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Synthesis and antiviral activity of tricyclic cis-fused pyrrolidines

Denis A. Tiunov, Anna A. Shtro, Svetlana S. Shmeleva, Dounya N. Ghorab, Daria N. Razgulyaeva, Ildar R. Iusupov, Evgeny R. Lukyanenko, Ekaterina V. Manasova and Alexander V. Kurkin

NMR spectra were recorded on Bruker Avance 400 instrument with operating frequency of 400 and 100 MHz, respectively, and calibrated using residual undeuterated chloroform (δH = 7.27 ppm) and $CDCl_3$ (δC = 77.16 ppm) as internal references. The following abbreviations are used to set multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. The purity of the final compounds was checked by liq-uid chromatography-mass-spectrometry (LCMS) in a Shimadzu LCMS-2010A using three types of detection systems: DAD, ELSD, and UV. High Resolution Mass Spectra (HRMS) were registered on a Sciex TripleTOF 5600+. We used commercial reagents and solvents without further purification. Reactions were monitored by thin-layer chromatography (TLC) performed on Merck TLC Silica gel plates (60 F254), using a UV light for visualization and basic aqueous potassium permanganate or iodine fumes as a developing agent. Flash column chromatography purification was performed using silica gel 60 (particle size 0.040–0.060 mm).

Cell cultures and viruses

Two cell lines were used: Vero (African green monkey kidney cells) and MRC-5 (a diploid cell line obtained from human fibroblasts sourced from lung tissue of a male fetus aborted at 14 weeks of gestation). Both cell lines were obtained from the cell culture collec-tion of the Laboratory of Chemotherapy of Viral Infections, Smorodintsev Research Insti-tute of Influenza, Ministry of Healthcare of Russian Federation.

Cell cultures were prepared by seeding 96-well flat-bottom culture plates with a con-centration of 3x104 cells/well a day prior to experimentation. The cultures were main-tained in DMEM growth medium (Biolot, Russia) supplemented with 10% fetal bovine serum (Biolot, Russia) and 20 μg/ml levofloxacin. Incubation was carried out at 37 °C in a 5% CO_2 atmosphere.

The following viruses were used in the study: cytomegalovirus strain AD169, herpes simplex virus type 1 strain EC, both were obtained from the working collection of the La-boratory of Chemotherapy for Viral Infections, Smorodintsev Research Institute of Influ-enza, Ministry of Healthcare of Russian Federation.

Assessment of compound cytotoxicity.

MTT assay was conducted to evaluate the cytotoxicity of the tested compounds. For this test uninfected cells were used. Initially, the growth medium was removed from the 96-well plate containing the cell culture. Subsequently, a series of 2-fold dilutions of the compounds (dissolved in DMSO) were added to the supporting medium (starting concen-tration 2000 μg/ml), while the control wells received medium without any compound. The 96-well plate containing the compound dilutions was then incubated for 3 days (for Vero cells) and 10 days (for MRC-5 cells).

Following the incubation period, the supporting medium was discarded and an MTT solution was added at a concentration of 0.5 μg/ml. The plate was incubated for 2 hours at 37 °C in a 5% CO_2 atmosphere. After the incubation, the MTT solution was removed and the formed precipitate was dissolved in DMSO. The absorbance of the resulting solution was measured at a wavelength of λ max = 630 nm using the Allsheng AMR-100 micro-plate reader (China). Based on data obtained, the CC_{50} (the compound concentration that induces 50% cell death) was determined using GraphPad Prism 5.0 software.

Antiviral activity assessment.

To assess the antiviral activity of the compounds against both viruses under investigation, we employed established non-toxic concentrations, with the highest being 1/2 CC50.

HSV1. To assess the antiviral activity of compounds against herpes simplex virus type 1(HSV1), a series of 3-fold dilutions of substances were prepared starting from 2 CC_{50} in Alpha-MEM medium (Biolot, Russia), supplemented with 20 μg/ml levofloxacin and 2% fetal bovine serum (Biolot, Russia).

The diluted test substances were then added to Vero cell culture at a volume of 100 μl per well in a 96-well plate, using a double concentration. Following this, 100 μl of the vi-rus with a concentration of at least 106 TID50/ml was introduced in seven 10-fold dilu-tions (10–1–10–7) were added and incubated for 1 hour at 37 °C in a 5% CO_2 atmosphere. The cells were then washed from the virus with supportive medium and test substance

dilutions were added to the wells, followed by adding 100 µl of supportive medium to each well. The plates were then incubated for 3 days at 37 °C with 5% CO_2 in a CO_2 incu-bator, after which cell viability was assessed using the MTT assay.

Totally, five different concentrations were used, and the virus titer was measured for each concentration. After that, a nonlinear regression analysis was performed to clarify the "virus titer" and "drug dose" relationship and the 50% inhibitory concentration (IC_{50}) was calculated from the results using GraphPad Prism 5.0 software. The selectivity index (SI) defined as the ratio of CC_{50} to IC_{50}, served as the criterion for the compound. Compounds with an SI greater than 8 are regarded as promising candidates for further inves-tigation.

CMV. To assess the antiviral activity of compounds against cytomegalovirus, a series of 3-fold dilutions of substances were prepared starting from 2 CC_{50} in Alpha-MEM me-dium (Biolot, Russia), supplemented with 20 µg/ml levofloxacin and 10% fetal bovine se-rum (Biolot, Russia).

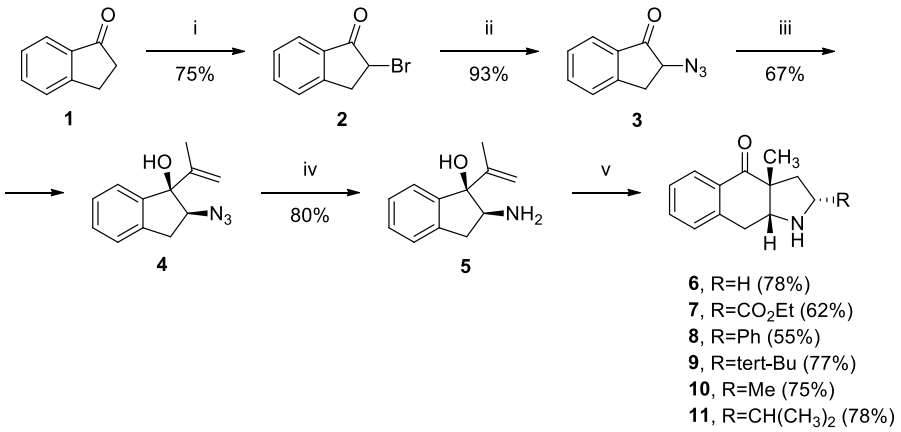
The prepared solutions of the test substances were added to MRC-5 cell at a volume of 100 µl per well in a 96-well plate, using a double concentration. Following this, 100 µl of the virus with a concentration of at least 106 TID50/ml was introduced in seven 10-fold dilutions (10–1–10–7) were added and incubated for 1 hour at 37 °C in a 5% CO_2 atmos-phere. The cells were then washed from the virus with supportive medium and test substance dilutions were added to the wells, followed by adding 100 µl of supportive medium to each well.

The plates were then incubated for 10 days at 37 °C in a 5% CO_2 atmosphere, and then cell viability was assessed using phase-contrast microscopy, specifically determining the decimal logarithm of the minimal virus dilution that induced cytopathic effect (CPE) for each concentration of the compound.

Totally, five different concentrations were used, and the virus titer was measured for each concentration. After that, a nonlinear regression analysis was performed to clarify the "virus titer" and "drug dose" relationship and the 50% inhibitory concentration (IC_{50}) was calculated from the results using GraphPad Prism 5.0 software. The selectivity index (SI) defined as the ratio of CC_{50} to IC_{50}, served as the criterion for the compound. Compounds with an SI greater than 8 are regarded as promising candidates for further inves-tigation.

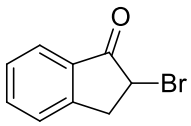
Statistical analysis

The results from multiple experiments are expressed as mean ± S.E. All data were analyzed using GraphPad Prism 5.0 software. one-way ANOVA followed by Dunnett's test were used for statistical comparisons between groups. Statistical significance was set at $p < 0.05$.



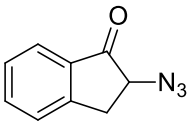
Scheme S1. *Reagents and conditions*:i, Br_2, Et_2O, room temperature, 0-25°C, 8 h; ii, NaN_3, MeCN, r.t., 8 h; iii, prop-1-en-2-ylmagnesium bromide, anhydrous $CeCl_3$, THF, -78C, 2 h; iv, $LiAlH_4$, THF, 0°C, 6 h; v, aldehyde, CSA (D-(+)-10-camphorsulfonic acid), Na_2SO_4, DCM (dichloromethane), r.t., 10 h.

2-Bromo-2,3-dihydro-1H-inden-1-one (**2**)



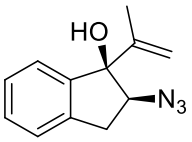
2,3-dihydro-1H-inden-1-one (50 g, 378 mmol, 1 eq) was dissolved in Et_2O (400 mL), cooled down to 0 °C, and Br_2 (19.38 mL, 378 mmol, 1 eq) was added dropwise. The reaction mixture was stirred overnight. The reaction mixture was then washed with a saturated solution of Na_2SO_3, a saturated solution of $NaHCO_3$, and brine. The organic phase was separated, dried over anhydrous Na_2SO_4, and the solvent was distilled under reduced pressure. The residue was purified by column chromatography. Yield: 59.89 g (75%), yellow oil. R_f = 0.7 in hexane/EtOAc (3:1). ^1H NMR (400 MHz, $CDCl_3$) δ: 3.44 (dd, 1 H), 3.85 (dd, *J* = 18.1, 7.5 Hz, 1 H), 4.67 (dd, *J* = 7.5, 3.2 Hz, 1 H), 7.40–7.50 (m, 2 H), 7.64–7.71 (m, 1 H), and 7.86 (d, J = 7.6 Hz, 1 H).

2-Azido-2,3-dihydro-1H-inden-1-one (**3**)



2-bromo-2,3-dihydro-1H-inden-1-one (60 g, 284 mmol, 1 eq) was dissolved in MeCN (285 mL), and NaN_3 (36.96 g, 568 mmol, 2 eq) was added and stirred overnight. The solvent was distilled under reduced pressure. The residue was diluted with water, extracted with EtOAc, and washed with brine. The organic phase was separated, dried over anhydrous Na_2SO_4, and the solvent was distilled under reduced pressure. The residue was purified by column chromatography. Yield: 45.79 g (93%), colorless oil. R_f = 0.7 in hexane/EtOAc (3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.94 (dd, 1 H), 3.51 (dd, *J* = 17.1, 8.2 Hz, 1 H), 4.33 (dd, *J* = 8.1, 4.6 Hz, 1 H), 7.40–7.48 (m, 2 H), 7.66 (td, *J* = 7.5, 1.2 Hz, 1 H), and 7.80 (d, *J* = 7.4 Hz, 1 H).

2-Azido-1-(prop-1-en-2-yl)-2,3-dihydro-1H-inden-1-ol (**4**)



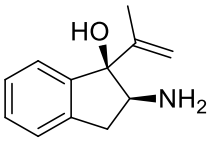
Anhydrous $CeCl_3$

$CeCl_3 \cdot 7H_2O$ (105.92 g, 210 mmol, 1 eq) and a magnetic stirrer were placed in a 3-neck round-bottom flask equipped with two glass stoppers and a glass stopcock. The flask was heated in an oil bath without stirring (90 < T < 100 °C). The oil level should be as high as possible, and the parts of the flask that are not covered with oil should be heated with a heat gun periodically under high vacuum (<1 Torr) for 1 h. Then the flask was heated un-der the same conditions but with slow stirring for one more hour. The white powder formed was $CeCl_3 \cdot H_2O$. Then the temperature was raised to 140–150 °C and maintained for 6–8 h. The flask was cooled to r.t. under high vacuum and filled with nitrogen.

Grignard Addition

Freshly distilled THF (583 mL) was added rapidly to the cooled anhydrous $CeCl_3$ prepared from $CeCl_3 \cdot 7H_2O$, and the resulting slurry was stirred under the nitrogen atmosphere at r.t. for 24 h. The $CeCl_3$ slurry in THF was cooled to −78 °C, and prop-1-en-2-ylmagnesium bromide (1M in THF, 315 mmol, 426 mL, 1.5 eq) was added dropwise at this temperature. The resulting mixture was stirred for 1 h at −78 °C before a solution of 2-azido-2,3-dihydro-1H-inden-1-one (36.31 g, 210 mmol, 1 eq) in THF (285 mL) was added dropwise at −78 °C. The mixture was stirred for 2 h at this temperature and then poured into a saturated NH_4Cl solution (1 L) containing acetic acid (24.37 mL, 315 mmol, 1.5 eq). The organic layer was separated, and the water layer was extracted with Et_2O. The combined organic phases were dried over Na_2SO_4, evaporated, and purified by column chromatography. Yield: 30.24 g (67%), light brown solid. R_f = 0.7 in hexane/EtOAc (3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.81 (d, *J* = 0.6 Hz, 3 H), 2.53 (s, 1 H), 3.06–3.29 (m, 2 H), 4.26 (t, *J* = 6.5 Hz, 1 H), 5.09 (d, *J* = 0.7 Hz, 1 H), 5.14 (t, *J* = 1.4 Hz, 1 H), 7.20–7.36 (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.4, 34.8, 67.2, 85.7, 114.4, 124.2, 124.9, 127.5, 129.1, 139.8, 143.3, and 144.7. HRMS (ESI): m/z for $C_{12}H_{13}N_3O$ $(M+Na)^+$: calcd 238.0951, found 238.0951.

2-Amino-1-(prop-1-en-2-yl)-2,3-dihydro-1H-inden-1-ol (**5**)

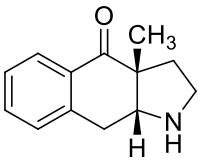


$LiAlH_4$ (7.85 g, 207 mmol, 1.5 eq) was suspended in THF (275 mL), cooled down to 0 °C, and a solution of 2-azido-1-(prop-1-en-2-yl)-2,3-dihydro-1H-inden-1-ol (29.68 g, 138 mmol, 1 eq) in THF (275 mL) was added dropwise; then the reaction mixture was stirred at 0 °C overnight. Following this, 7.85 mL of water, 7.85 mL of 15% NaOH solution, and 23.55 mL of water were added, and the resulting mixture was stirred for 30 min. The formed precipitate was filtered off, and the filtrate was evaporated and purified by column chromatography. Yield: 20.88 g (80%), light brown solid. R_f = 0.4 in DCM/MeOH (NH_3) (20:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.70 (s, 3 H), 2.73 (dd, *J* = 15.3, 7.7 Hz, 1 H), 3.18 (dd, *J* = 15.4, 7.2 Hz, 1 H), 3.68 (t, *J* = 7.5 Hz, 1 H), 5.09 (dd, *J* = 2.0, 1.5 Hz, 1 H), 5.23 (dd, *J* = 1.4, 0.7 Hz, 1 H), and 7.20–7.27 (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.4, 29.6, 61.9, 83.2, 112.6, 124.3, 124.5, 126.6, 128.0, 141.2, 144.6, and 145.8. HRMS (ESI): m/z for $C_{12}H_{15}NO$ $(M+H)^+$: calcd 190.1226, found 190.1222.

