Supporting Information

Expeditious one-pot synthesis of C3-piperazinyl-substituted quinolines: Key precursors to potent c-Met inhibitors

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Content

1. General Method

^{1}H NMR spectral data were recorded on Varian Mercury 300 NMR spectrometer and ^{13}C NMR data were recorded on Varian Mercury 400 or 600 NMR spectrometer. Chemical shifts (δ) are reported in parts per million (ppm), and the signals are described as br (broad singlet), d (doublet), dd (doublet of doublet), m (multiple), q (quarter), s (singlet), and t (triplet). Coupling constants (*J* values) are given in Hz. Low-resolution mass spectra (MS) and high-resolution mass spectra (HRMS) were recorded at an ionizing voltage of 70 eV on a Finnigan/MAT95 spectrometer.

Elemental analyses were performed on a CE 1106 elemental analyzer. Column chromatography was carried out on silica gel (200–300 mesh). Analytical TLC was performed silica gel plates and visualized under ultraviolet light (254 nm). Unless otherwise indicated, all reactions were done in dry nitrogen atmosphere. All solvents and reagents were of laboratory reagent grade and used without purification. Dry solvents were prepared by standard methods. Yields were of purified compounds and were not optimized.

2. Experiment Procedure

2-Methyl-3-nitro-5-(trifluoromethyl)aniline (6). To a solution of 2-methyl-1,3-dinitro-5-(trifluoromethyl)benzene (**5**, 20 g, 80.0 mmol) in refluxing ethanol (400 mL), a solution of ammonium sulfide in ethanol (200 mL) was added slowly over a period of 30 min. The mixture was stirred under reflux for approximately 8 h, and then evaporated. The precipitate of sulfur and inorganic salts was filtered off and washed with ethanol. The filtrate was concentrated and purified by chromatography (petroleum ether : EtOAc = 10 : 1) to yield the title compound **6** (16.18 g, 92%) as yellow powder. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (s, 1H), 7.06 (s, 1H), 4.13 (brs, 2H), 2.28 (s, 3H); MS (EI) *m/z* 220 (M^+).

1-Bromo-2-methyl-3-nitro-5-(trifluoromethyl)benzene (7). Sodium nitrite (3.8 g, 55 mmol) in H_2O (20 mL) was added slowly to a stirred solution of compound **6** (11.0g, 50 mmol) in 40 mL of 48% HBr at 0^{o}C. After stirring for 30 min, the mixture was added dropwise to a solution of cuprous bromide (7.1 g, 50 mmol) in 20 mL of 48% HBr. The mixture was heated at 100^{o}C for 30 min, and then cooled to rt. The reaction was extracted with EtOAc (2 x 400 mL). The combined organic portion was washed with 3N aqueous NH_4OH and brine, then dried (Na_2SO_4) and concentrated. The residue was subjected to chromatography (petroleum ether : ethyl acetate = 30 : 1) to afford compound **7** (12.2 g, 86%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.98 (s, 1H), 2.62 (s, 3H); MS (EI) *m/z* 282 (M^+).

2-Bromo-6-nitro-4-(trifluoromethyl)benzaldehyde (8). To a stirred solution of bromobenzene **7** (8.5 g, 30 mmol) in DMF (30 mL) was added DMF•DMA (10.7 g,

12.03 mL, 90 mmol). After heating at 135°C for 16 h, the dark red solution was cooled to 0°C, and then added to a rapidly stirring solution of $NaIO_4$ (19.3 g, 90 mmol) in H_2O (60 mL) and DMF (30 mL) at 0°C. The reaction was stirred at 0°C for 4 h then allowed to warm to rt. After stirred for additional 18 h, the orange solution was filtered over a pad of celite and rinsed with EtOAc (200 mL). The filtrate was then washed with H_2O (3 x 150 mL) and brine (150 mL), and then dried over anhydrous $MgSO_4$. After evaporation, the residue was purified by chromatography (petroleum ether : ethyl acetate = 10 : 1) to afford benzaldehyde **8** (4.9 g, 55%) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.27 (s, 1H), 8.31 (s, 1H), 8.19 (s, 3H); MS (EI) *m/z* 297 (M^+).

2-Amino-6-bromo-4-(trifluoromethyl)benzaldehyde (9). To a solution of **8** (2.97 g, 10 mmol) in ethanol (50 mL), was added iron powder (3.9 g, 70 mmol) followed by a solution of NH_4Cl (5.3 g, 100 mmol) in water (20 mL). The mixture was heated at reflux until the starting material was completely consumed. The solution was filtered over a pad of celite and the residue was washed with ethanol. The filtrate was concentrated, and the residue was subjected to chromatography (petroleum ether : ethyl acetate = 5 : 1) to afford 2-amino-4-(trifluoromethyl)benzaldehyde **9** (2.4 g, 90%) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.43 (s, 1H), 7.09 (s, 1H), 6.85 (s, 1H), 6.75 (brs, 2H); MS (EI) *m/z* 267 (M^+).

Typical procedure for synthesis of 3-(4-methylpiperazin-1-yl)-quinolines 11a-k.

To a solution of **9** (267 mg, 1.0 mmol) and an appropriate acetaldehyde **10a-k** (1.0 mmol) in EtOH, was added solid NaOH (400 mg, 10 mmol). The mixture was heated to 78°C and stirred until the complete consumption of the starting material (about 1h). The mixture was concentrated and the residue was subjected to chromatography ($CHCl_3$: MeOH = 20 : 1) to afford corresponding quinolines **11a-k**.

3-(4-Methylpiperazin-1-yl)-5-bromo-7-trifluoromethyl quinolines 11a: yellow solid (85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.85 (d, J = 2.4 Hz, 1H), 8.21 (s, 1H), 7.90 (s, 1H), 7.57 (d, J = 2.7 Hz, 1H), 3.46 (t, J = 4.8 Hz, 4H), 2.65 (m, 4H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.4, 145.2, 141.1, 130.0, 127.5 (q, J = 32.8 Hz),

126.4, 126.2, 123.3 (q, J = 270.5 Hz), 121.0, 113.8, 54.4, 47.7, 46.0; MS (EI) *m/z* 373 (M^+); HRMS calcd for $C_{15}H_{15}BrF_3N_3$ (M^+) 373.0401, found: 373.0404.

5-Bromo-3-(piperazin-1-yl)-7-(trifluoromethyl)quinoline (11b): Yellow powder (76%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.83 (d, J = 2.1 Hz, 1H), 8.20 (s, 1H), 7.89 (s, 1H), 7.54 (d, J = 2.1 Hz, 1H), 3.39 (t, J = 4.8 Hz, 4H), 2.66 (br, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.9, 141.3, 137.0, 126.2, 123.9 (q, J = 33.5 Hz), 122.1, 122.0, 119.4 (q, J = 273.0 Hz), 117.2, 110.4, 44.3, 41.2; MS (EI) *m/z* 359 (M^+); HRMS calcd for $C_{14}H_{13}BrF_3N_3$ (M^+) 359.0245, found: 359.0245.

5-Bromo-3-(4-ethyl-piperazin-1-yl)-7-(trifluoromethyl)quinoline (11c): Yellow powder (85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.82 (s, 1H), 8.18 (s, 1H), 7.86 (s, 1H), 7.51 (s, 1H), 3.45 (t, J = 4.8 Hz, 4H), 2.66 (m, 4H), 2.47 (q, J = 7.1 Hz, 2H), 1.14 (t, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.4, 145.1, 141.0, 130.0, 127.4 (q, J = 32.9 Hz), 126.4, 126.1, 123.4 (q, J = 270.8 Hz), 121.0, 113.6, 52.2, 47.7, 11.9; MS (EI) *m/z* 387 (M^+); HRMS calcd for $C_{16}H_{17}BrF_3N_3$ (M^+) 387.0558, found: 387.0559.

5-Bromo-3-(4-hydroxyethyl-piperazin-1-yl)-7-(trifluoromethyl)quinoline (11d): Yellow powder (86%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.73 (d, J = 2.4 Hz, 1H), 8.09 (s, 1H), 7.82 (s, 1H), 7.50 (d, J = 2.1 Hz, 1H), 3.66 (t, J = 5.4 Hz, 2H), 3.41 (t, J = 4.3 Hz, 4H), 2.73 (m, 4H), 2.60 (t, J = 5.4 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$+CD_3OD) δ 146.3, 145.0, 140.7, 130.0, 127.7 (q, J = 33.4 Hz), 126.3, 125.8, 123.2 (q, J = 270.4 Hz), 121.0, 114.2, 59.5, 57.9, 52.4, 47.4; MS (EI) *m/z* 403 (M^+); HRMS calcd for $C_{16}H_{17}BrF_3N_3O$ (M^+) 403.0507, found: 403.0530.

5-Bromo-3-(4-benzyl-piperazin-1-yl)-7-(trifluoromethyl)quinoline (11e): Yellow powder (75%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.84 (d, J = 3.0 Hz, 1H), 8.22 (s, 1H), 7.90 (s, 1H), 7.55 (d, J = 2.7 Hz, 1H), 7.34 (m, 5H), 3.61 (s, 2H), 3.45 (t, J = 5.1 Hz, 4H), 2.68 (t, J = 4.9 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.6, 145.3, 141.1, 137.5, 130.1, 129.0, 128.3, 127.3 (q, J = 32.8 Hz), 127.2, 126.5, 126.2, 123.4 (q, J = 270.6 Hz), 121.0, 113.7, 62.8, 52.4, 47.9; MS (EI) *m/z* 449 (M^+); HRMS calcd for $C_{21}H_{19}BrF_3N_3$ (M^+) 449.0714, found: 449.0725.

5-Bromo-3-(4-phenyl-piperazin-1-yl)-7-(trifluoromethyl)quinoline (11f): Yellow powder (83%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.89 (d, J = 2.4 Hz, 1H), 8.24 (s, 1H),

7.92 (s, 1H), 7.61 (d, J = 2.4 Hz, 1H), 7.33 (t, J = 7.6 Hz, 2 H), 7.01 (d, J = 8.7 Hz, 2H), 6.94 (t, J = 7.4 Hz, 1H), 3.60 (t, J = 4.8 Hz, 4H), 3.43 (t, J = 4.8 Hz, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 150.7, 146.4, 145.4, 141.4, 130.0, 129.2, 127.7 (q, J = 32.8 Hz), 126.5, 126.3, 123.4 (q, J = 270.4 Hz), 121.1, 120.5, 116.4, 114.1, 49.0, 48.0; MS (EI) *m/z* 435 (M^+); HRMS calcd for $C_{20}H_{17}BrF_3N_3$ (M^+) 435.0558, found: 435.0555.

4-(5-Bromo-7-(trifluoromethyl)quinolin-3-yl)morpholine (11g): Yellow powder (89%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.81 (s, 1H), 8.21 (s, 1H), 7.89 (s, 1H), 7.54 (s, 1H), 3.94 (t, J = 4.5 Hz, 4H), 3.39 (t, J = 4.6 Hz, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 146.5, 144.9, 141.5, 130.0, 127.8 (q, J = 33.3 Hz), 126.5, 126.3, 123.4 (q, J = 270.6 Hz), 121.1, 114.0, 66.4, 48.0; MS (EI) *m/z* 360 (M^+); HRMS calcd for $C_{14}H_{12}BrF_3N_2O$ (M^+) 360.0085, found: 360.0073.

(2S,6R)-4-(5-Bromo-7-(trifluoromethyl)quinolin-3-yl)-2,6-dimethylmorpholine (11h): Yellow powder (89%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.80 (d, J = 2.1 Hz, 1H), 8.20 (s, 1H), 7.88 (s, 1H), 7.49 (d, J = 1.8 Hz, 1H), 3.87 (m, 2H), 3.67 (d, J = 11.4 Hz, 2H), 2.62 (t, J = 11.4 Hz, 2H), 1.34 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.1, 145.0, 141.2, 130.0, 127.6 (q, J = 32.8 Hz), 126.5, 126.2, 123.3 (q, J = 270.7 Hz), 121.0, 113.7, 71.3, 53.1, 18.9; MS (EI) *m/z* 388 (M^+); HRMS calcd for $C_{16}H_{16}BrF_3N_2O$ (M^+) 388.0398, found: 388.0398.

5-Bromo-3-(piperidin-1-yl)-7-(trifluoromethyl)quinoline (11i): Yellow powder (84%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.81 (d, J = 2.4 Hz, 1H), 8.18 (s, 1H), 7.86 (s, 1H), 7.50 (d, J = 2.4 Hz, 1H), 3.40 (d, J = 5.2 Hz, 4H), 1.77 (m, 4H), 1.68 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 147.1, 145.7, 140.7, 130.3, 127.2 (q, J = 32.9 Hz), 126.3, 126.1, 123.5 (q, J = 270.8 Hz), 120.9, 113.5, 49.2, 25.3, 23.9; MS (EI) *m/z* 358 (M^+); HRMS calcd for $C_{15}H_{14}BrF_3N_2$ (M^+) 358.0292, found: 358.0290.

5-Bromo-3-(4-methoxypiperidin-1-yl)-7-(trifluoromethyl)quinoline (11j): Yellow powder (88%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.83 (d, J = 2.1 Hz, 1H), 8.19 (s, 1H), 7.87 (s, 1H), 7.55 (d, J = 1.5 Hz, 1H), 3.69 (m, 2H), 3.47 (m, 1H), 3.40 (s, 3H), 3.25 (m, 2H), 2.05 (m, 2H), 1.82 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.6, 145.7, 140.9, 130.1, 127.4 (q, J = 33.1 Hz), 126.4, 126.1, 123.4 (q, J = 270.8 Hz), 120.9,

113.8, 74.9 ,55.7 ,45.6 ,29.9; MS (EI) *m/z* 388 (M^+); HRMS calcd for $C_{16}H_{16}BrF_3N_2O$ (M^+) 388.0398, found: 388.0400.

5-Bromo-3-((3aR,6aS)-5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-7-(trifluoromethyl)quinoline (11k): Yellow powder (74%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (d, *J* = 2.4 Hz, 1H), 8.19 (s, 1H), 7.87 (s, 1H), 7.23 (d, *J* = 2.1 Hz, 1H), 3.71 (t, *J* = 8.7 Hz, 2H), 3.45 (t, *J* = 8.8 Hz, 2H), 3.12 (s, 2H), 2.69 (m, 4H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.5, 143.1, 139.9, 130.4, 126.6, 126.0, 125.9 (q, *J* = 33.0 Hz), 123.6 (q, *J* = 270.6 Hz), 120.3, 111.1, 62.9 , 54.4 , 42.1, 41.6; MS (EI) *m/z* 399 (M^+); HRMS calcd for $C_{21}H_{25}BrF_3N_3$ (M^+) 399.0558, found: 399.0556.

General procedure for the synthesis of acetaldehydes 17a-j. These compounds were prepared by condensation of **16a-i** and **9** in the presence of NaOH following a procedure similar to that of preparation of quinoline **11a-k**.

5-Bromo-2-methyl-3-(4-methylpiperazin-1-yl)-7-(trifluoromethyl)quinoline (17a): Yellow powder (23%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.88 (s, 1H), 7.86 (s, 1H), 3.14 (t, *J* = 4.4 Hz, 4H), 2.75 (s, 3H), 2.68 (m, 4H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 148.5, 142.9, 129.2 (q, *J* = 33.9 Hz), 129.0, 125.7, 125.2, 123.4 (q, *J* = 271.0 Hz), 121.3, 121.0, 55.0, 51.4, 46.0, 21.9; MS (EI) *m/z* 387 (M^+); HRMS calcd for $C_{16}H_{17}BrF_3N_3$ (M^+) 387.0558, found: 387.0565.

5-Bromo-2-cyclopropyl-3-(4-methylpiperazin-1-yl)-7-(trifluoromethyl)quinoline (17b): Yellow powder (67%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.80 (s, 1H), 7.75 (s, 1H), 3.23 (s, 4H), 2.69 (s, 4H), 2.57 (m, 1H), 2.40 (s, 3H), 1.34 (m, 2H), 1.11 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 148.2, 143.1, 128.8 (q, *J* = 32.8 Hz), 128.3, 125.8, 124.5, 123.5 (q, *J* = 271.0 Hz), 121.2, 119.5, 55.0, 51.6, 46.0, 13.3, 11.6; MS (EI) *m/z* 413 (M^+); HRMS calcd for $C_{18}H_{19}BrF_3N_3$ (M^+) 413.0714, found: 413.0723.

2-(4-(5-Bromo-2-cyclopropyl-7-(trifluoromethyl)quinolin-3-yl)piperazin-1-yl)ethanol (17c): Yellow powder (68%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.81 (s, 1H), 7.77 (s, 1H), 3.70 (t, *J* = 5.2 Hz, 2H), 3.41 (m, 4H), 2.80 (m, 4H), 2.68 (t, *J* = 5.4

Hz, 2H), 2.54 (m, 1H), 1.36 (m, 2H), 1.11 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 148.1, 143.2, 128.9 (q, J= 32.8 Hz), 128.3, 125.7, 124.5, 123.4 (q, J= 270.5 Hz), 121.2, 119.6, 59.2, 57.7, 52.8, 51.7, 13.3, 11.7; MS (EI) *m/z* 443 (M^+); HRMS calcd for $C_{19}H_{21}BrF_3N_3O$ (M^+) 443.0820, found: 443.0817.

***tert*-Butyl 4-(5-Bromo-2-cyclopropyl-7-(trifluoromethyl)quinolin-3-yl)piperazine-1-carboxylate (11d):** Yellow powder (61%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.82 (s, 1H), 7.76 (s, 1H), 3.69 (m, 4H), 3.17 (m, 4H), 2.58 (m, 1H), 1.51 (s, 9H), 1.36 (m, 2H), 1.45 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 154.6, 148.0, 143.4, 129.1 (q, J= 32.9 Hz), 128.2, 125.8, 124.6, 123.4 (q, J= 271.2 Hz), 121.3, 120.0, 80.0, 65.5, 59.2, 51.7, 28.3, 19.1, 13.7, 11.7; MS (EI) *m/z* 499 (M^+); HRMS calcd for $C_{22}H_{25}BrF_3N_3O_2$ (M^+) 499.1082, found: 499.1079.

4-(5-Bromo-2-cyclopropyl-7-(trifluoromethyl)quinolin-3-yl)morpholine (17e): Yellow powder (65%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.83 (s, 1H), 7.77 (s, 1H), 3.97 (m, 4H), 3.22 (m, 4H), 2.58 (m, 1H), 1.37 (m, 2H), 1.13 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 148.0, 143.3, 129.1 (q, J= 33.5 Hz), 128.3, 125.8, 124.6, 123.4 (q, J= 271.0 Hz), 121.5, 119.7, 66.9, 52.1, 13.3, 11.7; MS (EI) *m/z* 400 (M^+); HRMS calcd for $C_{17}H_{16}BrF_3N_2O$ (M^+) 400.0398, found: 400.0400.

(2S,6R)-4-(5-Bromo-2-cyclopropyl-7-(trifluoromethyl)quinolin-3-yl)-2,6-dimethyl morpholine (17f): Yellow powder (66%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.82 (s, 1H), 7.73 (s, 1H), 3.96 (m, 2H), 3.40 (d, J = 11.1 Hz, 2H), 2.56 (m, 3H), 1.36 (m, 2H), 1.31 (s, 3H), 1.29 (s, 3H), 1.12 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 147.7, 143.2, 129.0 (q, J= 32.8 Hz), 128.3, 125.8, 124.5, 123.4 (q, J= 270.6 Hz), 121.2, 119.6, 71.8, 57.4, 19.0, 13.4, 11.6; MS (EI) *m/z* 428 (M^+); HRMS calcd for $C_{19}H_{20}BrF_3N_2O$ (M^+) 428.0711, found: 428.0708.

5-Bromo-2-cyclopropyl-3-(piperidin-1-yl)-7-(trifluoromethyl)quinoline (17g): Yellow powder (67%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.81 (s, 1H), 7.72 (s, 1H), 3.15 (m, 4H), 2.58 (m, 1H), 1.83 (m, 4H), 2.08 (t, J = 5.0 Hz, 2H), 1.34 (m, 2H), 1.14 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 149.5, 142.9, 128.6 (q, J= 33.5 Hz), 128.5, 125.7, 124.5, 123.5 (q, J= 271.3 Hz), 121.1, 119.2, 53.1, 26.1, 24.0, 13.2, 11.7; MS (EI) *m/z* 398 (M^+); HRMS calcd for $C_{18}H_{18}BrF_3N_2$ (M^+) 398.0605,

found: 398.0615.

5-Bromo-2-cyclopropyl-3-(4-methoxypiperidin-1-yl)-7-(trifluoromethyl)quinoline (17h): Yellow powder 69%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.81 (s, 1H), 7.76 (s, 1H), 3.44 (m, 6H), 2.98 (t, *J* = 9.9 Hz, 2H), 2.57 (m, 1H), 2.11 (m, 2H), 1.88 (m, 2H), 1.34 (m, 2H), 1.12 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 148.8, 143.1, 128.8 (q, *J* = 32.8 Hz), 128.4, 125.8, 124.4, 123.5 (q, *J* = 271.1 Hz), 121.1, 119.5, 55.7, 49.4, 30.9, 13.1, 11.7; MS (EI) *m/z* 428 (M^+); HRMS calcd for $C_{19}H_{20}BrF_3N_2O$ (M^+) 428.0711, found: 428.0724.

5-Bromo-2-cyclopropyl-3-(pyrrolidin-1-yl)-7-(trifluoromethyl)quinoline (17i): Yellow powder (64%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.78 (s, 1H), 7.47 (s, 1H), 3.50 (t, *J* = 5.8 Hz, 4H), 2.42 (m, 1H), 2.05 (t, *J* = 6.4 Hz, 4H), 1.39 (m, 2H), 1.11 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 146.3, 141.3, 128.9, 127.0 (q, *J* = 32.8 Hz), 125.6, 124.6, 123.7 (q, *J* = 270.4 Hz), 120.2, 114.0, 51.6, 25.2, 16.0, 11.0; MS (EI) *m/z* 384 (M^+); HRMS calcd for $C_{17}H_{16}BrF_3N_2$ (M^+) 384.0449, found: 384.0441.

5-Bromo-3-(4-methylpiperazin-1-yl)-2-phenyl-7-(trifluoromethyl)quinoline (17j): Yellow powder (15%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (s, 1H), 8.02 (m, 2H), 7.91 (s, 1H), 7.86 (s, 1H), 7.50 (m, 3H), 3.05 (m, 4H), 2.46 (m, 4H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 147.4, 142.8, 139.2, 129.3, 128.4, 128.1, 126.6, 125.7, 122.0, 121.1, 120.3, 54.5, 50.6, 45.9; MS (EI) *m/z* 449 (M^+); HRMS calcd for $C_{21}H_{19}BrF_3N_3$ (M^+) 449.0714, found: 449.0722.

5-Bromo-2-((4-methylpiperazin-1-yl)methyl)-7-(trifluoromethyl)quinoline (18): Yellow powder (61%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (d, *J* = 8.7 Hz, 1H), 8.34 (s, 1H), 7.95 (s, 1H), 7.84 (d, *J* = 8.7 Hz, 1H), 3.87 (s, 2H), 2.59 (m, 4H), 2.48 (m, 4H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 147.1, 135.6, 131.4 (q, *J* = 33.7 Hz), 128.3, 126.8, 125.5, 123.1 (q, *J* = 270.4 Hz), 122.7, 121.7, 64.5, 55.0, 53.3, 46.0; MS (EI) *m/z* 387 (M^+); HRMS calcd for $C_{16}H_{17}BrF_3N_3$ (M^+) 387.0558, found: 387.0565.

1,7-Dibromo-3,9-bis(trifluoromethyl)-5,6,11,12-tetrahydro-6,12-epoxydibenzo[b,f

][1,5]diazocine (19): Yellow powder (40%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (s, 2H), 6.93 (s, 2H), 6.05 (d, *J* = 4.5 Hz, 2H), 5.48 (d, *J* = 3.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4, 132.3 (q, *J* = 33.3 Hz), 124.4, 122.8 (q, *J* = 271.0 Hz), 122.7, 119.4, 112.3, 76.2; MS (EI) *m/z* 515 (M^+); HRMS calcd for $C_{16}H_8Br_2F_6N_2O$ (M^+) 515.8908, found: 515.8910.

Preparation of 3-(4-Methylpiperazin-1-yl)-*N*-(3-nitrobenzyl)-7-(trifluoromethyl) quinolin-5-amine (1): A dried flask was charged with (±)-BINAP (16 mmol %), Cs_2CO_3 (3.0 mmol), (3-nitrophenyl)methanamine hydrochloride (1.2 mmol), $Pd_2(dba)_3$ (3.5 mmol %) and **11a** (1.0 mmol) in dry 1,4-dioxane (10 mL) under nitrogen. The mixture was heated to 110^{o}C and stirred for 12h. The reaction was cooled to rt and filtered. The filtrate was concentrated *in vacuum* and purified by chromatography ($CHCl_3$: MeOH = 10 : 1) to yield compound **1** (75%) as a yellow powder.

Genenral procedure for the preparation of quinolones 21a-k. A dried flask was charged with (±)-BINAP (16 mmol %), Cs_2CO_3 (1.4 mmol), **22a-k** (1.0 mmol), $Pd_2(dba)_3$ (3.5 mmol %), **11a** or **17b** (1.2 mmol), and dry 1,4-dioxane (10 mL) under nitrogen. The mixture was heated to 110^{o}C and stirred for 12h. The reaction was cooled to rt and filtered. The filtrate was concentrated *in vacuum* and purified by chromatography ($CHCl_3$: MeOH = 10 : 1) to yield corresponding quinoline **21a-k**.

***N*-([1,2,4]Triazolo[4,3-b]pyridazin-3-ylmethyl)-3-(4-methylpiperazin-1-yl)-7-(trifl uoromethyl)quinolin-5-amine (21a):** ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.78 (d, *J* = 2.7 Hz, 1H), 8.45 (dd, *J* = 1.5, 9.3 Hz, 1H), 8.16 (dd, *J* = 1.5, 9.3 Hz, 1H), 7.70 (s, 1H), 7.33 (d, *J* = 2.7 Hz, 1H), 7.17 (dd, *J* = 4.2, 9.6 Hz, 1H), 6.96 (s, 1H), 5.64 (t, *J* = 6.0 Hz, 1H), 5.10 (d, *J* = 6.0 Hz, 2H), 3.31 (t, *J* = 4.8 Hz, 4H), 2.58 (t, *J* = 4.8 Hz, 4H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.4, 145.3, 145.0, 144.6, 144.3, 142.2, 141.8, 128.2 (q, *J* = 31.2 Hz), 125.3, 123.2 (q, *J* = 270.4 Hz), 120.8, 120.0, 117.1, 109.2, 101.1, 54.6, 48.4, 48.0, 38.0; MS (EI) *m/z* 442 (M^+); HRMS calcd for $C_{21}H_{21}F_3N_8$ (M^+) 442.1841, found: 442.1840.

***N*-((6-Chloro-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl)-3-(4-methylpiperazin-1**

-yl)-7-(trifluoromethyl)quinolin-5-amine (21b): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.76 (s, 1H), 8.07 (d, *J* = 11.7 Hz, 1H), 7.68 (s, 1H), 7.33 (s, 1H), 7.14 (d, *J* = 7.5 Hz, 1H), 6.92 (s, 1H), 5.73 (t, *J* = 4.8 Hz, 1H), 5.06 (d, *J* = 4.8 Hz, 2H), 3.27 (s, 4H), 2.55 (s, 4H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$+CD_3OD) δ 150.0, 147.3, 144.7, 144.0, 142.8, 142.4, 141.2, 128.2 (q, *J* = 31.9 Hz), 126.1, 124.1 (q, *J* = 270.8 Hz), 123.0, 120.6, 115.3, 110.7, 100.3, 54.2, 47.8, 45.4, 37.1; MS (EI) *m/z* 476 (M^+); Anal. ($C_{21}H_{20}ClF_3N_8$) calcd: C 52.89, H 4.23, N 23.50, found C 52.78, H 4.22, N 23.29.

***N*-((6-Methyl-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl)-3-(4-methylpiperazin-1 -yl)-7-(trifluoromethyl)quinolin-5-amine (21c):** ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.63 (d, *J* = 2.1 Hz, 1H), 7.92 (d, *J* = 9.3 Hz, 1H), 7.53 (s, 1H), 7.48 (s, 1H), 7.00 (d, *J* = 9.3 Hz, 1H), 6.92 (s, 1H), 5.01 (s, 2H), 3.23 (s, 4H), 2.59 (s, 3H), 2.53 (t, *J* = 4.8 Hz, 4H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$+CD_3OD) δ 155.4, 147.5, 144.8, 144.1, 143.3, 142.6, 141.4, 128.1 (q, *J* = 32.4 Hz), 124.4 (q, *J* = 271.0 Hz), 124.0, 122.8, 120.7, 115.7, 110.5, 100.5, 54.3, 48.0, 45.6, 37.1, 37.0, 21.4; MS (EI) *m/z* 456 (M^+); Anal. ($C_{22}H_{23}F_3N_8 \cdot 0.2HCl \cdot 0.1H_2O$) calcd: C 56.76, H 5.07, N 24.07, found C 56.99, H 4.85, N 23.76.

***N*-((6-Methoxy-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl)-3-(4-methylpiperazin -1-yl)-7-(trifluoromethyl)quinolin-5-amine (21d):** ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.62 (s, 1H), 7.92 (d, *J* = 9.6 Hz, 1H), 7.60 (s, 1H), 7.24 (s, 1H), 6.82 (d, *J* = 9.3 Hz, 2H), 6.43 (s, 1H), 5.02 (d, *J* = 5.7 Hz, 2H), 4.09 (s, 3H), 2.98 (s, 4H), 2.36 (s, 4H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$+CD_3OD) δ 161.3, 147.7, 144.7, 144.0, 143.1, 142.7, 141.3, 127.9 (q, *J* = 31.4 Hz), 125.8, 124.3 (q, *J* = 270.1 Hz), 120.7, 116.9, 115.4, 110.5, 99.9, 55.1, 54.2, 47.9, 45.6, 36.7; MS (EI) *m/z* 472 (M^+); Anal. ($C_{22}H_{23}F_3N_8O \cdot 0.5HCl \cdot 0.2H_2O$) calcd: C 53.46, H 4.87, N 22.67, found C 53.77, H 4.50, N 22.42.

