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Unexpected hydrazine- and hydroxylamine-induced transformations of aza-14-crown-4 incorporating 4-oxopiperidine-3-carboxylate moiety

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1. Experimental Data

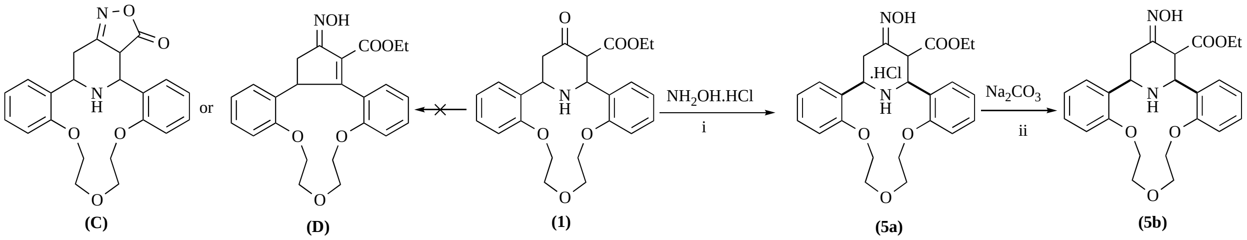
Chemicals and solvents

Reagents (hydrazine hydrate, hydrazine hydrochloride, hydroxylamine hydrochloride) and solvents (dichloromethane, ethanol) were purchased from commercial sources (Merck, Sigma-Aldrich) and used without any additional purification.

Instruments

TLC analysis was performed on commercially prepared silica gel plates (Merck, F254) and visualized by either UV irradiation or staining with I$_2$. Silica gel (0.063–0.2 mm) was used for column chromatography. Melting points were determined in capillary tubes on a digital Stuart SMP3 apparatus. Elemental analysis was conducted on Euro Vector EA-3000 analyzer. The LC/MS analysis was performed using an Agilent 1100 series chromatograph equipped with Agilent 1100 series DAD (wavelength 254±4 nm was used for detection), Sedex 75 ELSD and Agilent LC/MSD VL mass spectrometer (ionization in ESI mode). IR spectra were recorded on FTIR Affinity – 1S SHIMADZU instrument in the range of 400 and 4000 cm^{-1}. ^{1}H NMR spectra were recorded on a Bruker Advance 400 spectrometer (400 MHz) and Bruker Avance Neo 600 spectrometer (600 and 150 MHz, respectively) in CDCl$_3$ and DMSO at 25 °C with TMS used as internal standard.

Compound **1** was prepared as reported (see Ref. 4 of the main text).



Scheme S1

Synthetic procedures

Reaction of crown ether **1** and hydrazine hydrate

A solution of crown ether **1** (1.0 g, 2.4 mmol) and hydrazine hydrate (0.12 ml, 2.4 mmol) in EtOH (20 ml) was stirred at 60 °C for 3 h. The solvent was evaporated *in vacuo*, and the residue was divided into fractions by the chromatography on silica gel (SiO$_2$) using hexane and ethyl acetate 1:1 (v/v) as eluent. The solid was separated and recrystallized in ethanol/dichloromethane to give compound **2** (27%) and compound **3** (25%).

Reaction of crown ether **1** and hydrazine hydrochloride

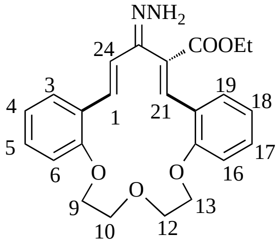
A solution of crown ether **1** (1.0 g, 2.4 mmol) and hydrazine hydrochloride (0.32 g, 4.6 mmol) in ethanol (30 ml) was stirred at 60 °C for 1 h. Then, the pH of mixture was adjusted to 11 by 5% sodium carbonate solution followed by extraction using ethyl acetate (3×25 ml). The organic phases were combined and dried over anhydrous MgSO$_4$. The solvent was evaporated under vacuum and the residue was divided into fractions by the chromatography on silica gel. The solid was obtained and recrystallized in ethanol/dichloromethane to give **2** (40%) and **4** (34%).

Reaction of crown ether **1** and hydroxylamine hydrochloride

A solution of azacrown ether **1** (1.0 g, 2.4 mmol) and hydroxylamine hydrochloride (0.25 g, 3.5 mmol) in ethanol (20 ml) was refluxed for 40 min. The reaction mixture was cooled, the precipitated crystals were filtered and washed with diethyl ether. The substance **5a** was obtained in 0.90 g (79%) yield as white crystals, mp 210-211 ºC. The substance **5a** was treated with Na_2CO_3 aq. to pH = 11, and the solution was extracted with ethyl acetate (3×20 ml) and dried over anhydrous $MgSO_4$. Organic solvent was removed *in vacuo* to afford compound **5b**.

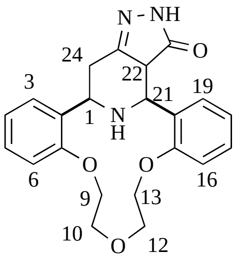
2. Spectral data of synthesized compounds:

*Compound **2***



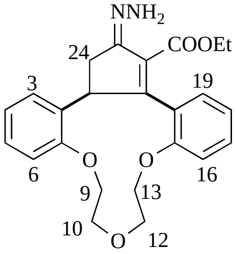
The compound **2** obtained in 0.41 g (40%) yield, white crystals, melting point is 218-220 ºC (R_f = 0.48, ethanol). IR (KBr), ν_{max}, cm^{-1}: 3336 (NH_2); 1735 (C=O); 1655 (C=N), 1224 (C-O). ^1H NMR ([D1] $CDCl_3$, 298 K) δ_H ppm: 1.096 (3H, t, *J* = 6 Hz, CH_2CH_3); 2.58 (1H, br.s., NH_2); 3.92-1.05 (4H, m, -OCH_2-CH_2-), 4.07-4.19 (2H, q, *J* = 6 Hz CH_2CH_3) 4.19-4.24 (4H, m, -OCH_2-CH_2), 6.16 (1H, d, *J* = 2.5 Hz, H_{24}) 6.78-6.79 (2H, d.d, *J* = 6.5 Hz and 1Hz, $H_{6,16}$), 6.90 (1H, t, *J* = 6 Hz, H_5) 6.99 (1H, t, *J* = 6.5 Hz, H_{17}), 7.16-7.19 (2H, t.d, *J* = 6 Hz and 1.5 Hz, $H_{4,18}$), 7.20-7.22 (1H, d.d, *J* = 6.5 Hz and 1.5 Hz, H_3), 7.31 – 7.34 (1H, t.d, *J* = 6 Hz and 1.5 Hz H_{19}), 8.38 (1H, d, *J* = 7 Hz, H_1 cis), 8.78 (1H, s, H_{21}) . ^{13}C-NMR, $CDCl_3$: δ_C ppm: 167.35 (-C=O ester), 157.17 (C-7, C-15), 155.82 (-C=NNH_2), 155.47 (C-21) 132.07(C-1), 131.94, 128.51, 127.87, 121.24, 120.94, 1117.95, 113.62, 111.77, 111.01, 68.68, 67.81, 59.36, 47.32 14.31. HRMS (ESI+), m/z Calc. for $[C_{24}H_{30}N_3O_5]^+$: 423.1920 $[M+H]^+$. Found: 423.1910 $[M+H]^+$.

*4,5-Dihydro-5-oxopyrazolo[3,4:22,23]-8,11,14-trioxa-25-azatetracyclo[19.3.1.$0^{2,7}$.$0^{15,20}$]pentacosa-2,4,6,15(20),16,18-hexaene (**3**)*



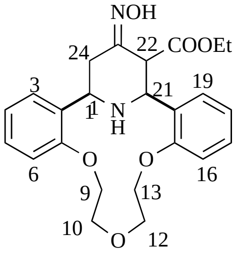
Obtained in 0.23 g (25 %) in a form of yellow crystals; Melting point 214-216 ºC (R_f= 0.24, ethanol). Found, %: C 66.98; H 5.71; N 10.72. $C_{22}H_{23}N_3O_4$. Calculated, %: C 67.16; H 5.89; N 10.68. *m/z* (ESI) (%) 394 (100) $[(M+H)^+]$. IR (KBr) ν_{max} cm^{-1}: 3400 & 3379 (NH), 1712 (C=O), 1621 and 1601 (C=N). ^1H NMR ([D6] DMSO, 298 K) δ_H ppm: 2.71 (2H, m, H-27), 3.50-4.30 (12H, m, $H_{aliph.}$, $H_{piperidine}$), 6.70-7.40 (8H, m, $H_{arom.}$), 8.31 (1H, s, NH-24).

