Electronic Supplementary Information

Gold(I)-Catalyzed 6-*endo-dig* Azide-Yne Cyclization: an Efficient Access to 2*H*-1,3-Oxazines

Geoffroy Hervé Lonca,[a] Ciputra Tejo,[b] Hui Ling Chan,[b] Shunsuke Chiba,*[b] and Fabien Gagosz*[a,c]

[a] Département de Chimie, UMR 7652 and 7653 CNRS, Ecole Polytechnique, 91128 Palaiseau, France.

[b] Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore.

[c] Department of Chemistry and Biomolecular Sciences, University of Ottawa, K1N 6N5, Ottawa, Canada.

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1. General

NMR analysis was performed at room temperature on Bruker AvanceIII 400 spectrometers operating at 400 MHz for ^{1}H spectra and 100 MHz for ^{13}C spectra. Residual solvent peaks of $CDCl_3$ were used as internal references: 7.26 ppm from ^{1}H spectra and 77.00 ppm for ^{13}C NMR. The following abbreviations were used to explain the multiplicities: s = singlet, brs = broad singlet, d = doublet, dd = doublet of doublet, t = triplet, q = quartet, m = multiplet. IR spectra were recorded on a Shimadzu IR Prestige-21 FT-IR Spectrometer. High-resolution mass spectra were obtained with a Q-Tof Premier LC HR mass spectrometer (for ESI characterization) and a JEOL jms-GC mate II HR mass spectrometer (for EI characterization). X-ray crystallography analysis was performed on Bruker X8 APEX X-ray diffractionmeter. Melting points were uncorrected and were recorded on a Buchi B-54 melting point apparatus. Flash column chromatography was performed using Merck silica gel 60 with distilled solvents. Selectfluor® (98%) was purchased from Alfa Aesar.

2. The safety issues for handling of azido compounds[1,2]

2.1. Sodium azide (NaN_3)

Sodium azide is toxic (LD_{50} oral = 27 mg/kg for rats) and can be absorbed through skin. Appropriate gloves are necessary when using it. It decomposes explosively upon heating to above 275 °C. Sodium azide is relatively safe especially in aqueous solution, *unless acidified to form* HN_3, which is volatile and highly toxic.

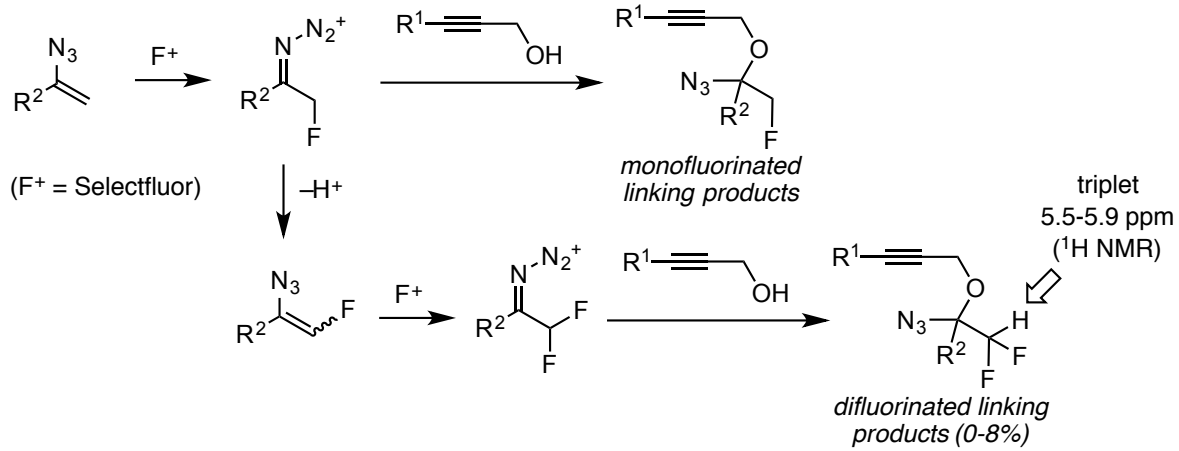
2.2. Organic azides

Organic azides are potentially explosive substances that can decompose with the slight input of energy from external sources (heat, light, pressure, etc). When designing the organic azides used for the project, we keep in mind the following equation. It is noted that this equation takes into account all nitrogen atoms in the organic azide, not just those in the azido group.

$$\frac{N_C + N_O}{N_N} \geq 3 \quad (N: \text{number of the atom})$$

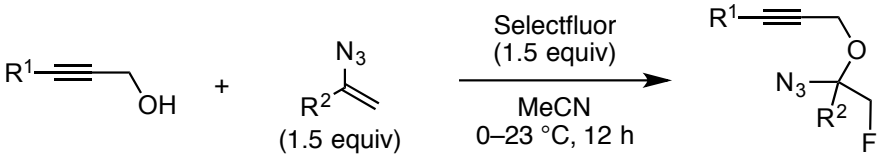
3. Synthesis of α-propargyloxy-β-haloalkylazides 1

The starting materials, α-propargyloxy-β-haloalkylazides **1**, were synthesized by the following procedures A-C based on our recent report.[3] It should be noted that during the coupling reaction of propargylic alcohols and vinyl azides with Selectfluor®, mono-fluorinated linking products were contaminated with a small amount (up to 8%) of those having a difluoromethyl moiety (having a triplet proton peak observed around at 5.5-5.9 ppm) (Scheme S1). This difluorinated linking side products are presumably formed via formation of mono-fluorinated vinyl azides through electrophilic fluorination followed by deprotonation. They are hardly separated from the mono-fluorinated linking products, while they do not affect the Au-catalysis reactivity in the present cyclization.



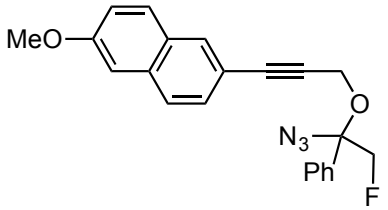
Scheme S1. Formation of difluorinated linking products

3.1. Procedure A:



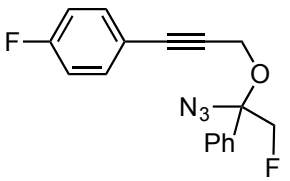
To a suspension of Selectfluor® (1.5 equiv) in MeCN (0.2 M) at 0 °C was added a solution of vinyl azide (1.5 equiv) and propargyl alcohol (1.0 equiv) in MeCN (0.2 M). After the reaction mixture was stirred at 0 °C for 1 h, and then at room temperature for 11 h, the reaction was quenched with H_2O. The organic materials were extracted with EtOAc (x2). The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting crude mixture was then purified by flash column chromatography to give the desired product.

2-(3-(1-azido-2-fluoro-1-phenylethoxy)prop-1-yn-1-yl)-6-methoxynaphthalene (1d)



Prepared following procedure A using SelectFluor® (2.14 g, 6.01 mmol), (1-azidovinyl)benzene[4] (871 mg, 6.00 mmol), 3-(6-methoxynaphthalen-2-yl)prop-2-yn-1-ol (849 mg, 4.00 mmol). Purification by flash column chromatography (silica gel, *n*-Hex/EtOAc = 30:1) gave 26% yield (390 mg, 1.04 mmol) of **1d** as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.68 (d, J = 9.2 Hz, 1H), 7.60 (d, J = 10.0 Hz, 1H), 7.59–7.56 (m, 2H), 7.47–7.41 (m, 4H), 7.15 (dd, J = 8.8, 2.4 Hz, 1H), 7.10 (d, J = 2.4 Hz, 1H), 4.70 (dd, J = 66.4, 9.6 Hz, 1H), 4.58 (dd, J = 66.4, 9.6 Hz, 1H), 4.47 (d, J = 16.0 Hz, 1H), 4.41 (d, J = 15.2 Hz, 1H), 3.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4, 134.7, 134.3, 131.7, 129.7, 129.3, 129.1, 128.8, 128.4, 127.1, 126.8, 119.4, 117.4, 105.8, 95.0 (d, J = 18.0 Hz), 86.9 (d, J = 186.0 Hz), 86.9, 84.0, 55.4, 53.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -222.3 (t, J = 47.0 Hz); IR (cm^{-1}, neat) 2226 (C≡C), 2116 (N_3), 1647, 1601, 1559, 1449; ESIHRMS: Found *m/z* 348.1399; Calcd for $C_{22}H_{19}FNO_2$ [M–N_2+H] 348.1400.

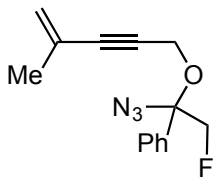
1-(3-(1-azido-2-fluoro-1-phenylethoxy)prop-1-yn-1-yl)-4-fluorobenzene (1g)



Prepared following procedure A using Selectfluor® (531 mg, 1.50 mmol), (1-azidovinyl)benzene (231 mg, 1.59 mmol), 3-(4-fluorophenyl)prop-2-yn-1-ol (154 mg, 1.02 mmol). Purification by flash column chromatography (silica gel, *n*-Hex/EtOAc = 30:1) gave 63% yield (198 mg, 0.632 mmol) of **1g** as pale yellow oil including approximately 5% of difluoromethyl derivative based on ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57–7.47 (m, 2H), 7.45–7.42 (m, 5H), 7.00 (t, J = 8.6 Hz, 2H), 4.68 (dd, J = 66.4, 10.0 Hz, 1H), 4.56 (dd, J = 66.4, 10.0 Hz, 1H), 4.40 (d, J = 15.6 Hz, 1H), 4.34 (d, J = 15.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7 (d, J = 249.0 Hz), 134.6, 133.8 (d, J = 3.0 Hz), 129.7, 128.8, 127.0, 118.6 (d, J = 3.0 Hz), 115.6 (d, J = 22.0 Hz), 95.0 (d, J = 19.0 Hz), 86.9 (d, J = 186.0 Hz), 85.3, 84.2, 53.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ -110.4 – -110.5 (m), -222.2 (t, J = 47.9 Hz);

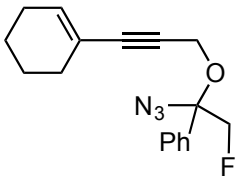
IR (cm^{-1}, neat) 3063, 2955, 2453, 2222 (C≡C), 2110 (N_3), 1894, 1601, 1450; ESIHRMS: Found *m/z* 286.1061; Calcd for $C_{17}H_{14}F_2NO$ [M–N_2+H] 286.1043.

(1-azido-2-fluoro-1-((4-methylpent-4-en-2-yn-1-yl)oxy)ethyl)benzene (1i)



Prepared following procedure A using 4-methylpent-4-en-2-yn-1-ol (618 mg, 6.43 mmol), (1-azidovinyl)benzene (1.41 g, 9.65 mmol) and Selectfluor® (3.42 g, 9.65 mmol). Purification by flash column chromatography (silica gel, PE/EtOAc = 99:1) gave 60% yield (546 mg, 2.10 mmol) of **1i** as colourless oil including approximately 8% of difluoromethyl derivative based on ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (dd, J = 7.8, 2.1 Hz, 2H), 7.45–7.39 (m, 3H), 5.33 (d, J = 1.9 Hz, 1H), 5.25 (p, J = 1.5 Hz, 1H), 4.67 (dd, J = 47.3, 9.8 Hz, 1H), 4.51 (dd, J = 46.9, 9.8 Hz, 1H), 4.30 (d, J = 15.7 Hz, 1H), 4.23 (d, J = 15.7 Hz, 1H), 1.89 (t, J = 1.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.8, 129.7, 128.9, 127.2, 126.3, 122.8, 94.9 (d, J = 18.2 Hz), 87.7, 86.9 (d, J = 186.8 Hz), 83.5, 53.4, 23.4; ^{19}F NMR (282 MHz, $CDCl_3$) δ -217.5 (t, J = 47.0 Hz); IR (cm^{-1}, neat) 3353, 2989, 2120 (N_3), 1898, 1819, 1686, 1612, 1493; EIHRMS: Found *m/z* 259.1115; Calcd for $C_{14}H_{14}FN_3O$ [M] 259.1121.

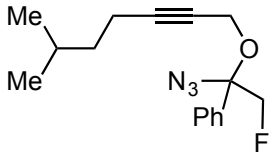
(1-azido-1-(3-cyclohexenylprop-2-ynyloxy)-2-fluoroethyl)benzene (1j)



Prepared following procedure A using 3-cyclohexenylprop-2-yn-1-ol (408 mg, 2.93 mmol), (1-azidovinyl)benzene (654 mg, 4.51 mmol) and Selectfluor® (616 mg, 4.54 mmol). Purification by flash column chromatography (silica gel, PE/EtOAc = 50:1) gave 60% yield (540 mg, 1.80 mmol) of **1j** as colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (m, 2H), 7.41 (m, 3H), 6.14 (m, 1H), 4.67 (dd, J = 47.3, 9.8 Hz, 1H), 4.50 (dd, J = 46.9, 9.8 Hz, 1H), 4.30 (d, J = 15.4 Hz, 1H), 4.22 (d, J = 15.4 Hz, 1H), 2.10 (m, 4H), 1.60 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.0, 134.8, 129.7, 128.8, 127.1, 120.1, 94.9 (d, J = 18.4 Hz), 88.3, 86.9 (d, J = 186.4 Hz), 81.6, 53.5, 29.1, 25.7, 22.3, 21.5; ^{19}F NMR (282 MHz, $CDCl_3$) δ -217.6 (t, J =

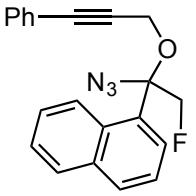
47.0 Hz); IR (cm^{-1}, CCl_4) 2935, 2258 (C≡C), 2122 (N_3), 1450, 1280, 1247; EIHRMS: Found *m/z* 271.1376; Calcd for $C_{17}H_{18}FNO$ [M-N_2] 271.1372.

(1-azido-2-fluoro-1-((6-methylhept-2-yn-1-yl)oxy)ethyl)benzene (1k)



Prepared following procedure A using 6-methylhept-2-yn-1-ol (505 mg, 4.00 mmol), (1-azidovinyl)benzene (871 mg, 6.00 mmol) and Selectfluor® (2.12 g, 5.99 mmol). Purification by flash column chromatography (silica gel, *n*-Hex/EtOAc = 99:1) gave 61% yield (706 mg, 2.44 mmol) of **1k** as colourless oil including approximately 5% of difluoromethyl derivative based on ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52–7.50 (m, 2H), 7.43–7.38 (m, 3H), 4.63 (dd, *J* = 66.0, 9.6 Hz, 1H), 4.52 (dd, *J* = 66.0, 9.6 Hz, 1H), 4.16 (dt, *J* = 14.8, 2.0 Hz, 1H), 4.08 (dt, *J* = 14.8, 2.0 Hz, 1H), 2.23 (tt, *J* = 7.2, 2.0 Hz, 2H), 1.67 (sept, *J* = 6.7 Hz, 1H), 1.41 (q, *J* = 7.2 Hz, 2H), 0.89 (d, *J* = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.8, 129.5, 128.7, 127.0, 94.8 (d, *J* = 18.0 Hz), 86.8 (d, *J* = 185.0 Hz), 87.5, 75.0, 53.3, 37.4, 27.2, 22.1, 16.8; ^{19}F NMR (282 MHz, $CDCl_3$) δ -222.4 (t, *J* = 35.4 Hz); IR (cm^{-1}, neat) 2955, 2932, 2870, 2122 (N_3), 1466, 1450, 1365, 1242; ESIHRMS: Found *m/z* 262.1604; Calcd for $C_{16}H_{21}NOF$ [M–N_2+H] 262.1607.

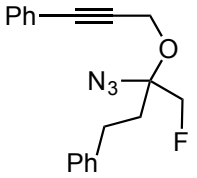
1-(1-azido-2-fluoro-1-((3-phenylprop-2-yn-1-yl)oxy)ethyl)naphthalene (1m)



Prepared following procedure A using 3-phenylprop-2-yn-1-ol (264 mg, 2.00 mmol), 1-(1-azidovinyl)naphthalene[5] (586 mg, 3.00 mmol) and Selectfluor® (1.06 g, 3.00 mmol). Purification by flash column chromatography (silica gel, *n*-Hex/EtOAc = 99:1) gave 45% yield (310 mg, 0.896 mmol) of **1m** as colourless oil including approximately 6% of difluoromethyl derivative based on ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.92–7.86 (m, 3H); 7.60 (dd, *J* = 8.8, 1.6 Hz, 1H) 7.58–7.52 (m, 2H), 7.44 (dd, *J* = 6.4, 1.6 Hz, 2H), 7.32–7.29 (m, 3H), 4.78 (dd, *J* = 68.0, 9.6 Hz, 1H), 4.66 (dd, *J* = 68.0, 9.6 Hz, 1H), 4.46 (d, *J* = 16.0 Hz, 1H), 4.38 (d, *J* = 16.0 Hz, 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ 133.7,

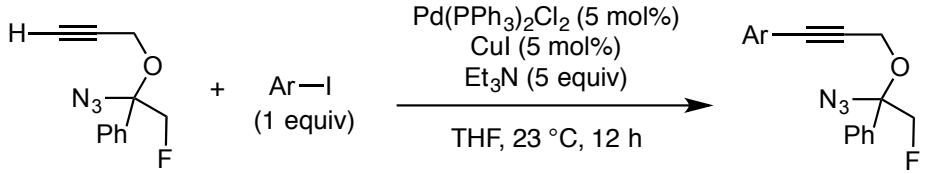
133.0, 131.8, 128.8, 128.6 (overlapped, 2C), 128.3 (overlapped, 2C), 127.7, 127.5, 127.2, 126.7, 123.6, 122.5, 95.1 (d, J = 18.0 Hz), 86.7 (d, J = 186.0 Hz), 86.5, 84.4, 53.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -222.4 (t, J = 47.2 Hz); IR (cm^{-1}, neat) 3057, 2953, 2924, 2226 (C≡C), 2116 (N_3), 1701, 1599, 1559, 1443; ESIHRMS: Found *m/z* 318.1299; Calcd for $C_{21}H_{17}FNO$ [M–N_2+H] 318.1294.

(3-((2-azido-1-fluoro-4-phenylbutan-2-yl)oxy)prop-1-yn-1-yl)benzene (1n)



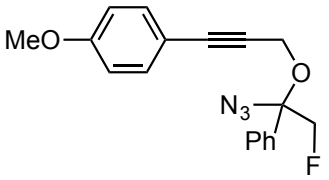
Prepared following procedure A using 3-phenylprop-2-yn-1-ol (211 mg, 1.60 mmol), (3-azidobut-3-en-1-yl)benzene[6] (400 mg, 2.31 mmol) and Selectfluor® (0.850 mg, 2.40 mmol). Purification by flash column chromatography (silica gel, PE/EtOAc = 99:1) gave 34% yield (0.178 mg, 0.550 mmol) of **1n** as colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (dd, J = 6.0, 3.6 Hz, 2H), 7.38–7.32 (m, 6H), 7.29–7.23 (m, 2H), 4.63 (q, J = 13.6 Hz, 1H), 4.62 (s, 2H), 4.47 (q, J = 13.6 Hz, 1H), 2.90–2.73 (m, 2H), 2.25–2.07 (m, 2H); ^{13}C NMR (100MHz, $CDCl_3$) δ 140.6, 131.8, 128.9, 128.7, 128.6, 128.3, 126.3, 122.4, 93.7 (d, J = 27.0 Hz), 85.5 (d, J = 171.0 Hz), 83.8, 81.4, 52.3, 35.6, 29.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ -228.2 (t, J = 46.8 Hz); IR (cm^{-1}, neat) 2933, 2226 (C≡C), 2108 (N_3), 1601, 1491, 1443; ESIHRMS: Found *m/z* 296.1462; Calcd for $C_{19}H_{19}FNO$ [M–N_2+H] 296.1451.

3.2. Procedure B:



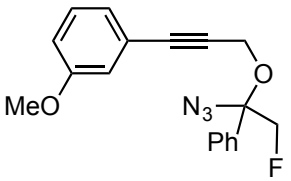
To a solution of the aromatic iodide (1.0 equiv) and (1-azido-2-fluoro-1-(prop-2-yn-1-yloxy)ethyl)benzene[3] in THF (0.5 M) were added copper iodide (5 mol%), bis(triphenylphosphine)palladium(II) chloride (5 mol%), and Et_3N (5.0 equiv). Upon completion of the reaction (monitored by TLC), the reaction was quenched with a saturated solution of NH_4Cl. The organic materials were extracted with Et_2O (x3), and the combined extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting crude residue was then purified by flash chromatography to give the product.

1-(3-(1-azido-2-fluoro-1-phenylethoxy)prop-1-ynyl)-4-methoxybenzene (1b)



Prepared following procedure B using (1-azido-2-fluoro-1-(prop-2-yn-1-yloxy)ethyl)benzene (110 mg, 0.502 mmol) and 4-iodoanisole (117 mg, 0.500 mmol). Purification by flash column chromatography (silica gel, PE/EtOAc = 50:1) gave 58% yield (94.0 mg, 0.289 mmol) of **1b** as colourless oil including approximately 7% of difluoromethyl derivative based on ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59–7.53 (m, 2H), 7.46–7.41 (m, 3H), 7.40 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 8.8 Hz, 2H), 4.71 (dd, J = 47.3, 9.8 Hz, 1H), 4.54 (dd, J = 46.9, 9.8 Hz, 1H), 4.41 (d, J = 15.5 Hz, 1H), 4.33 (d, J = 15.5 Hz, 1H), 3.81 (s, 3H); ^{13}C NMR δ 159.9, 134.8 (d, J = 2.0 Hz), 133.5, 129.7, 128.9, 127.2, 114.7, 114.0, 95.1 (d, J = 18.5 Hz), 86.9 (d, J = 186.5 Hz), 86.5, 83.1, 55.4, 53.6; ^{19}F NMR (282 MHz, $CDCl_3$) δ -217.5 (t, J = 46.8 Hz); IR (cm^{-1}, CCl_4) 2958, 2840, 2258 (C≡C), 2123 (N_3), 1607, 1510, 1443, 1366, 1292; EIHRMS: Found m/z 297.1172; Calcd for $C_{18}H_{16}FNO_2$ [M–N_2] 297.1165.

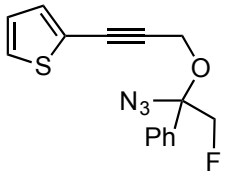
1-(3-(1-azido-2-fluoro-1-phenylethoxy)prop-1-ynyl)-3-methoxybenzene (1c)



Prepared following procedure B using (1-azido-2-fluoro-1-(prop-2-yn-1-yloxy)ethyl)benzene (110 mg, 0.502 mmol) and 3-iodoanisole (80.0 μL, 0.672 mmol). Purification by flash column chromatography (silica gel, PE/EtOAc = 50:1) gave 55% yield (89.4 mg, 0.274 mmol) of **1c** as colourless oil including approximately 5% of difluoromethyl derivative based on ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59–7.53 (m, 2H), 7.47–7.39 (m, 3H), 7.22 (t, J = 7.9 Hz, 1H), 7.06 (dt, J = 7.6, 1.2 Hz, 1H), 7.00 (dd, J = 2.7, 1.4 Hz, 1H), 6.89 (ddd, J = 8.4, 2.6, 1.0 Hz, 1H), 4.71 (dd, J = 47.2, 9.9 Hz, 1H), 4.54 (dd, J = 46.9, 9.9 Hz, 1H), 4.42 (d, J = 15.6 Hz, 1H), 4.35 (d, J = 15.6 Hz, 1H), 3.80 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.4, 134.7 (d, J = 2.0 Hz), 129.8, 129.5, 128.9, 127.2, 124.5, 123.6, 116.8, 115.3, 95.1 (d, J = 18.6 Hz), 86.9 (d, J = 186.7 Hz), 86.4, 84.4, 55.4, 53.5; ^{19}F NMR (282 MHz, $CDCl_3$) δ -217.5 (t, J = 47.6

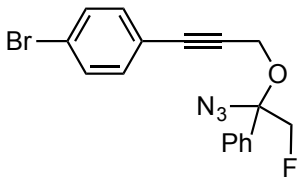
Hz); IR (cm^{-1}, CCl_4) 2960, 2259 (C≡C), 2123 (N_3), 1711, 1598, 1576, 1490, 1450, 1291, 1210; EIHRMS: Found *m/z* 297.1164; Calcd for $C_{18}H_{16}FNO_2$ [M–N_2] 297.1165.

2-(3-(1-azido-2-fluoro-1-phenylethoxy)prop-1-ynyl)thiophene (1e)



Prepared following procedure B using (1-azido-2-fluoro-1-(prop-2-yn-1-yloxy)ethyl)benzene (219 mg, 1.00 mmol) and 2-iodothiophene (0.110 mL, 1.00 mmol). Purification by flash column chromatography (silica gel, PE/EtOAc = 50:1) gave 51% yield (154 mg, 0.511 mmol) of **1e** as yellow oil including approximately 3% of difluoromethyl derivative based on ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58–7.53 (m, 2H), 7.47–7.39 (m, 3H), 7.26–7.23 (m, 2H), 6.97 (dd, J = 5.1, 3.6 Hz, 1H), 4.70 (dd, J = 47.2, 9.9 Hz, 1H), 4.53 (dd, J = 46.9, 9.9 Hz, 1H), 4.43 (d, J = 15.8 Hz, 1H), 4.35 (d, J = 15.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.5, 132.8, 129.8, 128.9, 127.6, 127.1, 127.0, 122.4, 95.0 (d, J = 18.3 Hz), 88.5, 86.9 (d, J = 187.3 Hz), 79.8, 53.4; ^{19}F NMR (282 MHz, $CDCl_3$) δ -217.5 (t, J = 46.8 Hz); IR (cm^{-1}, CCl_4) 2957, 2259 (C≡C), 2122 (N_3), 1450, 1372, 1244; EIHRMS: Found *m/z* 273.0630; Calcd for $C_{15}H_{12}FNOS$ [M–N_2] 273.0624.

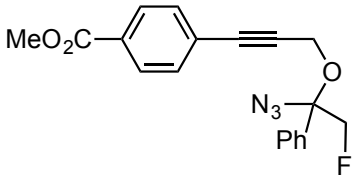
1-(3-(1-azido-2-fluoro-1-phenylethoxy)prop-1-ynyl)-4-bromobenzene (1f)



Prepared following procedure B using (1-azido-2-fluoro-1-(prop-2-yn-1-yloxy)ethyl)benzene (219 mg, 1.00 mmol) and 1-bromo-4-iodobenzene (283 mg, 1.00 mmol). Purification by flash column chromatography (silica gel, PE/EtOAc = 50:1) gave 49% yield (182 mg, 0.486 mmol) of **1f** as colorless oil including approximately 8% of difluoromethyl derivative based on ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (m, 2H), 7.44 (d, J = 8.6 Hz, 2H), 7.42 (m, 3H), 7.31 (d, J = 8.5 Hz, 2H), 4.70 (dd, J = 47.2, 9.9 Hz, 1H), 4.53 (dd, J = 46.9, 9.9 Hz, 1H), 4.38 (d, J = 15.7 Hz, 1H), 4.32 (d, J = 15.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.5, 133.4, 131.7, 129.9, 129.0, 127.1, 123.0, 121.5, 95.1 (d, J = 18.3 Hz), 87.1 (d, J = 187.0 Hz), 85.7, 85.4, 53.4; ^{19}F NMR (282 MHz, $CDCl_3$) δ -217.4 (t, J = 47.0 Hz); IR (cm^{-1}, CCl_4) 2259

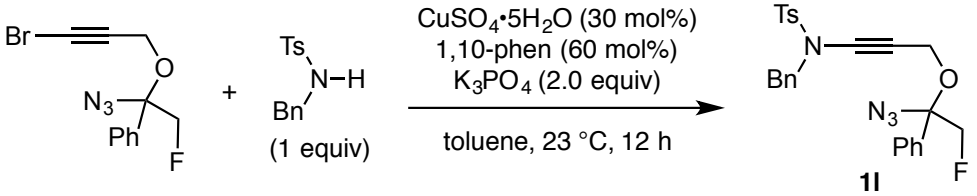
(C≡C), 2123 (N_3), 1487, 1247; ESIHRMS: Found *m/z* 346.0237; Calcd for $C_{17}H_{14}BrFNO$ [M–N_2+H] 346.0243.

methyl 4-(3-(1-azido-2-fluoro-1-phenylethoxy)prop-1-ynyl)benzoate (1h)



Prepared following procedure B using (1-azido-2-fluoro-1-(prop-2-yn-1-yloxy)ethyl)benzene (219 mg, 1.00 mmol) and methyl 4-iodobenzoate (262 mg, 1.00 mmol). Purification by flash column chromatography (silica gel, PE/EtOAc = 20:1) gave 65% yield (231 mg, 0.654 mmol) of **1h** as white solid including approximately 7% of difluoromethyl derivative based on ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59–7.54 (m, 2H), 7.47–7.39 (m, 4H), 7.21 (td, *J* = 6.8, 1.2 Hz, 1H), 7.20 (m, 1H), 7.13 (td, *J* = 7.2, 1.8 Hz, 1H), 4.63 (dd, *J* = 47.2, 9.8 Hz, 1H), 4.47 (dd, *J* = 46.9, 9.8 Hz, 1H), 4.40 (d, *J* = 15.6 Hz, 1H), 4.31 (d, *J* = 15.6 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.6, 134.5, 131.9, 129.94, 129.89, 129.6, 129.0, 127.2, 127.1, 95.1 (d, *J* = 18.4 Hz), 88.0, 87.3 (d, *J* = 186.7 Hz), 85.7, 53.4, 52.4; ^{19}F NMR (282 MHz, $CDCl_3$) δ -217.5 (t, *J* = 42. Hz); IR (cm^{-1}, CCl_4) 3031, 2989, 2453, 2226 (C≡C), 2121 (N_3), 1486, 1449, 1371, 1046; ESIHRMS: Found *m/z* 354.1259; Calcd for $C_{19}H_{17}FN_3O_3$ [M+H] 354.1254.

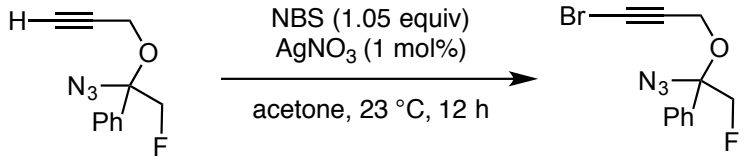
3.3. Procedure C:[7] synthesis of *N*-(3-(1-azido-2-fluoro-1-phenylethoxy)prop-1-yn-1-yl)-*N*-benzyl-4-methylbenzenesulfonamide (1l)



To a solution of (1-azido-1-((3-bromoprop-2-yn-1-yl)oxy)-2-fluoroethyl)benzene (447 mg, 1.50 mmol, the preparation method is shown below) and the *N*-benzyl-4-methylbenzenesulfonamide (392 mg, 1.50 mmol) in toluene (5 mL) were successively added $CuSO_4 \cdot 5H_2O$ (112 mg, 0.450 mmol), 1,10-phenanthroline (162 mg, 0.899 mmol) and K_3PO_4 (637 mg, 3.00 mmol). The mixture was stirred overnight at room temperature, filtered through celite, concentrated and purified by flash column chromatography (silica gel, PE/EtOAc =

20:1) to give 42% yield (300 mg, 0.627 mmol) of **1l** as colourless oil including approximately 8% of difluoromethyl derivative based on ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 8.2 Hz, 2H), 7.44 (m, 2H), 7.40 (m, 3H), 7.30 (m, 7H), 4.59 (dd, J = 47.3, 9.8 Hz, 1H), 4.51 (s, 1H), 4.48 (s, 1H), 4.42 (dd, J = 36.1, 11.0 Hz, 1H), 4.25 (d, J = 16.0 Hz, 1H), 4.18 (d, J = 16.1 Hz, 1H), 2.45 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.8, 134.8, 134.6, 134.5, 129.8, 129.7, 128.84, 128.79, 128.6, 128.4, 127.8, 127.0, 94.83 (d, J = 18.3 Hz), 86.92 (d, J = 186.6 Hz), 80.1, 67.7, 55.5, 53.2, 21.7; ^{19}F NMR (282 MHz, $CDCl_3$) δ -217.1 (t, J = 47.0 Hz); IR (cm^{-1}, CCl_4) 3068, 3035, 2927, 2264, 2248 (C≡C), 2121 (N_3), 1598, 1496, 1450, 1368; EIHRMS: Found *m/z* 450.1416; Calcd for $C_{25}H_{23}FN_2O_3S$ [M–N_2] 450.1413.

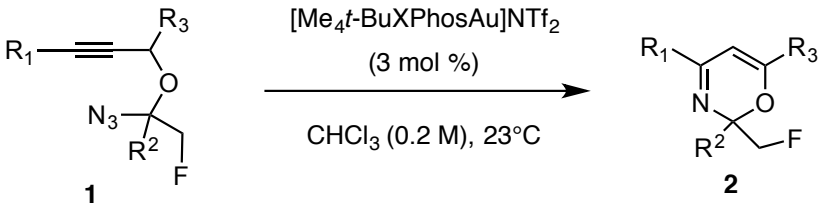
(1-azido-1-((3-bromoprop-2-yn-1-yl)oxy)-2-fluoroethyl)benzene



To a solution of the (1-azido-2-fluoro-1-(prop-2-yn-1-yloxy)ethyl)benzene (1.10 g, 5.02 mmol) and N-bromosuccinimide (935 mg, 5.25 mmol) in dry acetone (30 mL) was added $AgNO_3$ (8.50 mg, 0.0500 mmol). After completion, the mixture was filtered through celite, concentrated and purified by flash column chromatography (silica gel, PE/EtOAc = 100:1) to give 92% yield (1.37 g, 4.60 mmol) of the titled compound as colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52–7.47 (m, 2H), 7.45–7.39 (m, 3H), 4.67 (dd, J = 47.3, 9.9 Hz, 1H), 4.50 (dd, J = 46.9, 9.9 Hz, 1H), 4.21 (d, J = 15.4 Hz, 1H), 4.13 (d, J = 15.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.5 (d, J = 2.1 Hz), 129.9, 129.0, 127.1, 95.0 (d, J = 18.5 Hz), 86.9 (d, J = 187.0 Hz), 75.6, 53.6, 46.8; ^{19}F NMR (282 MHz, $CDCl_3$) δ -217.5 (t, J = 46.7 Hz); IR (cm^{-1}, CCl_4) 2226 (C≡C), 2123 (N_3), 1450, 1247, 1074; EIHRMS: Found *m/z* 254.9820; Calcd for $C_{11}H_9BrFO$ [M–N_3] 254.9821.

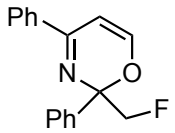
4. Au(I)-catalyzed 6-*endo-dig* azide-yne cyclization

4.1. Typical procedure (for Table 1 & Scheme 3):



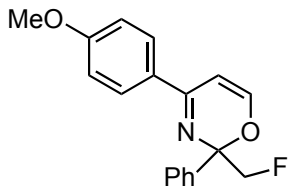
To a solution of substrate **1** in $CHCl_3$ (0.2 M) was added (2-di-*tert*-butylphosphino-3,4,5,6-tetramethyl-2′,4′,6′-triisopropylbiphenyl)gold(I) bis(trifluoromethanesulfonyl)imide (3 mol%). After completion of the reaction, volatile materials were removed in vacuo. The resulting crude product was purified by flash column chromatography to give 2*H*-1,3-oxazine **2**.

2-(fluoromethyl)-2,4-diphenyl-2*H*-1,3-oxazine (2a)



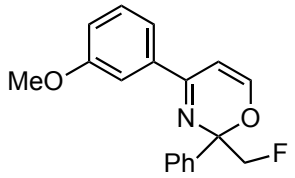
Prepared from **1a**[1] (59.4 mg, 0.201 mmol). Purification by flash column chromatography (silica gel, PE/EtOAc = 100:1) gave 89% yield (47.2 mg, 0.179 mmol) of **2a** as yellow solid. mp 60–61 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 8.1 Hz, 2H), 7.71 (d, J = 7.6 Hz, 2H), 7.52–7.45 (m, 3H), 7.44–7.38 (m, 3H), 7.11 (s, 1H), 5.94 (d, J = 5.8 Hz, 1H), 4.78 (d, J = 47.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 153.1, 139.1, 136.6, 131.0, 129.0, 128.7, 128.2, 126.9 (overlapped, 2C), 99.6, 93.0, 87.0 (d, J = 185.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –222.4 (t, J = 47.4 Hz); IR (cm^{-1}, CCl_4) 3067, 1683, 1640 (C=N), 1551, 1449, 1415, 1268, 1231; EIHRMS: Found *m/z* 267.1061; Calcd for $C_{17}H_{14}FNO$ [M] 267.1059.

2-(fluoromethyl)-4-(4-methoxyphenyl)-2-phenyl-2*H*-1,3-oxazine (2b)



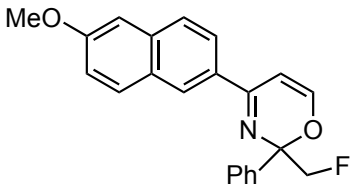
Prepared from **1b** (65.2 mg, 0.200 mmol). Purification by flash column chromatography (silica gel, PE/EtOAc = 50:1) gave 89% yield (53.1 mg, 0.178 mmol) of **2b** as pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 8.8 Hz, 2H), 7.67 (dd, J = 7.7, 2.1 Hz, 2H), 7.42–7.34 (m, 3H), 7.09 (brs, 1H), 6.95 (d, J = 8.8 Hz, 2H), 5.90 (d, J = 5.9 Hz, 1H), 4.73 (d, J = 46.6 Hz, 2H), 3.86 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.0, 159.9, 152.7, 139.4, 129.2, 128.9, 128.5, 128.1, 126.9, 114.0, 99.7, 99.4, 86.9 (d, J = 184.9 Hz), 55.5; ^{19}F NMR (282 MHz, $CDCl_3$) δ -217.6 (t, J = 47.3 Hz) ; IR (cm^{-1}, CCl_4) 3044, 2841, 1710, 1675, 1511, 1283; EIHRMS: Found *m/z* 297.1162; Calcd for for $C_{18}H_{16}FNO_2$ [M] 297.1165.

2-(fluoromethyl)-4-(3-methoxyphenyl)-2-phenyl-2*H*-1,3-oxazine (2c)



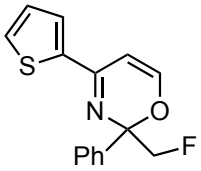
Prepared from **1c** (65.2 mg, 0.200 mmol). Purification by flash column chromatography (silica gel, PE/EtOAc = 50:1) gave 86% yield (51.1 mg, 0.172 mmol) of **2c** as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (dd, J = 7.4, 1.8 Hz, 2H), 7.49 (t, J = 2.2 Hz, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.41–7.32 (m, 4H), 7.08 (s, 1H), 7.03 (dd, J = 8.1, 2.4 Hz, 1H), 5.90 (d, J = 5.9 Hz, 1H), 4.74 (d, J = 46.7 Hz, 2H), 3.88 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.6, 159.9, 153.3, 139.2, 138.1, 129.6, 129.0, 128.2, 126.9, 119.4, 116.8, 112.2, 99.9, 99.6, 86.9 (d, J = 185.3 Hz), 55.5; ^{19}F NMR (282 MHz, $CDCl_3$) δ -217.6 (t, J = 48.6 Hz) ; IR (cm^{-1}, CCl_4) 3062, 2991, 2838, 1709, 1599, 1434, 1282; EIHRMS: Found *m/z* 297.1168; Calcd for $C_{18}H_{16}FNO_2$ [M] 297.1165.

2-(fluoromethyl)-4-(6-methoxynaphthalen-2-yl)-2-phenyl-2*H*-1,3-oxazine (2d)



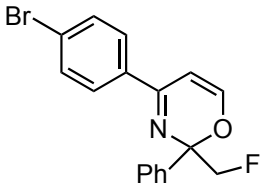
Prepared from **1d** (75.8 mg, 0.202 mmol). Purification by flash column chromatography (silica gel, *n*-Hex/AcMe = 98.5:1.5) gave 85% yield (59.3 mg, 0.171 mmol) of **2d** as white solid. mp 135–138 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 8.12 (dd, J = 8.8, 1.6 Hz, 1H), 7.82 (d, J = 5.2 Hz, 1H), 7.80 (d, J = 5.2 Hz, 1H); 7.73 (dd, J = 8.0, 1.6 Hz, 2H), 7.43–7.36 (m, 3H), 7.21–7.17 (m, 3H) 6.06 (d, J = 6.0 Hz, 1H), 4.79 (d, J = 47.6 Hz, 2H), 3.95 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.4, 158.9, 152.9, 139.2, 136.1, 131.7, 130.5, 128.8, 128.2, 128.0 (overlapped, 2C), 127.2, 126.9, 126.8, 124.4, 119.3, 105.8, 99.5, 86.9 (d, J = 184.0 Hz), 55.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ -222.4 (t, J = 45.1 Hz); IR (neat, cm^{-1}) 3055, 2980, 1626, 1558, 1485, 1418; ESIHRMS: Found *m/z* 348.1404; Calcd for $C_{22}H_{19}FNO_2$ [M+H] 348.1400.

2-(fluoromethyl)-2-phenyl-4-(thiophen-2-yl)-2*H*-1,3-oxazine (2e)



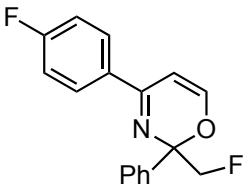
Prepared from **1e** (60.0 mg, 0.199 mmol). Purification by flash chromatography (silica gel, PE/EtOAc = 50:1) gave 90% yield (49.2 mg, 0.178 mmol) of **2e** as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (dd, J = 7.6, 2.2 Hz, 2H), 7.47 (dd, J = 5.1, 1.1 Hz, 1H), 7.43 (dd, J = 3.8, 1.1 Hz, 1H), 7.41–7.33 (m, 3H), 7.08 (dd, J = 5.0, 3.7 Hz, 1H), 7.05 (s, 1H) 5.85 (d, J = 5.8 Hz, 1H), 4.68 (t, J = 39.3 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6, 152.9, 142.6, 139.2, 130.1, 129.0, 128.22, 128.17, 127.7, 126.9, 99.4, 99.0, 86.9 (d, J = 185.3 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ -217.6 (t, J = 47.6 Hz); IR (cm^{-1}, CCl_4) 3054, 2984, 2957, 1709, 1663, 1552, 1415, 1291, 1230; EIHRMS: Found *m/z* 273.0625; Calcd for $C_{15}H_{12}FNOS$ [M] 273.0624.

4-(4-bromophenyl)-2-(fluoromethyl)-2-phenyl-2*H*-1,3-oxazine (2f)



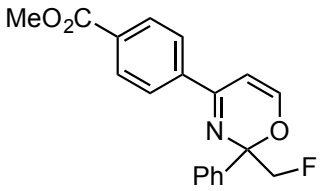
Prepared from **1f** (75.5 mg, 0.202 mmol). Purification by flash column chromatography (silica gel, PE/EtOAc = 100:1) gave 88% yield (61.2 mg, 0.177 mmol) of **2f** as colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 8.6 Hz, 2H), 7.66–7.62 (m, 2H), 7.57 (d, J = 8.6 Hz, 2H), 7.42–7.35 (m, 3H), 7.08 (s, 1H), 5.86 (d, J = 5.9 Hz, 1H), 4.73 (d, J = 46.5 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.8, 153.3, 138.9, 135.4, 131.8, 128.9 (d, J = 21.1 Hz), 128.5, 128.2, 126.7, 125.6, 98.9, 93.3, 87.0 (d, J = 185.4 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ -217.4 (t, J = 47.3 Hz); IR (cm^{-1}, CCl_4) 1639 (C=N), 1591, 1571, 1418; EIHRMS: Found *m/z* 345.0177; Calcd for $C_{17}H_{13}BrFNO$ [M] 345.0165.

4-(4-fluorophenyl)-2-(fluoromethyl)-2-phenyl-2*H*-1,3-oxazine (2g)



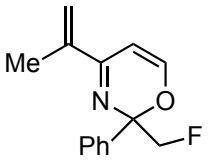
Prepared from **1g** (62.3 mg, 0.199 mmol). Purification by flash column chromatography (silica gel, *n*-Hex/EtOAc = 20:1) gave 71% yield (40.4 mg, 0.142 mmol) of **2g** as pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93–7.89 (m, 2H), 7.67–7.65 (m, 2H), 7.42–7.37 (m, 3H), 7.15–7.10 (m, 3H), 5.88 (d, J = 6.0 Hz, 1H), 4.72 (d, J = 11.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6 (d, J = 249.0 Hz), 159.5, 153.4, 139.0, 132.7 (d, J = 3.0 Hz), 129.0, 128.90, 128.87, 128.1, 126.7, 115.5 (d, J = 21.0 Hz), 99.0, 86.9 (d, J = 184.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -109.6, -222.4 (t, J = 47.4 Hz); IR (cm^{-1}, neat) 3064, 2953, 1632, 1603, 1549; ESIHRMS: Found *m/z* 286.1038; Calcd for $C_{17}H_{14}F_2NO$ [M+H] 286.1043.

methyl 4-(2-(fluoromethyl)-2-phenyl-2*H*-1,3-oxazin-4-yl)benzoate (2h)



Prepared from **1h** (71.2 mg, 0.201 mmol). Purification by flash column chromatography (silica gel, *n*-Hex/EtOAc = 25:1) gave 96% (62.0 mg, 0.191 mmol) of **2h** as white solid. mp 110–112 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, J = 8.5 Hz, 2H), 7.96 (d, J = 8.5 Hz, 2H), 7.66 (m, 2H), 7.39 (m, 3H), 7.10 (brs, 1H), 5.91 (d, J = 5.9 Hz, 1H), 4.75 (d, J = 47.2 Hz, 2H), 3.94 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.6, 160.0, 153.4, 140.5, 138.8, 132.1, 129.8, 129.0, 128.2, 126.9 (d, J = 7.6 Hz), 126.7, 99.2, 93.1, 87.0 (d, J = 185.7 Hz), 52.4; ^{19}F NMR (282 MHz, $CDCl_3$) δ -217.3 (t, J = 47.3 Hz); IR (cm^{-1}, CCl_4) 2955, 2251, 1722 (C=O), 1639 (C=N), 1574, 1438, 1420, 1283; EIHRMS: Found *m/z* 325.1106; Calcd for $C_{19}H_{16}FNO_3$ [M] 325.1114.

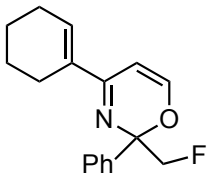
2-(fluoromethyl)-2-phenyl-4-(prop-1-en-2-yl)-2*H*-1,3-oxazine (2i)



Prepared from **1j** (59.8 mg, 0.200 mmol). Purification by flash column chromatography (silica gel, PE/EtOAc = 100:1) gave 68% yield (32.2 mg, 0.137 mmol) of **2j** as colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (dd, J = 7.3, 1.6 Hz, 2H), 7.42–7.34 (m, 3H), 6.93 (brs, 1H), 5.70 (d, J = 6.0 Hz, 1H), 5.55 (s, J = 9.0 Hz, 1H), 5.47 (t, J = 1.0 Hz, 1H), 4.68 (d, J = 42.2 Hz, 2H), 2.08 (t, J = 1.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.2, 151.5, 142.5, 139.3,

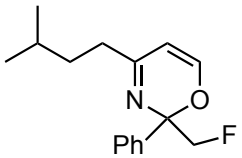
128.9, 128.1 (overlapped, 2C), 126.9, 119.5, 98.2, 87.0 (d, J = 176.7 Hz), 18.88; ^{19}F NMR (282 MHz, $CDCl_3$) δ -217.9 (t, J = 44.9 Hz); IR (cm^{-1}, CCl_4) 2958, 2259, 1644, 1555, 1423, 1236, 1030; EIHRMS: Found *m/z* 231.1048; Calcd for $C_{14}H_{14}FNO$ [M] 231.1059.

4-cyclohexenyl-2-(fluoromethyl)-2-phenyl-2*H*-1,3-oxazine (2j)



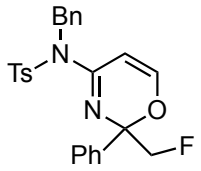
Prepared from **1i** (60.6 mg, 0.202 mmol) and *t*-Bu_2XPhosAu(MeCN)SbF_6. Purification by flash column chromatography (silica gel, PE/EtOAc = 100:1) gave 87% yield (46.9 mg, 0.173 mmol) of **2i** as colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 5.9 Hz, 2H), 7.42–7.32 (m, 3H), 6.90 (brs, 1H), 6.41 (t, J = 3.9 Hz, 1H), 5.67 (t, J = 10.3 Hz, 1H), 4.67 (d, J = 42.3 Hz, 2H), 2.53–2.37 (m, 2H), 2.26–2.16 (m, 2H), 1.77–1.68 (m, 2H), 1.67–1.60 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.2, 151.3, 139.6, 136.1, 133.3, 128.8, 128.1, 127.0, 98.3, 92.4, 87.0 (d, J = 185.3 Hz), 26.2, 24.5, 22.4, 22.0; ^{19}F NMR (282 MHz, $CDCl_3$) δ -217. (t, J = 47.1 Hz); IR (cm^{-1}, CCl_4) 2938, 2862, 1643 (C=N), 1552, 1449, 1425, 1228, 1030; EIHRMS: Found *m/z* 271.1368; Calcd for $C_{17}H_{18}FNO$ [M] 271.1372.

