Acid-Catalyzed Aza-Diels Alder Reactions for the Total Synthesis of (±)-Lapatin B

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Computational Methods: (a) All the geometries in Table S1 were fully optimized with GAUSSIAN (ref. b) at the B3LYP/6-31G(d) level followed by frequency calculations to determine the nature of the stationary points. The reported gas-phase enthalpies come from B3LYP/6-31+G(d,p) energy calculations on the geometries optimized at the lower level, and include enthalpy corrections (298 K) at the same level of the geometry, B3LYP/6-31G(d). Enthalpies in solution were computed by addition of the solvation free energies in Chloroform, Dichloromethane or Acetonitrile to the gas-phase enthalpies. Solvation free energies were computed as the energy differences between HF/6-31+G(d,p) single point energy calculations, on the DFT gas-phase geometries, in the corresponding solvent (PCM model (ref. c,d) and UAKS radii) and in gas-phase (ref. e). (b) Gaussian 03, Revision C.02, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, Jr., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; and Pople, J. A.; Gaussian, Inc., Wallingford CT, 2004. (c) Mennucci, B.; Cammi, R.; Tomasi, J. *J. Chem. Phys.* **1999**, *110*, 6858-6870; (d) Cossi, M.; Scalmani, G.; Rega, N.; Barone, V. *J. Chem. Phys.* **2002**, *117*, 43-54. (e) Takano, Y.; Houk, K. N. *J. Chem. Theory and Comput.* **2005**, *1*, 70-77.

Table S1.

	Gas-phase				$CHCl_3$	CH_2Cl_2	CH_3CN
	H_0	E	H_{298}	G_{298}	ΔG_{sol}	ΔG_{sol}	ΔG_{sol}
TS16 (exo)	–1332.858941	–1333.251839	–1332.833193	–1332.913631	0.20	–3.23	4.93
TS17 (endo)	–1332.862003	–1333.255069	–1332.836290	–1332.916813	1.61	–1.43	6.99

Coordinates:

TS16 (exo)

C	0.321371	0.228873	1.567822
C	-0.009822	1.823928	-0.606496
C	1.027296	-0.738080	-1.282085
C	0.736435	0.489385	-1.888398
H	1.563631	1.088331	-2.265260
H	-0.160120	0.517651	-2.504338
H	-0.253253	2.608039	-1.312210
C	1.051654	1.995557	0.315205
N	1.244058	1.161234	1.331907
O	1.964358	2.927854	0.015030
N	-1.148086	1.180546	-0.082501
C	-2.373877	1.325520	-0.793220
O	-2.425986	2.066448	-1.768219
C	-0.998331	0.268807	0.959794
N	-1.971964	-0.471489	1.428121
C	-3.209540	-0.336651	0.852861
C	-3.463531	0.545815	-0.229814
C	-4.753094	0.647196	-0.781051
H	-4.904086	1.325307	-1.614741
C	-4.284142	-1.100306	1.365426
H	-4.080523	-1.772206	2.193105
C	-5.789680	-0.107331	-0.261016
H	-6.787643	-0.028901	-0.682340
C	-5.547457	-0.984515	0.816793
H	-6.364809	-1.577096	1.219594
C	0.630228	-0.817304	2.589479
H	-0.279136	-1.171299	3.077167
H	1.105598	-1.677737	2.095420
H	1.342407	-0.422306	3.318094
C	0.018406	-1.817492	-1.137199
O	-1.172679	-1.809583	-1.422265
N	0.709533	-2.899457	-0.578866
C	2.284360	-1.261280	-0.799877
C	3.576280	-0.731822	-0.718457
H	3.775283	0.282036	-1.056494
C	2.054506	-2.600975	-0.378117
C	4.610845	-1.525410	-0.215636
H	5.617387	-1.122138	-0.151166
C	4.362705	-2.839084	0.199077
H	5.178642	-3.444218	0.584386
C	3.079225	-3.395969	0.120634
H	2.895825	-4.420130	0.433747
H	0.258036	-3.780214	-0.380584
C	3.162844	2.988460	0.826148
H	2.876452	3.173489	1.866042
H	3.664216	2.015689	0.787681
C	4.022791	4.104803	0.265124
H	4.943042	4.190690	0.852783
H	4.295739	3.905315	-0.776091
H	3.496145	5.063348	0.306227

TS17 (endo)

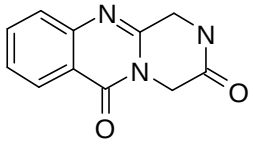
C	-0.849812	-0.281571	1.642172
C	-1.072730	-1.651907	-0.691834
C	-1.070294	1.163980	-1.091359
C	-1.269704	-0.016168	-1.818575
H	-2.292456	-0.217046	-2.131891
H	-0.506205	-0.319307	-2.531890
H	-1.120610	-2.397378	-1.475413
C	-2.148220	-1.513619	0.224423
N	-2.039111	-0.789712	1.338055
O	-3.325821	-1.993241	-0.166571
C	-4.515402	-1.530308	0.533264
H	-4.499758	-0.437447	0.528024
H	-4.467174	-1.880191	1.568975
C	-5.709500	-2.102551	-0.204936
H	-6.632111	-1.787123	0.294281
H	-5.737919	-1.741960	-1.237849
H	-5.681410	-3.197027	-0.217878
N	0.211880	-1.521955	-0.128619
C	1.316681	-2.041049	-0.860251
O	1.123426	-2.660250	-1.901059
C	0.377329	-0.719345	0.996117
N	1.541367	-0.413570	1.515064
C	2.660560	-0.924769	0.909481
C	2.603256	-1.744393	-0.250084
C	3.784169	-2.244568	-0.830974
H	3.698206	-2.862179	-1.719268
C	3.929552	-0.630659	1.463115
H	3.963587	-0.002800	2.347651
C	5.011968	-1.947098	-0.268576
H	5.924534	-2.335537	-0.711123
C	5.078381	-1.134570	0.883752
H	6.046389	-0.902514	1.320193
C	-0.742880	0.655949	2.802950
H	-0.101989	0.234165	3.585232
H	-0.267462	1.592871	2.488714
H	-1.738495	0.858653	3.200940
C	0.087828	2.016404	-0.922266
C	-0.333119	3.154405	-0.179583
C	1.418506	1.936113	-1.344585
C	0.537797	4.189335	0.136110
C	2.300310	2.972733	-1.029899
H	1.765805	1.079412	-1.916123
C	1.864738	4.084187	-0.299249
H	0.201523	5.056048	0.698738
H	3.334864	2.913922	-1.355063
H	2.564161	4.881554	-0.063854
C	-2.209114	1.839162	-0.426552
O	-3.381293	1.475949	-0.357835
N	-1.688371	3.012719	0.119175
H	-2.266162	3.693680	0.589638

Experimental Procedures

General remarks: All experiments were carried out under an argon atmosphere. Solvents and reagents were used without further purification. A Biotage Initiator Sixty as well as a Personal Chemistry Emrys Optimizer Microwave reactors were employed for reactions requiring microwave irradiation.

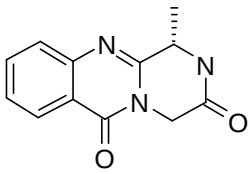
Preparation of Quinazolines **10**, **11** and **12**:

A mixture of anthranilic acid (2.74 g, 20 mmol), *N*-Boc-amino acid (20 mmol, 1equiv.) and triphenyl phosphite (5.77 mL, 22mmol, 1.1 equiv.) in pyridine (30 mL) was heated for 16 h at 55 °C. The reaction mixture was cooled down and glycine methyl ester hydrochloride (2.51g, 20 mmol, 1 equiv.) was added. The resulting mixture was dispatched into microwave adapted vials and each of them was heated at 210 °C for 10 minutes. The reaction mixtures were then combined and concentrated in *vacuo*, and the residue was purified by silica gel flash chromatography (using a gradient from a 1:1 mixture of dichloromethane: ethyl acetate to a 50:50:5 dichloromethane : ethyl acetate : methanol mixture as eluent).



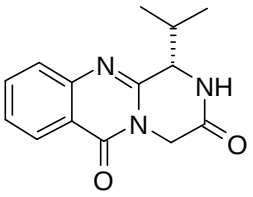
MW = 215.213
MF = $C_{11}H_9N_3O_2$

2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione (**10)**. 2.11 g, 49%. White solid. Mp 278-280 °C. MS (API-ES, positive), 216 (M+1). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 4.42 (d, *J* = *2*.6 Hz, 2H, CH_2), 4.52 (s, 2H, CH_2), 7.52 (dd, *J* = *7*.0, 8.1 Hz, 1H arom.), 7.63 (d, *J* = *7*.7 Hz, 1H arom.), 7.82 (ddd, *J* = *1*.4, 7.3, 8.4 Hz, 1H arom.), 8.11 (dd, J = 1.1, 7.7 Hz, 1H arom.), 8.58 (bs, 1H, N*H*). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 44.7 (CH_2), 44.8 (CH_2), 119.7 (C arom.), 126.2 (CH arom.), 126.7 (CH arom.), 126.8 (CH arom.), 134.7 (CH arom.), 147.1 (C arom.), 150.1 (CN), 159.8 (CO), 166.1 (CH_2*C*O). HRMS (DCI/NH_3): Calcd. for $C_{11}H_{10}N_3O_2$ m/z 216.0768; Found 216.0763.



MW = 229.240
MF = $C_{12}H_{11}N_3O_2$

(1*S*)-1-Methyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione **(11)**, 2.29 g, 50%. White solid. Mp 217-218 °C. MS (API-ES, positive), 230 (M+1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.73 (d, *J* = 7.0 Hz, 3H, Me), 4.70 (dq, *J* = 2.6, 7.0 Hz, 1H, C*H*Me), 4.76 (s, 2H, CH_2), 7.04 (bs, 1H, N*H*), 7.51 (ddd, *J* = 1.1, 7.0, 8.4 Hz, 1H arom.), 7.68 (dd, *J* = 1.1, 8.4 Hz, 1H arom.), 7.78 (ddd, *J* = 1.5, 7.3, 8.1 Hz, 1H arom.), 8.29 (dd, J = 1.1, 8.1 Hz, 1H arom.). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.3 (Me), 44.6 (CH_2), 51.5 (CH), 120.1 (C arom.), 126.9 (CH arom.), 127.3 (CH arom.), 127.4 (CH arom.), 134.8 (CH arom.), 147.1 (C arom.), 151.1 (CN), 160.6 (CO), 166.4 (CH_2*C*O).

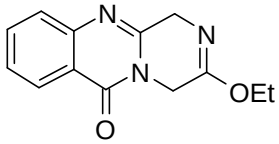


MW = 257.295
MF = $C_{14}H_{15}N_3O_2$

(1*S*)-1-isopropyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione (**12**), 2.06 g, 40%. White solid. Mp 194-196 °C. MS (API-ES, positive), 258 (M+1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.99 (d, *J* = 6.5 Hz, 3H, CHMe*Me*), 1.11 (d, *J* = 6.0 Hz, 3H, CH*Me*Me), 2.47 (m, 1H, C*H*Me$_2$), 4.39 (A of AB, J_{AB} = 9.0 Hz, 1H, C*H*H), 4.22 (q, *J* = 6.8 Hz, 2H, *CH*$_2$Me), 5.00 (B of AB, J_{AB} = 9.0 Hz, 1H, CH*H*), 6.54 (bs, 1H, NH), 7.52 (ddd, *J* = 1.1, 7.0 Hz, 1H arom.), 7.68 (dd, *J* = 1.2, 7.8 Hz, 1H arom.), 7.52 (ddd, *J* = 1.4, 7.2, 7.9 Hz, 1H arom.), 7.68 (dd, *J* = 1.5, 8.6 Hz, 1H arom.). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 17.0 (CHMe*Me*), 19.2 (CH*Me*Me), 35.1 (CH), 44.8 (CH), 61.8 (CH), 119.8 (C arom.), 126.9 (CH arom.), 127.1 (CH arom.), 127.4 (CH arom.), 135.0 (CH arom.), 146.9 (C arom.), 160.7 (CO), 166.0 (CO). HRMS (DCI/NH_3): Calcd. for $C_{14}H_{16}N_3O_2$ m/z 258.1235; Found 258.1237.

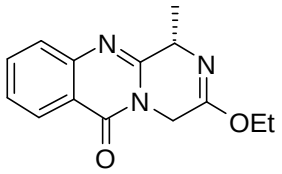
Preparation of iminoethers **13**, **14** and **15**:

To a solution of the quinazoline (**10**, **11**, **12**) (3 mmol) in anhydrous dichloromethane (200 mL), under argon, was added anhydrous sodium carbonate (1.95 g, 18.0 mmol) and triethyloxonium tetrafluoroborate (870 mg, 4.5 mmol). The mixture was stirred at room temperature for 24h. The solid was filtered off and the resulting filtrate was washed with saturated aqueous sodium carbonate solution and brine and dried over $MgSO_4$. After evaporation of the solvent the crude was purified by flash chromatography (SiO_2, hexane: ethyl acetate 1:1).



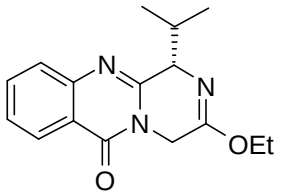
MW = 243.267
MF = $C_{13}H_{13}N_3O_2$

Iminoether **13**, 546 mg, 75%. White solid. Mp 152-155 °C. MS (API-ES, positive), 244 (M+1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.35 (t, *J* = 7.3 Hz, 3H, Me), 4.70 (q, *J* = 7.4 Hz, 2H, C*H*$_2$Me), 4.58 (AB , J_{AB} = 1.8, 1.9 Hz, 2H, C*H*$_2$), 4.76 (AB , J_{AB} = 1.4, 2.0 Hz, 2H, C*H*$_2$), 7.77 (ddd, *J* = 1.4, 7.0, 8.4 Hz, 1H arom.), 7.67 (dd, *J* = 1.2, 8.1 Hz, 1H arom.), 7.77 (ddd, *J* = 1.4, 7.0, 8.4 Hz, 1H arom.), 8.28 (dd, *J* = 1.2, 8.0 Hz, 1H arom.). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.5 (Me), 40.7 (CH_2), 51.5 (CH_2), 62.1 (CH_2), 120.0 (CH arom.), 126.7 (CH arom.), 126.9 (CH arom.), 134.7 (CH arom.), 147.5 (C arom.), 150.3 (CN), 160.0 (CNO), 160.8 (CO). HRMS (DCI/NH_3): Calcd. for $C_{13}H_{14}N_3O_2$ m/z 244.1081; Found 244.1078.



MW = 257.295
MF = $C_{14}H_{15}N_3O_2$

Iminoether **14**, 533 mg, 69%. White solid. Mp 155-157 °C. MS (API-ES, positive), 258 (M+1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.31 (t, *J* = 7.0 Hz, 3H, CH_2*Me*), 1.56 (d, *J* = 7.0 Hz, 3H, CH*Me*), 4.22 (dq, *J* = 1.5, 7.0 Hz, 2H, *CH*$_2$Me), 4.34 (A of AB, J_{AB} = 17.2 Hz, 1H, C*H*H), 4.73 (B of AB , J_{AB} = 17.2 Hz, 1H, CH*H*), 4.79 (q, *J* = 7.0 Hz, 1H, C*H*Me), 7.47 (dd, *J* = 1.1, 8.1 Hz, 1H arom.), 7.63 (d, *J* = 8.1 Hz, 1H arom.), 7.76 (ddd, *J* = 1.5, 6.9, 8.4 Hz, 1H arom.), 8.22 (dd, *J* = 1.5, 8.1 Hz, 1H arom.). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1 (Me), 21.8 (Me), 40.5 (CH_2), 56.6 (C*H*Me), 62.0 (*CH*$_2$Me), 119.8 (C arom.), 126.6 (2CH arom.), 127.1 (CH arom.), 134.6 (CH arom.), 147.6 (C arom.), 154.1 (CN), 159.1 (OCN), 160.9 (CO).

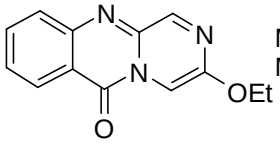


MW = 285.349
MF = $C_{16}H_{19}N_3O_2$

Iminoether **15**, 685 mg, 80%. White solid. Mp 102-104 °C. MS (API-ES, positive), 286 (M+1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.83 (d, *J* = 6.9 Hz, 3H, CHMe*Me*), 1.14 (d, *J* = 6.6 Hz, 3H, CH*Me*Me), 1.36 (t, *J* = 6.9 Hz, 3H, Me), 2.50 (hept, *J* = 6.9 Hz, 1H, C*H*Me$_2$) 4.30 (m, 3H, C*H*H+C*H*$_2$Me), 4.67 (d, *J* = 4.4 Hz, 1H), 4.73 (B of AB , J_{AB} = 18.7 Hz, 2H, C*H*$_2$), 7.47 (dd, *J* = 8.1, 7.0 Hz, 1H arom.), 7.68 (d, *J* = 7.7 Hz, 1H arom.), 7.76 (dd, *J* = 7.0, 8.4 Hz, 1H arom.), 8.27 (d, *J* = 8.0 Hz, 1H arom.). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.2 (Me), 17.1 (Me), 19.8 (Me), 35.6 (C*H*Me$_2$), 41.1 (CH_2), 61.8 (CH_2), 65.7 (CH), 119.7 (C arom.), 126.6 (2CH arom.), 127.0 (CH arom.), 134.7 (CH arom.), 147.5 (C arom.), 153.1 (CN), 157.9 (OCN), 161.1 (CO).

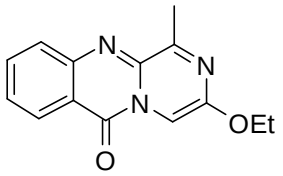
Preparation of dienes **7, 8** and **9**:

To a solution of the iminoether (**13**, **14** or **15**) (3mmol, 1equiv.) in benzene (55mL), at 50 °C, a solution of DDQ (750 mg, 3.3 mmol, 1.1 equiv.) in benzene (22mL) was added slowly. After the reaction was complete, the reaction mixture was cooled down and filtered through neutral alumina (the alumina was rinsed several times with dichloromethane). When necessary, a further purification by flash chromatography was performed (SiO_2, dichloromethane: ethyl acetate 90:10).



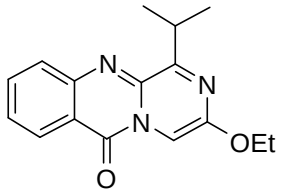
MW = 241.252
MF = $C_{13}H_{11}N_3O_2$

2-Aza-diene **8**, 369 mg, 51%. Yellow solid. Mp 129-130 °C. MS (API-ES, positive), 242 (M+1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.52 (t, *J* = 7.3 Hz, 3H, Me), 4.29 (q, *J* = 7.3 Hz, 2H, C*H*$_2$Me), 7.61 (m, 2H arom.), 7.92 (d , *J* = 4.2 Hz, 1H arom.), 8.07 (s, 1H, C=ONCH), 8.49 (d, *J* = 7.8 Hz, 1H arom.), 8.92 (s, 1H, CONCH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.6 (Me), 64.4 (CH_2), 97.3 (CH), 117.0 (C arom.), 127.0 (CH arom.), 127.1 (CH arom.), 127.9 (CH arom.), 134.9 (CH arom.), 139.5 (NC=O), 147.7 (C arom.), 152.4 (NC=N), 153.1 (CCHN), 157.5 (CO). HRMS (DCI/NH_3): Calcd. for $C_{13}H_{12}N_3O_2$ m/z 242.0924; Found 242.0925.



MW = 255.279
MF = $C_{14}H_{13}N_3O_2$

2-Aza-diene **7**, 613 mg, 80%. Yellow solid. Mp 149-151 °C. MS (API-ES, positive), 256 (M+1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.52 (t, *J* = 6.8 Hz, 3H, CH_2*Me*), 2.94 (s, 3H, Me), 4.22 (q, *J* = 6.8 Hz, 2H, *CH*$_2$Me), 7.58 (ddd, *J* = 1.5 Hz , *J* = 7.0, 8.4 Hz, 1H arom.), 7.87 (ddd, *J* = 1.5 Hz , *J* = 7.0, 8.0 Hz, 1H arom.), 7.91 (ddd, *J* = 1.1 Hz , *J* = 7.0, 8.4 Hz, 1H arom.), 7.97 (s, 1H arom.), 8.46 (ddd, *J* = 1.1 Hz , *J* = 7.3, 8.1 Hz, 1H arom.). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.6 (Me), 21.8 (Me), 64.3 (CH_2), 95.2 (CH), 117.0 (C arom.), 127.0 (2CH arom.), 128.3 (CH arom.), 134.6 (CH arom.), 139.1 (Me*C*N), 147.2 (C arom.), 151.2 (CN), 158.1 (NC=O), 162.0 (CO).



MW = 283.333
MF = $C_{16}H_{17}N_3O_2$

2-Aza-diene **9**, 679 mg, 80%. Yellow solid. Mp 120-123 °C MS (API-ES, positive), 284 (M+1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.41 (d, *J* = 6.5 Hz, 3H, Me), 1.53 (t, *J* = 7.0 Hz, 3H, Me), 4.25 (q, *J* = 6.9 Hz, 2H, C*H*$_2$Me), 4.32 (hept, *J* = 6.8 Hz, 1H, C*H*Me$_2$), 7.61 (ddd, *J* = 1.5, 7.0, 8.4 Hz, 1H, 1CH arom.), 7.88 (m , 2H, CH arom.), 7.98 (s, 1H, NCH), 8.45 (dd, *J* = 1.4, 7.4 Hz, 1H arom.). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.7 (CH_2Me), 21.0 (CH*Me*$_2$), 30.6 (C*H*Me$_2$), 64.1 (CH_2), 95.0 (CH), 116.9 (C arom.), 126.7 (CH arom.), 126.9 (CH arom.), 128.3 (CH arom.), 134.5 (CH arom.), 138.1 (NC=O), 147.2 (C arom.), 151.4 (NC=N), 158.2 (iPrCN), 159.0 (CO). HRMS (DCI/NH_3): Calcd. for $C_{16}H_{18}N_3O_2$ m/z 284.1394; Found 284.1392.

Aza Diels-Alder reactions:

Solvent studies:

To a solution of 2-aza-diene **7** (25.6 mg, 0.1 mmol) in chloroform (2.5mL) (or dichloromethane, or acetonitrile), methyleneoxindole (17.5 mg, 0.12 mmol, 1.2 equiv.) was added. After completion of the reaction, the reaction mixture was concentrated in vacuo and purified by flash chromatography (SiO_2, 7:3 to 6:4 hexane:ethyl acetate gradient) to afford the two diastereomers **16** and **17** (**16** being less polar than **17**).

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Conditions A:

To a solution of aza-diene **7** (25.6 mg, 0.1 mmol) in 2.5mL dichloromethane (2.5 mL), at −78 °C, 1 equiv. of Lewis acid was added. After 1 min, methyleneoxindole (17.5 mg, 0.12 mmol, 1.2 equiv.) was added and the reaction allowed to reach 0 °C. The reaction was complete upon reaching this temperature. The reaction was then quenched with an aqueous saturated solution of sodium bicarbonate. The aqueous phase was extracted three times with ethyl acetate. The organic layers were combined, washed with brine, and dried over sodium sulfate. After evaporation, the crude was purified by flash chromatography.

Conditions **B**:

Same as conditions **A**, the reaction using 1 equivalent of $BF_3{\cdot}Et_2O$ or $Cu(OTf)_2$ as Lewis acid was complete at −78 °C within 1 h.

Conditions **C**:

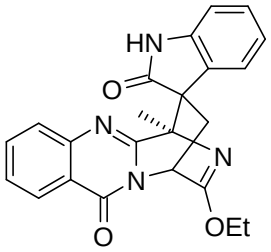
Same as conditions **A**, but the reaction mixture was constantly maintained at 0 °C.