*Ethyl 23-hydrazinylidene-8,11,14-trioxatetracyclo[19.3.0^{1,21}.0^{2,7}.0^{15,20}]pentacosa-2,4,6,15(20),16,18,21-heptaene-22-carboxylate (**4**)*



Obtained in 0.34 g (34%), yellow crystals; Melting point 183-185 °C. IR (KBr) ν_{max} cm^{-1}: 3305 (NH_2), 1732 (C=O), 1665 and 1631 (C=C-C=N). ^{1}H NMR ([D_1] $CDCl_3$, 298 K) δ_H ppm: 1.30 (3H, t, *J* = 6.5 Hz, $CH_2\underline{CH_3}$); 2.72 (1H, d.d, *J* = 12.5 and 2.0 Hz, H_{24}), 3.36 (1H, br.t, *J* = 10.0 Hz, H_1), 3.83-4.12 (11H, m, H_{24}, CH_2CH_3, OCH_2CH_2O-CH_2CH_2O), 6.76 (1H, d, *J* = 6.5 Hz, H_6), 6.83 (1H, d, *J* = 7 Hz, H_{16}), 6.86 (1H,t, *J* = 6 Hz, H_4), 6.91 (t, 1H, *J* = 6 Hz, H_{18}), 7.15 (1H, t, *J* = 6 Hz, H_5), 7.22 (2H, *J* = 6 Hz, $H_{3,17}$), 7.31 (d, 1H, *J* = 6 Hz, H_{19}). ^{13}C-NMR, $CDCl_3$: δ_C ppm: 170.16 (-C=O ester) ,159.78 (C-21$^{)}$, 157.13 (C-15), 156.95 (-C=NNH_2), 141.08, 129.39, 128.67, 120.62, 110.78, 69.97, 66.75, 64.32, 60.41, 26.65, 14.69. HRMS (ESI+), m/z Calc. for $[C_{24}H_{27}N_2O_5]^+$: 423.1920 $[M+H]^+$. Found: 423.2100 $[M+H]^+$

*Ethyl 23-hydroxyimino-8,11,14-trioxa-25-azatetracyclo[19.3.1.0^{2,7}.0^{15,20}]pentacosa-2,4,6,15(20),16,18-hexaene-22-carboxylate **(5b)** and its hydrochloride **(5a)**.*

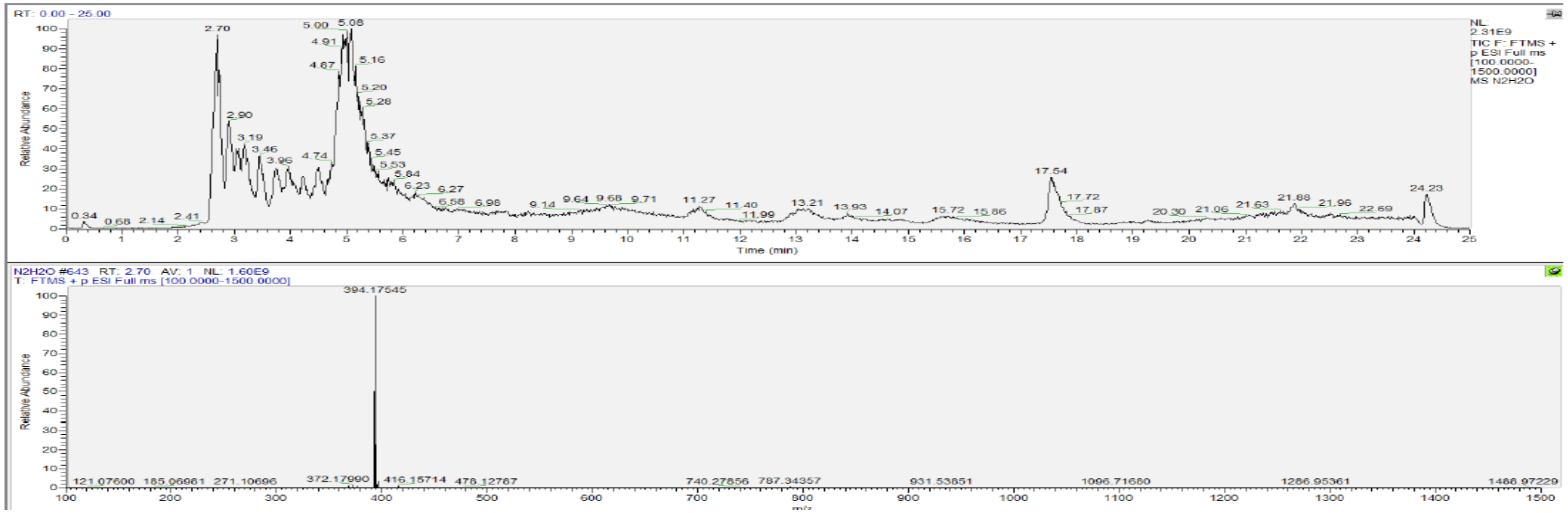


Substance **5a** was obtained in 0.90 g (79%) yield as white crystals, mp 210-211 ºC. Substance **5a** was treated with Na_2CO_3 aq. to pH = 11, and the solution was extracted with ethyl acetate and dried over anhydrous $MgSO_4$. The solvent was evaporated *in vacuo* affording 0.54 g (51%) azacrown **5b** as yellow crystals, mp 195-197ºC. IR (KBr) ν_{max} cm^{-1}: 3560 and 3397 (OH), 3186 (NH), 1732 (O=C-O), 1660 (C=N). ^{1}H NMR ([D1] $CDCl_3$, 298 K) δ_H ppm: 1.01 (3H, t, *J* = 6 Hz, $CH_2\underline{CH_3}$); 2.68 (1H, br.s., <u>NH</u>); 2.70 (1H, br.s., <u>NH</u>), 3.50 (1H, d, *J* = 8.5 Hz, H_{22}); 3.86 (2H, d, *J* = 7.5 Hz, H_{24}), 3.88-3.94 (1H, d, *J* = 8.5 Hz, H_{21}), 3.98 (2H, q, *J* = 6 Hz, $\underline{CH_2}CH_3$), 4.00-6.4.09 (9H, m, H_{24}, OCH2CH2O-CH_2CH_2O), 6.67-6.77 (1H, d, *J* = 6.5 Hz, H_6), 6.77-6.78 (1H, d, *J* = 6.5 Hz, H_{16}) 6.82 (1H, t, *J* = 6.5 Hz, H_4), 6.87 (1H, t, *J* = 6.5 Hz, H_{18}), 7.14 – 7.20 (4H, m, $H_{3,\ 5,\ 17,\ 19}$), 7.75 (1H, s, -OH). ^{13}C-NMR, $CDCl_3$: δ_C ppm: 170.67 (-C=O ester) ,163.25 (-C=NOH$^{)}$, 157.01 (C-15), 128.82, 120.87, 120.60, 110.93, 70.09, 70.03, 67.62, 66.43, 62.15, 60.47, 52.17, 28.89, 13.94. HRMS (ESI+), m/z Calc. for $[C_{24}H_{29}N_2O_6]^+$: 441.2025 $[M+H]^+$. Found: 441.2014 $[M+H]^+$.

Table S1 LC-MS of reaction mixture between azacrown **1** and hydrazine hydrate

Peak	Retention time	*m/z*	Detected compound
1	2.7	394	**3**
2	4.96	423	**2**

RT 2.70



RT 4.96

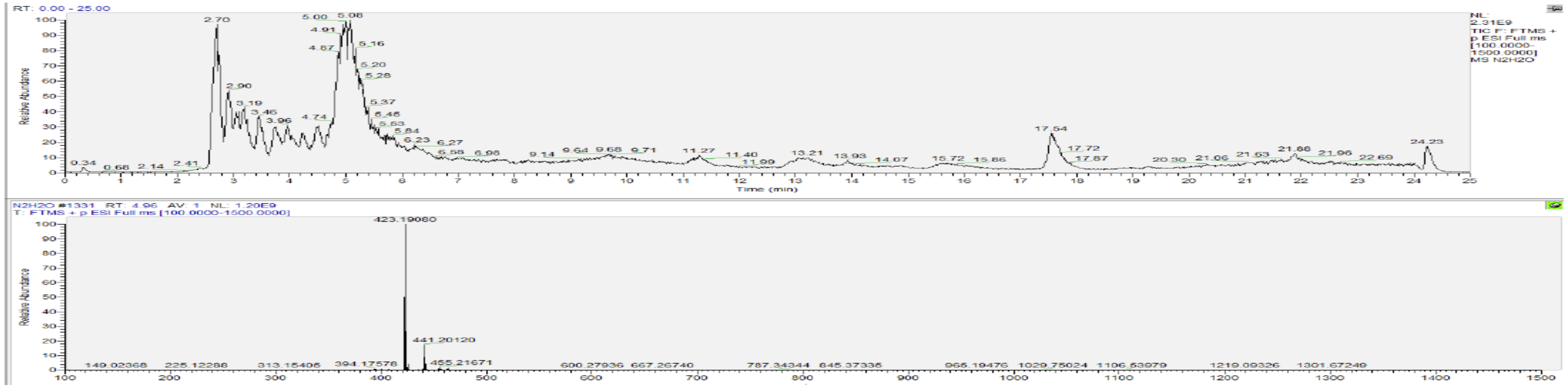


Figure S1. LC-MS of the reaction mixture between azacrown **1** and hydrazine hydrate