***N*-((6-Ethoxy-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl)-3-(4-methylpiperazin-1 -yl)-7-(trifluoromethyl)quinolin-5-amine (21e):** ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.69 (s, 1H), 7.93 (d, *J* = 9.9 Hz, 1H), 7.65 (s, 1H), 7.28 (s, 1H), 6.83 (d, *J* = 10.2 Hz, 2H), 6.10 (t, *J* = 5.7 Hz, 1H), 4.99 (d, *J* = 5.7 Hz, 2H), 4.48 (q, *J* = 6.9 Hz, 2H), 3.13 (s, 4H), 2.47 (s, 4H), 2.30 (s, 3H), 1.48 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$)

δ 160.8, 147.6, 144.8, 144.4, 143.4, 142.5, 141.7, 127.9 (q, *J* = 31.4 Hz), 126.0, 124.4 (q, *J* = 270.2 Hz), 120.8, 116.9, 116.6, 109.4, 100.2, 64.3, 54.4, 48.1, 45.9, 37.4, 14.0; MS (EI) *m/z* 486 (M^+); HRMS calcd for $C_{23}H_{25}F_3N_8O$ (M^+) 486.2103, found: 486.2094.

***N*-((6-(Dimethylamino)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl)-3-(4-methylpiperazin-1-yl)-7-(trifluoromethyl)quinolin-5-amine (21f):** ^{1}H NMR (300 MHz, $CDCl_3$+CD_3OD) δ 8.55 (s, 1H), 7.72 (d, *J* = 10.2 Hz, 1H), 7.62 (s, 1H), 7.45 (s, 1H), 6.92 (d, *J* = 9.9 Hz, 1H), 6.79 (s, 1H), 4.88 (s, 2H), 3.37 (s, 4H), 3.11 (s, 6H), 2.85 (s, 4H), 2.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$+CD_3OD) δ 155.0, 146.7, 144.0, 143.9, 143.1, 142.0, 141.7, 128.6 (q, *J* = 31.9 Hz), 124.4 (q, *J* = 270.1 Hz), 123.5, 120.5, 114.8, 113.9, 111.8, 100.1, 53.7, 47.1, 44.4, 38.3, 36.5; MS (EI) *m/z* 485 (M^+); Anal. ($C_{23}H_{26}F_3N_9$) calcd: C 52.03, H 5.32, N 23.74, found C 52.12, H 5.48, N 23.74.

3-(4-Methylpiperazin-1-yl)-*N*-((6-phenyl-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl)-7-(trifluoromethyl)quinolin-5-amine (21g): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.70 (s, 1H), 8.14 (d, *J* = 9.9 Hz, 1H), 7.97 (m, 2H), 7.66 (s, 1H), 7.56 (m, 4H), 7.34 (s, 1H), 6.91 (s, 1H), 6.10 (s, 1H), 5.15 (d, *J* = 5.4 Hz, 2H), 3.16 (s, 4H), 2.47 (s, 4H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 147.7, 144.8, 144.4, 143.7, 142.4, 141.7, 133.7, 131.2, 129.2, 127.9 (q, *J* = 31.9 Hz), 127.3, 125.0, 124.4 (q, *J* = 270.1 Hz), 120.8, 119.8, 116.7, 109.3, 100.6, 54.4, 48.1, 45.9, 38.0; MS (EI) *m/z* 518 (M^+); HRMS calcd for $C_{27}H_{25}F_3N_8$ (M^+) 518.2154, found: 518.2163.

3-(4-Methylpiperazin-1-yl)-*N*-((6-(thiophen-2-yl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl)-7-(trifluoromethyl)quinolin-5-amine (21h): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.77 (d, *J* = 2.7 Hz, 1H), 8.11 (d, *J* = 9.6 Hz, 1H), 7.72 (d, *J* = 3.9 Hz, 2H), 7.58 (d, *J* = 5.4 Hz, 1H), 7.40 (d, *J* = 9.6 Hz, 1H), 7.35 (d, *J* = 2.7 Hz, 1H), 7.20 (dd, *J* = 4.8, 3.9 Hz, 1H), 6.96 (s, 1H), 5.74 (t, *J* = 6.3 Hz, 1H), 5.12 (d, *J* = 6.3 Hz, 2H), 3.30 (t, *J* = 5.1 Hz, 4H), 2.57 (t, *J* = 5.1 Hz, 4H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.5, 147.4, 144.9, 141.7, 137.7, 128.4, 128.1, 127.8, 127.7 (q, *J* = 31.0 Hz), 124.9, 124.4 (q, *J* = 270.7 Hz), 120.8, 118.9, 116.9, 109.2, 100.8, 54.5, 48.2, 46.0, 38.1; MS (EI) *m/z* 524 (M^+); HRMS calcd for $C_{25}H_{23}F_3N_8S$ (M^+) 524.1718, found: 524.1687.

***N*-((6-(Furan-2-yl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl)-3-(4-methylpiper**

azin-1-yl)-7-(trifluoromethyl)quinolin-5-amine (21i): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.74 (d, *J* = 2.7 Hz, 1H), 8.09 (d, *J* = 8.4 Hz, 1H), 7.68 (s, 2H), 7.57 (d, *J* = 8.1 Hz, 1H), 7.35 (d, *J* = 2.1 Hz, 1H), 7.25 (s, 1H), 6.95 (s, 1H), 6.65 (dd, *J* = 3.6, 1.5 Hz, 1H), 5.94 (t, *J* = 6.0 Hz, 1H), 5.11 (d, *J* = 6.3 Hz, 2H), 3.23 (t, *J* = 5.1 Hz, 4H), 2.52 (t, *J* = 5.1 Hz, 4H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.1, 147.6, 146.0, 145.8, 144.9, 144.4, 143.7, 142.4, 141.7, 127.9 (q, *J* = 32.3 Hz), 124.9, 124.5 (q, *J* = 270.4 Hz), 120.8, 118.3, 116.8, 112.8, 109.3, 100.7, 54.4, 48.2, 45.9, 38.0; MS (EI) *m/z* 508 (M^+); HRMS calcd for $C_{25}H_{23}F_3N_8O$ (M^+) 508.1947, found: 508.1950.

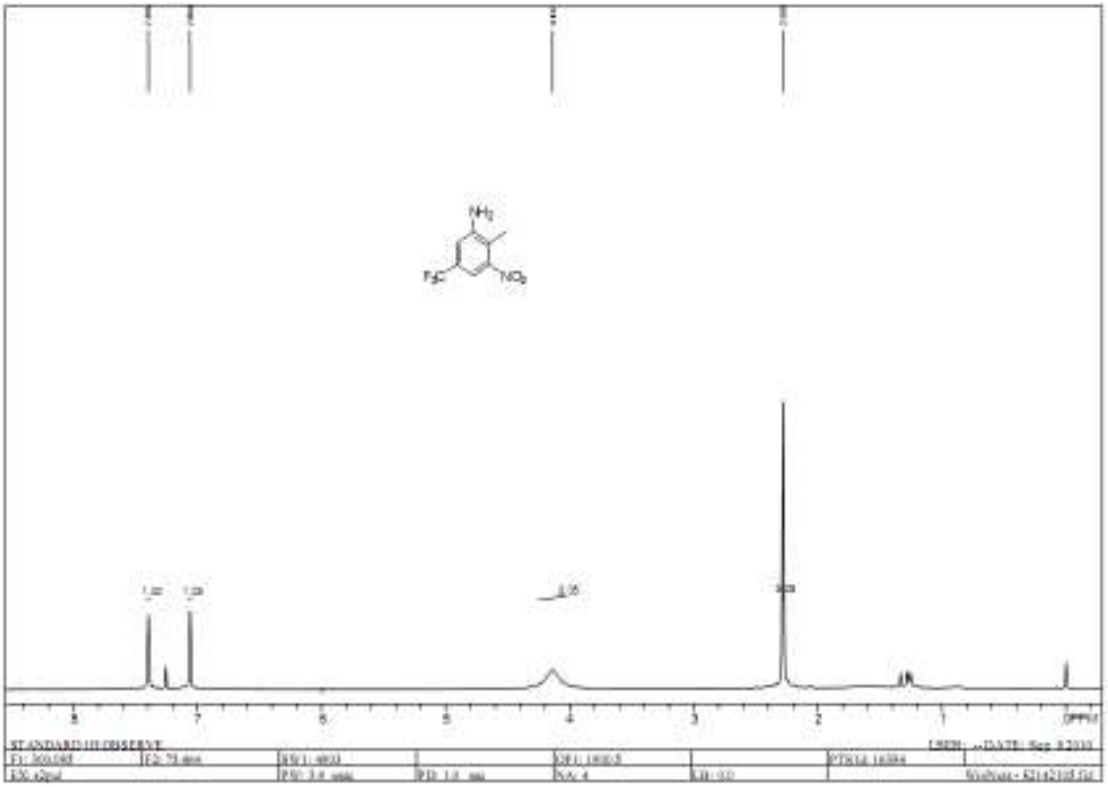
***N*-((6-(1-Methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl)-3-(4-methylpiperazin-1-yl)-7-(trifluoromethyl)quinolin-5-amine (21j):** ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.03 (m, 3H), 7.65 (s, 1H), 7.31 (m, 2H), 6.90 (s, 1H), 6.17 (s, 1H), 5.08 (d, *J* = 5.1 Hz, 2H), 4.00 (s, 3H), 3.13 (s, 4H), 2.44 (s, 4H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.8, 147.5, 144.8, 144.3, 143.6, 142.6, 141.6, 138.2, 129.8, 127.8 (q, *J* = 31.9 Hz), 124.8, 124.5 (q, *J* = 270.5 Hz), 120.8, 119.6, 117.8, 116.6, 109.3, 100.3, 54.3, 48.0, 45.8, 39.4, 37.7; MS (EI) *m/z* 522 (M^+); HRMS calcd for $C_{25}H_{25}F_3N_{10}$ (M^+) 522.2216, found: 522.2220.

2-Cyclopropyl-*N*-((6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl)-3-(4-methylpiperazin-1-yl)-7-(trifluoromethyl)quinolin-5-amine (21k): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (m, 3H), 7.52 (s, 1H), 7.50 (s, 1H), 7.22 (d, *J* = 9.9 Hz, 1H), 6.83 (s, 1H), 6.13 (s, 1H), 5.03 (d, *J* = 4.8 Hz, 2H), 3.95 (s, 3H), 2.92 (s, 4H), 2.47 (br, 5H), 2.21 (s, 3H), 1.24 (br, 2H), 0.99 (br, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 143.4, 142.2, 140.7, 138.4, 138.3, 137.8, 133.0, 124.6, 123.6 (q, *J* = 31.5 Hz), 129.5, 119.4 (q, *J* = 270.8 Hz), 114.3, 113.5, 112.6, 110.7, 109.1, 93.8, 49.8, 46.3, 40.7, 34.2, 32.5, 7.8, 5.8; MS (EI) *m/z* 562 (M^+); HRMS calcd for $C_{28}H_{29}F_3N_{10}$ (M^+) 562.2529, found: 562.2538.

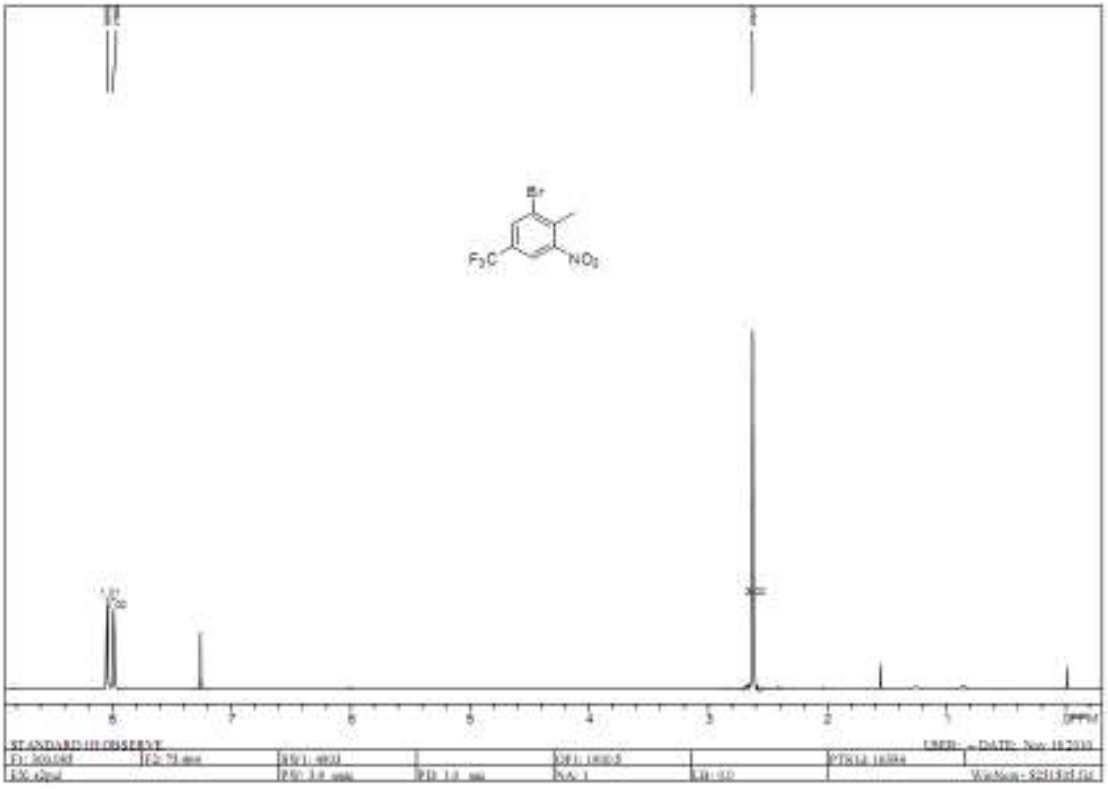
3. ELISA Kinase Assay. The tyrosine kinase activities were evaluated according to our reported protocol. Briefly, in enzyme-linked-immunosorbent assay (ELISA), 20 μg/ml Poly(Glu,Tyr) 4:1 (Sigma) was pre-coated as a substrate in 96-well plates. 50 μL of 10 μM ATP solution diluted in kinase reaction buffer (50 mM HEPES pH 7.4, 50 mM $MgCl_2$, 0.5 mM $MnCl_2$, 0.2 mM Na_3VO_4, 1mM DTT) was added to each well. Various concentrations of compounds diluted in 10 μL of 1% DMSO (v/v) were added to each reaction well, with 1% DMSO (v/v) used as the negative control. The kinase reaction was initiated by the addition of purified tyrosine kinase proteins diluted in 40 μL of kinase reaction buffer solution. After incubation for 60 min at 37°C, the plate was washed three times with Phosphate Buffered Saline (PBS) containing 0.1% Tween 20 (T-PBS). Next, 100 μL of anti-phosphotyrosine (PY99) antibody (1:500 diluted in 5 mg/mL BSA T-PBS) was added. After 30 min incubation at 37°C, the plate was washed three times. A solution of 100 μL horseradish peroxidase-conjugated goat anti-mouse IgG (1:2000 diluted in 5 mg/mL BSA T-PBS) was added. The plate was reincubated at 37°C for 30 min, and washed as before. Finally, 100 μL of a solution containing 0.03% H_2O_2 and 2 mg/mL *o*-phenylenediamine in 0.1mM citrate buffer, pH 5.5, was added and samples were incubated at room temperature until color emerged. The reaction was terminated by the addition of 50 μL of 2M H_2SO_4, and the plate was read using a multiwell spectrophotometer (VERSAmax™, Molecular Devices, Sunnyvale, CA,USA) at 490 nm. The inhibition rate (%) was calculated using the following equation: [1-(A490/A490 control)] x 100%. IC_{50} values were calculated from the inhibition curves.

