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Tubulin targeted antimitotic agents based on adamantane lead compound: synthesis, SAR and molecular modeling

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Molecular modeling

Computer molecular modeling was performed using a 3D model of the colchicine-binding site of α,β-tubulin dimer (PDB ID:4O2B). Water molecules and the compounds used for X-ray analysis of the protein were previously excluded from the model, all other molecules and ions at the interface of α- and β-subunits of the protein were maintained. Atomic charges of protein amino acids were assigned by standard Kollman method using AutoDock Tools 1.5.6 [S1]. Three-dimensional structures of the compounds were submitted to a conformational MMFF Amber ff14SB optimization using Gasteiger charges in USCF Chimera 1.13.1 program [S2]. Molecular docking was carried out with AutoDock Vina 1.1.2 [S1] (grid box 14.25Å×19.5Å ×20.25 Å, grid center size *x*=17.864 Å, *y*=68.048 Å, *z*=42.749 Å, exhaustiveness = 16). Complexes with the best values of scoring functions were selected and visualized using CLC Drug Discovery Workbench (Limited mode, Version 4).

Chemistry

All reaction temperatures correspond to internal temperatures unless otherwise noted. Solvents for extraction and chromatography were technical grade and were purified by standard procedures prior to use. Reactions were monitored by thin layer chromatography (TLC) carried out on TLC silica gel plates ALUGRAM Xtra G/UV254, using UV light for visualization. Column chromatography purification was performed using silica gel Macherey-Nagel (0.063–0.2 mm). ^{1}H and ^{13}C NMR spectra were recorded on spectrometer Agilent 400-MR (400 MHz for ^{1}H; 100 MHz for ^{13}C) at room temperature; chemical shifts were measured with reference to the solvent ($CDCl_3$, δ_H=7.24 ppm, δ_C=77.0 ppm). Chemical shifts (δ) are given in ppm, spin-spin coupling constants (*J*) are reported in Hz; multiplicities are indicated by s (singlet), d (doublet), t (triplet), m (multiplet). Elemental analysis for compound **6** was performed on CNH analyser "Carlo-Erba" ER-20. Electron impact mass spectra were obtained on a Bruker Autoflex II mass spectrometer with accelerating voltage of 20 kV.

General procedure A *(the Steglich esterification).* An acid was dissolved in CH_2Cl_2 (5–10 ml) under stirring at room temperature. An alcohol, equivalent (or indicated) amount of N,N'-

dicyclohexylcarbodiimide (DCC) and catalytic amount (0.01 g) of 4-dimethylaminopyridine (DMAP) was added, and the mixture was stirred at room temperature for 24 h. Then the solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate (10 ml) and kept at 4 °C for 1 hour. The precipitate was filtered off and washed with cold ethyl acetate, the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (the eluent is indicated for each compound).

General procedure B (*the Mitsunobu reaction*). To a solution of 2-(1-adamantyl)ethanol in THF (5 ml), the corresponding alcohol was added followed by Ph_3P (0.173 g, 0.66 mmol) and diisopropyl azodicarboxylate (DIAD, 0.133 g, 0.66 mmol) under inert atmosphere. The mixture was stirred at room temperature for 48 h and then the solvent was evaporated under reduced pressure. The residue was purified by column chromatography [eluent: ethyl acetate/petroleum ether (40–70°C) – 1:7].

5-Hydroxymethyl-2-methoxyphenyl cyclohexylacetate (**2a**) and **3-cyclohexylacetoxy-4-methoxybenzyl cyclohexylacetate** (**3a**) were prepared according to general procedure A from cyclohexylacetic acid (100 mg, 0.7 mmol) and 3-hydroxy-4-methoxybenzyl alcohol (130 mg, 0.84 mmol). Eluent for column chromatography: ethyl acetate/petroleum ether (40–70°C) – 1:6]. Yield of **3a** – 50 mg (18%), colourless oily liquid. Yield of **2a** – 70 mg (36%), white solid, m.p. 60–62°C.

For **2a**: ^{1}H NMR ($CDCl_3$, δ, J/Hz): 1.03 (2H, m, -C_6H_{11}), 1.17–1.24 (1H, m, -C_6H_{11}), 1.27–1.38 (2H, m, -C_6H_{11}), 1.66–1.78 (3H, m, -C_6H_{11}), 1.85–1.98 (3H, m, -C_6H_{11}), 2.15 (1H, br.s, CH_2OH), 2.45 (2H, d, $CH_2C(O)O$, J=7.0), 3.81 (3H, s, OCH_3), 4.57 (2H, s, CH_2OH), 6.93 (1H, d, C^3H, J=8.4), 7.03 (1H, d, C^6H, J=2.1), 7.16 (1H, dd, C^4H, J=2.1, 8.4).

^{13}C NMR ($CDCl_3$, δ): 26.01, 26.10, 32.90, 35.04, 41.78, 55.84 (OCH_3), 64.41 (CH_2OH), 112.22 (C^3), 121.78 (C^6), 125.34 (C^4), 133.62(C^1), 139.64(C^5), 150.46(C^2), 171.20 (C(O)O).

MS (MALDI-TOF), *m/z*: 278 $[M]^+$, 301 $[M+Na]^+$, 317 $[M+K]^+$. $C_{16}H_{22}O_4$. Calculated: 278.

For **3a:** ^{1}H NMR ($CDCl_3$, δ, J/Hz): 0.90–1.00 (2H, m, -C_6H_{11}), 1.03–1.17 (4H, m, -C_6H_{11}), 1.18–1.38 (6H, m, -C_6H_{11}), 1.68–1.78 (6H, m, -C_6H_{11}), 1.79–1.98 (4H, m, -C_6H_{11}), 2.21 (2H, d, $CH_2C(O)O$, J=7.1), 2.45 (2H, d, $CH_2C(O)O$, J=7.0), 3.82 (3H, s, OCH_3), 5.03 (2H, s, CH_2O), 6.93 (1H, d, C^3H, J=8.4), 7.03 (1H, d, C^6H, J=2.1), 7.19 (1H, dd, C^4H, J=2.1, 8.4).

^{13}C NMR ($CDCl_3$, δ): 25.95, 26.02, 26.08, 26.11, 32.92, 32.95, 34.83, 35.03, 41.76, 42.07, 55.83 (OCH_3), 65.22 (CH_2OH), 112.11 (C^3), 123.11 (C^6), 126.91 (C^4), 128.67 (C^5), 139.64 (C^1), 151.00 (C^2), 170.92 (C(O)O), 172.89 (C(O)O).

MS (MALDI-TOF), *m/z*: 402 $[M]^+$, 425 $[M+Na]^+$, 441 $[M+K]^+$. $C_{24}H_{34}O_5$. Calculated: 402.

5-Hydroxymethyl-2-methoxyphenyl (*rac*-*exo*-bicyclo[2.2.1]heptane-2-yl)acetate (**2b**) and **3-(*rac*-*exo*-bicyclo[2.2.1]heptan-2-yl)acetoxy)-4-methoxybenzyl (*rac*-*exo*-bicyclo[2.2.1]-heptan-2-yl)acetate** (**3b**) were prepared according to the general procedure A from (bicyclo[2.2.1]heptan-2-yl)acetic acid (100 mg, 0.65 mmol), 3-hydroxy-4-methoxybenzyl alcohol (100 mg, 0.65 mmol) and DCC (167 mg). Eluent for column chromatography: ethyl acetate/petroleum ether (40–70°C), gradient mixture – 1:6 – 1:3. Yield of **3b** – 42 mg (10%), colorless oily liquid. Yield of **2b** – 40 mg (21%), white solid, m.p. 64ºC.

For **2b**: ^{1}H NMR ($CDCl_3$, δ, J/Hz): 1.16–1.20 (3H, m, $H^{bicycl.}$), 1.25–1.30 (1H, m, $H^{bicycl.}$), 1.37–1.40 (1H, m, $H^{bicycl.}$, J=9.78), 1.46–1.63 (3H, m, $H^{bicycl.}$), 2.01–2.09 (1H, m, $H^{bicycl.}$), 2.13–2.14 (1H, m, $H^{bicycl.}$), 2.27 (1H, m, $H^{bicycl.}$), 2.53 (1H, dd, $CH_2^{bicycl.}$, J=7.8, 15.0), 2.39 (1H, dd, $CH_2^{bicycl.}$, J=7.8, 15.0), 3.81 (3H, s, CH_3), 4.58 (2H, s, CH_2OH), 6.91 (1H, d, C^3H, J=8.80), 7.02 (1H, d, C^5H, J=1.96), 7.16 (1H, dd, C^4H, J=1.96, 8.80).

^{13}C NMR: ($CDCl_3$, δ): 28.51, 29.73, 35.22, 36.74, 37.70, 38.56, 40.86, 41.04, 58.85 (OCH_3), 64.41 (CH_2OH), 112.22 (C^3), 121.74 (C^6), 125.34 (C^4), 133.62 (C^5), 139.66 (C^1), 150.46 (C^2), 171.23 (C(O)O).

MS (MALDI-TOF), *m/z*: 290 $[M]^+$, 313 $[M+Na]^+$, 329 $[M+K]^+$. $C_{17}H_{22}O_4$. Calculated: 290.

For **3b**: ^{1}H NMR ($CDCl_3$, δ, J/Hz): 1.02–1.12 (2H, m, $H^{bicycl.}$), 1.14–1.22 (5H, m, $H^{bicycl.}$), 1.24–1.31 (2H, m, $H^{bicycl.}$), 1.37–1.40 (1H, m, $H^{bicycl.}$), 1.46–1.58 (5H, m, $H^{bicycl.}$), 1.59–1.63 (1H, m, $H^{bicycl.}$), 1.90 (1H, m, $H^{bicycl.}$), 1.97 (1H, m, $H^{bicycl.}$), 2.05 (1H, m, $H^{bicycl.}$), 2.13–2.21 (3H, m, $H^{bicycl.}$, J=7.9, 15.0), 2.27–2.33 (2H, m, $H^{bicycl.}$, J=7.9, 15.0), 2.39 (1H, dd, $CH_2^{bicycl.}$, J=7.7, 15.0), 2.54 (1H, dd, $CH_2^{bicycl.}$, J=8.1, 15.0), 3.82 (3H, s, CH_3), 5.03 (2H, s, CH_2OH), 6.93 (1H, d, C^3H, J=8.3), 7.03 (1H, d, C^5H, J=2.1), 7.19 (1H, dd, C^4H, J=2.1, 8.3).

^{13}C NMR ($CDCl_3$, δ): 28.48, 28.52, 29.71, 29.75, 35.16, 35.24, 36.68, 36.76, 37.68, 37.73, 38.37, 38.56, 40.86, 41.09, 41.22, 55.85 (OCH_3), 65.24 (CH_2OH), 112.14 (C^3), 123.07 (C^6), 126.89 (C^4), 128.69 (C^5), 139.67 (C^1), 151.02 (C^2), 170.96 (C(O)O), 172.91 (C(O)O).

MS (MALDI-TOF), *m/z*: 426 $[M]^+$, 449 $[M+Na]^+$, 465 $[M+K]^+$. $C_{26}H_{34}O_5$. Calculated: 426.

2-Methoxyphenyl adamantane-1-acetate (**4a**) was prepared according to general procedure A from 2-methoxyphenol (56 µl, 0.51 mmol) and adamantine-1-acetic acid (100 mg, 0.51 mmol). Eluent for column chromatography: ethyl acetate/petroleum ether (40–70ºC) – 1:8. Yield of **4a** – 93 mg (61%), white solid, m.p. 93ºC.

