

Supporting Information

Double Heck Route to a Dibenzoxepine and Convergent Suzuki Cross-Coupling Strategy for Synthesis of an MR Antagonist

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Supporting information include general preparative experimental conditions, ¹NMR and ¹³NMR for compounds **1**, **2**, **6**, **7**, **8**, **9**, **10**, **14**, **17**, and **18**. IR spectrum for compounds **1**, **2**, **7**, **8**, **9**, **10**, **14**, and **18** are also included. A table of contents is included for searching the supporting information.

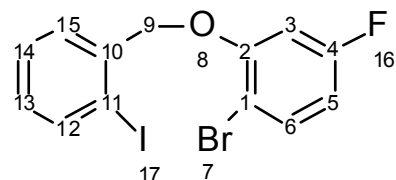
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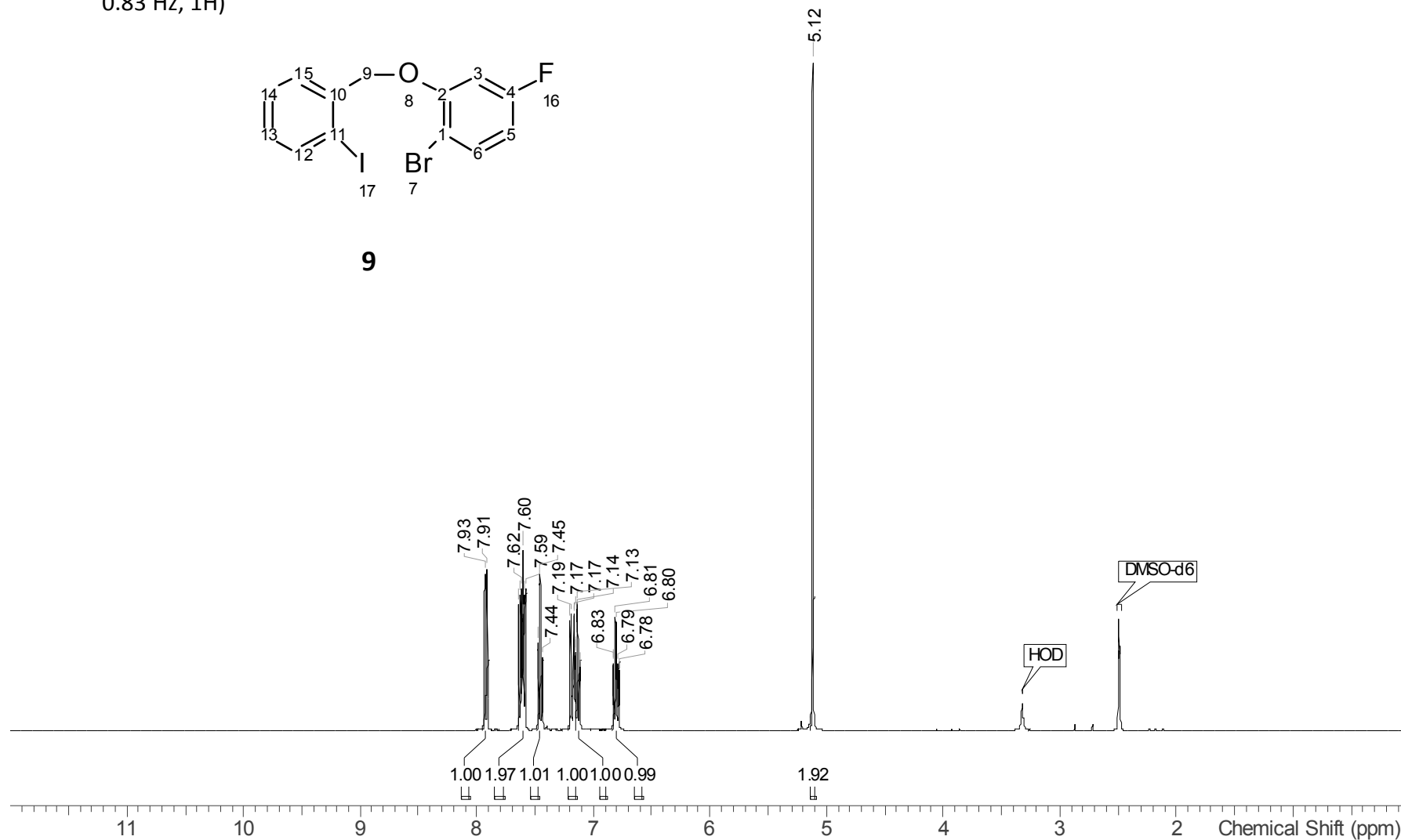
General. All commercial reagents were used as received without further purification. Known compounds were prepared according to reported procedures or were purchased from commercial sources. Melting points were determined by DSC using TA Instruments Discovery Series SA+ Differential Scanning Calorimeter, running the latest version of TRIOS software. IR spectra were recorded with Nicolet 6700 FT-IR with Smart OMNI sampler. All NMR data were collected with a 400 MHz Varian Spectrometer ATB probe. HRMS analyses were performed with a Thermo LTQ Orbitrap Discovery, using Electrospray ionization (ESI) technique, in the positive ion mode.

Compound # 9 ^1H NMR

^1H NMR (399 MHz, DMSO- d_6) δ 5.12 (s, 2H), 6.81 (td, $J=8.49, 2.77$ Hz, 1H), 7.14 (td, $J=7.64, 1.65$ Hz, 1H), 7.18 (dd, $J=10.90, 2.82$ Hz, 1H), 7.46 (td, $J=7.52, 0.92$ Hz, 1H), 7.60 (dd, $J=7.64, 1.41$ Hz, 1H), 7.62 (dd, $J=8.66, 6.23$ Hz, 1H), 7.92 (dd, $J=7.83, 0.83$ Hz, 1H)

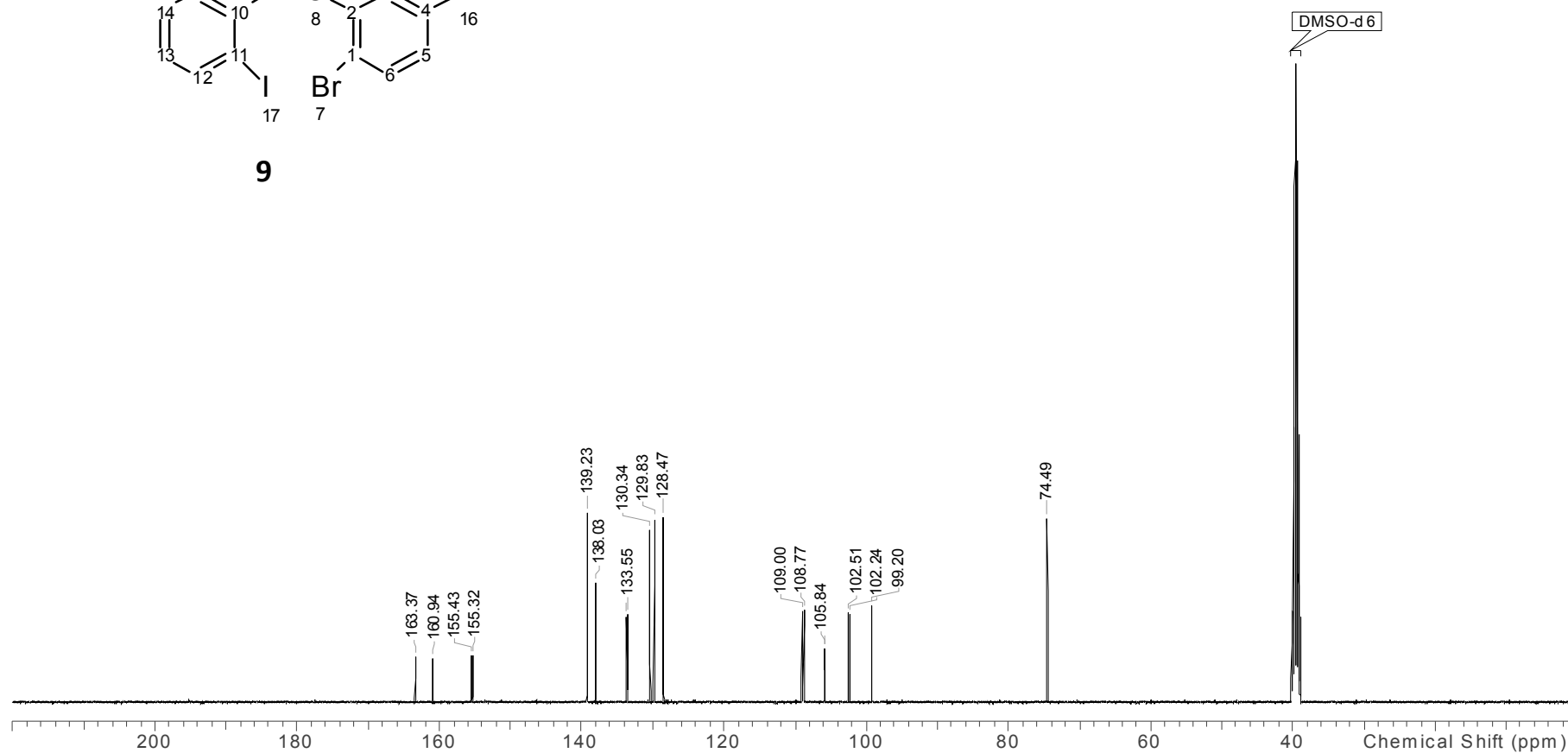
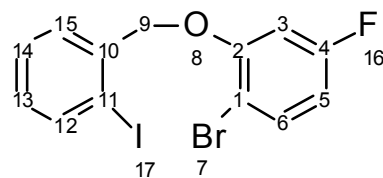


9



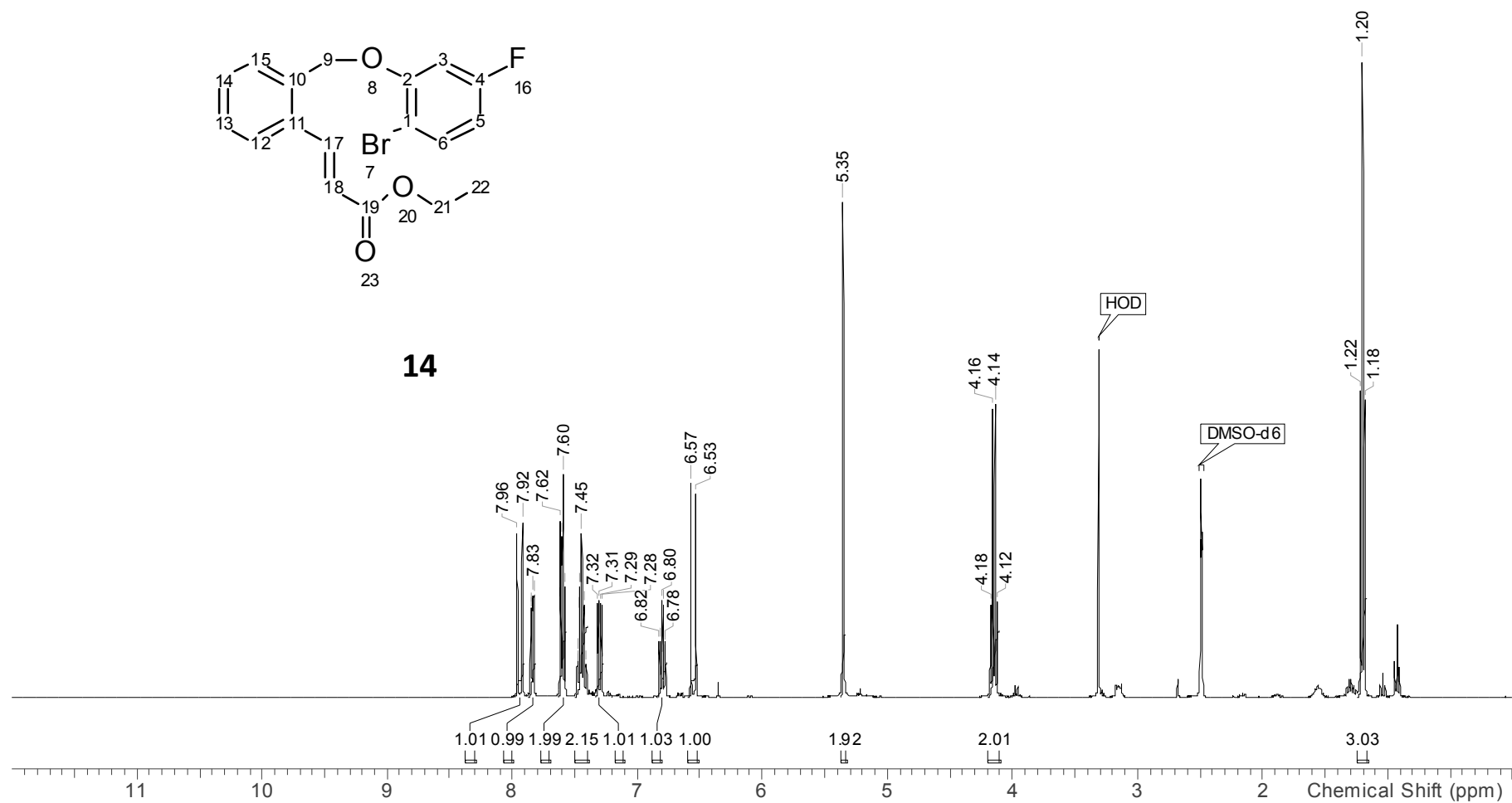
Compound #9 ^{13}C NMR

^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ ppm 74.5, 99.2, 102.4 (d, $J=27.1$ Hz), 105.8 (d, $J=3.4$ Hz), 108.9 (d, $J=22.5$ Hz), 128.5, 129.8, 130.3, 133.6 (d, $J=9.9$ Hz), 138.0, 139.2, 155.4 (d, $J=10.7$ Hz), 162.2 (d, $J=244.3$ Hz)



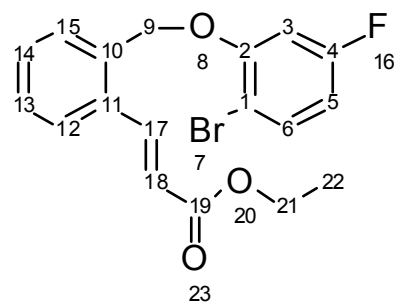
Compound # 14 ^1H NMR

^1H NMR (399 MHz, DMSO- d_6) δ 1.20 (t, $J=7.10$ Hz, 3H), 4.15 (q, $J=7.10$ Hz, 2H), 5.35 (s, 2H), 6.55 (d, $J=15.86$ Hz, 1H), 6.80 (td, $J=8.47$, 2.82 Hz, 1H), 7.30 (dd, $J=11.00$, 2.72 Hz, 1H), 7.44 (quind, $J=7.25$, 1.46 Hz, 2H), 7.60 (t, $J=6.62$ Hz, 1H), 7.61 (d, $J=6.42$ Hz, 1H), 7.84 (dd, $J=7.35$, 1.41 Hz, 1H), 7.94 (d, $J=15.86$ Hz, 1H)

