One-pot Synthesis of 2-Substituted Indoles from 2-Aminobenzyl Phosphonium Salts

A Formal Total Synthesis of Arcyriacyanin A

George A. Kraus* and Haitao Guo

Department of Chemistry, Iowa State University, Ames, IA 50011

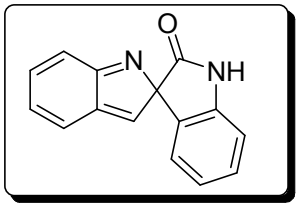
gakraus@iastate.edu

Supporting Information

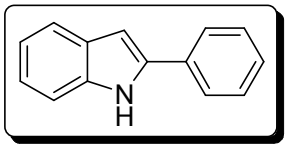
General. All ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz or 400 and 100 MHz respectively. All melting points are uncorrected. Except as otherwise indicated, reactions were carried out under argon. Microwave reactions were conducted in a capped vial using a CEM Discover System. Thin-layer chromatography was performed using commercially prepared 60-mesh silica gel plates (Whatman K6F), and visualization was effected with short wavelength UV light (254 nm). High resolution mass spectra were recorded on a Kratos MS50TC double focusing magnetic sector mass spectrometer using EI at 70 eV. All reagents were used directly as obtained commercially unless otherwise noted. All yields reported represent an average of at least two independent runs.

General procedure for the synthesis of 2-Substituted Indoles from 2-Aminobenzyl Phosphonium Salts

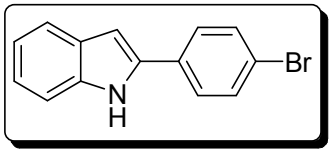
In a 10 mL microwave reaction vessel (CEM Discover System) equipped with a magnetic stir bar, phosphonium salt **1** ((2-Aminobenzyl) triphenylphosphonium bromide) (224 mg, 0.5 mmol), aldehyde (0.5 mmol) and glacial acetic acid (11.4 μL, 0.2 mmol) were added to 2.5 mL distilled mathanol. The vial was capped properly and placed in the microwave. Microwave was then run at 300 W, 80 ºC for 10 min. After cooling the vial to room temperature, methanol was removed by rotovap. 4 mL THF was added to the mixture and 0.8 mL 1 M *t*-BuOK solution in THF was added dropwise. The resulting mixture was stired at 25 ºC under the argon for 1 h. The saturated NH_4Cl solution (10 mL) was added to quench the reaction and was extracted with ethyl acetate (3 x 10 mL). The organic layers were combined and washed with brine (2 x 10 mL). The organic layer was separated, dried with Mg_2SO_4 and filtered. The filtrate was concentrated under vacuum and the residue was purified by silica gel column chromatography using a mixture of ethyl acetate and hexane as the eluent.



The product was purified by chromatography on silica gel (Rf = 0.25 in 75% hexanes/25% EtOAc). The product (**5**) was obtained as a white solid (101.0 mg, 86% yield). Mp ≥ 250 ºC. ^{1}H NMR (400 MHz, DMSO-d_6): 11.37 (br s, 1H), 8.54-8.56 (m, 1H), 8.09-8.11 (dd, *J*=8, 1.2 Hz, 1H), 7.73-7.76 (m, 1H), 7.41-7.45(td, *J* = 8.4, 1.2 Hz, 1H), 7.34-7.37 (m, 3H), 7.22-7.27 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): 147.2, 134.3, 134.1, 133.4, 129.7, 129.5, 123.7, 123.5, 123.1, 120.3, 115.5, 115.4, 113.6, 98.3. HRMS electrospray (m/z): calcd for $C_{15}H_{10}N_2O$, 234.0793; found, 234.0796.

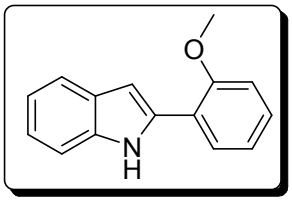


The product was purified by chromatography on silica gel (Rf = 0.3 in 83% hexanes/17% EtOAc). The product (**9a**) was obtained as a white solid (91.7 mg, 95% yield). Mp: 188-190 ºC (Lit. mp: 188-189 ºC) [1]. ^{1}H NMR (400 MHz, DMSO-d_6): 11.55 (s, 1H), 7.86-7.88 (d, *J*=8 Hz, 2H), 7.53-7.55 (d, *J*=8 Hz, 1H), 7.41-7.48 (q, *J*=8 Hz, 3H), 7.29-7.33 (t, *J*=7.2 Hz, 1H), 7.09-7.13 (t, *J*=7.2 Hz, 1H), 6.99-7.03 (t, *J*=7.6 Hz, 1H), 6.90 (d, *J*=1.6 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): 137.6, 137.1, 132.2, 128.9, 128.6, 127.4, 125.0, 121.6, 120.1, 119.4, 111.3, 98.7. HRMS electrospray (m/z): calcd for $C_{14}H_{11}N$, 193.0892; found, 193.0895.

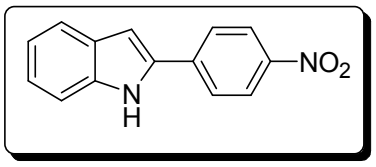


(1) Deprez, N. R.; Kalyani D.; Krause A.; Sanford M. S. *J. Am. Chem. Soc*. **2006**, *128*, 4972.

The product was purified by chromatography on silica gel (Rf = 0.45 in 80% hexanes/20% EtOAc). The product (**9b**) was obtained as a white solid (129.0 mg, 95% yield). Mp: 211-213 ºC (Lit. mp: 208-212 ºC).[1] ^{1}H NMR (400 MHz, Acetone-d_6): 10.73 (br s, 1H), 7.79-7.81 (d, *J*=8.4 Hz, 2H), 7.57-7.62 (m, 3H), 7.41-7.43 (d, *J*=8.4 Hz, 1H), 7.11-7.15 (t, *J*=7.2 Hz, 1H), 7.02-7.06 (t, *J*=7.6 Hz, 1H), 6.93 (s, 1H). ^{13}C NMR (100 MHz, Acetone-d_6): 139.0, 138.0, 133.3, 130.6, 128.2, 123.5, 121.9, 121.7, 121.1, 112.6, 101.1. HRMS electrospray (m/z): calcd for $C_{14}H_{10}BrN$, 270.9997; found, 271.0001.



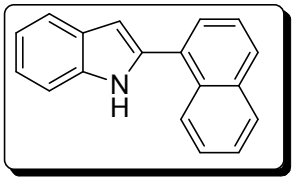
The product was purified by chromatography on silica gel (Rf = 0.40 in 80% hexanes/20% EtOAc). The product (**9c**) was obtained as a white solid (90.5 mg, 81% yield). Mp: 83 ºC (Lit. mp: 83 ºC).[2] ^{1}H NMR (400 MHz, $CDCl_3$): 9.69 (br s, 1H), 7.86-7.88 (d, *J*=7.6 Hz, 1H), 7.65-7.67 (d, *J*=7.6 Hz, 1H), 7.43-7.45 (d, *J*=8 Hz, 1H), 7.29-7.33 (t, *J*=7.2 Hz, 1H), 7.19-7.22 (t, *J*=7.2 Hz, 1H), 7.11-7.15 (t, *J*=7.2 Hz, 1H), 7.04-7.09 (t, *J*=8 Hz, 2H), 6.93 (s, 1H), 4.04 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 136.3, 136.2, 128.8, 128.5, 128.3, 122.0, 121.8, 120.8, 120.5, 120.0, 112.1, 111.1, 100.0. HRMS electrospray (m/z): calcd for $C_{15}H_{13}NO$, 223.0997; found, 223.1000.



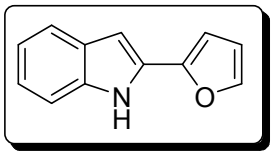
The product was purified by chromatography on silica gel (Rf = 0.35 in 83% hexanes/16% EtOAc). The product (**9d**) was obtained as a yellow solid (102.4 mg, 86%

(2) (i) So, C. M.; Lau, C. P.; Kwong, F. Y.; *Org. Lett.* **2007**, *9*, 2795. (ii) Cacchi, S.; Fabrizi, G.; Parisi, L. M. *Org. Lett.* **2003**, *5*, 3843.

yield). Mp: 248-250 ºC (Lit. mp: 249-251 ºC).[3] ^{1}H NMR (400 MHz, Acetone-d_6): 10.97 (br s, 1H), 8.31-8.33 (d, *J*=8.8 Hz, 2H), 8.11-8.13 (d, *J*=8.8 Hz, 2H), 7.63-7.65 (d, *J*=8 Hz, 1H), 7.45-7.47 (d, *J*=8 Hz, 1H), 7.16-7.21 (m, 2H), 7.06-7.10 (t, *J*=8 Hz, 1H). ^{13}C NMR (100 MHz, Acetone-d_6): 147.4, 139.8, 139.3, 136.4, 130.0, 126.3, 125.2, 124.2, 121.9, 121.2, 112.5, 103.6. HRMS electrospray (m/z): calcd for $C_{14}H_{10}N_2O_2$, 238.0742; found, 238.0747.



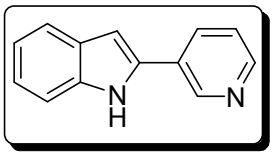
The product was purified by chromatography on silica gel (Rf = 0.45 in 83% hexanes/17% EtOAc). The product (**9e**) was obtained as a white solid (113.1 mg, 93% yield). Mp: 97-99 ºC (Lit. mp: 99-102 ºC).[1] ^{1}H NMR (400 MHz, $CDCl_3$): 8.11-8.36 (m, 2H), 7.91-7.94 (m, 2H), 7.73-7.75 (d, *J*=7.6 Hz, 1H), 7.65-7.67 (dd, *J*=6.8, 0.8 Hz, 1H), 7.53-7.58 (m, 3H), 7.46-7.48 (d, *J*=8 Hz, 1H), 7.19-7.29 (m, 2H), 6.82-6.83 (d, *J*=1.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 136.9, 136.6, 134.1, 131.7, 131.3, 129.0, 128.8, 128.7, 127.4, 126.9, 126.4, 125.9, 125.6, 122.4, 120.8, 120.4, 111.1, 103.9. HRMS electrospray (m/z): calcd for $C_{18}H_{13}N$, 243.1048; found, 243.1051.



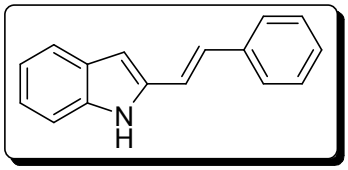
The product was purified by chromatography on silica gel (Rf = 0.3 in 83% hexanes/17% EtOAc). The product (**9f**) was obtained as a white solid (79.0 mg, 86% yield). Mp: 120-123 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): 8.44 (br s, 1H), 7.63-7.65 (d, *J*=7.6 Hz, 1H), 7.48-7.49 (d, *J*=1.6 Hz, 1H), 7.38-7.40 (d, *J*=8 Hz, 1H), 7.20-7.24 (td, *J*=8, 1.2 Hz, 1H), 7.13-7.17 (t, *J*=8 Hz, 1H), 6.77-6.78 (d, *J*=1.6 Hz, 1H), 6.64-6.65 (d, *J*=3.2 Hz, 1H), 6.52-6.54

(3) Le Corre, M.; Hercouet, A.; Le Stanc, Y.; Le Baron, H. *Tetrahedron* **1985**, *41*, 5313.

(multiple peaks, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 147.9, 141.9, 136.3, 129.4, 129.0, 122.7, 120.9, 120.6, 112.0, 111.1, 105.6, 99.0. HRMS electrospray (m/z): calcd for $C_{12}H_9NO$, 183.0684; found, 183.0686.

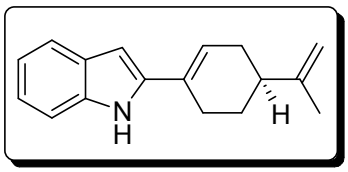


The product was purified by chromatography on silica gel (Rf = 0.20 in 60% hexanes/40% EtOAc). The product (**9g**) was obtained as a white solid (83.0 mg, 85% yield). Mp: 175-176 ºC (Lit. mp: 170-175 ºC).[4] ^{1}H NMR (400 MHz, Acetone-d_6): 10.90 (br s, 1H), 9.12-9.13 (m, 1H), 8.51-8.53 (dd, *J*=4.8, 1.6 Hz, 1H), 8.18-8.21 (dt, *J*=8, 2 Hz, 1H), 7.60-7.62 (d, *J*=8 Hz, 1H), 7.42-7.45 (m, 2H), 7.13-7.17 (td, *J*=8, 0.8 Hz 1H), 7.04-7.08 (td, *J*=8, 0.8 Hz, 1H), 7.02-7.03 (d, *J*=1.6 Hz, 1H). ^{13}C NMR (100 MHz, Acetone-d_6): 149.2, 147.4, 138.7, 135.8, 132.8, 130.1, 129.5, 124.7, 123.3, 121.4, 120.8, 112.2, 101.2. HRMS electrospray (m/z): calcd for $C_{13}H_{10}N_2$, 194.0844; found, 194.0846.