^{1}H NMR ($CDCl_3$, δ, J/Hz): 1.65–1.79 (12H, m, H(Ad)), 2.04 (3H, m, H(Ad)), 2.35 (2H, s, $AdCH_2$), 3.84 (3H, s, OCH_3), 6.92 (1H, d, C(3)H, J=7.83), 6.97 (1H, d, C(6)H, J=7.63), 7.03 (1H, d, C(5)H, J=7.43), 7.20 (1H, m, C(4)H).

^{13}C NMR: ($CDCl_3$, δ): 28.63, 33.02, 36.74, 42.21 (C(1-Ad)), 48.53 ($AdCH_2$), 55.60 (OCH_3), 112.30 (C(4)), 120.64 (C(6)), 122.90 (C(5)), 126.64 (C(4)), 139.74 (C(1)), 151.08 (C(2)), 169.55 (C=O).

MS (MALDI-TOF), *m/z*: 323 $[M+Na]^+$, 339 $[M+K]^+$. $C_{19}H_{24}O_3$. Calculated: 300.

4-Methoxyphenyl adamantane-1-acetate (**4b**) was prepared according to general procedure A from 4-methoxyphenol (63 mg, 0.51 mmol) and adamantine-1-acetic acid (100 mg, 0.51 mmol). Eluent for column chromatography: ethyl acetate/petroleum ether (40–70ºC) – 1:8. Yield of **4a** – 109 mg (72%), white solid, m.p. 71ºC.

^{1}H NMR ($CDCl_3$, δ, J/Hz): 1.64–1.75 (12H, m, H(Ad)), 2.03 (3H, m, H(Ad)), 2.30 (2H, s, AdCH_2), 3.80 (3H, s, OCH_3), 6.81 (2H, d, C(2)H, C(6)H, J=9.07), 7.02 (2H, d, C(3)H, C(5)H, J=8.91).

^{13}C NMR: ($CDCl_3$, δ): 28.56, 33.13, 36.65, 42.39 (C(1-Ad)), 48.63 (AdCH_2), 55.50 (OCH_3), 114.31 (C(3), C(5)), 122.37 (C(2), C(6)), 144.12 (C(1)), 157.05 (C(4)), 170.49 (C(O)O).

MS (MALDI-TOF), *m/z*: 300 $[M]^+$, 323 $[M+Na]^+$, 339 $[M+K]^+$. $C_{19}H_{24}O_3$. Calculated: 300.

5-Formyl-2-methoxyphenyl adamantane-1-acetate (**4c**) was prepared according to general procedure A from 3-hydroxy-4-methoxybenzaldehyde (78 mg, 0.51 mmol) and adamantine-1-acetic acid (100 mg, 0.51 mmol). Eluent for column chromatography: ethyl acetate/petroleum ether (40–70ºC) – 1:5. Yield of **4c** – 129 mg (77%), white solid, m.p. 136ºC.

^{1}H NMR ($CDCl_3$, δ, J/Hz): 1.64–1.70 (12H, m, H(Ad)), 1.98 (3H, m, H(Ad)), 2.29 (2H, s, AdCH_2), 3.85 (3H, s, OCH_3), 7.02 (1H, d, C(3)H, J=8.44), 7.51 (1H, d, C(6)H, J=1.83), 7.69 (1H, dd, C(4)H, J=1.83, J=8.44), 9.81 (1H, s, C(O)H).

^{13}C NMR: ($CDCl_3$, δ): 28.51, 32.99, 36.61, 42.14 (C(1-Ad)), 48.30 (AdCH_2), 55.93 (OCH_3), 111.83 (C(3)), 123.34 (C(6)), 129.80 (C(4)), 130.08 (C(5)), 140.20 (C(1)), 156.29 (C(2)), 169.13 (C(O)O), 190.02 (C(O)H).

MS (MALDI-TOF), *m/z*: 351 $[M+Na]^+$, 367 $[M+K]^+$. $C_{20}H_{24}O_4$. Calculated: 328.

4-Bromo-2-methoxyphenyl adamantane-1-acetate (**4d**) was prepared according to general procedure A from 4-bromo-2-methoxyphenol (104 mg, 0.51 mmol) and adamantine-1-acetic acid (100 mg, 0.51 mmol). Eluent for column chromatography: ethyl acetate/petroleum ether (40–70ºC) – 1:9. Yield of **4d** – 134 mg (69%), white solid, m.p. 103ºC.

^{1}H NMR ($CDCl_3$, δ, J/Hz): 1.64–1.75 (12H, m, H(Ad)), 2.02 (3H, m, H(Ad)), 2.32 (2H, s, AdCH_2), 3.82 (3H, s, OCH_3), 6.90 (1H, d, C(6)H, J=8.22), 7.06 (1H, d, C(3)H, J=2.35), 7.08 (1H, d, C(5)H, J=1.96).

^{13}C NMR: ($CDCl_3$, δ): 28.60, 33.04, 36.70, 42.21 (C(1-Ad)), 48.43 (AdCH_2), 55.90 (OCH_3), 115.85 (C(3)), 119.18 (C(4)), 123.56 (C(6)), 124.14 (C(5)), 138.94 (C(1)), 151.80 (C(2)), 169.26 (C(O)O).

MS (MALDI-TOF), *m/z*: 379 $[M]^+$. $C_{19}H_{23}BrO_3$. Calculated: 379.

1-[2-(5-Formyl-2-methoxyphenoxy)ethyl]adamantane (**5**) was prepared according to general procedure B from 2-(1-adamantyl)ethanol (100 mg, 0.55 mmol) and 3-hydroxy-4-methoxybenzaldehyde (84 mg, 0.55 mmol). Eluent for column chromatography: ethyl acetate/petroleum ether (40–70°C) – 1:7. Yield of **5** – 23 mg (13%), white solid, m.p. 62°C.

^{1}H NMR ($CDCl_3$, δ, J/Hz): 1.60 (6H, m, H(Ad)), 1.65–1.74 (8H, m, H(Ad)+AdCH_2), 1.98 (3H, m, H(Ad)), 3.96 (3H, s, CH_3), 4.14 (2H, t, AdCH_2, J=8.80), 6.96 (1H, d, C(3)H, J=7.83), 7.41 (1H, d, C(4), J=1.96), 7.44 (1H, dd, C(6)H, J=1.96, 7.83), 9.85 (1H, s, C(O)H).

^{13}C NMR: ($CDCl_3$, δ): 28.67, 31.86, 37.08, 42.64, 42.90 (C(1-Ad)); 56.03 (OCH_3); 65.46 (CH_2OAr); 111.43 (C(3)); 111.69 (C(6)); 125.35 (C(4)); 133.54 (C(5)); 148.71 (C(1)), 153.00 (C(2)), 190.46 (COH).

MS (MALDI-TOF), *m/z*: 314 $[M]^+$. $C_{20}H_{26}O_3$. Calculated: 314.

1-[2-(5-Hydroxymethyl-2-methoxyphenyl)ethyl]adamantane (**6**). To a solution of 1-[2-(5-formyl-2-methoxyphenoxy)ethyl]adamantane (**5**) (0.022 g, 0.07 mmol) in MeOH (3 ml) was added $NaBH_4$ (0.011 g, 0.29 mmol) by portions. The mixture was stirred at room temperature for 2 h and then the solvent was evaporated under reduced pressure. The residue was treated with water and extracted with dichloromethane (3×10 ml). Yield of **6** is 20 mg (90%), waxy solid.

^{1}H NMR ($CDCl_3$, δ, J/Hz): 1.60 (6H, m, H(Ad)), 1.65–1.74 (9H, m, H(Ad)), 1.97 (3H, m, H(Ad)), 3.87 (3H, s, AdCH_2), 4.10 (2H, t, CH_2, J=7.73), 4.63 (2H, s, C(3)H, J=8.44), 6.84 (1H, d, C(6)H, J=8.02), 6.88 (1H, dd, C(4)H, J=1.76, J=8.02), 6.94 (1H, d, C(O)H, J=1.76).

^{13}C NMR: ($CDCl_3$, δ): 28.61, 31.78, 37.05, 42.59, 42.83 (AdCH_2), 56.05 (OCH_3), 64.73 (CH_2OH), 65.42 (CH_2O), 111.36 (C(3)), 111.68 (C(6)), 119.22 (C(4)), 133.46 (C(5)), 148.71 (C(1)), 148.90 (C(2)).

MS (MALDI-TOF), *m/z*: 316 $[M]^+$. $C_{20}H_{28}O_3$. Calculated: 316.

Anal. calcd. for, %: $C_{20}H_{28}O_3$, %: C 75.91; H 8.92. Found, %: C 75.96; H 8.90.

1-[2-(2-Methoxyphenoxy)ethyl]adamantane (**7**) was prepared according to general procedure B from 2-methoxyphenol (68 mg, 60 μl, 0.55 mmol) and 2-(1-adamantyl)ethanol (100 mg, 0.55 mmol). Eluent for column chromatography: ethyl acetate/petroleum ether (40–70°C) – 1:7. Yield of **7** – 23 mg (14%), white solid, m.p. 84°C.

^{1}H NMR ($CDCl_3$, δ, J/Hz): 1.57–1.74 (14H, m, H(Ad), AdCH_2CH_2), 1.97 (3H, m, H(Ad)), 3.87 (3H, s, OCH_3), 4.10 (2H, t, $AdCH_2CH_2O$, *J*=7.9), 6.90 (4H, m, C(6)H, C(5)H, C(4)H, C(3)H).

^{13}C NMR: ($CDCl_3$, δ): 28.62, 31.78, 37.05, 42.59 (C(1-Ad)), 42.77 (AdCH_2CH_2), 55.90 (OCH_3), 64.66 ($AdCH_2CH_2$), 111.63 (C(3)), 112.63 (C(6)), 120.60 (C(4)), 120.75 (C(5)), 143.90 (C(1)), 146.95 (C(2)).

MS (MALDI-TOF), *m/z*: 286 $[M]^+$. $C_{19}H_{26}O_2$. Calculated: 286.

2. Biology

Immunofluorescence microscopy. A549 human lung epithelial carcinoma cells (CCL-185™) were cultured with Dulbecco's Modified Eagle medium (DMEM) containing 10% fetal bovine serum and 1% antibiotic penicillin/streptomycin at 37°C under a 5% CO_2 humidified atmosphere. The cells were cultured in 12-well plates on small glass coverslips (11 mm diameter) at a density of 20000 cells per coverslip and were incubated with tested compounds at concentrations of 100 μM (or 10 μM and 100 μM for compound **6**) for 24 h (0.5 % DMSO served as a negative control). The cells were fixed and stained as described in [S3]. Fixed cells were labelled for tubulin with mouse monoclonal antibody against α-tubulin at a dilution of 1:300 (Sigma, St. Louis. USA), followed by incubation of Alexa Fluor488 labelled goat anti-mouse IgG at a dilution of 1:300 (Invitrogen, Germany). Images of all samples were acquired with a Nikon Diaphot 300 inverted microscope (Nikon GmbH, Düsseldorf, Germany) equipped with a cooled charge-couple device camera system (SenSys; Photometrics, Munich, Germany).

