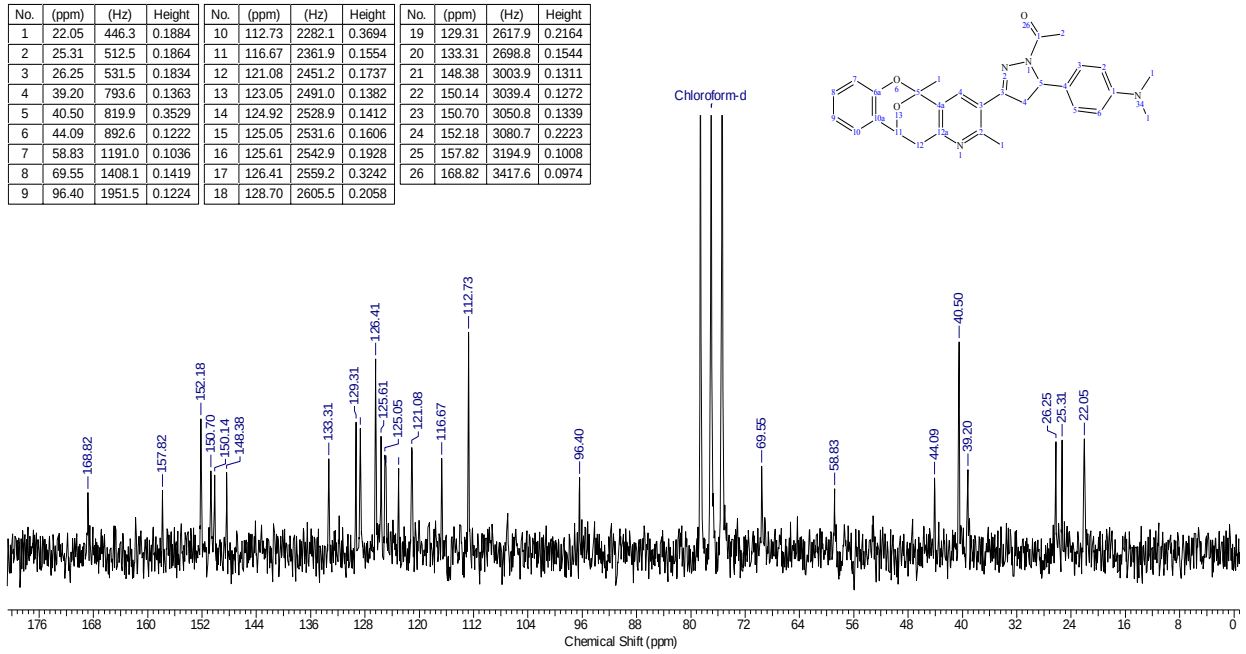


^{1}H (500 MHz, $CDCl_3$) and ^{13}C (126 MHz, $CDCl_3$) NMR Spectra of **5b**



	ppm	Hz	Hight
1	1.91	153.9	0.6
2	2.36	189.7	0.6
3	2.81	226.5	0.6
4	2.91	234.5	1.4
5	3.02	243.0	0.0
6	3.08	247.6	0.0
7	3.16	254.0	0.1
8	3.23	260.4	0.1
9	3.29	265.1	0.1
10	3.53	284.1	0.1
11	3.59	289.1	0.1
12	3.73	299.9	0.1
13	3.80	305.9	0.0
14	5.38	432.8	0.1

	ppm	Hz	Hight
1	5.44	437.8	0.1
2	5.52	444.6	0.0
3	5.58	449.5	0.0
4	6.62	533.1	0.1
5	6.67	537.0	0.1
6	6.73	541.9	0.2
7	6.77	545.1	0.1
8	6.87	553.0	0.1
9	6.93	558.1	0.1
10	6.95	559.7	0.0
11	7.01	564.6	0.2
12	7.05	567.8	0.2
13	7.08	570.2	0.1
14	7.16	576.6	0.1
15	7.63	613.9	0.2



No.	(ppm)	(Hz)	Height
1	22.05	446.3	0.1884
2	25.31	512.5	0.1864
3	26.25	531.5	0.1834
4	39.20	793.6	0.1363
5	40.50	819.9	0.3529
6	44.09	892.6	0.1222
7	58.83	1191.0	0.1036
8	69.55	1408.1	0.1419
9	96.40	1951.5	0.1224