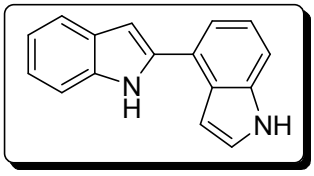


The product was purified by chromatography on silica gel (Rf = 0.40 in 83% hexanes/17% EtOAc). The product (**9h**) was obtained as a white solid (106.2 mg, 97% yield). Mp: 202-204 ºC (Lit. mp: 197-199 ºC).[5] ^{1}H NMR (400 MHz, $CDCl_3$): 8.24 (br s, 1H), 7.59-7.61 (d, *J*=7.6 Hz, 1H), 7.51-7.53 (d, *J*=7.6 Hz, 2H), 7.35-7.41 (t, *J*=7.2, 5.2 Hz, 3H), 7.29-7.31 (d, *J*=7.2 Hz, 1H), 7.19-7.23 (t, *J*=7.2 Hz, 1H), 7.10-7.16 (m, 2H), 6.90-6.94 (d, *J*=16.4 Hz, 1H), 6.64 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 137.1, 137.0, 136.5, 129.2, 129.0, 128.0, 127.3, 126.5, 123.1, 120.9, 120.4, 119.2, 110.8, 104.1. HRMS electrospray (m/z): calcd for $C_{16}H_{13}N$, 219.1048; found, 219.1052.

(4) Huffman, John W. *J. Org. Chem*. **1962**, *27*, 503.
(5) Arcadi, A.; Bianchi, G.; Marinelli, F. *Synth.* **2004**, *4*, 610.

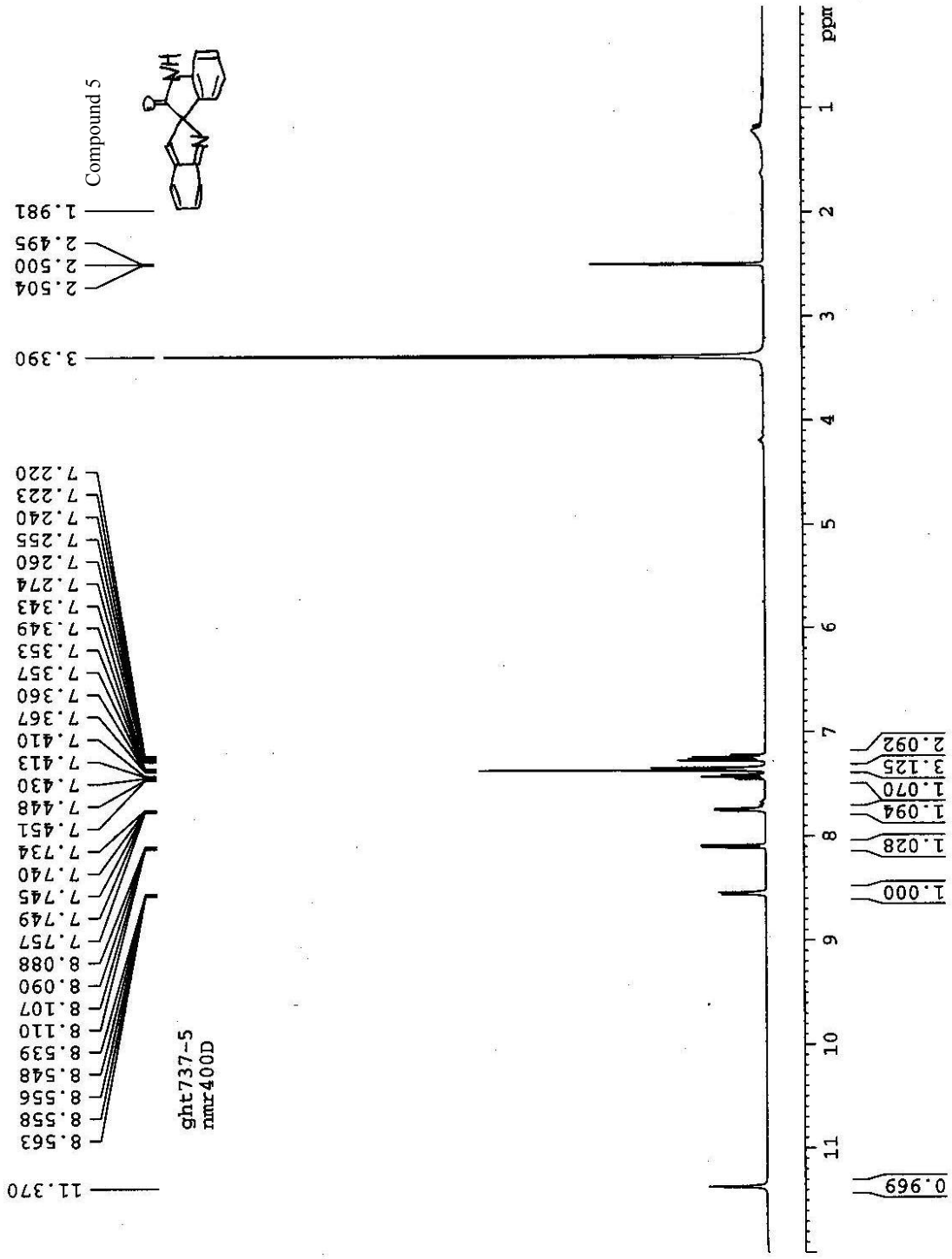


The product was purified by chromatography on silica gel (Rf = 0.45 in 90% hexanes/10% EtOAc). The product (**9i**) was obtained as a white solid (98.4 mg, 83% yield). Mp: 164-165 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): 8.10 (br s, 1H), 7.57-7.59 (d, *J*=7.6 Hz, 1H), 7.32-7.34 (d, *J*=8.4 Hz, 1H), 7.15-7.19 (t, *J*=8 Hz, 1H), 7.07-7.11 (t, *J*=8 Hz, 1H), 6.47 (s, 1H), 6.14-6.15 (t, *J*=2.4 Hz, 1H), 2.62-2.67 (m, 1H), 2.48-2.55 (m, 1H), 2.38-2.42 (m, 1H), 2.27-2.33 (m, 1H), 2.16-2.23 (m, 1H), 1.99-2.04 (m, 1H), 1.82 (s, 3H), 1.60-1.71(m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 149.7, 139.2, 136.4, 129.1, 129.0, 122.3, 122.1, 120.6, 120.0, 110.6, 109.2, 99.2, 41.1, 31.2, 27.7, 26.8, 21.1. HRMS electrospray (m/z): calcd for $C_{17}H_{19}N$, 237.1518; found, 237.1521.



The product was purified by chromatography on silica gel (Rf = 0.30 in 67% hexanes/33% EtOAc). The product (**9j**) was obtained as a white solid (101.1 mg, 87% yield). Mp: 202-203 ºC (Lit. mp: 199-202 ºC).[6] ^{1}H NMR (400 MHz, Acetone-d_6): 10.57 (br s, 1H), 10.47 (br s, 1H), 7.63-7.65 (d, *J*=7.6 Hz, 1H), 7.46-7.52 (m, 4H), 7.21-7.25 (t, *J*=7.6 Hz, 1H), 7.12-7.16 (t, *J*=7.2 Hz, 1H), 7.04-7.08 (t, *J*=7.2 Hz, 1H), 7.01 (s, 2H). ^{13}C NMR (100 MHz, Acetone-d_6): 139.4, 138.03, 138.02, 130.4, 126.5, 126.2, 125.9, 122.4, 122.3, 121.0, 120.3, 118.3, 112.0, 111.9, 102.3, 101.7. HRMS electrospray (m/z): calcd for $C_{16}H_{12}N_2$, 232.1001; found, 232.1004.