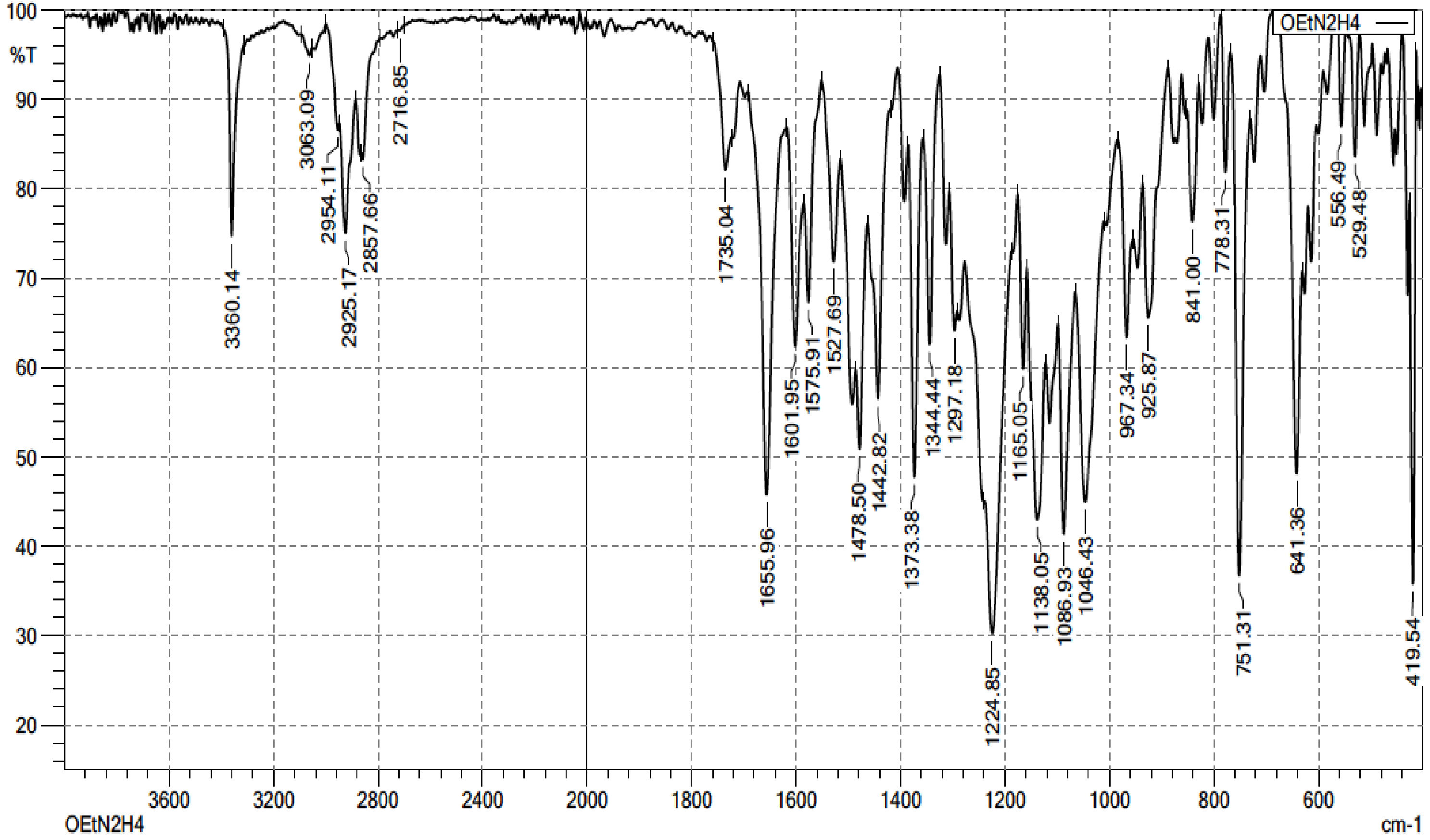


Figure S2. IR of compound **2**

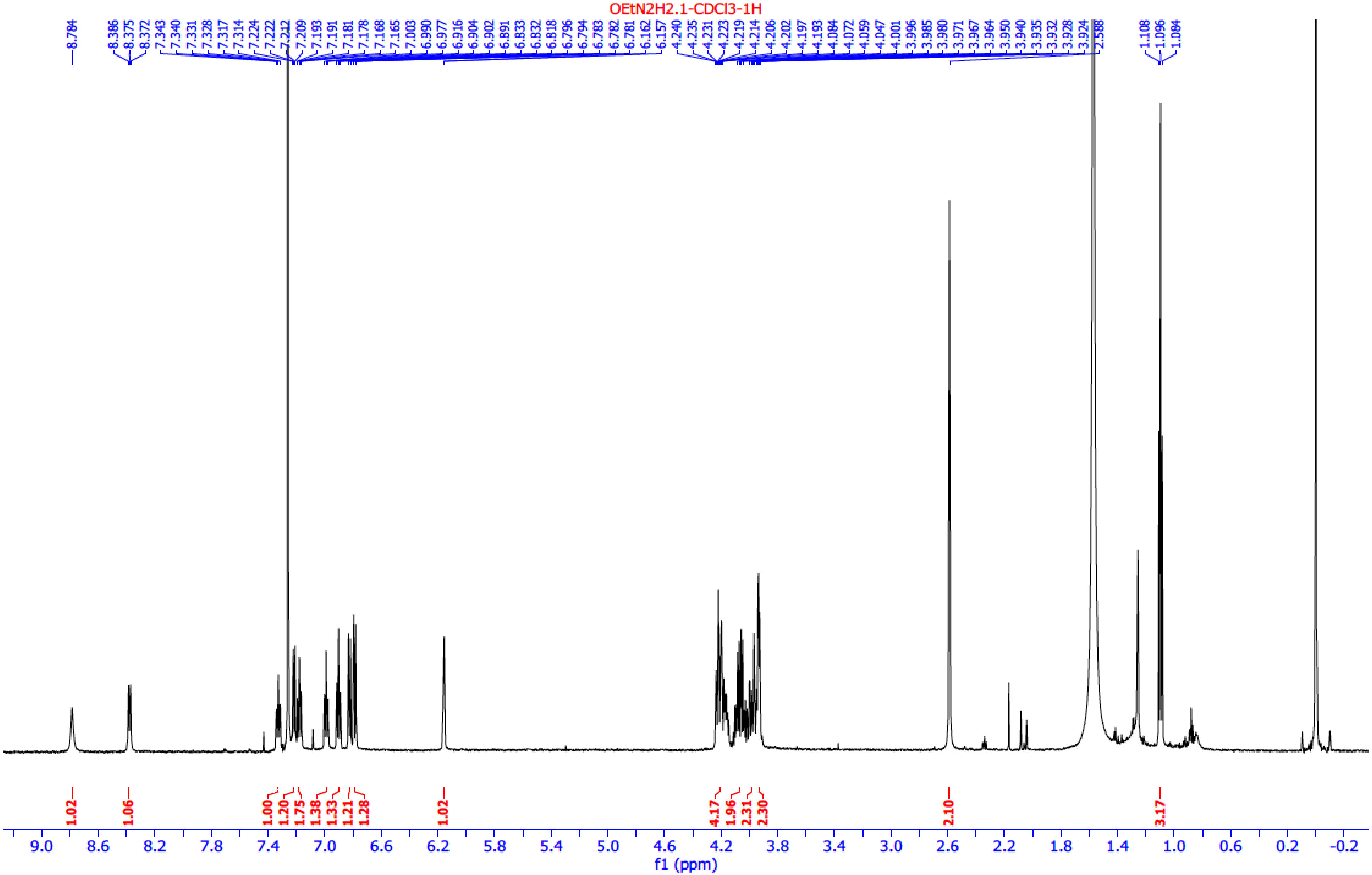


Figure S3. ^{1}H NMR of compound **2**

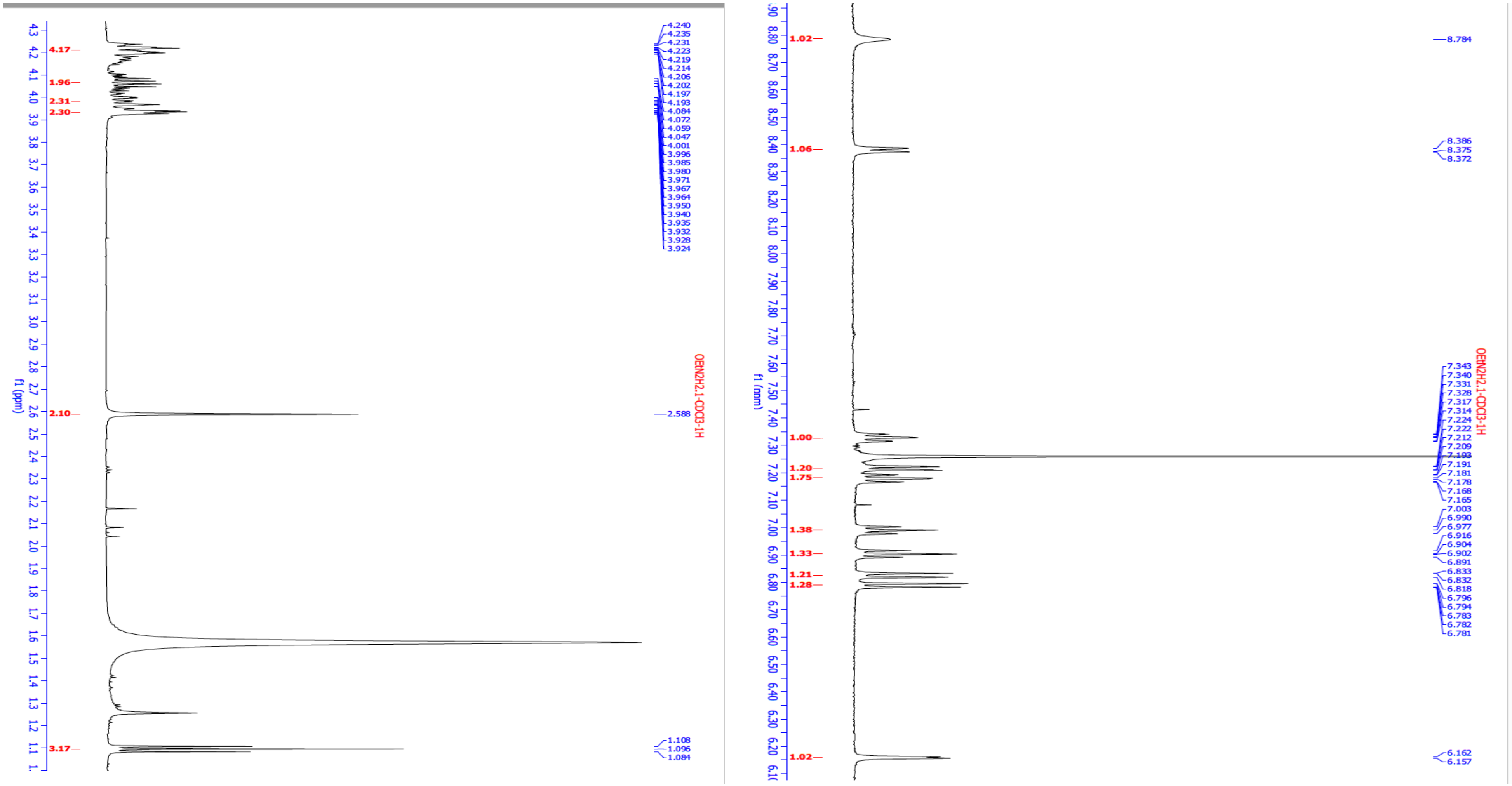


