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Catalytic enantioselective domino michael/transannular aldol reaction under bifunctional catalysis

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Contents

1. General Methods[1]

Monodimensional and/or bidimensional nuclear magnetic resonance proton and carbon spectra (^{1}H NMR and ^{13}C NMR) were acquired at 25 °C on a Bruker AC-300 spectrometer (300 MHz for ^{1}H and 75.5 MHz for ^{13}C) or a Bruker AC-500 spectrometer (500 MHz for ^{1}H and 125.7 MHz for ^{13}C) at the indicated temperature. Chemical shifts (δ) are reported in ppm relative to residual solvent signals[2] ($CHCl_3$, 7.26 ppm for ^{1}H NMR, $CDCl_3$, 77.16 ppm for ^{13}C NMR) and coupling constants (*J*) in hertz (Hz). The following abbreviations are used to indicate the multiplicity in NMR spectra: s, singlet; d, doublet; t, triplet; q, quartet; app, apparent; m, multiplet; bs, broad signal. ^{13}C NMR spectra were acquired on a broad band decoupled mode using DEPT experiments (Distorsionless Enhancement by Polarization Transfer) for assigning different types of carbon environment. Selective n.O.e., NOESY, COSY, HSQC and HMBC experiments were acquired to confirm precise molecular configurations and to assist in convoluting complex multiplet signals.[3] Infrared spectra (IR) were measured in a Jasco FT/IR (ATR) in the interval between 4000 and 400 cm^{-1} with a 4 cm^{-1} resolution. Only characteristic bands are given in each case. Mass spectra (MS) were recorded on an Agilent gas chromatograph with quadrupole mass spectrometer under electronic impact ionization (EI) 70 eV. The obtained data is presented in mass units (m/z) and the values found in brackets belong to the relative intensities comparing to the base peak (100%). High-resolution mass spectra (HRMS) were recorded on an Acquity UPLC coupled to a QTOF mass spectrometer (SYNAPT G2 HDMS) using electrospray ionization (ESI^{+} or ESI^{-}). Melting points (M.p.) were measured in a Stuart apparatus in open capillary tubes and are uncorrected. The enantiomeric excess (e.e.) of the products was determined by High Performance Liquid Chromatography (HPLC) on a chiral stationary phase in a Waters chromatograph coupled to a Waters photodiode array detector. Daicel Chiralpak IA, IC, AD-H, ASH, AZ-3, AY-3 and Chiralcel OD and OD-3 columns (0.46 × 25 cm) were used; specific conditions are indicated for each case. Specific optical rotations ($[\alpha]_D^{20}$) were measured at 20 °C on a Jasco polarimeter with sodium lamp at 589 nm and a path of length of 1 dm. Solvent and concentration are specified in each case. X-ray data collections were performed in an Agilent Supernova diffractometer equipped with an Atlas CCD area detector, and a CuKα micro-focus source with multilayer optics (λ = 1.54184 Å, 250 µm FWHM beam size). The sample was kept at 150 K with an Oxford Cryosystems Cryostream 700 cooler. The quality of the crystals was checked under a polarizing miscroscope, and a suitable crystal or fragment was mounted on a Mitegen Micromount^{TM} using Paratone N inert oil and transferred to the diffractometer.

Analytical grade solvents and commercially available reagents were used without further purification. Anhydrous solvents were purified and dried with activated molecular sieves prior to use.[4] For reactions carried out under inert conditions, the argon was previously dried through a column of P_2O_5 $CaCl_2$. All the glassware was dried for 12 hours prior to use in an oven at 140 °C, and allowed to cool under a dehumidified atmosphere. Reactions at reduced temperatures were carried out using a Thermo Haake refrigerator. Reactions were monitored using analytical thin layer chromatography (TLC), in pre-coated silica-backed plates (Merck Kiesegel). These were visualized by ultraviolet irradiation, *p*-anisaldehyde, phosphomolybdic acid or potassium permanganate stains.[5] For flash chromatography Silicycle 40-63, 230-400 mesh silica gel was used.[6] For the removal of the solvents under reduced pressure Büchi R-2 series rotatory evaporators were used. For precision weighing Sartorius Analytical Balance was used (± 0.1 mg).

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[1] SGIker technical support (MEC, GV/EJ and European Social Fund) is gratefully acknowledged (NMR, HRMS and X-ray analysis).

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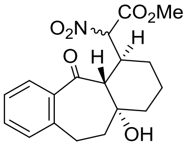
2. Experimental Procedures and Characterizations

2.1. Prepation of Starting Materials and Catalysts

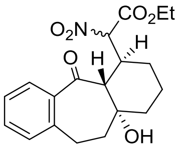
Compounds **1a-i** were synthesized according to our previous methodology.[7] Catalysts **3** were commercially available and used without further purification or prepared following procedures previously reported in the literature.[8] *tert*-Butylnitroacetate and benzylnitroacetate were synthesized following procedures described in the literature.[9]

2.2. Preparation of Policycles 4 and 5b

General Procedure A: To a solution of the corresponding substrate (1.0 equiv.) in anhydrous toluene (0.25 mmol/mL) was added catalyst **3f** (0.1 equiv.) and nucleophile (3.0 equiv.) under inert atmosphere. The reaction mixture was stirred at 25 ºC until consumption of the starting material was observed by TLC. The reaction mixture was concentrated under reduced pressure and the product was isolated by flash column chromatography (FC) with the indicated eluent in each case. The racemic standards for HPLC separation conditions were prepared under the same reaction conditions, using 1-[3,5-bis(trifluoromethyl)phenyl]-3-[2-(dimethylamino)ethyl]thiourea as catalyst.[10]



Methyl 2-((4*S*,4a*R*,11a*R*)-11a-hydroxy-5-oxo-2,3,4,4a,5,10,11,11a-octahydro-1*H*-dibenzo [*a*,*d*][7]annulen-4-yl)-2-nitroacetate (4a). Following the *General Procedure A*, compound **4a** (53.0 mg, 0.15 mmol) was isolated by FC (0.3% MeOH in CH_2Cl_2) after 40 h starting from **1a** (35.0 mg, 0.15 mmol) and methyl nitroacetate (42 µL, 0.45 mmol) in the presence of catalyst **3f** (7.5 mg, 0.015 mmol) using dry toluene (0.6 mL) as solvent. Yield: 99% (d.r.: 1.8:1) (e.e.: 90/91%). White solid. ^{1}H NMR (δ, ppm) (500 MHz, $CDCl_3$) (*denotes minor diastereomer resonances): 7.72-7.61 (m, 1H), 7.44-7.34 (m, 1H), 7.34-7.17 (m, 2H), 5.50 (d, *J* = 3.6, 1.7 Hz, 1H), 5.24* (d, *J* = 3.4, 1.7 Hz, 1H), 3.84 (s, 3H), 3.56* (s, 3H), 3.39* (t, *J* = 11.8 Hz, 1H), 3.27 (t, *J* = 11.6 Hz, 1H), 3.14* (d, *J* = 11.3 Hz, 1H), 3.09-2.92 (m, 3H), 2.35-2.21 (m, 1H), 2.08-1.77 (m, 3H), 1.79-1.60 (m, 4H), 1.51-1.32 (m, 1H), 1.32-1.17* (m, 1H). ^{13}C NMR (δ, ppm) (75.5 MHz, $CDCl_3$) (*denotes minor diastereomer resonances): 203.93, 203.88*, 164.5, 164.4*, 143.4, 139.4, 131.99, 131.88*, 130.26, 130.22*, 128.6, 128.4*, 126.8, 126.7*, 88.5, 87.9*, 73.5, 73.2*, 57.8*, 57.7, 53.4, 52.9*, 44.2, 44.1*, 36.9, 36.7*, 35.3, 35.2*, 31.0, 26.1*, 25.2, 20.7, 20.5*. IR (ATR) cm^{-1}: 3500 (O-H st), 1757 (C=O st), 1673 (C=O st), 1556 (N-O st), 1250 (N-O st). MS (EI, 70 eV) *m/z* (%): 329 (M^+ - H_2O, 3), 282 (17), 167 (14), 250 (33), 221 (32), 209 (23), 165 (19), 133 (100), 115 (26), 103 (26), 91 (37), 77 (27), 55 (15). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{18}H_{21}NNaO_6]^+$: 370.1267 [$(M+Na)^+$]; found: 370.1268. The e.e. was determined by HPLC using a Chiralpak AZ-3 column [*n*-hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major1} = 50.83 min (90% e.e.), τ_{major2} = 127.06 min; τ_{minor1} = 66.98 min (91% e.e.), τ_{minor2} = 90.34 min.



Ethyl 2-((4*S*,4a*R*,11a*R*)-11a-hydroxy-5-oxo-2,3,4,4a,5,10,11,11a-octahydro-1*H*-dibenzo [*a*,*d*][7]annulen-4-yl)-2-nitroacetate (4b). Following the *General Procedure A*, compound **4b** (50.4 mg, 0.14 mmol) was isolated by FC (0.3% MeOH in CH_2Cl_2) after 65 h starting from **1a** (34.9 mg, 0.15 mmol)

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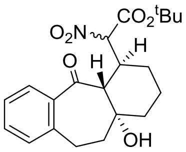
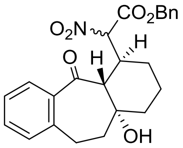
[10] Achiral thiourea was prepared following a literature reported methodology: N. Dolan, D. P. Gavin, A. Eshwika, K. Kavanagh, J. McGinley and J. C. Stephens, *Bioorg. Med. Chem. Lett.* **2016**, *26*, 630.

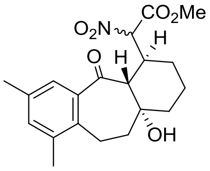
and ethyl nitroacetate (50 µL, 0.45 mmol) in the presence of catalyst **3f** (7.5 mg, 0.015 mmol) using dry toluene (0.6 mL) as solvent. Yield: 91% (d.r.: 1.6:1) (e.e.: 92/91%). Colorless oil. ^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$) (*denotes minor diastereomer resonances): 7.68 (t, *J* = 6.7 Hz, 1H), 7.43-7.33 (m, 1H), 7.34-7.17 (m, 2H), 5.48 (d, *J* = 3.4 Hz, 1H), 5.21* (d, *J* = 3.2 Hz, 1H), 4.29 (q, *J* = 7.0 Hz, 2H), 4.02* (q, *J* = 7.0 Hz, 2H), 3.46-3.33 (m, 1H), 3.32-3.20* (m, 1H), 3.18-2.92 (m, 3H), 2.34-2.19 (m, 1H), 2.12-1.80 (m, 3H), 1.80-1.63 (m, 4H), 1.49-1.36 (m, 1H), 1.31 (t, *J* = 7.1 Hz, 3H), 0.93* (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (δ, ppm) (75.5 MHz, $CDCl_3$) (*denotes minor diastereomer resonances): 203.9, 203.8*, 163.95*, 163.89, 143.5*, 143.4, 139.39, 139.36*, 131.92, 131.92, 130.24*, 130.18, 128.51, 128.48*, 126.75, 126.66*, 88.62, 87.68*, 73.4, 73.2*, 62.9, 62.5*, 57.8*, 57.7, 44.1, 44.0*, 36.9, 36.7*, 35.2, 35.0*, 31.06*, 30.99, 25.9*, 25.1, 20.7, 20.4*, 14.1, 13.6* (OCH_2CH_3). IR (ATR) cm^{-1}: 3522 (O-H st), 1748 (C=O st), 1674 (C=O st), 1554 (N-O st). HRMS (UPLC MS ESI^+): Calculated for $[C_{19}H_{23}NNaO_6]^+$: 384.1423 $[(M+Na)^+]$; found: 384.1426. The e.e. was determined by HPLC using a Chiralpak AZ-3 column [*n*-hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major1} = 15.28 min (92% e.e.), τ_{major2} = 48.12 min; τ_{minor1} = 19.98 min (91% e.e.), τ_{minor2} = 25.05 min.



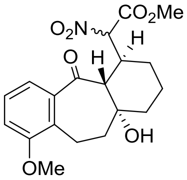
***tert*-butyl-2-((4*S*,4a*R*,11a*R*)-11a-hydroxy-5-oxo-2,3,4,4a,5,10,11,11a-octahydro-1*H*-dibenzo[*a*,*d*][7]annulen-4-yl)-2-nitroacetate (4c).** Following the *General Procedure A*, compound **4c** (50.6 mg, 0.13 mmol) was isolated by FC (0.3% MeOH in CH_2Cl_2) after 7 days starting from **1a** (34.5 mg, 0.15 mmol) and *tert*-butyl nitroacetate (72.0 mg, 0.45 mmol) in the presence of catalyst **3f** (7.5 mg, 0.015 mmol) using dry toluene (0.6 mL) as solvent. Yield: 86% (d.r.: 1.7:1) (e.e.: 90/90%). Colorless oil. ^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$) (*denotes minor diastereomer resonances): 7.70 (t, *J* = 6.4 Hz, 1H), 7.45-7.34 (m, 1H), 7.34-7.28 (m, 1H), 7.24-7.16 (m, 1H), 5.40 (d, *J* = 3.4 Hz, 1H), 5.08* (d, *J* = 3.1 Hz, 1H), 3.40-3.26 (m, 1H), 3.26-3.14 (m, 1H), 3.04-2.92 (m, 2H, *H*-10), 2.33-2.21 (m, 1H), 2.16-1.98 (m, 1H), 1.94-1.60 (m, 6H), 1.50 (s, 9H), 1.44-1.20 (m, 1H), 1.16* (s, 9H). ^{13}C NMR (δ, ppm) (75.5 MHz, $CDCl_3$) (*denotes minor diastereomer resonances): 204.1*, 203.6, 162.9*, 162.8, 143.8, 143.3*, 139.5, 139.4*, 132.0, 131.9*, 130.3, 130.2*, 128.6*, 128.5, 126.7, 89.1, 88.0*, 84.6, 84.4*, 73.5*, 73.2, 57.9, 57.8*, 44.2*, 44.1, 36.9*, 36.8, 35.2*, 34.8, 31.2, 31.0*, 28.0*, 27.6, 25.5, 25.0*, 20.8*, 20.5. IR (ATR) cm^{-1}: 3479 (O-H st), 1744 (C=O st), 1672 (C=O st), 1552 (N-O st). MS (EI, 70 eV) *m/z* (%): 355 (1), 281 (14), 207 (88), 181 (21), 165 (24), 147 (18), 133 (100), 107 (67), 91 (76), 77 (69), 55 (42). HRMS (UPLC MS ESI^+): Calculated for $[C_{21}H_{27}NNaO_6]^+$: 412.1736 $[(M+Na)^+]$; found: 412.1736. The e.e. was determined by HPLC using a Chiralpak AZ-3 column [*n*-hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major1} = 10.97 min (90% e.e.), τ_{major2} = 30.52 min; τ_{minor1} = 13.68 min (90% e.e.), τ_{minor2} = 15.76 min.



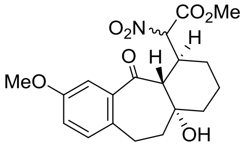
benzyl-2-((4*S*,4a*R*,11a*R*)-11a-hydroxy-5-oxo-2,3,4,4a,5,10,11,11a-octahydro-1*H*-dibenzo [*a*,*d*][7]annulen-4-yl)-2-nitroacetate (4d). Following the *General Procedure A*, compound **4d** (47.8 mg, 0.11 mmol) was isolated by FC (Et_2O/hexanes gradient from 1:2 to 2:1) after 65 h starting from **1a** (34.6 mg, 0.15 mmol) and benzyl nitroacetate (88.0 mg, 0.45 mmol) in the presence of catalyst **3f** (7.5 mg, 0.015 mmol) using dry toluene (0.6 mL) as solvent. Yield: 74% (d.r.: 1.6:1) (e.e.: 92/88%). Colorless oil. ^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$) (*denotes minor diastereomer resonances): 7.74-7.61 (m, 1H), 7.47-7.17 (m, 7H), 7.07-7.01 (m, 1H), 5.54* (d, *J* = 3.6 Hz, 1H), 5.30-5.22 (m, 3H), 5.13* (d, *J* = 11.9 Hz, 1H), 4.89* (d, *J* = 11.9 Hz, 1H), 3.42-3.21 (m, 1H), 3.08-2.93 (m, 2H), 2.93-2.67 (m, 1H), 2.32-2.13 (m, 1H), 2.12-1.83 (m, 2H), 1.79-1.60 (m, 4H), 1.55-0.99 (m, 2H). ^{13}C NMR (δ, ppm) (75.5 MHz, $CDCl_3$) (*denotes minor diastereomer resonances): 203.90, 203.86*, 164.0*, 163.8, 143.5, 143.4*, 139.4, 139.3*, 134.5, 134.4*, 131.96, 131.87*, 130.3*, 130.2, 128.9, 128.81, 128.78*, 128.6, 128.5, 128.4*, 126.8, 126.7*, 88.5, 87.6*, 73.5, 73.2*, 68.4, 68.0*, 57.8, 57.7*, 44.2, 44.0*, 36.9, 36.7*, 35.3, 35.0*, 31.0, 30.9*, 26.0, 25.1*, 20.6, 20.4*. IR (ATR) cm^{-1}: 3487 (O-H st), 1749 (C=O st), 1654 (C=O st), 1556 (N-O st). HRMS (UPLC MS ESI^+): Calculated for $[C_{24}H_{25}NNaO_6]^+$: 446.1580 $[(M+Na)^+]$; found: 446.1584. The e.e. was determined by HPLC using a Chiralpak AZ-3 column [*n*-hexane/*i*-PrOH (70:30)]; flow rate 1.0 mL/min; τ_{major1} = 17.79 min (92% e.e.), τ_{major2} = 35.38 min; τ_{minor1} = 18.97 min (88% e.e.), τ_{minor2} = 24.52 min.



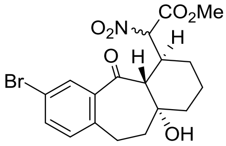
Methyl 2-((4*S*,4a*R*,11a*R*)-11a-hydroxy-7,9-dimethyl-5-oxo-2,3,4,4a,5,10,11,11a-octahydro-1*H*-dibenzo[*a,d*][7]annulen-4-yl)-2-nitroacetate (4f). Following the *General Procedure A*, compound **4f** (56.3 mg, 0.15 mmol) was isolated by FC (0.3% MeOH in CH$_2$Cl$_2$) after 72 h starting from **1b** (37.9 mg, 0.15 mmol) and methyl nitroacetate (42 µL, 0.45 mmol) in the presence of catalyst **3f** (7.5 mg, 0.015 mmol) using dry toluene (0.6 mL) as solvent. Yield: 99% (d.r.: 1.7:1) (e.e.: 89/89%). White solid. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$) (*denotes minor diastereomer resonances): 7.37-7.30 (m, 1H), 7.08 (t, J = 2.6 Hz, 1H), 5.44 (d, J = 3.5 Hz, 1H), 5.19* (d, J = 3.4 Hz, 1H), 3.83 (s, 3H), 3.52* (s, 3H), 3.37 (tt, J = 12.1, 3.3 Hz, 1H), 3.24* (tt, J = 11.9, 3.1 Hz, 1H), 3.14-2.93 (m, 2H), 2.76-2.58 (m, 1H), 2.33-2.18 (m, 7H), 2.06-1.82 (m, 3H), 1.76-1.60 (m, 4H), 1.47-1.16 (m, 1H). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$) (*denotes minor diastereomer resonances): 204.7, 164.41, 164.39*, 140.0*, 139.9, 139.04, 138.94*, 136.78*, 136.71, 135.8, 135.7*, 134.6, 134.5*, 126.9, 126.7*, 88.5, 87.8*, 73.6, 73.4*, 58.0*, 57.9, 53.4, 52.8*, 43.8, 43.6*, 36.2, 36.0*, 35.2, 35.1*, 26.3*, 26.2, 26.0*, 25.1, 20.78, 20.75*, 20.66, 20.5*, 20.4. IR (ATR) cm^{-1}: 3508 (O-H st), 1755 (C=O st), 1672 (C=O st), 1554 (N-O st). HRMS (UPLC MS ESI$^+$): Calculated for [C$_{20}$H$_{25}$NNaO$_6$]$^+$: 398.1580 [(M+Na)$^+$]; found: 398.1574. The e.e. was determined by HPLC using a Chiralpak AZ-3 column [*n*-hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major1} = 16.54 min (89% e.e.), τ_{major2} = 22.68 min; τ_{minor1} = 21.16 min (89% e.e.), τ_{minor2} = 25.19 min. M.p.: 126-128 °C (hexanes/EtOAc).



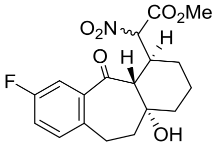
Methyl 2-((4*S*,4a*R*,11a*R*)-11a-hydroxy-9-methoxy-5-oxo-2,3,4,4a,5,10,11,11a-octahydro-1*H*-dibenzo[*a,d*][7]annulen-4-yl)-2-nitroacetate (4g). Following the *General Procedure A*, compound **4g** (50.7 mg, 0.13 mmol) was isolated by FC (0.3% MeOH in CH$_2$Cl$_2$) after 7 days starting from **1c** (38.1 mg, 0.15 mmol) and methyl nitroacetate (42 µL, 0.45 mmol) in the presence of catalyst **3f** (7.5 mg, 0.015 mmol) using dry toluene (0.6 mL) as solvent. Yield: 91% (d.r.: 1.7:1) (e.e.: 89/92%). Colorless oil. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$) (*denotes minor diastereomer resonances): 7.35-7.16 (m, 2H), 7.04-6.91 (m, 1H), 5.45 (d, J = 3.6 Hz, 1H), 5.20* (d, J = 3.4 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.84* (s, 3H), 3.55* (s, 3H), 3.47-3.33 (m, 1H), 3.31-3.19* (m, 1H), 3.15* (d, J = 11.4 Hz, 1H), 3.03 (d, J = 11.2 Hz, 1H), 2.65-2.47 (m, 1H), 2.28* (d, J = 7.4 Hz, 1H), 2.23 (d, J = 7.4 Hz, 1H), 2.06-1.85 (m, 2H), 1.77-1.52 (m, 6H), 1.48-1.22 (m, 1H). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$) (*denotes minor diastereomer resonances): 204.2, 164.4, 157.04*, 157.01, 141.0*, 140.9, 132.4, 132.3*, 127.4, 127.3*, 120.3, 120.2*, 113.7, 113.5*, 88.5, 87.9*, 73.8, 73.6*, 58.2*, 58.0, 56.0, 53.5, 52.9*, 43.8, 43.6*, 36.3, 36.1*, 35.25, 35.18*, 26.2*, 25.2, 22.6*, 22.5, 20.7, 20.5*. IR (ATR) cm^{-1}: 3518 (O-H st), 1755 (C=O st), 1677 (C=O st), 1557 (N-O st). HRMS (UPLC MS ESI$^+$): Calculated for [C$_{19}$H$_{23}$NNaO$_7$]$^+$: 400.1372 [(M+Na)$^+$]; found: 400.1375. The e.e. was determined by HPLC using a Chiralpak AZ-3 column [*n*-hexane/*i*-PrOH (95:05)]; flow rate 1.0 mL/min; τ_{major1} = 93.91 min (89% e.e.), τ_{major2} = 217.44 min; τ_{minor1} = 123.75 min (92% e.e.), τ_{minor2} = 197.62 min.



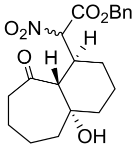
Methyl 2-((4*S*,4a*R*,11a*R*)-11a-hydroxy-7-methoxy-5-oxo-2,3,4,4a,5,10,11,11a-octahydro-1*H*-dibenzo[*a,d*][7]annulen-4-yl)-2-nitroacetate (4h). Following the *General Procedure A*, compound **4h** (57.0 mg, 0.15 mmol) was isolated by FC (Et$_2$O/hexanes 1:2) after 48 h starting from **1d** (39.1 mg, 0.15 mmol) and methyl nitroacetate (42 µL, 0.45 mmol) in the presence of catalyst **3f** (7.5 mg, 0.015 mmol) using dry toluene (0.6 mL) as solvent. Yield: 99% (d.r.: 1.6:1) (e.e.: 90/88%). Colorless oil. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$) (*denotes minor diastereomer resonances): 7.17 (dd, J = 8.5, 3.0 Hz, 1H), 7.11 (d, J = 8.7 Hz, 1H), 6.99-6.86 (m, 1H), 5.50 (d, J = 3.5 Hz, 1H), 5.23* (d, J = 3.3 Hz, 1H), 3.84* (s, 3H), 3.81 (s, 3H), 3.58 (s, 3H), 3.47-3.19 (m, 1H), 3.14* (d, J = 11.4 Hz, 1H), 3.02 (d, J = 11.2 Hz, 1H), 2.96-2.84 (m, 2H), 2.37-2.18 (m, 1H), 2.08-1.76 (m, 3H), 1.74-1.61 (m, 4H), 1.49-1.14 (m, 1H). ^{13}C NMR (δ, ppm) (75.5 MHz, CDCl$_3$) (*denotes minor diastereomer resonances): 203.6, 203.5*, 164.5*, 164.4, 158.22, 158.18*, 140.1, 135.97*, 135.93, 131.56*, 131.50, 118.9, 118.8*, 112.0, 111.9*, 88.5, 87.9*, 73.5, 73.3*, 57.8*, 57.7, 55.63*, 55.59, 53.4, 52.9*, 44.5, 44.4*, 36.9*, 36.8, 35.3, 35.2*, 30.3*, 30.2, 26.0*, 25.1, 20.7, 20.4*. IR (ATR) cm^{-1}: 3526 (O-H st), 1754 (C=O st), 1673 (C=O st), 1553 (N-O st). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{19}H_{23}NNaO_7]^+$: 400.1372 [(M+Na)$^+$]; found: 400.1377. The e.e. was determined by HPLC using a Chiralpak AZ-3 column [*n*-hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major1} = 23.56 min (90% e.e.), τ_{major2} = 39.20 min; τ_{minor1} = 28.17 min (88% e.e.), τ_{minor2} = 30.13 min.



Methyl 2-((4*S*,4a*R*,11a*R*)-7-bromo-11a-hydroxy-5-oxo-2,3,4,4a,5,10,11,11a-octahydro-1*H*-dibenzo[*a,d*][7]annulen-4-yl)-2-nitroacetate (4i). Following the *General Procedure A*, compound **4i** (64.0 mg, 0.15 mmol) was isolated by FC (0.3% MeOH in CH_2Cl_2) after 44 h starting from **1e** (46.5 mg, 0.15 mmol) and methyl nitroacetate (42 µL, 0.45 mmol) in the presence of catalyst **3f** (7.5 mg, 0.015 mmol) using dry toluene (0.6 mL) as solvent. Yield: 99% (d.r.: 1.7:1) (e.e.: 90/92%). White solid. ^{1}H NMR (δ, ppm) (500 MHz, $CDCl_3$) (*denotes minor diastereomer resonances): 7.81 (d, *J* = 2.2 Hz, 1H), 7.76* (d, *J* = 2.2 Hz, 1H), 7.53-7.47 (m, 1H), 7.13* (d, *J* = 8.4 Hz, 1H), 7.10 (d, *J* = 8.2 Hz, 1H), 5.44 (d, *J* = 3.5 Hz, 1H), 5.21* (d, *J* = 3.3 Hz, 1H), 3.85 (s, 3H), 3.63* (s, 3H), 3.41-3.32* (m, 1H), 3.29-3.22 (m, 1H), 3.14* (d, *J* = 11.4 Hz, 1H), 2.99 (d, *J* = 11.2 Hz, 1H), 2.94 (dt, *J* = 10.7, 5.3 Hz, 1H), 2.33-2.24 (m, 1H), 2.07-1.96 (m, 1H), 1.96-1.83 (m, 1H), 1.76-1.65 (m, 5H), 1.36 (td, *J* = 12.9, 3.9 Hz, 1H), 1.32-1.21 (m, 1H). ^{13}C NMR (δ, ppm) (75.5 MHz, $CDCl_3$): 202.4*, 202.3, 164.4*, 164.2, 142.2, 142.1*, 140.9*, 140.8, 134.7, 134.6*, 132.0, 131.3, 131.1*, 120.8, 120.7*, 88.4, 87.9*, 73.5, 73.3*, 57.9*, 57.8, 53.5, 53.1*, 44.0, 43.9*, 37.0, 36.9*, 35.2, 30.6, 30.5*, 26.3*, 25.1, 20.6, 20.4*. IR (ATR) cm^{-1}: 3465 (O-H st), 1764 (C=O st), 1659 (C=O st), 1555 (N-O st). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{18}H_{20}BrNNaO_6]^+$: 448.0372 [(M+Na)$^+$]; found: 448.0370. The e.e. was determined by HPLC using a Chiralpak AZ-3 column [*n*-hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major1} = 20.03 min (90% e.e.), τ_{major2} = 27.90 min; τ_{minor1} = 25.25 min (92% e.e.), τ_{minor2} = 21.36 min. M.p.: 126-129 °C (hexanes/EtOAc).

