Ru(II)-catalysed synthesis of (1*H*)-isothiochromenes by oxidative coupling of benzylthioethers with internal alkynes

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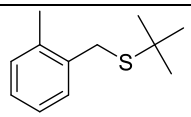
ESI1.- General methods

All reactions were carried out in Young's flasks, without protecting atmosphere. Solvents were used as received from commercial sources: they were not distilled nor subjected to additional purification. Flash column liquid chromatographies were performed on aluminium oxide 90 neutral (50-200 μm) or silica gel (70-230 μm). ^{1}H and ^{13}C NMR spectra were all recorded in $CDCl_3$ or acetone-d_6 solutions at 25 °C on Bruker AV500, AV400 or AV300 spectrometers (δ in ppm, *J* in Hz) at ^{1}H operating frequencies of 500.13, 400.13 or 300.13 MHz, respectively, and were referenced using the solvent signal as internal standard. The assignment of ^{1}H NMR peaks has been performed through standard 2D $^{1}H-COSY$ (2K points in t_2 using a spectral width of 10 ppm; 128 t_1 experiments were recorded and zero-filled to 1K; for each t_1 value four scans were signal-averaged using a recycle delay of 1 s) and selective 1D 1H-NOESY experiments. Typical mixing times in the case of selective 1D-NOESY experiments were in the range 800 ms - 1.2 s, as a function of the irradiated signal. These values of optimized mixing times were set equal to the longitudinal relaxation time T_1, determined using the inversion−recovery sequence. The ^{13}C NMR peaks were identified using standard $^{1}H-^{13}C$ edited-HSQC and $^{1}H-^{13}C$ HMBC 2D-experiments. In both cases 4K points in t_2 using spectral widths of 10 ppm (^{1}H) and 200 ppm (^{13}C) were used, with averaged values of the coupling constants $^{1}J_{CH}$ = 145 Hz and long-range $^{n}J_{CH}$ = 10 Hz. Typically, 256 t_1 experiments were recorded and zero-filled to 2K. For each t_1 value 8 (HSQC) or 16 (HMBC) scans were signal-averaged using a recycle delay of 2 s. HRMS and ESI (ESI+) mass spectra were recorded using an MicroToF Q, API-Q-ToF ESI with a mass range from 20 to 3000 m/z and mass resolution 15000 (FWHM). Some products could not be adequately characterized by high-resolution MS. In these cases, elemental analyses (CHNS) were provided instead, which were performed on a PerkinElmer 2400 Series II microanalyser. The synthesis of $[Ru(p\text{-cymene})Cl_2]_2$ has been carried out following published procedures.[1]

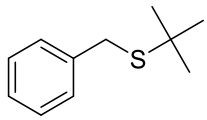
(1) M. A. Bennett, T.-N. Huang, T. W. Matheson, A. K. Smith, S. Ittel and W. Nickerson, *Inorg. Synth.* 1982, **21**, 74.

ESI2.- Preparation and characterization of starting materials. Procedure for the synthesis of *tert*-butyl thioethers 1a-1n

Starting thioethers (**1a-1n**) were synthetized as follows. To a mixture of the corresponding benzylbromide (2.5 mmol), aliquat (50 mg, 0.12 mmol) and NaOH (225 mg, 5.6 mmol) in toluene/water (2.5:2.5 mL), *tert*-butylthiol (2.5 mmol) was added dropwise. The resulting mixture was stirred for 1 h at 25 °C. After this time, the reaction was quenched by addition of HCl 1M (10 mL), then extracted with Et_2O (2×10mL). The organic phase was washed with brine (5×30 mL), dried over $MgSO_4$ and evaporated to dryness to yield the pure products as oils.

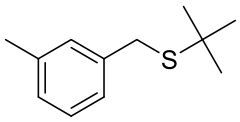
 **1a**	*tert*-butyl(2-methylbenzyl)sulfane **1a**

Dark yellow oil (427 mg, 88 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.16 (m, 1H, C_6H_4), 7.02 (m, 3H, C_6H_4), 3.63 (s, 2H, CH_2), 2.30 (s, 3H, CH_3), 1.29 (s, 9H, $C(CH_3)_3$). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ = 136.7 (C), 135.9 (C), 130.5 (CH), 129.9 (CH), 127.2 (CH), 126.1 (CH), 42.7 (C), 31.2 (CH_2), 30.8 (CH_3), 19.1 (CH_3). Anal. Calcd for $C_{12}H_{18}S$: C, 74.17; H, 9.34; S, 16.50. Found: C, 73.95; H, 9.05; S, 16.80.

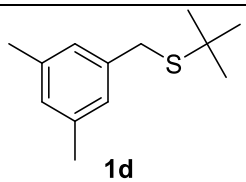
 **1b**	benzyl(*tert*-butyl)sulfane **1b**

Yellow oil (379 mg, 84 %).[2] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33 (m, 5H, C_6H_5), 3.81 (s, 2H, CH_2), 1.40 (s, 9H, $C(CH_3)_3$).

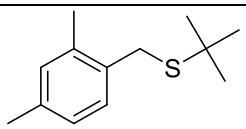
(2) K. N. Nguyen, F. Duus and T. X. T. Luu, *J. Sulfur Chem.* 2016, **37**, 349.

 **1c**	*tert*-butyl(3-methylbenzyl)sulfane **1c**

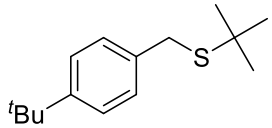
Yellow dark oil (413 mg, 85 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.20 (m, 3H, C_6H_4), 7.06 (d, 1H, C_6H_4, $^3J_{HH}$ = 7.5 Hz), 3.77 (s, 2H, CH_2), 2.36 (s, 3H, CH_3), 1.40 (s, 9H, $C(CH_3)_3$). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ = 138.3 (C), 138.1 (C), 129.7 (CH), 128.4 (CH), 127.5 (CH), 126.0 (CH), 42.8 (C), 33.4 (CH_2), 30.9 (CH_3), 21.3 (CH_3). Anal. Calcd for $C_{12}H_{18}S$: C, 74.17; H, 9.34; S, 16.50. Found: C, 74.18; H, 9.38; S, 16.24.

 **1d**	*tert*-butyl(3,5-dimethylbenzyl)sulfane **1d**

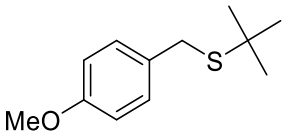
Yellow dark oil (429 mg, 82 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.99 (m, 2H, C_6H_3), 6.88 (m, 1H, C_6H_3), 3.73 (s, 2H, CH_2), 2.32 (s, 6H, CH_3), 1.40 (s, 9H, $C(CH_3)_3$). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 138.1 (C), 138.0 (C), 128.5 (CH), 126.8 (CH), 42.8 (C), 33.2 (CH_2), 30.9 (CH_3), 21.2 (CH_3). Anal. Calcd for $C_{13}H_{20}S$: C, 74.94; H, 9.68; S, 15.39. Found: C, 74.85; H, 9.56; S, 15.17.

 **1e**	*tert*-butyl(2,4-dimethylbenzyl)sulfane **1e**

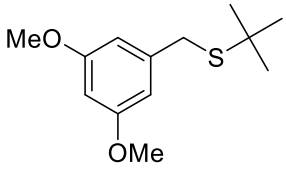
Yellow oil (427 mg, 82 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.06 (d, 1H, C_6H_3, $^3J_{HH}$ = 7.5 Hz), 6.85 (m, 2H, C_6H_3), 3.62 (s, 2H, CH_2), 2.28 (s, 3H, CH_3), 2.19 (s, 3H, CH_3), 1.30 (s, 9H, $C(CH_3)_3$). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 136.7 (C), 136.4 (C), 132.7 (C), 131.3 (CH), 129.8 (CH), 126.8 (CH), 42.6 (C), 30.9 (CH_2), 30.8 (CH_3), 21.0 (CH_3), 19.0 (CH_3). Anal. Calcd for $C_{13}H_{20}S$: C, 74.94; H, 9.68; S, 15.39. Found: C, 74.72; H, 9.78; S, 15.22.

 **1f**	*tert*-butyl(4-(*tert*-butyl)benzyl)sulfane **1f**

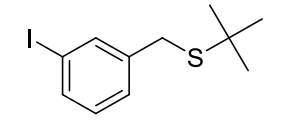
Yellow oil (556 mg, 94 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33 (m, 4H, C_6H_4), 3.80 (s, 2H, CH_2), 1.42 (s, 9H, $C(CH_3)_3$), 1.36 (s, 9H, $C(CH_3)_3$). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 149.7 (C), 135.4 (C), 128.6 (CH), 125.4 (CH), 42.8 (C), 34.5 (C), 33.0 (CH_2), 31.4 (CH_3), 30.9 (CH_3). Anal. Calcd for $C_{15}H_{24}S$: C, 76.21; H, 10.23; S, 13.56. Found: C, 76.40; H, 10.21; S, 13.71.

 **1g**	*tert*-butyl(4-methoxibenzyl)sulfane **1g**

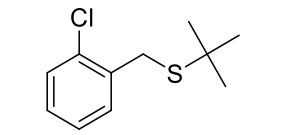
Yellow oil (478 mg, 91 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.28 (m, 2H, C_6H_4), 6.85 (m, 2H, C_6H_4), 3.80 (s, 3H, OCH_3), 3.75 (s, 2H, CH_2), 1.37 (s, 9H, $C(CH_3)_3$). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$): δ = 158.5 (C), 130.4 (C), 130.0 (CH), 113.9 (CH), 55.3 (CH_3), 42.7 (C), 32.7 (CH_2), 30.9 (CH_3). Anal. Calcd for $C_{12}H_{18}OS$: C, 68.52; H, 8.63; S, 15.24. Found: C, 68.32; H, 8.48; S, 15.51.

 **1h**	*tert*-butyl(3,5-dimethoxibenzyl)sulfane **1h**

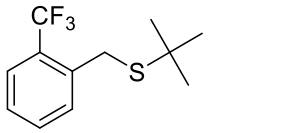
Red oil (337 mg, 56 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.54 (d, 2H, C_6H_3, $^{4}J_{HH}$ = 2.3 Hz), 6.35 (t, 1H, C_6H_3, $^{4}J_{HH}$ = 2.3 Hz), 3.80 (s, 6H, OCH_3), 3.73 (s, 2H, CH_2), 1.37 (s, 9H, $C(CH_3)_3$). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$): δ = 160.8 (C), 141.0 (C), 106.9 (CH), 99.0 (CH), 55.3 (CH_3), 42.9 (C), 33.7 CH_2), 30.9 (CH_3). Anal. Calcd for $C_{13}H_{20}O_2S$: C, 64.96; H, 8.39; S, 13.34. Found: C, 65.28; H, 8.50; S, 13.54.

 **1i**	*tert*-butyl(3-iodobenzyl)sulfane **1i**

Dark orange oil (360 mg, 47 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.72 (m, 1H, C_6H_4), 7.56 (d, 1H, C_6H_4, $^{3}J_{HH}$ = 7.9 Hz), 7.32 (m, 1H, C_6H_4), 7.03 (t, 1H, C_6H_4, $^{3}J_{HH}$ = 7.7 Hz), 3.69 (s, 2H, CH_2), 1.36 (s, 9H, $C(CH_3)_3$). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$): δ = 141.1 (C), 137.9 (CH), 135.8 (CH), 130.1 (CH), 128.3 (CH), 94.3 (C), 43.1 (C), 32.8 (CH_2), 30.9 (CH_3). Anal. Calcd for $C_{11}H_{15}IS$: C, 43.15; H, 4.94; S, 10.47. Found: C, 42.89; H, 5.23; S, 10.38.

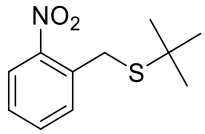
 **1j**	*tert*-butyl(2-chlorobenzyl)sulfane **1j**

Dark yellow oil (483 mg, 90 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43 (m, 1H, C_6H_4), 7.35 (m, 1H, C_6H_4), 7.19 (m, 2H, C_6H_4), 3.89 (s, 2H, CH_2), 1.40 (s, 9H, $C(CH_3)_3$). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$): δ = 136.2 (C), 133.8 (C), 131.0 (CH), 129.6 (CH), 128.2 (CH), 126.9 (CH), 43.1 (C), 30.8 (CH_3), 30.7 (CH_2). Anal. Calcd for $C_{11}H_{15}ClS$: C, 61.52; H, 7.04; S, 14.93. Found: C, 61.66; H, 7.20; S, 14.64.

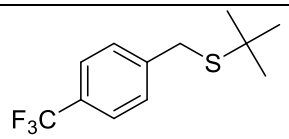
 **1k**	*tert*-butyl(2-(trifluoromethyl)benzyl)sulfane **1k**

Yellow oil (440 mg, 71 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.64 (m, 2H, C_6H_4), 7.49 (m, 1H, C_6H_4), 7.32 (m, 1H, C_6H_4), 3.93 (s, 2H, CH_2), 1.39 (s, 9H, $C(CH_3)_3$). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$): δ = 137.1 (C), 131.9 (CH), 131.8 (CH, q, $^{5}J_{CF}$ = 0.9 Hz), 126.8 (CH), 125.9 (CH, q, $^{4}J_{CF}$ = 5.9 Hz), 124.3

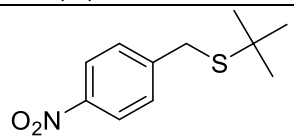
(C, q, CF_3, $^1J_{CF}$ = 273.3 Hz), 43.3 (C), 30.7 (CH_3), 29.4 (CH_2). One quaternary C atom was not observed, despite long accumulation times employed. Anal. Calcd for $C_{12}H_{15}F_3S$: C, 58.05; H, 6.09; S, 12.91. Found: C, 58.24; H, 6.18; S, 13.14.

 **1l**	*tert*-butyl(2-nitrobenzyl)sulfane **1l**

Dark yellow oil (451 mg, 80 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.91 (m, 1H, C_6H_4), 7.54 (m, 2H, C_6H_4), 7.38 (m, 1H, C_6H_4), 4.10 (s, 2H, CH_2), 1.35 (s, 9H, $C(CH_3)_3$). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 149.1 (C), 134.0 (C), 132.9 (CH), 132.2 (CH), 127.9 (CH), 125.0 (CH), 43.3 (C), 30.7 (CH_3), 30.1 (CH_2). Anal. Calcd for $C_{11}H_{15}NO_2S$: C, 58.64; H, 6.71; N, 6.22; S, 14.23. Found: C, 58.82; H, 6.64; N, 6.06; S, 14.04.

 **1m**	*tert*-butyl(4-(trifluoromethyl)benzyl)sulfane **1m**

Orange solid (472 mg, 76 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41 (d, 2H, $^3J_{HH}$ = 8.2 Hz, C_6H_4), 7.32 (d, 2H, $^3J_{HH}$ = 8.2 Hz, C_6H_4), 3.65 (s, 2H, CH_2), 1.22 (s, 9H, $C(CH_3)_3$). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 143.1 (C), 129.2 (CH), 128.7 (C, q), 125.3 (CH, m), 124.1 (C, q, CF_3, $^1J_{CF}$ = 271.8 Hz)), 43.1 (C), 33.0 (CH_2), 30.8 (CH_3). Anal. Calcd for $C_{12}H_{15}F_3S$: C, 58.05; H, 6.09; S, 12.91. Found: C, 57.99; H, 6.11; S, 12.88.

 **1n**	*tert*-butyl(4-nitrobenzyl)sulfane **1n**

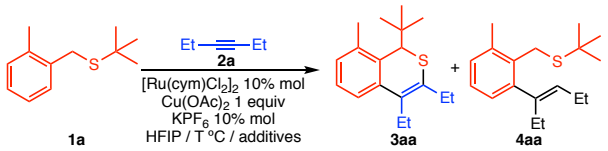
Orange solid (434 mg, 77 %). ^{1}H NMR (300 MHz, CDCl3): δ = 8.08 (d, 2H, $^3J_{HH}$ = 8.6 Hz, C_6H_4), 7.44 (d, 2H, $^3J_{HH}$ = 8.6 Hz, C_6H_4), 3.75 (s, 2H, CH_2), 1.28 (s, 9H, $C(CH_3)_3$). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 146.9 (C), 146.8 (C), 129.8 (CH), 123.6 (CH), 43.5 (C), 33.0 (CH_2), 30.9 (CH_3). Anal. Calcd for $C_{11}H_{15}NO_2S$: C, 58.64; H, 6.71; N, 6.22; S, 14.23. Found: C, 58.62; H, 6.57; N, 6.50; S, 13.98.

ESI3.- Optimization of the synthesis of 3aa

The optimization of this reaction started from the conditions reported for the hydroarylation of thioethers: 1 mmol thioether **1a**, 2 mmol akyne **2a**, 10% mol Ru catalyst, 10% mol KPF_6, 1 mmol $Cu(OAc)_2$, hexafluoroisopropanol (HFIP) as solvent, 100 °C, 24 h. Under these conditions, only the hydroarylation product **4aa** was obtained (Table S1, entry 1). When the reaction between **1a** and **2a** was performed in presence of 1 mmol of K_2CO_3 **4aa** was obtained in 36%, while **3aa** was formed in 57% yield (entry 2). Further optimization of the synthesis of **3aa** was attempted increasing the amount of base, aiming to suppress the presence of **4aa**. When 2 mmol of K_2CO_3 were used (entry 3), the amount of **3aa** increased up to 68%, but the amount of starting material increased as well, leaving a 22% of **1a**. The reaction is sensitive to the change of base, and when NaOAc, Na_2CO_3 and $CaCO_3$ were used (entries 4, 5 and 6, respectively) full conversions were observed, but only equimolecular mixtures of **3aa** and **4aa** were obtained. The use of Cs_2CO_3 (2 mmol) improved notably this distribution of products (entry 7), because a 79% of **3aa** was detected at the end of the reaction, while only a 10% of **4aa** was formed, and a similar amount of **1a** remained unreacted. The nature of the oxidant proved to be critical, because any change in this direction was deleterious for the reaction. The change of $Cu(OAc)_2$ to AgOAc (entry 8) drops the conversion to a marginal 31%, where only a 18% corresponds to **3aa**. Back to $Cu(OAc)_2$ as oxidant, the amount of **3aa** reached a 91% by increasing the amount of oxidant to 2 mmol (entry 9).

Despite the presence of high amounts of base and oxidant, a 10% of **4aa** still remains. The complete suppression of **4aa** was finally achieved by changing the reaction temperature (entries 10-12), suggesting that the problem is of kinetic nature. When the reaction was carried out at 60 °C using 2 mmol of base and 2 mmol of oxidant (entry 10) only **3aa** was detected, being isolated in an excellent yield. In addition, once the temperature was set to 60 °C, we realized that neither the additional base (entry 11) nor the excess of oxidant (entry 12) were necessary (isolated yield = 94%).

Table S1. Optimization conditions for synthesis of 3aa.[a]

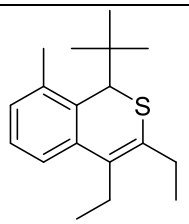


Entry	T °C	Additives	**ratio 1a/3aa/4aa** (%)
1	100	$Cu(OAc)_2$[b]	0/0/100
2	100	$Cu(OAc)_2$[b] + K_2CO_3[b]	7/57/36
3	100	$Cu(OAc)_2$[b] + K_2CO_3[c]	22/68/10
4	100	$Cu(OAc)_2$[b] + NaOAc[c]	0/46/54
5	100	$Cu(OAc)_2$[b] + Na_2CO_3[c]	0/55/45
6	100	$Cu(OAc)_2$[b] + $CaCO_3$[c]	0/45/55
7	100	$Cu(OAc)_2$[b] + Cs_2CO_3[c]	11/79/10
8	100	AgOAc[c] + Cs_2CO_3[c]	69/18/13
9	100	$Cu(OAc)_2$[c] + Cs_2CO_3[c]	0/91/9
10	60	$Cu(OAc)_2$[c] + Cs_2CO_3[c]	0/100/0
11	60	$Cu(OAc)_2$[c]	0/100/0
12	60	$Cu(OAc)_2$[b]	0/100/0

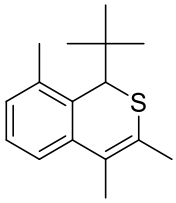
a) Conditions: **1a** (1 mmol), **2a** (2 mmol), [Ru] (0.1 mmol), additive, KPF_6 (0.1 mmol); conversion of **1a** to **3aa:4aa** determined by ^1H NMR. b) 1mmol. c) 2 mmol.

ESI4.- General procedure for the catalytic coupling of benzylthioethers 1 with alkynes 2

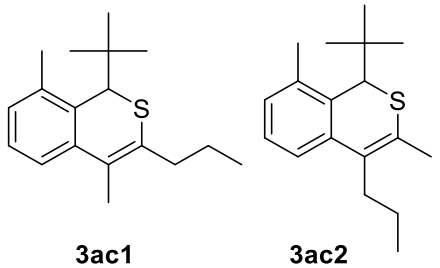
To a suspension of $[RuCl_2(p\text{-cymene})]_2$ (61.2 mg, 0.1 mmol), $K[PF_6]$ (18.7 mg, 0.1 mmol) and $Cu(OAc)_2$ (181.6 mg, 1 mmol) in HFIP (3 mL), the corresponding thioether **1** (1 mmol) and internal alkyne **2** (2 mmol) were added. The reaction mixture was stirred for 24 h at 60 °C. After the reaction time the solvent was evaporated to dryness, the residue was dissolved in CH_2Cl_2 and purified by flash column chromatography using neutral alumina as support and CH_2Cl_2 as eluent. The collected fraction was evaporated to dryness and the oily residue was further purified by column chromatography using silica gel as support and a mixture of Et_2O/hexane as eluent, affording isothiochromenes (**3**) as yellow oils, which solidifed on standing in most of the cases.

 **3aa**	1-(*tert*-butyl)-3,4-diethyl-8-methyl-1*H*-isothiochromene **3aa**

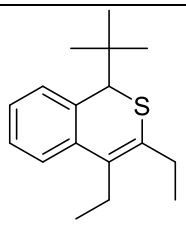
Yellow waxy solid (258 mg, 94 %). Purified by column chromatography on silica gel, eluting with hexane/Et_2O 99:1. ^{1}H NMR (300 MHz, acetone-d_6): δ = 7.35 (m, 1 H, C_6H_3), 7.17 (m, 2 H, C_6H_3), 3.94 (s, 1H, CH), 2.68 (m, 3H, CH_2CH$_3$), 2.42 (s, 3H, CH$_3$), 2.17 (m, 1H, CH_2CH$_3$), 1.26 (t, 3H, CH$_2$CH_3, $^3J_{HH}$ = 7.5 Hz), 1.16 (t, 3H, CH$_2$CH_3, $^3J_{HH}$ = 7.5 Hz), 0.93 (s, 9H, C-(CH$_3$)$_3$). ^{13}C{^{1}H} NMR (75 MHz, acetone-d^6): δ = 135.6 (C), 135.1 (C), 131.7 (C), 130.5 (C), 129.3 (CH), 128.1 (C), 126.0 (CH), 121.5 (CH), 46.4 (CH), 39.4 (C), 27.1 (CH$_2$), 26.8 (CH$_3$), 21.4 (CH$_2$), 20.5 (CH$_3$), 13.5 (2 overlapped CH$_3$). HRMS (ESI-TOF) *m/z:* $[M+Na+O]^+$ calcd for $C_{18}H_{26}NaOS$ 313.1597, obtained 313.1588.

 **3ab**	1-(*tert*-butyl)-3,4,8-trimethyl-1*H*-isothiochromene **3ab**

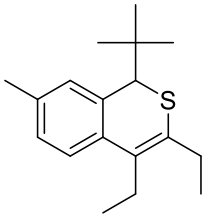
Yellow waxy solid (96 mg, 39 %). Purified by column chromatography on silica gel, eluting with hexane/Et_2O 99:1. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.16 (m, 1H, C_6H_3), 7.07 (m, 2H, C_6H_3), 3.71 (s, 1H, CH), 2.32 (s, 3H, CH$_3$), 2.03 (q, 3H, CH$_3$, $^5J_{HH}$ = 0.9 Hz), 1.96 (q, 3H, CH$_3$, $^5J_{HH}$ = 0.9 Hz), 0.82 (s, 9H, (C(CH$_3$)$_3$).^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 136.9 (C), 134.8 (C), 129.4 (CH), 128.1 (C), 126.0 (CH), 125.9 (C), 125.2 (C), 121.5 (CH), 47.5 (CH), 39.4 (C), 27.3 (CH$_3$), 21.2 (CH$_3$), 20.1 (CH$_3$), 15.6 (CH$_3$). HRMS (ESI-TOF) *m/z:* $[M+Na+O]^+$ calcd for $C_{16}H_{22}NaOS$ 285.1284, obtained 285.1275.

 **3ac1** **3ac2**	1-(*tert*-butyl)-4,8-dimethyl-3-propyl-1*H*-isothiochromene **3ac1** 1-(*tert*-butyl)-3,8-dimethyl-4-propyl-1*H*-isothiochromene **3ac2**

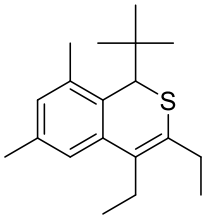
Compounds **3ac1** y **3ac2** were obtained as a mixture and were not separated. Yellow oil (225 mg, 82 % total, 30 % and 52 % respectively). The mixture was purified from other components by column chromatography on silica gel, eluting with hexane/Et_2O 99:1. Major isomer **3ac1**. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.29 (m, 1H, C_6H_3), 7.16 (m, 2H, C_6H_3), 3.82 (s, 1H, CH), 2.57 (m, 2H, C*H*$_2$CH$_2$CH$_3$), 2.43 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 1.58 (m, 2H, CH_2C*H*$_2$CH$_3$), 1.06 (t, 3H, CH_2CH_2C*H*$_3$, $^3J_{HH}$ = 7.3 Hz), 0.93 (s, 9H, C(CH_3)$_3$). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ = 135.6 (C), 135.1 (C), 130.5 (C), 129.4 (CH), 128.1 (C), 126.0 (CH), 125.6 (C), 121.6 (CH), 47.2 (CH), 39.8 (C), 31.9 (CH_2), 27.3 (CH_3), 22.4 (CH_2), 21.3 (CH_3), 20.1 (CH_3), 14.7 (CH_3). Minor isomer **3ac2**. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.29 (m, 1H, C_6H_3), 7.16 (m, 2H, C_6H_3), 3.86 (s, 1H, CH), 2.54 (m, 1H, C*H*$_2$CH$_2$CH$_3$), 2.43 (s, 3H, CH_3), 2.20 (m, 1H, C*H*$_2$CH$_2$CH$_3$), 2.15 (s, 3H, CH_3), 1.71 (m, 2H, CH_2C*H*$_2$CH$_3$), 1.04 (t, 3H, CH_2CH_2C*H*$_3$, $^3J_{HH}$ = 7.3 Hz), 0.93 (s, 9H, C(CH_3)$_3$). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ = 137.1 (C), 134.7 (C), 130.5 (C), 129.5 (CH), 127.9 (C), 126.0 (CH), 125.4 (C), 121.6 (CH), 47.1 (CH), 39.3 (C), 36.6 (CH_2), 27.4 (CH_3), 22.3 (CH_2), 21.2 (CH_3), 15.5 (CH_3), 14.4 (CH_3). HRMS (ESI-TOF) *m/z:* $[M+Na+O]^+$ calcd for $C_{18}H_{26}NaOS$ 313.1597, obtained 313.1591.

