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Supporting information

Copper-Catalysed Cross-Coupling Affected by the Smiles Rearrangement: A New Chapter on Diversifying the Synthesis of Chiral Fluorinated 1,4-Benzoxazine Derivatives

Saba Alapour,[†] Deresh Ramjugernath,[‡] and Neil A. Koorbanally*,[†]

[†] School of Chemistry, University of KwaZulu-Natal, Private Bag X54001, Durban 4000, South Africa

[‡] School of Chemical Engineering, University of KwaZulu-Natal, Private Bag X54001, Durban 4000, South Africa

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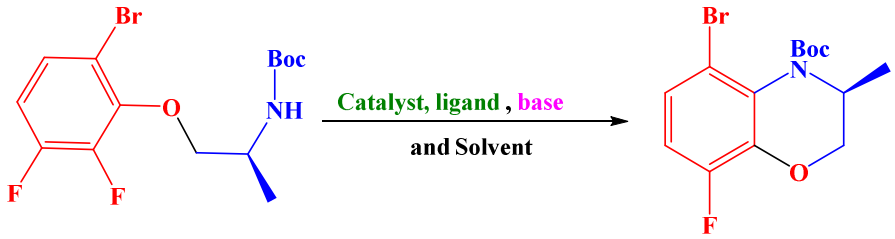
General

Material and Methods

Reagents and solvents were purchased from Sigma Aldrich and used as received. Commercially available Merck Kieselgel 60 F_{254} aluminium backed plates were used for TLC analysis. Visualisation of TLC plates was achieved by UV fluorescence and iodine vapour. Compounds were purified by column chromatography packed with 60-200 mesh Silica gel.

All NMR spectra were recorded on Bruker AVANCE III 400 or 600 MHz instruments. Chemical shifts are quoted in parts per million (ppm) downfield from TMS as the internal standard and the coupling constants are reported in Hertz. Multiplicities of the NMR resonances are abbreviated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Assignments of ^{1}H NMR, ^{13}C NMR and ^{19}F NMR resonances were made with the aid of COSY, NOESY, HMBC and HSQC experiments. High resolution spectrometric data were obtained using a Waters micromass LCT premier TOF-MS instrument. Infra-red spectra were recorded in the range 4000-600 cm^{-1} on a Perkin Elmer Spectrum as neat films onto a NaCl window. Elemental analysis was carried out on a Thermo Scientific Flash 2000. Melting points were obtained on a Stuart Melting Point apparatus SMP11 and are uncorrected. Abbreviations used are: w (weak), m (medium), s (strong) and br (broad). Optical rotations were measured using a Perkin-Elmer 341 polarimeter.

Table 1. Optimization of conditions for formation of Boc-[1,4]benzoxazine.

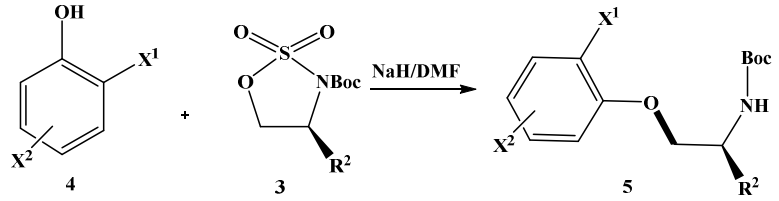


No.	cat.	ligand	base	solvent	temp.[a]	yield[b,c]
Solvent optimisation						
1	$Cu(OAc)_2.H_2O$	none	Cs_2CO_3	THF	90	trace
2	$Cu(OAc)_2.H_2O$	none	Cs_2CO_3	toluene	90	trace
3	$Cu(OAc)_2.H_2O$	none	Cs_2CO_3	dioxan	90	75
4	$Cu(OAc)_2.H_2O$	none	Cs_2CO_3	DMSO	90	75
5	$Cu(OAc)_2.H_2O$	none	Cs_2CO_3	DMF	90	95
6	$Cu(OAc)_2.H_2O$	none	Cs_2CO_3	NMP	90	98
catalyst optimisation						
7	CuBr	none	Cs_2CO_3	NMP	90	60
8	CuI	none	Cs_2CO_3	NMP	90	66
9	$CuSO_4$	none	Cs_2CO_3	NMP	90	79
10	$Cu(OAc)_2.H_2O$	none	Cs_2CO_3	NMP	90	98
11	none	none	Cs_2CO_3	NMP	90	None
Base optimisation						
12	$Cu(OAc)_2.H_2O$	none	None	NMP	90	none
13	$Cu(OAc)_2.H_2O$	none	TEA[d]	NMP	90	trace
14	$Cu(OAc)_2.H_2O$	none	$NaOC(CH_3)_3$	NMP	90	73
15	$Cu(OAc)_2.H_2O$	none	KOH	NMP	90	80
16	$Cu(OAc)_2.H_2O$	none	K_2CO_3	NMP	90	87
17	$Cu(OAc)_2.H_2O$	none	Cs_2CO_3	NMP	90	98
Ligand optimisation						
18	$Cu(OAc)_2.H_2O$	1,2-diamine	Cs_2CO_3	NMP	90	80
19	$Cu(OAc)_2.H_2O$	Hyp[e]	Cs_2CO_3	NMP	90	83
20	$Cu(OAc)_2.H_2O$	xantphos	Cs_2CO_3	NMP	90	85
21	$Cu(OAc)_2.H_2O$	*L*-proline	Cs_2CO_3	NMP	90	90
22	$Cu(OAc)_2.H_2O$	none	Cs_2CO_3	NMP	90	98
Temperature optimisation						
23	$Cu(OAc)_2.H_2O$	none	Cs_2CO_3	NMP	25	90

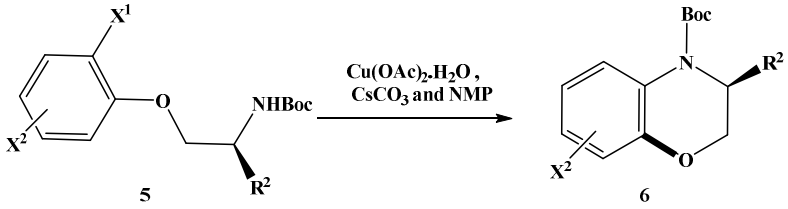
[a] Temperature (°C). [b] Isolated yield (%). [c] The reaction time for all reactions is 24 hours. [d] TEA: triethylamine [e] Hyp: *trans*-4-Hydroxy-*L*-proline

Experimental Procedures

Compounds **2-4** were prepared according to standard procedures reported in the literature.[1, 2]

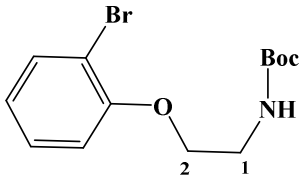


General experimental procedure for the preparation of adduct 5: NaH (60 % dispersion in mineral oil, 40 mg, 1.01 mmol) was added to a solution of phenol **4** (211 mg, 1.01 mmol) in anhydrous DMF (10 mL) and the resultant mixture stirred at r.t. for 5 minutes. Cyclic sulfamidate **3** (200 mg, 0.84 mmol) was added and the mixture stirred at r.t. for 15 h prior to being concentrated in vacuo. The mixture was washed with saturated aq. NaCl and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were concentrated in vacuo to afford amine **5**. This material was suitable for subsequent applications without any further purification. For analysis, a small portion was isolated by Column chromatography (EtOAc/hexane: 5:95).



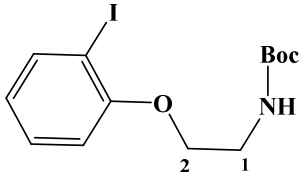
General experimental procedure for the preparation of dihydrobenzo[1,4]oxazines 6: In a 10 mL round bottom flask, $Cu(OAc)_2.H_2O$ (0.2 equiv), Cs_2CO_3 (3 equiv), and compound **5** (60 mg) were dissolved in NMP (5.0 mL). The mixture was stirred at 90 °C, and the progress of the reaction monitored by TLC. After 24 h the solvent was evaporated in vacuo and the residue diluted with CH_2Cl_2 (20 mL), washed with water (2×10 mL) and brine (2×10 mL), dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography (EtOAc/hexane: 10:90) to afford Boc-benzoxazine **6**.

Characterisation data for compounds 5a-i and 6a, 6c, 6d and 6f



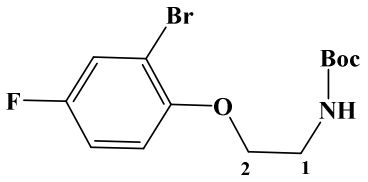
***tert*-butyl (2-(2-bromophenoxy)ethyl)carbamate (5a)**:

colourless oil; ν_{max} /cm^{-1}(film) 3441 (m), 2978 (m), 2934 (m), 1712 (s), 1587 (m), 1574 (m), 1509 (s), 1481 (s), 1278 (m), 1057 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.41 (9H, s, $NCO_2C(C\underline{H}_3)_3$), 3.51 (2H, m, 2C1-<u>H</u>), 4.00 (2H, t, 2C2-<u>H</u> , *J*=5.2), 5.24 (1H, br s, N<u>H</u>), 6.79 (2H, m, Ar<u>C</u>H), 7.18 (1H, m, Ar<u>C</u>H), 7.46 (1H, dd, *J*=7.8, 1.5 Hz, Ar<u>C</u>H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 28.4 ($NCO_2C(\underline{C}H_3)_3$), 40.0 (<u>C</u>-1), 68.5 (<u>C</u>-2), 76.9 ($NCO_2\underline{C}(CH_3)_3$), 113.7 (Ar<u>C</u>H), 122.3 (Ar<u>C</u>H), 128.5 (Ar<u>C</u>H), 133.2 (Ar<u>C</u>H), 154.9 (s, C=O). The signals for the two aromatic quaternary carbons were not observed in the ^{13}C NMR spectrum. HRMS–ES$^+$: *m/z* [M+Na] calcd for $C_{13}H_{18}BrNO_3$: 338.0368, found: 338.0376.



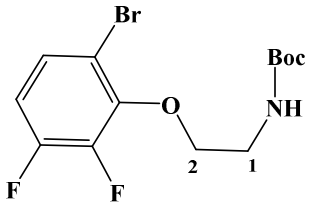
***tert*-butyl (2-(2-iodophenoxy)ethyl)carbamate (5b)**:

colourless oil; ν_{max}/cm^{-1}(film) 3355 (m), 2977 (m), 2934(m), 1711 (s), 1582(m), 1520 (s), 1475 (s), 1276 (m), 1247 (s), 1056 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.37 (9H, s, $NCO_2C(C\underline{H}_3)_3$), 3.49 (2H, m, 2C1-<u>H</u>), 3.96 (2H, t, 2C2-<u>H</u> , *J*=5.1 Hz), 5.08 (1H, br, s, N<u>H</u>), 6.63 (1H, td, Ar<u>C</u>H, *J*=7.6, 1.0 Hz), 6.71 (1H, dd, Ar<u>C</u>H, *J*=7.3, 0.8 Hz), 7.18 (1H, m, Ar<u>C</u>H), 7.67 (1H, td, Ar<u>C</u>H, *J*=7.8, 1.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 28.4 ($NCO_2C(\underline{C}H_3)_3$), 40.0 (<u>C</u>-1), 68.6 (<u>C</u>-2), 79.5 ($NCO_2\underline{C}(CH_3)_3$), 86.8 (Ar<u>C</u>-I), 112.5 (Ar<u>C</u>H), 123.0 (Ar<u>C</u>H), 129.6, (Ar<u>C</u>H), 139.4 (Ar<u>C</u>H), 155.9 (s, C=O), 157.0 (Ar<u>C</u>). HRMS–ES$^+$: *m/z* [M+Na] calcd for $C_{13}H_{18}INO_3$: 386.0229; found: 386.0230.



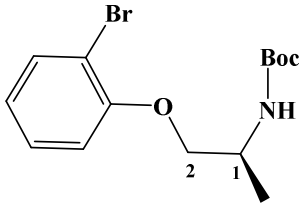
***tert*-butyl (2-(2-bromo-4-fluorophenoxy)ethyl)carbamate (5c)**:

colourless oil; ν_{max}/cm^{-1}(film) 3356 (m), 2979 (m), 2935 (m), 1712 (s), 1593 (m), 1493 (s), 1257 (m), 1171 (m), 1048 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.37 (9H, s, $NCO_2C(C\underline{H}_3)_3$), 3.47 (2H, m, 2C1-H), 3.95 (2H, t, 2C2-H , *J*=5.0 Hz), 5.06 (1H, br, s, NH), 6.76 (1H, dd, ArCH, *J*=9.0, 4.7 Hz), 6.88 (1H, m, ArCH), 7.20 (1H, dd, ArCH, *J*=7.8, 3.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 28.4 ($NCO_2C(\underline{C}H_3)_3$), 40.0 (C-1), 69.4 (C-2), 79.6 ($NCO_2\underline{C}(CH_3)_3$), 114.3 (d, *J*= 8.3 Hz, Ar<u>C</u>H), 114.8 (d, *J*= 22.5 Hz, Ar<u>C</u>H), 120.4 (d, *J*= 25.7 Hz, Ar<u>C</u>H), 151.6 (d, *J*=2.9 Hz, ArC), 156.0 (s, 2C, C=O, ArC-O),156.9 (d, *J*=243.5 Hz, Ar<u>C</u>). HRMS–ES$^+$: *m/z* [M+Na] calcd for $C_{13}H_{17}BrFNO_3$: 356.0274; found: 356.0276.



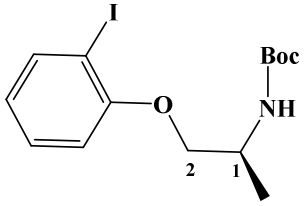
***tert*-butyl (2-(6-bromo-2,3-difluorophenoxy)ethyl)carbamate (5d):**

colourless oil; ν_{max}/cm^{-1}(film) 3359 (m), 2979 (s), 2934 (s), 1705 (s), 1612 (m), 1584 (m), 1487 (s), 1292 (m), 1171 (s), 1054 (m). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.36 (9H, s, $NCO_2C(CH_3)_3$), 3.43 (2H, m, 2C1-H), 4.10 (2H, t, 2C2-H , J=4.98), 5.24 (1H, br, s, NH), 6.73 (1H, ddd, ArCH, *J*=9.2, 9.12, 7.7), 7.15 (1H, ddd, ArCH, *J*=9.0, 5.4, 2.5). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 28.4 ($NCO_2C(CH_3)_3$), 40.6 (C-1), 73.6 (C-2), 79.4 ($NCO_2C(CH_3)_3$), 112.6 (d, *J*= 18.3, ArCH), 126.7 (dd, *J*= 7.5, 4.2, ArCH), 144.9 (dd, *J*= 250.9, 14.3, ArC), 145.4 (d, *J*=8.2, ArC), 150.5 (dd, *J*=250.2, 11.3, ArC), 155.9 (ArC). HRMS–ES$^+$: *m/z* [M+Na] calcd for $C_{13}H_{17}BrFNO_3$: 374.0179; found: 374.0189.



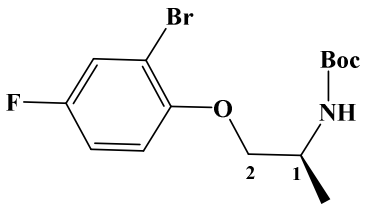
***tert*-butyl (*S*)-(1-(2-bromophenoxy)propan-2-yl)carbamate (5e)**:

colourless crystal; mp 53-55 ºC; $[\alpha]_D^{20}$ -32.20º (c=0.35 , MeOH); ν_{max}/cm^{-1}(film) 3431 (m), 2978 (s), 2934 (m), 1715 (s), 1586 (m), 1574 (m), 1504 (s), 1483 (s), 1169 (m), 1053 (m). ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 1.32 (3H, d, *J*=6.8 Hz, C1-C$\underline{H}_3$), 1.43 (9H, s, $NCO_2C(C\underline{H}_3)_3$), 3.95 (1H, s, br, C1-$\underline{H}$), 4.07 (2H, s, br, 2C2-$\underline{H}$), 5.01 (1H, br, s, N$\underline{H}$), 6.80 (1H, t, *J*=7.6 Hz, ArC$\underline{H}$), 6.85 (1H, d, *J*=8.2 Hz, ArC$\underline{H}$), 7.20 (1H, t, *J*=7.7 Hz, ArC$\underline{H}$), 7.49 (1H, d, *J*=7.8 Hz, ArC$\underline{H}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 17.9 (C1-$\underline{C}H_3$), 28.4 ($NCO_2C(\underline{C}H_3)_3$), 45.8 ($\underline{C}$-1), 72.1 ($\underline{C}$-2), 113.4 (Ar$\underline{C}$H), 122.2 (Ar$\underline{C}$H), 122.4 (Ar$\underline{C}$), 128.5 (Ar$\underline{C}$H), 133.3 (Ar$\underline{C}$H), 155.0 (s, 2C, C=O, ArC-O). The signal for the quaternary Boc carbon was not observed in the ^{13}C NMR spectrum. HRMS–ES$^+$: *m/z* [M+Na] calcd for $C_{14}H_{20}BrNO_3$: 352.0524; found: 352.0529.



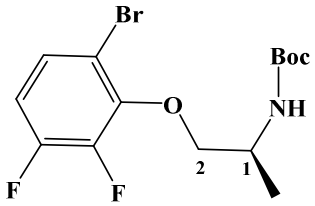
***tert*-butyl (*S*)-(1-(2-iodophenoxy)propan-2-yl)carbamate (5f)**:

colourless crystal; mp 60-62 ºC; $[\alpha]_D^{20}$ -33.7º (c=0.5 , MeOH); ν_{max}/cm^{-1}(film) 3425 (m), 2977 (s), 2933 (m), 1715 (s), 1583 (m), 1571 (m), 1502 (m), 1366 (m), 1246 (s), 1051 (m). ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 1.36 (3H, d, *J*=6.9 Hz, C1-C$\underline{H}_3$), 1.44 (9H, s, $NCO_2C(C\underline{H}_3)_3$), 3.94 (1H, s, br, C1-$\underline{H}$), 4.10 (2H, s, br, 2C2-$\underline{H}$), 5.0 (1H, br, s, N$\underline{H}$), 6.68 (1H, t, *J*=7.5 Hz, ArC$\underline{H}$), 6.76 (1H, d, *J*=8.2 Hz, ArC$\underline{H}$), 7.25 (1H, m, ArC$\underline{H}$), 7.73 (1H, dd, *J*=7.7, 1.3, ArC$\underline{H}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 18.2 (C1-$\underline{C}H_3$), 28.4 ($NCO_2C(\underline{C}H_3)_3$), 45.8 ($\underline{C}$-1), 72.1 ($\underline{C}$-2), 86.6 (ArC-I), 112.2 (Ar$\underline{C}$H), 122.8 (Ar$\underline{C}$H), 129.6 (Ar$\underline{C}$H), 139.3 (Ar$\underline{C}$H), 155.3 (s, C=O), 157.0 (Ar$\underline{C}$-O). The signal for the quaternary Boc carbon was not observed in the ^{13}C NMR spectrum. HRMS–ES$^+$: *m/z* [M+Na] calcd for $C_{14}H_{20}INO_3$: 400.0386; found: 400.0396.



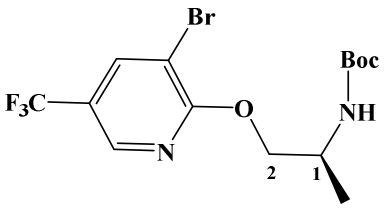
***tert*-butyl (*S*)-(1-(2-bromo-4-Sfluorophenoxy)propan-2-yl)carbamate (5g)**:

colourless oil; $[\alpha]_D^{20}$ -28.25º (c=0.4 , MeOH); ν_{max}/cm^{-1}(film) 3347 (m), 2978 (m), 2934 (m),1699 (s), 1493 (s), 1470 (m), 1392 (m),1367 (m), 1260 (s), 1191 (s), 1046 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.25 (3H, d, *J*=6.7 Hz, C1-C$\underline{H}_3$), 1.37 (9H, s, $NCO_2C(C\underline{H}_3)_3$), 3.86 (2H, d, *J*=3.6 Hz, 2C2-$\underline{H}$), 3.98 (1H, s, C1-$\underline{H}$), 4.82 (1H, br, s, N$\underline{H}$), 6.75 (1H, dd, *J*=9.0, 4.7, ArC$\underline{H}$), 6.87 (1H, m, ArC$\underline{H}$), 7.19 (1H, dd, *J*=7.8, 2.9, ArC$\underline{H}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 17.9 (C1-$\underline{C}H_3$), 28.4 ($NCO_2C(\underline{C}H_3)_3$), 50.5 (C-1), 72.8 (C-2), 114.0 (d, *J*=8.6 Hz, Ar$\underline{C}$H), 114.7 (d, *J*= 22.6 Hz, Ar$\underline{C}$H), 120.4 (d, *J*= 25.8 Hz, Ar$\underline{C}$H), 158.0 (s, C=O). The signals for the quaternary carbons were not observed in the ^{13}C NMR spectrum. HRMS–ES$^+$: *m/z* [M+Na] calcd for $C_{14}H_{19}BrFNO_3$: 370.0430; found: 370.0419.



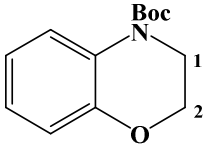
***tert*-butyl (*S*)-(1-(6-bromo-2,3-difluorophenoxy)propan-2-yl)carbamate (5h)**:

colourless crystals; mp 55-57 ºC; $[\alpha]_D^{20}$ -21.7º (c=0.35 , MeOH). ν_{max}/cm^{-1}(film) 3342 (m), 2979 (m), 2933 (m), 1713 (s), 1612 (m), 1584 (m), 1488 (s), 1391 (m), 1367 (m), 1170 (s), 1049 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.28 (3H, d, *J*=6.8 Hz, C1-C$\underline{H}_3$), 1.37 (9H, s, $NCO_2C(C\underline{H}_3)_3$), 3.92 (1H, s, C1-$\underline{H}$), 4.40 (2H, s, 2C2-$\underline{H}$), 4.89 (1H, br, s, N$\underline{H}$), 6.74 (1H, m, ArC$\underline{H}$), 7.18 (1H, m, ArC$\underline{H}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 17.6 (C1-$\underline{C}H_3$), 28.5 ($NCO_2C(\underline{C}H_3)_3$), 46.5 (C-1), 77.0 (C-2), 79.4 ($NCO_2\underline{C}(CH_3)_3$), 111.5 (d, *J*=3.6 Hz, Ar$\underline{C}$), 112.5 (d, *J*= 18.4 Hz, Ar$\underline{C}$H), 126.8 (dd, *J*= 7.6, 4.2 Hz, Ar$\underline{C}$H), 144.9 (dd, *J*= 252.8, 14.3 Hz, Ar$\underline{C}$), 145.6 (dd, *J*=7.9, 2.2 Hz**,** Ar$\underline{C}$), 150.8 (dd, *J*=250.3, 11.4 Hz, Ar$\underline{C}$), 155.3 (s, C=O). HRMS–ES$^+$: *m/z* [M+Na] calcd for $C_{14}H_{18}BrF_2NO_3$: 388.0336; found: 388.0335.



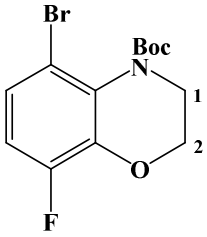
***tert*-butyl (*S*)-(1-((3-bromo-5-(trifluoromethyl)pyridin-2-yl)oxy)propan-2-yl)carbamate (5i)**:

white powder; mp 68-70 ºC; $[\alpha]_D^{20}$ -21.83º (c=0.35 , MeOH); ν_{max}/cm^{-1}(film) 3348 (m), 2979 (m), 2934 (m), 1704 (s), 1604 (m), 1482 (s), 1367 (m), 1320 (m), 1162 (s), 1055 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.22 (3H, d, *J*=6.8 Hz, C1-C<u>H</u>$_3$), 1.37 (9H, s, $NCO_2C(C\underline{H}_3)_3$), 4.07 (1H, s, C1-<u>H</u>), 4.31 (2H, m, 2C2-<u>H</u>), 4.66 (1H, br, s, N<u>H</u>), 7.94 (1H, d., *J*=1.7 Hz, ArC<u>H</u>), 8.27 (1H, s, ArC<u>H</u>); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 17.8 (C1-<u>C</u>H$_3$), 28.4 ($NCO_2C(\underline{C}H_3)_3$), 45.5 (<u>C</u>-1), 70.7 (<u>C</u>-2), 107.4 (Ar<u>C</u>), 121.4 (q, *J*= 33.4 Hz, ArC), 123.0 (q, *J*= 271.6 Hz, <u>C</u>F$_3$), 138.6 (q, *J*= 3.1 Hz, Ar<u>C</u>H), 143.2 (q, *J*= 4.3 Hz, Ar<u>C</u>H), 155.2 (C=O), 161.7 (Ar<u>C</u>-O). HRMS–ES$^+$: *m/z* [M+Na] calcd for $C_{14}H_{18}BrF_3N_2O_3$: 421.0351; Found: 421.0363.