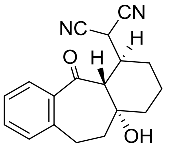


Methyl 2-((4*S*,4a*R*,11a*R*)-7-fluoro-11a-hydroxy-5-oxo-2,3,4,4a,5,10,11,11a-octahydro-1*H*-dibenzo[*a,d*][7]annulen-4-yl)-2-nitroacetate (4j). Following the *General Procedure A*, compound **4j** (55.0 mg, 0.15 mmol) was isolated by FC (0.3% MeOH in CH_2Cl_2) after 44 h starting from **1f** (37.1 mg, 0.15 mmol) and methyl nitroacetate (42 µL, 0.45 mmol) in the presence of catalyst **3f** (7.5 mg, 0.015 mmol) using dry toluene (0.6 mL) as solvent. Yield: 99% (d.r.: 1.7:1) (e.e.: 91/92%). White solid. ^{1}H NMR (δ, ppm) (500 MHz, $CDCl_3$) (*denotes minor diastereomer resonances): 7.42-7.30 (m, 1H), 7.24-7.14 (m, 1H), 7.14-7.03 (m, 1H), 5.53-5.38 (m, 1H), 5.26-5.17* (m, 1H), 3.84 (s, 3H), 3.63* (s, 3H), 3.45-3.10 (m, 1H), 3.06-2.86 (m, 3H), 2.40-2.20 (m, 1H), 2.10-1.82 (m, 2H), 1.82-1.56 (m, 5H), 1.47-1.20 (m, 1H). ^{13}C NMR (δ, ppm) (75.5 MHz, $CDCl_3$): 202.4, 164.5, 164.3*, 161.3 (d, $^1J_{CF}$ = 246.8 Hz), 140.8, 140.7*, 139.30, 139.26*, 132.0 (d, $^3J_{CF}$ = 7.2 Hz), 118.9 (d, $^2J_{CF}$ = 21.5 Hz), 118.7* (d, $^2J_{CF}$ = 21.5 Hz), 115.0 (d, $^2J_{CF}$ = 22.7 Hz), 114.8* (d, $^2J_{CF}$ = 22.7 Hz), 88.4, 88.0*, 73.5, 73.2*, 57.8, 57.7*, 53.4, 53.0*, 44.1, 44.0*, 37.0, 36.9*, 35.23, 35.17*, 30.3, 26.3*, 25.1, 20.6, 20.4*. IR (ATR) cm^{-1}: 3500 (O-H st), 1763 (C=O st), 1673 (C=O st), 1553 (N-O st). MS (EI, 70 eV) *m/z* (%): 347 (M$^+$ - H_2O, 3), 300 (23), 268 (48), 239 (45), 207 (25), 175 (23), 151 (100), 133 (70), 109 (53), 79 (53), 55 (30). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{18}H_{20}FNNaO_6]^+$: 388.1172 [(M+Na)$^+$]; found: 388.1172. The e.e. was determined by HPLC using a Chiralpak AY3 column [*n*-hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major1} = 14.80 min (91% e.e.), τ_{major2} = 25.44 min; τ_{minor1} = 20.27 min (92% e.e.), τ_{minor2} = 47.99 min. M.p.: 112-116 °C (hexanes/EtOAc).



Benzyl 2-((1*S*,4a*S*,9a*R*)-4a-hydroxy-9-oxodecahydro-1*H*-benzo[7]annulen-1-yl)-2-nitroacetate (4k). Following the *General Procedure A*, compound **4k** (26.2 mg, 0.07 mmol) was isolated by FC (Et_2O/hexanes 1:2) after 6 days starting from **1g** (29.2 mg, 0.15 mmol) and benzyl nitroacetate (58.0 mg, 0.30 mmol) in the presence of catalyst **3f** (15.0 mg, 0.030 mmol) using dry toluene (0.6 mL) as solvent. Yield: 45% (d.r.: 1.7:1) (e.e.: 80/85%). Colorless oil. ^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$) (*denotes minor diastereomer resonances): 7.50-7.31 (m, 5H), 5.33* (d, *J* = 11.9 Hz, 1H), 5.27-5.19 (m, 2H), 5.15* (d, *J* = 12.0 Hz, 1H), 5.10 (d, *J* = 3.4 Hz, 1H), 4.89* (d, *J* = 2.9 Hz, 1H), 3.20-2.92 (m, 1H), 2.86 (d, *J* = 11.5 Hz, 1H), 2.75-2.61 (m, 1H), 2.59-2.31 (m, 1H), 2.07-1.42 (m, 11H), 1.42-0.98 (m, 2H). ^{13}C NMR (δ, ppm) (75.5

MHz, $CDCl_3$): 214.5*, 214.4, 164.0*, 163.4, 134.45*, 134.40, 129.2*, 129.1, 128.97*, 128.93*, 128.8, 128.6, 89.5, 88.7, 70.7, 70.3*, 68.6*, 68.5, 57.0, 56.4*, 46.4, 46.3*, 45.2, 44.8, 40.0, 39.9*, 36.6, 26.3*, 25.1, 22.8, 21.6, 21.5*, 20.5, 20.2* . IR (ATR) cm^{-1}: 3544 (O-H st), 1751 (C=O st), 1692 (C=O st), 1554 (N-O st). MS (EI, 70 eV) *m/z* (%): 281 (6), 207 (35), 108 (61), 91 (49), 79(95), 77 (100), 51 (58). HRMS (UPLC MS ESI$^+$): Calculated for [$C_{20}H_{25}NNaO_6$]$^+$: 398.1580 [(M+Na)$^+$]; found: 398.1590. The e.e. was determined by HPLC using a Chiralpak AY3 column [*n*-hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major1} = 33.44 min, τ_{major2} = 52.96 min (80% e.e.); τ_{minor1} = 20.34 min, τ_{minor2} = 23.11 min (85% e.e.). M.p.: 112-116 °C (hexanes/EtOAc).

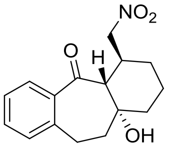


2-((4*R*,4a*R*,11a*R*)-11a- hydroxy -5-oxo-2,3,4,4a,5,10,11,11a-octahydro-1*H*-dibenzo[*a,d*][7] annulen-4-yl)malononitrile (5b). Following the *General Procedure A*, compound **5b** (35.4 mg, 0.12 mmol) was isolated by FC (Et_2O/hexanes gradient from 1:2 to 1:1) after 5 days starting from **1a** (34.8 mg, 0.15 mmol) and malononitrile (29.7 mg, 0.45 mmol) in the presence of catalyst **3f** (7.5 mg, 0.015 mmol) using dry toluene (0.6 mL) as solvent. Yield: 79% (e.e.: 46%). White solid. ^{1}H NMR (δ, ppm) (500 MHz, $CDCl_3$): 7.75 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.50-7.43 (m, 1H), 7.36-7.31 (m, 1H), 7.31-7.26 (m, 1H), 4.18 (d, *J* = 3.8 Hz, 1H), 3.15-3.00 (m, 4H), 2.36 (ddd, *J* = 14.6, 7.3, 1.4 Hz, 1H), 2.25 (dt, *J* = 13.0, 3.5 Hz, 1H), 2.02-1.92 (m, 1H), 1.91-1.73 (m, 5H), 1.52-1.41 (m, 1H). ^{13}C NMR (δ, ppm) (75.5 MHz, $CDCl_3$): 202.4, 144.2, 138.2, 132.7, 130.6, 128.7, 127.0, 112.4, 111.3, 73.5, 58.7, 44.2, 37.0, 35.2, 31.2, 27.0, 26.2, 20.1. IR (ATR) cm^{-1}: 3526 (O-H st), 1666 (C=O st). MS (EI, 70 eV) *m/z* (%): 294 (M$^+$, 5), 276 (M$^+$ - H_2O, 11), 240 (25), 211 (41), 193 (17), 133 (100), 118 (21), 103 (22), 91 (25), 79 (27), 67 (13), 55 (9). HRMS (UPLC MS ESI$^+$): Calculated for [$C_{18}H_{17}N_2O_2$]$^-$: 293.1290 [(M-H)$^-$]; found: 293.1284. The e.e. was determined by HPLC using a Chiralpak ASH column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 1.0 mL/min; τ_{major} = 43.98 min, τ_{minor} = 23.98 min (46% e.e.). $[\alpha]_D^{20}$: +19.4 (*c* = 1.15, $CHCl_3$). M.p.: 133-137 °C (hexanes/EtOAc).

2.3. Synthesis of Adducts 6

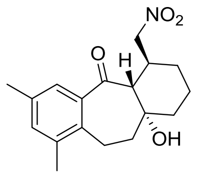
General Procedure B: To a solution of the corresponding adduct **4** in dioxane (0.10 mmol/mL) at 80 °C was added aqueous solution of LiOH (1.7 eq, 1.0 mmol/mL) and it was stirred at that temperature for the time indicated in each case. Then reaction mixture was diluted with Et_2O and aqueous phase was extracted with Et_2O. Combined organic layers were dried with anhydrous Na_2SO_4, concentrated under reduced pressure and purified by column chromatography to afford pure products.

General Procedure C: To a solution of the corresponding adduct **4** in MeOH (3mL) was added Pd/C and it was subjected to hydrogenation conditions at room temperature (H_2, 30 psi) until full conversion was observed by TLC. Reaction crude was filtered through a plug of Celite, concentrated under reduced pressure and purified by column chromatography.

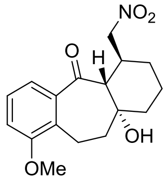


(4S,4a*R*,11a*R*)-11a-hydroxy-4-(nitromethyl)-1,2,3,4,4a,10,11,11a-octahydro-5*H*-dibenzo [*a,d*][7]annulen-5-one (6a). Following the *General Procedure B* compound **6a** (12.5 mg, 0.043 mmol) was isolated by FC (EtOAc/hexanes 2:8) after 3 days, starting from adduct **4a** (27.8 mg, 0.08 mmol) and LiOH (5.7 mg, 0.13 mmol). Yield: 54% (e.e.: 90%). Colorless oil. ^{1}H NMR (δ, ppm) (500 MHz, $CDCl_3$): 7.74 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.43 (td, *J* = 7.5, 1.6 Hz, 1H), 7.36-7.31 (m, 1H), 7.27 (d, *J* = 7.6 Hz, 1H), 4.49-4.29 (m, 2H), 3.14-2.95 (m, 4H), 2.31 (ddd, *J* = 14.6, 6.9, 1.8 Hz, 1H), 2.00-1.87 (m, 2H), 1.82-1.65 (m, 5H), 1.24 (dddd, *J* = 16.6, 14.7, 10.0, 2.7 Hz, 1H). ^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$): 203.8, 143.5, 139.6, 131.9, 130.3, 128.4, 126.8, 79.2, 73.1, 57.9, 44.1, 36.8, 32.8, 31.2, 28.4, 20.5. IR (ATR) cm^{-1}: 3497 (O-H st), 1677 (C=O st), 1544 (N=O st), 735 (C-N st). MS (EI, 70 eV) *m/z* (%): 271 (M$^+$ - H_2O, 2), 242 (8), 223 (19), 195 (23), 181 (20), 157 (18), 147 (15), 133 (100), 117 (23), 107 (73), 91 (59), 77 (41), 67 (16), 55 (24). HRMS (UPLC MS ESI$^+$): Calculated for [$C_{16}H_{19}NNaO_4$]$^+$: 312.1212 [(M+Na)$^+$]; found: 312.1222. The e.e. was determined by HPLC using a Chiralpak AZ-3 column [*n*-hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 25.38 min, τ_{minor} = 34.74 min (90% e.e.). $[\alpha]_D^{20}$: +4.58 (*c* = 1.19, $CHCl_3$).

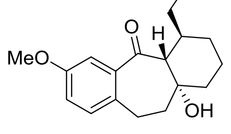
Alternatively, following the *General Procedure C* compound **6a** (19.4 mg, 0.067 mmol) was isolated by FC (hexanes/EtOAc 7:3) after 6 h, starting from adduct **4d** (38.6 mg, 0.09 mmol) and Pd/C (6.0 mg) in 3.0 mL of MeOH. Yield: 74% (90% e.e.).



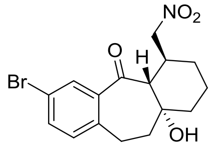
(4S,4a*R*,11a*R*)-11a-hydroxy-7,9-dimethyl-4-(nitromethyl)-1,2,3,4,4a,10,11,11a-octahydro-5*H*-dibenzo[*a,d*][7]annulen-5-one (6f). Following the *General Procedure B* compound **6f** (9.80 mg, 0.031 mmol) was isolated by FC (EtOAc/hexanes 2:8) after 3 days, starting from adduct **4f** (17.5 mg, 0.047 mmol) and LiOH (3.4 mg, 0.08 mmol). Yield: 66% (e.e.: 90%). White solid. ^{1}H NMR (δ, ppm) (500 MHz, CDCl$_3$): 7.34 (s, 1H), 7.11 (s, 1H), 4.36 (dd, *J* = 11.4, 2.9 Hz, 1H), 4.30-4.22 (m, 1H), 3.09-2.94 (m, 3H), 2.69 (dd, *J* = 18.0, 12.0 Hz, 1H), 2.31 (s, 3H), 2.30 (s, 3H), 2.25 (ddd, *J* = 14.7, 7.4, 1.2 Hz, 1H), 1.97-1.84 (m, 2H), 1.78-1.65 (m, 5H), 1.23-1.13 (m, 1H). ^{13}C NMR (δ, ppm) (75 MHz, CDCl$_3$): 204.7, 140.2, 139.1, 136.9, 136.0, 134.6, 126.7, 79.1, 73.2, 58.2, 43.8, 36.0, 32.7, 28.4, 26.5, 20.8, 20.51, 20.46. IR (ATR) cm^{-1}: 3443 (O-H st), 1663 (C=O st), 1544 (N=O st), 754 (C-N st). MS (EI, 70 eV) *m/z* (%): 317 (M$^+$, 1), 175 (12), 163 (100), 161 (18), 145 (8), 119 (16), 107 (11), 91 (20), 79 (9), 67 (4), 55 (7). HRMS (UPLC MS ESI$^+$): Calculated for [C$_{18}$H$_{23}$NNaO$_4$]$^+$: 340.1525 [(M+Na)$^+$]; found: 340.1534. The e.e. was determined by HPLC using a Chiralpak IA column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 1.0 mL/min; τ_{major} = 10.89 min, τ_{minor} = 13.42 min (90% e.e.). [α]$_D^{20}$: +30.26 (*c* = 0.58, CHCl$_3$). M.p.: 65-68 °C (hexanes/EtOAc).



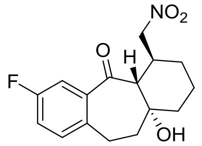
(4*S*,4a*R*,11a*R*)-11a-hydroxy-9-methoxy-4-(nitromethyl)-1,2,3,4,4a,10,11,11a-octahydro-5*H*-dibenzo[*a,d*][7]annulen-5-one (6g). Following the *General Procedure B* compound **6g** (13.1 mg, 0.041 mmol) was isolated by FC (EtOAc/hexanes 2:8) after 3 days, starting from adduct **4g** (32.0 mg, 0.085 mmol) and LiOH (6.0 mg, 0.144 mmol). Yield: 48% (e.e.: 90%). Colorless oil. ^{1}H NMR (δ, ppm) (500 MHz, CDCl$_3$): 7.34-7.27 (m, 2H), 7.01 (dd, *J* = 7.4, 1.9 Hz, 1H), 4.38 (dd, *J* = 11.4, 3.1 Hz, 1H), 4.34-4.30 (m, 1H), 3.89 (s, 3H), 3.44 (ddd, *J* = 18.5, 7.5, 1.3 Hz, 1H), 3.08-2.98 (m, 2H), 2.59 (dd, *J* = 18.5, 12.2 Hz, 1H), 2.27 (ddd, *J* = 14.7, 7.5, 1.2 Hz, 1H), 2.02-1.86 (m, 2H), 1.78-1.64 (m, 5H), 1.21 (ddt, *J* = 15.1, 12.7, 5.7 Hz, 1H). ^{13}C NMR (δ, ppm) (75 MHz, CDCl$_3$): 204.1, 157.1, 141.2, 132.5, 127.4, 120.1, 113.6, 79.1, 73.4, 58.3, 56.0, 43.7, 36.2, 32.7, 28.4, 22.6, 20.5. IR (ATR) cm^{-1}: 3493 (O-H st), 1677 (C=O st), 1546 (N=O st), 1259 (C-O st). MS (EI, 70 eV) *m/z* (%): 319 (M$^+$, 12), 281 (4), 207 (20), 187 (10), 165 (100), 147 (9), 128 (7), 115 (14), 91 (32), 77 (23), 55 (12). HRMS (UPLC MS ESI$^+$): Calculated for [C$_{17}$H$_{21}$NNaO$_5$]$^+$: 342.1317 [(M+Na)$^+$]; found: 342.1324. The e.e. was determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 1.0 mL/min; τ_{major} = 28.99 min, τ_{minor} = 40.59 min (90% e.e.). [α]$_D^{20}$: +12.15 (*c* = 0.05, CHCl$_3$).



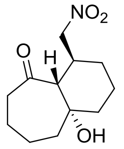
(4*S*,4a*R*,11a*R*)-11a-hydroxy-7-methoxy-4-(nitromethyl)-1,2,3,4,4a,10,11,11a-octahydro-5*H*-dibenzo[*a,d*][7]annulen-5-one (6h). Following the *General Procedure B* compound **6h** (13.9 mg, 0.043 mmol) was isolated by FC (EtOAc/hexanes 2:8) after 3 days, starting from adduct **4h** (33.0 mg, 0.087 mmol) and LiOH (6.2 mg, 0.15 mmol). Yield: 50% (e.e.: 90%). Colorless oil. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$): 7.22 (d, *J* = 2.8 Hz, 1H), 7.15 (d, *J* = 8.4 Hz, 1H), 6.96 (dd, *J* = 8.4, 2.9 Hz, 1H), 4.47-4.28 (m, 2H), 3.83 (s, 3H), 3.09-2.99 (m, 2H), 2.99-2.90 (m, 2H), 2.27 (ddd, *J* = 14.6, 6.1, 2.6 Hz, 1H), 1.96-1.83 (m, 2H), 1.76-1.61 (m, 5H), 1.30-1.14 (m, 1H). ^{13}C NMR (δ, ppm) (75 MHz, CDCl$_3$): 203.5, 158.3, 140.3, 136.0, 131.6, 118.9, 111.9, 79.2, 73.1, 57.9, 55.7, 44.5, 36.8, 32.8, 30.4, 28.4, 20.5. IR (ATR) cm^{-1}: 3558 (O-H st), 1677 (C=O st), 1547 (N=O st), 754 (C-N st). MS (EI, 70 eV) *m/z* (%): 319 (M$^+$, 12), 254 (5), 225 (4), 211 (4), 187 (8), 165 (100), 147 (4), 121 (13), 91 (12), 77 (11). HRMS (UPLC MS ESI$^+$): Calculated for [C$_{17}$H$_{21}$NNaO$_5$]$^+$: 342.1317 [(M+Na)$^+$]; found: 342.1323. The e.e. was determined by HPLC using a Chiralpak IA column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 1.0 mL/min; τ_{major} = 19.17 min, τ_{minor} = 23.19 min (90% e.e.). [α]$_D^{20}$: +47.31 (*c* = 0.34, CHCl$_3$).



(4*S*,4a*R*,11a*R*)-7-bromo-11a-hydroxy-4-(nitromethyl)-1,2,3,4,4a,10,11,11a-octahydro-5*H*-dibenzo[*a,d*][7]annulen-5-one (6i). Following the *General Procedure B* compound **6i** (8.70 mg, 0.024 mmol) was isolated by FC (EtOAc/hexanes 2:8) after 3 days, starting from adduct **4i** (26.3 mg, 0.062 mmol) and LiOH (4.4 mg, 0.10 mmol). Yield: 38% (e.e.: 90%). White solid. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$): 7.83 (d, J = 2.3 Hz, 1H), 7.50 (dd, J = 8.1, 2.2 Hz, 1H), 7.13 (d, J = 8.2 Hz, 1H), 4.43-4.31 (m, 2H), 3.08-2.88 (m, 4H), 2.38-2.20 (m, 1H), 1.98-1.80 (m, 2H), 1.81-1.60 (m, 5H), 1.56 (s, 1H). ^{13}C NMR (δ, ppm) (75 MHz, CDCl$_3$): 202.3, 142.2, 141.1, 134.6, 132.1, 131.2, 120.8, 79.0, 73.1, 57.9, 43.9, 36.9, 32.8, 30.7, 28.4, 20.5. IR (ATR) cm^{-1}: 3522 (O-H st), 1680 (C=O st), 1544 (N=O st), 758 (C-N st). MS (EI, 70 eV) *m/z* (%): 369 (1), 303 (13), 288 (10), 212 (53), 194 (14), 165 (22), 128 (31), 107 (100), 89 (42), 69 (13), 55 (30). HRMS (UPLC MS ESI$^+$): Calculated for [$C_{16}H_{18}BrNNaO_4$]$^+$: 390.0317 [(M+Na)$^+$]; found: 390.0314. The e.e. was determined by HPLC using a Chiralpak ADH column [*n*-hexane/*i*-PrOH (95:05)]; flow rate 1.0 mL/min; τ_{major} = 39.71 min, τ_{minor} = 51.34 min (90% e.e.). [α]$_D^{20}$: +16.57 (*c* = 0.95, CHCl$_3$). M.p.: 68-70 °C (hexanes/EtOAc).



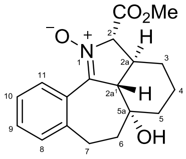
(4*S*,4a*R*,11a*R*)-7-fluoro-11a-hydroxy-4-(nitromethyl)-1,2,3,4,4a,10,11,11a-octahydro-5*H*-dibenzo[*a,d*][7]annulen-5-one (6j). Following the *General Procedure B* compound **6j** (10.3 mg, 0.033 mmol) was isolated by FC (EtOAc/hexanes 3:7) after 4 days, starting from adduct **4j** (35.8 mg, 0.098 mmol) and LiOH (7.0 mg, 0.17 mmol). Yield: 34% (e.e.: 90%). Colorless oil. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$): 7.41 (dd, J = 8.9, 2.8 Hz, 1H), 7.22 (dd, J = 8.5, 5.2 Hz, 1H), 7.18 - 7.03 (m, 1H, 4.46-4.34 (m, 2H), 3.06-2.91 (m, 4H), 2.36-2.23 (m, 1H), 1.97-1.83 (m, 2H), 1.79-1.61 (m, 5H), 1.57 (s, 1H). ^{13}C NMR (δ, ppm) (75 MHz, CDCl$_3$): 202.4, 161.5 (d, $^1J_{CF}$ =246.8 Hz), 141.1 (d, $^3J_{CF}$ = 5.9 Hz), 139.2 (d, $^4J_{CF}$ = 3.2 Hz), 132.1 (d, $^3J_{CF}$ = 7.2 Hz), 118.8 (d, $^2J_{CF}$ =21.4 Hz), 115.0 (d, $^2J_{CF}$ = 22.6 Hz), 79.1, 73.1, 57.8, 44.2, 36.9, 32.8, 30.5, 28.4, 20.5. IR (ATR) cm^{-1}: 3526 (O-H st), 1679 (C=O st), 1547 (N=O st). MS (EI, 70 eV) *m/z* (%): 261 (M$^+$-NO$_2$, 2), 241 (14), 213 (16), 199 (15), 175 (22), 151 (72), 133 (35), 122 (21), 107 (100), 93 (28), 79 (30), 67 (20), 55 (31). HRMS (UPLC MS ESI$^+$): Calculated for [$C_{16}H_{18}FNNaO_4$]$^+$: 330.1118 [(M+Na)$^+$]; found: 330.1124. The e.e. was determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 23.69 min, τ_{minor} = 27.55 min (90% e.e.). [α]$_D^{20}$: +20.13 (*c* = 1.42, CHCl$_3$).



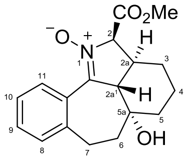
(4S,4a*R*,9a*S*)-9a-hydroxy-4-(nitromethyl)decahydro-5*H*-benzo[7]annulen-5-one (6k). Following the *General Procedure C* compound **6k** (6.9 mg, 0.029 mmol) was isolated by FC (EtOAc/hexanes 3:7) after 15 h, starting from adduct **4k** (17.0 mg, 0.045 mmol) and Pd/C (3.3 mg) in 3.0 mL of MeOH. Yield: 63%. Colorless oil. ^{1}H NMR (δ, ppm) (300 MHz, CDCl$_3$) (*denotes partially overlapped resonances): 4.37-4.19 (m, 2H), 2.91 (d, J = 11.6 Hz, 1H), 2.84-2.65 (m, 2H), 2.61-2.45 (m, 1H), 2.04-1.88 (m, 1H), 2.00* (s, 1H), 1.88-1.52 (m, 7H), 1.42-1.13 (m, 4H). ^{13}C NMR (δ, ppm) (75 MHz, CDCl$_3$): 214.6, 79.9, 70.5, 56.9, 46.5, 45.1, 39.8, 34.2, 28.4, 23.0, 21.7, 20.5. IR (ATR) cm^{-1}: 3483 (O-H st), 1695 (C=O st), 1548 (N=O st). MS (EI, 70 eV) *m/z* (%): 234 (1), 147 (22), 133 (18), 121 (17), 110 (69), 93 (51), 81 (66), 67 (50), 55 (100). [α]$_D^{20}$: + 234.0 (*c* = 0.34, CHCl$_3$).

2.4 Synthesis of Nitrones **7a** and **7’a**

To a solution of adduct **4a** (66.0 mg, 0.19 mmol) in anhydrous MeOH (0.6 mL) was added under inert atmosphere Pd/C 10% weight (6.6 mg) and ammonium formate (120 mg, 1.9 mmol). The mixture was stirred at room temperature for 6 h, filtered through a celite pad and concentrated under reduced pressure. The crude was then purified by FC (EtOAc/hexanes gradient from 7:3 to 8:2) to afford pure nitrones **7a** (16.3 mg, 0.052 mmol) and **7’a** (12.0 mg, 0.038 mmol) in 47% overall yield.



(2S,2a*S*,2a^1*S*,5a*R*)-5a-hydroxy-2-(methoxycarbonyl)-2a,2a^1,3,4,5,5a,6,7-octahydro-2*H*-benzo[6,7]cyclohepta[1,2,3-*cd*]isoindole 1-oxide (7a): White solid. ^{1}H NMR (δ, ppm) (500 MHz, $CDCl_3$): 9.14-9.06 (m, 1H), 7.33-7.30 (m, 2H), 7.23-7.16 (m, 1H), 4.64-4.55 (m, 1H), 3.93 (s, 3H), 3.04-2.91 (m, 3H), 2.86 (ddd, *J* = 14.8, 6.0, 3.6 Hz, 1H), 2.15-2.00 (m, 2H), 1.98-1.83 (m, 2H), 1.81-1.71 (m, 2H), 1.54-1.41 (m, 2H), 1.36 (s, 1H). ^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$): 168.1, 143.5, 141.0, 130.8, 130.2, 128.6, 128.4, 126.7, 79.3, 71.2, 56.1, 53.1, 42.6, 40.73, 40.68, 31.6, 26.5, 21.9. IR (ATR) cm^{-1}: 3361 (O-H st), 1752 (C=O st), 1199 (C-O st). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{18}H_{21}FNNaO_4]^+$: 338.1368 [(M+Na)$^+$]; found: 338.1373. The e.e. was determined by HPLC using a Chiralpak AZ-3 column [*n*-hexane/*i*-PrOH (70:30)]; flow rate 1.0 mL/min; τ_{major} = 36.50 min, τ_{minor} = 53.82 min (94% e.e.). $[\alpha]_D^{20}$: -29.77 (*c* = 0.89, $CHCl_3$). M.p.: 170-173 °C (hexanes/EtOAc).



