Electronic Supplementary Material (ESI) for Medicinal Chemistry Communications

Supporting Information

Synthesis and biological evaluation of novel quinoxalinone-based HIV-1 reverse transcriptase inhibitors

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General information Melting points were measured on a Yanaco micro melting point apparatus and are uncorrected. ^{1}H NMR on a spectrometer of Varian Mercury 300 or Varian 400 MHz Plus was recorded in DMSO-d_6 or $CDCl_3$. Chemical shifts are reported in δ (ppm) units relative to the internal standard tetramethylsilane (TMS). High resolution mass spectra (HRMS) were obtained on an Agilent Technologies LC/MSD TOF spectrometer. All chemicals and solvents used were of reagent grade without purified or dried before use. All the reactions were monitored by thin-layer chromatography (TLC) on pre-coated silica gel G plates at 254 nm under a UV lamp. Column chromatography separations were performed with silica gel (200-300 mesh).

Experimental procedure and spectra data

Methyl 5-chloro-3-(7-chloro-2-methyl-3-oxo-3,4-dihydroquinoxalin-1(2*H*)-ylsulfonyl)-thiophene-2-carboxylate (1b).

The mixture of 6-chloro-3-methyl-3,4-dihydroquinoxalin-2(1*H*)-one (1.5 g, 7.6 mmol), methyl 5-chloro-3-(chorosulfonyl)thiophene-2-carboxylate (4.2 g, 15.25 mmol) and pyridine (3.01 g, 38 mmol) in CH_2Cl_2 (6 mL) was separated into 2 microwave tubes and irradiated (microwave power: 150 W, temperature: 80 ℃) for 30 min. The reaction mixture was poured into saturated $CuSO_4$ aqueous solution and extracted with EtOAc. The organic layer was washed with water and brine, and dried over anhydrous $MgSO_4$. After concentration, the crude product was obtained and purified bycolumn chromatography on silica gel with petroleum ether-EtOAc (v/v = 4:1). Compound **1b** was obtained as yellow solid (1.9 g, 57%). mp 167-168℃; ^{1}H-NMR(400 MHz, Acetone-d_6, δ ppm) δ: 9.59 (brs, 1H), 7.61 (d, J = 1.2 Hz, 1H), 7.29 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H), 7.26 (s, 1H), 7.02 (d, J = 8.4 Hz, 1H), 4.97 (q, J = 7.2 Hz, 1H), 3.74 (s, 3H), 1.29 (d, J = 7.6

Hz, 3H); ^{13}C-NMR(100 MHz, Acetone-d_6) δ ppm) δ: 168.43, 159.10, 139.89, 135.30, 132.40, 131.11, 128.55, 127.95, 127.16, 123.87, 118.06, 117.99, 55.56, 53.73, 17.30; HRMS (ESI): *m/z*, calcd. for $C_{15}H_{13}Cl_2N_2O_5S_2$ [M + H^+]: 434.9637, found 434.9618.

Methyl 5-bromo-3-(7- chloro-2-methyl-3-oxo-3,4-dihydroquinoxalin-1(2*H*)-ylsulfonyl)-thiophene-2-carboxylate (1c).

Methyl 5-bromo-3-(chorosulfonyl)thiophene-2-carboxylate

Sulfuric acid (98%, 10 mL) was added to a solution of methyl 3-(chlorosulfonyl)thiophene-2-carboxylate (4.8 g, 20 mmol)) in trifluoroacetic acid (40 mL). The resulting reaction mixture was cooled to 0℃, and *N*-bromosuccinimide (5.3 g, 30 mmol) was added in portions over a period of 30 min. After stirred for a further 1 h, the mixture was warmed to room temperature and stirred for 20 h. The reaction mixture was poured into ice-water and extracted with EtOAc. The organic layer was washed with water and brine, and dried over anhydrous $MgSO_4$. After concentration, the crude product was obtained and purified by column chromatography on silica gel with petroleum ether-EtOAc (v/v = 120:1). The title compound was obtained as yellow solid (3.3 g, 52%); mp 78-80℃; ^{1}H-NMR(300 MHz, $CDCl_3$ δ ppm) δ: 7.62 (s, 1H), 3.98 (s, 3H).

Methyl 5-bromo-3-(7- chloro-2-methyl-3-oxo-3,4-dihydroquinoxalin-1(2*H*)-ylsulfonyl)-thiophene-2-carboxylate (1c).

