Electronic supplementary materials *Mendeleev Commun.*, 2020, **30**, 313-314

Base-determinant chemodivergent transformations of chiral 2,3-dibromopropanamide derivative

Natalya K. Selezneva, Adeliya M. Galeeva, Leonard M. Khalilov, Zuleykha R. Valiullina and Mansur S. Miftakhov

IR spectra were obtained on an IR Prestige-21 Shimadzu spectrophotometer in a film or in Nujol mulls. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVANCE-500 spectrometer with operating frequencies of 500.13 and 125.77 MHz, respectively, using TMS as the internal standard. Mass spectra were obtained on an LCMS-2010EV mass spectrometer (Shimadzu) (syringe injection, a solution of the sample in chloroform/acetonitrile, flow rate 0.1 ml min^{-1}, acetonitrile/water (95:5) as the eluent, positive and negative ion detection mode, at 4.5 and -3.5 kV potentials of a needle ionizing electrode, respectively; interface capillary temperature 250 °C, interface capillary voltage 5 V. Elemental analysis data were obtained on a Evro EA-3000 CHN analyzer. The reaction was monitored by TLC on "Sorbfil" plates (Krasnodar, Russia) with detection of compounds by wetting the plates with solutions of anisaldehyde and sulfuric acid in ethanol or phosphomolybdic acid in ethanol followed by heating at 120-150 °C. The synthesized products were isolated by column chromatography on silica gel (30-60 g of the adsorbent per 1 g of a compound).

2-Methyl-*N*-[(1*R*)-1-phenylethyl]acrylamide 1. Triethylamine (2.6 ml, 18.81 mmol) and then 1-phenylethylamine (1.39 g, 11.49 mmol) were added dropwise with stirring at 0 °C to a solution of methacryloyl chloride (1.0 g, 9.57 mmol) in anhydrous CH_2Cl_2 (10 ml). The mixture was stirred for 4 h at room temperature, CH_2Cl_2 (10 ml) was added. The mixture was then washed with saturated NaCl solution (2×10 ml), the organic layer was dried with $MgSO_4$ and filtered, and the solution was evaporated. Purification of the residue by SiO_2 column chromatography (petroleum ether-ethyl acetate, 5:1) gave 1.5 g (83%) of crystalline amide **1**. M.p. 93 °C, $[\alpha]_D^{20}$ +83.0^{o} (*c* 2.40, CH_2Cl_2). IR, ν, cm^{-1}: 3335, 1652, 1615, 1519, 1455, 1221, 759, 702. ^{1}H NMR (500 MHz) $CDCl_3$, δ: 1.50 (d, 3H, CH_3, *J* 6.9 Hz), 1.95 (s, 3H, CH_3), 5.20 (p, 1H, CH-N, *J* 7.0 Hz), 5.30 (s, 1H, CH_2=), 5.68 (s, 1H, CH_2=), 6.20 (br.s, NH), 7.20 (m, 1H, Ar) and 7.32 (m, 4H, Ar). ^{13}C NMR (125 MHz) $CDCl_3$, δ: 18.73 (CH_3), 21.70 (CH_3), 48.83 (CH-N), 119.50 (C^3), 126.62, 127.38, 128.70, 143.24 (C_{Ar}), 140.14 (C^2) and 167.66 (C=O). Found, %: C 76.01, H 7.87, N 4.21.

Calc. for $C_{12}H_{15}NO$, %: C 76.16, H 7.99, N 7.40. MS (EI, m/z, %): 190 (100 $[M+H]^+$), 188 (100 $[M-H]^-$), 347 (50 $[M-H+MeCN+H_2O]^-$).

(2*RS*)-2,3-Dibromo-2-methyl-*N*-[(1*R*)-1-phenylethyl]propanamide 2. A solution of Br_2 (1.0 g, 6.25 mmol) in CH_2Cl_2 (3 ml) was added to a solution of amide **3** (0.40 g, 2.12 mmol) in anhydrous CH_2Cl_2 (10 ml), and the mixture was stirred for 1 h (TLC control). After that, the mixture was washed with an aqueous $Na_2S_2O_3$ solution (2×5 ml) and saturated NaCl solution (2×5 ml). The organic layer was dried with $MgSO_4$, filtered, and evaporated. Purification of the residue by SiO_2 column chromatography (petroleum ether-ethyl acetate, 10:1) gave 0.54 g (73%) of oily dibromide **2**. Individual samples of **2a** and **2b** were isolated by repeated chromatography of on fine SiO_2 (40-60 mm, Sigma-Aldrich). IR, ν, cm^{-1}: 3307, 1652, 1615, 1538, 1456, 1377, 758, 698. Found, %: C 41.10, H 4.49, Br 45.51, N 4.18. Calc. for $C_{12}H_{15}Br_2NO$, %: C 41.29, H 4.33, Br 45.78, N 4.01.

(2*R*)-2,3-Dibromo-2-methyl-*N*-[(1*R*)-1-phenylethyl]propanamide 2a. R_f 0.57 (petroleum ether-ethyl acetate, 4:1). M.p. 106-107 ºC, $[\alpha]_D^{20}$ +45.0º (*c* 1.40, $CHCl_3$). ^{1}H NMR (500 MHz) $CDCl_3$, *δ*: 1.50 (d, 3H, CH_3, *J* 7.0 Hz), 2.00 (s, 3H, CH_3), 3.89 (d, 1H, H^{3A}, *J* 10.7 Hz), 3.93 (d, 1H, H^{3B}, *J* 10.7 Hz), 5.10 (p, 1H, CH-N, *J* 7.0 Hz), 6.80 (br.s, 1H, NH), 7.30-7.40 (m, 5H, Ar). MS (EI, m/z, %): 350 (100 $[M+H]^+$).

(2*S*)-2,3-Dibromo-2-methyl-*N*-[(1*R*)-1-phenylethyl]propanamide 2b. R_f 0.6 (petroleum ether-ethyl acetate, 4:1). M.p. 120-121 ºC, $[\alpha]_D^{20}$ +15.0º (*c* 2.04, $CHCl_3$). ^{1}H NMR (500 MHz) $CDCl_3$, *δ*: 1.51 (d, 3H, CH_3, *J* 6.9 Hz), 2.10 (s, 3H, CH_3), 3.89 (d, 1H, H^{3A}, *J* 10.7 Hz), 4.00 (d, 1H, H^{3B}, *J* 10.7 Hz), 5.10 (p, 1H, CH-N, *J* 6.9 Hz), 6.80 (br.s, 1H, NH), 7.30 (m, 1H), 7.45 (m, 4H, Ar). ^{13}C NMR (125 MHz) $CDCl_3$, *δ*: 21.54 (CH_3), 29.06 (CH_3), 41.33 (C^3), 50.03 (CH-N), 63.97 (C^2), 125.98, 127.57, 128.78, 142.29 (C_{Ar}) and 167.57 (C=O). MS (EI, m/z, %): 350 (100 $[M+H]^+$).

Transformation of dibromide 2 in DBU-benzene system. A solution of dibromide **2** (0.05 g, 0.14 mmol) and DBU (0.05 g, 0.33 mmol) in anhydrous benzene (5 ml) was stirred for 2 h. The mixture was washed with an aqueous solution of $Na_2S_2O_3$ (1×2 ml) and saturated NaCl solution (1×3 ml). The organic layer was dried with $MgSO_4$, filtered, and evaporated. Purification of the residue by SiO_2 column chromatography (petroleum ether-ethyl acetate, 10:1→8:1→5:1) gave 0.02 g (52%) of compound **3a** and 0.01 g (26%) of compound **3b**. Found, %: C 53.59, H 5.38, Br 29.71, N 5.39. Calc. for $C_{12}H_{14}BrNO$, %: C 53.75, H 5.26, Br 29.80, N 5.22.

(2*E*)-3-Bromo-2-methyl-N-[(1*R*)-1-phenylethyl] acrylamide 3a. R_f 0.5 (petroleum ether-ethyl acetate, 4:1). $[\alpha]_D^{20}$ +29.0º (*c* 1.72, $CHCl_3$). IR, ν, cm^{-1}: 3341, 1633, 1525, 760, 699. ^{1}H NMR (500 MHz) $CDCl_3$, *δ*: 1.52 (d, 3H, CH_3, *J* 7.1 Hz), 2.00 (s, 3H, CH_3), 5.15 (p, 1H, CH-

N, *J* 7.0 Hz), 6.00 (br.s, NH), 7.10 (s, H^3), 7.25-7.40 (m, 5H, Ar). ^{13}C NMR (125 MHz) $CDCl_3$, δ: 16.23 (CH_3), 21.55 (CH_3), 49.22 (CH-N), 116.28 (C^3), 126.18, 127.60, 128.81, 142.72 (C_{Ar}), 137.51 (C^2) and 165.36 (C=O). MS (EI, m/z, %): 268/270 (100/95 $[M+H]^+$), 309/311 (28/30 $[M+MeCN+H]^+$).

(2*Z*)-3-Bromo-2-methyl-*N*-[(1*R*)-1-phenylethyl]acrylamide 3b. R_f 0.2 (petroleum ether-ethyl acetate, 4:1). $[\alpha]_D^{20}$ -12.2° (*c* 0.46, $CHCl_3$). IR, ν, cm^{-1}: 3266, 1644, 1541, 1450, 1236, 699. ^{1}H NMR (500 MHz) $CDCl_3$, δ: 1.60 (d, 3H, CH_3, *J* 6.9 Hz), 2.00 (s, 3H, CH_3), 5.22 (p, 1H, CH-N, *J* 7.0 Hz), 6.20 (br. s, NH), 6.23 (d, 1H, H^3, *J* 1.5 Hz), 7.25-7.40 (m, 5H, Ar). ^{13}C NMR (125 MHz) $CDCl_3$, δ: 21.12 (CH_3), 21.62 (CH_3), 49.21 (CH-N), 103.43 (C^3), 126.35, 127.50, 128.71, 142.61 (C_{Ar}), 138.52 (C^2) and 166.19 (C=O). MS (EI, m/z, %): 268/270 (100/80 $[M+H]^+$).

3-Methylidene-1-[(1*R*)-phenylethyl]azetidin-2-one 4. Dibromide **2** (0.1 g, 0.3 mmol) was added in an argon atmosphere to a suspension of Bu^tOK (0.06 g, 1.71 mmol) in THF (4 ml). The mixture was stirred for 6 h (TLC control). A saturated solution of NH_4Cl (2 ml) was added, THF was evaporated, and the residue was extracted with CH_2Cl_2 (3×5 ml). The combined organic layers were washed with saturated NaCl (1×3 ml), dried with $MgSO_4$, filtered, and evaporated. Purification of the residue by SiO_2 column chromatography (petroleum ether-ethyl acetate, 4:1) gave 0.045 g (73%) of oily compound **4**. IR, ν, cm^{-1}: 1766, 1389, 1271, 700. $[\alpha]_D^{20}$ +72.0° (*c* 1.50, $CHCl_3$).^{1}H NMR (500 MHz) $CDCl_3$, δ: 1.63 (d, 3H, CH_3, *J* 7.0 Hz), 3.51 (d, 1H, H^{4A}, *J* 7.5 Hz), 3.72 (d, 1H, H^{4B}, *J* 7.5 Hz), 5.03 (q, 1H, CH-N, *J* 7.0 Hz), 5.12 (d, 1H, H_2C=, *J* 1.5 Hz), 5.70 (d, 1H, H_2C=, *J* 1.5 Hz), 7.25-7.40 (m, 5H, Ar). ^{13}C NMR (125 MHz) $CDCl_3$, δ: 18.35 (CH_3), 45.94 (C^4), 51.55 (CH-N), 109.41 (H_2C=), 126.74, 127.73, 128.79, 144.45 (C_{Ar}), 140.32 (C^3) and 163.00 (C=O). Found, %: C 76.79, H 7.13, N 7.56. Calc. for $C_{12}H_{13}NO$, %: C 76.98, H 7.00, N 7.48. MS (EI, m/z, %): 188 (100 $[M+H]^+$).

Cyclization of dibromide 2 in the NaH-THF system. Dibromides **2a,b** (0.1 g, 0.30 mmol) were added in an argon atmosphere to NaH (60% oil dispersion, 0.03 g, 0.83 mmol) in anhydrous THF (5 ml). The reaction mixture was stirred for 2 h. A saturated solution of NH_4Cl (2 ml) was added to the reaction mixture, THF was evaporated, and the residue was extracted with CH_2Cl_2 (3×10 ml). The combined organic layers were washed with saturated NaCl (1×3 ml), dried with $MgSO_4$, filtered, and evaporated. Purification of the residue by SiO_2 column chromatography (petroleum ether-ethyl acetate, 5:1) gave 0.03 g (39%) of compound **5a** and 0.03 g (38%) of compound **5b**.

