Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Synthesis of pyrazolo[5,1-*a*]isoquinolins via a silver(I)-rhodium(I) cooperative catalysis in the reaction of *N′*-(2-alkynylbenzylidene)hydrazide with cycloprop-2-ene-1,1-dicarboxylate

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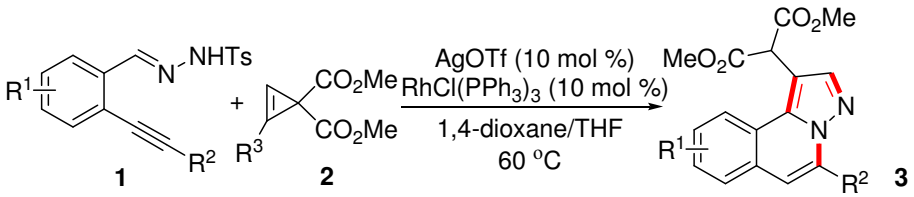
Supporting Information

General experimental methods:

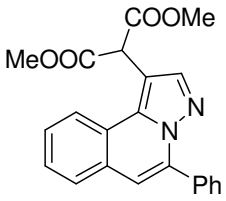
Unless otherwise stated, all commercial reagents were used as received. All solvents were dried and distilled according to standard procedures. Flash column chromatography was performed using silica gel (60-Å pore size, 32–63μm, standard grade). Analytical thin–layer chromatography was performed using glass plates pre-coated with 0.25 mm 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Thin layer chromatography plates were visualized by exposure to ultraviolet light. Organic solutions were concentrated on rotary evaporators at ~20 Torr at 25–35°C. Nuclear magnetic resonance (NMR) spectra are recorded in parts per million from internal tetramethylsilane on the δ scale. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker DRX-400 spectrometer operating at 400 MHz and 100 MHz, respectively. All chemical shift values are quoted in ppm and coupling constants quoted in Hz. High resolution mass spectrometry (HRMS) spectra were obtained on a micrOTOF II Instrument.

General procedure for the synthesis of pyrazolo[5,1-a]isoquinolines via a tandem reaction of N′-(2-alkynylbenzylidene)hydrazides 1 with cycloprop-2-ene-1,1-dicarboxylate 2

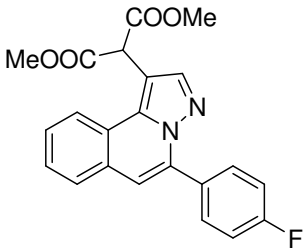


A mixture of *N′*-(2-alkynylbenzylidene)hydrazide **1** (0.5 mmol) and AgOTf (7.7mg, 10 mol %) in 1,4-dioxane (2.0 mL) was heated at 60 °C with vigorous stirring for 1 hour. Then, $RhCl(PPh_3)_3$ (27.7mg, 10 mol %) and dimethyl cycloprop-2-ene-1,1-dicarboxylate **2** (0.36 mmol), and THF (2.0 mL) were added. The reaction mixture was stirred vigorously at 60 °C overnight until completion of the reaction. The reaction mixture was diluted with ethyl acetate (5.0 mL), and quenched with water (5.0 mL). The organic layer was washed with brine, dried over Na_2SO_4

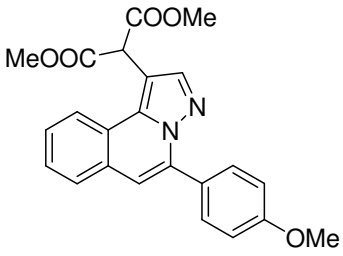
and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to provide the desired product **3**.



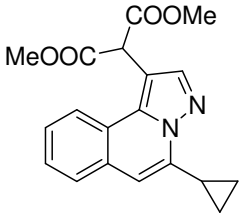
Dimethyl 2-(5-phenylpyrazolo[5,1-*a*]isoquinolin-1-yl)malonate **3a**. White solid; melting point: 118.2-119.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 3.81 (s, 6H), 5.47 (s, 1H), 7.05 (s, 1H), 7.50-7.58 (m, 5H), 7.76 (d, J = 6.9 Hz, 1H), 7.81 (d, J = 6.9 Hz, 2H), 8.11 (s, 1H), 8.22 (d, J = 7.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 49.7, 53.2, 106.3, 113.3, 123.0, 124.2, 127.5, 127.7, 128.1, 128.4, 129.4, 129.5, 130.1, 133.7, 135.8, 138.7, 141.6, 168.5; HRMS calcd for $C_{22}H_{19}N_2O_4$: ($M + H^+$) 375.1339, found: 375.1342.



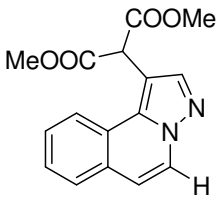
Dimethyl 2-(5-(4-fluorophenyl)pyrazolo[5,1-*a*]isoquinolin-1-yl)malonate **3b**. White solid; melting point: 135.1-136.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 3.81 (s, 6H), 5.47 (s, 1H), 7.02 (s, 1H), 7.20 (t, J = 8.2 Hz, 2H), 7.57-7.62 (m, 2H), 7.75 (d, J = 7.3 Hz, 1H), 7.81-7.84 (m, 2H), 8.11 (s, 1H), 8.22 (d, J = 7.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 49.7, 53.2, 106.4, 113.2, 115.5 (d, $^{2}J_{CF}$ = 22 Hz), 123.0, 124.2, 127.7, 128.2, 129.7, 130.0, 131.6 (d, $^{3}J_{CF}$ = 9 Hz), 135.8, 137.6, 141.7, 163.4 (d, $^{1}J_{CF}$ = 248 Hz), 168.4; HRMS calcd for $C_{22}H_{18}FN_2O_4$: ($M + H^+$) 393.1245, found: 393.1243.



Dimethyl 2-(5-(4-methoxyphenyl)pyrazolo[5,1-*a*]isoquinolin-1-yl)malonate **3c**. White solid; melting point: 142.6-143.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 3.80 (s, 6H), 3.84 (s, 3H), 5.47 (s, 1H), 6.98-7.02 (m, 3H), 7.49-7.56 (m, 2H), 7.70 (d, *J* = 6.9 Hz, 1H), 7.76 (d, *J* = 7.8 Hz, 2H), 8.12 (s, 1H), 8.19 (d, *J* = 7.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 49.7, 53.2, 55.4, 106.2, 112.6, 113.8, 122.9, 123.9, 126.0, 127.3, 127.5, 128.0, 130.2, 130.9, 135.8, 138.4, 141.5, 160.4, 168.5; HRMS calcd for $C_{23}H_{21}N_2O_5$: ($M + H^+$) 405.1445, found: 405.1433.

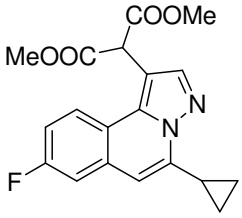


Dimethyl 2-(5-cyclopropylpyrazolo[5,1-*a*]isoquinolin-1-yl)malonate **3d**. Colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$): 0.87-0.90 (m, 2H), 1.15-1.20 (m, 2H), 2.64-2.69 (m, 1H), 3.80 (s, 6H), 5.46 (s, 1H), 6.68 (s, 1H), 7.50-7.52 (m, 2H), 7.64-7.66 (m, 1H), 8.16-8.18 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.0, 11.5, 49.7, 53.1, 106.2, 107.6, 122.8, 123.4, 126.8, 127.0, 127.8, 130.1, 135.3, 140.9, 141.4, 168.5; HRMS calcd for $C_{19}H_{19}N_2O_4$: ($M + H^+$) 339.1339, found: 339.1332.

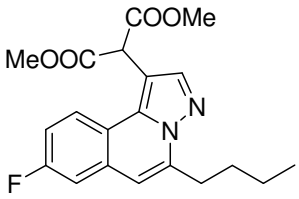


Dimethyl 2-(pyrazolo[5,1-*a*]isoquinolin-1-yl)malonate **3e**. White solid; melting point: 103.8-105.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 3.81 (s, 6H), 5.42 (s, 1H), 6.99 (d, *J* = 7.3 Hz, 1H), 7.55-7.61 (m, 2H), 7.72 (d, *J* = 7.3 Hz, 1H), 8.12 (s, 1H), 8.17-8.23 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 49.6, 53.2, 105.9, 112.7, 123.2, 124.7, 126.7,

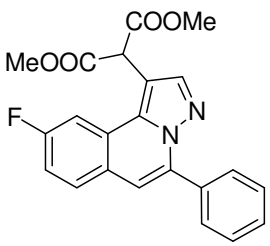
127.7, 127.8, 128.0, 129.8, 134.9, 142.0, 168.4; HRMS calcd for $C_{16}H_{15}N_2O_4$: (M + H^+) 299.1026, found: 299.1025.



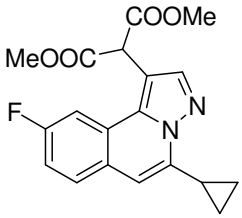
Dimethyl 2-(5-cyclopropyl-8-fluoropyrazolo[5,1-*a*]isoquinolin-1-yl)malonate **3f**. White solid; melting point: 88.5-89.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 0.88-0.92 (m, 2H), 1.17-1.22 (m, 2H), 2.65-2.70 (m, 1H), 3.81 (s, 6H), 5.37 (s, 1H), 6.60 (s, 1H), 7.24-7.30 (m, 2H), 8.16-8.18 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.2, 11.5, 49.6, 53.2, 105.8, 106.8, 111.8 (d, $^2J_{CF}$ = 21 Hz), 115.3 (d, $^2J_{CF}$ = 23 Hz), 120.1, 125.3 (d, $^3J_{CF}$ = 9 Hz), 132.1 (d, $^3J_{CF}$ = 9 Hz), 135.1, 141.7, 142.2, 161.8 (d, $^1J_{CF}$ = 247 Hz), 168.4; HRMS calcd for $C_{19}H_{18}FN_2O_4$: (M + H^+) 357.1245, found: 357.1237.



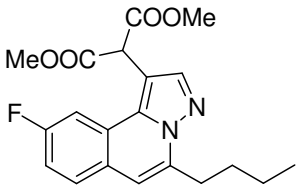
Dimethyl 2-(5-butyl-8-fluoropyrazolo[5,1-*a*]isoquinolin-1-yl)malonate **3g**. White solid; melting point: 69.9-71.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 0.97-1.01 (m, 3H), 1.48-1.53 (m, 2H), 1.77-1.89 (m, 2H), 3.13-3.17 (m, 2H), 3.81 (s, 6H), 5.37 (s, 1H), 6.78 (s, 1H), 7.23-7.33 (m, 2H), 8.14-8.19 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 22.6, 28.9, 30.8, 49.7, 53.2, 105.6, 109.5, 111.7 (d, $^2J_{CF}$ = 22 Hz), 115.2 (d, $^2J_{CF}$ = 23 Hz), 120.3, 125.3 (d, $^3J_{CF}$ = 9 Hz), 132.1 (d, $^3J_{CF}$ = 9 Hz), 135.1, 140.9, 141.5, 161.8 (d, $^1J_{CF}$ = 247 Hz), 168.4; HRMS calcd for $C_{20}H_{22}FN_2O_4$: (M + H^+) 373.1558, found: 373.1545.



Dimethyl 2-(9-fluoro-5-phenylpyrazolo[5,1-*a*]isoquinolin-1-yl)malonate **3h**. White solid; melting point: 129.3-130.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 3.83 (s, 6H), 5.38 (s, 1H), 7.02 (s, 1H), 7.29-7.33 (m, 1H), 7.46-7.53 (m, 3H), 7.72-7.81 (m, 3H), 7.89-7.91 (m, 1H), 8.14 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 49.5, 53.3, 106.8, 108.8 (d, $^{2}J_{CF}$ = 24 Hz), 112.6, 116.8 (d, $^{2}J_{CF}$ = 24 Hz), 125.2 (d, $^{3}J_{CF}$ = 10 Hz), 126.7, 128.5, 129.5, 129.8 (d, $^{3}J_{CF}$ = 9 Hz), 133.5, 135.1, 135.2, 138.1, 141.8, 161.6 (d, $^{1}J_{CF}$ = 247 Hz), 168.3; HRMS calcd for $C_{22}H_{18}FN_2O_4$: ($M + H^+$) 393.1245, found: 393.1233.

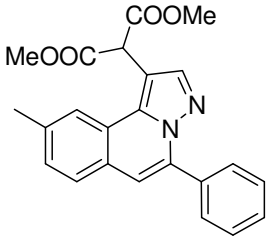


Dimethyl 2-(5-cyclopropyl-9-fluoropyrazolo[5,1-*a*]isoquinolin-1-yl)malonate **3i**. White solid; melting point: 120.9-122.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 0.86-0.91 (m, 2H), 1.16-1.21 (m, 2H), 2.61-2.68 (m, 1H), 3.82 (s, 6H), 5.36 (s, 1H), 6.67 (s, 1H), 7.24-7.28 (m, 1H), 7.62-7.66 (m, 1H), 7.84-7.86 (m, 1H), 8.20 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 6.9, 11.5, 49.4, 53.2, 106.6, 107.2, 108.6 (d, $^{2}J_{CF}$ = 24 Hz), 116.5 (d, $^{2}J_{CF}$ = 23 Hz), 124.3 (d, $^{3}J_{CF}$ = 9 Hz), 126.6, 129.1 (d, $^{3}J_{CF}$ = 9 Hz), 134.7, 140.3, 141.5, 161.2 (d, $^{1}J_{CF}$ = 245 Hz), 168.3; HRMS calcd for $C_{19}H_{18}FN_2O_4$: ($M + H^+$) 357.1245, found: 357.1231.