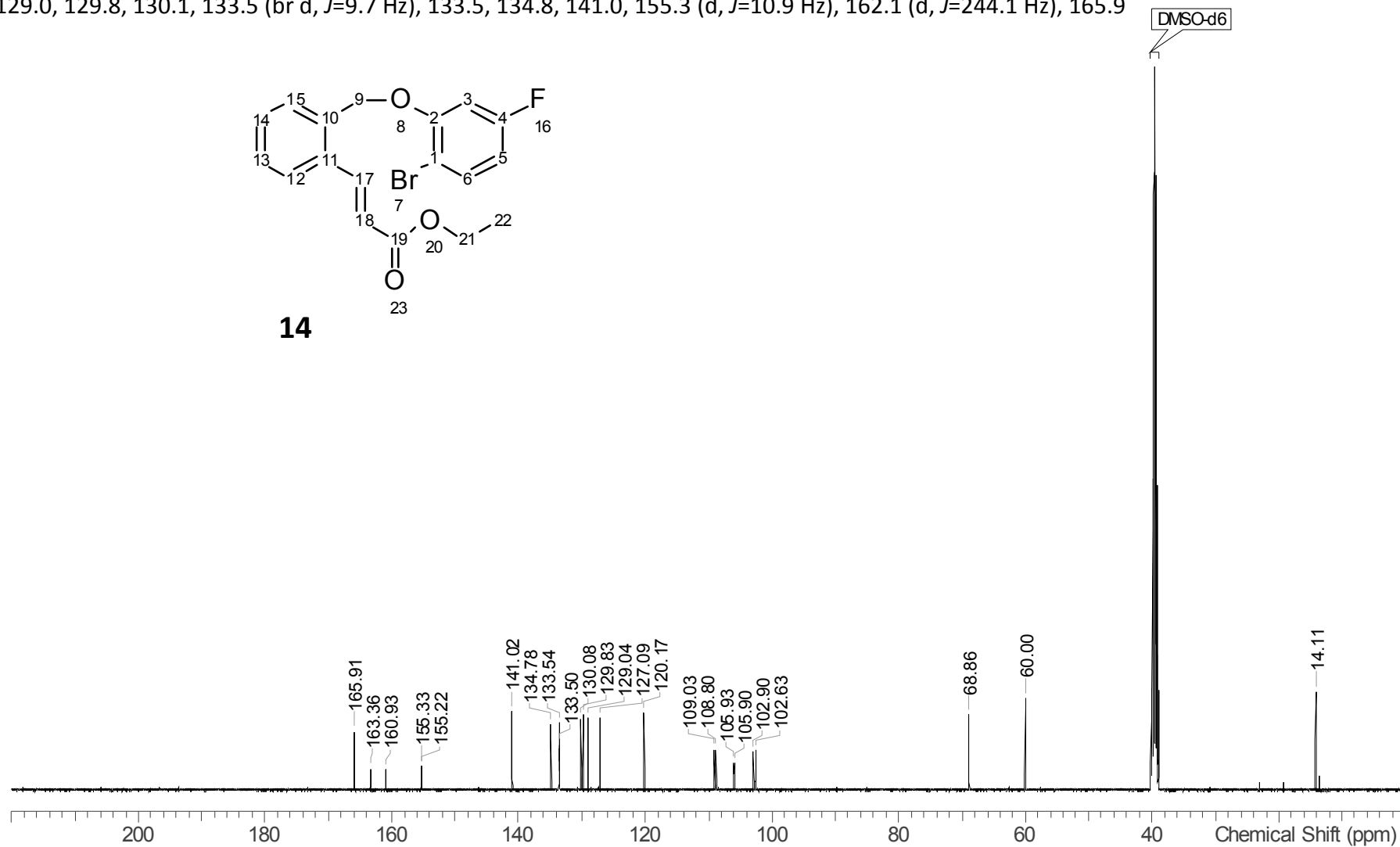


Compound # 14 ^{13}C NMR

^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ ppm 14.1, 60.0, 68.9, 102.8 (d, $J=27.3$ Hz), 105.9 (d, $J=3.4$ Hz), 108.9 (d, $J=22.5$ Hz), 120.2, 127.1, 129.0, 129.8, 130.1, 133.5 (br d, $J=9.7$ Hz), 133.5, 134.8, 141.0, 155.3 (d, $J=10.9$ Hz), 162.1 (d, $J=244.1$ Hz), 165.9

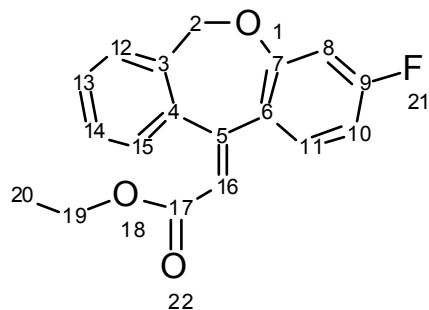


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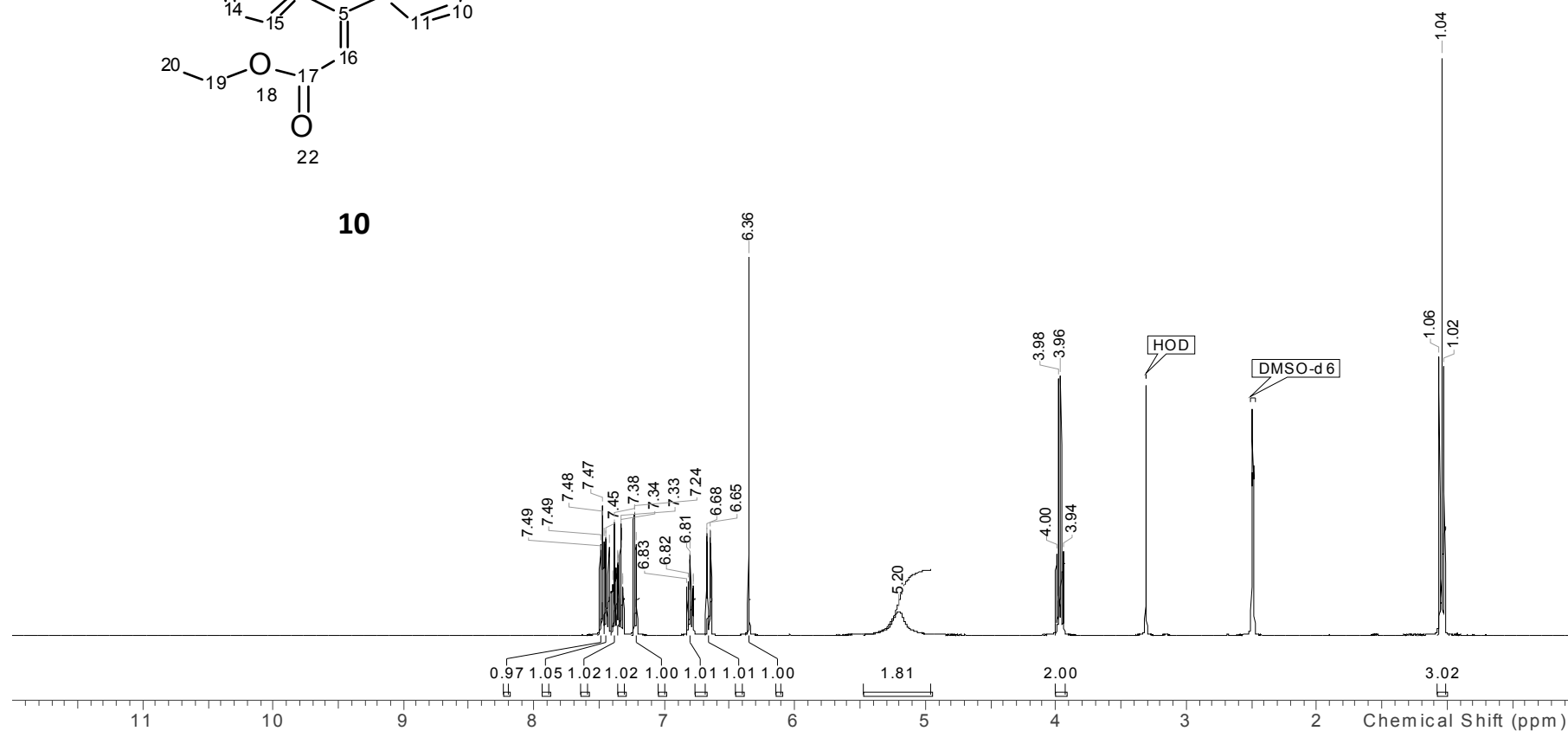


Compound # 10 ^1H NMR

^1H NMR (399 MHz, DMSO- d_6) δ 1.04 (t, $J=7.10$ Hz, 3H), 3.97 (q, $J=7.10$ Hz, 2H), 5.20 (br s, 2H), 6.36 (s, 1H), 6.66 (dd, $J=10.51$, 2.63 Hz, 1H), 6.80 (td, $J=8.37$, 2.63 Hz, 1H), 7.22 (dd, $J=7.44$, 0.92 Hz, 1H), 7.34 (td, $J=7.44$, 1.36 Hz, 1H), 7.39 (td, $J=7.37$, 1.31 Hz, 1H), 7.45 (dd, $J=8.81$, 6.86 Hz, 1H), 7.49 (dd, $J=7.30$, 1.07 Hz, 1H)

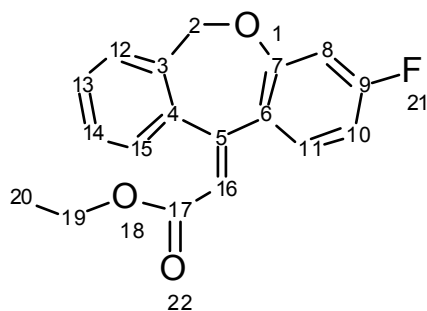


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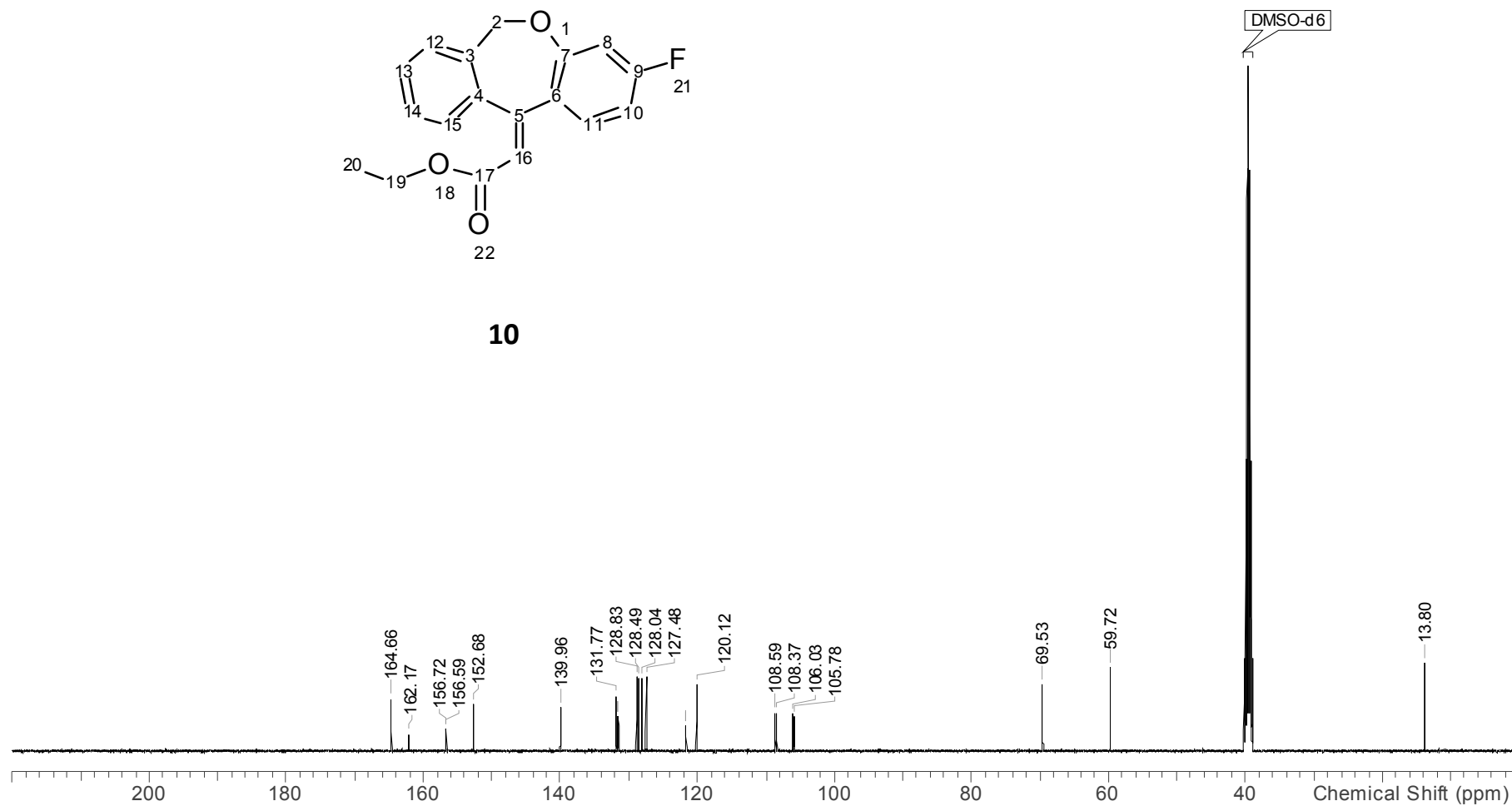


Compound # 10 ^{13}C NMR

^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ ppm 13.8, 59.7, 69.5, 105.9 (d, $J=24.4$ Hz), 108.5 (d, $J=21.6$ Hz), 120.1, 121.6 (d, $J=3.1$ Hz), 127.5, 128.0, 128.5, 128.8, 131.6 (d, $J=9.9$ Hz), 131.8, 140.0, 152.7, 156.7 (d, $J=12.4$ Hz), 163.4 (d, $J=246.4$ Hz), 164.7