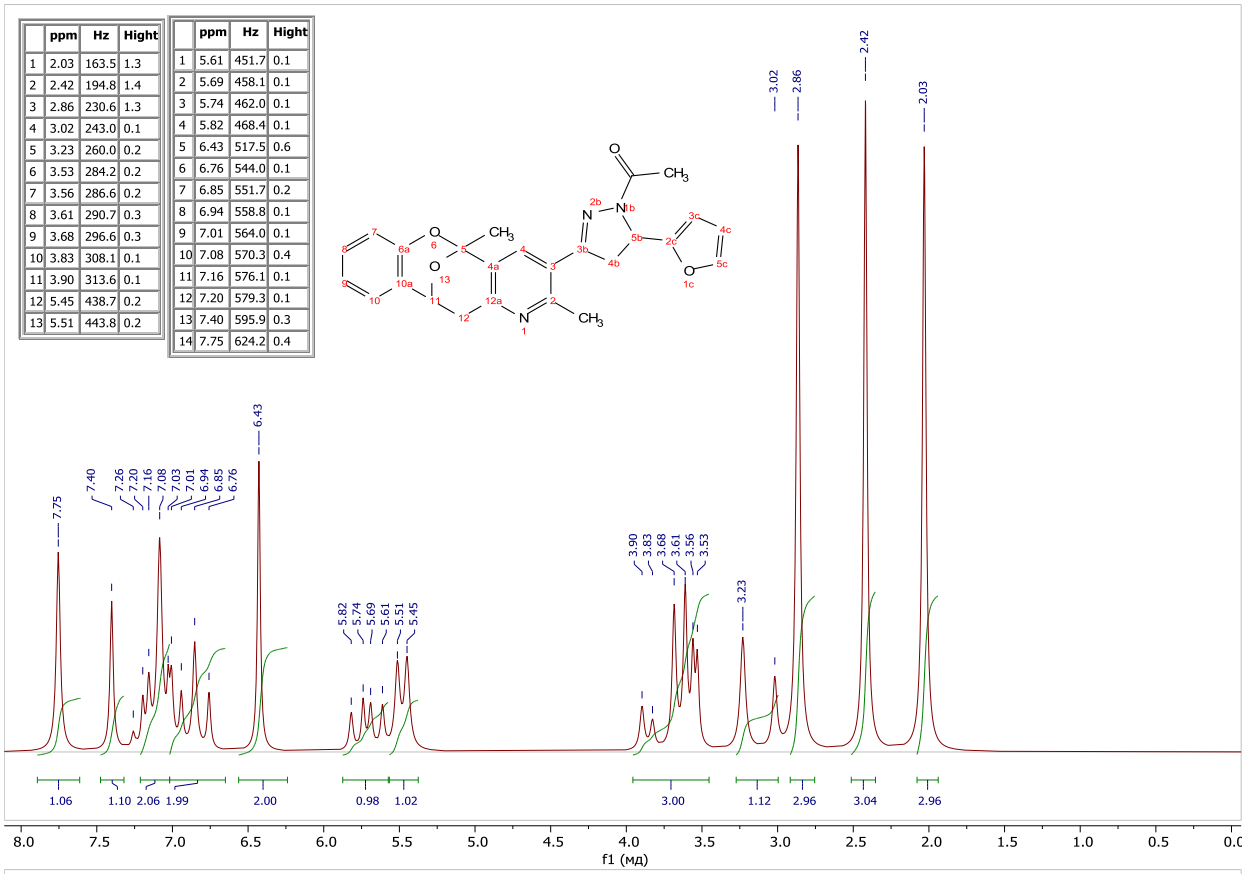
No.	(ppm)	(Hz)	Height
10	112.73	2282.1	0.3694
11	116.67	2361.9	0.1554
12	121.08	2451.2	0.1737
13	123.05	2491.0	0.1382
14	124.92	2528.9	0.1412
15	125.05	2531.6	0.1606
16	125.61	2542.9	0.1928
17	126.41	2559.2	0.3242
18	128.70	2605.5	0.2058

No.	(ppm)	(Hz)	Height
19	129.31	2617.9	0.2164
20	133.31	2698.8	0.1544
21	148.38	3003.9	0.1311
22	150.14	3039.4	0.1272
23	150.70	3050.8	0.1339
24	152.18	3080.7	0.2223
25	157.82	3194.9	0.1008
26	168.82	3417.6	0.0974

