Supporting Information

Microwave-assisted Intramolecular Suzuki-Miyaura Reaction to Macrocycle, a Concise Asymmetric Total Synthesis of Biphenomycin B

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General information

Melting points were recorded using Reichert melting point apparatus.

Mass spectra were obtained either from an AEI MS-50 instrument using electron impact ionization (EI), from an AEI MS-9 using electron spray (ES), or from a MALDI-TOF type of instrument for the high resolution mass spectra (HRMS).

Proton NMR (^{1}H) spectra were at 500 MHz or 300 MHz spectrometer. Carbon NMR (^{13}C) spectra were similarly recorded at 125 or 75 MHz spectrometer, using a broadband decoupled mode with the multiplicities obtained using a JMOD or DEPT sequence.

Chemical shifts (δ) are reported in parts per million (ppm) from tetramethylsilane. NMR experiments were carried out in $CDCl_3$, or D_2O. The following abbreviations are used for the multiplicities: s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet, brs: broad singlet for proton spectra. Coupling constants (*J*) are reported in Hertz (Hz).

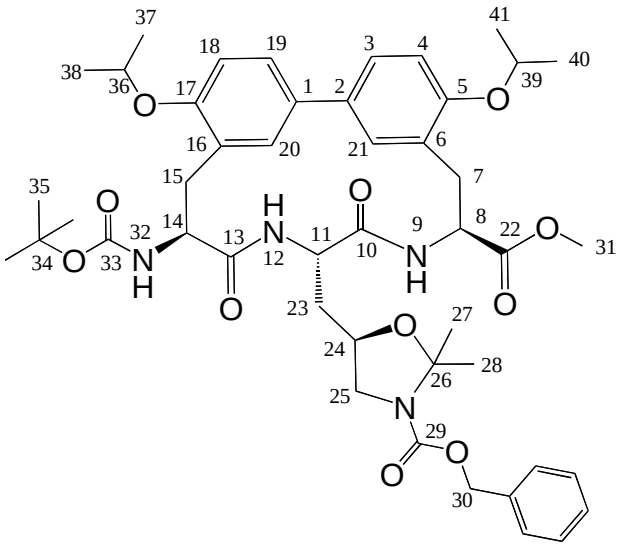
Infrared spectra were recorded on a Nicolet 205 FT-IR spectrometer.

Flash chromatography was performed using Kieselgel Si 60, 40-63 ⌈m particle sized silica gel (200-400 mesh). Visualization was achieved under a UVP mineralight UVGL-58 lamp, and by developing the plates with Draggendorf's reagent or potassium permanganate ($KMnO_4$).

Microwave experiments were conduced using a Discover microwave reactor from CEM. All experiments were performed in sealed tubes (capacity 10mL) under argon atmosphere. The temperature of the contents of the vessel was monitored using a calibrated infrared temperature control mounted under the reaction vessel. Microwave irradiation of 20W was used, the temperature being ramped from room temperature to 110°C in 2 minutes. Once this temperature was reached, the reaction mixture was held at 110°C for 30 minutes.

All reagents were obtained from commercial suppliers unless otherwise stated.

Synthesis and physical data of Compound 20:



In a 10-mL glass tube were placed the linear tripeptide **4** (11.3 mg, 0.0103 mmol), 5.0 mL of degassed toluene, 1.0 mL of distilled water, K_2CO_3 (8.8 mg, 0.072 mmol), a catalytic amount of tetrabutylammonium bromide (one crystal), catalyst **24** (0.61mg, 0.00061 mmol), and a magnetic stir bar. The vessel was sealed with a septum and placed into the microwave cavity. Microwave irradiation of 20W was used, the temperature being ramped from room temperature to 110°C. Once 110°C was reached, the reaction mixture was held at this temperature for 30 min. After being cooled to room temperature, the reaction mixture was diluted by addition of water and the aqueous phase was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and evaporated to dryness under reduced pressure. This crude residue was purified by column chromatography on silica gel (eluant: CH_2Cl_2/Acetone = 9/1) to give protected biphenomycin B **20** as a white solid (4.3 mg, 50% yield).

mp = 238°C

α_D **=** + 1.6 (*c* 1.4, $CHCl_3$)

IR ν 3271, 2972, 2926, 1744, 1709, 1648, 1486 cm^{-1}.

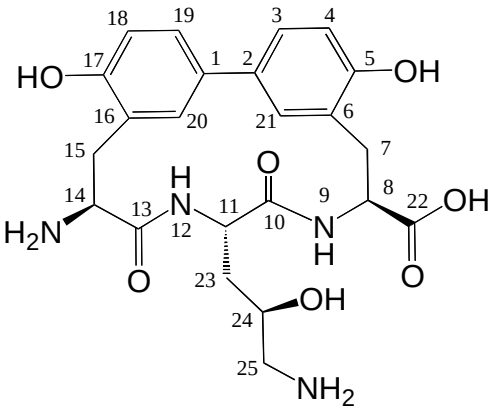
H^1 NMR ($CDCl_3$, 500MHz) δ (ppm) 1.25 (d, 3H, *J* = 6.0 Hz), 1.27 (d, 3H, *J* = 6.0 Hz), 1.28 (d, 3H, *J* = 6.0 Hz), 1.32 (d, 3H, *J* = 6.0 Hz), 1.36 (s, 9H), 1.45, 1.49 (brs, 6H), 1.89-1.94 (m, 2H), 2.85-2.88 (dd, 1H, *J* = 3.1 and 14.8 Hz), 2.96-3.05 (m, 1H), 3.04-3.09 (m, 1H), 3.31-3.35 (m, 2H), 3.69-3.70 (m, 1H), 3.72 (s, 3H), 4.11-4.17 (m, 1H), 4.35-4.38 (m, 1H), 4.46 (septet, 1H, *J* = 6 Hz), 4.50 (septet, 1H, *J* = 6.3 Hz), 4.67-4.73 (m, 1H), 4.87-4.91 (m, 1H), 5.00-5.08 (m, 2H), 5.36-5.42 (m, 1H), 6.47-6.51 (m, 1H), 6.67-6.72 (m, 1H), 6.76 (d, 1H, *J* = 2.8 Hz), 6.78 (d, 1H, *J* = 2.5 Hz), 7.06 (brd, 1H), 7.18 (brd, 1H), 7.22-7.32 (m, 7H).

^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 22.1, 22.2, 22.3 (2C), 24.2, 26.2, 28.4 (3C), 30.1, 31.4, 37.2, 50.2, 50.6, 51.9, 52.6, 54.9, 66.5, 70.1, 70.7 (2C), 79.6, 94.3, 113.0, 113.4, 124.5, 124.9, 125.6, 125.9, 127.9 (2C), 128.0 (2C),128.1, 128.5, 128.7, 131.7, 131.9, 136.7, 152.1, 154.6, 154.7, 155.3, 170.3, 170.8, 171.9.

MS (ESI^+) m/z 867 ($M+Na^+$)

HRMS (ESI^+) m/z calculated for $C_{46}H_{60}N_4O_{11}$ ($M+Na^+$) 867.4156, found 867.4134.

Synthesis and physical data of Biphenomycin B.



• 2 HCl

To a solution of fully protected biphenomycin B (25.6 mg, 0.03 mmol) in dichloromethane (0.6 ml) cooled to 0°C, was added boron trichloride (1M solution in dichloromethane, 0.6 ml, 0.6 mmol). The mixture was stirred under argon atmosphere for 4 hours. Then, the solution was quenched with dry methanol and the volatiles were removed *in vacuo*. The crude product was dissolved in a mixture of dioxane and water (1/1). Then, a

solution of 2N lithium hydroxide in water (0.15 ml, 0.15 mmol) was added. After 24 hours of stirring at room temperature, the mixture was quenched with a 0.2 N solution of $KHSO_4$. Dioxane and water were then removed under reduced pressure. The crude product was purified by HPLC (column symmetry shield C18 4.6*150mm, water + 0.1%TFA/ acetonitrile + 0.1%TFA = 85/15; retention time = 7.37 min.) to give after salt formation the **biphenomicyn B.2HCl** as a white solid (16 mg, 95% yield)

α_D = + 4.3 (*c* 3.0, 1N HCl)

IR ν 2957, 1732, 1719, 1638, 1615, 1545, 1499, 1441 cm^{-1}.