Figure S4. ^{1}H NMR of compound **2** *(continued)*

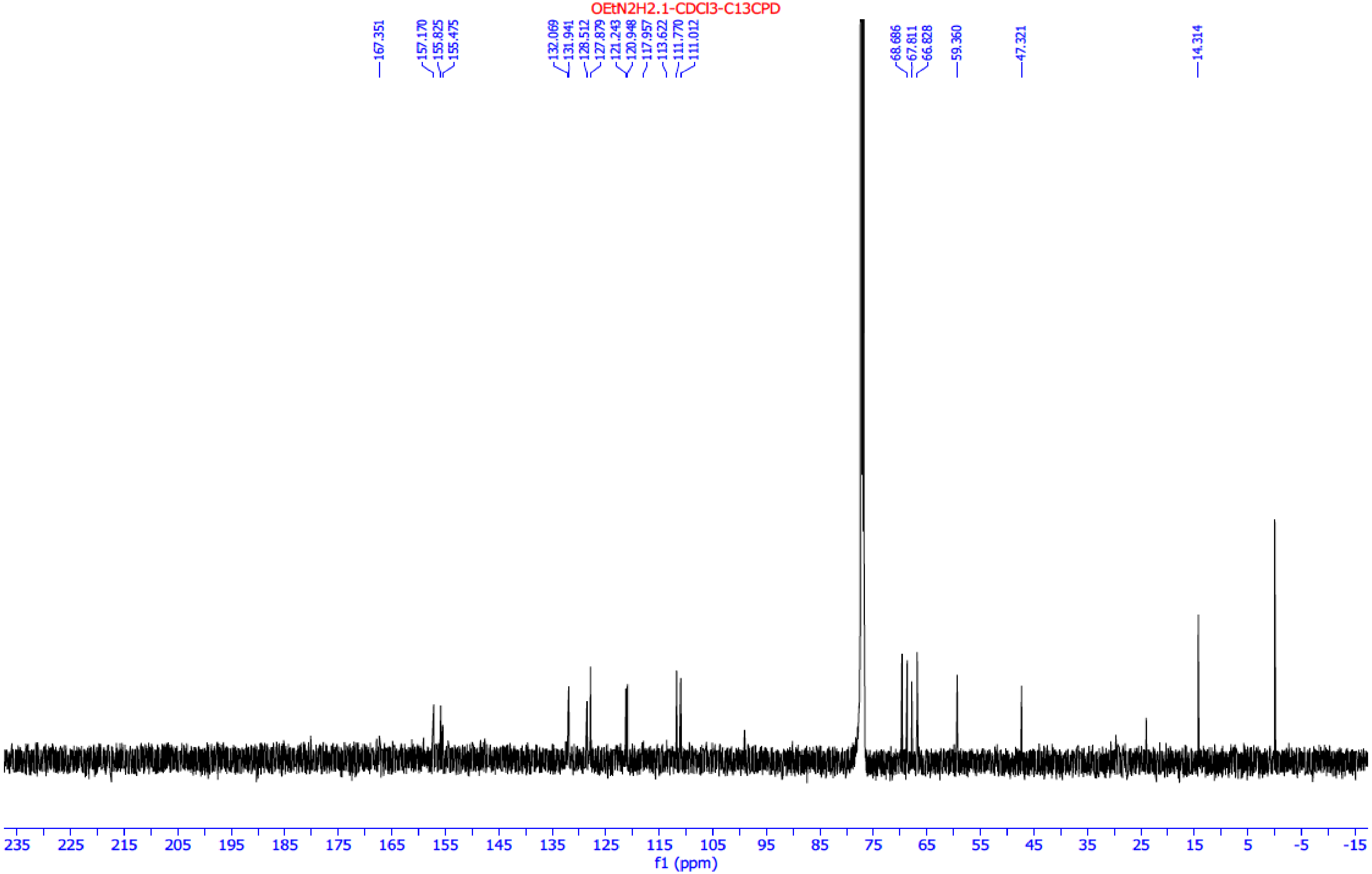


Figure S5. ^{13}C NMR of compound **2**

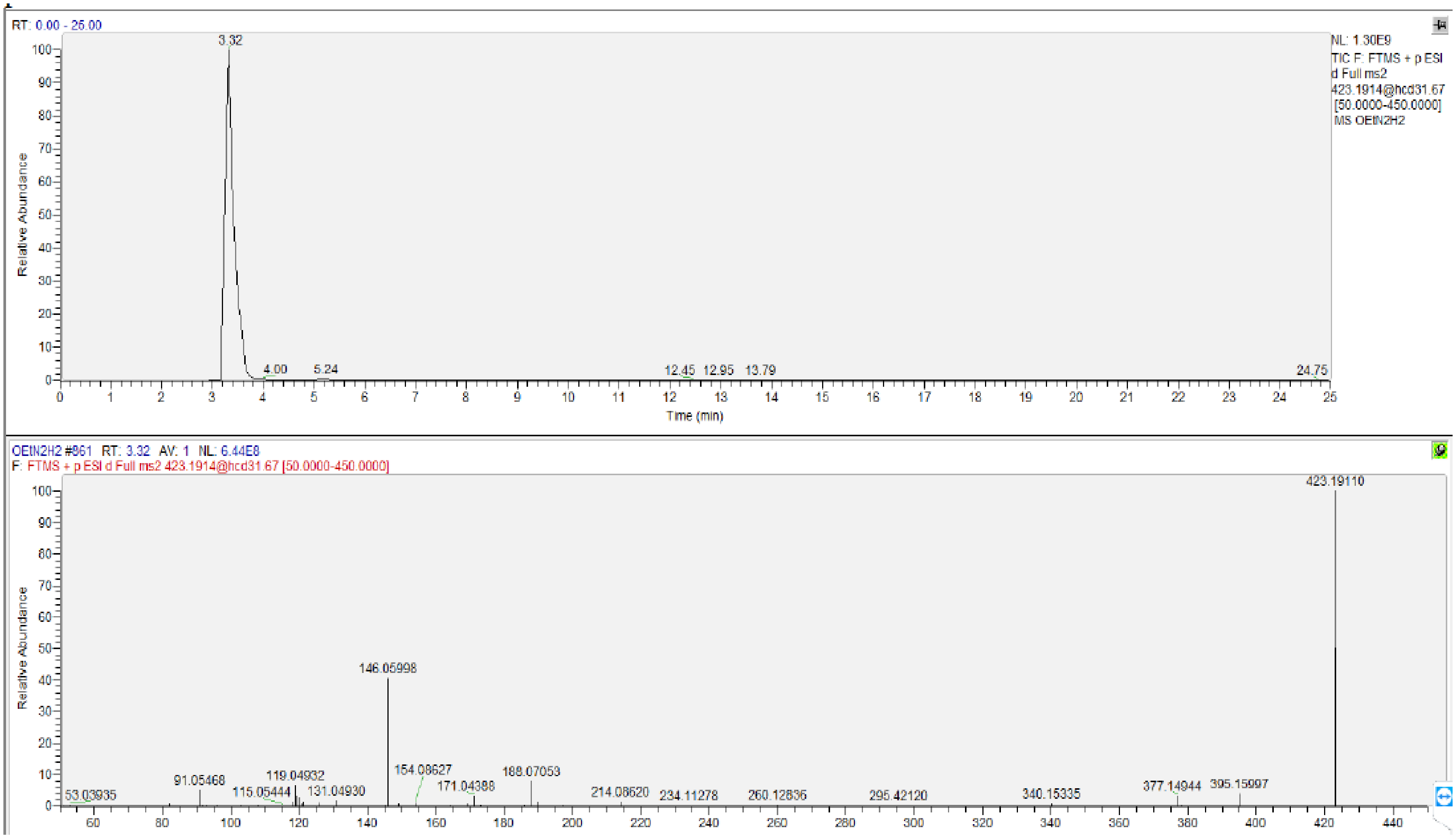


Figure S6. LC-HRMS of compound **2**