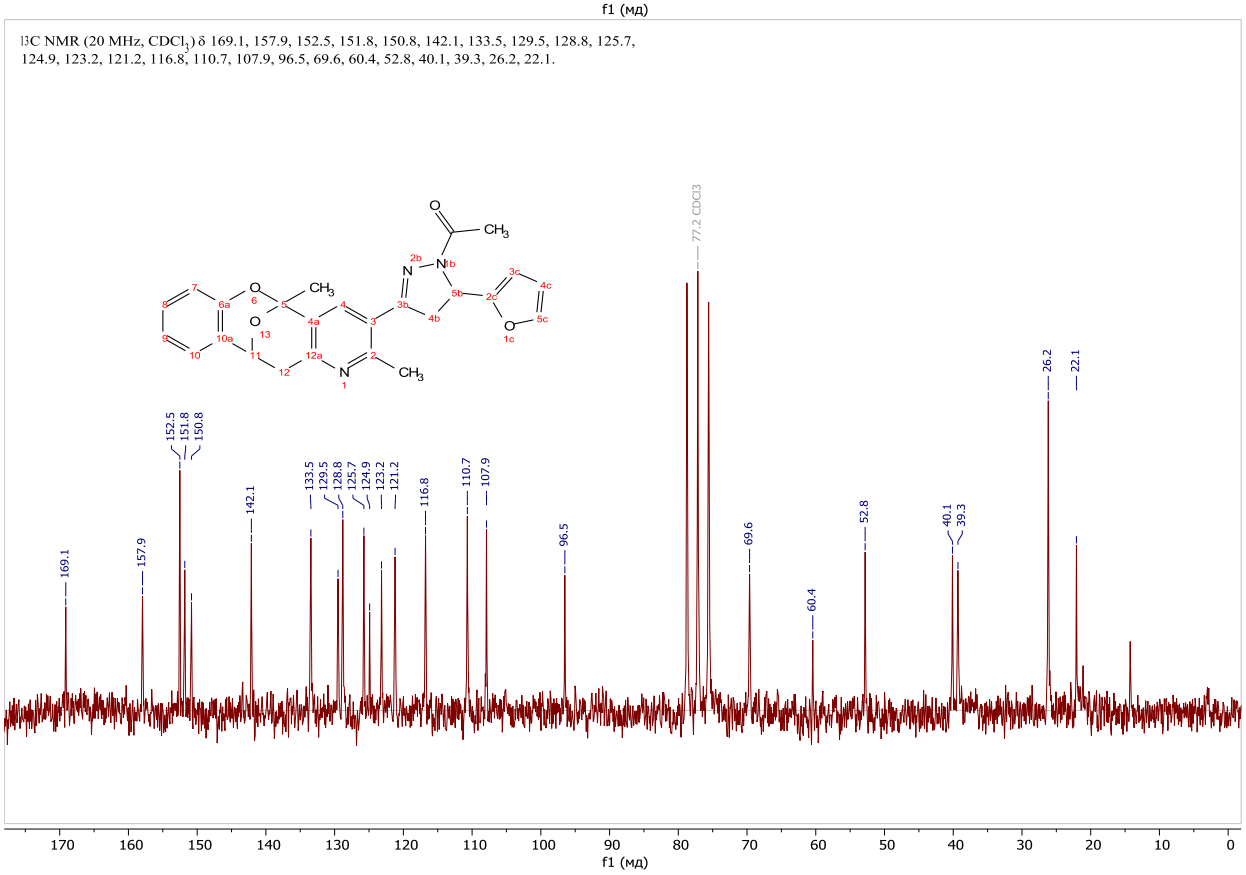
^{1}H (81 MHz, $CDCl_3$) and ^{13}C (20 MHz, $CDCl_3$) NMR Spectra of **5c**

	ppm	Hz	Hight
1	2.03	163.5	1.3
2	2.42	194.8	1.4
3	2.86	230.6	1.3
4	3.02	243.0	0.1
5	3.23	260.0	0.2
6	3.53	284.2	0.2
7	3.56	286.6	0.2
8	3.61	290.7	0.3
9	3.68	296.6	0.3
10	3.83	308.1	0.1
11	3.90	313.6	0.1
12	5.45	438.7	0.2
13	5.51	443.8	0.2