4. Copies of 1H and 13C NMR spectra of the final quinolines

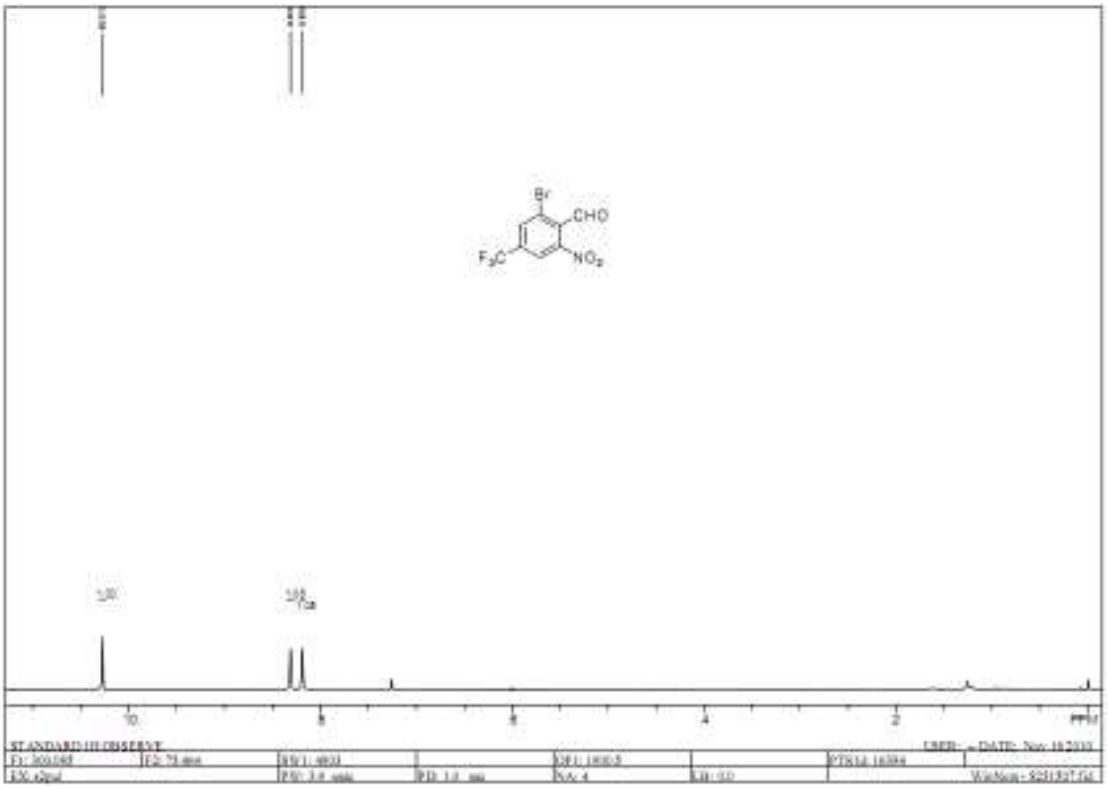
^{1}H NMR spectrum of **6**



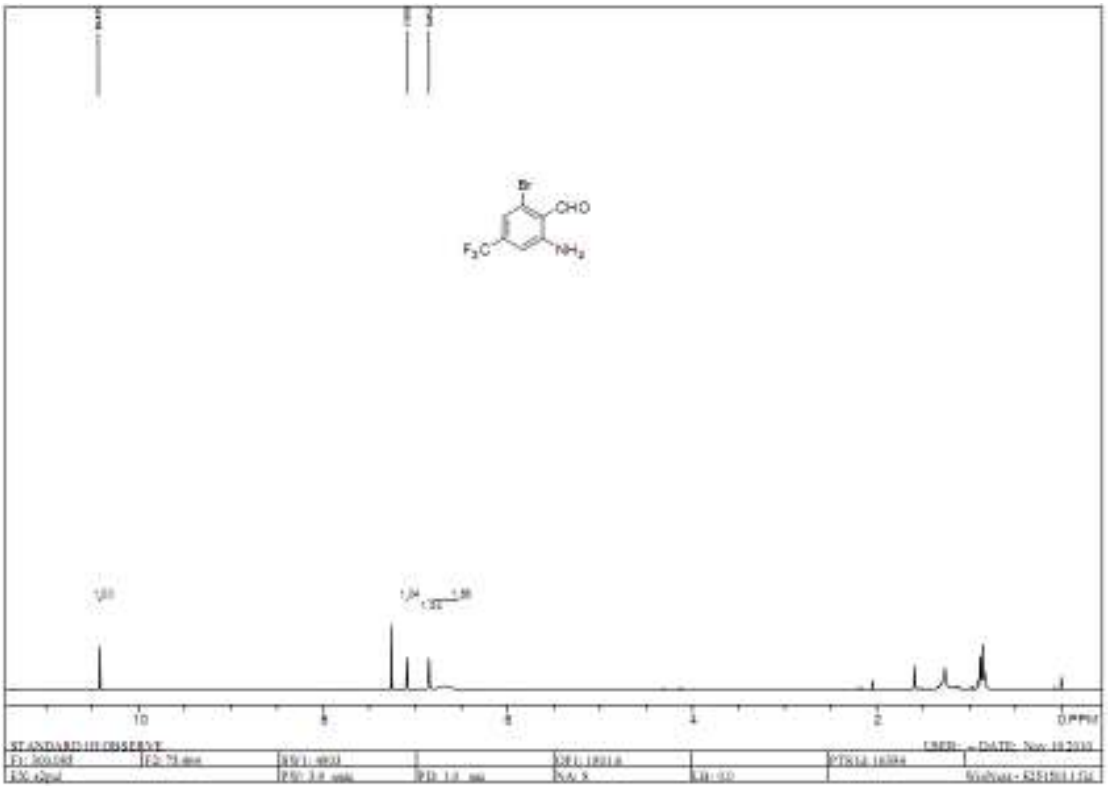
^{1}H NMR spectrum of **7**



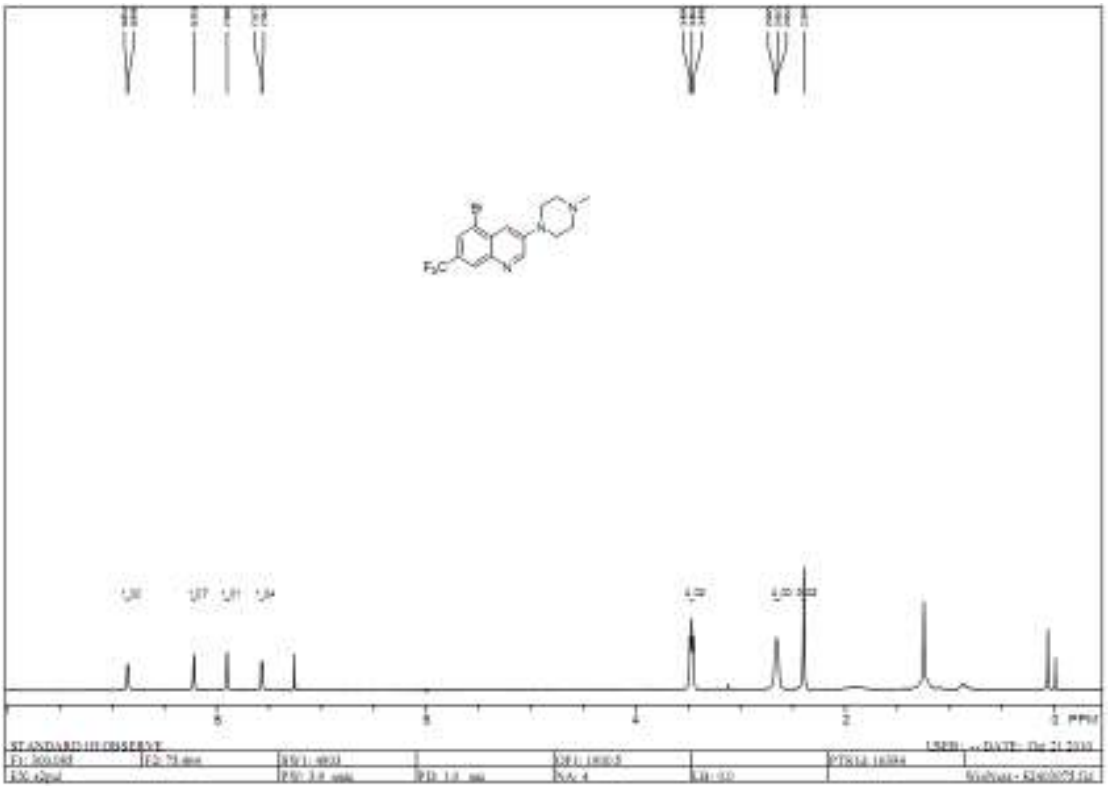
^{1}H NMR spectrum of **8**



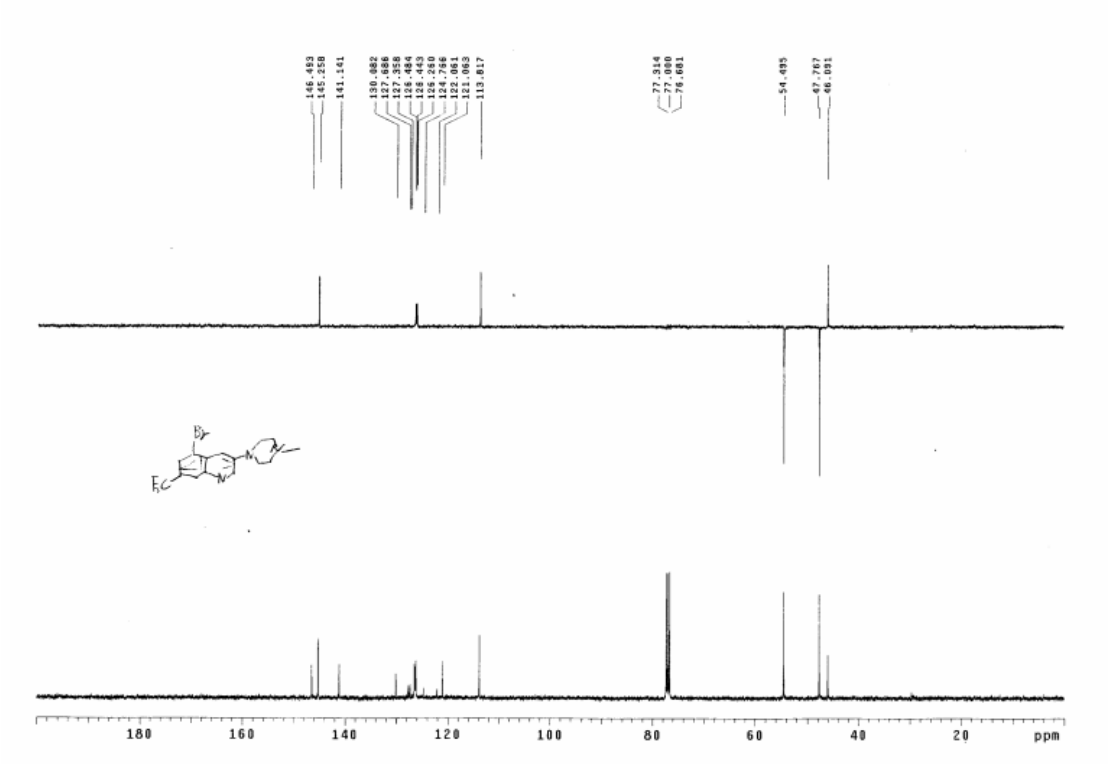
^{1}H NMR spectrum of **9**



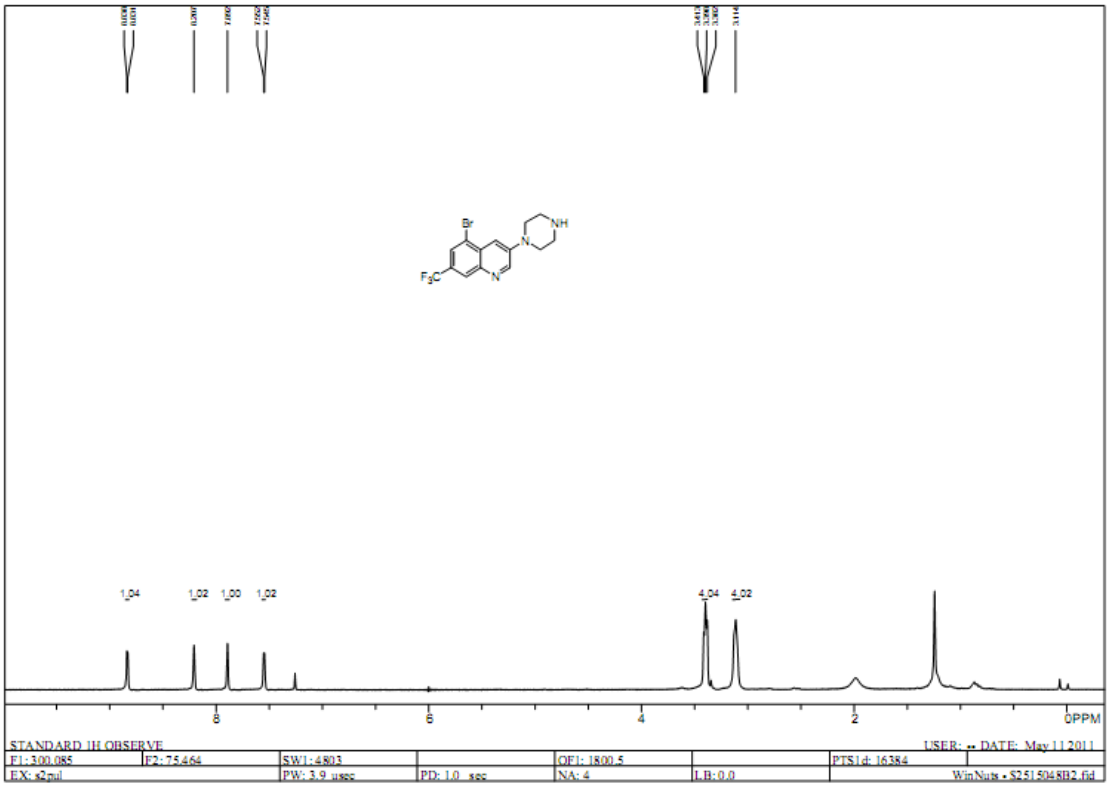
^{1}H NMR spectrum of **11a**



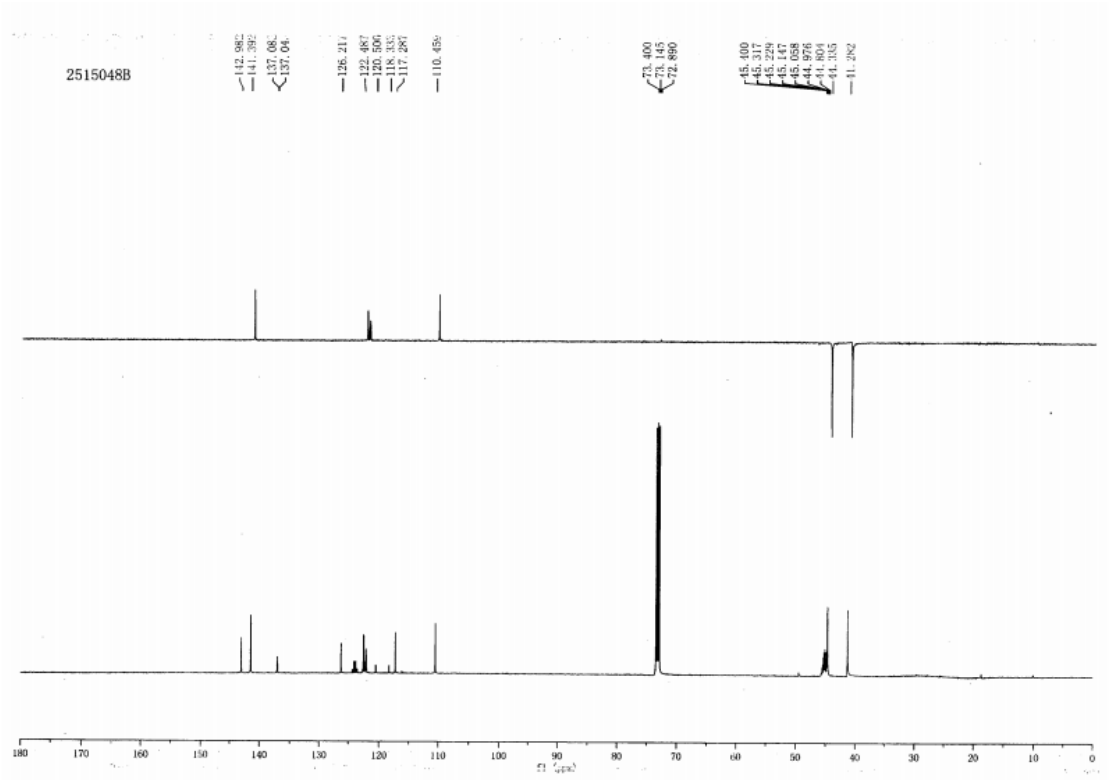
^{13}C NMR spectrum of **11a**



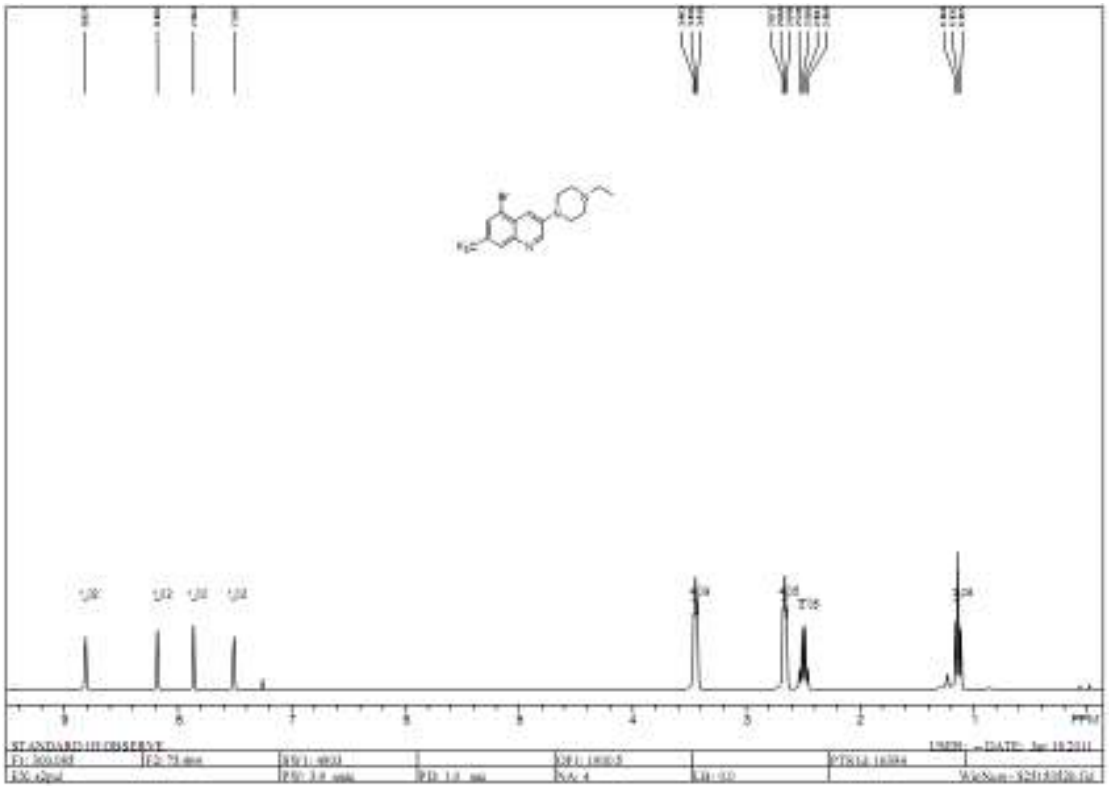
^{1}H NMR spectrum of **11b**



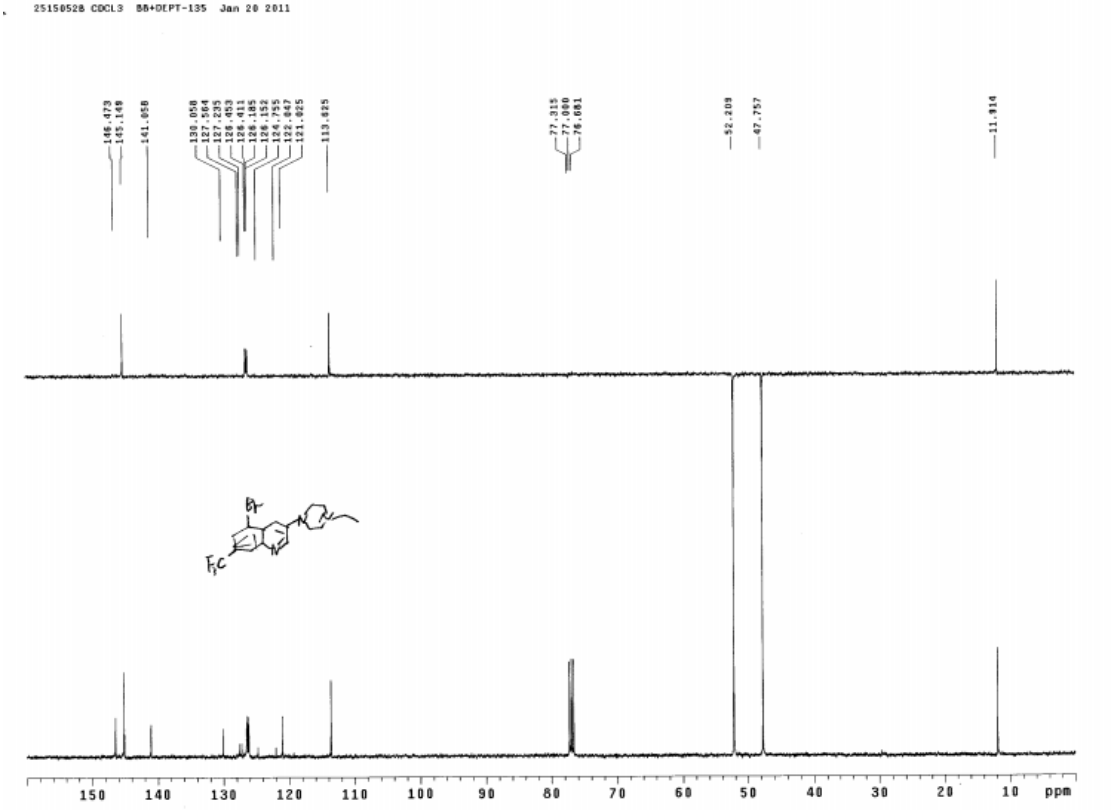
^{13}C NMR spectrum of **11b**



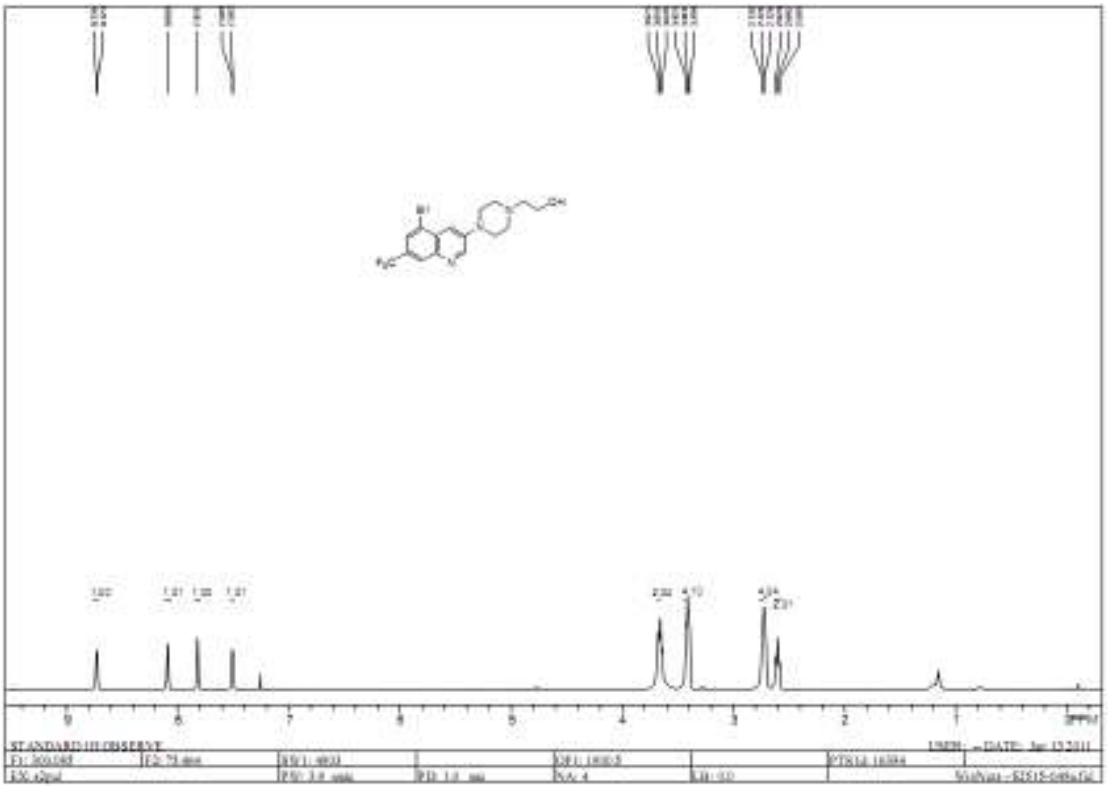
^{1}H NMR spectrum of **11c**



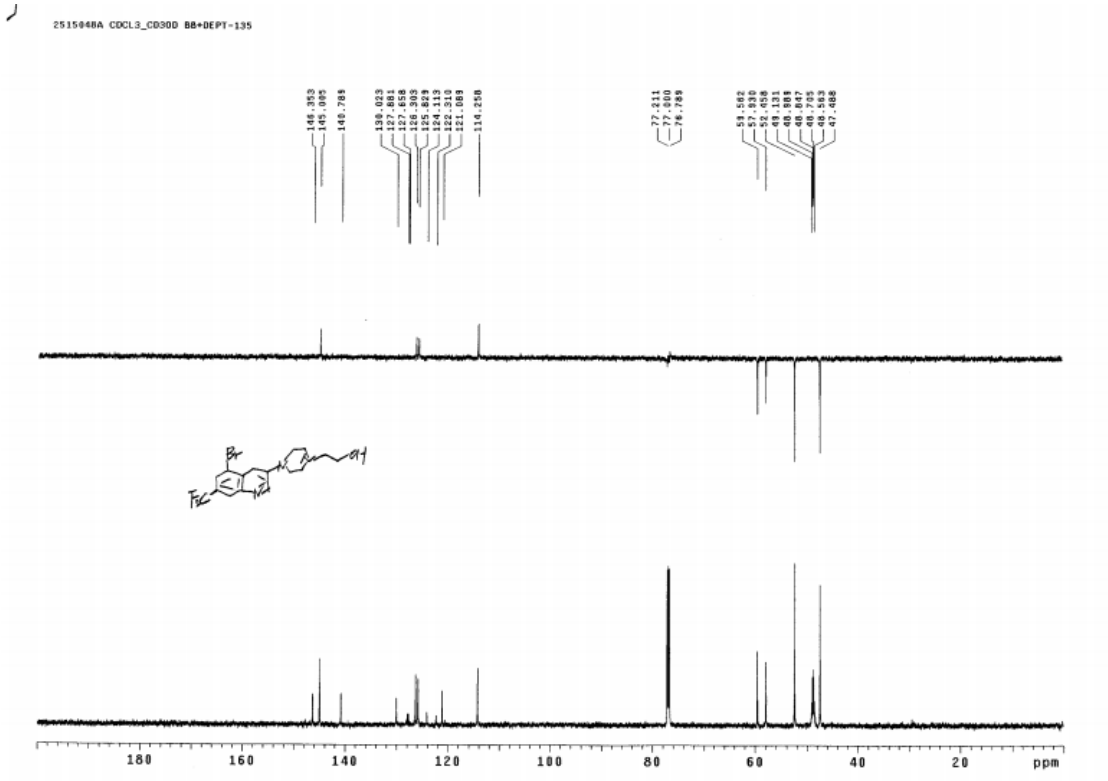
^{13}C NMR spectrum of **11c**



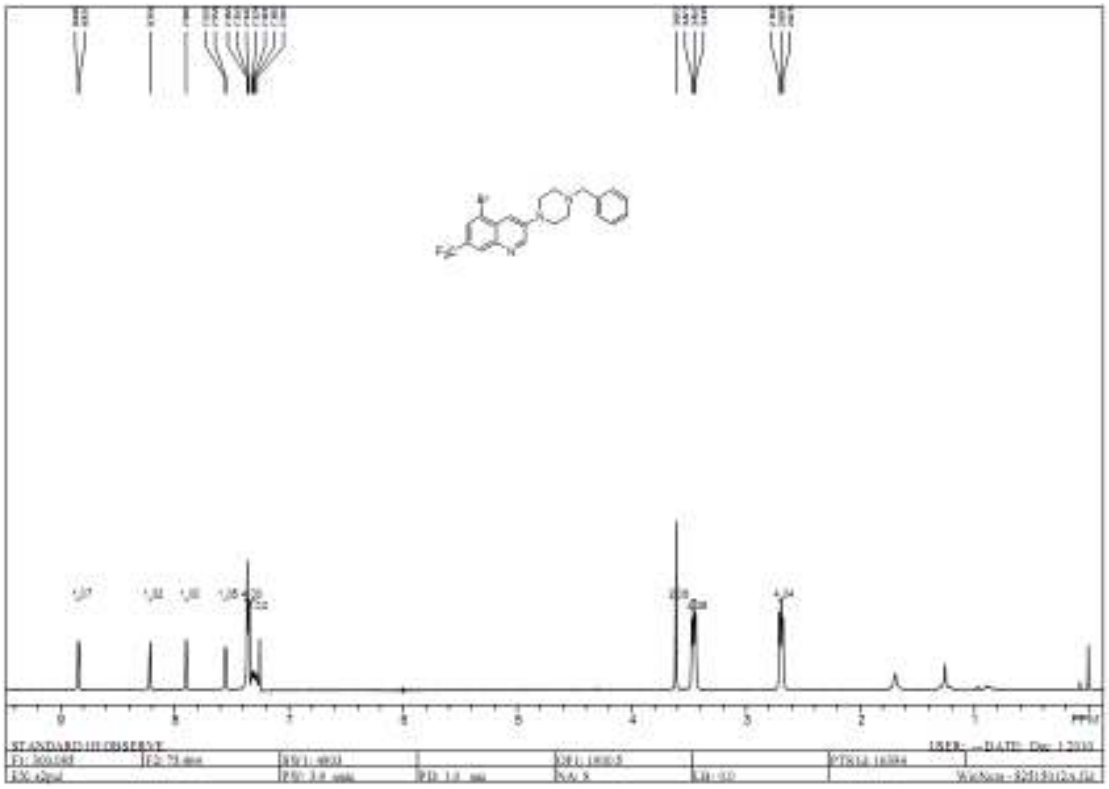
^{1}H NMR spectrum of **11d**