General procedure for tandem aza-Cope/Mannich

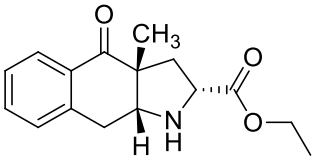
2-amino-1-(prop-1-en-2-yl)-2,3-dihydro-1H-inden-1-ol (2 g, 10.6 mmol, 1 eq) was dissolved DCM (100 mL), and the corresponding aldehyde (21.2 mmol, 2 eq), Na_2SO_4 (10.51 g, 74.2 mmol, 7 eq), CSA (2.21 g, 9.5 mmol, 0.9 eq) were added; the resulting mixture stirred at r.t. overnight. The reaction mixture was poured into a saturated solution of $NaHCO_3$ and extracted with EtOAc. The organic phase was separated and washed with water and brine. The organic phase was then dried over anhydrous Na_2SO_4, and the solvent was distilled under reduced pressure. Residue was purified by column chromatography.

(3a*SR*,9a*SR*)-3a-methyl-3,3a,9,9a-tetrahydro-1H-benzo[f]indol-4(2H)-one (**6**).



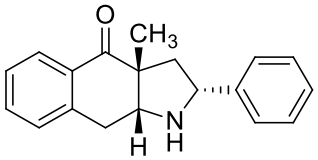
Yield 78% (1.66 g), brown oil, R_f = 0.5 in hexane/EtOAc (3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.31 (s, 3 H), 1.77 (ddd, *J* = 12.8, 9.6, 7.2 Hz, 1 H), 2.17 (br. s., 1 H), 2.64 (ddd, *J* = 12.9, 8.3, 4.6 Hz, 1 H), 2.85 - 2.94 (m, 1 H), 2.96 - 3.03 (m, 1 H), 3.08 (dd, *J* = 17.3, 3.1 Hz, 1 H), 3.25 - 3.33 (m, 1 H), 3.41 (dd, *J* = 4.3, 3.3 Hz, 1 H), 7.25 (d, *J* = 7.6 Hz, 1 H), 7.33 (t, *J* = 7.6 Hz, 1 H), 7.51 (td, *J* = 7.5, 1.4 Hz, 1 H), 8.02 (dd, *J* = 7.8, 1.0 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.1, 28.7, 36.8, 42.7, 51.8, 62.6, 126.6, 127.2, 129.0, 130.2, 133.4, 139.0, 201.2. HRMS (ESI): m/z for $C_{13}H_{15}NO$ $(M+H)^+$: calcd 202.1226, found 202.1225.

(2*SR*,3a*SR*,9a*SR*)-ethyl 3a-methyl-4-oxo-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]indole-2-carboxylate (**7**).



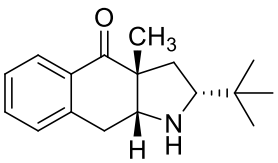
Yield 62% (1.79 g), brown oil, R_f = 0.5 in hexane/EtOAc (3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.17 (t, *J* = 7.1 Hz, 3 H), 1.26 (s, 3 H), 2.10 (dd, *J* = 13.3, 10.3 Hz, 1 H), 2.41 (br. s., 1 H), 2.84 (dd, *J* = 13.4, 4.0 Hz, 1 H), 3.09 - 3.17 (m, 1 H), 3.25 - 3.34 (m, 1 H), 3.37 - 3.45 (m, 1 H), 3.79 (dd, *J* = 10.3, 3.7 Hz, 1 H), 3.97 - 4.12 (m, 2 H), 7.24 (d, *J* = 7.6 Hz, 1 H), 7.31 (t, *J* = 7.5 Hz, 1 H), 7.46 - 7.53 (m, 1 H), 7.97 (d, *J* = 7.8 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.5, 19.9, 28.4, 41.5, 51.7, 56.6, 60.9, 63.2, 126.8, 127.4, 129.2, 130.0, 133.5, 138.5, 173.6, 200.3. HRMS (ESI): m/z for $C_{16}H_{19}NO_3$ $(M+H)^+$: calcd 274.1438, found 274.1435.

(2*SR*,3a*SR*,9a*SR*)-3a-methyl-2-phenyl-3,3a,9,9a-tetrahydro-1H-benzo[f]indol-4(2H)-one (**8**).



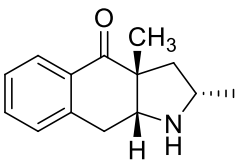
Yield 55% (1.61 g), brown oil, R_f = 0.5 in hexane/EtOAc (3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.35 (s, 3 H), 2.24 (dd, *J* = 13.5, 9.3 Hz, 1 H), 2.62 (dd, *J* = 13.4, 6.5 Hz, 1 H), 3.11 (dd, *J* = 17.4, 2.8 Hz, 1 H), 3.35 (dd, *J* = 17.4, 4.5 Hz, 1 H), 3.59 (dd, *J* = 4.4, 2.9 Hz, 1 H), 4.31 (dd, *J* = 9.3, 6.6 Hz, 1 H), 7.13–7.27 (m, 6 H), 7.35 (t, *J* = 7.6 Hz, 1 H), 7.52 (td, *J* = 7.5, 1.4 Hz, 1 H), 8.05 (dd, *J* = 7.8, 1.0 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.9, 29.7, 45.4, 51.8, 59.2, 63.4, 126.6 (s, 3 C), 126.7, 127.5, 128.1 (s, 2 C), 129.0, 130.7, 133.4, 139.6, 144.0, 202.2. HRMS (ESI): m/z for $C_{19}H_{19}NO$ $(M+H)^+$: calcd 278.1539, found 278.1539.

(2*SR*,3a*SR*,9a*SR*)-2-(tert-butyl)-3a-methyl-3,3a,9,9a-tetrahydro-1H-benzo[f]indol-4(2H)-one (**9**).



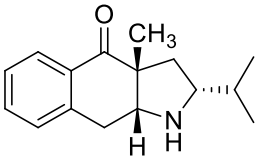
Yield 77% (2.09 g), brown oil, R_f = 0.5 in hexane/EtOAc (3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.71 (s, 9 H), 1.26 (s, 3 H), 1.51 - 1.76 (m, 2 H), 2.41 (dd, *J* = 13.6, 6.7 Hz, 1 H), 2.94 (dd, *J* = 9.4, 6.8 Hz, 1 H), 3.03 (dd, *J* = 17.3, 2.7 Hz, 1 H), 3.26 (dd, *J* = 17.3, 4.2 Hz, 1 H), 3.35 - 3.41 (m, 1 H), 7.22 (d, *J* = 7.5 Hz, 1 H), 7.30 (t, *J* = 7.5 Hz, 1 H), 7.44 - 7.51 (m, 1 H), 7.99 (d, *J* = 7.8 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.1, 25.7, 29.5, 32.6, 38.4, 51.3, 62.8, 65.1, 126.3, 127.2, 128.8, 130.6, 133.0, 139.5, 202.4. HRMS (ESI): m/z for $C_{17}H_{23}NO$ $(M+H)^+$: calcd 258.1852, found 258.1852.

(2*SR*,3a*RS*,9a*RS*)-2,3a-dimethyl-3,3a,9,9a-tetrahydro-1H-benzo[f]indol-4(2H)-one (**10**).



Yield 75% (1.71 g), brown oil, R_f = 0.5 in hexane/EtOAc (3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.01 (d, *J* = 6.4 Hz, 3 H), 1.27 (s, 3 H), 1.61 (br. s, 1 H), 1.94 (dd, *J* = 13.2, 8.7 Hz, 1 H), 2.18 – 2.26 (m, 1 H), 3.04 (dd, *J* = 17.4, 2.5 Hz, 1 H), 3.22 – 3.36 (m, 2 H), 3.39 – 3.43 (m, 1 H), 7.24 (d, *J* = 7.8 Hz, 1 H), 7.33 (t, *J* = 7.9 Hz, 1 H), 7.50 (t, *J* = 7.5 Hz, 1 H), 8.01 (d, *J* = 7.7 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.9, 21.8, 29.2, 45.0, 51.0, 52.0, 63.5, 126.7, 127.5, 129.1, 130.4, 133.4, 139.1, 202.3. HRMS (ESI): m/z for $C_{14}H_{17}NO$ $(M+H)^+$: calcd 216.1383, found 216.1386.

(2*RS*,3a*RS*,9a*RS*)-2-isopropyl-3a-methyl-3,3a,9,9a-tetrahydro-1H-benzo[f]indol-4(2H)-one (**11**).



Yield 78% (2.01 g), brown oil, R_f = 0.5 in hexane/EtOAc (3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.99 (dd, *J* = 7.8, 1.0 Hz, 1 H), 7.49 (td, *J* = 7.5, 1.4 Hz, 1 H), 7.31 (t, *J* = 7.5 Hz, 1 H), 7.23 (d, *J* = 7.6 Hz, 1 H), 3.39 (dd, *J* = 4.6, 2.8 Hz, 1 H), 3.20 - 3.32 (m, 1 H),

3.04 (dd, *J* = 17.4, 2.8 Hz, 1 H), 2.78 - 2.89 (m, 1 H), 2.32 (dd, *J* = 13.4, 6.7 Hz, 1 H), 1.83 (dd, *J* = 13.4, 8.8 Hz, 1 H), 1.66 (br. s., 1 H), 1.29 - 1.41 (m, 1 H), 1.27 (s, 3 H), 0.80 (dd, *J* = 6.6, 3.5 Hz, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.4, 20.0, 21.4, 29.9, 33.7, 41.5, 51.8, 62.7, 63.4, 126.8, 127.7, 129.2, 130.8, 133.5, 139.8, 202.9. HRMS (ESI): m/z for $C_{16}H_{21}NO$ $(M+H)^+$: calcd 244.1696, found 244.1694.