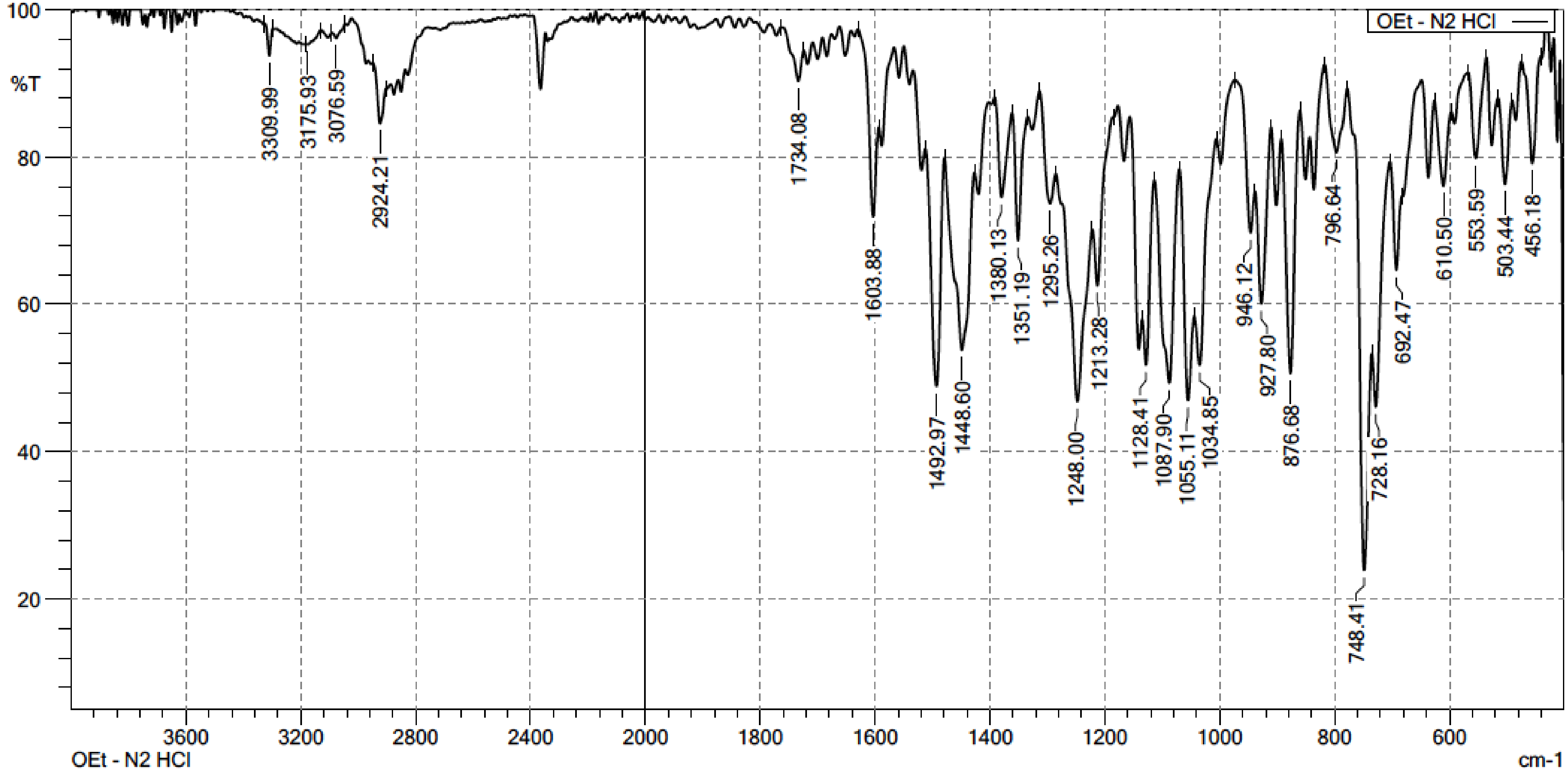


Figure S7. IR of compound **4**

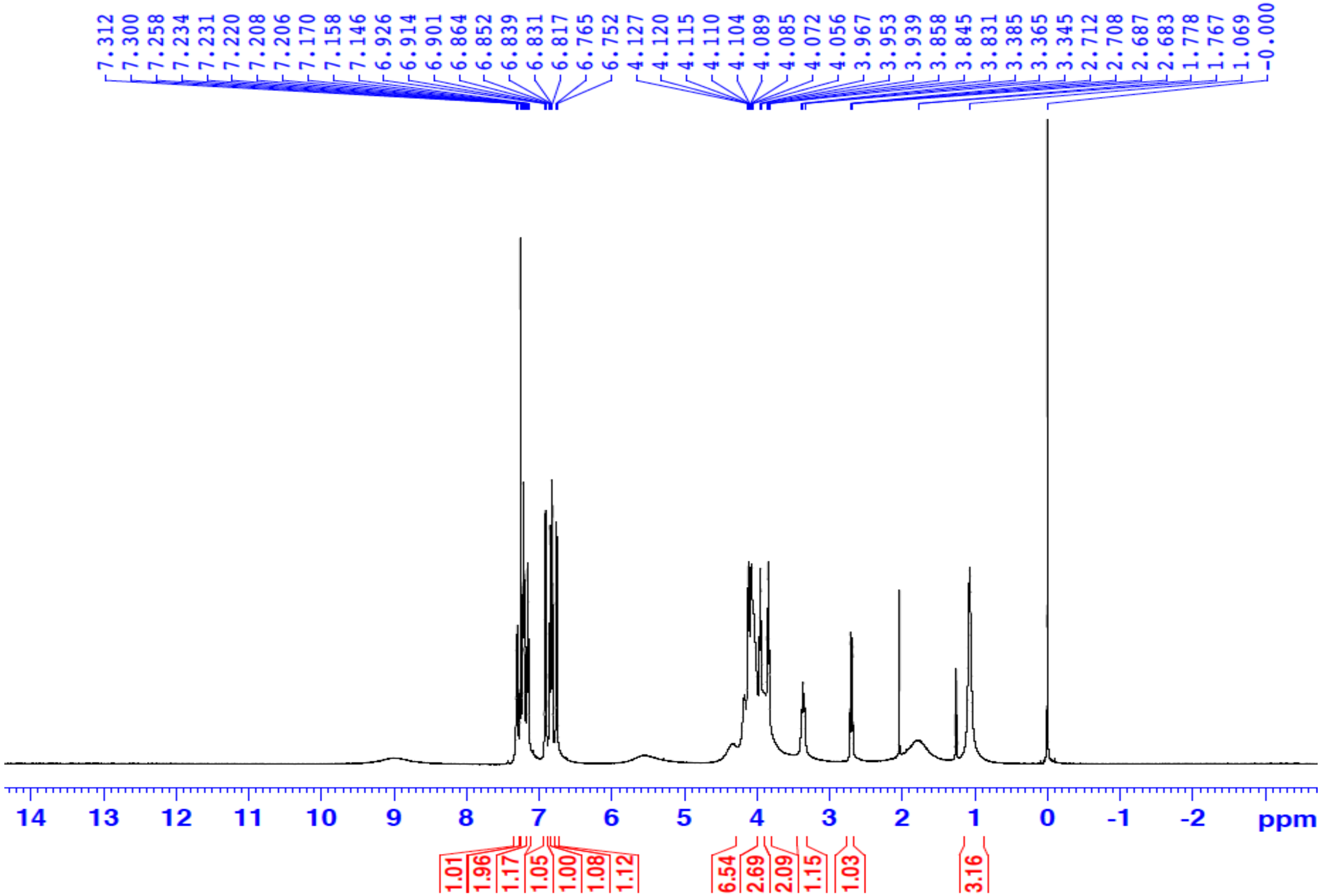


Figure S8. ^{1}H NMR of compound **4**

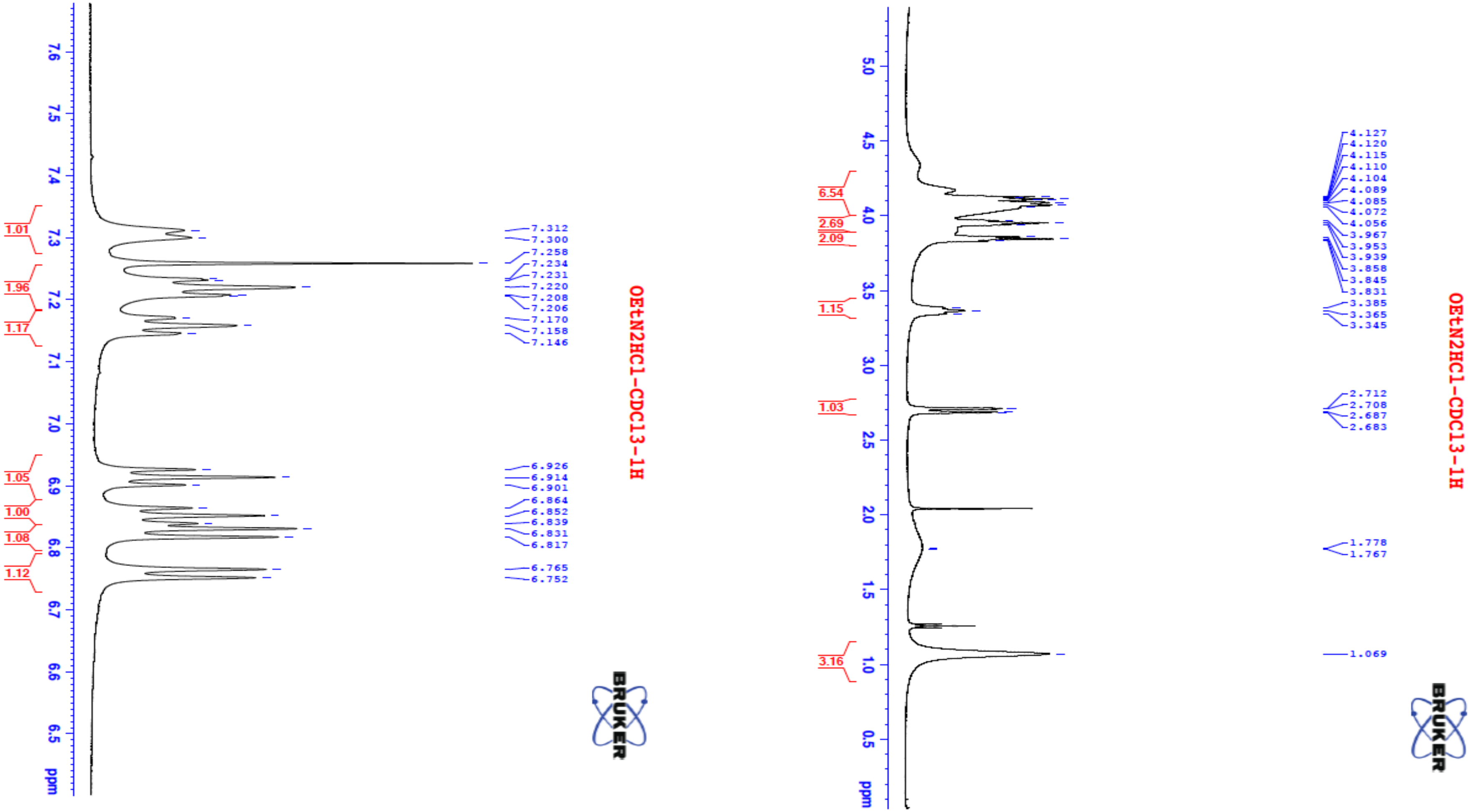