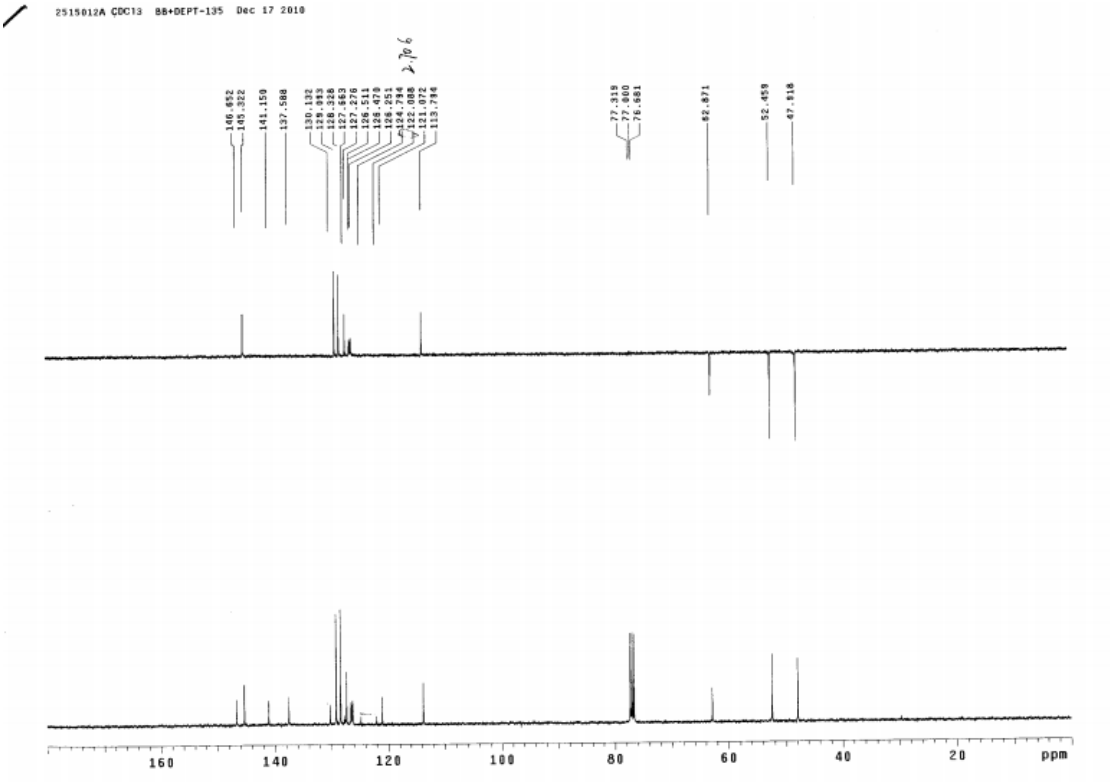
^{13}C NMR spectrum of **11d**



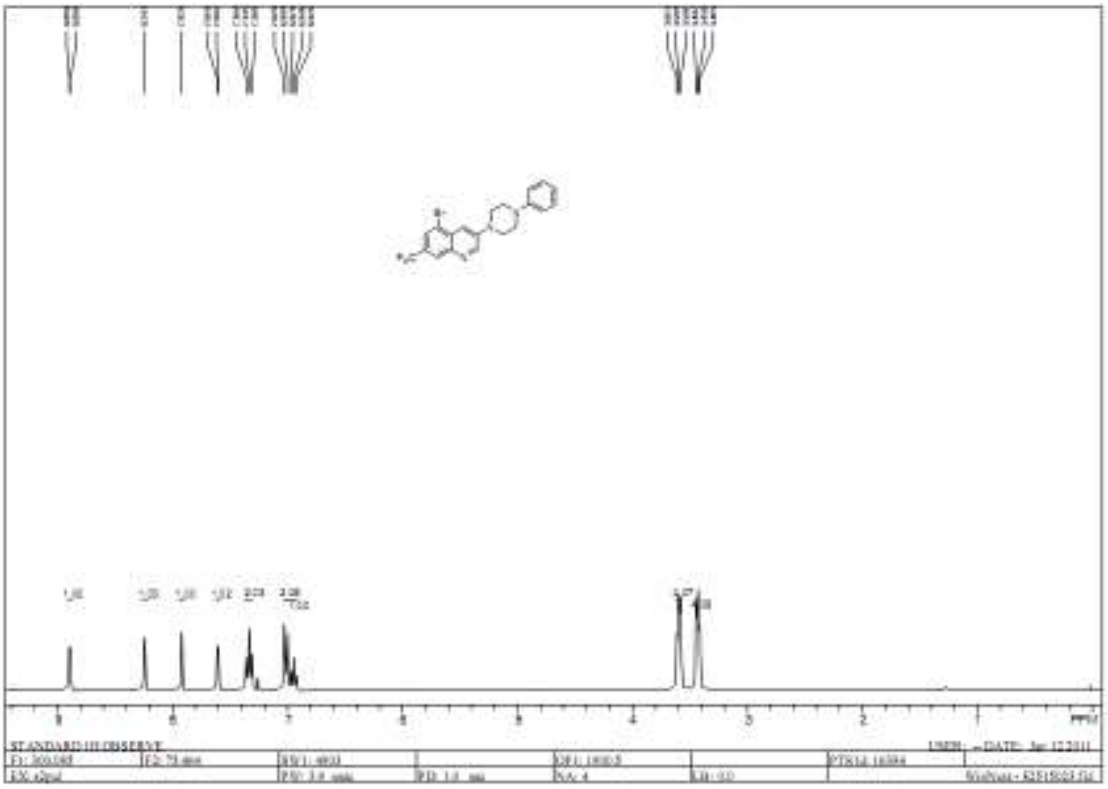
^{1}H NMR spectrum of **11e**



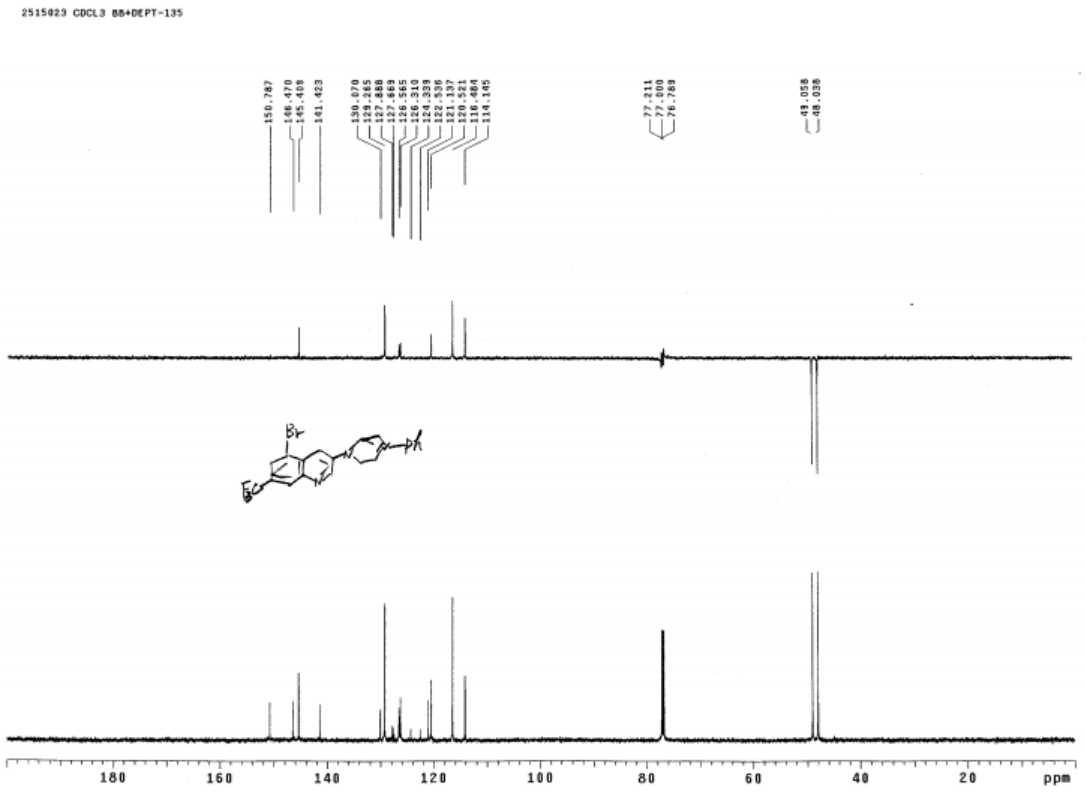
^{13}C NMR spectrum of **11e**



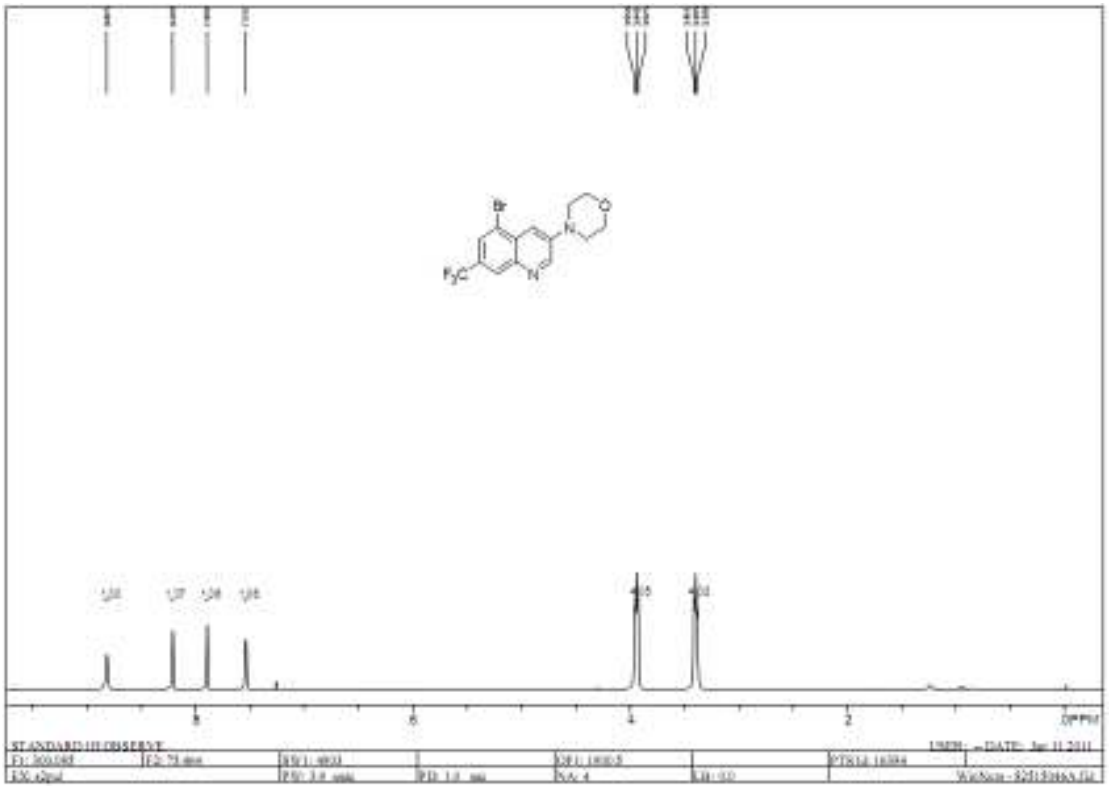
^{1}H NMR spectrum of **11f**



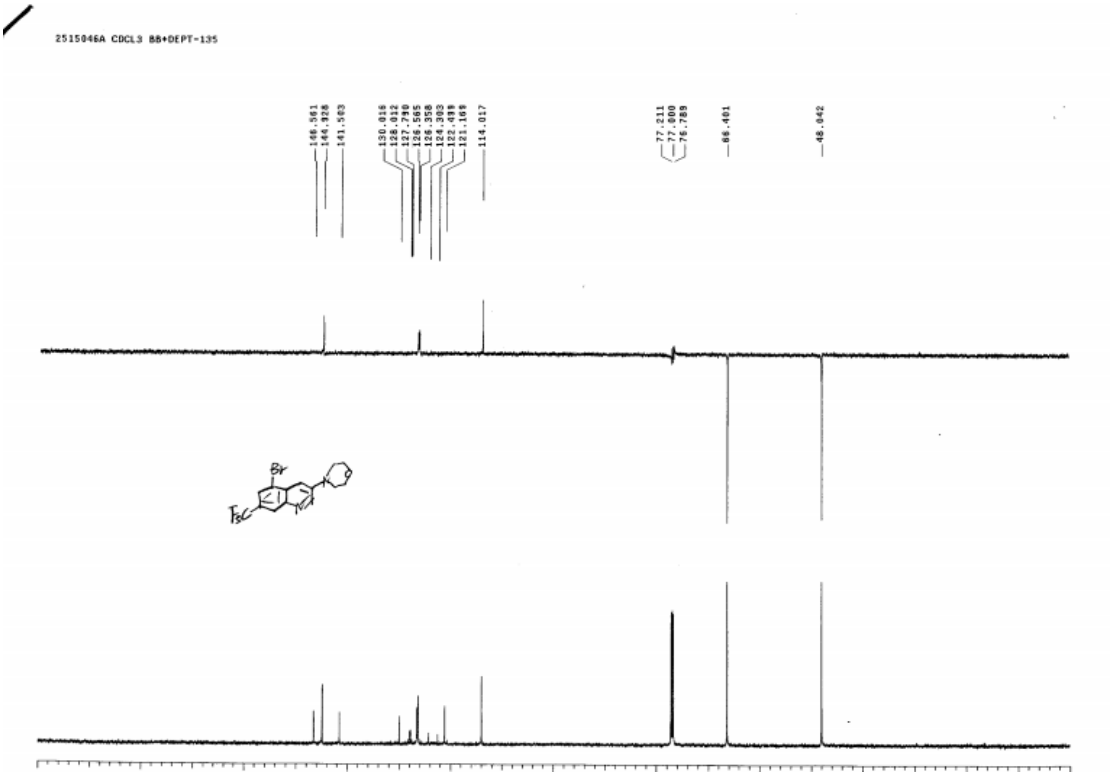
^{13}C NMR spectrum of **11f**



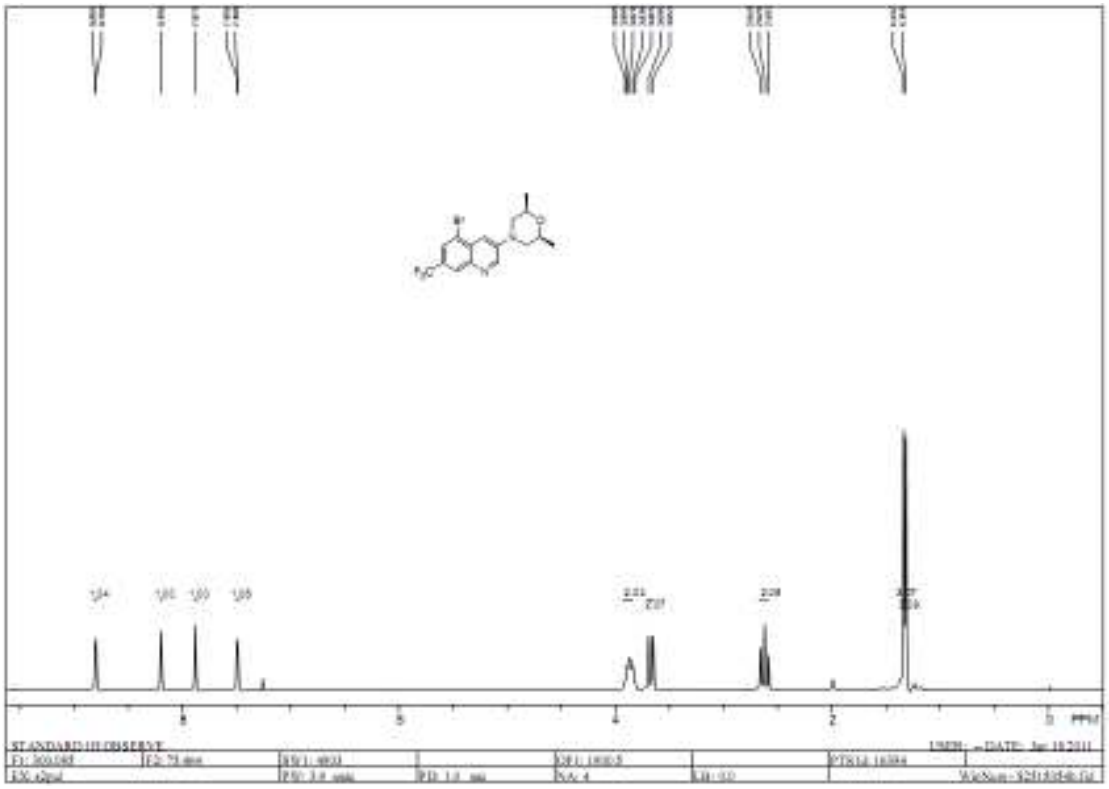
^{1}H NMR spectrum of **11g**



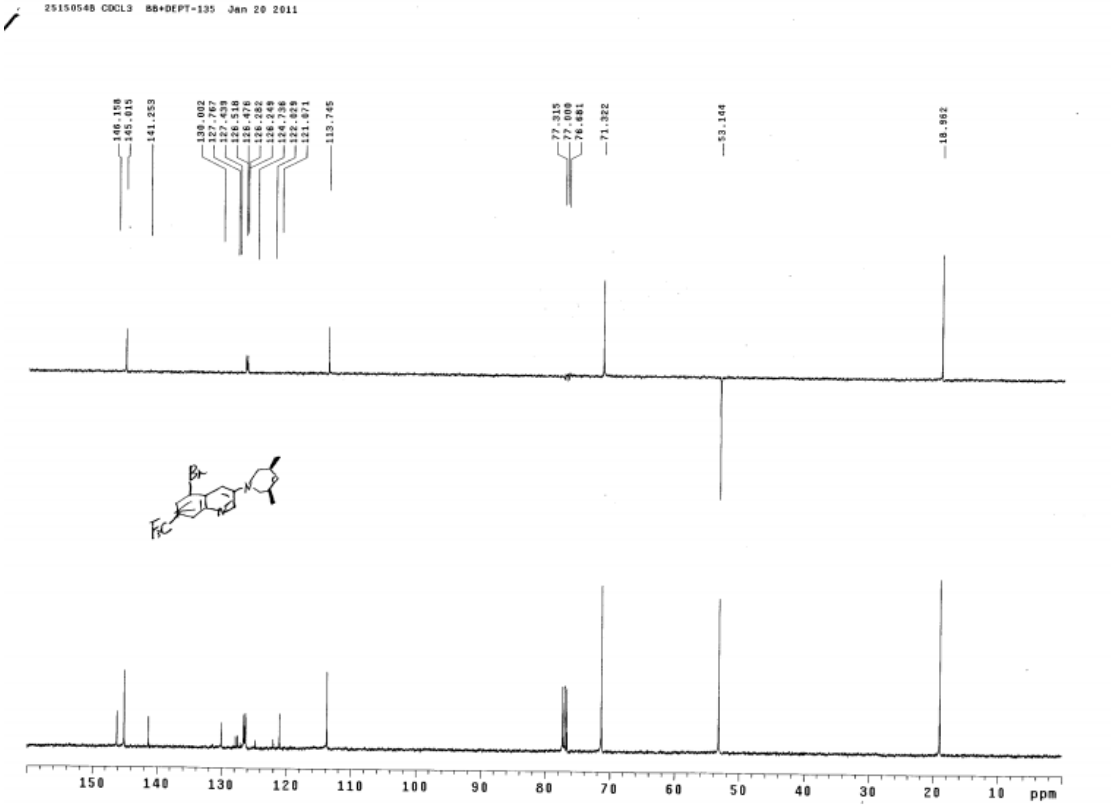
^{13}C NMR spectrum of **11g**



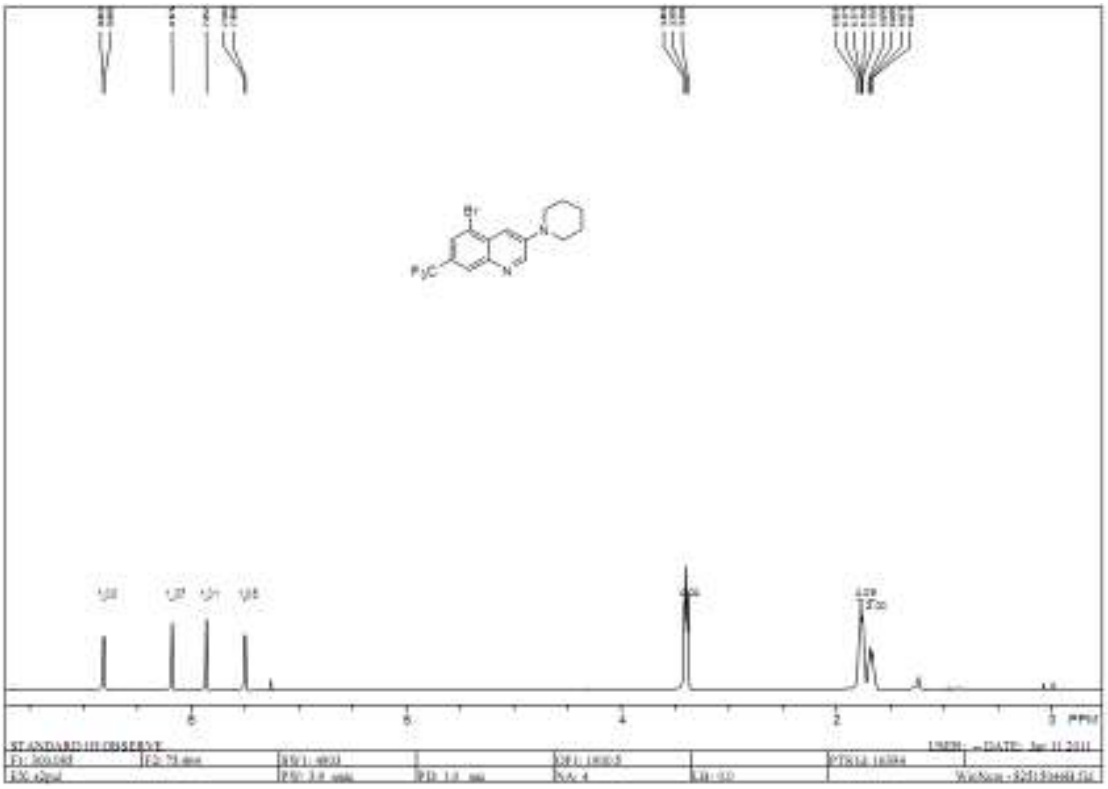
^{1}H NMR spectrum of **11h**



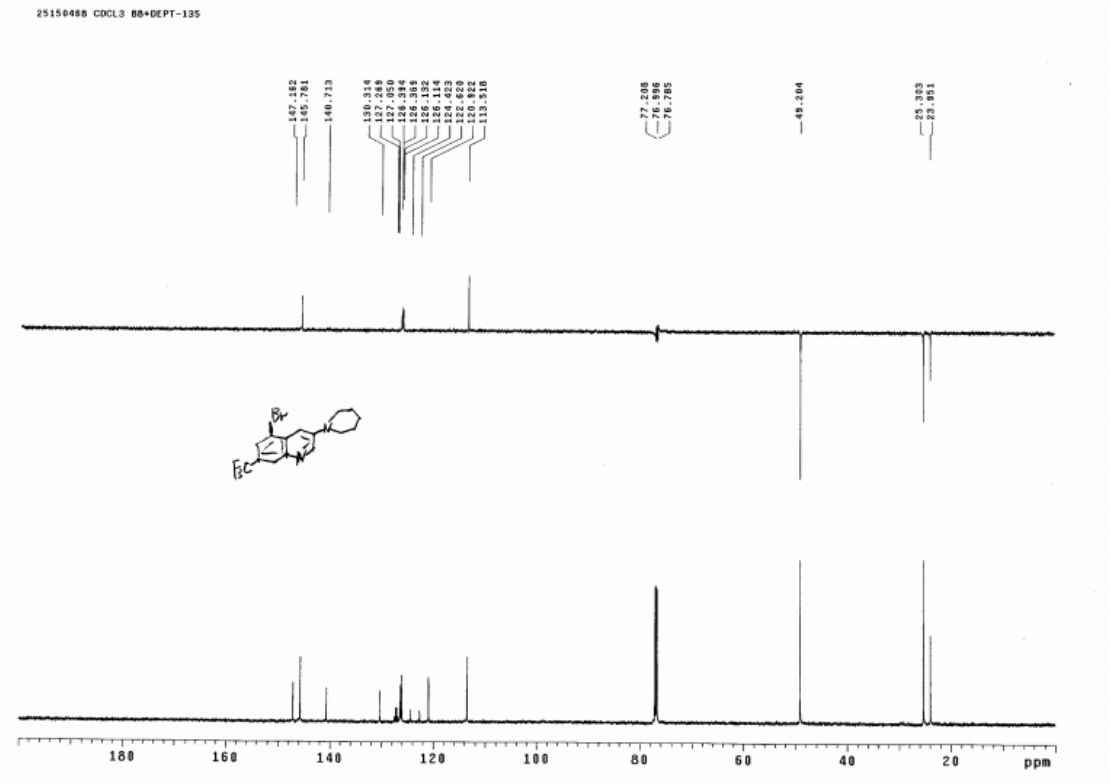
^{13}C NMR spectrum of **11h**



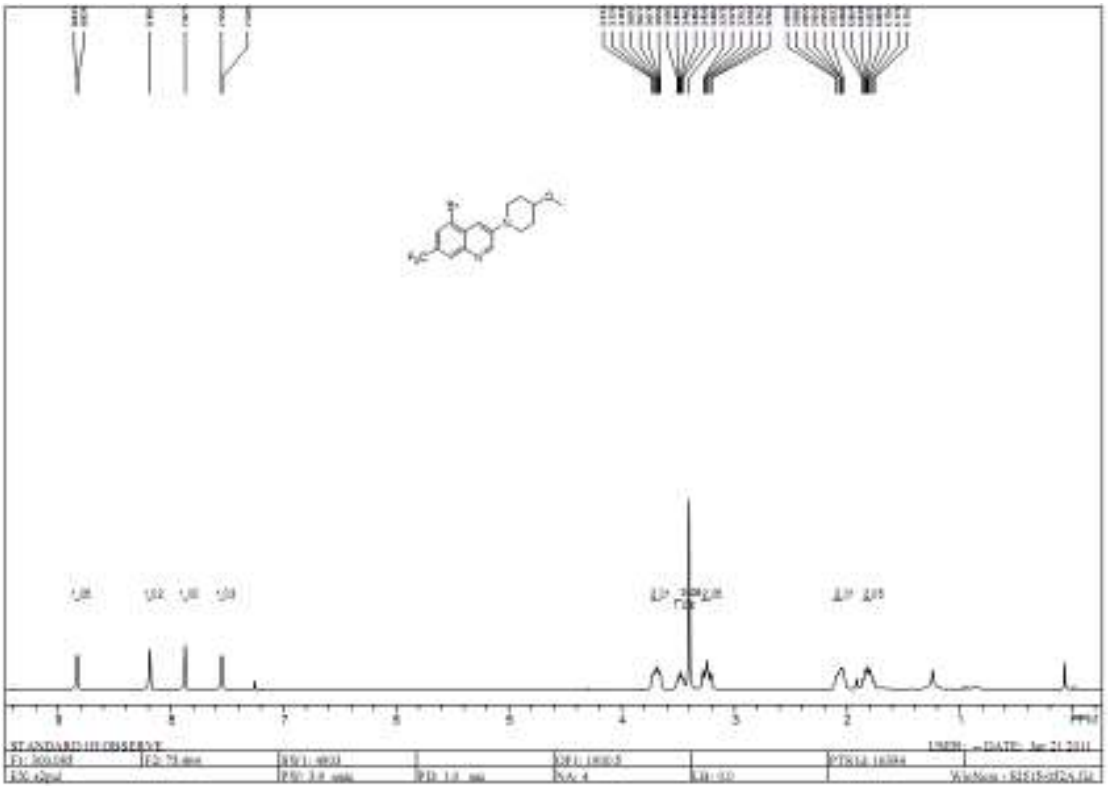
^{1}H NMR spectrum of **11i**



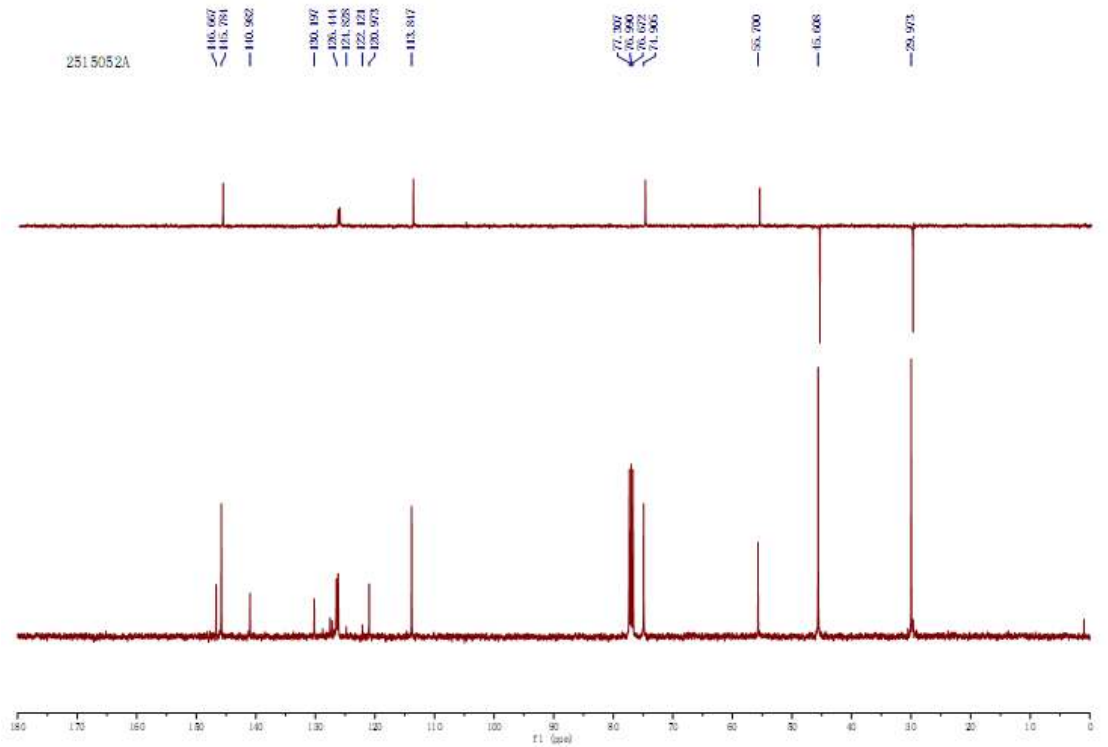
^{13}C NMR spectrum of **11i**



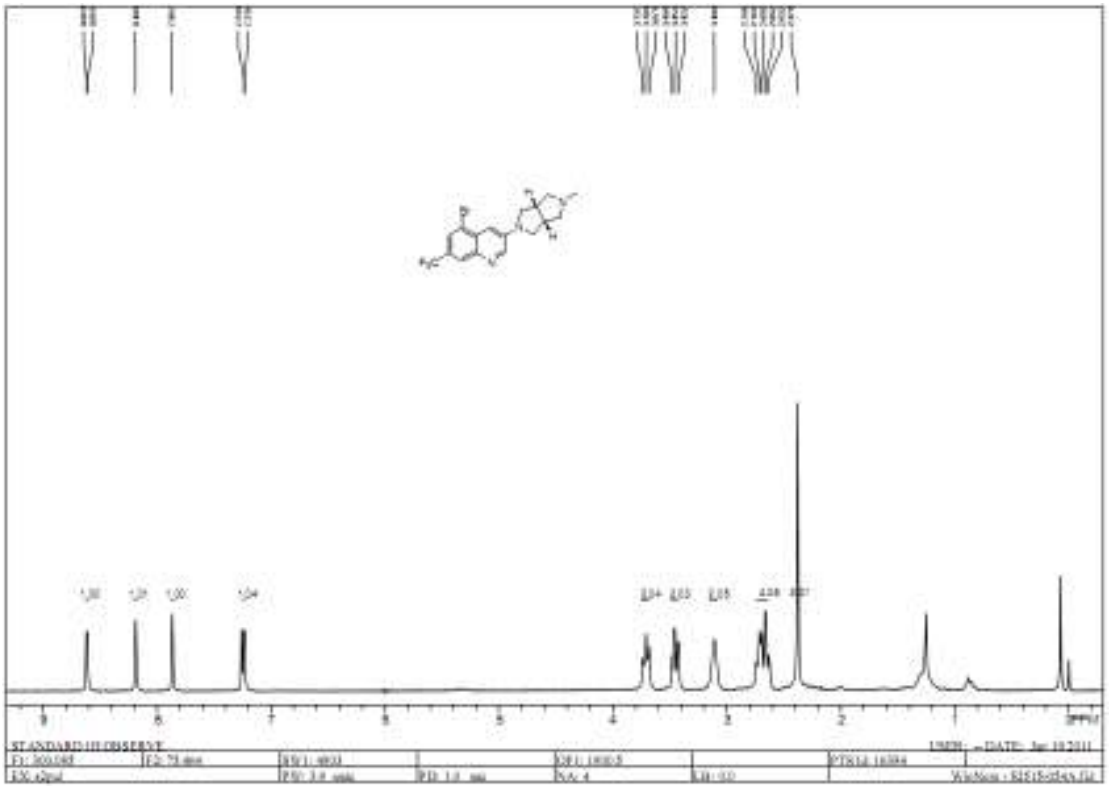
^{1}H NMR spectrum of **11j**



