Efficient Two-Step Synthesis of 9-Aryl-6-hydroxy-3*H*-xanthen-3-one Fluorophores

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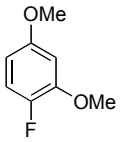
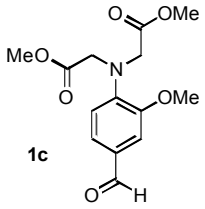
Experimental Procedures

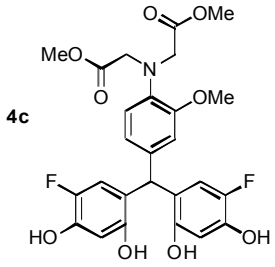


1-Fluoro-2,4-dimethoxybenzene. SelectFluor® (4.35 g, 12.28 mmol) was dissolved in 20 mL MeCN containing 2 mL of H_2O. To this cloudy solution was added 1,3-dimethoxybenzene (3.22 mL, 24.56 mmol) and the reaction mixture was heated to 50 °C and stirred for 30 min. After cooling to room temperature, the reaction was diluted with H_2O (20 mL) and organics extracted with Et_2O (2 × 75 mL). The Et_2O layer was dried with $MgSO_4$, filtered and concentrated in vacuo. The crude light brown oil was purified by silica gel flash chromatography with 2.5% Et_2O/hexanes as eluant to give 1-fluoro-2,4-dimethoxybenzene as a clear oil (1.31 g, 68%).

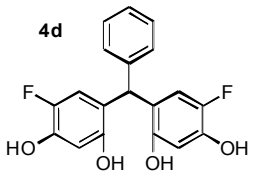


[(4-Formyl-2-methoxy-phenyl)-methoxycarbonylmethyl-amino]-acetic acid methyl ester (1c). To a flame-dried flask equipped with a magnetic stir bar was added 10 mL anhydrous DMF. The flask was flushed with argon and cooled in an ice-water bath. To the stirring DMF at 0 ºC was added dropwise $POCl_3$ (5.0 mL, 53.50 mmol). After stirring for 10 min, [methoxycarbonylmethyl-(2-methoxy-phenyl)-amino]-acetic acid methyl ester (1.43 g, 5.35 mmol) was added dropwise as a solution in 10 mL anhydrous DMF. The resulting yellow solution was allowed to warm to room temperature and then heated to 100 ºC for 30 min. After cooling to room temperature, the reaction mixture was poured into 200 mL of ice water. The pH was adjusted to ~7 by addition of solid $NaHCO_3$ and organics extracted with EtOAc (3 × 200 mL). The combined organic extracts were dried with $MgSO_4$, filtered and concentrated in vacuo. The crude

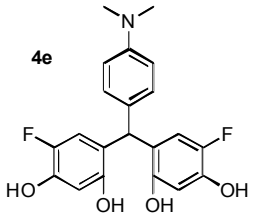
brown oil was purified by silica gel flash chromatography (50% EtOAc/hexanes) to give **1c** as a viscous light yellow oil (1.42 g, 90%): ^{1}H NMR (400 MHz, d_6-DMSO, 298 K) δ 9.75 (s, 1 H), 7.40 (d, J = 8.5 Hz, 1 H), 7.34 (s, 1 H), 6.72 (d, J = 8.3 Hz, 1 H), 4.21 (s, 4 H), 3.74 (s, 3 H), 3.67 (s, 6 H); ^{13}C NMR (125 MHz, d_6-DMSO, 298 K) δ 190.6, 170.8, 149.4, 144.4, 128.8, 125.6, 115.7, 111.1, 55.8, 54.0, 51.6; IR (thin film) 2956, 2835, 2735, 1749, 1682, 1597, 1398, 1263, 1204, 1165, 1135 cm^{-1}; TLC R_f = 0.50 (60% EtOAc/hexanes); LRMS (ESI) *m*/*z* (relative intensity): 236(5), 318(100); HRMS (CI) *m*/*z* calcd for $C_{14}H_{17}NO_6Na$ [M+Na]$^+$, 318.0954 found 318.0949.



({4-[Bis-(5-fluoro-2,4-dihydroxy-phenyl)-methyl]-2-methoxy-phenyl}-methoxycarbonylmethyl-amino)-acetic acid methyl ester (4c). As described in the general procedure, 4-fluororesorcinol (50 mg, 0.390 mmol) and aldehyde **1c** (58 mg, 0.195 mmol) were stirred for 2 h and subjected to the work-up procedure. Purification by silica gel flash chromatography (15-35% acetone/toluene + 1% AcOH) gave **4c** as an orange/brown powder (85 mg, 81%): mp 180-182 ºC (toluene); ^{1}H NMR (400 MHz, d_6-DMSO, 298 K) δ 9.43 (s, 2 H), 9.01 (s, 2 H), 6.56 (d, J = 8.2 Hz, 1 H), 6.51 (d, J = 1.7 Hz, 1 H), 6.41 (d, J = 7.9 Hz, 2 H), 6.35 (dd, J = 1.7, 8.2 Hz, 1 H), 6.26 (d, J = 12.4 Hz, 2 H), 5.63 (s, 1 H), 4.04 (s, 4 H), 3.62 (s, 6 H), 3.56 (s, 3 H); ^{13}C NMR (125 MHz, d_6-DMSO, 298 K) δ 171.4, 150.6, 150.0, 143.7 (d, J = 225 Hz), 142.7 (d, J = 13 Hz), 136.6 (d, J = 63 Hz), 120.9 (d, J = 25 Hz), 117.2, 115.8, 113.3, 104.4, 55.6, 53.4, 51.3, 43.1; IR (thin film) 3315.7, 3164.4, 2355.8, 2334.2, 1752.7, 1626.3, 1508.1, 1438.2 cm^{-1}; TLC R_f = 0.25 (50% acetone/toluene + 1% AcOH); LRMS (ESI) *m*/*z* (relative intensity): 534(8), 556(100); HRMS (CI) *m*/*z* calcd for $C_{26}H_{25}F_2NO_9Na$ [M+Na]$^+$, 556.1395, found 556.1406.

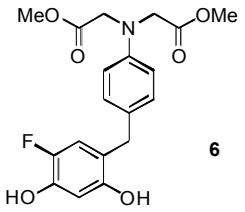


4-Fluoro-6-((5-fluoro-2,4-dihydroxyphenyl)(phenyl)methyl)benzene-1,3-diol (4d). As described in the general procedure, 4-fluororesorcinol (50 mg, 0.390 mmol) and benzaldehyde (19.8 μL, 0.195 mmol) were stirred for 2 h. Purification by silica gel flash chromatography (10-30% acetone/toluene + 1% AcOH) gave **4e** as a yellow powder (57 mg, 85%): mp 202-205 ºC (toluene); ^{1}H NMR (500 MHz, d_6-DMSO, 298 K) δ 9.47 (s, 2 H), 9.06 (s, 2 H), 7.27-7.22 (m, 2H), 7.18-7.14 (m, 1 H), 6.97-6.94 (m, 2 H), 6.43 (d, J = 7.9 Hz, 2 H), 6.25 (d, J = 12.5 Hz, 2 H), 5.73 (s, 1 H); ^{13}C NMR (125 MHz, d_6-DMSO, 298 K) δ 151.4, 144.7 (d, J = 228 Hz), 144.7, 143.6 (d, J = 13 Hz), 129.4, 128.7, 126.4, 121.4, 116.7 (d, J = 25 Hz), 105.1, 42.4; IR (thin film) 3130.2 (v. br.), 2257.4, 1633.6, 1537.9, 1454.8, 1192.7 cm^{-1}; TLC R_f = 0.20 (20% acetone/toluene + 1% AcOH); LRMS (ESI) m/z (relative intensity): 217(100) (fragmentation from $MeSO_3H$); HRMS (CI) m/z calcd for $C_{13}H_{10}FO_2$ $[M]^+$, 217.0665 found 217.0673.



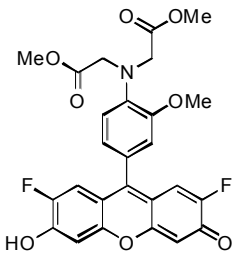
4-((4-Dimethylamino)phenyl)(5-fluoro-2,4-dihydroxyphenyl)methyl)-6-flourobenzene-1,3-diol (4e). As described in the general procedure, 4-fluororesorcinol (50 mg, 0.390 mmol) and 4-dimethylaminobenzaldeyhde (29 mg, 0.195 mmol) were stirred for 2 h. The initial reaction mixture appeared to be biphasic, but became homogeneous as a dark brown precipitate formed over the 2 h reaction time. Upon addition of $NaHCO_3$ in the work-up, this precipitate became soluble and the work-up was continued as usual. Purification of the crude product by silica gel flash chromatography (20-30% acetone/toluene + 1% AcOH) gave **4d** as a rose-colored powder (53 mg, 71%): mp 183-185 ºC (toluene);

^{1}H NMR (500 MHz, d_6-DMSO, 298 K) δ 9.40 (s, 2 H), 8.96 (s, 2 H), 6.76 (d, J = 8.6 Hz, 2 H), 6.62 (d, J = 8.8 Hz, 2 H), 6.40 (d, J = 8.0 Hz, 2 H), 6.25 (d, J = 12.5 Hz, 2 H), 5.61 (s, 1 H), 2.83 (s, 6 H); ^{13}C NMR (125 MHz, d_6-DMSO, 298 K) δ 150.6, 148.6, 144.0 (d, J = 225 Hz); 142.6 (d, J = 13 Hz), 131.5, 129.2, 121.6, 116.0 (d, J = 25 Hz), 112.3, 104.4, 40.7, 30.4; IR (thin film) 3418.2 (v. br.), 1636.1, 1518.4, 1443.6, 1176.2 cm^{-1}; TLC R_f = 0.30 (40% acetone/toluene + 1% AcOH); LRMS (ESI) m/z (relative intensity): 388(100), 410(15); HRMS (CI) m/z calcd for $C_{21}H_{20}F_2NO_4$ $[M+H]^+$, 388.1360, found 388.1361.



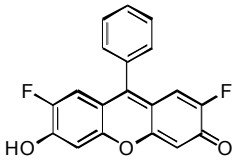
6

{[4-(5-Fluoro-2,4-dihydroxy-benzyl)-phenyl]-methoxycarbonylmethyl-amino}-acetic acid methyl ester (6). To a flame-dried flask equipped with a magnetic stir bar was added **4b** (50 mg, 0.100 mmol), $MeSO_3H$ (0.5 mL) and Et_3SiH (48 μL, 0.300 mmol). The resulting solution was stirred for 45 min at room temperature, then poured into 20 mL of H_2O containing 1 g of $NaHCO_3$. The pH was adjusted to ~5 by addition of conc. HCl. Organics were extracted with EtOAc (3 × 20 mL), dried with $MgSO_4$, filtered and concentrated in vacuo. The resultant yellow oil was purified by silica gel flash chromatography (10-40% acetone/toluene + 1% AcOH) to give **6** as a pale yellow oil (30.5 mg, 81%): ^{1}H NMR (500 MHz, d_6-DMSO, 298 K) δ 9.39 (s, 1 H), 9.09 (s, 1 H), 6.97 (d, J = 8.9 Hz, 2 H), 6.66 (d, J = 12.1 Hz, 1 H), 6.43 (d, J = 8.9 Hz, 2 H), 6.42 (d, J = 7.6 Hz, 1 H), 4.16 (s, 4 H), 3.63 (s, 6 H), 3.59 (s, 2 H); ^{13}C NMR (125 MHz, d_6-DMSO, 298 K) δ 171.2, 150.7, 145.7, 144.4 (d, J = 225 Hz), 142.7 (d, J = 13 Hz), 129.9, 129.2, 118.5, 116.4 (d, J = 19 Hz), 111.7, 104.4, 52.6, 51.6, 33.3; IR (thin film) 3401.6, 2987.5, 1718.1, 1508.2, 1169.4 cm^{-1}; TLC R_f = 0.58 (30% acetone/toluene + 1% AcOH); LRMS (ESI) m/z (relative intensity): 400(100), 777(12); HRMS (CI) m/z calcd for $C_{19}H_{20}FNO_6Na$ $[M+Na]^+$, 400.1172, found 400.1174.



