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Original catalytic synthesis of macrodiolides containing a 1*Z*,5*Z*-diene moiety

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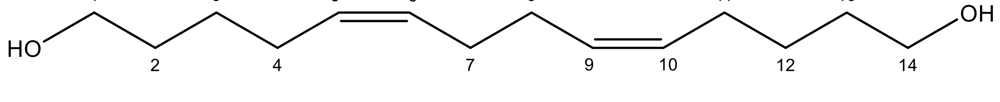
All reactions were carried out in an inert atmosphere. Chloroform was distilled over P_2O_5 prior to use. The ethereal and aromatic solvents were dried over Na. Commercial 5-hexyn-1-ol, $Cu(OTf)_2$ and Cp_2TiCl_2 (Aldrich) were used without preliminary purification. One- (^{1}H, ^{13}C) and two-dimensional heteronuclear (HSQC, HMBC) NMR spectra were recorded in $CDCl_3$ on Bruker Avance-400 [(400.13 MHz (^{1}H), 100.62 MHz (^{13}C)] and Bruker Avance-500 [(500 MHz (^{1}H), 125 MHz (^{13}C)]. IR spectra were recorded on Bruker VERTEX 70V using KBr discs over the range of 400–4000 cm^{-1}. Elemental analyses were measured on a 1106 Carlo Erba apparatus. Mass spectra were obtained on MALDI TOF/TOF spectrometer in a sinapic acid matrix.

2-(Hepta-5,6-dien-1-yloxy)tetrahydro-2*H*-pyran 1 was prepared from commercial hex-5-yn-1-ol by a reported procedure [V. A. D'yakonov, A. A. Makarov, E. Kh. Makarova, L. M. Khalilov and U. M. Dzhemilev, *Russ. Chem. Bull., Int. Ed.*, 2012, **61**, 1943].

2,2'-[(5*Z*,9*Z*)-Tetradeca-5,9-diene-1,14-diylbis(oxy)]bistetrahydro-2*H*-pyran (3). Diethyl ether (30 ml), 1,2-diene **1** (0.59 g, 3.0 mmol), EtMgBr (a 1.5 *M* solution in Et_2O, 4 ml, 6.0 mmol), Mg powder (0.17 g, 7.2 mmol), and Cp_2TiCl_2 (0.08 g, 0.3 mmol) were charged into a glass reactor with stirring under argon (~0ºC). The reaction mixture was warmed-up to room temperature (20−22 °C) and stirred for 24 h. The mixture was treated with a 5% solution of NH_4Cl in H_2O. The products were extracted with diethyl ether, the extracts were dried with $MgSO_4$, the solvent was evaporated, and the residue was chromatographed on a column (SiO_2, elution with petroleum ether/EtOAc, 30:1) to afford product **3**. All analytical data recorded for compound **3** were in full accord with previously published data [V. A. D'yakonov, A. A. Makarov, E. Kh. Makarova and U. M. Dzhemilev, *Tetrahedron*, 2013, **69**, 8516].

(5*Z*,9*Z*)-Tetradeca-5,9-diene-1,14-diol (4). A solution of THP ether **3** (2.0 g, 5 mmol) and TsOH (0.09 g, 0.5 mmol) in $CHCl_3$/MeOH mixture (1:1, 200 ml) was stirred at 55 °C for 2 h. The mixture was quenched with saturated aq $NaHCO_3$ and extracted three times with chloroform. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/EtOAc, 1:1).

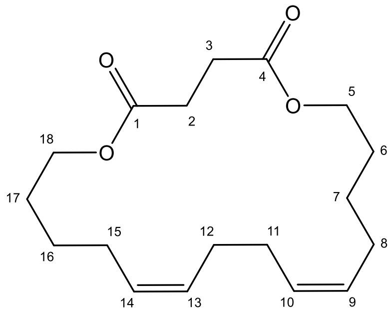


Yield: 98%, MS (MALDI-TOF), *m/z*: 226 [M]$^+$. Found (%):C, 74.33; H, 11.52. Calc. for $C_{14}H_{26}O_2$ (%): C, 74.29; H, 11.58. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.38-1.41 (4H, m, C<u>H</u>$_2$, H^2, H^{13}), 1.52-1.57 (4H, m, C<u>H</u>$_2$, H^3, H^{12}), 2.00-2.07 (8H, m, =CH-C<u>H</u>$_2$, H^4, H^7, H^8, H^{11}), 3.57-3.60 (4H, m, O-C<u>H</u>$_2$, H^1, H^{14}), 5.33-5.40 (4H, m, =C<u>H</u>, H^5, H^6, H^9, H^{10}). ^{13}C NMR (100.62 MHz,

$CDCl_3$) δ: 129.9 (CH, C^5, C^{10}), 129.5 (CH, C^6, C^9), 62.5 ($\underline{C}H_2OH$, C^1, C^{14}), 32.2 (CH_2, C^2, C^{13}), 27.4 (CH_2, C^4, C^{11}), 26.9 (CH_2, C^7, C^8), 25.8 (CH_2, C^3, C^{13}).

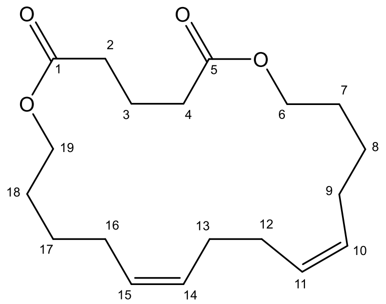
General procedure for the synthesis of macrodiolides. Dicarboxylic acid **5a-e** (0.2 mmol, 1.0 equiv.) and (5*Z*,9*Z*)-tetradeca-5,9-diene-1,14-diol **4** (0.045 g, 0.2 mmol, 1.0 equiv.) were dissolved in toluene (40 ml). Then $Cu(OTf)_2$ (8.5 mg, 0.02 mmol, 0.1 equiv.) was added, and the mixture was heated to 110 °C and stirred at this temperature for 16-18 h. After cooling to room temperature, silica gel (~ 1 ml) was added and the slurry was concentrated under reduced pressure. The residue was purified by column chromatography (elution with petroleum ether/EtOAc, 20:1) to afford the desired product **6a-e** as a colorless oil.

1,6-Dioxacycloicosa-11*Z*,15*Z*-diene-2,5-dione (6a).



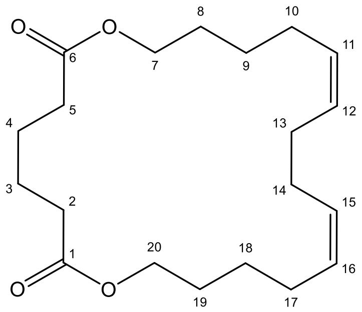
Yield: 59%, colourless oil. MS (MALDI-TOF), *m/z*: 308 $[M]^+$. Found (%): C, 70.14; H, 9.19. Calc. for $C_{18}H_{28}O_4$: (%): C, 70.10; H, 9.15.). IR (ν / cm^{-1}): 1734 (C=O), 1246, 1180 (C–O). ^1H NMR (500 MHz, $CDCl_3$) δ: 1.44-1.47 (4H, m, $C\underline{H}_2$, H^7, H^{16}), 1.61-1.67 (4H, m, $C\underline{H}_2$, H^6, H^{17}), 2.03-2.12 (8H, m, =CH-$C\underline{H}_2$, H^8, H^{11}, H^{12}, H^{15}), 2.63-2.65 (4H, m, $C\underline{H}_2$, H^2, H^3), 4.10-4.13 (4H, m, O-$C\underline{H}_2$, H^5, H^{18}), 5.35-5.47 (4H, m, =$C\underline{H}$, H^9, H^{10}, H^{13}, H^{14}). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.0 ($\underline{C}OO$, C^1, C^4), 129.7 (CH, C^9, C^{14}), 129.7 (CH, C^{10}, C^{13}), 64.5 ($\underline{C}H_2O$, C^5, C^{18}), 29.8 (CH_2, C^2, C^3), 28.0 (CH_2, C^6, C^{17}), 27.6 (CH_2, C^8, C^{15}), 26.5 (CH_2, C^{11}, C^{12}), 25.8 (CH_2, C^7, C^{16}).

1,7-Dioxacyclohenicosa-12*Z*,16*Z*-diene-2,6-dione (6b).