MTT Cytotoxicity Assay. The MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2*H*-tetrazolium bromid, Roth GmbH, Karlsruhe, Germany) quantitative colorimetric assay [S4] was used to measure the cytotoxicity, viability and metabolic activity of compound **6**. Cells A549 were seeded in 96-well plates at a density of 3000 cells per well. Stock solution of compound **6** was prepared in DMSO at concentration 20 mM. Cells were treated for 24 h with the test compound at 1 – 100 μM (8 wells for each concentration). DMSO (0.5%) served as a negative control. Optical density was measured at 550 nm with 690 nm reference filter using a EL808 Ultra Microplate Reader (BioTek Instruments, Winooski, USA). Experiments were repeated 3 times and EC_{50} value was determined by sigmoid curve fitting using Excel-based software.

Proliferation assay for compound 6. Cells A549 were incubated with 10 μM or 100 μM of compounds during 24 and 48 h (0.5% DMSO was used as a control). After culturing the cells were re-suspended in PBS and counted directly by phase-contract microscopy using hemocytometer.

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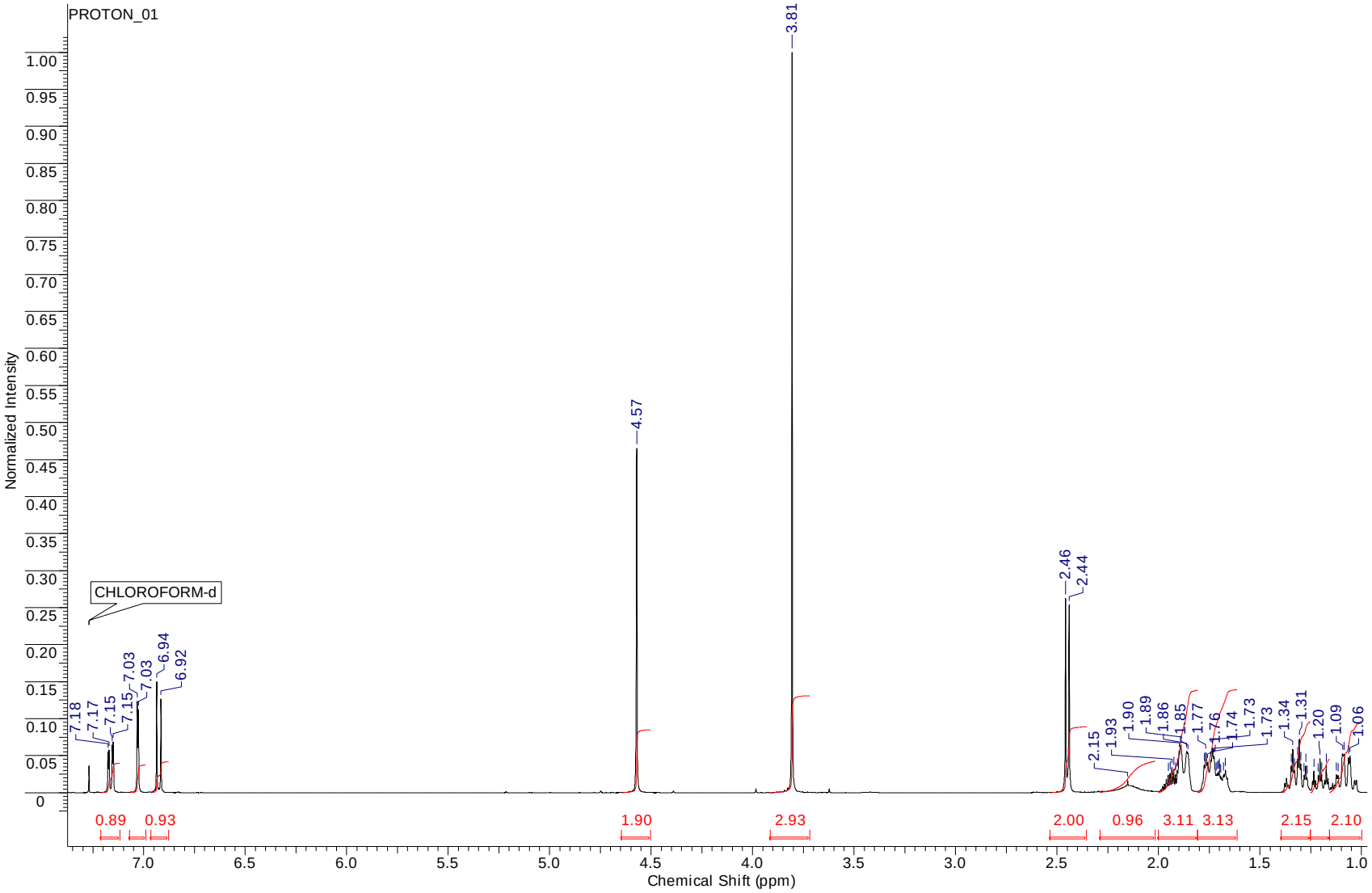
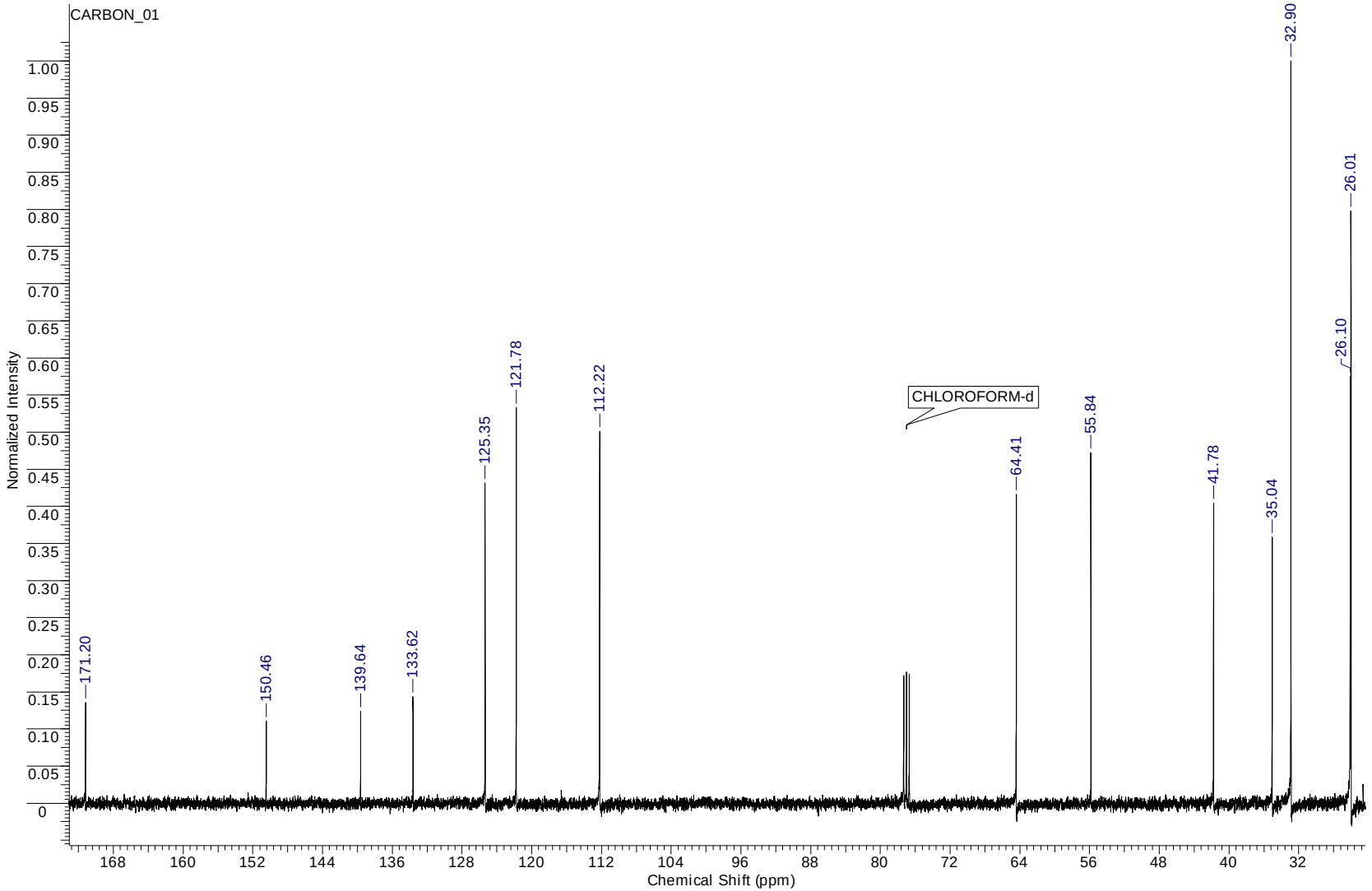
^{1}H and ^{13}C NMR spectra of representative compounds

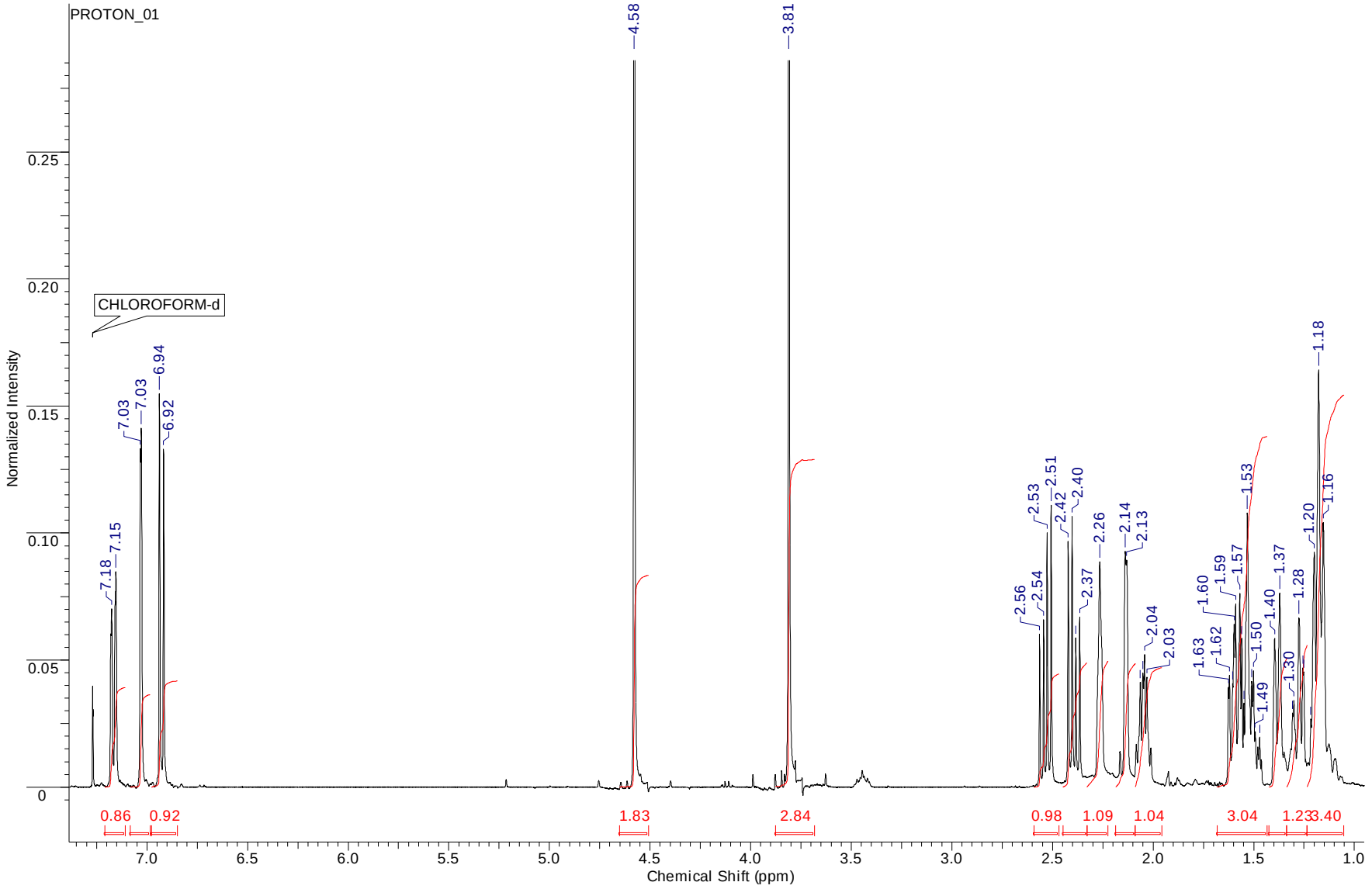
*^{1}H NMR spectrum of 5-hydroxymethyl-2-methoxyphenyl cyclohexylacetate (**2a**)*



