An Aryne-Based Route to Substituted Benzoisothiazoles

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Supporting Information

Content

1. Experimental:

All procedures below were conducted under inert nitrogen atmosphere unless stated otherwise. Reagents were purchased from Sigma-Aldrich, Alfa Aesar, Acros and Fluorochem and were used as supplied unless stated otherwise. TMSCl was distilled fresh before use. Triethylamine (TEA) and diisoprolylamine were distilled from CaH_2 and stored over KOH. EtOH was dried and distilled fresh from magnesium turnings and tetrachloromethane and stored over KOH. All other dry solvents i.e. THF, MeOH, MeCN and toluene were dried over 4 Å molecular sieves and through anhydrous alumina columns using an Innovative Technology Inc. PS-400-7 solvent purification system. Other solvents, including work-up solvents, were employed directly from commercial sources, i.e. Sigma-Aldrich unless stated otherwise. Petroleum ether refers to the fractions collected between 40-60 ℃ b.p.

Reactions were monitored *via* thin layer chromatography (TLC) on pre-coated aluminium plates (Merck Kieselgel 60 F_{254}). Products were visualized by UV light (254 nm) and/or with $KMnO_4$ stain. Flash column chromatography was conducted using silica gel 60 (Geduran Si 60, 40-63 μm) with head pressure from hand bellows.

^1H NMR, ^{13}C NMR and ^{19}F NMR data were obtained from a Bruker Avance AV 500 or a Bruker Avance AV 400 NMR spectrometer. Chemical shifts (δ) are referenced to the residual solvent as $CDCl_3$ or DMSO-d_6 in the unit of parts per million (ppm). Coupling constants *J* are quoted in the unit of hertz (Hz). Proton and carbon multiplicity is recorded as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m) and broad (b). All compounds examined were dried *in vacuo* to remove residual solvents. Determination of inseparable regioisomers were carried out on 500 MHz ^1H NMR, 125 MHz ^{13}C NMR and 376 MHz ^{19}F NMR spectra.

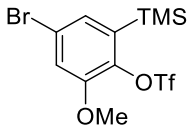
Low resolution mass spectra (LRMS) were recorded on a Fisons Platform II spectrometer. High resolution mass spectrometry (HRMS) was performed on a Bruker MicroTof spectrometer using electrospray ionization method (ESI) or on a Micromass LCT spectrometer using filed ionization method (FI) or electron ionization (EI).

Infra-red spectra were recorded neat on a Bruker Tensor 27 FT-IR spectrometer using a PIKE Miracle ATR module.

All compounds listed in the paper are >95% purity. 3-Chloro-benzoisothiazole products appear to be very hydroscopic therefore some of the products have 0.2 - 0.5 mol equivalents of water (relatively 2 - 5 wt%) present in the proton NMR spectra as shown below.

2. Synthesis of benzyne precursors

2-Methoxy-4-bromo-6-(trimethylsilyl)phenyl trifluoromethanesulfonate

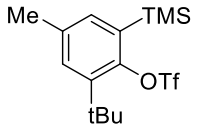


2,4-Dibromo-6-methoxyphenol[1] (2.16 g, 10.0 mmol) was added to a solution of HMDS (4.3 mL, 20.0 mmol, 2.0 eq.) in dry THF (10 mL) under nitrogen. The mixture was heated to 85 ℃ and stirred for 5 h prior to cooling to room temperature. Unreacted HMDS and by-product NH_3 were removed *in vacuo*. The crude (2,4-dibromo-6-methoxyphenoxy)trimethylsilane was used directly in the next step.

n-BuLi (12.5 mL, 1.6M in toluene, 20.0 mmol, 2.0 eq.) was added dropwise to a solution of the crude (2,4-dibromo-6-methoxyphenoxy)trimethylsilane in THF (10 mL) at -90 ℃ over a period of 10 min. The mixture was stirred for 1 h before triflate anhydride (3.31 mL, 20.0 mmol, 2.0 eq.) was added dropwise over a period of 15 min. The reaction mixture was stirred at -90℃ for 1 h. Water (10 mL) was then added, and the crude product was extracted with Et_2O (3 × 20 mL). Combined organic layer was washed by brine (2 × 20 mL), dried over $MgSO_4$, filtered and concentrated. Flash column chromatography (100% petroleum ether) afforded the desired product as a colourless oil (2.52 g, 74%).

^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.08 (d, J = 2.4 Hz, 1H, H_{Ar}), 7.07 (d, J = 2.4 Hz, 1H, H_{Ar}), 3.79 (s, 3H, OCH_3), 0.31 (s, 9H, Si(CH_3)$_3$); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ 151.5, 142.8, 138.3, 129.9, 122.7 (q, $J_{C\text{-}F}$ = 321 Hz, CF_3), 122.8, 118.0, 56.6, 0.0. **HRMS** (FI) calcd for $C_{11}H_{14}BrF_3O_4SSi$ [M]$^+$ 405.9518 and 407.9497, found 405.9514 and 407.9508. **IR** ν_{max} (film): 2956, 1592, 1554, 1413, 1398, 1286, 1270, 1254, 1203, 1129, 1089, 1048, 881, 838 cm^{-1}.

6-*tert*-Butyl-4-methyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate



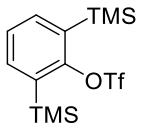
The procedure was based on the modification of S. Bonner *et. al.*[2] 2-Bromo-4-methyl-6-*tert*-butylphenol[3] (1.21 g, 5.0 mmol) was mixed with HMDS (1.5 mL, 7.0 mmol, 1.2 eq.) and TMSCl (1.09 g, 10.0 mmol, 2.0 eq.) under nitrogen. The mixture was heated to 85 ℃ for 2 weeks before cooling to room temperature. Unreacted HMDS, TMSCl and by-product NH3 were removed *in vacuo*. The crude 1-bromo-2-trimethylsilyloxy-3-methyl-5-*tert*-butyl-benzene was confirmed by ^{1}H NMR spectroscopy and used directly in the next step.

n-BuLi (5.0 mL, 1.6M in THF, 8.0 mmol, 2.0 eq.) was added dropwise over a period of 10 min to a solution of the crude 1-bromo-2-trimethylsilyloxy-3-*tert*-butyl-5-methyl-benzene (1.26 mg, 4.0 mmol) in THF (10 mL) at -100℃. The mixture was stirred for 3 h at that temperature and then allowed to warm up to room temperature over 12 h. Aqueous NH_4Cl (10 mL) was added. The crude product was extracted with Et_2O (3 × 10 mL). Organic layer was combined, washed with brine (2 × 10 mL), dried over $MgSO_4$, filtered and concentrated. Flash column chromatography (100% petroleum ether) afforded 2-trimethylsilyl-4-methyl-6-*tert*-butylphenol as a colourless oil (760 mg, 79%). The product was used directly in the next step.

n-BuLi (2.5 mL, 1.6M in THF, 4.0 mmol, 2.0 eq.) was added dropwise to 2-trimethylsilyl-4-methyl-6-*tert*-butylphenol (484 mg, 2.0 mmol) in THF (10 mL) at -100 ℃. The mixture was stirred for 3 h at that temperature and then allowed to warm up to room temperature over 12 h. Then the reaction mixture was cooled to -100℃ and triflate anhydride (0.6 mL, 4.0 mmol, 2.0 eq.) was added dropwise. Then the reaction mixture was stirred at -90℃, then warmed up to room temperature. After 12 h, saturated $NaHCO_3$ (10 mL) solution was added. The crude product was extracted with Et_2O (3 × 10 mL) and the organic layer was combined, washed with brine (2 × 10 mL), dried over $MgSO_4$, filtered and concentrated. Flash column chromatography (100% petroleum ether) afforded the desired product as a colourless oil (590 mg, 79%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (d, J = 2.1 Hz, 1H, H_{Ar}), 6.97 (d, J = 2.1 Hz, 1H, H_{Ar}), 2.15 (s, 3H, CH_3), 1.22 (s, 9H, C(CH_3)$_3$), 0.15 (s, 9H, Si(CH_3)$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 144.7, 142.0, 135.9, 135.2, 134.6, 131.4, 117.5 (q, J_{C-F} = 320 Hz, CF$_3$), 35.1, 30.9, 19.9, 0.0. **HRMS** (FI) calcd for $C_{15}H_{23}O_3F_3SSi$ [M]$^+$ 368.1089, found 368.1071. **IR** ν_{max} (film): 2963, 2359, 1587, 1394, 1251, 1212, 1157, 1140, 1056, 925, 871, 846, 611 cm^{-1}.

2,6-Bis(trimethylsilyl)phenyl trifluoromethanesulfonate



Synthesised following the modified procedure of T. Akawa *et. al.*[4] 2-Bromo-6-(trimethylsilyl)phenol[5] (1.96 g, 8.0 mmol) was added dropwise to a solution of imidazole (0.82 g, 12.0 mmol, 1.5 eq.) in dry THF (30 mL) under nitrogen. Freshly distilled trimethylsilyl chloride (1.52 mL, 12.0 mmol, 1.5 eq.) was added dropwise into the mixture under vigorous stirring. White precipitant formed instantly, the reaction mixture was left at room temperature for 12 h. Saturated $NaHCO_3$ (20 mL) was added and the aqueous phase was extracted with Et_2O (3 × 20 mL). The combined organic phase was dried over $MgSO_4$, filtered and concentrated to give the crude {3-bromo-2-[(trimethylsilyl)oxy]phenyl}trimethylsilane as a colourless oil (1.51 g, 60%). The compound was highly unstable either on silica column or in pure state, so the crude product was directly used in the next step without further purification.

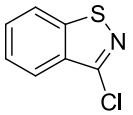
n-BuLi (6.25 mL, 1.6M in toluene, 10.0 mmol, 1.0 eq.) was added dropwise to a solution of {3-bromo-2-[(trimethylsilyl)oxy]phenyl}trimethylsilane (2.46 g, 10.0 mmol) in dry THF (40 mL) under nitrogen at -100 ℃ with stirring. The reaction mixture was then stirred at -100 ℃ for 3 h. Triflate anhydride (1.68 mL, 10.0 mmol, 1.0 eq.) was added slowly. After stirring for another 2 h, the reaction mixture was quenched with $NaHCO_3$ solution (50 mL) and then extracted with Et_2O (3 × 30 mL). The combined organic phase was dried over $MgSO_4$, concentrated and purified by flash column chromatography (100% petroleum ether) to give the titled product as a colourless oil (2.37 g, 64 %).

^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.37 (d, J = 7.3 Hz, 2H, H_{Ar}), 7.15 (d, J = 7.3 Hz, 1H, H_{Ar}), 0.15 (s, 18H, 2 × Si(CH_3)$_3$)); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ 154.5, 137.9, 134.6, 127.0, 118.1 (q, $J_{C\text{-}F}$ = 320 Hz, CF_3), 0.0. **HRMS** (FI) calcd for $C_{13}H_{21}F_3O_3SSi_2$ [M]$^+$ 370.0702, found 370.0694. **IR** ν_{max} (film): 2957, 1598, 1396, 1363, 1253, 1212, 1138, 1047, 875, 844, 781, 653 cm^{-1}.

3. Synthesis of 3-chloro-1,2-benzoisothiazoles using 3,4-dichloro-1,2,5-thiadiazole

GENERAL PROCEDURE A for the synthesis of **benzoisothiazole derivatives** using CsF**:**

3-Chloro-1,2-benzoisothiazole (3a)



3,4-Dichloro-1,2,5–thiadiazole **2a** (47 μL, 0.5 mmol) was added dropwise to a suspension of freshly oven dried CsF (217 mg, 1.4 mmol, 2.8 eq.) in dry THF (1.5 mL) under nitrogen at room temperature. After 5 min, 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **1a** (169 μL, 0.7 mmol, 1.4 eq.) was then added dropwise. The mixture was stirred at 65 ℃ and monitored by TLC. Upon completion (normally after 17 h), water (10 mL) was added, and the mixture extracted with DCM (3 × 10 mL). The combined organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified *via* flash column chromatography (10% Et_2O in petroleum ether), affording the titled compound as a colourless oil (64 mg, 76%).

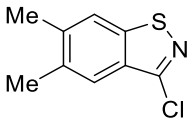
^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.95 (d, J = 8.1 Hz, 1H, H_{Ar}), 7.84 (d, J = 8.2 Hz, 1H, H_{Ar}), 7.53 (app. t, J = 8.2 Hz, 1H, H_{Ar}), 7.44 (app. t, J =8.1 Hz, 1H, H_{Ar}); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ 152.1, 145.2, 132.1, 128.9, 125.7, 123.8, 120.2. **HRMS** (FI) calcd for C_7H_4NSCl [M] $^+$ 168.9753, found 168.9756. **IR** ν_{max} (film): 2919, 2849, 2360, 1261, 1023, 617 cm^{-1}. **M.p.**: 39 ℃. The data recorded are consistent with the literature.[6]

GENERAL PROCEDURE B for the synthesis of **benzoisothiazole derivative** using TBAF**:**

3-Chloro-1,2-benzoisothiazole (3a)

2-(Trimethylsilyl)phenyl trifluoromethanesulfonate **1a** (169 μL, 0.7 mmol, 1.4 eq.) was added dropwise to a solution of 3,4-dichloro-1,2,5-thiadiazole **2a** (47 μL, 0.5 mmol) in dry THF (1.5 mL), and the mixture was cooled to -60 ℃ under nitrogen . Then a solution of tetrabutylammonium fluoride (TBAF) (1.0 mL, 1 M in toluene, 1.0 mmol, 2.0 eq.) was added dropwise over 10 min. The reaction was then stirred for 20 min at that temperature prior to warming to room temperature After 12 h, water (10 mL) was then added, and the resultant mixture extracted with DCM (3 × 10 mL). Combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified *via* flash column chromatography (10% Et_2O in petroleum ether) to give the titled compound as a colourless oil (63 mg, 75%). Data were consistent with the result from General Procedure A.

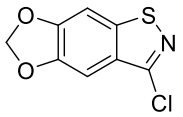
3-Chloro-5,6-dimethyl-1,2-benzoisothiazole (Table 2, entry 1)



General Procedure A was followed using 4,5-dimethyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate[7] (228 mg, 0.7 mmol), 3,4-dichloro-1,2,5-thiadiazole **2a** (47 μL, 0.5 mmol) and CsF (217 mg, 1.4 mmol). The product was purified by flash column chromatography (10% Et_2O in petroleum ether) to give 3-chloro-5,6-dimethyl-1,2-benzoisothiazole as a white solid (93 mg, 96%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (s, 1H, H_{Ar}), 7.58 (s, 1H, H_{Ar}), 2.37 (s, 6H, 2 × CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 150.2, 145.3, 139.5, 135.6, 130.8, 123.4, 120.1, 20.7, 20.2. **LRMS** (ESI, *m/z*) 198.0 ([M+H]$^+$, 100%). **HRMS** (ESI) calcd for C_9H_9NClS [M+H]$^+$ 198.0139, found 198.0138. **IR** ν_{max} (film): 2980, 2922, 1725, 1591, 1554, 1469, 1385, 1326, 1303, 1274, 1210, 1165, 1091, 1052, 1018, 954, 853 cm^{-1}. **M.p.**: 112-113 ℃.

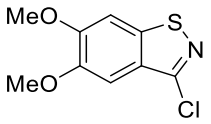
3-Chloro-5,6-dioxolo-1,2-benzoisothiazole (Table 2, entry 2)



General Procedure A was followed using 6-(trimethylsilyl)benzo[1,3]dioxol-5-yl trifluoromethanesulfonate[8] (240 mg, 0.7 mmol), 3,4-dichloro-1,2,5-thiadiazole **2a** (47 μL, 0.5 mmol) and CsF (217 mg, 1.4 mmol). The product was purified by flash column chromatography (10% Et_2O in petroleum ether) to give 3-chloro-5,6-dioxolo-1,2-benzoisothiazole as a colourless oil (104 mg, 96%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, J = 0.4 Hz, 1H, H_{Ar}), 7.11 (d, J = 0.4 Hz, 1H, H_{Ar}), 6.06 (s, 2H, 2 × CH_2); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 151.1, 148.5, 148.3, 144.7, 127.4, 102.7, 101.1, 98.6. **LRMS** (ESI, *m/z*) 214.0 ([M+H]$^+$, 100%). **HRMS** (ESI) calcd for $C_8H_5O_2NClS$ [M+H]$^+$ 213.9724, found 213.9722. **IR** ν_{max} (film): 2917, 1859, 1617, 1595, 1500, 1476, 1460, 1410, 1397, 1210, 1139, 1126, 1071, 1028, 944, 917, 831 cm^{-1}.

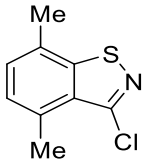
3-Chloro-5,6-dimethoxy-1,2-benzoisothiazole (Table 2, entry 3)



General Procedure A was followed using 4,5-dimethoxy-2-(trimethylsilyl)phenyl trifluoromethanesulfonate[9] (107 mg, 0.3 mmol), 3,4-dichloro-1,2,5-thiadiazole **2a**(47 μL, 0.5 mmol) and CsF (217 mg, 1.4 mmol). The product was purified by flash column chromatography (10% Et_2O in petroleum ether) to give 3-chloro-5,6-dimethoxy-1,2-benzoisothiazole as a white solid (63 mg, 93%).

^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.20 (s, 1H, H_{Ar}), 7.17 (s, 1H, H_{Ar}), 3.93 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ 152.2, 149.4, 146.6, 144.8, 125.9, 102.9, 100.4, 56.4, 56.3. **LRMS** (ESI, *m/z*) 230.1 ([M+H]$^+$, 100%). **HRMS** (ESI) calcd for $C_9H_8NClSO_2$ [M]$^+$ 228.9964, found 228.9967. **IR** ν_{max} (film): 2947, 1661, 1585, 1533, 1435, 1324, 1182, 1085, 891, 791cm^{-1}. **M.p.**: 235-237 ℃.

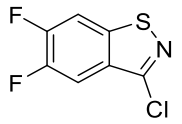
3-Chloro-4,7-dimethyl-1,2-benzoisothiazole (Table 2, entry 4)



General Procedure A was followed using 3,6-dimethyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate[10] (65 mg, 0.2 mmol), 3,4-dichloro-1,2,5-thiadiazole **2a** (23 μL, 0.3 mmol) and CsF (62 mg, 0.4 mmol). The product was purified by flash column chromatography (10% Et_2O in petroleum ether) to give 3-chloro-4,7-dimethyl-1,2-benzoisothiazole as a white solid (27 mg, 67%).

^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.11 (d, J = 7.2 Hz, 1H, H_{Ar}), 7.06 (d, J = 7.2 Hz, 1H, H_{Ar}), 2.79 (s, 3H, CH_3), 2.42 (s, 3H, CH_3); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ 153.9, 146.8, 133.1, 130.0, 128.8, 128.5, 128.0, 20.1, 19.0. **LRMS** (ESI, *m/z*) 198.1 ([M+H]$^+$, 100%). **HRMS** (ESI) calcd for C_9H_9NClS [M]$^+$ 198.0139, found 198.0135. **IR** ν_{max} (film): 2964, 2928, 2856, 1714, 1578, 1490, 1455, 1381, 1278, 1083, 917, 817 cm^{-1}. **M.p.**: 68-70 ℃.

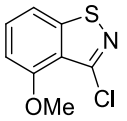
3-Chloro-5,6-difluoro-1,2-benzoisothiazole (Table 2, entry 5)



General Procedure A was followed using 4,5-difluoro-2-(trimethylsilyl)phenyl trifluoromethanesulfonate[9] (107 mg, 0.3 mmol), 3,4-dichloro-1,2,5-thiadiazole **2a** (47 µL, 0.5 mmol) and CsF (217 mg, 1.4 mmol). The product was purified by flash column chromatography (10% Et_2O in petroleum ether) to give 3-chloro-5,6-fluoro-1,2-benzoisothiazole as a white solid (63 mg, 52%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (dd, J = 8.9, 6.8 Hz, 1H, H_{Ar}), 7.63 (dd, J = 8.9, 6.8 Hz, 1H, H_{Ar}); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 151.4 (dd, $^1J_{C\text{-}F}$ = 258, $^2J_{C\text{-}F}$ = 16 Hz, C_{Ar}), 149.0 (dd, $^1J_{C\text{-}F}$ = 252, $^2J_{C\text{-}F}$ = 16 Hz, C_{Ar}), 146.9 (dd, $^3J_{C\text{-}F}$ = 8, $^4J_{C\text{-}F}$ = 1 Hz, C_{Ar}), 144.4 (d, $^4J_{C\text{-}F}$ = 5 Hz, C_{Ar}), 127.3 (dd, $^3J_{C\text{-}F}$ = 8, $^4J_{C\text{-}F}$ = 1 Hz, C_{Ar}), 109.9 (d, $^2J_{C\text{-}F}$ = 20 Hz, C_{Ar}), 107.0 (d, $^2J_{C\text{-}F}$ = 22 Hz, C_{Ar}). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -130.8 (ddd, J = 19.7, 8.9, 6.8 Hz, 1F, F_{Ar}), -135.9 (ddd, J =19.7, 8.9, 6.8 Hz, 1F, F_{Ar}); **HRMS** (EI) calcd for $C_7H_2NF_2ClS$ [M]$^+$ 204.9565, found 204.9563. **IR** ν_{max} (film): 3109, 3051, 2919, 2851, 1571, 1482, 1419, 1299, 1207, 1165, 1040, 819, 799 cm^{-1}. **M.p.**: 107-109 ℃.

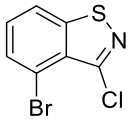
3-Chloro-4-methoxy-1,2-benzoisothiazole (Table 2, entry 6)



General Procedure A was followed using 2-methoxy-6-(trimethylsilyl)phenyl trifluoromethanesulfonate[11] (200 mg, 0.6 mmol), 3,4-dichloro-1,2,5-thiadiazole **2a** (47 µL, 0.5 mmol) and CsF (217 mg, 1.4 mmol). The product was purified by flash column chromatography (10% Et_2O in petroleum ether), resulted in the titled compound as a white solid (120 mg, 70%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.37 (m, 1H, H_{Ar}), 7.34 (dd, J = 8.2, 0.7 Hz, 1H, H_{Ar}), 6.72 (d, J = 7.7 Hz, 1H, H_{Ar}), 3.93 (s, 3H, OCH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.9, 155.4, 144.7, 130.5, 122.2, 112.1, 105.6, 55.8. **LRMS** (ESI, *m/z*) 200.0 ([M+H]$^+$, 100%), 202.0 (36%). **HRMS** (ESI) calcd for C_8H_6ONSCl [M+H]$^+$ 199.9931, found 199.9931. **IR** ν_{max} (film): 2970, 1573, 1449, 1323, 1284, 1106, 1068, 1048, 937 cm^{-1}. **M.p.**: 112-114 ℃.

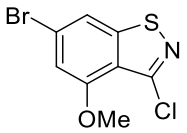
3-Chloro-4-bromo-1,2-benzoisothiazole (Table 2, entry 7)

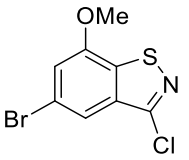


General Procedure A was followed using 2-bromo-6-(trimethylsilyl)phenyl trifluoromethanesulfonate[12] (180 mg, 0.5 mmol), 3,4-dichloro-1,2,5-thiadiazole **2a** (102 μL, 1.5 mmol) and CsF (217 mg, 1.4 mmol). The product was purified by flash column chromatography (5% Et_2O in petroleum ether) to give 3-chloro-4-bromo-1,2-benzoisothiazole as a white solid (49 mg, 40%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (dd, J = 8.2, 0.8 Hz, 1H, H_{Ar}), 7.65 (dd, J = 7.5, 0.8 Hz, 1H, H_{Ar}), 7.31 (dd, J = 8.1, 7.6 Hz, 1H, H_{Ar}); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 155.0, 145.9, 131.5, 129.4, 128.9, 119.6, 118.2. **HRMS** (FI) calcd for $C_7H_3NBrClS$ [M]$^+$ 246.8858 and 248.8835, found 246.8865 and 248.8857. **IR** ν_{max} (film): 3076, 3056, 2925, 2852, 1580, 1538, 1459, 1263, 1197, 1168, 1091, 977, 788 cm^{-1}. **M.p.**: 125-127 ℃.

3-Chloro-4-methoxy-6-bromo-1,2-benzoisothiazole and 3-chloro-5-bromo-7-methoxy-1,2-benzoisothiazole (Table 2, entry 8)





General Procedure A was followed using 4-bromo-2-methoxy-6-(trimethylsilyl)phenyl trifluoromethanesulfonate (121 mg, 0.3 mmol), 3,4-dichloro-1,2,5-thiadiazole **2a** (19 μL, 0.2 mmol) and CsF (93 mg, 0.6 mmol). The product was purified by flash column chromatography (10% Et_2O in petroleum ether) to give 3-chloro-4-methoxy-6-bromo-1,2-benzoisothiazole (38 mg, 69%) as a white solid and 3-chloro-5-methoxy-7-bromo-1,2-benzoisothiazole(5 mg, 9%) as a white solid, in a ratio of 8:1.

3-Chloro-4-methoxy-6-bromo-1,2-benzoisothiazole

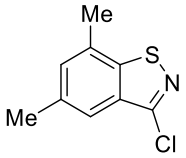
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J = 1.3 Hz, 1H, H_{Ar}), 6.82 (d, J = 1.3 Hz, 1H, H_{Ar}), 3.92 (s, 3H, OCH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.5, 156.4, 144.7, 125.1, 121.4, 114.7, 109.9, 56.2. **HRMS** (EI) calcd for $C_8H_5NBrClOS$ [M+H]$^+$ 276.8964 and 278.8941, found 276.8961 and 278.8938. **IR** ν_{max} (film): 3076, 2824, 2852, 1576, 1556, 1452, 1428, 1274, 1260, 1088, 1039, 687, 834, 816, 794 cm^{-1}. **M.p.**: 173-175 ℃.

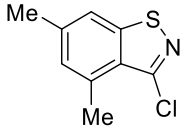
3-Chloro-5-bromo-7-methoxy-1,2-benzoisothiazole

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, J = 1.3 Hz, 1H, H_{Ar}), 6.97 (d, J = 1.3 Hz, 1H, H_{Ar}), 3.95 (s, 3H, OCH_3). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 152.9, 145.1, 141.6, 134.7, 120.6, 118.3, 111.7, 56.3. **HRMS** (EI) calcd for $C_8H_5NBrClOS$ [M]$^+$ 276.8964 and 278.8941, found 276.8962 and 278.8938. **IR** ν_{max} (film): 3076, 2927, 2870, 1567, 1483, 1346, 1292, 1106, 1005, 837, 806, 784 cm^{-1}. **M.p.**: 170-172 ℃.

Regioisomers were distinguished by HMBC spectrum.

3-Chloro-5,7-dimethyl-1,2-benzoisothiazole and 3-chloro-4,6-dimethyl-1,2-benzoisothiazole (Table 2, entry 9)





General Procedure A was followed using 2,4-dimethyl-6-(trimethylsilyl)phenyl trifluoromethanesulfonate[13] (228 mg, 0.7 mmol), 3,4-dichloro-1,2,5-thiadiazole **2a** (47 µL, 0.5 mmol) and CsF (217 mg, 1.4 mmol). The product was purified by flash column chromatography (10% Et_2O in petroleum ether) to give 3-chloro-5,7-dimethyl-1,2-benzoisothiazole and 3-chloro-4,6-dimethyl-1,2-benzoisothiazole as an inseparable colourless oil (82 mg, 83%), in a ratio of 1.3:1.

General Procedure B was followed using the same amount of starting materials and TBAF (1.4 mL, 1M in toluene, 1.4 mmol). A colourless inseparable oil (79 mg, 80%) was isolated in a ratio of 1:1.

3-Chloro-5,7-dimethyl-1,2-benzoisothiazole

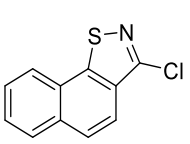
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (s, 1H, H_{Ar}), 7.13 (s, 1H, H_{Ar}), 2.45 (s, 3H, CH_3), 2.44 (s, 3H, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 146.2, 140.3, 135.0, 134.4, 131.1, 130.0, 120.7, 21.3, 19.4. **LRMS** (ESI, *m/z*) 198.1 ($[M+H]^+$, 100%). **HRMS** (ESI) calcd for C_9H_9NClS $[M+H]^+$ 198.0139, found 198.0138.

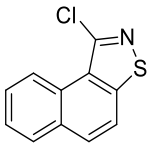
3-Chloro-4,6-dimethyl-1,2-benzoisothiazole

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (s, 1H, H_{Ar}), 6.96 (s, 1H, H_{Ar}), 2.79 (s, 3H, CH_3), 2.39 (s, 3H, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 154.2, 145.8, 139.7, 136.7, 135.2, 130.0, 117.7, 21.5, 20.4. **LRMS** (ESI, *m/z*) 198.1 ($[M+H]^+$, 100%). **HRMS** (ESI) calcd for C_9H_9NClS $[M+H]^+$ 198.0139, found 198.0138.

IR ν_{max} (film, mixture): 2980, 2919, 1597, 1481, 1459, 1410, 1381, 1341, 1304, 1274, 1215, 1174, 1112, 980, 855 cm^{-1}.

1-Chloronaphtho-1,2-isothiazole and 3-chloronaphtho-2,1-isothiazole (Table 2, entry 10)





General Procedure A was followed using 1-(trimethylsilyl)naphthalen-2-yl trifluoromethanesulfonate[14] (243 mg, 0.7 mmol), 3,4-dichloro-1,2,5-thiadiazole **2a** (47 μL, 0.5 mmol) and CsF (217 mg, 1.4 mmol). The product was purified by flash column chromatography (8% Et_2O in petroleum ether) yielded 1-chloronaphtho-1,2-isothiazole as a white solid (63 mg, 58%) and 3-chloronaphtho-2,1-isothiazole as a white solid (43 mg, 39%), in a ratio of 1.5:1.

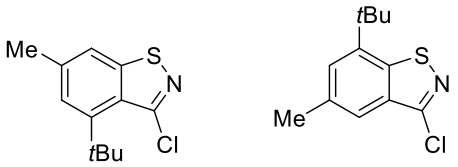
1-Chloronaphtho-1,2-isothiazole

^{1}**H NMR** (400 MHz, $CDCl_3$) δ 8.06-7.99 (m, 1H, H_{Ar}), 7.98-7.91 (m, 1H, H_{Ar}), 7.85-7.75 (m, 2H, H_{Ar}), 7.67-7.58 (m, 2H, H_{Ar}); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ 153.7, 147.0, 132.4, 129.9, 129.1, 128.8, 127.7, 127.5, 126.1, 124.5, 119.9. **LRMS** (ESI, *m/z*) 220.0 ([M+H]$^+$, 100%), 222.0 (40%). **IR** ν_{max} (film): 2989, 2870, 2361, 1589, 1558, 1442, 1413, 1301, 1258, 1210, 1141, 1080, 809, 746 cm^{-1}. **HRMS** (ESI) calcd for $C_{11}H_6NSCl$ [M+H]$^+$ 219.9982, found 219.9983. **M.p.**: 110-112 ℃.

3-Chloronaphtho-2,1-isothiazole

^{1}**H NMR** (400 MHz, $CDCl_3$) δ 9.29 (d, J = 8.5 Hz, 1H, H_{Ar}), 7.96-7.90 (m, 1H, H_{Ar}), 7.85 (d, J = 8.8 Hz, 1H, H_{Ar}), 7.78-7.74 (m, 1H, H_{Ar}), 7.71-7.64 (m, 1H, H_{Ar}), 7.63-7.54 (m, 1H, H_{Ar}); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ 154.7, 146.0, 131.9, 130.9, 129.1, 128.5, 128.1, 126.8, 126.1, 122.7, 117.3. **LRMS** (ESI, *m/z*) 220.0 ([M+H]$^+$, 100%), 222 (40%). **IR** ν_{max} (film): 2993, 2362, 1558, 1438, 1283, 1222, 806, 743 cm^{-1}. **HRMS** (ESI) calcd for $C_{11}H_6NSCl$ [M+H]$^+$ 219.9982, found 219.9979. **M.p.**: 72-75 ℃.

3-Chloro-4-*tert*-butyl-6-methyl-1,2-benzoisothiazole & 3-chloro-5-methyl-7-*tert*-butyl-1,2-benzoisothiazole (Table 2, entry 11)



General Procedure A was followed using 2-bromo-6-(*tert*-butyl)-4-methylphenyl trifluoromethanesulfonate (110 mg, 0.3 mmol), 3,4-dichloro-1,2,5-thiadiazole **2a** (19 μL, 0.2 mmol) and CsF (93 mg, 0.6 mmol). The product was purified by flash column chromatography (1% Et_2O in petroleum ether) to give 3-Chloro-4-*tert*-butyl-6-methyl-1,2-benzoisothiazole and 3-chloro-5-methyl-7-*tert*-butyl-1,2-benzoisothiazole as an inseparable white crystal (39 mg, 82%), in a ratio of 2.2:1.

3-Chloro-4-*tert*-butyl-6-methyl-1,2-benzoisothiazole

^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.47 (d, J = 0.9 Hz, 1H, H_{Ar}), 7.23 (d, J =0.9 Hz, 1H, H_{Ar}), 2.41 (s, 3H, CH_3), 1.58 (s, 9H, C(CH_3)$_3$); ^{13}**C NMR** (125 MHz, $CDCl_3$) δ 155.6, 147.2, 143.5, 137.5, 127.0, 124.8, 117.0, 35.0, 31.7, 20.6. **HRMS** (EI) calcd for $C_{12}H_{14}NClS$ [M]$^+$ 239.0535, found 239.0532.

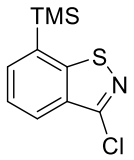
3-Chloro-5-methyl-7-*tert*-butyl-1,2-benzoisothiazole

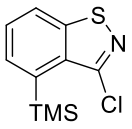
^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.60 (d, J = 0.8 Hz, 1H, H_{Ar}), 7.27 (d, J = 0.8 Hz, 1H, H_{Ar}), 2.46 (s, 3H, CH_3), 1.42 (s, 9H, C(CH_3)$_3$); ^{13}**C NMR** (125 MHz, $CDCl_3$) δ 146.2, 145.1, 142.9, 135.3, 132.2, 126.6, 120.2, 34.8, 28.9, 20.5. **HRMS** (EI) calcd for $C_{12}H_{14}NClS$ [M]$^+$ 239.0535, found 239.0532.

IR ν_{max} (film, mixture): 2964, 2922, 2871, 1601, 1542, 1478, 1459, 1397, 1366, 1334, 1296, 1259, 1203, 1188, 1134, 1080, 974, 856, 821 cm^{-1}.

Regioisomers were distinguished by HMBC spectrum.

3-Chloro-6-trimethylsilyl-1,2-benzoisothiazole & 3-chloro-4-trimethylsilyl-1,2-benzoisothiazole (Table 2, entry 12)





General Procedure A was followed using 2,6-bis(trimethylsilyl)phenyl trifluoromethanesulfonate (74 mg, 0.2 mmol), 3,4-dichloro-1,2,5-thiadiazole **2a** (19 μL, 0.2 mmol) and CsF (93 mg, 0.6 mmol). The product was purified by flash column chromatography (100% petroleum ether) to give 3-chloro-6-trimethylsilyl-1,2-benzoisothiazole (21 mg, 43%) as a colourless oil and 3-chloro-4-trimethylsilyl-1,2-benzoisothiazole (10 mg, 21%) as a colourless oil, in a ratio of 2:1.

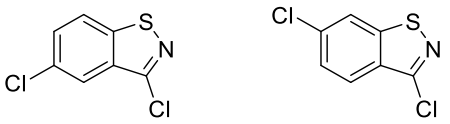
3-Chloro-6-trimethylsilyl-1,2-benzoisothiazole

^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.94 (dd, *J* = 8.1, 1.1 Hz, 1H, H_{Ar}), 7.63 (dd, *J* = 6.9, 1.1 Hz, 1H, H_{Ar}), 7.43 (dd, *J* = 8.1, 6.9 Hz, 1H, H_{Ar}), 0.36 (s, 9H, $Si(CH_3)_3$); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ 158.7, 147.9, 136.0, 134.4, 132.4, 126.7, 125.8, 0.0. **LRMS** (ESI, *m/z*) 242.0 ([M+H]$^+$, 100%). **HRMS** (ESI) calcd for $C_{10}H_{13}NClSSi$ [M+H]$^+$ 242.0221, found 242.0224. **IR** ν_{max} (film): 2956, 1574, 1552, 1463, 1439, 1362, 1306, 1294, 1252, 1147, 1091, 1027, 855, 840, 791, 754 cm^{-1}.

3-Chloro-4-trimethylsilyl-1,2-benzoisothiazole

^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 8.2, 0.9 Hz, 1H, H_{Ar}), 7.66 (dd, *J* = 7.0, 0.9 Hz, 1H, H_{Ar}), 7.44 (dd, *J* = 8.2, 7.0 Hz, 1H, H_{Ar}), 0.46 (s, 9H, $Si(CH_3)_3$); ^{13}**C NMR** (125 MHz, $CDCl_3$) δ 151.5, 145.1, 135.9, 133.7, 131.9, 125.6, 119.4, 0.0. **LRMS** (ESI, *m/z*) 241.9 ([M+H]$^+$, 100%). **HRMS** (ESI) calcd for $C_{10}H_{13}NClSSi$ [M+H]$^+$ 242.0221, found 242.0224. **IR** ν_{max} (film): 2960, 2360, 1567, 1464, 1413, 1307, 1263, 1210, 1163, 1105, 1060, 1027, 982, 859, 841, 765, 748 cm^{-1}.

3,5-Dichloro-1,2-benzoisothiazole and 3,6-dichloro-1,2-benzoisothiazole (Table 2, entry 13)



General Procedure A was followed using 4-chloro-2-(trimethylsilyl)phenyl trifluoromethanesulfonate[14] (231 mg, 0.7 mmol), 3,4-dichloro-1,2,5-thiadiazole **2a** (47 µL, 0.5 mmol) and CsF (217 mg, 1.4 mmol). The product was purified by flash column chromatography (10% Et_2O in petroleum ether) to yield the titled regioisomers as an inseparable colourless oil which solidified on sitting (77 mg, combined yield: 76%, ratio: 1.9:1).

3,5-Dichloro-1,2-benzoisothiazole

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 1.9 Hz, 1H, H_{Ar}), 7.76 (d, J = 8.7 Hz, 1H, H_{Ar}), 7.48 (dd, J = 8.7, 1.9 Hz, 1H, H_{Ar}); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 149.4, 144.2, 132.3, 131.3, 128.7, 122.2, 120.2. **HRMS** (FI) calcd for $C_7H_3NSCl_2$ [M]$^+$ 202.9363, found 202.9362.