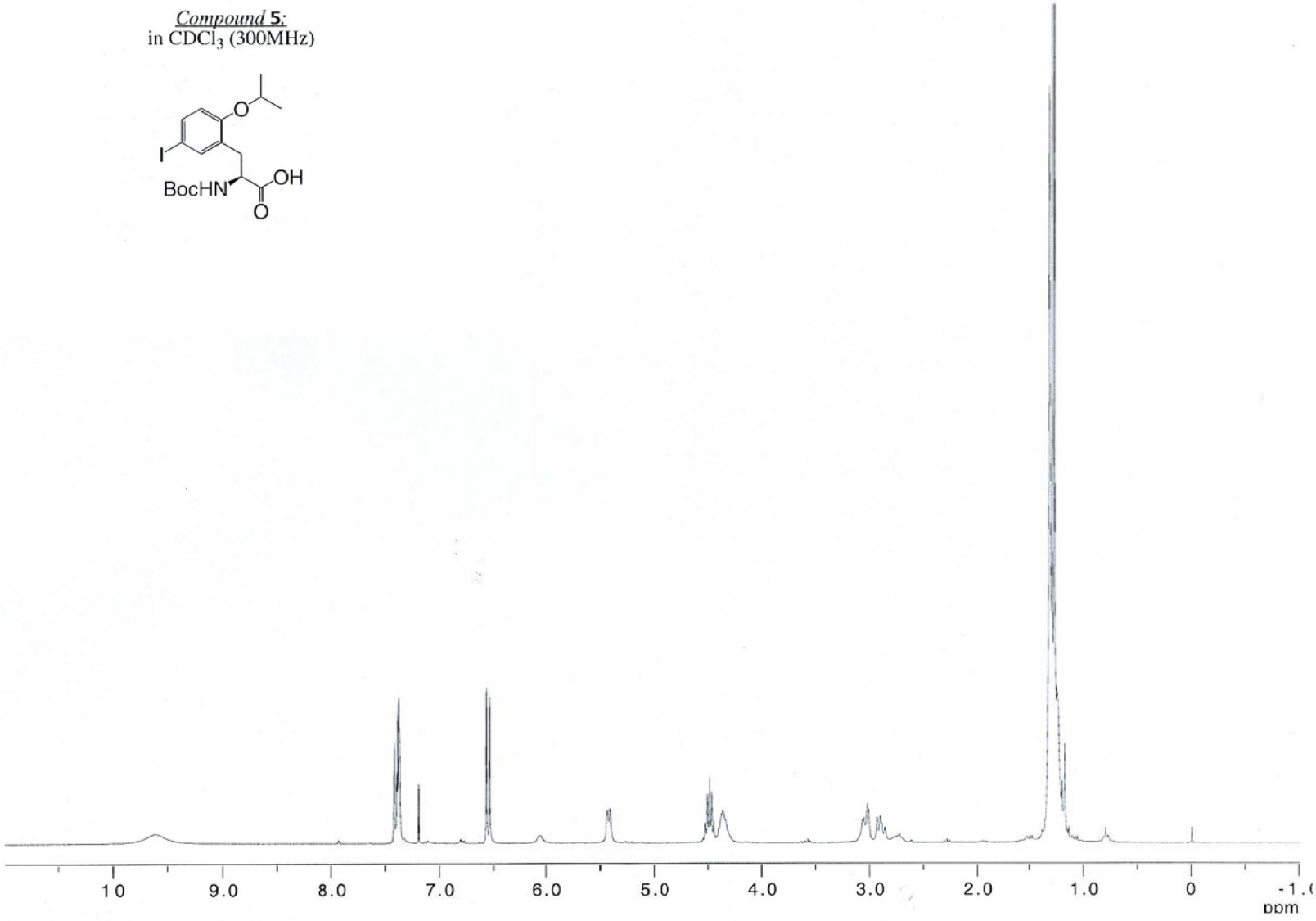
H^1 NMR (D_2O, 500MHz) δ (ppm) 1.97-2.03 (m, 1H, $H_{23'}$), 2.10-2.17 (m, 1H, H_{23}), 2.85 (dd, 1H, *J* = 16.0 and 11.3 Hz, $H_{7'}$), 3.03 (dd, 1H, *J* = 13.0 and 9.8 Hz, $H_{25'}$), 3.20 (dd, 1H, *J* = 15.1 and 2.8 Hz, $H_{15'}$), 3.23 (dd, 1H, *J* = 13.0 and 2.8 Hz, H_{25}), 3.55 (dd, 1H, *J* = 16.0 and 1.9 Hz, H_7), 3.70 (dd, 1H, *J* = 15.1 and 5.0 Hz, H_{15}), 4.05 (m, 1H, H_{24}), 4.56 (dd, 1H, *J* = 5.0 and 2.8 Hz, H_{14}), 4.63 (dd, 1H, *J* = 11.3 and 1.9 Hz, H_8), 4.97 (dd, 1H, *J* = 9.8 and 6.0 Hz, H_{11}), 7.04 (d, 1H, *J* = 8.0 Hz, H_4), 7.06 (d, 1H, *J* = 8.2 Hz, H_{18}), 7.11 (d, 1H, *J* = 2.2 Hz, H_{20}), 7.45 (brs, 1H, H_{21}), 7.47 (dd, 1H, *J* = 8.0 and 1.9 Hz, H_3), 7.54 (dd, 1H, *J* = 8.2 and 2.2 Hz, H_{19}).

^{13}C NMR (D_2O, 125 MHz) δ (ppm) 29.0 (C7), 29.8 (C15), 37.1 (C23), 45 (C25), 50.8 (C11), 54.8 (C14), 56.2 (C8), 64.8 (C24), 116.2 (C4 and C18), 120.0 (C16), 125.0 (C3 and C1), 126.5 (C6 and C19), 127.6 (C21), 130.4 (C20), 132.4 (C2), 152.8 (C5), 154.4 (C17), 168.8 (C13), 172.2 (C10), 178.8 (C22).

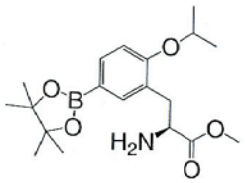
MS ($MALD^+$-TOF) m/z 473 (M-2HCl+H^+), 495 (M-2HCl+Na^+), 511 (M-2HCl+K^+)

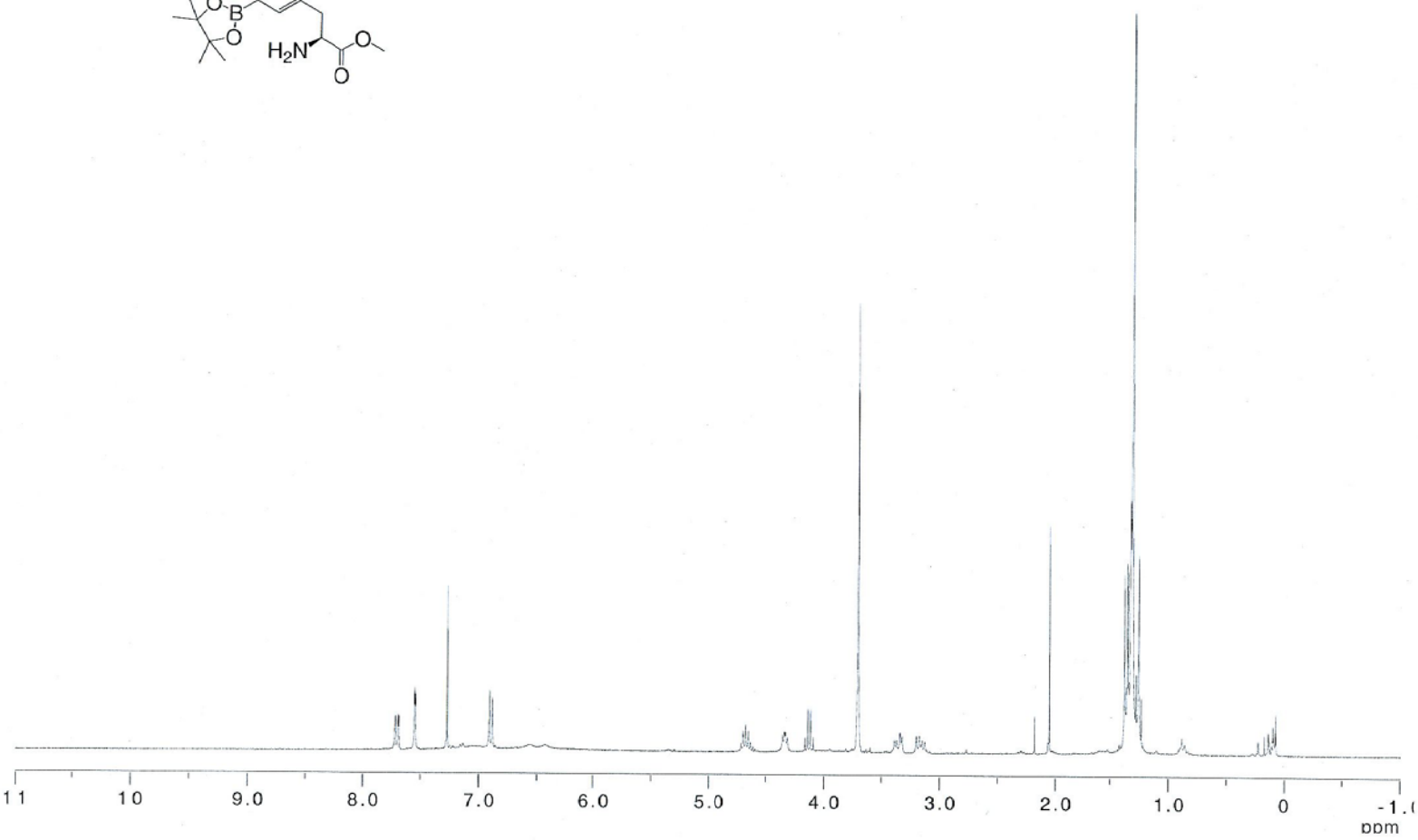
HRMS ($MALD^+$-TOF) m/z calculated for $C_{23}H_{29}N_4O_7$ (M-2HCl+H^+) 473.2036, found 473.2053.

