Electronic supplementary materials *Mendeleev Communications*, 2022, **32**, 433–435

Oligoglycol carbonate prodrugs of 5-modified 2'-deoxyuridines: synthesis and antibacterial activity

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General information

Commercial reagents were purchased from Acros, Aldrich, and Fluka. Column chromatography was performed on silica gel 60 0.040–0.063 mm (Merck, Germany). Thin layer chromatography (TLC) was performed on silica gel 60 F_{254} plates (Merck, Germany). NMR spectra were registered on an AMX III-400 spectrometer (Bruker, USA) with the working frequency of 300.13 MHz for ^{1}H NMR (solvent – DMSO-d_6, Me_4Si as an internal standard) and 75.47 MHz for ^{13}C NMR (with the carbon–proton interaction decoupling). UV spectra were recorded on a Perkin Elmer lambda 25 (Perkin Elmer, USA) in ethanol. High-resolution mass spectra were recorded on a Bruker Daltonics micrOTOF-Q II device by an electrospray ionization mass spectrometry. Measurements were carried out in positive ion mode in accordance with the previously applied conditions [L. Alexandrova *et al*, *Antiviral Res*., 2017, **145**, 175, S. Negrya *et al*, *J. Antibiot (Tokyo)*., 2020, **73**, 236]. Parent 5-alkyloxymethyl-2'-deoxyuridines **1a-d** were obtained as in [E. Shmalenyuk *et al*, *Russ. Chem. Bull. Int. Ed.,* 2014, **63**, 119, E. Shmalenyuk *et al*, *Bioorg. Med. Chem*., 2013, **21**, 4874].

Chemical hydrolysis of compounds

Compounds (0.02 mmol) were dissolved in DMSO (0.5 ml) and 100 µl of this solution was added to the 0.2 M glycine + 0.2 M HCl buffer (pH 2.2, 1.9 ml), 0.1 M potassium phosphate buffer (pH 7.5, 1.9 ml), or 0.2 M glycine + 0.2 M NaOH buffer (pH 9.0, 1.9 ml) and incubated for 24 h at 37 °C. Aliquots (0, 0.5, 2, 4, 8, 12, 16, 24 h) were taken out and analyzed by TLC (in chloroform/ethanol 9:1 v/v).

Hydrolysis of compounds in human blood serum

Compounds (0.02 mmol) were dissolved in DMSO (1 ml), and 4 µl of this solution was added to human blood serum (100%, 196 µl). The mixture was incubated at 37 °C for 24 h. Aliquots (15 µl) were taken out after certain intervals, ethanol (60 µl) was added, the mixture was kept for 20 min at −20 °C, and centrifuged. The supernatants were evaporated, the residues were dissolved in ethanol (10 µl) and analyzed by HPLC or TLC.

Enzymatic hydrolysis of compound 3c

Carboxylesterase (5 units) was dissolved in 28 µL of buffer 1 (25 mM Tris-HCl, 50 mM KCl, pH 8.0). The solution was combined with 5 µL of 20 mM compound in ethanol, 40 µL of buffer 2 (50 mM Tris-HCl, 6 mM $CaCl_2$, 350 mM NaCl, pH 7.6), and 127 µL of H_2O. The reaction mixture thus obtained was incubated at 37 °C for 3 h. Aliquots (15 µL) were collected at several time points and combined with ethanol (60 µL). The mixture was incubated at –20 °C for 20 min and centrifuged (14000 rpm, 10 min). The supernatant was collected and evaporated to obtain a dry pellet. The pellets were dissolved in ethanol (10 µL) and examined by chromatography–mass spectrometry or TLC in chloroform:ethanol 9:1.

Hydrolysis of compounds 3c and 6b upon incubation with *Staphylococcus aureus* FDA 209P.

Compounds (3.3 mg) were dissolved in a MeOH/H_2O mixture (1:1, 5 mL). The resulting solution (180 µL) was added to 2820 µL of Gause's no. 2 medium inoculated with *S. aureus* FDA 209P (106 cells per mL). The samples were incubated at 37 °C. Aliquots (300 µL) were collected after incubation for 0, 1, 2, 4, and 8 h and incubated in ice for 5 min. The supernatant was collected

by centrifugation (13000 rpm, Eppendorf, 5 min). Then the supernatant (300 μL) was combined with 1 mL of ethanol, and the mixture was incubated at –20°C for 20 min. The resulting suspension was centrifuged as above, the supernatant was collected and evaporated to obtain a dry pellet, and the pellet was dissolved in ethanol (20 μL) and analyzed by chromatography–mass spectrometry or TLC. The pellet that contained bacterial cells was supplemented with 100 μL of 10 μg/μL lysozyme (an aqueous solution), and the mixture was shaken on a vortex mixer for 1 min and incubated in a thermostat at 37°C for 30 min. Total disruption of *S. aureus* cells was confirmed by microscopy after incubation. Ethanol (800 μL) was added into the tube, the sample was incubated at –20°C for 20 min, and the supernatant was collected and analyzed as above.

Study of the antibacterial effect

The following test strains were used: Gram-positive bacteria *Bacillus subtilis* ATCC 6633, *Staphylococcus aureus* INA 00761 (MRSA), *Staphylococcus aureus* FDA 209 P (MSSA), *Leuconostoc mesenteroides* VKPM B-4177, *Micrococcus luteus* NCTC 8340, *Mycobacterium smegmatis* mc^2 155 and *Mycobacterium smegmatis* VKPM Ac 1339; Gram-negative bacteria *Pseudomonas aeruginosa* ATCC 27853; fungi *Aspergillus niger* INA 00760 and *Saccharomyces cerevisiae* INA 01129 from the collection of the Gause Institute of New Antibiotics. Test strains were incubated in modified Gause′s nutrient medium No. 2. The level of infection with test cultures was 10^6 cells·ml^{-1}. A compound being tested was dissolved in 30% aq. methanol. Ten volume percent of tested compound was added to the nutrient medium. Samples without the addition of substances, antibiotics in medical use (amikacin, ciprofloxacin, isoniazid, rifampicin, oxacillin and vancomycin), and samples of medium supplemented with a mixture of solvents served as controls of the test culture growth. Fungal test cultures and *L. mesenteroides* were incubated at 28 °C, and all other strains were incubated at 37 °C.

5-Hexadecyloxymethyl-2'-deoxyuridine (1e)

N-Bromosuccinimide (2.5 g, 13.8 mmol) and azobisisobutyronitrile (189 mg, 1.15 mmol) were added to a solution of 3',5'-di-*O*-acetylthymidine (1.5 g, 4.6 mmol) in dichloroethane (70 mL), and the reaction mixture was refluxed for 3 h. The reaction mixture was cooled and evaporated in vacuum. The resulting mixture was dissolved in DMF (5 mL) followed by the addition of the hexadecan-1-ol (1.67 g, 6.9 mmol). The mixture was heated at 37 °C for 24 h in the argon atmosphere. The solvent was evaporated in vacuum, the residue was dissolved in ethanol (20 mL), followed by the addition of aqueous ammonia (20 mL). The reaction mixture was kept overnight at 25 °C, followed by the evaporation in vacuum. The product was isolated by column chromatography in the chloroform/ethanol (20:1 v/v) eluting system. Yield 0.93 g (42%). ^{1}H NMR: δ 0.86 (t, *J* = 6.7 Hz, 3H, -$OC_{15}H_{30}C\underline{H}_3$), 1.22-1.27 (m, 26H, -$OC_2H_4C_{13}\underline{H}_{26}CH_3$), 1.47 (m, 2H, -$OCH_2C\underline{H}_2C_{14}H_{29}$), 1.99-2.18 (m, 2H, CH_2-2'), 3.37 (t, *J* = 6.6 Hz, 2H, -$OC\underline{H}_2C_{15}H_{31}$), 3.50-3.63 (m, 2H, CH_2-5'), 3.79 (dt, *J* = 3.7, 3.7 Hz, 1H, H-4'), 4.07 (s, 2H, CH_2-5), 4.20-4.28 (m, 1H, H-3'), 4.98 (t, *J* = 5.1 Hz, 1H, OH-5'), 5.23 (d, *J* = 4.2 Hz, 1H, OH-3'), 6.17 (t, *J* = 6.8 Hz, 1H, H-1'), 7.86 (s, 1H, H-6), 11.33 (s, 1H, NH). ^{13}C NMR: δ 14.40 (-$C_{15}H_{30}\underline{C}H_3$), 22.56 (-$OC_{14}H_{28}\underline{C}H_2CH_3$), 26.12 (-$OC_{13}H_{26}\underline{C}H_2C_2H_5$), 29.17-29.62 (-$OC_2H_4\underline{C}_{11}H_{22}C_3H_7$), 31.77 (-$OCH_2\underline{C}H_2C_{14}H_{29}$), 40.18 (C-2'), 61.81 (C-5'), 64.95 (-$O\underline{C}H_2C_{15}H_{31}$), 70.07 (C-3'), 70.93 ($CH_2$-5), 84.62 (C-4'), 87.90 (C-1'), 111.20 (C-5), 139.14 (C-6), 150.77 (C-2), 163.12 (C-4). UV: λ_{max} 262.2 nm (ε 9800). MS (ESI) calcd for $C_{26}H_{46}N_2O_6$ 483.3429 $[M+H]^+$, found 483.3432.

Method A. General procedure for obtaining of 5'-(*tert*-butyl)dimethylsilyl derivatives

A nucleoside (0.7 mmol) was dissolved in dry pyridine (5 ml), and (*tert*-butyl)dimethylchlorosilane (129 mg, 0.85 mmol) was added. The mixture was kept at 4 °C for 16 h and then evaporated. The product was isolated by column chromatography in the chloroform/ethanol (50:1 v/v) eluting system.

5'-*O*-(*tert*-Butyl)dimethylsilyl-5-decyloxymethyl-2'-deoxyuridine (2a)

Obtained from **1a** by method **A**. Yield: 312 mg (87%). ^{1}H NMR δ 0.07 (s, 6H, -Si(CH_3)$_2$), 0.80-0.93 (m, 13H, -SiC(CH_3)$_3$ + -O$C_9H_{18}C\underline{H}_3$), 1.24-1.30 (m, 14H, -O$C_2H_4C_7\underline{H}_{14}CH_3$), 1.44-1.53 (m, 2H, -O$CH_2C\underline{H}_2C_8H_{17}$), 2.03 (ddd, *J* = 13.4, 7.8, 6.0 Hz, 1H, H_a-2'), 2.16 (ddd, *J* = 13.2, 5.9, 2.8 Hz, 1H, H_b-2'), 3.37 (t, *J* = 6.5 Hz, 2H, -O$C\underline{H}_2C_9H_{19}$), 3.68-3.81 (m, 2H, CH_2-5'), 3.83-3.87 (m, 1H, H-4'), 4.01-4.13 (m, 2H, CH_2-5), 4.17-4.22 (m, 1H, H-3'), 5.28 (d, *J* = 4.2 Hz, 1H, OH-3'), 6.17 (dd, J = 7.8, 6.0 Hz, 1H, H-1'), 7.60 (s, 1H, H-6), 11.39 (s, 1H, NH). UV: λ_{max} 263.2 nm (ε 9800). MS (ESI) calcd for $C_{26}H_{48}N_2O_6Si$ 513.3354 $[M+H]^+$, found 513.3358.

5'-*O*-(*tert*-Butyl)dimethylsilyl-5-undecyloxymethyl-2'-deoxyuridine (2b)

Obtained from **1b** by method **A**. Yield: 302 mg (82%). ^{1}H NMR δ 0.02 (s, 6H, -Si(CH_3)$_2$), 0.81-0.86 (m, 12H, -SiC(CH_3)$_3$ + -O$C_{10}H_{20}C\underline{H}_3$), 1.23-1.28 (m, 16H, -O$C_2H_4C_8\underline{H}_{16}CH_3$), 1.48-1.56 (m, 2H, -O$CH_2C\underline{H}_2C_9H_{19}$), 2.02-2.16 (m, 2H, CH_2-2'), 3.37 (t, 2H, *J* = 6.5 Hz, -O$C\underline{H}_2C_{10}H_{21}$), 3.67-3.78 (m, 2H, CH_2-5'), 3.84-3.87 (m, 1H, H-4'), 4.02-4.11 (s, 2H, CH_2-5), 4.18-4.22 (m, 1H, H-3'), 5.26 (d, 1H, *J* = 4.2 Hz, OH-3'), 6.17 (dd, 1H, *J* = 7.2, 5.5 Hz, H-1'), 7.60 (s, 1H, H-6), 11.42 (s, 1H, NH). UV: λ_{max} 263.4 nm (ε 9800). MS (ESI) calcd for $C_{27}H_{50}N_2O_6Si$ 527.3511 $[M+H]^+$, found 527.3513.

5'-*O*-(*tert*-Butyl)dimethylsilyl-5-dodecyloxymethyl-2'-deoxyuridine (2c)

Obtained from **1c** by method **A**. Yield: 313 mg (83%). ^{1}H NMR δ 0.02 (s, 6H, -Si(CH_3)$_2$), 0.78-0.84 (m, 12H, -SiC(CH_3)$_3$ + -O$C_{11}H_{22}C\underline{H}_3$), 1.19-1.25 (m, 18H, -O$C_2H_4C_9\underline{H}_{18}CH_3$), 1.41-1.45 (m, 2H, -O$CH_2C\underline{H}_2C_{10}H_{21}$), 1.98 (ddd, 1H, *J* = 13.4, 7.9, 5.9 Hz, H-2'(a)), 2.11 (ddd, 1H, *J* = 13.2, 5.9, 2.8 Hz, H-2'(b)), 3.32 (t, 2H, *J* = 6.5 Hz, -$C\underline{H}_2C_{11}H_{23}$), 3.64-3.75 (m, 2H, CH_2-5'), 3.78-3.81 (m, 1H, H-4'), 3.97-4.06 (s, 2H, CH_2-5), 4.13-4.16 (m, 1H, H-3'), 5.23 (d, 1H, *J* = 4.2 Hz, OH-3'), 6.11 (dd, 1H, *J* = 6.8, 5.9 Hz, H-1'), 7.54 (s, 1H, H-6), 11.35 (s, 1H, NH). UV: λ_{max} 263.4 nm (ε 9780). MS (ESI) calcd for $C_{28}H_{52}N_2O_6Si$ 541.3667 $[M+H]^+$, found 541.3666.

5'-*O*-(*tert*-Butyl)dimethylsilyl-5-tetradecyloxymethyl-2'-deoxyuridine (2d)

Obtained from **1d** by method **A**. Yield: 334 mg (84%). ^{1}H NMR δ 0.08 (s, 6H, -Si(CH_3)$_2$), 0.80-0.87 (m, 12H, -SiC(CH_3)$_3$ + -O$C_{13}H_{26}C\underline{H}_3$), 1.21-1.26 (m, 22H, -O$C_2H_4C_{11}\underline{H}_{22}CH_3$), 1.41-1.44 (m, 2H, -O$CH_2C\underline{H}_2C_{12}H_{25}$), 2.00-2.15 (m, 2H, CH_2-2'), 3.34 (t, 2H, *J* = 6.5 Hz, -$C\underline{H}_2C_{13}H_{27}$), 3.63-3.73 (m, 2H, CH_2-5'), 3.82-3.86 (m, 1H, H-4'), 3.99-4.09 (s, 2H, CH_2-5), 4.16-4.20 (m, 1H, H-3'), 5.25 (d, 1H, *J* = 4.2 Hz, OH-3'), 6.15 (dd, 1H, *J* = 6.6, 5.8 Hz, H-1'), 7.58 (s, 1H, H-6), 11.32 (s, 1H, NH). UV: λ_{max} 264.2 nm (ε 9780). MS (ESI) calcd for $C_{30}H_{56}N_2O_6Si$ 569.3980 $[M+H]^+$, found 569.3981.

5'-*O*-(*tert*-Butyl)dimethylsilyl-5-hexadecyloxymethyl-2'-deoxyuridine (2e)

Obtained from **1e** by method **A**. Yield: 325 mg (78%). ^{1}H NMR δ 0.07 (s, 6H, -Si(CH_3)$_2$), 0.83-0.87 (m, 12H, -SiC(CH_3)$_3$ + -O$C_{15}H_{30}C\underline{H}_3$), 1.23-1.29 (m, 26H, -O$C_2H_4C_{13}\underline{H}_{26}CH_3$), 1.43-1.52 (m, 2H, -O$CH_2C\underline{H}_2C_{14}H_{29}$), 2.02 (ddd, 1H, *J* = 13.4, 7.8, 6.0 Hz, H-2'(a)), 2.15 (ddd, 1H, *J* = 13.1, 5.9, 2.7 Hz, H-2'(b)), 3.36 (t, 2H, *J* = 6.6 Hz, -$C\underline{H}_2C_{15}H_{31}$), 3.68-3.79 (m, 2H, CH_2-5'), 3.83-3.86 (m, 1H, H-4'), 4.01-4.10 (m, 2H, CH_2-5), 4.16-4.21 (m, 1H, H-3'), 5.28 (d, 1H, *J* = 4.2 Hz, OH-3'), 6.16 (dd, 1H, *J* = 7.8, 6.0 Hz, H-1'), 7.58 (s, 1H, H-6), 11.39 (s, 1H, NH). UV: λ_{max} 263.3 nm (ε 9780). MS (ESI) calcd for $C_{32}H_{61}N_2O_6Si$ 597.4293 $[M+H]^+$, found 597.4293.

Method B. General procedure for insertion of a carbonyl tri- or tetraethylene glycol group

A nucleoside (0.28 mmol) was dissolved in dry DMF (1ml), and CDI (137 mg, 0.84 mmol) was added. The mixture was heated at 37 °C for 24 h. Then anhydrous tri- or tetraethylene glycol (1.65 g for triethylene glycol, 2.1 g for tetraethylene glycol, 11 mol) and dioxane (0.5 ml) were added. The mixture was heated at 37 °C for 24 h and then evaporated to leave crude oil with constant volume. The product was extracted in the chloroform–water system, the organic layer was evaporated. The product was isolated by column chromatography in the chloroform/ethyl acetate:ethanol (5:5:0.1 v/v) eluting system.

Method C. General procedure for deprotection of a (*tert*-butyl)dimethylsilyl group

A nucleoside (0.062 mmol) was dissolved in dioxane (3 ml), then tetrabutylammonium fluoride trihydrate (21.5 mg, 0.068 mmol) was added. The mixture was kept at 25 °C for 8 h and then evaporated. The product was isolated by column chromatography in the chloroform/ethanol (9:1 v/v) eluting system.

