SUPPORTING INFORMATION

Synthesis of isoquinolines and naphthyridines by electrophilic ring closure of iminoalkynes

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General procedure for preparation of the iminoalkynes. To a solution of the aryl halide (5.0 mmol) and the terminal alkyne (6.0 mmol, 1.2 equivs) in Et_3N (20 ml) were added $PdCl_2(PPh_3)_2$ (70 mg, 2 mol %) and CuI (10 mg, 1 mol %). The resulting mixture was then heated under an Ar atmosphere at 50 °C. The reaction was monitored by TLC to establish completion. When the reaction was complete, the mixture was allowed to cool to room temperature, and the ammonium salt was removed by filtration. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel to afford the corresponding arylalkyne. To the purified arylalkyne in a 4 dram vial was added *t*-$BuNH_2$ (6 equiv). The mixture was then stirred under an Ar atmosphere at room temperature for 24 h. The resulting mixture was extracted with ether. The combined organic layers were dried (Na_2SO_4) and filtered. Removal of the solvent afforded the corresponding iminoalkyne.

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***N*-(2-Phenylethynylbenzylidene)-*tert*-butylamine (1).** 2-Bromobenzaldehyde (0.93 g, 5.0 mmol) and phenylacetylene (0.61 g, 6.0 mmol) were employed to afford 1.20 g of the indicated compound in 92% overall yield with spectral properties identical to those previously reported[1]: mp 53-54 °C (lit.[1] mp 52-53 °C).

***N*-[2-(3,4,5-Trimethoxyphenylethynyl)benzylidene]-*tert*-butylamine (6).** 3,4,5-Trimethoxyiodobenzene (1.47 g, 5.0 mmol) and 2-ethynylbenzaldehyde (0.78 g, 6.0 mmol) were employed to afford 1.33 g of the indicated compound in 76% overall yield as a yellow liquid: ^{1}H NMR ($CDCl_3$) δ 1.36 (s, 9H), 3.89 (s, 9H), 6.77 (s, 2H), 7.35-7.38 (m, 2H), 7.53 (dd, J = 3.0, 6.0 Hz, 1H), 8.05 (dd, J = 3.6, 6.0 Hz, 1H), 8.92 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 29.9, 56.3, 58.0, 61.2, 86.1, 95.1, 108.9, 118.3, 124.0, 126.2, 128.8, 129.9, 132.2, 138.0, 139.3, 153.4, 154.3; IR (neat, cm^{-1}) 2958, 2206, 1698; HRMS Calcd for $C_{22}H_{25}O_3N$: 351.1834. Found: 351.1839.

***N*-[2-(Cyclohex-1-enylethynyl)benzylidene]-*tert*-butylamine (8).** 2-Bromobenzaldehyde (0.93 g, 5.0 mmol) and 1-cyclohexenylacetylene (0.64 g, 6.0 mmol) were employed to afford 1.15 g of the indicated compound in 87% overall yield with spectral properties identical to those previously reported.[1]

***N*-[2-(Cyclohexylethynyl)benzylidene]-*tert*-butylamine (12).** 2-Bromobenzaldehyde (0.93 g, 5.0 mmol) and cyclohexylacetylene (0.65 g, 6.0 mmol)

were employed to afford 1.24 g of the indicated compound in 93% overall yield with spectral properties identical to those previously reported.[1]

***N*-[2-(4-(Tetrahydropyran-2-yloxy)but-1-ynyl)benzylidene]-*tert*-butylamine (14).** 2-Bromobenzaldehyde (0.93 g, 5.0 mmol) and 2-(3-butynyloxy)tetrahydro-2*H*-pyran (0.93 g, 6.0 mmol) were employed to afford 1.32 g of the indicated compound in 84% overall yield with spectral properties identical to those previously reported.[1]

***N*-[(2-Phenylethynyl)pyridin-3-ylmethylene]-*tert*-butylamine (16).** 2-Bromopyridine-3-carboxaldehyde[2] (0.94 g, 5.0 mmol) and phenylacetylene (0.61 g, 6.0 mmol) were employed to afford 1.26 g of the iminoalkyne in 96% overall yield as a yellow liquid: ^{1}H NMR ($CDCl_3$) δ 1.35 (s, 9H), 7.29 (ddd, J = 0.3, 3.6, 6.0 Hz, 1H), 7.38-7.41 (m, 3H), 7.59-7.62 (m, 2H), 8.36 (dd, J = 1.5, 6.0 Hz, 1H), 8.63 (dd, J = 1.5, 3.6 Hz, 1H), 8.88 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 29.8, 58.4, 86.3, 94.5, 122.2, 123.3, 128.7, 129.4, 132.1, 133.9. 134.2, 143.5, 151.3, 152.5; IR (neat, cm^{-1}) 3057, 2967, 2928, 2218, 1699; HRMS Calcd for $C_{18}H_{18}N_2$: 262.1470. Found: 262.1475.

***N*-[2-(1-Octyn-1-yl)pyridin-3-ylmethylene]-*tert*-butylamine (18).** 2-Bromopyridine-3-carboxaldehyde[2] (0.94 g, 5.0 mmol) and 1-octyne (0.49 g, 6.0 mmol) were employed to afford 1.28 g of the iminoalkyne in 95% overall yield as a yellow liquid: ^{1}H NMR ($CDCl_3$) δ 0.87-0.92 (m, 3H), 1.29-1.34 (m, 13H), 1.46-1.52 (m, 2H), 1.60-1.71 (m, 2H), 2.52 (t, J = 6.9 Hz, 2H), 7.23 (dd, J = 4.8, 7.8 Hz, 1H), 8.30 (dd, J =

1.8, 7.8 Hz, 1H), 8.55 (dd, J = 1.8, 4.8 Hz, 1H), 8.74 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.2, 19.7, 22.7, 28.6, 28.9, 29.8, 31.5, 58.2, 78.1, 96.6, 122.8, 133.7, 133.8, 144.1, 151.1, 152.9; IR (neat, cm^{-1}) 3056, 2961, 2928, 2858, 2227, 1636, 1578; HRMS Calcd for $C_{18}H_{26}N_2$: 270.2096. Found: 270.2099.

General procedure for the electrophilic cyclization of iminoalkynes by I_2, ICl, PhSeCl, PhSCl and *p*-$O_2NC_6H_4SCl$. The electrophile (6 or 2 equivs), the solvent (5 ml), and the base, where required (3 equivs), were placed in a 2 dram vial. The iminoalkyne (0.25 mmol) in 2 ml of the solvent was added dropwise to the vial. The vial was flushed with Ar and the reaction was stirred at room temperature for the indicated period of time. The reactions were monitored by TLC to establish completion. The reaction mixture was then diluted with 25 ml of ether, washed with either 25 ml of saturated $Na_2S_2O_3$ (for the reactions of I_2 and ICl) or saturated NaCl, dried (Na_2SO_4) and filtered. The solvent was evaporated under reduced pressure and the product was isolated by chromatography on a silica gel column.

General procedure for the silver-catalyzed cyclization of iminoalkynes. 5 Mol % of $AgNO_3$ and 5 ml of $CHCl_3$ were placed into a 2 dram vial. The iminoalkyne (0.25 mmol) in 2 ml of $CHCl_3$ was added dropwise to the vial. The vial was then flushed with Ar and heated at 50 °C for the indicated period of time. The reaction was cooled, diluted with 25 ml of ether, washed with 25 ml of saturated NaCl, dried (Na_2SO_4) and filtered.

The solvent was evaporated under reduced pressure and the product was isolated by chromatography on a silica gel column.

4-Iodo-3-phenylisoquinoline (2). Purification by flash chromatography (3:1 hexane/EtOAc) afforded 56 mg (68%) (Table 1, entry 1) or 55 mg (67%) (Table 1, entry 2) of the product from I_2 or ICl, respectively, as a yellow solid: mp 84-85 °C; ^{1}H NMR ($CDCl_3$) δ 7.26-7.52 (m, 3H), 7.61-7.70 (m, 3H), 7.70-7.85 (m, 2H), 7.95 (d, J = 8.1 Hz, 1H), 8.22 (d, J = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 98.3, 128.1, 128.2, 128.3, 128.5, 130.3, 132.4, 132.6, 138.8, 143.9, 152.2, 157.4 (one sp^2 carbon missing due to overlap); IR ($CHCl_3$, cm^{-1}) 3055, 1630, 1549; HRMS Calcd for $C_{15}H_{10}IN$: 330.9858. Found: 330.9862.

3-Phenyl-4-(phenylselenyl)isoquinoline (3). Purification by flash chromatography (3:1 hexane/EtOAc) afforded 69 mg (76%) of the product as a yellow solid: mp 112-114 °C, ^{1}H NMR ($CDCl_3$) δ 7.04-7.08 (m, 5H), 7.39-7.42 (m, 3H), 7.55-7.56 (m, 3H), 7.71 (ddd, J = 1.2, 6.9, 8.1 Hz, 1H), 8.02 (d, J = 7.5 Hz, 1H), 8.45 (d, J = 8.1 Hz, 1H), 9.35 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 121.8, 126.4, 127.8, 127.9, 128.3, 128.4, 128.4, 128.9, 129.4, 129.9, 130.1, 132.1, 133.3, 138.9, 142.0, 153.3, 158.4; IR ($CHCl_3$, cm^{-1}) 3056, 2924, 1575; HRMS Calcd for $C_{21}H_{15}NSe$: 361.0370. Found: 361.0378.

3-Phenylisoquinoline (4). Purification by flash chromatography (3:1 hexane/EtOAc) afforded 42 mg (82%) of the product as a yellow solid with spectral properties identical to those previously reported[3]: mp 102-103 °C (lit.[3] mp 101-102 °C).

3-Phenyl-4-(4-nitrophenylsulfenyl)isoquinoline (5). Purification by flash chromatography (3:1 hexane/EtOAc) afforded 42 mg (47%) of the product as a yellow solid: mp 193-195 °C; ^{1}H NMR ($CDCl_3$) δ 6.97-6.99 (m, 2H), 7.40-7.42 (m, 3H), 7.57-7.60 (m, 2H), 7.68-7.80 (m, 2H), 7.97-8.00 (m, 2H), 8.13 (d, J = 8.4 Hz, 1H), 8.27 (d, J = 8.4 Hz, 1H), 9.46 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 119.5, 124.4, 125.6, 126.1, 128.2, 128.3, 128.5, 128.8, 128.9, 129.7, 132.7, 138.1, 140.2, 145.4, 147.8, 154.6, 159.0; IR ($CHCl_3$, cm^{-1}) 3019, 2926, 1518; HRMS Calcd for $C_{21}H_{14}N_2O_2S$: 358.007. Found: 358.0781.

4-Phenylselenyl-3-(3,4,5-trimethoxyphenyl)isoquinoline (7). Purification by flash chromatography (2:1 hexane/EtOAc) afforded 107 mg (95%) of the product as a yellow liquid: ^{1}H NMR ($CDCl_3$) δ 3.70 (s, 6H), 3.88 (s, 3H), 6.76 (s, 2H), 7.04-7.11 (m, 5H), 7.65 (dt, J = 0.6, 5.5 Hz, 1H), 7.75 (dt, J = 0.9, 5.8 Hz, 1H), 8.03 (d, J = 5.8 Hz, 1H), 8.49 (d, J = 6.3 Hz, 1H), 9.34 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 56.0, 61.0, 107.0, 121.0, 126.1, 127.7, 128.2, 128.3, 128.7, 129.4, 129.5, 132.0, 133.8, 137.7, 138.0, 139.1, 152.6, 153.3, 158.4; IR (neat, cm^{-1}) 3057, 2936, 2833, 1607; HRMS Calcd for $C_{24}H_{21}SeO_3N$: 451.0687. Found: 451.0695.

3-(Cyclohex-1-enyl)-4-(phenylselenyl)isoquinoline (9). Purification by flash chromatography (3:1 hexane/EtOAc) afforded 88 mg (96%) of the product as a yellow solid: mp 103-105 °C; ^{1}H NMR ($CDCl_3$) δ 1.69-1.82 (m, 4H), 2.15-2.21 (m, 2H), 2.44-2.48 (m, 2H), 5.67-5.70 (m, 1H), 7.09-7.14 (m, 5H), 7.52-7.65 (m, 2H), 7.94 (d, J = 8.1 Hz, 1H), 8.30 (d, J = 8.4 Hz, 1H), 9.23 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 22.0, 22.9, 25.5, 29.1, 120.8, 126.1, 127.0, 128.1, 128.2, 128.4, 129.2, 129.3, 129.9, 131.4, 133.8, 138.4, 140.0, 153.1, 161.2; IR ($CHCl_3$, cm^{-1}) 3019, 2936, 1571; HRMS Calcd for $C_{21}H_{19}SeN$: 365.0684. Found: 365.0690.

3-(Cyclohex-1-enyl)-4-iodoisoquinoline (10). Purification by flash chromatography (3:1 hexane/EtOAc) afforded 56 mg (67%) of the product as a yellow liquid: ^{1}H NMR ($CDCl_3$) δ 1.73-1.79 (m, 2H), 1.84-1.92 (m, 2H), 2.25-2.29 (m, 2H), 2.40-2.43 (m, 2H), 5.85 (s, 1H), 7.57-7.60 (m, 1H), 7.73-7.78 (m, 1H), 7.87 (d, J = 8.1 Hz, 1H), 8.14 (d, J = 8.4 Hz, 1H), 9.06 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 22.1, 22.9, 25.3, 28.5, 97.7, 127.6, 128.0, 128.2, 129.5, 132.0, 132.2, 138.7, 141.8, 152.1, 159.7; IR (neat, cm^{-1}) 3019, 2936, 1618; HRMS Calcd for $C_{15}H_{14}IN$: 335.0165. Found: 335.0168.

3-(Cyclohex-1-enyl)-4-(phenylsulfenyl)isoquinoline (11). Purification by flash chromatography (3:1 hexane/EtOAc) afforded 36 mg (45%) of the product as a yellow solid: mp 130-131 °C; ^{1}H NMR ($CDCl_3$) δ 1.68-1.79 (m, 4H), 2.15-2.17 (m, 2H), 2.41-2.43 (m, 2H), 5.77-5.79 (m, 1H), 6.96-6.98 (m, 2H), 7.03-7.07 (m, 1H), 7.11-7.15 (m,

2H), 7.56 (t, J = 5.4 Hz, 1H), 7.65 (t, J = 5.4 Hz, 1H), 7.97(d, J = 6.0 Hz, 1H), 8.31 (d, J = 6.6 Hz, 1H), 9.26 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 22.0, 23.0, 25.5, 28.9, 121.4, 125.3, 126.0, 127.1, 127.2, 128.2, 128.2, 129.0, 129.2, 131.6, 138.3, 138.7, 138.7, 153.2, 161.2; IR ($CHCl_3$, cm^{-1}) 3019, 2936, 1630; HRMS Calcd for $C_{21}H_{19}SN$: 317.1238. Found: 317.1241.

3-Cyclohexylisoquinoline (13). Purification by flash chromatography (3:1 hexane/EtOAc) afforded 40 mg (75%) of the product as a white solid with spectral properties identical to those of previously reported[1]: mp 40-41 °C (lit.[1] mp 40-41°C).

3-[2-(Tetrahydropyran-2-yloxy)ethyl]isoquinoline (15). Purification by flash chromatography (3:1 hexane/EtOAc) afforded 39 mg (62%) of the product as a yellow liquid with spectral properties identical to those of previously reported.[1]

8-Iodo-7-phenyl-1,6-naphthyridine (17). Purification by flash chromatography (2:1 hexane/EtOAc) afforded 75 mg (90%) (Table 1, entry 12) or 76 mg (92%) (Table 1, entry 13) of the product from I_2 or ICl, respectively, as a yellow solid: mp 163-164 °C; ^{1}H NMR ($CDCl_3$) δ 7.45-7.52 (m, 3H), 7.59-7.62 (dd, J = 3.3, 6.3 Hz, 1H), 7.69 (dd, J = 1.2, 6.0 Hz, 2H), 8.29 (dd, J = 1.5, 6.0 Hz, 1H), 9.16 (s, 1H), 9.21 (dd, J = 1.2, 3.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 101.8, 123.1, 123.4, 128.2, 128.9, 130.0, 136.4, 143.0, 151.1, 152.3, 156.0, 161.1; IR ($CHCl_3$, cm^{-1}) 3048, 1618; HRMS Calcd for $C_{14}H_9IN_2$: 331.9810. Found: 331.9816.

