Electronic Supplementary Information

for

Novel latonduine derived proligands and their copper(II) complexes show cytotoxicity in the nanomolar range in human colon adenocarcinoma cells and *in vitro* cancer selectivity

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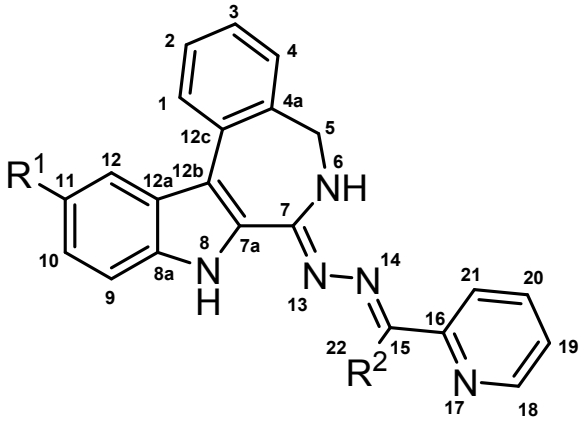
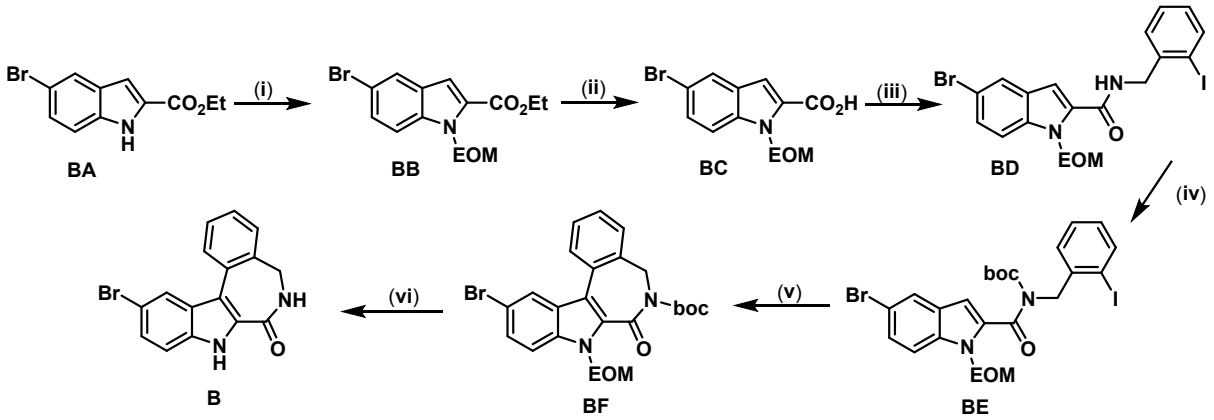
Content

Figure S32. ESI-MS spectrum of **4**.



$R^1 = R^2 = H$ (**HL^1**)
$R^1 = Br$, $R^2 = H$ (**HL^2**)
$R^1 = H$, $R^2 = CH_3$ (**HL^3**)
$R^1 = Br$, $R^2 = CH_3$ (**HL^4**)

Scheme S1. Atom numbering scheme for ^{1}H and ^{13}C NMR data for **HL^1** – **HL^4**.



Scheme S2. Synthesis of **B**.[a]

[a]Reagents and conditions: (**i**) sodium hydride, ethoxy methylchloride, DMF abs., 0 °C to room temperature, overnight; (**ii**) lithium hydroxide monohydrate, ethanol/water, reflux, 2 h; (**iii**) 2-iodobenzylamine,[1] dimethylaminopyridine, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide-hydrochloride, dichloromethane, 0 °C to room temperature, overnight; (**iv**) di-*tert*-butyl-dicarbonate, dimethylaminopyridine, acetonitrile abs., room temperature, overnight; (**v**) palladium(II) acetate, triphenylphosphine, silver(I) carbonate, DMF abs., 100 °C, 2 h; (**vi**) hydrochloric acid, dioxane, 80 °C, overnight.

Synthesis of B

Ethyl 5-bromo-1-(ethoxymethyl)-1*H*-indole-2-carboxylate (BB). 5-bromoindole-2-carboxylic ester (**BA**) (6.0 g, 22.38 mmol) was dissolved in dry DMF (44 mL) under inert conditions. The solution was cooled to 0°C and sodium hydride (60% in mineral oil) (1.34 g, 33.57 mmol) was carefully added. The resulting mixture was stirred for one hour at room temperature. Then ethoxy-methylchloride (4.26 mL, 43.18 mmol) was added dropwise at 0° C. The reaction was allowed to reach room temperature and stirred overnight. On the next day, the solvent was removed under reduced pressure. The residue was taken up in water (50 mL) and extracted with dichloromethane (4 × 70 mL). The combined organic phases were dried over magnesium sulfate and the solvent was evaporated. The product was purified on a silica column using hexane/ethylacetate 95 : 5 as eluent. Yield: 6.44 g, 88%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.94 (d, J = 1.7 Hz, 1H, $H_{(Ar)}$), 7.69 (d, J = 8.9 Hz, 1H, $H_{(Ar)}$), 7.49 (dd, J = 8.9, 1.9 Hz, 1H, $H_{(Ar)}$), 7.32 (s, 1H, $H_{(Ar)}$), 5.96 (s, 2H, CH_2), 4.33 (q, J = 7.1 Hz, 2H, CH_2), 3.38 (q, J = 7.0 Hz, 2H, CH_2), 1.33 (t, J = 7.1 Hz, 3H, CH_3), 1.01 (t, J = 7.0 Hz, 3H, CH_3).

5-bromo-1-(ethoxymethyl)-1*H*-indole-2-carboxylic acid (BC). Ethyl-5-bromo-1-(ethoxymethyl)-1*H*-indole-2-carboxylate (**BB**) (6.44 g, 19.74 mmol) was dissolved in ethanol (55 mL) and lithium hydroxide monohydrate (0.99 g, 23.69 mmol) dissolved in water (5 mL) was added. The reaction was refluxed for two hours. After cooling to room temperature, the solvent was evaporated and the residue was taken up in water (30 mL). The resulting mixture was acidified with 1 M HCl (30 mL) and extracted with ethyl acetate (3 × 60 mL). The combined organic phases were dried over magnesium sulfate and the solvent was removed under reduced pressure. The crude product was recrystallized from ethyl acetate, giving colorless needles. Yield: 5.55 g, 94%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.25 (s, 1H, COOH), 7.92 (d, J = 1.9 Hz, 1H, $H_{(Ar)}$), 7.66 (d, J = 8.9 Hz, 1H, $H_{(Ar)}$), 7.47 (dd, J = 8.9, 2.0 Hz, 1H, $H_{(Ar)}$), 7.27 (d, J = 0.4 Hz, 1H, $H_{(Ar)}$), 5.98 (s, 2H, CH_2), 3.40 – 3.36 (m, 2H, CH_2 (overlapped water signal)), 1.00 (t, J = 7.0 Hz, 3H, CH_3).

5-bromo-1-(ethoxymethyl)-*N*-(2-iodobenzyl)-1*H*-indole-2-carboxamide (BD)

5-bromo-1-(ethoxymethyl)-1*H*-indole-2-carboxylic acid (**BC**) (4.18 g, 17.94 mmol) and 2-iodo-benzylamine[1] were dissolved in dry dichloromethane (140 mL) under inert conditions. After cooling to 0 °C, 4-(dimethylamino)pyridine (1.83 g, 17.94 mmol) and

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimid-hydrochloride (3.44 g, 19.73 mmol) were added. The resulting mixture was stirred for four hours at 0 °C, afterwards it was allowed to reach room temperature and further stirred overnight. The next day, water (30 mL) was added and the mixture was acidified using 6 M HCl (pH ≈ 1). The organic phase was separated and the aqueous phase was extracted with dichloromethane (3 × 50 mL). The combined organic phases were dried over magnesium sulfate and the solvent was removed. The residue was washed with diethyl ether yielding a white solid. Yield: 7.17 g, 86%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.26 (t, J = 5.8 Hz, 1H, NH), 7.93 (d, J = 1.8 Hz, 1H, $H_{(Ar)}$), 7.89 (d, J = 7.1 Hz, 1H, $H_{(Ar)}$), 7.64 (d, J = 8.9 Hz, 1H, $H_{(Ar)}$), 7.46 – 7.36 (m, 2H, $H_{(Ar)}$), 7.31 (d, J = 6.7 Hz, 1H, $H_{(Ar)}$), 7.23 (s, 1H, $H_{(Ar)}$), 7.05 (t, J = 6.8 Hz, 1H, $H_{(Ar)}$), 5.96 (s, 2H, CH_2), 4.41 (d, J = 5.8 Hz, 2H, CH_2), 3.37 – 3.32 (m, 2H, CH_2 (overlapped water signal), 0.99 (t, J = 7.0 Hz, 3H, CH_3).

tert-butyl (5-bromo-1-(ethoxymethyl)-1*H*-indole-2-carbonyl)(2-iodobenzyl)carbamate (BE). 5-bromo-1-(ethoxymethyl)-*N*-(2-iodobenzyl)-1*H*-indole-2-carboxamide (**BD**) (7.13 g, 13.89 mmol) was dissolved in dry acetonitrile (120 mL) under inert conditions, then di-tert-butyl dicarbonate (4.85 g, 22.22 mmol) in dry acetonitrile (20 mL) and a catalytic amount of 4-(dimethylamino)pyridine were added. The resulting mixture was stirred overnight at room temperature. The next day, the solvent was removed. The residue was dissolved in ethyl acetate (90 mL) and washed with water (60 mL). The aqueous phase was extracted with ethyl acetate (2 × 90 mL). The combined organic phases were dried over magnesium sulfate and evaporated. The crude product was purified on silica, using hexan/ethyl acetate 85 : 15 as eluent. Yield: 8.39 g, 98%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.94 – 7.89 (m, 2H, $H_{(Ar)}$), 7.69 (d, J = 8.9 Hz, 1H, $H_{(Ar)}$), 7.49 – 7.39 (m, 2H, $H_{(Ar)}$), 7.24 – 7.18 (m, 1H, $H_{(Ar)}$), 7.07 (td, J = 7.8, 1.4 Hz, 1H, $H_{(Ar)}$), 7.03 (s, 1H, $H_{(Ar)}$), 5.73 (s, 2H, CH_2), 4.87 (s, 2H, CH_2), 3.43 (q, J = 7.0 Hz, 2H, CH_2), 1.10 (s, 9H, C(CH_3)$_3$), 1.06 (t, J = 7.0 Hz, 3H, CH_3).

11-bromo-6-tert-butyl-8-(ethoxymethyl)-5-dihydroindolo[2,3-*d*][2]benzazepin-7-one (BF). tert-butyl (5-bromo-1-(ethoxymethyl)-1H-indole-2-carbonyl)(2-iodobenzyl)carbamate (**BE**) (8.12 g, 13.24 mmol) was dissolved in dry DMF (200 mL) under inert conditions, then triphenylphosphine (1.74 g, 6.62 mmol), palladium(II) acetate (743 mg, 3.31 mmol) and silver(I) carbonate (9.13 g, 33.1 mmol) were added. The resulting mixture was stirred for two hours at 100 °C. Then, the solvent was

removed under reduced pressure. The black residue was taken up in dichloromethane and filtered over celite. The filtrate was evaporated and the residue was purified on silica using hexane/ethyl acetate 85 : 15 as eluent. Yield: 5.49 g, 85%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.15 (d, J = 1.8 Hz, 1H, $H_{(Ar)}$), 8.03 (d, J = 7.6 Hz, 1H, $H_{(Ar)}$), 7.83 (d, J = 8.9 Hz, 1H, $H_{(Ar)}$), 7.66 – 7.59 (m, 2H, $H_{(Ar)}$), 7.57 (d, J = 6.7 Hz, 1H, $H_{(Ar)}$), 7.50 – 7.45 (m, 1H, $H_{(Ar)}$), 6.01 (d, J = 10.9 Hz, 1H, CH_2), 5.91 (d, J = 10.8 Hz, 1H, CH_2), 5.09 (d, J = 15.1 Hz, 1H, CH_2), 4.25 (d, J = 15.0 Hz, 1H, CH_2), 3.52 – 3.32 (m, 2H, CH_2 (overlapped water signal), 1.47 (d, J = 5.5 Hz, 9H, C(CH_3)$_3$), 1.03 (t, J = 7.0 Hz, 3H, CH_3).

11-bromo-5,8-dihydroindolo[2,3-*d*][2]benzazepin-7(6*H*)-one (B). 11-bromo-6-tert-butyl-8-(ethoxymethyl)-5-dihydroindolo[2,3-*d*][2]benzazepin-7-one (**BF**) (2.0 g, 4.12 mmol) was dissolved in dioxane (100 ml) and 1 M hydrochloric acid (50 mL) was added. The resulting mixture was stirred overnight at 80 °C. The next day saturated sodim bicarbonate solution and a small amount of sat. potassium carbonate solution were added (pH ≈ 11). It was extracted with dichloromethane (3 × 100 mL). The combined organic phases were dried over magnesium sulfate and the solvent was evaporated. The residue was recrystallized from ethyl acetate. The white solid was filtered off, washed with ethyl acetate and dried *in vacuo*. Yield: 1.20 g, 89%. ^{1}H NMR (500 MHz, DMSO) δ 12.27 (s, 1H, N*H*), 8.49 (t, J = 5.3 Hz, 1H, N*H*), 8.11 (d, J = 1.3 Hz, 1H, $H_{(Ar)}$), 7.89 (d, J = 7.5 Hz, 1H, $H_{(Ar)}$), 7.54 – 7.42 (m, 4H, $H_{(Ar)}$), 7.35 (t, J = 7.4 Hz, 1H, $H_{(Ar)}$), 4.07 (d, J = 5.0 Hz, 2H, CH_2).

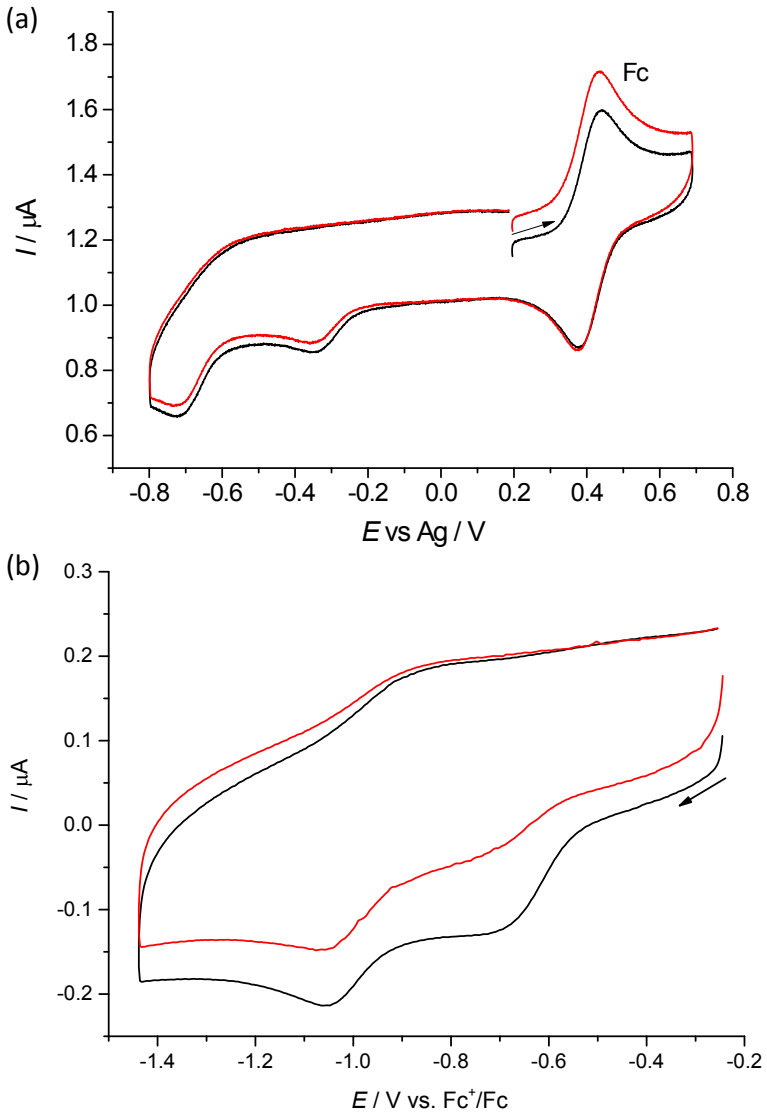


Figure S1. Cyclic voltammograms of (a) **3** in the presence of internal standard ferrocene and (b) **2** in DMSO/nBu$_4$NPF$_6$ at scan rate of 100 mV s^{-1} and at GC working electrode (black traces represent the first scan, while red traces the second scan).