Following the same procedure as 5.1.2, the mixture of 6-chloro-3-methyl-3,4-dihydroquinoxalin-2(1*H*)-one (630 mg, 3.2 mmol), methyl 5-bromo-3-(chorosulfonyl)thiophene-2-carboxylate (2.04 g, 6.4 mmol) and pyridine (1.3 mL, 16 mmol) in CH_2Cl_2 (4 mL) was loaded into 2 microwave tubes separately and irradiated (microwave power: 150W, temperature: 80℃) for 30 min. Compound **1c** was obtained as yellow solid (1.0 g, 66%); mp 158-160℃; ^{1}H-NMR(400 MHz, $CDCl_3$, δ ppm) δ: 9.03 (s, 1H), 7.73 (d, J = 2.0 Hz, 1H), 7.30 (s, 1H), 7.19 (dd, J_1 = 8.4 Hz, J_1 = 2.0 Hz, 1H), 6.79 (d, J = 8.4 Hz, 1H), 5.19 (q, J = 7.6 Hz, 1H), 3.76 (s, 3H), 1.37 (d, J = 7.2 Hz, 3H); ^{13}C-NMR(150 MHz, $CDCl_3$, δ ppm) δ: 169.48, 158.43, 139.99, 135.41, 134.03, 129.50, 129.01, 127.61, 126.35, 123.19, 118.02, 116.74, 54.90, 53.43, 17.32; HRMS (ESI): *m/z*, calcd. for $C_{15}H_{13}O_5N_2BrClS_2$ [M + H^+]: 478.9132, found 478.9147.

Methyl 5-iodo-3-(7- chloro-2-methyl-3-oxo-3,4-dihydroquinoxalin-1(2*H*)-ylsulfonyl)-thiophene-2-carboxylate (1d).

Methyl 5-iodo-3-(chorosulfonyl)thiophene-2-carboxylate

Sulfuric acid (98%, 5 mL) was added to a solution of methyl 3-(chlorosulfonyl)thiophene-2-carboxylate (2.4 g, 10 mmol)) in trifluoroacetic acid (20 mL). The resulting reaction mixture was cooled to 0℃, and *N*-iodosuccinimide (3.37 g, 15 mmol) was added in portions over a period of 20 min. After stirred a further 1 h, the mixture was warmed to room temperature and stirred for 20 h. Following the same procedure as 5.1.3.1, the title compound was obtained as yellow solid (1.35 g, 37%); mp 103-104℃; ^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm) δ: 7.77 (s, 1H), 3.98 (s, 3H).

Methyl 5-iodo-3-(7- chloro-2-methyl-3-oxo-3,4-dihydroquinoxalin-1(2*H*)-ylsulfonyl)-thiophene-2-carboxylate (1d).

Following the same procedure as 5.1.2, the mixture of 6-chloro-3-methyl-3,4-dihydroquinoxalin-2(1*H*)-one (196 mg, 1 mmol), methyl 5-iodo-3-(chorosulfonyl)thiophene-2-carboxylate (732 mg, 2 mmol) and pyridine (0.4 mL, 5 mmol) in CH_2Cl_2 (2 mL) was loaded into 2 separate microwave tubes and irradiated (microwave power: 150W, temperature: 80℃) for 30 min. compound **1d** was obtained as yellow solid (320 mg, 61%).

mp 154-156℃; ^{1}H-NMR(400 MHz, $CDCl_3$, δ ppm) δ: 9.33 (s, 1H), 7.73 (d, *J* = 2.0 Hz, 1H), 7.47 (s, 1H), 7.18 (d, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1H), 6.81 (d, *J* = 8.4 Hz, 1H), 5.17 (q, *J* = 7.2 Hz, 1H), 3.765 (s, 3H), 1.37 (d, *J* = 7.2 Hz, 3H); ^{13}C-NMR(100 MHz, $CDCl_3$, δ ppm) δ: 169.99, 158.30, 140.62, 140.48, 139.87, 129.49, 128.96, 127.51, 126.14, 123.16, 117.02, 80.02, 53.35, 17.25; HRMS (ESI): *m/z*, calcd. for $C_{15}H_{13}O_5N_2ClIS_2$ [M + H^+]: 526.8994, found 526.9006.

