Electronic supplementary materials *Mendeleev Commun.*, 2024, **34**, 272–273

An efficient access to tetrahydropyrrolo[2,1-*a*]isoquinoline derivatives based on phosphoranylidene succinimide

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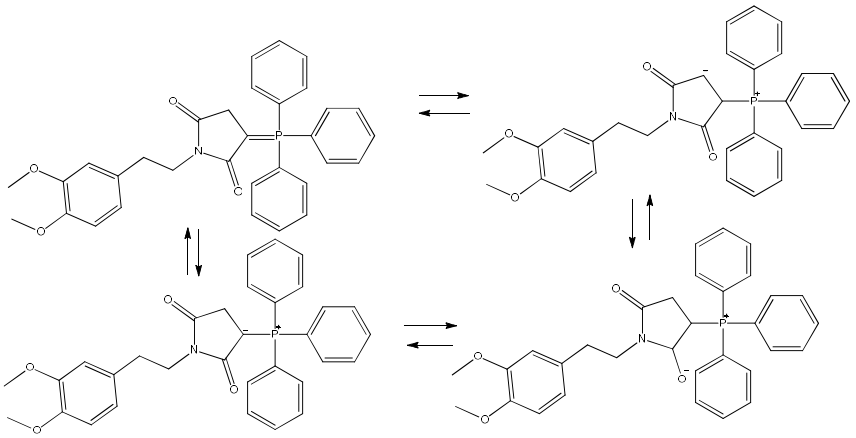
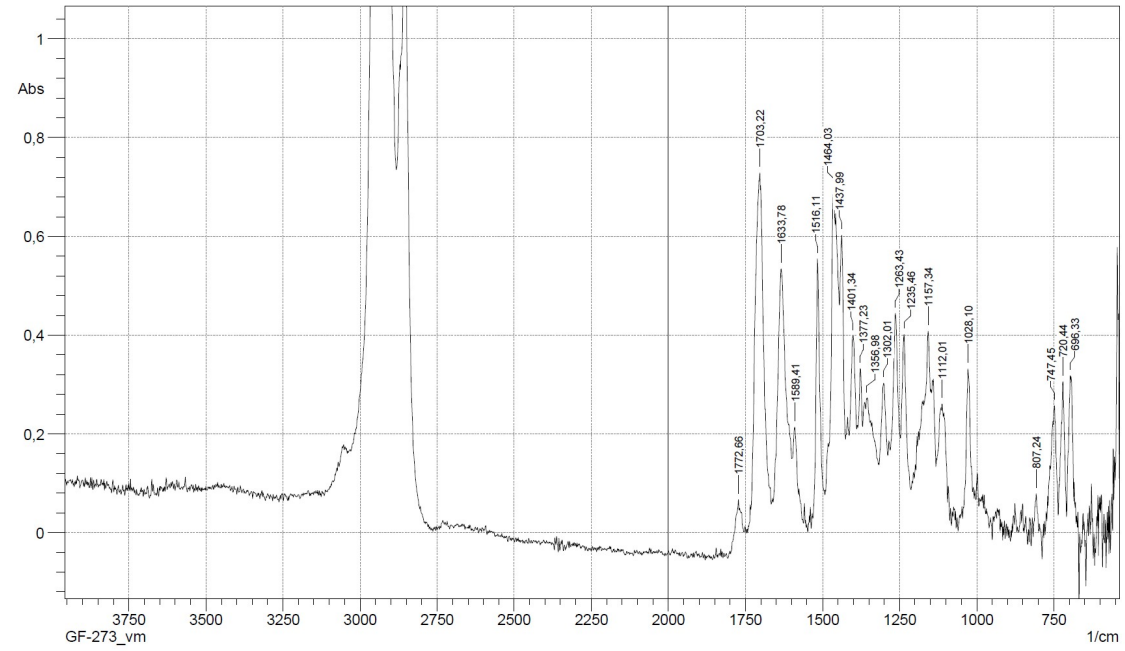
General. IR spectra were recorded on an IR-Prestige-21 Fourier Transform Spectrophotometer (Shimadzu) in Vaseline oil. NMR spectra were obtained on a Bruker-AM 500 spectrometer with an operating frequency of 500.13 MHz (^{1}H), 125.76 MHz (^{13}C), using tetramethylsilane as the internal standard (TMS). The reaction was monitored using thin-layer chromatography on Sorbfil PTSH-AF-A plates. The compounds were detected by UV-irradiation, iodine vapor, and by spraying the plates with ninhydrin developer solution or anise aldehyde solution followed by heating at 100-120°C. The melting temperature was determined on a Boetius heating table. The reaction products were separated by column chromatography on Chemapol silica gel with a particle size of 40/100 μm. Elemental analysis was performed using an EURO EA - 3000 automatic CHNS-analyzer.

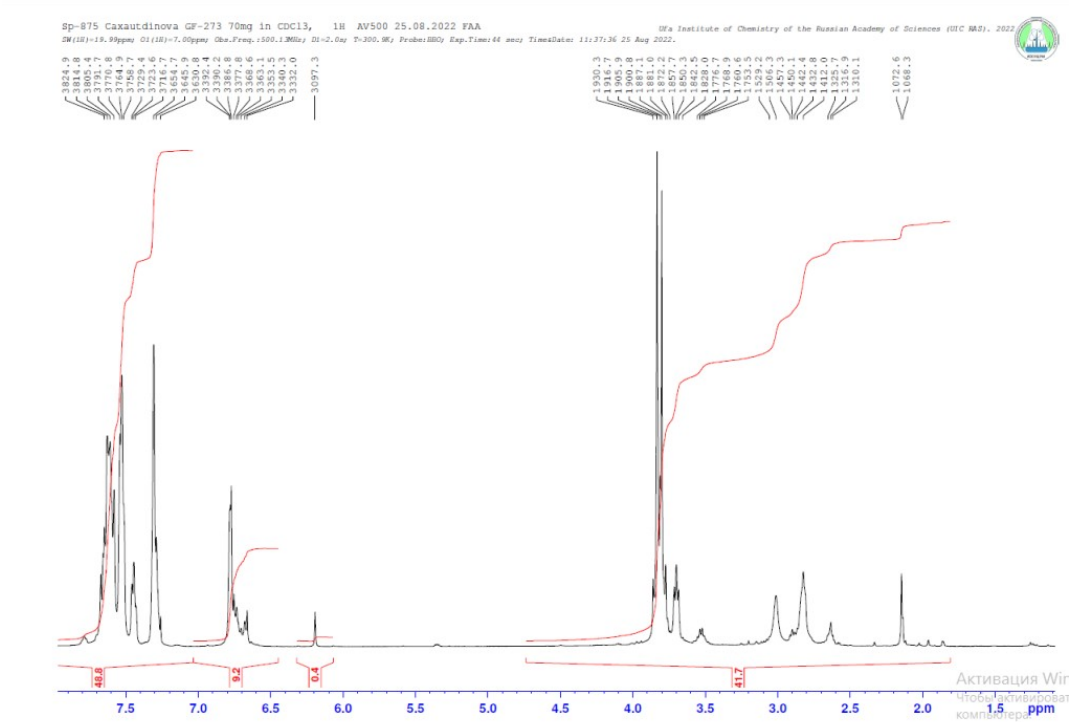
Procedure for synthesizing phosphorane (2).



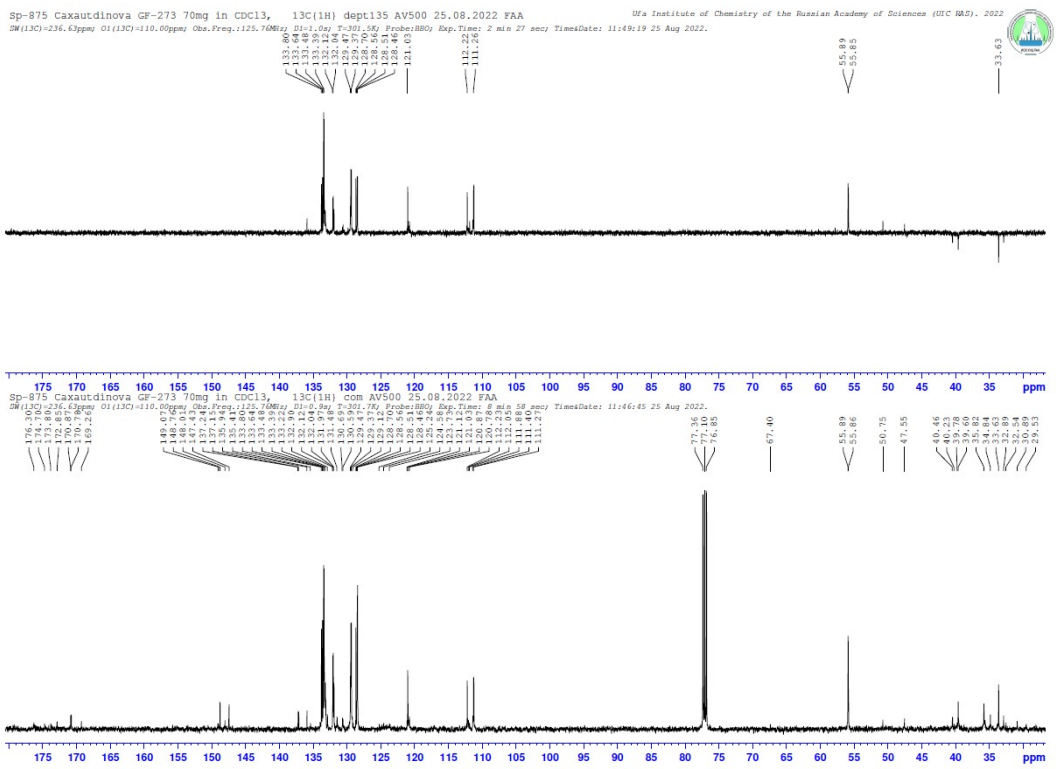
The synthesis was performed in a 100 ml round bottom flask. *N*-Homoveratryl-maleinimide **1** (0.5 g, 1.92 mmol) and triphenylphosphine (0.5 g, 1.92 mmol) were dissolved in minimum acetone, and this was stirred for 2.5 hours at room temperature. The solvent was distilled off, and the resulting burgundy oil-like phosphorane **2** as a red oily substance was used without further purification, yield 69%. IR spectrum (Nujol, ν, cm^{-1}): 1703, 1633, 1516, 1464, 1437, 1263, 1235, 1157, 1028, 747, 720, 696. ^{1}H NMR ($CDCl_3$, δ, ppm, *J*/Hz): 2.64 and 3.01 (2H, m, CH_2), 2.82 (2H, m, CH_2), 3.51 and 3.71 (2H, m, CH_2), 3.79 (3H, s, CH_3), 3.83 (3H, s, CH_3), 6.64-6.79 (3H, m, 3×CHar), 7.25-7/69 (15H, m, 15×CHar). ^{13}C NMR ($CDCl_3$, δ, ppm): 32.54 and 33.63 (C=P), 32.89 (CH_2), 34.84 (CH_2), 39.60 and 39.78 (CH_2), 55.86 (CH_3), 55.89 (CH_3), 111.27 (CHar), 112.05 (CHar), 120.03 (CHar), 128.51-128.70 (6×CHar), 130.56 and 130.69 (3×CHar), 133.39-033.80 (6×CHar), 135.94 and 137.24 (3×Car), 148.01 (Car), 148.76 (Car), 169.26 (O=C), 170.87 (O=C).