Compound **5**:
in $CDCl_3$ (300MHz)

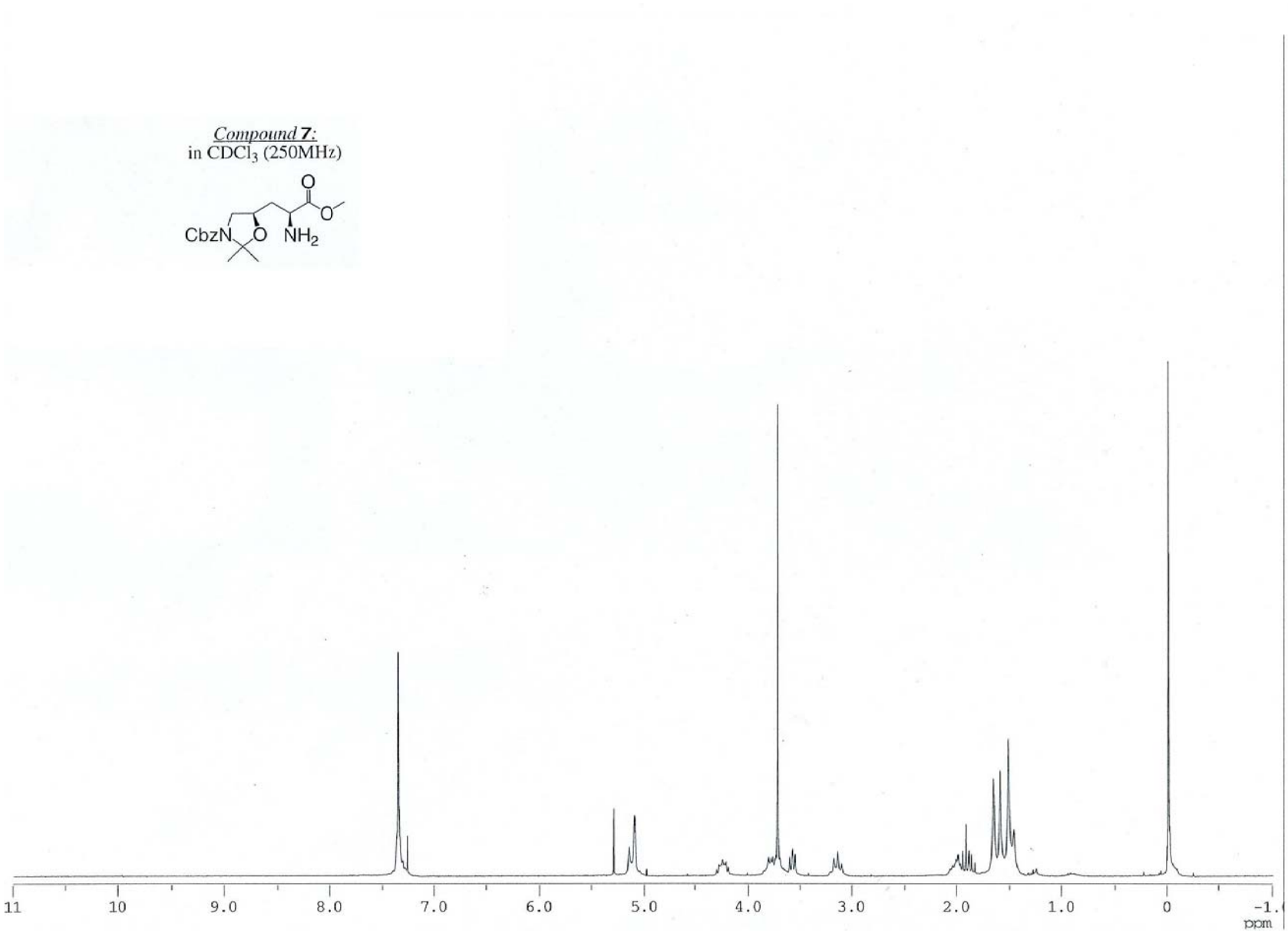


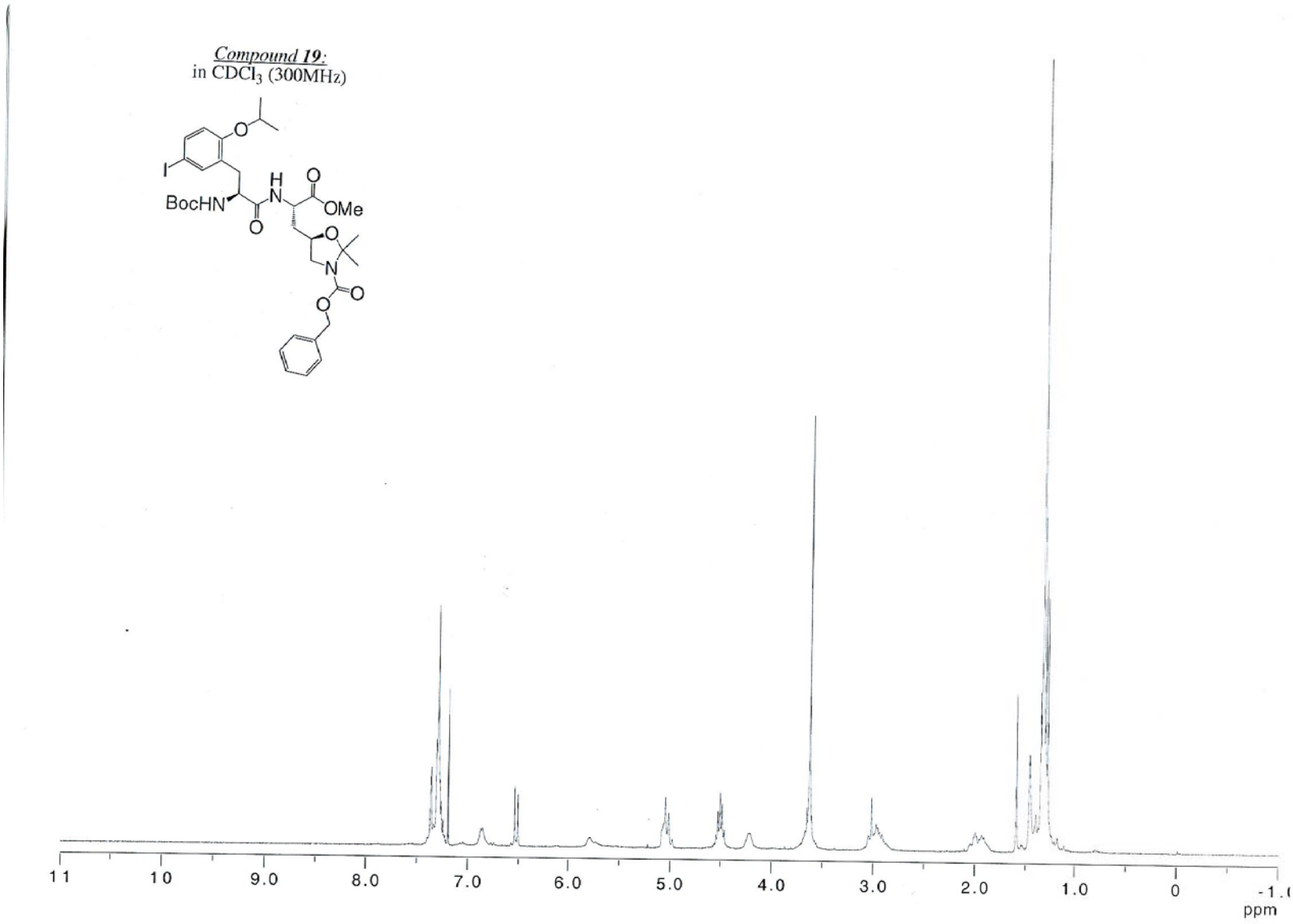
*Compound **6**:*
in $CDCl_3$ (300MHz)