Conditions **D**:

Same as conditions **A**, but the reaction mixture was constantly maintained at −20 °C.

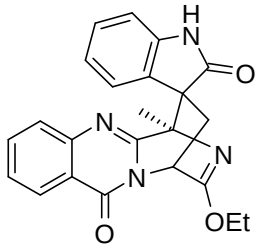
Conditions **E**:

Same as conditions **A**, but the reaction mixture was allowed to reach room temperature and stay for 12 h at this temperature. Alantrypinone **1** was obtained by precipitation in dichloromethane.



MW = 400.441
MF = $C_{23}H_{20}N_4O_3$

Iminoether **16**. White solid. Mp 234-235 °C. MS (API-ES, positive), 401 (M+1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.42 (t, *J* = 7.0 Hz, 3H, CH_2*Me*), 1.53 (s, 3H, Me), 2.24 (A of ABX, J_{AB} = 13.7 Hz, J_{AX} = 2.9 Hz, 1H, CH*H*), 2.56 (B of ABX, J_{AB} = 13.7 Hz, J_{BX} = 2.2 Hz, 1H, C*H*H), 4.35 (m, 2H, *CH*$_2$Me), 6.05 (dd, *J* = 2.6, 2.9 Hz, 1H, CH), 6.70 (d, *J* = 7.7 Hz, 1H arom.), 7.04 (m, 2H arom.), 7.20 (dd, *J* = 1.5 Hz , *J* = 7.7 Hz, 1H arom.), 7.48 (m, 1H), 7.73 (d, *J* = 3.3 Hz, 1H), 8.22 (s, 1H, NH), 8.32 (d, *J* = 7.7 Hz, 1H arom.). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.2 (Me), 16.8 (Me), 37.8 (CH_2), 47.6 (CH), 54.7 (C), 63.7(CH_2), 67.0 (C), 109.9 (CH arom.), 120.3 (C arom.), 122.9 (CH arom.), 124.3 (CH arom.), 126.7 (CH arom.), 126.8 (CH arom.), 128.0 (CH arom.), 128.9 (CH arom.), 130.8 (C arom.), 134.2 (CH arom.), 141.3 (C arom.), 147.6 (C arom.), 154.2 (NC=N), 159.4 (NC=O), 172.7 (N=COEt), 178.1 (HNC=O).

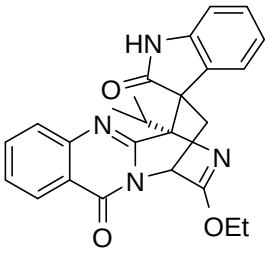


MW = 400.441
MF = $C_{23}H_{20}N_4O_3$

Iminoether **17**. White solid. Mp 257-259 °C. MS (API-ES, positive), 401 (M+1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.40 (t, *J* = 7.0 Hz, 3H, CH_2*Me*), 1.60 (s, 3H, Me), 2.25 (A of ABX, J_{AB} = 13.7 Hz, J_{AX} = 3.3 Hz, 1H, CH*H*), 2.58 (B of ABX, J_{AB} = 13.7 Hz, J_{BX} = 0.7 Hz, 1H, C*H*H), 4.27 (m, 1H, *C*H*H*Me), 4.42 (m, 1H, *CH*HMe), 5.84 (d, *J* = 7.7 Hz, 1H arom.), 6.06 (s, 1H, CH), 6.72 (t, *J* = 7.7 Hz, 1H arom.), 6.85 (d, *J* = 7.7 Hz, 1H arom.), 7.16 (t, *J* = 7.7 Hz, 1H arom.), 7.55 (t, *J* = 7.3 Hz, 1H arom.), 7.73 (d, *J* = 8.1 Hz, 1H arom.), 7.79 (dd, *J* = 7.0, 8.4 Hz, 1H arom.), 7.88 (s, 1H, NH), 8.38 (d, *J* = 7.7 Hz, 1H arom.). ^{13}C NMR (100 MHz, $CDCl_3$)δ: 14.1 (Me), 17.0 (Me), 37.2 (CH_2), 48.1 (CH), 53.1 (C), 63.9 (CH_2), 67.2 (C), 109.5 (CH arom.), 120.2 (C arom.), 122.7 (CH arom.), 123.4 (CH arom.), 126.9 (CH arom.), 127.2 (CH arom.), 128.2 (CH arom.), 128.9 (CH arom.), 130.2 (C arom.), 134.7 (CH arom.), 141.0 (C arom.), 147.2 (C arom.), 153.8 (NC=N), 159.2 (NC=O), 171.5 (N=COEt), 178.1 (HNC=O).

To a solution of aza-diene **9** (47 mg, 0.17 mmol) in dichloromethane (2.5 mL), at –20 °C, triflic acid (4 μL, 0.2 equiv.) was added. After 1 min, methyleneoxindole (29 mg, 0.2 mmol, 1.2 equiv.) was added. The reaction was complete after 1 h. The reaction was then quenched with an aqueous saturated solution of sodium bicarbonate. The aqueous phase was extracted three times with ethyl acetate. The organic layers were combined, washed with brine, and dried over sodium sulfate. After

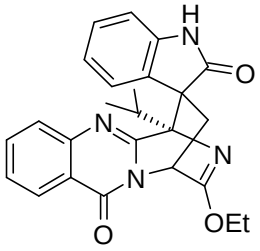
evaporation, the crude was purified by flash chromatography. SiO_2, 8:2 to 7:3 hexane:ethyl acetate gradient) to afford the **18** (53 mg, 75%).



MW = 428.495
MF = $C_{25}H_{24}N_4O_3$

Iminoether **18**. White solid. Mp 240-242 °C. MS (API-ES, positive), 429 (M+1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.21 (d, *J* = 6.6 Hz, 3H, CHMe*Me*), 1.29 (d, *J* = 7.1 Hz, 3H, CHMe*Me),* 1.41 (d, *J* = 7.1, 6.6 Hz, 3H, CH_2*Me*), 2.10 (A of ABX, J_{AB} = 13.4 Hz, J_{AX} = 1.9 Hz, 1H, CH*H*), 2.31 (hept, *J* = 7.1 Hz, 1H, C*H*MeMe), 2.50 (B of ABX, J_{AB} = 13.4 Hz, J_{BX} = 3.6 Hz, 1H, C*H*H), 4.40 (m, 1H, *C*H_2Me), 5.99 (m, 1H, CH), 6.70 (d, *J* = 7.7 Hz, 1H arom.), 7.01 (dd, *J* = 7.7, 8.2 Hz, 1H arom.), 7.23 (m, 2H arom.), 7.47 (m, 1H arom.), 7.72 (m, 2H arom.), 8.06 (s, 1H, NH), 8.32 (d, *J* = 7.7 Hz, 1H arom.). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.3 (Me), 17.4 (Me), 19.1 (Me), 34.0 (CH), 41.9 (CH_2), 47.1 (CH), 53.9 (C), 63.4 (CH_2), 71.8 (C), 110.1 (CH arom.), 120.3 (C arom.), 122.9 (CH arom.), 124.9 (CH arom.), 126.5 (CH arom.), 126.7 (CH arom.), 128.3 (CH arom.), 128.8 (CH arom.), 131.6 (C arom.), 134.0 (CH arom.), 140.4 (C arom.), 147.4 (C arom.), 153.4 (NC=N), 159.8 (NC=O), 171.7 (N=COEt), 179.4 (HNC=O). HRMS (DCI/NH_3): Calcd. for $C_{25}H_{25}N_4O_3$ m/z 429.1921; Found 429.1917.

To a solution of aza-diene **9** (39 mg, 0.14 mmol) in dichloromethane (4 mL), at room temperature, $Eu(fod)_3$ (143mg, 0.14 mmol, 1 equiv.) was added. After 1 min, methyleneoxindole (24 mg, 0.17 mmol, 1.2 equiv.) was added. The reaction was complete after 16 h. The reaction was then quenched with an aqueous saturated solution of sodium bicarbonate. The aqueous phase was extracted three times with ethyl acetate. The organic layers were combined, washed with brine, and dried over sodium sulfate. After evaporation, the crude was purified by flash chromatography. SiO_2, 9:1 to 8:2 hexane:ethyl acetate gradient) to afford the **19** (42 mg, 71%).

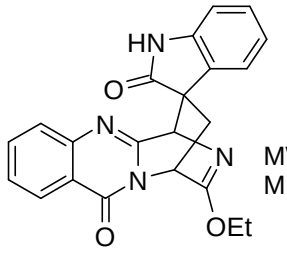


MW = 428.495
MF = $C_{25}H_{24}N_4O_3$

Iminoether **19.** White solid. Mp 235-237 °C. MS (API-ES, positive), 429 (M+1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.09 (d, *J* = 6.6 Hz, 3H, CHMe*Me*), 1.16 (d, *J* = 6.9 Hz, 3H, CH*Me*Me), 1.41 (dd, *J* = 7.3, 6.9 Hz, 3H, CH_2*Me*), 2.05 (A of ABX, J_{AB} = 13.6 Hz, J_{AX} = 2.9 Hz, 1H, CH*H*), 2.53 (B of ABX, J_{AB} = 13.6 Hz, J_{BX} = 2.2 Hz, 1H, C*H*H), 2.59 (m, 1H, C*H*MeMe), 4.36 (m, 1H, *C*H*H*Me), 4.49 (m, 1H, *CH*HMe), 6.01 (d, *J* = 8.1 Hz, 1H arom.), 6.02 (m, 1H, CH), 6.73 (td, *J* = 7.7, 1.1 Hz,

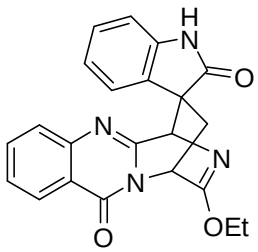
1H arom.), 6.83 (d, *J* = 7.3 Hz, 1H arom.), 7.15 (td, *J* = 7.7, 1.1 Hz, 1H arom.), 7.56 (td, *J* = 1.5, 8.1 Hz, 1H arom.), 7.77 (d, *J* = 8.1 Hz, 1H arom.), 7.72-7.83 (m, 3H, 1NH +2H arom.), 8.38 (dd, *J* = 1.5, 8.1 Hz, 1H arom.). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.2 (Me), 18.3 (Me), 19.5 (Me), 31.1 (CH), 42.0 (CH_2), 47.2 (CH), 52.5 (C), 63.6 (CH_2), 71.4 (C), 109.6 (CH arom.), 120.2 (C arom.), 122.8 (CH arom.), 123.9 (CH arom.), 126.8 (CH arom.), 127.2 (CH arom.), 128.4 (CH arom.), 128.6 (CH arom.), 131.1 (C arom.), 134.5 (CH arom.), 140.4 (C arom.), 147.1 (C arom.), 153.1 (NC=N), 159.2 (NC=O), 170.2 (N=COEt), 178.1 (HNC=O). HRMS (DCI/NH_3): Calcd. for $C_{25}H_{25}N_4O_3$ m/z 429.1921; Found 429.1918.

To a solution of aza-diene **8** (72 mg, 0.30 mmol) in dichloromethane (7 mL), at –20 °C, triflic acid (5 μL, 0.2 equiv.) was added. After 1 min, methyleneoxindole (52 mg, 0.36 mmol, 1.2 equiv.) was added. The reaction was complete after 1 h. The reaction was then quenched with an aqueous saturated solution of sodium bicarbonate. The aqueous phase was extracted three times with ethyl acetate. The organic layers were combined, washed with brine, and dried over sodium sulfate. After evaporation, the crude was purified by flash chromatography. SiO_2, 6:4 to 5:5 hexane : ethyl acetate gradient) to afford the **20** (37 mg, 32%) and **21** (38mg, 33%) (**20** being less polar than **21**).



MW = 386.414
MF = $C_{22}H_{18}N_4O_3$

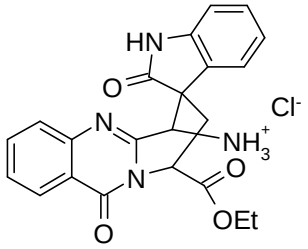
Iminoether **20**. White solid. Mp 277-278 °C. MS (API-ES, positive), 387 (M+1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.44 (t, *J* = 7.0 Hz, 3H, CH_2*Me*), 2.20 (A of ABX, J_{AB} = 13.6 Hz, J_{AX} = 2.4 Hz, 1H, CH*H*), 2.57 (B of ABX, J_{AB} = 13.8 Hz, J_{BX} = 3.1 Hz, 1H, C*H*H), 4.38 (m, 2H, *CH*$_2$Me), 4.85 (s, 1H, CH), 6.06 (dd, *J* = 2.4, 3.1 Hz, 1H, CH), 6.76 (d, *J* = 7.7 Hz, 1H arom.), 7.02 (ddd, *J* = 1.1, 7.3, 7.7 Hz, 1H arom.), 7.05 (dd, *J* = 1.5 Hz , *J* = 7.7 Hz, 1H arom.), 7.22 (td, *J* = 1.5, 7.7 Hz, 1H arom.), 7.48 (m, 1H arom.), 7.68 (d, *J* = 7.3 Hz, 1H), 7.74 (m, 1H arom.), 8.27 (s, 1H, NH), 8.32 (dd, *J* = 1.0, 7.1 Hz, 1H arom.). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.2 (Me), 36.0 (CH_2), 48.3 (CH), 51.1 (C), 64.0 (CH_2), 65.9 (CH), 110.2 (CH arom.), 120.7 (C arom.), 122.8 (CH arom.), 124.4 (CH arom.), 126.9 (CH arom.), 127.0 (CH arom.), 127.6 (CH arom.), 128.9 (CH arom.), 130.8 (C arom.), 134.2 (CH arom.), 141.3 (C arom.), 147.6 (C arom.), 154.2 (NC=N), 159.4 (NC=O), 172.7 (N=COEt), 178.1 (HNC=O). HRMS (DCI/NH_3): Calcd. for $C_{22}H_{19}N_4O_3$ m/z 387.1452; Found 387.1449.



MW = 386.414
MF = $C_{22}H_{18}N_4O_3$

Iminoether **21**. White solid. Mp 165-170 °C. MS (API-ES, positive), 387 (M+1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.42 (dd, *J* = 7.0, 7.3 Hz, 3H, CH_2*Me*), 2.26(A of ABX, J_{AB} = 13.9 Hz, J_{AX} = 3.3 Hz, 1H, CH*H*), 2.54 (B of ABX, J_{AB} = 13.9 Hz, J_{BX} = 2.2 Hz, 1H, C*H*H), 4.25-4.33 (m, 1H, *CH*HMe), 4.39-4.47 (m, 1H, *CH**H*Me), 4.86 (s, 1H, CH), 5.98 (d, *J* = 7.3 Hz, 1H arom.), 6.07 (m, 1H, CH), 6.75 (ddd, *J* = 1.1, 6.7, 7.7 Hz, 1H arom.), 6.87 (d, *J* = 7.7 Hz, 1H arom.), 7.17 (ddd, *J* = 1.1, 7.7, 8.1 Hz, 1H arom.), 7.48 (ddd, *J* = 1.1, 7.0, 8.5 Hz, 1H arom.), 7.66 (dd, *J* = 7.7 Hz, 1H), 7.79 (ddd, *J* = 1.5, 7.3, 8.1 Hz, 1H arom.), 8.13 (s, 1H, NH), 8.39 (dd, *J* = 1.1, 8.1 Hz, 1H arom.). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.0 (Me), 35.0 (CH_2), 48.5 (CH), 49.7(C), 64.1(CH_2), 66.0 (CH), 110.0 (CH arom.), 120.5 (C arom.), 122.6 (CH arom.), 123.6 (CH arom.), 127.0 (CH arom.), 127.3 (CH arom.), 127.8 (CH arom.), 129.2 (CH arom.), 129.3 (C arom.), 134.8 (CH arom.), 140.6 (C arom.), 147.2 (C arom.), 151.9 (NC=N), 158.9 (NC=O), 172.3 (N=COEt), 178.4 (HNC=O). HRMS (DCI/NH_3): Calcd. for $C_{22}H_{19}N_4O_3$ m/z 387.1452; Found 387.1449.

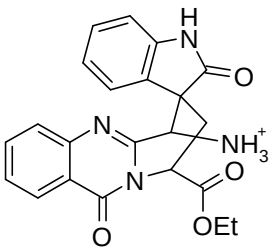
Iminoether **20** (22.3 mg, 0.058 mmol) was dissolved in 1.0 mL of ethyl acetate, and 1.05 equivalent of 2N HCl (30 μL) was added at room temperature. A precipitate was observed. 15.2 mg (0.035 mmol, 60%) of the salt **22** were isolated by filtration.



MW = 438.874
MF = $C_{22}H_{19}ClN_4O_4$

Ammonium chloride **22**. White solid. decomp 235 °C. MS (API-ES, positive), 405 (M+1). ^{1}H NMR (500 MHz, MeOD) δ: 0.95 (t, *J* = 7.2 Hz, 3H, CH_2*Me*), 2.65 (A of ABX, J_{AB} = 15.0 Hz, J_{AX} = 1.4 Hz, 1H, CH*H*), 3.04 (B of ABX, J_{AB} = 15.0 Hz, J_{BX} = 8.8 Hz, 1H, C*H*H), 3.96 (m, 2H, *CH*$_2$Me), 5.58 (m, 1H), 6.93 (m, 1H arom.), 7.01 (d, *J* = 7.0 Hz, 1H arom.), 7.07 (d, *J* = 7.7 Hz, 1H arom.), 7.34 (ddd, *J* = 1.0, 7.7, 8.0 Hz 1H arom.), 7.66 (m, 1H arom.), 7.85 (d, *J* = 7.9 Hz, 1H arom.), 7.93 (ddd, *J* = 1.5, 7.4, 8.4 Hz, 1H arom.), 8.28 (dd, *J* = 1.0, 8.1 Hz, 1H arom.). ^{13}C NMR (125 MHz, MeOD) δ: 14.0 (Me), 33.5 (CH_2), 50.3 (C), 53.2 (CH), 54.0 (CH), 63.4 (CH_2), 112.2 (CH arom.), 121.7 (C arom.), 123.2 (CH arom.), 123.9 (CH arom.), 127.8 (CH arom.), 127.8 (CH arom.), 128.6 (CH arom.), 129.5 (CH arom.), 131.7 (C arom.), 136.6 (CH arom.), 143.6 (C arom.), 147.0 (C arom.), 149.0 (NC=N), 163.1(NC=O), 169.7 (N=COEt), 178.2 (HNC=O).

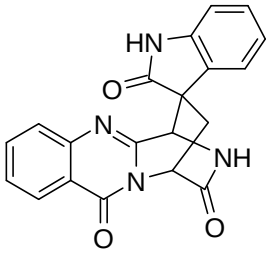
Iminoether **21** (190 mg, 0.49 mmol) was dissolved in 20 mL of ethyl acetate, and 1.0 equivalent of 1N HCl (500 μL) was added at room temperature. A precipitate was observed after 30 min. 102mg (0.24 mmol, 49%) of the salt **23** were isolated by filtration.



MW = 438.874
MF = $C_{22}H_{19}ClN_4O_4$

Ammonium chloride **23**. White solid. decomp 230 °C. MS (API-ES, positive), 405 (M+1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.29 (t, *J* = 7.1 Hz, 3H, CH_2*Me*), 2.43 (m, 2H, CH_2), 4.29(m, 2H, CH_2), 4.88 (bs, 1H, CH), 5.12 (t, *J* = 8.5 Hz, 1H, CH), 6.47 (d, *J* = 7.5 Hz, 1H, arom), 6.87 (t, *J* = 7.5 Hz, 1H arom.), 7.25 (t, *J* = 7.4 Hz, 1H arom.), 7.33 (d, *J* = 7.8 Hz, 1H arom.), 7.58 (t, *J* = 7.6 Hz, 1H arom.), 7.81 (dd, *J* = 7.0, 7.4 Hz, 1H), 7.94 (d, *J* = 7.8 Hz, 1H arom.), 8.30 (dd, *J* = 7.0, 7.8 Hz, 1H arom.), 8.67(bs, 3H), 11.31(s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.0 (Me), 35.0 (CH_2), 48.5 (CH), 49.7(C), 64.1(CH_2), 66.0 (CH), 110.0 (CH arom.), 120.5 (C arom.), 122.6 (CH arom.), 123.6 (CH arom.), 127.0 (CH arom.), 127.3 (CH arom.), 127.8 (CH arom.), 129.2 (CH arom.), 129.3 (C arom.), 134.8 (CH arom.), 140.6 (C arom.), 147.2 (C arom.), 151.9 (NC=N), 158.9 (NC=O), 172.3 (N=COEt), 178.4 (HNC=O).

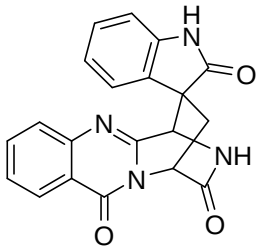
Iminoether **20** (20 mg, 0.052 mmol) was dissolved in 2.0 mL of ethyl acetate, and 1 equivalent of 2N HCl (25 μL) was added at room temperature. After 30 min at room temperature, the reaction mixture was refluxed for 90 min (LCMS analysis showed completion of the reaction). 9 mg of the lapatine B **3** were isolated by filtration. The filtrate was quenched with a saturated solution of sodium carbonate, and the aqueous phase extracted with ethyl acetate. The combined organic phases were washed with water and dried over sodium sulfate. After concentration, an additional 6.4 mg of **3** was isolated. Global yield is 83%



MW = 358.360
MF = $C_{20}H_{14}N_4O_3$

(±)-Lapatin B **3**. White solid. Mp 285 °C. MS (API-ES, positive), 387 (M+1). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.39 (d, *J* = 2.5 Hz, 2H, CH_2), 4.32 (d, *J* = 5.4 Hz, 1H, CH), 5.55 (m, 1H, CH), 6.93 (d, *J* = 7.6 Hz, 1H arom.), 7.08 (m, 1H arom.), 7.19 (d, *J* = 7.2 Hz, 1H arom.), 7.30 (ddd, *J* = 1.5, 7.6, 8.1 Hz, 1H arom.), 7.59 (m, 1H arom.), 7.66 (d, *J* = 7.8 Hz, 1H), 7.86 (m, 1H arom.), 8.21 (dd, *J* = 1.0, 8 Hz, 1H arom.), 9.64 (m, 1H, NH), 10.69 (s, 1H, NH). 13C NMR (125 MHz, DMSO- d_6) δ: 34.8 (CH_2), 51.2 (CH), 52.7 (C), 59.0(CH), 110.1 (CH arom.), 120.4 (C arom.), 122.1 (CH arom.), 124.1 (CH arom.), 126.4 (CH arom.), 127.2 (CH arom.), 127.4 (CH arom.), 129.1 (CH arom.), 130.7 (C arom.), 134.8 (CH arom.), 141.9 (C arom.), 147.1 (C arom.), 151.2 (NC=N), 158.3 (NC=O), 169.5 (N=COEt), 176.6 (HNC=O). HRMS (DCI/NH3): Calcd. for C20H15N4O3 m/z 359.1139; Found 359.1139.

Iminoether **21** (48 mg, 0.124 mmol) was dissolved in 3.0 mL of ethyl acetate, and 1.05 equivalent of 2N HCl (65 μL) was added at room temperature. After 30 min at room temperature, the reaction mixture was refluxed for 90 min (LCMS analysis showed completion of the reaction). The reaction mixture was quenched with a saturated solution of sodium carbonate, and the aqueous phase extracted with ethyl acetate. The combined organic phases were washed with water and dried over sodium sulfate. After concentration in *vacuo*, 15. 6mg (0.044 mmol, 35%) of (±)-*epi*-lapatin B **24** were isolated.