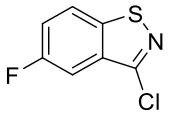
3,6-Dichloro-1,2-benzoisothiazole

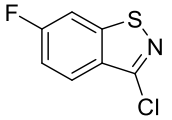
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 8.6 Hz, 1H, H_{Ar}), 7.81 (d, J = 1.7 Hz, 1H, H_{Ar}), 7.39 (dd, J =8.6, 1.7 Hz, 1H, H_{Ar}); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 152.1, 144.9, 135.3, 129.7, 125.9, 123.6, 118.8. **HRMS** (FI) calcd for C_8H_6NSCl [M]$^+$ 202.9363, found 202.9362. The data recorded are consistent with the literature.[15]

IR ν_{max} (neat): 3096, 3077, 1590, 1549, 1455, 1422, 1323, 1298, 1255, 1134, 1106, 1076, 1048, 809, 782 cm^{-1}. Combined **m.p.**: 62-64 ℃.

Regioisomers were distinguished by HMBC spectrum.

3-Chloro-5-fluoro-1,2-benzoisothiazole & 3-chloro-6-fluoro-1,2-benzoisothiazole (Table 2, entry 14)





General Procedure A was followed using 4-fluoro-2-(trimethylsilyl)phenyl trifluoromethanesulfonate[14] (221 mg, 0.7 mmol), 3,4-dichloro-1,2,5-thiadiazole **2a** (47 μL, 0.5 mmol) and CsF (217 mg, 1.4 mmol). The product was purified by flash column chromatography (1% Et_2O in petroleum ether) to give 3-chloro-5-fluoro-1,2-benzoisothiazole and 3-chloro-6-fluoro-1,2-benzoisothiazole as an inseparable white solid (63 mg, 68%), in a ratio of 2:1.

General Procedure B was followed using the same amount of starting materials and TBAF (1.4 mL, 1 M in toluene, 1.4 mmol). No product was detected.

3-Chloro-5-fluoro-1,2-benzoisothiazole

^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.80 (ddd, J = 9.0, 4.2, 0.5 Hz, 1H, H_{Ar}), 7.60 (ddd, J = 8.4, 2.2, 0.5 Hz, 1H, H_{Ar}), 7.36-7.29 (m, 1H, H_{Ar}); ^{13}**C NMR** (125 MHz, $CDCl_3$) δ 161.1 (d, $^1J_{C\text{-}F}$ = 246.9 Hz, C_{Ar}), 146.9 (d, $^4J_{C\text{-}F}$ = 1.0 Hz, C_{Ar}), 144.4 (d, $^4J_{C\text{-}F}$ = 5.3 Hz, C_{Ar}), 133.3 (d, $^3J_{C\text{-}F}$ = 9.6 Hz, C_{Ar}), 120.6 (d, $^3J_{C\text{-}F}$ = 9.2 Hz, C_{Ar}), 117.7 (d, $^2J_{C\text{-}F}$ =26.1 Hz, C_{Ar}), 108.0 (d, $^2J_{C\text{-}F}$ = 24.2 Hz, C_{F2}, C_{Ar}). **LRMS** (ESI, *m/z*) 186.0 ([M+H]$^+$, 100%). **HRMS** (ESI) calcd for C_7H_2NClFS [M+H]$^+$ 185.9586, found 185.9582.

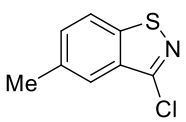
3-Chloro-6-fluoro-1,2-benzoisothiazole

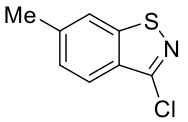
^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.92 (dd, J = 8.9, 4.8 Hz, 1H, H_{Ar}), 7.51 (dd, J = 8.0, 2.2 Hz, 1H, H_{Ar}), 7.20 (app. td, J = 8.7, 2.2 Hz, 1H, H_{Ar}); ^{13}**C NMR** (125 MHz, $CDCl_3$) δ 162.2 (d, $^1J_{C\text{-}F}$ = 253.7 Hz, C_{Ar}), 152.6 (d, $^3J_{C\text{-}F}$ = 10.7 Hz, C_{Ar}), 144.8 (s, C_{F5}), 128.0 (d, $^4J_{C\text{-}F}$ = 1.0 Hz, C_{Ar}), 124.5 (d, $^3J_{C\text{-}F}$ = 10.4 Hz, C_{Ar}), 114.5 (d, $^2J_{C\text{-}F}$ = 25.8 Hz, C_{Ar}), 105.2 (d, $^2J_{C\text{-}F}$ = 26.0 Hz, C_{Ar}). **LRMS** (ESI, *m/z*) 186.0 ([M+H]$^+$, 100%). **HRMS** (ESI) calcd for C_7H_2NClFS [M+H]$^+$ 185.9586, found 185.9582.

IR ν_{max} (film, mixture): 3070, 2981, 1887, 1733, 1606, 1564, 1476, 1427, 1406, 1331, 1300, 1272, 1242, 1203, 1173, 1138, 1071, 1044, 993, 889, 808 cm^{-1}.

Regioisomers were distinguished by ^{13}C NMR spectrum, as 3-chloro-6-fluoro-1,2-benzoisothiazole has one carbon four bonds away (δ 128.0 (d, $^4J_{C\text{-}F}$ = 1.0 Hz, C_{F4})) and one carbon five bonds away (δ 144.8(s, C_{F5})) from the fluorine atom, while 3-chloro-5-fluoro-1,2-benzoisothiazole only has two carbons which are four bonds away (δ146.9 (d, J = 1.0 Hz, C_{F4}), and 144.4 (d, J = 5.3 Hz, C_{F4})) from the fluorine atom.

3-Chloro-5-methyl-1,2-benzoisothiazole and 3-chloro-6-methyl-1,2-benzoisothiazole (Table 2, entry 15)





General Procedure A was followed using 4-methyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate[14] (220 mg, 0.7 mmol), 3,4-dichloro-1,2,5-thiadiazole **2a** (47 µL, 0.5 mmol) and CsF (217 mg, 1.4 mmol). The product was purified by flash column chromatography (10% Et_2O in petroleum ether) yielded the titled regioisomers as an inseparable colourless oil (58 mg, 64%), in a ratio of 1:1.

General Procedure B was followed using same amount of starting materials and TBAF (1.4 mL, 1 M in toluene, 1.4 mmol) instead of CsF. The same inseparable product mixture was obtained in 43 mg, 47% combined yield.

3-Chloro-5-methyl-1,2-benzoisothiazole

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 0.9 Hz, 1H, H_{Ar}), 7.71 (d, *J* = 8.3 Hz, 1H, H_{Ar}), 7.35 (dd, *J* = 8.3, 0.9 Hz, 1H, H_{Ar}), 2.47 (s, 3H, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 148.5, 144.5, 134.9, 131.4, 126.7, 122.2, 118.7, 20.3. **HRMS** (FI) calcd for C_8H_6NSCl [M]$^+$ 182.9910, found 182.9906.

3-Chloro-6-methyl-1,2-benzoisothiazole

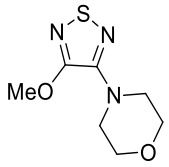
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.3 Hz, 1H, H_{Ar}), 7.60 (s, 1H, H_{Ar}), 7.24 (d, *J* = 8.3 Hz, 1H, H_{Ar}), 2.47 (s, 3H, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 151.6, 144.8, 138.8, 129.9, 129.2, 122.2, 118.7, 20.8. **HRMS** (FI) calcd for C_8H_6NSCl [M]$^+$ 182.9910, found 182.9906.

IR ν_{max} (film): 2962, 2936, 1602, 1482, 1468, 1302, 1285, 1250, 1175, 1139, 1020, 986, 808 cm^{-1}

Regioisomers were distinguished by HMBC and HSQC spectrum.

4. Synthesis of 1,2,5-thiadiazoles

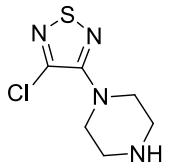
3-Methoxy-4-morpholinyl-1,2,5-thiadiazole (2g)



Sodium methoxide solution (0.68 mL, 25 wt% in MeOH, 3.0 mmol) was added dropwise to a solution of 3-chloro-4-morpholinyl-1,2,5-thiadiazole **2f**[16] (510 mg, 2.5 mmol) in dry MeOH (5 mL) under nitrogen. After stirring at reflux for 12 h, the mixture was cooled to room temperature and water (20 mL) was then added. The mixture was extracted in Et_2O (3 × 10 mL). The combined organic layer was washed with water (2 × 10 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The product was purified by flash column chromatography (30% EtOAc in petroleum ether) to yield the titled compound as a white solid (479 mg, 95%).

^{1}**H NMR** (400 MHz, $CDCl_3$) δ 4.02 (s, 3H, OC*H*$_3$), 3.79-3.69 (m, 4H, 2 × C*H*$_2$), 3.47-3.38 (m, 4H, 2 × C*H*$_2$); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ 154.6, 149.9, 66.5, 57.5, 47.9. **HRMS** (FI) calcd for $C_7H_{11}O_2N_3S$ [M]$^+$ 201.0572, found 201.0576. **IR** ν_{max} (neat): 2854, 1623, 1538, 1446, 1404, 1263, 1112, 1070, 942, 924 cm^{-1}. **M.p.**: 75-77 ℃.

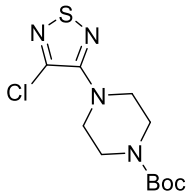
3-Chloro-4-piperazinyl-1,2,5-thiadiazole (SI-2l-1)



3,4-Dichloro-1,2,5-thiadiazole **2a** (1.0 mL, 10.0 mmol) was added dropwise to a solution of piperazine (3.50 g, 20.0 mmol) in dry DMF (5 mL) at 0 ℃ under nitrogen. The reactant was heated to 70℃ and kept stirring for 4 h. After cooled to room temperature NaOH solution (10 mL, 1 M) was poured in slowly to basify the mixture. DCM (3 × 15 mL) was used for extraction. The combined organic phase was washed with brine (2 × 10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Flash column chromatography (5% triethylamine in DCM) yielded the titled compound as a colourless oil (1.18 g, 59%).

^{1}**H NMR** (400 MHz, $CDCl_3$) δ 3.37 (t, *J* = 5.0 Hz, 4H, 2 × C*H*$_2$), 2.95 (t, *J* = 5.0 Hz, 4H, 2 × C*H*$_2$), 1.74 (b, s, 1H, N*H*); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ 159.4, 135.4, 50.0, 45.6. **LRMS** (ESI, *m/z*) 205.1 ([M+H]$^+$, 100%), 207.0 (40%). **HRMS** (ESI) calcd for $C_6H_9N_4SCl$ [M+H]$^+$ 205.0309, found 205.0306. **IR** ν_{max} (film): 2845, 1504, 1451, 1412, 1268, 1135, 1033, 810, 733 cm^{-1}

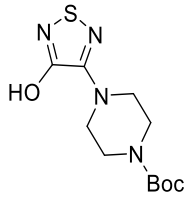
3-Chloro-4-(4-boc-piperazinyl)-1,2,5-thiadiazole (SI-2l-2)



Freshly distilled triethylamine (0.76 mL, 5.5 mmol) was added dropwise to 3-chloro-4-piperazinyl-1,2,5-thiadiazole **SI-2l-1** (0.50 g, 2.5 mmol) in dry MeCN (5 mL). Cold (0 ℃) di-*tert*-butyl dicarbonate (1.10 g, 5.5 mmol) was added and the mixture was heated to reflux. Aqueous hydrochloric acid (1 M solution, 5 mL) was added to the reaction mixture and the aqueous phase was extracted with Et_2O (3 × 10 mL). Combined organic phase was washed with water (10 mL) and dried over $MgSO_4$. The solvent was removed and the crude product was purified by flash column chromatography (15% Et_2O in petroleum ether) to obtain the titled compound as a white solid (0.61 g, 80%).

^{1}**H NMR** (400 MHz, $CDCl_3$) δ 3.52 (t, *J* = 4.9 Hz, 4H, 2 × C*H*$_2$), 3.35 (t, *J* = 4.9 Hz, 4H, 2 × C*H*$_2$), 1.41 (s, 9H, C(C*H*$_3$)$_3$); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ 159.0, 154.6, 135.5, 80.2, 48.8, 43.3 (b), 28.4. **LRMS** (ESI, *m/z*) 327.1 ([M+Na]$^+$, 100%), 329.0 (30%). **HRMS** (ESI) calcd for $C_{11}H_{17}O_2N_4ClS$ [M+Na]$^+$ 327.0653, found 327.0649. **IR** ν_{max} (film): 2976, 1698, 1505, 1414, 1366, 1280, 1246, 1170, 1027,811 cm^{-1}. **M.p.**: 94-96 ℃.

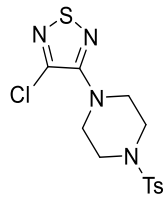
3-Hydroxy-4-(4-boc-piperazinyl)-1,2,5-thiadiazole (2l)



3-Chloro-4-(4-boc-piperazinyl)-1,2,5-thiadiazole **SI-2d-2** (0.916 g, 3.0 mmol) was added dropwise to a solution of potassium hydroxide (1.200 g, 20.0 mmol) in water (10 mL) and DMSO (3 mL). The system was heated to reflux and stirred with vigorously for 4 h. Additional water (10 mL) was added and the mixture was cooled in ice bath. Concentrated HCl was added dropwise to acidify the mixture to pH = 2 during which white precipitant crushed out. The solid was filtered, washed with water and dried, to give the titled compound (0.050 g, 6%).

^{1}**H NMR** (400 MHz, DMSO-*d6*) δ 3.42 (s, 8H, 4 × C*H*$_2$), 1.41 (s, 9H, C(C*H*$_3$)$_3$); ^{13}**C NMR** (100 MHz, DMSO-*d6*) δ 154.4, 154.2, 150.6, 79.6, 47.3, 42.9, 28.5. **LRMS** (ESI, *m/z*) 309.1 ([M+Na]$^+$, 100%). **HRMS** (ESI) calcd for $C_{11}H_{17}O_3N_4S$ [M-H]$^+$ 285.1027, found 285.1028. **IR** ν_{max} (neat): 2977, 2846, 1686, 1518, 1416, 1364, 1248, 1221, 1162, 1123, 945, 763 cm^{-1}. **M.p.**: 197-200 ℃.

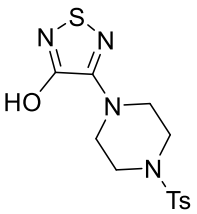
3-Chloro-4-(4-tosylpiperazinyl)-1,2,5-thiadiazole (SI-2m)



To a solution of 3-chloro-4-piperazinyl-1,2,5-thiadiazole **SI-2d-1** (102 mg, 0.5 mmol) in dry DCM (2 mL), tosylchloride (191 mg, 1.0 mmol) was added after which triethylamine (133 μL, 1.0 mmol) was added dropwise. The reaction mixture was gradually heated to 45 ℃ and was allowed to stir further for 12 h. Upon completion the mixture was cooled to room temperature and was quenched by water (10 mL). DCM (3 × 10 mL) was used to extract the organic component and the combined organic phase was dried over $MgSO_4$. Solvent was removed to yield the titled product as a white solid (166 mg, 98%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.2 Hz, 2H, H_{Ar}), 7.26 (d, *J* = 8.2 Hz, 2H, H_{Ar}), 3.58-3.36 (m, 4H, 2 × CH_2), 3.16-3.00 (m, 4H, 2 × CH_2), 2.34 (s, 3H, Ts-CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.4, 144.0, 135.2, 132.3, 129.9, 127.8, 48.2, 45.5, 21.6. **LRMS** (ESI, *m/z*) 359.0 ([M+H]$^+$, 100%), 381.0 ([M+Na]$^+$, 80%). **HRMS** (ESI) calcd for $C_{13}H_{16}O_2N_4S_2Cl$ [M+H]$^+$ 359.0398, found 359.0391.

3-Hydroxy-4-(4-tosylpiperazinyl)-1,2,5-thiadiazole (2m)

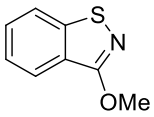


3-Chloro-4-(4-tosylpiperazinyl)-1,2,5-thiadiazole **SI-2m** (140 mg, 0.4 mmol) was added dropwise to a solution of potassium hydroxide (112 mg, 2.0 mmol) in water (2 mL) and DMSO (1 mL). The system was heated to reflux and vigorously stirred for 4 h. Additional water (10 mL) was added and the mixture was cooled in ice bath. Concentrated HCl was added dropwise to acidify the mixture to pH = 2 during which white precipitant appeared. The solid was filtered, washed with water and dried, to give the titled compound (93 mg, 68%).

^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.88 (b, s, 1H, O*H*), 7.65 (d, *J* = 7.4 Hz, 2H, H_{Ar}), 7.47 (d, *J* = 7.4 Hz, 2H, H_{Ar}), 3.59-3.50 (m, 4H, 2 × CH_2), 3.09-2.90 (m, 4H, 2 × CH_2), 2.42 (s, 3H, Ts-CH_3); **^{13}C NMR** (100 MHz, DMSO-*d6*) δ 154.1, 150.0, 144.3, 132.2, 130.4, 128.1, 46.7, 45.8, 21.5. **LRMS** (ESI, *m/z*) 339.0 ([M-H]$^+$, 100%). **HRMS** (ESI) calcd for $C_{13}H_{15}O_3N_4S_2$ [M-H]$^+$ 339.0591, found 339.0588. **IR** ν_{max} (neat): 3029, 2919, 2858, 2637, 1631, 1595, 1549, 1511, 1441, 1390, 1345, 1301, 1263, 1223, 1164, 951, 725 cm^{-1}. **M.p.**: 198-201 ℃.

5. Synthesis of 3-substituted-1,2-benzoisothiazoles using 1,2,5-thiadiaozles (2b-2m)

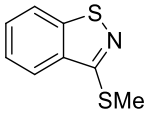
3-Methoxy-1,2-benzoisothiazole (Table 3, entry 1)



General Procedure A was followed using 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **1a** (170 μL, 0.7 mmol), 3,4-dimethoxy-1,2,5-thiadiazole **2b**[17] (73 mg, 0.5 mmol) and CsF (217 mg, 1.4 mmol). The product was purified by flash column chromatography (15% Et_2O in petroleum ether) to provide the titled compound as a colourless oil (67 mg, 81%).

^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.0 Hz, 1H, H_{Ar}), 7.68 (d, *J* = 8.1 Hz, 1H, H_{Ar}), 7.42 (app. t, *J* = 8.1 Hz, 1H, H_{Ar}), 7.29 (app. t, *J* = 8.0 Hz, 1H, H_{Ar}), 4.11 (s, 3H, OCH_3); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ 163.6, 151.7, 128.6, 125.3, 124.4, 123.0, 120.2, 55.9. **LRMS** (ESI, *m/z*) 166.1 ([M+H]$^+$, 100%). **HRMS** (ESI) calcd for C_8H_7ONS [M+H]$^+$ 166.0321, found 166.0322. **IR** ν_{max} (film): 2923, 1596, 1571, 1513, 1469, 1439, 1366, 1260, 1147, 1116, 734 cm^{-1}.

3-Thiomethyl-1,2-benzoisothiazole (Table 3, entry 3)



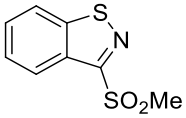
General Procedure A was followed using 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **1a** (170 μL, 0.7 mmol), 3-methoxy-4-thiomethyl-1,2,5-thiadiazole **2d**[18] (81 mg, 0.5 mmol) and CsF (155 mg, 1.0 mmol). The product was purified by flash column chromatography (5% Et_2O in petroleum ether) to provide an inseparable 1:1 mixture of the titled compound and 3-methoxy-1,2-benzoisothiazole as a colourless oil (49 mg, combined yield: 61%). 3-thiomethyl-1,2-benzoisothiazole was then isolated through HPLC to confirm the structure.

The spectra data of 3-methoxy-1,2-benzoisothiazole is consistent with the data above.

3-thiomethyl-1,2-benzoisothiazole:

^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.9 Hz, 1H, H_{Ar}), 7.76 (d, *J* = 7.9 Hz, 1H, H_{Ar}), 7.40 (app. t, *J* = 7.9 Hz, 1H, H_{Ar}), 7.27 (app. t, *J* = 7.9 Hz, 1H, H_{Ar}), 2.70 (s, 3H, SCH_3); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ 159.6, 151.8, 133.7, 128.2, 124.6, 122.8, 120.0, 13.4. **LRMS** (ESI, *m/z*) 182.0 ([M+H]$^+$, 100%). **HRMS** (ESI) calcd for $C_8H_7NS_2$ [M+H]$^+$ 182.0093, found 182.0092. Combined **IR** ν_{max} (film): 2833, 1594, 1572, 1514, 1461, 1439, 1368, 1324, 1290, 1252, 1197, 1147, 1116, 761, 732 cm^{-1}

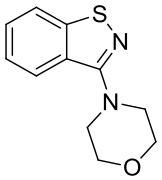
3-Methylsulfonyl-1,2-benzoisothiazole (Table 3, entry 4)



General Procedure A was followed using 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **1a** (170 μL, 0.7 mmol), 3-methoxy-4-methylsulfonyl-1,2,5-thiadiazole **2e**[18] (97 mg, 0.5 mmol) and CsF (217 mg, 1.4 mmol). The product was purified by flash column chromatography (20% EtOAc in petroleum ether) 63% of starting material thiadiazole was recovered, and the titled product was isolated as a colourless oil (29 mg, 24%).

^{1}**H NMR** (400 MHz, $CDCl_3$) δ 8.54 (d, *J* = 8.2 Hz, 1H, H_{Ar}), 7.95 (d, *J* = 8.1 Hz, 1H, H_{Ar}), 7.58 (app. t, *J* = 8.1 Hz, 1H, H_{Ar}), 7.51 (app. t, *J* = 8.2 Hz, 1H, H_{Ar}), 3.36 (s, 3H, SO_2CH_3); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ 160.2, 154.0, 131.0, 129.0, 126.6, 124.8, 119.8, 42.0. **LRMS** (ESI, *m/z*) 236.0 ([M+Na]$^+$, 100%). **HRMS** (ESI) calcd for $C_8H_7O_2NS_2$ [M+Na]$^+$ 235.9180, found 235.9809. **IR** ν_{max} (film): 2865, 1314, 1144, 769 cm^{-1}.

3-Morpholino-1,2-benzoisothiazole (Table 3, entry 7)

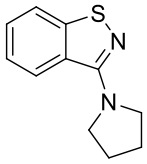


General Procedure A was followed using 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **1a** (170 μL, 0.7 mmol), 3-hydroxy-4-morpholino-1,2,5-thiadiazole **2h**[16] (94 mg, 0.5 mmol) and CsF (217 mg, 1.4 mmol). The product was purified by flash column chromatography (25% EtOAc in petroleum ether) to yield the titled product as a colourless oil which solidified on sitting (106 mg, 96%).

^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.1 Hz, 1H, H_{Ar}), 7.76 (d, *J* = 8.1 Hz, 1H, H_{Ar}), 7.41 (ddd, *J* = 8.1, 7.0, 1.0 Hz, 1H, H_{Ar}), 7.30 (ddd, *J* = 8.1, 7.0, 1.0 Hz, 1H, H_{Ar}), 3.87 (t, *J* = 4.7 Hz, 4H, 2 × CH_2), 3.47 (t, *J* =4.7 Hz, 4H, 2 × CH_2); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ 163.7, 152.9, 127.8, 127.7, 124.1, 123.8, 120.7, 66.8, 50.6. **LRMS** (ESI, *m/z*) 221.1 ([M+H]$^+$, 100%). **HRMS** (ESI) calcd for $C_{11}H_{12}ON_2S$ [M+H]$^+$ 221.0743, found 211.07408. **IR** ν_{max} (film): 2998, 2918, 1736, 1493, 1369, 1262, 1152, 1117, 909, 734 cm^{-1}. **M.p.**: 52-55 ℃.

The data recorded are consistent with the literature.[19]

3-Pyrrolidinyl-1,2-benzoisothiazole (Table 3, entry 8)

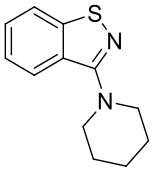


General Procedure A was followed using 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **1a** (170 μL, 0.7 mmol), 3-hydroxy-4-pyrrolidinyl-1,2,5-thiadiazole **2i**[16] (93 mg, 0.5 mmol) and CsF (217 mg, 1.4 mmol). The product was purified by flash column chromatography (5% EtOAc in petroleum ether) to yield the titled product as a colourless oil which solidified on sitting (85 mg, 83%).

^{1}**H NMR** (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.2 Hz, 1H, H_{Ar}), 7.68 (d, *J* = 8.1 Hz, 1H, H_{Ar}), 7.34 (app. t, *J* = 8.1 Hz, 1H, H_{Ar}), 7.21 (app. t, *J* = 8.2 Hz, 1H, H_{Ar}), 3.79 (t, *J* = 6.7 Hz, 4H, CH_2), 1.96 (t, *J* = 6.7 Hz, 4H, CH_2); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ 160.4, 153.3, 127.5, 127.3, 124.7, 123.4, 120.4, 49.6, 25.7. **LRMS** (ESI, *m/z*) 205.1 ([M+H]$^+$, 100%). **HRMS** (ESI) calcd for $C_{11}H_{12}N_2S$ [M+H]$^+$ 205.0794, found 205.0791. **IR** ν_{max} (film): 2764, 1563, 1485, 1433, 733 cm^{-1}. **M.p.**: 49-51 ℃.

The data recorded are consistent with the literature.[20]

3-Piperidinyl-1,2-benzoisothiazole (Table 3, entry 9)

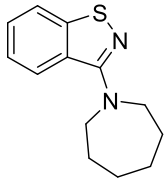


General Procedure A was followed using 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **1a** (170 μL, 0.7 mmol), 3-hydroxy-4-piperidinyl-1,2,5-thiadiazole **2j**[16] (93 mg, 0.5 mmol) and CsF (217 mg, 1.4 mmol). The product was purified by flash column chromatography (5% EtOAc in petroleum ether) to yield the titled product as a colourless oil (85 mg, 78%).

^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.1 Hz, 1H, H_{Ar}), 7.70 (d, *J* = 8.1 Hz, 1H, H_{Ar}), 7.36 (app. t, *J* = 8.1 Hz, 1H, H_{Ar}), 7.25 (app. t, *J* = 8.1 Hz, 1H, H_{Ar}), 3.46-3.32 (m, 4H, 2 × CH_2), 1.75-1.65 (m, 4H, 2 × CH_2), 1.66-1.51 (m, 2H, CH_2); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ 165.0, 152.6, 128.4, 127.4, 124.1, 123.8, 120.5, 51.5, 26.0, 24.7. **LRMS** (ESI, *m/z*) 219.0 ([M+H]$^+$, 100%). **HRMS** (ESI) calcd for $C_{12}H_{14}N_2S$ [M+H]$^+$ 219.0951, found 219.0946. **IR** ν_{max} (film): 2852, 1561, 1492, 1467, 1425, 1282, 1257, 1117, 1065, 736 cm^{-1}.

The data recorded are consistent with the literature.[21]

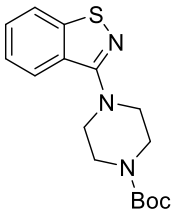
3-Azapanyl-1,2-benzoisothiazole (Table 3, entry 10)



General Procedure A was followed using 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **1a** (170 μL, 170 mmol), 3-azapanyl-4-hydroxy-1,2,5-thiadiazole **2k**[16] (100 mg, 0.5 mmol) and CsF (217 mg, 1.4 mmol). The product was purified by flash column chromatography (5% Et_2O in petroleum ether) to yield the titled product as a colourless oil (107 mg, 93%).

^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.2 Hz, 1H, H_{Ar}), 7.68 (d, *J* = 8.2 Hz, 1H, H_{Ar}), 7.34 (app. t, *J* = 8.2 Hz, 1H, H_{Ar}), 7.22 (app. t, *J* = 8.2 Hz, 1H, H_{Ar}), 3.82-3.64 (m, 4H, 2 × NCH_2), 1.93-1.80 (m, 4H, 2 × CH_2), 1.64-1.51 (m, 4H, 2 × CH_2); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ 162.3, 153.3, 127.3, 127.1, 124.7, 123.5, 120.5, 50.6, 29.4, 27.6. **LRMS** (ESI, *m/z*) 233.1 ([M+H]$^+$, 100%). **IR** ν_{max} (film): 2926, 2852, 1591, 1561, 1506, 1469, 1429, 1369, 1261, 1168, 734 cm^{-1}.

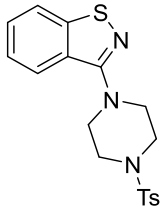
3-(4-Boc-piperazinyl)-1,2-benzoisothiazole (Table 3, entry 11)



General Procedure A was followed using 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **1a** (80 μL, 0.3 mmol), 3-hydroxy-4-(4-boc-piperazinyl)-1,2,5-thiadiazole **2l** (57 mg, 0.2 mmol) and CsF (93 mg, 0.6 mmol). The product was purified by flash column chromatography (15% Et_2O in petroleum ether) to give 3-(4-boc-piperazinyl)-1,2-benzoisothiazole as a white solid (47 mg, 73%).

^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.1 Hz, 1H, H_{Ar}), 7.75 (d, *J* = 8.1 Hz, 1H, H_{Ar}), 7.41 (app. t, *J* = 8.1 Hz, 1H, H_{Ar}), 7.30 (app. t, *J* = 8.1 Hz, 1H, H_{Ar}), 3.61-3.56 (m, 4H, 2 × CH_2), 3.46-3.42 (m, 4H, 2 × CH_2), 1.42 (s, 9H, CH_3); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ 163.8, 154.9, 152.8, 127.9, 127.7, 124.1, 123.7, 120.6, 80.0, 50.0 (b), 43.20 (b), 28.4. **LRMS** (ESI, *m/z*) 320.1 ([M+H]$^+$, 100%). **HRMS** (ESI) calcd for $C_{16}H_{21}O_2N_3S$ [M+H]$^+$ 320.1427, found 320.1421. **IR** ν_{max} (film): 1739, 1695, 1417, 1365, 1246, 1168, 1000, 864 cm^{-1}. **M.p.**: 105-108 ℃.

3-(4-Tosylpiperazinyl)-1,2-benzoisothiazole (Table 3, entry 12)

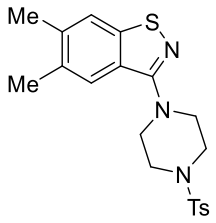


General Procedure A was followed using 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **1a** (170 μL, 0.7 mmol), 3-hydroxy-4-(4-tosylpiperazinyl)-1,2,5-thiadiazole **2m** (170 mg, 0.5 mmol) and CsF (217 mg, 1.4 mmol). The product was purified by flash column chromatography (40% Et_2O in petroleum ether) to give 3-(4-tosylpiperazinyl)-1,2-benzoisothiazole as a white solid (158 mg, 85%).

^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.2 Hz, 1H, H_{Ar}), 7.70 (d, *J* = 8.2 Hz, 1H, H_{Ar}), 7.62 (d, *J* = 8.2 Hz, 2H, $H_{Ts\text{-}Ar}$), 7.39 (app. t, *J* = 8.0 Hz, 1H, H_{Ar}), 7.29 (d, *J* = 8.2 Hz, 2H, $H_{Ts\text{-}Ar}$), 7.25 (app. t, *J* = 8.0 Hz, 1H, H_{Ar}), 3.62-3.47 (m, 4H, 2 × CH_2), 3.24-3.11 (m, 4H, 2 × CH_2), 2.38 (s, 3H, Ts-CH_3); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ 163.0, 152.9, 143.9, 132.6, 129.8, 127.9, 127.8, 127.7, 124.1, 123.4, 120.7, 49.4, 45.8, 21.6. **LRMS** (ESI, *m/z*) 374.0 ([M+H]$^+$, 100%), 396.0 ([M+Na]$^+$, 80%). **HRMS** (ESI) calcd for $C_{18}H_{20}O_2N_3S_2$ [M+H]$^+$ 374.0991, found 374.0985. **IR** ν_{max} (film): 2852, 1596, 1493, 1452, 1423, 1384, 1347, 1326, 1264, 1166, 943, 728, 652 cm^{-1}. **M.p.**: 125-127 ℃.

6. Synthesis of 3-piperazinyl-1,2-benzoisothiazoles using 3-hydroxy-4-piperazinyl-1,2,5-thiadiaozles

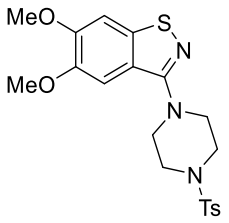
3-(4-Tosylpiperazinyl)-5,6-dimethyl-1,2-benzoisothiazole (4a)



General Procedure A was followed using 4,5-dimethyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate[7] (98 mg, 0.3 mmol), 3-hydroxy-4-(4-tosylpiperazinyl)-1,2,5-thiadiazole **2m** (68 mg, 0.2 mmol) and CsF (93 mg, 0.6 mmol). The product was purified by flash column chromatography (40% Et_2O in petroleum ether) to give 3-(4-tosylpiperazinyl)-5,6-dimethyl-1,2-benzoisothiazole as a white solid (69 mg, 86%).

^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.62 (d, J = 8.1 Hz, 2H, H_{Ar}), 7.47 (s, 1H, H_{Ar}), 7.42 (s, 1H, H_{Ar}), 7.29 (d, J = 8.1 Hz, 2H, H_{Ar}), 3.60-3.47 (m, 4H, 2 × CH_2), 3.22-3.10 (m, 4H, 2 × CH_2), 2.38 (s, 3H, Ts-CH_3), 2.30 (s, 3H, CH_3), 2.28 (s, 3H, CH_3); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ 162.6, 150.9, 143.9, 138.0, 133.6, 132.6, 129.8, 127.9, 126.3, 123.2, 120.6, 49.4, 45.8, 21.6, 20.4, 20.3. **LRMS** (ESI, *m/z*) 402.1 ([M+H]$^+$, 100%). **HRMS** (ESI) calcd for $C_{20}H_{24}O_2N_3S_2$ [M+H]$^+$ 402.1304, found 402.1296. **IR** ν_{max} (film): 2920, 2854, 1597, 1549, 1492, 1452, 1419, 1370, 1348, 1308, 1266, 1167, 1135, 1117, 1093, 941, 728, 649 cm^{-1}. **M.p.**: 126-128 ℃.

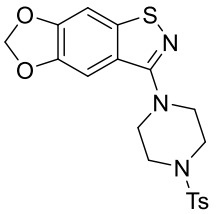
3-(4-Tosylpiperazinyl)-5,6-dimethoxy-1,2-benzoisothiazole (4b)



General Procedure A was followed using 4,5-dimethoxy-2-(trimethylsilyl)phenyl trifluoromethanesulfonate[9] (107 mg, 0.3 mmol), 3-hydroxy-4-(4-tosylpiperazinyl)-1,2,5-thiadiazole **2m** (68 mg, 0.2 mmol) and CsF (93 mg, 0.6 mmol). The product was purified by flash column chromatography (40% EtOAc in petroleum ether) to give 3-(4-tosylpiperazinyl)-5,6-dimethoxy-1,2-benzoisothiazole as a white solid (73 mg, 85%).

^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.63 (d, J = 8.1 Hz, 2H, H_{Ar}), 7.29 (d, J = 8.1 Hz, 2H, H_{Ar}), 7.09 (s, 1H, H_{Ar}), 6.96 (s, 1H, H_{Ar}), 3.88 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.58-3.40 (m, 4H, 2 × CH_2), 3.23-3.11 (m, 4H, 2 × CH_2), 2.38 (s, 3H, Ts-CH_3); ^{13}**C NMR** (125 MHz, $CDCl_3$) δ 162.6, 151.1, 147.9, 147.2, 143.9, 132.7, 129.8, 127.9, 121.0, 103.5, 101.1, 56.3, 56.2, 49.4, 45.7, 21.6. **LRMS** (ESI, *m/z*) 434.1 ([M+H]$^+$, 100%). **HRMS** (ESI) calcd for $C_{20}H_{24}O_4N_3S_2$ [M+H]$^+$ 434.1203, found 434.1204. **IR** ν_{max} (film): 2851, 1605, 1502, 1468, 1453, 1421, 1346, 1327, 1228, 1258, 1212, 1166, 1137, 1092, 1055, 1027, 812, 729 cm^{-1}. **M.p.**: 248-250 ℃.

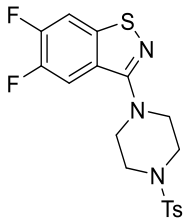
3-(4-Tosylpiperazinyl)-5,6-dioxolo-1,2-benzoisothiazole (4c)



General Procedure A was followed using 6-(trimethylsilyl)benzo[1,3]dioxol-5-yl trifluoromethanesulfonate[8] (103 mg, 0.3 mmol), 3-hydroxy-4-(4-tosylpiperazinyl)-1,2,5-thiadiazole **2m** (68 mg, 0.2 mmol) and CsF (93 mg, 0.6 mmol). The product was purified by flash column chromatography (60% Et_2O in petroleum ether) to give 3-(4-tosylpiperazinyl)-5,6-dioxolo-1,2-benzoisothiazole as a white solid (61 mg, 73%).

^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.62 (d, J = 8.1 Hz, 2H, H_{Ar}), 7.29 (d, J = 8.1 Hz, 2H, H_{Ar}), 7.03 (s, 1H, H_{Ar}), 6.95 (s, 1H, H_{Ar}), 6.00 (s, 2H, CH_2), 3.47-3.39 (m, 4H, 2 × CH_2), 3.20-3.10 (m, 4H, 2 × CH_2), 2.38 (s, 3H, Ts-CH_3); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ 162.6, 149.8, 148.7, 147.0, 143.9, 132.6, 129.8, 127.9, 122.4, 102.3, 101.0, 99.2, 49.4, 45.9, 21.6. **LRMS** (ESI, *m/z*) 418.1 ([M+H]$^+$, 100%). **HRMS** (ESI) calcd for $C_{19}H_{20}O_4N_3S_2$ [M+H]$^+$ 418.0890, found 418.0887. **IR** ν_{max} (film): 2897, 2854, 1598, 1484, 1441, 1371, 1347, 1326, 1275, 1247, 1166, 1115, 1093, 1038, 979, 852, 728 cm^{-1}. **M.p.**: 111-114 ℃.

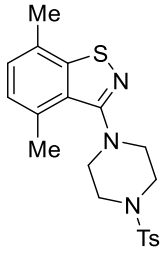
3-(4-Tosylpiperazinyl)-4,5-difluoro-1,2-benzoisothiazole (4d)



General Procedure A was followed using 4,5-difluoro-2-(trimethylsilyl)phenyl trifluoromethanesulfonate[9] (100 mg, 0.3 mmol), 3-hydroxy-4-(4-tosylpiperazinyl)-1,2,5-thiadiazole **2m** (68 μL, 0.2 mmol) and CsF (93 mg, 0.6 mmol). The product was purified by flash column chromatography (40% Et_2O in petroleum ether) to give 3-(4-tosylpiperazinyl)-4,5-difluoro-1,2-benzoisothiazole as a white solid (76 mg, 93%).