7-*n*-Hexyl-8-phenylselenyl-1,6-naphthyridine (19). Purification by flash chromatography (2:1 hexane/EtOAc) afforded 56 mg (61%) of the product as a yellow liquid: ^{1}H NMR ($CDCl_3$) δ 0.83-0.87 (m, 3H), 1.24-1.36 (m, 6H), 1.67-1.76 (m, 2H), 3.31-3.36 (m, 2H), 7.09-7.13 (m, 3H), 7.20-7.24 (m, 2H), 7.50 (dd, J = 4.2, 8.4 Hz, 1H), 8.28 (dd, J = 1.8, 8.4 Hz, 1H), 9.14 (dd, J = 1.8, 4.2 Hz, 1H), 9.28 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.2, 22.7, 29.5, 30.4, 31.8, 39.5, 122.2, 122.6, 124.4, 126.3, 129.1, 130.4, 133.0, 136.3, 151.8, 153.4, 155.4, 165.1; IR (neat, cm^{-1}) 3056, 2925, 1602; HRMS Calcd for $C_{20}H_{22}SeN_2$: 370.0948. Found: 370.0952.

7- *n*-Hexyl-8-phenylsulfenyl-1,6-naphthyridine (20). Purification by flash chromatography (2:1 hexane/EtOAc) afforded 32 mg (40%) of the product as a yellow liquid: ^{1}H NMR ($CDCl_3$) δ 0.85 (t, J = 6.9 Hz, 3H), 1.24-1.37 (m, 6H), 1.67-1.76 (m, 2H), 3.30 (t, J = 8.4 Hz, 2H), 7.00-7.13 (m, 5H), 7.51 (dd, J = 4.2, 8.1 Hz, 1H), 8.30 (dd, J = 1.8, 8.1 Hz, 1H), 9.15 (dd, J = 1.8, 4.2 Hz, 1H), 9.29 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.2, 22.7, 29.5, 30.2, 31.8, 37.6, 122.3, 122.8, 124.4, 125.4, 127.2, 128.9, 136.4, 137.9, 151.8, 153.5, 155.6, 165.7; IR (neat, cm^{-1}) 3056, 2925, 2854, 2221, 1602; HRMS Calcd for $C_{20}H_{22}SN_2$: 322.1504. Found: 322.1508.

7- *n*-Hexyl-8-iodo-1,6-naphthyridine (21). Purification by flash chromatography (2:1 hexane/EtOAc) afforded 65 mg (76%) of the product as a yellow liquid: ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J = 7.5 Hz, 3H), 1.31-1.51 (m, 6H), 1.77-1.88 (m, 2H), 3.31-3.36 (m,

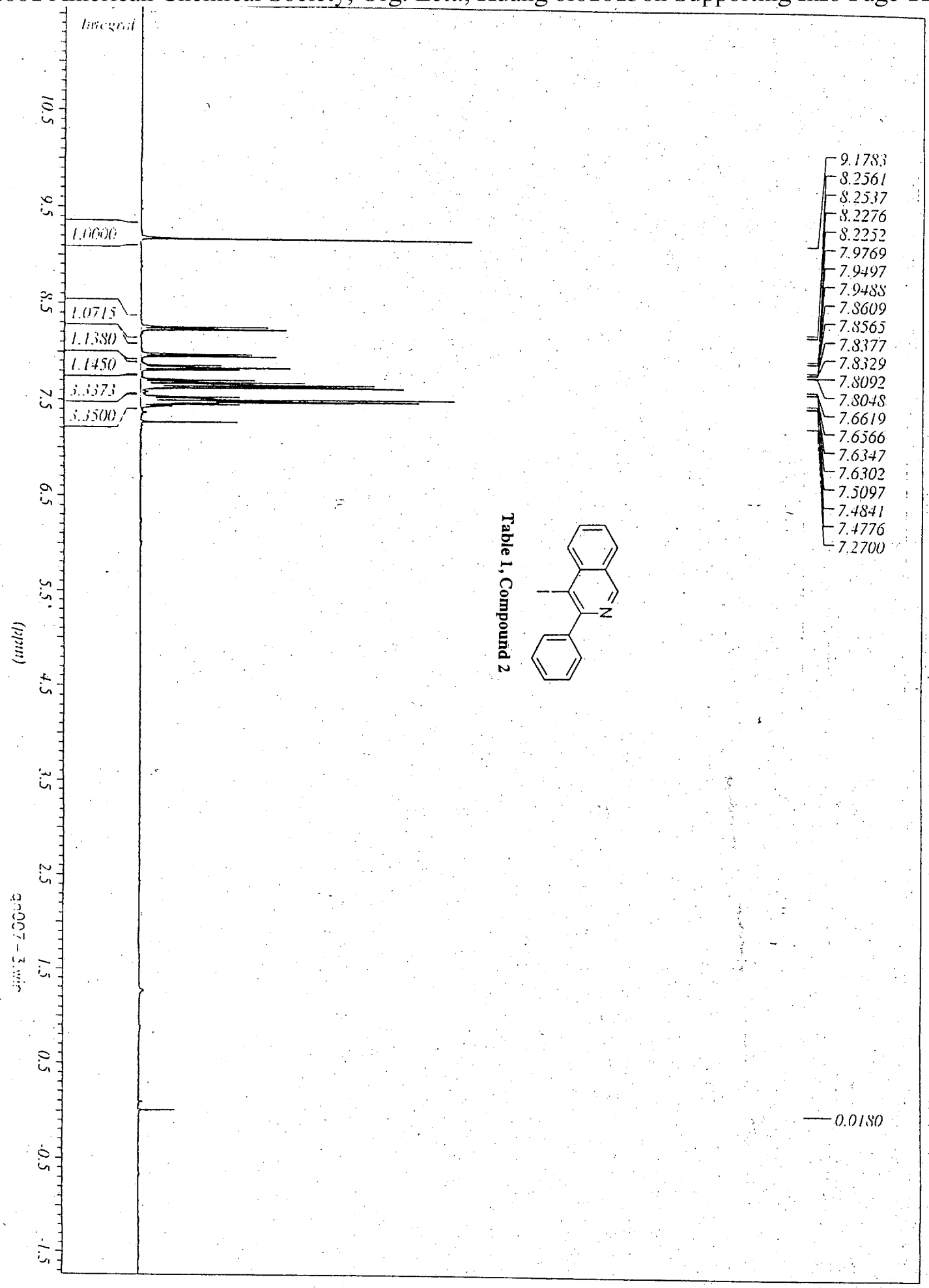
2H), 7.53 (dd, J = 4.2, 8.1 Hz, 1H), 8.22 (dd, J = 1.5, 8.1 Hz, 1H), 9.06 (s, 1H), 9.15 (dd, J = 1.5, 4.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.2, 22.7, 29.3, 29.5, 31.8, 42.7, 102.3, 122.6, 122.6, 136.2, 150.6, 152.1, 155.5, 163.1; IR (neat, cm^{-1}) 3018, 2955, 2925, 2854, 1603, 1579; HRMS Calcd for $C_{14}H_{17}IN_2$: 340.0436. Found: 340.0441.

References

1. Roesch, K. R.; Larock, R. C. *Org. Lett.*, **1999**, *4*, 553.

2. (a) Melnyk, P.; Gasche, J.; Thal, C. *Synth. Commun.*, **1993**, 2727. (b) Bjork, P.; Aakermann, T.; Hornfeldt, A.; Gronowitz, S. *J. Heterocycl. Chem.* **1995**, *32*, 751.

3. Sard, H. *J. Heterocycl. Chem.* **1994**, *31*, 1085.



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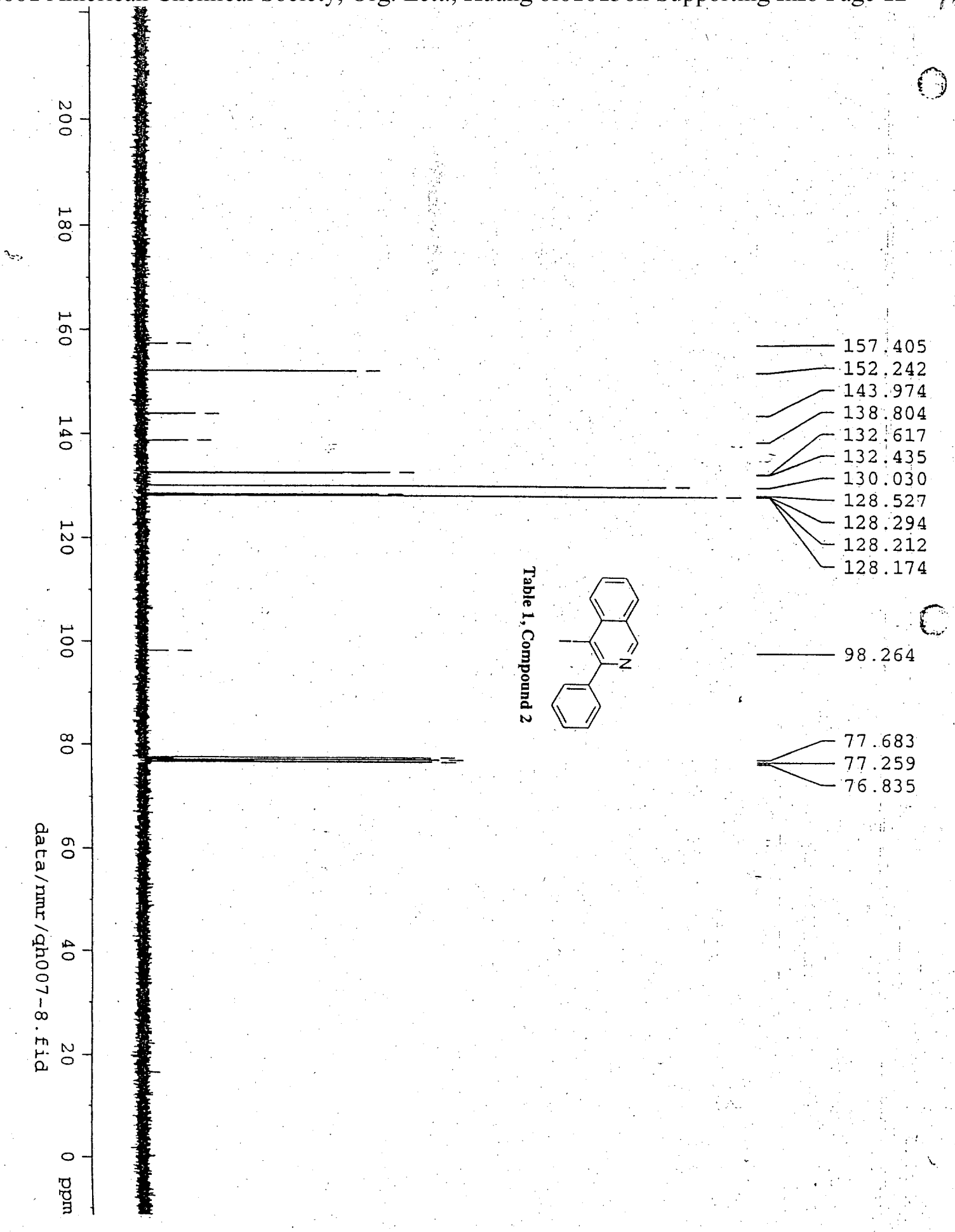

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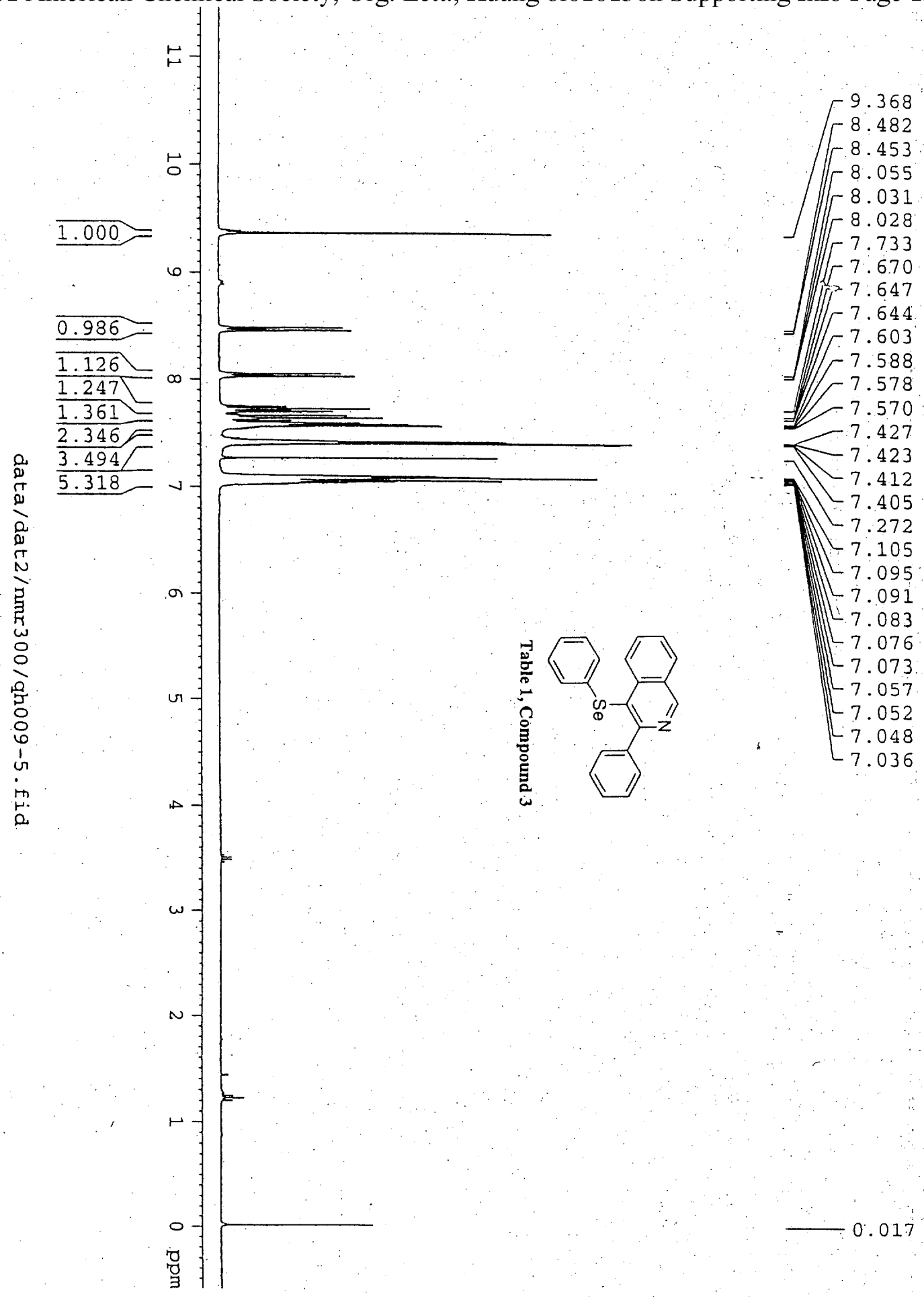