NMR spectra

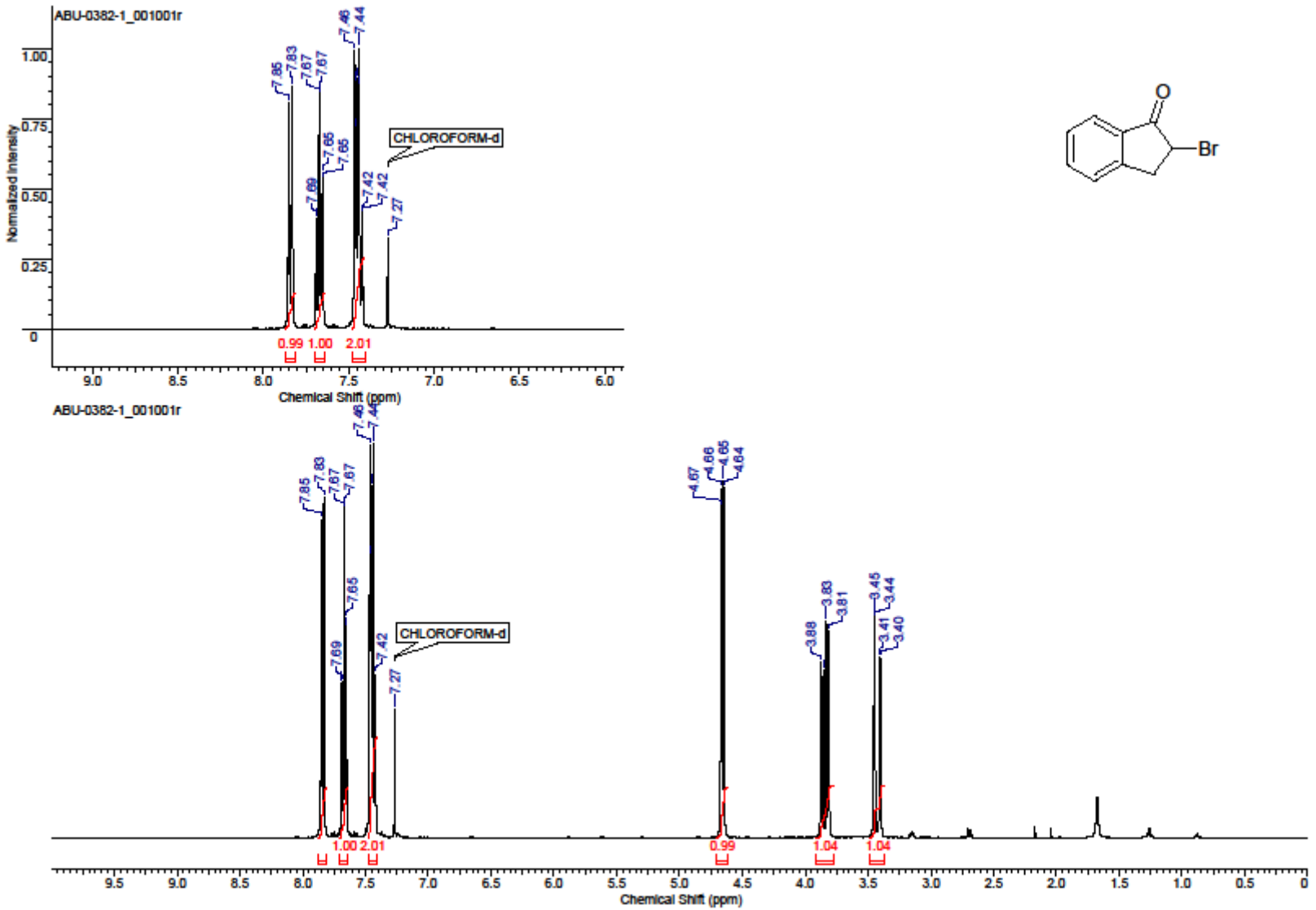


Figure S1. [1]H-NMR of compound **2**

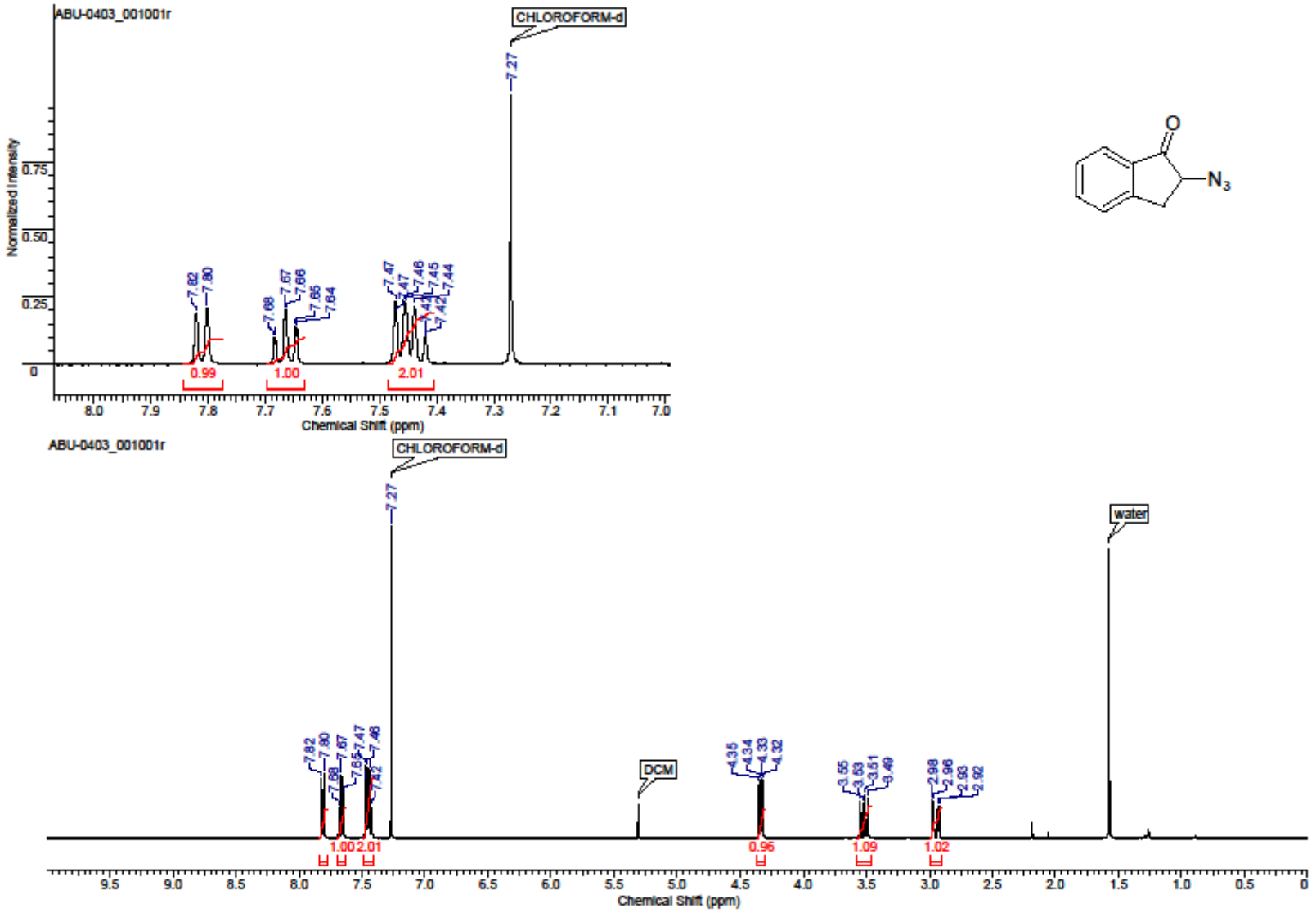


Figure S2. ^{1}H-NMR of compound **3**

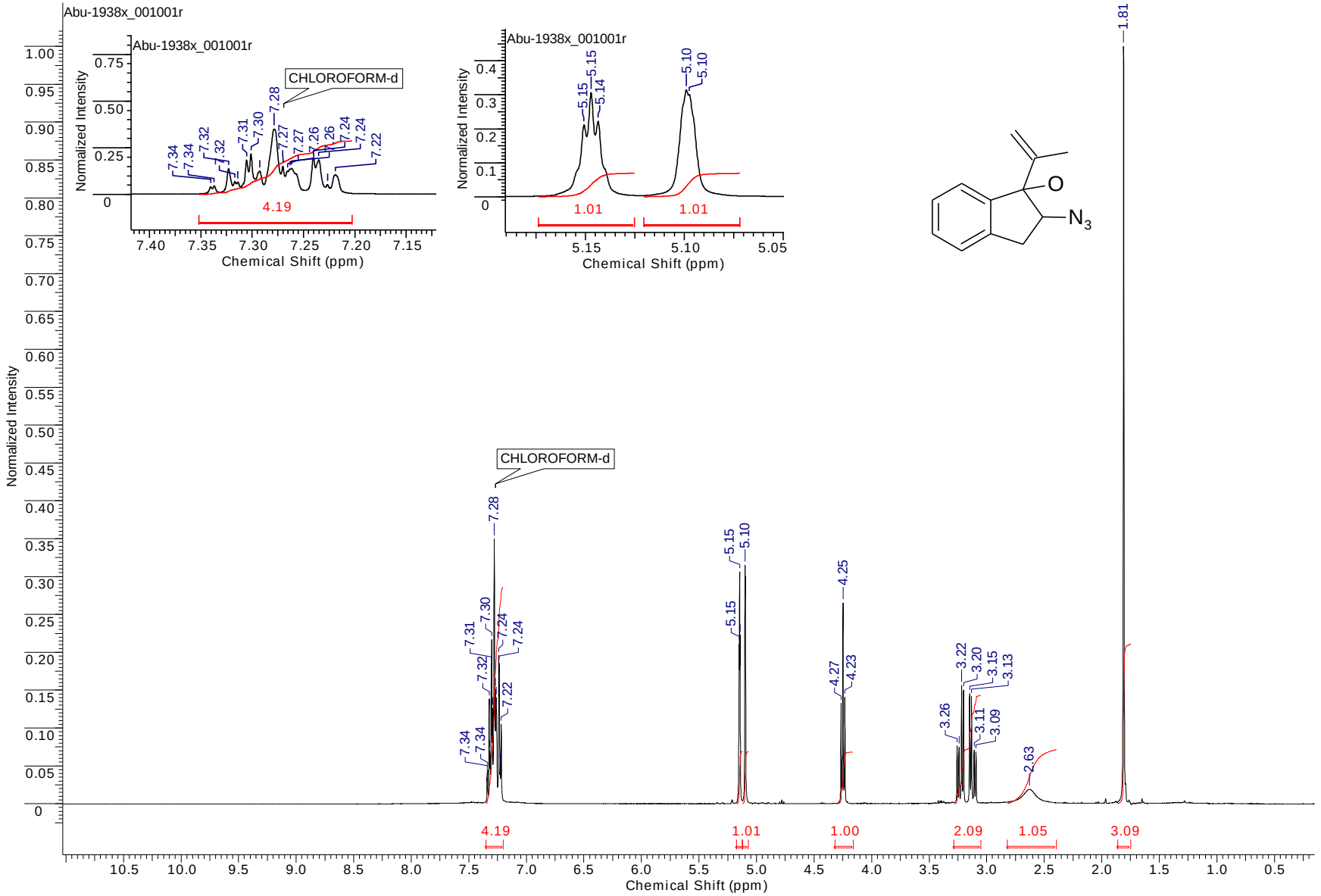


Figure S3. ^{1}H-NMR of compound **4**

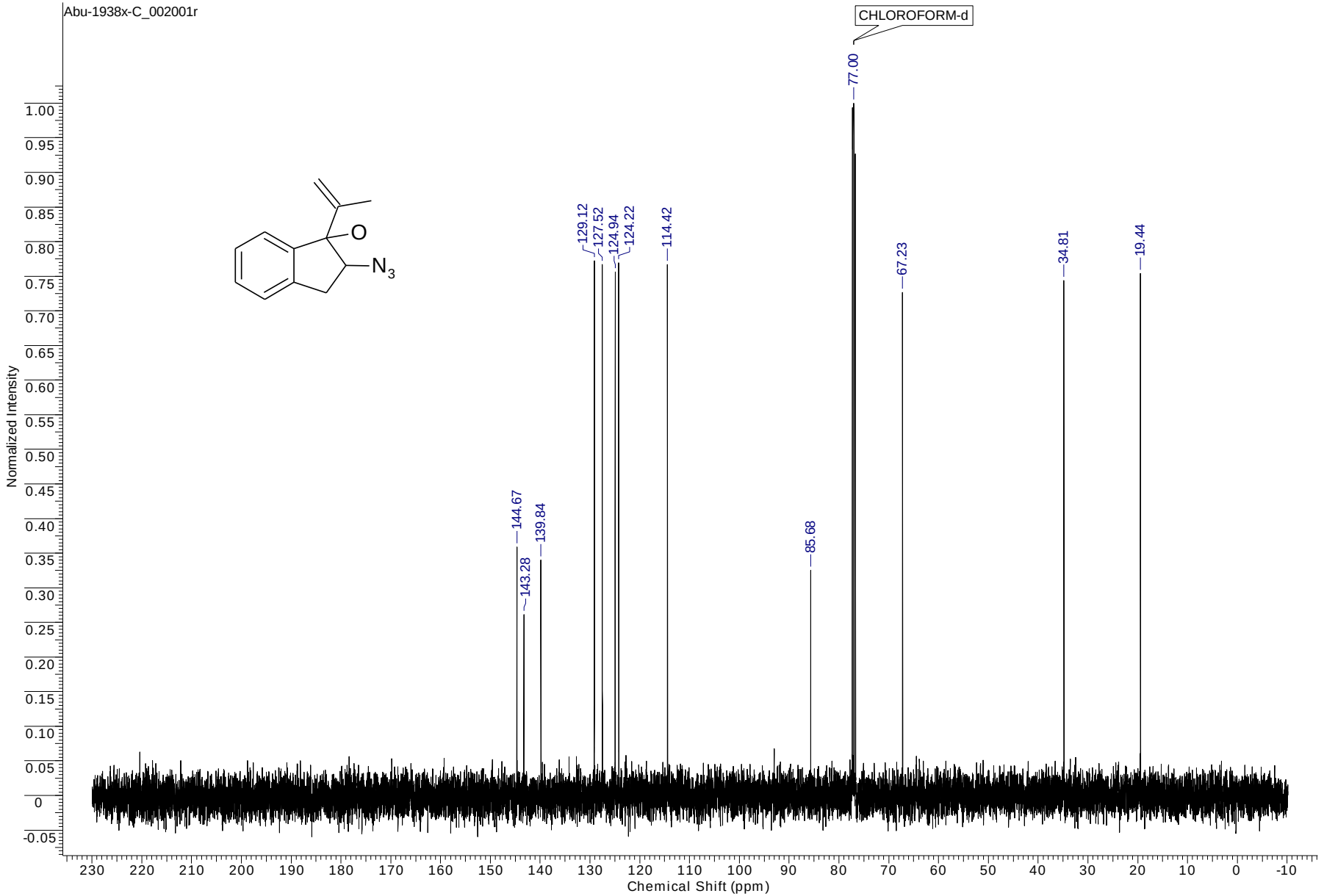


Figure S4. ^{13}C-NMR of compound **4**