(2*R*,2a*S*,2a^1*S*,5a*R*)-5a-hydroxy-2-(methoxycarbonyl)-2a,2a^1,3,4,5,5a,6,7-octahydro-2*H*-benzo[6,7]cyclo*H*epta[1,2,3-*cd*]isoindole 1-oxide (7'a): Colorless oil. ^{1}H NMR (δ, ppm) (500 MHz, Acetone-*d*$_6$): 9.18 (dd, *J* = 7.7, 1.7 Hz, 1H, 7.33-7.17 (m, 3H), 4.69 (dd, *J* = 9.1, 1.0 Hz, 1H), 3.80 (s, 3H), 3.23-3.12 (m, 2H), 3.00 (d, *J* = 11.2 Hz, 1H), 2.90-2.78 (m, 2H), 2.06-1.97 (m, 1H), 1.96-1.82 (m, 3H), 1.77-1.64 (m, 2H), 1.58-1.47 (m, 1H), 1.26-1.10 (m, 1H). ^{13}C NMR (δ, ppm) (75 MHz, Acetone): 168.8, 143.1, 131.1, 130.90, 130.90, 130.74, 129.0, 126.5, 80.2, 71.5, 57.4, 52.7, 42.1, 41.1, 37.4, 31.9, 26.5, 22.6. IR (ATR) cm^{-1}: 3322 (O-H st), 1745 (C=O st), 1207 (C-O st). HRMS (UPLC MS ESI$^+$): Calculated for $[C_{18}H_{21}FNNaO_4]^+$: 338.1368 [(M+Na)$^+$]; found: 338.1374. The e.e. was determined by HPLC using a Chiralpak IA column [*n*-hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 22.92 min, τ_{minor} = 39.06 min (92% e.e.). $[\alpha]_D^{20}$: -85.29 (*c* = 0.33, $CHCl_3$).

3. X-Ray Analysis of Compound 6i and 7a

Crystal Data for **6i** $C_{16}H_{18}NO_4Br$ (CCDC 2010938) (M =368.22 g/mol): monoclinic, space group $P2_1$ (no. 4), a = 10.42782(17) Å, b = 7.69850(11) Å, c = 11.51764(17) Å, β = 106.5299(17)°, V = 886.41(2) Å^3, Z = 2, T = 150.00(10) K, μ(CuKα) = 3.303 mm^{-1}, $Dcalc$ = 1.380 g/cm^3, 16349 reflections measured (8° ≤ 2Θ ≤ 149.54°), 3542 unique (R_{int} = 0.0380, R_{sigma} = 0.0286) which were used in all calculations. The final R_1 was 0.0573 (>2sigma(I)) and wR_2 was 0.1885 (all data).

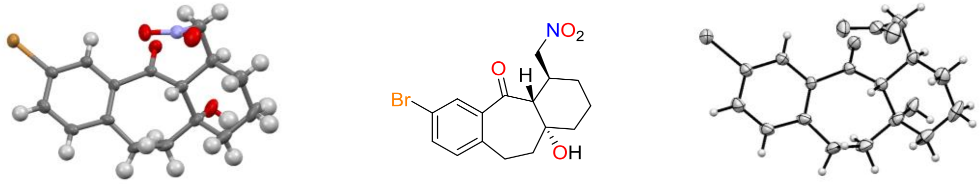


Figure ESI-1. Structure and absolute configuration of compound **6i** determined by X-ray diffraction analysis. ORTEP diagram (thermal ellipsoids are set at a 50% probability level)

Table ESI-1 Crystal data and structure refinement for **6i**

Identification code	a20190047_RM1098rem
Empirical formula	$C_{16}H_{18}NO_4Br$
Formula weight	368.22
Temperature/K	150.00(10)
Crystal system	monoclinic
Space group	$P2_1$
a/Å	10.42782(17)
b/Å	7.69850(11)
c/Å	11.51764(17)
α/°	90.00
β/°	106.5299(17)
γ/°	90.00
Volume/Å^3	886.41(2)
Z	2
ρ_{calc}g/cm^3	1.380
μ/mm^{-1}	3.303
F(000)	376.0
Crystal size/mm^3	0.651 × 0.132 × 0.11
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	8 to 149.54
Index ranges	$-12 \leq h \leq 13$, $-9 \leq k \leq 9$, $-14 \leq l \leq 12$
Reflections collected	16349
Independent reflections	3542 [R_{int} = 0.0380, R_{sigma} = 0.0286]
Data/restraints/parameters	3542/1/201
Goodness-of-fit on F^2	1.195
Final R indexes [I>=2σ (I)]	R_1 = 0.0573, wR_2 = 0.1850
Final R indexes [all data]	R_1 = 0.0596, wR_2 = 0.1885
Largest diff. peak/hole / e Å^{-3}	1.85/-0.44
Flack parameter	0.00(4)

Table ESI-2. Fractional Atomic Coordinates ($\times10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2\times10^3$) for **6i**. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
Br1	-3277.9(4)	-2110.4(9)	-1017.0(5)	38.4(3)
C15	-6649(8)	4643(9)	-2098(7)	40.2(16)
C10	-11238(6)	2906(12)	-2456(5)	39.1(11)
C3	-6461(6)	1319(8)	-2203(5)	27.3(12)
C4	-5898(5)	2949(9)	-1809(4)	30.2(9)
C5	-4536(5)	3000(9)	-1167(4)	33.0(11)
O1	-8247(4)	-170(5)	-3566(3)	32.6(8)
C9	-10319(5)	1542(7)	-2783(5)	30.2(11)
C1	-4353(6)	-62(7)	-1322(5)	30.5(11)
C6	-3757(6)	1514(8)	-920(5)	33.2(12)
C2	-5687(5)	-175(7)	-1982(5)	29.3(11)
C14	-7638(7)	4718(8)	-3358(6)	40.0(14)
C16	-10282(6)	-148(8)	-2076(5)	36.3(12)
C13	-9046(6)	3955(7)	-3465(5)	32.6(12)
C11	-11298(7)	4559(10)	-3188(6)	46.1(16)
C7	-7901(5)	1064(7)	-2871(5)	27.1(11)
C8	-8927(5)	2329(7)	-2631(4)	27.5(10)
C12	-9935(7)	5284(8)	-3124(5)	40.6(14)
O3	-10158(6)	707(8)	-83(5)	52.1(14)
O2	-9575(4)	3371(6)	-4684(3)	39.1(10)
O4	-8375(4)	-316(7)	-419(4)	46.4(11)
N1	-9546(5)	77(7)	-770(5)	37.3(11)

Table ESI-3. Anisotropic Displacement Parameters (Å^2×10^3) for **6i**. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
Br1	26.3(3)	31.5(3)	50.2(4)	2.5(3)	-0.7(2)	1.5(2)
C15	47(4)	19(3)	46(3)	5(2)	-1(3)	0(3)
C10	39(3)	42(3)	32(2)	-9(3)	2.5(19)	3(3)
C3	23(3)	25(3)	25(2)	2(2)	-7(2)	-1(2)
C4	35(2)	22(2)	27(2)	1(2)	-3.3(17)	-8(3)
C5	34(2)	26(2)	31(2)	4(2)	-3.8(18)	-8(3)
O1	32.2(19)	28.1(18)	29.3(17)	-5.9(15)	-4.4(15)	2.0(16)
C9	28(3)	30(3)	27(2)	-2(2)	-2(2)	4(2)
C1	27(3)	27(3)	32(2)	1(2)	-1(2)	-4(2)
C6	28(3)	34(3)	30(2)	0(2)	-3(2)	-6(2)
C2	27(3)	22(2)	32(2)	0(2)	-1(2)	-2(2)
C14	52(4)	23(2)	37(3)	9(2)	-1(3)	0(3)
C16	30(3)	31(3)	43(3)	-2(2)	2(2)	-4(2)
C13	42(3)	25(3)	22(2)	2.2(19)	-6(2)	5(2)
C11	51(4)	48(4)	34(3)	7(3)	4(3)	29(3)
C7	28(3)	22(2)	24(2)	0.8(19)	-3.7(19)	-3(2)
C8	30(3)	24(2)	23(2)	-2.0(17)	-0.2(19)	0.2(18)
C12	57(4)	28(3)	30(3)	4(2)	2(3)	14(3)
O3	54(3)	62(4)	35(2)	7(2)	5(2)	10(3)
O2	43(2)	43(3)	21.2(16)	-0.7(14)	-6.5(15)	17.8(17)
O4	27(2)	51(3)	53(3)	18(2)	-1.8(18)	2(2)
N1	33(3)	31(2)	42(3)	10(2)	2(2)	-2(2)

Crystal Data for **7a** $C_{18}H_{21}NO_4$ (CCDC 2010939) (M =315.36 g/mol): orthorhombic, space group $P2_12_12_1$ (no. 19), a = 9.19139(11) Å, b = 11.21187(14) Å, c = 15.13619(18) Å, V = 1559.82(3) Å^3, Z = 4, T = 150.00(10) K, μ(CuKα) = 0.775 mm^{-1}, $Dcalc$ = 1.343 g/cm^3, 16448 reflections measured (9.82° ≤ 2Θ ≤ 148.84°), 3134 unique (R_{int} = 0.0369, R_{sigma} = 0.0240) which were used in all calculations. The final R_1 was 0.0293 (>2sigma(I)) and wR_2 was 0.0751 (all data).

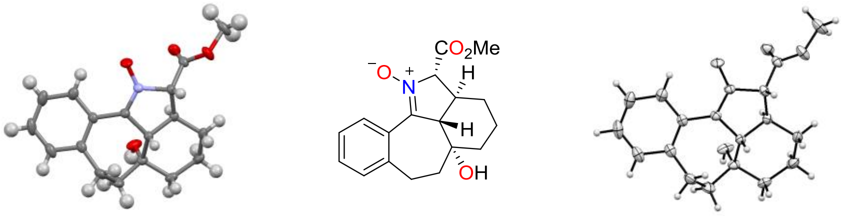


Figure ESI-2. Structure and absolute configuration of compound **7a** determined by X-ray diffraction analysis. ORTEP diagram (thermal ellipsoids are set at a 50% probability level)

Table ESI-4. Crystal data and structure refinement for **7a**

Identification code	a20180380_RM998f1
Empirical formula	$C_{18}H_{21}NO_4$
Formula weight	315.36
Temperature/K	150.00(10)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	9.19139(11)
b/Å	11.21187(14)
c/Å	15.13619(18)
α/°	90.00
β/°	90.00
γ/°	90.00
Volume/Å^3	1559.82(3)
Z	4
ρ_{calc}g/cm^3	1.343
μ/mm^{-1}	0.775
F(000)	672.0
Crystal size/mm^3	0.41 × 0.09 × 0.09
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	9.82 to 148.84
Index ranges	$-11 \leq h \leq 11$, $-13 \leq k \leq 13$, $-17 \leq l \leq 18$
Reflections collected	16448
Independent reflections	3134 [R_{int} = 0.0369, R_{sigma} = 0.0240]
Data/restraints/parameters	3134/0/211
Goodness-of-fit on F^2	1.055
Final R indexes [I>=2σ (I)]	R_1 = 0.0293, wR_2 = 0.0731
Final R indexes [all data]	R_1 = 0.0321, wR_2 = 0.0751
Largest diff. peak/hole / e Å^{-3}	0.19/-0.13
Flack parameter	-0.13(16)

Table ESI-5. Fractional Atomic Coordinates ($\times10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2\times10^3$) for **7a**. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor

Atom	*x*	*y*	*z*	U(eq)
O001	2439.4(13)	9883.7(9)	2023.0(6)	31.1(2)
O4	3171.3(11)	13155.1(10)	2039.5(7)	34.3(3)
O2	2475.1(12)	10115.9(11)	5234.9(6)	35.8(3)
N004	1965.3(12)	10344.4(10)	2754.5(7)	22.0(2)
C005	1348.9(14)	9799.7(12)	3425.9(8)	21.1(3)
C006	1927.7(16)	7723.7(13)	2954.5(10)	29.1(3)
C007	1944.2(14)	11764.3(11)	3868.2(8)	20.8(3)
O3	4626.6(11)	11764.7(10)	2640.7(7)	32.5(2)
C009	100.6(16)	8048.8(13)	4090.8(9)	26.1(3)
C010	2035.1(15)	11669.2(12)	2868.4(8)	22.3(3)
C011	912.4(15)	10739.0(11)	4095.3(8)	20.3(3)
C012	784.5(18)	6046.9(14)	3648.6(12)	39.3(4)
C013	1110.7(15)	8512.9(12)	3479.2(9)	22.8(3)
C014	-35.3(17)	6811.9(14)	4159.9(10)	33.3(3)
C015	3441.8(15)	12162.1(12)	2499.2(8)	24.2(3)
C016	-69(2)	9480.3(15)	5388.9(10)	40.1(4)
C017	-872.3(18)	8819.4(14)	4654.5(10)	34.0(3)
C018	1469.3(16)	12916.7(12)	4301.4(10)	28.6(3)
C019	1765.1(18)	6494.0(14)	3047.7(12)	37.3(4)
C020	1521.7(18)	12713.9(14)	5301.5(10)	33.7(3)
C021	999.8(16)	10459.4(13)	5085.5(8)	24.4(3)
C022	634.6(15)	11626.5(13)	5578.0(9)	27.4(3)
C023	4439.2(19)	13788.4(15)	1708.8(12)	40.3(4)

Table ESI-6. Anisotropic Displacement Parameters (Å^2×10^3) for **7a**. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O001	41.9(6)	35.8(6)	15.5(4)	-2.3(4)	5.6(4)	0.4(5)
O4	29.4(6)	33.6(6)	39.9(5)	18.7(5)	-5.5(4)	-8.5(5)
O2	37.0(6)	53.2(7)	17.2(4)	4.9(5)	0.3(4)	23.2(5)
N004	26.0(6)	23.6(5)	16.5(5)	0.2(4)	-0.4(4)	-1.1(5)
C005	23.2(6)	23.7(6)	16.4(5)	0.0(5)	-1.2(5)	-0.7(5)
C006	25.1(7)	27.3(7)	35.0(7)	-3.6(6)	-4.3(6)	0.7(6)
C007	20.6(6)	20.4(6)	21.3(6)	0.6(5)	-1.4(5)	1.4(5)
O3	26.1(5)	34.6(5)	36.8(6)	7.0(4)	1.9(4)	1.2(5)
C009	26.8(7)	25.9(7)	25.6(7)	4.1(5)	-7.8(5)	-5.2(5)
C010	23.6(6)	21.3(6)	21.9(6)	4.4(5)	-2.2(5)	-0.8(5)
C011	20.8(6)	21.5(6)	18.6(6)	0.9(5)	-0.7(5)	0.9(5)
C012	39.0(9)	20.7(7)	58.3(10)	6.8(7)	-19.3(8)	-2.6(7)
C013	23.3(6)	22.1(7)	23.0(6)	1.5(5)	-4.5(5)	-2.3(5)
C014	33.3(8)	28.8(8)	37.6(8)	10.7(6)	-12.0(6)	-9.8(6)
C015	28.2(7)	25.3(6)	19.1(6)	2.7(5)	-2.5(5)	-3.7(6)
C016	58.8(11)	37.6(9)	23.8(7)	1.9(6)	11.2(7)	-8.4(8)
C017	33.2(8)	35.4(8)	33.5(8)	5.6(6)	8.1(7)	-8.3(6)
C018	25.7(7)	20.1(6)	40.0(8)	-2.6(6)	3.1(6)	1.4(6)
C019	33.8(9)	25.8(7)	52.3(9)	-6.0(7)	-12.2(7)	5.5(6)
C020	32.2(8)	34.1(7)	34.9(7)	-14.5(6)	6.0(6)	0.2(6)
C021	27.4(7)	28.6(7)	17.3(6)	1.3(5)	0.1(5)	3.6(6)
C022	22.3(7)	36.9(8)	23.0(6)	-6.2(6)	1.8(5)	4.6(6)
C023	34.7(9)	41.7(9)	44.6(9)	19.8(7)	-5.1(7)	-14.2(7)