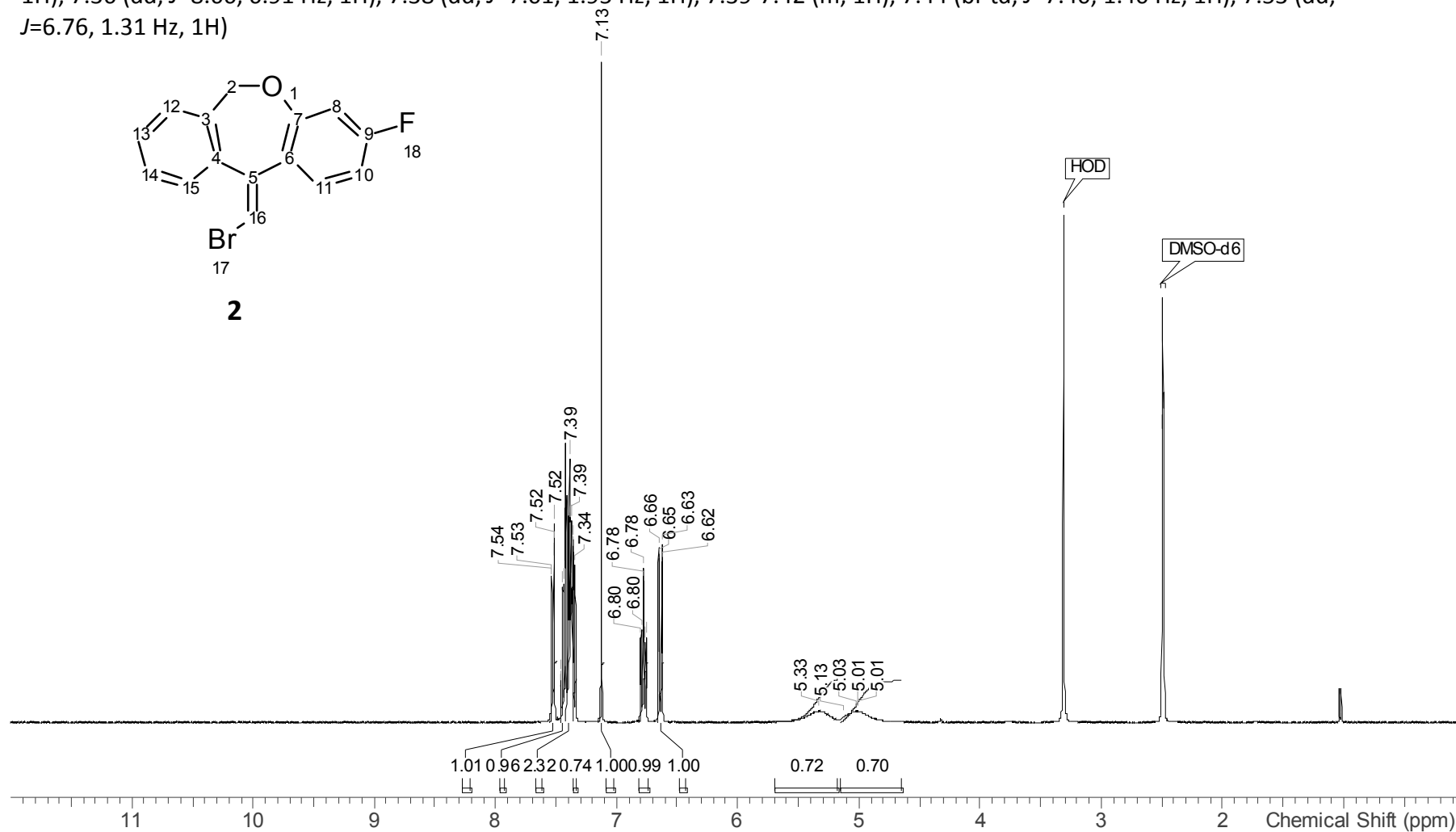
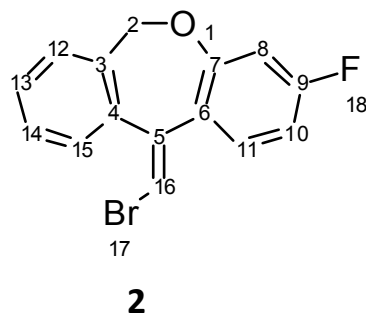


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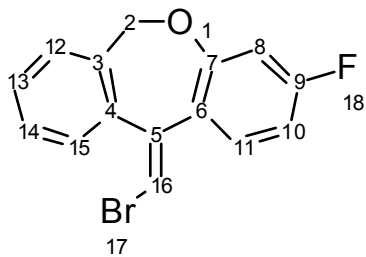
Compound # 2 ¹H NMR

¹H NMR (399 MHz, DMSO-d₆) δ 5.03 (br s, 1H), 5.33 (br s, 1H), 6.64 (dd, *J*=10.61, 2.63 Hz, 1H), 6.78 (td, *J*=8.37, 2.63 Hz, 1H), 7.13 (s, 1H), 7.36 (dd, *J*=8.66, 6.91 Hz, 1H), 7.38 (dd, *J*=7.01, 1.95 Hz, 1H), 7.39-7.42 (m, 1H), 7.44 (br td, *J*=7.40, 1.40 Hz, 1H), 7.53 (dd, *J*=6.76, 1.31 Hz, 1H)

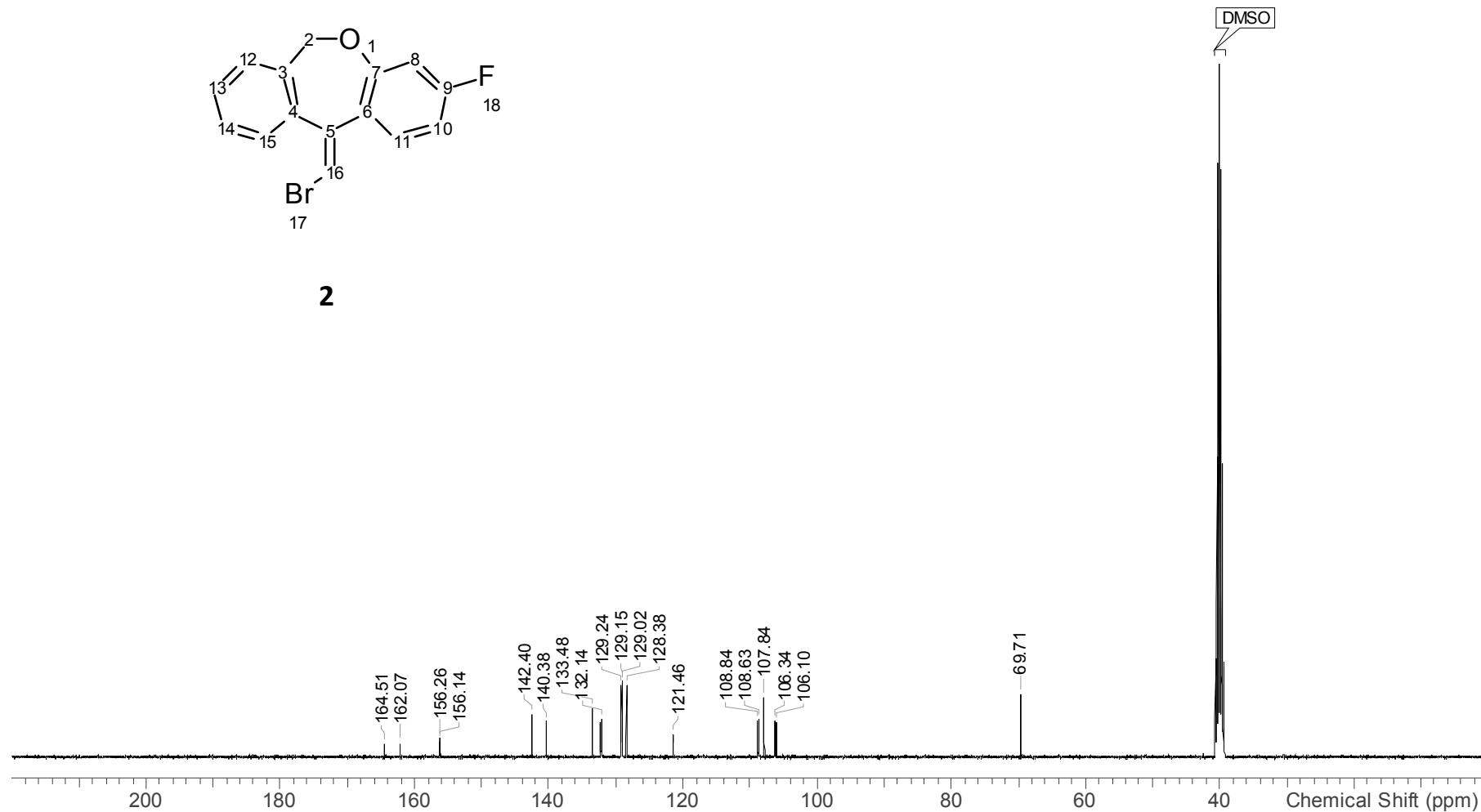


Compound # 2 ¹³CNMR

¹³C NMR (100 MHz, DMSO-*d*₆) δ ppm 69.7, 106.2 (d, *J*=24.4 Hz), 107.8, 108.7 (d, *J*=21.4 Hz), 121.5 (d, *J*=3.1 Hz), 128.4, 129.0, 129.2, 129.2, 132.2 (d, *J*=9.9 Hz), 133.5, 140.4, 142.4, 156.2 (d, *J*=12.4 Hz), 163.3 (d, *J*=245.3 Hz)

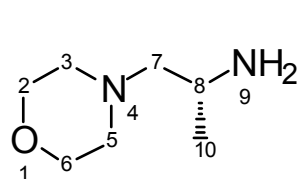


2



Compound # 17 ¹H NMR

¹H NMR (399 MHz, ACETONITRILE-d₃) δ 1.39 (d, *J*=6.71 Hz, 3H), 3.12-3.18 (m, 2H), 3.28 (br dd, *J*=14.60, 3.70 Hz, 3H), 3.49 (dd, *J*=14.45, 8.51 Hz, 1H), 3.81-3.86 (m, 1H), 3.87-3.94 (m, 2H)

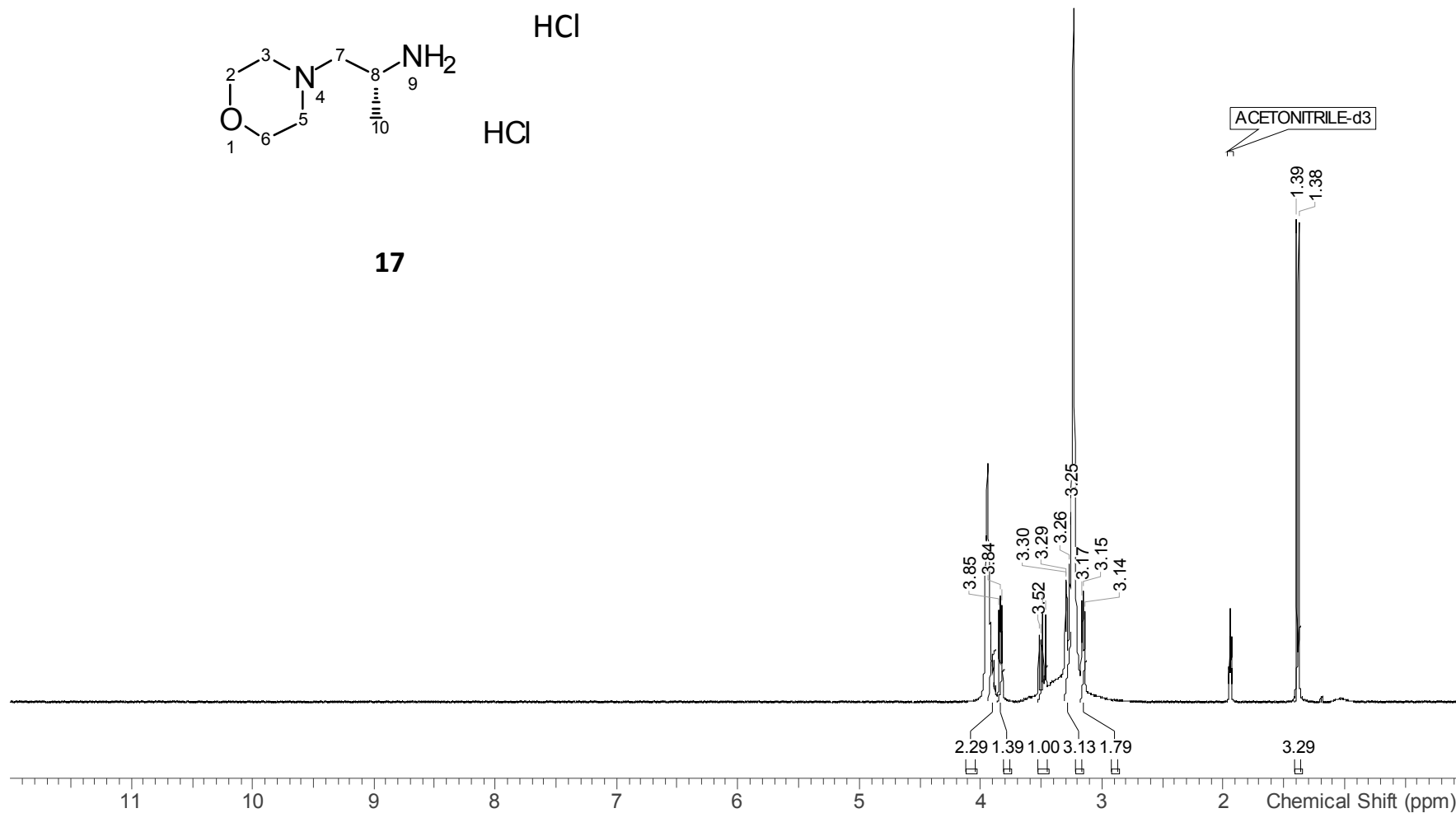


HCl

HCl

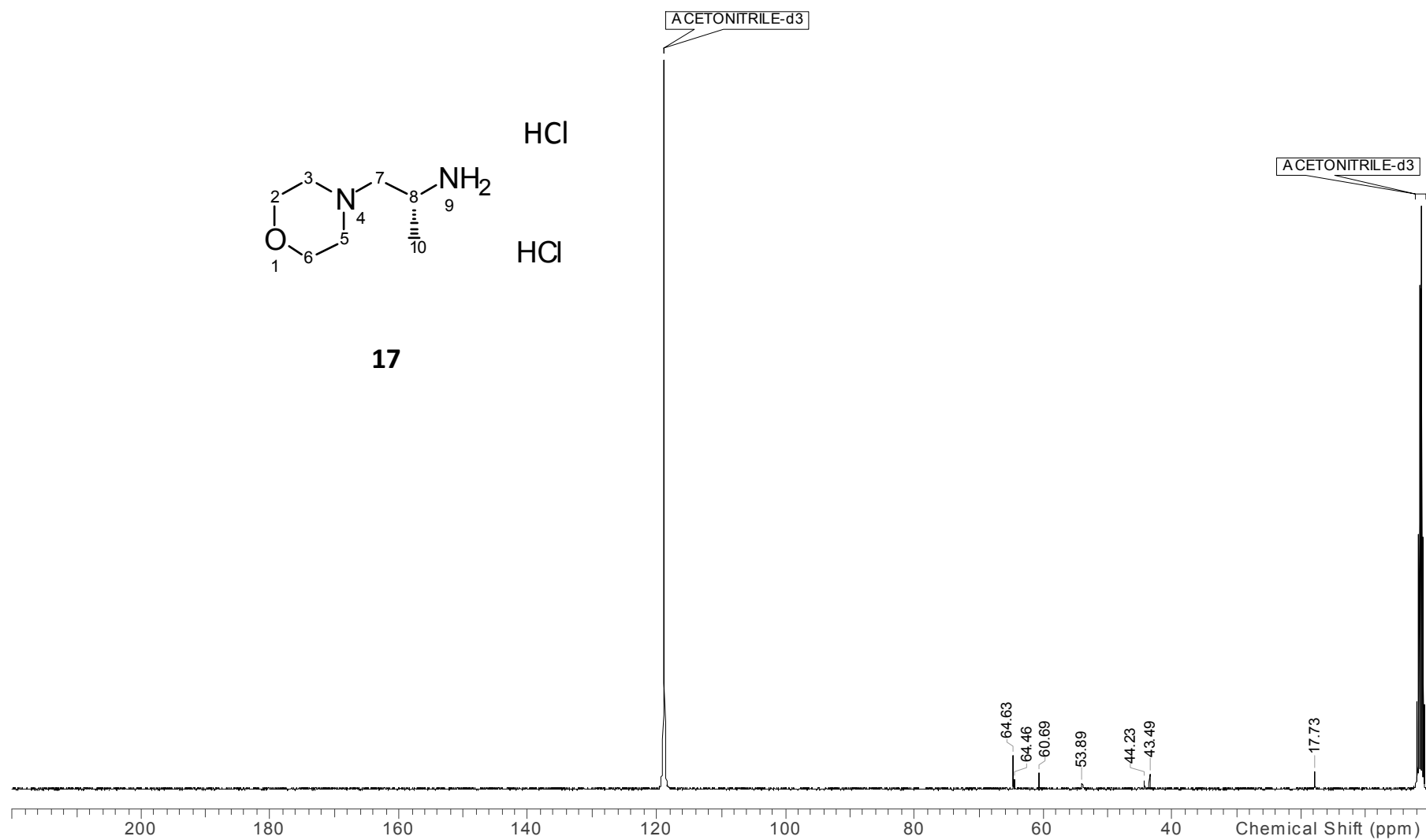
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ACETONITRILE-d₃