 **3ba**	1-(*tert*-butyl)-3,4-diethyl-1*H*-isothiochromene **3ba**

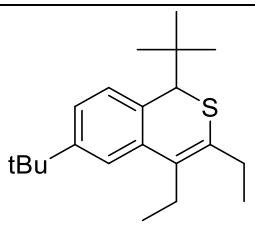
Pale yellow solid (216 mg, 83 %). Purified by column chromatography on silica gel, eluting with hexane/Et_2O 99:1. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.34 (dd, 1H, C_6H_4, $^3J_{HH}$ = 7.9, $^4J_{HH}$ = 1.4 Hz), 7.16 (m, 1H, C_6H_4), 7.11 (td, 1H, C_6H_4, $^3J_{HH}$ = 7.4, $^4J_{HH}$ = 1.4 Hz), 6.99 (dd, 1H, C_6H_4, $^3J_{HH}$ = 7.5, $^4J_{HH}$ = 1.7 Hz), 3.43 (s, 1H, CH), 2.59 (m, 3H, C*H*$_2$CH$_3$), 2.08 (m, 1H, C*H*$_2$CH$_3$), 1.19 (t, 3H, CH_2C*H*$_3$, $^3J_{HH}$ = 7.5 Hz), 1.05 (t, 3H, CH_2C*H*$_3$, $^3J_{HH}$ = 7.5 Hz), 0.83 (s, 9H, C(CH_3)$_3$). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 135.6 (C), 135.3 (C), 133.3 (C), 130.5 (CH), 129.6 (C), 126.9 (CH), 125.8 (CH), 123.7 (CH), 53.3 (CH), 38.4 (C), 27.7 (CH_2), 27.1 (CH_3), 21.5 (CH_2), 14.1 (CH_3), 14.0(CH_3). HRMS (ESI-TOF) *m/z:* $[M+H+O]^+$ calcd for $C_{17}H_{25}OS$ 277.1621, obtained 277.1612.

 **3ca**	1-(*tert*-butyl)-3,4-diethyl-7-methyl-1*H*-isothiochromene **3ca**

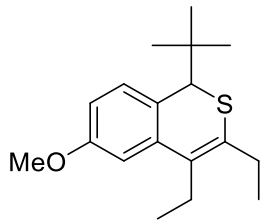
Yellow solid (255 mg, 93 %). Purified by column chromatography on silica gel, eluting with hexane/Et_2O 99:1. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.22 (d, 1H, C_6H_3, $^3J_{HH}$ = 8.1 Hz), 6.99 (m, 1H, C_6H_3), 6.79 (m, 1H, C_6H_3), 3.37 (s, 1H, CH), 2.56 (m, 3H, C*H*$_2$CH$_3$), 2.25 (s, 3H, CH_3), 2.07 (dq, 1H, C*H*$_2$CH$_3$, $^2J_{HH}$ = 14.9, $^3J_{HH}$ = 7.6 Hz), 1.17 (t, 3H, CH_2C*H*$_3$, $^3J_{HH}$ = 7.5 Hz), 1.03 (t, 3H, CH_2C*H*$_3$, $^3J_{HH}$ = 7.5 Hz), 0.83 (s, 9H, $C(CH_3)_3$). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 135.4 (C), 132.7 (C), 131.1 (CH), 131.0 (C), 129.7 (C), 129.6 (C), 127.7 (CH), 123.7 (CH), 53.4 (CH), 38.4 (C), 27.6 (CH_2), 27.2 (CH_3), 21.5 (CH_2), 21.0 (CH_3), 14.1 (CH_3), 14.0 (CH_3). HRMS (ESI-TOF) *m/z:* $[M+Na+O]^+$ calcd for $C_{18}H_{26}NaOS$ 313.1597, obtained 313.1590.

 **3ea**	1-(*tert*-butyl)-3,4-diethyl-6,8-dimethyl-1*H*-isothiochromene **3ea**

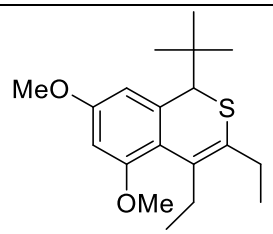
Yellow waxy solid (57 mg, 89 %). Purified by column chromatography on silica gel, eluting with hexane/Et_2O 99:1. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.02 (m, 1H, C_6H_2), 6.88 (m, 1H, C_6H_2), 3.72 (s, 1H, CH), 2.57 (m, 3H, C*H*$_2$CH$_3$), 2.28 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 2.10 (dq, 1H, C*H*$_2$CH$_3$, $^2J_{HH}$ = 14.0, $^3J_{HH}$ = 7.5 Hz), 1.17 (t, 3H, CH_2C*H*$_3$, $^3J_{HH}$ = 7.5 Hz), 1.09 (t, 3H, CH_2C*H*$_3$, $^3J_{HH}$ = 7.5 Hz), 0.83 (s, 9H, $C(CH_3)_3$). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 135.5 (C), 135.2 (C), 135.0 (C), 131.8 (C), 130.6 (C), 130.3 (CH), 125.5 (C), 122.4 (CH), 46.7 (CH), 39.7 (C), 27.4 (CH_3), 27.2 (CH_2), 21.8 (CH_2), 21.3 (CH_3), 21.2 (CH_3), 14.1 (CH_3), 14.0 (CH_3). HRMS (ESI-TOF) *m/z:* $[M+Na+O]^+$ calcd for $C_{19}H_{28}NaOS$ 327.1753, obtained 327.1744.

 **3fa**	1,6-di-*tert*-butyl-3,4-diethyl-1*H*-isothiochromene **3fa**

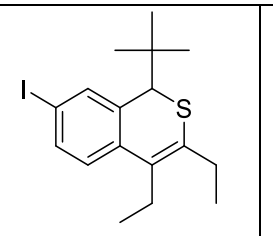
Yellow waxy solid (263 mg, 83 %). Purified by column chromatography on silica gel, eluting with hexane/Et_2O 99:1. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.34 (d, 1H, C_6H_3, $^4J_{HH}$ = 2.0 Hz), 7.12 (dd, 1H, C_6H_3, $^3J_{HH}$ = 8.0, $^4J_{HH}$ = 1.9 Hz), 6.90 (d, 1H, C_6H_3, $^3J_{HH}$ = 8.0 Hz), 3.40 (s, 1H, CH), 2.58 (m, 3H, C*H*$_2$CH$_3$), 2.08 (dq, 1H, C*H*$_2$CH$_3$, $^2J_{HH}$ = 15.0, $^3J_{HH}$ = 7.6 Hz), 1.24 (s, 9H, $C(CH_3)_3$), 1.19 (t, 3H, CH_2C*H*$_3$, $^3J_{HH}$ = 7.5 Hz), 1.06 (t, 3H, CH_2C*H*$_3$, $^3J_{HH}$ = 7.5 Hz), 0.83 (s, 9H, $C(CH_3)_3$). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 149.4 (C), 134.6 (C), 131.9 (C), 130.1 (CH), 130.0 (C), 126.9 (C), 122.9 (CH), 120.7 (CH), 53.1 (CH), 38.5 (C), 34.6 (C) 31.4 (CH_3), 27.7 (CH_2), 27.2 (CH_3), 21.6 (CH_2), 14.1 (CH_3), 14.0 (CH_3). HRMS (ESI-TOF) *m/z:* $[M+Na+O]^+$ calcd for $C_{21}H_{32}NaOS$ 355.2066, obtained 355.2057.

 **3ga**	1-(*tert*-butyl)-3,4-diethyl-6-methoxi-1*H*-isothiochromene **3ga**

Yellow oil (279 mg, 96 %). Purified by column chromatography on silica gel, eluting with hexane/Et_2O 99:1. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.90 (d, 1H, C_6H_3, $^3J_{HH}$ = 8.4 Hz), 6.87 (d, 1H, C_6H_3, $^4J_{HH}$ = 2.6 Hz), 6.67 (dd, 1H, C_6H_3, $^3J_{HH}$ = 8.4, $^4J_{HH}$ = 2.6 Hz), 3.74 (s, 3H, OCH_3), 3.39 (s, 1H, CH), 2.55 (m, 3H, C*H*$_2$CH$_3$), 2.08 (dq, 1H, C*H*$_2$CH$_3$, $^2J_{HH}$ = 15.1, $^3J_{HH}$ = 7.6 Hz), 1.18 (t, 3H, CH$_2$C*H*$_3$, $^3J_{HH}$ = 7.6 Hz), 1.05 (t, 3H, CH$_2$C*H*$_3$, $^3J_{HH}$ = 7.6 Hz), 0.81 (s, 9H, $C(CH_3)_3$). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 158.6 (C), 136.5 (C), 133.1 (C), 131.3 (CH), 129.4 (C), 122.5 (C), 110.7 (CH), 109.8 (CH), 55.3 (CH_3), 52.9 (CH), 38.5 (C), 27.8 (CH_2), 27.1 (CH_3) 21.6 (CH_2), 14.1 (CH_3), 14.0 (CH_3). HRMS (ESI-TOF) *m/z:* $[M+Na+O]^+$ calcd for $C_{18}H_{26}NaO_2S$ 329.1546, obtained 329.1538.

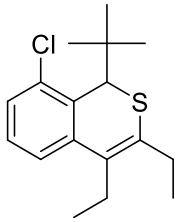
 **3ha**	1-(*tert*-butyl)-3,4-diethyl-5,7-dimethoxi-1*H*-isothiochromene **3ha**

Yellow oil (160 mg, 50 %). Purified by column chromatography on silica gel, eluting with hexane/Et_2O 99:1. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.33 (d, 1H, C_6H_2, $^4J_{HH}$ = 2.5 Hz), 6.19 (d, 1H, C_6H_2, $^4J_{HH}$ = 2.5 Hz), 3.73 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 3.28 (s, 1H, CH), 2.74 (dq, 1H, C*H*$_2$CH$_3$, $^2J_{HH}$ = 14.7, $^3J_{HH}$ = 7.4 Hz), 2.48 (m, 2H, C*H*$_2$CH$_3$), 2.23 (dq, 1H, C*H*$_2$CH$_3$, $^2J_{HH}$ = 14.9, $^3J_{HH}$ = 7.6 Hz), 1.15 (t, 3H, CH$_2$C*H*$_3$, $^3J_{HH}$ = 7.5 Hz), 0.96 (t, 3H, CH$_2$C*H*$_3$, $^3J_{HH}$ = 7.3 Hz), 0.90 (s, 9H, $C(CH_3)_3$). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 158.0 (C), 157.6 (C), 136.1 (C), 131.2 (C), 130.5 (C), 119.9 (C), 107.2 (CH), 97.8 (CH), 55.3 (CH_3), 55.3 (CH_3), 54.8 (CH), 37.8 (C) 28.1 (CH_3), 27.6 (CH_2), 24.1 (CH_2), 14.0 (CH_3), 13.4 (CH_3). HRMS (ESI-TOF) *m/z:* $[M+Na+O]^+$ calcd for $C_{19}H_{28}NaO_3S$ 359.1651, obtained 359.1652.

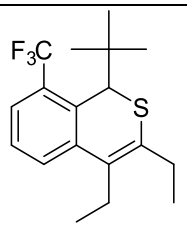
 **3ia**	1-(*tert*-butyl)-3,4-diethyl-7-iodo-1*H*-isothiochromene **3ia**

Yellow oil (205 mg, 53 %). Purified by column chromatography on silica gel, eluting with hexane/Et_2O 99:1. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.49 (dd, 1H, C_6H_3, $^3J_{HH}$ = 8.4, $^4J_{HH}$ = 2.0 Hz), 7.32 (dd, 1H, C_6H_3, $^4J_{HH}$ = 2.0, $^5J_{HH}$ = 0.5 Hz), 7.05 (d, 1H, C_6H_3, $^3J_{HH}$ = 8.5 Hz), 3.34 (s, 1H, CH), 2.54 (m, 3H, C*H*$_2$CH$_3$), 2.07 (dq, 1H, C*H*$_2$CH$_3$, $^2J_{HH}$ = 14.0, $^3J_{HH}$ = 7.6 Hz), 1.17 (t, 3H, CH$_2$C*H*$_3$, $^3J_{HH}$ = 7.5 Hz), 1.01 (t, 3H, CH$_2$C*H*$_3$, $^3J_{HH}$ = 7.5 Hz), 0.82 (s, 9H, $C(CH_3)_3$). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ

= 138.8 (CH), 135.8 (CH), 135.0 (C), 133.5 (C), 131.7 (C), 129.1 (C), 125.5 (CH), 90.2 (C), 52.7 (CH), 38.5 (C), 27.7 (CH_2), 27.0 (CH_3), 21.3 (CH_2), 14.0 (CH_3), 13.8 (CH_3). HRMS (ESI-TOF) *m/z:* $[M+Na+O]^+$ calcd for $C_{17}H_{23}INaOS$ 425.0407, obtained 425.0402.

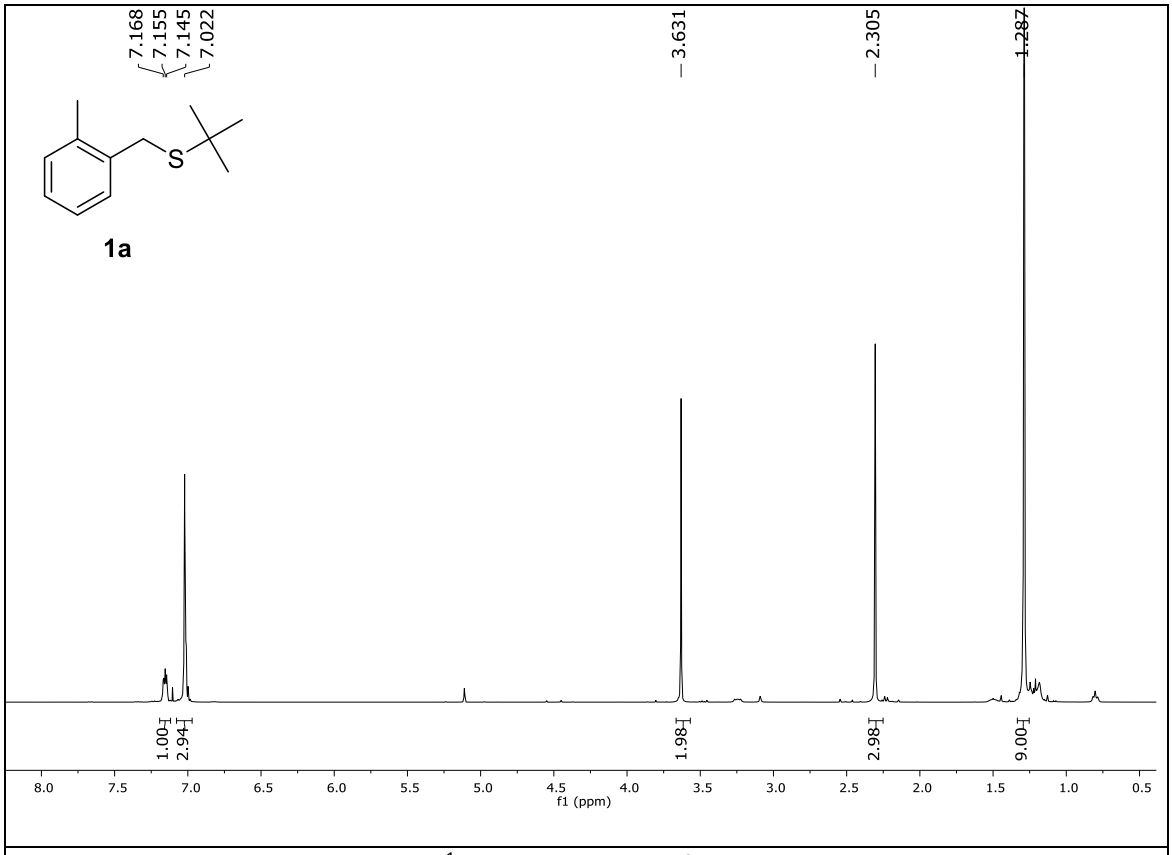
 **3ja**	1-(*tert*-butyl)-8-chloro-3,4-diethyl-1*H*-isothiochromene **3ja**

Yellow waxy solid (153 mg, 52 %). Purified by column chromatography on silica gel, eluting with hexane/Et_2O 99:1. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.35 (m, 2H, C_6H_3), 7.19 (t, 1H, C_6H_3, $^3J_{HH}$ = 7.9 Hz), 4.28 (s, 1H, CH), 2.66 (m, 3H, C*H*$_2$CH$_3$), 2.21 (dt, 1H, C*H*$_2$CH$_3$, $^2J_{HH}$ = 14.1, $^3J_{HH}$ = 7.6 Hz), 1.29 (t, 3H, CH$_2$C*H*$_3$, $^3J_{HH}$ = 7.5 Hz), 1.17 (t, 3H, CH$_2$C*H*$_3$, $^3J_{HH}$ = 7.5 Hz), 0.96 (s, 9H, C(CH$_3$)$_3$). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 137.6 (C), 134.4 (C), 134.2 (C), 133.7 (C), 129.9 (C), 127.9 (CH), 127.1 (CH), 122.3 (CH), 46.9 (CH), 39.8 (C), 27.5 (CH_2), 27.1 (CH_3), 21.7 (CH_2), 14.0 (CH_3), 13.9 (CH_3). HRMS (ESI-TOF) *m/z:* $[M+Na+O]^+$ calcd for $C_{17}H_{23}ClNaOS$ 333.1050, obtained 333.1051.

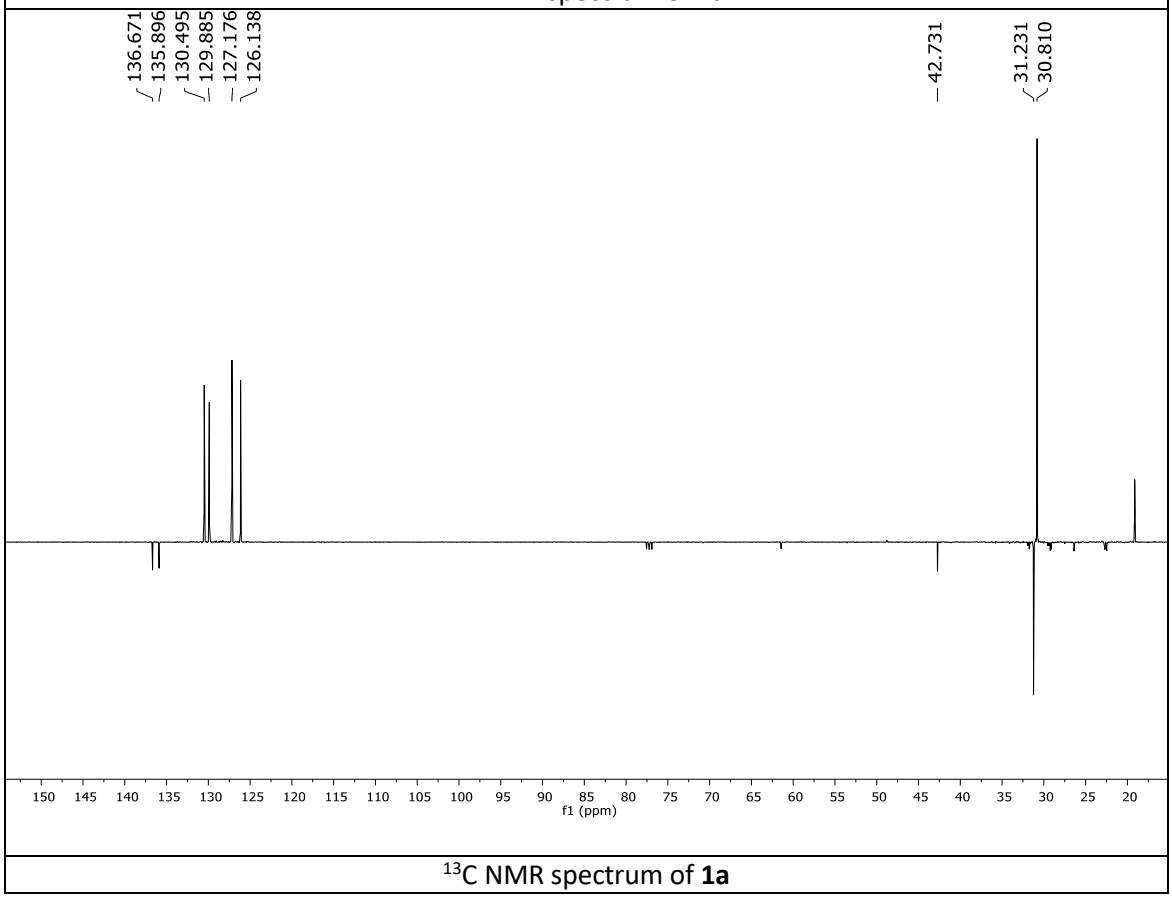
 **3ka**	1-(*tert*-butyl)-3,4-diethyl-8-(trifluoromethyl)-1*H*-isothiochromene **3ka**

Yellow waxy solid (122 mg, 37 %). Purified by column chromatography on silica gel, eluting with hexane/Et_2O 99:1. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.52 (m, 2H, C_6H_3), 7.26 (m, 1H, C_6H_3), 3.93 (s, 1H, CH), 2.56 (m, 3H, C*H*$_2$CH$_3$), 2.15 (m, 1H, C*H*$_2$CH$_3$), 1.19 (t, 3H, CH$_2$C*H*$_3$, $^3J_{HH}$ = 7.5 Hz), 1.11 (t, 3H, CH$_2$C*H*$_3$, $^3J_{HH}$ = 7.5 Hz), 0.79 (s, 9H, C(CH$_3$)$_3$). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 136.7 (C), 135.4 (C), 134.9 (C), 130.4 (C), 126.9 (C), 126.7 (CH), 126.2 (CH), 125.0 (CH, q), 124.8 (C, q, CF_3, $^1J_{CF}$ = 271 Hz), 46.0 (CH), 38.8 (C), 27.8 (CH_3), 27.2 (CH_2), 21.8 (CH_2), 14.0 (CH_3), 13.8 (CH_3). HRMS (ESI-TOF) *m/z:* $[M+Na+O]^+$ calcd for $C_{18}H_{23}F_3NaOS$ 367.1314, obtained 367.1318.