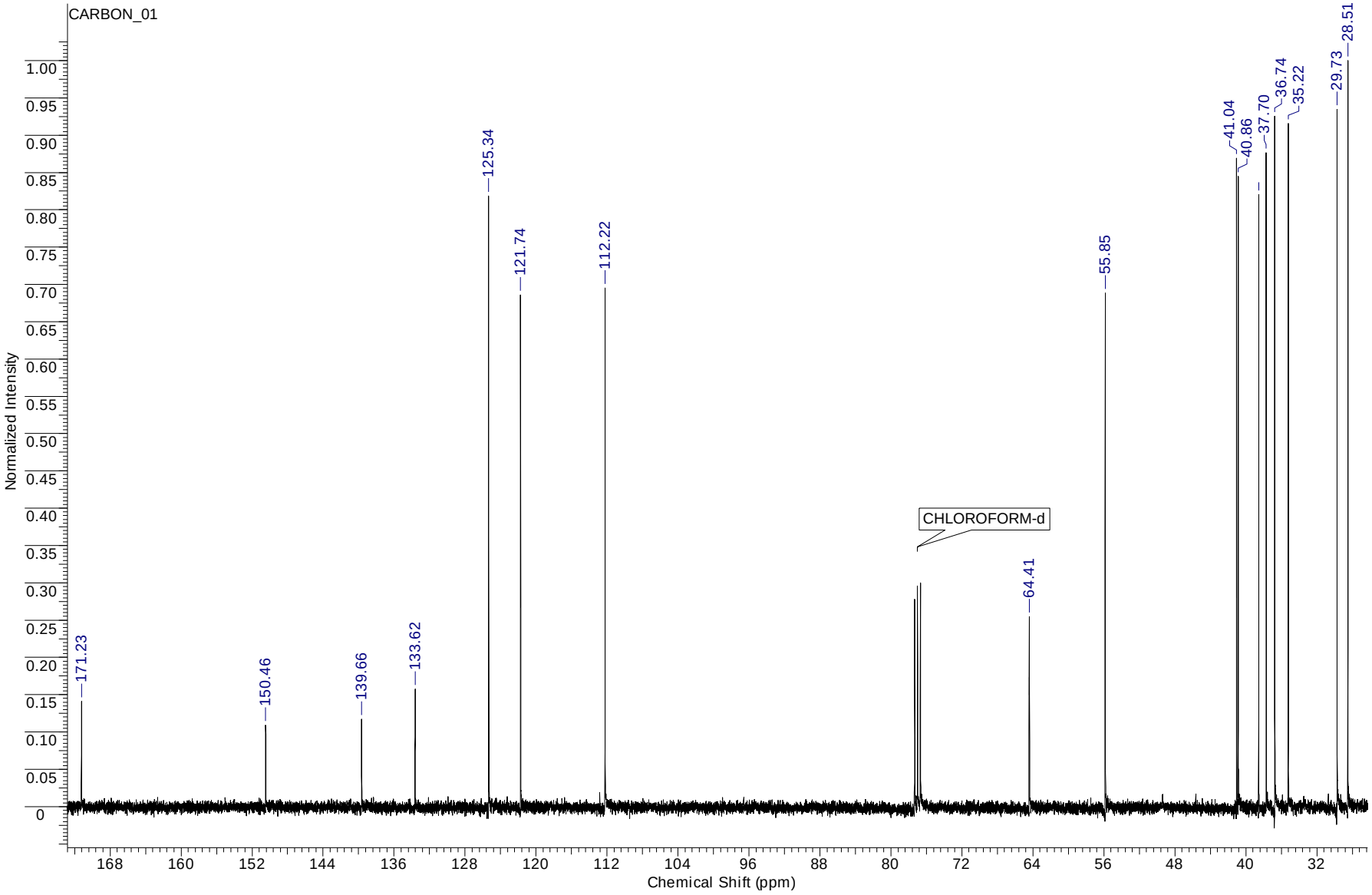
*^{13}C NMR spectrum 5-hydroxymethyl-2-methoxyphenyl cyclohexylacetate (**2a**)*



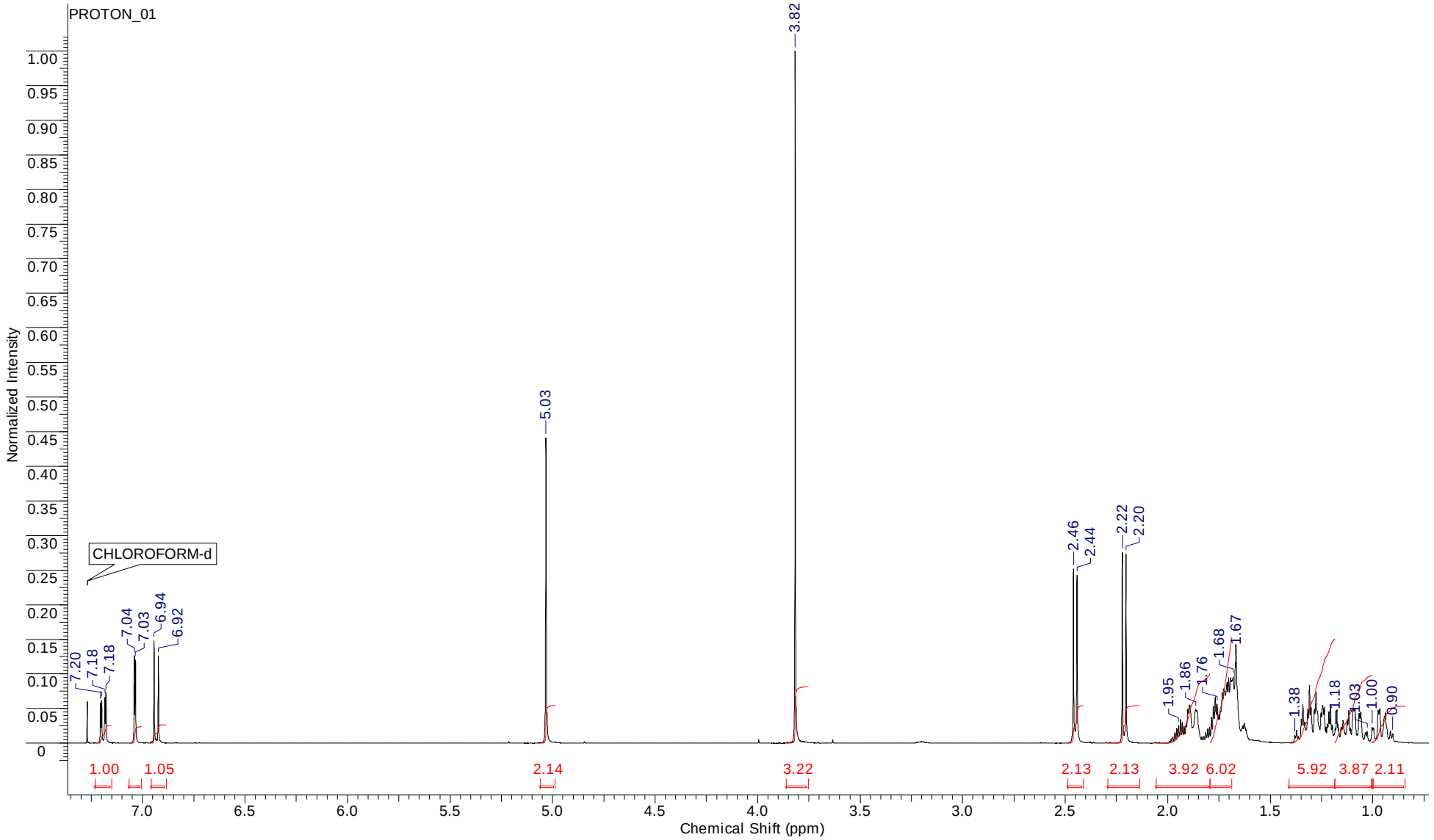
*^{1}H NMR spectrum of 5-hydroxymethyl-2-methoxyphenyl (rac-exo-bicyclo[2.2.1]heptane-2-yl)acetate (**2b**)*



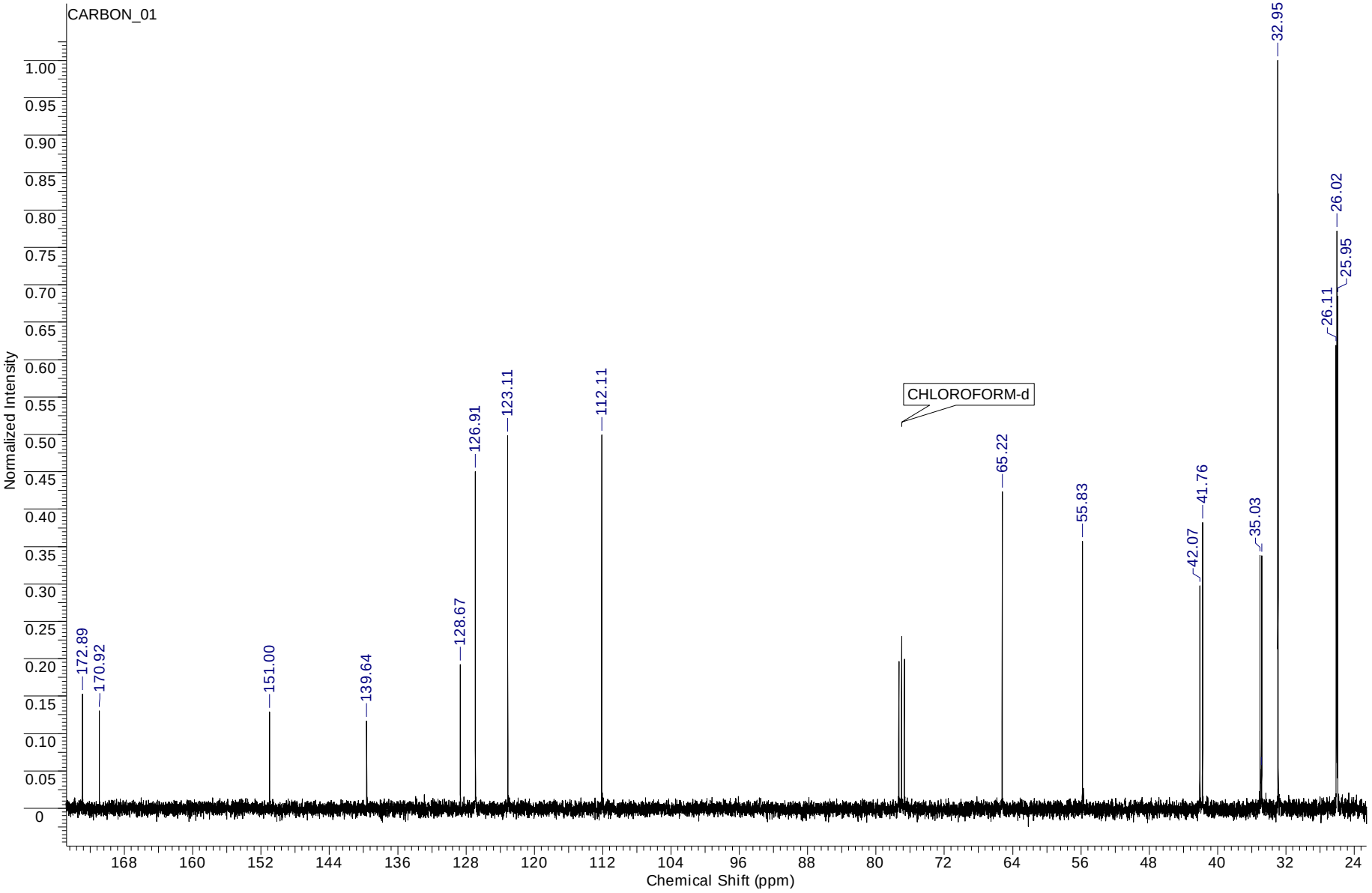
*^{13}C NMR spectrum of 5-hydroxymethyl-2-methoxyphenyl (rac-exo-bicyclo[2.2.1]heptane-2-yl)acetate (**2b**)*



