New Cyclopalladated Benzothiophenes: A Catalyst Precursor for the Suzuki Coupling of Deactivated Aryl Chlorides

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General Information

All reactions were carried out in oven dried glassware under an atmosphere of dry nitrogen. Chemicals were purchased from Aldrich and used as received unless mentioned otherwise. All solvents used were dried before use. Product purification by column chromatography was accomplished using silica gel 60–120 mesh. Technical grade solvents were used for chromatography and distilled prior to use. NMR spectra were recorded in Fourier transform mode. The ^{1}H NMR, ^{31}P NMR and ^{19}F NMR spectra were recorded on a Bruker-Avance (300 MHz) and Varian-Inova (400 MHz) spectrometer using $CDCl_3$ and C_6D_6 solvents and TMS as the internal standard. ^{31}P and ^{19}F are refernced to an external standard 85% H_3PO_4 and $CFCl_3$ respectively. Multiplicities in the ^{1}H NMR spectra are described as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad; coupling constants are reported in Hz. Elemental (CHN) analyse were performed in Vario MICRO cube. The benzothiophene based palladacycles were prepared according to published procedure

Optimization of Suzuki reaction

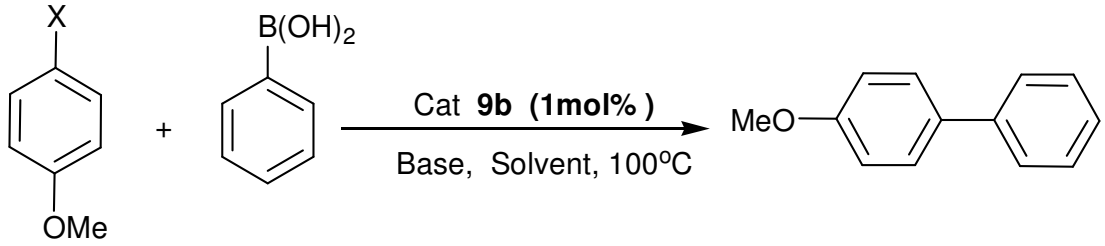
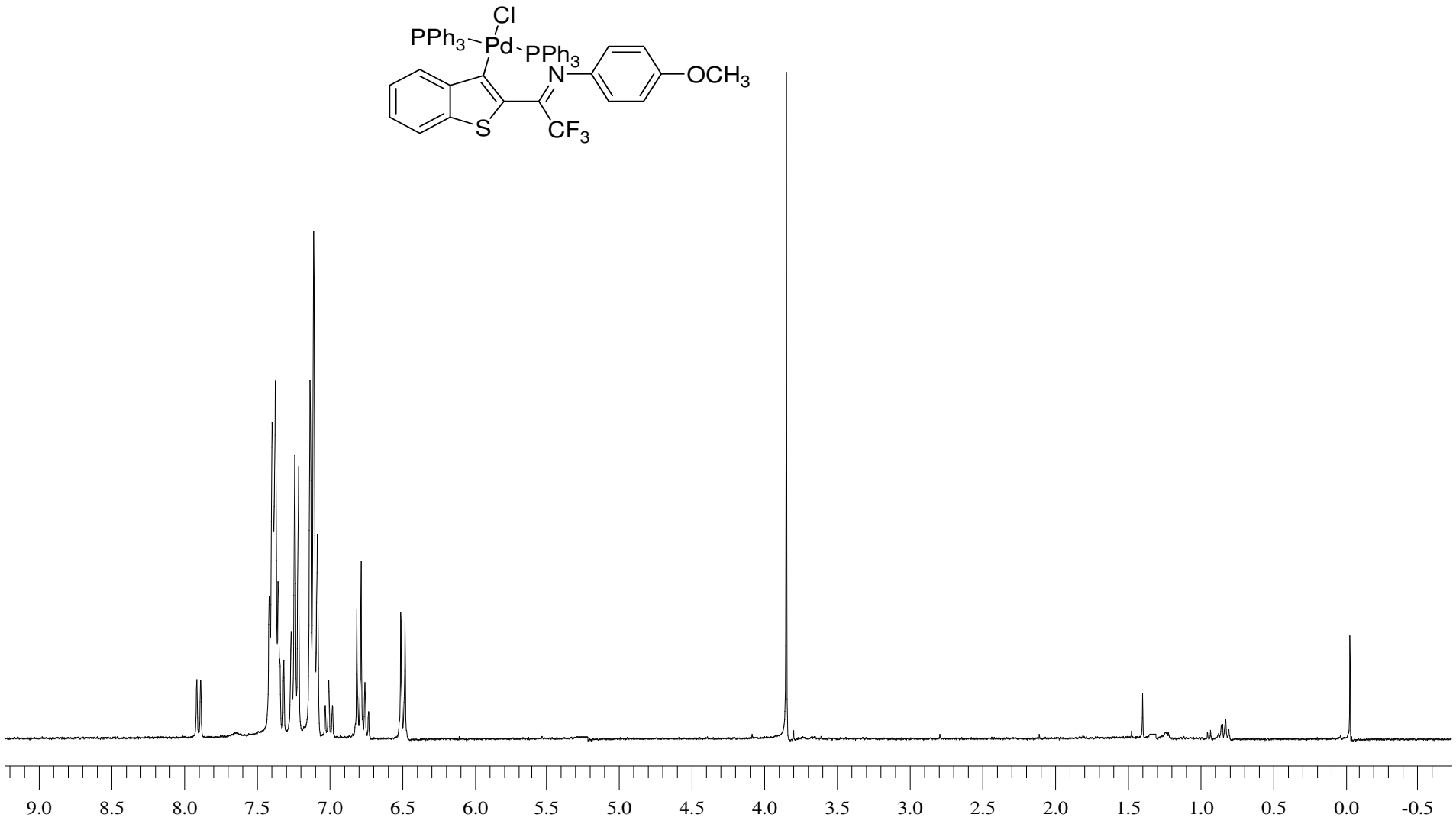
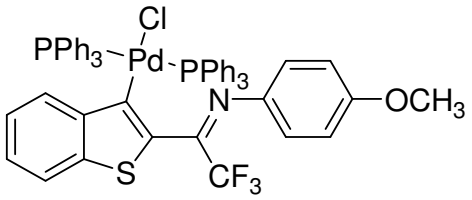


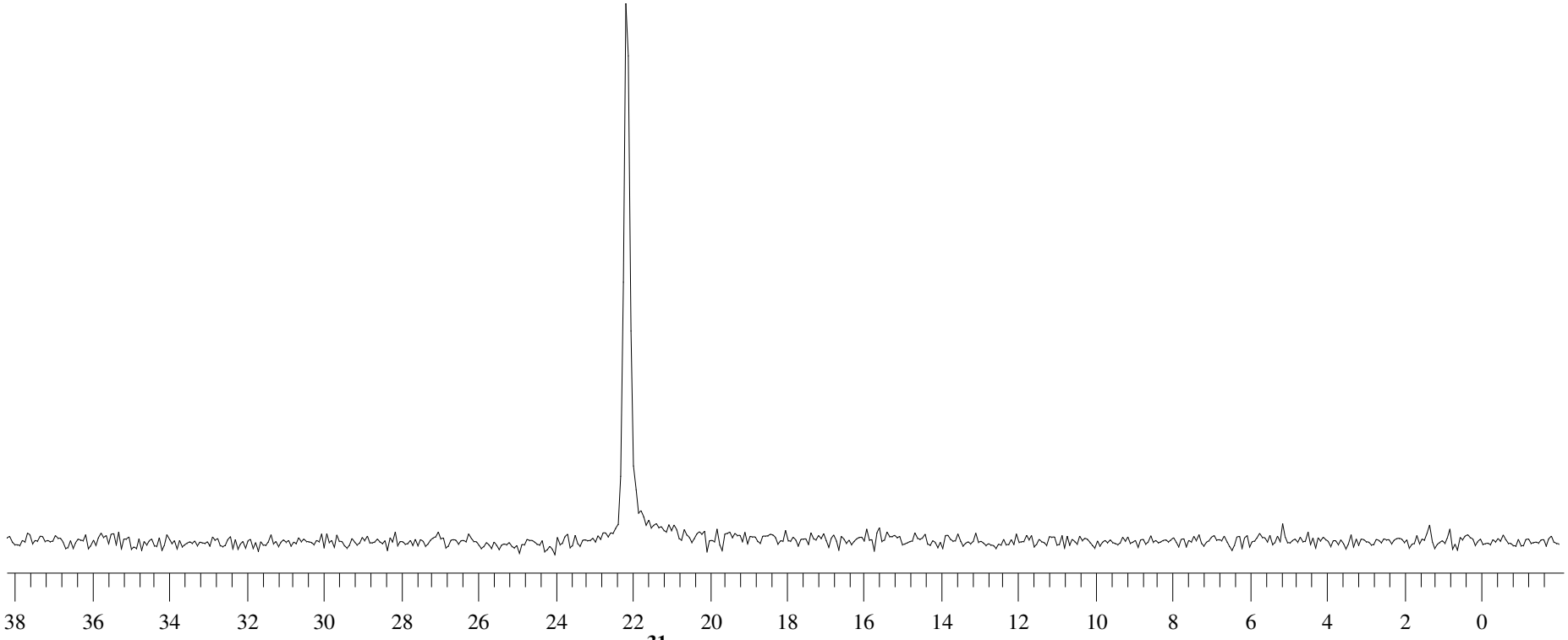
Table 1.

entry	base	solvent	time (hr)	Isolated yield(%)
1	Et_3N	Toluene	10	34
2.	Na_2CO_3	Toluene	10	56
3	$K_3PO_4.H_2O$	Toluene	10	45
4	Cs_2CO_3	Toluene	8	78
5	Cs_2CO_3	DMF	8	67
6	Cs_2CO_3	1,4-Dioxane	6	94