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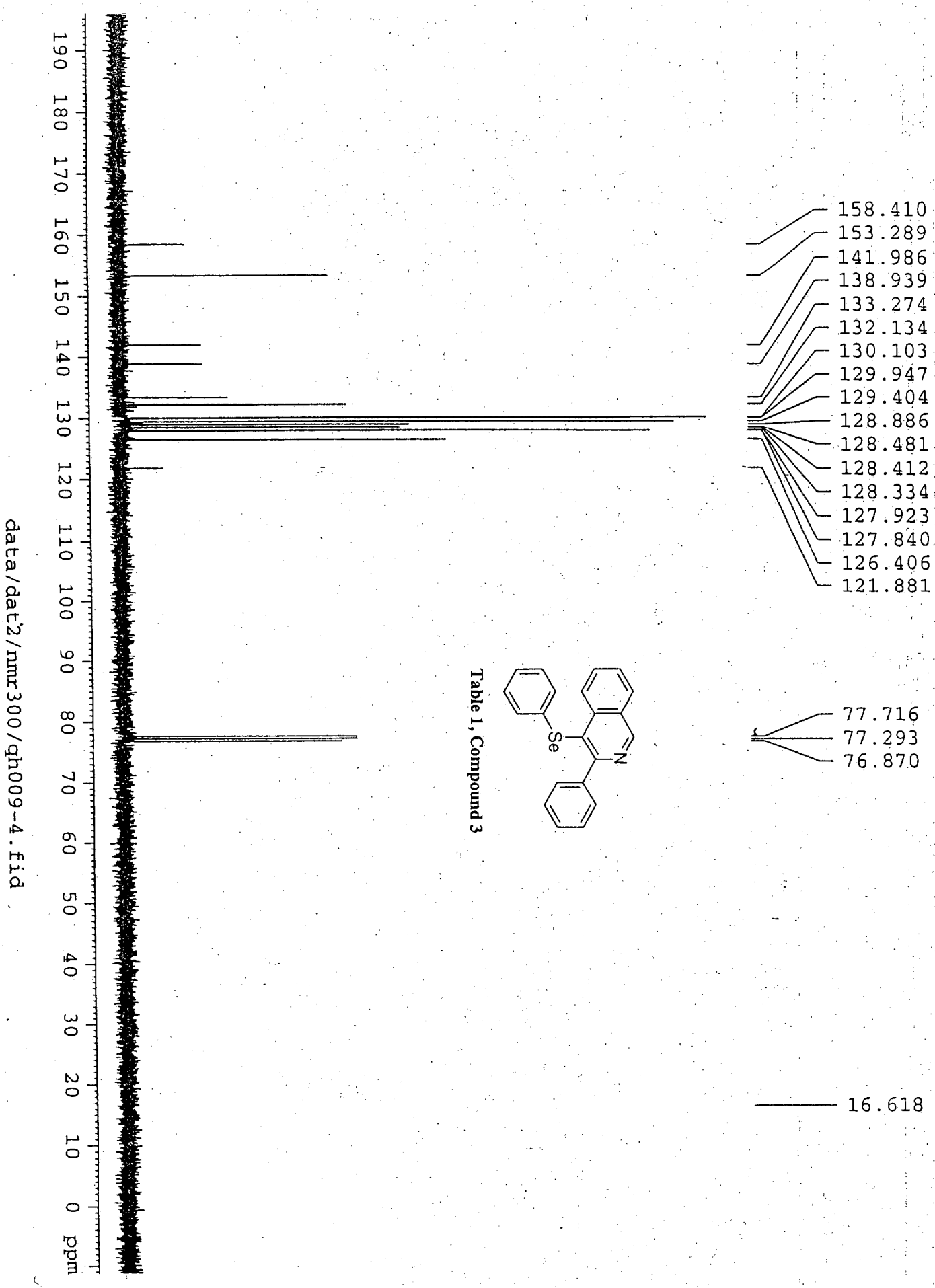

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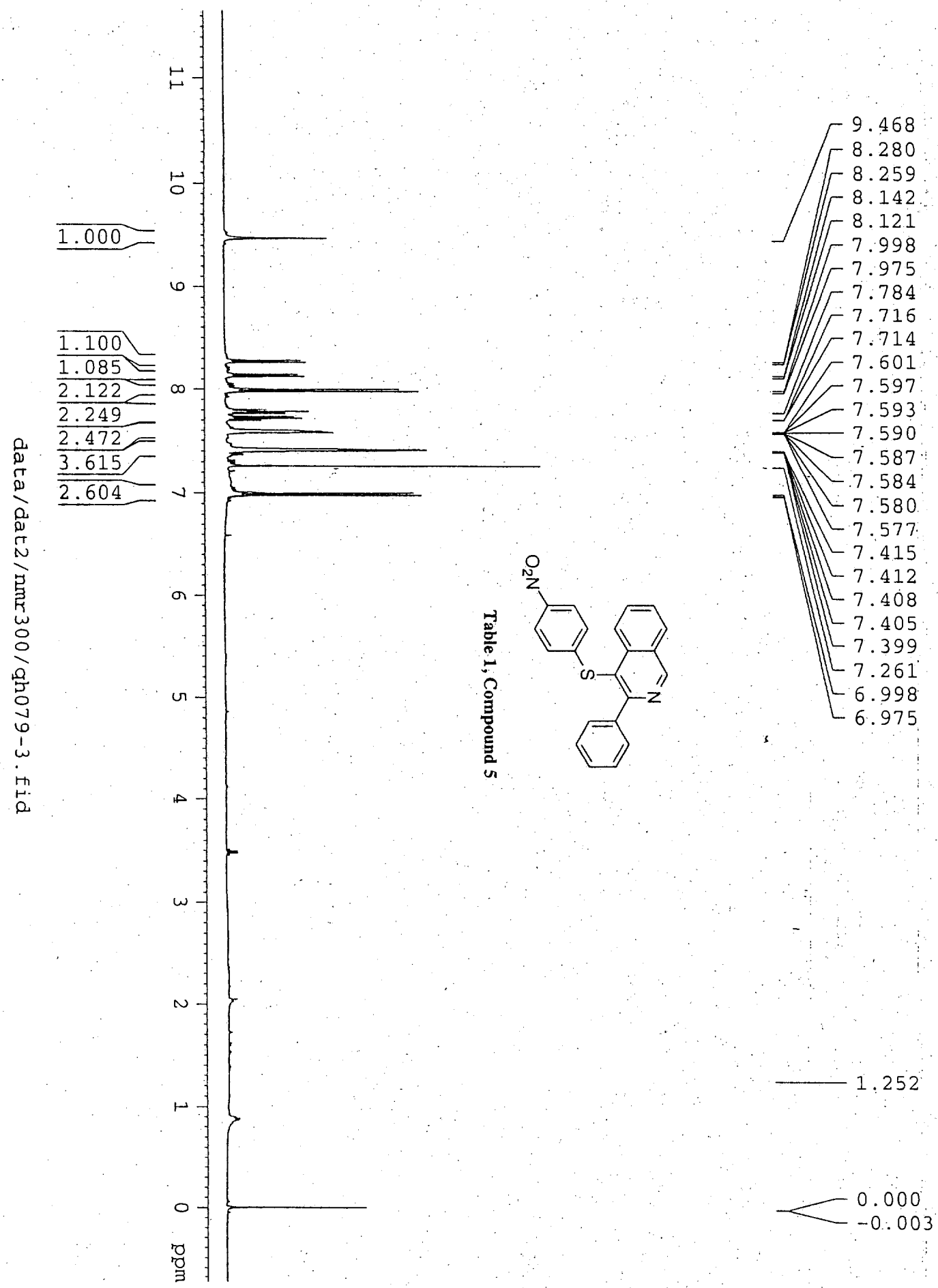

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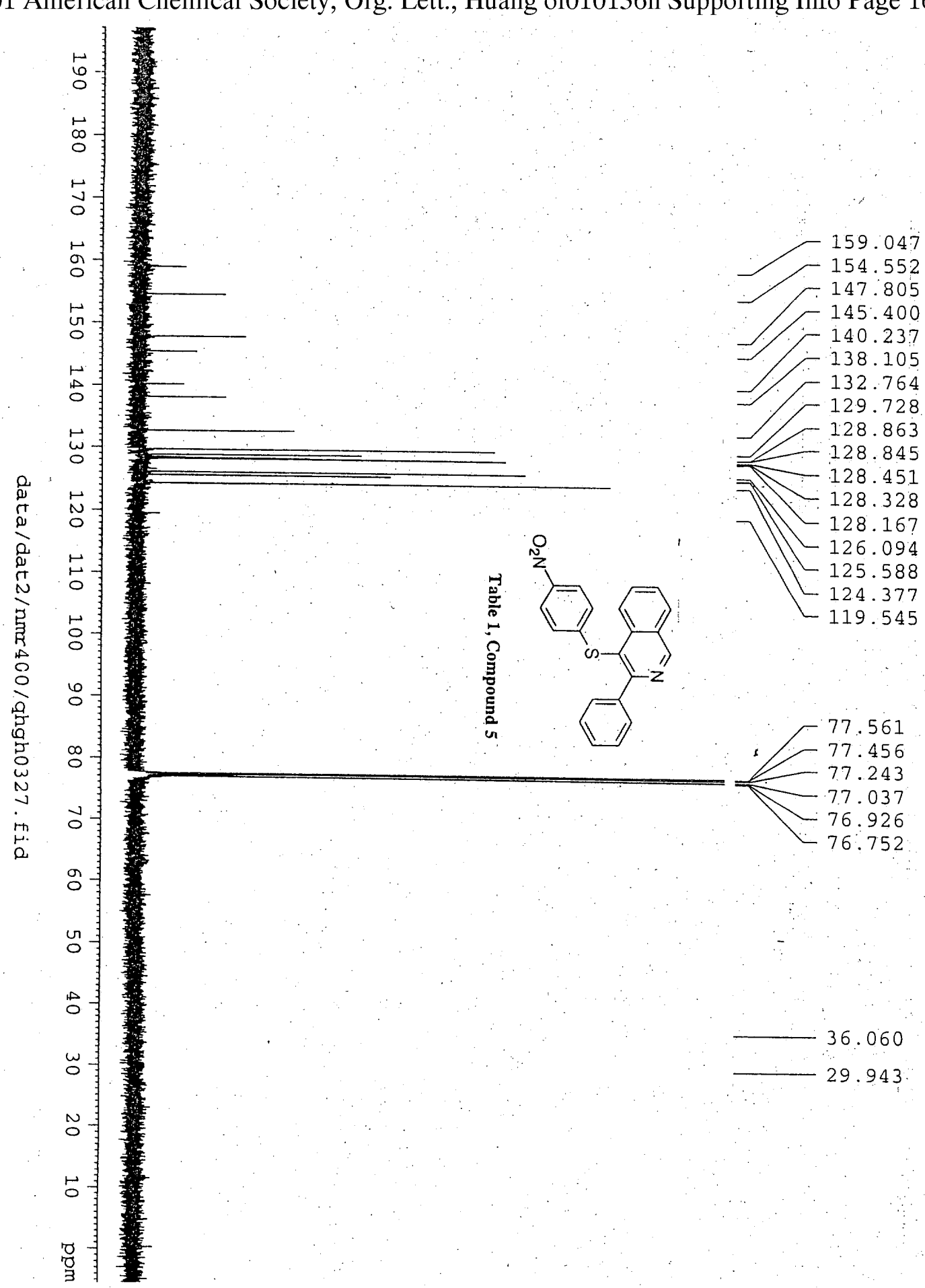
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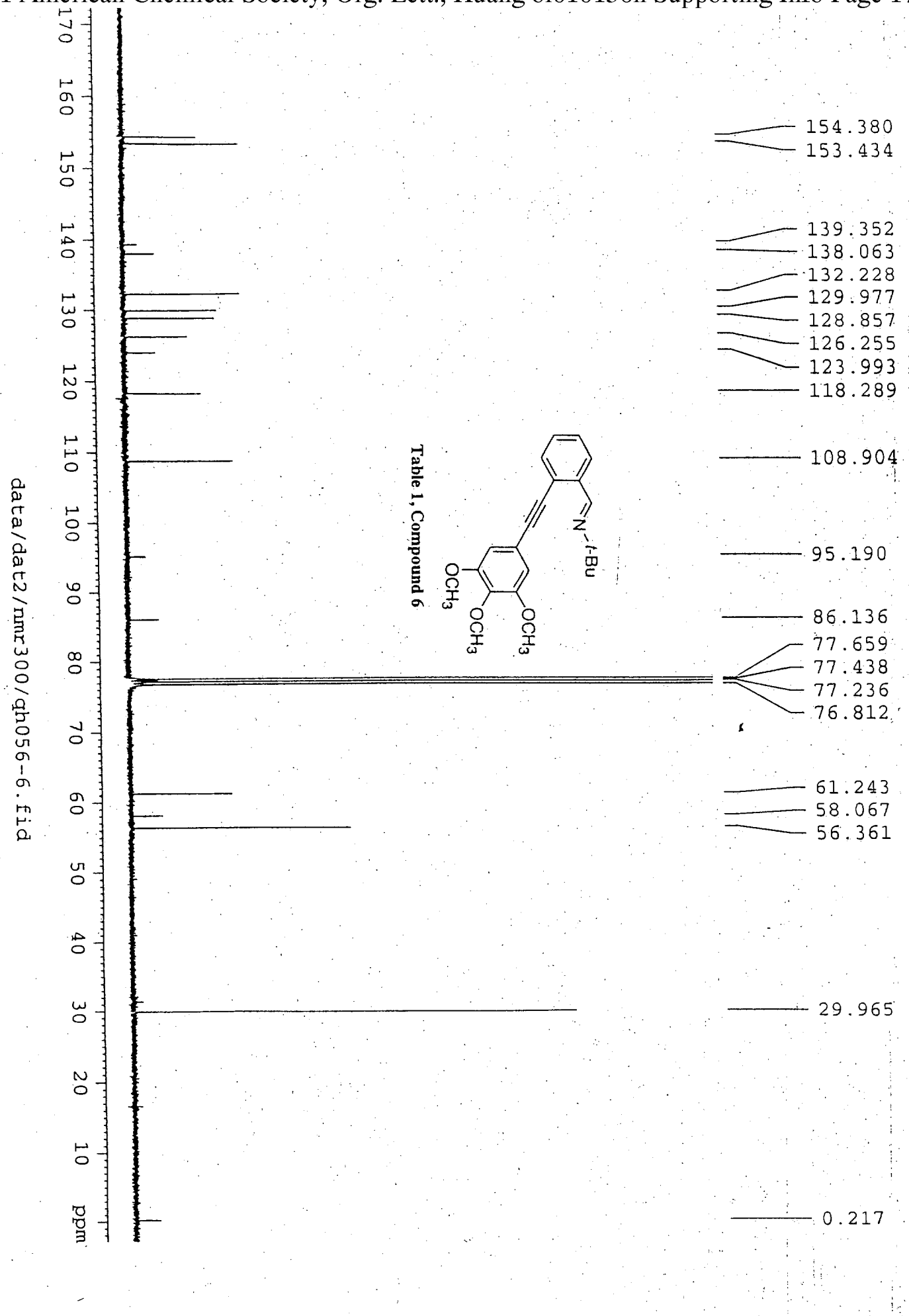