2-(fluoromethyl)-4-isopentyl-2-phenyl-2*H*-1,3-oxazine (2k)



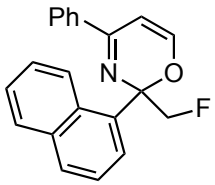
Prepared from **1k** (86.5 mg, 0.314 mmol). Purification by flash column chromatography (silica gel, PE/EtOAc 100:1) gave 22% yield (16.8 mg 0.068 mmol) of **2k** as colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62–7.52 (m, 2H), 7.36 (dd, J = 5.0, 2.3 Hz, 3H), 6.86 (brs, 1H), 5.31 (d, J = 5.6 Hz, 1H), 4.61 (d, J = 49.7 Hz, 2H), 2.32 (dd, J = 9.6, 6.5 Hz, 2H), 1.59–1.53 (m, 1H), 1.47 (dt, J = 9.7, 6.7 Hz, 2H), 0.92 (d, J = 6.4 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.7, 151.8, 139.3, 128.8, 128.1, 126.9, 101.9, 91.2, 86.9 (d, J = 185.3 Hz), 36.3, 35.6, 28.0, 22.6; ^{19}F NMR (282 MHz, $CDCl_3$) δ -217.6 (t, J = 47.9 Hz); IR (cm^{-1}, CCl_4) 3062, 2960, 2119, 1710, 1677, 1547, 1091; EIHRMS: Found *m/z* 261.1529; Calcd for $C_{16}H_{20}FNO$ [M] 261.1529.

_N_-benzyl-_N_-(2-(fluoromethyl)-2-phenyl-2_H_-1,3-oxazin-4-yl)-4-methylbenzenesulfonamide (2l)



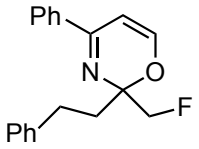
Prepared from **1l** (96.4 mg, 0.201 mmol). Purification by flash column chromatography (silica gel, PE/EtOAc = 50:1) gave 92% yield (83.2 mg, 0.184 mmol) of **2l** as colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 8.4 Hz, 2H), 7.42 (d, J = 6.5 Hz, 2H), 7.37–7.24 (m, 6H), 7.18 (t, J = 7.6 Hz, 2H), 7.10 (d, J = 7.1 Hz, 2H), 6.83 (d, J = 6.2 Hz, 1H), 6.11 (d, J = 6.2 Hz, 1H), 5.10 (s, J = 15.8 Hz, 2H), 4.34 (dq, J = 22.1, 9.2 Hz, 2H), 2.45 (s, J = 3.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.3, 152.4, 144.4, 138.5, 137.4, 136.4, 129.9, 128.7, 128.5, 127.9, 127.8, 127.4, 127.3, 126.6, 97.7, 93.7 (d, J = 17.9 Hz), 86.7 (d, J = 186.3 Hz) 49.9, 21.7; ^{19}F NMR (282 MHz, $CDCl_3$) δ -217.1 (t, J = 47.2 Hz); IR (cm^{-1}, CCl_4) 3067, 2251, 1641, 1599, 1566, 1410, 1359, 1266, 1227, 1168, 1092, 1027; ESIHRMS: Found m/z 417.1280; Calcd for $C_{24}H_{21}N_2O_3S$ [M– CH_2F] 417.1273.

2-(fluoromethyl)-2-(naphthalen-1-yl)-4-phenyl-2_H_-1,3-oxazine (2m)



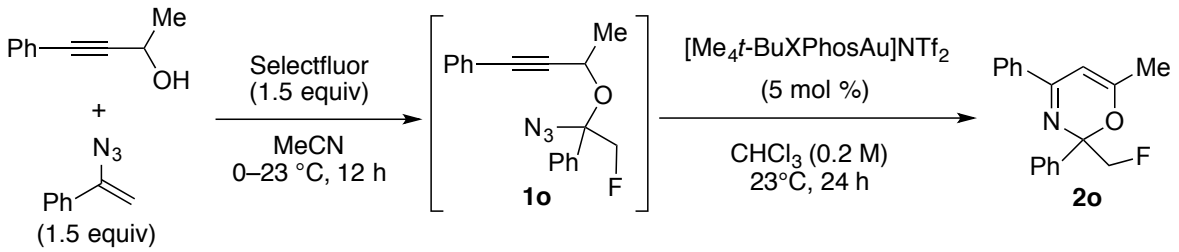
Prepared from **1m** (64.7 mg, 0.200 mmol) and 5 mol% of Me_4t-BuXPhosAuNTf$_2$. Purification by flash column chromatography (silica gel, PE/EtOAc = 99:1) gave 55% yield (34.8 mg, 0.110 mmol) of **2m** as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.97 (dd, J = 7.6, 1.2 Hz, 2H), 7.92–7.87 (m, 3H), 7.83 (dd, J = 8.4, 1.6 Hz, 1H), 7.55–7.47 (m, 5H), 7.18 (brs, 1H), 5.96 (d, J = Hz, 1H), 4.86 (d, J = 47.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 153.2, 136.5, 136.4, 133.5, 132.7, 130.9, 129.1, 128.6, 128.5, 127.9, 127.6, 126.8, 126.6, 126.5, 126.3, 124.2, 99.6, 86.9 (d, J = 193 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -222.4 (t, J = 43.8 Hz); IR (cm^{-1}, neat) 3060, 2986, 2953, 1728, 1639, 1634, 1549, 1447, 1414; ESIHRMS: Found m/z 318.1287; Calcd for $C_{21}H_{17}FNO$ [M+H] 318.1294.

2-(fluoromethyl)-2-phenethyl-4-phenyl-2*H*-1,3-oxazine (2n)



Prepared from **1n** (64.7 mg, 0.200 mmol). Purification by flash column chromatography (silica gel, PE/EtOAc = 99:1) gave 38% yield (22.3 mg, 0.076 mmol) of **2n** as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (dd, J = 7.6, 1.2 Hz, 2H) 7.49–7.40 (m, 3H), 7.30–7.16 (m 5H), 6.95 (d, J = 5.6 Hz, 1H), 5.80 (d, J = 6.0 Hz, 1H), 4.76–4.40 (m, 2H), 2.88–2.83 (m, 2H), 2.32 (brs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 152.8, 141.8, 136.7, 130.7, 128.5, 128.41, 128.38, 126.5, 126.3, 125.9, 96.6, 83.8 (d, J = 181.0 Hz) 37.7, 29.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -230.8 (t, J = 47.4 Hz); IR (cm^{-1}, neat) 3061, 3026, 2957, 2934, 1726, 1635, 1582, 1551, 1496, 1416; ESIHRMS: Found *m/z* 296.1456; Calcd for $C_{19}H_{19}FNO$ [M+H] 296.1451.

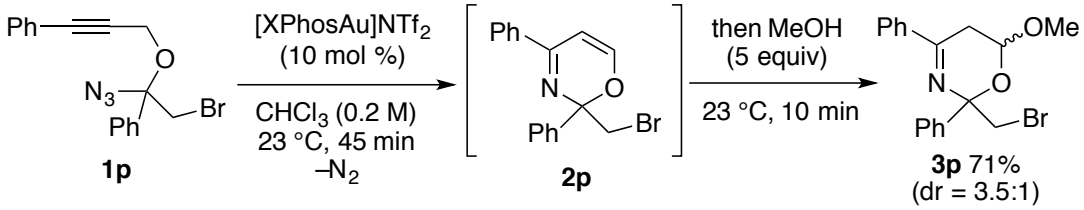
2-(fluoromethyl)-6-methyl-2,4-diphenyl-2*H*-1,3-oxazine (2o)



Due to instablity of the corresponding azide **1o**, we adopted a two-step method starting from vinyl azide and propargyl alcohol as shown above. To a suspension of Selectfluor® (359 mg, 1.01 mmol) in MeCN (3 mL) at 0 °C was added a solution of vinyl azide (145 mg, 1.00 mmol) and propargyl alcohol (73.4 mg, 0.502 mmol) in MeCN (3 mL), After 1 h stirring at 0 °C, the reaction was then stirred at room temperature for 11 h. The reaction was then quenched with H_2O, and the organic materials were extracted with EtOAc (x2). The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting crude mixture was then passed through short pad of silica gel (*n*-Hex/EtOAc = 98:2) to give the roughly purified azide (112 mg). It was then dissolved in $CDCl_3$ (1.8 mL) and (acetonitrile)(2-di-*tert*-butylphosphino-3,4,5,6-tetramethyl-2′,4′,6′-triisopropylbiphenyl) gold(I) hexafluoroantimonate (17.5 mg, 0.0183 mmol) was added. The reaction was stirred at room temperature for 24 h, and then the volatile materials were removed in vacuo. The resulting crude residue was purified by flash column chromatography (silica gel, *n*-

Hex/EtOAc = 99:1) to give 43% yield over two steps (60.5 mg, 0.215 mmol) of **2o** as colourless crystal (CCDC 1503986). mp 72–74 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 6.0 Hz, 2H), 7.66–7.64 (m, 2H), 7.47–7.42 (m ,3H), 7.40–7.36 (m, 3H), 5.81 (s, 1H), 4.83–4.60 (m, 2H), 2.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 162.1, 139.7, 137.0, 130.6, 128.7, 128.5 (overlapped, 2C), 128.0, 126.9, 126.4, 96.9, 87.1 (d, J = 184.0 Hz), 20.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ -222.4 (t, J = 47.4 Hz); IR (cm^{-1}, neat) 2990, 2953, 2876, 1645, 1553, 1447; ESIHRMS: Found *m/z* 282.1289; Calcd for $C_{18}H_{17}FNO$ [M+H] 282.1294.

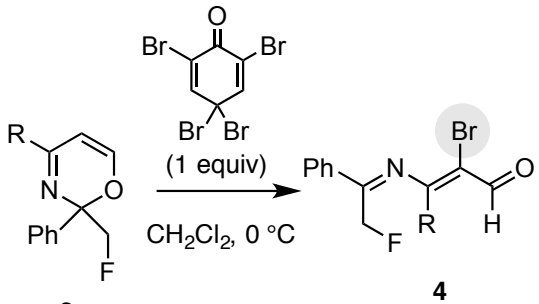
4.2. Procedure for synthesis of 3p (for Scheme 4):



Due to instability of oxazine **2p**, the oxazine was isolated as product **3p** after reaction with methanol as shown above. To the solution of **1p**[1] (95.1 mg, 0.267 mmol) in $CHCl_3$ (0.2 M) was added $XPhosAuNTf_2$ (25.5 mg, 0.0267 mmol) and stirred at 23 °C for 45 min. Subsequently, MeOH (54 μL, 1.34 mmol) was added to the reaction mixture and stirred at the same temperature for 10 min. Removal of the volatile materials in vacuo gave the crude mixture, that was purified by flash column chromatography (silica gel, *n*-Hex/EtOAc = 99:1) to give 71% yield (68.2 mg, 0.190 mmol, dr = 3.5:1) of **3p** as colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 – 7.94 (m, 4H), 7.78 – 7.73, (m, 4H), 7.48–7.44 (m, 6H), 7.42–7.31 (m, 6H), 5.22 (dd, J = 4.4, 2.2 Hz, 1H, minor), 4.61 (dd, J = 8.4, 3.2 Hz, 1H, major), 3.96–3.81 (m, 4H), 3.61 (s, 3H, major), 3.08 (s, 3H, minor), 2.96 (dd, J = 16.8, 4.4 Hz, 1H, minor), 2.87 (dd, J = 16.8, 3.2 Hz, 1H, major), 2.77–2.66 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 161.9, 143.2, 141.7, 138.2, 137.7, 130.8, 130.6, 128.51, 128.49, 128.45, 128.37, 128.00, 127.98, 126.7, 126.6, 126.5, 126.4, 96.4, 95.0, 91.9, 87.8, 56.2, 55.7, 43.8, 43.0, 32.2, 30.9; IR (cm^{-1}, neat) 3061, 3026, 3009, 2965, 2932, 2841, 1645, 1447, 1417, 1391, 1342; ESIHRMS: Found *m/z* 360.0603; Calcd for $C_{18}H_{19}{}^{79}BrNO_2$ [M+H] 360.0599.

5. Derivatization of 2*H*-1,3-oxazines 2

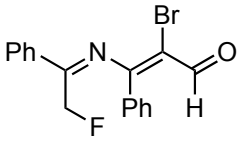
5.1. Typical procedure: Brominative ring-opening of 2*H*-1,3-oxazines 2 (Scheme 5a and 5b)

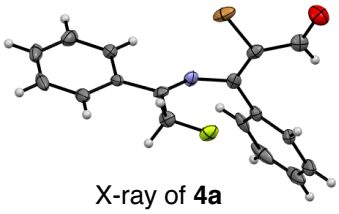


2 **4**

To a solution of **2** in CH_2Cl_2 (0.1 M) at 0 °C was added 2,4,4,6-tetrabromocyclohexa-2,5-dien-1-one (TBCO, 1.0 equiv). After the completion of the reaction, the mixture was concentrated and the resulting residue was purified by flash column chromatography.

(*Z*)-2-bromo-3-(((*Z*)-2-fluoro-1-phenylethylidene)amino)-3-phenylacrylaldehyde (4a)

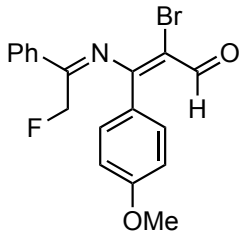




X-ray of **4a**

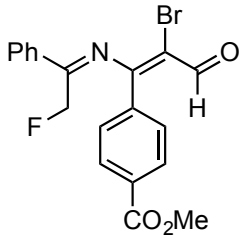
Prepared using **2a** (581 mg, 2.17 mmol) and TBCO (2.17 mmol, 891.1 mg). Purification by flash column chromatography (silica gel, *n*-Hex/EtOAc = 1:9) gave 71% yield (536 mg, 1.54 mmol) of **4a** as pale yellow crystal (CCDC 1503987). mp 120–122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (s, 1H), 7.83–7.77 (m, 2H), 7.57–7.52 (m, 3H), 7.52–7.40 (m, 5H), 5.48 (d, J = 46.6 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.0, 166.9, 159.9 (d, J = 15.2 Hz), 133.9, 133.3, 132.3, 130.8, 129.5, 128.9, 128.7, 127.7 (d, J = 1.7 Hz), 106.2, 81.6 (d, J = 183.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -221.9 (t, J = 46.6 Hz); IR (cm^{-1}, neat) 3061, 2928, 2857, 1695, 1647, 1578, 1379; EIHRMS: Found *m/z* 345.0159; Calcd for $C_{17}H_{13}{}^{79}BrFNO$ [M] 345.0165.

(*Z*)-2-bromo-3-(((*Z*)-2-fluoro-1-phenylethylidene)amino)-3-(4-methoxyphenyl) acrylaldehyde (4b)



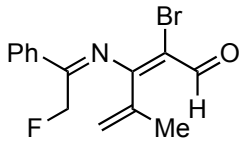
Prepared using **2b** (89.5 mg, 0.301 mmol) and TBCO (123 mg, 0.300 mmol). Purification by flash column chromatography (silica gel, *n*-Hex/EtOAc = 1:5) gave 78% yield (88.6 mg, 0.235 mmol) of **4b** as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.22 (s, 1H), 7.81 (d, J = 7.6 Hz, 2H), 7.55–7.53 (m, 1H), 7.49–7.46 (m, 4H), 6.95 (d, J = 8.4 Hz, 2H), 5.41 (d, J = 46.4 Hz, 2H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.1, 166.6, 161.8, 159.9 (d, J = 15.0 Hz), 133.4, 132.2, 131.1, 128.9, 127.8, 126.1, 114.2, 105.6 (d, J = 3.0 Hz), 81.7 (d, J = 195.0 Hz), 55.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -221.8 (t, J = 46.6 Hz); IR (cm^{-1}, neat) 3007, 2965, 2934, 1645, 1605, 1574; ESIHRMS: Found *m/z* 376.0361; Calcd for $C_{18}H_{16}{}^{79}BrFNO_2$ [M+H] 376.0348.

methyl 4-((*Z*)-2-bromo-1-(((*Z*)-2-fluoro-1-phenylethylidene)amino)-3-oxoprop-1-en-1-yl)benzoate (4h)



Prepared using **2h** (95.9 mg, 0.295 mmol) and TBCO (122 mg, 0.298 mmol). Purification by flash column chromatography (silica gel, *n*-Hex/EtOAc = 1:5) gave 60% yield (71.4 mg, 0.176 mmol) of **4h** as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.15 (s, 1H), 8.09 (d, J = 8.4 Hz, 2H), 7.78 (d, J = 7.6 Hz, 2H), 7.62 (d, J = 8.0 Hz, 2H), 7.57–7.54 (m, 1H), 7.50–7.46 (m, 2H), 5.51 (d, J = 46.4 Hz, 2H), 3.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.4, 166.0, 165.6, 160.4 (d, J = 15.0 Hz), 138.1, 133.1, 132.6, 132.0, 129.8, 129.5, 129.0, 127.7, 106.6 (d, J = 4.0 Hz), 81.8 (d, J = 183.0 Hz), 52.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ -222.1 (t, J = 48.1 Hz); IR (cm^{-1}, neat) 2955, 2361, 2330, 1721, 1636, 1435, 1404, 1280; ESIHRMS: Found *m/z* 404.0205; Calcd for $C_{19}H_{16}{}^{79}BrFNO_3$ [M+H] 404.0298.

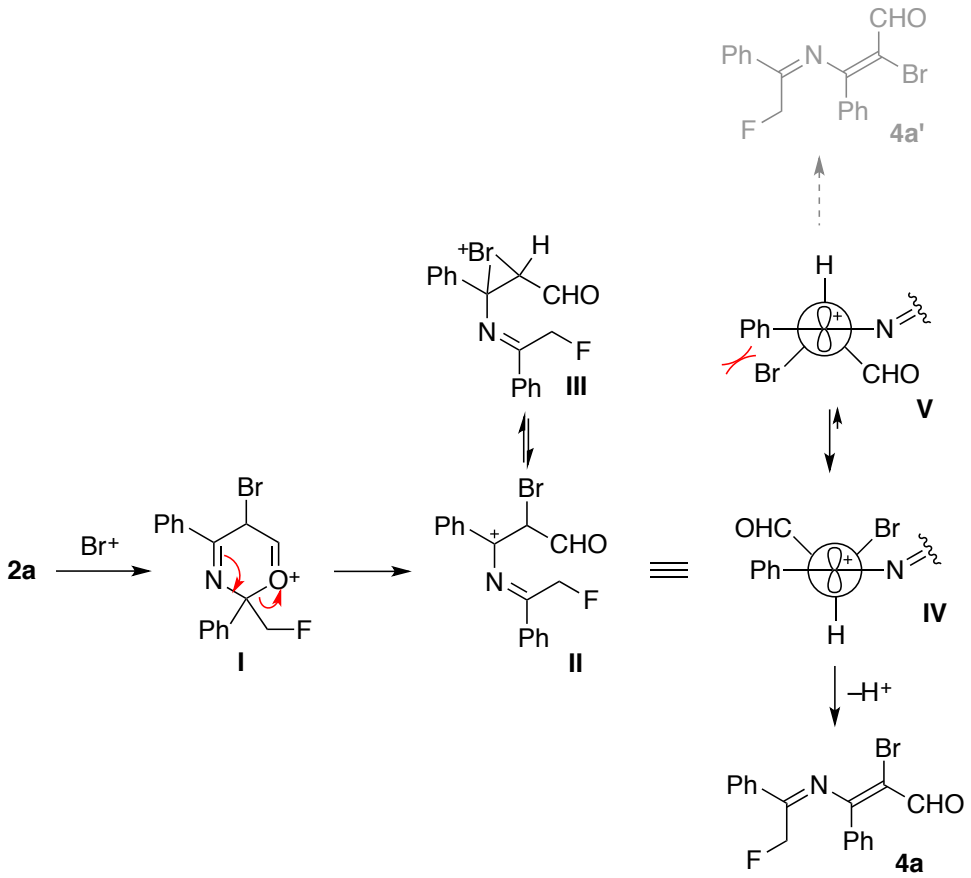
(*Z*)-2-bromo-3-(((*Z*)-2-fluoro-1-phenylethylidene)amino)-4-methylpenta-2,4-dienal (4i)



Prepared using **2i** (86.7 mg, 0.375 mmol) and TBCO (151 mg, 0.368 mmol). Purification by flash column chromatography (silica gel, *n*-Hex/EtOAc = 1:9) gave 51% yield (56.4 mg, 0.182 mmol) of **4i** as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.51 (s, 1H), 7.81 (d, J = 7.6 Hz, 2H), 7.57–7.53 (m, 1H), 7.50–7.46 (m, 2H), 5.43 (d, J = 46.8 Hz, 2H), 5.43 (t, J = 1.4 Hz, 1H), 5.28 (s, 1H), 2.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.1, 168.6, 160.6 (d, J = 16.0 Hz), 138.5, 133.4, 132.3, 128.9, 127.9 (d, J = 2.0 Hz), 121.9, 107.7 (d, J = 3.0 Hz), 81.2 (d, J = 182.0 Hz), 21.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ -211.2 (t, J = 46.6 Hz); IR (cm^{-1}, neat) 2980, 2924, 2855, 2725, 1738, 1634, 1447; ESIHRMS: Found *m/z* 310.0255; Calcd for $C_{14}H_{14}{}^{79}BrFNO$ [M+H] 310.0243.

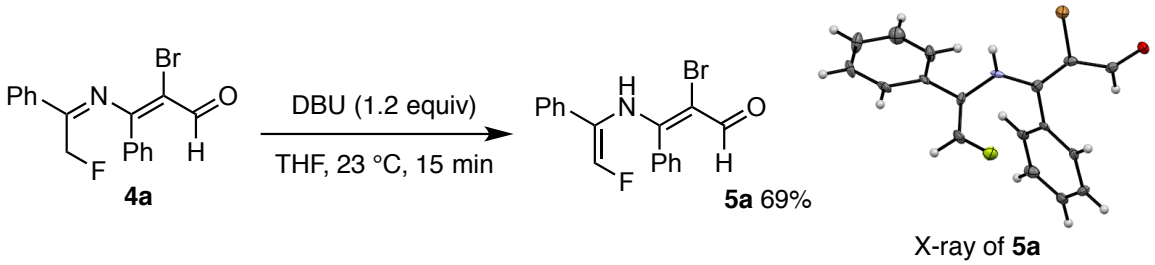
5.2. Proposed mechanism of ring-opening of oxazines 2 with TBCO

The reaction of 2*H*-1,3-oxazines **2** with TBCO afforded 4-formyl-4-bromo-2-azadienes **4** in stereoselective fashion (Scheme 4). A mechanistic proposal was described in Scheme S2. At first, electrophilic bromination of **2a** generates oxonium intermediate **I**, that undergoes ring-opening to give acyclic carbocation **II**. This carbocation might be stabilized by the adjacent bromine atom via formation of bromonium ion intermediate **III**. The formation of C=C bond through deprotonation occurs from more stable configuration **IV** (configuration **V** has steric repulsion between Br and Ph groups) to give **4a** stereoselectively.



Scheme S2.

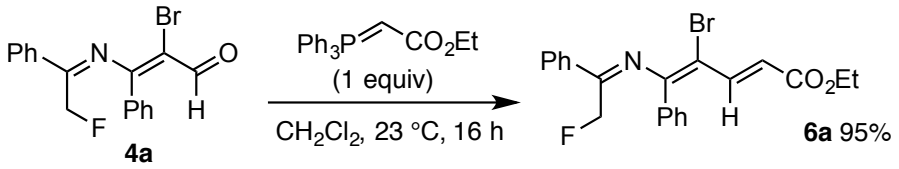
5.3. Conversion of 4a: imine-enamine isomerization for synthesis of (*Z*)-2-bromo-3-(((*Z*)-2-fluoro-1-phenylvinyl)amino)-3-phenylacrylaldehyde (5a) (Scheme 5c)



To a solution of aldehyde **4a** (69.9 mg, 0.201 mmol) in THF (2 mL) was added 1,8-diazabicycloundec-7-ene (34.0 μL, 0.228 mmol) and the reaction mixture was stirred at 23 °C. After being stirred for 15 min, the reaction was quenched with H_2O, and the organic materials were extracted with EtOAc. The combined extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting crude residue was then purified by flash column chromatography (silica gel, *n*-Hex:EtOAc = 9:1) to give 69% yield (47.8 mg, 0.138 mmol, E/Z = 1:20) of **5a** as pale yellow crystal, (CCDC 1503988). mp 50-52

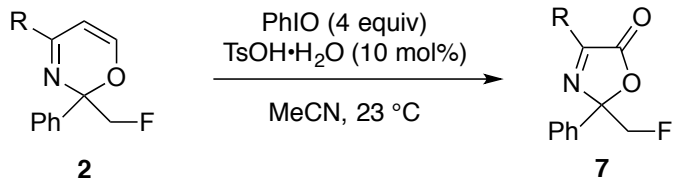
°C; ^{1}H NMR (400 MHz, $CDCl_3$, major isomer) δ 8.79 (s, 1H), 7.30–7.28 (m, 1H), 7.21–7.15 (m, 5H), 7.09 (d, J = 7.2 Hz, 3H), 6.98 (d, J = 7.2 Hz, 2H), 6.66 (d, J = 78.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.9, 161.2, 142.1 (d, J = 264.0 Hz), 132.8, 131.0, 130.3, 129.7, 128.8, 128.6, 128.0, 126.1 (d, J = 3.0 Hz), 124.8 (d, J = 7.0 Hz), 103.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ -134.7 (d, J = 78.2 Hz); IR (cm^{-1}, neat) 3055, 2847, 2337, 1635, 1558. 1543, 1489; ESIHRMS: Found *m/z* 346.0241; Calcd for $C_{17}H_{14}{}^{79}BrFNO$ [M+H] 346.0243.

5.4. Conversion of 4a: Witting reaction for synthesis of ethyl (2*E*,4*Z*)-4-bromo-5-(((*Z*)-2-fluoro-1-phenylethylidene)amino)-5-phenylpenta-2,4-dienoate (6a) (Scheme 5c)



To solution of aldehyde **4a** (69.8 mg, 0.201 mmol) in CH_2Cl_2 (2 mL) was added ethyl 2-(triphenyl-λ^5-phosphanylidene)acetate (77.0 mg, 0.221 mmol) and the reaction was stirred at 23 °C for 16 h. The reaction mixture was then concentrated and the resulting residue was purified by flash column chromatography (silica gel, *n*-Hex:EtOAc = 12:1) to give 95% yield (78.6 mg, 0.189 mmol) of **6a** as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J = 6.4 Hz, 2H), 7.56–7.43 (m, 9H) 6.23 (d, J = 14.4 Hz, 1H), 5.38 (d, J = 47.2 Hz, 2H), 4.20 (q, J = 7.2 Hz, 2H), 1.29 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 162.7, 155.1, 140.4, 135.4, 134.4, 131.7, 129.7, 129.0, 128.7, 128.6, 127.9 (d, J = 2.0 Hz), 120.8, 103.9, 80.8 (d, J = 178.0 Hz), 60.3, 14.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ -220.9 (t, J = 47.0 Hz); IR (cm^{-1}, neat) 3348, 3210, 2978, 1697, 1604, 1543, 1450, 1365; ESIHRMS: Found *m/z* 416.0664; Calcd for $C_{21}H_{20}{}^{79}BrFNO_2$ [M+H] 416.0661.

5.5. Ring-contraction of 2*H*-1,3-oxazines 2 (Scheme 6)

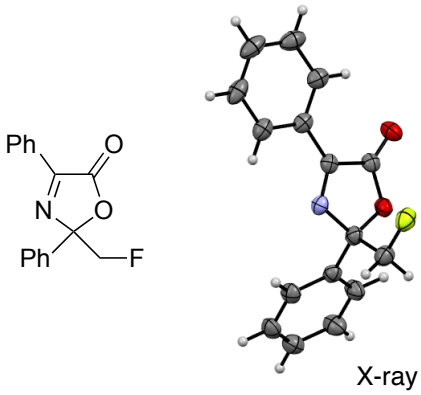


Typical procedure: Synthesis of 2-(fluoromethyl)-2-phenyloxazol-5(2*H*)-ones (7)

To a suspension of oxazine **2** and PhIO (4.0 equiv) in MeCN (0.1 M) was added TsOH•H_2O (10 mol%) and the reaction was stirred at 23 °C. Upon completion, the reaction was quenched with H_2O, extracted with EtOAc, washed with brine, dried over $MgSO_4$ and concentrated

under reduced pressure. The crude mixture was then purified by flash column chromatography.

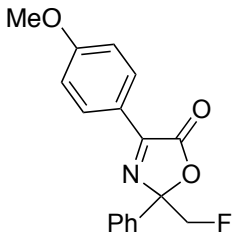
2-(fluoromethyl)-2,4-diphenyloxazol-5(2*H*)-one (7a)



X-ray of **7a**

Prepared using **2a** (53.5 mg, 0.201 mmol) and PhIO (176 mg, 0.800 mmol) for 22 h. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc = 49:1) to give 36% yield (19.3 mg, 0.072 mmol) of **7a** as pale yellow crystals (CCDC 1503989). mp 61–63 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, J = 7.2 Hz, 2H), 7.73–7.71 (m, 2H), 7.59 (d, J = 7.2 Hz, 1H), 7.53–7.49 (m, 2H), 7.47–7.44 (m, 3H), 4.80 (dq, J = 46.0, 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 158.0, 134.0 (d, J = 4.0 Hz), 132.9, 129.9, 129.0, 128.9, 128.8, 128.3, 126.7, 104.2 (d, J = 18.0 Hz), 83.3 (d, J = 190.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -223.7 (t, J = 46.8 Hz); IR (cm^{-1}, neat) 3063, 2957, 1782, 1614, 1574, 1493, 1451; ESIHRMS: Found *m/z* 270.0939; Calcd for $C_{16}H_{13}FNO_2$ [M+H] 270.0930.

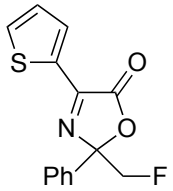
2-(fluoromethyl)-4-(4-methoxyphenyl)-2-phenyloxazol-5(2*H*)-one (7b)



Prepared using **2b** (59.2 mg, 0.199 mmol) and PhIO (176 mg, 0.800 mmol) for 16 h. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc = 97:3) to give 57% yield (34.4 mg, 0.114 mmol) of **7b** as colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, J = 8.8 Hz, 2H), 7.72–7.69 (m, 2H), 7.45–7.43 (m, 3H), 6.99 (d, J = 9.2 Hz, 2H), 4.77 (d, J = 46.0 Hz, 2H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0, 163.4, 157.0, 134.4, 130.9, 129.8, 128.8, 126.7, 121.0, 114.2, 103.9 (d, J = 18.0 Hz), 83.4 (d, J = 189.0 Hz), 55.5; ^{19}F

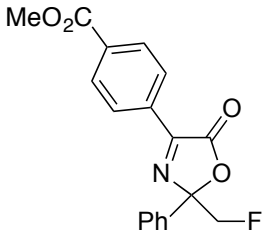
NMR (376 MHz, $CDCl_3$) δ -223.7 (t, J = 46.8 Hz); IR (cm^{-1}, neat) 2956, 1782, 1607, 1514, 1493, 1260, 1169; ESIHRMS: Found *m/z* 300.1042; Calcd for $C_{17}H_{15}FNO_3$ [M+H] 300.1036.

2-(fluoromethyl)-2-phenyl-4-(thiophen-2-yl)oxazol-5(2*H*)-one (7e)



Prepared using **2e** (34.7 mg, 0.127 mmol) and PhIO (112 mg, 0.506 mmol) for 12 h. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc = 99:1) to give 39% yield (13.7 mg, 0.0498 mmol) of **7e** as colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (dd, J = 4.0, 1.0 Hz, 1H), 7.70–7.67 (m, 3H), 7.46–7.44 (m, 3H), 7.20 (dd, J = 4.8, 4.0, Hz, 1H), 4.77 (d, J = 46.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 153.4, 134.00, 133.96, 133.2, 131.1, 129.9, 128.8, 128.6, 126.7, 104.9 (d, J = 18.0 Hz), 83.2 (d, J = 190.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -223.5 (t, J = 46.8 Hz); IR (cm^{-1}, neat) 2957, 1786, 1616, 1449, 1425; ESIHRMS: Found *m/z* 276.0493; Calcd for $C_{14}H_{11}FNO_2S$ [M+H] 276.0495.

methyl 4-(2-(fluoromethyl)-5-oxo-2-phenyl-2,5-dihydrooxazol-4-yl)benzoate (7h)

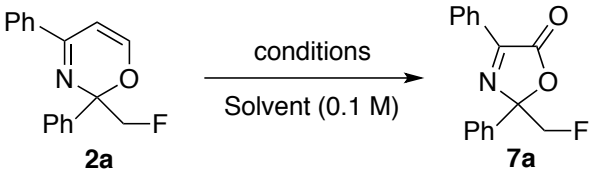


Prepared using **2h** (91.9 mg, 0.282 mmol) for 23 h. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc = 97:3) to give 55% yield (50.7 mg, 0.155 mmol) of **7h** as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, J = 8.4 Hz, 2H), 8.16 (d, J = 8.4 Hz, 2H), 7.72–7.70 (m, 2H), 7.47–7.45 (m, 3H), 4.81 (dq, J = 46.0, 10.0 Hz, 2H), 3.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 163.1, 157.4, 133.7, 133.6 (d, J = 3.0 Hz), 131.9, 130.0, 129.8, 128.92, 128.89, 126.6, 104.5 (d, J = 18.0 Hz), 83.1 (d, J = 191.0 Hz), 52.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ -223.5 (t, J = 45.5 Hz); IR (cm^{-1}, neat) 2955, 1784, 1724, 1622, 1451, 1437, 1281; ESIHRMS: Found *m/z* 328.0990; Calcd for $C_{18}H_{15}FNO_4$ [M+H] 328.0985.

5.6. Screening of the reaction conditions for oxidation of 2*H*-1,3-oxazine 2a

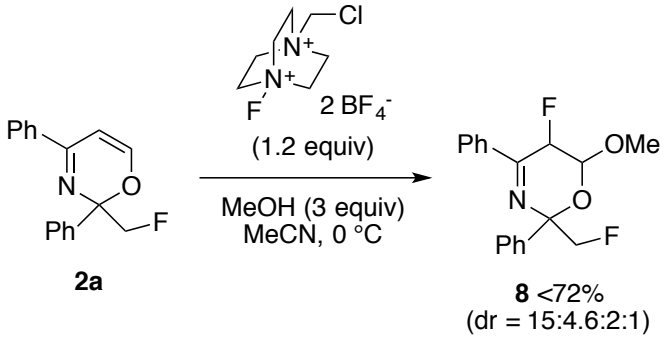
Our initial attempt was to oxidize enol moiety to introduce a C-O bond at the α-position of the C=N bond. Thus, the reactions of **2a** with various oxidants were screened as shown in Table S1. Although treatment with *m*-CPBA and $PhI(OAc)_2$ did not provide any expected oxidized product (either complex mixture of unidentified mixtures or fluoroacetophenone generated by hydrolysis of **2a** was given) (entries 1-4), the reactions with PhIO in the presence of a catalytic amount of TsOH either in CH_2Cl_2/HFIP or CH_3CN as the solvent resulted in ring-contraction to afford **7a** (entries 7 and 8). Other acids such as CF_3CO_2H and TfOH did not perform well (entries 9 and 10), whereas use of $Cu(OTf)_2$ afforded comparable yields of **7a** (entries 11 and 12). However, the conversions of other substrates **2b**, **2e**, and **2h** with $Cu(OTf)_2$ additive did not work well as those with TsOH.

Table S1 Screening of oxidants



Entry	Additive (equiv)	Oxidant (equiv)	Solvent	Temp (°C)	Time (h)	Conversion (%)	Yield (%)
1	-	*m*-CPBA (1.5)	CH_2Cl_2	0-23	4	100	0
2	Na_2HPO_4 (0.75)	*m*-CPBA (1.5)	CH_2Cl_2	0-23	4	100	0
3	-	$PhI(OAc)_2$ (1.5)	CH_2Cl_2	23	24	100	0
4	AcOH (1)	$PhI(OAc)_2$ (1.5)	CH_2Cl_2	23	24	100	0
5	-	PhIO (1.5)	$(CHCl_2)_2$	40	18	<5	0
6	TsOH (0.1)	PhIO (3)	CH_2Cl_2	23	18	<5	0
7	TsOH (0.1)	PhIO (3)	CH_2Cl_2/HFIP (3:1)	0	0.2	100	27
8	TsOH (0.1)	PhIO (4)	MeCN	23	22	100	36
9	CF_3CO_2H (0.1)	PhIO (4)	MeCN	23	24	<5	0
10	CF_3SO_3H (0.1)	PhIO (4)	MeCN	23	0.4	100	19
11	$Cu(OTf)_2$ (0.2)	PhIO (4)	MeCN	23	0.2	100	32
12	$Cu(OTf)_2$ (0.2)	PhIO (4)	DMF	23	5	100	40

5.7. Fluorination of 2a: synthesis of 5-fluoro-2-(fluoromethyl)-6-methoxy-2,4-diphenyl-5,6-dihydro-2*H*-1,3-oxazine (8) (ref. 18)



To a solution of oxazine **2a** (53.5 mg, 0.200 mmol) and Selectfluor® (70.4 mg, 0.199 mmol) in MeCN at 0 °C was added MeOH (24 μL, 0.59 mmol). The reaction was then stirred at the same temperature for 1.5 h. The reaction was quenched with H_2O, and the organic materials were extracted with EtOAc. The combined extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting crude residue was then purified by flash column chromatography (silica gel, *n*-Hex:EtOAc = 24:1) to give <72% yield (45.7 mg, 0.144 mmol) of **8** as pale yellow oil as a mixture of four diastereomers A-D (A:B:C:D = 15:4.6:2:1 based on the integration of ^{1}H NMR peaks of the methoxy group protons) with a small amount of unidentified complexes. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 7.2 Hz, 2H for isomer B), 7.93 (d, J = 6.8 Hz, 2H, for isomer C), 7.78 (d, J = 7.2 Hz, 2H for isomer D), 7.72 (d, J = 7.2 Hz, 2H for isomer A), 7.49–7.30 (m, 12H, overlapped), 5.90 (d, J = 6.0 Hz, 1H, C*H*OMe for isomer D), 5.50 (dd, J = 49.2, 4.0 Hz, 1H, C*H*F for isomer C), 5.38 (d, J = 6.0 Hz, 1H, C*H*F for isomer B), 5.30–5.25 (m, 3H, C*H*OMe, overlapped for isomers A, B, and C), 5.01 (d, J = 48.4, 2.0 Hz, 1H, C*H*F for isomer A), 4.74–4.53 (m, 9H, CH_2F for all isomers A-D and C*H*F for isomer D), 3.62 (s, 3H for isomer B), 3.59 (s, 3H isomer C), 3.12 (s, 3H for isomer A), 3.09 (s, 3H, for isomer C); IR (cm^{-1}, neat) 3063, 2994, 2955, 2893, 1651, 1450, 1080; ESIHRMS: Found *m/z* 318.1333; Calcd for $C_{18}H_{18}F_2NO_2$ [M+H] 318.1306.

6. References

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9. ^{1}H and ^{13}C of new compounds

Figure S1. ^{1}H spectrum of 2-(3-(1-azido-2-fluoro-1-phenylethoxy)prop-1-yn-1-yl)-6-methoxynaphthalene (1d)

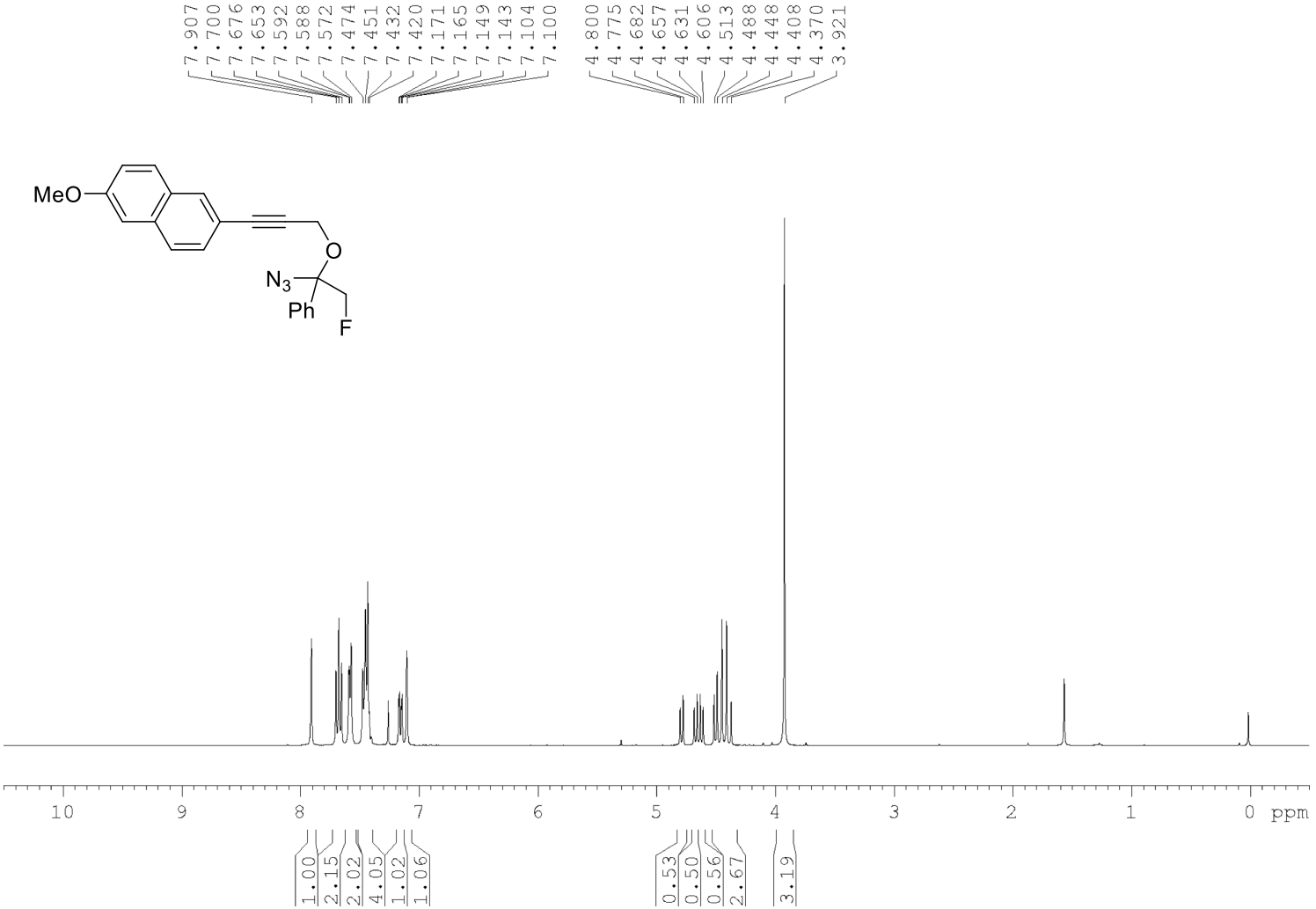

Figure S2. ^{13}C spectrum of 2-(3-(1-azido-2-fluoro-1-phenylethoxy)prop-1-yn-1-yl)-6-methoxynaphthalene (1d)

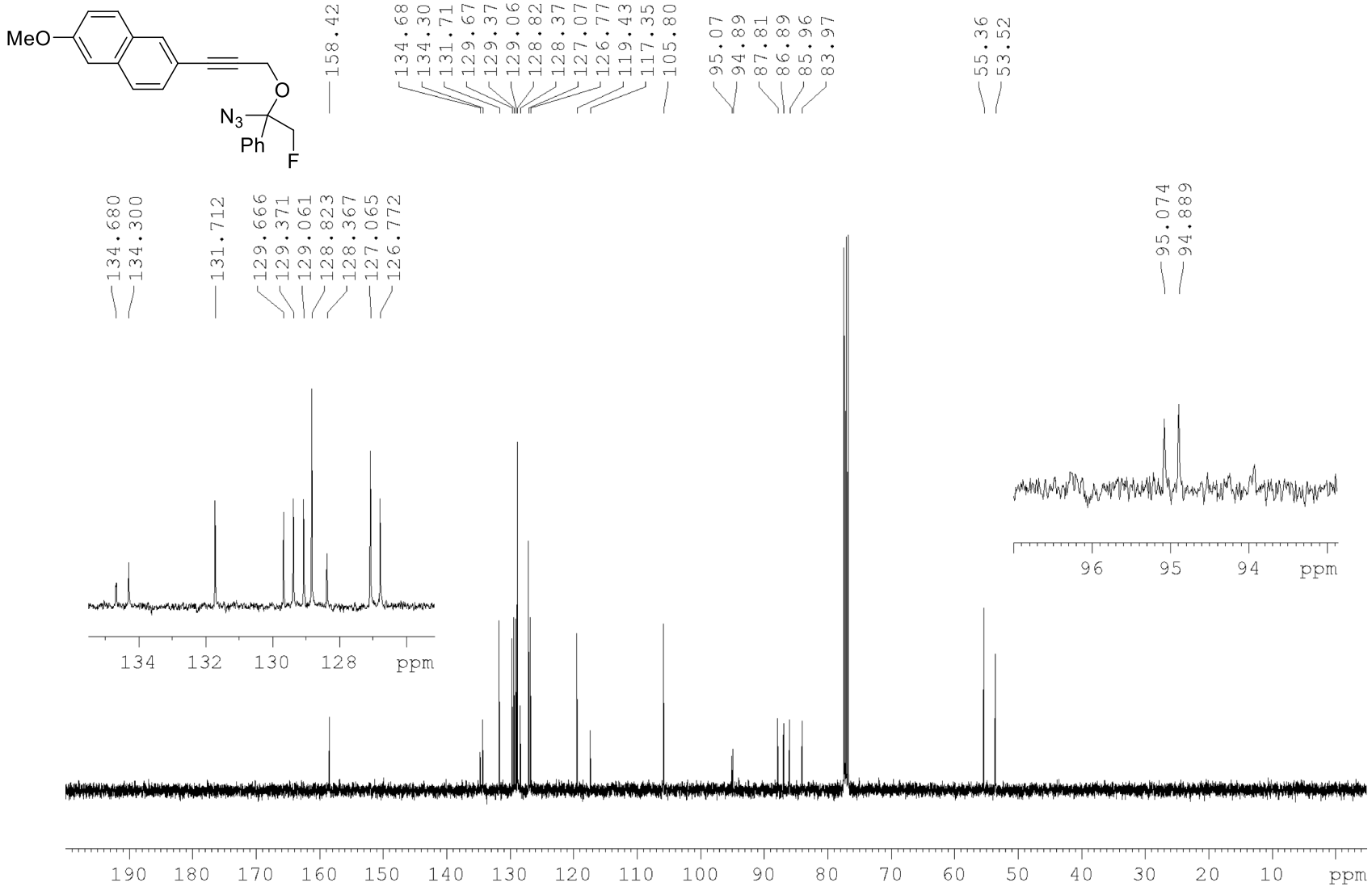

Figure S3. ^{1}H spectrum of 1-(3-(1-azido-2-fluoro-1-phenylethoxy)prop-1-ynyl)-4-fluorobenzene (1g)

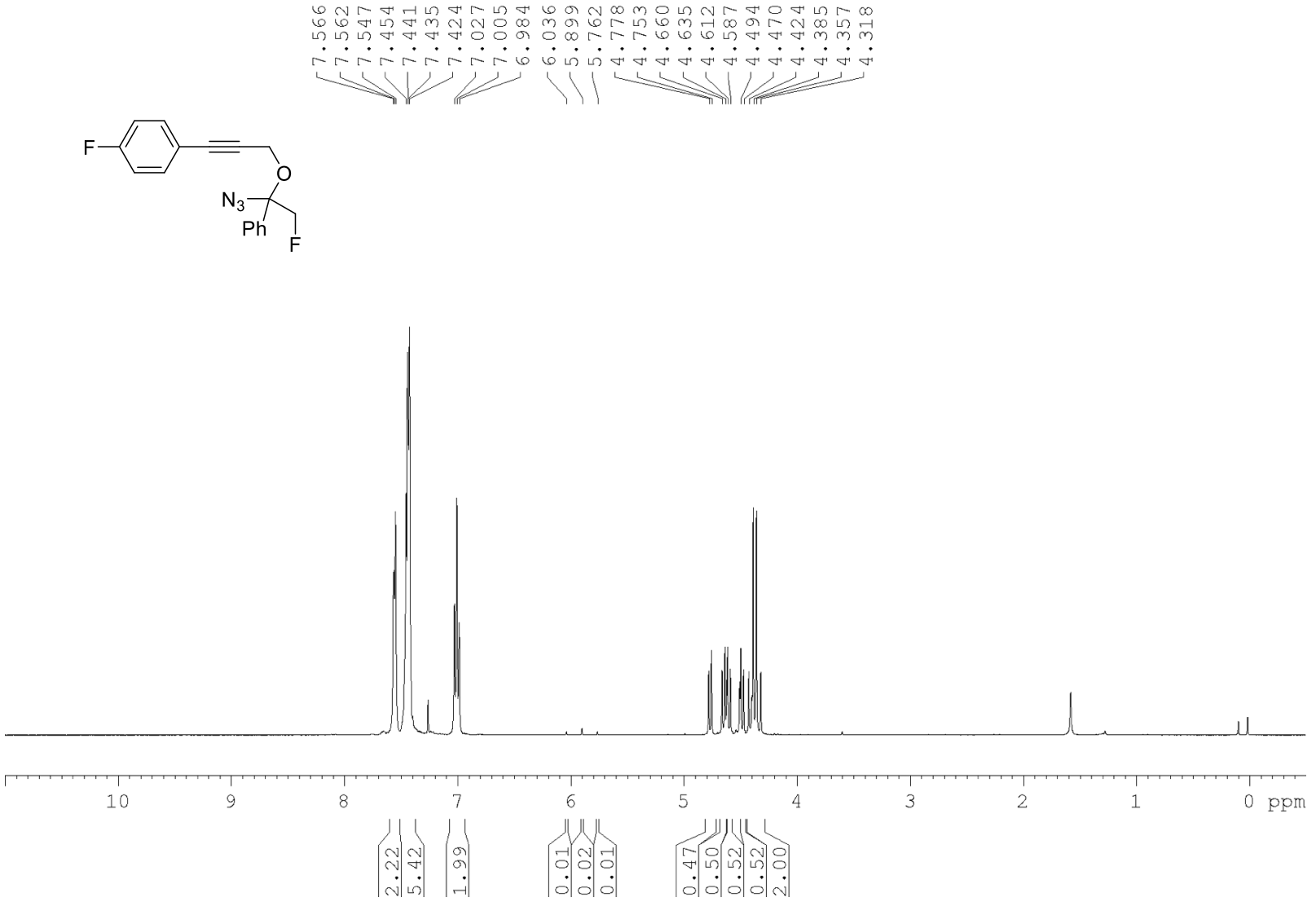

Figure S4. ^{13}C spectrum of 1-(3-(1-azido-2-fluoro-1-phenylethoxy)prop-1-ynyl)-4-fluorobenzene (1g)