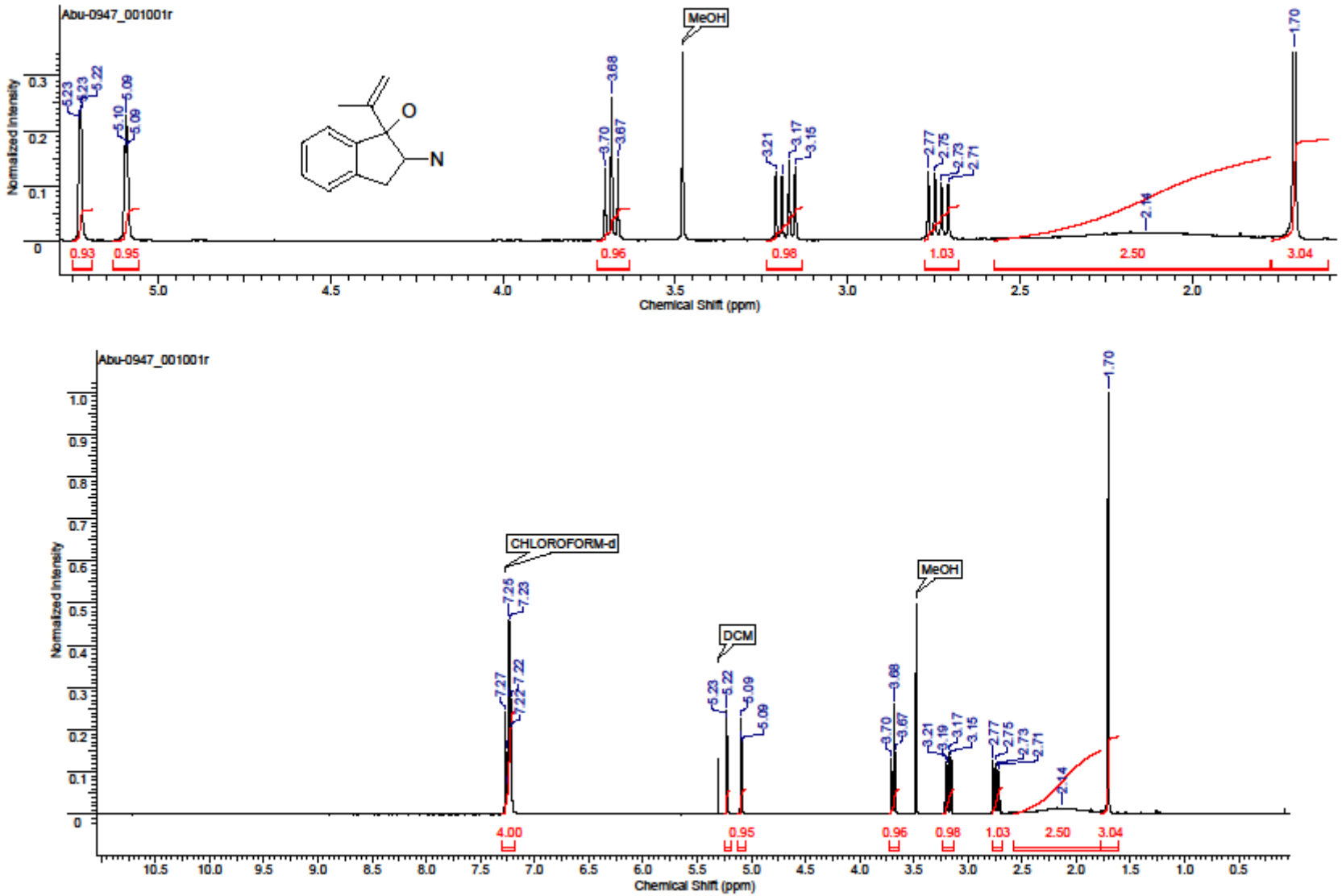


Figure S5. ^{1}H-NMR of compound **5**

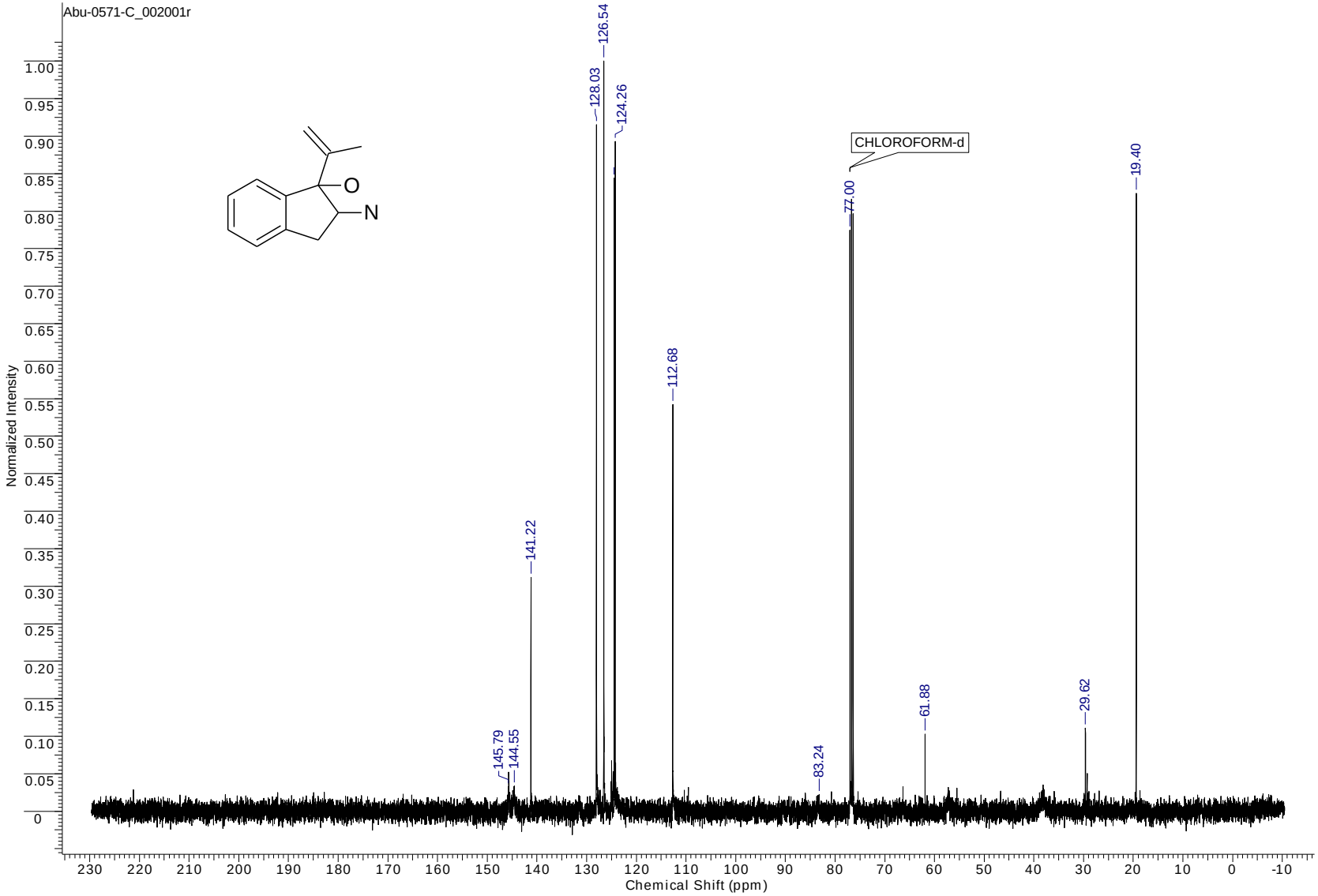


Figure S6. ^{13}C-NMR of compound **5**

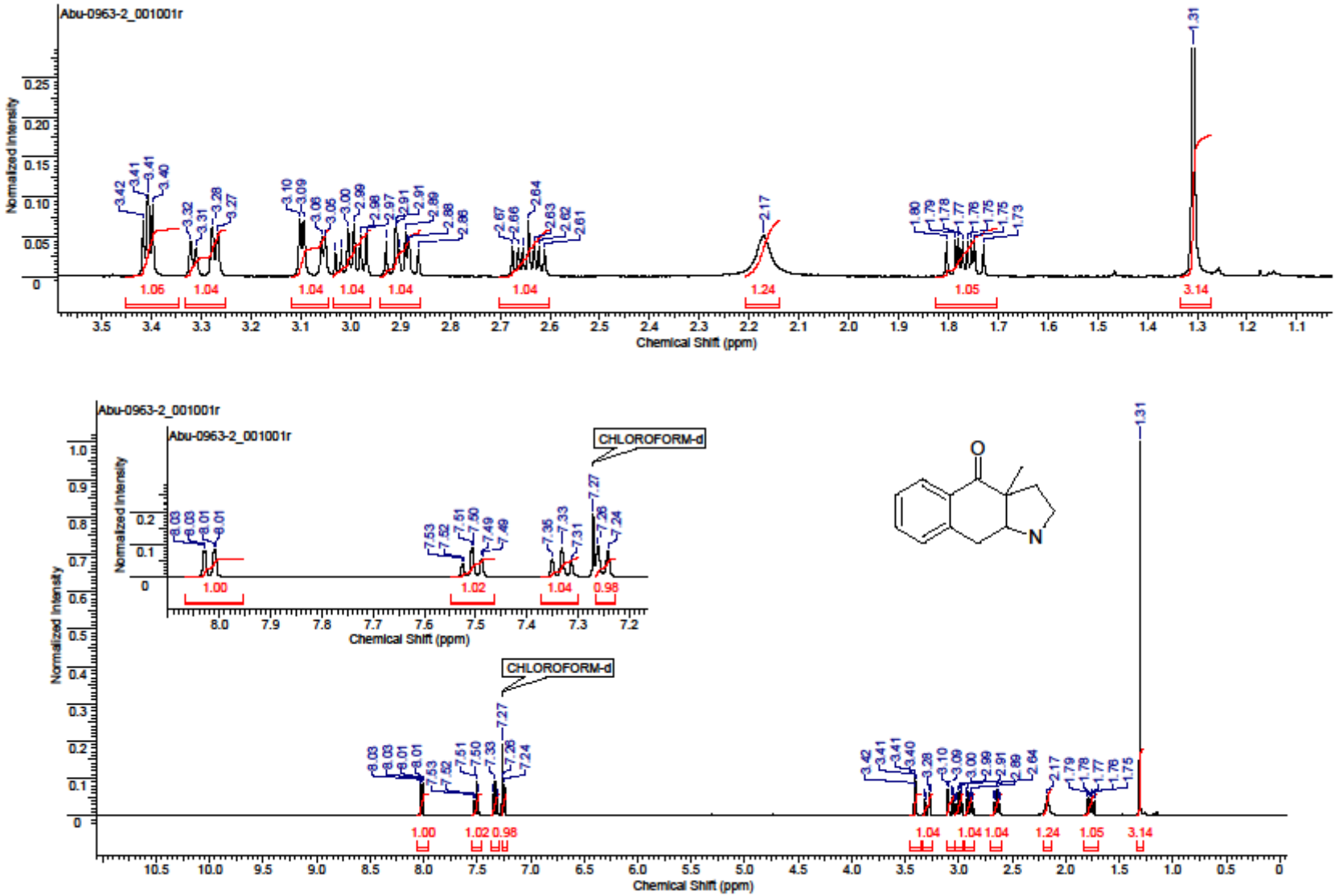


Figure S7. ^{1}H-NMR of compound **6**

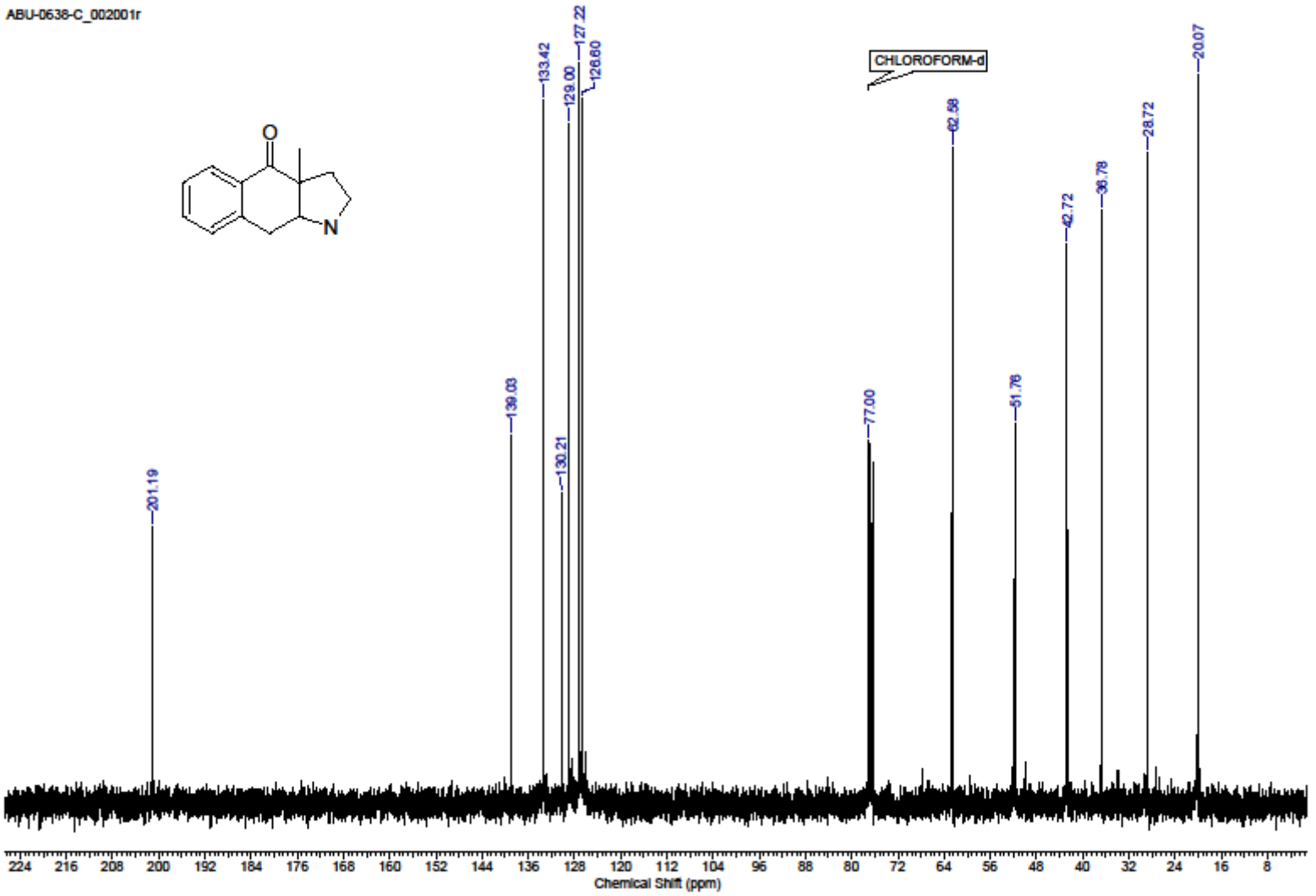


Figure S8. ^{13}C-NMR of compound **6**

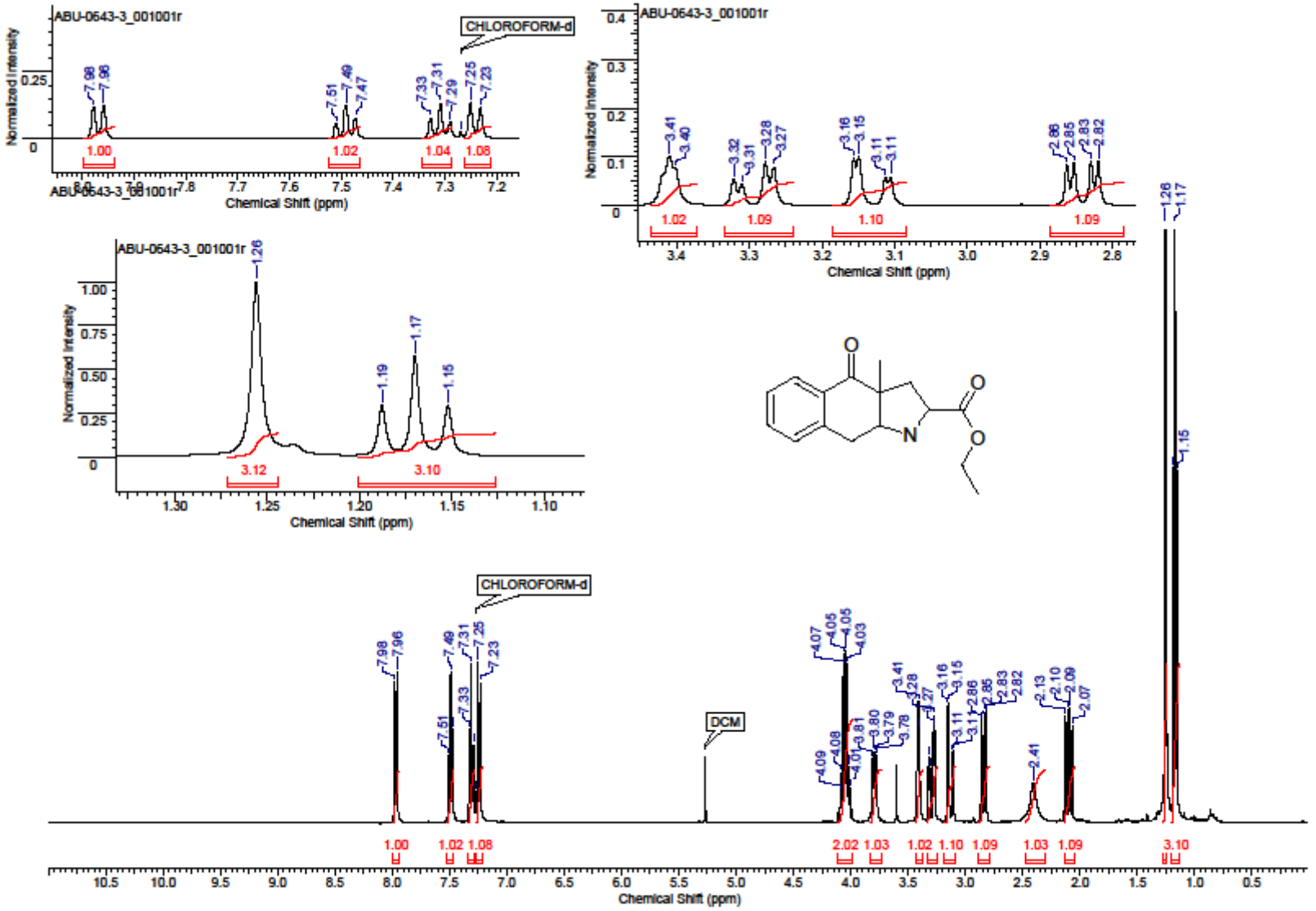