6-Chloro-3-methyl-4-(2-phenylthiophen-3-ylsulfonyl)-3,4-dihydroquinoxalin-2(1*H*)-one (1e)

The mixture of compound **1c** (48 mg, 0.1 mmol), phenylboronic acid (18 mg, 0.15 mmol), $Pd(OAc)_2$ (5 mg, 0.02 mmol), xantphos (23 mg, 0.04mmol) was purged with argon. Toluene (5 mL) and triethylamine (0.07 mL, 0.5 mmol) were added and the resulting reaction mixture was heated at 80℃ for 48 h. The reaction mixture was concentrated, the crude product was obtained and purified by column chromatography on silica gel with petroleum CH_2Cl_2-EtOAc (v/v = 40:1, v/v = 30:1). Compound **1e** was obtained as off-white solid (30 mg, 62%). mp 83-86℃; ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) δ: 8.62 (brs, 1H), 7.80 (s, 1H), 7.48-7.53 (m, 3H), 7.38 (brs, 3H), 7.11 (, *J* = 8.0 Hz, 1H), 6.70 (d, *J* = 8.4 Hz, 1H), 5.24 (q, *J* = 7.2 Hz, 1H), 3.76 (s, 3H), 1.38 (d, *J* = 6.8 Hz, 3H); ^{13}C-NMR(150 MHz, $CDCl_3$, δ ppm) δ: 169.66, 159.45, 148.14, 139.94, 132.24, 131.40, 129.81, 129.45, 129.40, 128.79, 127.26, 127.20, 126.20, 126.15, 123.43, 116.68, 54.86, 53.16, 17.41; HRMS (ESI): *m/z*, calcd. for $C_{21}H_{18}O_5N_2ClS_2$ [M + H^+]: 477.0340, found 477.0348.

6-Chloro-3-methyl-4-(2-(3-methoxyphenyl)thiophen-3-ylsulfonyl)-3,4-dihydro-quinoalin-2(1*H*)-one (1f)

The mixture of compound **1c** (58 mg, 0.12 mmol), 3-methoxyphenylboronic acid (28 mg, 0.18 mmol), $Pd(OAc)_2$ (6 mg, 0.024 mmol), dppf (13 mg, 0.024mmol) was purged with argon. Toluene (5 mL) and triethylamine (0.09 mL, 0.6 mmol) were added and the reaction mixture was heated at 80℃ for 48 h. The reaction mixture was concentrated, the crude product was obtained and purified by column chromatography on silica gel with petroleum CH_2Cl_2-EtOAc (v/v = 40:1, v/v = 33:1). Compound **1f** was obtained as off-white solid (15 mg, 25%). mp 83-85℃; ^{1}H-NMR(300 MHz, DMSO-d_6, δ ppm) δ: 10.69 (s, 1H), 7.71 (s, 1H), 7.54 (d, *J* = 2.1 Hz, 1H), 7.38 (t, *J* = 7.8 Hz, 1H), 7.30 (dd, J_1 = 8.4 Hz, J_2 = 2.1 Hz, 1H), 7.22 (m, 2H), 7.02 (dd, J_1 = 8.4 Hz, J_2 = 1.8 Hz, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 4.83 (q, *J* = 7.2 Hz, 1H), 3.82 (s, 3H), 3.67 (s, 3H), 1.20 (d, *J* = 7.2 Hz, 3H); ^{13}C-NMR(150 MHz, DMSO-d_6, δ ppm) δ: 167.36, 159.85, 158.94, 147.17, 138.68, 132.11, 132.08, 131.29, 130.60, 127.55, 126.62, 126.06, 125.79, 122.47, 118.48, 117.23, 116.03, 111.20, 55.38, 54.05, 53.14, 16.77; HRMS (ESI): *m/z*, calcd. for $C_{22}H_{20}O_6N_2ClS_2$ [M + H^+]: 507.0446, found 507.0457.