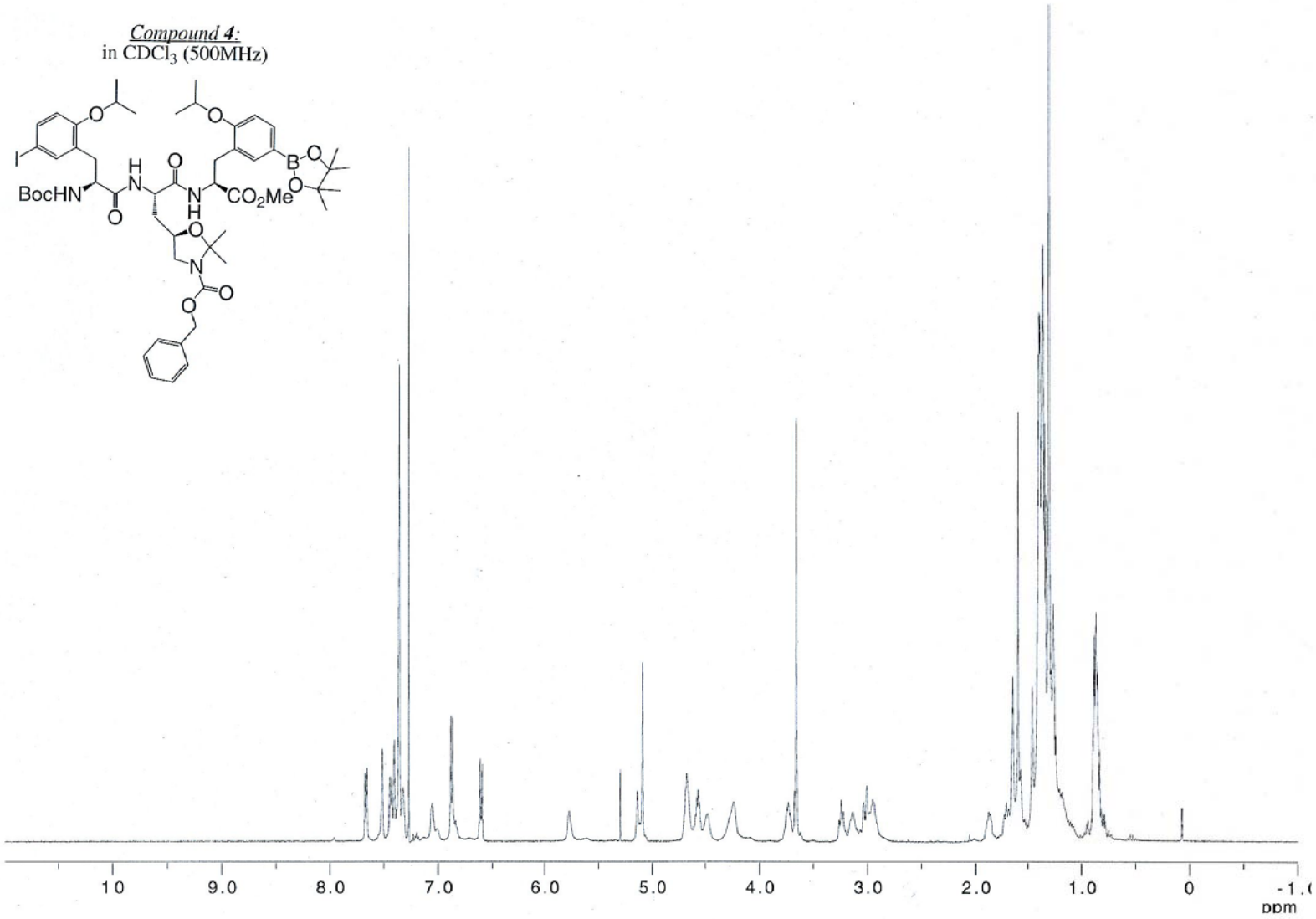


Compound **7**:
in $CDCl_3$ (250MHz)

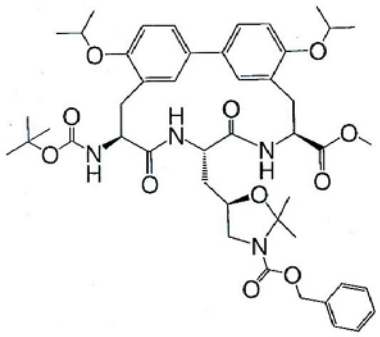


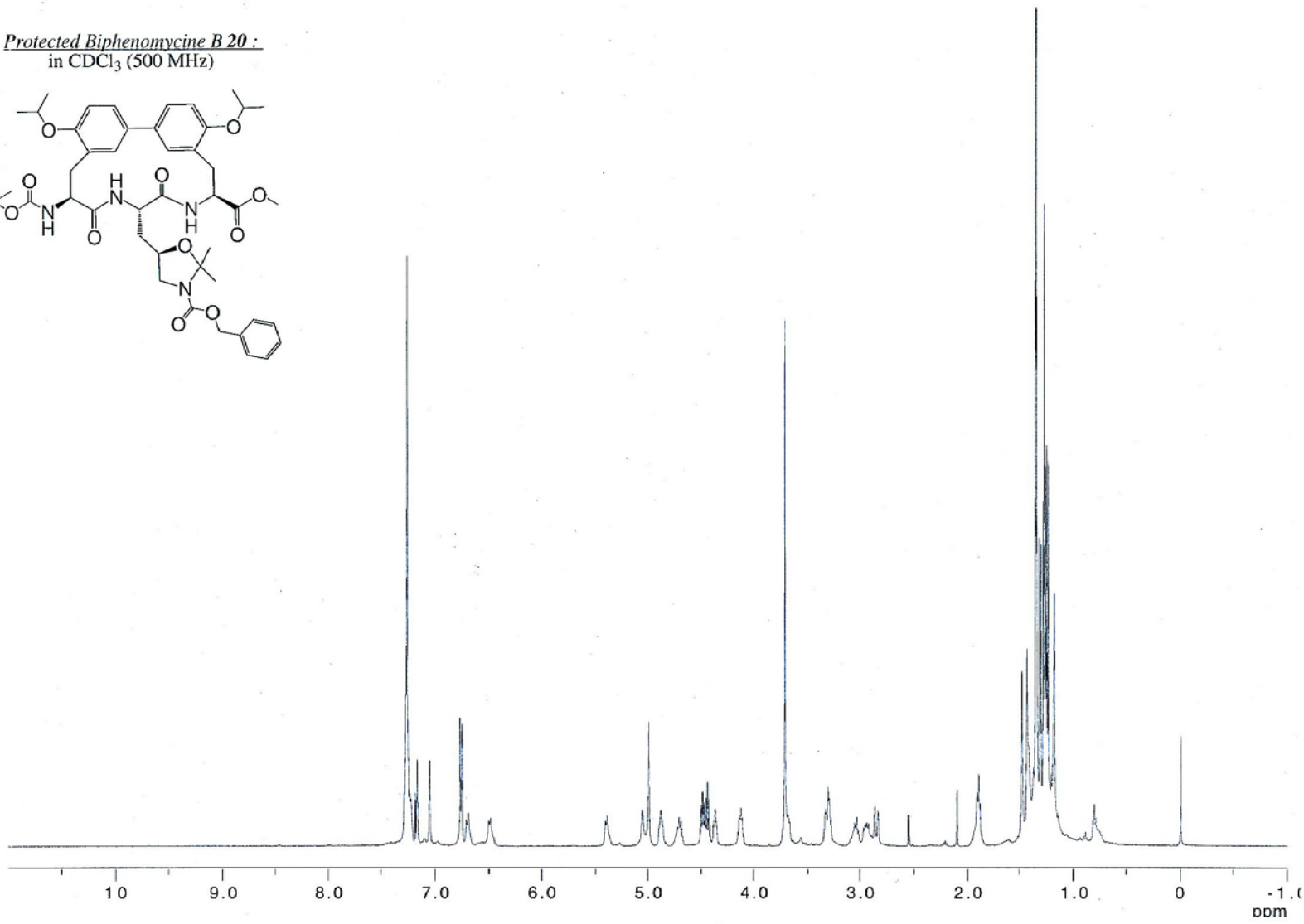

Compound 19:
in CDCl3 (300MHz)
I
O
BocHN
H
N
O
O
OMe
O
N
O
O
11
10
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
ppm

Compound 4:
in $CDCl_3$ (500MHz)



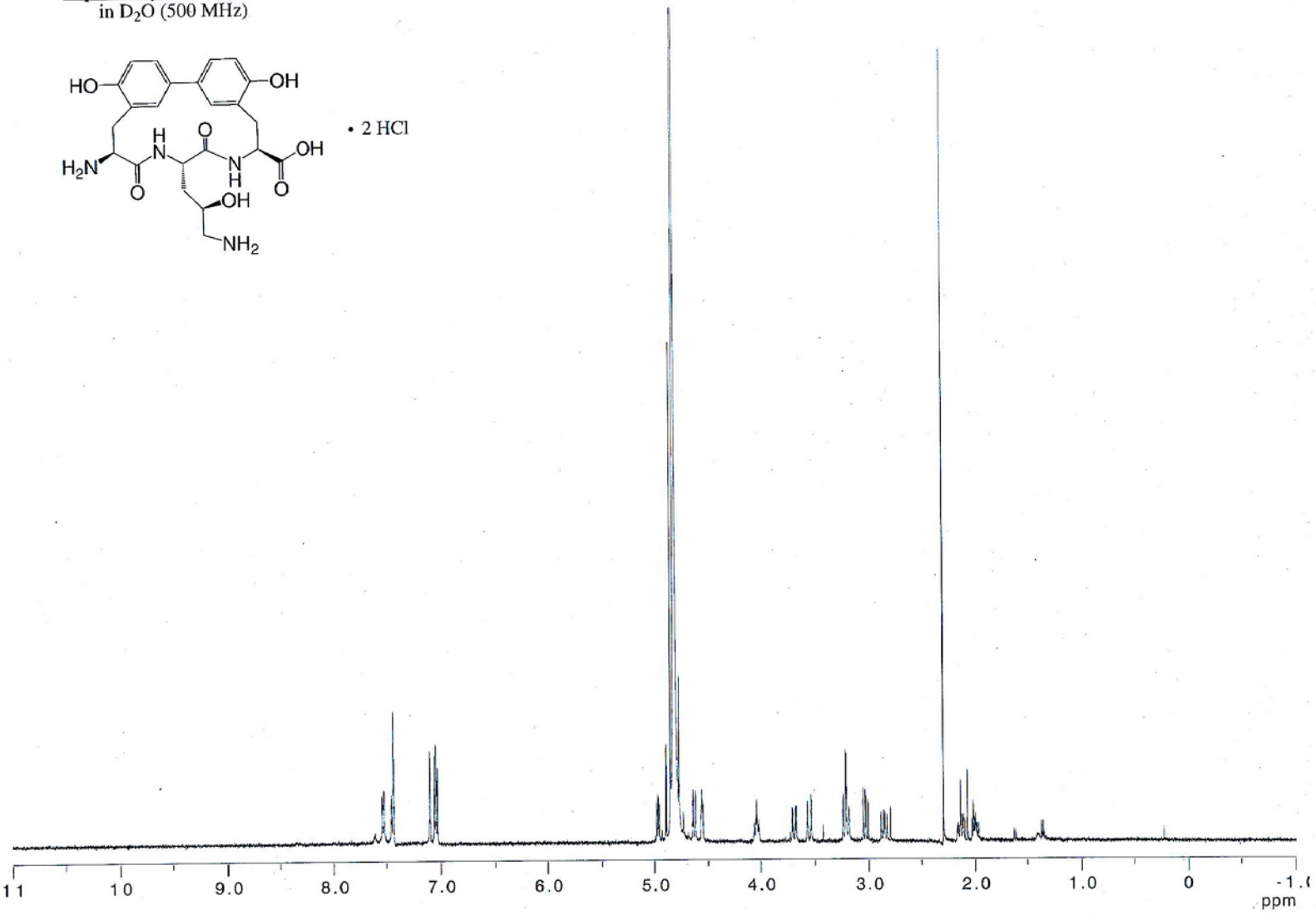
Protected Biphenomycine B ***20*** *:*
in $CDCl_3$ (500 MHz)