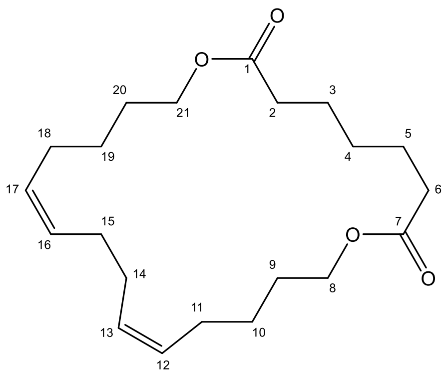
Yield: 61%, colourless oil. MS (MALDI-TOF), *m/z*: 322 $[M]^+$. Found (%): C, 70.71; H, 9.33. Calc. for $C_{19}H_{30}O_4$: (%):C, 70.77; H, 9.38. IR (ν / cm^{-1}): 1735 (C=O), 1243, 1180 (C–O). ^1H NMR (400 MHz, $CDCl_3$) δ: 1.40-1.47 (4H, m, $C\underline{H}_2$, H^8, H^{17}), 1.61-1.68 (4H, m, $C\underline{H}_2$, H^7, H^{18}), 1.98 -2.10 (10H, m, $C\underline{H}_2$, =CH-$C\underline{H}_2$, H^3, H^9, H^{12}, H^{13}, H^{16}), 2.38 (4H, t, J=7.1 Hz, $C\underline{H}_2$, H^2, H^4), 4.09-4.12 (4H, m, O-$C\underline{H}_2$, H^6, H^{19}), 5.35-5.46 (4H, m, =$C\underline{H}$, H^{10}, H^{11}, H^{14}, H^{15}). ^{13}C NMR (100.62 MHz, $CDCl_3$) δ: 172.9 ($\underline{C}OO$, C^1, C^5), 129.7 (CH, C^{10}, C^{15}), 129.6 (CH, C^{11}, C^{14}), 64.3 ($\underline{C}H_2O$, C^6, C^{19}), 33.4 (CH_2, C^2, C^4), 28.2 (CH_2, C^7, C^{18}), 27.5 (CH_2, C^9, C^{16}), 26.7 (CH_2, C^{12}, C^{13}), 26.0 (CH_2, C^8, C^{17}), 20.6 (CH_2, C^3).

1,8-Dioxacyclodocosa-13*Z*,17*Z*-diene-2,7-dione (6c).



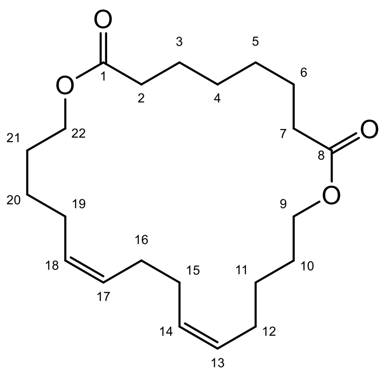
Yield: 65%, colourless oil. MS (MALDI-TOF), *m/z*: 336 $[M]^+$. Found (%): C, 71.46; H, 9.64. Calc. for $C_{20}H_{32}O_4$: (%): C, 71.39; H, 9.59. IR (ν / cm^{-1}): 1735 (C=O), 1244, 1177 (C–O). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.42-1.46 (4H, m, C<u>H</u>$_2$, H^9, H^{18}), 1.61-1.70 (8H, m, C<u>H</u>$_2$ H^3, H^4, H^8, H^{19}), 2.07-2.12 (8H, m, =CH-C<u>H</u>$_2$, H^{10}, H^{13}, H^{14}, H^{17}), 2.34 (4H, s, C<u>H</u>$_2$, H^2, H^5), 4.10 (4H, t, J=6.6 Hz, O-C<u>H</u>$_2$, H^7, H^{20}), 5.37-5.44 (4H, m, =C<u>H</u>, H^{11}, H^{12}, H^{15}, H^{16}). ^{13}C NMR (100.62 MHz, $CDCl_3$) δ: 173.3 (<u>C</u>OO, C^1, C^6), 129.7 (CH, C^{11}, C^{16}), 129.7 (CH, C^{12}, C^{15}), 64.3 (<u>C</u>H$_2$O, C^7, C^{20}), 34.2 (CH_2, C^2, C^5), 28.1 (CH_2, C^8, C^{19}), 27.5 (CH_2, C^{10}, C^{17}), 26.6 (CH_2, C^{13}, C^{14}), 25.9 (CH_2, C^9, C^{18}), 24.6 (CH_2, C^3, C^4).

1,9-Dioxacyclotricosa-14*Z*,18*Z*-diene-2,8-dione (6d).



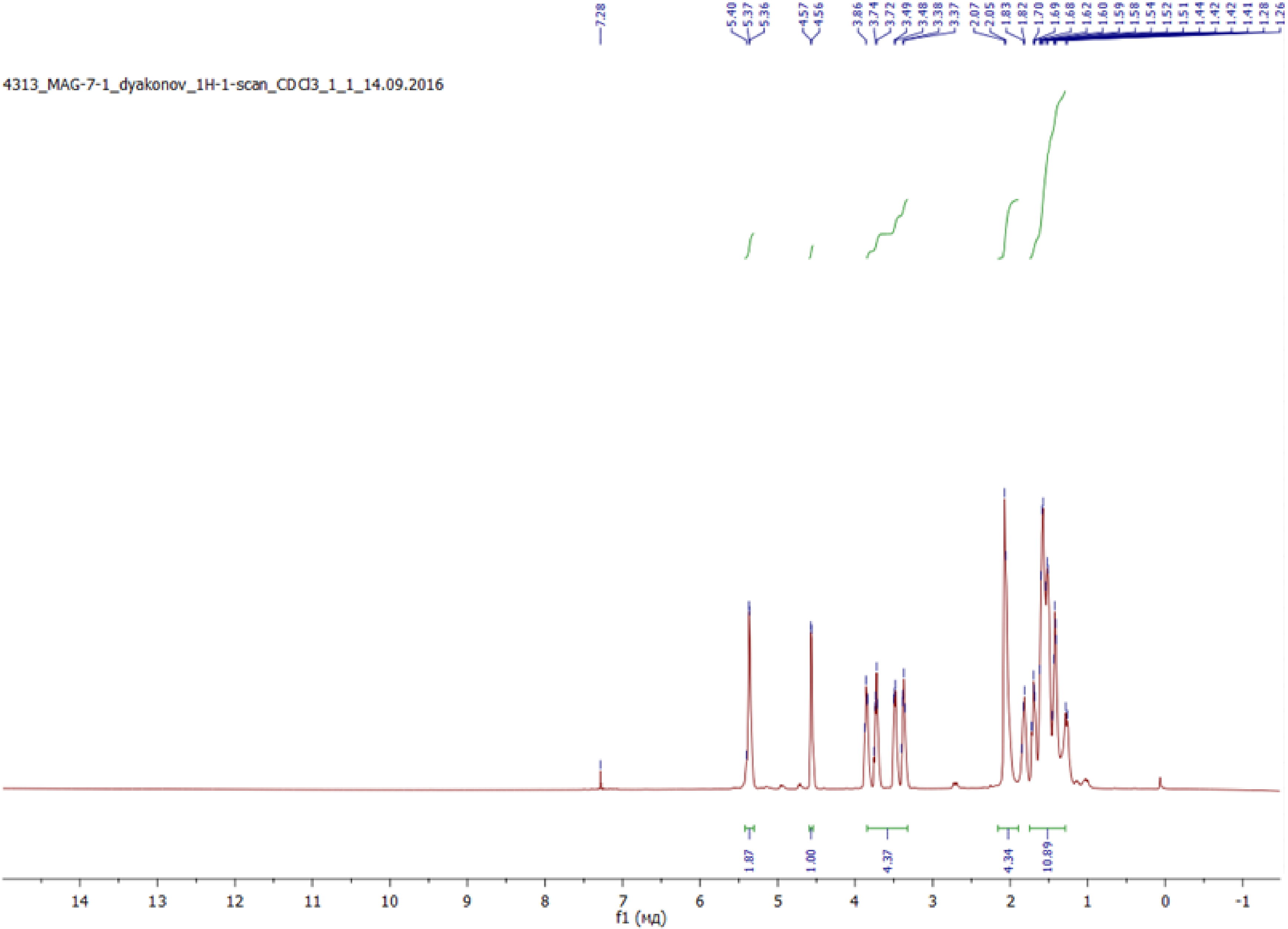
Yield: 67%, colourless oil. MS (MALDI-TOF), *m/z*: 350 $[M]^+$. Found (%):C, 71.89; H, 9.74. Calc. for $C_{21}H_{34}O_4$: (%): C, 71.96; H, 9.78. IR (ν / cm^{-1}): 1734 (C=O), 1241, 1174 (C–O). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.33 –1.45 (10H, m, C<u>H</u>$_2$, H^3, H^4, H^5, H^{10}, H^{19}), 1.62-1.68 (4H, m, C<u>H</u>$_2$, H^9, H^{20}), 2.06 -2.10 (8H, m, =CH-C<u>H</u>$_2$, H^{11}, H^{14}, H^{15}, H^{18}), 2.33 (4H, t, J=6.7 Hz, C<u>H</u>$_2$, H^2, H^6), 4.11 (4H, t, J=6.1 Hz, O-C<u>H</u>$_2$, H^8, H^{21}), 5.37-5.44 (4H, m, =C<u>H</u>, H^{12}, H^{13}, H^{16}, H^{17}). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 173.6 (<u>C</u>OO, C^1, C^7), 129.7 (CH, C^{12}, C^{17}), 129.6 (CH, C^{13}, C^{16}), 64.2 (<u>C</u>H$_2$O, C^8, C^{21}), 34.3 (CH_2, C^2, C^6), 28.2 (CH_2, C^4, C^9, C^{20}), 27.5 (CH_2, C^{11}, C^{18}), 26.7 (CH_2, C^{14}, C^{15}), 26.2 (CH_2, C^{10}, C^{19}), 24.6 (CH_2, C^3, C^5).