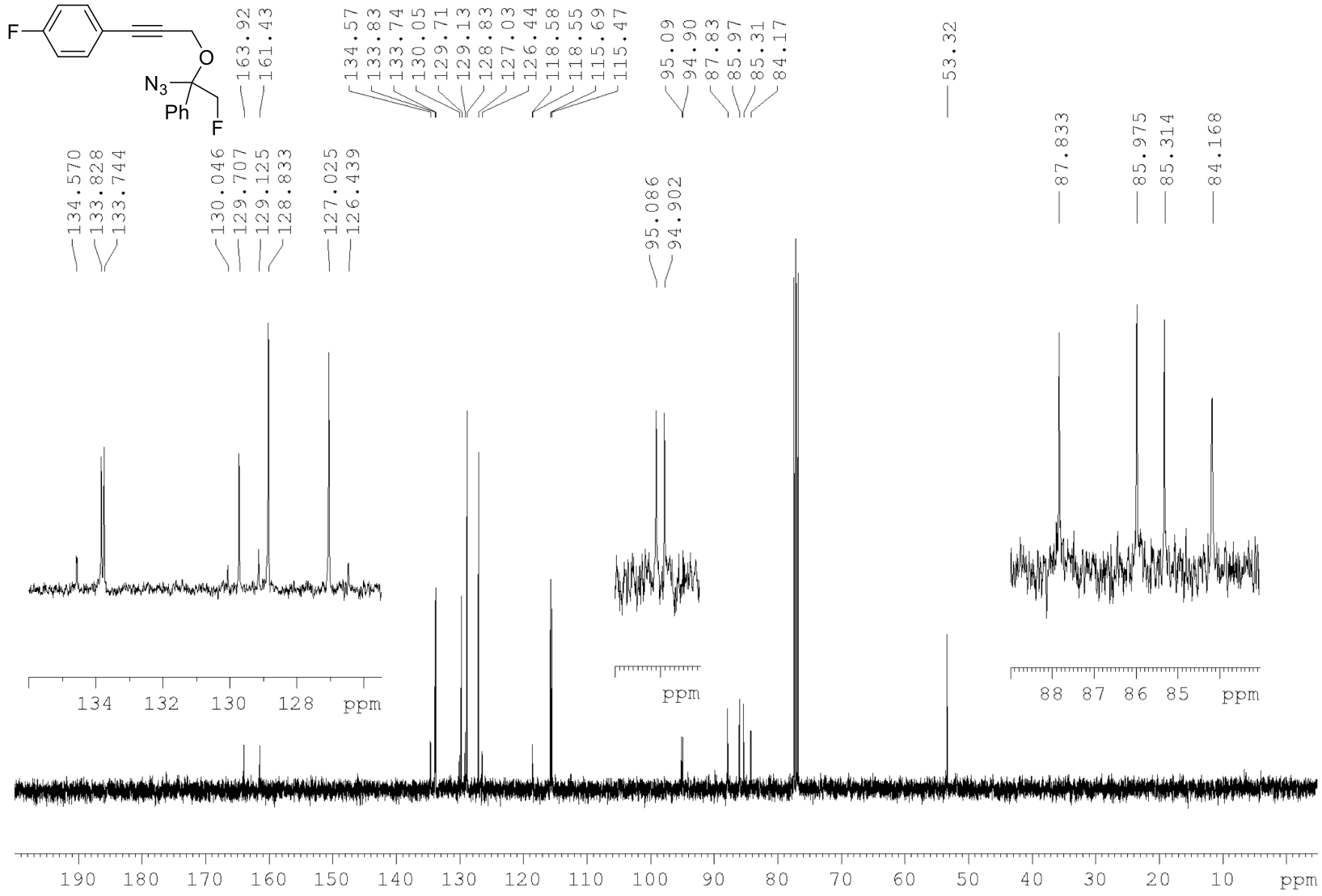

Figure S5. ^{1}H spectrum of (1-azido-2-fluoro-1-((4-methylpent-4-en-2-yn-1-yl)oxy)ethyl)benzene (1i)

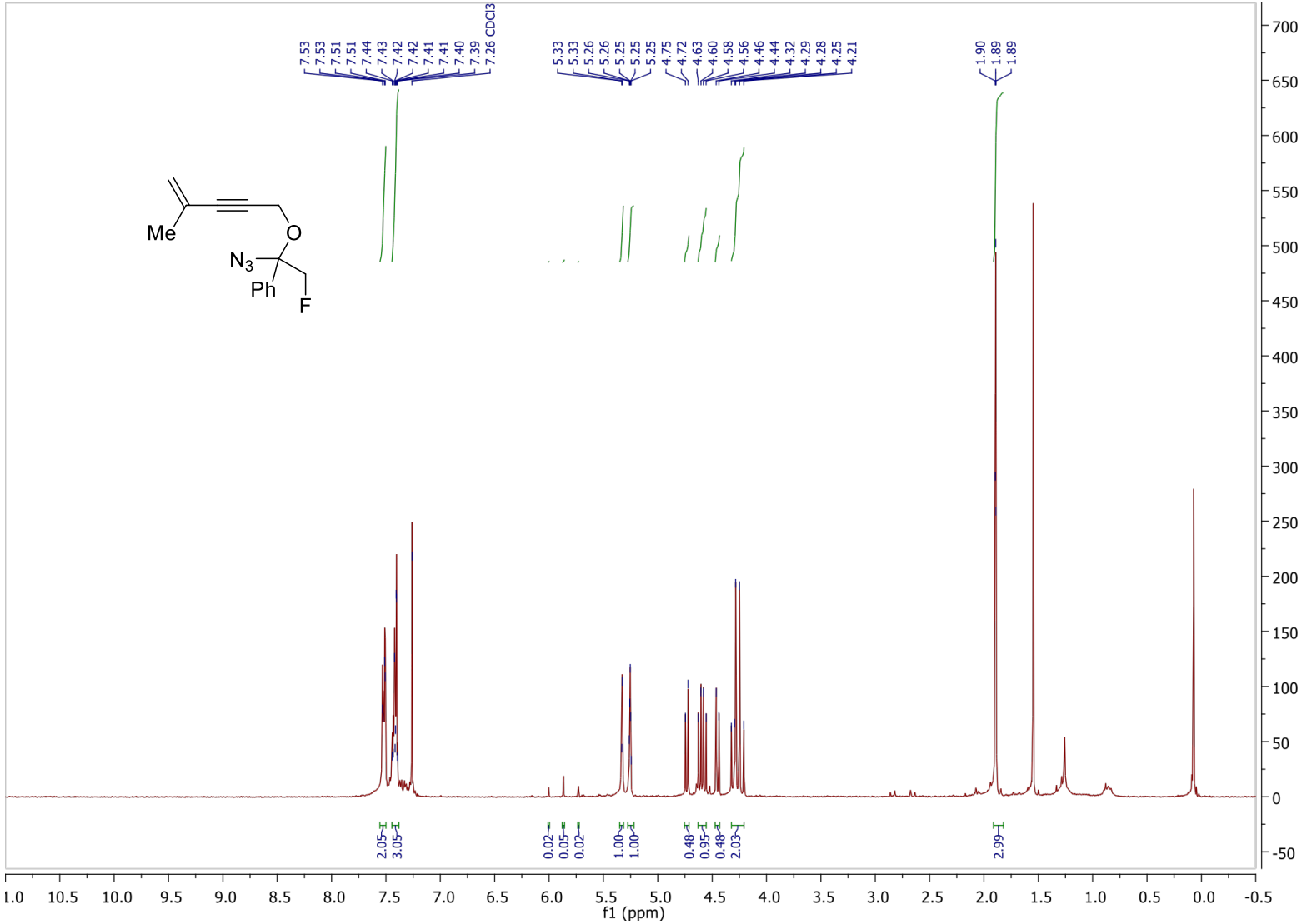

Figure S6. ^{13}C spectrum of (1-azido-2-fluoro-1-((4-methylpent-4-en-2-yn-1-yl)oxy)ethyl)benzene (1i)

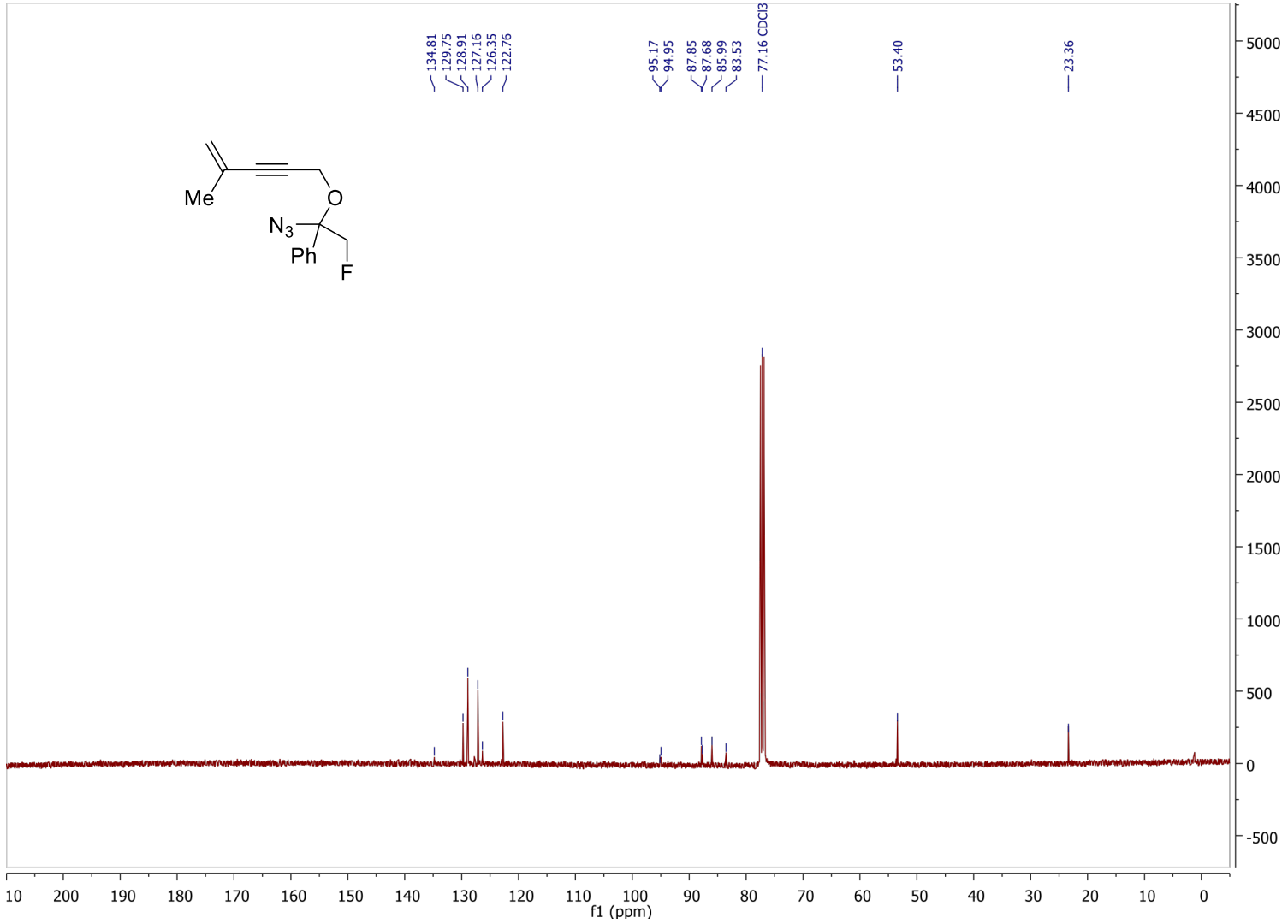

Figure S7. ^{1}H spectrum of (1-azido-1-(3-cyclohexenylprop-2-ynyloxy)-2-fluoroethyl)benzene (1j)

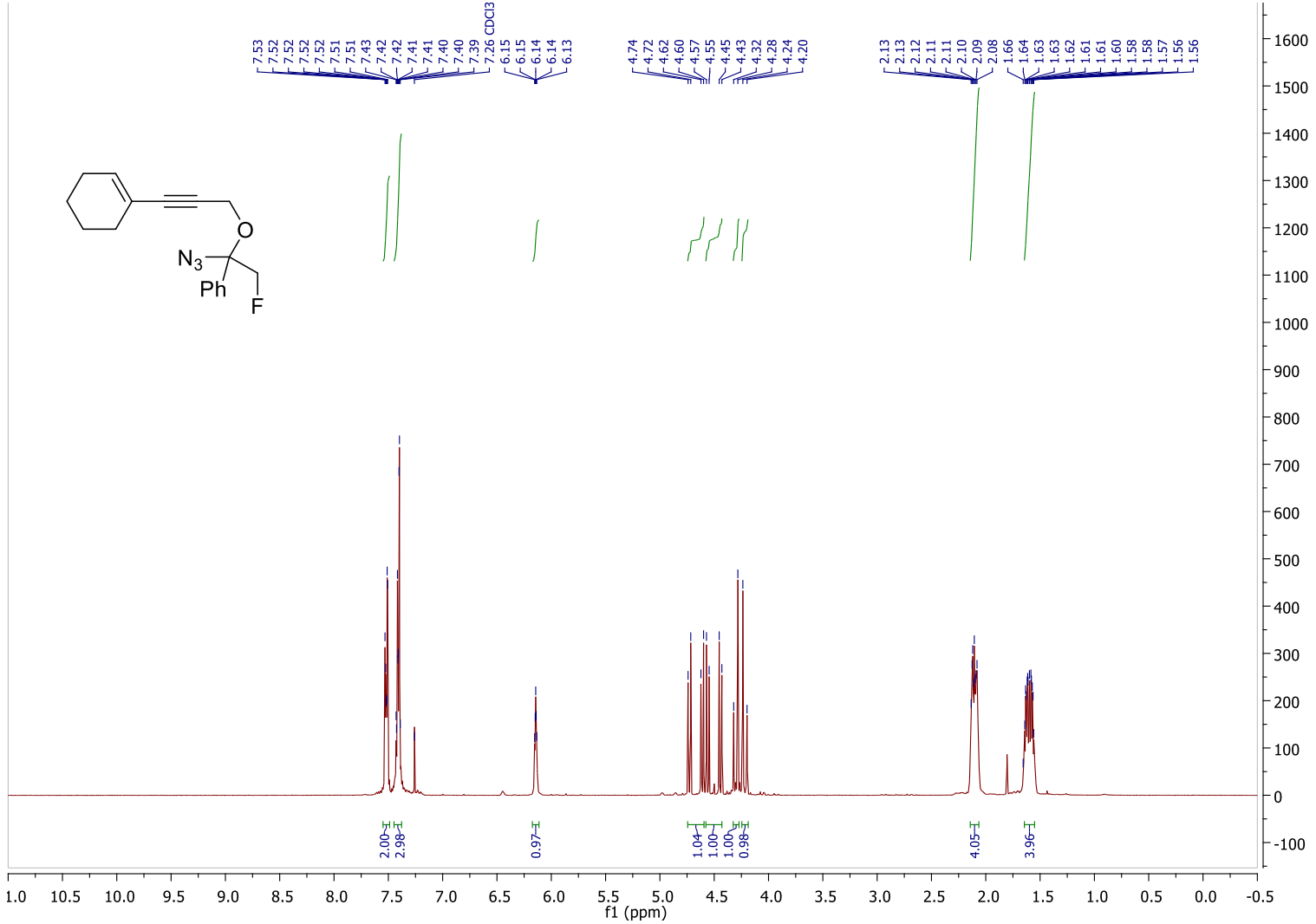

Figure S8. ^{13}C spectrum of (1-azido-1-(3-cyclohexenylprop-2-ynyloxy)-2-fluoroethyl)benzene (1j)

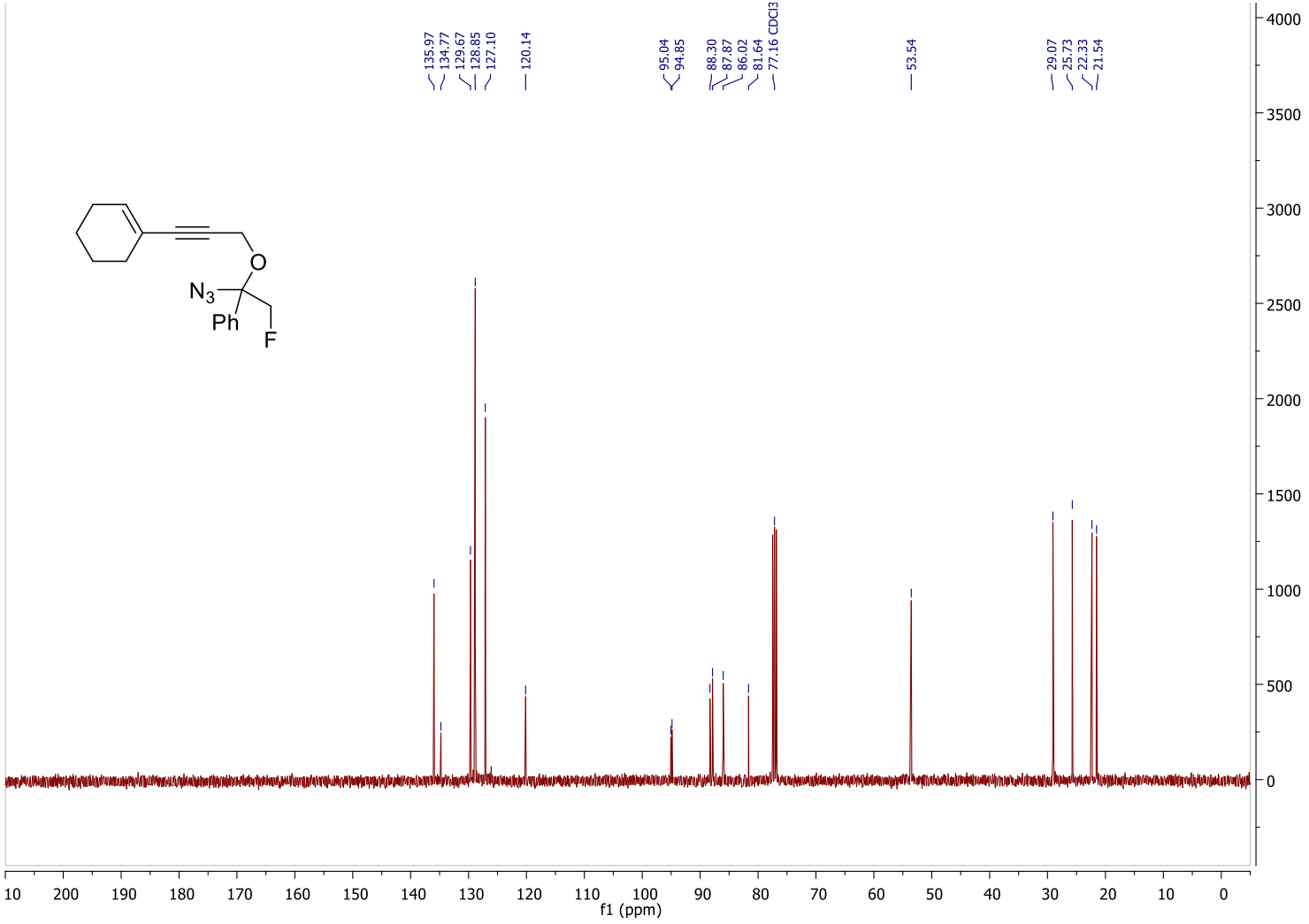

Figure S9. ^{1}H spectrum of (1-azido-2-fluoro-1-((6-methylhept-2-yn-1-yl)oxy)ethyl)benzene (1k)

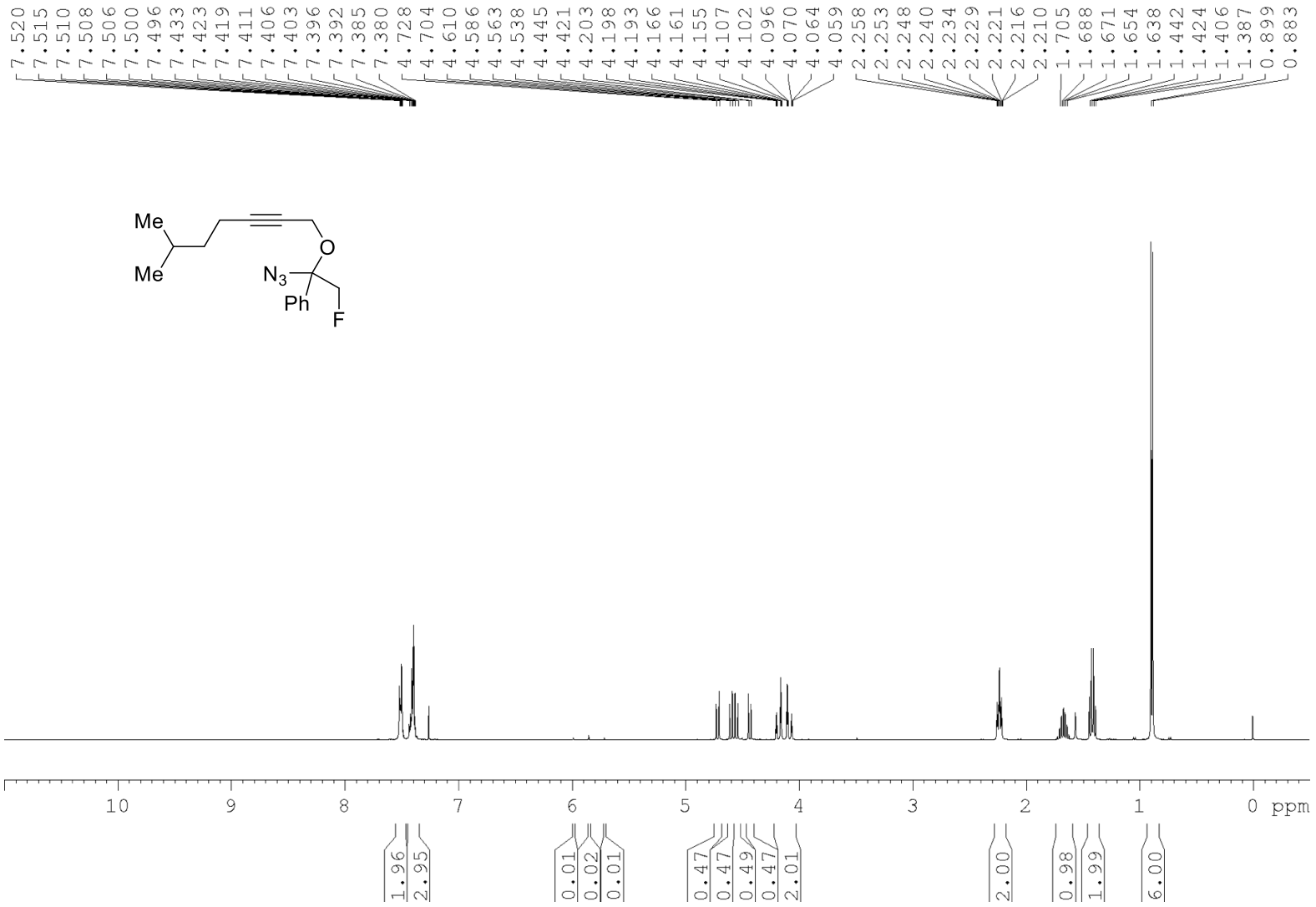

Figure S10. ^{13}C spectrum of (1-azido-2-fluoro-1-((6-methylhept-2-yn-1-yl)oxy)ethyl)benzene (1k)

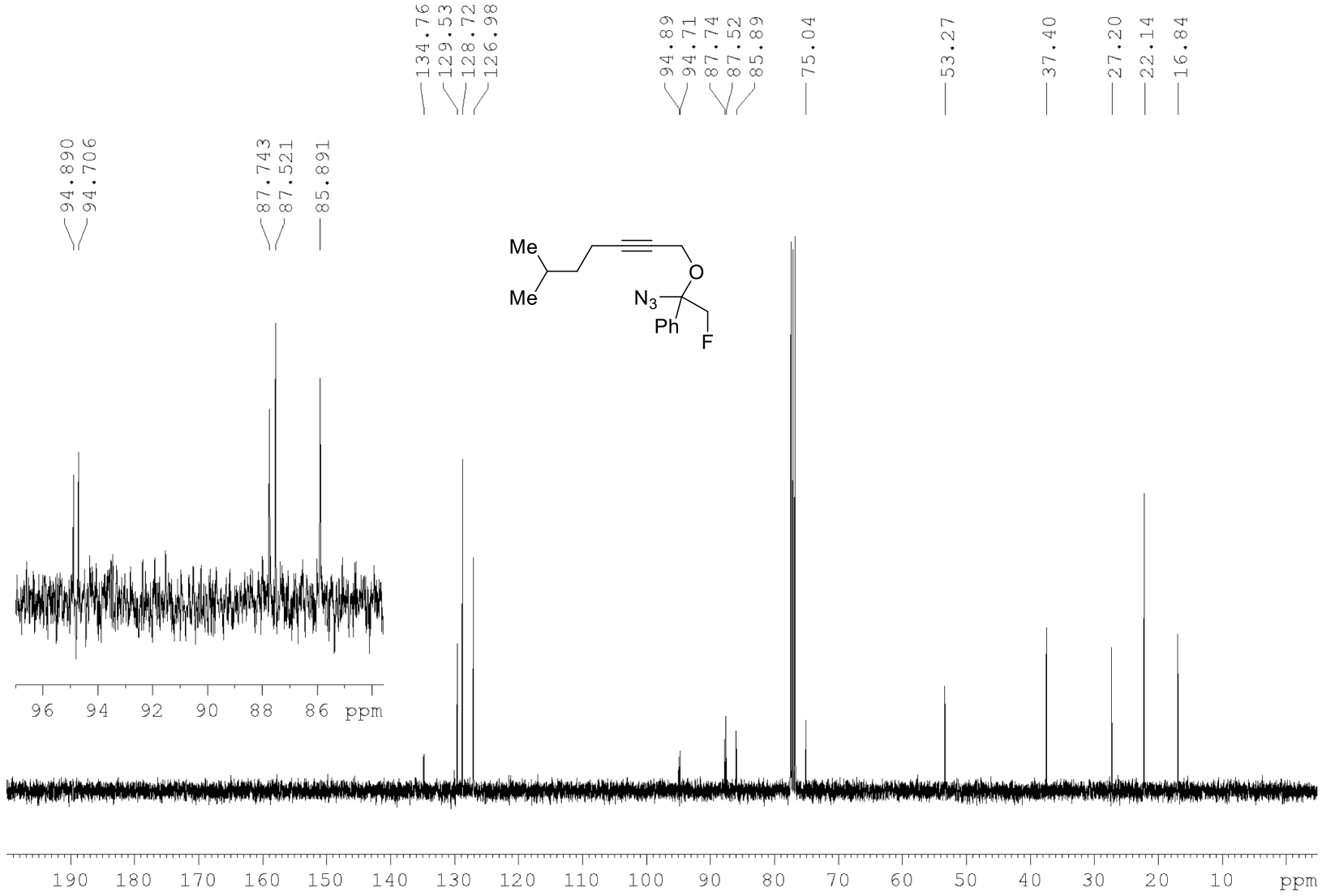

Figure S11. ^{1}H spectrum of 1-(1-azido-2-fluoro-1-((3-phenylprop-2-yn-1-yl)oxy)ethyl)naphthalene (1m)

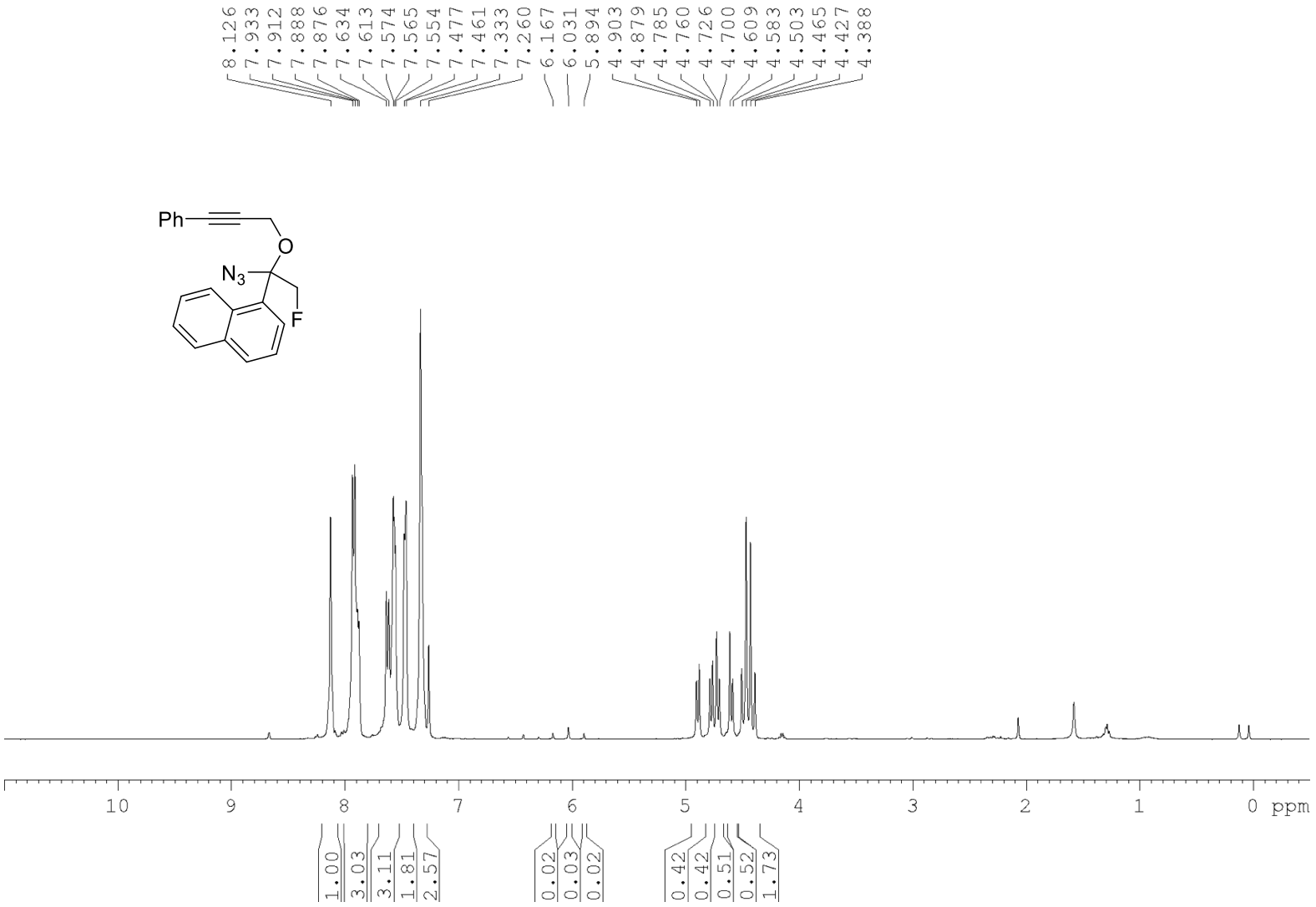

Figure S12. ^{13}C spectrum of 1-(1-azido-2-fluoro-1-((3-phenylprop-2-yn-1-yl)oxy)ethyl)naphthalene (1m)

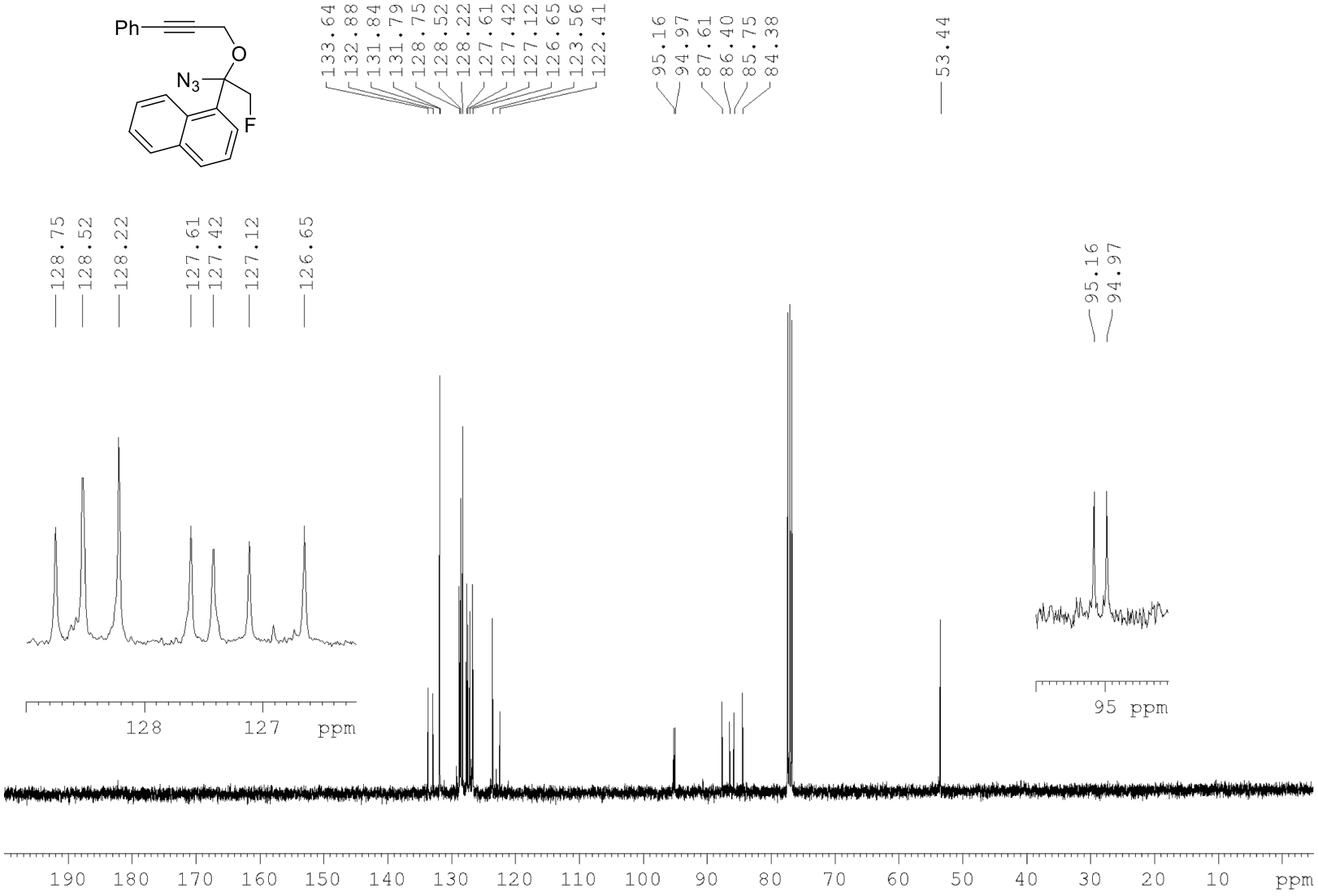

Figure S13. ^{1}H spectrum of (3-((2-azido-1-fluoro-4-phenylbutan-2-yl)oxy)prop-1-yn-1-yl)benzene (1n)

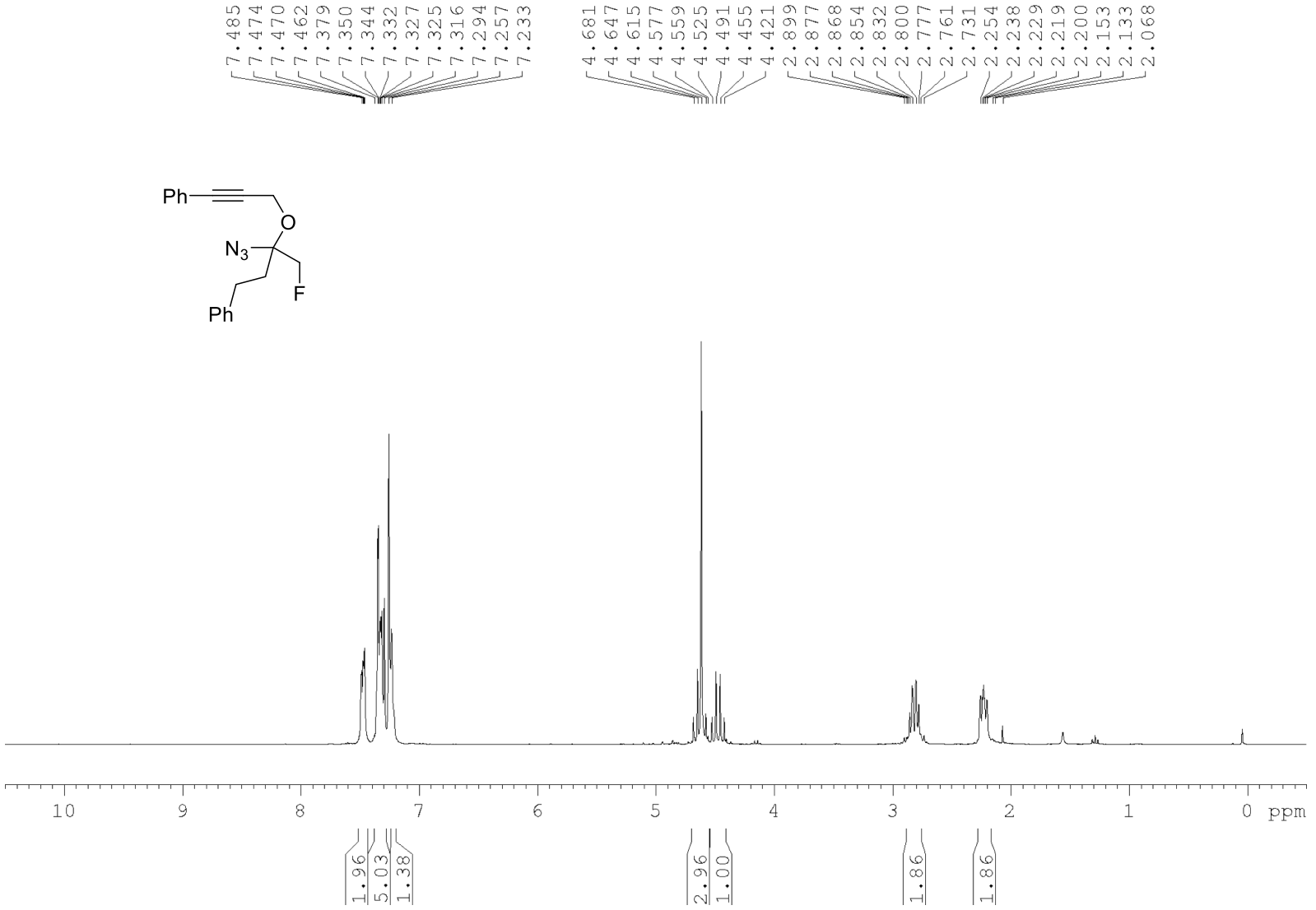

Figure S14. ^{13}C spectrum of (3-((2-azido-1-fluoro-4-phenylbutan-2-yl)oxy)prop-1-yn-1-yl)benzene (1n)

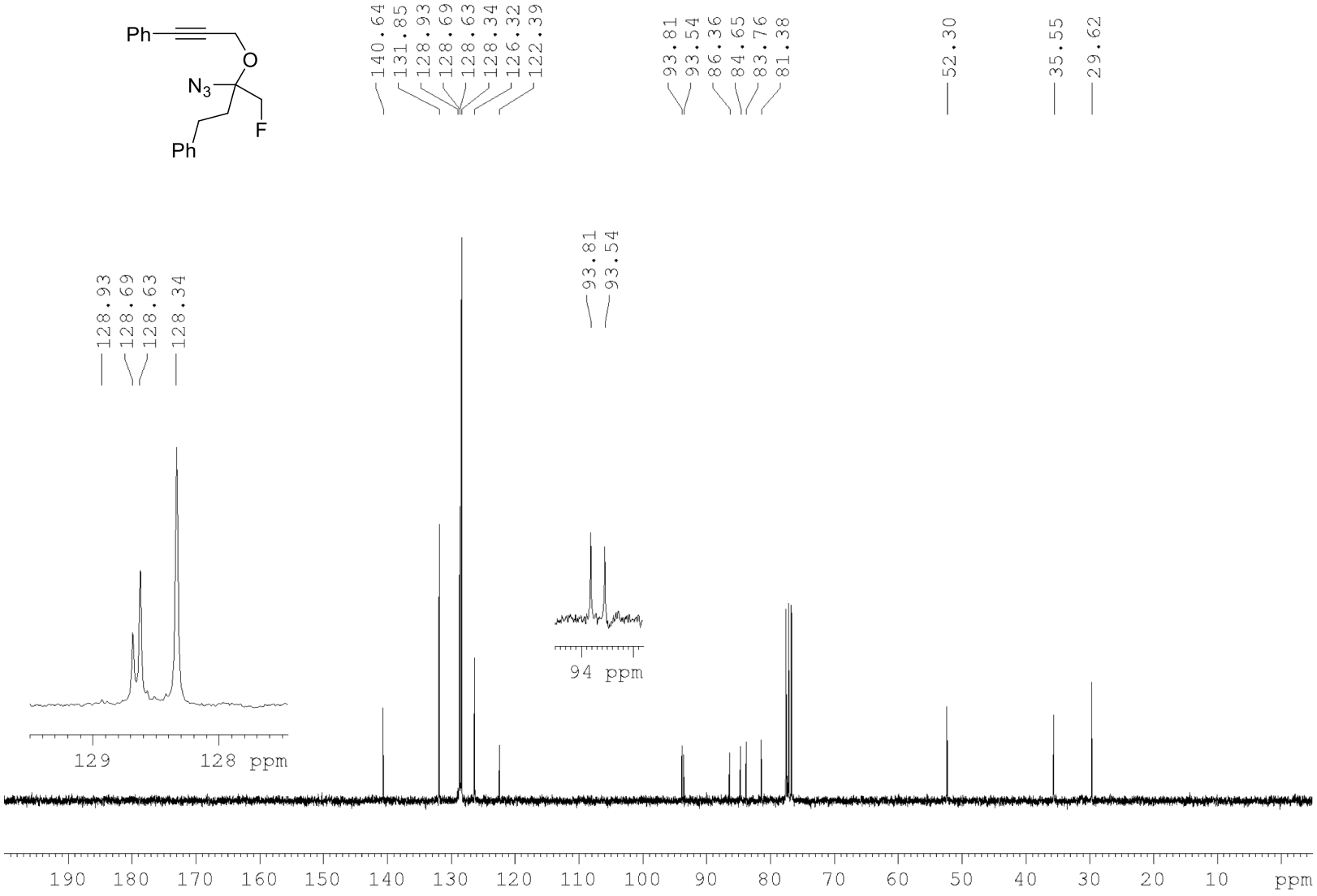

Figure S15. ^{1}H spectrum of 1-(3-(1-azido-2-fluoro-1-phenylethoxy)prop-1-ynyl)-4-methoxybenzene (1b)

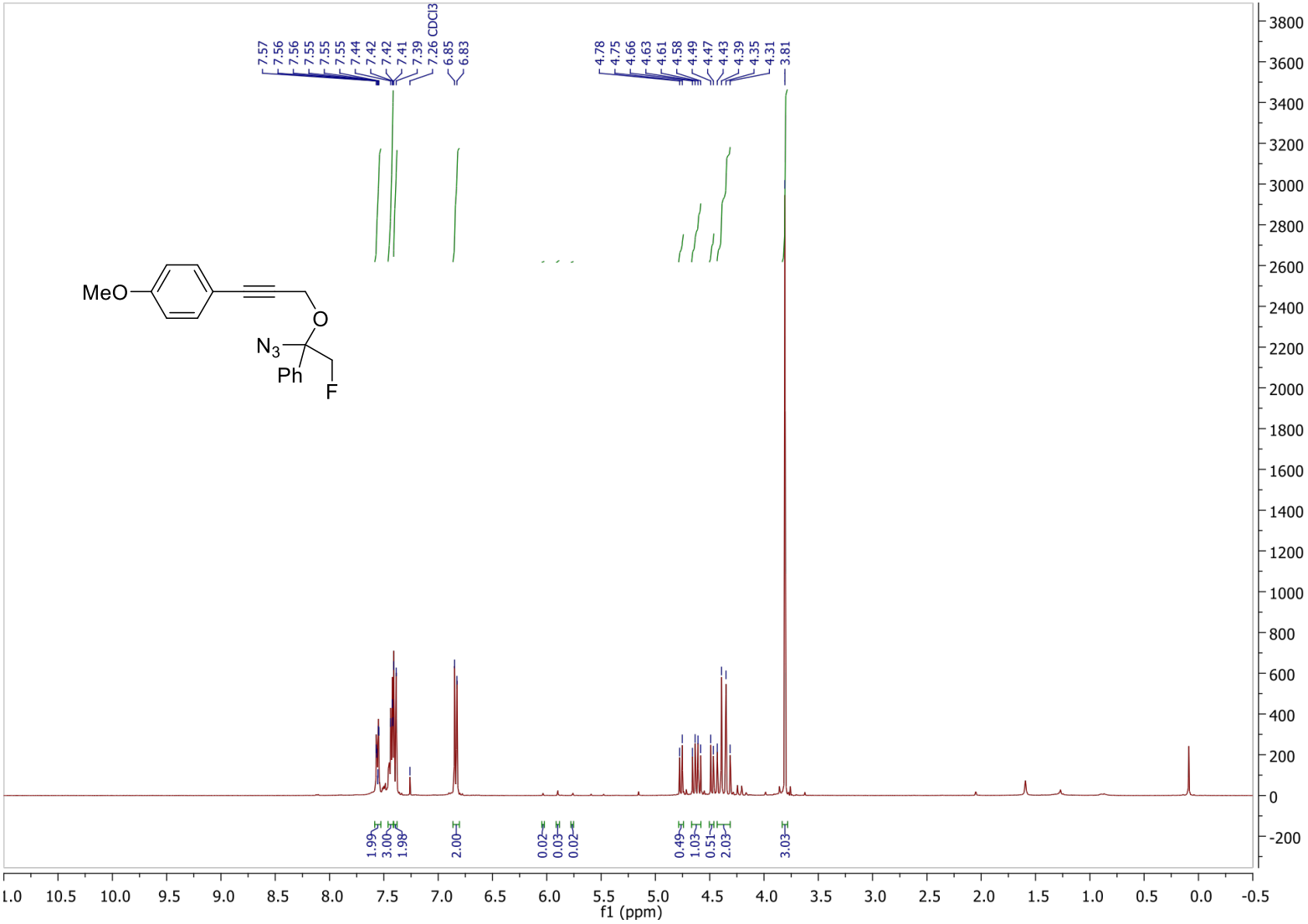

Figure S16. ^{13}C spectrum of 1-(3-(1-azido-2-fluoro-1-phenylethoxy)prop-1-ynyl)-4-methoxybenzene (1b)

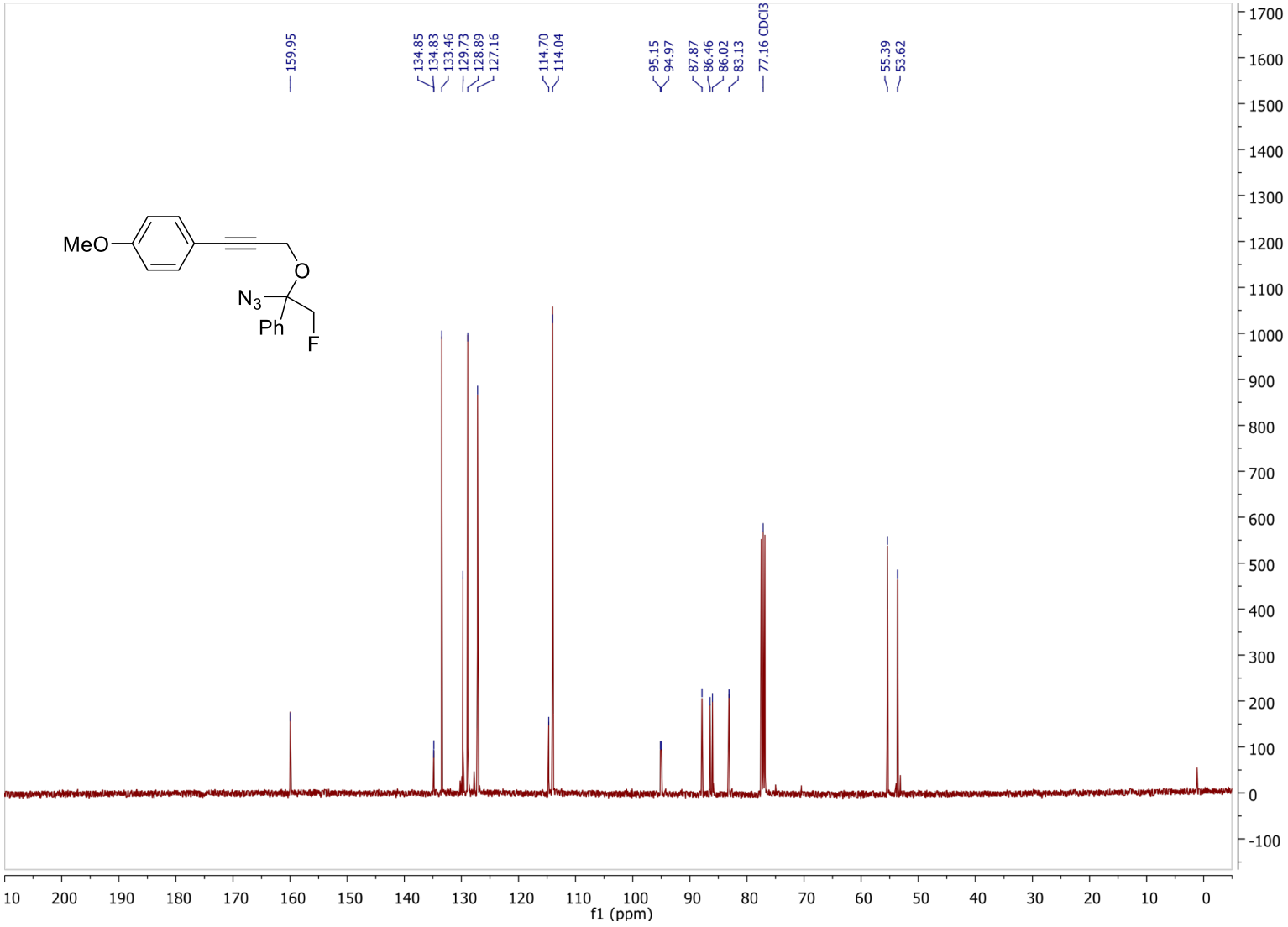

Figure S17. ^{1}H spectrum of 1-(3-(1-azido-2-fluoro-1-phenylethoxy)prop-1-ynyl)-3-methoxybenzene (1c)