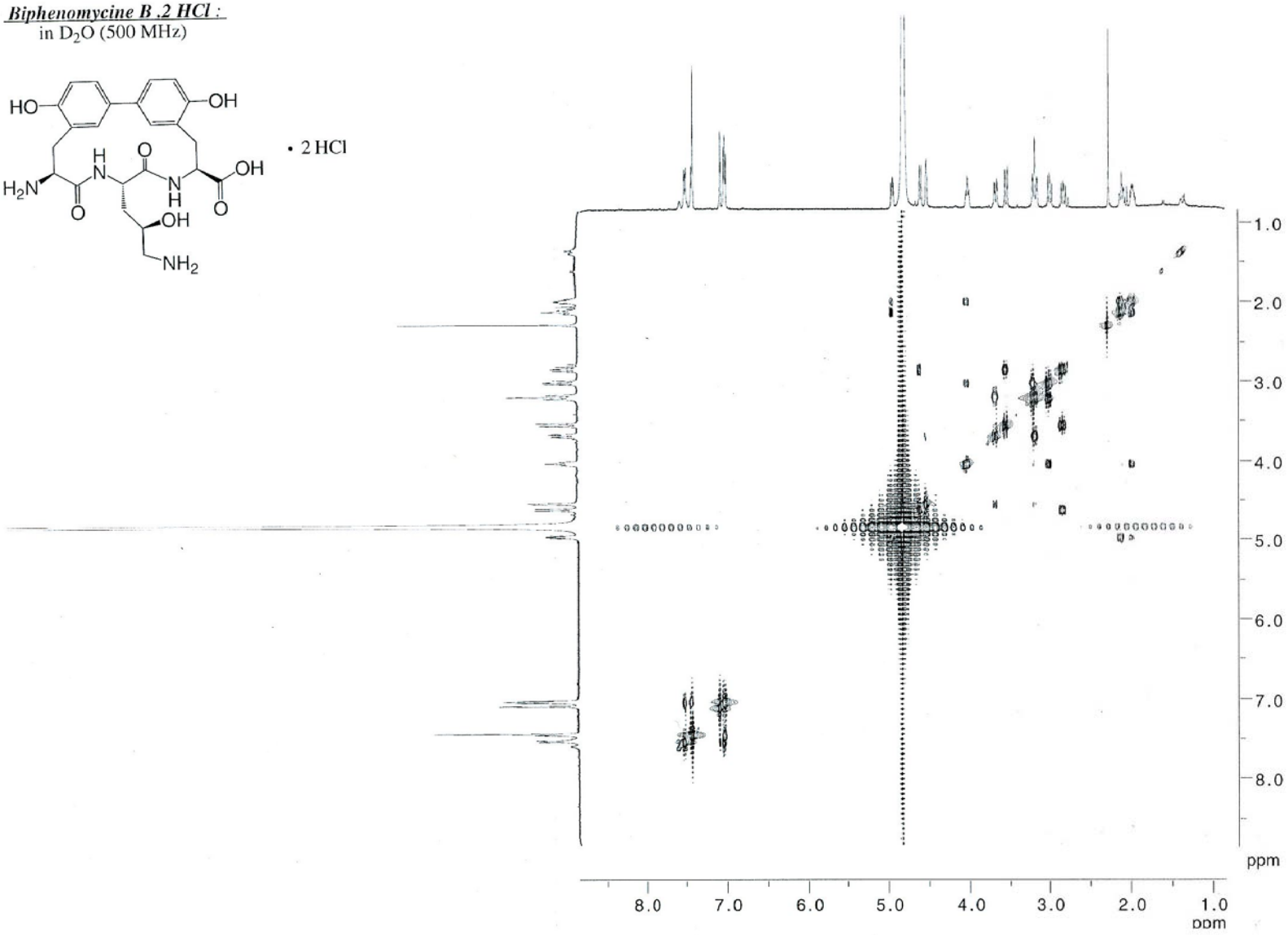
Biphenomycine B ,2 HCl :
in D_2O (500 MHz)