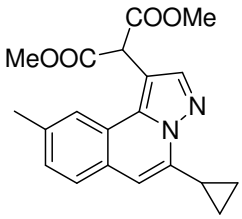


Dimethyl 2-(5-butyl-9-fluoropyrazolo[5,1-*a*]isoquinolin-1-yl)malonate **3j**. White solid; melting point: 106.1-107.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 0.98-1.01 (m, 3H), 1.48-1.53 (m, 2H), 1.81-1.87 (m, 2H), 3.13-3.17 (m, 2H), 3.82 (s, 6H), 5.36 (s, 1H), 6.83 (s, 1H), 7.26-7.30 (m, 1H), 7.65-7.69 (m, 1H), 7.83-7.86 (m, 1H), 8.15 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 22.6, 28.9, 30.7, 49.4, 53.2, 106.5, 108.5 (d, $^{2}J_{CF}$ = 24 Hz), 109.6, 116.5 (d, $^{2}J_{CF}$ = 23 Hz), 124.6 (d, $^{3}J_{CF}$ = 9 Hz), 126.6, 129.0 (d, ^{3}J

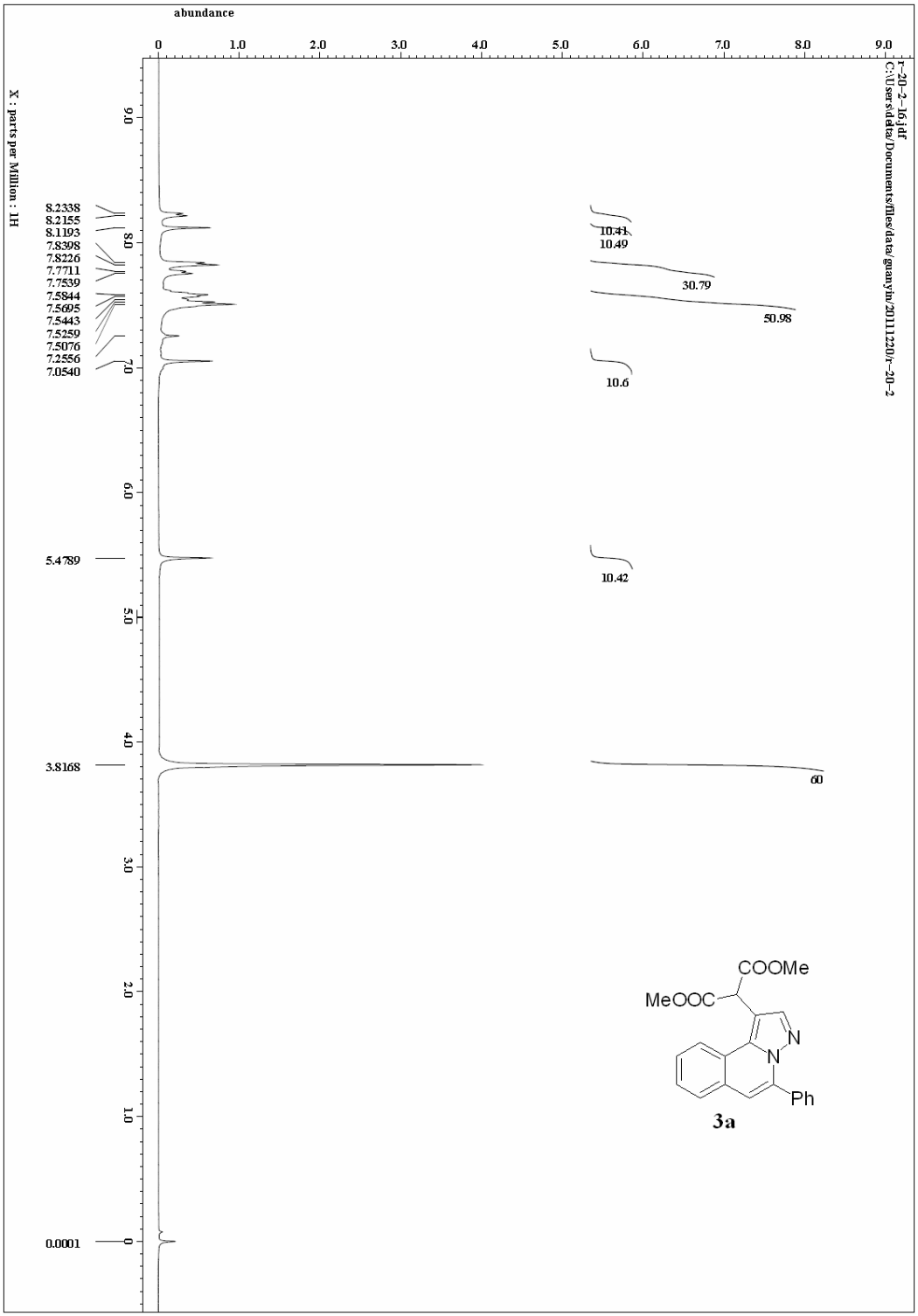
$_{CF}$ = 9 Hz), 134.7, 139.0, 141.3, 161.1 (d, $^{1}J_{CF}$ = 245 Hz), 168.3; HRMS calcd for $C_{20}H_{22}FN_2O_4$: (M + H^+) 373.1558, found: 373.1576.



Dimethyl 2-(9-methyl-5-phenylpyrazolo[5,1-*a*]isoquinolin-1-yl)malonate **3k**. Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): 2.55 (s, 3H), 3.81 (s, 6H), 5.49 (s, 1H), 7.00 (s, 1H), 7.38 (d, *J* = 7.8 Hz, 1H), 7.48-7.50 (m, 3H), 7.63 (d, *J* = 8.3 Hz, 1H), 7.81 (d, *J* = 6.9 Hz, 2H), 8.00 (s, 1H), 8.09 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.1, 49.9, 53.1, 106.1, 113.2, 122.8, 124.3, 127.5, 127.9, 128.4, 129.3, 129.5, 129.6, 133.9, 135.6, 137.5, 137.9, 141.5, 168.5; HRMS calcd for $C_{23}H_{21}N_2O_4$: (M + H^+) 389.1496, found: 389.1490.



Dimethyl 2-(5-cyclopropyl-9-methylpyrazolo[5,1-*a*]isoquinolin-1-yl)malonate **3l**. White solid; melting point: 125.0-126.6 ℃; ^{1}H NMR (400 MHz, $CDCl_3$): 0.86-0.90 (m, 2H), 1.13-1.19 (m, 2H), 2.60-2.68 (m, 1H), 3.77 (s, 3H), 3.81 (s, 6H), 5.47 (s, 1H), 6.65 (s, 1H), 7.33 (d, *J* = 7.8 Hz, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.95 (s, 1H), 8.16 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 6.8, 11.5, 22.0, 49.8, 53.1, 106.0, 107.6, 122.7, 123.6, 126.9, 127.8, 129.4, 135.2, 136.7, 140.0, 141.2, 168.6; HRMS calcd for $C_{20}H_{21}N_2O_4$: (M + H^+) 353.1496, found: 353.1487.



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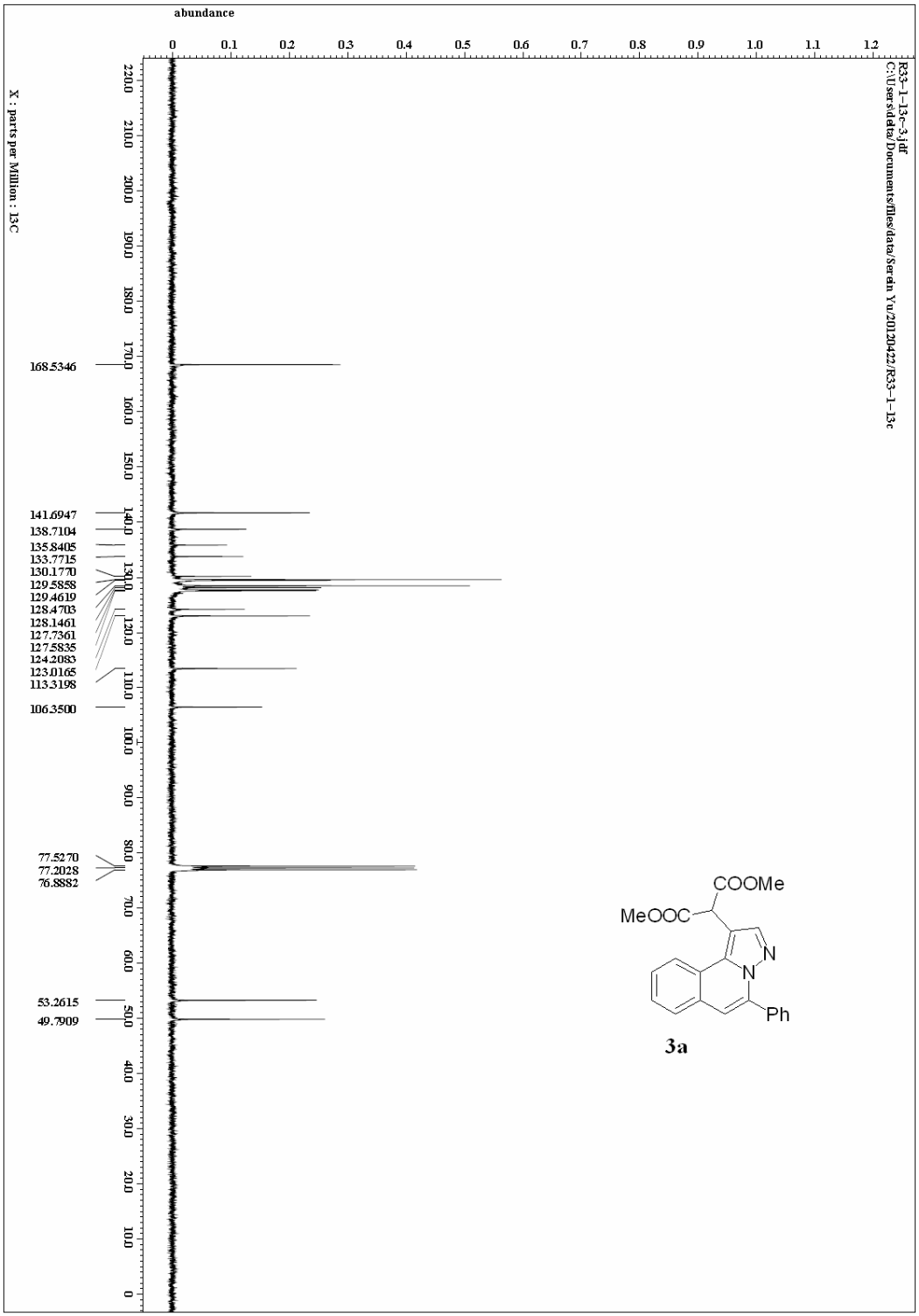
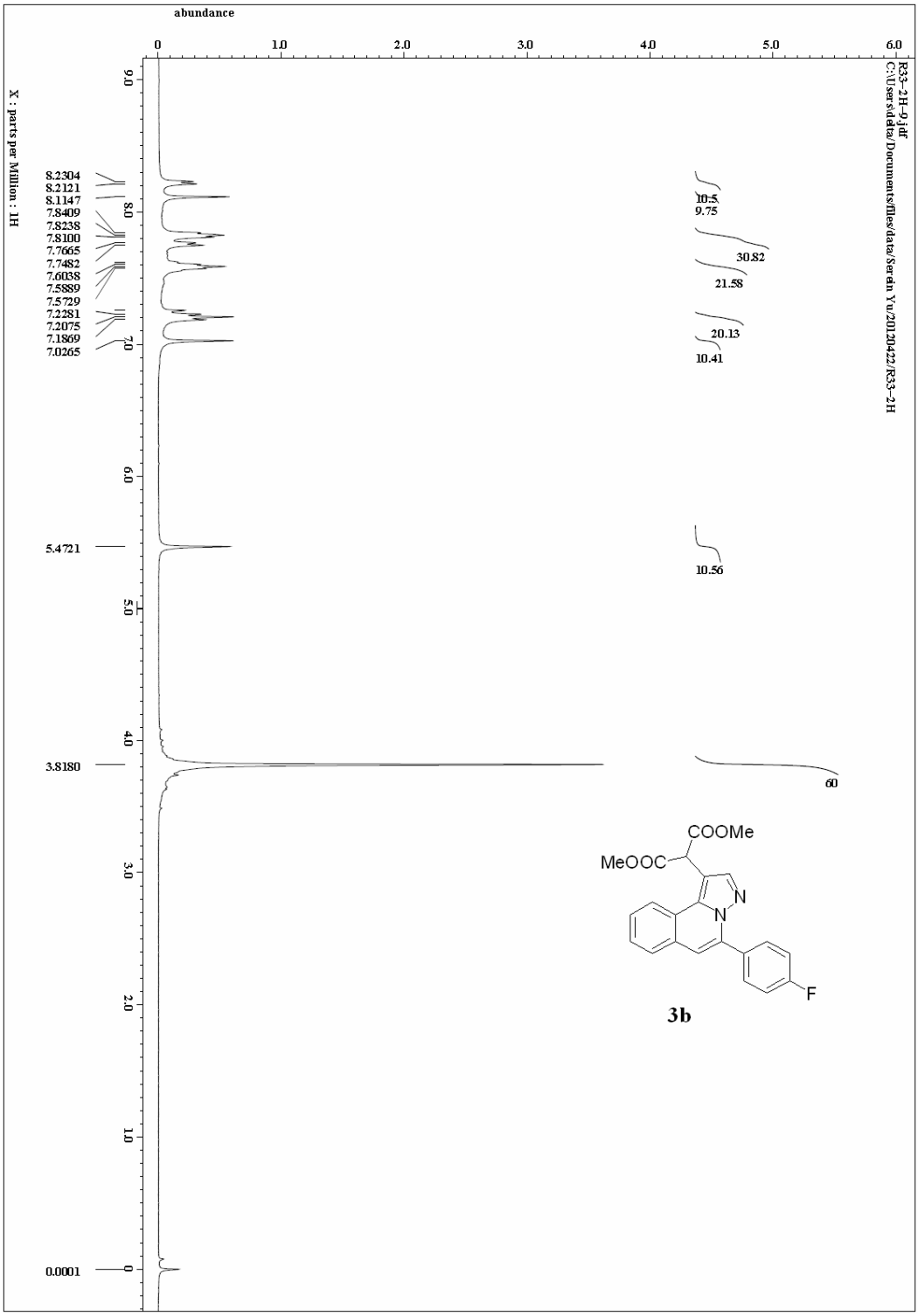