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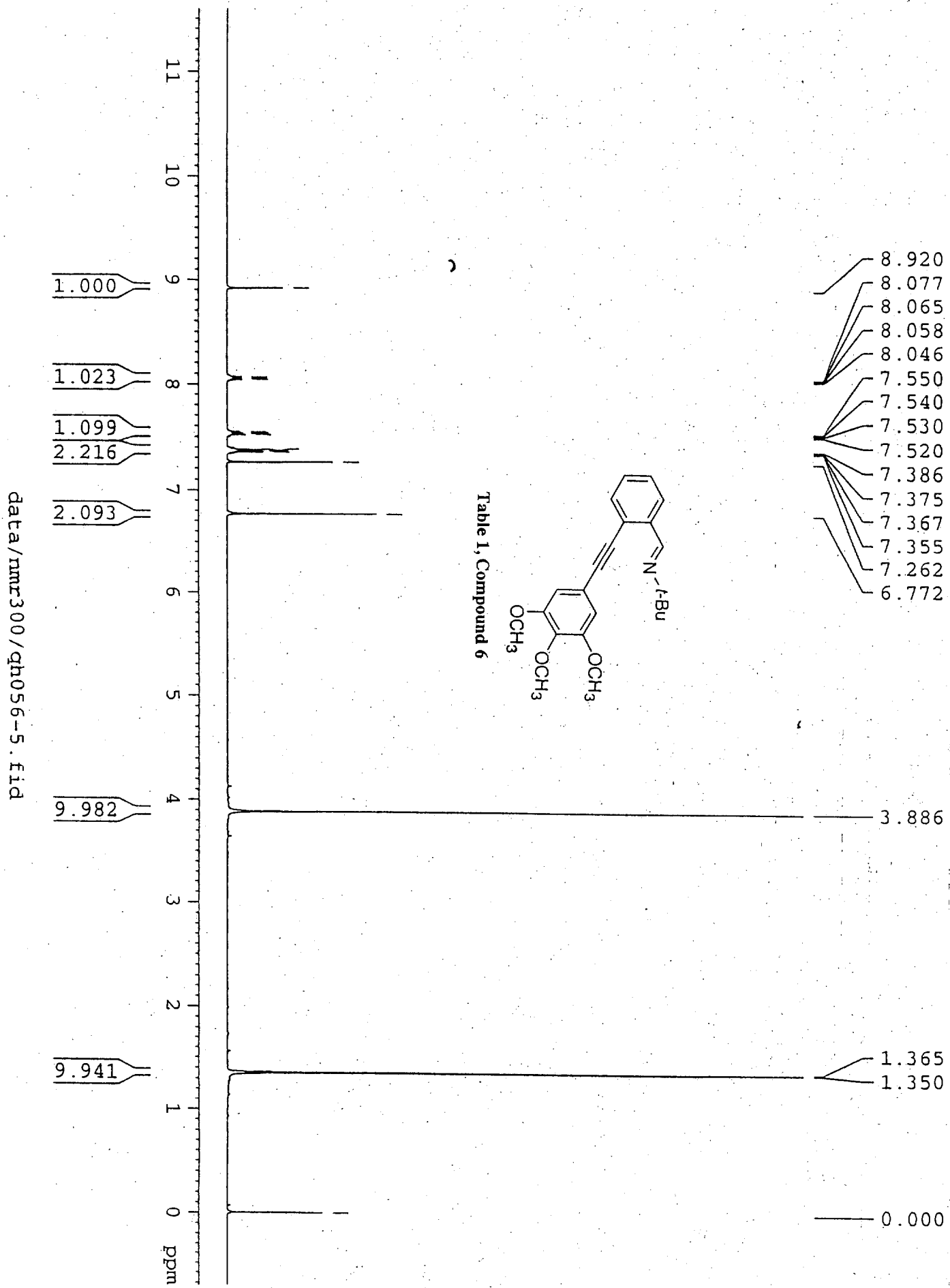

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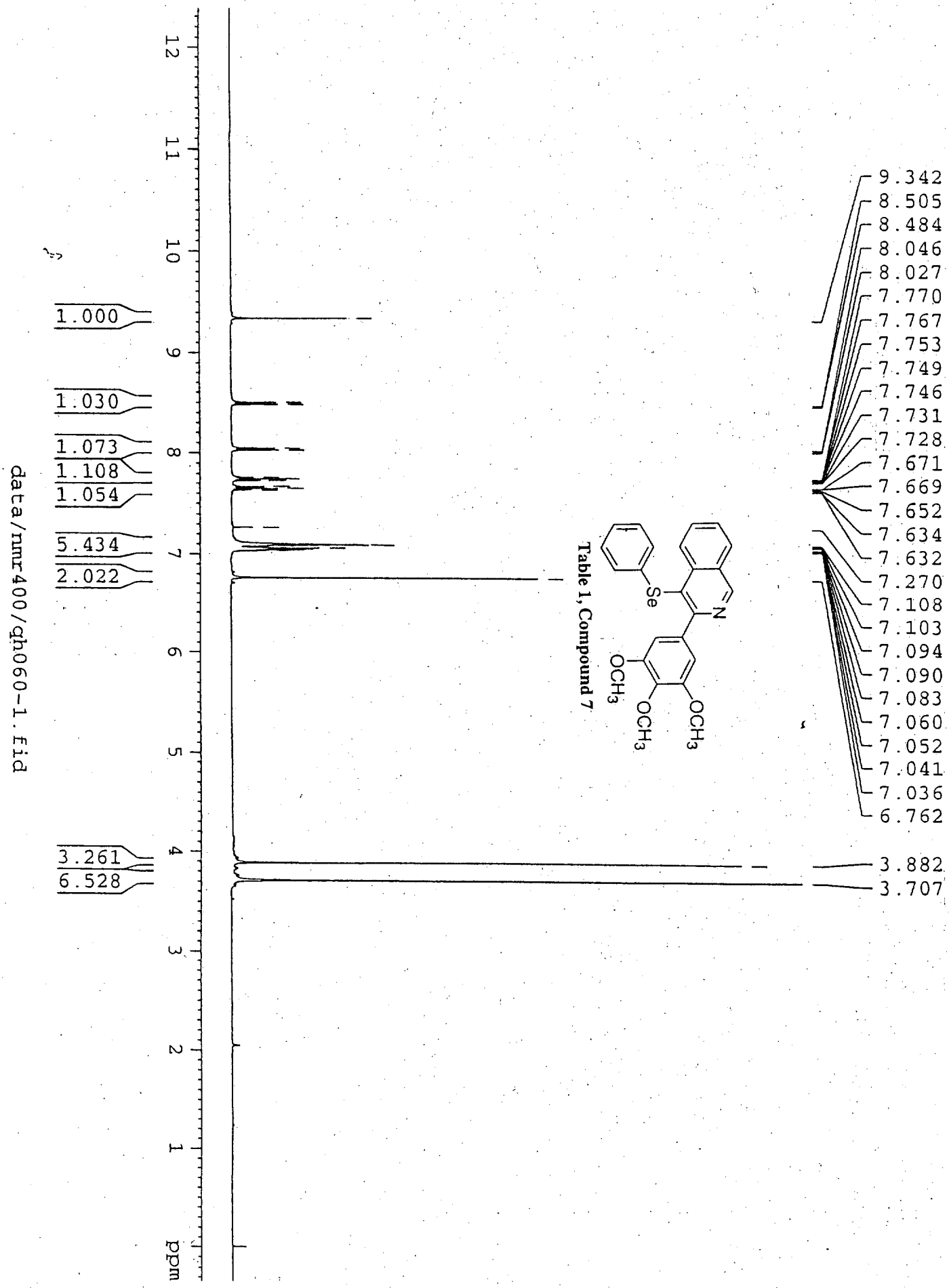

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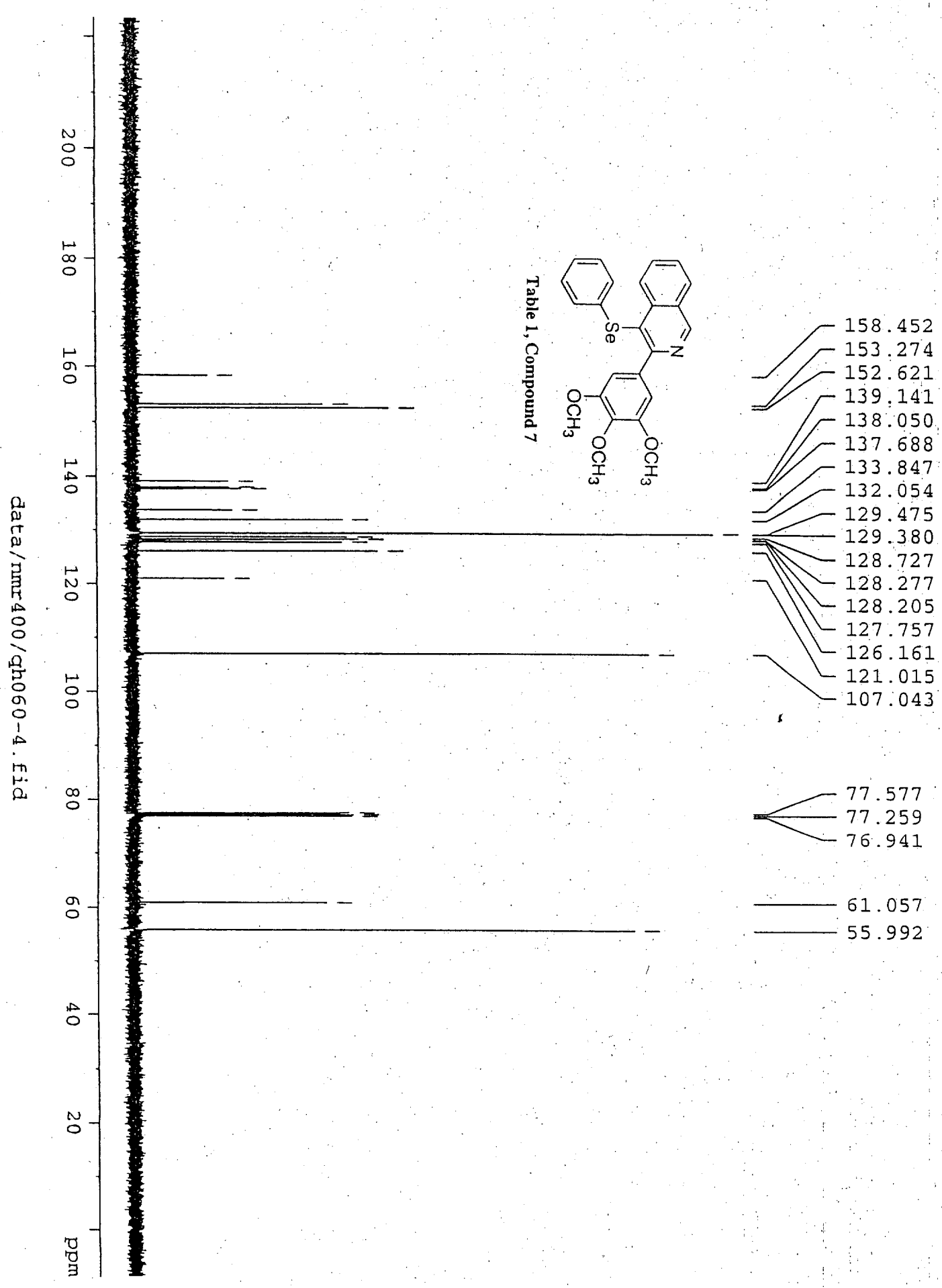
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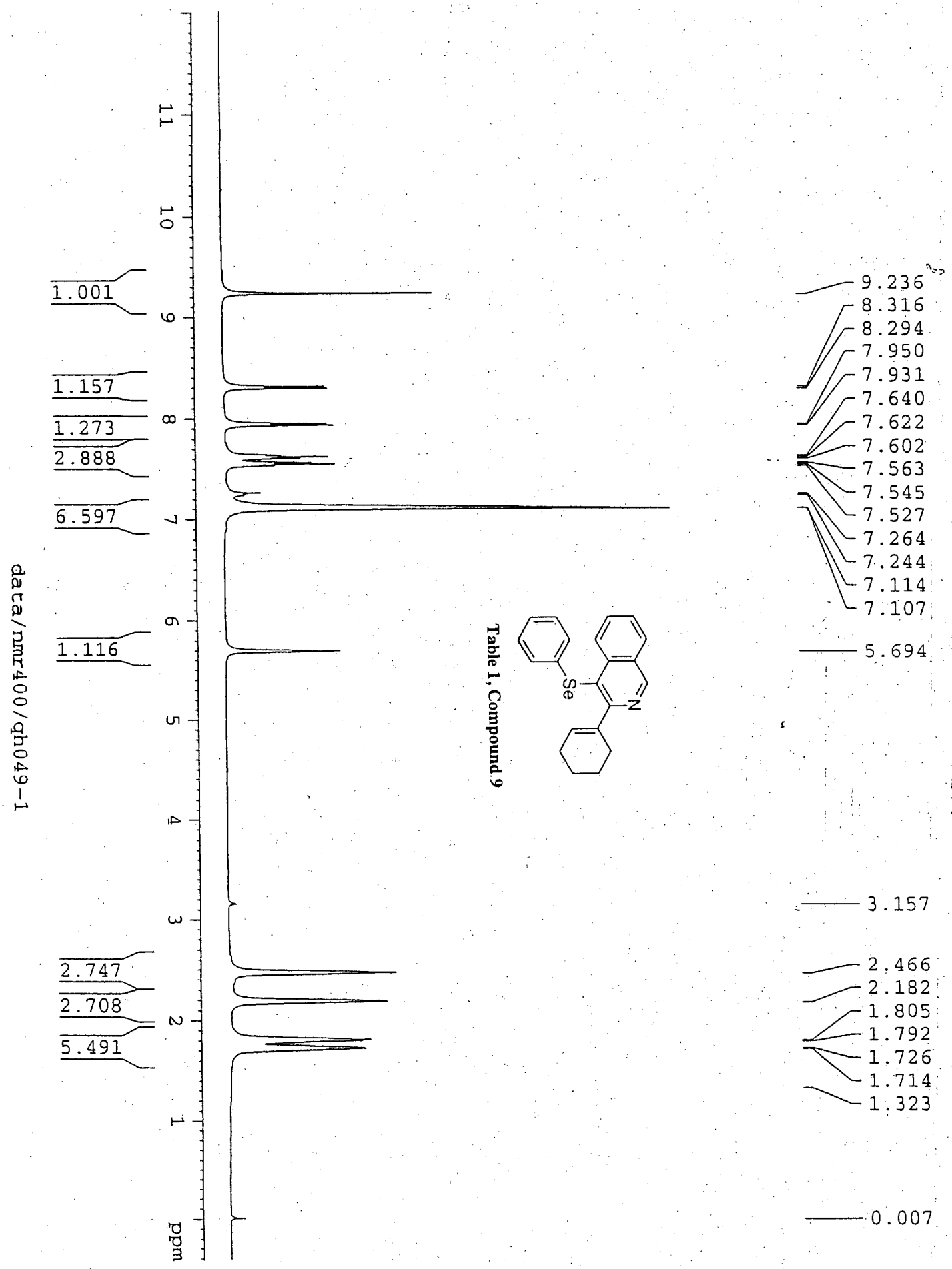