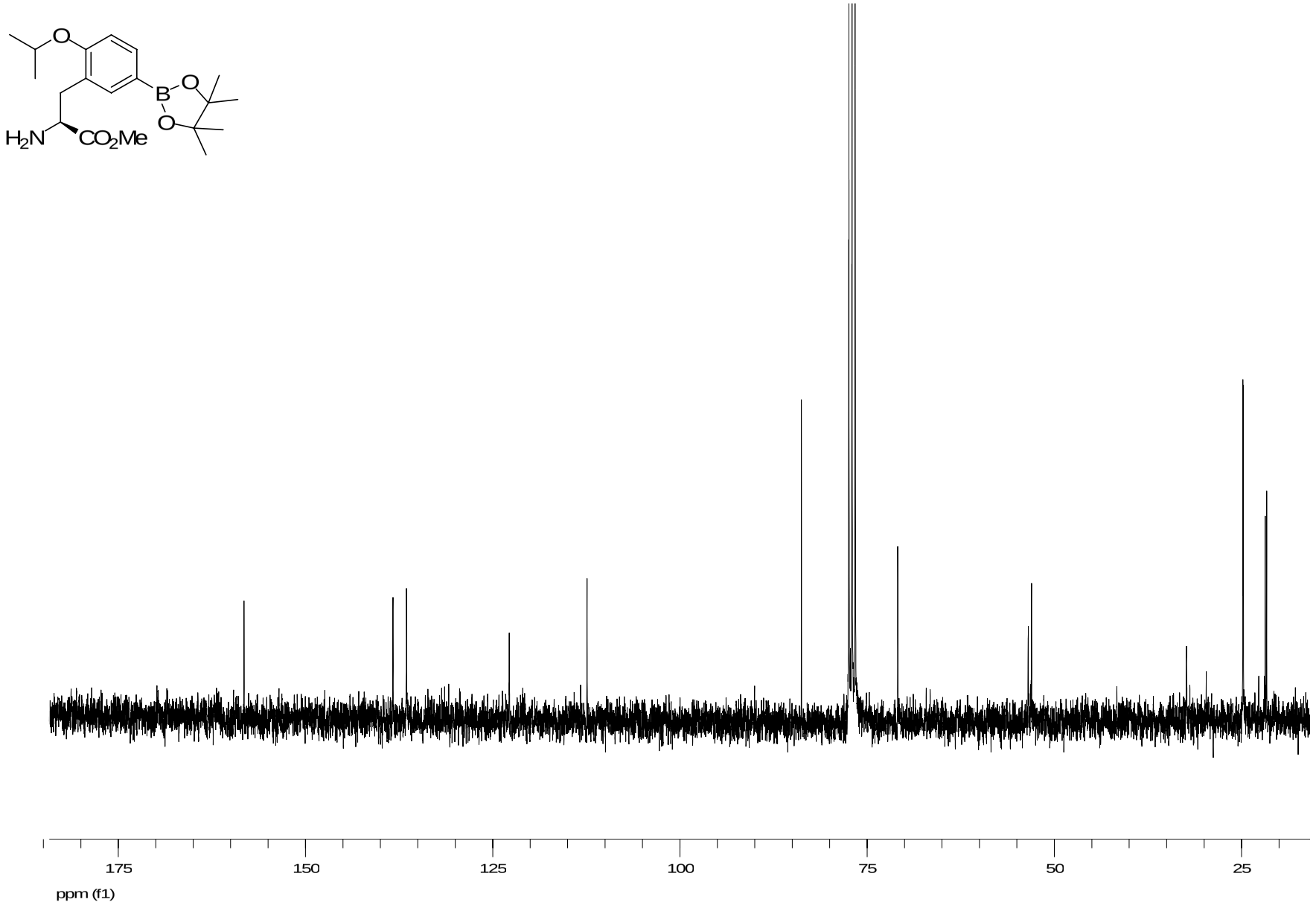
• 2 HCl

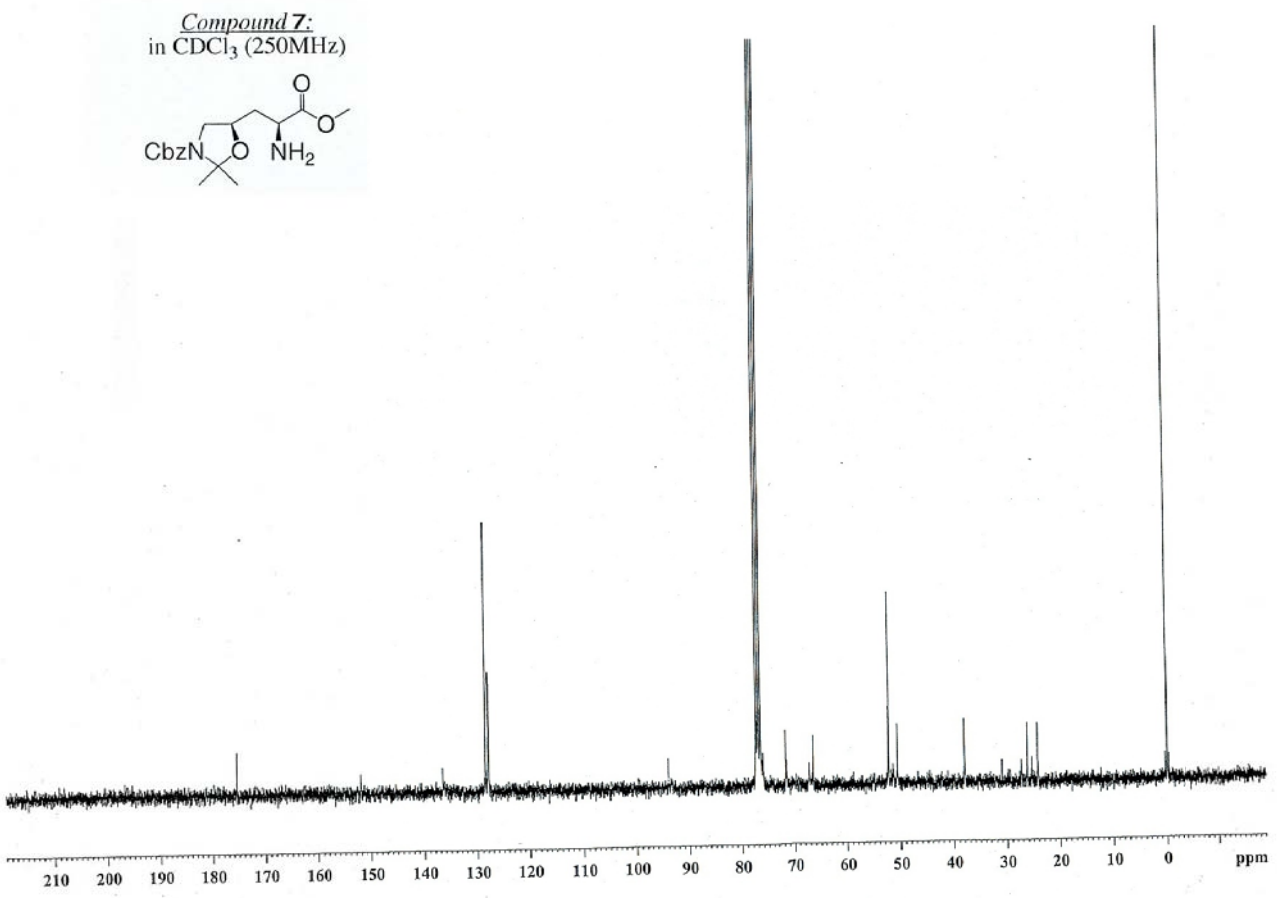


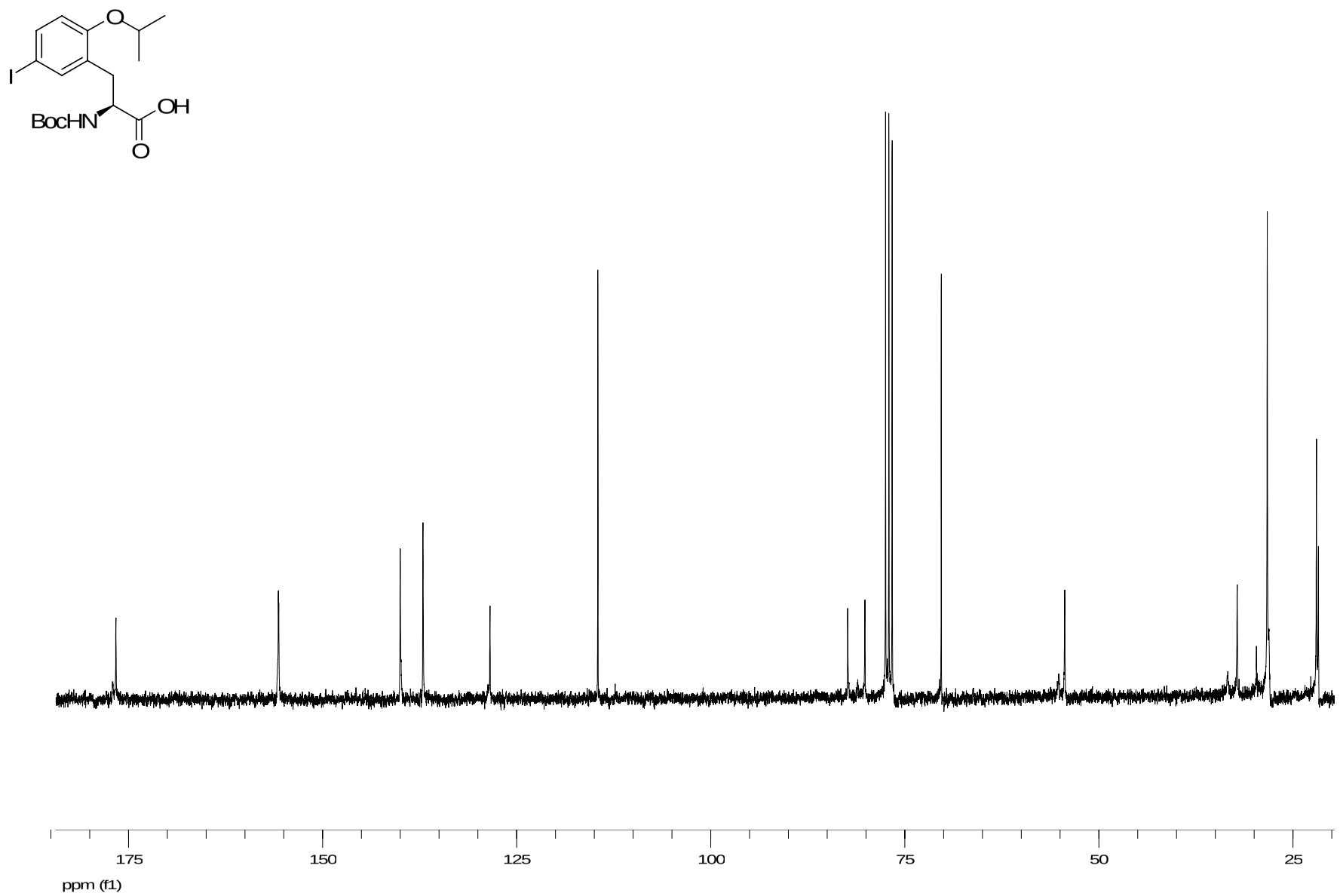
Biphenomycine B .2 HCl :
in D_2O (500 MHz)