3a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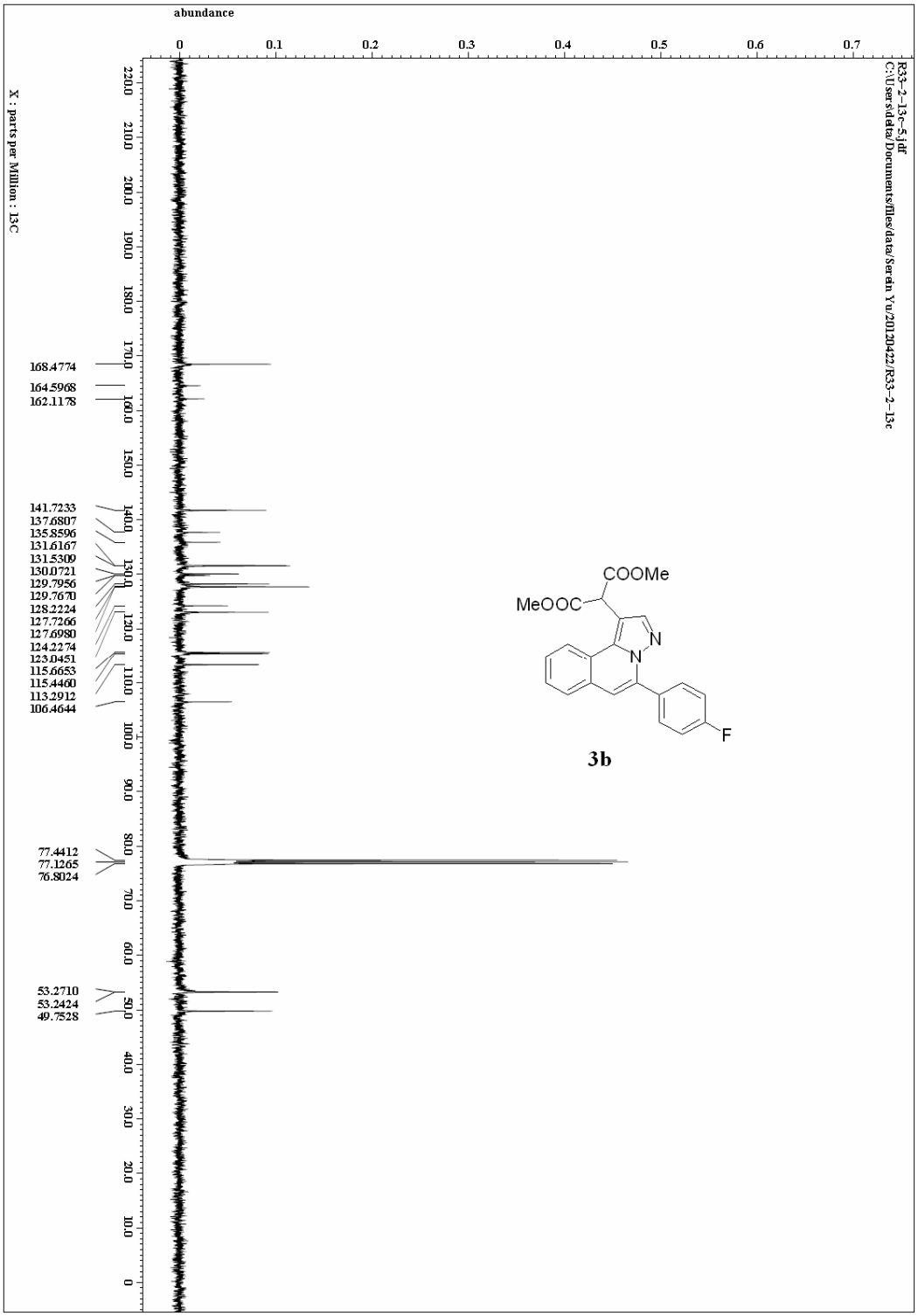
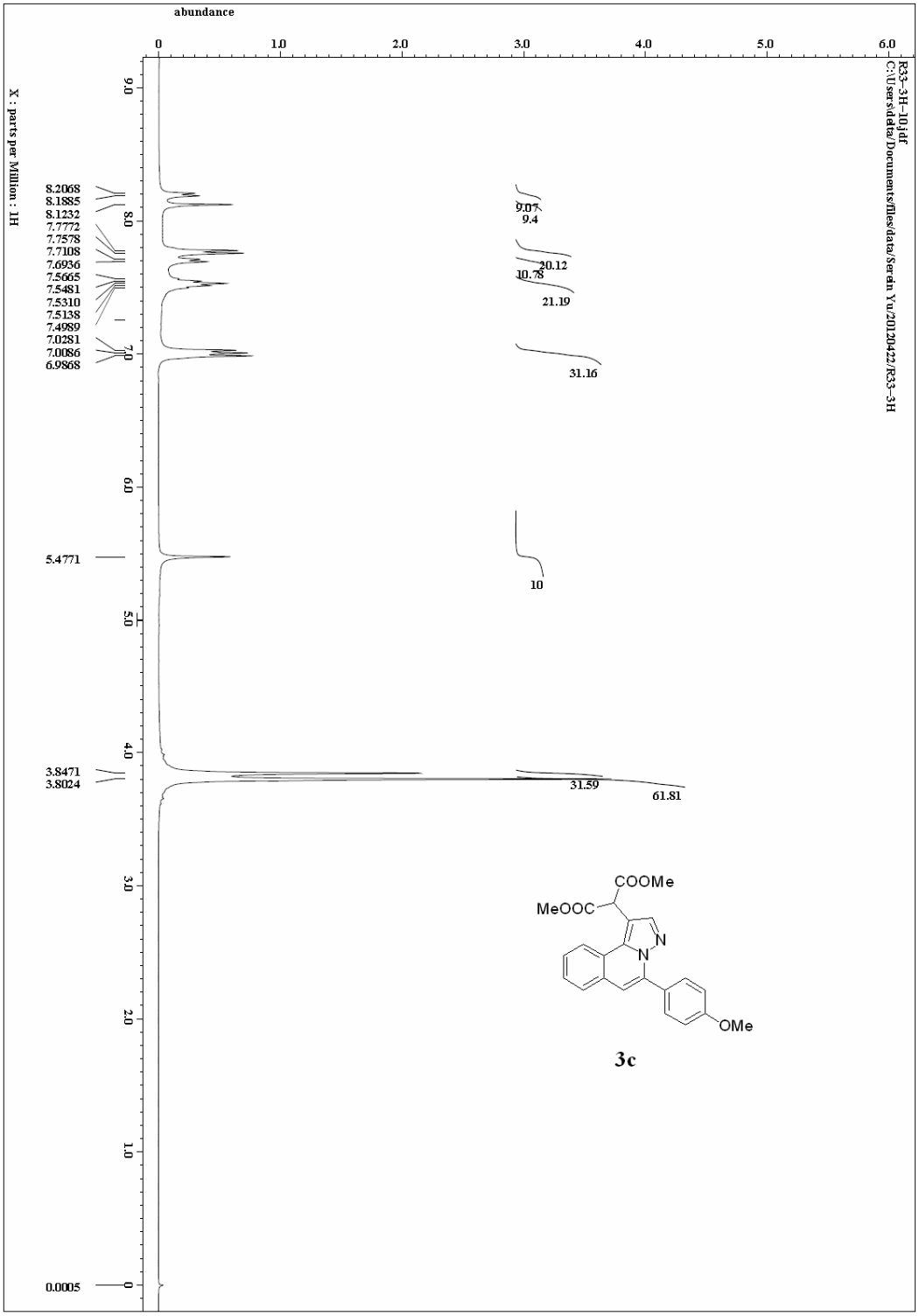
3b





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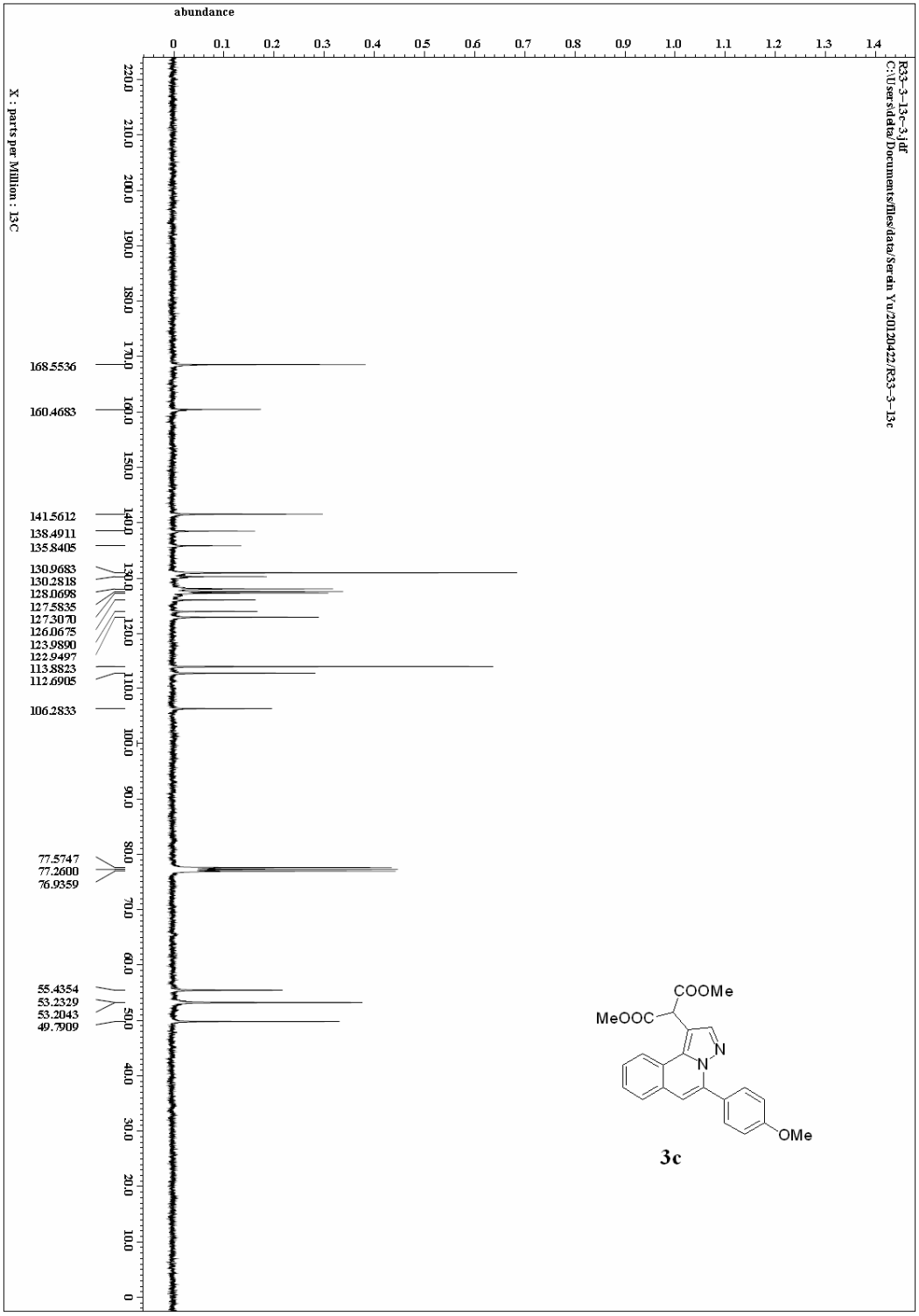