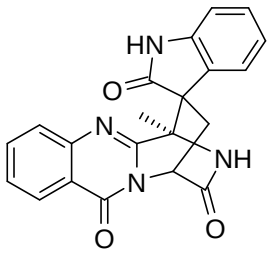


MW = 358.360
MF = $C_{20}H_{14}N_4O_3$

(±)-*epi*-Lapatin B **24**. White solid. Mp 280 °C. MS (API-ES, positive), 359 (M+1). ^{1}H NMR (400 MHz, DMSO- d_6) δ: 2.34 (dd, *J* = 3.2, 14.2 Hz, 1H, CH*H*), 2.51 (m, 1H, C*H*H), 4.39 (d, *J* = 5.3 Hz, 1H, CH), 5.33 (m, 1H, CH), 6.03 (d, *J* = 7.6 Hz 1H, CH), 6.66 (ddd, *J* = 1.0, 7.0, 7.6 Hz, 1H arom.), 6.89 (d, *J* = 7.8 Hz, 1H arom.), 7.16 (m,1H arom.), 7.63 (m, 2H arom.), 7.87 (ddd, *J* = 1.5, 6.8, 7.3 Hz, 1H arom.), 8.25 (dd, *J* = 1.5, 8.5 Hz, 1H arom.), 9.24 (m, 1H, NH), 10.72 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 33.8 (CH_2), 49.3 (CH), 52.7 (C), 58.9 (CH_2), 109.8 (CH arom.), 120.5 (C arom.), 121.4 (CH arom.), 123.8 (CH arom.), 126.6 (CH arom.), 127.5 (CH arom.), 127.7 (CH arom.), 129.0 (CH arom.), 129.2 (C arom.), 135.0 (CH arom.), 141.9 (C arom.), 146.6 (C arom.), 150.8 (NC=N), 158.2 (NC=O), 168.7 (N=COEt), 171.5 (HNC=O). HRMS (DCI/NH_3): Calcd. for $C_{20}H_{15}N_4O_3$ m/z 359.1139; Found 359.1136.

Compounds **16**, **17**, **18** and **19** hydrolysis:

Iminoether **16** (65 mg, 0.16 mmol) was dissolved in 1.5 mL of ethyl acetate, and 1.05 equivalent of 1N HCl (170 μL) was added at room temperature. A precipitate was observed. 60 mg (0.15 mmol, 93%) of (±)-alantrypinone **1** was isolated by filtration.

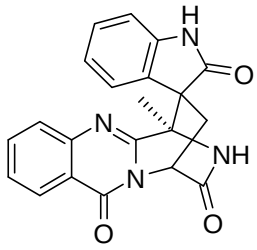


MW = 372.387
MF = $C_{21}H_{16}N_4O_3$

(±)-Alantrypinone **1**. White solid, decomp 354 °C. MS (API-ES, positive), 373 (M+1). ^{1}H NMR (500 MHz, DMSO- d_6) δ: 1.21 (s, 3H, Me), 2.39 (m, 2H, CH_2), 5.55 (dd, *J* = 2.6, 3.1 Hz, 1H, CH),

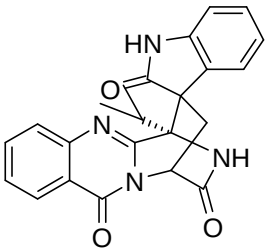
6.90 (d, *J* = 7.9 Hz, 1H arom.), 7.09 (ddd, *J* = 1.0, 7.5, 8.0z, 1H arom.), 7.17 (d, *J* = 7.4 Hz, 1H arom.), 7.30 (ddd, *J* = 1.0, 7.5, 8 Hz, 1H arom.), 7.59 (ddd, *J* = 1.2, 7.3, 8.2 Hz, 1H arom.), 7.67 (d, *J* = 1.0, 7.5 Hz, 1H arom.), 7.85 (ddd, *J* = 1.5, 7.4, 8.0 Hz, 1H arom.), 8.20 (dd, *J* = 1.5, 8.0 Hz), 9.54(s, NH), 10.6(s, NH). HSQC in agreement with the literature[1]. HRMS (DCI/NH_3): Calcd. for $C_{21}H_{17}N_4O_3$ m/z 373.12952; Found 373.12953.

Iminoether **17** (44 mg, 0.11 mmol) was dissolved in 4 mL of ethyl acetate, and 1 mL of a 1N HCl was added at room temperature. After completion of the reaction (30 min), the reaction was quenched by addition of a saturated solution of sodium carbonate. The aqueous layer was extracted three times with ethyl acetate and the combined organic phases were washed with water. After concentration in *vacuo*, 37 mg (0.10 mmol, 90%) of (±)-*epi*-alantrypinone **25** were isolated.



MW = 372.387
MF = $C_{21}H_{16}N_4O_3$

(±)-*epi*-Alantrypinone **25**. White solid, decomp 330 °C. MS (API-ES, positive), 373 (M+1). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.21 (s, 3H, Me), 2.48 (A of ABX, J_{AB} = 14.0 Hz, J_{AX} = 3.9 Hz, 1H, CH*H*), 2.53 (B of ABX, J_{AB} = 14.0 Hz, J_{BX} = 1.8 Hz, 1H, C*H*H), 5.54 (m, 1H, CH), 5.85 (d, *J* = 7.4 Hz, 1H arom.), 6.64 (dd, *J* = 1.0, 7.4, 7.8 Hz, 1H arom.), 6.85 (d, *J* = 7.7 Hz, 1H arom.), 7.13 (dt, *J* = 1.0, 7.7 Hz, 1H arom.), 7.62 (dd, *J* = 1.0, 7.6, 7.8 Hz, 1H arom.), 7.67 (d, *J* = 7.7 Hz, 1H arom.), 7.86 (ddd, *J* = 1.5, 7.2, 8.1 Hz, 1H arom.), 8.25 (dd, *J* = 1.5, 8.1 Hz, 1H arom.), 9.28(s, NH), 10.7(s, NH). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 13.3 (Me), 35.2 (CH_2), 52.2 (C), 52.6 (CH), 61.9 (C), 109.5 (CH arom.), 120.1 (C arom.), 121.6 (CH arom.), 123.3 (CH arom.), 126.6 (CH arom.), 127.7 (CH arom.), 127.8 (CH arom.), 128.9 (CH arom.), 129.2 (CH arom.), 135.0 (CH, arom), 142.4 (C arom.), 146.3 (C arom.), 152.4 (NC=N), 158.2 (NC=O), 168.9 (NC=O), 177.1 (HNC=O). HRMS (DCI/NH_3): Calcd. for $C_{21}H_{17}N_4O_3$ m/z 373.12952; Found 373.12971.
Iminoether **18** (32 mg, 0.075 mmol) was dissolved in 1.5mL of ethyl acetate, and 1.05 equivalent of 2N HCl (40µL) was added at room temperature. A precipitate was observed. The compound **26** (20 mg, 0.05 mmol, 67%) was isolated by filtration.

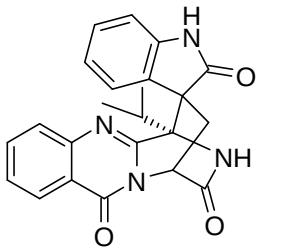


MW = 400.441
MF = $C_{23}H_{20}N_4$

[1] Chen, Z.; Fan, J.; Kende, A. S. *J. Org. Chem.* **2004**, *69*, 79-85.

Compound **26**. White solid. Mp 269-270 °C. MS (API-ES, positive), 401 (M+1). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.12 (d, *J = 6*.8 Hz, 3H, CHMe*Me*), 1.20 (d, *J = 6*.8 Hz, 3H, CHMe*Me),* 1.98 (m, 1H, C*H*MeMe), 2.41 (A of ABX, J_{AB} = 14 Hz, J_{AX} = 1.5 Hz, 1H, CH*H*), 2.50 (B of ABX, J_{AB} = 14.2 Hz, J_{BX} = 4.0 Hz, 1H, C*H*H), 5.53 (m, 1H, CH), 6.90 (d, *J = 7*.8 Hz, 1H arom.), 7.07 (m, 1H arom.), 7.30 (m, 2H arom.), 7.67 (d, *J = 8*.0 Hz, 1H arom.), 7.85(m, 1H arom.), 8.19 (dd, *J = 1*.0, 8.0 Hz, 1H arom.), 9.50 (s, 1H, NH), 10.63 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 17.2 (Me), 19.1 (Me), 31.5 (CH), 40.8 (CH_2), 52.0 (CH), 54.8 (C), 67.7 (C), 110.9 (CH arom.), 120.7 (C arom.), 123.0 (CH arom.), 124.7 (CH arom.), 126.9 (CH arom.), 127.9 (CH arom.), 128.6 (CH arom.), 129.8 (CH arom.), 131.0 (C arom.), 135.3 (CH arom.), 142.5 (C arom.), 147.3 (C arom.), 151.7 (NC=N), 159.3 (NC=O), 170.5 (NC=O), 176.6 (HNC=O). HRMS (DCI/NH_3): Calcd. for $C_{23}H_{21}N_4O_3$ m/z 401.1608; Found 401.1611.

Iminoether **19** (12 mg, 0.03 mmol) was dissolved in 1 mL of ethyl acetate, and 1 equivalent of 2N HCl (15 μL) was added at room temperature. After 30 min, TLC showed completion of the reaction. The reaction mixture was quenched with a saturated solution of sodium carbonate, and extracted three times with ethyl acetate. The combined organic layers were washed with water and dried over sodium sulfate. After concentration in *vacuo*, 3.5 mg (29%) of the compound **27** were obtained.

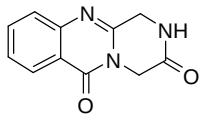


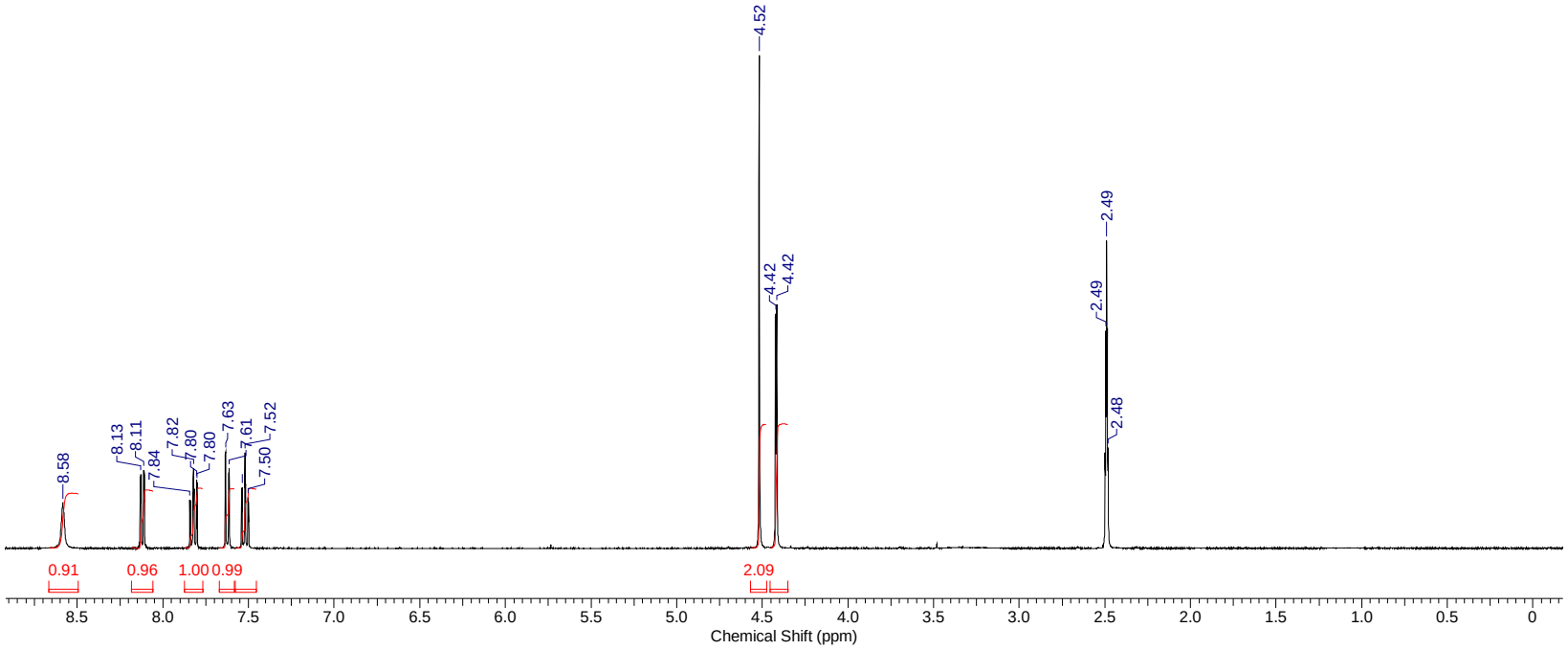
MW = 400.441
MF = $C_{23}H_{20}N_4O_3$

Compound **27**. White solid. Mp 266-268 °C. MS (API-ES, positive), 401 (M+1). ^{1}H NMR (500 MHz, MeOD) δ: 1.01 (d, *J = 7*.7 Hz, 3H, CHMe*Me*), 1.15 (d, *J = 7*.7 Hz, 3H, CH*Me*Me*),* 2.20 (A of ABX, J_{AB} = 14.0 Hz, J_{AX} = 2.2 Hz, 1H, CH*H*), 2.55 (hept, *J = 7*.7 Hz, 1H, C*H*Me_2), 2.50 (B of ABX, J_{AB} = 14.0 Hz, J_{BX} = 1.6 Hz, 1H, C*H*H), 5.73 (m, 1H, CH), 5.96 (d, *J = 7*.7 Hz, 1H arom.), 6.68 (t, *J = 7*.7 Hz, 1H arom.), 6.87 (d, *J = 7*.7 Hz, 1H arom.), 7.15 (t, *J = 7*.7 Hz, 1H arom.), 7.63 (dd, *J = 7*.30, 8.1 Hz, 1H arom.), 7.75 (d, *J = 8*.4 Hz, 2H arom.), 7.88 (dd, *J = 7*.3, *J = 8*.1 Hz, 1H arom.), 8.31 (d, *J = 8*.1 Hz, 1H arom.). ^{13}C NMR (125 MHz, MeOD) δ: 18.1 (Me), 19.0 (Me), 30.9 (CH), 41.9 (CH_2), 53.3 (CH), 54.1 (C), 69.7 (C), 111.2 (CH arom.), 121.7 (C arom.), 123.5 (CH arom.), 124.8 (CH arom.), 127.8 (CH arom.), 129.1 (CH arom.), 130.2 (CH arom.), 131.8 (CH arom.), 136.2 (C arom.), 143.0 (CH arom.), 148.1 (C arom.), 148.1 (C arom.), 152.5 (NC=N), 160.5 (NC=O), 172.1 (NC=O), 180.4 (HNC=O). HRMS (DCI/NH_3): Calcd. for $C_{23}H_{21}N_4O_3$ m/z 401.1608; Found 401.1604.

Nucleus	1H	Solvent	DMSO-D6	Frequency (MHz)	400.13

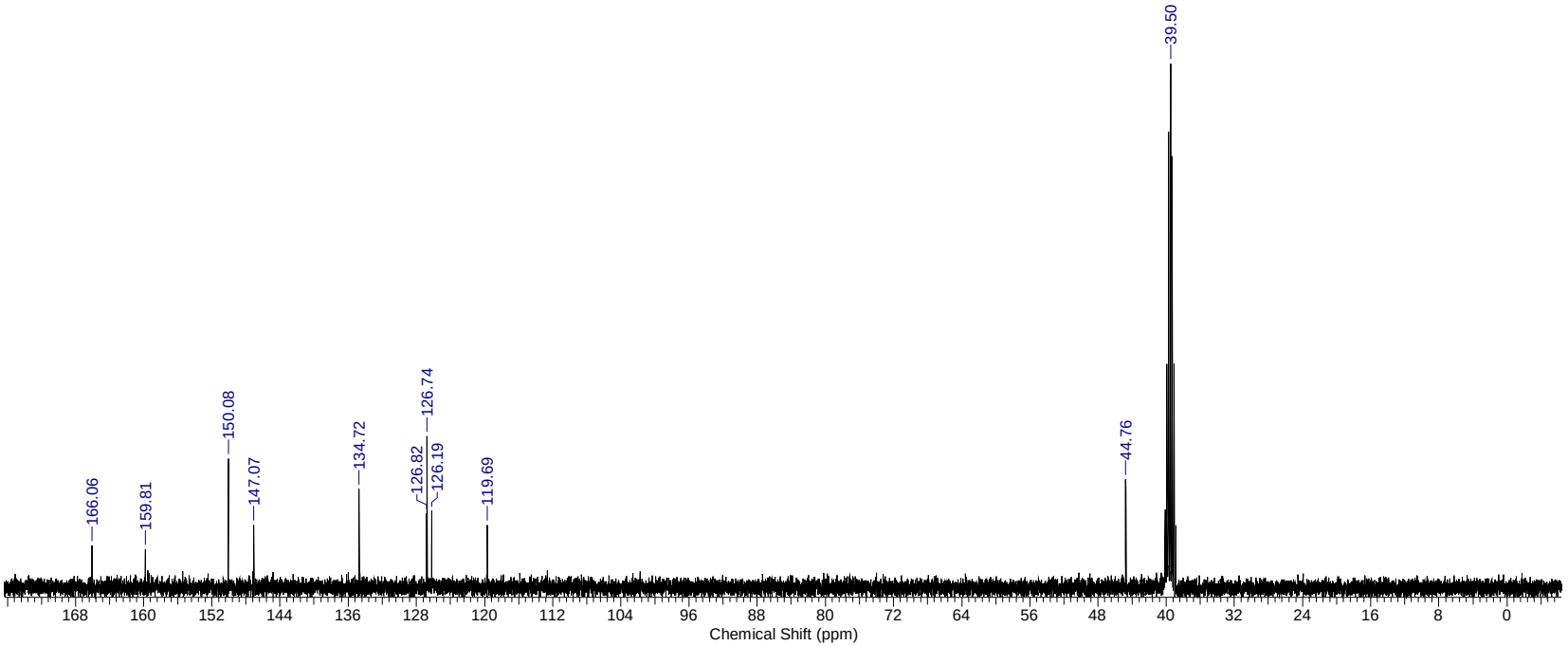
10





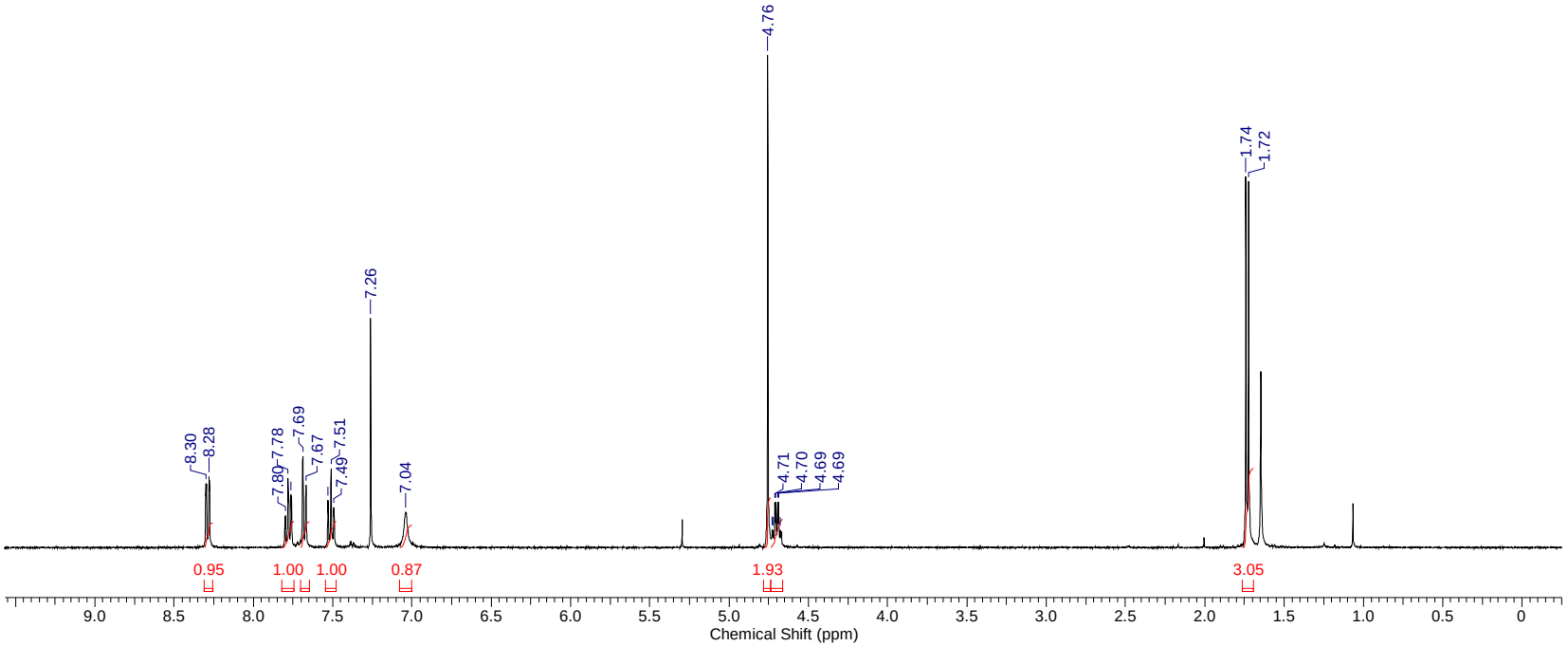
Nucleus	13C	Solvent	DMSO-D6	Frequency (MHz)	100.63

10



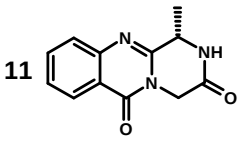
Nucleus	1H	Frequency (MHz)	400.13	Solvent	CHLOROFORM-D