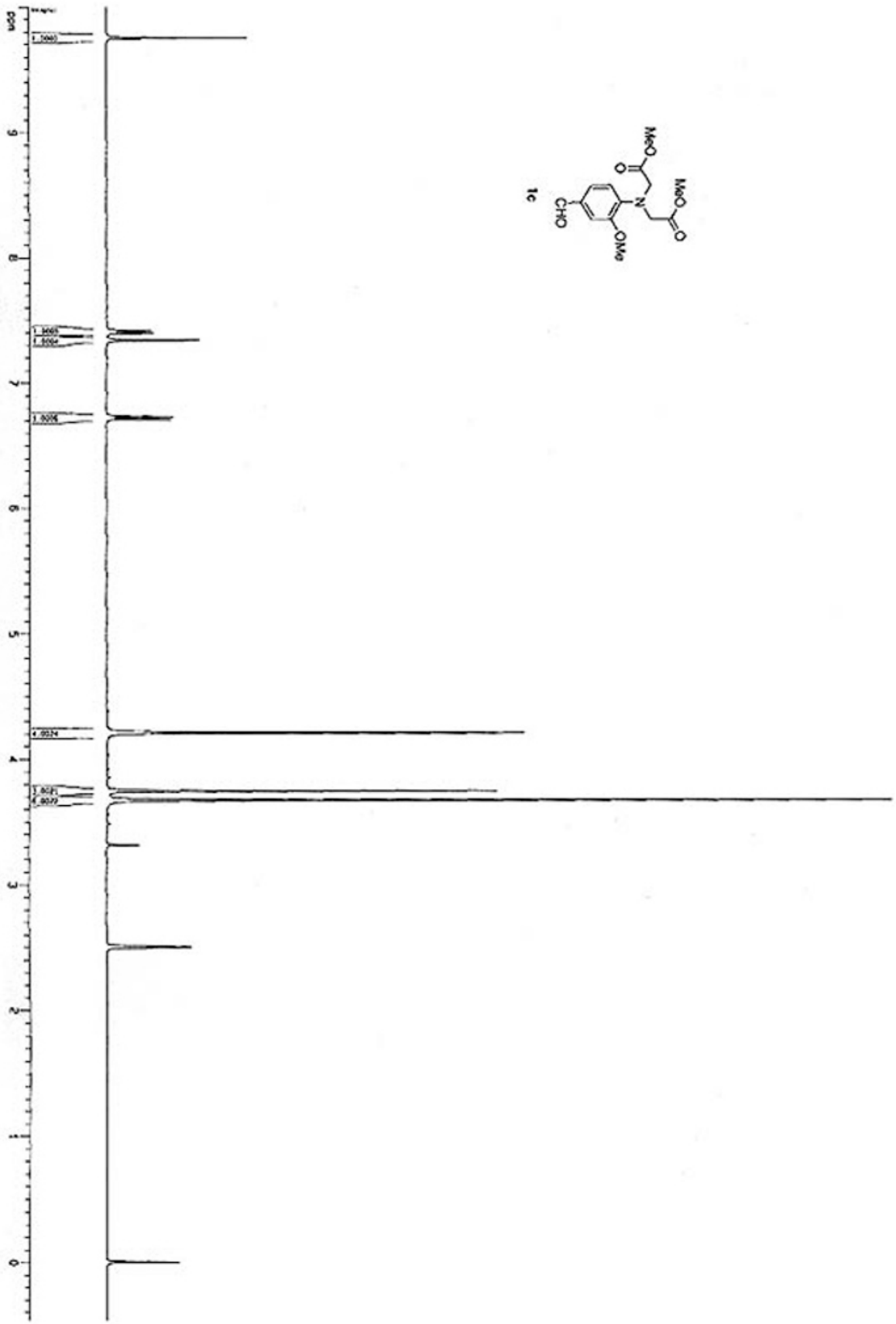
7c

{[4-(2,7-Difluoro-6-hydroxy-3-oxo-3*H*-xanthen-9-yl)-2-methoxy-phenyl]-methoxycarbonylmethyl-amino}-acetic acid methyl ester (7c). As described in the general procedure, triarylmethane **4c** (12.5 mg, 0.024 mmol) was dissolved in 2 mL 1:1 AcOH/benzene. DDQ (10.7 mg, 0.048 mmol) was added dropwise as a solution in 1 mL of 1:1 AcOH/benzene. After stirring for 15 min at room temperature, the reaction mixture was concentrated in vacuo and partially purified by silica gel flash chromatography as described in the general procedure. The crude product was further purified by preparative RP-HPLC (25-60% MeCN/0.1% TFA-H_2O) to give **7c** as a dark brown powder (8.4mg, 70%): mp 282-284 ºC (H_2O); ^{1}H NMR (500 MHz, d_6-DMSO, 323 K) δ 7.03 (d, J = 1.8 Hz, 1 H), 6.99 (d, J = 11.7 Hz, 2 H), 6.94 (dd, J = 1.8, 8.2 Hz, 1 H), 6.88 (d, J = 8.2 Hz, 1 H), 6.80 (d, J = 7.0 Hz, 2H), 4.19 (s, 4 H), 3.72 (s, 3 H), 3.67 (s, 6 H); ^{13}C NMR (125 MHz, d_6-DMSO, 323 K) δ 171.7, 158.8 (d, J = 36 Hz), 154.1, 153.6, 151.6, 151.0, 150.5, 140.7, 124.3, 123.0, 117.7, 114.6, 112.7(d, J = 21 Hz), 105.4, 56.6, 54.2, 52.0; ^{19}F NMR (377 MHz, d_6-DMSO, 298 K) δ -75.13; IR (KBr) 3396.2, 2948.8, 1688.2, 1516.1, 1301.1, 1193.5 cm^{-1}; TLC R_f = 0.23 (10% MeOH/$CHCl_3$); LRMS (ESI) m/z (relative intensity): 514(100); HRMS (CI) m/z calcd for $C_{26}H_{21}F_2NO_8Na$ $[M+Na]^+$ 536.1133, found 536.1121.