Figure S9. ^{1}H-NMR of compound **7**

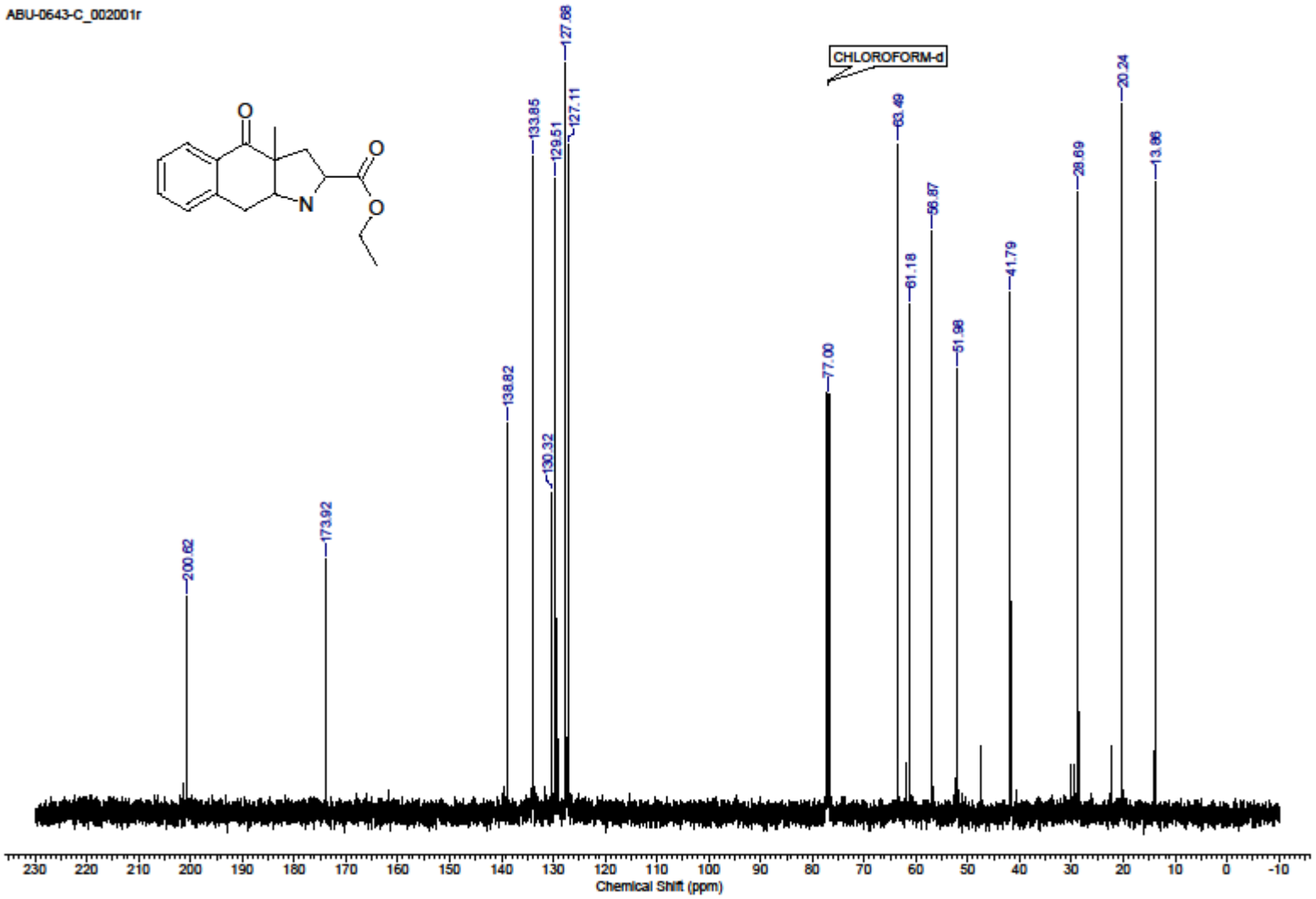


Figure S10. ^{13}C-NMR of compound **7**

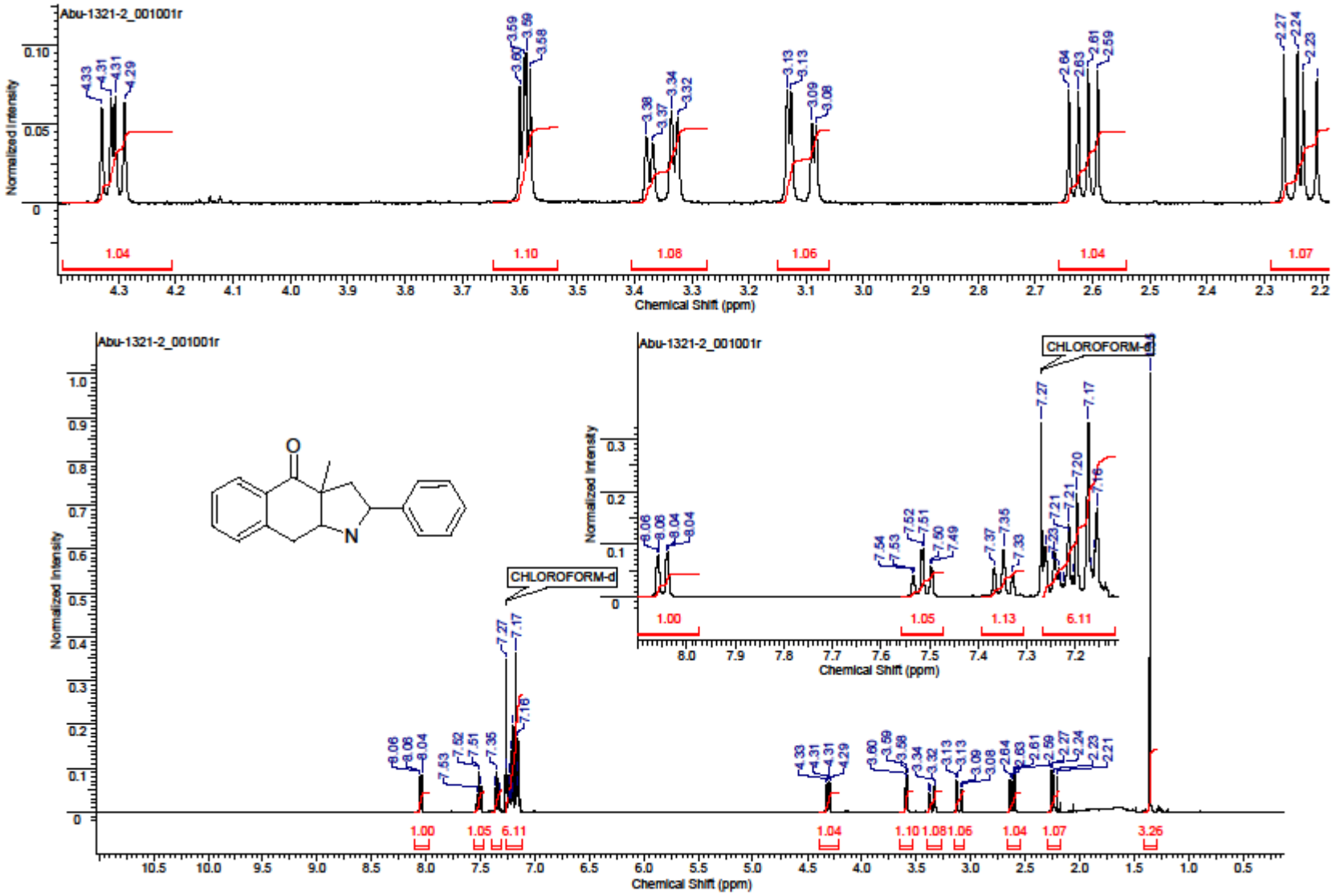


Figure S11. ^{1}H-NMR of compound **8**

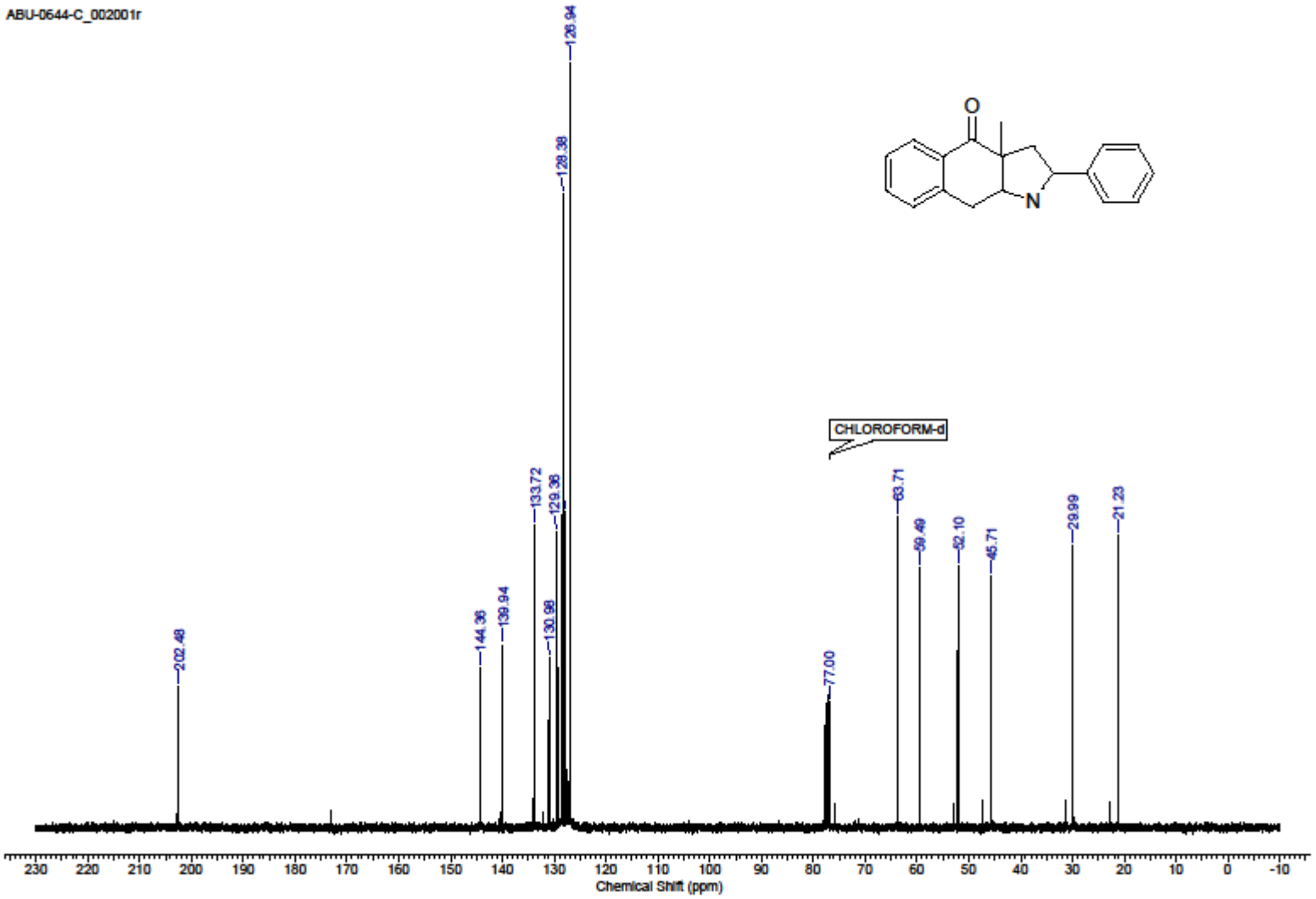


Figure S12. ^{13}C-NMR of compound **8**

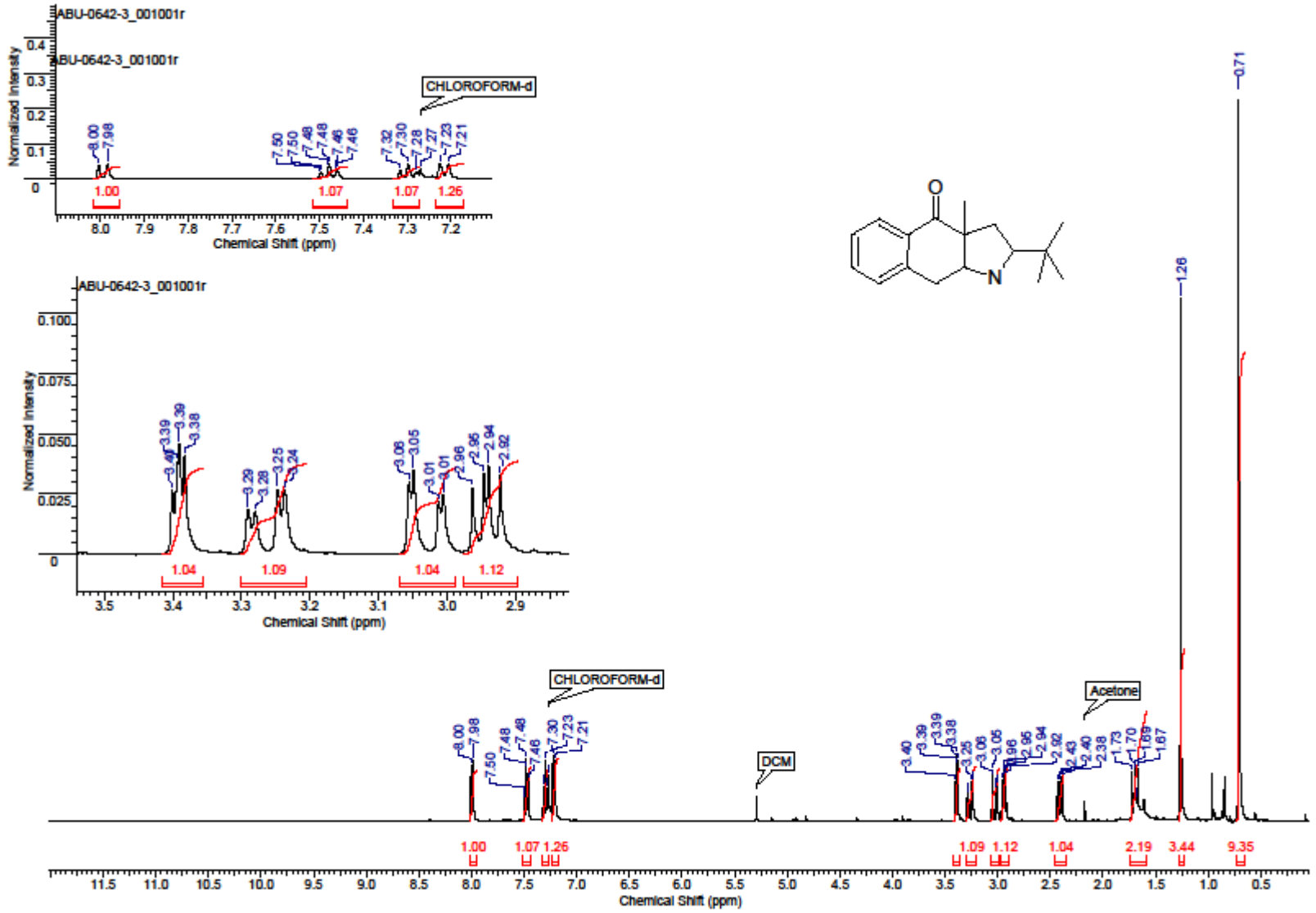