Figure S9. ^{1}H NMR of compound **4** *(continued)*

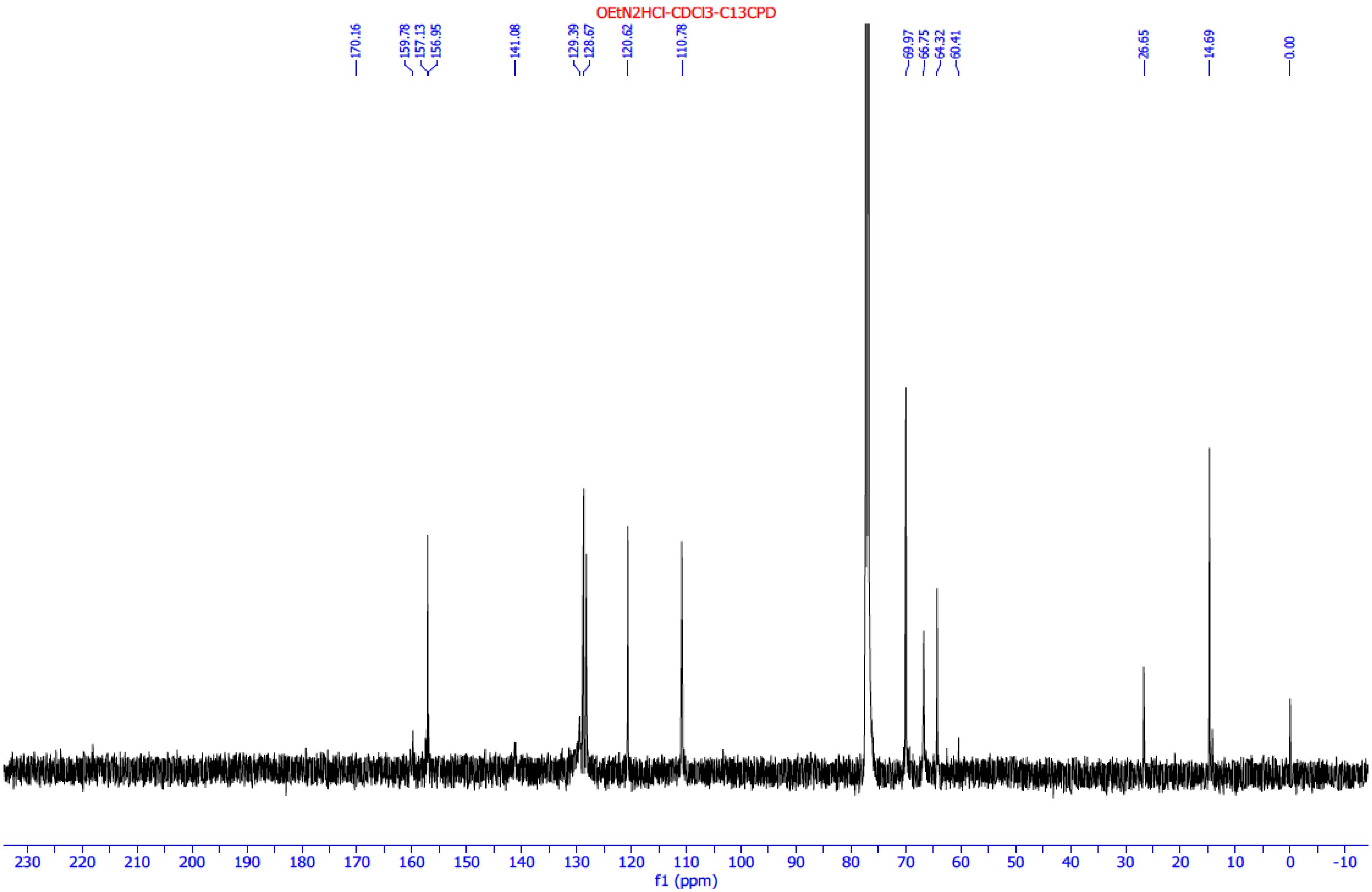


Figure S10. ^{13}C NMR of compound **4**

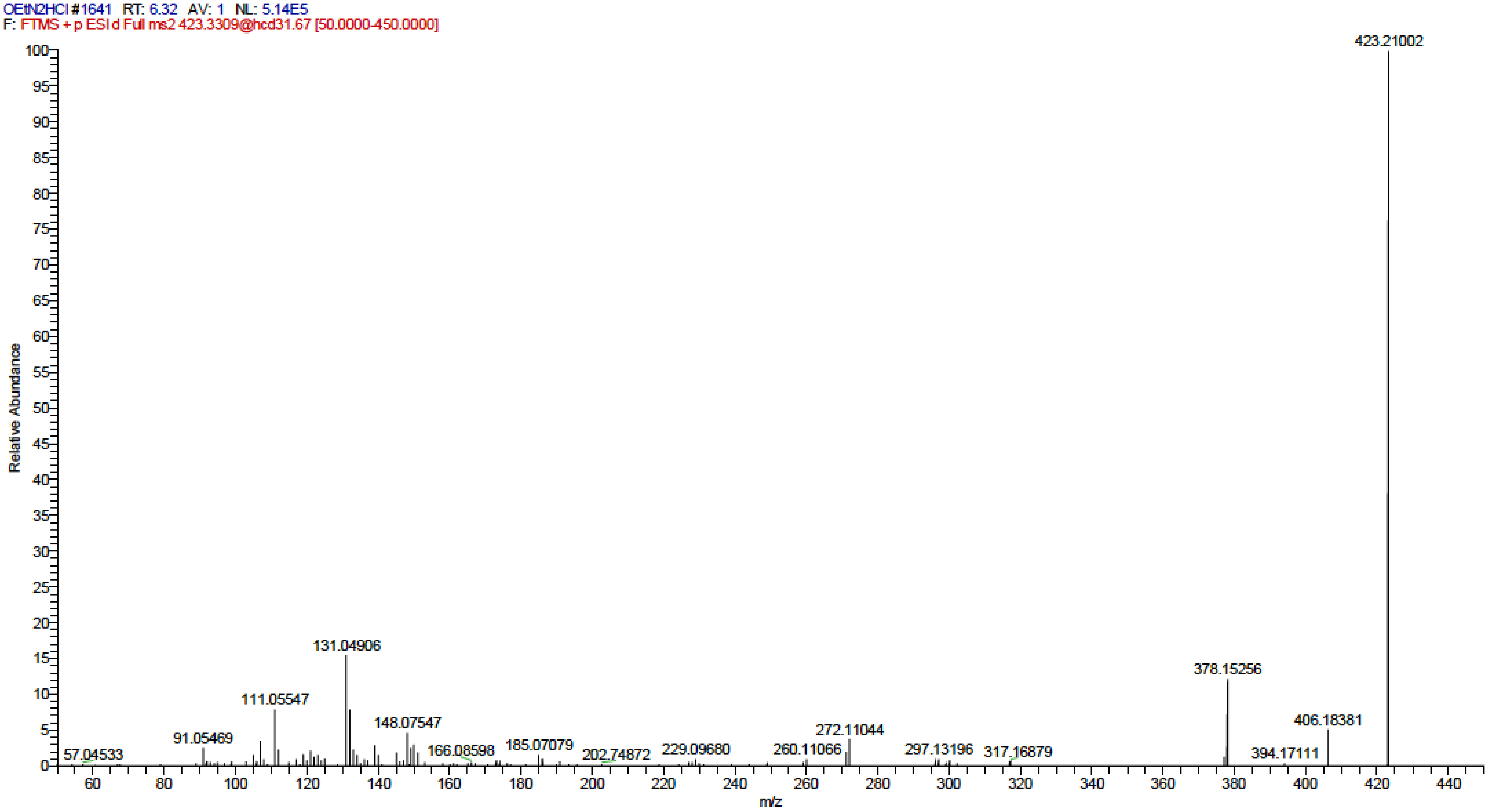


Figure S11. LC-HRMS of compound **4**