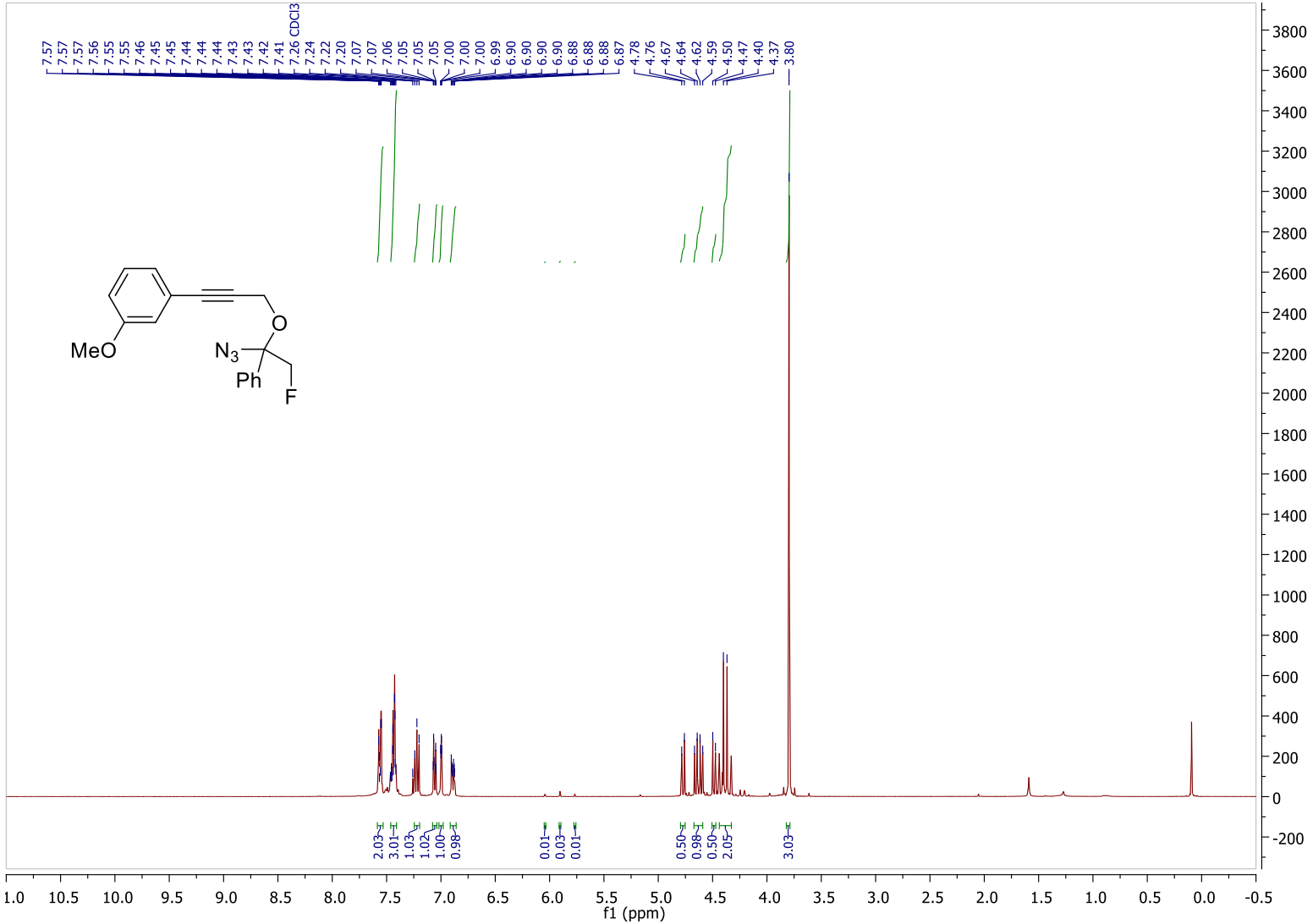

Figure S18. ^{13}C spectrum of 1-(3-(1-azido-2-fluoro-1-phenylethoxy)prop-1-ynyl)-3-methoxybenzene (1c)

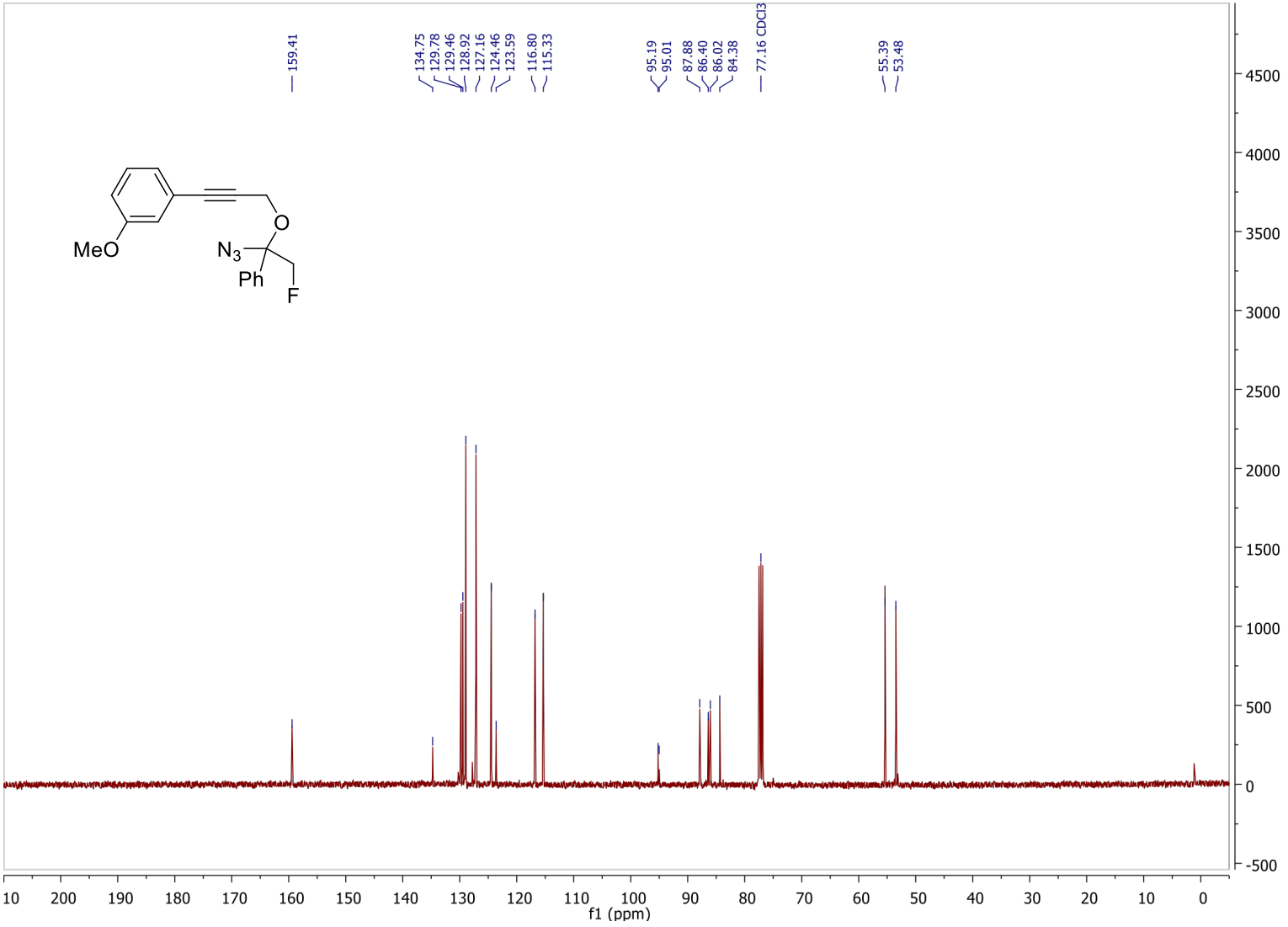

Figure S19. ^{1}H spectrum of 2-(3-(1-azido-2-fluoro-1-phenylethoxy)prop-1-ynyl)thiophene (1e)

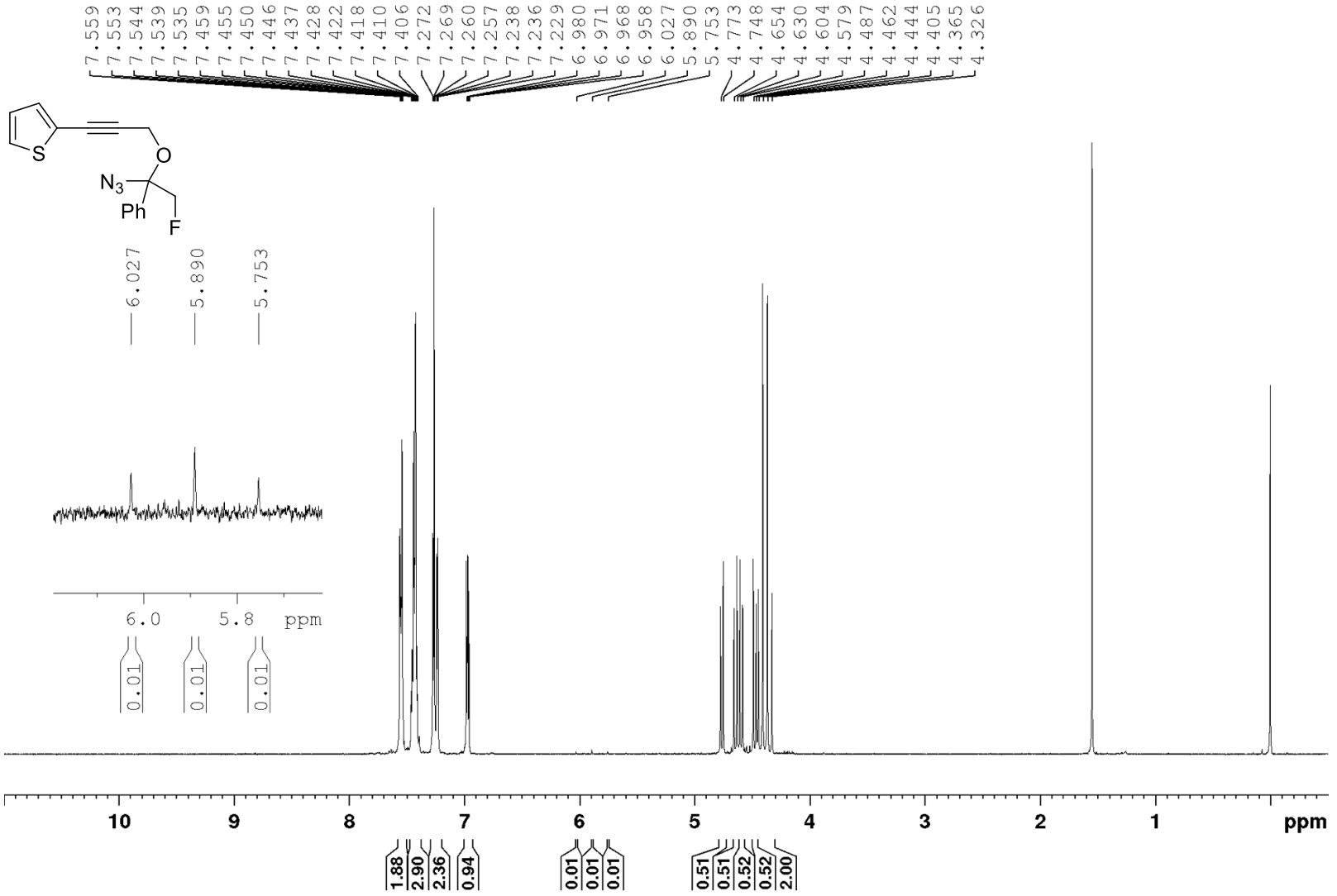

Figure S20. ^{13}C spectrum of 2-(3-(1-azido-2-fluoro-1-phenylethoxy)prop-1-ynyl)thiophene (1e)

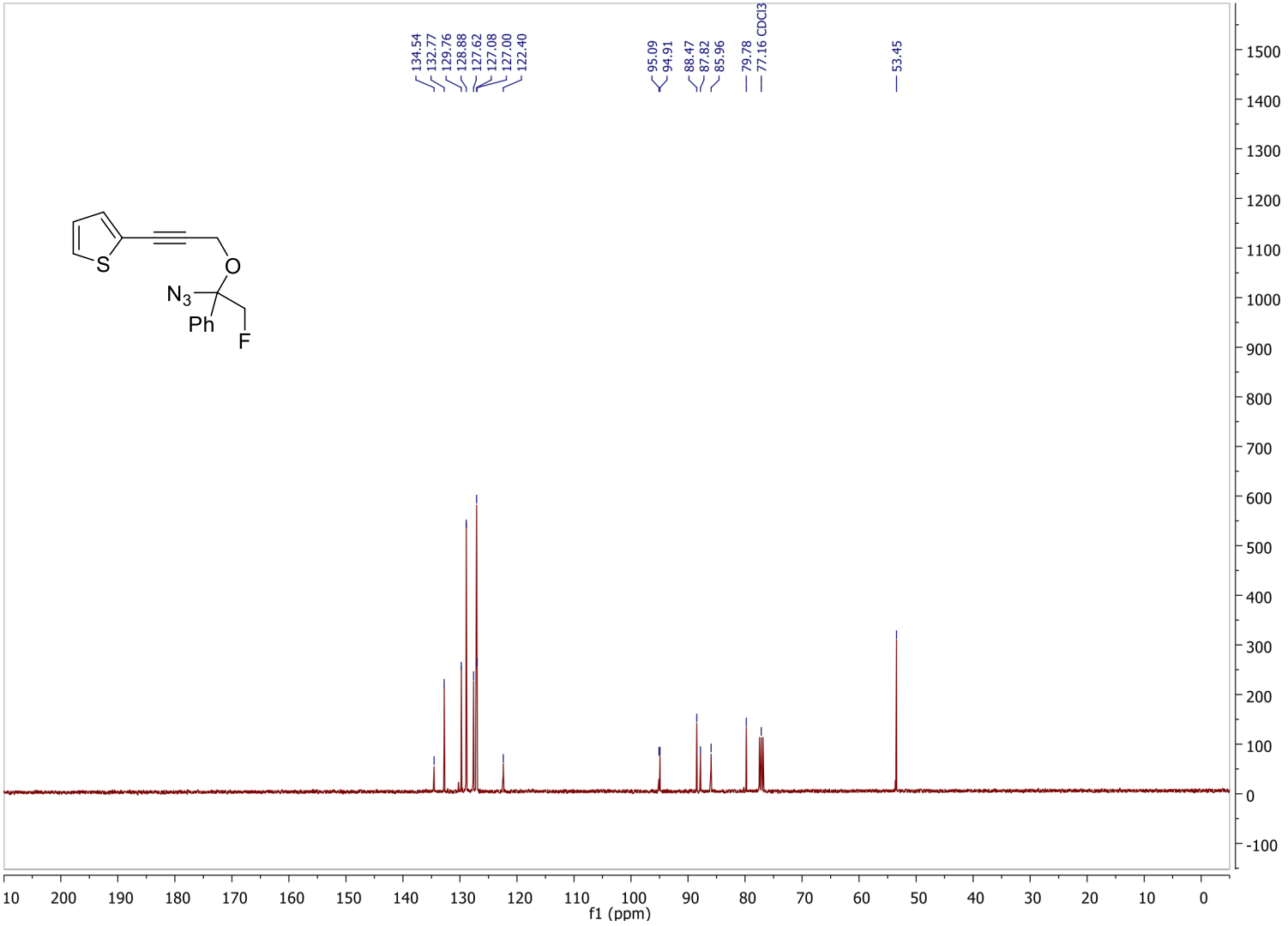

Figure S21. ^{1}H spectrum of 1-(3-(1-azido-2-fluoro-1-phenylethoxy)prop-1-ynyl)-4-bromobenzene (1f)

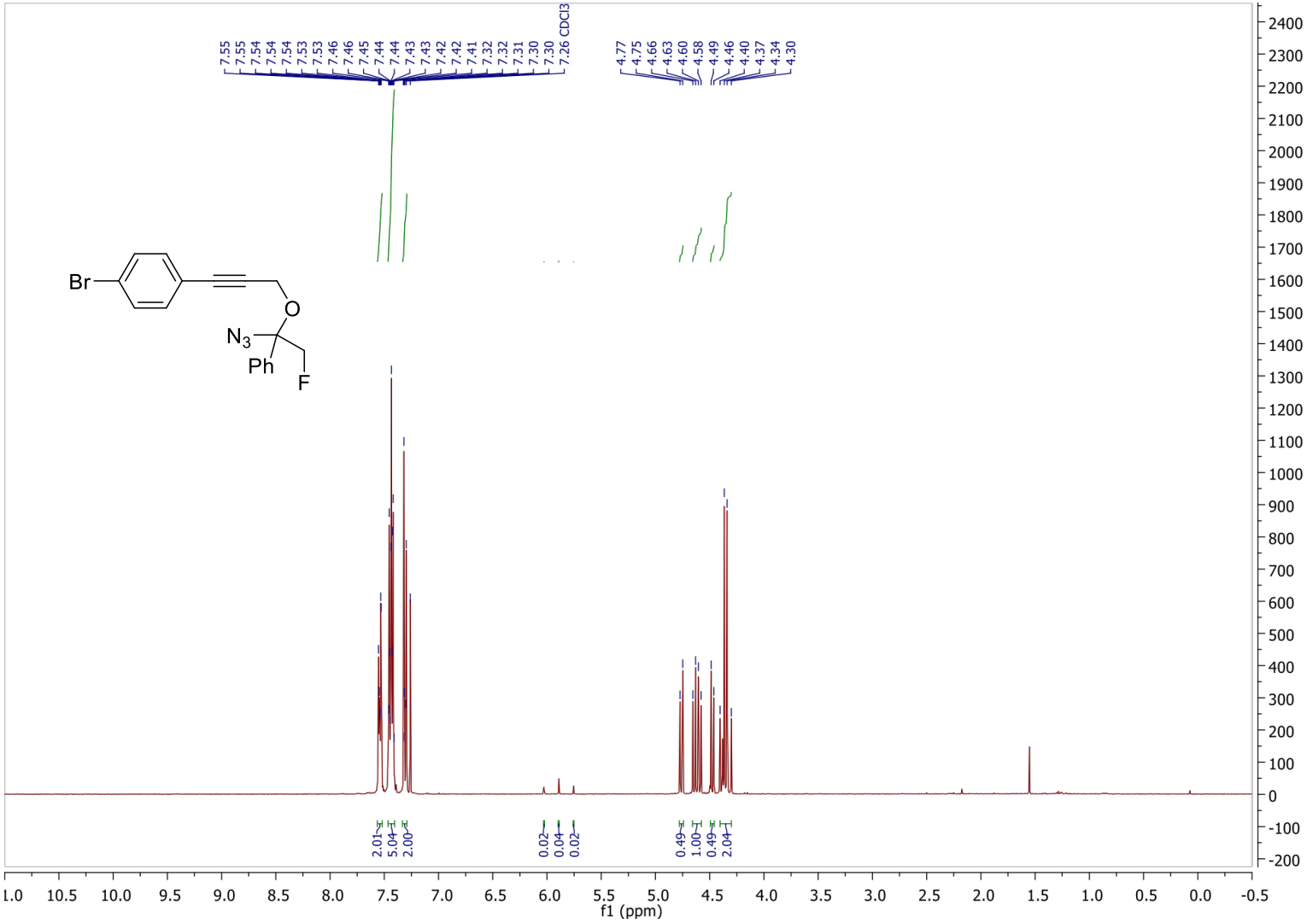

Figure S22. ^{1}H spectrum of 1-(3-(1-azido-2-fluoro-1-phenylethoxy)prop-1-ynyl)-4-bromobenzene (1f)

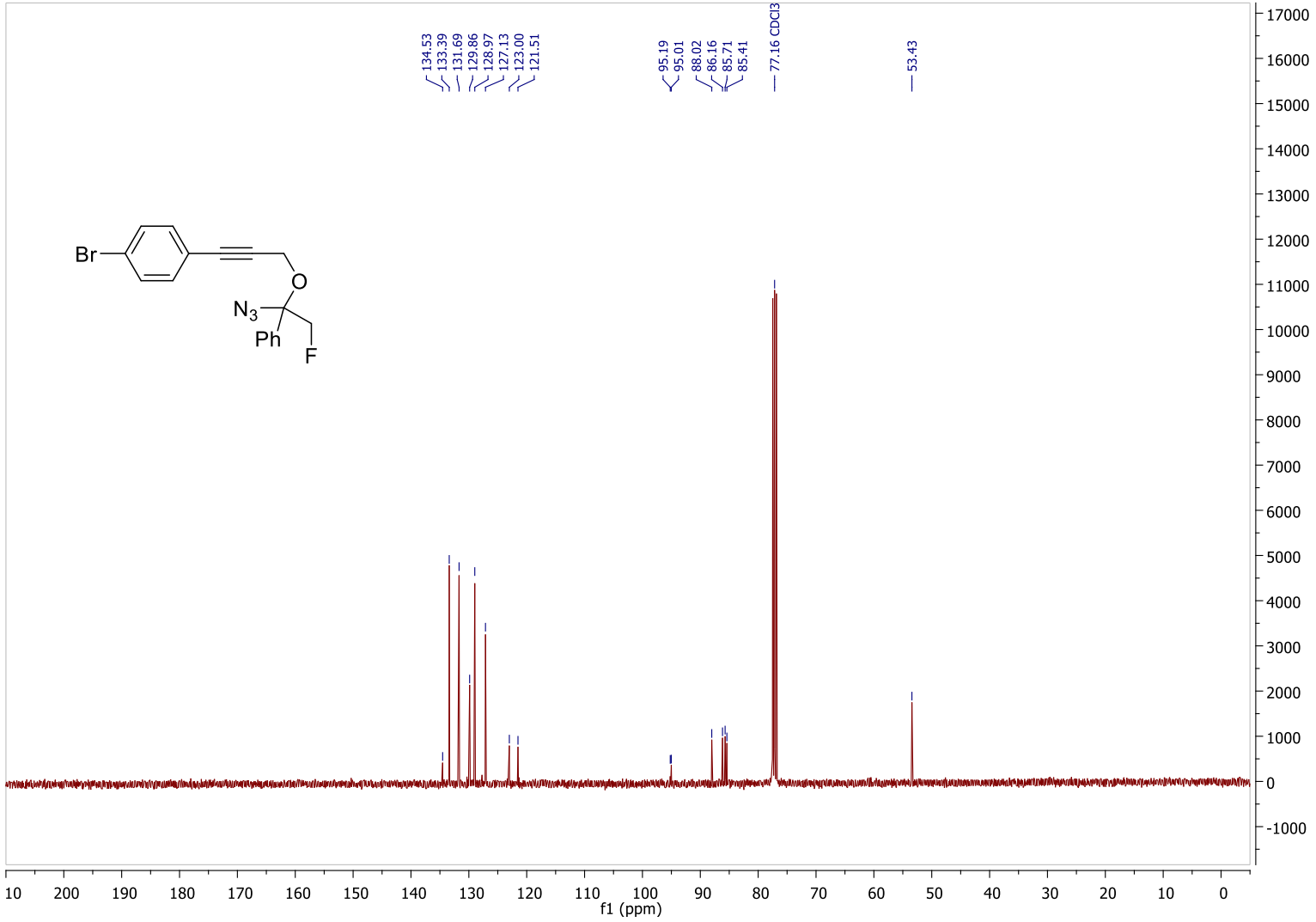

Figure S23. ^{1}H spectrum of methyl 4-(3-(1-azido-2-fluoro-1-phenylethoxy)prop-1-ynyl)benzoate (1h)

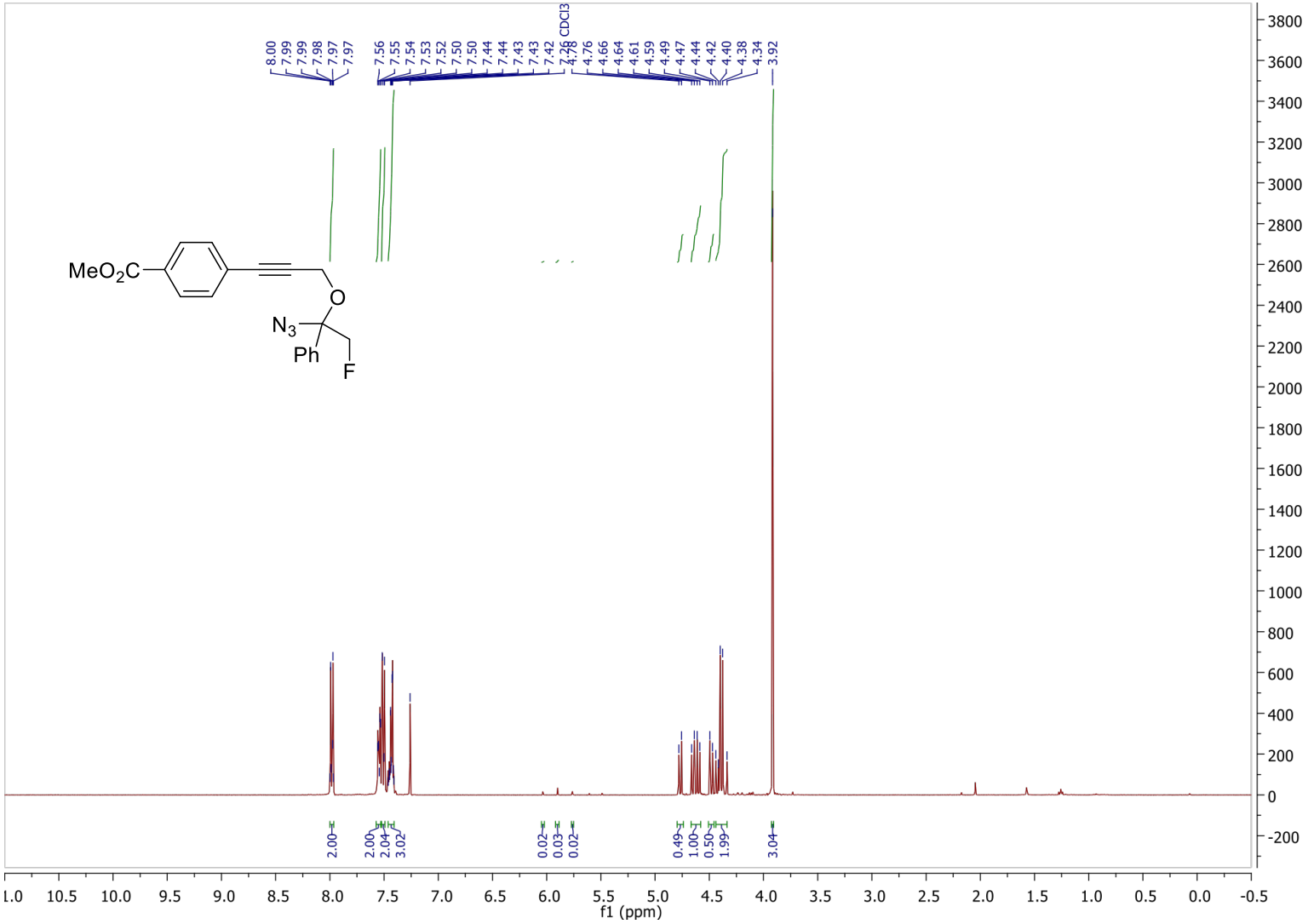

Figure S24. ^{13}C spectrum of methyl 4-(3-(1-azido-2-fluoro-1-phenylethoxy)prop-1-ynyl)benzoate (1h)

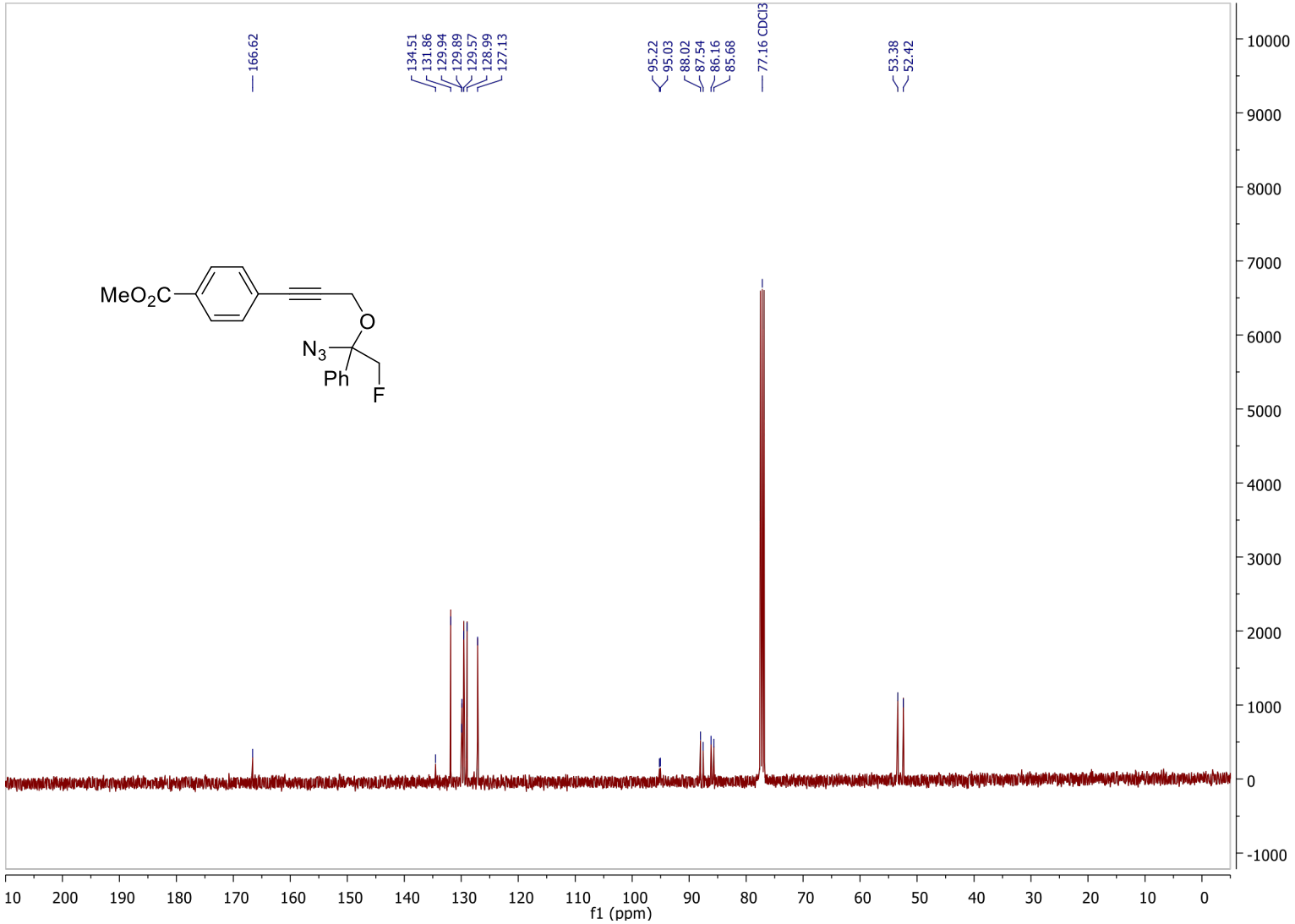

Figure S25. ^{1}H spectrum of N-(3-(1-azido-2-fluoro-1-phenylethoxy)prop-1-yn-1-yl)-N-benzyl-4-methylbenzenesulfonamide (1l)

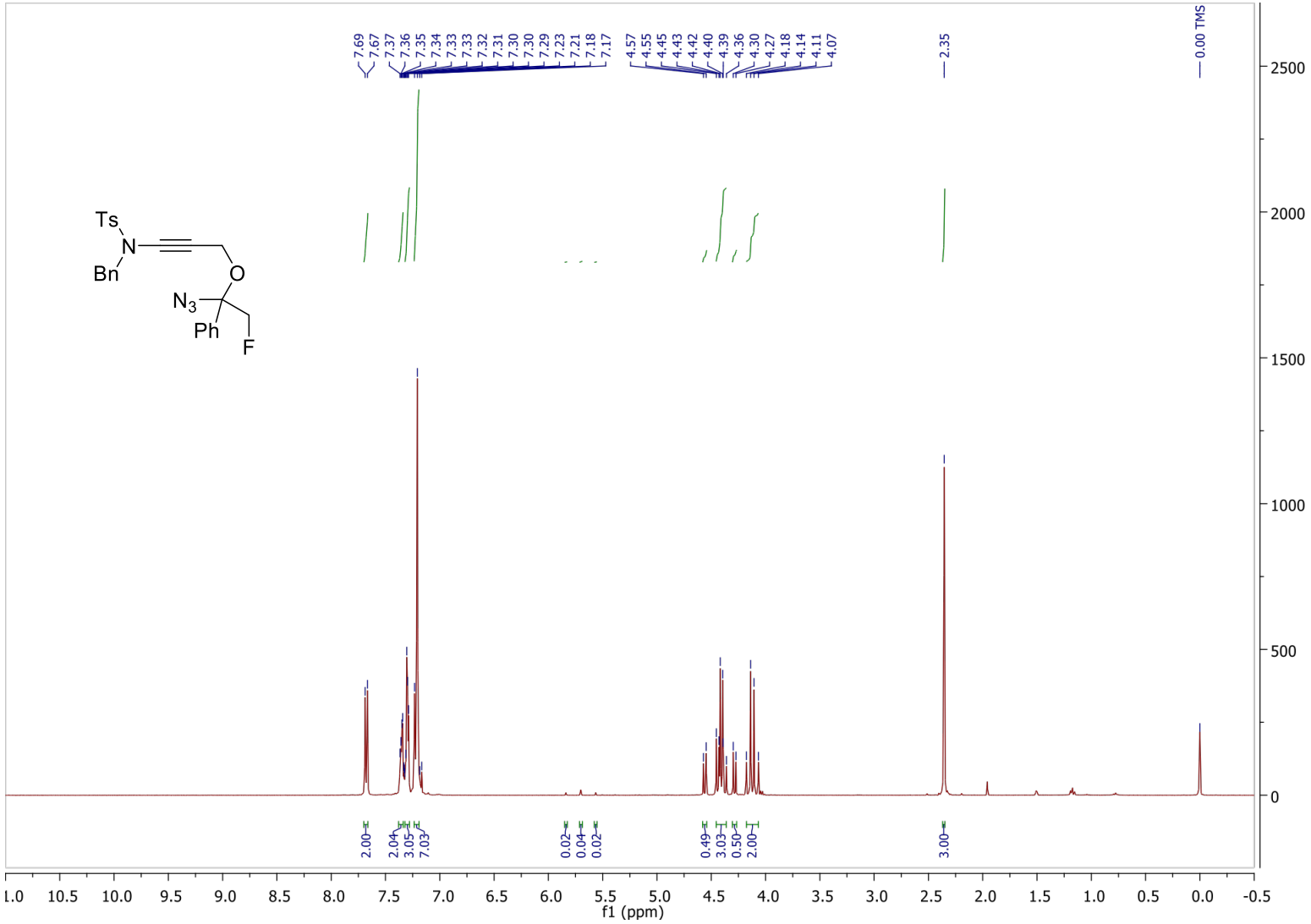

Figure S26. ^{13}C spectrum of N-(3-(1-azido-2-fluoro-1-phenylethoxy)prop-1-yn-1-yl)-N-benzyl-4-methylbenzenesulfonamide (1l)

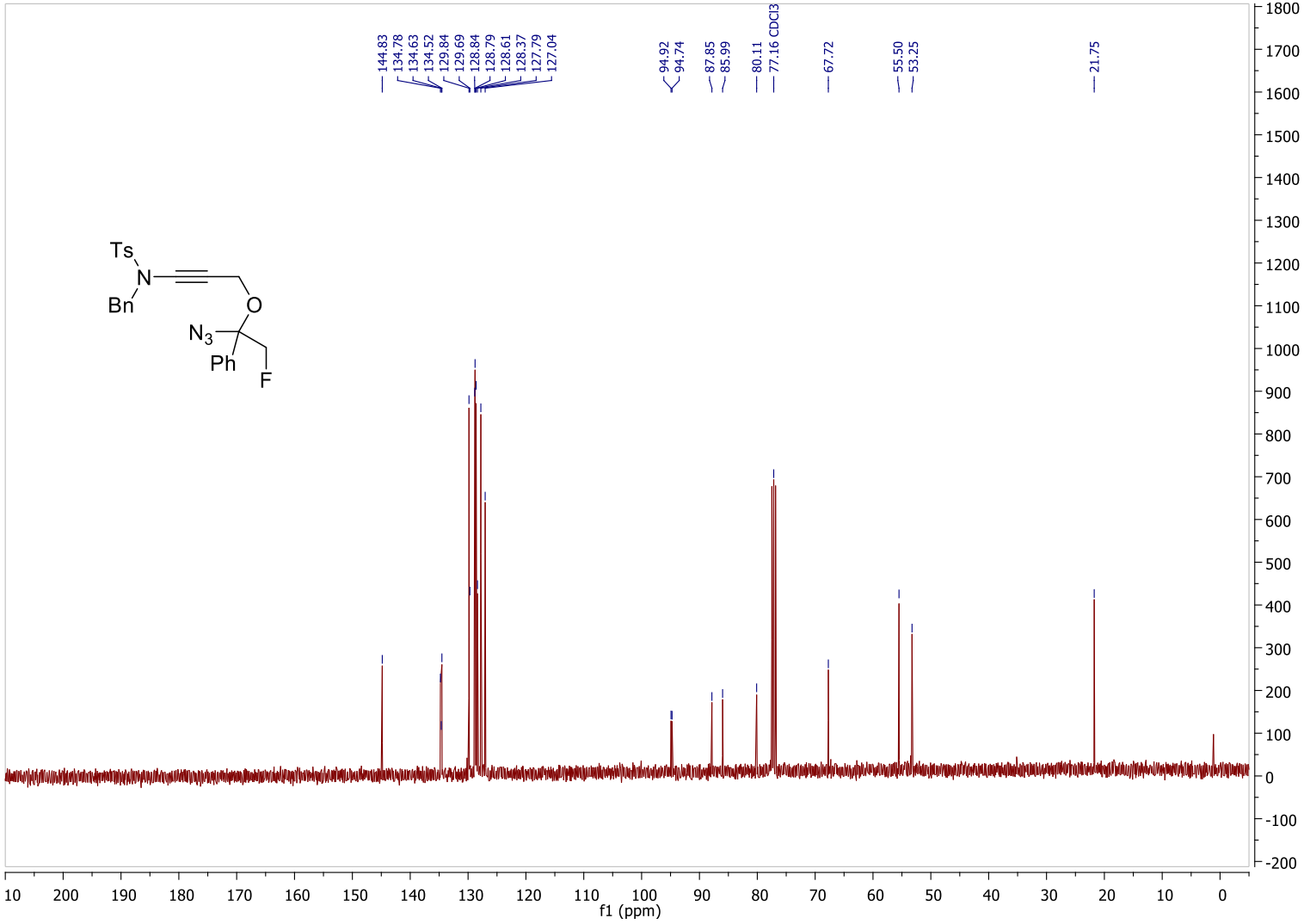

Figure S27. ^{1}H NMR spectrum of 2-(fluoromethyl)-2,4-diphenyl-2*H*-1,3-oxazine (2a)

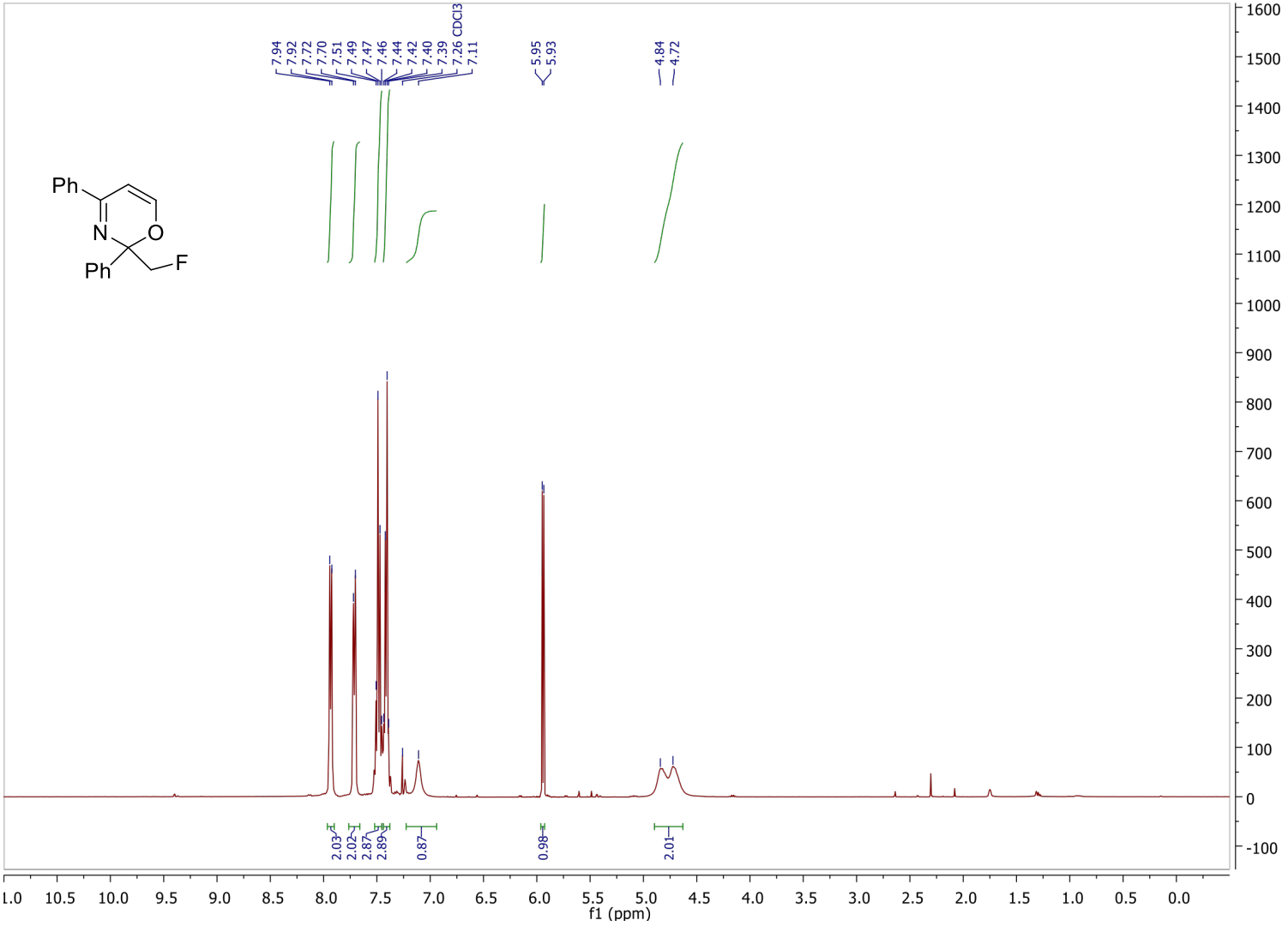

Figure S28. ^{13}C NMR spectrum of 2-(fluoromethyl)-2,4-diphenyl-2*H*-1,3-oxazine (2a)

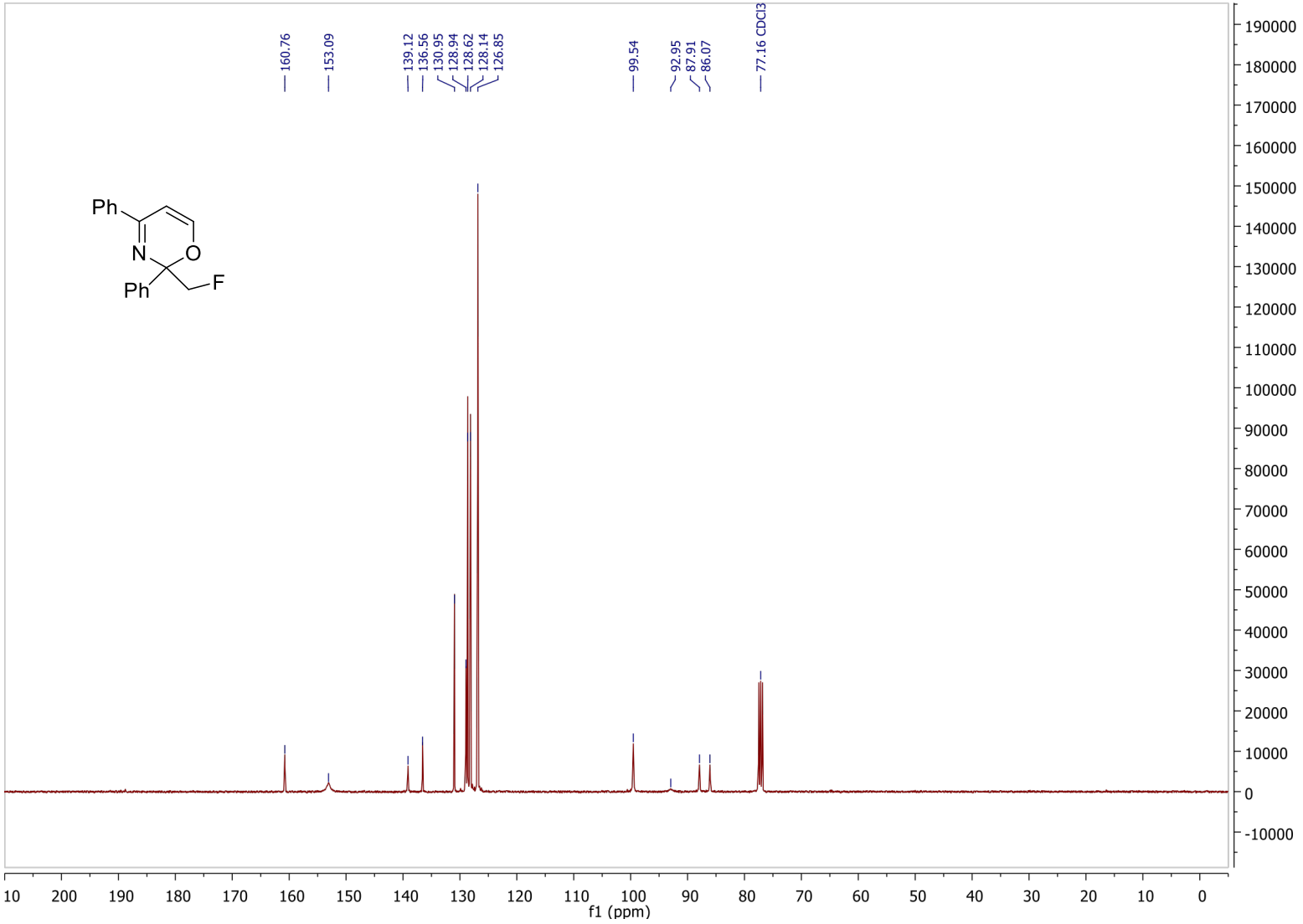

Figure S29. ^{1}H NMR spectrum of 2-(fluoromethyl)-4-(4-methoxyphenyl)-2-phenyl-2*H*-1,3-oxazine (2b)