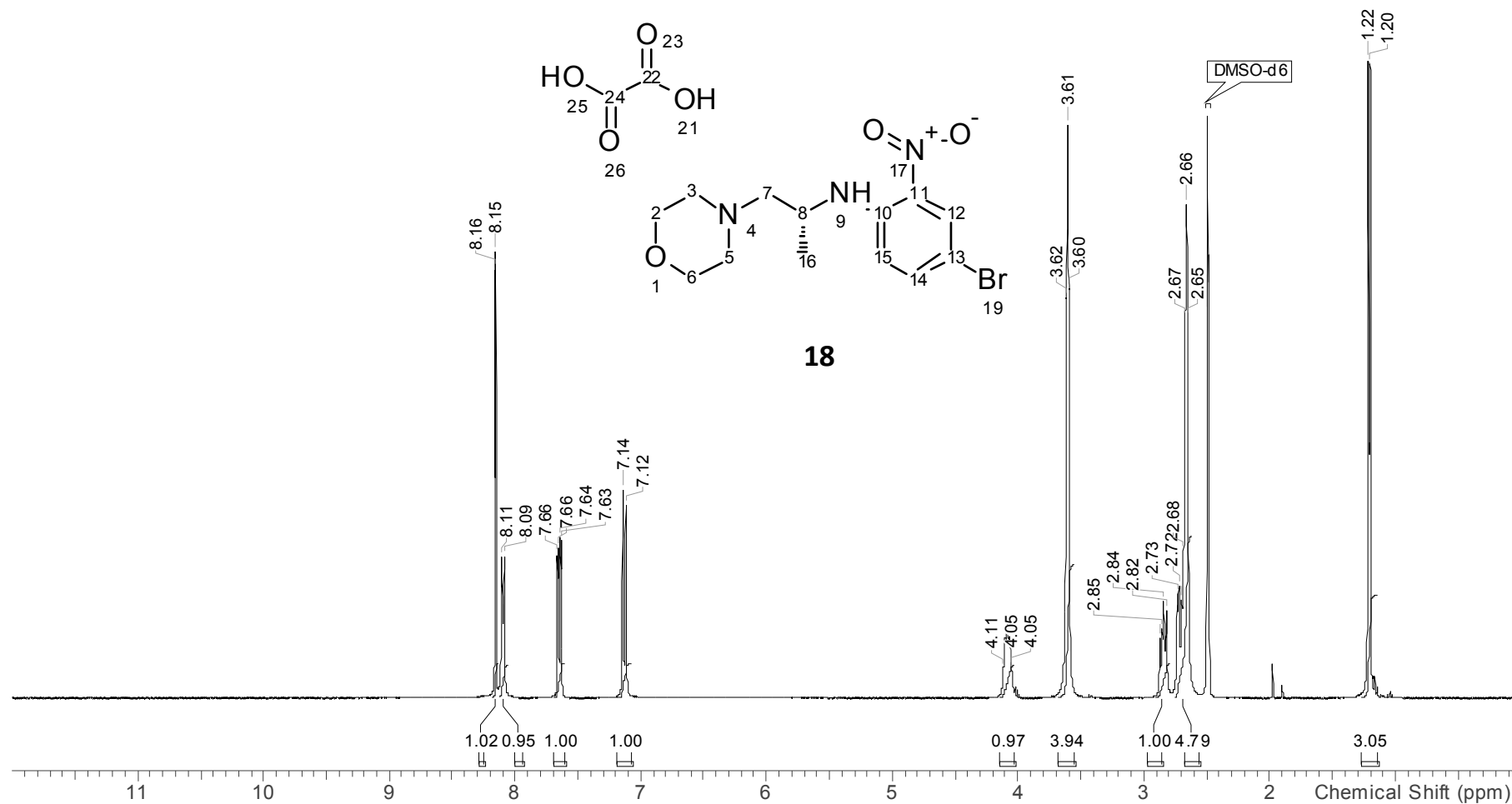
Compound # 17 ^{13}C NMR

^{13}C NMR (100 MHz, ACETONITRILE- d_3) δ 17.7, 43.5, 44.2, 53.9, 60.7, 64.5, 64.6



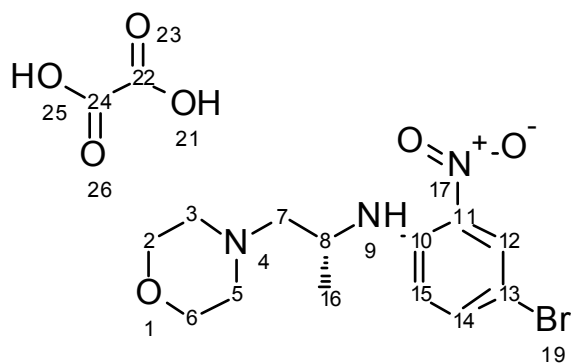
Compound # 18 ^1H NMR

^1H NMR (399 MHz, DMSO- d_6) δ 1.21 (d, $J=6.03$ Hz, 3H), 2.66 (br t, $J=3.80$ Hz, 4H), 2.71 (br dd, $J=13.33$, 5.06 Hz, 1H), 2.85 (dd, $J=12.75$, 7.88 Hz, 1H), 3.61 (br t, $J=3.94$ Hz, 4H), 4.03-4.14 (m, 1H), 7.13 (d, $J=9.34$ Hz, 1H), 7.65 (dd, $J=9.15$, 2.24 Hz, 1H), 8.10 (br d, $J=7.20$ Hz, 1H), 8.16 (d, $J=2.43$ Hz, 1H)

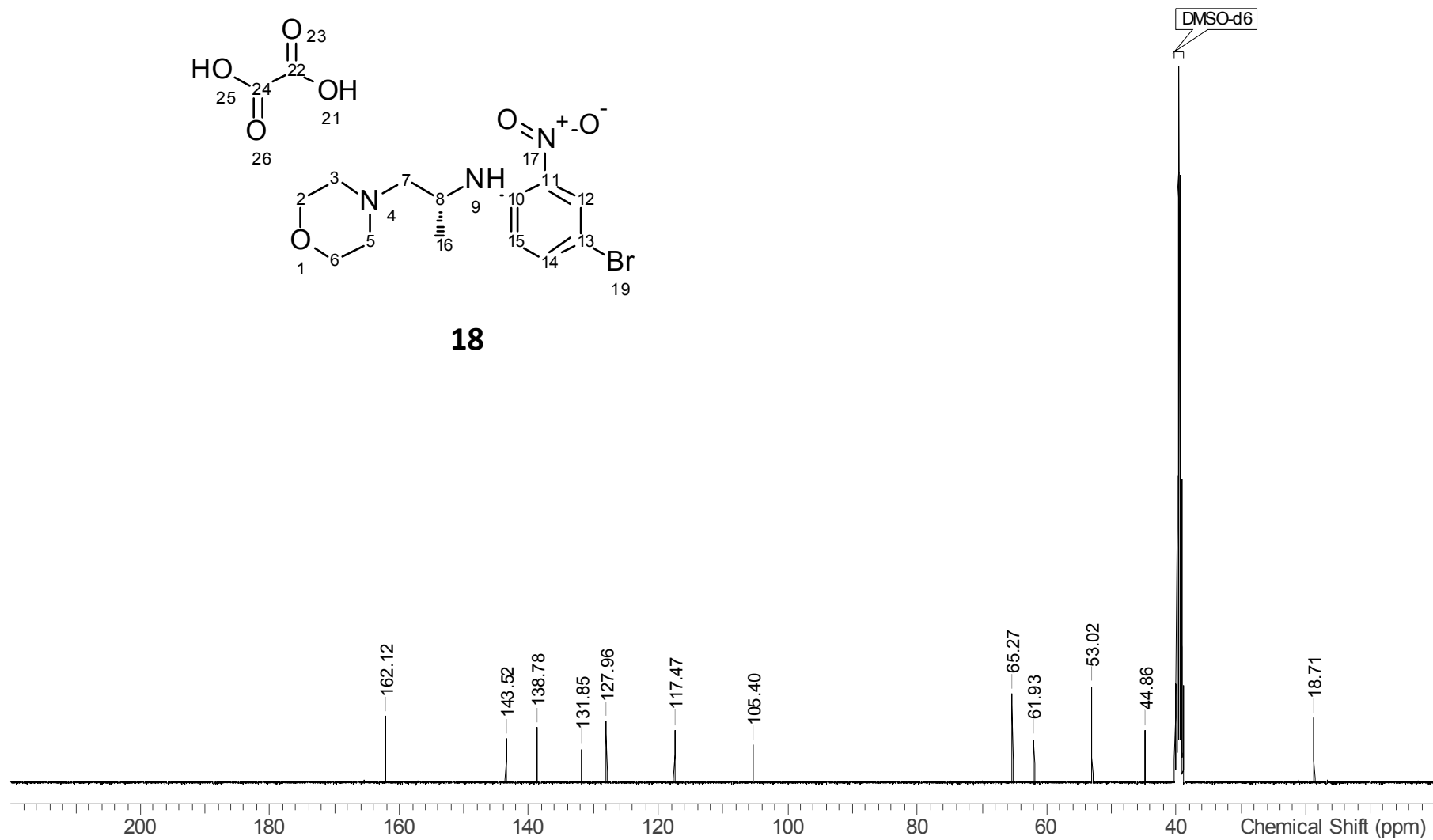


Compound # 18 ¹³CNMR

¹³C NMR (100 MHz, DMSO-d₆) δ 18.7, 44.9, 53.0, 61.9, 65.3, 105.4, 117.5, 128.0, 131.8, 138.8, 143.5, 162.1