4. NMR Spectra

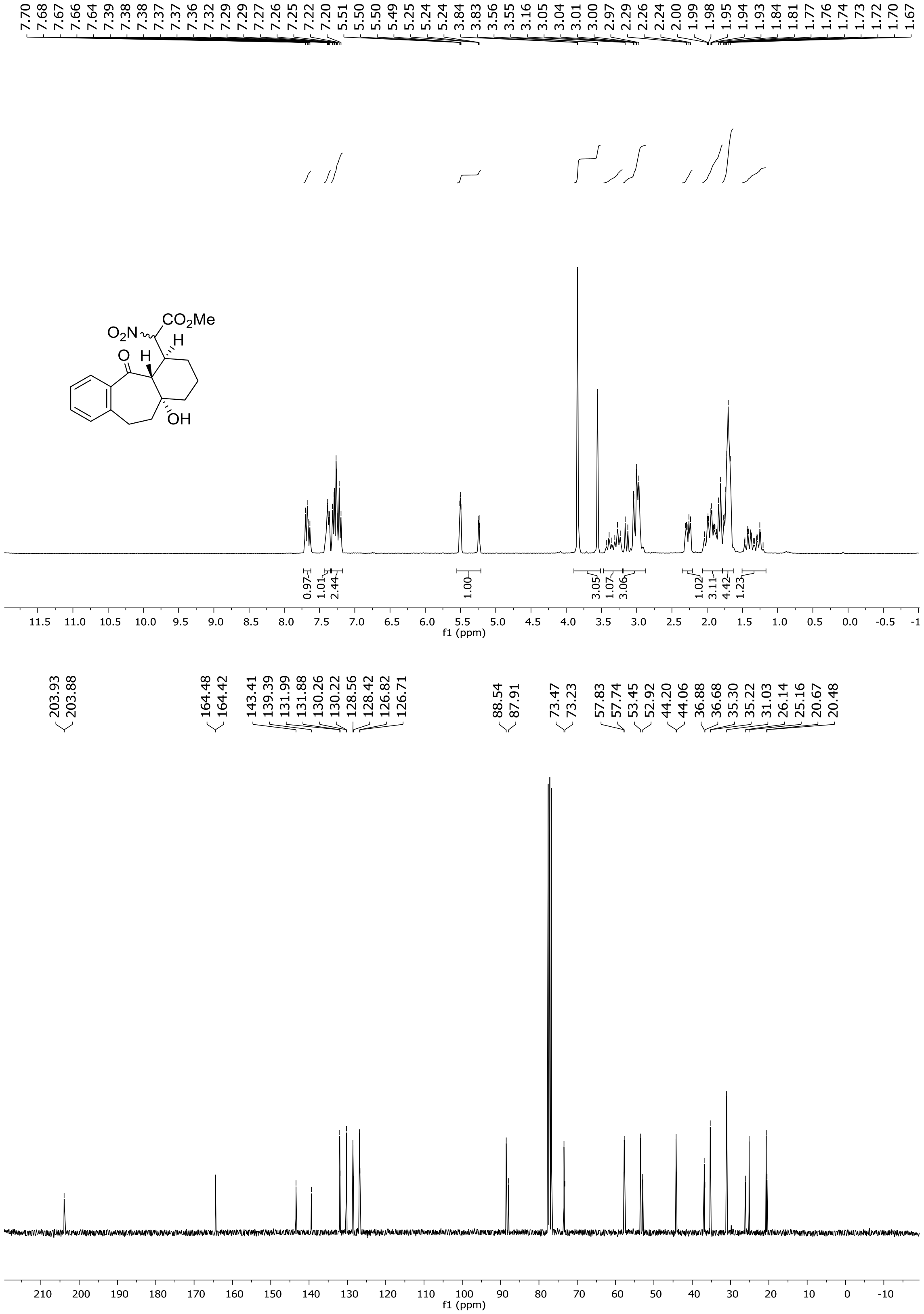


Figure ESI-3. NMR spectra of compound **4a**

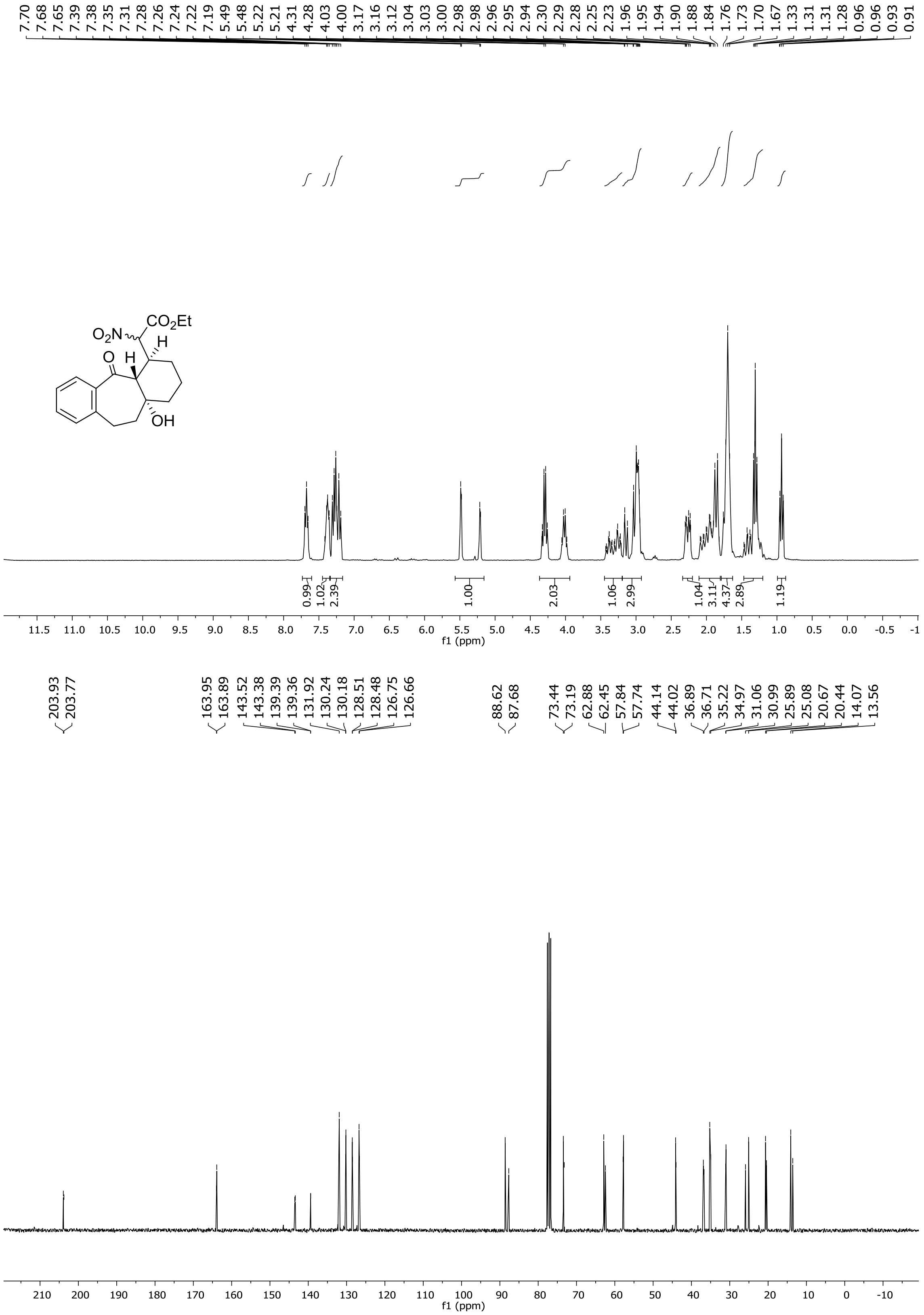


Figure ESI-4. NMR spectra of compound **4b**

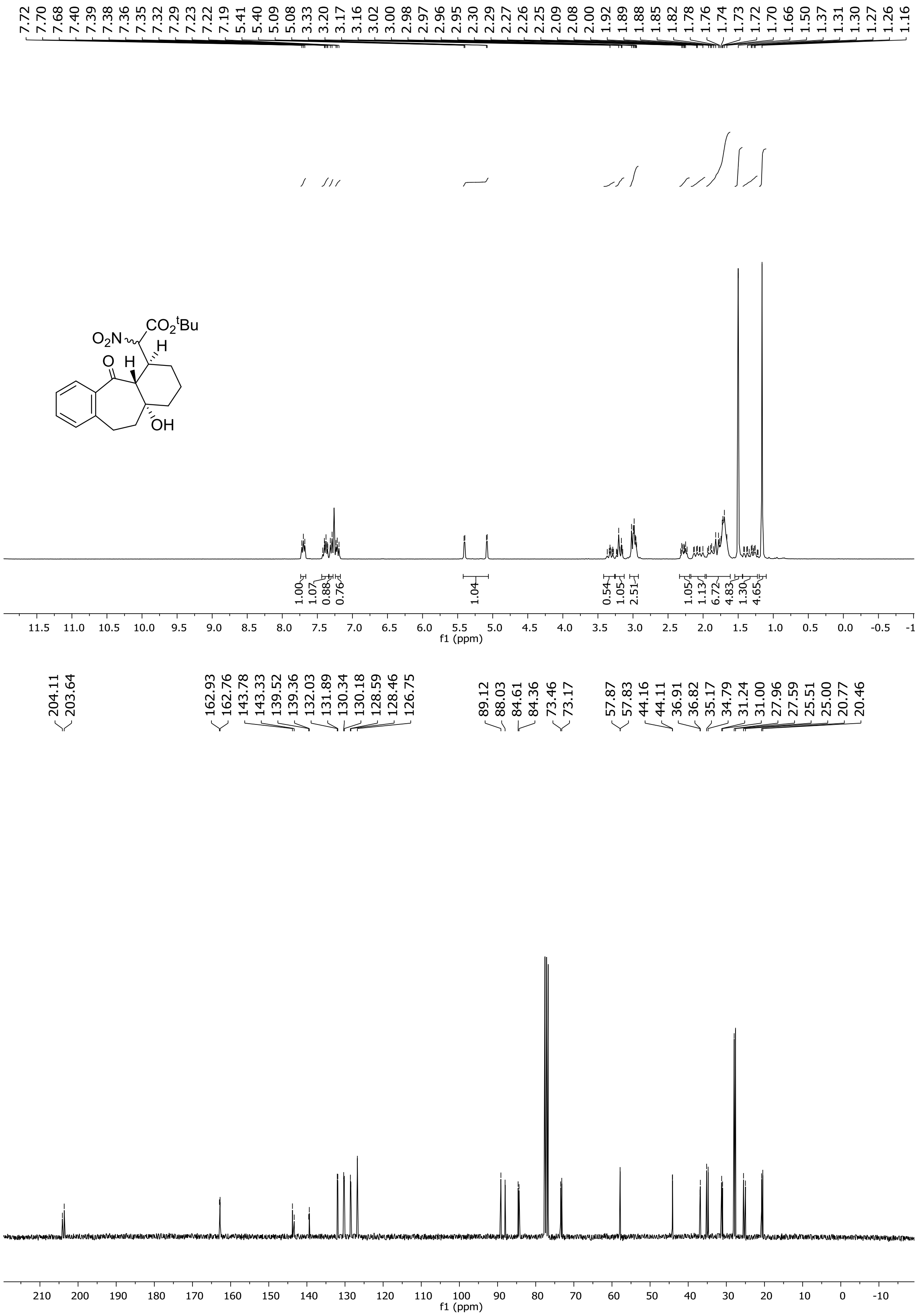


Figure ESI-5. NMR spectra of compound **4c**

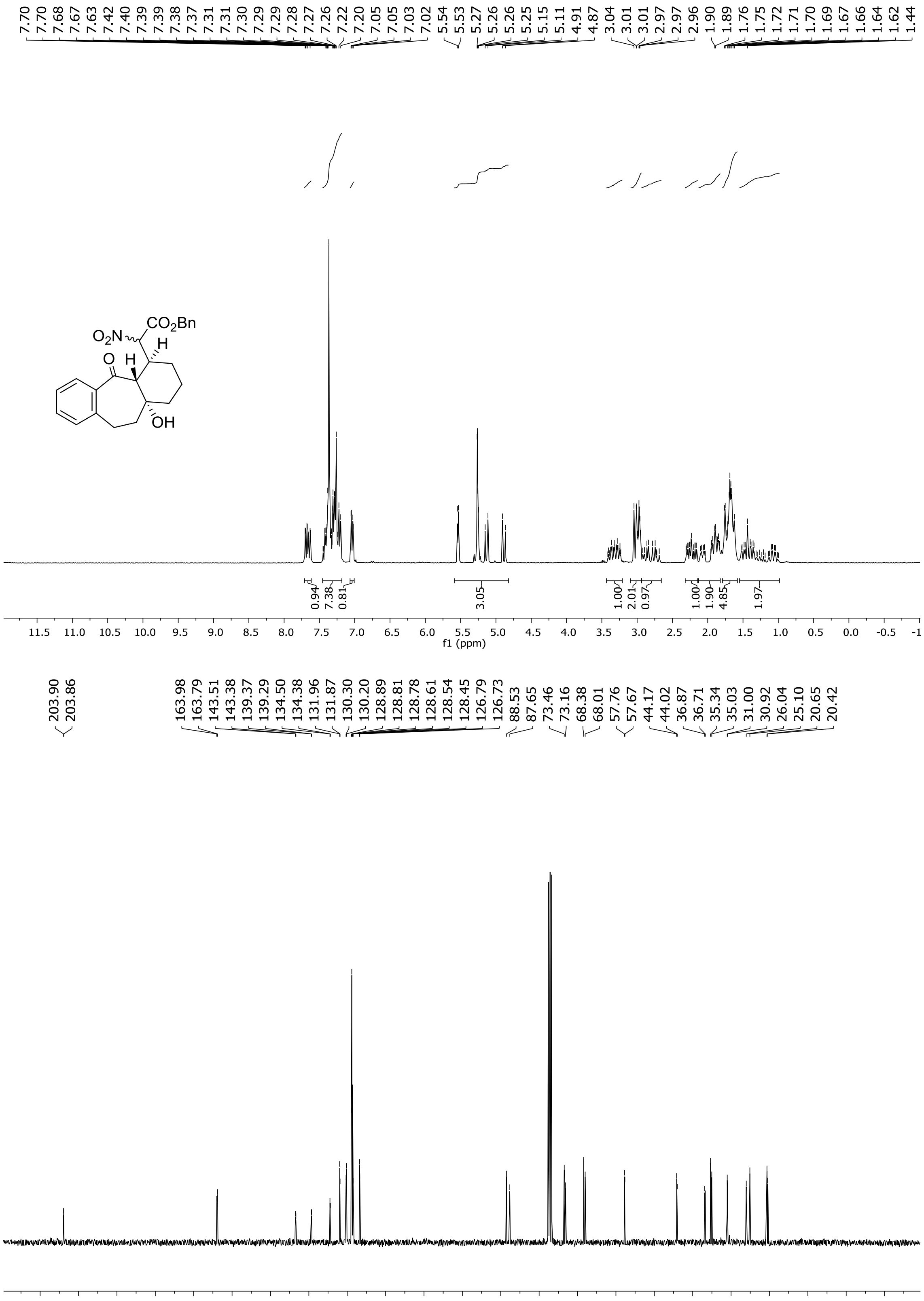


Figure ESI-6. NMR spectra of compound **4d**

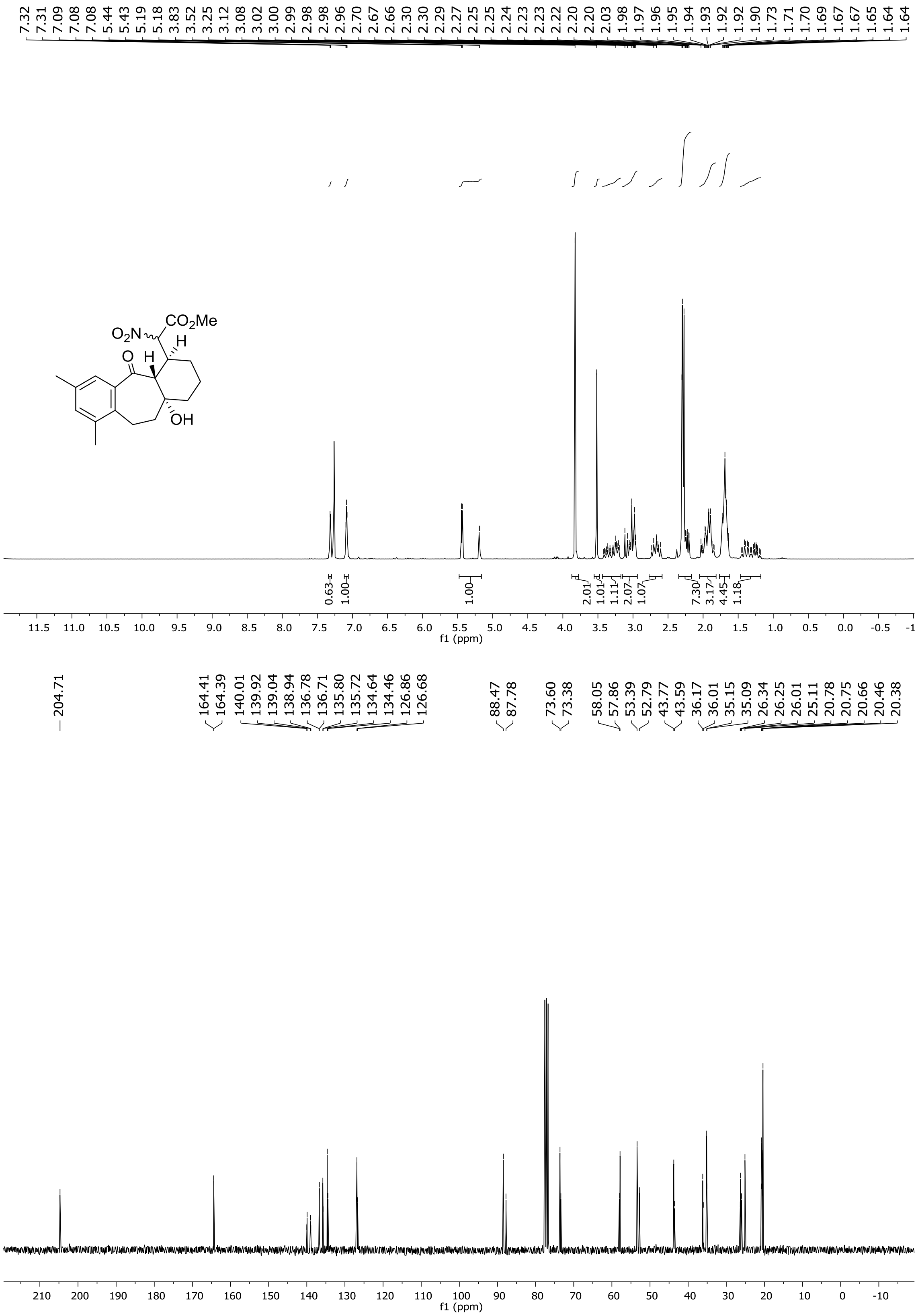


Figure ESI-7. NMR spectra of compound **4f**

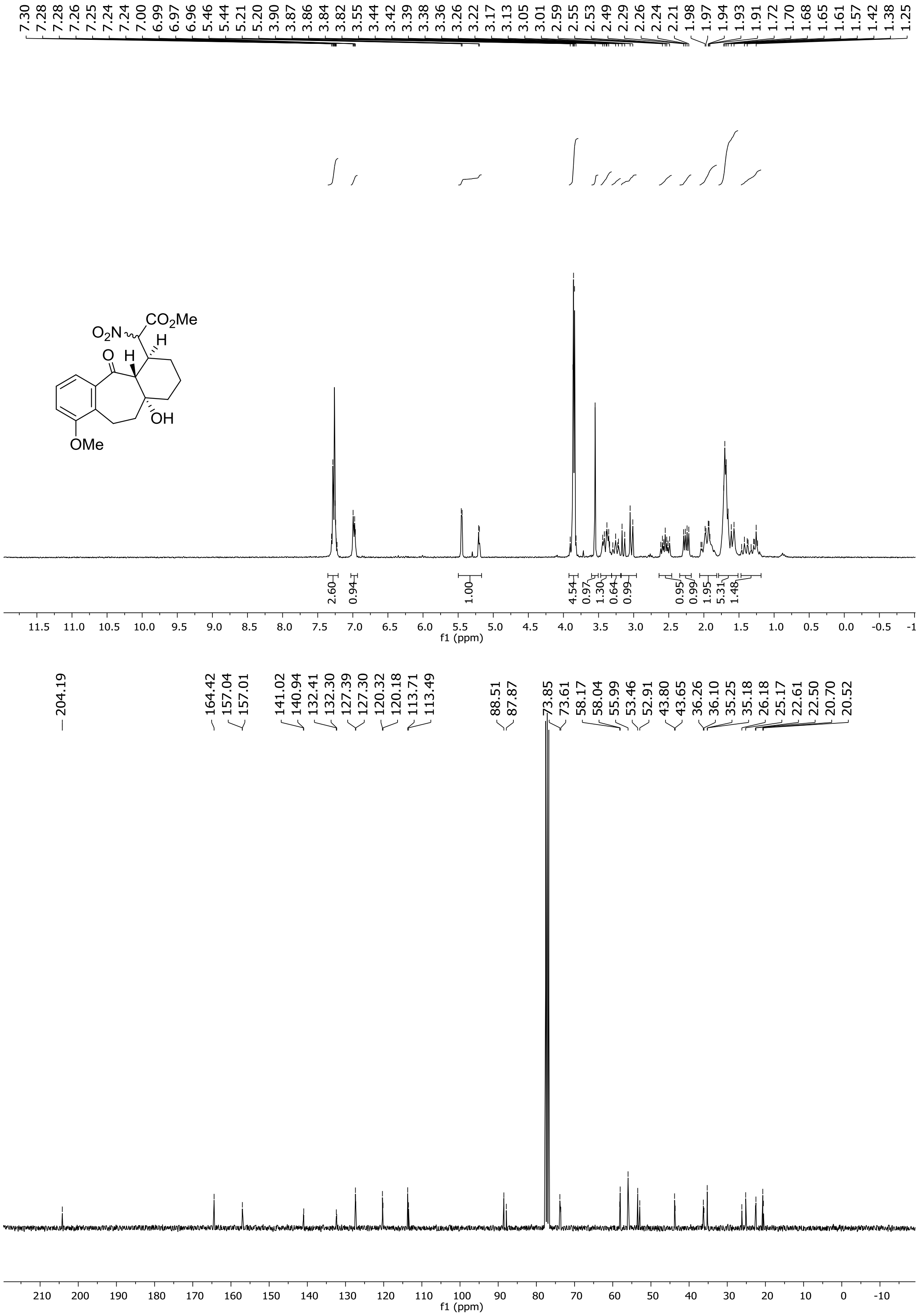


Figure ESI-8. NMR spectra of compound **4g**

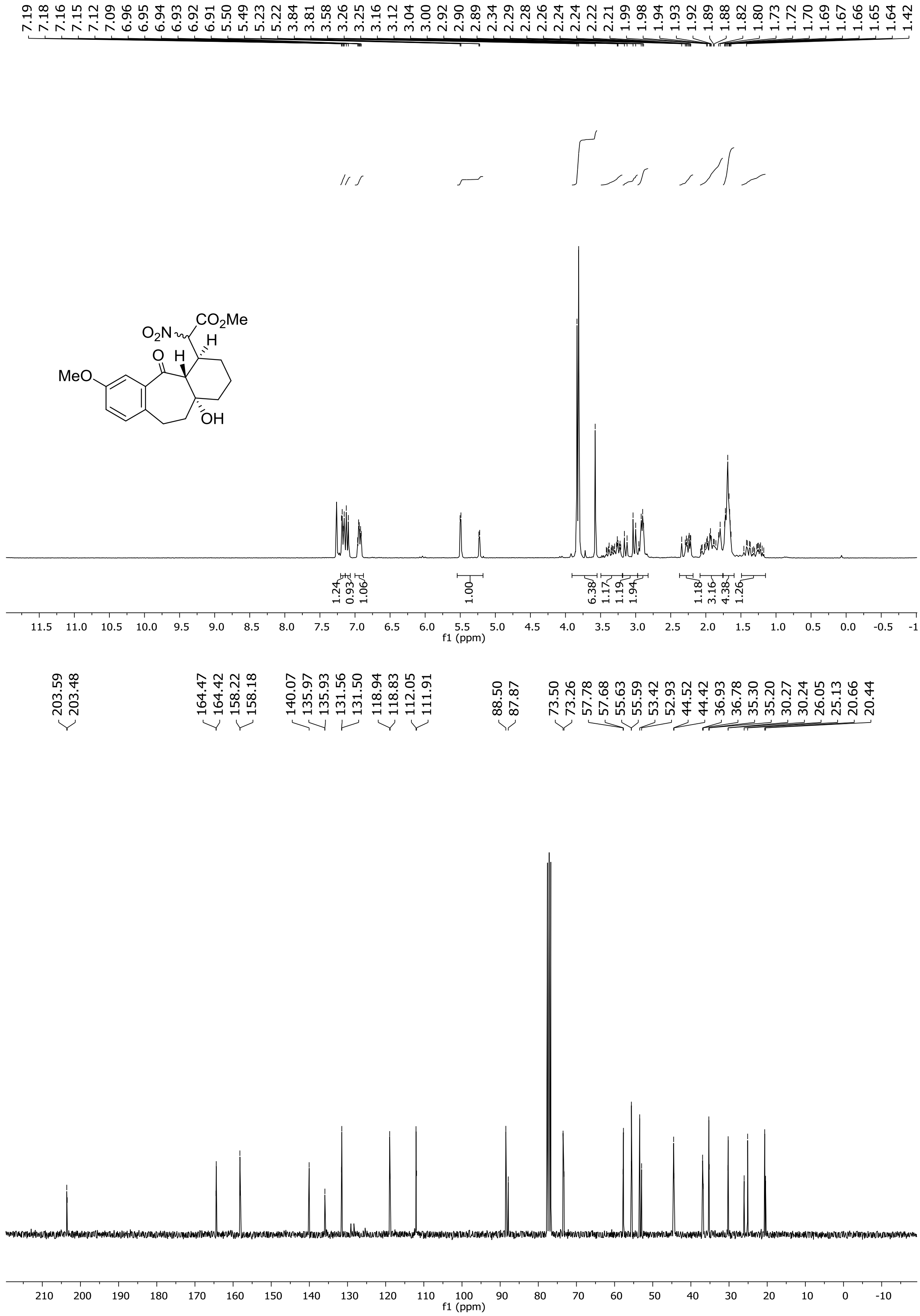


Figure ESI-9. NMR spectra of compound **4h**

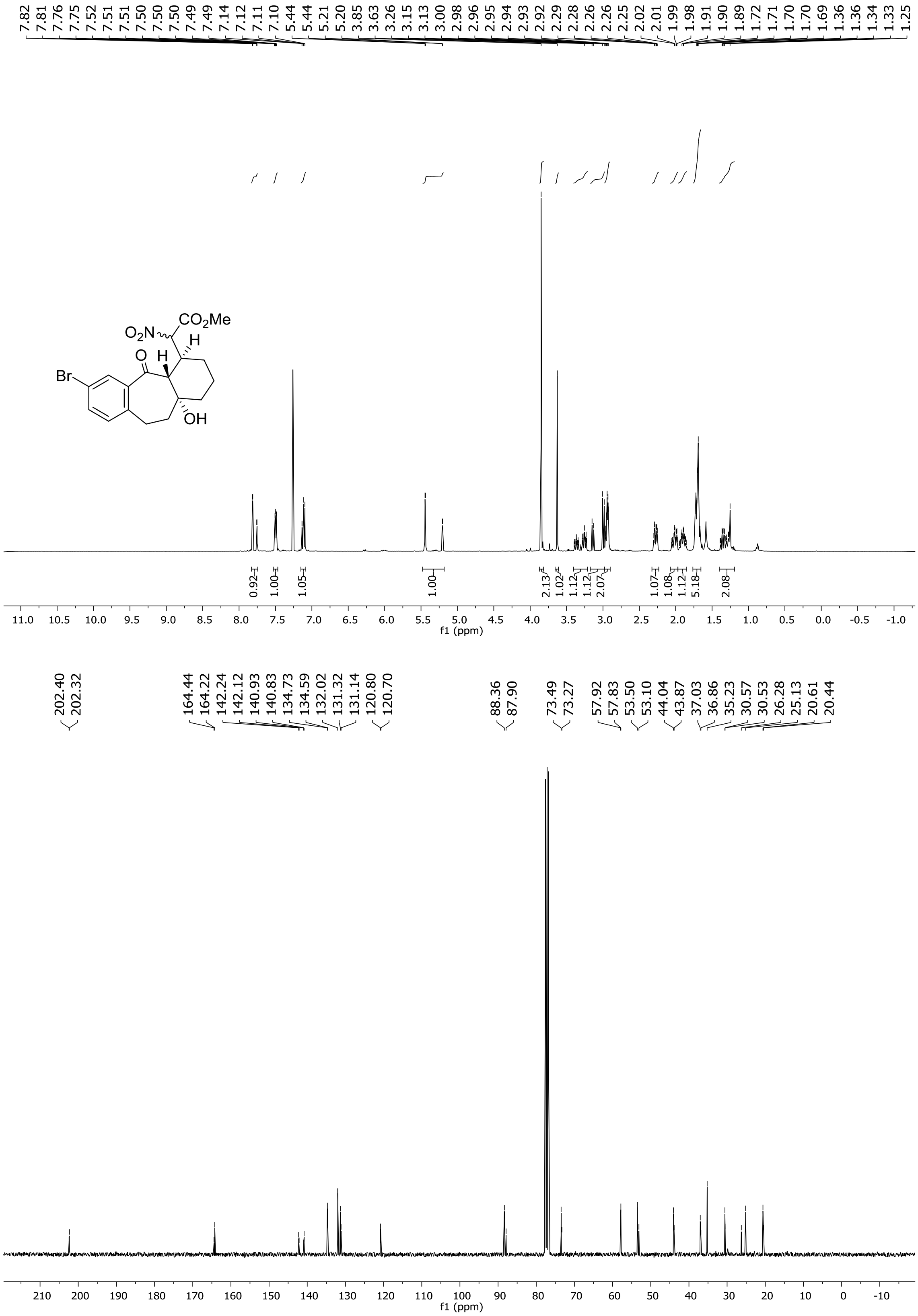


Figure ESI-10. NMR spectra of compound **4i**

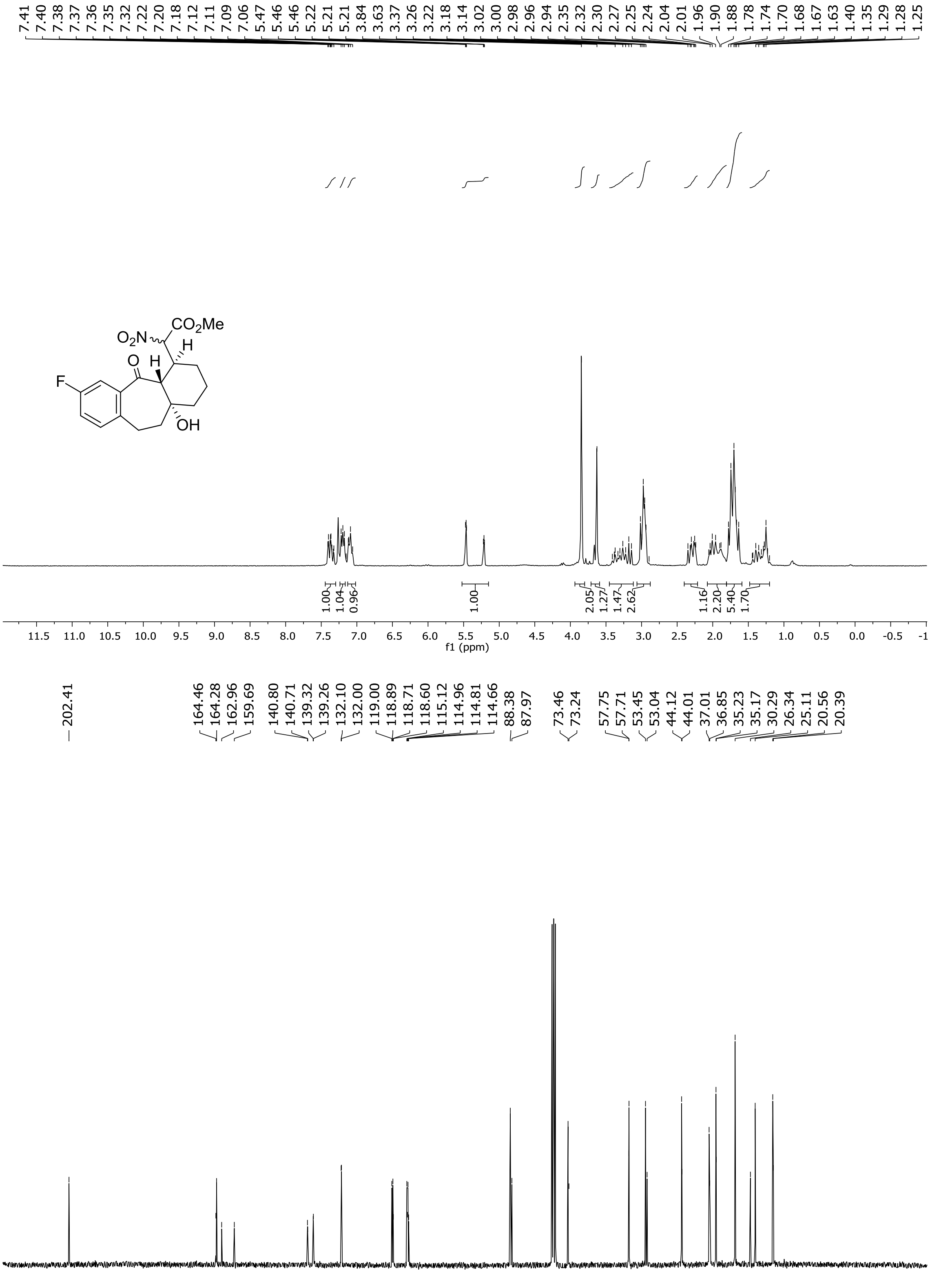


Figure ESI-11. NMR spectra of compound **4j**

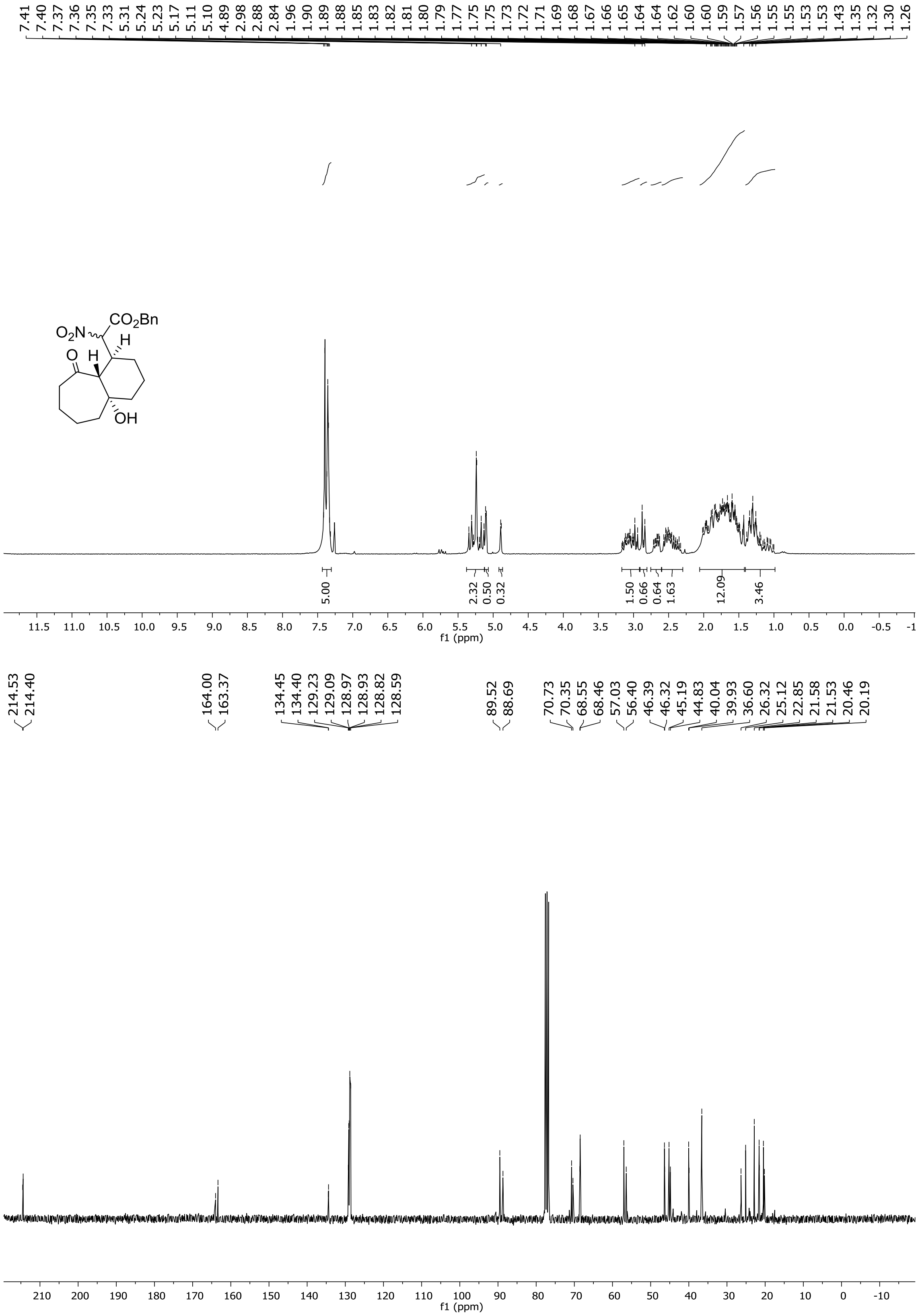


Figure ESI-12. NMR spectra of compound **4k**

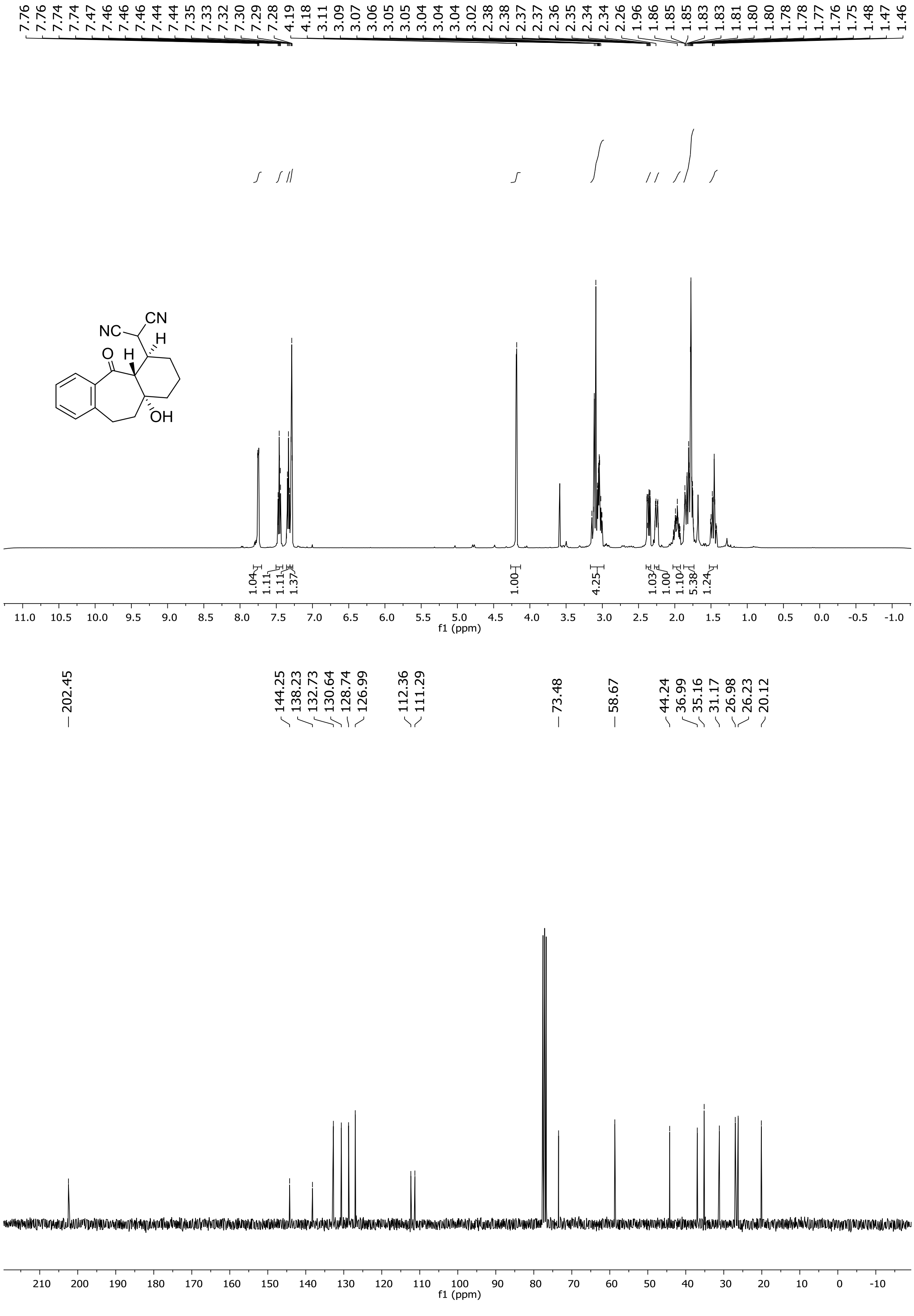


Figure ESI-13. NMR spectra of compound **5b**

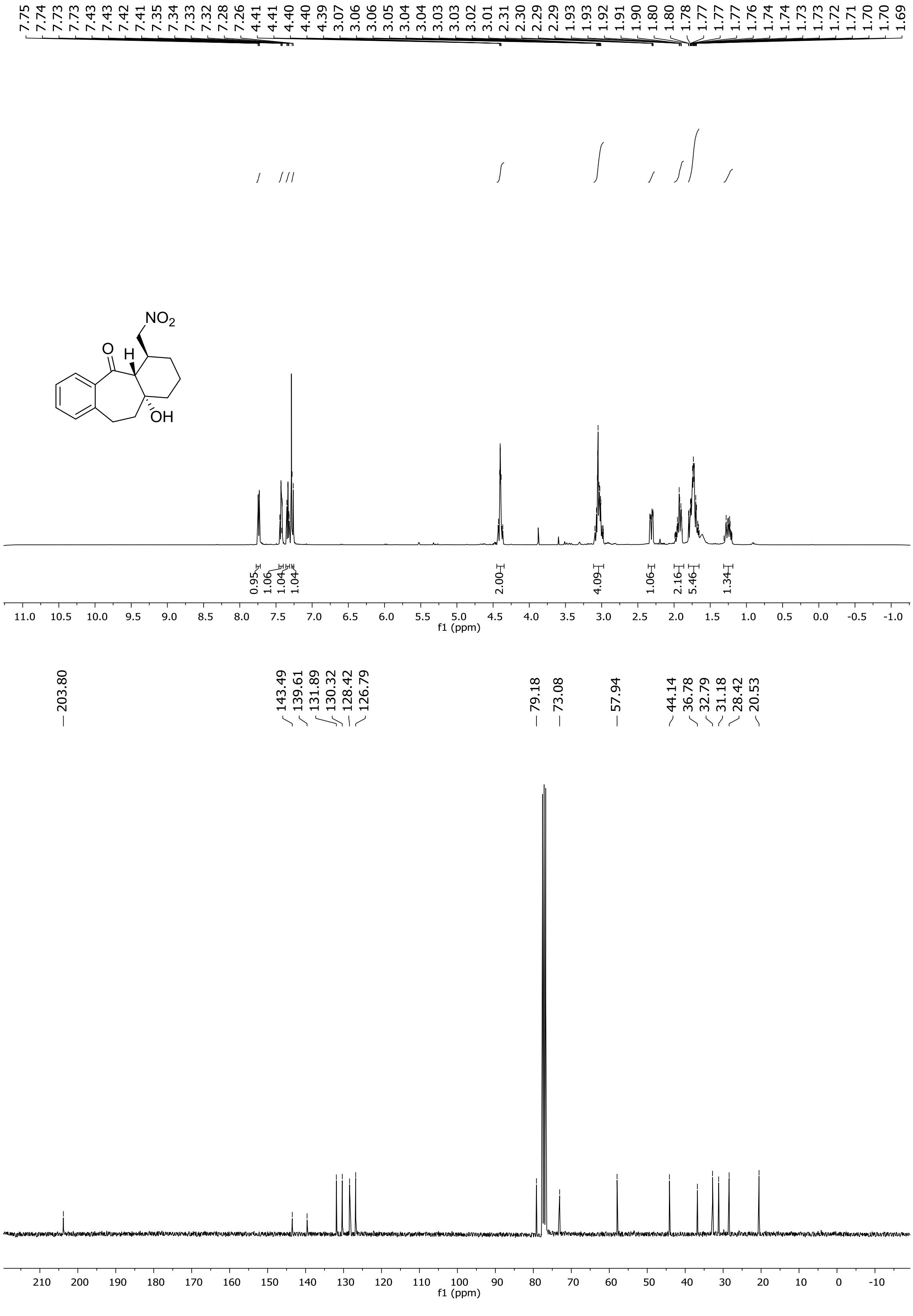


Figure ESI-14. NMR spectra of compound **6a**

Figure ESI-15. NMR spectra of compound **6f**

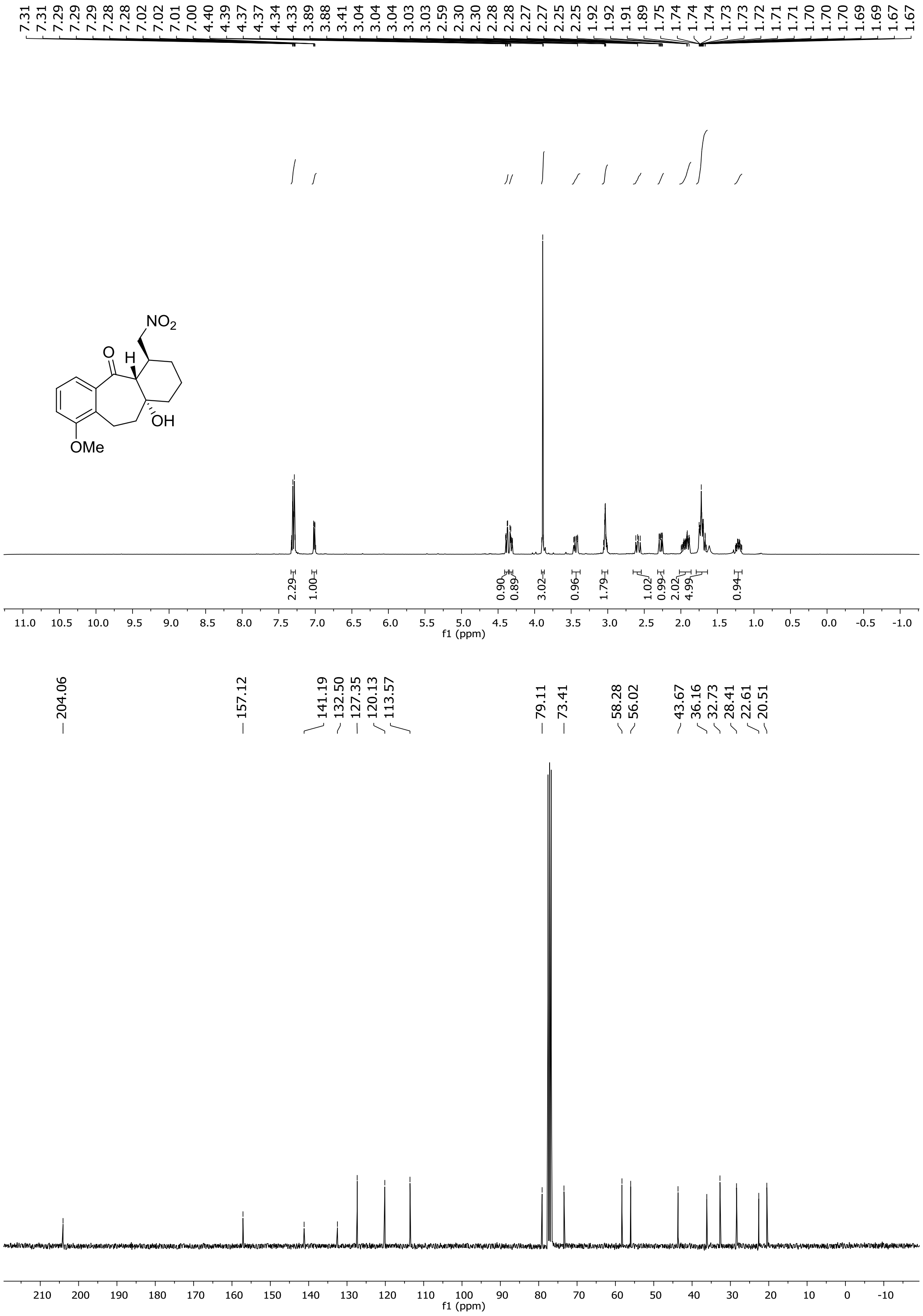


Figure ESI-16. NMR spectra of compound **6g**

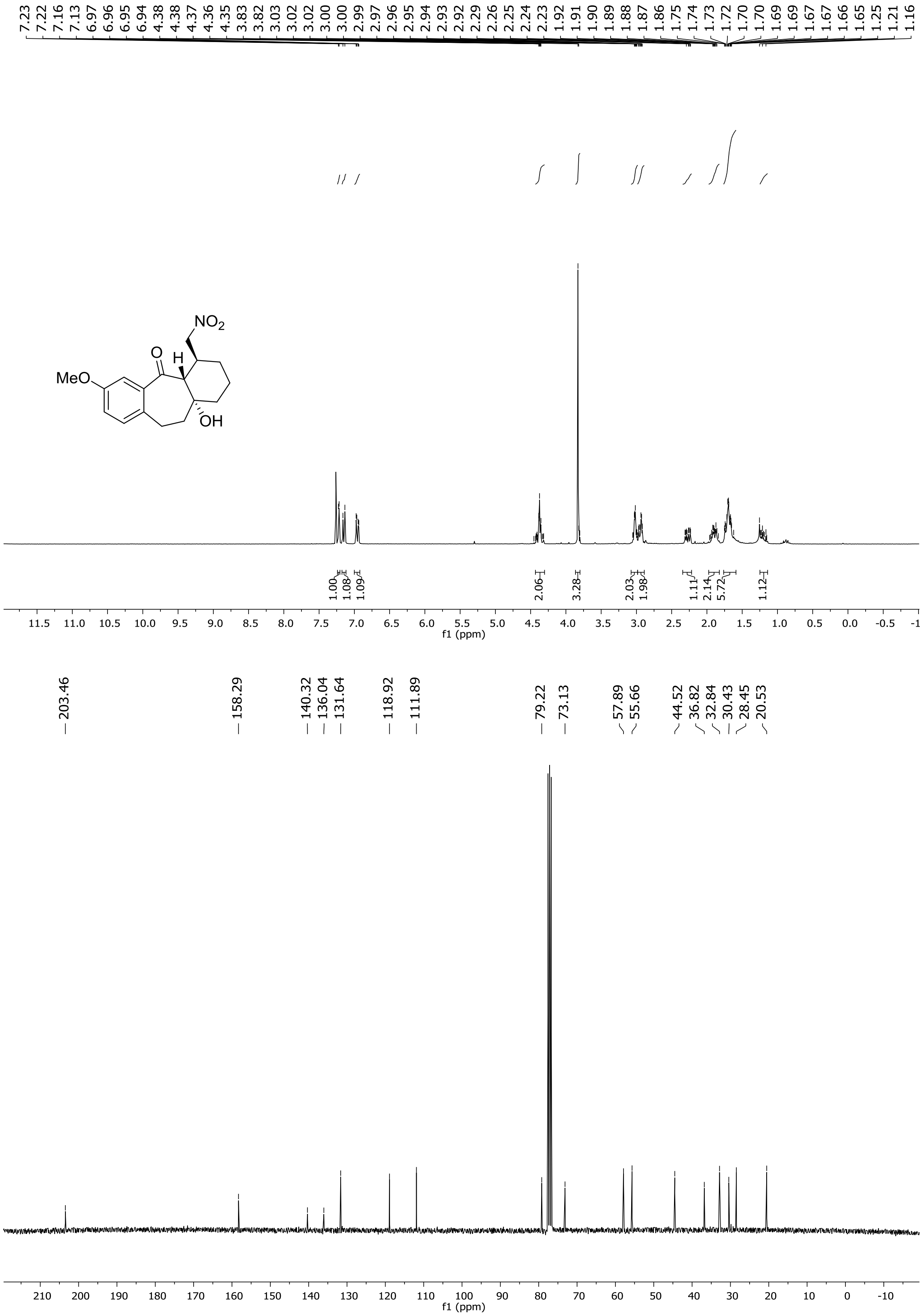


Figure ESI-17. NMR spectra of compound **6h**

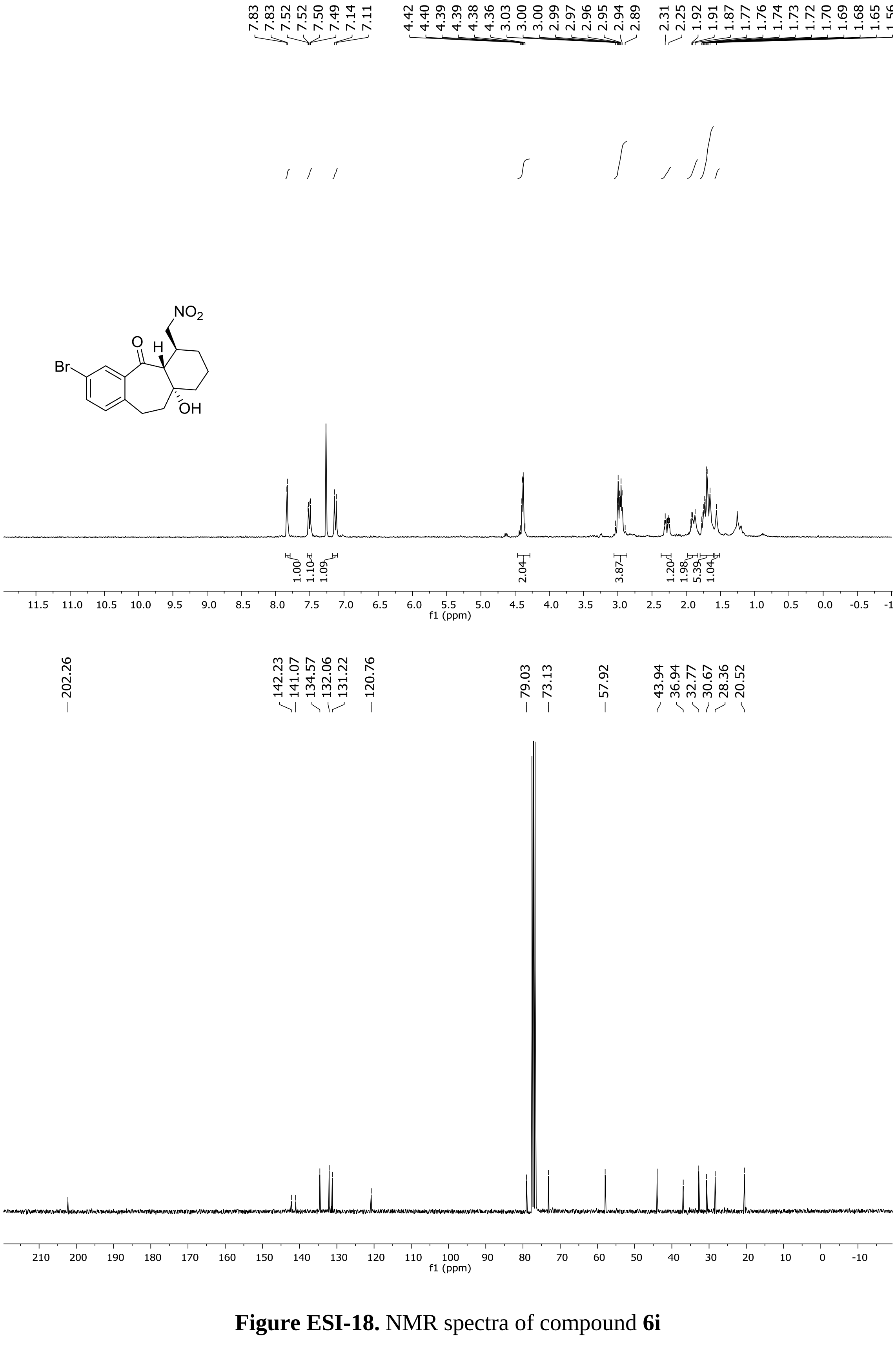


Figure ESI-18. NMR spectra of compound **6i**