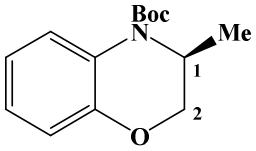
***tert*-butyl 2,3-dihydro-4*H*-benzo[*b*][1,4]oxazine-4-carboxylate (6a)**:

colourless oil; ν_{max}/cm^{-1}(film) 2977 (s), 2932 (s), 1705 (s), 1605 (m), 1586 (m), 1497 (m), 1380 (s), 1148 (s), 1062 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.47 (9H, s, $NCO_2C(C\underline{H}_3)_3$), 3.78 (2H, t, *J*= 4.5 Hz, 2C1-<u>H</u>), 4.17 (2H, t, *J*= 4.4 Hz, 2C2-<u>H</u>), 6.80 (2H, m, ArC<u>H</u>), 6.90 (1H, m, ArC<u>H</u>), 7.70 (1H, m, ArC<u>H</u>); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 28.3 ($NCO_2C(\underline{C}H_3)_3$), 42.1 (<u>C</u>-1), 65.6 (<u>C</u>-2), 81.6 ($NCO_2\underline{C}(CH_3)_3$), 117.0 (Ar<u>C</u>H), 120.2 (Ar<u>C</u>H), 123.5 (Ar<u>CH</u>), 124.4 (Ar<u>CH</u>), 145.9 (Ar<u>C</u>-O). The resonances for the C=O group and the aromatic C-N were not observed in ^{13}C NMR spectrum. The spectroscopic properties of this compound were consistent with the data available in the literature.[2]



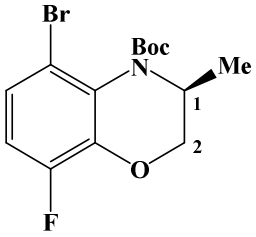
***tert*-butyl 5-bromo-8-fluoro-2,3-dihydro-4*H*-benzo[*b*][1,4]oxazine-4-carboxylate(6c):**

colourless crystal; ν_{max}/cm^{-1}(film) 2979 (s), 2936 (s), 2890 (m), 1713 (s), 1609 (m), 1582 (m), 1483 (s), 1368 (s), 1161 (s), 1043 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.41 (9H, s, $NCO_2C(C\underline{H}_3)_3$), 4.15 (2H, m, 2C1-H), 4.40 (2H, br, 2C2-H), 6.75 (1H, dd, ArCH, *J*=10.1, 8.9), 6.99 (1H, dd, ArCH, *J*=8.8, 5.0); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 28.0 ($NCO_2C(\underline{C}H_3)_3$), 66.6 (C-1), 68.1 (C-2), 82.5 ($NCO_2\underline{C}(CH_3)_3$), 113.6 (d, *J*= 19.0, Ar<u>C</u>H), 115.0 (d, *J*= 3.5, Ar<u>C</u>), 123.0 (d, *J*= 7.4 Ar<u>C</u>H), 150.9 (d, *J*=246, Ar<u>C</u>F). The resonances for the C=O group and the quaternary aromatic C-O carbon were not observed in ^{13}C NMR spectrum. The sample did not ionise properly and as such a HRMS could not be obtained.



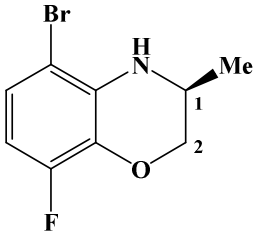
***tert*-butyl (*S*)-3-methyl-2,3-dihydro-4*H*-benzo[*b*][1,4]oxazine-4-carboxylate (6d)**:

colourless oil; $[\alpha]_D^{20}$- 26.6º (c =0.18, MeOH); ν_{max}/cm^{-1}(film) 2976 (s), 2930 (s), 2876 (m), 1698 (s), 1605 (m), 1585 (m), 1496 (s), 1368 (m), 1171 (m), 1064 (m). ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 1.34 (3H, d, *J*= 6.8 Hz, C1-C<u>H</u>$_3$), 1.47 (9H, s, $NCO_2C(C\underline{H}_3)_3$), 4.04 (1H, d, *J*= 2.0 Hz, C1-H), 4.60 (2H, m, 2C2-H), 6.81 (2H, m, 2ArCH), 6.89 (1H, m, ArCH), 7.78 (1H, m, ArCH); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 15.6 (C1-$\underline{C}H_3$), 28.4 ($NCO_2C(\underline{C}H_3)_3$), 46.2 (C-1), 69.0 (C-2), 81.5 ($NCO_2\underline{C}(CH_3)_3$), 116.7 (Ar<u>C</u>H), 120.5 (Ar<u>C</u>H), 123.7 (Ar<u>C</u>H), 123.9 (Ar<u>C</u>H). The resonances for the C=O and quaternary aromatic C-O and C-N carbons were not observed in ^{13}C NMR spectrum. The ^{1}H and ^{13}C NMR data were consistent with that available in the literature.[2]



***tert*-butyl (S)-5-bromo-8-fluoro-3-methyl-2,3-dihydro-4*H*-benzo[*b*][1,4]oxazine-4-carboxylate (6f)**:

colourless oil; $[\alpha]_D^{20}$ - 25.5º (c =0.2, $CHCl_3$). ν_{max}/cm^{-1}(film) 2979 (m), 2935 (m), 2889 (m), 1712 (s), 1608 (m), 1585 (m), 1450 (m), 1369 (m), 1171 (m), 1033 (m). ^1H NMR (400 MHz, $CDCl_3$) δ_H 1.10 (3H, d, *J*= 7.2 Hz, C1-C$\underline{H}_3$), 1.47 (9H, s, $NCO_2C(C\underline{H}_3)_3$), 4.19 (2H, m, C2-$\underline{H}$), 4.78 (1H, br s, C1-$\underline{H}$), 6.83 (1H, m, ArC$\underline{H}$), 7.07 (1H, m, ArC$\underline{H}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 15.5 (C1-$\underline{C}H_3$), 28.1 ($NCO_2C(\underline{C}H_3)_3$), 45.9 (C-1), 70.3 (C-2), 82.5 ($NCO_2\underline{C}(CH_3)_3$), 113.6 (d, *J*= 18.9 Hz, Ar$\underline{C}$H), 116.3 (s, Ar$\underline{C}$), 123.4 (d, *J*= 7.3 Hz, Ar$\underline{C}$H), 150.6 (d, *J*= 245.8 , Ar$\underline{C}$F). The resonances for the C=O group and the quaternary aromatic C-O carbon were not observed in ^{13}C NMR spectrum. The sample did not ionise properly and as such a HRMS could not be obtained. Elemental Anal. Calcd. for $C_{14}H_{17}BrFNO_3$: C, 48.57; H, 4.95; N, 4.05%. Found: C, 48.75; H, 4.68; N, 3.98%. To confirm the structure of **6e** we deprotected it and were able to obtain HRMS data for the deprotected structure (presented below).



(S)-5-bromo-8-fluoro-3-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (6f deprotected):

colourless oil; $[\alpha]_D^{20}$ +13.5º (c =0.2, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ_H 1.28 (3H, d, *J*= 6.4 Hz, C1-C$\underline{H}_3$), 3.63 (1H, m, C1-$\underline{H}$), 3.80 (1H, dd, *J*= 10.4, 7.8 Hz, C2-$\underline{H}$), 4.26 (1H, br N$\underline{H}$), 4.29 (1H, m, C2-$\underline{H}$), 6.42 (1H, m, ArC$\underline{H}$), 6.95 (1H, m, ArCH); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C 17.6 (C1-$\underline{C}H_3$), 45.3 (C-1), 70.4 (C-2), 102.9 (Ar$\underline{C}$, d, 2.2 Hz), 103.7 (d, *J*= 19.9 Hz, Ar$\underline{C}$H), 123.2 (d,

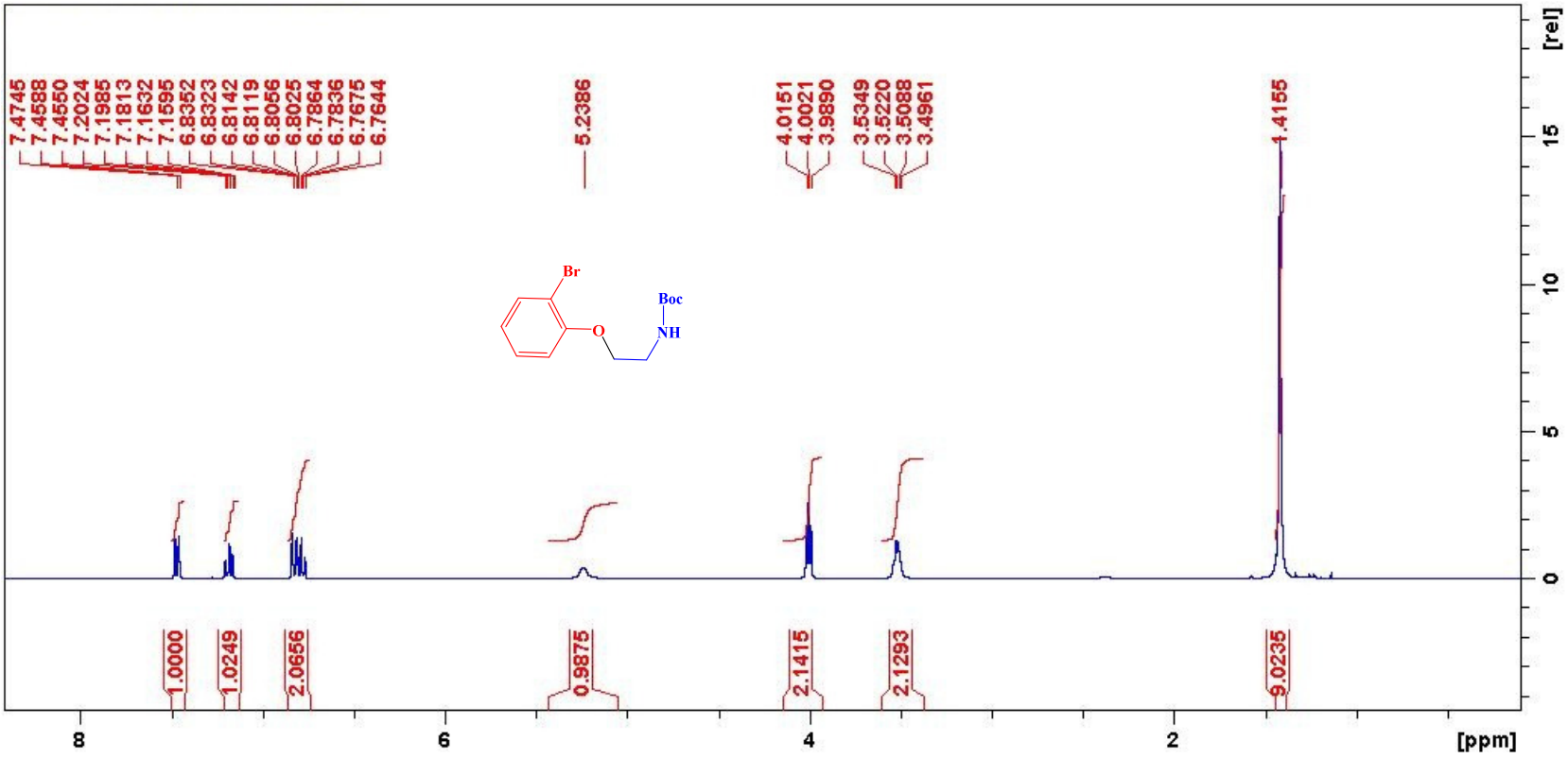
J= 8.6 Hz, Ar<u>C</u>H), 132.2 (d, *J*= 14.9 Hz, Ar<u>C</u>), 133.2 (d, *J*= 4.4 Hz, Ar<u>C</u>), 151.0 (d, *J*= 242.2 , Ar<u>C</u>F). HRMS–ES$^+$: *m/z* [M+H] calcd for $C_9H_{10}NOFBr$: 245.9930; found: 245.9931.

References

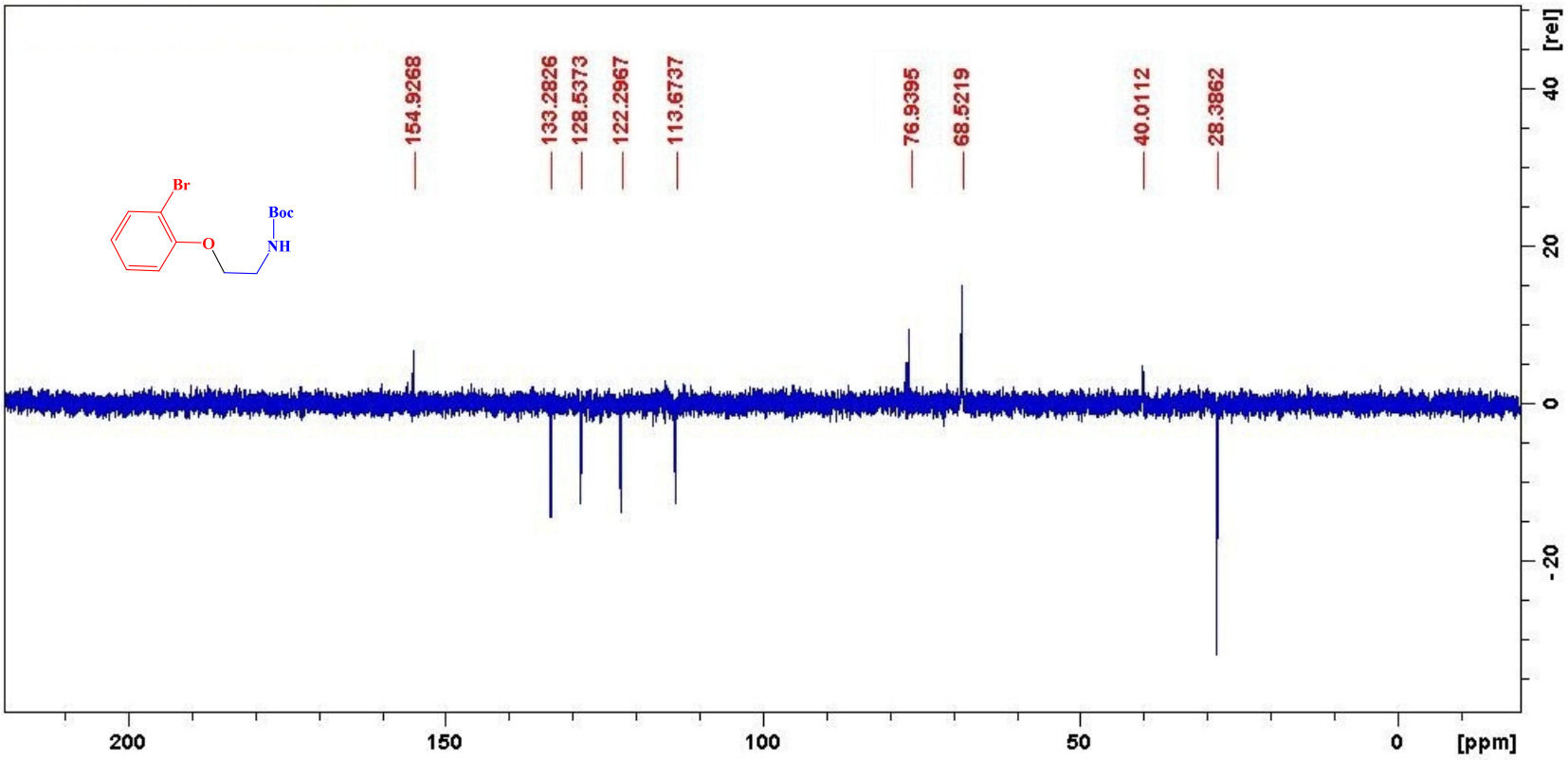
1. J. F. Bower, P. Szeto and T. Gallagher, *Org. Lett.*, 2007, **9**, 3283-3286.
2. P. Jangili, J. Kashanna and B. Das, *Tetrahedron Lett.*, 2013, **54**, 3453-3456.