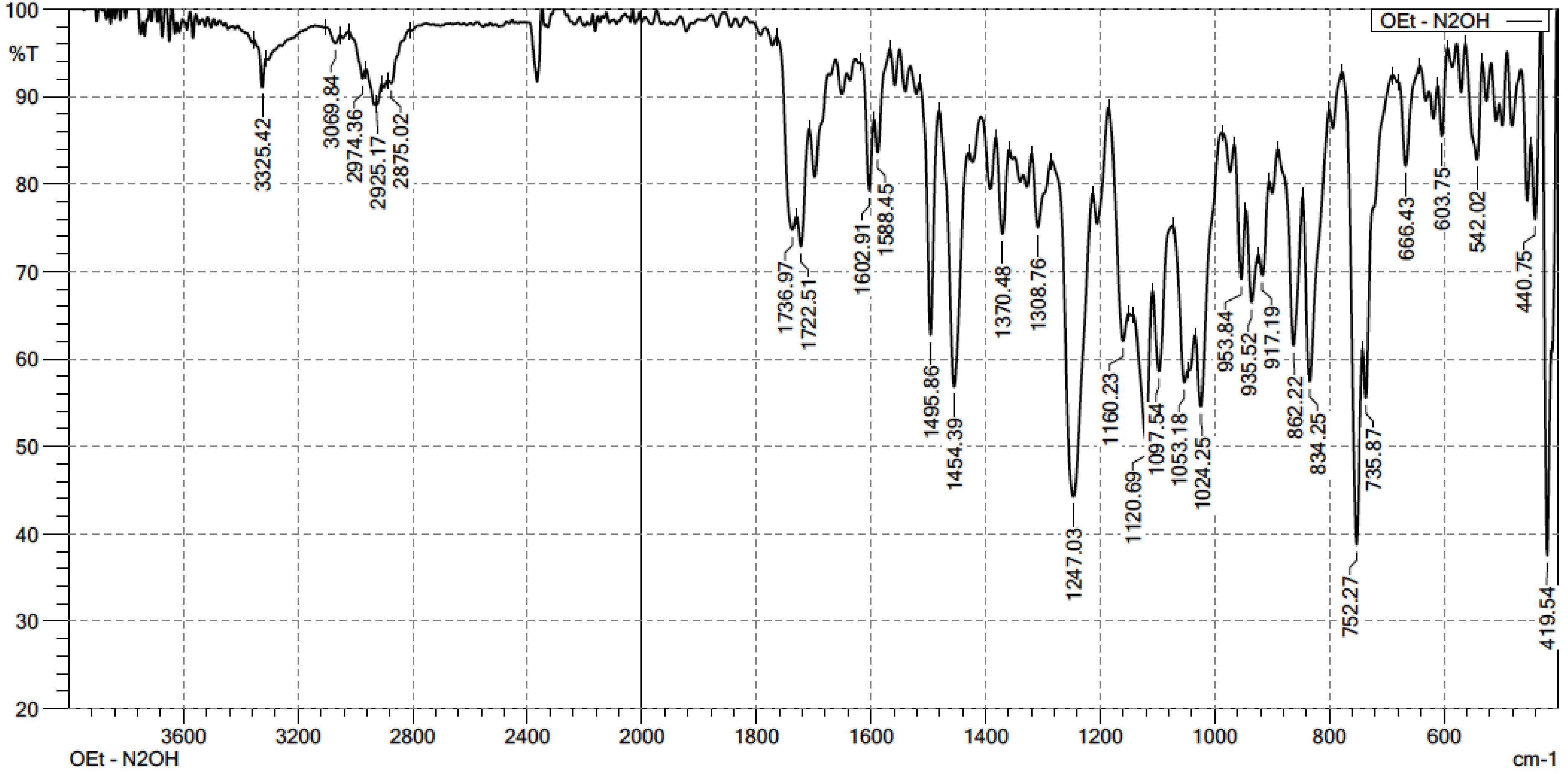


Figure S12. IR of compound **5**

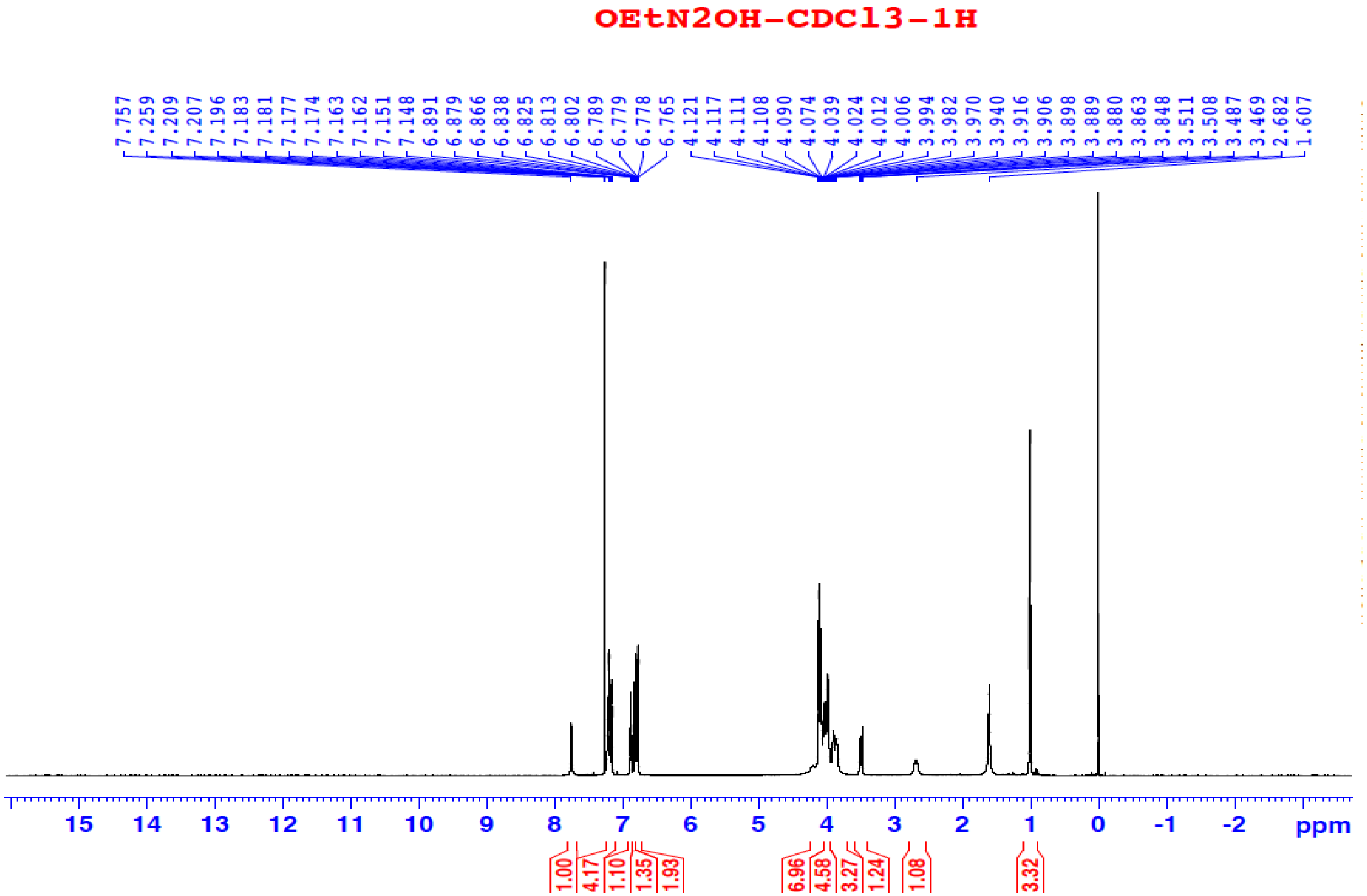


Figure S13. ^{1}H NMR of compound **5**

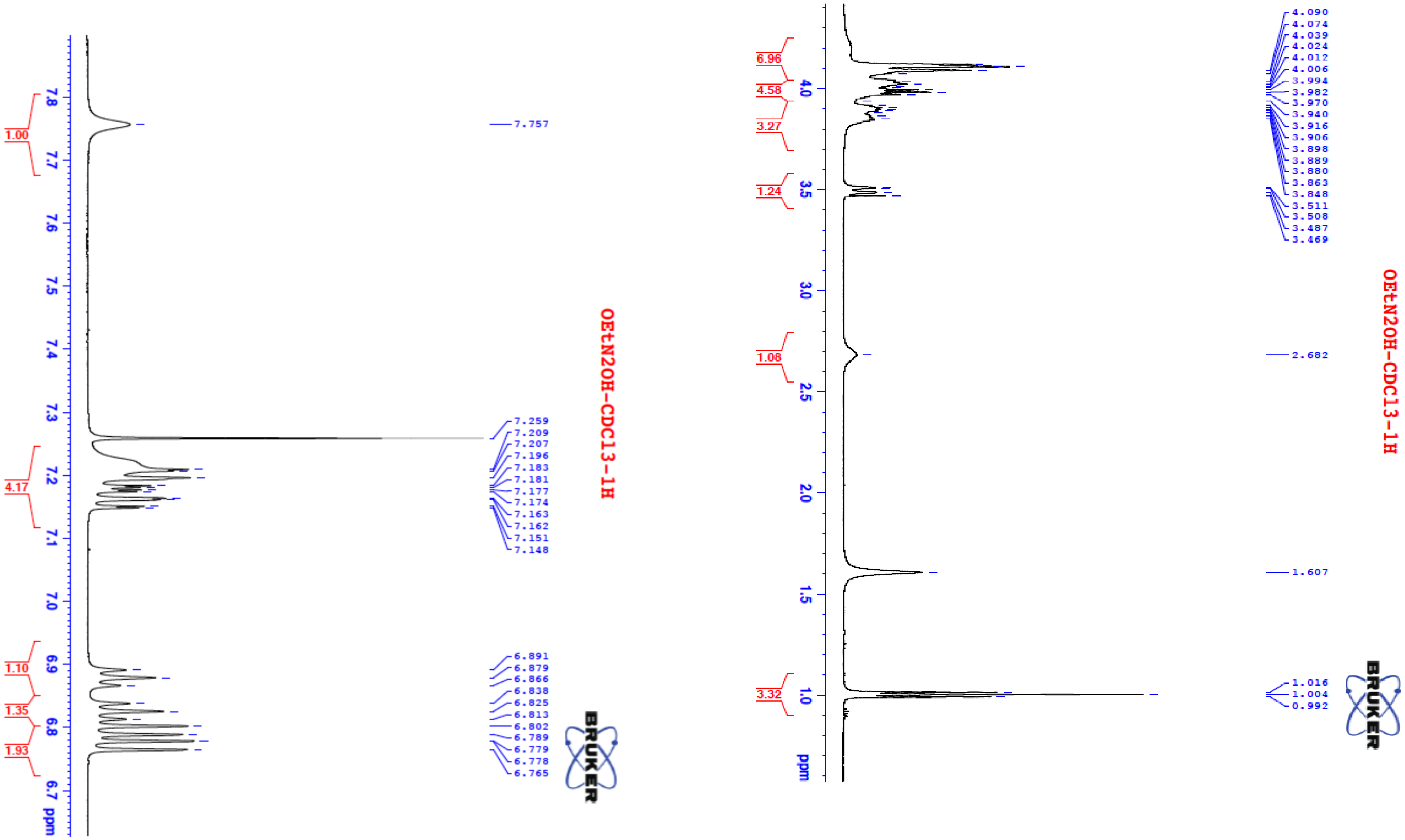