6-Chloro-3-methyl-4-(2-(2-thienyl)thiophen-3-ylsulfonyl)-3,4-dihydroquinoxalin-2(1*H*)-one (1g)

Following the same procedure as 5.1.5, the mixture of compound **1c** (60 mg, 0.125 mmol), thiophen-2-ylboronic acid (24 mg, 0.1875 mmol), $Pd(OAc)_2$ (6 mg, 0.025 mmol), xantphos (29 mg, 0.05mmol) was purged with argon. Toluene (8 mL) and triethylamine (0.097 mL, 0.6 mmol) were added and the reaction heated at 80℃ for 48 h. Compound **1g** was obtained as yellow solid (37 mg, 62%). mp 83-84℃; ^{1}H-NMR(400 MHz, $CDCl_3$, δ ppm) δ: 8.66 (s, 1H), 7.90 (s, 1H), 7.37 s, 1H), 7.33 (d, *J* = 4.8 Hz, 1H), 7.21 (d, *J* = 3.2 Hz, 1H), 7.13 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H), 7.01 (t, *J* = 4.4 Hz, 1H), 6.72 (d, *J* = 8.4 Hz, 1H), 5.22 (q, *J* = 7.2 Hz, 1H), 3.76 (s, 3H), 1.38 (d, *J* = 7.2 Hz, 3H); ^{13}C-NMR(100 MHz, $CDCl_3$, δ ppm) δ: 169.61, 159.26, 141.36, 140.02, 133.93, 131.16, 129.44, 128.84, 128.43, 127.61, 127.31, 127.15, 126.44, 126.12, 123.37, 116.69, 54.87, 53.16, 17.39; HRMS (ESI): *m/z*, calcd. for $C_{19}H_{16}O_5N_2ClS_3$ [M + H^+]: 482.9904, found 482.9914.

6-Chloro-3-methyl-4-(2-(2-furyl)thiophen-3-ylsulfonyl)-3,4-dihydroquinoxalin-2(1*H*)-one (1h)

Following the same procedure as 5.1.5, the mixture of compound **1c** (60 mg, 0.125 mmol), furan-2-ylboronic acid (21 mg, 0.19 mmol), $Pd(OAc)_2$ (6 mg, 0.025 mmol), xantphos (29 mg, 0.05mmol) was purged with argon. Toluene (8 mL) and triethylamine (0.097 mL, 0.6 mmol) were added and the reaction was heated at 80℃ for 48 h. Compound **1h** was obtained as yellow solid (27 mg, 46%). mp 85-87℃; ^{1}H-NMR(400 MHz, $CDCl_3$, δ ppm) δ: 9.15 (s, 1H), 7.78 (s, 1H), 7.46 (s, 1H), 7.41 (s, 1H), 7.12 (d, *J* = 8.0 Hz, 1H), 6.75 (d, *J* = 8.4 Hz, 1H), 6.66 (s, 1H), 6.46 (s, 1H), 5.22 (q, *J* = 6.8 Hz, 1H), 3.74 (s, 3H), 1.38 (d, *J* = 6.8 Hz, 3H); ^{13}C-NMR(100 MHz, $CDCl_3$, δ ppm) δ: 170.05, 159.33, 146.56, 143.77, 140.27, 137.13, 130.73, 129.37, 128.81, 127.20, 126.00, 125.84, 123.41, 116.85, 112.39, 108.95, 54.84, 53.09, 17.36; HRMS (ESI): *m/z*, calcd. for $C_{19}H_{16}O_6N_2ClS_2$ [M + H^+]: 467.0133, found 467.0140.

3-(7-Chloro-2-methyl-3-oxo-3,4-dihydroquinoxalin-1(2*H*)-ylsulfonyl)thiophene-2-carboxylic acid (2a).

The reaction mixture of compound **1a** (600 mg, 1.5 mmol), LiOH aqueous solution (2 M, 3 mL), methanol (3 mL) and THF (3 mL) was stirred at room temperature until the starting material disappeared. The reaction mixture was concentrated and then dissolved in water (50 mL). The aqueous phase was washed with EtOAc (30 mL x 3), and was adjusted to pH = 3-4 with 5 % HCl aqueous solution, and then extracted with EtOAc (50 ml x 3). The organic layer was dried over anhydrous $MgSO_4$, concentrated and purified with column chromatography on silica gel to afford compound **2a** as off-white solid (518 mg, 89 %); mp 118-120℃; ^{1}H-NMR(400 MHz, DMSO-d_6, δ ppm) δ: 10.62 (s, 1H, -NH), 7.88 (d, *J* = 5.2 Hz, 1H), 7.50 (s, 1H), 7.29 (s, *J* = 5.6 Hz, 1H), 7.23 (d, J_1 = 8.4 Hz, J_1 = 2.0 Hz, 1H), 6.88 (d, *J* = 8.8 Hz, 1H), 4.87 (q, *J* = 7.2 Hz, 1H), 1.18 (d, *J* = 7.6 Hz, 3H); ^{13}C-NMR(100 MHz, DMSO-d_6, δ ppm) δ: 167.62, 159.95, 138.16, 136.34, 131.19, 131.07, 130.86, 126.89, 125.95, 124.57, 122.80, 117.20, 54.01, 17.06; HRMS (ESI): *m/z*, calcd. for $C_{14}H_{12}ClN_2O_5S_2$ [M + H^+]: 386.9871, found 386.9861.