NMR spectra

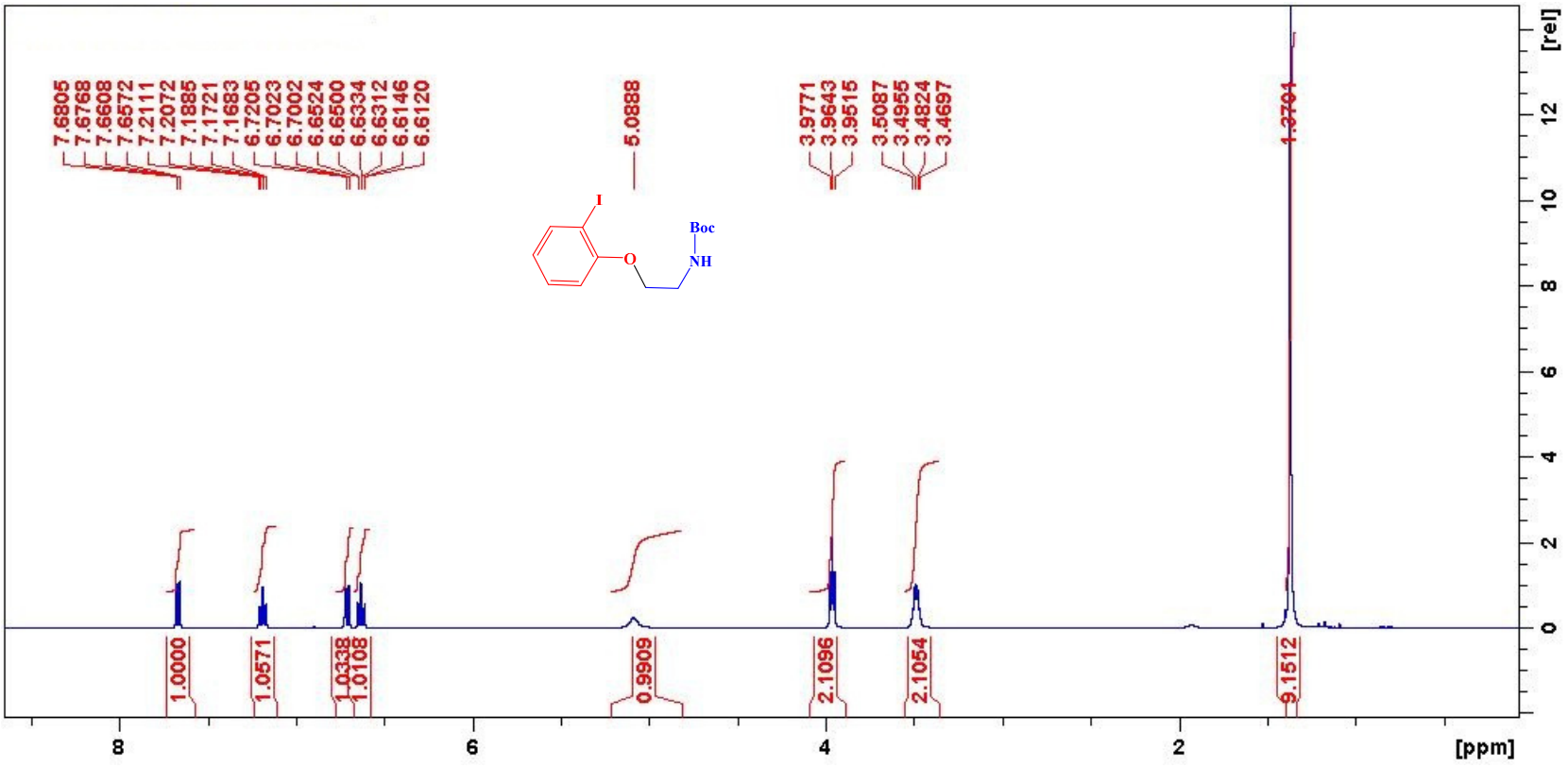
^{1}H NMR spectra of 5a



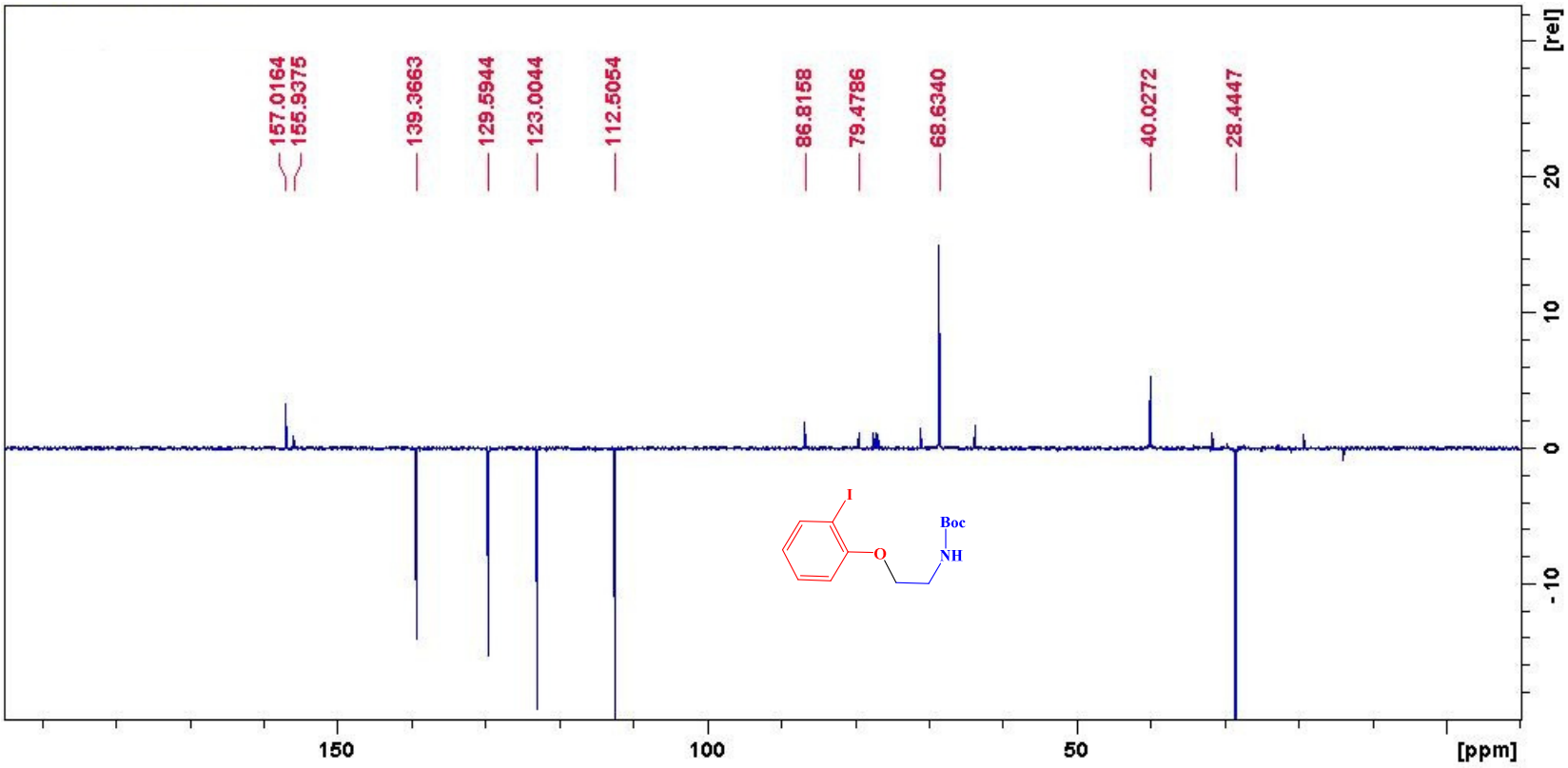
^{13}C NMR spectra of 5a



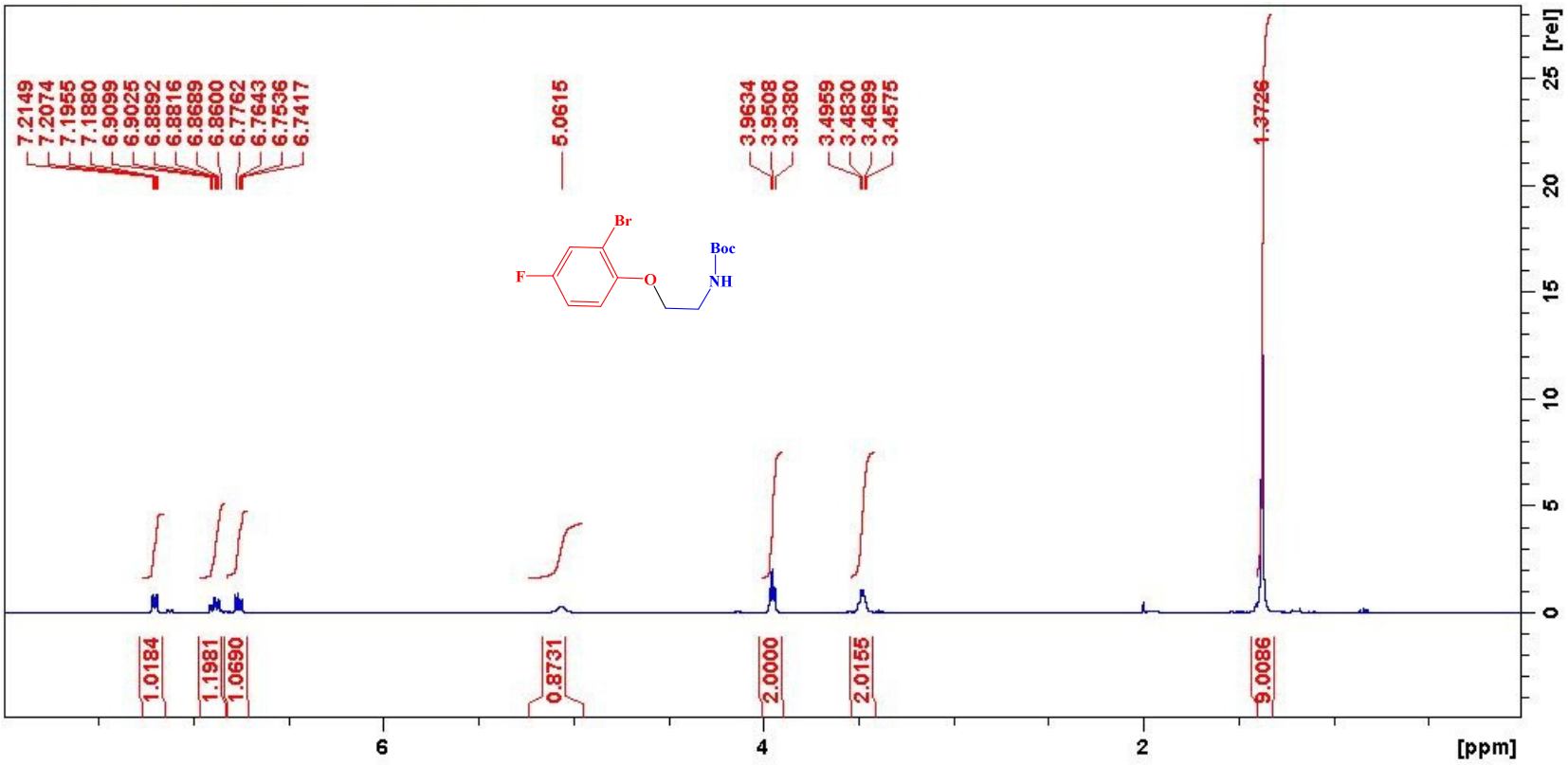
^{1}H NMR spectra of 5b



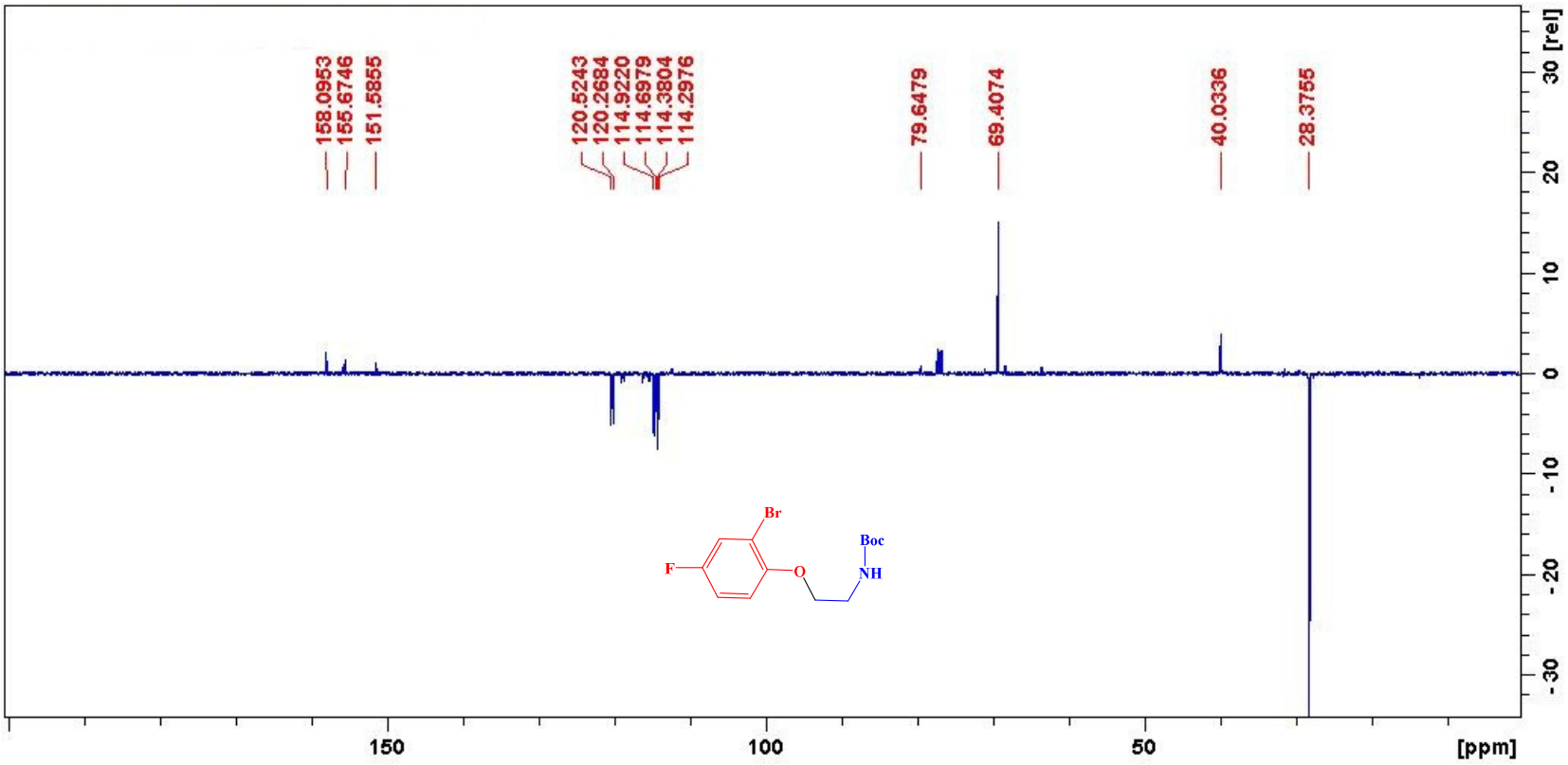
^{13}C NMR spectra of 5b



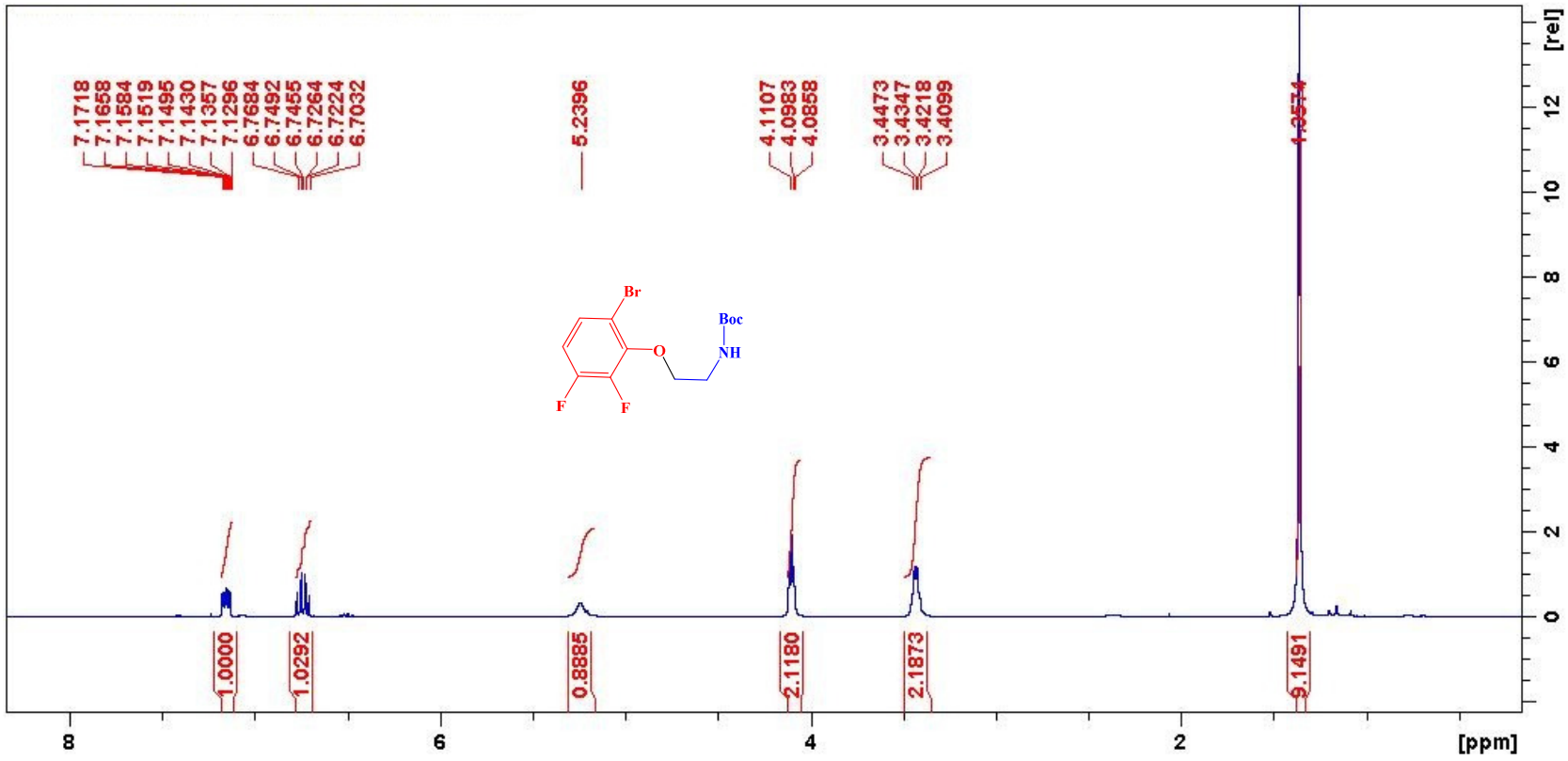
^{1}H NMR spectra of 5c



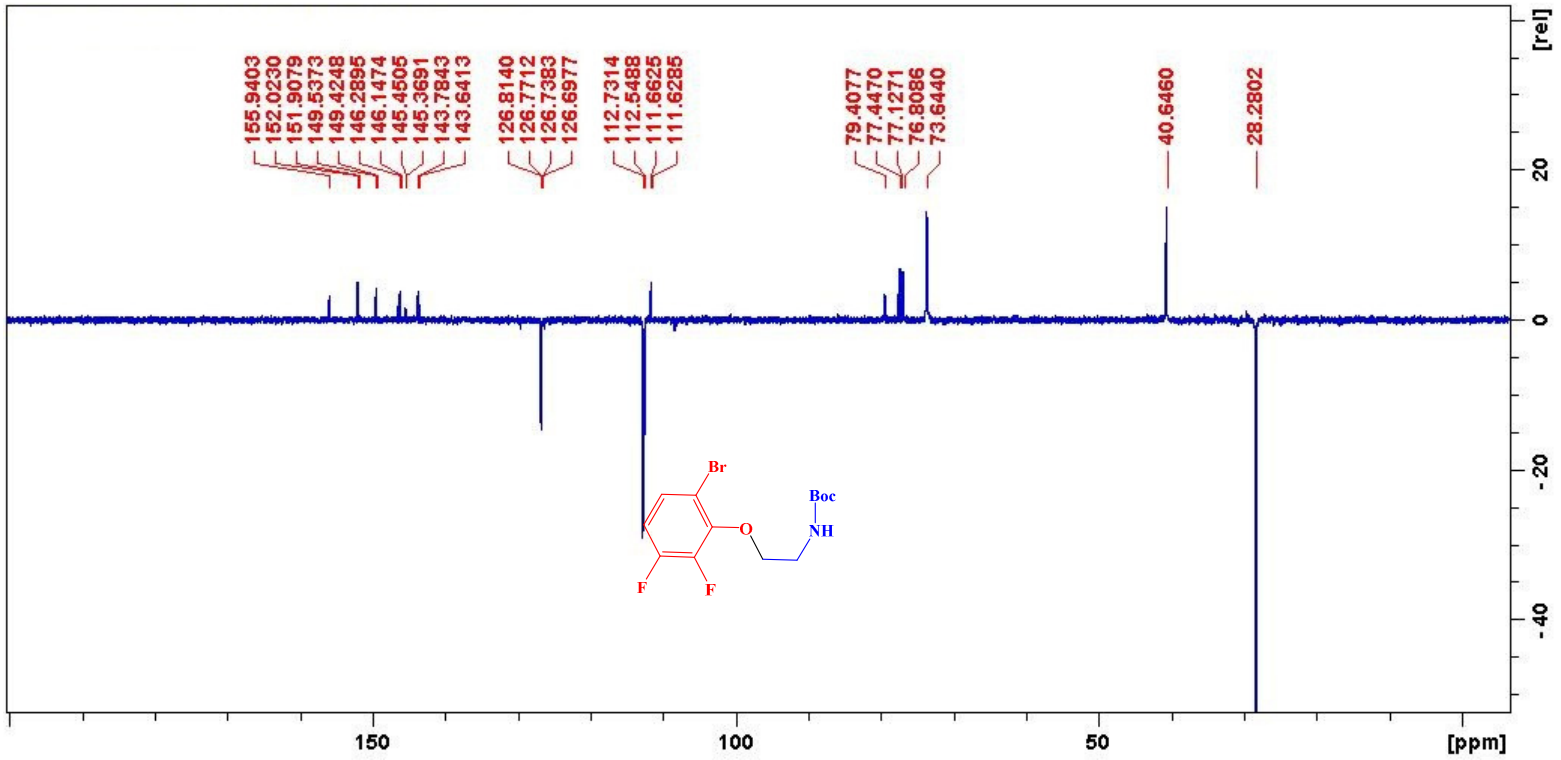
^{13}C NMR spectra of 5c



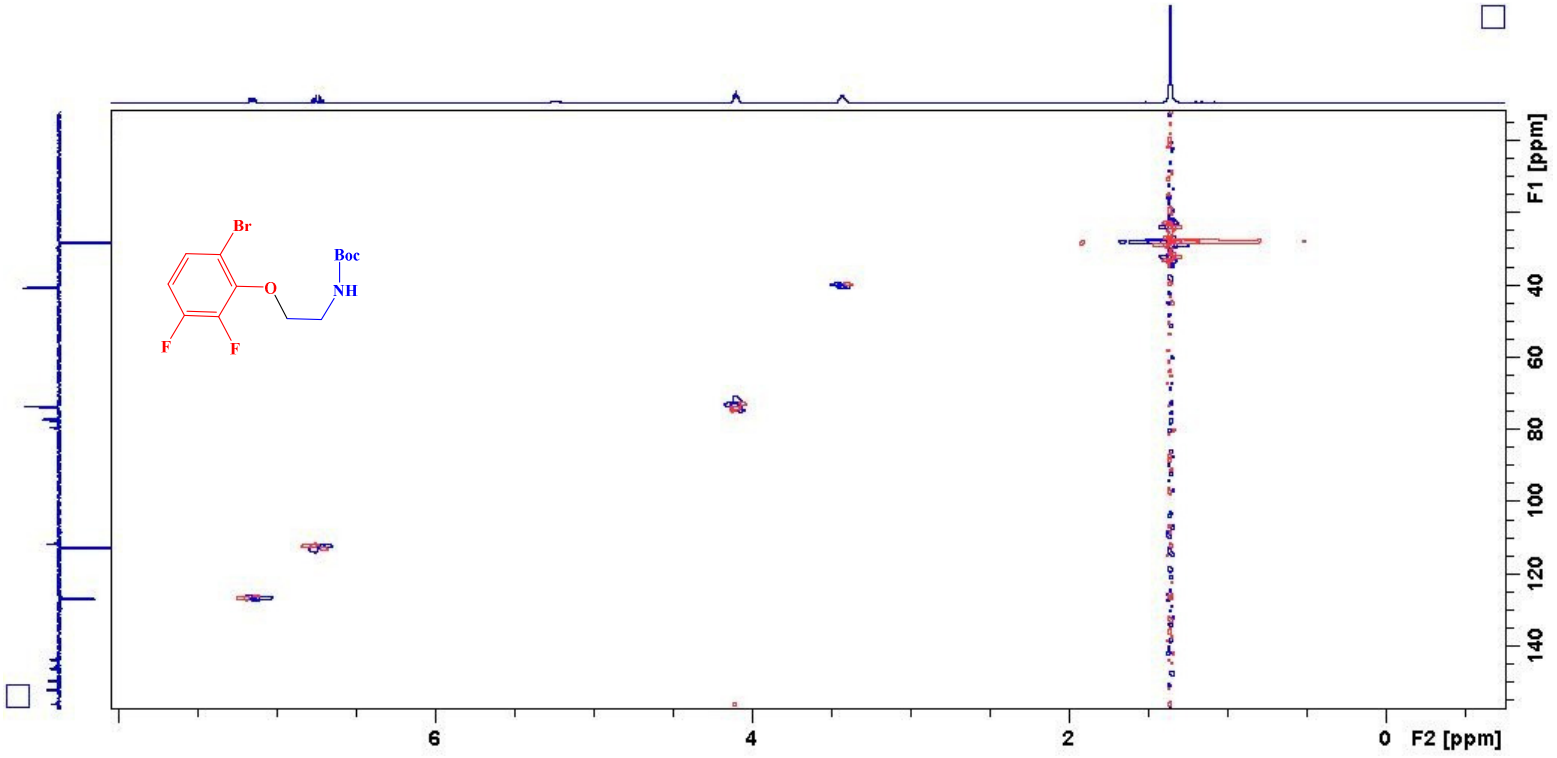
^{1}H NMR spectra of **5d**



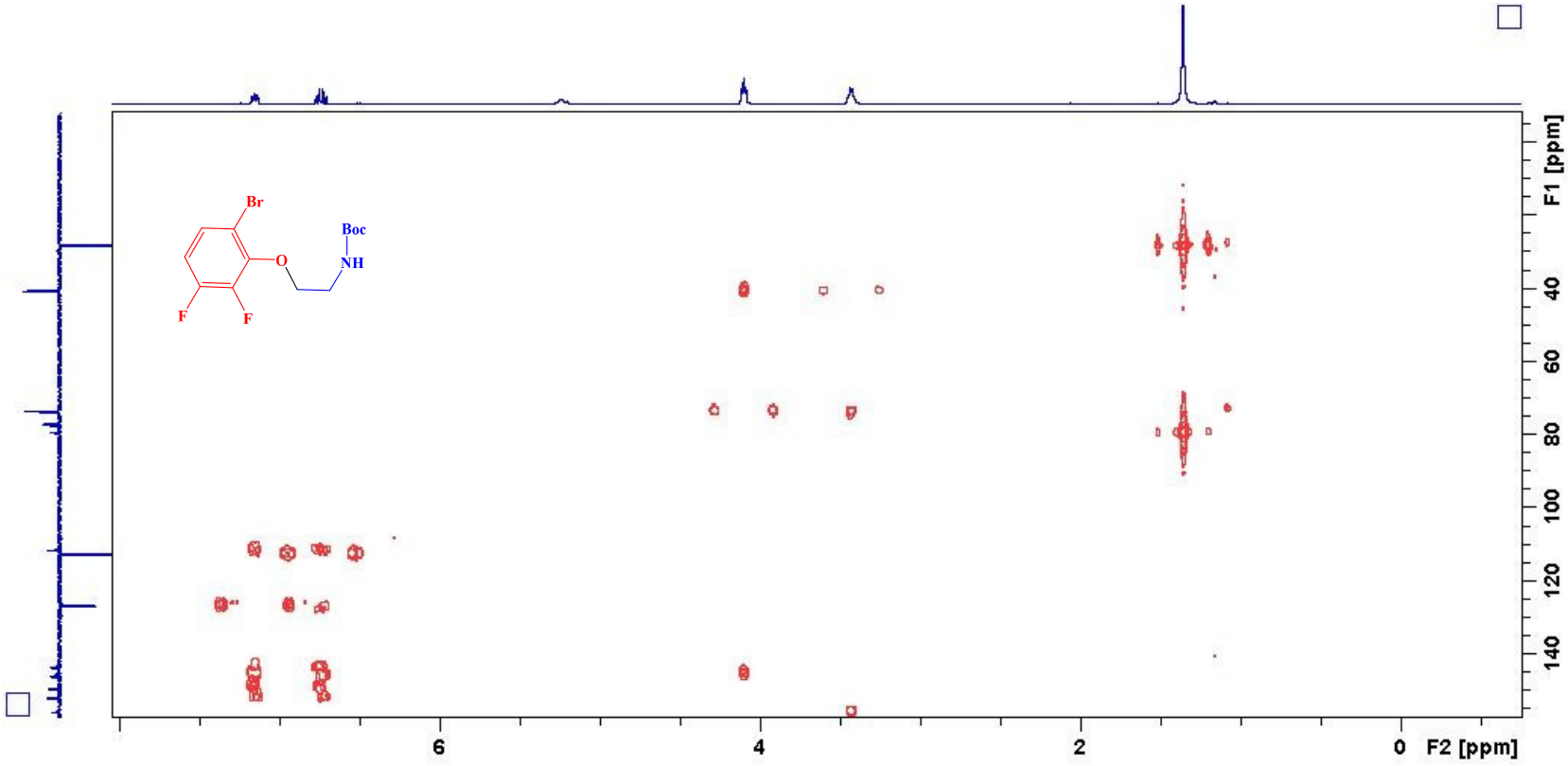
^{13}C NMR spectra of **5d**