7d

2,7-Difluoro-6-hydroxy-9-phenyl-xanthen-3-one (7d). As described in the general procedure, triarylmethane **4d** (14.0 mg, 0.04 mmol) was dissolved in 2.5 mL 1:1 AcOH/benzene. DDQ (18.0 mg, 0.08 mmol) was added dropwise as a solution in 2.5 mL of 1:1 AcOH/benzene. After stirring for 15 min at room temperature, the reaction mixture was concentrated in vacuo and partially purified by silica gel flash chromatography as described in the general procedure. The crude product was further purified by preparative RP-HPLC as described in the general procedure to give **7e** as a dark brown powder (5.5 mg, 39%): mp dec. 300 ºC (H_2O); ^{1}H NMR (500 MHz, d_6-DMSO, 373 K) δ 7.04 (d, J = 9.5 Hz, 1 H), 7.02 (d, J = 11.7 Hz, 2 H), 6.94 (d, J = 8.2 Hz, 1 H), 6.84 (d, J = 8.2 Hz, 1 H), 6.81 (d, J = 6.3 Hz, 2H), 4.21 (s, 4 H), 3.72 (s, 3 H), 3.69 (s, 6 H); ^{13}C NMR (125 MHz, d_6-DMSO, 298 K) δ 175.9, 175.2, 165.9, 152.0, 150.1, 143.3, 140.1, 139.7, 135.5, 131.6, 130.0, 129.2(d, J = 23 Hz), 129.0, 109.4, 105.2; ^{19}F NMR (377 MHz, d_6-DMSO, 298 K) δ -74.48; IR (KBr) 3423.2, 1680.1, 1502.7, 1301.1, 1206.9, 1134.4, 1002.7 cm^{-1}; TLC R_f = 0.41 (10% MeOH/$CHCl_3$).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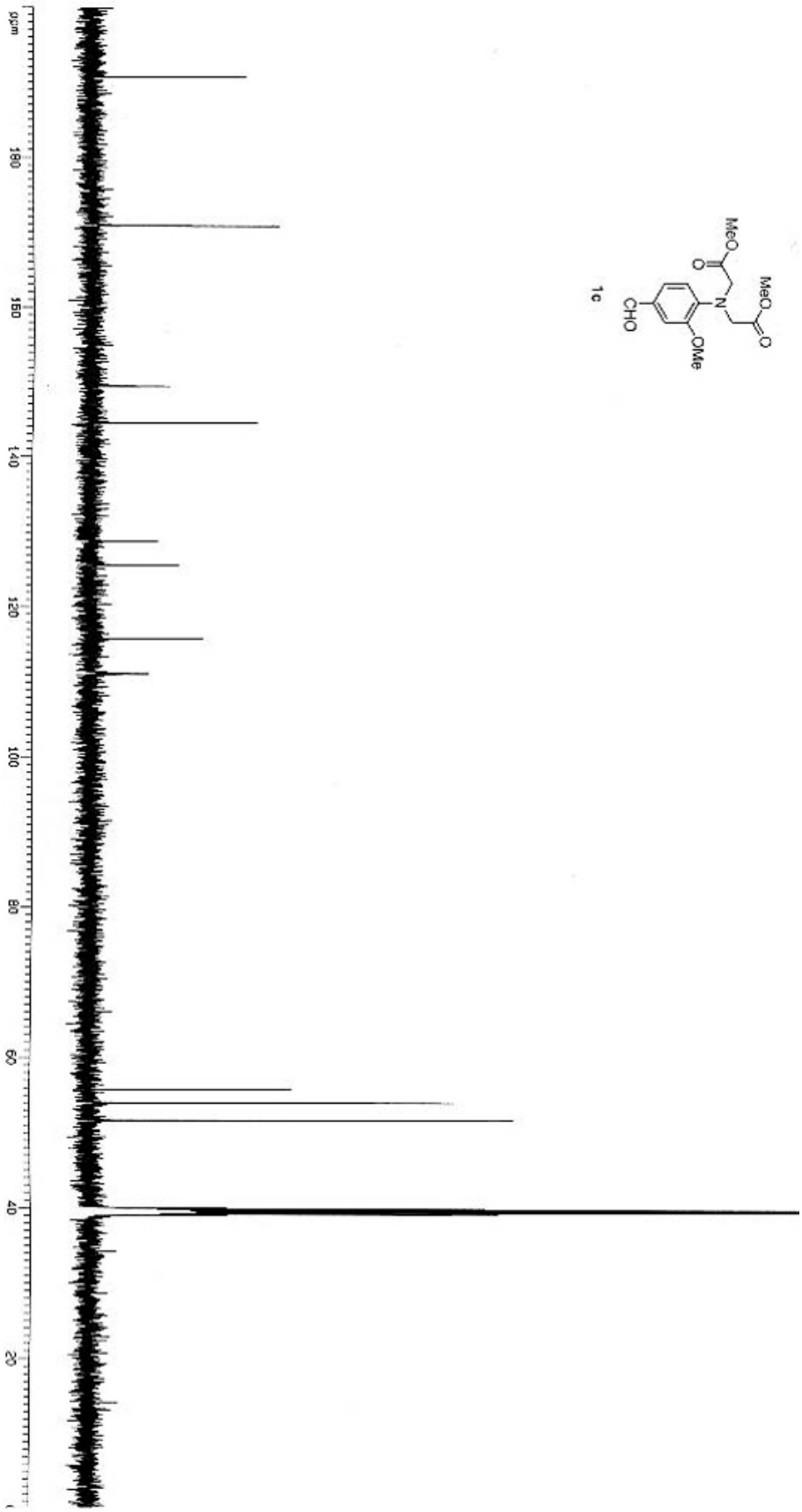