5-Chloro-3-(7-chloro-2-methyl-3-oxo-3,4-dihydroquinoxalin-1(2*H*)-ylsulfonyl)-thiophene-2-carboxylic acid (2b).

The reaction mixture of compound **1b** (325 mg, 0.75 mmol), LiOH aqueous solution (2 M, 1.5 mL), methanol (1.5 mL) and THF (1.5 mL) was stirred at room temperature for 30 min. The reaction mixture was concentrated and then dissolved in water (20 mL). The aqueous phase was washed with EtOAc (20 mL x 3), and was adjusted to pH = 3-4 with 2N HCl aqueous solution, and then extracted with EtOAc (30 ml x 3). The organic layer was dried over anhydrous $MgSO_4$, concentrated and purified with column chromatography on silica gel to afford compound **2b** as off-white solid (306 mg, yield 97 %); mp 206-208℃; ^{1}H-NMR(400 MHz, DMSO-d_6, δ ppm) δ: 10.68 (s, 1H, -NH), 7.54 (s, 1H), 7.19 ~ 7.22 (m, 2H), 6.94 (d, *J* = 8.4 Hz, 1H), 5.01 (q, *J* = 7.2 Hz, 1H), 1.15 (d, *J* = 6.8 Hz, 3H); ^{13}C-NMR(100 MHz, DMSO-d_6, δ ppm) δ: 167.92, 159.19, 130.75, 129.28, 126.48, 125.82, 124.34, 123.07, 117.15, 53.85, 17.10; HRMS (ESI): *m/z*, calcd. for $C_{14}H_{11}Cl_2N_2O_5S_2$ [M + H^+]: 420.9481, found 420.9472.

Isopropyl 3-(7-chloro-2-methyl-3-oxo-3,4-dihydroquinoxalin-1(2*H*)-ylsulfonyl)-thiophene-2-carboxylate (3a).

The reaction mixture of compound **2a** (518 mg, 1.33 mmol), *iso*-propanol (5 mL) and 5 drops concentrated H_2SO_4 was heated at 85℃ for 15.5 h. The mixture was concentrated under reduced pressure and the resulting residue was dissolved in saturated $NaHCO_3$. The aqueous layer was

extracted with EtOAc (50 mL x 3), and then the combined organic phase was washed with brine (100 mL x 1) and dried over anhydrous $MgSO_4$. After concentration, the crude product was obtained and purified by column chromatography on silica gel to afford title compound as light yellow solid (101 mg, 18%); mp 125-127℃; ^{1}H-NMR(300 MHz, $CDCl_3$, δ ppm) δ: 8.95 (s, 1H), 7.72 (s, 1H), 7.36 (d, *J* = 4.8 Hz, 1H), 7.26 (s, 1H), 7.13 (d, *J* = 8.7 Hz, 1H), 7.74 (d, *J* = 8.4 Hz, 1H), 5.32 (q, *J* = 7.2 Hz, 1H), 5.13 (heptet, *J* = 6.3 Hz, 1H), 1.36 (d, *J* = 7.2 Hz, 3H), 1.31 (d, *J* = 6.3 Hz, 3H), 1.27 (d, *J* = 6.3 Hz, 3H); ^{13}C-NMR(150 MHz, $CDCl_3$, δ ppm) δ: 170.00, 158.41, 139.31, 135.57, 131.41, 129.47, 128.89, 128.81, 127.24, 126.13, 123.46, 116.69, 70.75, 54.69, 21.76, 21.68, 17.44; HRMS (ESI): *m/z*, calcd. for $C_{17}H_{18}ClN_2O_5S_2$ [M + H^+]: 429.0340, found 429.0331.