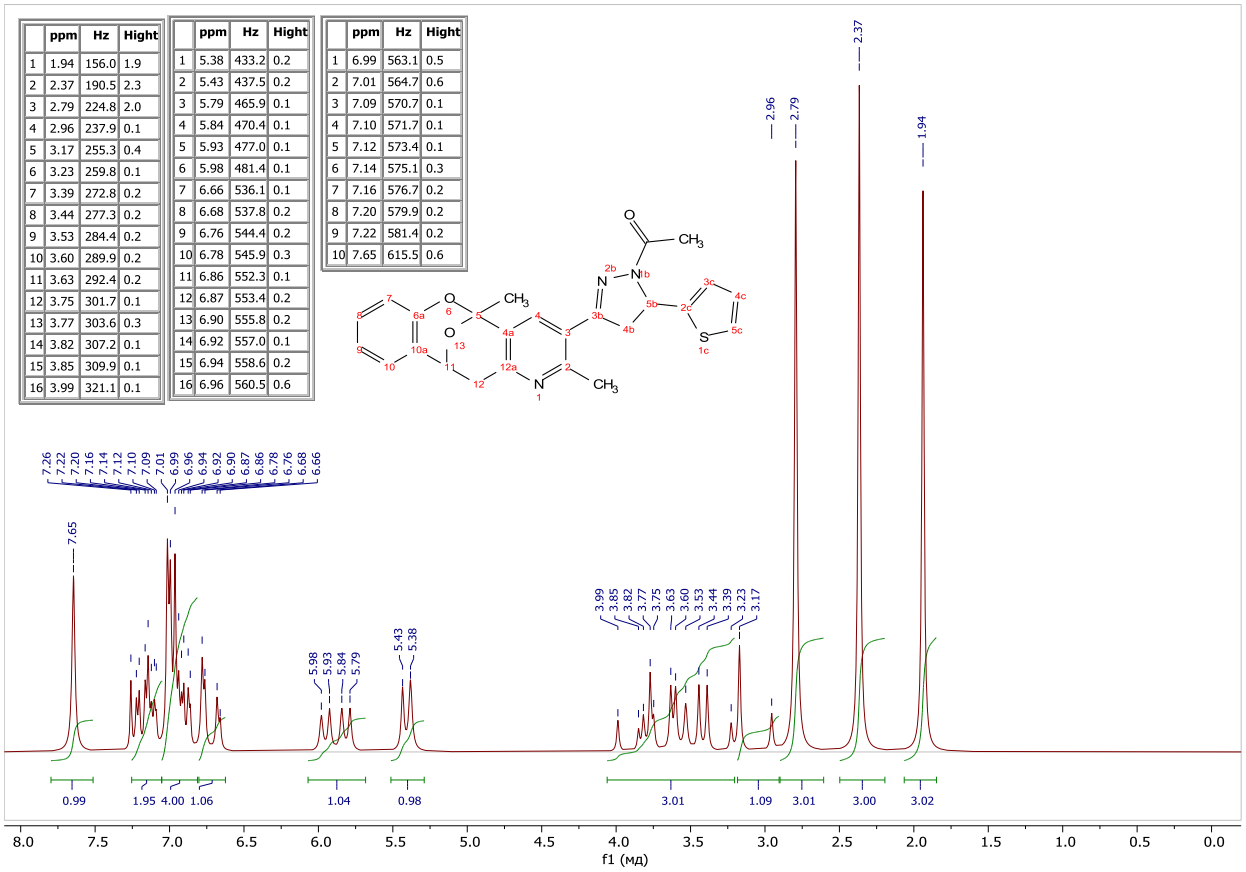
	ppm	Hz	Hight
1	5.61	451.7	0.1
2	5.69	458.1	0.1
3	5.74	462.0	0.1
4	5.82	468.4	0.1
5	6.43	517.5	0.6
6	6.76	544.0	0.1
7	6.85	551.7	0.2
8	6.94	558.8	0.1
9	7.01	564.0	0.1
10	7.08	570.3	0.4
11	7.16	576.1	0.1
12	7.20	579.3	0.1
13	7.40	595.9	0.3
14	7.75	624.2	0.4



^{13}C NMR (20 MHz, $CDCl_3$) δ 169.1, 157.9, 152.5, 151.8, 150.8, 142.1, 133.5, 129.5, 128.8, 125.7, 124.9, 123.2, 121.2, 116.8, 110.7, 107.9, 96.5, 69.6, 60.4, 52.8, 40.1, 39.3, 26.2, 22.1.