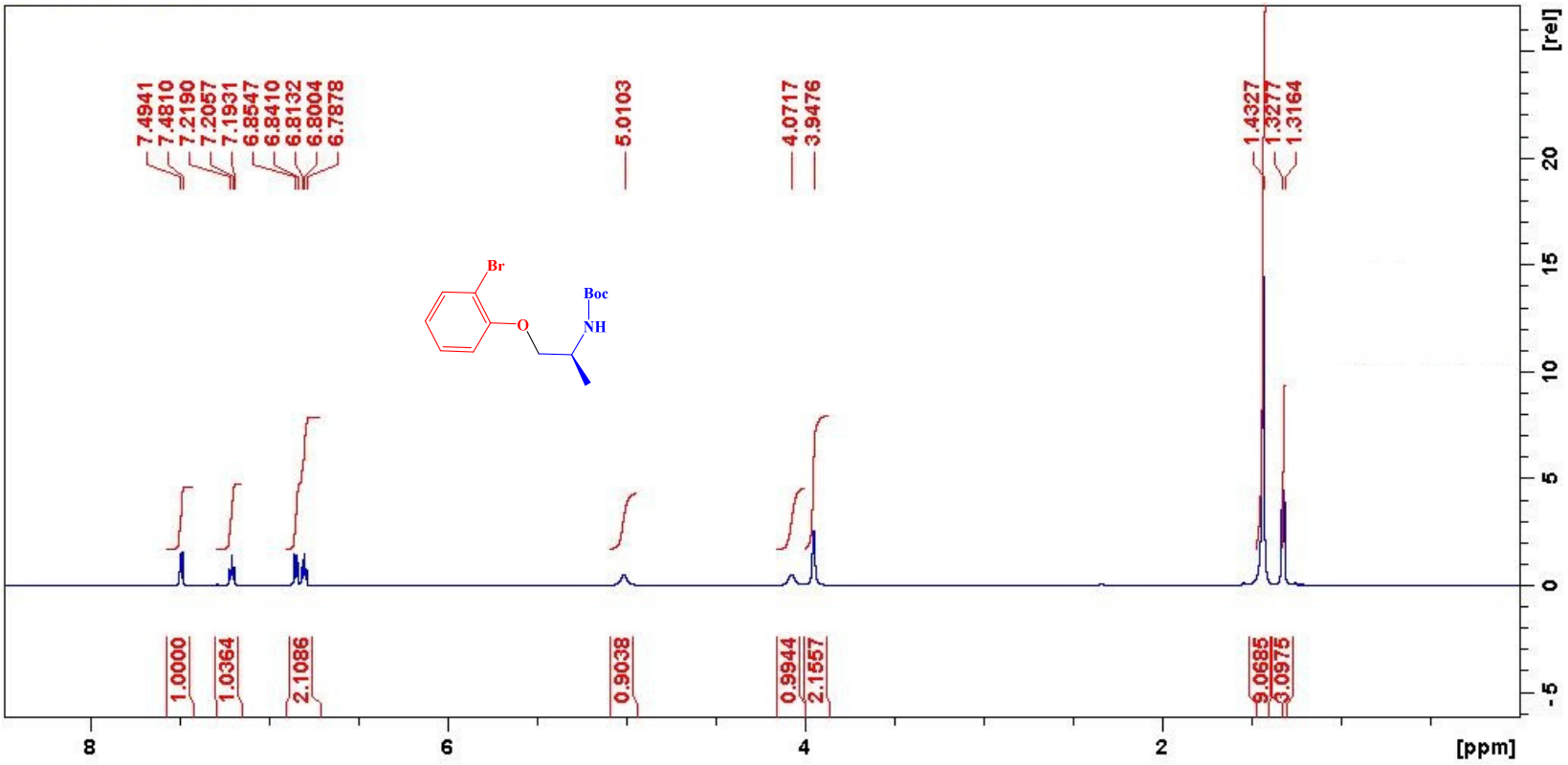
HSQC spectra of **5d**



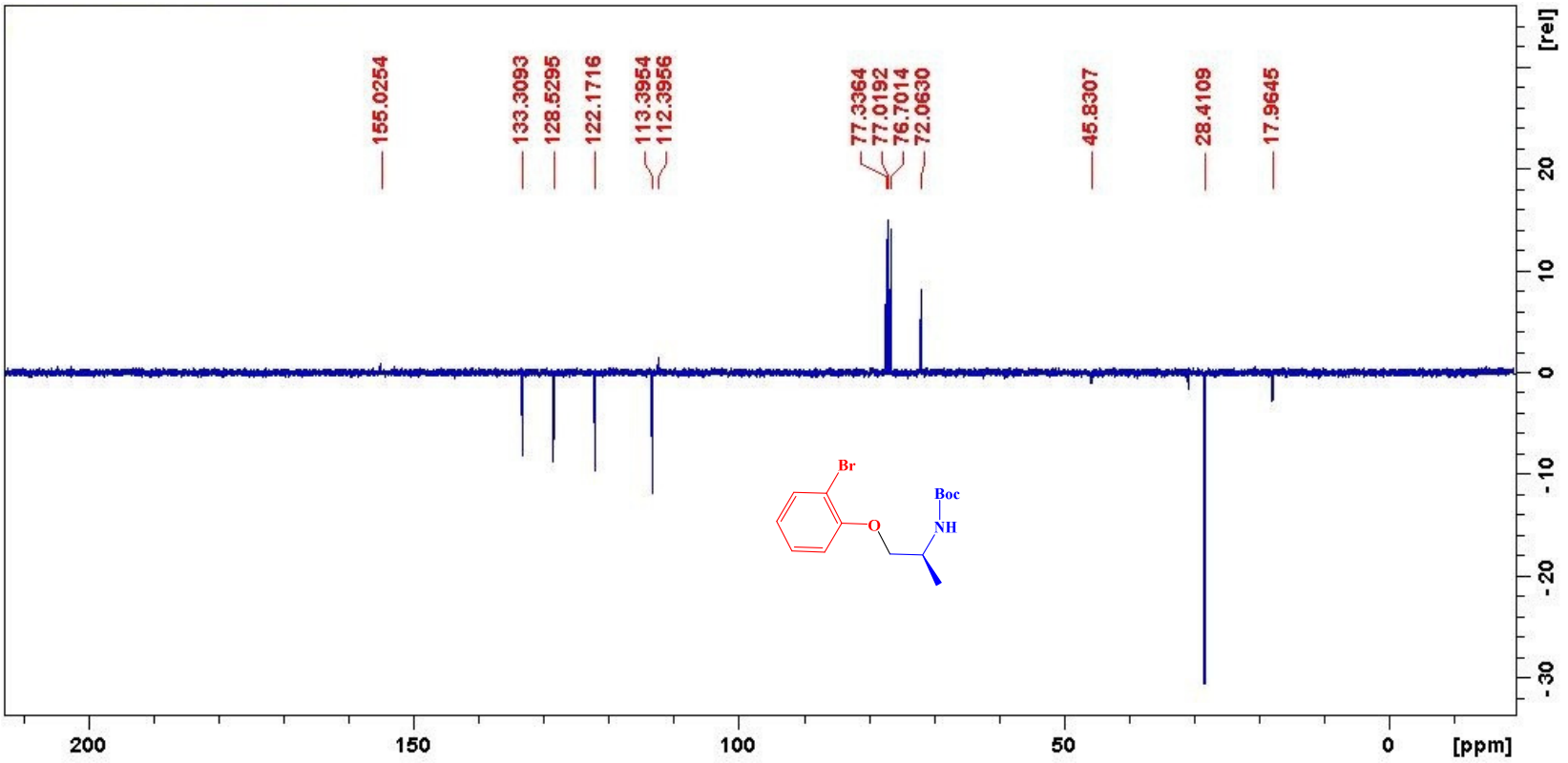
HMBC spectra of **5d**



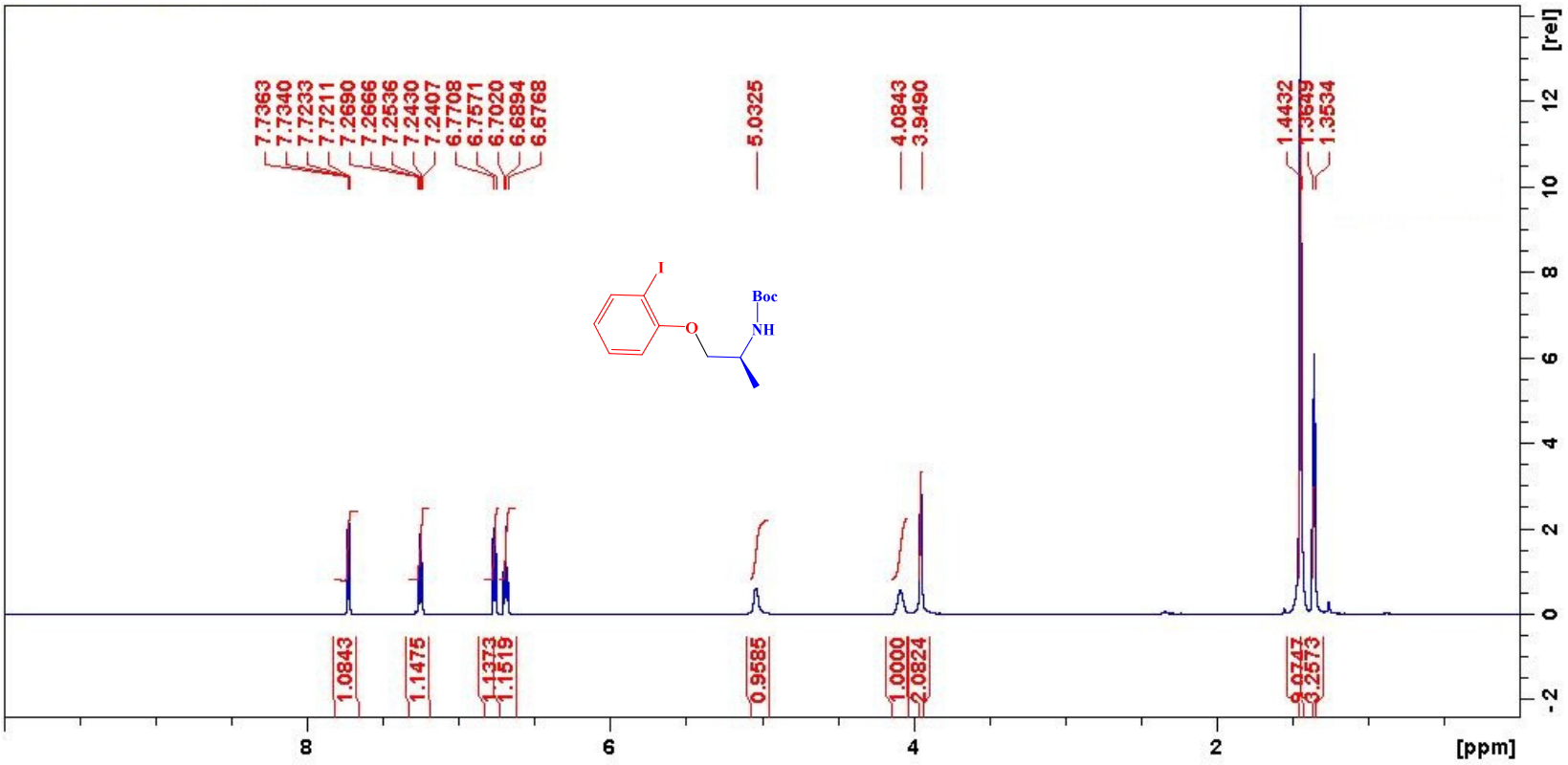
^{1}H NMR spectra of **5e**



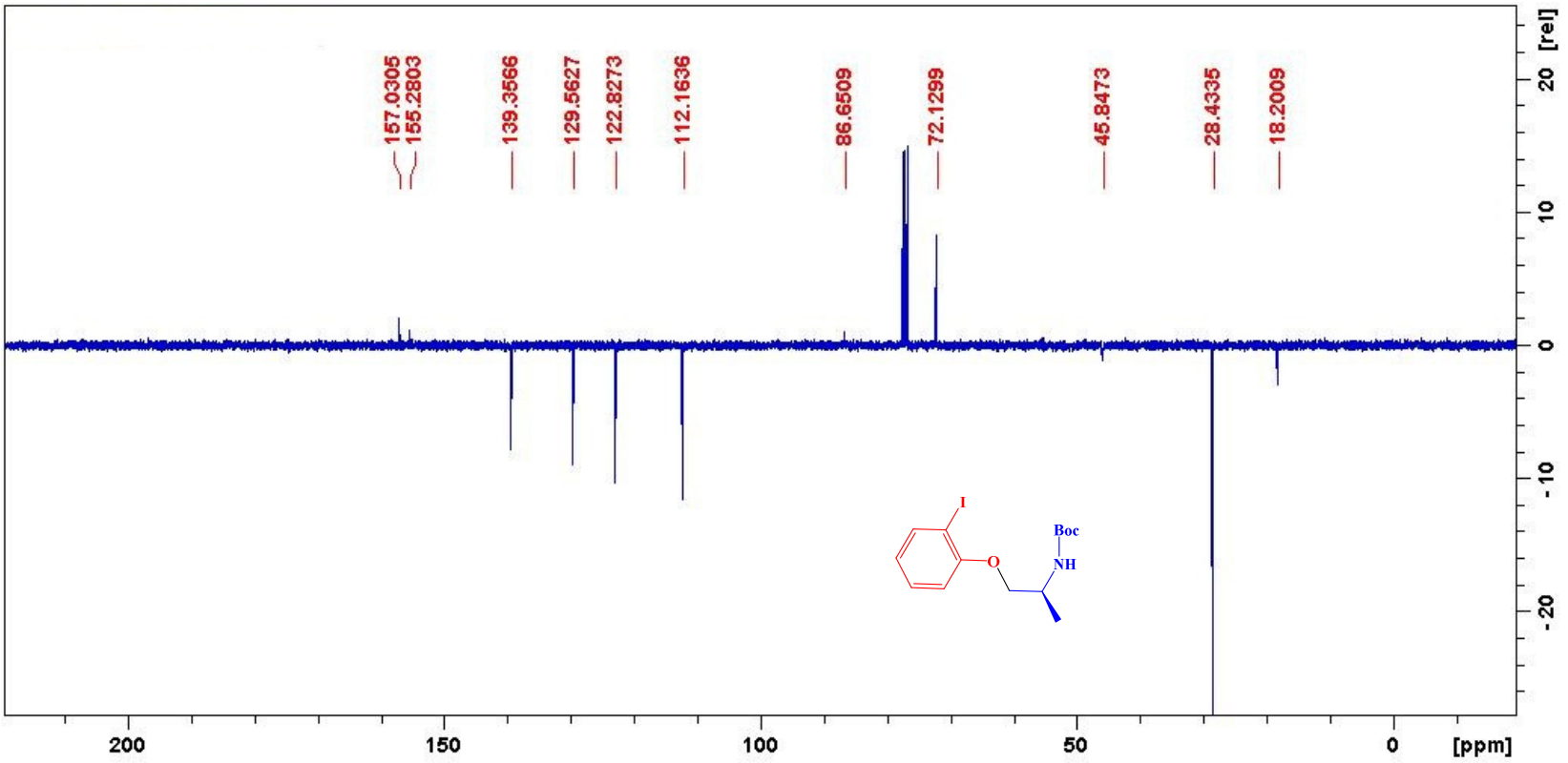
^{13}C NMR spectra of 5e



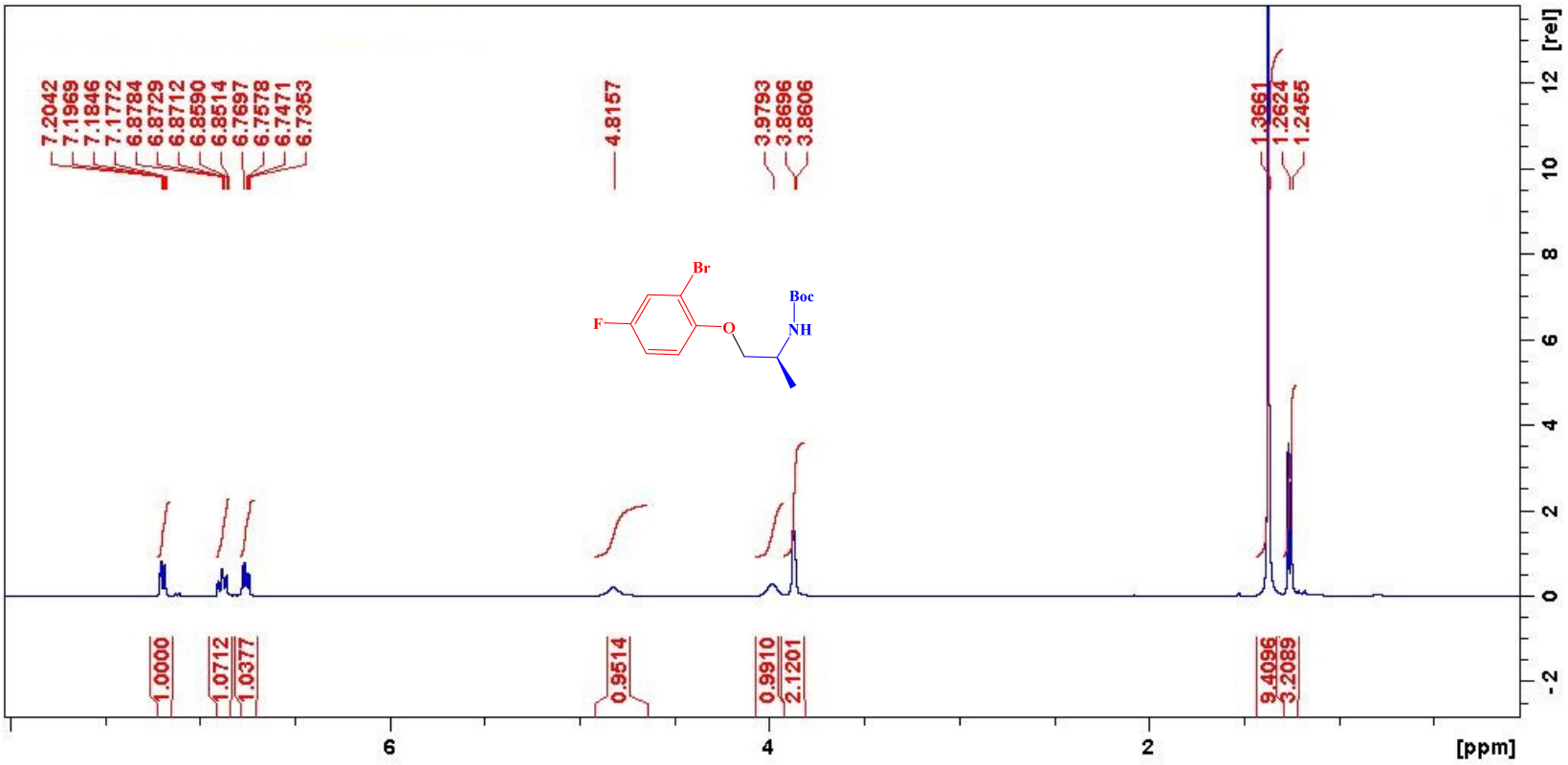
^{1}H NMR spectra of 5f



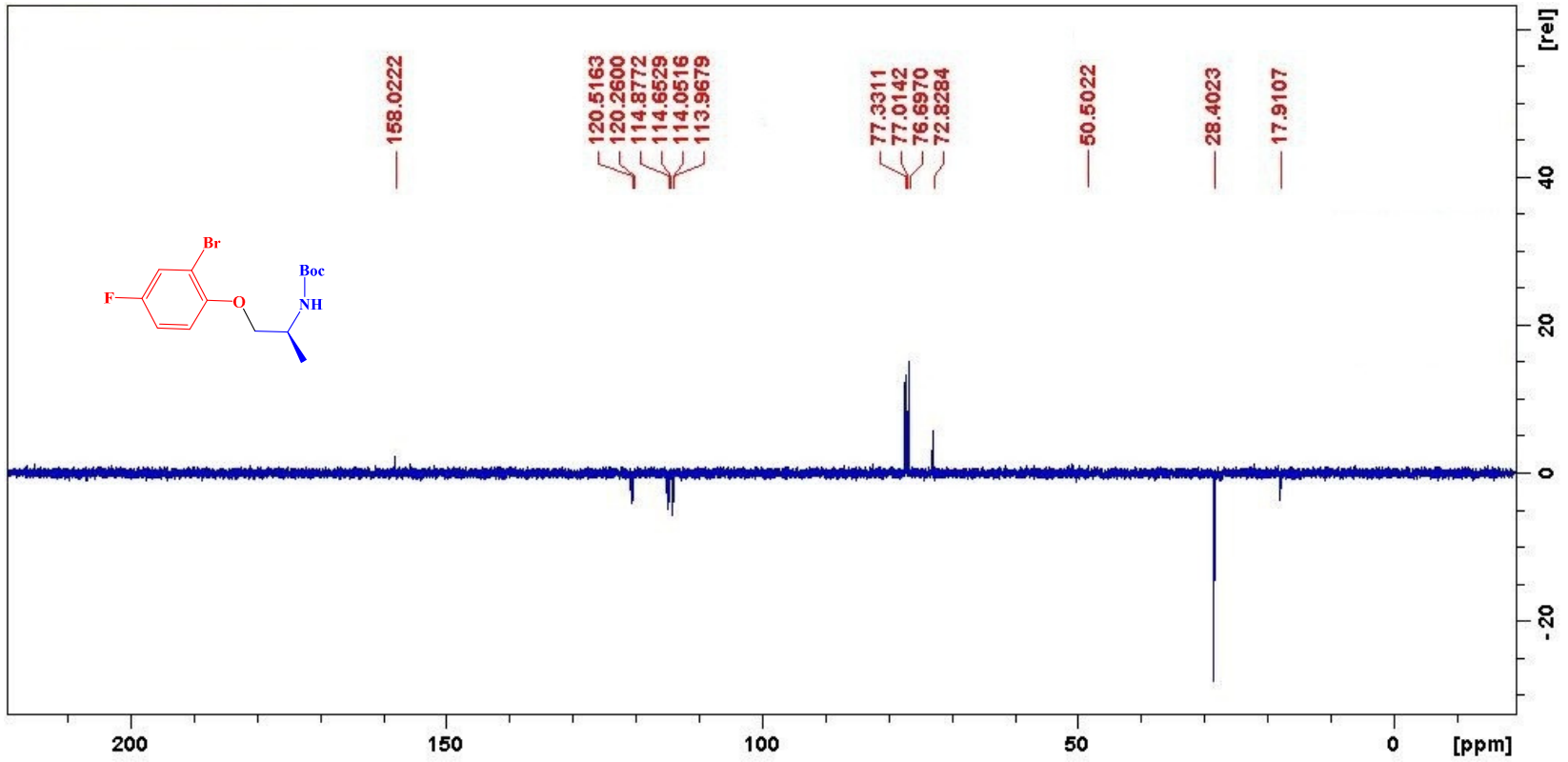
^{13}C NMR spectra of 5f



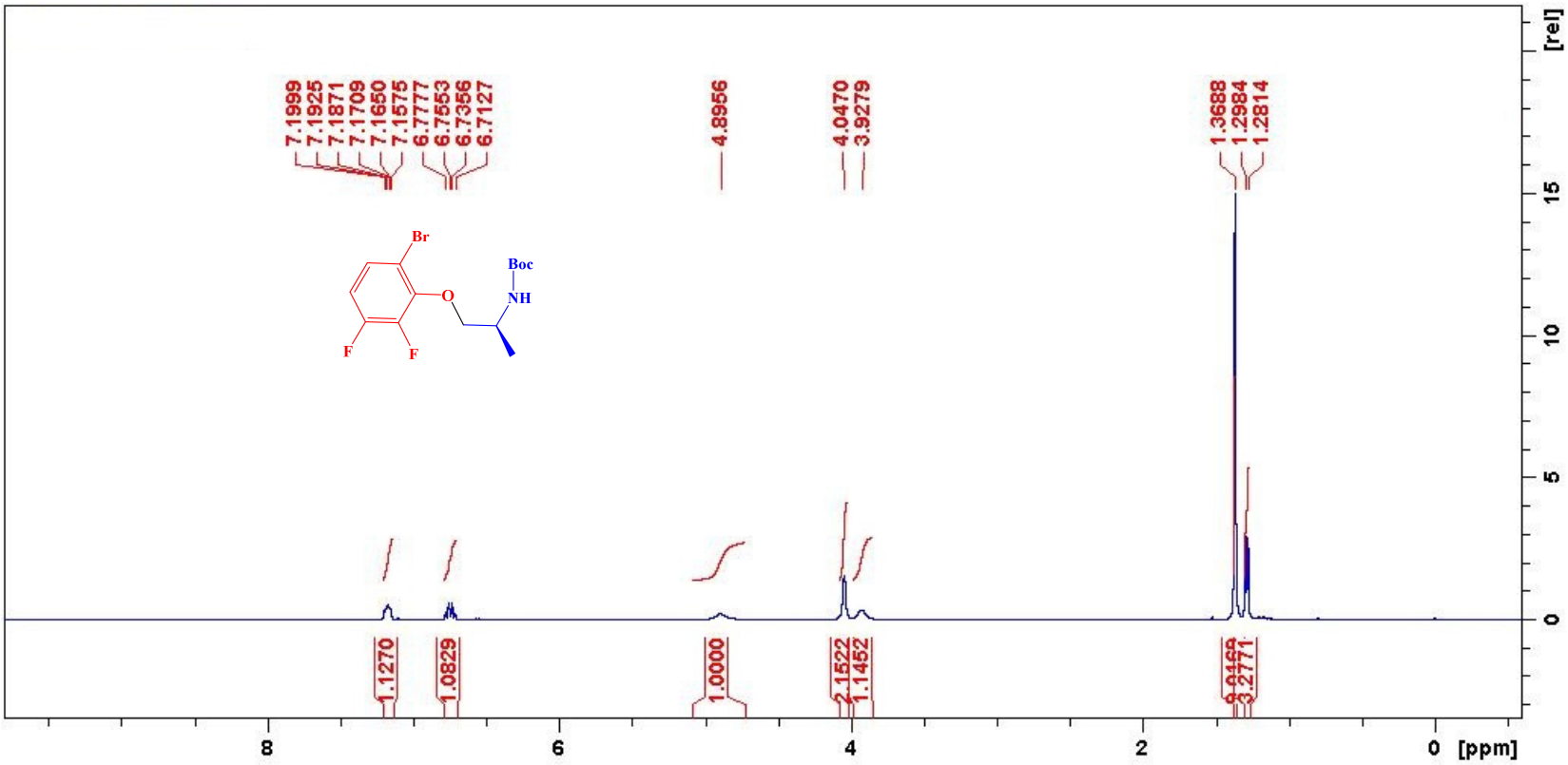
^{1}H NMR spectra of 5g



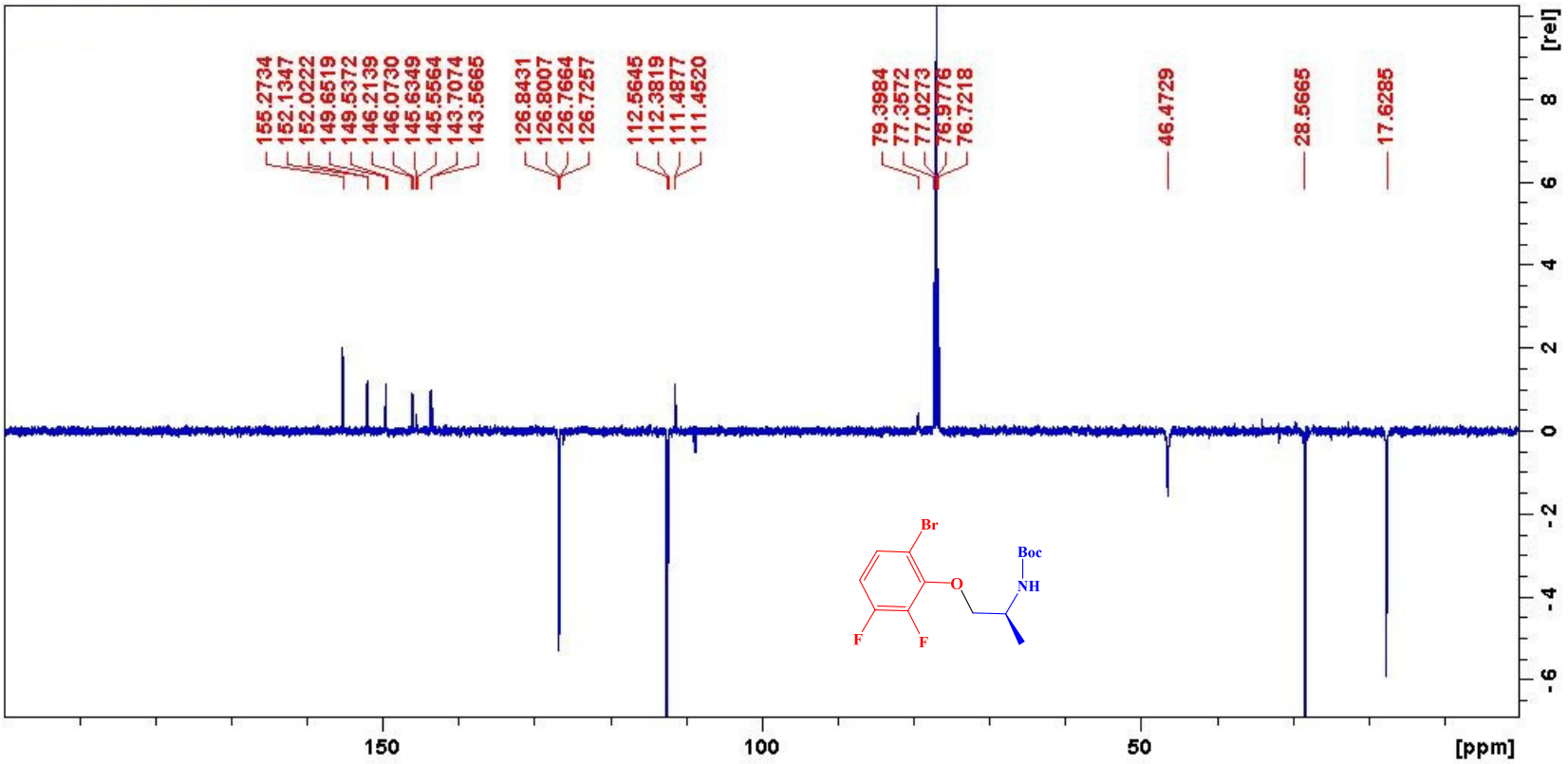
^{13}C NMR spectra of 5g