IR for **2**



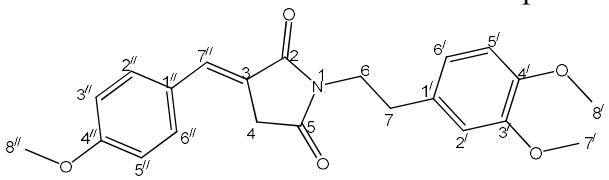
^{1}H NMR for **2**



^{13}C NMR for **2**

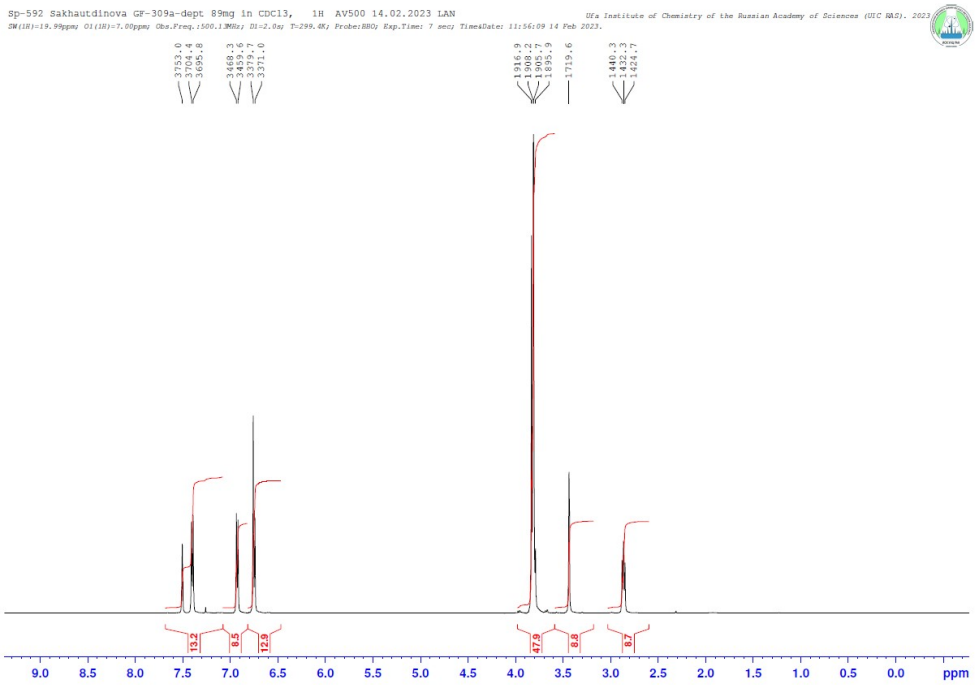
Synthesis of olefins 3a and 3b based on anisic and veratric aldehydes

The synthesis was performed in a flat-bottom flask (25 ml). Equimolar amounts of phosphorene **2** (0.43 g, 0.82 mmol) and an aldehyde (0.82 mmol) were mixed in 10 ml of toluene under reflux. The dissolved mixture was kept for 24 h. The precipitate that formed was filtered off and washed with toluene and then with petroleum ether.

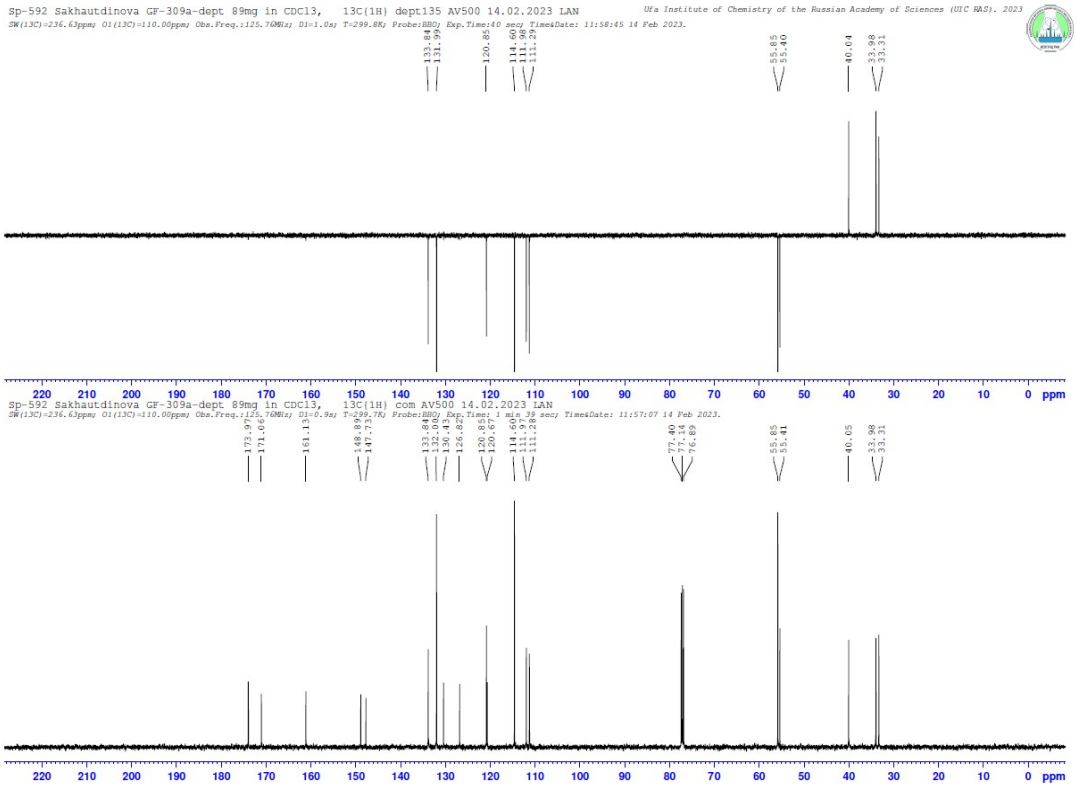


3a

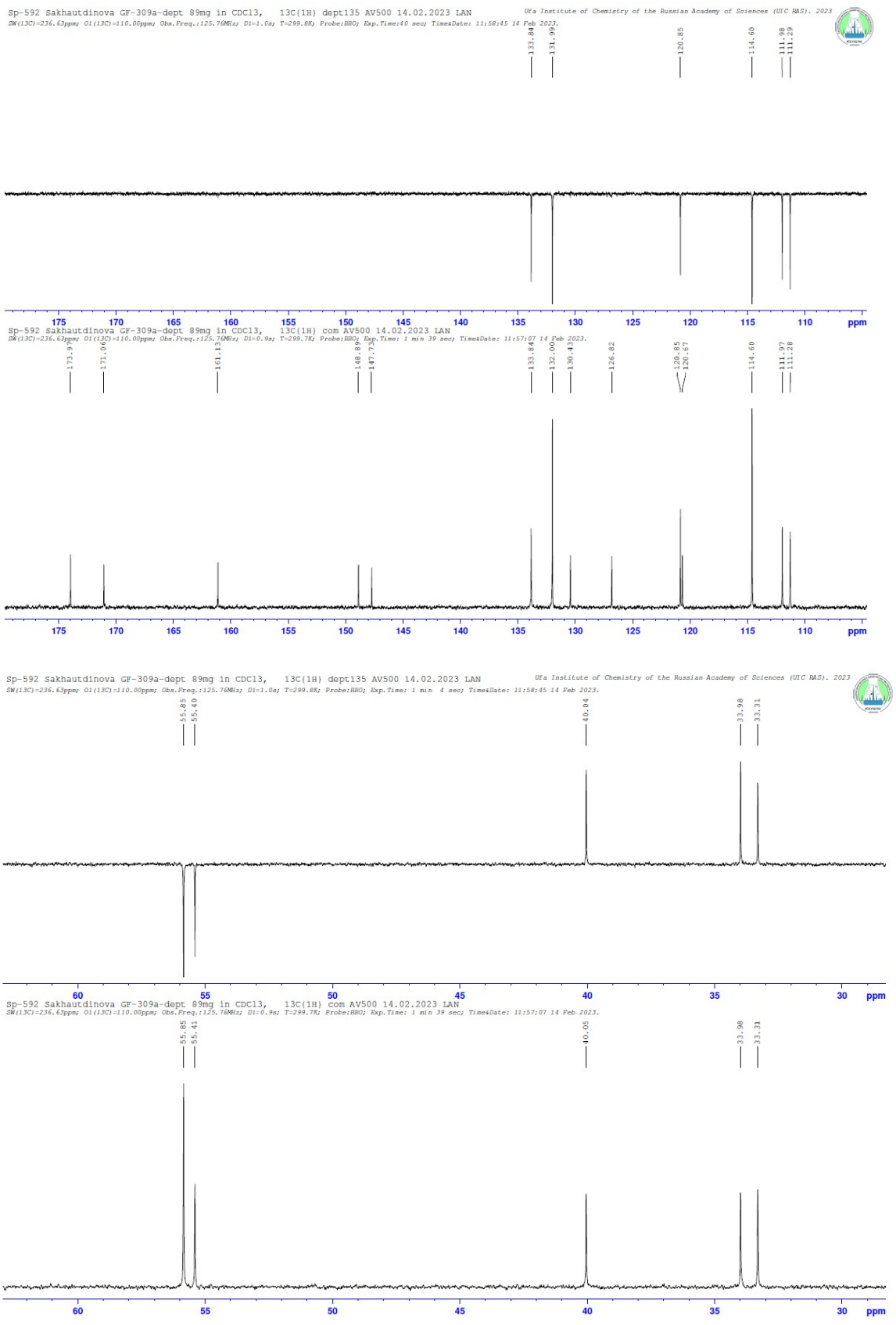
(*E*)-1-[2-(3,4-Dimethoxyphenyl)ethyl]-3-(4-methoxybenzylidene)pyrrolidine-2,5-dione (3a). Yield 69%. The product was isolated as a white solid substance. IR spectrum (Nujol, ν, cm^{-1}): 3432, 1694, 1653, 1465, 1376, 1272, 1139. ^{1}H NMR ($CDCl_3$, δ, ppm, *J*/Hz): 2.87 (2H, t, J=8, CH_2-7), 3.44 (2H, s, CH_2-4), 3.77 (2H, m, CH_2-6), 3.79 (6H, s, CH_3-8', 7'), 3.82 (3H, s, CH_3-8"), 6.72 (3H, m, CH-2', 5', 6'), 6.91 (2H, d, J=8.6, CH_4-5", CH-3'), 7.98 (2H, d, CH-6", 2"), 7.50 (H, s, CH-7"). ^{13}C NMR ($CDCl_3$, δ, ppm): 33.31 (C-4), 33.98 (C-7), 40.05 (C-6), 55.41 (C-8'), 55.85 (C-7',8"), 111.28 (C-5'), 111.97 (C-2'), 114.60 (C-5", 3"), 120.67 (=C-3), 120.85 (C-6), 126.82 (C-1'), 130.43 (C-1"), 132.00 (C-6", 2"), 133.84 (=C-7"), 147.73 (C-3'), 148.89 (C-4'), 161.13 (C- 4"), 171.06 (O=C-5), 173.97 (O=C-2). MW 381,42. Found, %: C 69.3, H 6.11, N 3.66. Calculated for $C_{22}H_{23}NO_5$, %: s, 69.28; H, 6.08; O, 20.97; N 3.67.