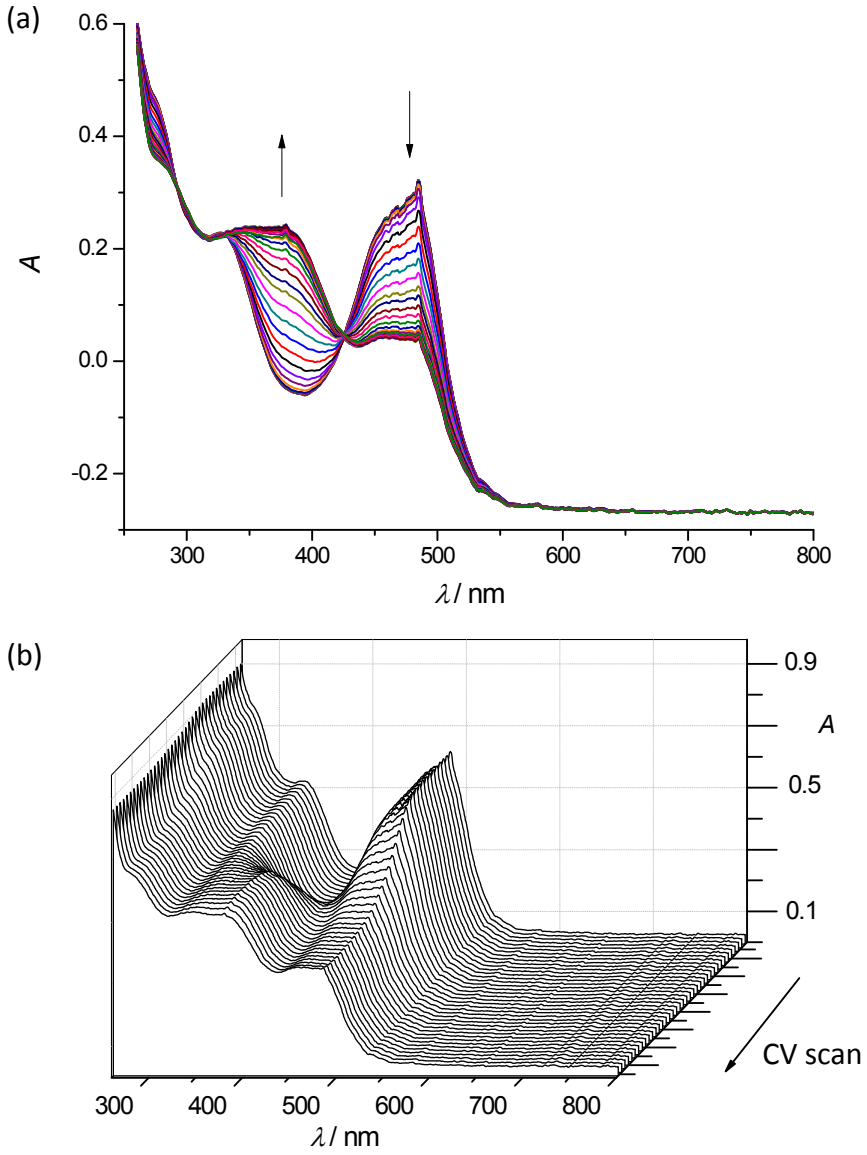


Figure S2. *In situ* UV-vis-NIR spectroelectrochemistry for **3** in DMSO/nBu_4NPF_6 (scan rate of 10 mV s^{-1}, Pt-microstructured honeycomb working electrode): (a) evolution of UV−vis spectra in 2D projection in forward scan in the region of the first reduction peak; (b) UV-vis spectra detected simultaneously upon the cyclic voltammetric scan in 3D projection.

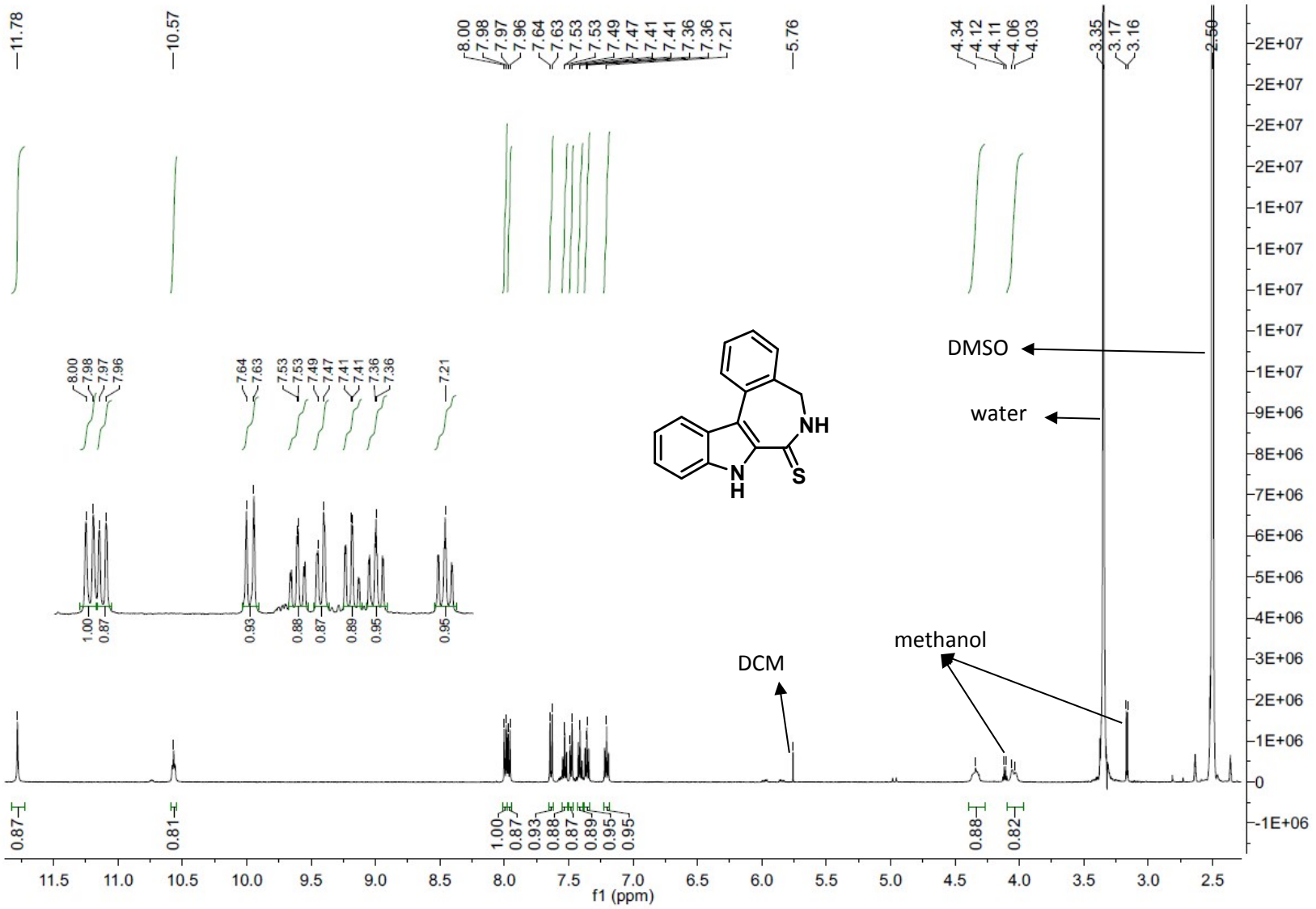


Figure S3. ^{1}H NMR spectrum of **C** in DMSO (500 MHz).

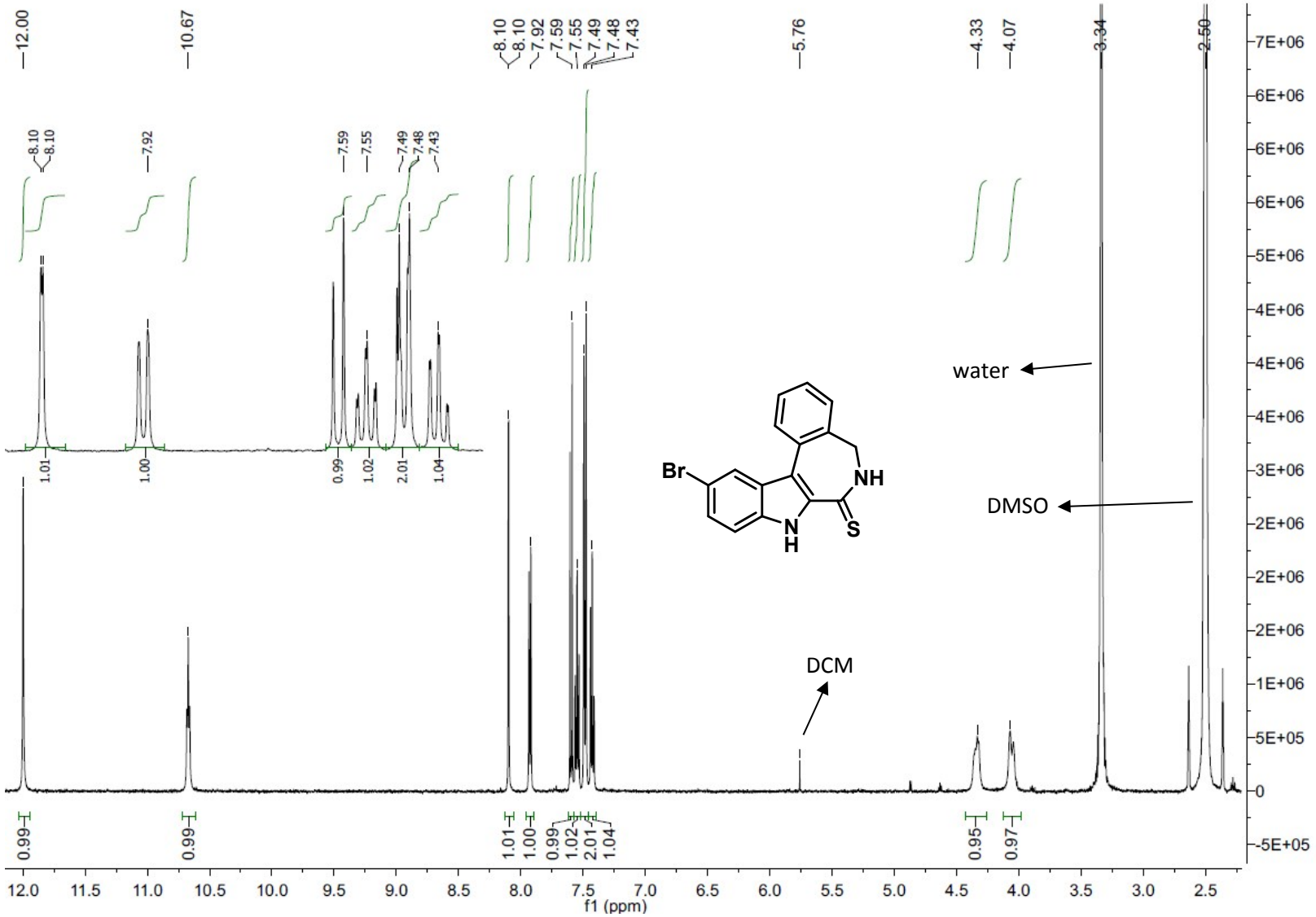


Figure S4. ^{1}H NMR spectrum of **D** in DMSO (500 MHz).

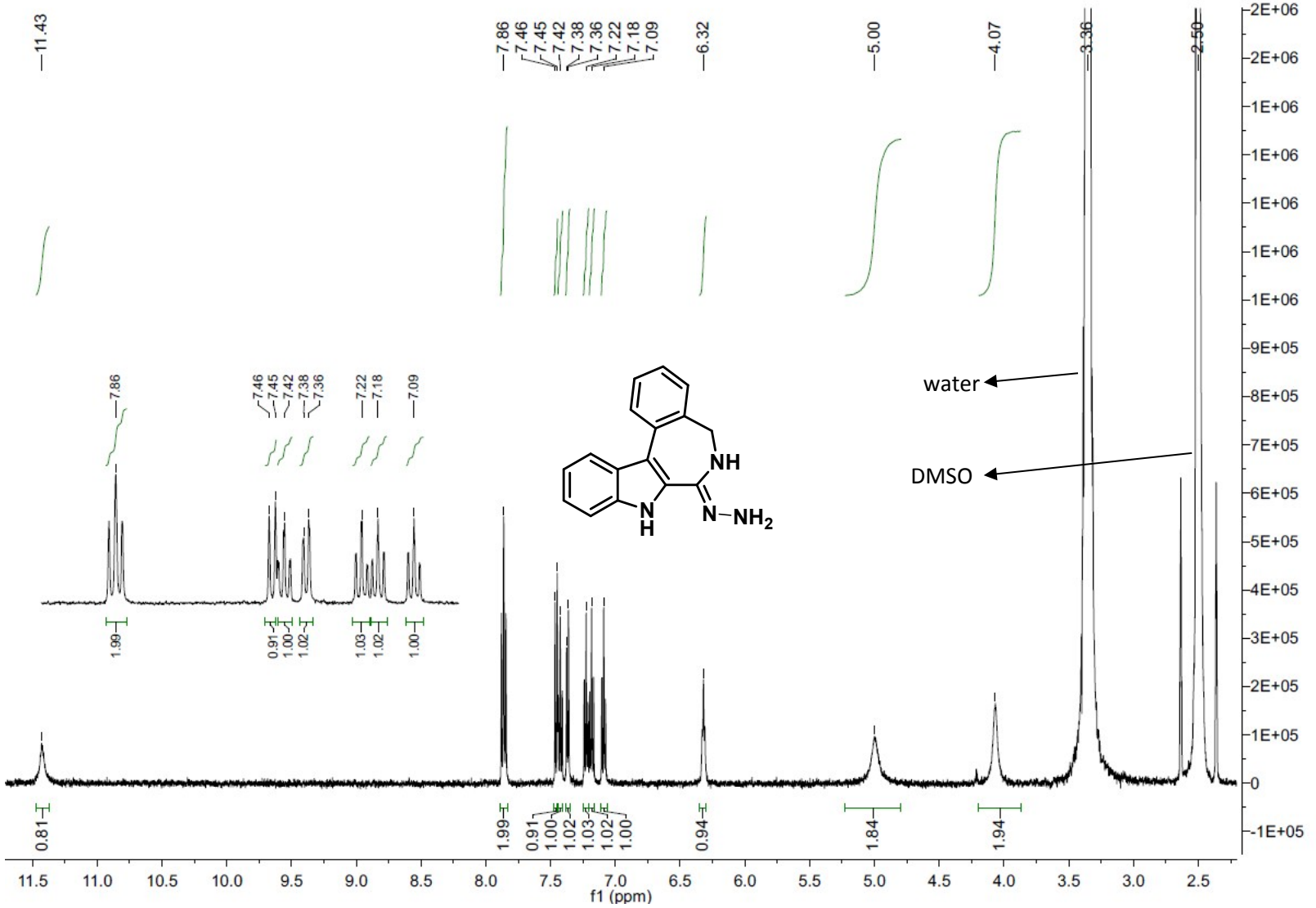


Figure S5. ^{1}H NMR spectrum of **E** in DMSO (500 MHz).

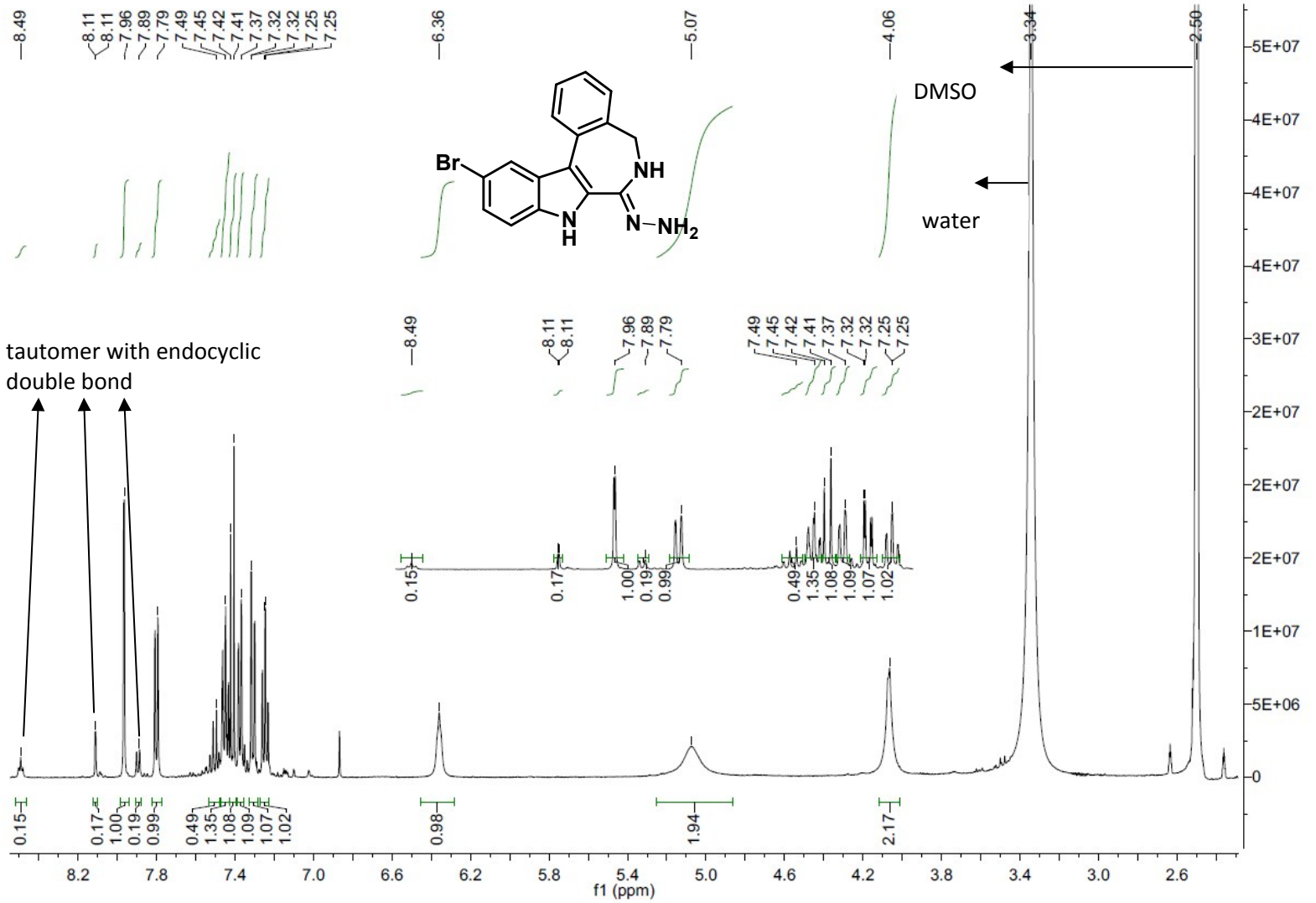


Figure S6. ^{1}H NMR spectrum of **F** in DMSO (500 MHz).