3-Methylbut-2-enyl 3-(7-chloro-2-methyl-3-oxo-3,4-dihydroquinoxalin-1(2*H*)-ylsulfonyl)thiophene-2-carboxylate (3b).

To the solution of compound **2a** (200 mg, 0.5 mmol) and K_2CO_3 (141 mg, 1.02 mmol) in acetone (5 mL), 1-bromo-3-methylbut-2-ene (150 mg, 1.0 mmol) was added at 0℃. The reaction mixture was stirred for 2.5 h and then concentrated. The resulting residue was dissolved in water (30 mL). The aqueous layer was extracted with EtOAc (20 mL x 3), and then the combined organic phase was washed with brine (50 mL x 1) and dried over anhydrous $MgSO_4$. After concentration, the crude product was obtained and purified by column chromatography on silica gel with petroleum ether-EtOAc (v/v = 2:1) to afford title compound as light yellow solid (75 mg, 33%); mp 139-140℃; ^{1}H-NMR(400 MHz, $CDCl_3$, δ ppm) δ: 9.23 (s, 1H), 7.71 (s, 1H), 7.40 (d, *J* = 5.2 Hz, 1H), 7.29 (d, *J* = 5.2 Hz, 1H), 7.14 (d, J_1 = 8.4 Hz, J_2 =1.6 Hz, 1H), 6.78 (d, *J* = 8.4 Hz, 1H), 5.36 (t, *J* = 7.2 Hz, 1H), 5.26 (q, *J* = 7.2 Hz, 1H), 4.73-4.78 (m, 1H), 4.62 ~ 4.67 (m, 1H), 1.76(s, 3H), 1.72(s, 3H), 1.36 (d, *J* = 7.2 Hz, 3H); ^{13}C-NMR(100 MHz, $CDCl_3$, δ ppm) δ: 170.20, 158.97, 140.30, 139.30, 135.22, 131.45, 129.52, 129.20, 128.77, 127.24, 126.08, 123.47, 117.58, 116.88, 63.37, 54.57, 25.78, 18.11, 17.27; HRMS (ESI): *m/z*, calcd. for $C_{19}H_{20}ClN_2O_5S_2$ [M + H^+]: 455.0497, found 455.0499.

Isopropyl 5-chloro-3-(7-chloro-2-methyl-3-oxo-3,4-dihydroquinoxalin-1(2*H*)-ylsulfonyl)thiophene-2-carboxylate (3c).

The reaction mixture of compound **2b** (306 mg, 0.73 mmol), *iso*-propanol (0.5 mL, 6.5 mmol), EDC.HCl (277 mg, 1.45 mmol) and DMAP (177 mg, 1.45 mmol) in CH_2Cl_2 (4 mL) was stirred at room temperature for 12 h. The reaction was quenched by adding water (20 mL) and the resulting mixture was extracted with CH_2Cl_2 (20 mL x 3). The organic layer was washed with brine and dried over anhydrous $MgSO_4$. After concentration, the crude product was obtained and purified by column chromatography on silica gel with petroleum ether-EtOAc (v/v = 3:1) to afford the title compound as white solid (216 mg, 64%); mp 114-117℃; ^{1}H-NMR(400 MHz, Acetone-d_6, δ ppm) δ: 9.58 (s, 1H), 7.61 (d, *J* = 1.6 Hz, 1H), 7.28 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H), 7.16 (s, 1H), 7.02 (d, *J* = 8.8 Hz, 1H), 5.02~5.10 (m, 2H), 1.28~1.33 (m, 9H); ^{13}C-NMR(100 MHz, Acetone-d_6, δ ppm) δ: 168.49, 157.86, 139.77, 135.00, 132.39, 130.80, 128.50, 127.90, 127.05, 123.77, 117.97, 117.90, 71.80, 55.39, 21.69, 21.65, 17.35; HRMS (ESI): *m/z*, calcd. for $C_{17}H_{17}Cl_2N_2O_5S_2$ [M + H^+]: 462.9950, found 462.9956.

3-(7-chloro-2-methyl-3-oxo-3,4-dihydroquinoxalin-1(2*H*)-ylsulfonyl)-*N*-methoxy-*N*-methylthiophene-2-carboxamide (3d).