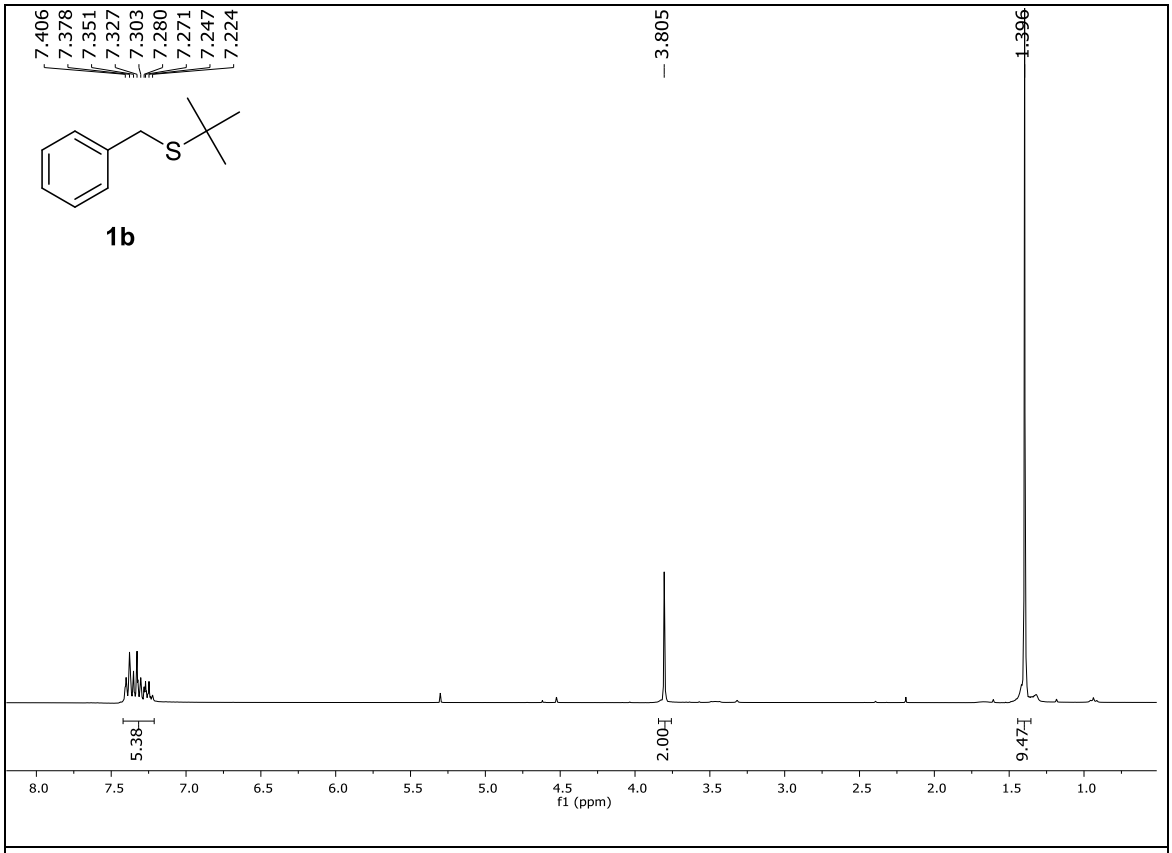
ESI5.- ^{1}H and ^{13}C NMR spectra of all prepared compounds