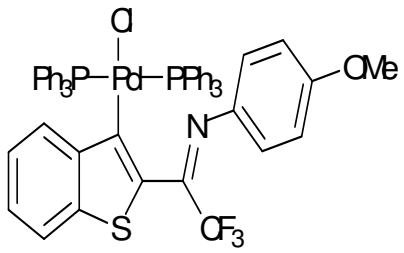


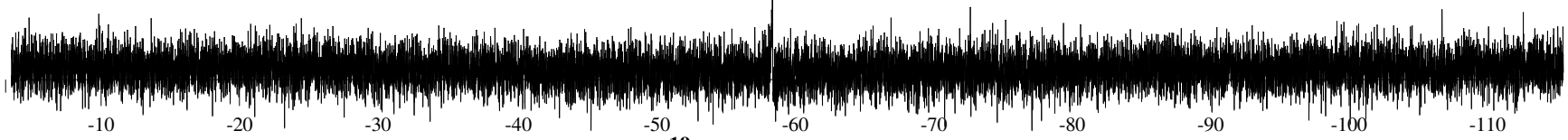
^{1}H NMR of 9a



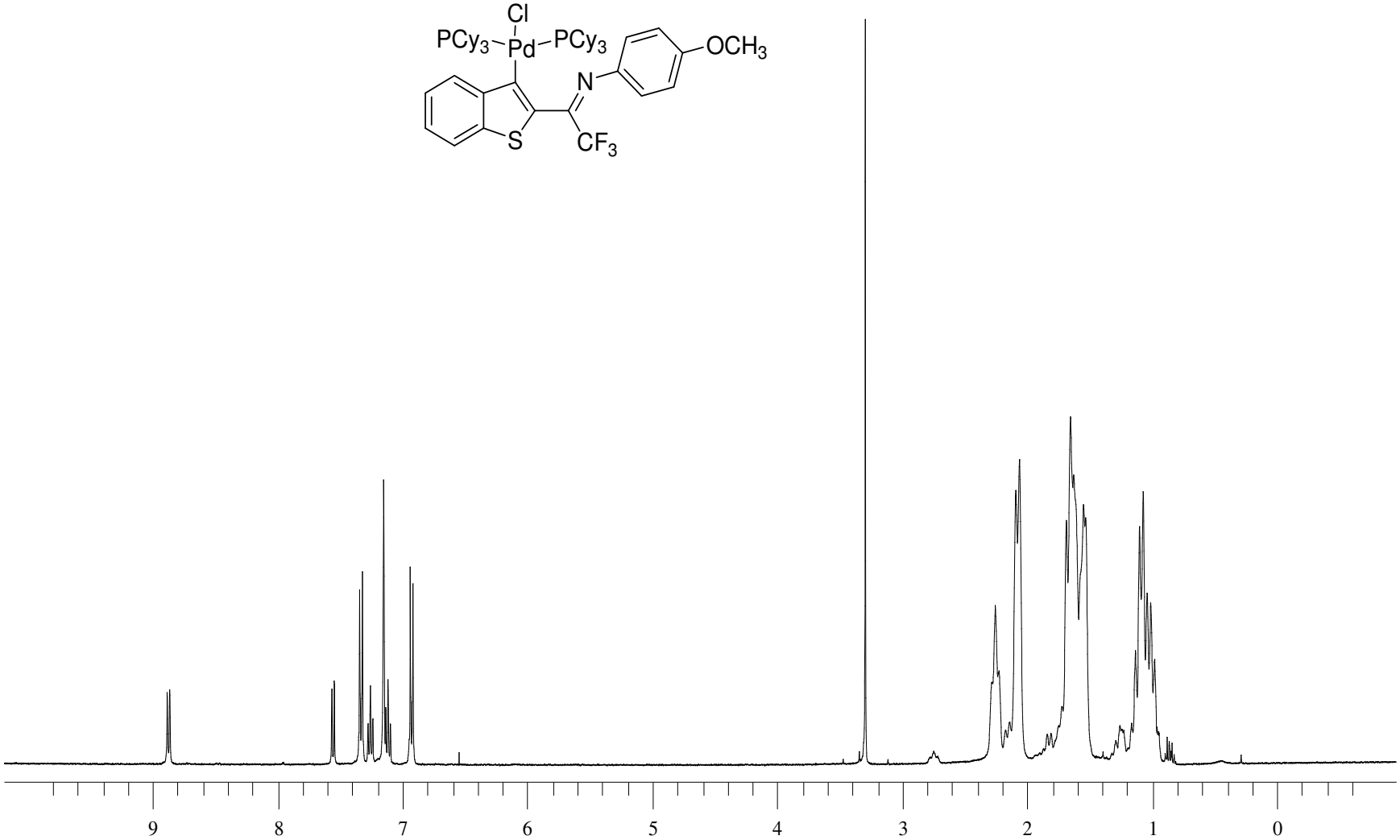


^{31}P NMR of 9a

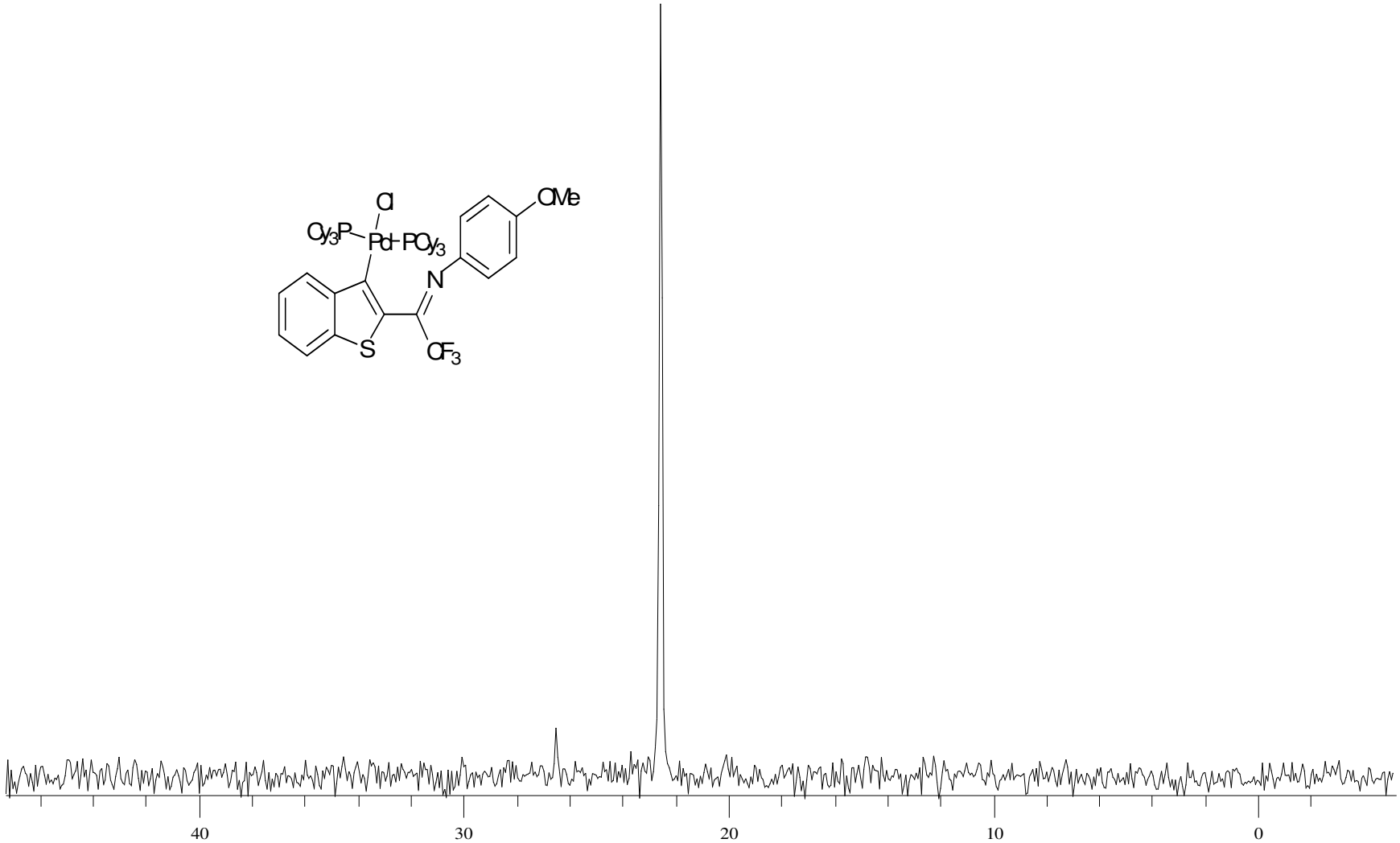




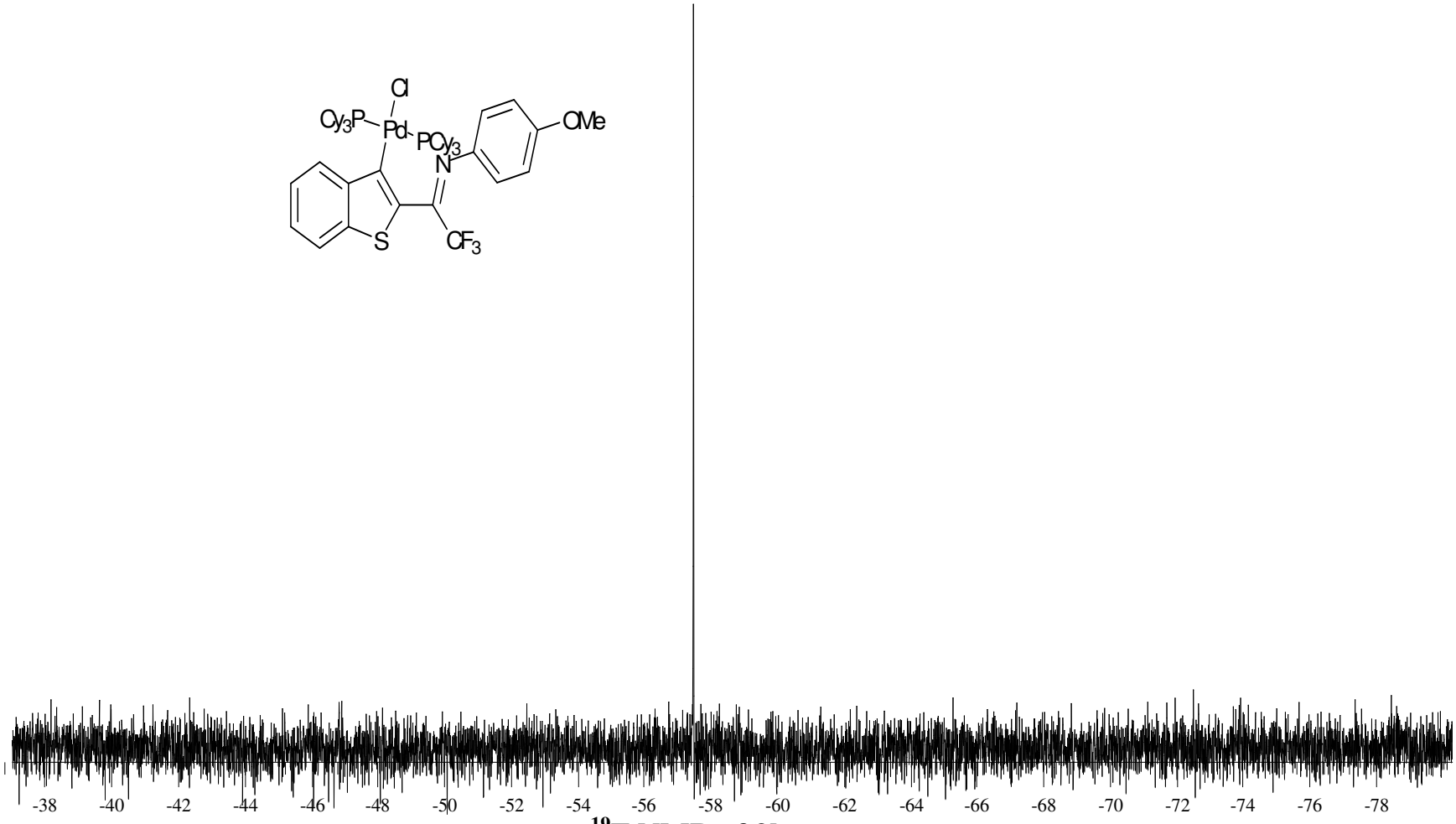
^{19}F NMR of 9a



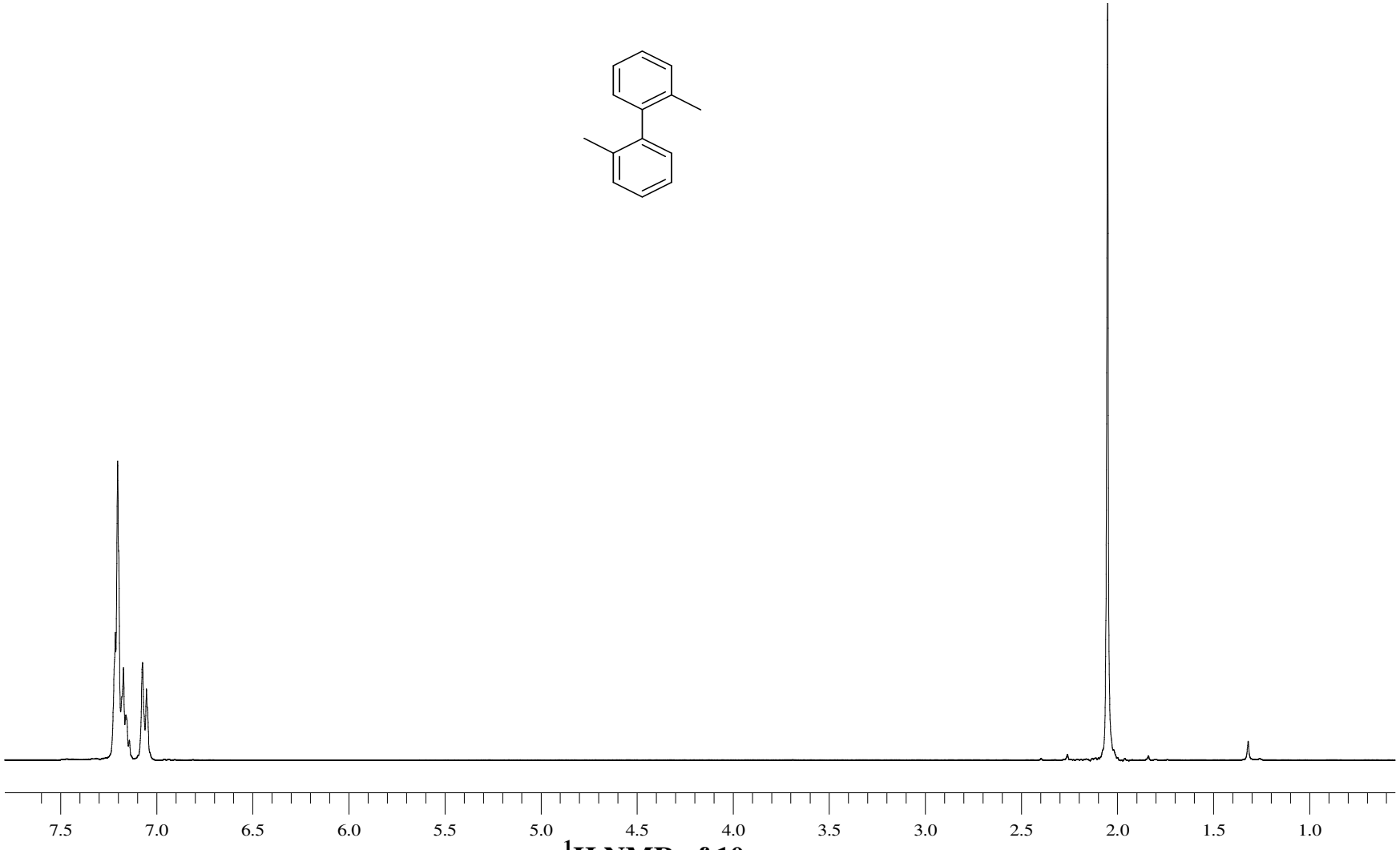
^{1}H NMR of 9b



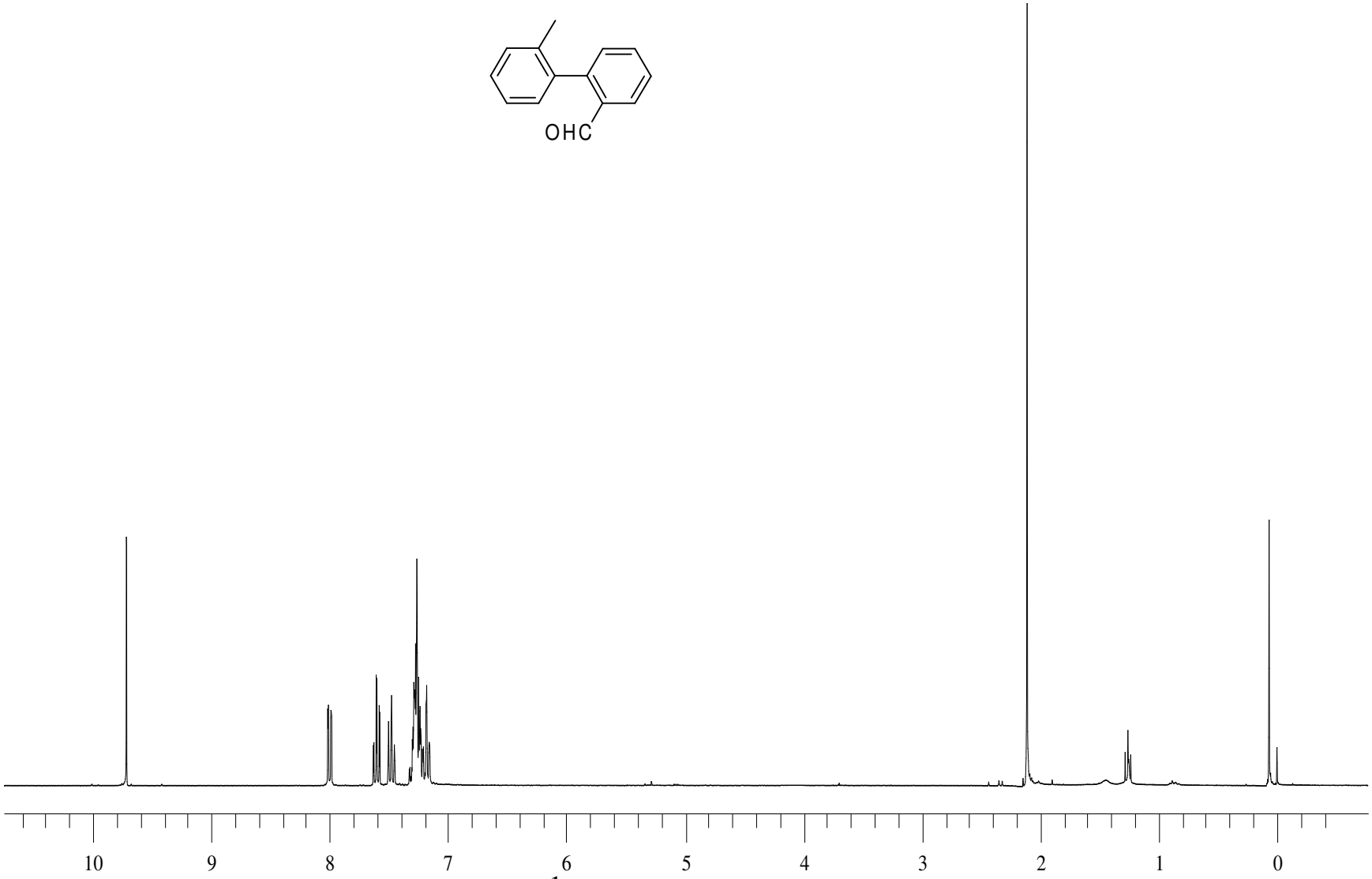
^{31}P NMR of 9b


Cl
Cy3P
Pd
PCy3
N
OMe
S
CF3
-38
-40
-42
-44
-46
-48
-50
-52
-54
-56
-58
-60
-62
-64
-66
-68
-70
-72
-74
-76
-78