3'-*O*-(8-Hydroxy-3,6-dioxaoct-1-yloxy)carbonyl-5-decyloxymethyl-2'-deoxyuridine (3a)

Obtained from 5'-*O*-(*tert*-butyl)dimethylsilyl-5-decyloxymethyl-2'-deoxyuridine (**2a**) by methods **B** and **C**. Yield 34 mg (56% for two stages). ^{1}H NMR δ 0.84-0.88 (m, 3H, -$C_9H_{18}C\underline{H}_3$), 1.24-1.30 (m, 14H, -$C_2H_4C_7\underline{H}_{14}CH_3$), 1.44-1.51 (m, 2H, -$CH_2C\underline{H}_2C_8H_{17}$), 2.26-2.42 (m, 2H, CH_2-2'), 3.36-3.66 (m, 14H, -$C\underline{H}_2C_9H_{19}$ + -$C\underline{H}_2(OC_2\underline{H}_4)_2OH$ + CH_2-5'), 4.07-4.10 (m, 3H, CH_2-5 + H-4'), 4.22-4.25 (m, 2H, -$C\underline{H}_2CH_2(OC_2H_4)_2OH$), 4.56 (t, 1H, *J* = 5.4 Hz, -$(OC_2H_4)_3O\underline{H}$), 5.16-5.22 (m, 2H, H-3' + OH-5'), 6.18 (dd, 1H, *J* = 6.0, 8.4 Hz, H-1'), 7.91 (s, 1H, H-6), 11.40 (s, 1H, NH). ^{13}C NMR δ 14.38 (-$OC_9H_{18}\underline{C}H_3$), 22.35-31.76 (-$OCH_2\underline{C}_8H_{16}CH_3$), 37.23 (C-2'), 60.69 ($CH_2$-5'), 61.79 ($CH_2$-5), 64.93-72.84 (-$(OC_2H_4)_3OH$ + -$O\underline{C}H_2C_9H_{19}$), 79.01 (C-3'), 84.55 (C-4'), 84.98 (C-1'), 111.58 (C-5), 138.88 (C-6), 150.75 (C-2), 154.31 (-OC(O)O-), 163.05 (C-4). UV: λ_{max} 263.3 nm (ε 9780). MS (ESI) calcd for $C_{27}H_{46}N_2O_{11}$ 575.3174 $[M+H]^+$ found 575.3172.

3'-*O*-(8-Hydroxy-3,6-dioxaoct-1-yloxy)carbonyl-5-undecyloxymethyl-2'-deoxyuridine (3b)

Obtained from 5'-*O*-(*tert*-butyl)dimethylsilyl-5-undecyloxymethyl-2'-deoxyuridine (**2b**) by methods **B** and **C**. Yield 34 mg (49% for two stages). ^{1}H NMR δ 0.83-0.88 (m, 3H, -$C_{10}H_{20}C\underline{H}_3$), 1.24-1.30 (m, 16H, -$C_2H_4C_8\underline{H}_{16}CH_3$), 1.44-1.53 (m, 2H, -$CH_2C\underline{H}_2C_9H_{19}$), 2.25-2.42 (m, 2H, CH_2-2'), 3.36-3.66 (m, 14H, -$C\underline{H}_2C_{10}H_{21}$ + -$C\underline{H}_2(OC_2\underline{H}_4)_2OH$ + CH_2-5'), 4.06-4.10 (m, 3H, CH_2-5 + H-4'), 4.21-4.24 (m, 2H, -$C\underline{H}_2CH_2(OC_2H_4)_2OH$), 4.54 (t, 1H, *J* = 5.4 Hz, -$(OC_2H_4)_3O\underline{H}$), 5.16-5.19 (m, 2H, H-3' + OH-5'), 6.17 (dd, 1H, *J* = 5.8, 8.2 Hz, H-1'), 7.90 (s, 1H, H-6), 11.40 (s, 1H, NH). ^{13}C NMR δ 14.38 (-$OC_{10}H_{20}\underline{C}H_3$), 22.55-31.77 (-$OCH_2\underline{C}_9H_{18}CH_3$), 37.23 (C-2'), 60.70 ($CH_2$-5'), 61.80 ($CH_2$-5), 64.93-72.84 (-$(OC_2H_4)_3OH$ + -$O\underline{C}H_2C_{10}H_{21}$), 78.99 (C-3'), 84.55 (C-4'), 84.97 (C-1'), 111.59 (C-5), 138.87 (C-6), 150.75 (C-2), 154.32 (-OC(O)O-), 163.05 (C-4). UV: λ_{max} 263.3 nm (ε 9780). MS (ESI) calcd for $C_{28}H_{48}N_2O_{11}$ 589.3331 $[M+H]^+$ found 589.3328.

3'-*O*-(8-Hydroxy-3,6-dioxaoct-1-yloxy)carbonyl-5-dodecyloxymethyl-2'-deoxyuridine (3c)

Obtained from 5'-*O*-(*tert*-butyl)dimethylsilyl-5-dodecyloxymethyl-2'-deoxyuridine (**2c**) by methods **B** and **C**. Yield 35 mg (54% for two stages). ^{1}H NMR δ 0.84-0.88 (m, 3H, -$C_{11}H_{22}C\underline{H}_3$), 1.25-1.33 (m, 18H, -$C_2H_4C_9\underline{H}_{18}CH_3$), 1.43-1.52 (tt, 2H, *J* = 13.3, 7.0 Hz, -$CH_2C\underline{H}_2C_{10}H_{21}$), 2.26-2.41 (m, 2H, CH_2-2'), 3.36-3.66 (m, 14H, -$C\underline{H}_2C_{11}H_{23}$ + -$C\underline{H}_2(OC_2\underline{H}_4)_2OH$ + CH_2-5'), 4.07-4.09 (m, 3H, CH_2-5 + H-4'), 4.21-4.24 (m, 2H, -$C\underline{H}_2CH_2(OC_2H_4)_2OH$), 4.55 (t, 1H, *J* = 5.4 Hz, -$(OC_2H_4)_3O\underline{H}$), 5.16-5.19 (m, 2H, H-3' + OH-5'), 6.17 (dd, 1H, *J* = 6.1, 8.3 Hz, H-1'), 7.90 (s, 1H, H-6), 11.41 (s,

1H, NH). ^{13}C NMR δ 14.39 (-OC$_{11}$H$_{22}$CH$_3$), 22.55-31.76 (-OCH$_2$C$_{10}$H$_{20}$CH$_3$), 37.22 (C-2'), 60.70 (CH$_2$-5'), 61.80 (CH$_2$-5), 64.93-72.82 (-(OC$_2$H$_4$)$_3$OH + -OCH$_2$C$_{11}$H$_{23}$), 78.98 (C-3'), 84.54 (C-4'), 84.95 (C-1'), 111.58 (C-5), 138.88 (C-6), 150.75 (C-2), 154.31 (-OC(O)O-), 163.05 (C-4). UV: λ_{max} 262.9 nm (ε 9780). MS (ESI) calcd for $C_{29}H_{50}N_2O_{11}$ 603.3487 $[M+H]^+$ found 603.3488.

3'-*O*-(13-Hydroxy-2,5,8,11-tetraoxatridecanoyl)-5-dodecyloxymethyl-2'-deoxyuridine (3d)

Obtained from 5'-*O*-(*tert*-butyl)dimethylsilyl-5-dodecyloxymethyl-2'-deoxyuridine (**2d**) by methods **B** and **C**. Yield 35 mg (50% for two stages). ^{1}H NMR δ 0.83-0.88 (m, 3H, -C$_{11}$H$_{22}$CH$_3$), 1.24-1.30 (m, 18H, -C$_2$H$_4$C$_9$H$_{18}$CH$_3$), 1.44-1.53 (m, 2H, -CH$_2$CH$_2$C$_{10}$H$_{21}$), 2.25-2.41 (m, 2H, CH$_2$-2'), 3.32-3.65 (m, 18H, -CH$_2$C$_{11}$H$_{23}$ + -CH$_2$(OC$_2$H$_4$)$_3$OH + CH$_2$-5'), 4.05-4.12 (m, 3H, CH$_2$-5 + H-4'), 4.21-4.24 (m, 2H, -CH$_2$CH$_2$(OC$_2$H$_4$)$_3$OH), 4.55 (t, 1H, *J* = 5.4 Hz, -(OC$_2$H$_4$)$_4$OH), 5.16-5.20 (m, 2H, H-3' + OH-5'), 6.17 (dd, 1H, *J* = 6.0, 8.4 Hz, H-1'), 7.90 (s, 1H, H-6), 11.35 (s, 1H, NH). ^{13}C NMR δ 14.39 (-OC$_{11}$H$_{22}$CH$_3$), 22.55-31.76 (-OCH$_2$C$_{10}$H$_{21}$CH$_3$), 37.22 (C-2'), 60.70 (CH$_2$-5'), 61.80 (CH2-5), 64.93-72.82 (-(OC$_2$H$_4$)$_4$OH + -OCH$_2$C$_{11}$H$_{23}$), 78.98 (C-3'), 84.54 (C-4'), 84.95 (C-1'), 111.58 (C-5), 138.88 (C-6), 150.75 (C-2), 154.31 (-OC(O)O-), 163.05 (C-4). UV: λ_{max} 263.4 nm (ε 9780). MS (ESI) calcd for $C_{29}H_{50}N_2O_{11}$ 603.3487 $[M+H]^+$ found 603.3487.

3'-*O*-(8-Hydroxy-3,6-dioxaoct-1-yloxy)carbonyl-5-tetradecyloxymethyl-2'-deoxyuridine (3e)

Obtained from 5'-*O*-(*tert*-butyl)dimethylsilyl-5-tetradecyloxymethyl-2'-deoxyuridine (**2e**) by methods **B** and **C**. Yield 36 mg (48% for two stages). ^{1}H NMR δ 0.84-0.88 (m, 3H, -C$_{13}$H$_{26}$CH$_3$), 1.24-1.31 (m, 22H, -C$_2$H$_4$C$_{11}$H$_{22}$CH$_3$), 1.45-1.53 (m, 2H, -CH$_2$CH$_2$C$_{12}$H$_{25}$), 2.26-2.42 (m, 2H, CH$_2$-2'), 3.36-3.66 (m, 14H, -CH$_2$C$_{13}$H$_{27}$ + -CH$_2$(OC$_2$H$_4$)$_2$OH + CH$_2$-5'), 4.06-4.11 (m, 3H, CH$_2$-5 + H-4'), 4.22-4.25 (m, 2H, -CH$_2$CH$_2$(OC$_2$H$_4$)$_2$OH), 4.56 (t, 1H, *J* = 5.4 Hz, -(OC$_2$H$_4$)$_2$OH), 5.17-5.22 (m, 2H, H-3' + OH-5'), 6.18 (dd, 1H, *J* = 6.1, 8.4 Hz, H-1'), 7.91 (s, 1H, H-6), 11.40 (s, 1H, NH). ^{13}C NMR δ 14.38 (-OC$_{13}$H$_{26}$CH$_3$), 22.55-31.76 (-OCH$_2$C$_{12}$H$_{24}$CH$_3$), 37.23 (C-2'), 60.69 (CH$_2$-5'), 61.79 (CH$_2$-5), 64.93-72.84 (-(OC$_2$H$_4$)$_3$OH + -OCH$_2$C$_{13}$H$_{27}$), 79.01 (C-3'), 84.55 (C-4'), 84.98 (C-1'), 111.58 (C-5), 138.88 (C-6), 150.75 (C-2), 154.31 (-OC(O)O-), 163.05 (C-4). UV: λ_{max} 263.1 nm (ε 9780). MS (ESI) calcd for $C_{31}H_{54}N_2O_{11}$ 631.3800 $[M+H]^+$ found 631.3798.

3'-*O*-(8-Hydroxy-3,6-dioxaoct-1-yloxy)carbonyl-5-hexadecyloxymethyl-2'-deoxyuridine (3f)

Obtained from 5'-*O*-(*tert*-butyl)dimethylsilyl-5-hexadecyloxymethyl-2'-deoxyuridine (**2f**) by methods **B** and **C**. Yield 38 mg (47% for two stages). ^{1}H NMR δ 0.83-0.88 (m, 3H, -C$_{15}$H$_{30}$CH$_3$), 1.24-1.30 (m, 26H, -C$_2$H$_4$C$_{13}$H$_{26}$CH$_3$), 1.44-1.53 (m, 2H, -CH$_2$CH$_2$C$_{14}$H$_{29}$), 2.25-2.41 (m, 2H, CH$_2$-2'), 3.35-3.66 (m, 14H, -CH$_2$C$_{15}$H$_{31}$ + -CH$_2$(OC$_2$H$_4$)$_2$OH + CH$_2$-5'), 4.06-4.09 (m, 3H, CH$_2$-5 + H-4'), 4.21-4.24 (m, 2H, -CH$_2$CH$_2$(OC$_2$H$_4$)$_2$OH), 4.56 (t, 1H, *J* = 5.4 Hz, -(OC$_2$H$_4$)$_2$OH), 5.16-5.20 (m, 2H, H-3' + OH-5'), 6.17 (dd, 1H, *J* = 6.0, 8.4 Hz, H-1'), 7.90 (s, 1H, H-6), 11.41 (s, 1H, NH). ^{13}C NMR δ 14.39 (-OC$_{15}$H$_{30}$CH$_3$), 22.55-31.76 (-OCH$_2$C$_{14}$H$_{28}$CH$_3$), 37.21 (C-2'), 60.68 (CH$_2$-5'), 61.79 (CH$_2$-5), 64.92-72.83 (-(OC$_2$H$_4$)$_3$OH + -OCH$_2$C$_{15}$H$_{31}$), 78.99 (C-3'), 84.53 (C-4'), 84.95 (C-1'), 111.58 (C-5), 138.88 (C-6), 150.75 (C-2), 154.31 (-OC(O)O-), 163.06 (C-4). UV: λ_{max} 263.1 nm (ε 9780). MS (ESI) calcd for $C_{33}H_{59}N_2O_{11}$ 659.4113 $[M+H]^+$ found 659.4112.

3'-*O*-(13-Hydroxy-2,5,8,11-tetraoxatridecanoyl)-5-hexadecyloxymethyl-2'-deoxyuridine (3g)

Obtained from 5'-*O*-(*tert*-butyl)dimethylsilyl-5-hexadecyloxymethyl-2'-deoxyuridine (**2g**) by methods **B** and **C**. Yield 35 mg (42% for two stages). ^{1}H NMR δ 0.84-0.88 (m, 3H, -$C_{15}H_{30}C\underline{H}_3$), 1.24-1.30 (m, 26H, -$C_2H_4C_{13}\underline{H}_{26}CH_3$), 1.44-1.53 (m, 2H, -$CH_2C\underline{H}_2C_{14}H_{29}$), 2.26-2.42 (m, 2H, CH_2-2'), 3.35-3.66 (m, 18H, -$C\underline{H}_2C_{15}H_{23}$ + -$C\underline{H}_2(OC_2\underline{H}_4)_3OH$ + CH_2-5'), 4.07-4.10 (m, 3H, CH_2-5 + H-4'), 4.21-4.24 (m, 2H, -$C\underline{H}_2CH_2(OC_2H_4)_3OH$), 4.53 (t, 1H, *J* = 5.4 Hz, -$(OC_2H_4)_4O\underline{H}$), 5.15-5.19 (m, 2H, H-3' + OH-5'), 6.17 (dd, 1H, *J* = 6.0, 8.4 Hz, H-1'), 7.90 (s, 1H, H-6), 11.40 (s, 1H, NH). ^{13}C NMR δ 14.38 (-$OC_{15}H_{30}\underline{C}H_3$), 22.55-31.76 (-$OCH_2\underline{C}_{14}H_{28}CH_3$), 37.22 (C-2'), 60.70 ($CH_2$-5'), 61.80 ($CH_2$-5), 64.93-72.82 (-$(OC_2H_4)_4OH$ + -$O\underline{C}H_2C_{15}H_{31}$), 78.98 (C-3'), 84.55 (C-4'), 84.95 (C-1'), 111.58 (C-5), 138.87 (C-6), 150.75 (C-2), 154.32 (-OC(O)O-), 163.05 (C-4). UV: λ_{max} 263.3 nm (ε 9780). MS (ESI) calcd for $C_{35}H_{62}N_2O_{12}$ 703.4376 $[M+H]^+$ found 703.4376.

Method D. General procedure for obtaining of 3'-(*tert*-butyl)dimethylsilyl derivatives

A nucleoside (0.53 mmol) was dissolved in dry pyridine (7 ml), then 4,4'-dimethoxytrityl chloride (280 mg, 0.83 mmol) was added. The reaction mixture was heated at 37 °C for 18 h. Then the mixture was evaporated, dissolved in $CHCl_3$, and washed with saturated NaCl water solution. The organic layer was dried with Na_2SO_4. Then the mixture was filtered, evaporated, and dissolved in dimethylformamide (5 ml) and then imidazole (145 mg, 2.1 mmol) and (*tert*-butyl)dimethylchlorosilane (161 mg, 1 mmol) were added. The reaction mixture was heated at 37 °C for 8 h, then evaporated and extracted in the chloroform–water system. The organic layer was dried with Na_2SO_4 and then acetic acid (8 ml) and water (2 ml) were added. The mixture was heated at 37 °C for 25 min and then evaporated. The product was isolated by column chromatography in the chloroform/ethanol (50:1 v/v) eluting system.

3'-*O*-(*tert*-Butyl)dimethylsilyl-5-undecyloxymethyl-2'-deoxyuridine (5a)

Obtained from **1b** by method **D**. Yield 202 mg (72%). ^{1}H NMR δ 0.08 (s, 6H, -$Si(Me)_2$), 0.83-0.87 (m, 12H, -$SiC(CH_3)_3$ + -$C_{10}H_{20}C\underline{H}_3$), 1.22-1.28 (m, 18H, -$C_2H_4C_8\underline{H}_{18}CH_3$), 1.47-1.54 (m, 2H, -$CH_2C\underline{H}_2C_9H_{19}$), 2.07-2.23 (m, 2H, CH_2-2'), 3.36 (t, 2H, *J* = 6.9 Hz, -$C\underline{H}_2C_{10}H_{21}$), 3.50-3.59 (m, 2H, CH_2-5'), 3.75-3.80 (m, 1H, H-4'), 4.03-4.12 (m, 2H, CH_2-5), 4.40-4.45 (m, 1H, H-3'), 5.16 (d, 1H, *J* = 4.6 Hz, OH-3'), 6.15 (dd, 1H, *J* = 6.8, 5.7 Hz, H-1'), 7.61 (s, 1H, H-6), 11.42 (s, 1H, NH). UV: λ_{max} 263.5 nm (ε 9780). MS (ESI) calcd for $C_{27}H_{50}N_2O_6Si$ 527.3511 $[M+H]^+$ found 527.3510.

3'-*O*-(*tert*-Butyl)dimethylsilyl-5-dodecyloxymethyl-2'-deoxyuridine (5b)

Obtained from **1c** by method **D**. Yield 201 mg (70%). ^{1}H NMR δ 0.09 (s, 6H, -$Si(CH_3)_2$), 0.79-0.85 (m, 12H, -$SiC(CH_3)_3$ + -$C_{11}H_{22}C\underline{H}_3$), 1.20-1.25 (m, 18H, -$C_2H_4C_9\underline{H}_{18}CH_3$), 1.44-1.49 (m, 2H, -$CH_2C\underline{H}_2C_{10}H_{21}$), 2.09-2.26 (m, 2H, CH_2-2'), 3.34 (t, 2H, *J* = 6.4 Hz, -$C\underline{H}_2C_{11}H_{23}$), 3.64-3.76 (m, 2H, CH_2-5'), 3.80-3.84 (m, 1H, H-4'), 4.39-4.45 (m, 1H, H-3'), 5.13 (t, 1H, *J* = 4.4 Hz, OH-5'), 6.13 (dd, 1H, *J* = 6.5, 5.9 Hz, H-1'), 7.59 (s, 1H, H-6), 11.43 (s, 1H, NH). UV: λ_{max} 264.0 nm (ε 9780). MS (ESI) calcd for $C_{28}H_{52}N_2O_6Si$ 541.3667 $[M+H]^+$ found 541.3669.