^{1}H NMR for **3a**

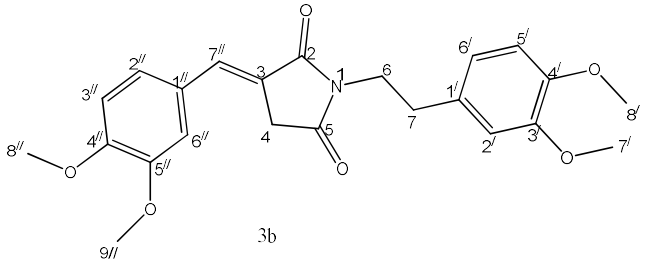


^{13}C NMR for **3a**

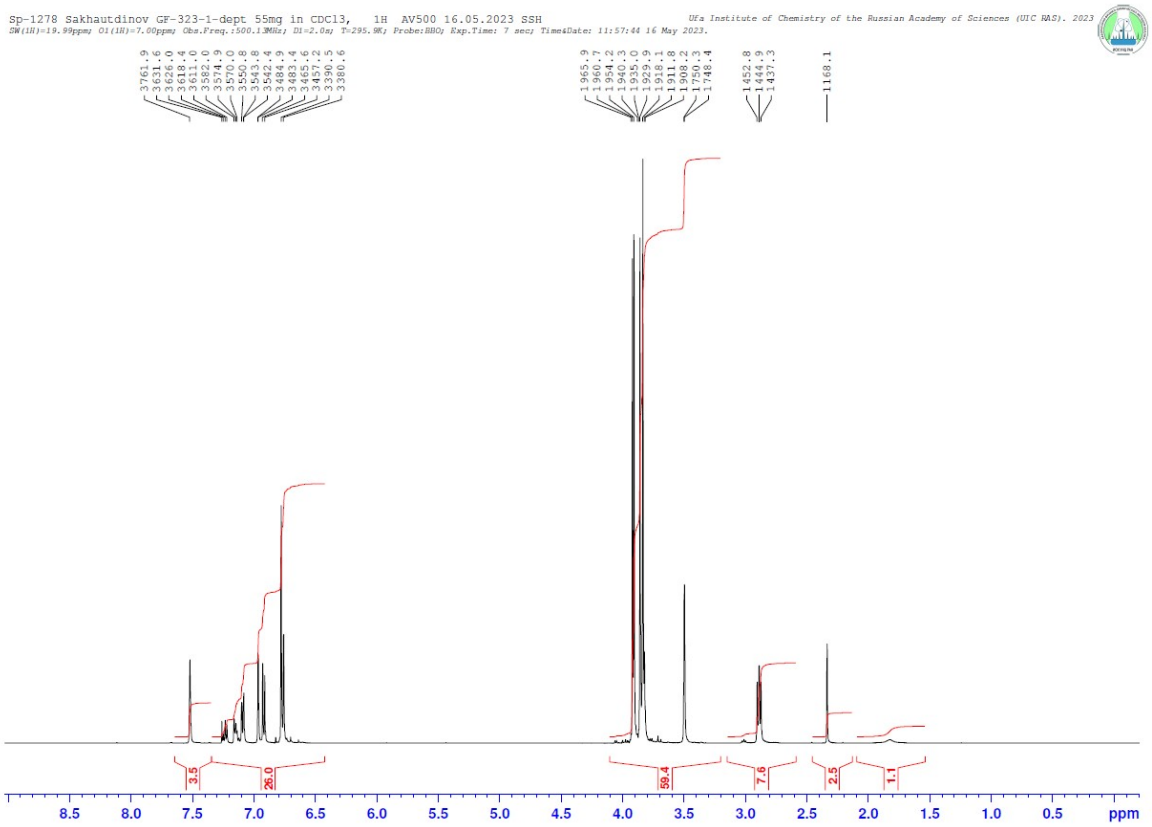


^{13}C NMR for **3a** (fragments)

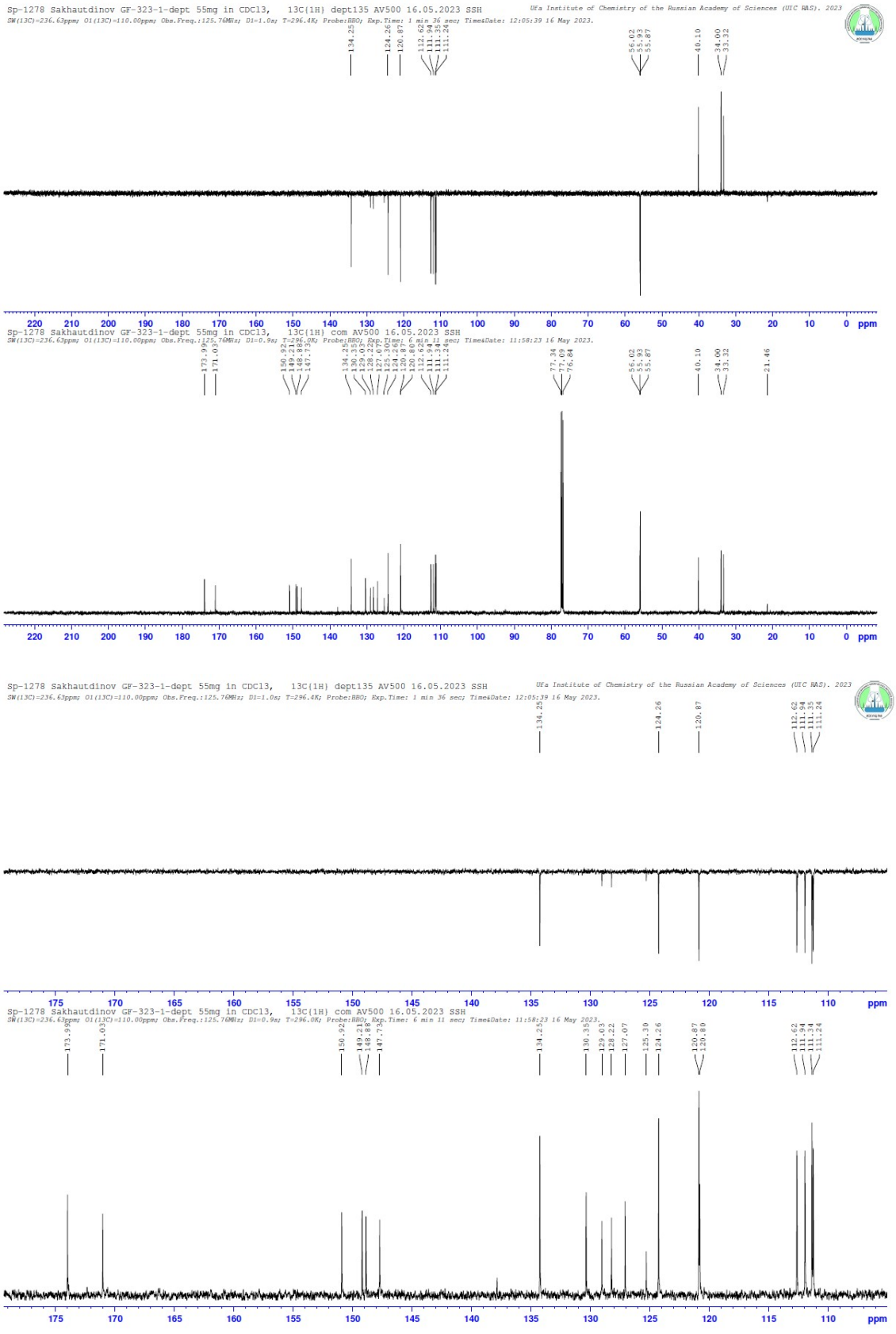
(*E*)-3-(3,4-Dimethoxybenzylidene)-1-[2-(3,4-dimethoxyphenyl)ethyl]pyrrolidine-2,5-dione (3b). Yield 52%. The product was isolated as a pale-yellow solid substance. IR spectrum (Nujol, ν, cm^{-1}): 1764, 1694, 1645, 1592, 1514, 1464, 1377, 1347, 1160, 1025, 751. ^{1}H NMR ($CDCl_3$, δ, ppm, *J*/Hz): 2.90 (2H, t, J=7.9, CH_2-7), 3.48 (2H, s, CH_2-4), 3.81 (2H, m, CH_2-6), 3.83 (3H, s, CH_3-8',), 3.85 (3H, s, CH_3-7'), 4.00 (3H, s, CH_3-9''), 4.02 (3H, s, CH_3-8''), 6.63 (3H, m, CH-2', 5',6'), 6.91 (H, d, J=8.4, CH-5''), 6.96 (H, s, CH-2''), 7.08 (H, d, J=8.4, CH-6''), 7.51 (H, s, =CH-7''). ^{13}C NMR ($CDCl_3$, δ, ppm): 33.32 (C-4), 34.00 (C-7), 40.10 (C-6), 55.87 (C-7', 8'), 55.93 (C-8''), 56.02 (C- 9''), 111.24 (C-5'), 111.34 (C-5''), 114.94 (C-2'), 112.62 (C-2''), 120.80 (C-3), 120.87 (C-6'), 124.26 (C-6''), 127.07 (C-1''), 130.35 (C-1'), 134.25 (=C-7''), 147.73 (C-3'), 147.88 (C-4'), 149.21 (C-3''), 150.92 (C- 4''), 171.03 (O=C-5), 173.99 (O=C-2). *MW* 411.45. Found, %: C 67.16, H 6.14, N 3.42. Calculated for $C_{23}H_{25}NO_6$, %: C, 67.14; H, 6.12; O, 23.33; N 3.4.