1,10-Dioxacyclotetracosa-15*Z*,19*Z*-diene-2,9-dione (6e).

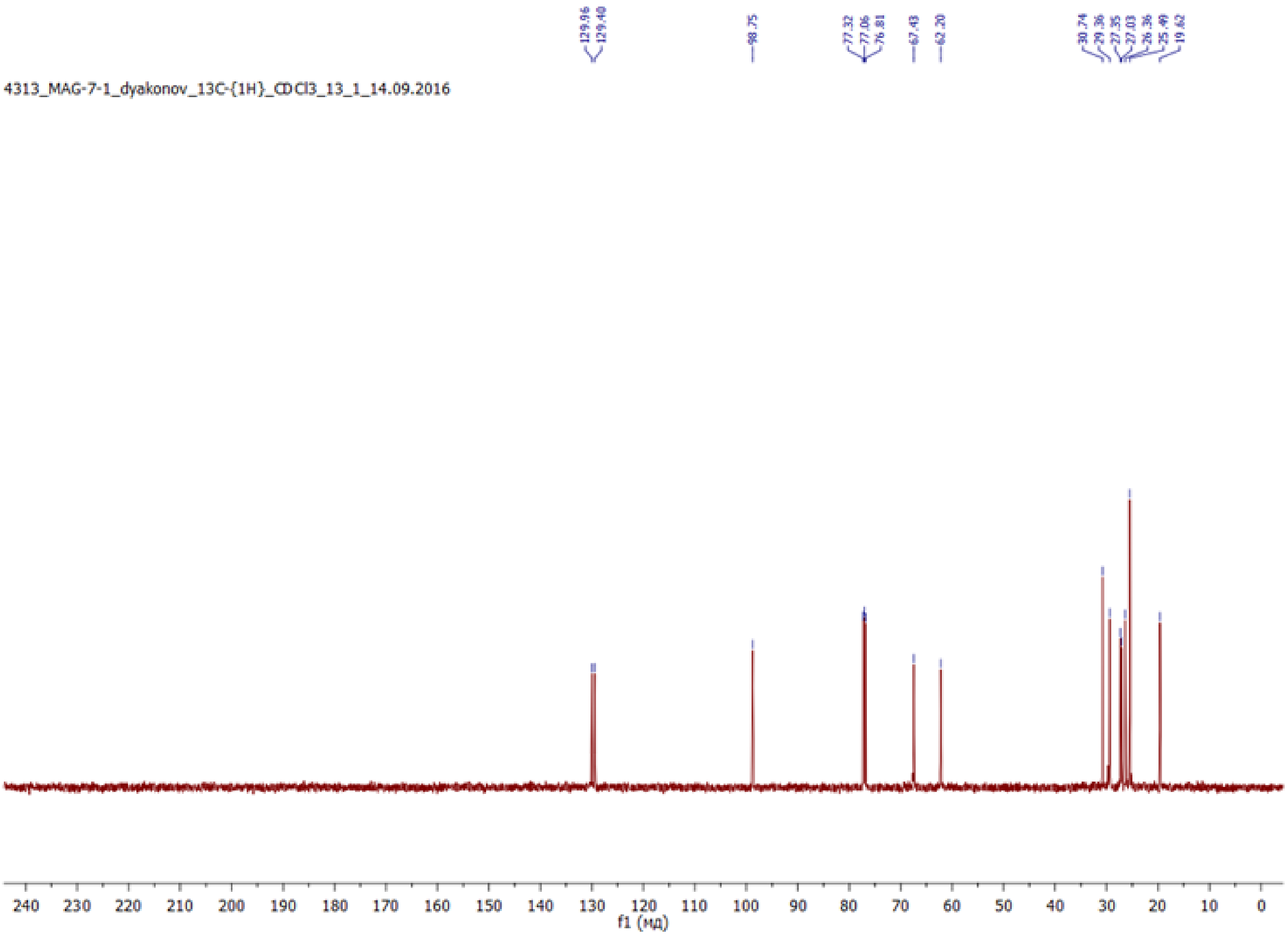


Yield: 70 %, colourless oil. MS (MALDI-TOF), *m/z*: 364 $[M]^+$. Found (%): C, 72.41; H, 9.84. Calc. for $C_{22}H_{36}O_4$: (%):C, 72.49; H, 9.95. IR (ν / cm^{-1}): 1734 (C=O), 1241, 1177 (C–O). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.34 - 1.47 (8H, m, C<u>H</u>$_2$, H^4, H^5, H^{11}, H^{20}), 1.62-1.74 (8H, m, C<u>H</u>$_2$, H^3, H^6, H^{10}, H^{21}), 1.99 -2.13 (8H, m, =CH-C<u>H</u>$_2$, H^{12}, H^{15}, H^{16}, H^{19}), 2.32 (4H, t, J=7.0 Hz, C<u>H</u>$_2$, H^2, H^7), 4.11 (4H, t, J=6.4 Hz, O-C<u>H</u>$_2$, H^9, H^{22}), 5.33-5.43 (4H, m, =C<u>H</u>, H^{13}, H^{14}, H^{17}, H^{18}). ^{13}C NMR (100.62 MHz, $CDCl_3$) δ: 173.8 (<u>C</u>OO, C^1, C^8), 129.7 (CH, C^{12}, C^{19}), 129.6 (CH, C^{14}, C^{17}), 64.1 (<u>C</u>H_2O, C^9, C^{22}), 34.4 (CH_2, C^2, C^7), 28.3 (CH_2, C^3, C^6), 28.2 (CH_2, C^{10}, C^{21}), 27.4 (CH_2, C^{12}, C^{19}), 26.7 (CH_2, C^{15}, C^{16}), 26.0 (CH_2, C^{11}, C^{20}), 24.9 (CH_2, C^4, C^5).