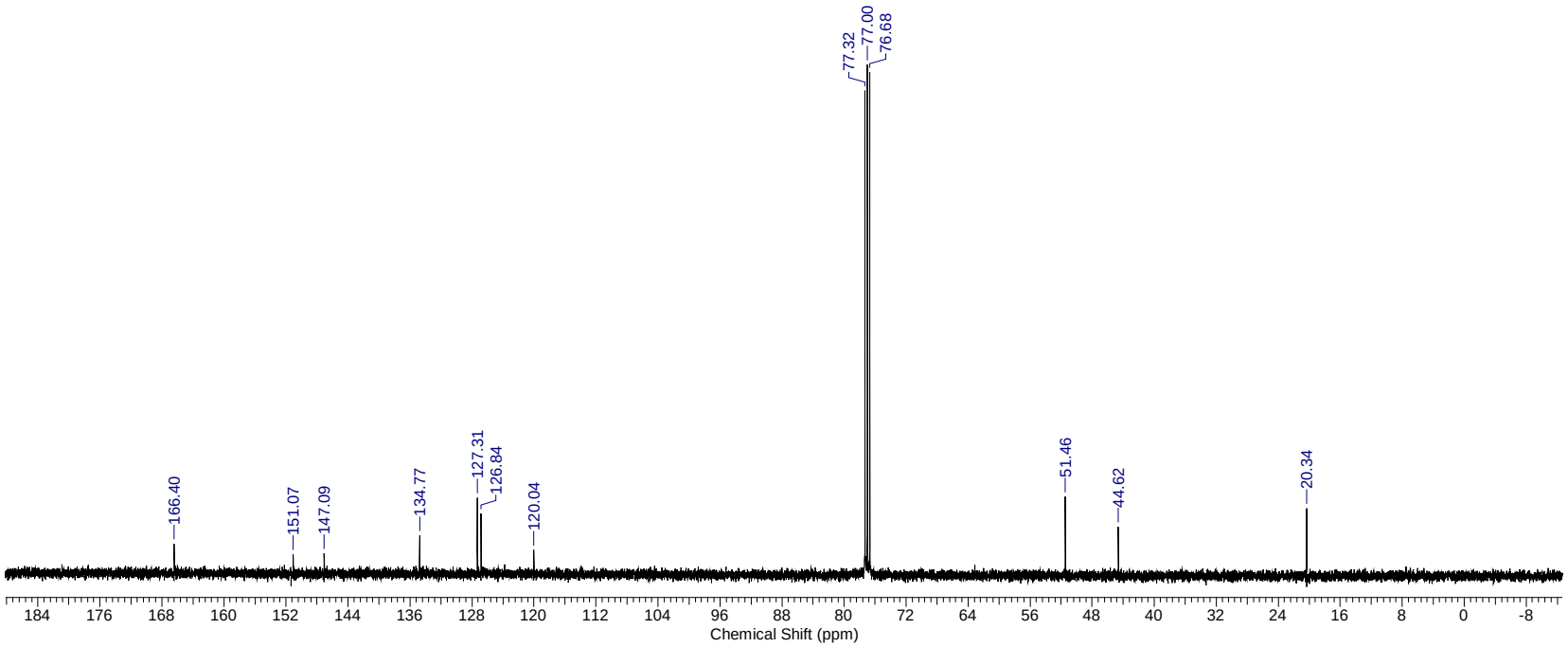
11



Nucleus	13C	***Solvent***	CHLOROFORM-D	***Frequency (MHz)***	100.63

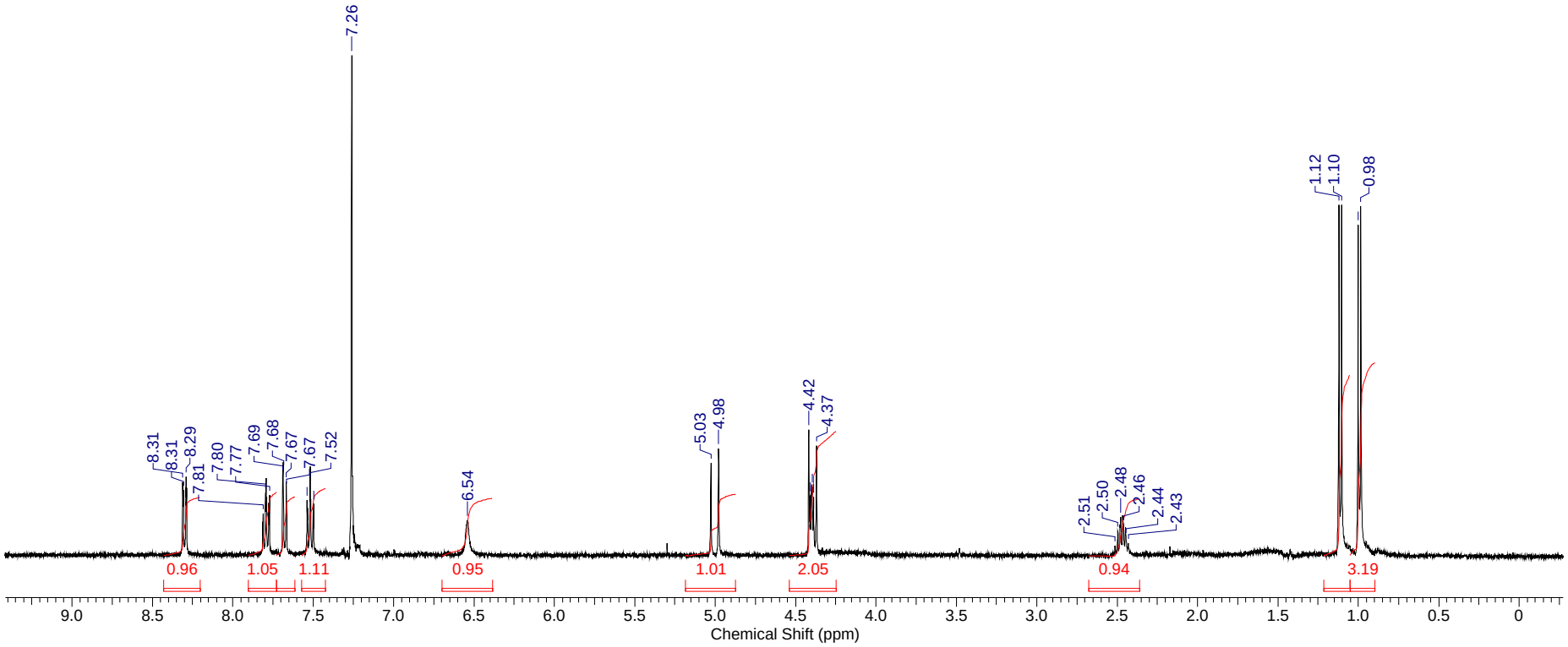
11





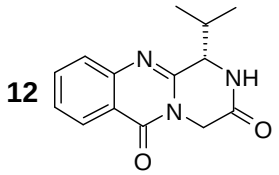
Frequency (MHz)	400.13	***Nucleus***	1H	***Solvent***	CHLOROFORM-D

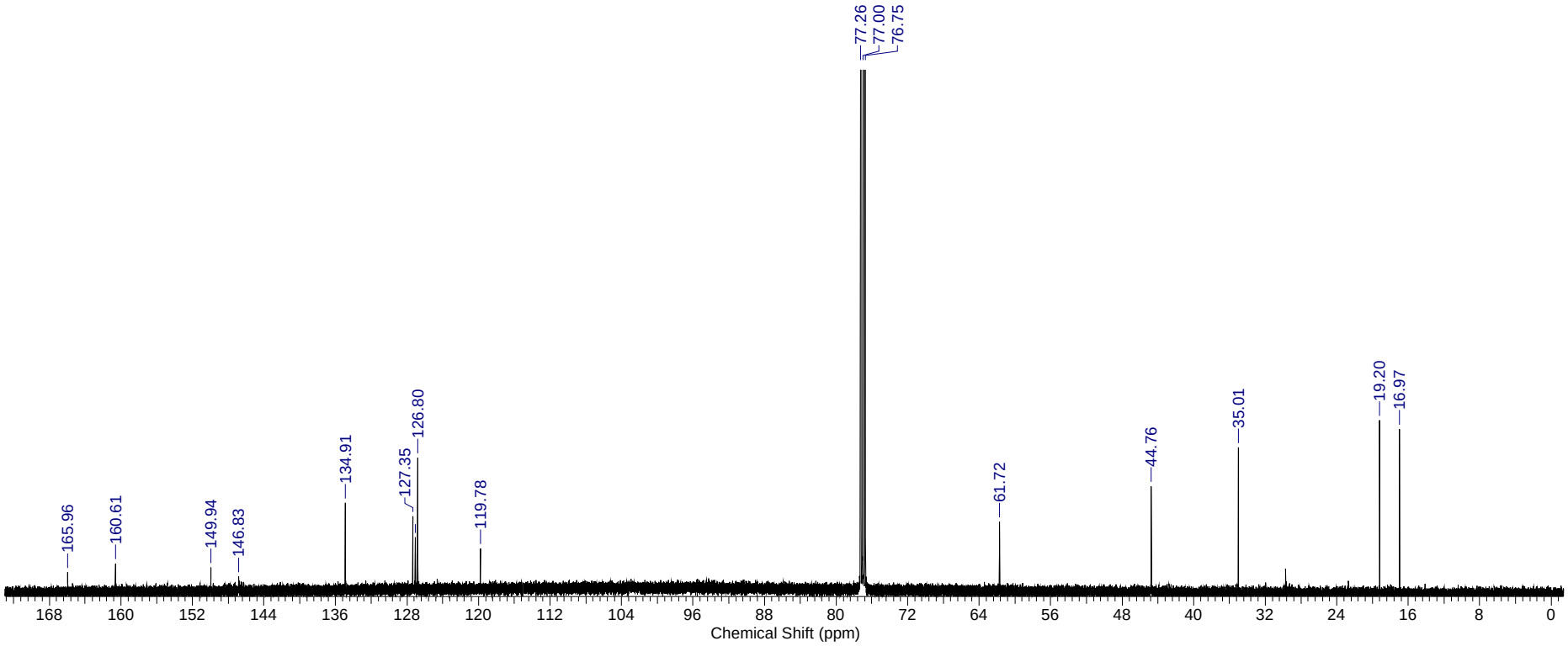
12



Nucleus	13C	Solvent	CHLOROFORM-D	Frequency (MHz)	125.72

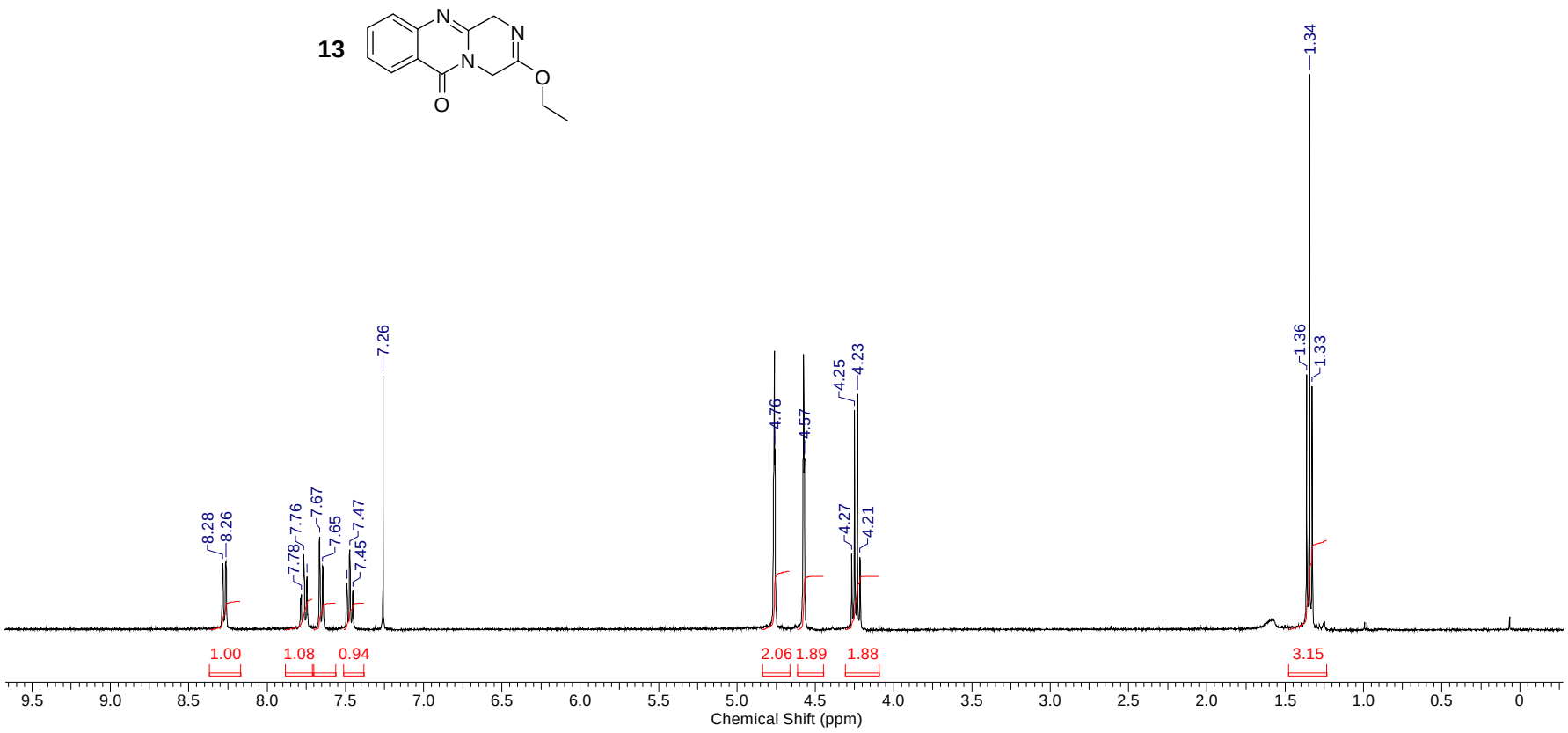
12



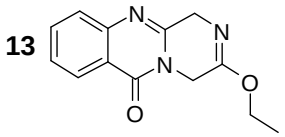


Nucleus	1H	Frequency (MHz)	400.13	Solvent	CHLOROFORM-D

13

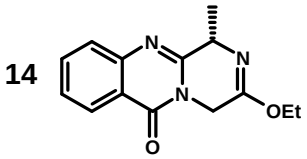


Nucleus	13C	Solvent	CHLOROFORM-D	Frequency (MHz)	100.63

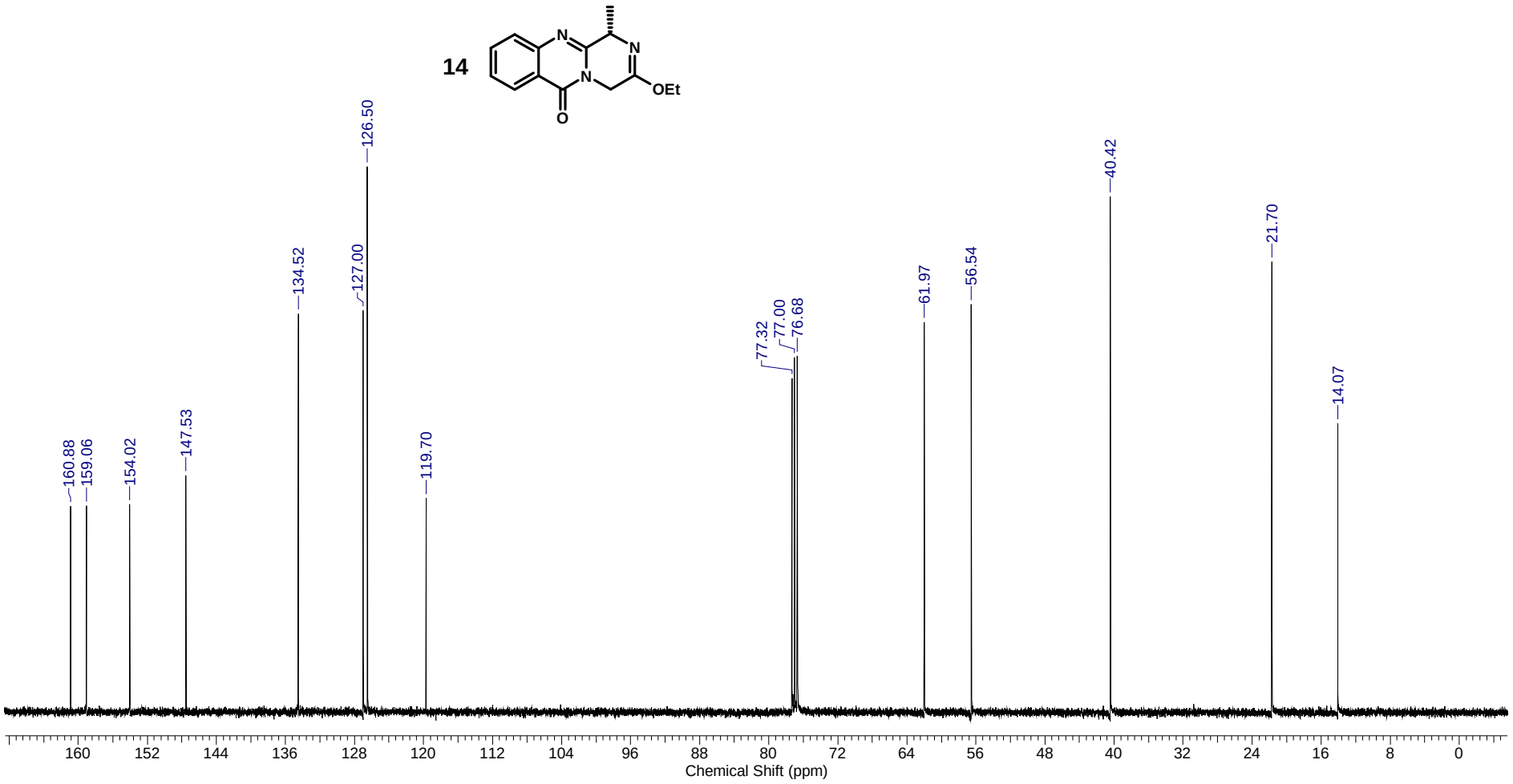


Nucleus	1H	Frequency (MHz)	400.13	Solvent	CHLOROFORM-D

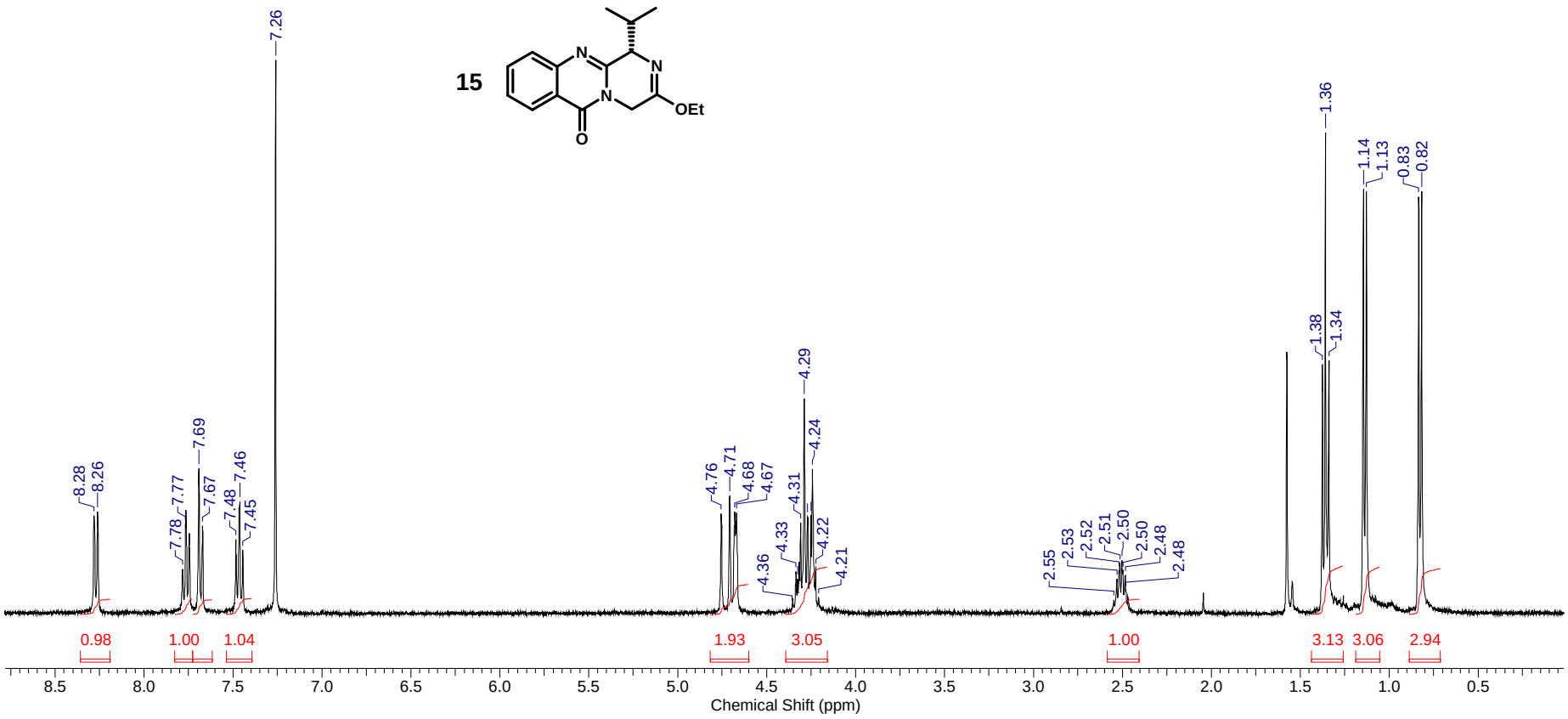
14



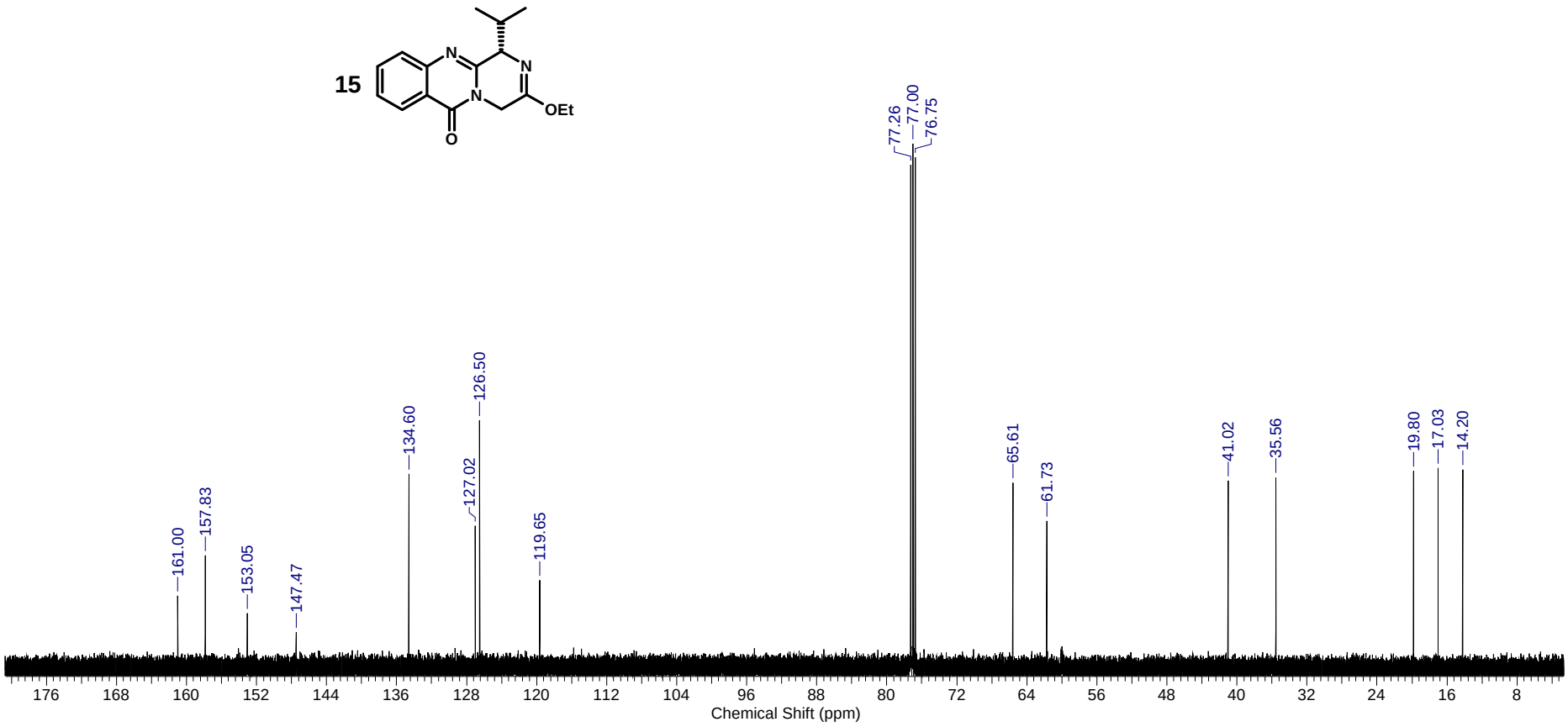
Nucleus	13C	Solvent	CHLOROFORM-D	Frequency (MHz)	100.63