Figure S13. ^{1}H-NMR of compound **9**

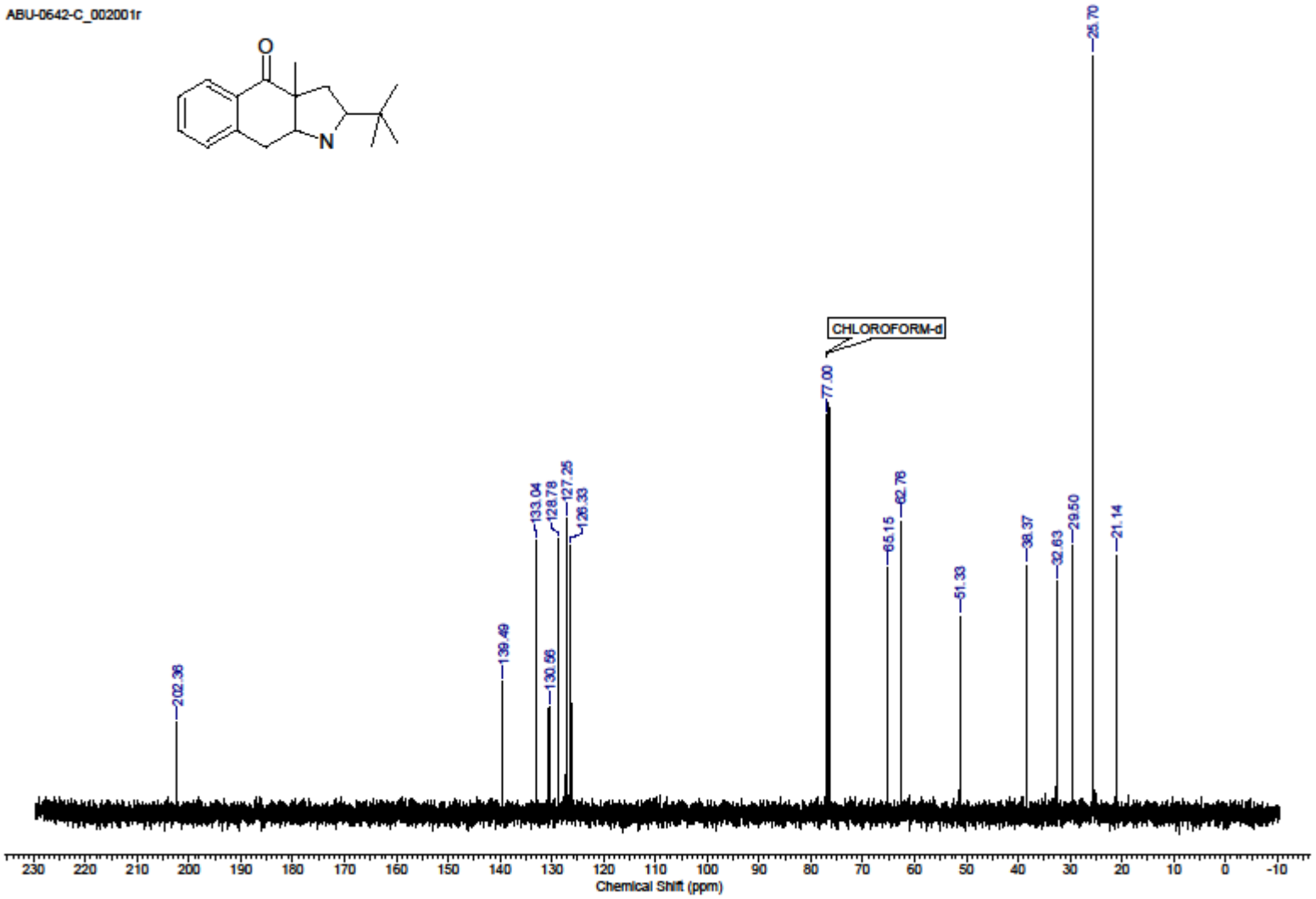


Figure S14. ^{13}C-NMR of compound **9**

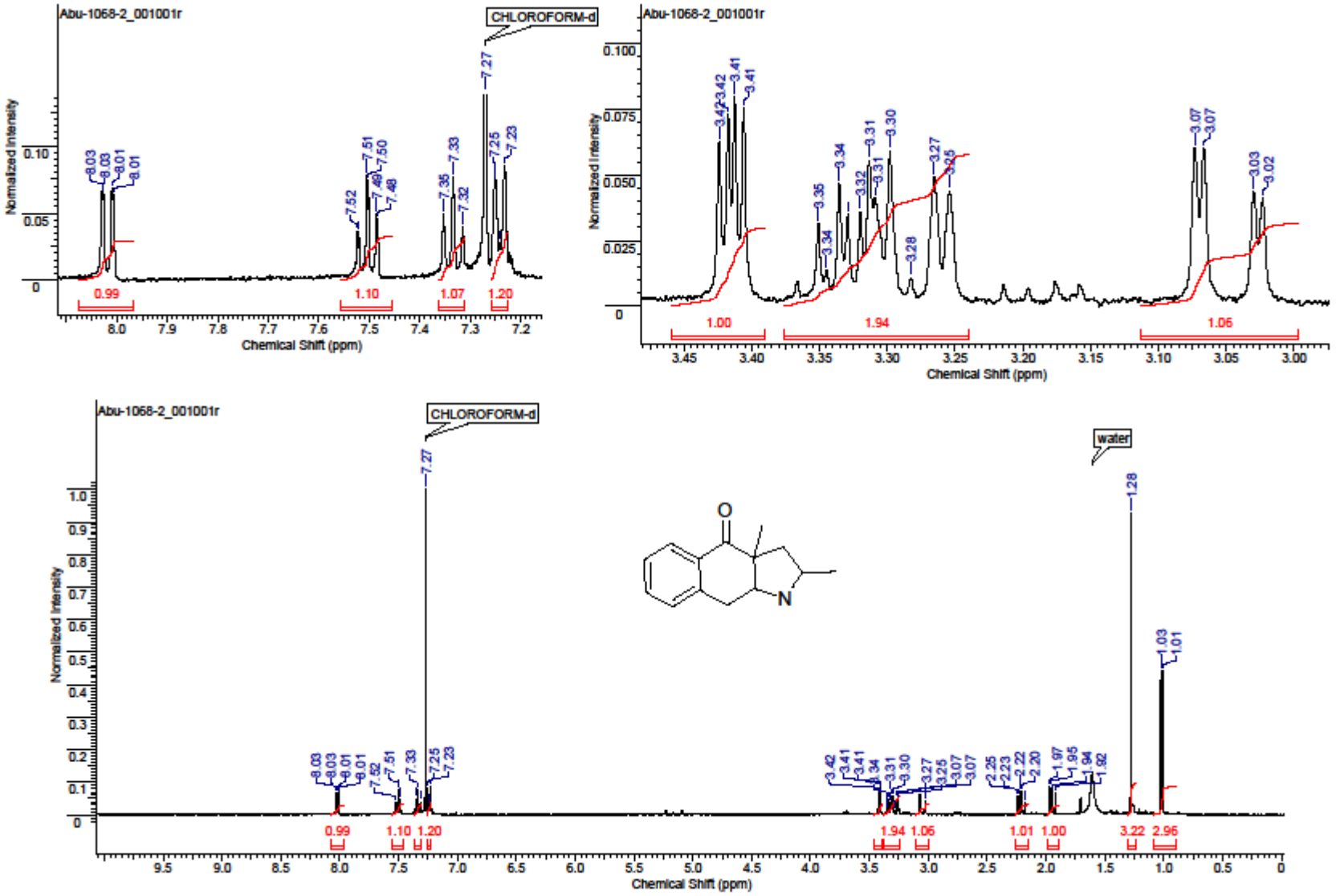


Figure S15. ^{1}H-NMR of compound **10**

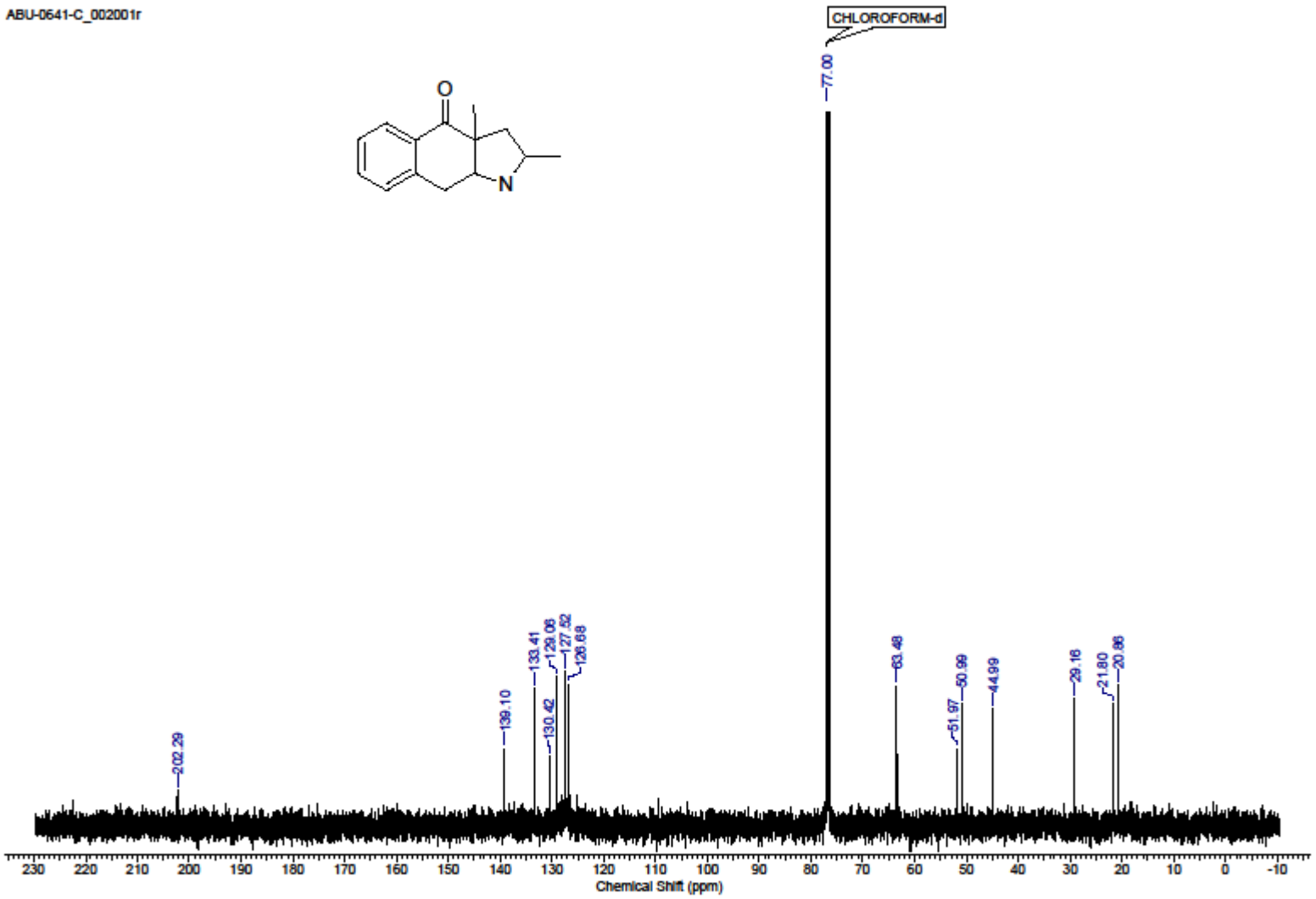


Figure S16. ^{13}C-NMR of compound **10**

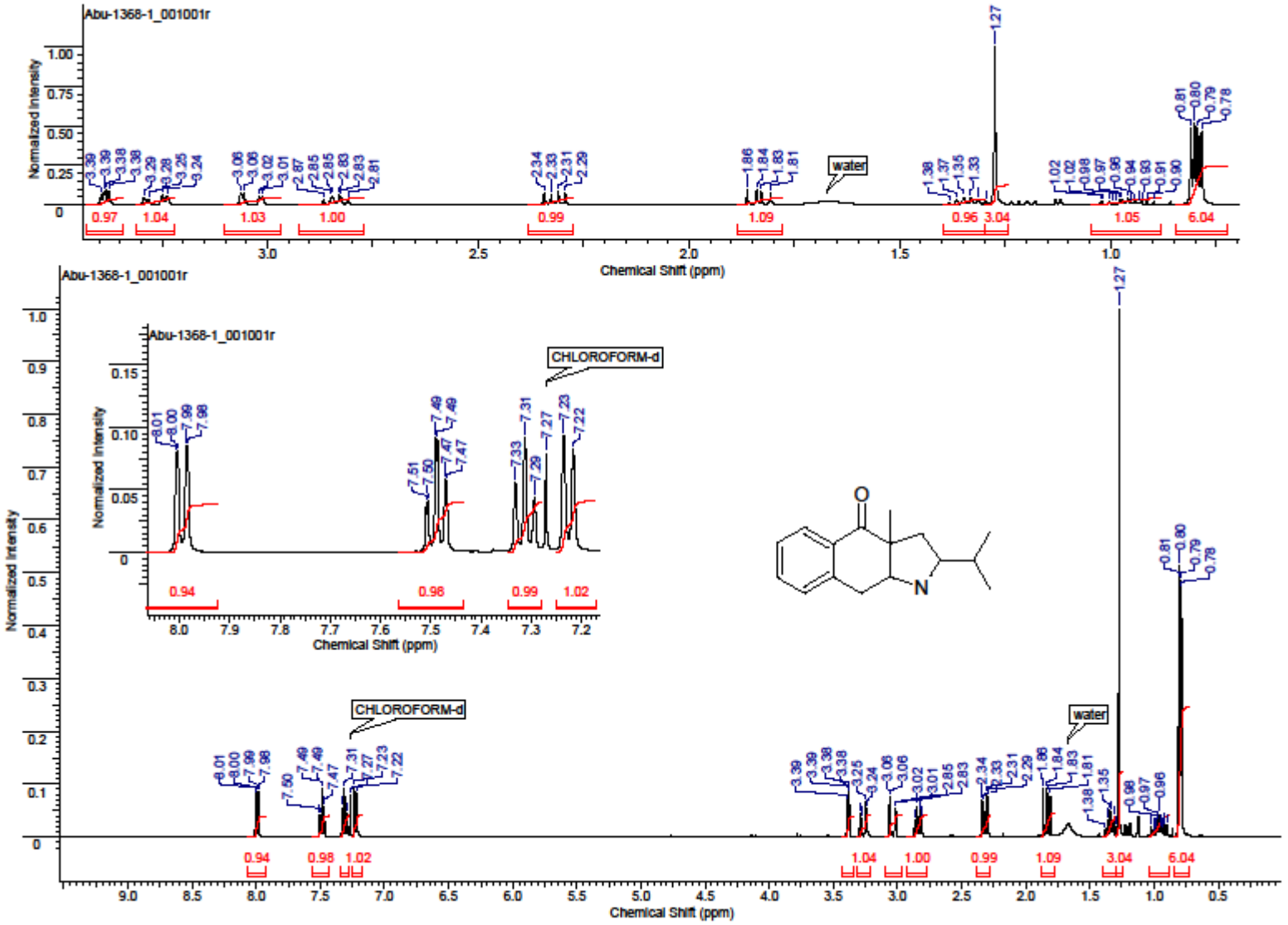


Figure S17. ^{1}H-NMR of compound **11**