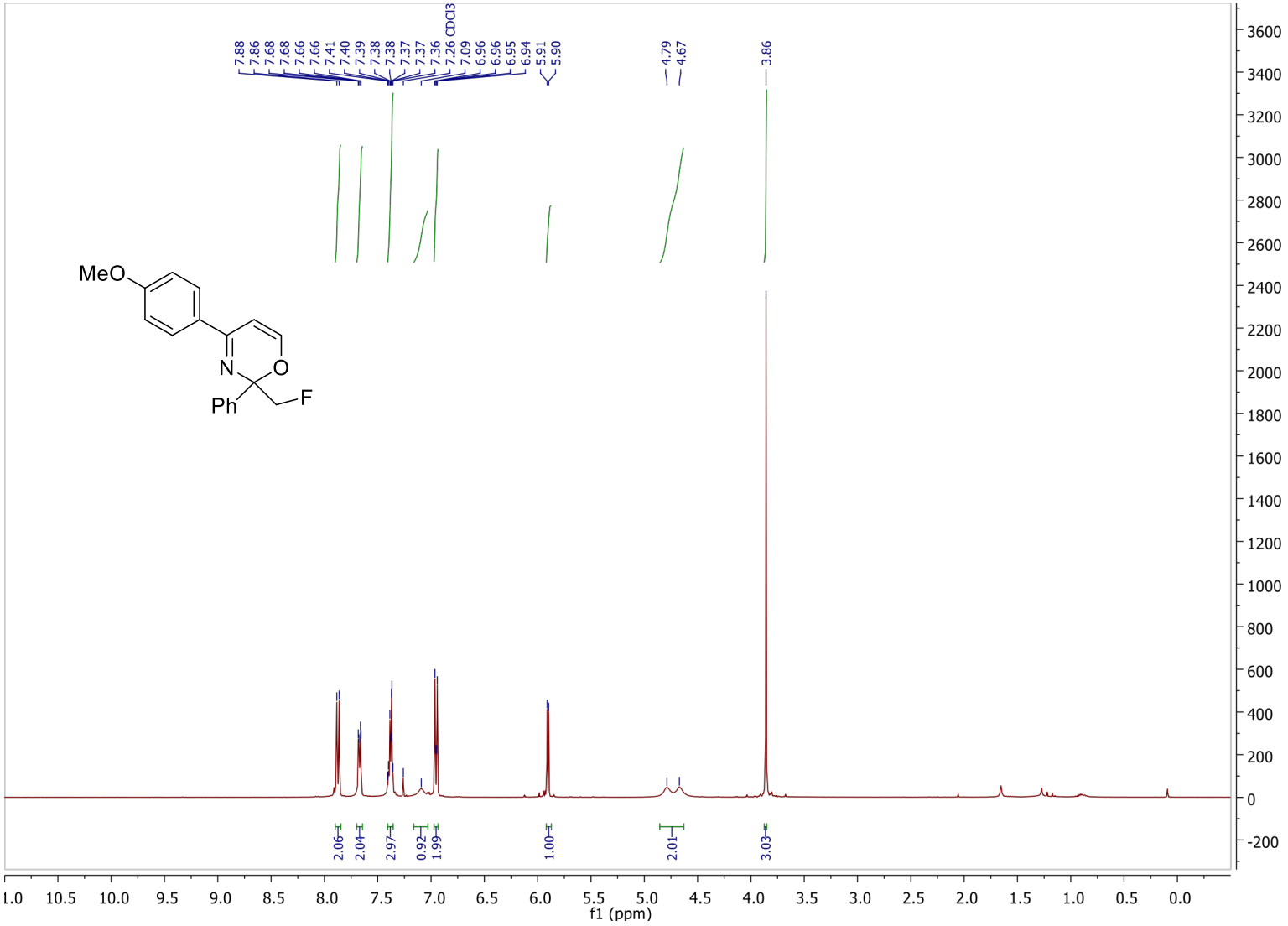

Figure S30. ^{13}C NMR spectrum of 2-(fluoromethyl)-4-(4-methoxyphenyl)-2-phenyl-2*H*-1,3-oxazine (2b)

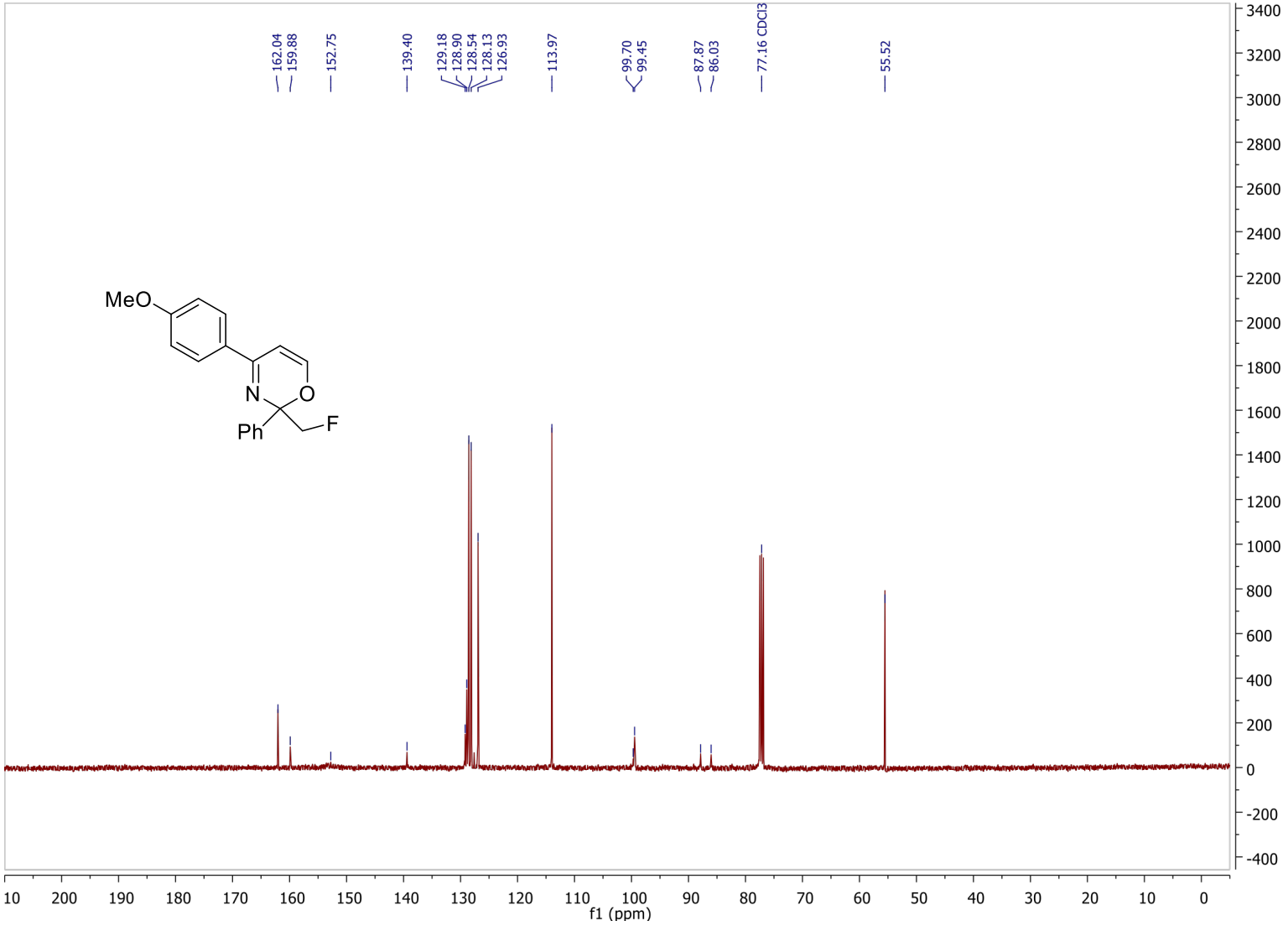

Figure S31. ^{1}H NMR spectrum of 2-(fluoromethyl)-4-(3-methoxyphenyl)-2-phenyl-2*H*-1,3-oxazine (2c)

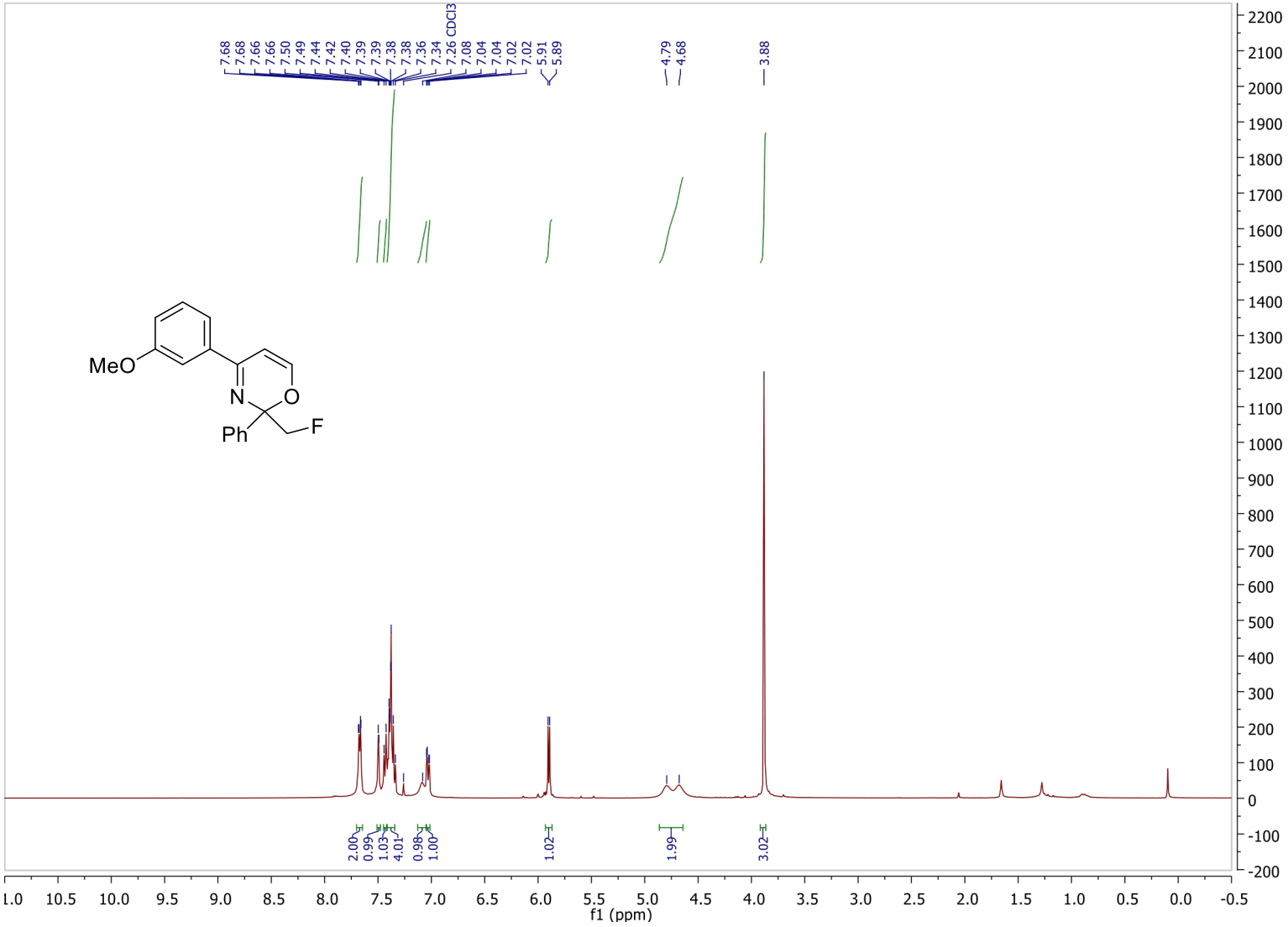

Figure S32. ^{13}C NMR spectrum of 2-(fluoromethyl)-4-(3-methoxyphenyl)-2-phenyl-2*H*-1,3-oxazine (2c)

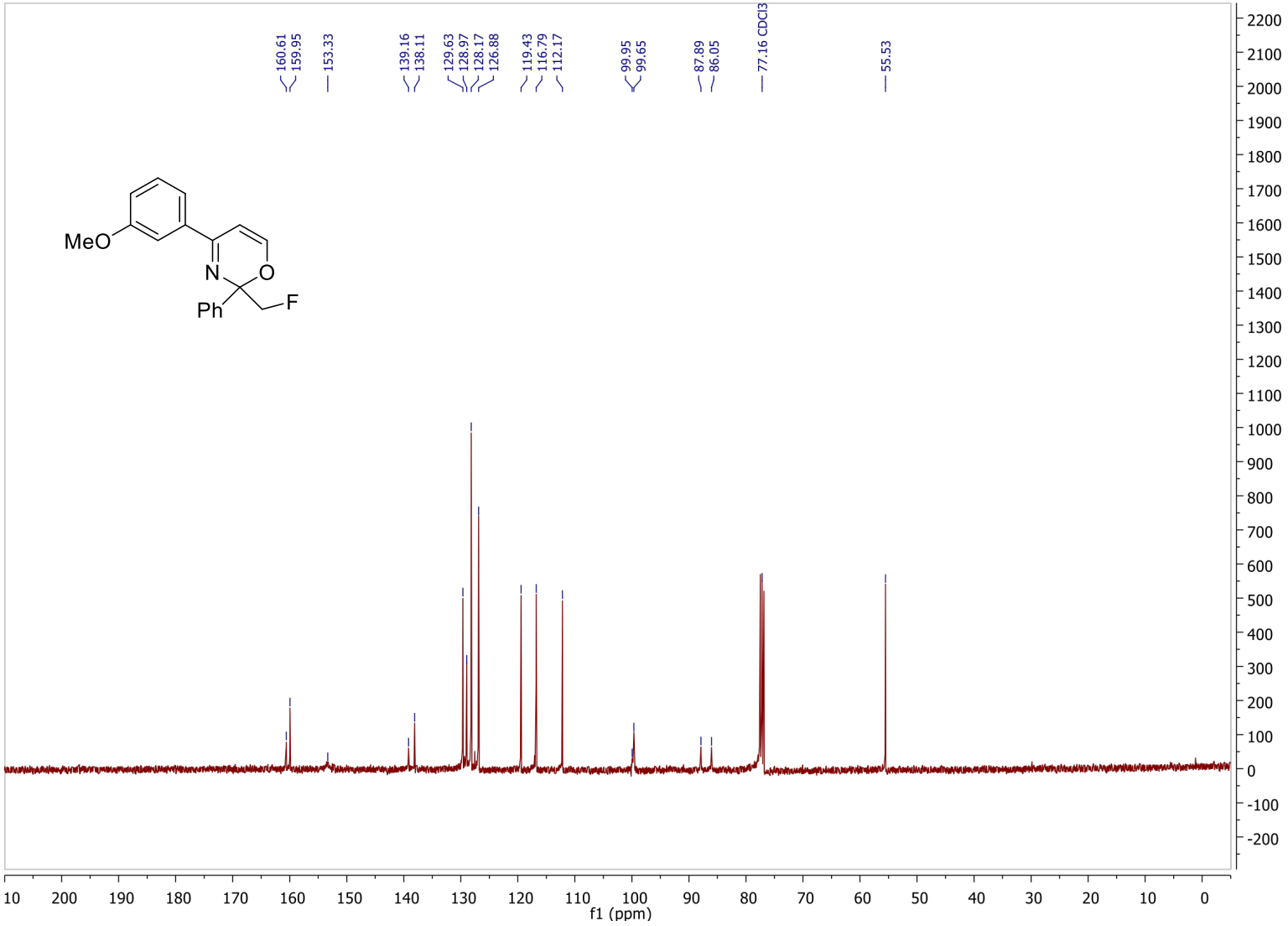

Figure S33. ^{1}H NMR spectrum of 2-(fluoromethyl)-4-(6-methoxynaphthalen-2-yl)-2-phenyl-2*H*-1,3-oxazine (2d)

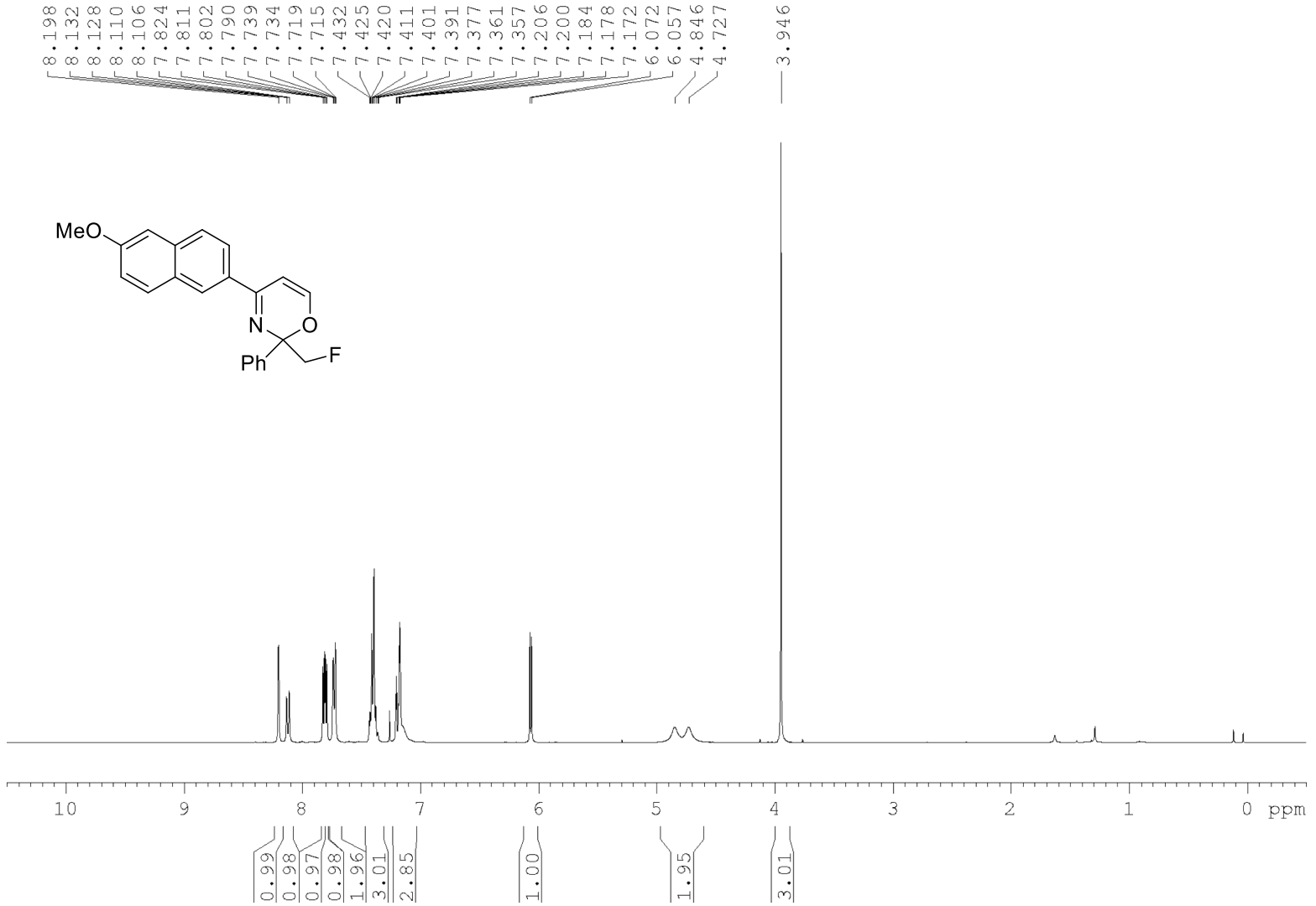

Figure S34. ^{13}C NMR spectrum of 2-(fluoromethyl)-4-(6-methoxynaphthalen-2-yl)-2-phenyl-2*H*-1,3-oxazine (2d)

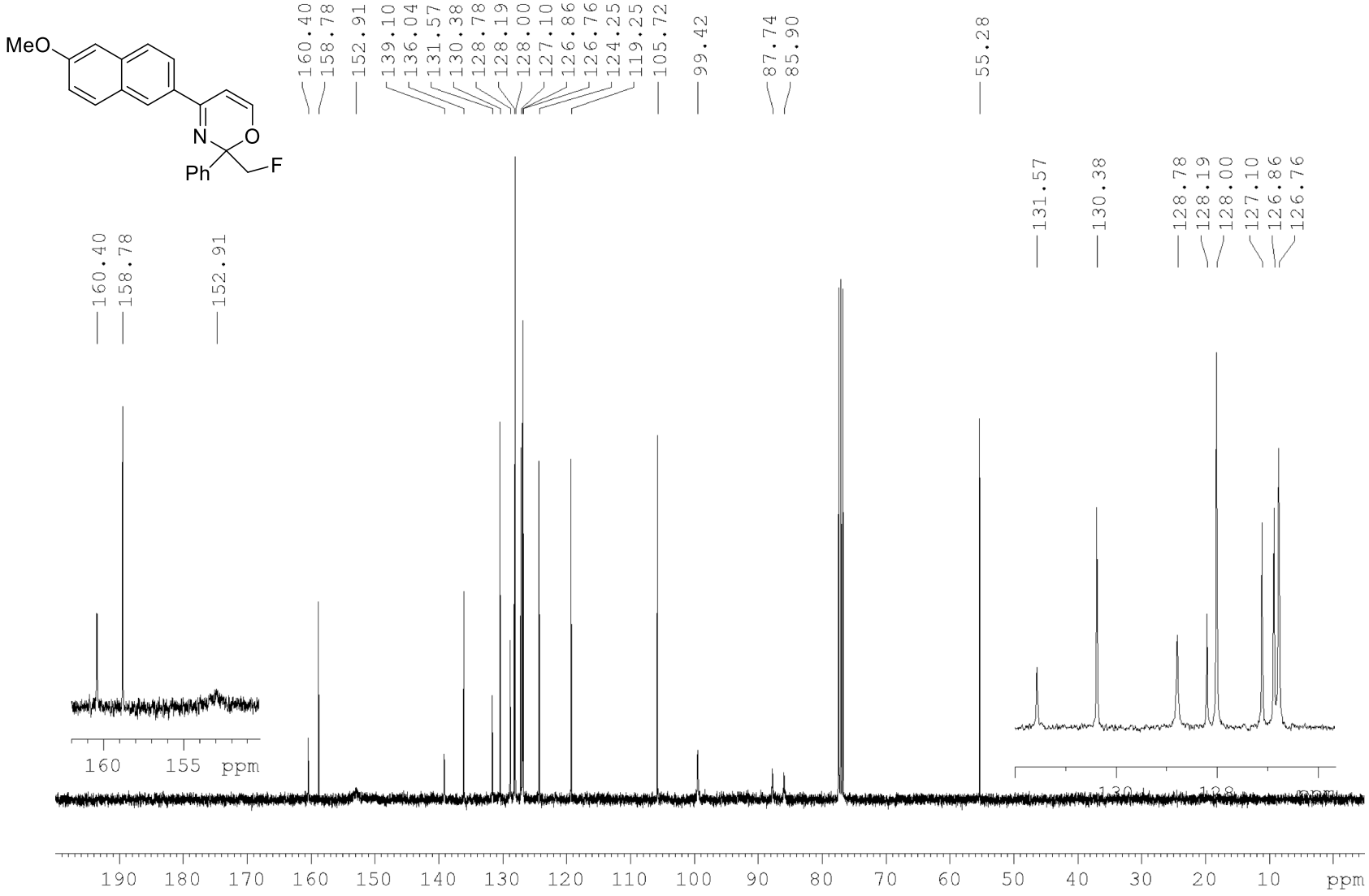

Figure S35. ^{13}C NMR spectrum of 2-(fluoromethyl)-2-phenyl-4-(thiophen-2-yl)-2*H*-1,3-oxazine (2e)

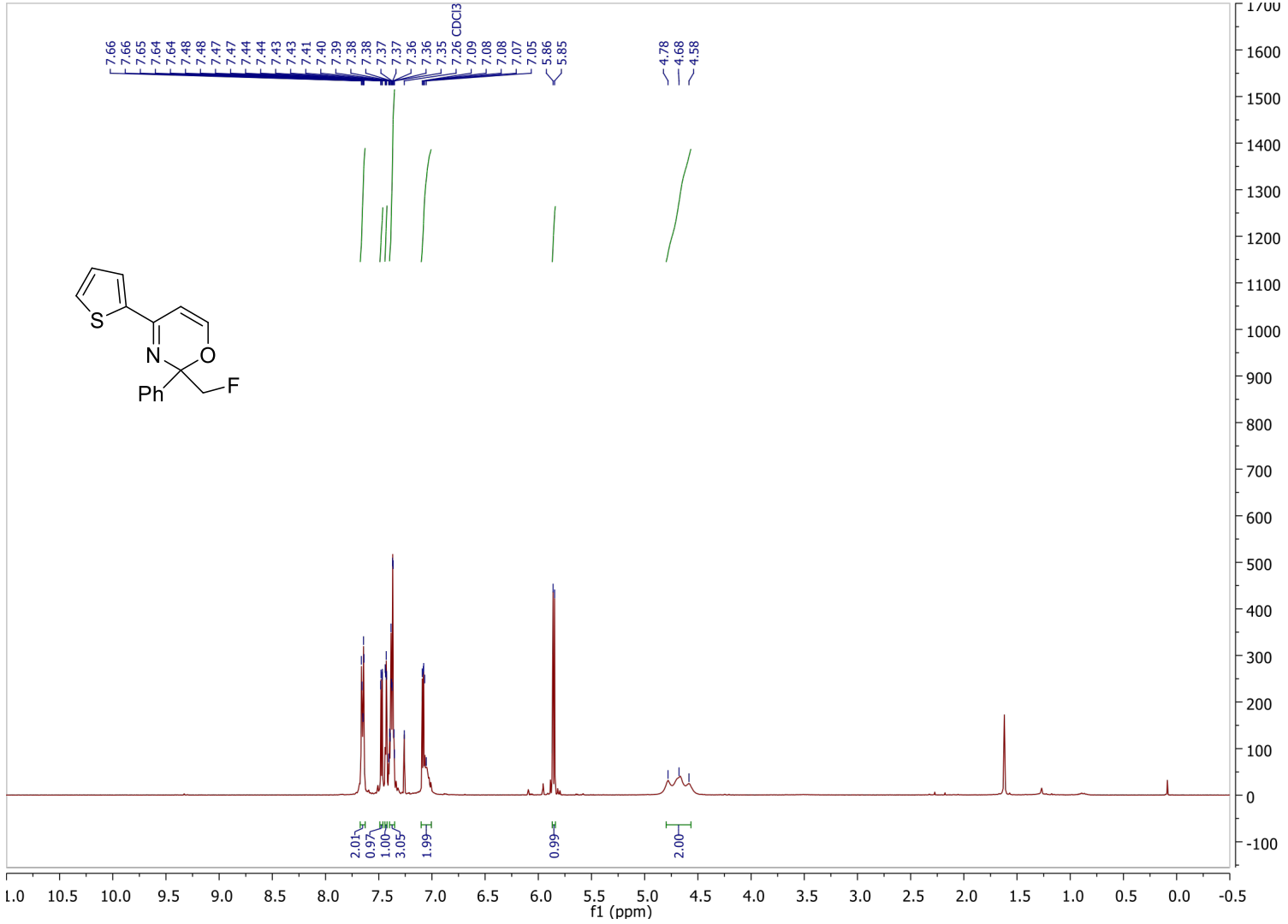

Figure S36. ^{13}C NMR spectrum of 2-(fluoromethyl)-2-phenyl-4-(thiophen-2-yl)-2*H*-1,3-oxazine (2e)

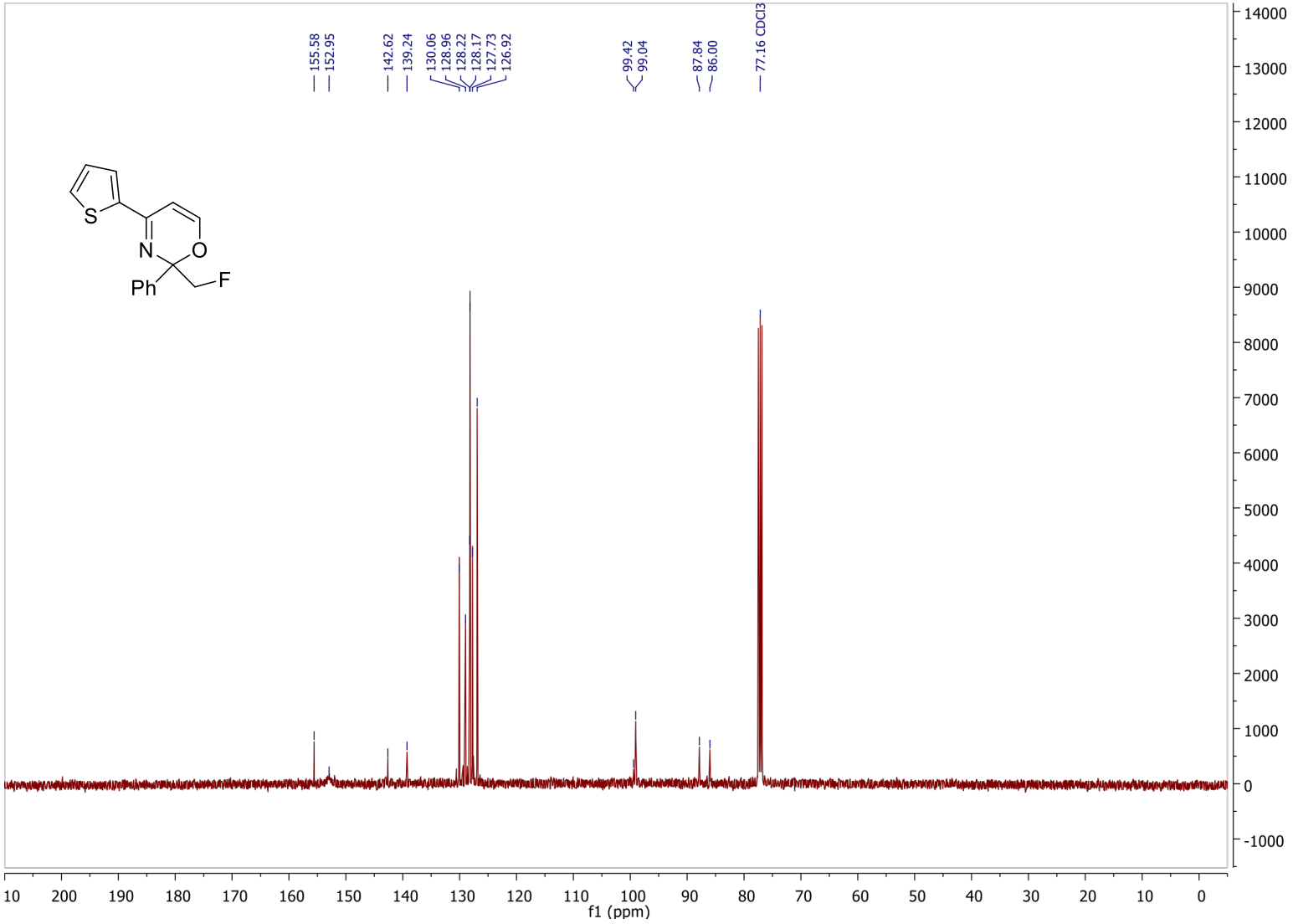

Figure S37. ^{1}H NMR spectrum of 4-(4-bromophenyl)-2-(fluoromethyl)-2-phenyl-2*H*-1,3-oxazine (2f)

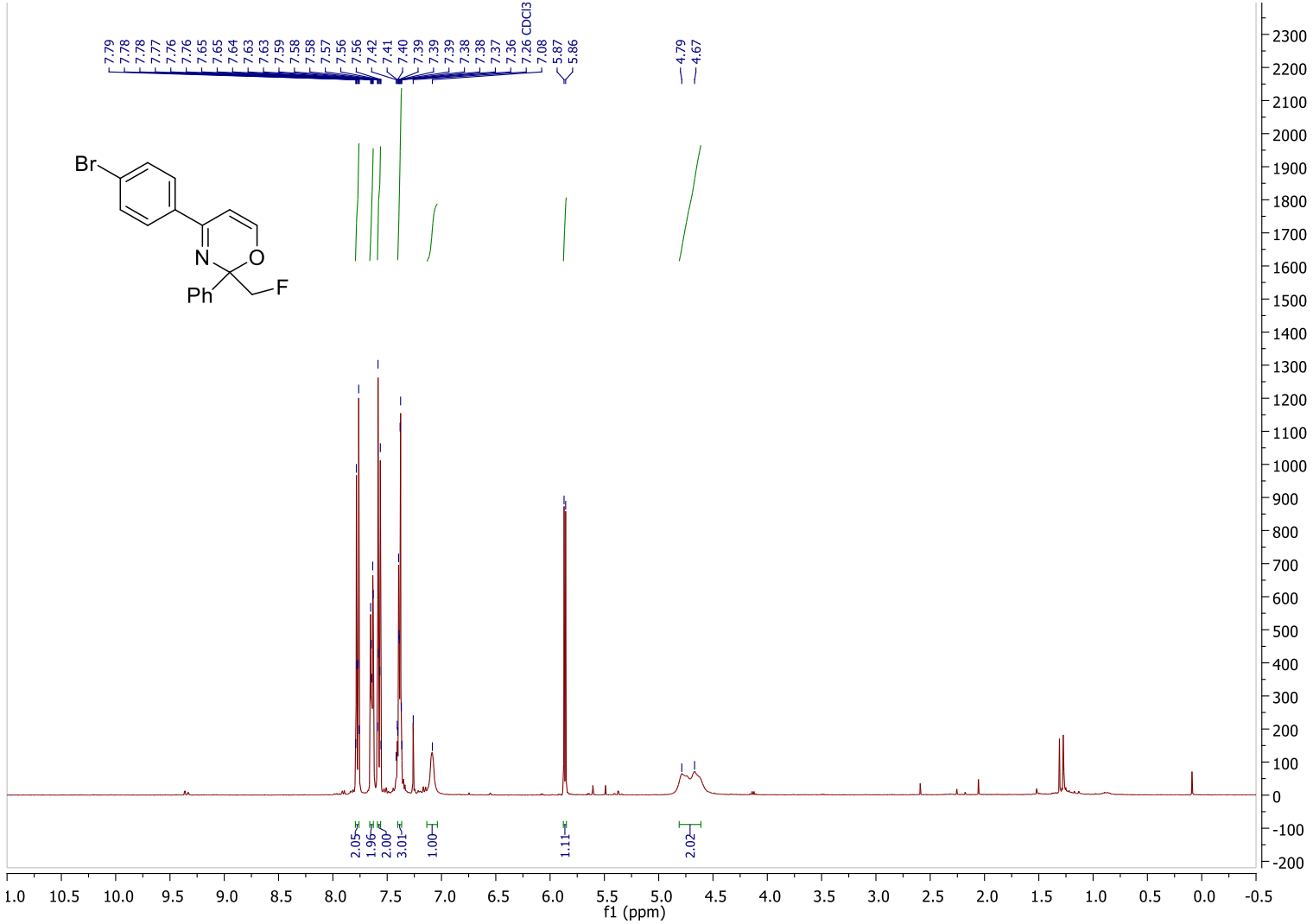

Figure S38. ^{13}C NMR spectrum of 4-(4-bromophenyl)-2-(fluoromethyl)-2-phenyl-2*H*-1,3-oxazine (2f)

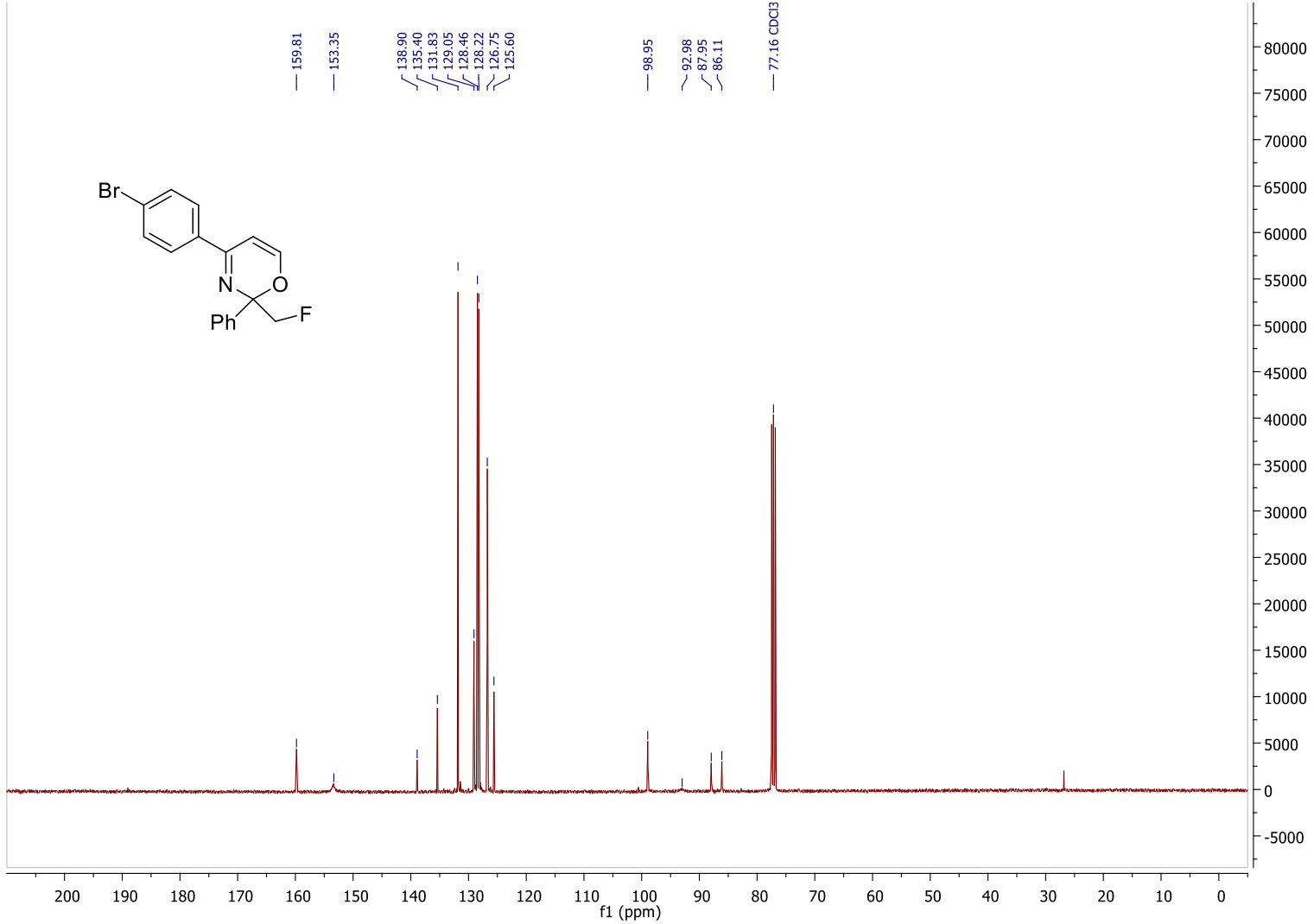

Figure S39. ^{1}H NMR spectrum of 4-(4-fluorophenyl)-2-(fluoromethyl)-2-phenyl-2*H*-1,3-oxazine (2g)

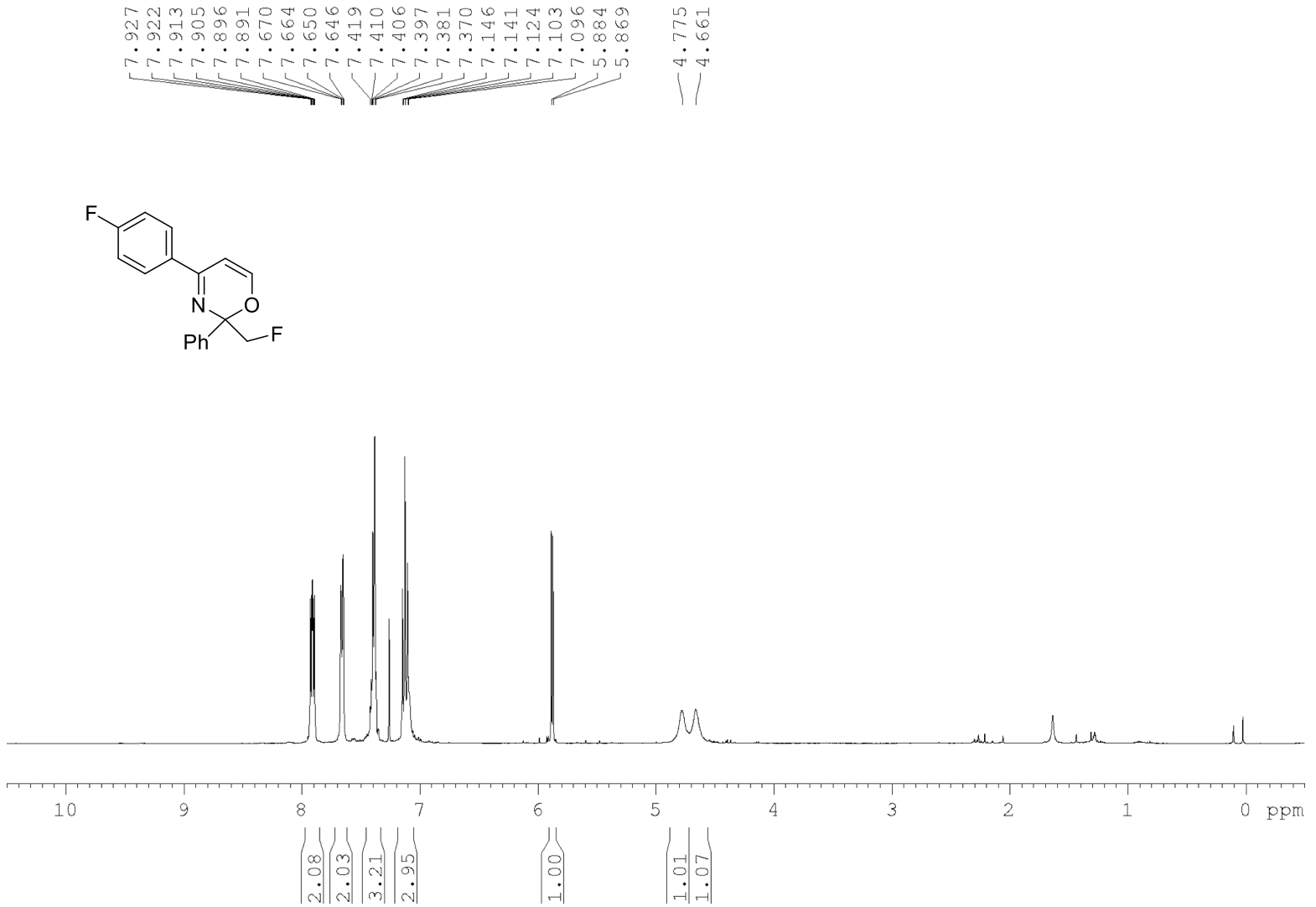

Figure S40. ^{13}C NMR spectrum of 4-(4-fluorophenyl)-2-(fluoromethyl)-2-phenyl-2*H*-1,3-oxazine (2g)

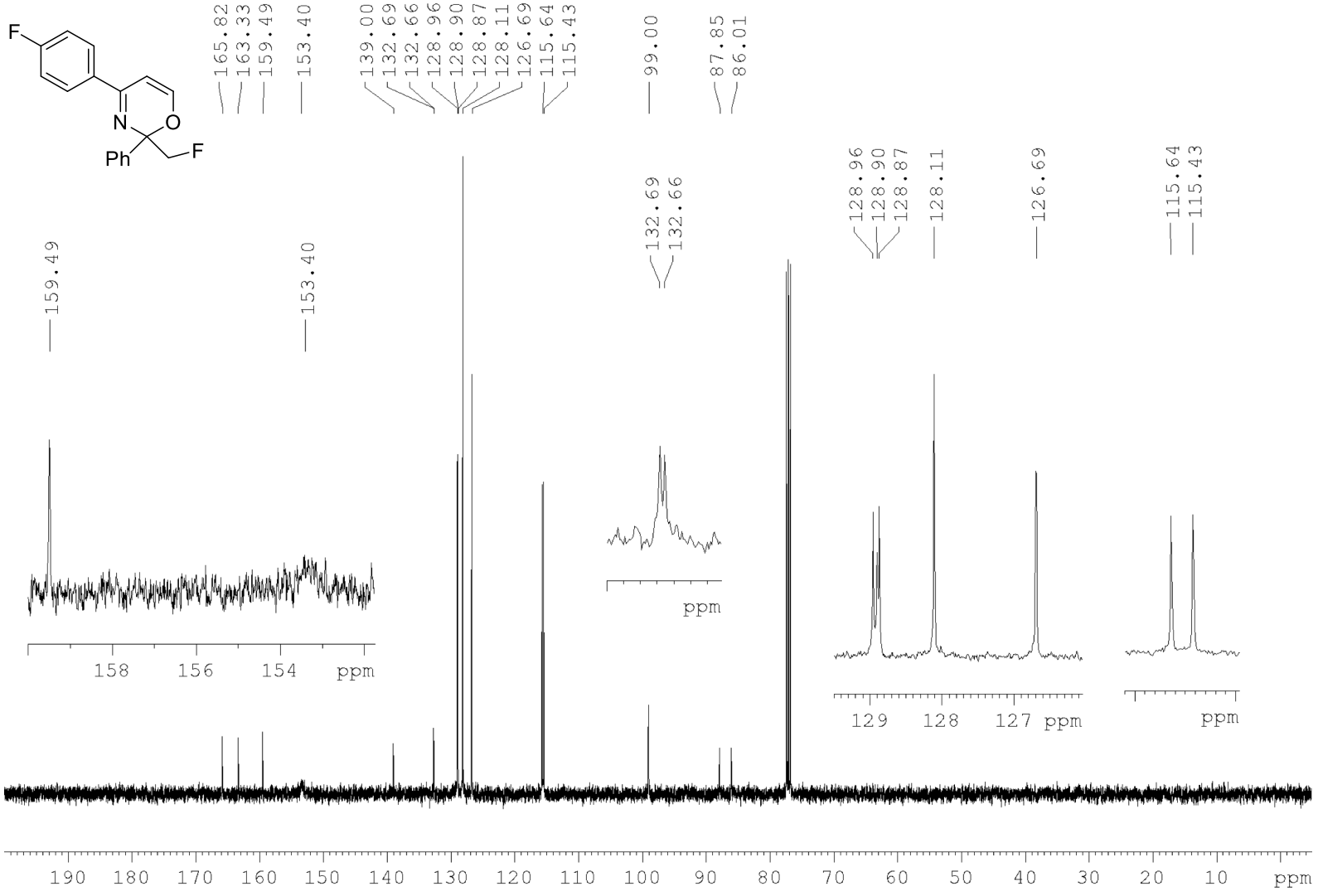

Figure S41. ^{1}H NMR spectrum of methyl 4-(2-(fluoromethyl)-2-phenyl-2*H*-1,3-oxazin-4-yl)benzoate (2h)

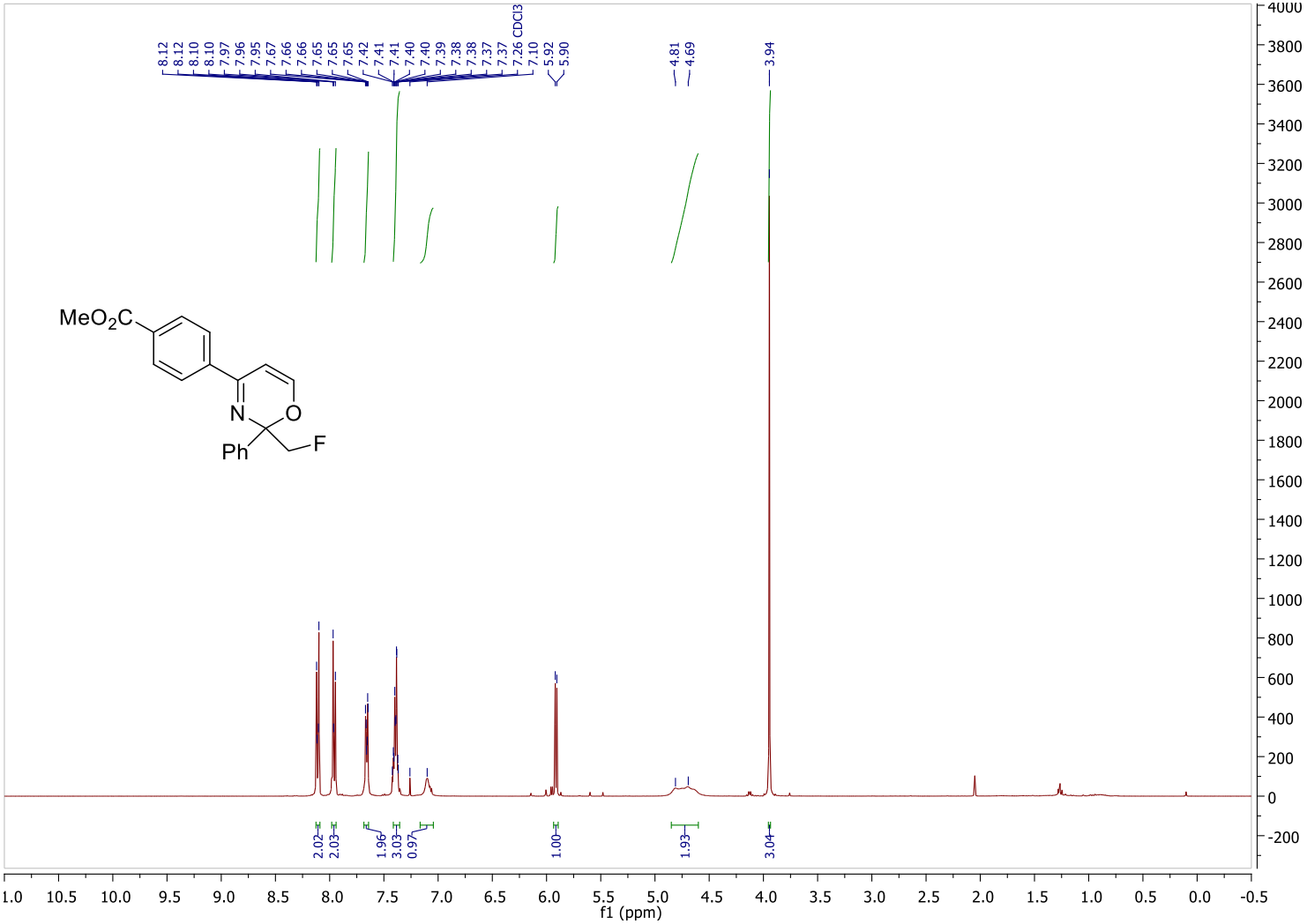

Figure S42. ^{13}C NMR spectrum of methyl 4-(2-(fluoromethyl)-2-phenyl-2*H*-1,3-oxazin-4-yl)benzoate (2h)