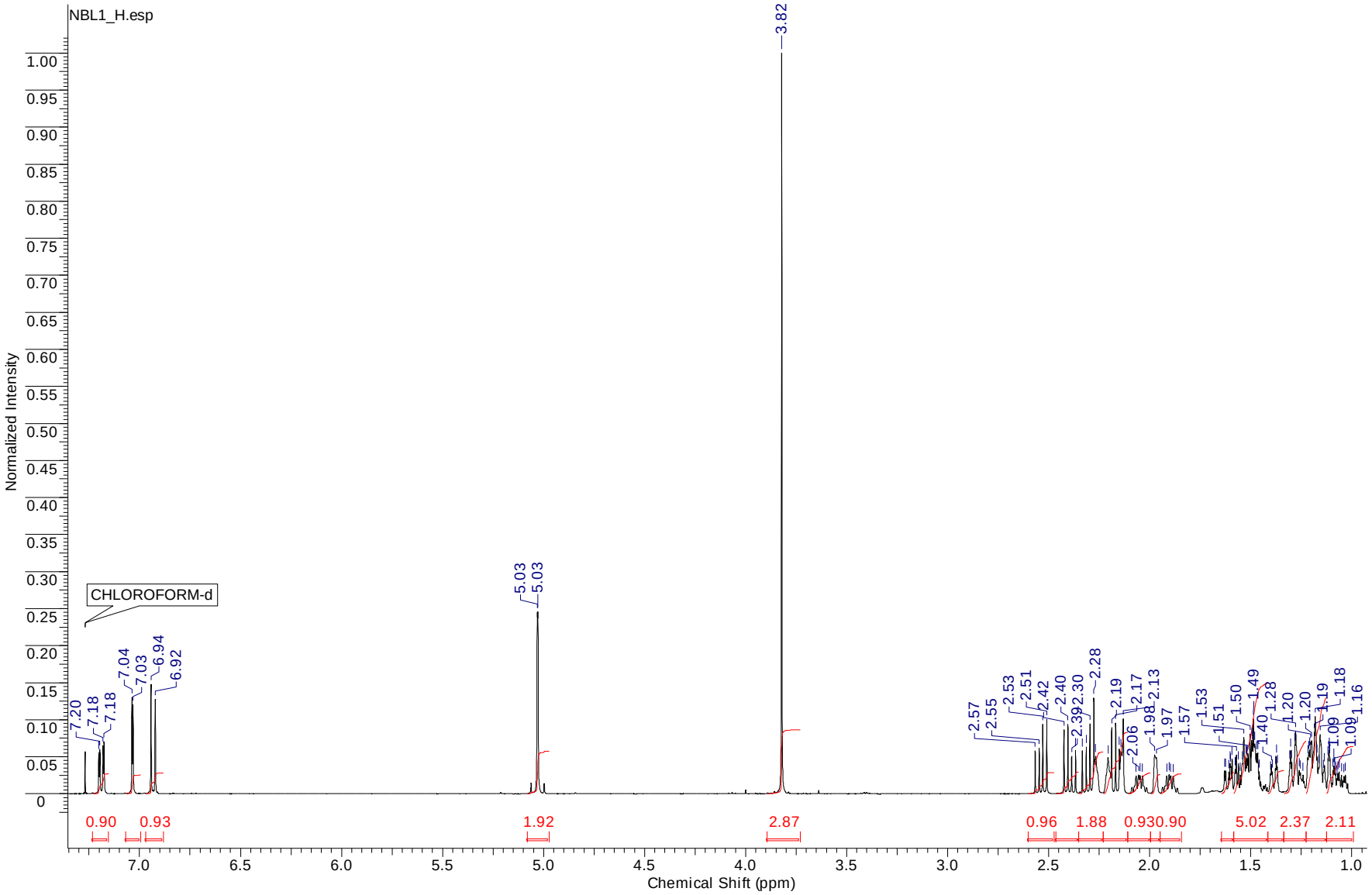
*^{1}H NMR spectrum of 3-cyclohexylacetoxy-4-methoxybenzyl cyclohexylacetate (**3a**)*



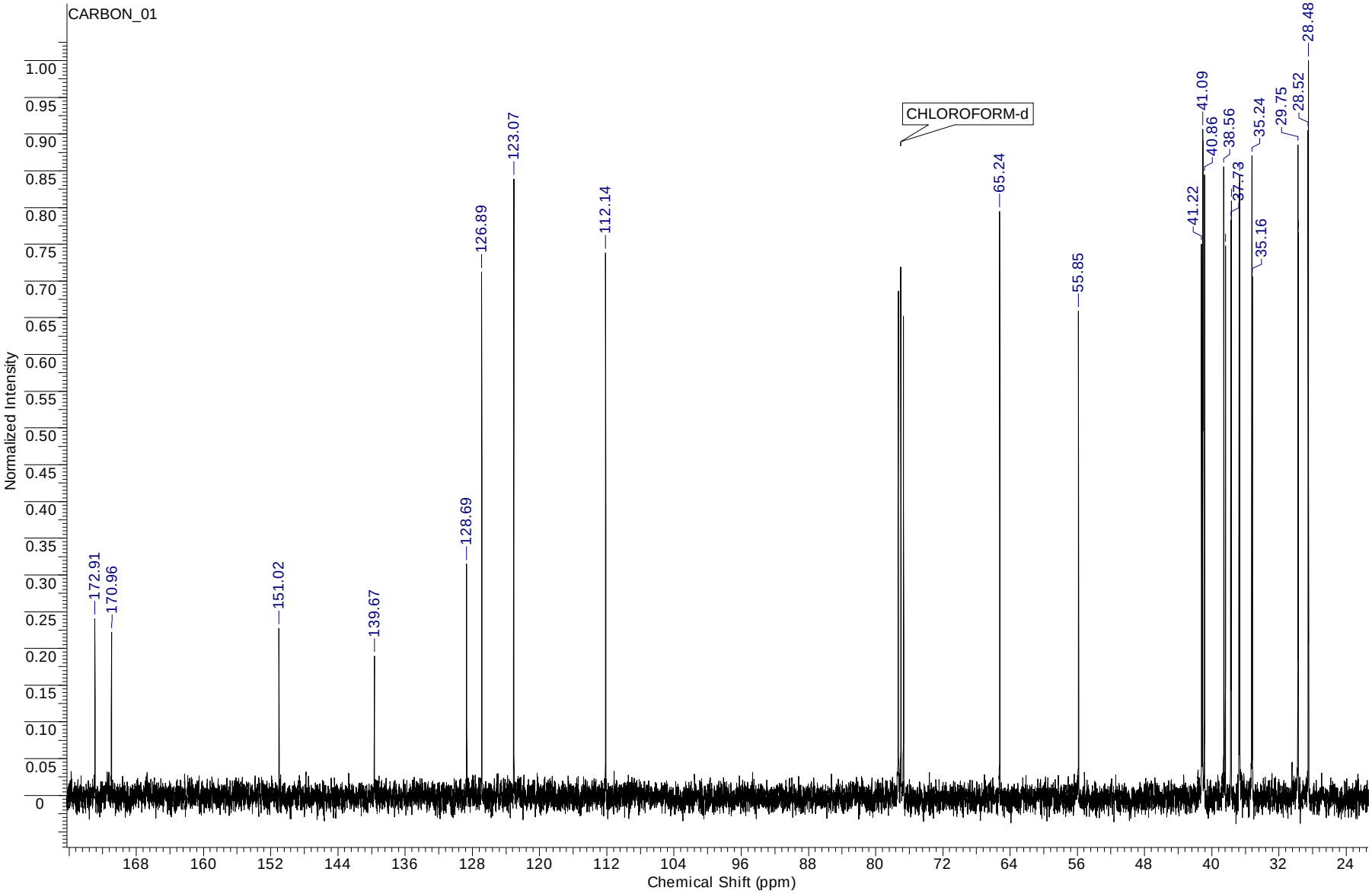
*^{13}C NMR spectrum of 3-cyclohexylacetoxy-4-methoxybenzyl cyclohexylacetate (**3a**)*