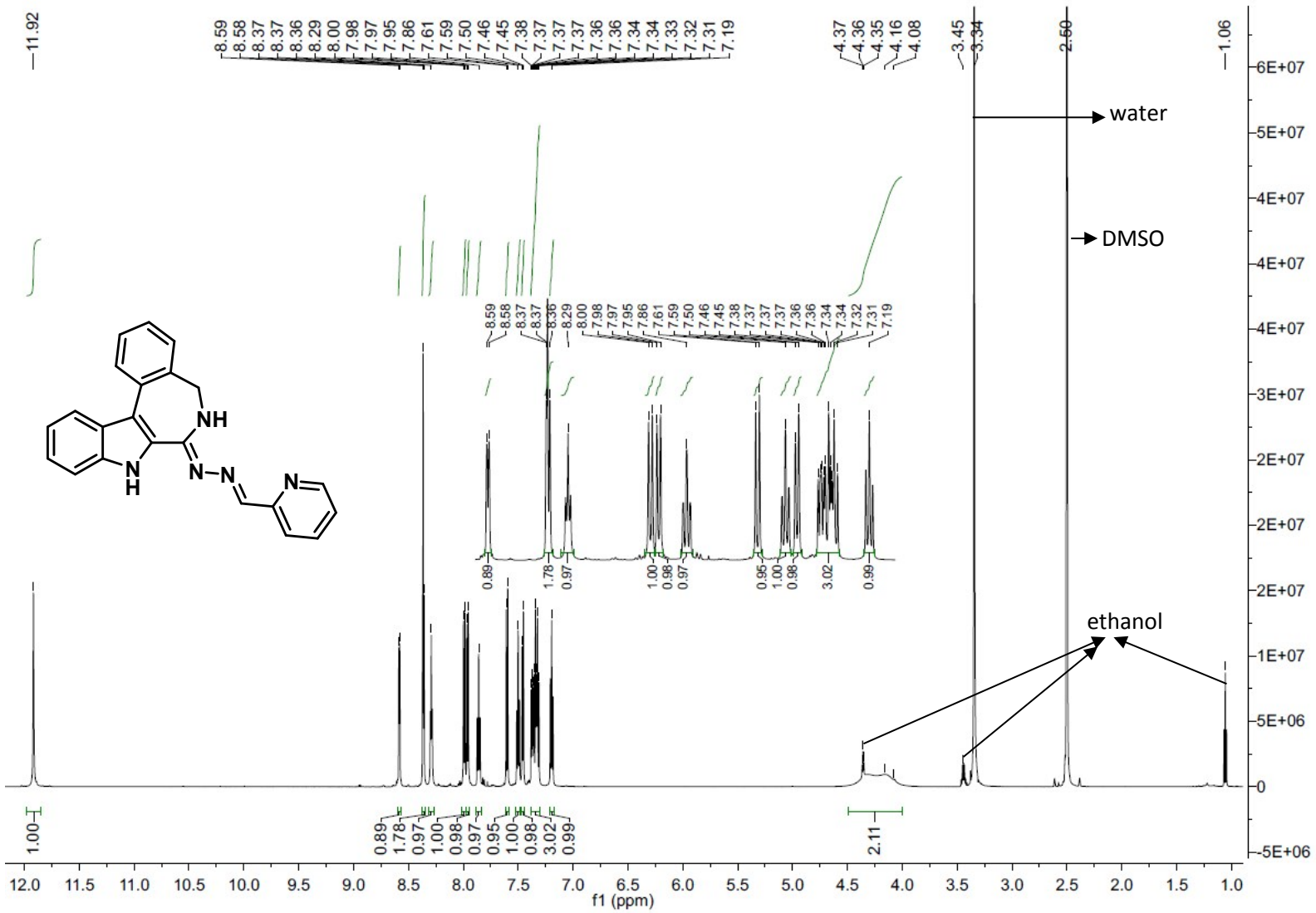


Figure S7. ^{1}H NMR spectrum of **HL^{1}** in DMSO (600 MHz).

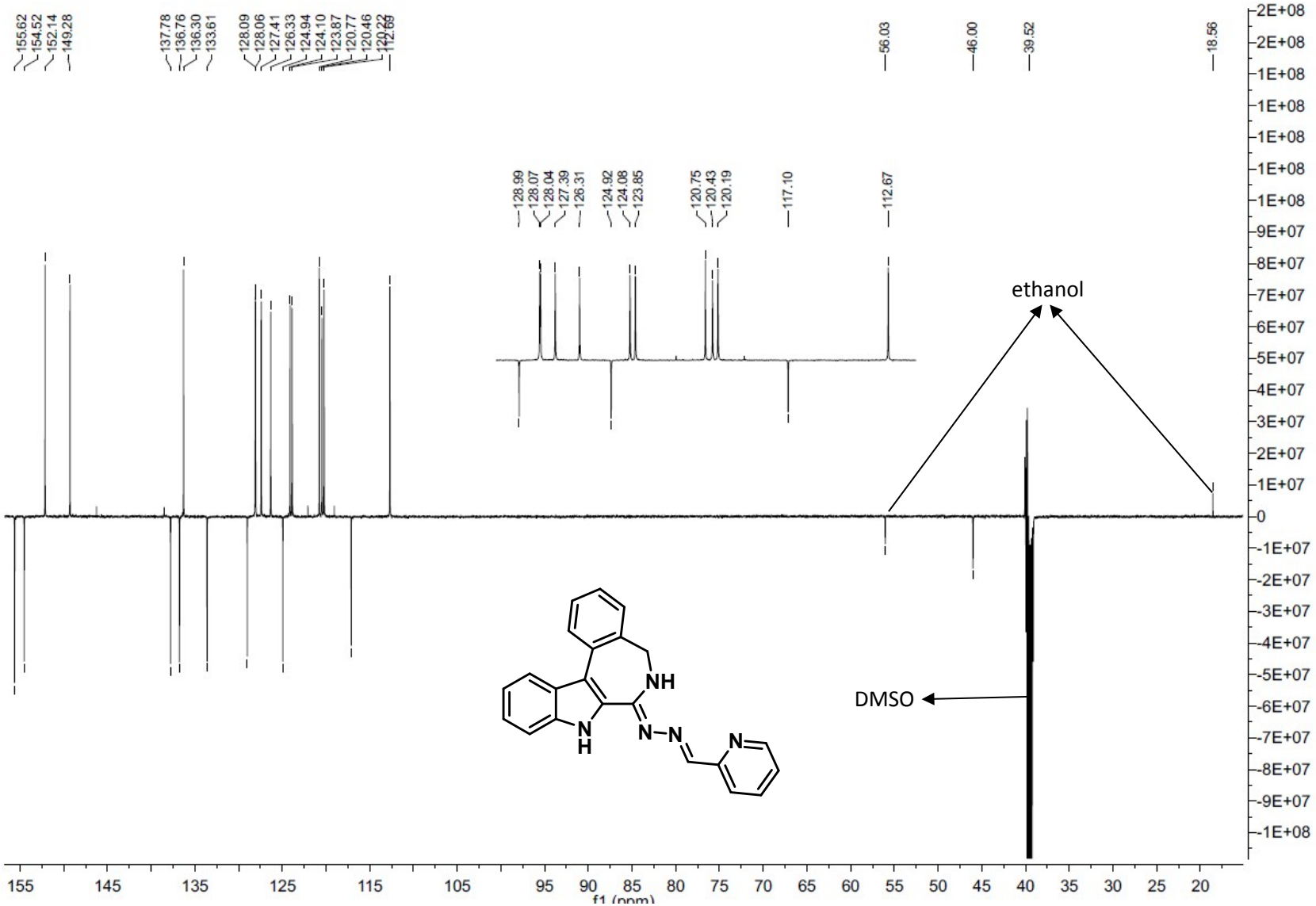


Figure S8. ^{13}C NMR spectrum of **HL¹** in DMSO (151 MHz).

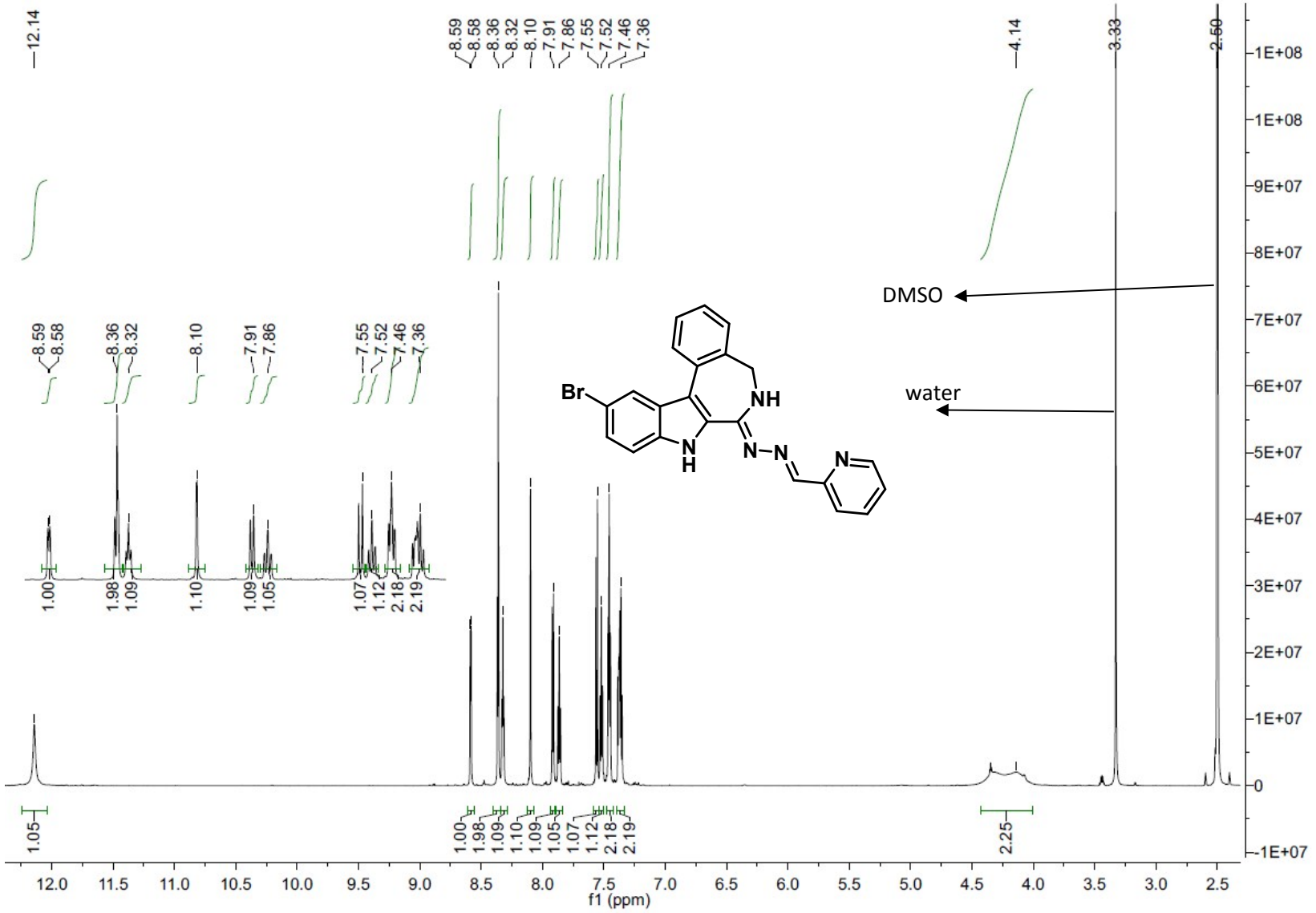


Figure S9. ^{1}H NMR spectrum of **HL²** in DMSO (700 MHz).

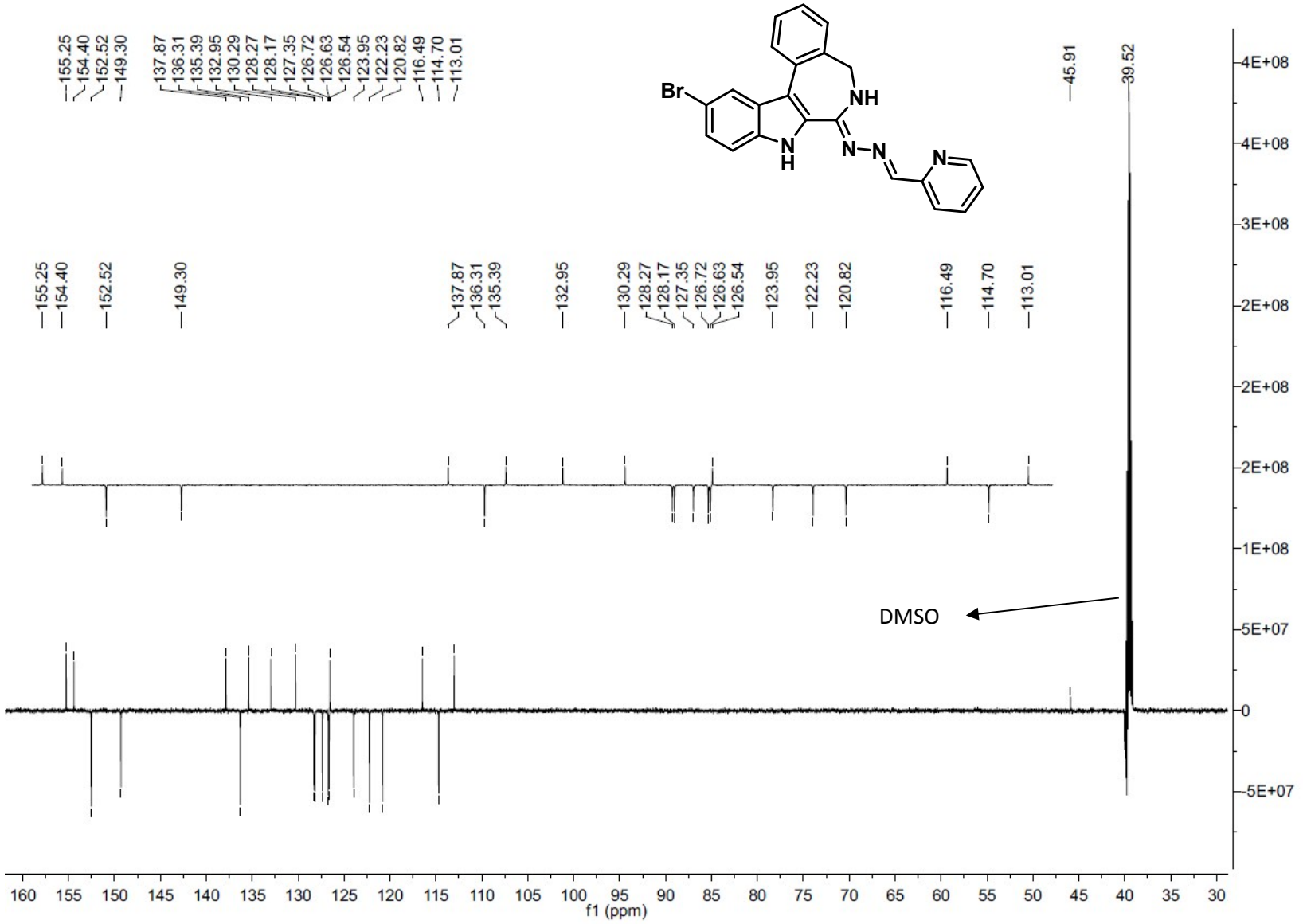


Figure S10. ^{13}C NMR spectrum of **HL²** in DMSO (176 MHz).