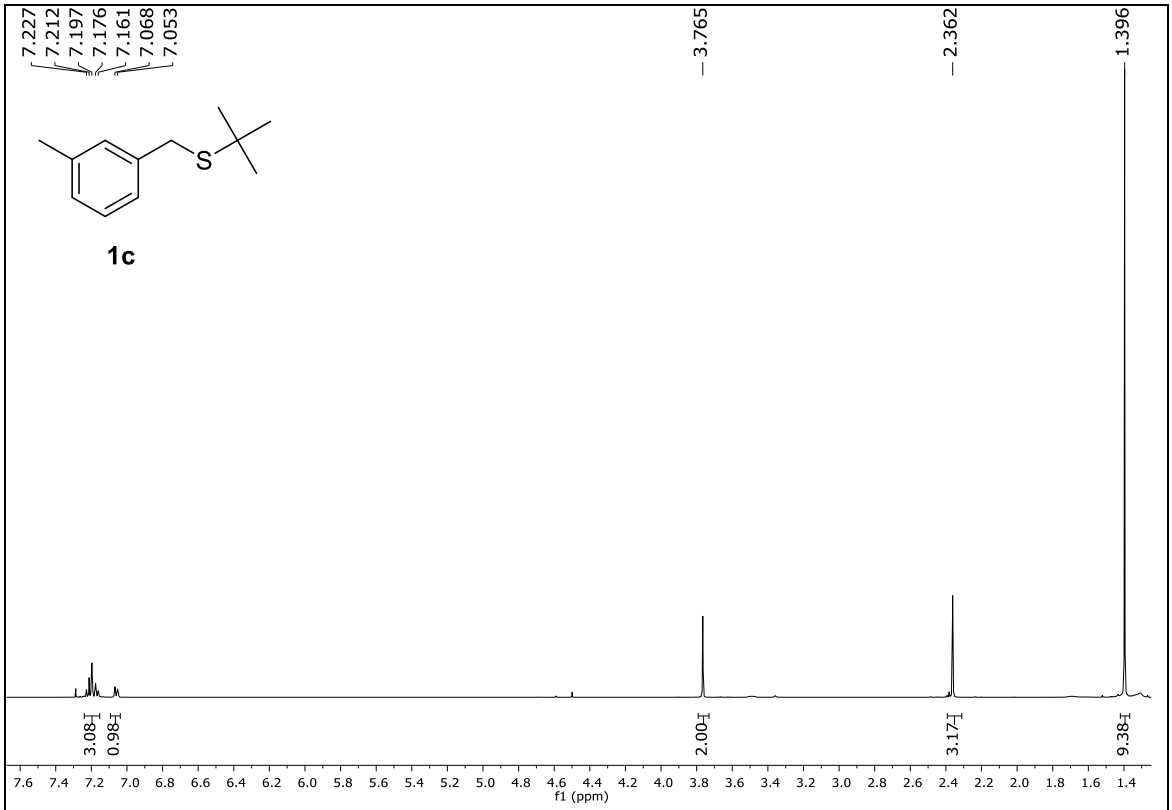
^{1}H NMR spectrum of **1a**



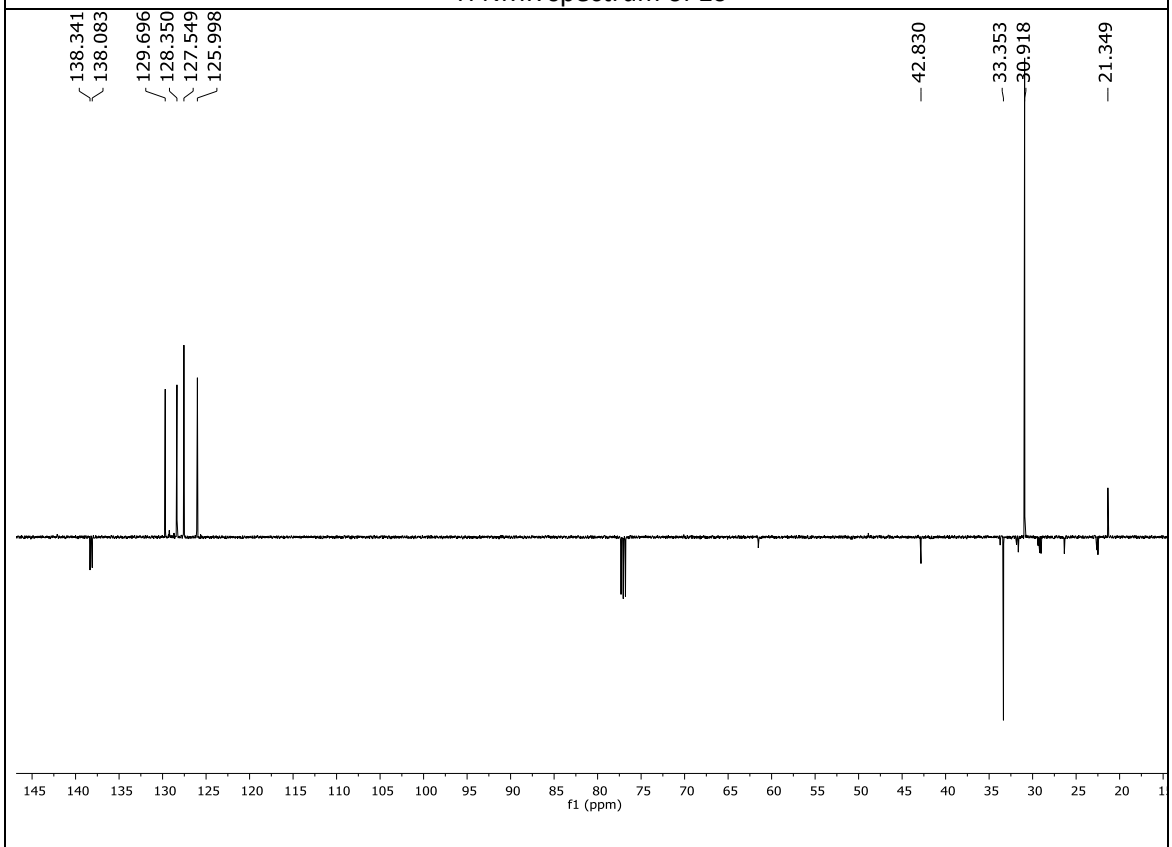
^{13}C NMR spectrum of **1a**



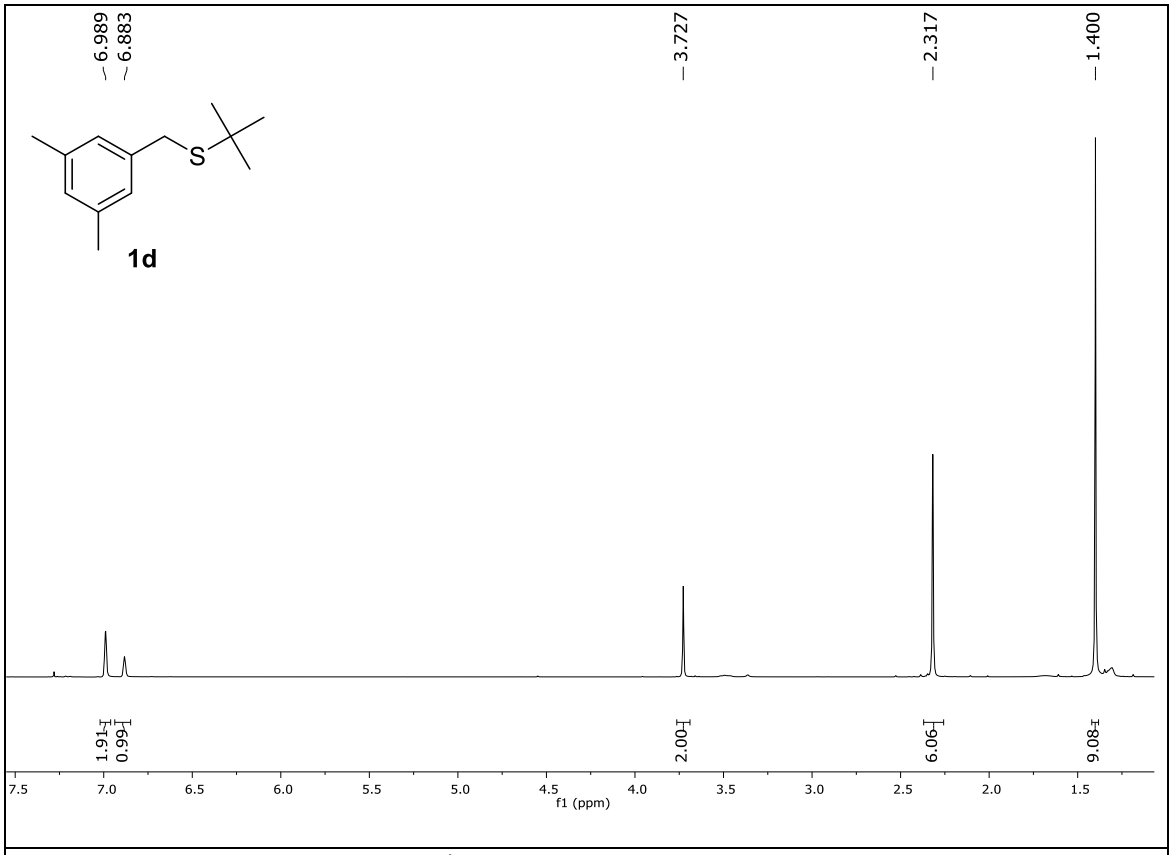
^{1}H NMR spectrum of **1b**



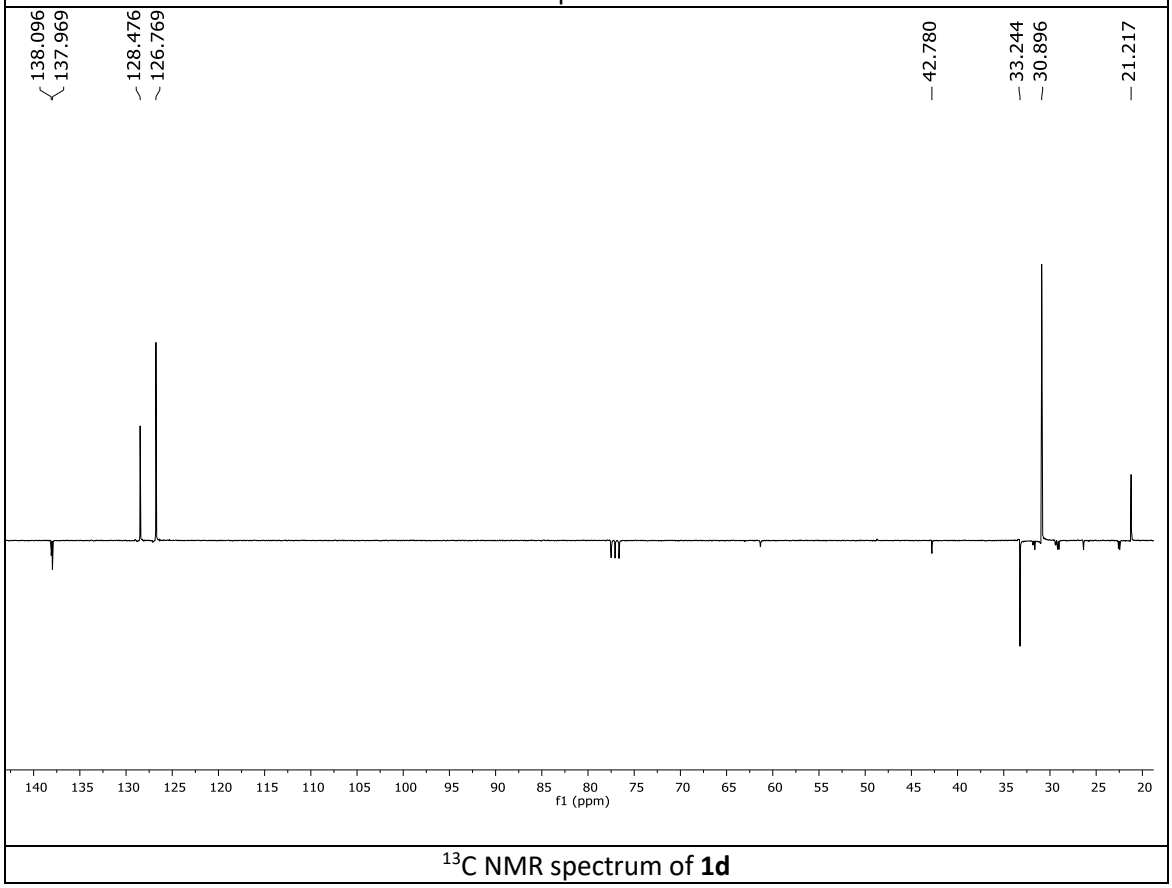
^{1}H NMR spectrum of **1c**



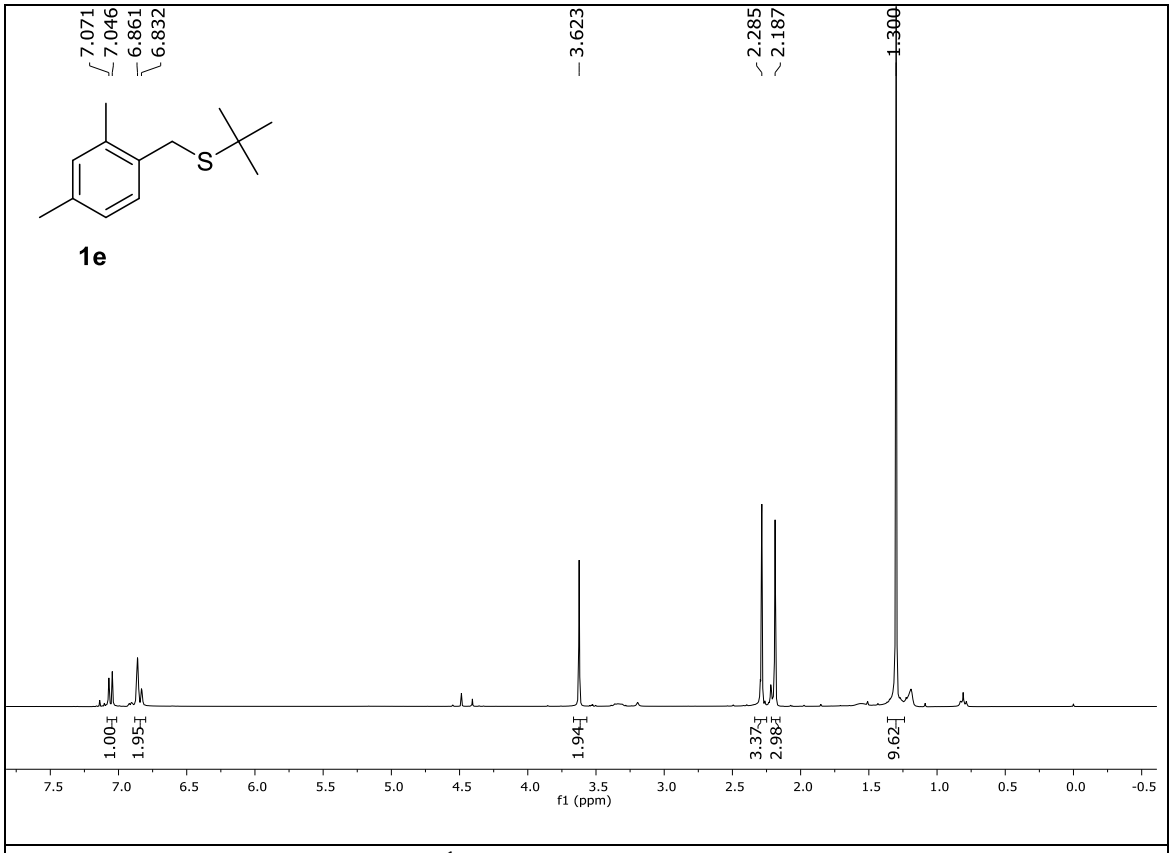
^{13}C NMR spectrum of **1c**



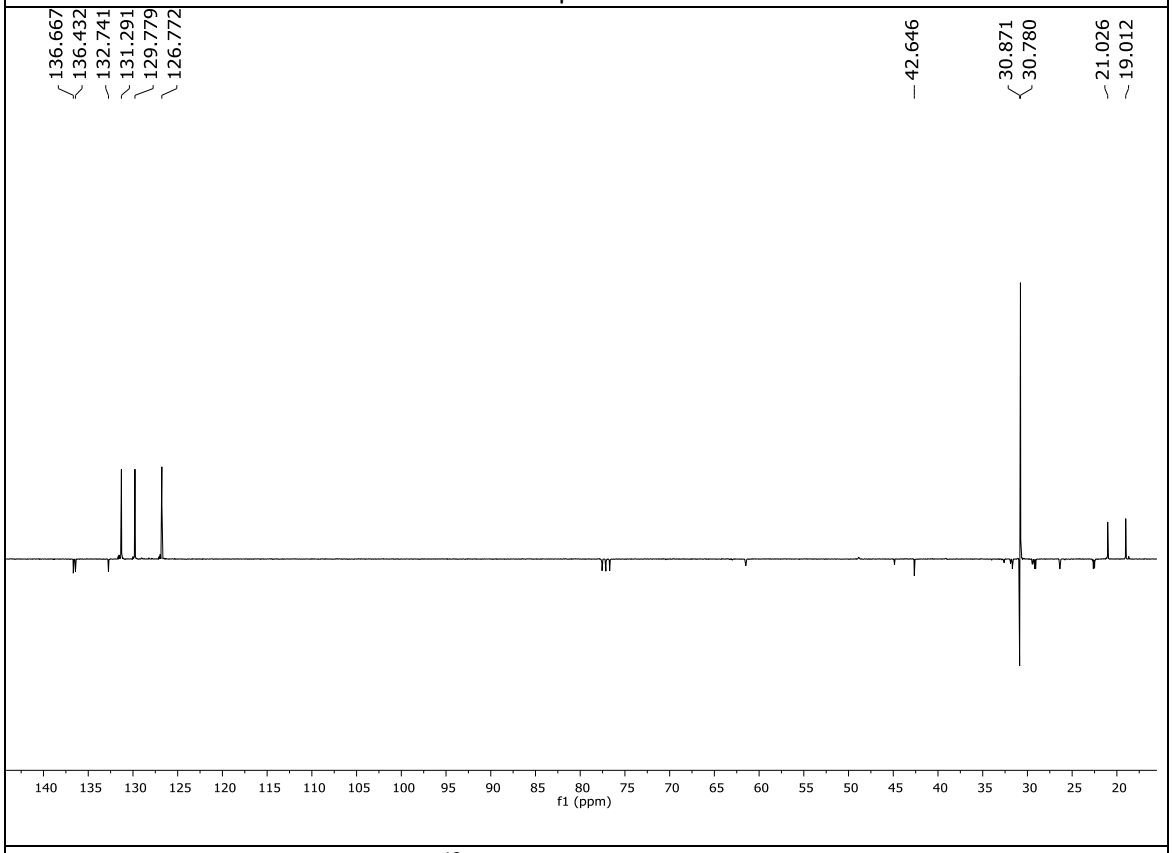
^{1}H NMR spectrum of **1d**



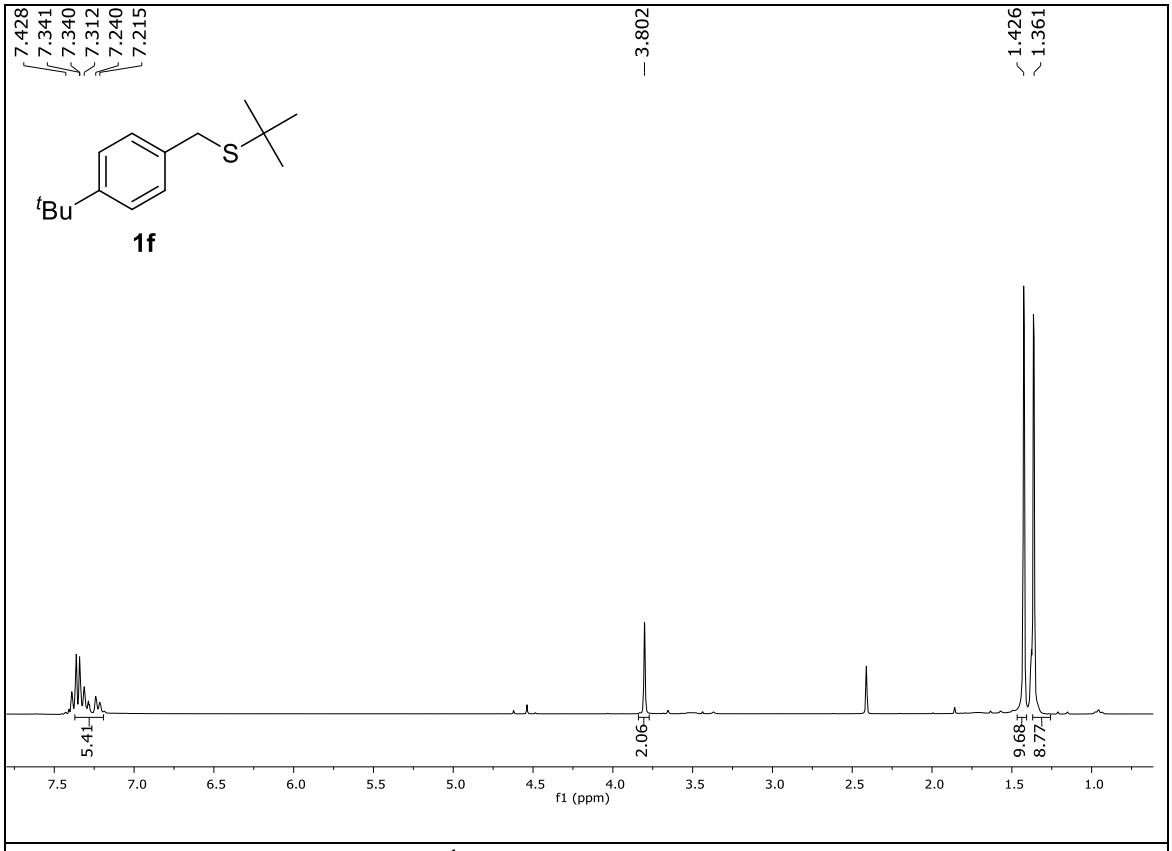
^{13}C NMR spectrum of **1d**



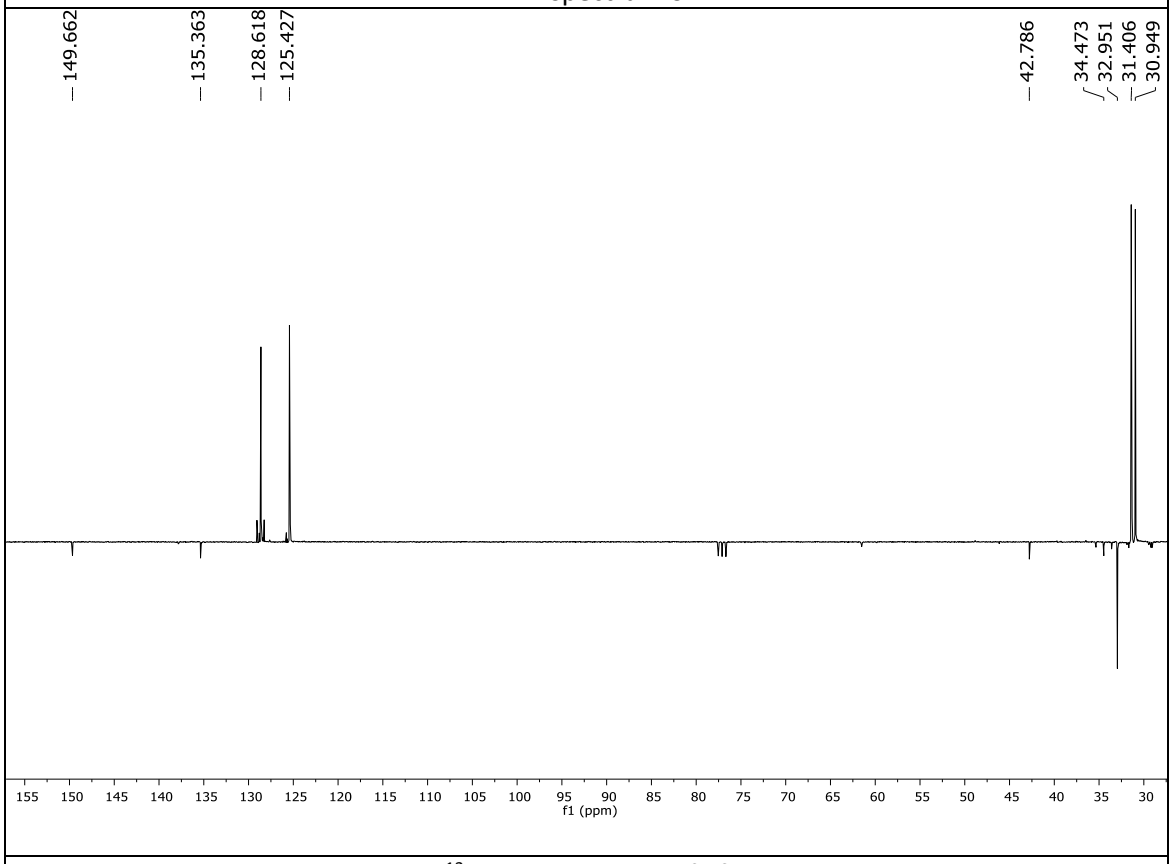
^{1}H NMR spectrum of **1e**



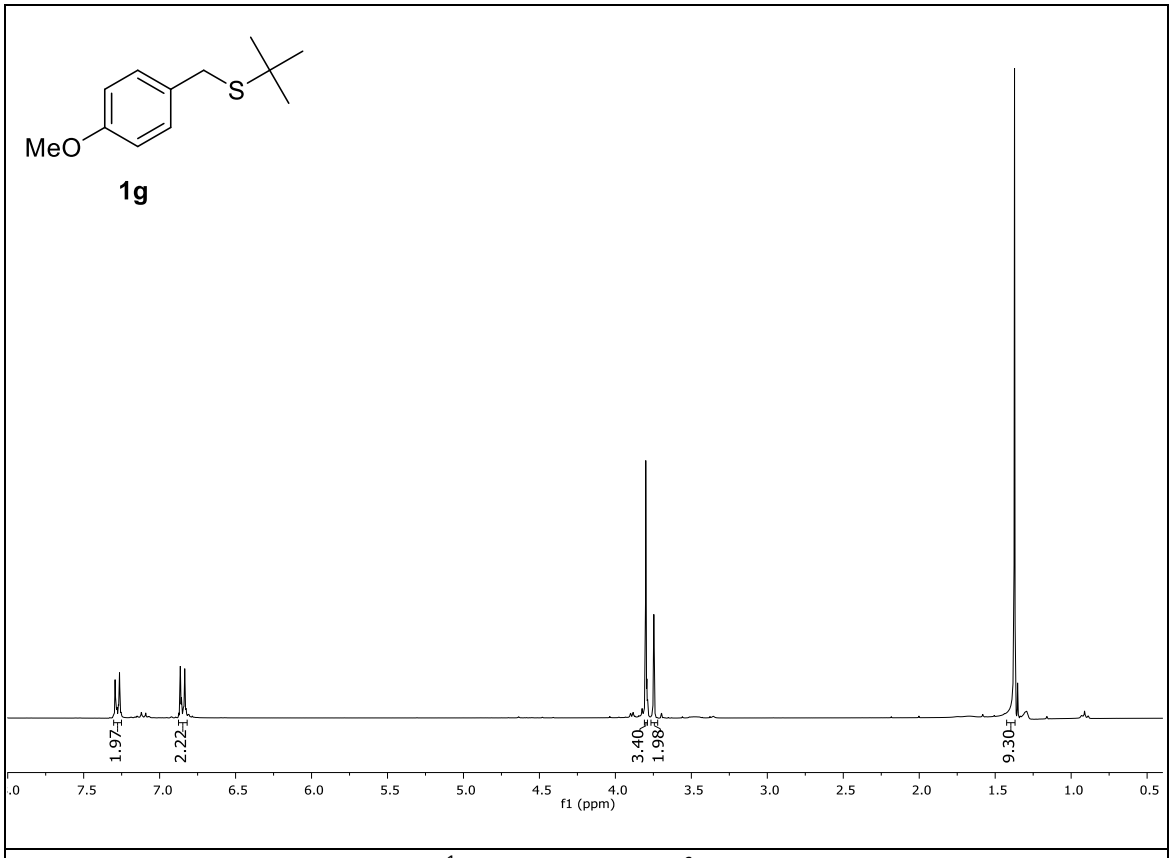
^{13}C NMR spectrum of **1e**



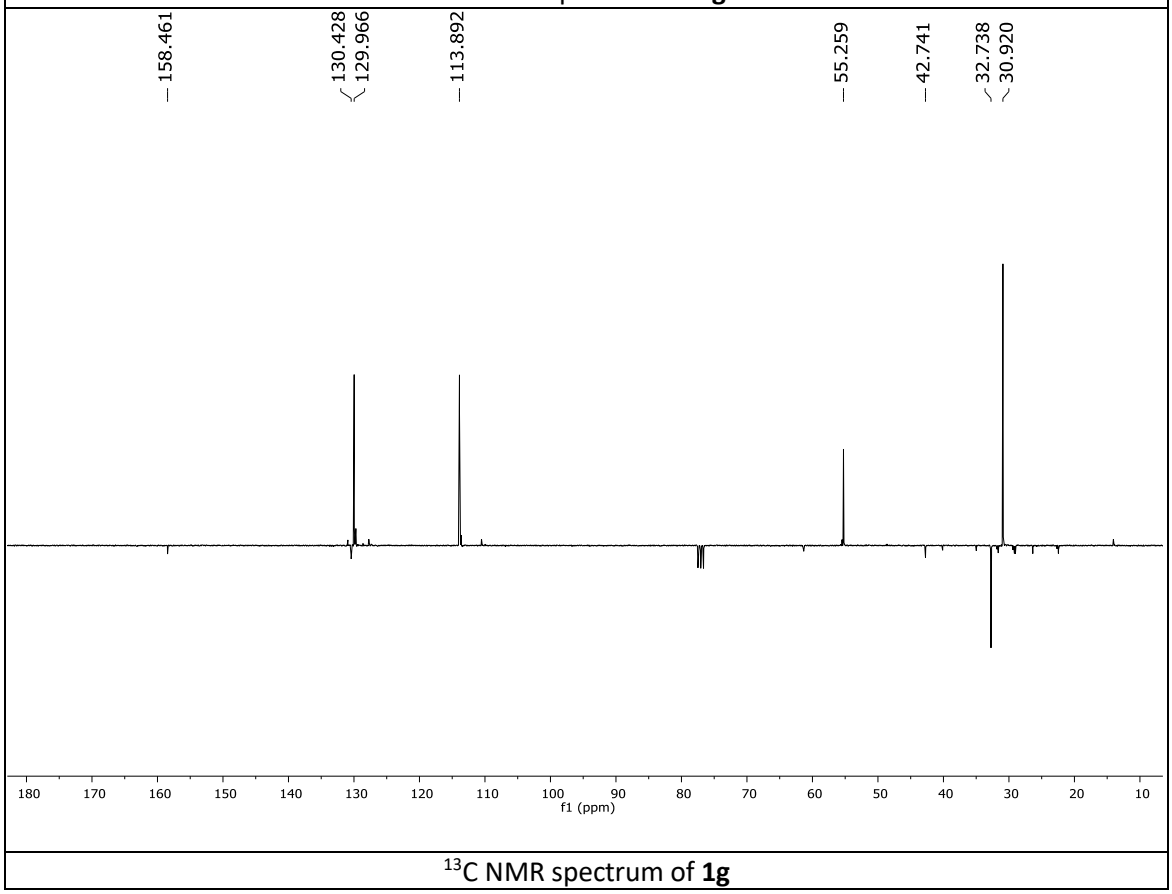
^{1}H NMR spectrum of **1f**



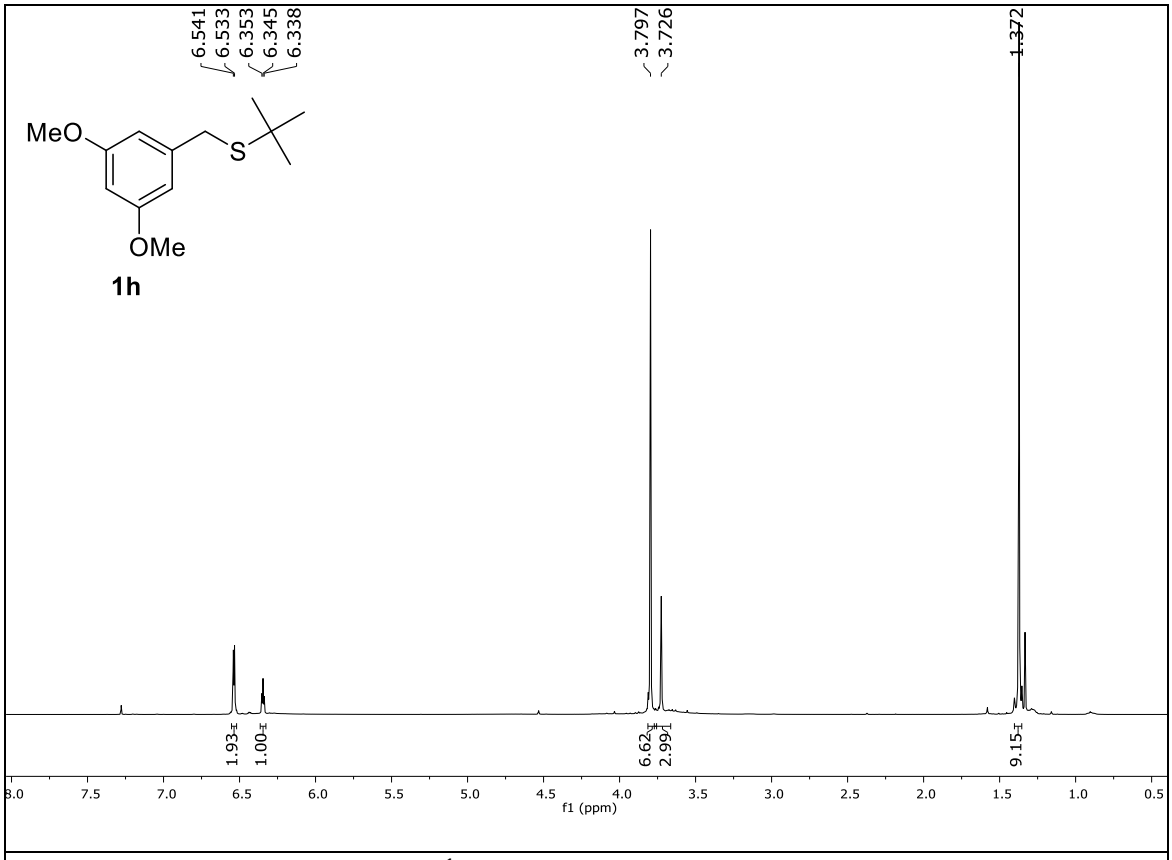
^{13}C NMR spectrum of **1f**



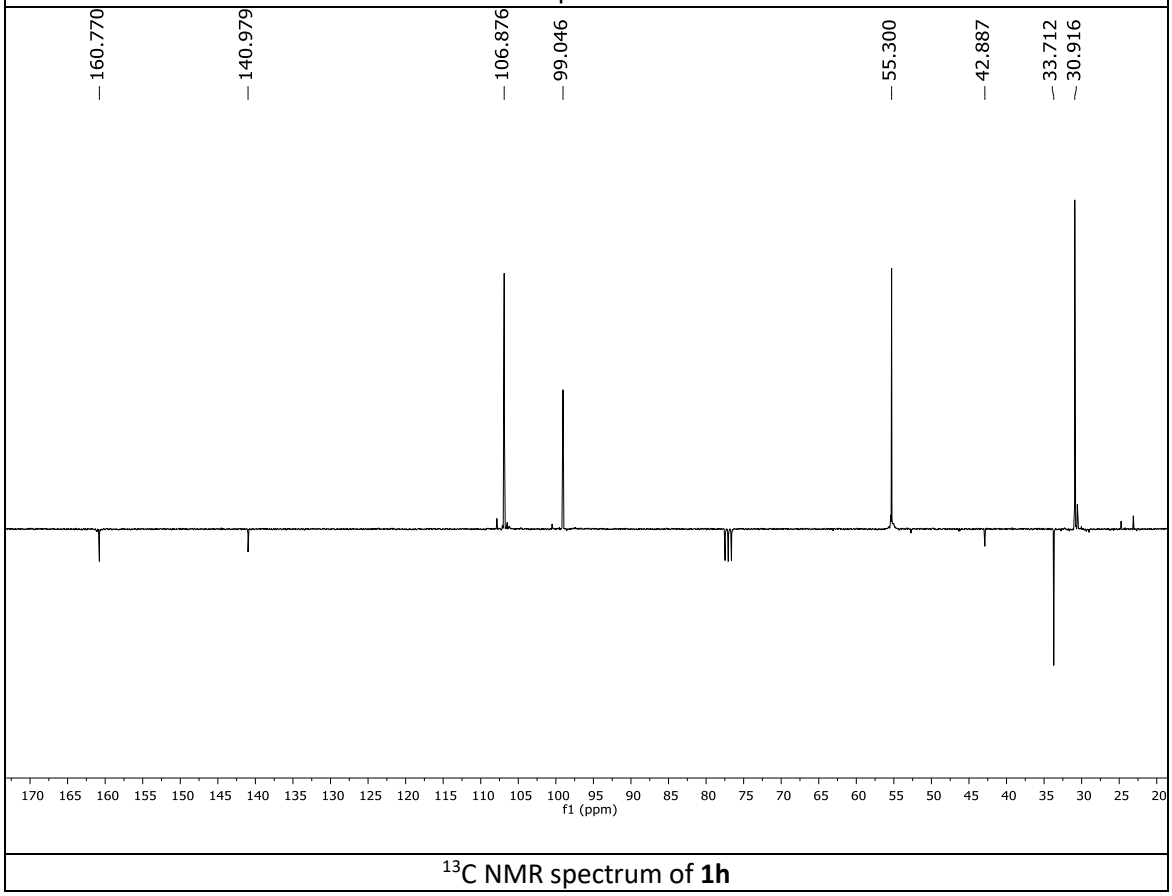