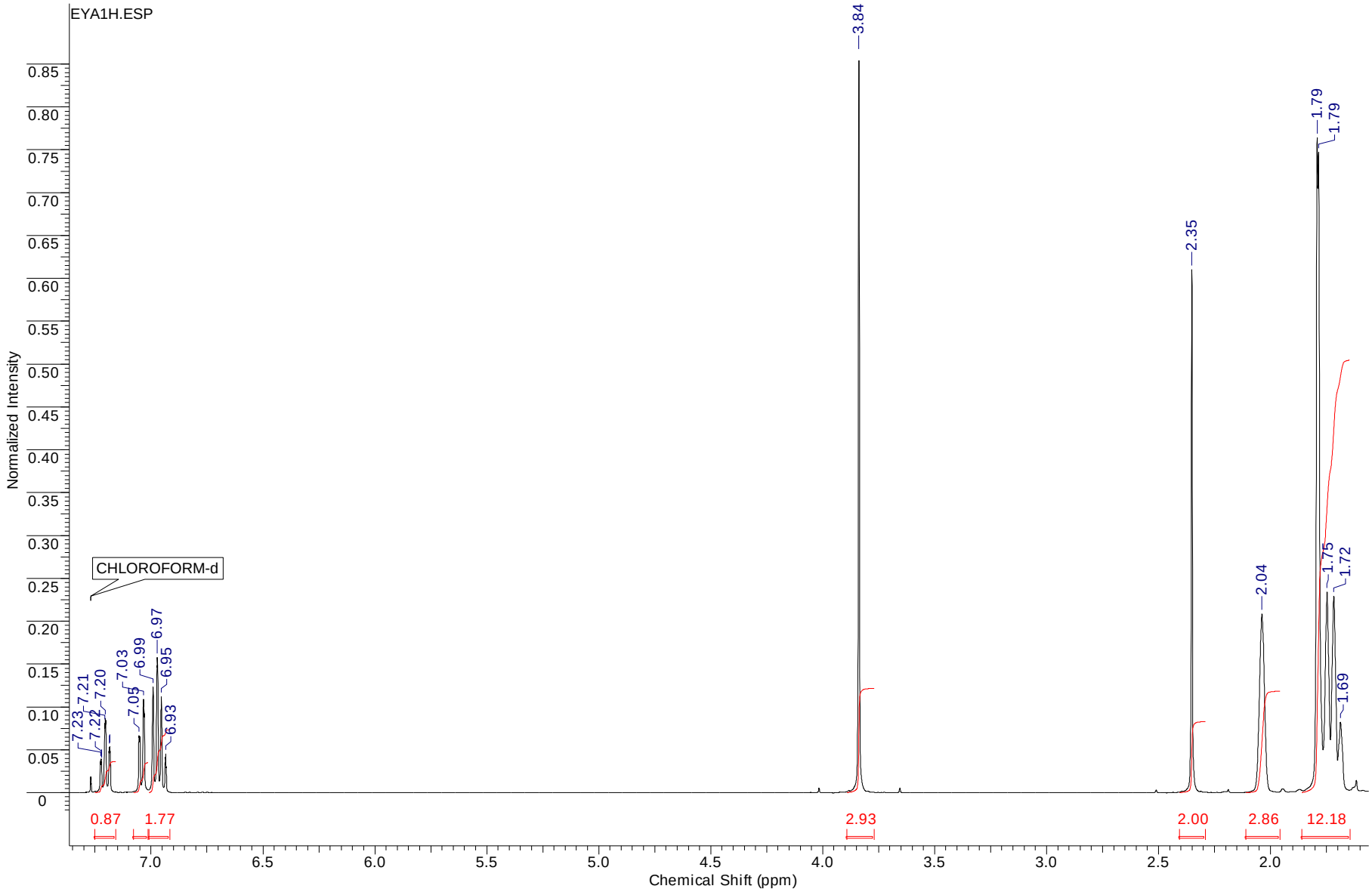
*^{1}H NMR spectrum of 3-[(rac-exo-bicyclo[2.2.1]heptan-2-yl)acetoxy]-4-methoxybenzyl (rac-exo-bicyclo[2.2.1]heptan-2-yl)acetate (**3b**)*



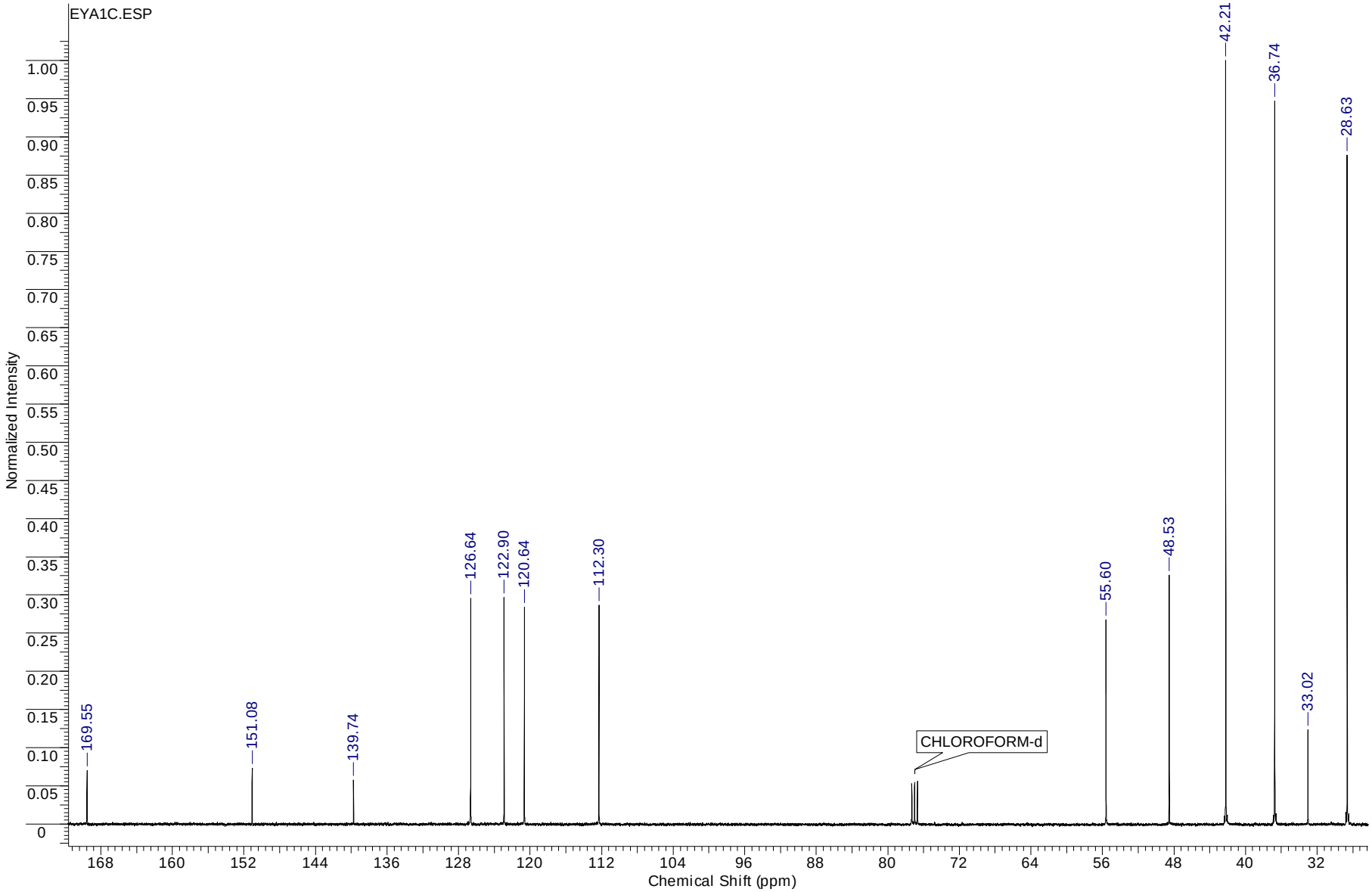
*^{13}C NMR spectrum of 3-[(rac-exo-bicyclo[2.2.1]heptan-2-yl)acetoxy]-4-methoxybenzyl (rac-exo-bicyclo[2.2.1]heptan-2-yl)acetate (**3b**)*



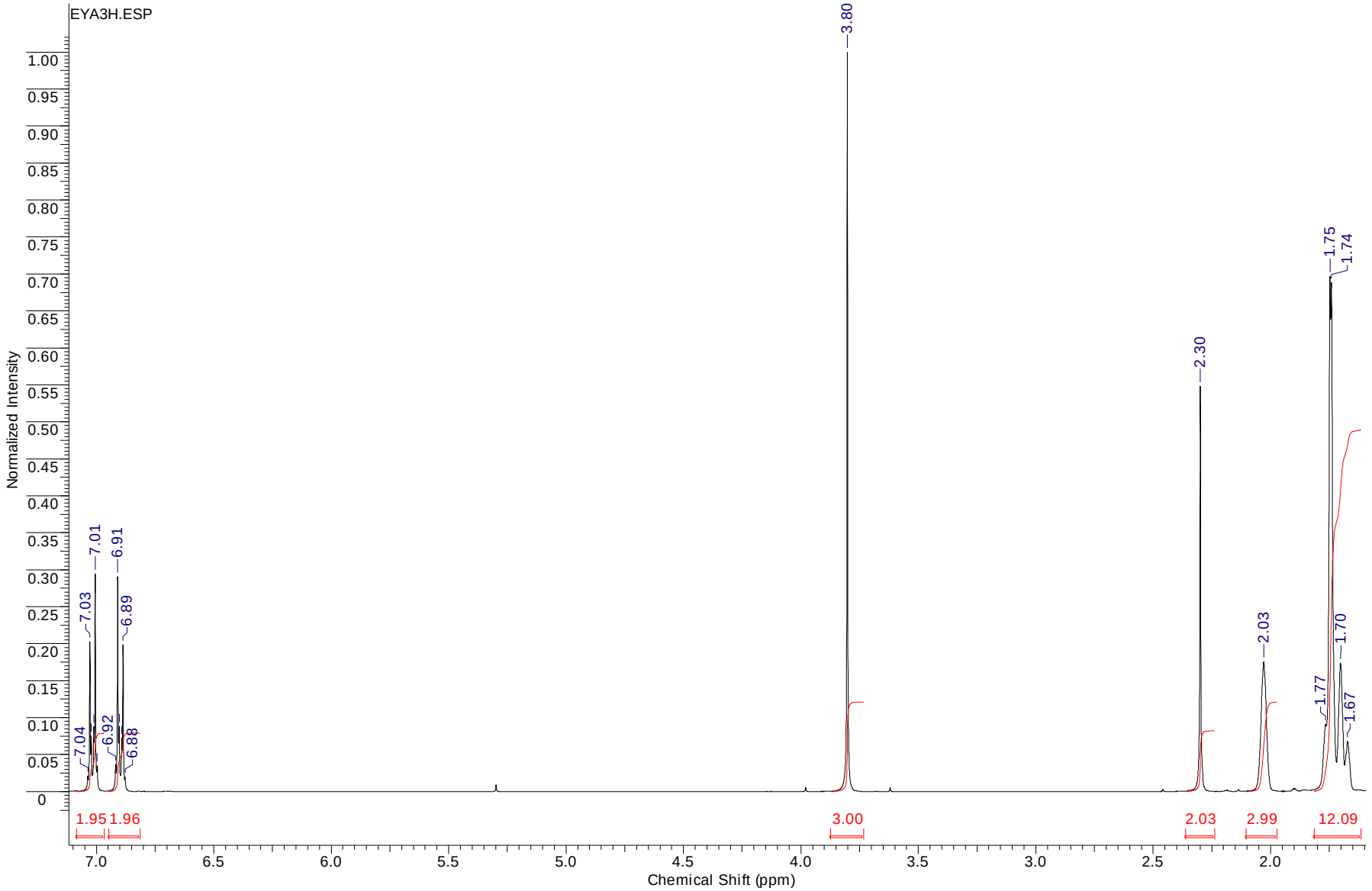
*^{1}H NMR spectrum of 2-methoxyphenyl adamantane-1-acetate (**4a**)*