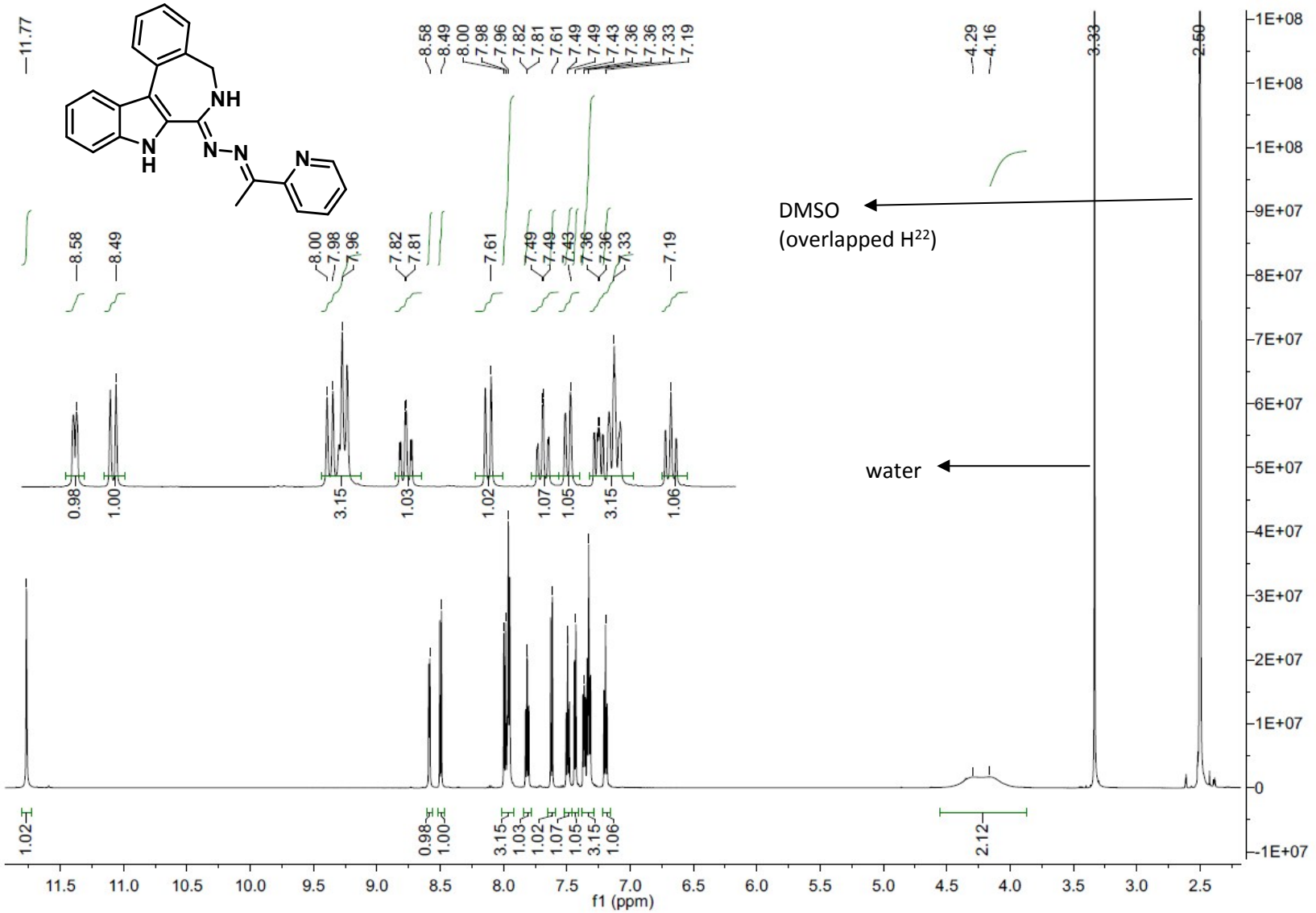


Figure S11. ^{1}H NMR spectrum of **HL^{3}** in DMSO (600 MHz).

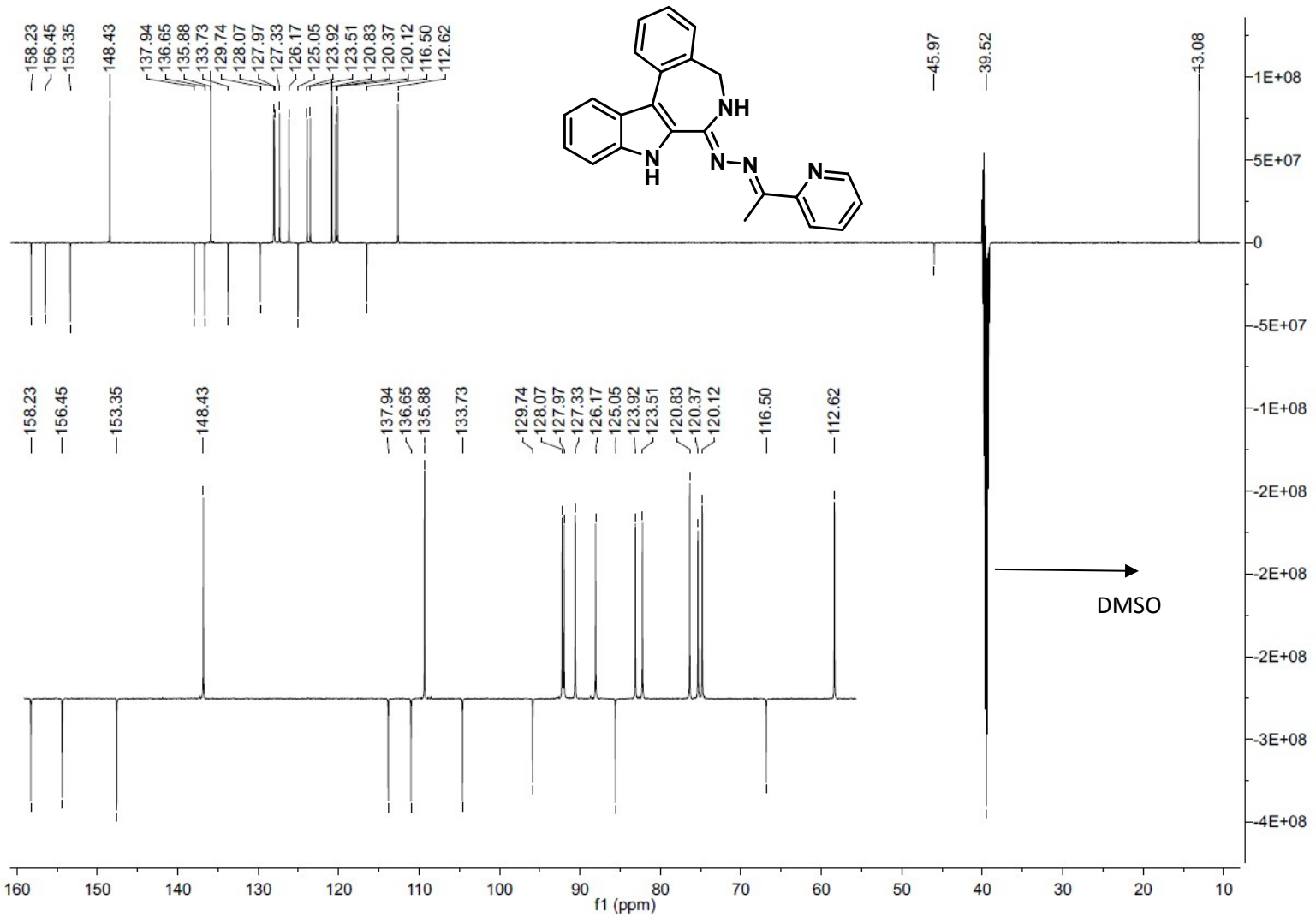


Figure S12. ^{13}C NMR spectrum of **HL³** in DMSO (151 MHz).

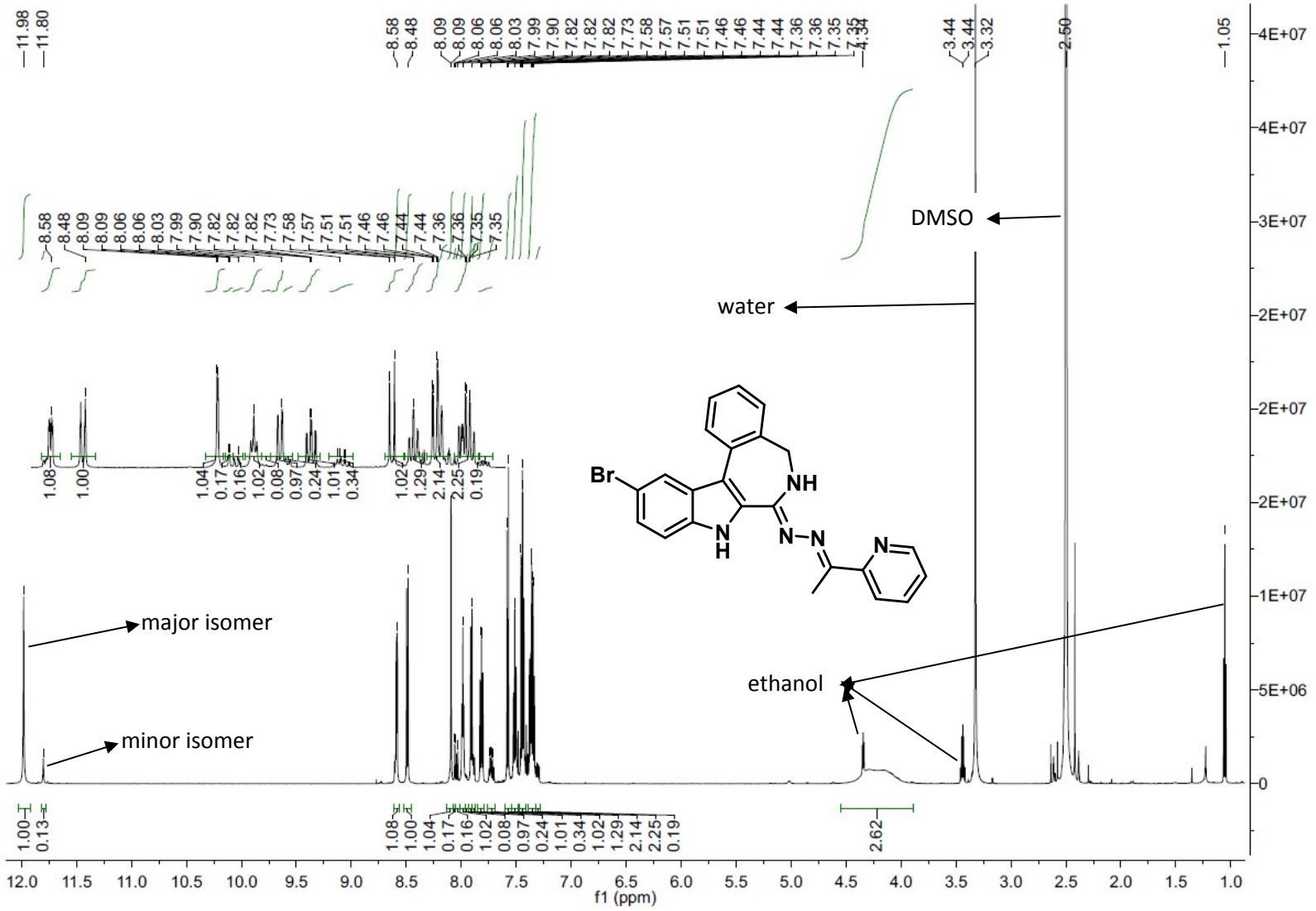


Figure S13. ^{1}H NMR spectrum of **HL^{4}** in DMSO (600 MHz).

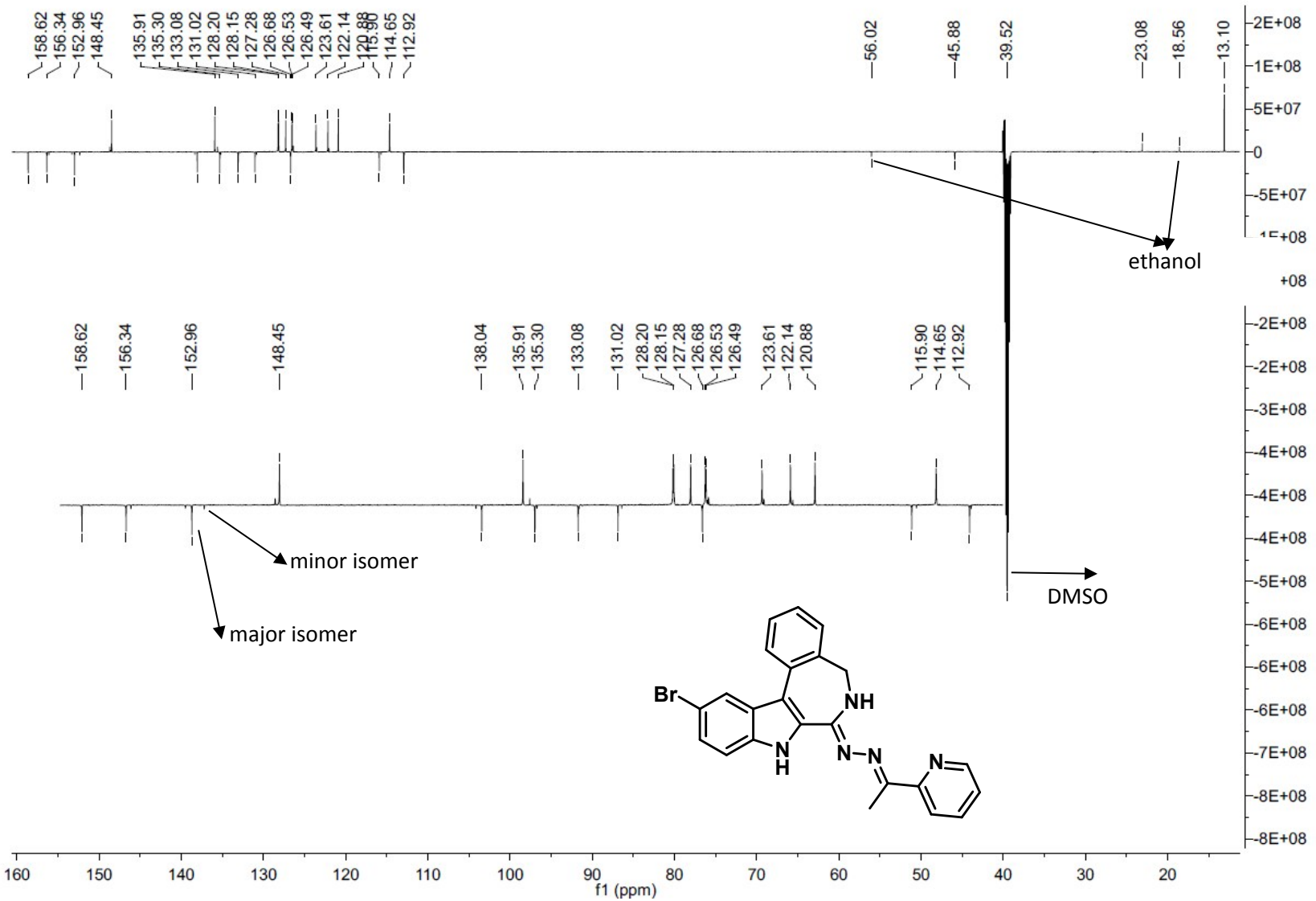


Figure S14. ^{13}C NMR spectrum of **HL^4** in DMSO (151 MHz).