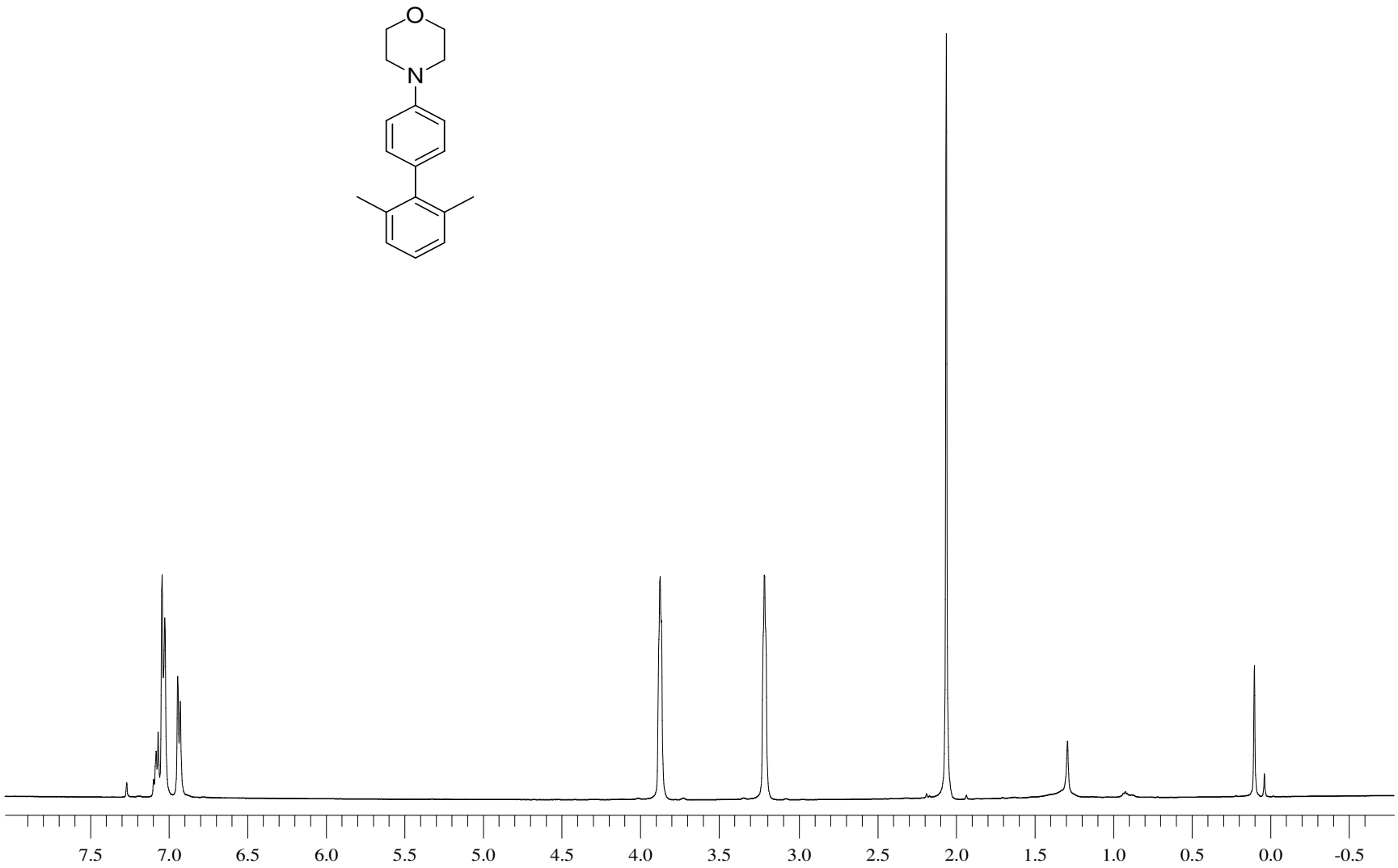
^{19}F NMR of 9b



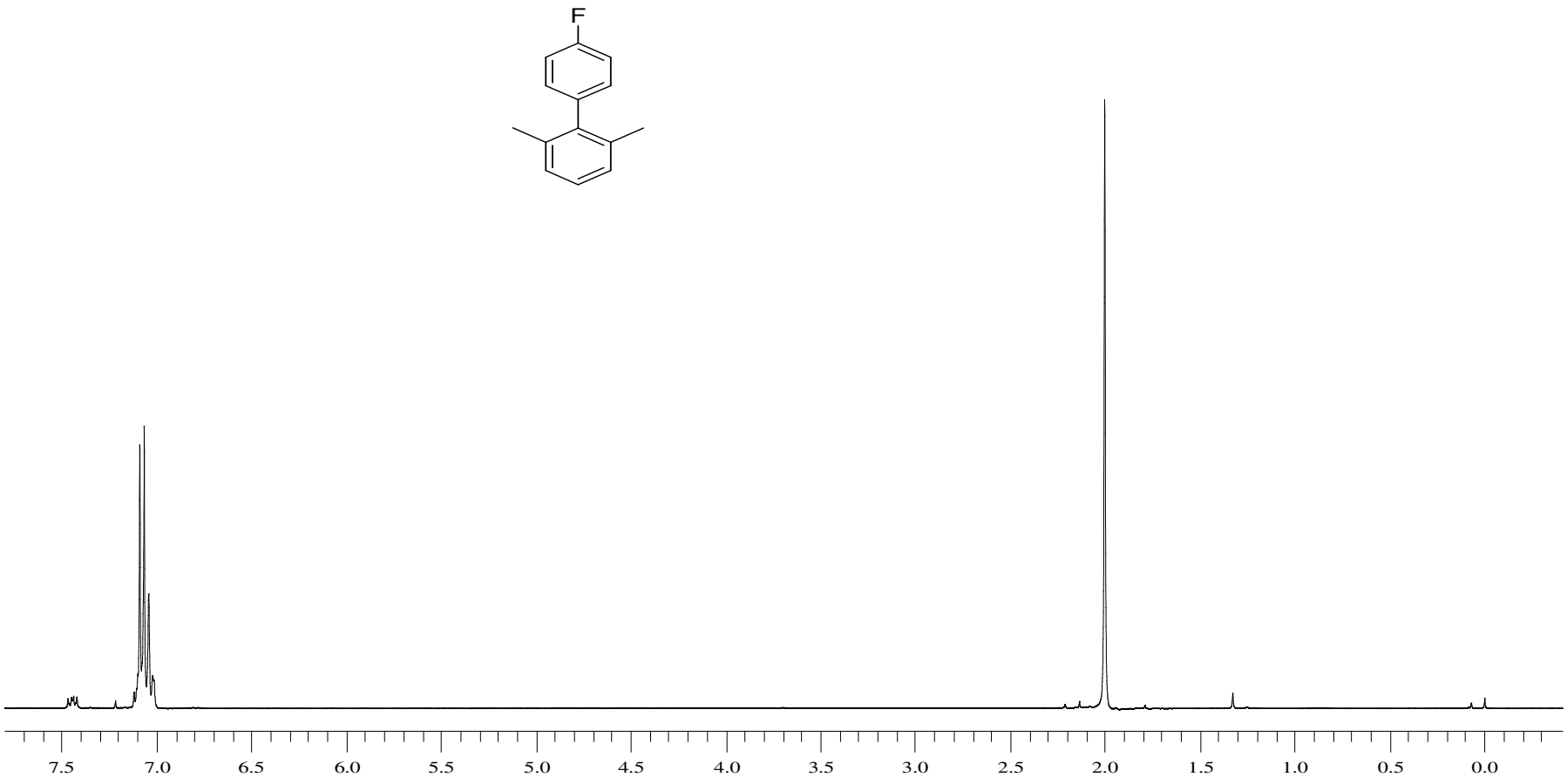
^{1}H NMR of 10a



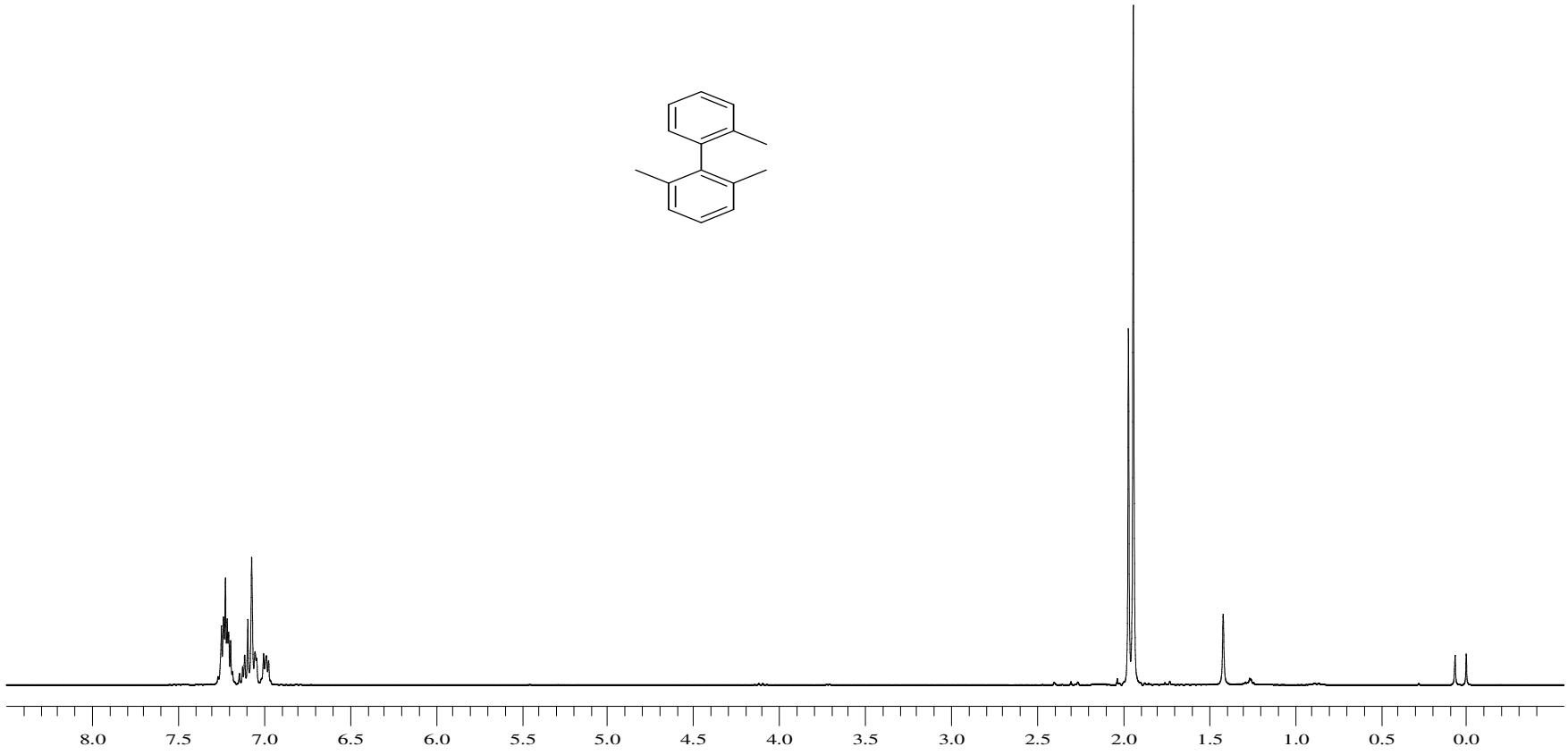
^{1}H NMR of 10b



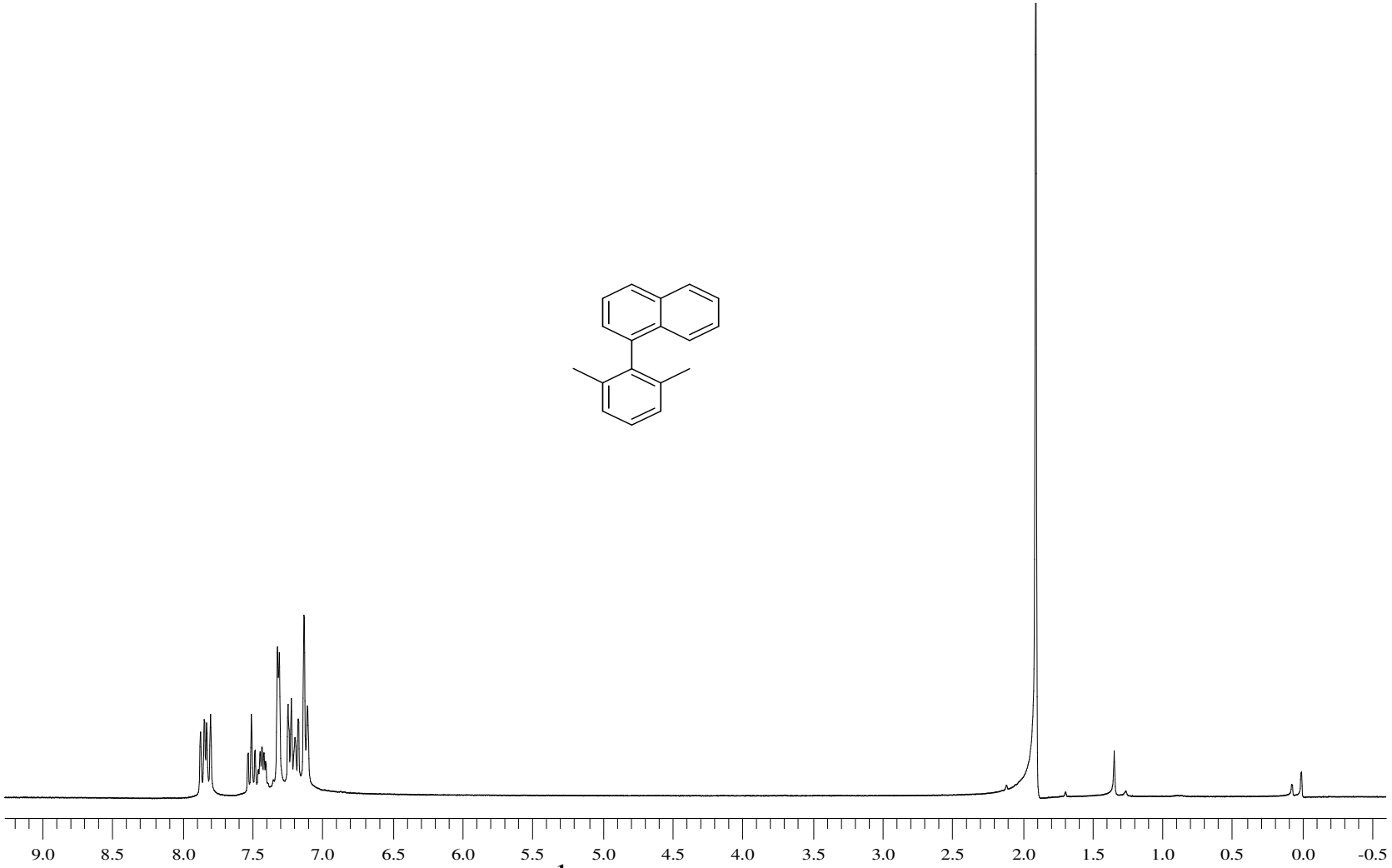
^{1}H NMR of 10c



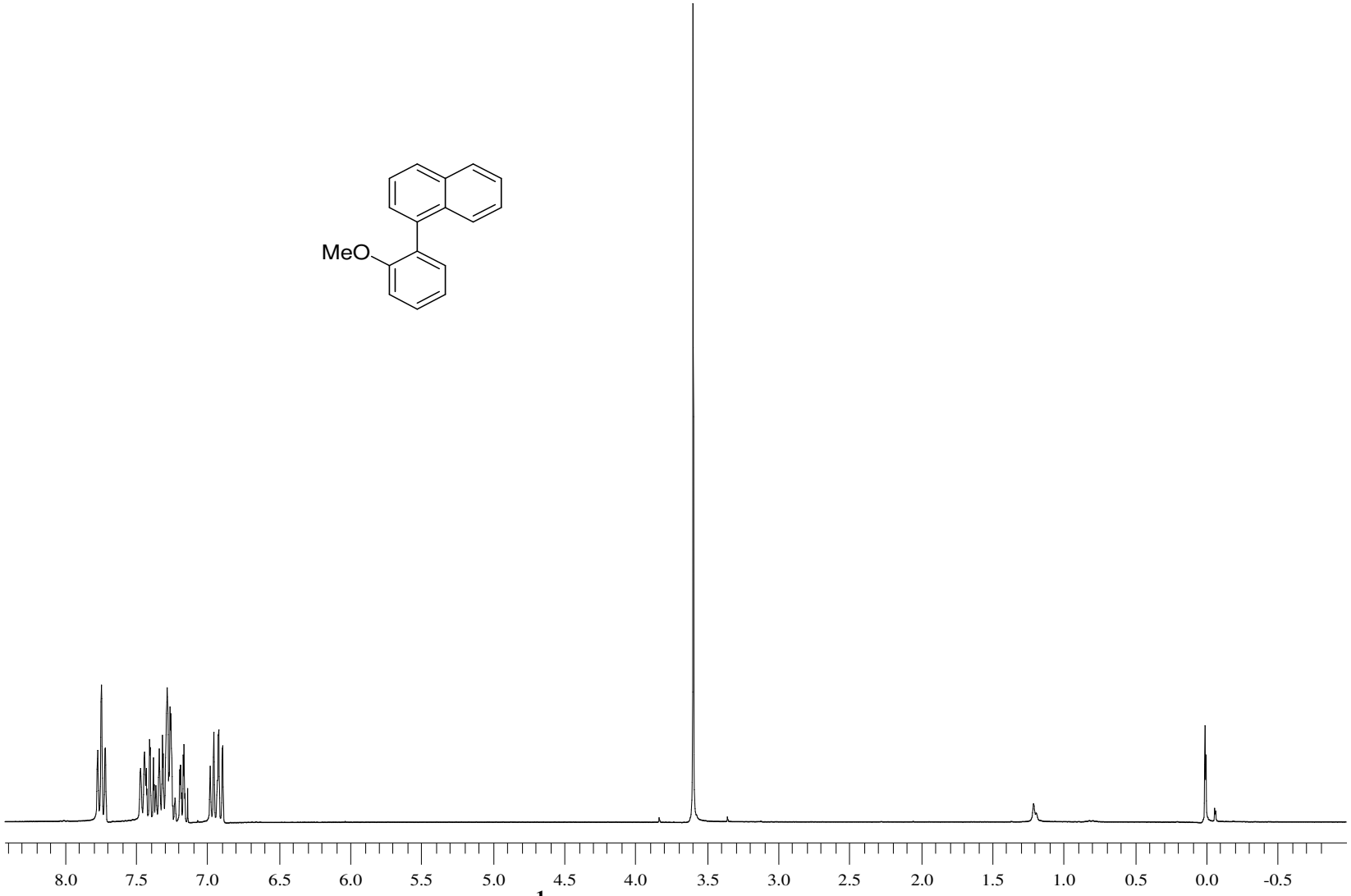
^{1}H NMR of 10d



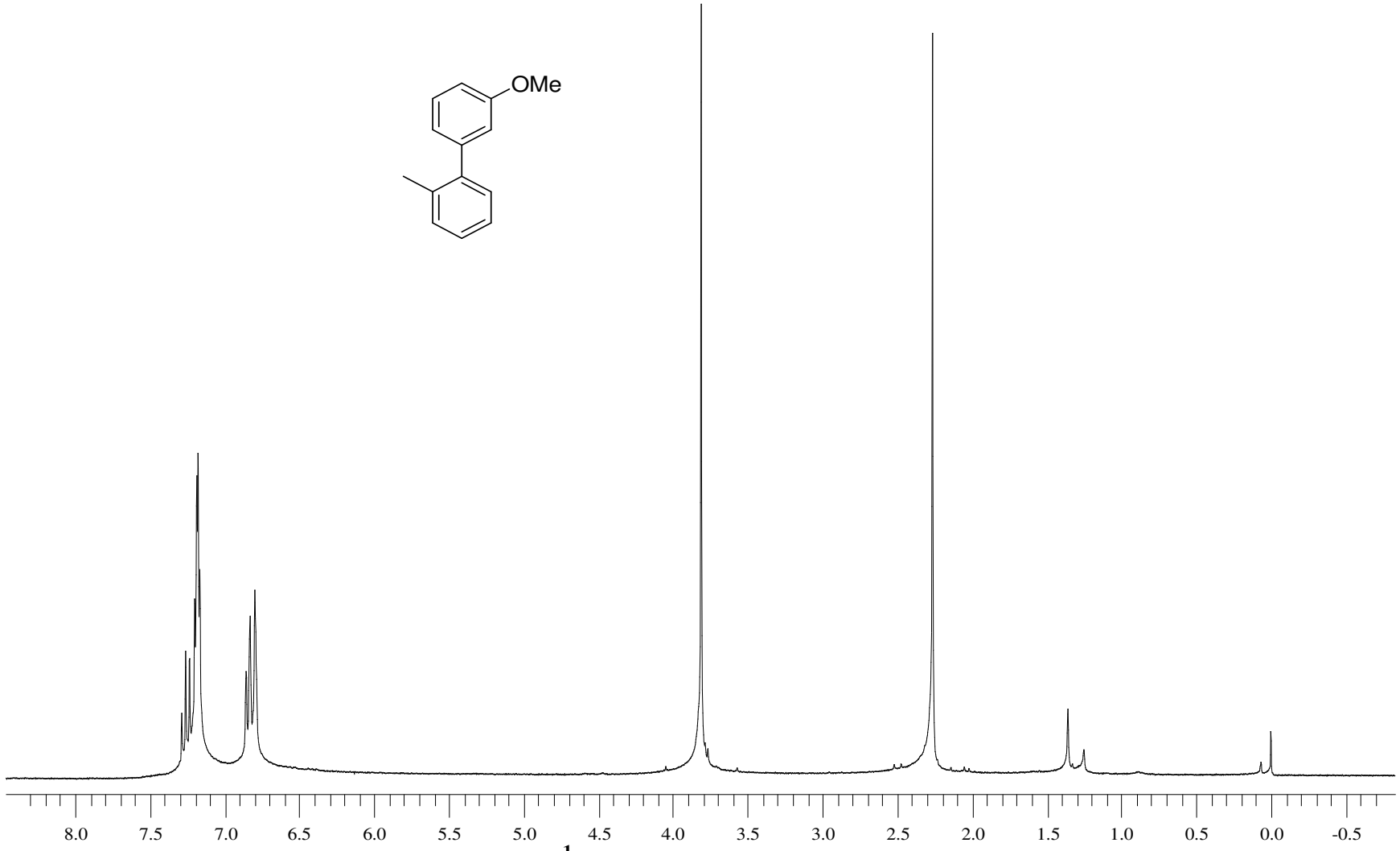
^{1}H NMR of 10e



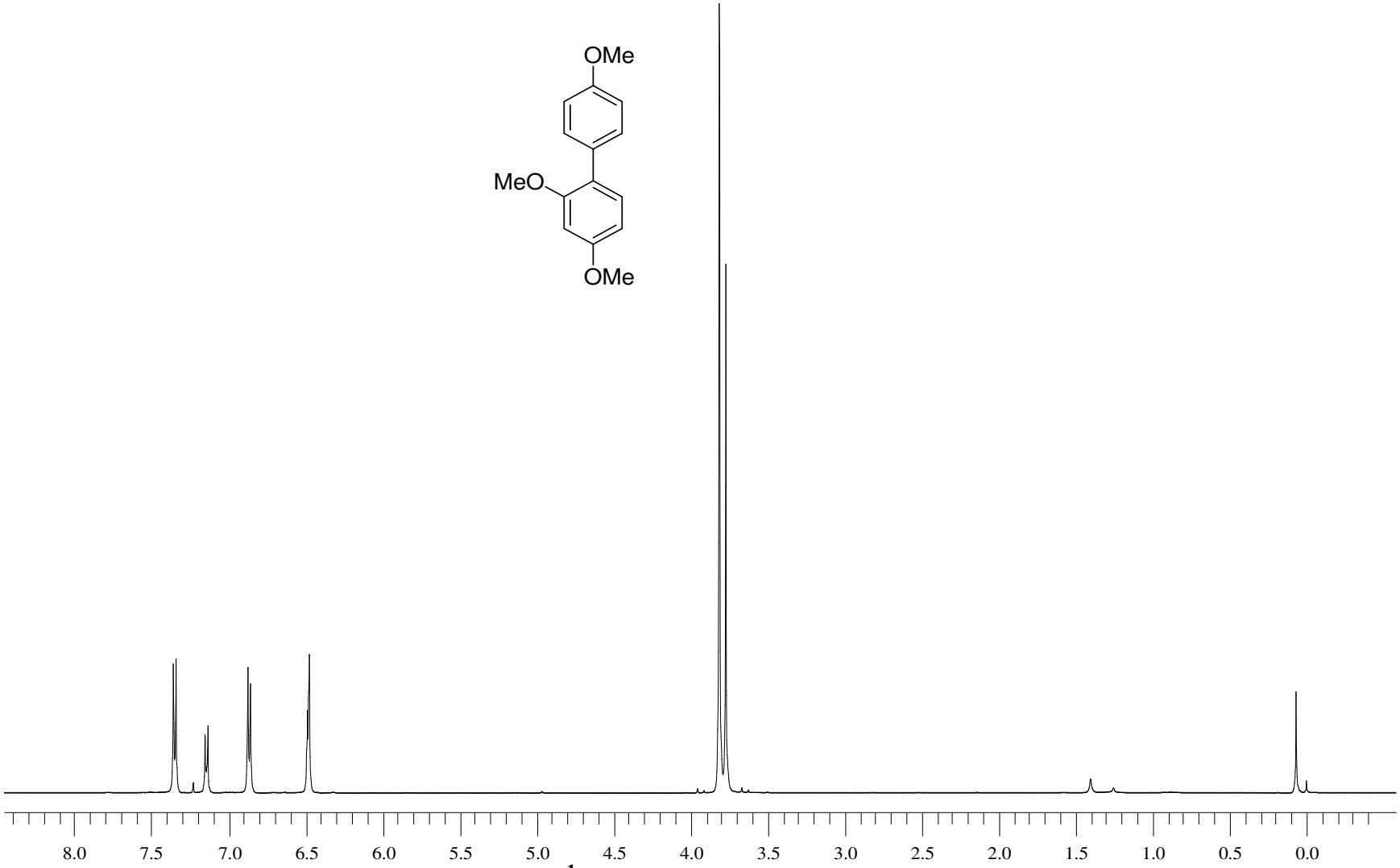
^{1}H NMR of 10f



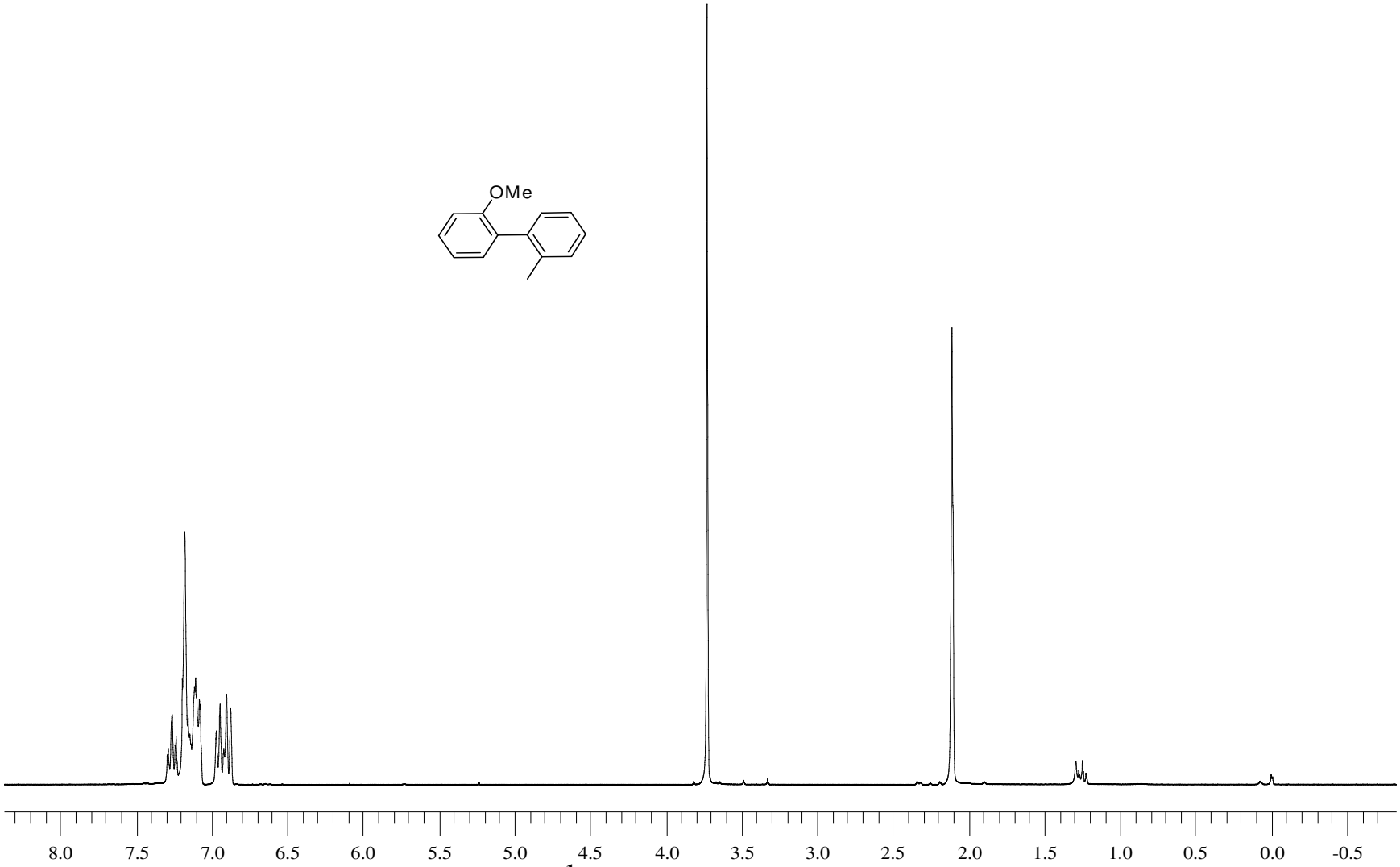
^{1}H NMR of 10g



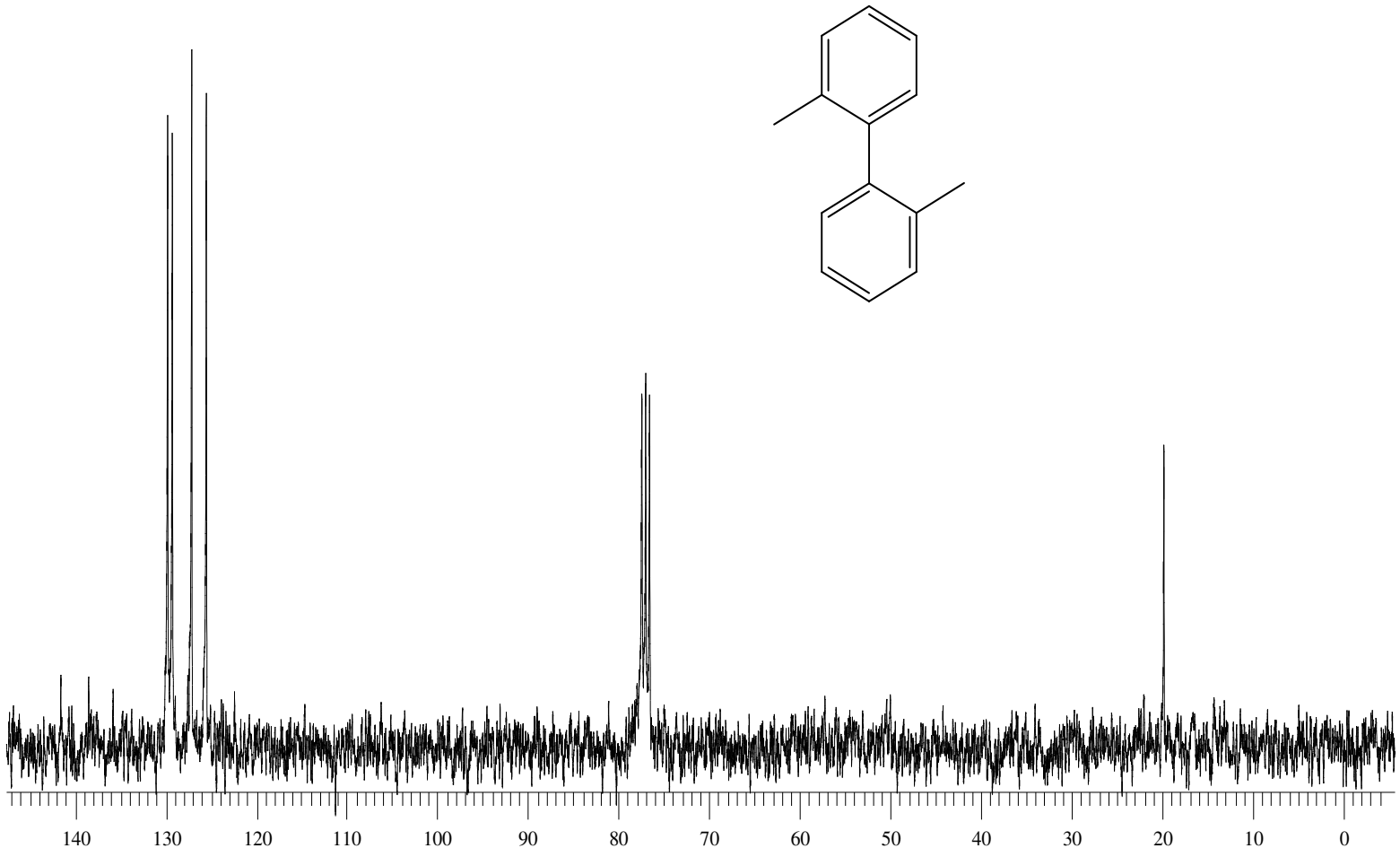
^{1}H NMR of 10h



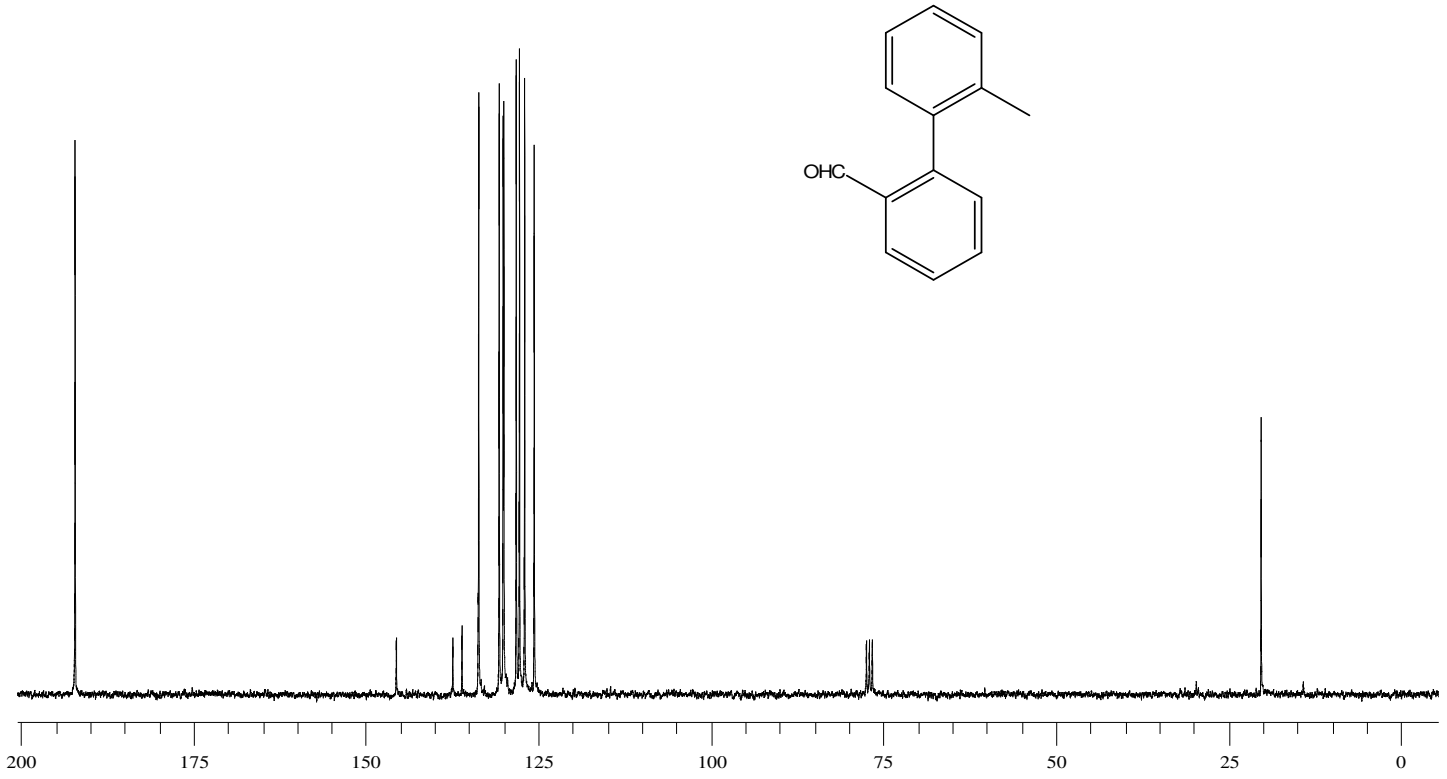
^{1}H NMR of 10i



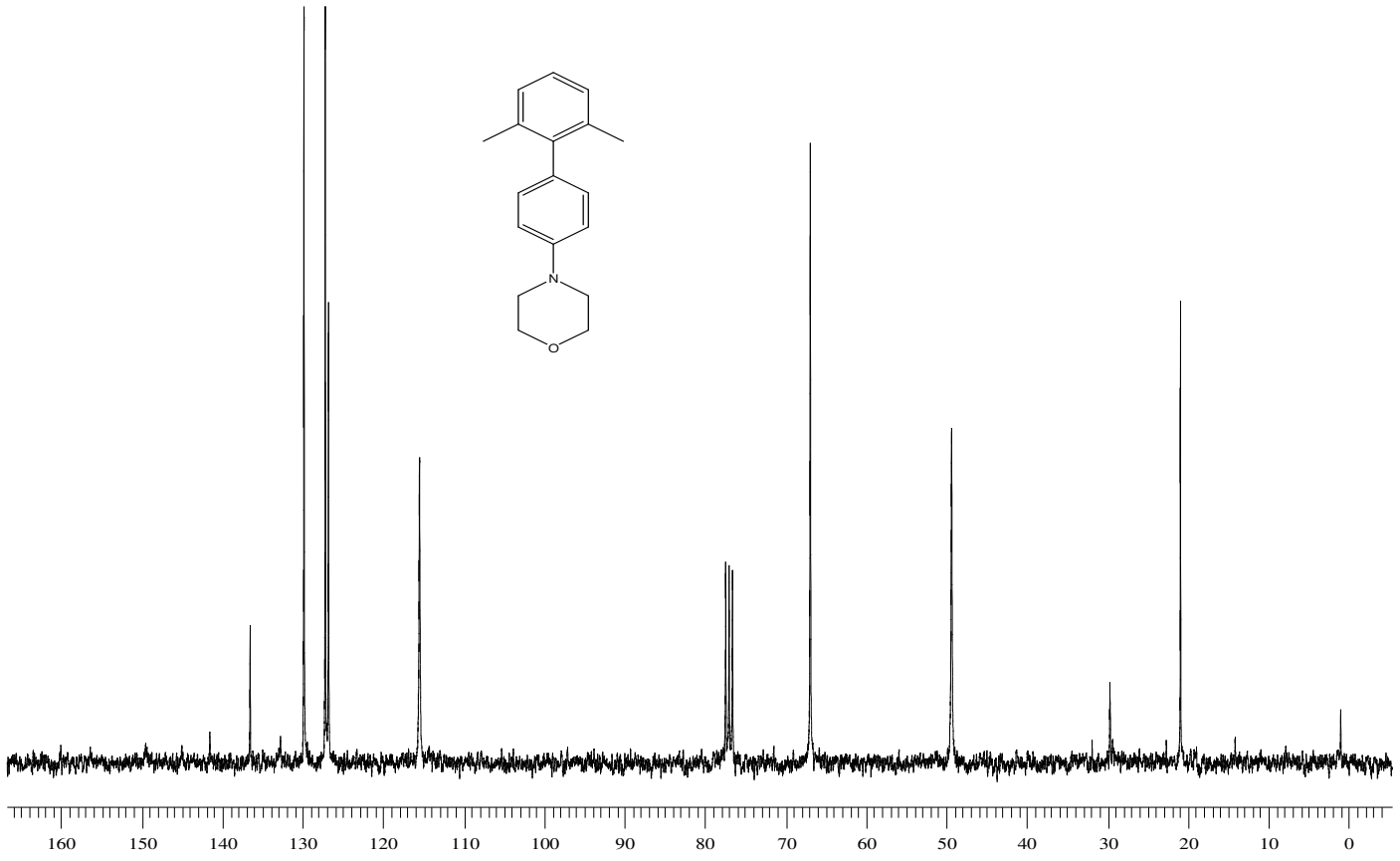