3b



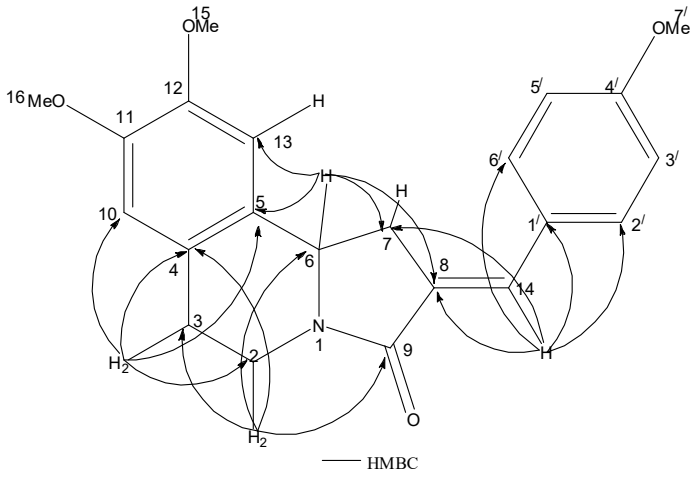
^{1}H NMR for **3b**



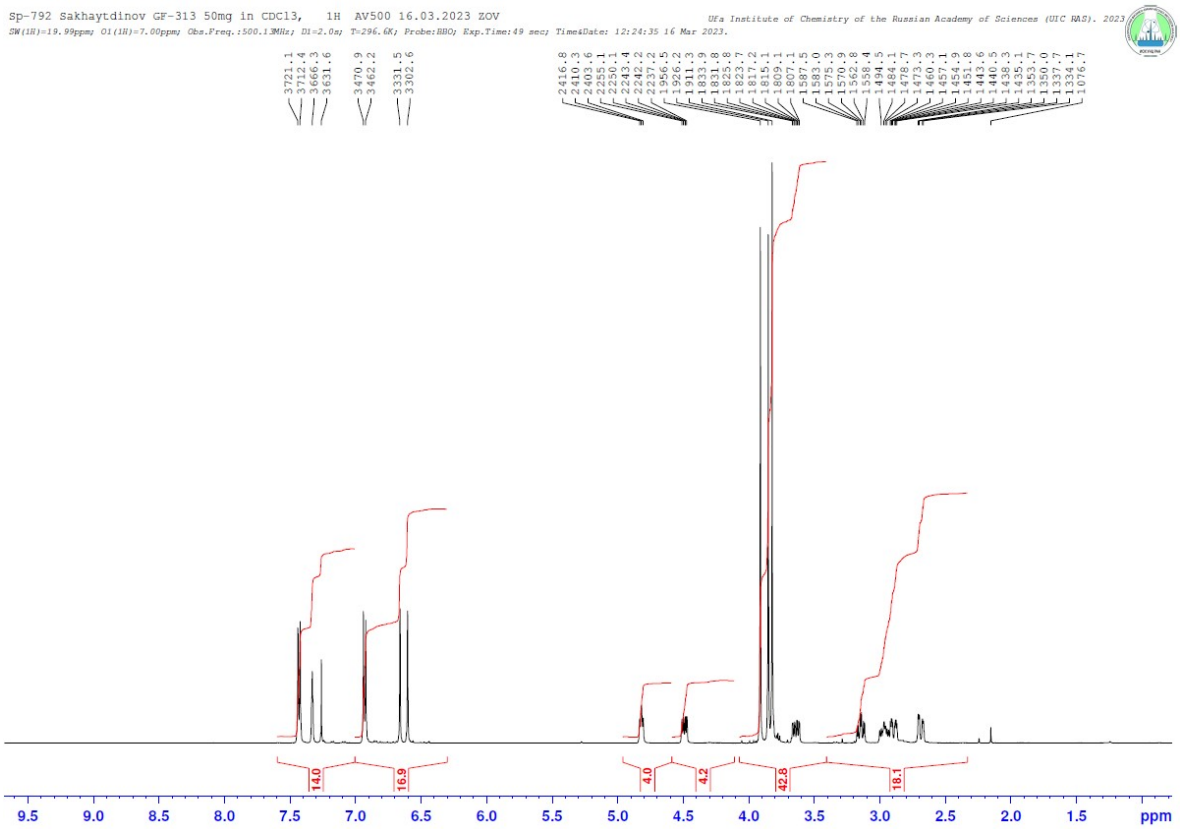
^{13}C NMR for **3b**

General procedure for cyclization of amines by the Pictet–Spengler reaction. Excess $NaBH_4$ (8 mmol) was added portionwise to a solution of imide **3a,b** (1.8 mmol) in a 10 ml MeOH-$CHCl_3$ (9:1), and the mixture was stirred for 2 h at room temperature. Concentrated HCl was added to achieve acidic pH, and the mixture was refluxed for 3 h (TLC control). The reaction mixture was evaporated. The residue was dissolved in H_2O, extracted with $CHCl_3$ and chromatographed on SiO_2 (petroleum ether/ethyl acetate=1:1).

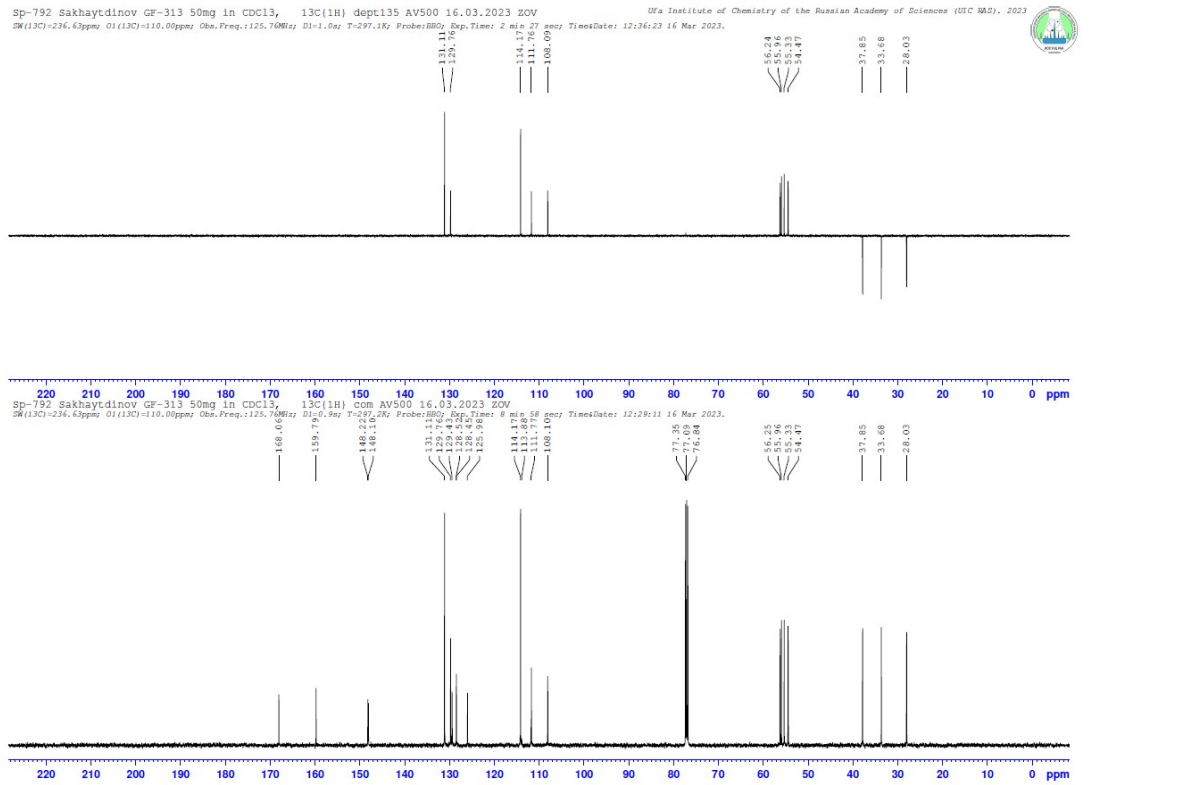
(*E*)-7,8-Dimethoxy-1-(4-methoxybenzylidene)-1,5,10,10a-tetrahydropyrrolo[1,2-*a*]-isoquinolin-3(2*H*)-one 4a. Yield 88%. The product was isolated as yellow crystals. IR spectrum (Nujol, ν, cm^{-1}): 1676, 1645, 1604, 1512, 1446, 1559, 1226, 1184, 1105, 1129, 864. ^1H NMR ($CDCl_3$, δ, ppm, *J*/Hz): 2.69 (H, dd, J-16, J=3.6, CH_2-3a), 2.88 (H, m, CH_2-7a), 3.02 (H, m, CH_2-3b,), 3.15 (H, m, CH_2 - 2a), 3.64 (H, m, CH_2-7b), 3.79 (3H, s, C H_3-7'), 3.84 (3H, s, CH_3-15), 3.93 (3H, s, CH_3-16), 4.48 (H, m, CH_2-2b), 4.82 (H, m, CH_2-6), 6.58 (H, s, CH-10), 6.67 (H, s, CH-13), 6.94 (2H, d, J=8.7, CH-3', 5'), 7.32 (1H, s, CH-14), 7.43 (2H, d, J=8.7, CH-6', 2'). ^{13}N NMR ($CDCl_3$, δ, ppm): 28.03 (C-3), 33.68 (C-7), 37.85 (C-2), 54.47 (C-6), 55.33 (C-7'), 55.96 (C-15), 56.25 (C-16), 108.10 (C-13), 111.77 (C-10), 113.88 (C-3', 5'), 125.98 (C-4), 128.45 (C-5), 129.43 (=C-14), 129.76 (C-1', =C-8), 131.11 (C-6', 2'), 148.10 (C-12), 148.22 (C-11), 159.79 (C-4'), 168.06 (O=C-9). MW 365,42. Found, %: C 72.26, H 6.21, N 3.79. Calculated for $C_{22}H_{23}NO_4$, %: C, 72.31; H, 6.34; O, 17.51; N 3.83.