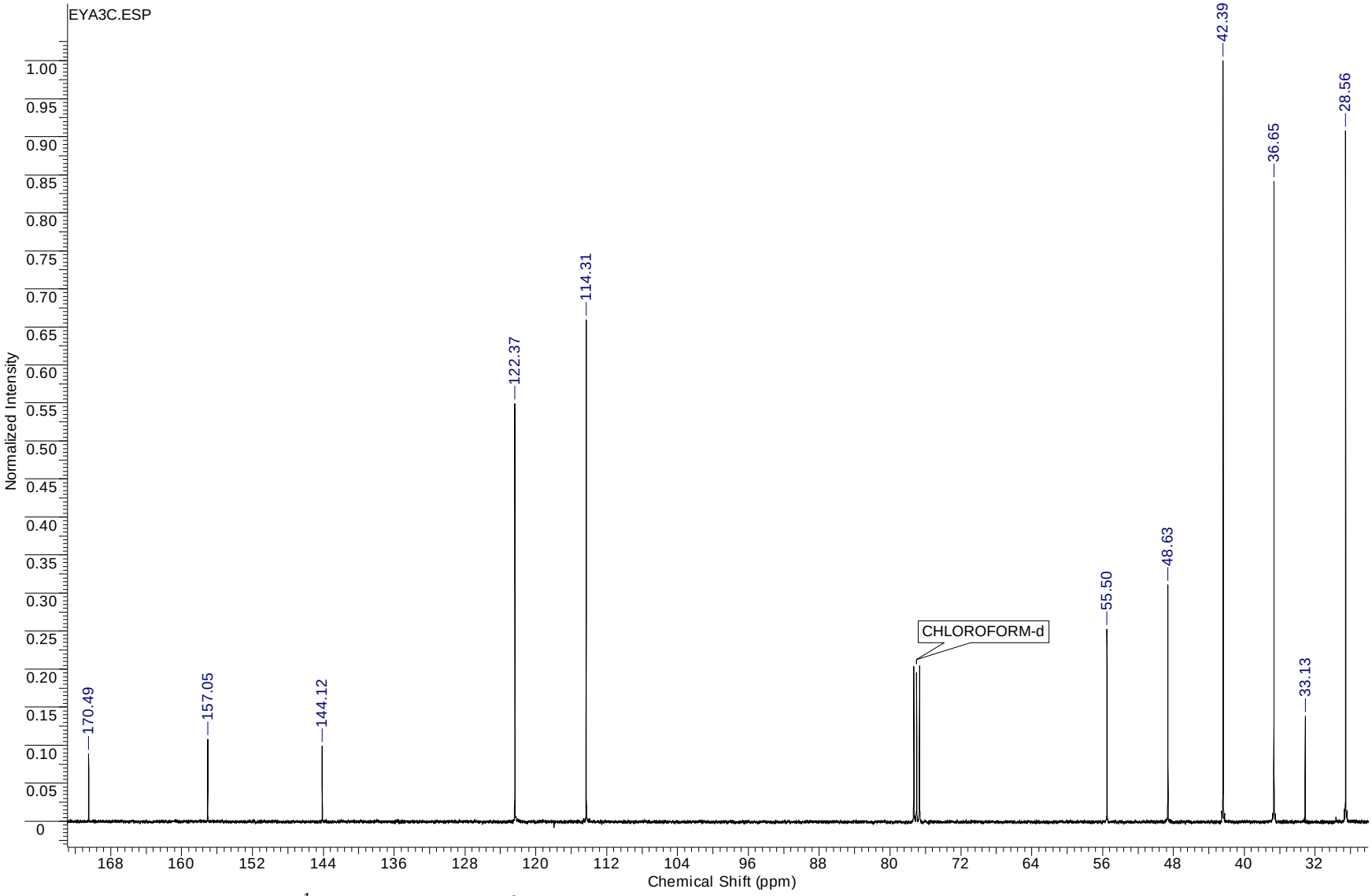
*^{13}C NMR spectrum of 2-methoxyphenyl adamantane-1-acetate (**4a**)*



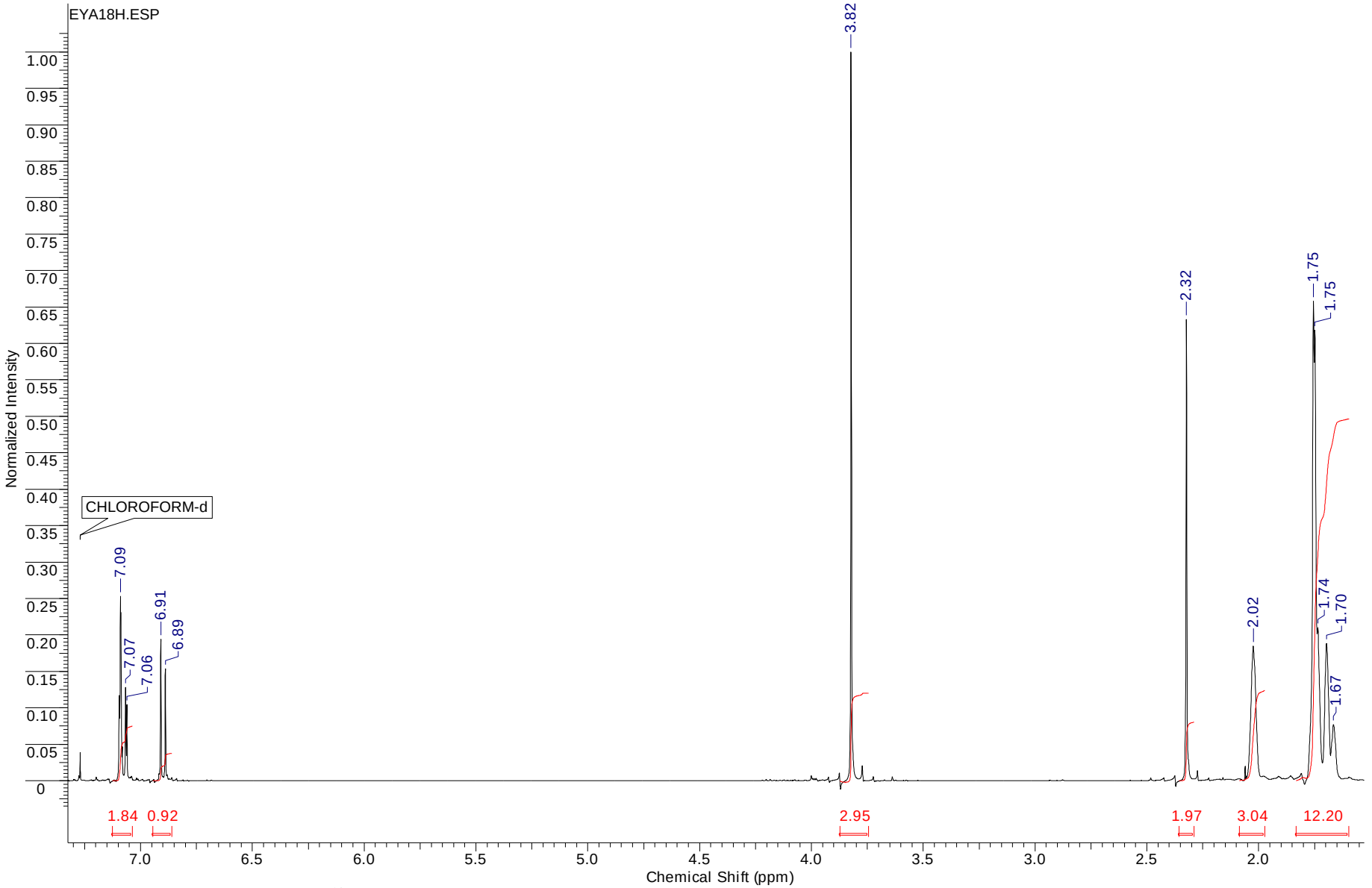
*^{1}H NMR spectrum of 4-methoxyphenyl adamantane-1-acetate (**4b**)*



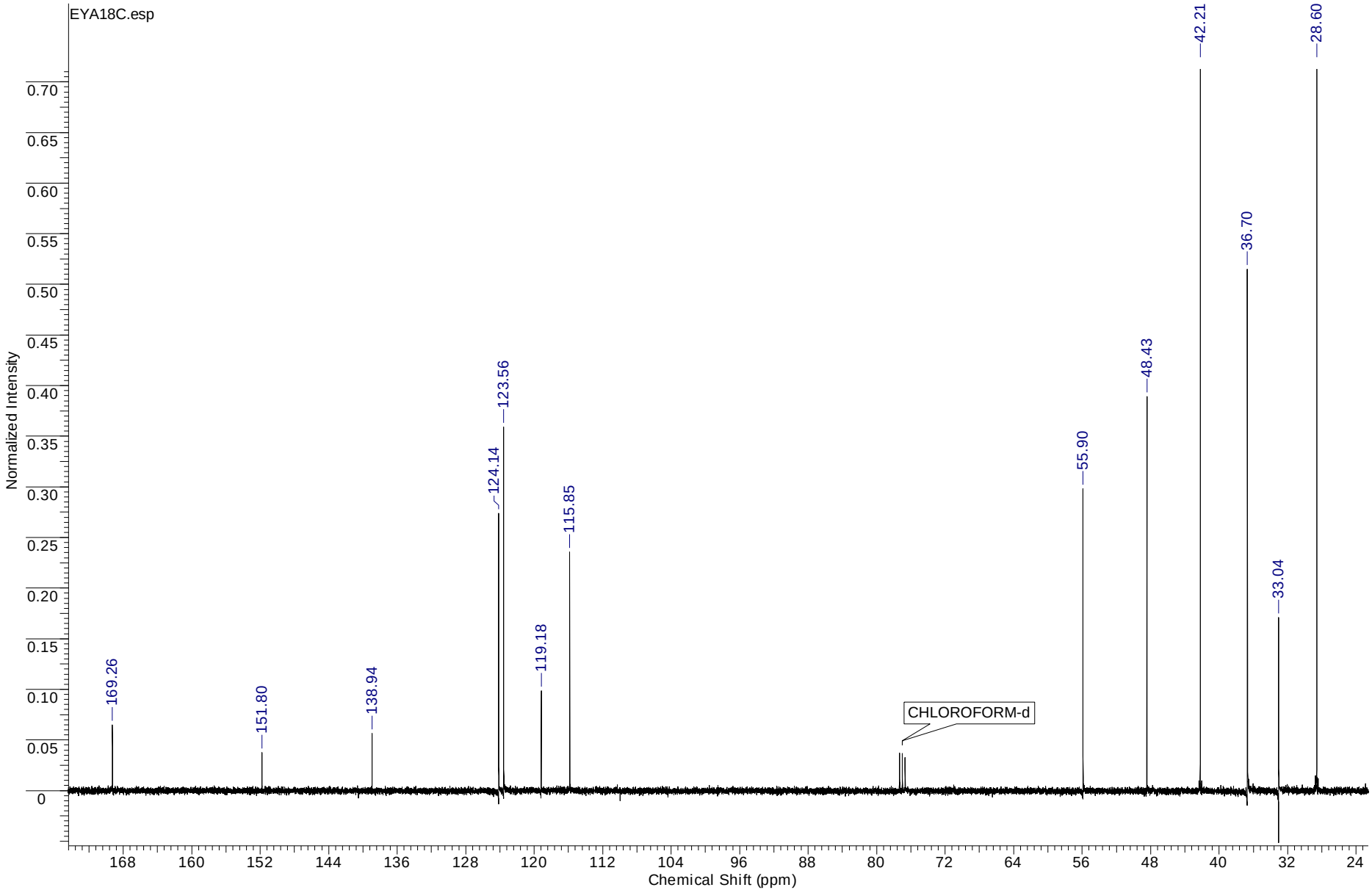
*^{13}C NMR spectrum 4-methoxyphenyl adamantane-1-acetate (**4b**)*