The mixture of compound **2a** (200 mg, 0.52 mmol), *N*,*O*-dimethylhydroxyamine hydrochloride (152 mg, 1.56 mmol), EDC.HCl (195 mg, 1.0 mmol) and DMAP (125 mg, 1.0 mmol) in CH_2Cl_2

(3 mL) was stirred at room temperature until the starting material disappeared. The reaction was quenched by adding water (20 mL) and the resulting mixture was extracted with CH_2Cl_2 (20 mL x 2). The organic layer was washed with brine and dried over anhydrous $MgSO_4$. After concentration, the crude product was obtained and purified by column chromatography on silica gel with DCM-acetone (v/v = 15:1) to afford title compound as orange solid (164 mg, 75%); mp 173-174℃; ^{1}H-NMR(400 MHz, Acetone-d_6, δ ppm) δ: 9.54 (s, 1H), 7.67 (d, J = 5.6 Hz, 1H), 7.64 (d, J = 1.2 Hz, 1H), 7.29 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H), 7.02 (d, J = 8.4 Hz, 1H), 6.93 (d, J = 5.2 Hz, 1H), 4.93 (q, J = 7.2, 1H), 3.54 (s, 3H), 3.24 (s, 3H), 1.25 (d, J = 7.6 Hz, 3H); ^{13}C-NMR(100 MHz, Acetone-d_6, δ ppm) δ: 168.46, 141.21, 135.85, 132.30, 128.72, 128.30, 127.78, 127.64, 126.02, 124.00, 117.88, 61.59, 55.06, 17.42; HRMS (ESI): *m/z*, calcd. for $C_{16}H_{17}ClN_3O_5S_2$ [M + H^+]: 430.0293, found 430.0297.

3-(7-chloro-2-methyl-3-oxo-3,4-dihydroquinoxalin-1(2*H*)-ylsulfonyl)-*N*-isopropyl-thiophene-2-carboxamide (3e).

Following the procedure of 5.1.14, the reaction mixture of compound **2a** (200 mg, 0.52 mmol), *iso*-propylamine (0.5 mL), BOP (442 mg, 1.0 mmol) and Et_3N (101 mg, 1.0 mmol) in CH_2Cl_2 (3 mL) was stirred at room temperature to afford the title compound as white solid (68 mg, 31%); mp 99-101℃; ^{1}H-NMR(300 MHz, Acetone-d_6, δ ppm) δ: 9.54 (s, 1H), 7.70 (s, 1H), 7.62 (d, J = 5.1 Hz, 1H), 7.60 (d, J = 2.1 Hz, 1H), 7.34 (dd, J_1 = 8.4 Hz, J_2 = 2.1 Hz, 1H), 6.99 (d, J = 8.4 Hz, 1H), 6.97 (d, J = 5.1 Hz, 1H), 4.77 (q, J = 7.2 Hz, 1H), 3.92 (m, 1H), 1.26 (d, J = 7.2 Hz, 3H); 1.18 (d, J = 6.9 Hz, 3H); ^{13}C-NMR(150 MHz, Acetone-d_6, δ ppm) δ: 168.17, 158.74, 145.41, 132.93, 132.90, 129.43, 129.37, 129.30, 128.70, 128.04, 128.34, 118.35, 55.41, 43.07, 22.26, 22.18, 16.91; HRMS (ESI): *m/z*, calcd. for $C_{17}H_{19}ClN_3O_4S_2$ [M + H^+]: 428.0500, found 428.0502.

6-Chloro-4-(2-hydroxymethyl)thiophen-3-ylsulfonyl)-3-methyl-3,4-dihydroquinoxalin-2(1*H*)-one (4a).