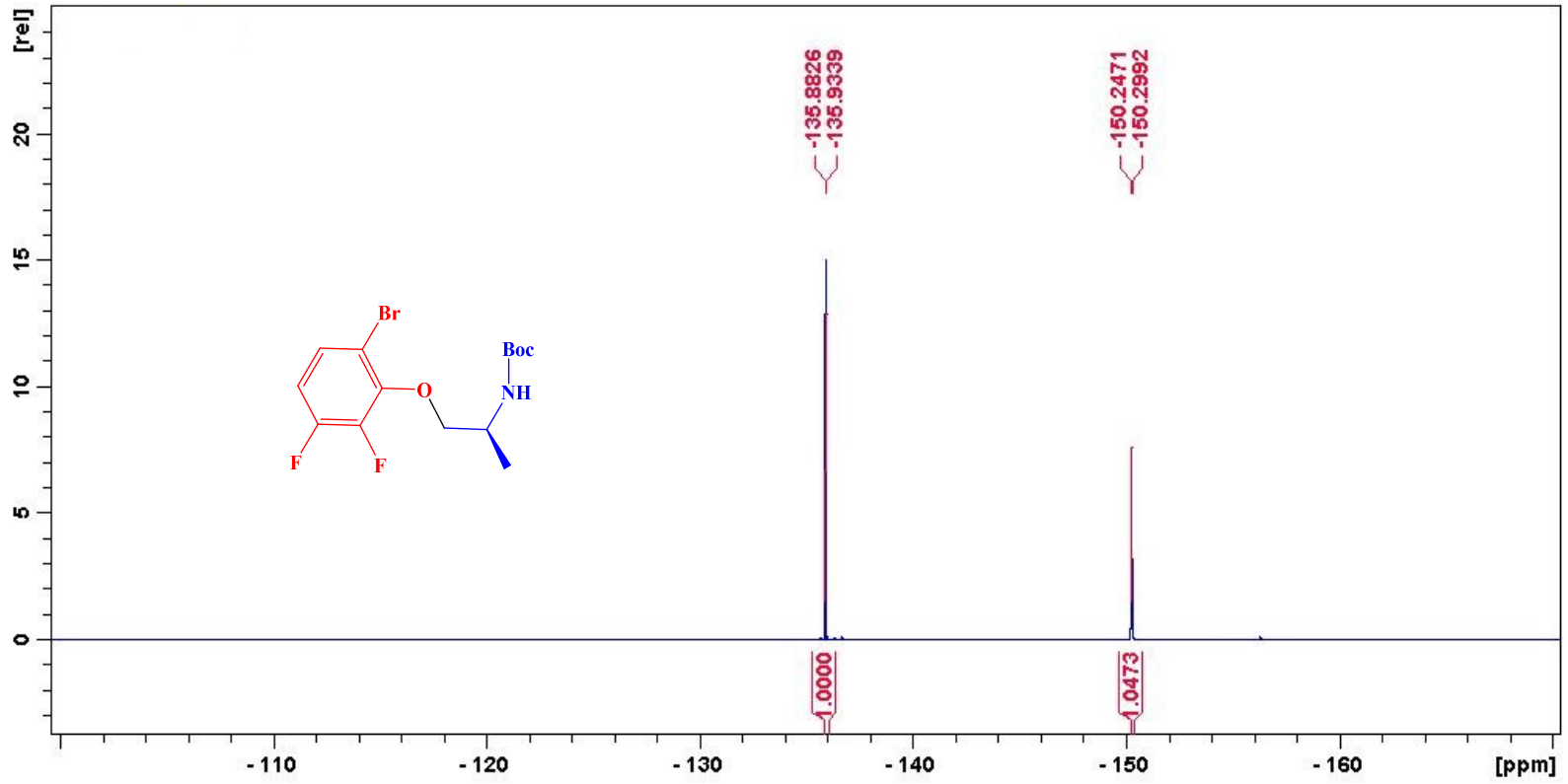
^{1}H NMR spectra of 5h



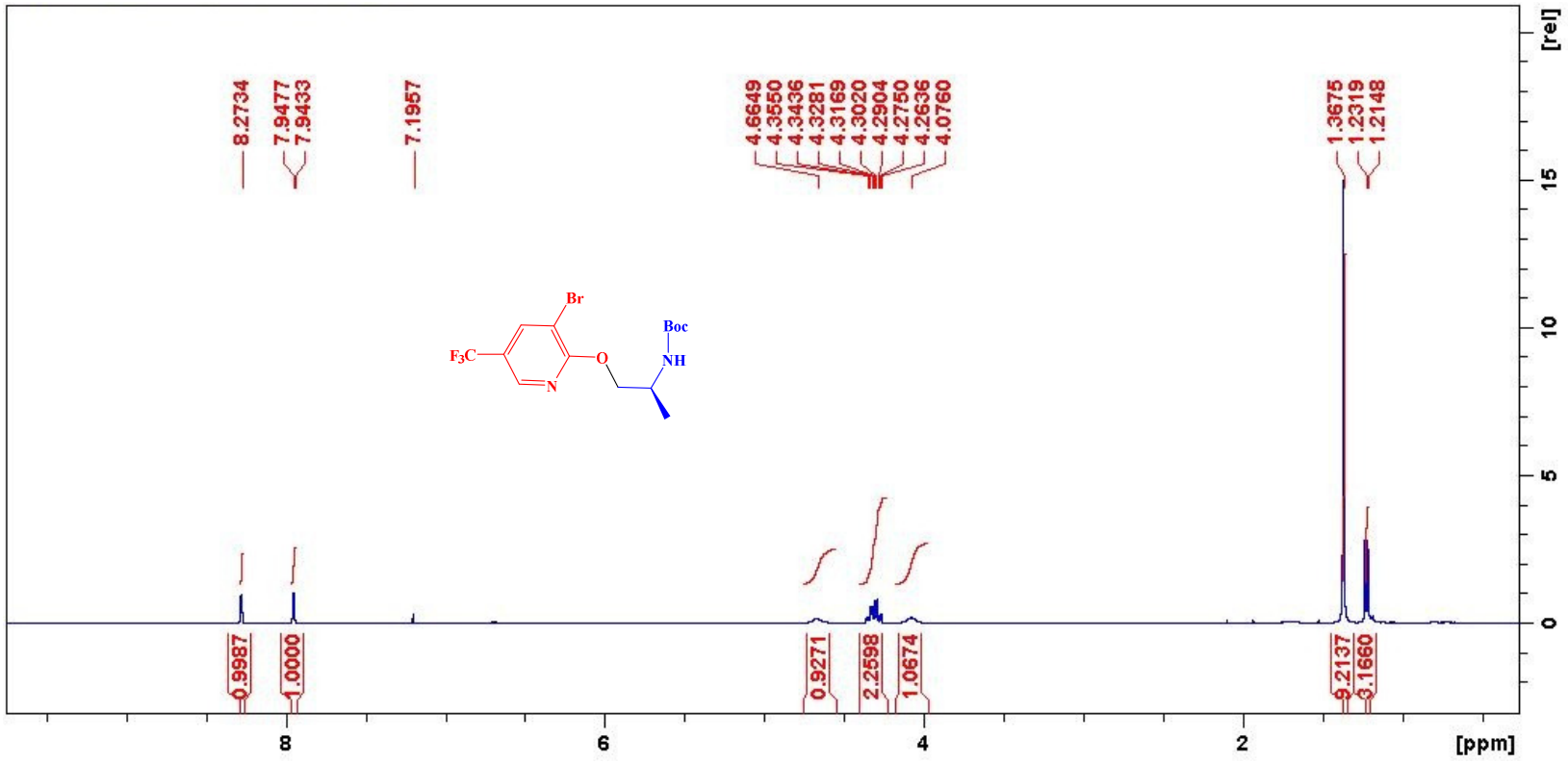
^{13}C NMR spectra of 5h



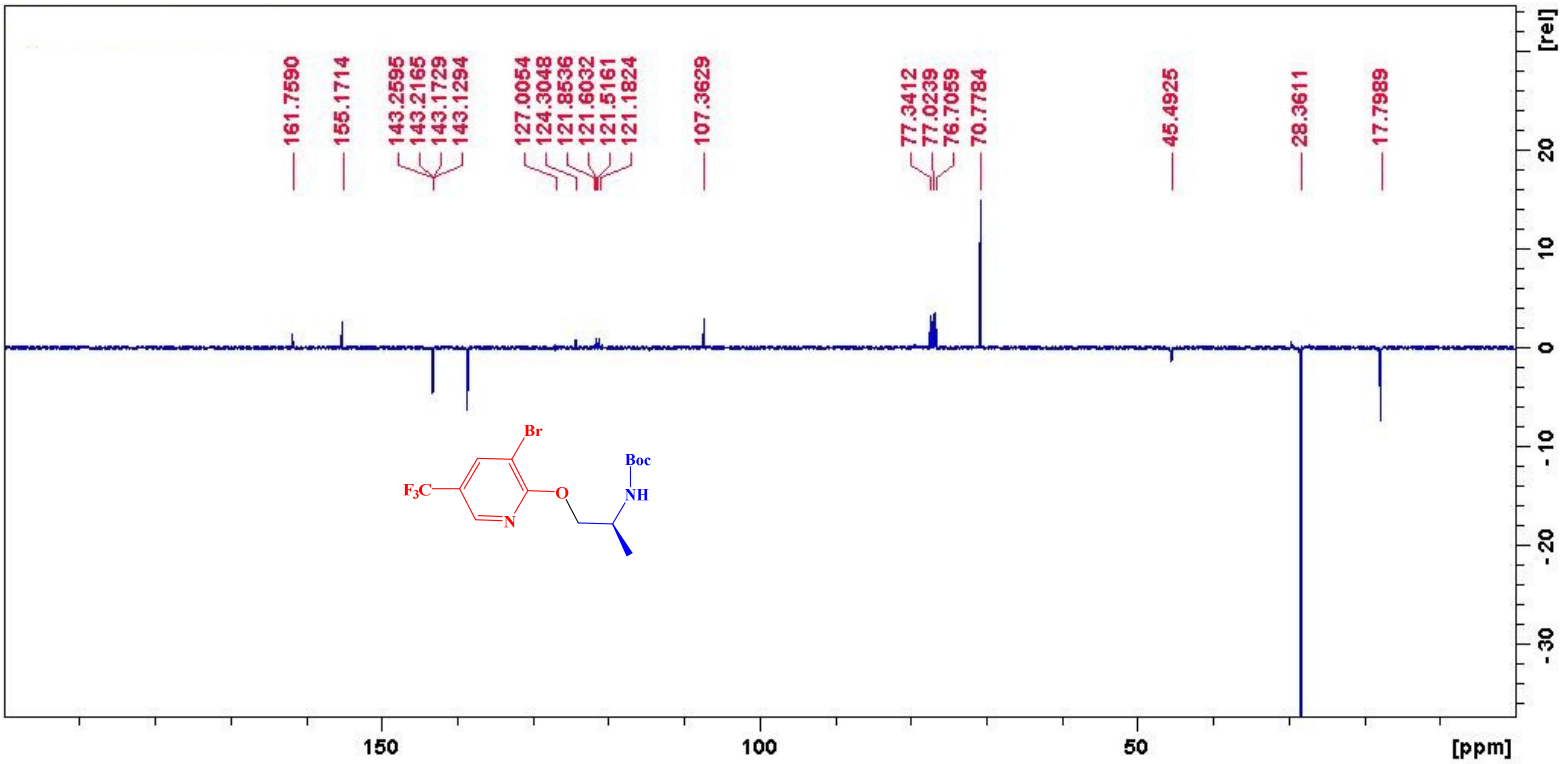
^{19}F NMR spectra of 5h



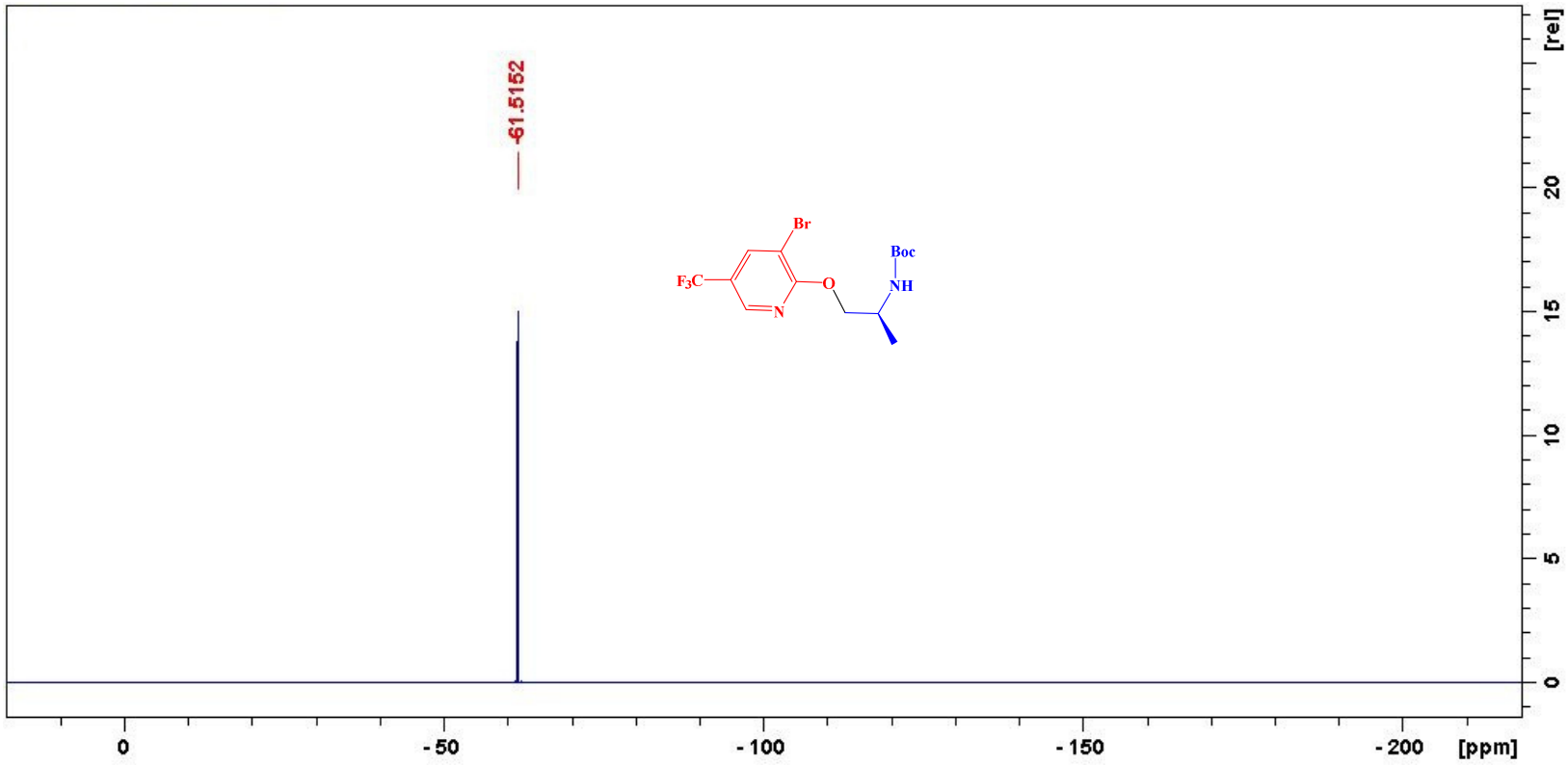
^{1}H NMR spectra of 5i



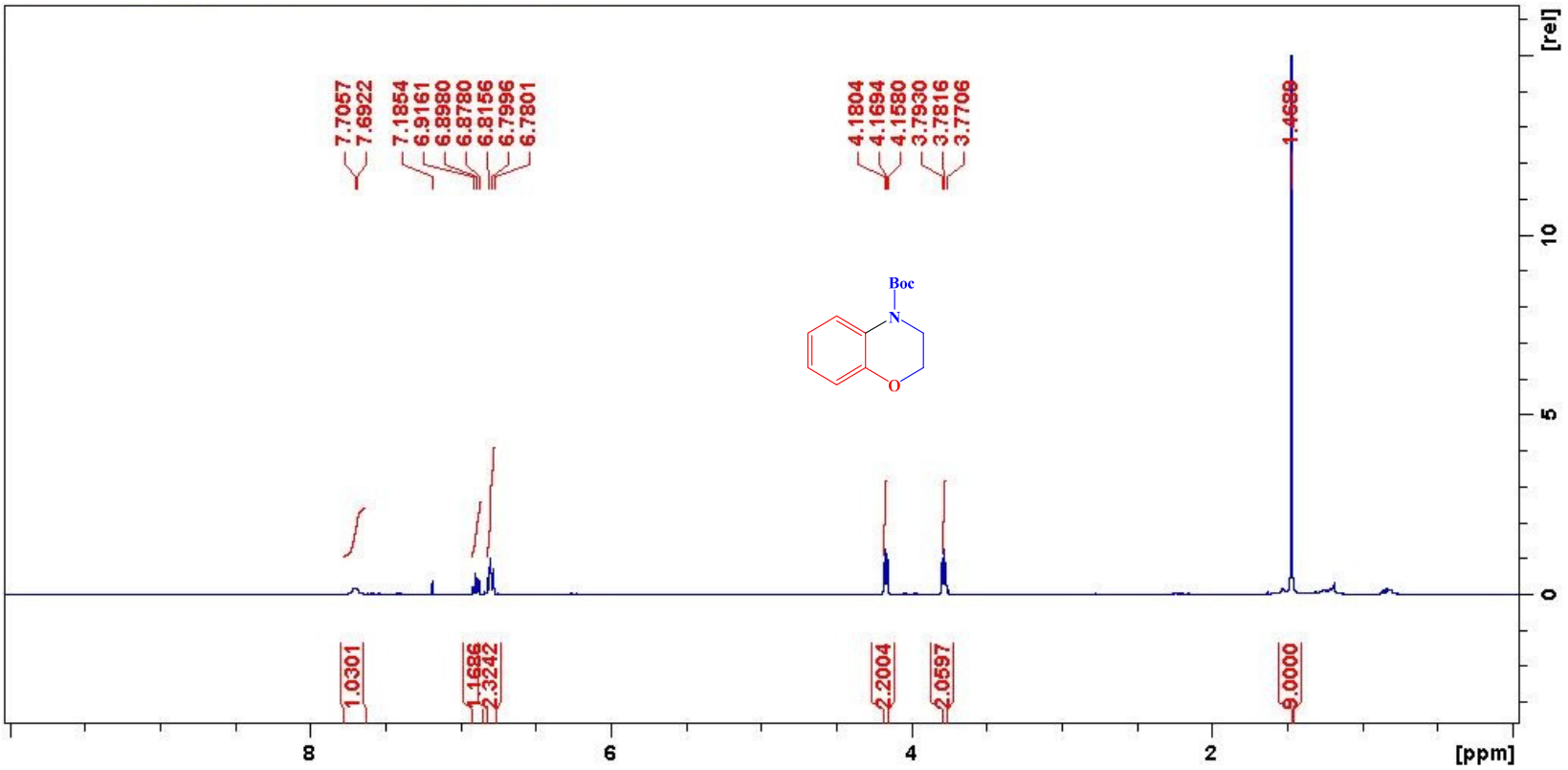
^{13}C NMR spectra of 5i



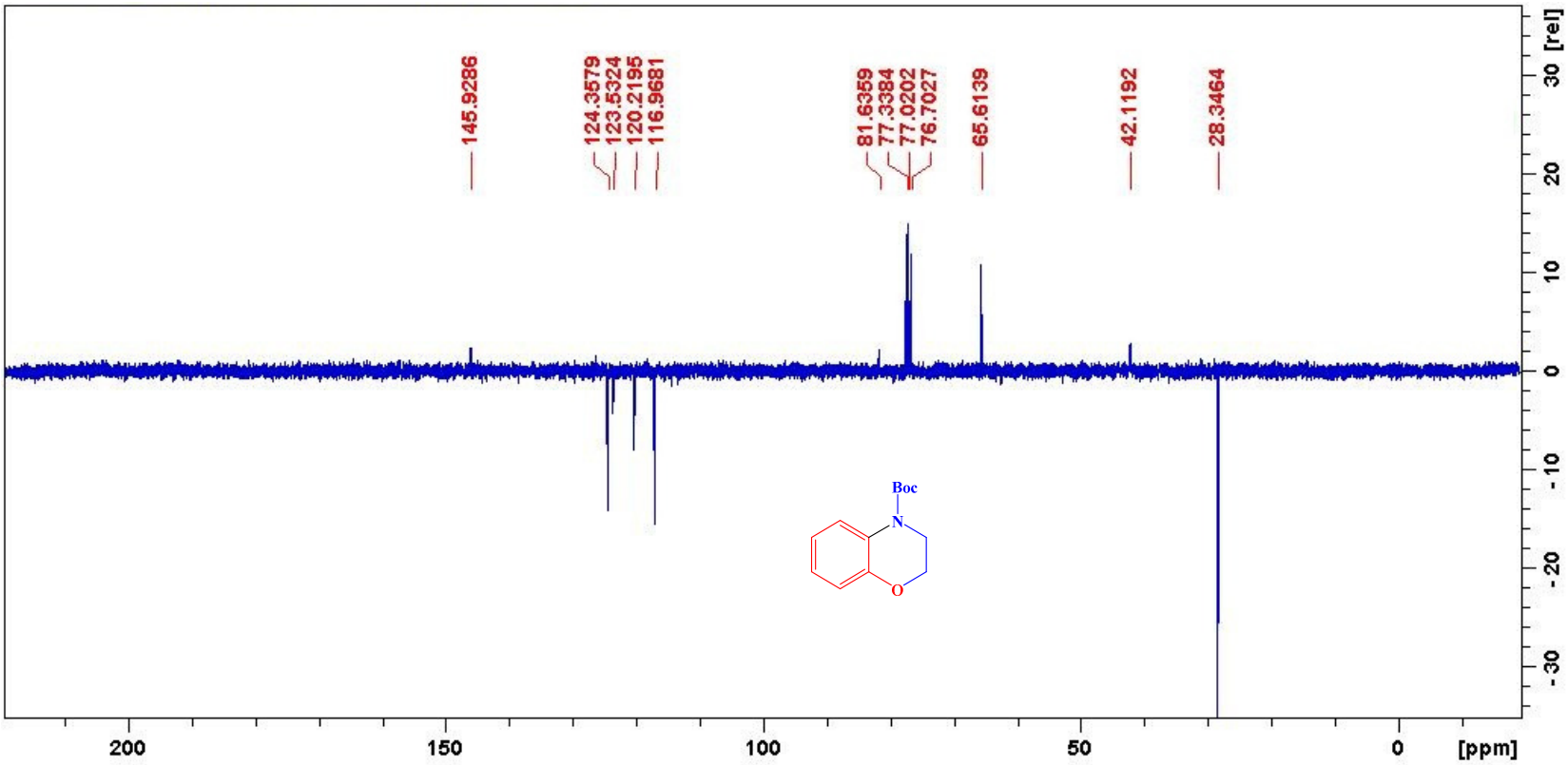
^{19}F NMR spectra of 5i



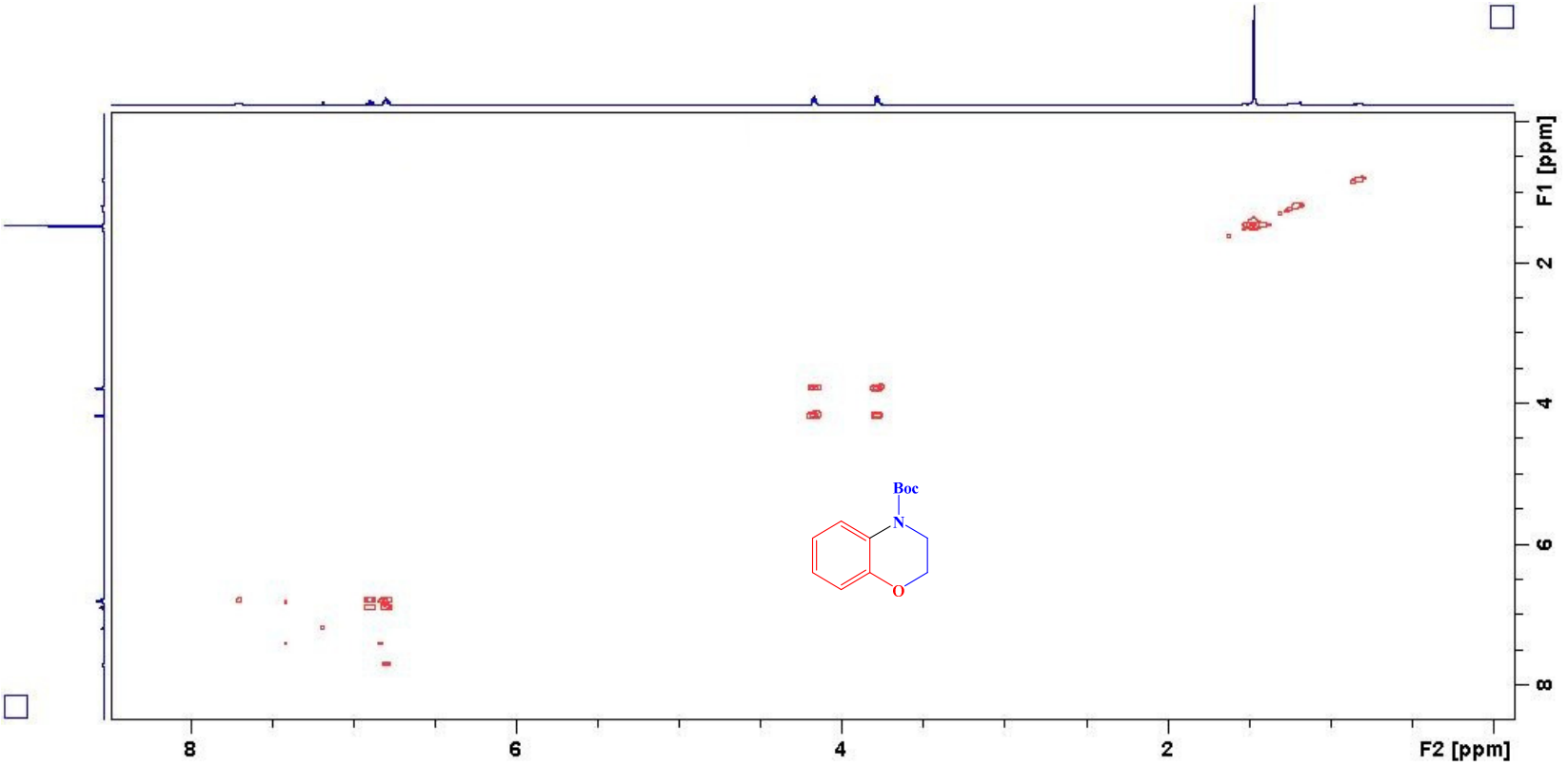
^{1}H NMR spectra of 6a



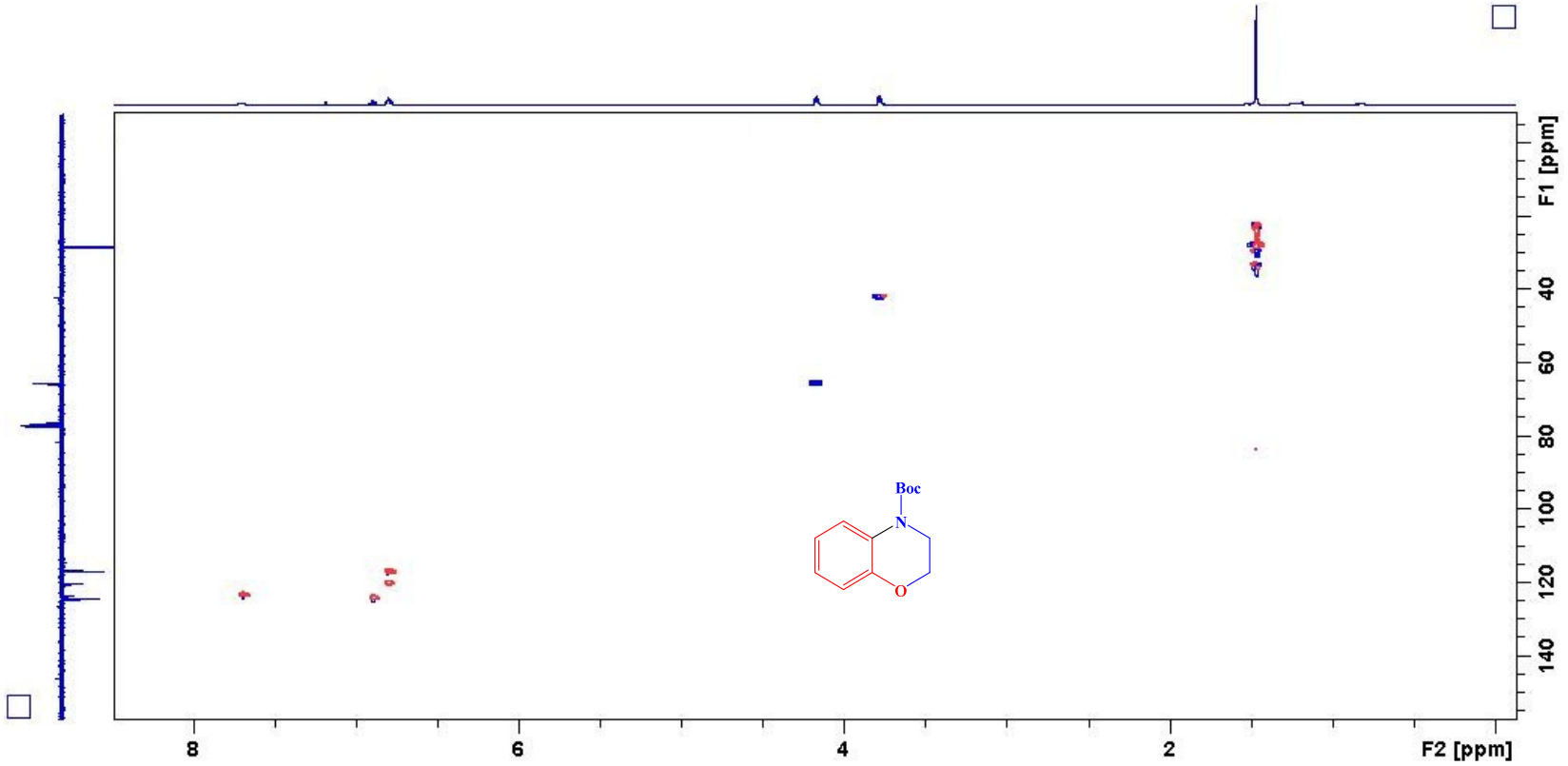
^{13}C NMR spectra of 6a



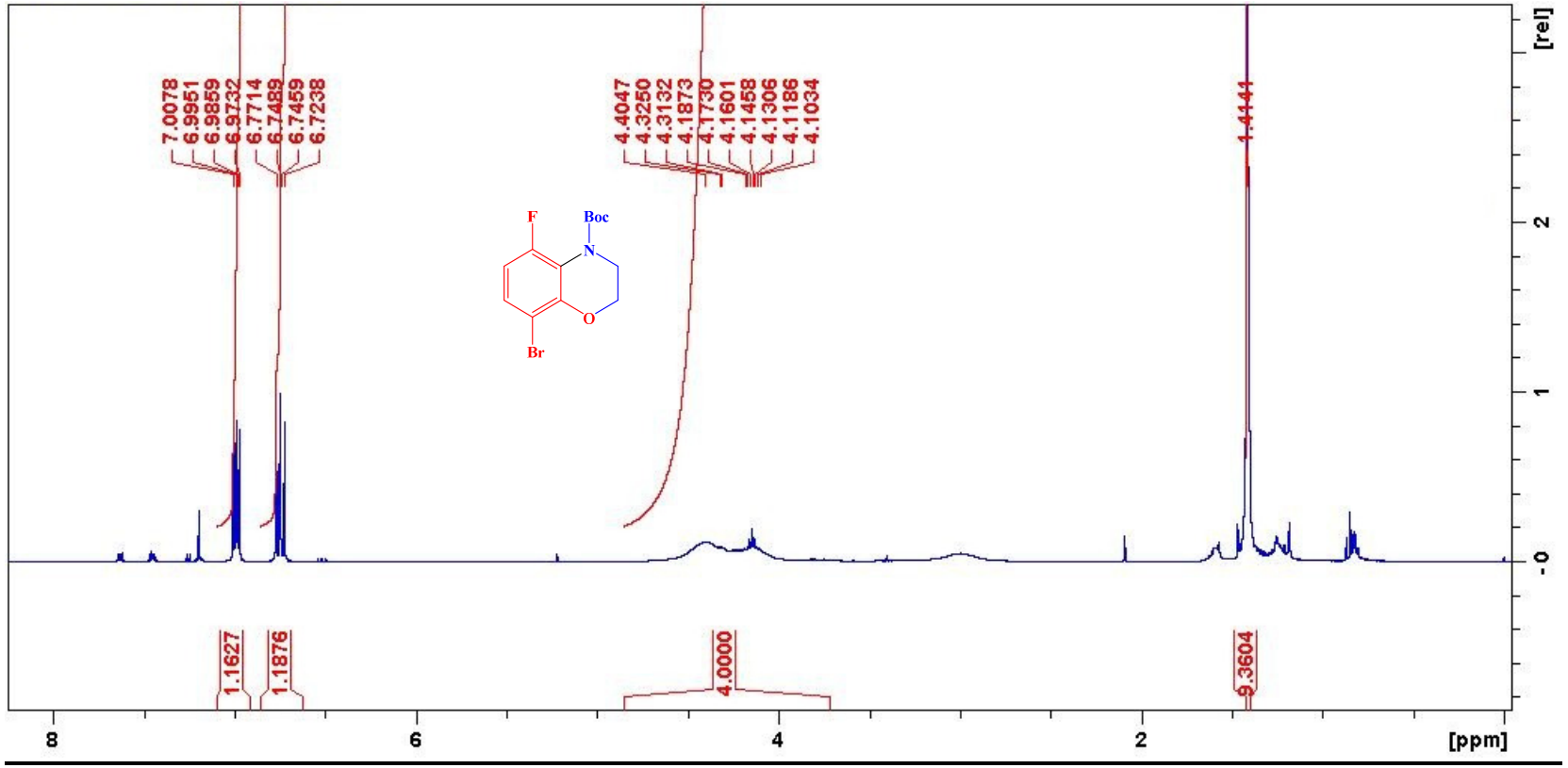