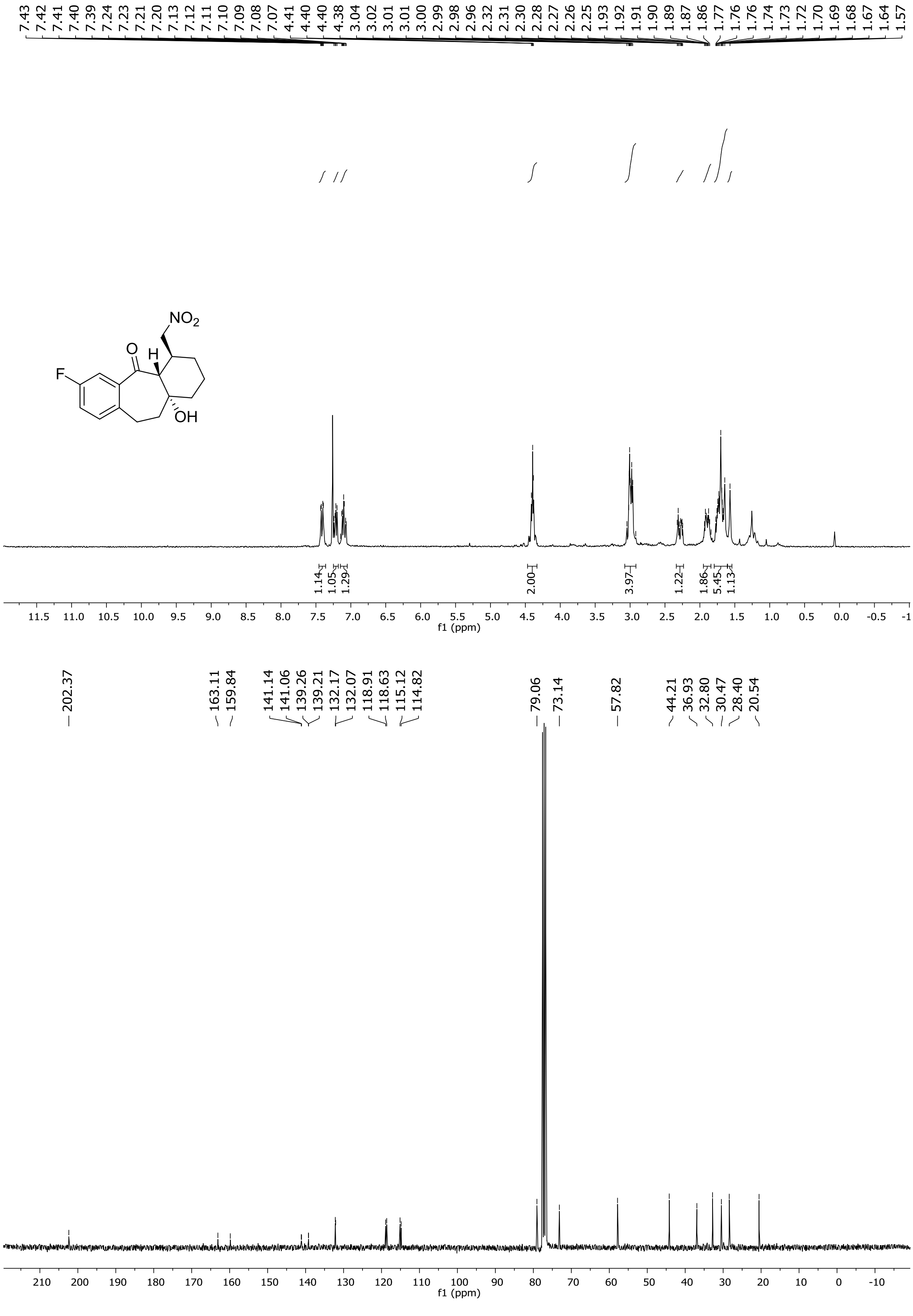


Figure ESI-19. NMR spectra of compound **6j**

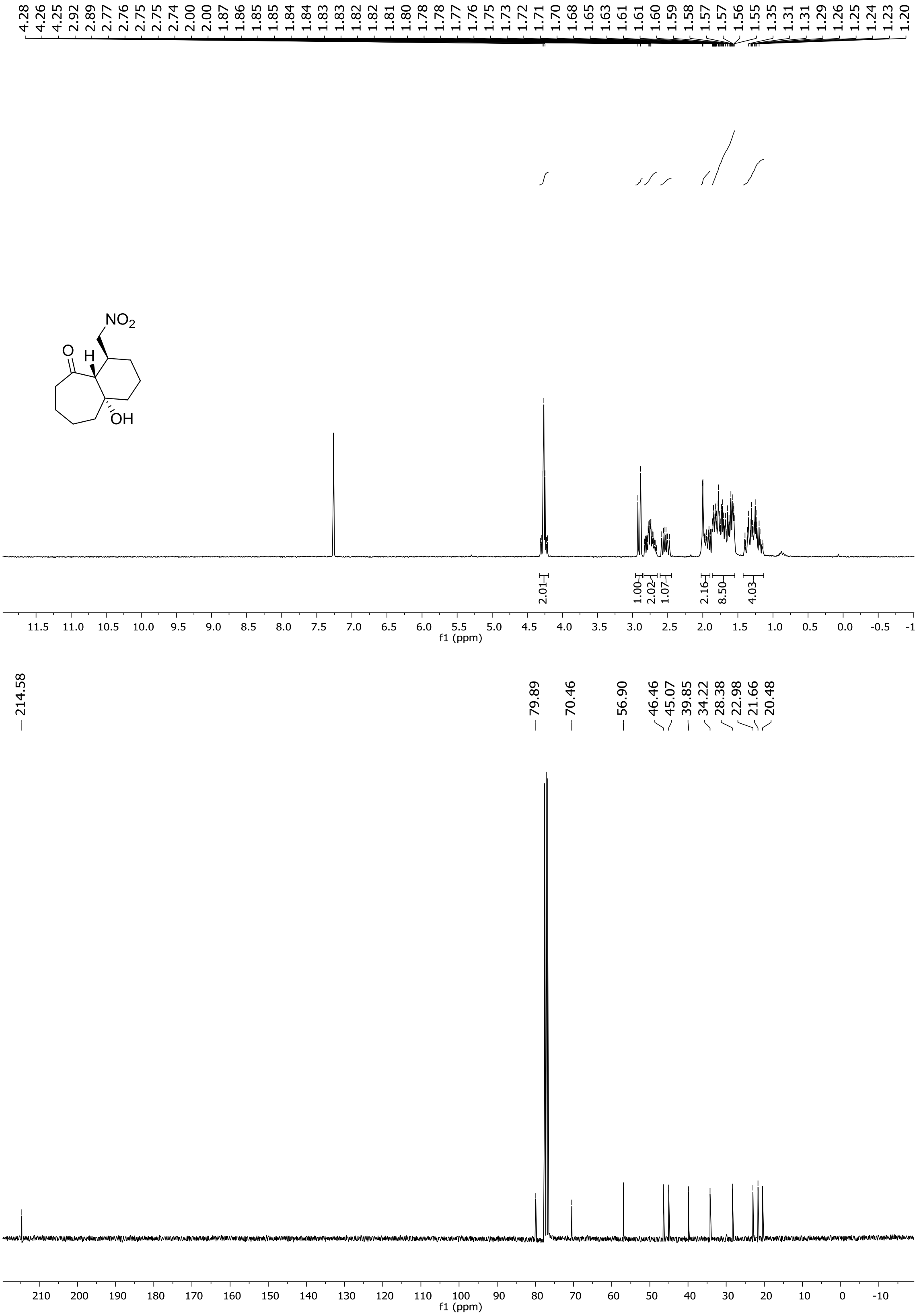


Figure ESI-20. NMR spectra of compound **6k**

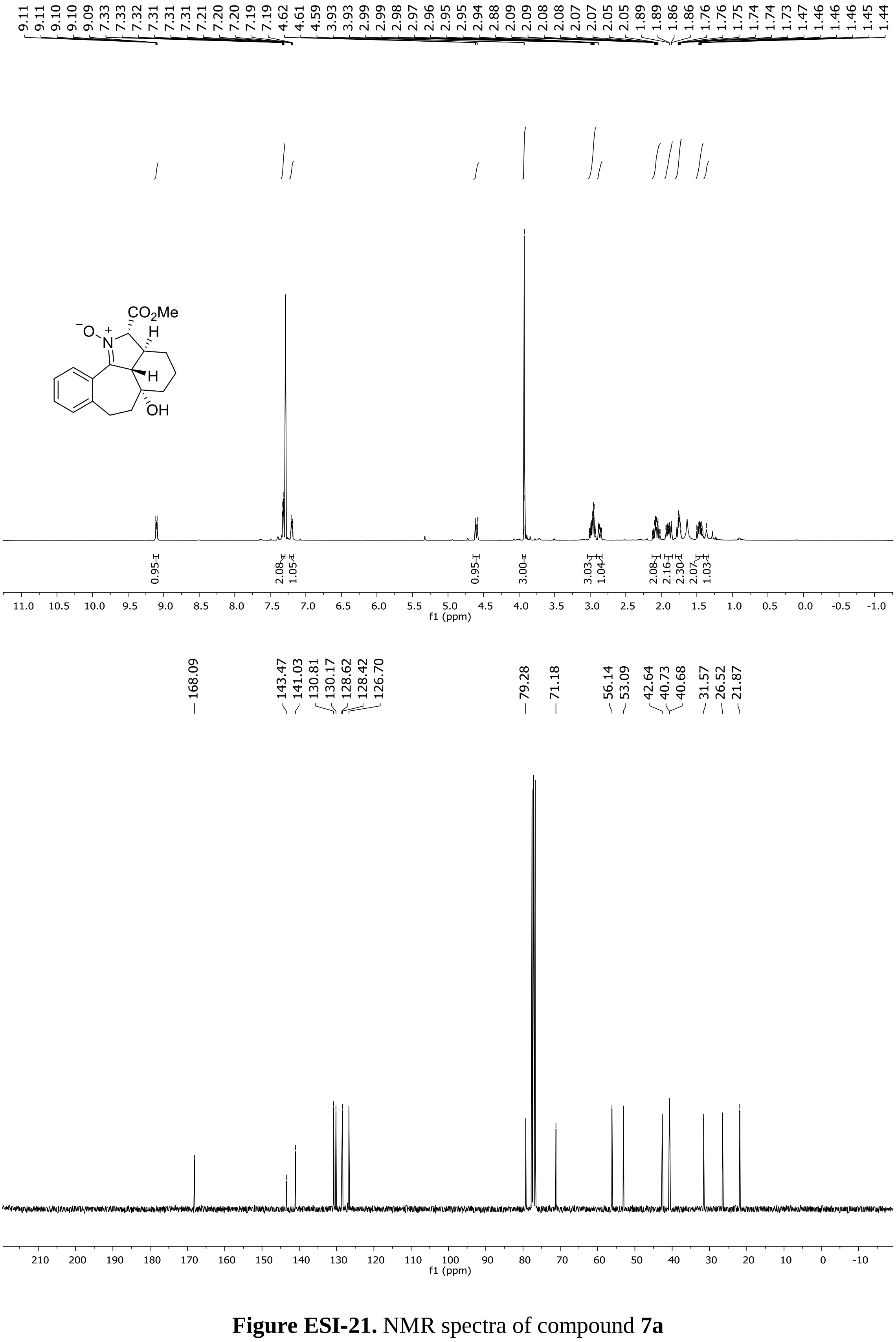


Figure ESI-21. NMR spectra of compound **7a**

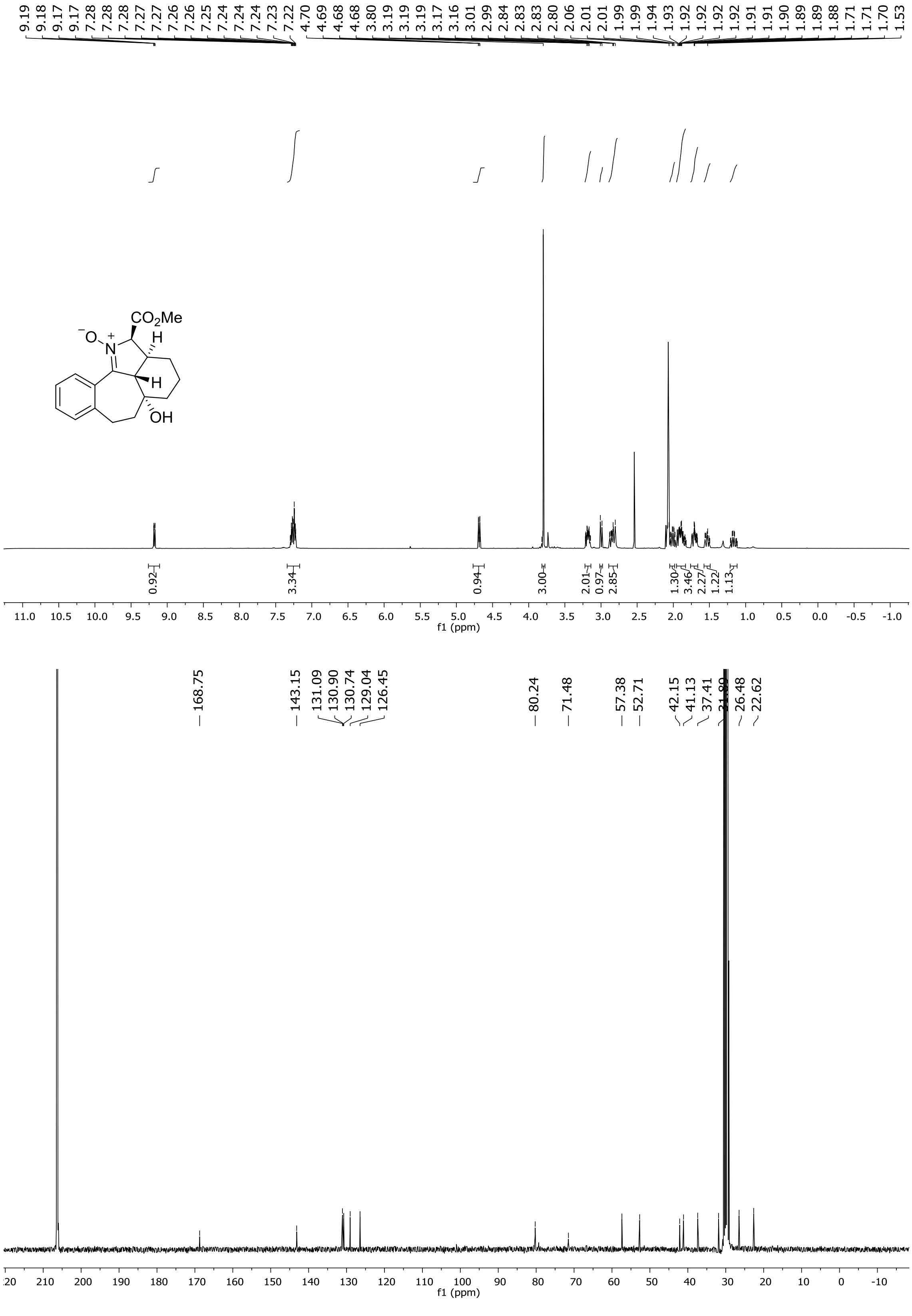
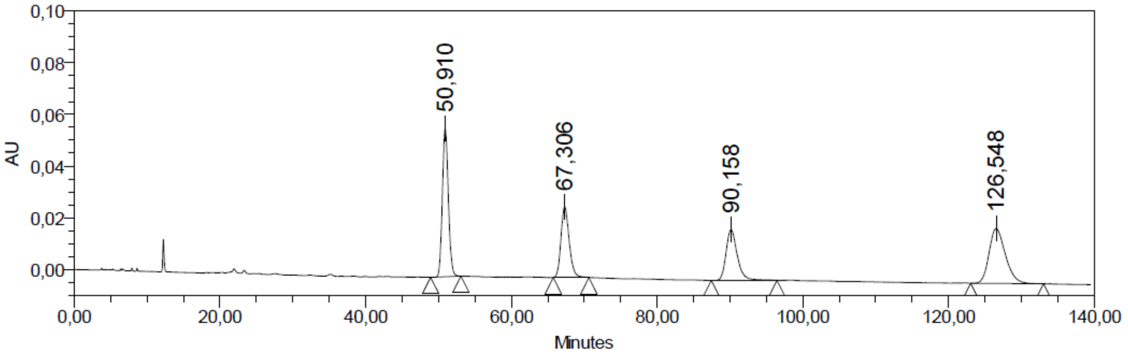


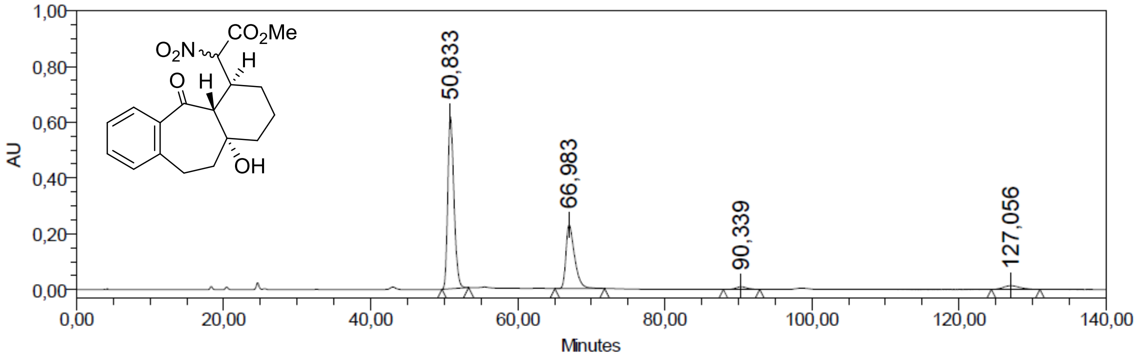
Figure ESI-22. NMR spectra of compound **7’a**

5. HPLC Traces



Peak Results

	RT	Area	Height	% Area
1	50,910	3266645	57289	30,20
2	67,306	2139690	27387	19,78
3	90,158	2102452	19643	19,44
4	126,548	3307301	21265	30,58



Peak Results

	RT	Area	Height	% Area
1	50,833	36156448	616968	62,66
2	66,983	18679956	227891	32,37
3	90,339	902866	8992	1,56
4	127,056	1964571	12878	3,40

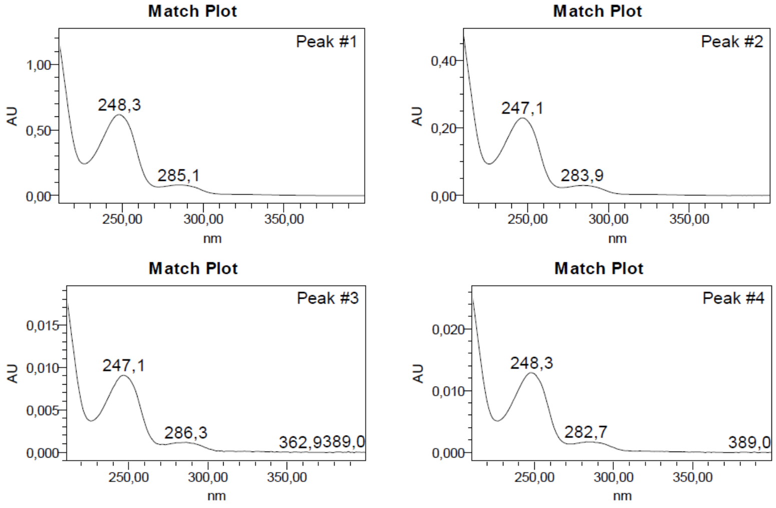
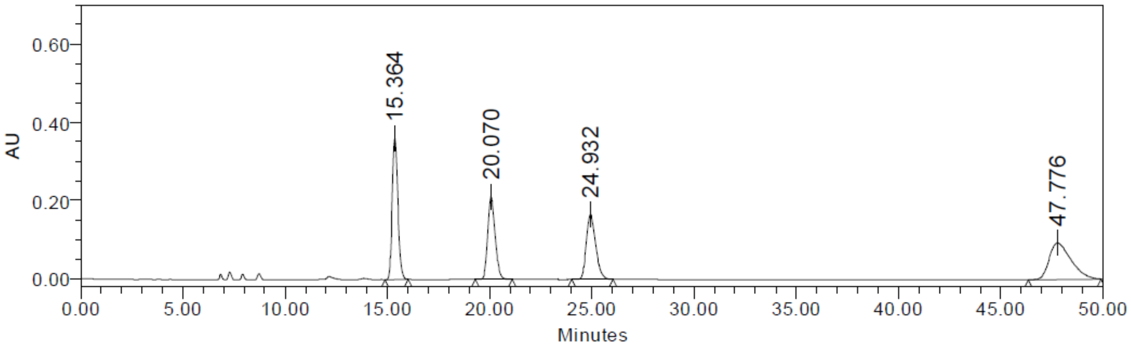
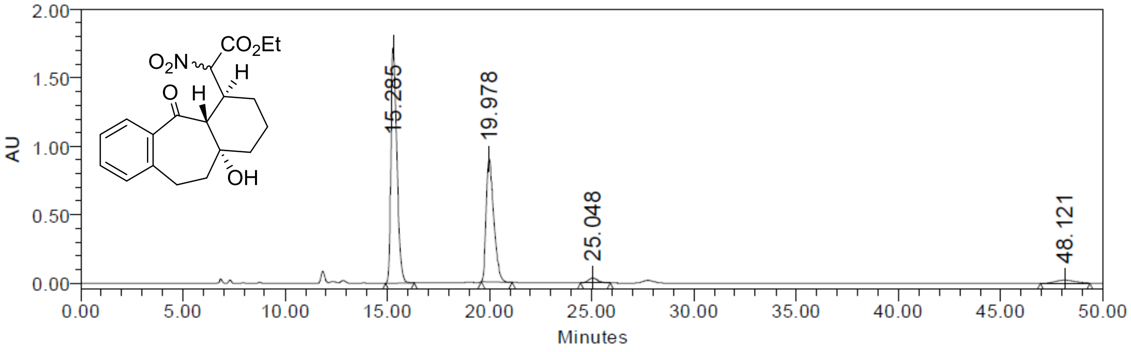


Figure ESI-24. HPLC chromatogram of compound **4a**



Peak Results

	RT	Area	Height	% Area
1	15.364	6991330	361866	28.44
2	20.070	5339372	211953	21.72
3	24.932	5323301	166526	21.66
4	47.776	6927452	93497	28.18



Peak Results

	RT	Area	Height	% Area
1	15.285	34760399	1719924	57.38
2	19.978	23228473	897846	38.34
3	25.048	1134699	35871	1.87
4	48.121	1458504	21769	2.41

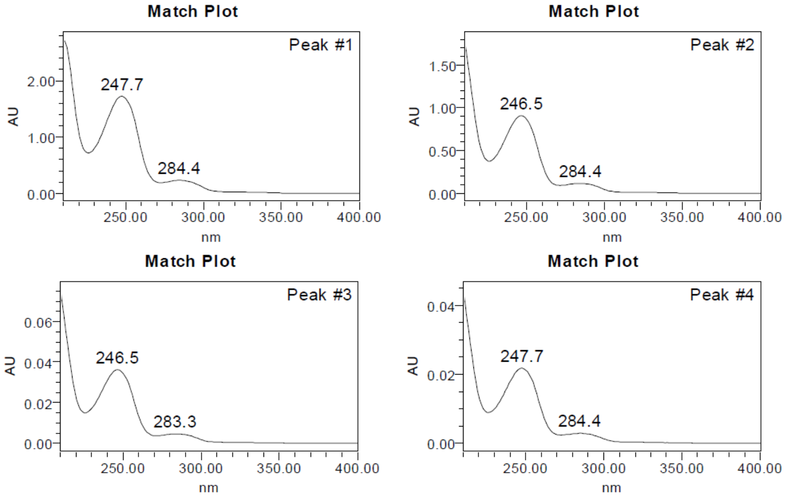
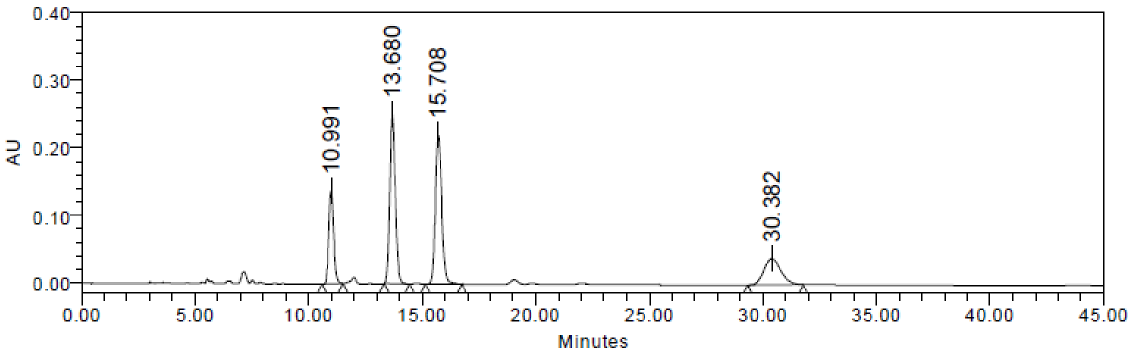
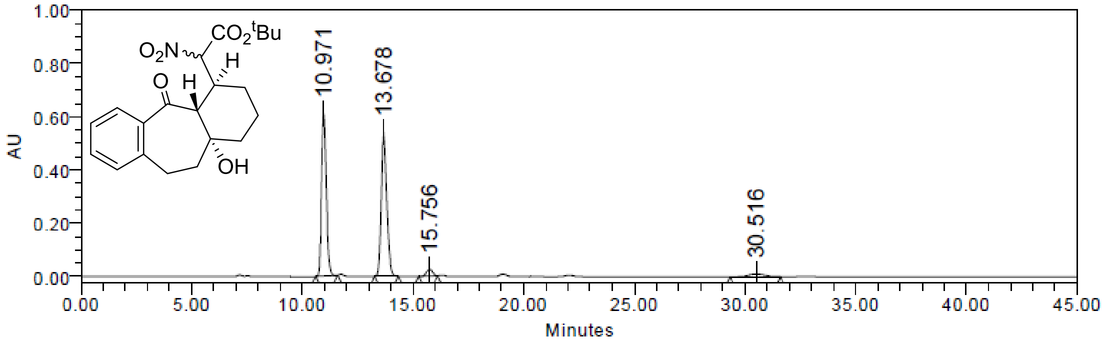


Figure ESI-25. HPLC chromatogram of compound **4b**