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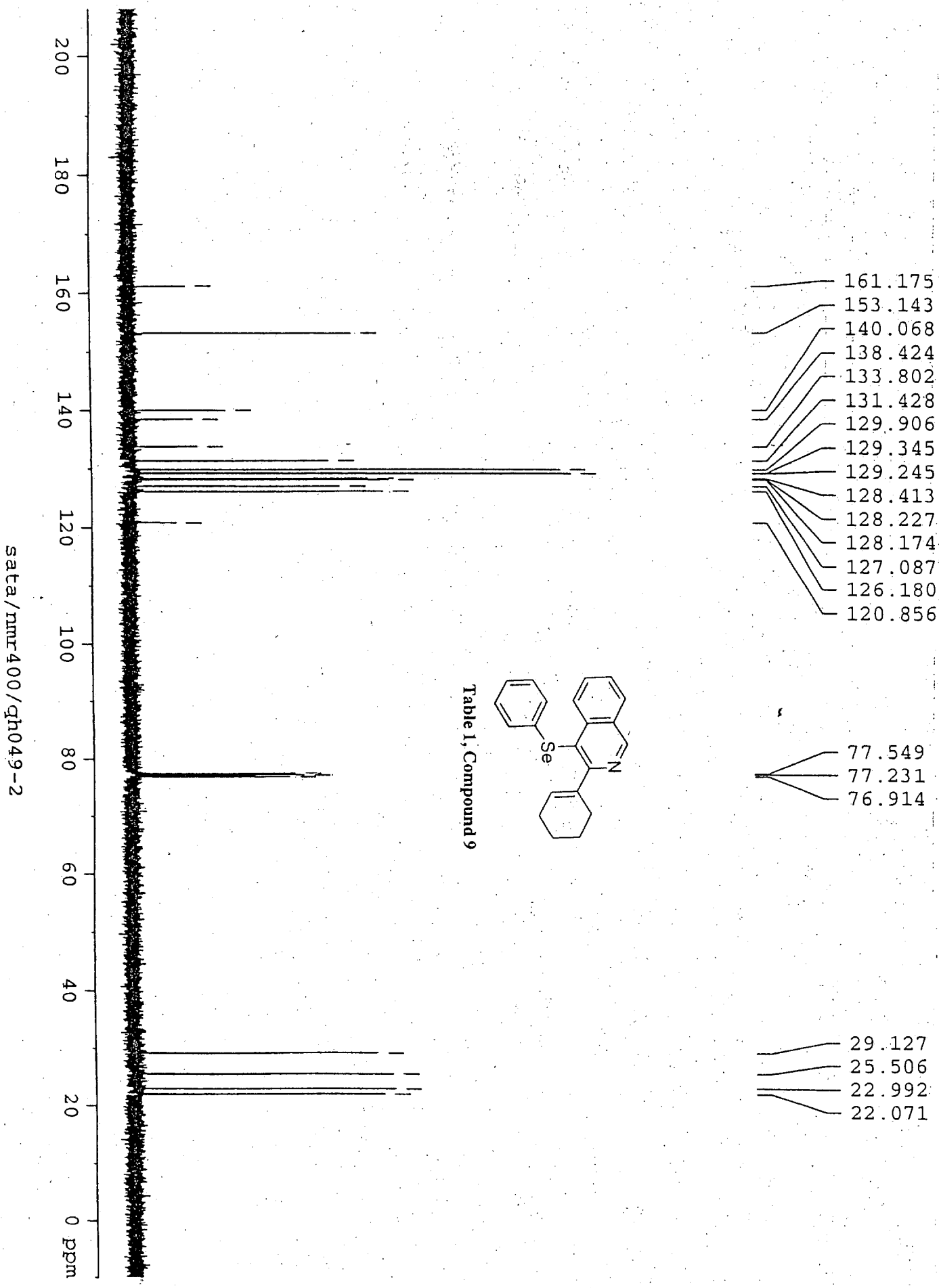