^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.61 (d, J = 8.1 Hz, 2H, H_{Ar}), 7.48 (dd, J = 9.0, 6.8 Hz, 1H, H_{Ar}), 7.43 (dd, J = 10.0, 7.0 Hz, 1H, H_{Ar}), 7.29 (d, J = 8.1 Hz, 2H, H_{Ar}), 3.51-3.43 (m, 4H, 2 × CH_2), 3.20-3.12 (m, 4H, 2 × CH_2), 2.38 (s, 3H, Ts-CH_3); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ 162.4 (d, $^4J_{C\text{-}F}$ = 4 Hz, C_{Ar}), 151.2 (dd, $^1J_{C\text{-}F}$ = 252, $^2J_{C\text{-}F}$ = 13 Hz, C_{Ar}), 148.6 (dd, $^1J_{C\text{-}F}$ = 245, $^2J_{C\text{-}F}$ = 12 Hz, C_{Ar}), 148.6 (d, $^3J_{C\text{-}F}$ = 8 Hz, C_{Ar}), 144.0, 132.5, 129.9, 127.9, 123.6 (d, $^3J_{C\text{-}F}$ = 6 Hz, C_{Ar}), 110.5 (d, $^2J_{C\text{-}F}$ = 19.1 Hz, C_{Ar}), 108.2 (d, $^2J_{C\text{-}F}$ = 21 Hz, C_{Ar}), 49.4, 45.7, 21.6. ^{19}**F NMR** (376 MHz, $CDCl_3$) δ -133.3 (ddd, J = 20.1, 9.8, 6.8 Hz, 1F, F_{Ar}), -138.4 (ddd, J = 20.1, 9.8, 6.8 Hz, 1F, F_{Ar}); **LRMS** (ESI, m/z) 410.0 ([M+H]$^+$, 100%). **HRMS** (ESI) calcd for $C_{18}H_{17}N_3O_2F_2S_2Na$ [M+Na]$^+$ 432.0623, found 432.0621. **IR** ν_{max} (film): 2855, 1711, 1598, 1508, 1455, 1438, 1349, 1328, 1290, 1222, 1166, 1136, 947, 728 cm^{-1}. **M.p.**: 153-155 ℃.

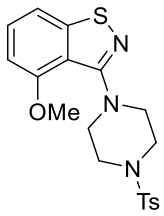
3-(4-Tosylpiperazinyl)-4,7-dimethyl-1,2-benzoisothiazole (4e)



General Procedure A was followed using 3,6-dimethyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate[10] (98 mg, 0.3 mmol), 3-hydroxy-4-(4-tosylpiperazinyl)-1,2,5-thiadiazole **2m** (68 mg, 0.2 mmol) and CsF (93 mg, 0.6 mmol). The product was purified by flash column chromatography (20% Et_2O in petroleum ether) to give 3-(4-tosylpiperazinyl)-4,7-dimethyl-1,2-benzoisothiazole as a white solid (55 mg, 68%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, J = 8.1 Hz, 2H, H_{Ar}), 7.38 (d, J = 8.1 Hz, 2H, H_{Ar}), 7.12 (d, J = 7.2 Hz, 1H, H_{Ar}), 7.06 (d, J = 7.2 Hz, 1H, H_{Ar}), 3.42-3.32 (m, 4H, 2 × CH_2), 3.29-3.07 (b, s, 4H, 2 × CH_2), 2.65 (s, 3H, Ts-CH_3), 2.47 (s, 3H, CH_3), 2.45 (s, 3H, CH_3); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 167.0, 154.4, 144.2, 133.5, 132.6, 130.3, 128.3, 128.2, 128.2, 128.1, 127.8, 51.8, 46.1, 22.0, 19.6, 19.2. **LRMS** (ESI, *m/z*) 402.1 ([M+H]$^+$, 100%). **HRMS** (ESI) calcd for $C_{20}H_{24}O_2N_3S_2$ [M+H]$^+$ 402.1294, found 402.1304. **IR** ν_{max} (film): 2918, 2849, 1738, 1451, 1373, 1343, 1326, 1263, 1240, 1166, 1093, 1046, 946, 821, 731 cm^{-1}. **M.p.**: 193-195 ℃.

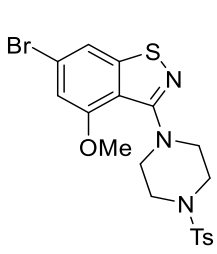
3-(4-Tosylpiperazinyl)-4-methoxy-1,2-benzoisothiazole (4f)

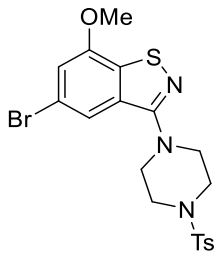


General Procedure A was followed using 2-methoxy-6-(trimethylsilyl)phenyl trifluoromethanesulfonate[11] (98 mg, 0.3 mmol), 3-hydroxy-4-(4-tosylpiperazinyl)-1,2,5-thiadiazole **2m** (68 mg, 0.2 mmol) and CsF (93 mg, 0.6 mmol). The product was purified by flash column chromatography (40% Et_2O in petroleum ether) to give 3-(4-tosylpiperazinyl)-4-methoxy-1,2-benzoisothiazole as a white solid (70 mg, 87%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 8.3 Hz, 2H, H_{Ar}), 7.37-7.30 (m, 1H, H_{Ar}), 7.29-7.28 (m, 2H, H_{Ar}), 7.28-7.27 (m, 1H, H_{Ar}), 6.63 (dd, J = 7.5, 0.8 Hz, 1H, H_{Ar}), 3.83 (s, 3H, OCH_3), 3.46-3.39 (m, 4H, 2 × CH_2), 3.20-3.11 (m, 4H, 2 × CH_2), 2.38 (s, 3H, Ts-CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.6, 155.8, 155.7, 143.8, 132.8, 129.7, 129.4, 127.9, 118.8, 112.8, 105.0, 55.7, 50.4, 45.8, 21.6. **LRMS** (ESI, *m/z*) 404.0 ([M+H]$^+$, 100%). **HRMS** (ESI) calcd for $C_{19}H_{22}O_3N_3S_2$ [M+H]$^+$ 404.1097, found 404.1084. **IR** ν_{max} (film): 2980, 2852, 1712, 1589, 1570, 1484, 1451, 1383, 1348, 1275, 1216, 1166, 1042, 945, 728 cm^{-1}. **M.p.**: 153-155 ℃.

3-(4-Tosylpiperazinyl)-4-methoxy-6-bromo-1,2-benzoisothiazole and 3-(4-tosylpiperazinyl)-5-bromo-7-methoxy-1,2-benzoisothiazole (4g, 4g')





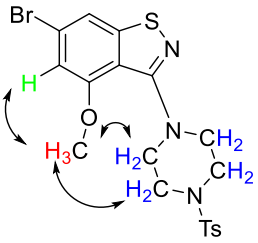
General Procedure A was followed using 4-bromo-2-methoxy-6-(trimethylsilyl)phenyl trifluoromethanesulfonate (121 mg, 0.3 mmol), 3-hydroxy-4-(4-tosylpiperazinyl)-1,2,5-thiadiazole **2m** (68 mg, 0.2 mmol) and CsF (93 mg, 0.6 mmol). The product was purified by flash column chromatography (40% Et_2O in petroleum ether) to give 3-(4-tosylpiperazinyl)-4-methoxy-6-bromo-1,2-benzoisothiazole (70 mg, 73%) as a white solid and 3-(4-tosylpiperazinyl)-5-bromo-7-methoxy-1,2-benzoisothiazole (9 mg, 9%) as a white solid, in a ratio of 8:1.

3-(4-Tosylpiperazinyl)-4-methoxy-6-bromo-1,2-benzoisothiazole (4g)

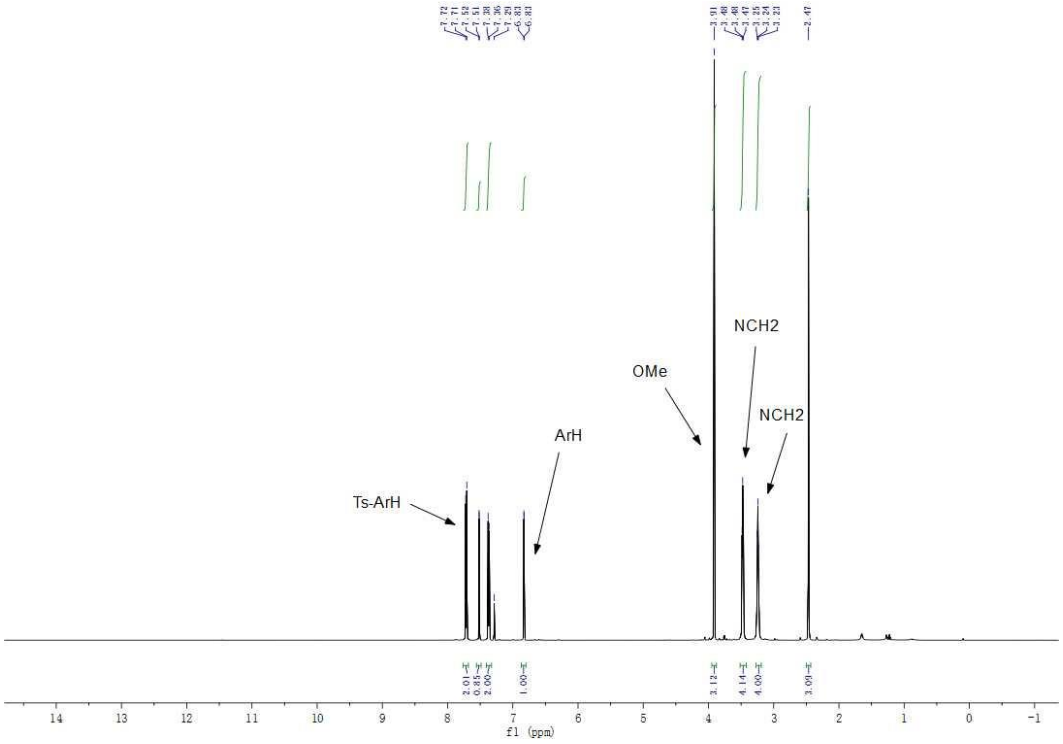
^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.71 (d, J = 8.2 Hz, 2H, H_{Ar}), 7.52 (d, J = 1.3 Hz, 1H, H_{Ar}), 7.37 (d, J = 8.2 Hz, 2H, H_{Ar}), 6.83 (d, J = 1.3 Hz, 1H, H_{Ar}), 3.91 (s, 3H, OCH_3), 3.49-3.46 (m, 4H, 2 × CH_2), 3.26-3.22 (m, 4H, 2 × CH_2), 2.47 (s, 3H, Ts-CH_3); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ 163.3, 157.0, 155.5, 143.8, 132.8, 129.8, 127.9, 123.9, 117.9, 115.4, 109.1, 56.2, 50.4, 45.7, 21.6. **LRMS** (ESI, *m/z*) 482 and 484 ([M+H]$^+$, 100%). **HRMS** (ESI) calcd for $C_{19}H_{21}N_3O_3S_2Br$ [M+H]$^+$ 482.0202 and 484.0180, found 482.0202 and 484.0182. **IR** ν_{max} (film, mixture): 2852, 1574, 1561, 1452, 1379, 1347, 1327, 1268, 1166, 1043, 943, 728 cm^{-1}. **M.p.**: 193-196 ℃.

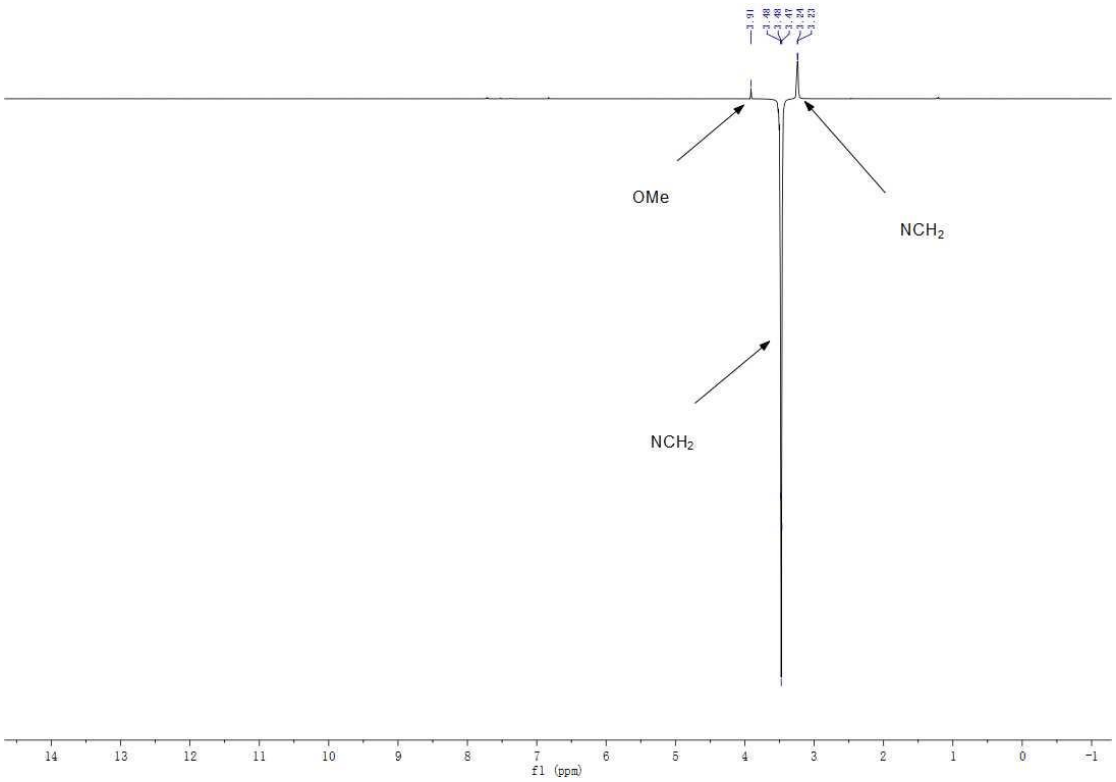
3-(4-Tosylpiperazinyl)-5-bromo-7-methoxy-1,2-benzoisothiazole (4g')

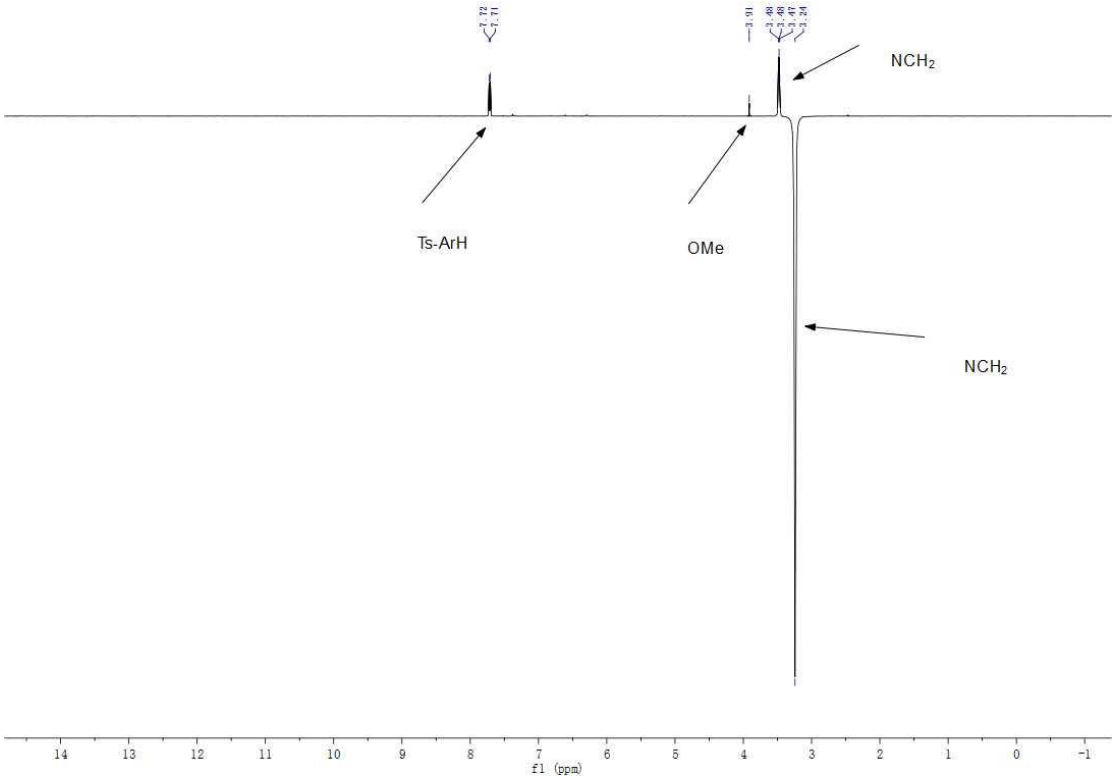
^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.62 (d, J = 8.1 Hz, 2H, H_{Ar}), 7.39 (d, J = 1.3 Hz, 1H, H_{Ar}), 7.30 (d, J = 8.1 Hz, 2H, H_{Ar}), 6.84 (d, J = 1.3 Hz, 1H, H_{Ar}), 3.89 (s, 3H, OCH_3), 3.53-3.46 (m, 4H, 2 × CH_2), 3.22-3.11 (m, 4H, 2 × CH_2), 2.38 (s, 3H, Ts-CH_3); **LRMS** (ESI, *m/z*) 482.0 and 484.0 ([M+H]$^+$, 100%). **HRMS** (ESI) calcd for $C_{19}H_{21}N_3O_3S_2Br$ [M+H]$^+$ 482.0203 and 484.0180, found 482.0202 and 484.0183. **IR** ν_{max} (film, mixture): 2852, 1598, 1566, 1493, 1449, 1377, 1350, 1328, 1267, 1166, 1057, 952, 728 cm^{-1}. **M.p.**: 128-130 ℃.

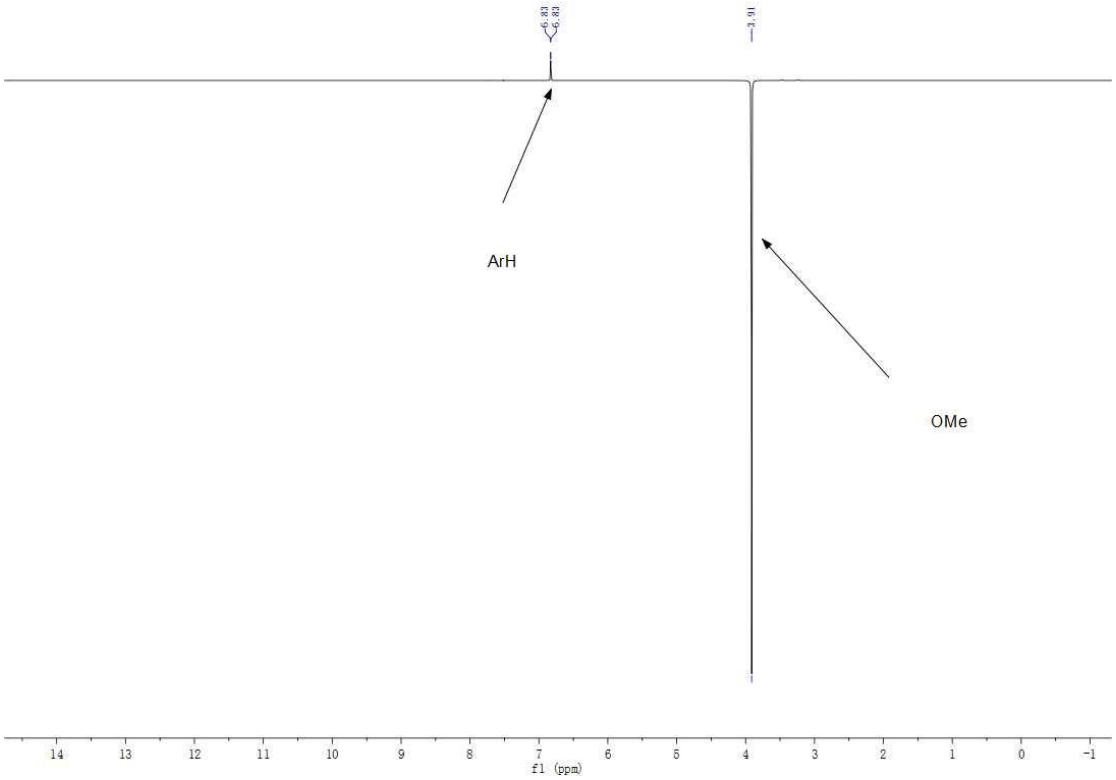


Regioisomers were distinguished by NOE spectrum as presented below. Protons on OMe group of 3-(4-tosylpiperazinyl)-4-methoxy-6-bromo-1,2-benzoisothiazole (δ 3.91 (s, 3H, OC*H*$_2$)) have shown remote interaction with protons on both CH_2 of the piperazine group (δ 3.49-3.46 (m, 4H, 2 × C*H*$_2$) and 3.26-3.22 (m, 4H, 2 × C*H*$_2$)). Remote interaction was also observed between protons on OMe group and proton on the aromatic ring (δ 6.83 (d, J = 1.3 Hz, 1H, H_{Ar})) next to it.



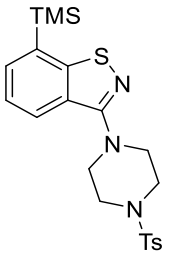

OMe
NCH2
NCH2
f1 (ppm)

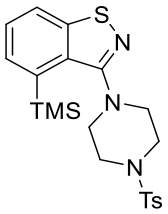

Ts-ArH
OMe
NCH2
NCH2
f1 (ppm)



^{1}H and NOE spectra of **3-(4-Tosylpiperazinyl)-4-methoxy-6-bromo-1,2-benzoisothiazole**

3-(4-Tosylpiperazinyl)-6-trimethylsilyl-1,2-benzoisothiazole and 3-(4-Tosylpiperazinyl)-4-trimethylsilyl-1,2-benzoisothiazole (4h, 4h')





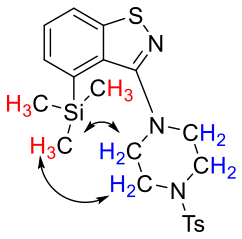
General Procedure A was followed using 2,6-bis(trimethylsilyl)phenyl trifluoromethanesulfonate (74 mg, 0.2 mmol), 3-hydroxy-4-(4-tosylpiperazinyl)-1,2,5-thiadiazole **2m** (68 mg, 0.2 mmol) and CsF (93 mg, 0.6 mmol). The product was purified by flash column chromatography (20% Et_2O in petroleum ether) to give 3-(4-tosylpiperazinyl)-6-trimethylsilyl-1,2-benzoisothiazole (52 mg, 58%) as a white crystal and 3-(4-tosylpiperazinyl)-4-trimethylsilyl-1,2-benzoisothiazole (10 mg, 11%) as a white crystal, in a ratio of 5:1.

3-(4-Tosylpiperazinyl)-6-trimethylsilyl-1,2-benzoisothiazole (4h)

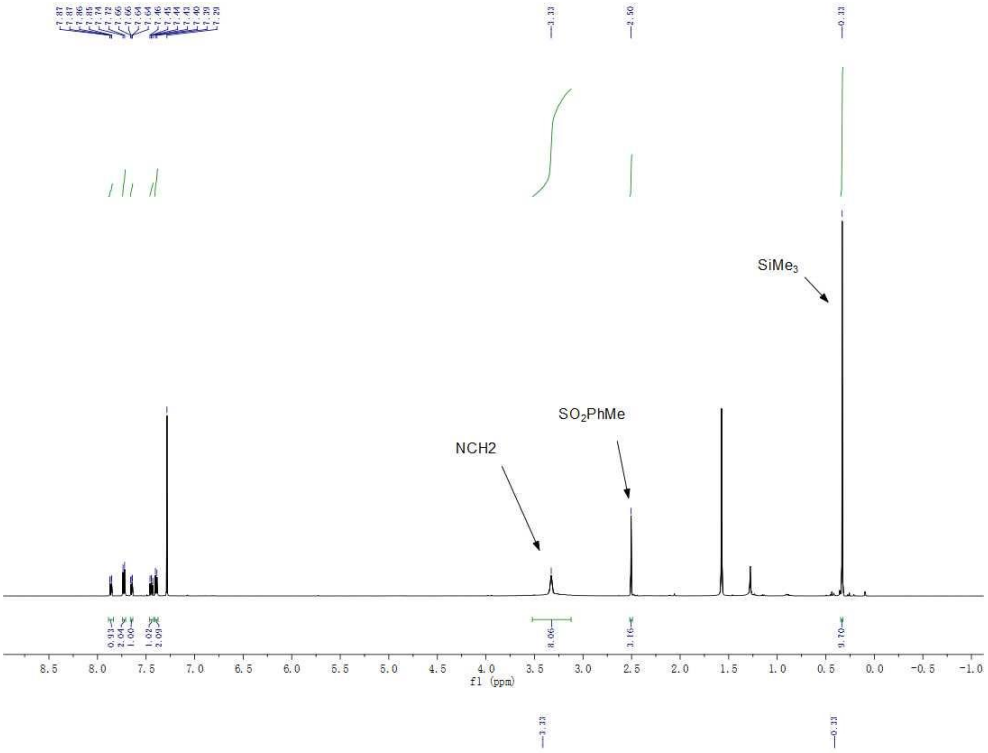
^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.68 (dd, J = 8.2, 1.1 Hz, 1H, H_{Ar}), 7.62 (d, J = 8.3 Hz, 2H, H_{Ar}), 7.50 (dd, J = 6.9, 1.1 Hz, 1H, H_{Ar}), 7.29 (d, J = 8.3 Hz, 2H, H_{Ar}), 7.24 (dd, J = 8.2, 6.9 Hz, 1H, H_{Ar}), 3.61-3.42 (m, 4H, 2 × CH_2), 3.22-3.12 (m, 4H, 2 × CH_2), 2.38 (s, 3H, Ts-CH_3), 0.32 (s, 9H, Si(CH_3)$_3$); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ 164.7, 159.6, 145.3, 134.9, 134.6, 134.1, 131.3, 129.3, 127.9, 125.5, 125.1, 51.0, 47.3, 23.0, 0.0. **LRMS** (ESI, *m/z*) 446.1 ([M+H]$^+$, 100%). **HRMS** (ESI) calcd for $C_{21}H_{28}N_3O_2S_2Si$ [M+H]$^+$ 446.1387, found 446.1386. **IR** ν_{max} (film): 2955, 2924, 2853, 1598, 1557, 1484, 1452, 1391, 1350, 1265, 1251, 1168, 947, 915, 728 cm^{-1}. **M.p.**: 164-166 ℃.

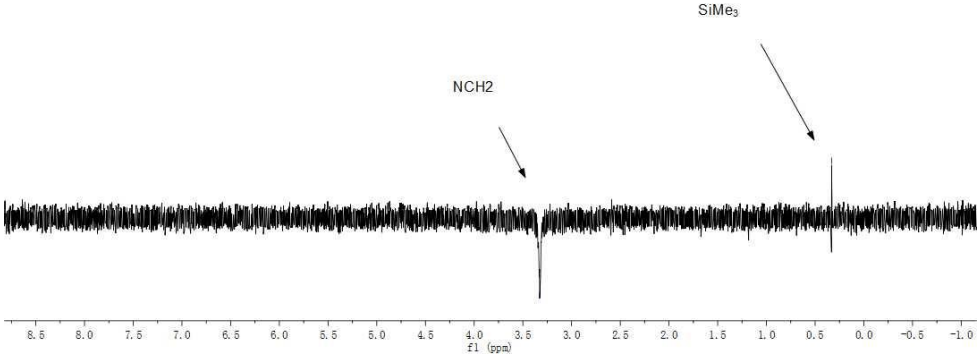
3-(4-Tosylpiperazinyl)-4-trimehylsilyl-1,2-benzoisothiazole (4h')

^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.77 (dd, J = 8.1, 0.9 Hz, 1H, H_{Ar}), 7.64 (d, J = 8.1 Hz, 2H, H_{Ar}), 7.56 (dd, J = 7.0, 0.9 Hz, 1H, H_{Ar}), 7.35 (dd, J = 8.1, 7.0 Hz, 1H, H_{Ar}), 7.30 (d, J = 8.1 Hz, 2H, H_{Ar}), 3.32-3.17 (b, s, 8H, 4 × CH_2), 2.41 (s, 3H, Ts-CH_3), 0.24 (s, 9H, Si(CH_3)$_3$); ^{13}**C NMR** (125 MHz, $CDCl_3$) δ 166.7, 152.0, 142.3, 135.6, 132.0, 131.7, 131.6, 128.3, 126.5, 125.2, 119.6, 50.6, 43.5, 20.2, 0.0. **LRMS** (ESI, *m/z*) 446.1 ([M+H]$^+$, 100%). **HRMS** (ESI) calcd for $C_{21}H_{28}N_3O_2S_2Si$ [M+H]$^+$ 446.1387, found 446.1386. **IR** ν_{max} (film): 2919, 2851, 2359, 1457, 1350, 1264, 1168, 1101, 945, 859, 731 cm^{-1}. **M.p.**: 189-192 ℃.



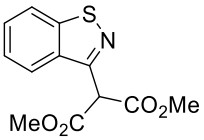
Regioisomers were distinguished by NOE spectrum as presented below. Protons on TMS group (δ 0.24 (s, 9H, Si(C*H*$_3$)$_3$)) of 3-(4-tosylpiperazinyl)-4-trimehylsilyl-1,2-benzoisothiazole have shown remote interaction with protons on piperazine group (δ 3.32-3.17 (b, 8H, C*H*$_2$)).





7. Cascade process for the formation of C-substituted benzoisothiazole

Dimethyl 2,1-benzoisothiazole-3-malonate (5)



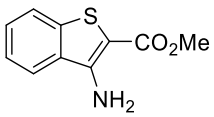
Sodium acetate (33 mg, 0.4 mmol) was added to a solution of dimethyl malonate (53 mg, 0.4 mmol) in dry THF : EtOH (1:1, 2 mL). After stirring under nitrogen for 5 min, 3-chloro-1,2-benzoisothiazole (33 mg, 0.2 mmol) was added into the suspension and the resulting mixture was stirred at room temperature for 30 min prior to refluxing for 24 h. Water (10 mL) was added and the mixture was extracted with DCM (3 × 10 mL). Combined organic phase was dried over $MgSO_4$, filtered and concentrated. The product was purified by flash column chromatography (30% Et_2O in petroleum ether), 12 mg (36%) of starting material benzoisothiazole was recovered and the titled compound was isolated as a colourless oil which solidified on sitting (30 mg, 57%).

Same product was obtained with the one-pot method below:

3,4-Dichloro-1,2,5 –thiadiazole **2a** (94 μL, 1.0 mmol) was added dropwise into a freshly oven dried suspension of CsF (320 mg, 2.8 mmol, 2.8 eq.) in dry THF (1.5 mL) under nitrogen at room temperature. 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **1a** (417 mg, 1.4 mmol, 1.4 eq.) was then added dropwise. The mixture was stirred at 65 ℃ and monitored by TLC. After consumption of starting material 3,4-dichloro-1,2,5 –thiadiazole, dimethyl malonate (254 mg, 1.5 mmol) was added dropwise together with sodium methoxide (320 μL, 25 wt% in MeOH, 1.4 mmol). The reaction mixture was then stirred at room temperature for 12 h before quenching with water (10 mL) and extracting with DCM (3 × 10 mL). The combined organic phase was dried over $MgSO_4$, filtered and concentrated. The crude product was purified *via* flash column chromatography (30% Et_2O in petroleum ether), resulting in the titled product as a colourless oil which solidified on sitting (180 mg, 68%). Methyl 3-aminobenzothiophene-2-carboxylate **6** was also obtained (22 mg, 11%). ^1H and ^{13}C NMR spectrum match the result above.

^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (app. dt, J = 8.2, 0.9 Hz, 1H, H_{Ar}), 7.87 (app. dt, J = 8.2, 0.9 Hz, 1H, H_{Ar}), 7.47 (ddd, J = 8.2, 5.1, 1.1 Hz, 1H, H_{Ar}), 7.38 (ddd, J = 8.2, 5.2, 1.1 Hz, 1H, H_{Ar}), 5.33 (s, 1H, C*H*), 3.71 (s, 6H, 2 × COOCH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.7, 156.2, 153.0, 133.9, 127.9, 125.1, 123.7, 119.9, 55.5, 53.2. **LRMS** (ESI, *m/z*) 266.0 ([M+H]$^+$, 100%). **HRMS** (ESI) calcd for $C_{12}H_{12}O_4NS$ [M+H]$^+$ 266.0482, found 266.0482. **IR** ν_{max} (film): 2954, 1736, 1595, 1480, 1435, 1311, 1259, 1198, 1154, 1090, 1024, 933, 770 cm^{-1}. **M.p.**: 77-79 ℃.

Methyl 3-aminobenzothiophene-2-carboxylate (6)



Sodium methoxide solution (33 μL, 25 wt% in MeOH, 0.4 mmol) was added to a solution of dimethyl malonate (53 mg, 0.4 mmol) in dry MeOH (2 mL). After stirring under nitrogen for 5 min, the sodium enolate was added dropwise to 3-chlorobenzoisothiazole (34 mg, 0.2 mmol) and the resulting mixture was stirred at room temperature for 30 min, until the starting material was fully consumed. The product was purified by flash column chromatography (40% Et_2O in petroleum ether), resulting in the titled compound as a white solid (36 mg, 88%).

Same product was obtained using sodium acetate (2 eq.) and dimethyl malonate (2 eq.) in MeOH. Reflux for 12 h afforded 40% yield of the product while 43% of starting material benzoisothiazole was recovered.

^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.66 (d, J = 8.1 Hz, 1H, H_{Ar}), 7.57 (d, J = 8.1 Hz, 1H, H_{Ar}), 7.40 (ddd, J = 8.1, 7.2, 1.2 Hz, 1H, H_{Ar}), 7.30 (ddd, J = 8.1, 7.2, 1.0 Hz, 1H, H_{Ar}), 5.85 (b, s, 2H, NH_2), 3.82 (s, 3H, OCH_3); ^{13}**C NMR** (100 MHz, DMSO-*d6*) δ 165.4, 150.3, 139.3, 131.9, 129.0, 124.4, 123.6, 123.6, 94.9, 51.7. **LRMS** (ESI, *m/z*) 208.0 ($[M+H]^+$, 100%). **HRMS** (ESI) calcd for $C_{10}H_{10}O_2NS$ $[M+H]^+$ 208.0427, found 208.0429. **M.p.**: 111-113 ℃.