^{1}H NMR spectrum of **1g**



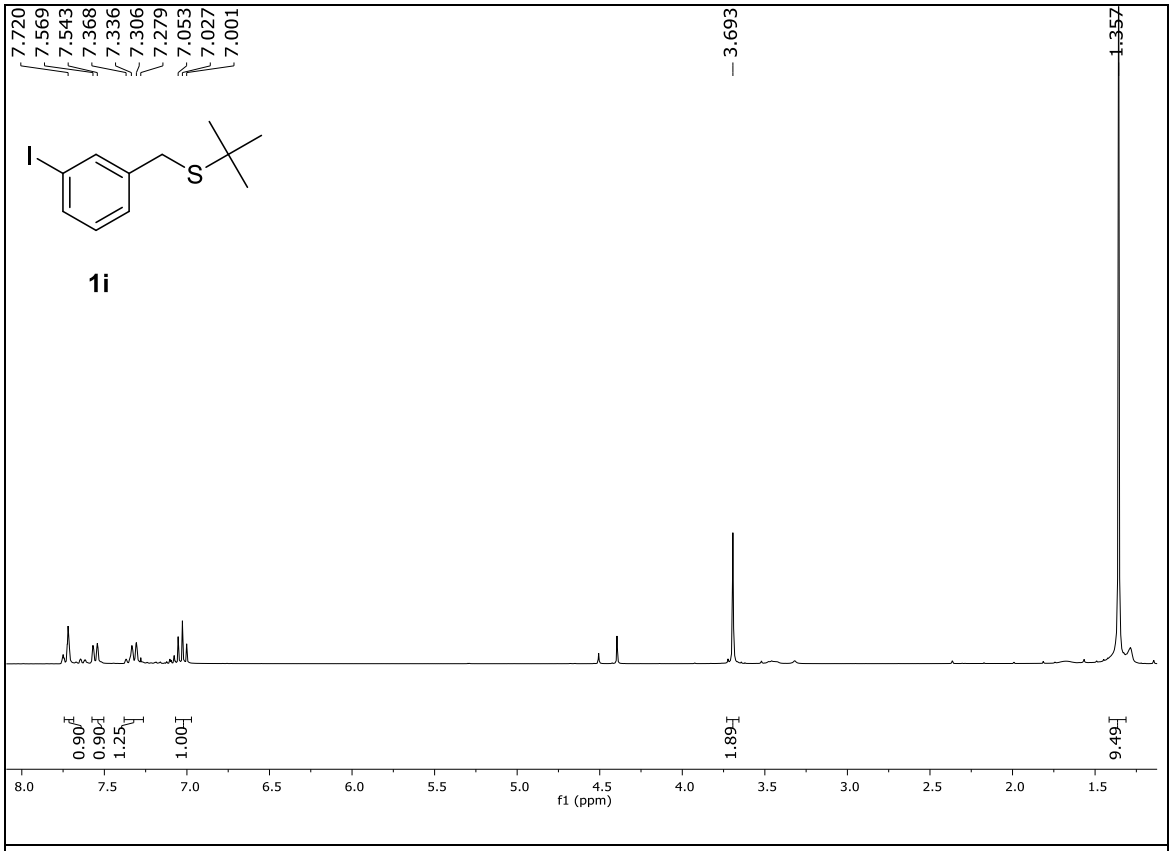
^{13}C NMR spectrum of **1g**



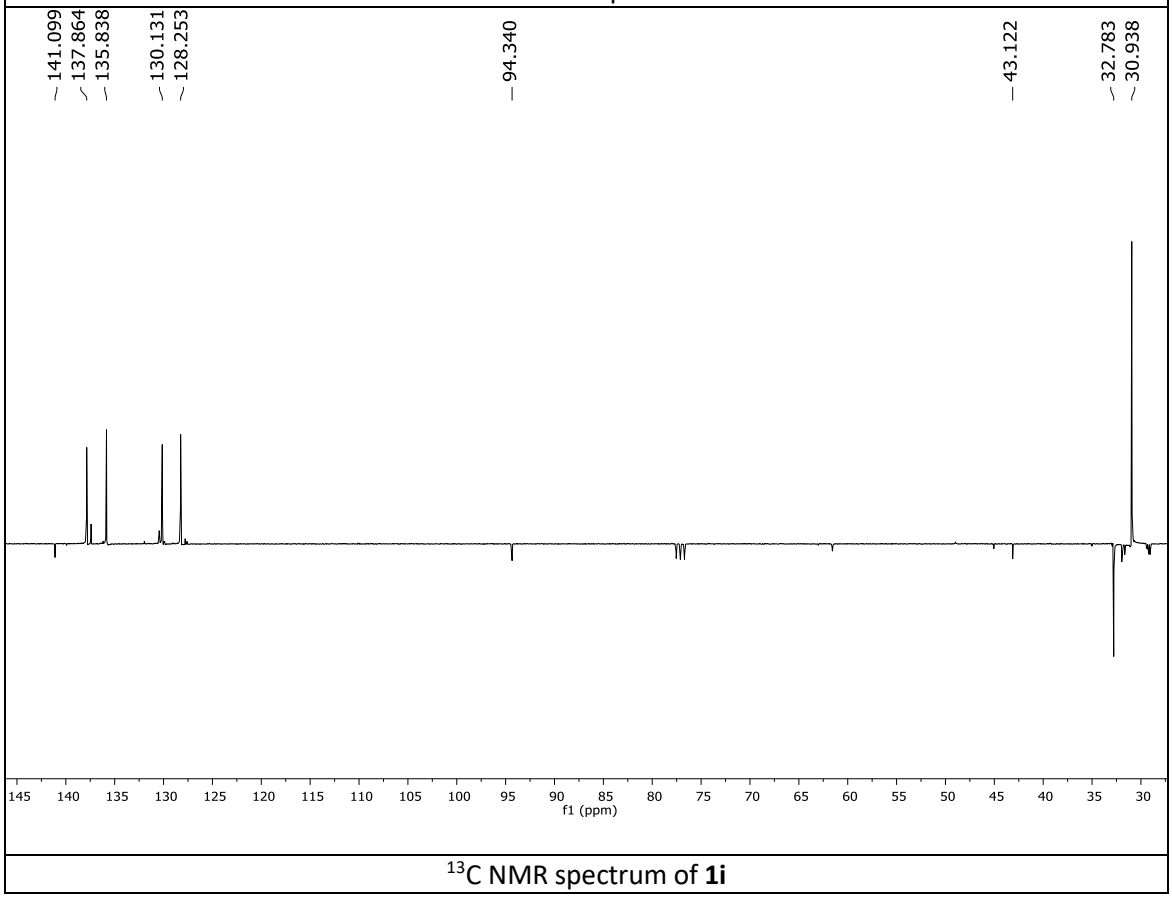
^{1}H NMR spectrum of **1h**



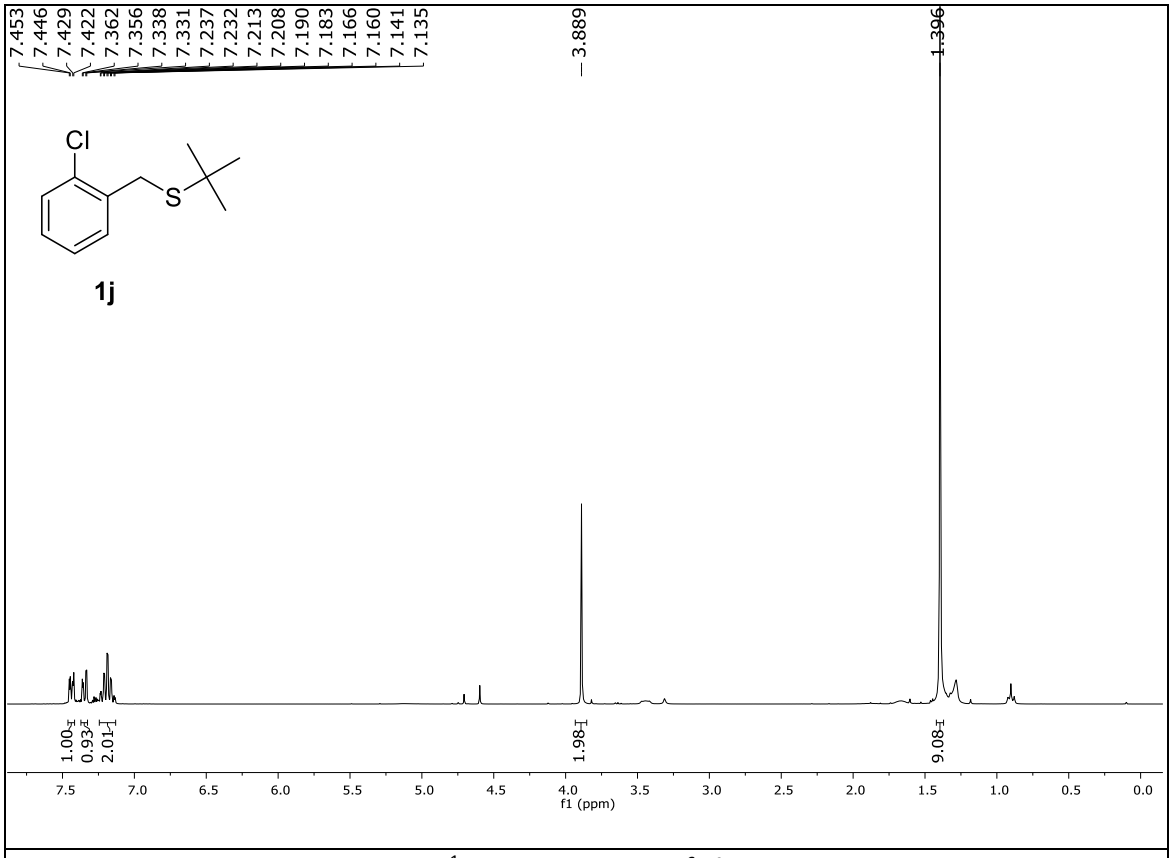
^{13}C NMR spectrum of **1h**



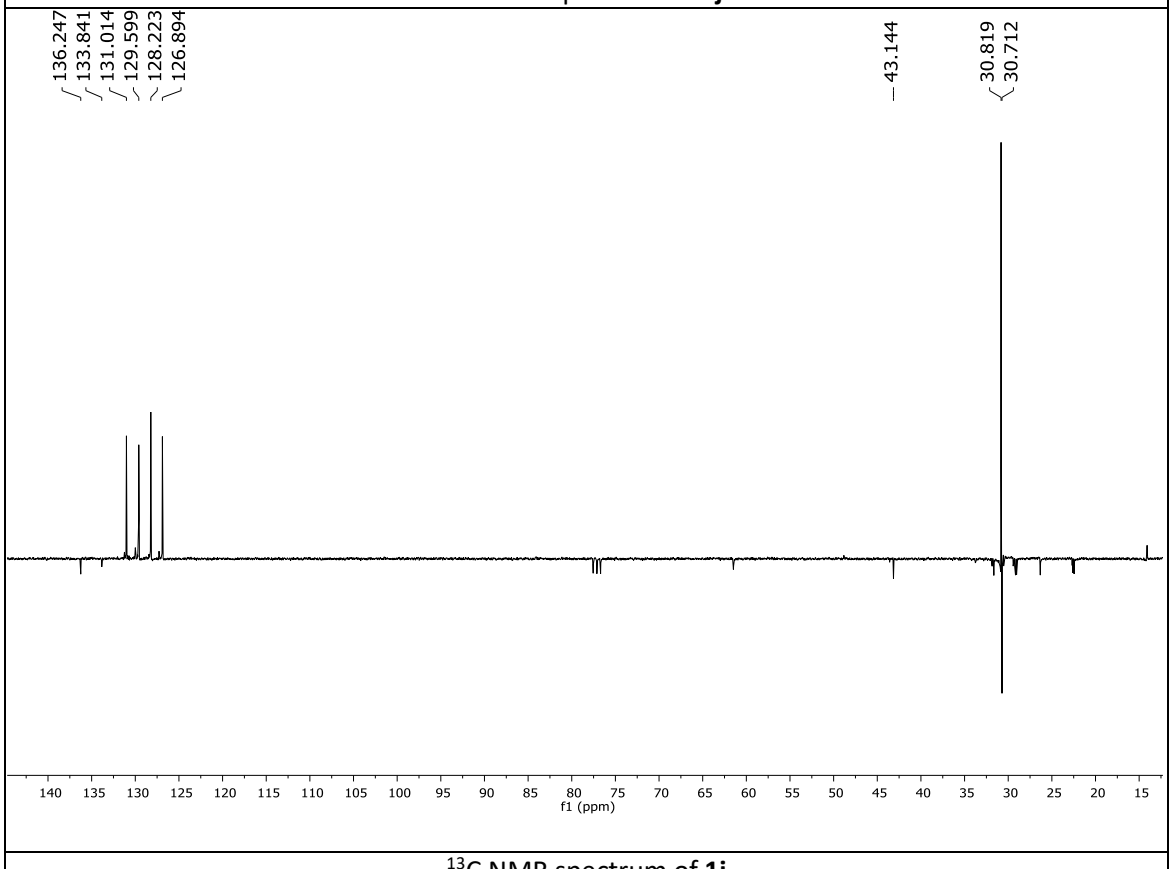
^{1}H NMR spectrum of **1i**



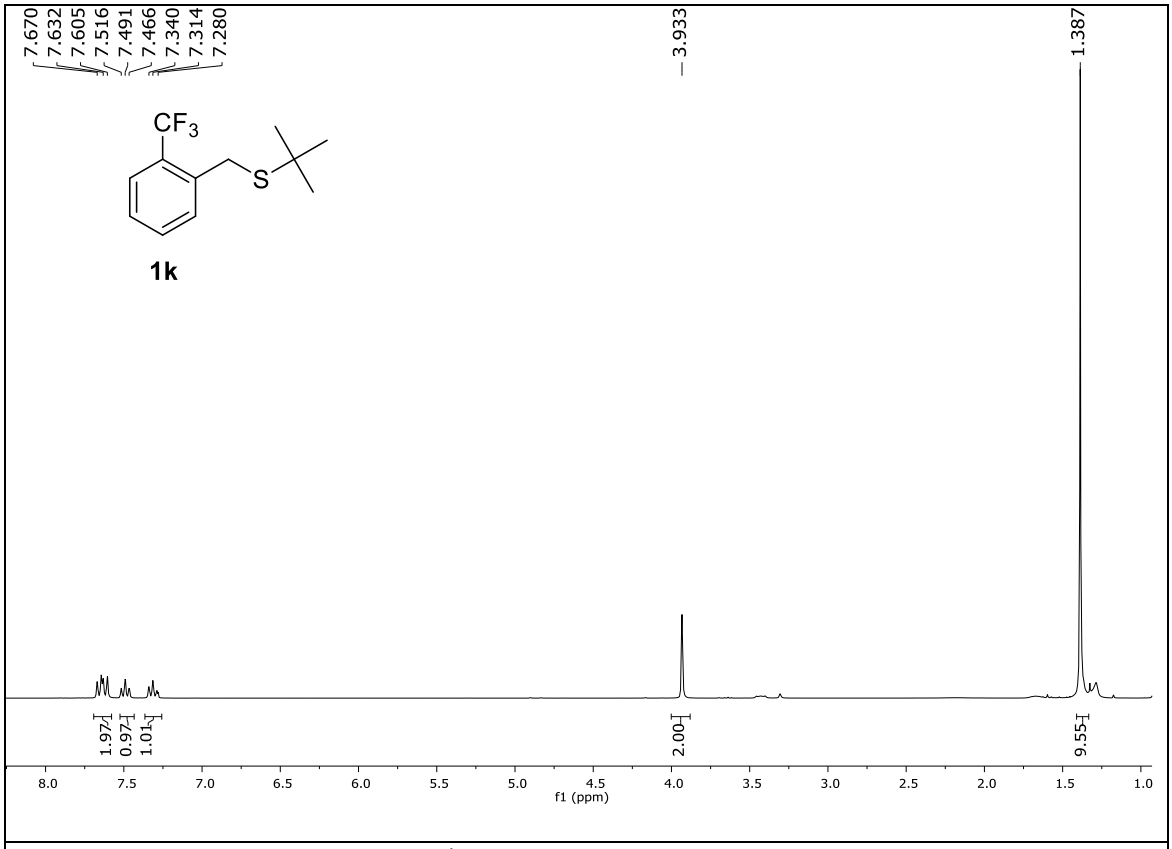
^{13}C NMR spectrum of **1i**



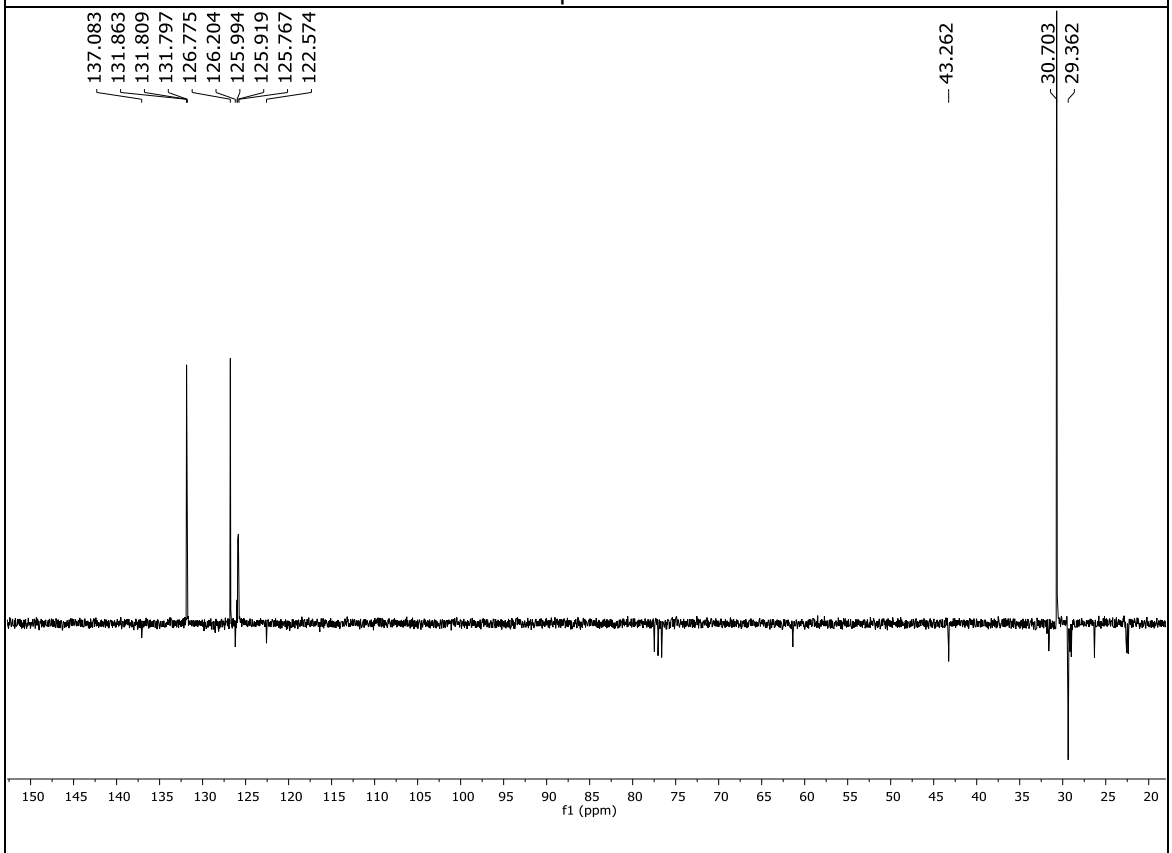
^{1}H NMR spectrum of **1j**



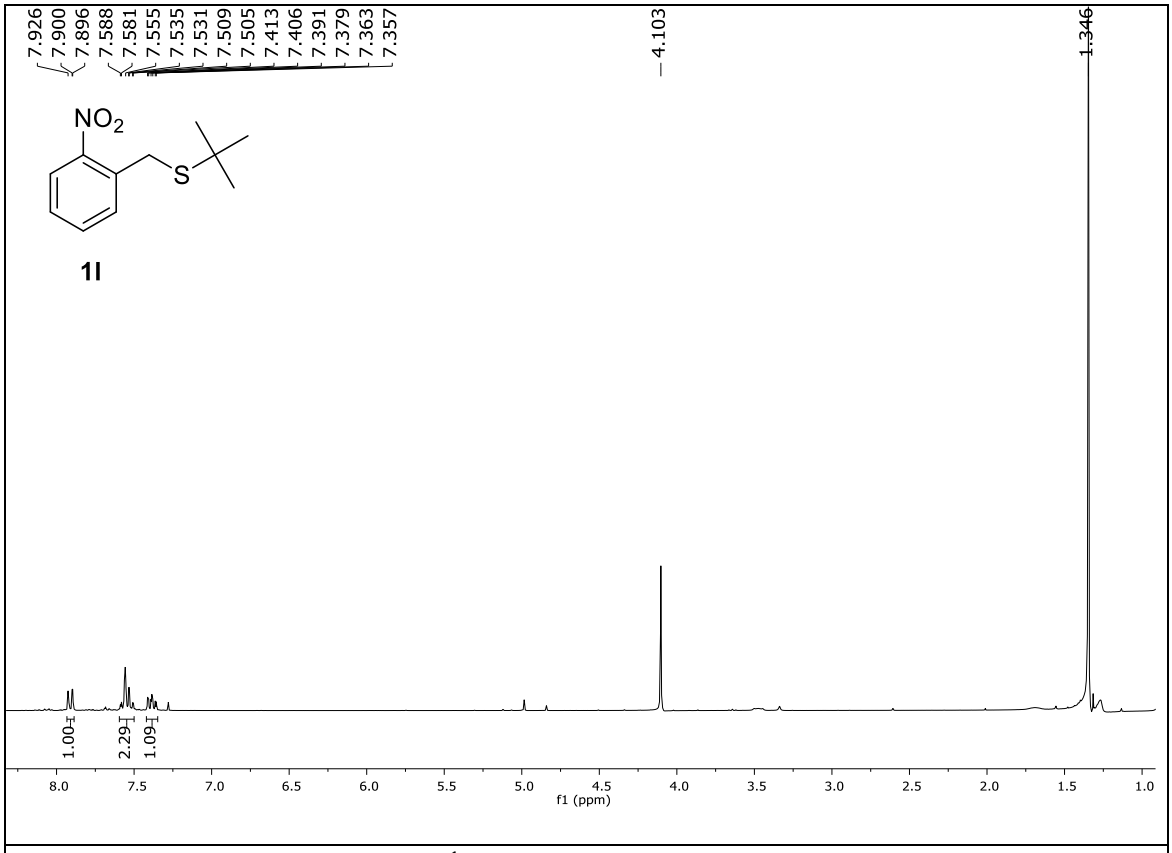
^{13}C NMR spectrum of **1j**



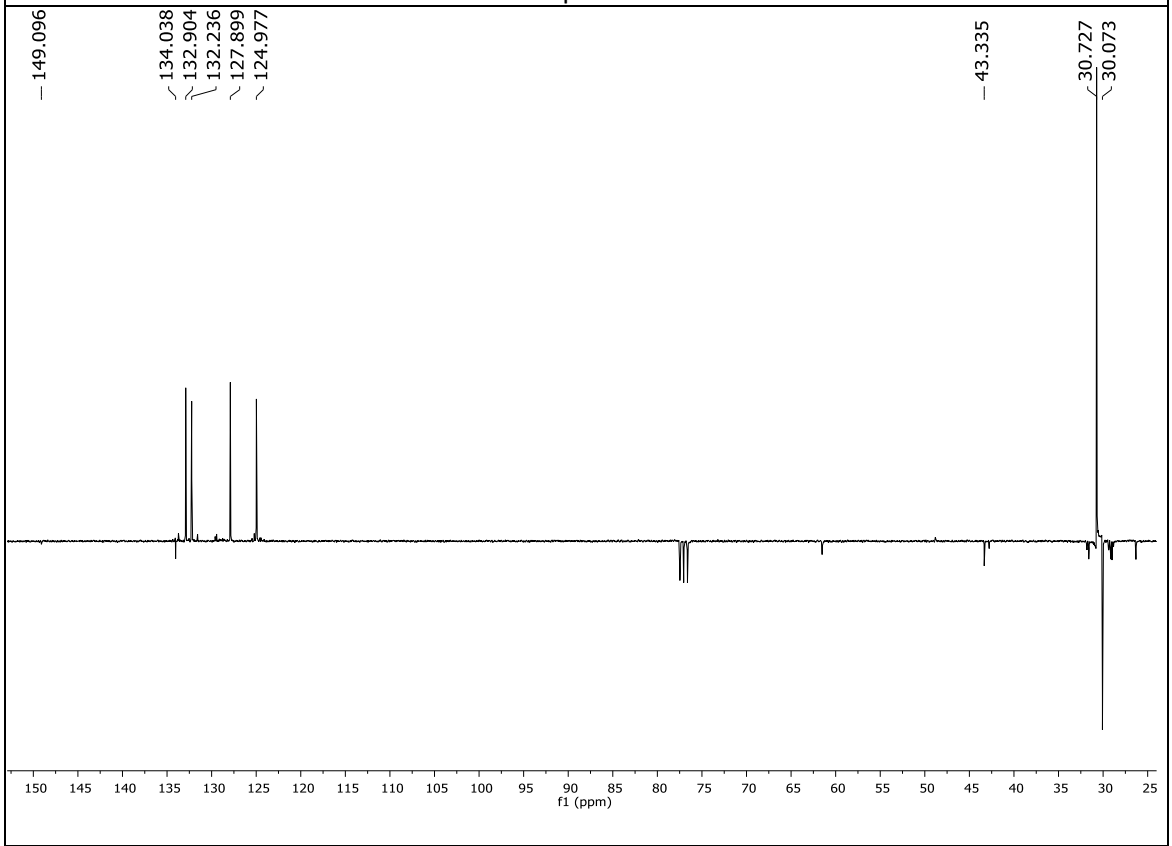
^{1}H NMR spectrum of **1k**



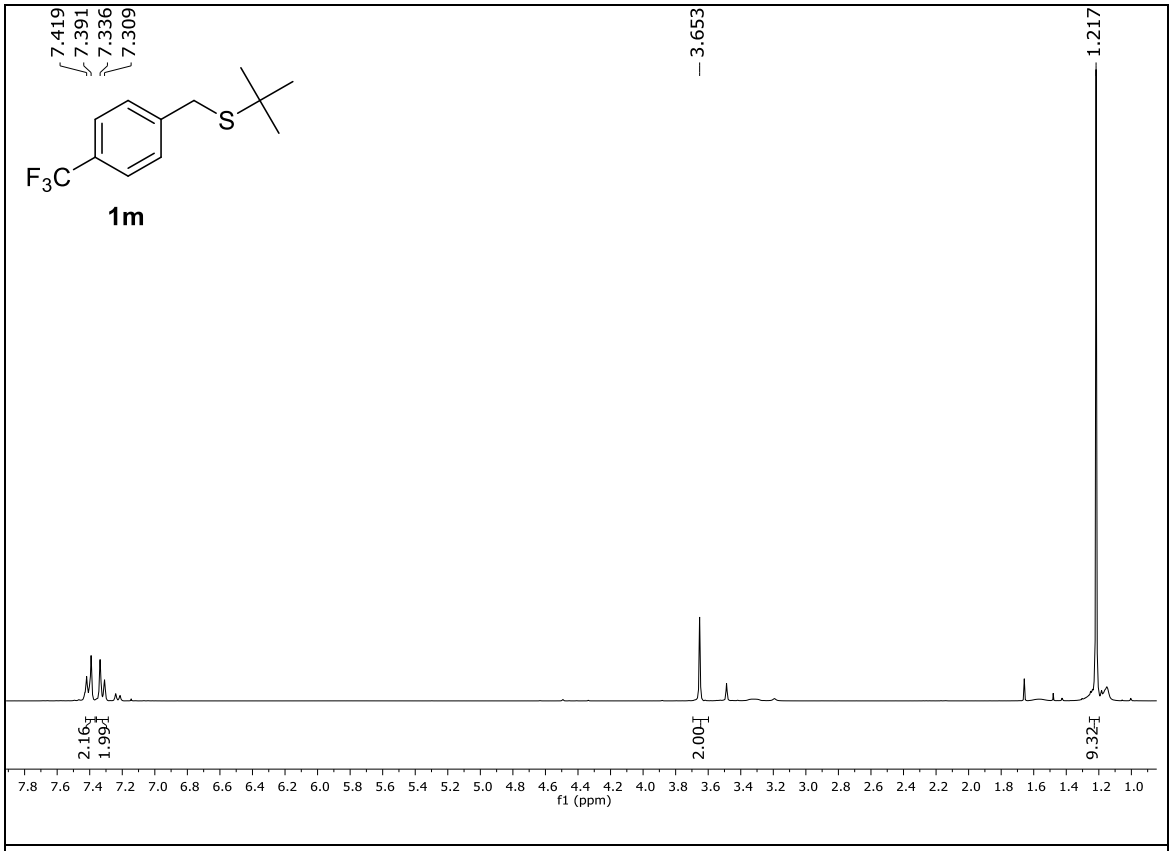
^{13}C NMR spectrum of **1k**



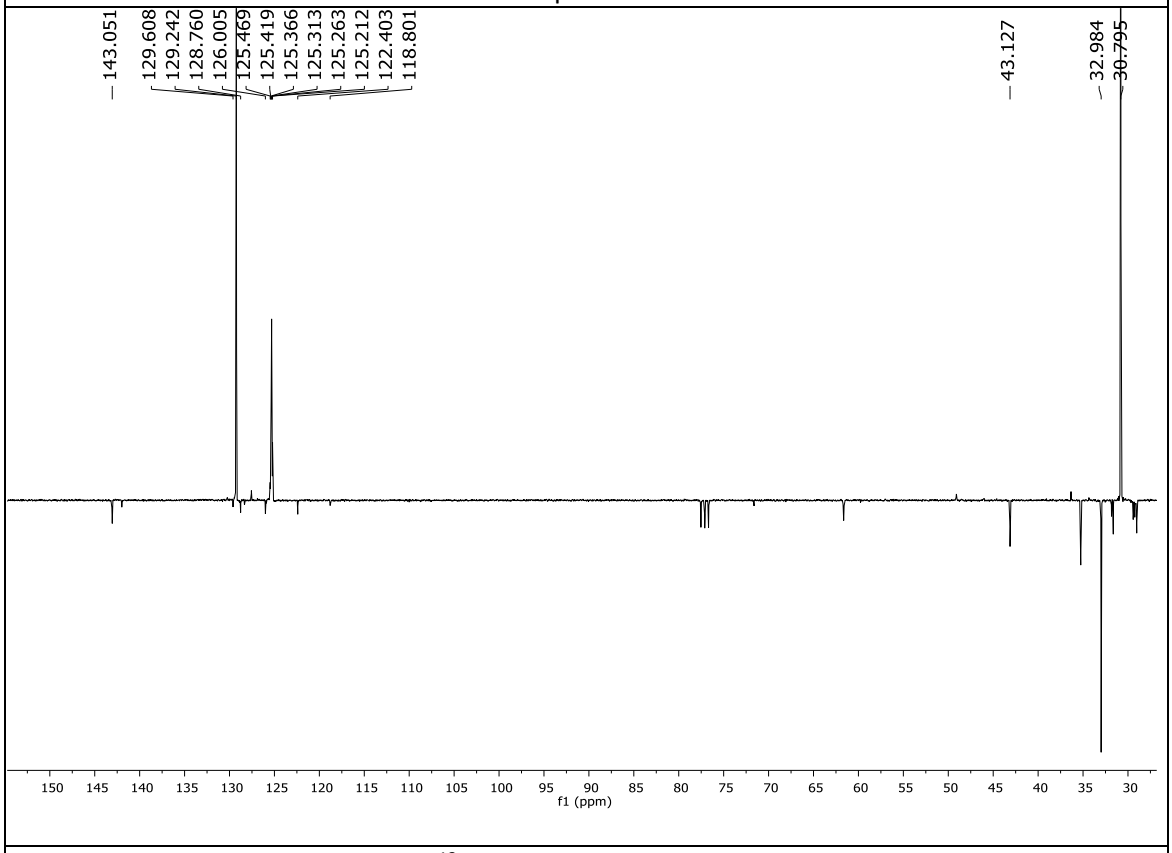
^{1}H NMR spectrum of **1l**



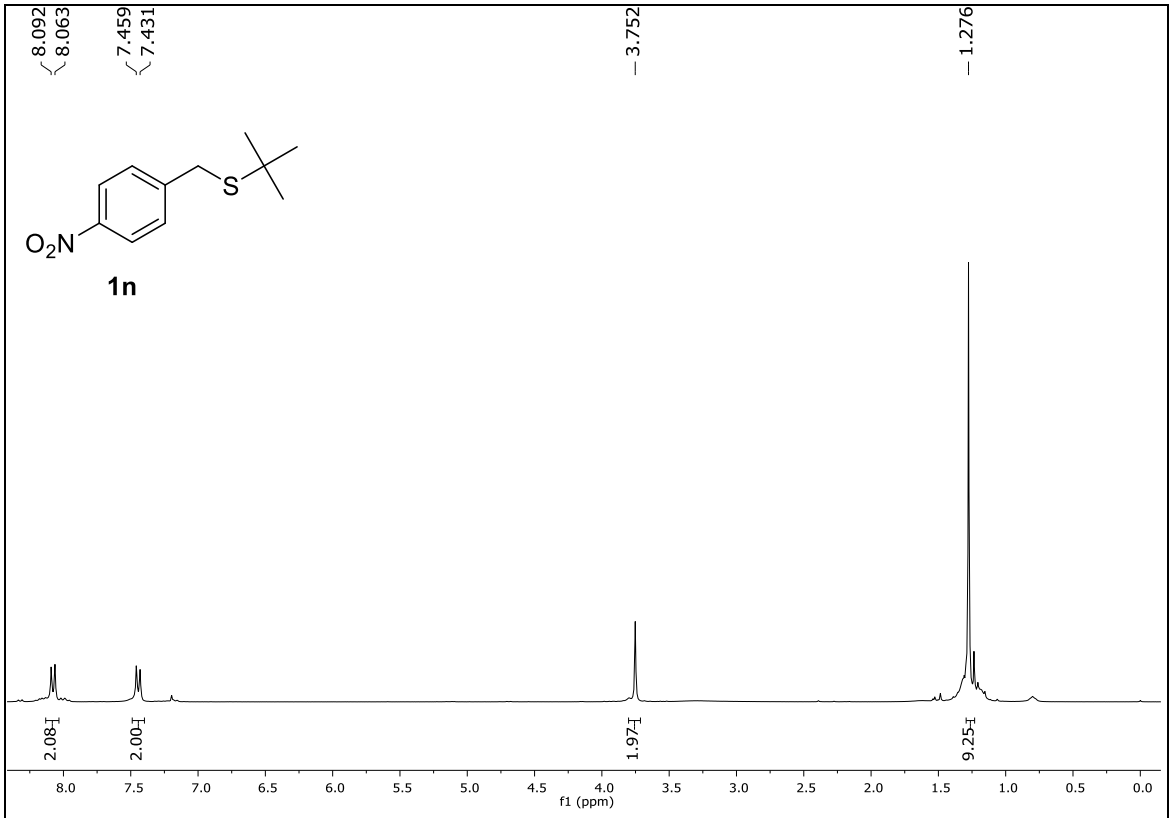
^{13}C NMR spectrum of **1l**



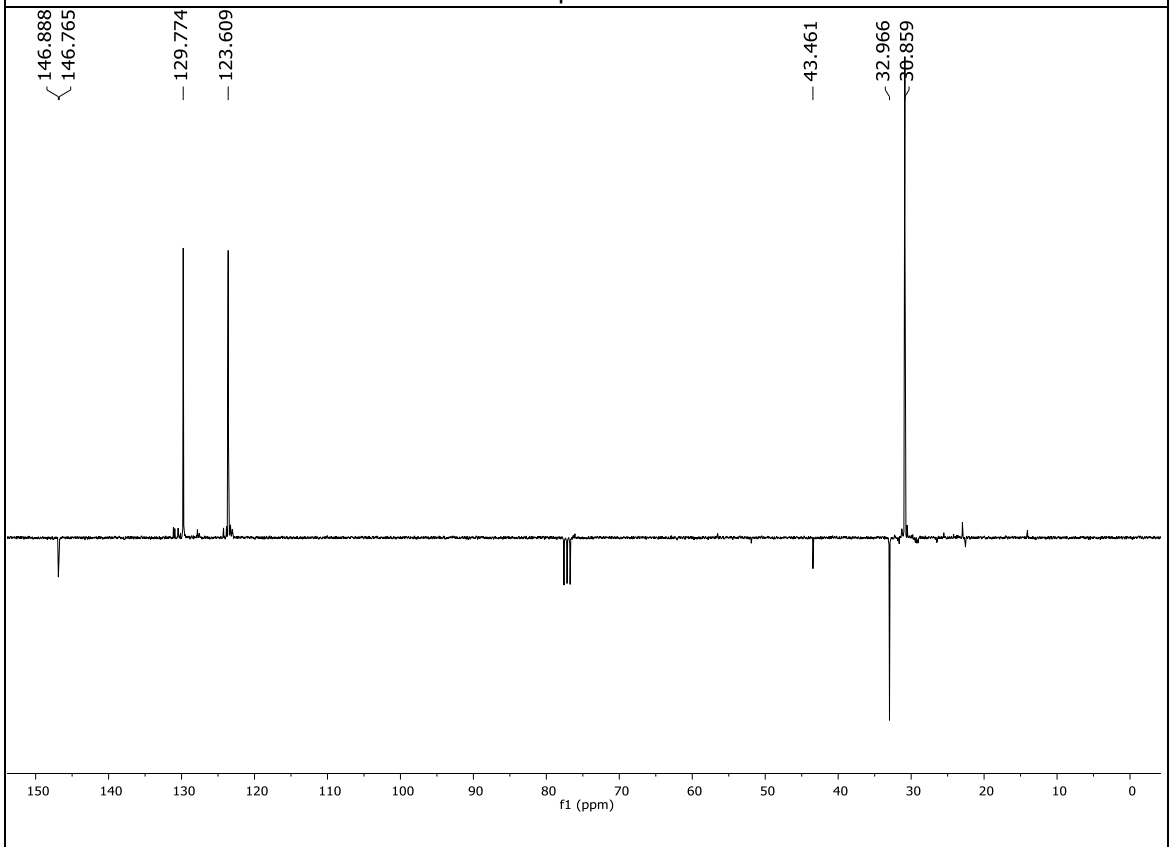