(3*S*)-3-Bromo-3-methyl-1-[(1*R*)-1-phenylethyl]azetidin-2-one 5a. $[\alpha]_D^{20}$ +31.0° (*c* 1.22, $CHCl_3$). IR, ν, cm^{-1}: 1758, 1454, 1391, 1271, 1184, 764, 701. ^{1}H NMR (500 MHz) $CDCl_3$, δ: 1.60 (d, 3H, CH_3, *J* 7.1 Hz), 1.84 (s, 3H, CH_3), 3.30 (d, 1H, H^{4A}, *J* 6.0 Hz), 3.58 (d, 1H, H^{4B}, *J* 6.0 Hz),

4.90 (q, 1H, CH-N, *J* 7.0 Hz), 7.25-7.40 (m, 5H, Ar). ^{13}C NMR (125 MHz) $CDCl_3$, δ: 18.10 (CH_3), 24.75 (CH_3), 51.79 (CH-N), 55.66 (CH_2), 57.11 (C^3), 126.59, 127.93, 128.88, 139.52 (C_{Ar}) and 166.25 (C=O). Found, %: C 53.89, H 5.11, Br 29.97, N 5.38. Calc. for $C_{12}H_{14}BrNO$, %: C 53.75, H 5.26, Br 29.80, N 5.22. MS (EI, m/z, %): 268/270 (100/85 $[M+H]^+$), 309/311 (90/50 $[M+MeCN+H]^+$).

(3*R*)-3-Bromo-3-methyl-1-[(1*R*)-1-phenylethyl]azetidin-2-one 5b. $[\alpha]_D^{20}$ +80.0° (*c* 1.35, $CHCl_3$). IR, ν, cm^{-1}: 1762, 1454, 1392, 1271, 1184, 764, 700. ^{1}H NMR (500 MHz) $CDCl_3$, δ: 1.60 (d, 3H, CH_3, *J* 7.0 Hz), 1.90 (s, CH_3), 3.40 (s, 2H, CH_2Br), 4.90 (q, 1H, CH-N, *J* 7.0 Hz), 7.25-7.40 (m, 5H, Ar). ^{13}C NMR (125 MHz) $CDCl_3$, δ: 18.41 (CH_3), 24.97 (CH_3), 51.87 (CH-N), 55.75 (CH_2), 57.09 (C^3), 126.58, 127.95, 128.92, 139.51 (C_{Ar}) and 166.33 (C=O). Found, %: C 53.91, H 5.39, Br 29.71, N 5.31. Calc. for $C_{12}H_{14}BrNO$, %: C 53.75, H 5.26, Br 29.80, N 5.22. MS (EI, m/z, %): 268/270 (49/49 $[M+H]^+$), 309/311 (70/100 $[M+MeCN+H]^+$).

Reactions of individual **2a** or **2b** in NaH-THF system were performed similarly to afford isomers **5a** or **5b**, respectively, in yields above 90%.

SPECTRA OF COMPOUNDS

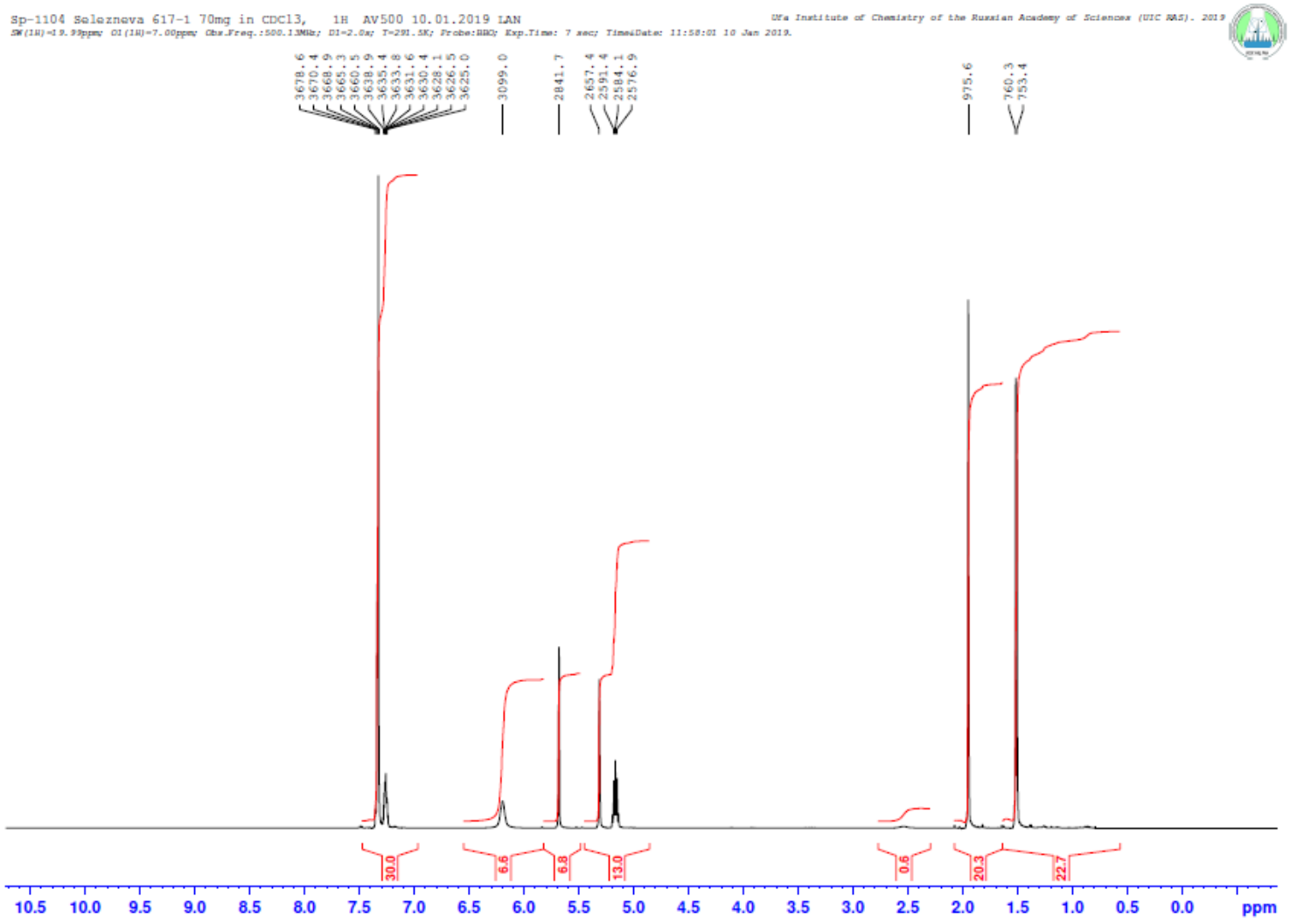

Figure S1. 500 MHz ^{1}H NMR of 1

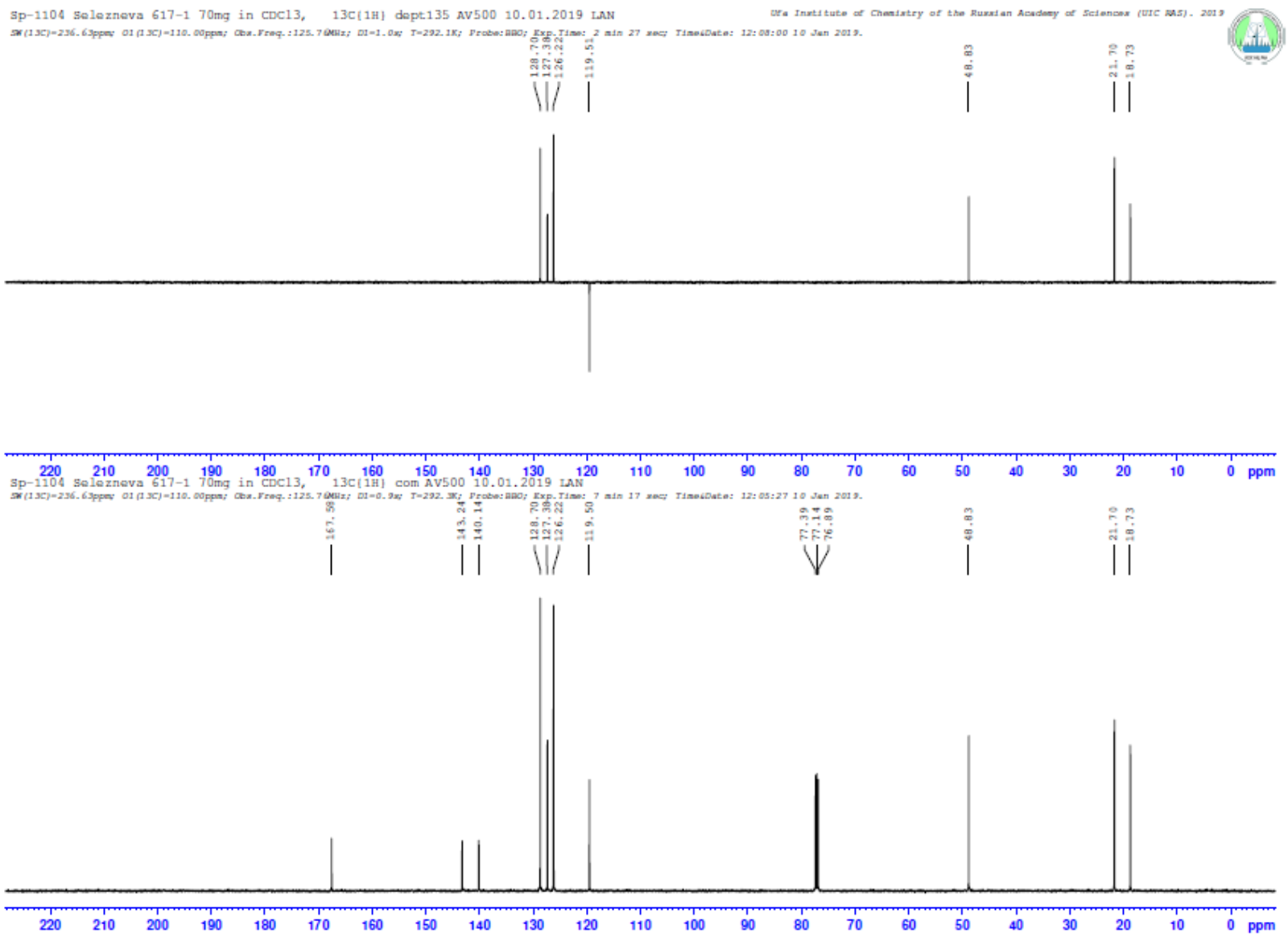

Figure S2. 125 MHz ^{13}C NMR of 1

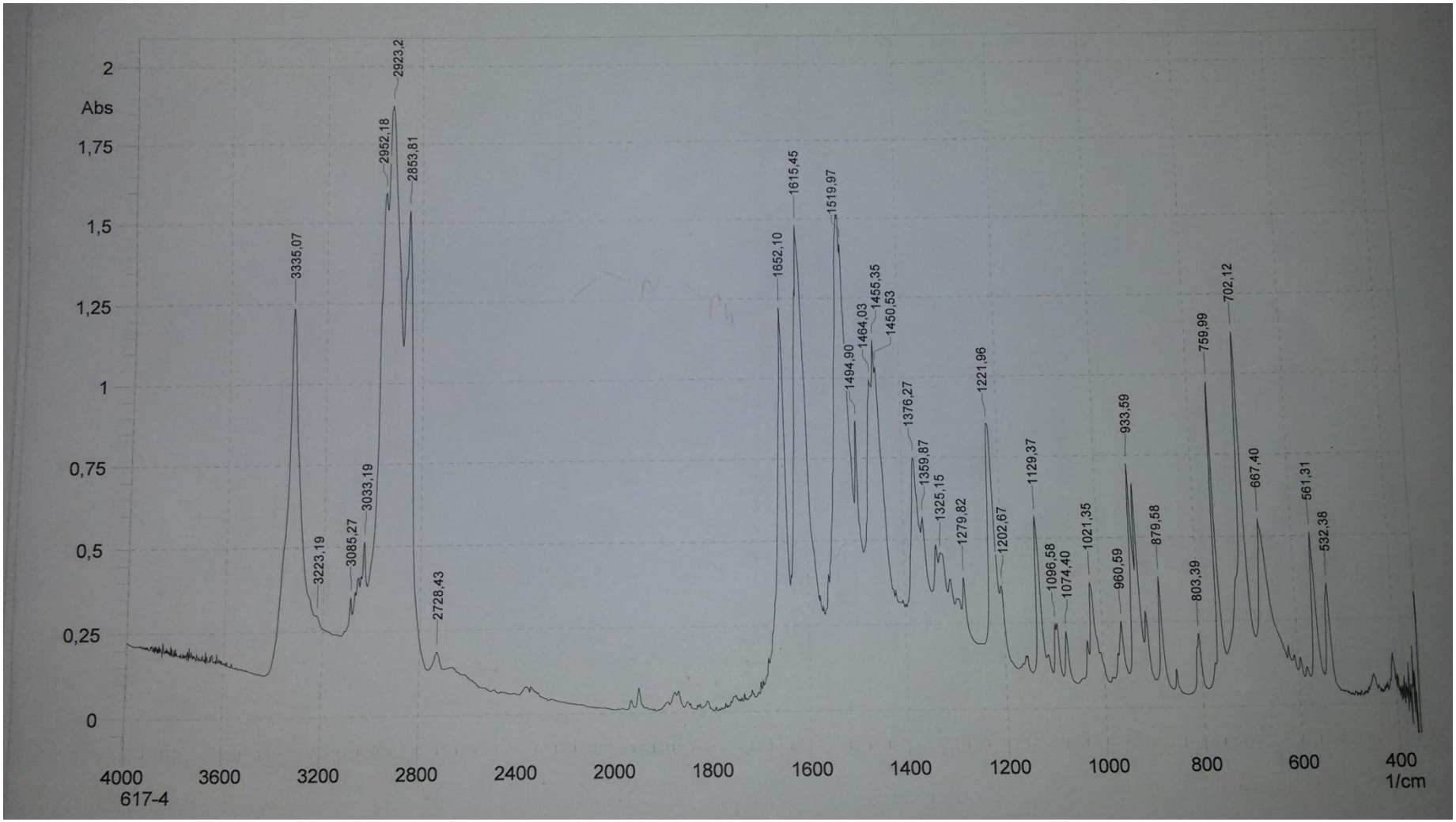

Figure S3. IR spectrum of compound 1.