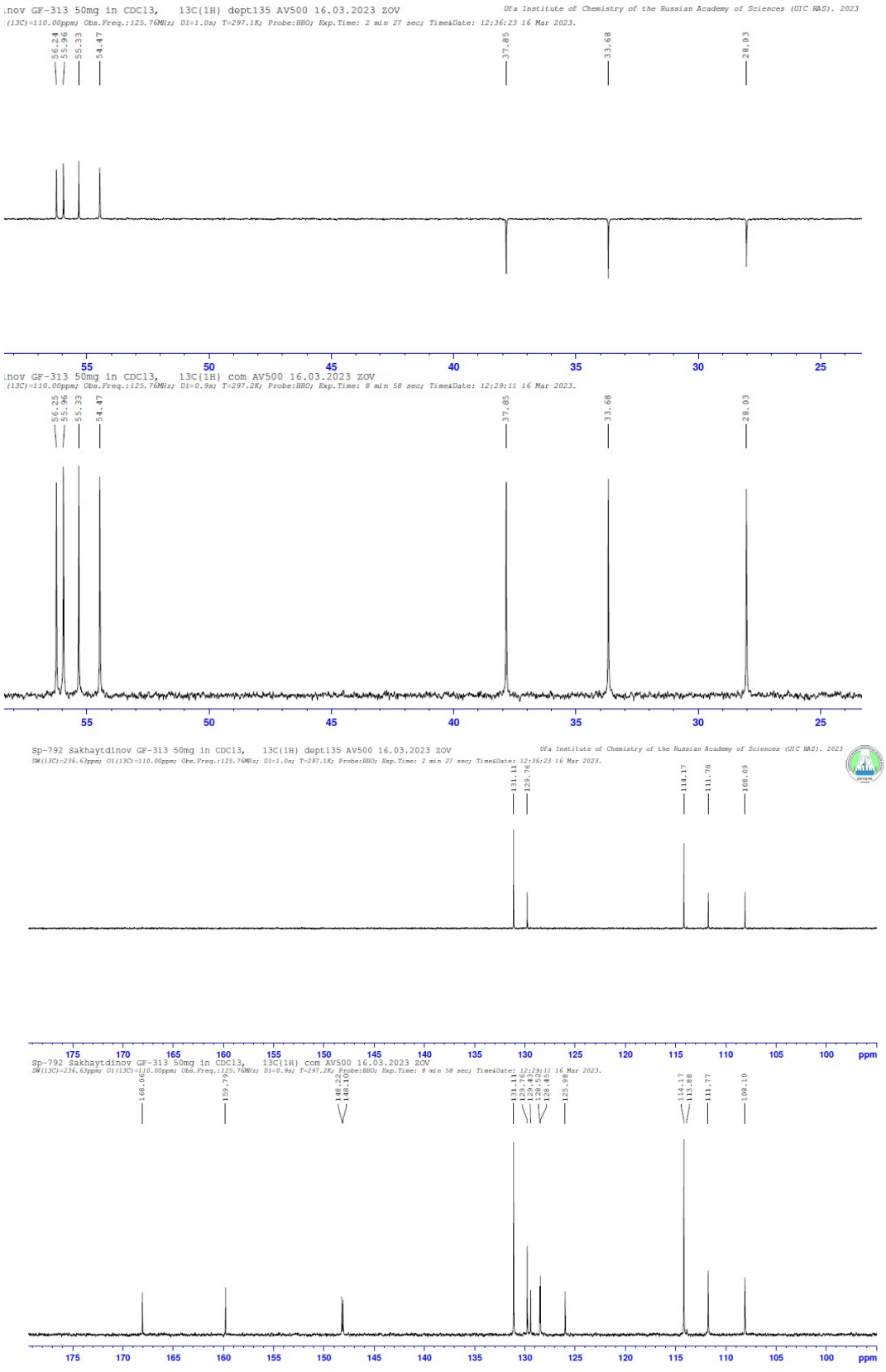
Atom numbering is given for assignment and does not coincide with the systematic