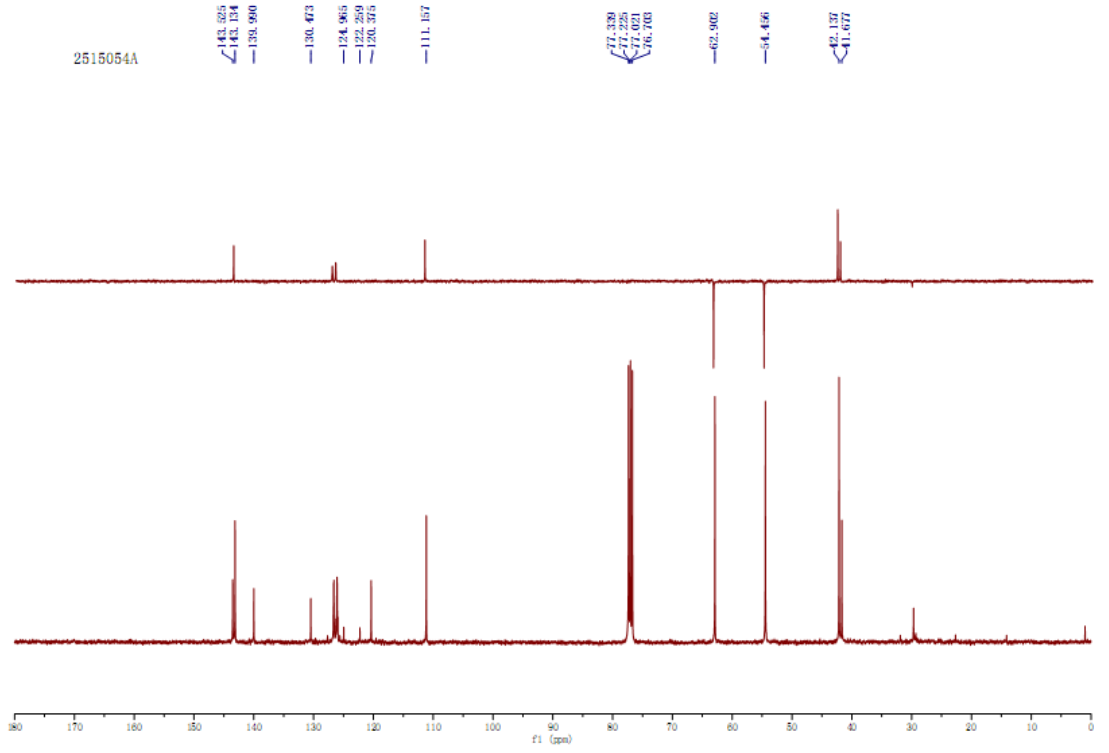
^{13}C NMR spectrum of **11j**



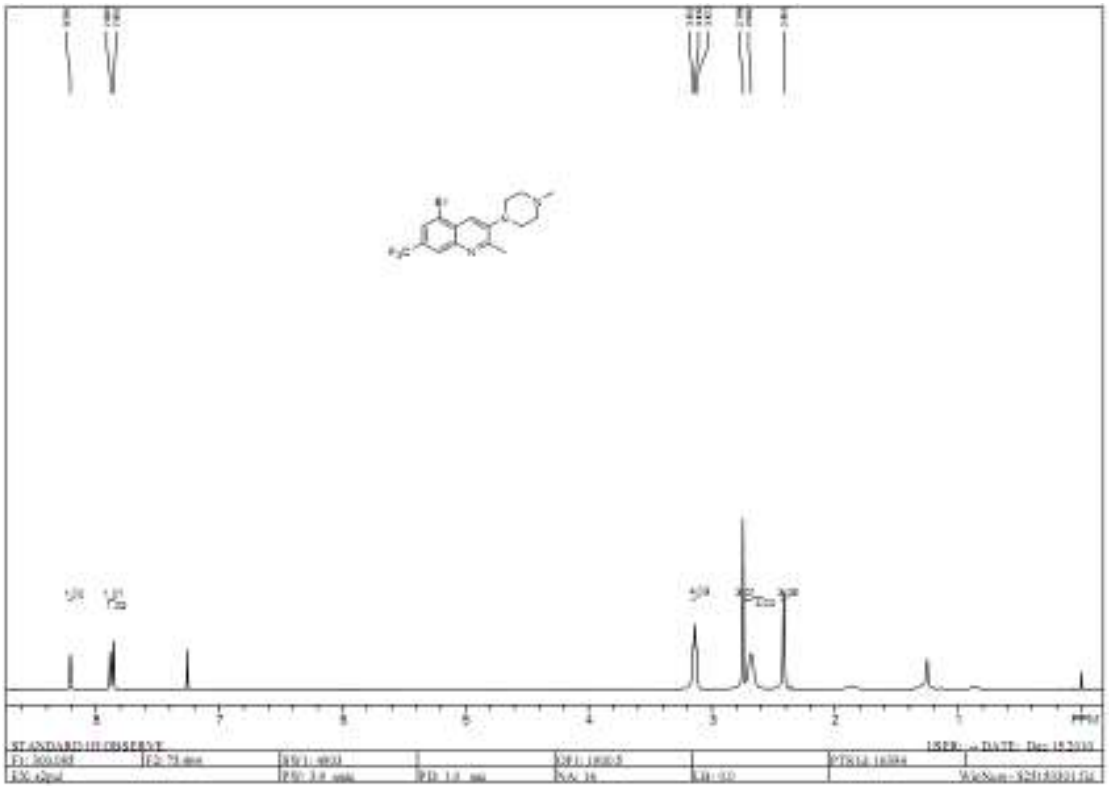
^{1}H NMR spectrum of **11k**



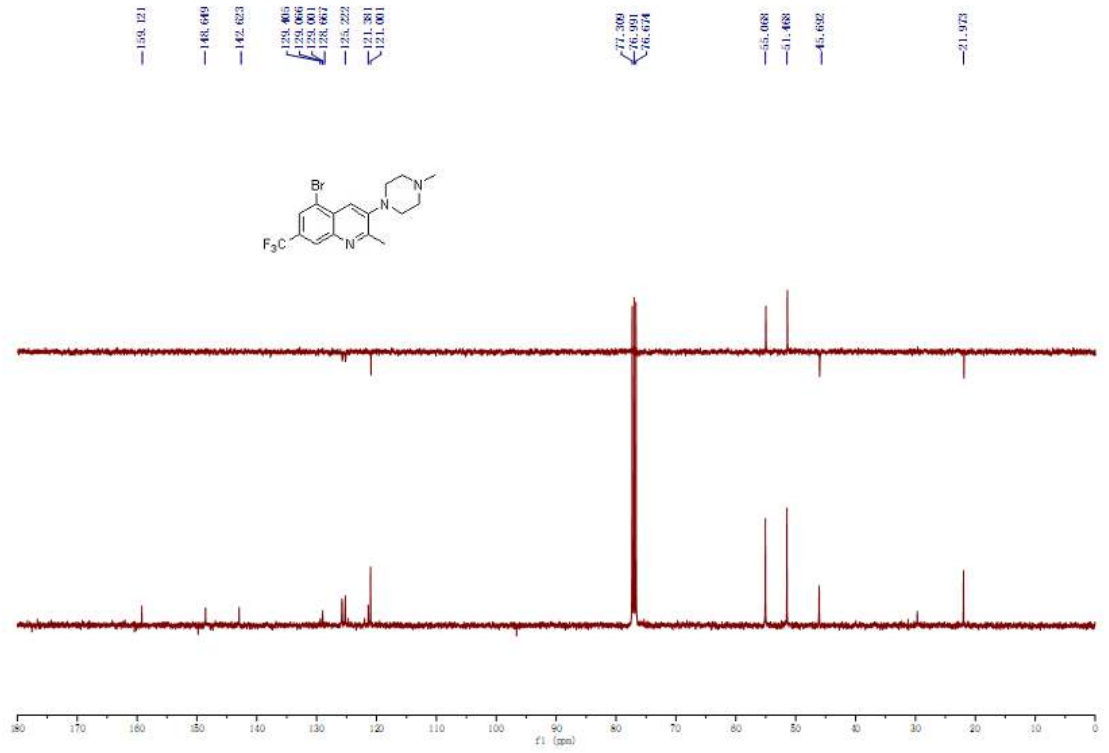
^{13}C NMR spectrum of **11k**



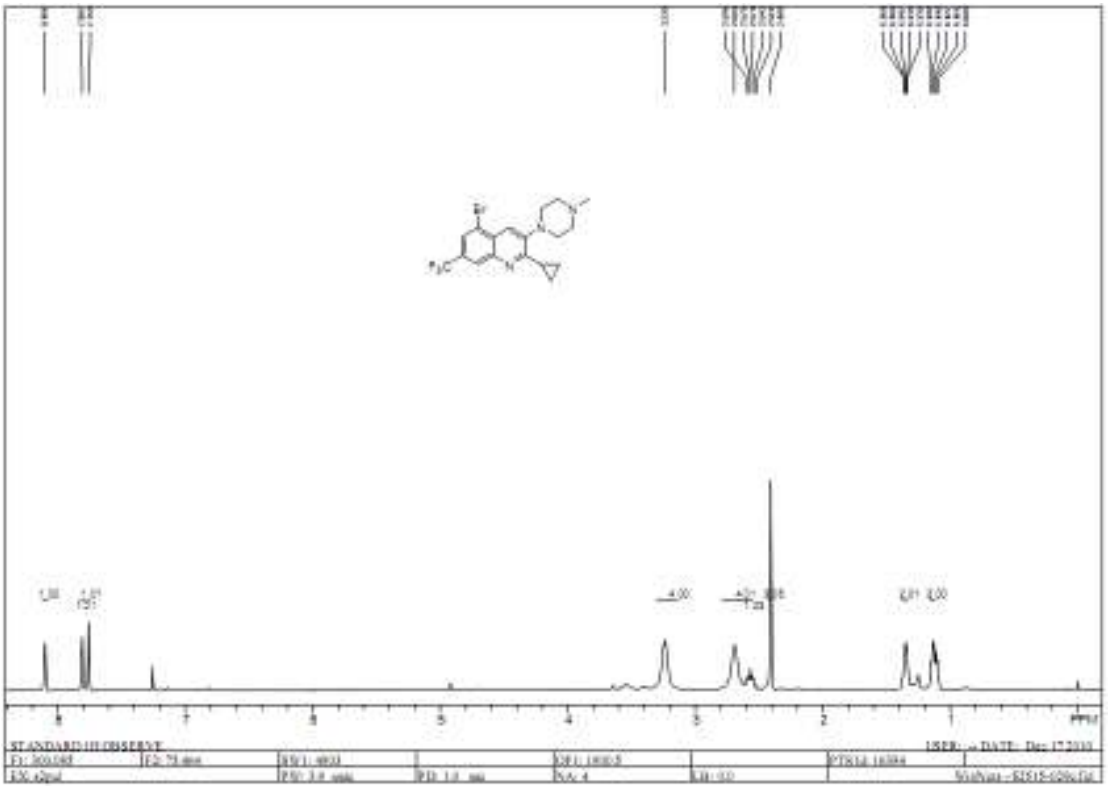
^{1}H NMR spectrum of **17a**



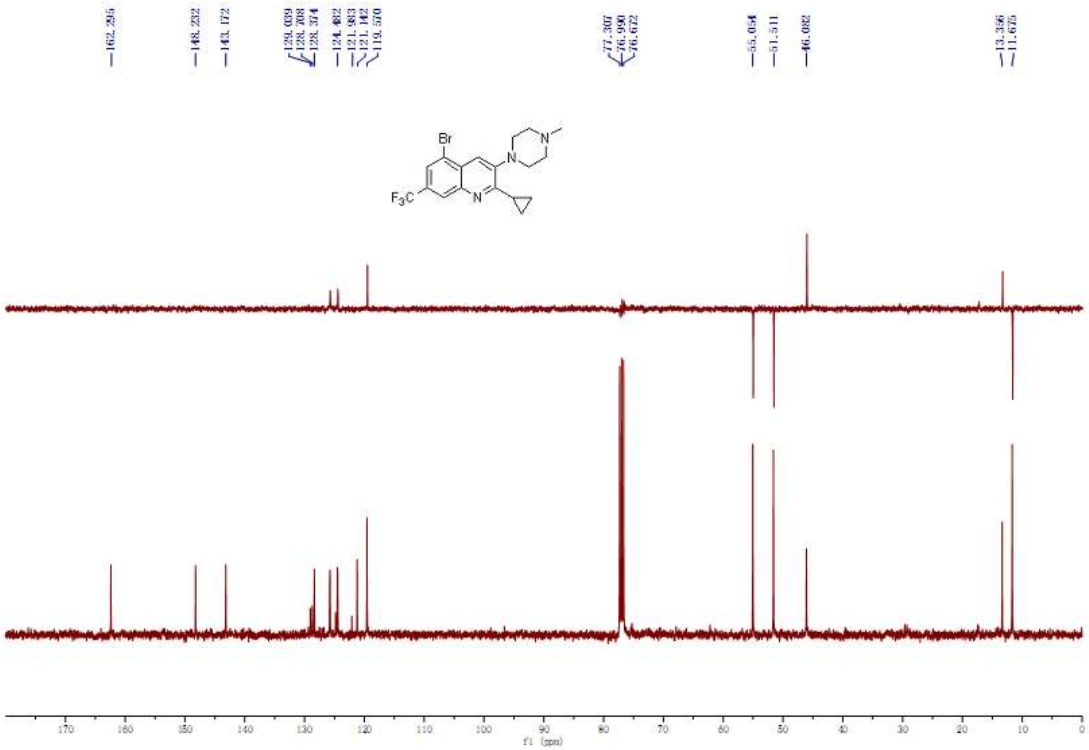
^{13}C NMR spectrum of **17a**



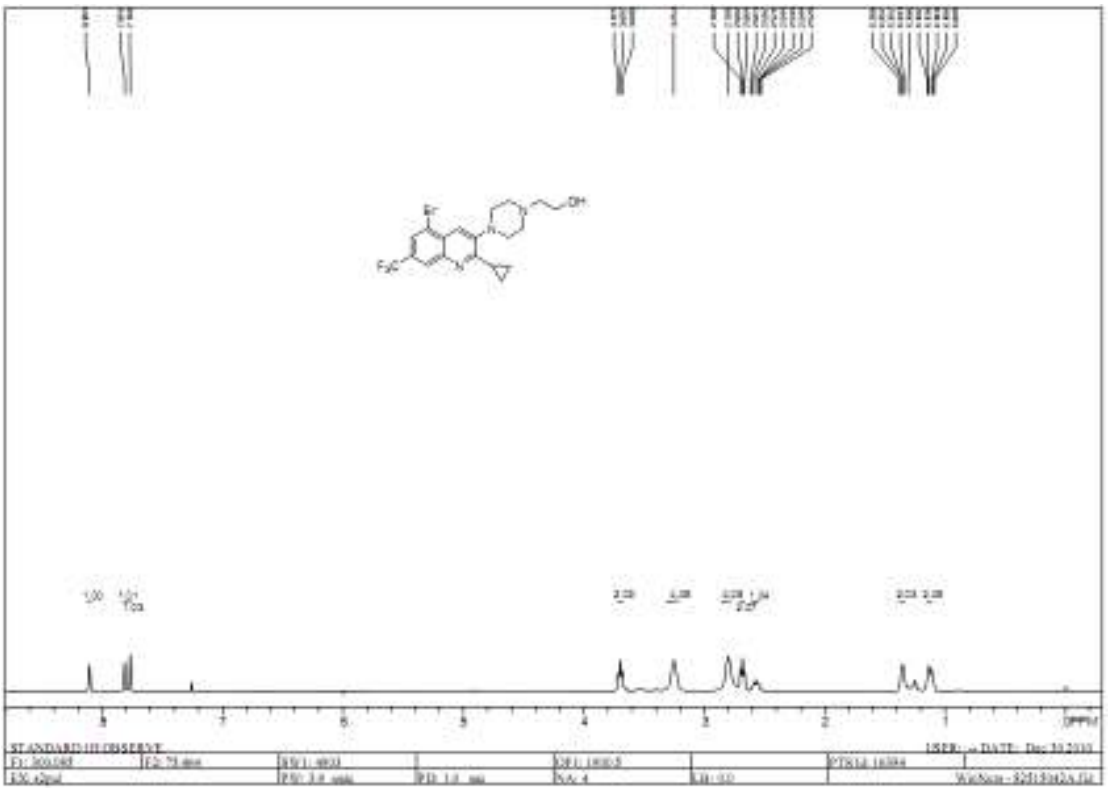
^{1}H NMR spectrum of **17b**



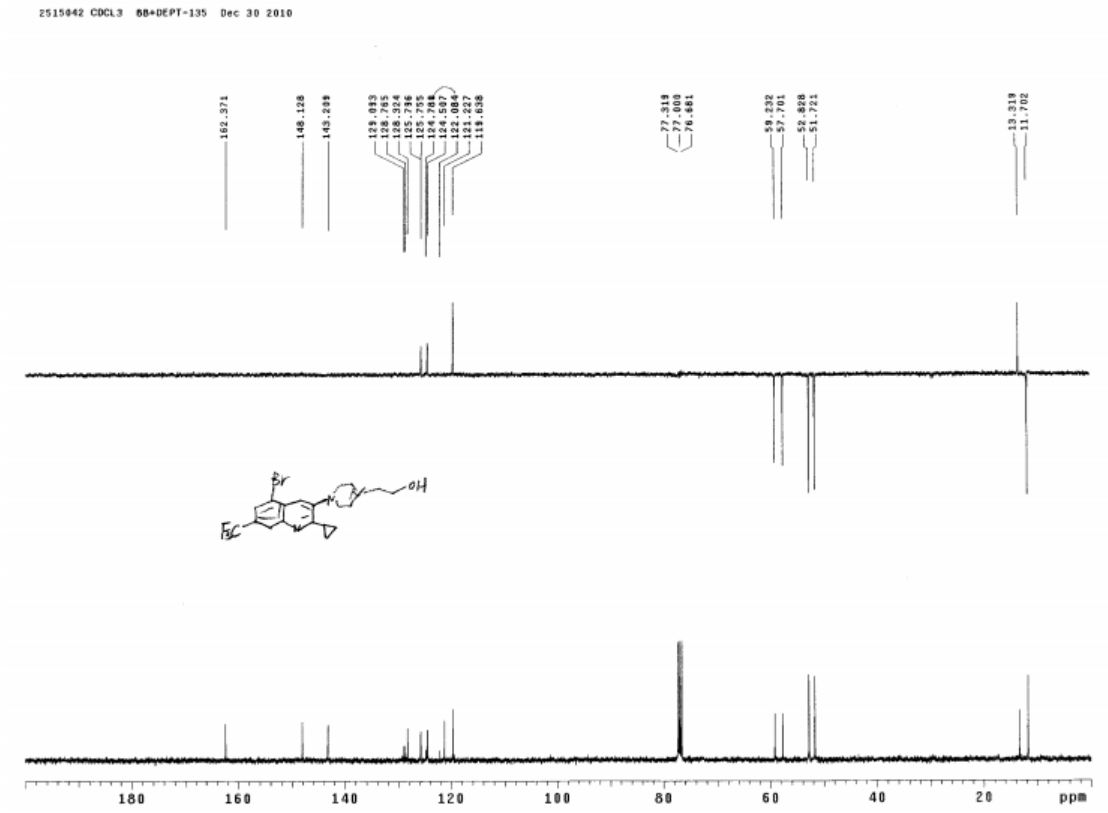
^{13}C NMR spectrum of **17b**



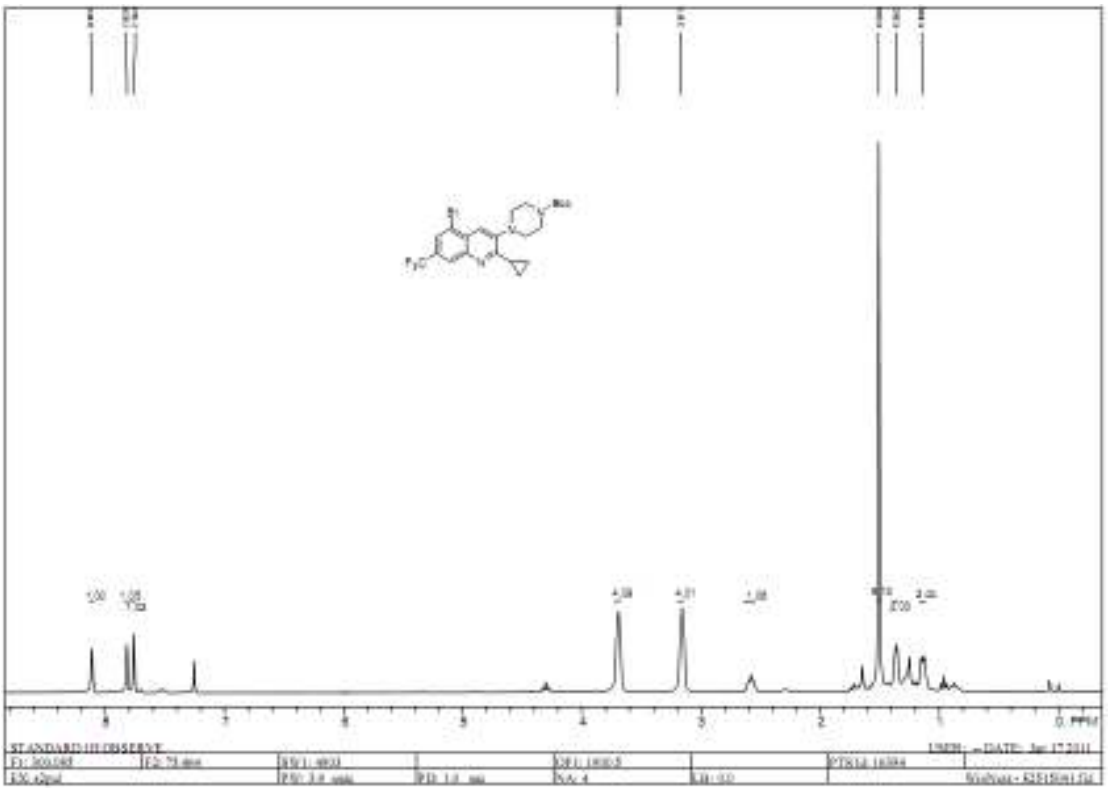
^{1}H NMR spectrum of **17c**



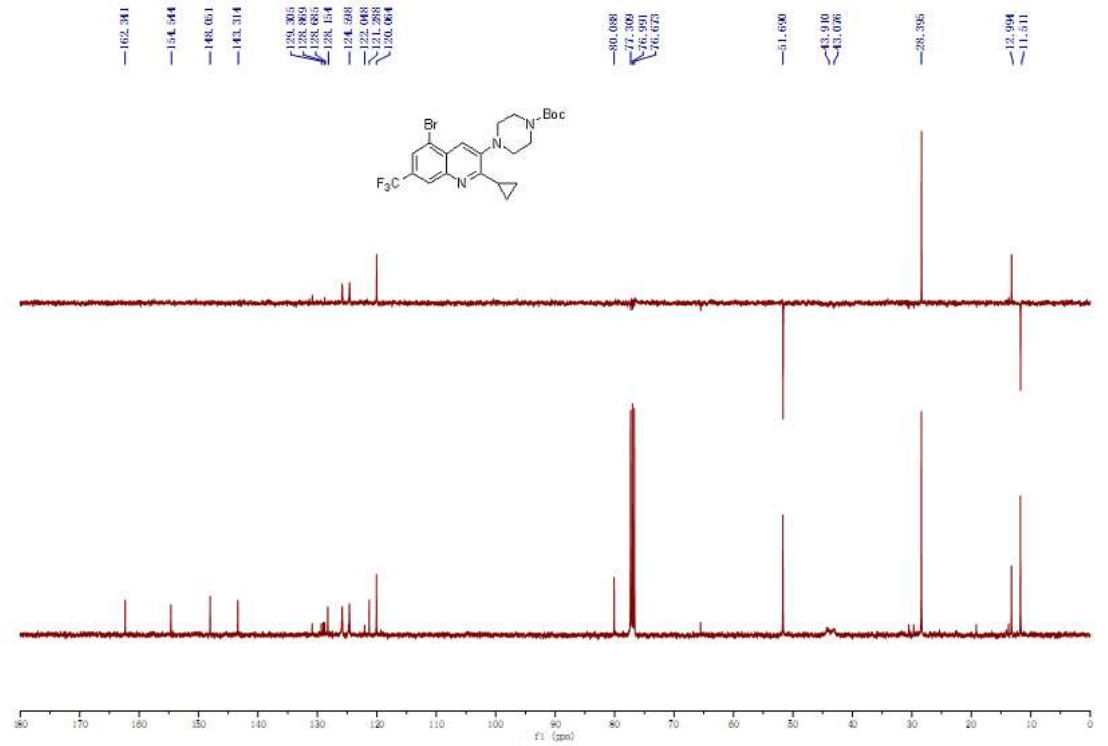
^{13}C NMR spectrum of **17c**



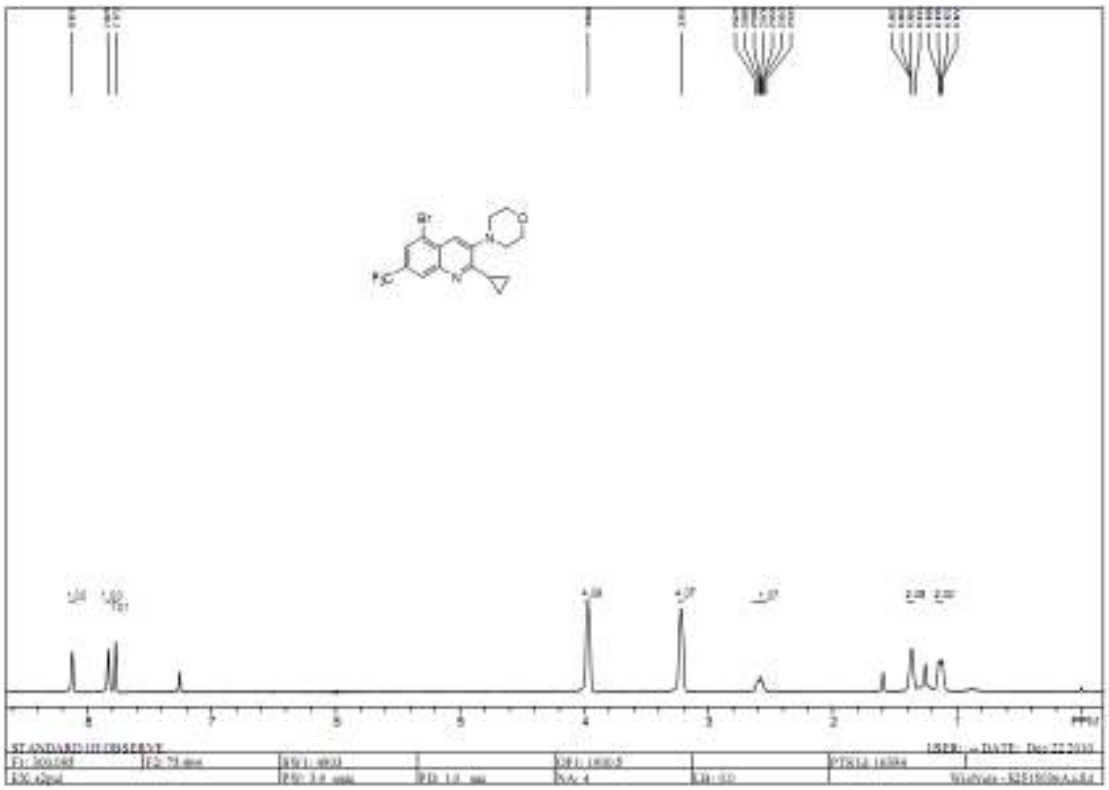
^{1}H NMR spectrum of **17d**



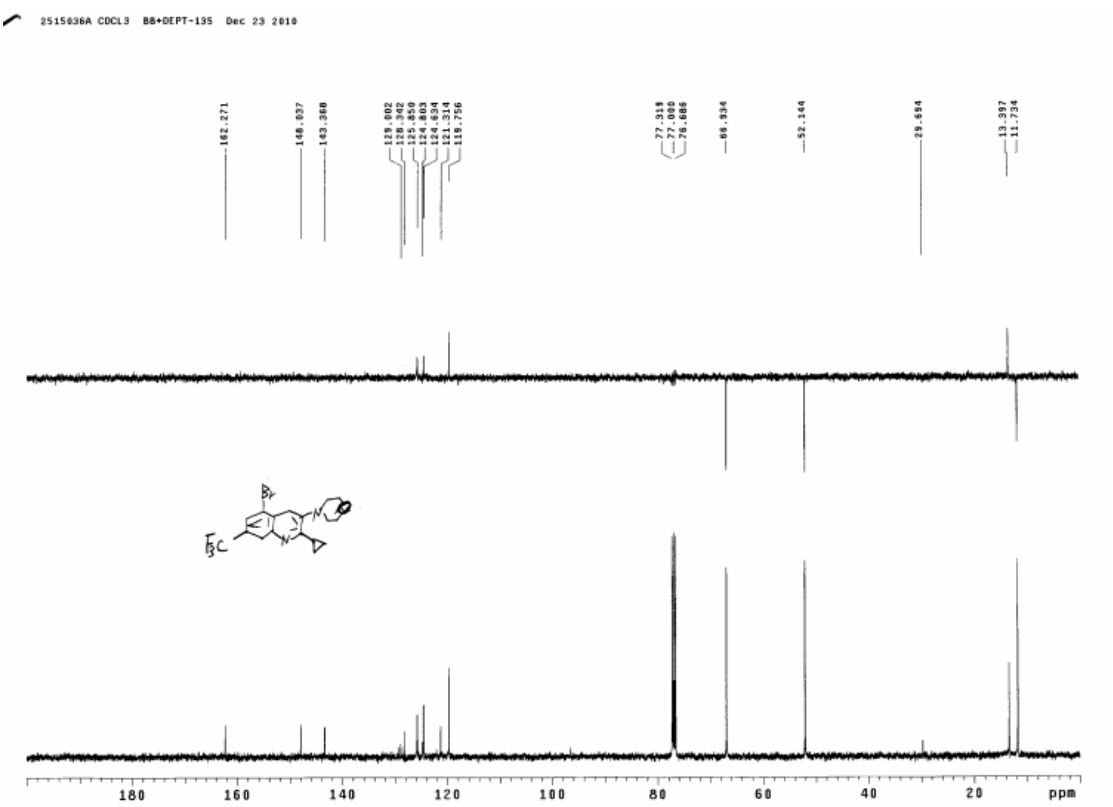
^{13}C NMR spectrum of **17d**



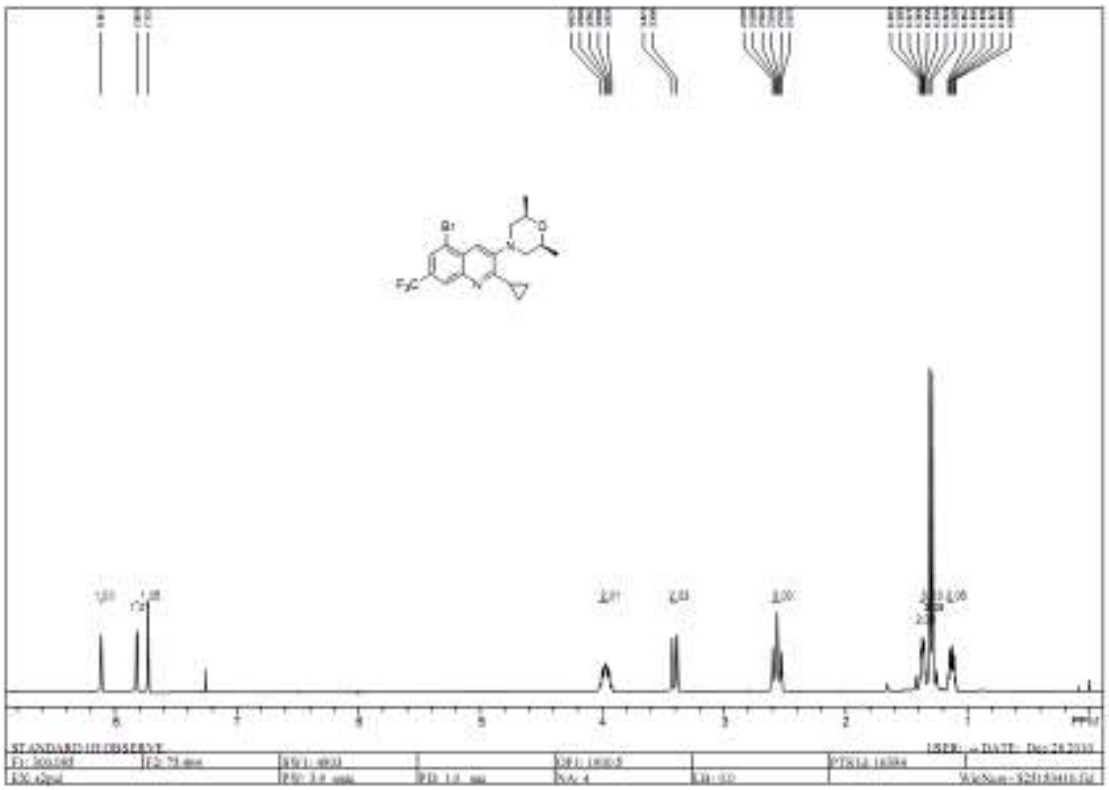
^{1}H NMR spectrum of **17e**