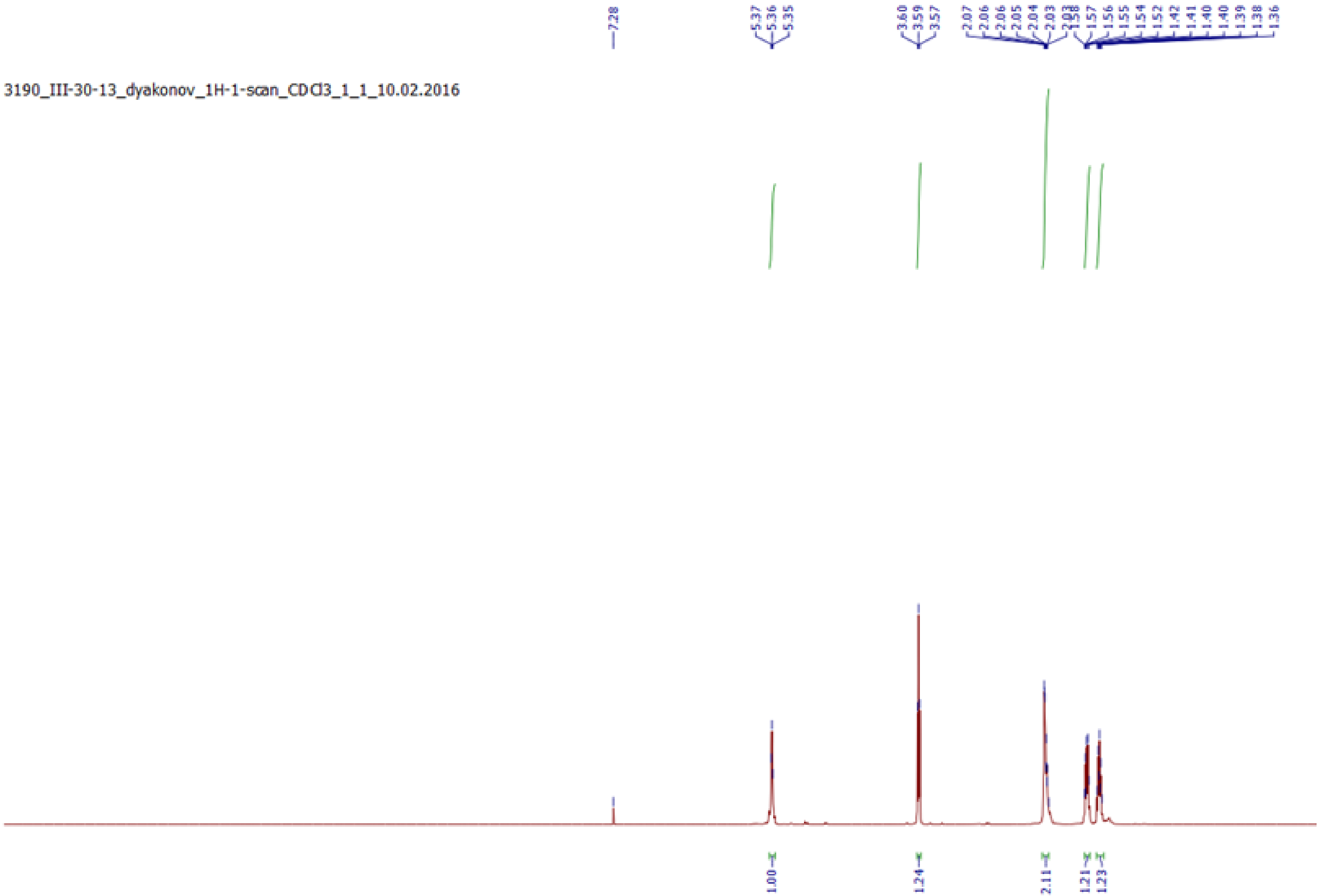
Compound 3 (^{1}H NMR)



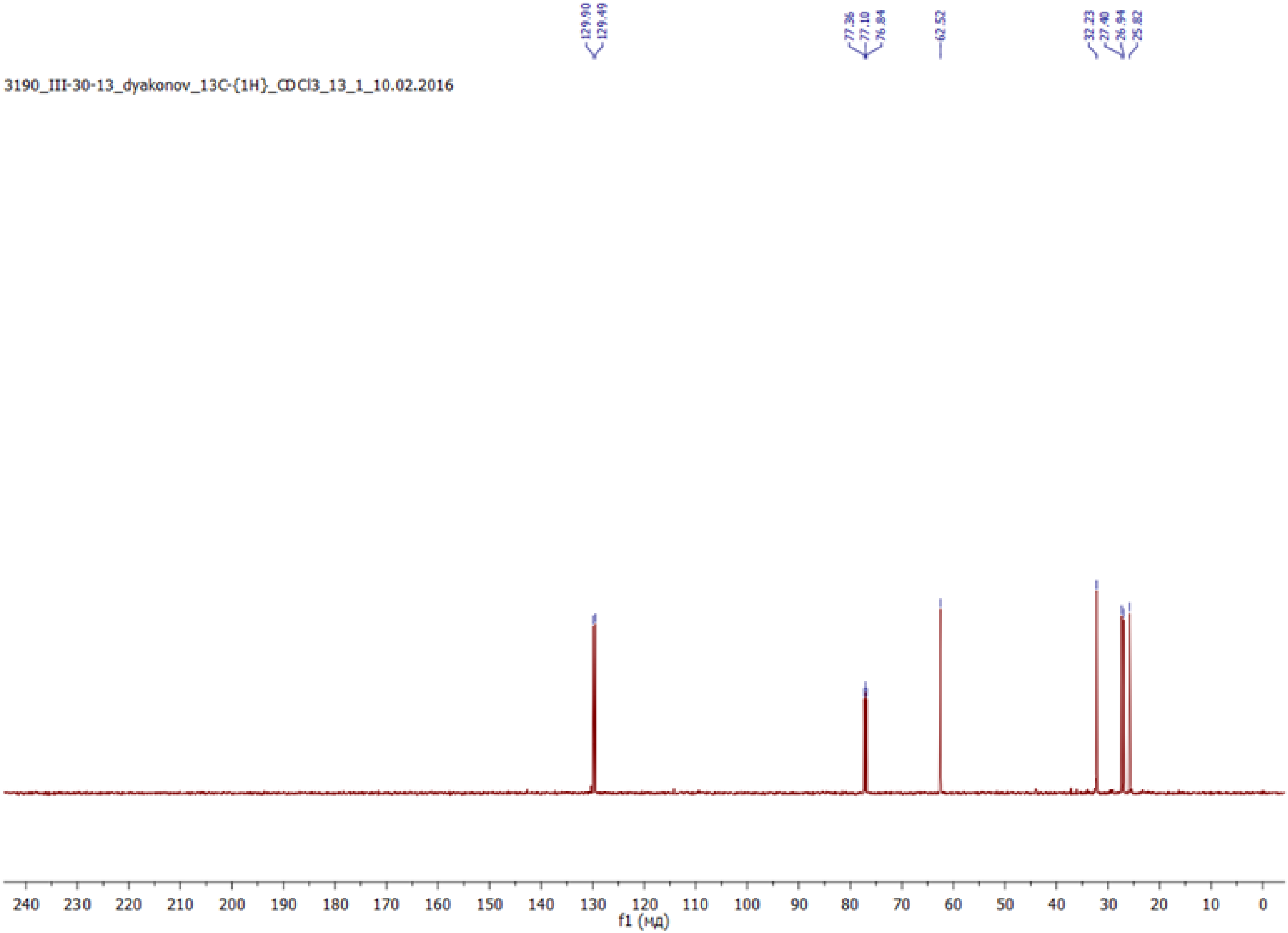
Compound 3 (^{13}C NMR)