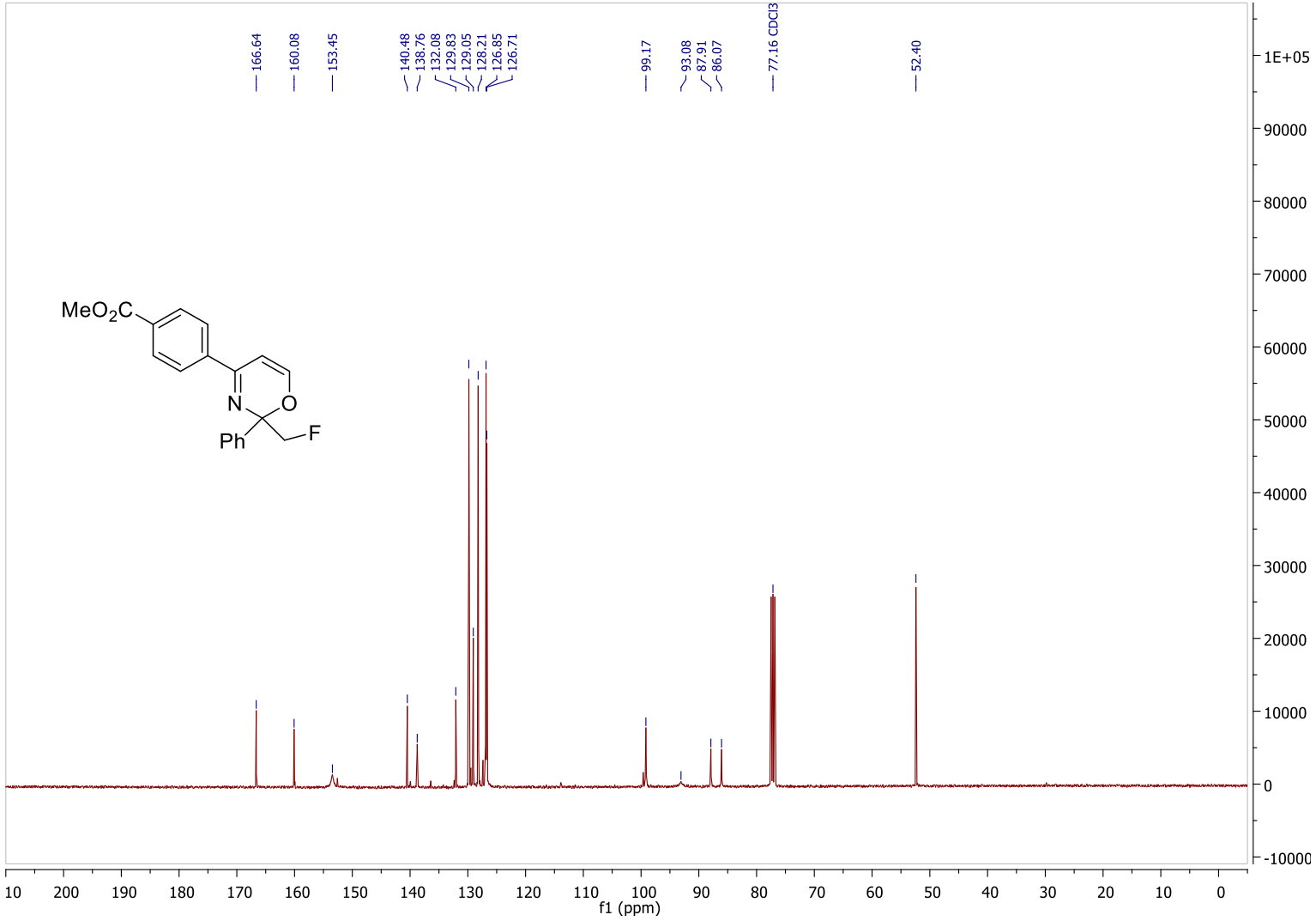

Figure S43. ^{1}H NMR spectrum of 2-(fluoromethyl)-2-phenyl-4-(prop-1-en-2-yl)-2*H*-1,3-oxazine (2i)

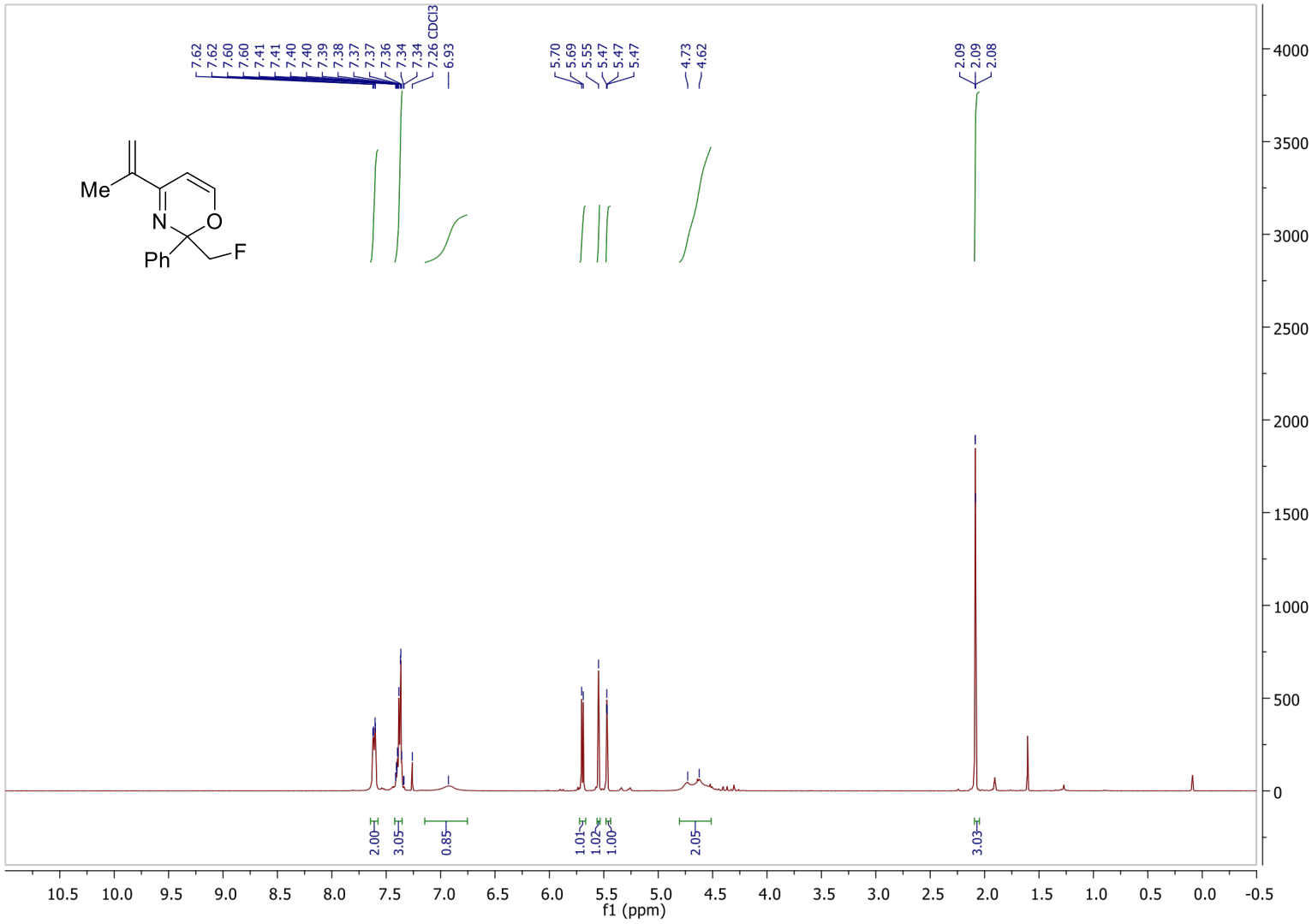

Figure S44. ^{1}H NMR spectrum of 2-(fluoromethyl)-2-phenyl-4-(prop-1-en-2-yl)-2*H*-1,3-oxazine (2i)

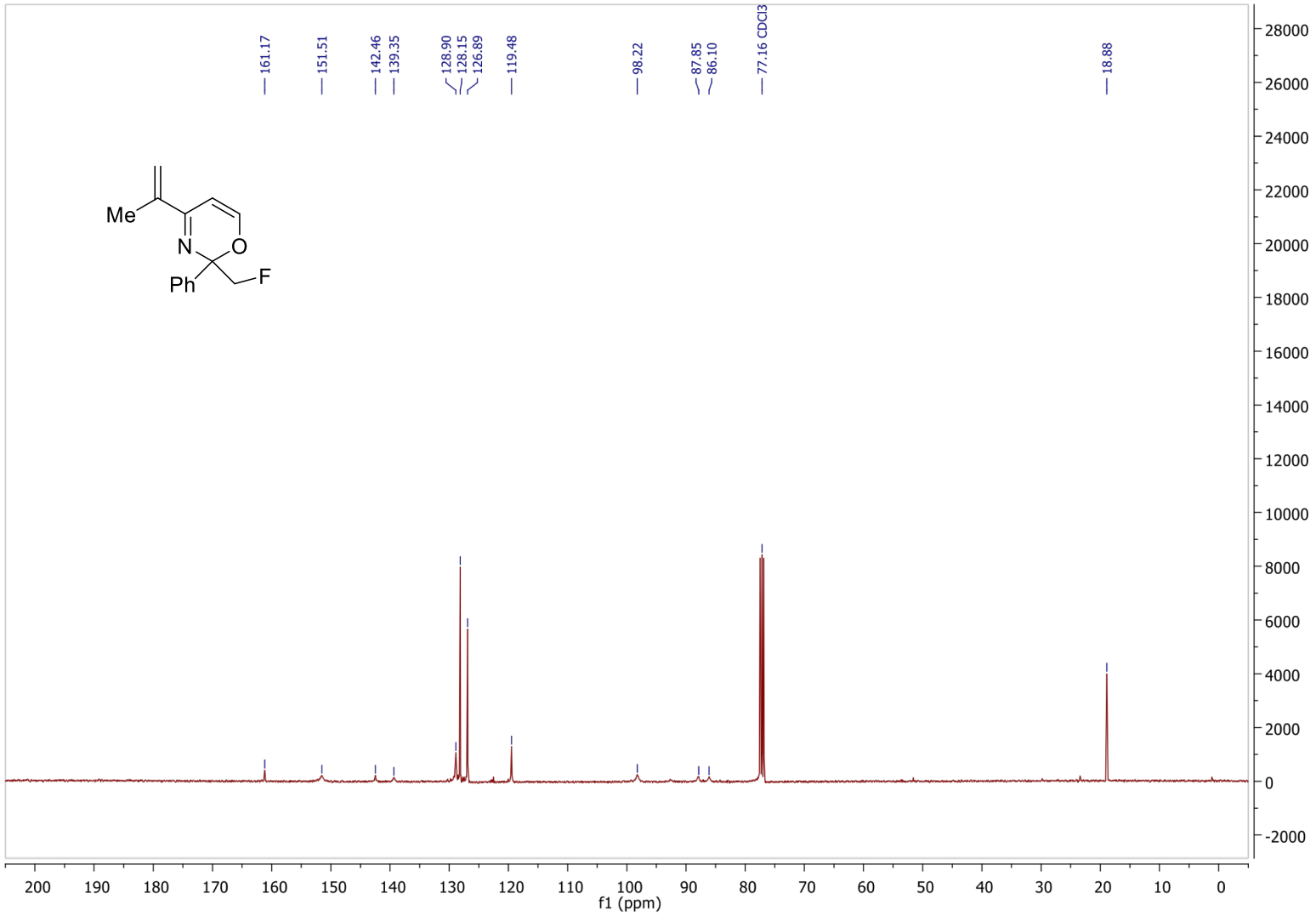

Figure S45. ^{1}H NMR spectrum of 4-cyclohexenyl-2-(fluoromethyl)-2-phenyl-2*H*-1,3-oxazine (2j)

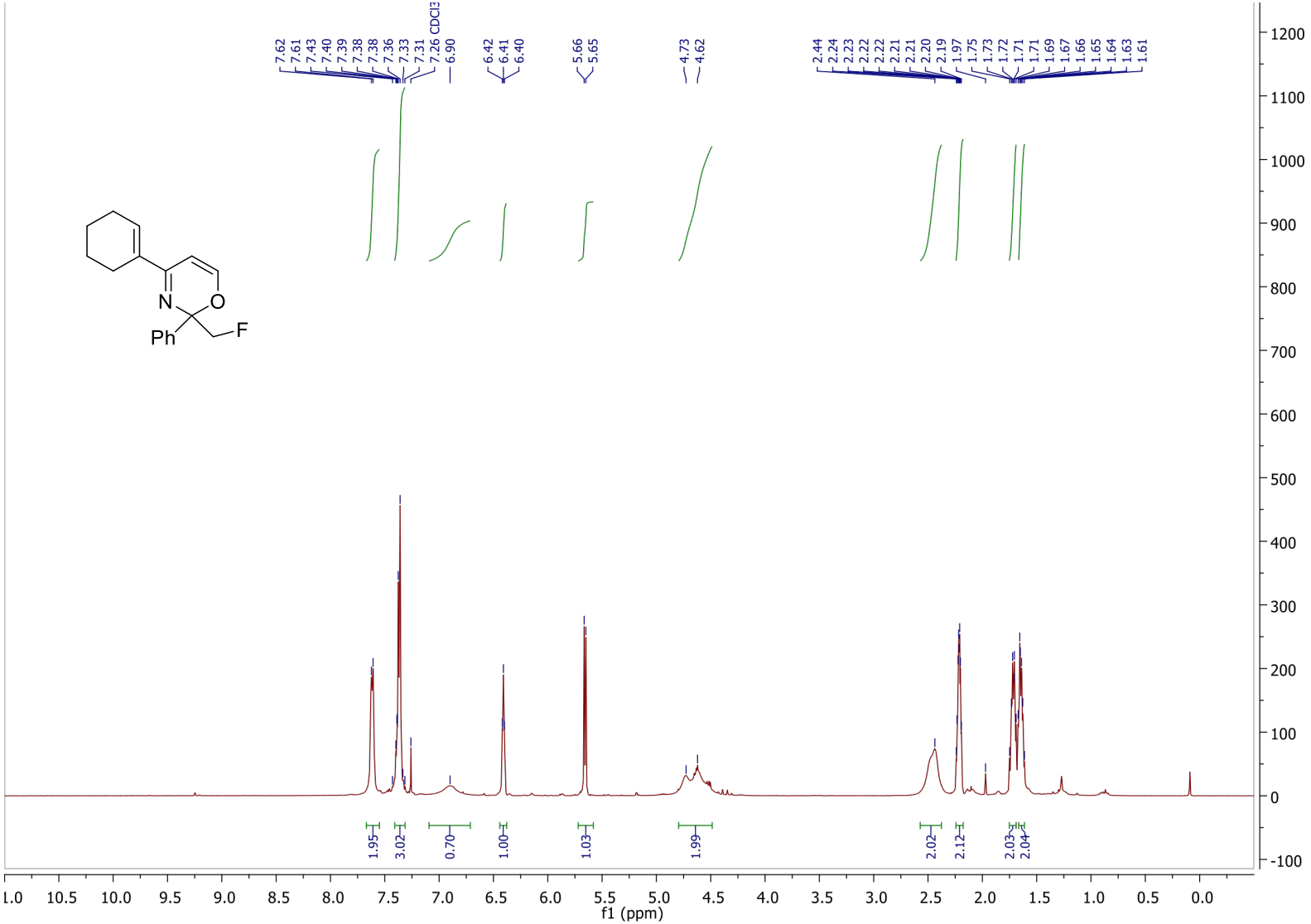

Figure S46. ^{13}C NMR spectrum of 4-cyclohexenyl-2-(fluoromethyl)-2-phenyl-2*H*-1,3-oxazine (2j)

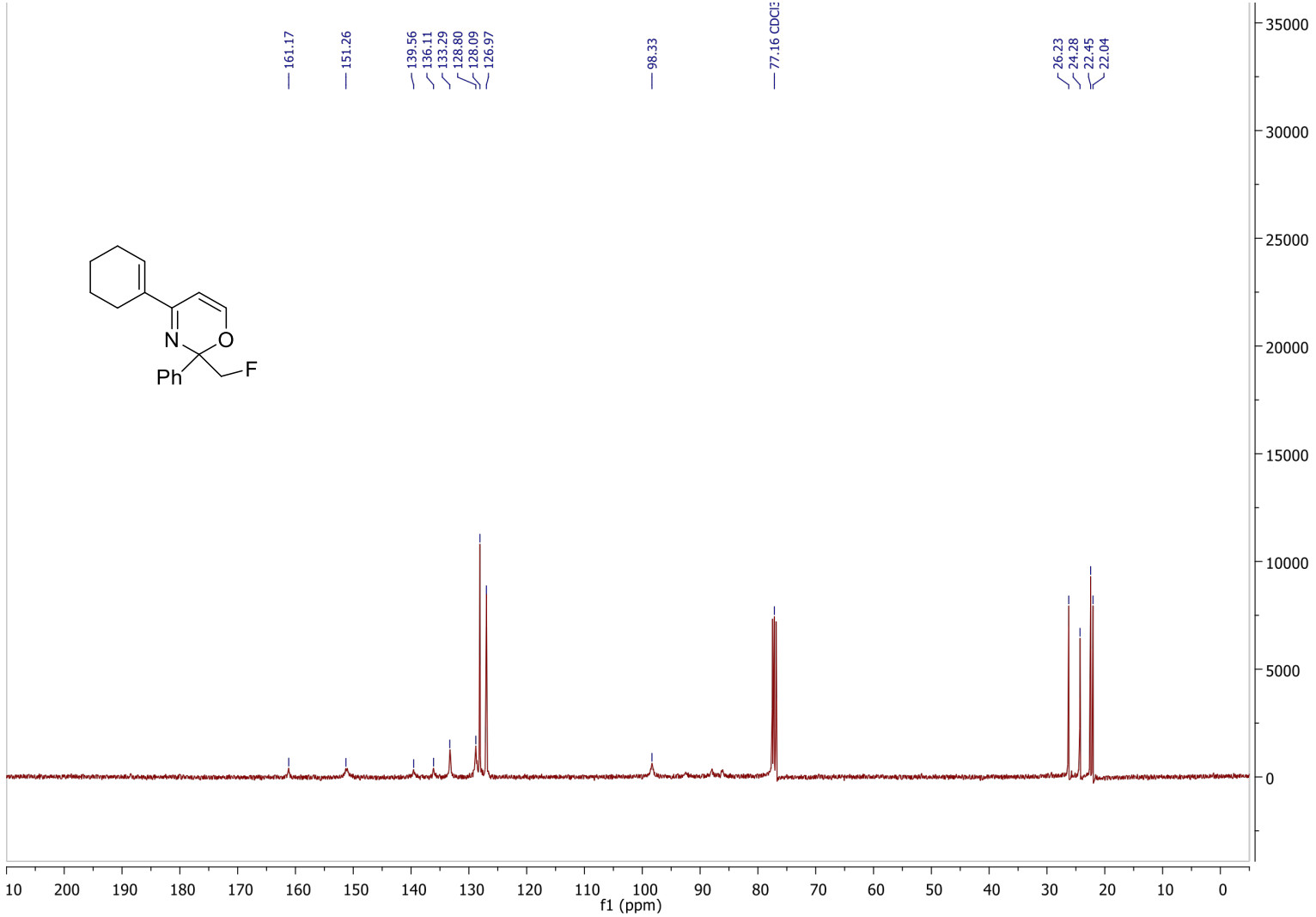

Figure S47. ^{1}H NMR spectrum of 2-(fluoromethyl)-4-isopentyl-2-phenyl-2*H*-1,3-oxazine (2k)

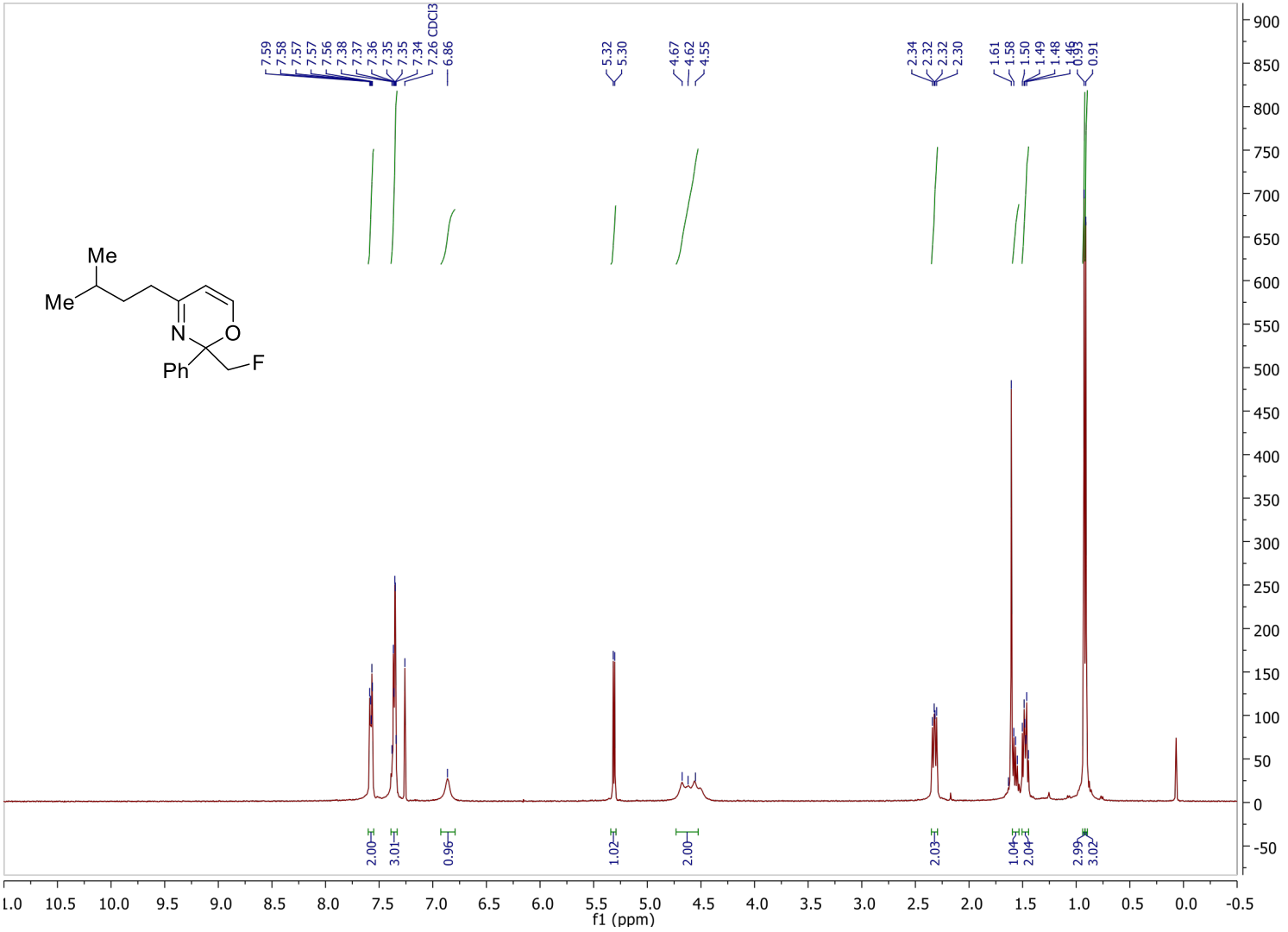

Figure S48. ^{13}C NMR spectrum of 2-(fluoromethyl)-4-isopentyl-2-phenyl-2*H*-1,3-oxazine (2k)

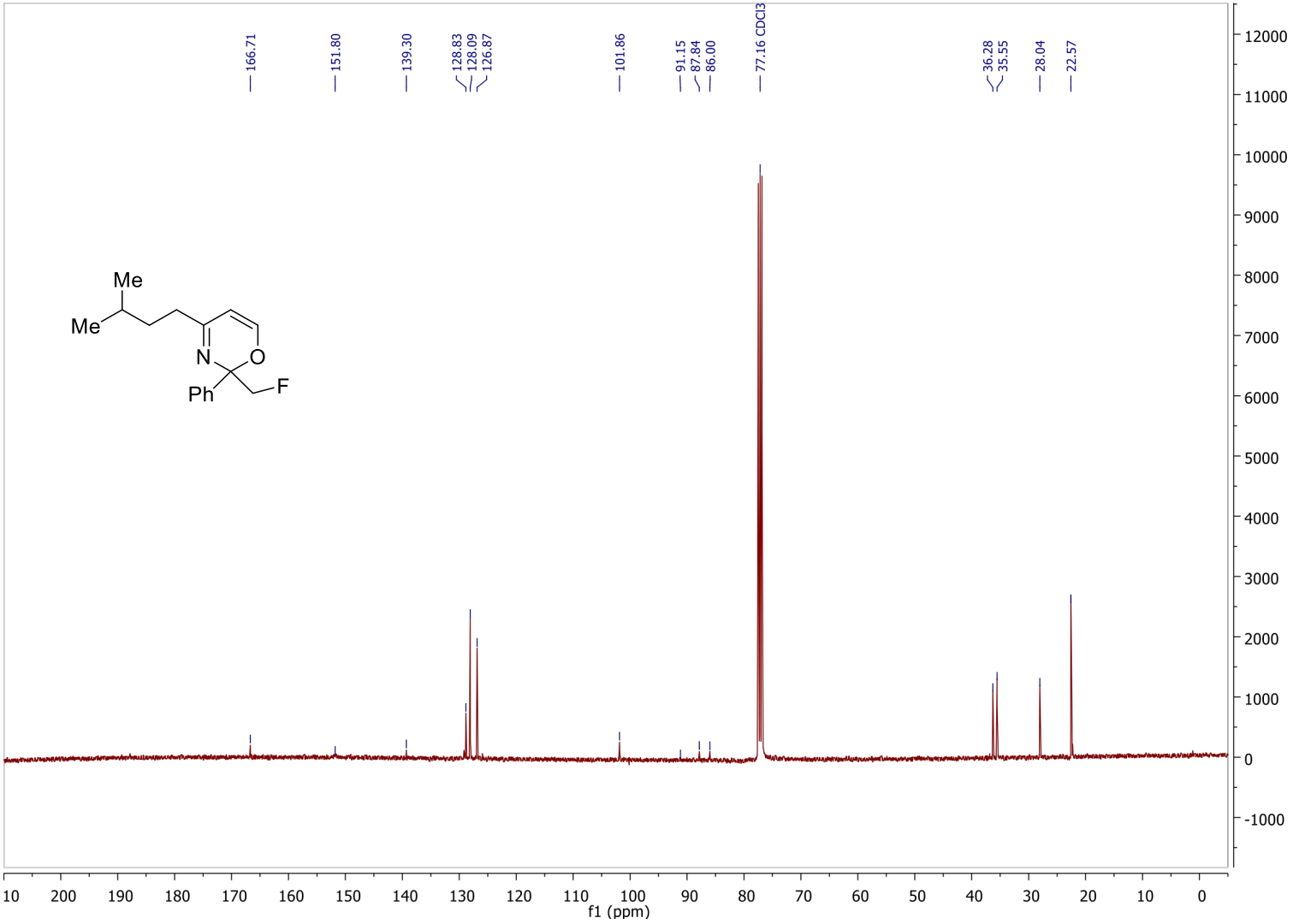

Figure S49. ^{1}H NMR spectrum of *N*-benzyl-*N*-(2-(fluoromethyl)-2-phenyl-2*H*-1,3-oxazin-4-yl)-4-methylbenzenesulfonamide (2l)

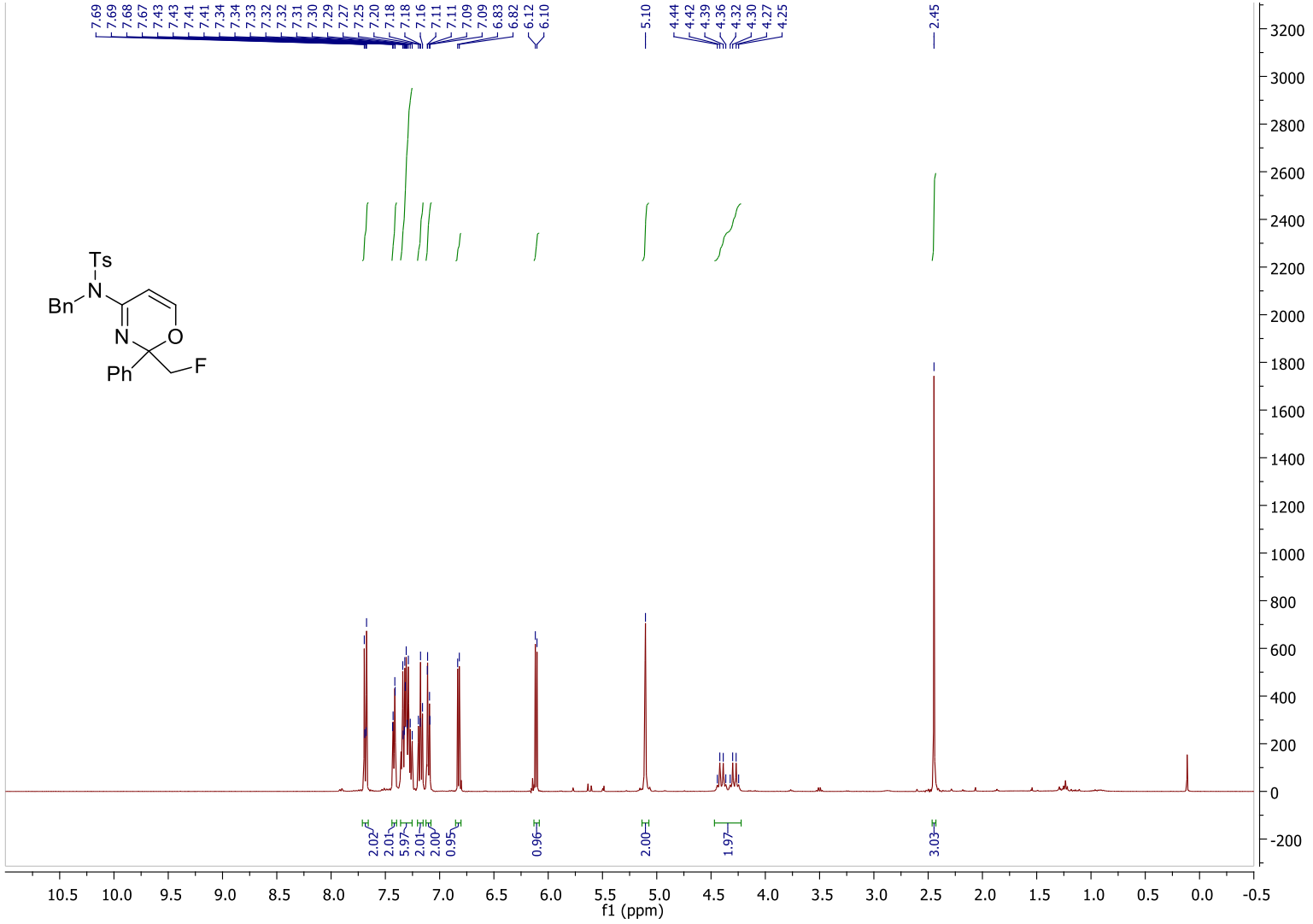

Figure S50. ^{13}C NMR spectrum of *N*-benzyl-*N*-(2-(fluoromethyl)-2-phenyl-2*H*-1,3-oxazin-4-yl)-4-methylbenzenesulfonamide (2l)

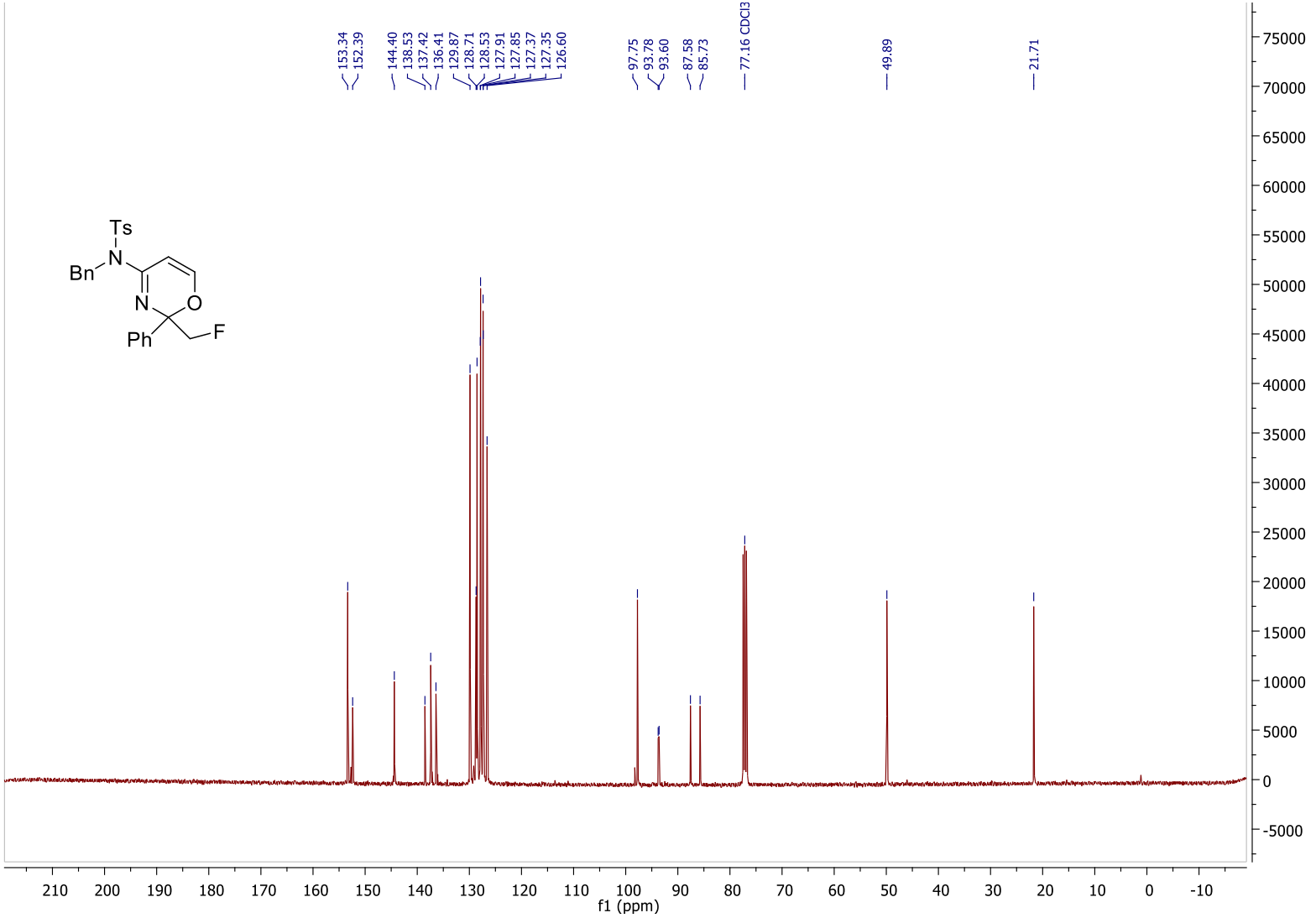

Figure S51. ^{1}H NMR spectrum of 2-(fluoromethyl)-2-(naphthalen-1-yl)-4-phenyl-2*H*-1,3-oxazine (2m)

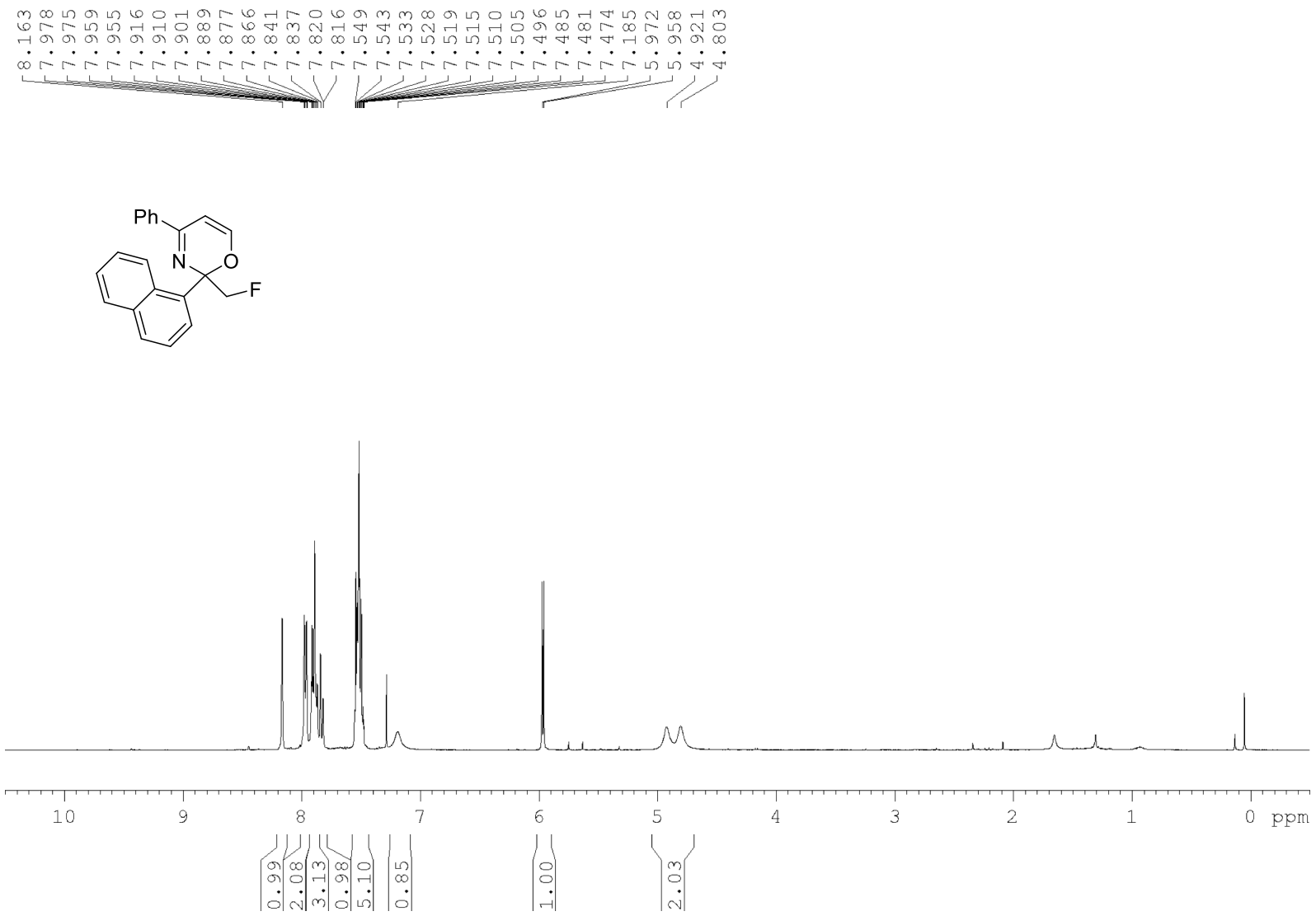

Figure S52. ^{13}C NMR spectrum of 2-(fluoromethyl)-2-(naphthalen-1-yl)-4-phenyl-2*H*-1,3-oxazine (2m)

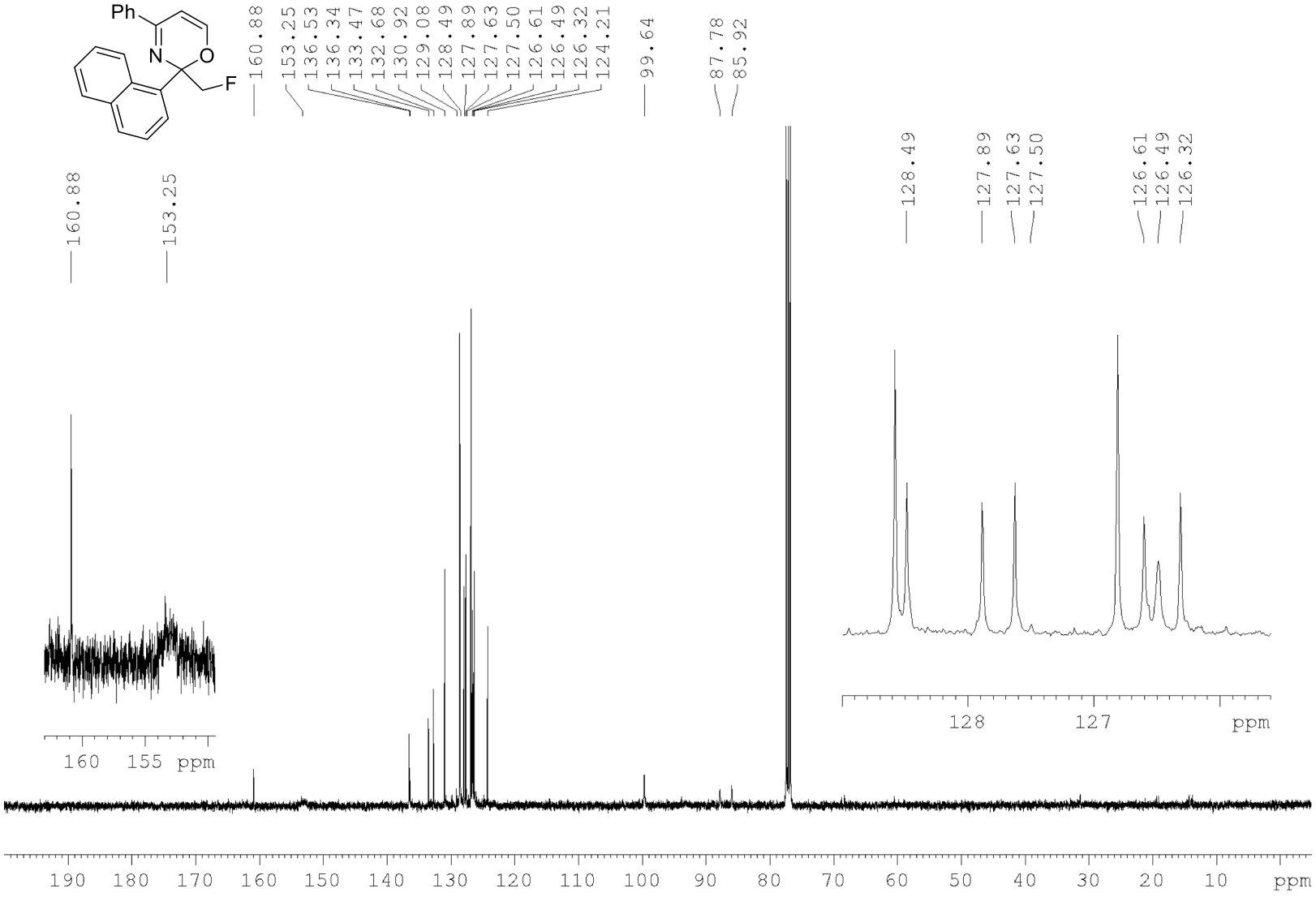

Figure S53. ^{1}H NMR spectrum of 2-(fluoromethyl)-2-phenethyl-4-phenyl-2*H*-1,3-oxazine (2n)

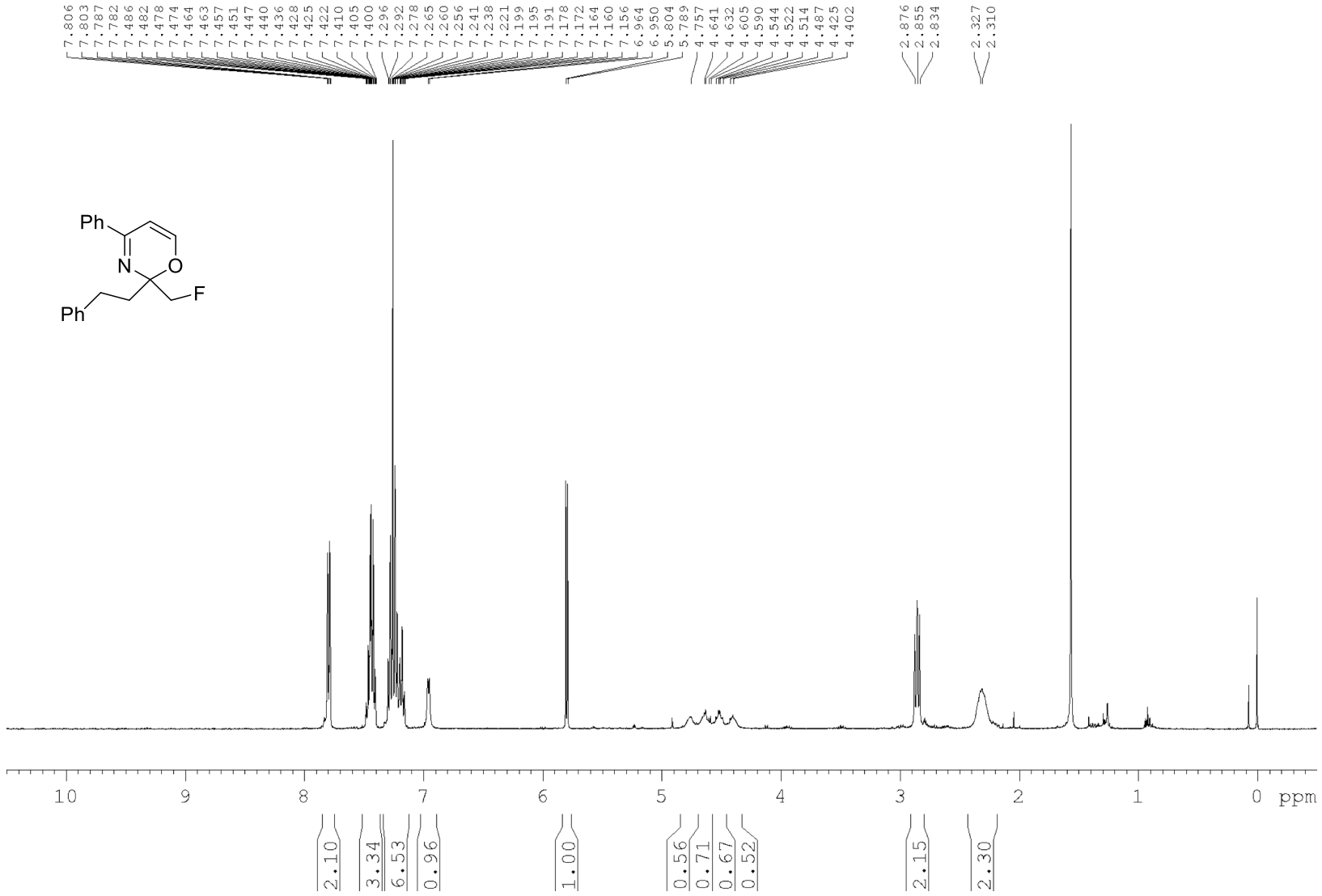

Figure S54. ^{13}C NMR spectrum of 2-(fluoromethyl)-2-phenethyl-4-phenyl-2*H*-1,3-oxazine (2n)

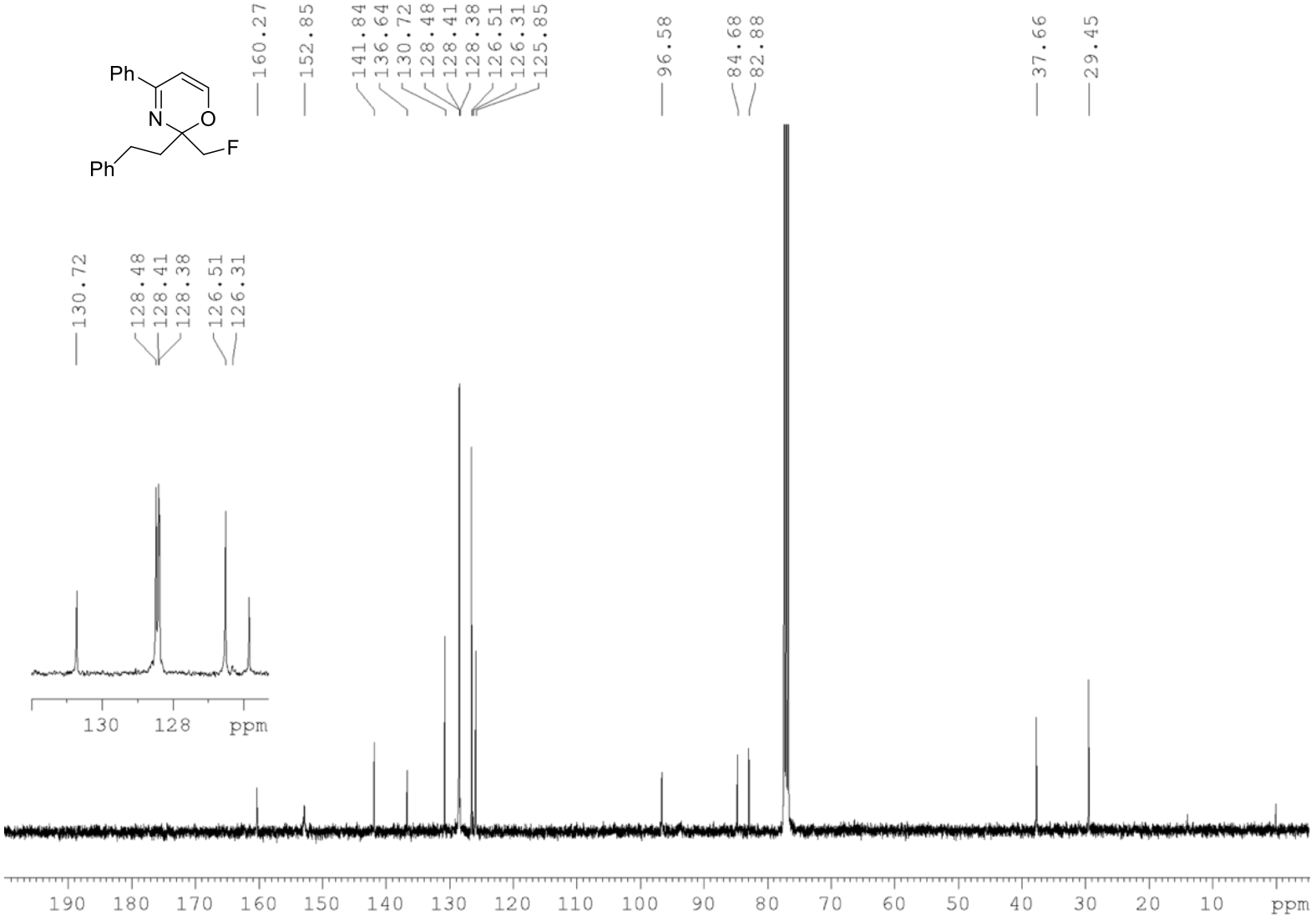

Figure S55. ^{1}H NMR spectrum of 2-(fluoromethyl)-6-methyl-2,4-diphenyl-2*H*-1,3-oxazine (2o)