Nucleus	1H	Solvent	CHLOROFORM-D	Frequency (MHz)	499.92

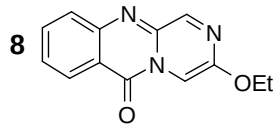


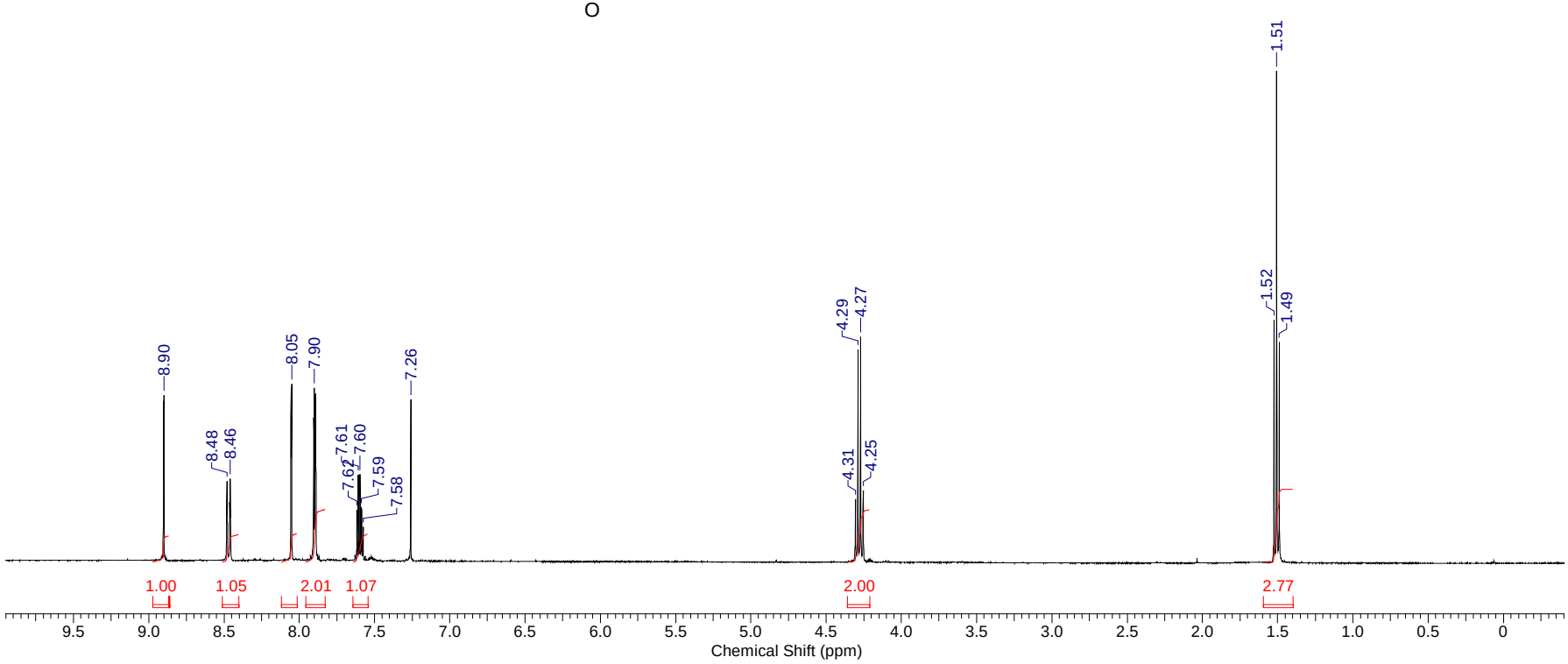
Nucleus	13C	Solvent	CHLOROFORM-D	Frequency (MHz)	125.72



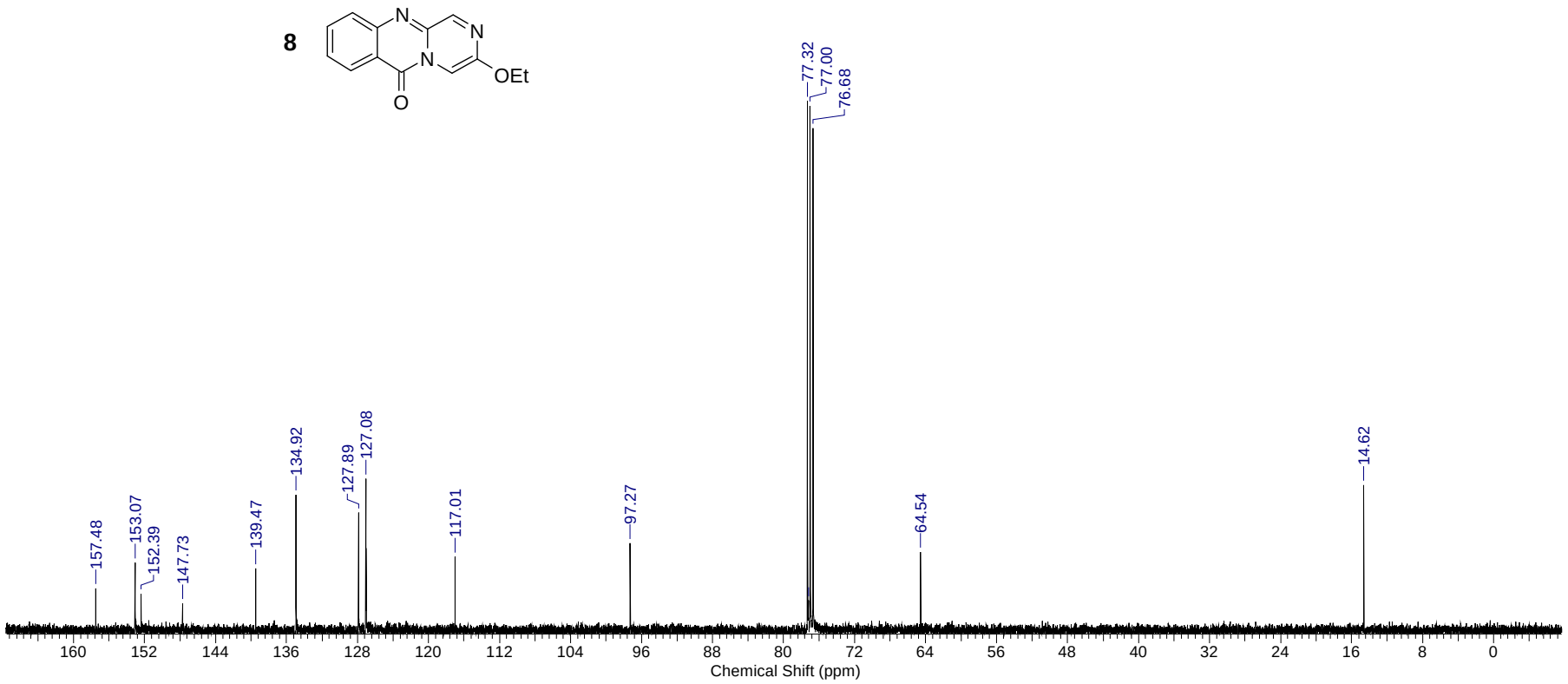
Nucleus	1H	Frequency (MHz)	400.13	Solvent	CHLOROFORM-D

8

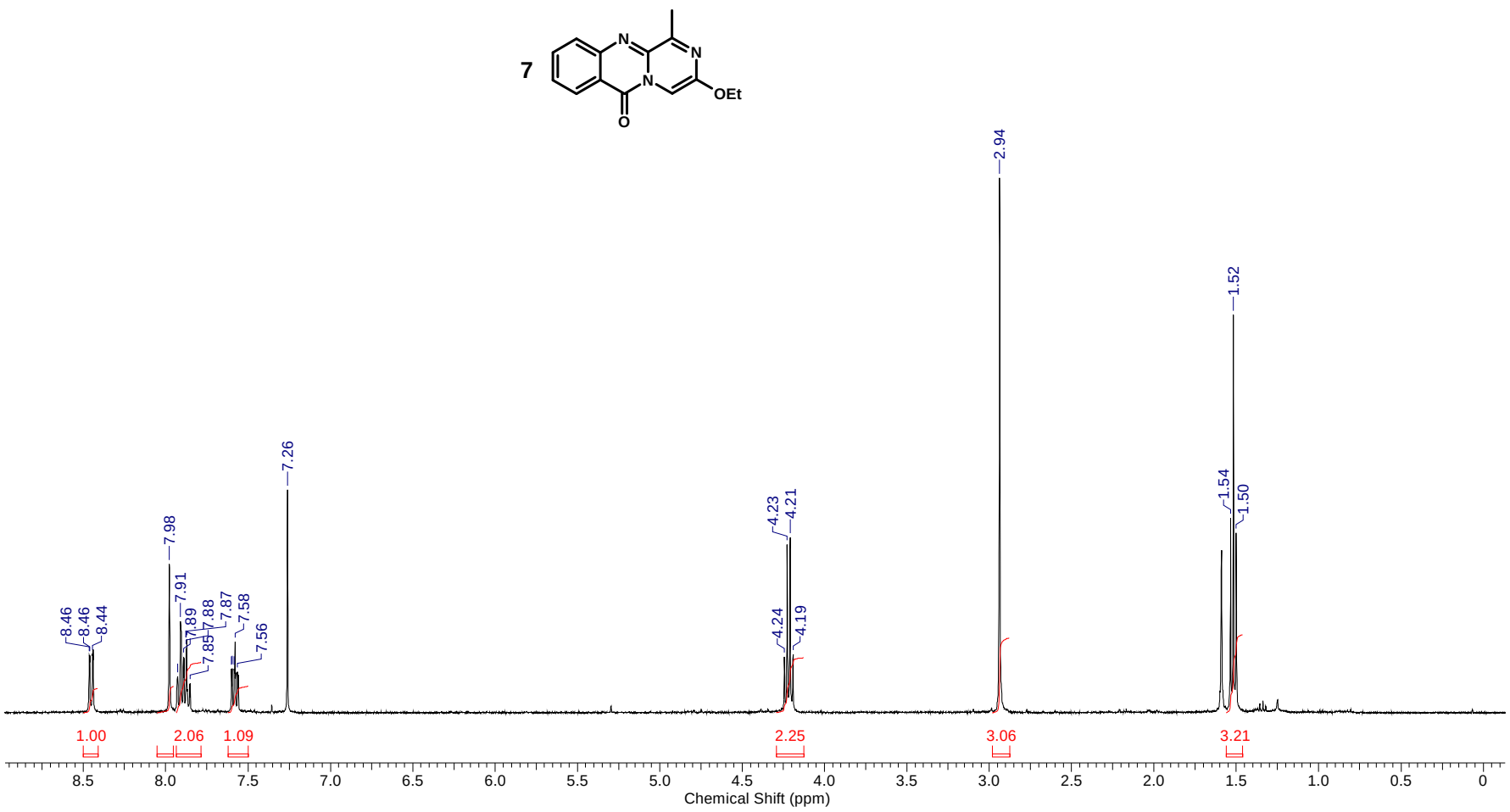




Nucleus	13C	Solvent	CHLOROFORM-D	Frequency (MHz)	100.63

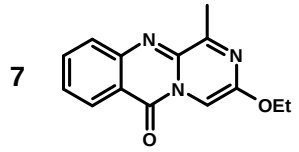


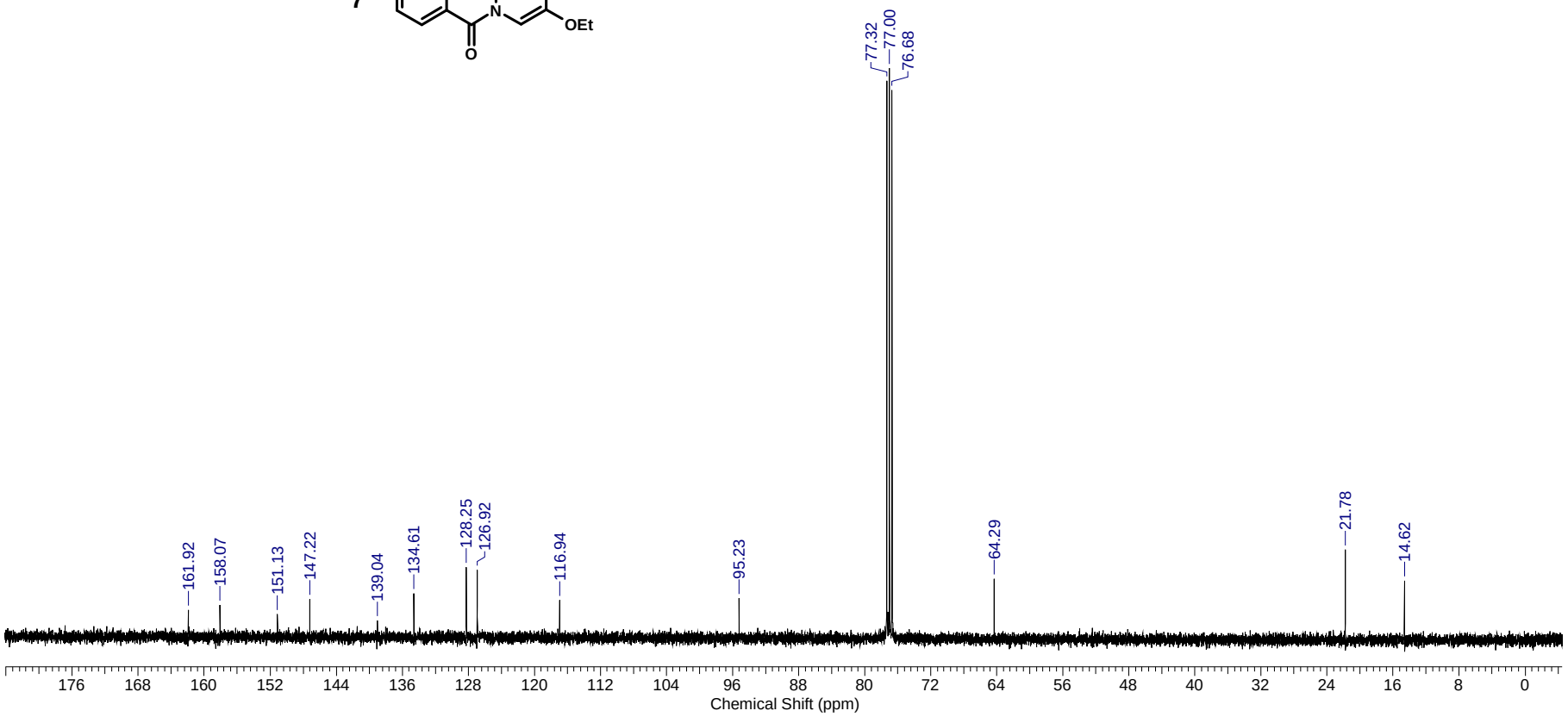
Nucleus	1H	Frequency (MHz)	400.13	Solvent	CHLOROFORM-D