Peak Results

	RT	Area	Height	% Area
1	10.991	2048971	136911	15.93
2	13.680	4390171	251099	34.13
3	15.708	4417436	220009	34.35
4	30.382	2004665	38687	15.59



Peak Results

	RT	Area	Height	% Area
1	10.971	9094677	612478	46.25
2	13.678	9591914	542803	48.78
3	15.756	481817	26053	2.45
4	30.516	496210	9694	2.52

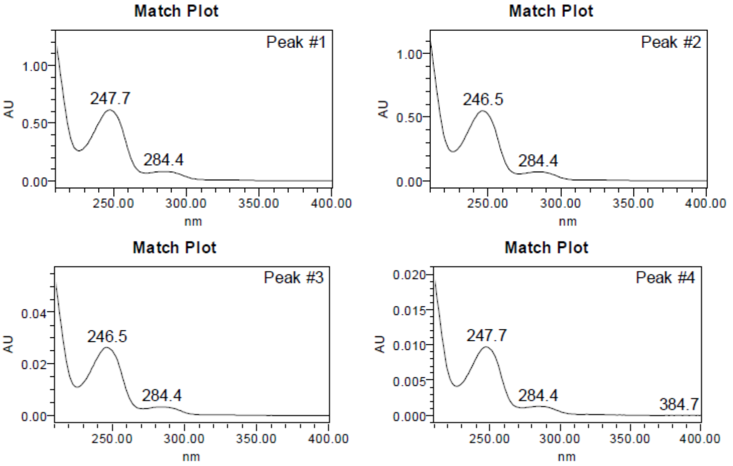
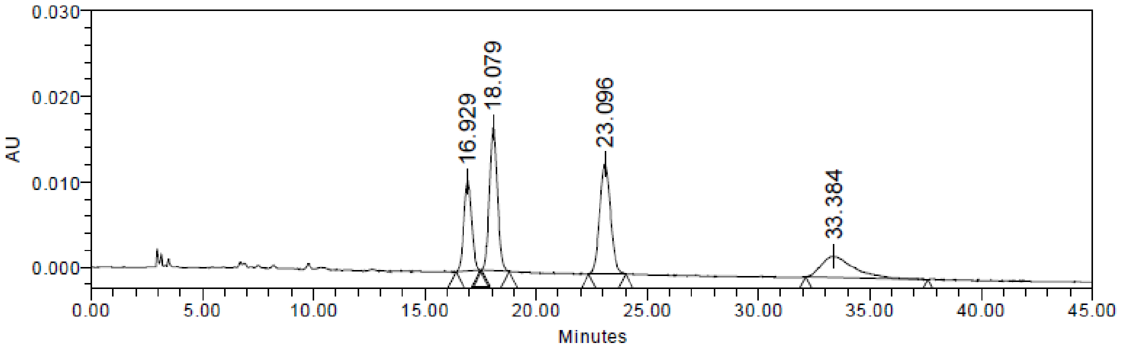
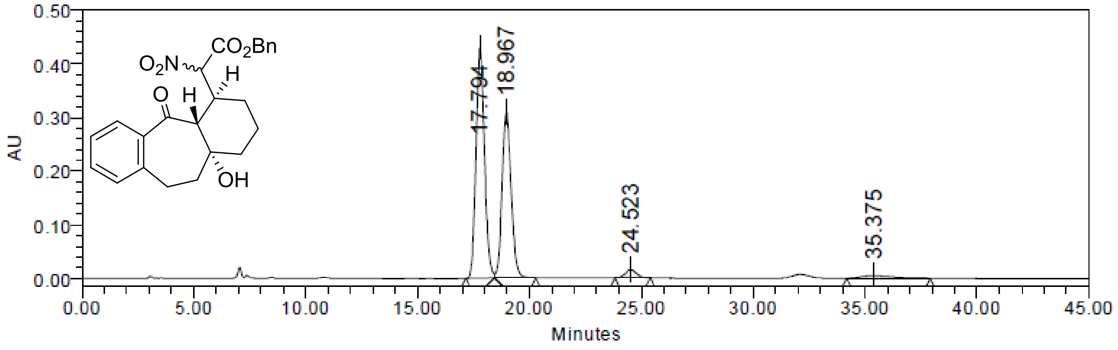


Figure ESI-26. HPLC chromatogram of compound **4c**



Peak Results

	RT	Area	Height	% Area
1	16.929	257585	10546	18.84
2	18.079	426615	16736	31.20
3	23.096	434037	12831	31.75
4	33.384	249017	2434	18.21



Peak Results

	RT	Area	Height	% Area
1	17.794	11414485	430243	53.92
2	18.967	8704692	309086	41.12
3	24.523	546480	15122	2.58
4	35.375	503467	5195	2.38

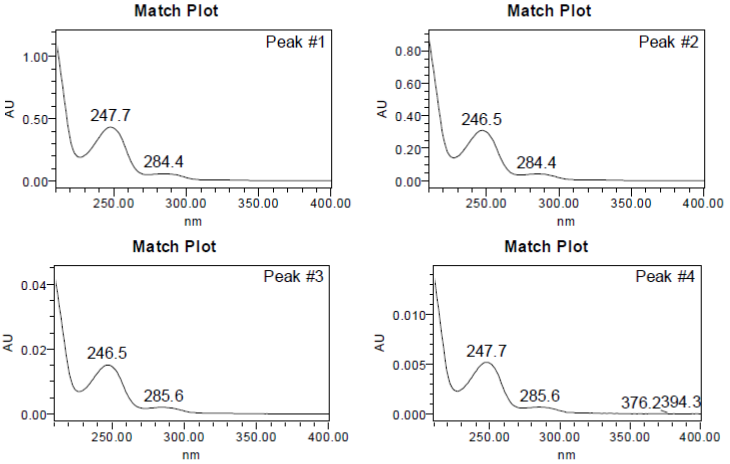
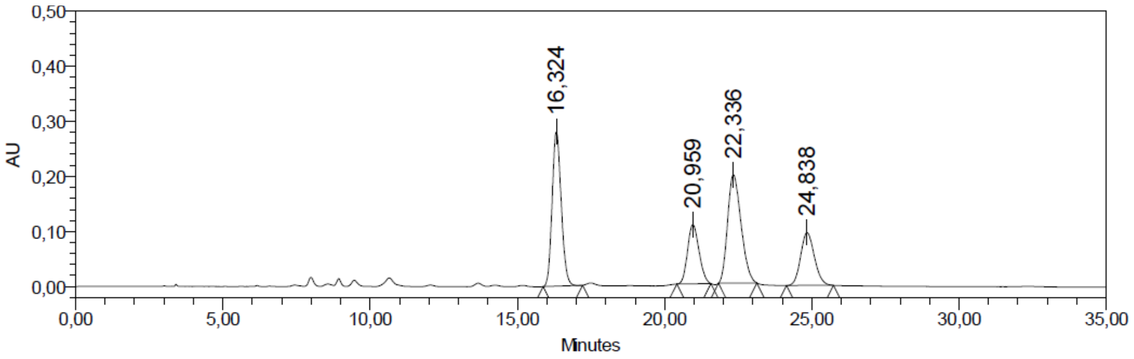
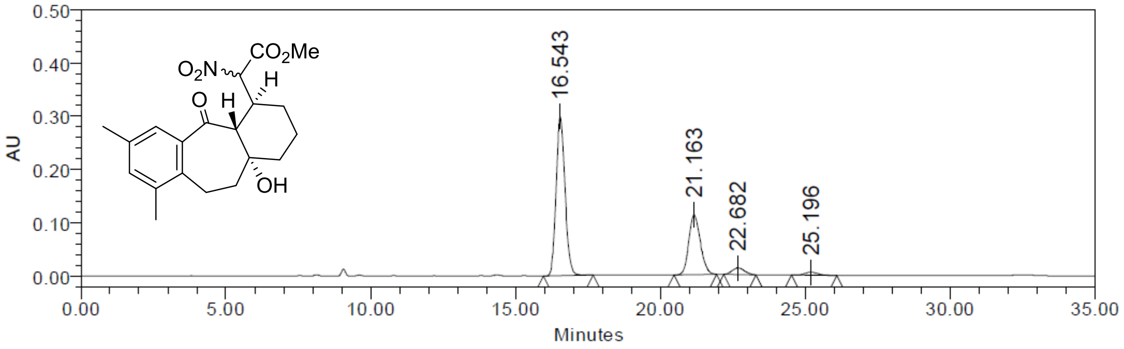


Figure ESI-27. HPLC chromatogram of compound **4d**



Peak Results

	RT	Area	Height	% Area
1	16,324	6020399	280217	32,85
2	20,959	2922839	107649	15,95
3	22,336	6266019	196839	34,19
4	24,838	3116000	95718	17,00



Peak Results

	RT	Area	Height	% Area
1	16.543	6376016	298203	63.49
2	21.163	3107820	112201	30.94
3	22.682	371374	12289	3.70
4	25.196	188063	5836	1.87

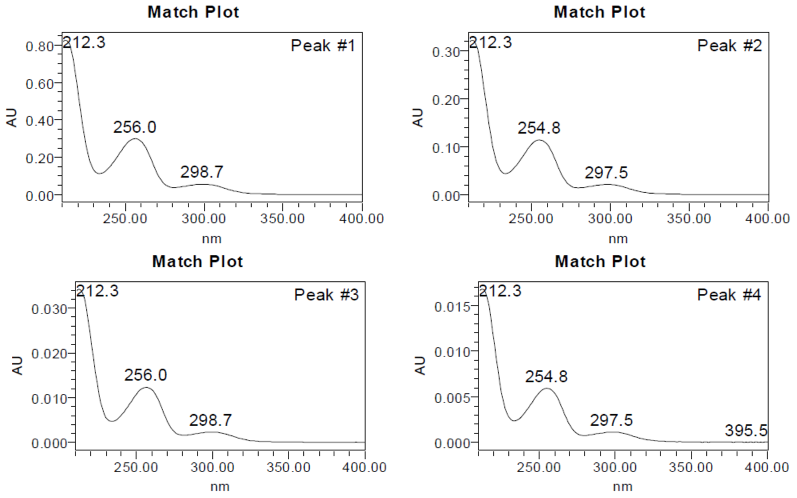
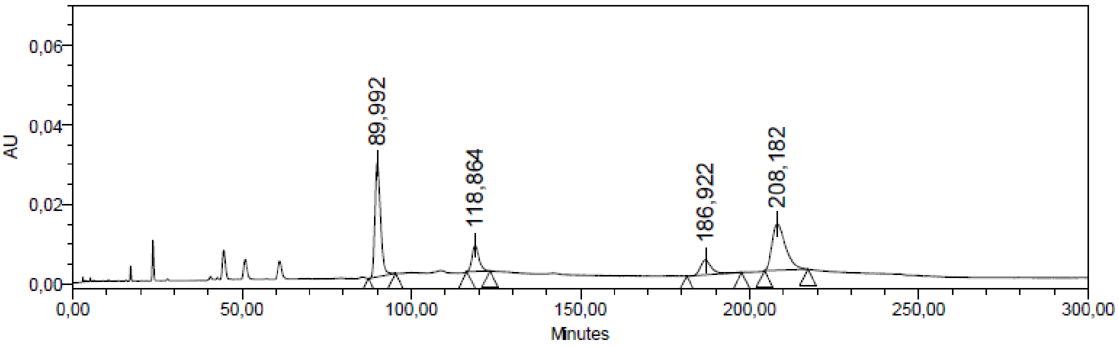
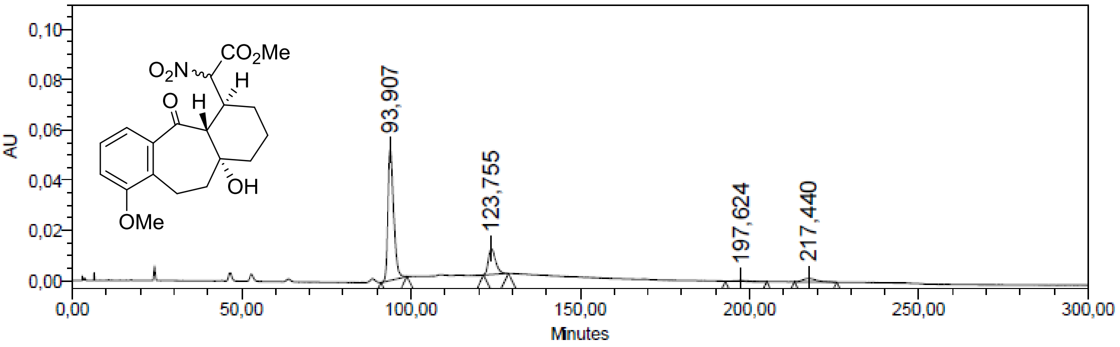