^{1}H NMR of 10j



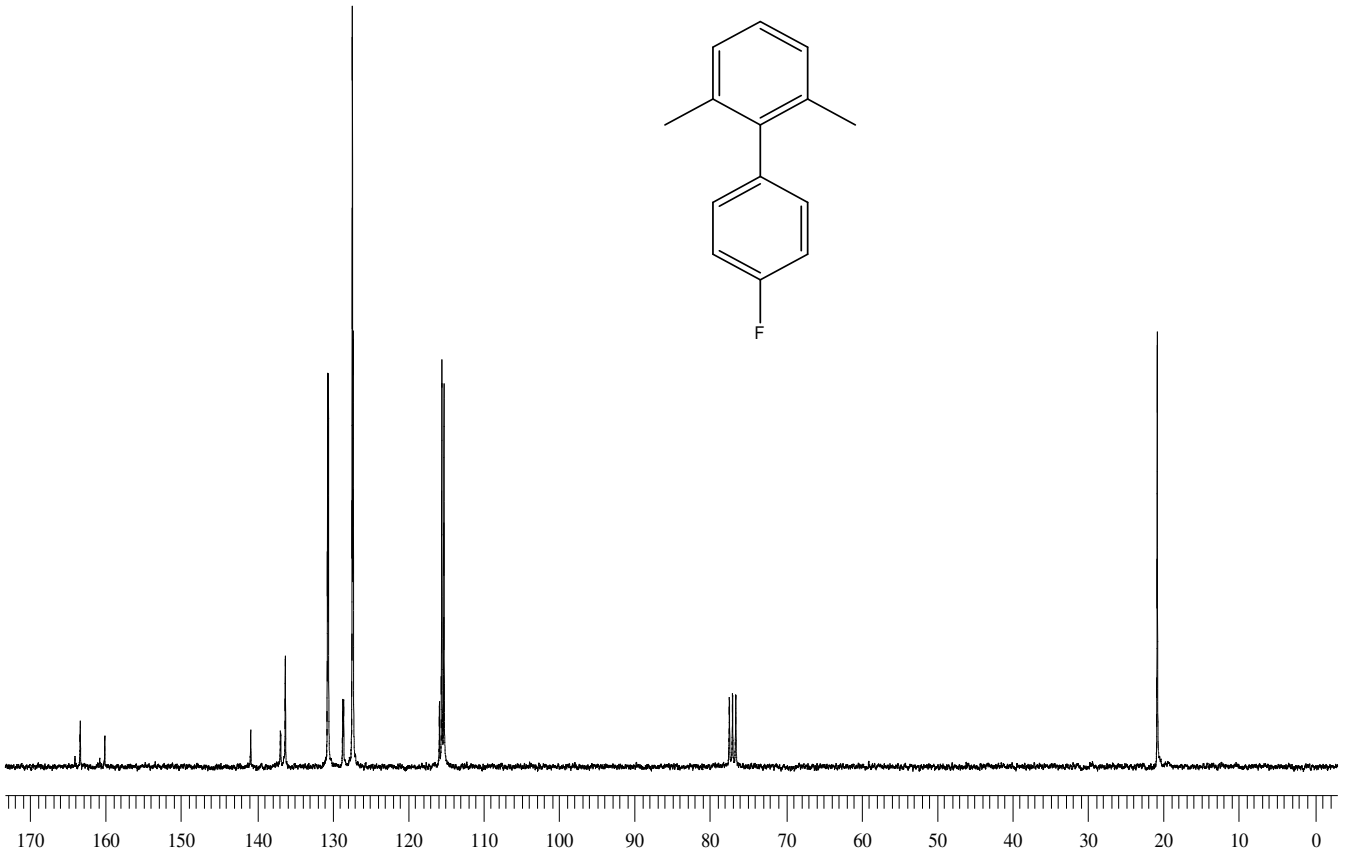
^{13}C NMR of 10a



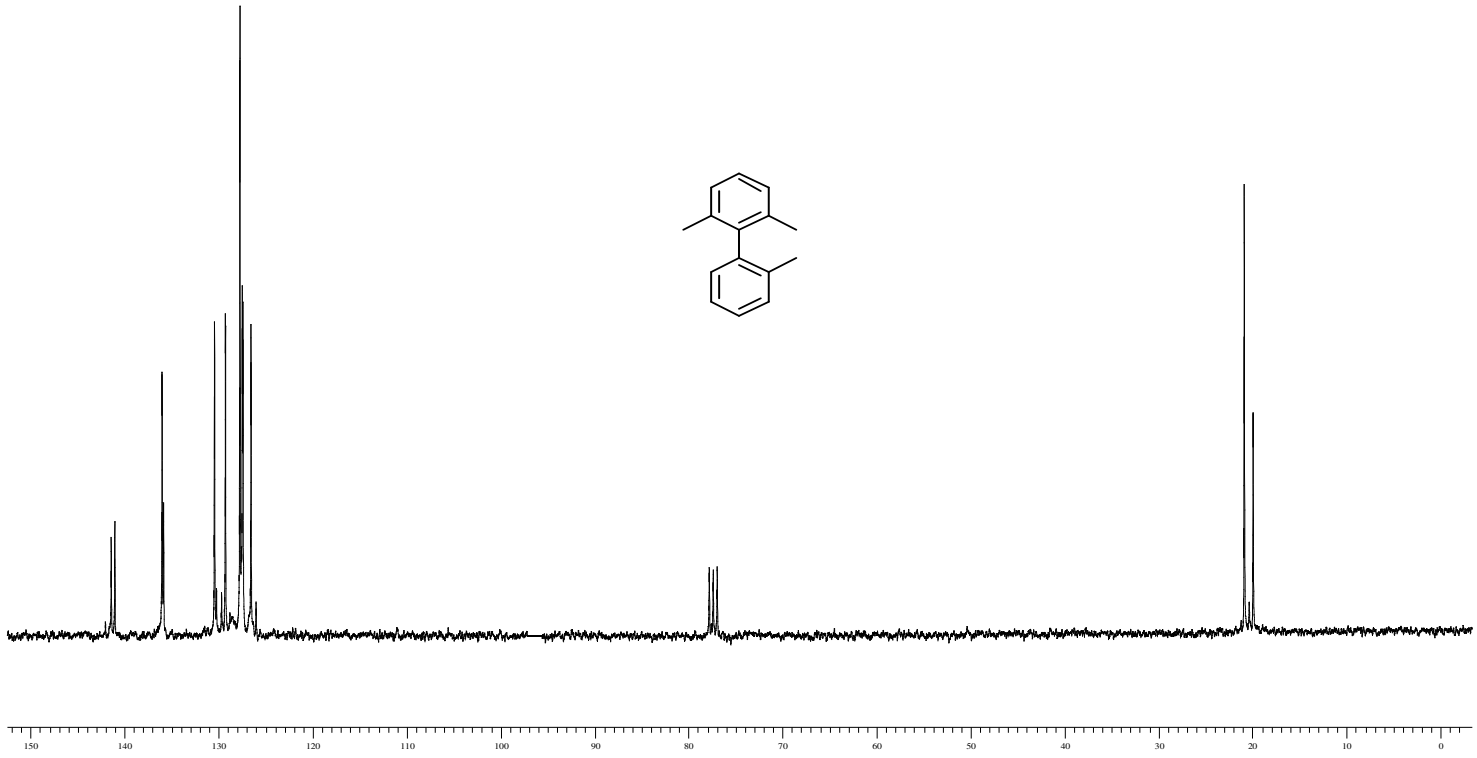
^{13}C NMR of 10b



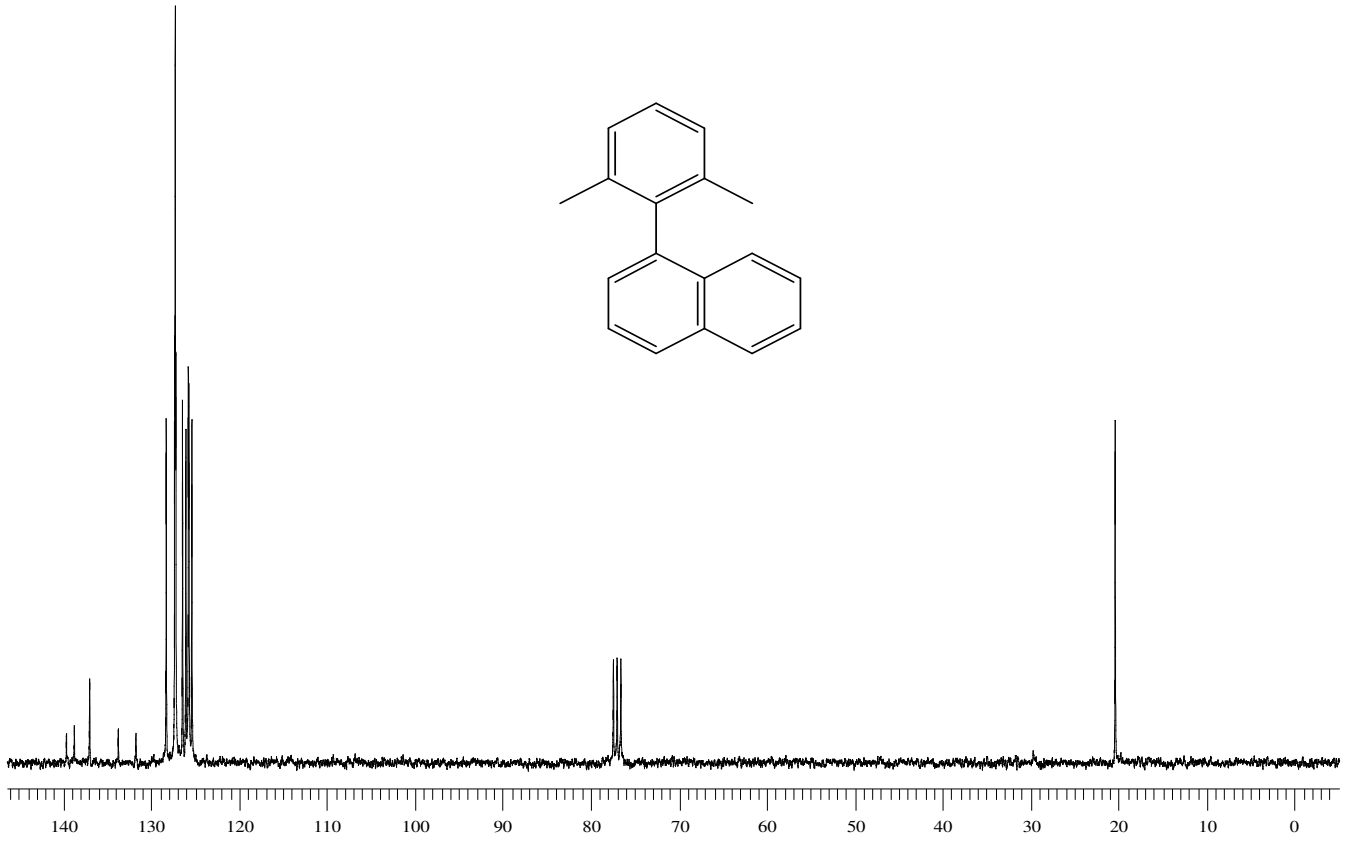
^{13}C NMR of 10c



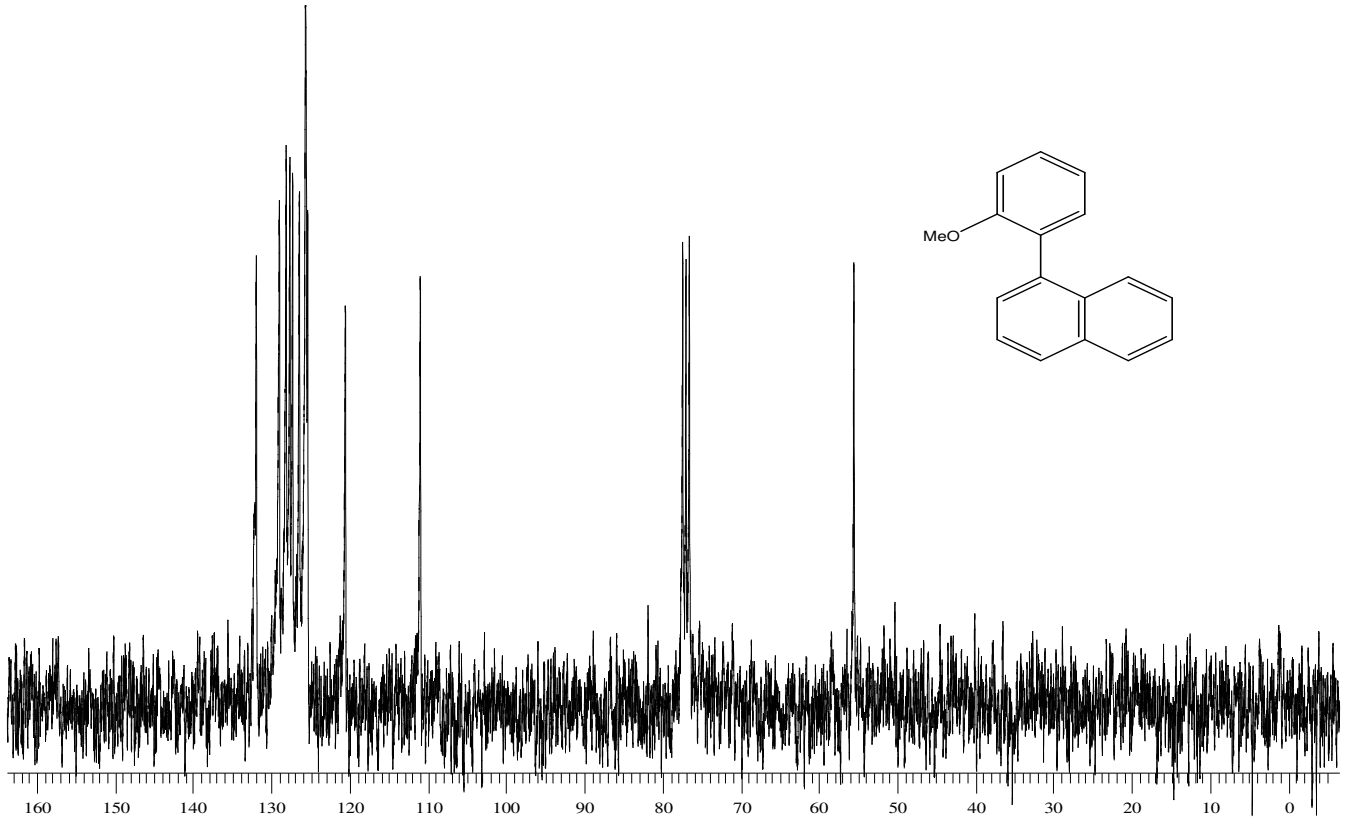
^{13}C NMR of 10d



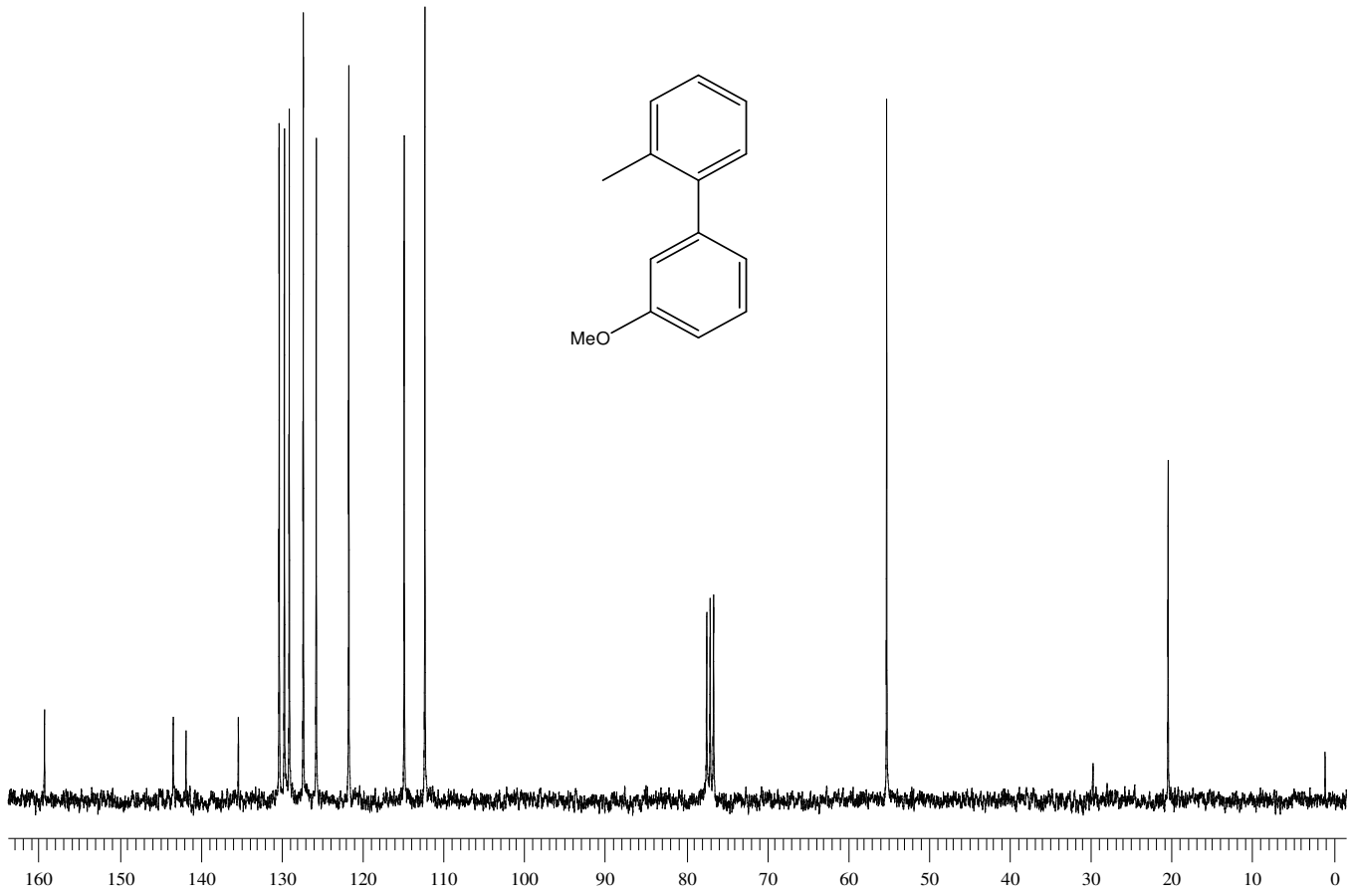
^{13}C NMR of 10e



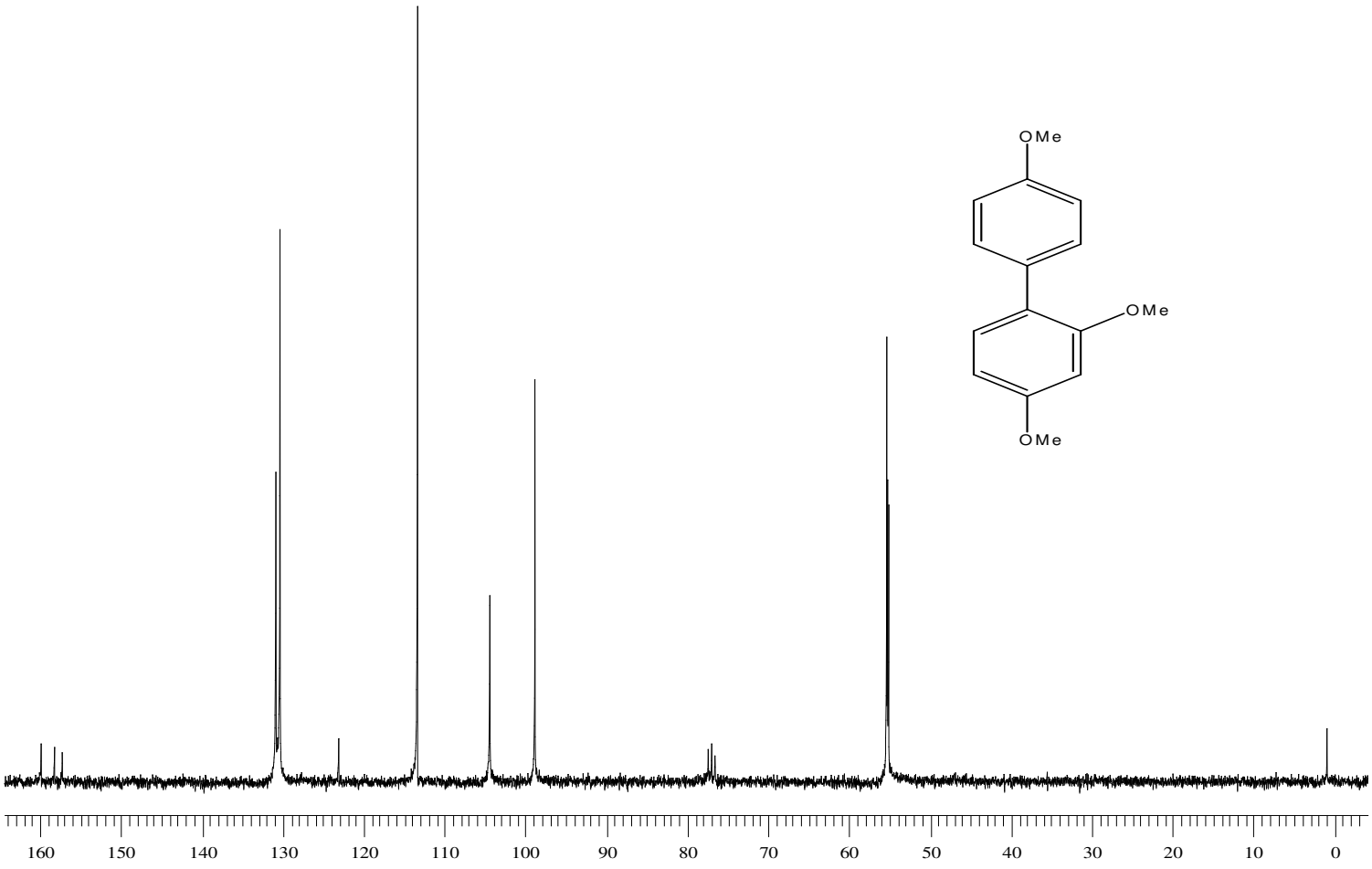
^{13}C NMR of 10f



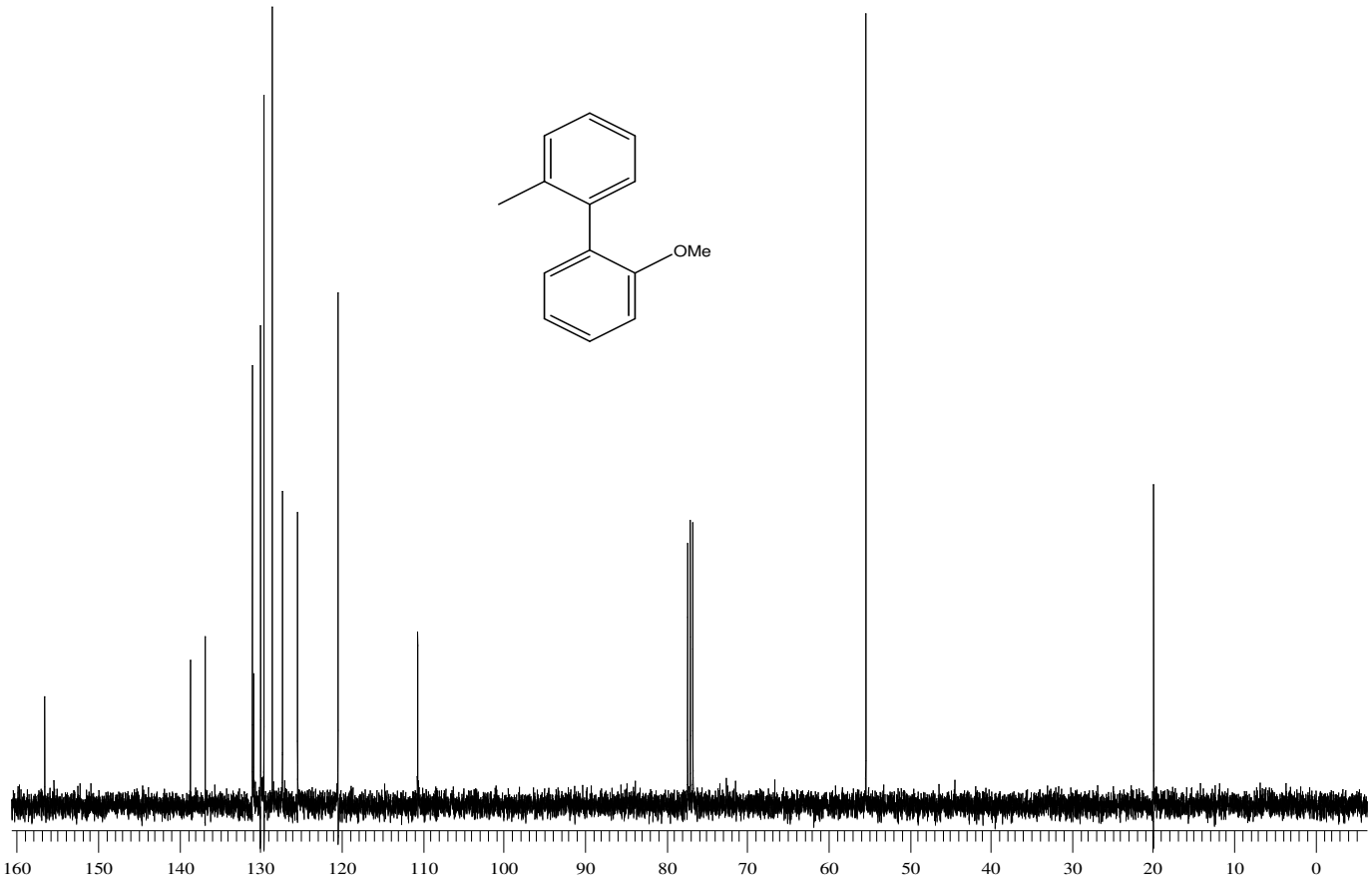
^{13}C NMR of 10g



^{13}C NMR of 10h



^{13}C NMR of 10i



^{13}C NMR of 10j

1. Membrane Permeability Study

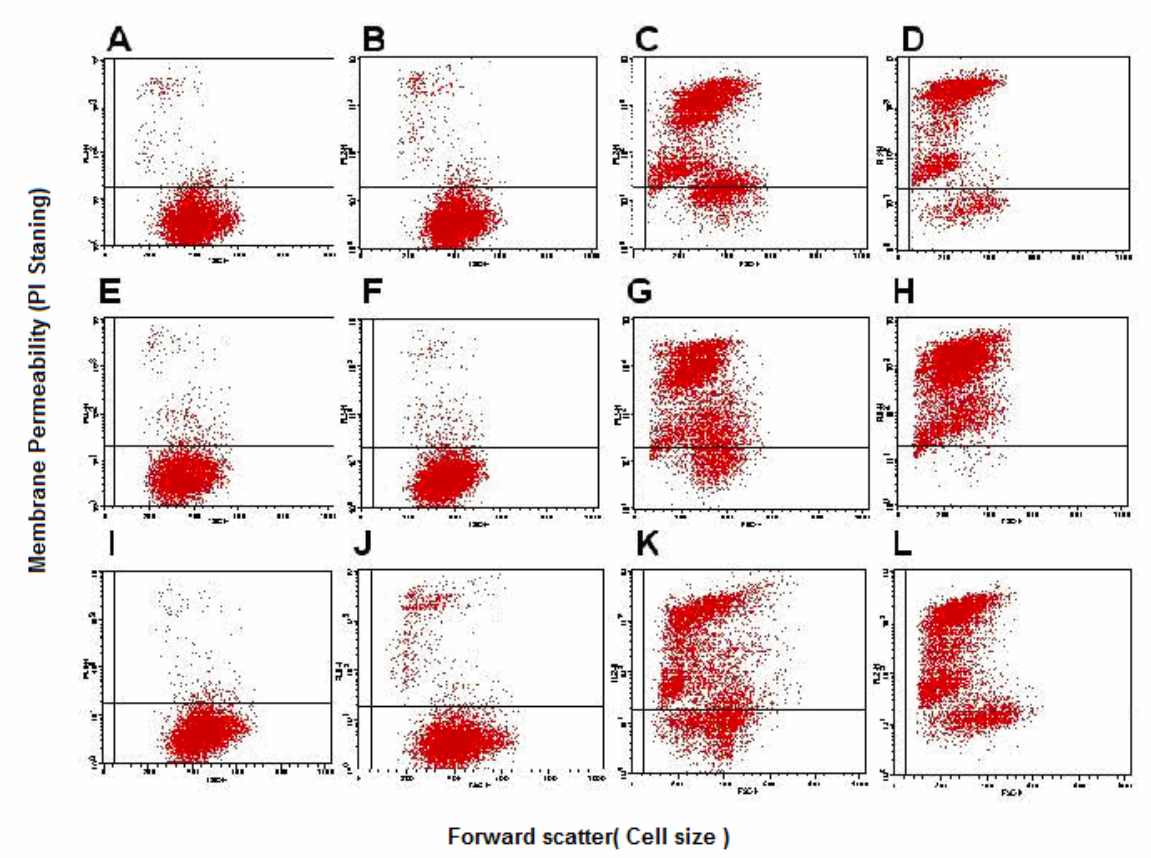


Figure legend

1. **A,E,I** Cells treated with **no compounds** (control)