(6) Murase, M.; Watanabe, K.; Kurihara, T.; Tobinaga, S. *Chem. Pharm. Bull.* **1998**, *46*, 889.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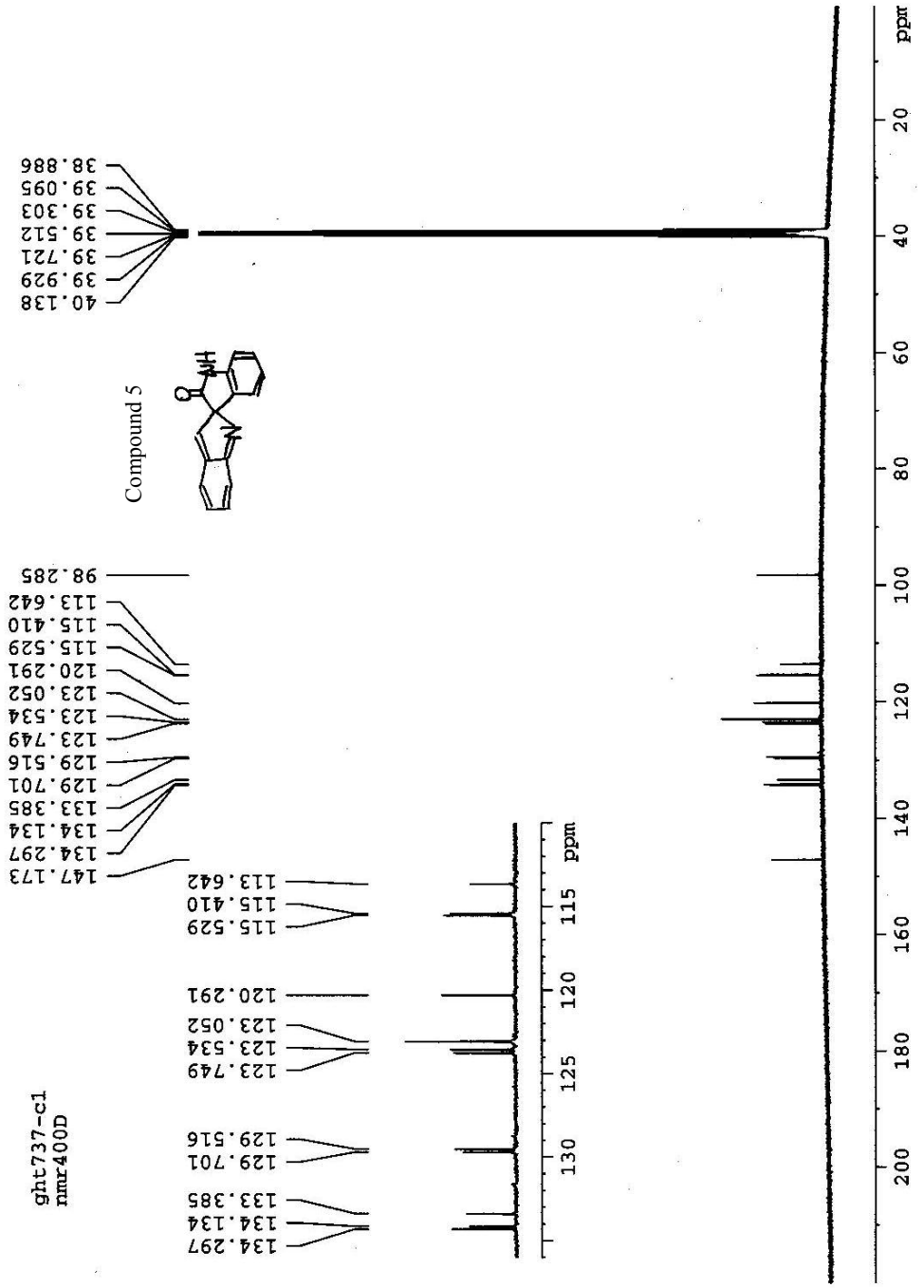
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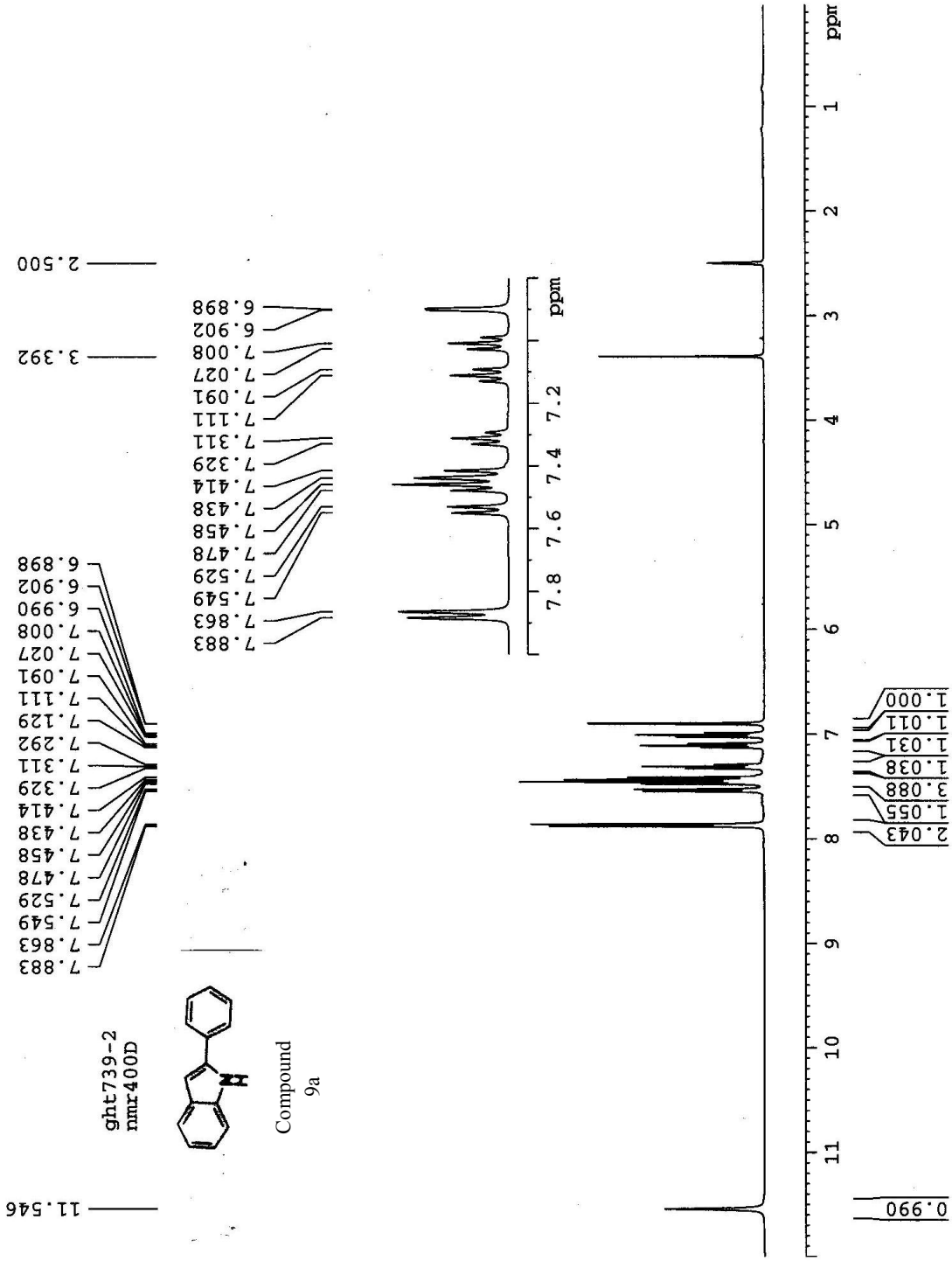