^{1}H NMR spectrum of **1m**



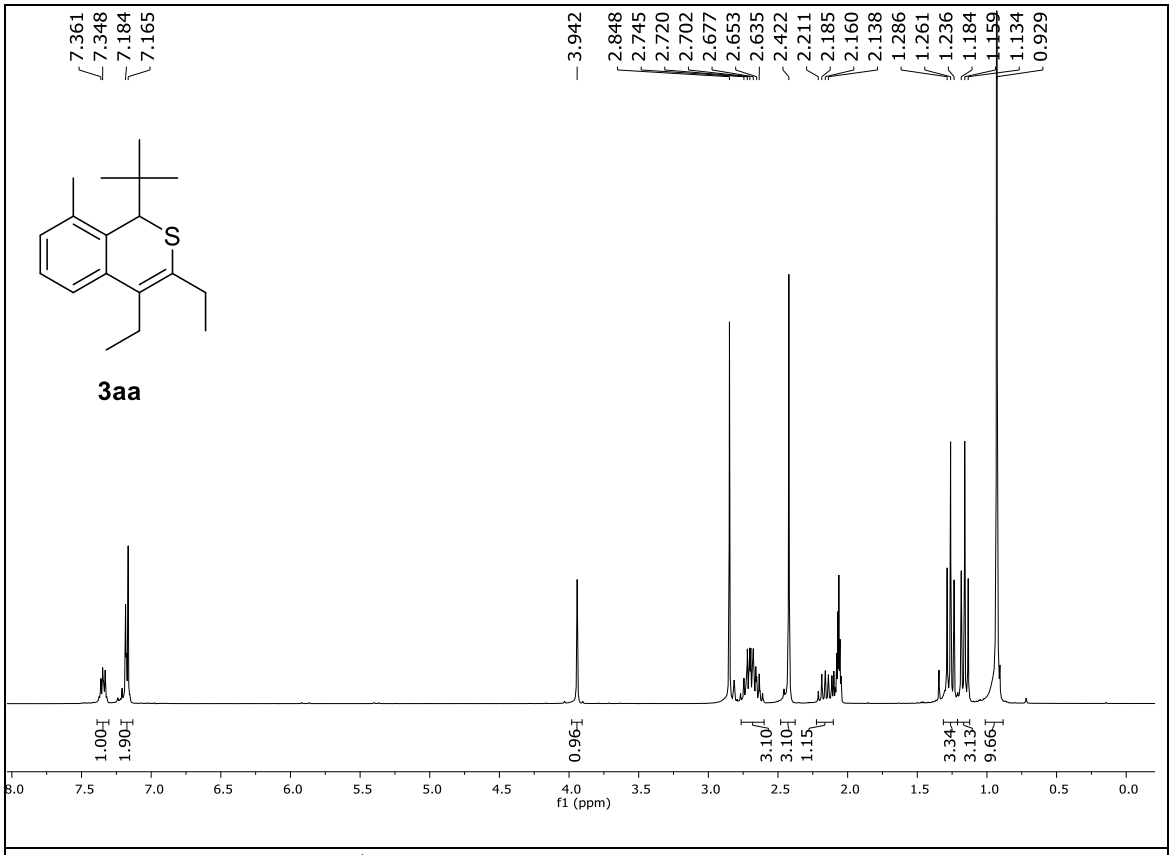
^{13}C NMR spectrum of **1m**



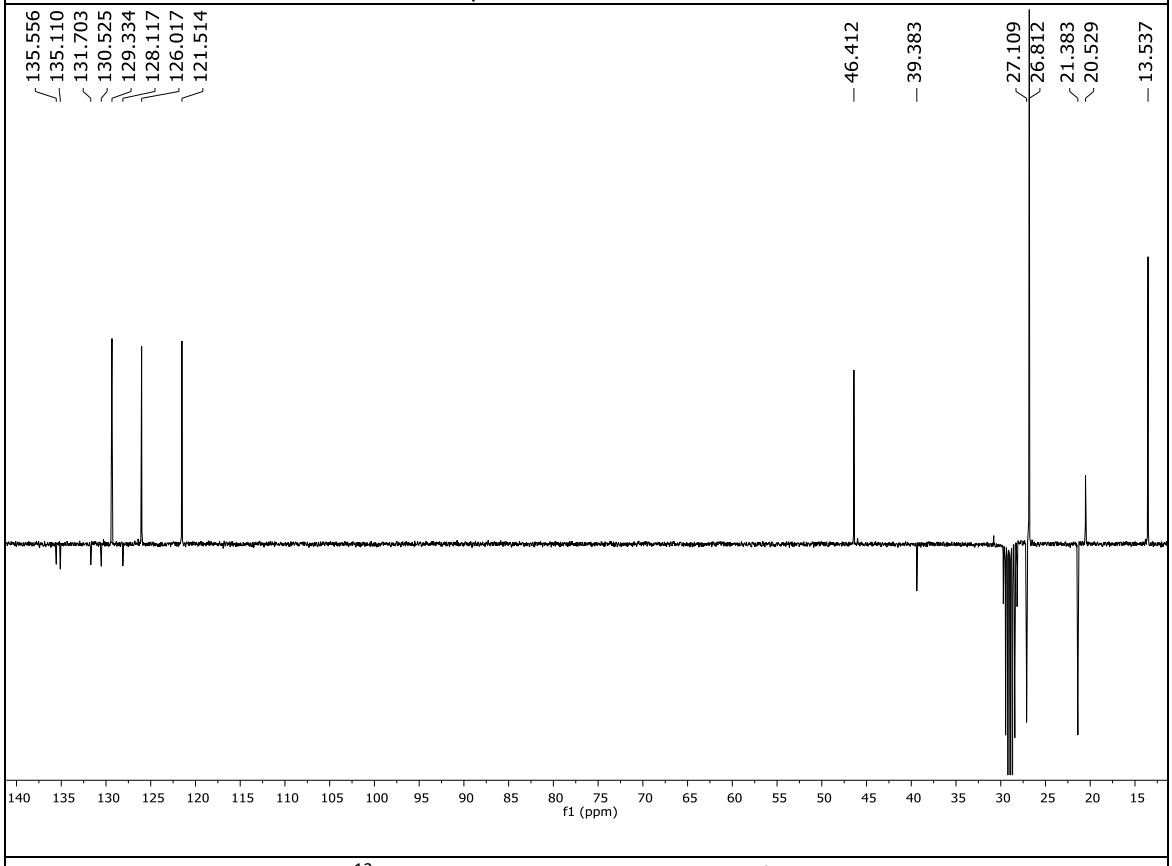
^{1}H NMR spectrum of **1n**



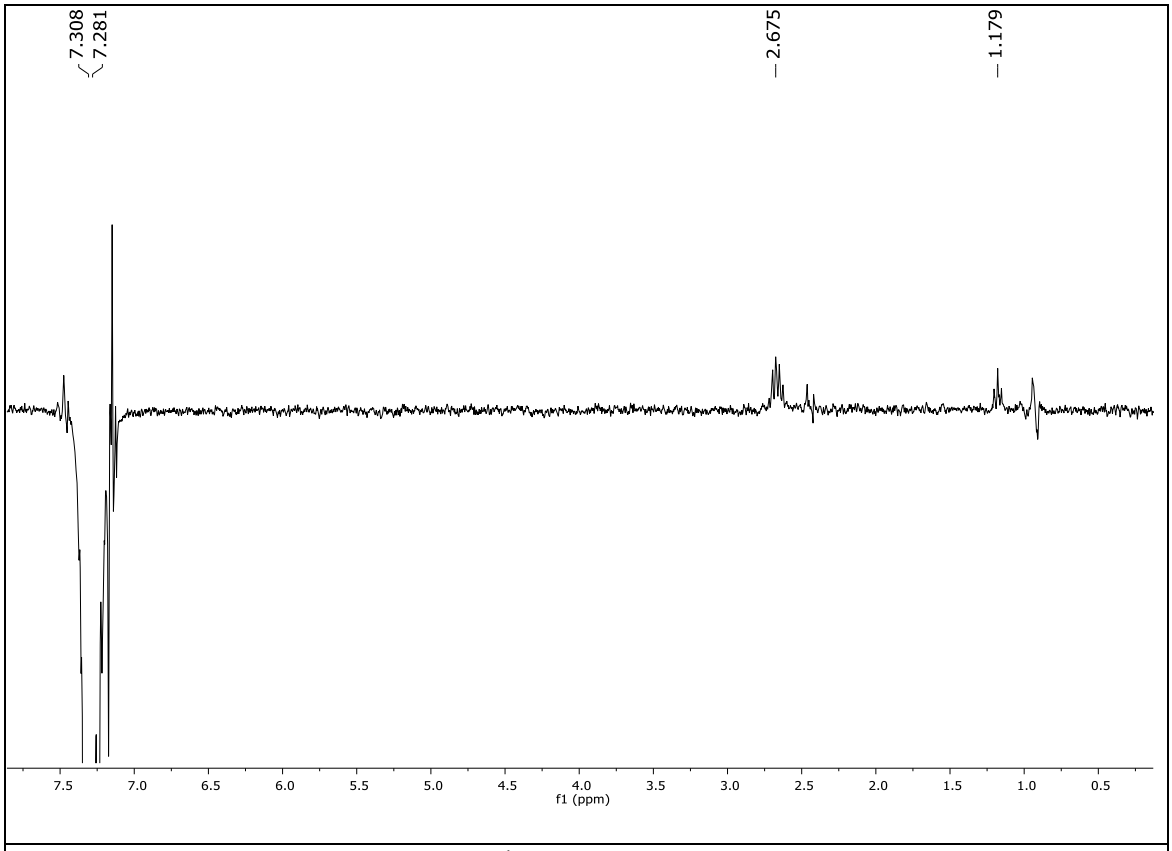
^{13}C NMR spectrum of **1n**



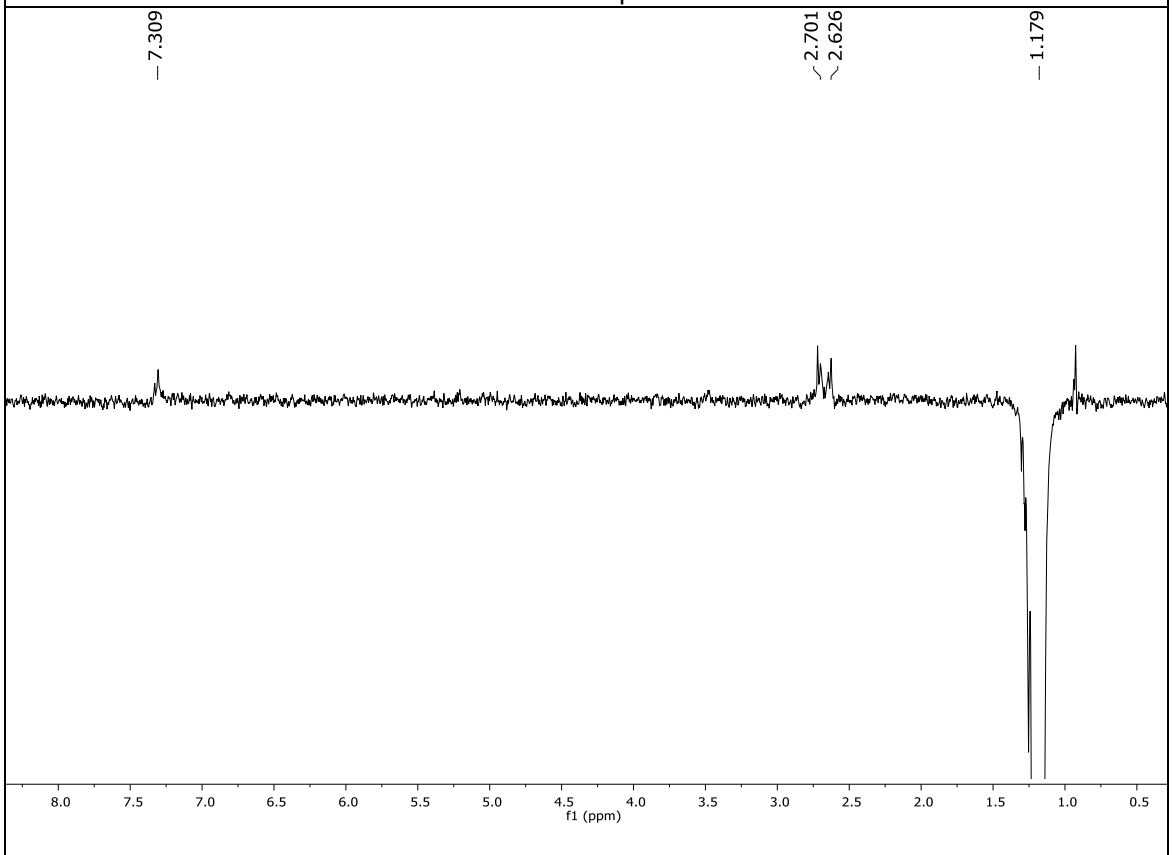
^{1}H NMR spectrum in acetone-d_6 of **3aa**



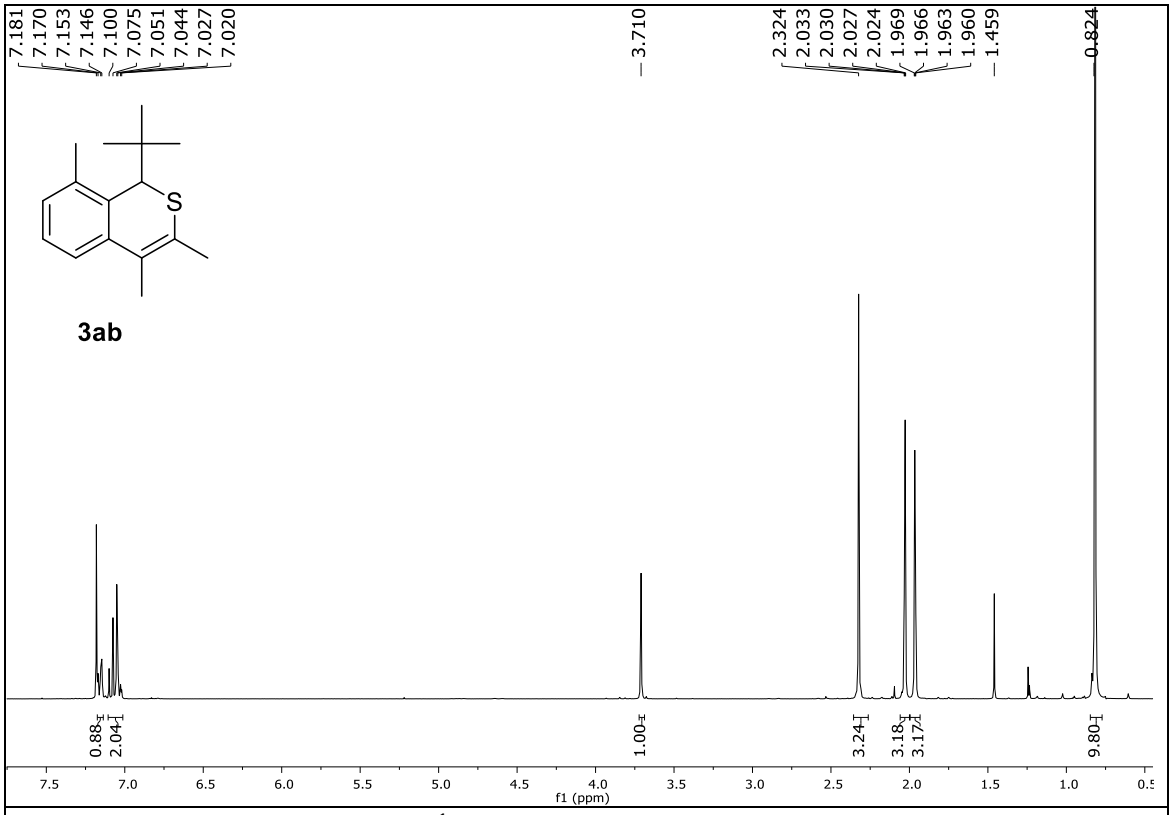
^{13}C NMR spectrum in acetone-d_6 of **3aa**



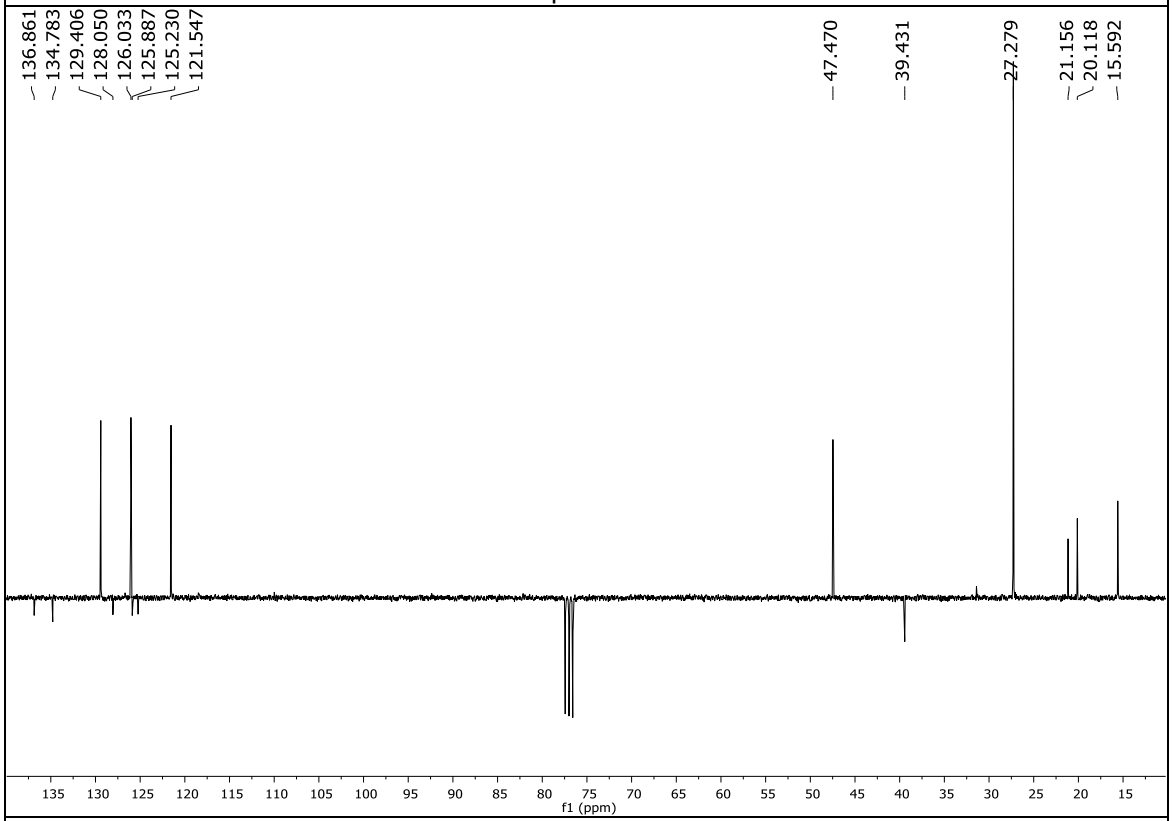
1D-NOESY-^{1}H-NMR spectrum of **3aa**



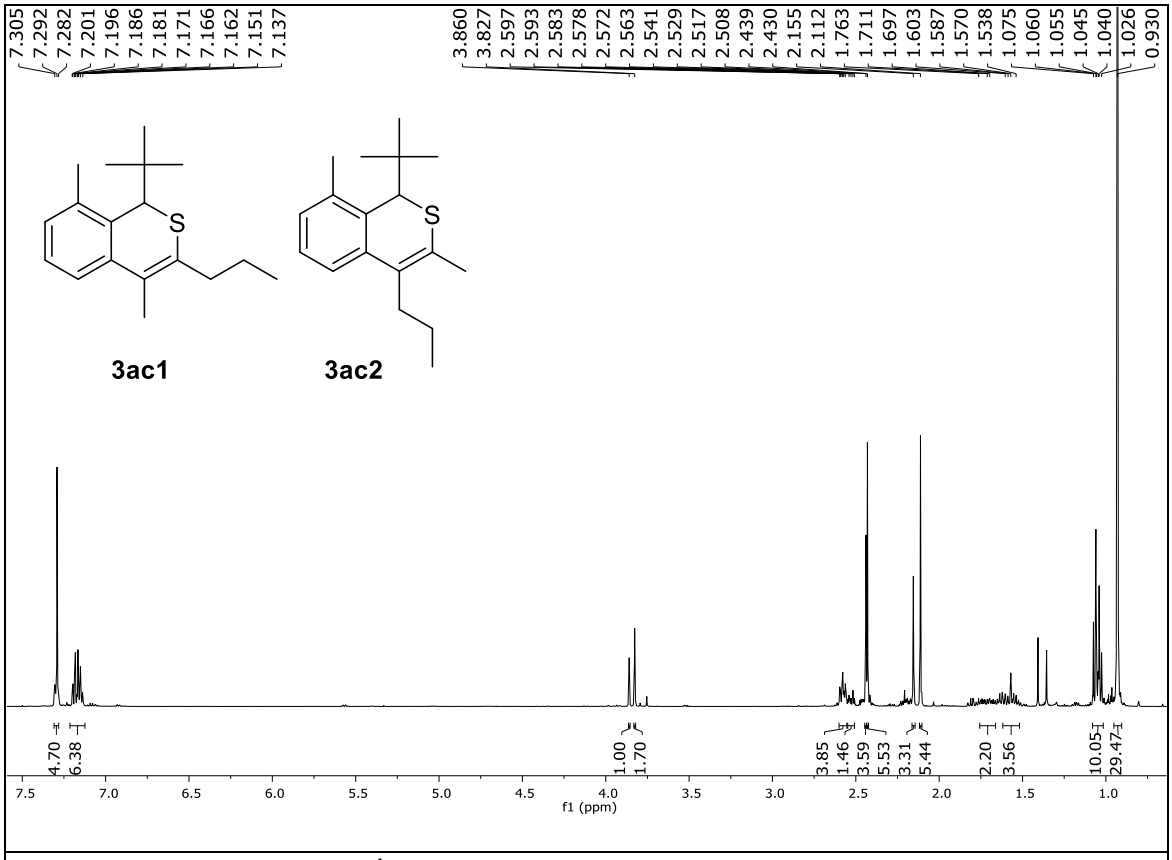
1D-NOESY-^{1}H-NMR spectrum of **3aa**



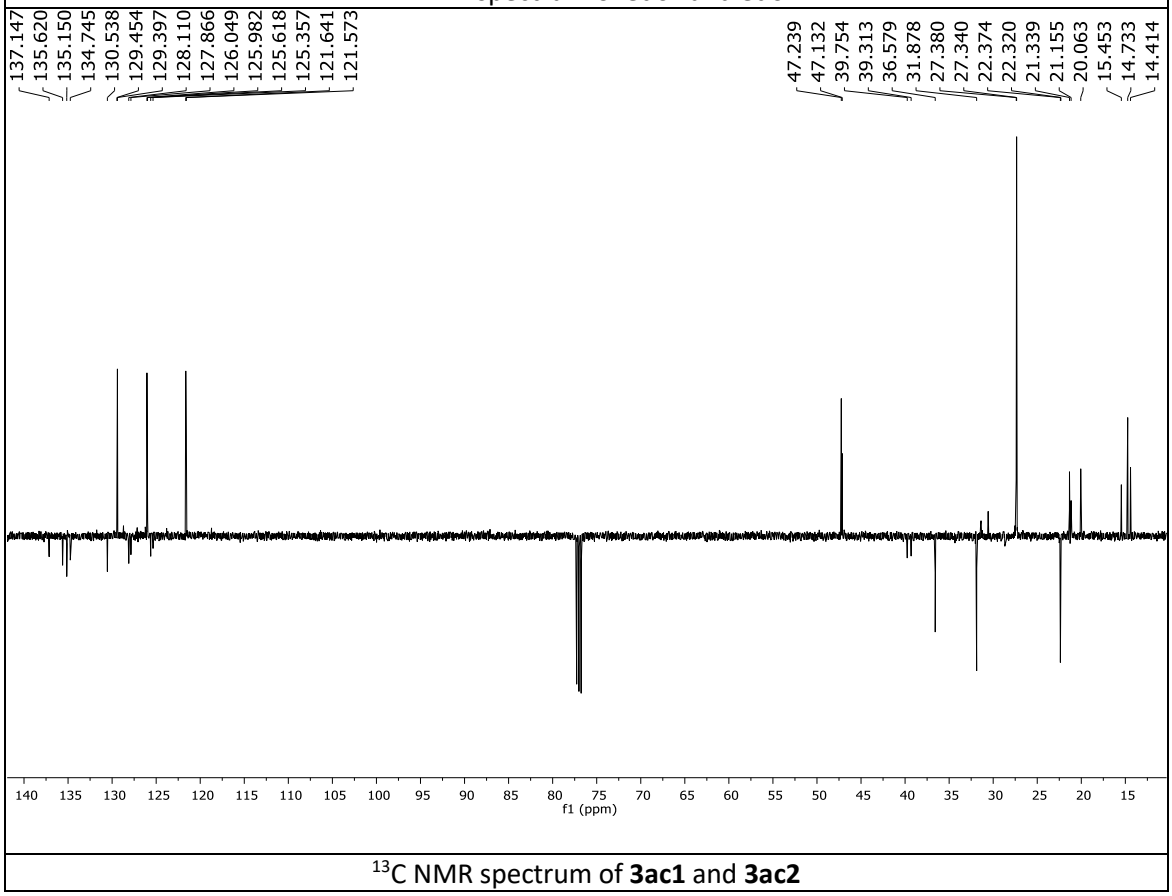
^{1}H NMR spectrum of **3ab**



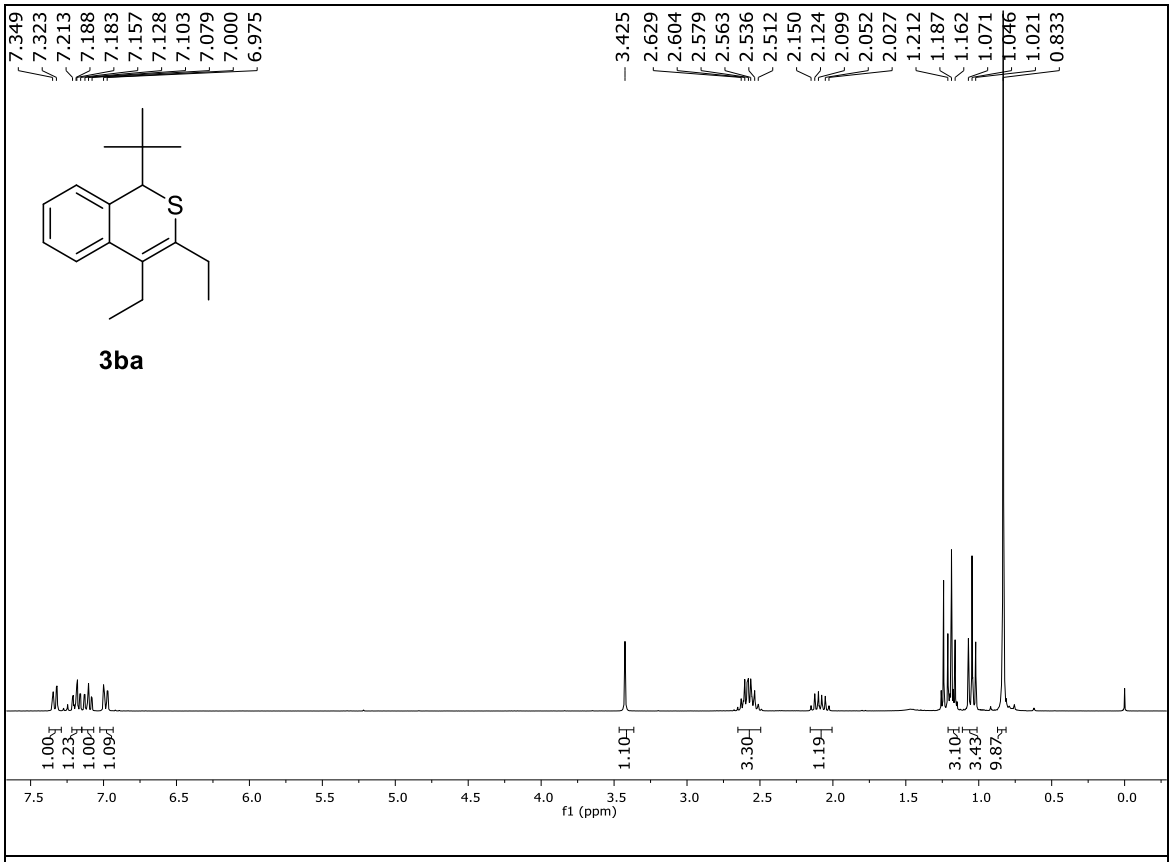
^{13}C NMR spectrum of **3ab**



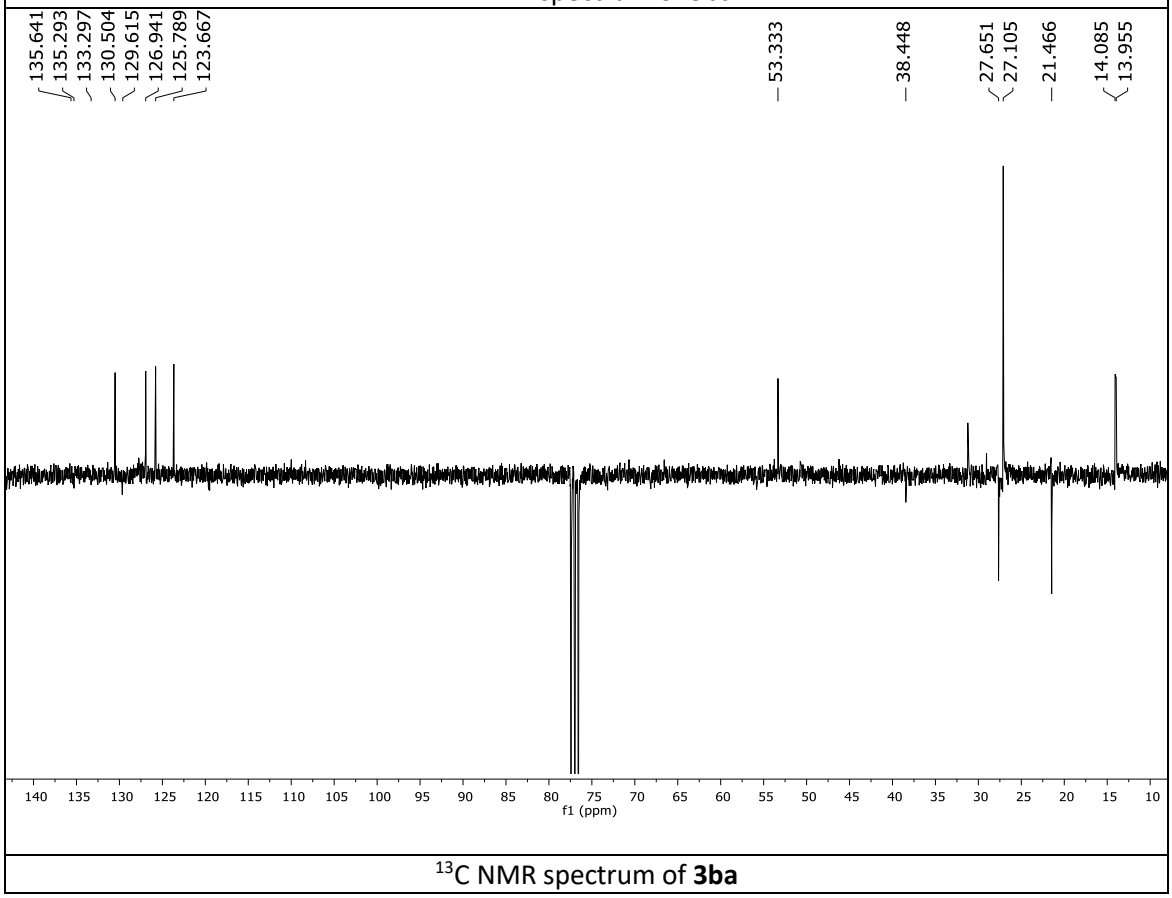
^{1}H NMR spectrum of **3ac1** and **3ac2**