2. **B,F,J** Cells treated with **DMSO** (Vehicle control)
3. **C,G,K** Cells treated with **compound 6**
4. **D,H,L** Cells treated with **compound 8**
5. **A,B,C,D** **HL60** cells
6. **E,F,G,H** **K562** cells
7. **I,J,K,L** **CCRF** cells

2. Apopotosis Study (Annexin V)

Apoptosis analysis of compound **6** and **8** in HL60 cells (*Human promyelocytic leukemia cells)*

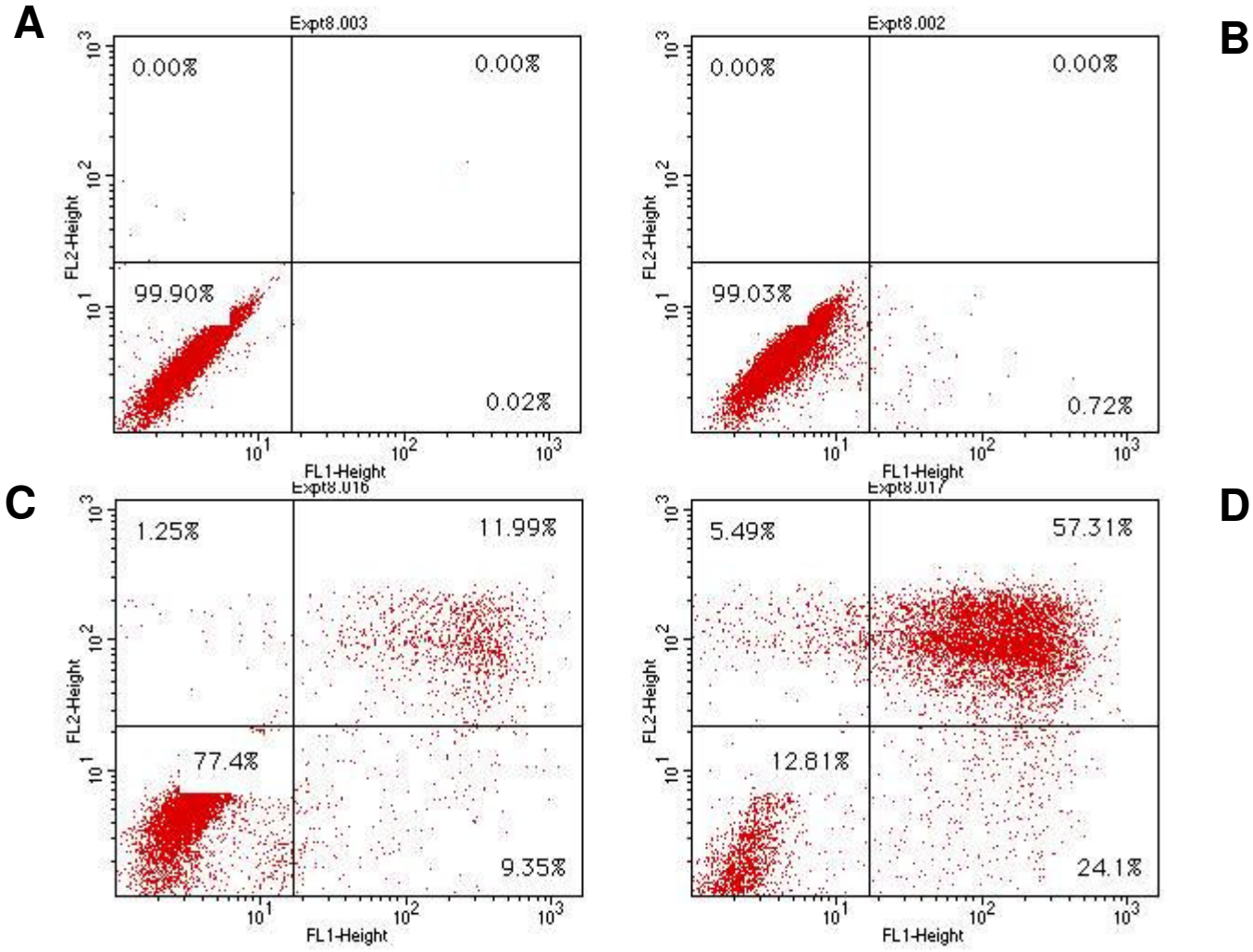


Figure legend
A Control cells (Cells with out any treatment)
B Solvent control (Cells treated with DMSO)
C Cells treated with Compound 8
D Cells treated with compound 6

Note: In each figure the lower right quadrant represents the percentage of apoptosis.