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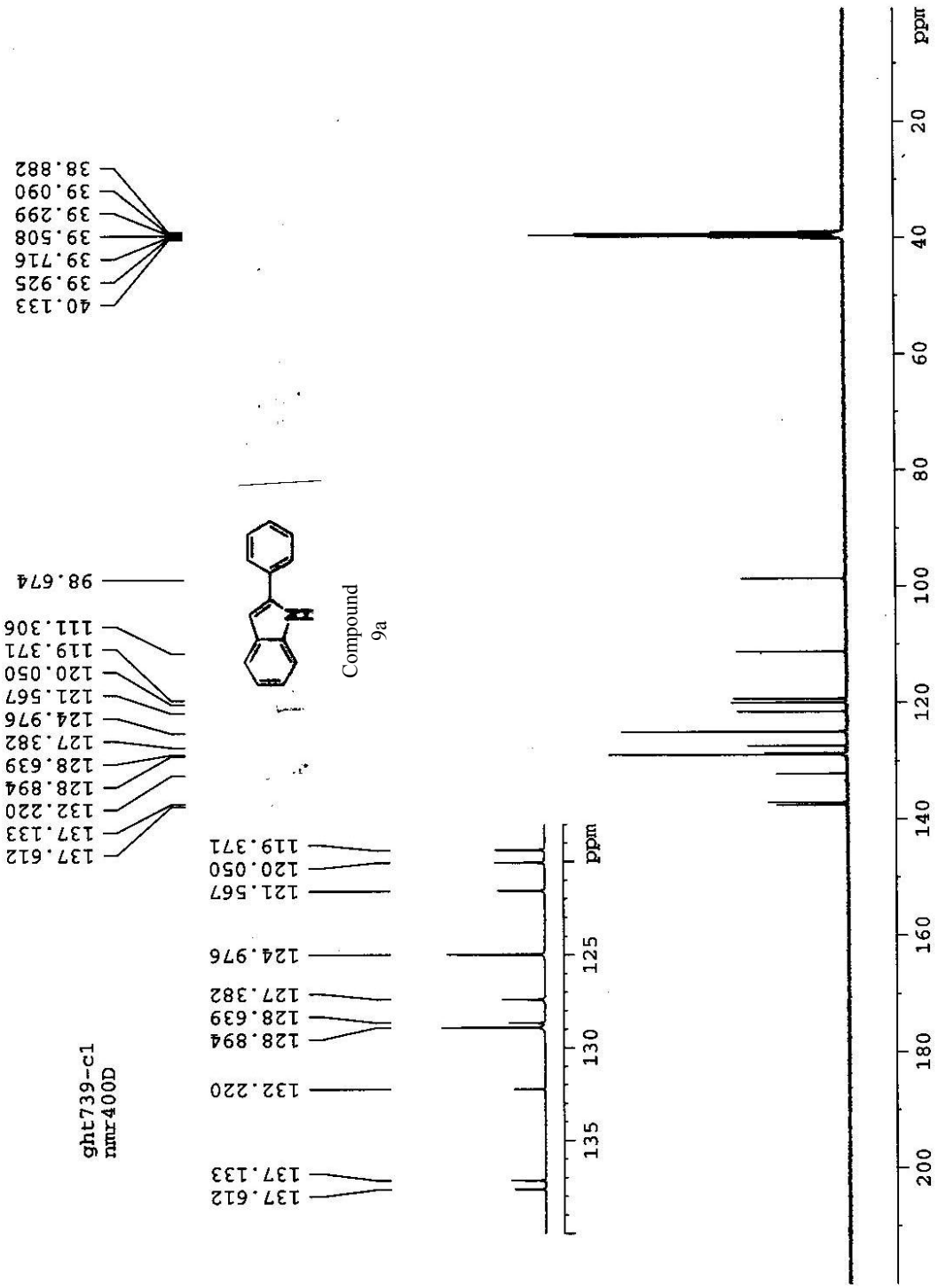
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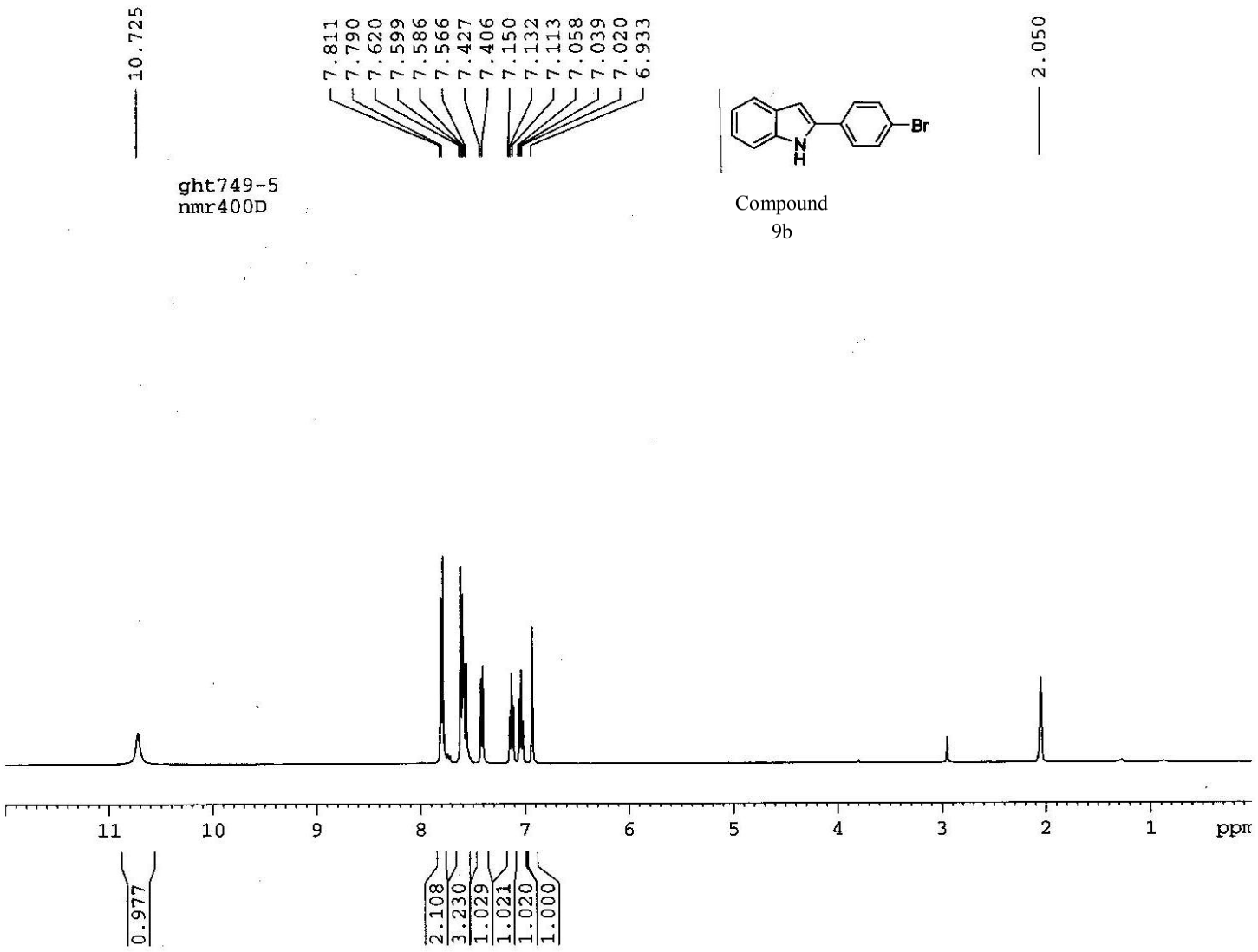
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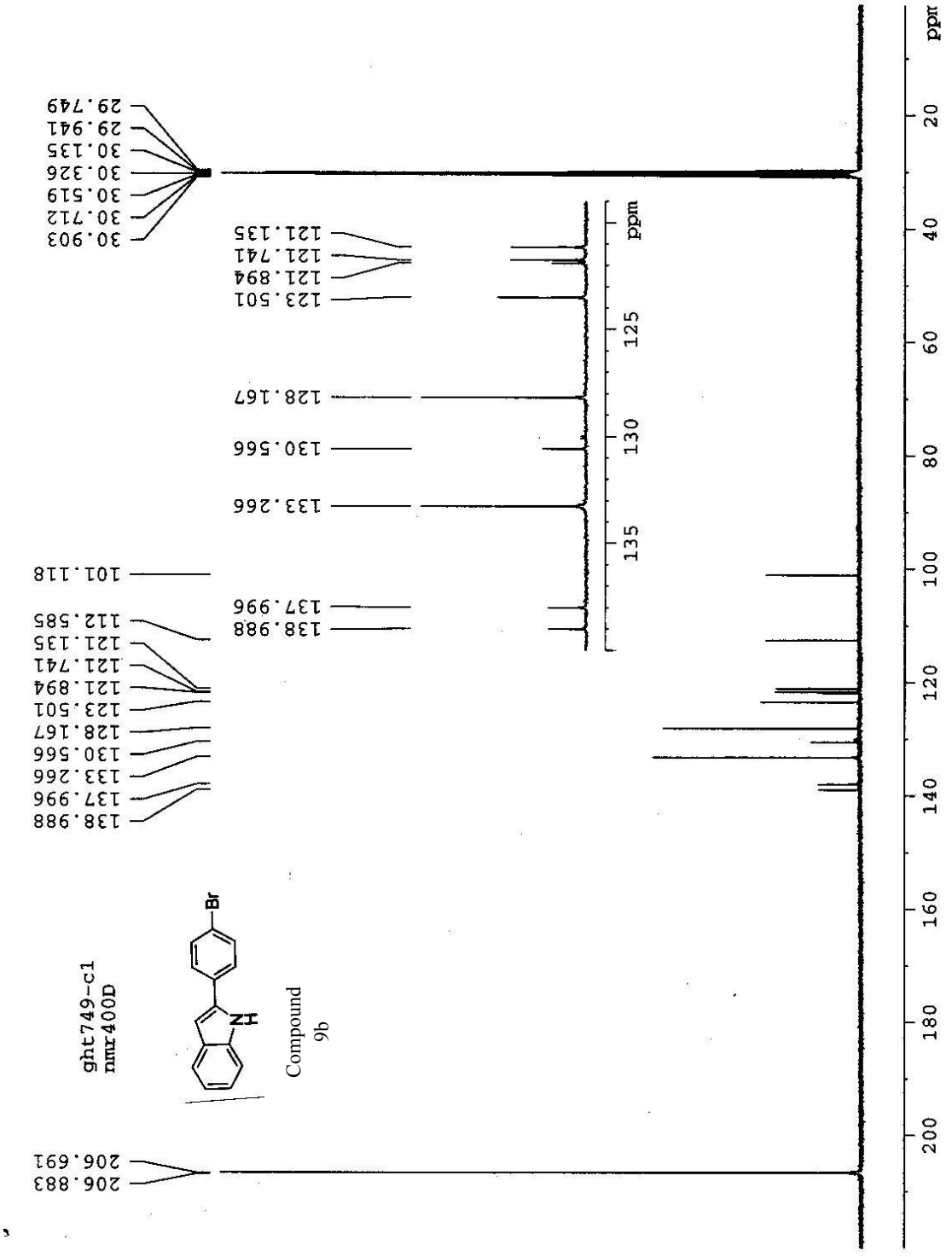
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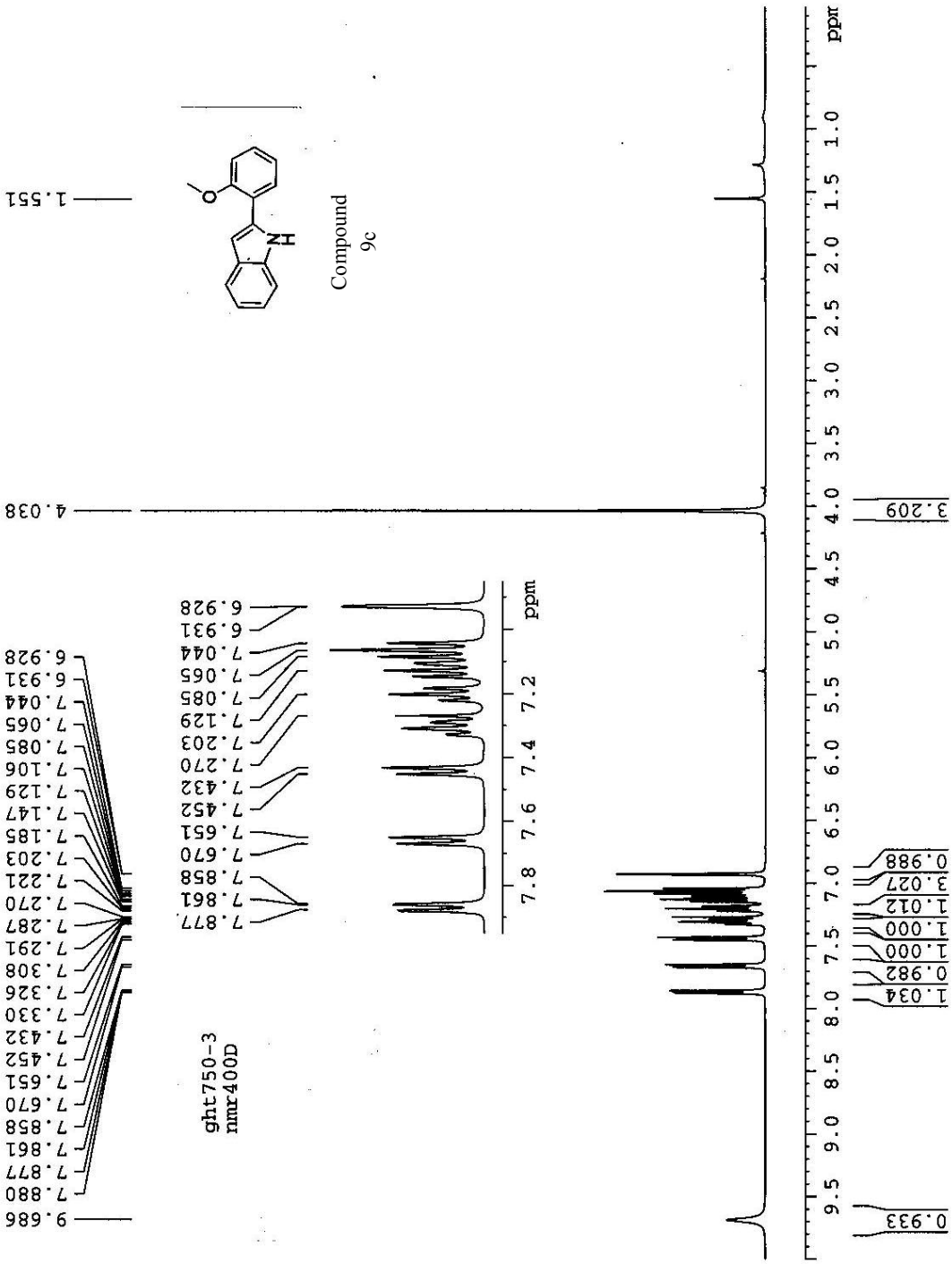