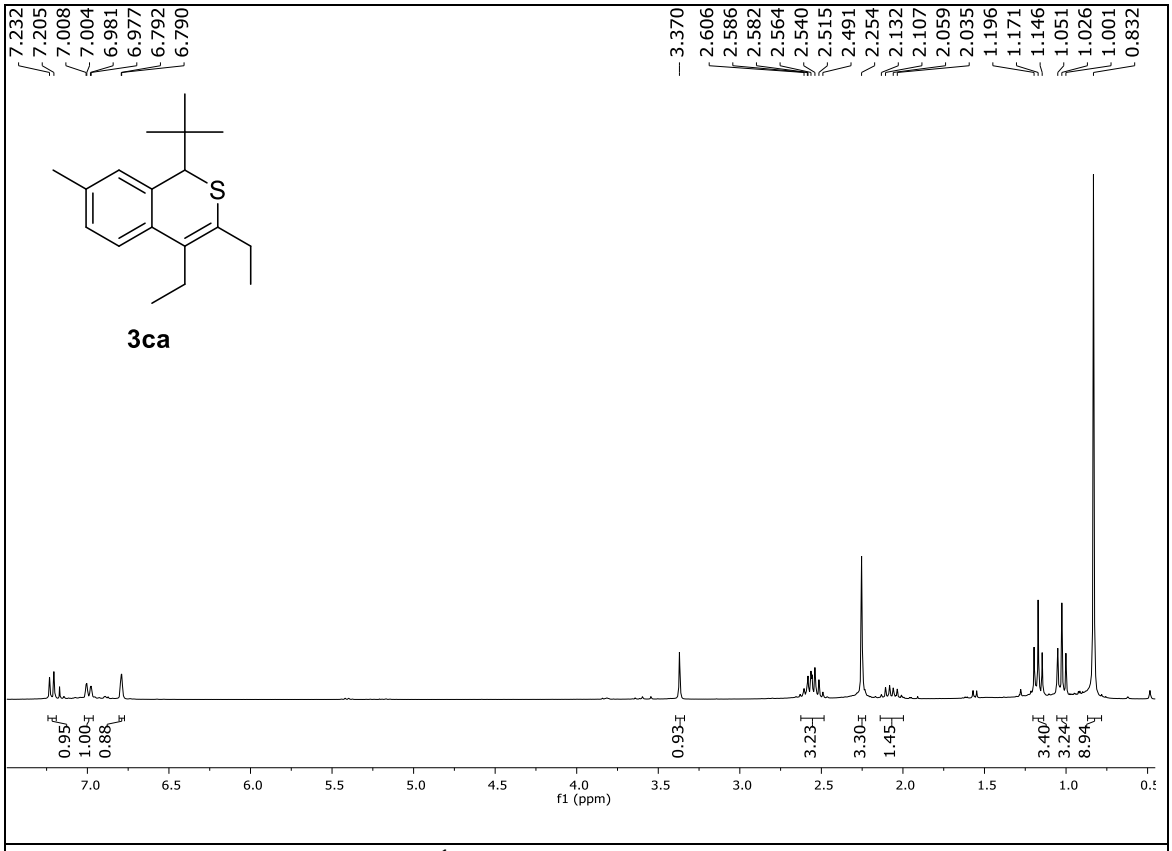
^{13}C NMR spectrum of **3ac1** and **3ac2**