Figure S14. ^{1}H NMR of compound **5** *(continued)*

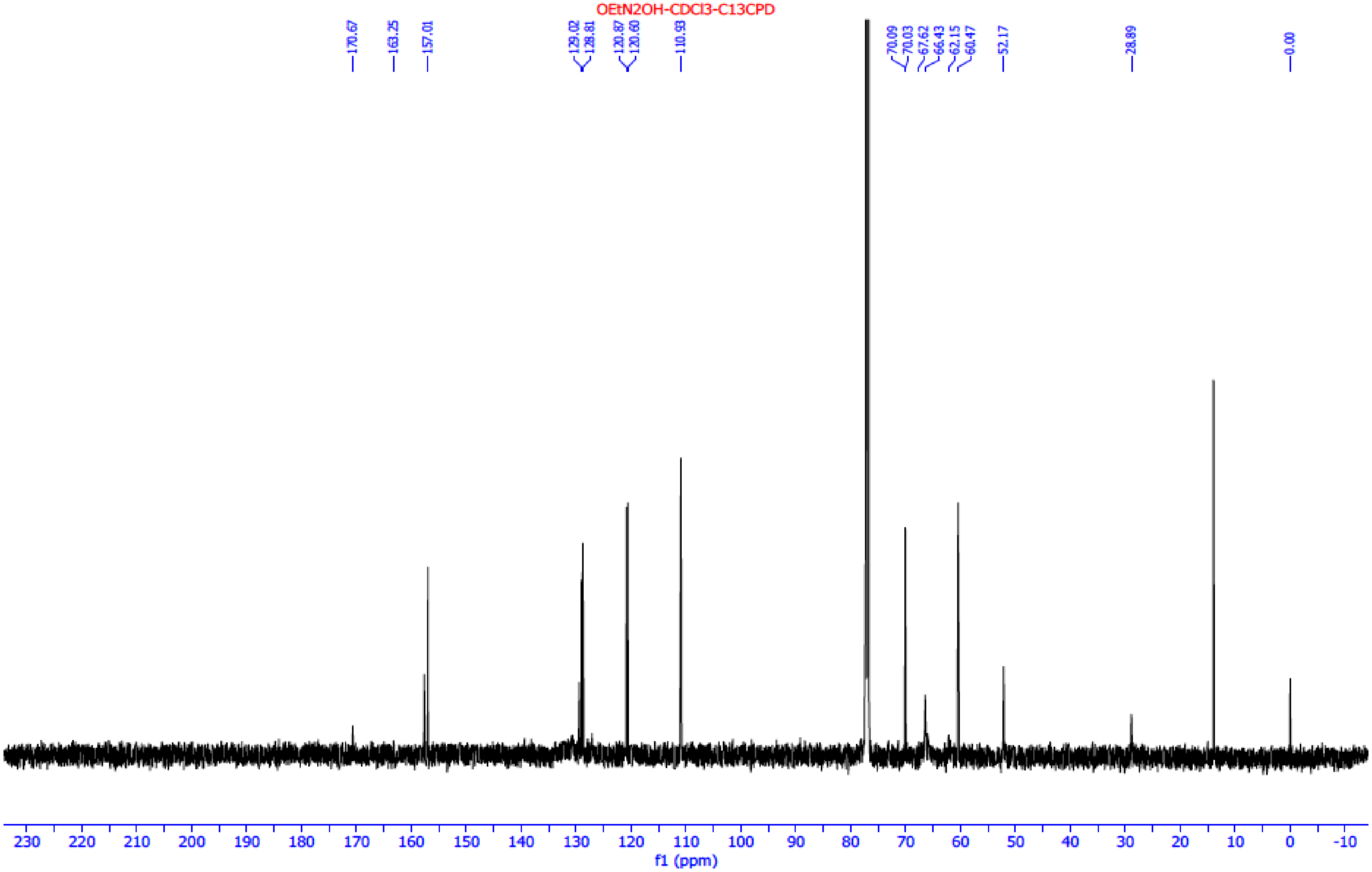


Figure S15. ^{13}C NMR of compound **5**

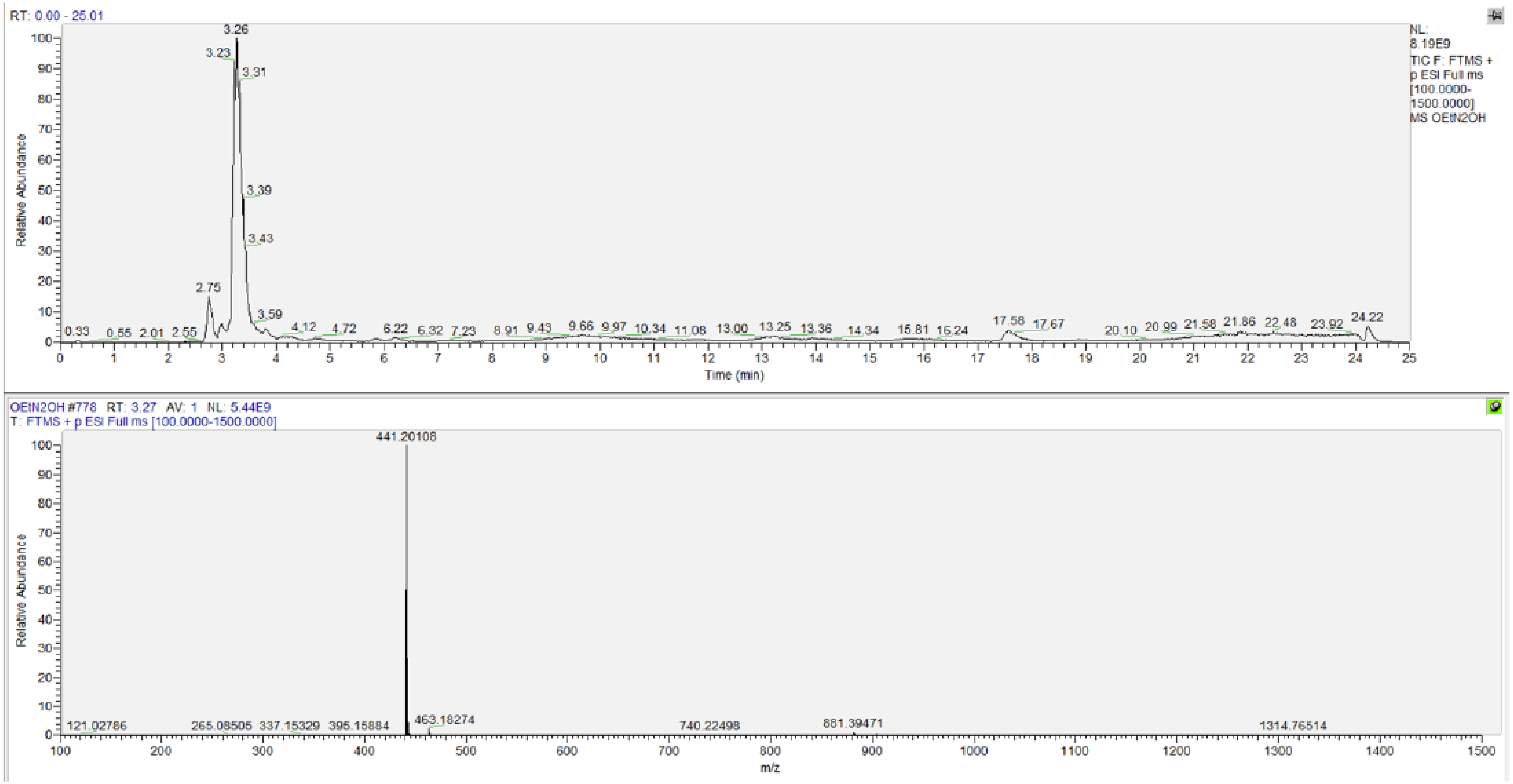


Figure S16. LC-HRMS of compound **5**