Table 1, Compound 9

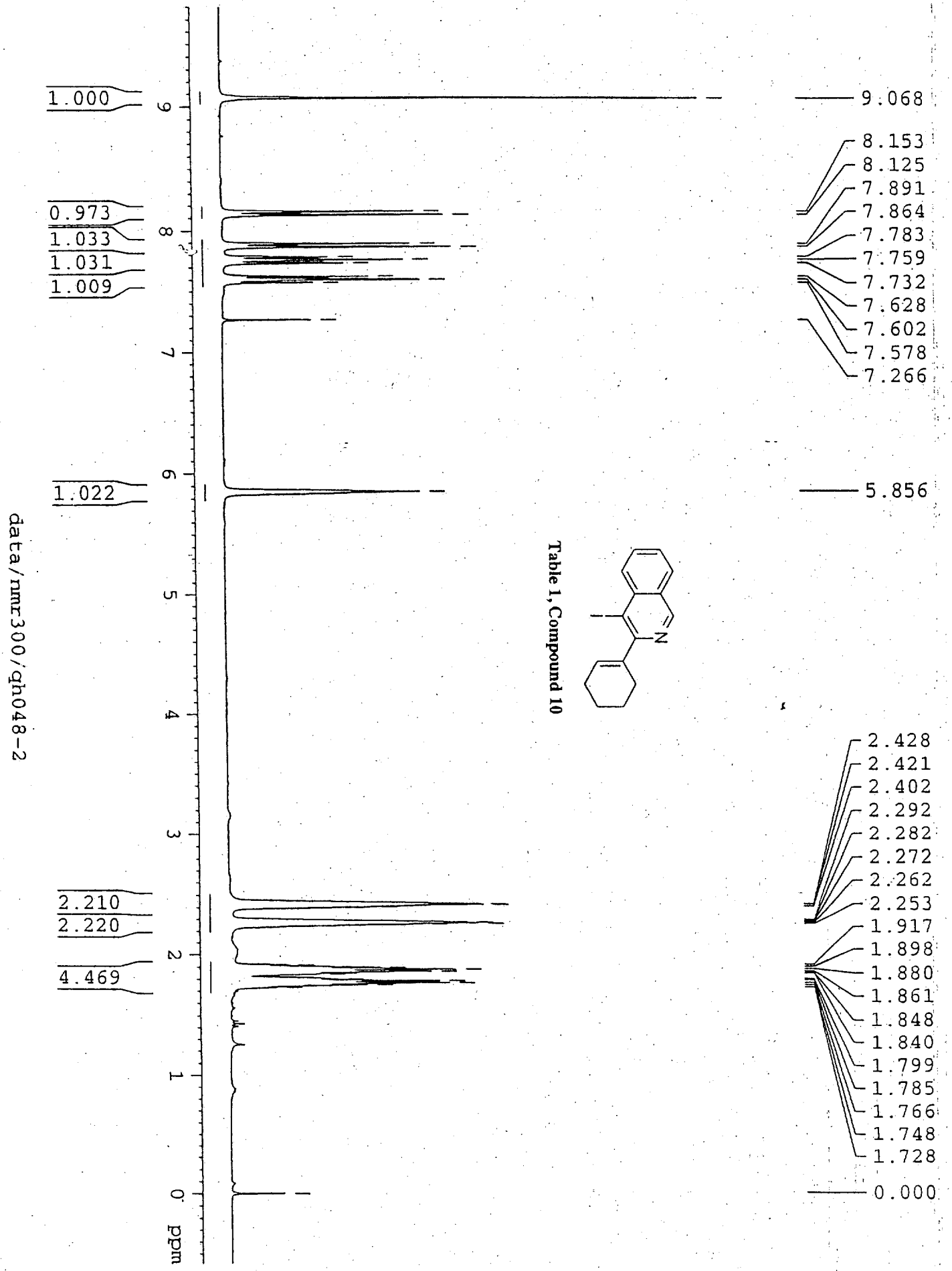


Table 1, Compound 10

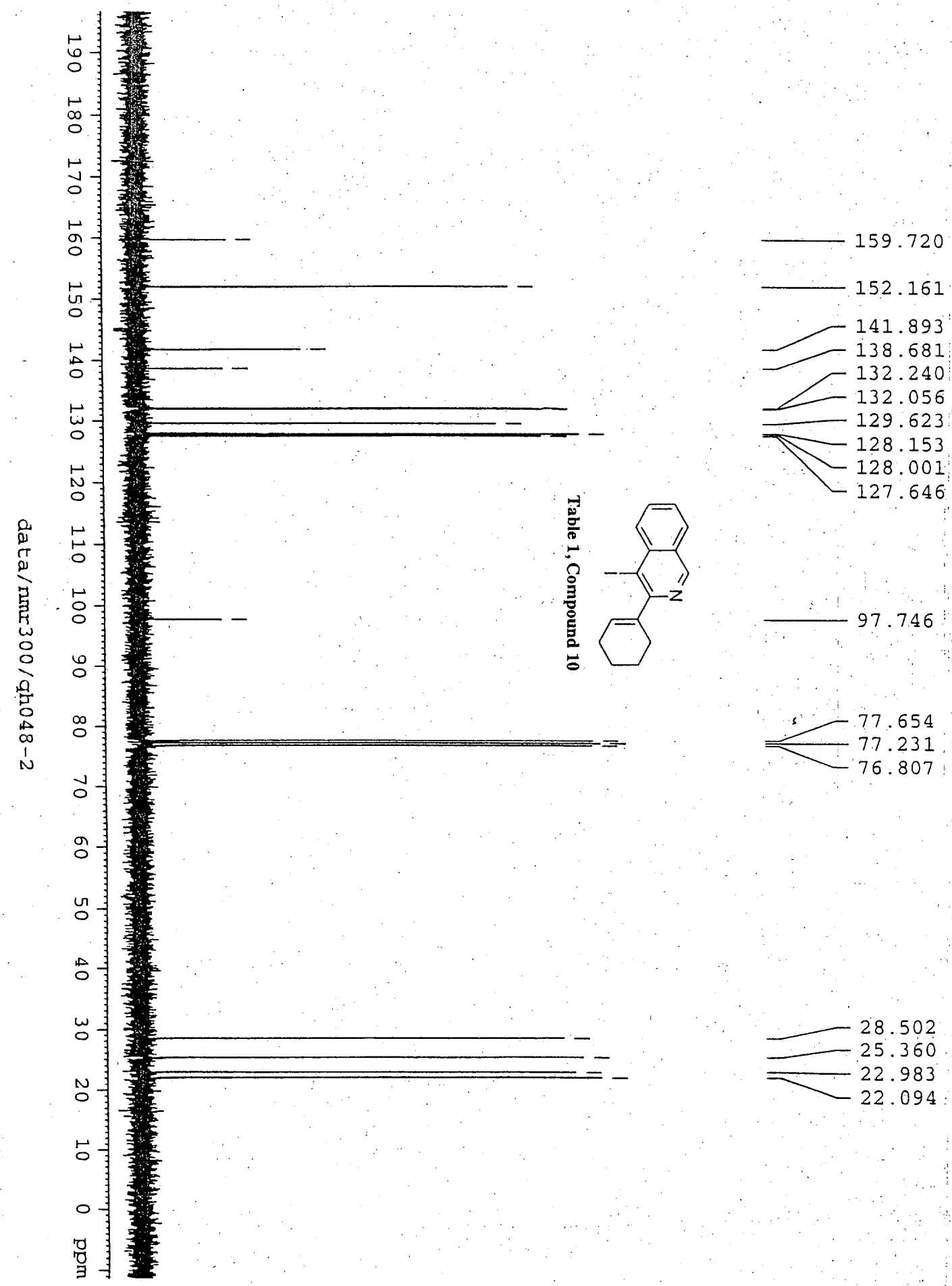


Table 1, Compound 10

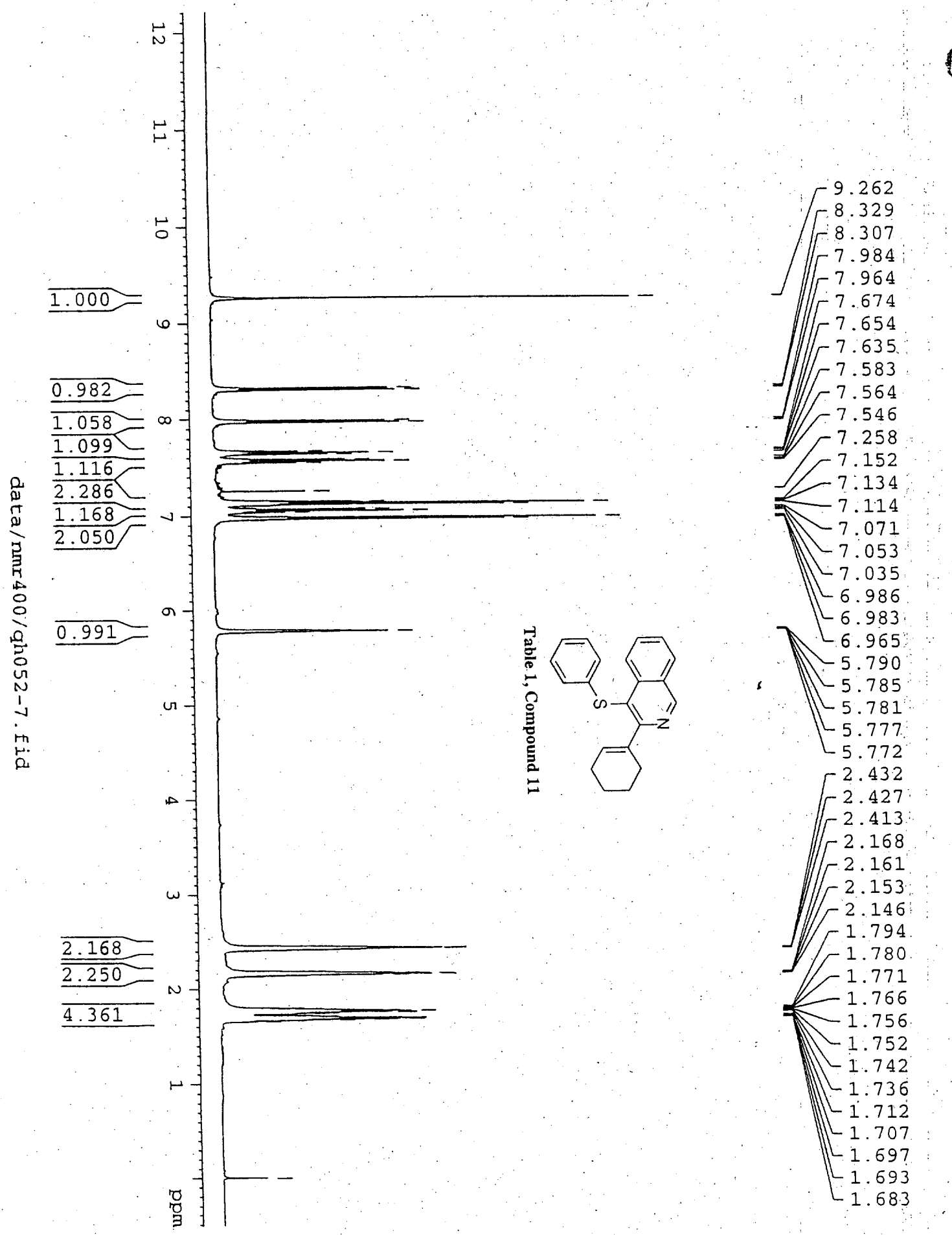


Table 1, Compound 11

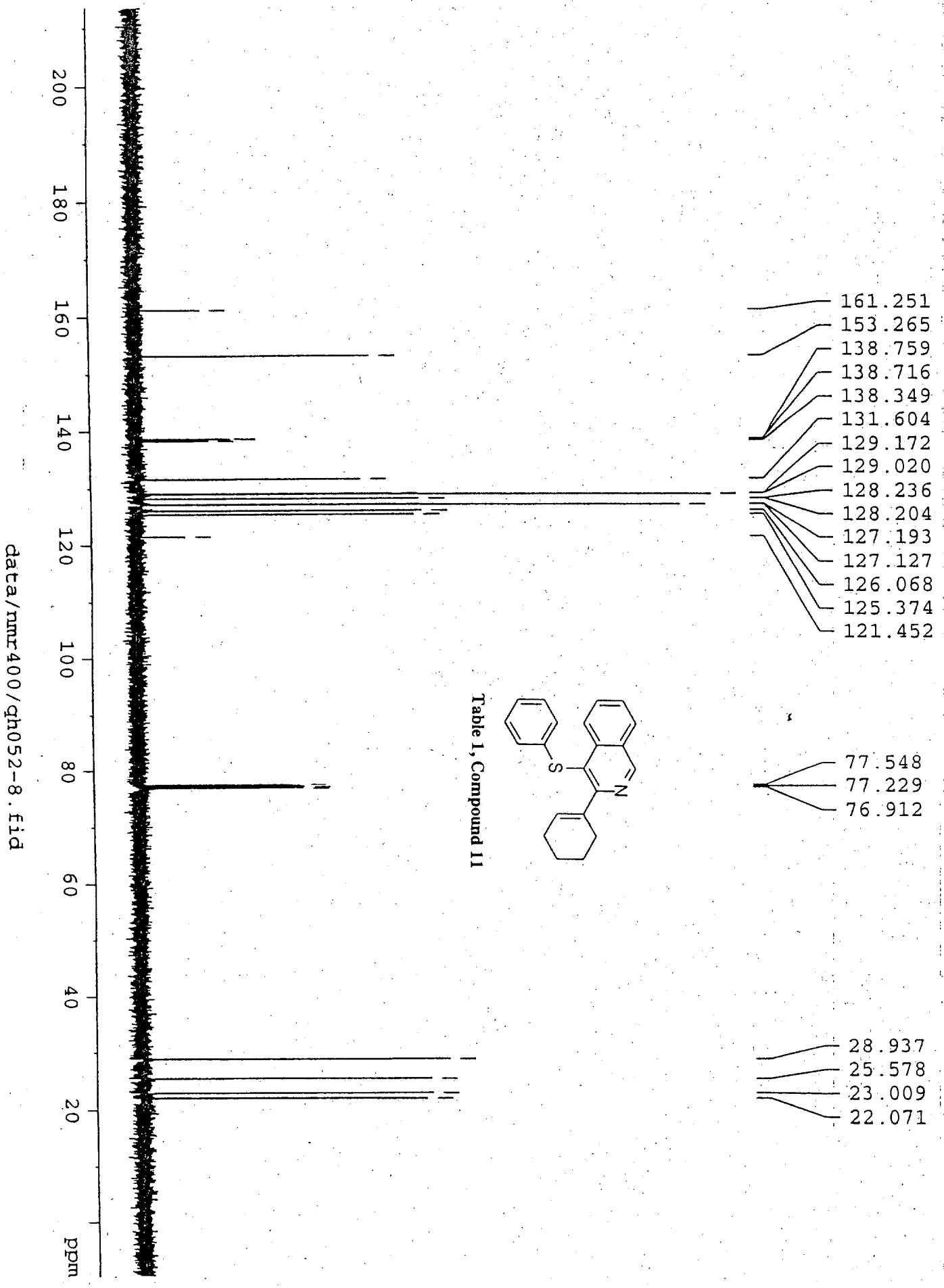


Table 1, Compound 11

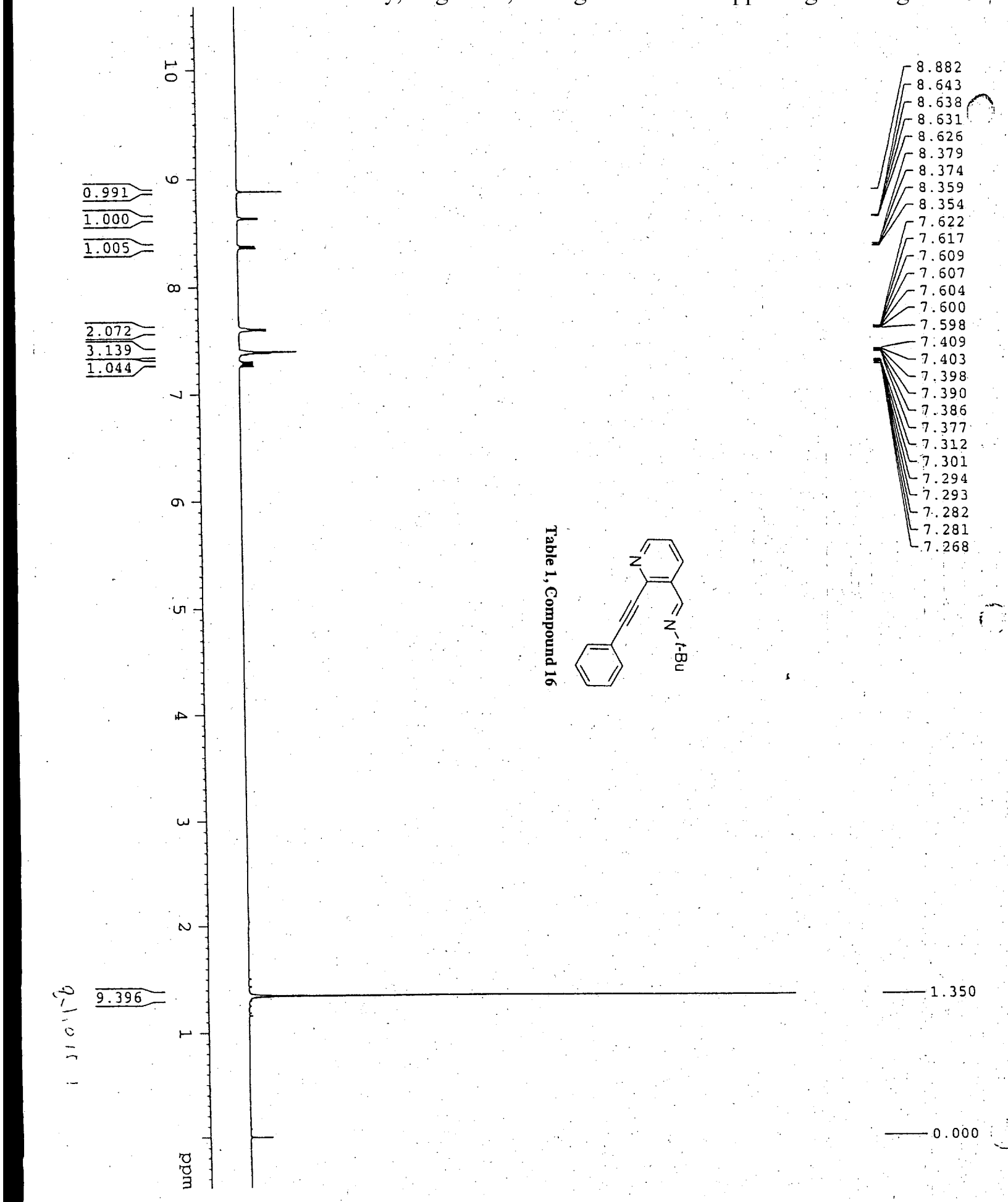
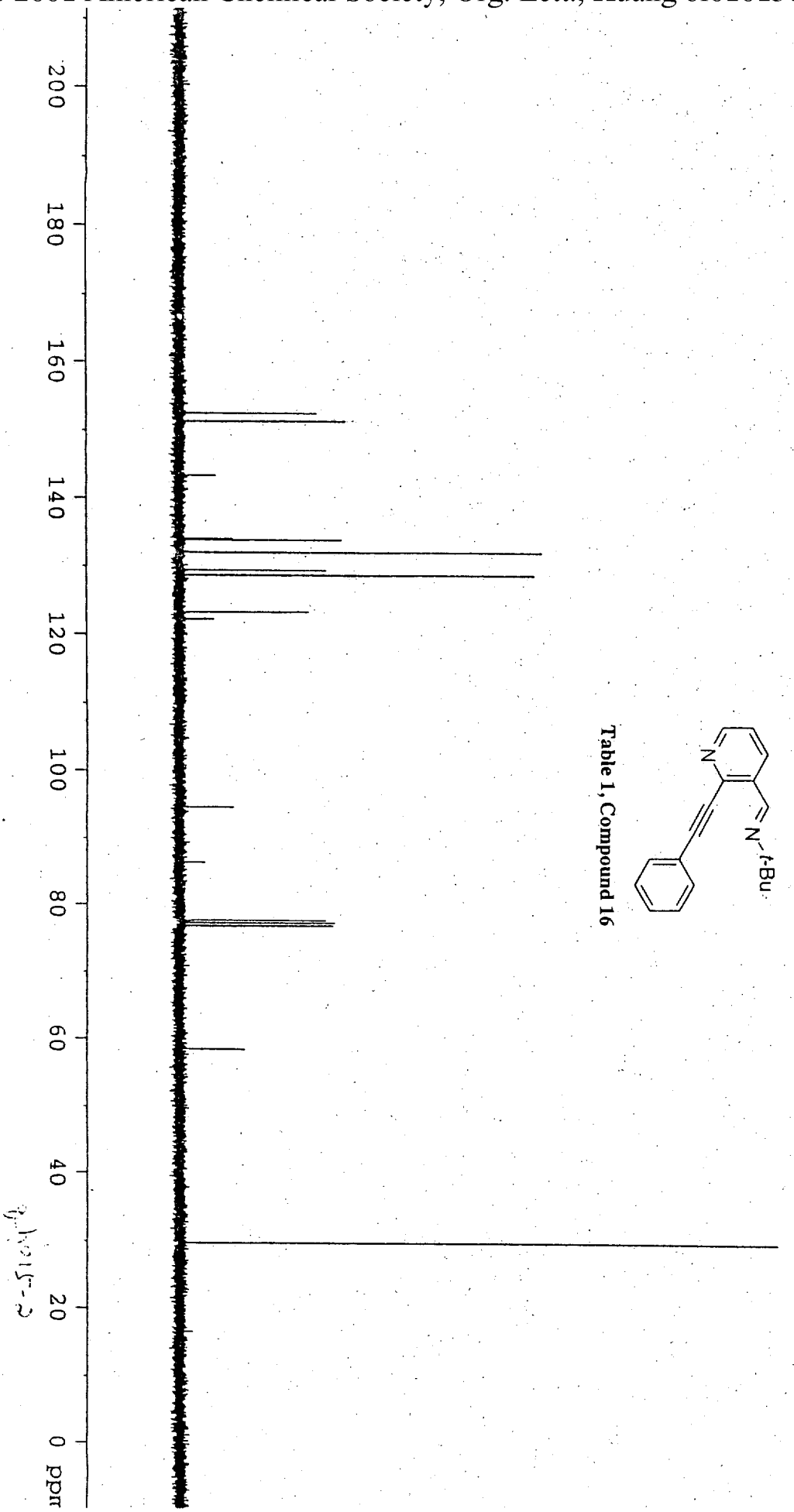


Table 1, Compound 16