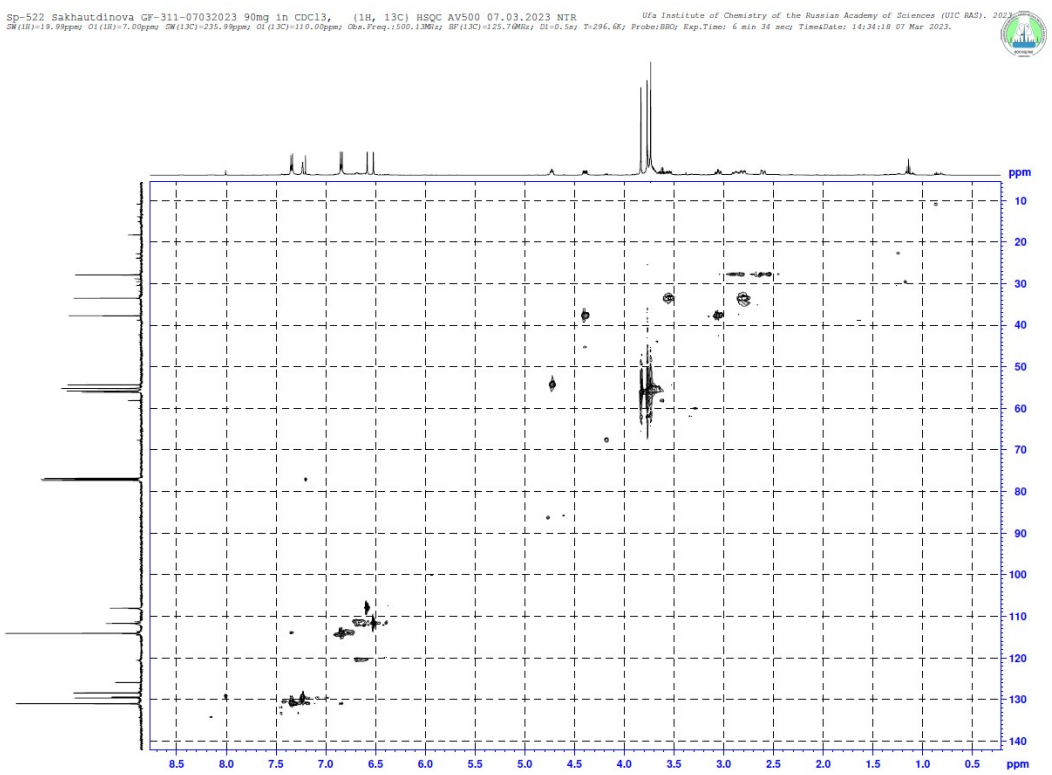
^{1}H NMR for **4a**



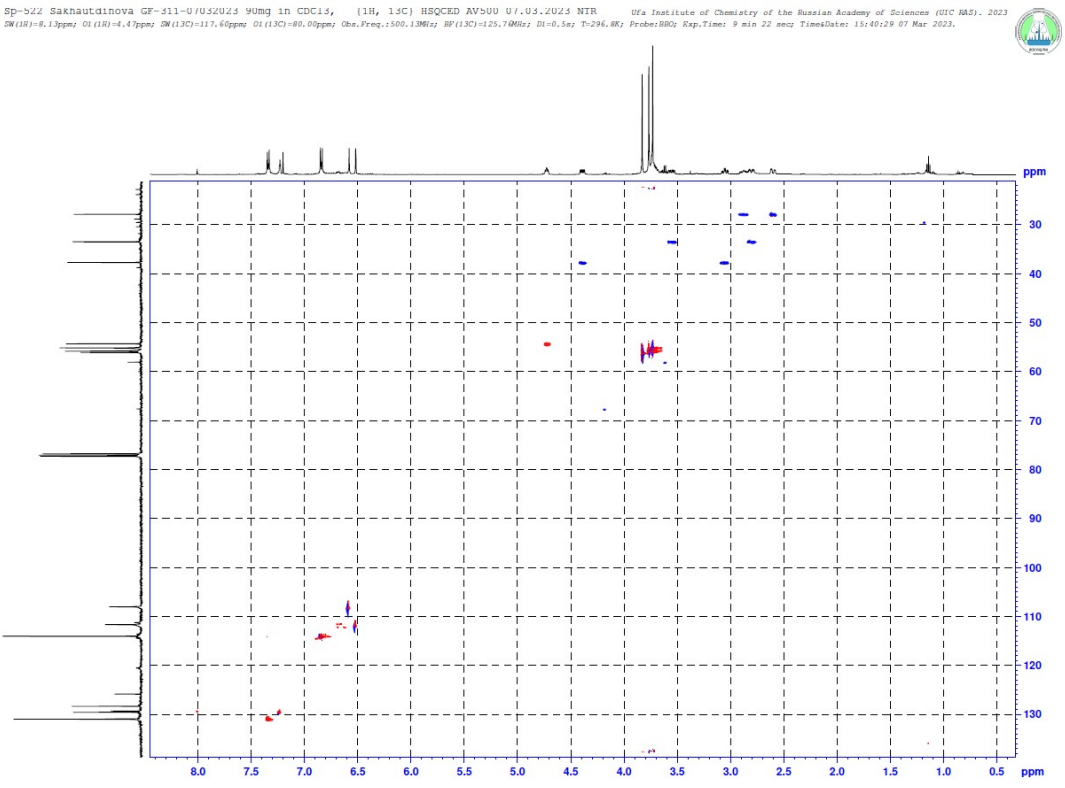
^{13}C NMR for **4a**



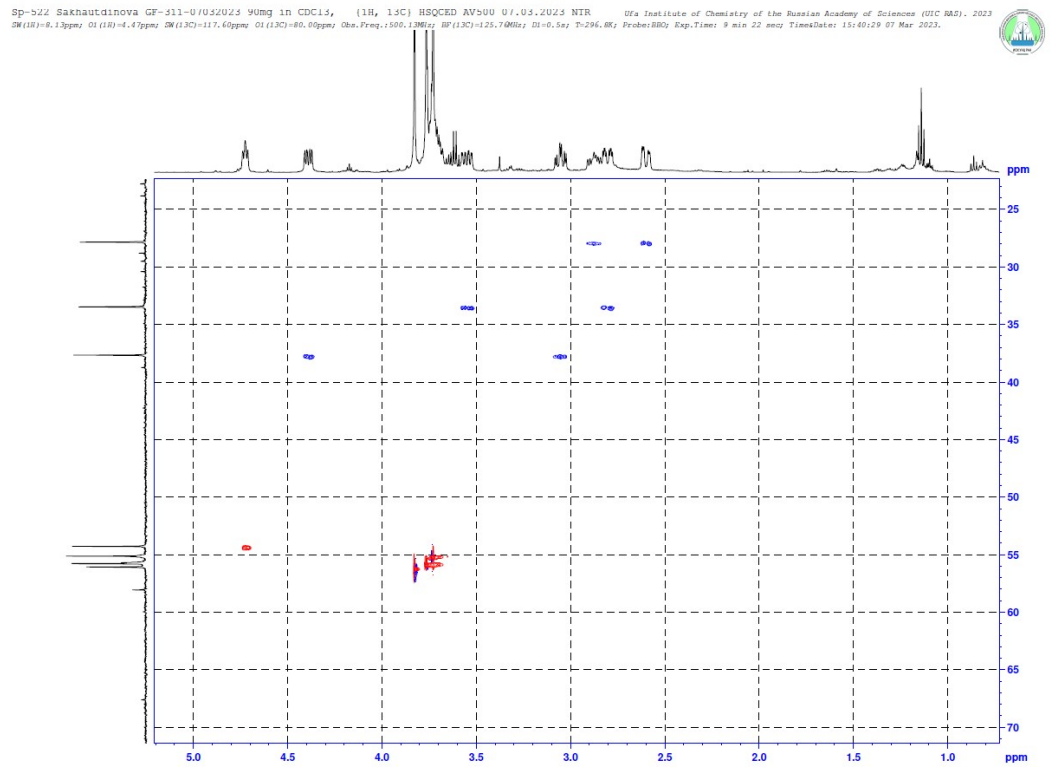
^{13}C NMR for **4a**



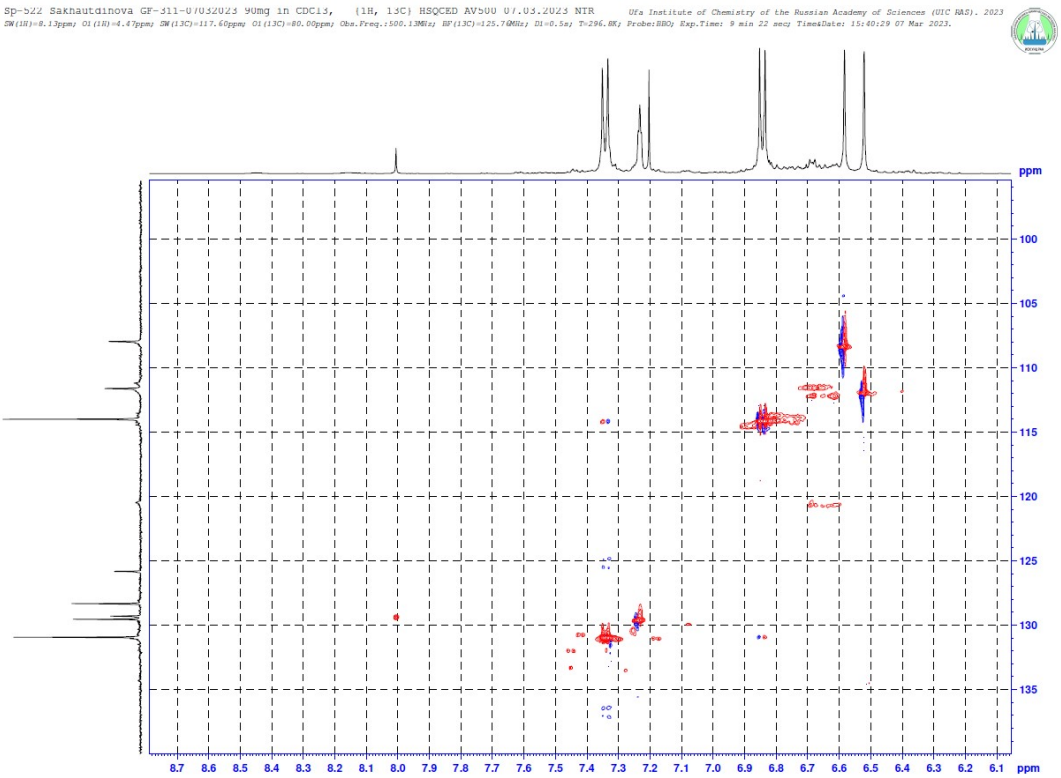
2D NMR correlation spectra (^{1}H,^{13}C HSQC) for **4a**



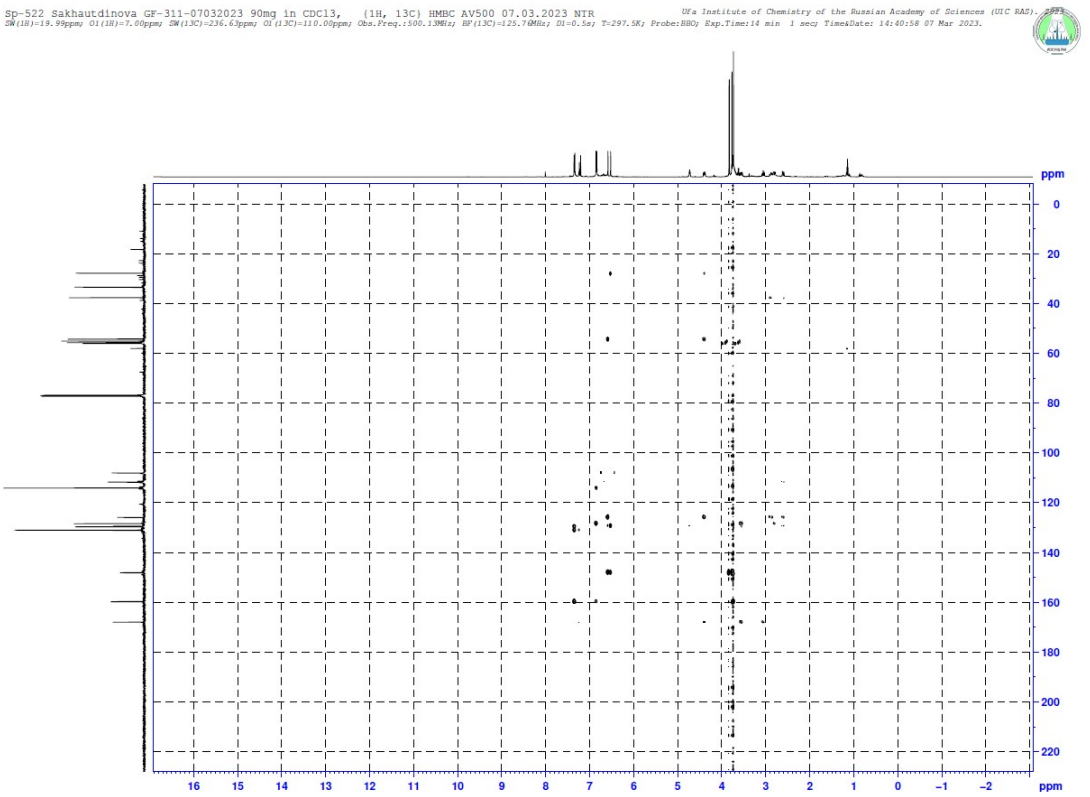
2D NMR correlation spectra (^{1}H,^{13}C HSQCED) for **4a**



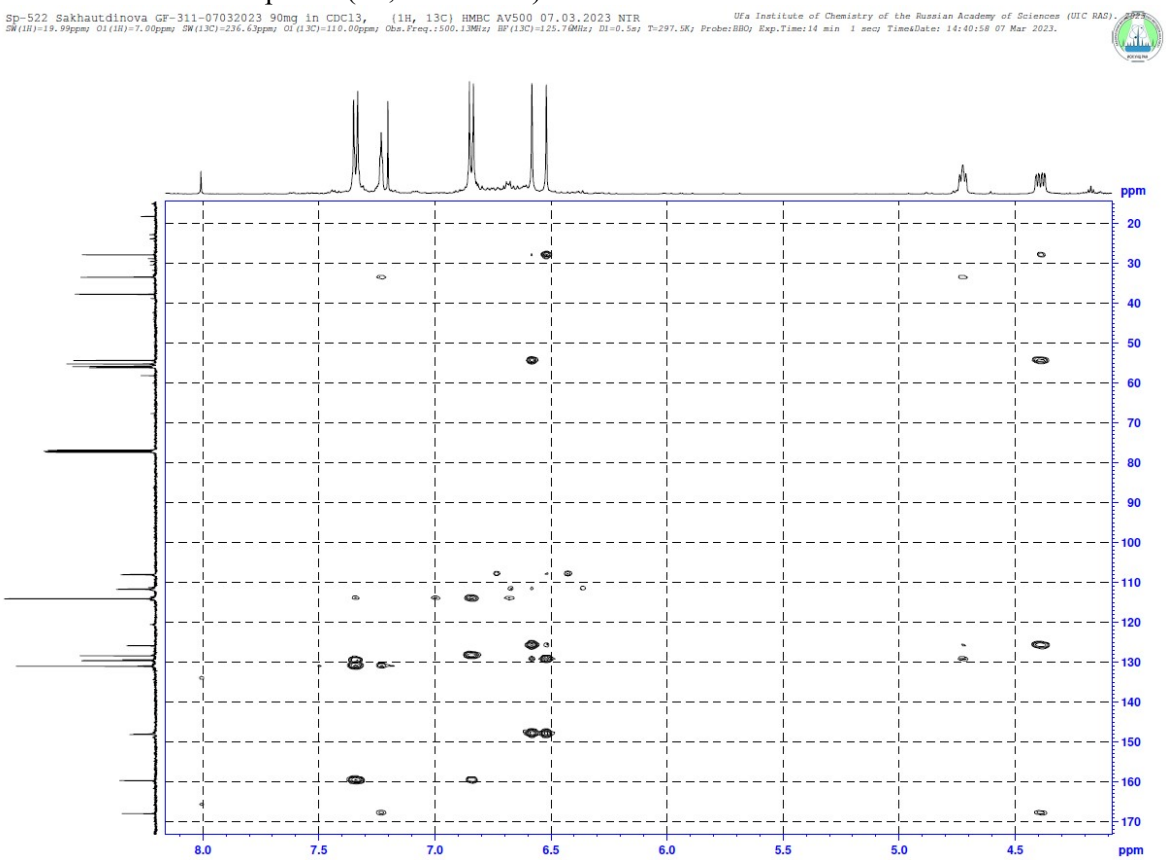
2D NMR correlation spectra ($^{1}H,^{13}C$ HSQCED) for **4a**