5'-*O*-(8-Hydroxy-3,6-dioxaoct-1-yloxy)carbonyl-5-undecyloxymethyl-2'-deoxyuridine (6a)

Obtained from 3'-*O*-(*tert*-butyl)dimethylsilyl-5-undecyloxymethyl-2'-deoxyuridine **(5a)** by methods **B** and **C**. Yield 35 mg (60% for two stages). ^{1}H NMR δ 0.84-0.88 (m, 3H, -$C_{10}H_{20}C\underline{H}_3$), 1.24-1.28 (m, 16H, -$C_2H_4C_8\underline{H}_{16}CH_3$), 1.44-1.53 (m, 2H, -$CH_2C\underline{H}_2C_9H_{19}$), 2.17 (ddd, 2H, *J* = 6.8, 5.1, 2.0 Hz, CH_2-2'), 3.35-3.65 (m, 12H, -$C\underline{H}_2C_{10}H_{21}$ + -$C\underline{H}_2(OC_2\underline{H}_4)_2OH$), 3.96 (dt, 1H, *J* = 5.8, 3.9 Hz, H-4'), 4.09 (s, 2H, CH_2-5), 4.20-4.33 (m, 5H, -$C\underline{H}_2CH_2(OC_2H_4)_2OH$ + H-3' + CH_2-5'), 4.53 (t, 1H, *J* = 5.4 Hz, -$(OC_2H_4)_3O\underline{H}$), 5.44 (d, 1H, *J* = 4.4 Hz, OH-3'), 6.18 (t, 1H, *J* = 6.8, Hz, H-1'), 7.59 (s, 1H,

H-6), 11.37 (s, 1H, NH). ^{13}C NMR δ 14.37 (-OC$_{10}$H$_{20}$CH$_3$), 22.56-31.77 (-OCH$_2$C$_9$H$_{18}$CH$_3$), 39.24 (C-2'), 60.69 (CH$_2$-5), 64.83-70.67 (-(C$_2$H$_4$O)$_3$OH + C-3' + -OCH$_2$C$_{10}$H$_{21}$), 72.85 (CH$_2$-5'), 84.08 (C-4'), 84.93 (C-1'), 111.56 (C-5), 139.98 (C-6), 150.69 (C-2), 154.87 (-OC(O)O-), 163.05 (C-4). UV: λ_{max} 263.5 nm (ε 9780). MS (ESI) calcd for $C_{28}H_{48}N_2O_{11}$ 583.3331 $[M+H]^+$ found 583.3331.

5'-*O*-(8-Hydroxy-3,6-dioxaoct-1-yloxy)carbonyl-5-dodecyloxymethyl-2'-deoxyuridine (6b)

Obtained from 3'-*O*-(*tert*-butyl)dimethylsilyl-5-dodecyloxymethyl-2'-deoxyuridine (**5b**) by methods **B** and **C**. Yield 36 mg (56% for two stages). ^{1}H NMR δ 0.85 (dd, 3H, *J* = 6.7, 7.0 Hz, -C$_{11}$H$_{22}$CH$_3$), 1.20-1.28 (m, 18H, -C$_2$H$_4$C$_9$H$_{18}$CH$_3$), 1.44-1.50 (m, 2H, -CH$_2$CH$_2$C$_9$H$_{19}$), 2.16 (m, 2H, CH$_2$-2'), 3.35-3.63 (m, 12H, -CH$_2$C$_{11}$H$_{23}$ + -CH$_2$(OC$_2$H$_4$)$_2$OH), 3.95 (dt, 1H, *J* = 5.9, 3.8 Hz, H-4'), 4.08 (s, 2H, CH$_2$-5), 4.19-4.31 (m, 5H, -CH$_2$CH$_2$(OC$_2$H$_4$)$_2$OH + H-3' + CH$_2$-5'), 4.53 (t, 1H, *J* = 5.5 Hz, -(OC$_2$H$_4$)$_3$OH), 5.44 (d, 1H, *J* = 4.5 Hz, OH-3'), 6.17 (dd, 1H, *J* = 6.7, 7.0 Hz, H-1'), 7.58 (s, 1H, H-6), 11.37 (s, 1H, NH). ^{13}C NMR δ 13.86 (-OC$_{11}$H$_{22}$CH$_3$), 22.03-31.24 (-OCH$_2$C$_{10}$H$_{20}$CH$_3$), 38.70 (C-2'), 60.16 (CH$_2$-5), 64.30-70.14 (-(C$_2$H$_4$O)$_3$OH + C-3' + -OCH$_2$C$_{11}$H$_{23}$), 72.32 (CH$_2$-5'), 83.55 (C-4'), 84.40 (C-1'), 111.03 (C-5), 138.47 (C-6), 150.00316 (C-2), 154.34 (-OC(O)O-), 162.52 (C-4). UV: λ_{max} 263.8 nm (ε 9780). MS (ESI) calcd for $C_{29}H_{50}N_2O_{11}$ 603.3487 $[M+H]^+$ found 603.3485.

3'-Azido-5-dodecyloxymethyl-2',3'-dideoxyuridine (8)

1. 3'-Azidothymidine (**7**) (1 g, 3.75 mmol) was dissolved in pyridine (20 ml), then acetic anhydride (531 ml, 5.62 mmol) was added. The reaction mixture was kept for 16 h at 25 °C. The product was isolated by column chromatography in the chloroform/ethanol (20:1) eluting system. Yield 1.1 g (95%).

2. Obtained 3'-azido-5'-*O*-acetyl-3'-deoxythymidine (1 g, 3.2 mmol) was used to prepare 3'-azido-5-dodecyloxymethyl-2',3'-dideoxyuridine by method described for **1e** using *N*-bromosuccinimide (1.73 g, 9.7 mmol), azobisisobutyronitrile (132 mg, 0.8 mmol), dichloroethane (70 mL), then DMF (5 mL), docecan-1-ol (900 mg, 4.8 mmol), then ethanol (20 mL) and aqueous ammonia (20 mL). The product was isolated by column chromatography in the chloroform:ethanol (20:1 v/v) eluting system. Yield 548 mg (38%). ^{1}H NMR δ 0.83-0.88 (m, 3H, -OC$_{11}$H$_{22}$CH$_3$), 1.24-1.30 (m, 18H, -OC$_2$H$_4$C$_{19}$H$_{18}$CH$_3$), 1.44-1.53 (m, 2H, -OCH$_2$CH$_2$C$_{10}$H$_{21}$), 2.28-2.44 (m, 2H, CH$_2$-2'), 3.37 (t, 2H, *J* = 6.6 Hz, -OCH$_2$C$_{11}$H$_{23}$), 3.56-3.68 (m, 2H, CH$_2$-5'), 3.83-3.88 (m, 1H, H-4'), 4.08 (s, 2H, CH$_2$-5), 4.38 (dt, 1H, *J* = 7.0, 5.1 Hz, H-3'), 5.18 (t, 1H, *J* = 5.2 Hz, OH-5'), 6.09 (t, 1H, *J* = 6.4 Hz, H-1'), 7.85 (s, 1H, H-6), 11.37 (s, 1H, NH). UV: λ_{max} 264.8 nm (ε 9000). MS (ESI) calcd for $C_{22}H_{37}N_5O_5$ 452.2867 $[M+H]^+$, found 452.2867.

3'-Amino-5'-*O*-(*tert*-butyl)dimethylsilyl-5-dodecyloxymehtyl-2',3'-dideoxyuridine (9)

1. 3'-azido-5'-*O*-(*tert*-butyl)dimethylsilyl-5-dodecyloxymethyl-2',3'-dideoxyuridine was obtained from 3'-azido-5-dodecyloxymethyl-2',3'-dideoxyuridine (**8**) by method **A**. Yield 174 mg (74 %).

2. To a stirred solution of 3'-azido-5'-*O*-(*tert*-butyl)dimethylsilyl-5-dodecyloxymethyl-2',3'-dideoxyuridine (60 mg, 0.11 mmol) in ethanol (5 mL) under argon atmosphere dithiothreitol was added (77 mg, 0.50 mmol) followed by the addition of aqueous ammonia (0.1 mL). The reaction mixture was stirred for 18 hours at room temperature and evaporated then under vacuum. The product was isolated by column chromatography in the chloroform/methanol (gradient 9:1 to 4:1, v/v) eluting system. Yield 27 mg (45%). ^{1}H NMR δ 0.07 (s, 6H, -Si(CH$_3$)$_2$), 0.83-0.89 (m, 12H, -SiC(CH$_3$)$_3$ + -OC$_{11}$H$_{22}$CH$_3$), 1.24-1.30 (m, 18H, -OC$_2$H$_4$C$_9$H$_{18}$CH$_3$), 1.44-1.52 (m, 2H, -OCH$_2$CH$_2$C$_{10}$H$_{21}$), 2.06 (t, 2H, *J* = 6.4, CH$_2$-2'), 3.34-3.39 (m, 3H, -CH$_2$C$_{11}$H$_{23}$ + H-3'), 3.62 (ddd, 1H, *J* = 5.5, 4.3, 3.1 Hz, H-4'), 3.72 (dd, 1H, *J* = 11.3, 4.5 Hz, H-5'(a)), 3.83 (dd, 1H, *J* = 11.3, 3.1

Hz, H-5'(b)), 4.02-4.11 (m, 2H, CH_2-5), 6.11 (t, 1H, *J* = 6.1 Hz, H-1'), 7.58 (s, 1H, H-6). UV: λ_{max} 265.1 nm (ε 9000). MS (ESI) calcd for $C_{28}H_{53}N_3O_5Si$ 540.3827 $[M+H]^+$, found 540.3829.

5-Dodecyloxymethyl-3'-*N*-(8-hydroxy-3,6-dioxaoct-1-yloxy)carbonyl-2',3'-dideoxy-3'-aminouridine (10)

Obtained from 3'-amino-5'-*O*-(*tert*-butyl)dimethylsilyl-5-dodecyloxymehtyl-2',3'-dideoxyuridine (**9**) by methods **B** and **C**. Yield 34 mg (41% for two stages). ^{1}H NMR δ 0.84-0.88 (m, 3H, -$C_{11}H_{22}C\underline{H}_3$), 1.24-1.30 (m, 18H, -$C_2H_4C_9\underline{H}_{18}CH_3$), 1.44-1.53 (m, 2H, -$CH_2C\underline{H}_2C_{10}H_{21}$), 2.19 (ddd, 2H, *J* = 10.4, 7.1, 7.1 Hz, CH_2-2'), 3.35-3.67 (m, 14H, -$C\underline{H}_2C_{11}H_{23}$ + -$C\underline{H}_2(OC_2\underline{H}_4)_2OH$ + CH_2-5'), 3.78-3.82 (m, 1H, H-4'), 4.06-4.16 (m, 5H, -$C\underline{H}_2CH_2(OC_2H_4)_2OH$ + CH_2-5 + H-3'), 4.56 (t, 1H, *J* = 5.4 Hz, -$(OC_2H_4)_3O\underline{H}$), 5.03 (t, 1H, *J* = 5.2 Hz, OH-5'), 6.14 (t, 1H, *J* = 6.3 Hz, H-1'), 7.71 (d, 1H, *J* = 7.4 Hz, NH-3'), 7.93 (s, 1H, H-6), 11.35 (s, 1H, NH). ^{13}C NMR δ 14.41 (-$OC_{11}H_{22}\underline{C}H_3$), 22.55-31.76 (-$OC_{11}H_{22}$), 37.97 (C-2'), 51.00 (C-3'), 60.70 (CH_2-5'), 61.62-72.83 (CH_2-5 + -$(OC_2H_4)_3OH$), 84.36 (C-4'), 85.39 (C-1'), 111.15 (C-5), 139.38 (C-6), 150.70 (C-2), 154.31 (-OC(O)O-), 163.16 (C-4). UV: λ_{max} 264.7 nm (ε 9000). MS (ESI) calcd for $C_{29}H_{51}N_3O_{10}Si$ 602.3647 $[M+H]^+$, found 602.3648.

3'-5'-Bis-*O*-(8-Hydroxy-3,6-dioxaoct-1-yloxy)carbonyl-5-dodecyloxymethyl-2'-deoxyuridine (11)

Compound **1c** (119 mg, 0.28 mmol) was dissolved in dry DMF (1 ml) and CDI (274 mg, 1.68 mmol) was added. The mixture was heated at 37 °C for 24 h. Then anhydrous triethylene glycol (3.3 g, 22 mmol) and dioxane (0.5 ml) were added. The mixture was heated at 37 °C for 24 h and then evaporated to leave crude oil with constant volume. The product was extracted in the chloroform–water system, the organic layer was evaporated. The product was isolated by column chromatography in the chloroform/ethyl acetate:ethanol (5:5:0.1 v/v) eluting system. Yield 72 mg (33%). ^{1}H NMR δ 0.84-0.88 (m, 3H, -$C_{11}H_{22}C\underline{H}_3$), 1.24-1.30 (m, 18H, -$C_2H_4C_9\underline{H}_{18}CH_3$), 1.44-1.52 (m, 2H, -$CH_2C\underline{H}_2C_{10}H_{21}$), 2.42 (ddd, 2H, *J* = 13.9, 7.4, 4.5 Hz, CH_2-2'), 3.36-3.66 (m, 22H, -$C\underline{H}_2C_{11}H_{23}$ + -$C\underline{H}_2(OC_2\underline{H}_4)_2OH$ (3') + -$C\underline{H}_2(OC_2\underline{H}_4)_2OH$ (5')), 4.09 (s, 2H, CH_2-5), 4.20-4.40 (m, 7H, -$C\underline{H}_2CH_2(OC_2H_4)_2OH$ (3') + -$C\underline{H}_2CH_2(OC_2H_4)_2OH$ (5') + H-4' + CH_2-5'), 4.54 (broad s, 2H, -$(OC_2H_4)_3O\underline{H}$ (3') + -$(OC_2H_4)_3O\underline{H}$ (5')), 5.18 (dt, 1H, *J* = 5.9, 3.0 Hz, H-3'), 6.17 (t, 1H, *J* = 6.2 Hz, H-1'), 7.64 (s, 1H, H-6), 11.44 (s, 1H, NH). ^{13}C NMR δ 14.38 (-$C_{11}H_{22}\underline{C}H_3$), 22.55-31.76 (-$C_{11}H_{22}$), 36.15 (C-2'), 60.68 ($CH_2$-5), 64.81-72.83 (-$(\underline{C}_2H_4O)_3OH$ (3') + -$(\underline{C}_2H_4O)_3OH$ (5') + CH_2-5'), 77.79 (C-3') 81.30 (C-4'), 85.18 (C-1'), 111.75 (C-5), 139.98 (C-6), 150.69 (C-2), 154.23-154.74 (-OC(O)O- (3') + -OC(O)O- (5')), 163.01 (C-4). UV: λ_{max} 264.2 nm (ε 9780). MS (ESI) calcd for $C_{36}H_{63}N_2O_{16}$ 779.4172 $[M+H]^+$ found 779.4175.

Table S1. Water solubility values of 5-alkyloxymethyl-2'-deoxyuridines.

Cmpd.	5-Alkyl substituent	Sugar substituent	Water solubility (mg/mL)	Cmpd.	5-Alkyl substituent	Sugar substituent	Water solubility (mg/mL)
1a	$C_{10}H_{21}$	–	0.028	**3d**	$C_{12}H_{25}$	3'-*O*–C(O)TetEG**	2.1
1b	$C_{11}H_{23}$	–	0.017	**3e**	$C_{14}H_{29}$	3'-*O*–C(O)TEG	0.42
1c	$C_{12}H_{25}$	–	0.009	**3f**	$C_{16}H_{33}$	3'-*O*–C(O)TEG	0.15
1d	$C_{14}H_{29}$	–	0.003	**3g**	$C_{16}H_{33}$	3'-*O*–C(O)TetEG	0.19
1e	$C_{16}H_{33}$	–	0.001	**6a**	$C_{11}H_{23}$	5'-*O*–C(O)TEG	2.26
3a	$C_{10}H_{21}$	3'-*O*–C(O)TEG*	4.46	**6b**	$C_{12}H_{25}$	5'-*O*–C(O)TEG	0.85
3b	$C_{11}H_{23}$	3'-*O*–C(O)TEG	3.61	**10**	$C_{12}H_{25}$	3'-*N*–C(O)TEG	1.07
3c	$C_{12}H_{25}$	3'-*O*–C(O)TEG	1.30	**11**	$C_{12}H_{25}$	3',5'-bis-*O*–C(O)TEG	>5

*TEG – triethylene glycol.
**TetEG – tetraethylene glycol.

Table S2. Hydrolysis half-life times for the obtained glycol prodrugs.

Cmpd	5-Alkyl substituent	Sugar substituent	$t_{1/2}$ (h ± 0.5)	Cmpd	5-Alkyl substituent	Sugar substituent	$t_{1/2}$ (h ± 0.5)
3a	$C_{10}H_{21}$	3'-*O*–C(O)TEG*	2	**3g**	$C_{16}H_{33}$	3'-*O*–C(O)TetEG	14
3b	$C_{11}H_{23}$	3'-*O*–C(O)TEG	3	**6a**	$C_{11}H_{23}$	5'-*O*–C(O)TEG	3
3c	$C_{12}H_{25}$	3'-*O*–C(O)TEG	4	**6b**	$C_{12}H_{25}$	5'-*O*–C(O)TEG	5
3d	$C_{12}H_{25}$	3'-*O*–C(O)TetEG**	7	**10**	$C_{12}H_{25}$	3'-*N*–C(O)TEG	>24
3e	$C_{14}H_{29}$	3'-*O*–C(O)TEG	6	**11**	$C_{12}H_{25}$	3',5'-bis-*O*–C(O)TEG	18
3f	$C_{16}H_{33}$	3'-*O*–C(O)TEG	10	**Ac$_2$T**		3',5'-bis-*O*–Ac	3

*TEG – triethylene glycol.
**TetEG – tetraethylene glycol.