The data recorded are consistent with the literature.[22]

8. References:

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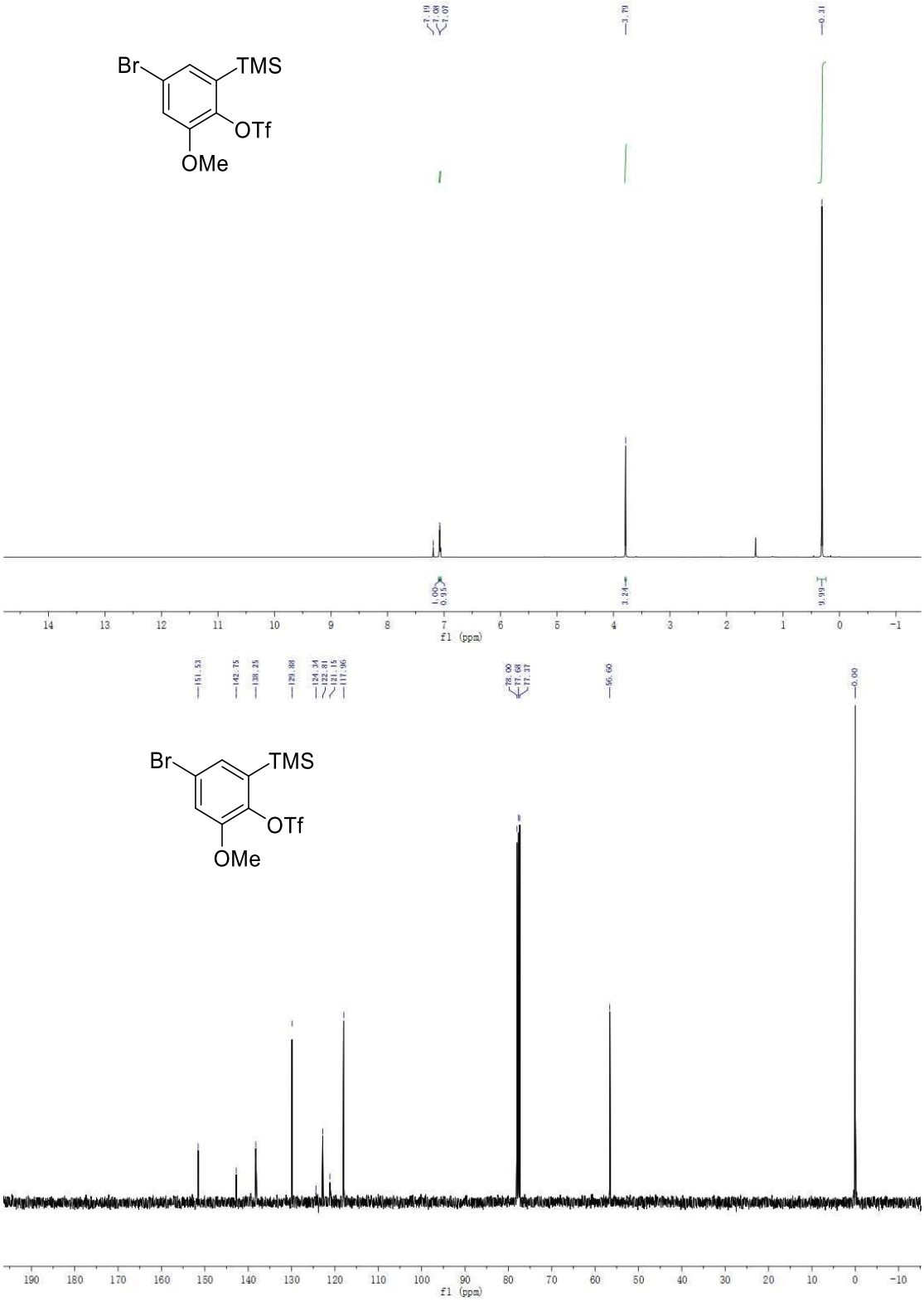
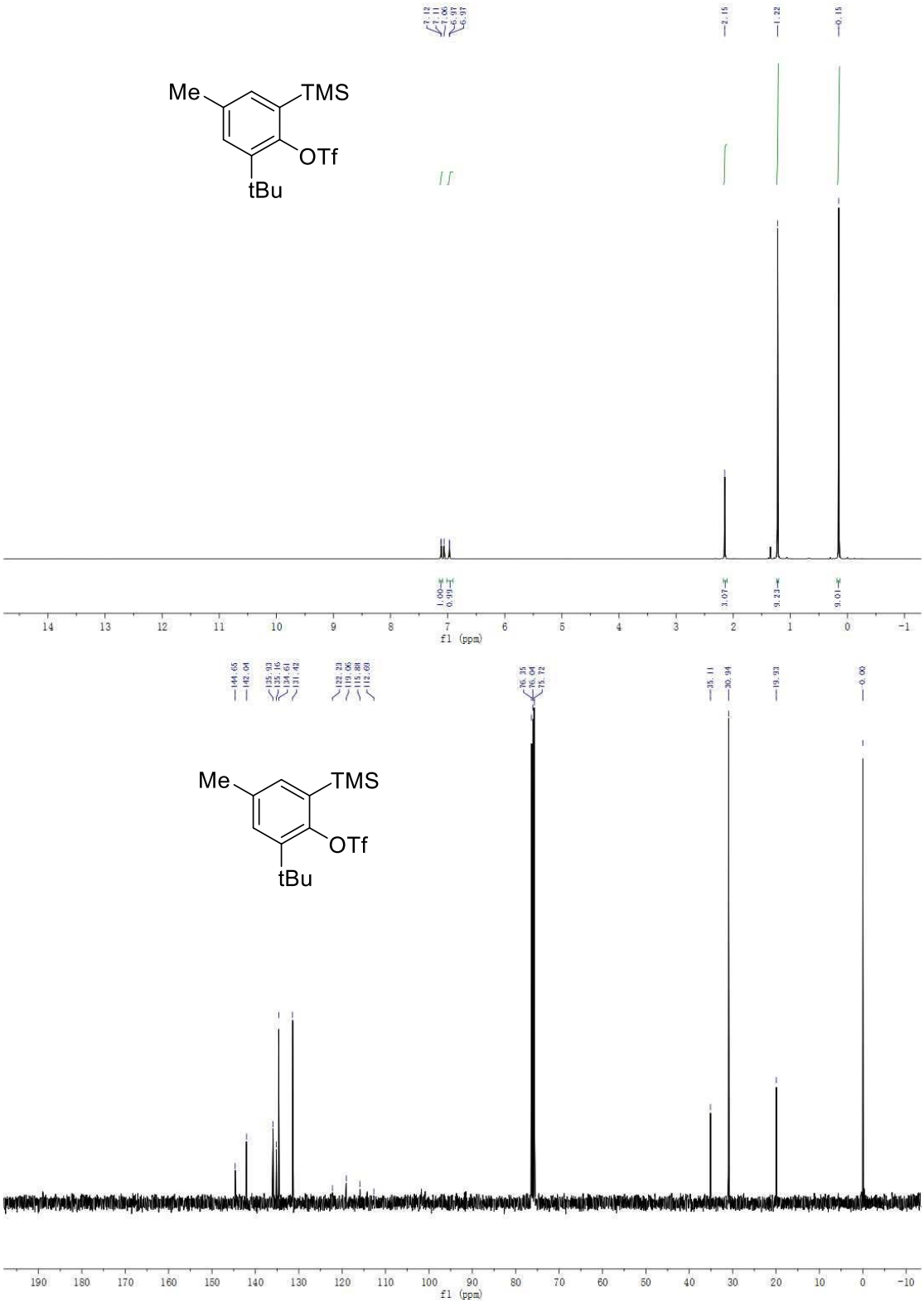
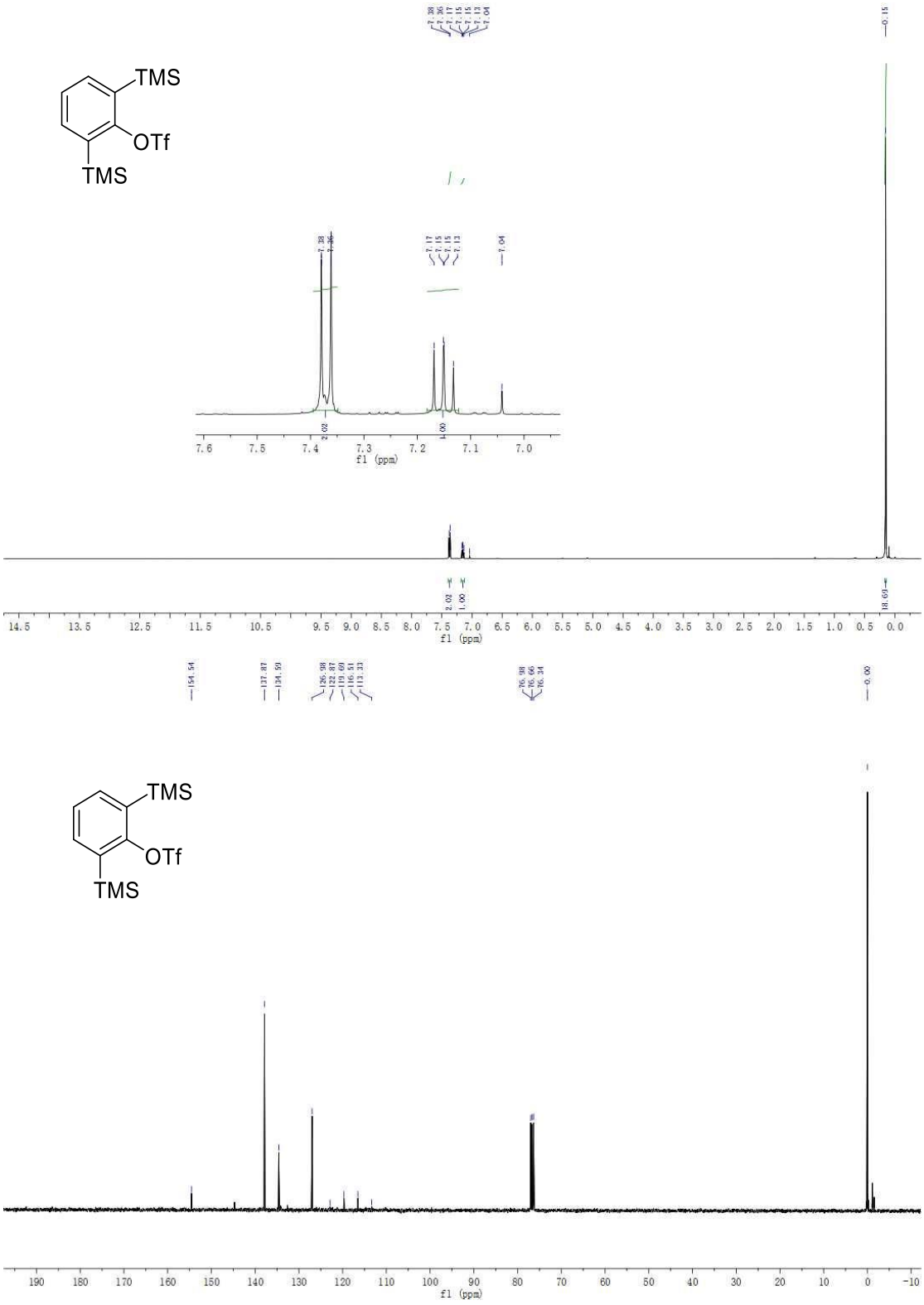
9. ^{1}H NMR and ^{13}C NHR spectra



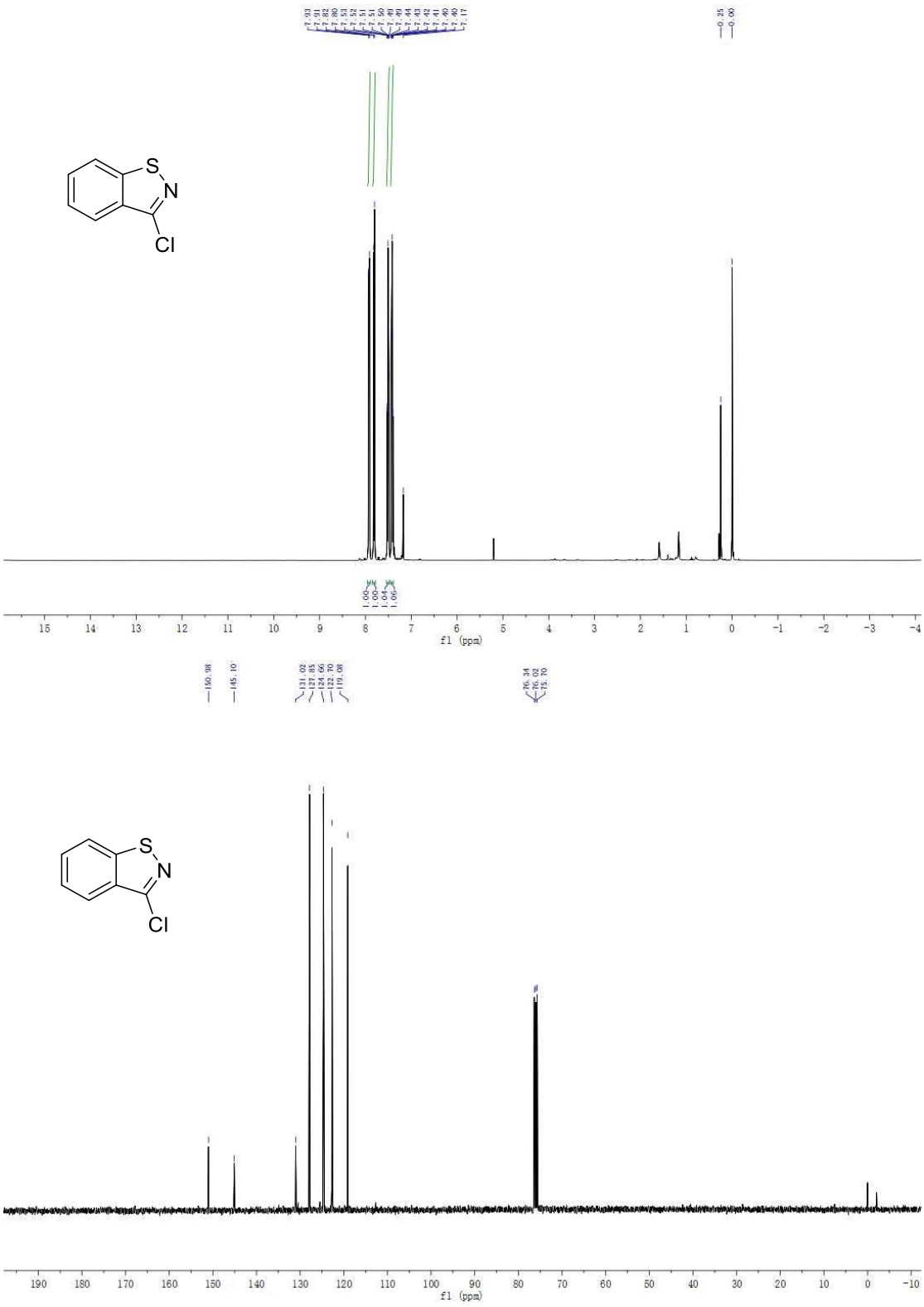
^{1}H NMR and ^{13}C NHR spectrum of **2-Methoxy-4-bromo-6-(trimethylsilyl)phenyl trifluoromethanesulfonate**



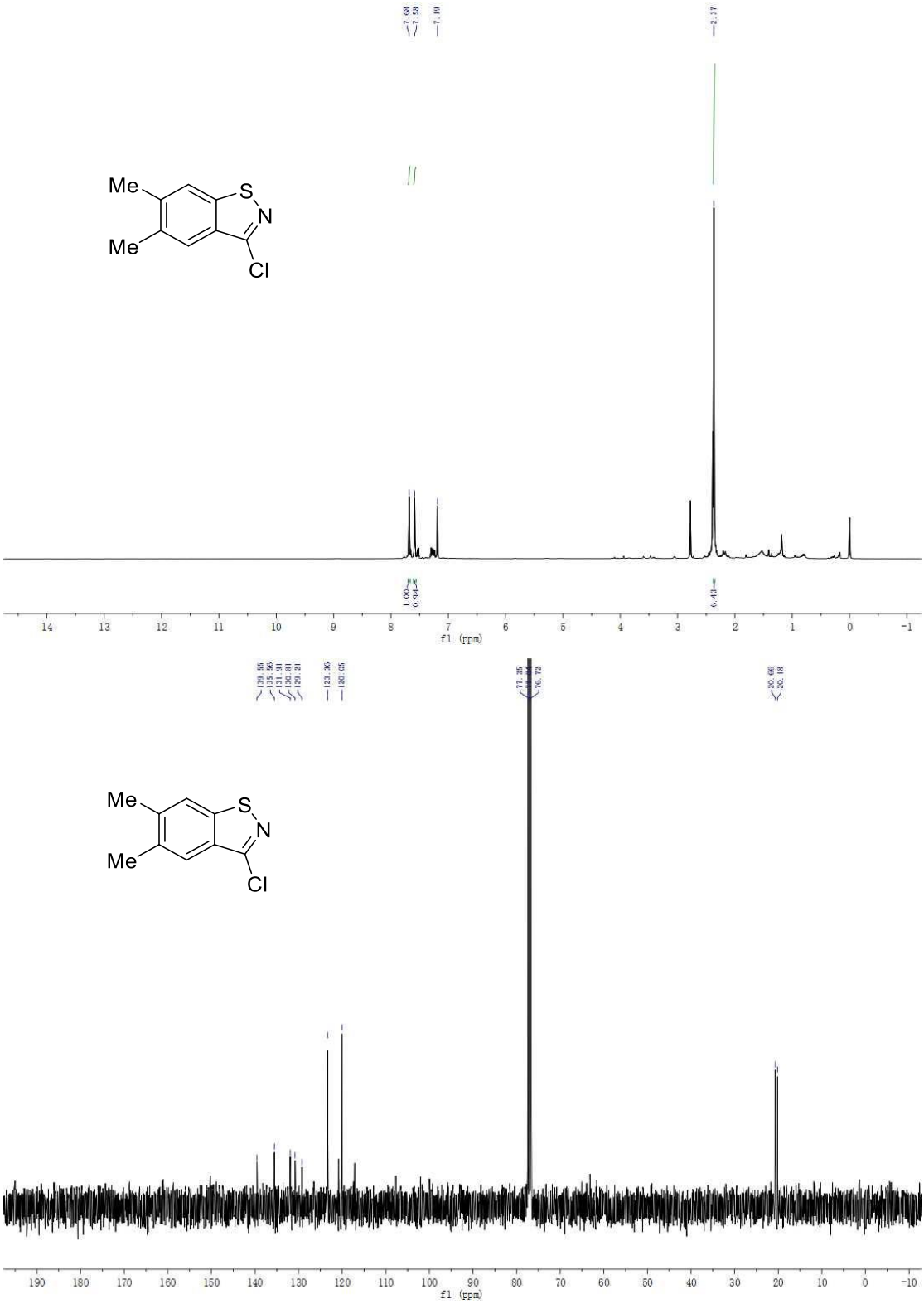
^{1}H NMR and ^{13}C NHR spectrum of **2-*tert*-Butyl-4-methyl-6-(trimethylsilyl)phenyl trifluoromethanesulfonate**



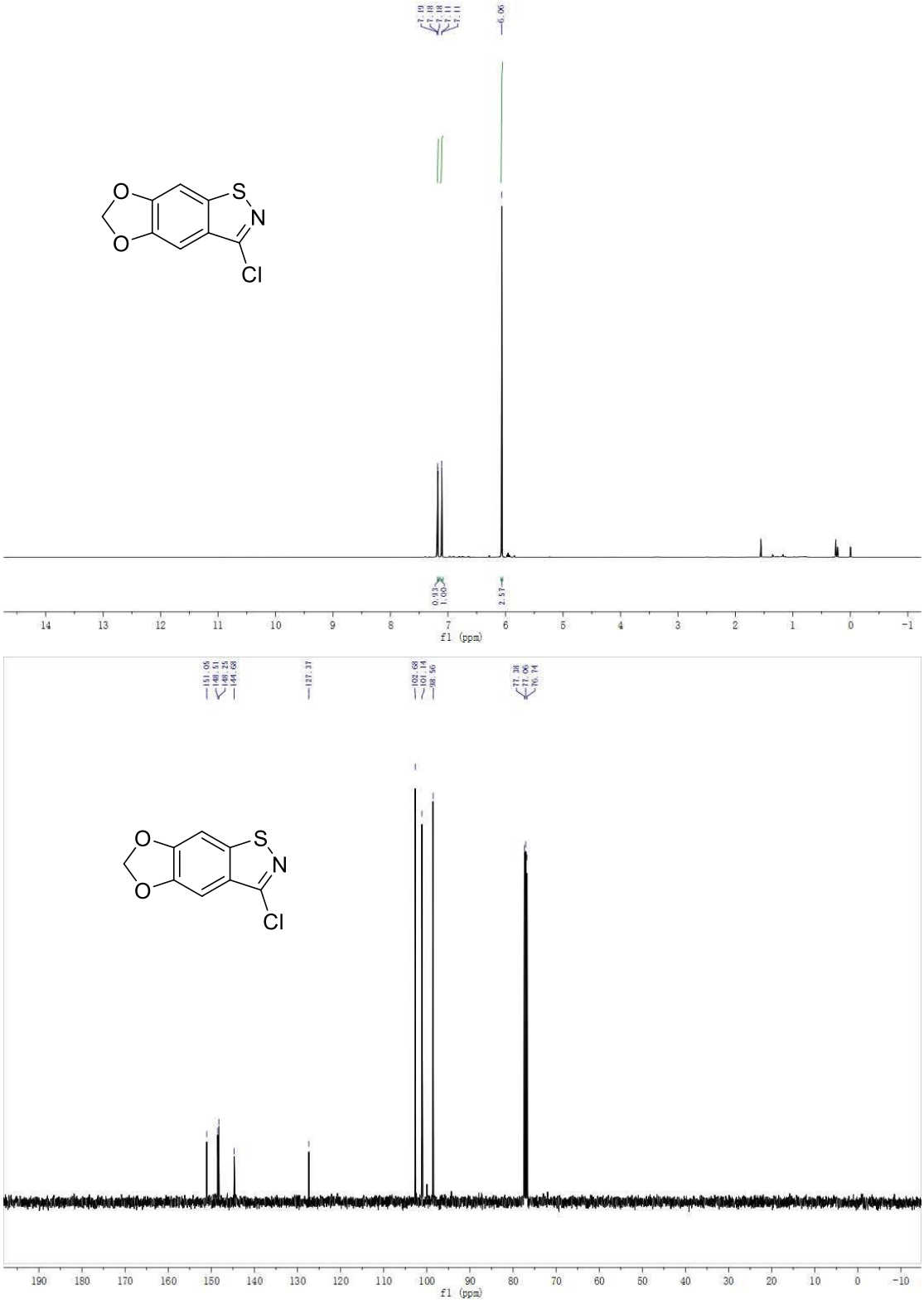
^{1}H NMR and ^{13}C NHR spectrum of **2,6-Bis(trimethylsilyl)phenyl trifluoromethanesulfonate**



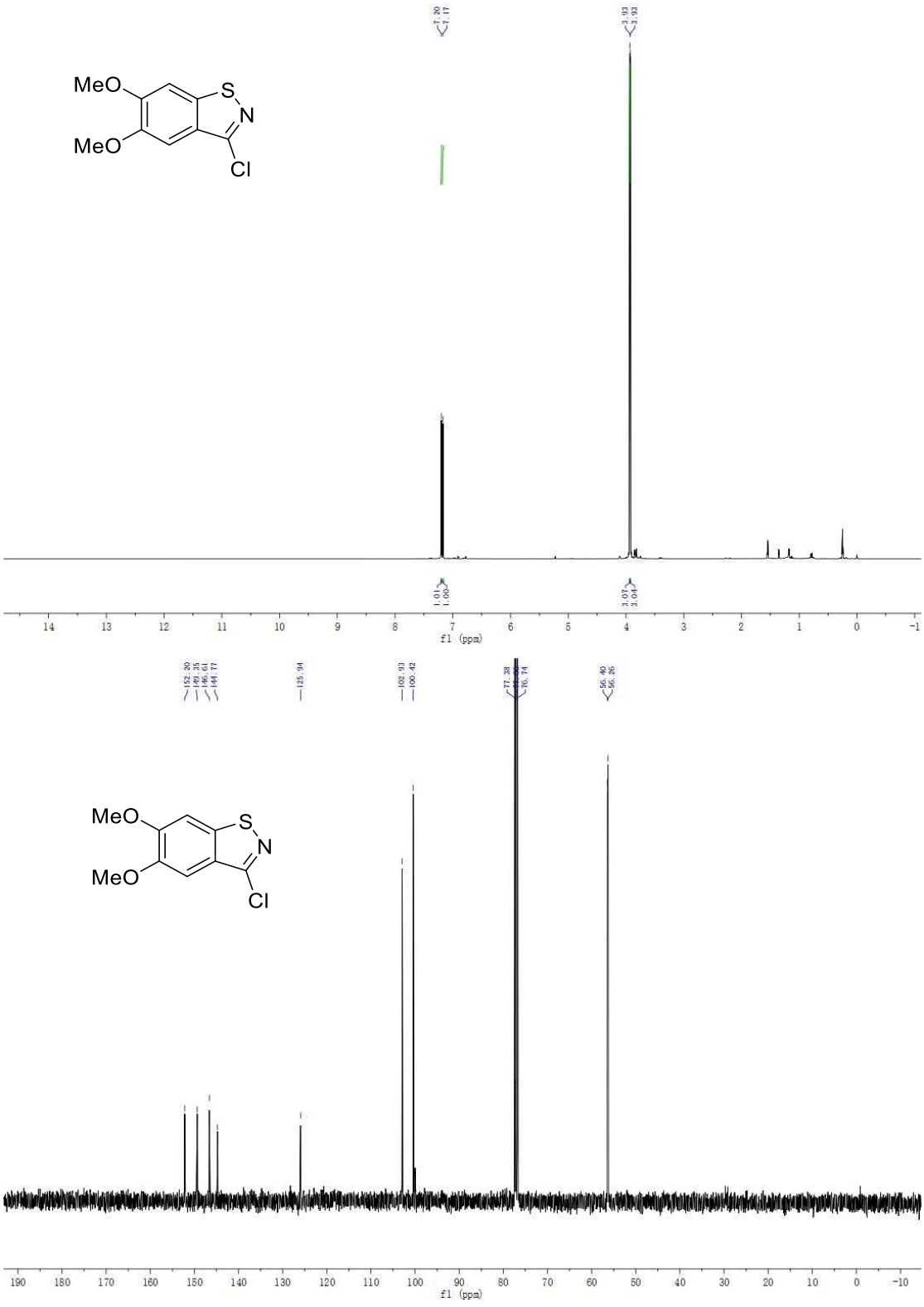
^{1}H NMR and ^{13}C NHR spectrum of ***3-chloro-1,2-benzoisothiazole (3a)***



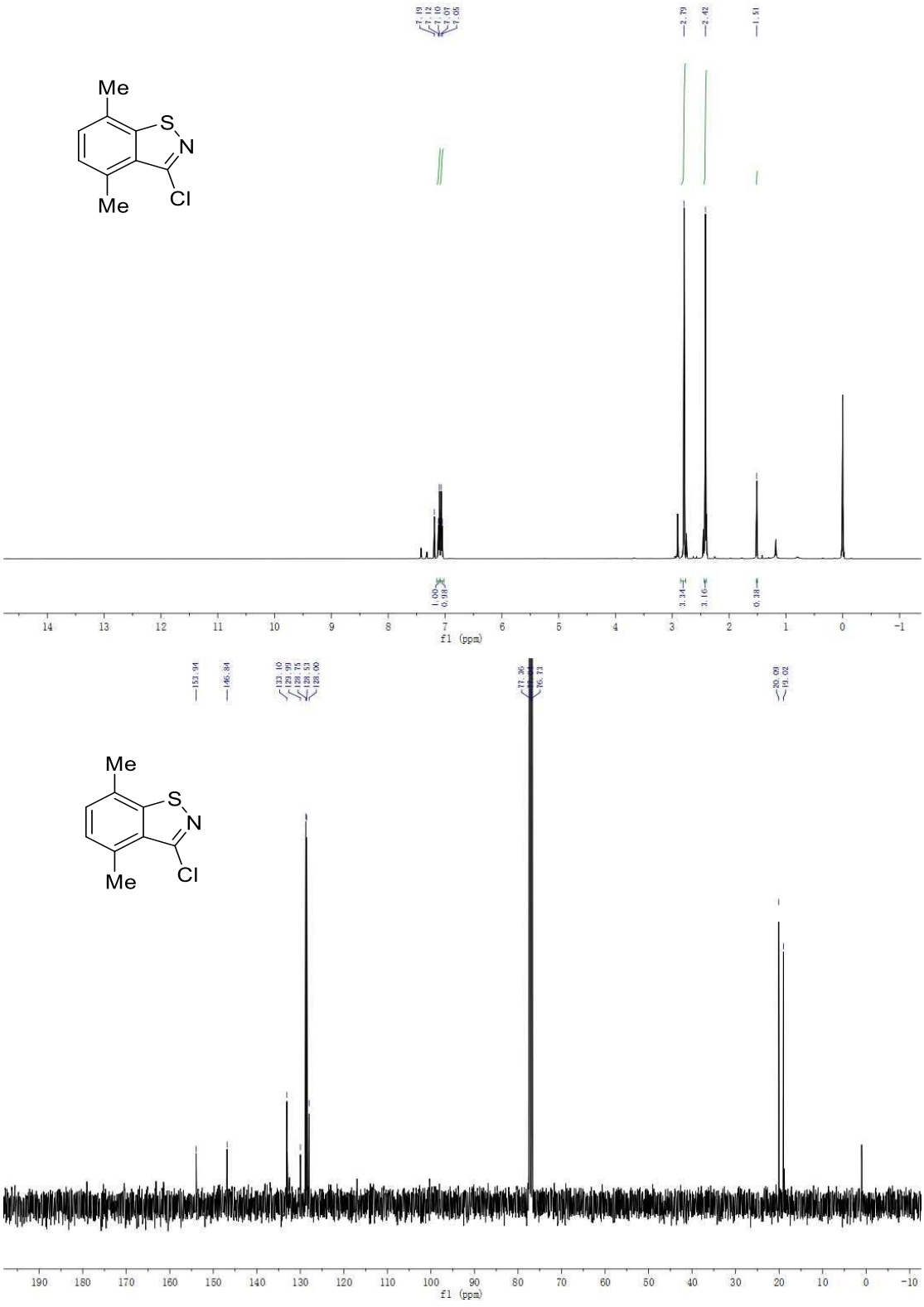
^{1}H NMR and ^{13}C NHR spectrum of **3-Chloro-5,6-dimethyl-1,2-benzoisothiazole (Table 2, entry 1)**



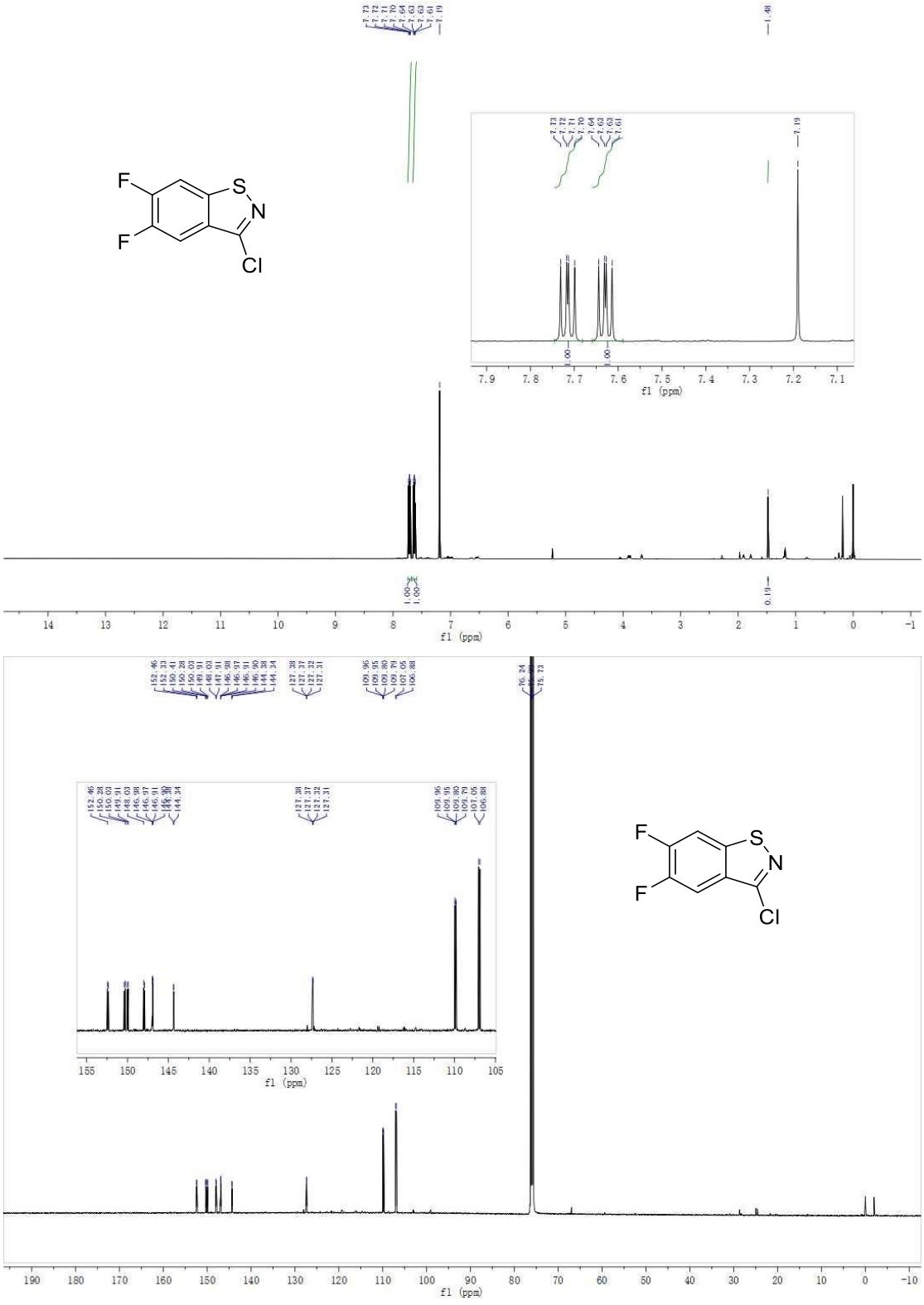
^{1}H NMR and ^{13}C NHR spectrum of ***3*-Chloro-*5*,*6*-dioxolo-1,*2*-benzoisothiazole (Table *2*, entry *2*)**



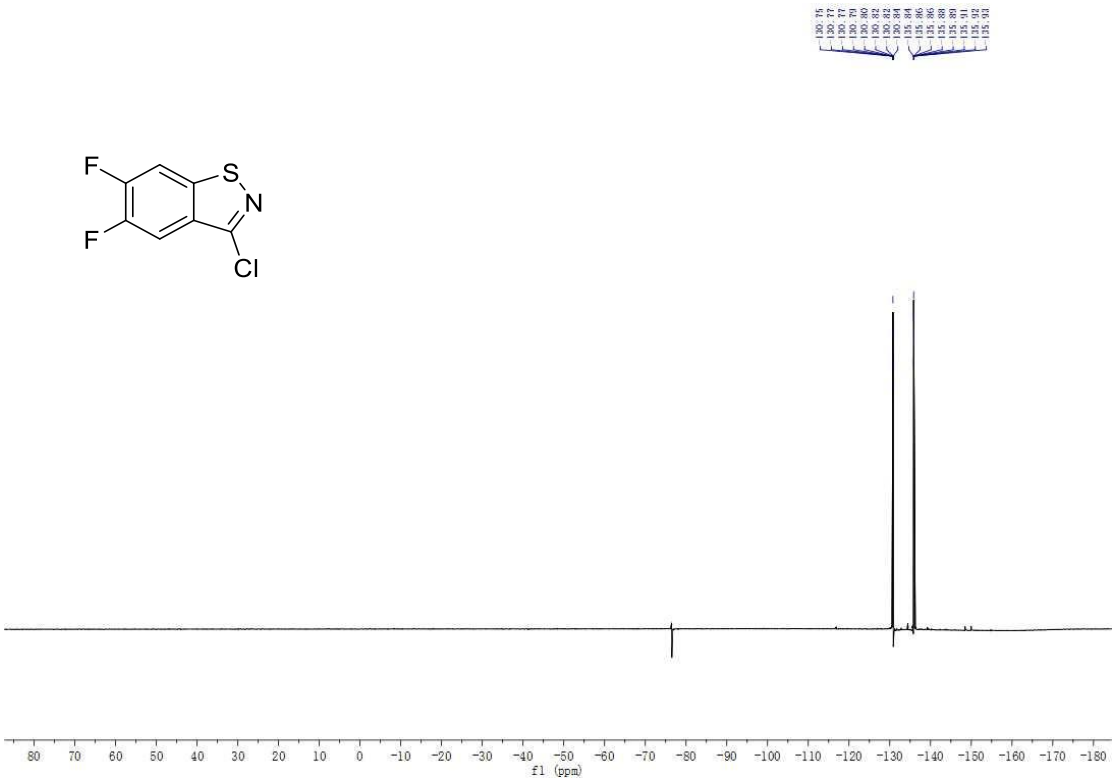
^{1}H NMR and ^{13}C NHR spectrum of **3-Chloro-5,6-dimethoxy-1,2-benzoisothiazole (Table 2, entry 3)**



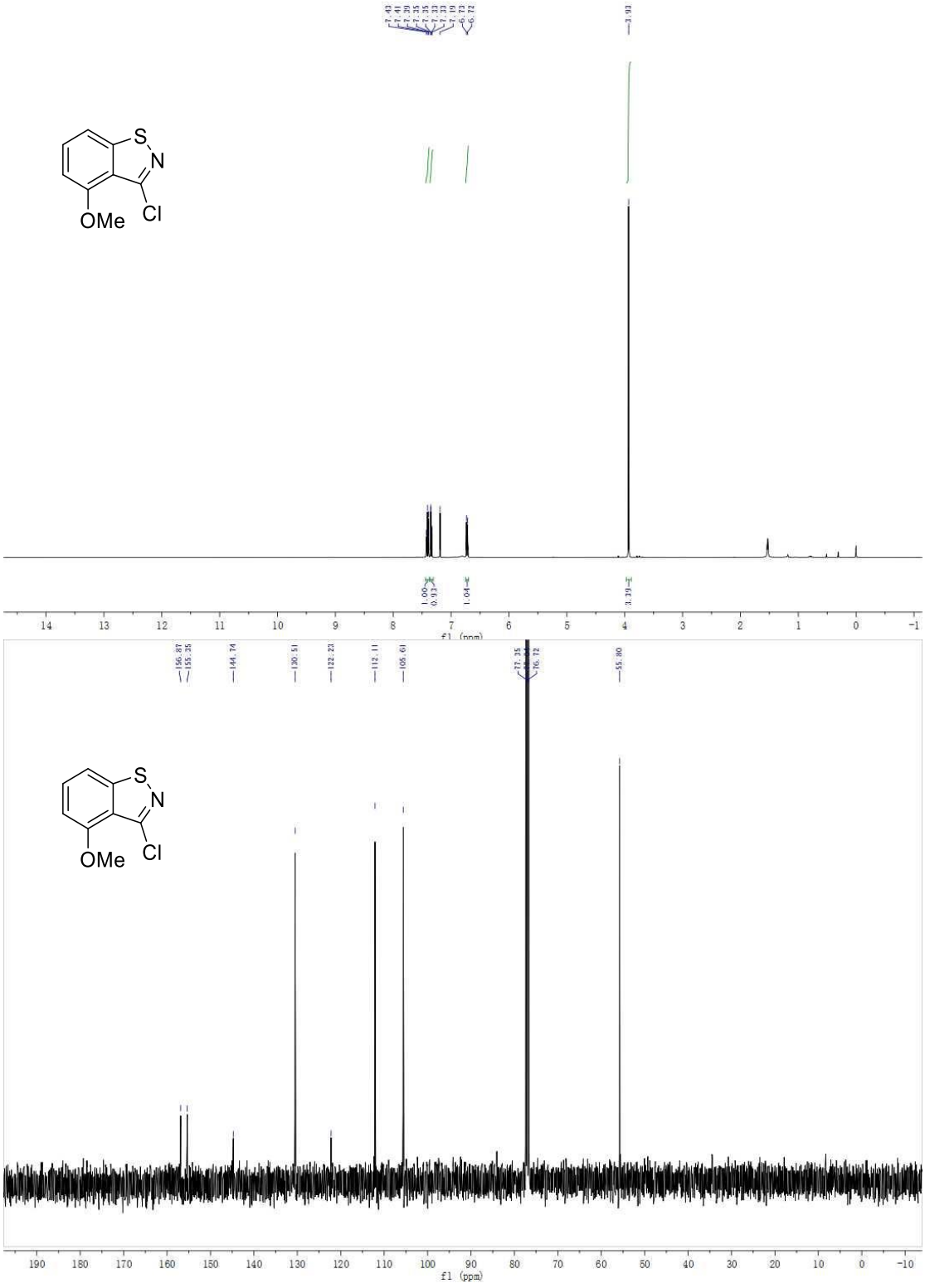
^{1}H NMR and ^{13}C NHR spectrum of **3-Chloro-4,7-dimethyl-1,2-benzoisothiazole (Table 2, entry 4)**