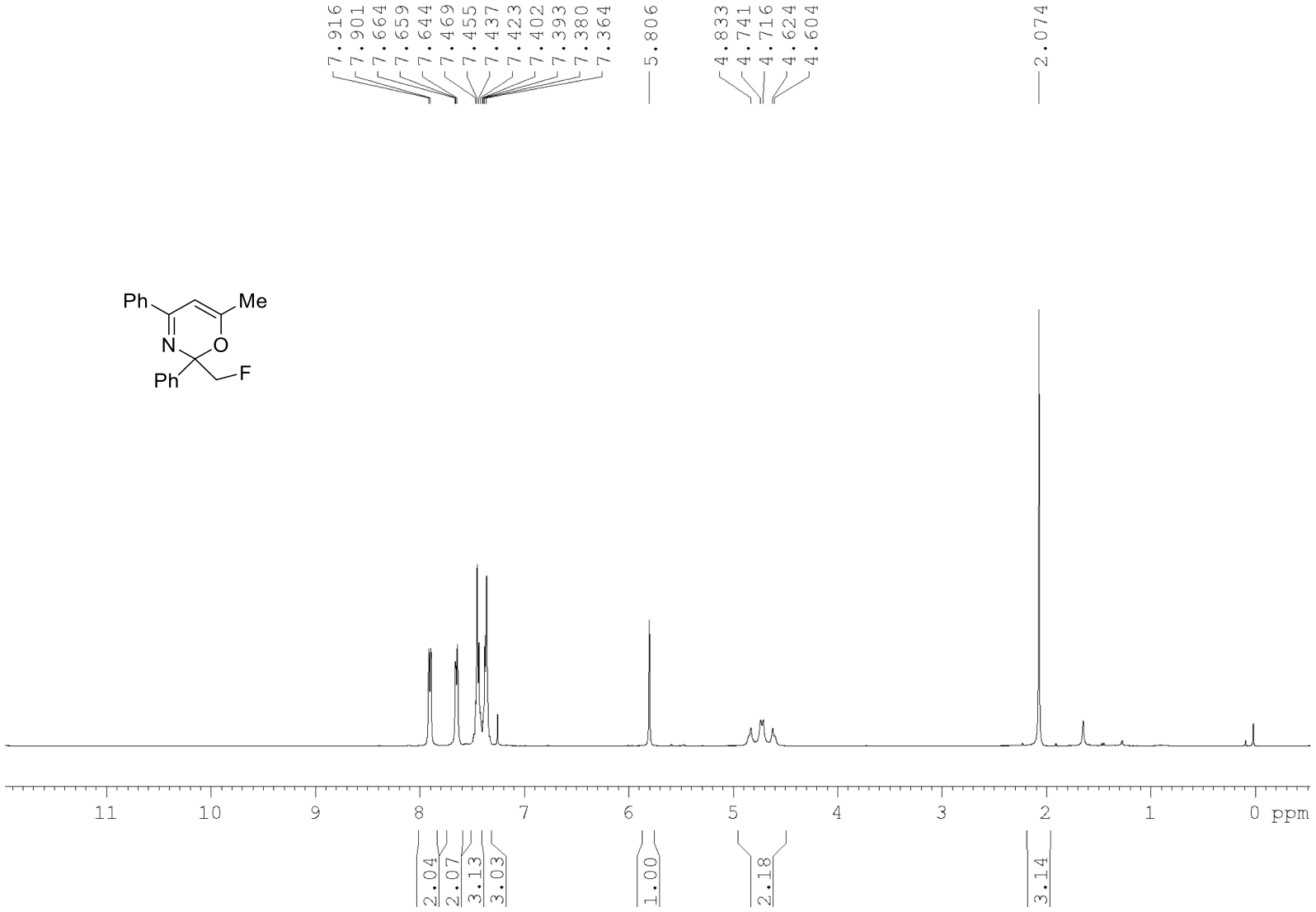

Figure S56. ^{13}C NMR spectrum of 2-(fluoromethyl)-6-methyl-2,4-diphenyl-2*H*-1,3-oxazine (2o)

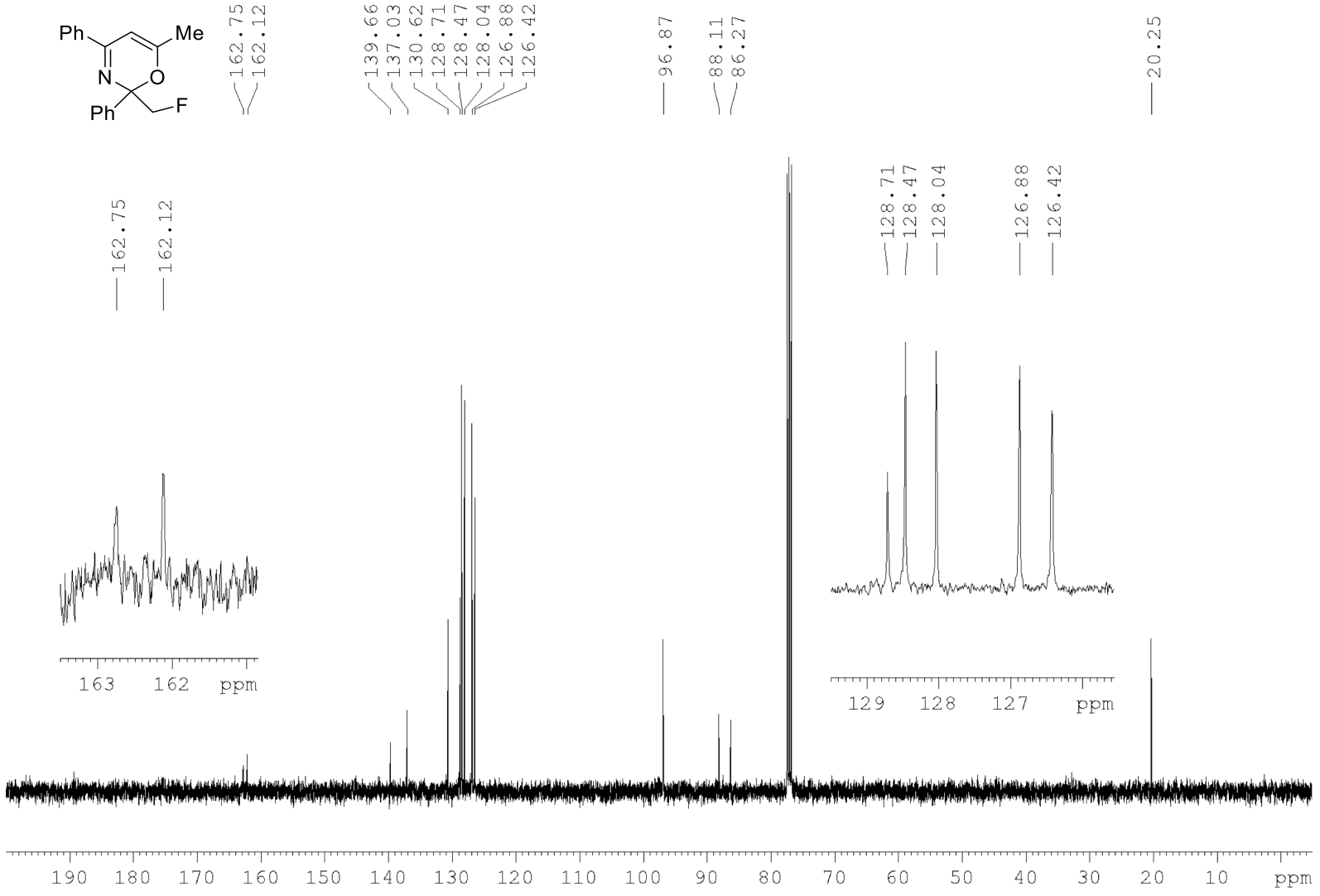

Figure S57. ^{1}H NMR spectrum of 2-(bromomethyl)-6-methoxy-2,4-diphenyl-5,6-dihydro-2*H*-1,3-oxazine (3p)

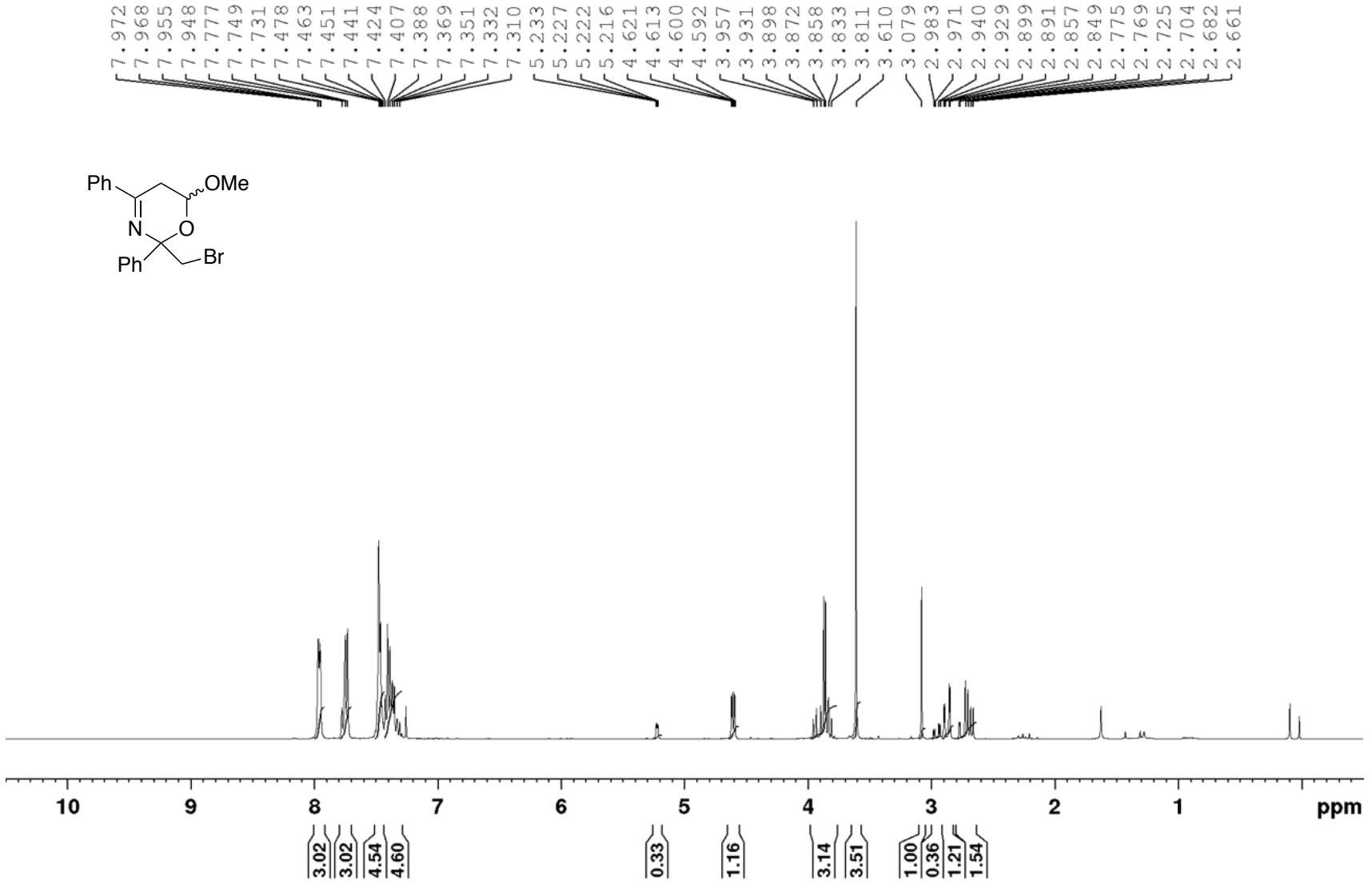

Figure S58. ^{13}C NMR spectrum of 2-(bromomethyl)-6-methoxy-2,4-diphenyl-5,6-dihydro-2*H*-1,3-oxazine (3p)

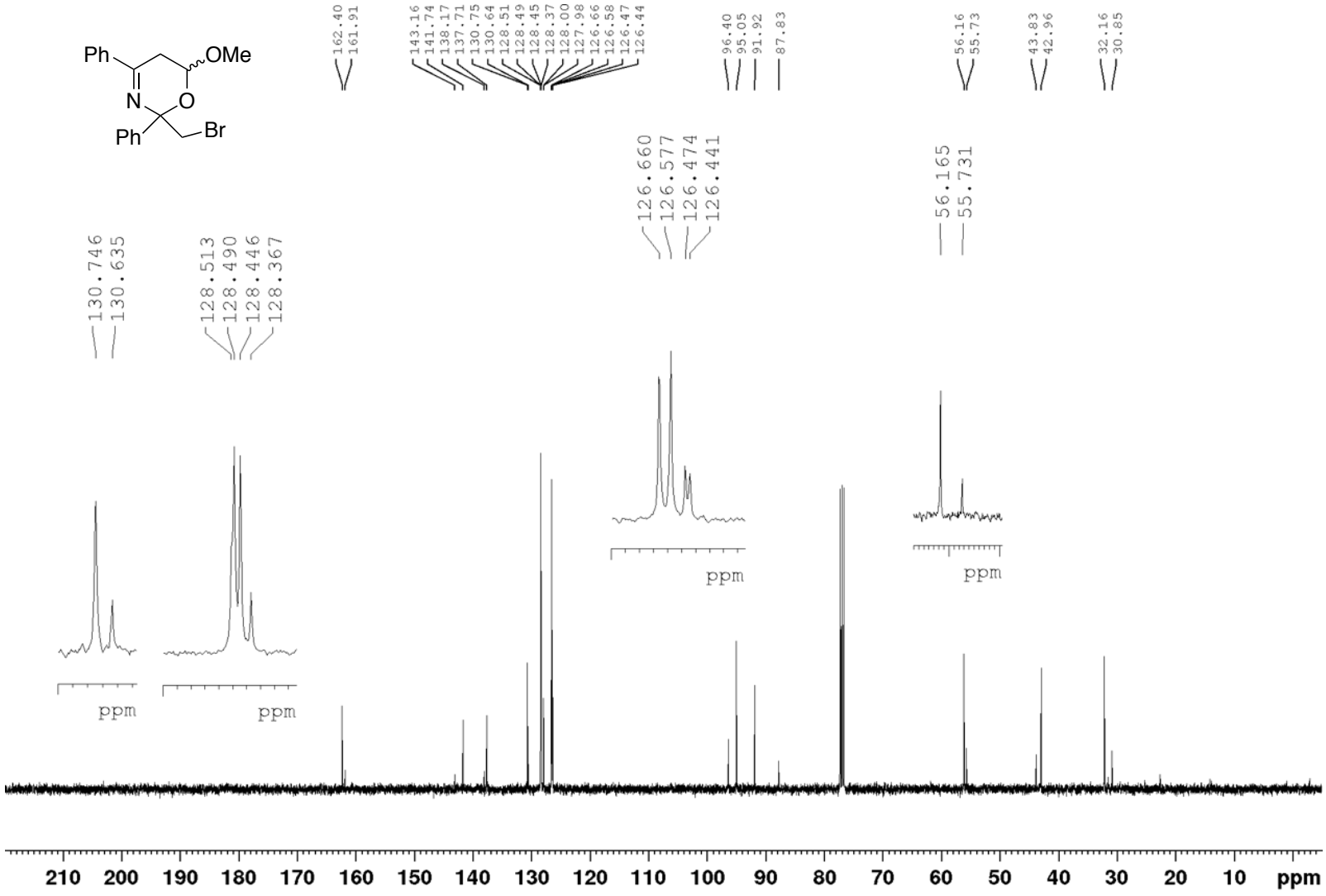

Figure S59. ^{1}H NMR spectrum of (*Z*)-2-bromo-3-(((*Z*)-2-fluoro-1-phenylethylidene)amino)-3-phenylacrylaldehyde (4a)

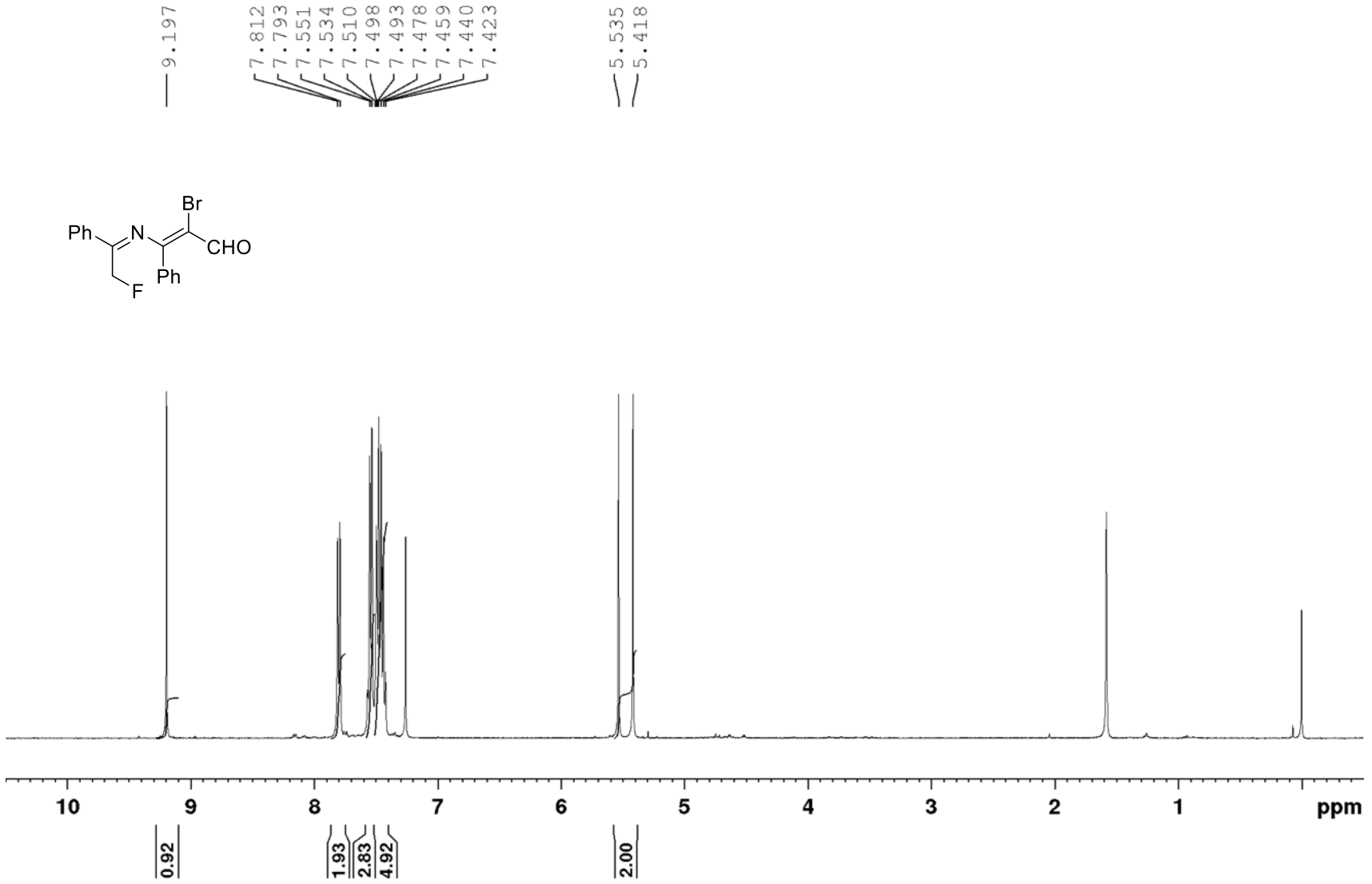

Figure S60. ^{13}C NMR spectrum of (*Z*)-2-bromo-3-(((*Z*)-2-fluoro-1-phenylethylidene)amino)-3-phenylacrylaldehyde (4a)

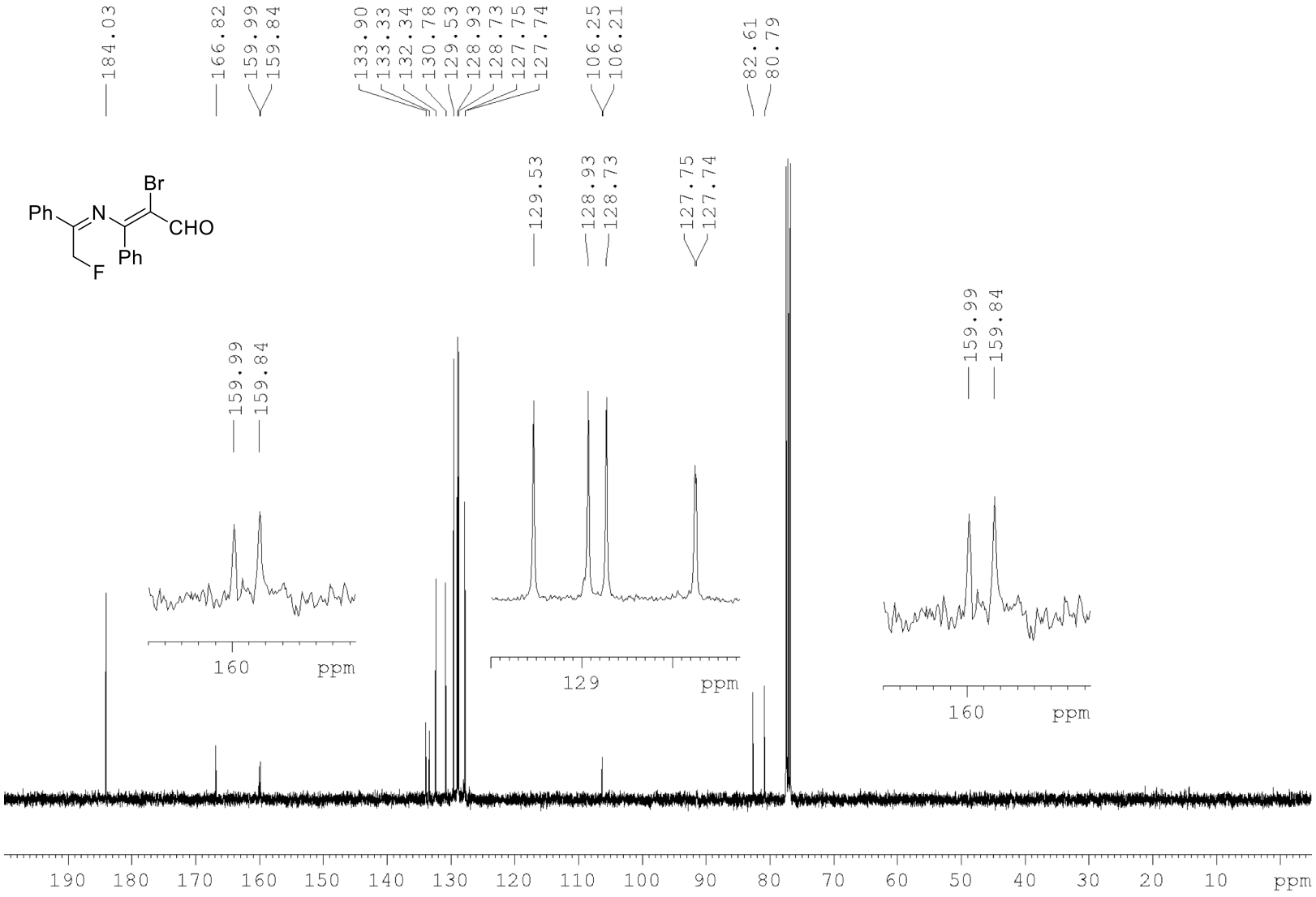

Figure S61. ^{1}H NMR spectrum of (*Z*)-2-bromo-3-(((*Z*)-2-fluoro-1-phenylethylidene)amino)-3-(4-methoxyphenyl) acrylaldehyde (4b)

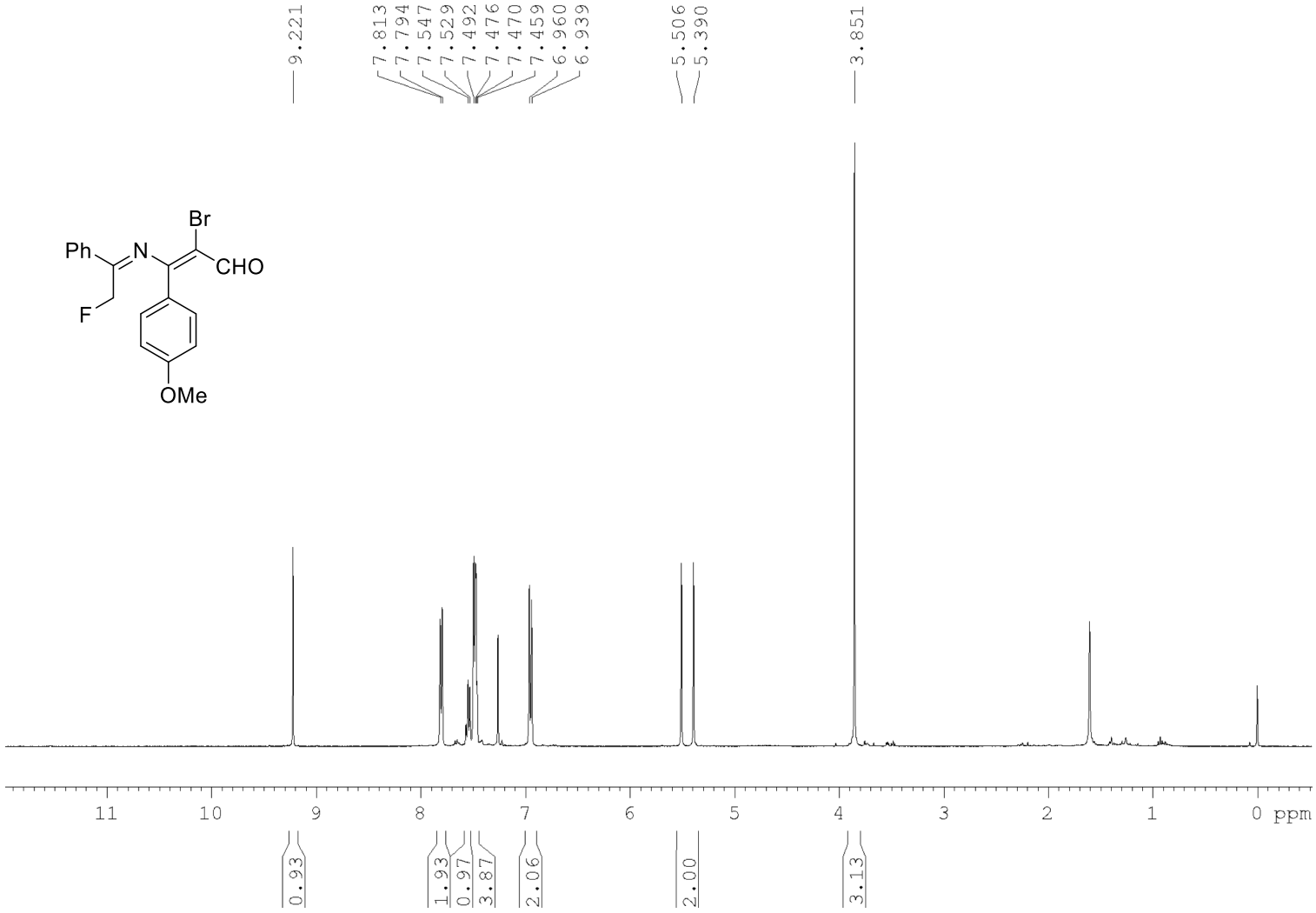

Figure S62. ^{13}C NMR spectrum of (*Z*)-2-bromo-3-(((*Z*)-2-fluoro-1-phenylethylidene)amino)-3-(4-methoxyphenyl) acrylaldehyde (4b)

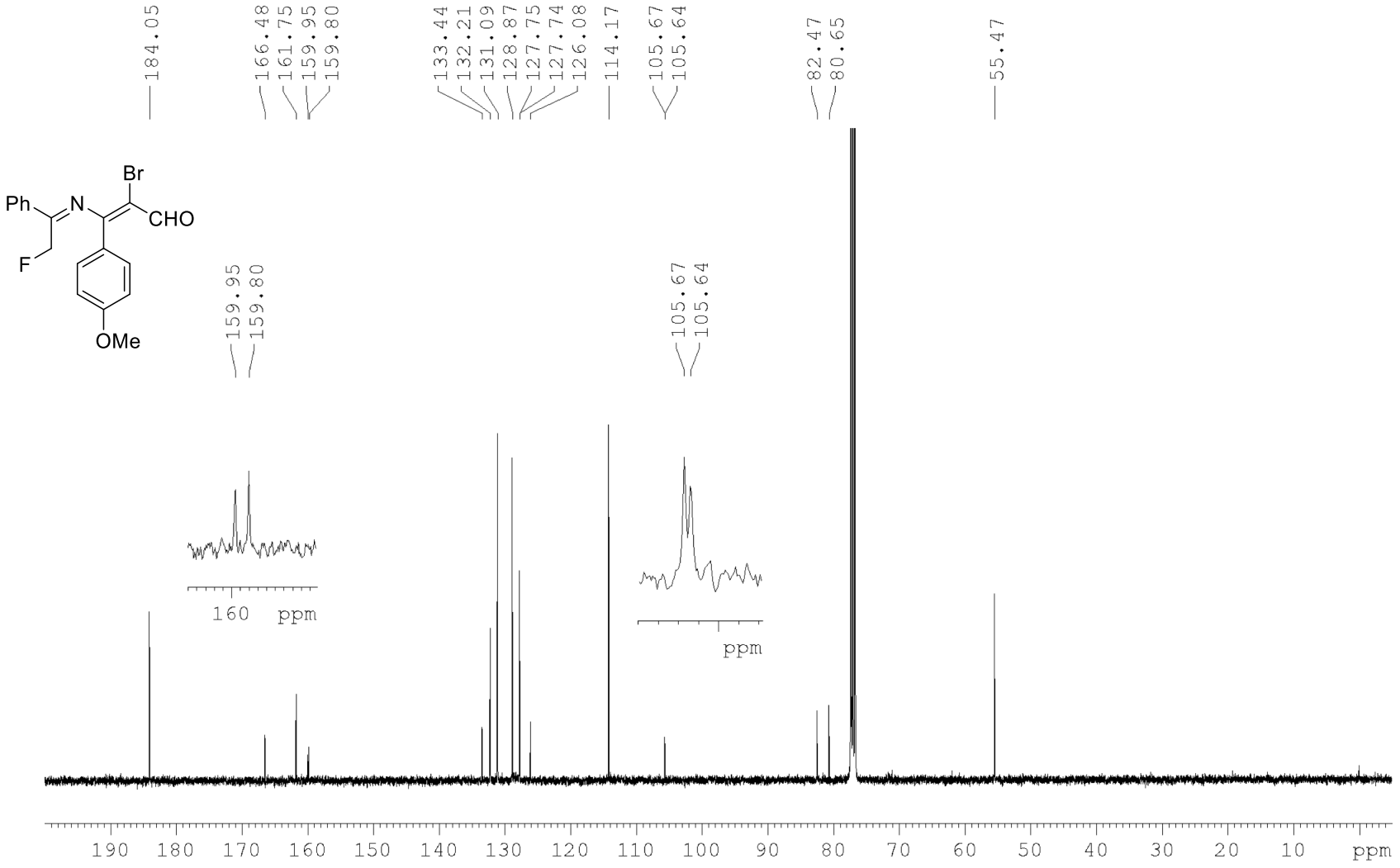

Figure S63. ^{1}H NMR spectrum of methyl 4-((*Z*)-2-bromo-1-(((*Z*)-2-fluoro-1-phenylethylidene)amino)-3-oxoprop-1-en-1-yl)benzoate (4h)

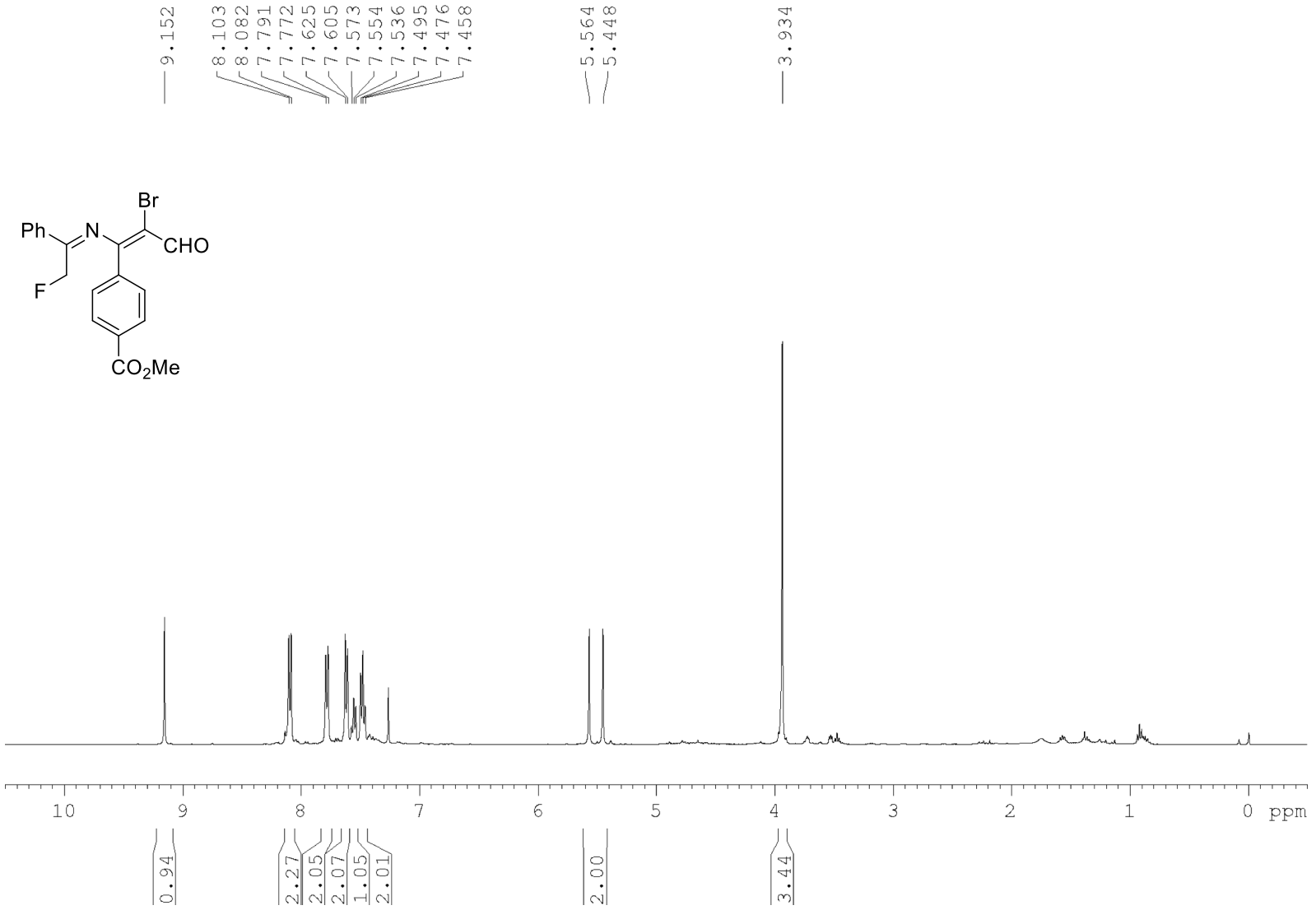

Figure S64. ^{13}C NMR spectrum of methyl 4-((*Z*)-2-bromo-1-(((*Z*)-2-fluoro-1-phenylethylidene)amino)-3-oxoprop-1-en-1-yl)benzoate (4h)

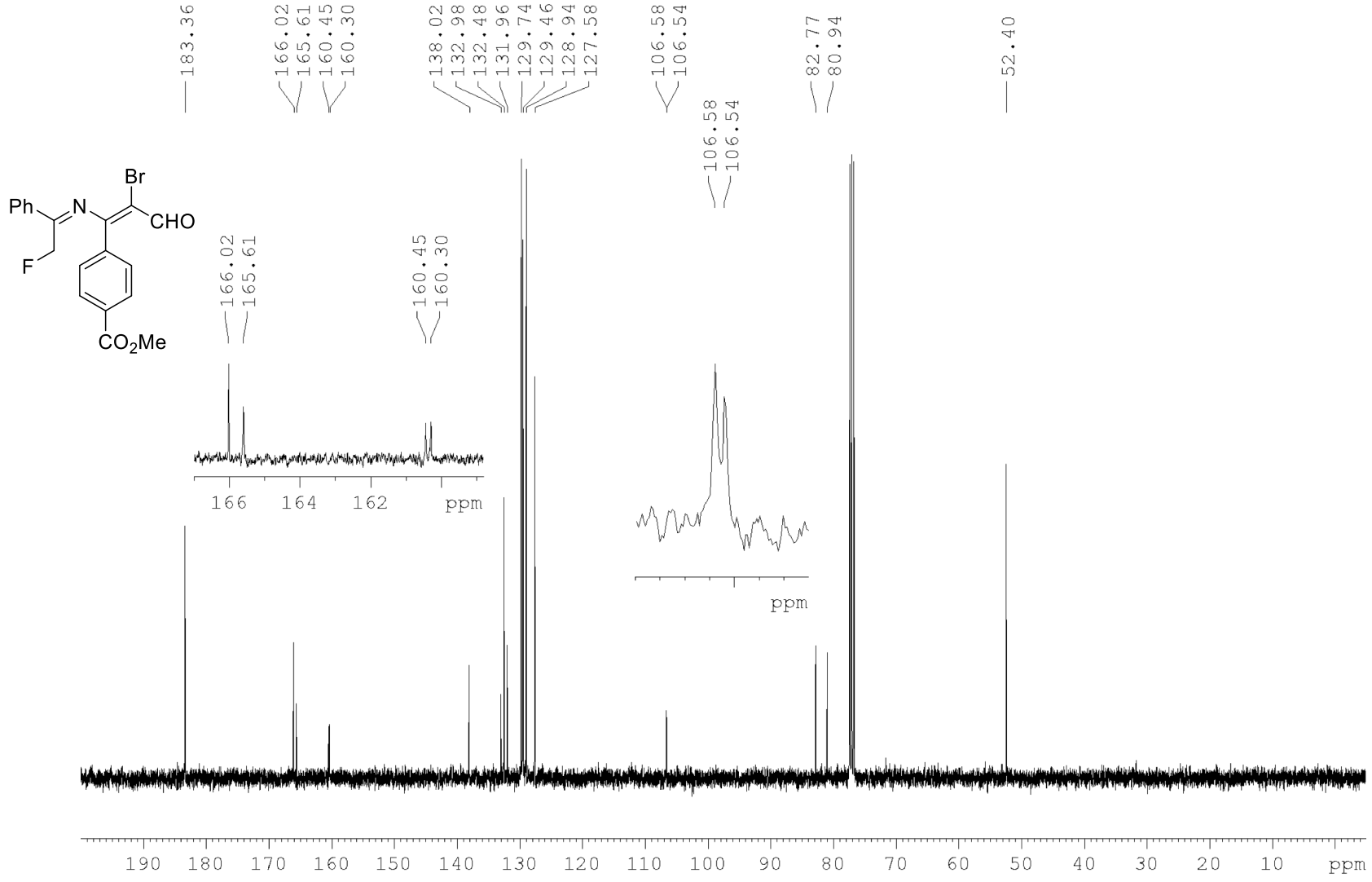

Figure S65. ^{1}H NMR spectrum of (*Z*)-2-bromo-3-(((*Z*)-2-fluoro-1-phenylethylidene)amino)-4-methylpenta-2,4-dienal (4l)

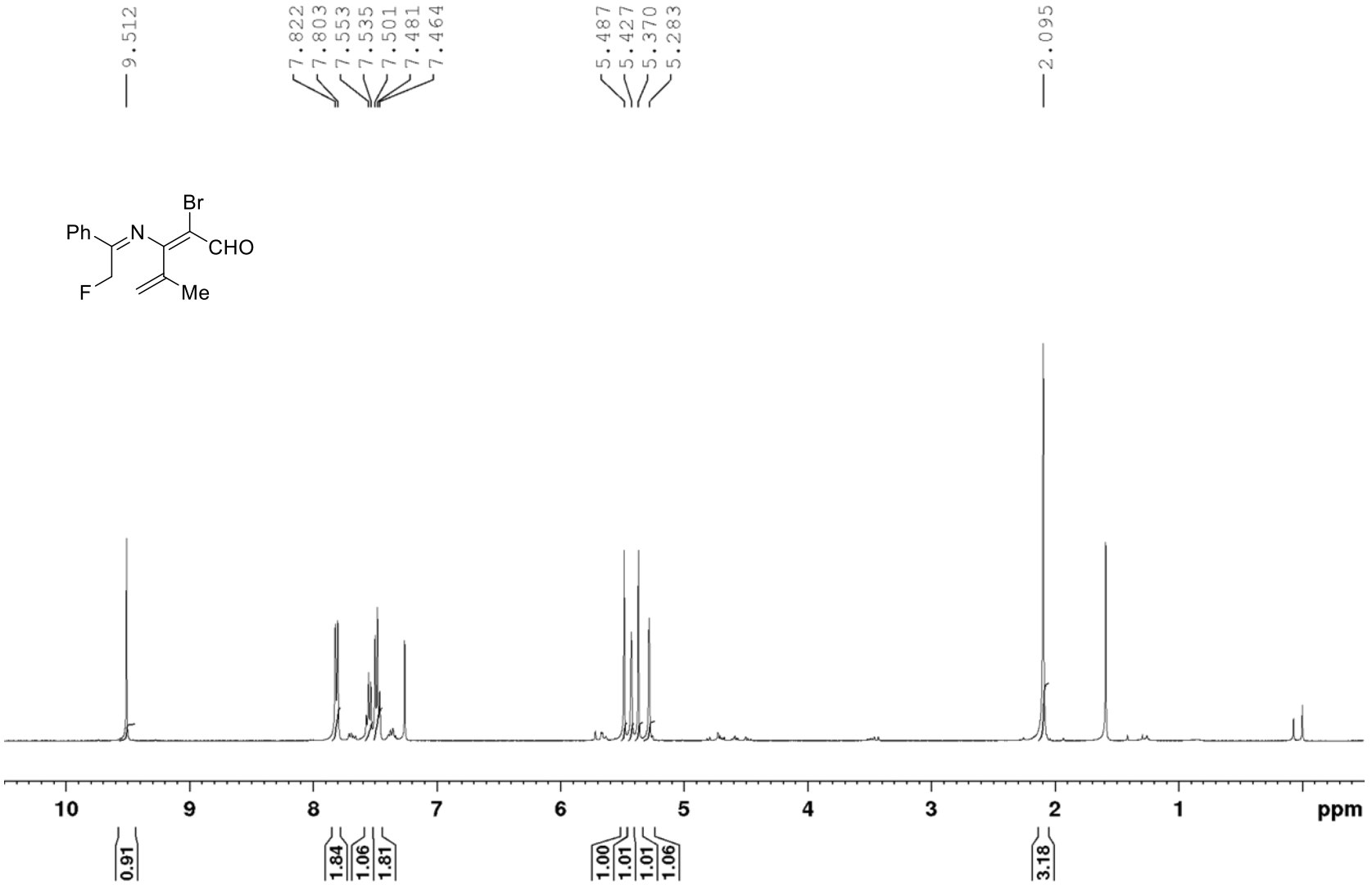

Figure S66. ^{13}C NMR spectrum of (*Z*)-2-bromo-3-(((*Z*)-2-fluoro-1-phenylethylidene)amino)-4-methylpenta-2,4-dienal (4l)

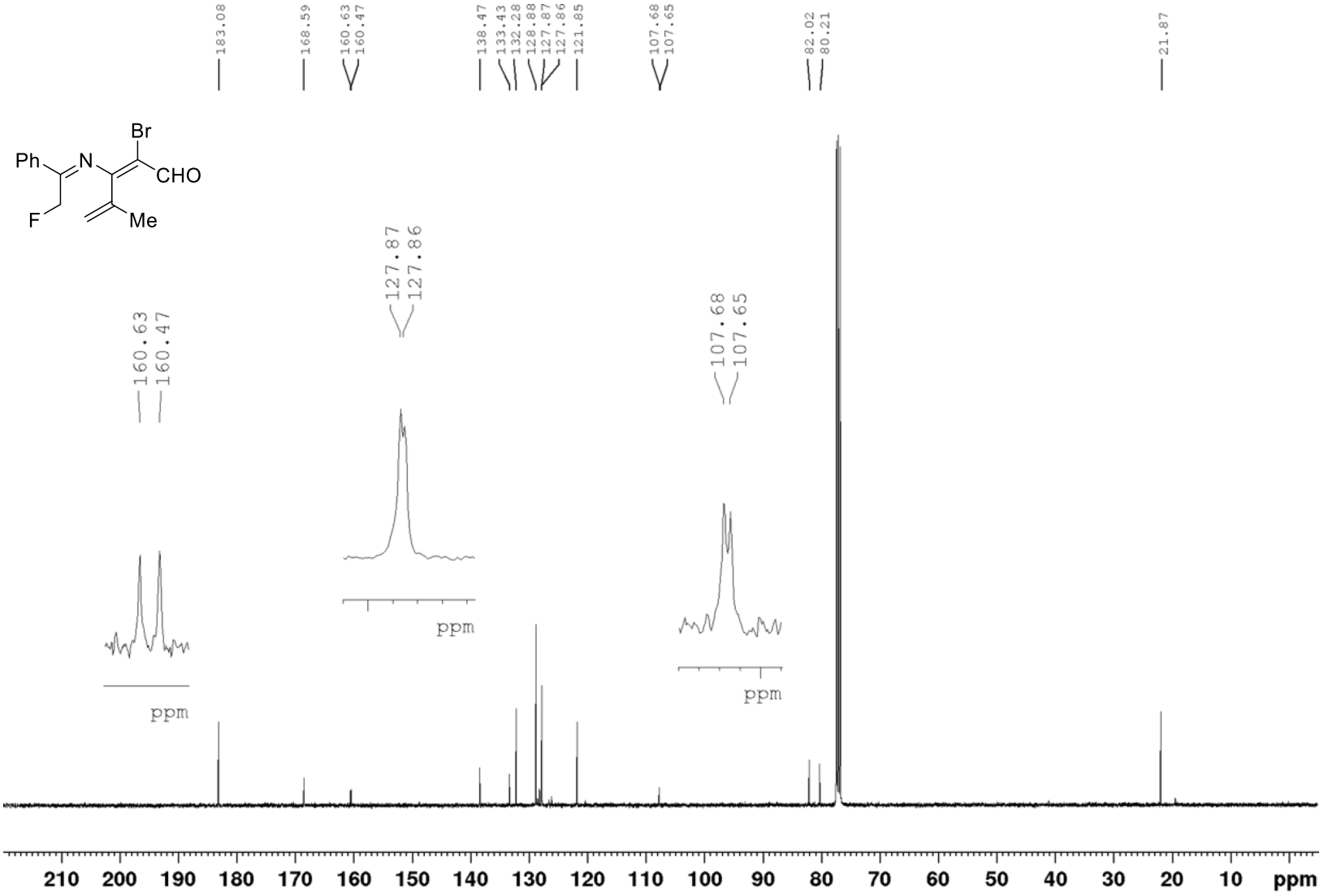

Figure S67. ^{1}H NMR spectrum of (*Z*)-2-bromo-3-(((*Z*)-2-fluoro-1-phenylvinyl)amino)-3-phenylacrylaldehyde (5a)