COSY spectra of 6a



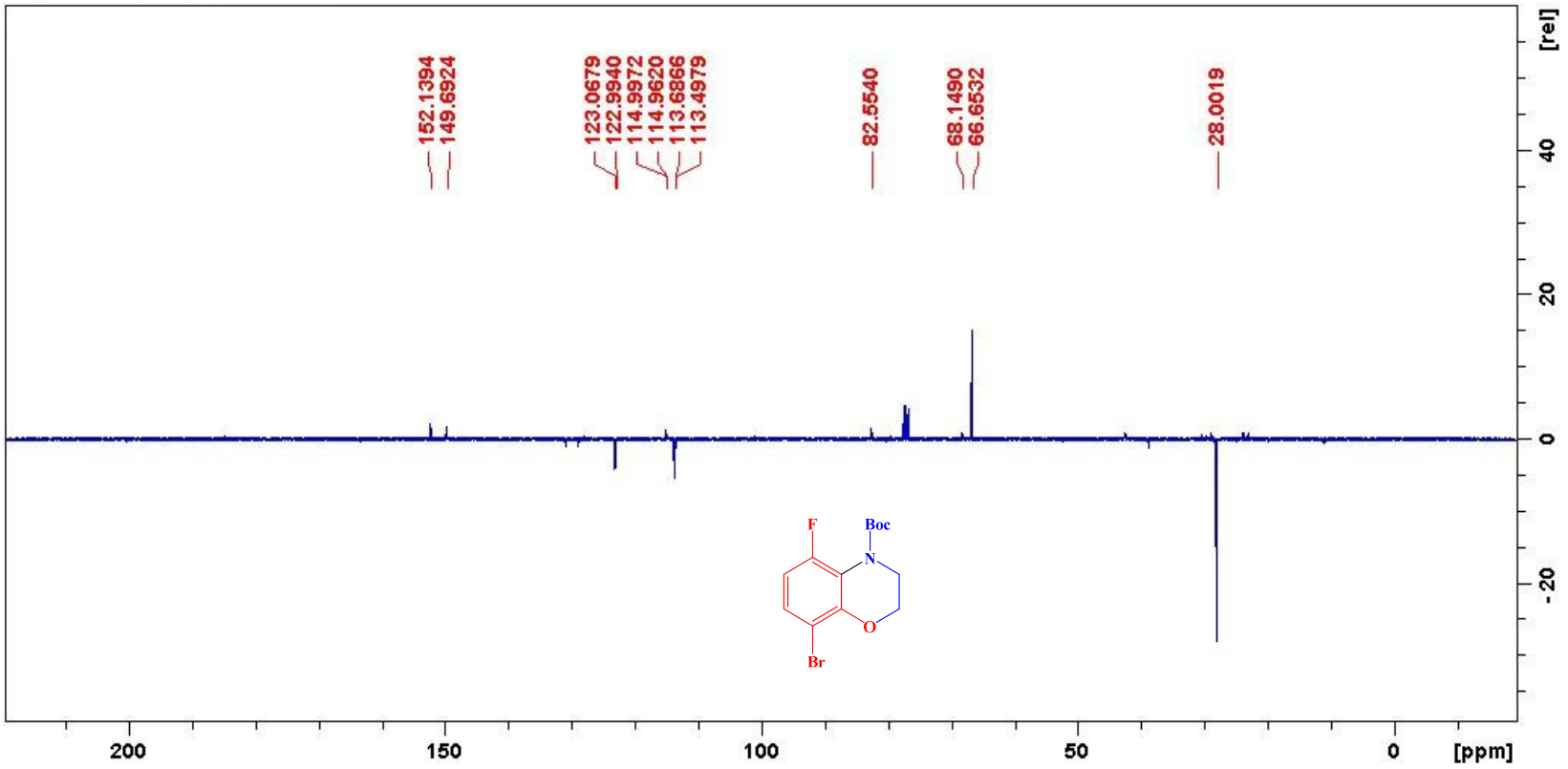
HSQC spectra of 6a



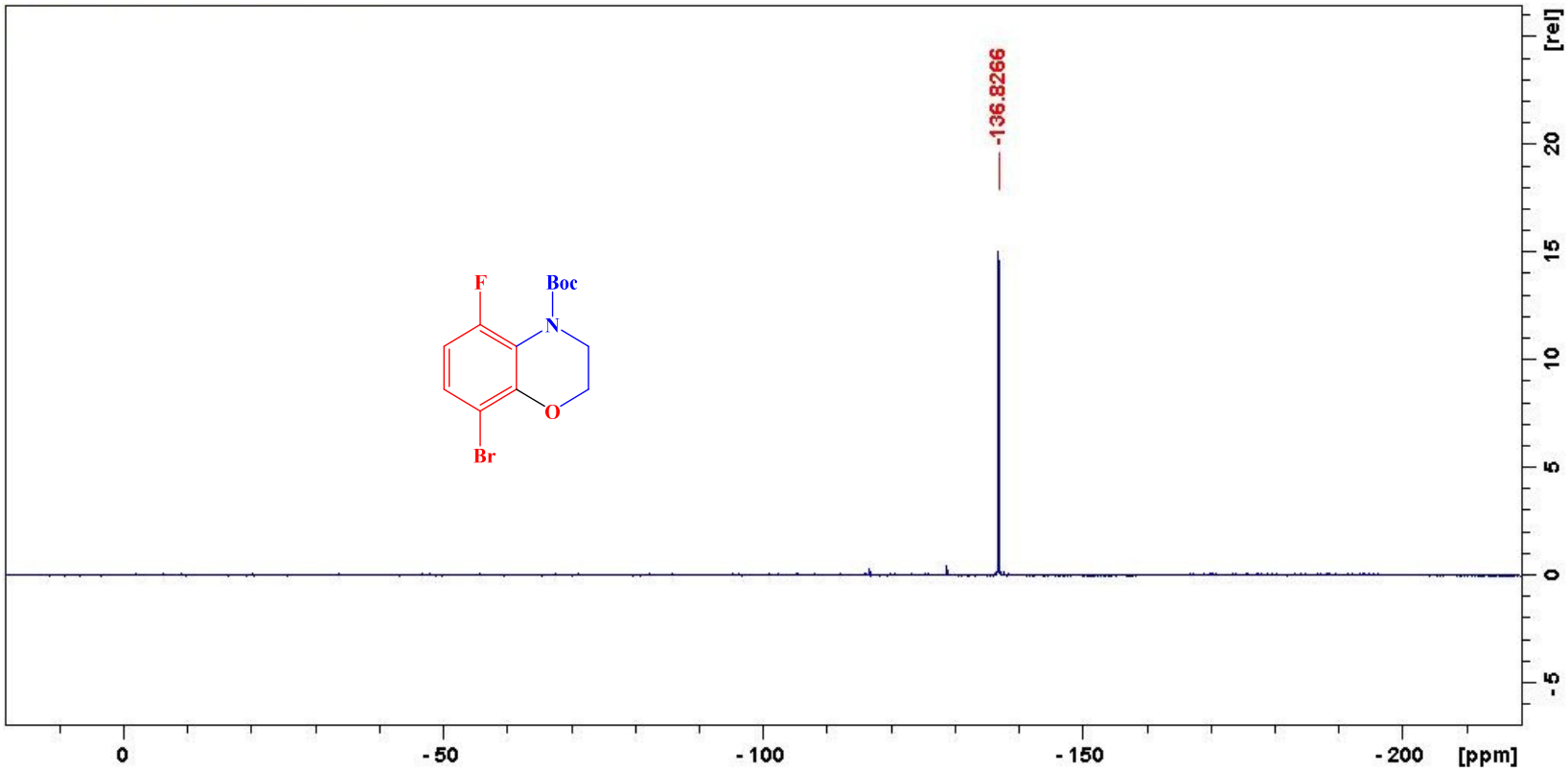
^{1}H NMR spectra of **6c**



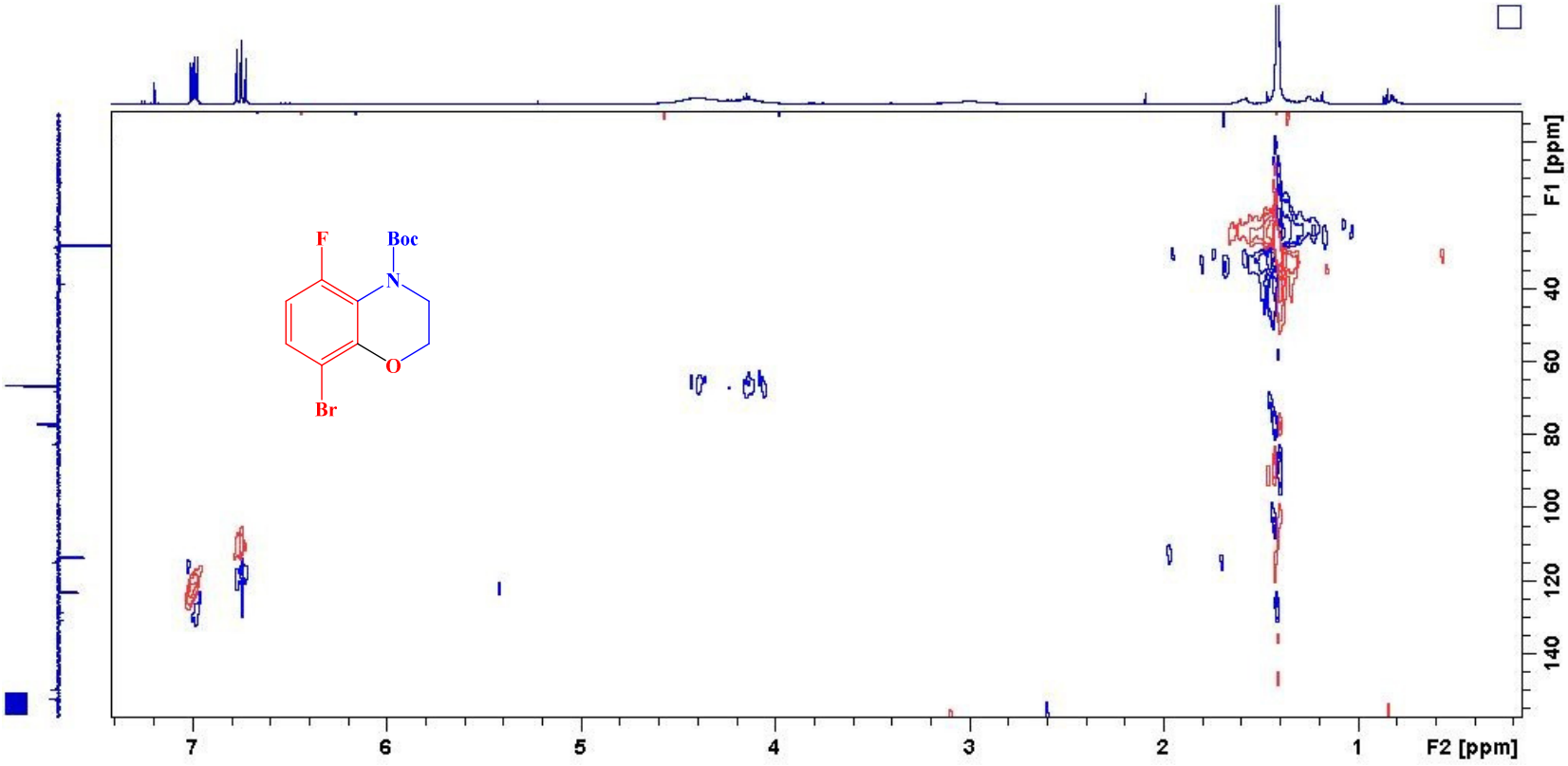
^{13}C NMR spectra of **6c**



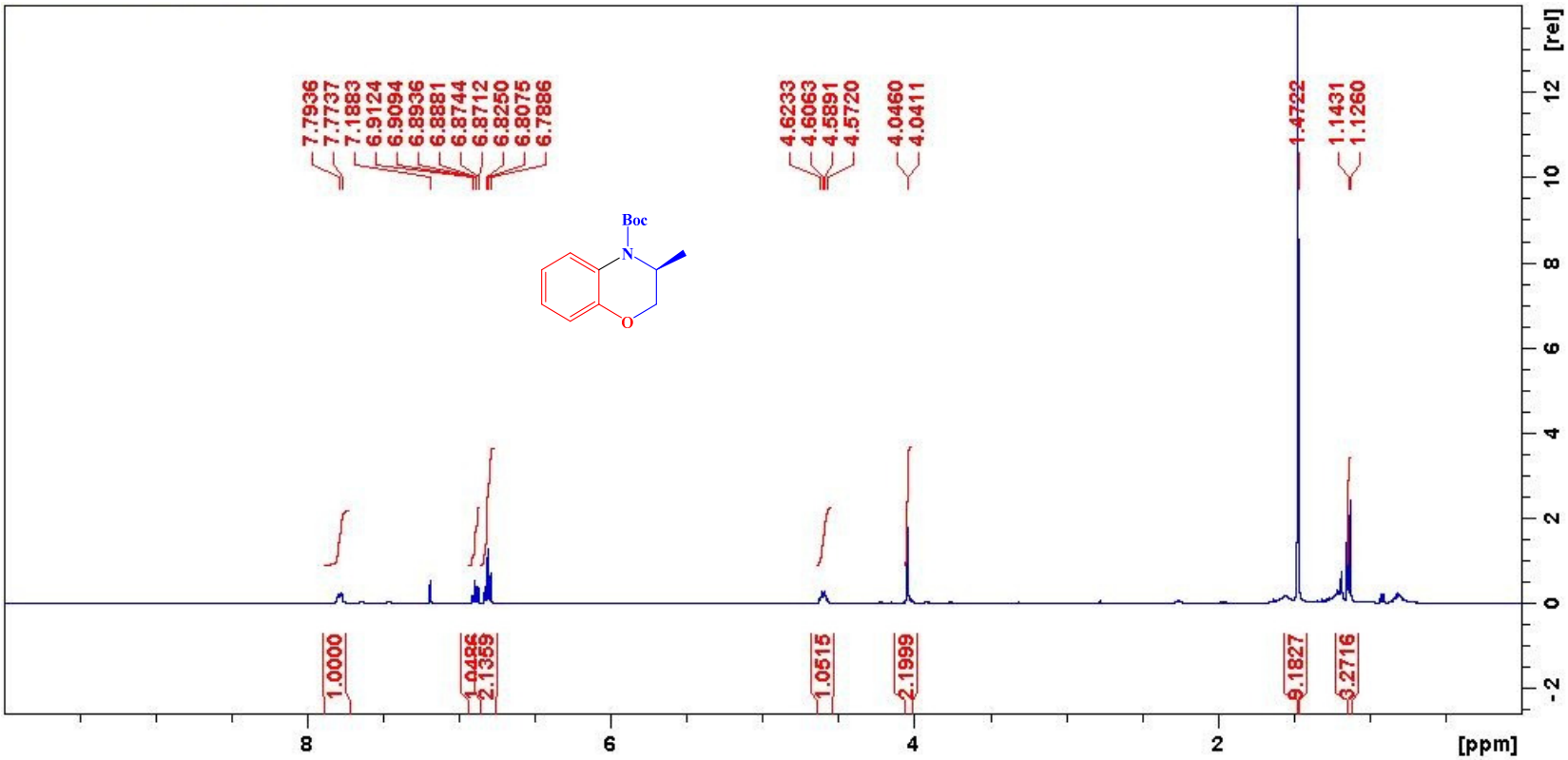
^{19}F NMR spectra of **6c**



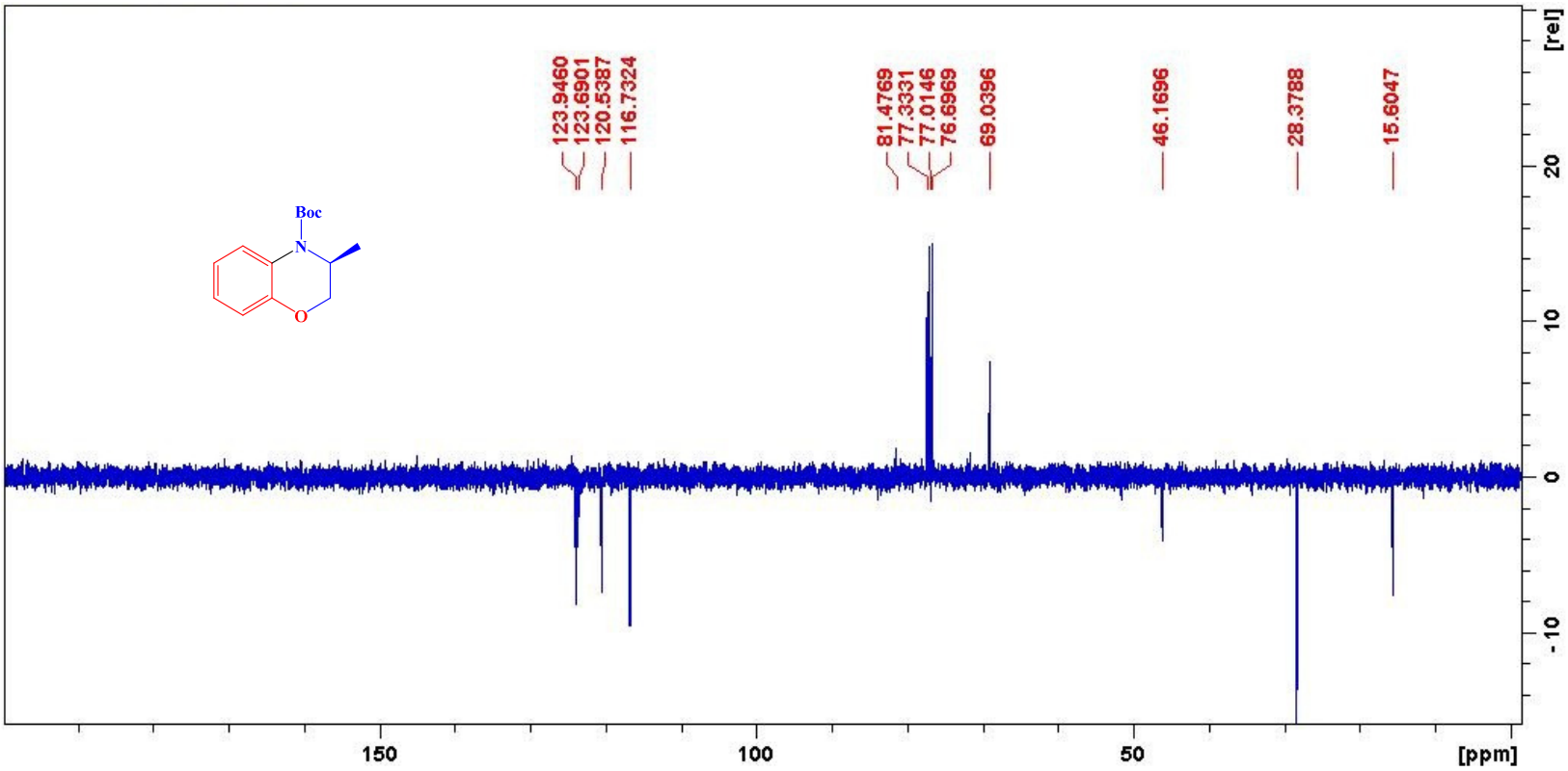
HSQC spectra of **6c**



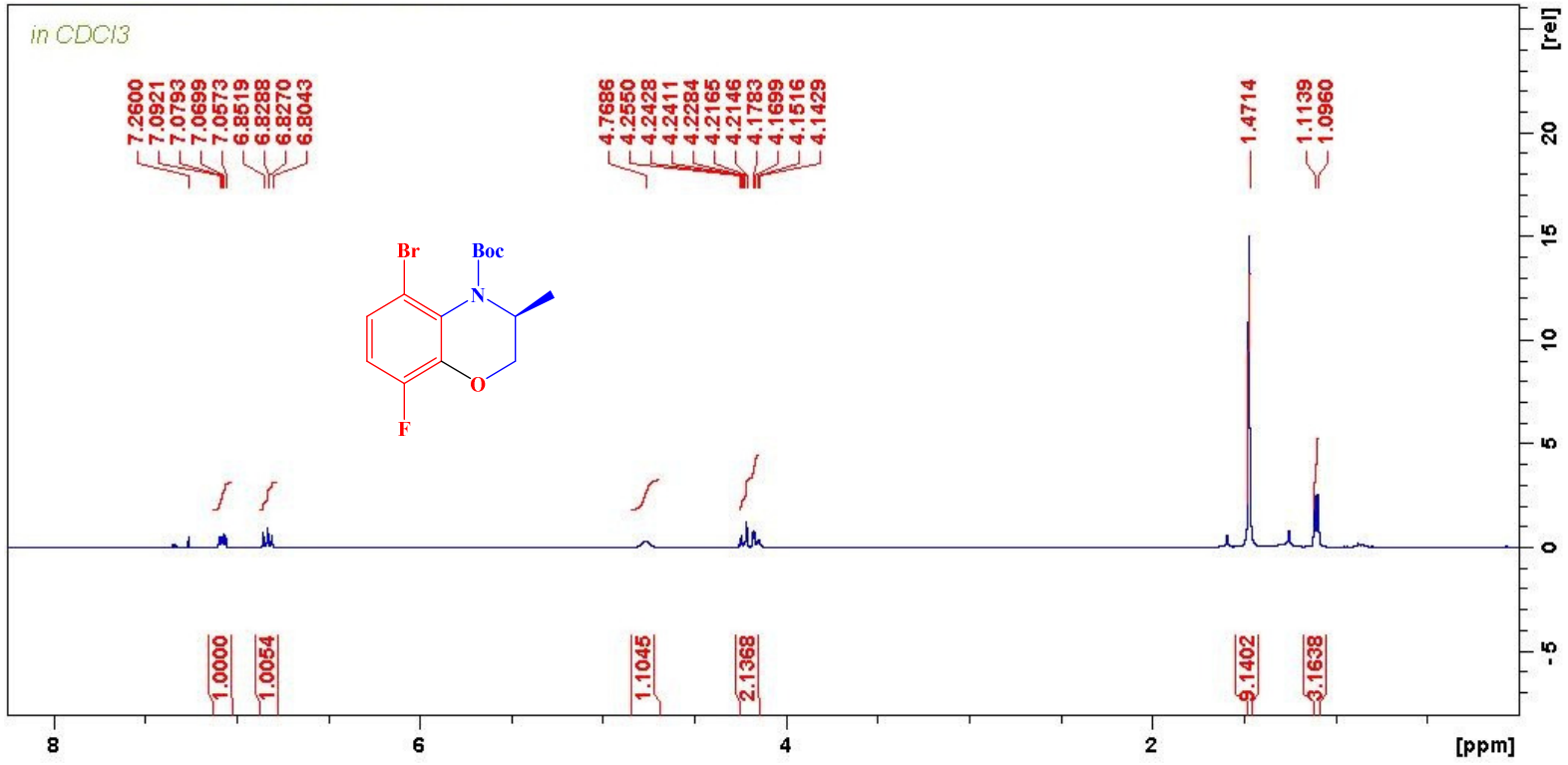
^{1}H NMR spectra of 6d



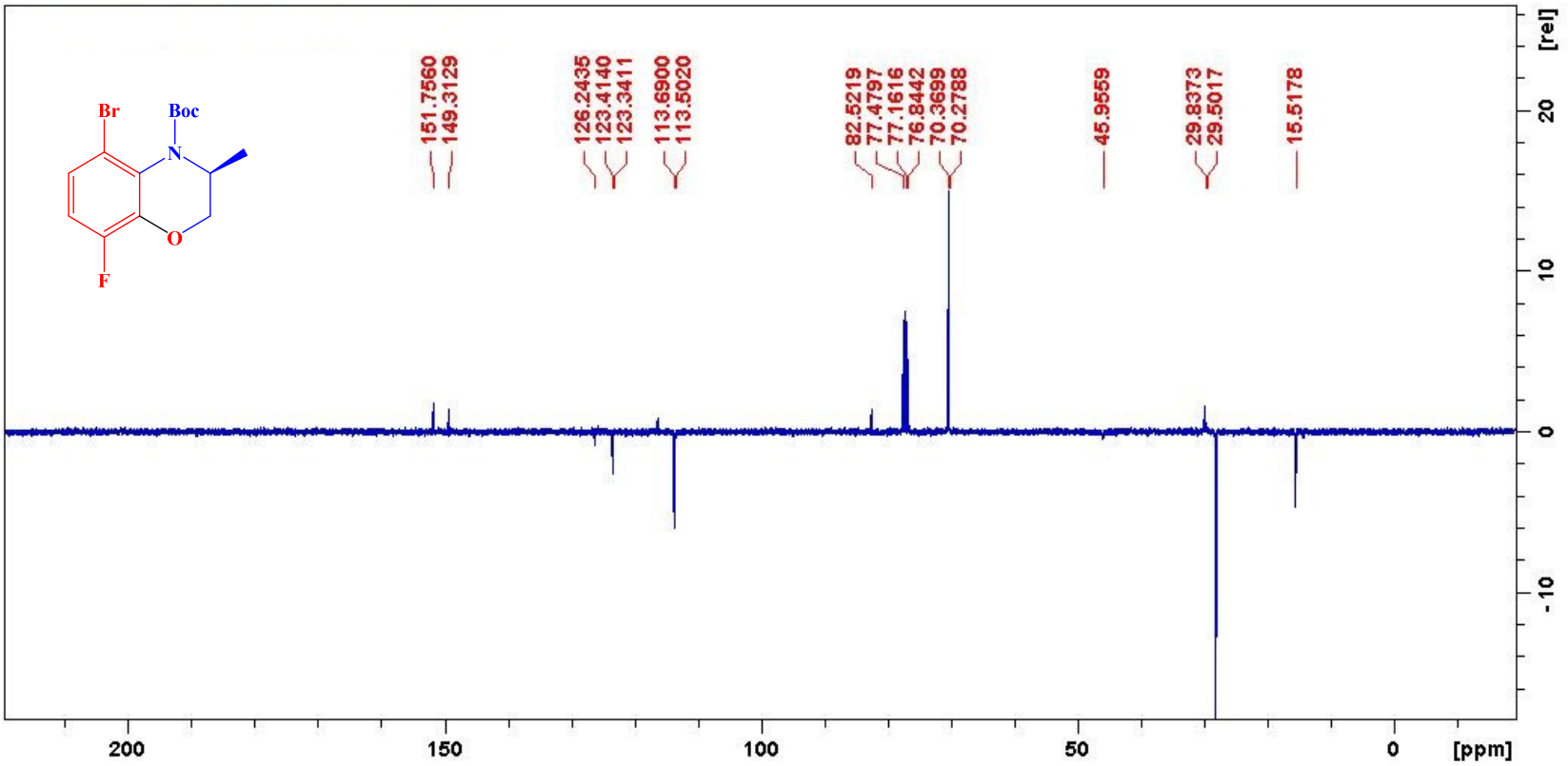
^{13}C NMR spectra of 6d



^{1}H NMR of 6f


in CDCl3
7.2600
7.0921
7.0793
7.0699