NMR spectra of new compounds

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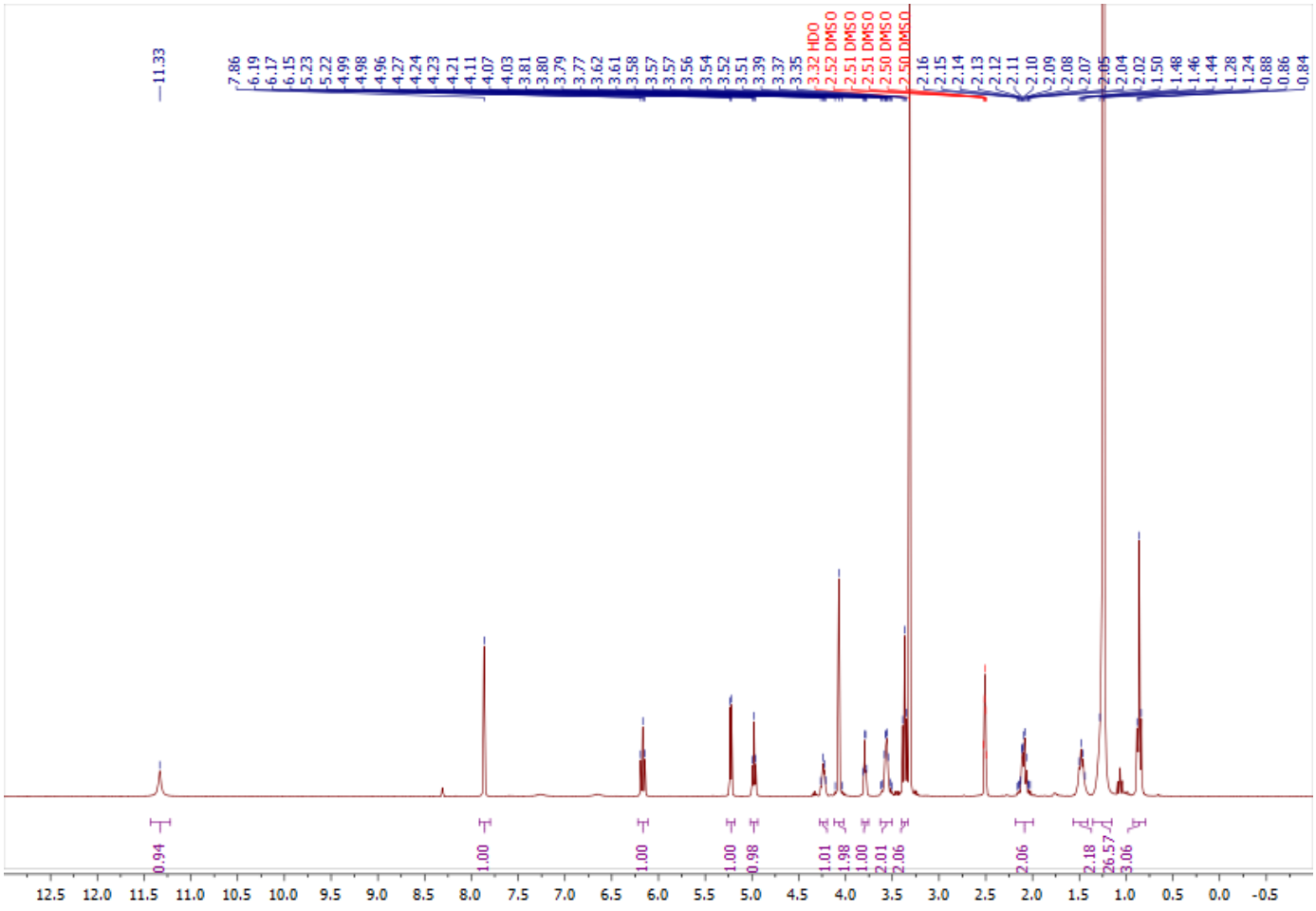
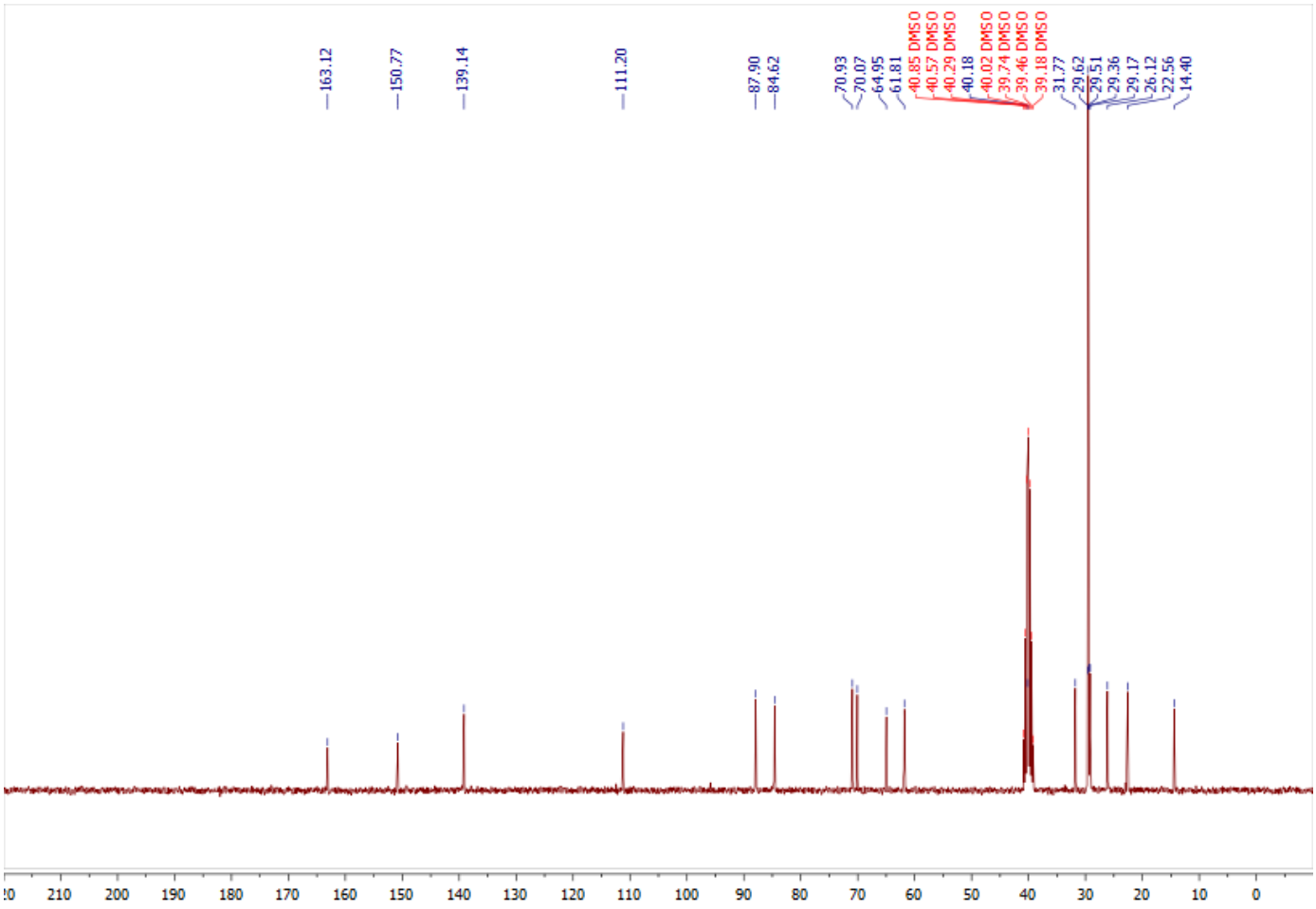