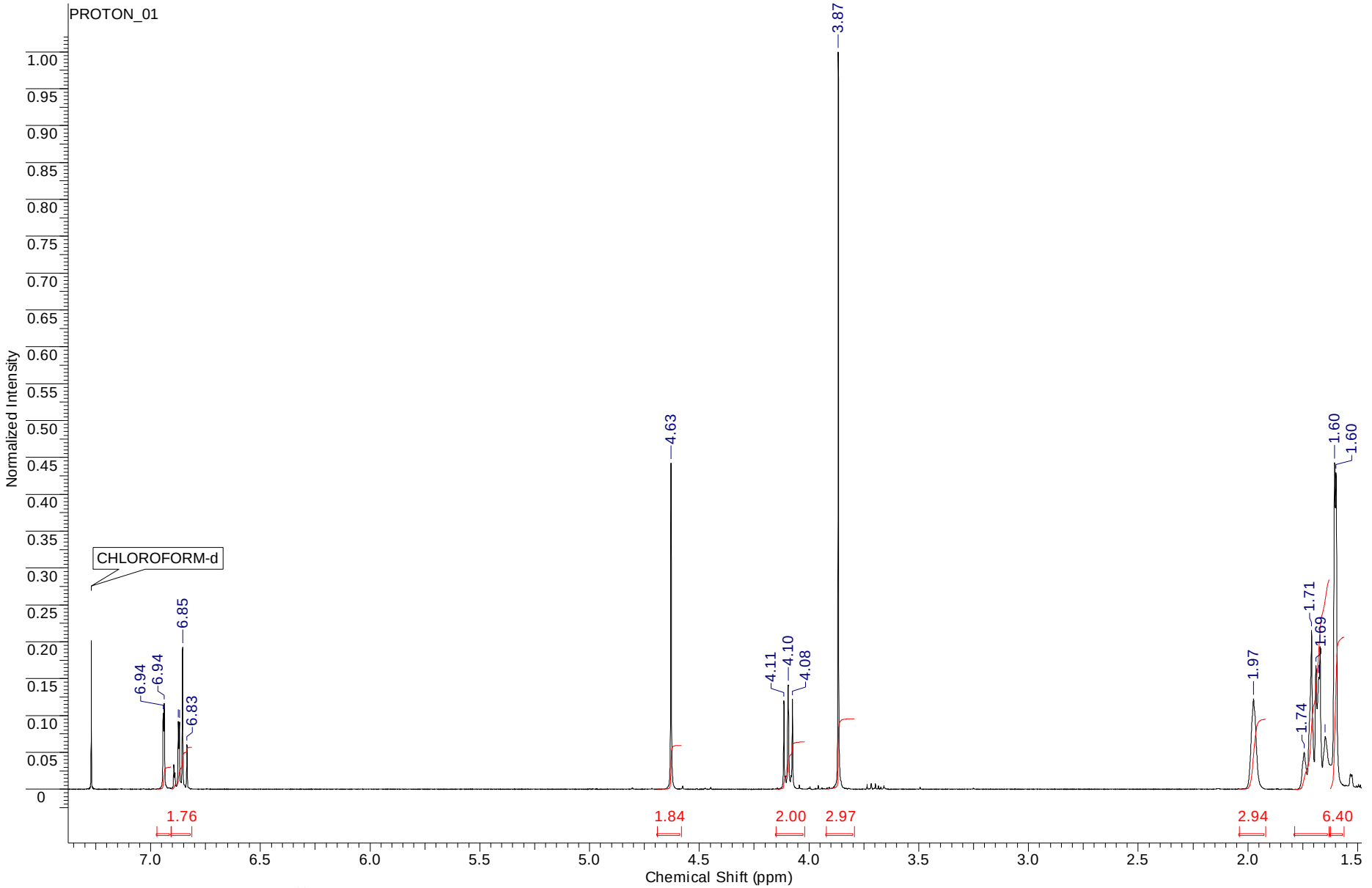
*^{1}H NMR spectrum of 4-bromo-2-methoxyphenyl adamantane-1-acetate (**4d**)*



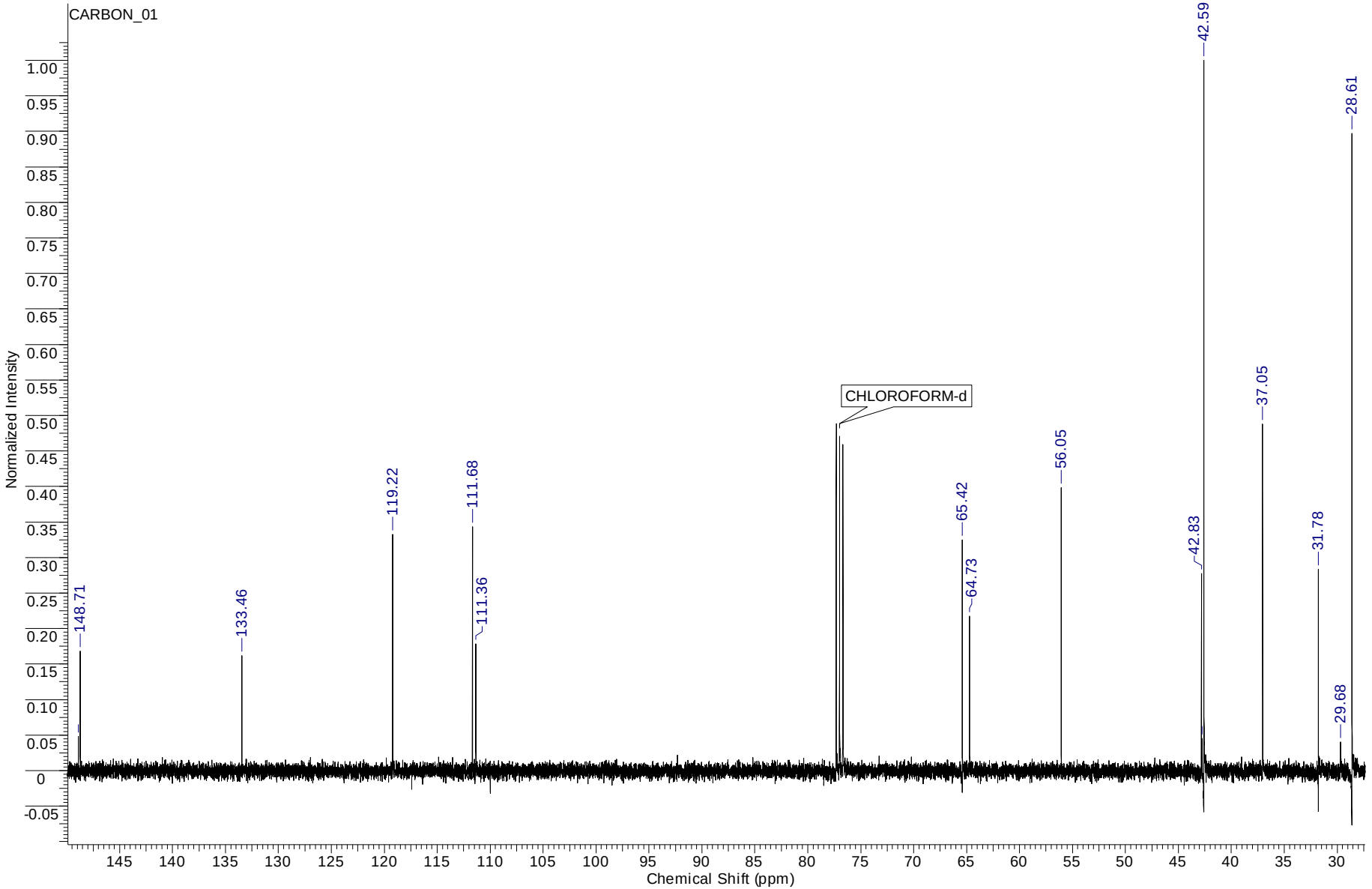
*^{13}C NMR spectrum 4-bromo-2-methoxyphenyl adamantane-1-acetate (**4d**)*



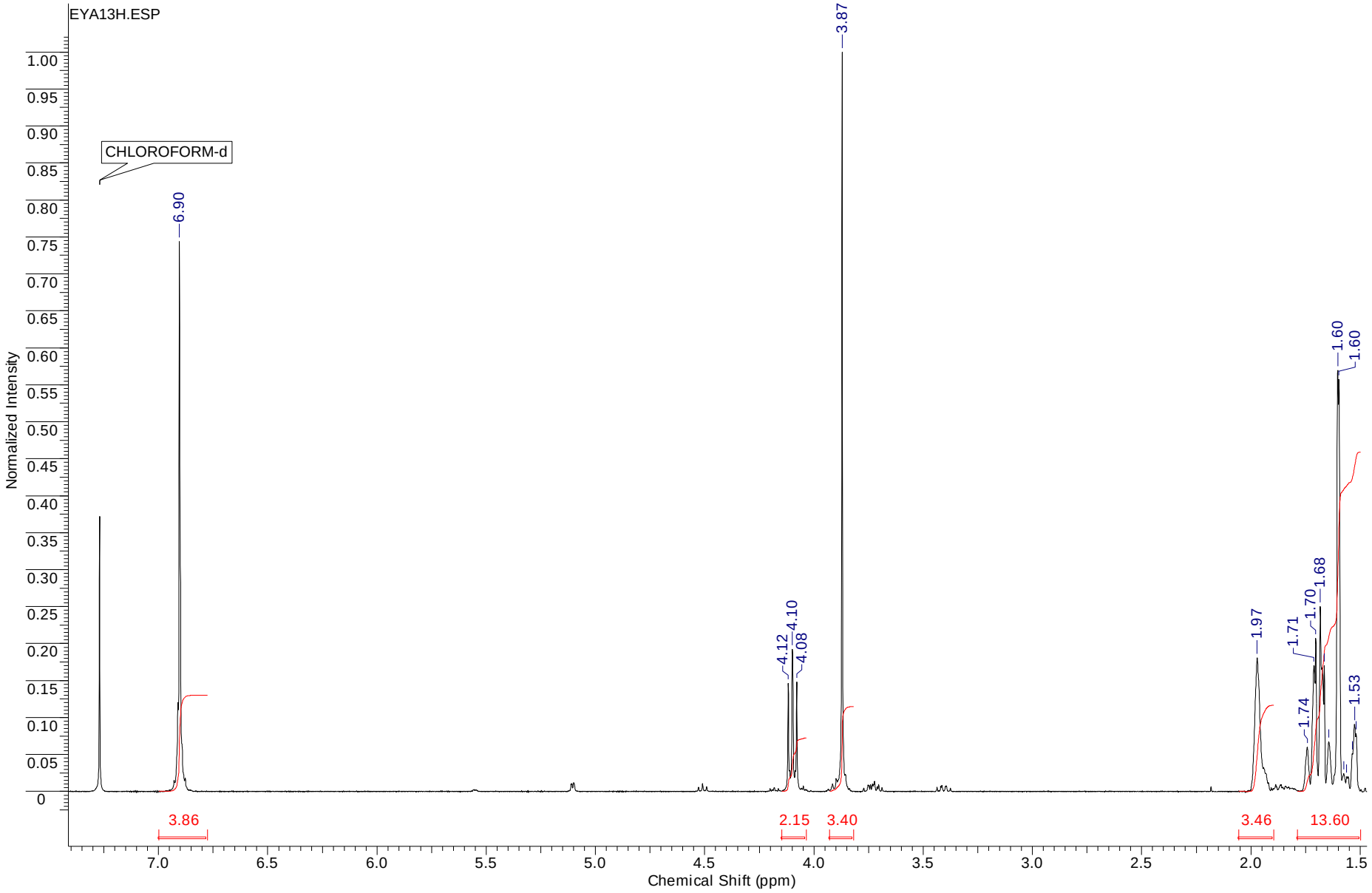
*^{1}H NMR spectrum of 1-[2-(5-hydroxymethyl-2-methoxyphenyl)ethyl]adamantane (**6**)*



^{13}C NMR spectrum 1-[2-(5-hydroxymethyl-2-methoxyphenyl)ethyl]adamantane ***(6)***



*^{1}H NMR spectrum of 1-[2-(2-methoxyphenoxy)ethyl]adamantane (**7**)*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6.90
3.87
4.12
4.10
4.08
1.97
1.71
1.70
1.68
1.74
1.60
1.60
1.53
3.86
2.15
3.40
3.46
13.60
Normalized Intensity
Chemical Shift (ppm)