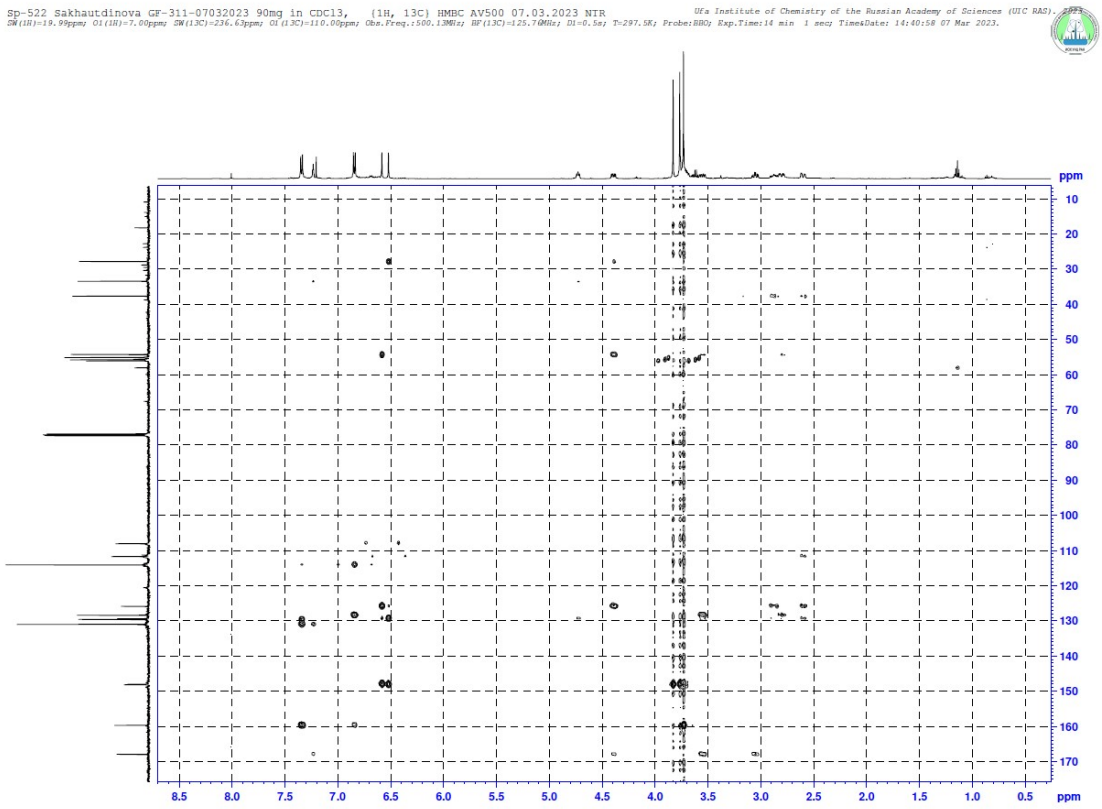
2D NMR correlation spectra ($^{1}H,^{13}C$ HSQCED) for **4a**



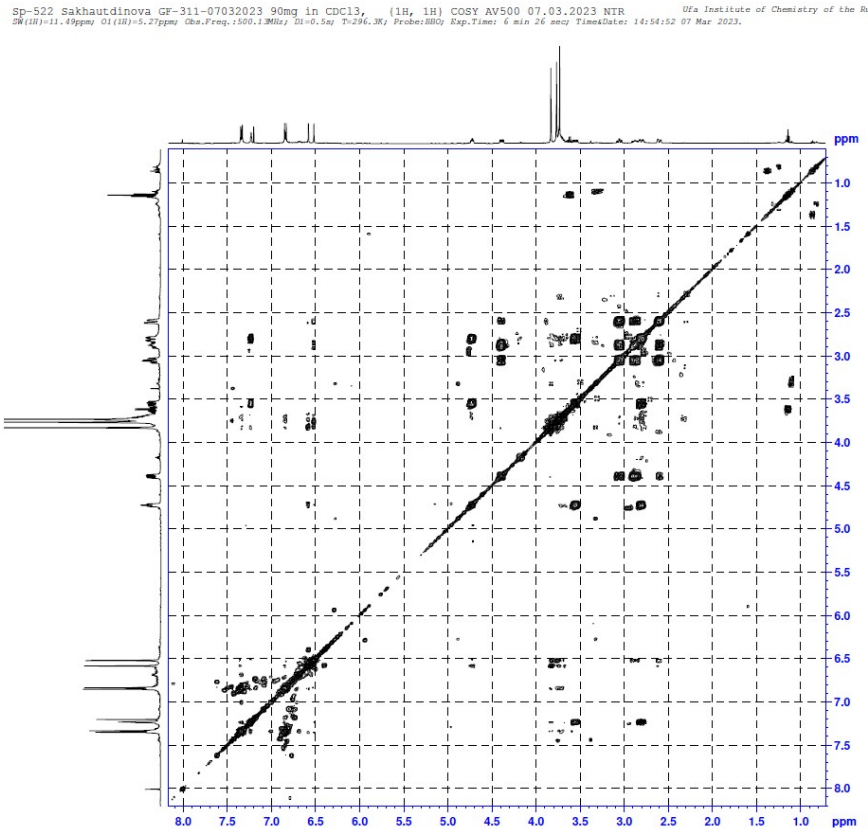
2D NMR correlation spectra (^{1}H,^{13}C HMBC) for **4a**



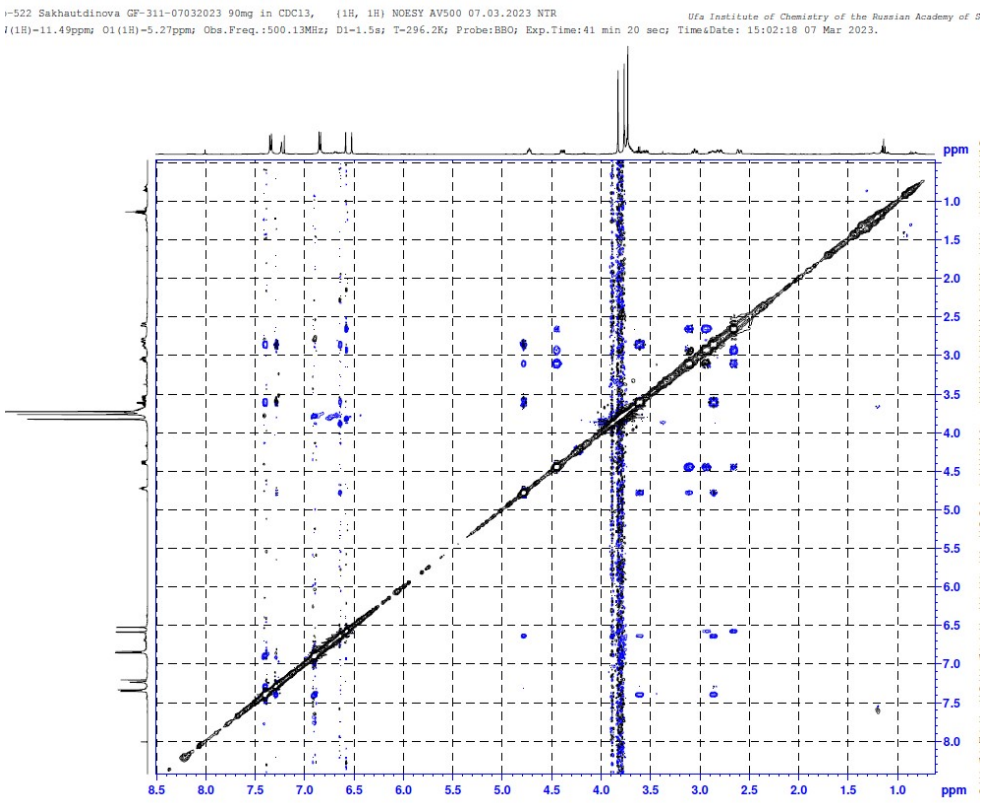
2D NMR correlation spectra (^{1}H,^{13}C HMBC) for **4a**