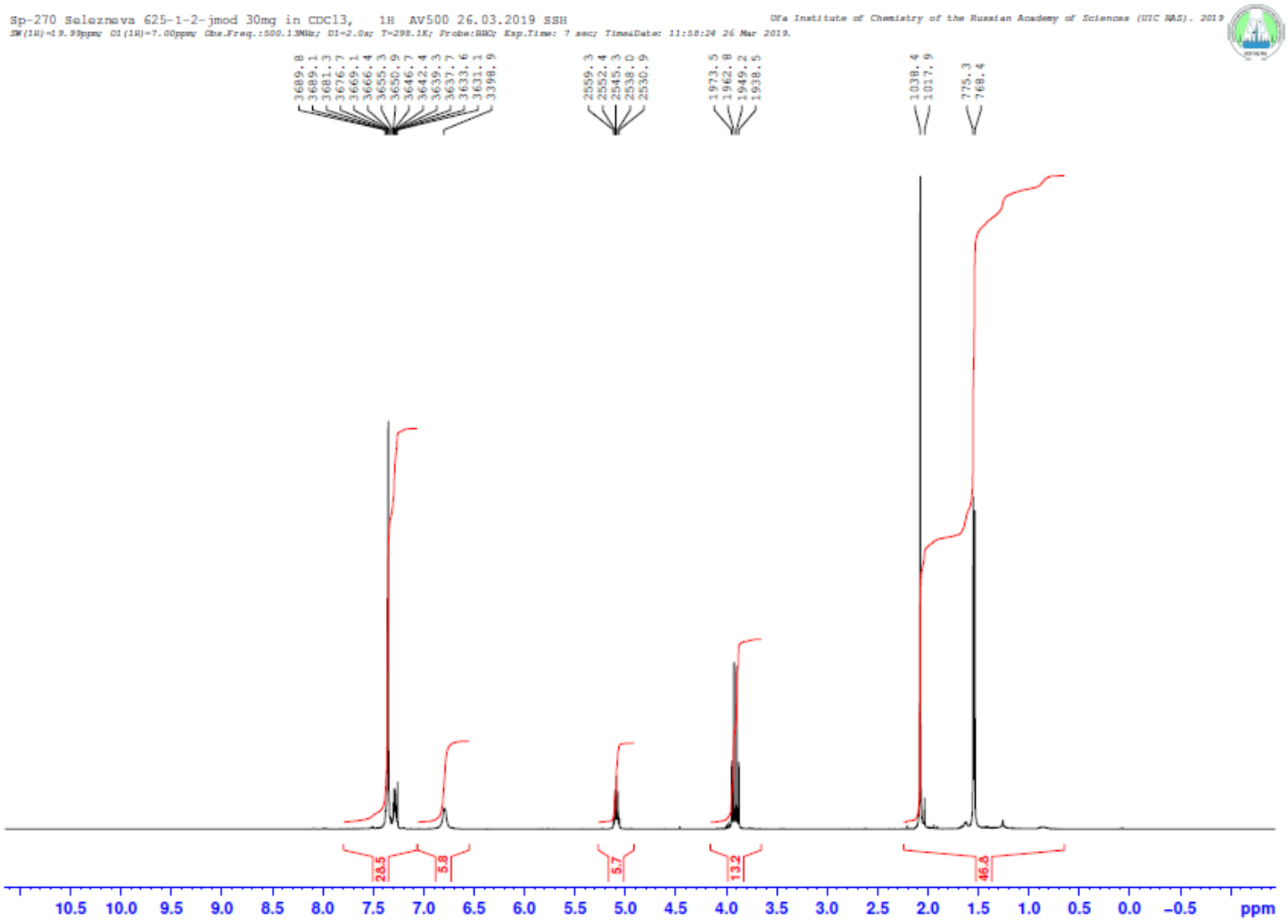

Figure S4. 500 MHz ^{1}H NMR of 2a

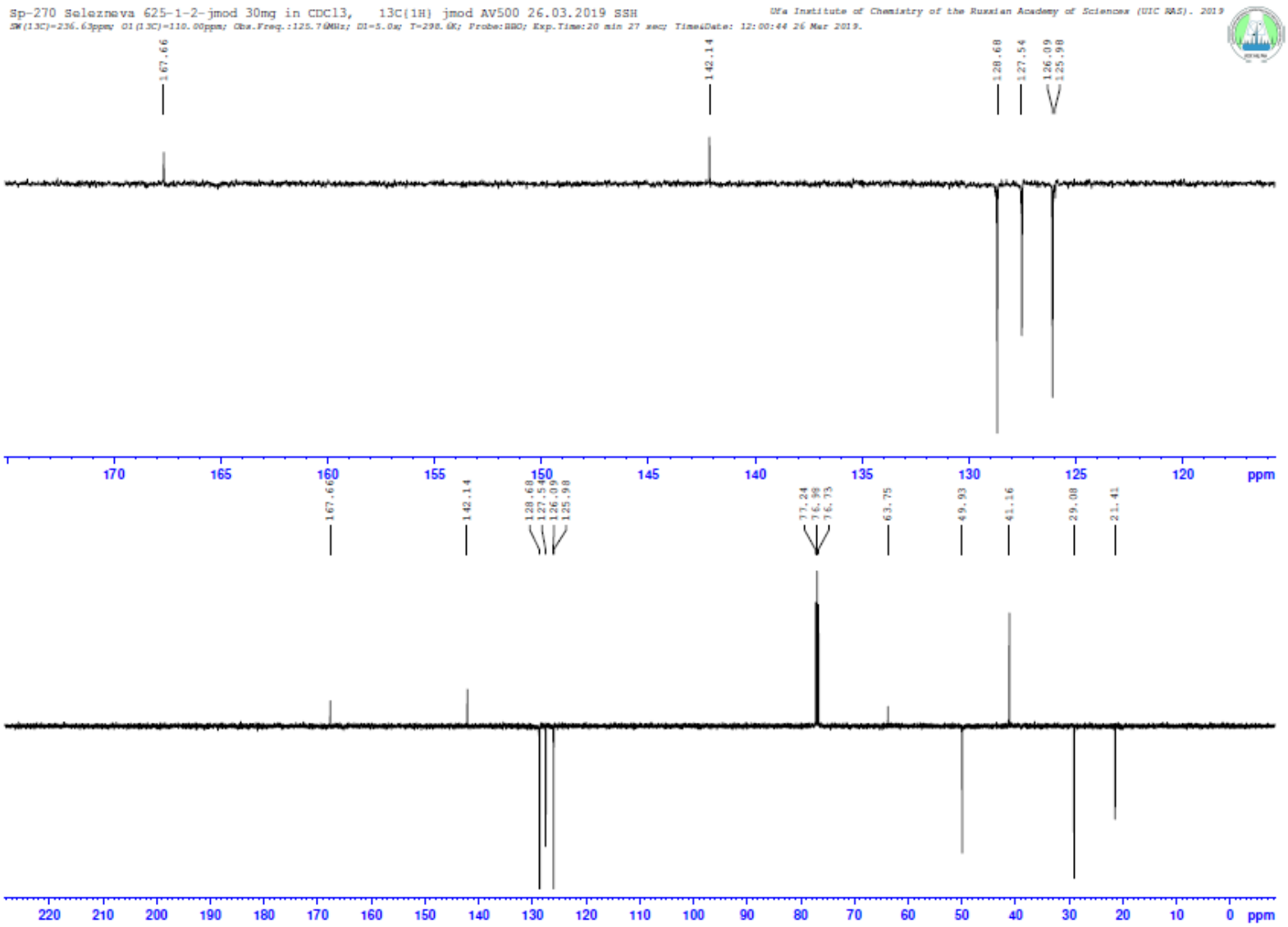

Figure S5. 125 MHz ^{13}C NMR of 2a

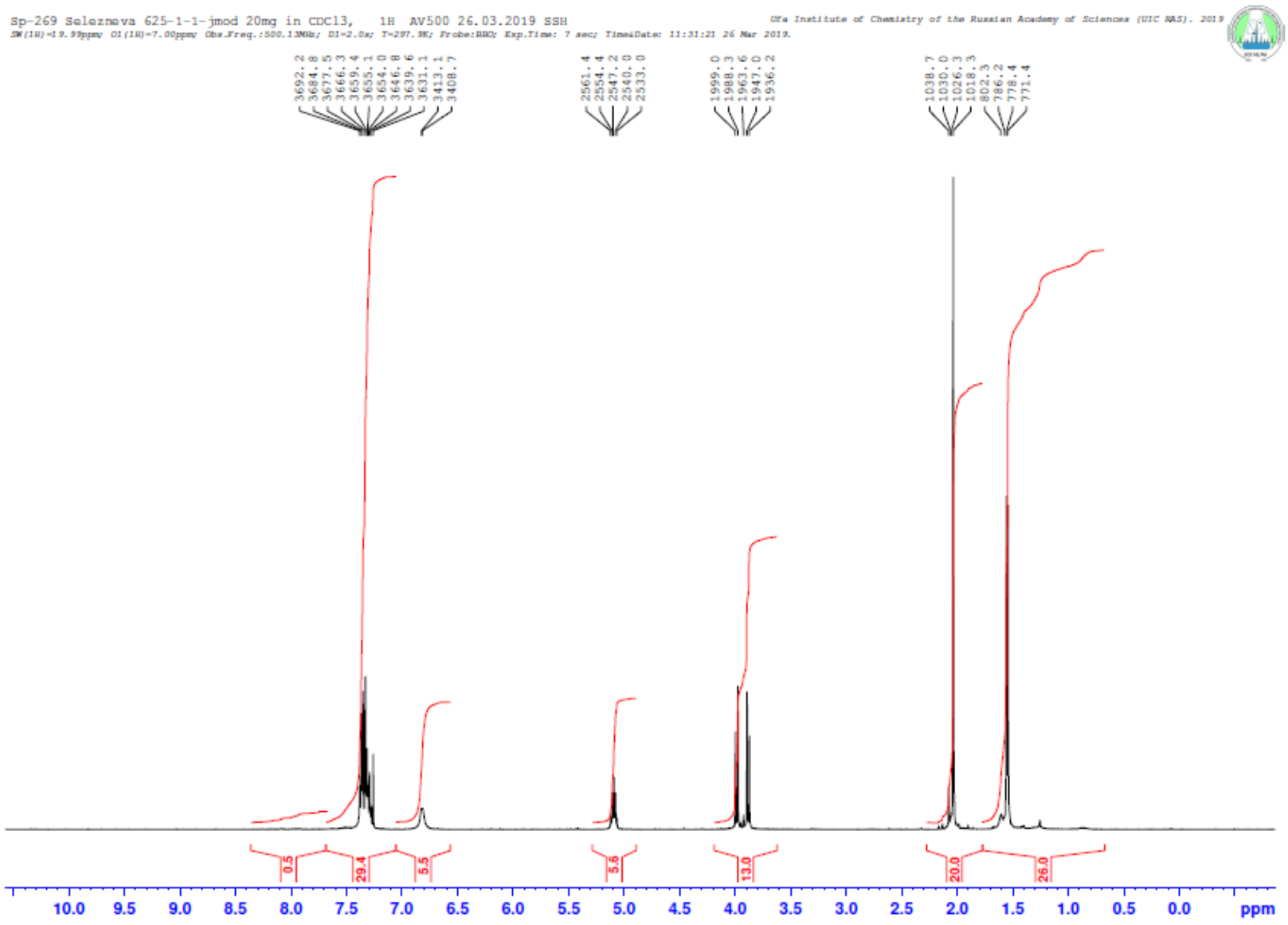