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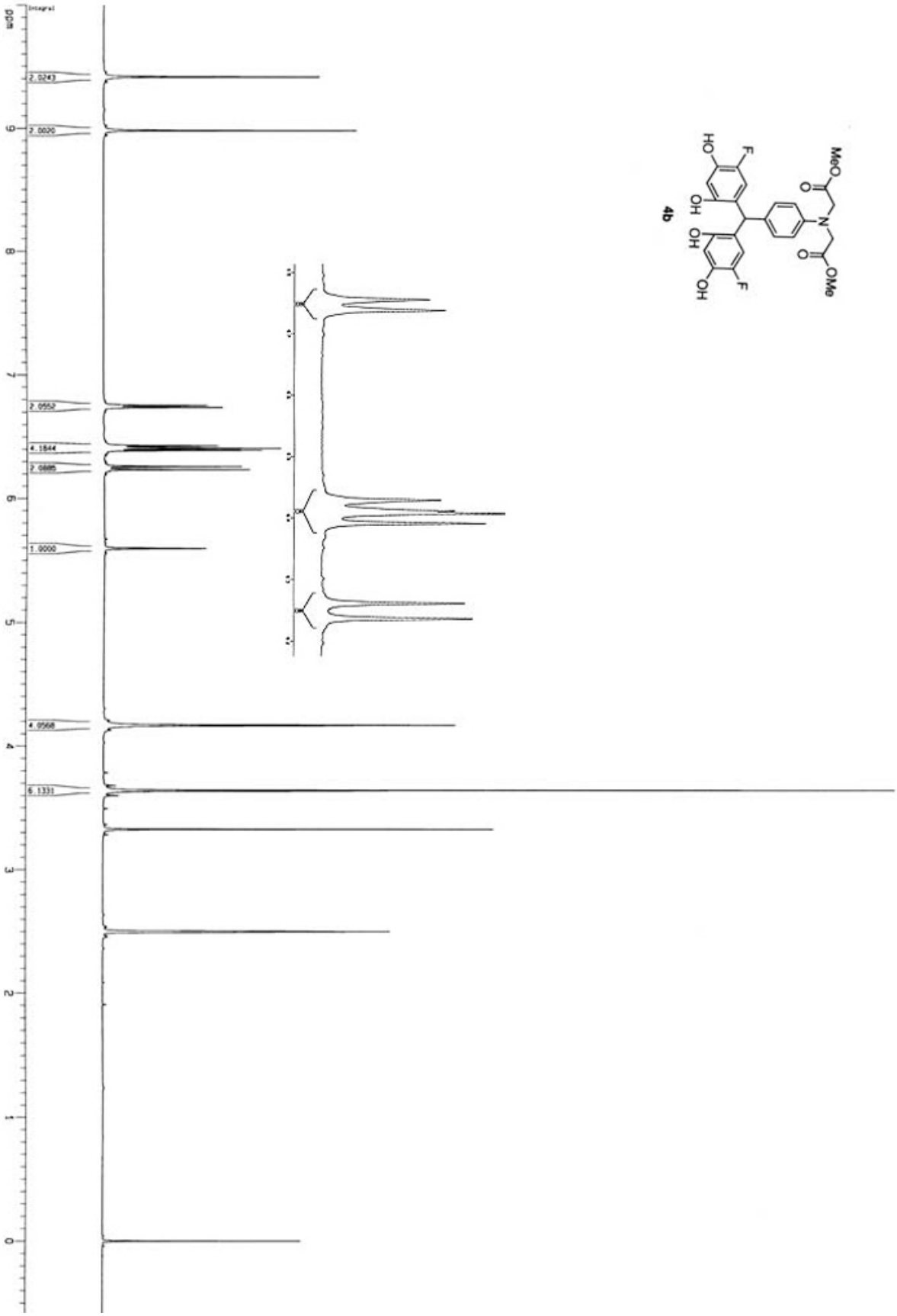
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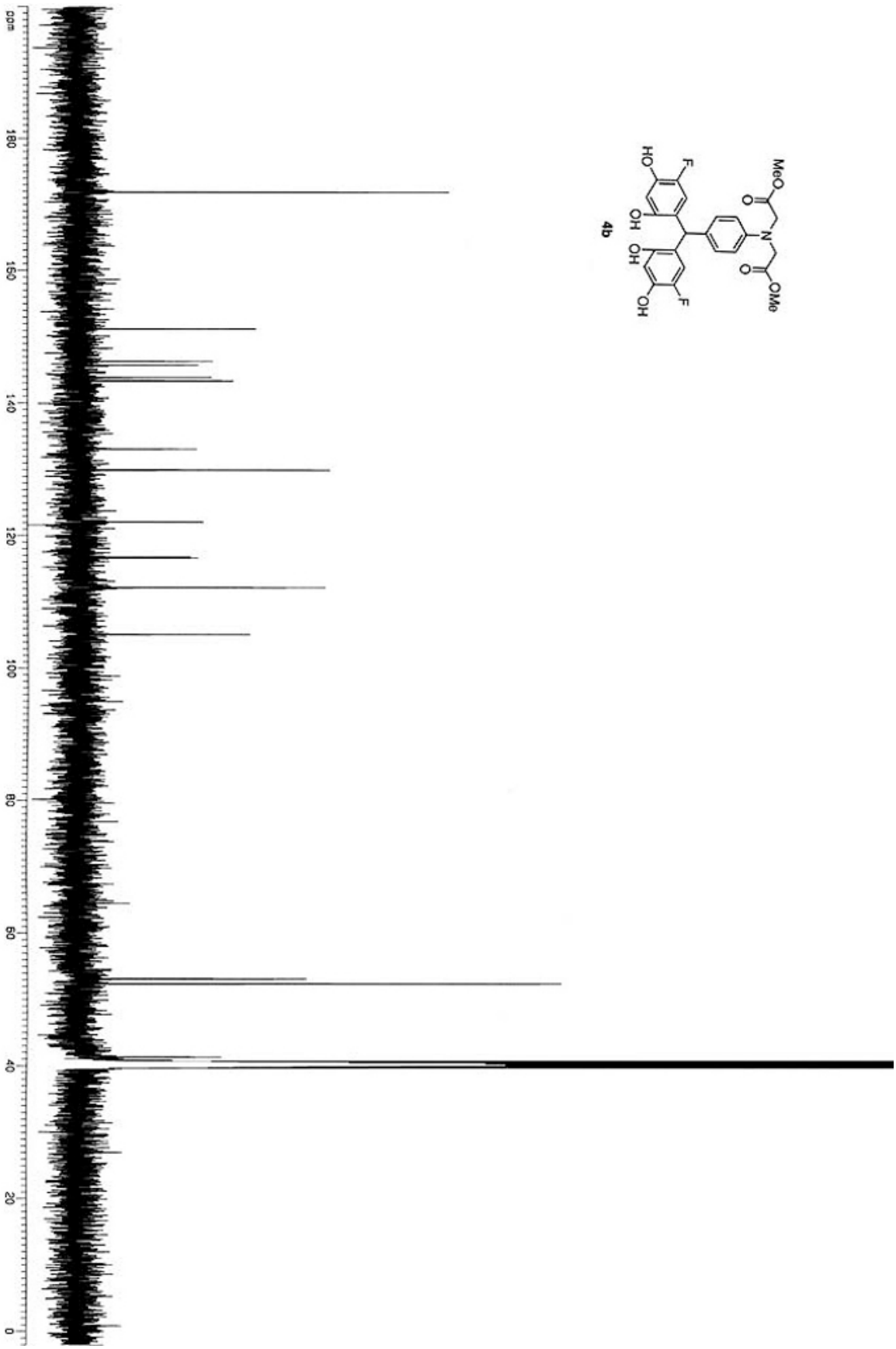
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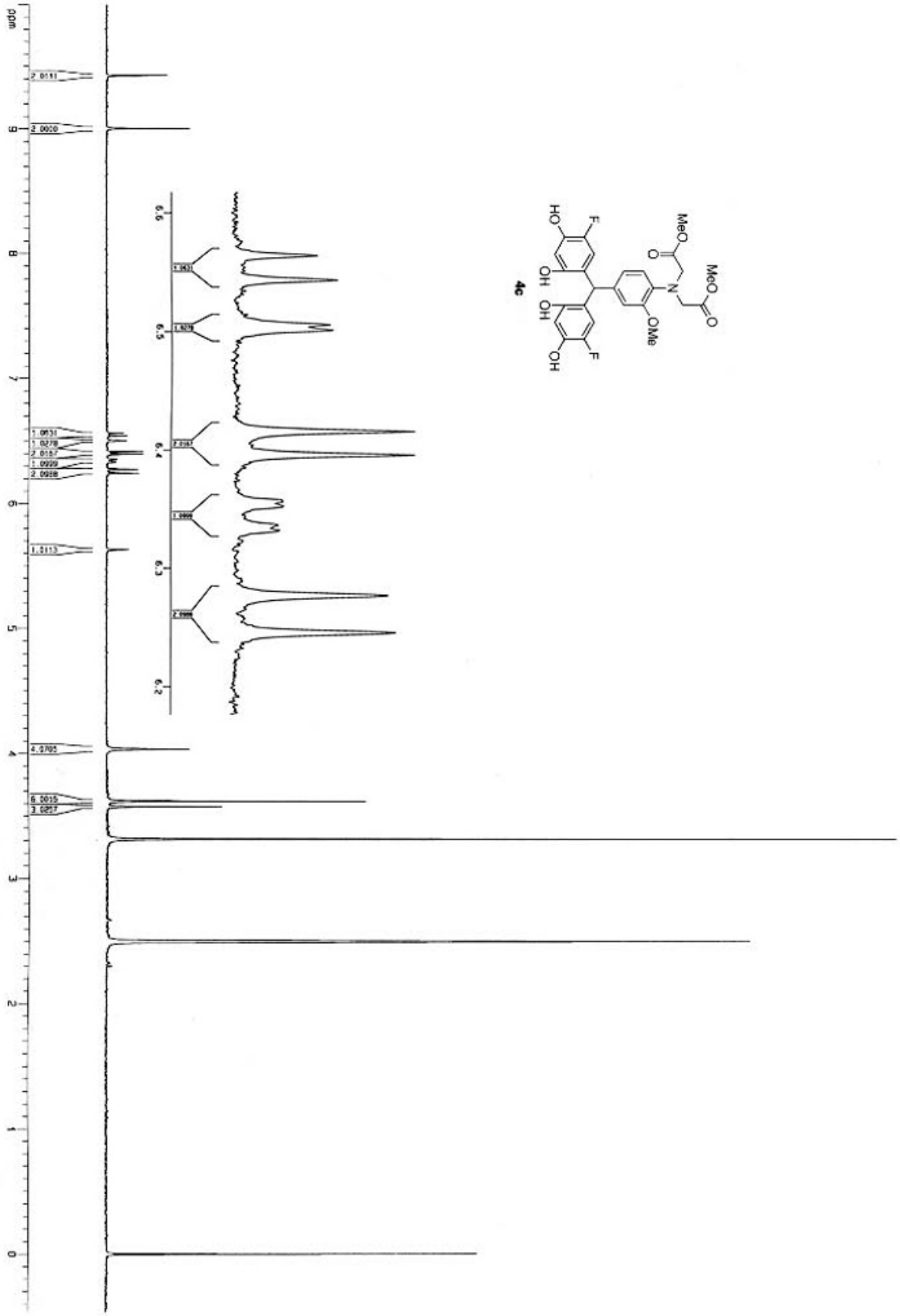
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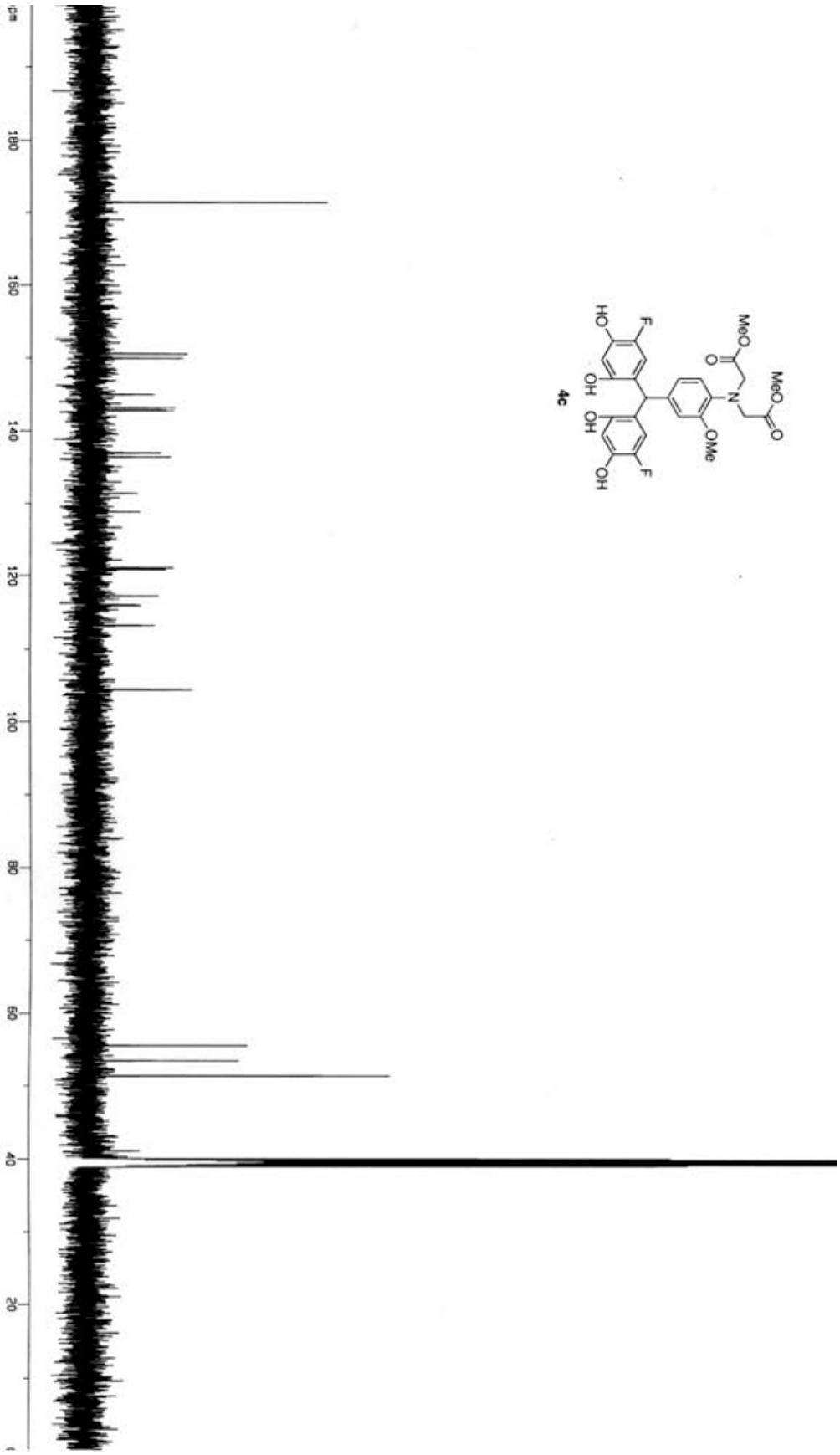
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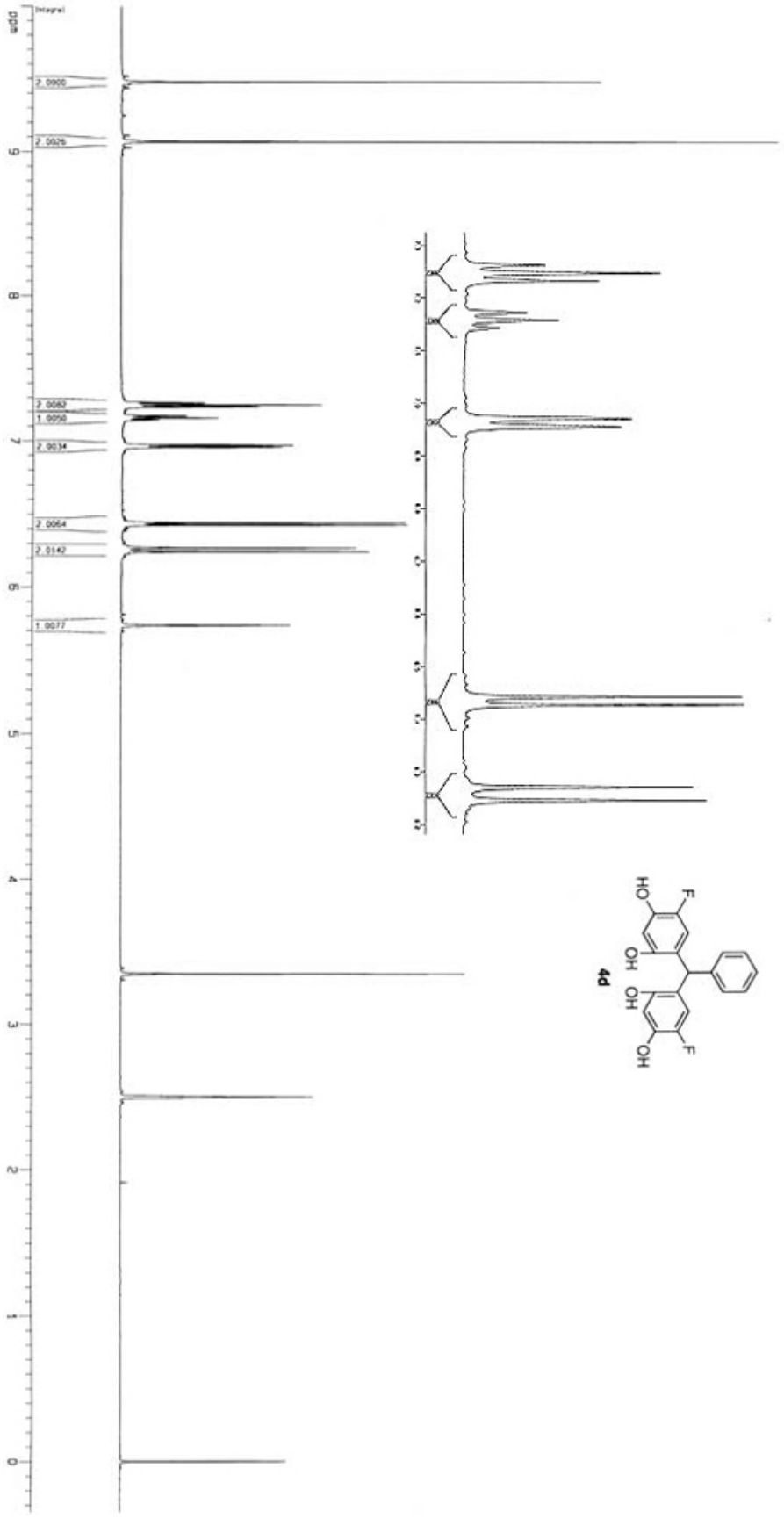