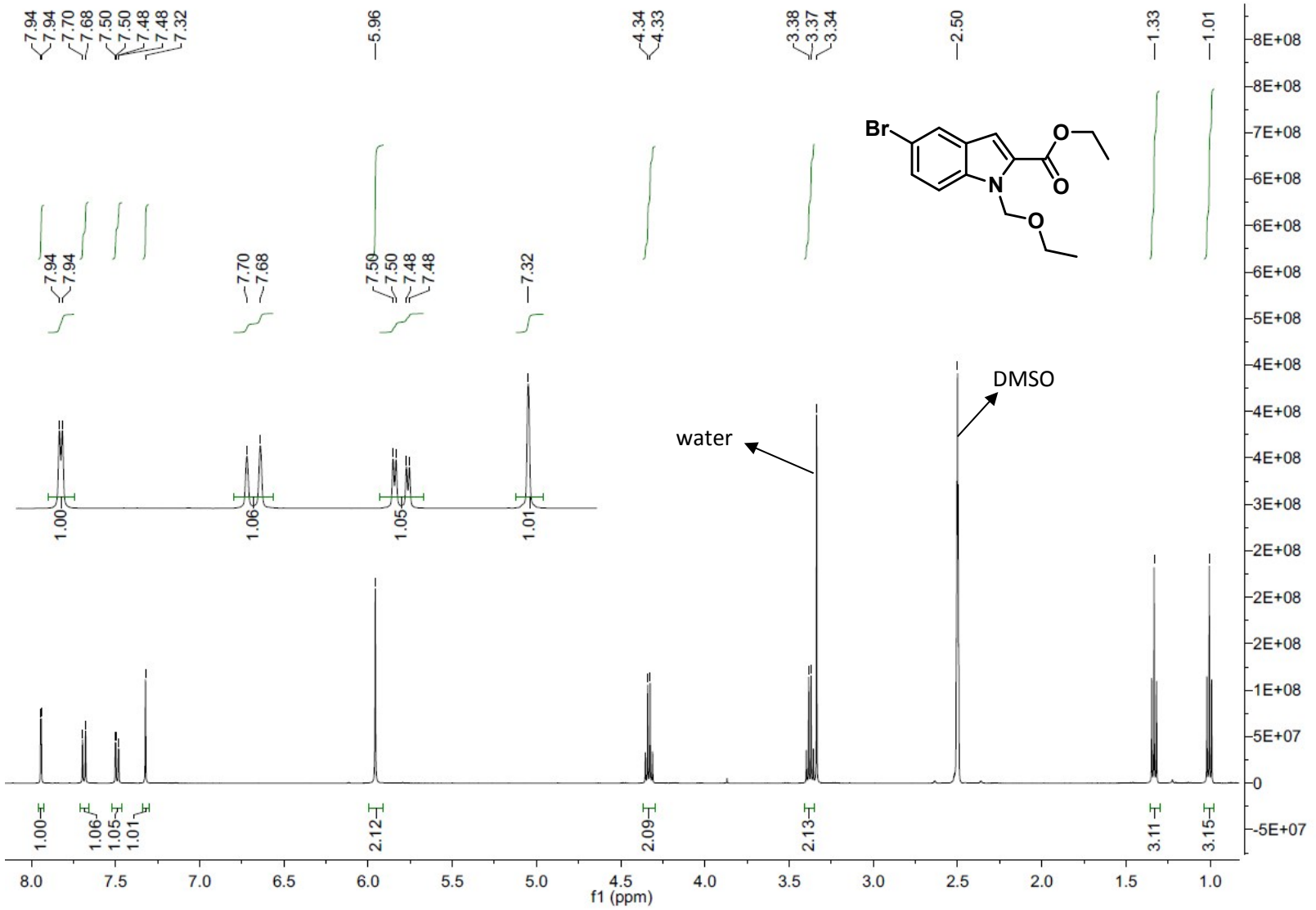


Figure S15. ^{1}H NMR spectrum of **BB** in DMSO (500 MHz).

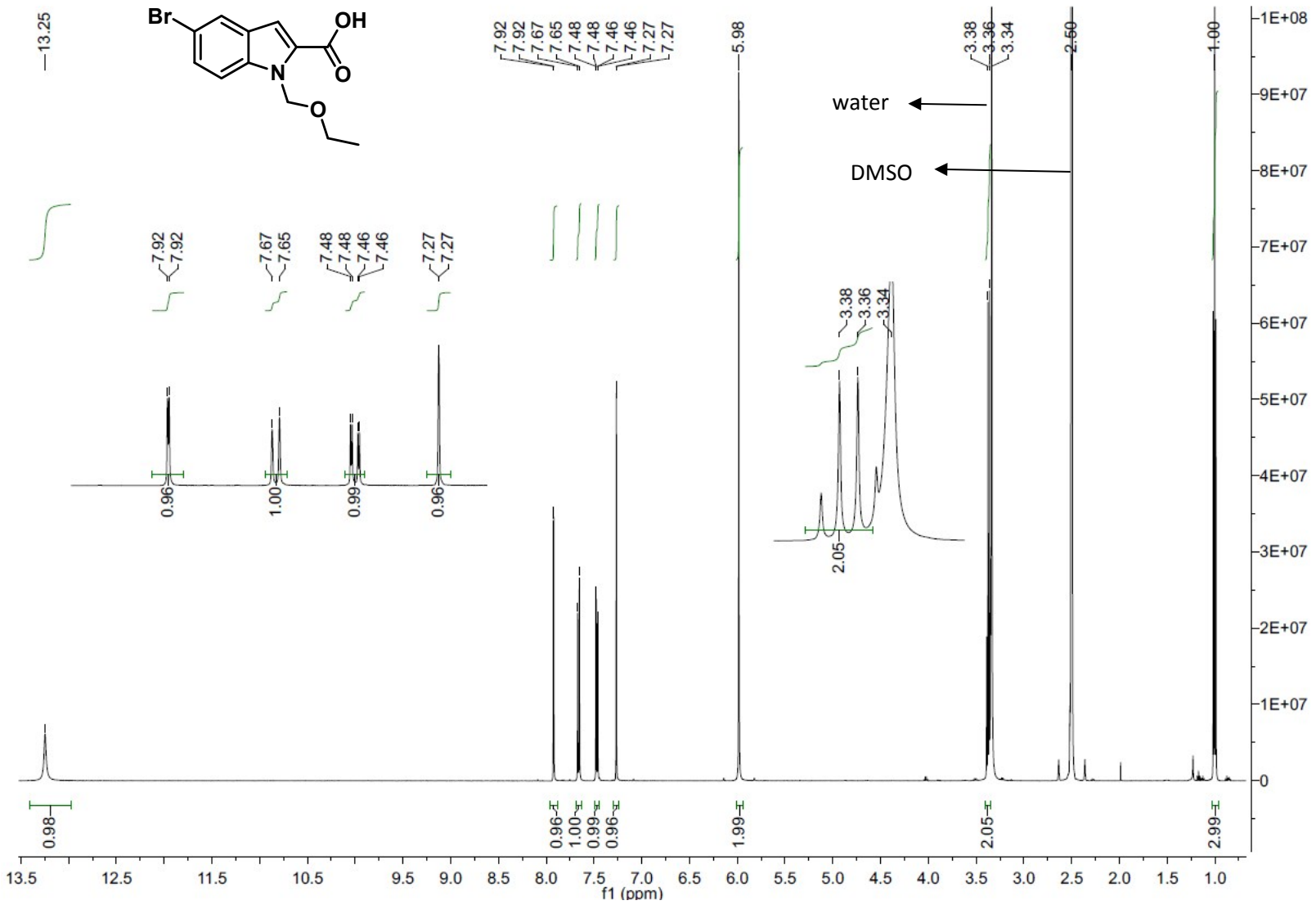


Figure S16. ^{1}H NMR spectrum of **BC** in DMSO (500 MHz).

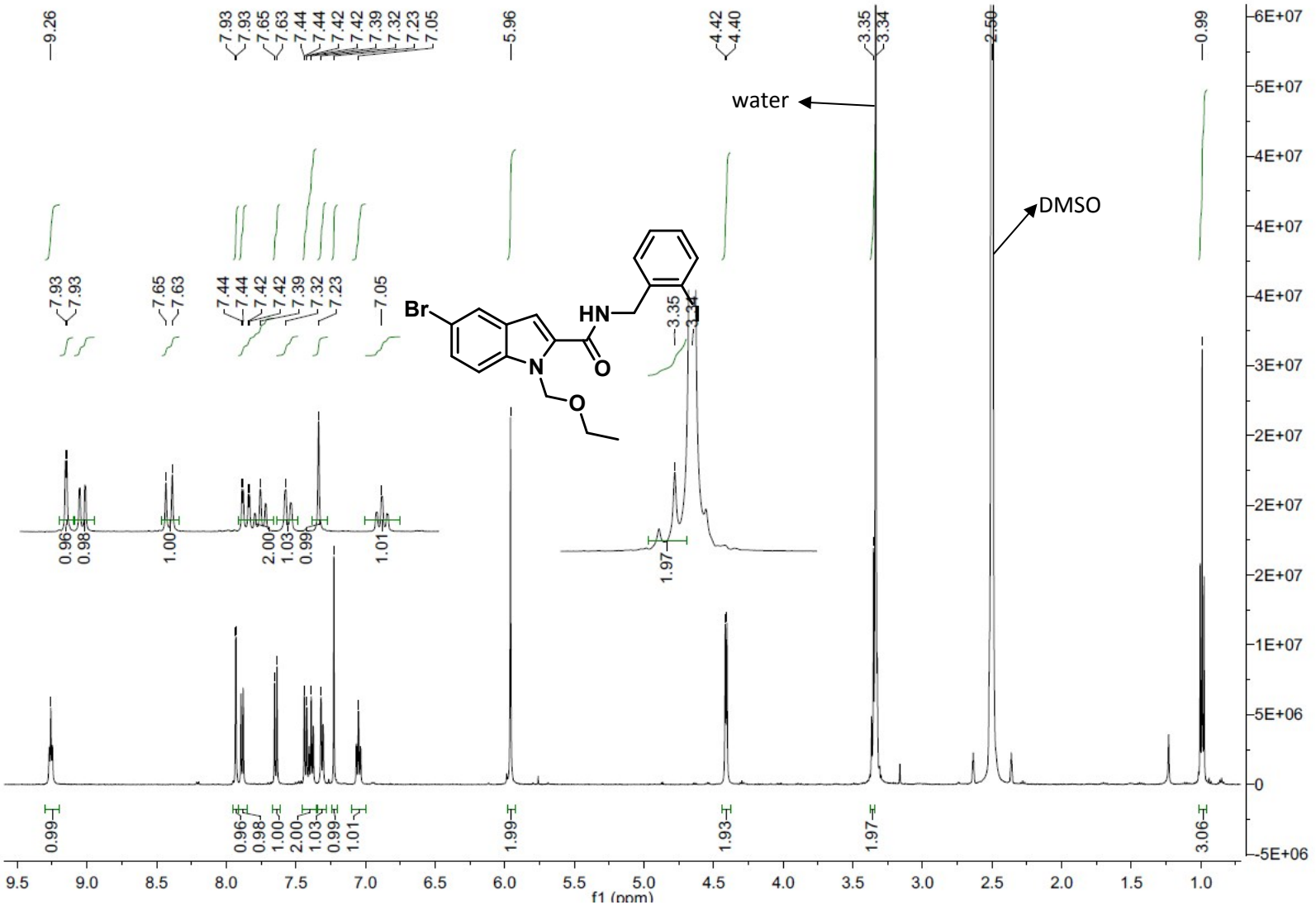


Figure S17. ^{1}H NMR spectrum of **BD** in DMSO (500 MHz).

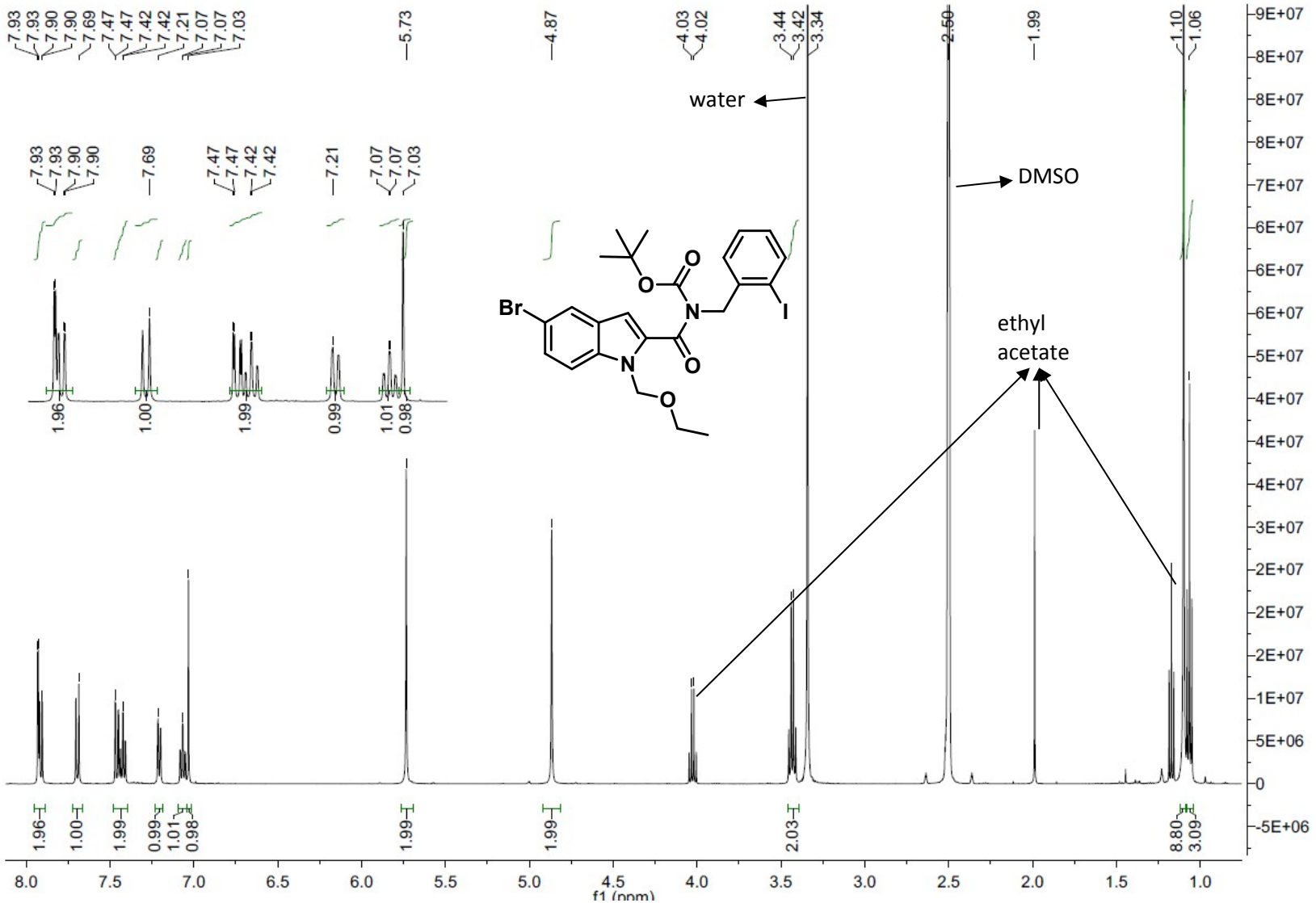


Figure S18. ^{1}H NMR spectrum of **BE** in DMSO (500 MHz).

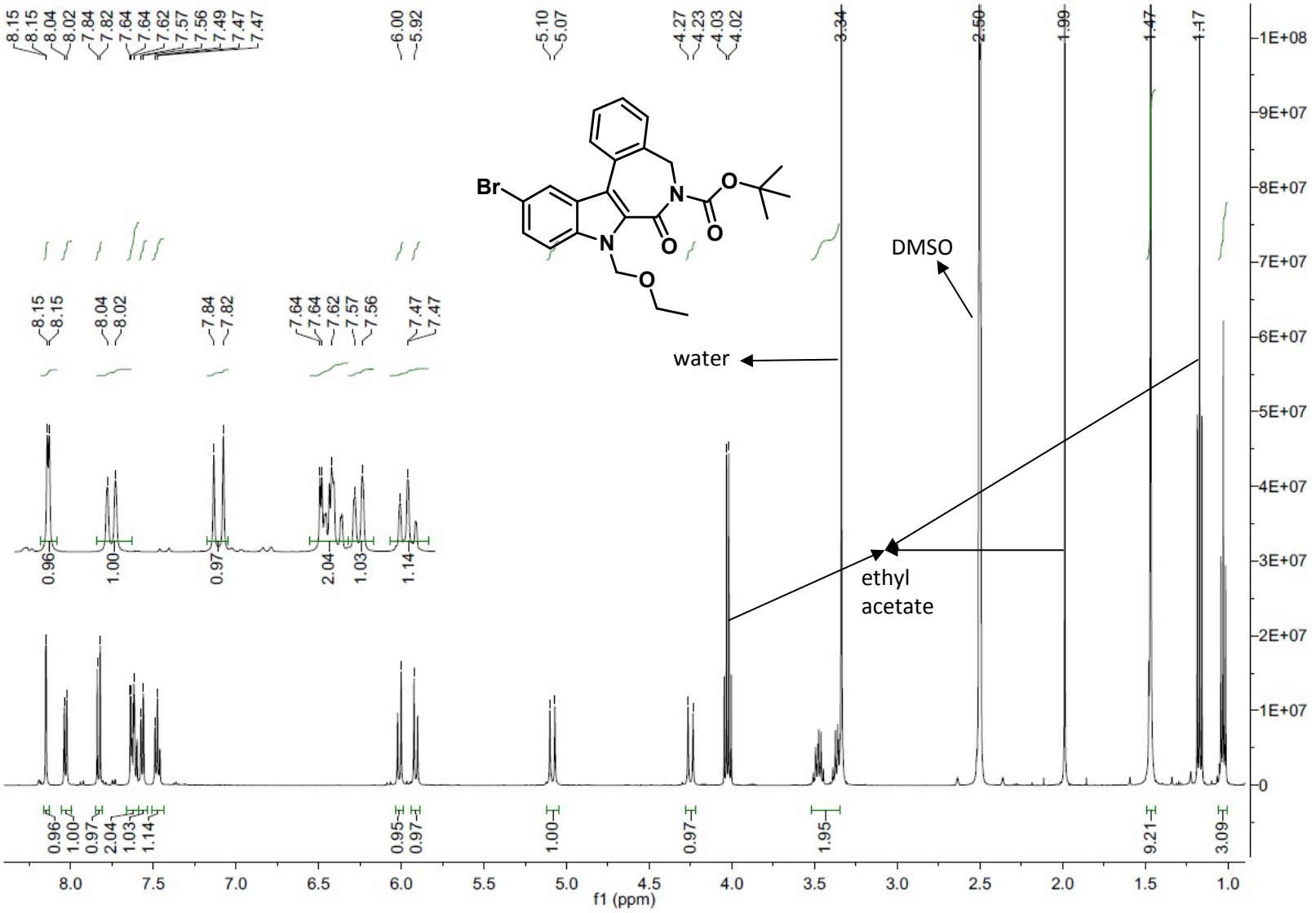


Figure S19. ^{1}H NMR spectrum of **BF** in DMSO (500 MHz).