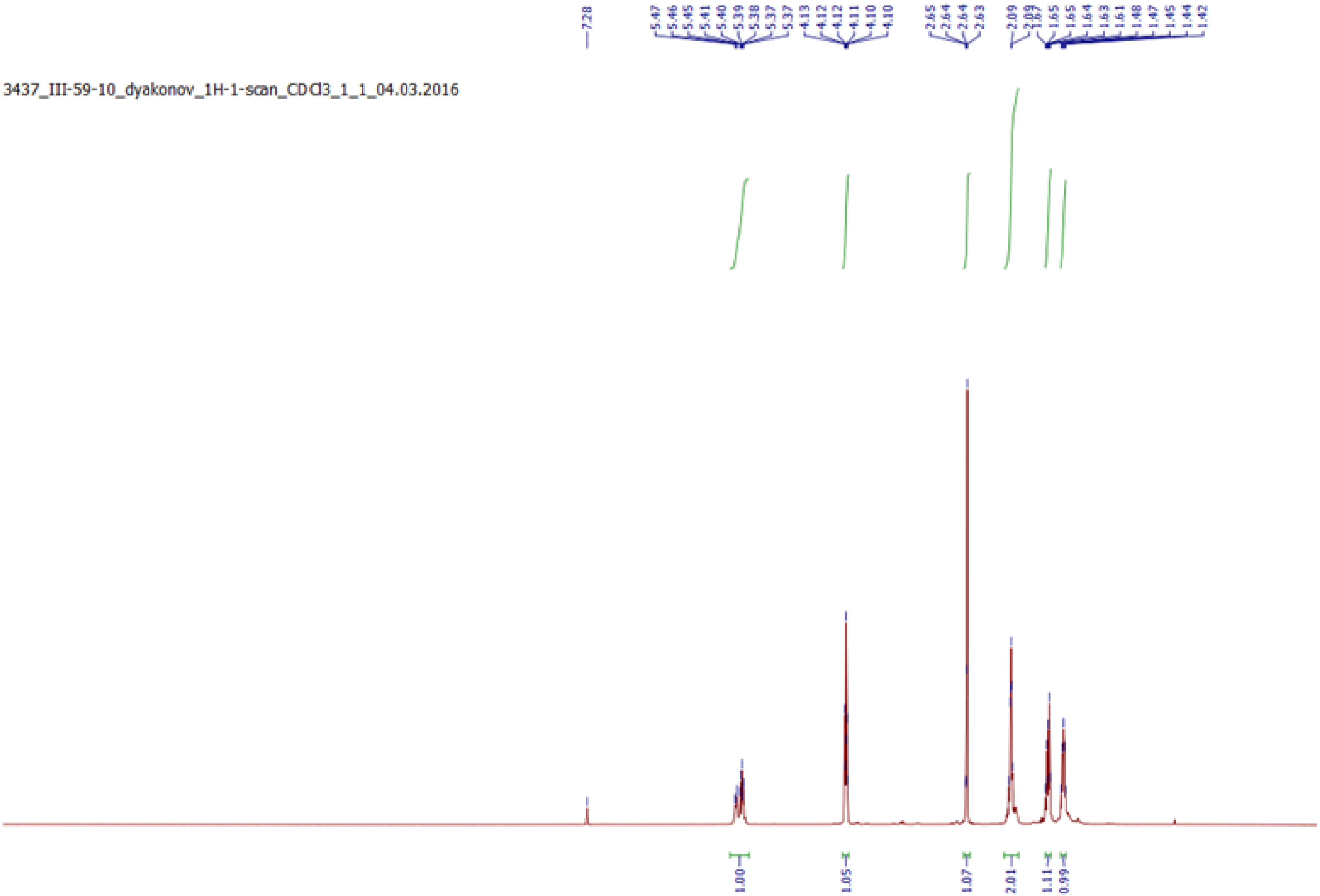
Compound 4 (^{1}H NMR)



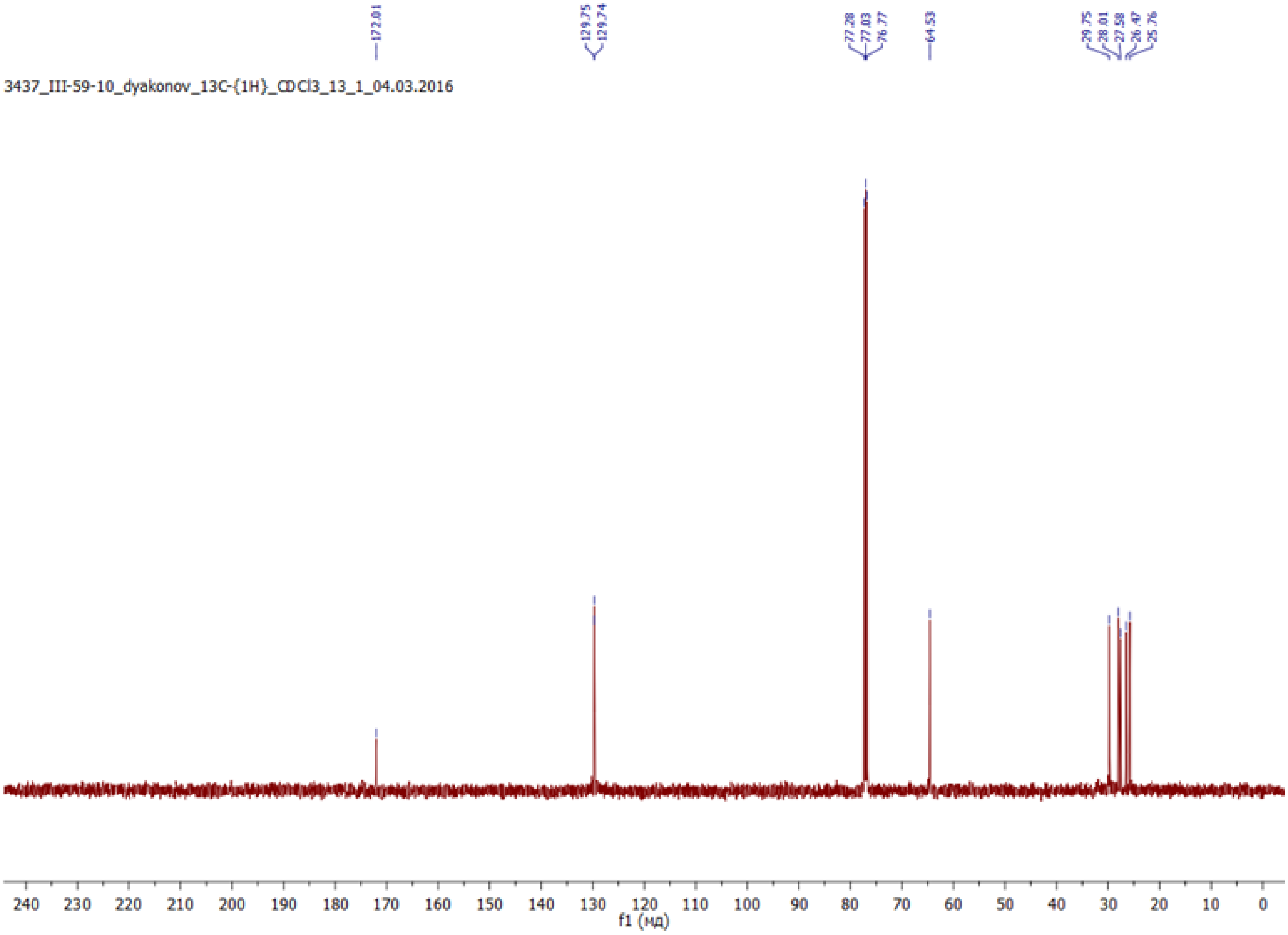
Compound 4 (^{13}C NMR)



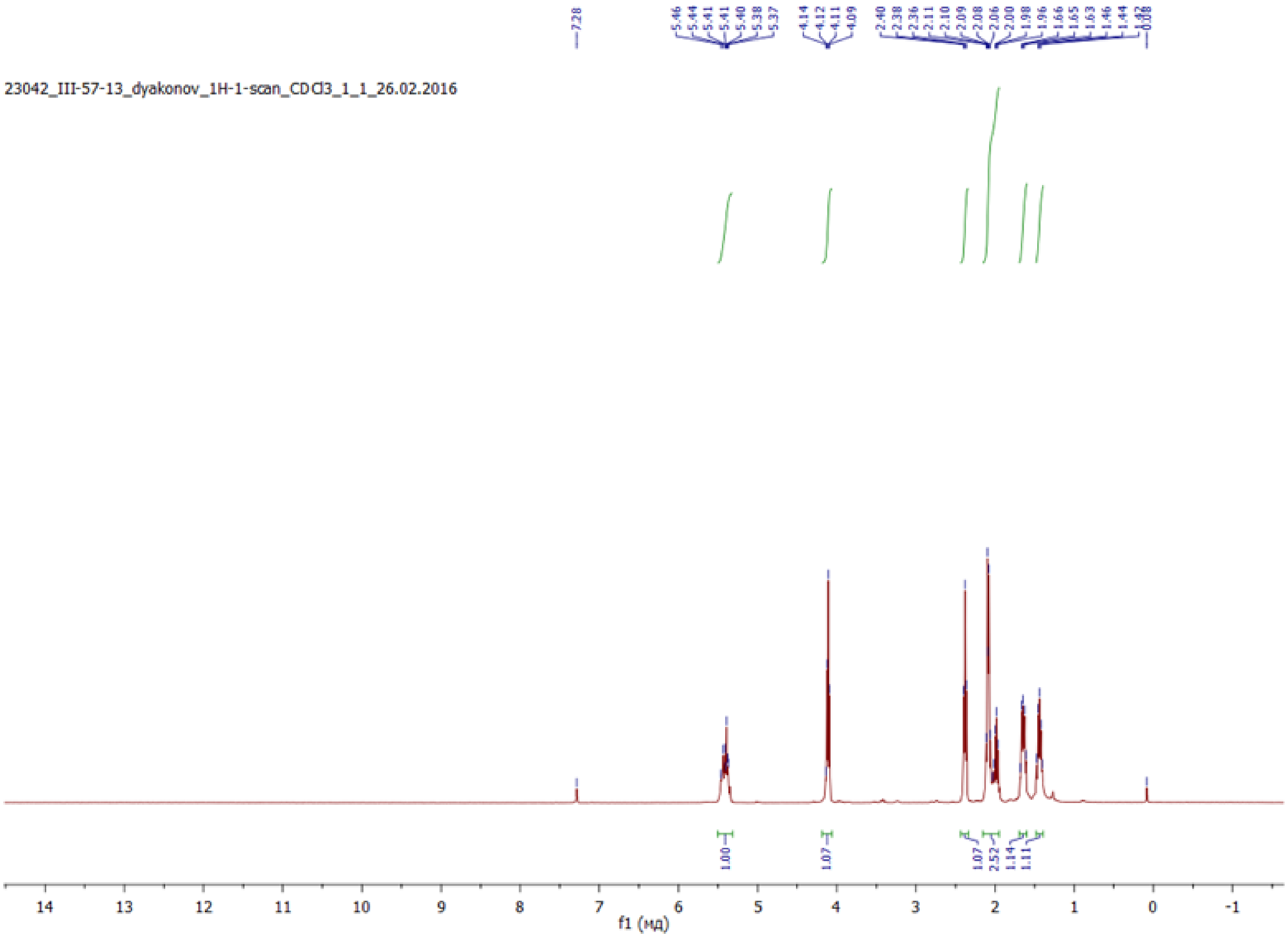
Compound 6a (^{1}H NMR)