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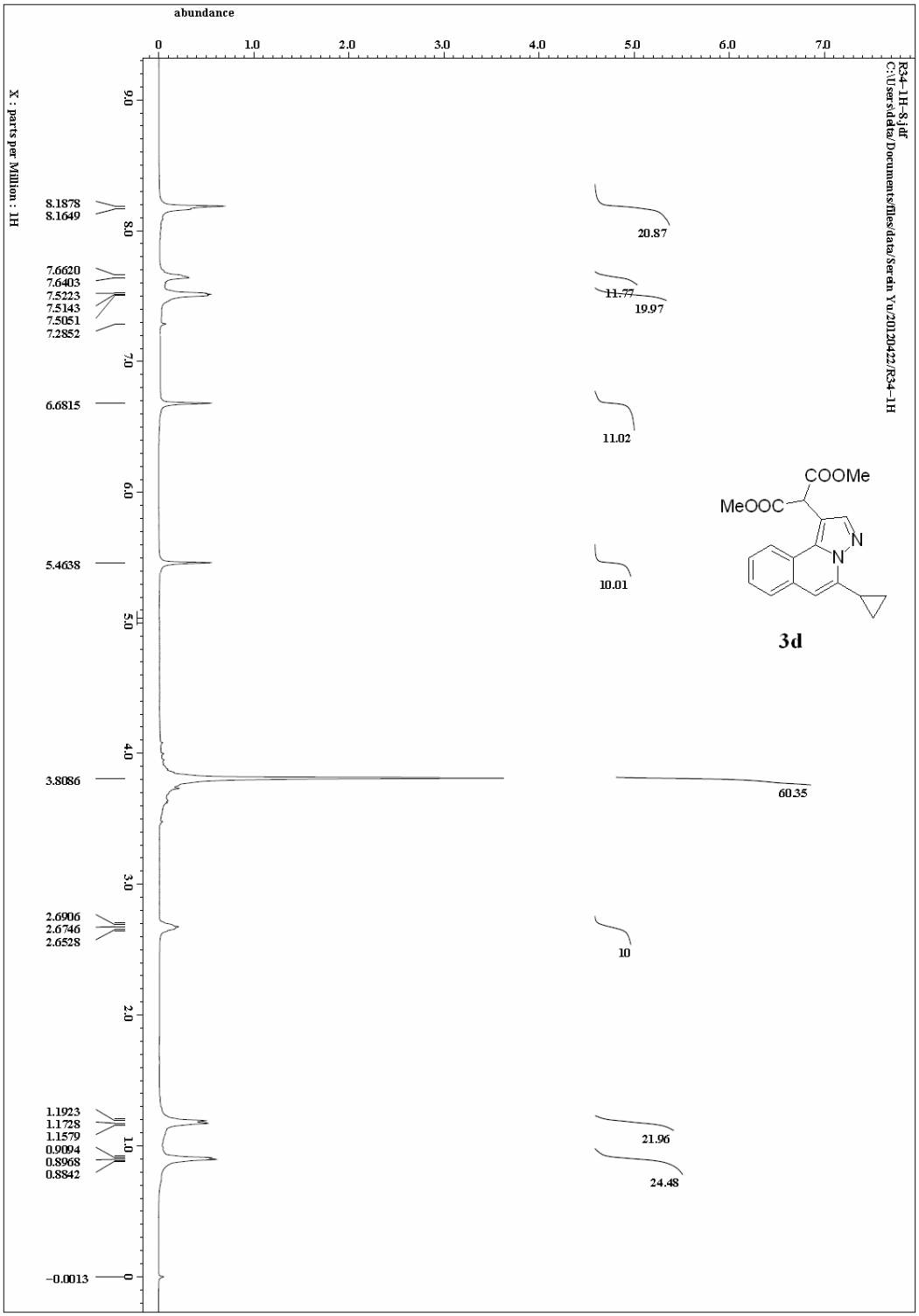
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X : parts per Million : 1H
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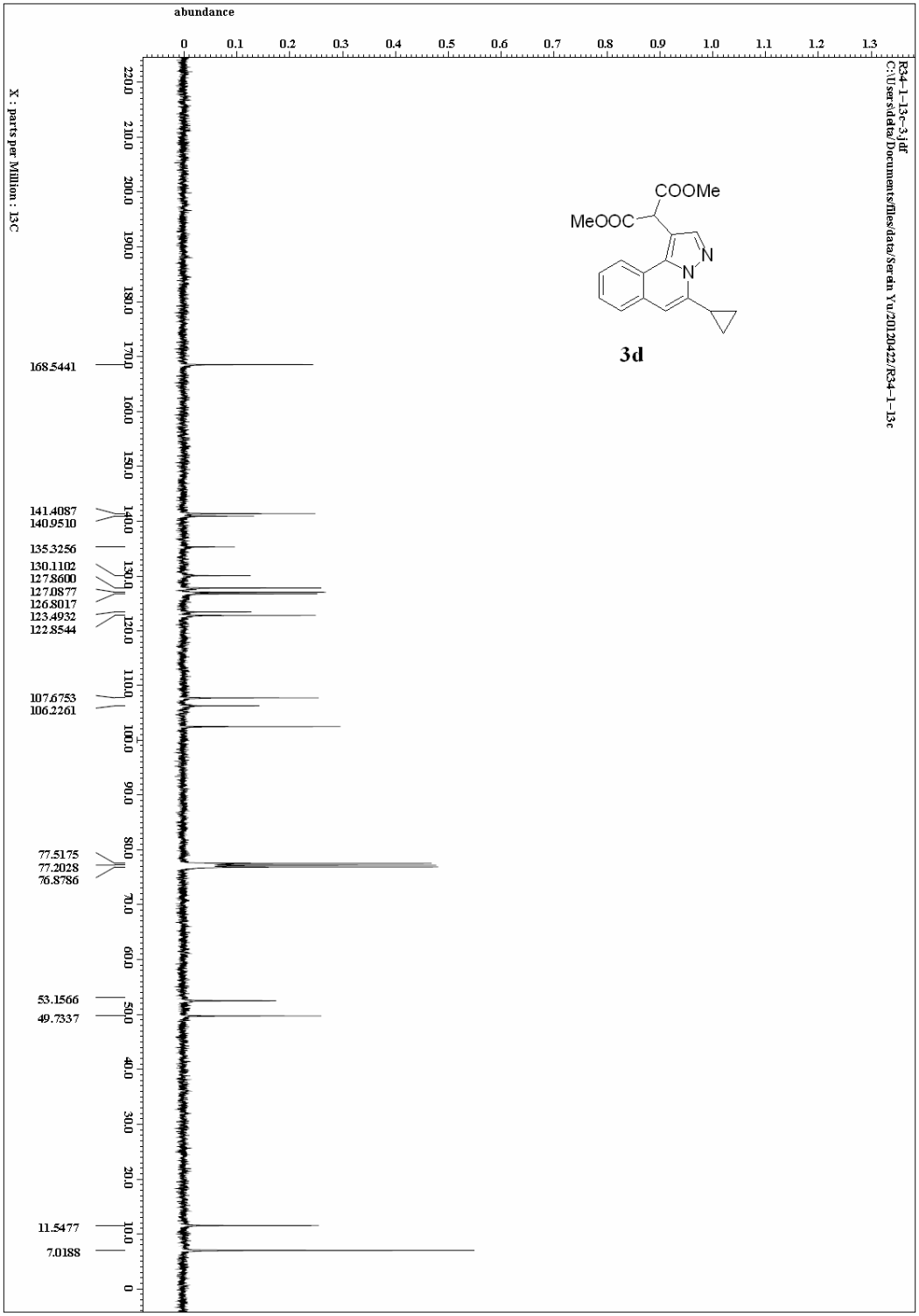