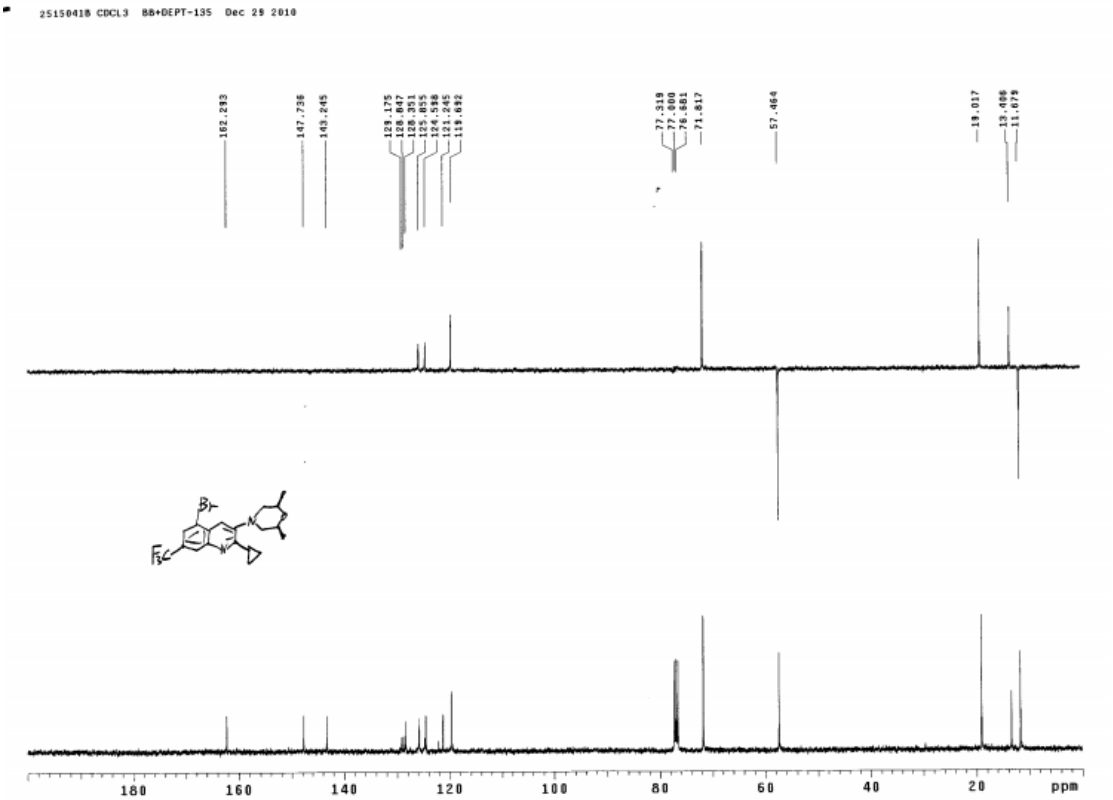
^{13}C NMR spectrum of **17e**



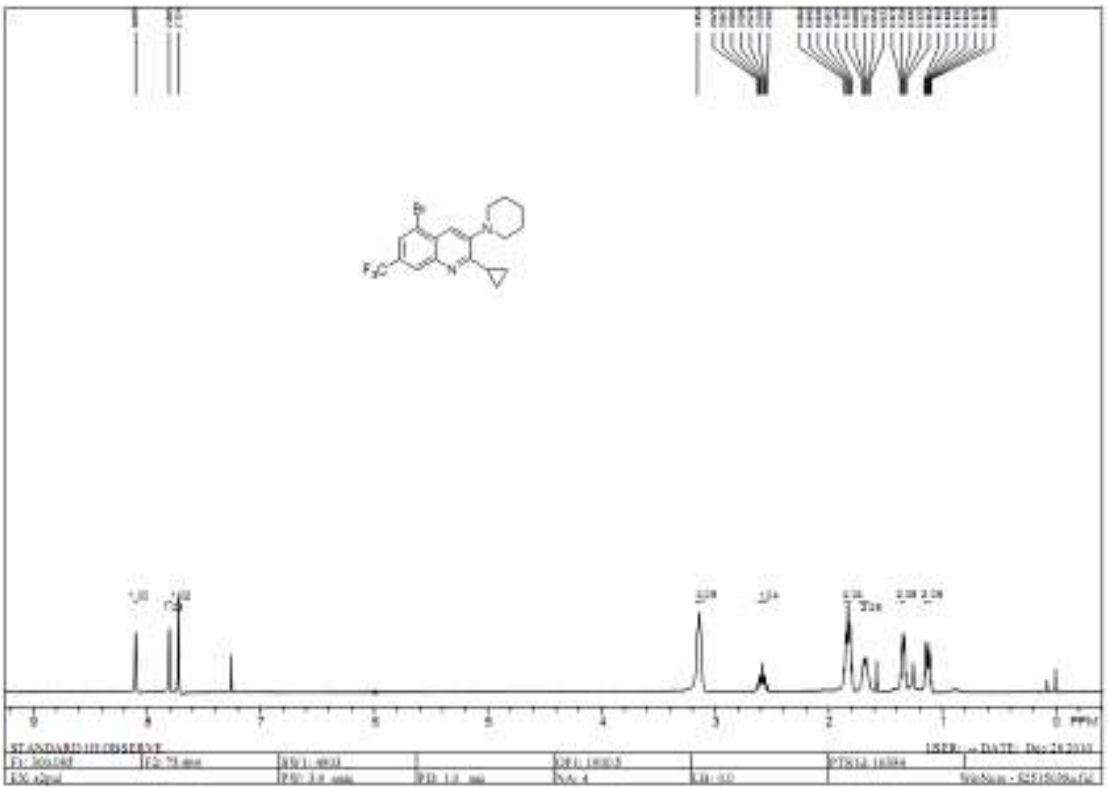
^{1}H NMR spectrum of **17f**



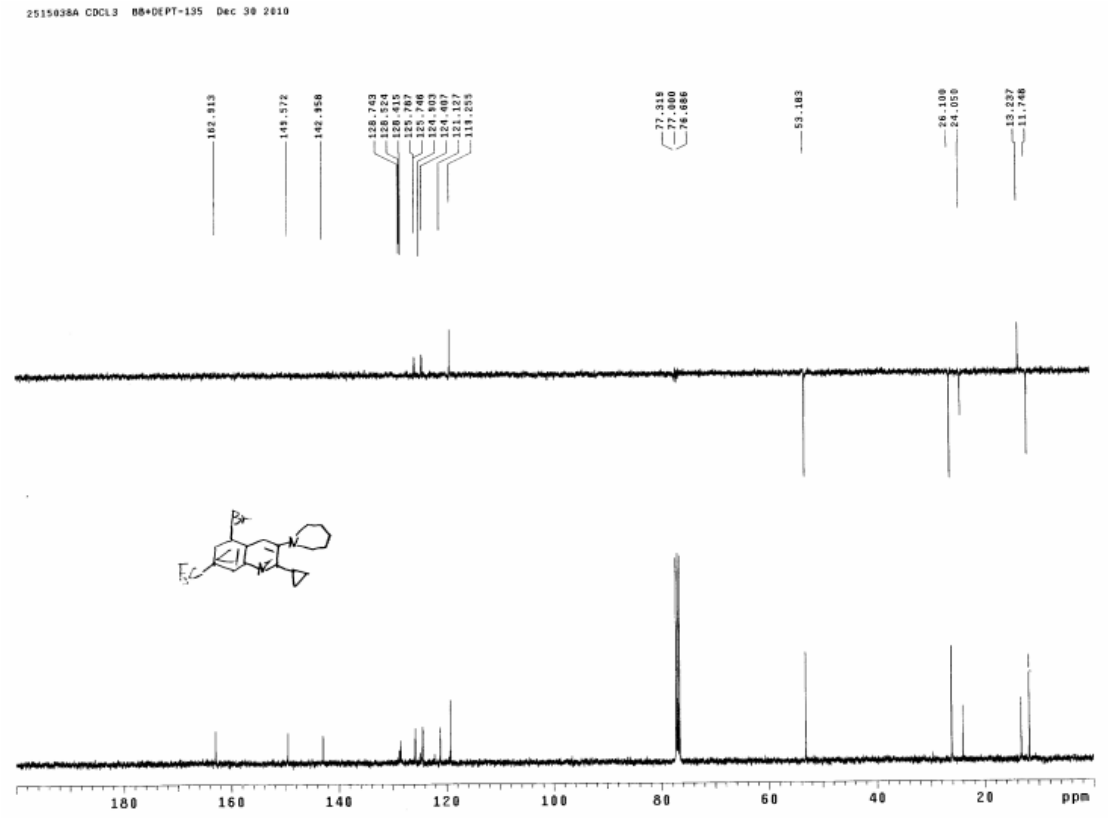
^{13}C NMR spectrum of **17f**



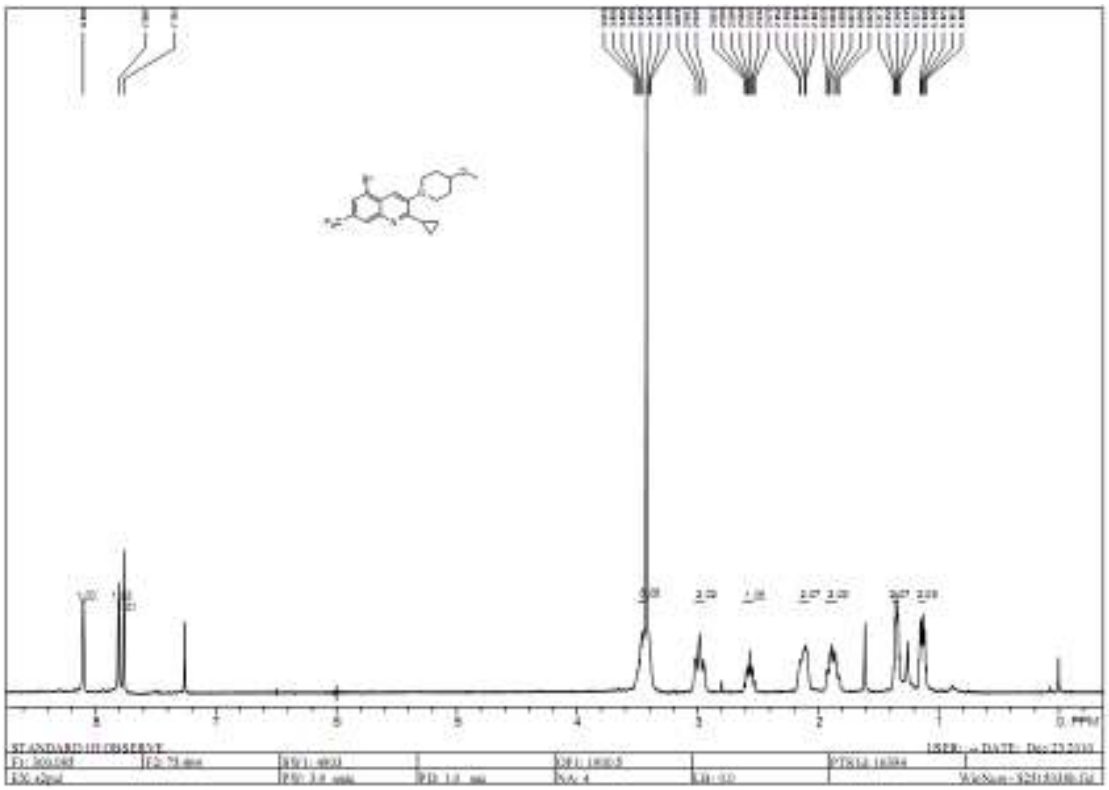
^{1}H NMR spectrum of **17g**



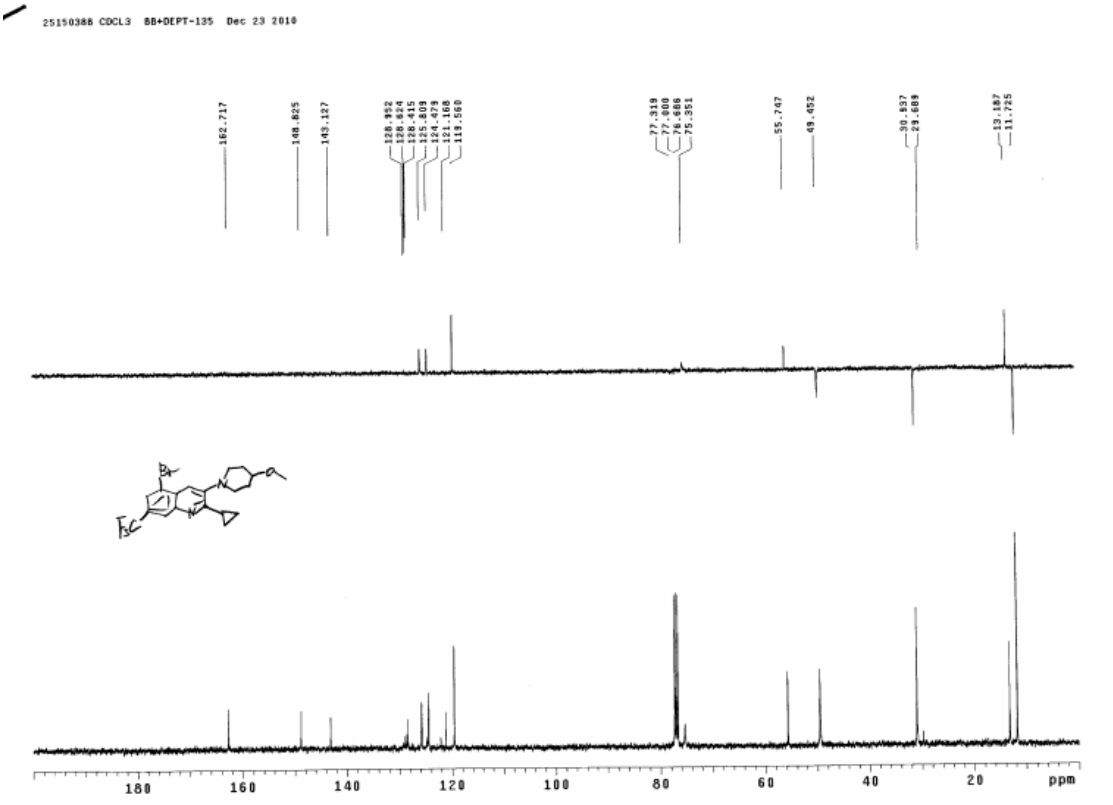
^{13}C NMR spectrum of **17g**



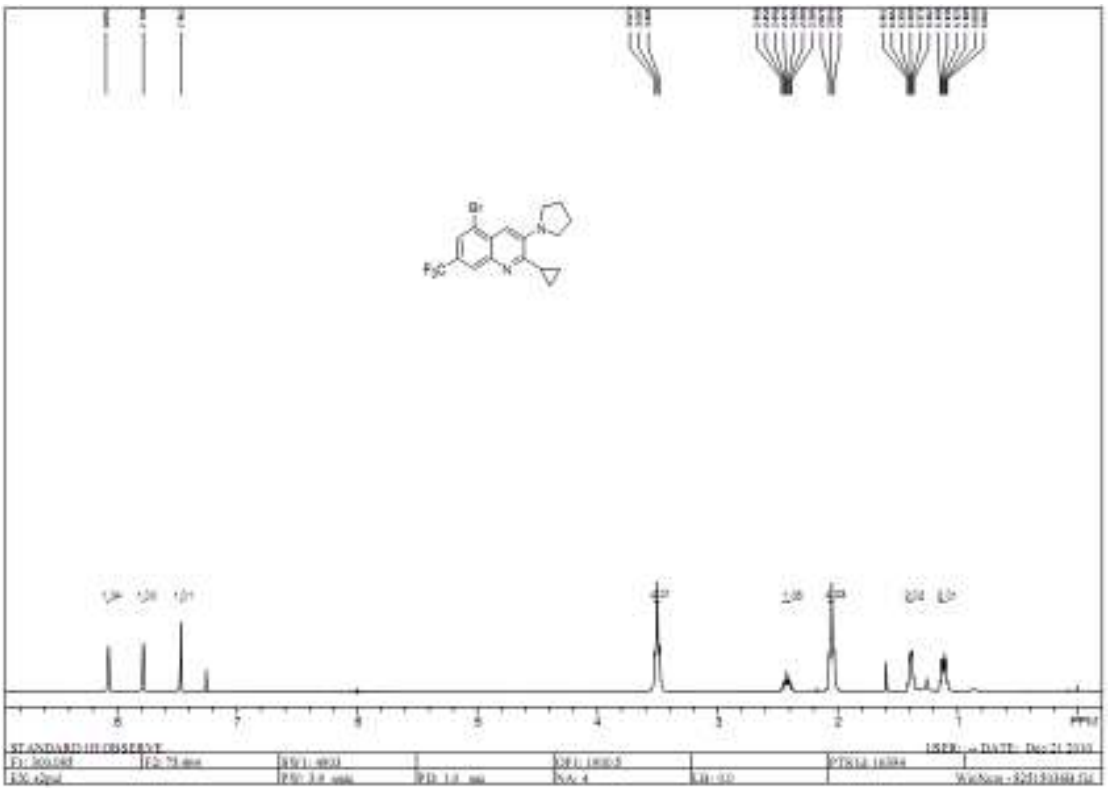
^{1}H NMR spectrum of **17h**



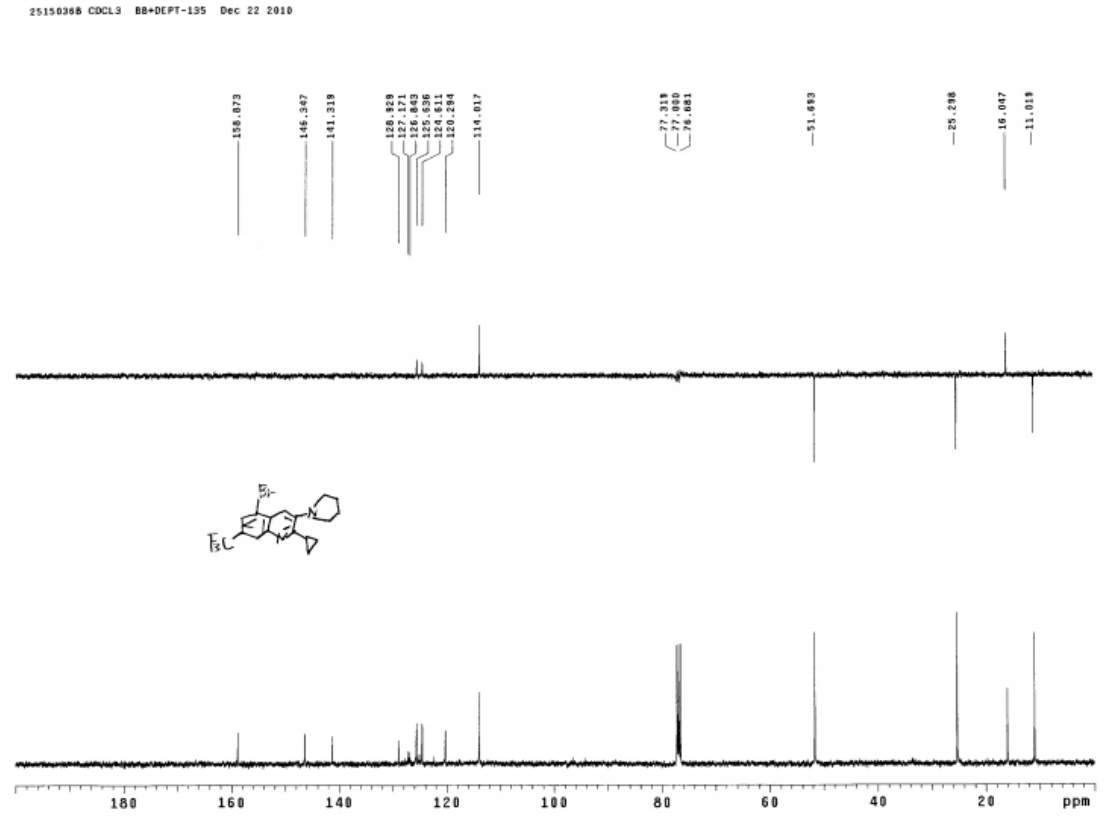
^{13}C NMR spectrum of **17h**



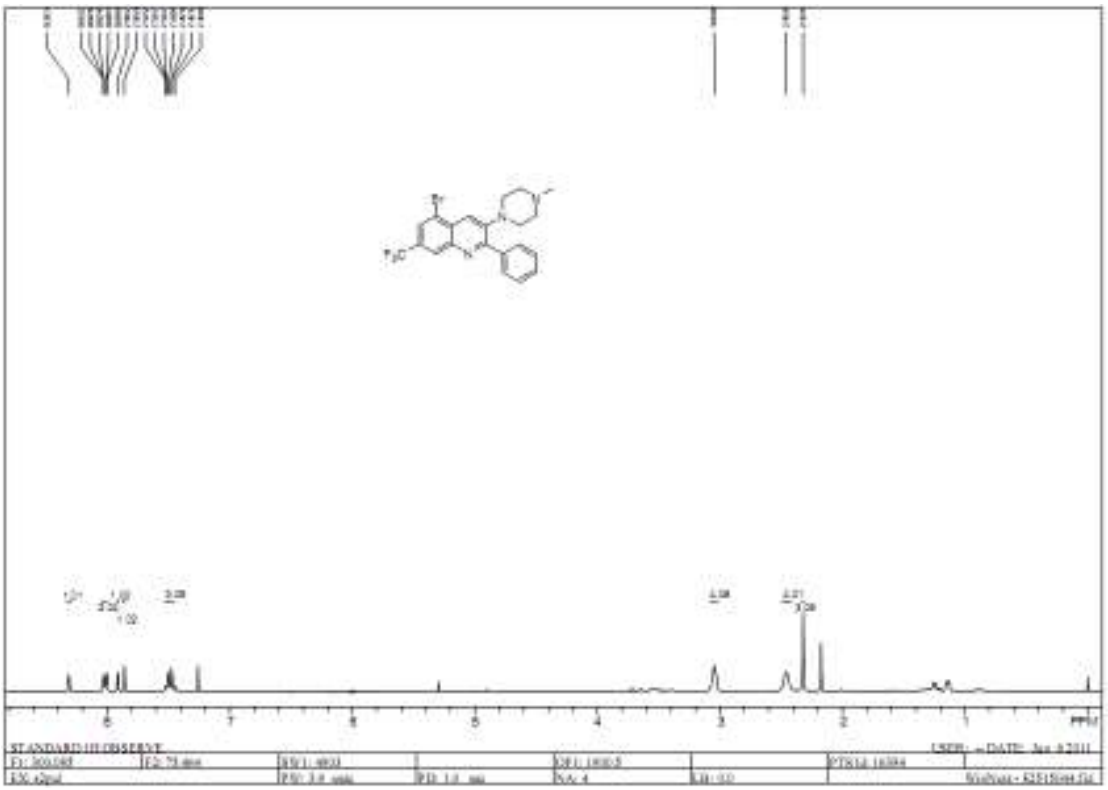
^{1}H NMR spectrum of **17i**



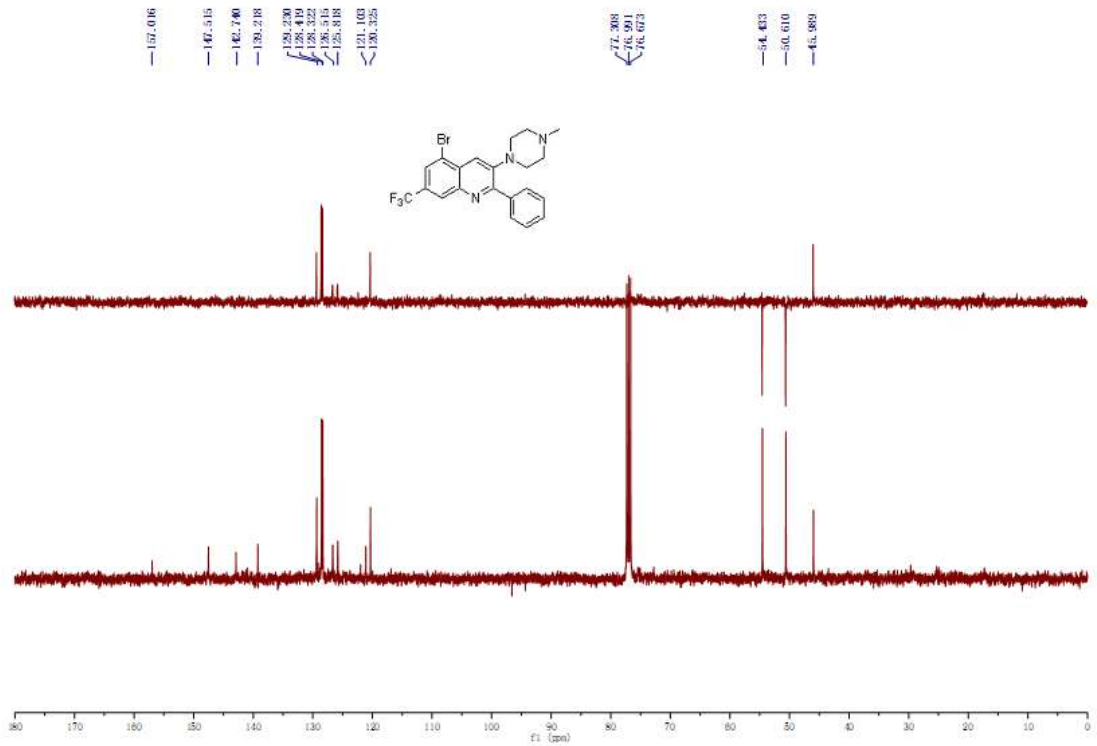
^{13}C NMR spectrum of **17i**



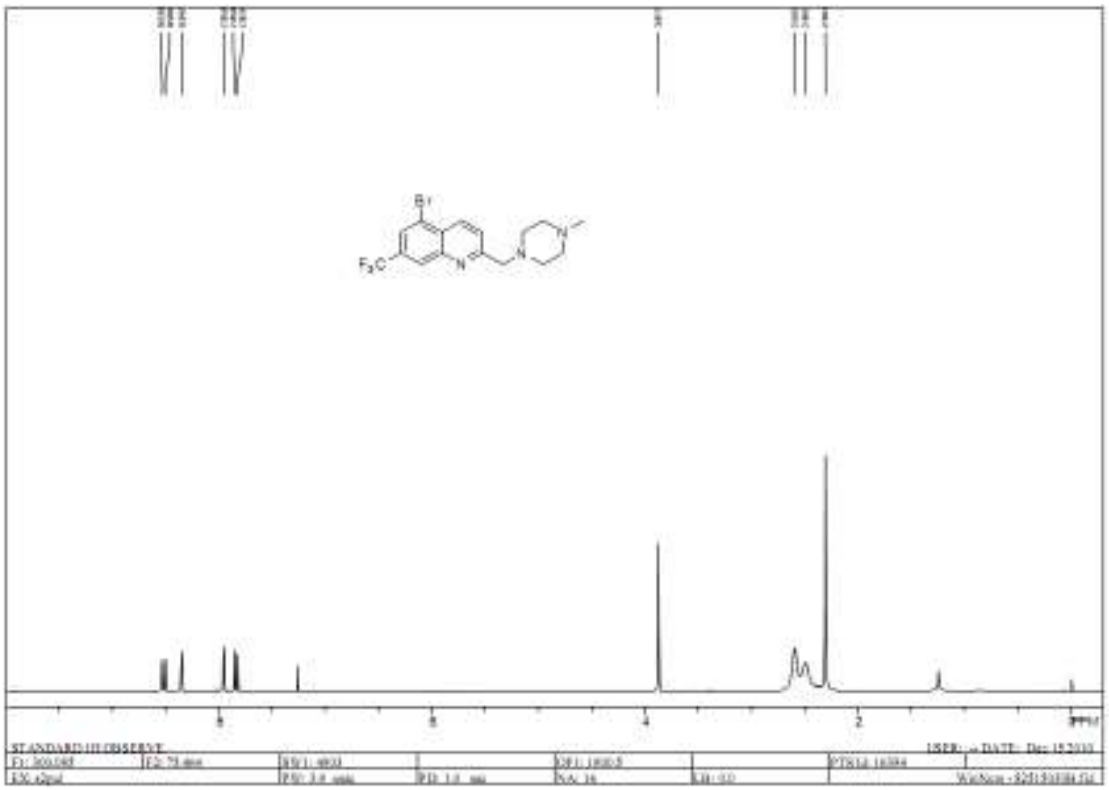
^{1}H NMR spectrum of **17j**



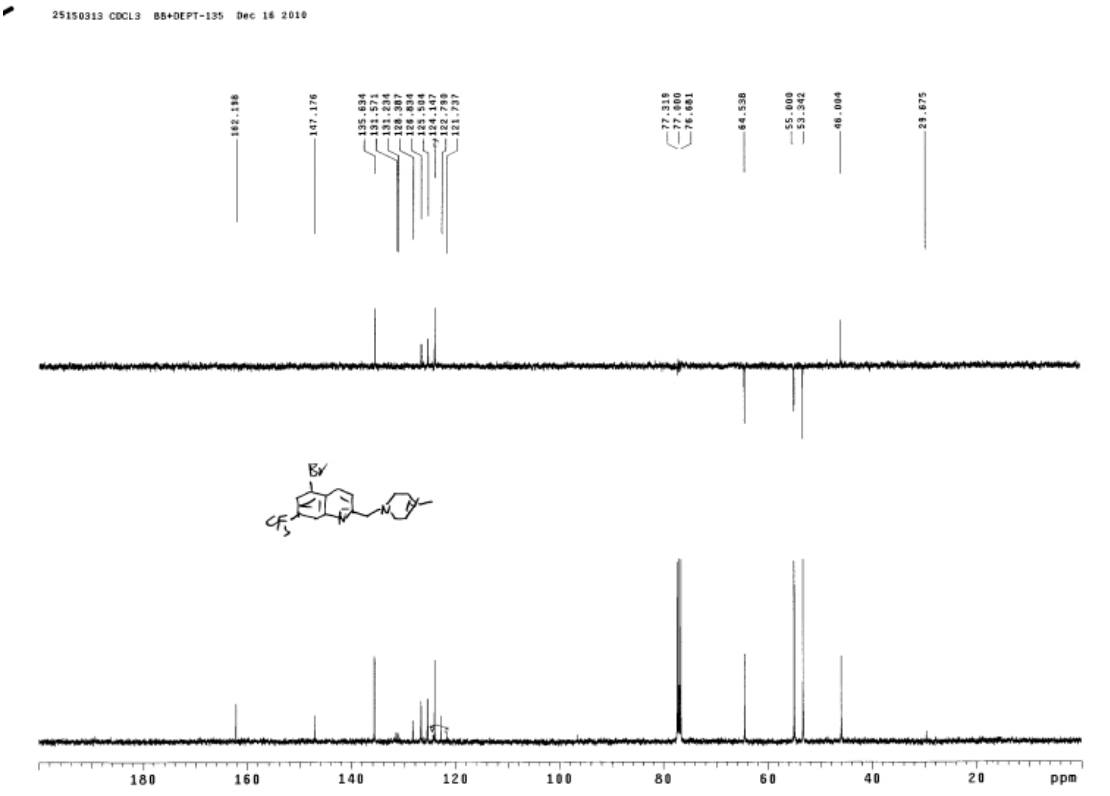
^{13}C NMR spectrum of **17j**



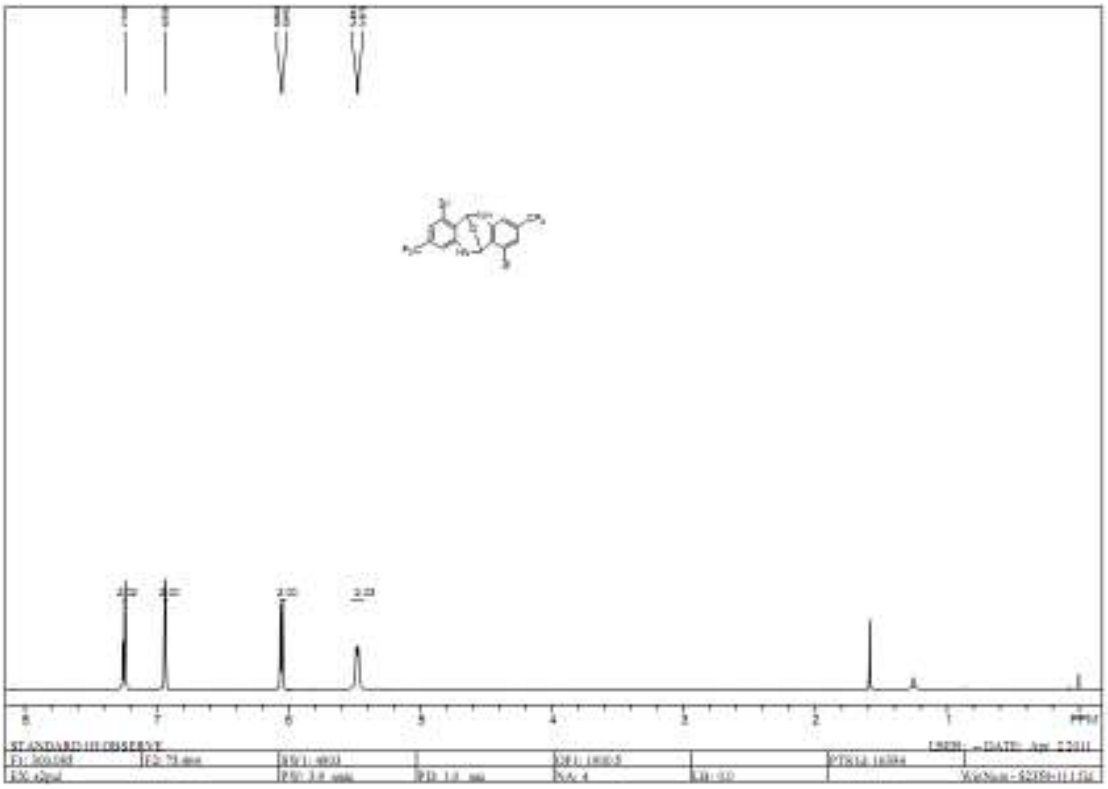