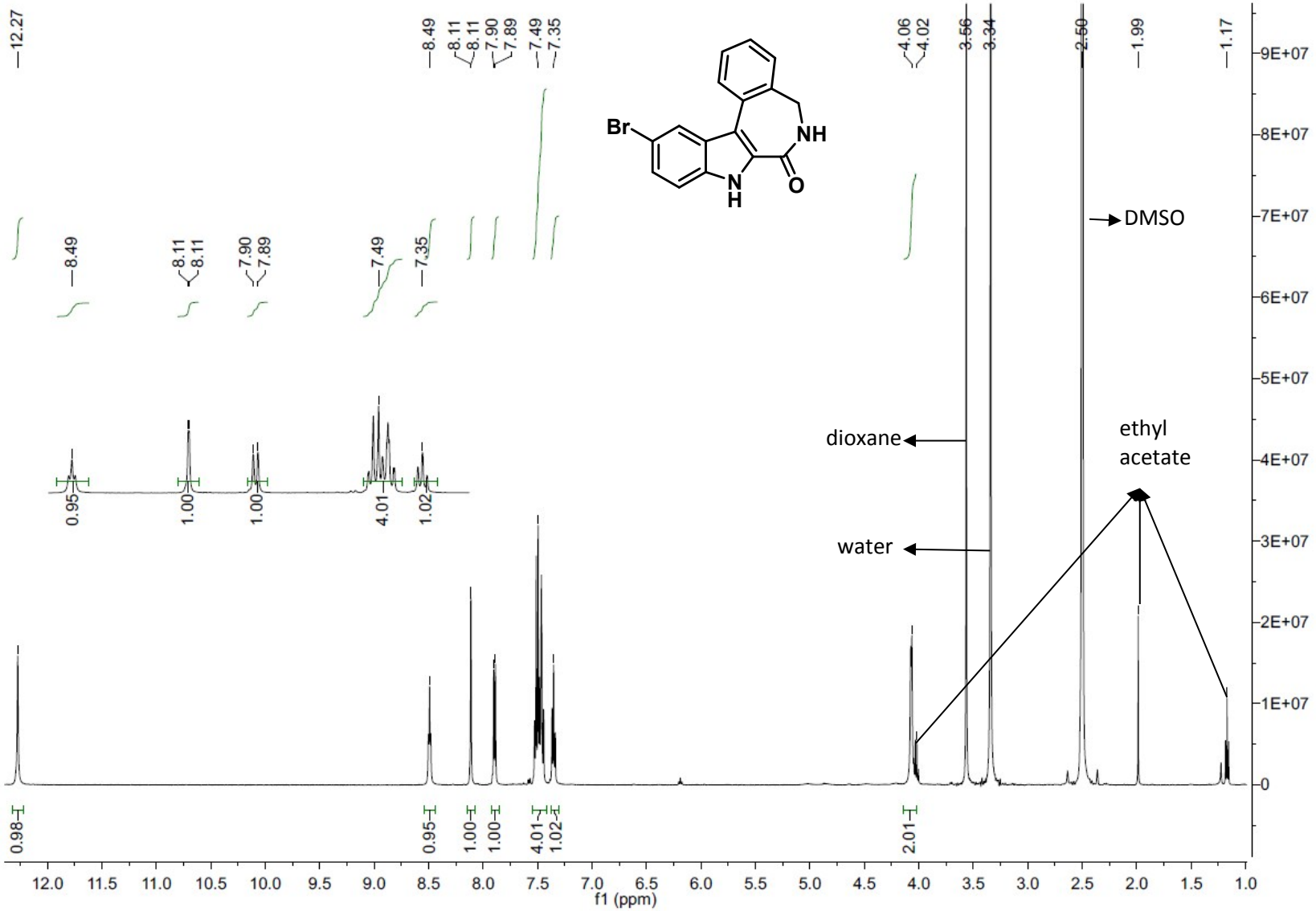


Figure S20. ^{1}H NMR spectrum of **B** in DMSO (500 MHz).

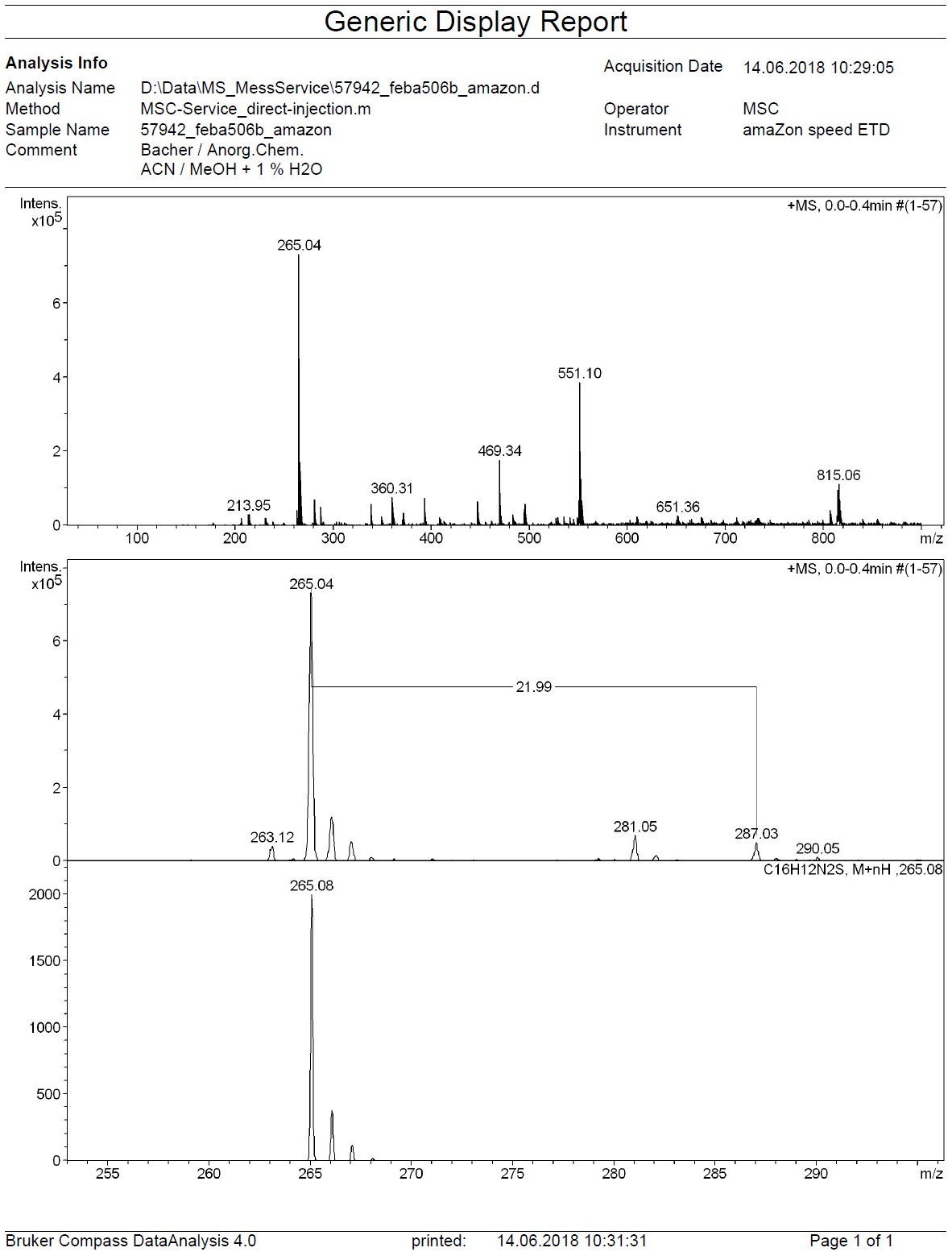


Figure S21. ESI-MS spectrum of **C**.

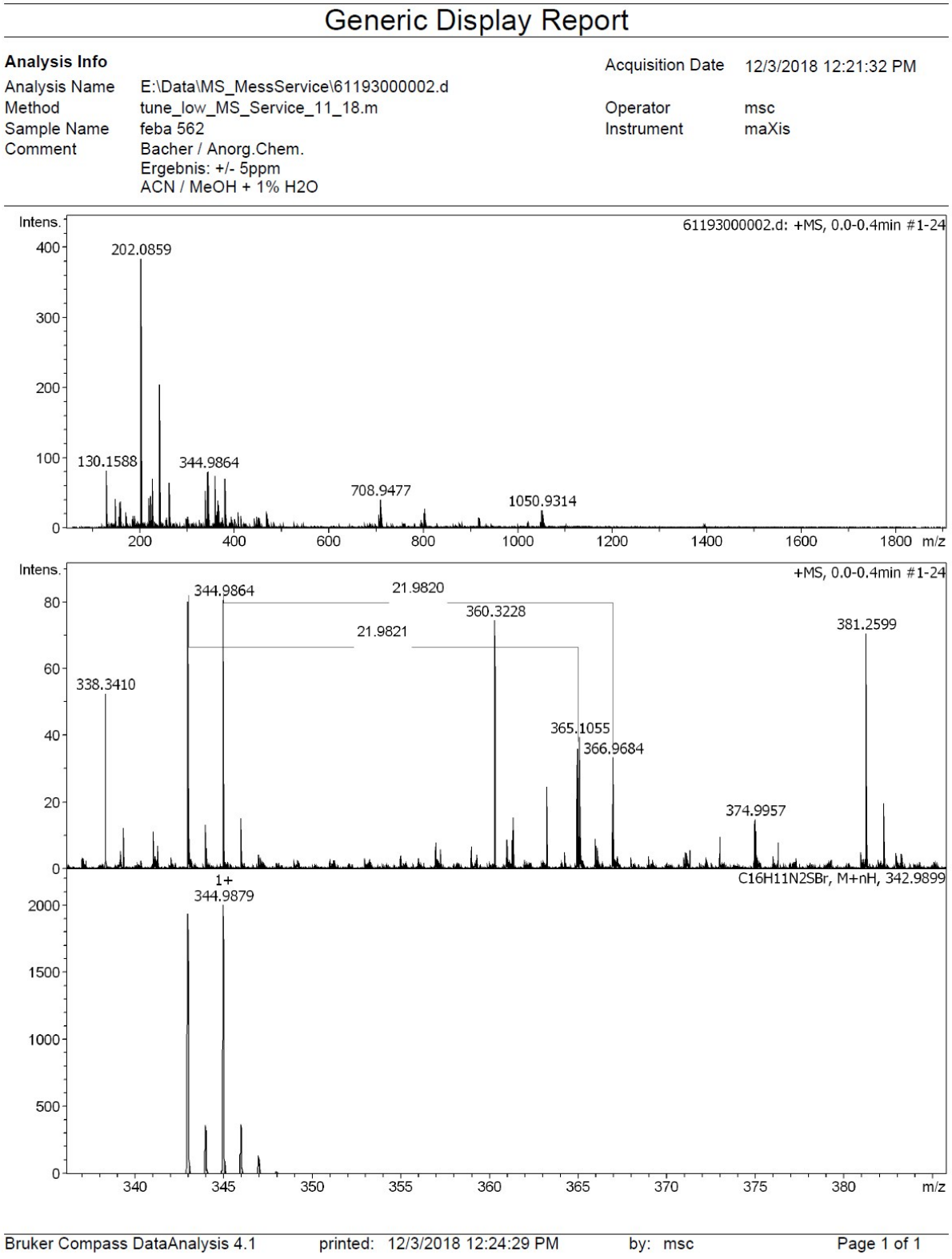


Figure S22. ESI-MS spectrum of **D**.

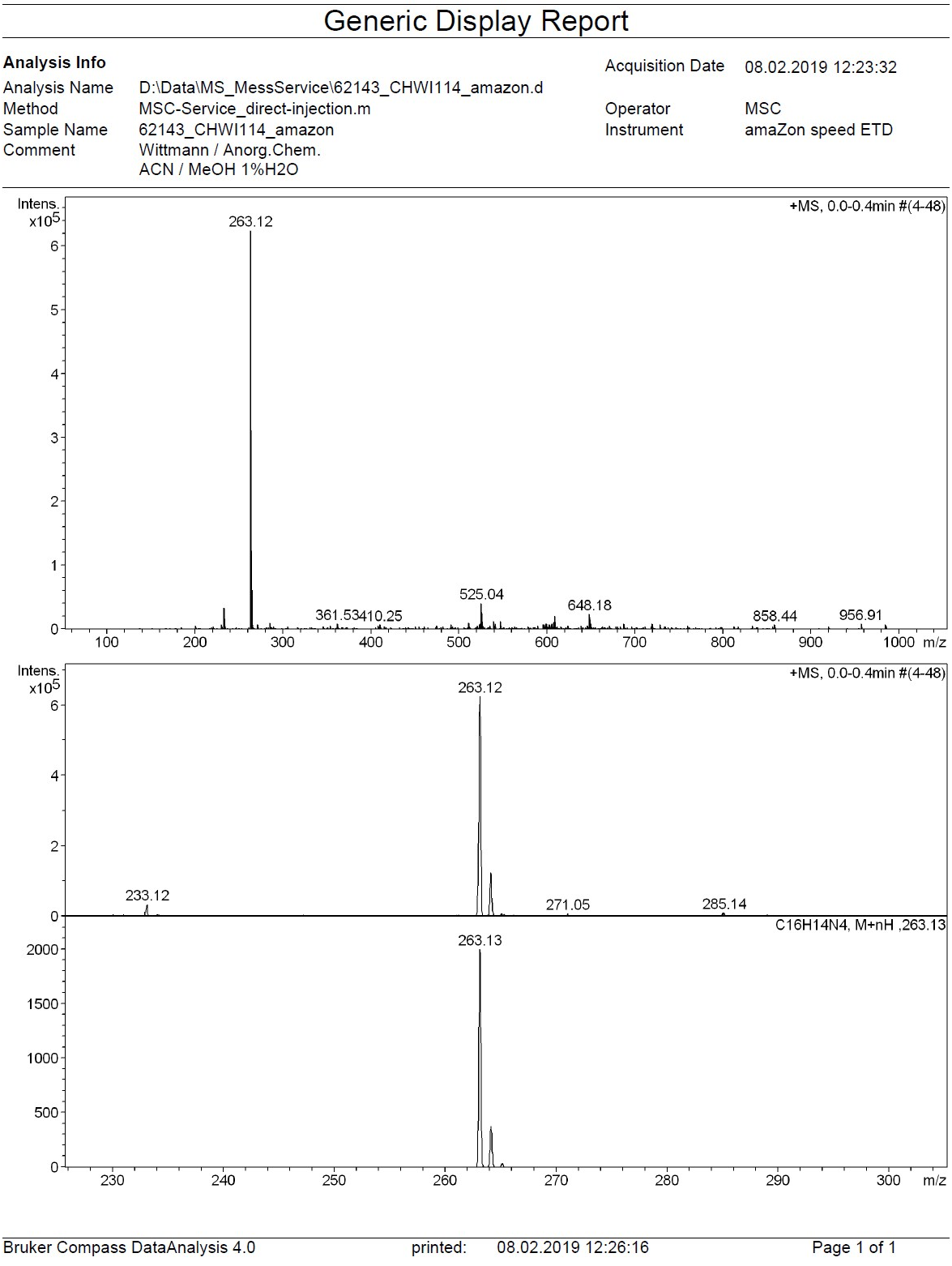


Figure S23. ESI-MS spectrum of **E**.