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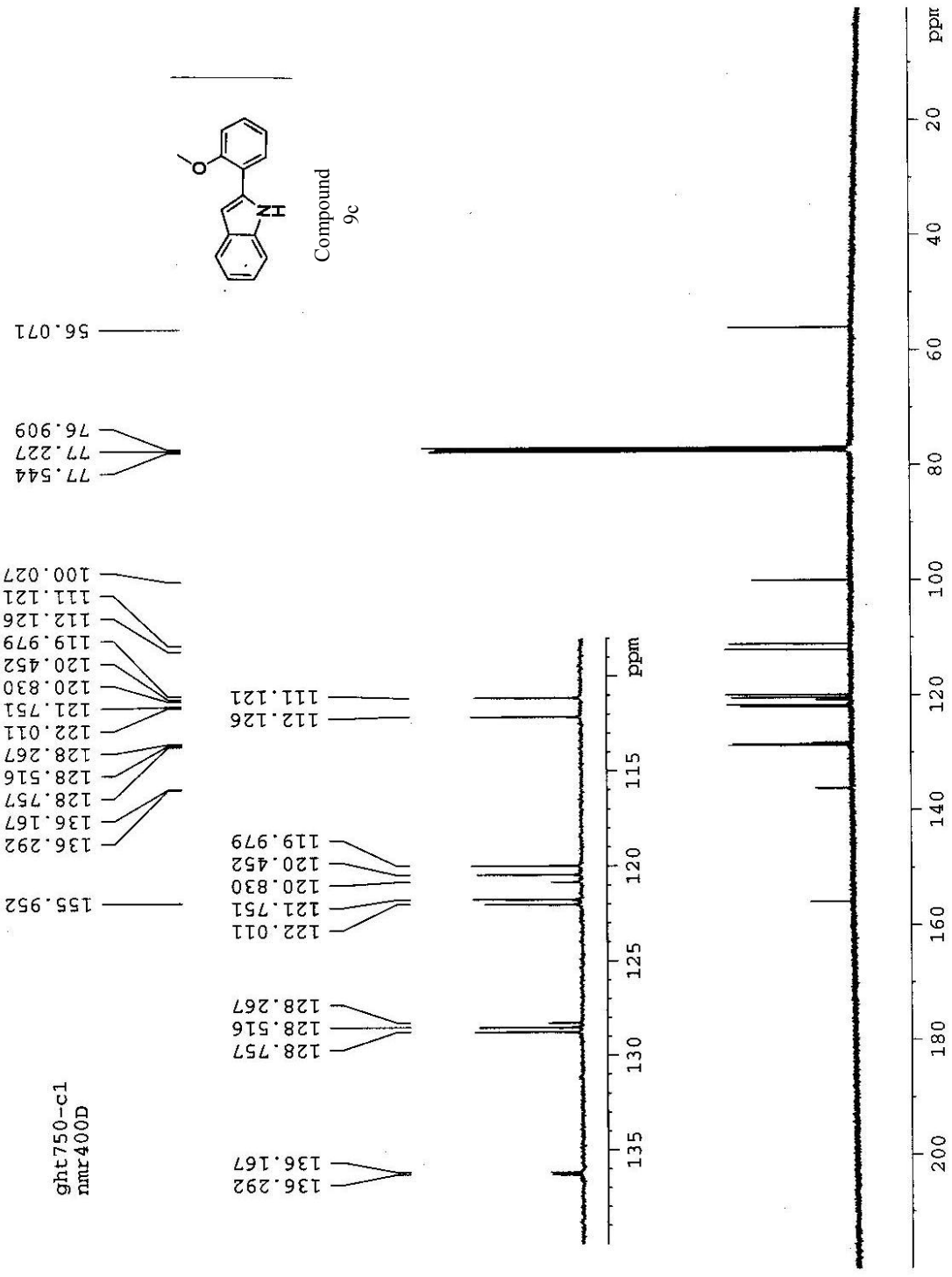
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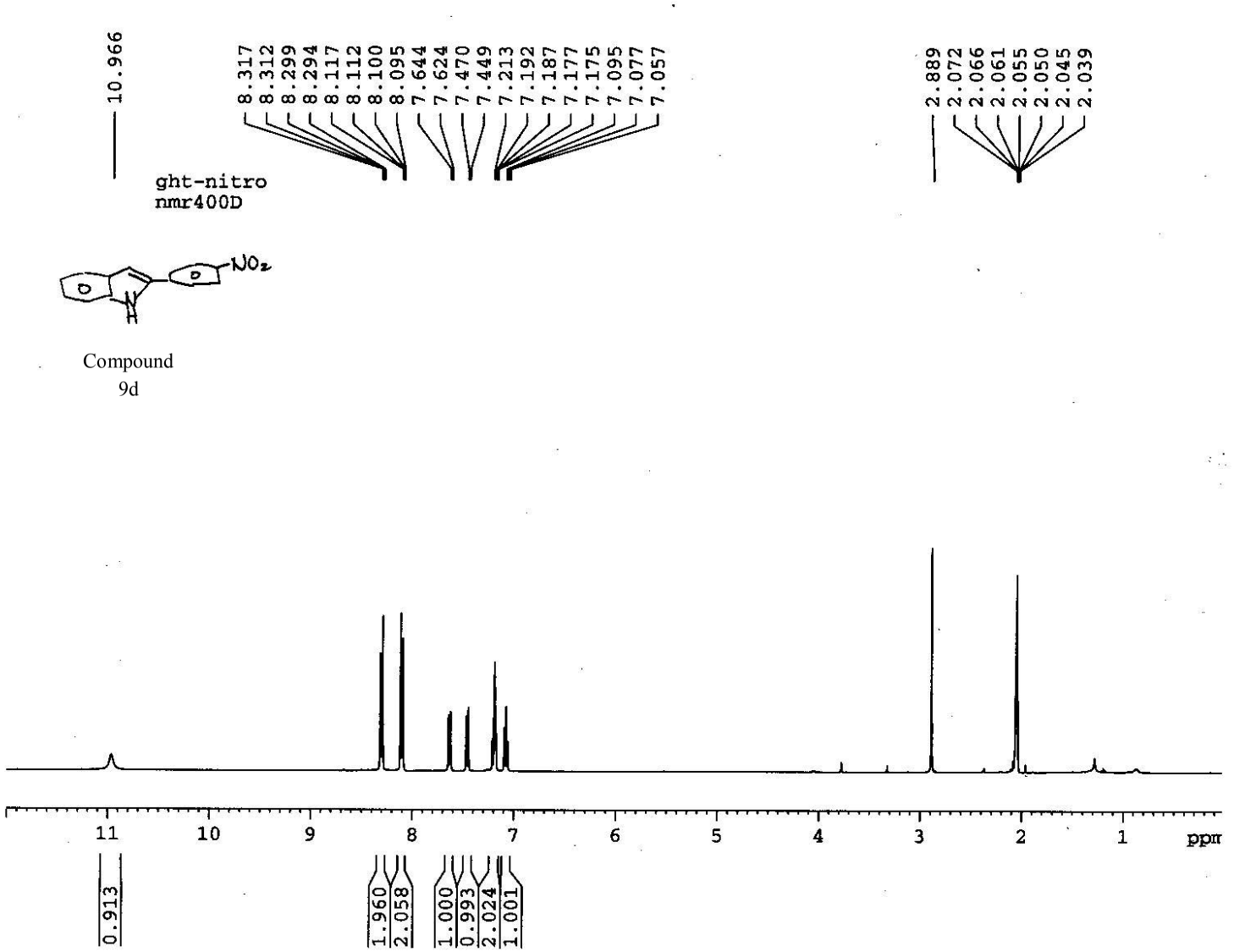
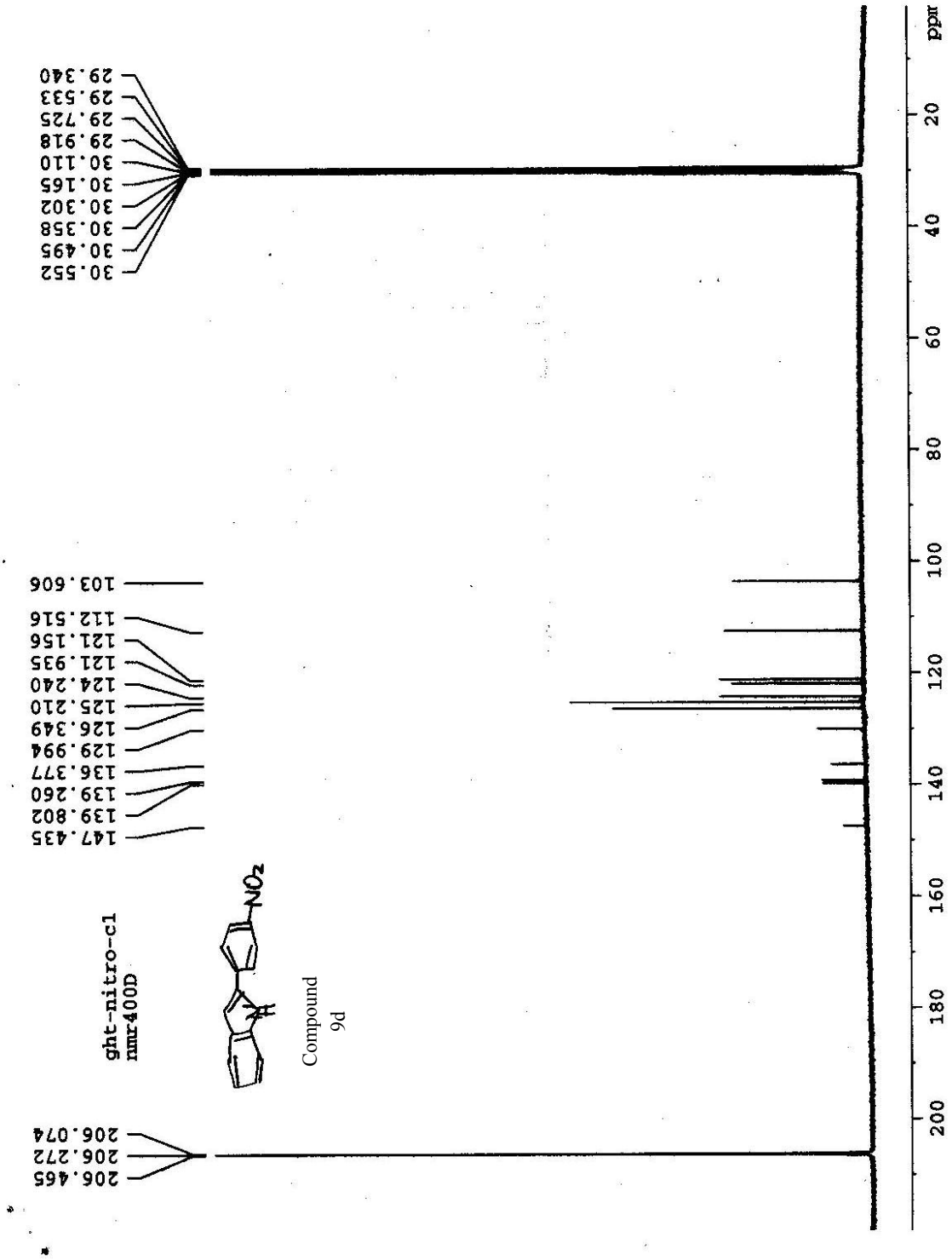
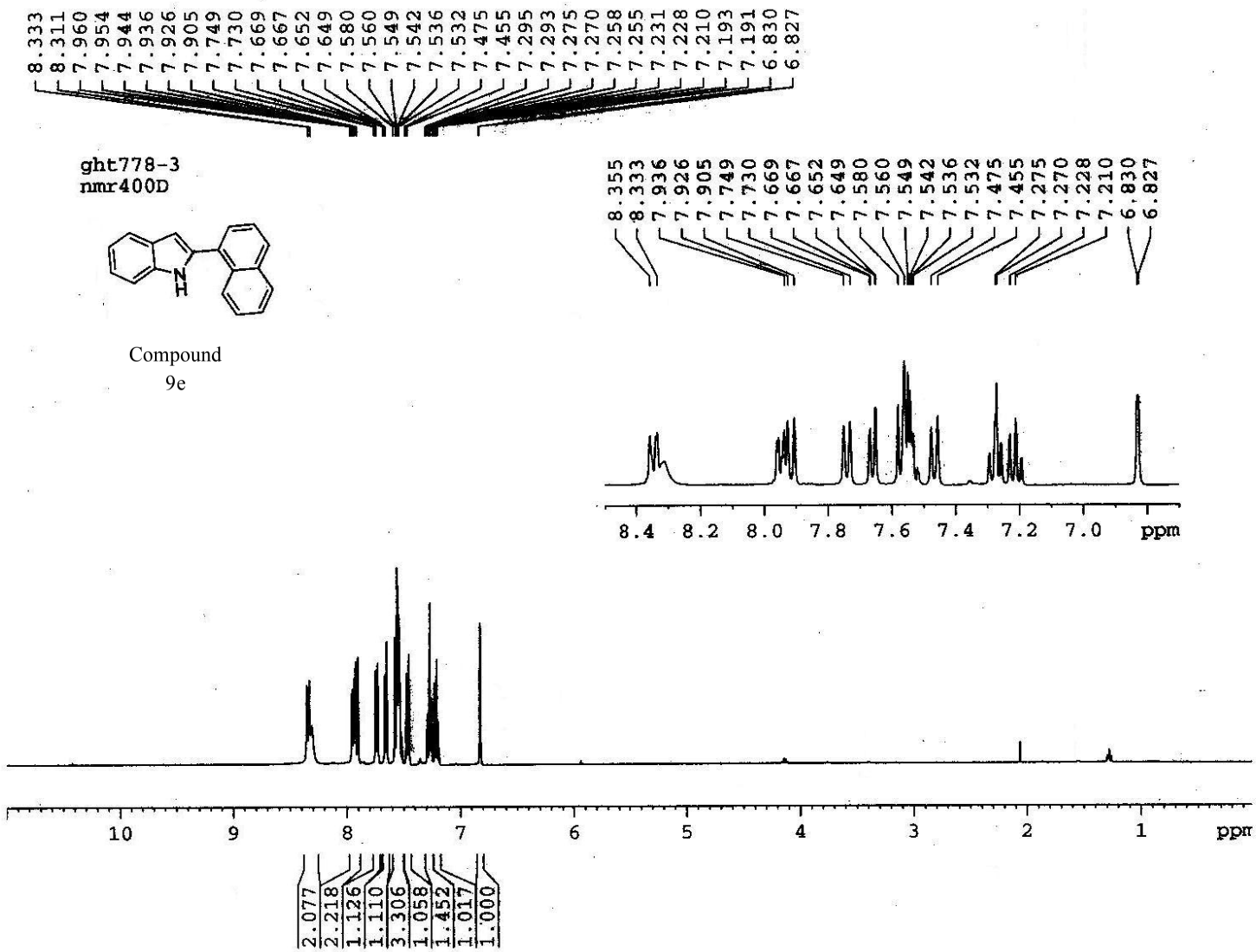
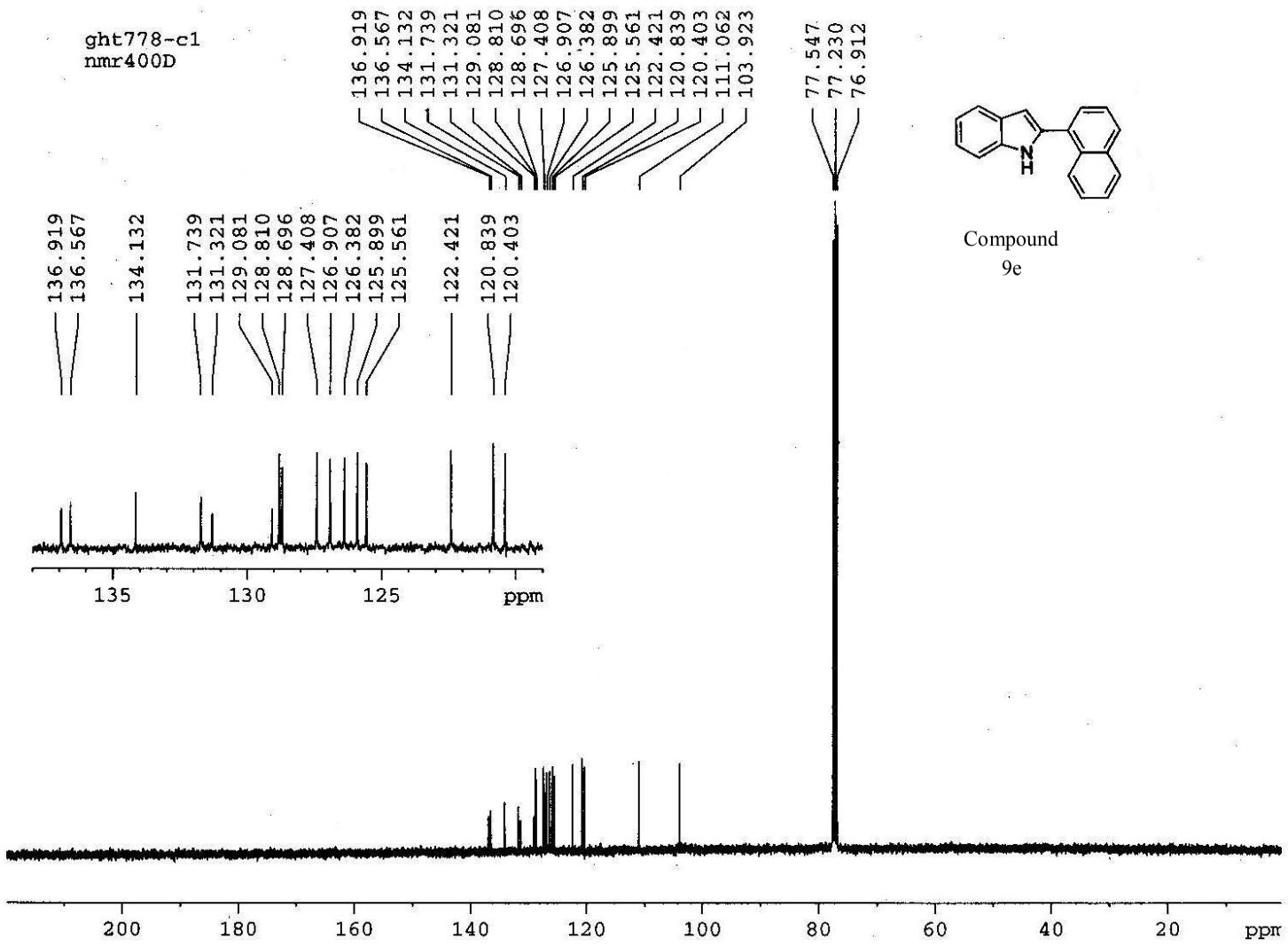