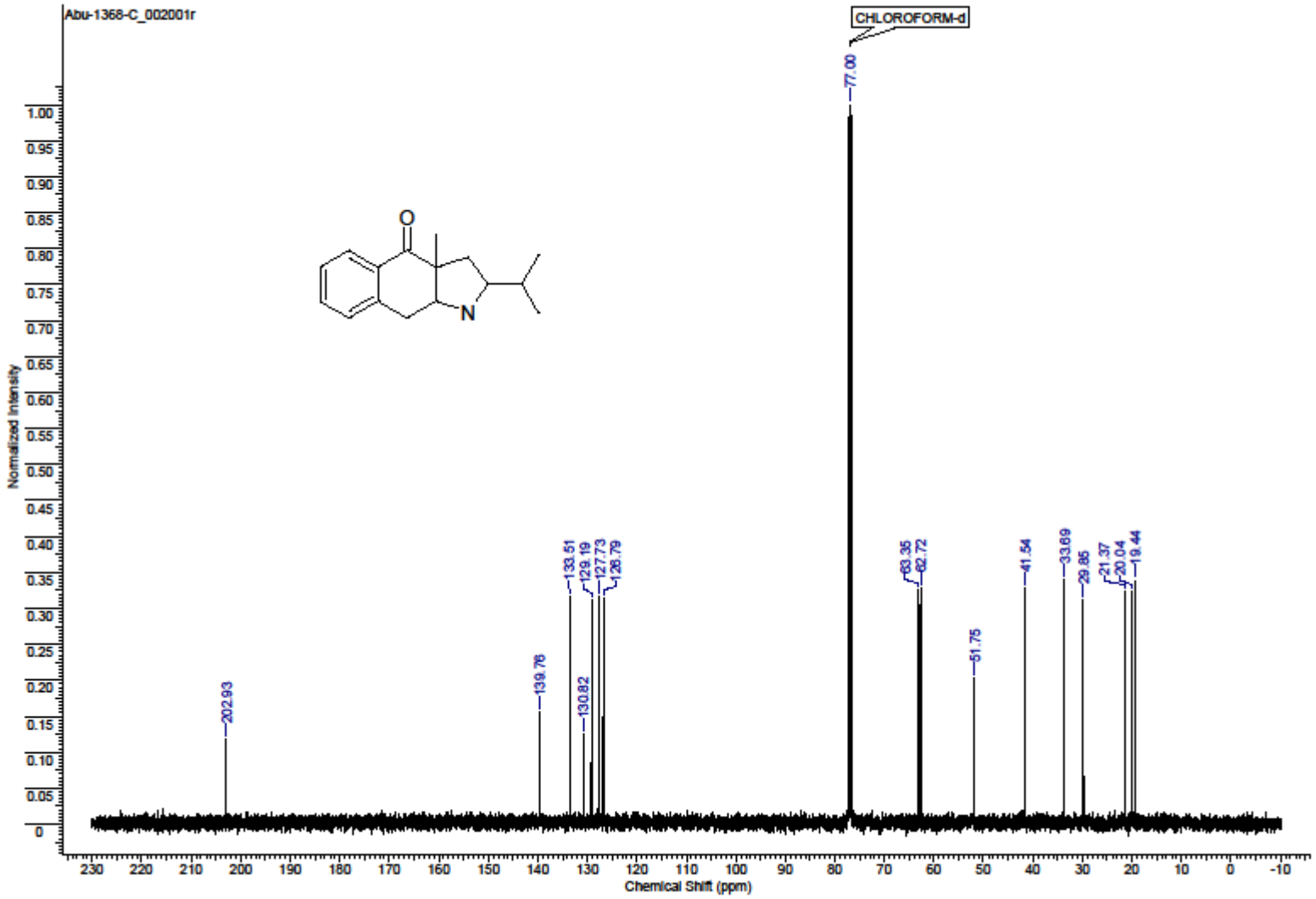


Figure S18. ^{13}C-NMR of compound **11**

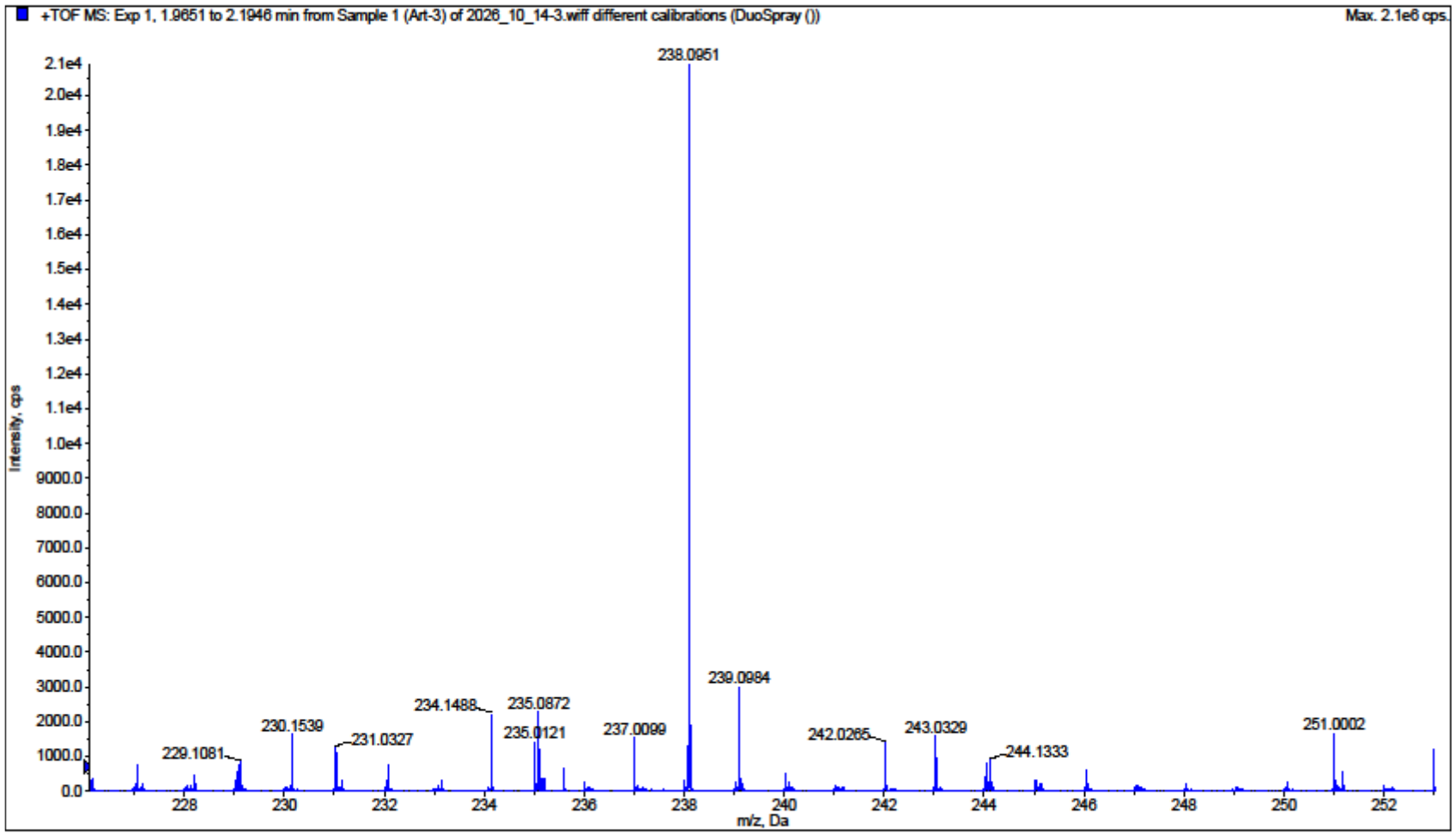


Figure S19. HRMS of compound **4**

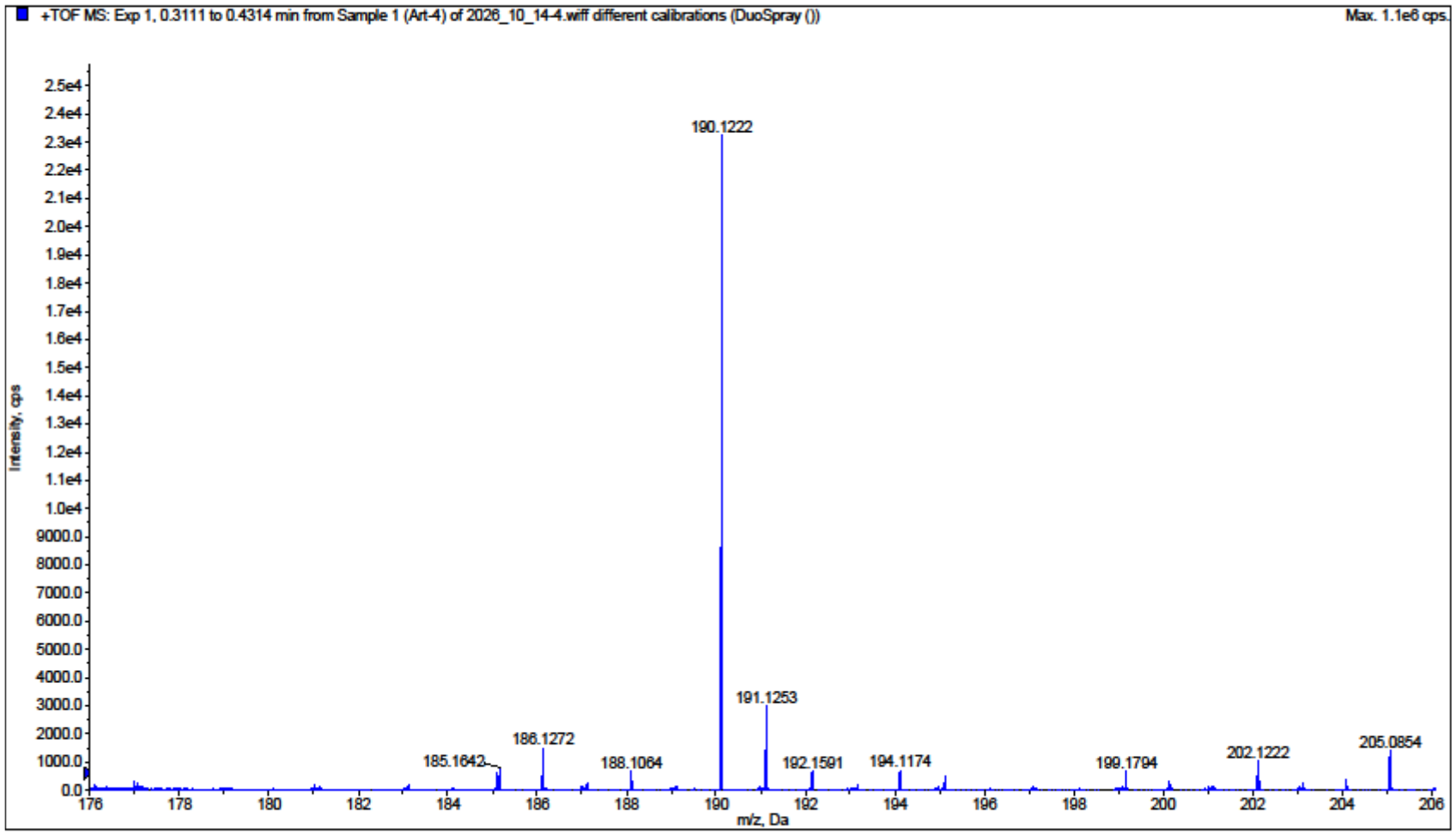


Figure S20. HRMS of compound **5**

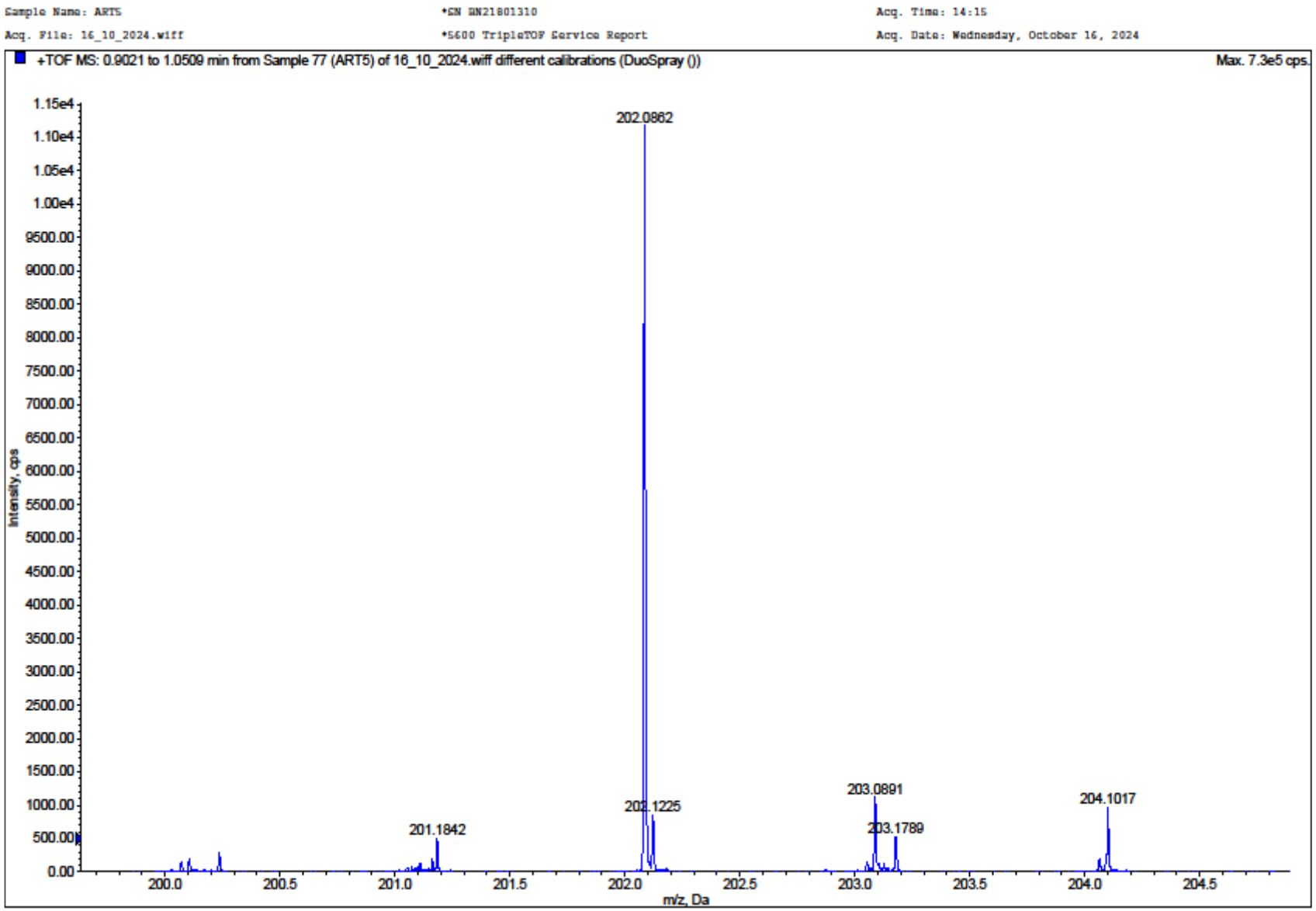


Figure S21. HRMS of compound **6**

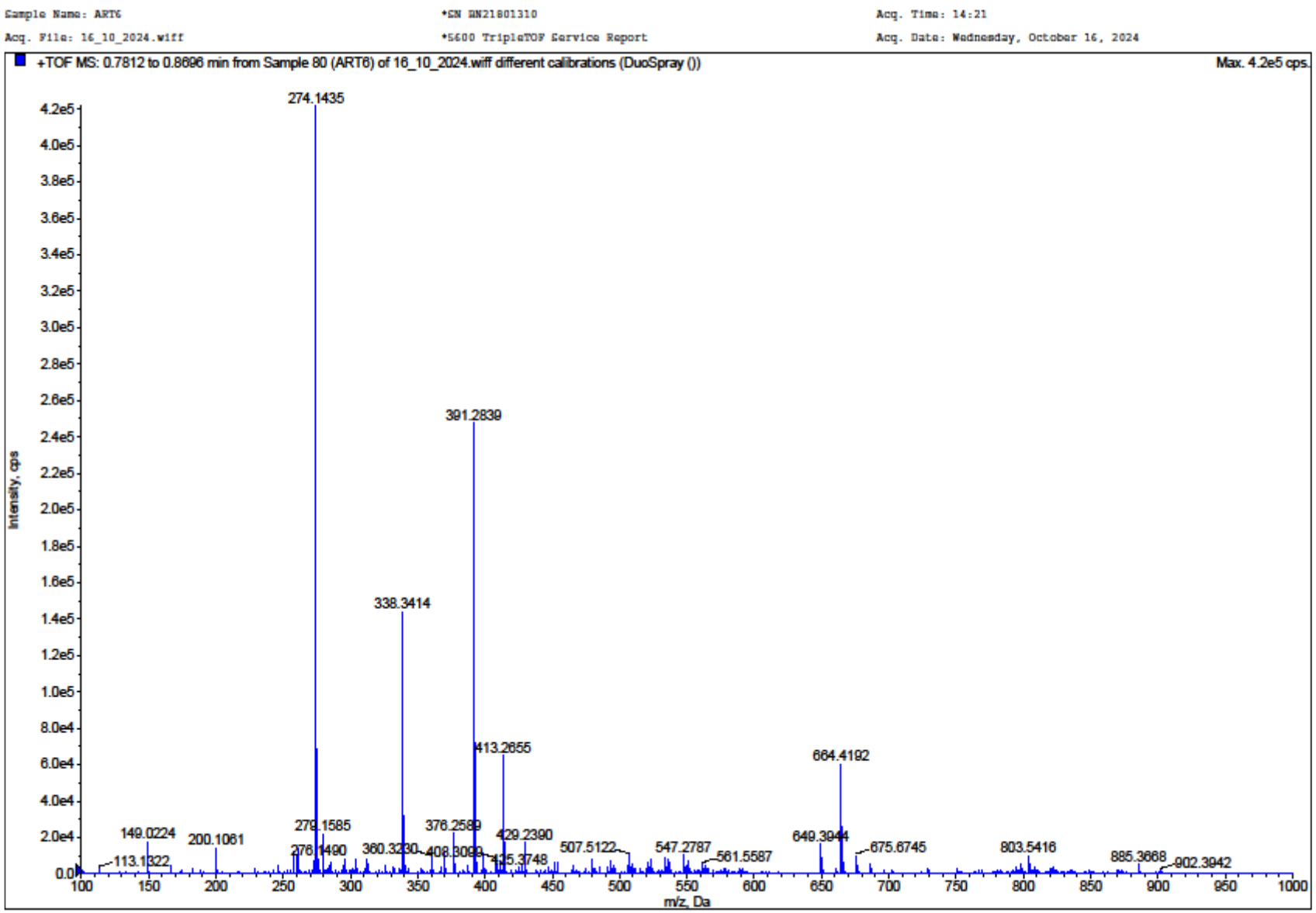