1e, ^{13}C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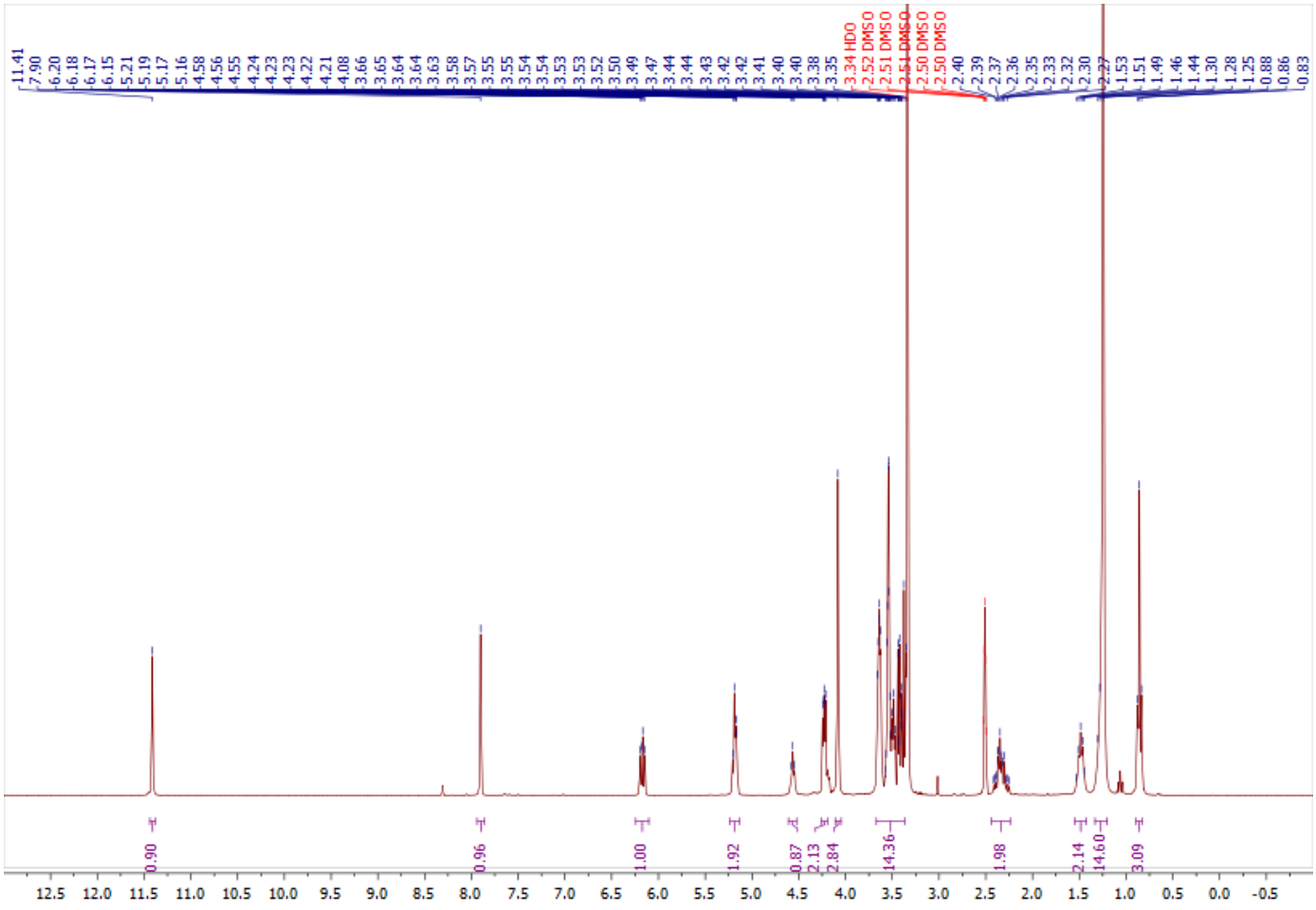
3a, ^{1}H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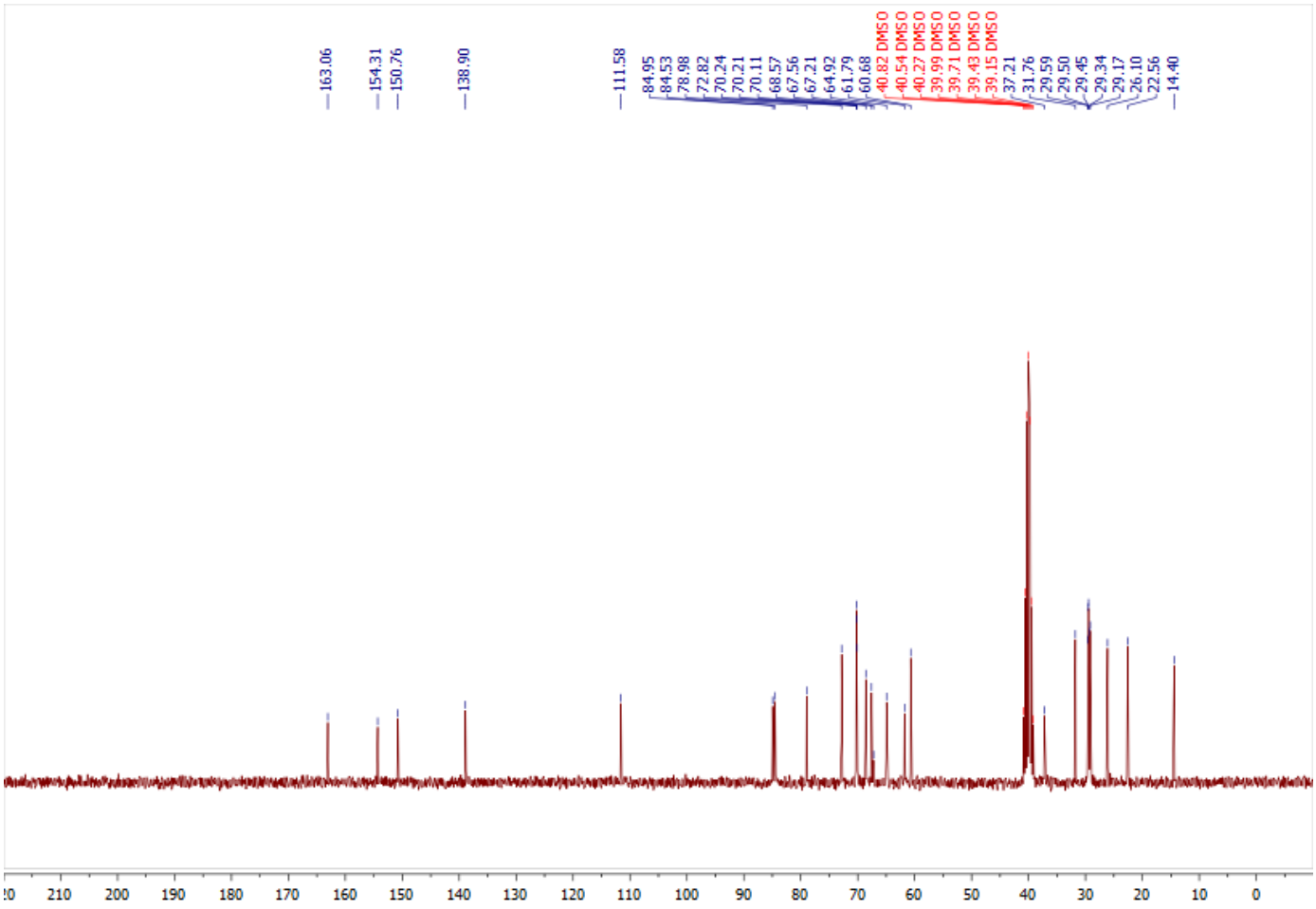
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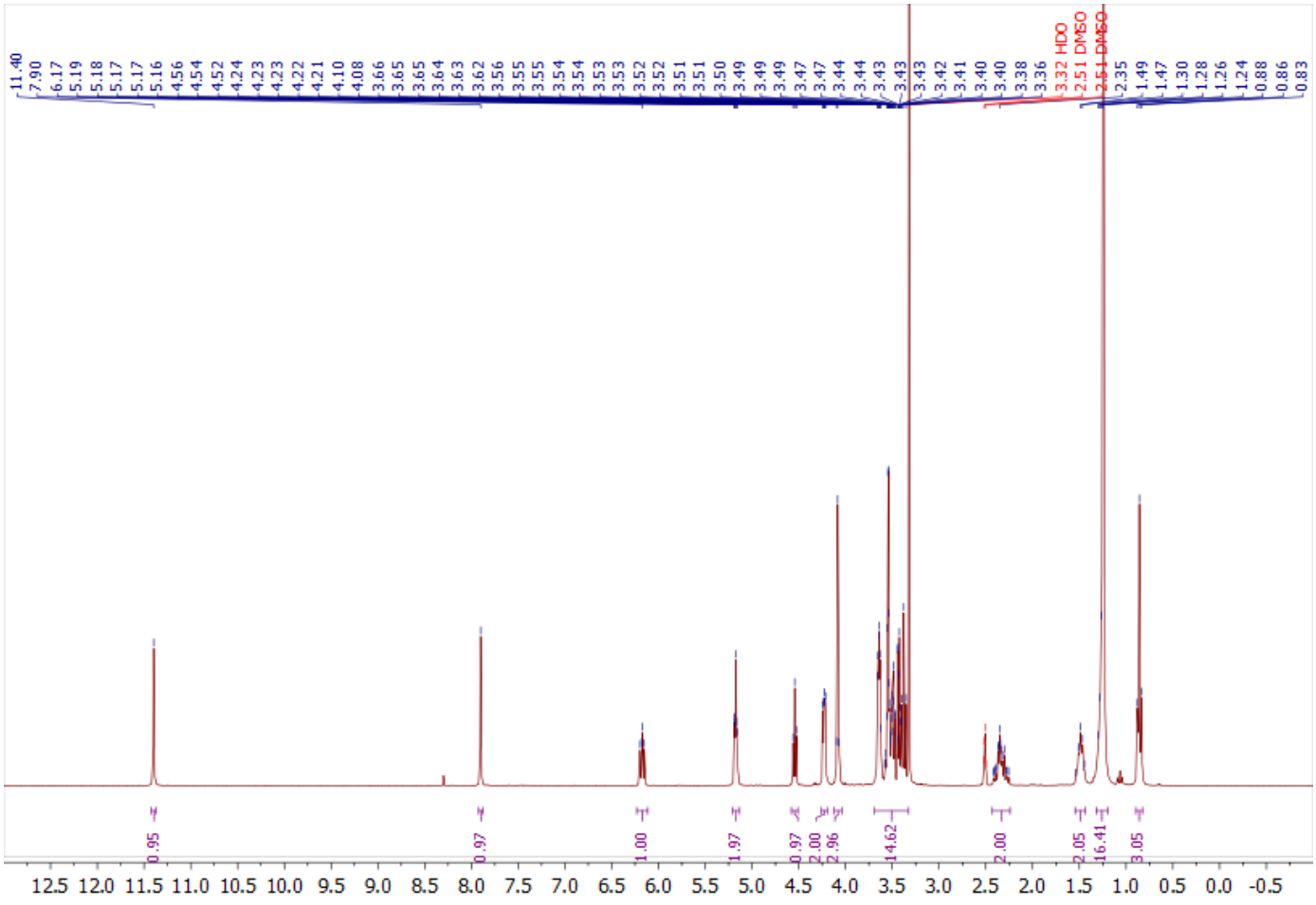
3b, ^{1}H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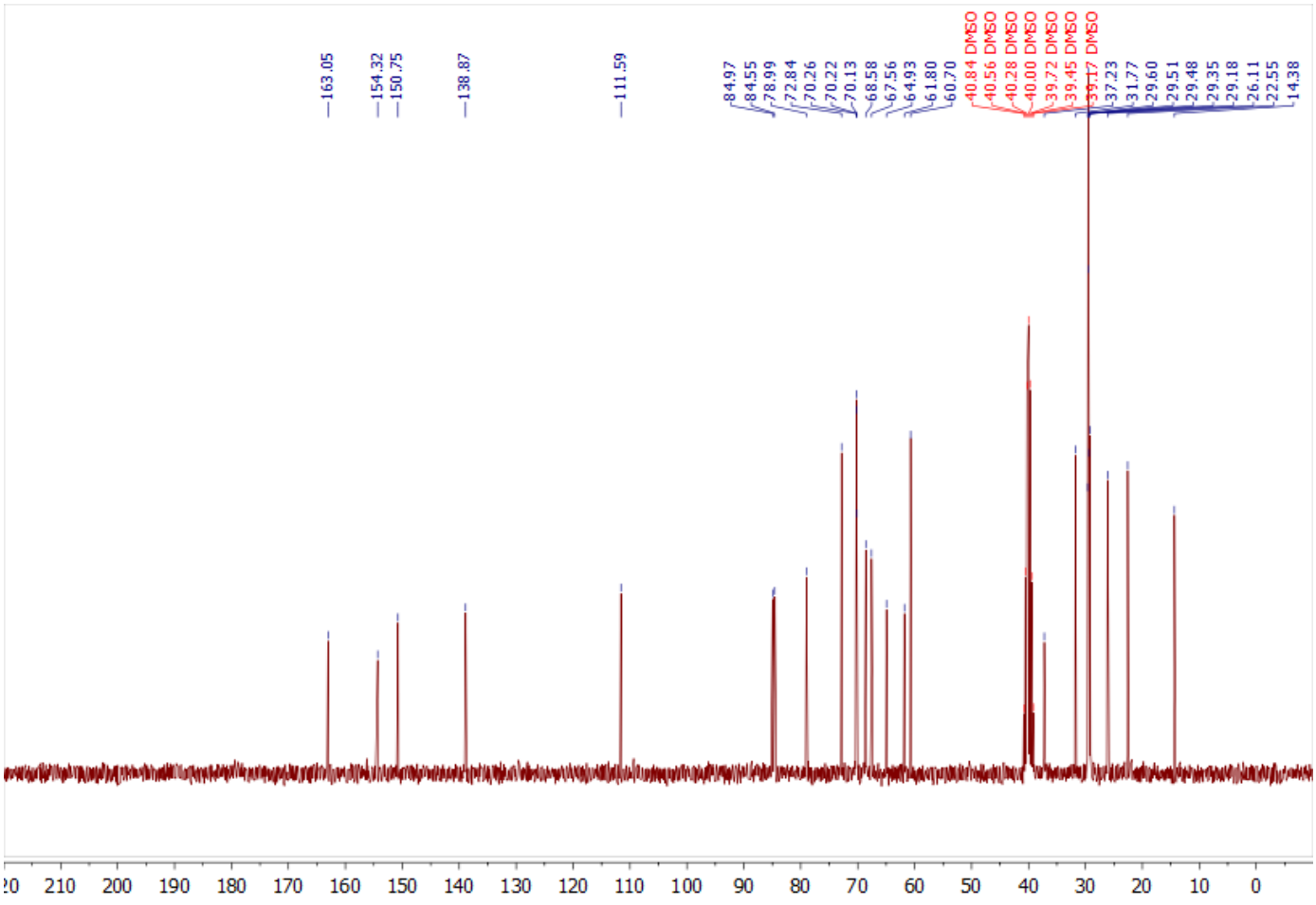
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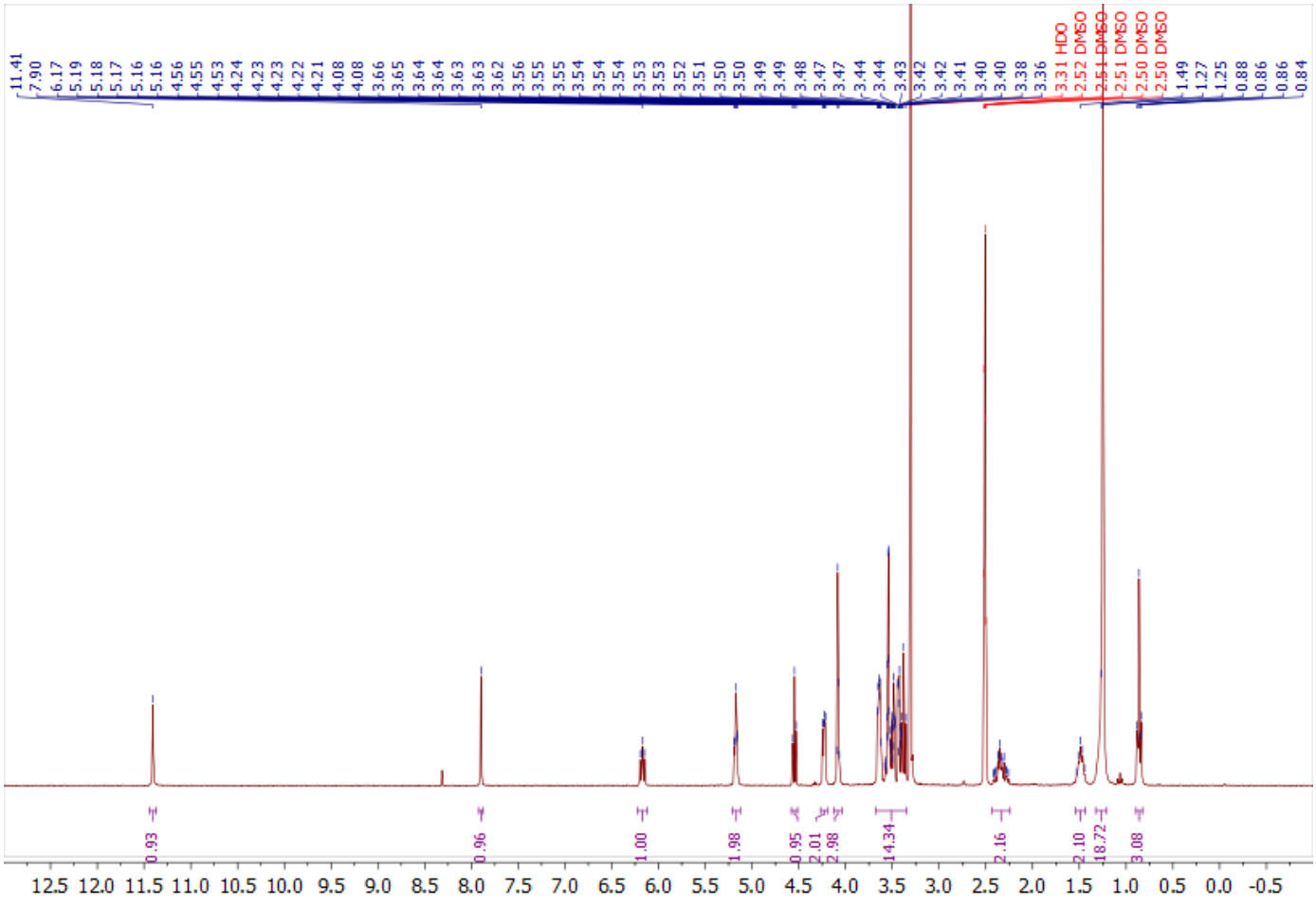
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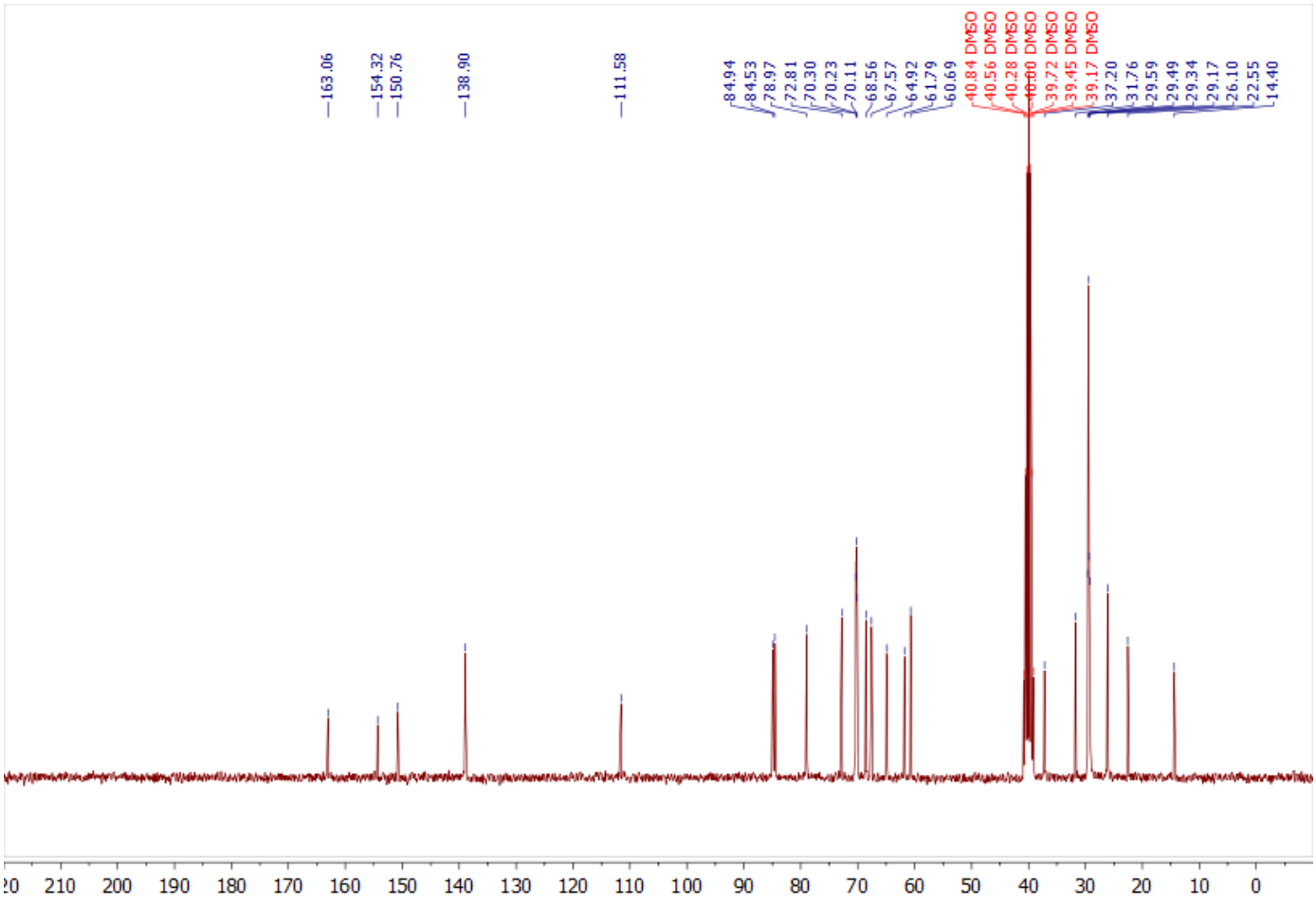
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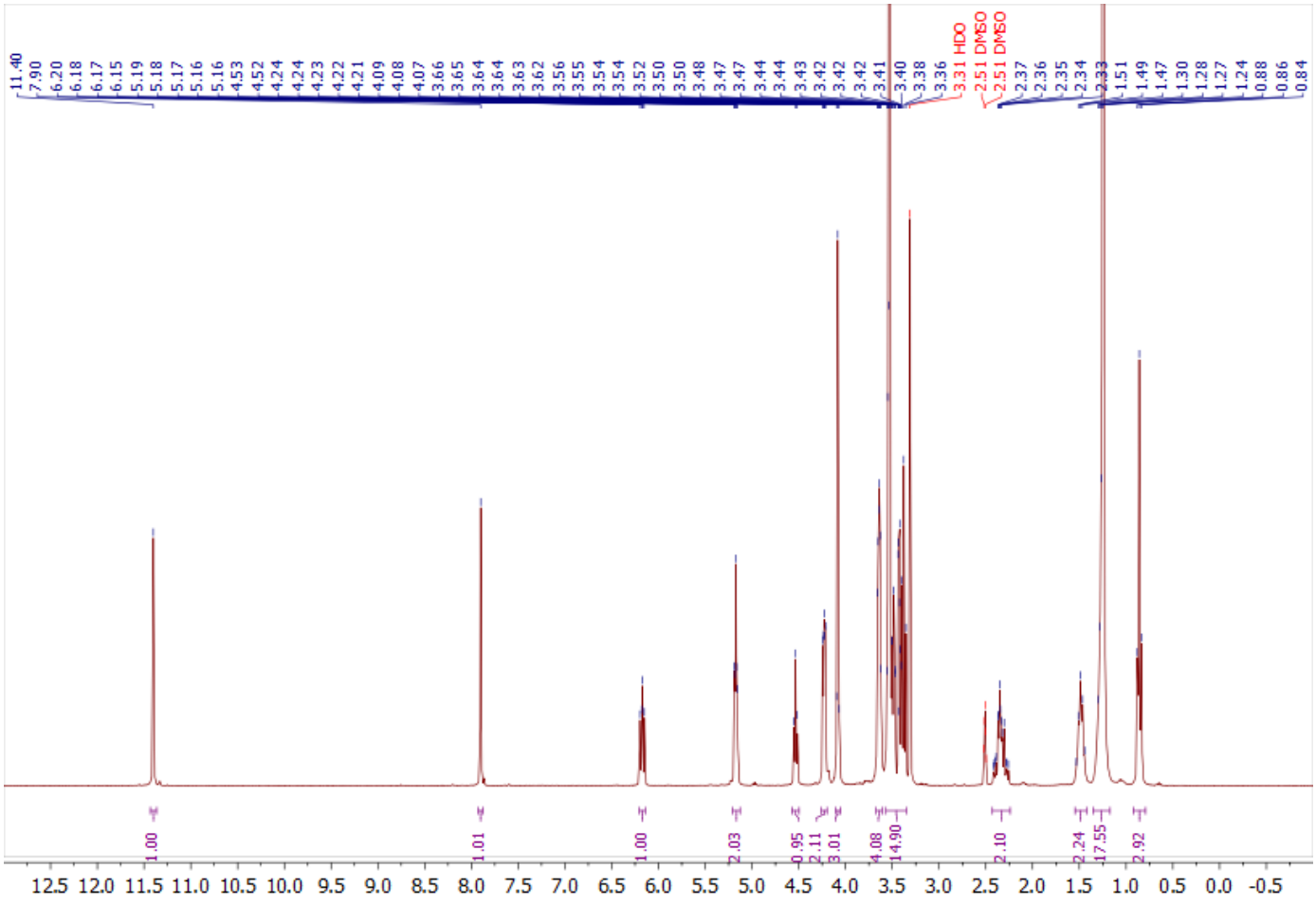
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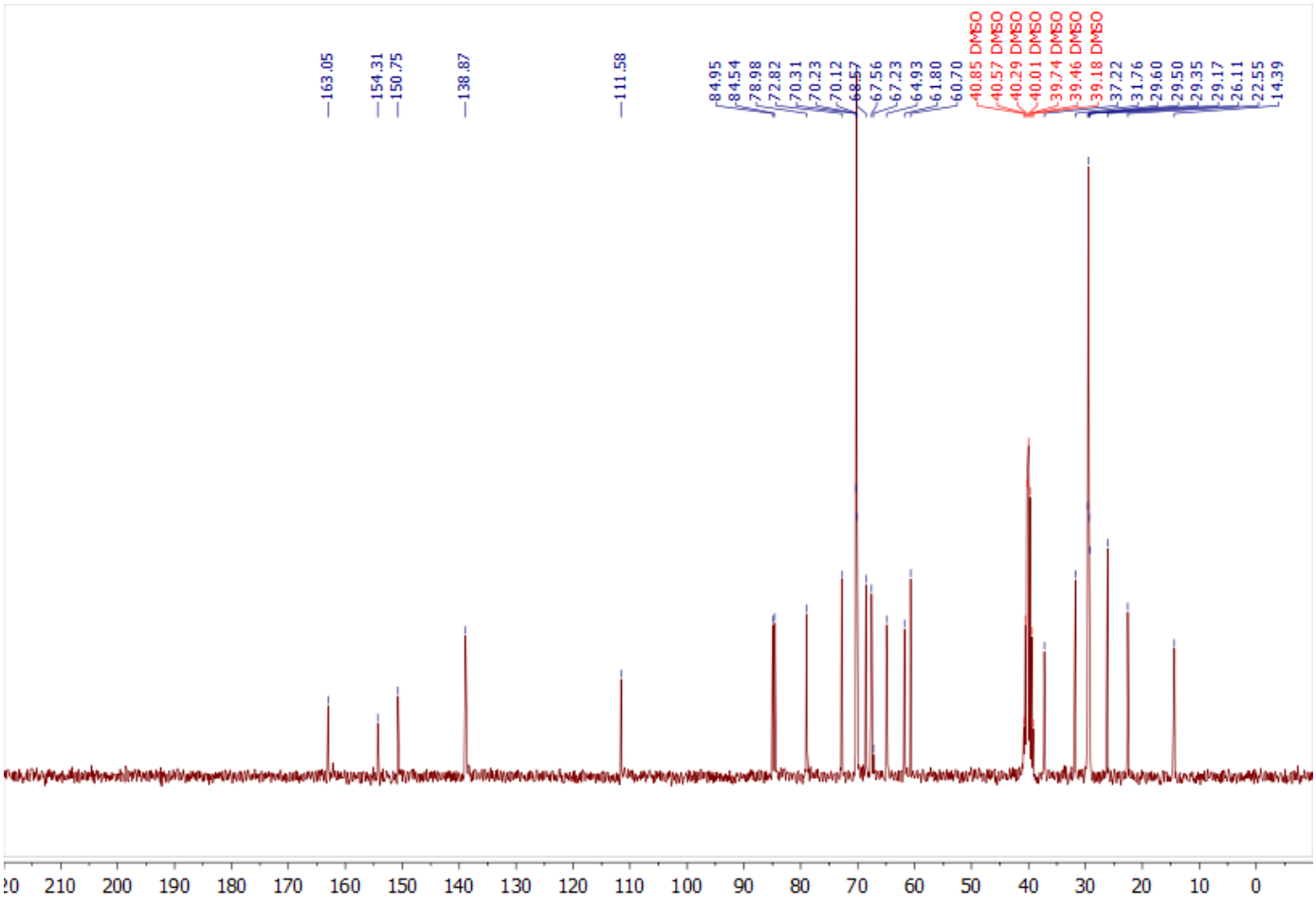
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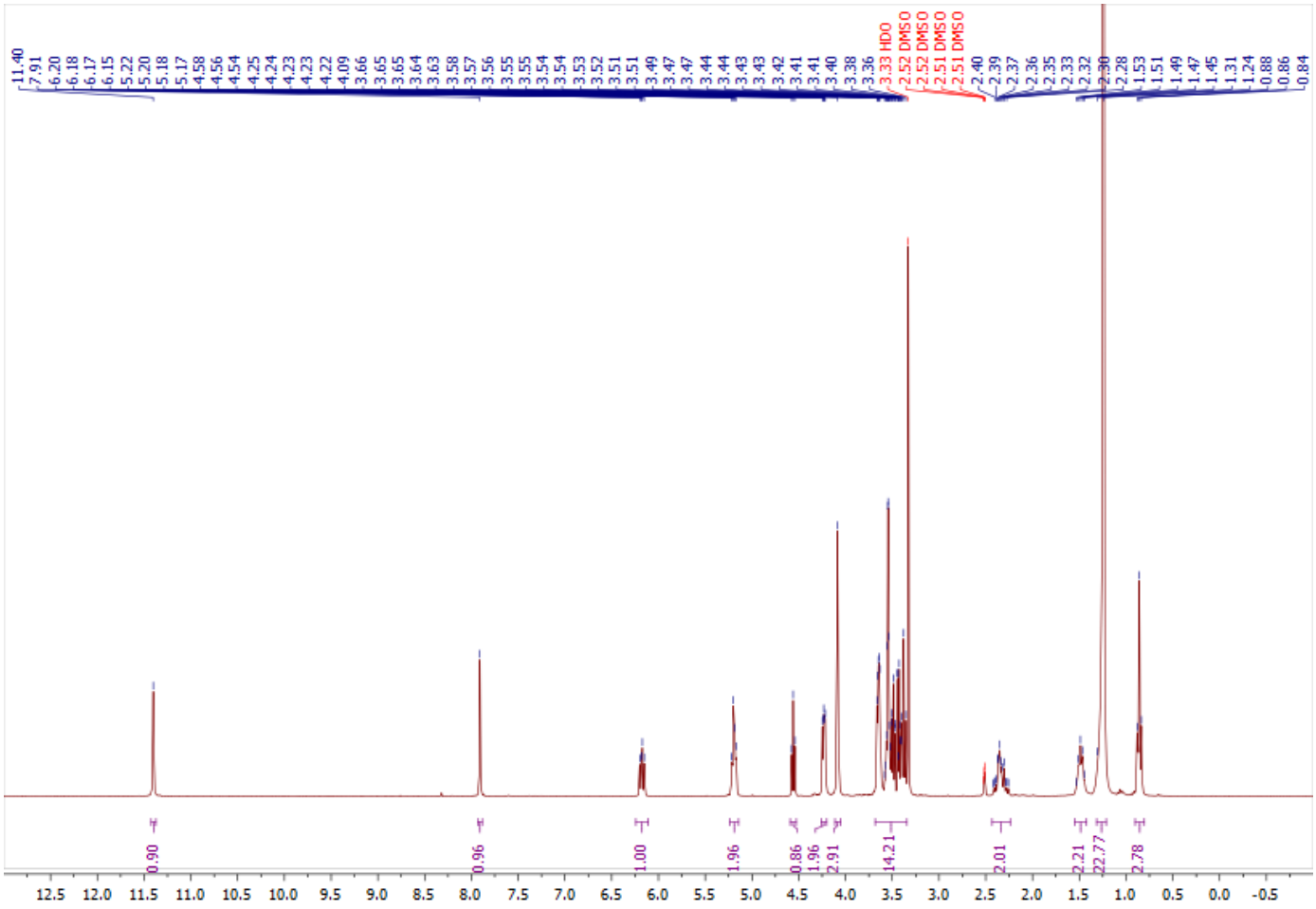
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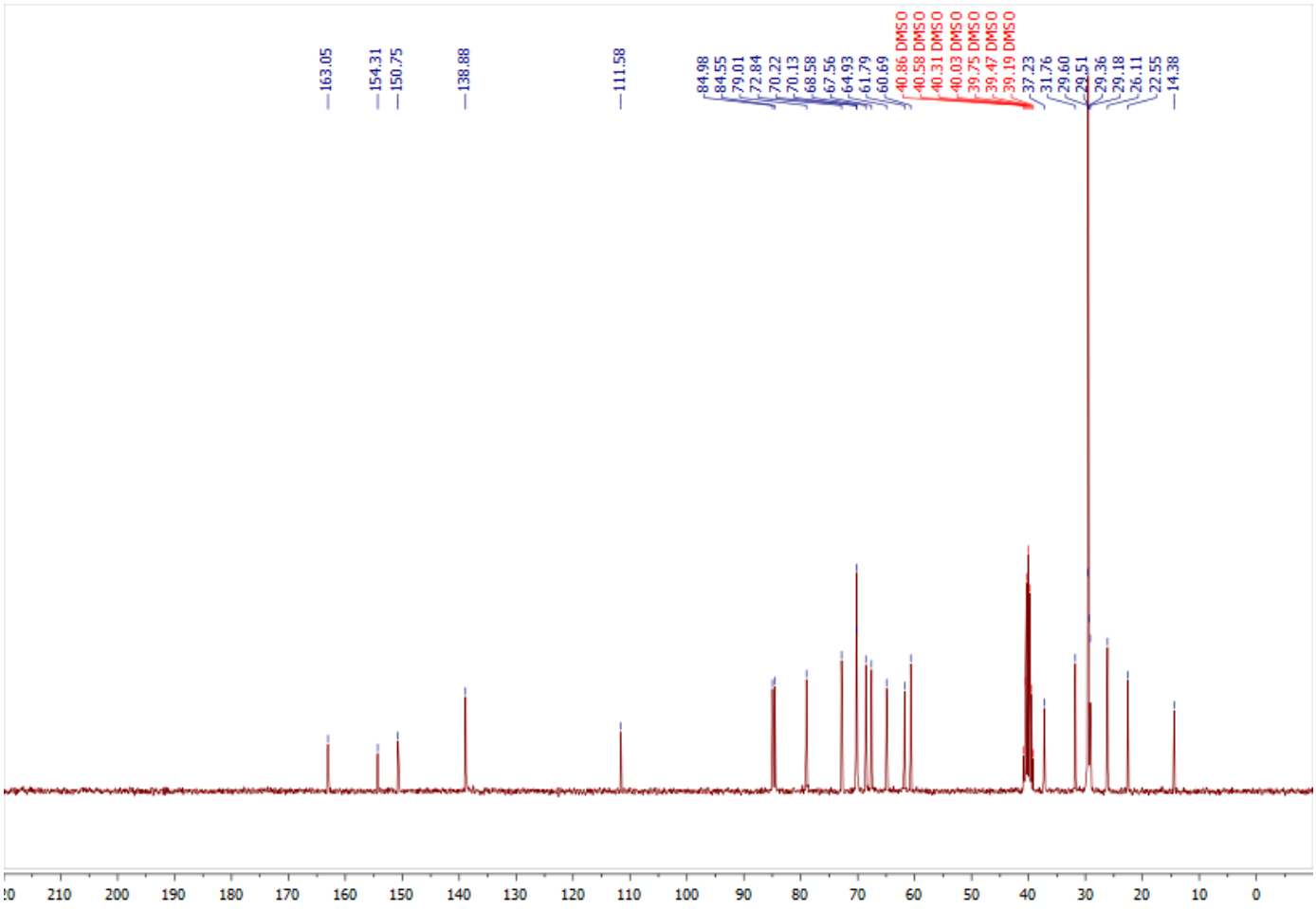
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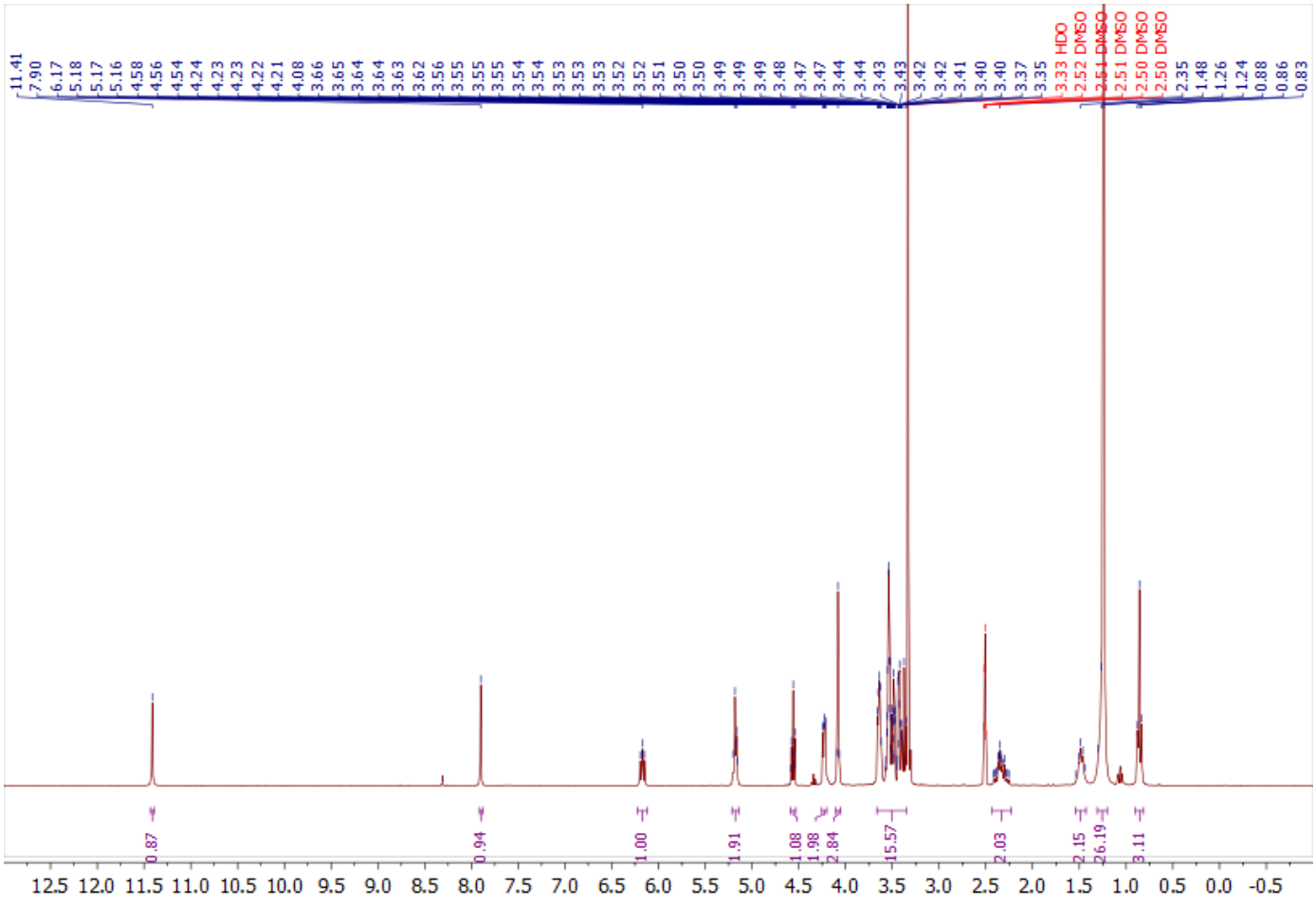
3f, ^{1}H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4.21
4.08
3.66
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3.64
3.64
3.63
3.62
3.56
3.55
3.55
3.55
3.54
3.54
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3.49
3.48
3.47
3.47
3.44
3.44
3.43
3.43
3.42
3.42
3.41
3.40
3.40
3.37
3.35
3.33 HDO
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2.51 DMSO
2.50 DMSO
2.50 DMSO
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1.26
1.24
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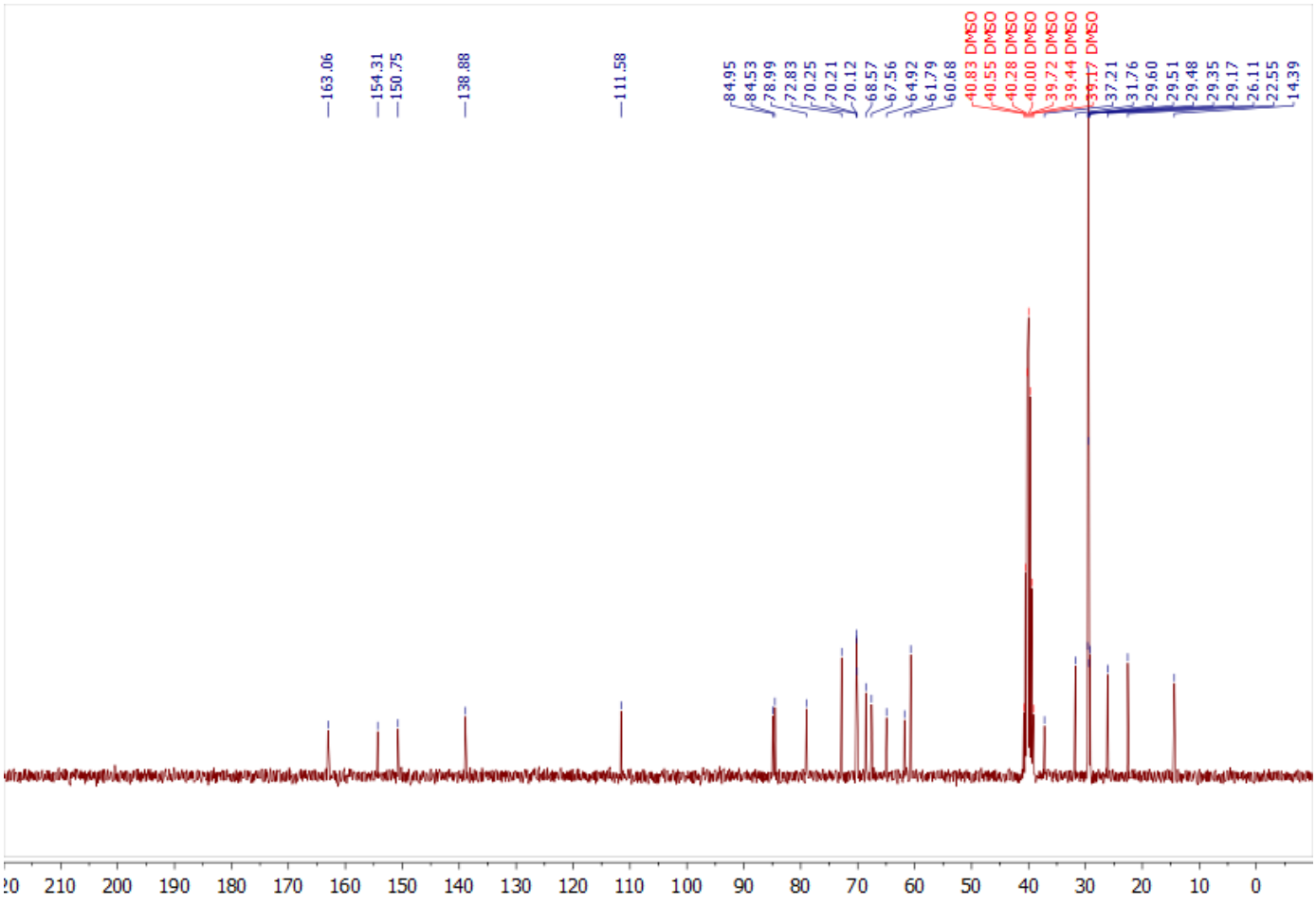
0.86
0.83
0.87
0.94
1.00
1.91
1.08
1.98
2.84
15.57
2.03
2.15
26.19
3.11
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5