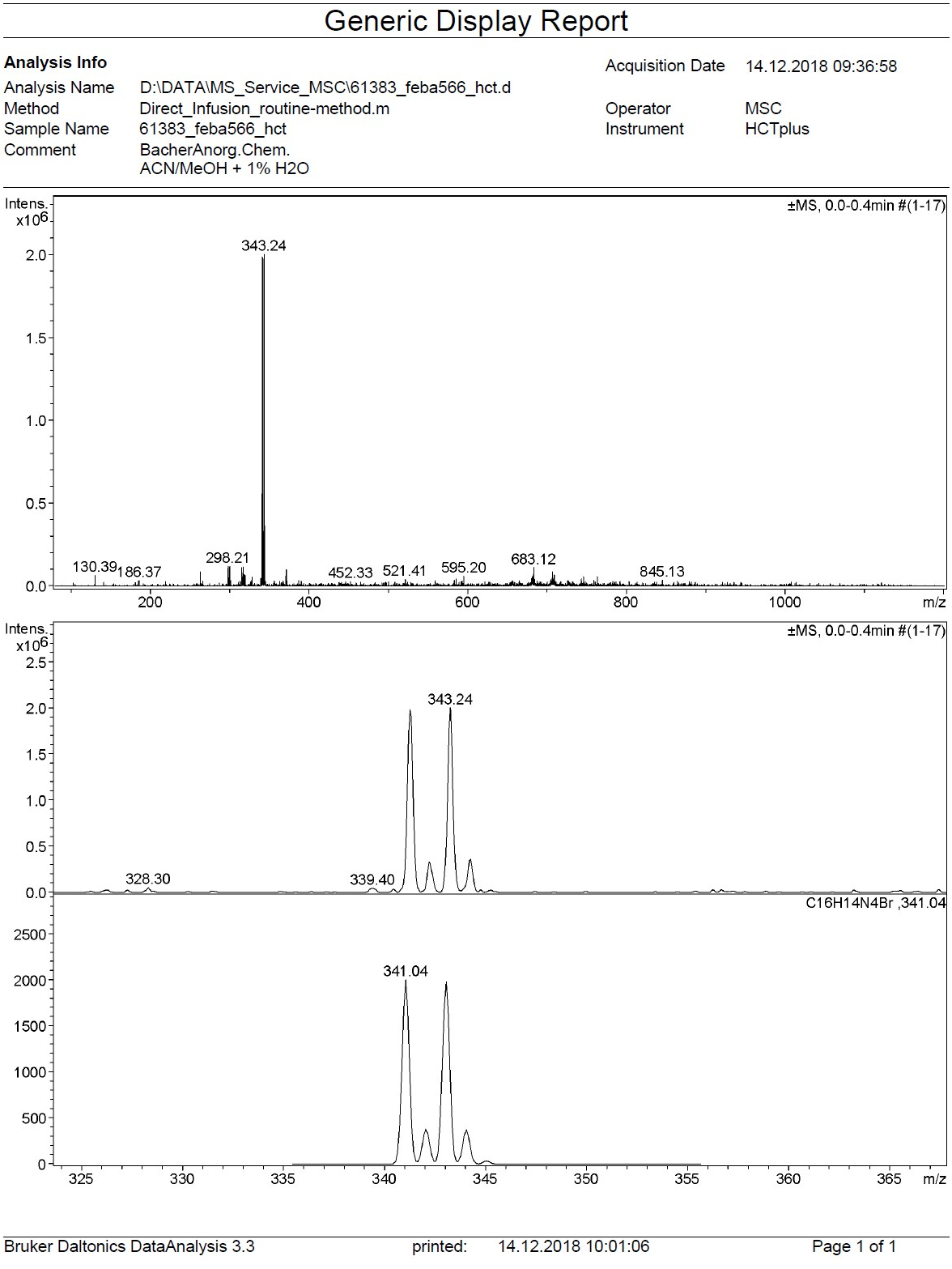


Figure S24. ESI-MS spectrum of **F**.

Generic Display Report

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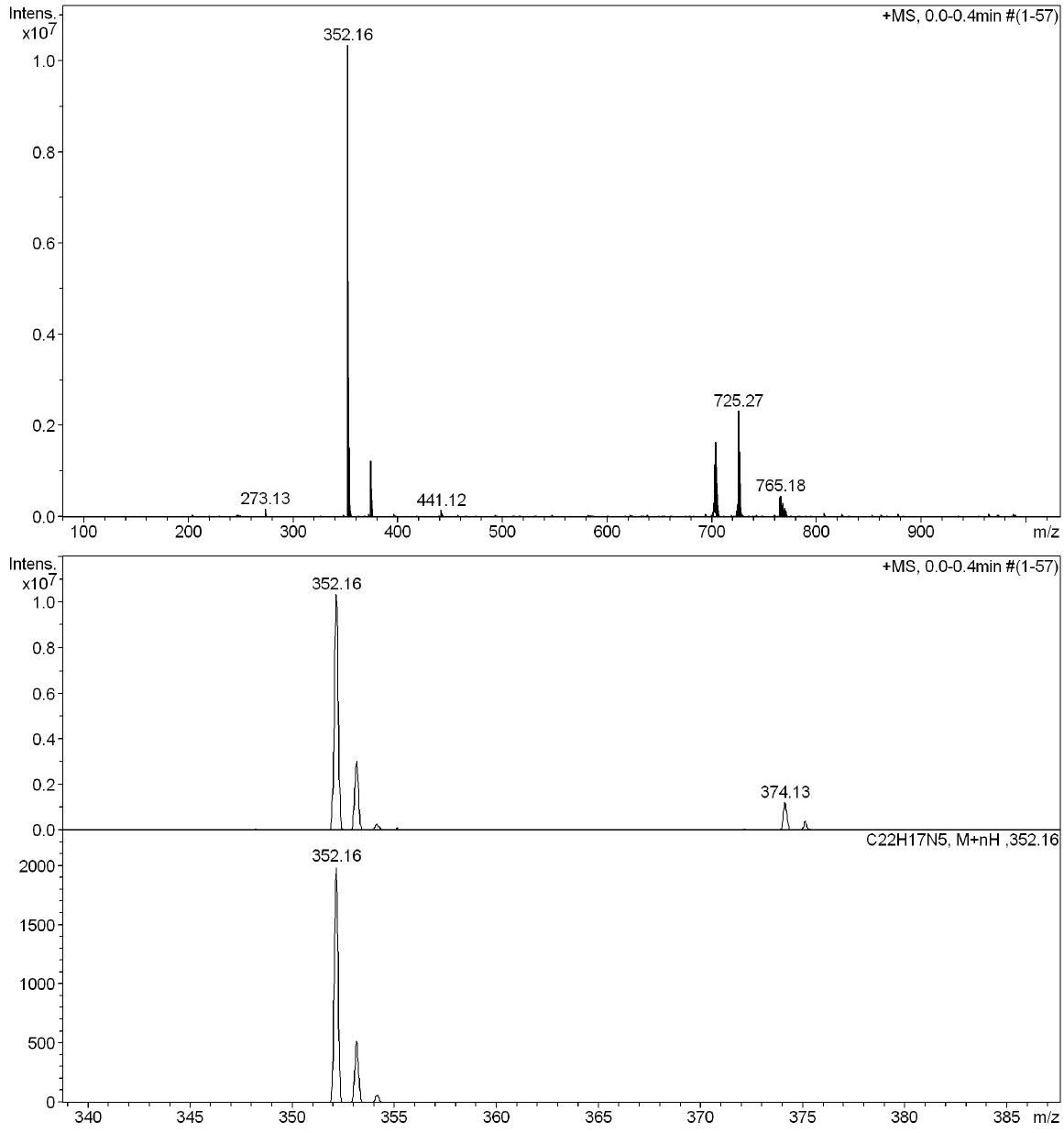

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Figure S25. ESI-MS spectrum of **HL[1]**.

Generic Display Report

Analysis Info

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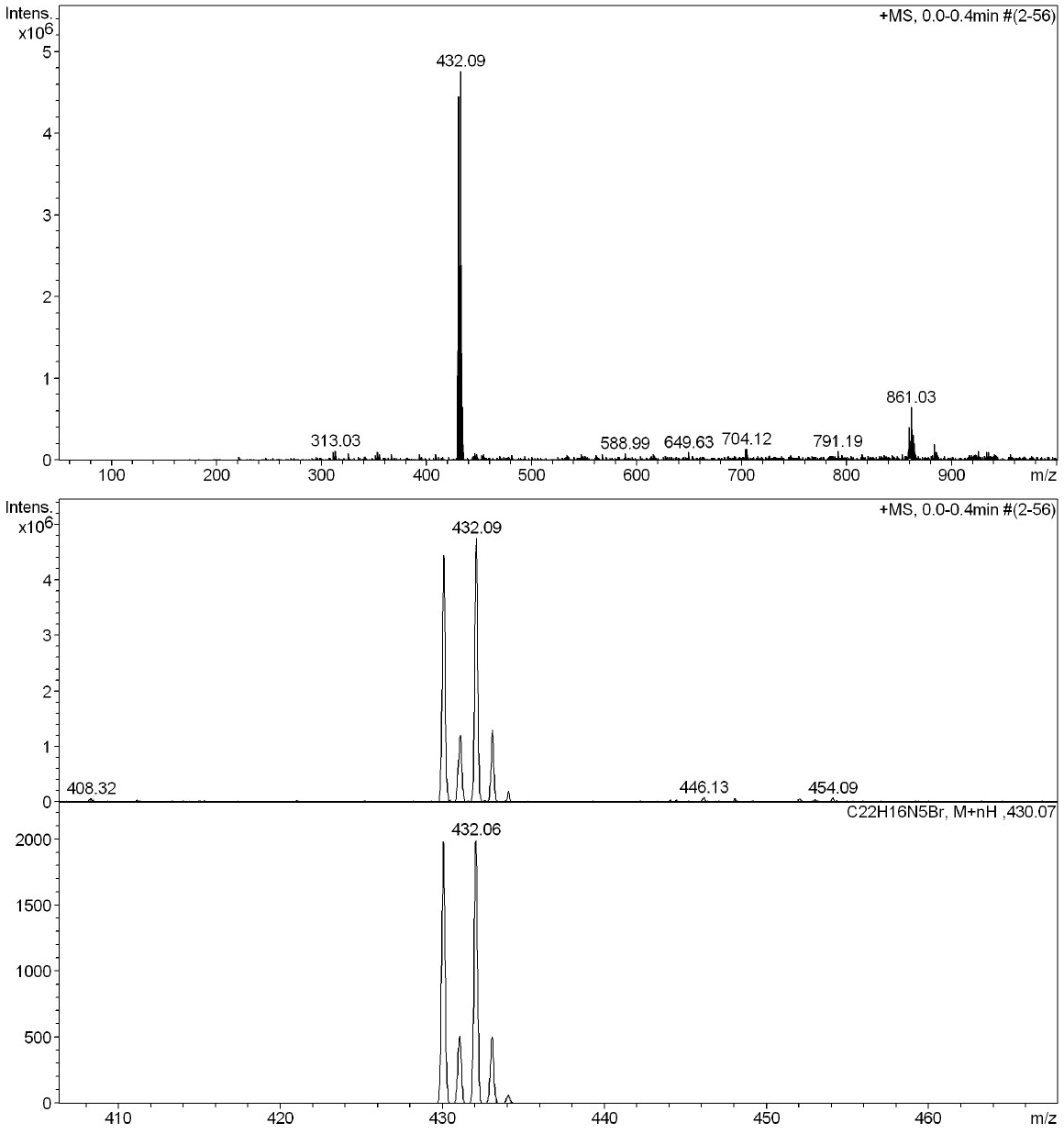

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Figure S26. ESI-MS spectrum of **HL²**.

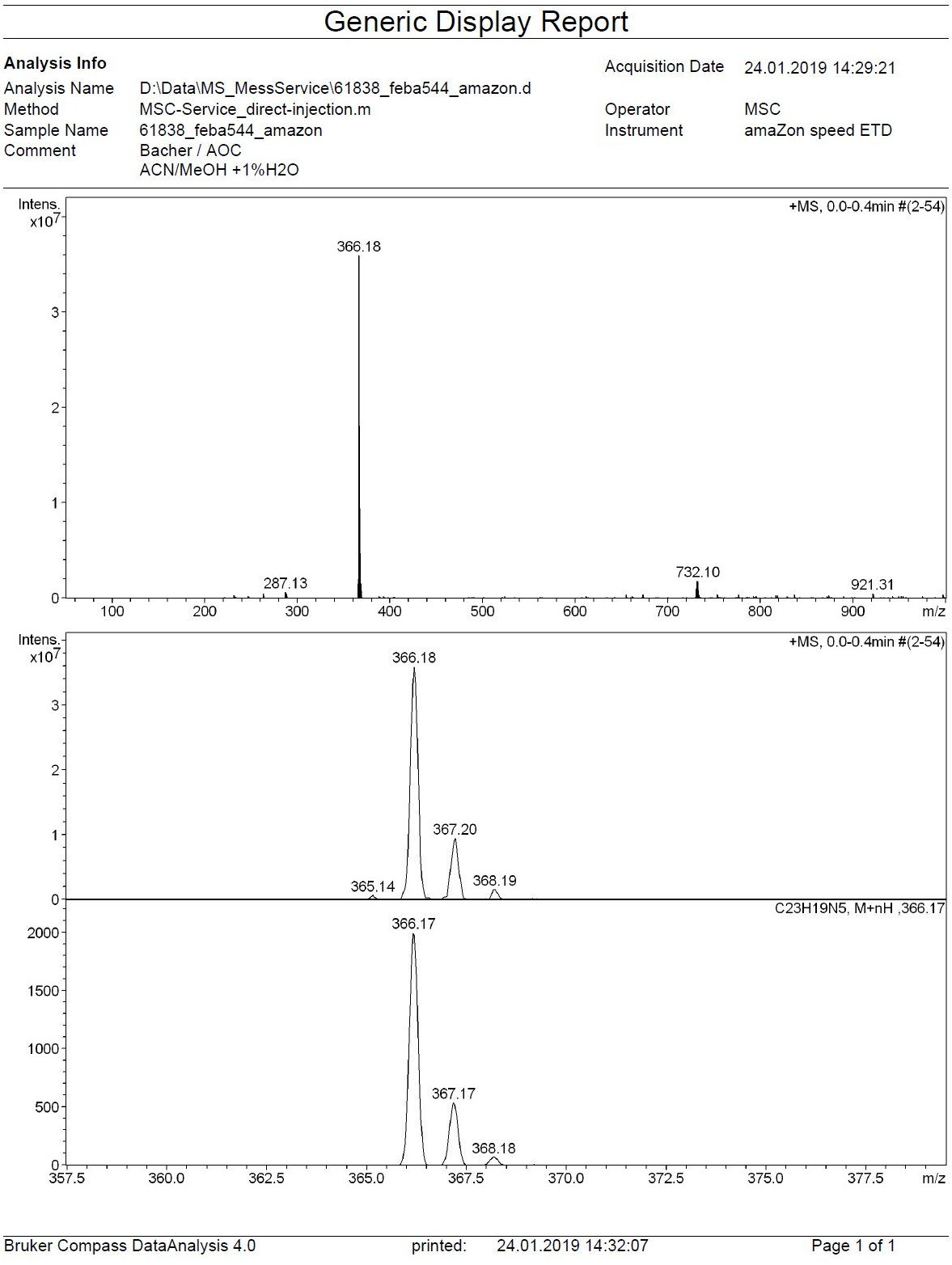

Figure S27. ESI-MS spectrum of **HL³**.

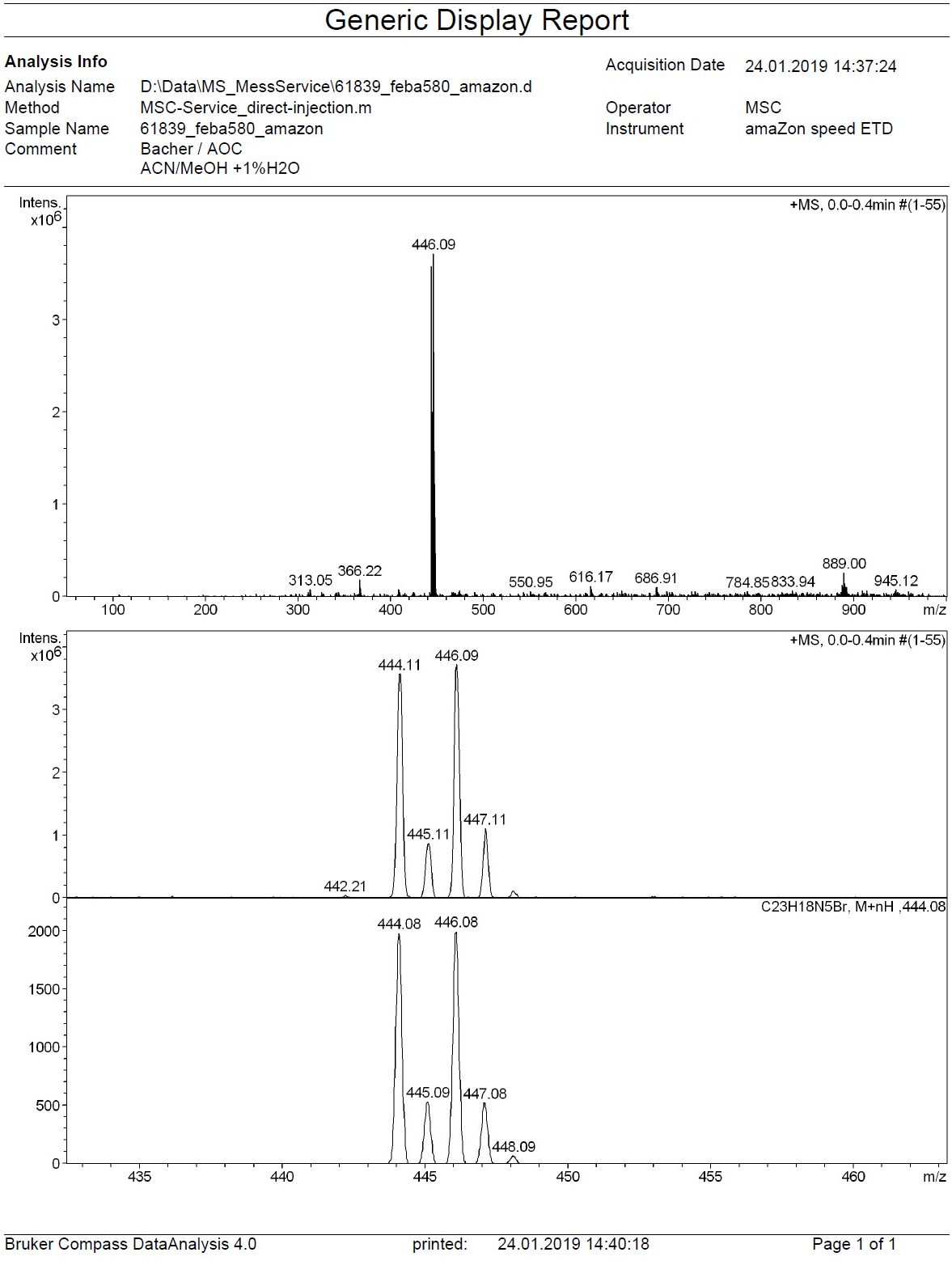

Figure S28. ESI-MS spectrum of **HL[4]**.