10.966
8.317
8.312
8.299
8.294
8.117
8.112
8.100
8.095
7.644
7.624
7.470
7.449
7.213
7.192
7.187
7.177
7.175
7.095
7.077
7.057
2.889
2.072
2.066
2.061
2.055
2.050
2.045
2.039
ght-nitro
nmr400D
NO2
11
10
9
8
7
6
5
4
3
2
1
ppm
0.913
1.960
2.058
1.000
0.993
2.024
1.001

Compound
9d

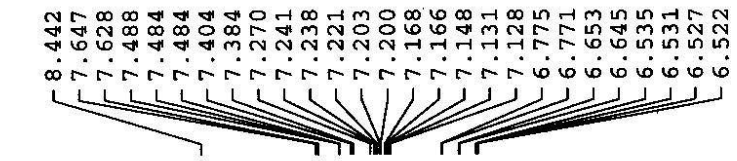

ght-nitro-cl
nmr400D
Compound
9d
NO2
206.465
206.272
206.074
147.435
139.802
139.260
136.377
129.994
126.349
125.210
124.240
121.935
121.156
112.516
103.606
30.552
30.495
30.358
30.302
30.165
30.110
29.918
29.725
29.533
29.340
ppm
20
40
60
80
100
120
140
160
180
200


8.333
8.311
7.960
7.954
7.944
7.936
7.926
7.905
7.749
7.730
7.669
7.667
7.652
7.649
7.580
7.560
7.549
7.542
7.536
7.532
7.475
7.455
7.295
7.293
7.275
7.270
7.258
7.255
7.231
7.228
7.210
7.193
7.191
6.830
6.827
ght778-3
nmr400D
8.355
8.333
7.936
7.926
7.905
7.749
7.730
7.669
7.667
7.652
7.649
7.580
7.560
7.549
7.542
7.536
7.532
7.475
7.455
7.275
7.270
7.228
7.210
6.830
6.827
8.4
8.2
8.0
7.8
7.6
7.4
7.2
7.0
ppm
10
9
8
7
6
5
4
3
2
1
ppm
2.077
2.218
1.126
1.110
3.306
1.058
1.452
1.017
1.000

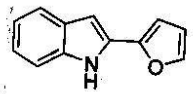
Compound
9e


ght778-c1
nmr400D
136.919
136.567
134.132
131.739
131.321
129.081
128.810
128.696
127.408
126.907
126.382
125.899
125.561
122.421
120.839
120.403
111.062
103.923
77.547
77.230
76.912
135
130
125
ppm
200
180
160
140
120
100
80
60
40
20
ppm