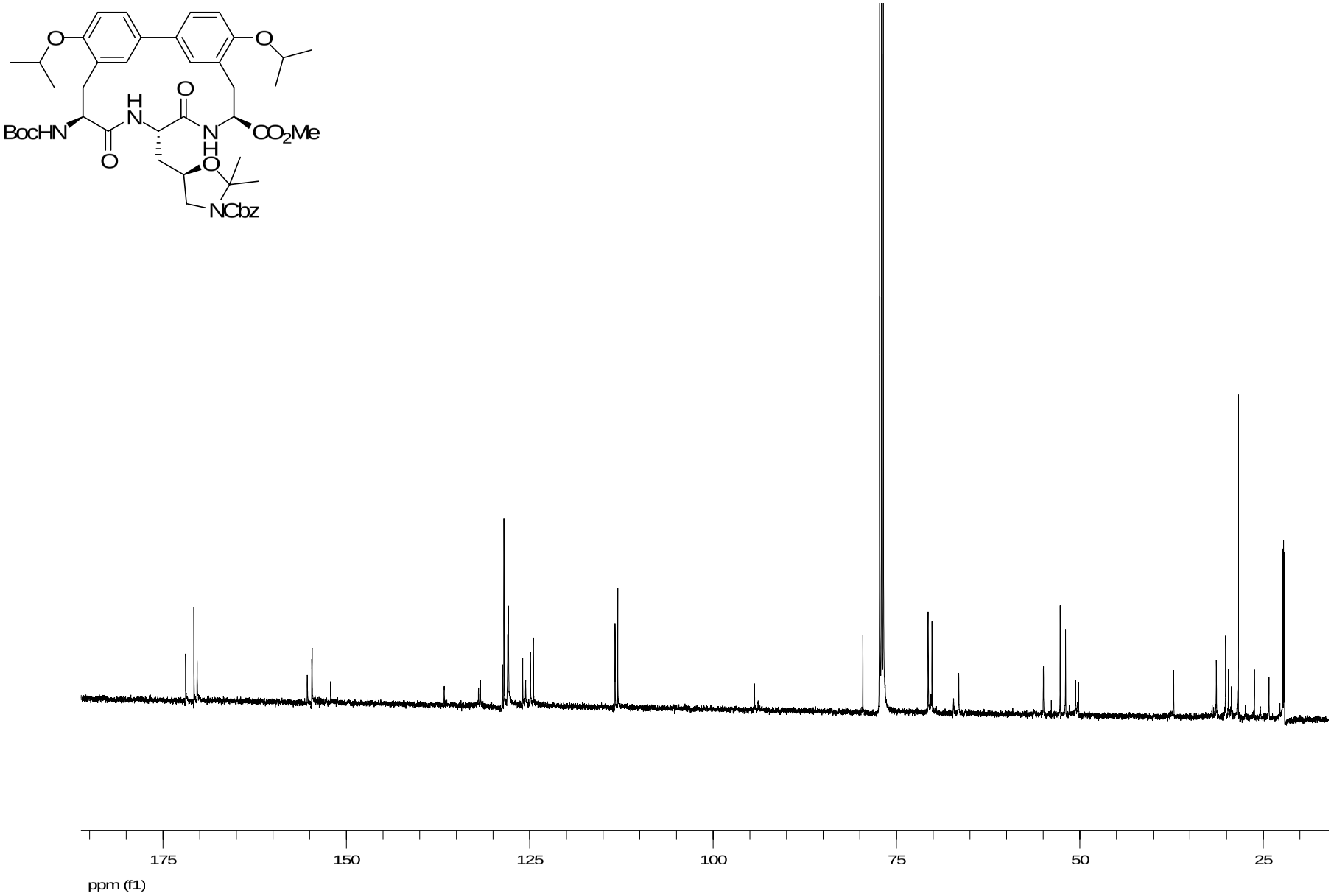
• 2 HCl

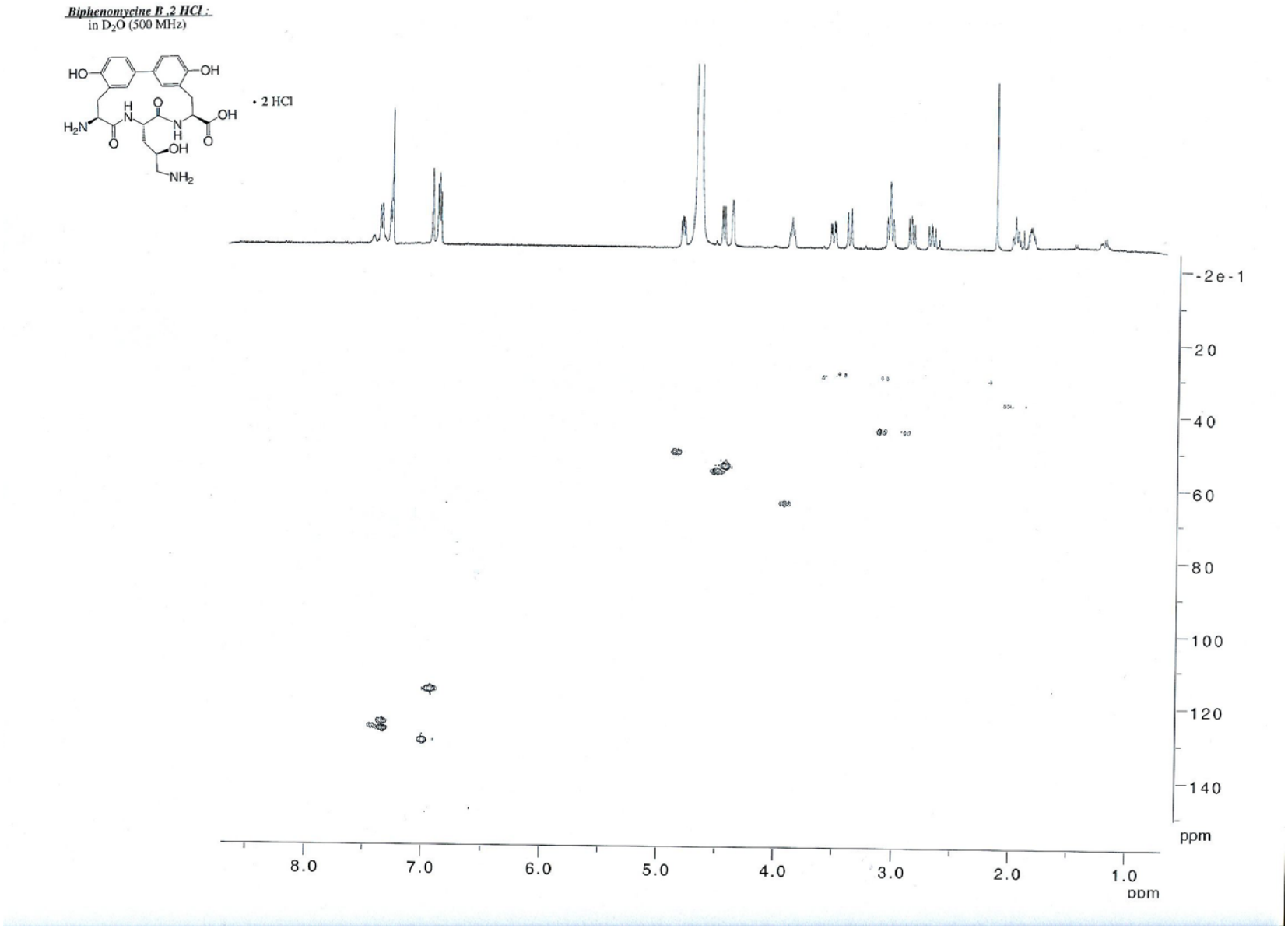


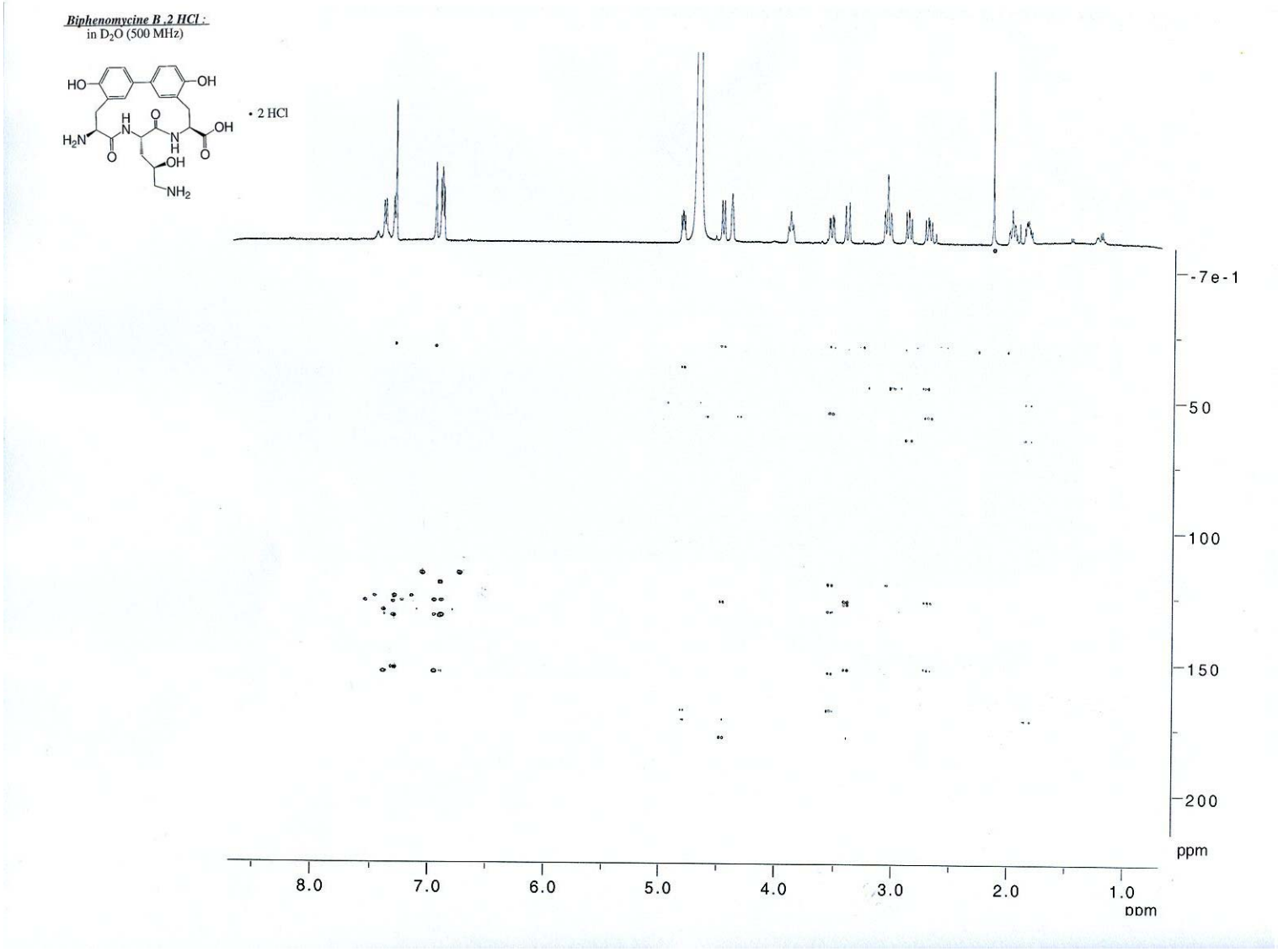

O
B
O
O
H2N
CO2Me
175
150
125
100
75
50
25
ppm (f1)