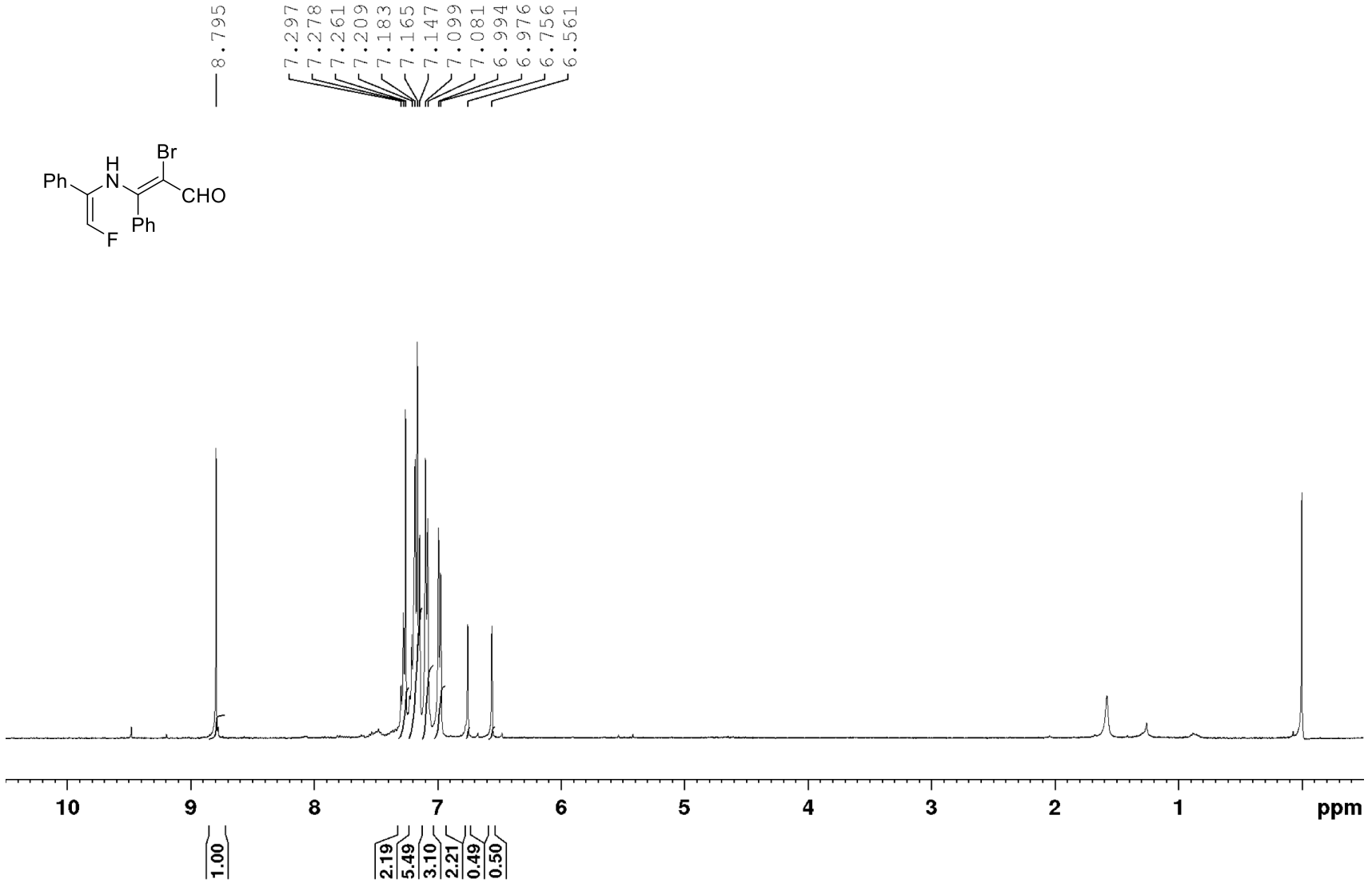

Figure S68. ^{13}C NMR spectrum of (*Z*)-2-bromo-3-(((*Z*)-2-fluoro-1-phenylvinyl)amino)-3-phenylacrylaldehyde (5a)

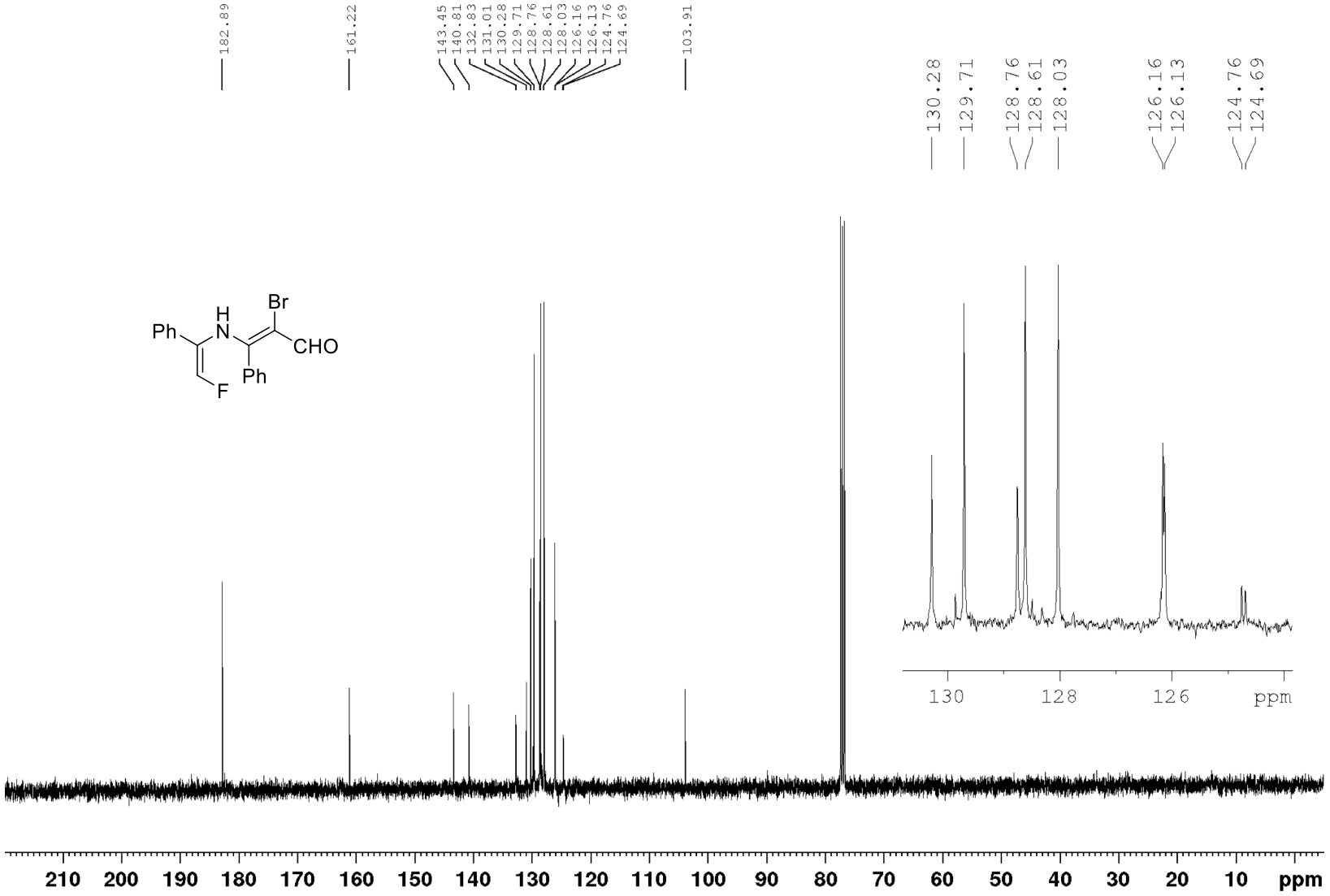

Figure S69. ^{1}H NMR spectrum of ethyl (2*E*,4*Z*)-4-bromo-5-(((*Z*)-2-fluoro-1-phenylethylidene)amino)-5-phenylpenta-2,4-dienoate (6a)

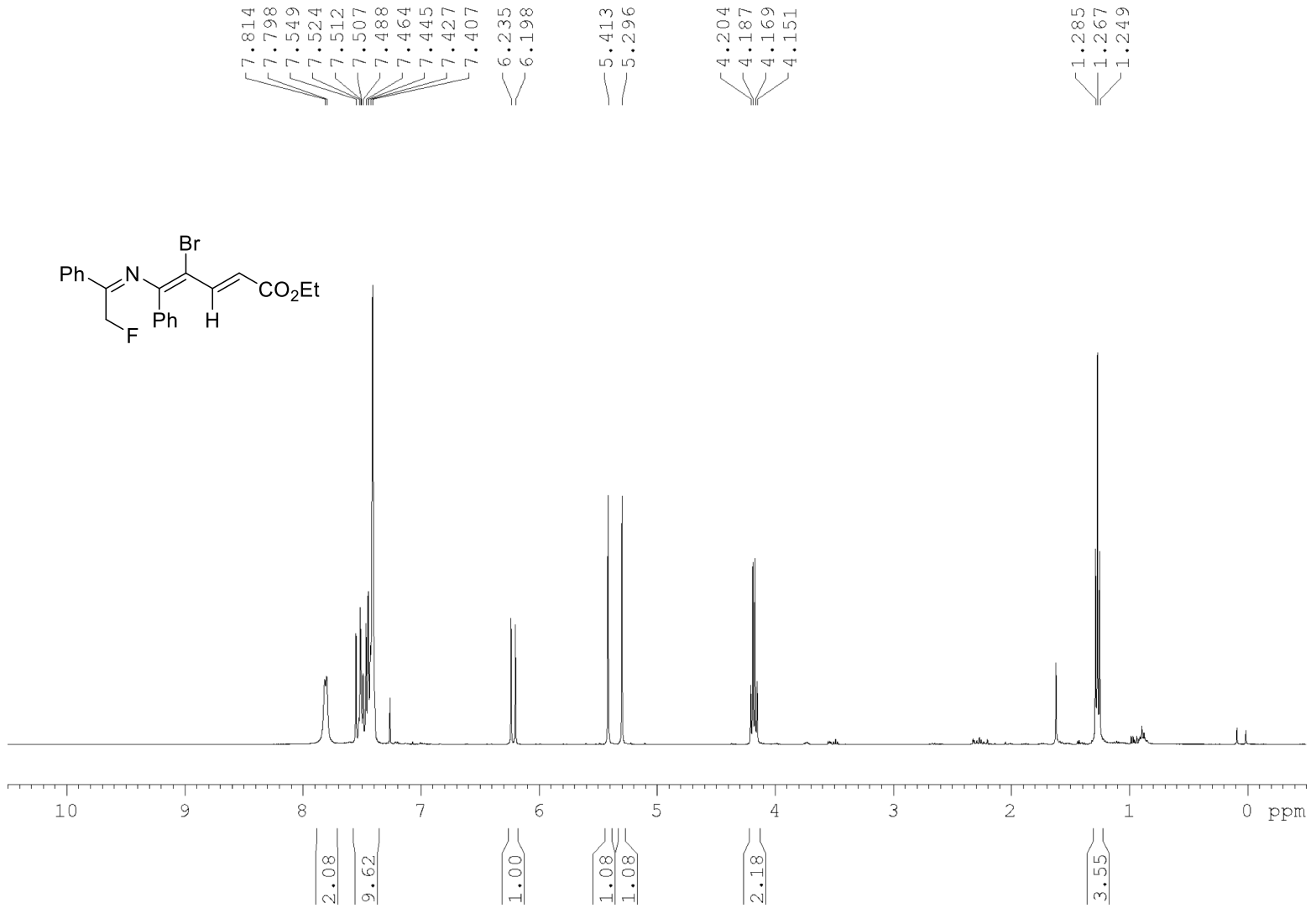

Figure S70. ^{13}C NMR spectrum of ethyl (2*E*,4*Z*)-4-bromo-5-(((*Z*)-2-fluoro-1-phenylethylidene)amino)-5-phenylpenta-2,4-dienoate (6a)

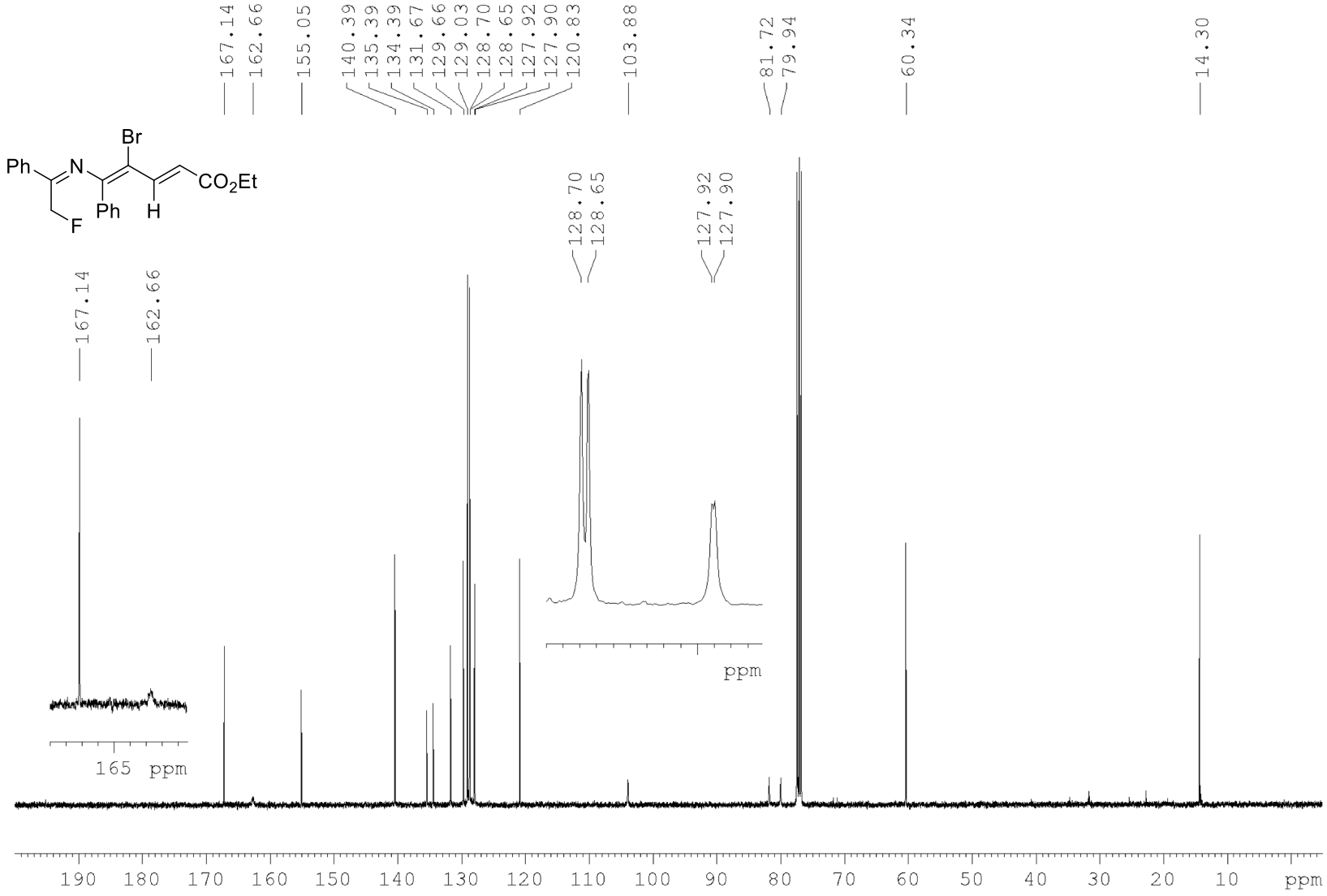

Figure S71. ^{1}H NMR spectrum of 2-(fluoromethyl)-2,4-diphenyloxazol-5(2*H*)-one (7a)

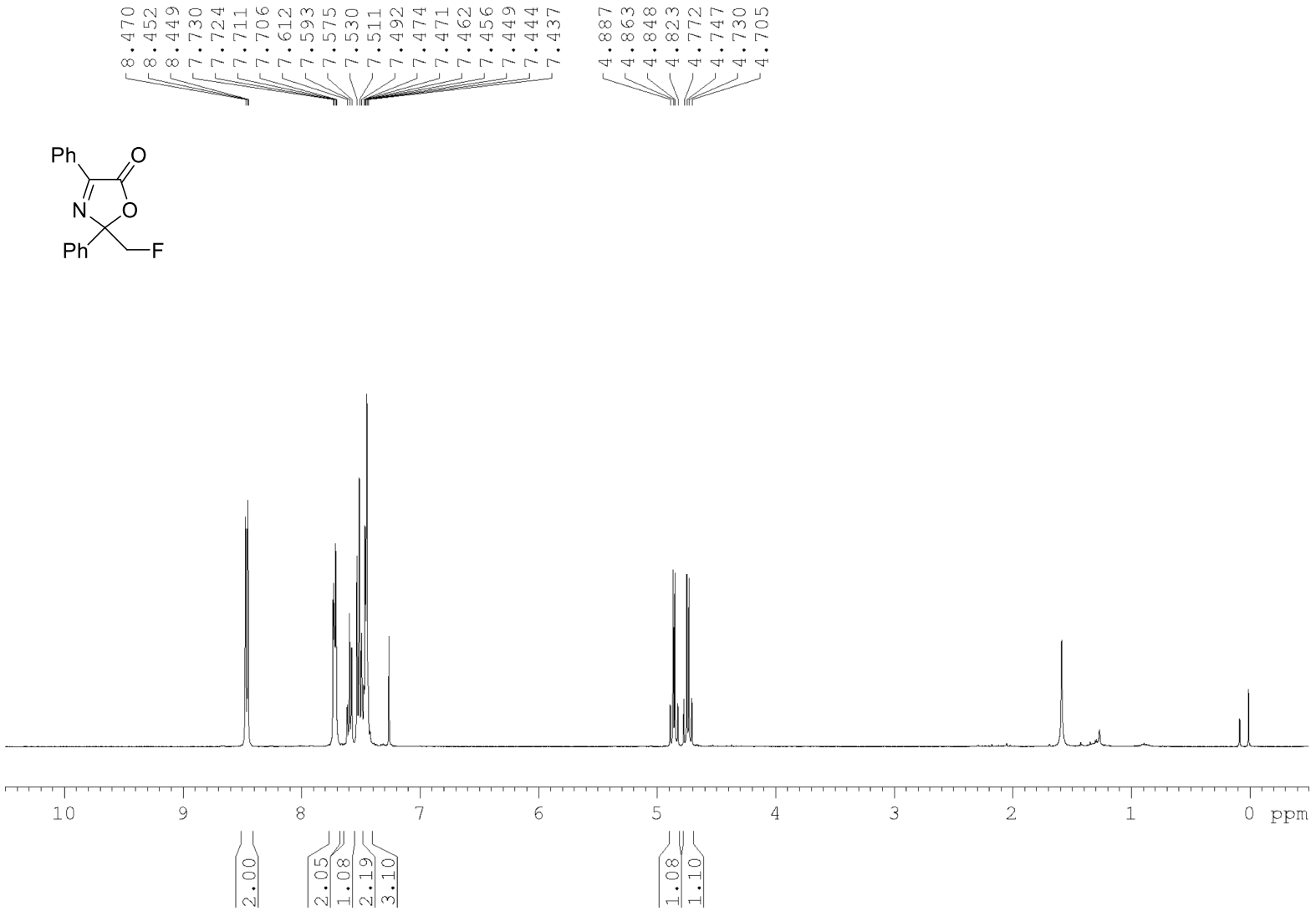

Figure S72. ^{13}C NMR spectrum of 2-(fluoromethyl)-2,4-diphenyloxazol-5(2*H*)-one (7a)

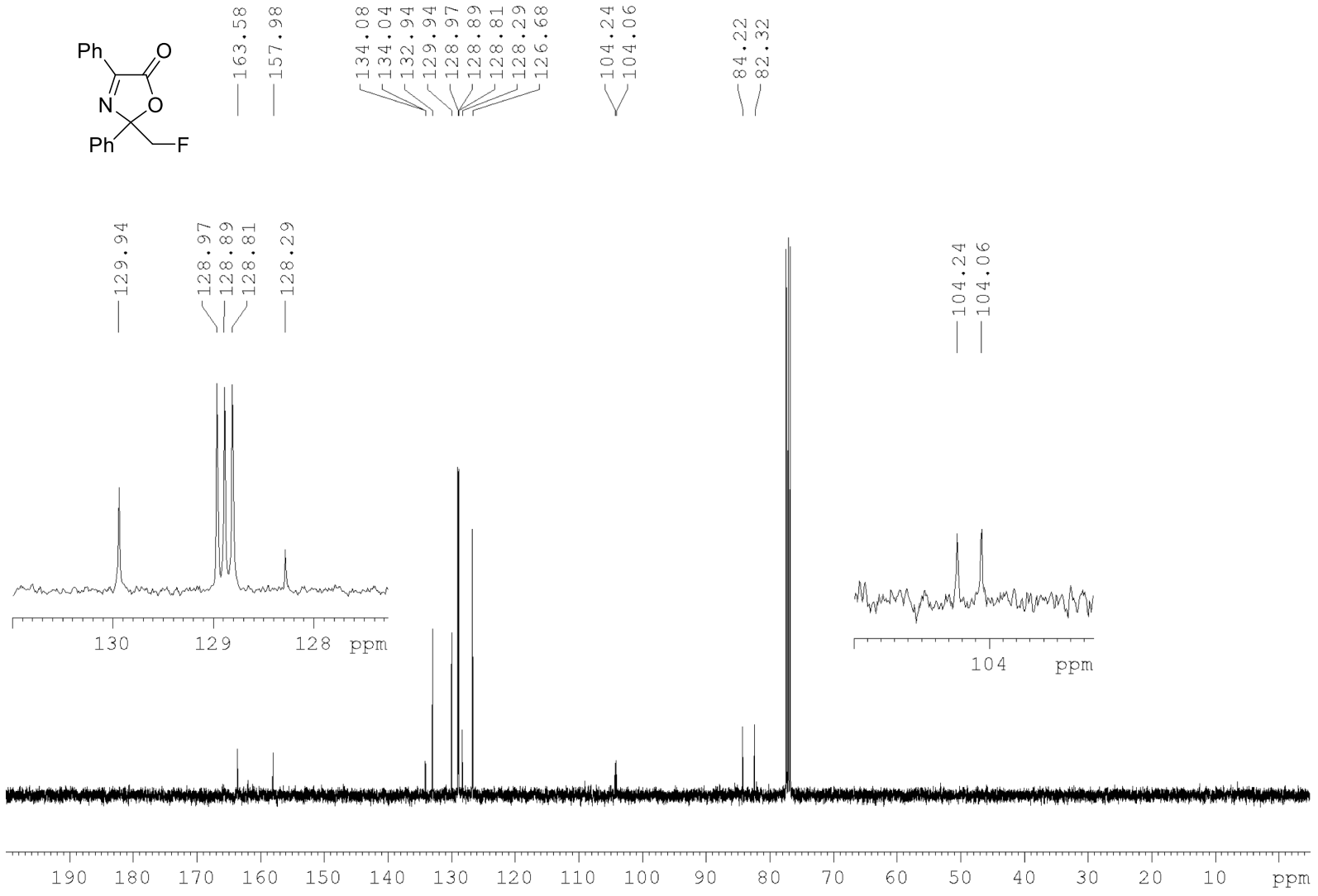

Figure S73. ^{1}H NMR spectrum of 2-(fluoromethyl)-4-(4-methoxyphenyl)-2-phenyloxazol-5(2*H*)-one (7b)

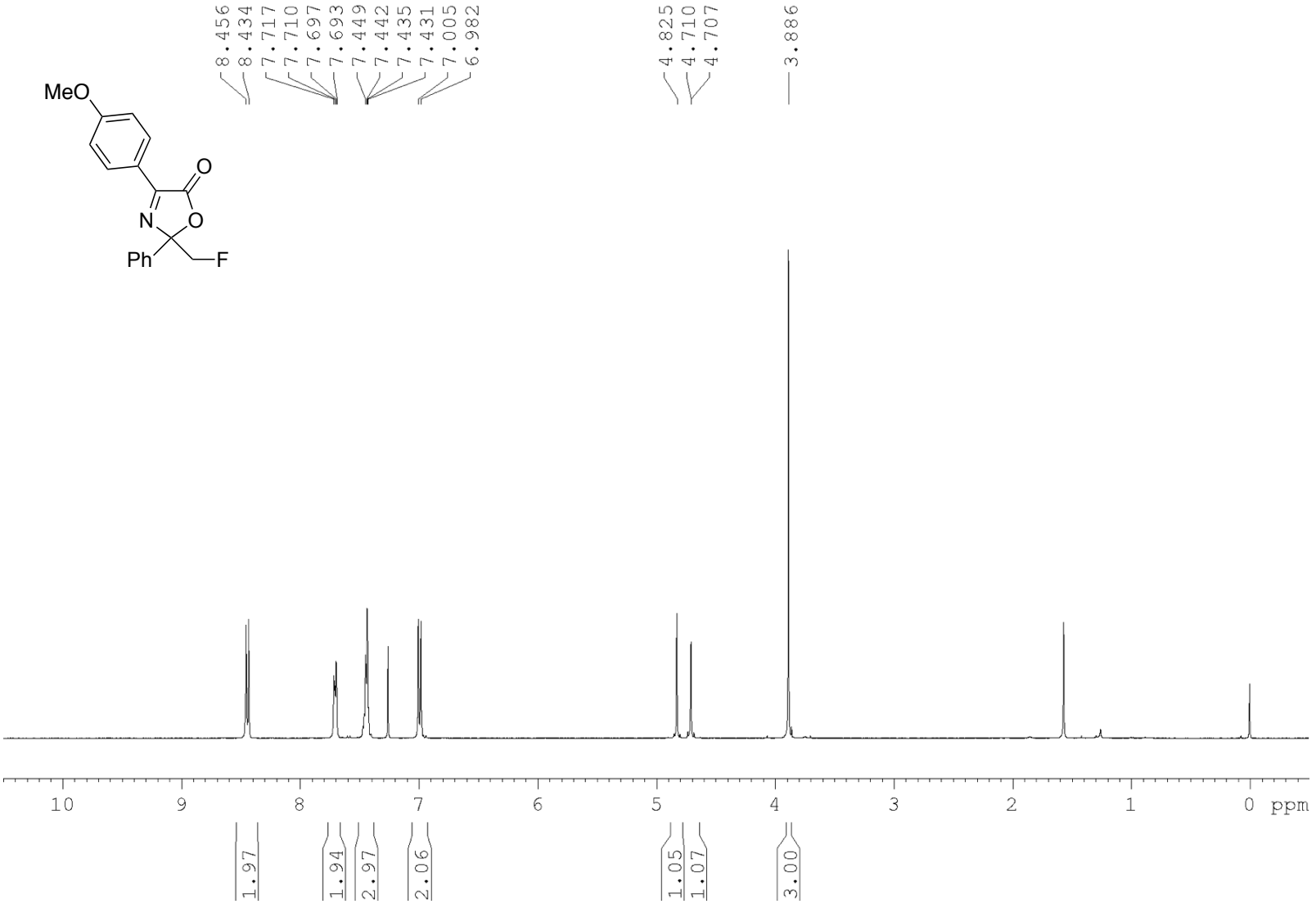

Figure S74. ^{13}C NMR spectrum of 2-(fluoromethyl)-4-(4-methoxyphenyl)-2-phenyloxazol-5(2*H*)-one (7b)

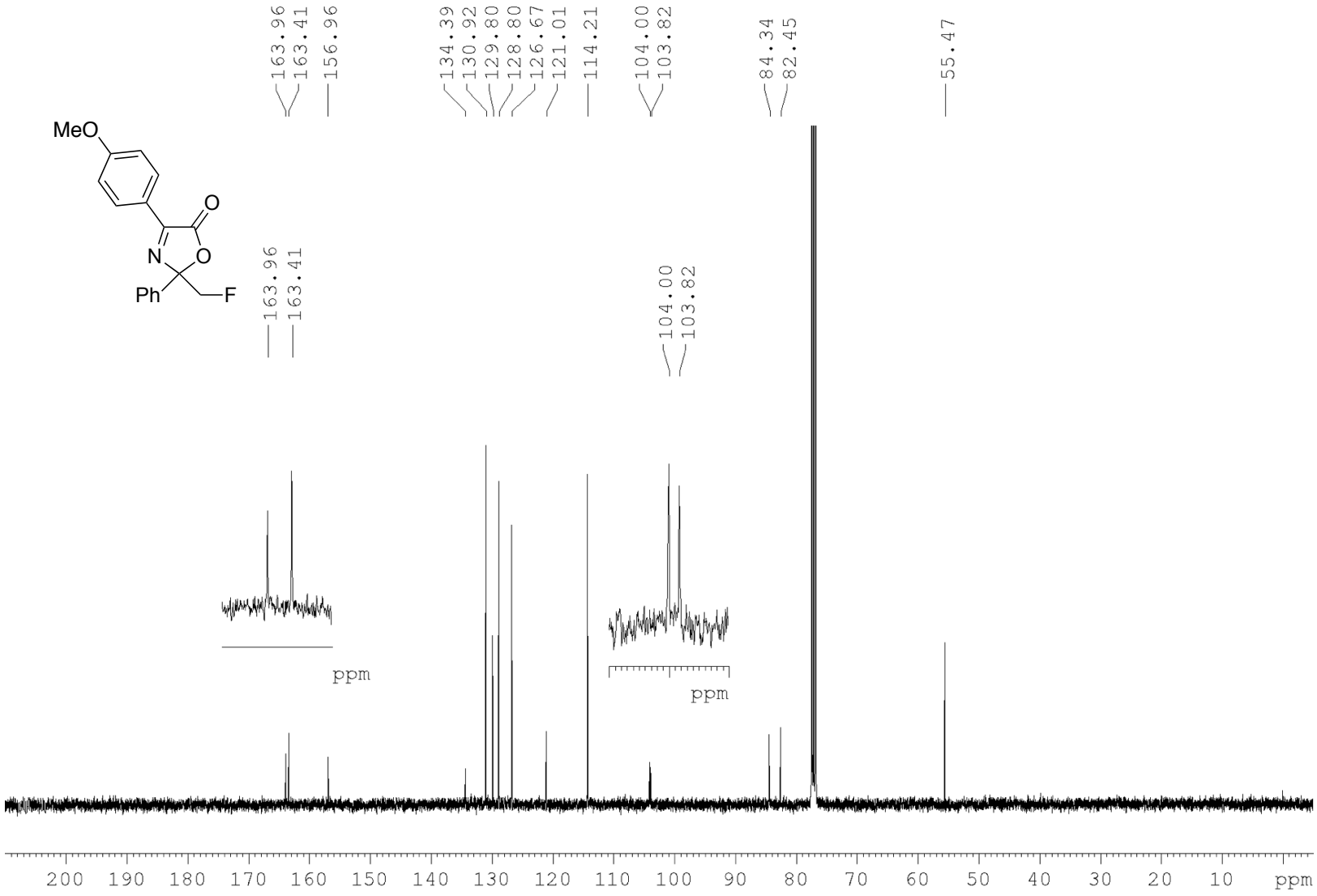

Figure S75. ^{1}H NMR spectrum of 2-(fluoromethyl)-2-phenyl-4-(thiophen-2-yl)oxazol-5(2*H*)-one (7e)

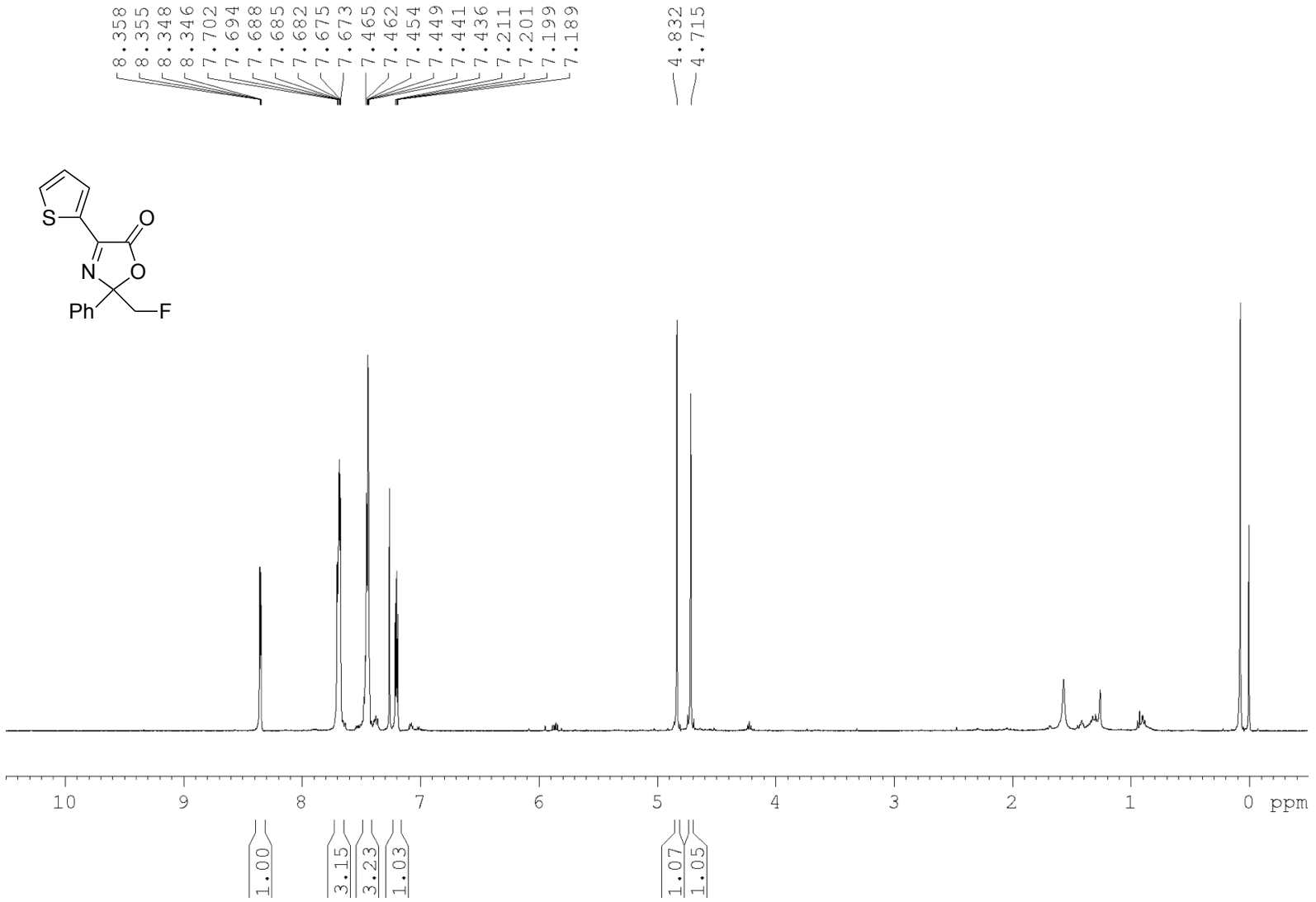

Figure S76. ^{13}C NMR spectrum of 2-(fluoromethyl)-2-phenyl-4-(thiophen-2-yl)oxazol-5(2*H*)-one (7e)

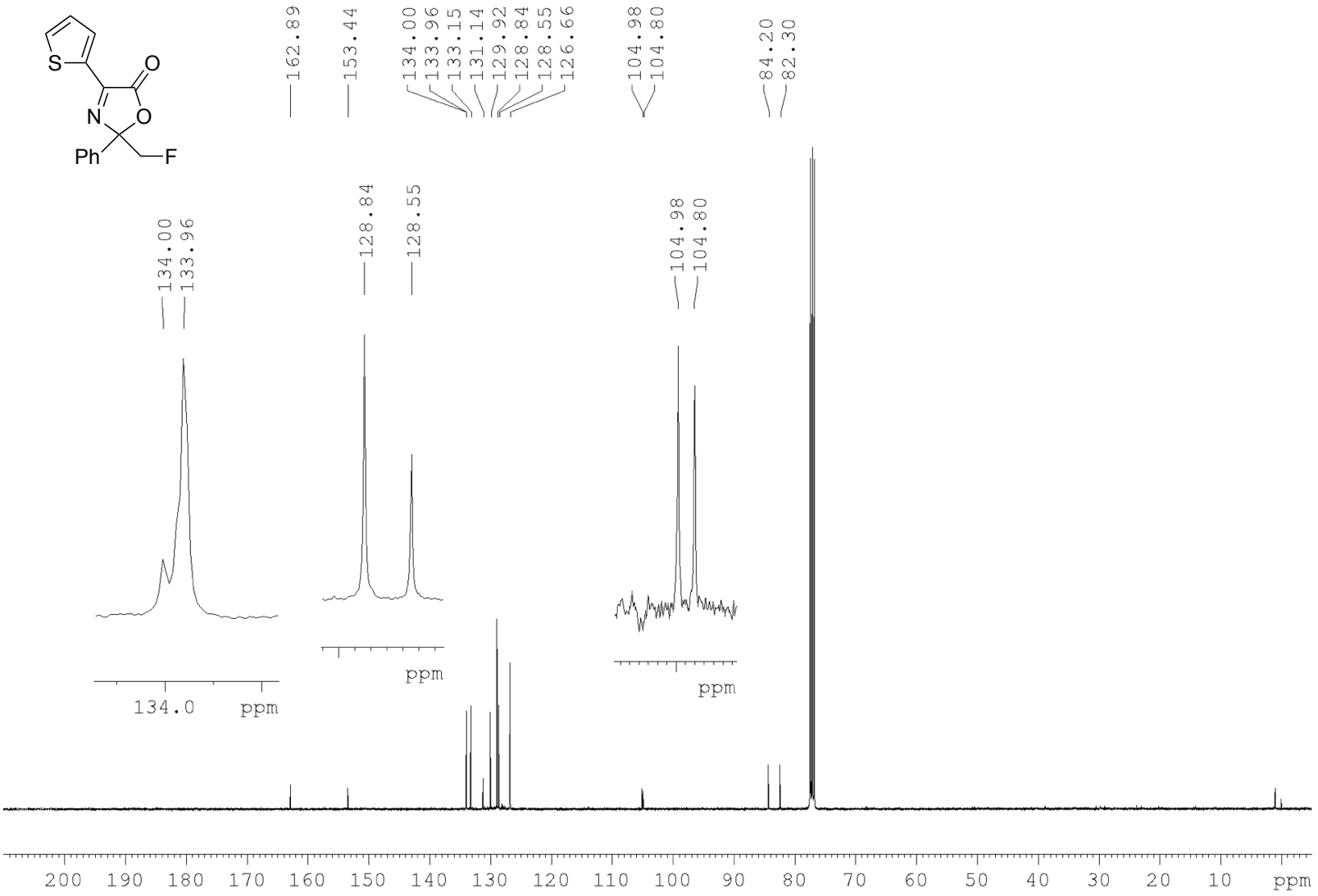

Figure S77. ^{1}H NMR spectrum of methyl 4-(2-(fluoromethyl)-5-oxo-2-phenyl-2,5-dihydrooxazol-4-yl)benzoate (7h)

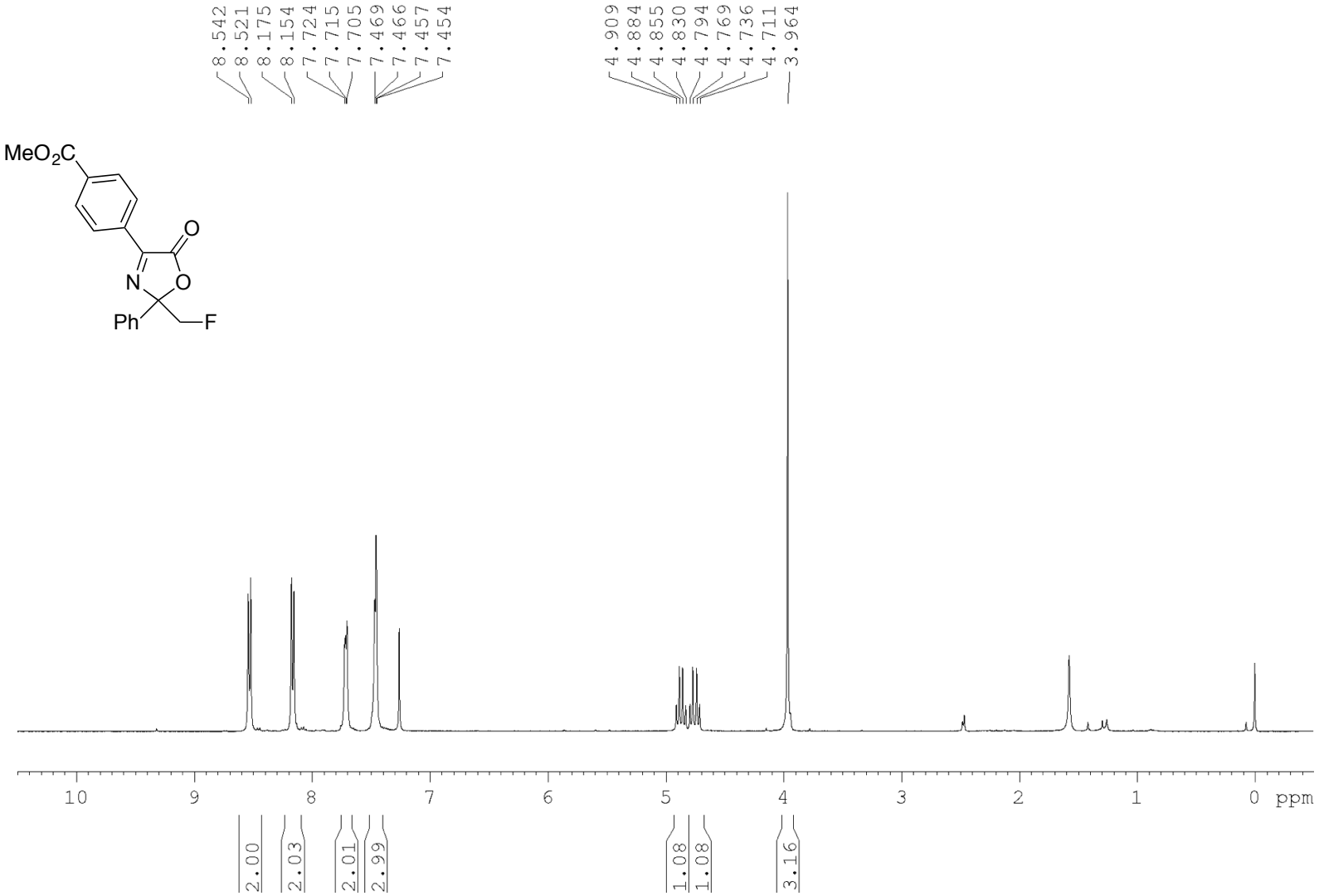

Figure S78. ^{13}C NMR spectrum of methyl 4-(2-(fluoromethyl)-5-oxo-2-phenyl-2,5-dihydrooxazol-4-yl)benzoate (7h)

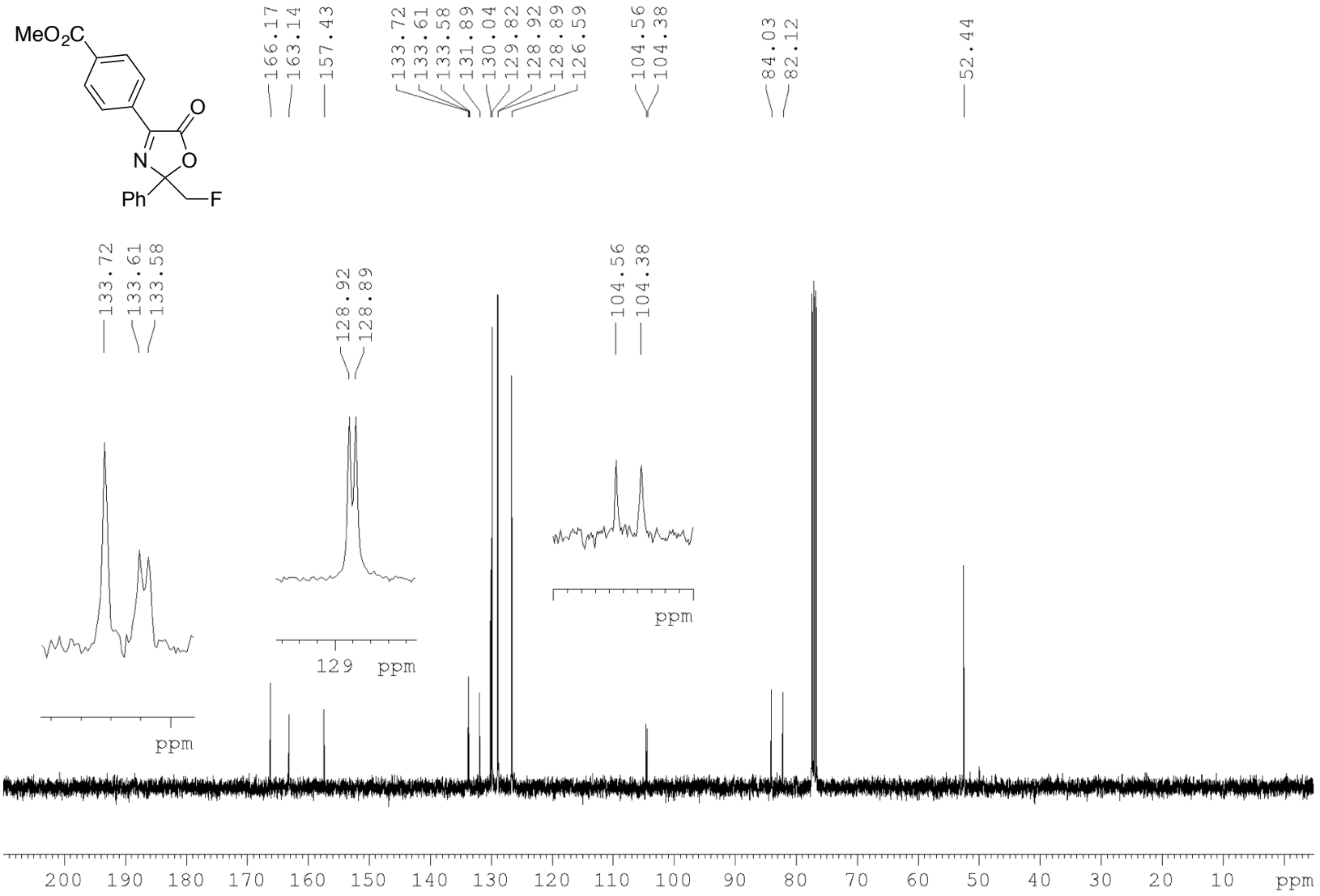

Figure S79. ^{1}H NMR spectrum of 5-fluoro-2-(fluoromethyl)-6-methoxy-2,4-diphenyl-5,6-dihydro-2*H*-1,3-oxazine (8)

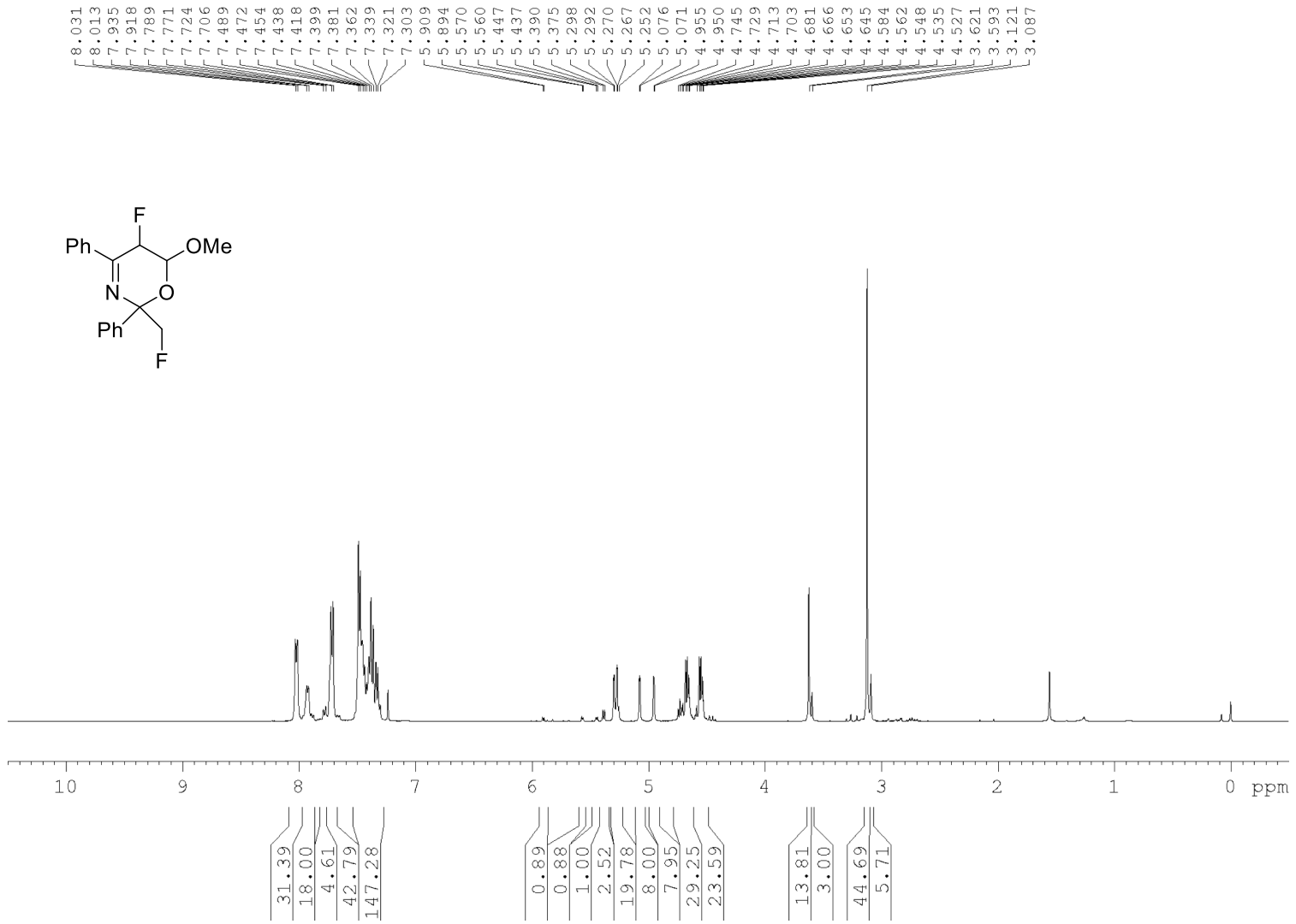

Figure S80. ^{13}C NMR spectrum of 5-fluoro-2-(fluoromethyl)-6-methoxy-2,4-diphenyl-5,6-dihydro-2*H*-1,3-oxazine (8)