3f, ^{13}C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78.99
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70.21
70.12
68.57
67.56
64.92
61.79
60.68
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40.55 DMSO
40.28 DMSO
40.00 DMSO
39.72 DMSO
39.44 DMSO
39.17 DMSO
37.21
31.76
29.60
29.51
29.48
29.35
29.17
26.11
22.55
14.39
210
200
190
180
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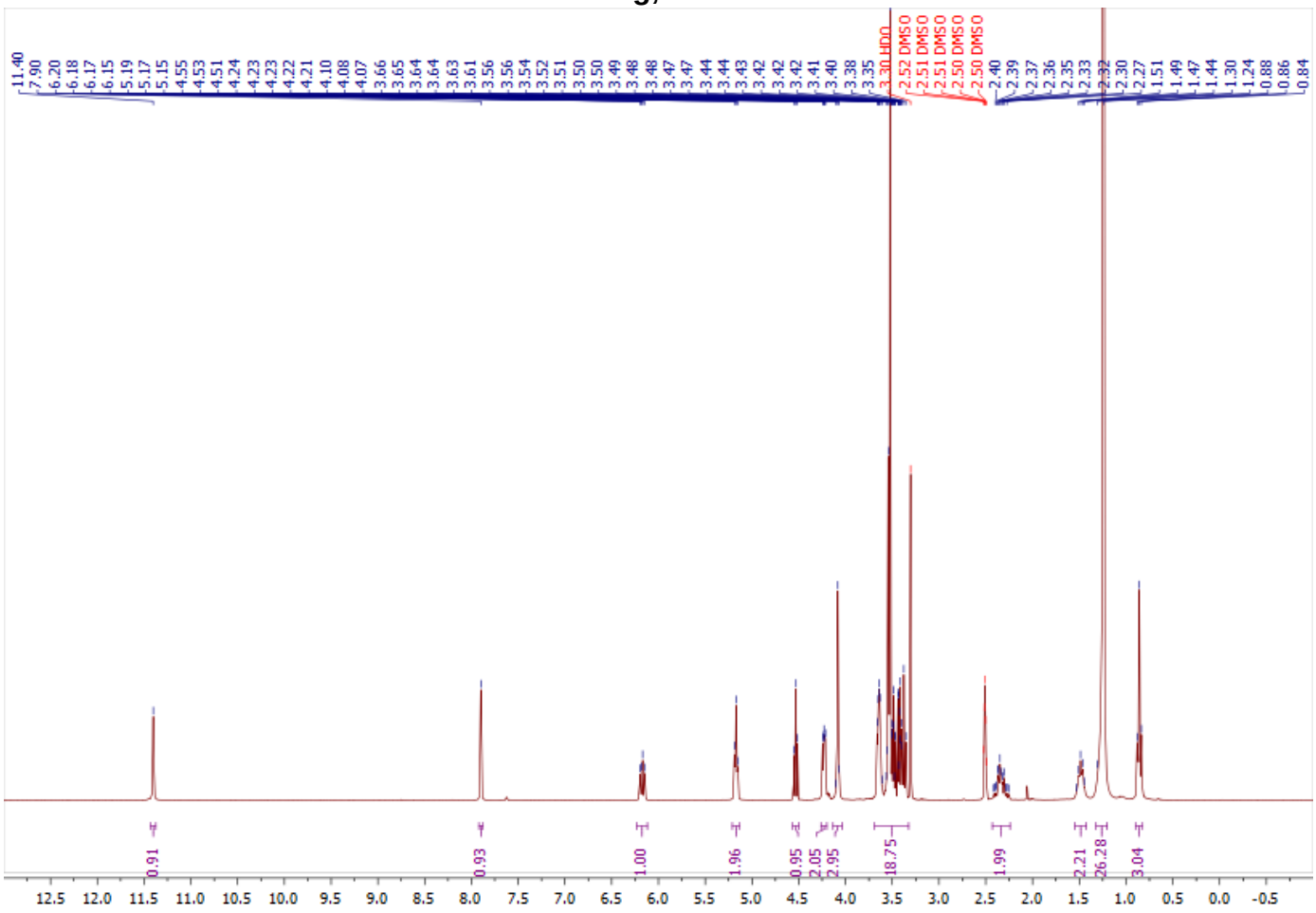
3g, ^{1}H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4.23
4.23
4.22
4.21
4.10
4.08
4.07
3.66
3.65
3.64
3.64
3.63
3.61
3.56
3.56
3.54
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3.50
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3.44
3.44
3.43
3.42
3.42
3.42
3.41
3.40
3.38
3.35
3.30 HDO
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2.51 DMSO
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2.50 DMSO
2.50 DMSO
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2.35
2.33
2.32
2.30
2.27
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1.49
1.47
1.44
1.30
1.24
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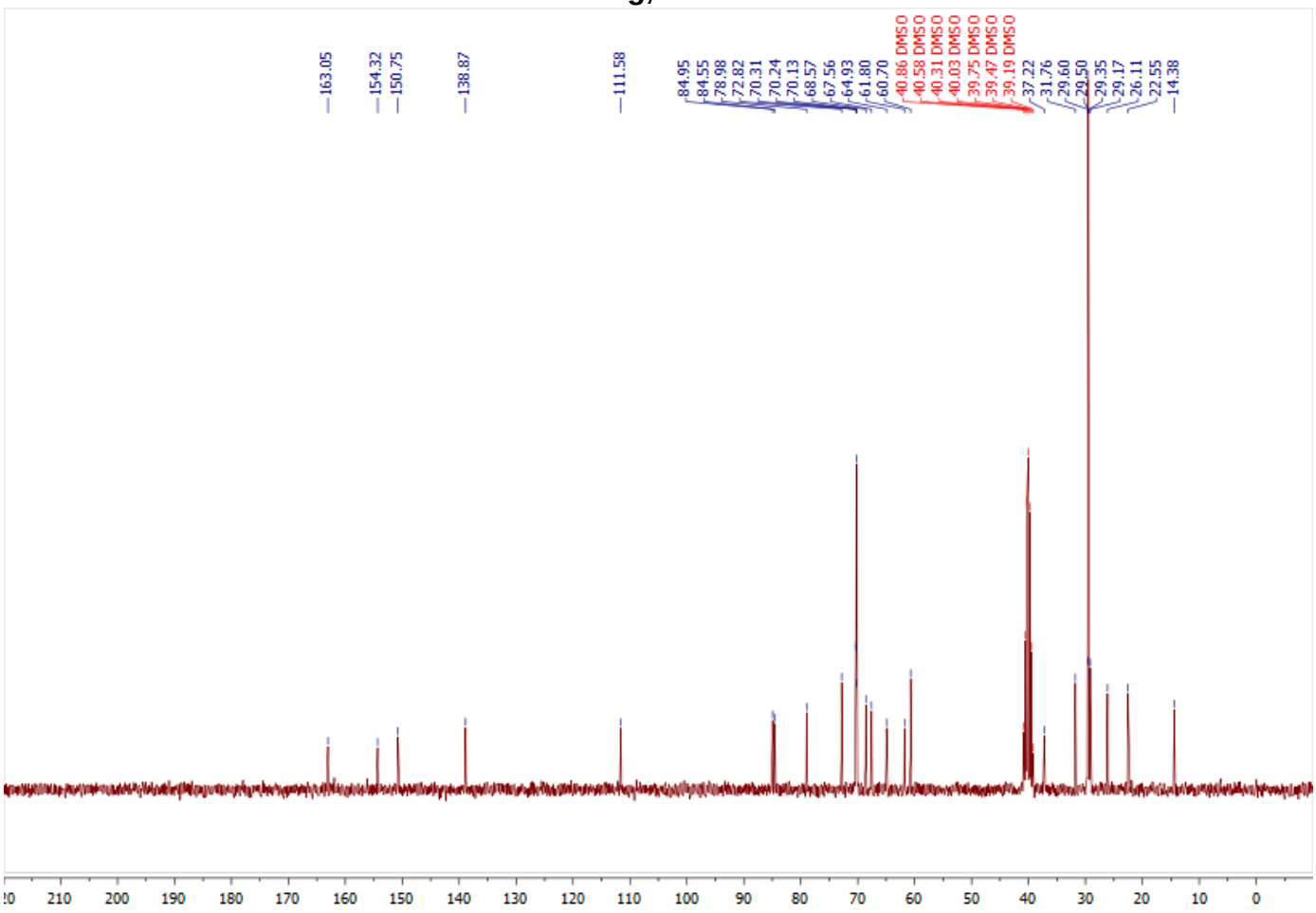
0.86
0.84
0.91
0.93
1.00
1.96
0.95
2.05
2.95
18.75
1.99
2.21
26.28
3.04
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5