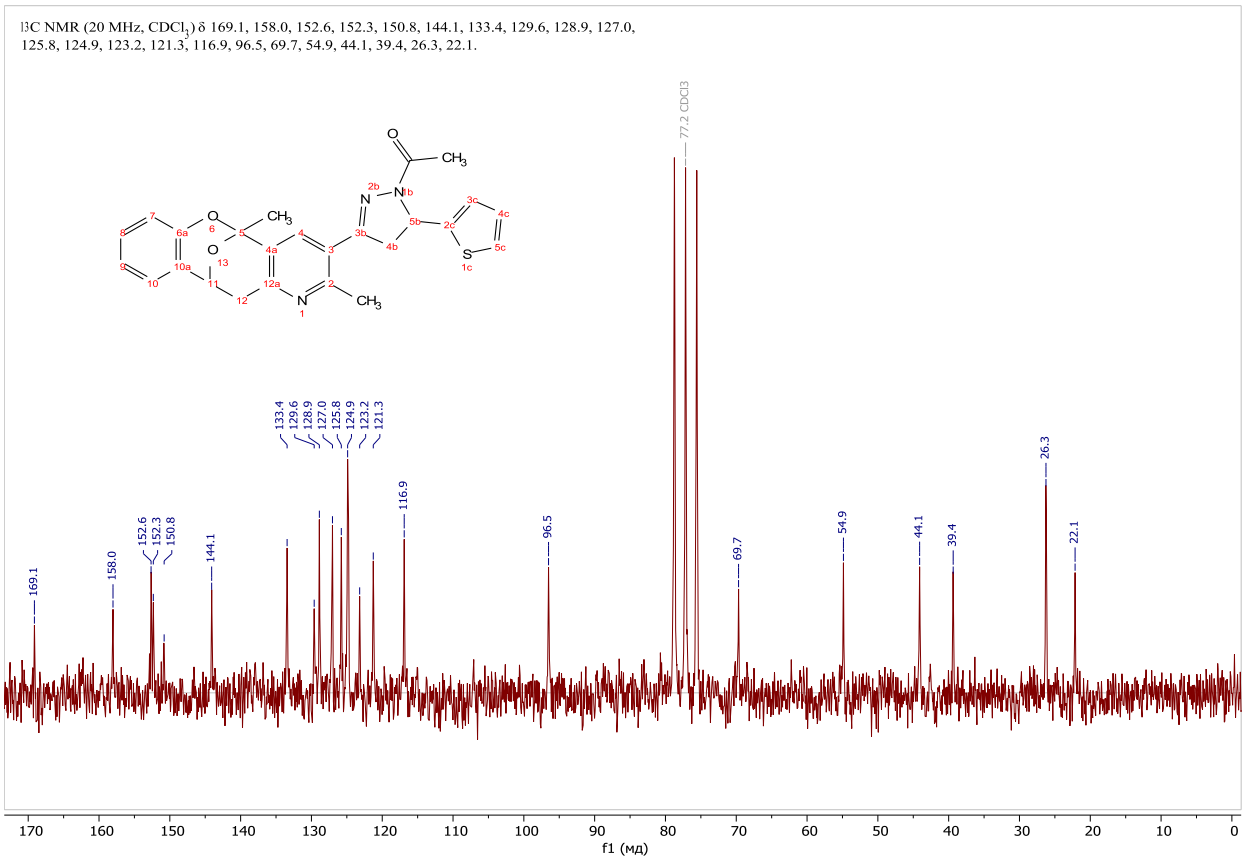
^{1}H (81 MHz, $CDCl_3$) and ^{13}C (20 MHz, $CDCl_3$) NMR Spectra of **5d**



	ppm	Hz	Hight
1	1.94	156.0	1.9
2	2.37	190.5	2.3
3	2.79	224.8	2.0
4	2.96	237.9	0.1
5	3.17	255.3	0.4
6	3.23	259.8	0.1
7	3.39	272.8	0.2
8	3.44	277.3	0.2
9	3.53	284.4	0.2
10	3.60	289.9	0.2
11	3.63	292.4	0.2
12	3.75	301.7	0.1
13	3.77	303.6	0.3
14	3.82	307.2	0.1
15	3.85	309.9	0.1
16	3.99	321.1	0.1