Figure S6. 500 MHz ^{1}H NMR of 2b

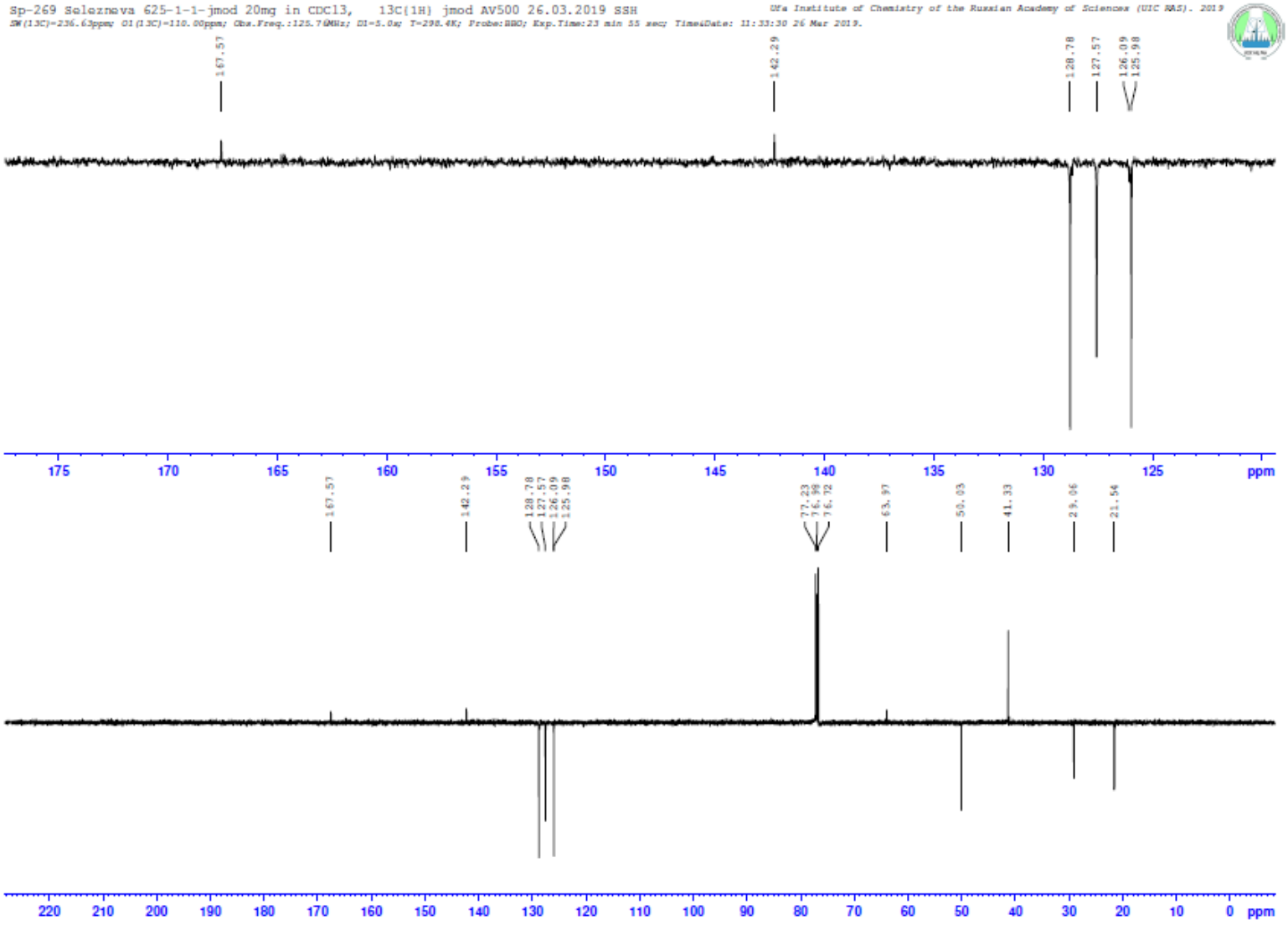

Figure S7. 125 MHz ^{13}C NMR of 2b

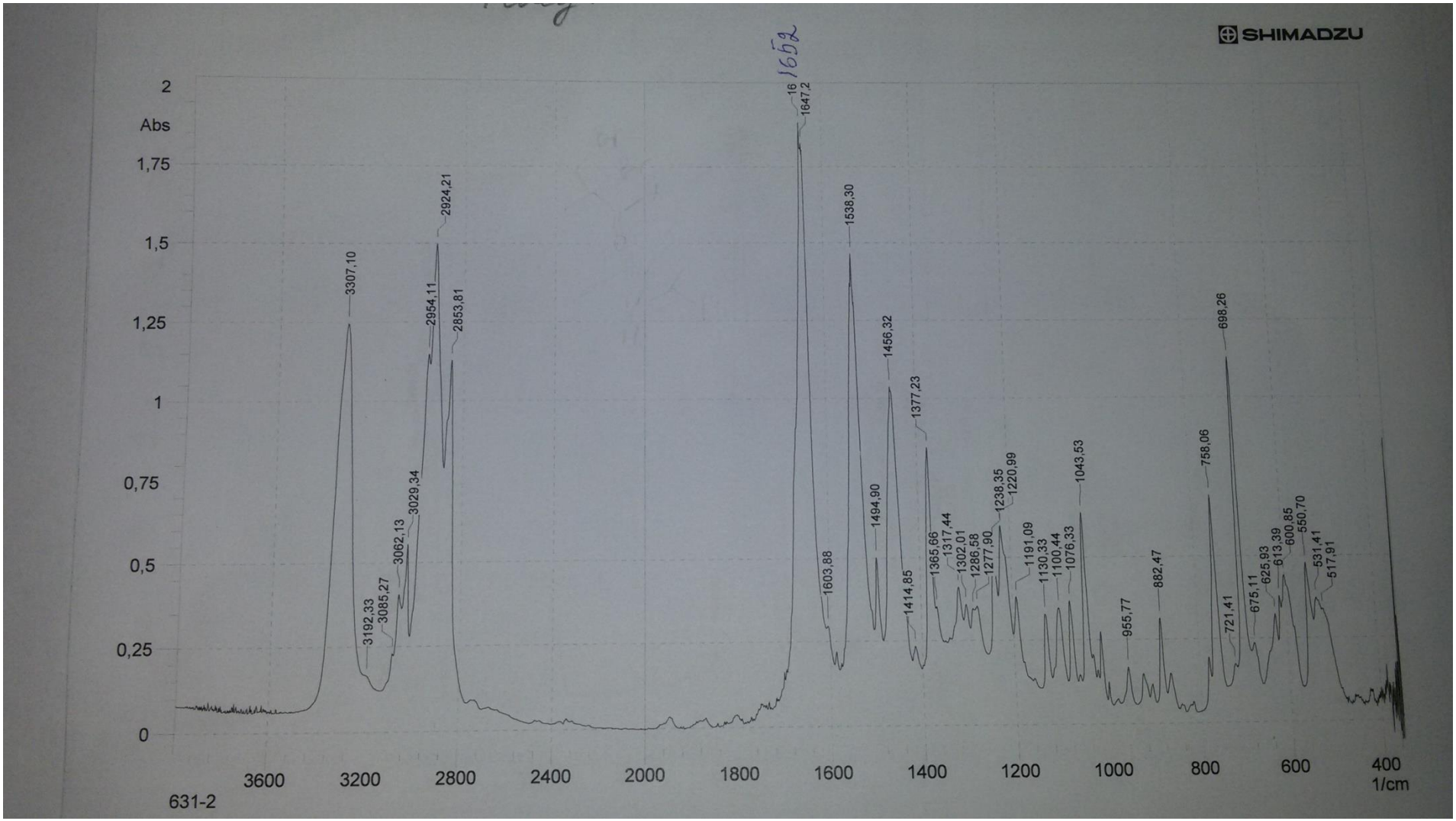

Figure S8. IR spectrum for compounds 2a,b.