3g, ^{13}C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70.24
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68.57
67.56
64.93
61.80
60.70
40.86 DMSO
40.58 DMSO
40.31 DMSO
40.03 DMSO
39.75 DMSO
39.47 DMSO
39.19 DMSO
37.22
31.76
29.60
29.50
29.35
29.17
26.11
22.55
14.38
210
200
190
180
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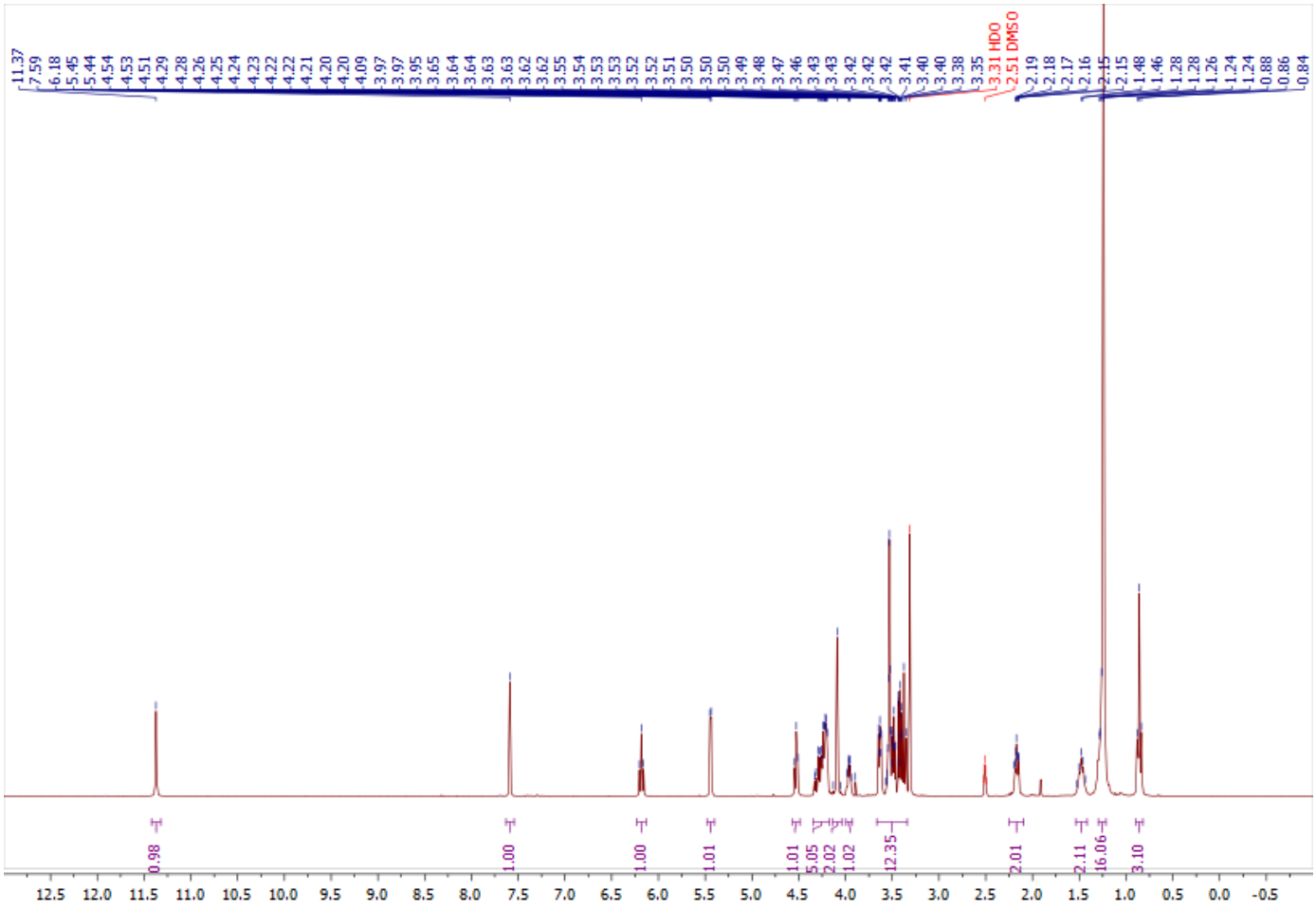
0

6a, ^{1}H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4.22
4.22
4.21
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4.20
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3.97
3.97
3.95
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3.64
3.64
3.63
3.63
3.62
3.62
3.55
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3.42
3.41
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3.40
3.38
3.35
3.31 HDO
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2.15
2.15
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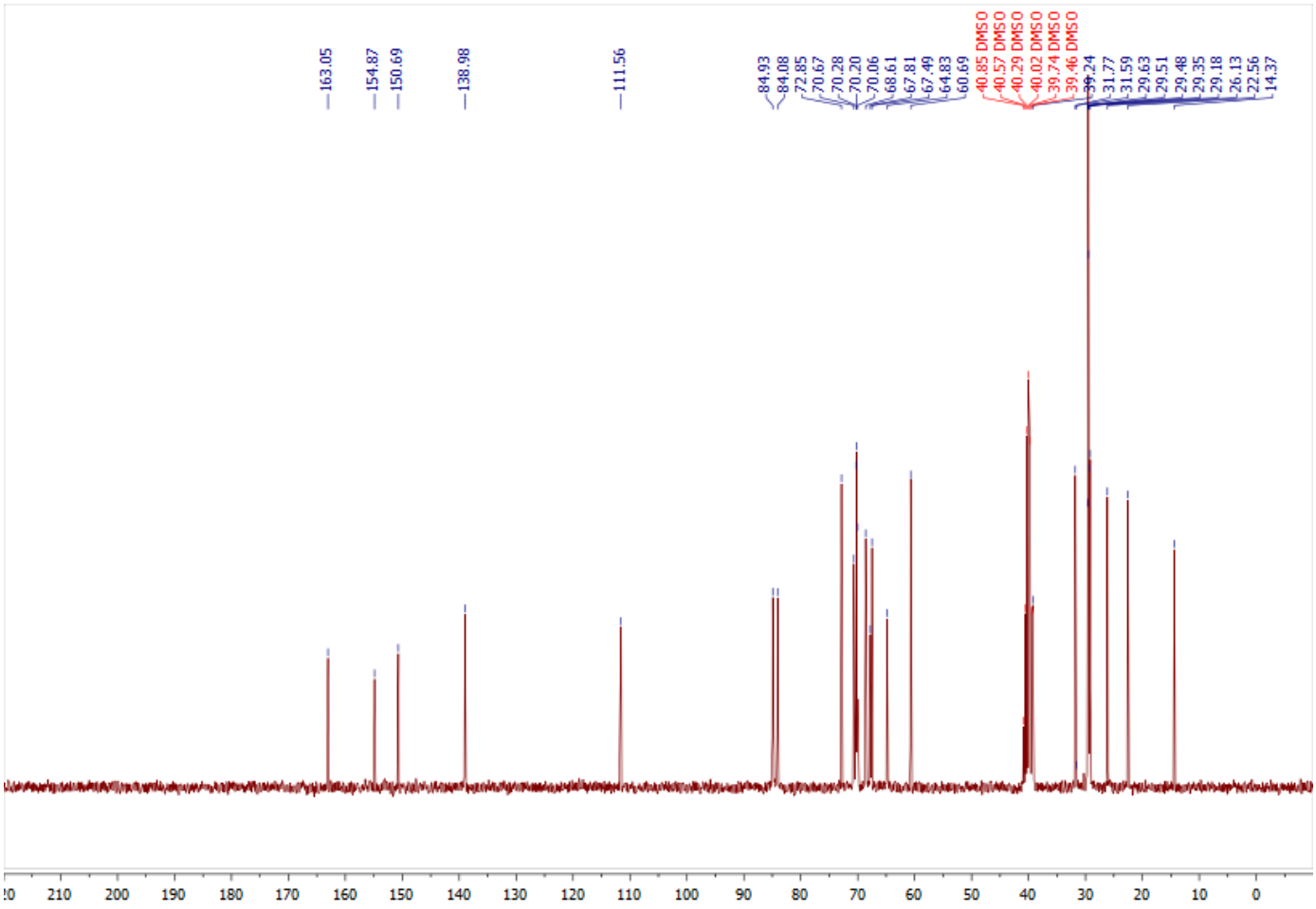
1.46
1.28
1.28
1.26
1.24
1.24
0.88
0.86
0.84
0.98
1.00
1.00
1.01
1.01
5.05
2.02
1.02
12.35
2.01
2.11
16.06
3.10
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5

6a, ^{13}C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67.81
67.49
64.83
60.69
40.85 DMSO
40.57 DMSO
40.29 DMSO
40.02 DMSO
39.74 DMSO
39.46 DMSO
39.24
31.77
31.59
29.63
29.51
29.48
29.35
29.18
26.13
22.56
14.37
210
200
190
180
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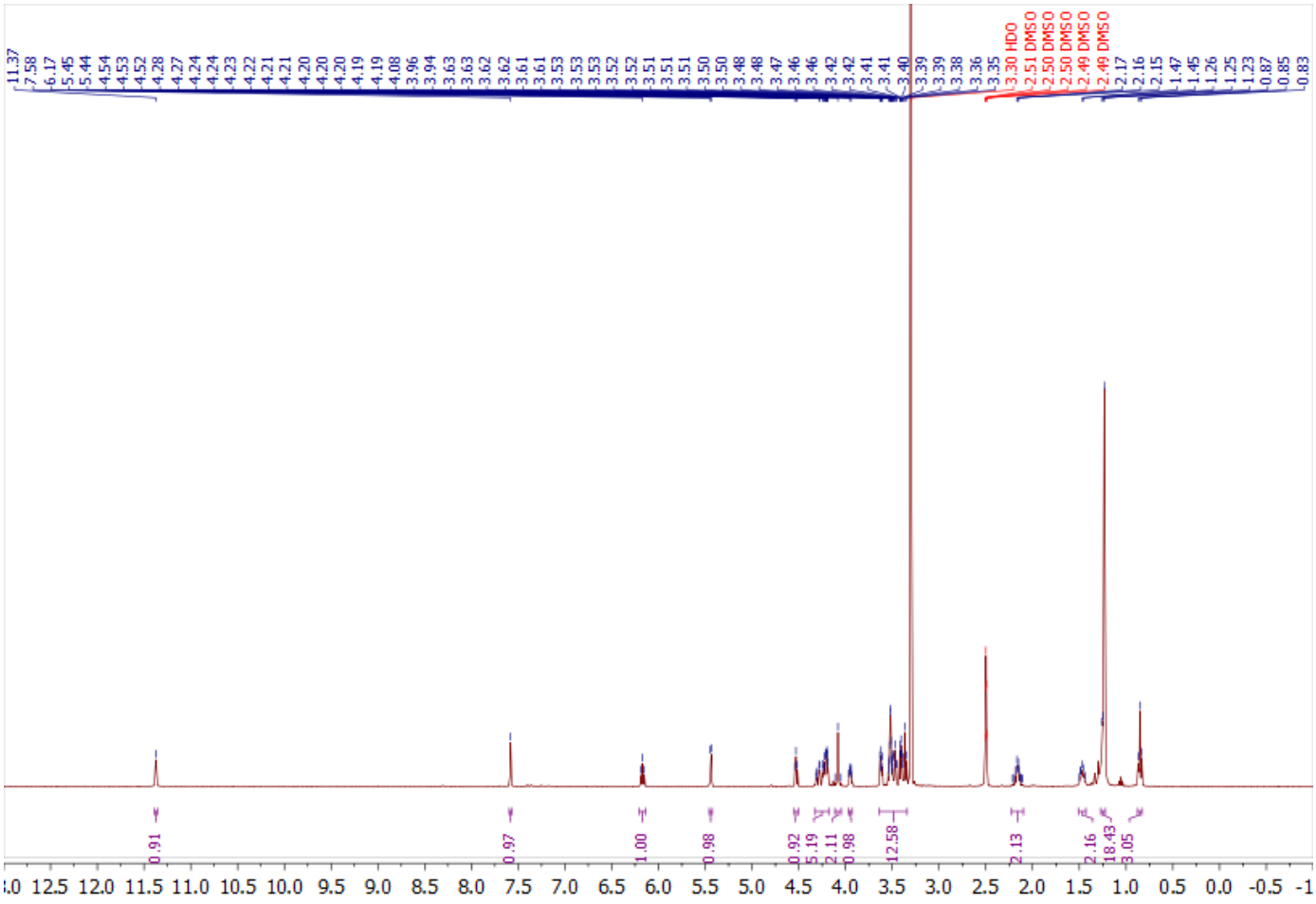
6b, ^{1}H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4.22
4.21
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3.46
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3.41
3.41
3.40
3.39
3.39
3.38
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3.35
3.30 HDO
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2.50 DMSO
2.50 DMSO
2.49 DMSO
2.49 DMSO
2.17
2.16
2.15
1.47
1.45
1.26
1.25
1.23
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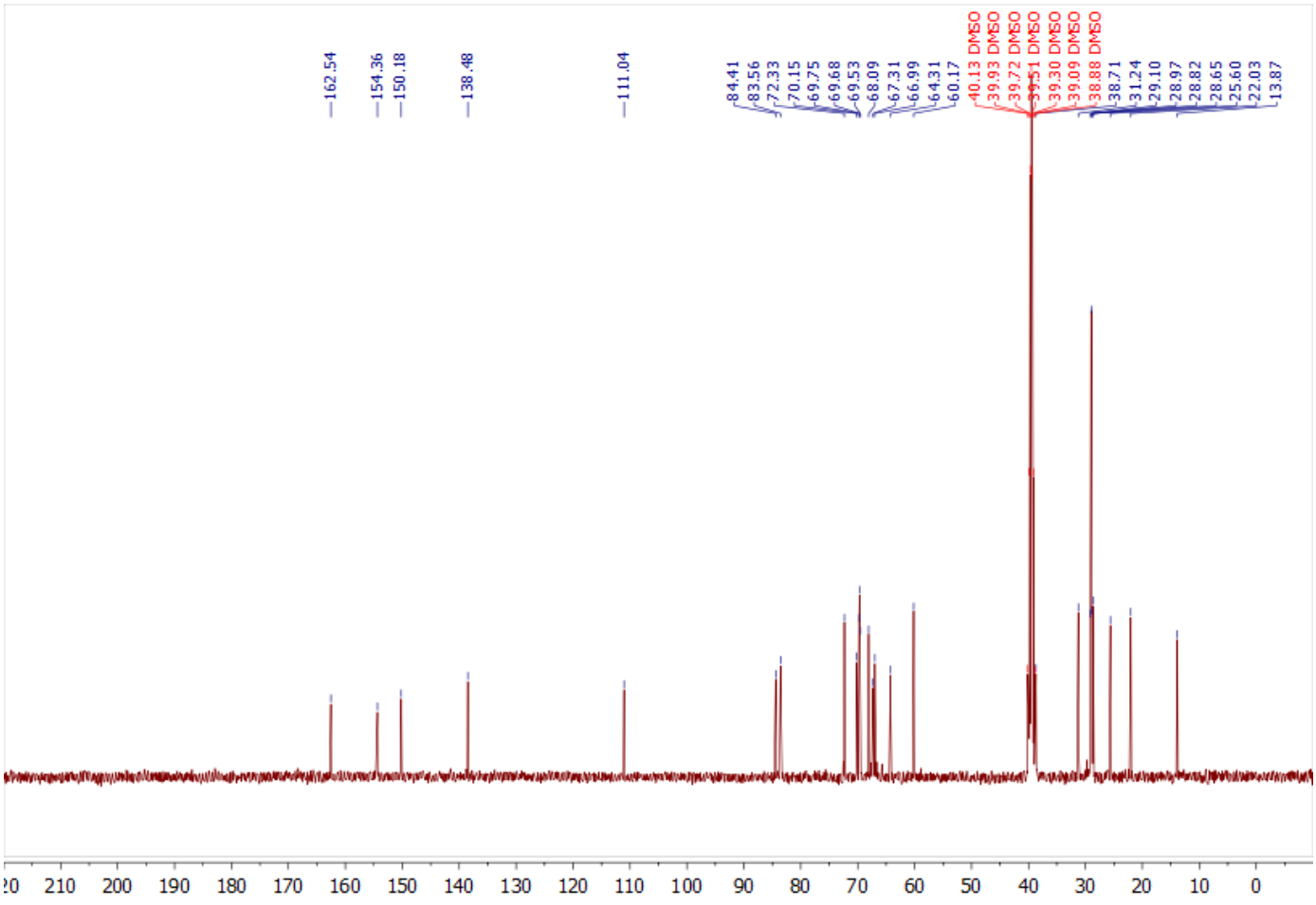
0.85
0.83
0.91
0.97
1.00
0.98
0.92
5.19
2.11
0.98
12.58
2.13
2.16
18.43
3.05
.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1