^{1}H NMR spectrum of **18**



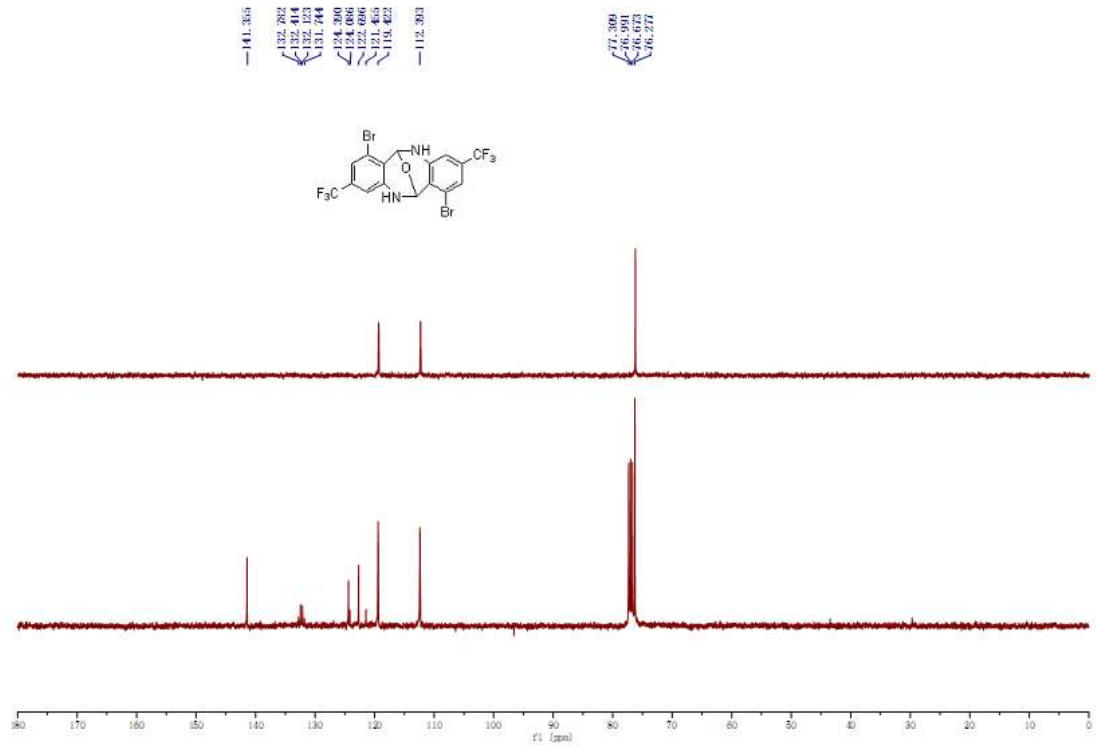
^{13}C NMR spectrum of **18**



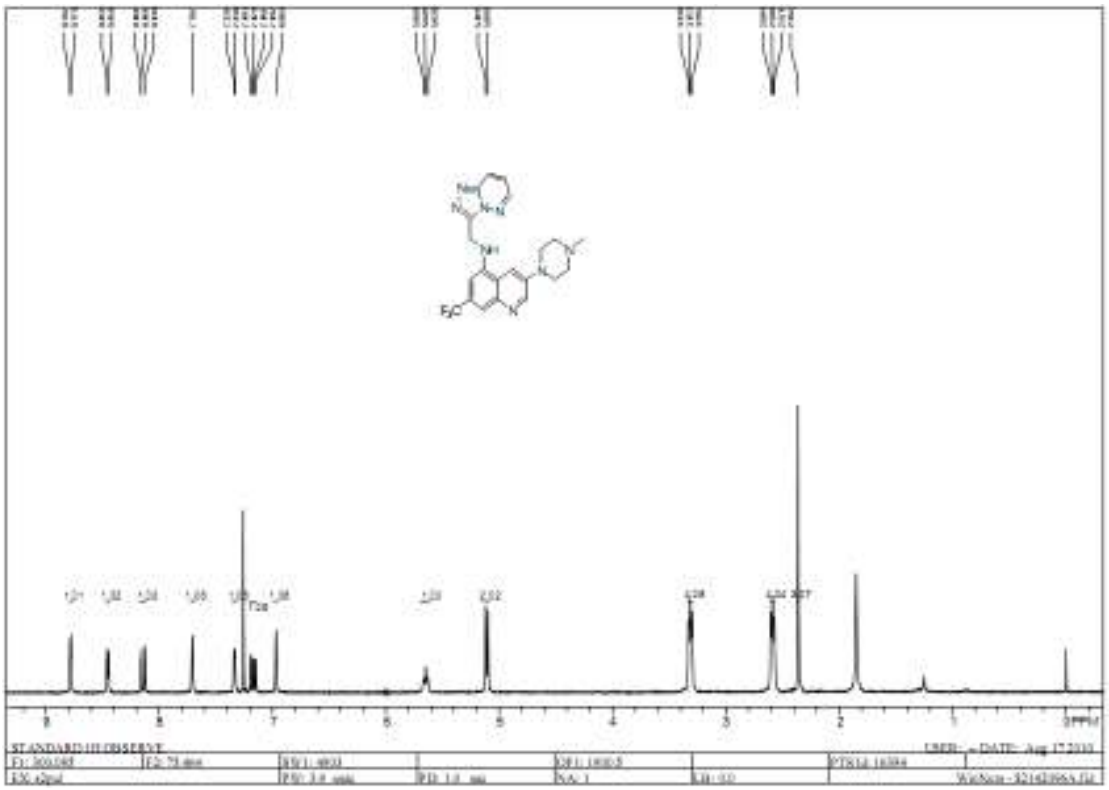
^{1}H NMR spectrum of **19**



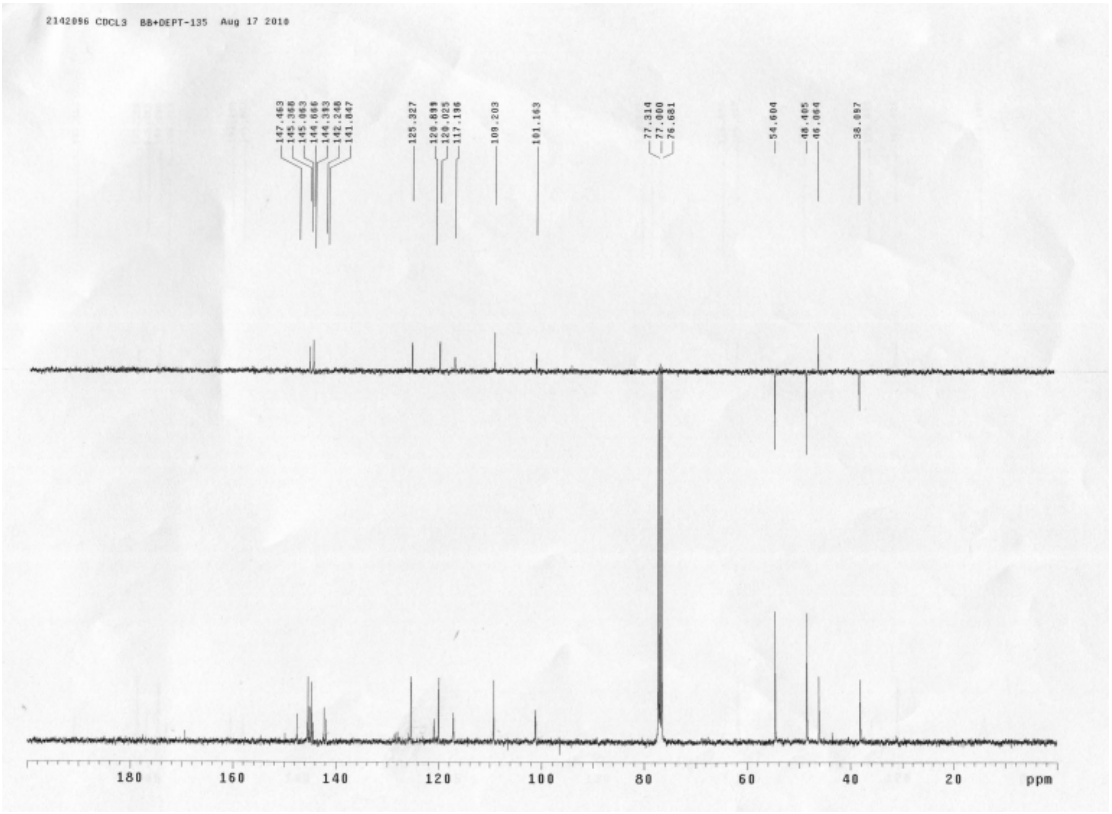
^{13}C NMR spectrum of **19**



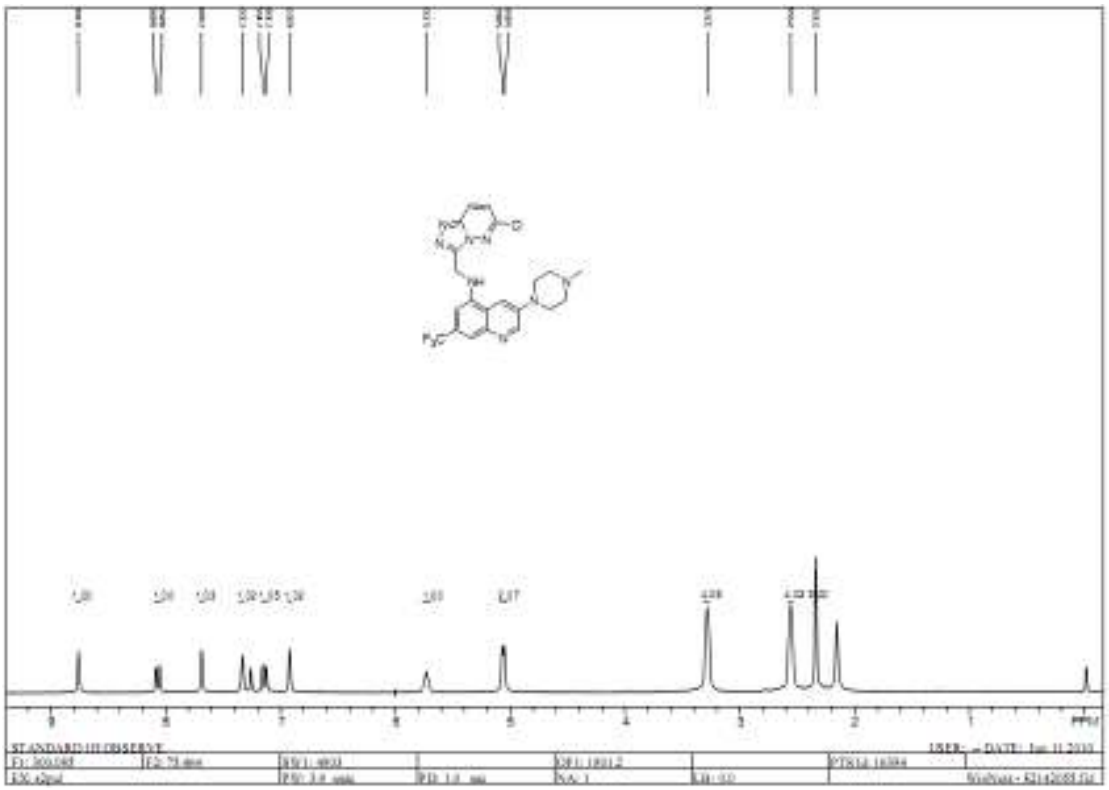
^{1}H NMR spectrum of **21a**



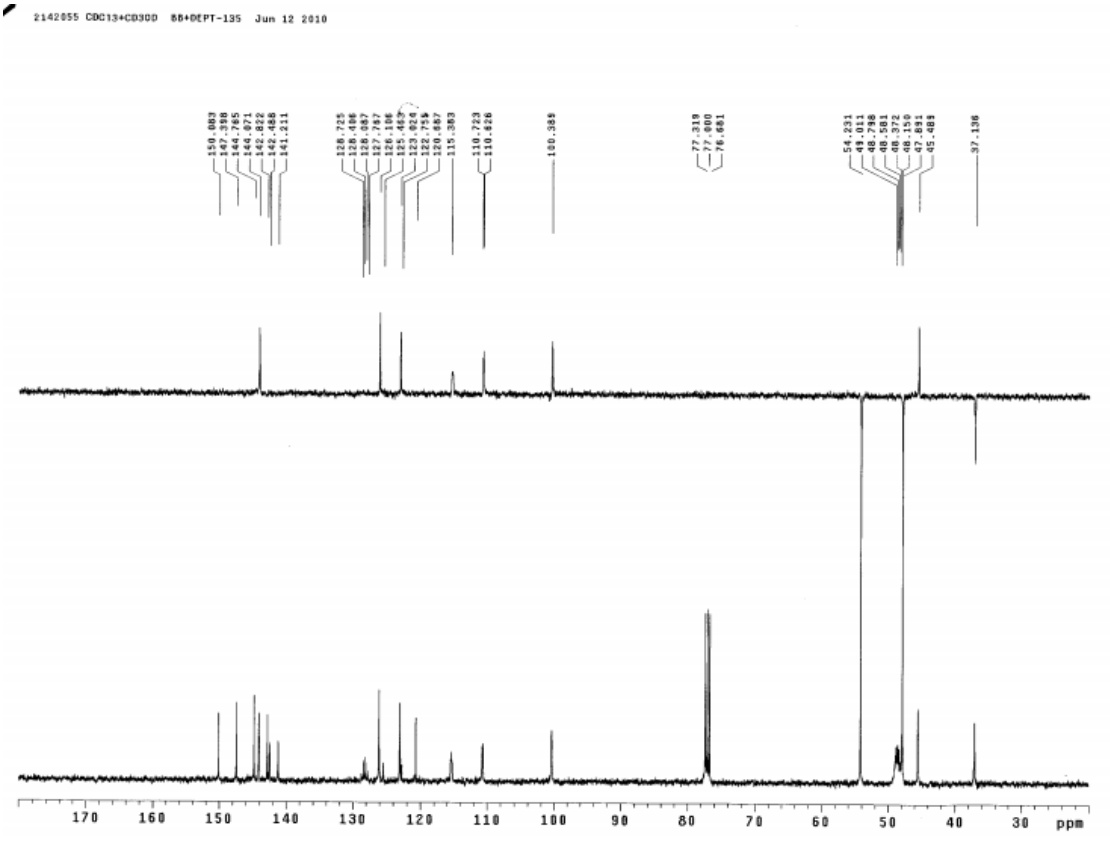
^{13}C NMR spectrum of **21a**



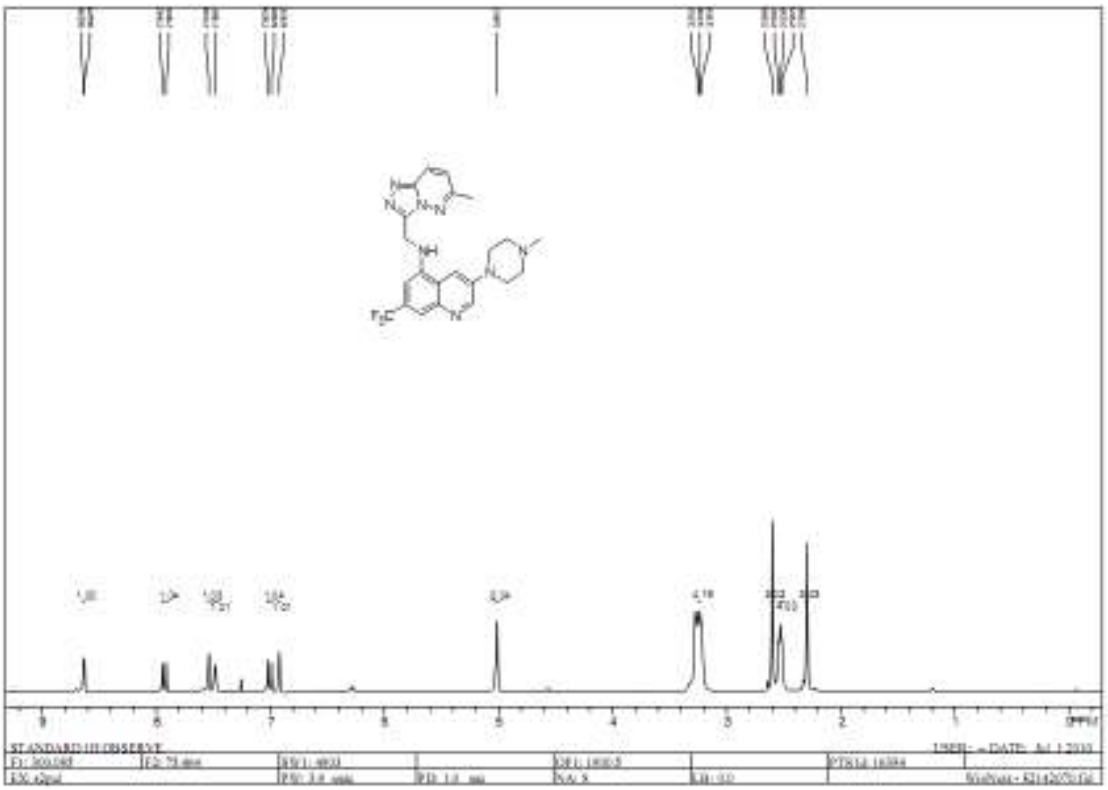
^{1}H NMR spectrum of **21b**



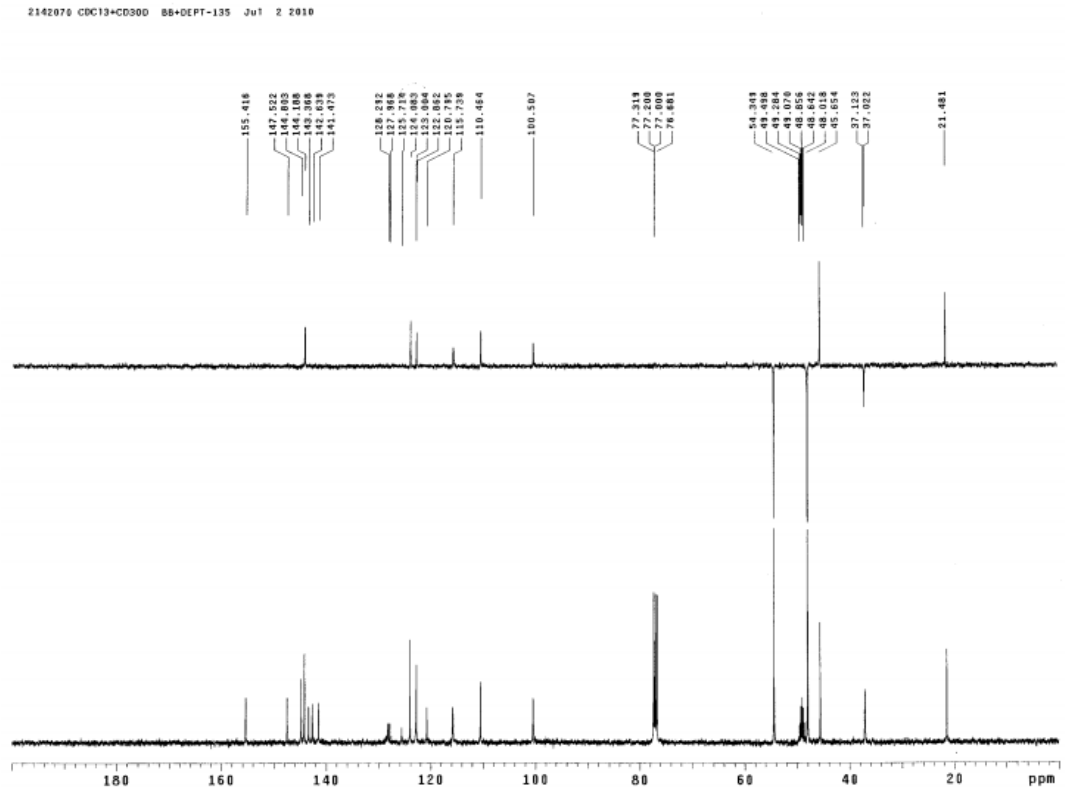
^{13}C NMR spectrum of **21b**



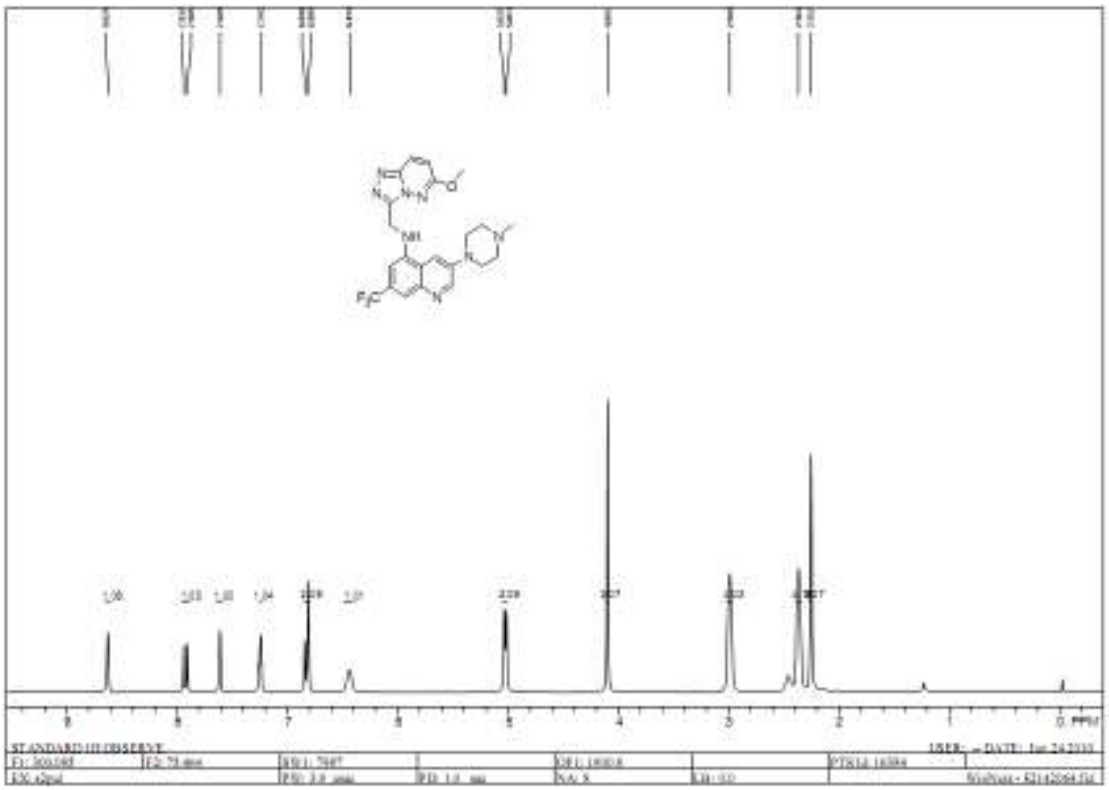
^{1}H NMR spectrum of **21c**



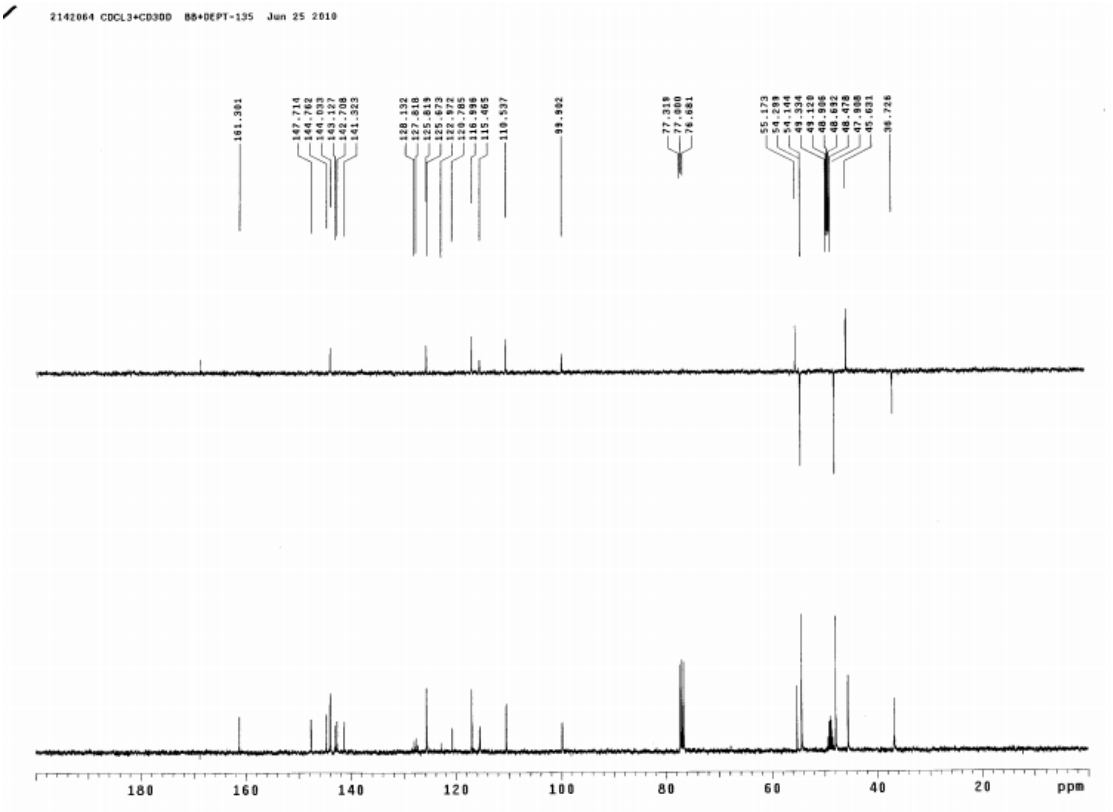
^{13}C NMR spectrum of **21c**



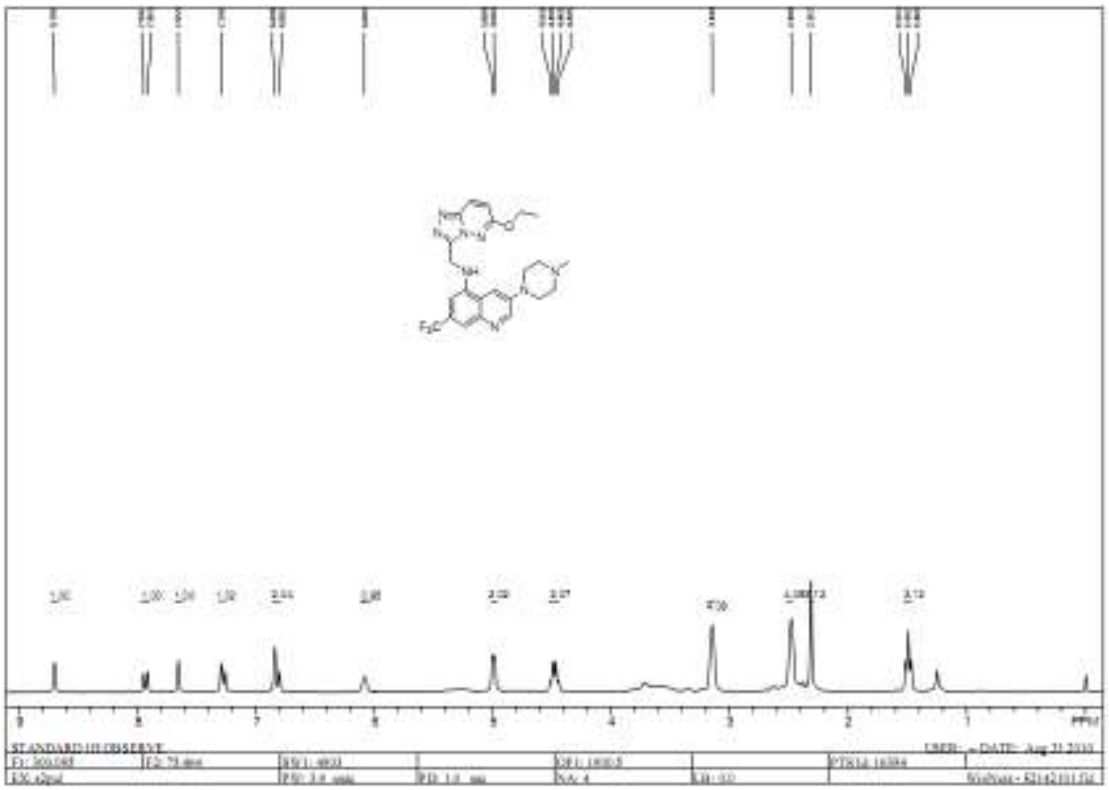
^{1}H NMR spectrum of **21d**



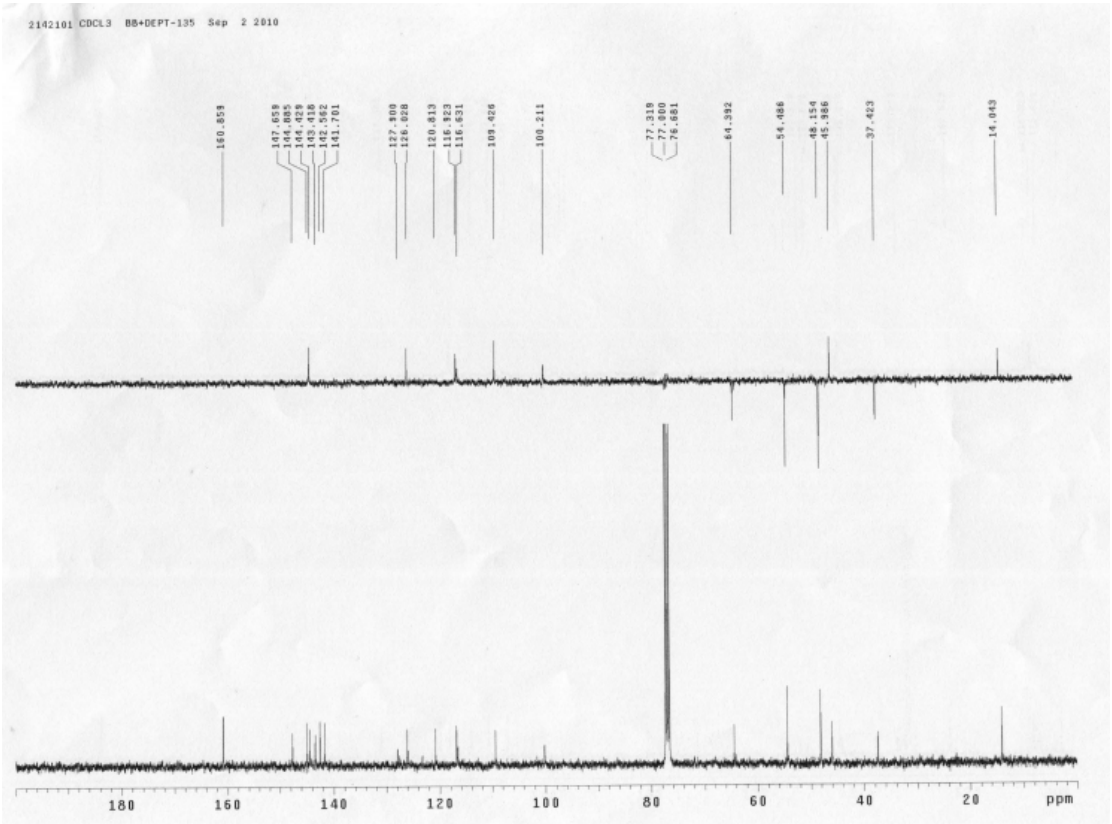
^{13}C NMR spectrum of **21d**



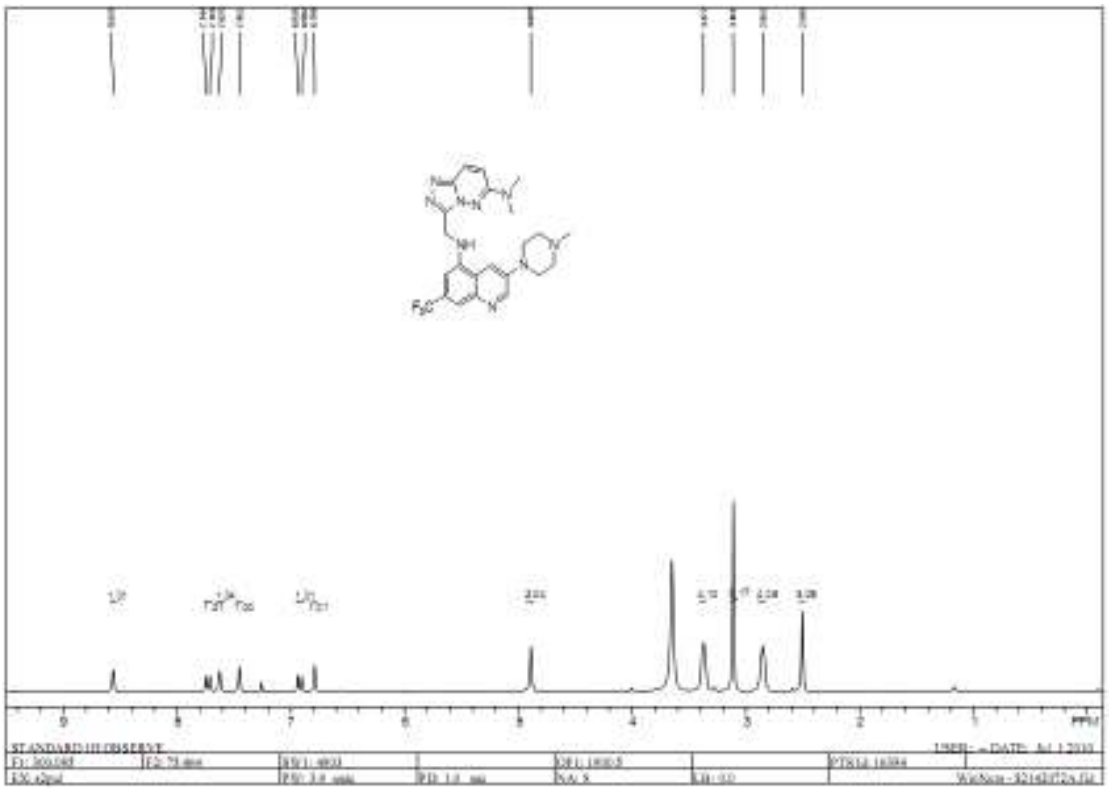