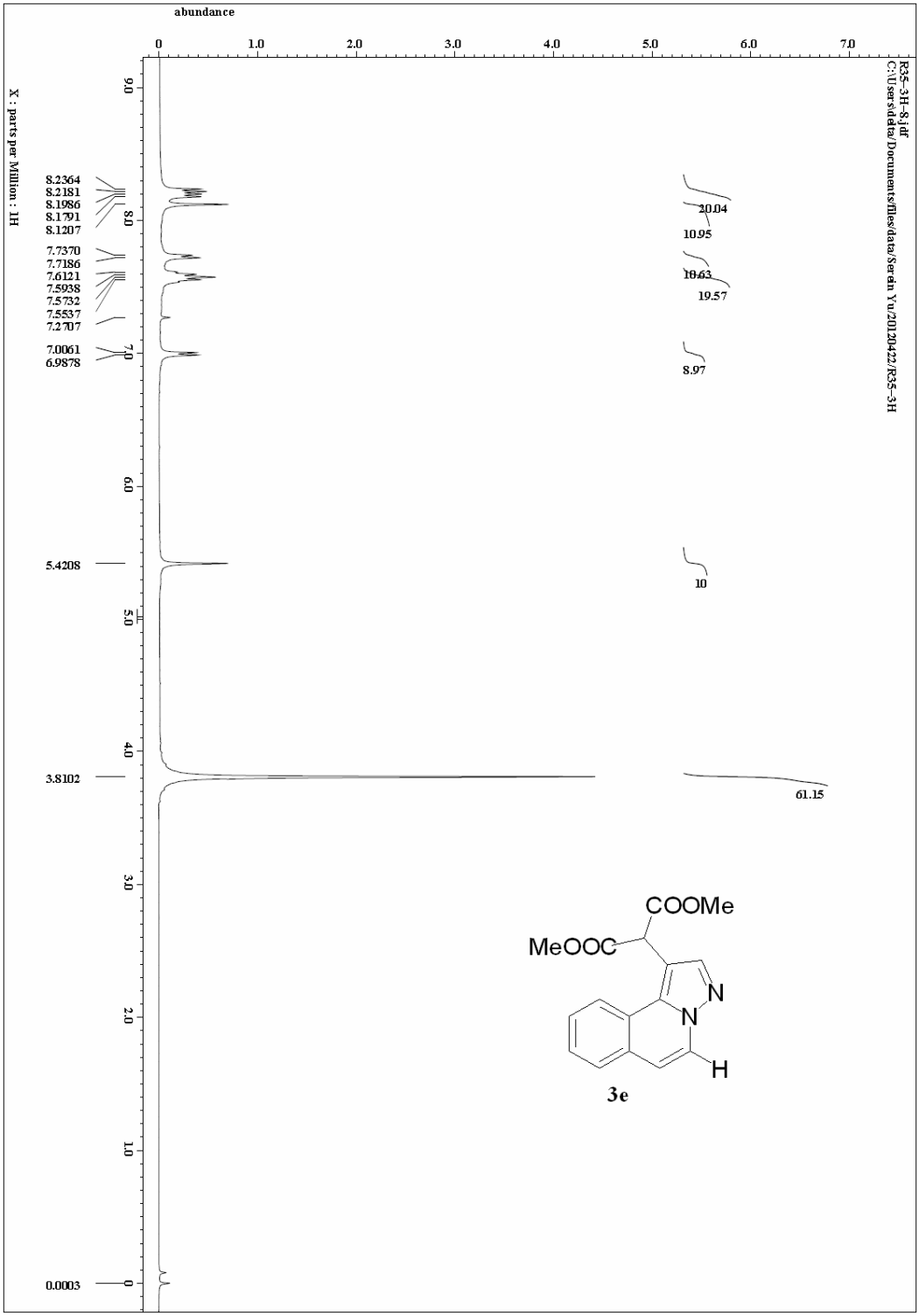
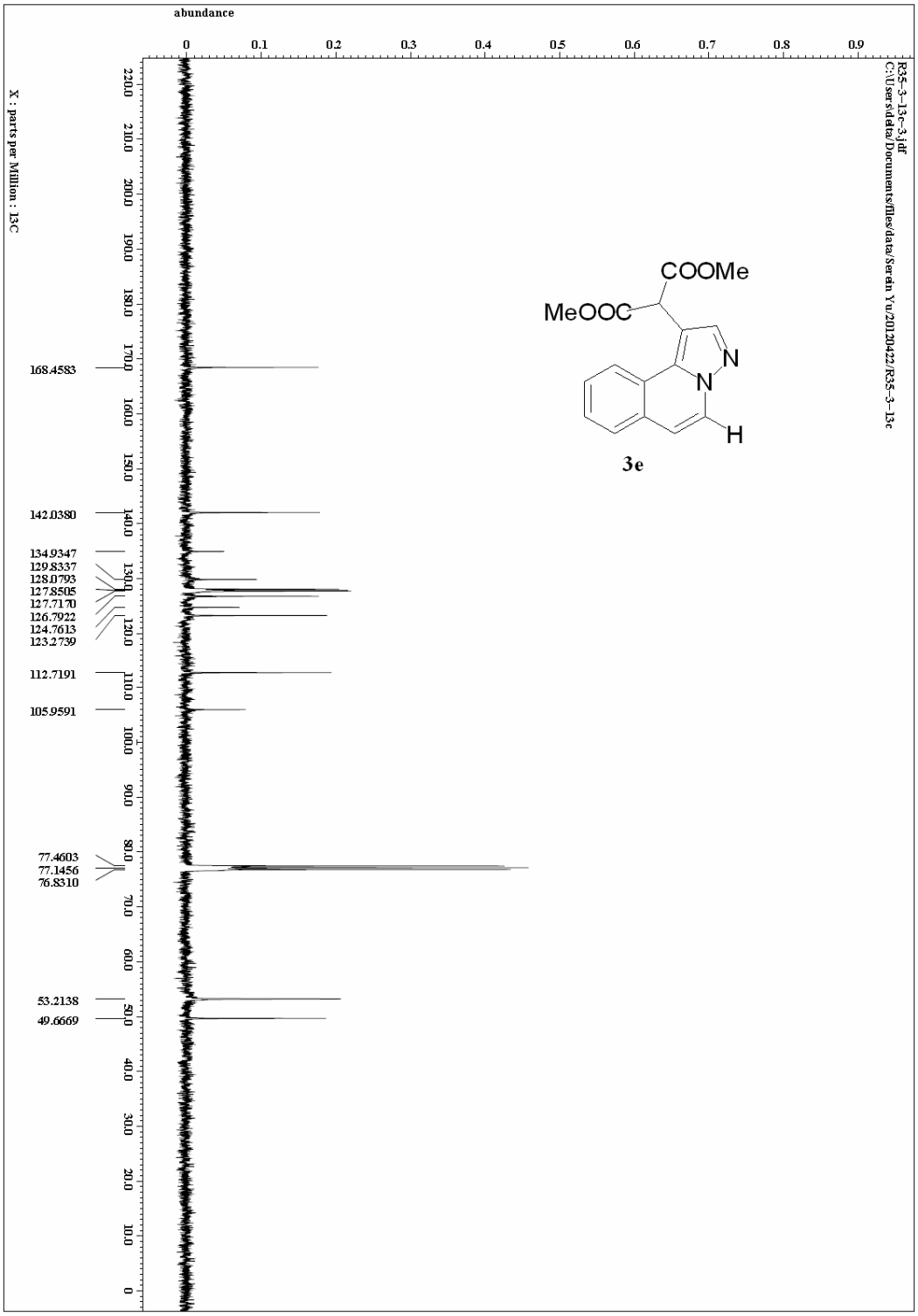
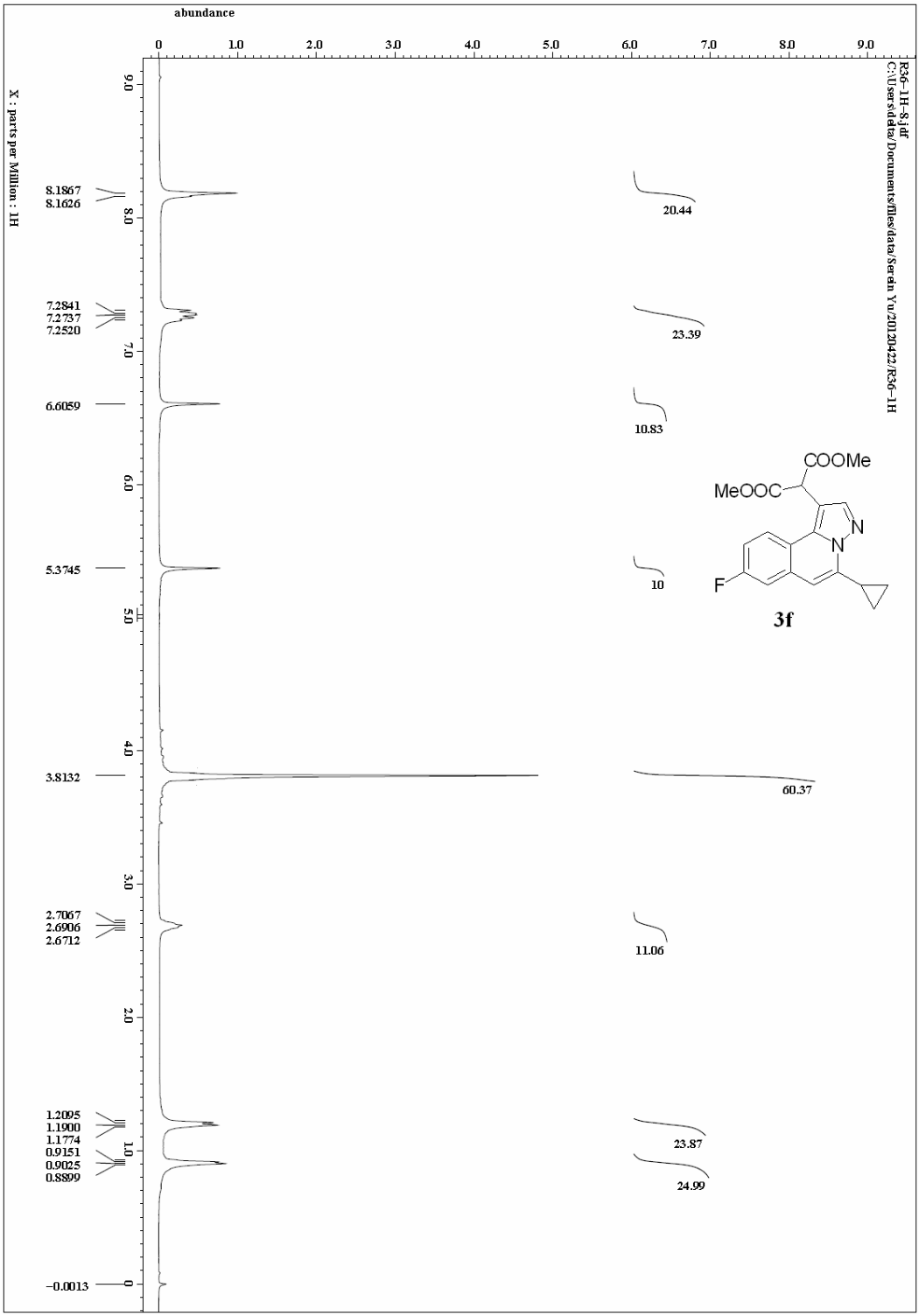
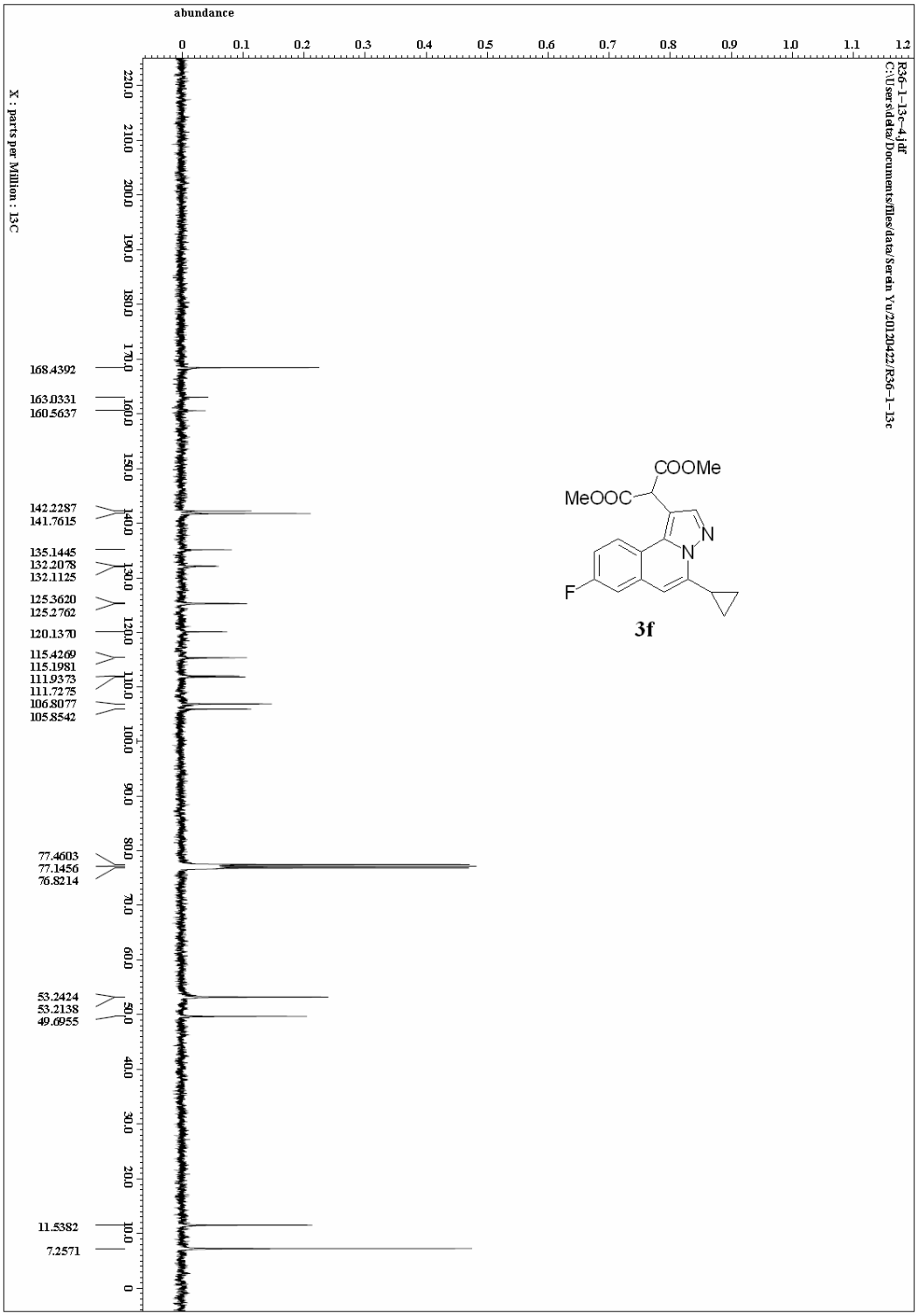
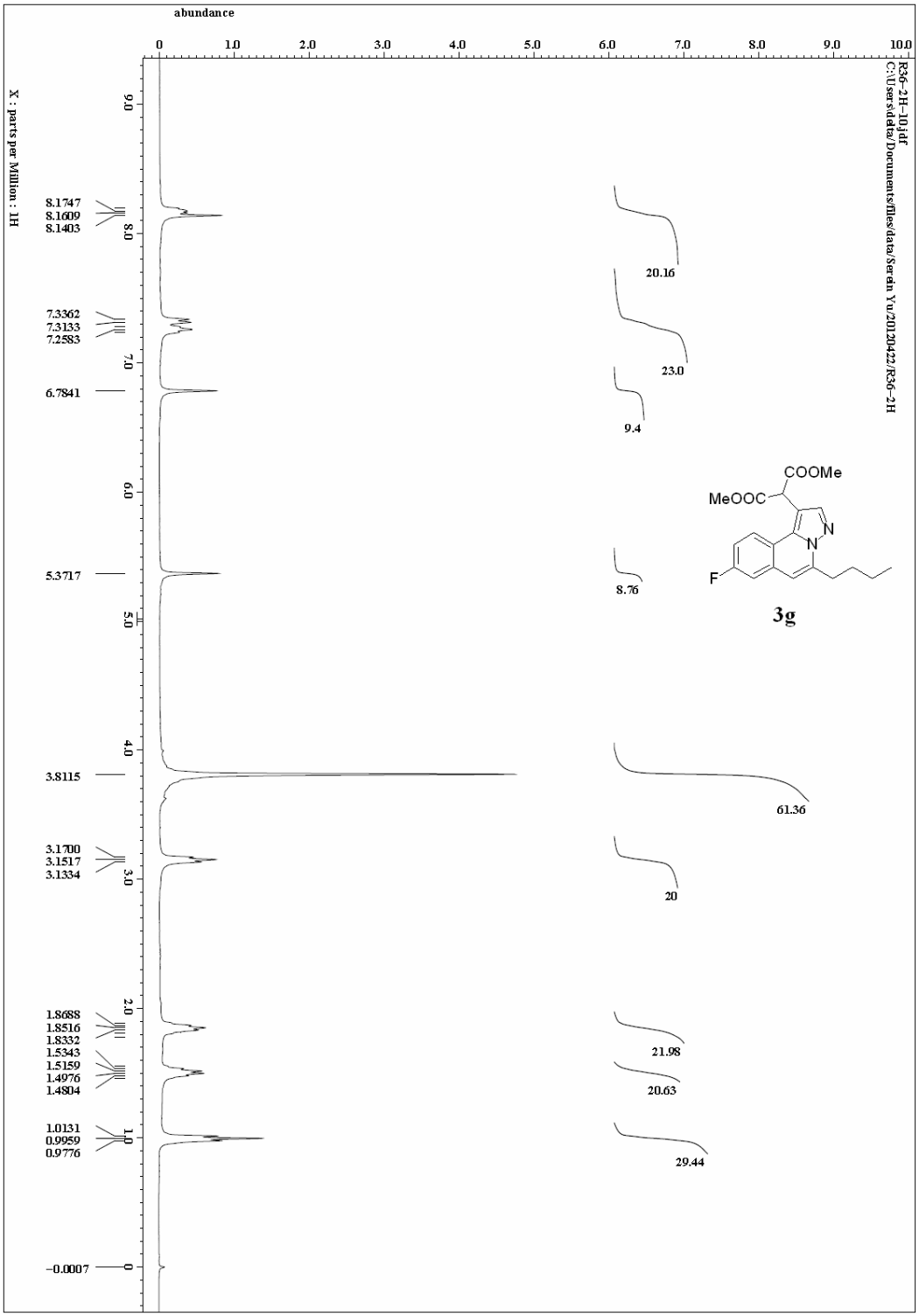