7.0573
6.8519
6.8288
6.8270
6.8043
4.7686
4.2550
4.2428
4.2411
4.2284
4.2165
4.2146
4.1783
4.1699
4.1516
4.1429
1.4714
1.1139
1.0960
Br
Boc
N
O
F
1.0000
1.0054
1.1045
2.1368
9.1402
3.1638
8
6
4
2
[ppm]
[rel]
20
15
10
5
0
-5

^{13}C NMR of 6f


Br
Boc
N
O
F
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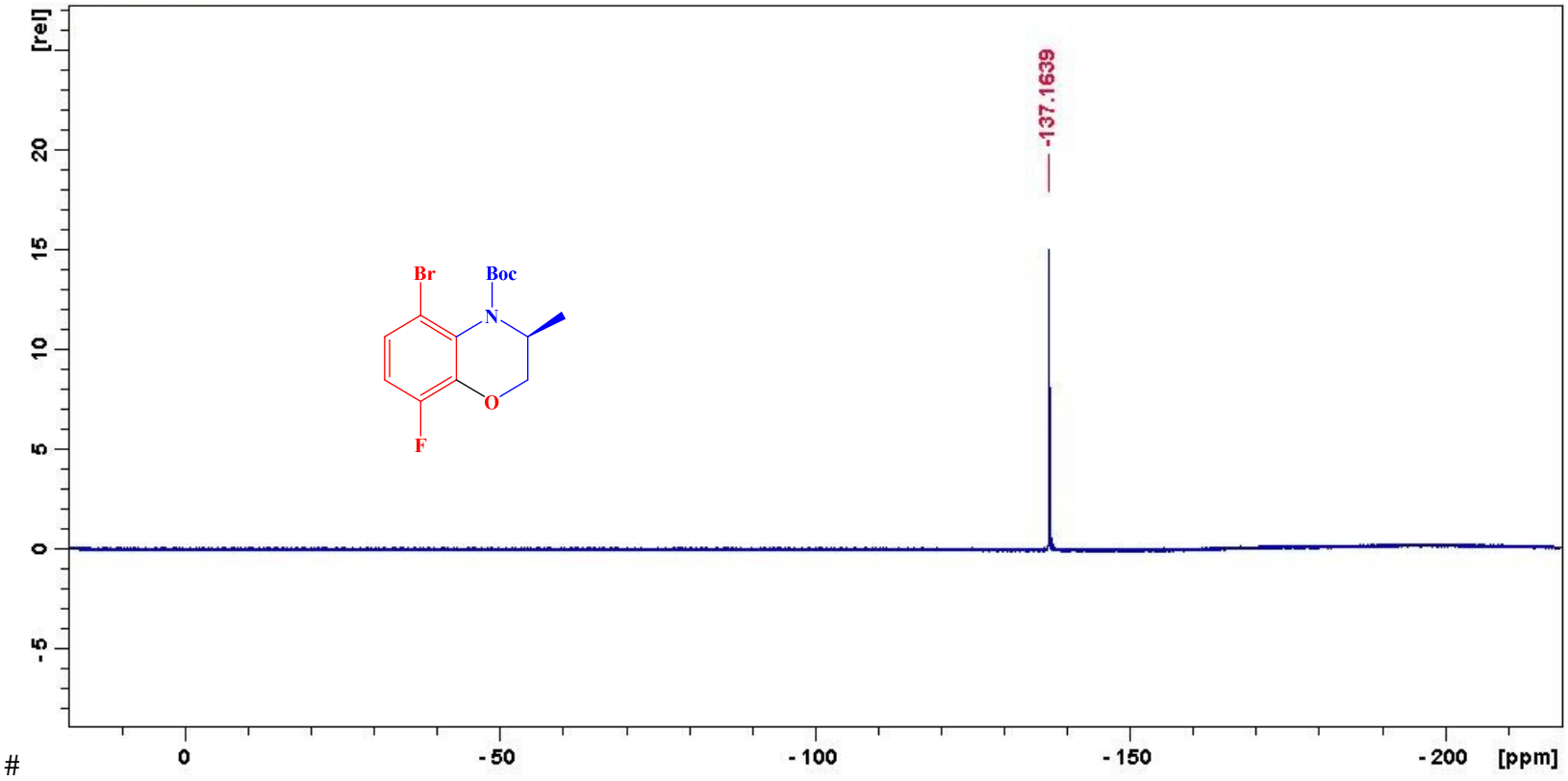
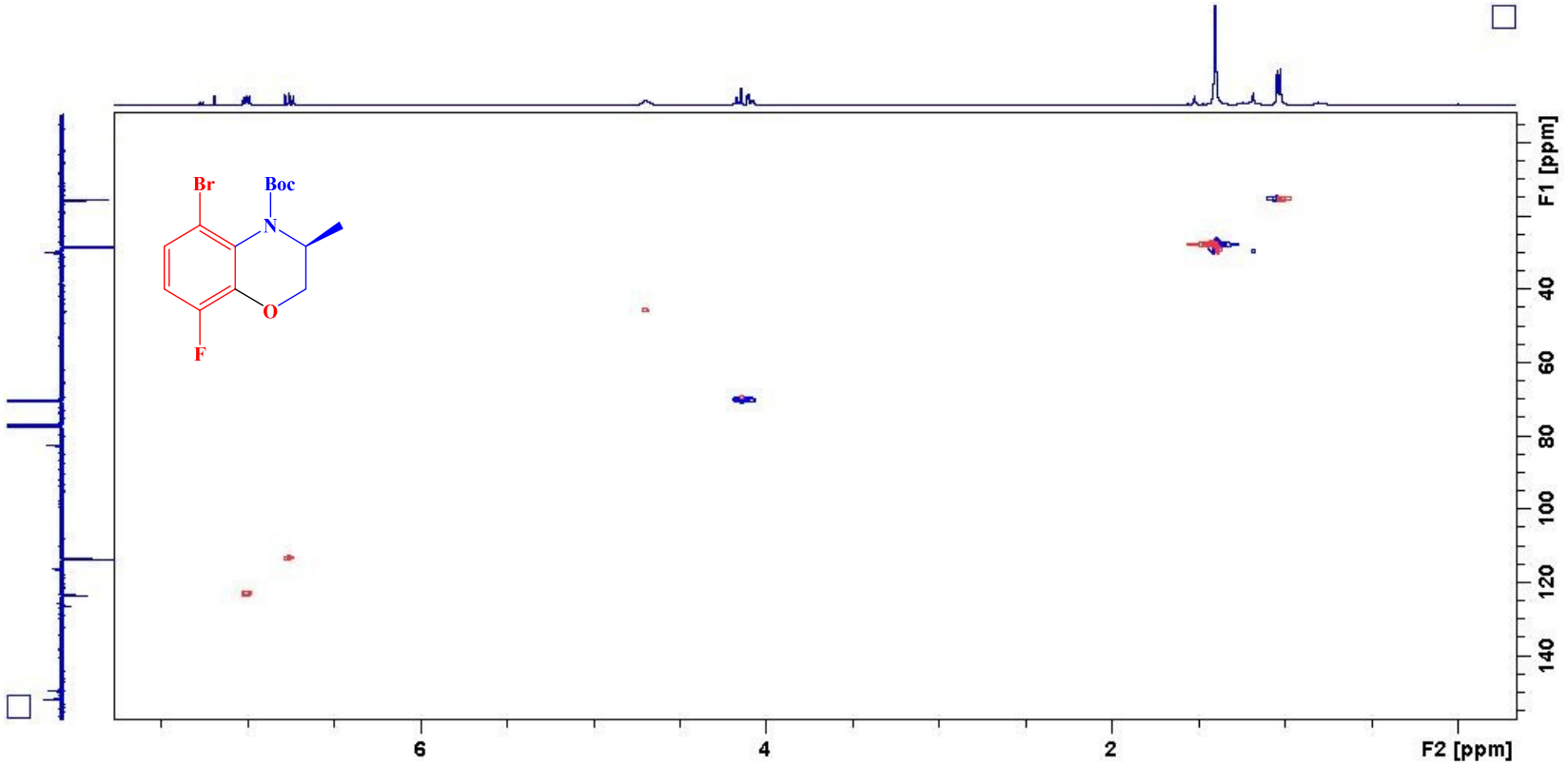
149.3129
126.2435
123.4140
123.3411
113.6900
113.5020
82.5219
77.4797
77.1616
76.8442
70.3699
70.2788
45.9559
29.8373
29.5017
15.5178
[rel]
20
10
0
-10
200
150
100
50
0
[ppm]