Figure S22. HRMS of compound **7**

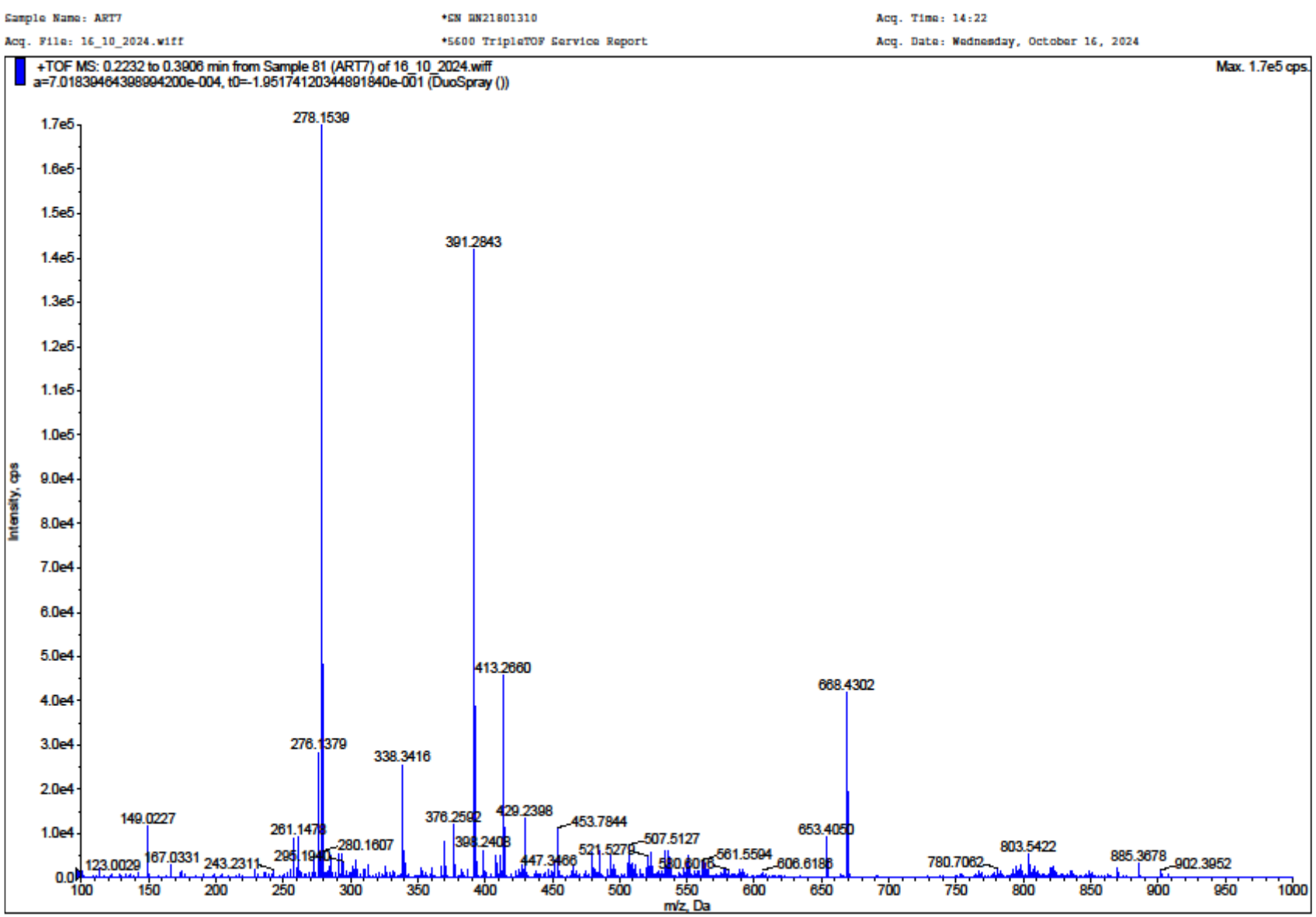


Figure S23. HRMS of compound **8**

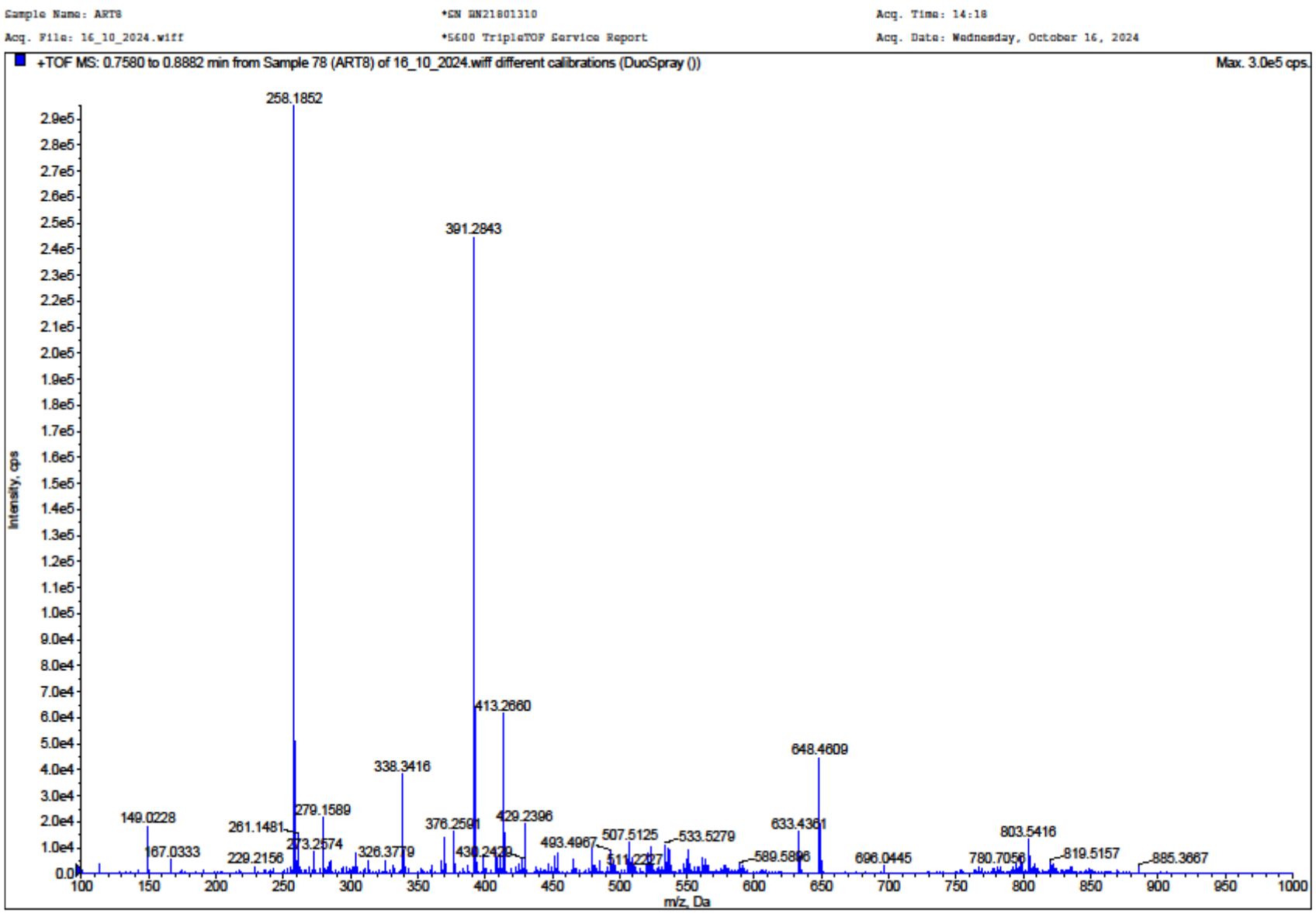


Figure S24. HRMS of compound **9**

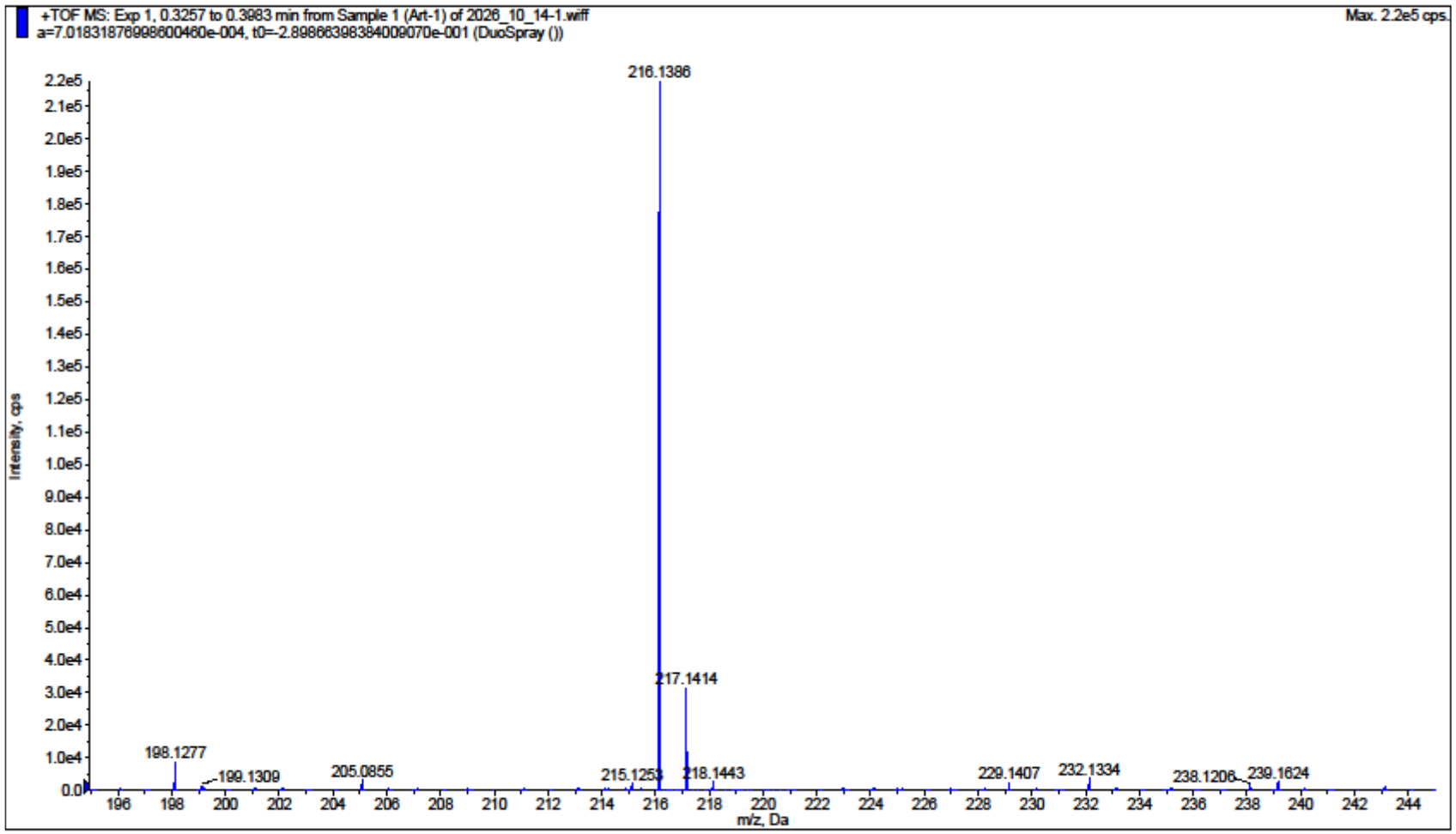


Figure S25. HRMS of compound **10**

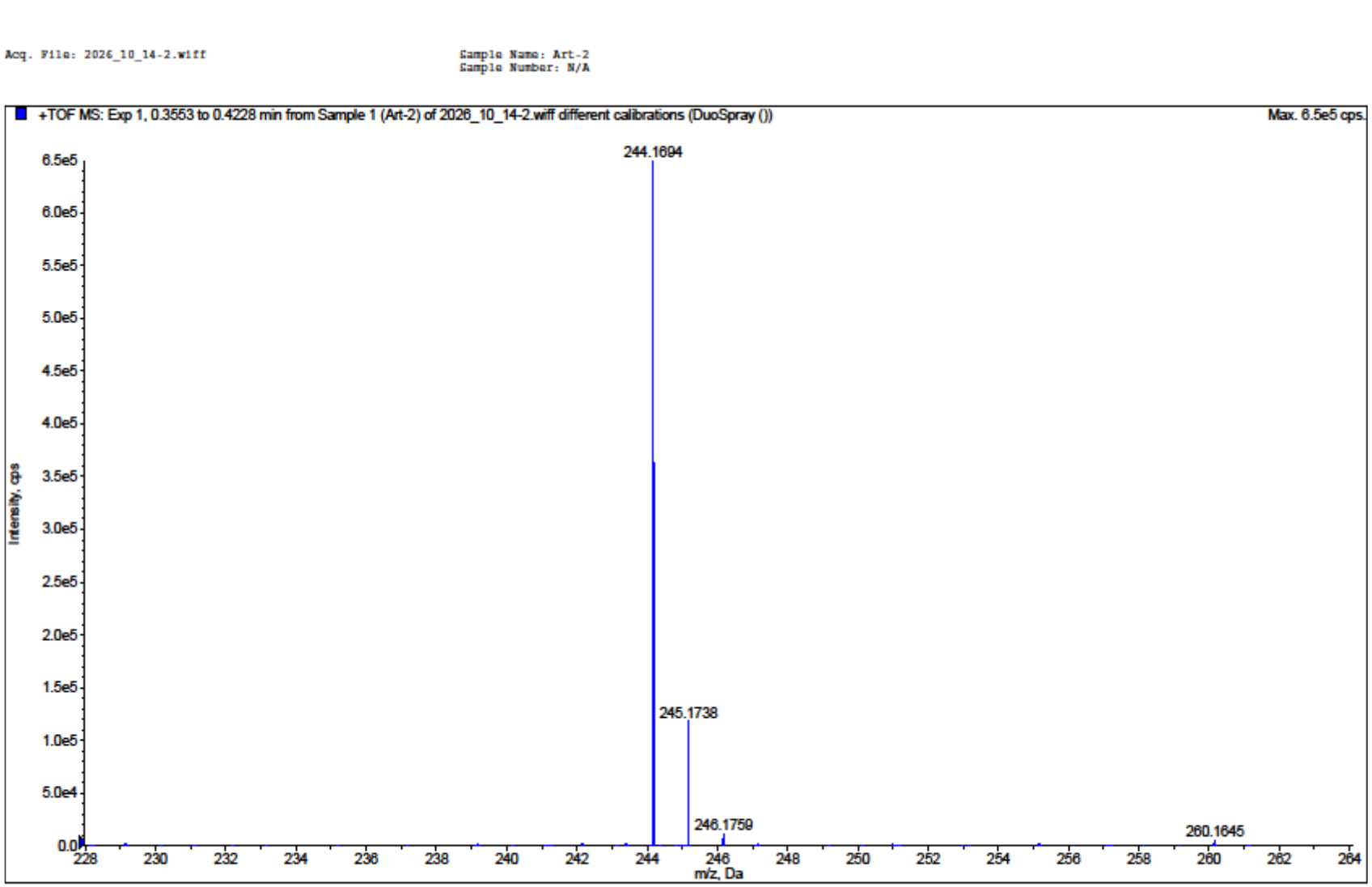


Figure S26. HRMS of compound **11**