^{1}H NMR spectrum of **3ba**

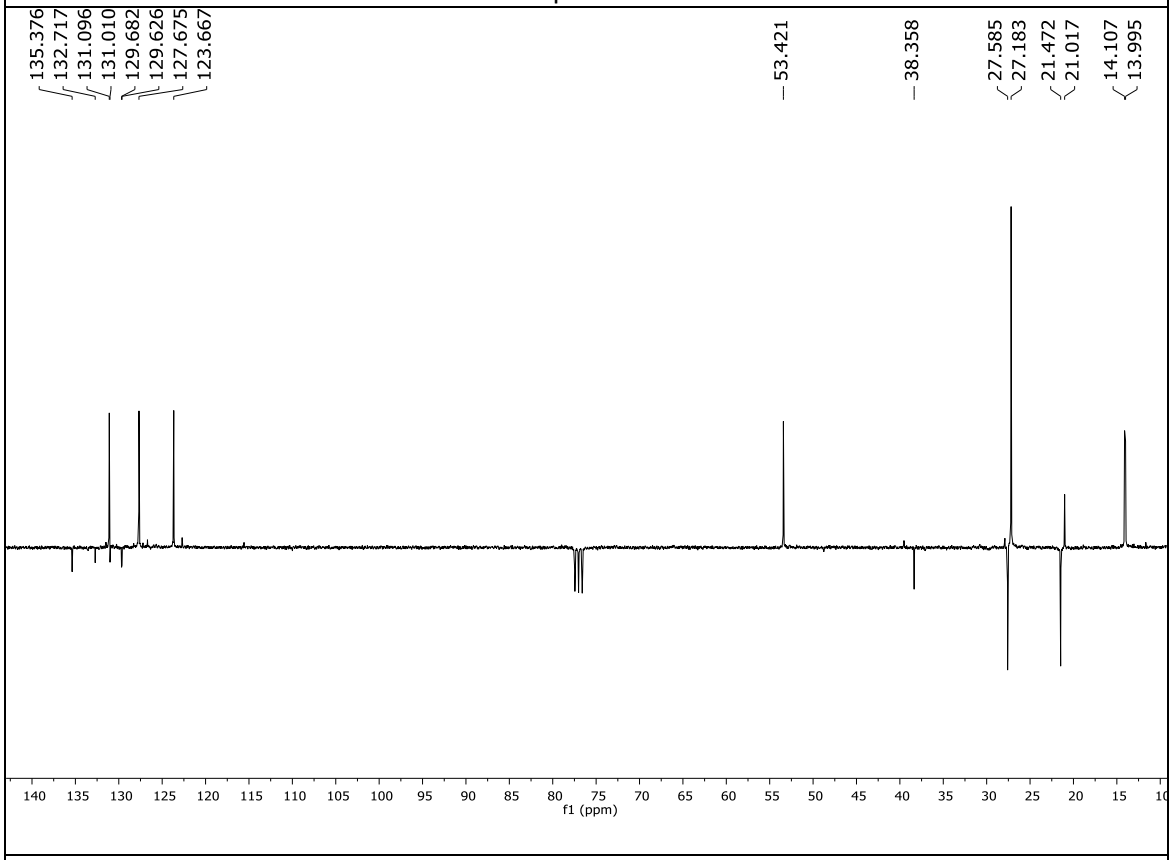


^{13}C NMR spectrum of **3ba**

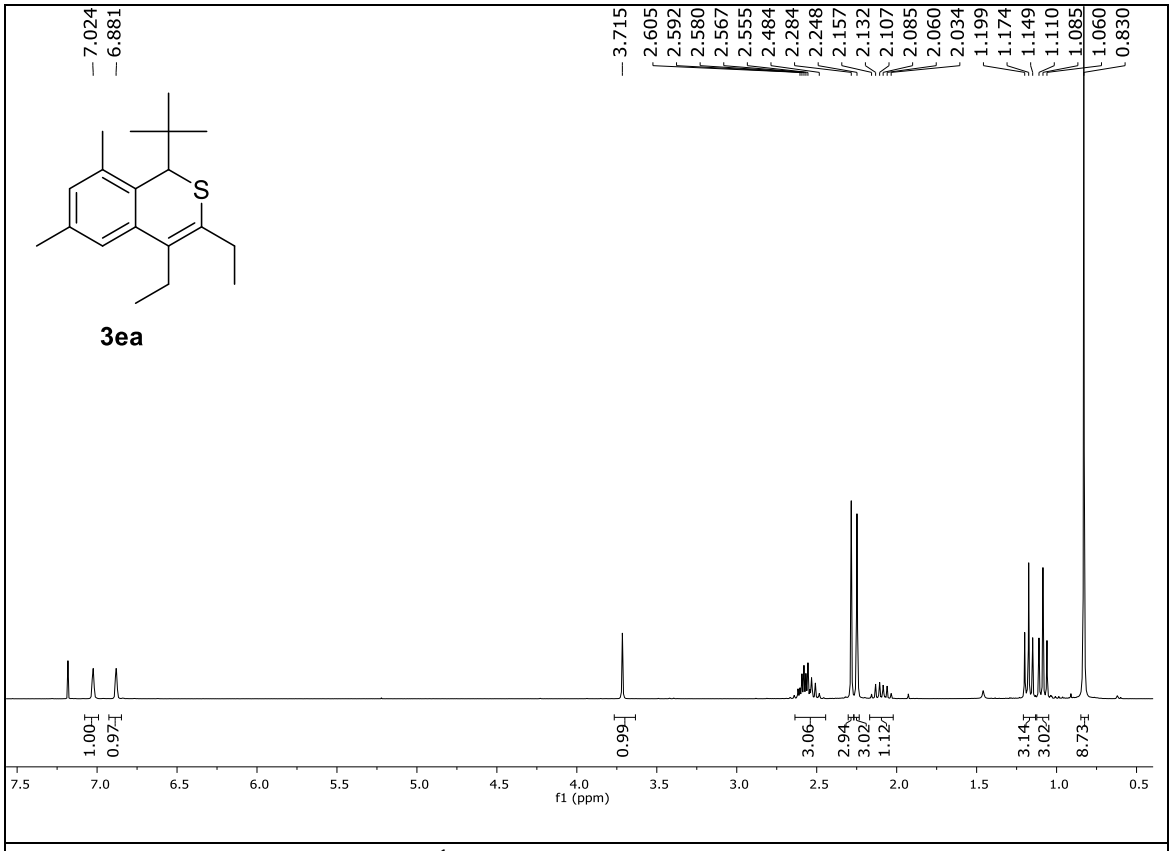


3ca

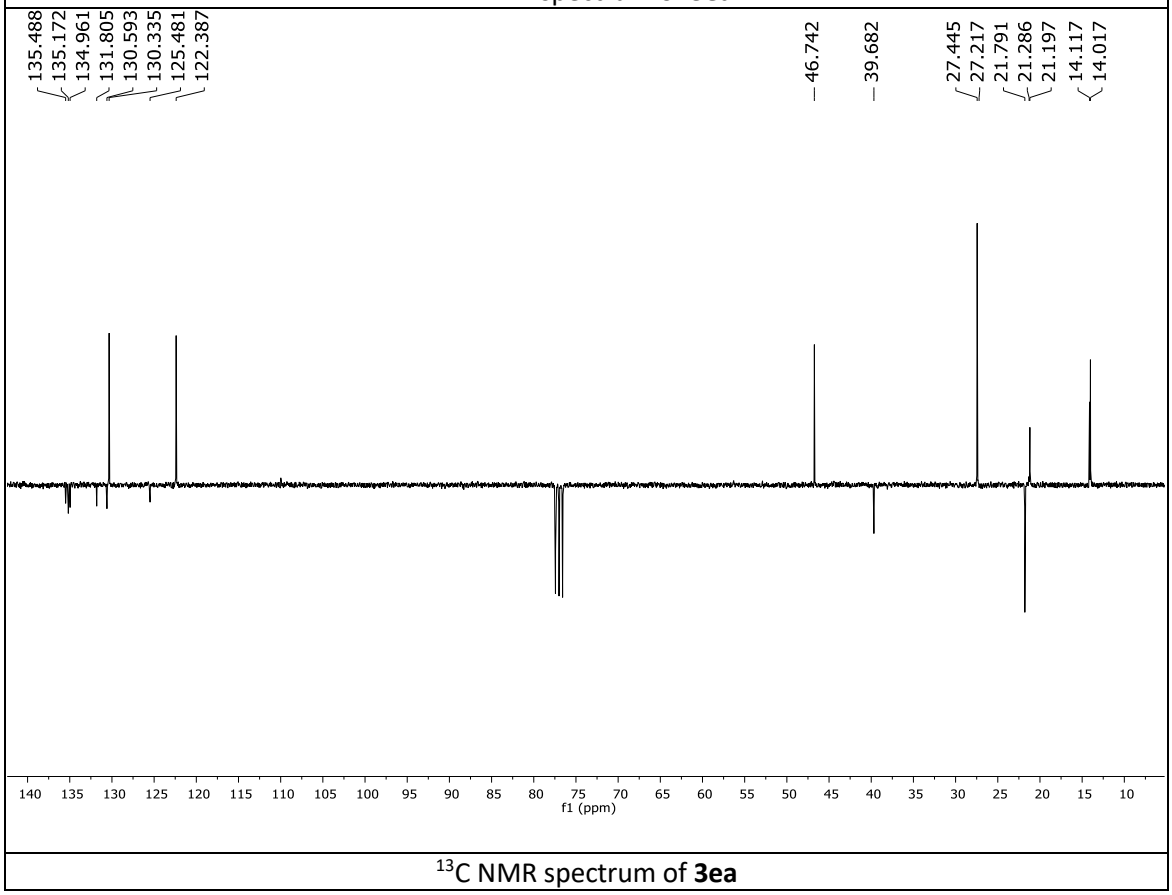
^{1}H NMR spectrum of **3ca**



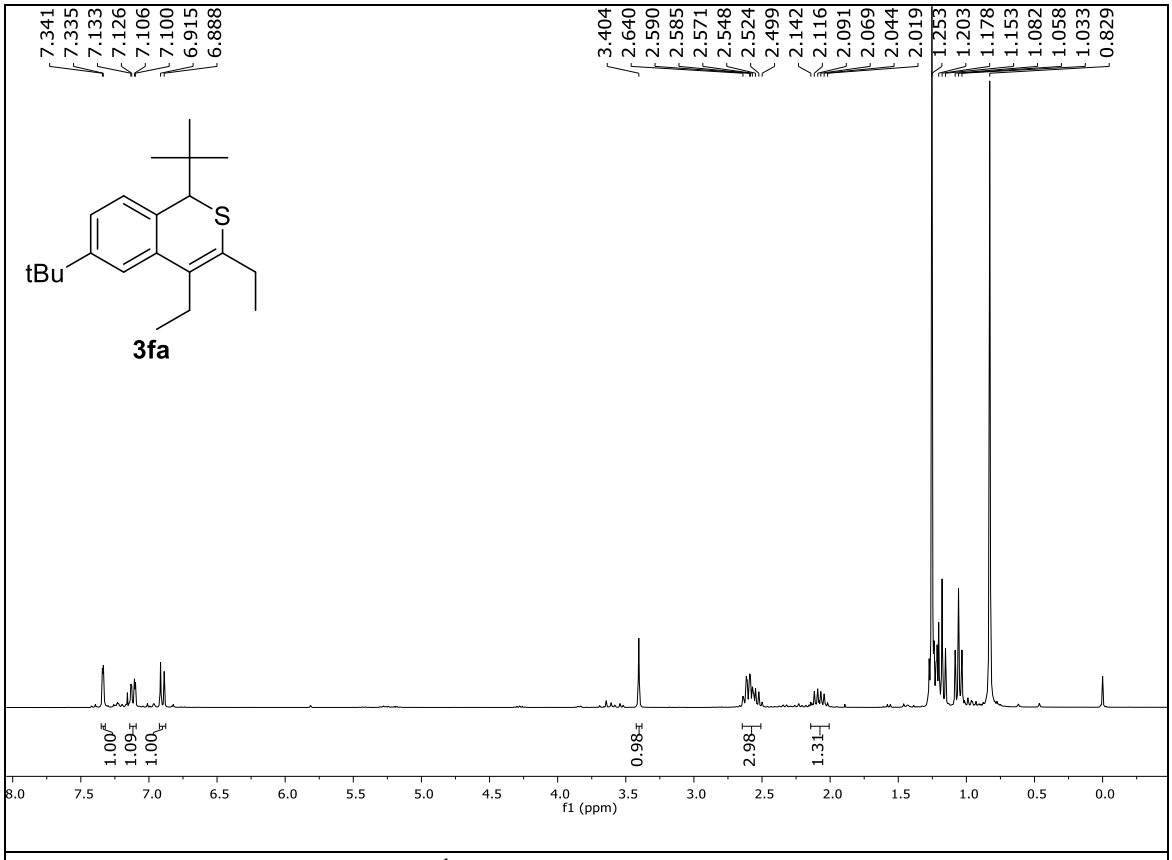
^{13}C NMR spectrum of **3ca**



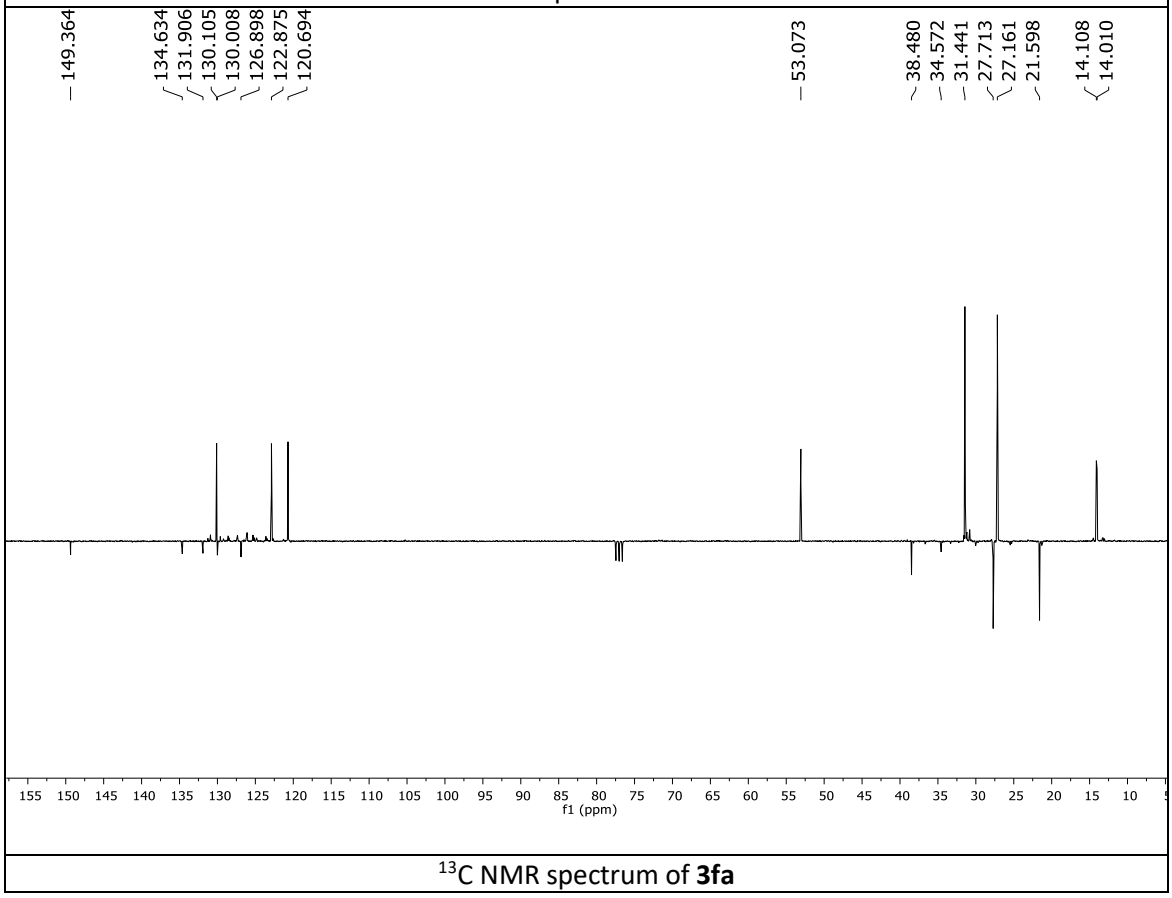
^{1}H NMR spectrum of **3ea**



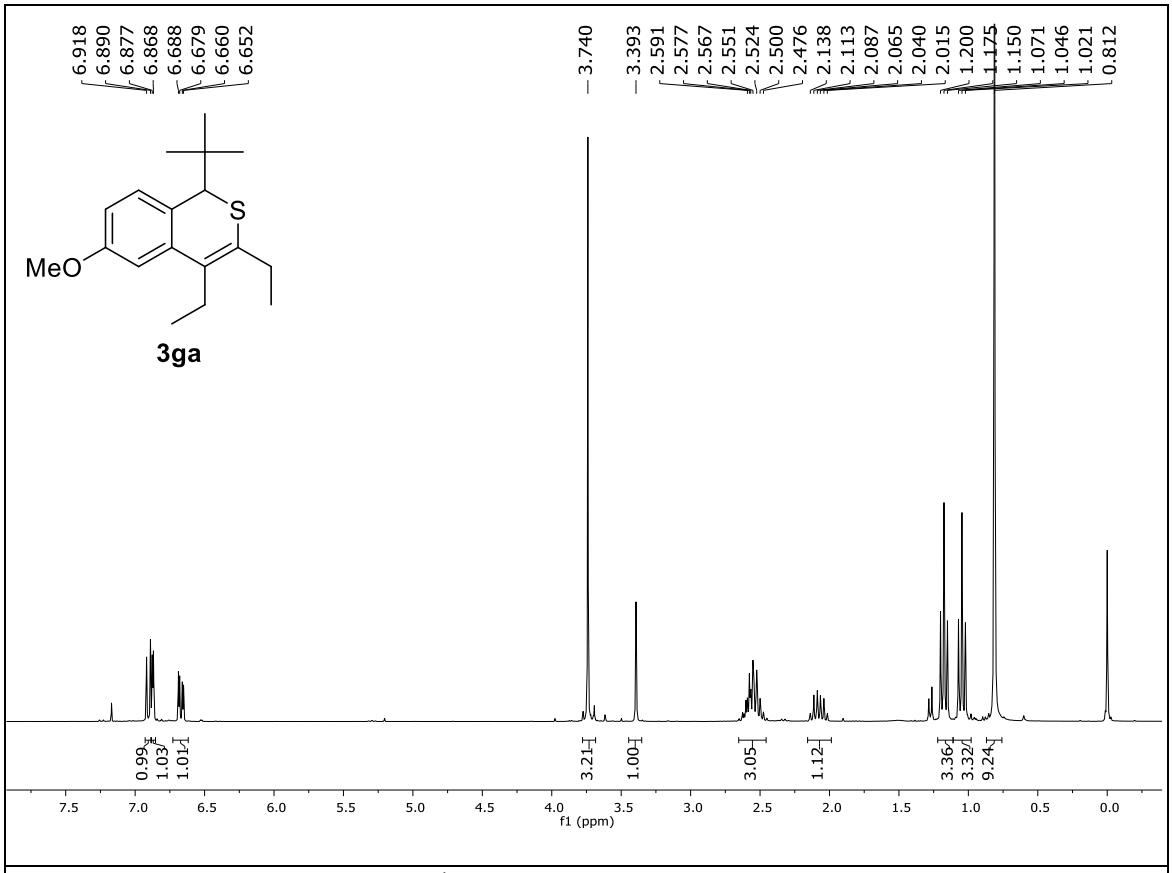
^{13}C NMR spectrum of **3ea**



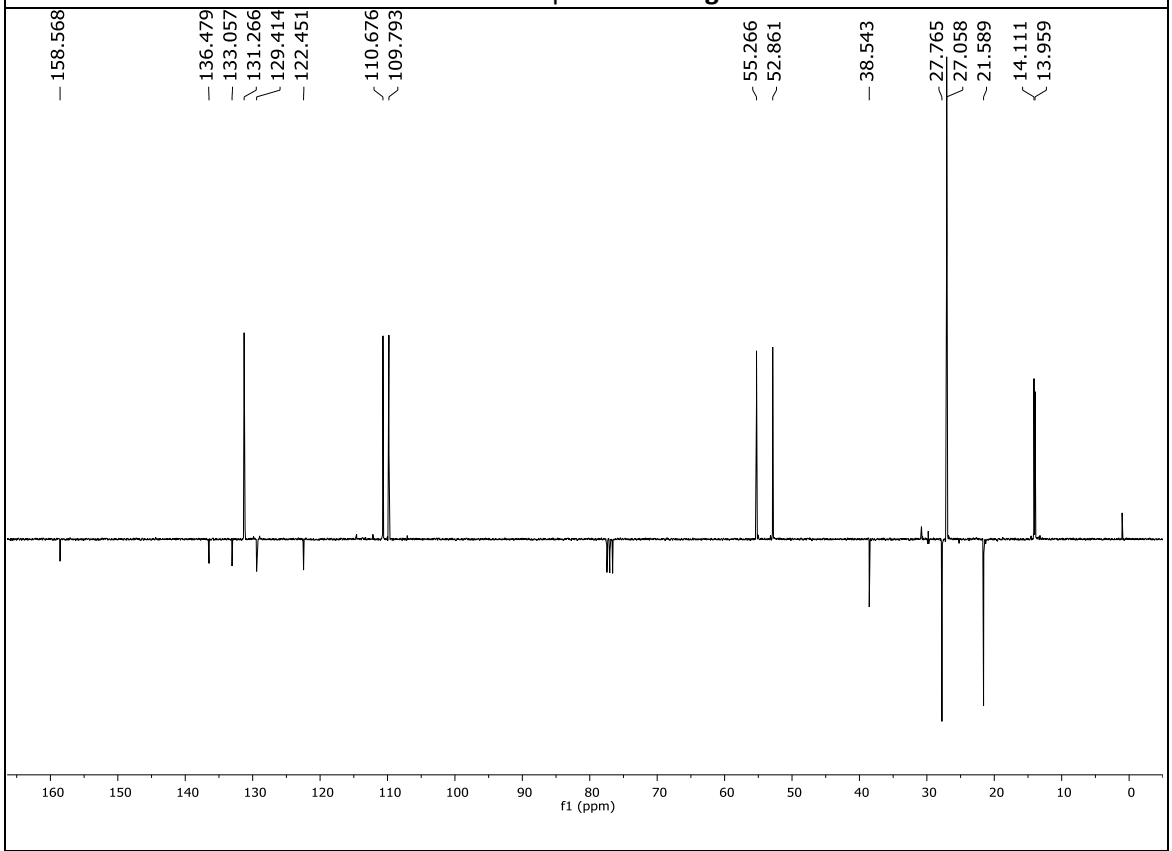
^{1}H NMR spectrum of **3fa**



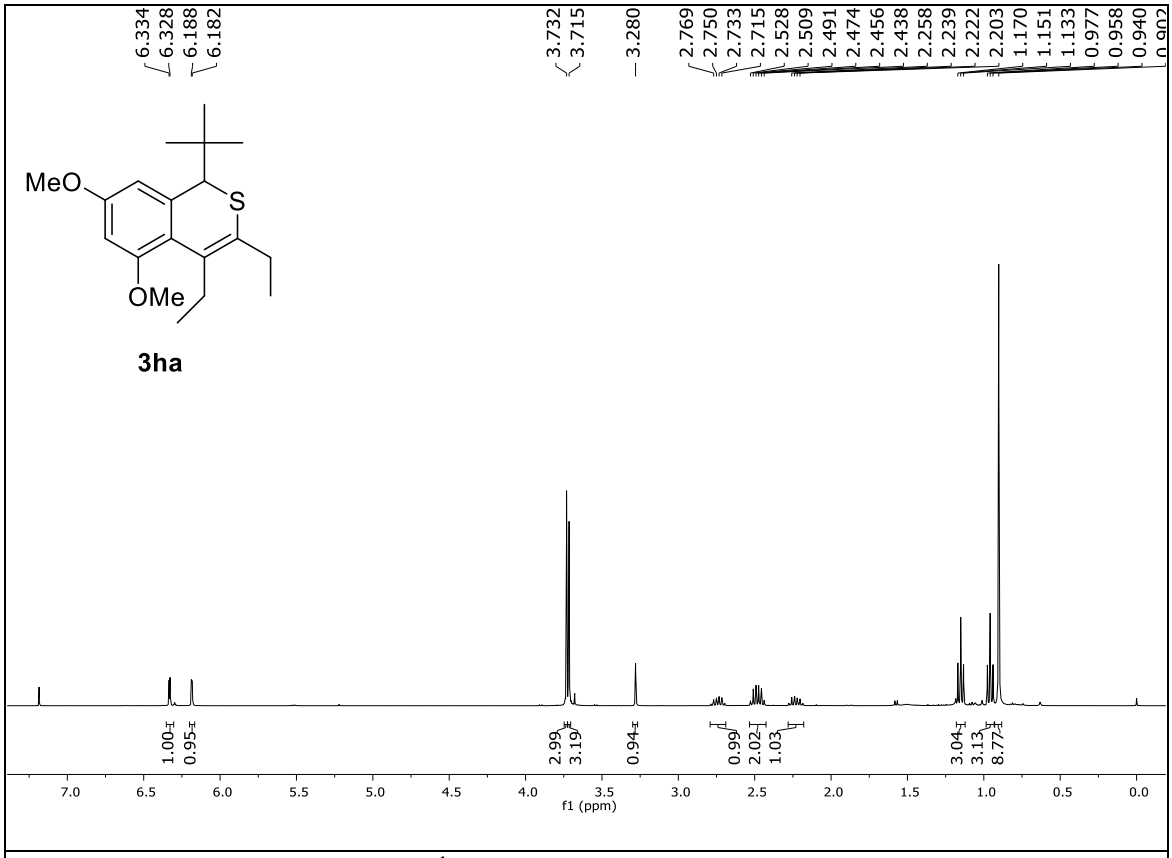
^{13}C NMR spectrum of **3fa**



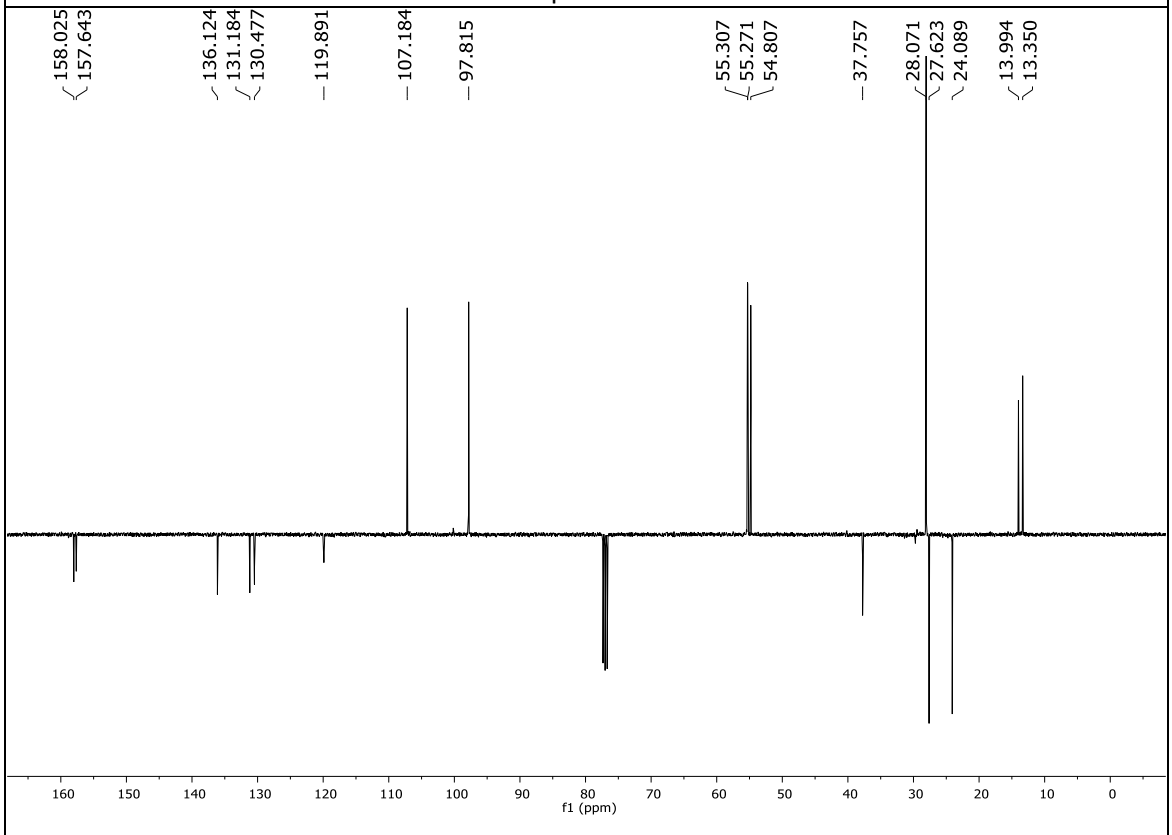
^{1}H NMR spectrum of **3ga**



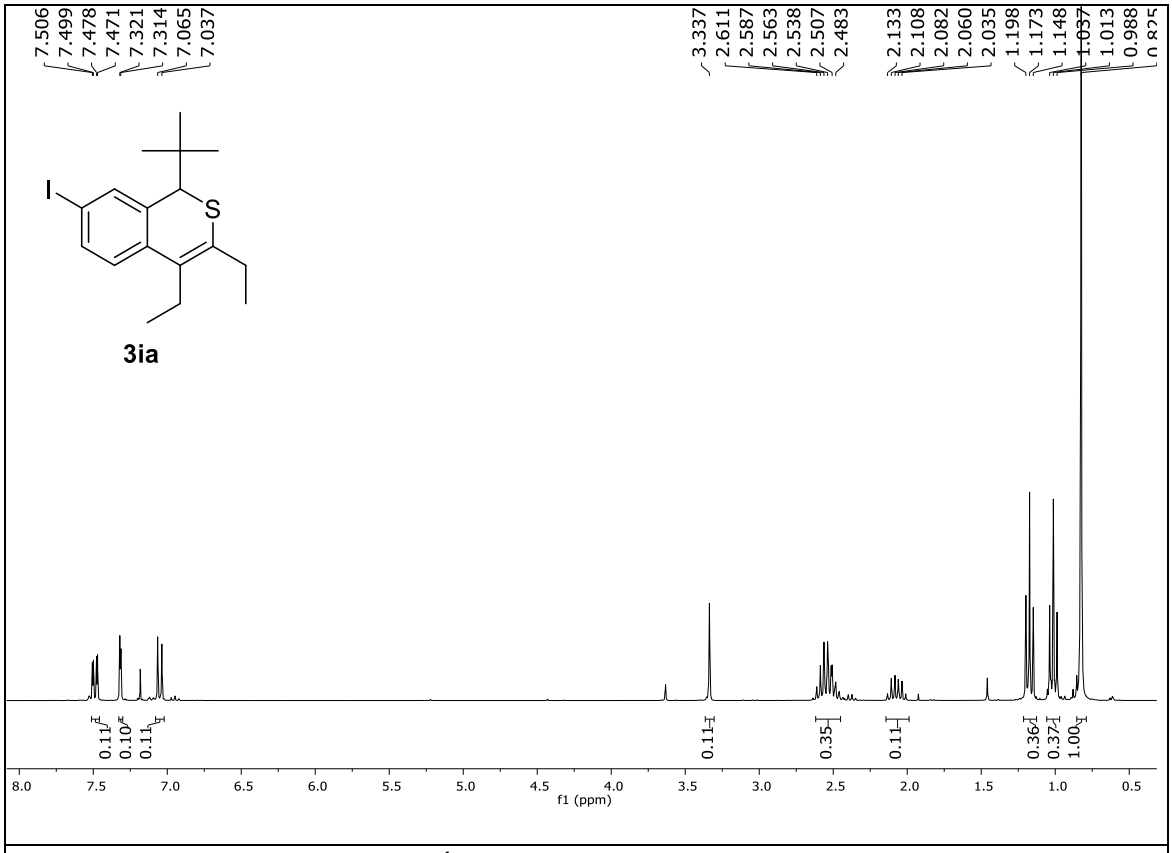
^{13}C NMR spectrum of **3ga**



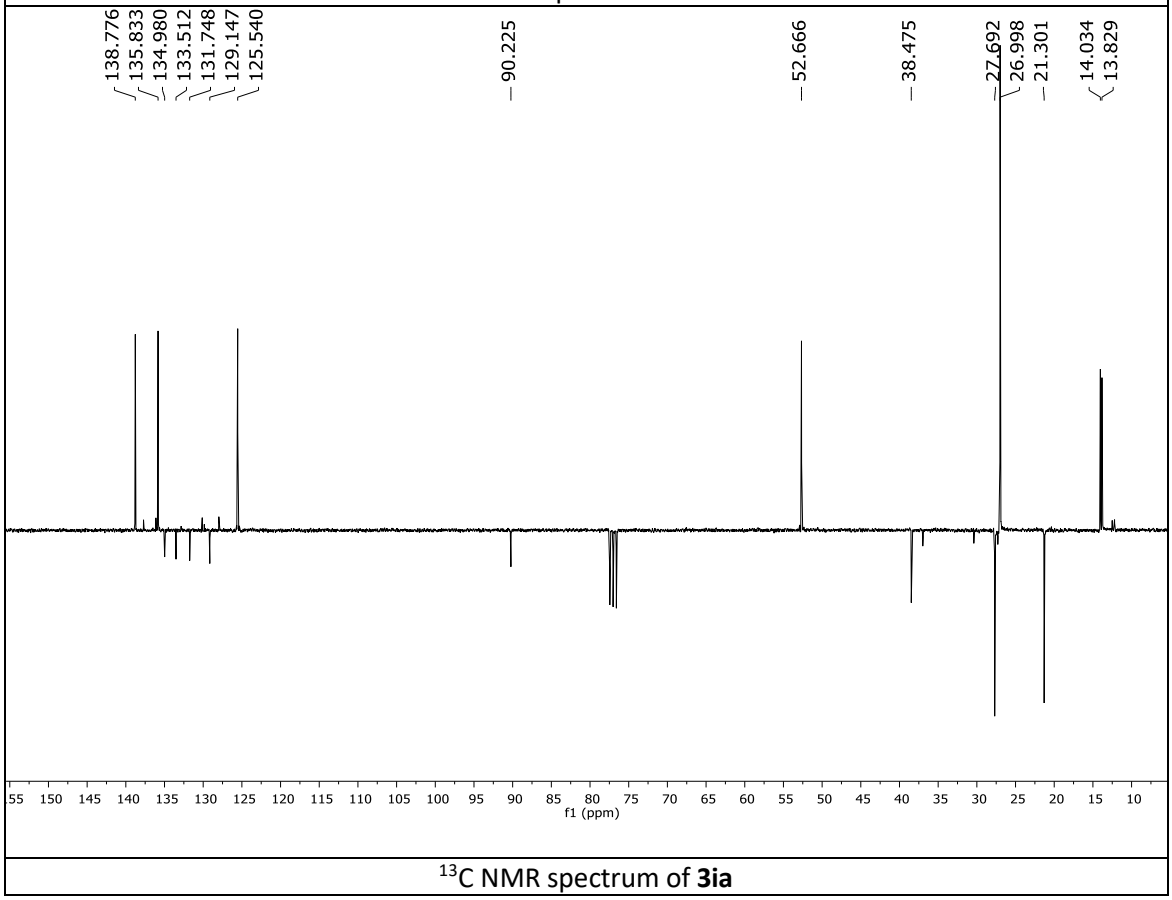
^{1}H NMR spectrum of **3ha**



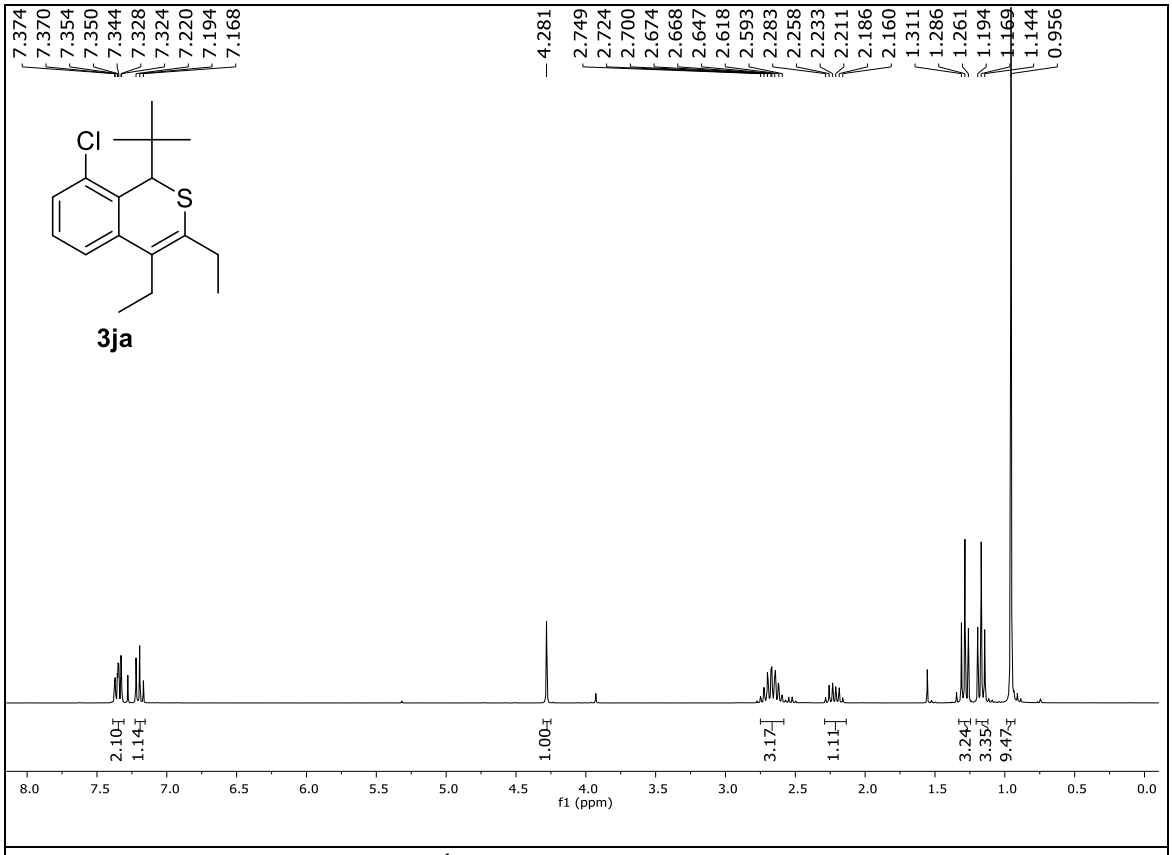
^{13}C NMR spectrum of **3ha**



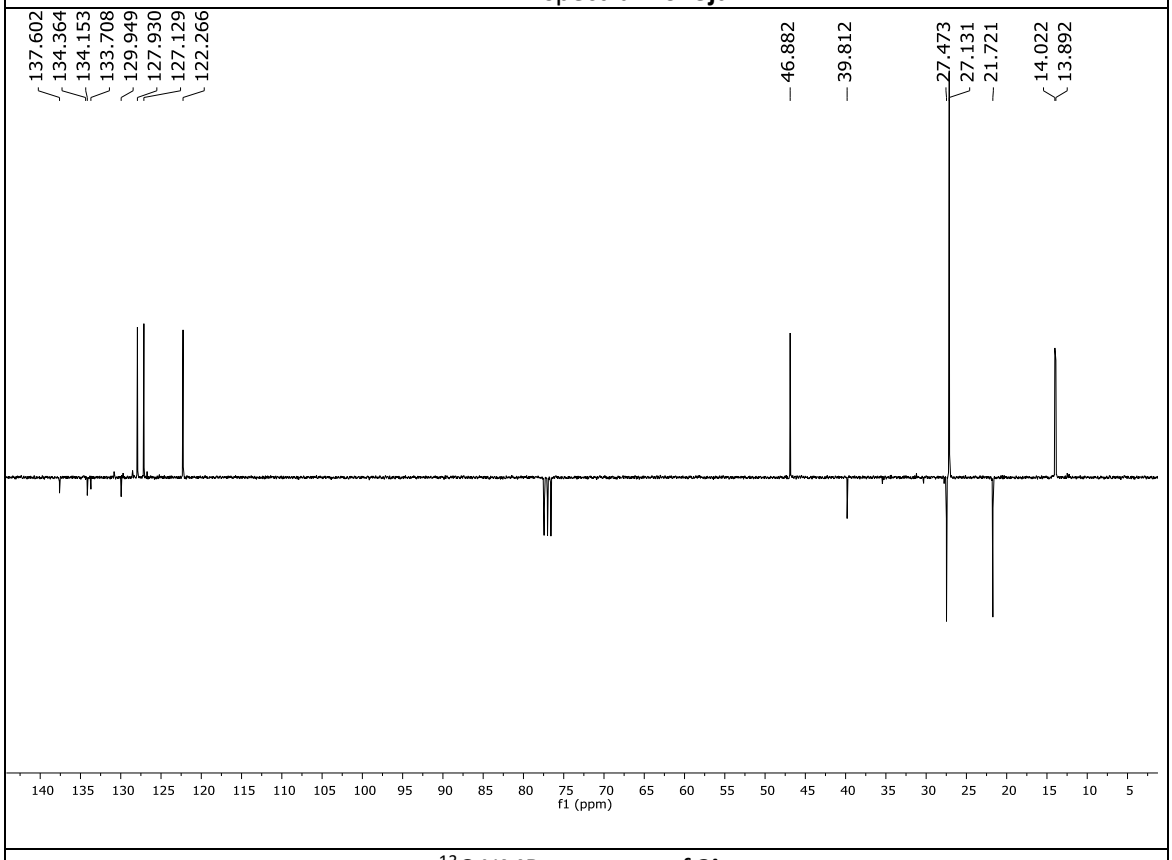
^{1}H NMR spectrum of **3ia**



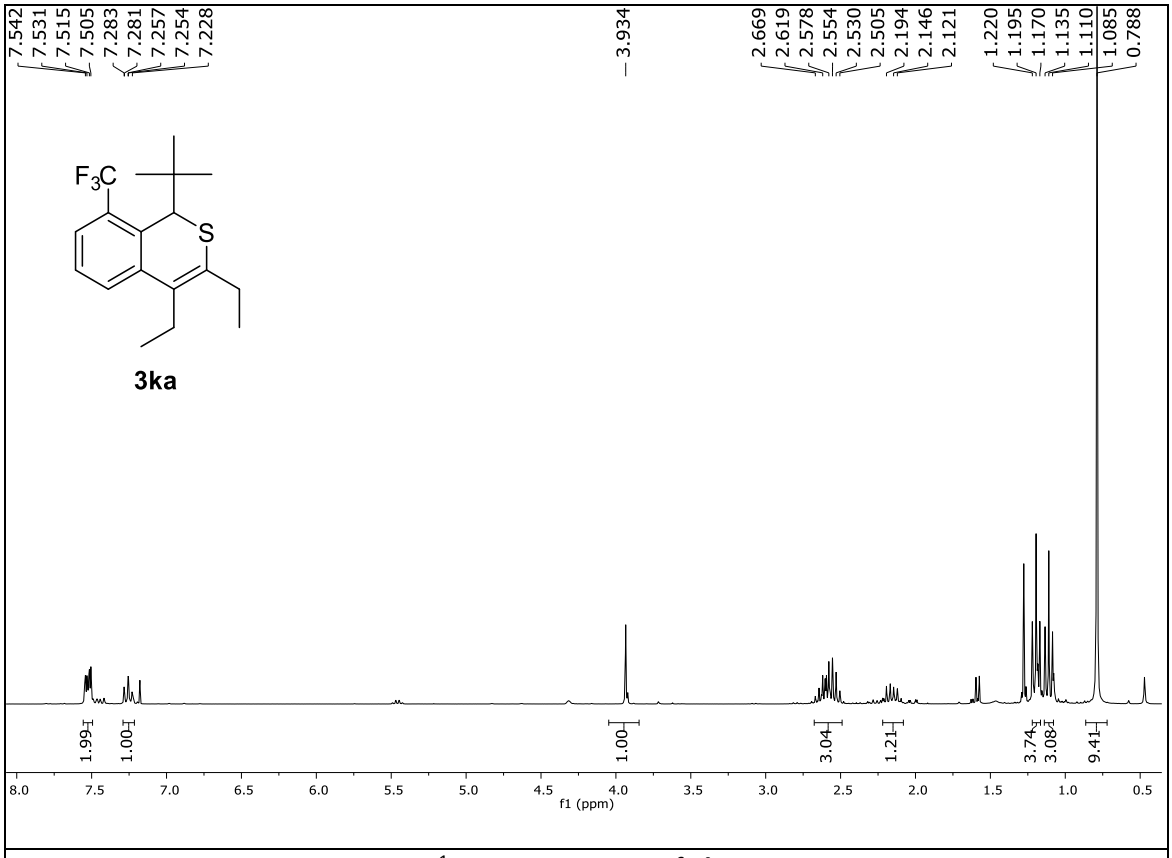
^{13}C NMR spectrum of **3ia**



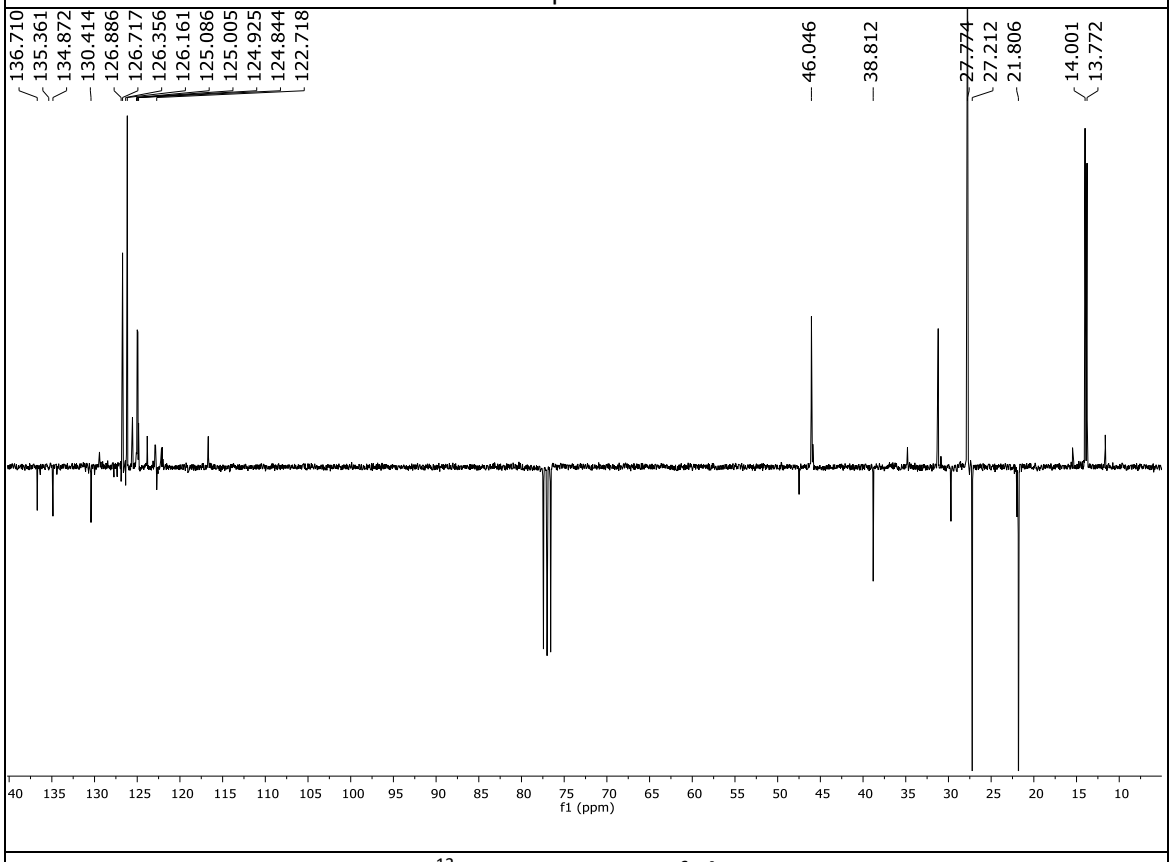
^{1}H NMR spectrum of **3ja**



^{13}C NMR spectrum of **3ja**



^{1}H NMR spectrum of **3ka**



^{13}C NMR spectrum of **3ka**