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151.368
143.548
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133.961
132.135
129.456
128.730
123.338
122.269
94.574
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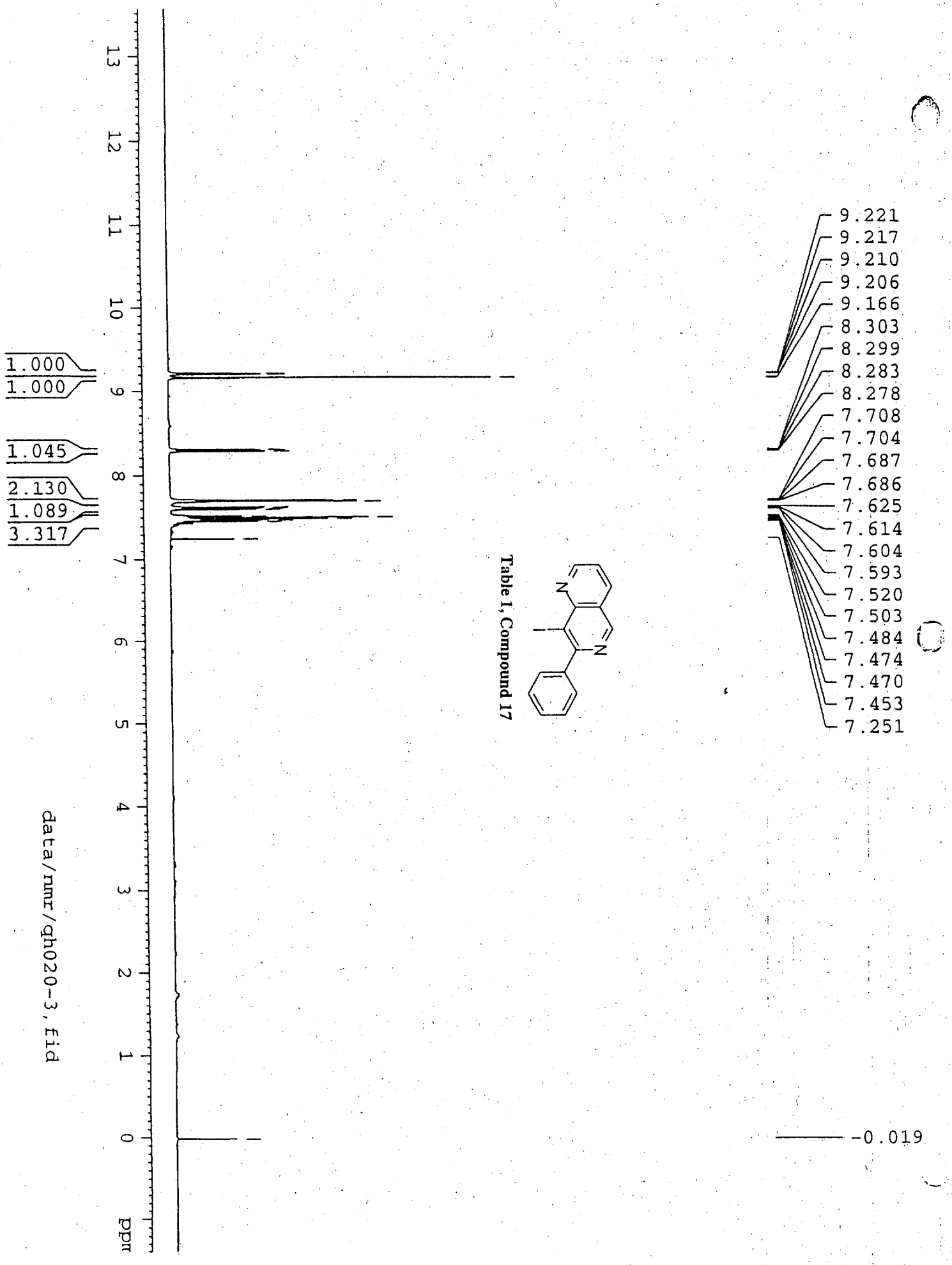
77.228
76.805
58.442
29.818

Table 1, Compound 16



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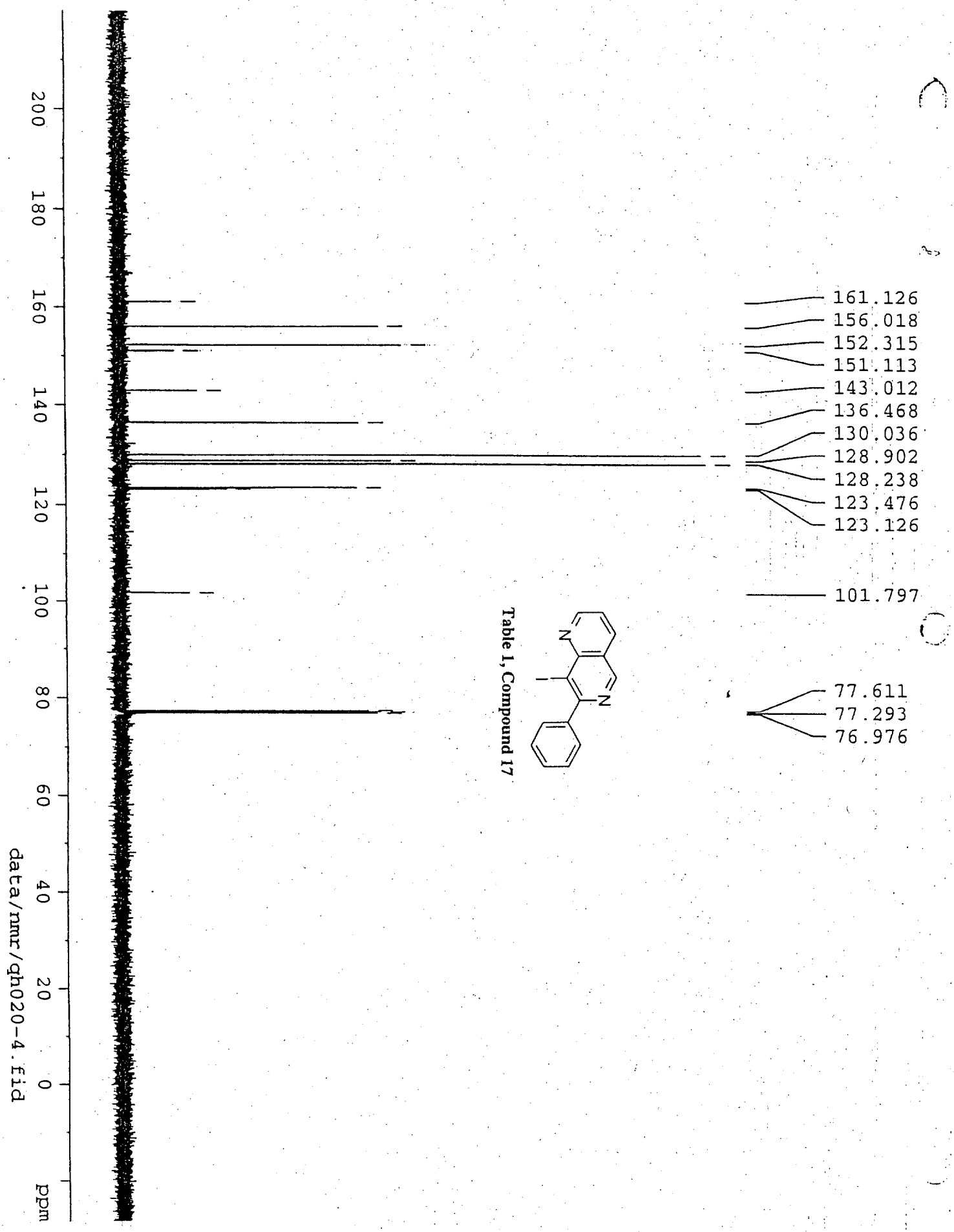