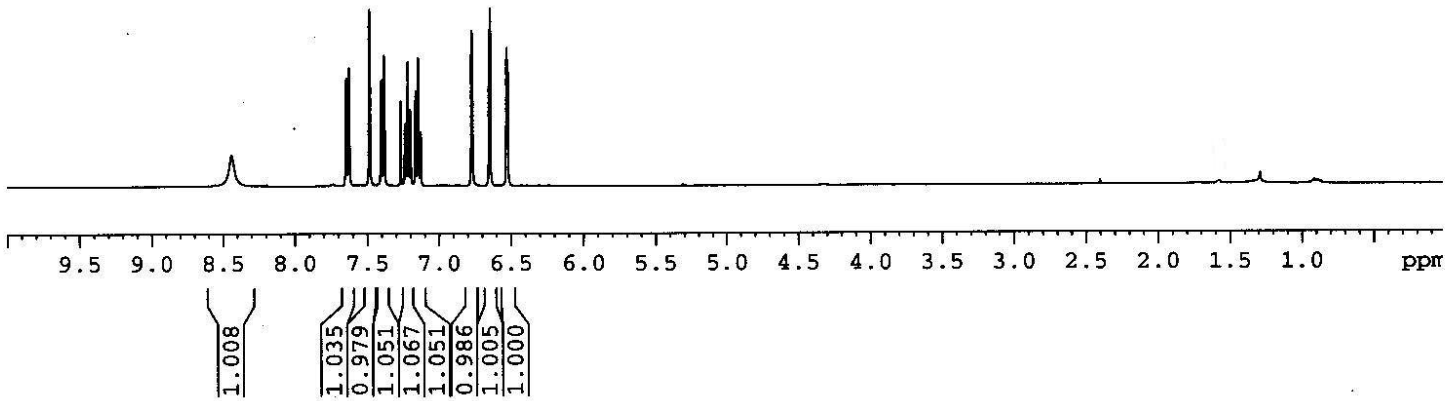
Compound
9e



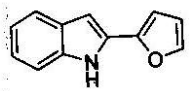
ght741-3
nmr400D



Compound 9f

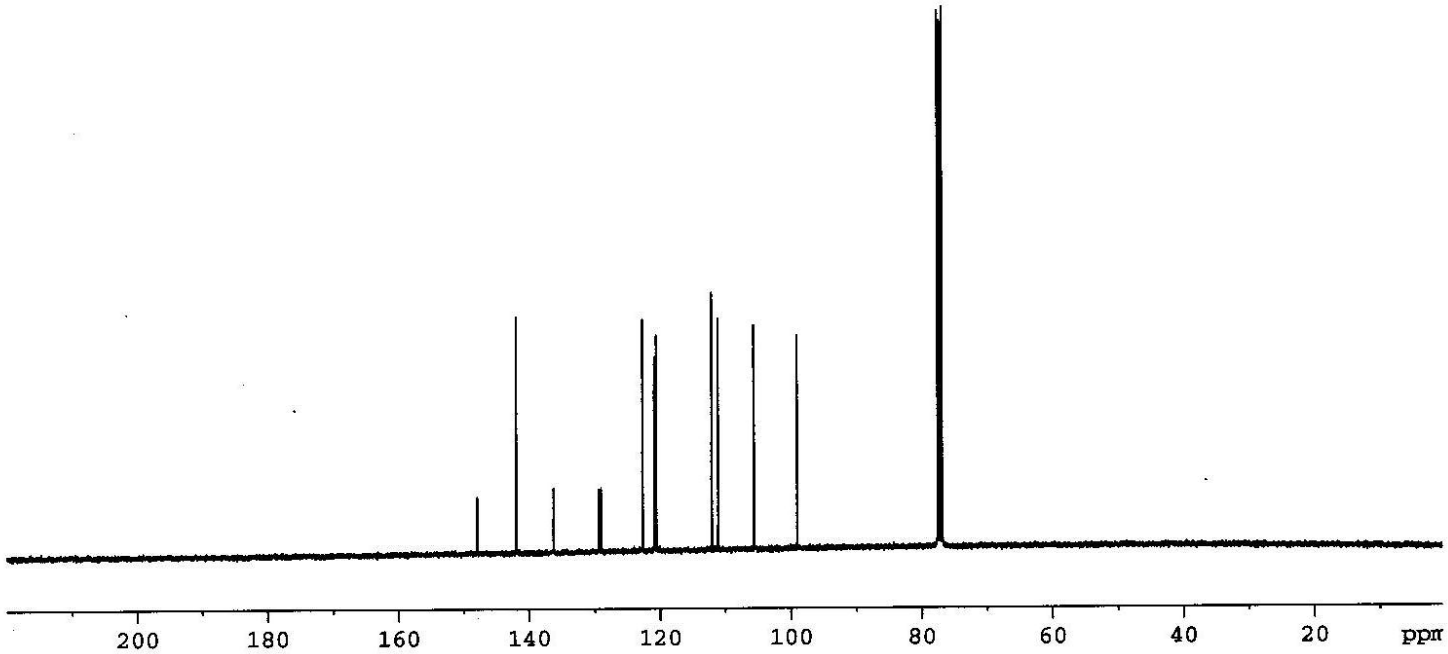


ght741-c1
nmr400D

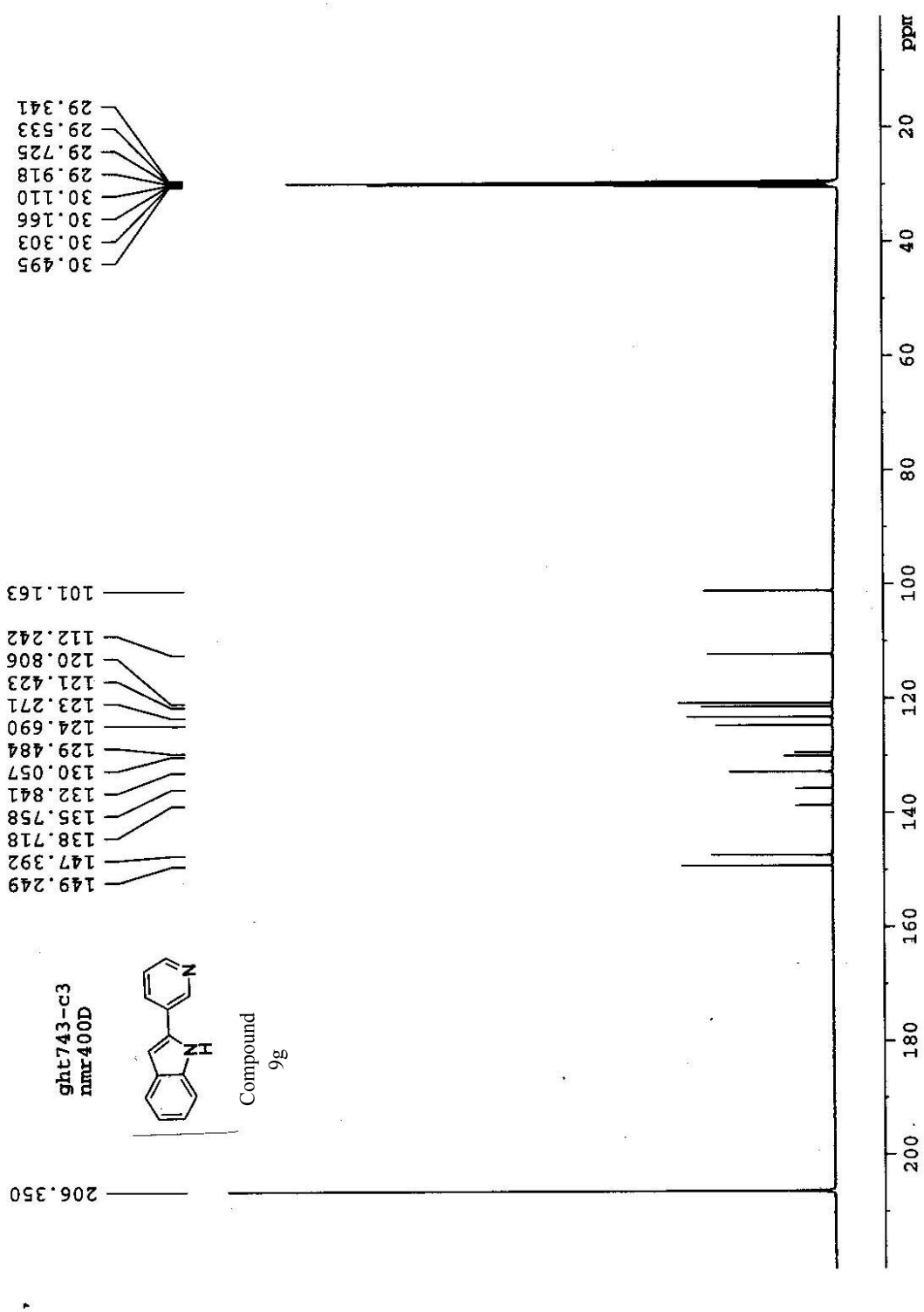


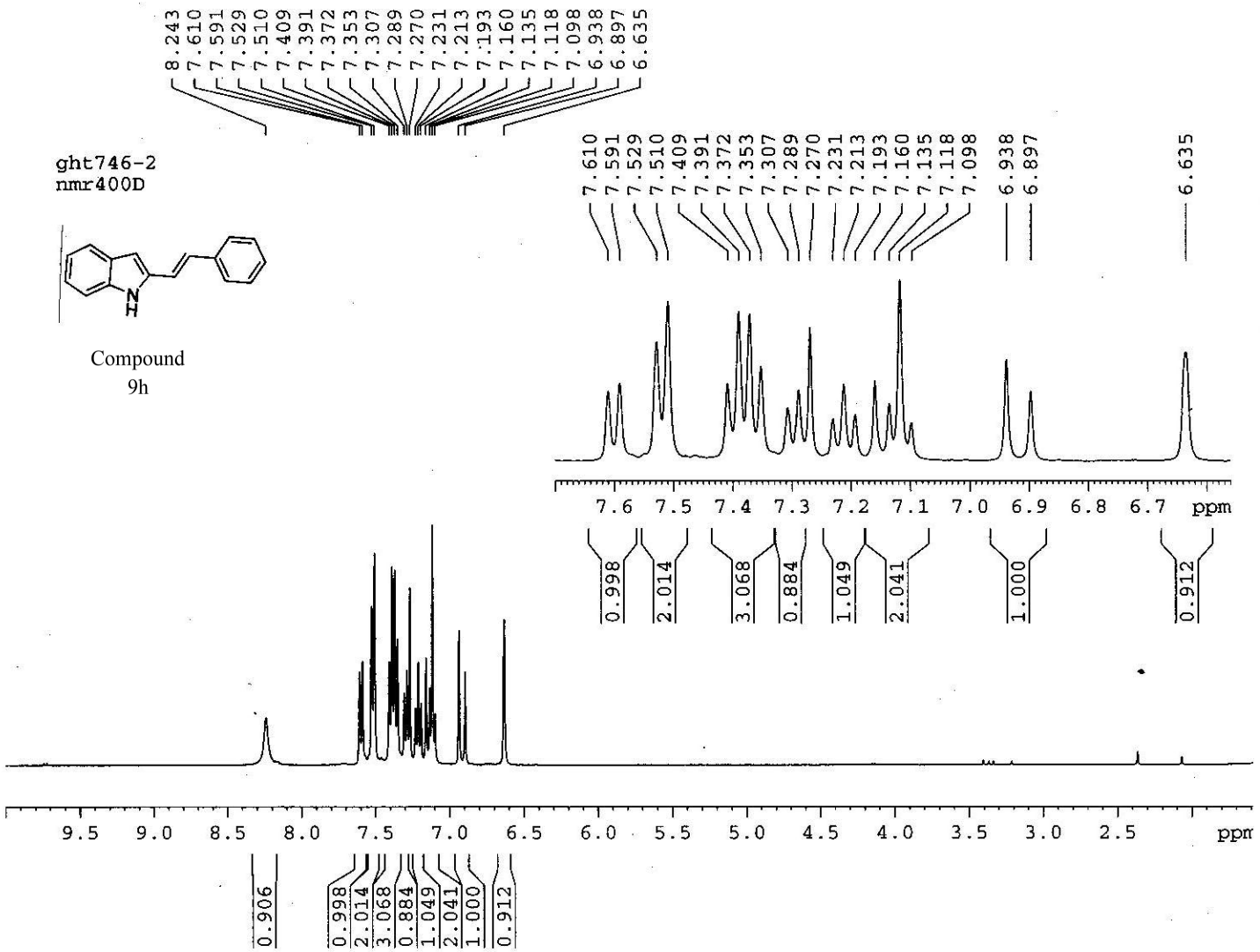
Compound 9f

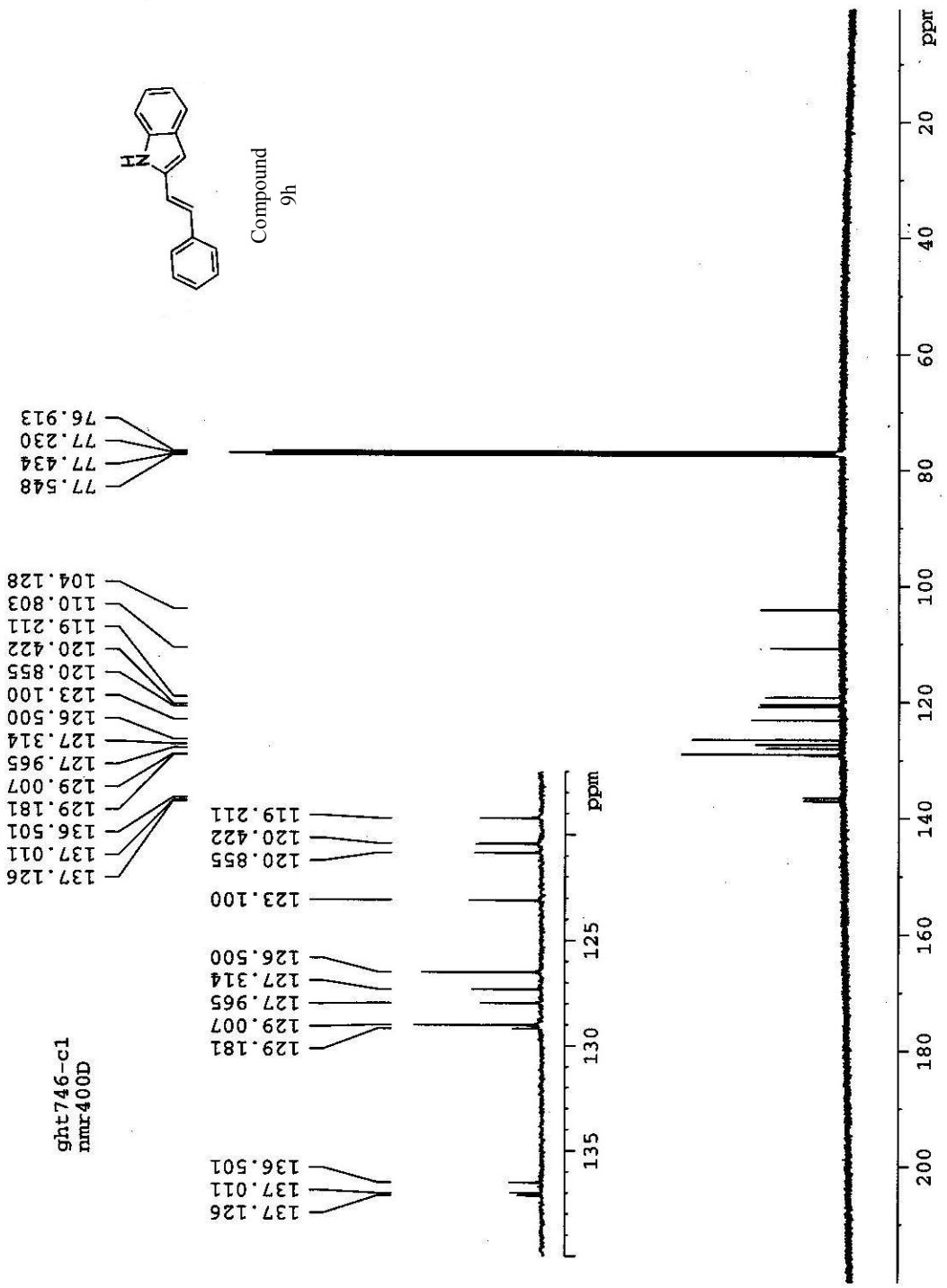
147.931
141.933
136.268
129.407
129.031
122.661
120.871
120.553
112.039
111.055
105.616
99.032
77.552
77.235
76.917