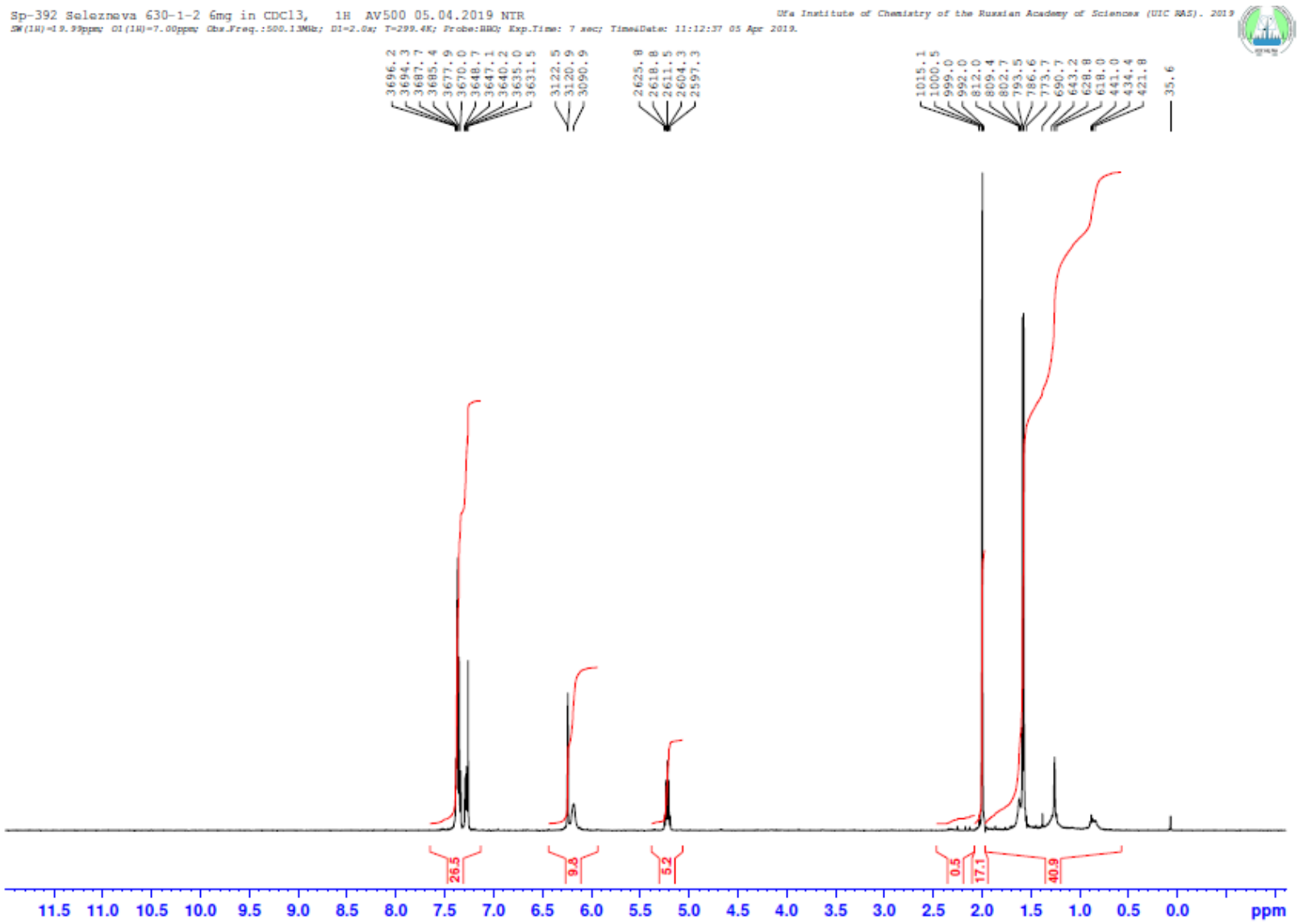

Figure S9. 500 MHz ^{1}H NMR of 3b

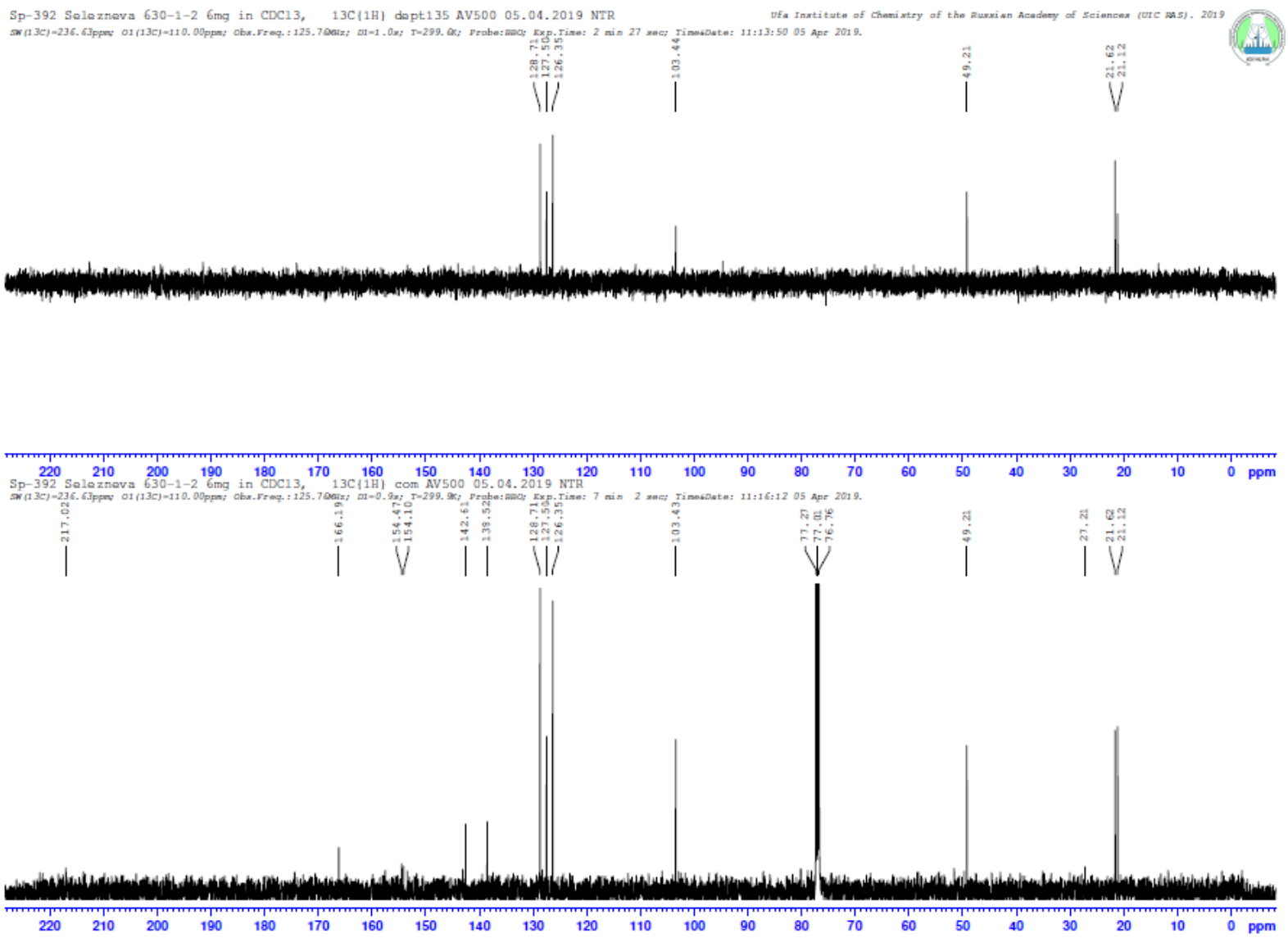

Figure S10. 125 MHz ^{13}C NMR of 3b

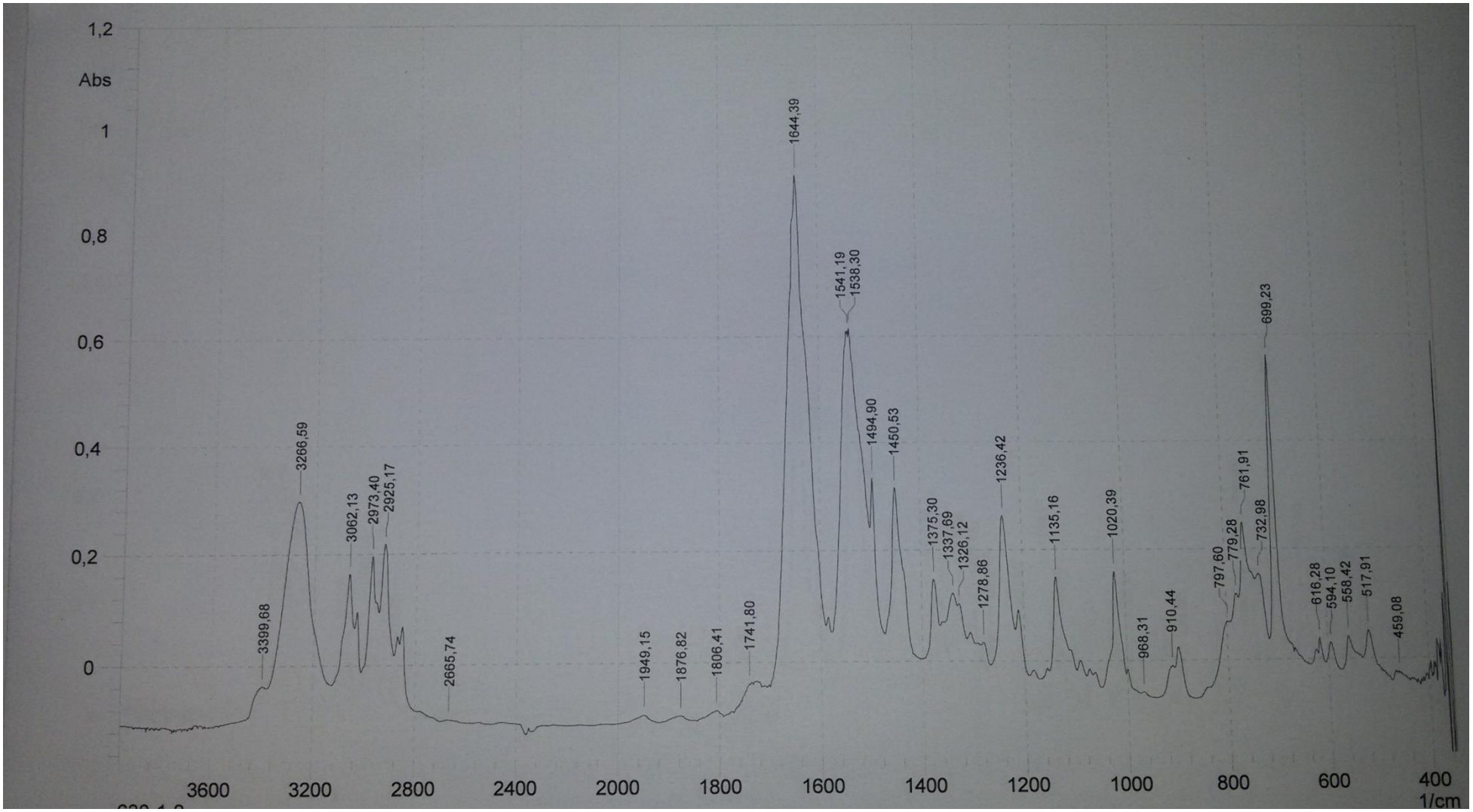

Figure S11. IR spectrum of compound 3b.

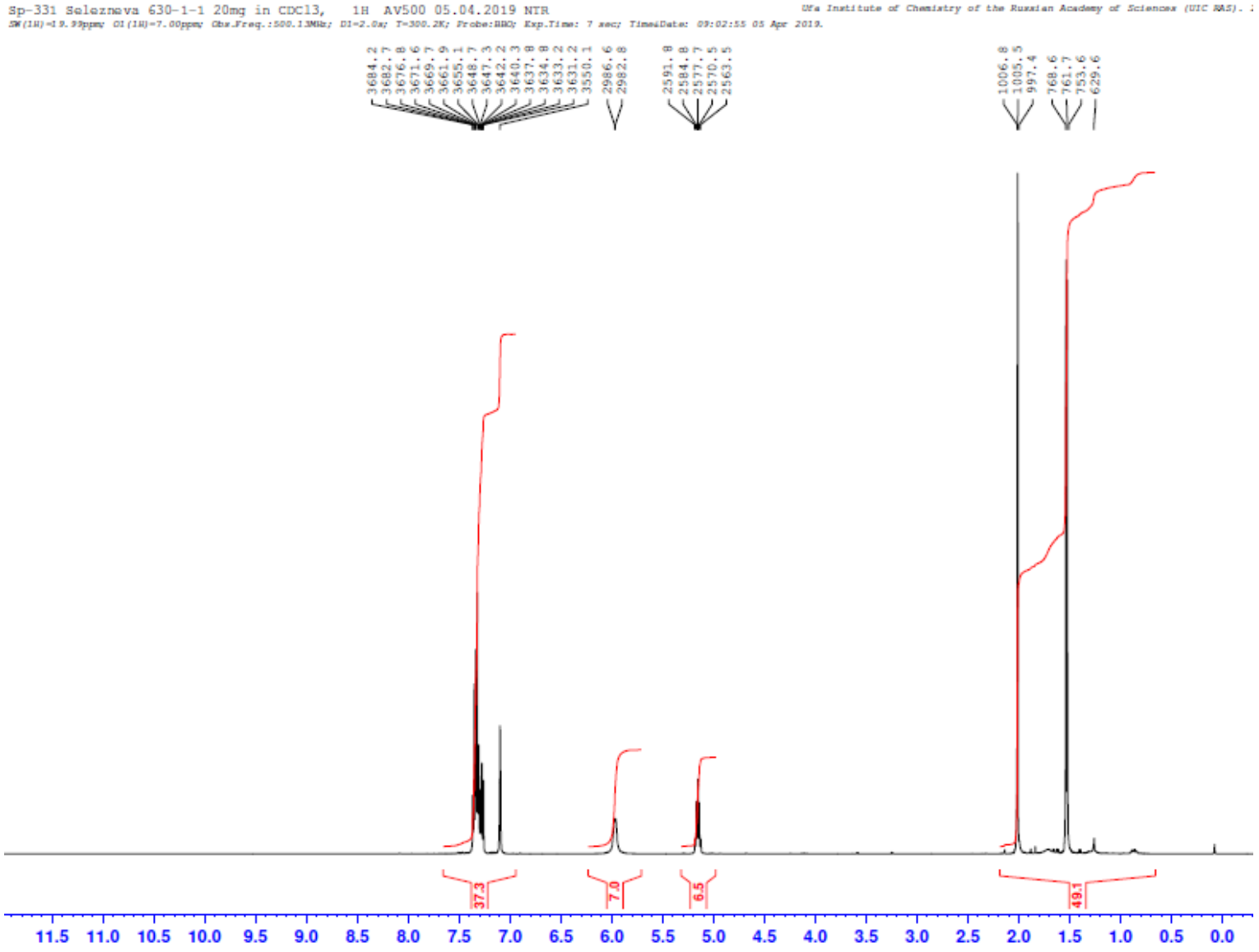

Figure S12. 500 MHz ^{1}H NMR of 3a.

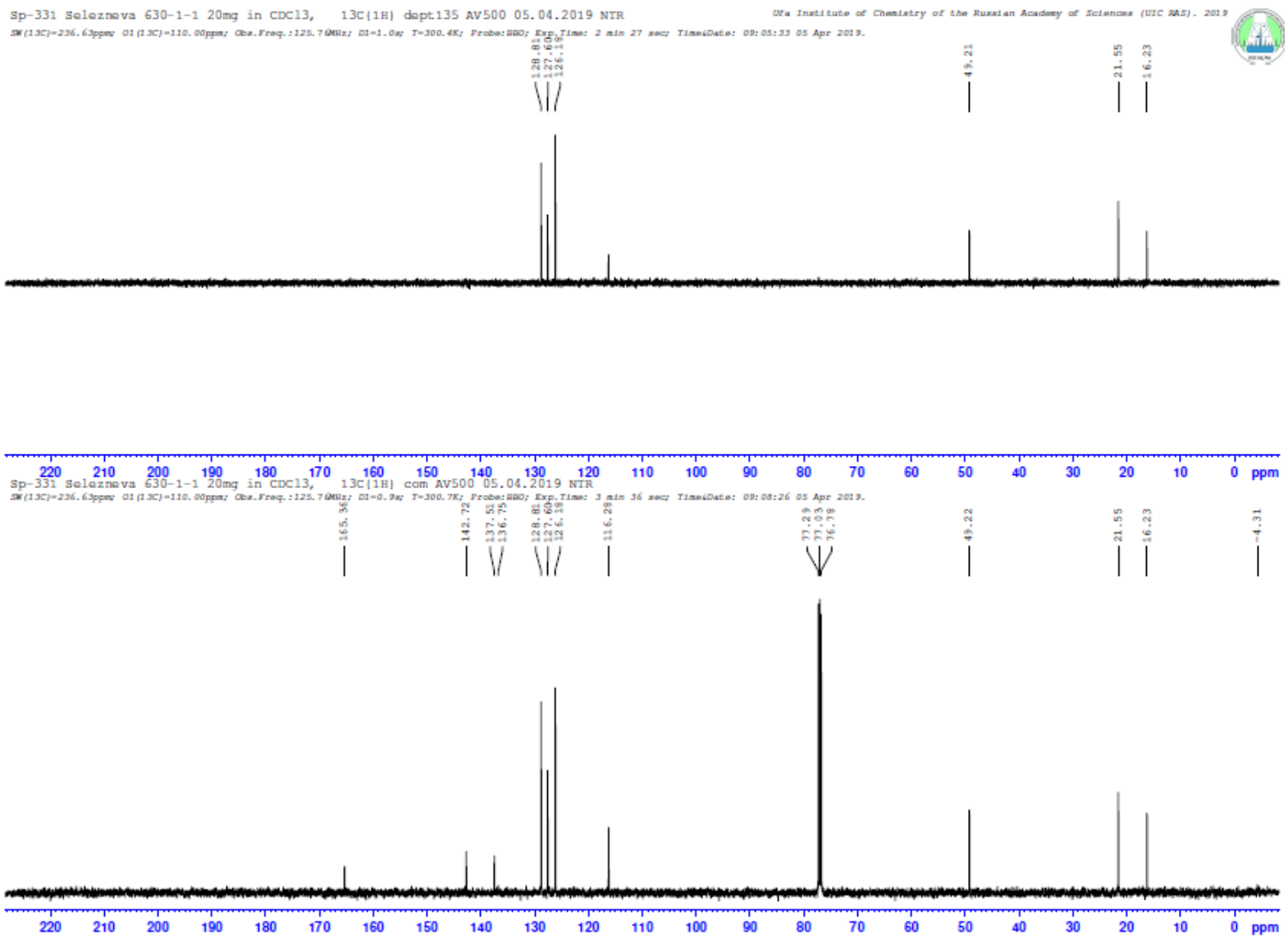

Figure S13. 125 MHz ^{13}C NMR of 3a.