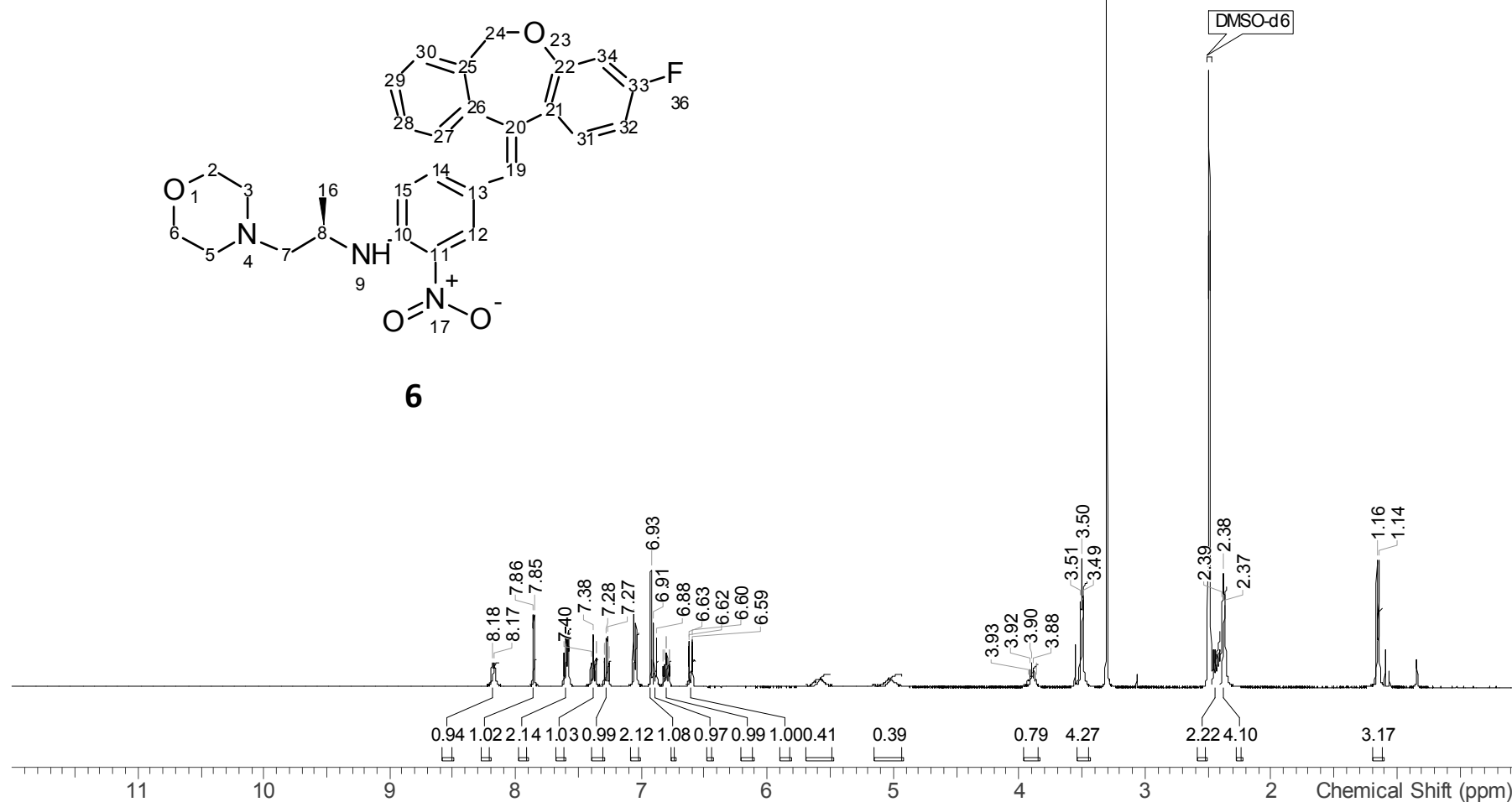


18



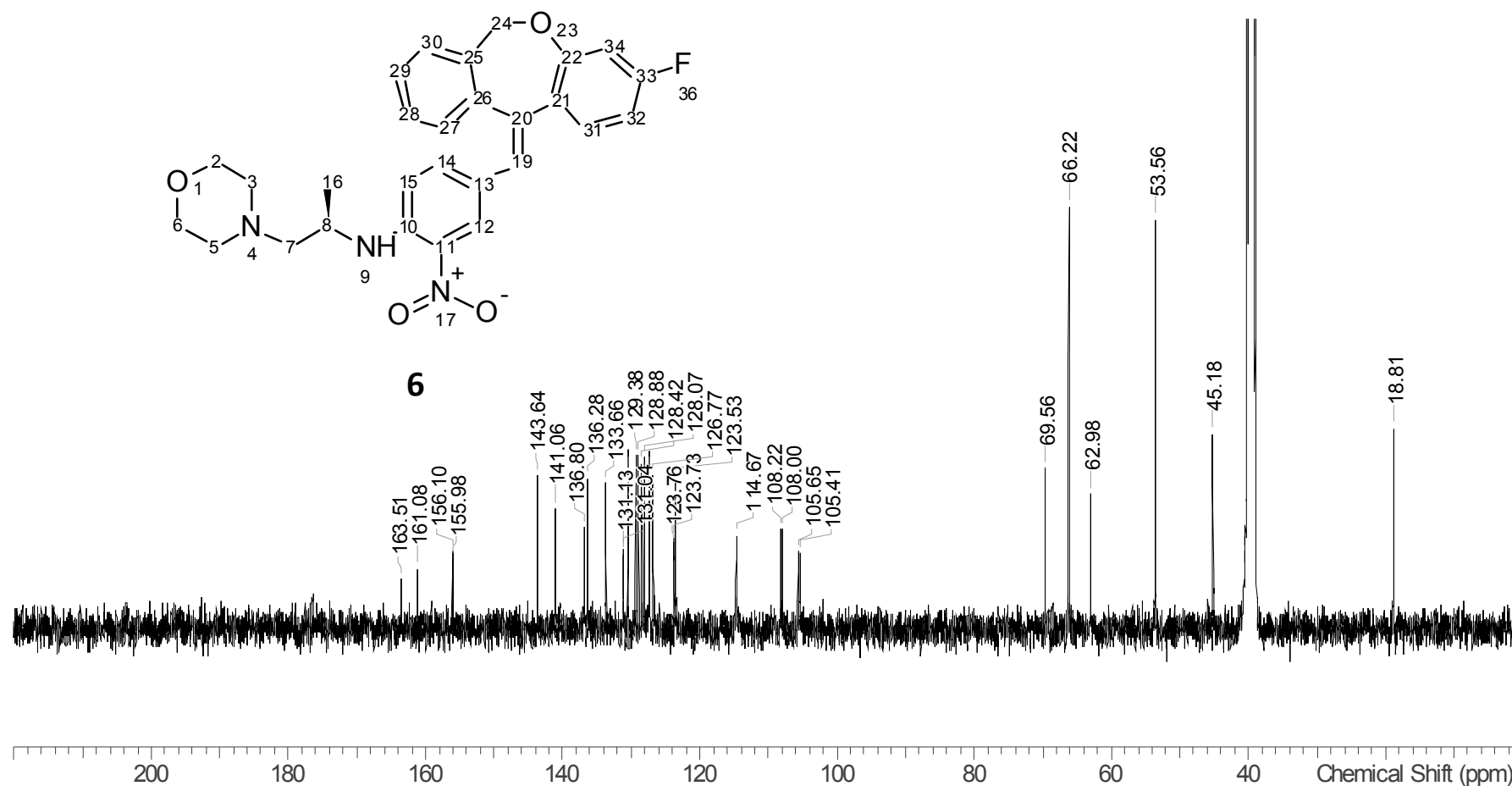
Compound # 6 ^1H NMR

^1H NMR (399 MHz, DMSO- d_6) δ 1.15 (d, $J=6.13$ Hz, 3H), 2.38 (br t, $J=3.94$ Hz, 4H), 2.40-2.47 (m, 2H), 3.50 (br t, $J=4.38$ Hz, 4H), 3.90 (quin, $J=6.54$ Hz, 1H), 4.93-5.15 (m, 1H), 5.50-5.70 (m, 1H), 6.61 (dd, $J=10.61$, 2.63 Hz, 1H), 6.80 (td, $J=8.37$, 2.72 Hz, 1H), 6.89 (d, $J=9.24$ Hz, 1H), 6.93 (s, 1H), 7.02-7.09 (m, 2H), 7.28 (td, $J=7.54$, 1.07 Hz, 1H), 7.35-7.42 (m, 1H), 7.57-7.63 (m, 2H), 7.86 (d, $J=1.95$ Hz, 1H), 8.18 (br d, $J=6.62$ Hz, 1H)



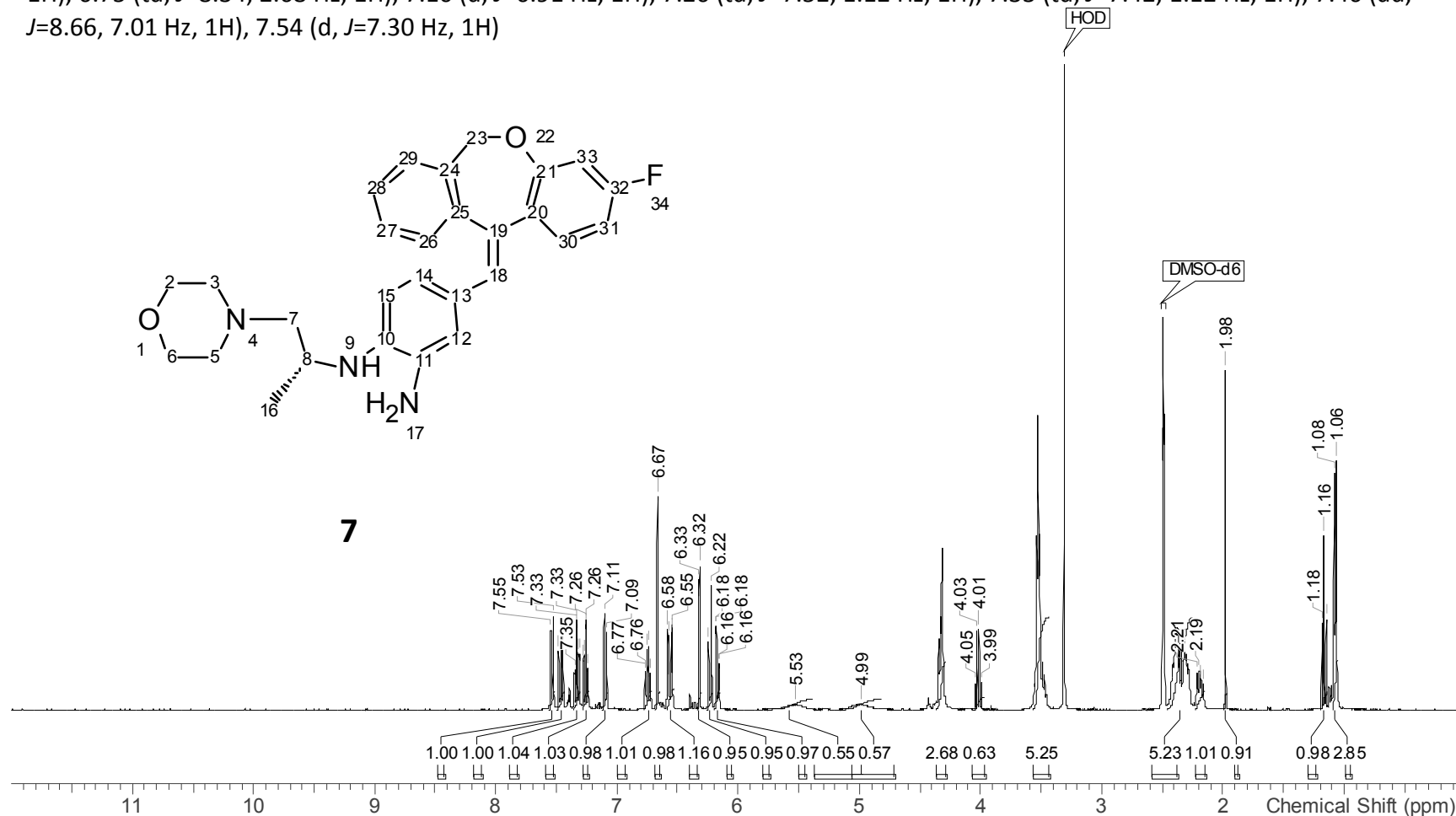
Compound # 6 ¹³CNMR

¹³C NMR (100 MHz, DMSO-*d*₆) δ ppm 18.8 (s), 45.2 (s), 53.6 (s), 63.0 (s), 66.2 (s), 69.6 (s), 105.5 (br d, *J*=24.4 Hz), 108.1 (br d, *J*=21.4 Hz), 114.7 (br s), 123.5 (s), 123.7 (d, *J*=3.1 Hz), 126.8 (s), 127.4 (s), 128.1 (s), 128.4 (s), 128.9 (s), 129.4 (s), 130.5 (s), 131.1 (br d, *J*=9.2 Hz), 133.7 (s), 136.3 (s), 136.8 (br s), 141.1 (s), 143.6 (s), 156.0 (d, *J*=12.2 Hz), 162.3 (d, *J*=243.8 Hz)



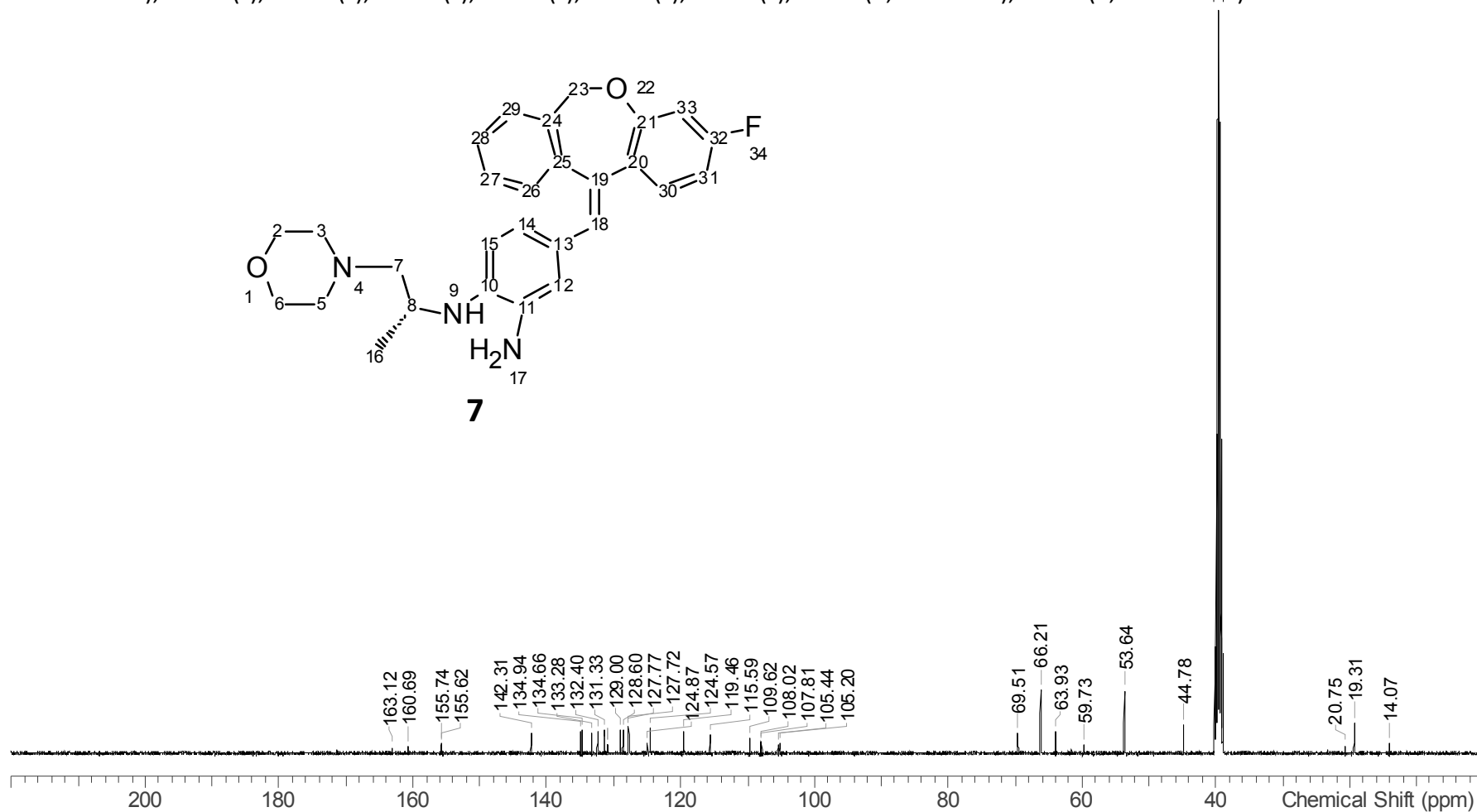
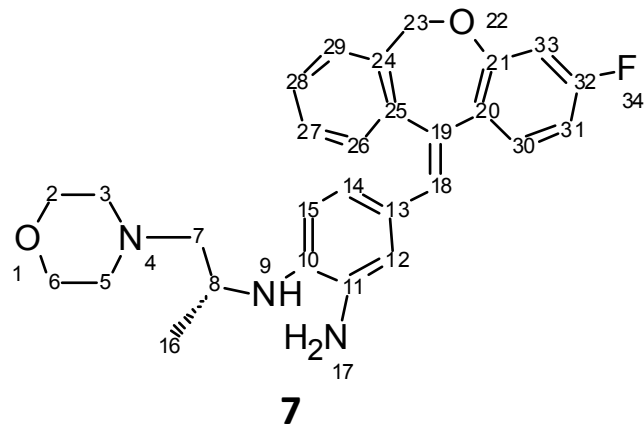
Compound # 7 ¹H NMR

¹H NMR (399 MHz, DMSO-d₆) δ 1.07 (d, *J*=6.13 Hz, 3H), 1.16 (t, *J*=7.10 Hz, 1H), 1.98 (s, 1H), 2.19 (br dd, *J*=12.12, 7.15 Hz, 1H), 2.25-2.46 (m, 5H), 3.44-3.57 (m, 1H), 3.52 (t, *J*=4.57 Hz, 3H), 4.02 (q, *J*=7.10 Hz, 1H), 4.32 (s, 1H), 4.34 (br d, *J*=6.62 Hz, 1H), 4.99 (br s, 1H), 5.53 (br s, 1H), 6.17 (dd, *J*=8.37, 1.65 Hz, 1H), 6.23 (d, *J*=8.47 Hz, 1H), 6.32 (d, *J*=1.75 Hz, 1H), 6.56 (dd, *J*=10.61, 2.63 Hz, 1H), 6.67 (s, 1H), 6.75 (td, *J*=8.34, 2.68 Hz, 1H), 7.10 (d, *J*=6.91 Hz, 1H), 7.26 (td, *J*=7.52, 1.12 Hz, 1H), 7.33 (td, *J*=7.42, 1.12 Hz, 1H), 7.46 (dd, *J*=8.66, 7.01 Hz, 1H), 7.54 (d, *J*=7.30 Hz, 1H)