Figure ESI-28. HPLC chromatogram of compound **4f**



Peak Results

	RT	Area	Height	% Area
1	89,992	3196427	28645	38,99
2	118,864	943781	6564	11,51
3	186,922	835605	3763	10,19
4	208,182	3222534	11602	39,31



Peak Results

	RT	Area	Height	% Area
1	93,907	6188740	52062	75,67
2	123,755	1561520	10256	19,09
3	197,624	67308	335	0,82
4	217,440	361153	1318	4,42

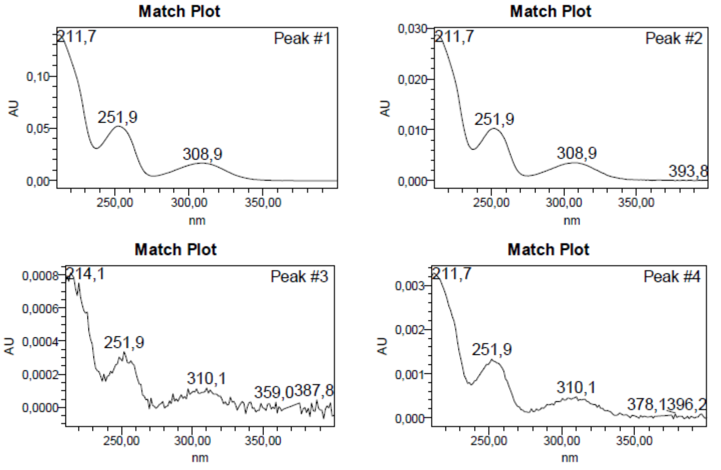
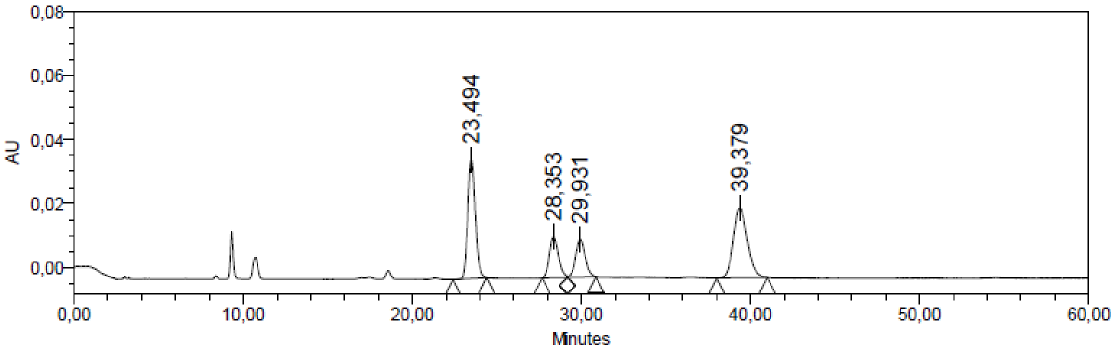
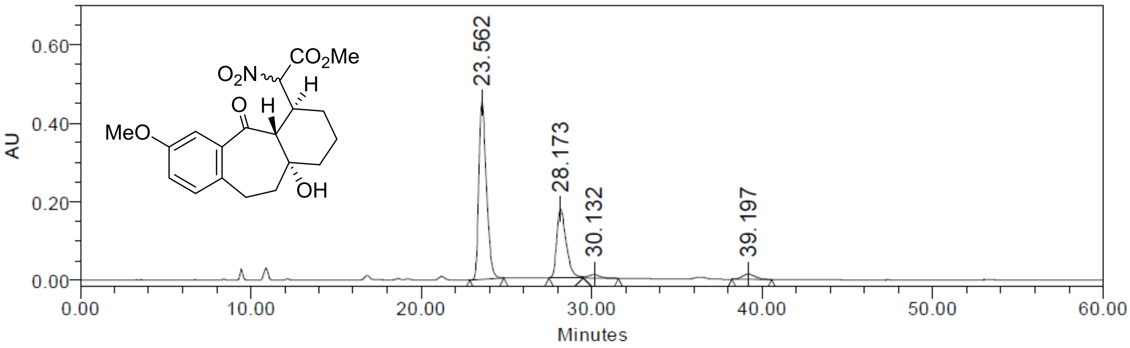


Figure ESI-29. HPLC chromatogram of compound **4g**



Peak Results

	RT	Area	Height	% Area
1	23,494	1146890	37030	34,56
2	28,353	471179	12607	14,20
3	29,931	459594	11717	13,85
4	39,379	1241062	21761	37,40



Peak Results

	RT	Area	Height	% Area
1	23.562	14021475	449723	64.11
2	28.173	6702822	174298	30.65
3	30.132	426421	8905	1.95
4	39.197	719642	13253	3.29

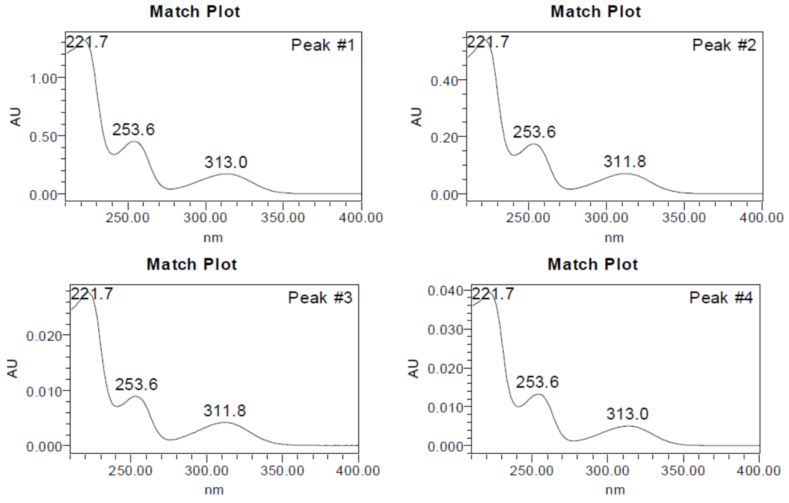
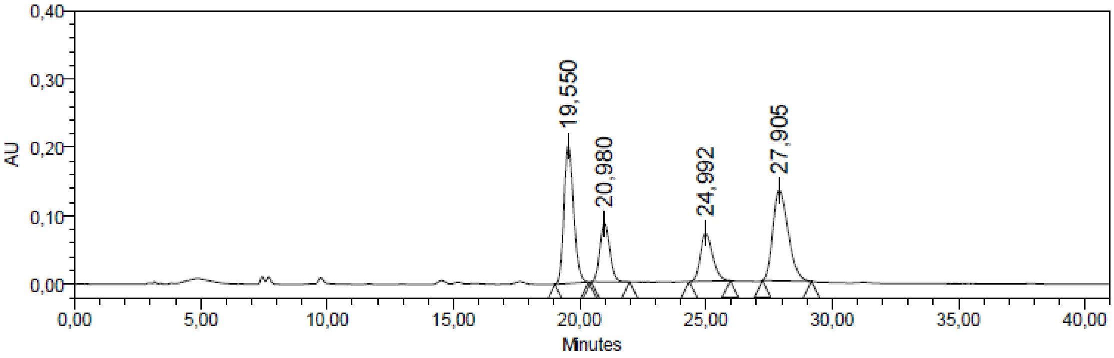
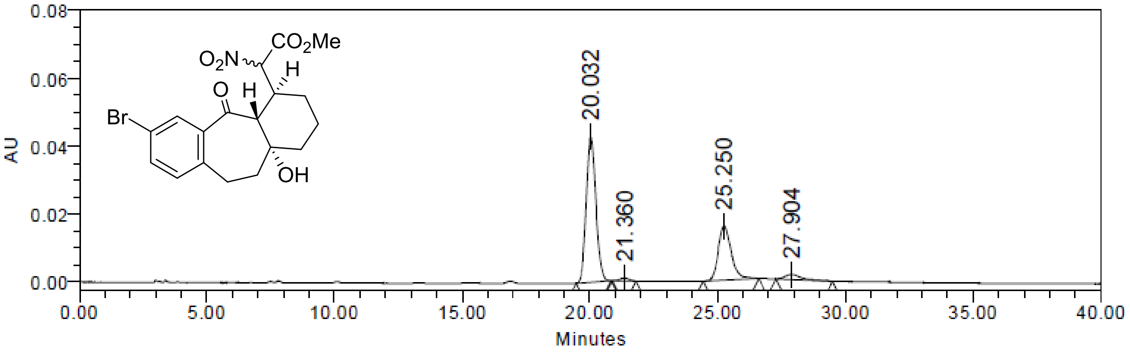


Figure ESI-30. HPLC chromatogram of compound **4h**



Peak Results

	RT	Area	Height	% Area
1	19,550	5233198	200331	33,80
2	20,980	2330423	84874	15,05
3	24,992	2377030	69671	15,35
4	27,905	5544285	132369	35,80



Peak Results

	RT	Area	Height	% Area
1	20.032	1113297	42824	63.53
2	21.360	21678	871	1.24
3	25.250	555304	15926	31.69
4	27.904	62226	1478	3.55

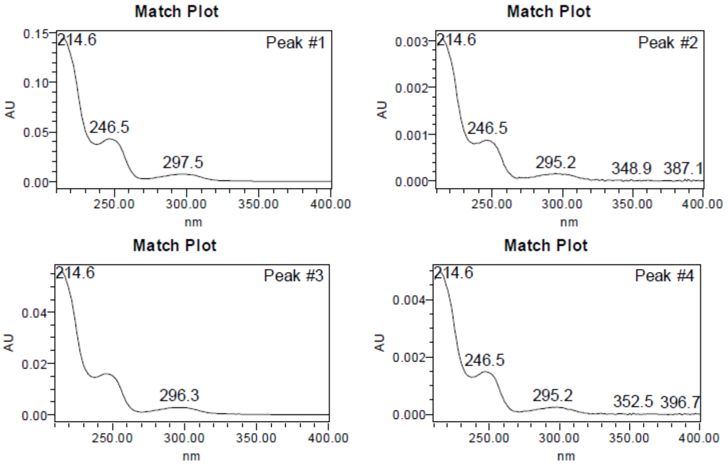
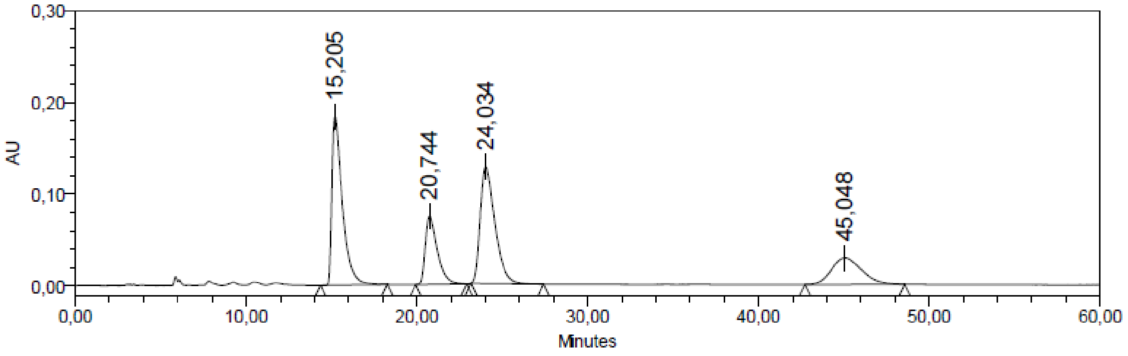
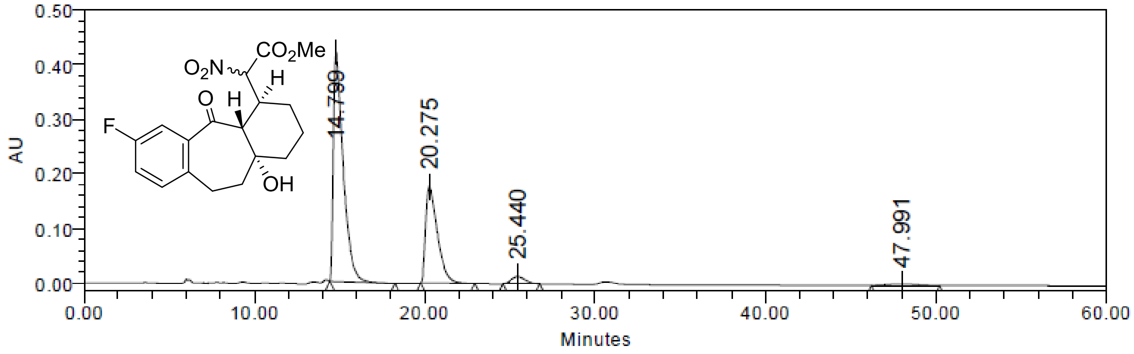


Figure ESI-31. HPLC chromatogram of compound **4i**



Peak Results

	RT	Area	Height	% Area
1	15,205	7863915	183248	34,55
2	20,744	3658026	74538	16,07
3	24,034	7659614	127242	33,65
4	45,048	3581616	29048	15,73



Peak Results

	RT	Area	Height	% Area
1	14.799	16572851	419999	63.65
2	20.275	8376397	177078	32.17
3	25.440	745777	13401	2.86
4	47.991	341348	2948	1.31

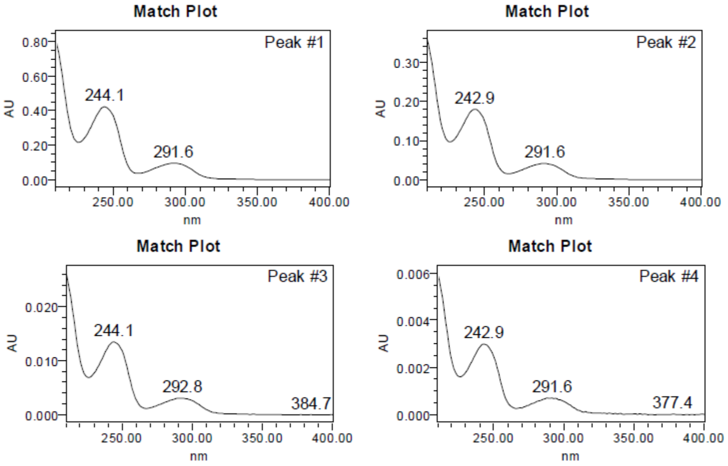
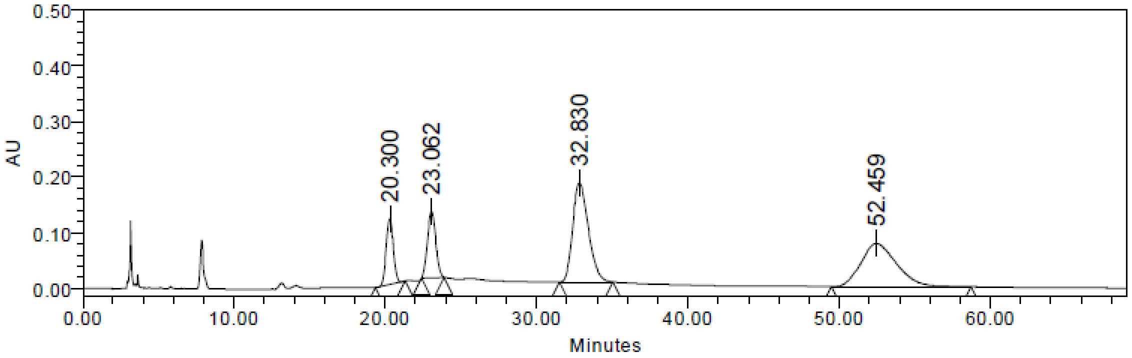
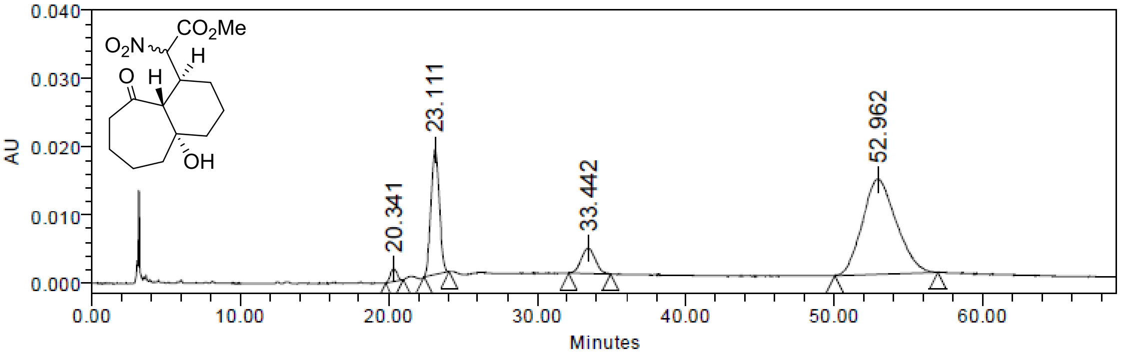


Figure ESI-32. HPLC chromatogram of compound **4j**



Peak Results

	RT	Area	Height	% Area
1	20.300	3868006	117446	11.40
2	23.062	4562450	119187	13.44
3	32.830	12821457	177998	37.78
4	52.459	12684517	77708	37.38



Peak Results

	RT	Area	Height	% Area
1	20.341	58259	1905	1.80
2	23.111	710307	18260	21.98
3	33.442	245644	3722	7.60
4	52.962	2218015	13908	68.62

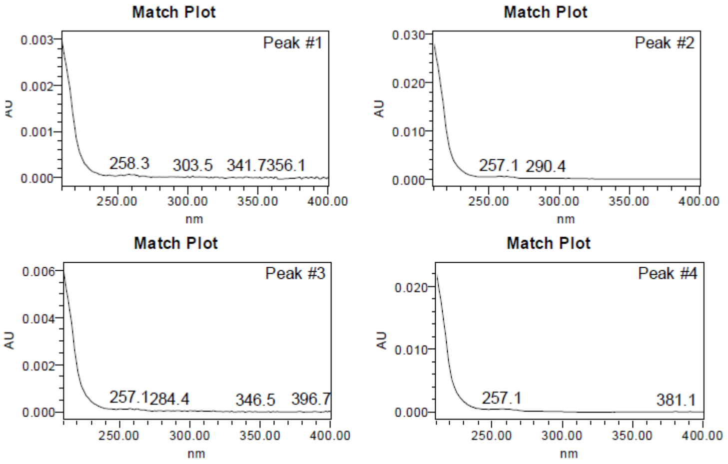
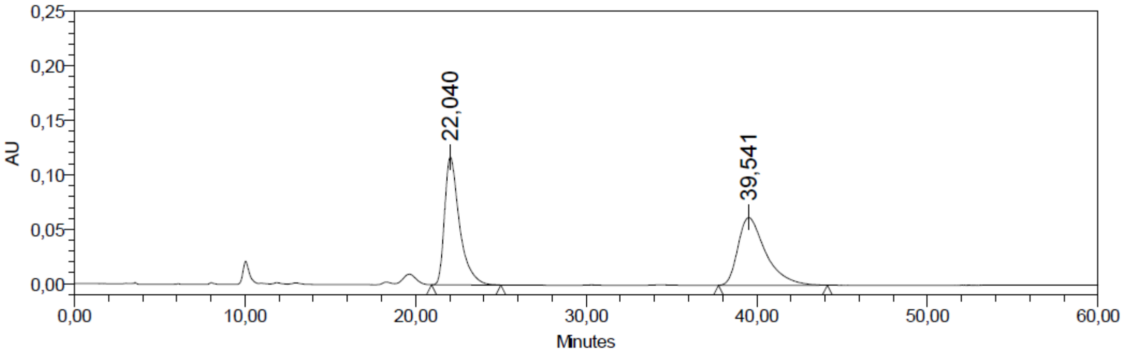
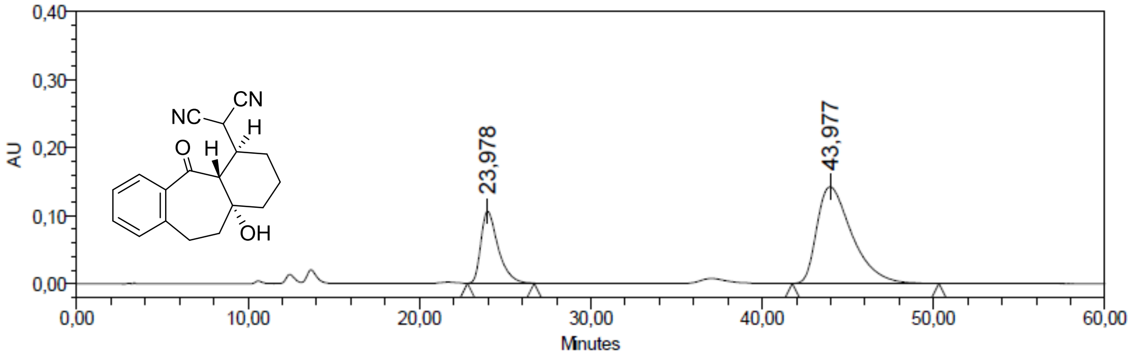


Figure ESI-33. HPLC chromatogram of compound **4k**



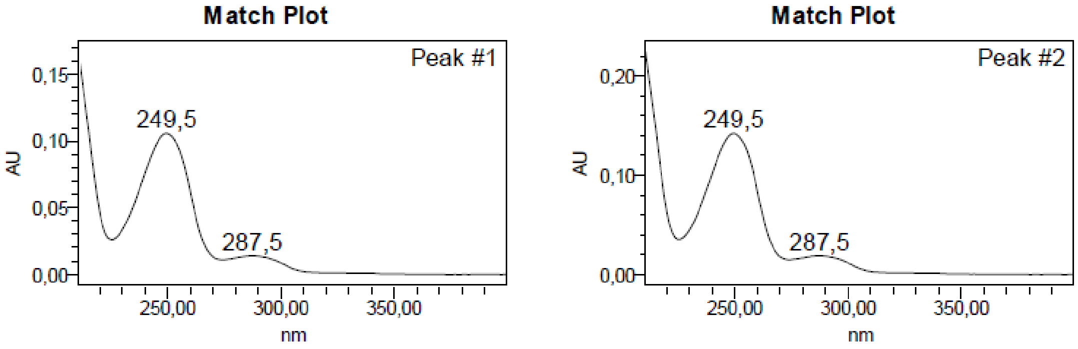
Peak Results

	RT	Area	Height	% Area
1	22,040	7105543	117163	50,33
2	39,541	7010978	62100	49,67



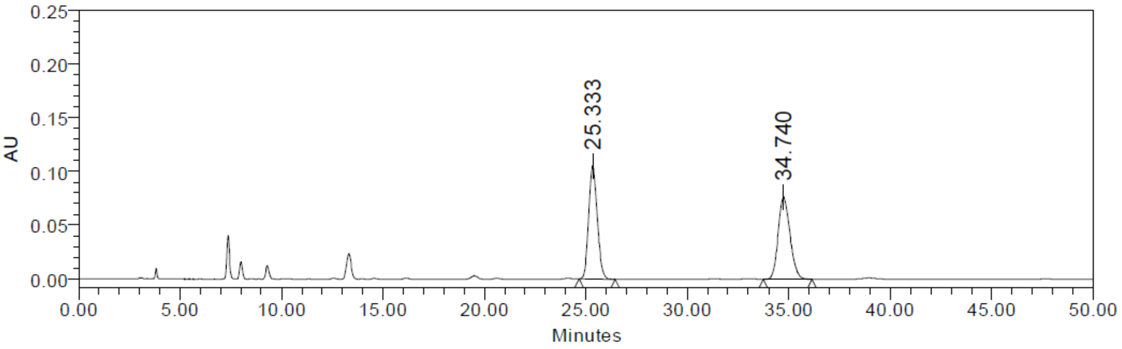
Peak Results

	RT	Area	Height	% Area
1	23,978	7390372	105602	26,79
2	43,977	20199336	142050	73,21


Match Plot

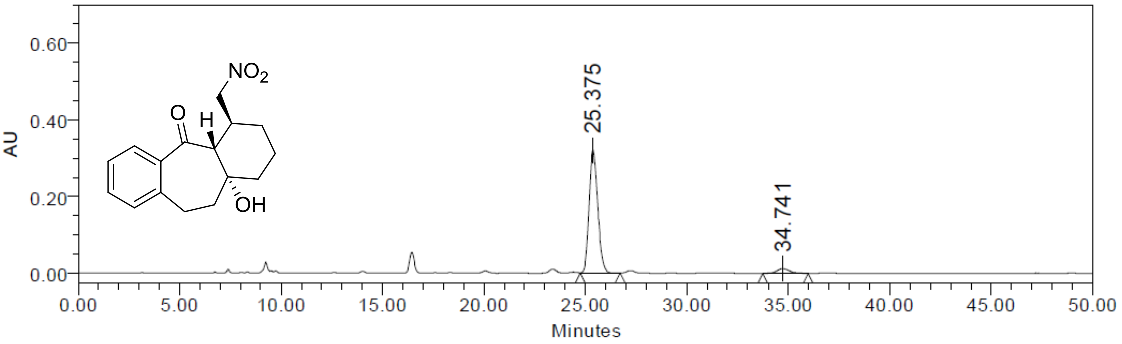
Match Plot

Figure ESI-34. HPLC chromatogram of compound **5b**



Peak Results

	RT	Area	Height	% Area
1	25.333	3108229	105537	49.93
2	34.740	3117140	76418	50.07



Peak Results

	RT	Area	Height	% Area
1	25.375	9481053	319948	94.87
2	34.741	512942	12673	5.13

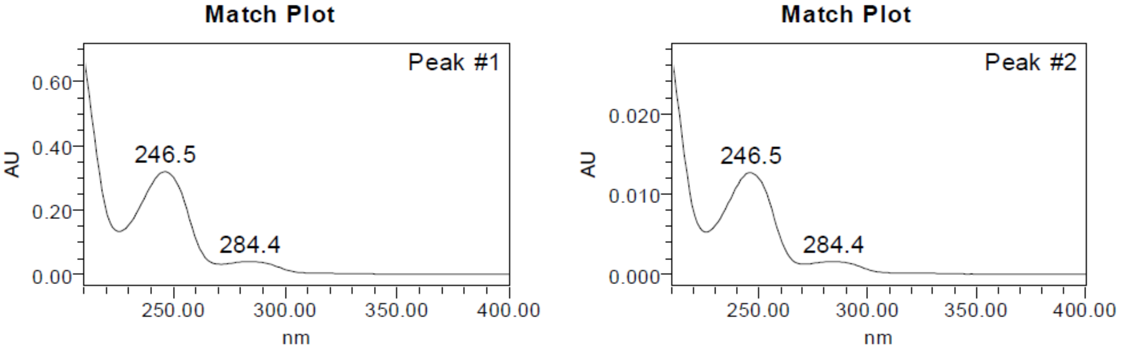
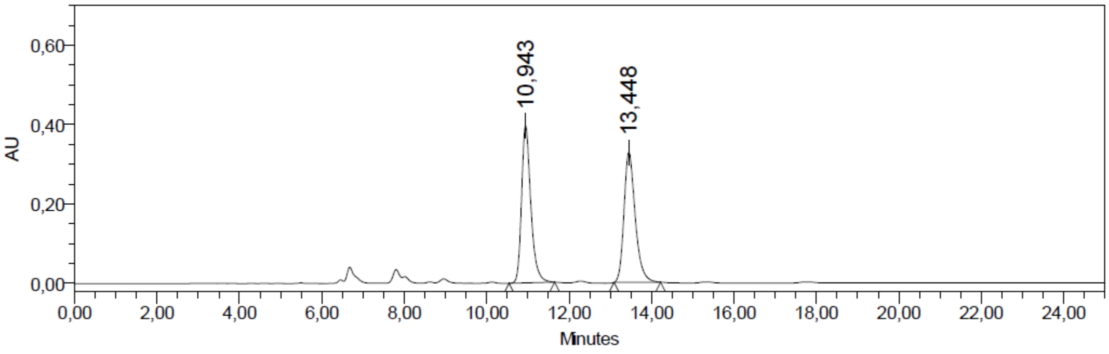
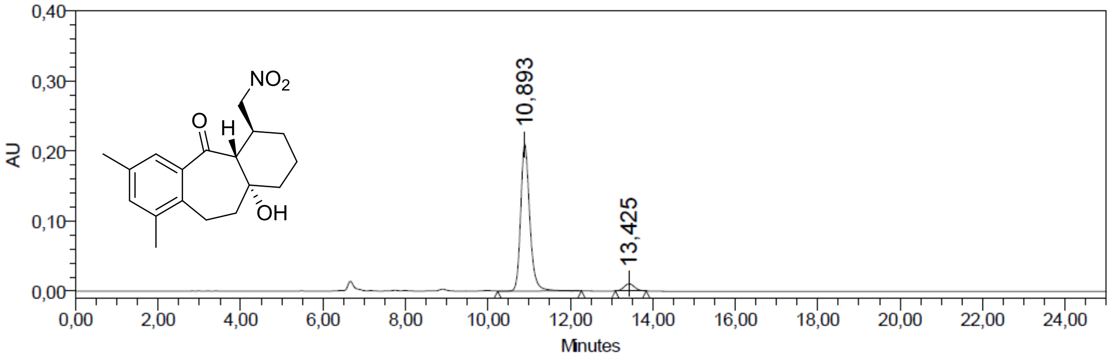