X-ray data write up for compound 9a

X-ray data of compound **9a** was collected at room temperature using a Bruker Smart Apex CCD diffractometer with graphite monochromated MoKα radiation (λ=0.71073Å) with ω-scan method.[1] Preliminary lattice parameters and orientation matrices were obtained from four sets of frames. Unit cell dimensions were determined from the setting angles of 8306 reflections for **9a**.

Integration and scaling of intensity data were accomplished using SAINT program.[2] The structures were solved by Direct Methods using SHELXS97[3] and refinement was carried out by full-matrix least-squares technique using SHELXL97.[3] Anisotropic displacement parameters were included for all non-hydrogen atoms. The hydrogen atoms attached to nitrogen atoms were located in a difference density map and refined isotropically. All other H atoms were positioned geometrically and treated as riding on their parent C atoms, with C-H distances of 0.93--0.97 Å, and with $U_{iso}(H) = 1.2U_{eq}(C)$ for other H atoms. The atoms F1/F2/F3 were disordered over two positions with site occupancies of 0.573(6) and 0.427(6). The disordered groups F1/F2/F3 and F11/F21/F31 were restrained to have similar atomic displacement parameters. The $CHCl_3$ shows a large displacement parameter and the anisotropic displacement parameters of atoms C55/CL5/ CL6/CL7/CL8 were restrained to be similar [SIMU instruction in SHELXL97 (Sheldrick, 2008)], and the direction of motion along the axis between these atoms were also restrained (DELU instruction in SHELXL97). CCDC 756102 contains the supplementary crystallographic data for **9a**.

References:

1. Cory, A. H.; Owen, T. C.; Barltrup, J. A.; Cory, J. G. (1991), Cancer Commun. 3, 207.

2. SMART & SAINT. Software Reference manuals. Versions 6.28a & 5.625, Bruker Analytical X-ray Systems Inc., Madison, Wisconsin, U.S.A., 2001.

3. Sheldrick, G. M. (2008). Acta Cryst. A64, 112--122.