Nucleus	13C	Solvent	CHLOROFORM-D	Frequency (MHz)	100.63

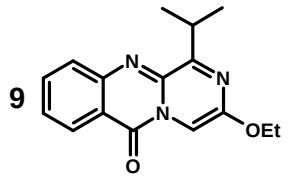
7

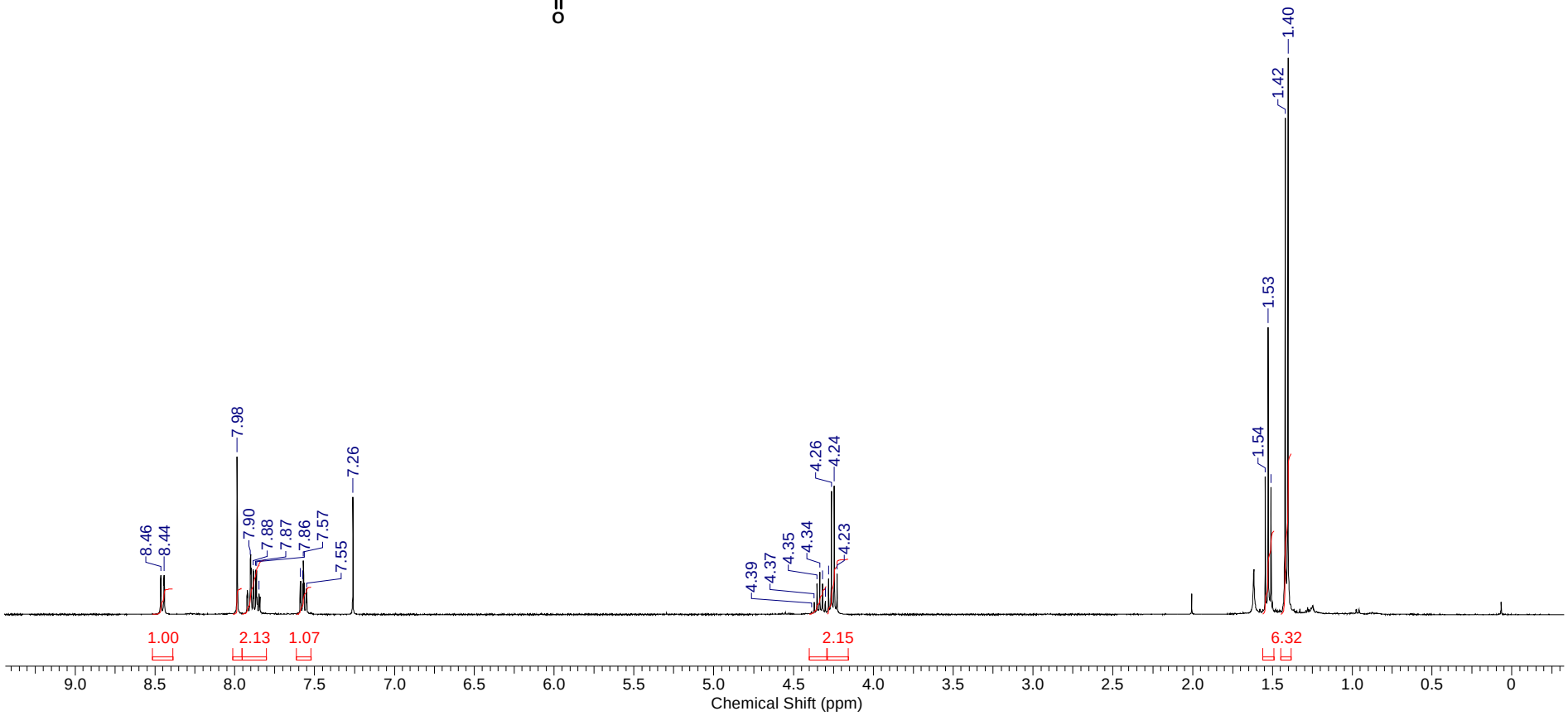




Frequency (MHz)	400.13	***Nucleus***	1H	***Solvent***	CHLOROFORM-D

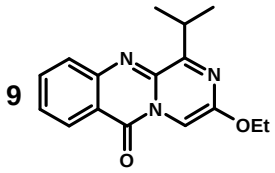
9

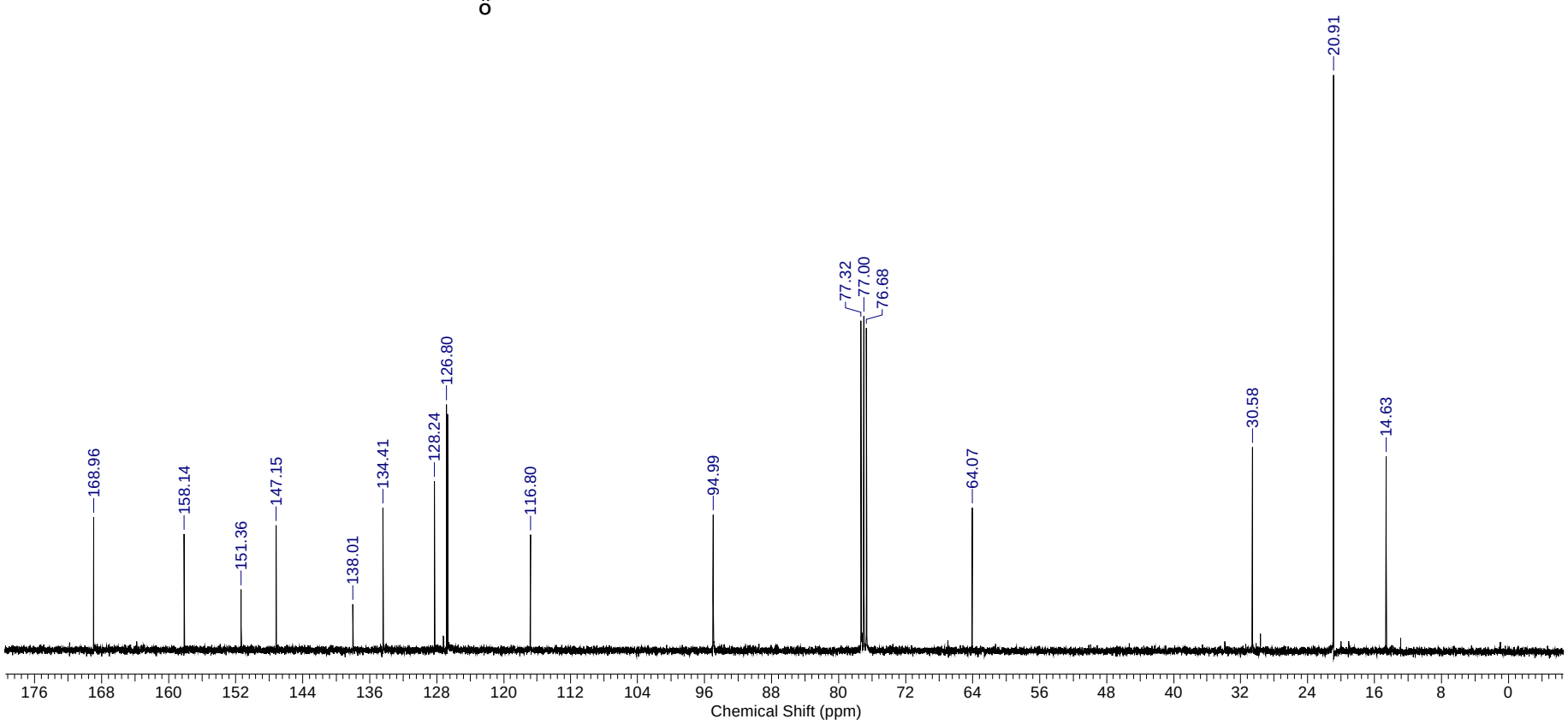




Nucleus	13C	Solvent	CHLOROFORM-D	Frequency (MHz)	100.63

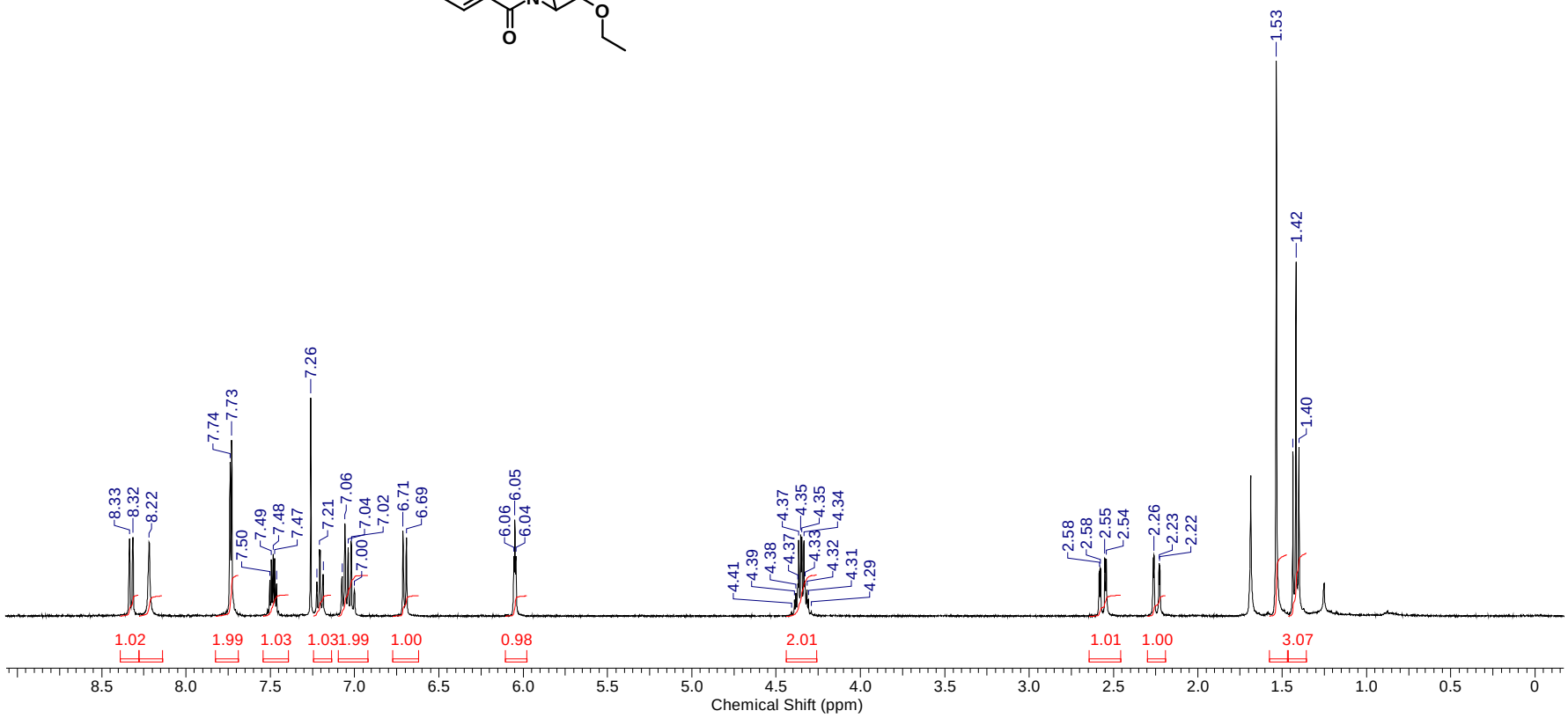
9



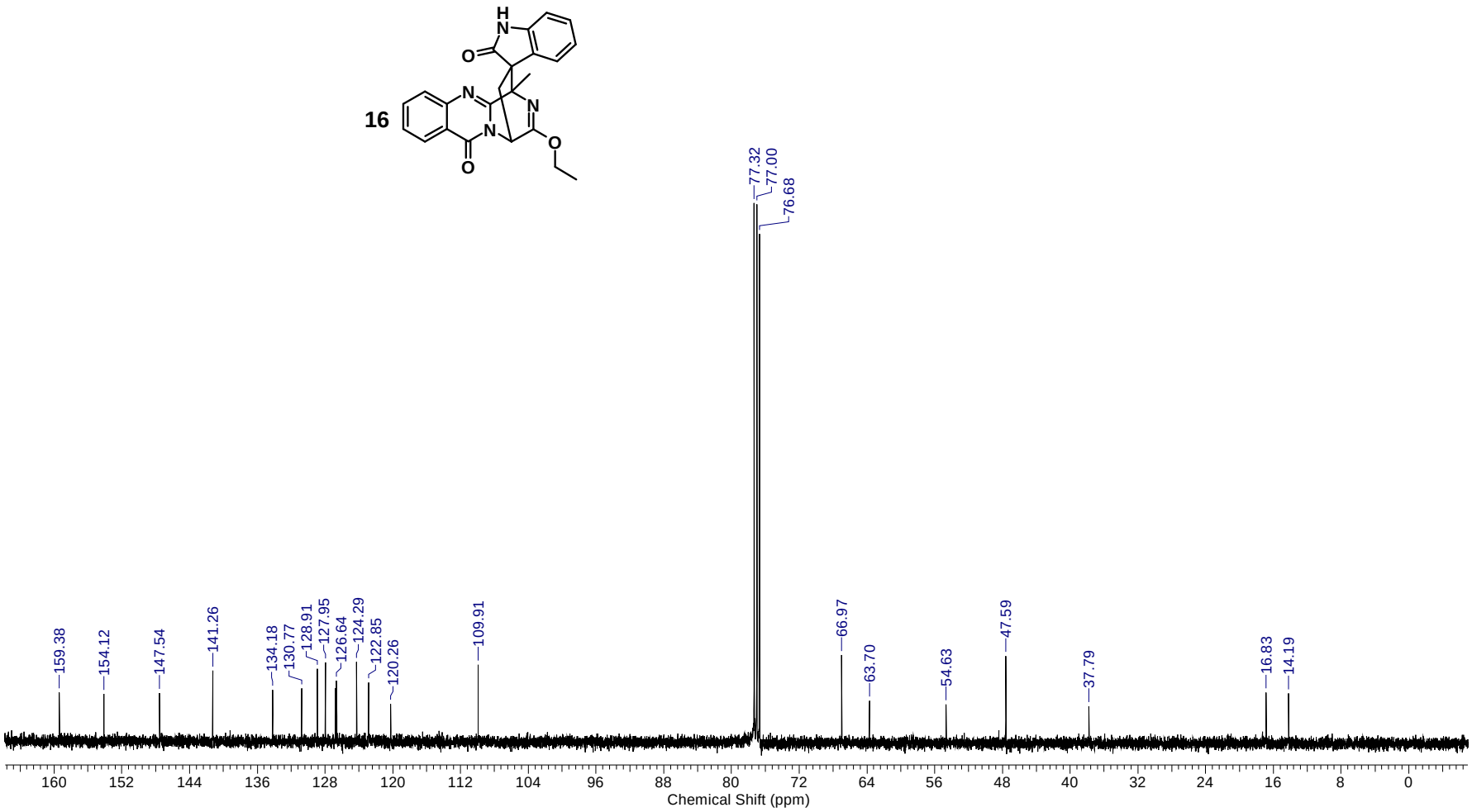


Nucleus	1H	Frequency (MHz)	400.13	Solvent	CHLOROFORM-D

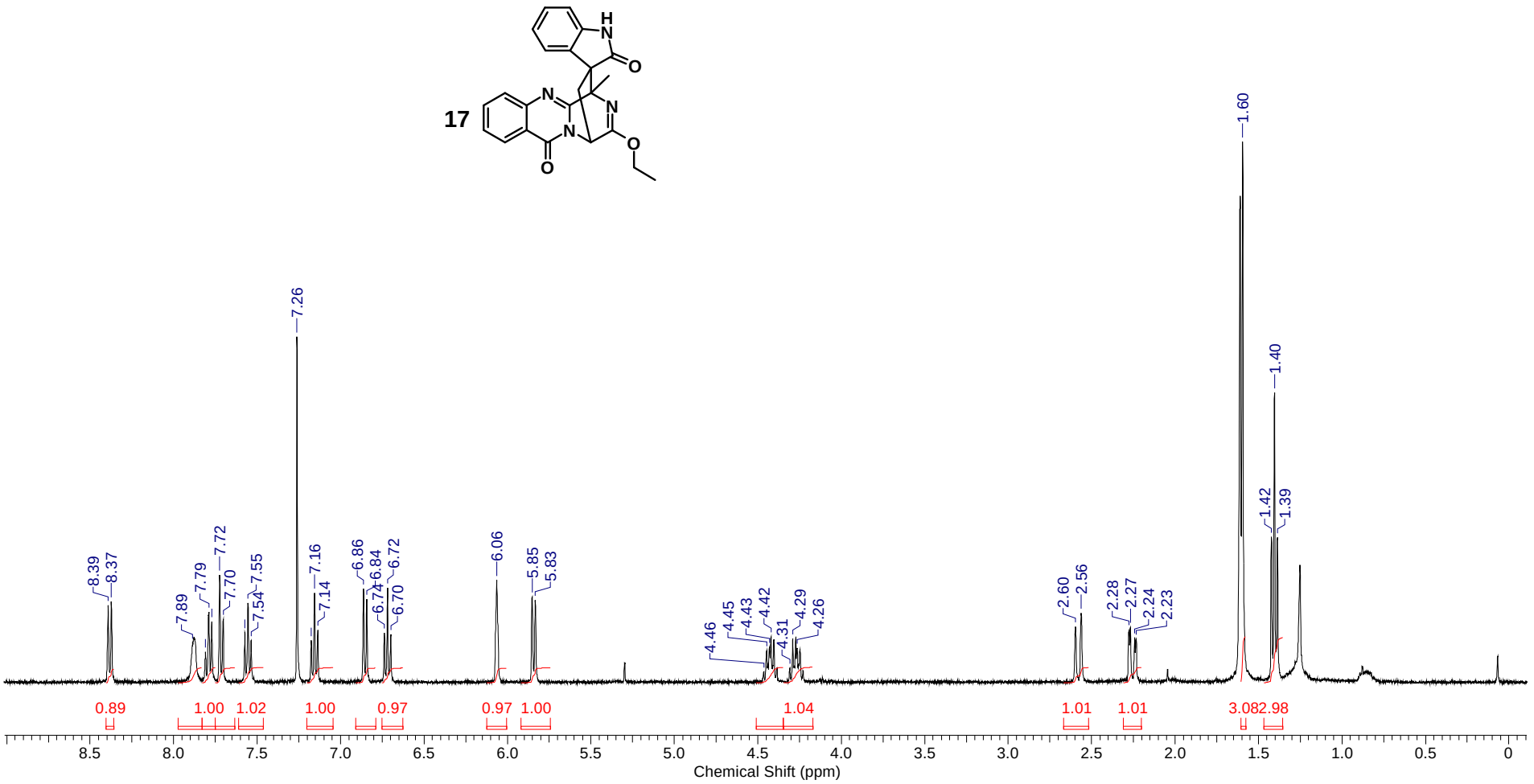
16



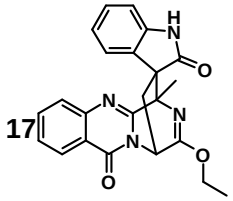
Nucleus	13C	Solvent	CHLOROFORM-D	Frequency (MHz)	100.63

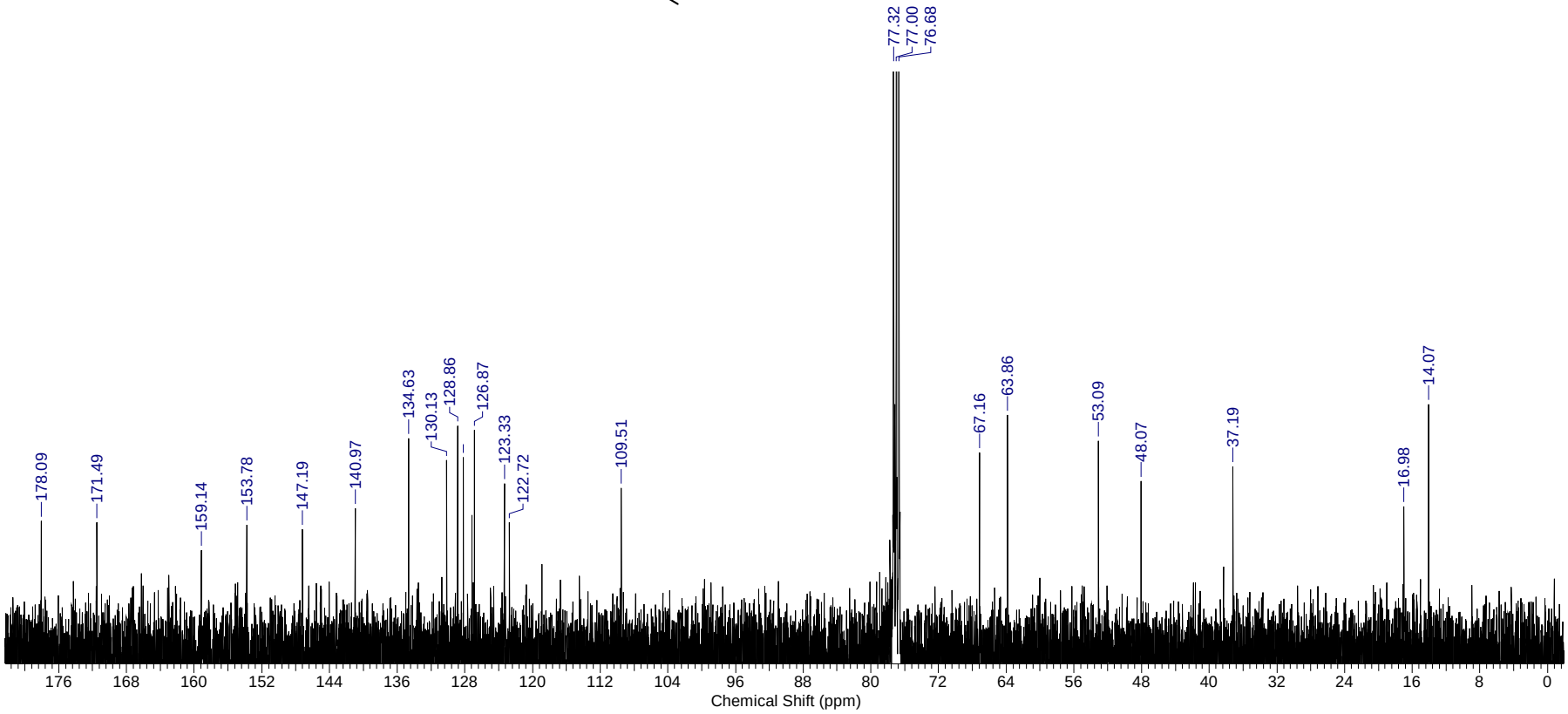


Nucleus	1H	Frequency (MHz)	400.13	Solvent	CHLOROFORM-D



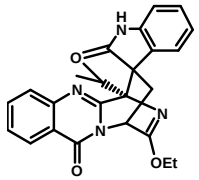
Nucleus	13C	Solvent	CHLOROFORM-D	Frequency (MHz)	100.63