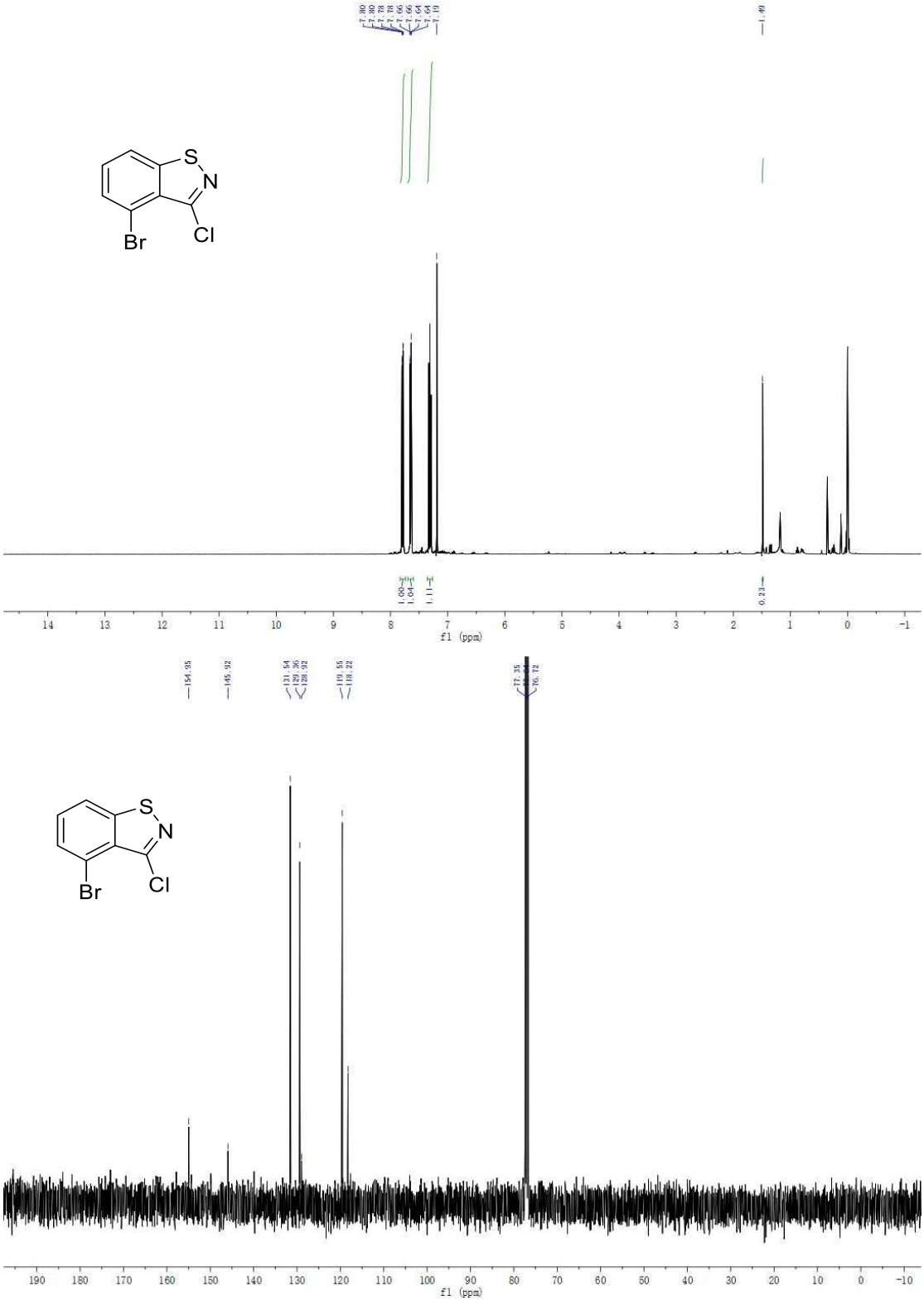
^{1}H NMR and ^{13}C NHR spectrum of **3-Chloro-5,6-difluoro-1,2-benzoisothiazole (Table 2, entry 5)**



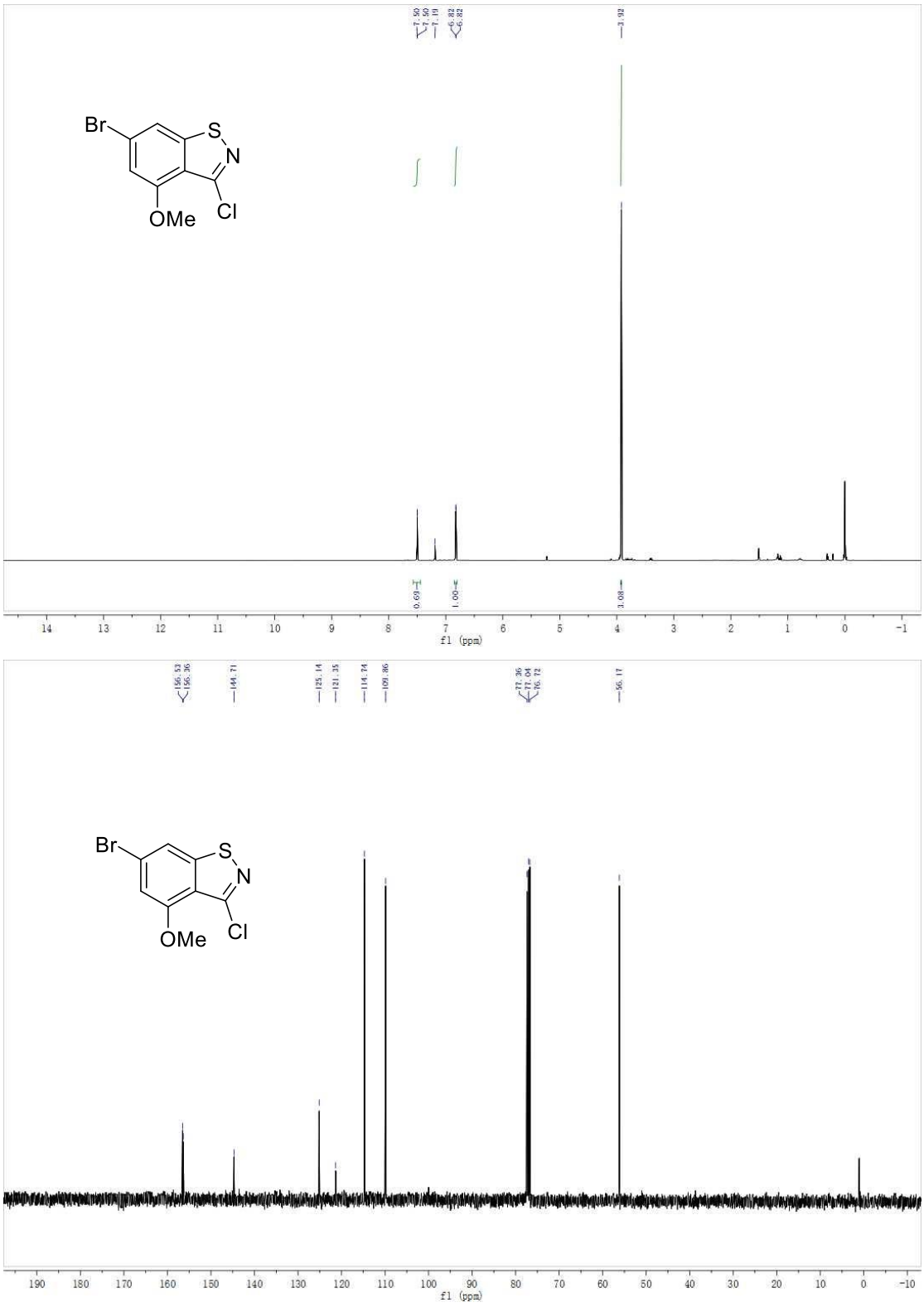
^{19}F NMR spectrum of **3-Chloro-5,6-difluoro-1,2-benzoisothiazole (Table 2, entry 5)**



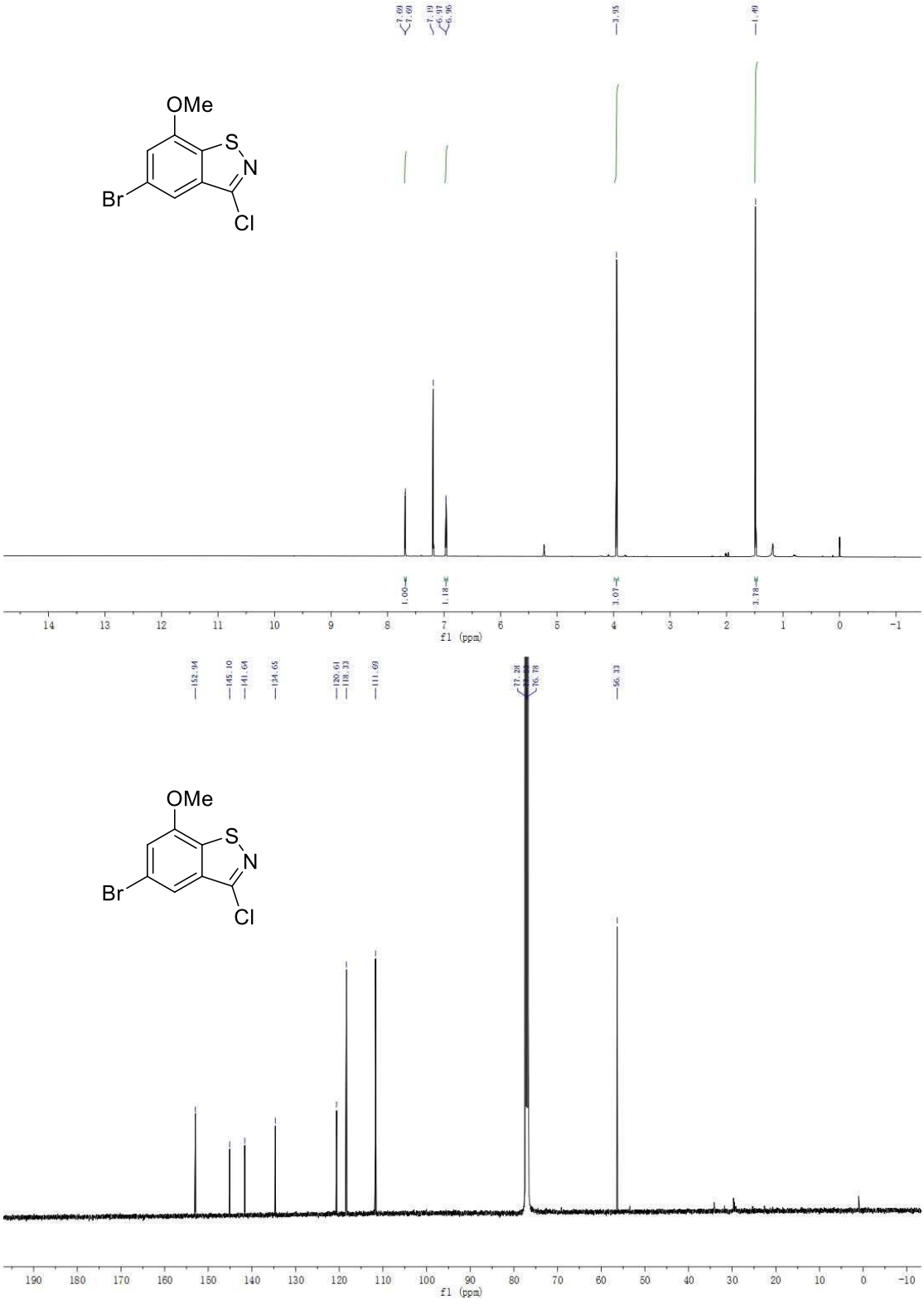
^{1}H NMR and ^{13}C NHR spectrum of **3-Chloro-4-methoxy-1,2-benzoisothiazole (Table 2, entry 6)**



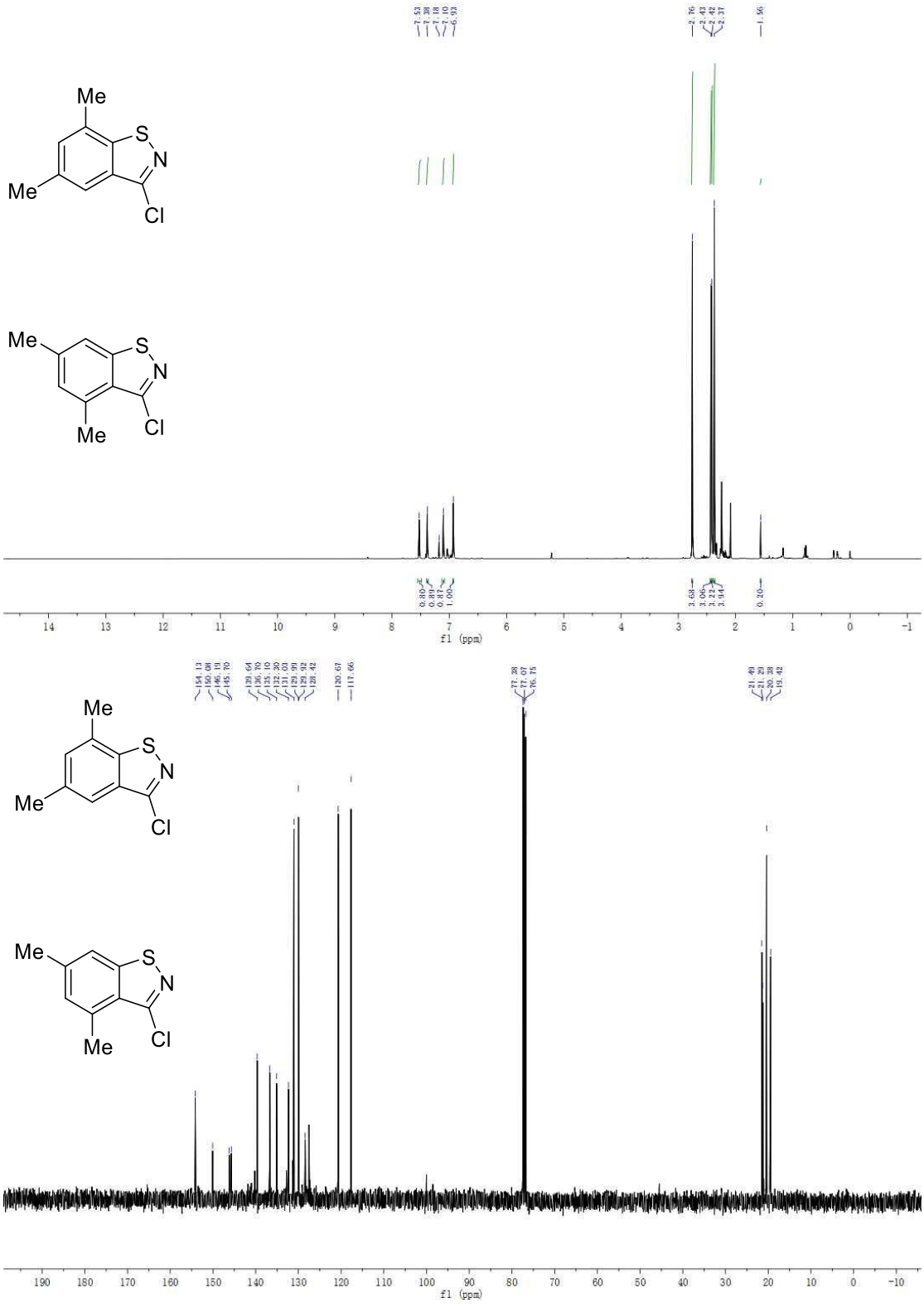
^{1}H NMR and ^{13}C NHR spectrum of **3-Chloro-4-bromo-1,2-benzoisothiazole (Table 2, entry 7)**



^{1}H NMR and ^{13}C NHR spectrum of **3-Chloro-4-methoxy-6-bromo-1,2-benzoisothiazole (Table 2, entry 8)**

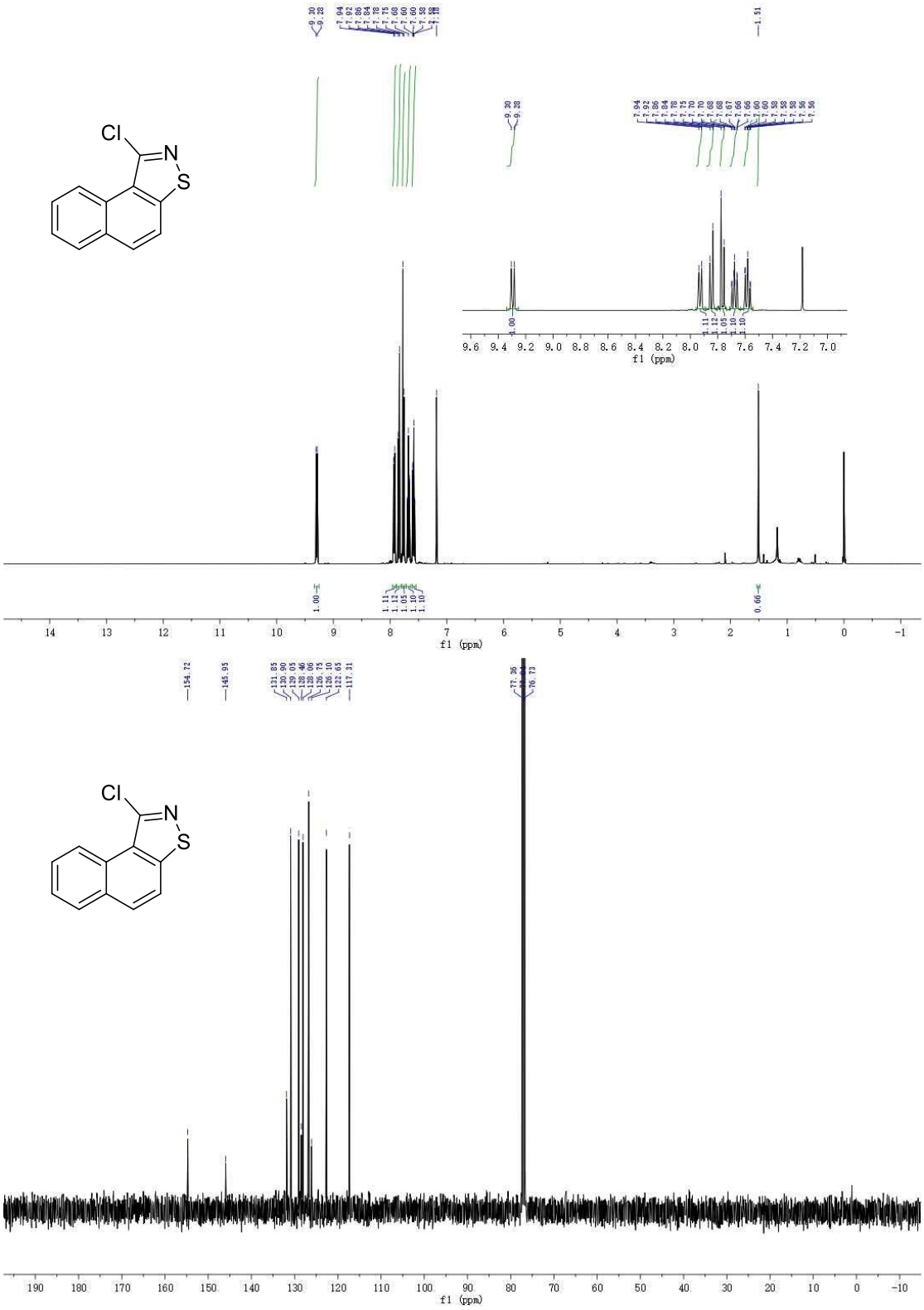


^{1}H NMR and ^{13}C NHR spectrum of **3-chloro-5-bromo-7-methoxy-1,2-benzoisothiazole (Table 2, entry 8)**

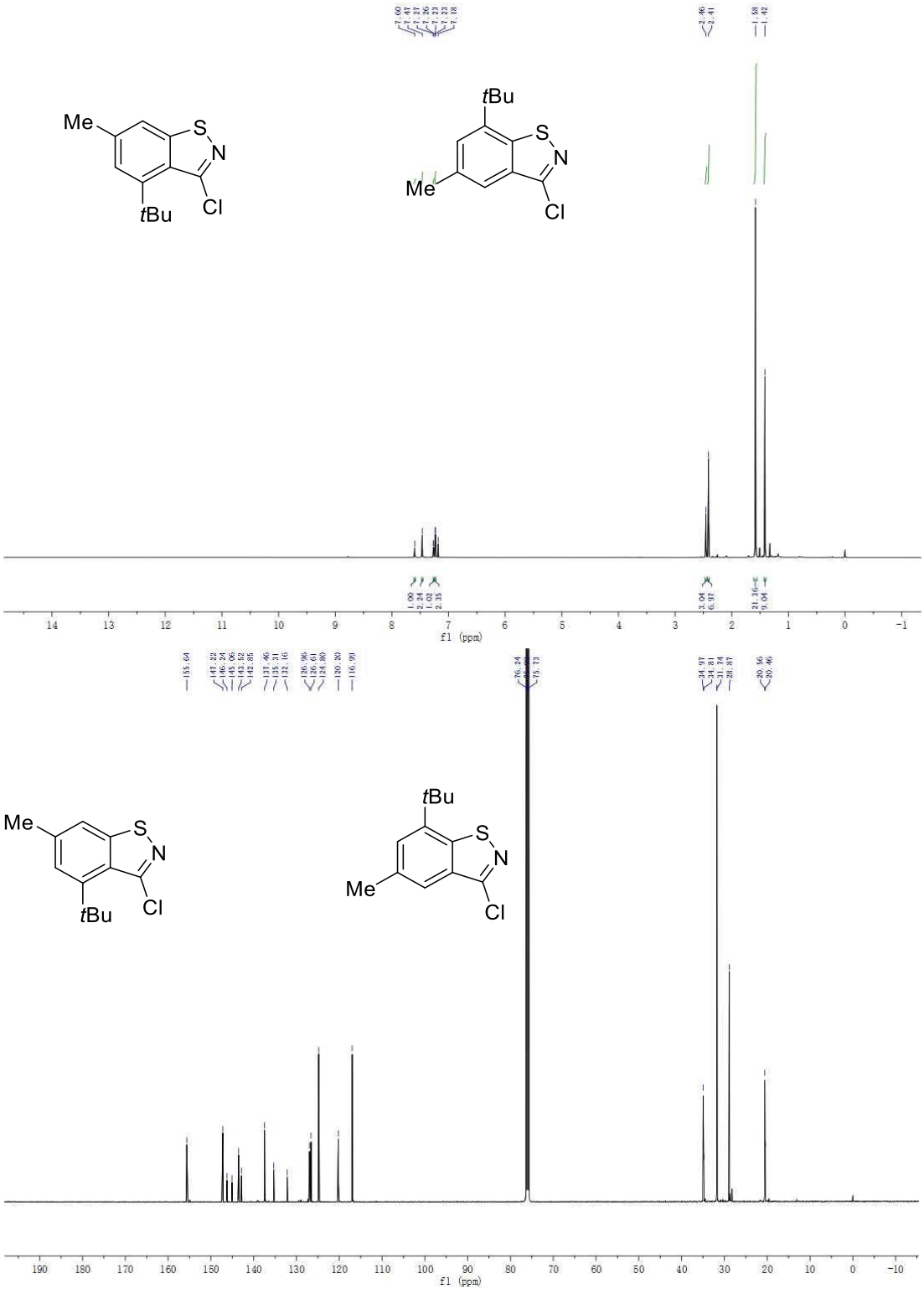


^{1}H NMR and ^{13}C NHR spectrum of **3-Chloro-5,7-dimethyl-1,2-benzoisothiazole & 3-chloro-4,6-dimethyl-1,2-benzoisothiazole (Table 2, entry 9)**

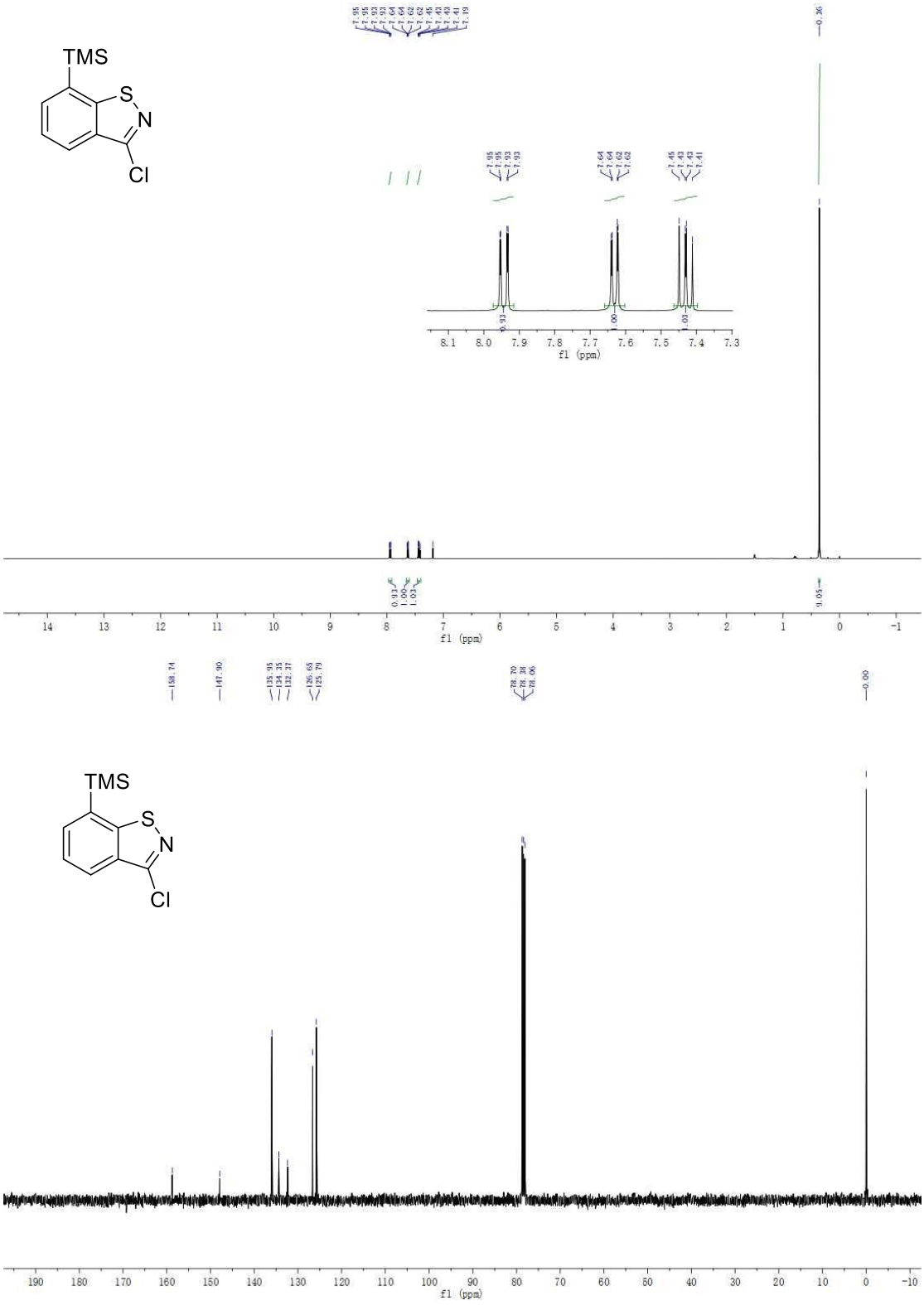
^{1}H NMR and ^{13}C NHR spectrum of **3-Chloronaphtho-2,1-isothiazole (Table 2, entry 10)**



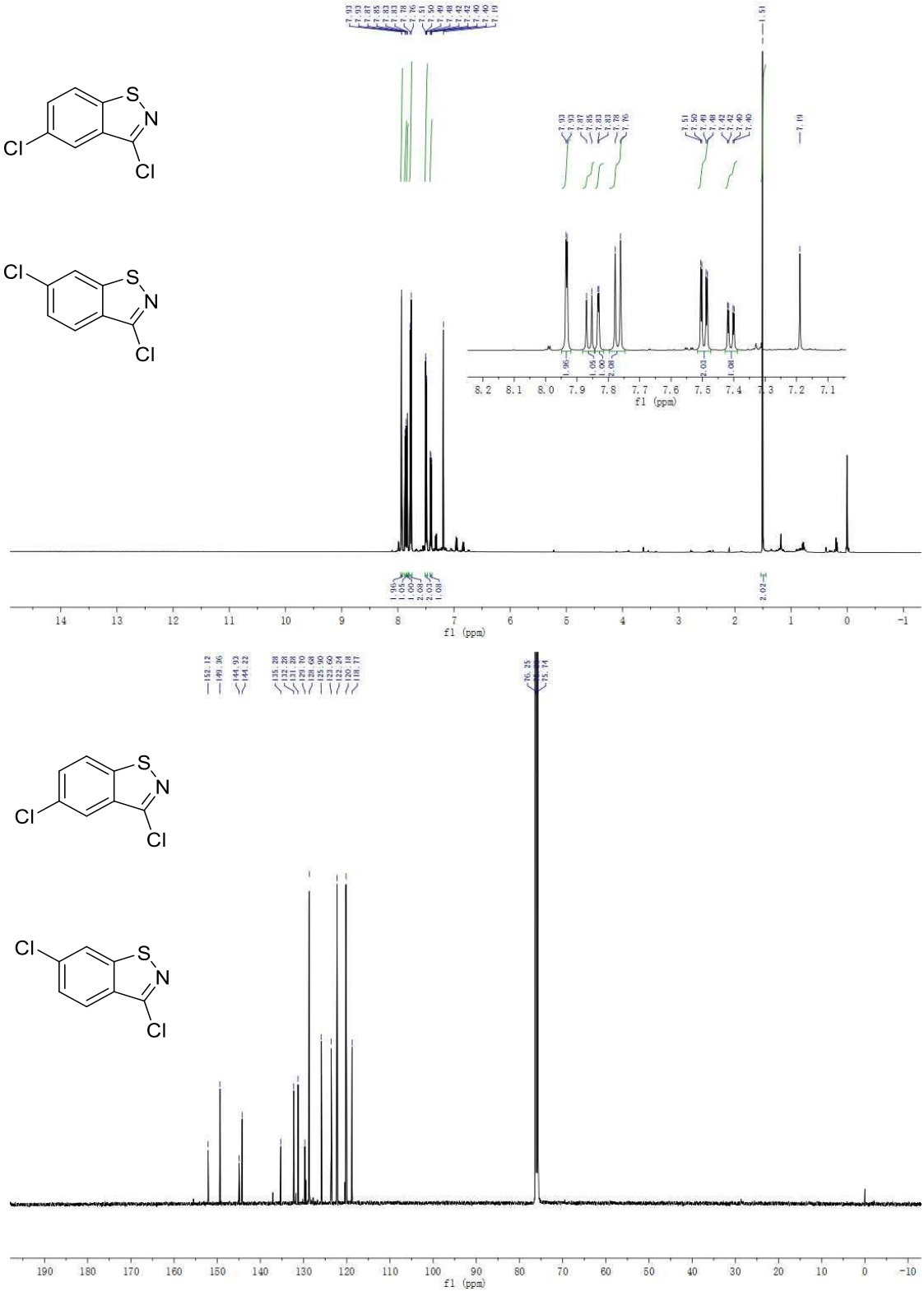
^{1}H NMR and ^{13}C NHR spectrum of **3-Chloronaphtho-2,1-isothiazole (Table 2, entry 10)**



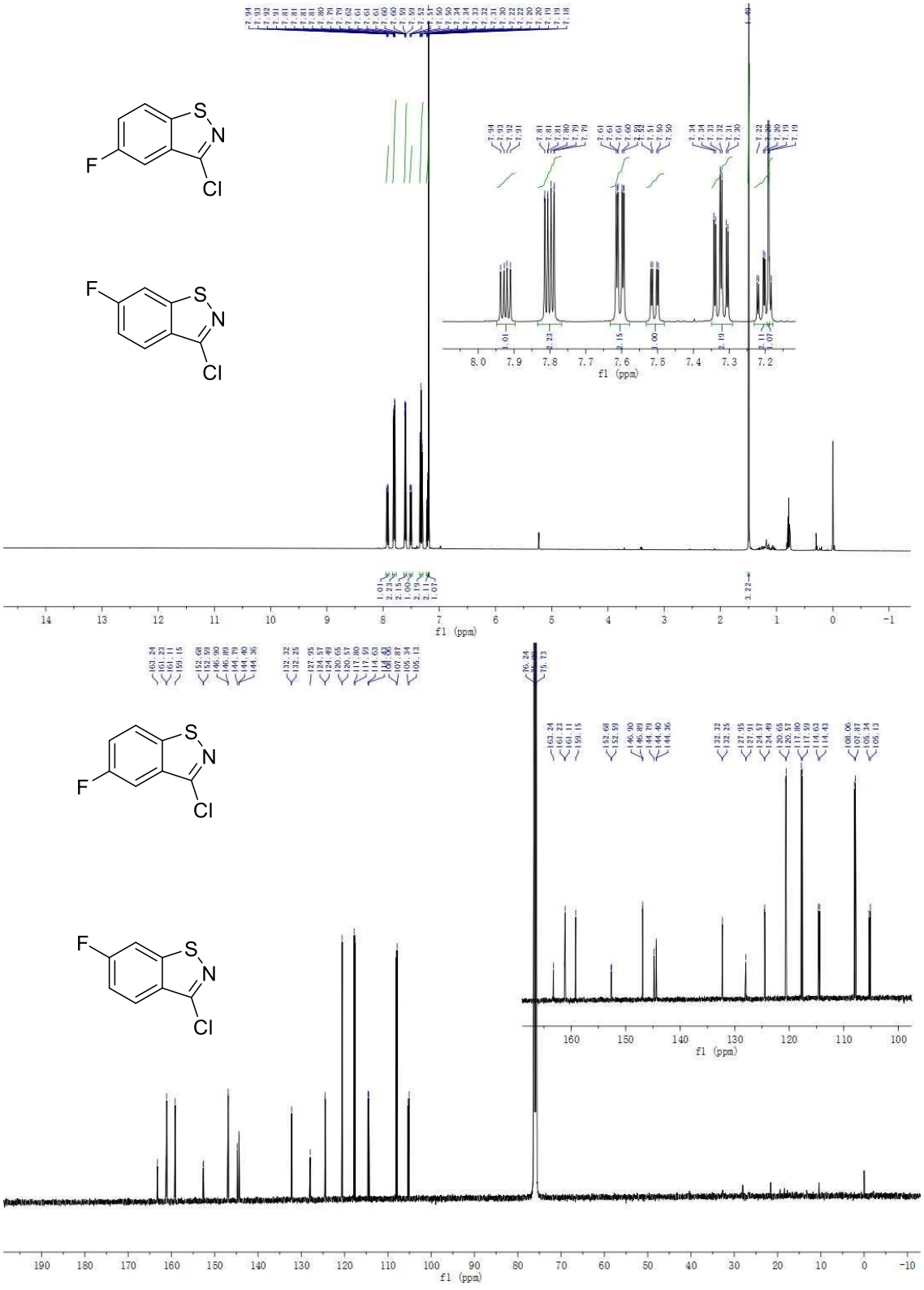
^{1}H NMR and ^{13}C NHR spectrum of **3-Chloro-4-*tert*-butyl-6-methyl-1,2-benzoisothiazole & 3-chloro-5-methyl-7-*tert*-butyl-1,2-benzoisothiazole mixture (Table 2, entry 11)**



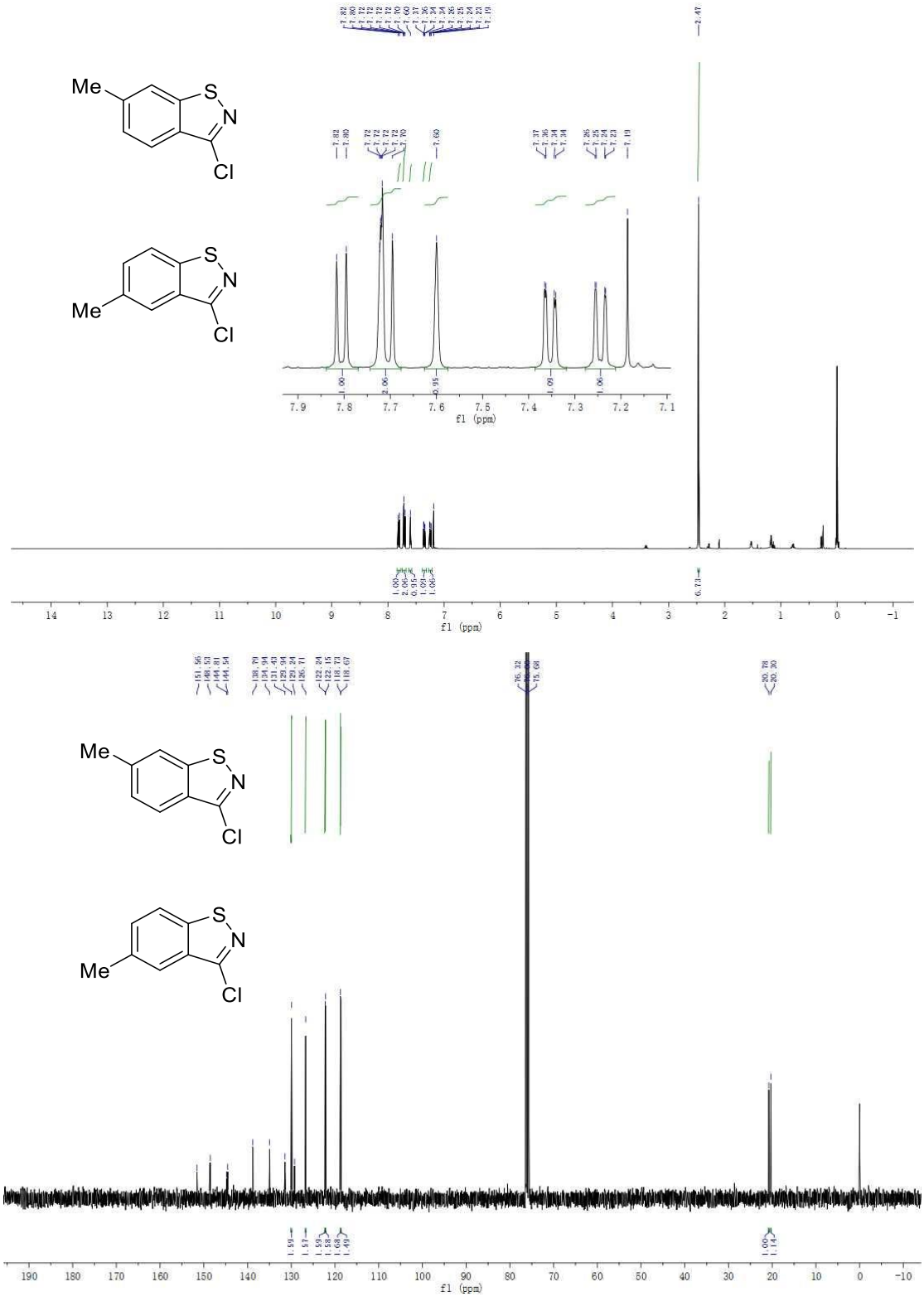
^{1}H NMR and ^{13}C NHR spectrum of **3-Chloro-6-trimethylsilyl-1,2-benzoisothiazole (Table 2, entry 12)**