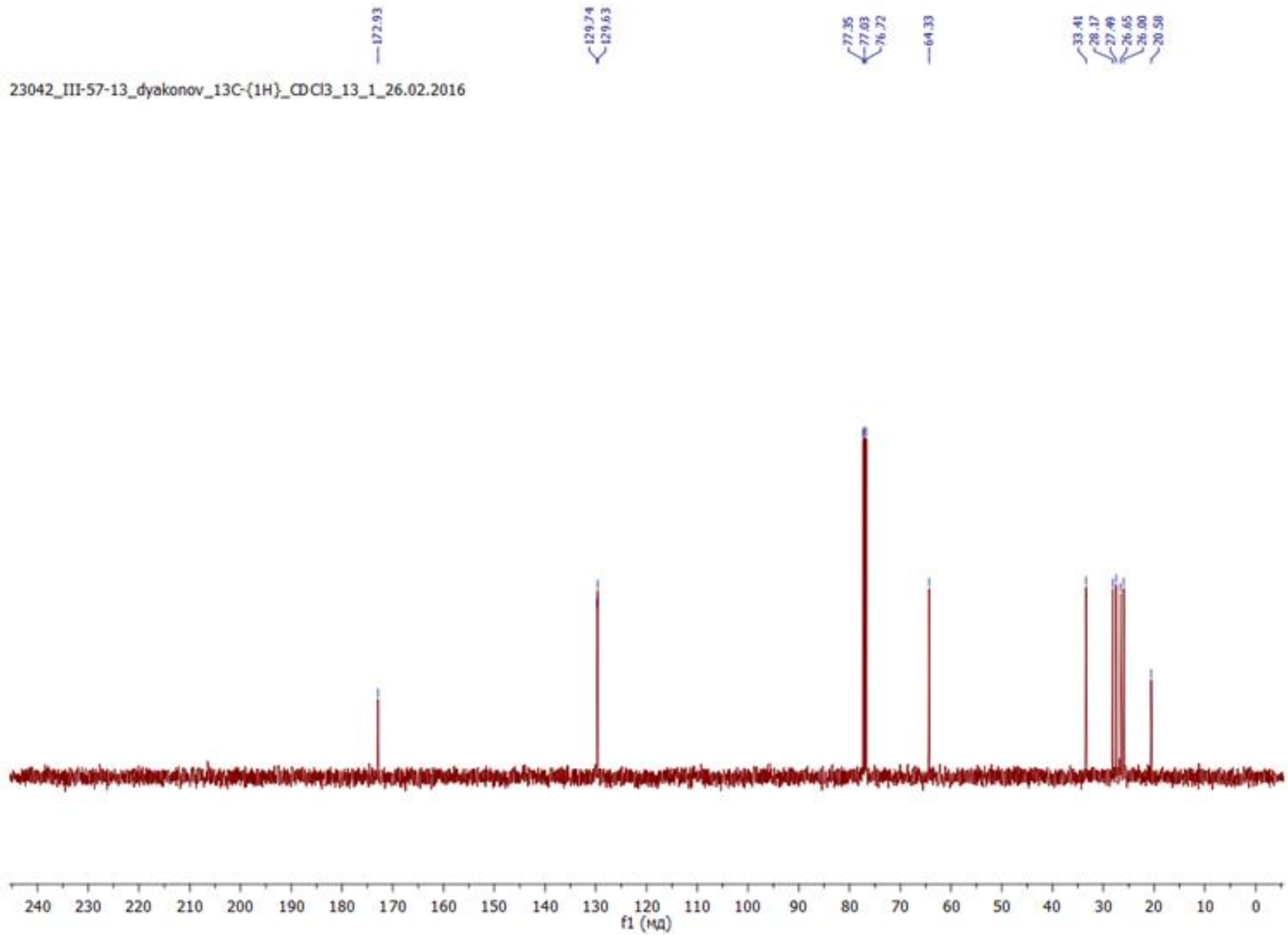
Compound 6a (^{13}C NMR)



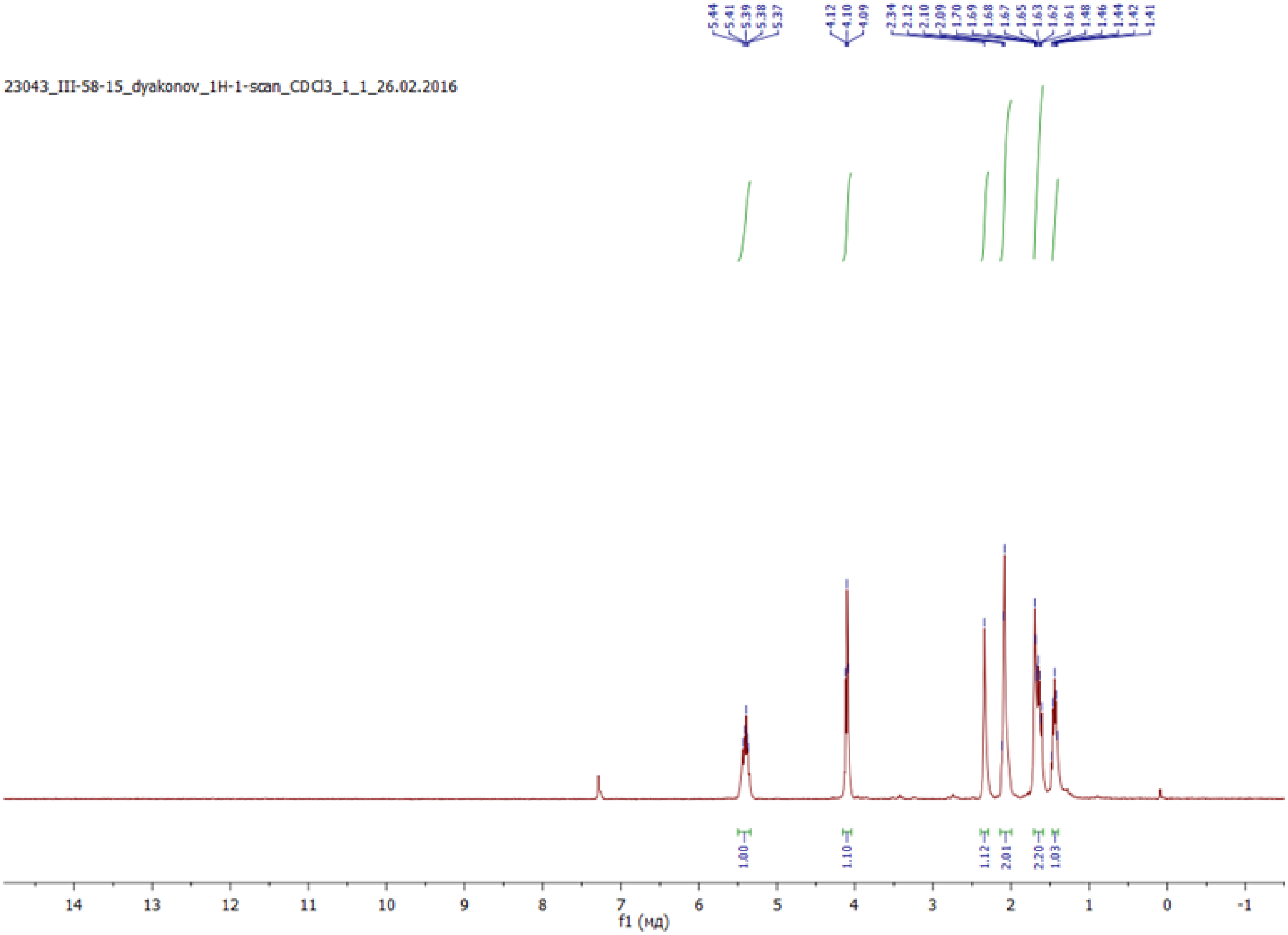
Compound 6b (^{1}H NMR)