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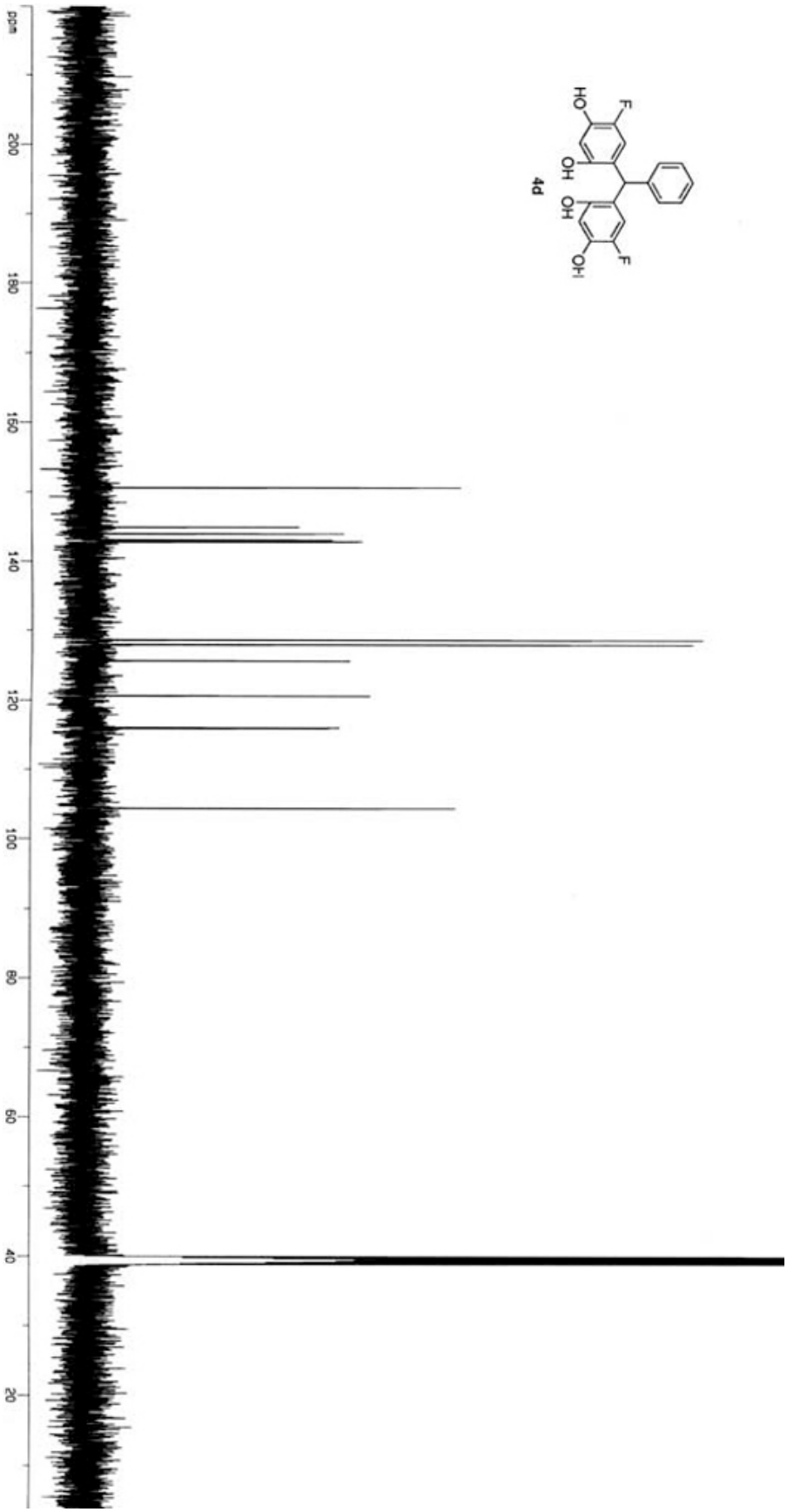
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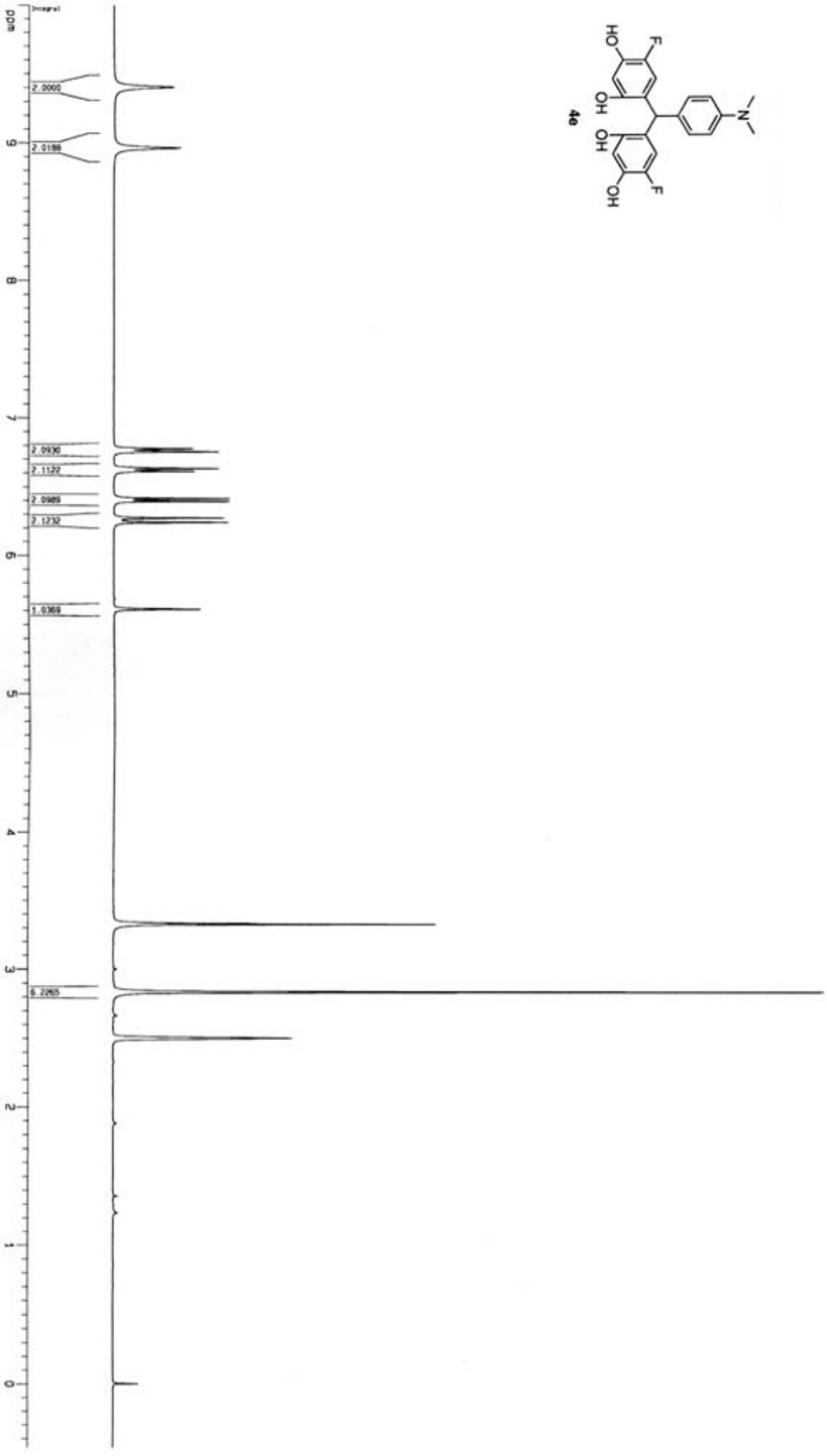
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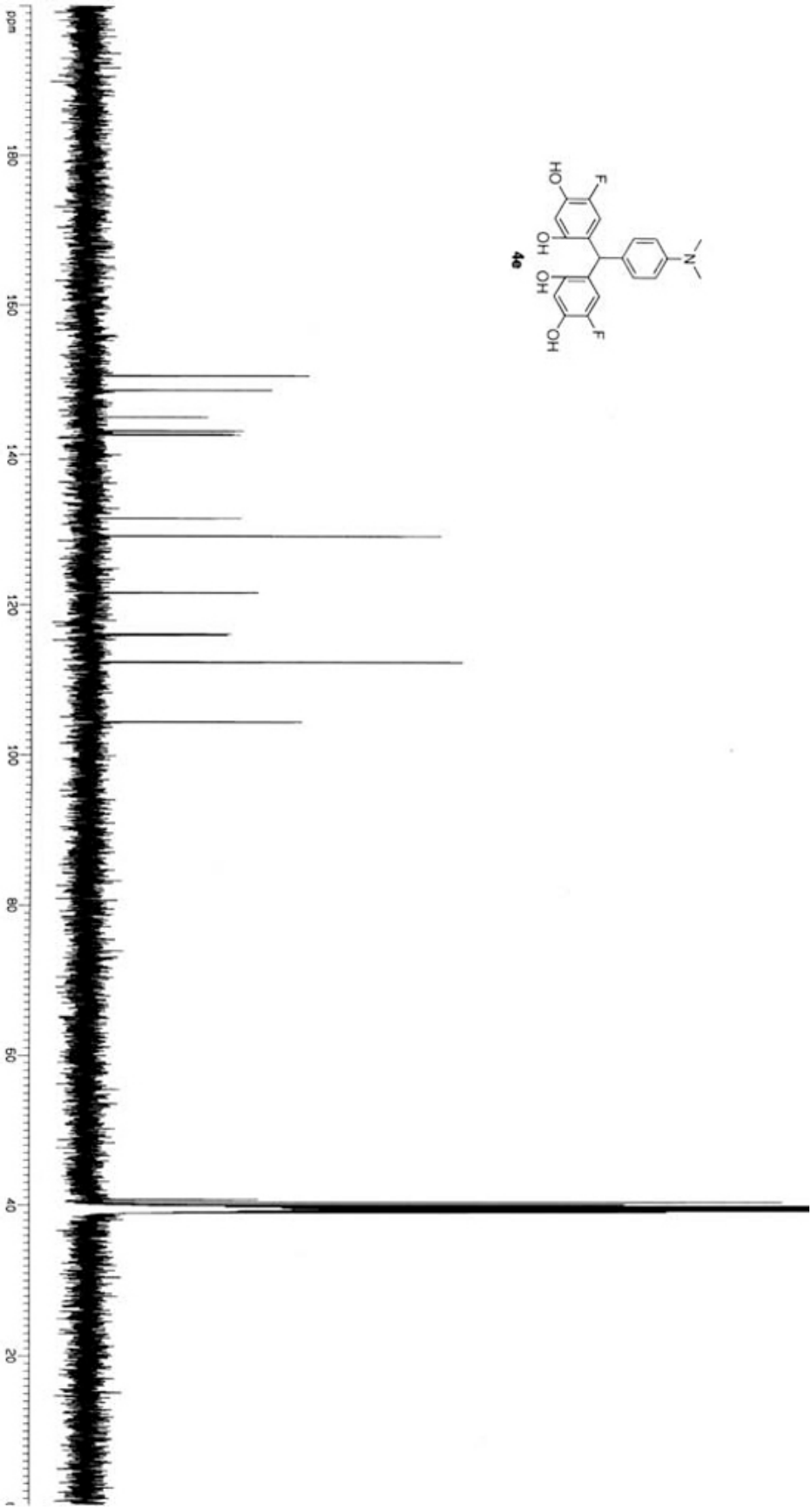
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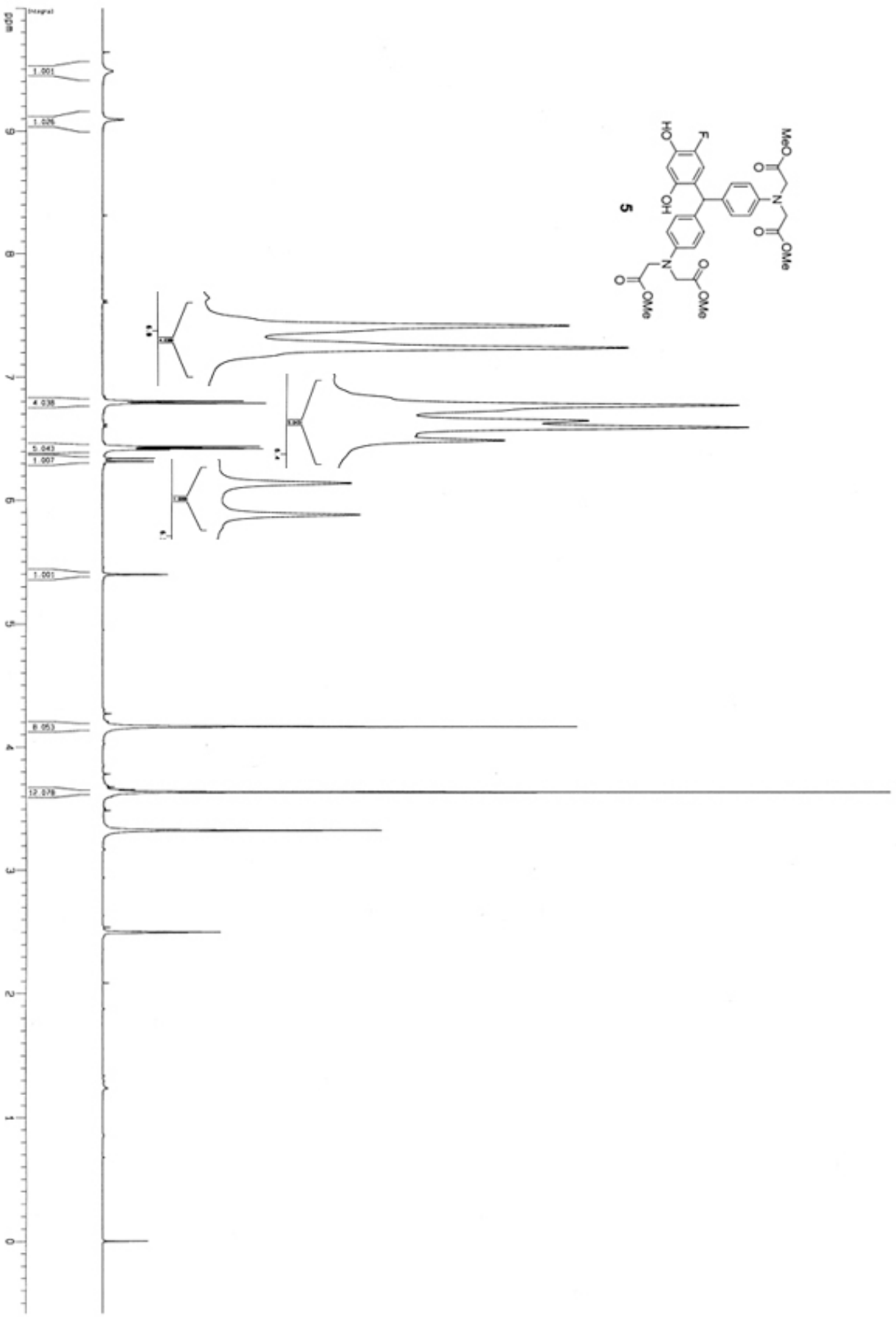
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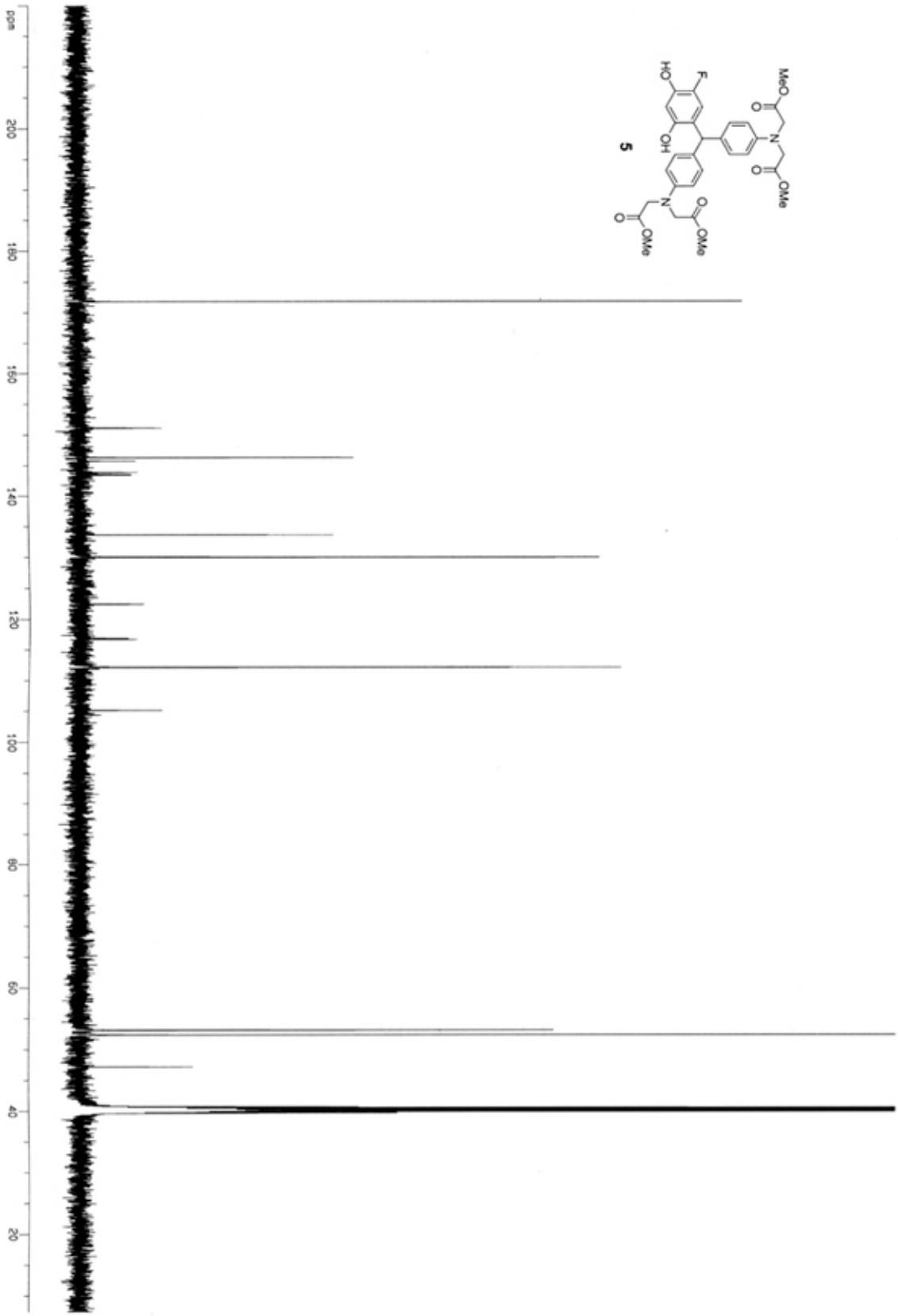
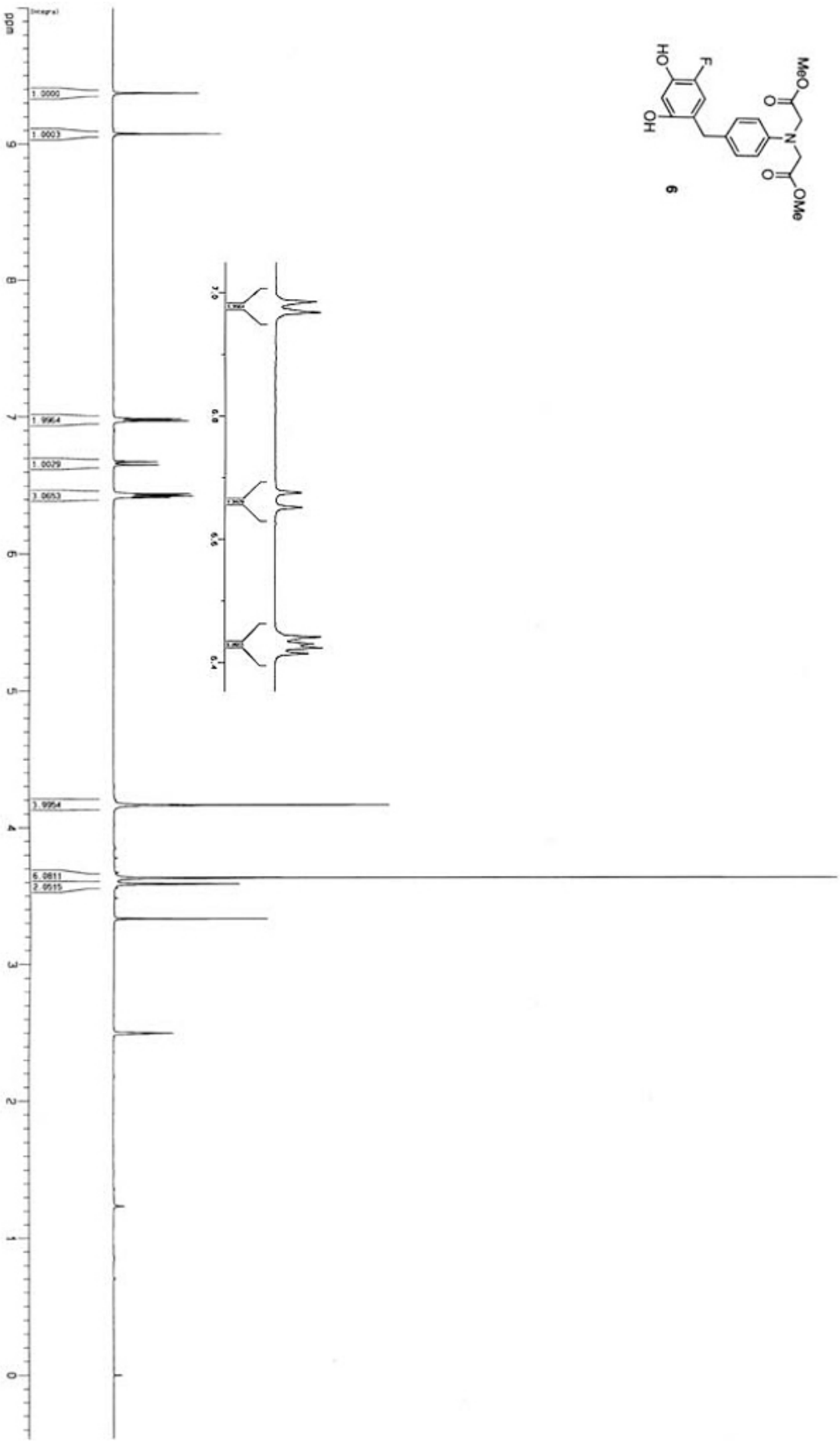
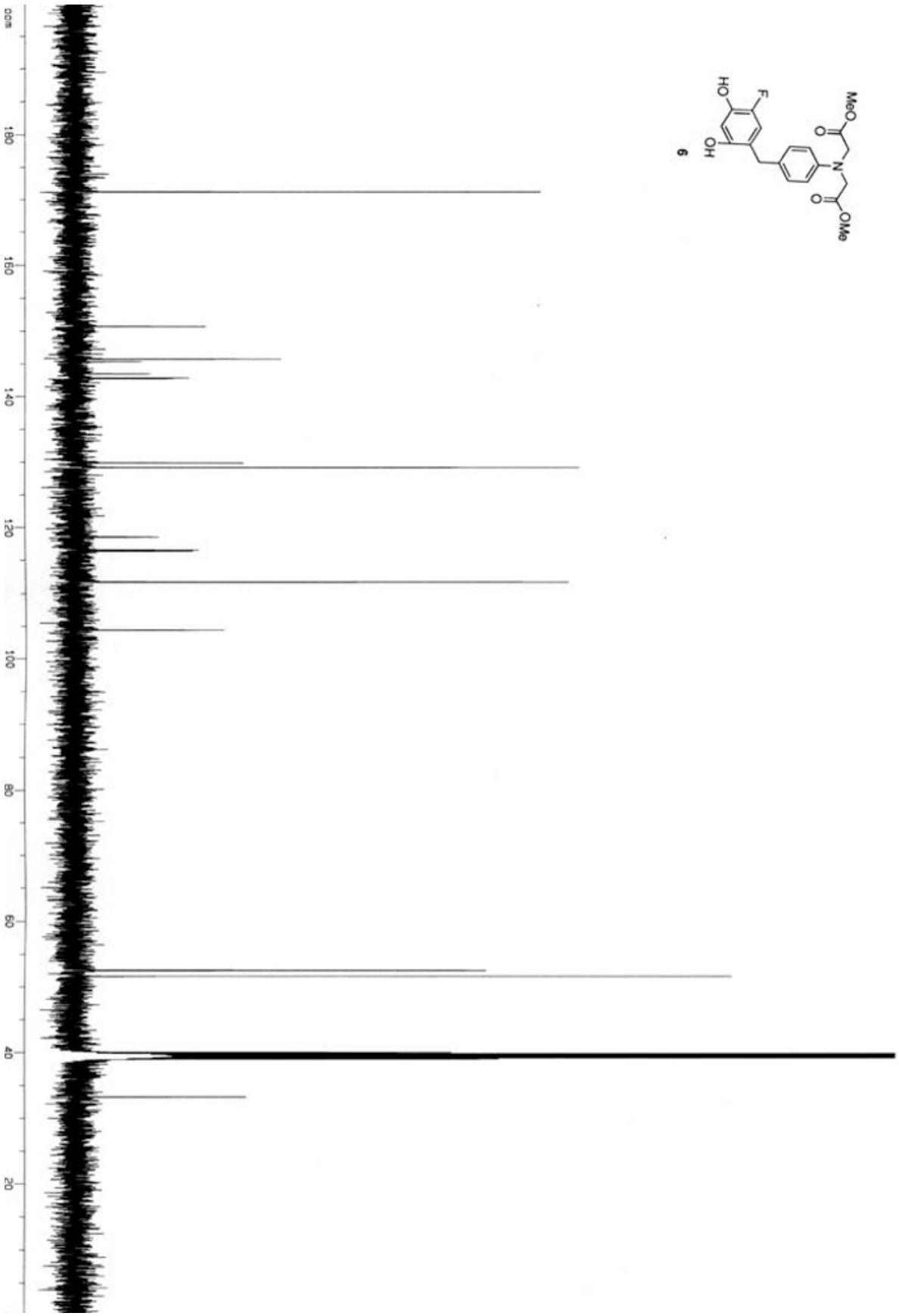
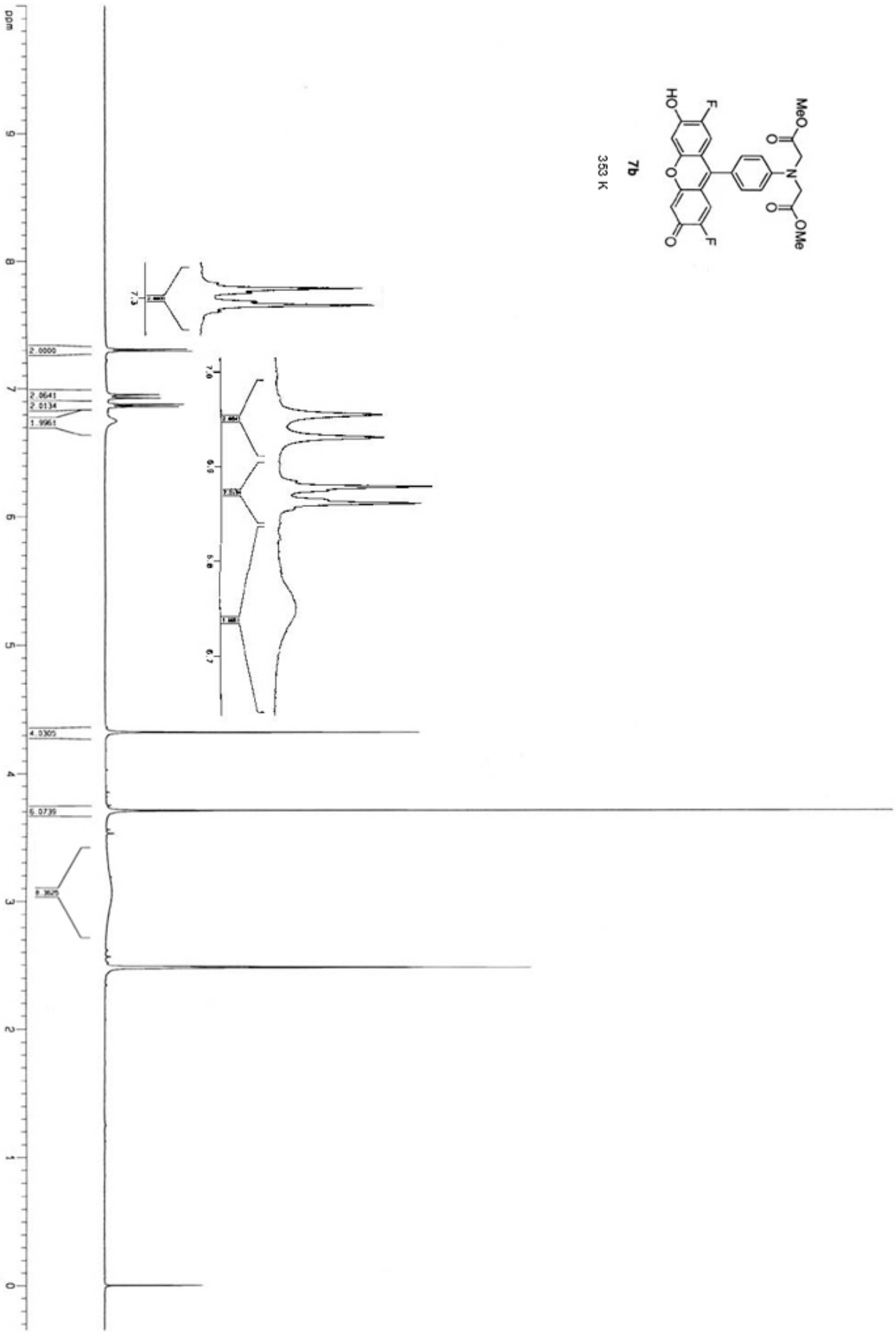
HO
F
OH
MeO
OMe
OMe
OMe
OMe
N
N
5