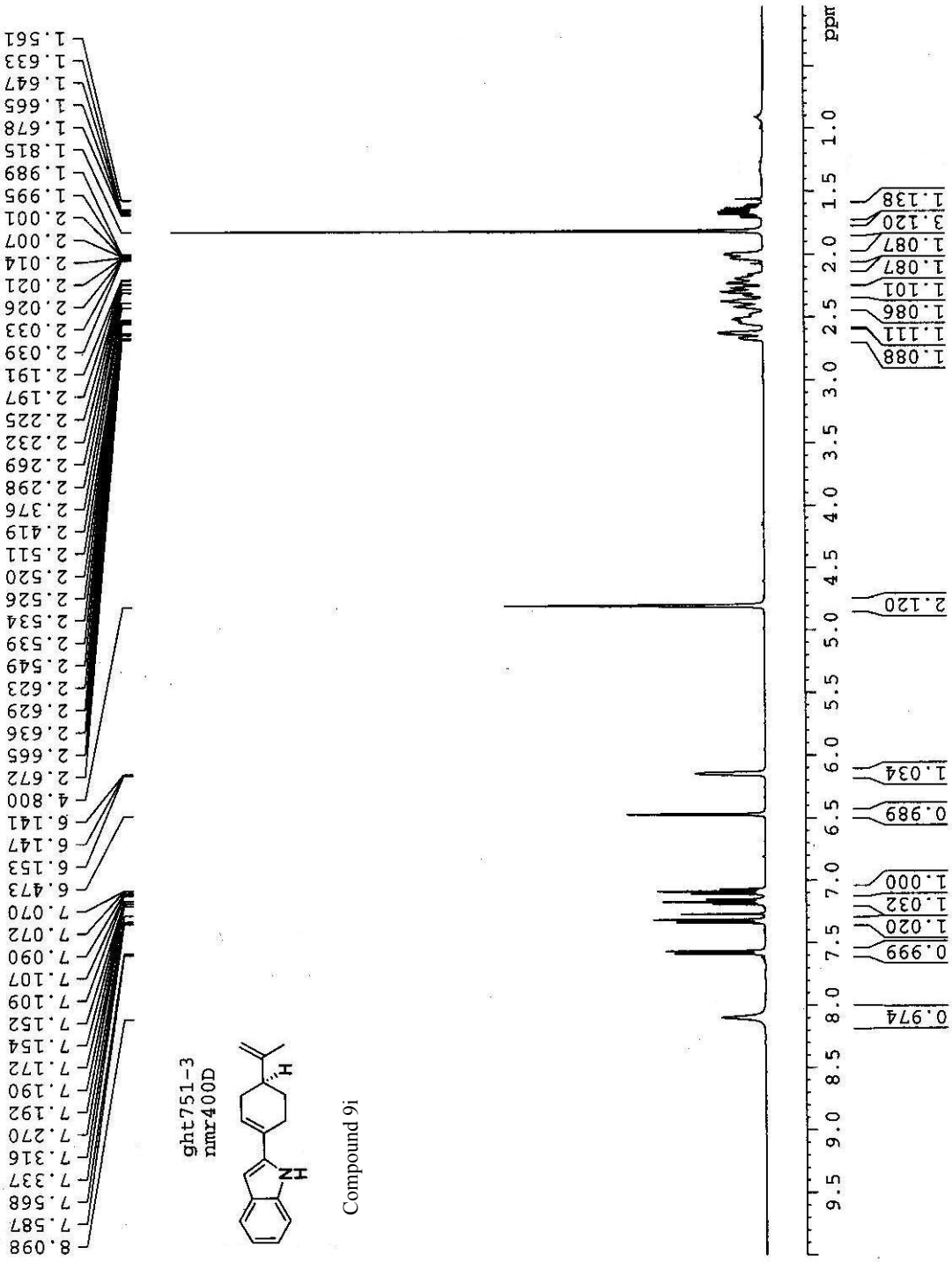


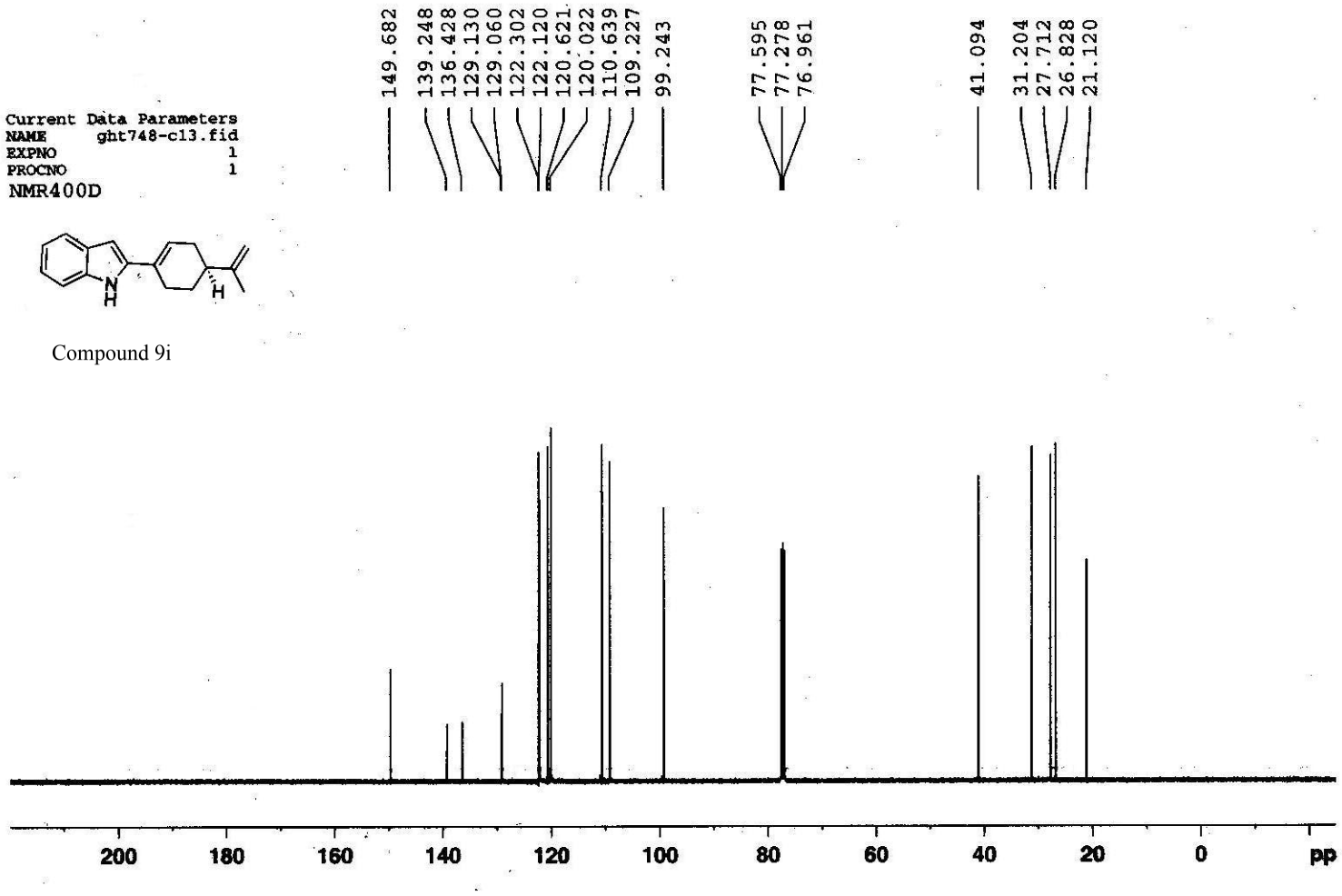
ght735-5
nmr400D
Compound
9g
10.895
9.125
9.121
9.120
8.526
8.522
8.514
8.510
8.208
8.203
8.198
8.188
8.183
8.179
7.617
7.597
7.450
7.439
7.438
7.430
7.420
7.418
7.171
7.169
7.151
7.134
7.131
7.078
7.076
7.058
7.056
7.041
7.039
7.026
7.022
7.021
3.047
2.066
2.061
2.055
2.050
2.045
2.039
0.911
1.000
0.969
1.015
1.024
1.988
1.003
0.997
0.969
ppm


ght743-c3
nmr400D
Compound
9g
206.350
149.249
147.392
138.718
135.758
132.841
130.057
129.484
124.690
123.271
121.423
120.806
112.242
101.163
30.495
30.303
30.166
30.110
29.918
29.725
29.533
29.341
ppm

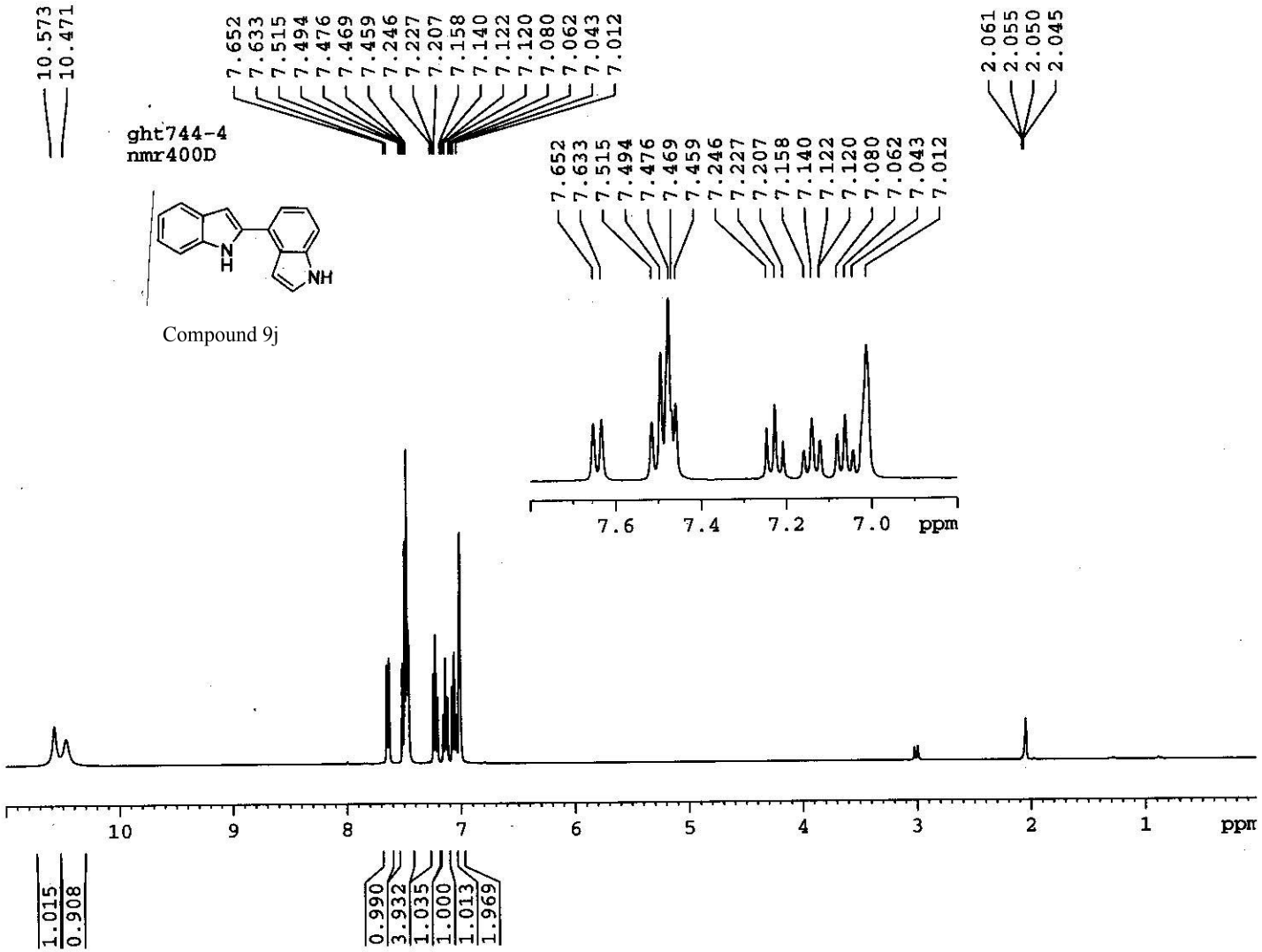

8.243
7.610
7.591
7.529
7.510
7.409
7.391
7.372
7.353
7.307
7.289
7.270
7.231
7.213
7.193
7.160
7.135
7.118
7.098
6.938
6.897
6.635
ght746-2
nmr400D
Compound
9h
7.6 7.5 7.4 7.3 7.2 7.1 7.0 6.9 6.8 6.7 ppm
0.998
2.014
3.068
0.884
1.049
2.041
1.000
0.912
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 ppm
0.906
0.998
2.014
3.068
0.884
1.049
2.041
1.000
0.912


Compound
9h
ght746-c1
nmr400D
ppm

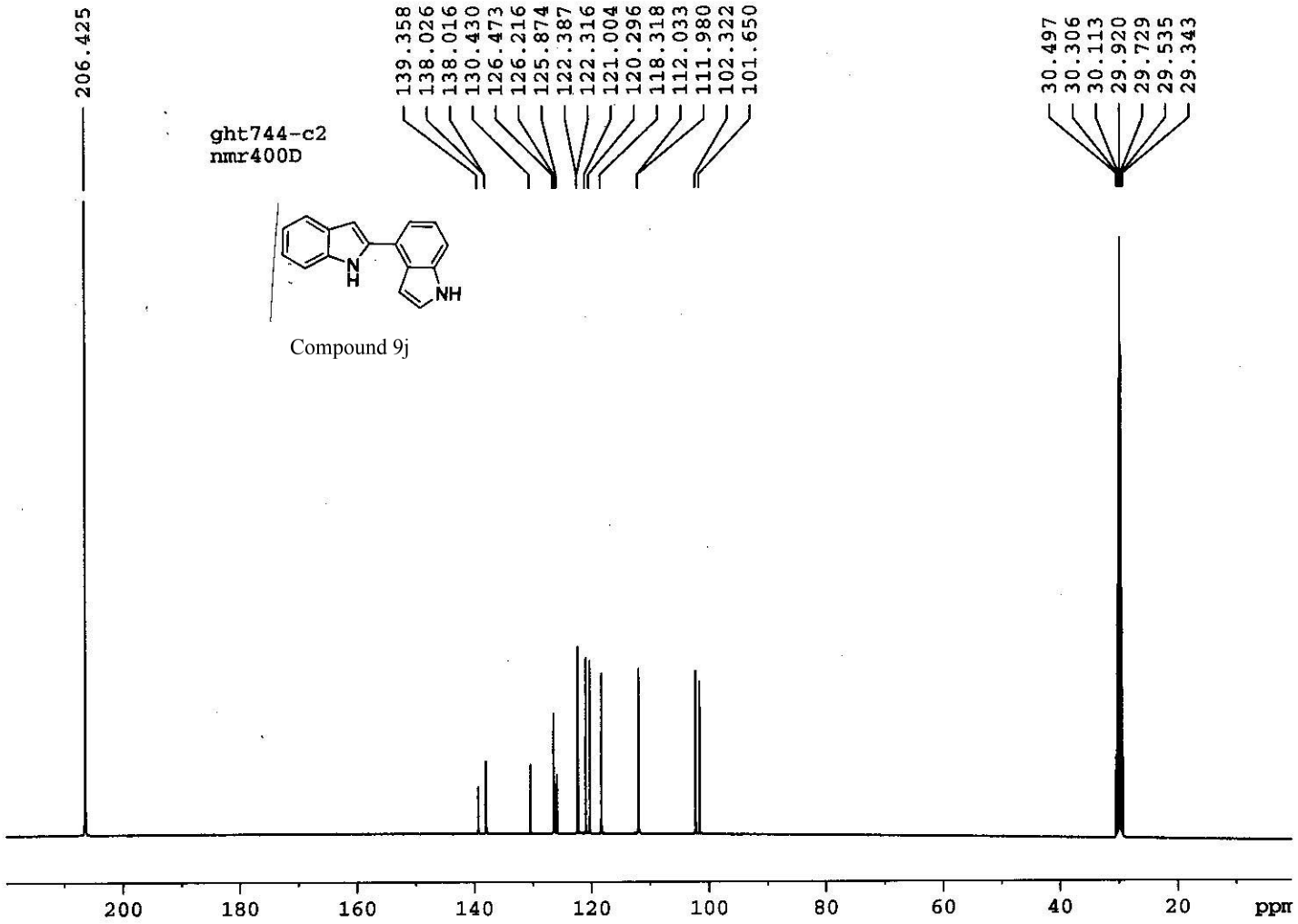

ppm
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
0.974
0.999
1.020
1.032
1.000
0.989
1.034
2.120
1.088
1.111
1.086
1.101
1.087
1.087
3.120
1.138
ght751-3
nmr400D
Compound 9i


Current Data Parameters
NAME ght748-c13.fid
EXPNO 1
PROCNO 1
NMR400D
149.682
139.248
136.428
129.130
129.060
122.302
122.120
120.621
120.022
110.639
109.227
99.243
77.595
77.278
76.961
41.094
31.204
27.712
26.828
21.120
200
180
160
140
120
100
80
60
40
20
0
pp

Compound 9i


10.573
10.471
7.652
7.633
7.515
7.494
7.476
7.469
7.459
7.246
7.227
7.207
7.158
7.140
7.122
7.120
7.080
7.062
7.043
7.012
2.061
2.055
2.050
2.045
ght744-4
nmr400D
NH
7.6
7.4
7.2
7.0
ppm
10
9
8
7
6
5
4
3
2
1
ppm
1.015
0.908
0.990
3.932
1.035
1.000
1.013
1.969

Compound 9j


206.425
139.358
138.026
138.016
130.430
126.473
126.216
125.874
122.387
122.316
121.004
120.296
118.318
112.033
111.980
102.322
101.650
30.497
30.306
30.113
29.920
29.729
29.535
29.343
ght744-c2
nmr400D
N
H
NH
200
180
160
140
120
100
80
60
40
20
ppm

Compound 9j