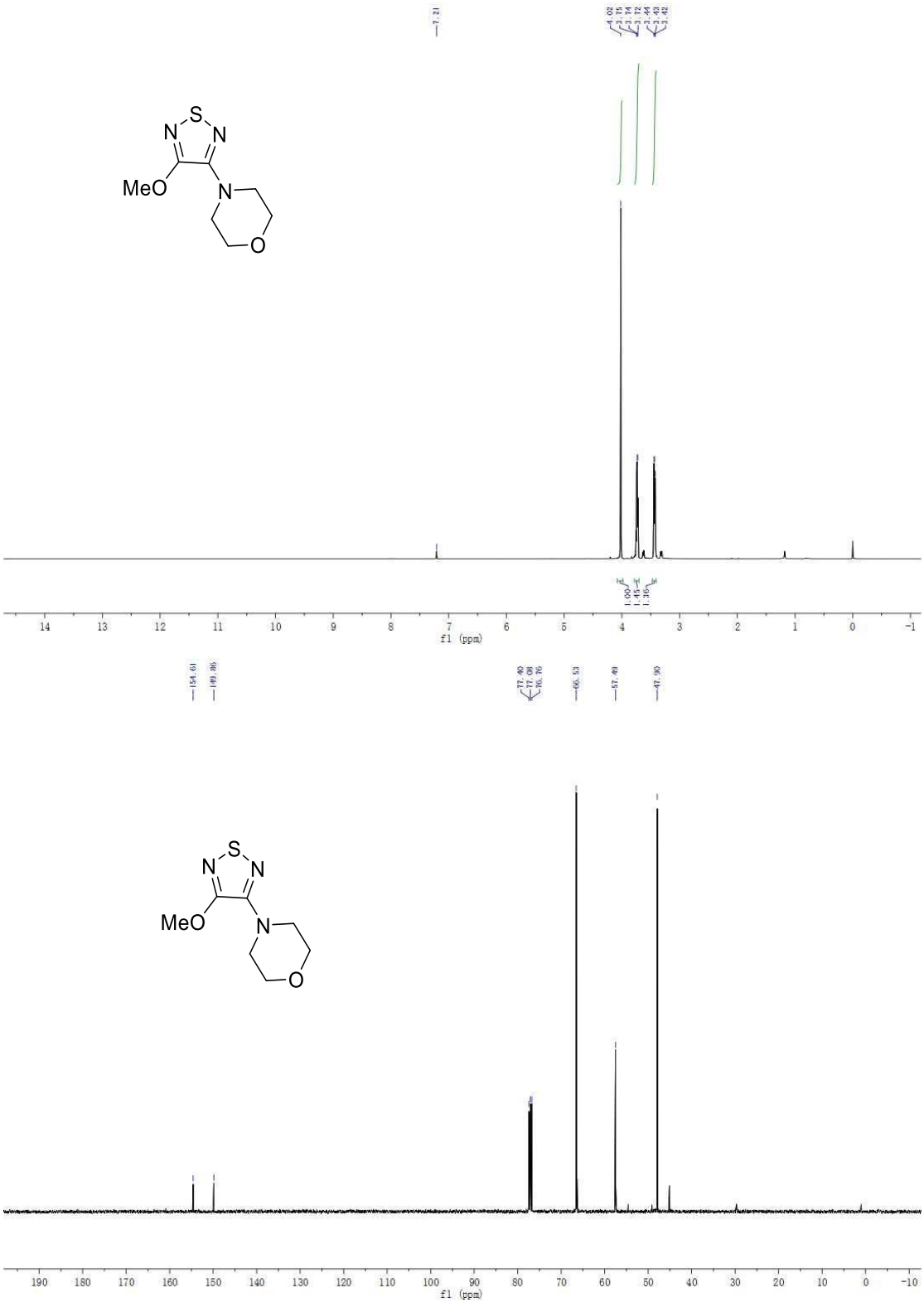
^{1}H NMR and ^{13}C NHR spectrum of **3,5-Dichloro-1,2-benzoisothiazole and 3,6-dichloro-1,2-benzoisothiazole (Table 2, entry 13)**



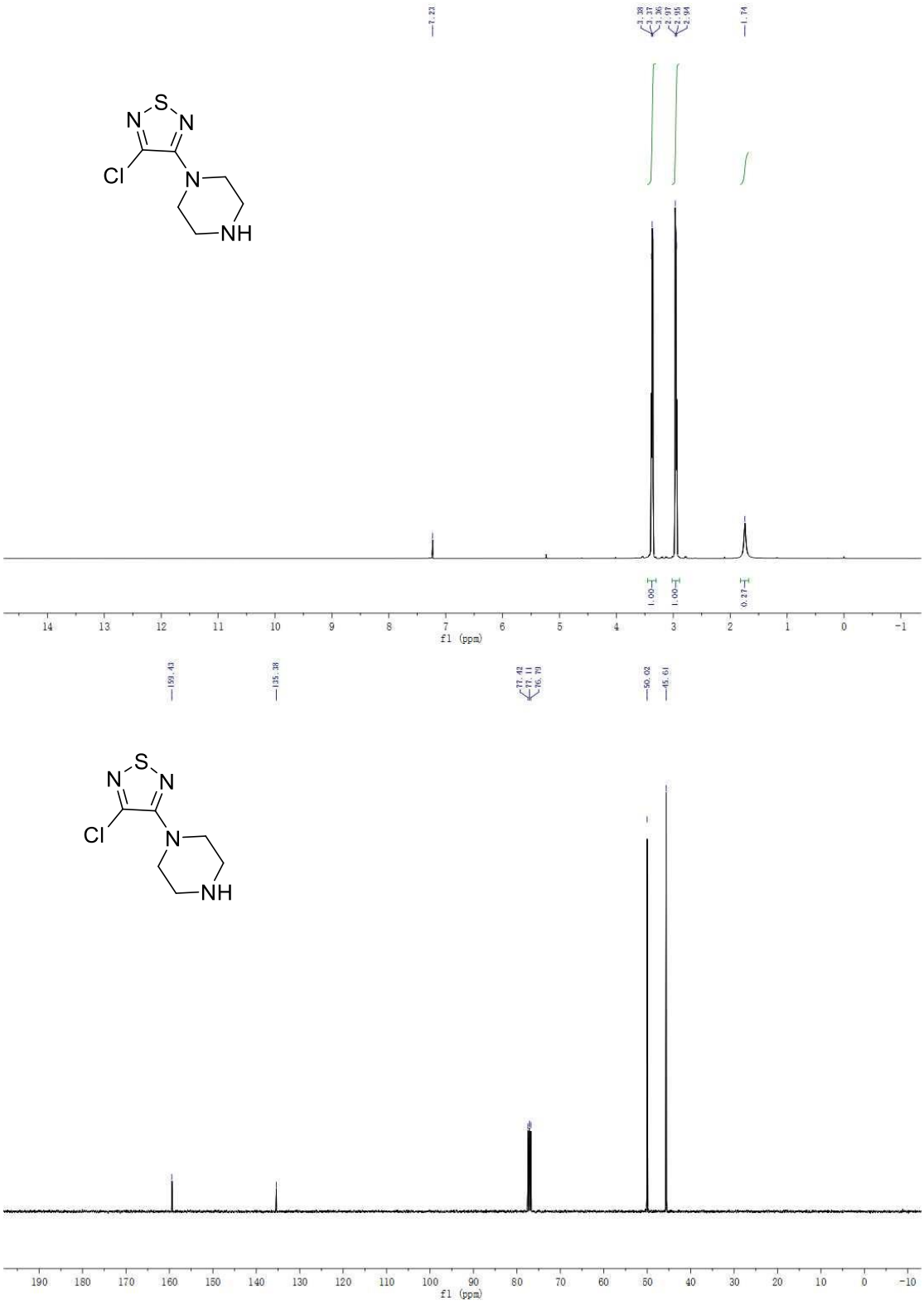
^{1}H NMR and ^{13}C NHR spectrum of **3-Chloro-5-fluoro-1,2-benzoisothiazole & 3-chloro-6-fluoro-1,2-benzoisothiazole mixture (Table 2, entry 14)**



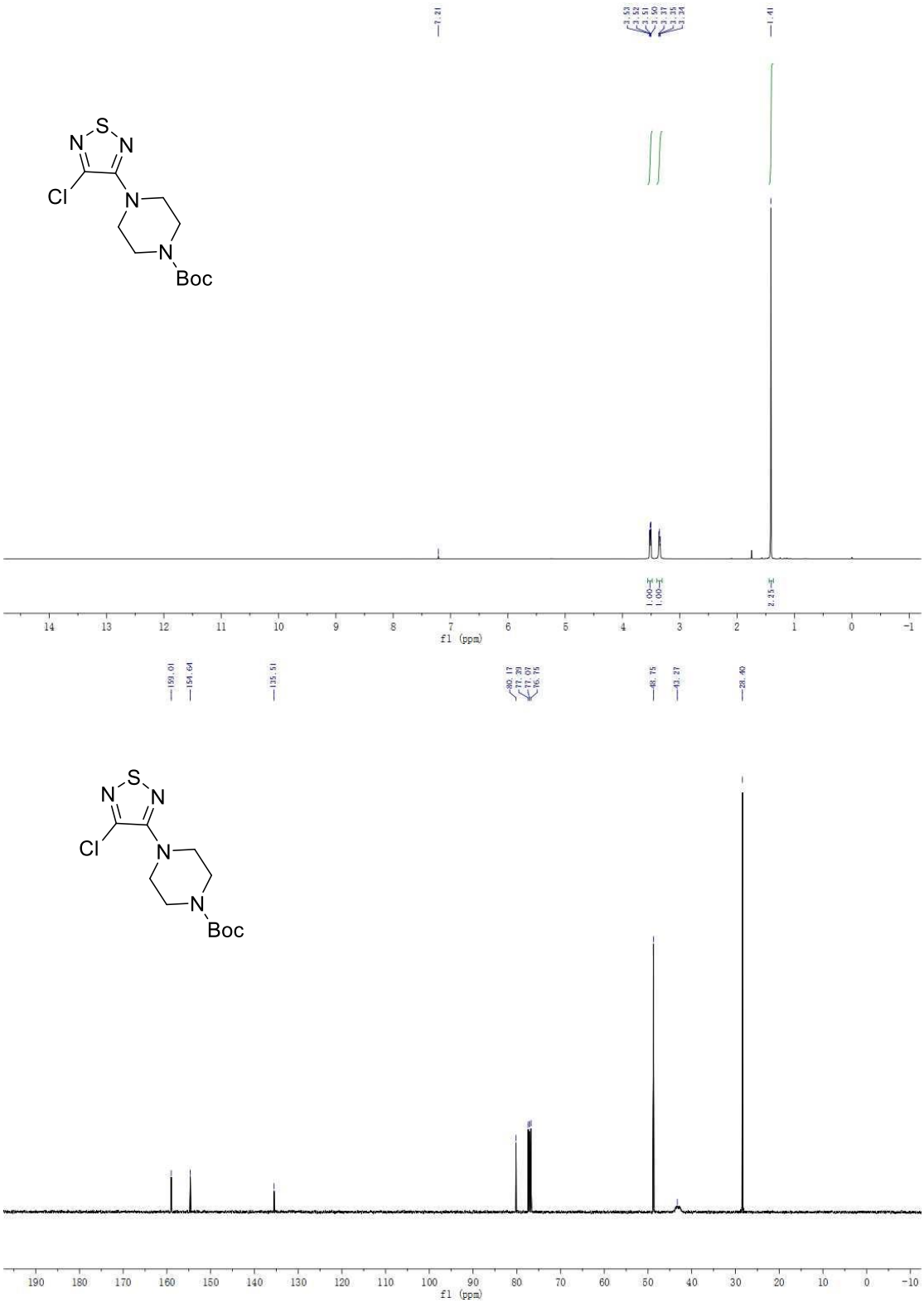
^{1}H NMR and ^{13}C NHR spectrum of ***3-Chloro-5-Methyl-1,2-benzoisothiazole and 3-chloro-6-methyl-1,2-benzoisothiazole (Table 2, entry 15)***



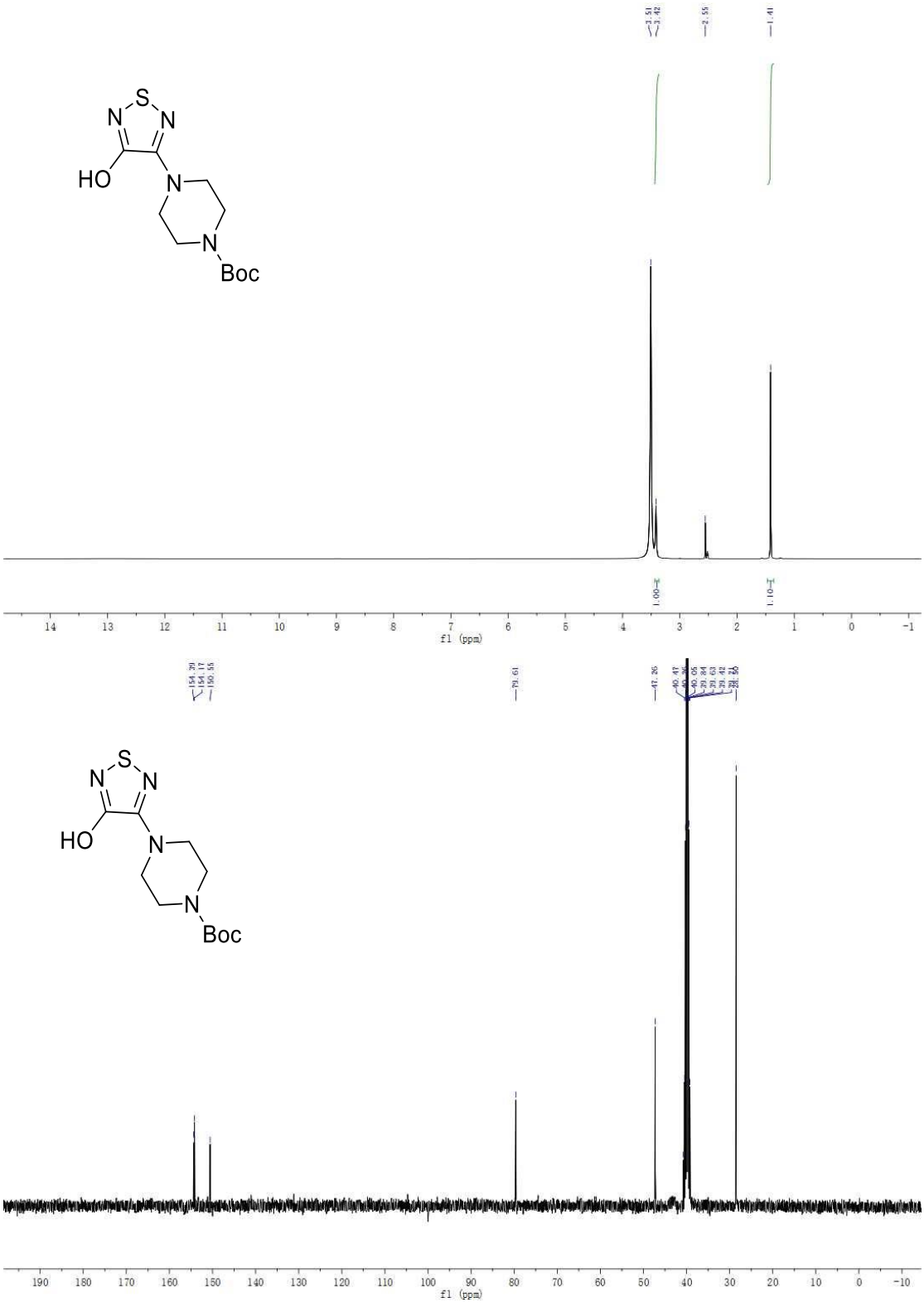
^{1}H NMR and ^{13}C NHR spectrum of **3-methoxy-4-morpholinyl-1,2,5-thiadiazole (2g)**



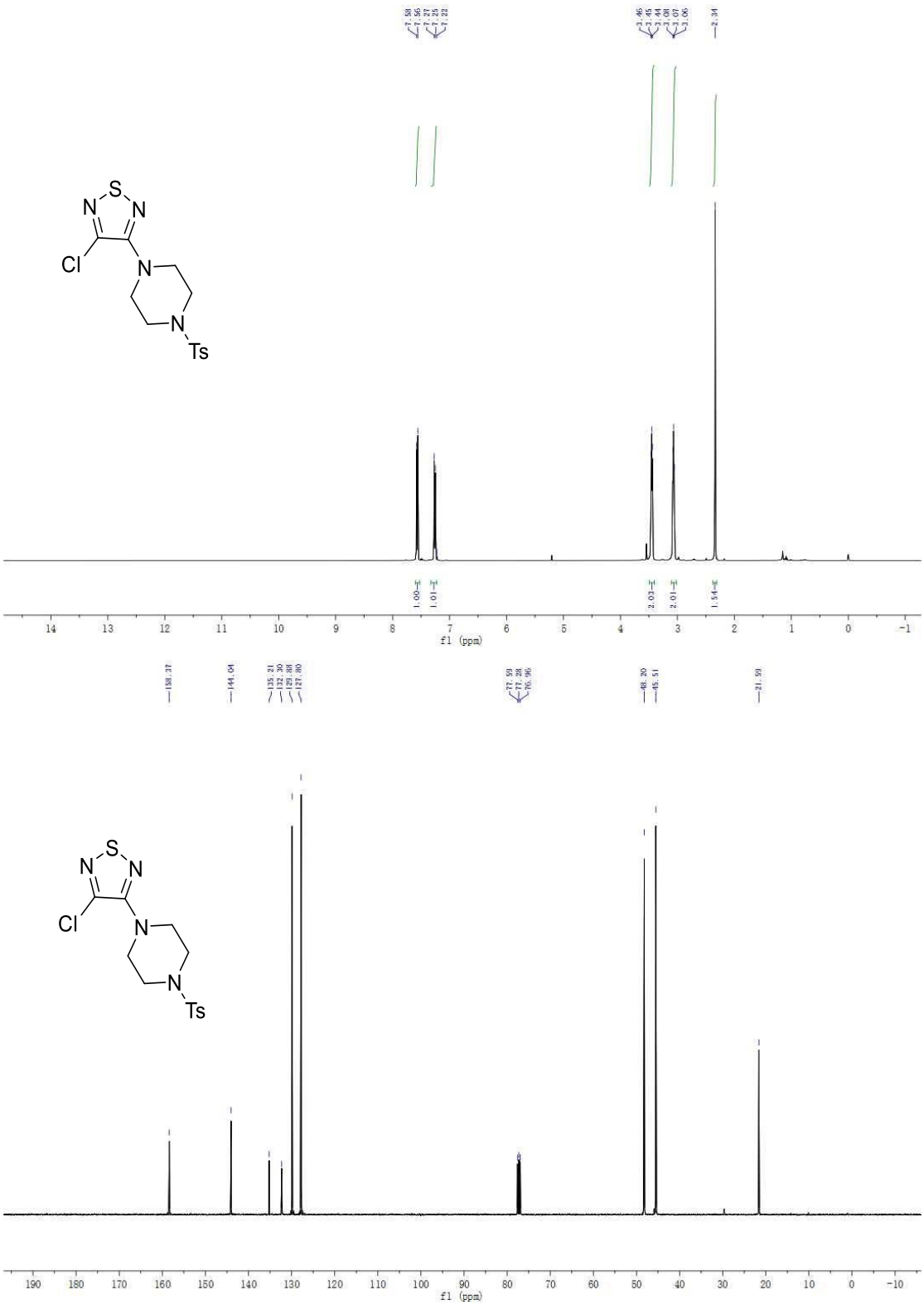
^{1}H NMR and ^{13}C NHR spectrum of **3-Chloro-4-piperazinyl-1,2,5-thiadiazole (SI-2l-1)**



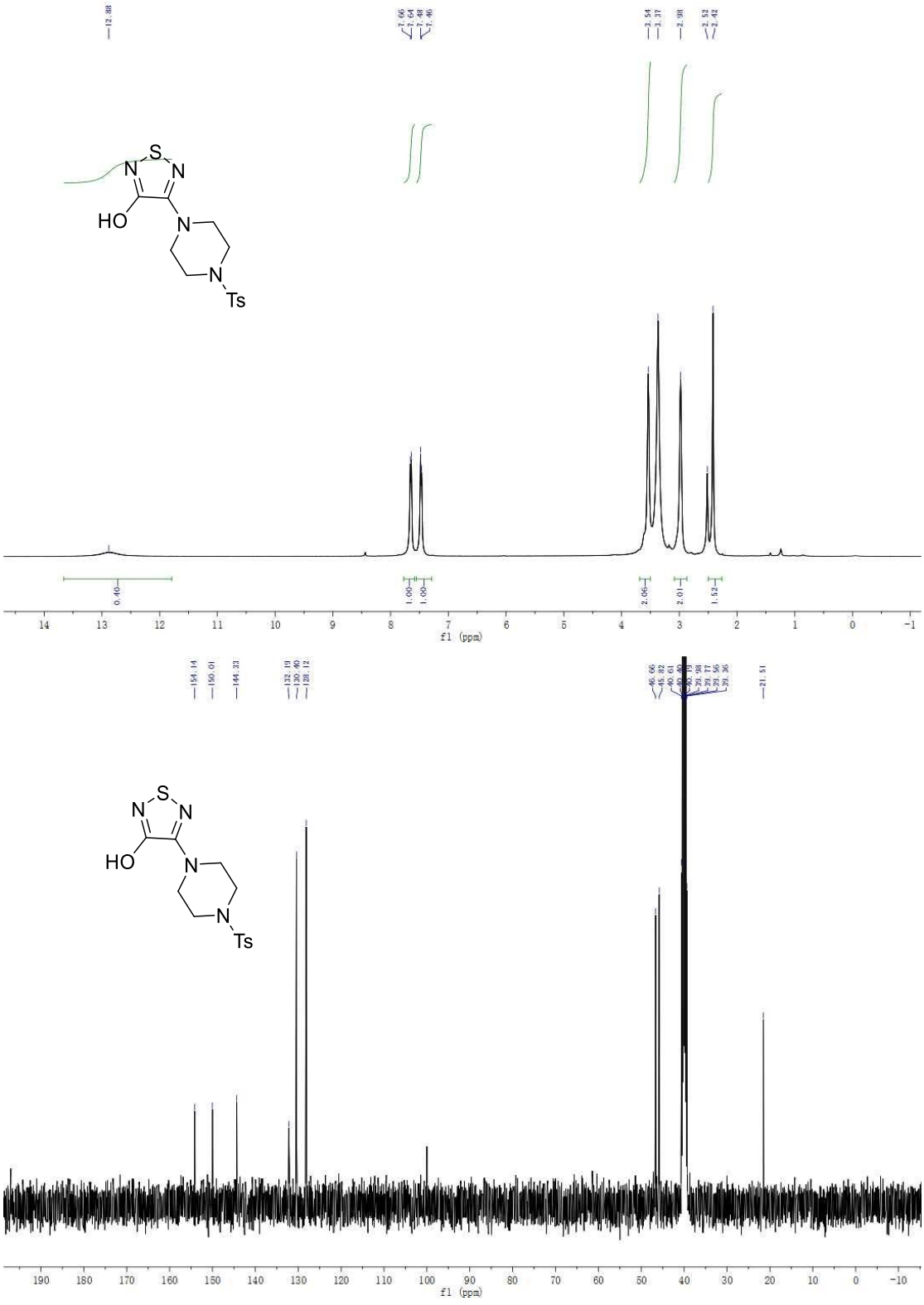
^{1}H NMR and ^{13}C NHR spectrum of **3-Chloro-4-(4-boc-piperazinyl)-1,2,5-thiadiazole (SI-2l-2)**



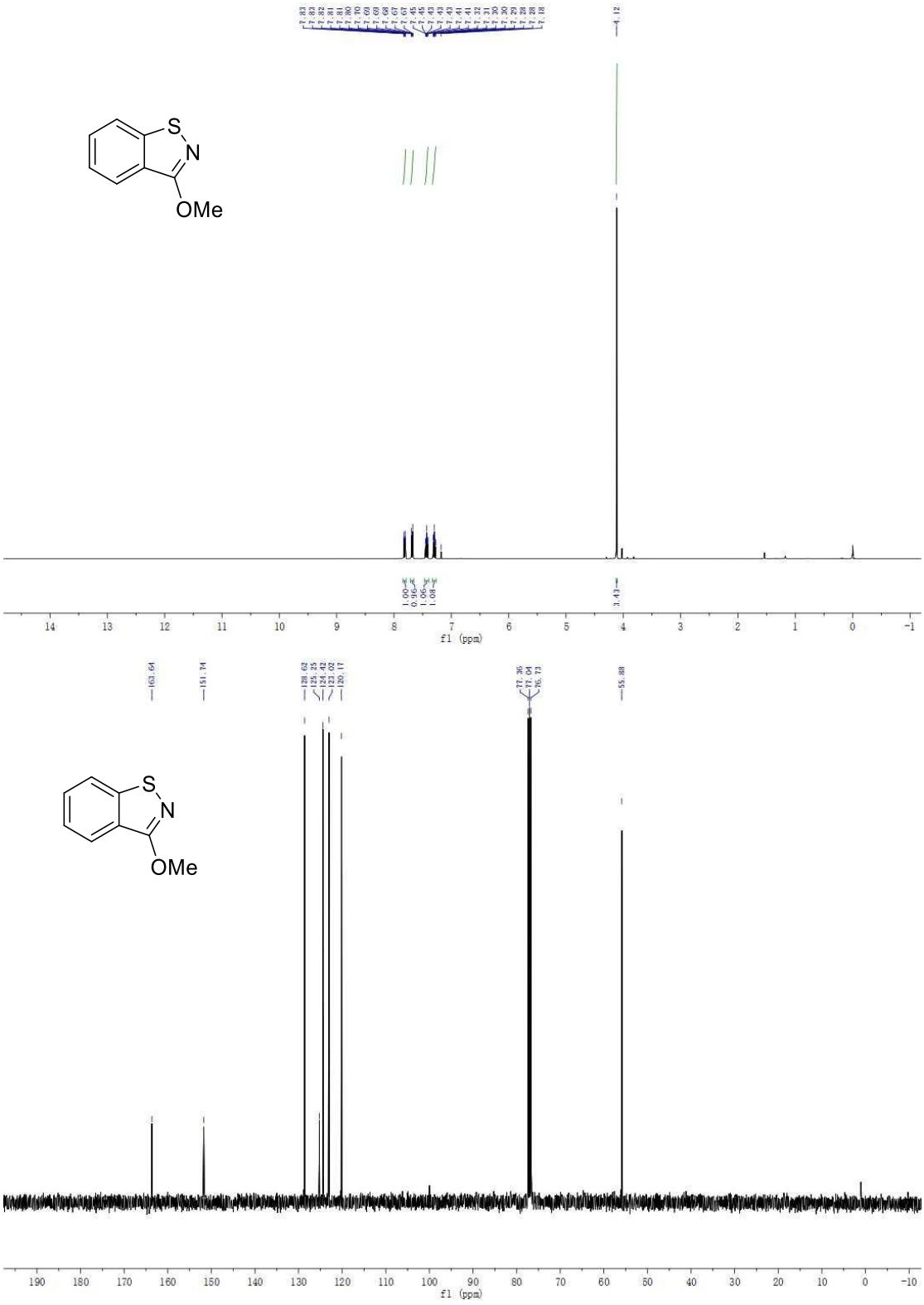
^{1}H NMR and ^{13}C NHR spectrum of **3-Hydroxy-4-(4-boc-piperazinyl)-1,2,5-thiadiazole (2l)**



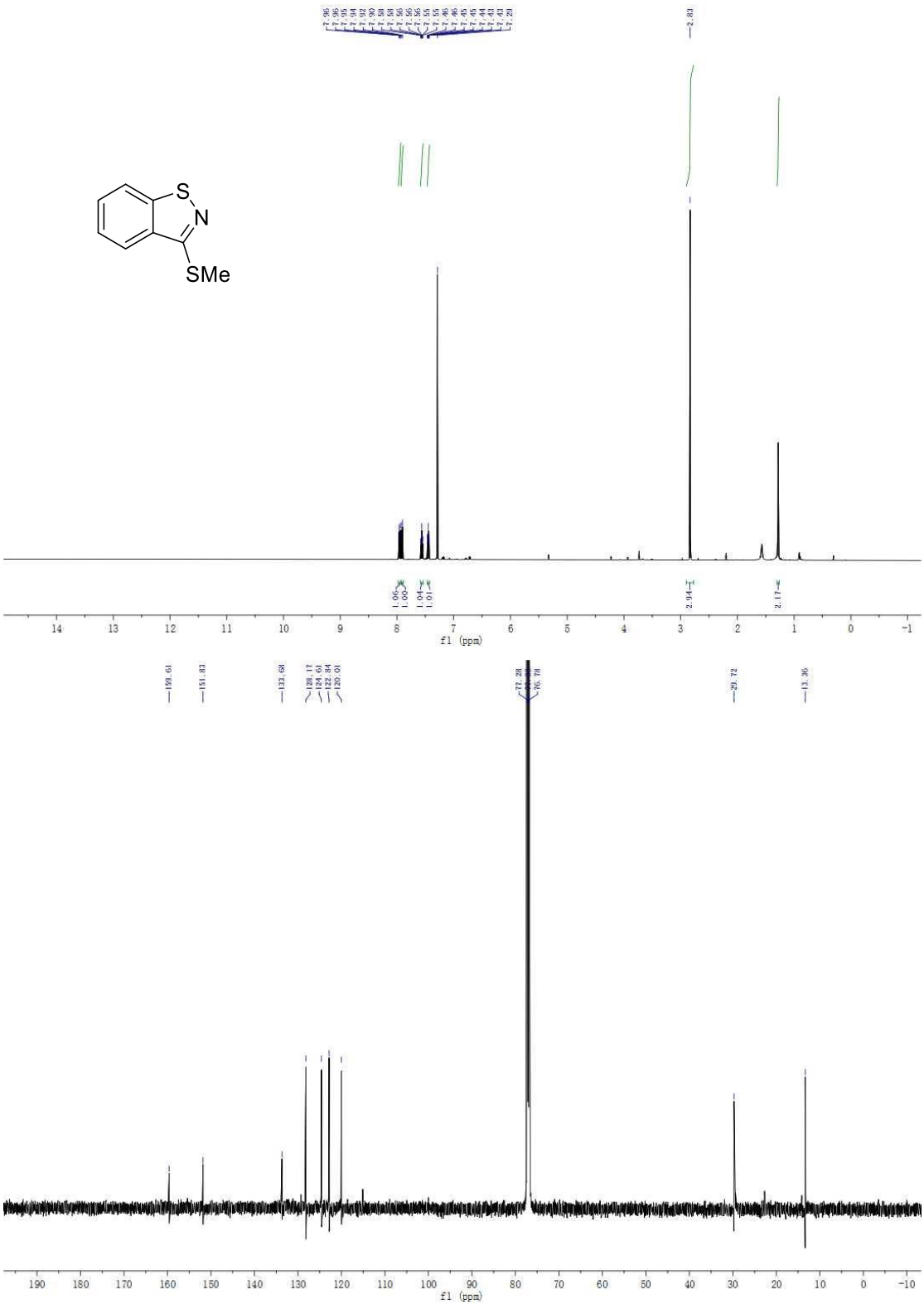
^{1}H NMR and ^{13}C NHR spectrum of **3-Chloro-4-(4-tosylpiperazinyl)-1,2,5-thiadiazole (SI-2m)**



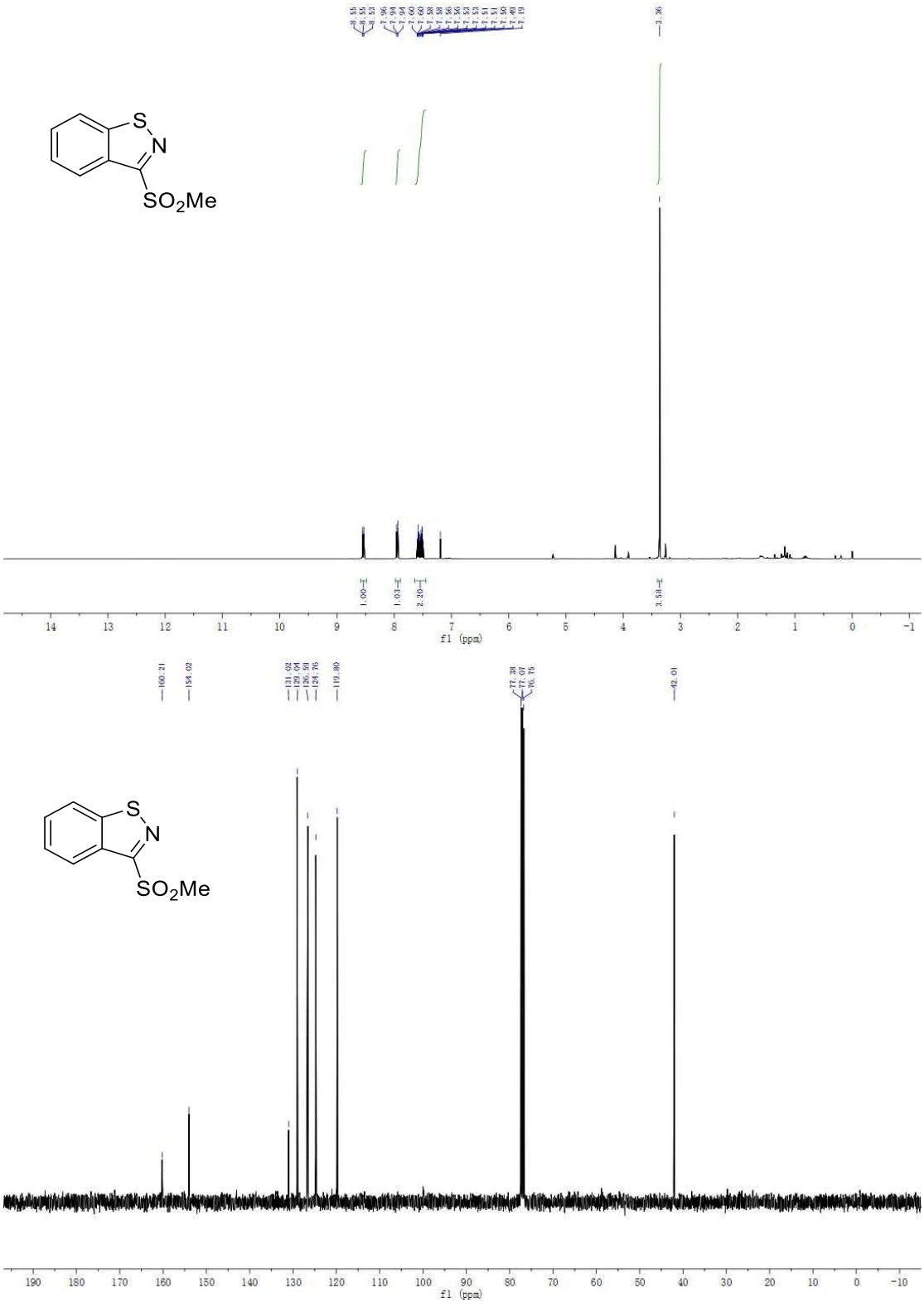
^{1}H NMR and ^{13}C NHR spectrum of **3-Hydroxy-4-(4-tosylpiperazinyl)-1,2,5-thiadiazole (2m)**



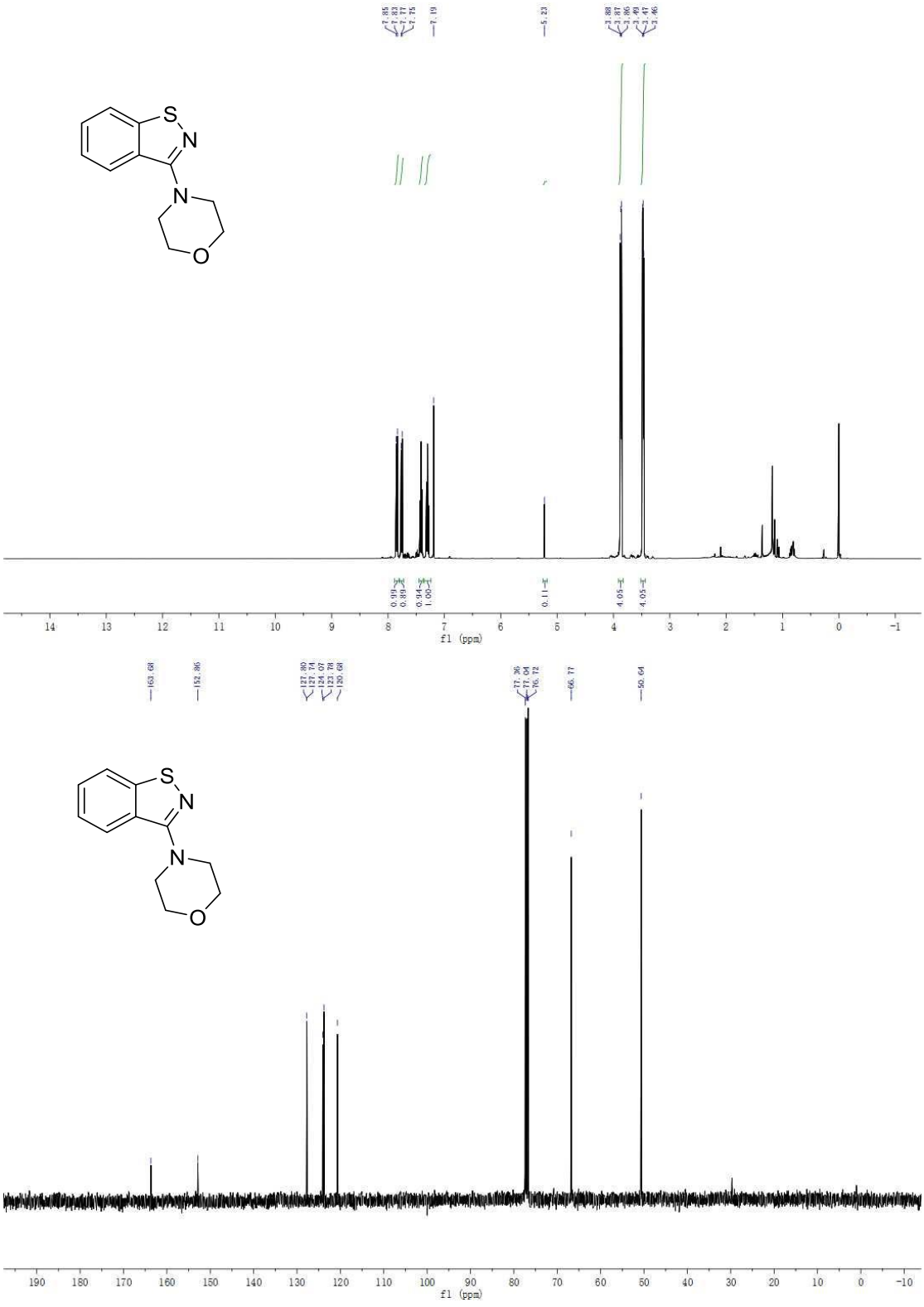
^{1}H NMR and ^{13}C NHR spectrum of **3-Methoxy-1,2-benzoisothiazole (Table 3, entry 1)**