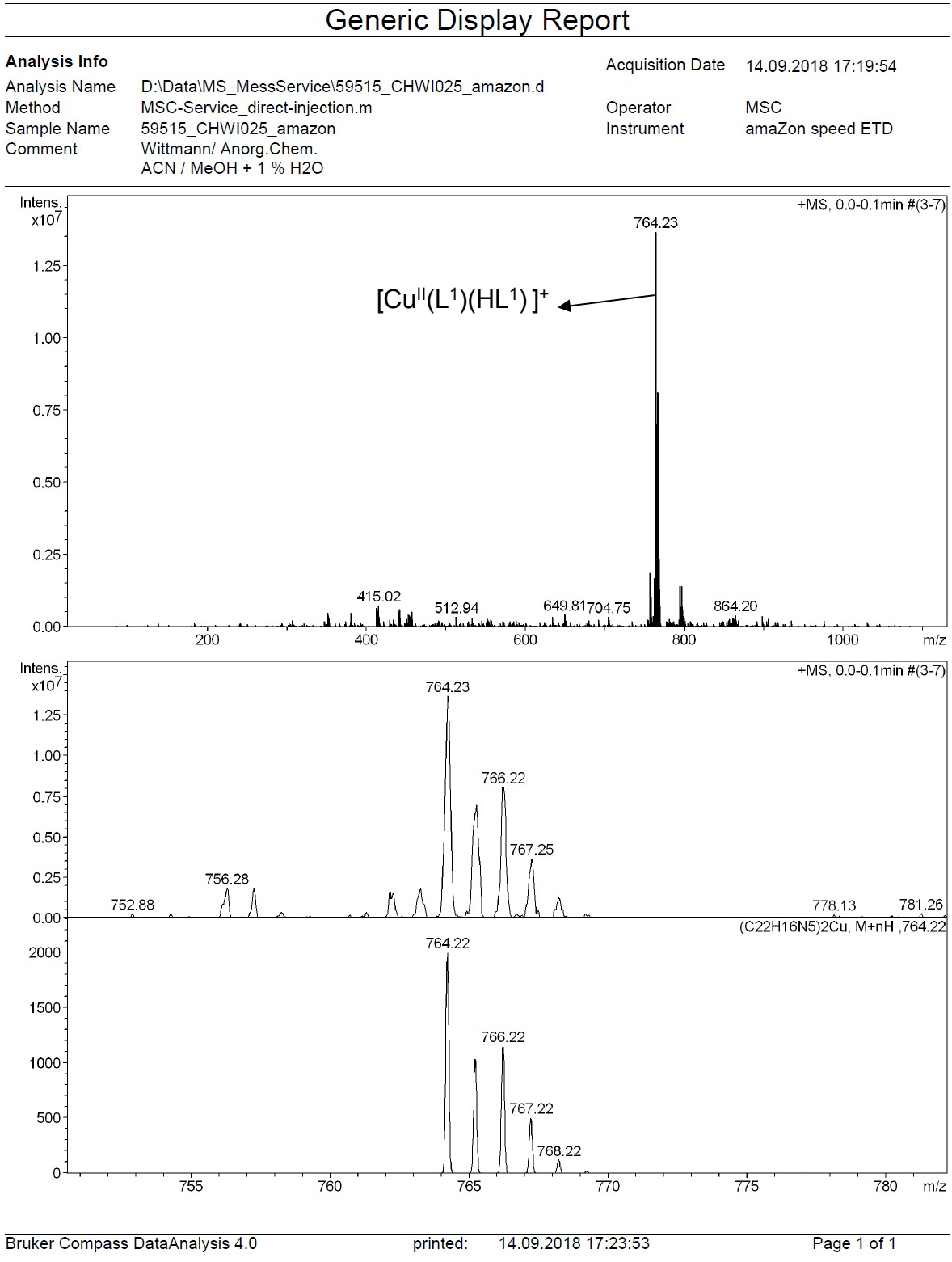

Figure S29. ESI-MS spectrum of **1**.

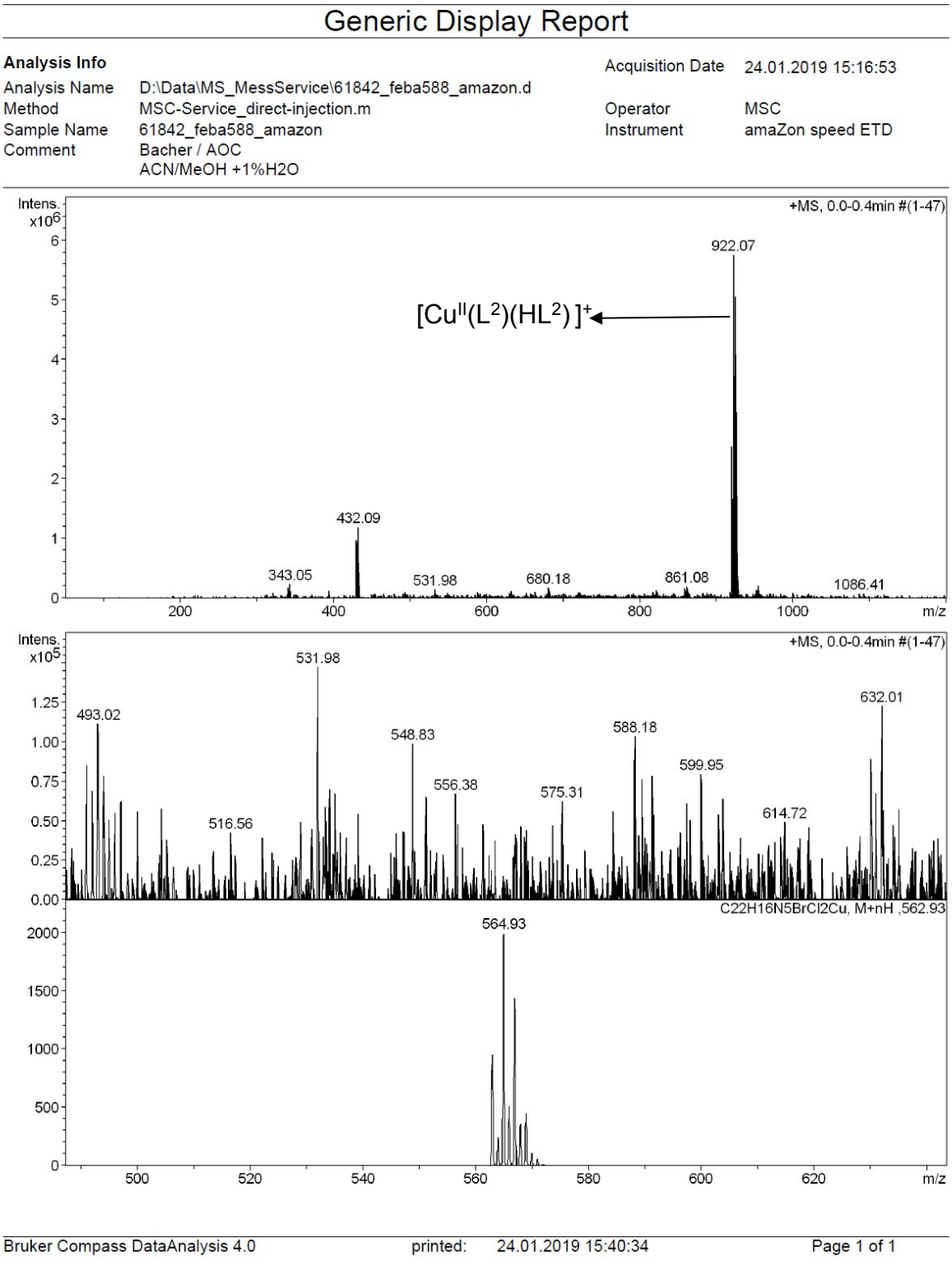

Figure S30. ESI-MS spectrum of **2**.

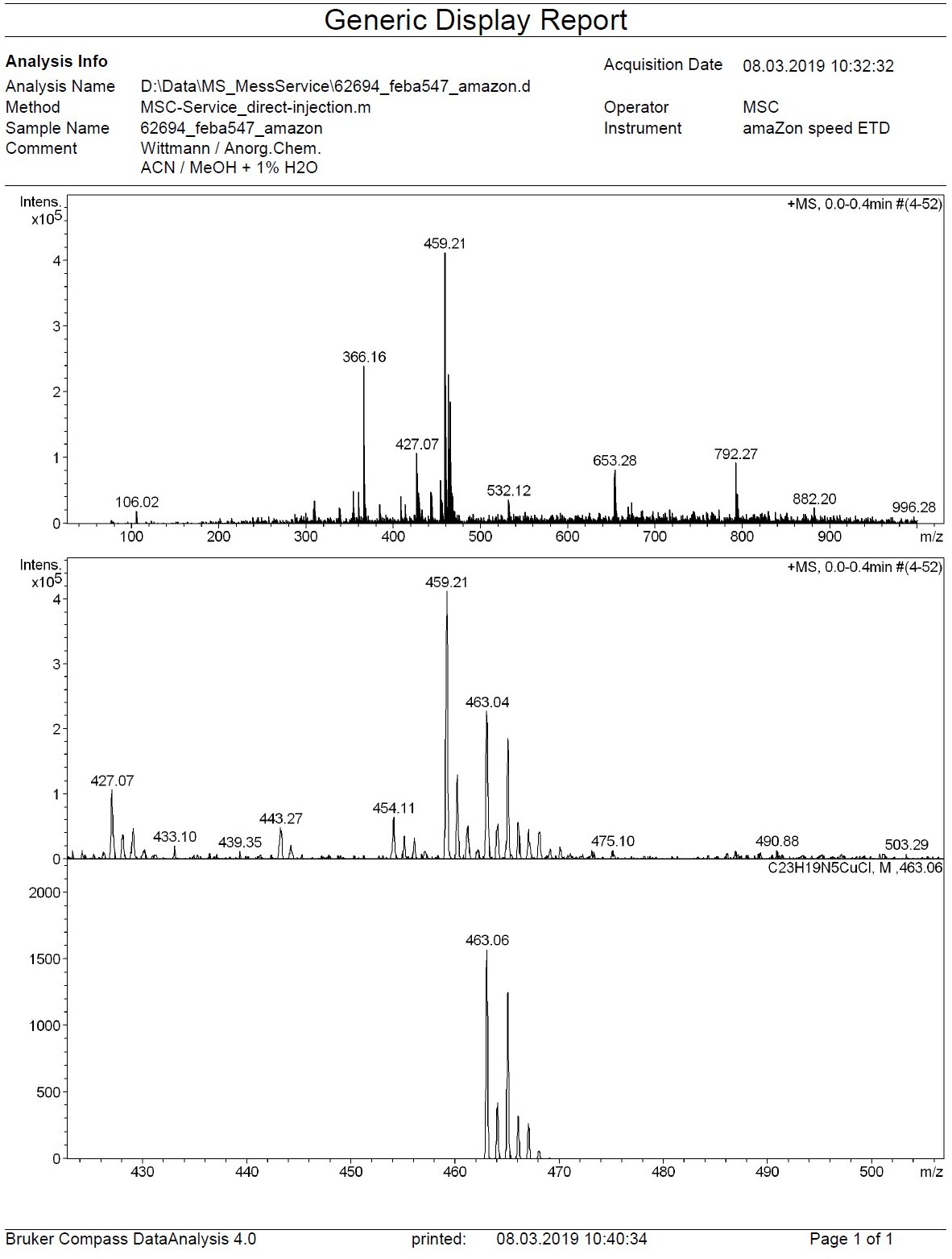

Figure S31. ESI-MS spectrum of **3**.

Generic Display Report

Analysis Info

Analysis Name	D:\Data\MS_MessService\61676_feba583_amazon.d	Acquisition Date	16.01.2019 12:18:16
Method	MSC-Service_direct-injection.m	Operator	MSC
Sample Name	61676_feba583_amazon	Instrument	amaZon speed ETD
Comment	Bacher / AOC ACN / MeOH + 1% H2O		

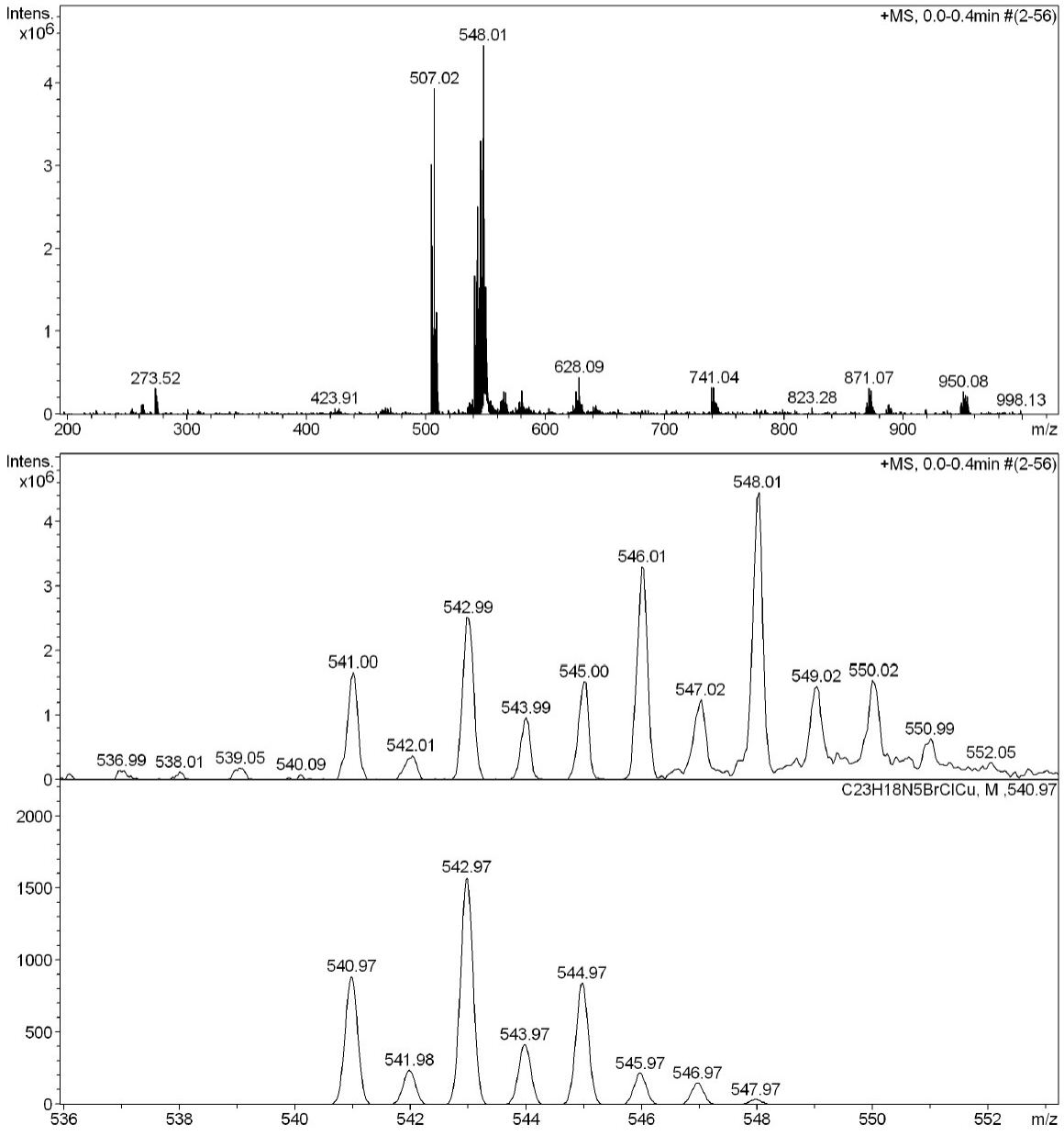

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Figure S32. ESI-MS spectrum of **4**.