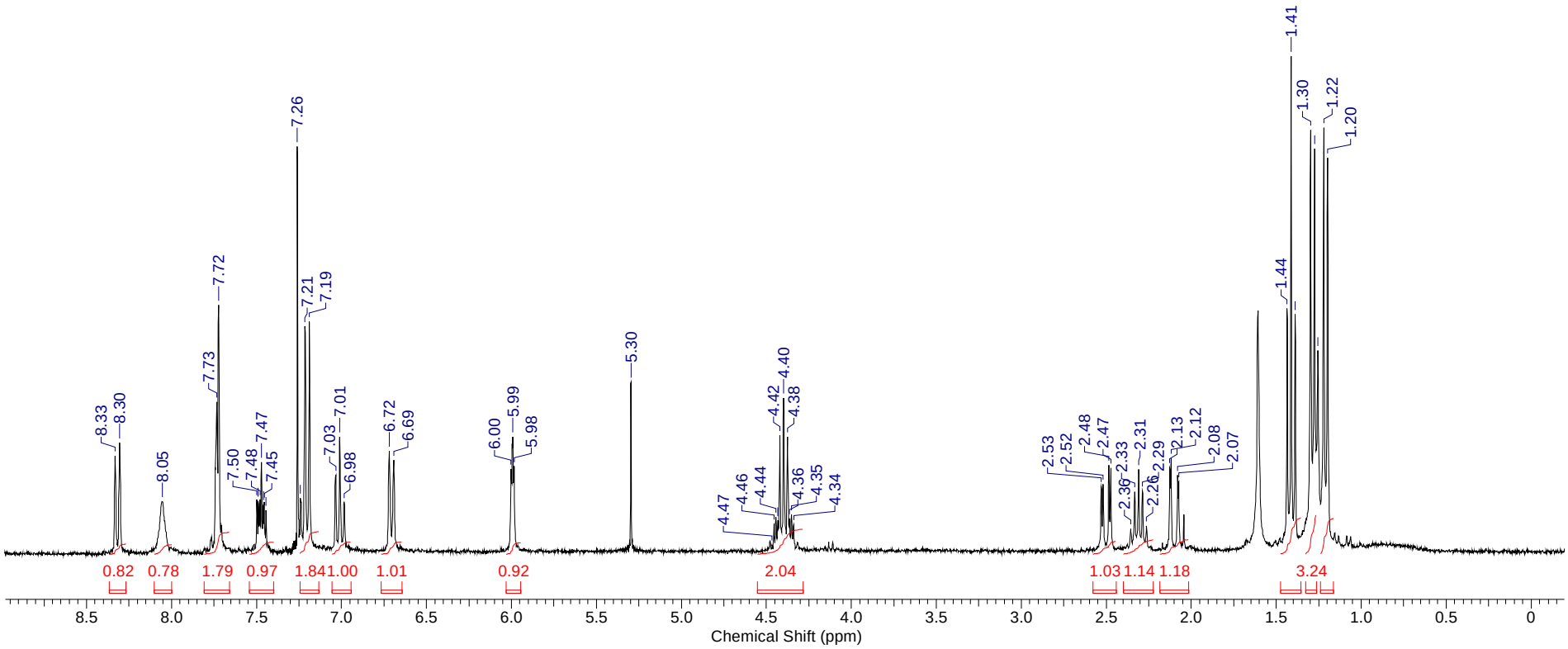




Nucleus	1H	Solvent	CHLOROFORM-D	Frequency (MHz)	300.13

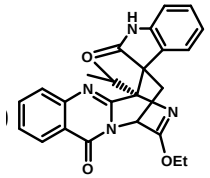
18

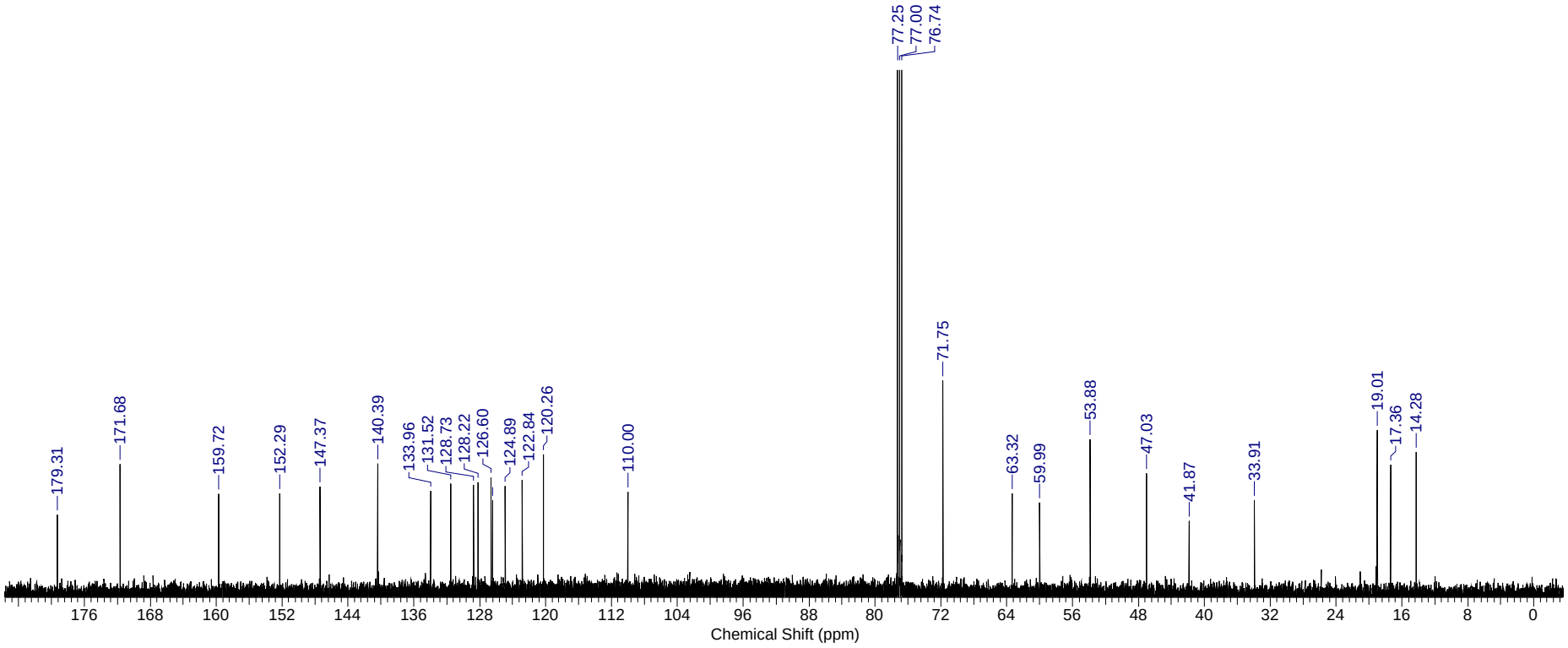




Nucleus	13C	Solvent	CHLOROFORM-D	Frequency (MHz)	125.72

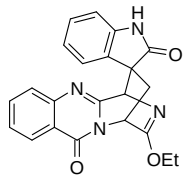
18

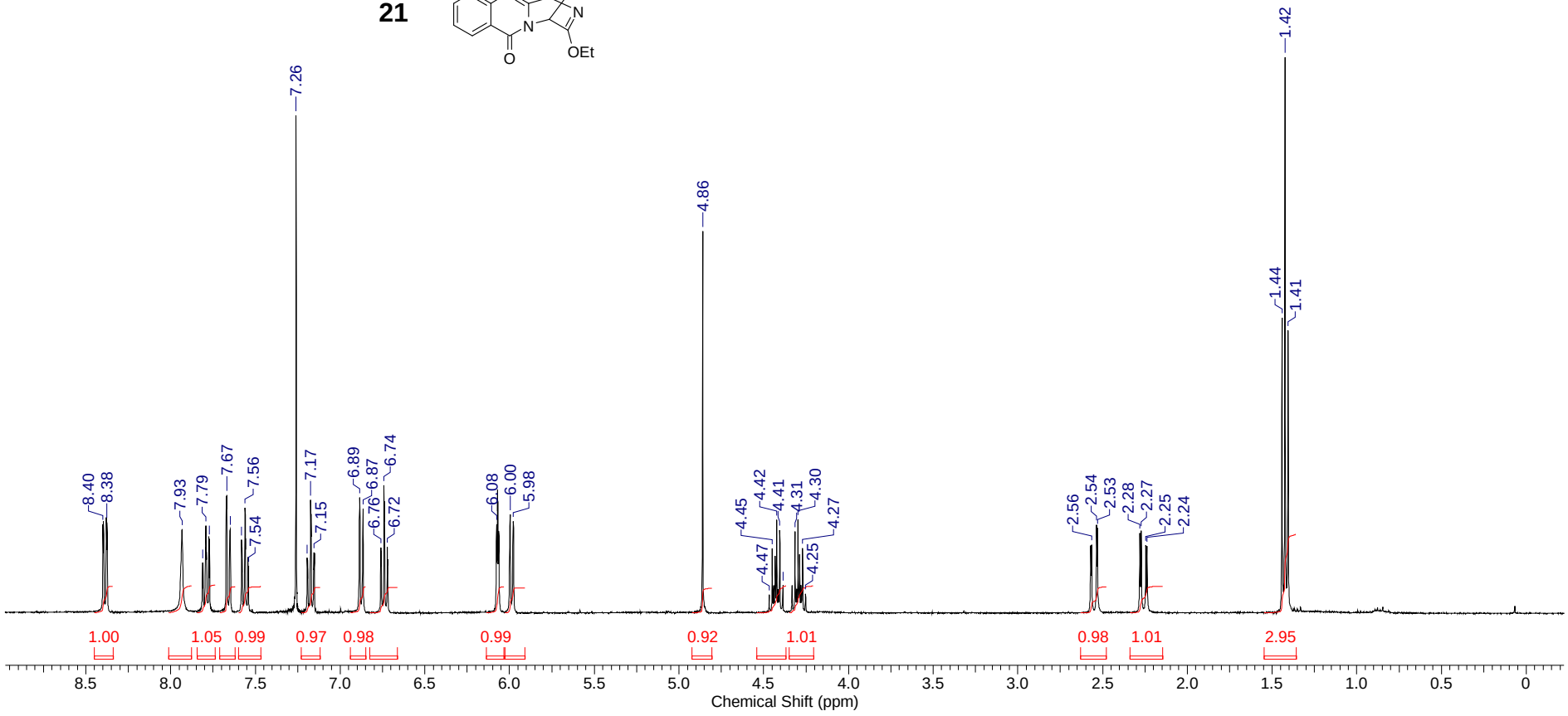




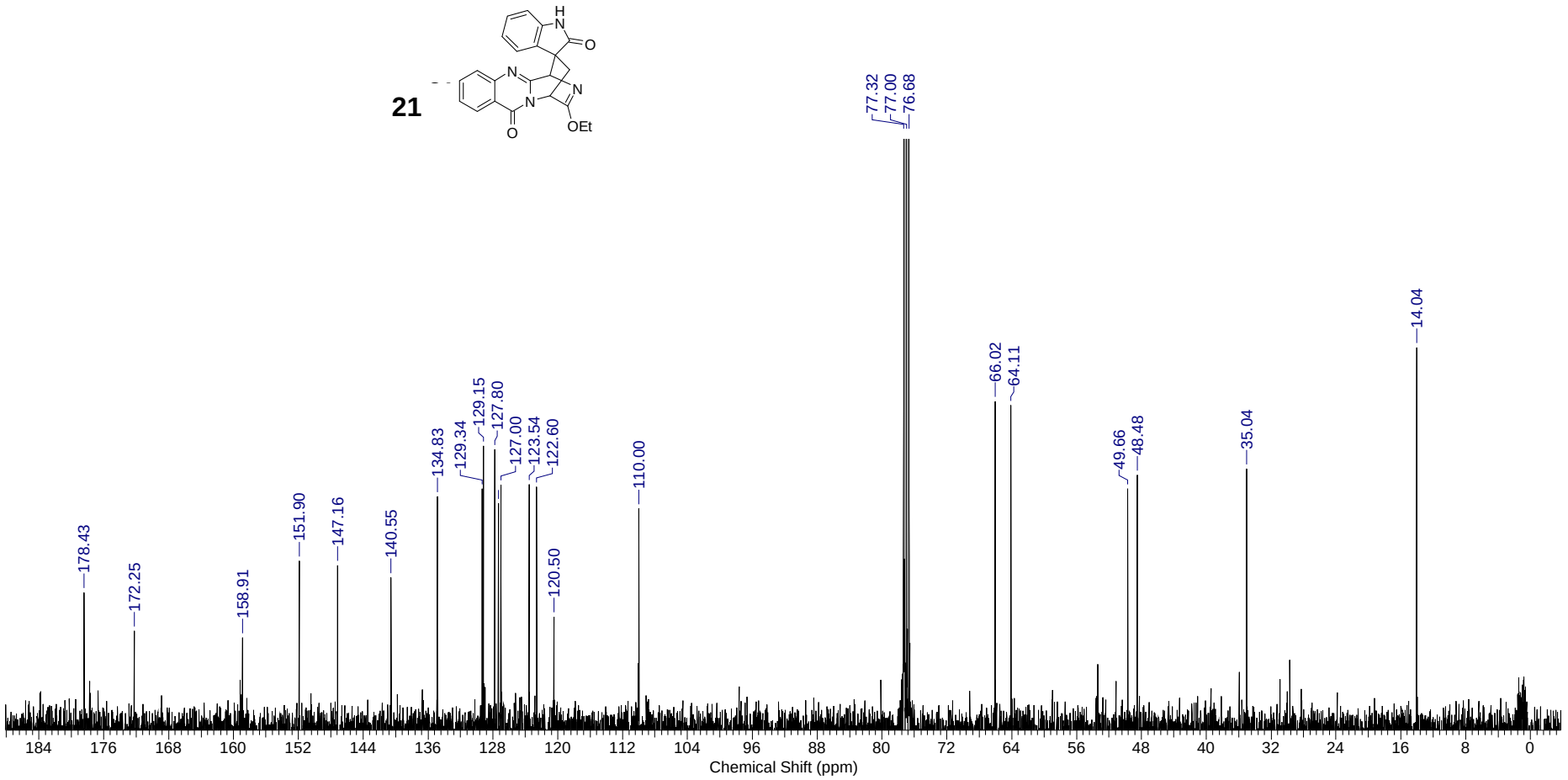
Nucleus	1H	Solvent	CHLOROFORM-D	Frequency (MHz)	400.13

21

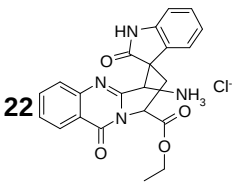


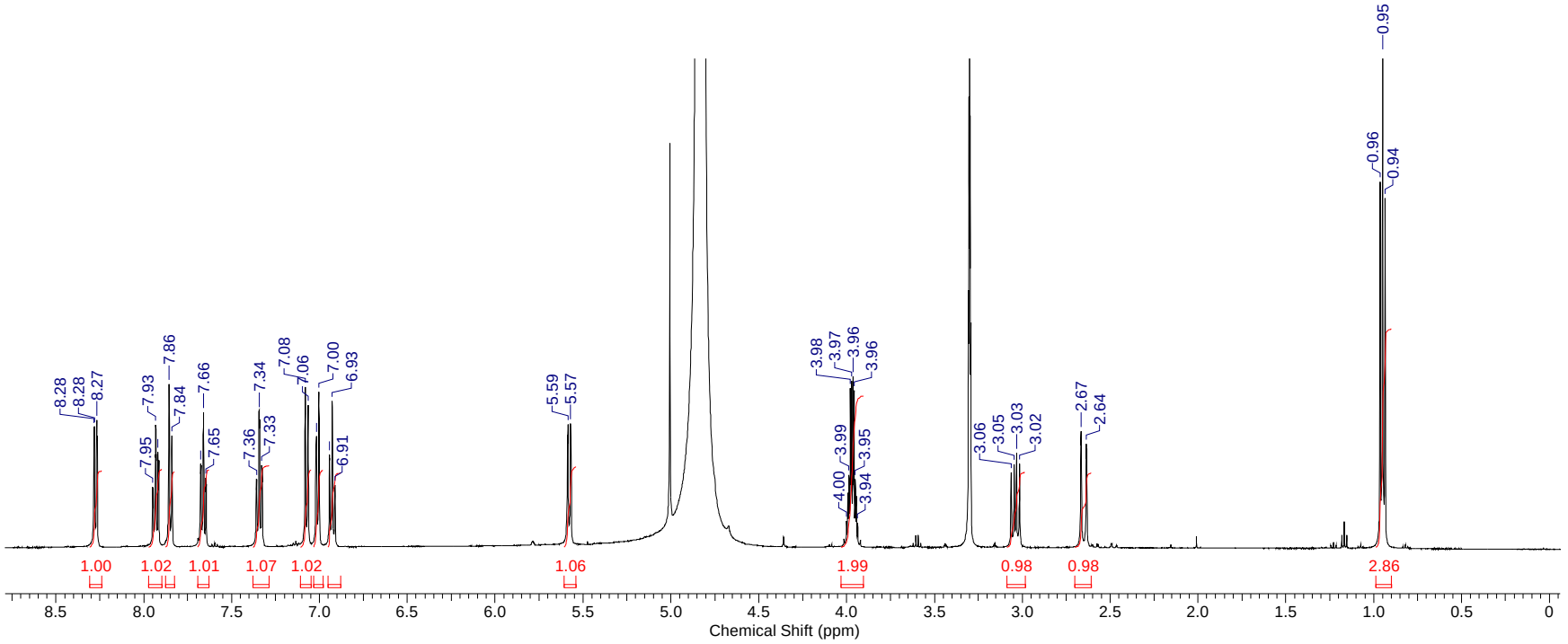


Nucleus	13C	Solvent	CHLOROFORM-D	Frequency (MHz)	100.63



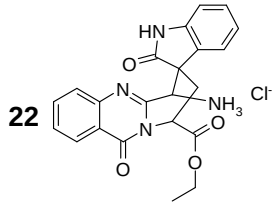
Nucleus	1H	Solvent	METHANOL-D4	Frequency (MHz)	499.92

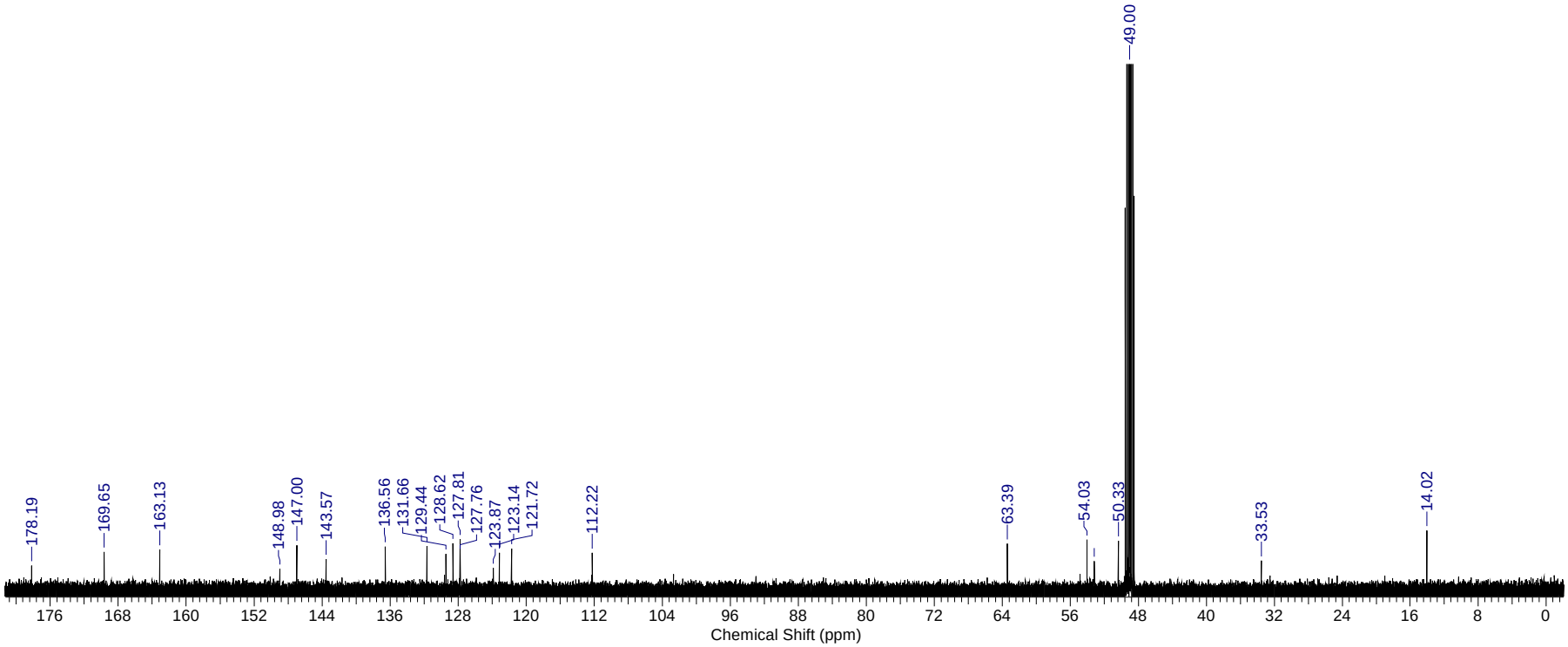




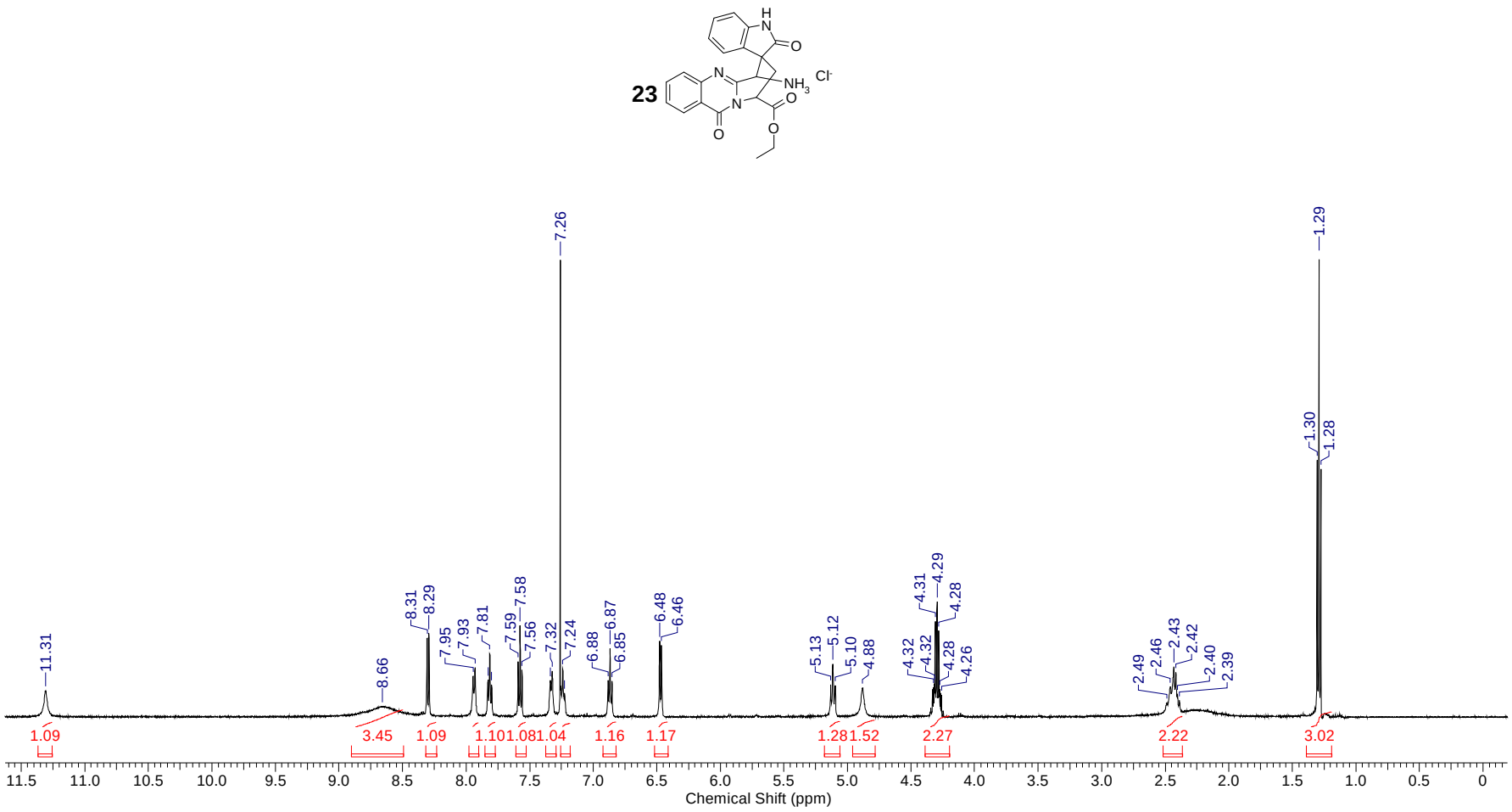
Nucleus	13C	Solvent	METHANOL-D4	Frequency (MHz)	125.72