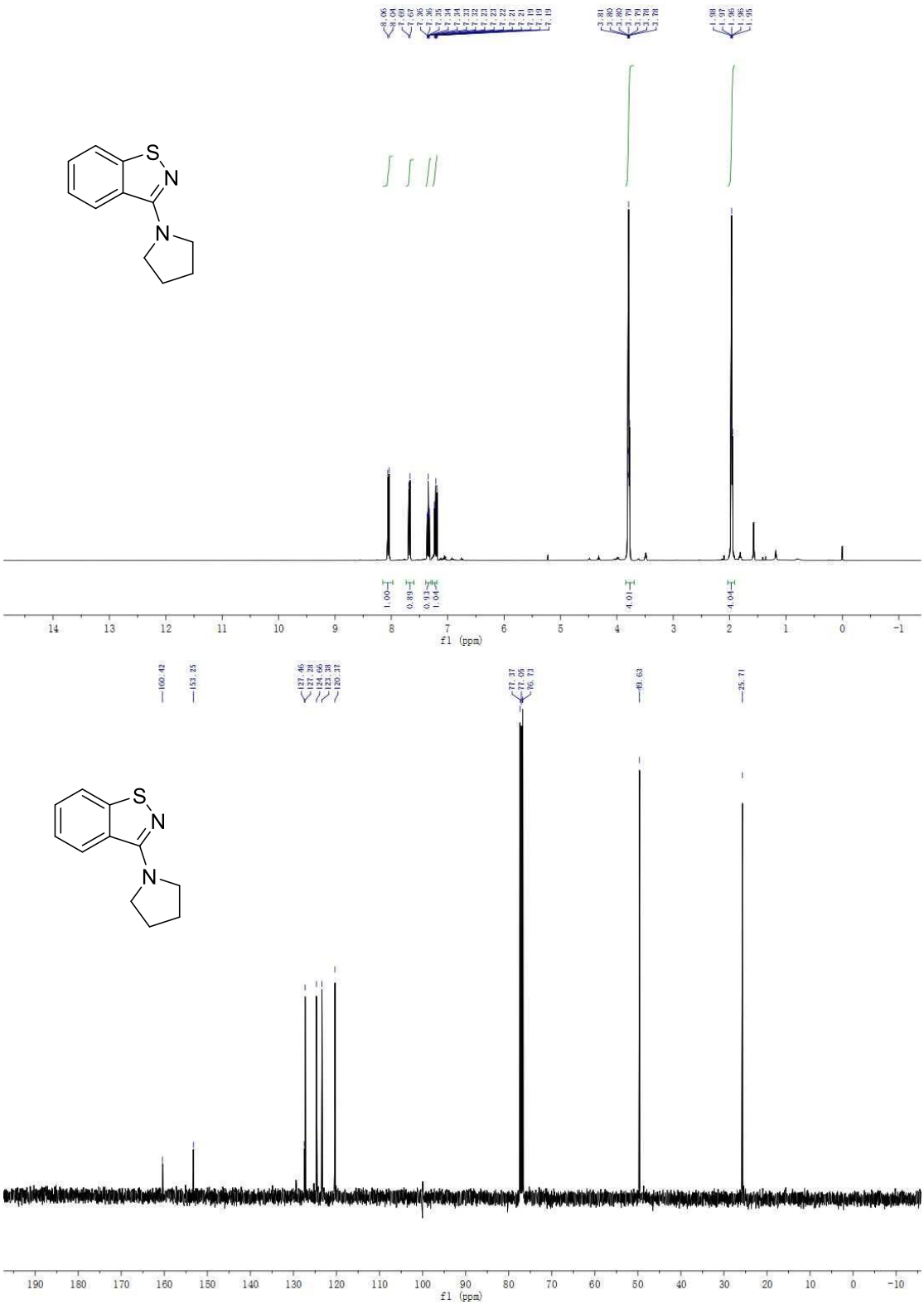
^{1}H NMR and ^{13}C NHR spectrum of **3-Thiomethyl-1,2-benzoisothiazole (Table 3, entry 3)**



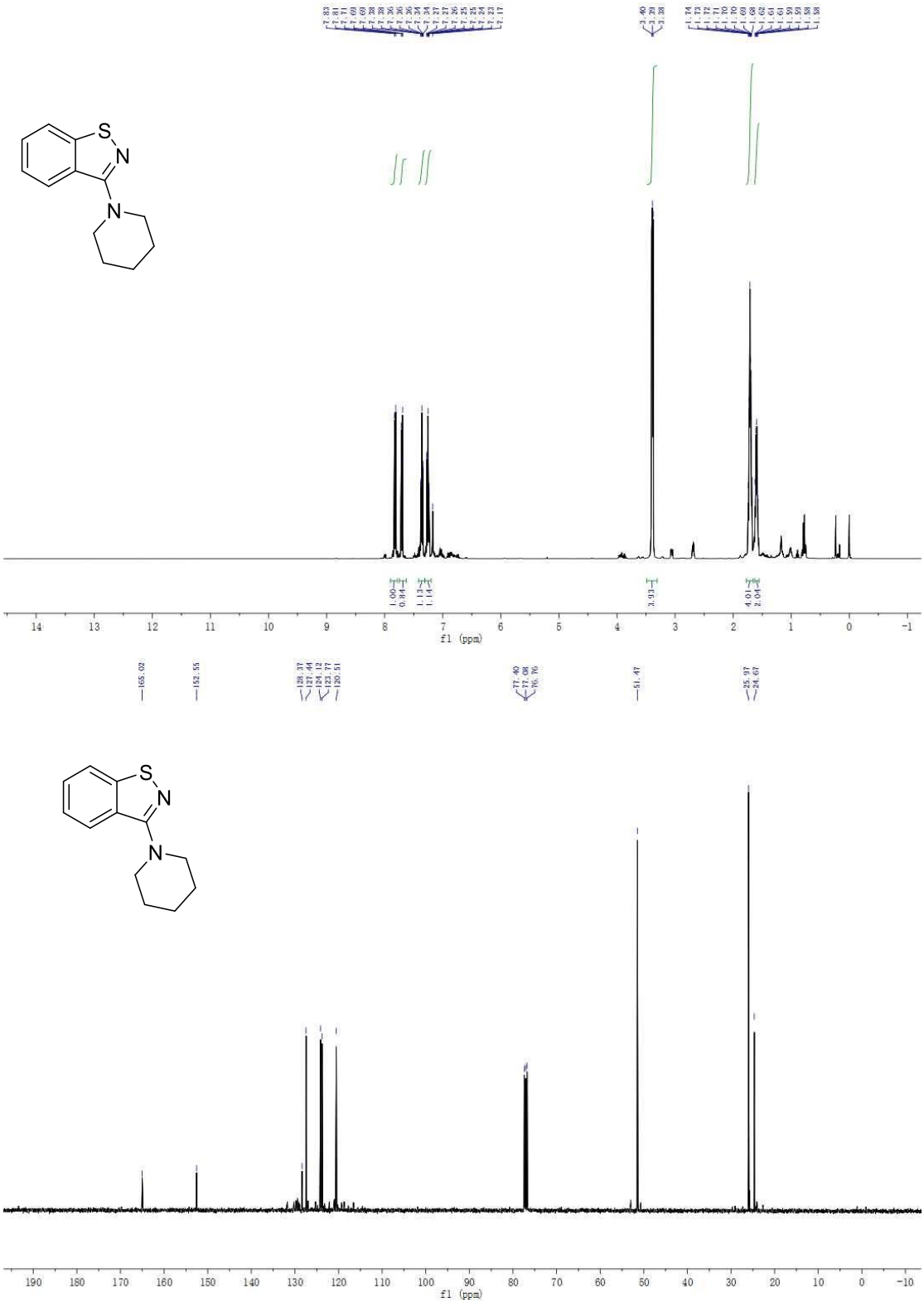
^{1}H NMR and ^{13}C NHR spectrum of **3-Methylsulfonyl-1,2-benzoisothiazole (Table 3, entry 4)**



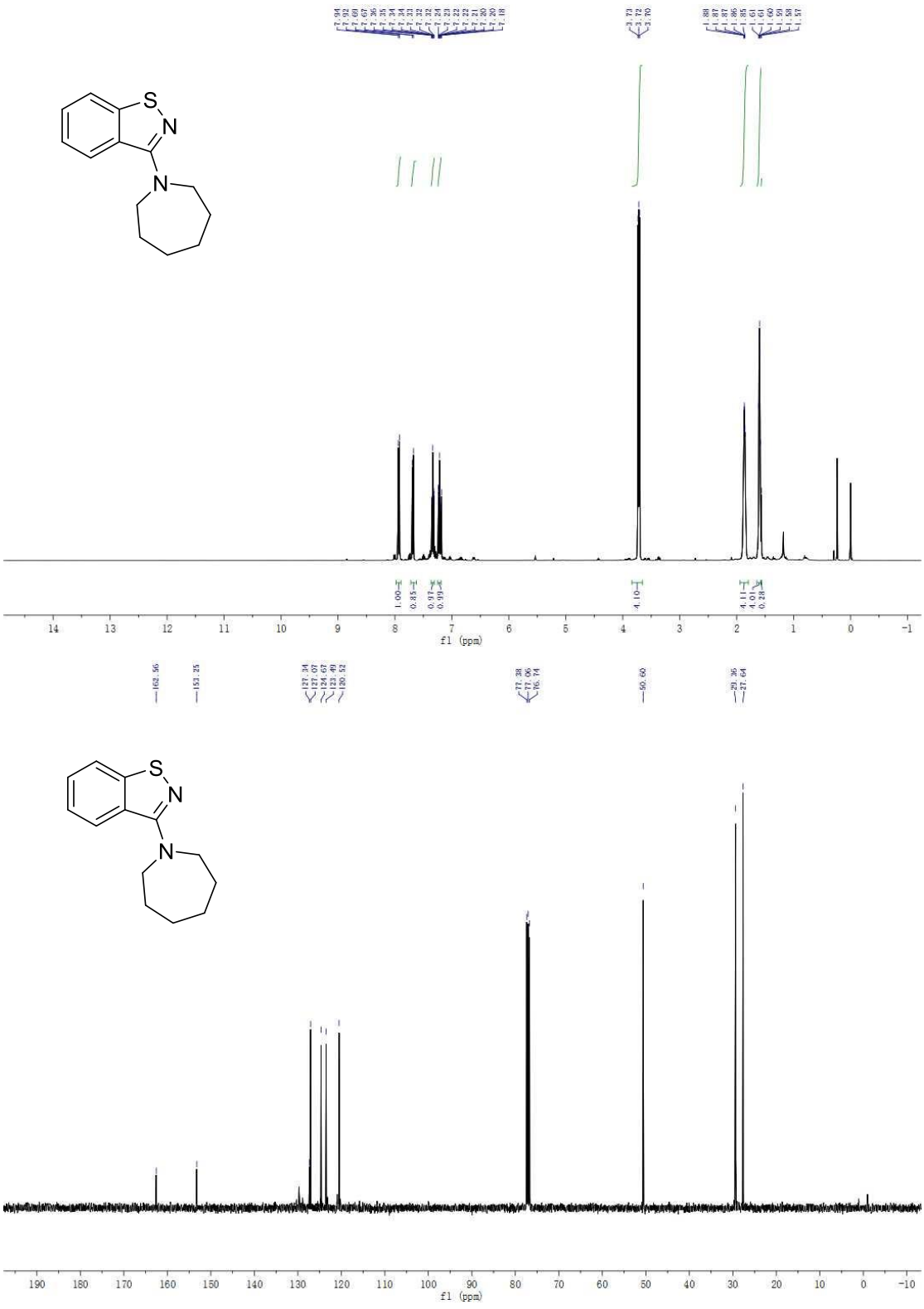
^{1}H NMR and ^{13}C NHR spectrum of ***3*-Morpholino-1,2-benzoisothiazole (Table *3*, entry 7)**



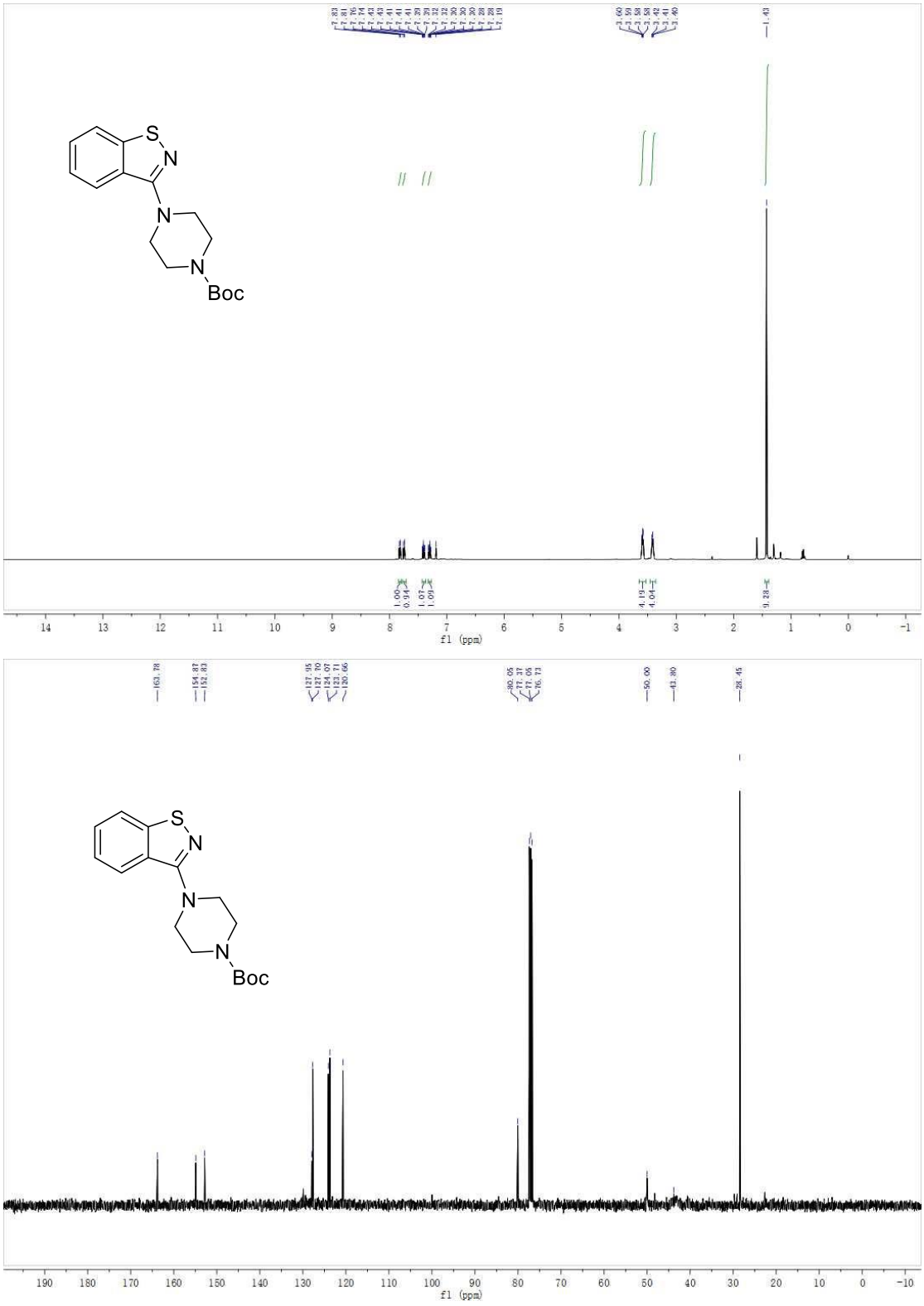
^{1}H NMR and ^{13}C NHR spectrum of **3-Pyrrolidinyl-1,2-benzoisothiazole (Table 3, entry 8)**



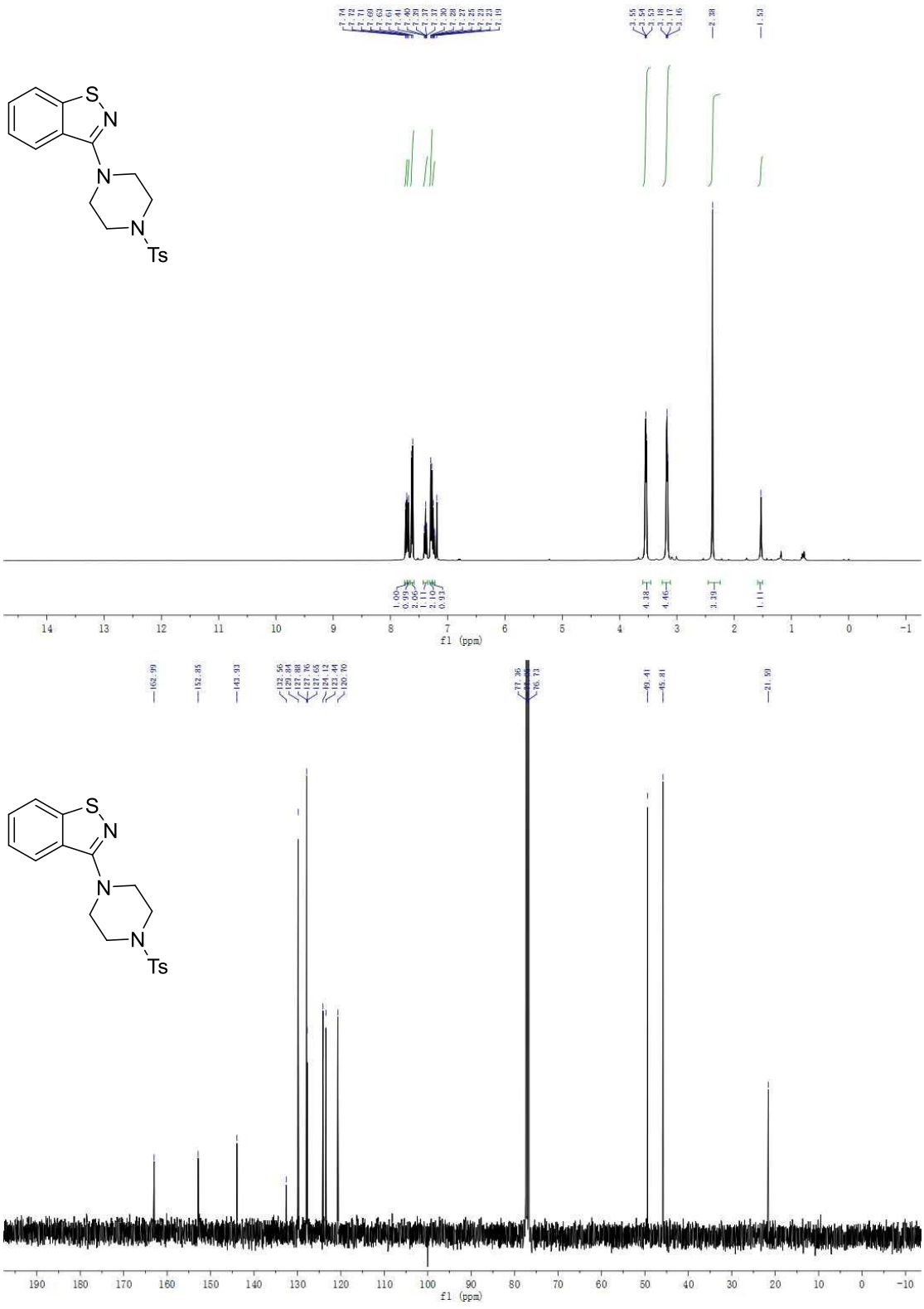
[1]H NMR and [13]C NHR spectrum of ***3*-Piperidinyl-1,2-benzoisothiazole (Table *3*, entry *9*)**



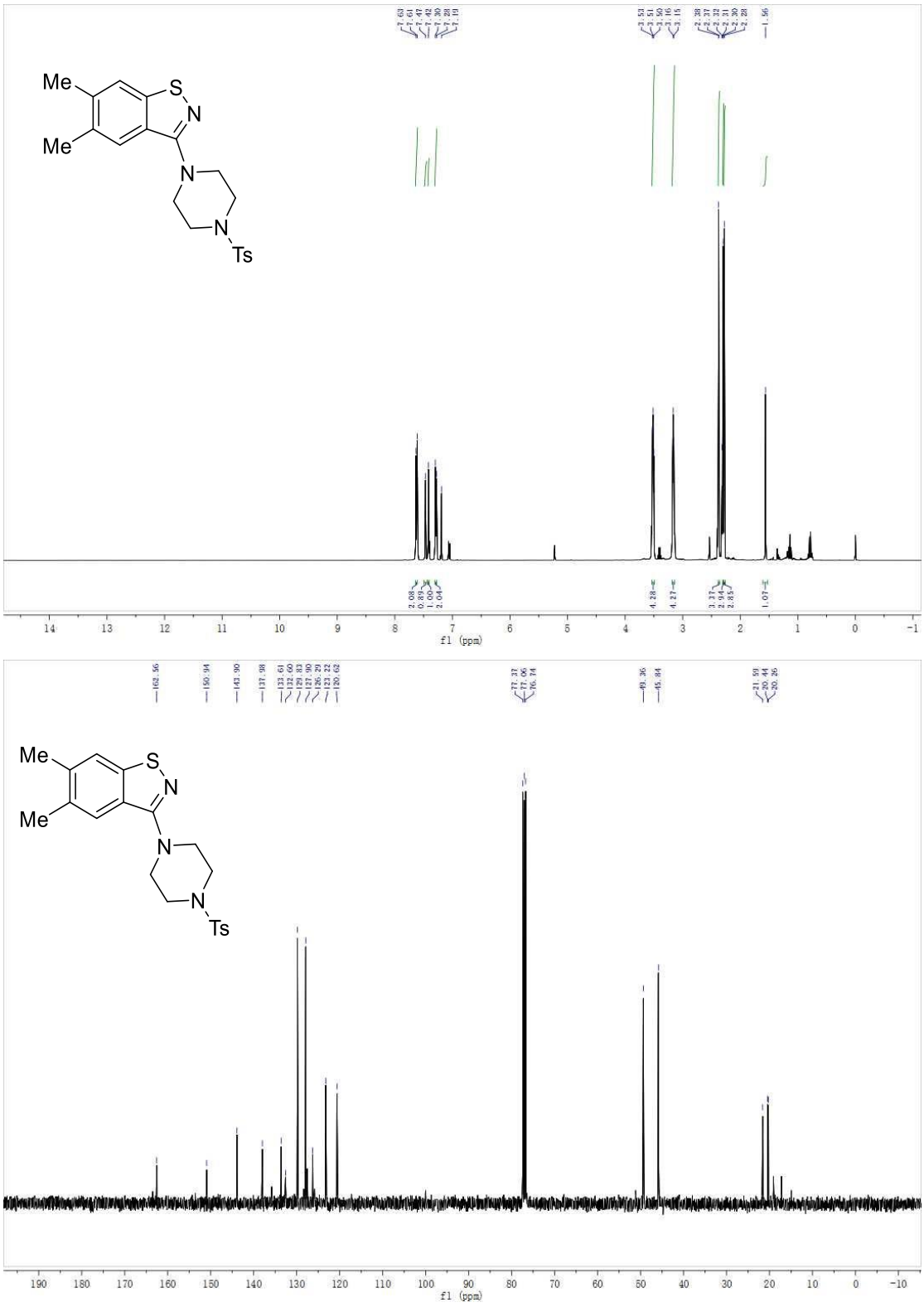
^{1}H NMR and ^{13}C NHR spectrum of **3-Azapanyl-1,2-benzoisothiazole (Table 3, entry 10)**



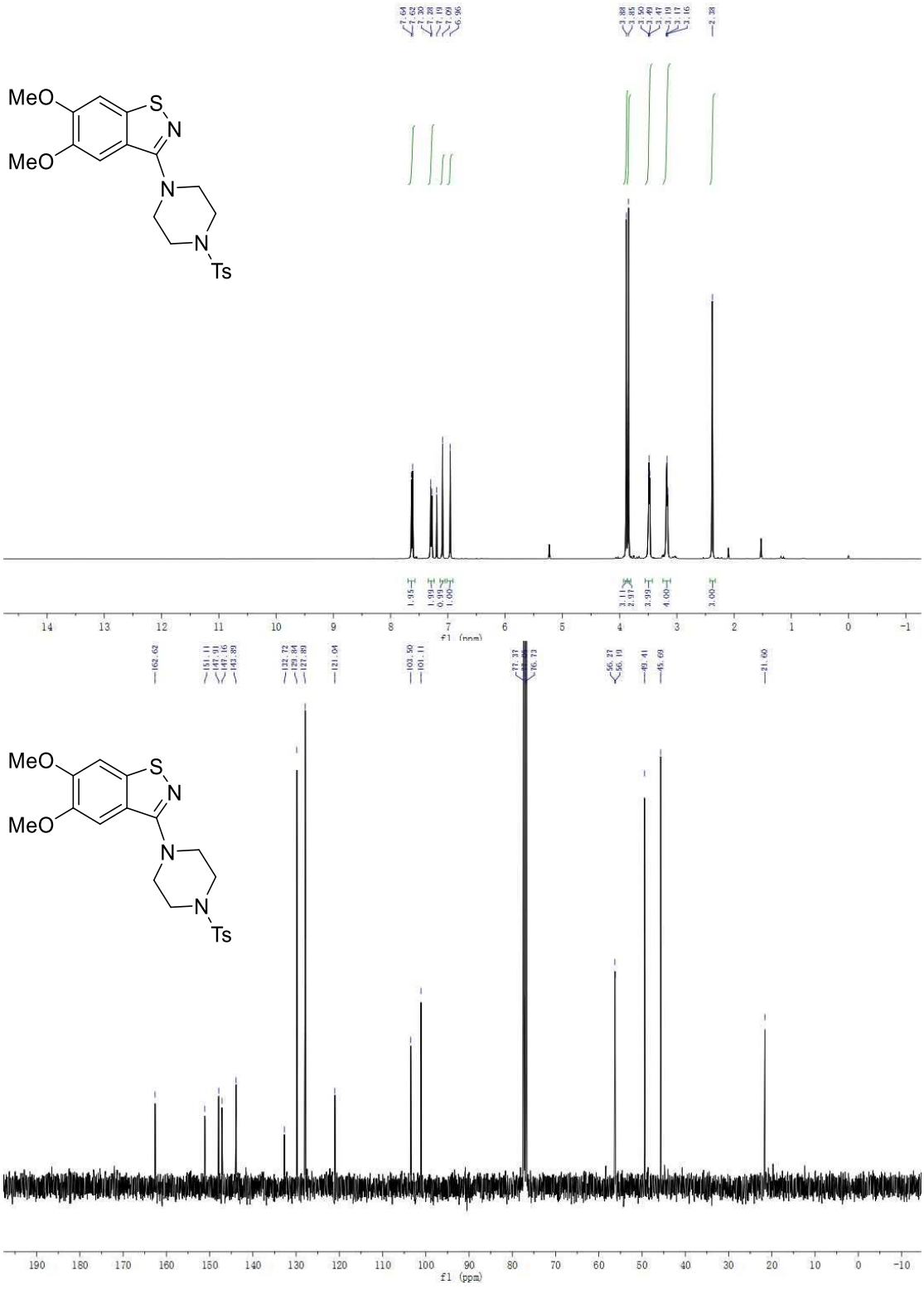
^{1}H NMR and ^{13}C NHR spectrum of **3-(4-boc-piperazinyl)-1,2-benzoisothiazole (Table 3, entry 11)**



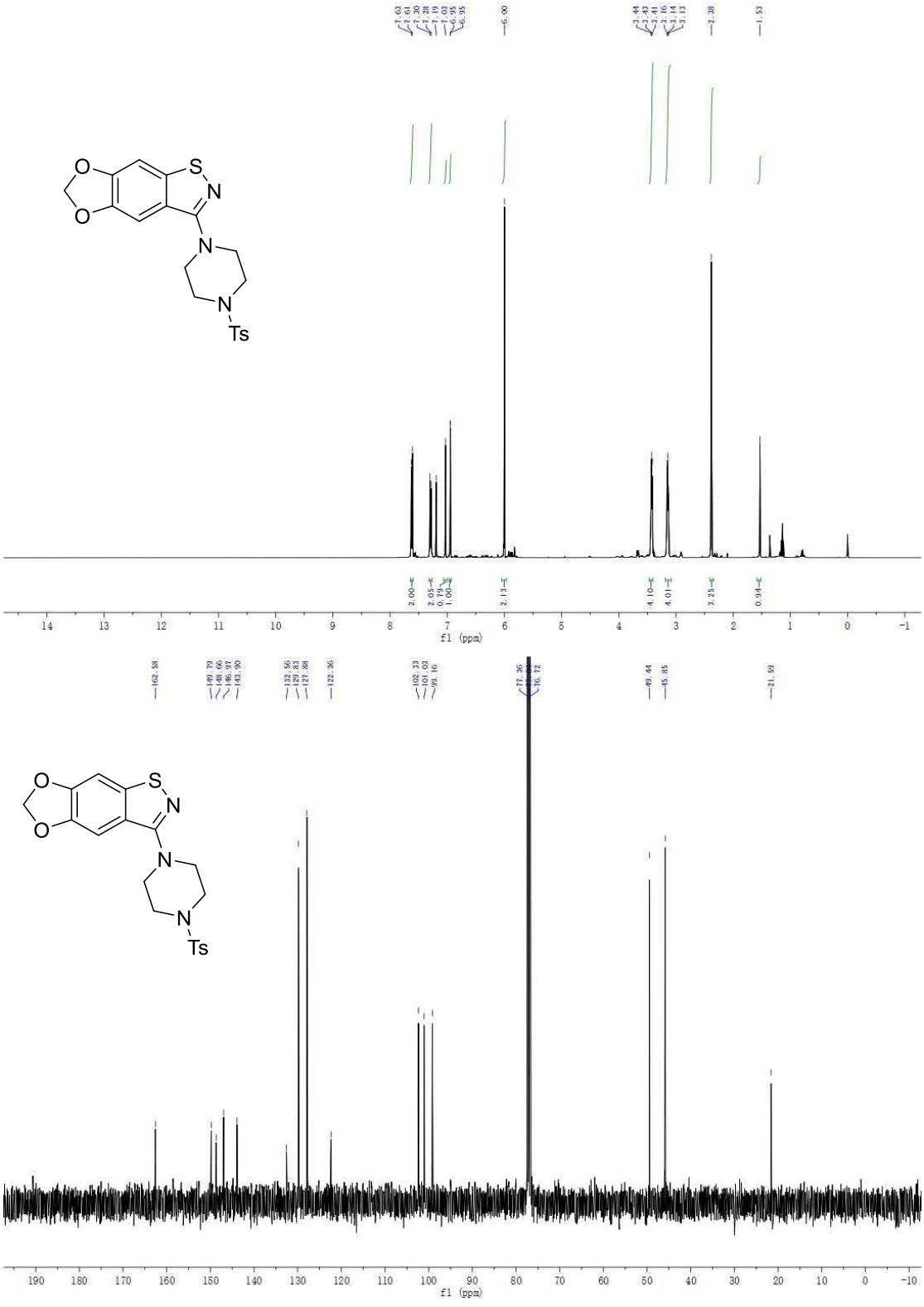
^{1}H NMR and ^{13}C NHR spectrum of **3-(4-Tosylpiperazinyl)-1,2-benzoisothiazole (Table 3, entry 12)**



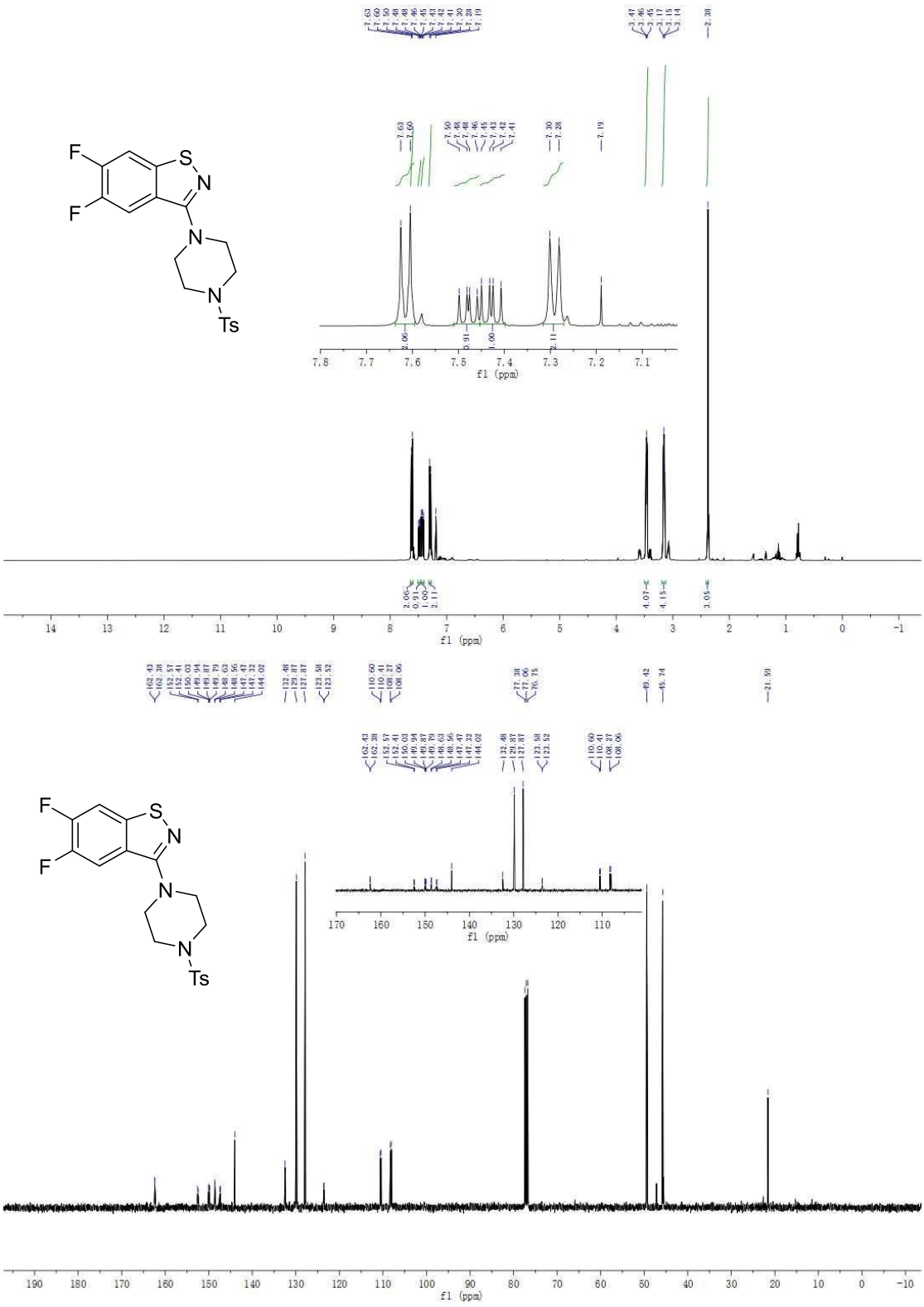
^{1}H NMR and ^{13}C NHR spectrum of ***3-(4-Tosylpiperazinyl)-5,6-dimethyl-1,2-benzoisothiazole (4a)***



^{1}H NMR and ^{13}C NHR spectrum of **3-(4-Tosylpiperazinyl)-5,6-dimethoxy-1,2-benzoisothiazole (4b)**

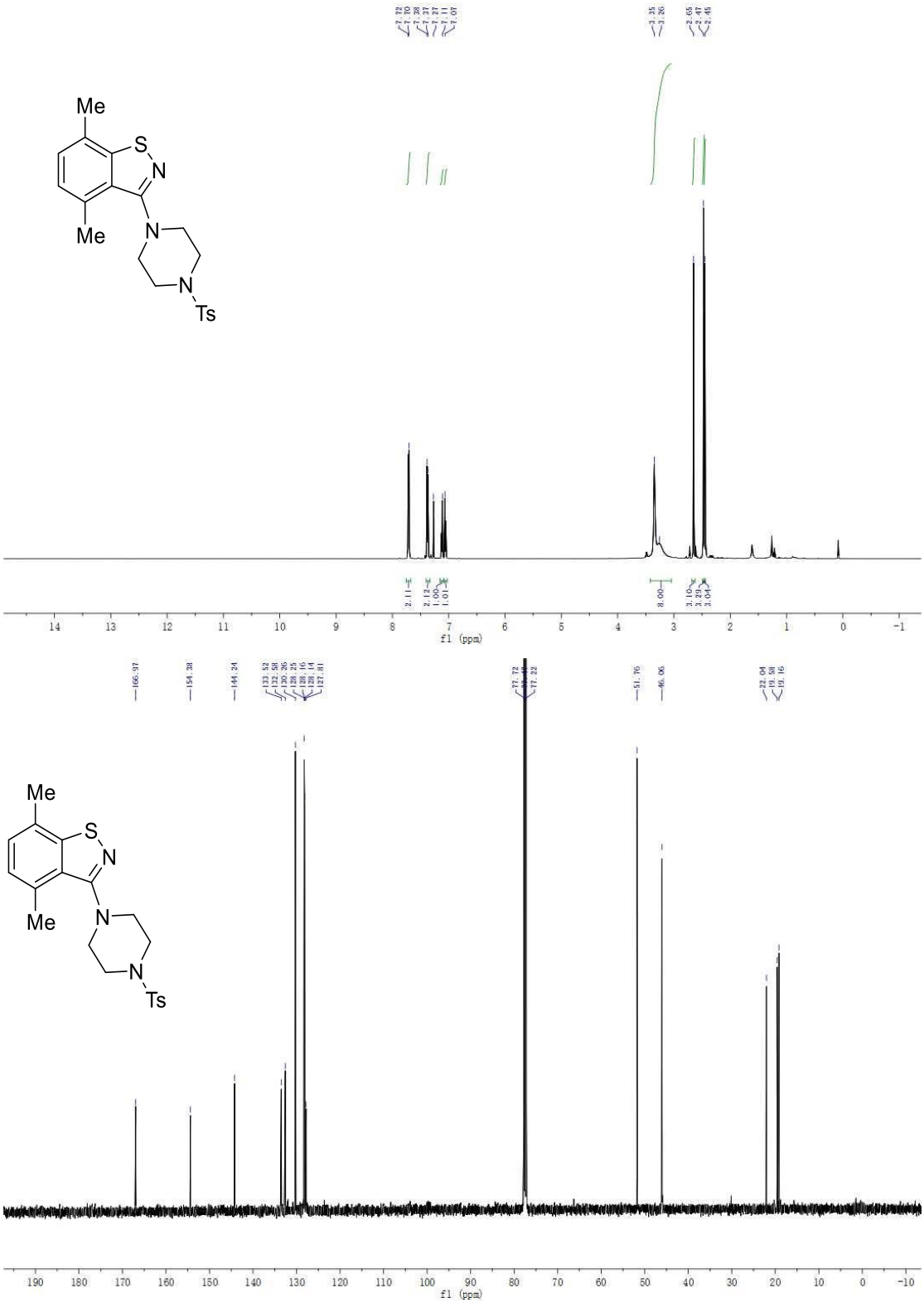


^{1}H NMR and ^{13}C NHR spectrum of **3-(4-tosylpiperazinyl)-5,6-dioxolo-1,2-benzoisothiazole (4c)**