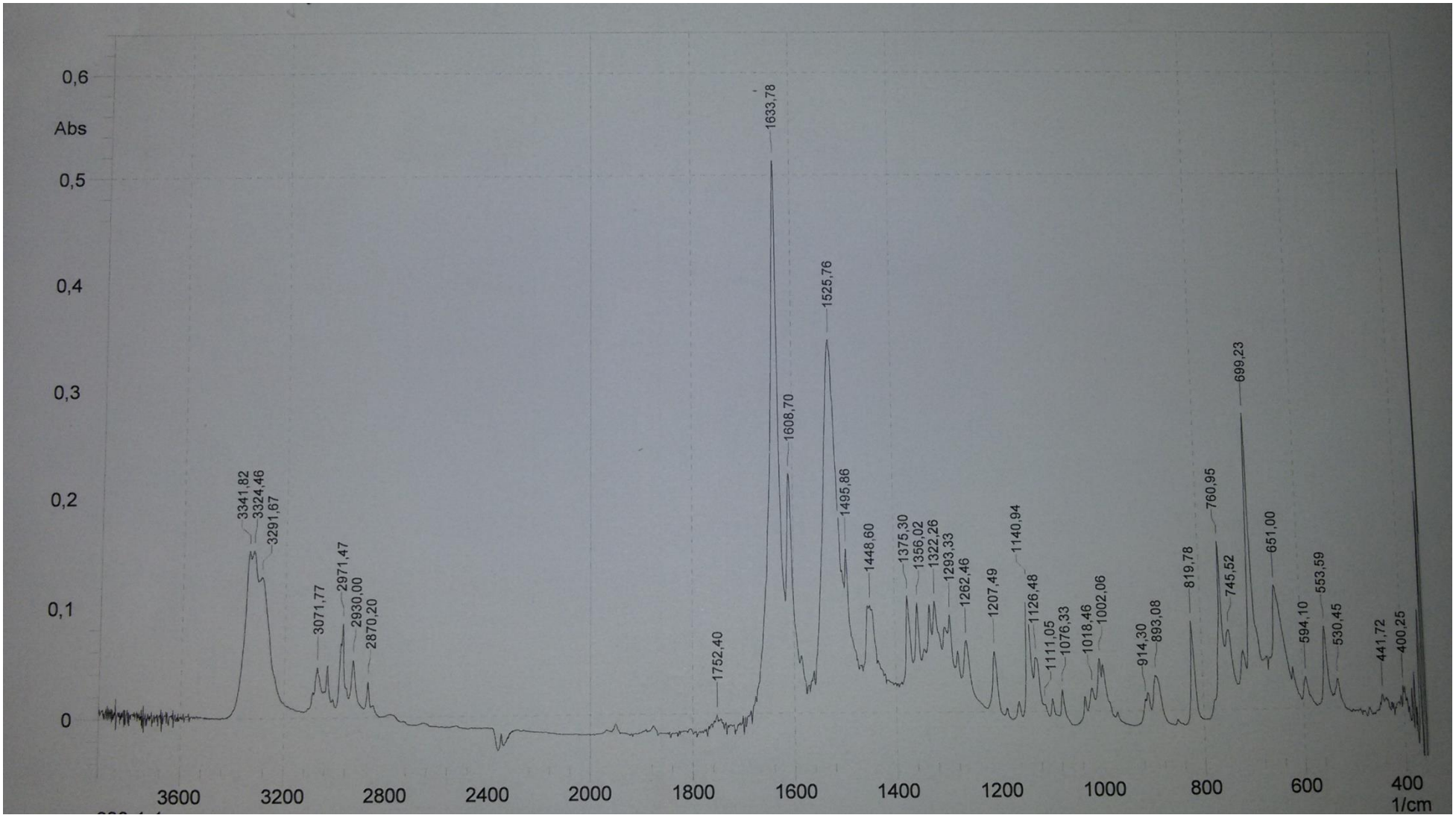

Figure S14. IR spectrum of compound 3a.

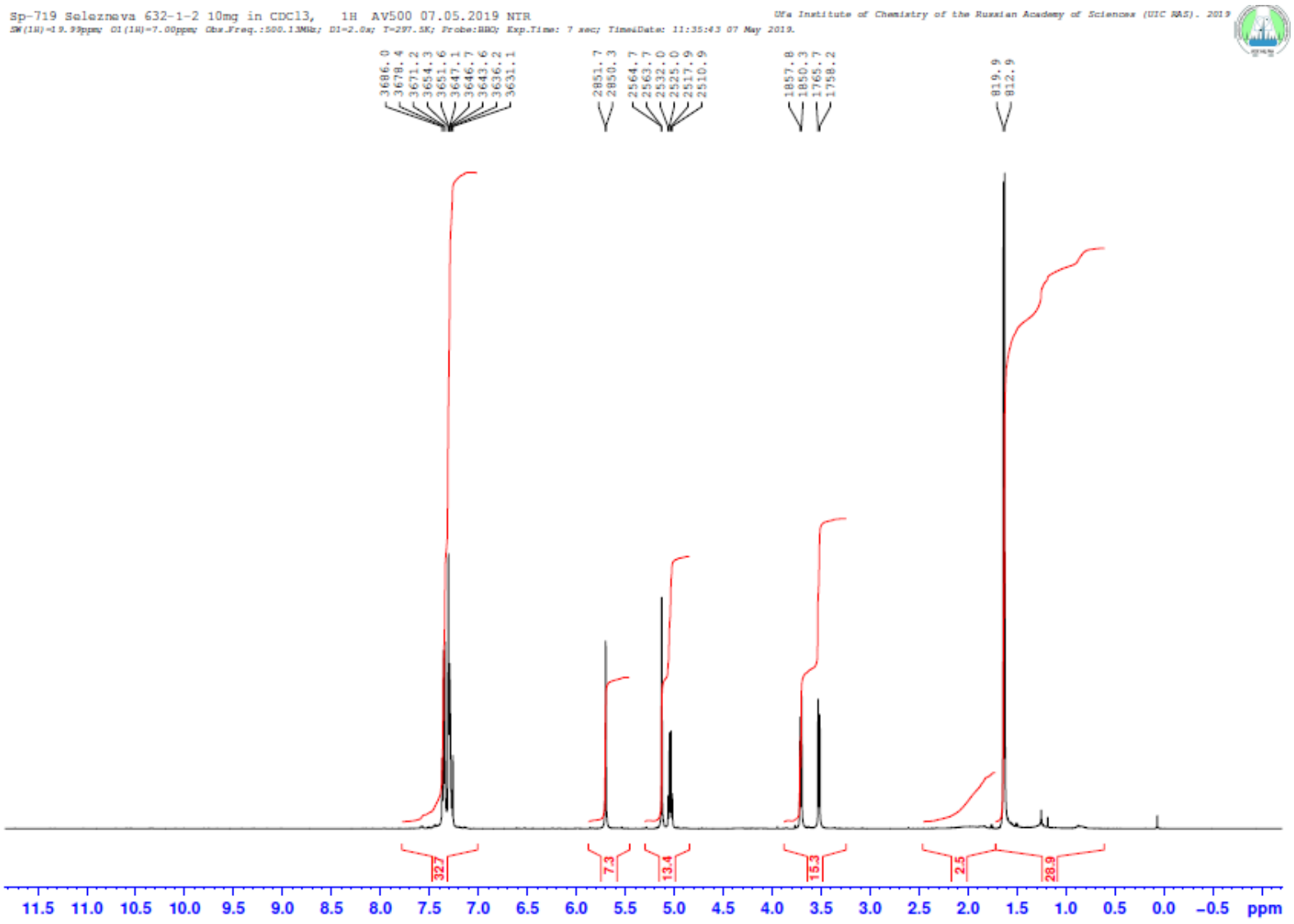

Figure S15. 500 MHz ^{1}H NMR of 4.

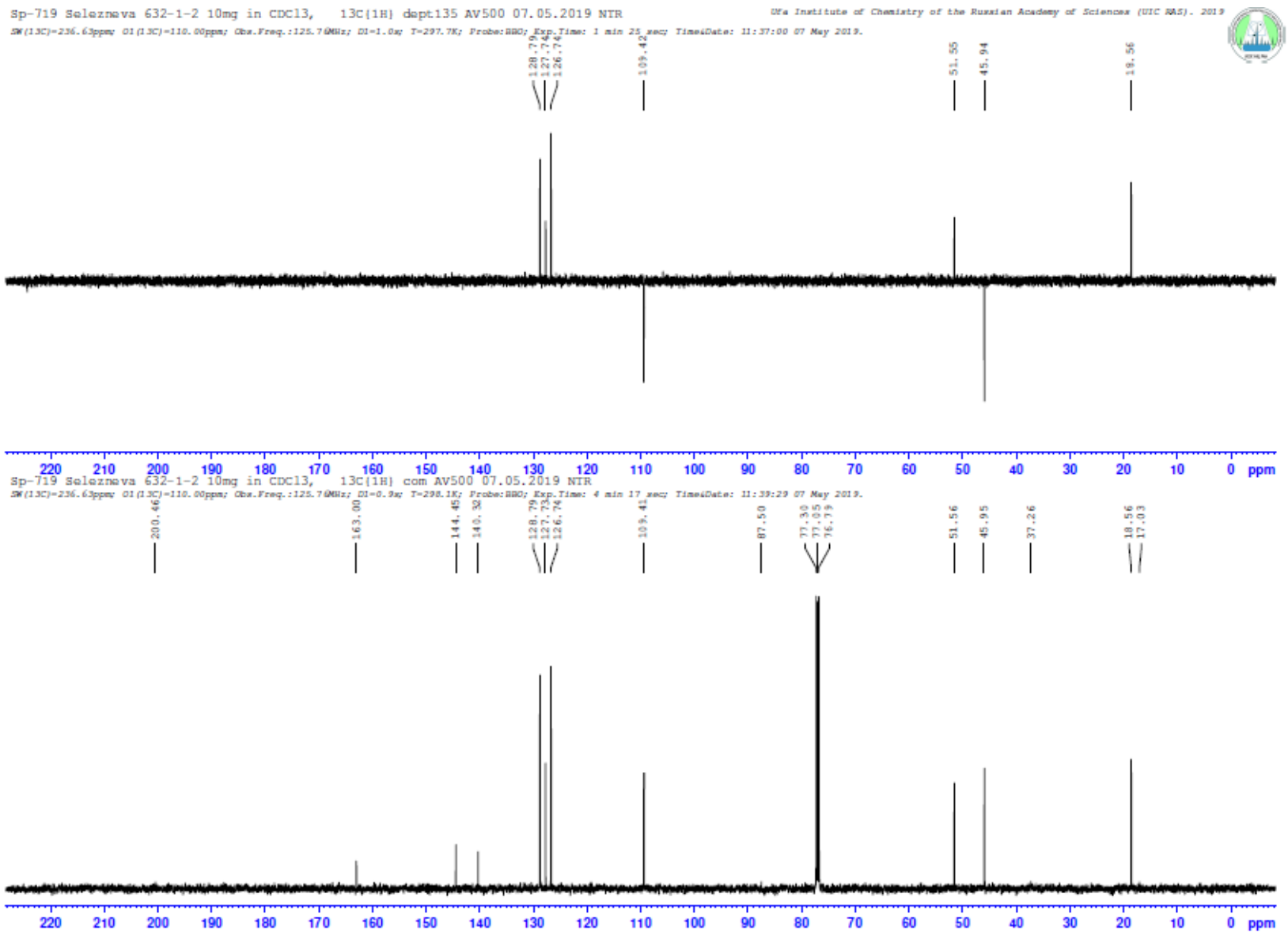

Figure S16. 125 MHz ^{13}C NMR of 4.