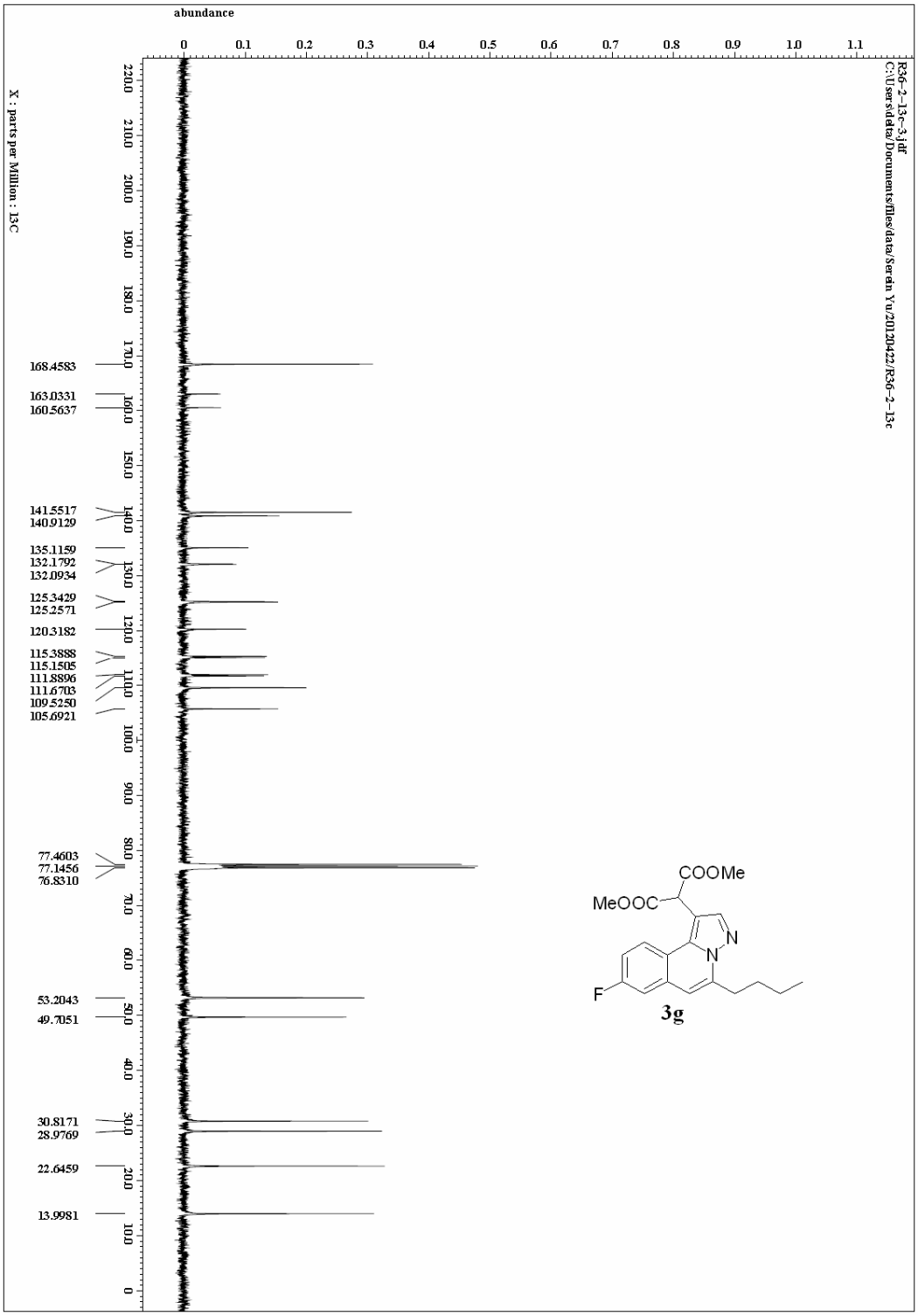


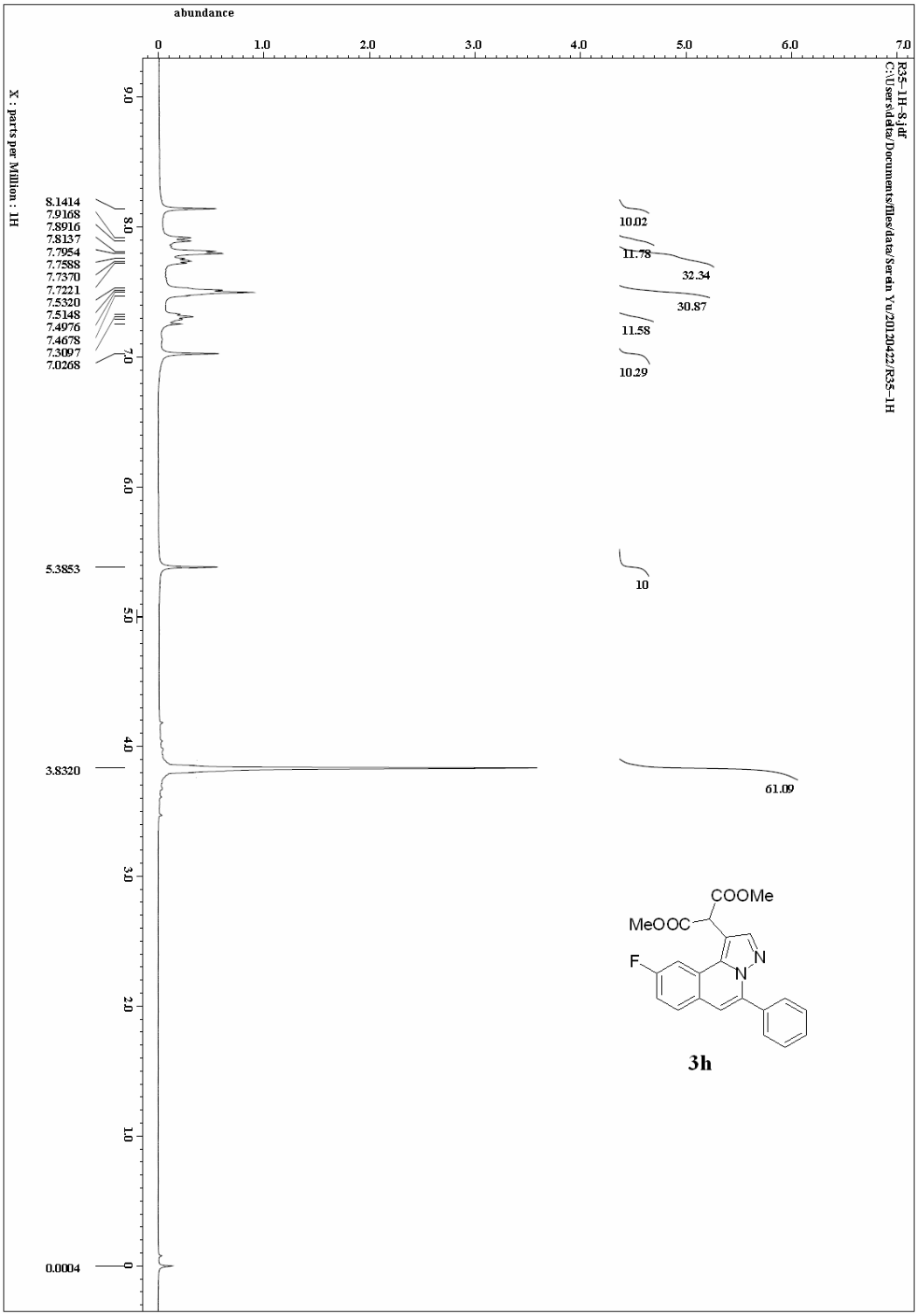


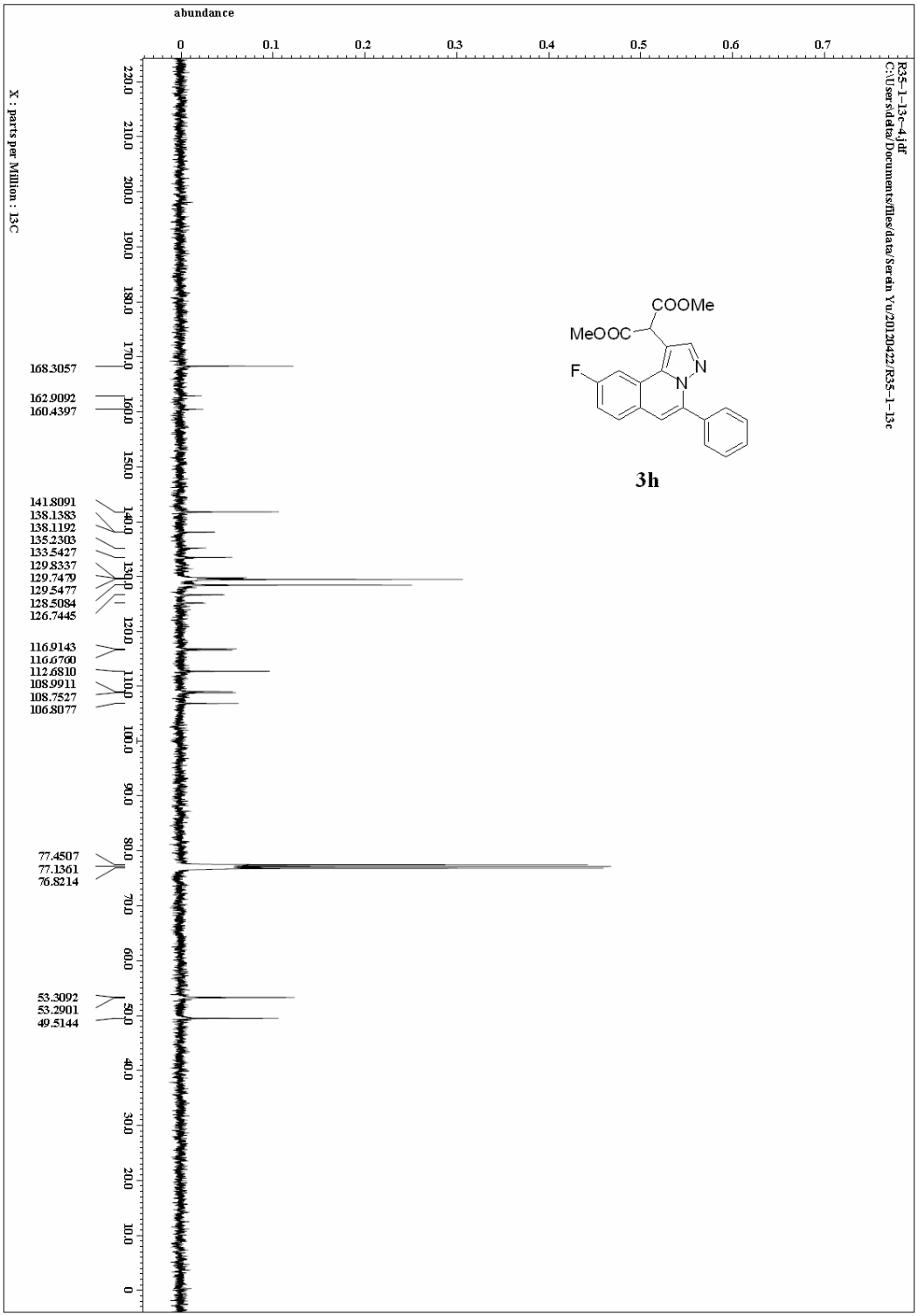

abundance
X : parts per Million : 1H
R36-1H-8.1.dff
C:\Users\data\Documents\files\data\Seredin Yu\20120422\R36-1H
8.1867
8.1626
7.2841
7.2737
7.2520
6.6059
5.3745
3.8132
2.7067
2.6906
2.6712
1.2095
1.1900
1.1774
0.9151
0.9025
0.8899
−0.0013
20.44
23.39
10.83
10
60.37
11.06
23.87
24.99
COOMe
MeOOC
N
F
3f

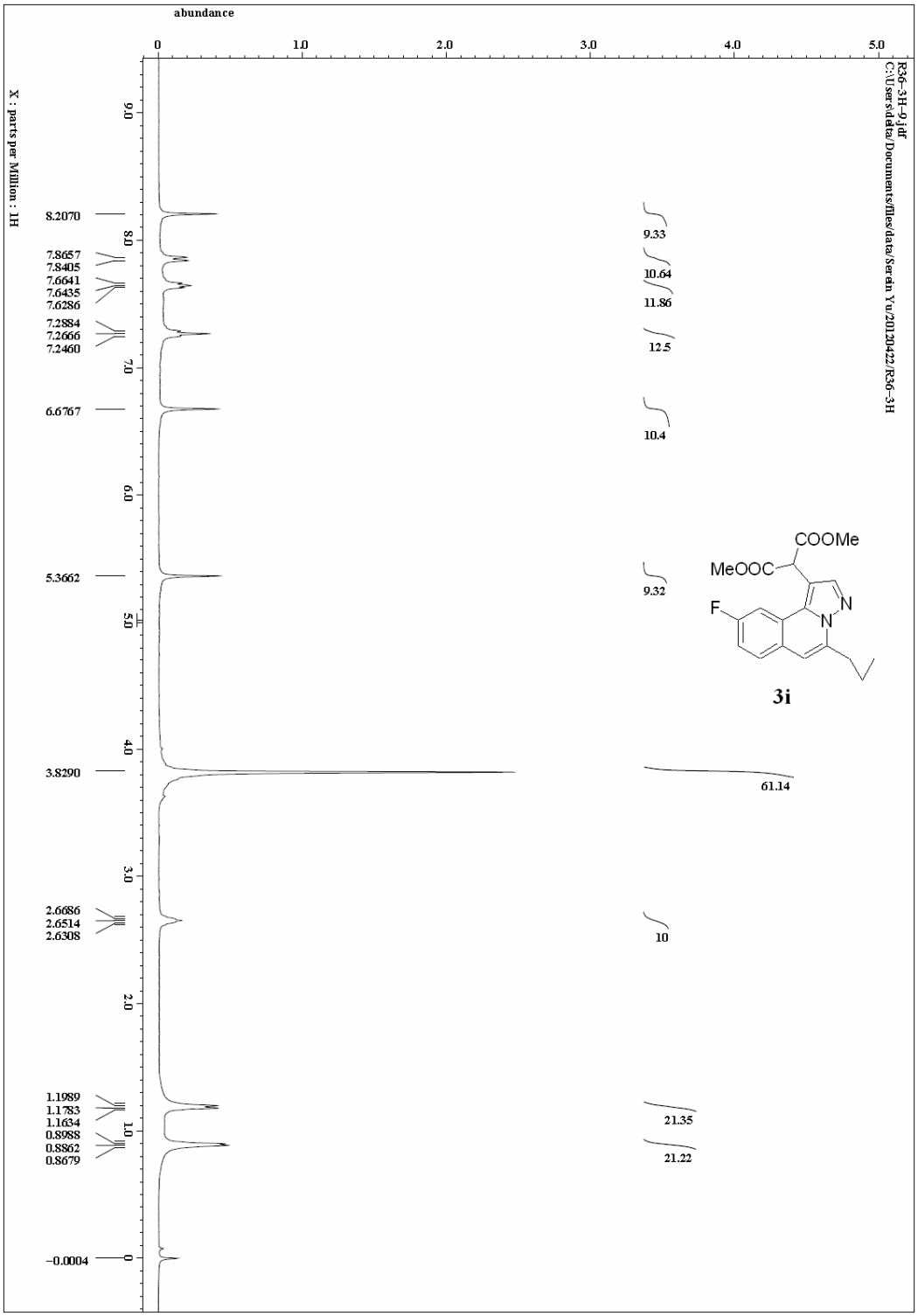



abundance
X : parts per Million : 1H
R36-2H-10.jdf
C:\Users\data\Documents\fliesydata\Serein Yu\20120422\R36-2H
8.1747
8.1609
8.1403
7.3362
7.3133
7.2583
6.7841
5.3717
3.8115
3.1700
3.1517
3.1334
1.8688
1.8516
1.8332
1.5343
1.5159
1.4976
1.4804
1.0131
0.9959
0.9776
-0.0007
20.16
23.0
9.4
8.76
61.36
20
21.98
20.63
29.44
COOMe
MeOOC
N
N
F
3g