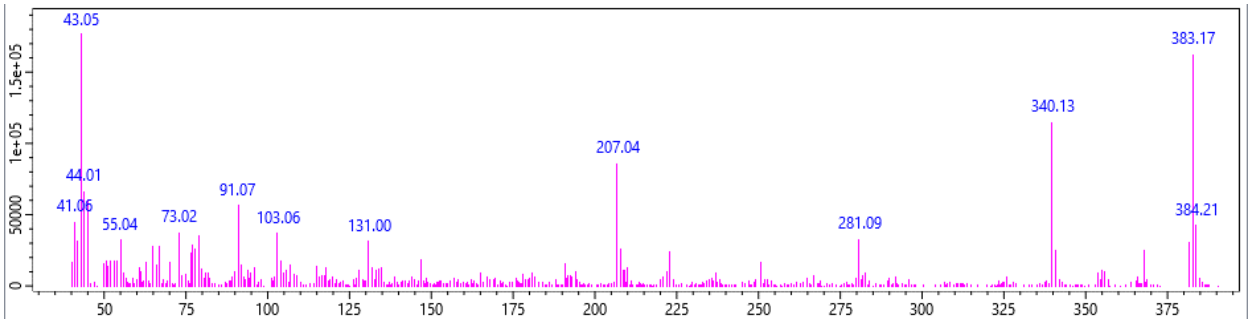
	ppm	Hz	Hight
1	5.38	433.2	0.2
2	5.43	437.5	0.2
3	5.79	465.9	0.1
4	5.84	470.4	0.1
5	5.93	477.0	0.1
6	5.98	481.4	0.1
7	6.66	536.1	0.1
8	6.68	537.8	0.2
9	6.76	544.4	0.2
10	6.78	545.9	0.3
11	6.86	552.3	0.1
12	6.87	553.4	0.2
13	6.90	555.8	0.2
14	6.92	557.0	0.1
15	6.94	558.6	0.2
16	6.96	560.5	0.6

	ppm	Hz	Hight
1	6.99	563.1	0.5
2	7.01	564.7	0.6
3	7.09	570.7	0.1
4	7.10	571.7	0.1
5	7.12	573.4	0.1
6	7.14	575.1	0.3
7	7.16	576.7	0.2
8	7.20	579.9	0.2
9	7.22	581.4	0.2
10	7.65	615.5	0.6