22



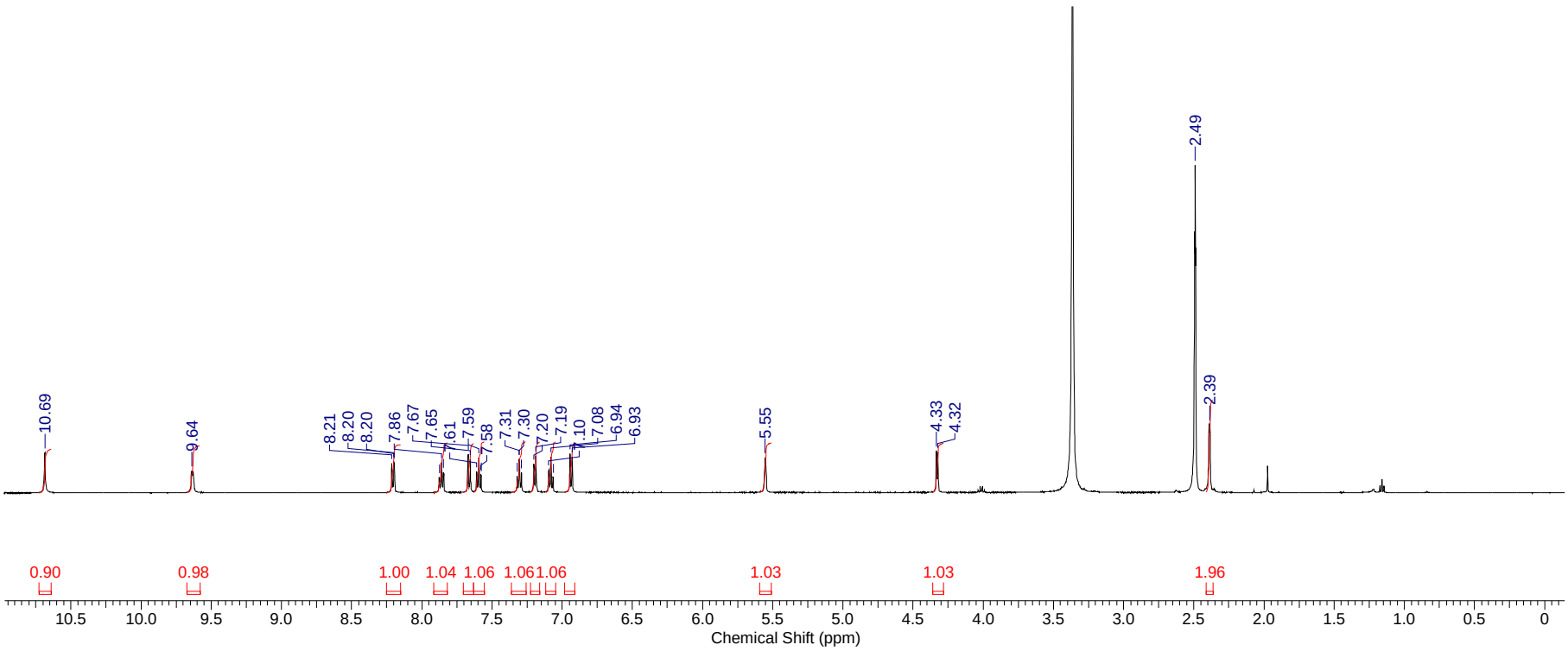


Nucleus	1H	Solvent	CHLOROFORM-D	Frequency (MHz)	499.91

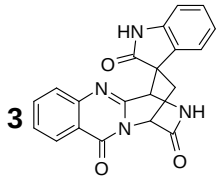


Nucleus	1H	Solvent	DMSO-D6	Frequency (MHz)	499.92

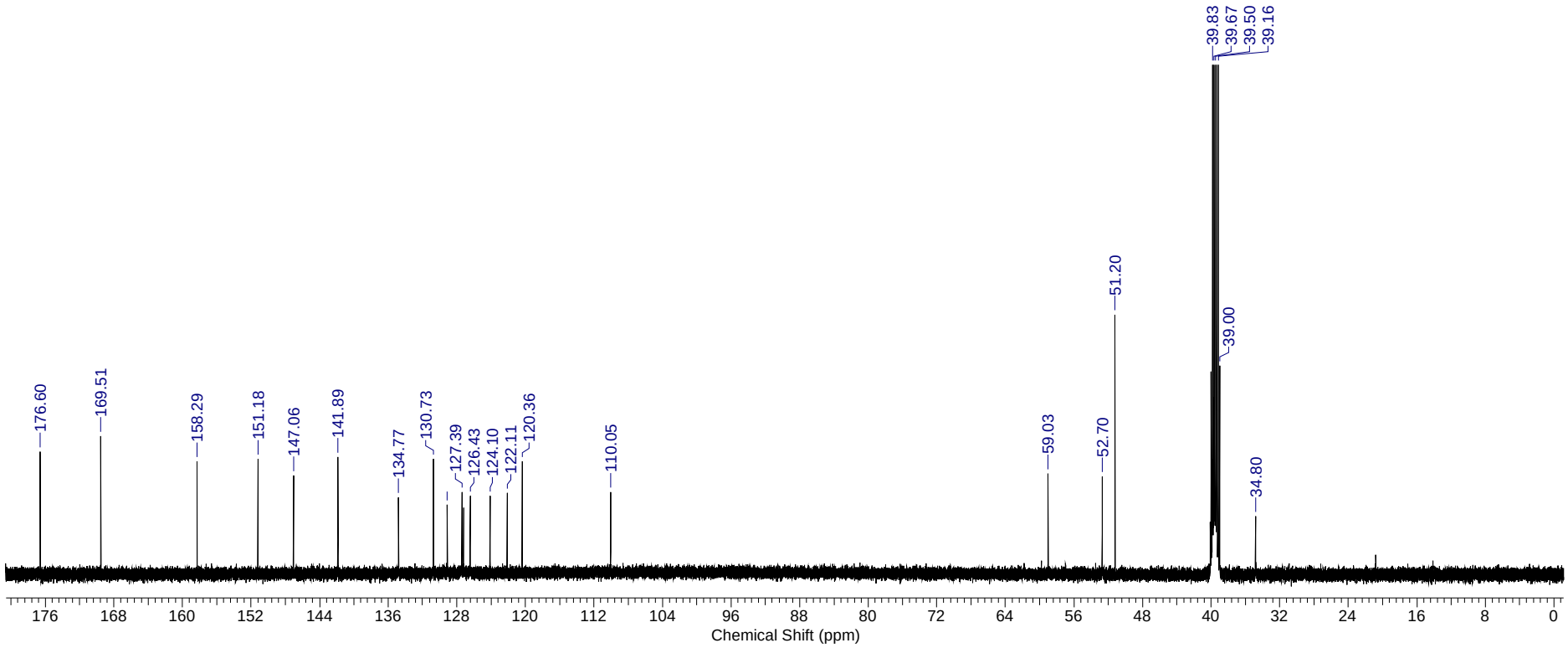
3



Nucleus	13C	Solvent	DMSO-D6	Frequency (MHz)	125.72

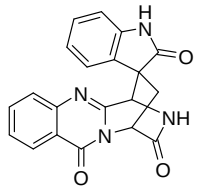


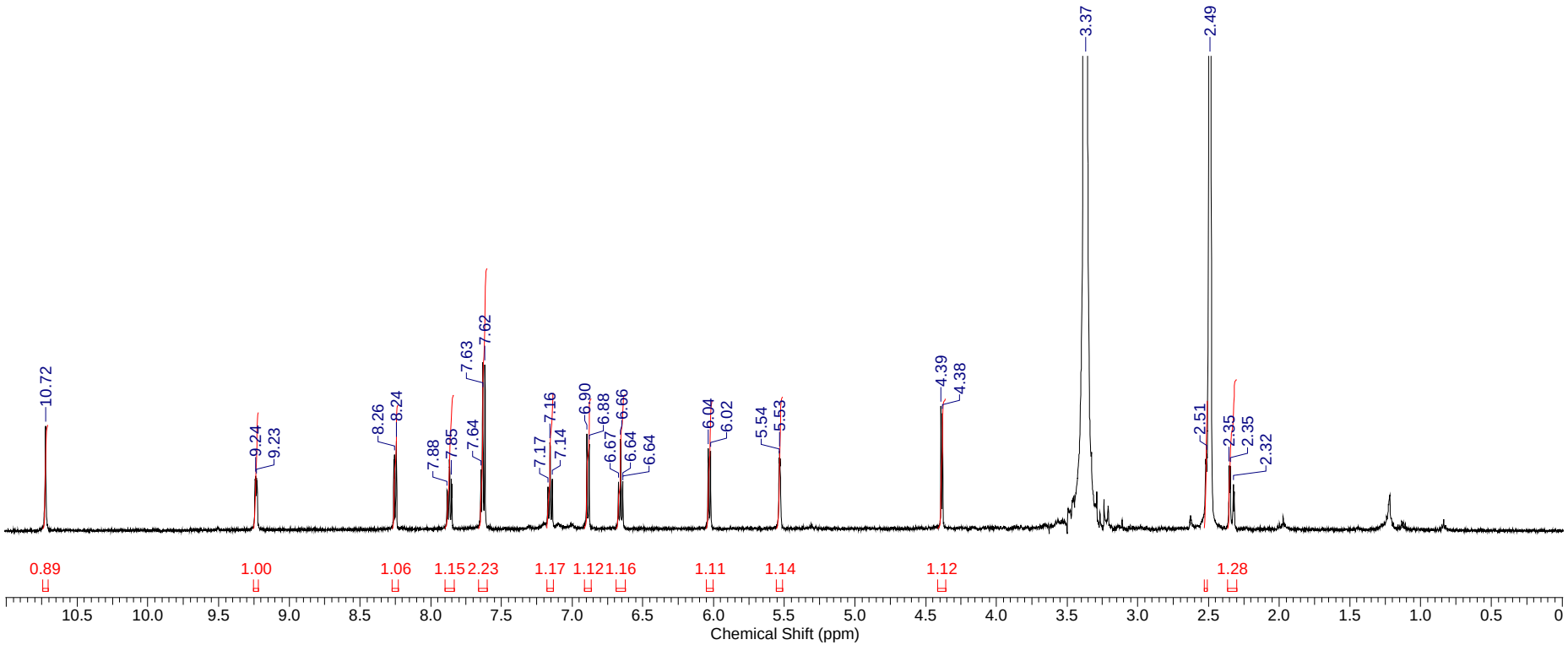
3



Nucleus	1H	Solvent	DMSO-D6	Frequency (MHz)	499.92

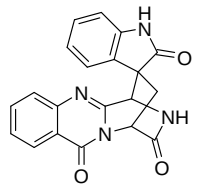
24

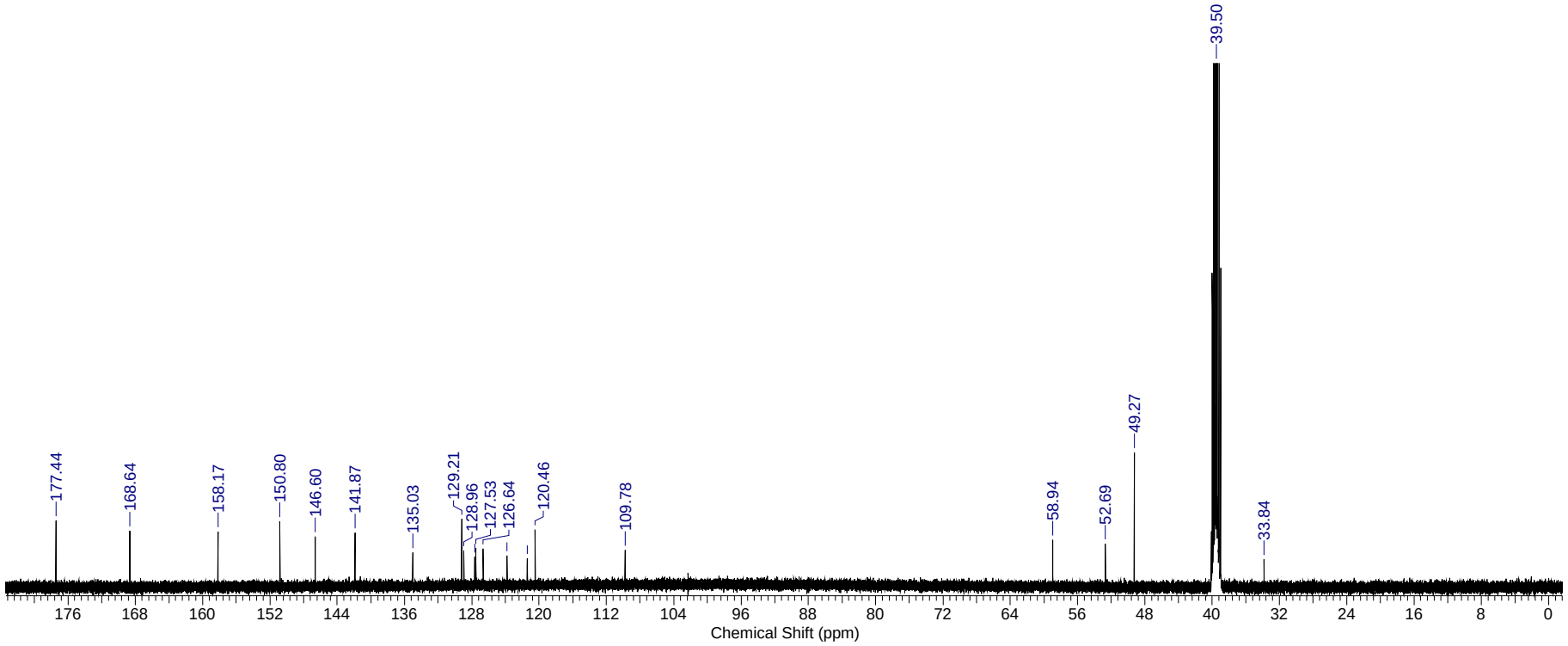




Nucleus	13C	Solvent	DMSO-D6	Frequency (MHz)	125.72

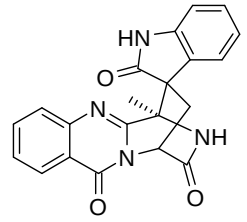
24

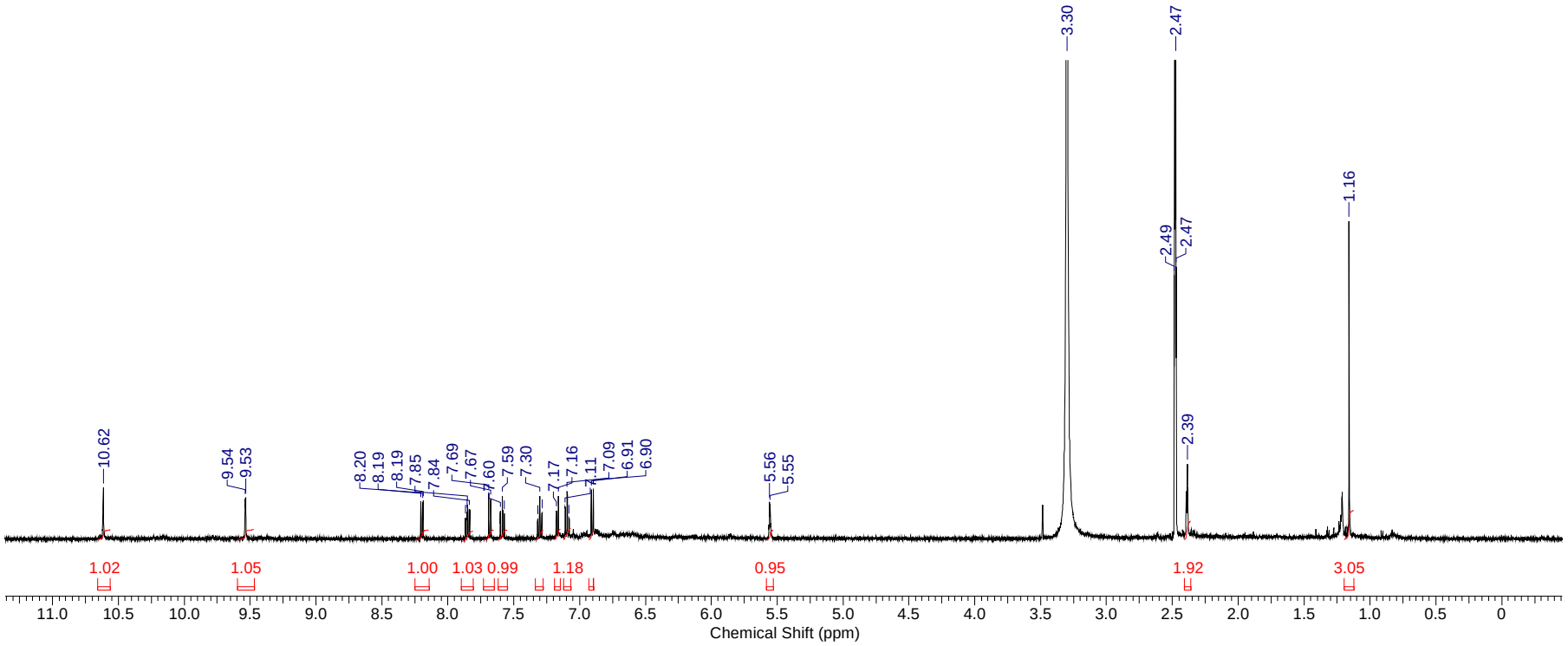




Nucleus	1H	Solvent	DMSO-D6	Frequency (MHz)	499.92

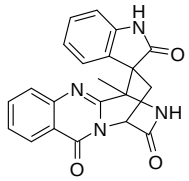
1

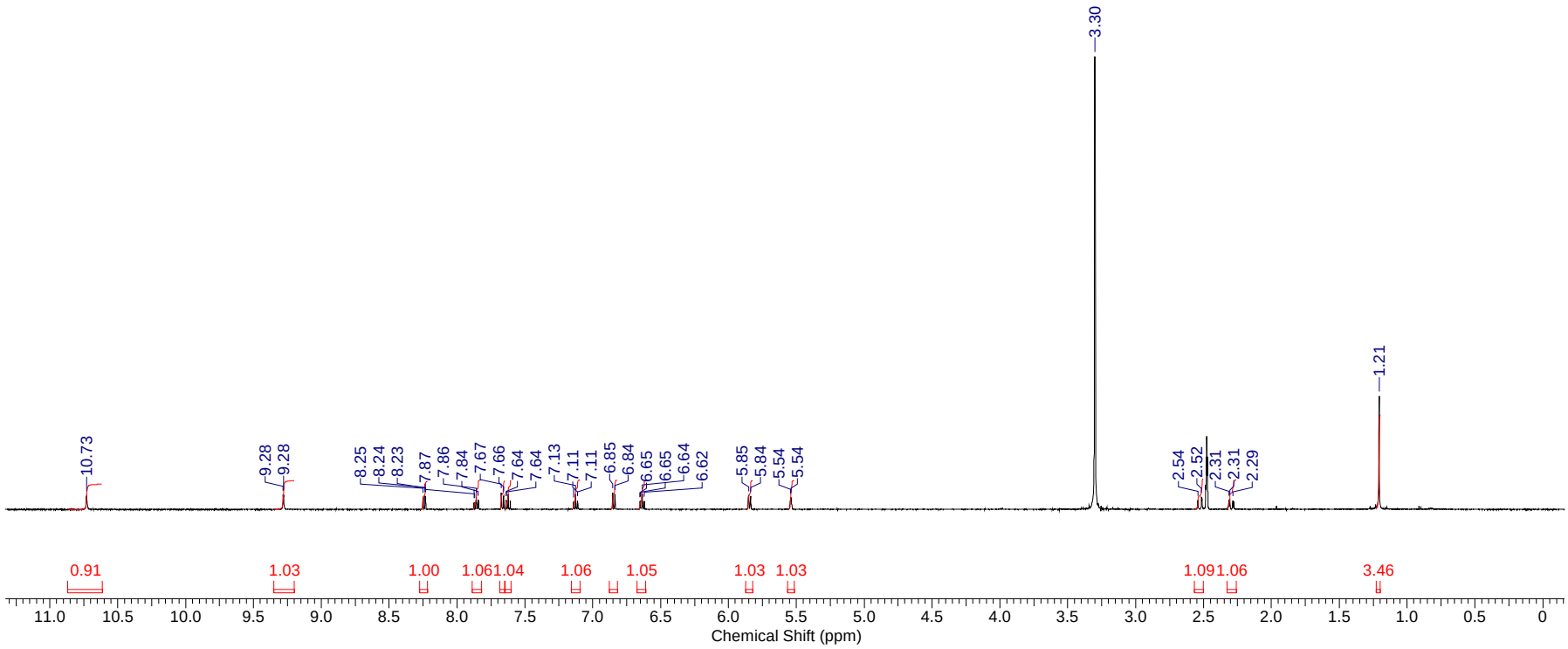




Nucleus	1H	Solvent	DMSO-D6	Frequency (MHz)	499.92

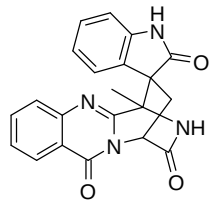
25

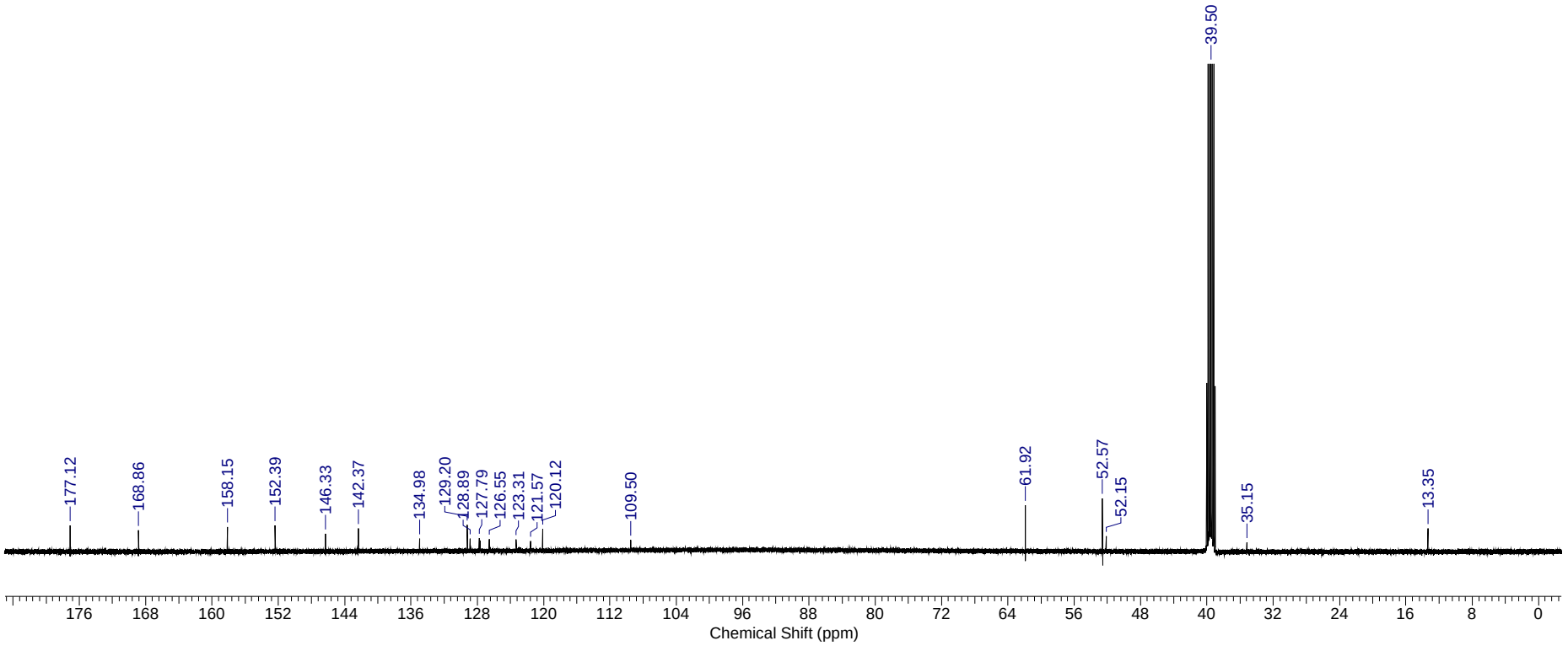




Nucleus	13C	Solvent	DMSO-D6	Frequency (MHz)	125.72

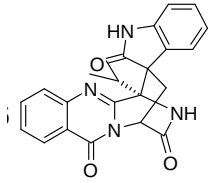
25

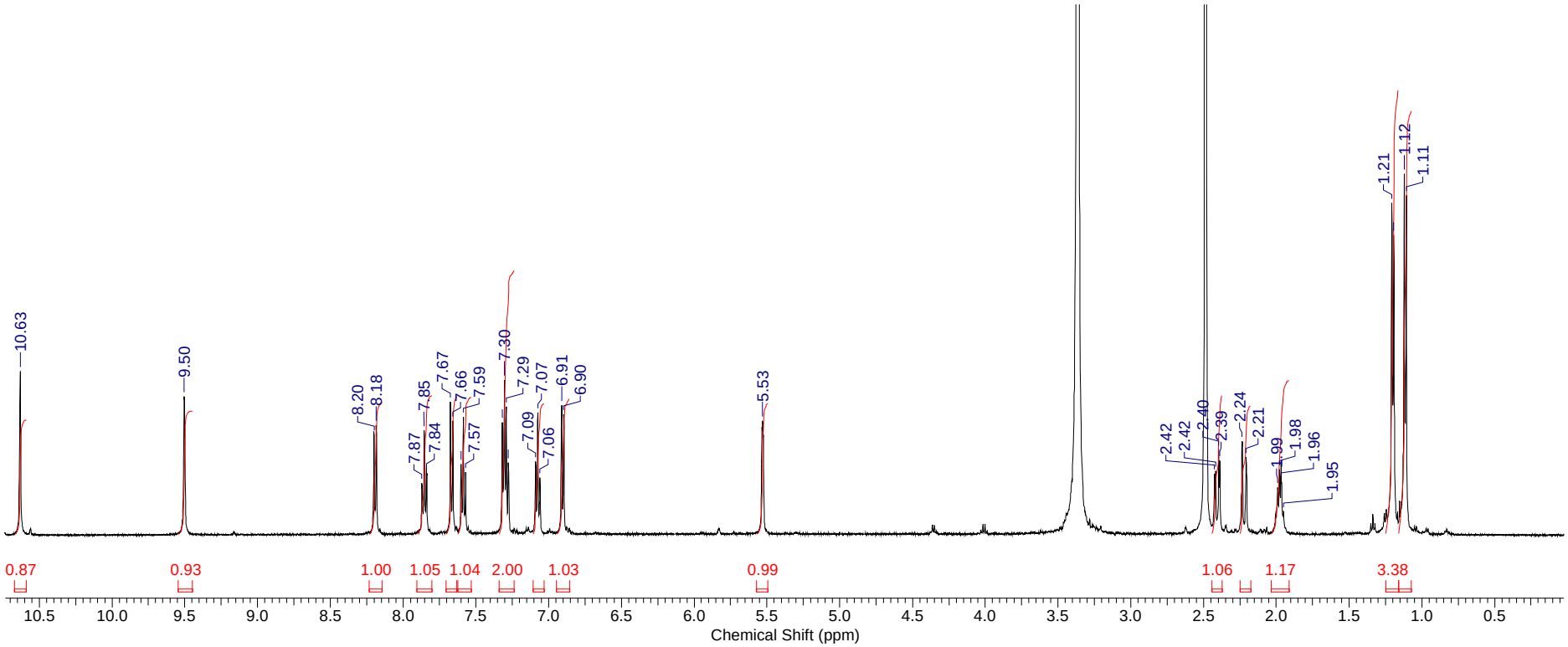




Nucleus	1H	Solvent	DMSO-D6	Frequency (MHz)	499.92

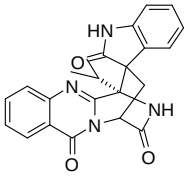
26

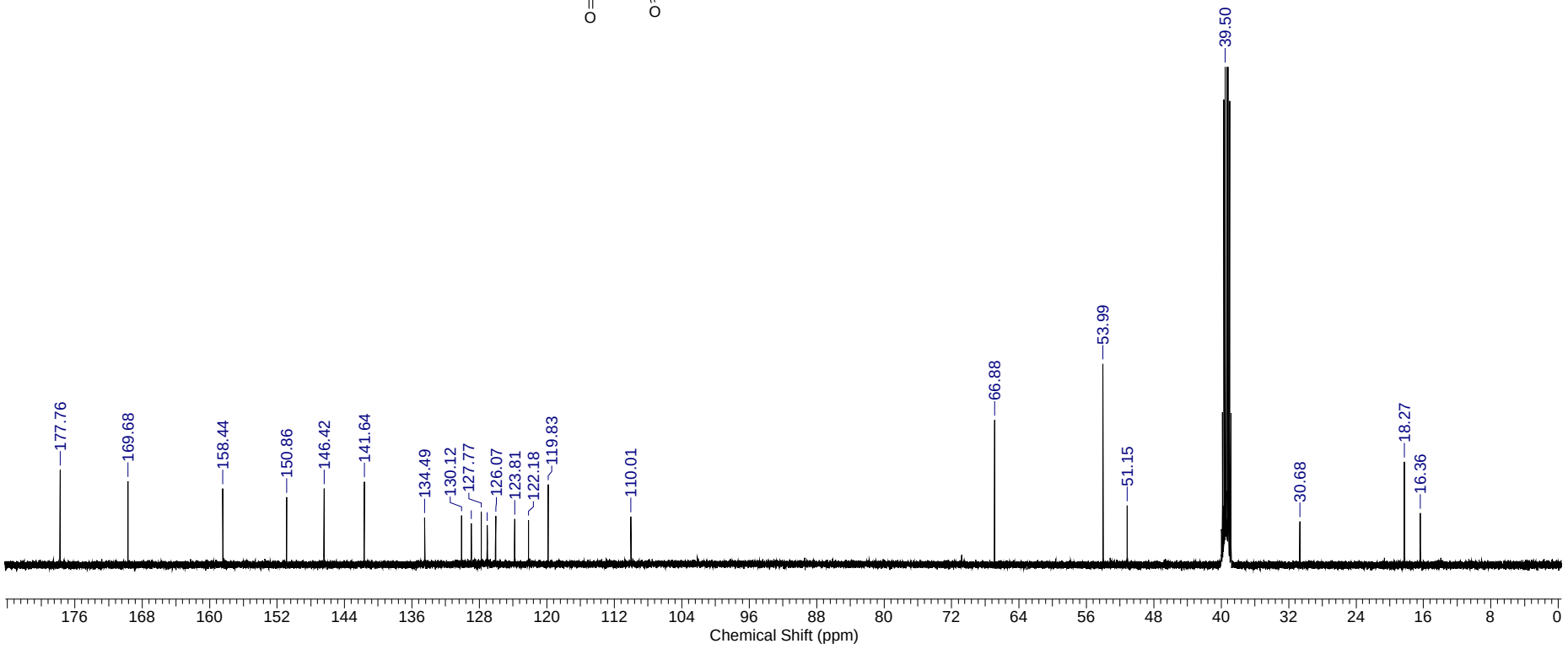




Nucleus	13C	Solvent	DMSO-D6	Frequency (MHz)	125.72

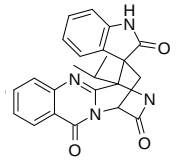
26





Nucleus	1H	Solvent	CHLOROFORM-D	Frequency (MHz)	400.13

27



Nucleus	13C	Solvent	METHANOL-D4	Frequency (MHz)	125.72

27