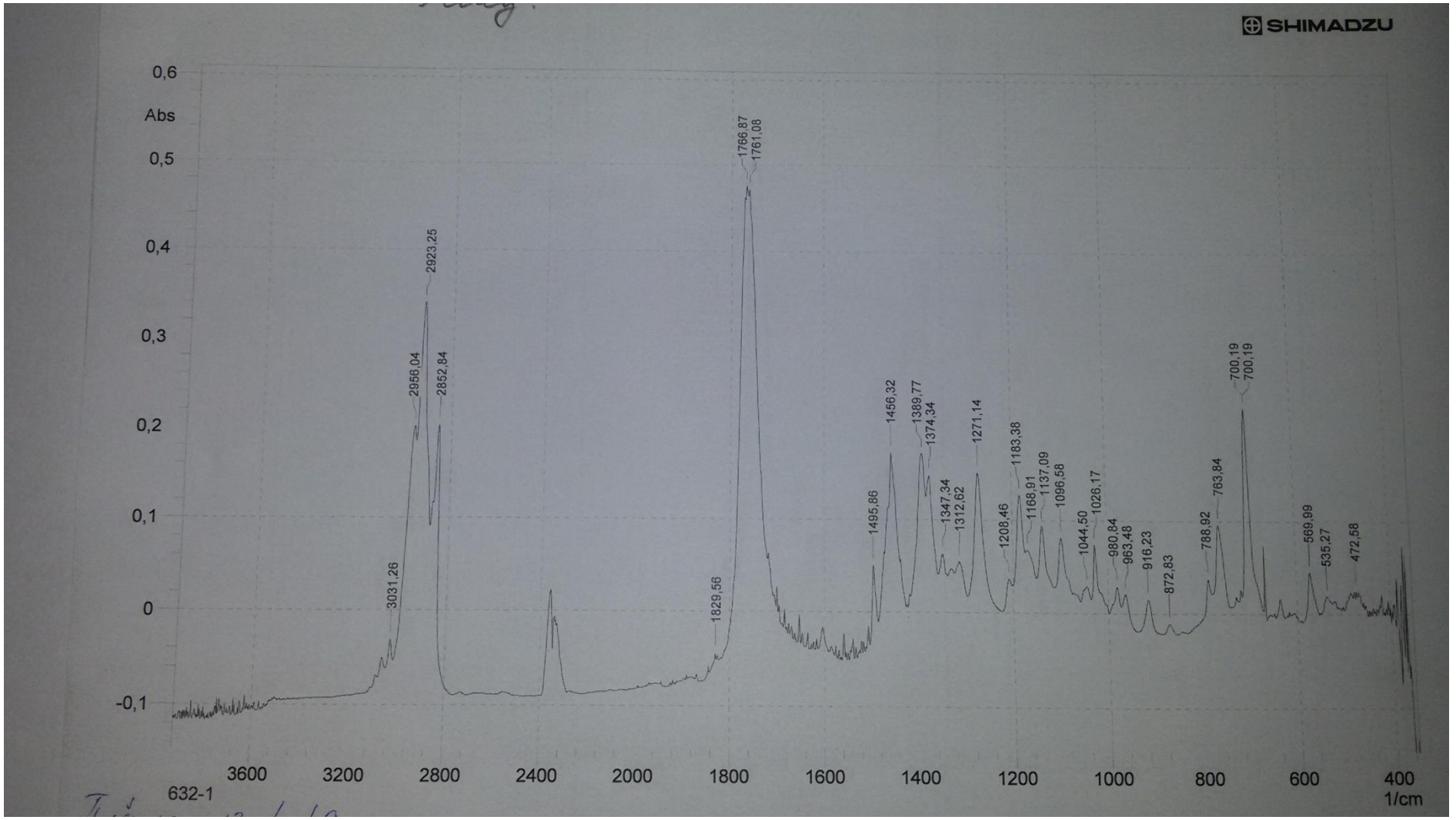

Figure S17. IR spectrum of compound 4.

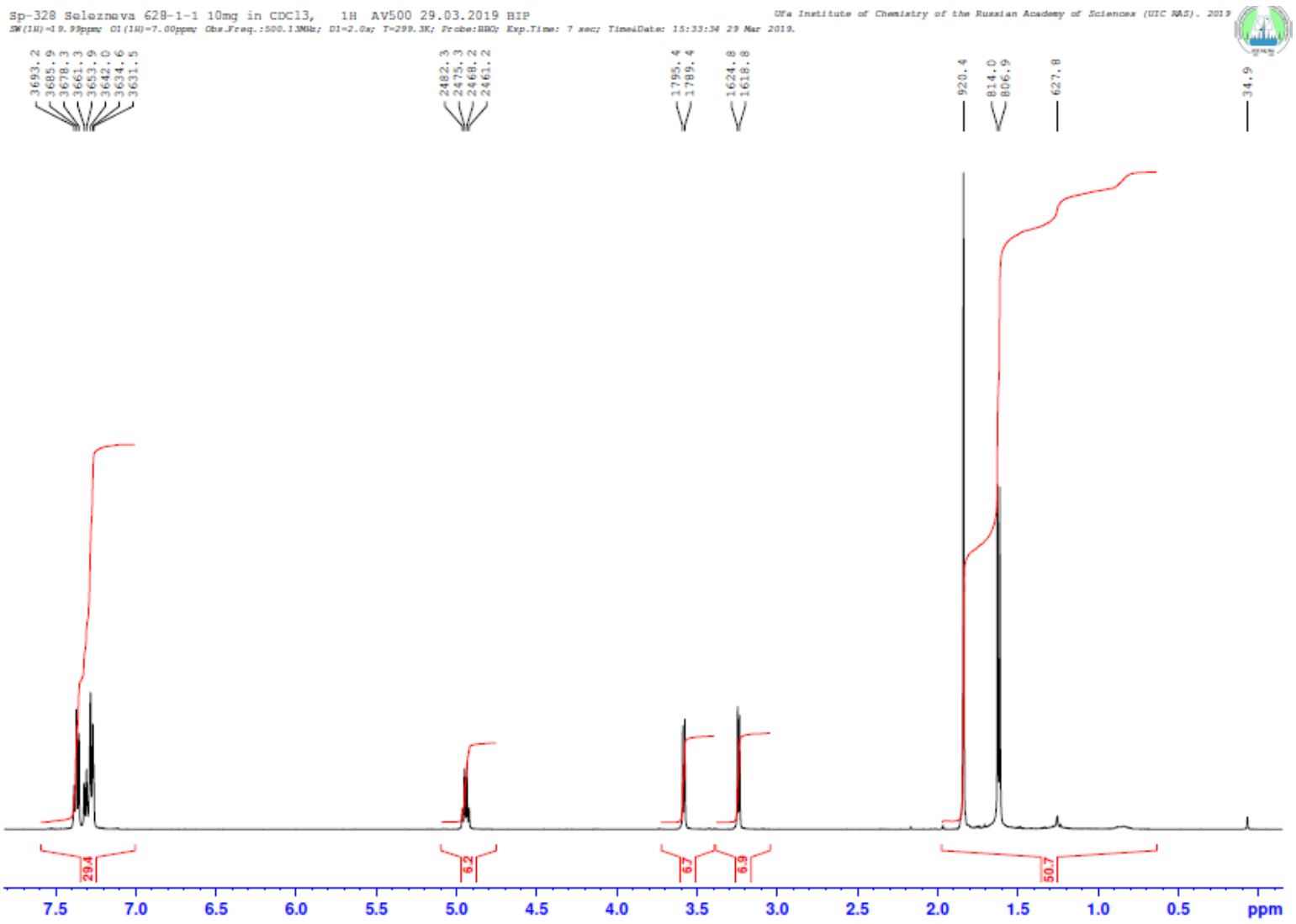

Figure S18. 500 MHz ^{1}H NMR of 5a.

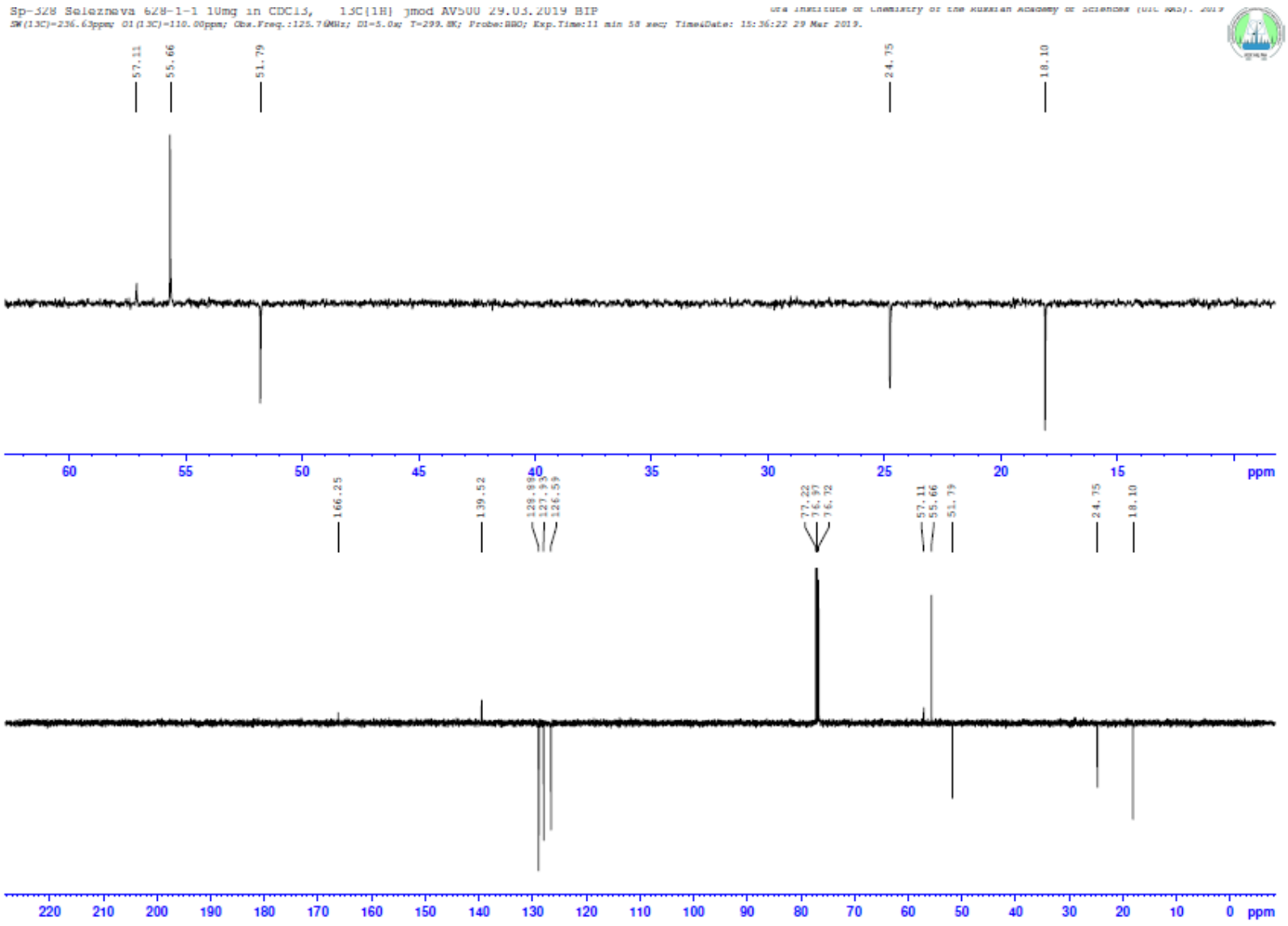

Figure S19. 125 MHz ^{13}C NMR of 5a.

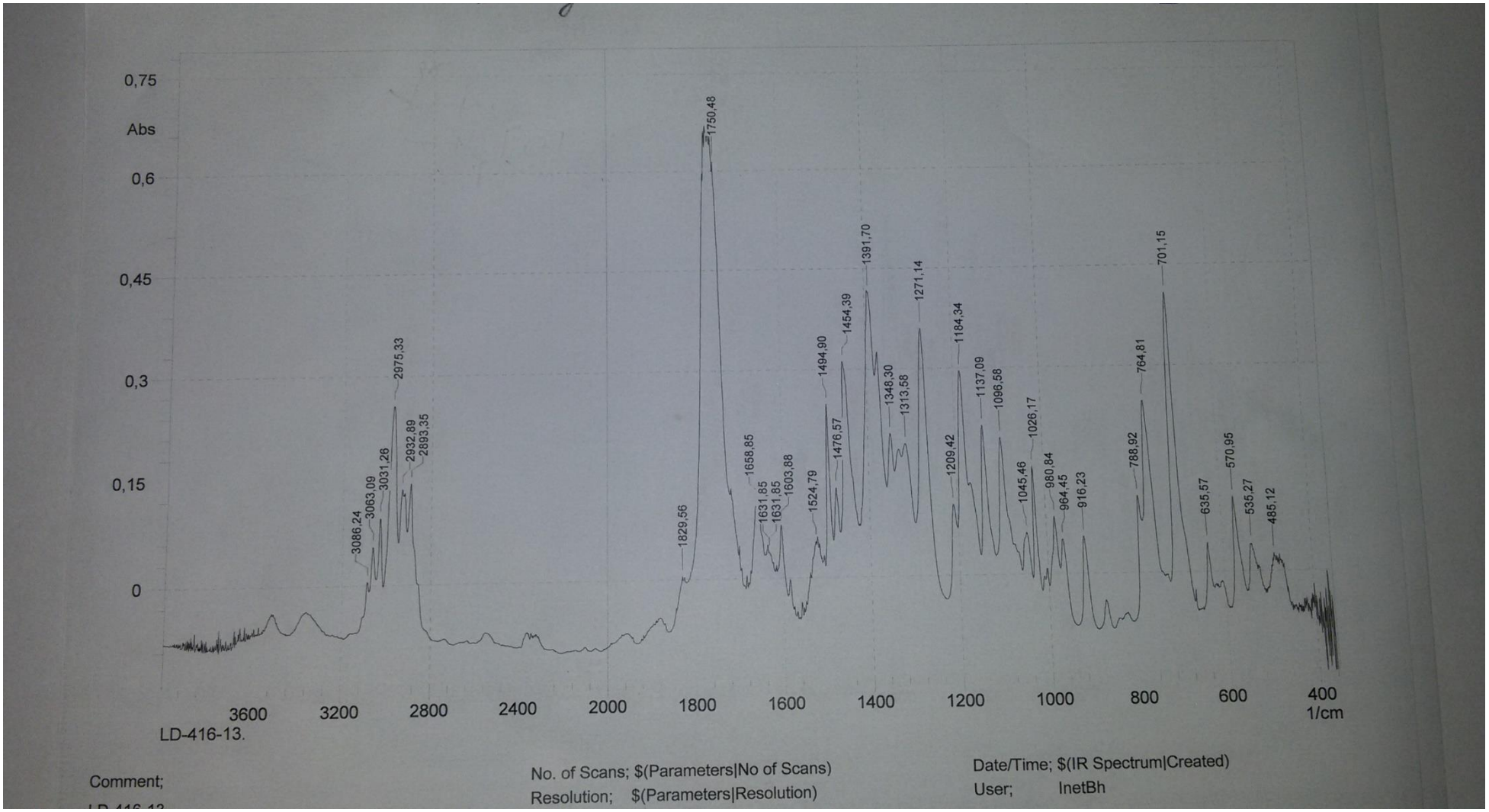

Figure S20. IR spectrum of compound 5a.