Table 1, Compound 17

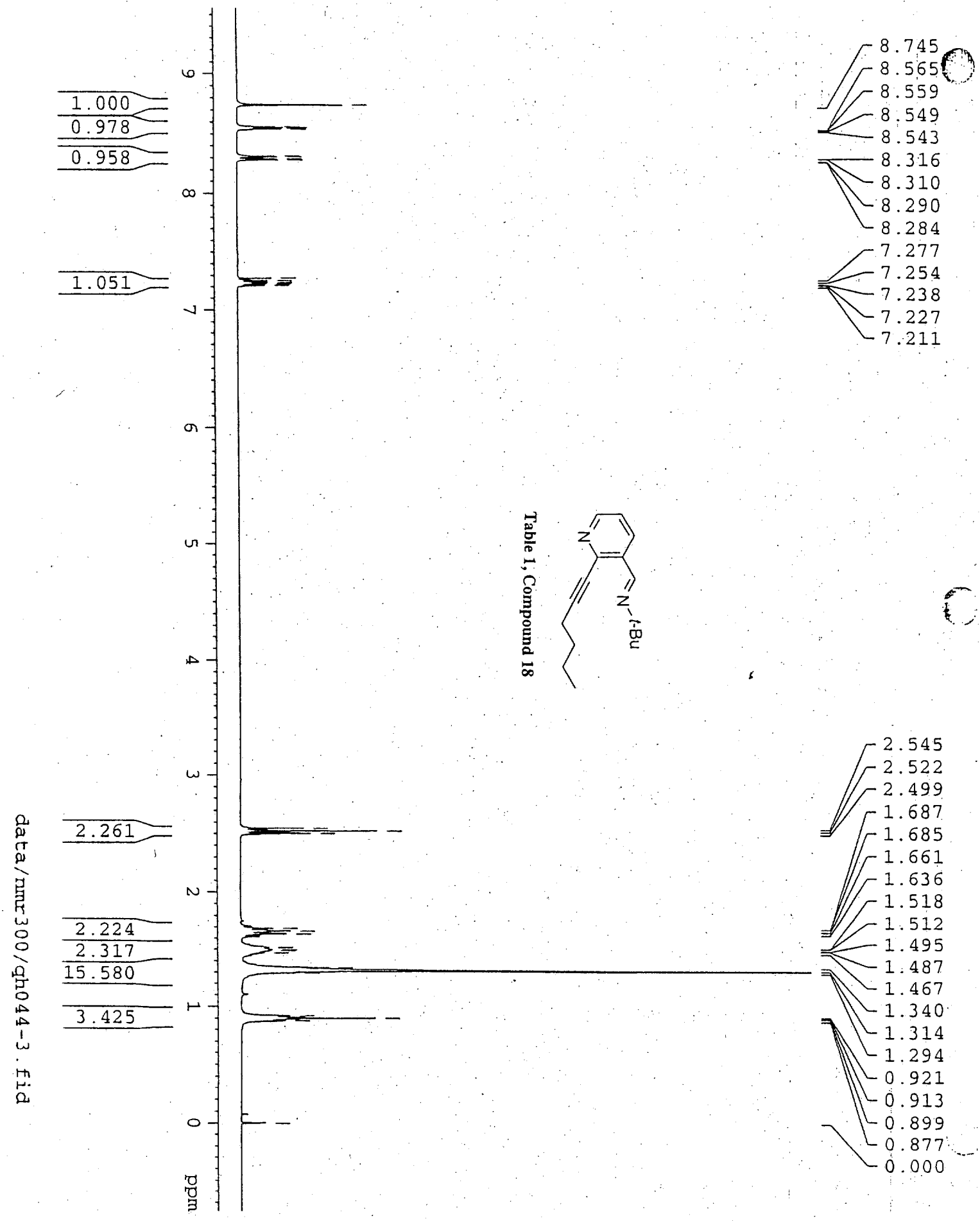


Table 1, Compound 18

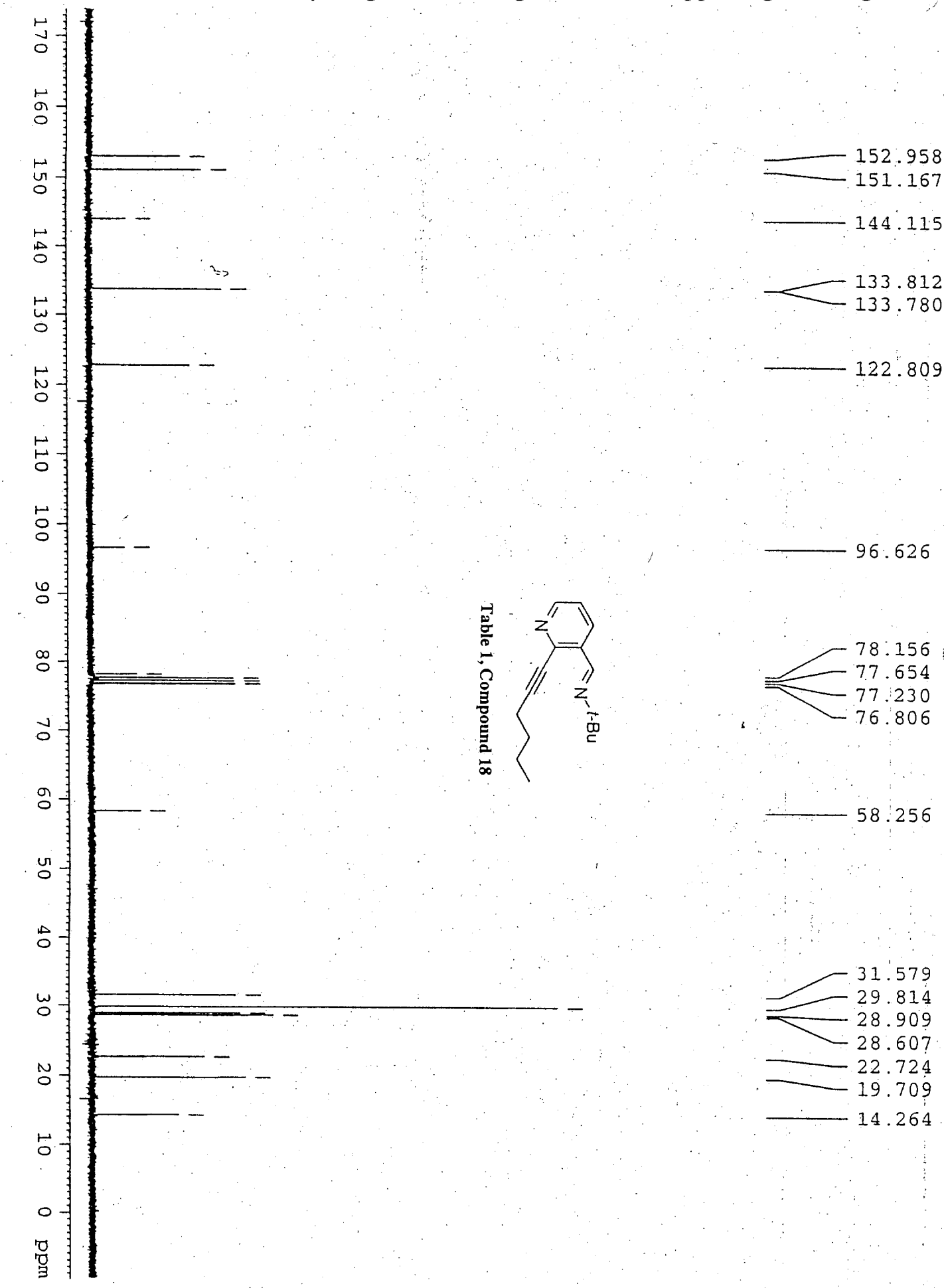


Table 1, Compound 18

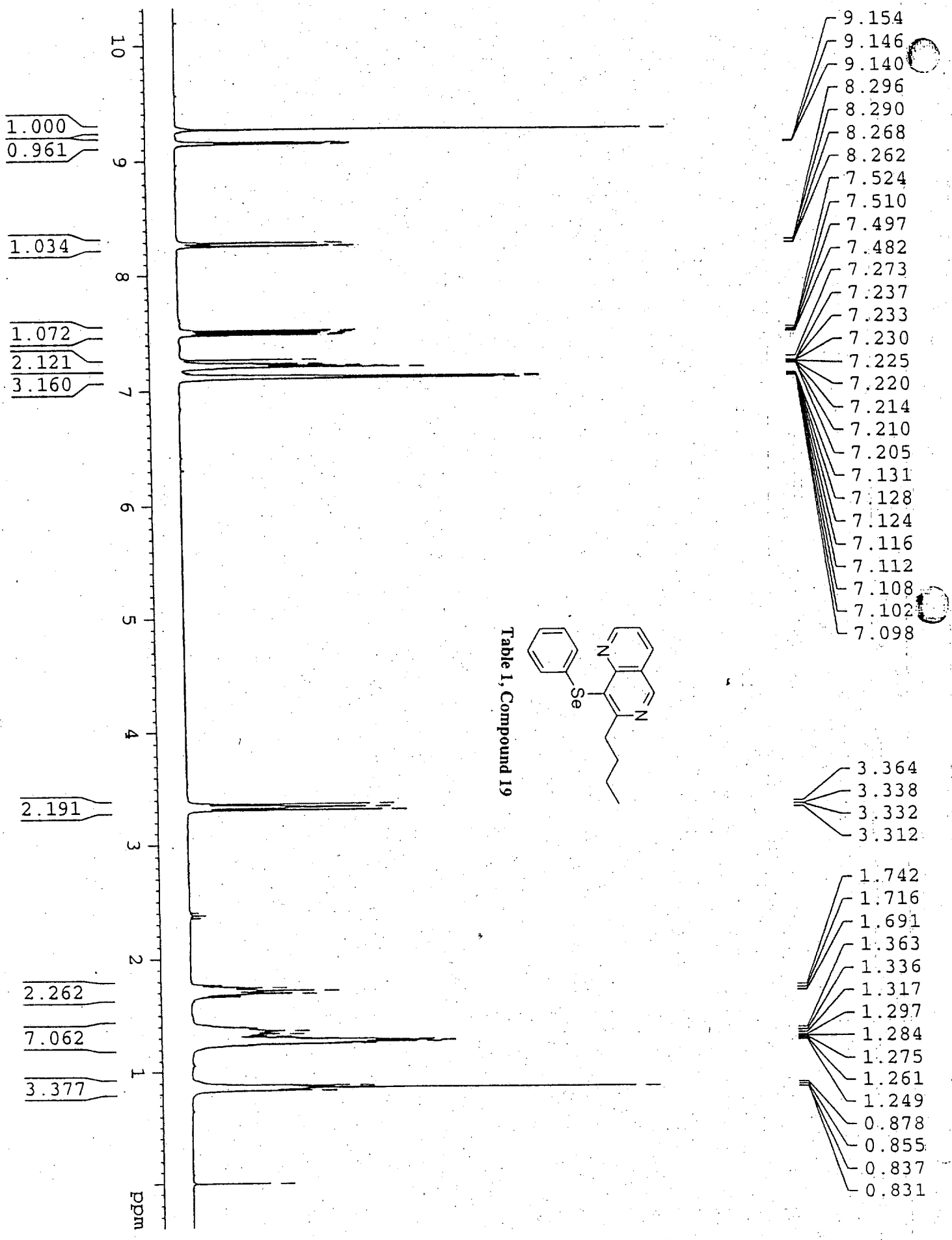


Table 1, Compound 19

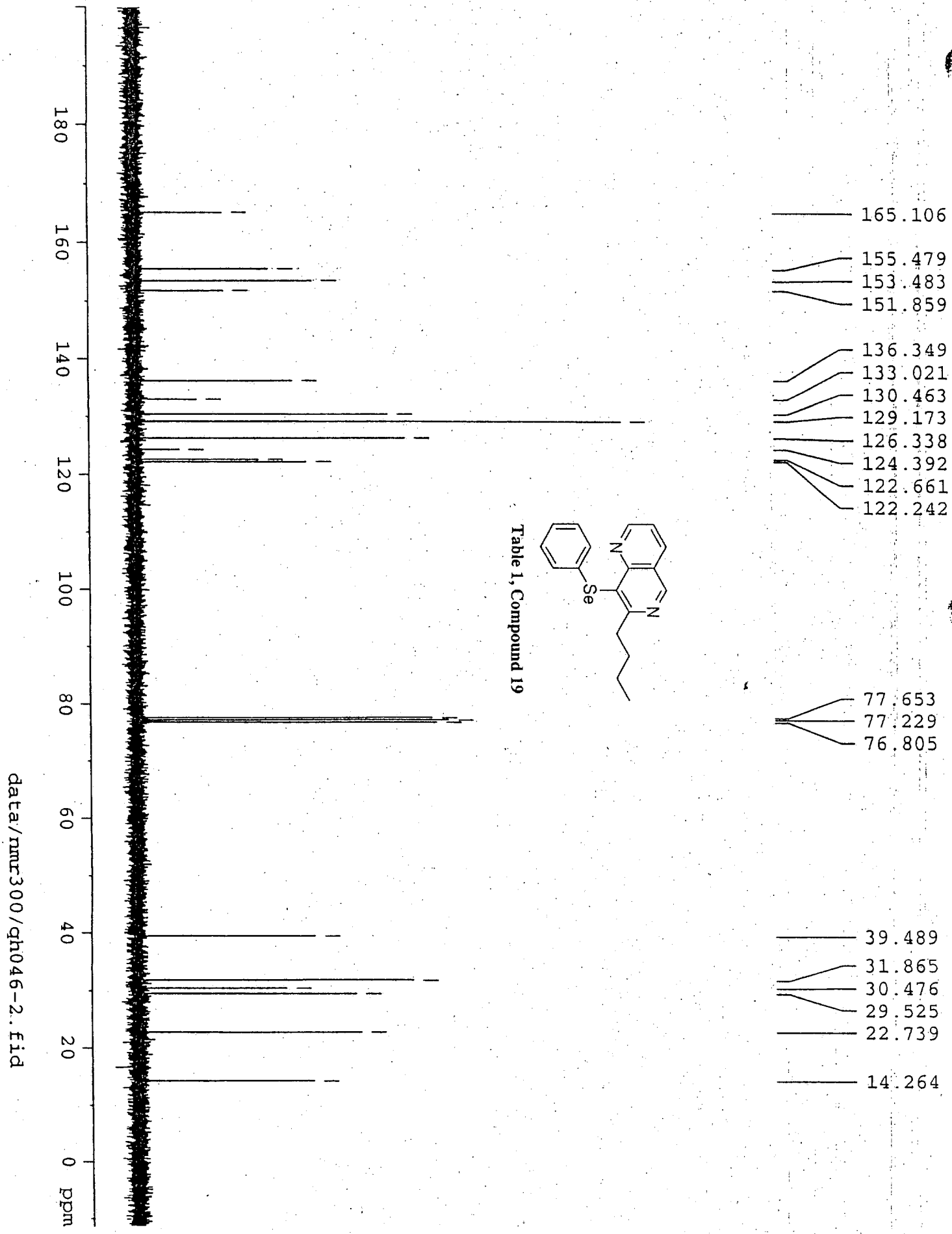


Table 1, Compound 19

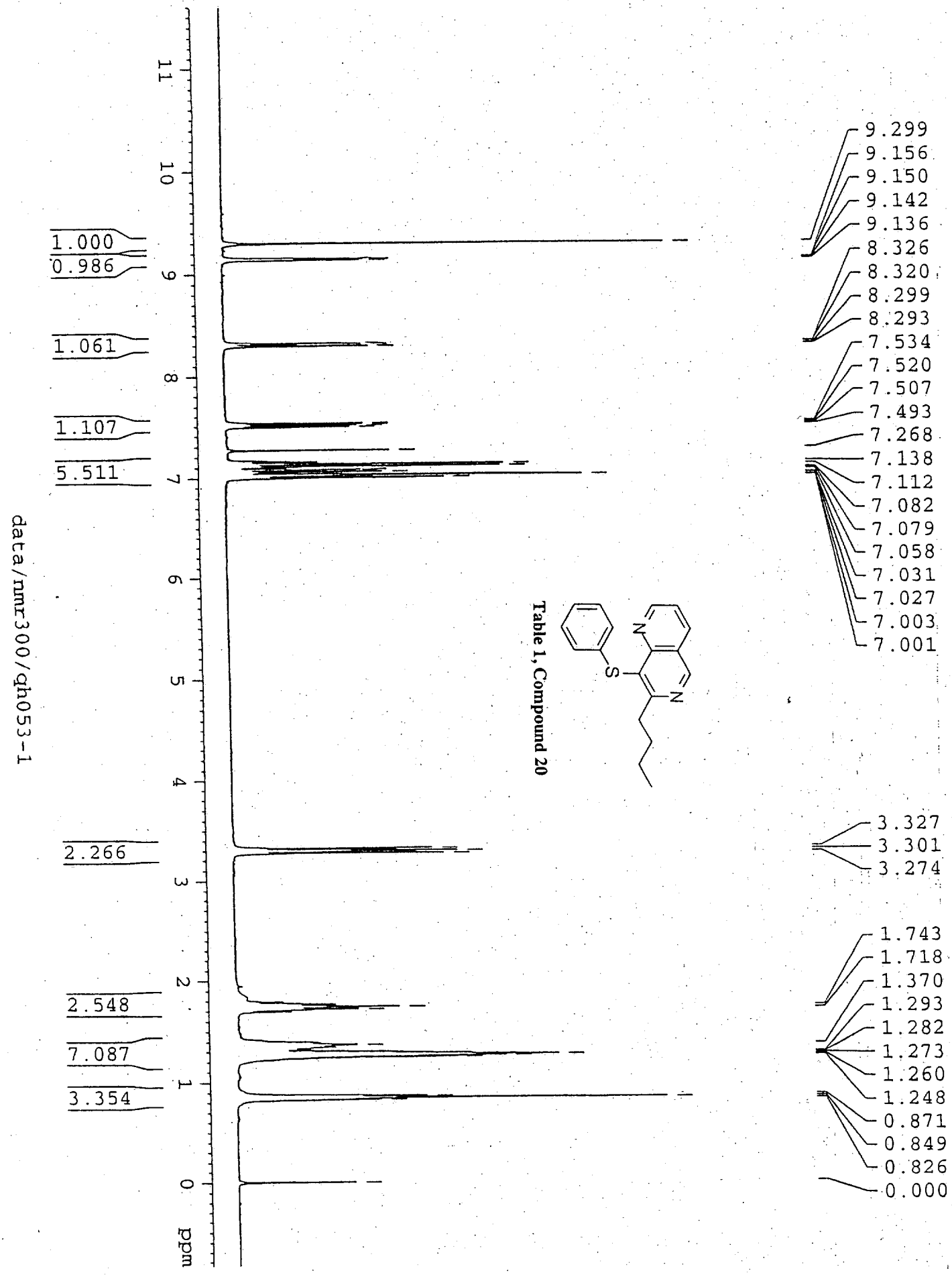
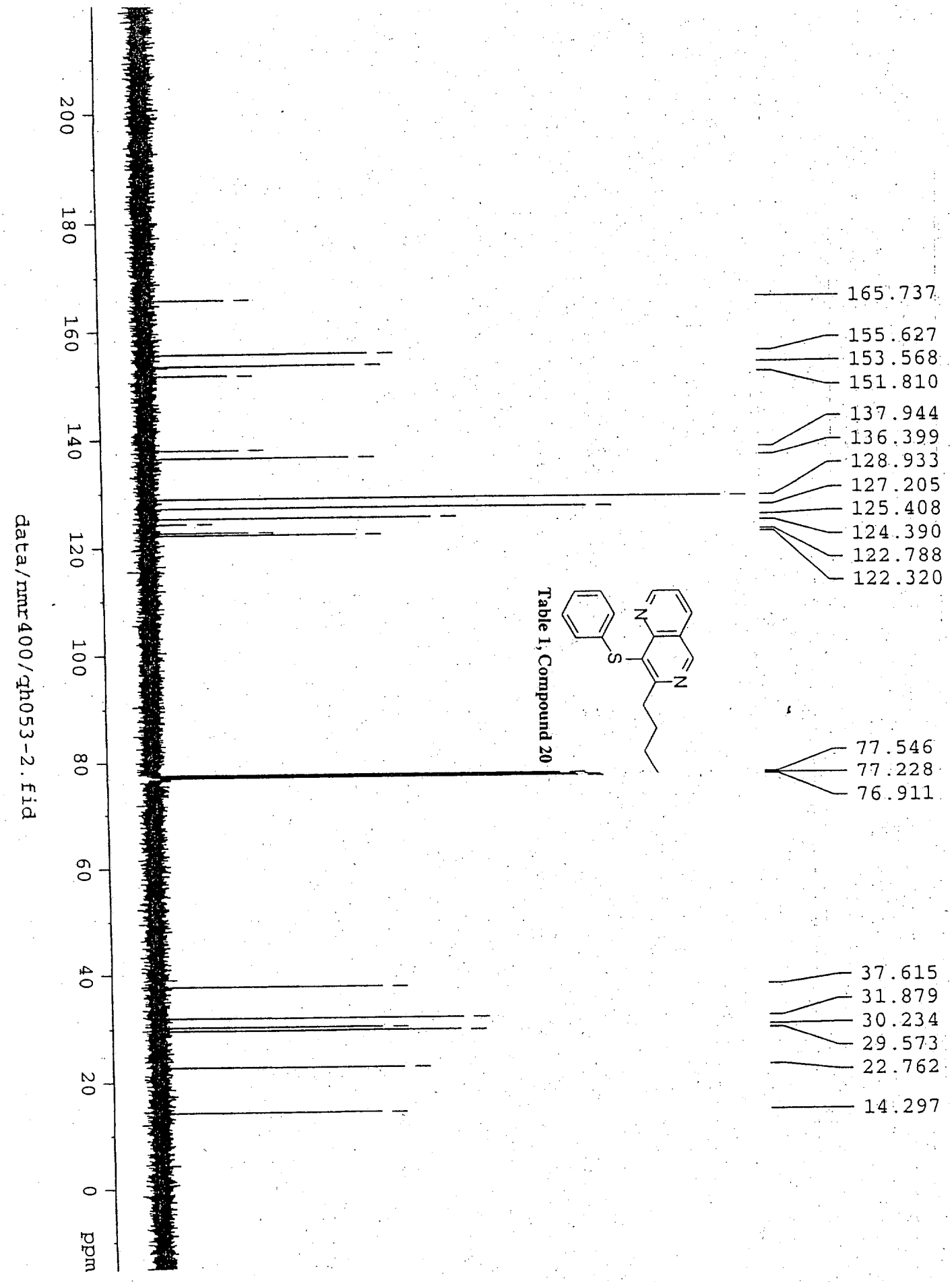


Table 1, Compound 20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153.568
151.810
137.944
136.399
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127.205
125.408
124.390
122.788
122.320
77.546
77.228
76.911
37.615
31.879
30.234
29.573
22.762
14.297
200
180
160
140
120
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80
60
40
20
0
ppm
data/nmr400/qh053-2.fid
Table 1, Compound 20
N
S
N

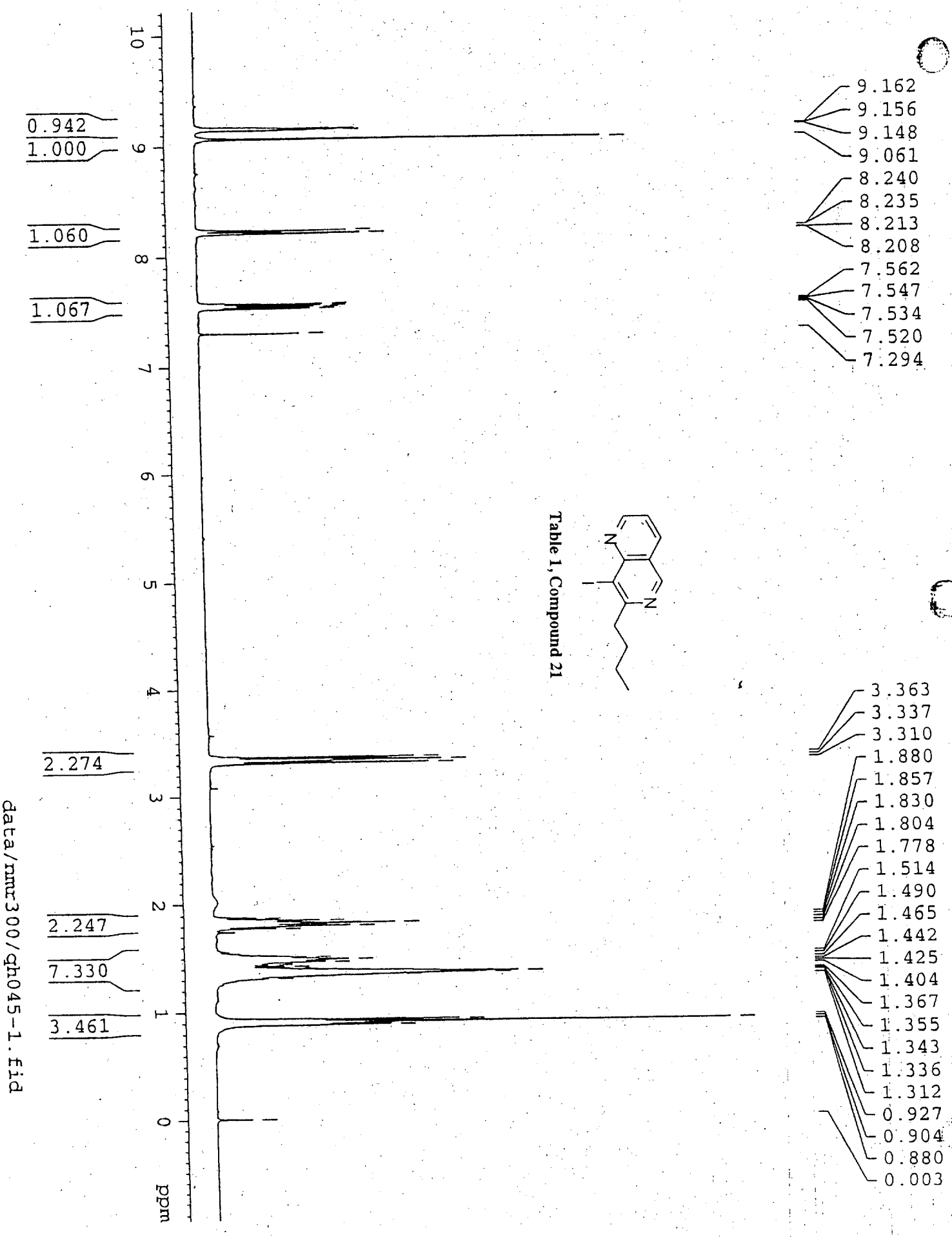

Table 1, Compound 21

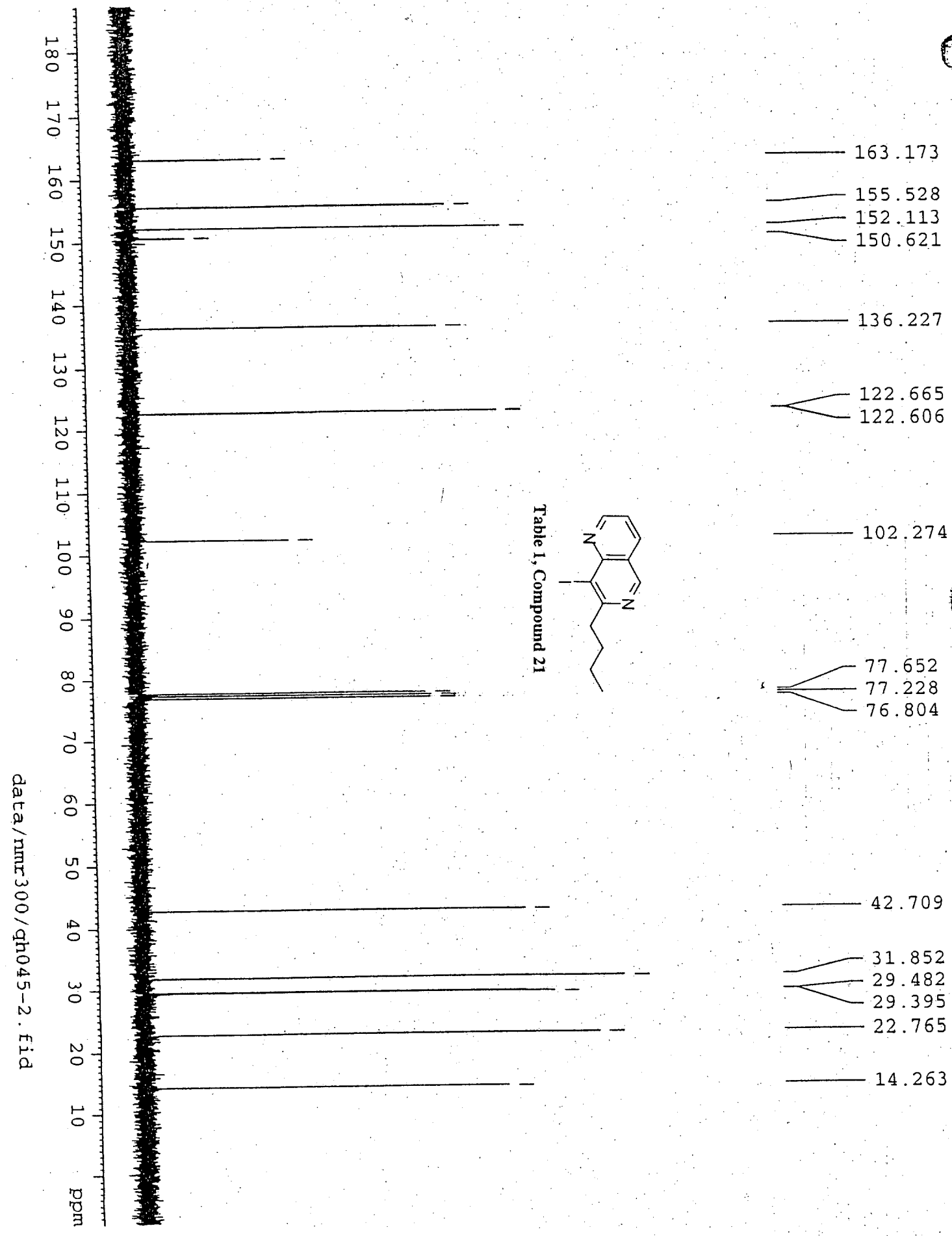

Table 1, Compound 21