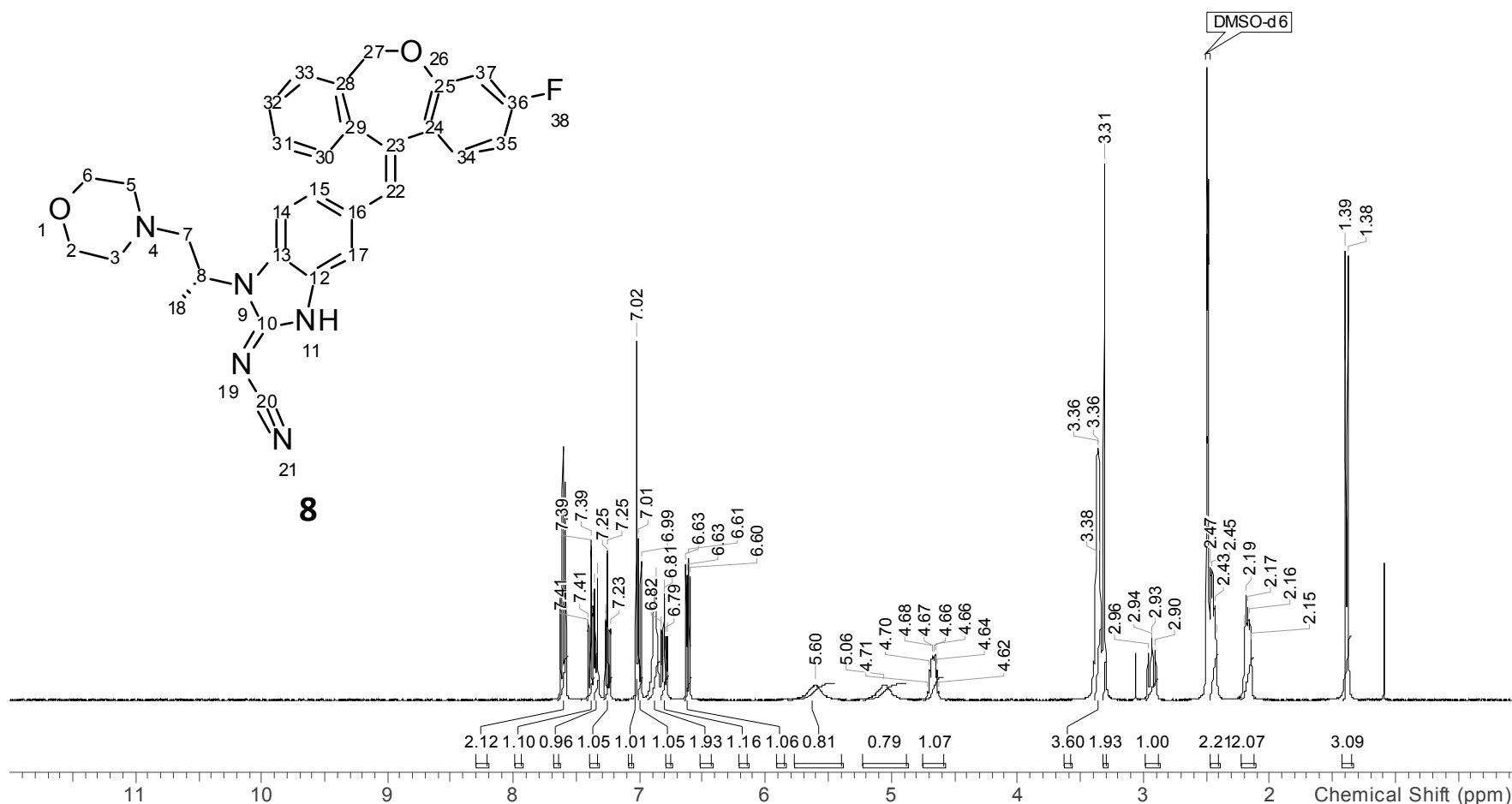
Compound # 7 ^{13}C NMR

^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ ppm 14.1 (s), 19.3 (s), 20.7 (s), 44.8 (s), 53.6 (s), 59.7 (s), 63.9 (s), 66.2 (s), 69.5 (s), 105.3 (d, $J=24.0$ Hz), 107.9 (d, $J=21.0$ Hz), 109.6 (s), 115.6 (s), 119.5 (s), 124.6 (s), 124.9 (d, $J=3.1$ Hz), 127.7 (d, $J=5.0$ Hz), 128.5 (s), 129.0 (s), 130.8 (d, $J=9.5$ Hz), 131.3 (s), 132.4 (s), 133.3 (s), 134.7 (s), 134.9 (s), 142.3 (s), 155.7 (d, $J=11.8$ Hz), 161.9 (d, $J=243.4$ Hz)



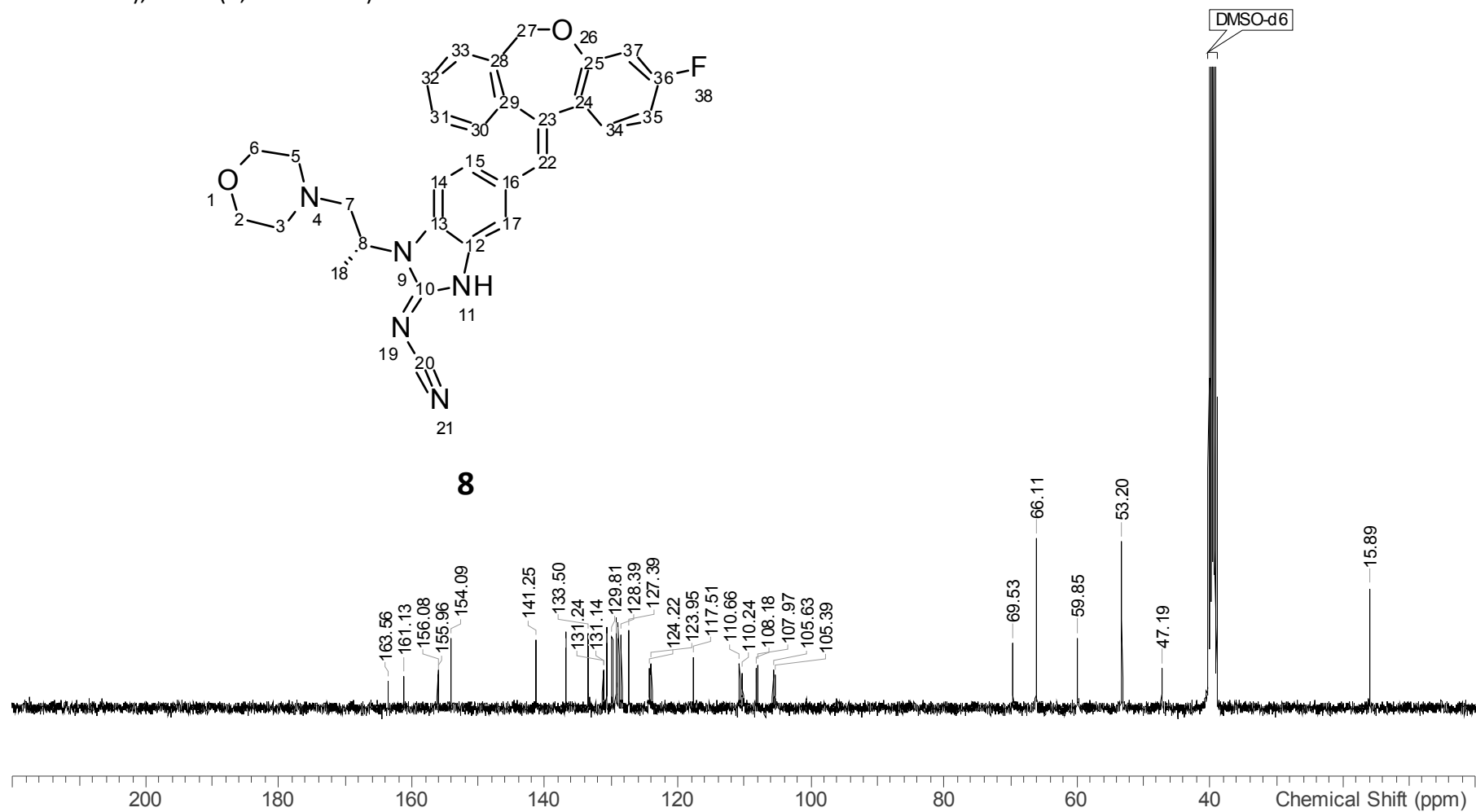
Compound # 8 ¹H NMR

¹H NMR (399 MHz, DMSO-d₆) δ 1.38 (d, *J*=6.91 Hz, 3H), 2.12-2.23 (m, 2H), 2.40-2.47 (m, 2H), 2.93 (br dd, *J*=12.80, 10.07 Hz, 1H), 3.31 (s, 2H), 3.33-3.39 (m, 4H), 4.58-4.75 (m, 1H), 5.06 (br s, 1H), 5.60 (br s, 1H), 6.62 (dd, *J*=10.51, 2.63 Hz, 1H), 6.80 (td, *J*=8.37, 2.63 Hz, 1H), 6.84-6.93 (m, 2H), 7.00 (d, *J*=7.40 Hz, 1H), 7.02 (s, 1H), 7.25 (td, *J*=7.54, 0.97 Hz, 1H), 7.34 (d, *J*=8.47 Hz, 1H), 7.39 (td, *J*=7.52, 1.02 Hz, 1H), 7.56-7.66 (m, 2H), 7.56-7.66 (m, 2H), 12.51 (br s, 1H)



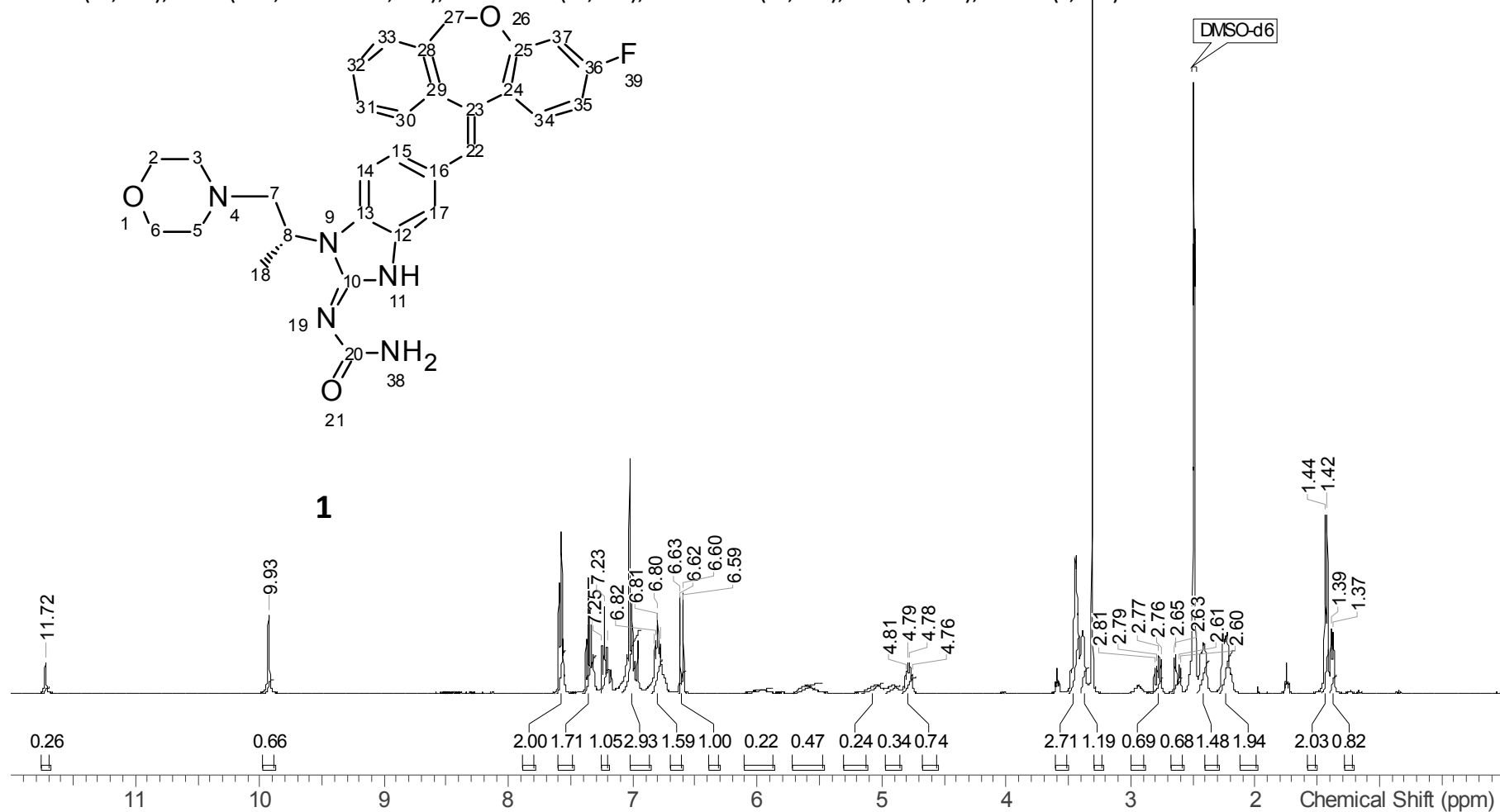
Compound # 8 ^{13}C NMR

^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ ppm 15.9, 47.2, 53.2, 59.9, 66.1, 69.5, 105.5 (br d, $J=24.0$ Hz), 108.1 (br d, $J=21.2$ Hz), 110.2, 110.7, 117.5, 123.9 (d, $J=2.9$ Hz), 124.2, 127.4, 128.4, 128.8, 129.3, 129.8, 130.7, 131.2 (br d, $J=9.7$ Hz), 133.5, 136.9, 141.2, 154.1, 156.0 (d, $J=12.0$ Hz), 162.3 (d, $J=244.1$ Hz)



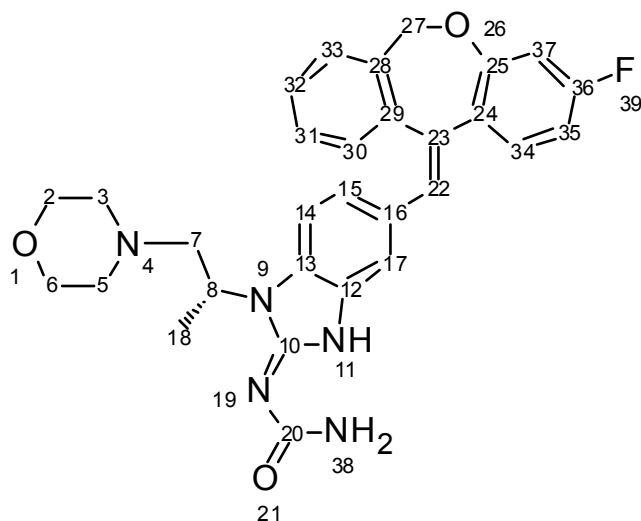
Compound # 1 ^1H NMR

^1H NMR (399 MHz, DMSO- d_6) δ 1.38 (br d, $J=6.91$ Hz, 1H), 1.43 (d, $J=6.81$ Hz, 2H), 2.17-2.29 (m, 2H), 2.36-2.47 (m, 1H), 2.62 (dd, $J=13.38, 5.01$ Hz, 1H), 2.78 (dd, $J=13.33, 7.88$ Hz, 1H), 3.34-3.40 (m, 1H), 3.41-3.50 (m, 3H), 4.72-4.85 (m, 1H), 4.86-4.97 (m, 1H), 4.99-5.17 (m, 1H), 5.48-5.72 (m, 1H), 5.87-6.10 (m, 1H), 6.61 (dd, $J=10.51, 2.63$ Hz, 1H), 6.80 (td, $J=8.30, 2.68$ Hz, 2H), 6.94-7.09 (m, 3H), 7.23 (br t, $J=7.54$ Hz, 1H), 7.30-7.41 (m, 2H), 7.54-7.62 (m, 2H), 9.93 (s, 1H), 11.72 (s, 1H)