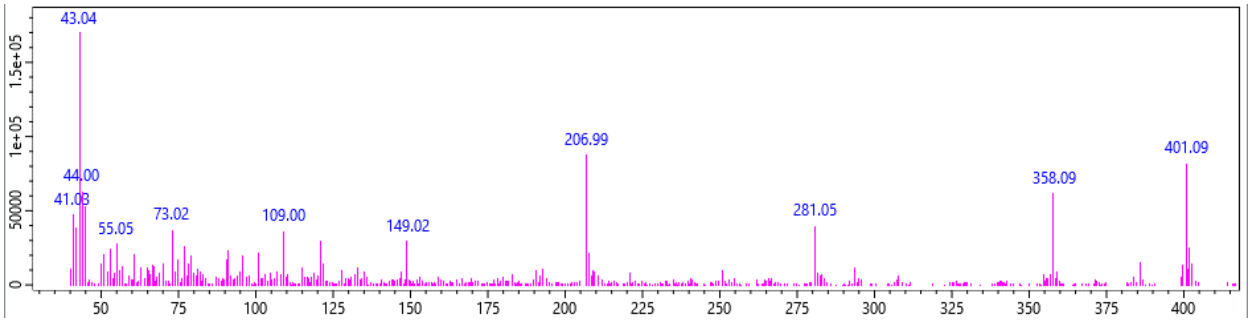


^{1}H (81 MHz, $CDCl_3$) and ^{13}C (20 MHz, $CDCl_3$) NMR Spectra of **5e**

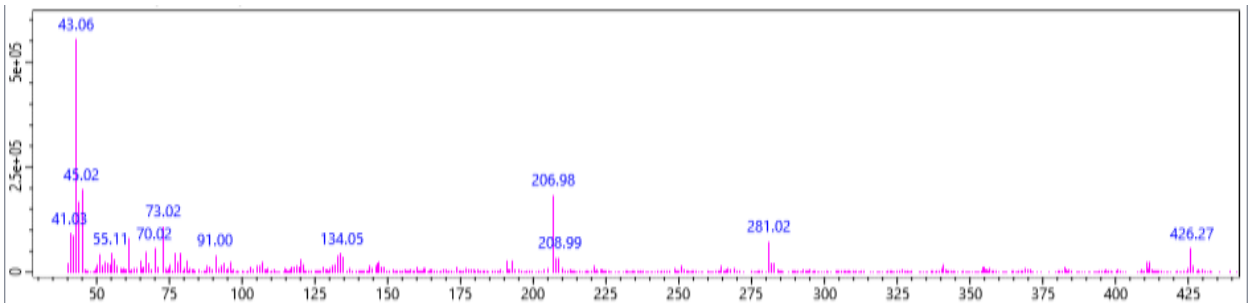
Copies of MS Spectra



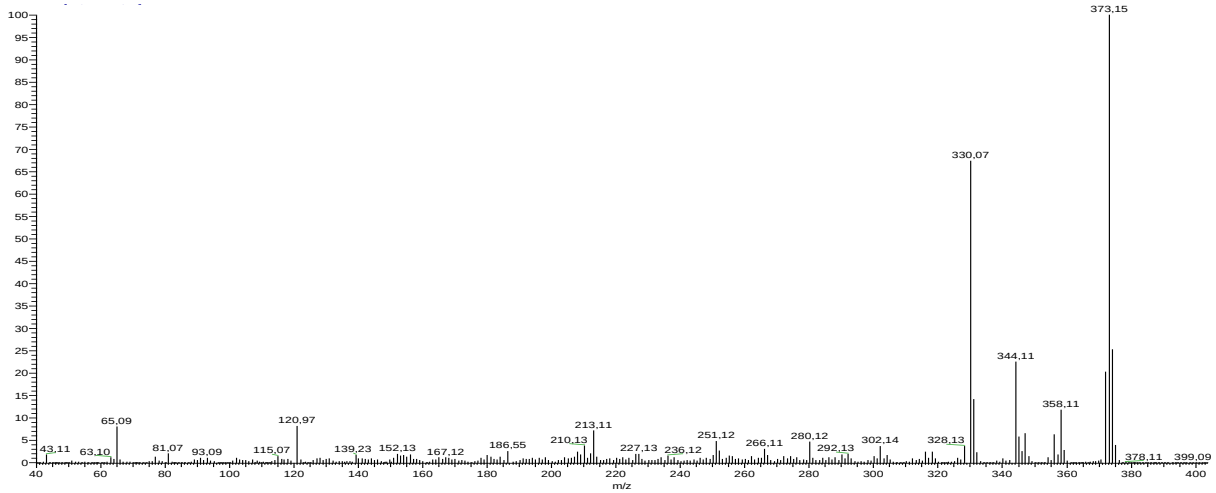
Mass spectrum of **4a**



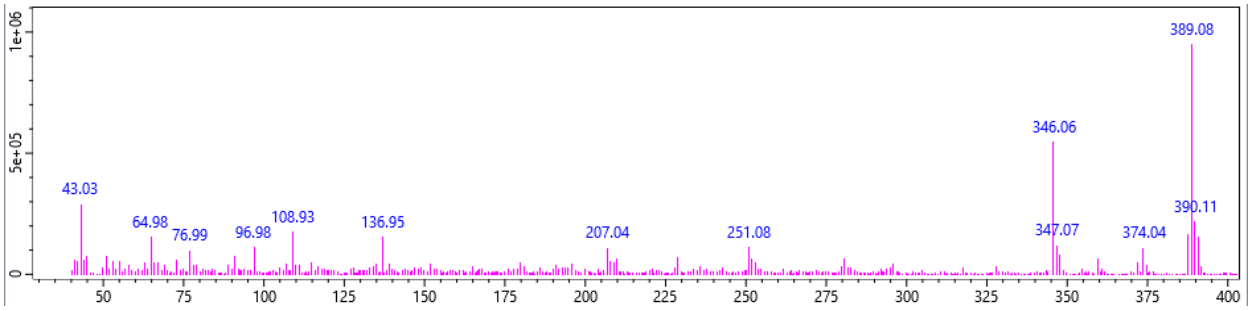
Mass spectrum of **4b**



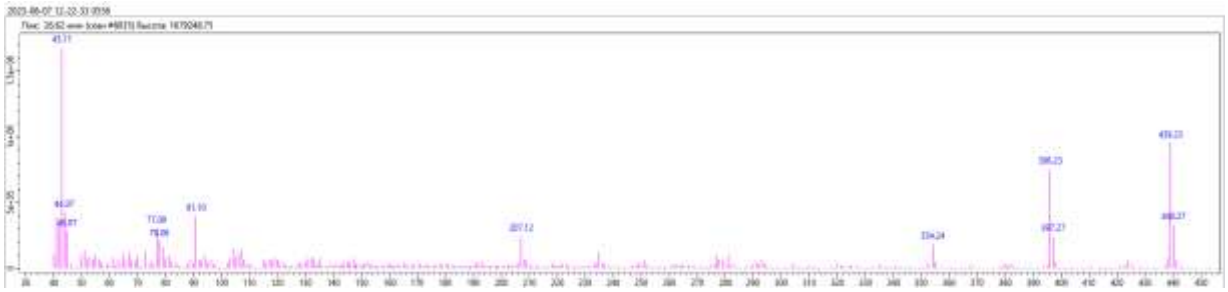