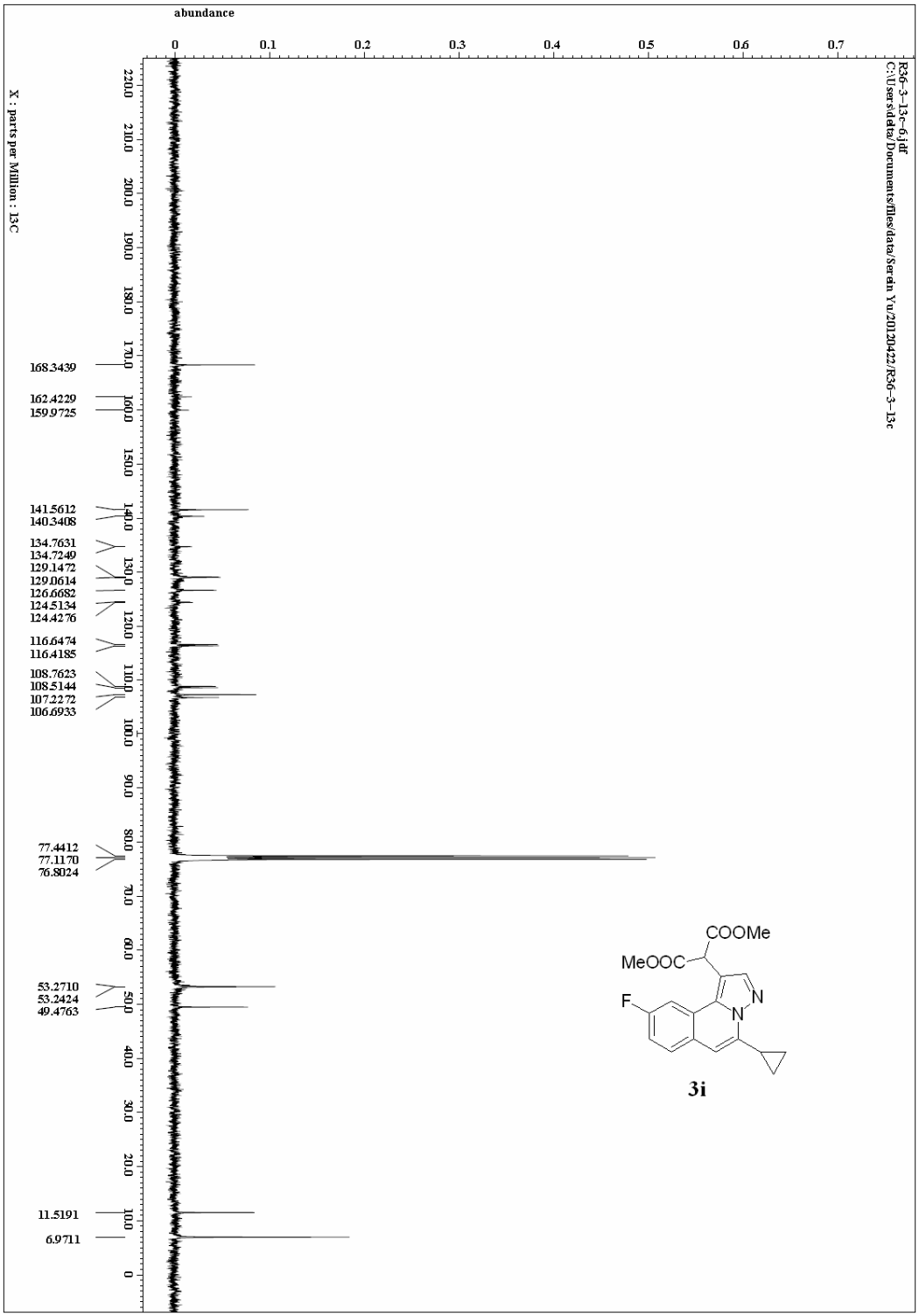



abundance
X : parts per Million : 1H
R35-1H-8.1.dff
C:\Users\data\Documents\files\data\Serein Yu\20120422\R35-1H
8.1414
7.9168
7.8916
7.8137
7.7954
7.7588
7.7370
7.7221
7.5320
7.5148
7.4976
7.4678
7.3097
7.0268
5.3853
3.8320
0.0004
10.02
11.78
32.34
30.87
11.58
10.29
10
61.09
COOMe
MeOOC
F
N
N
3h

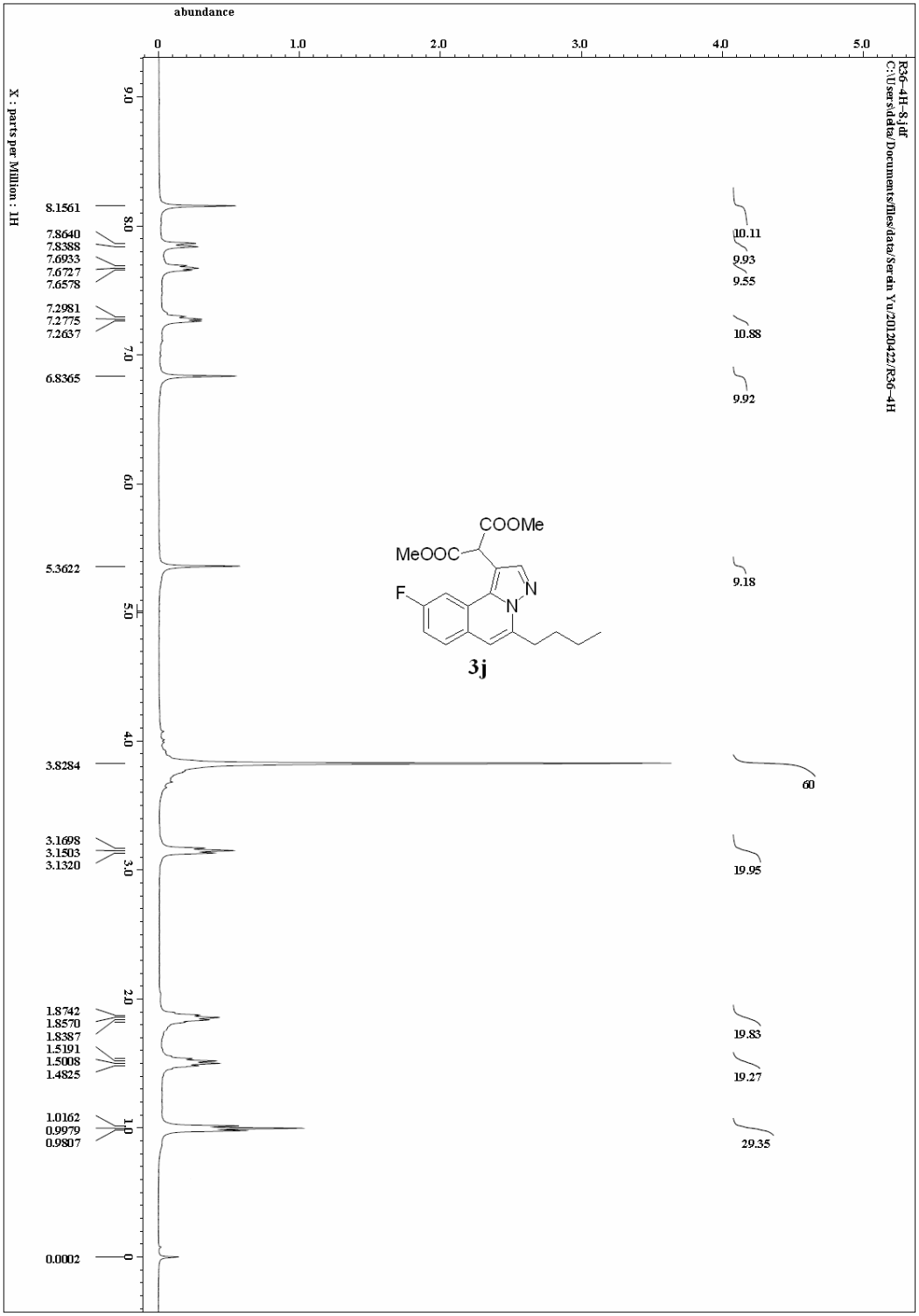


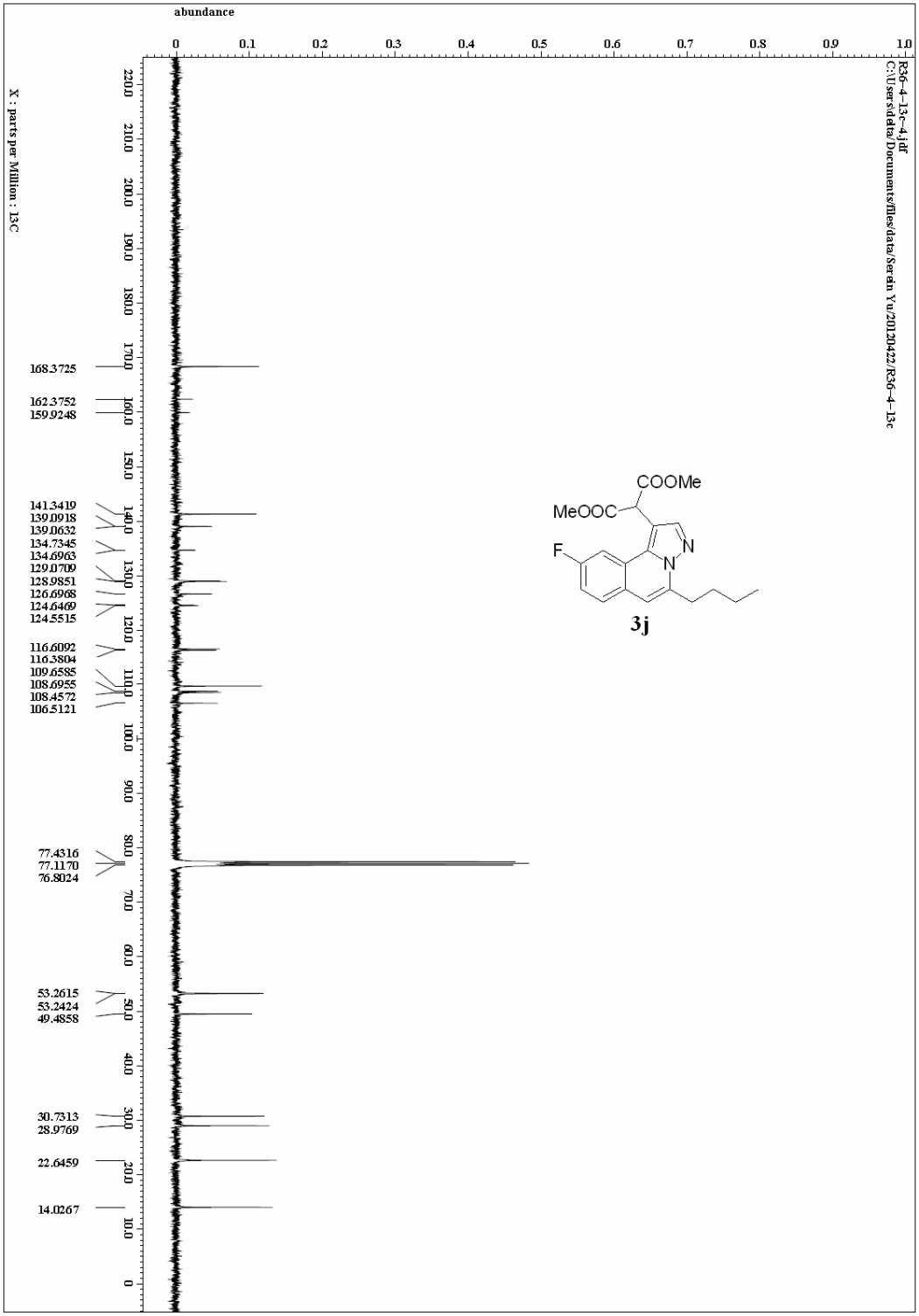


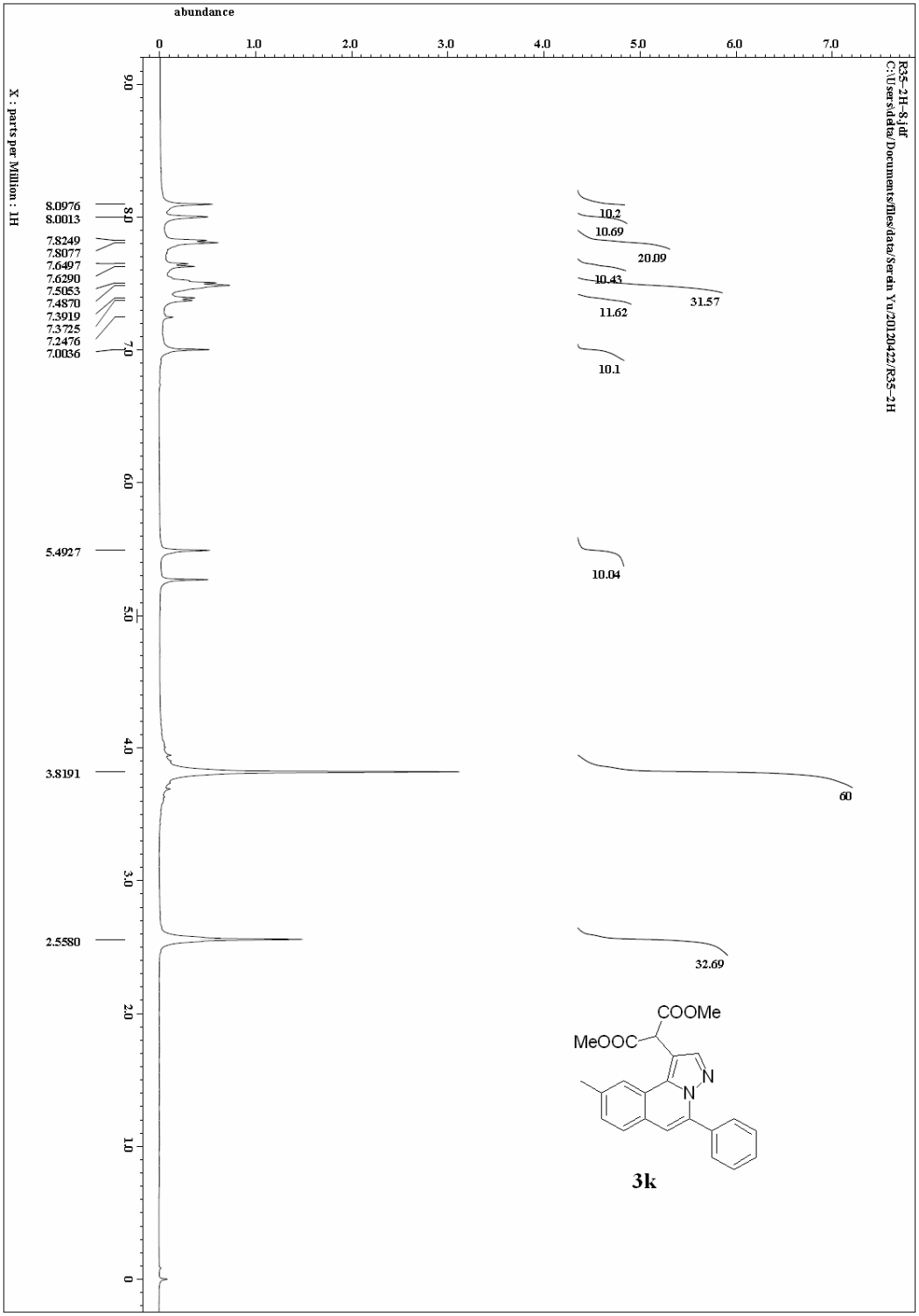
3i


abundance
X : parts per Million : 13C
R36-3--13c-6.jdf
C:\Users\data\Documents\files\data\Seren Yu\20120422\R36-3--13c
168.3439
162.4229
159.9725
141.5612
140.3408
134.7631
134.7249
129.1472
129.0614
126.6682
124.5134
124.4276
116.6474
116.4185
108.7623
108.5144
107.2272
106.6933
77.4412
77.1170
76.8024
53.2710
53.2424
49.4763
11.5191
6.9711
COOMe
MeOOC
F
N
N