6b, ^{13}C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72.33
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69.75
69.68
69.53
68.09
67.31
66.99
64.31
60.17
40.13 DMSO
39.93 DMSO
39.72 DMSO
39.51 DMSO
39.30 DMSO
39.09 DMSO
38.88 DMSO
38.71
31.24
29.10
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28.82
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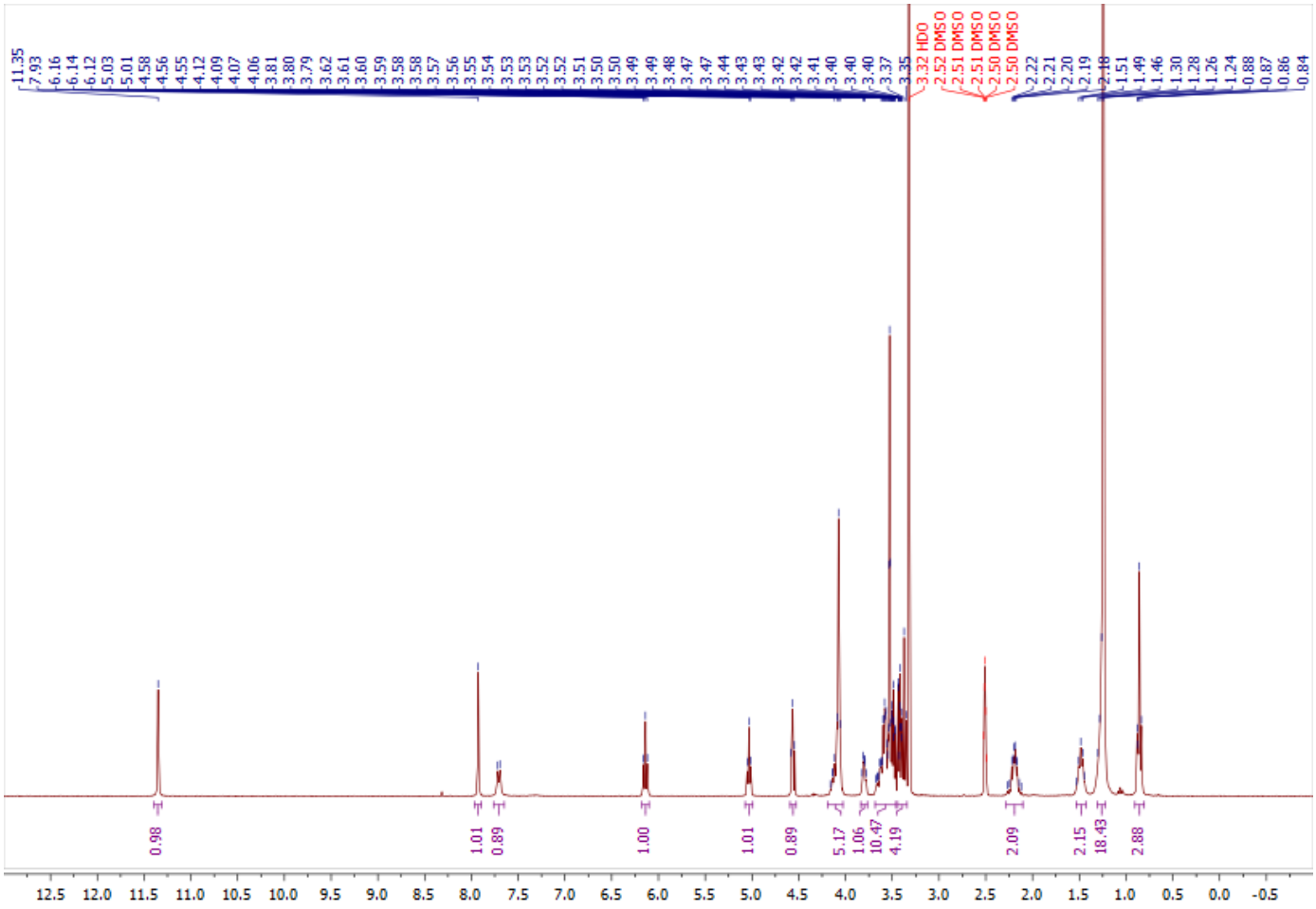
25.60
22.03
13.87
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

10, ^{1}H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4.09
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4.06
3.81
3.80
3.79
3.62
3.61
3.60
3.59
3.58
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3.43
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3.42
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3.32 HDO
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2.50 DMSO
2.50 DMSO
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2.21
2.20
2.19
2.18
1.51
1.49
1.46
1.30
1.28
1.26
1.24
0.88
0.87
0.86
0.84
0.98
1.01
0.89
1.00
1.01
0.89
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1.06
10.47
4.19
2.09
2.15
18.43
2.88
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12.0
11.5
11.0
10.5
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9.5
9.0
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6.5
6.0
5.5
5.0
4.5
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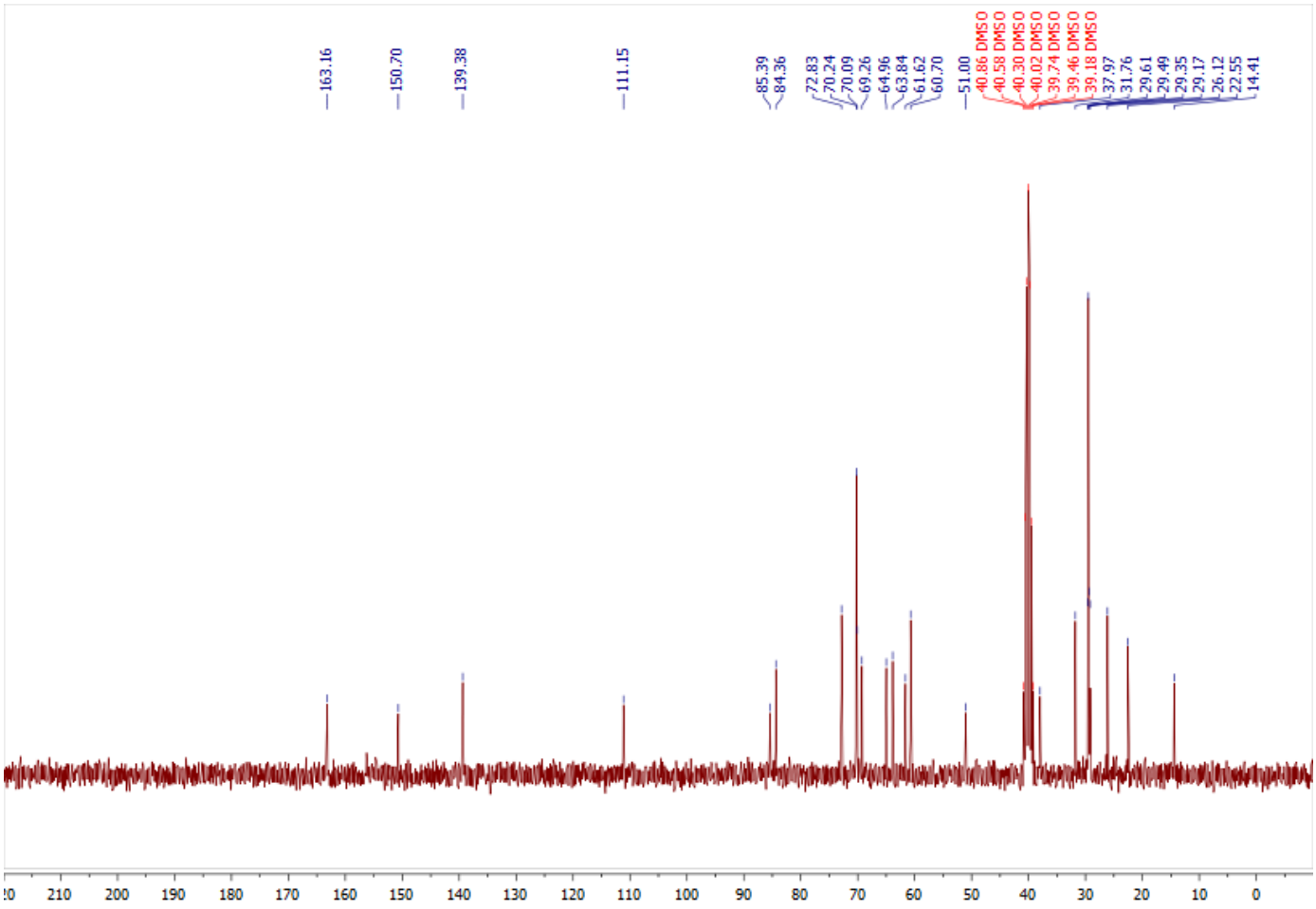
0.5
0.0
-0.5

10, ^{13}C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69.26
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61.62
60.70
51.00
40.86 DMSO
40.58 DMSO
40.30 DMSO
40.02 DMSO
39.74 DMSO
39.46 DMSO
39.18 DMSO
37.97
31.76
29.61
29.49
29.35
29.17
26.12
22.55
14.41
210
200
190
180
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120
110
100
90
80
70
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50
40
30
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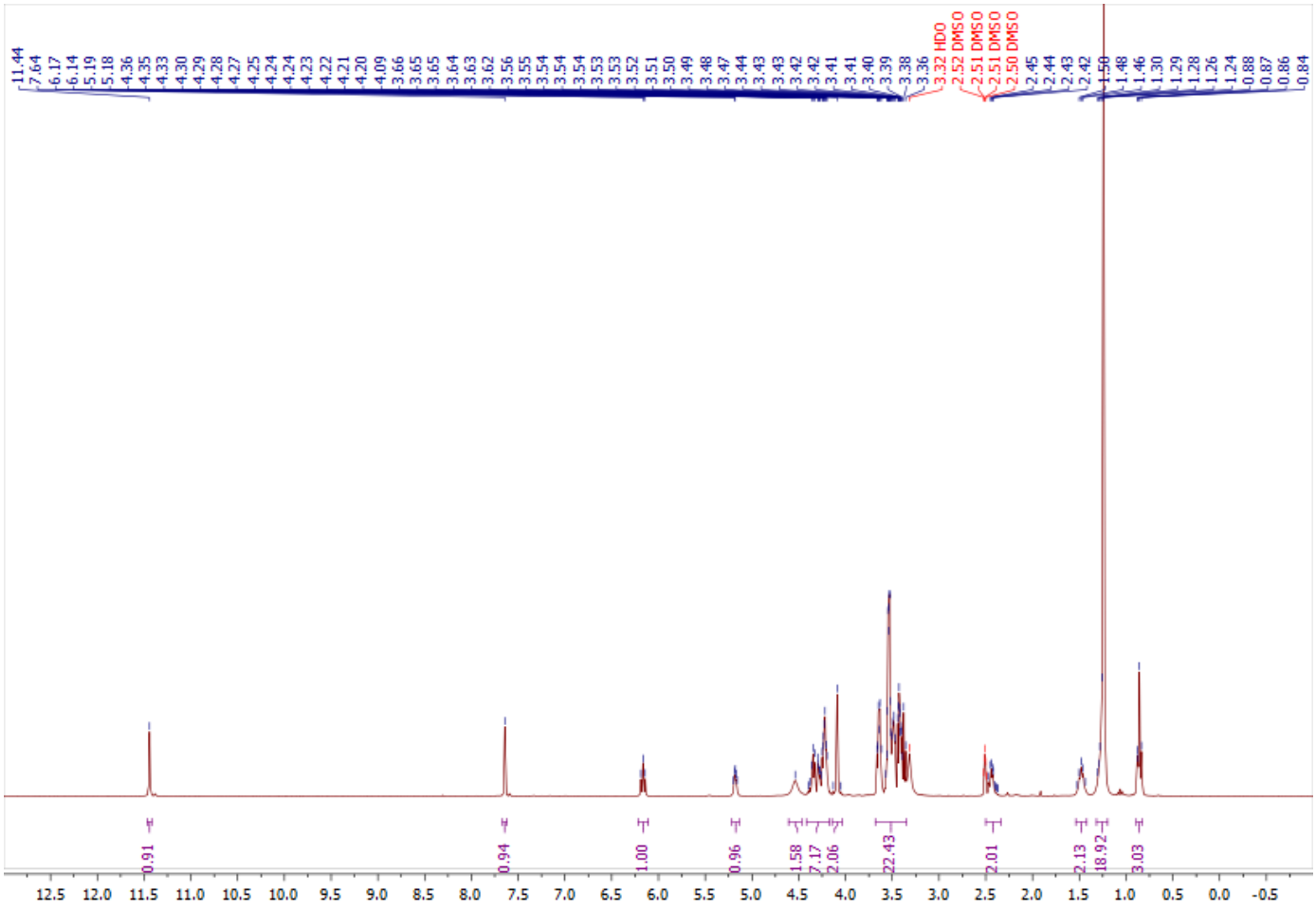
10
0

11, ^{1}H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3.39
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3.36
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2.06
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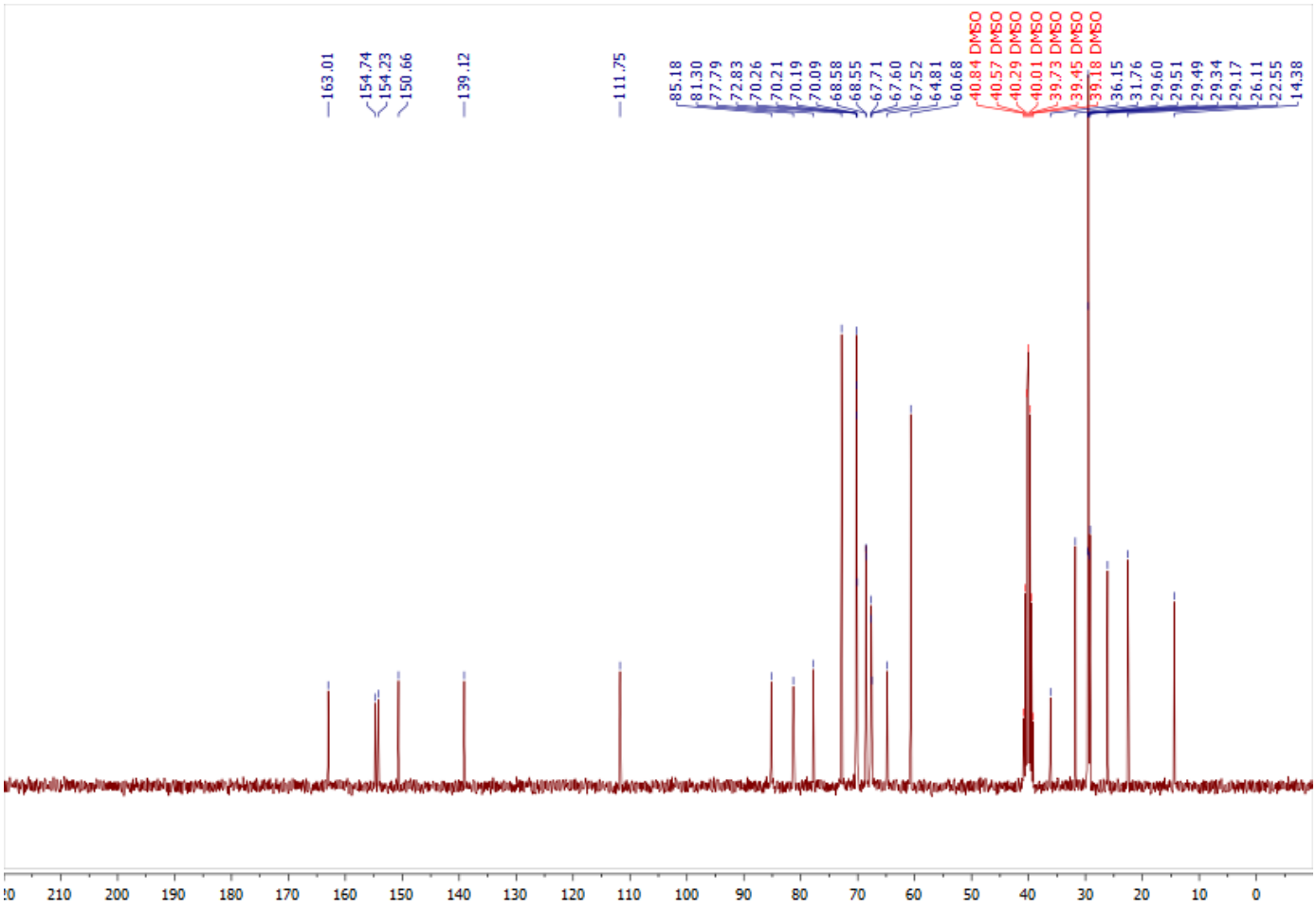
-0.5

11, ^{13}C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70.09
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68.55
67.71
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60.68
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40.57 DMSO
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40.01 DMSO
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39.45 DMSO
39.18 DMSO
36.15
31.76
29.60
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29.49
29.34
29.17
26.11
22.55
14.38
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200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

Comparison of the fragments of ^{1}H-NMR spectra of compounds 1c and 6b