ppm
200
180
160
140
120
100
80
60
40
20
HO
F
OH
N
MeO
OMe
5


ppm
1.0000
1.0003
1.9964
1.0079
3.0053
3.9954
6.0811
2.0515
HO
F
OH
MeO
O
N
O
OMe
6


ppm
180
160
140
120
100
80
60
40
20
HO
F
OH
MeO
O
N
O
OMe
6


7b
353 K
HO
F
O
O
F
O
N
O
MeO
OMe
ppm
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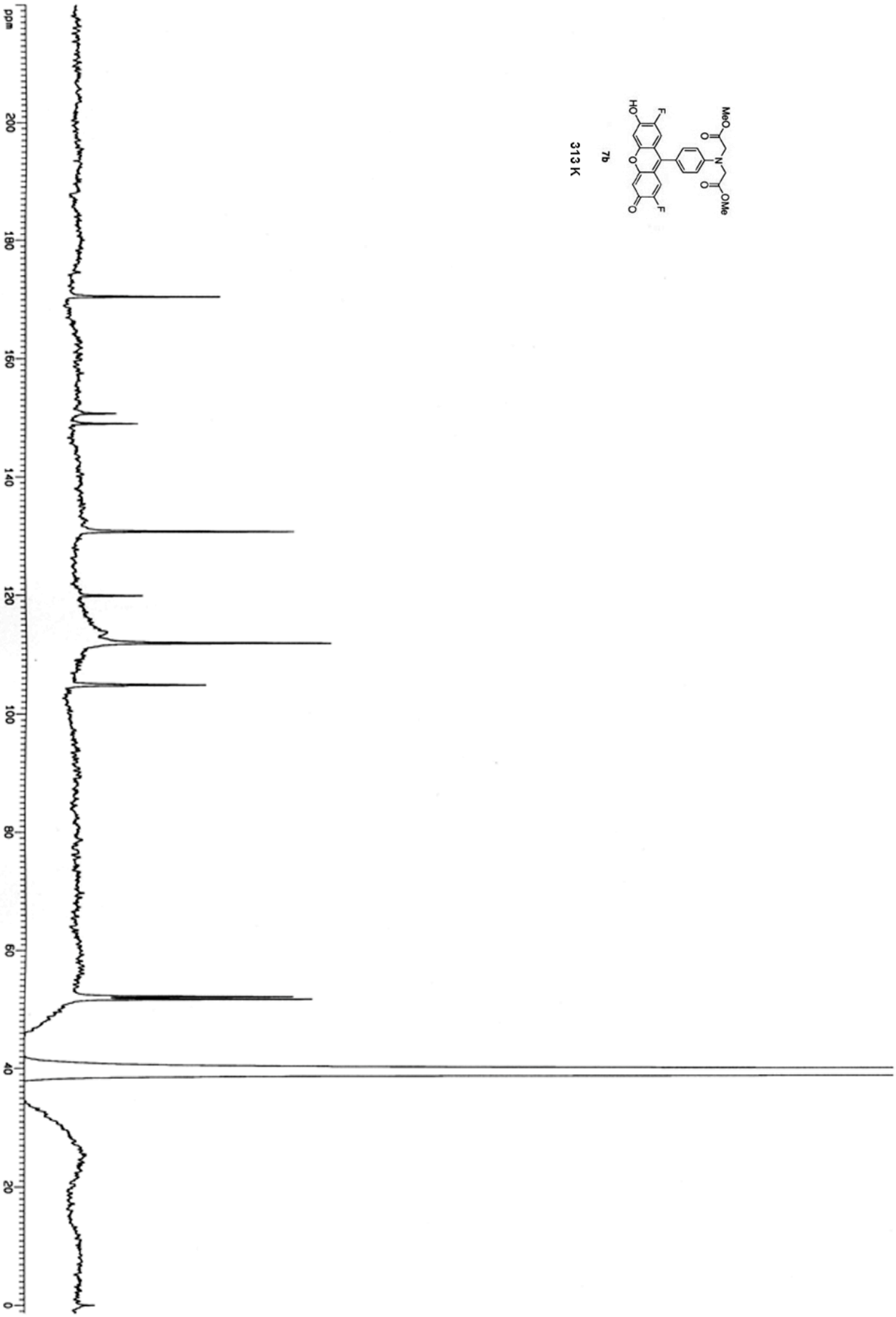
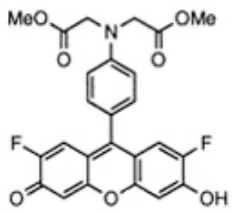
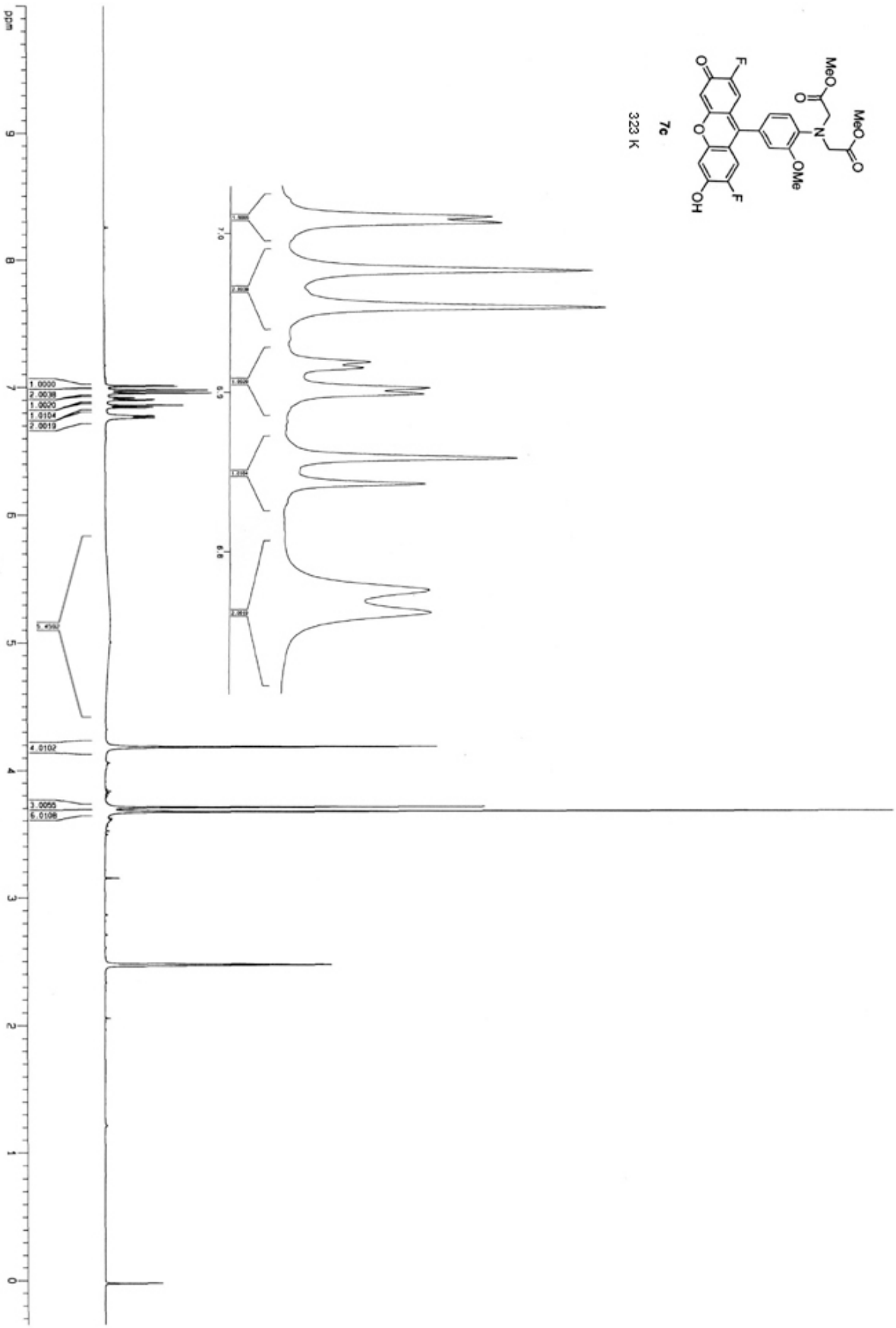
2.0641
2.0134
1.9961
4.0305
6.0739
8.3625