Figure ESI-35. HPLC chromatogram of compound **6a**



Peak Results

	RT	Area	Height	% Area
1	10,943	6192327	396179	50,00
2	13,448	6193536	327406	50,00



Peak Results

	RT	Area	Height	% Area
1	10,893	3213262	209506	94,58
2	13,425	184239	10282	5,42

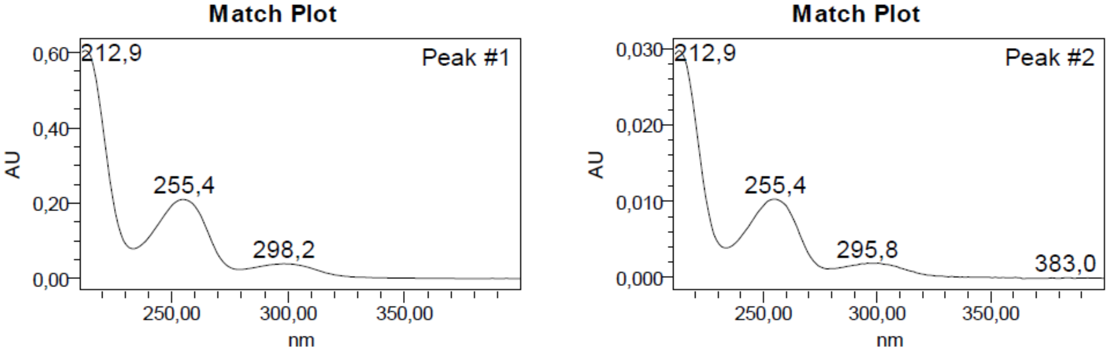
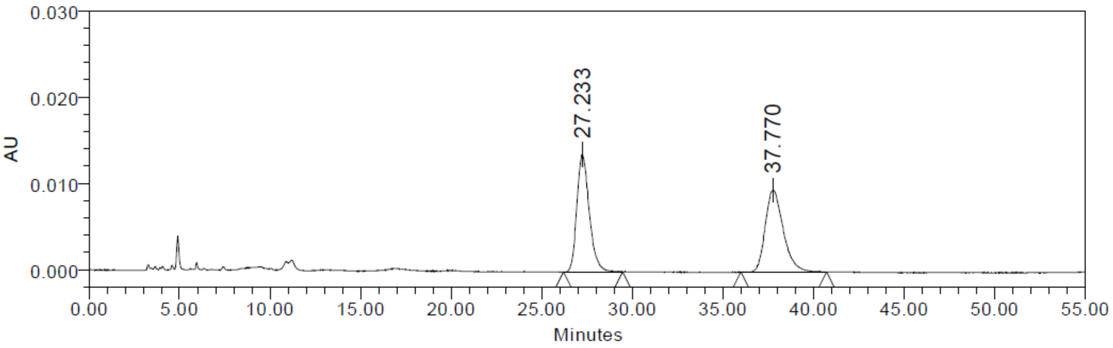
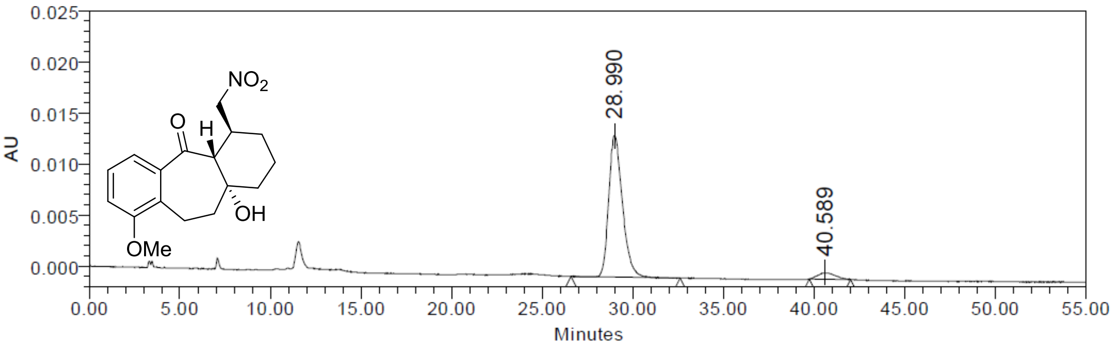


Figure ESI-36. HPLC chromatogram of compound **6f**



Peak Results

	RT	Area	Height	% Area
1	27.233	648521	13607	49.69
2	37.770	656505	9477	50.31



Peak Results

	RT	Area	Height	% Area
1	28.990	733566	13875	94.60
2	40.589	41872	624	5.40

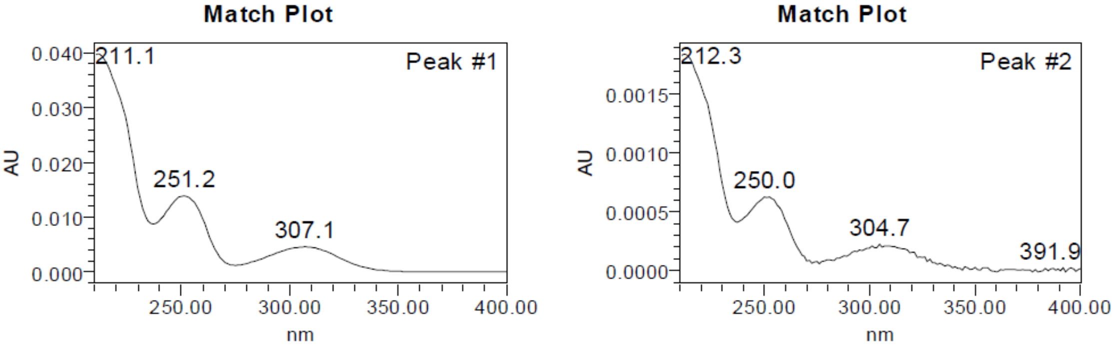
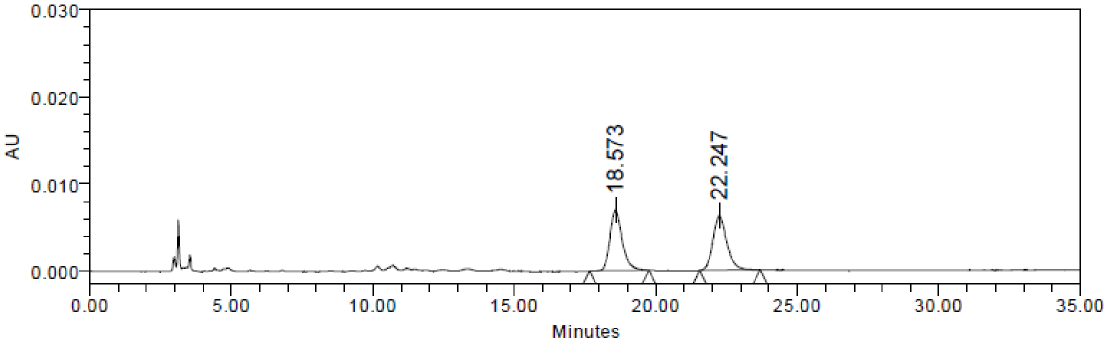
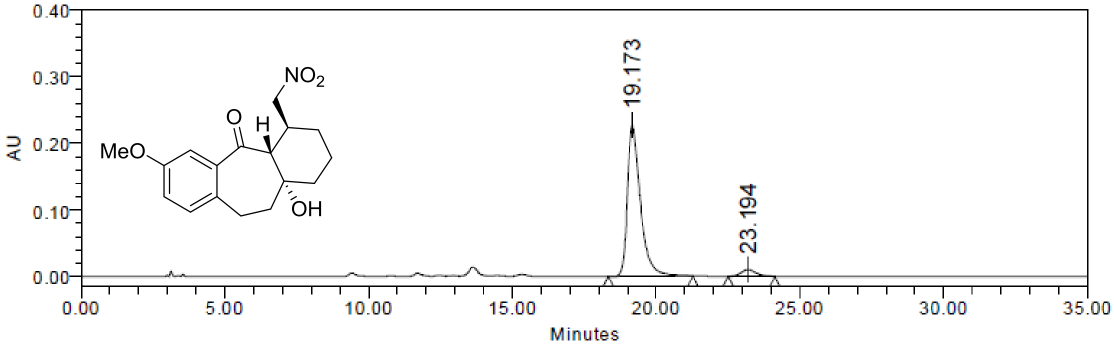


Figure ESI-37. HPLC chromatogram of compound **6g**



Peak Results

	RT	Area	Height	% Area
1	18.573	211671	7009	49.65
2	22.247	214652	6240	50.35



Peak Results

	RT	Area	Height	% Area
1	19.173	7120427	226939	95.39
2	23.194	344122	9785	4.61

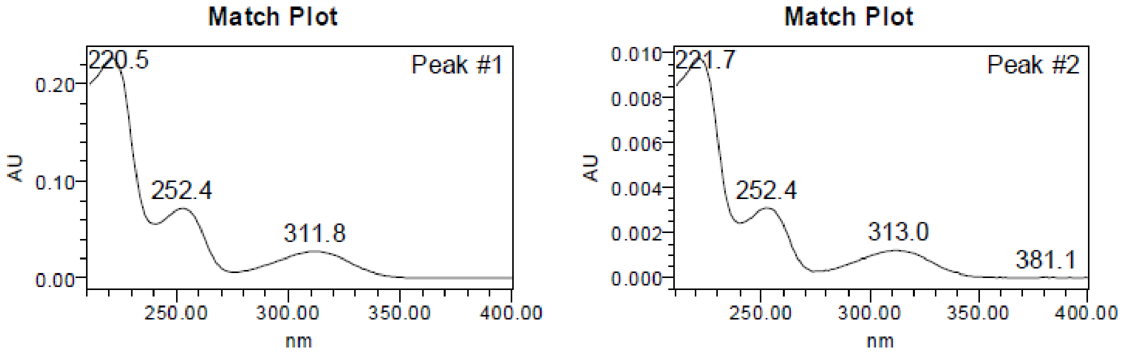
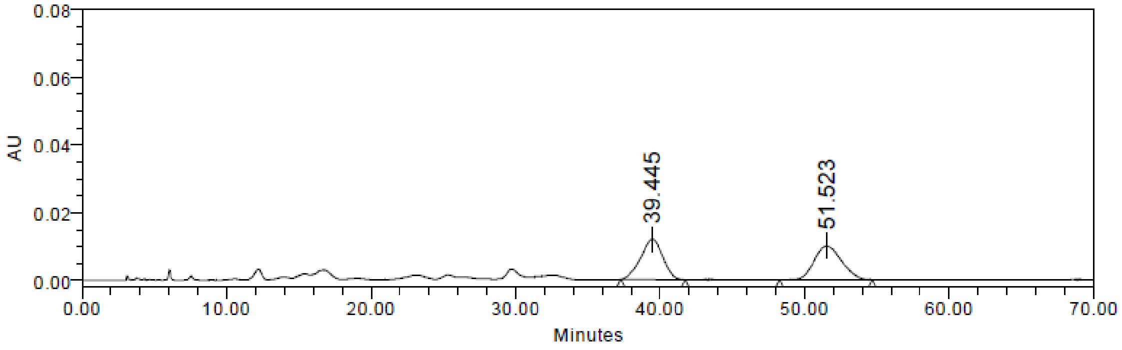
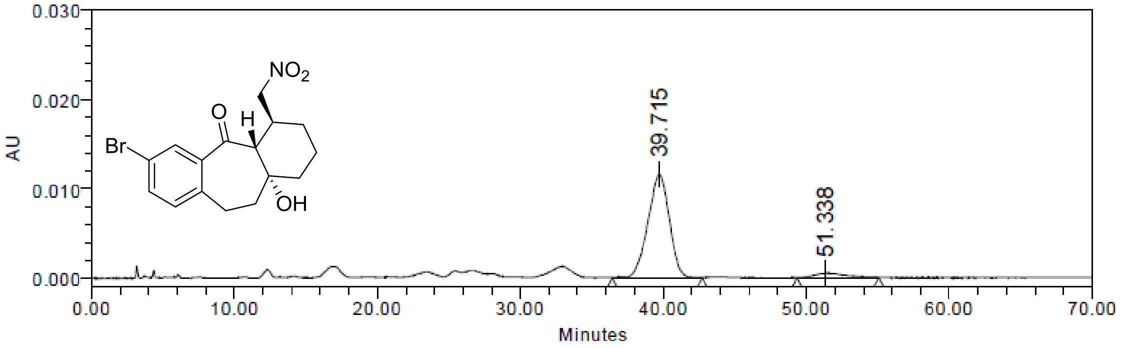


Figure ESI-38. HPLC chromatogram of compound **6h**



Peak Results

	RT	Area	Height	% Area
1	39.445	1257516	11891	49.26
2	51.523	1295146	9961	50.74



Peak Results

	RT	Area	Height	% Area
1	39.715	1187302	11553	94.46
2	51.338	69587	480	5.54

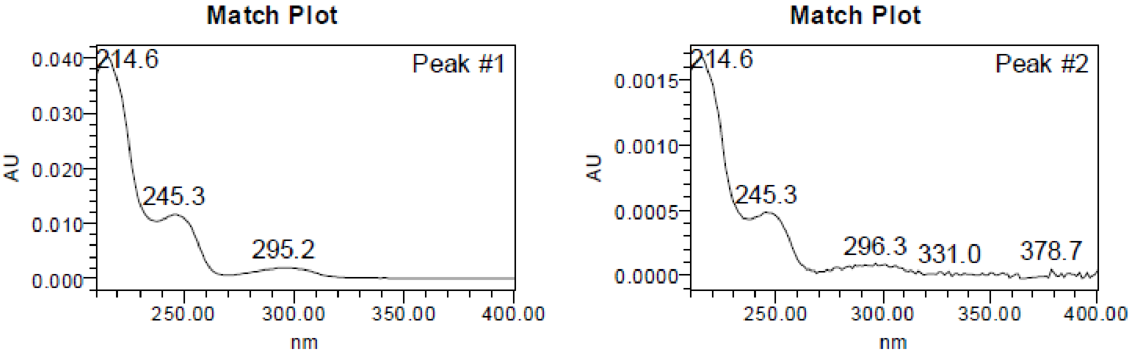
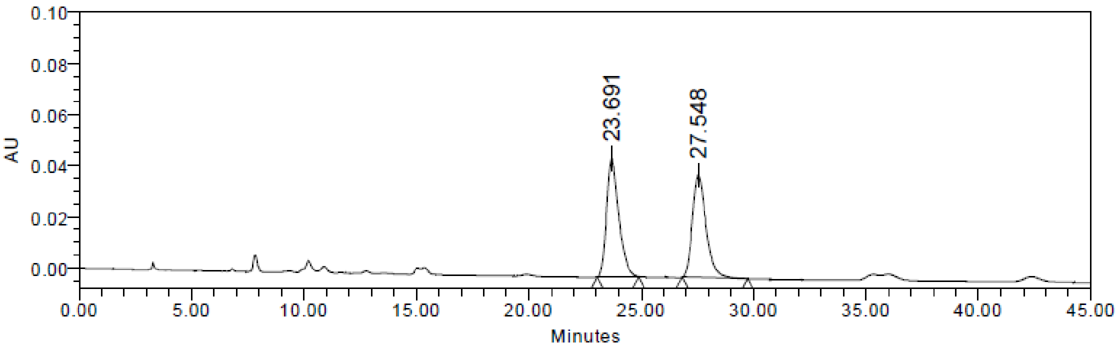
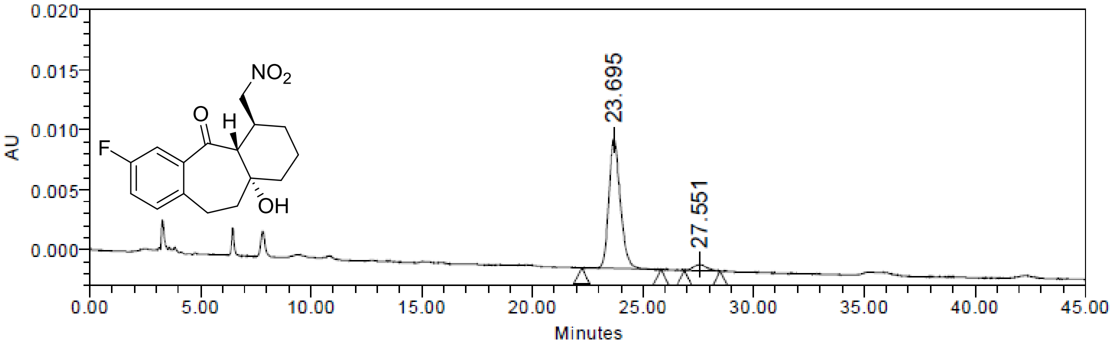


Figure ESI-39. HPLC chromatogram of compound **6i**



Peak Results

	RT	Area	Height	% Area
1	23.691	1737227	46123	50.65
2	27.548	1692658	39899	49.35



Peak Results

	RT	Area	Height	% Area
1	23.695	391181	10780	95.07
2	27.551	20296	509	4.93

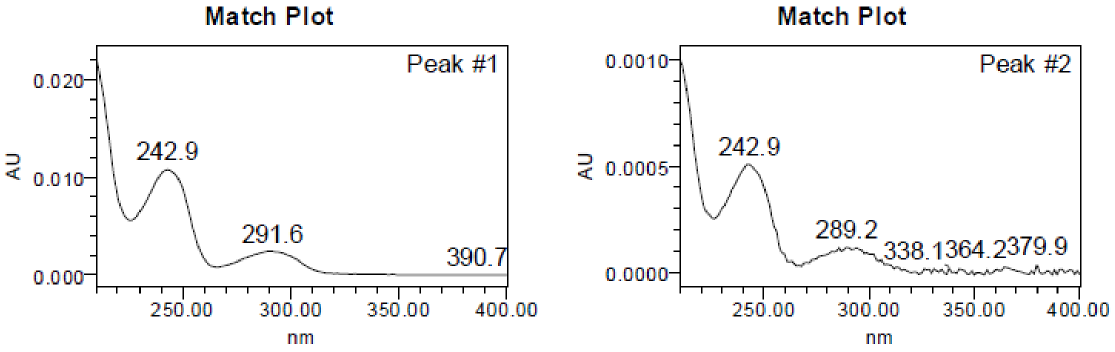
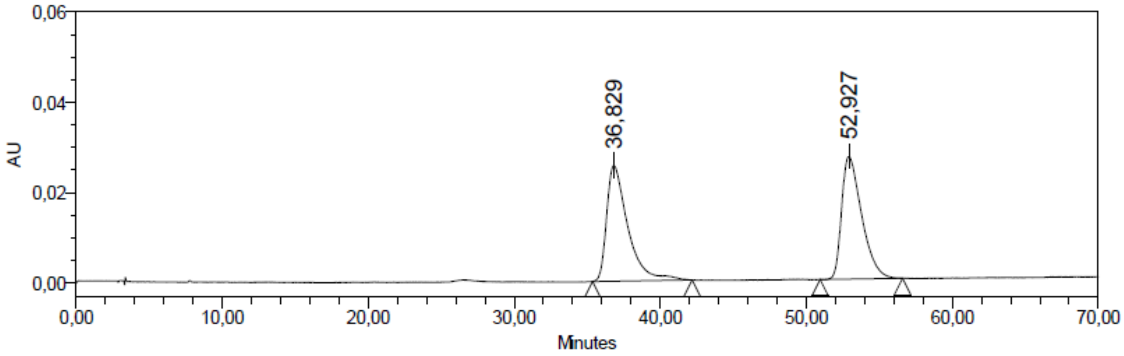
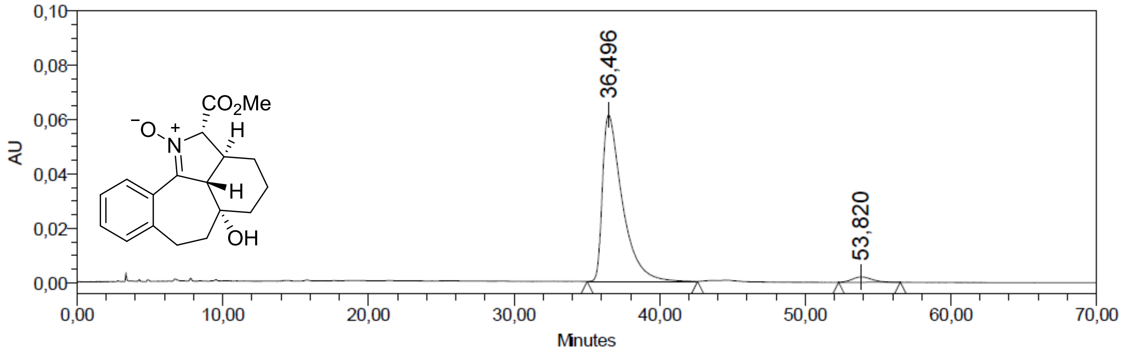


Figure ESI-40. HPLC chromatogram of compound **6j**



Peak Results

	RT	Area	Height	% Area
1	36,829	2574922	25597	49,88
2	52,927	2587537	27144	50,12



Peak Results

	RT	Area	Height	% Area
1	36,496	5792753	61251	97,00
2	53,820	178856	1957	3,00

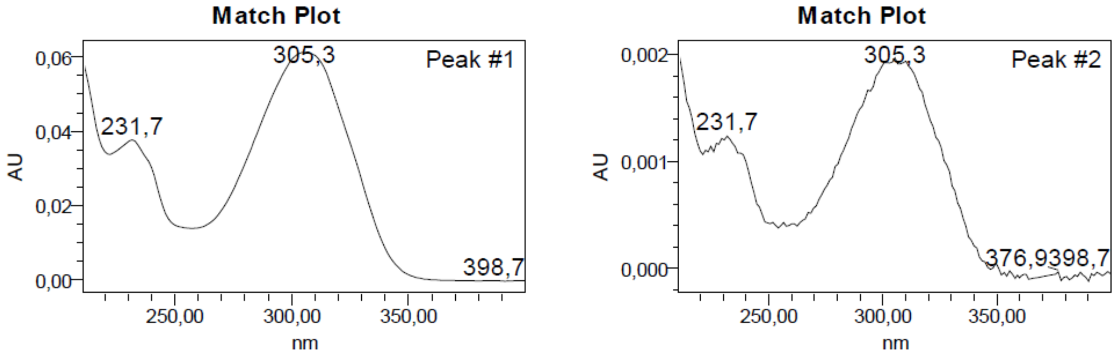
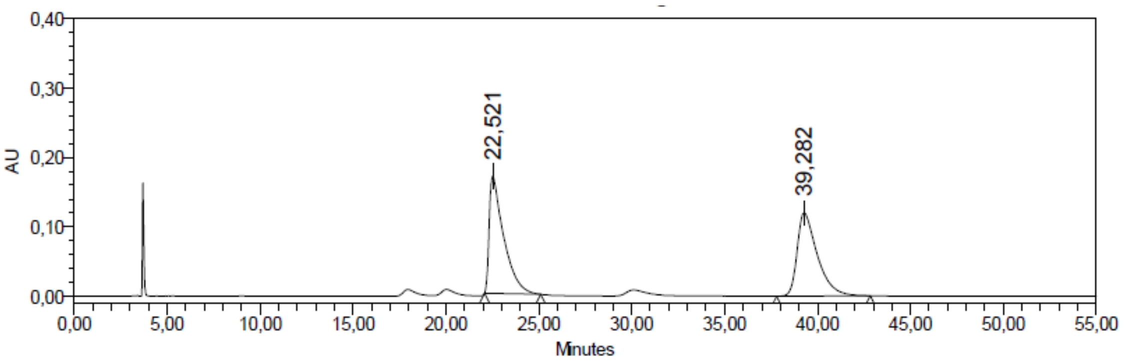
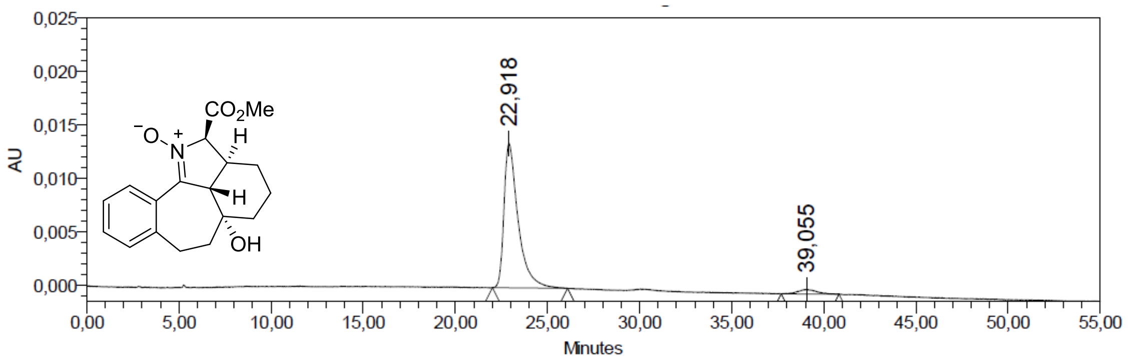


Figure ESI-41. HPLC chromatogram of compound **7a**



Peak Results

	RT	Area	Height	% Area
1	22,521	9169520	169116	50,40
2	39,282	9024696	120076	49,60



Peak Results

	RT	Area	Height	% Area
1	22,918	718133	13537	95,92
2	39,055	30562	427	4,08

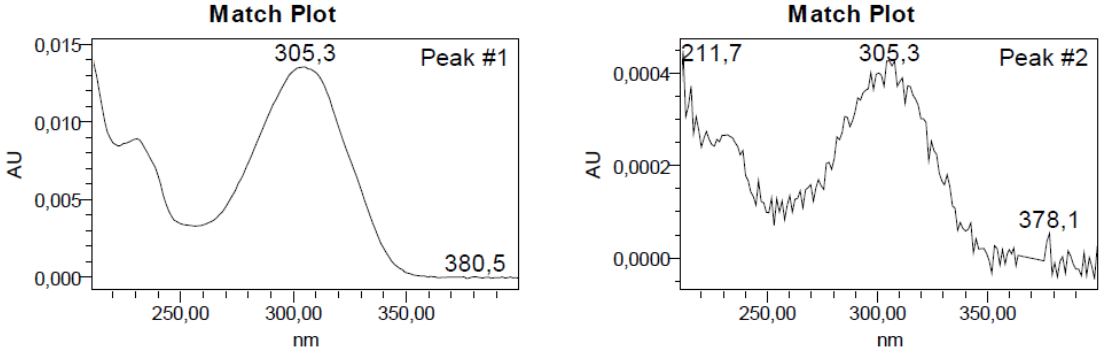


Figure ESI-42. HPLC chromatogram of compound **7’a**