Compound 7:
in CDCl3 (250MHz)
O
O
CbzN
O
NH2
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

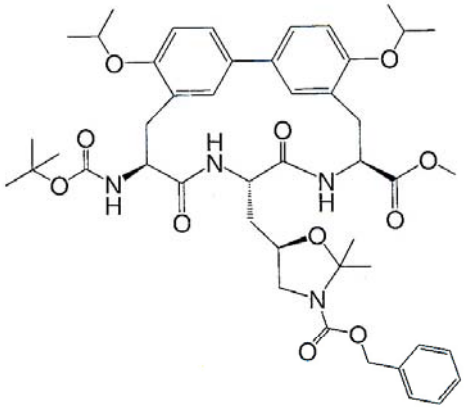

O
I
BocHN
OH
O
175
150
125
100
75
50
25
ppm (f1)

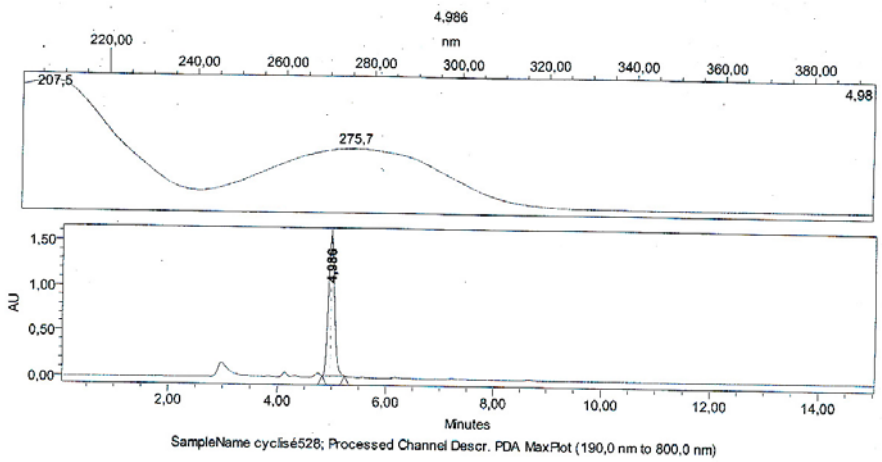

O
O
H
N
O
BocHN
N
CO2Me
O
H
O
NCbz
175
150
125
100
75
50
25
ppm (f1)


Biphenomycine B ,2 HCl :
in D2O (500 MHz)
HO
OH
H2N
OH
OH
NH2
• 2 HCl
-2e-1
20
40
60
80
100
120
140
ppm
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm

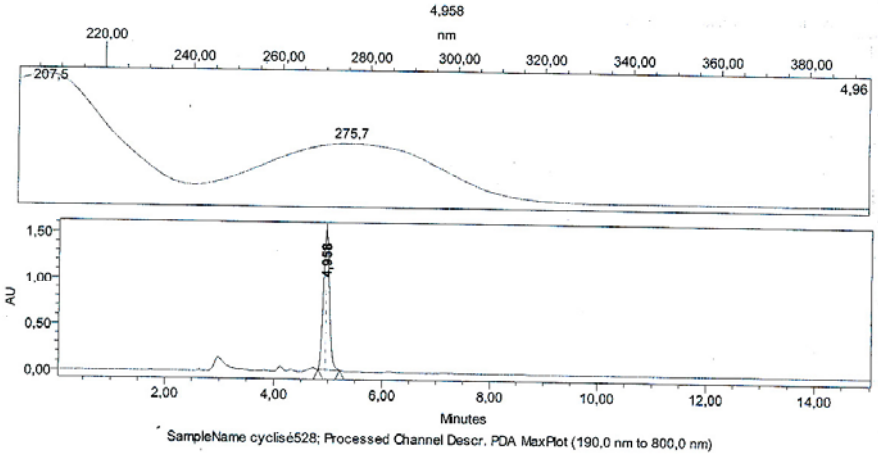

Biphenomycine B .2 HCl :
in D2O (500 MHz)
HO
OH
H2N
OH
NH2
• 2 HCl
-7e-1
50
100
150
200
ppm
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm

Protected Biphenomycin B:
retention time = 4.97 min.





SampleName cyclisé528; Processed Channel Descr. PDA MaxPlot (190,0 nm to 800,0 nm)



SampleName cyclisé528; Processed Channel Descr. PDA MaxPlot (190,0 nm to 800,0 nm)

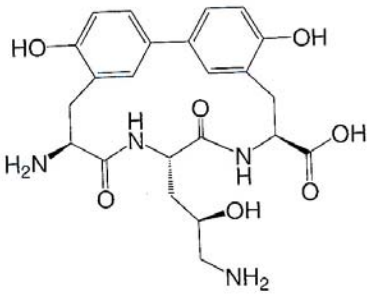
Peak Results
SampleName: cyclisé528

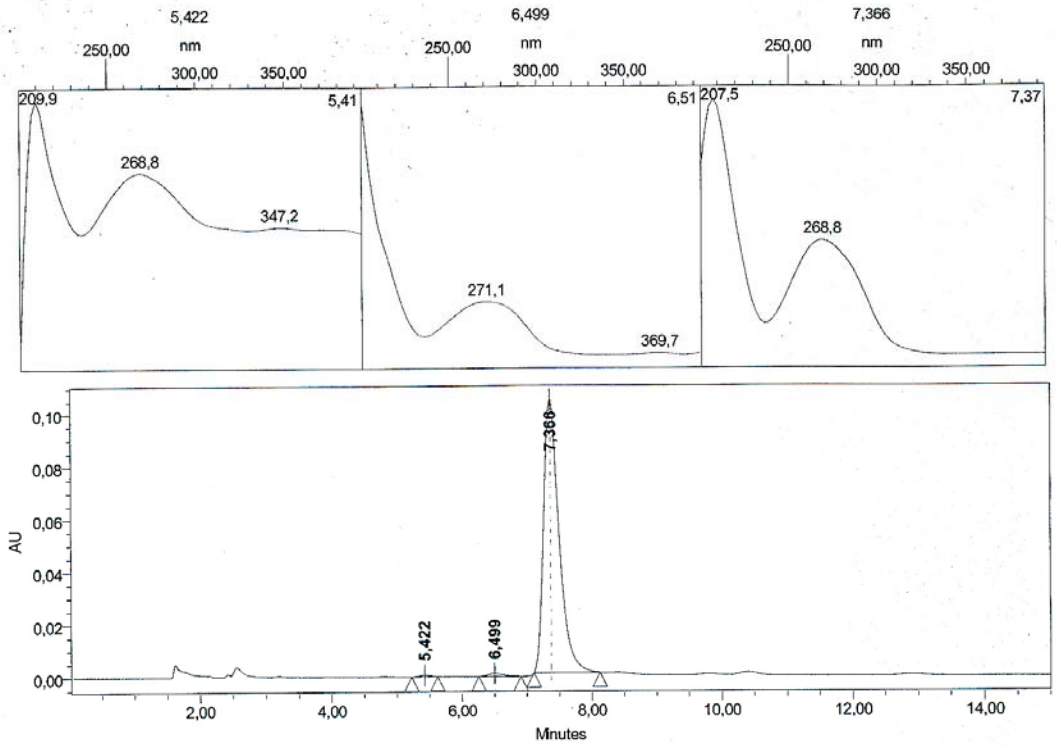
	SampleName	RT	Area	Height	% Area
1	cyclisé528	4,958	11906340	1516110	100,00
2	cyclisé528	4,986	12306061	1555268	100,00

	Time	Flow	%A	%B	%C	%D	Curve
1	0.01	1.00	5	95	0.0	0.0	6
2	20.00	1.00	0.0	100.0	0.0	0.0	6

A = H_2O
B = MeCN
Column symmetry C18 4,6*250 mm

Biphenomycin B :
retention time = 7.37 min.





SampleName rice574a; Processed Channel Descr. PDA 260,0 nm

Time	Flow	%A	%B	%C	%D	Curve
20	1.00	85	15	0.0	0.0	6

A = H_2O + 0.1% TFA
B = MeCN + 0.1% TFA
Column symmetryshield C18 4.6*150 mm

Peak Results
SampleName: rice574a

	SampleName	RT	Area	Height	% Area
1	rice574a	5,422	7405	665	0,42
2	rice574a	6,499	19628	1192	1,12
3	rice574a	7,366	1724159	104246	98,46