^{19}F NMR of 6f

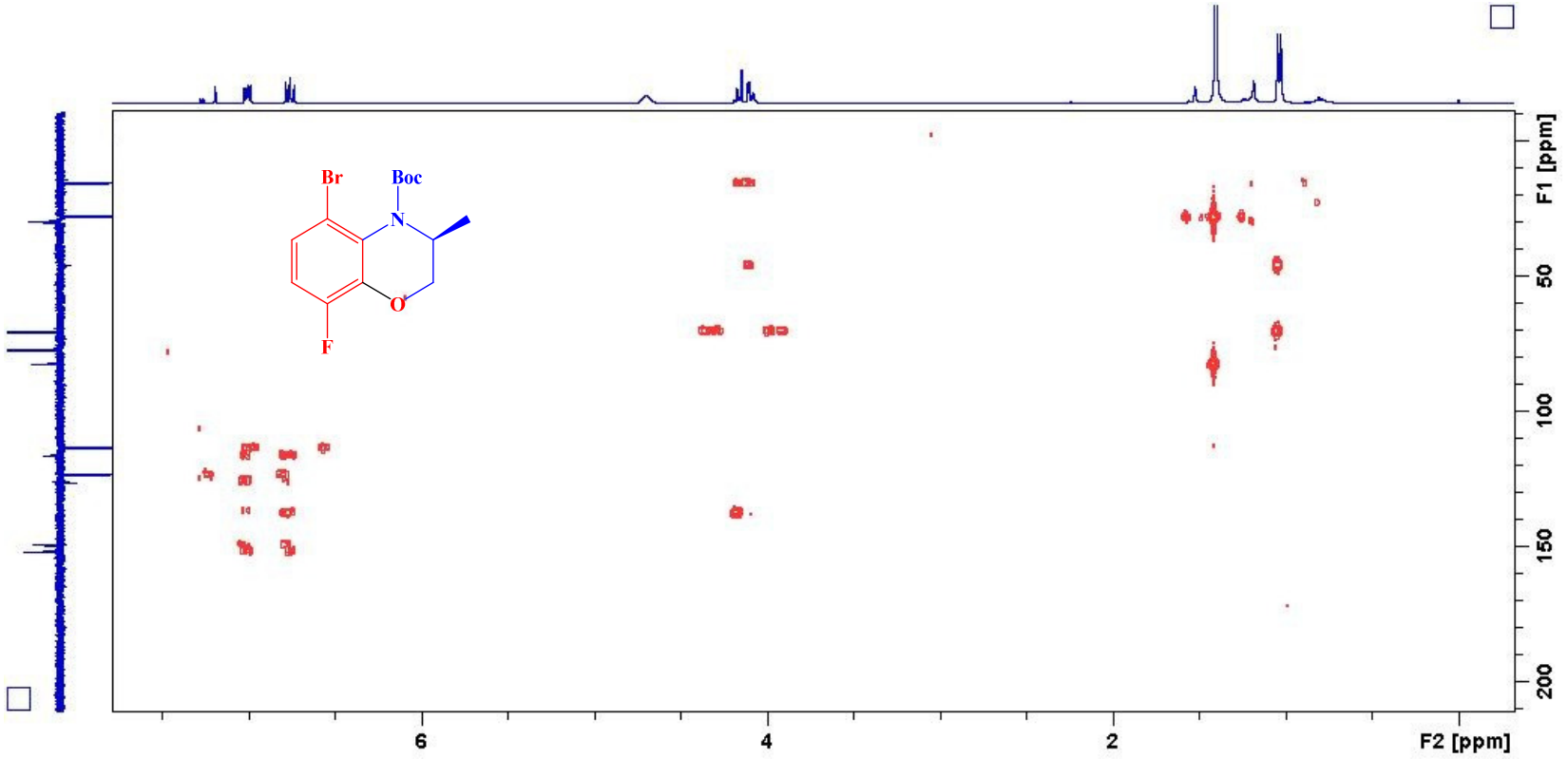


#

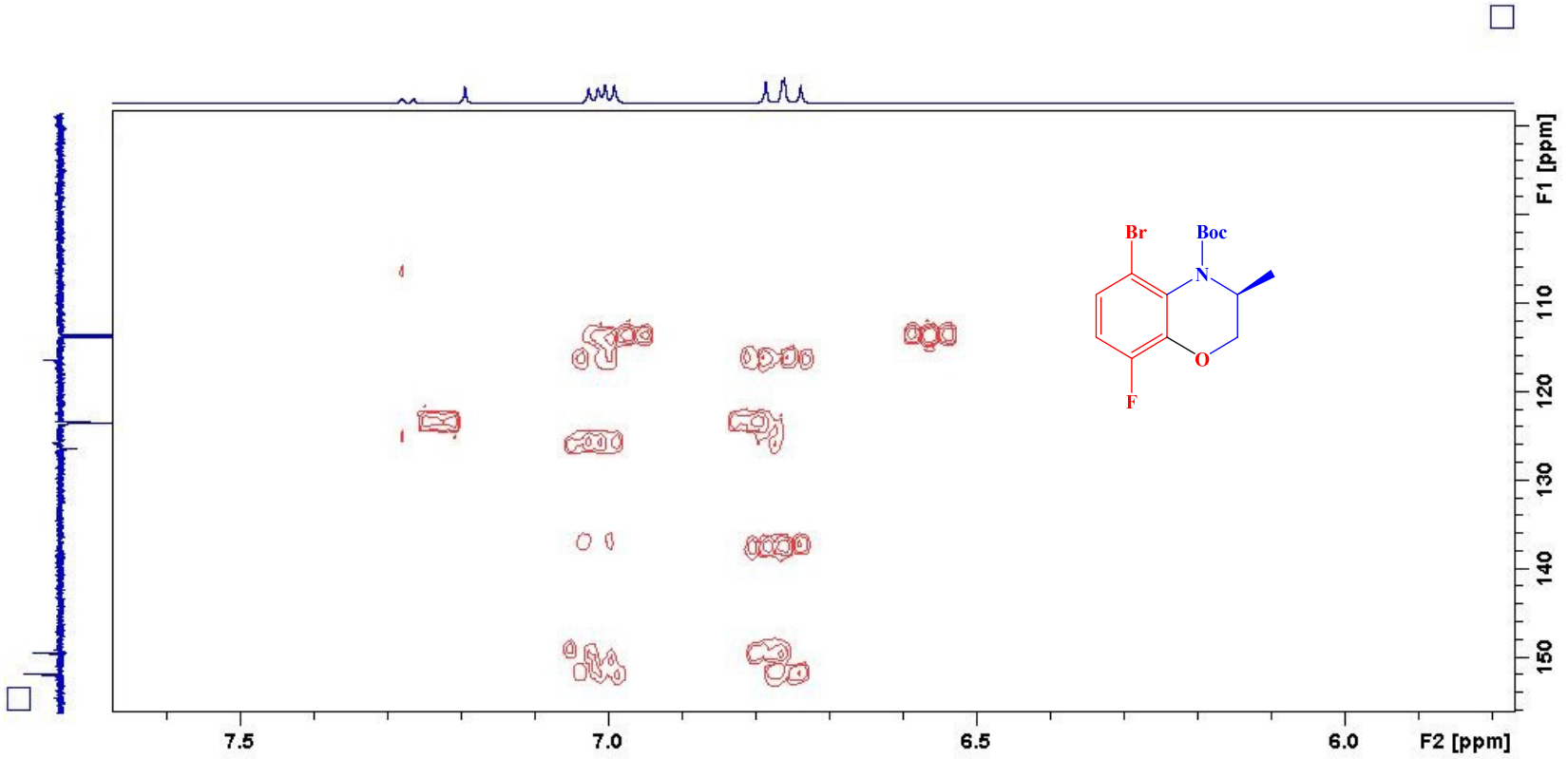
HSQC spectra of 6f



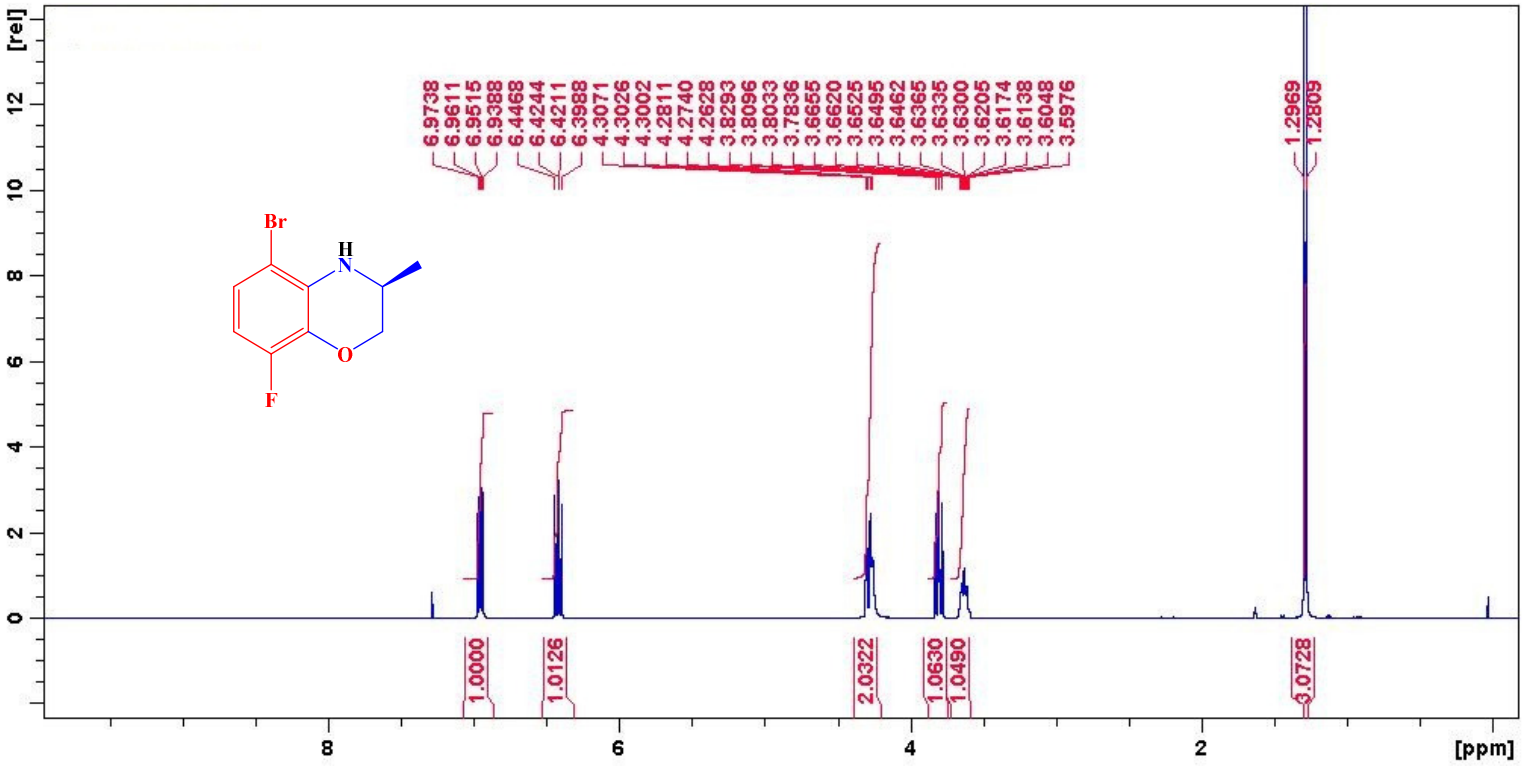
HMBC spectra of 6f



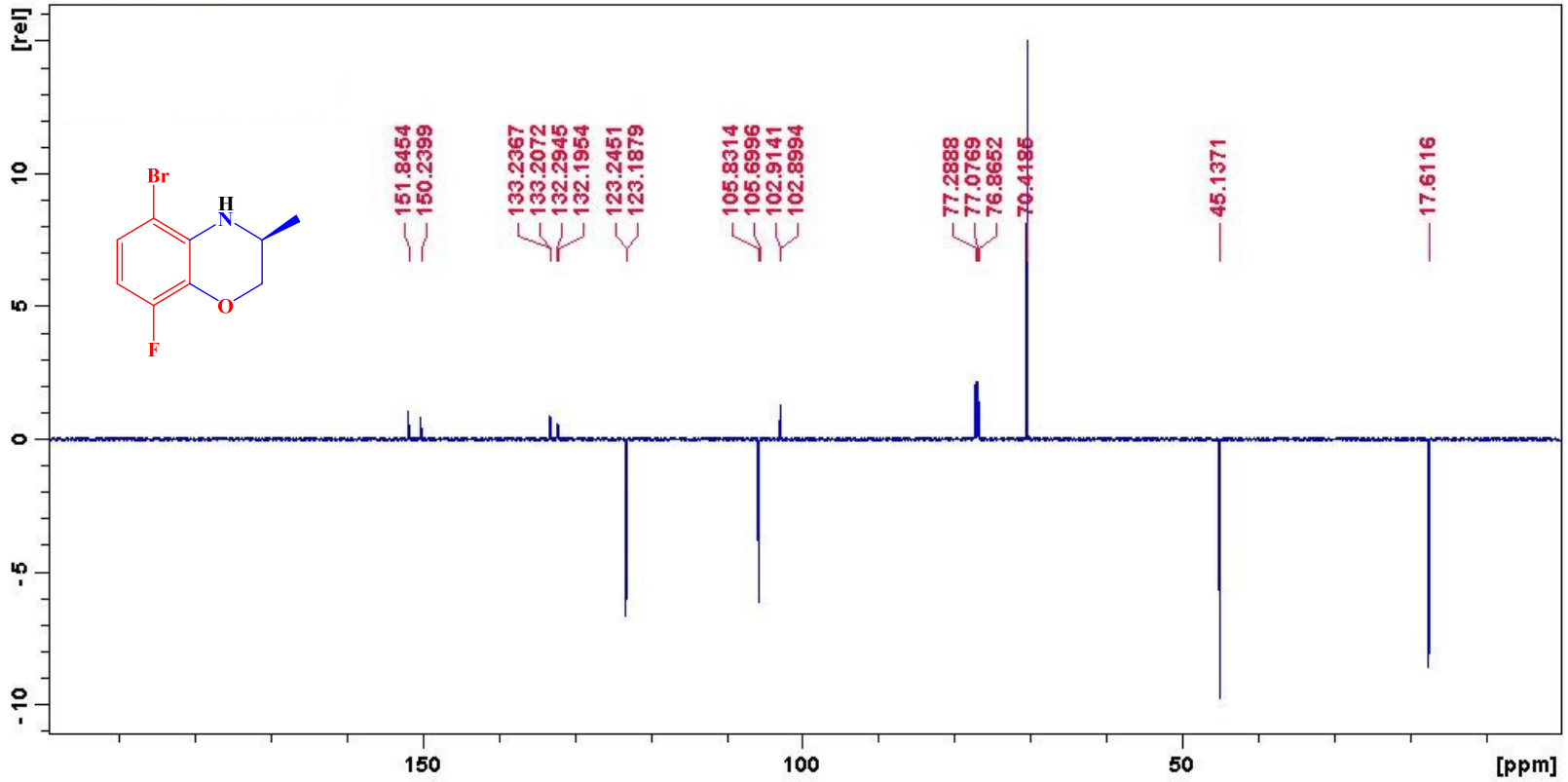
Expansion of HMBC spectra of 6f



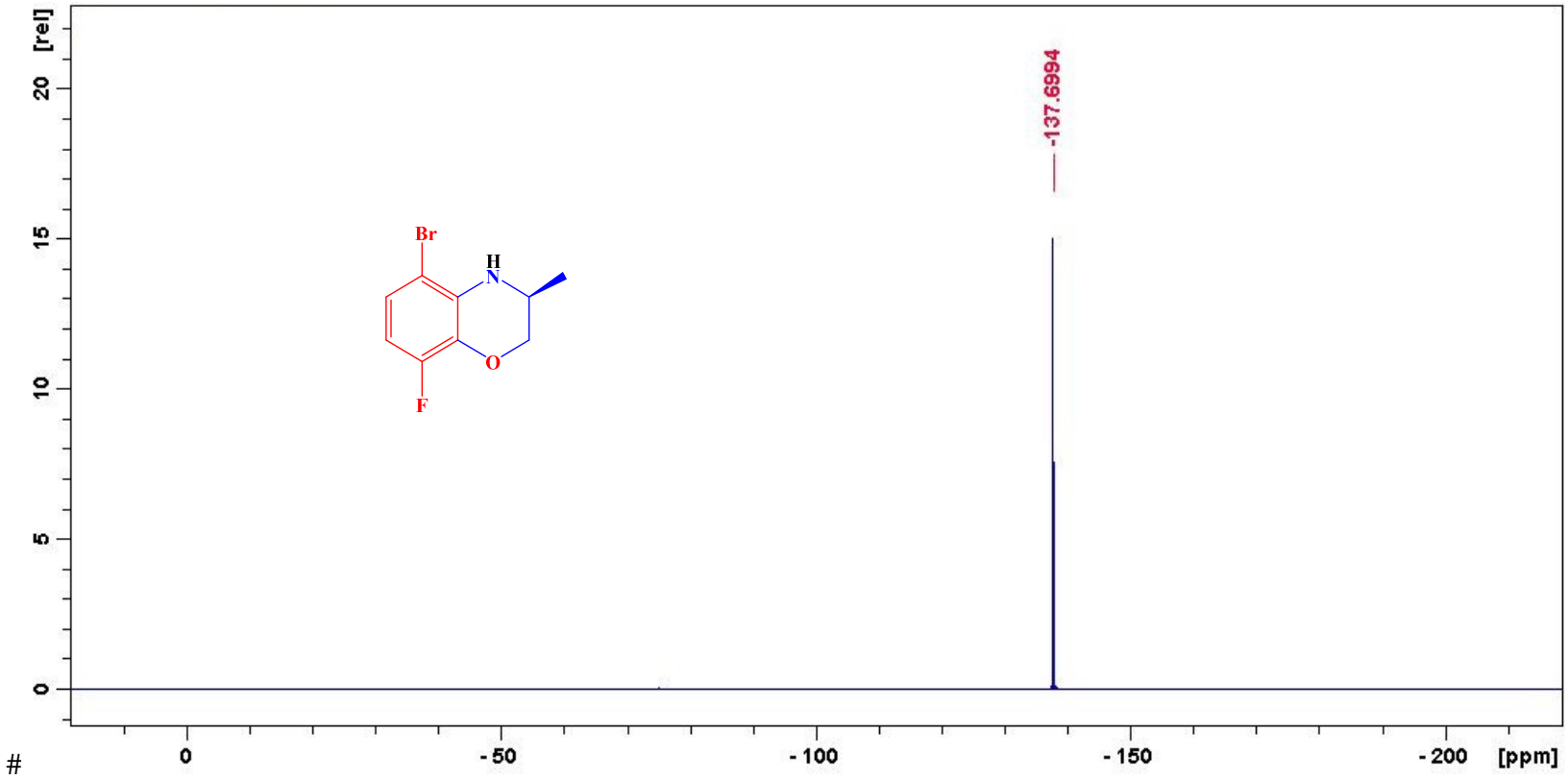
^{1}H NMR of (S)-5-bromo-8-fluoro-3-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (6f deprotected):



^{13}C NMR of (S)-5-bromo-8-fluoro-3-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (6f deprotected):



^{19}F NMR of (S)-5-bromo-8-fluoro-3-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (6f deprotected):



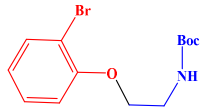
HRMS

5a

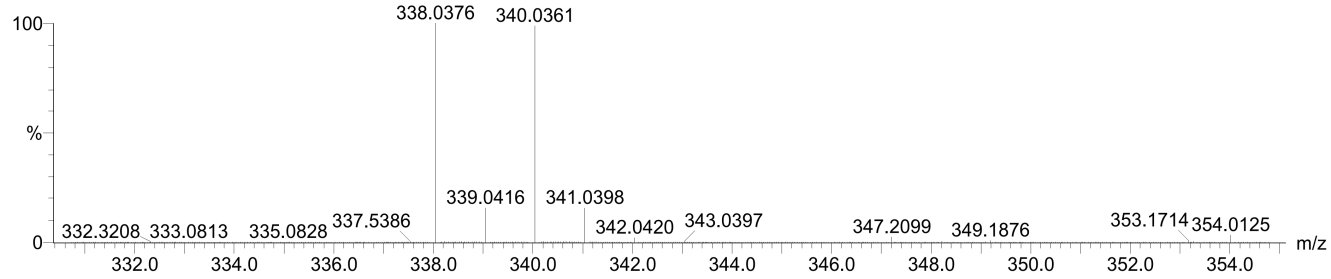
Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
36 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 10-15 H: 15-20 N: 0-5 O: 0-5 Na: 1-1 Br: 0-1
SZBr 56 (1.856) Cm (1:61)
TOF MS ES+



2.15e+005



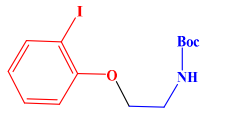
Minimum:				-1.5									
Maximum:		5.0	5.0	100.0									
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula						
338.0376	338.0368	0.8	2.4	4.5	612.6	0.0	C13	H18	N	O3	Na	Br	

5b

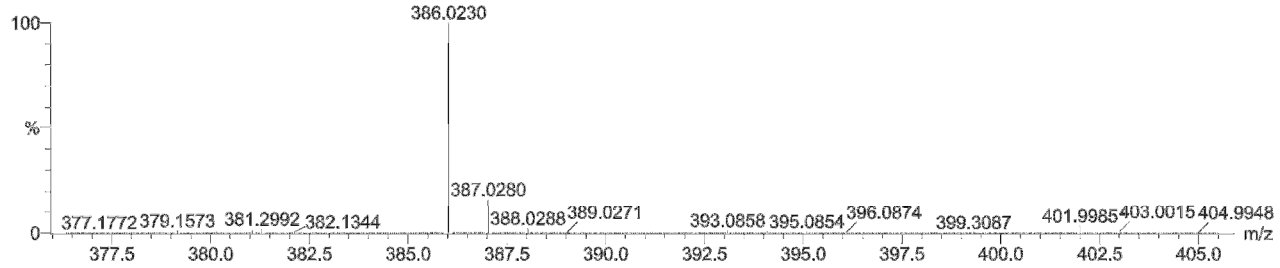
Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
46 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 10-15 H: 15-20 N: 0-5 O: 0-5 Na: 1-1 I: 0-1



SZI 8 (0.236) Cm (1:61)
TOF MS ES+
4.39e+005



Minimum:				-1.5								
Maximum:		5.0	5.0	100.0								
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula					
386.0230	386.0229	0.1	0.3	4.5	640.5	0.0	C13	H18	N	O3	Na	I

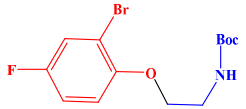
5c

Elemental Composition Report

Single Mass Analysis

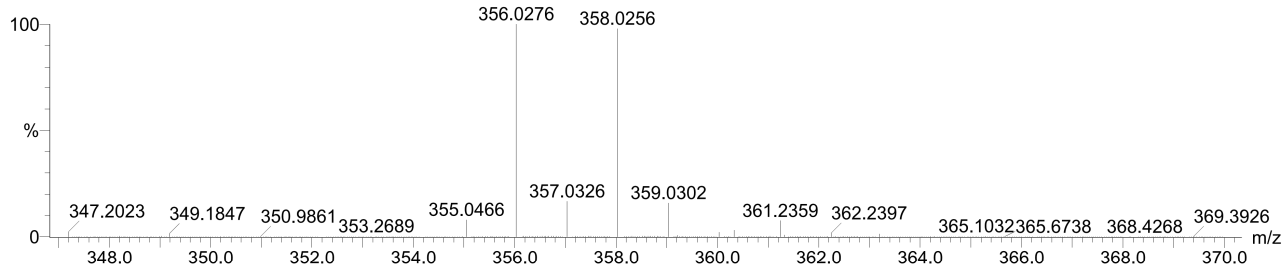
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
82 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 10-15 H: 15-20 N: 0-5 O: 0-5 F: 0-1 Na: 1-1 Br: 0-1



SZ1F 58 (1.923) Cm (1:61)
TOF MS ES+

4.01e+005



Minimum:				-1.5			
Maximum:		5.0	5.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
356.0276	356.0274	0.2	0.6	4.5	643.4	0.0	C13 H17 N O3 F Na Br

5d

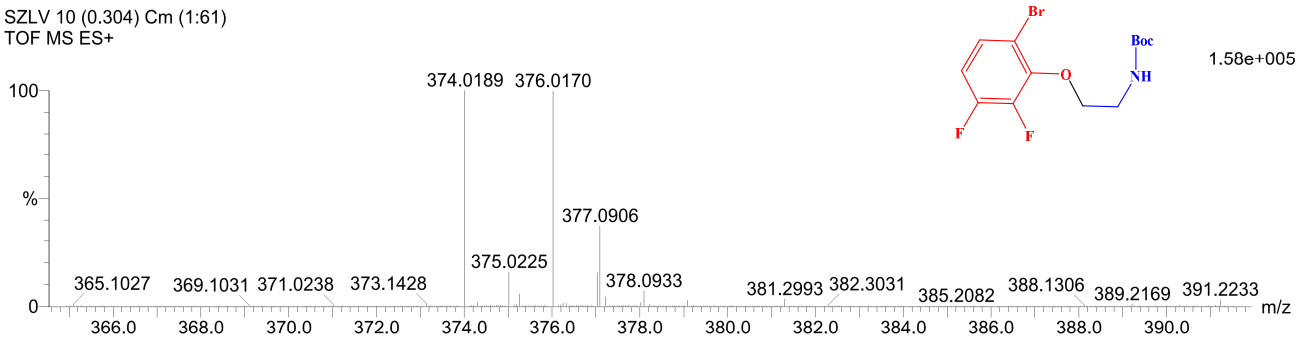
Elemental Composition Report

Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
129 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 10-15 H: 15-20 N: 0-5 O: 0-5 F: 0-2 Na: 1-1 Br: 0-1

SZLV 10 (0.304) Cm (1:61)
TOF MS ES+



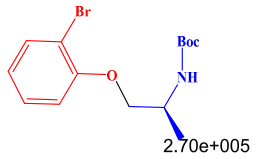
Minimum:				-1.5			
Maximum:		5.0	5.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
374.0189	374.0179	1.0	2.7	4.5	586.2	0.0	C13 H16 N O3 F2 Na Br

5e

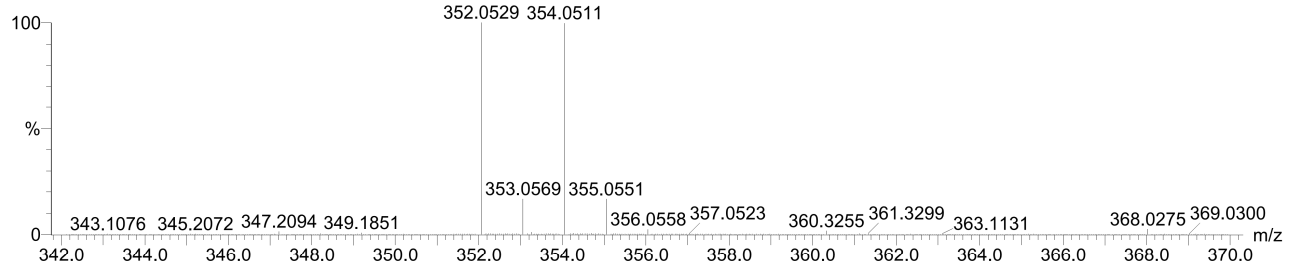
Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
87 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 10-15 H: 20-25 N: 0-5 O: 0-5 Br: 0-1 Na: 0-1



SZBrMe 2 (0.034) Cm (1:61)
TOF MS ES+
2.70e+005



Minimum:				-1.5			
Maximum:		5.0	5.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
352.0529	352.0524	0.5	1.4	4.5	639.4	0.0	C14 H20 N O3 Br Na

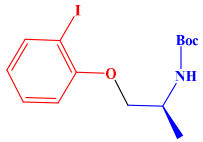
5f

Elemental Composition Report

Single Mass Analysis

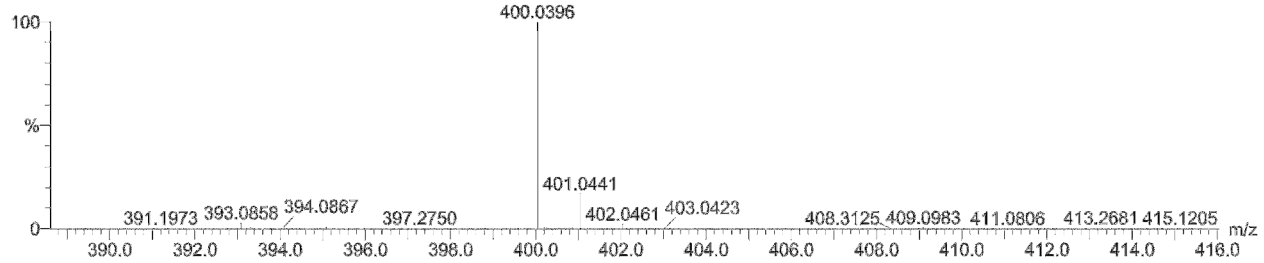
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
48 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 10-15 H: 15-20 N: 0-5 O: 0-5 I: 0-1 Na: 1-1



SZIMe 57 (1.690) Cm (1:61)
TOF MS ES+

3.75e+005



Minimum:				-1.5			
Maximum:		5.0	5.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
400.0396	400.0386	1.0	2.5	4.5	642.4	0.0	C14 H20 N O3 I Na

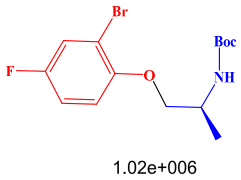
5g

Elemental Composition Report

Single Mass Analysis

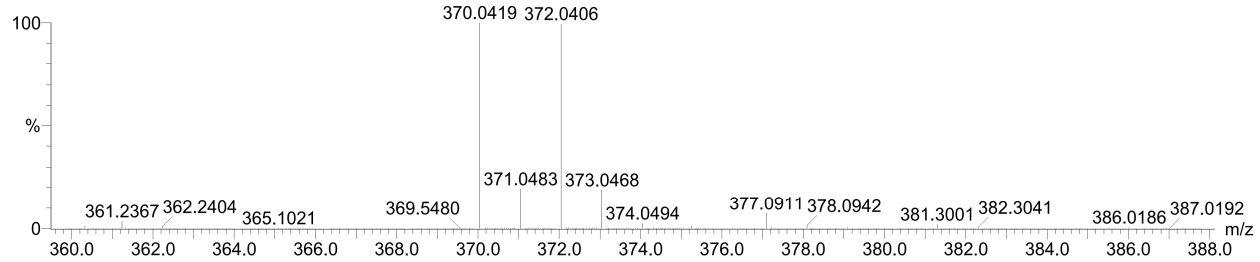
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
87 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 10-15 H: 15-20 N: 0-5 O: 0-5 F: 0-1 Na: 1-1 Br: 0-1



SZ1FMe 8 (0.236) Cm (1:61)
TOF MS ES+

1.02e+006



Minimum:				-1.5			
Maximum:		5.0	5.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
370.0419	370.0430	-1.1	-3.0	4.5	680.6	0.0	C14 H19 N O3 F Na Br

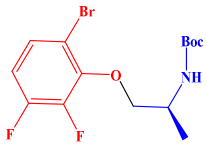
5h

Elemental Composition Report

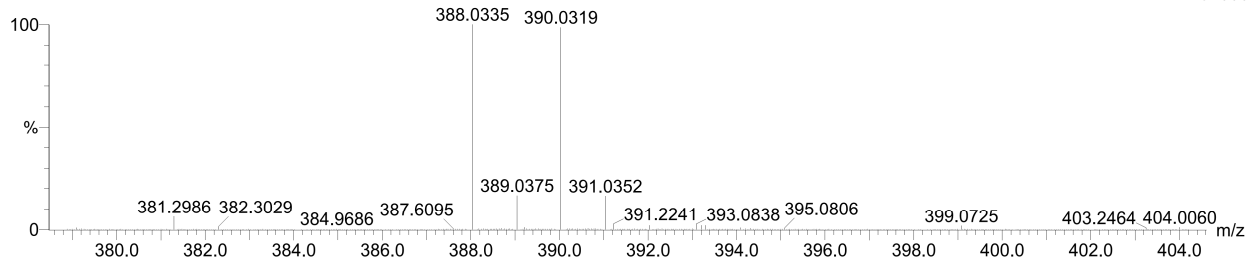
Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
138 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 10-15 H: 15-20 N: 0-5 O: 0-5 F: 0-2 Na: 1-1 Br: 0-1



SZLVMe 1 (0.034) Cm (1:60)
TOF MS ES+



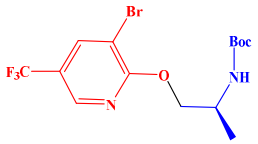
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
Minimum:				-1.5			
Maximum:		5.0	5.0	100.0			
388.0335	388.0336	-0.1	-0.3	4.5	603.8	0.0	C14 H18 N O3 F2 Na Br

5i

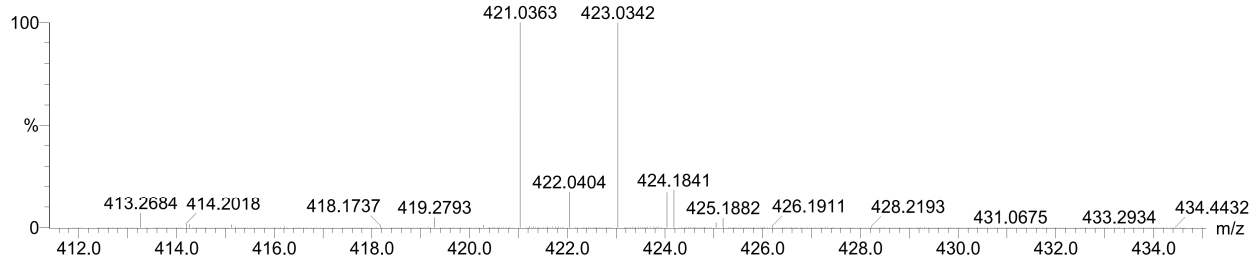
Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
212 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 10-15 H: 15-20 N: 0-5 O: 0-5 F: 0-3 Br: 0-1 Na: 1-1



SZCF3NMe 52 (1.720) Cm (1:61)
TOF MS ES+
2.79e+005

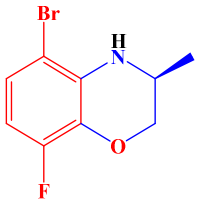


Minimum:				-1.5			
Maximum:		5.0	5.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
421.0363	421.0351	1.2	2.9	4.5	602.5	0.0	C14 H18 N2 O3 F3 Br Na

(S)-5-bromo-8-fluoro-3-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine:

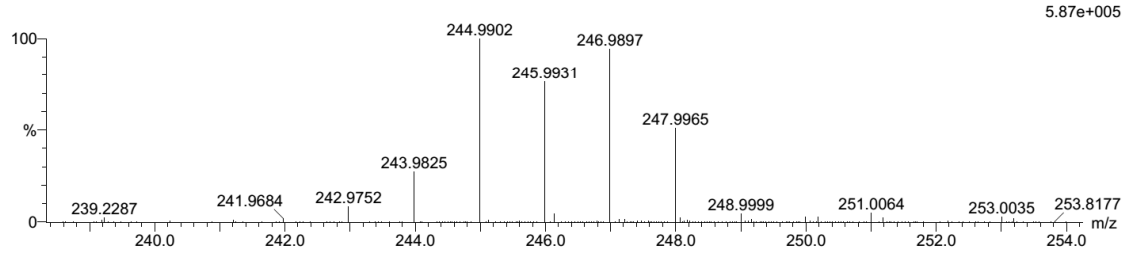
Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3



Monoisotopic Mass, Even Electron Ions
66 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 5-10 H: 5-10 N: 0-5 O: 1-5 F: 0-1 Br: 0-1

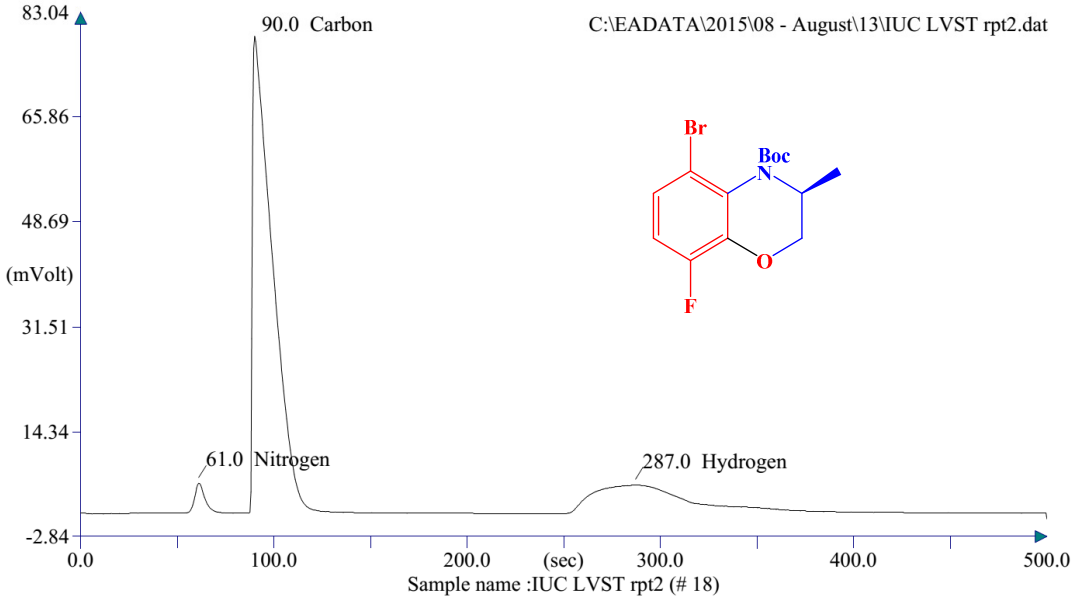
DepLVST AP+ 45 (1.484) Cm (1:61)
TOF MS AP+



Minimum:				-1.5			
Maximum:		5.0	5.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
245.9931	245.9930	0.1	0.4	4.5	796.6	0.0	C9 H10 N O F Br

Elemental analysis for 6f:

Elemental Analysis
CHNS



Retention Time (min)	Element Name	Element %
1.017	Nitrogen	3.981
1.500	Carbon	48.752
4.783	Hydrogen	4.684
		57.418