Mass spectrum of **4c**



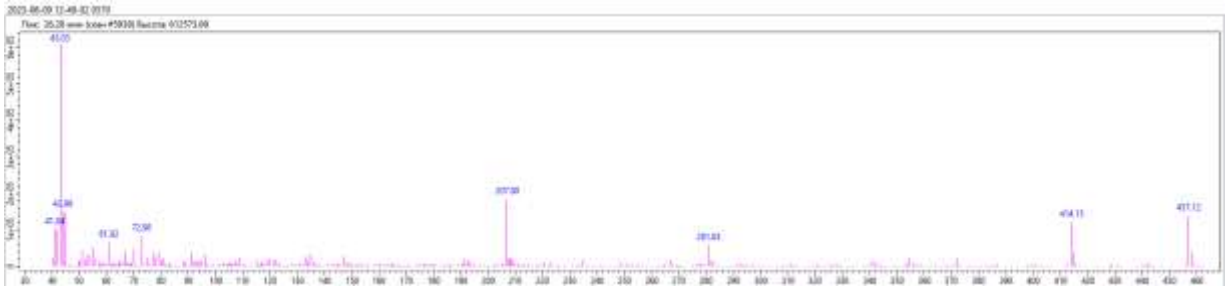
Mass spectrum of **4d**



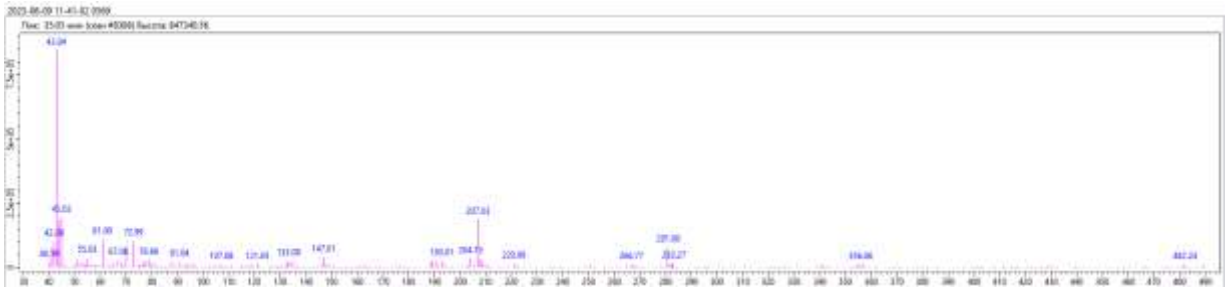
Mass spectrum of **4e**



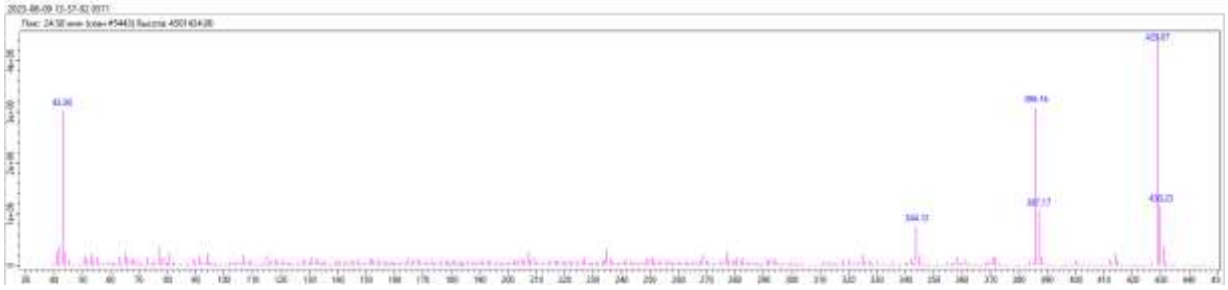
Mass spectrum of **5a**



Mass spectrum of **5b**



Mass spectrum of **5c**



Mass spectrum of **5d**

Mass spectrum of **5e**