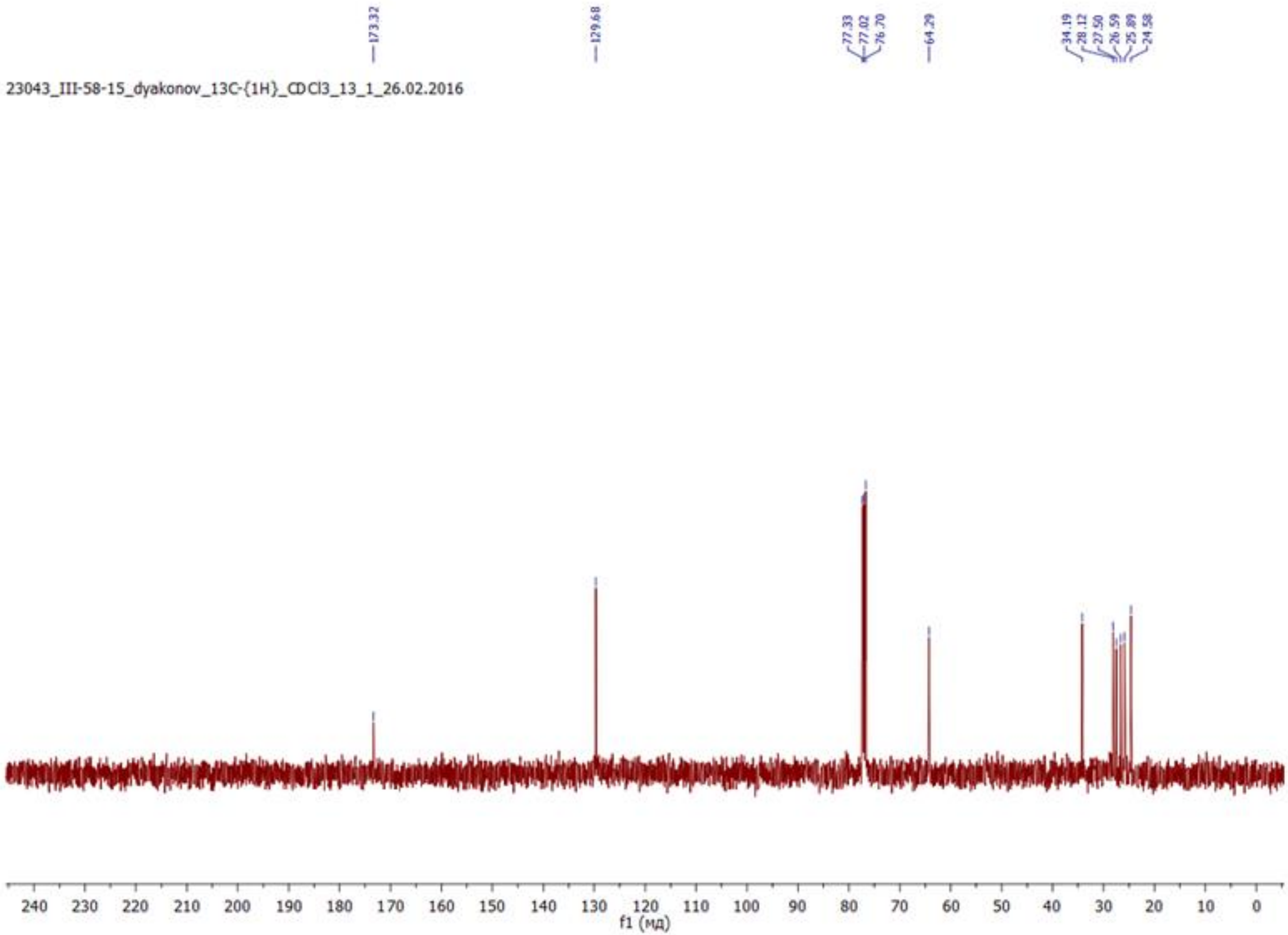
Compound 6b (^{13}C NMR)



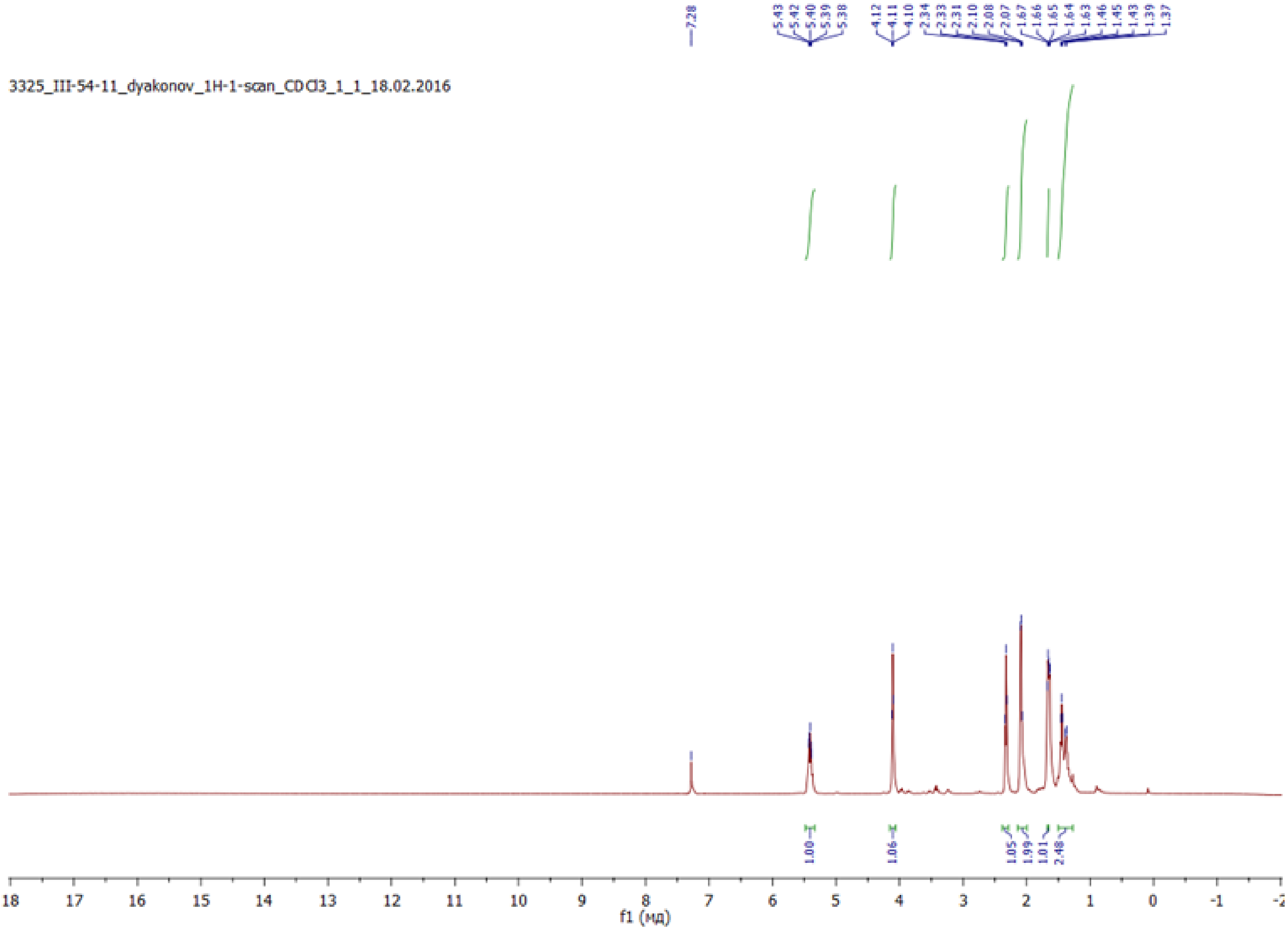
Compound 6c (^{1}H NMR)