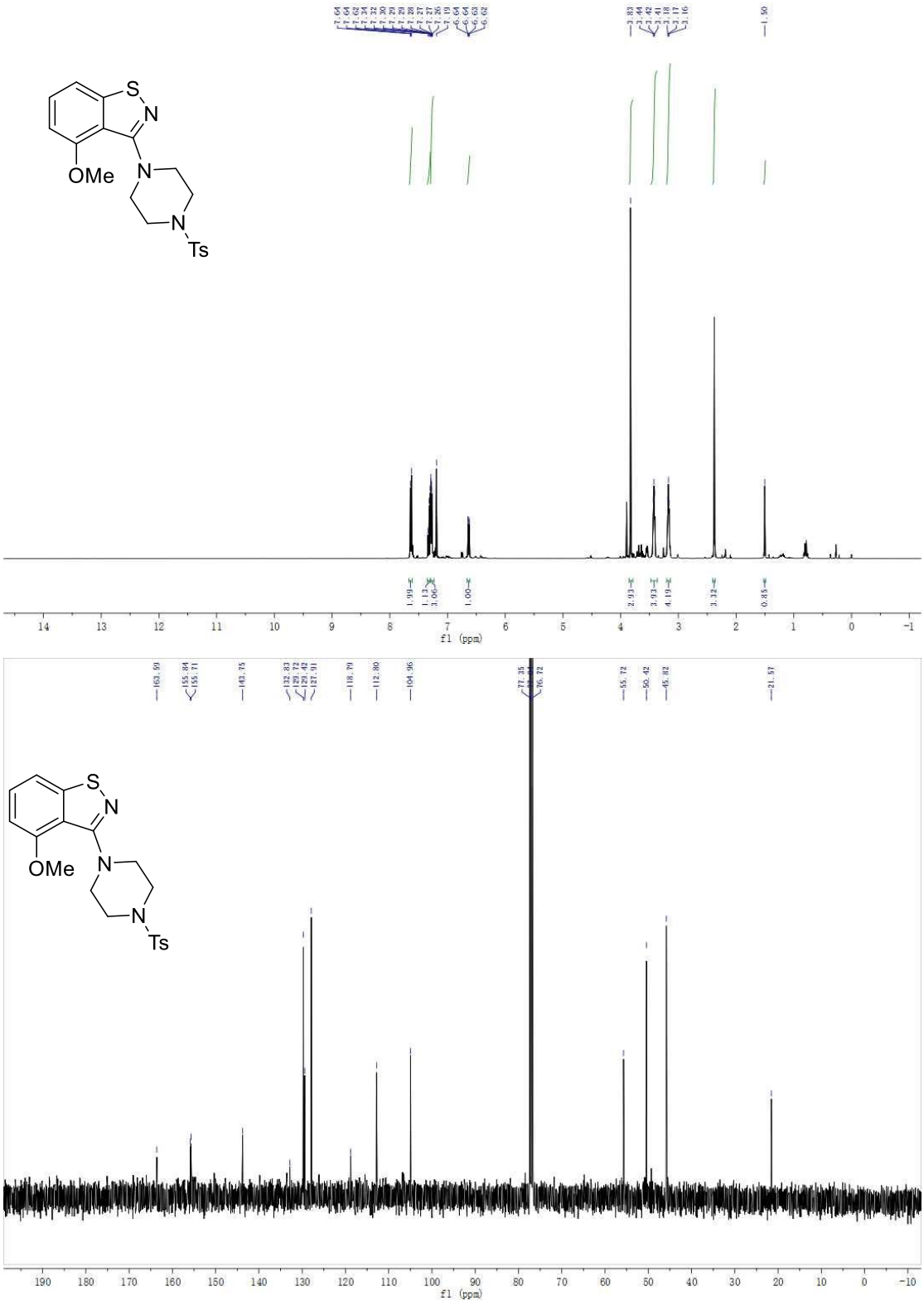


^{1}H NMR and ^{13}C NHR spectrum of **3-(4-Tosylpiperazinyl)-4,5-difluoro-1,2-benzoisothiazole (4d)**

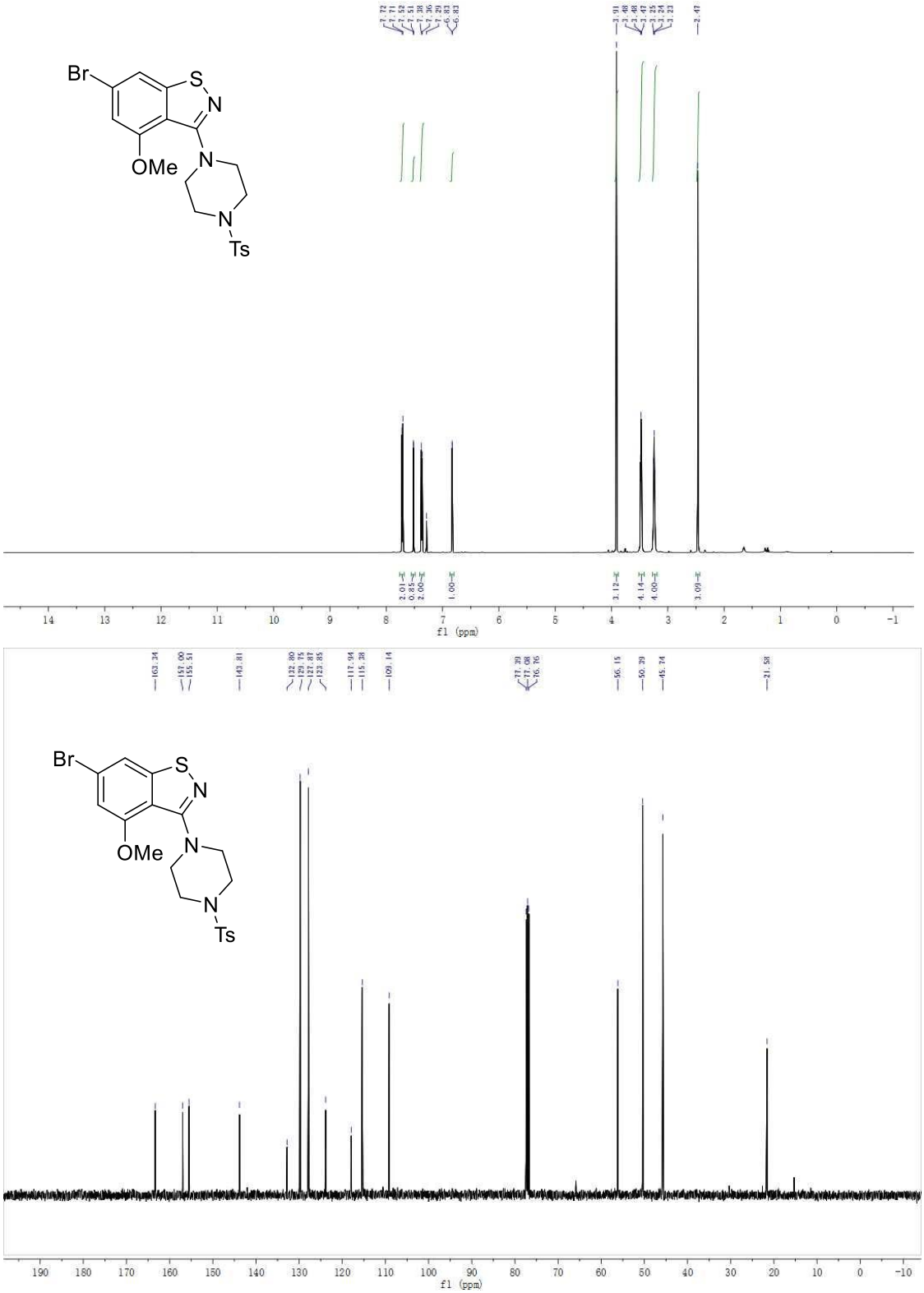
^{19}F NMR spectrum of **3-(4-Tosylpiperazinyl)-4,5-difluoro-1,2-benzoisothiazole (4d)**



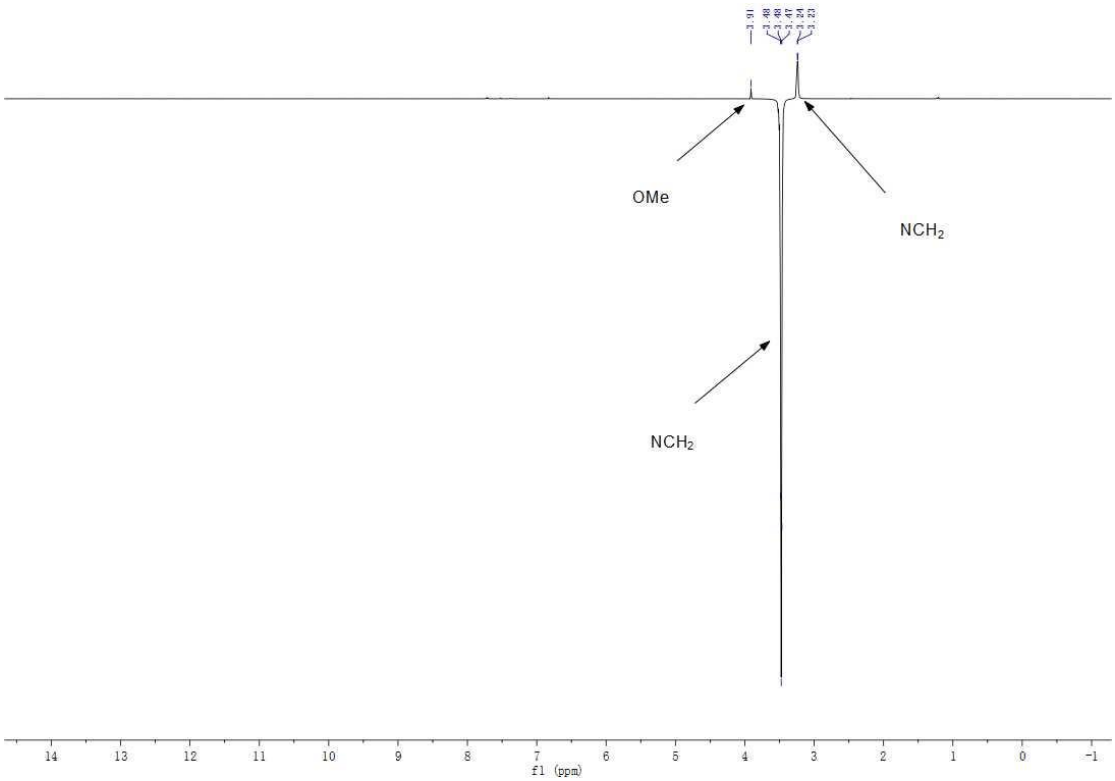
^{1}H NMR and ^{13}C NHR spectrum of **3-(4-Tosylpiperazinyl)-4,7-dimethyl-1,2-benzoisothiazole (4e)**

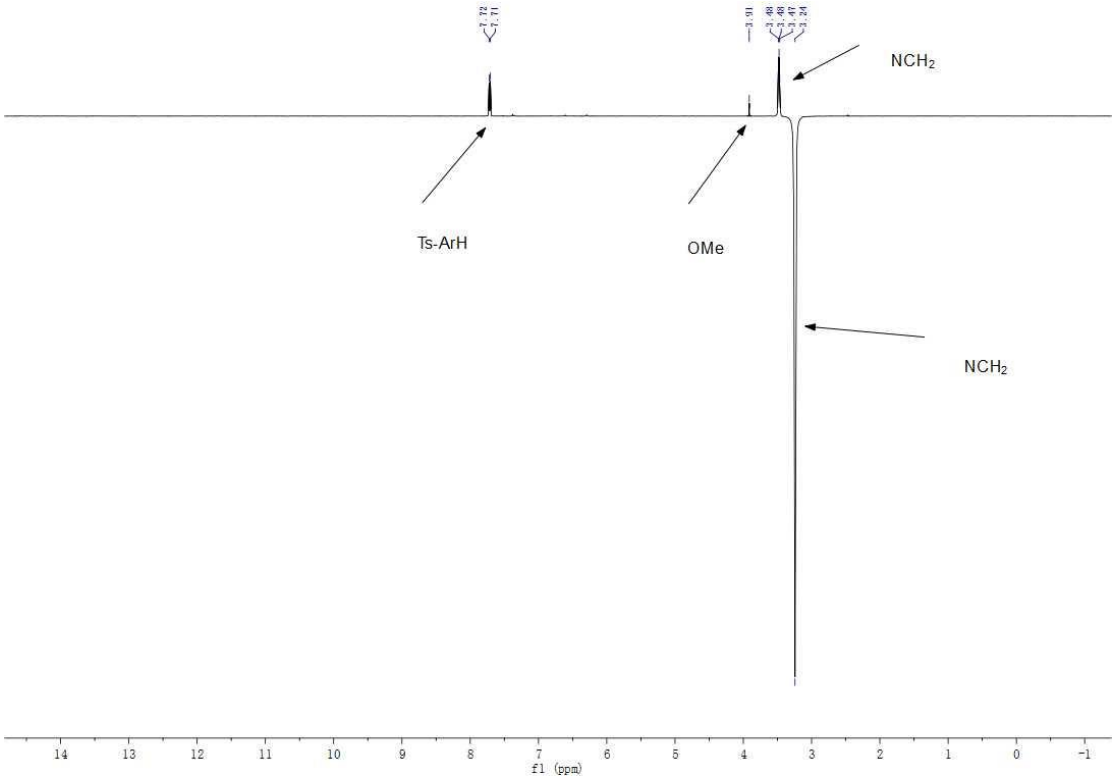


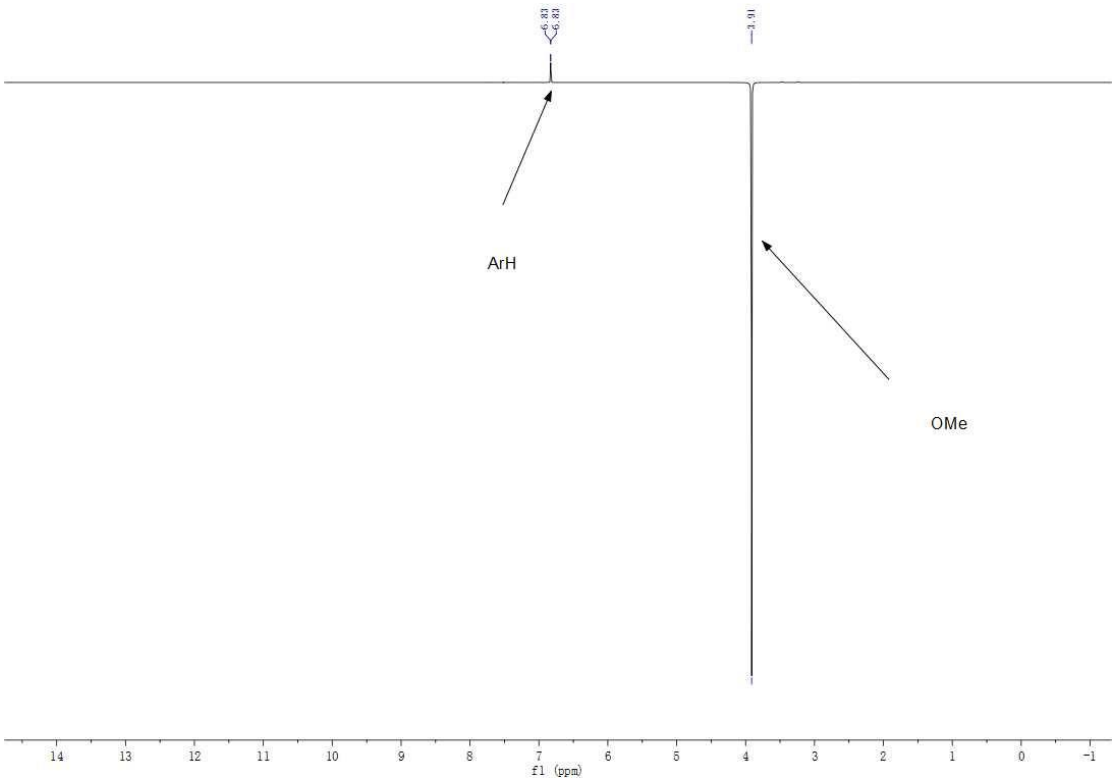
^{1}H NMR and ^{13}C NHR spectrum of **3-(4-Tosyl-piperazinyl)-4-methoxy-1,2-benzoisothiazole (4f)**



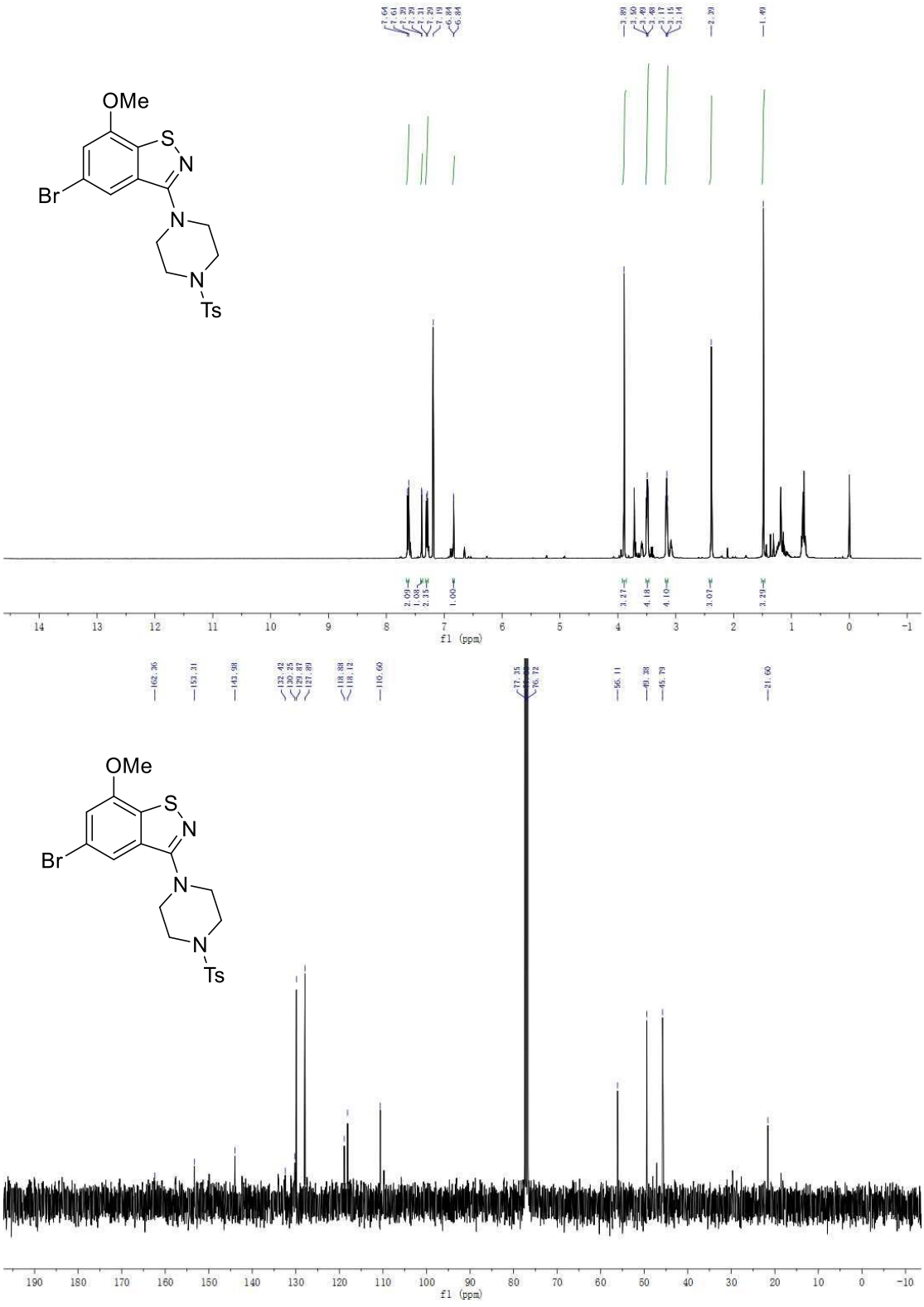
^{1}H NMR and ^{13}C NHR spectrum of **3-(4-Tosylpiperazinyl)-4-methoxy-6-bromo-1,2-benzoisothiazole (4g)**


OMe
NCH2
NCH2
f1 (ppm)

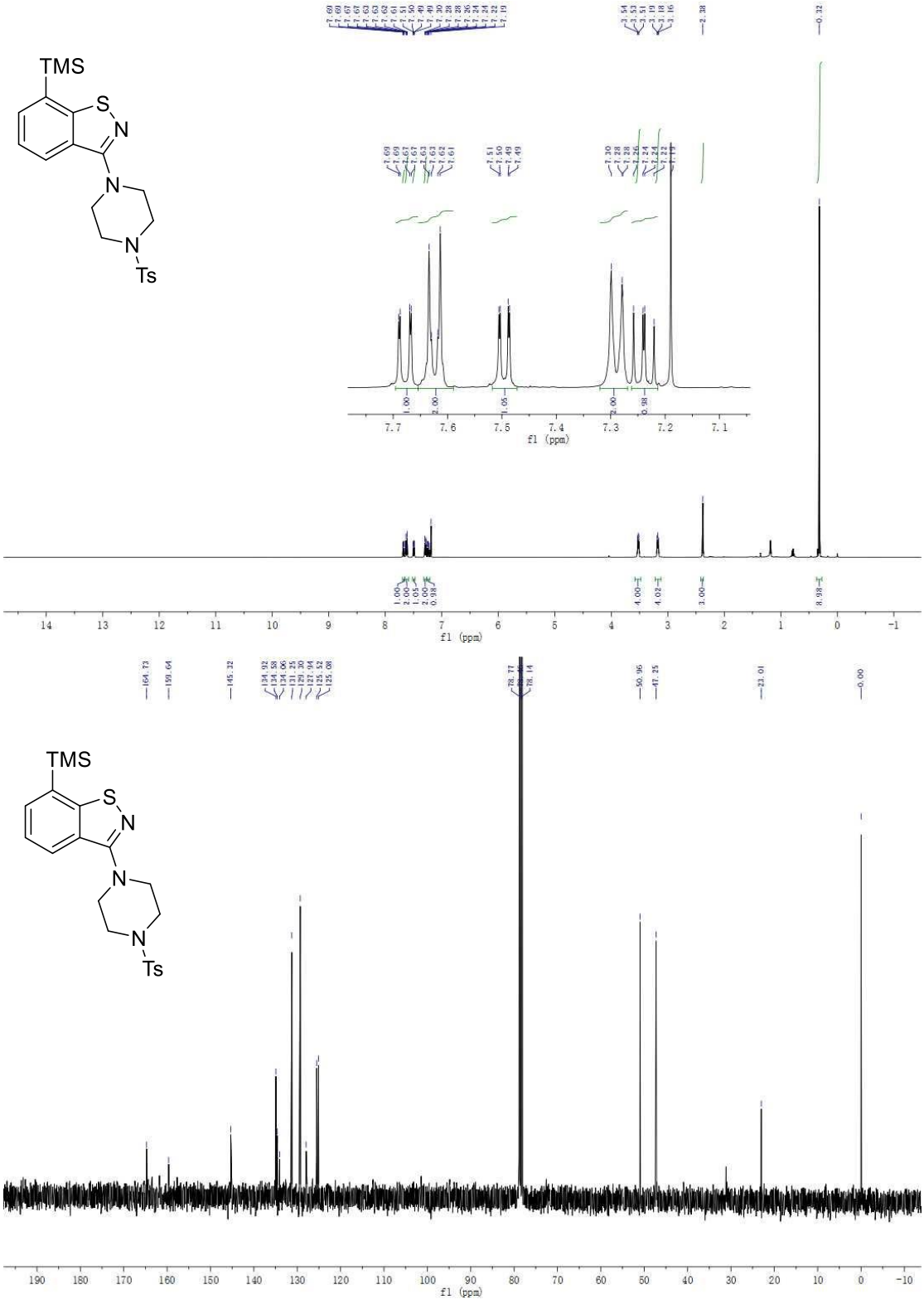

NCH2
Ts-ArH
OMe
NCH2
f1 (ppm)



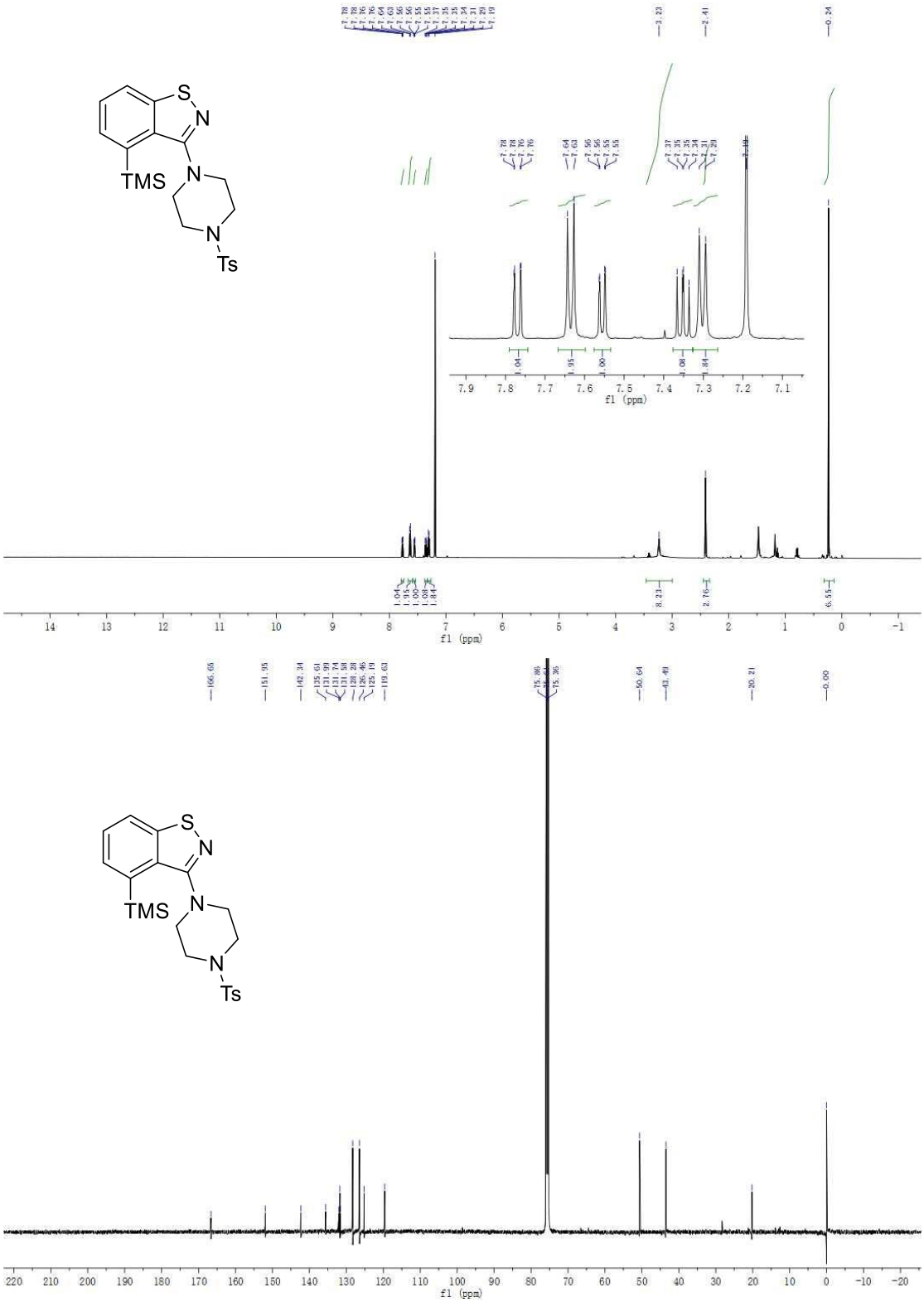
NOE spectra of **3-(4-Tosylpiperazinyl)-4-methoxy-6-bromo-1,2-benzoisothiazole (4g)**



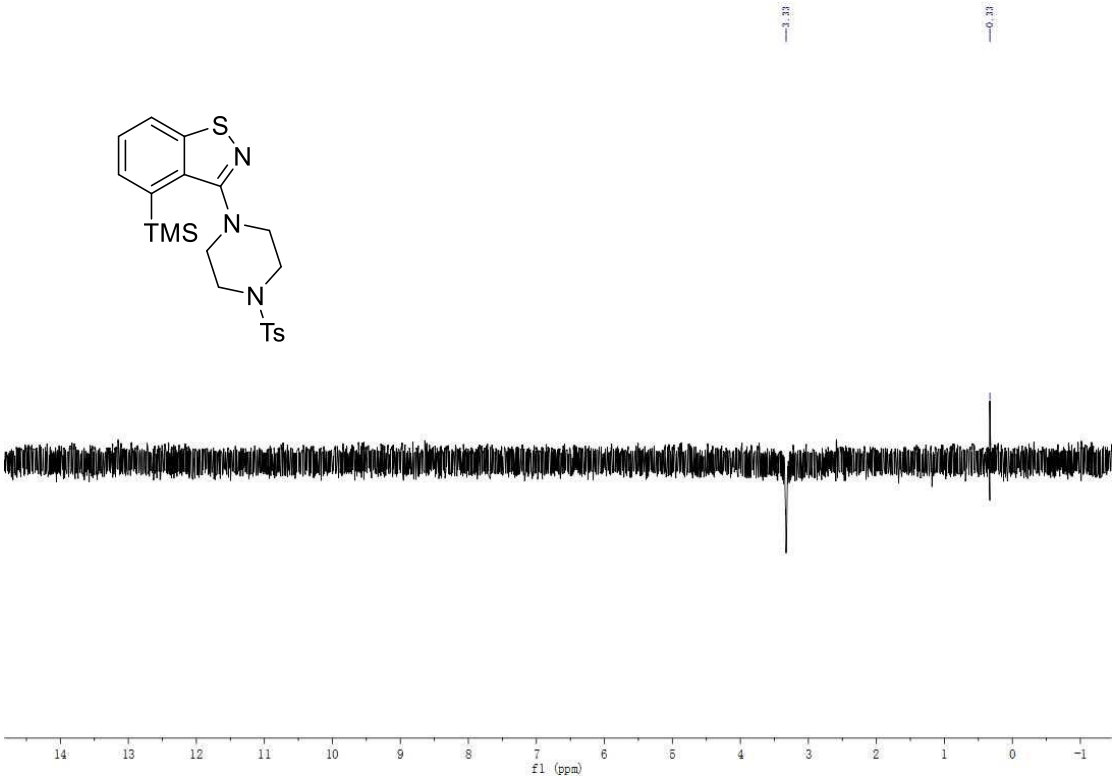
^{1}H NMR and ^{13}C NHR spectrum of **3-(4-Tosylpiperazinyl)-5-bromo-7-methoxy-1,2-benzoisothiazole (4g')**



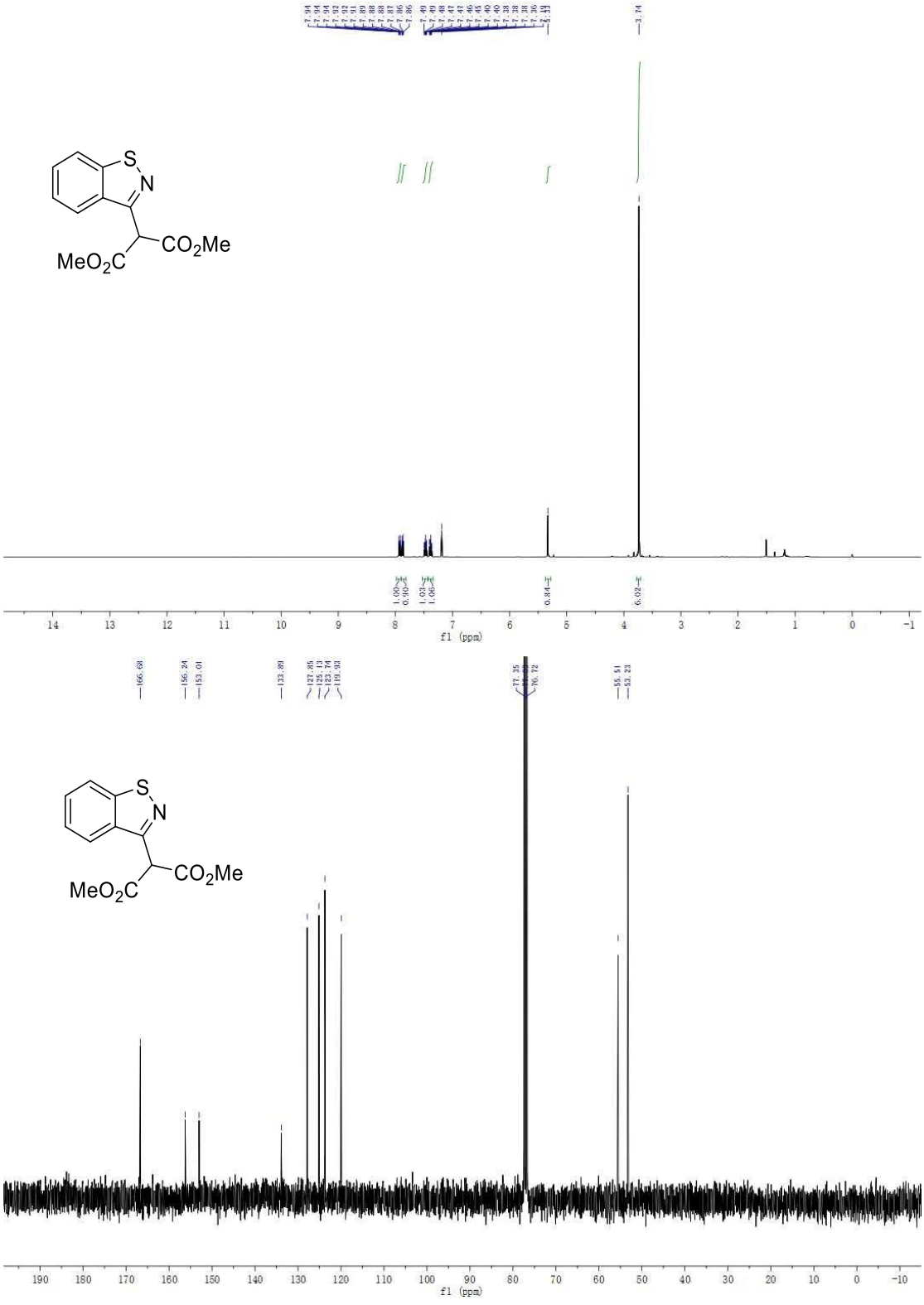
^{1}H NMR and ^{13}C NHR spectrum of **3-(4-Tosylpiperazinyl)-6-trimethylsilyl-1,2-benzoisothiazole (4h)**



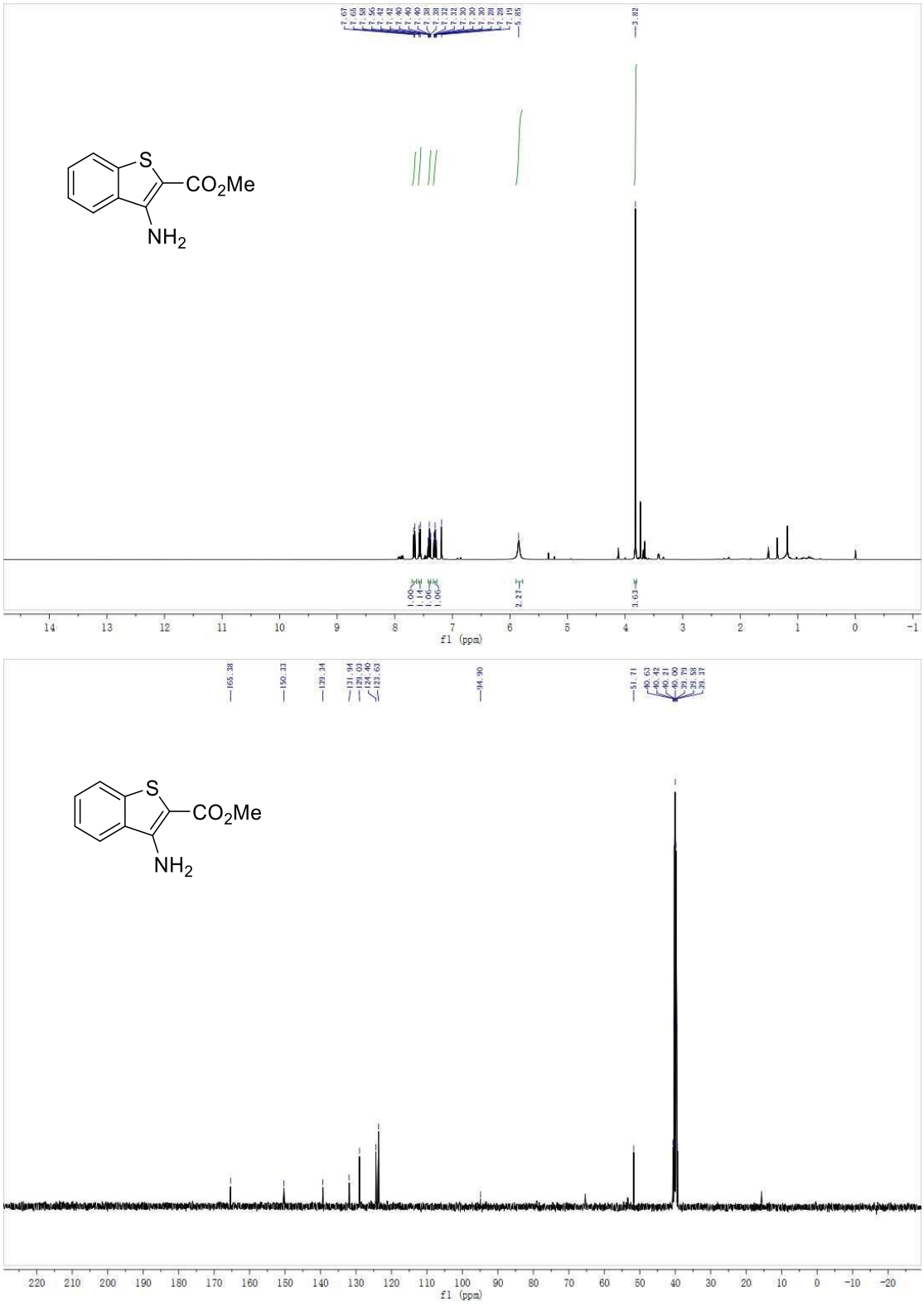
^{1}H NMR and ^{13}C NHR spectrum of **3-(4-Tosylpiperazinyl)-4-trimehylsilyl-1,2-benzoisothiazole (4h')**



NOE spectrum of **3-(4-Tosylpiperazinyl)-4-trimehylsilyl-1,2-benzoisothiazole (4h')**



^{1}H NMR and ^{13}C NHR spectrum of **Dimethyl 2,1-benzoisothiazole-3-malonate (5)**



^{1}H NMR and ^{13}C NHR spectrum of **Methyl 3-aminobenzothiophene-2-carboxylate (6)**