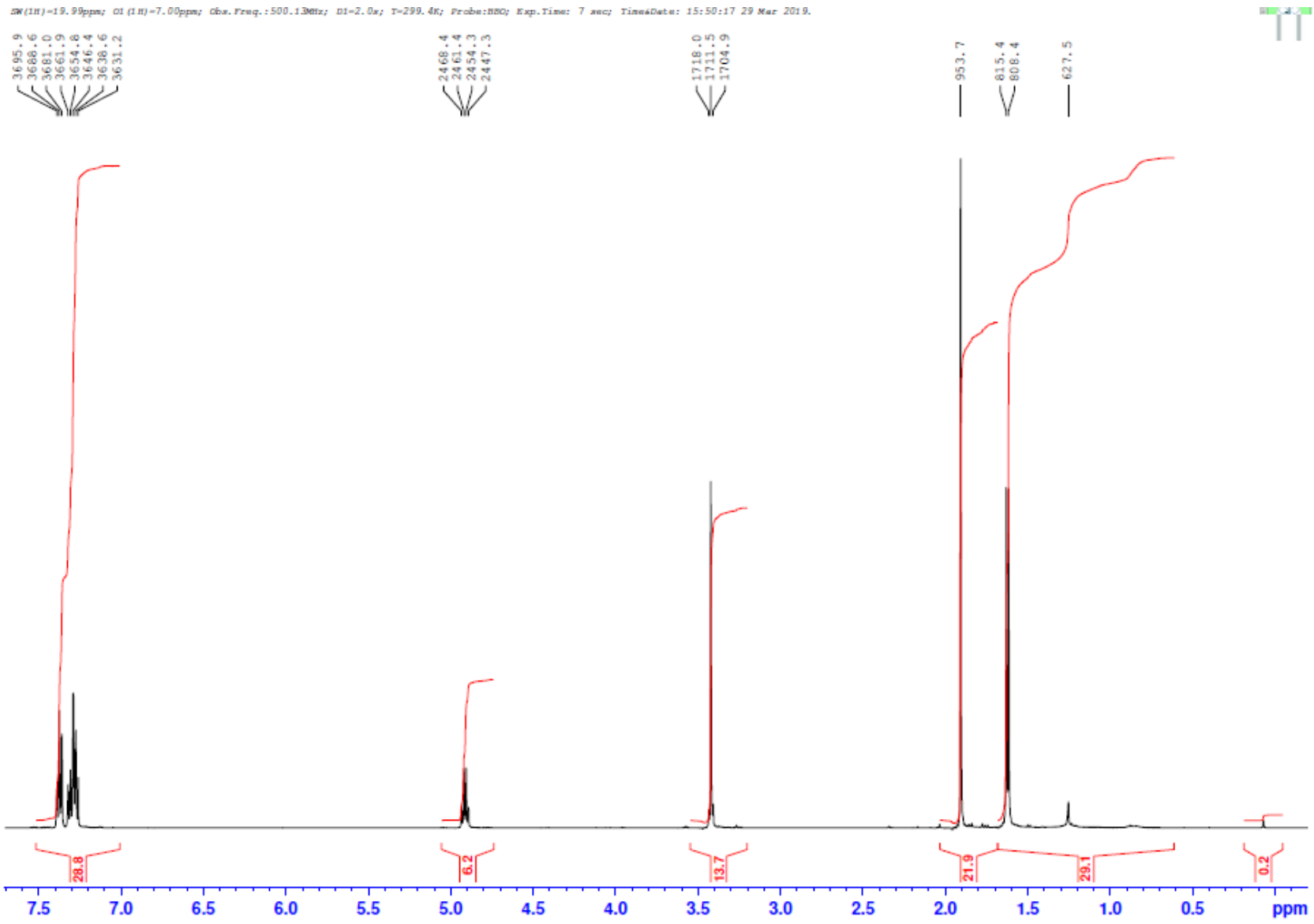

Figure S21. 500 MHz ^{1}H NMR of 5b.

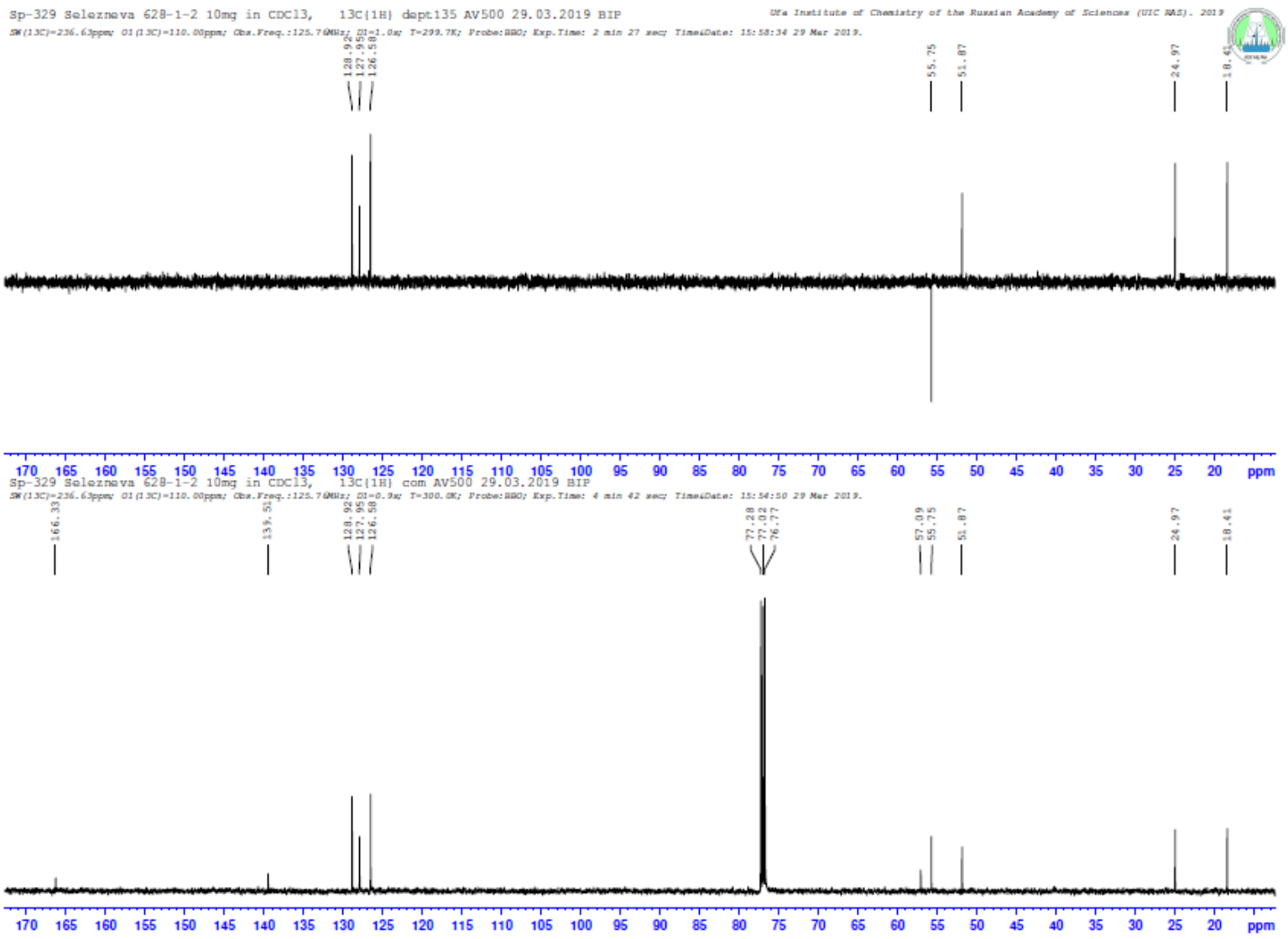

Figure S22. 125 MHz ^{13}C NMR of 5b.

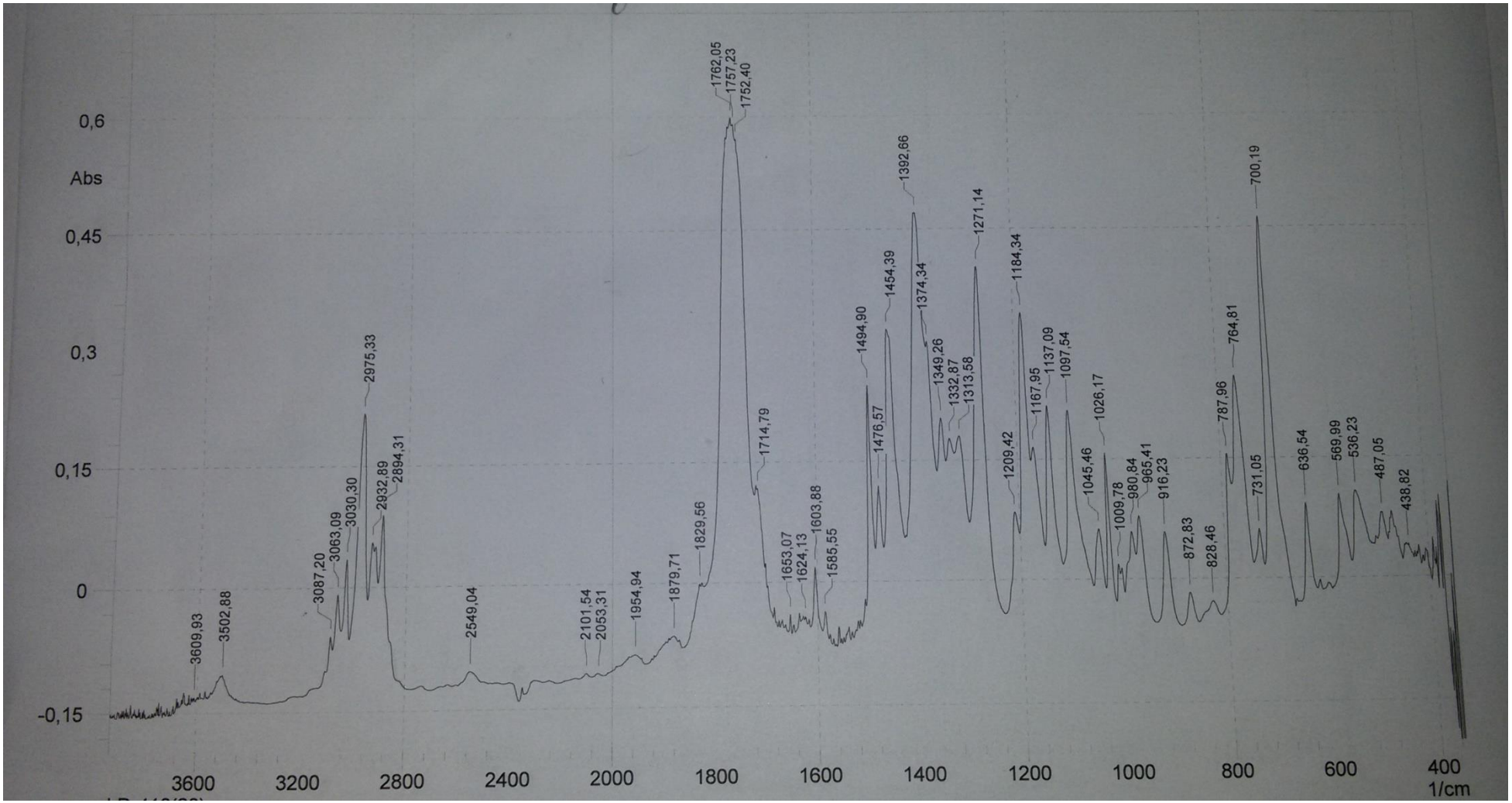

Figure S23. IR spectrum of compound 5b.