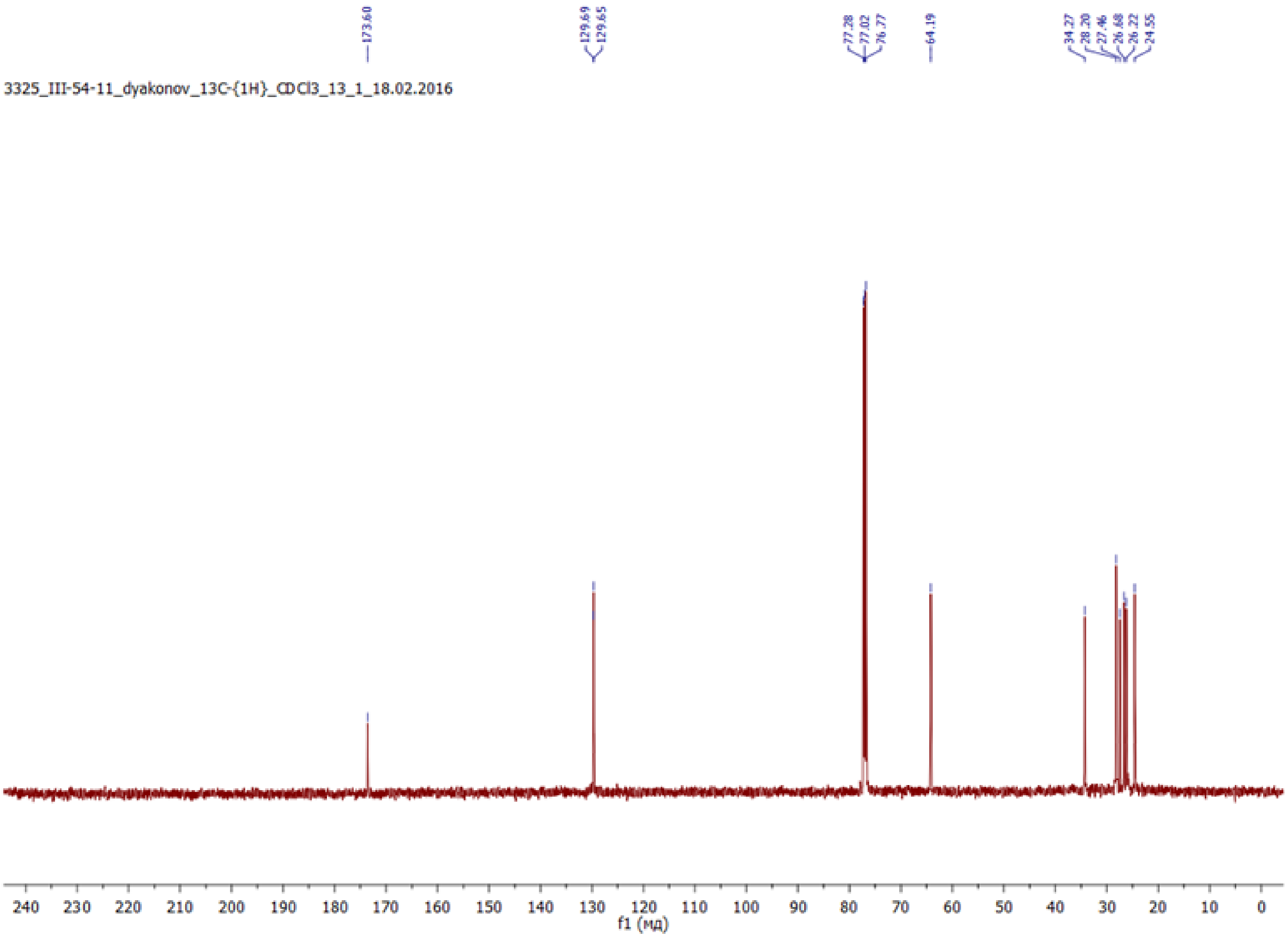
Compound 6c (^{13}C NMR)



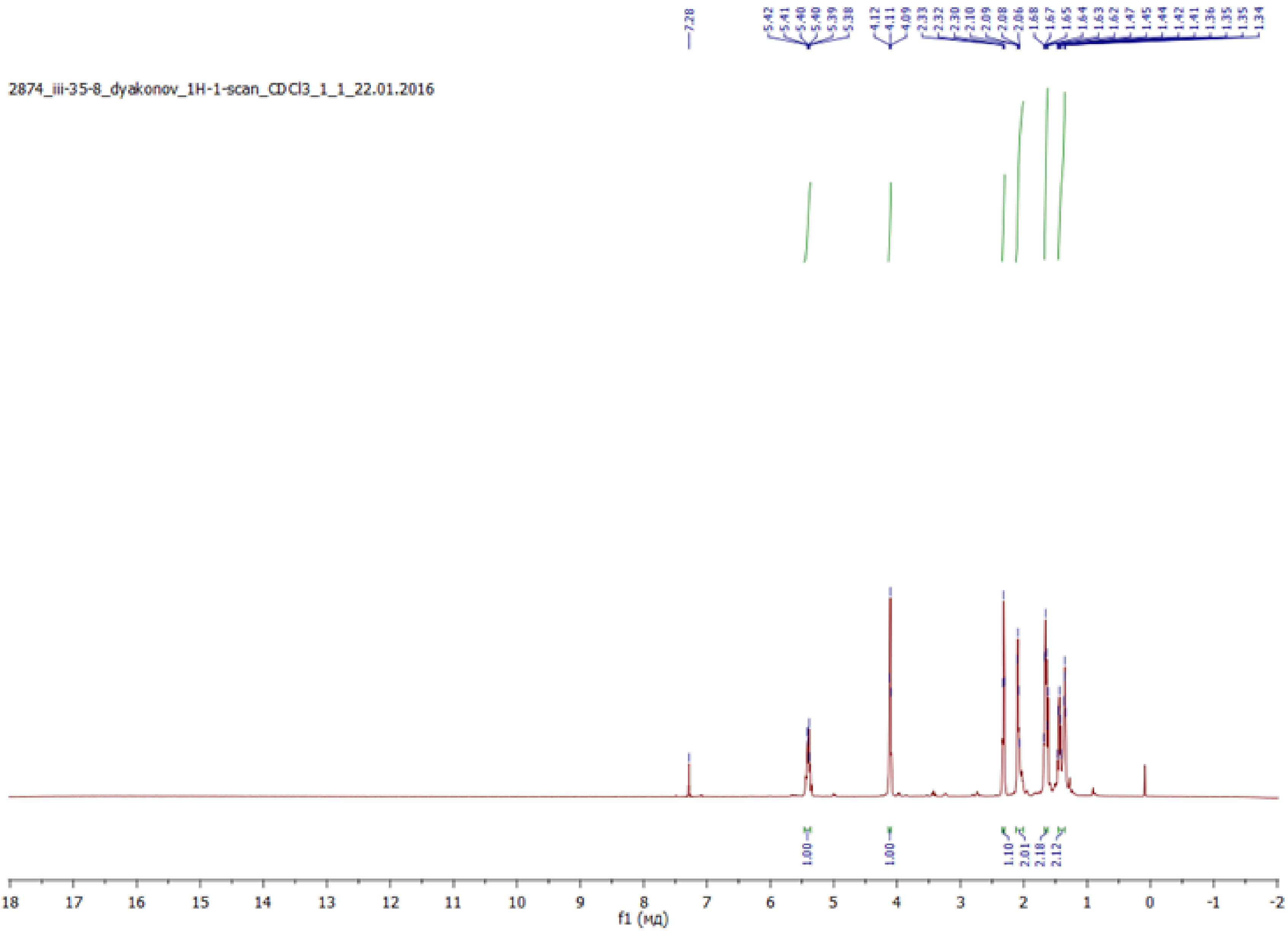
Compound 6d (^{1}H NMR)



Compound 6d (^{13}C NMR)



Compound 6e (^{1}H NMR)



Compound 6e (^{13}C NMR)