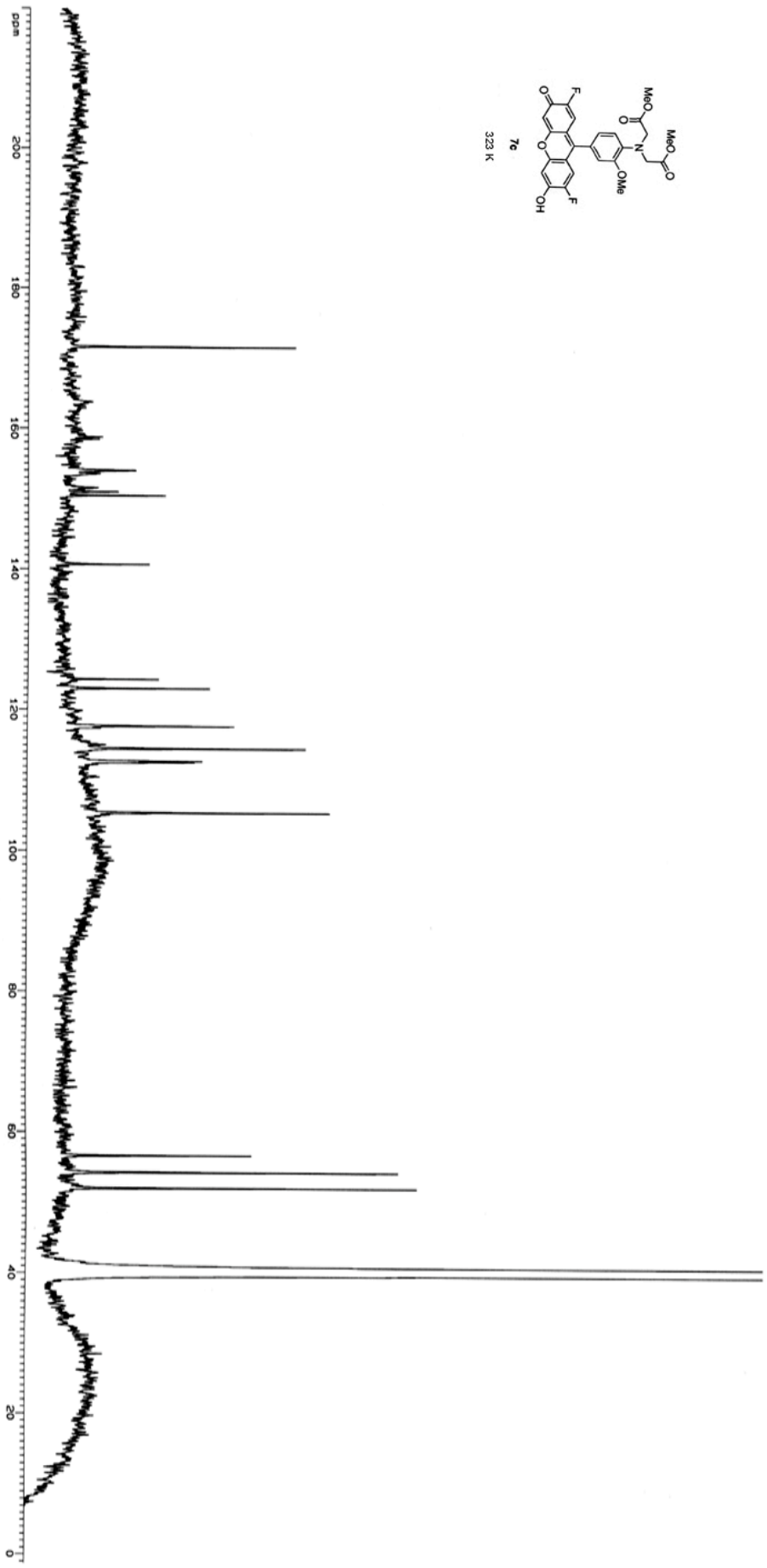

ppm
200
180
160
140
120
100
80
60
40
20
0
HO
F
O
O
N
MeO
OMe
O
O
F
7b
313 K

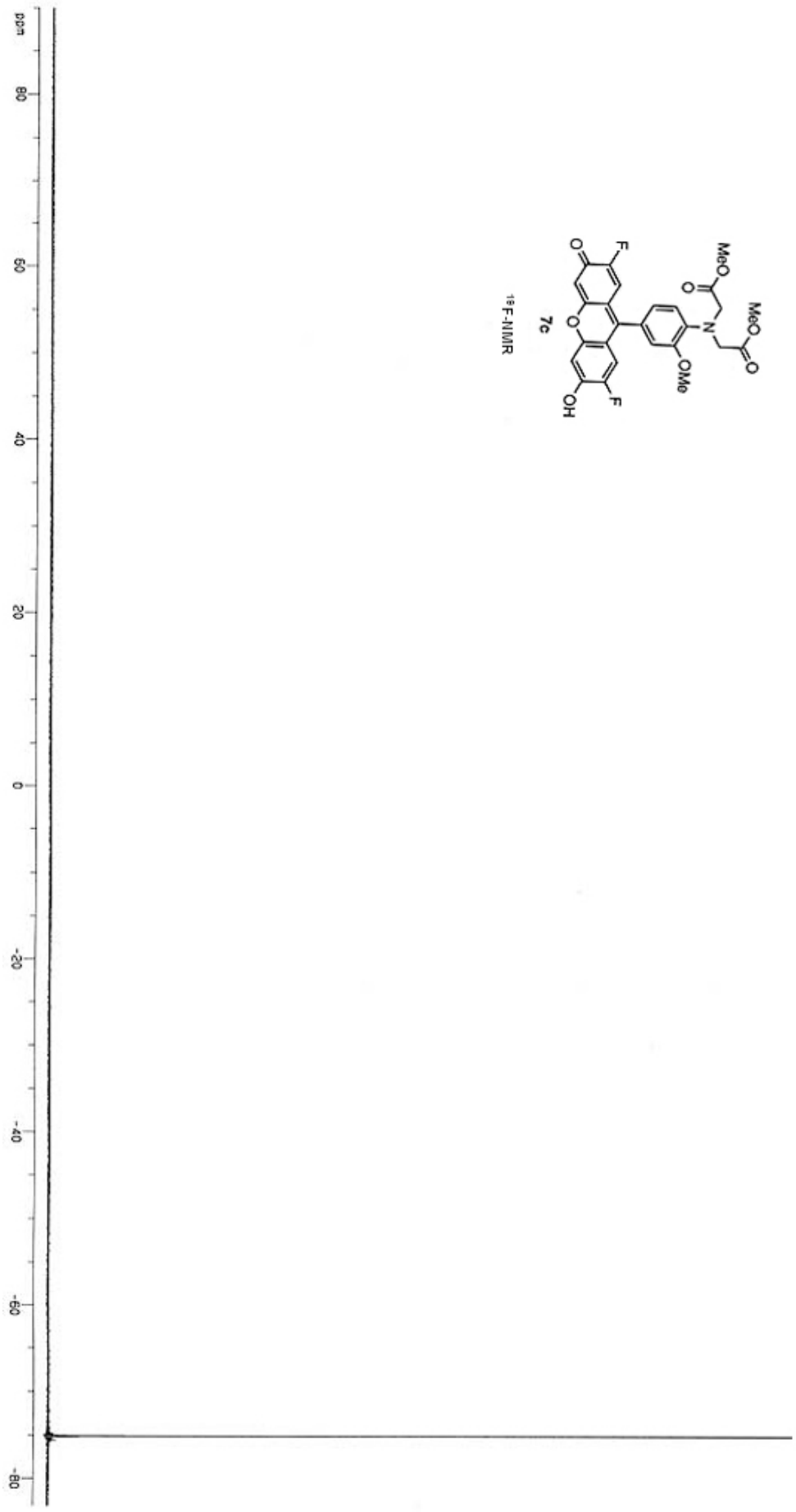


7b

^{19}F-NMR

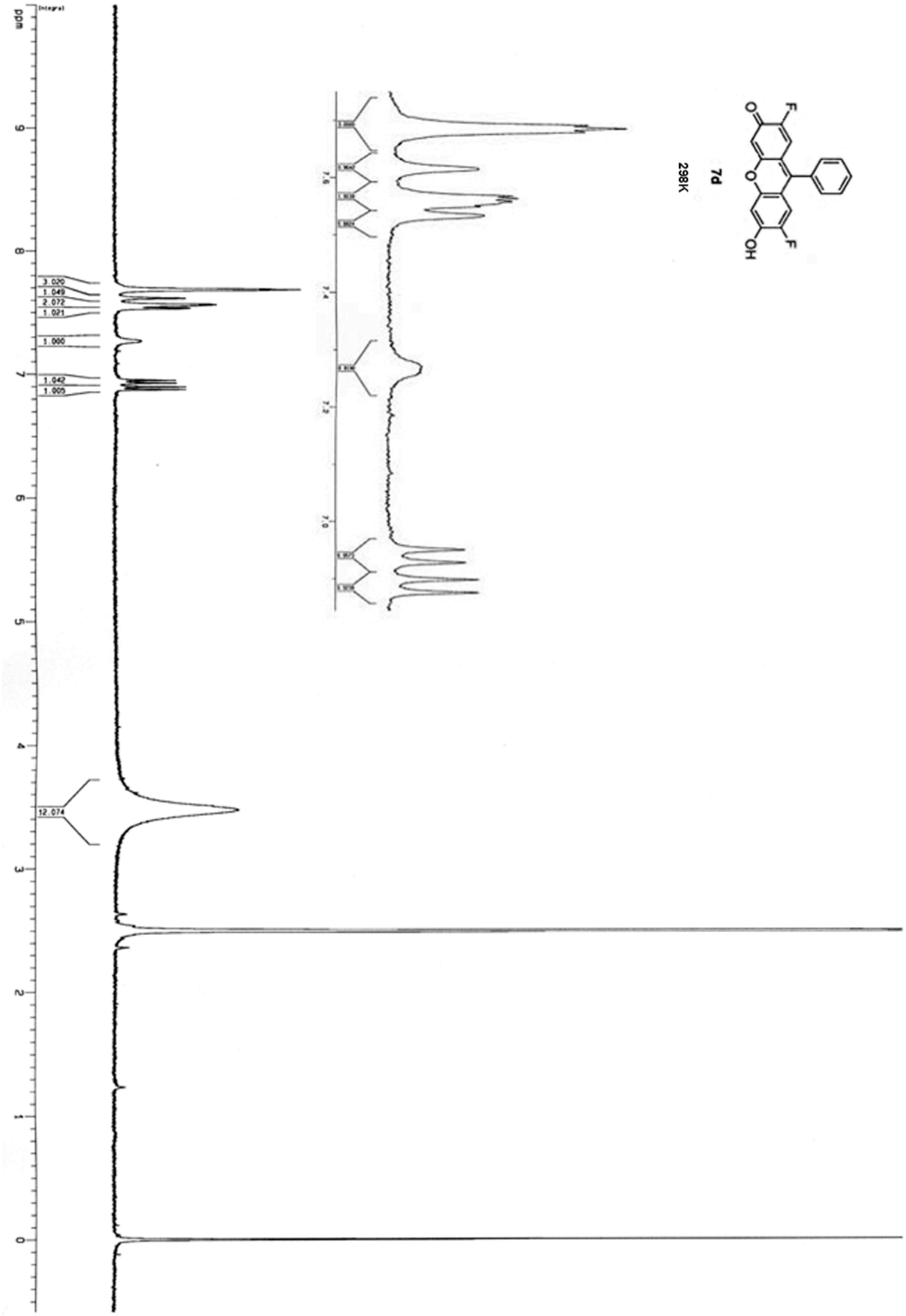

7c
323 K
MeO
MeO
N
OMe
F
OH
F
O
O
O
ppm
1.0000
2.0038
1.0020
1.0104
2.0019
4.0102
3.0055
6.0108


ppm
200
180
160
140
120
100
80
60
40
20
0
7c
323 K
F
O
O
MeO
O
N
MeO
O
OMe
F
OH



7c

^{19}F-NMR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Integral
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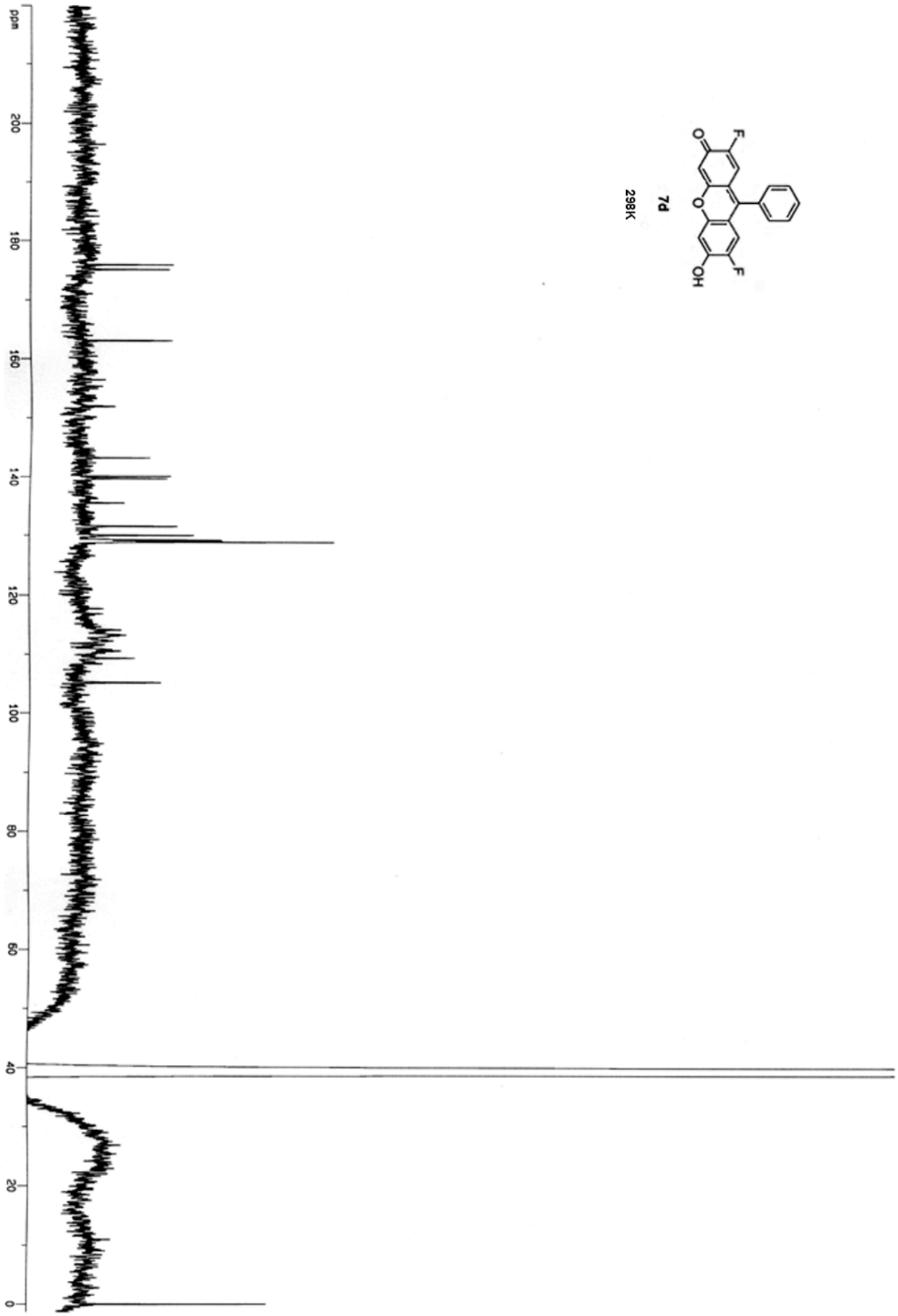
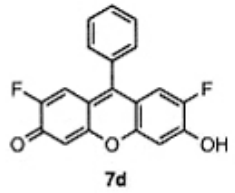
1.049
2.072
1.021
1.000
1.042
1.005
12.074
7d
298K
F
O
O
OH
F


ppm
200
180
160
140
120
100
80
60
40
20
0
7d
298K
F
O
O
F
OH



7d

^{19}F-NMR