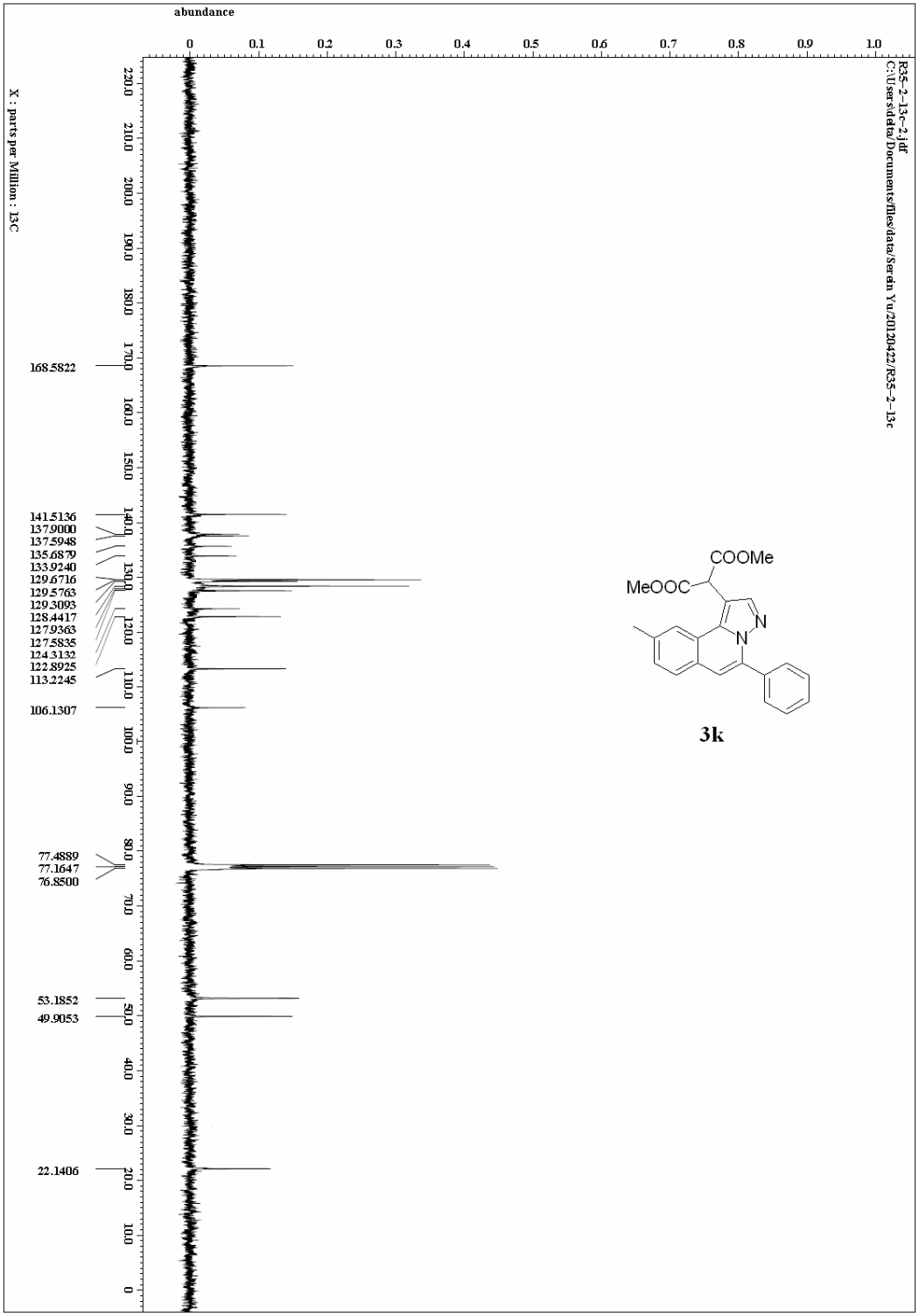
3i



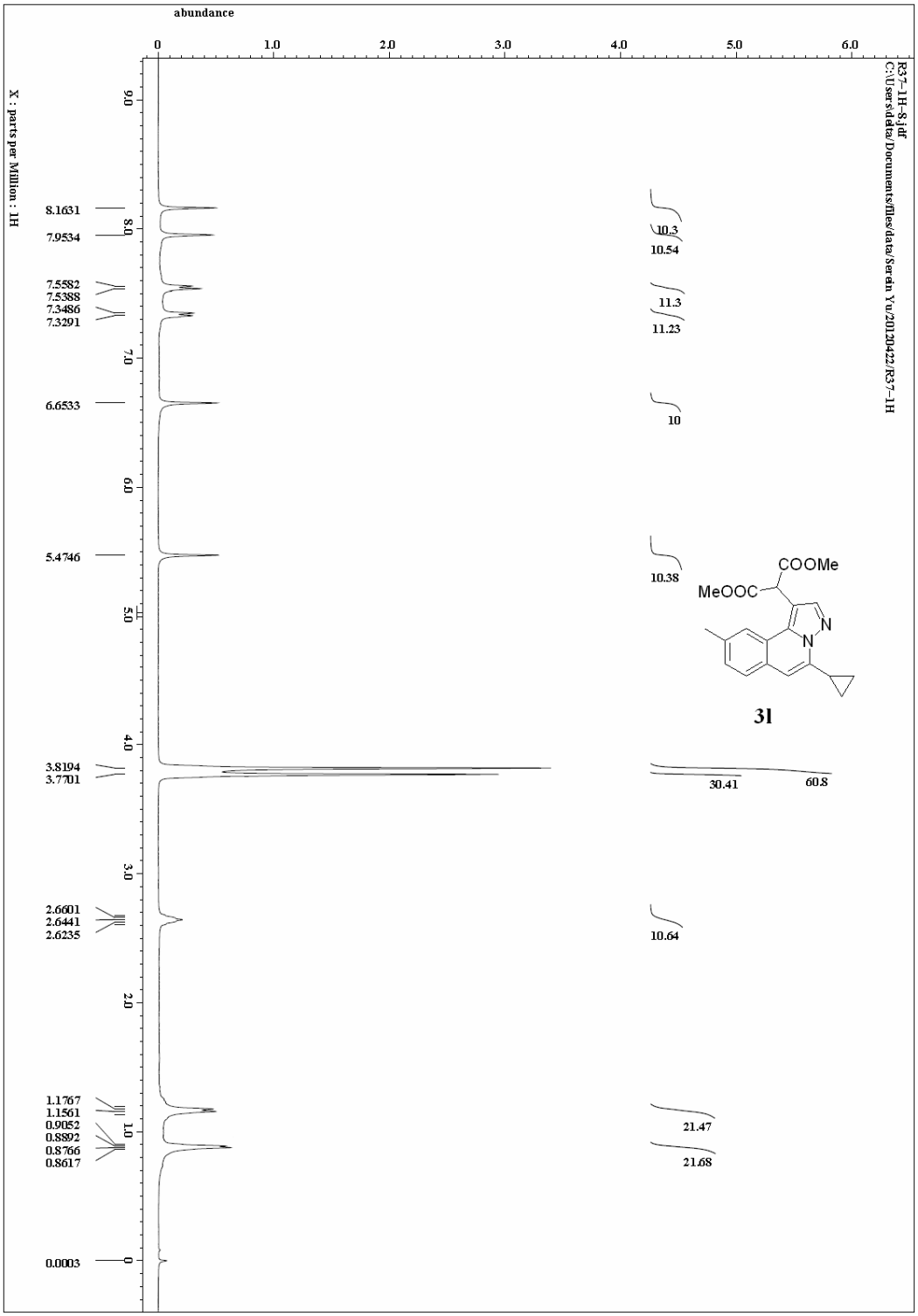

abundance
X : parts per Million : 13C
R36-4-13c-4.jdf
C:\Users\data\Documents\flexdata\Serein Yu\20120422\R36-4-13c
168.3725
162.3752
159.9248
141.3419
139.0918
139.0632
134.7345
134.6963
129.0709
128.9851
126.6968
124.6469
124.5515
116.6092
116.3804
109.6585
108.6955
108.4572
106.5121
77.4316
77.1170
76.8024
53.2615
53.2424
49.4858
30.7313
28.9769
22.6459
14.0267
COOMe
MeOOC
F
N
N
3j



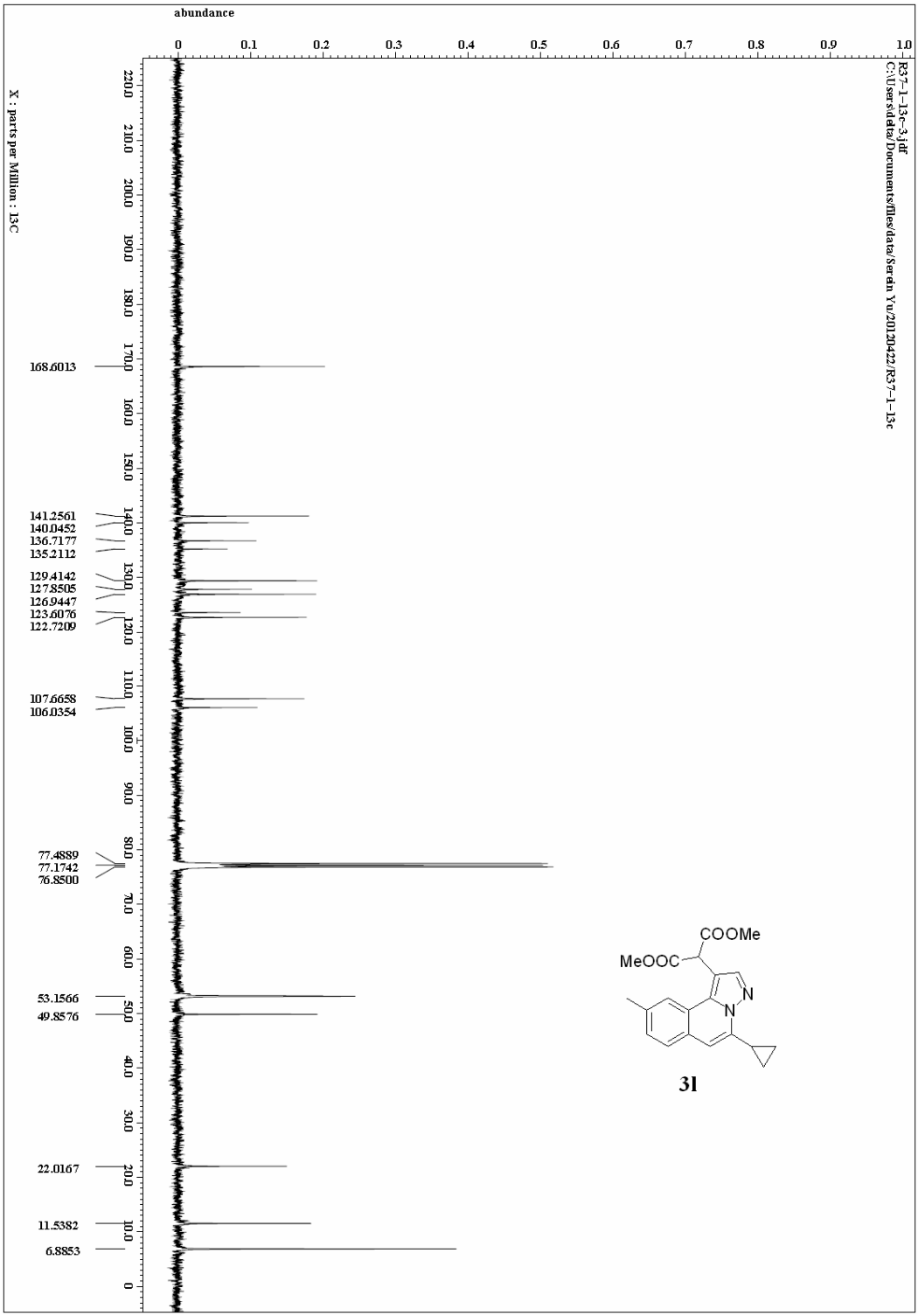
3k



3k


abundance
X : parts per Million : 1H
C:\Users\data\Documents\fliesydata\Serein Yu\20120422\R37-1H
R37-1H-8.1.dff
8.1631
7.9534
7.5582
7.5388
7.3486
7.3291
6.6533
5.4746
3.8194
3.7701
2.6601
2.6441
2.6235
1.1767
1.1561
0.9052
0.8892
0.8766
0.8617
0.0003
10.3
10.54
11.3
11.23
10
10.38
30.41
60.8
10.64
21.47
21.68
COOMe
MeOOC
N
N

3l



3l