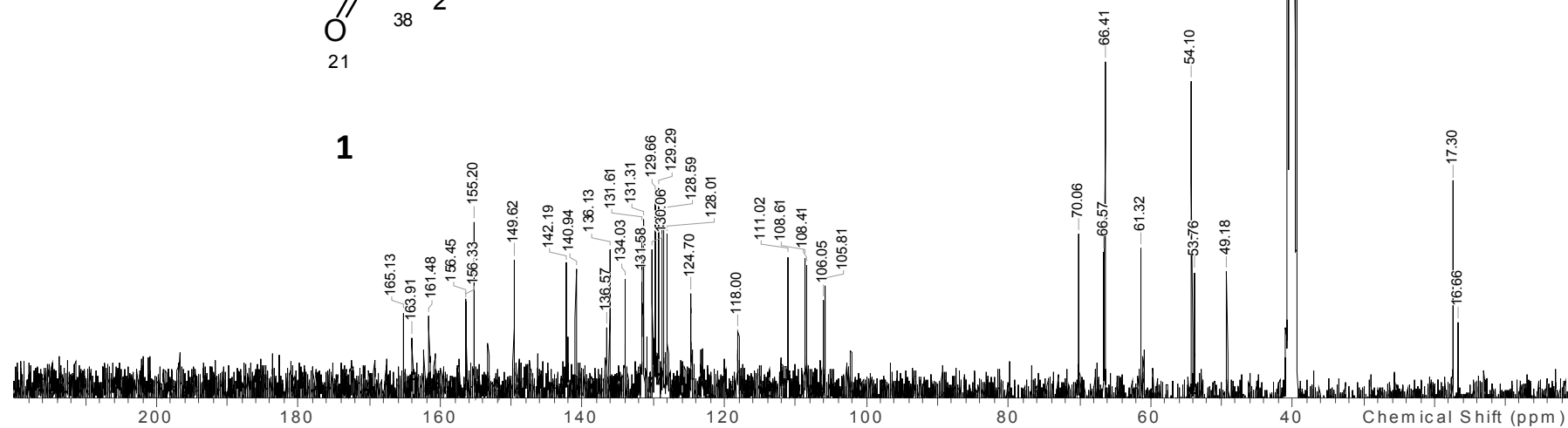


Compound # 1 ^{13}C NMR

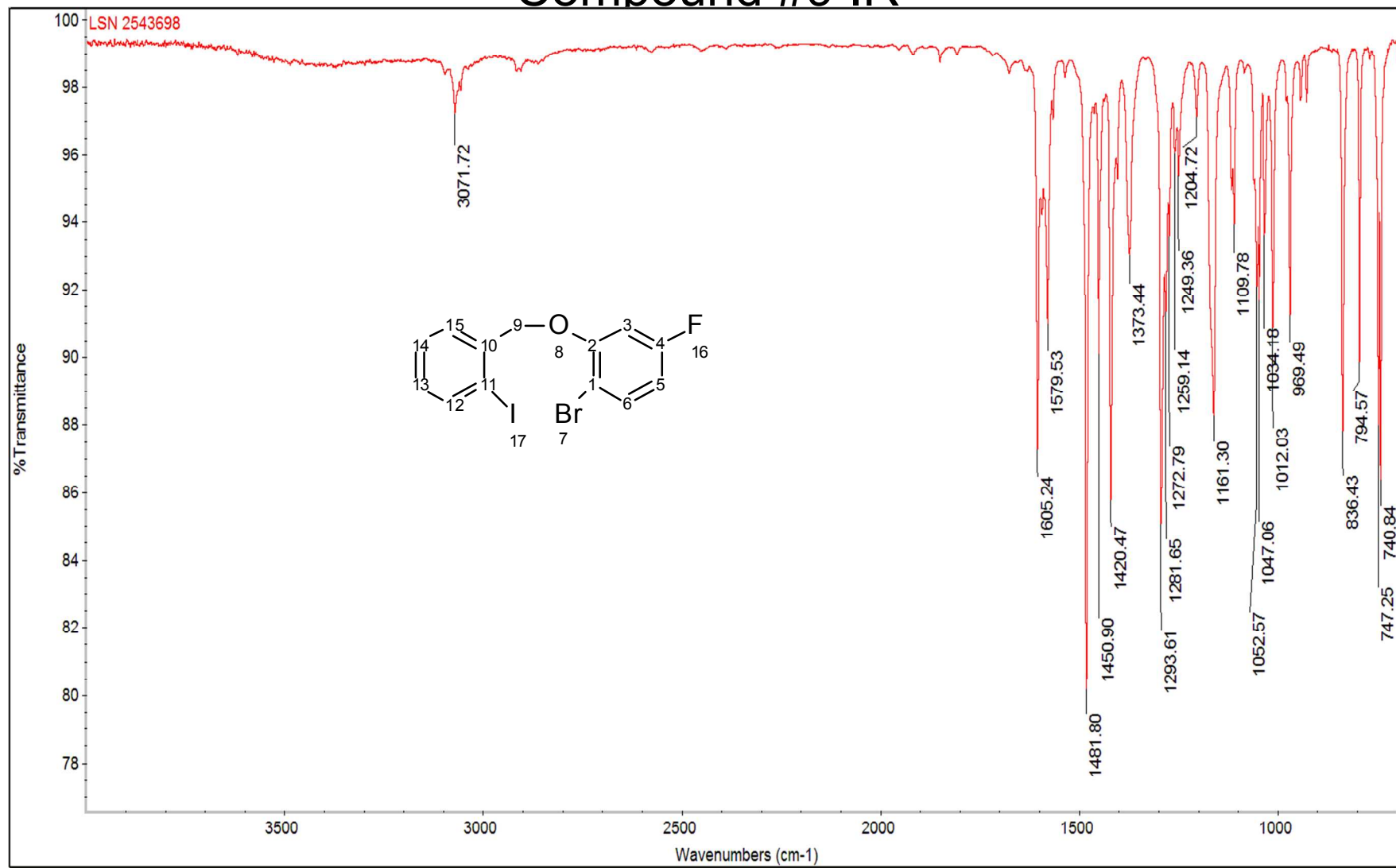
^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ ppm 16.7, 17.3, 49.2, 53.8, 54.1, 61.3, 66.4, 66.6, 70.1, 105.9 (d, $J=24.4$ Hz), 108.5 (d, $J=21.0$ Hz), 111.0, 118.0, 124.7 (d, $J=2.6$ Hz), 128.0, 128.6, 129.3, 129.7, 130.1, 131.3, 131.5 (br d, $J=9.5$ Hz), 131.6, 134.0, 136.1, 136.6, 140.9, 142.2, 149.6, 155.2, 156.4 (d, $J=11.8$ Hz), 162.7 (br d, $J=243.8$ Hz), 165.1



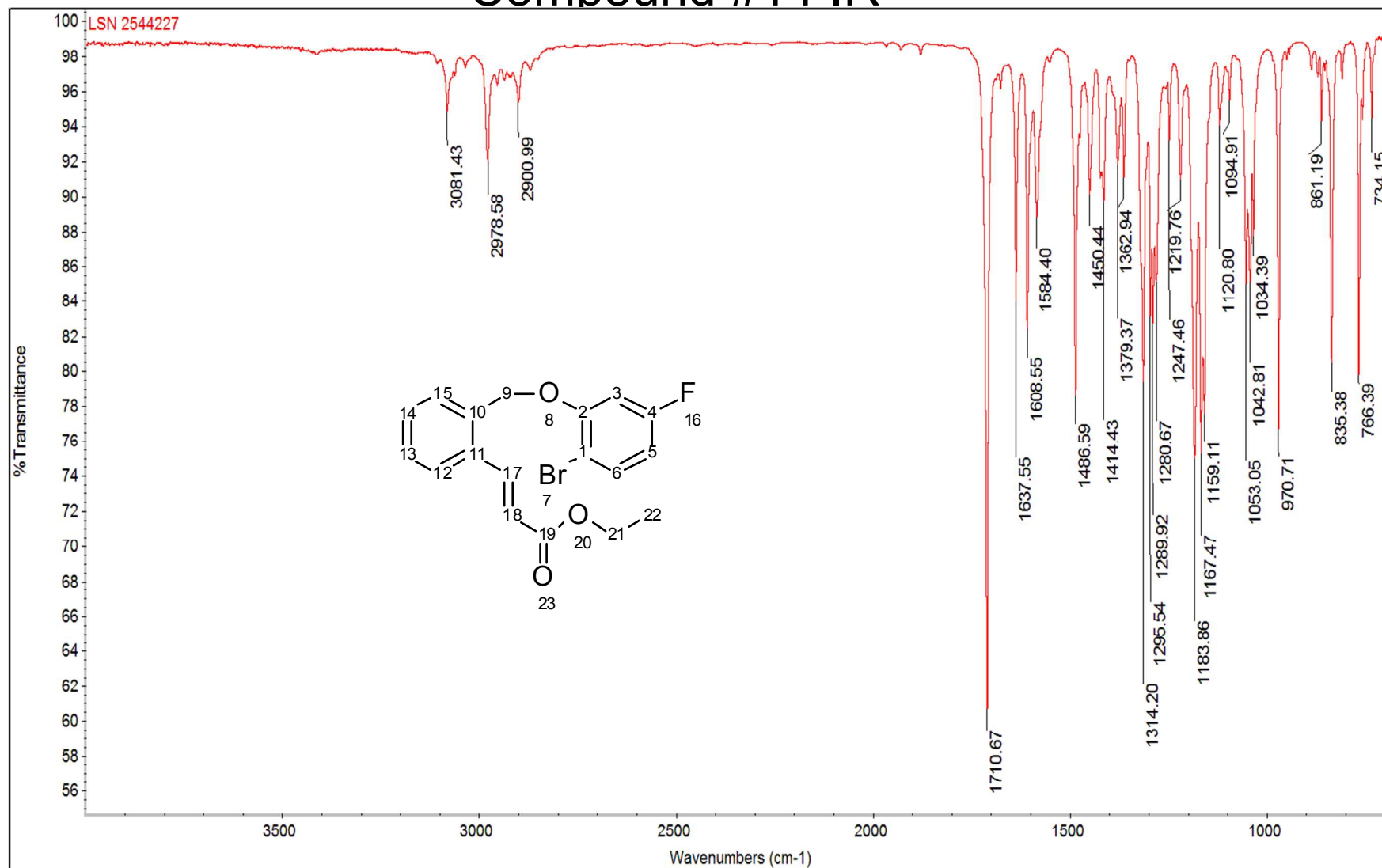
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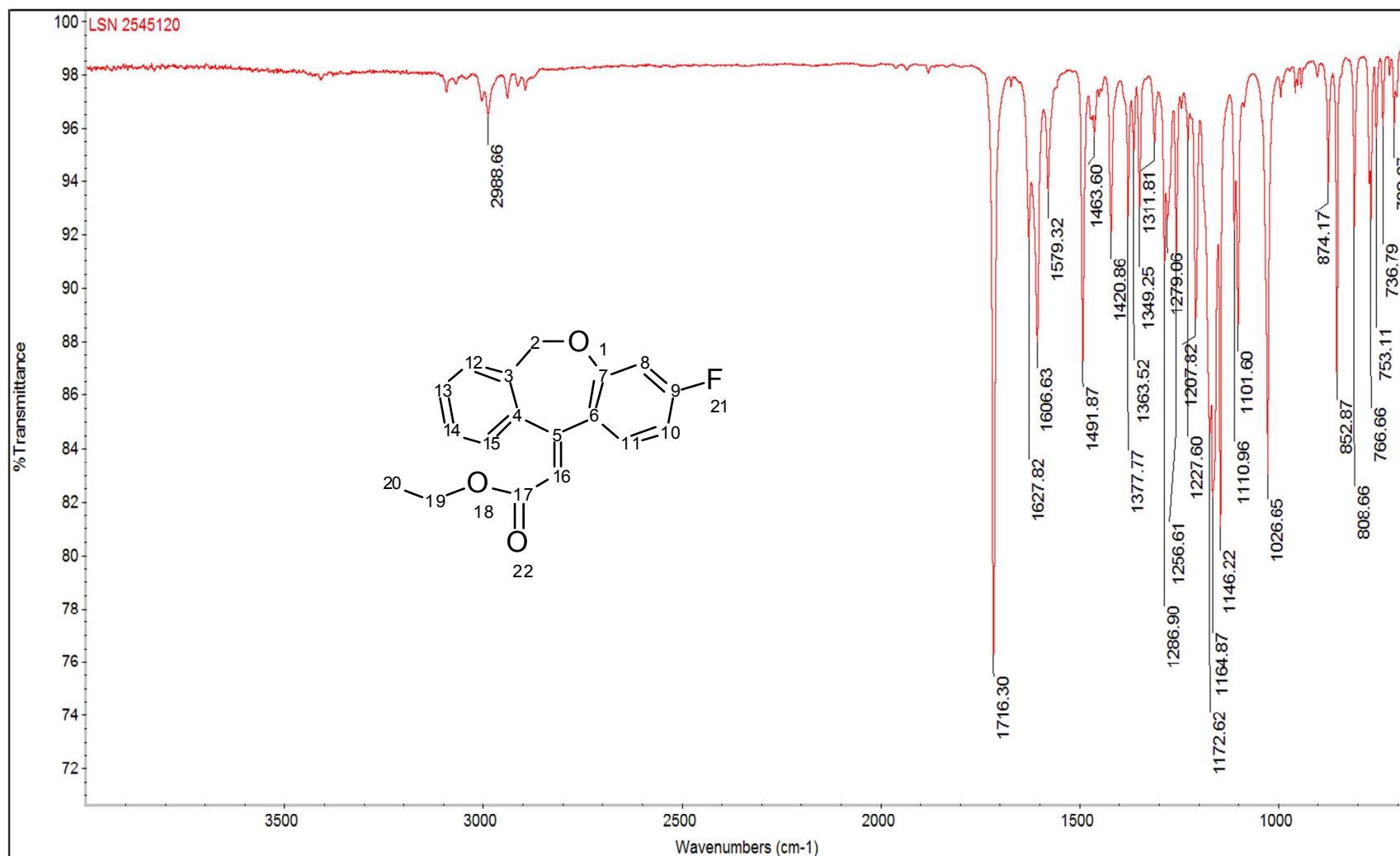
Compound #9 IR