2D NMR correlation spectra (^{1}H,^{13}C HMBC) for **4a**

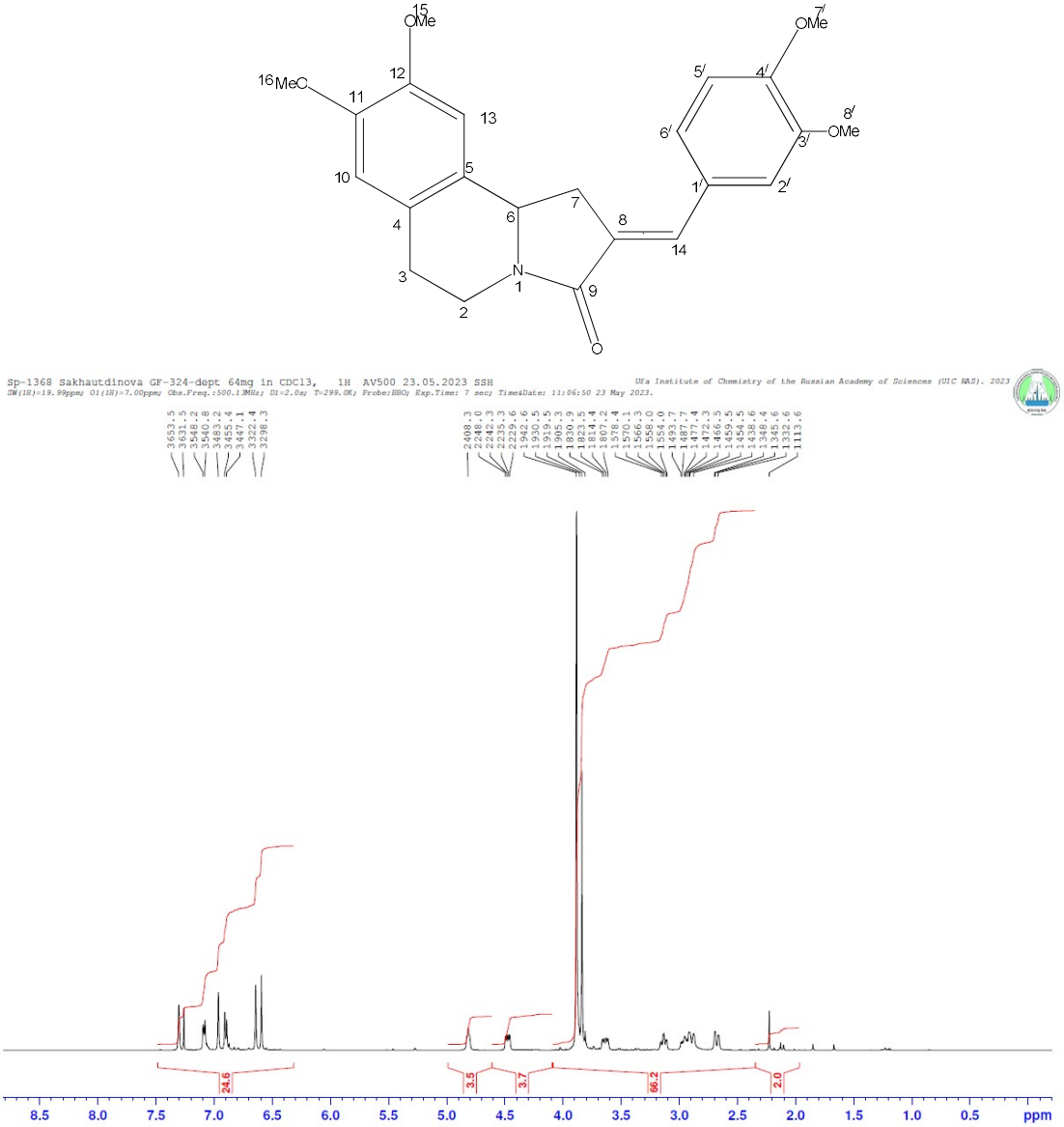


2D NMR correlation spectra (^{1}H,^{1}H COSY) for **4a**

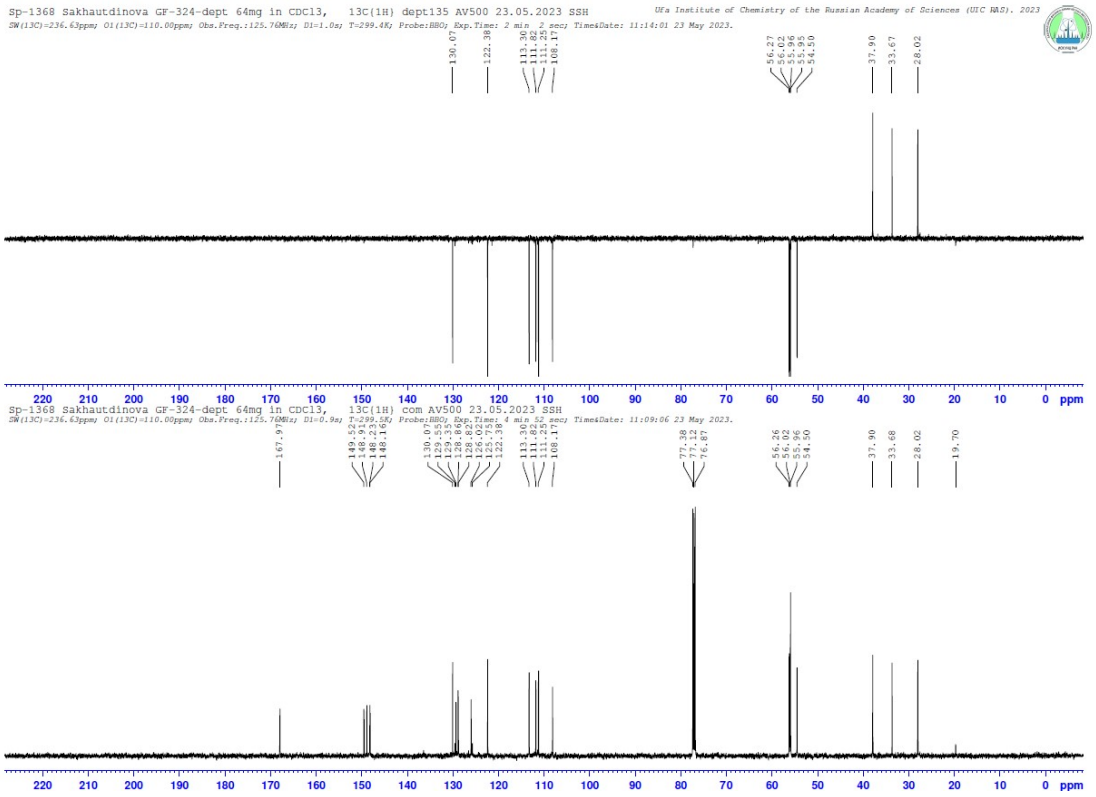


2D NMR correlation spectra (^{1}H,^{1}H NOESY) for **4a**

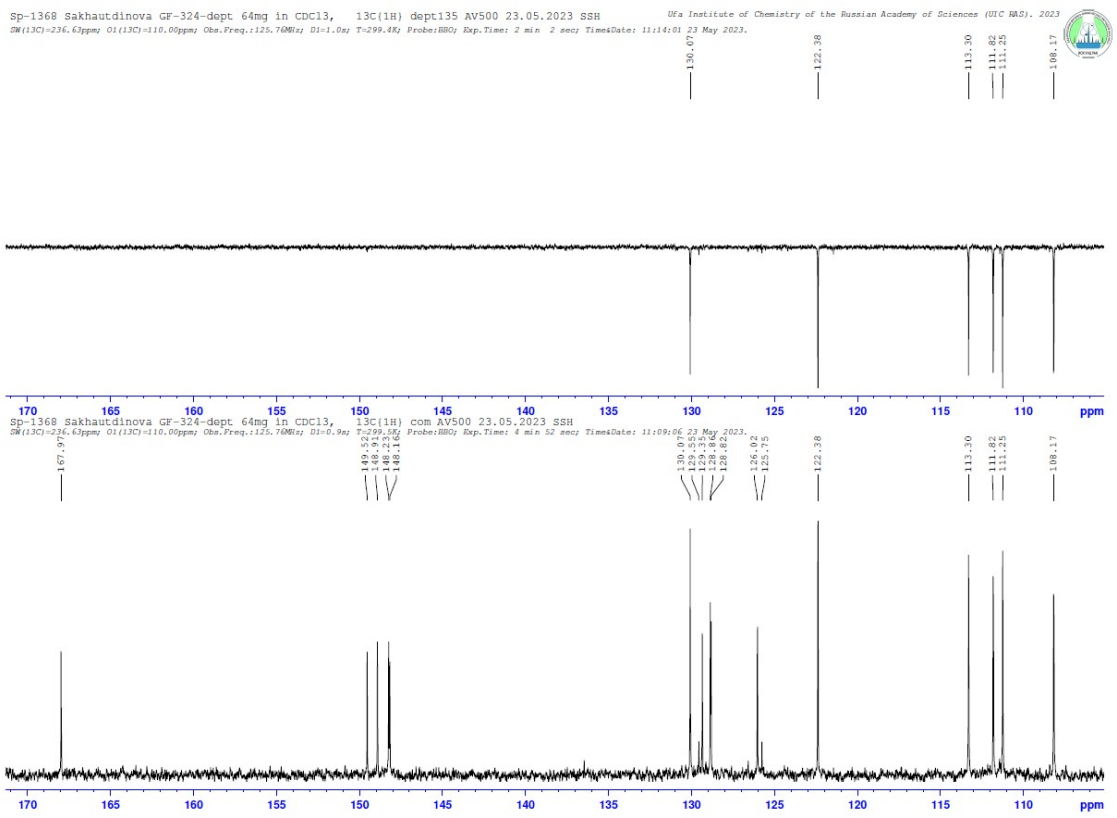
(*E*)-1-(3,4-Dimethoxybenzylidene)-7,8-dimethoxy-1,5,10,10a-tetrahydropyrrolo[1,2-*a*]-isoquinolin-3(2*H*)-one 4b. Yield 45%. The product was isolated as a yellow crystal. IR spectrum (Nujol, ν, cm^{-1}): 1682, 1647, 1599, 1517, 1465, 1330, 1259, 1145, 1025, 733. ^{1}H NMR ($CDCl_3$, δ, ppm, *J*/Hz): 2.68 (H, dd, J-15.8, J=2.9, CH_2-3a), 2.89 (H, m, CH_2-7a), 2.95 (H, m, CH_2-3b,), 3.14 (H, m, CH_2 - 2a), 3.64 (H, m, CH_2-7b), 3.71 (3H, s, CH_3-7'), 3.85 (9H, s, CH_3-8', 15, 16), 4.49 (H, m, CH_2-2b), 4.72 (H, m, CH_2-6), 6.58 (H, s, CH-10), 6.67 (H, s, CH-13), 6.89 (H, d, J=8.3, CH-5'), 6.96 (1H, s, CH-2'), 7.08 (H, d, J=8.3, CH-6'), 7.31(H, s, CH-14). ^{13}C NMR ($CDCl_3$, δ, ppm): 28.02 (C-3), 33.67 (C-7), 37.90 (C-2), 54.50 (C-6), 55.96 (C-15), 55.96 (C-7'), 56.02 (C-8'), 56.27 (C -16), 108.00 (C-13), 111.25 (C-5'), 111.82 (C-10), 113,3 (C-2'), 122.38 (C-6'), 126.02 (C-5), 128.82 (C-1'), 128.86 (C-4), 129.35 (C-8), 130.07 (=C-14), 148.16 (C-12), 148.23 (C-11), 148,91 (C-3'), 149,52 (C-4'), 167.97 (O=C-9). MW 395,45. Found, %: C 69.86, H 6.36, N 3.53. Calculated for $C_{23}H_{25}NO_5$, %: C, 69.86; H, 6.37; O, 20.23; N 3.54.



^{1}H NMR for **4b**



^{13}C NMR for **4b**



^{13}C NMR for **4b** (fragment)