^{1}H NMR spectrum of **21e**



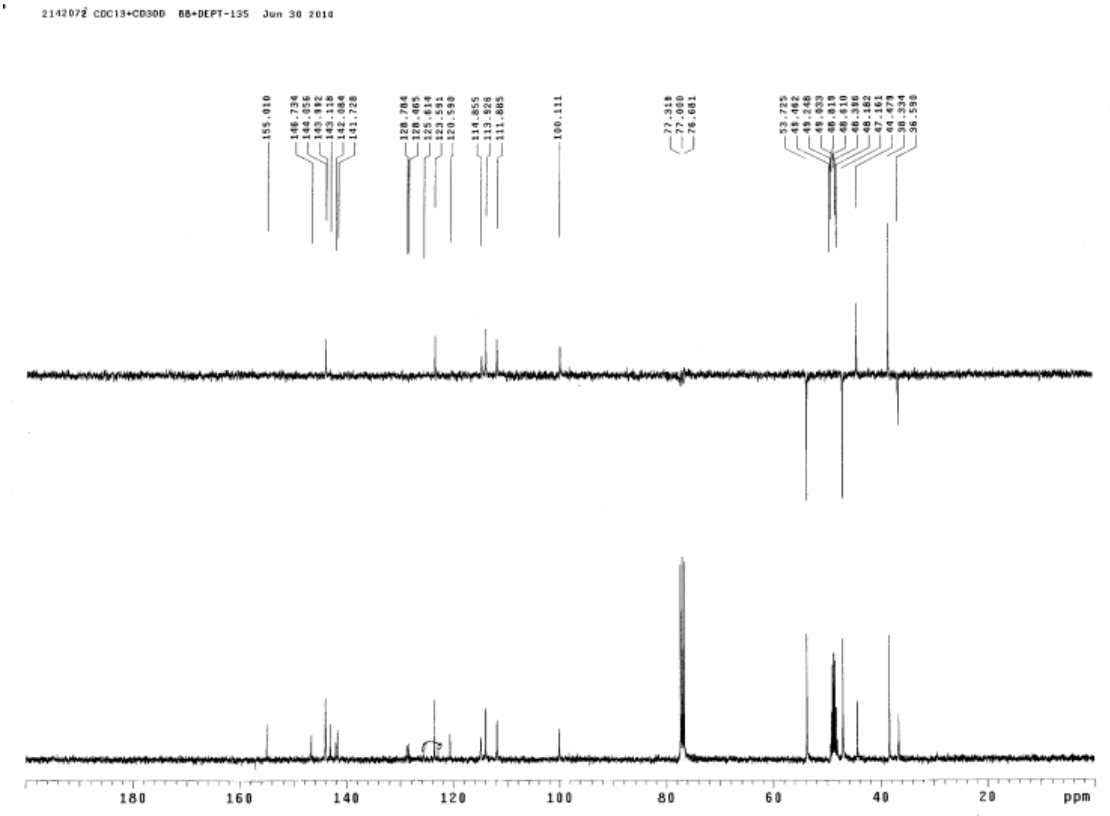
^{13}C NMR spectrum of **21e**



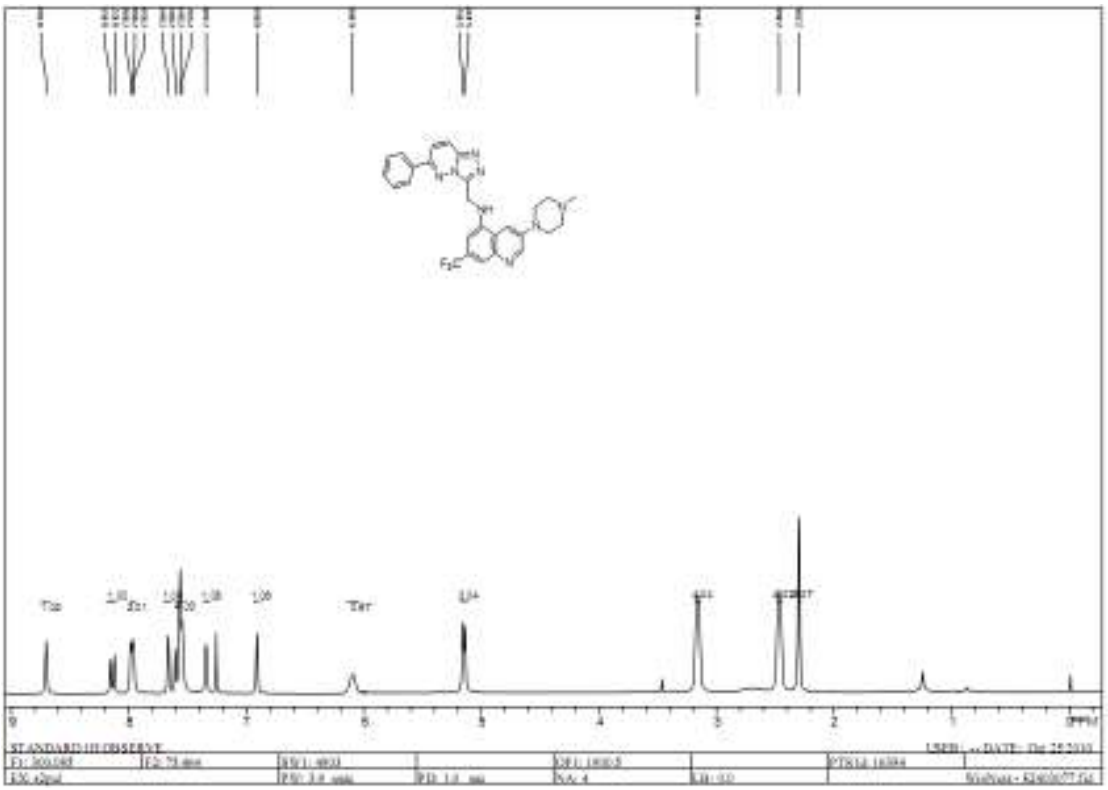
^{1}H NMR spectrum of **21f**



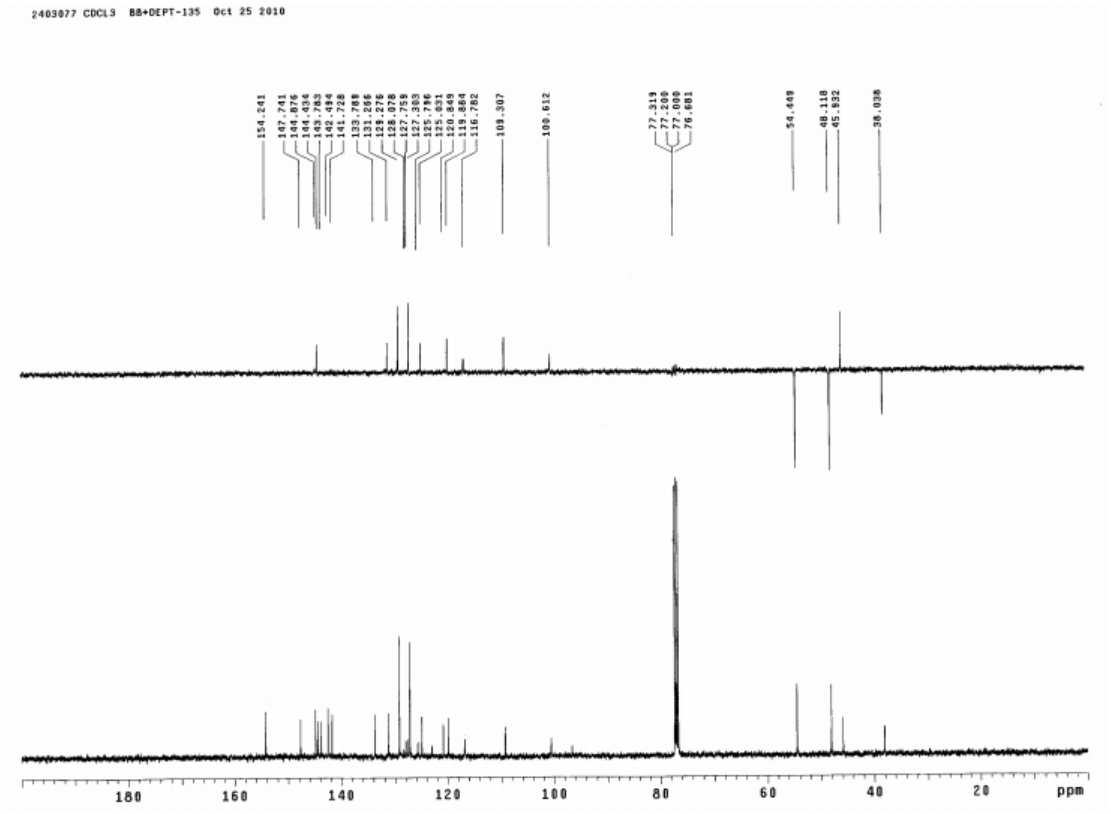
^{13}C NMR spectrum of **21f**



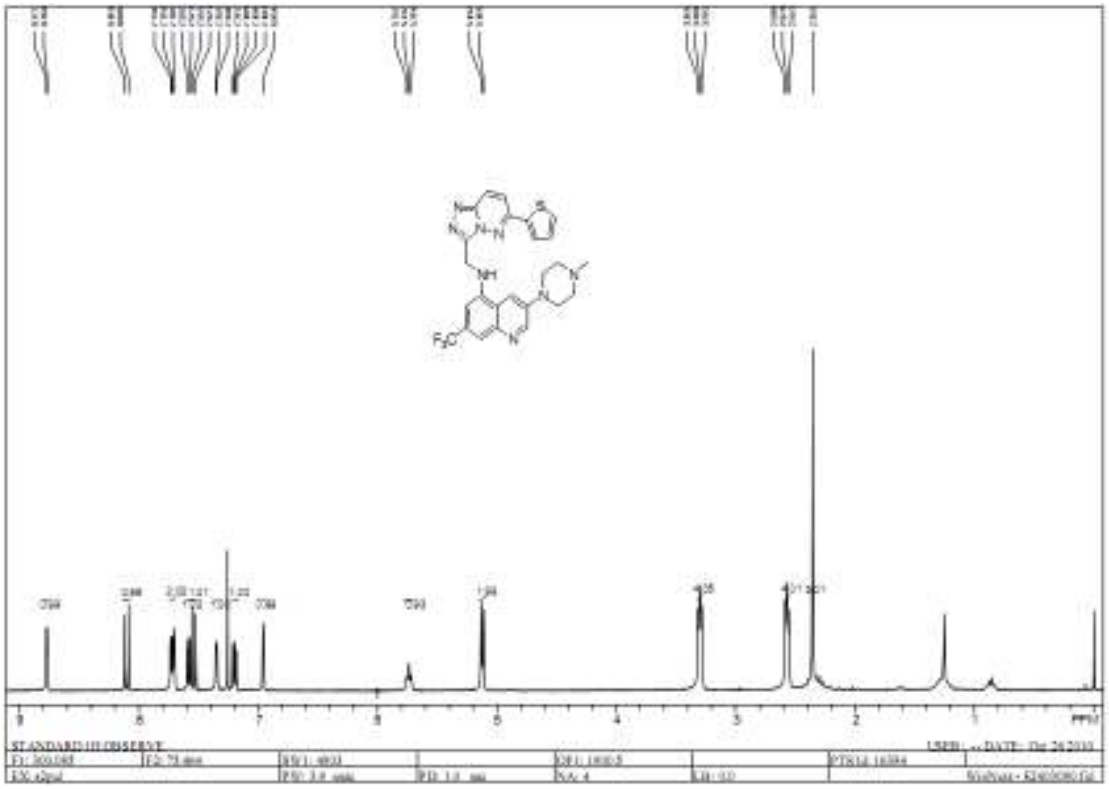
^{1}H NMR spectrum of **21g**



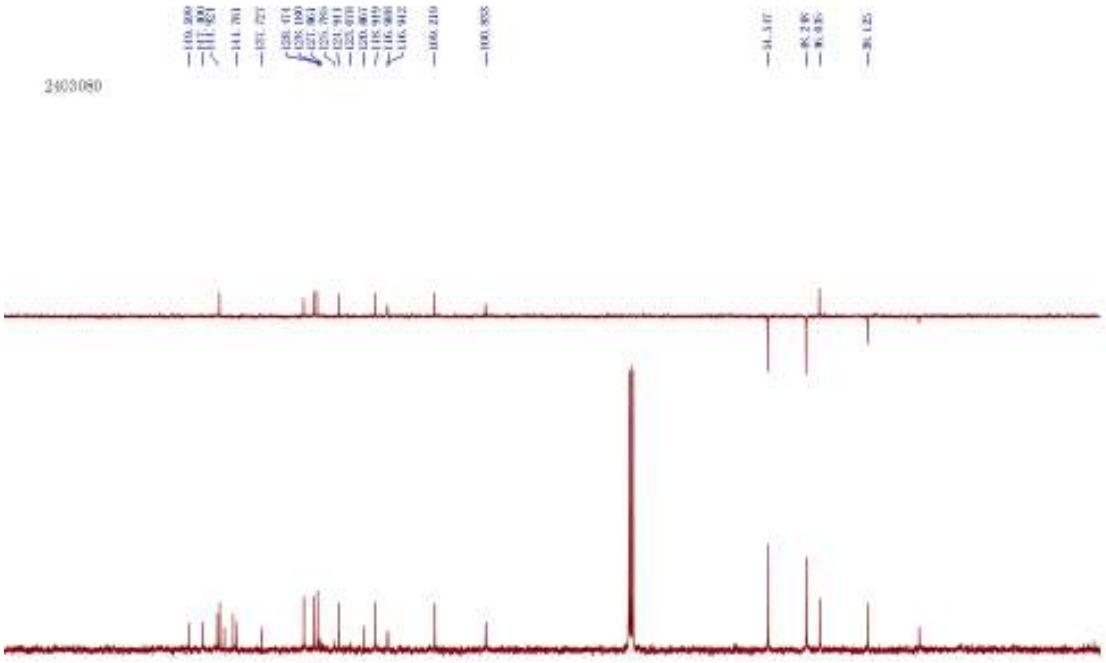
^{13}C NMR spectrum of **21g**



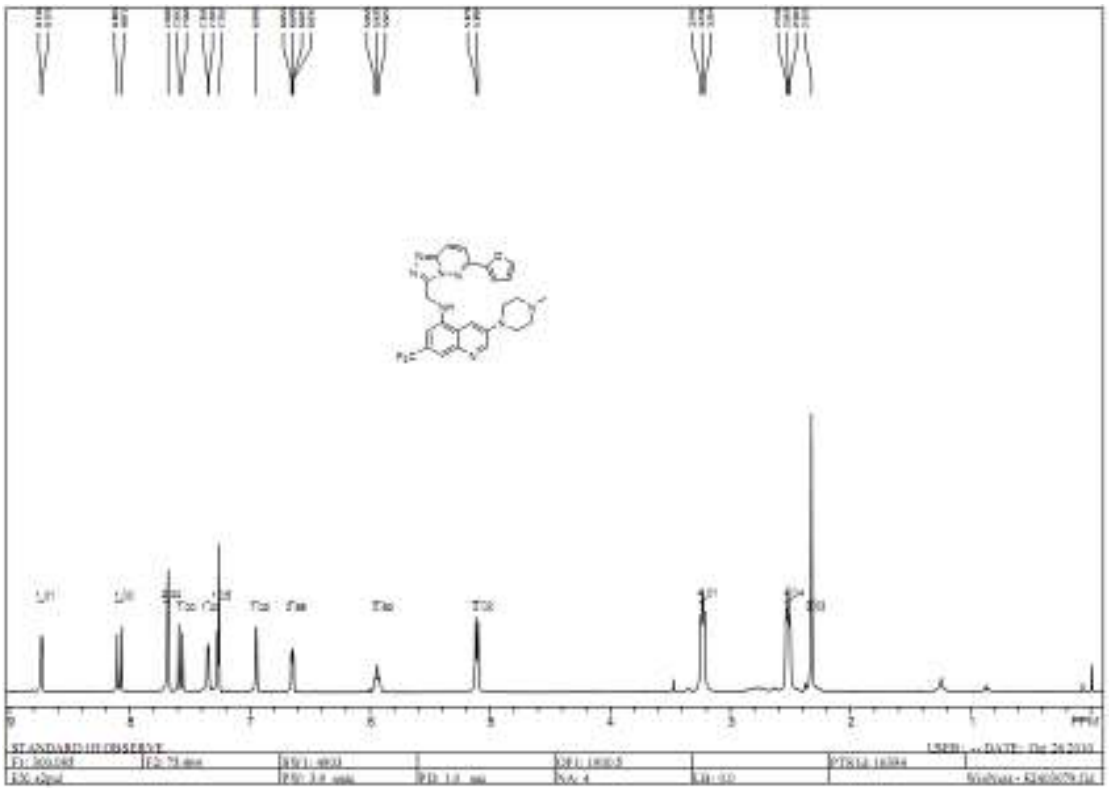
^{1}H NMR spectrum of **21h**



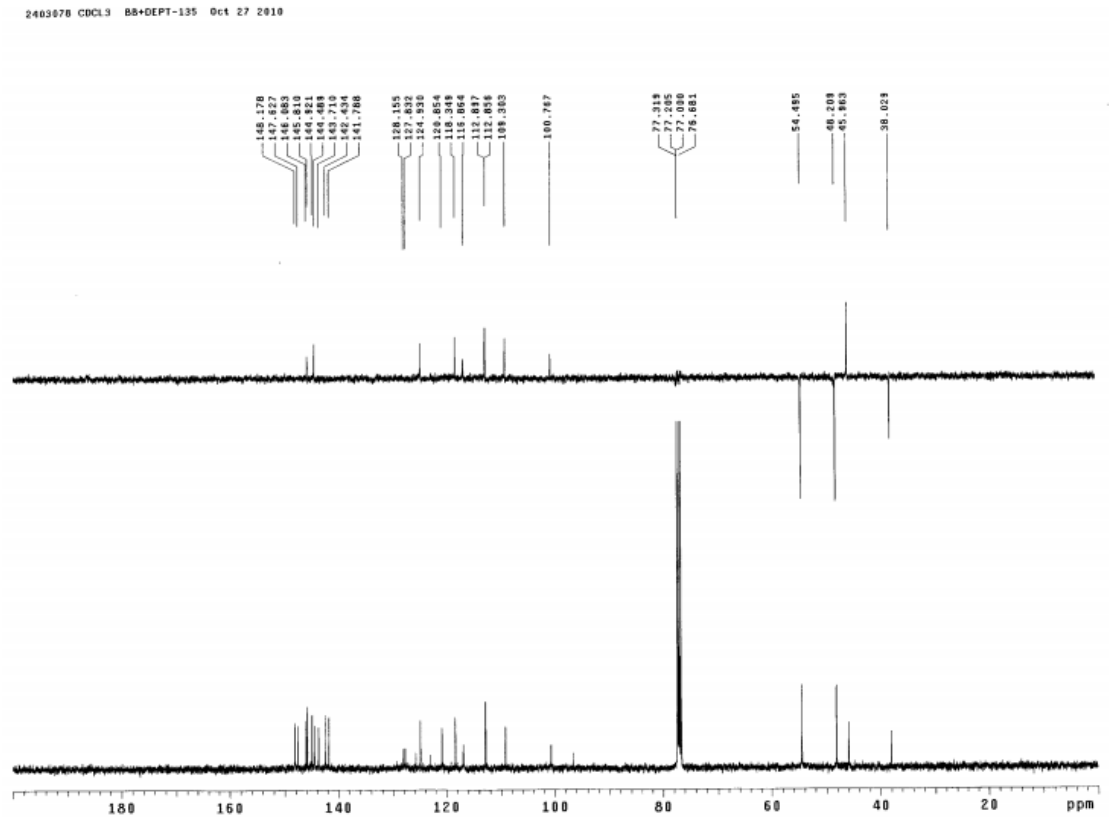
^{13}C NMR spectrum of **21h**



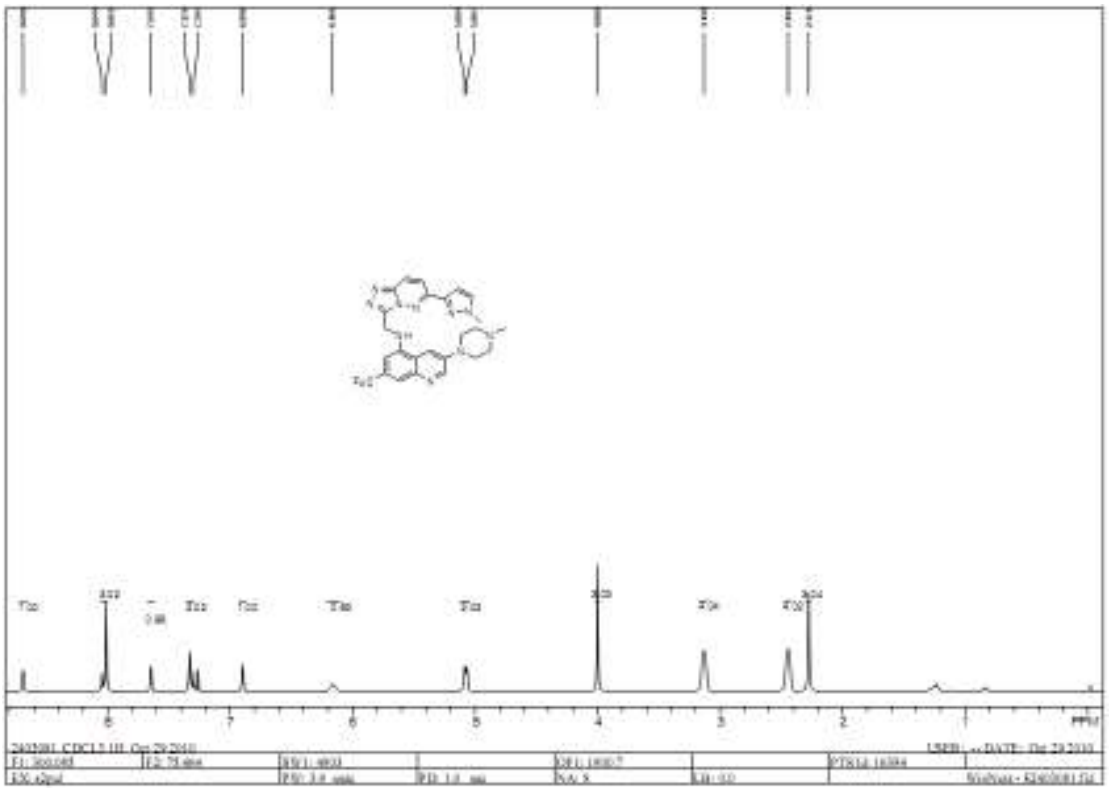
^{1}H NMR spectrum of **21i**



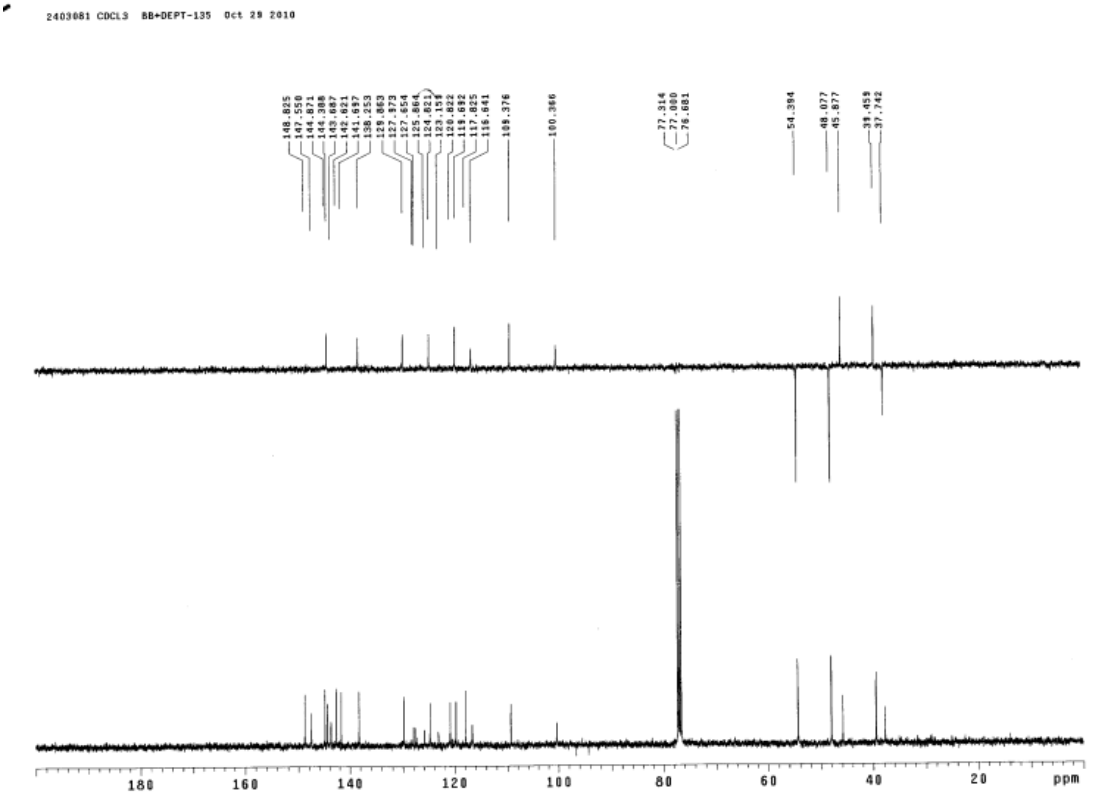
^{13}C NMR spectrum of **21i**



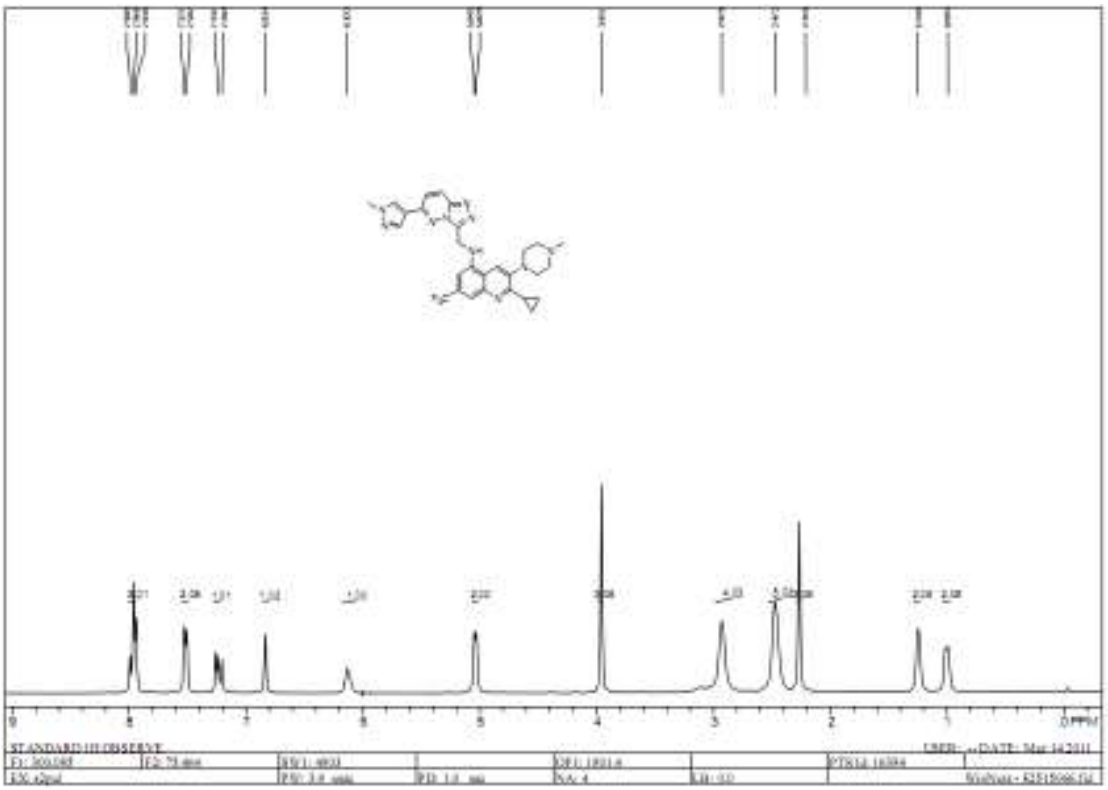
^{1}H NMR spectrum of **21j**



^{13}C NMR spectrum of **21j**



^{1}H NMR spectrum of **21k**



^{13}C NMR spectrum of **21k**