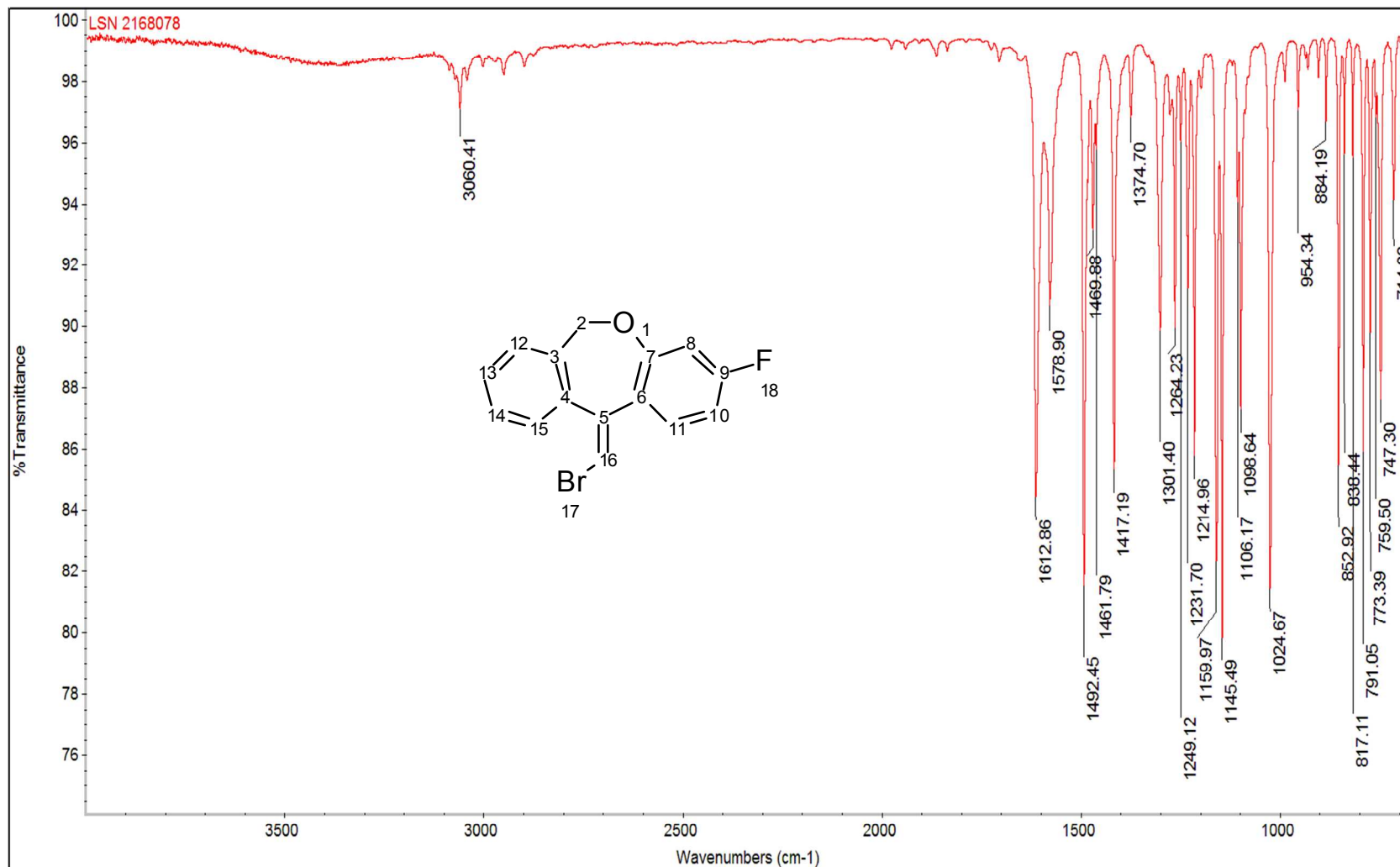
Compound #14 IR



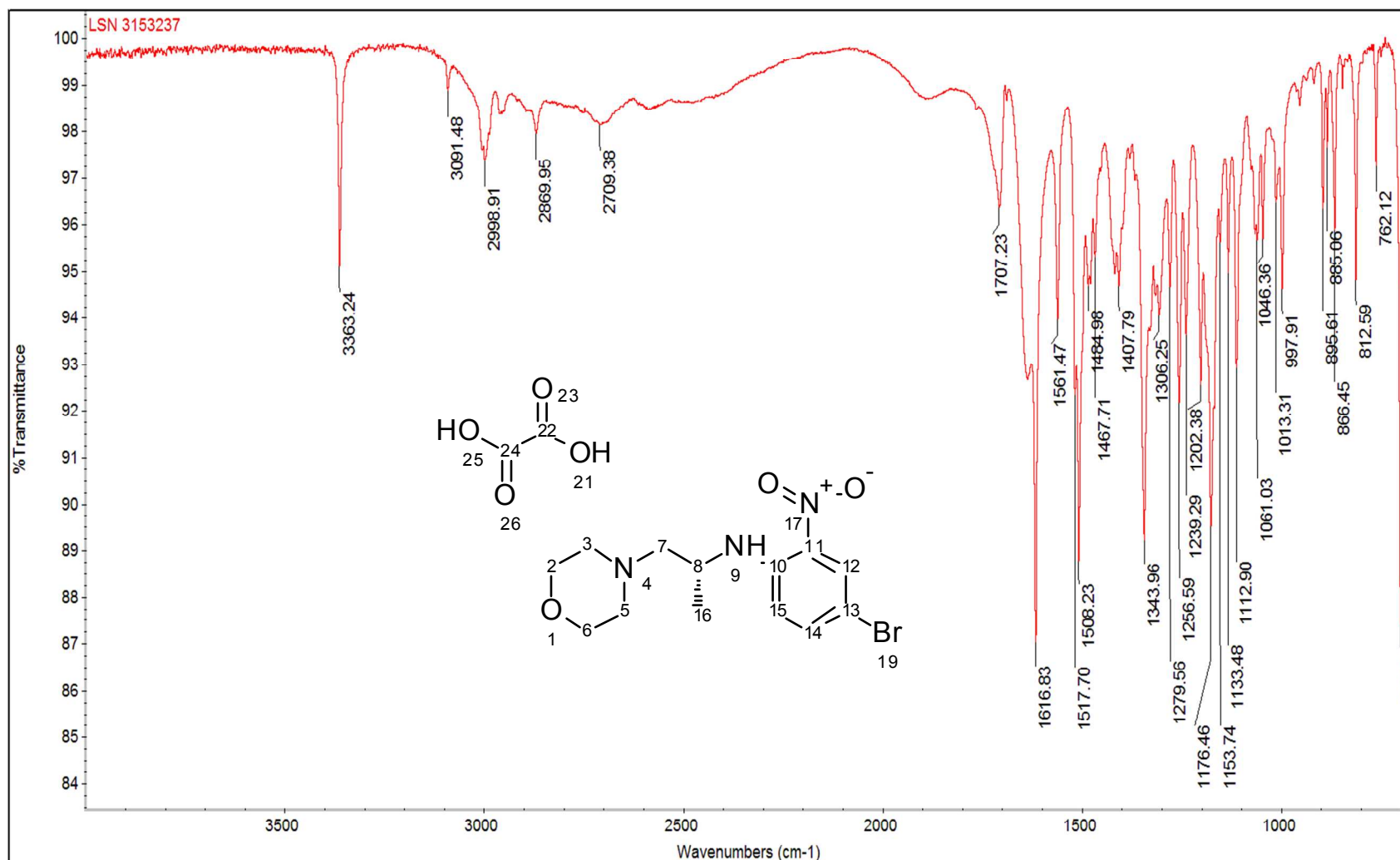
Compound #10 IR



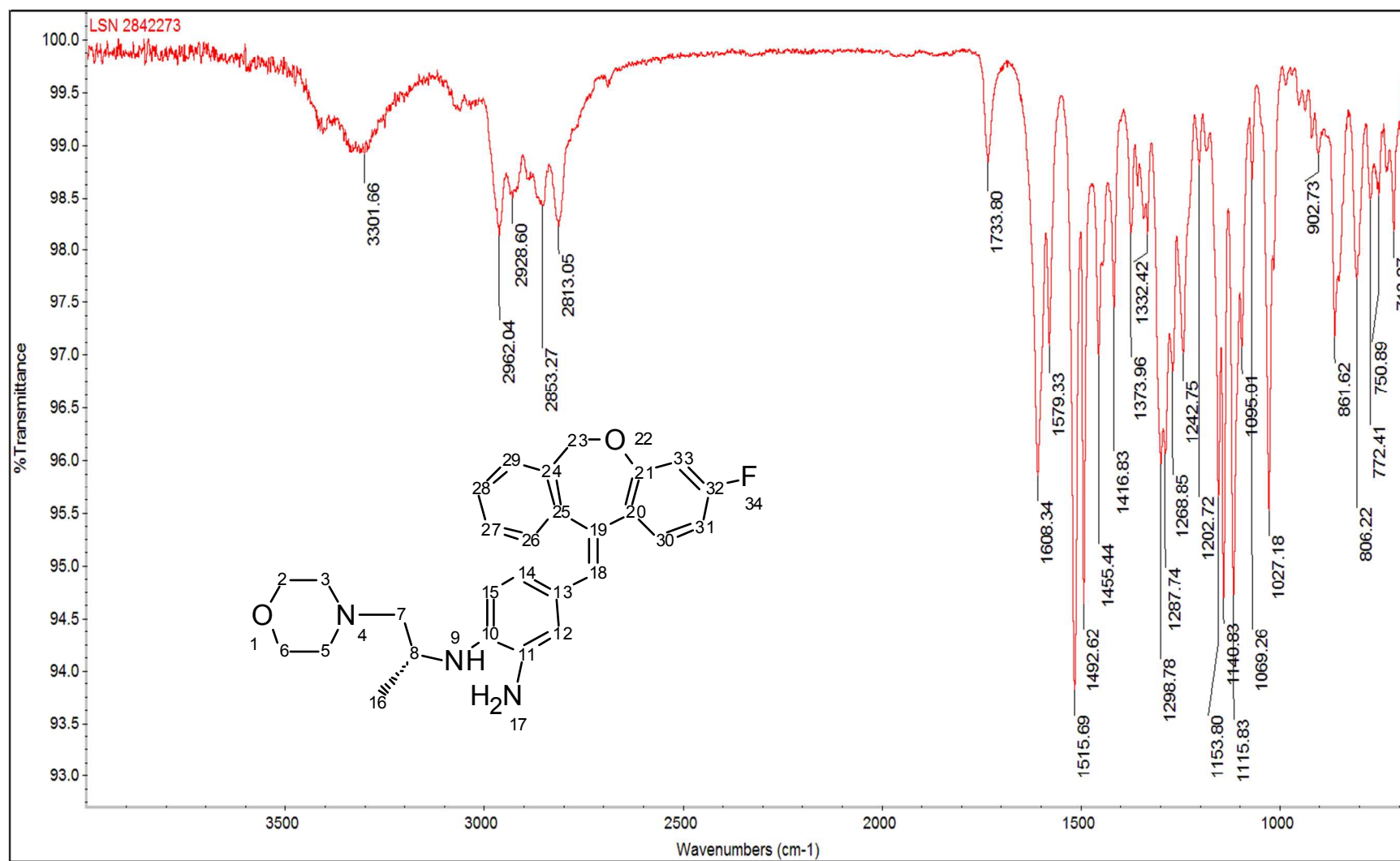
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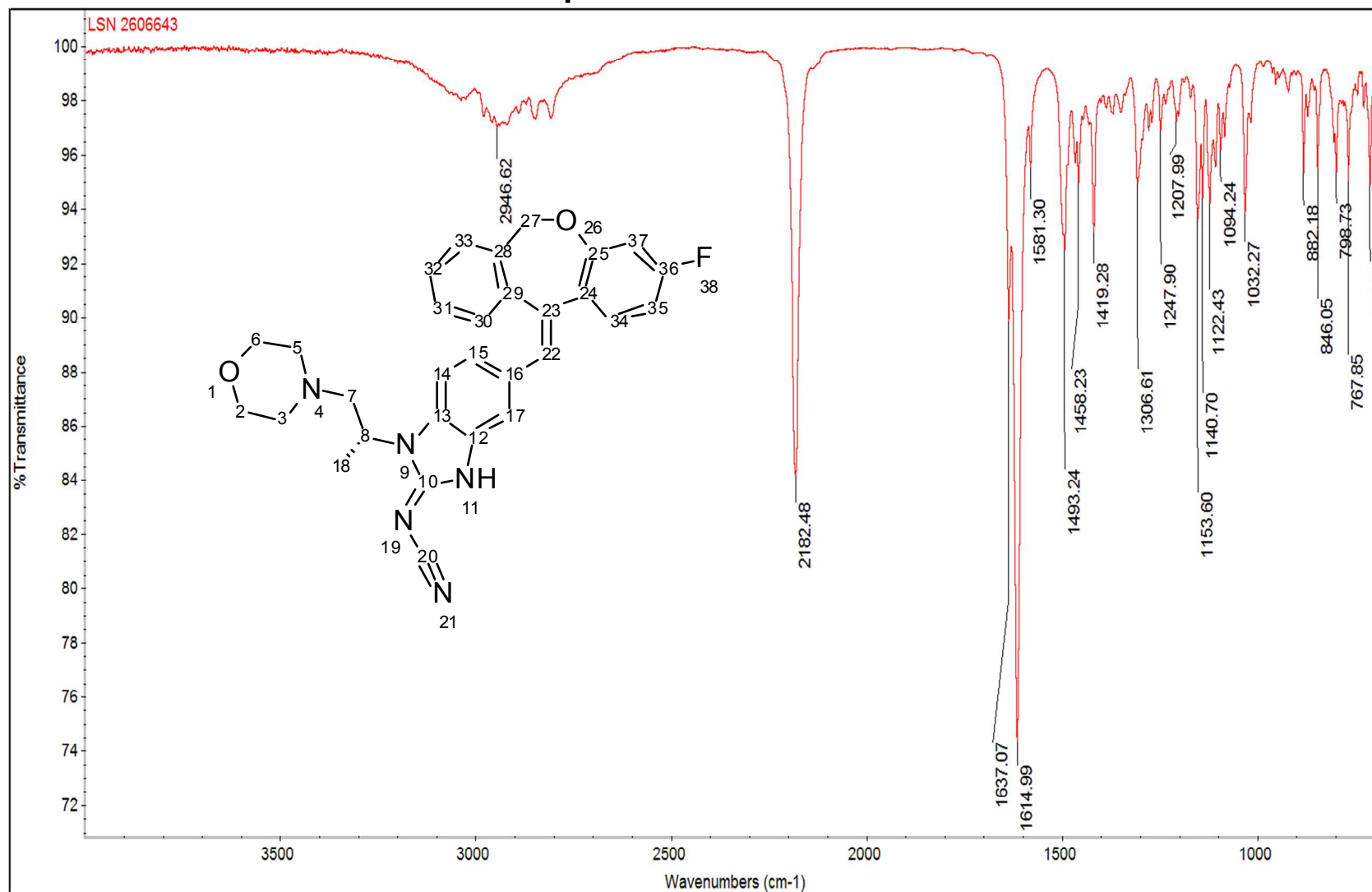
Compound #18 IR



Compound #7 IR



Compound #8 IR



Compound #1 IR