The solution of compound **1a** (4.2 g, 10.5 mmol) in anhydrous THF (50 mL) was cooled in ice-salt bath. $LiAlH_4$ (596 mg, 16 mmol) was added to the above solution in several portions and the resulting mixture was stirred for 30 min. The reaction was quenched by adding small amount of water carefully. The reaction mixture was concentrated and the residue was dissolved in EtOAc (100 mL) and washed with 1N HCl (50 mL x1) and water (50 mL x 3). The organic layer was dried over anhydrous $MgSO_4$ and concentrated to give the crude product, which was purified by column chromatograph on silica gel with petroleum ether-EtOAc (v/v = 2:1) to afford the title compound as off-white solid (2.5 g, 64%); mp 180-181℃; ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) δ: 8.53 (s, 1H), 7.72 (s, 1H), 7.24 (d, J = 2.0 Hz, 1H), 7.14 (d, J = 5.2 Hz, 1H), 6.76 (d, J = 5.6 Hz, 1H), 6.72 (d, J = 8.4 Hz, 1H), 4.92 (d, J = 15.2 Hz, 1H), 4.82 (q, J = 7.2 Hz, 1H), 4.57 (d, J = 15.2 Hz, 1H), 3.32 (brs, 1H), 1.31 (d, J = 7.2 Hz, 3H); ^{13}C-NMR(100 MHz, $CDCl_3$, δ ppm) δ: 169.12, 152.30, 130.39, 129.17, 128.78, 128.67, 127.36, 125.02, 123.06, 116.75, 58.30, 54.47, 16.43; HRMS (ESI): *m/z*, calcd. for $C_{14}H_{13}ClN_2O_4S_2Na$ [M + Na^+]: 394.9897, found 394.9903.

6-Chloro-4-(5-chloro-2-(hydroxymethyl)thiophen-3-ylsulfonyl)-3-methyl-3,4-dihydro-quinoxalin-2(1*H*)-one (4b).

Following the procedure of 5.1.16, the mixture of compound **1b** (1.2 g, 2.8 mmol) and $LiAlH_4$ (142 mg, 4.2 mmol) in anhydrous THF (20 mL) was stirred at 0℃ for 40 min to afford the title compound as off-white solid (905 mg, 79%); mp 182-183℃; ^{1}H-NMR (400 MHz, DMSO-d_6, δ ppm) δ: 10.73 (s, 1H), 7.49 (d, J = 1.6 Hz, 1H), 7.40 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1H), 6.90 (d, J = 8.4 Hz, 1H), 6.81 (s, 1H), 6.17 (t, J = 4.8 Hz, 1H), 4.63 (dd, J_1 = 16.0 Hz, J_2 = 4.4 Hz, 1H), 4.55

(q, *J* = 7.6 Hz, 1H), 3.95 (dd, J_1 = 16.0 Hz, J_2 = 4.8 Hz, 1H), 1.17 (d, *J* = 7.2 Hz, 3H); ^{13}C-NMR(100 MHz, DMSO-d_6, δ ppm) δ: 167.08, 155.37, 132.26, 128.80, 127.67, 127.55, 127.15, 126.03, 125.56, 121.76, 117.29, 57.73, 54.10, 16.41; HRMS (ESI): *m/z*, calcd. for $C_{14}H_{12}Cl_2N_2O_4S_2$ [M + Na^+]: 428.9508, found 428.9507.

3-(7-chloro-2-methyl-3-oxo-3,4-dihydroquinoxalin-1(2*H*)-ylsulfonyl)thiophene-2-Carbaldehyde (5a).

The mixture of compound **4a** (374 mg, 1.0 mmol) and PDC (752 mg, 2.0 mmol) in dichloromethane (5 mL) was stirred at room temperature for 4 h. Dichloromethane (50 mL) was added to the reaction mixture, which was filtered. The filtrate was concentrated and the residue was purified by column chromatograph on silica gel with petroleum ether-EtOAc (v/v = 2:1) to afford the title compound as off-white solid (155 mg, 42%); mp 255-257℃; ^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm) δ: 10.54 (s, 1H), 9.34 (s, 1H), 8.21 (d, *J* = 4.8 Hz, 1H), 7.58 (d, *J* = 2.4 Hz, 1H), 7.41(dd, J_1 = 8.7 Hz, J_2 = 2.4 Hz, 1H), 7.24 (d, *J* = 5.4 Hz, 1H), 6.81 (d, *J* = 8.7 Hz, 1H), 4.63 (q, *J* = 7.2 Hz, 1H), 1.19 (d, *J* = 7.2 Hz, 3H); HRMS (ESI): *m/z*, calcd. for $C_{14}H_{12}ClN_2O_4S_2$ [M + H^+]: 370.9922, found 370.9920.

5-chloro-3-(7-chloro-2-methyl-3-oxo-3,4-dihydroquinoxalin-1(2*H*)-ylsulfonyl)-thiophene-2-Carbaldehyde (5b).

Following the procedure of 5.1.18, the mixture of compound **4b** (905 mg, 2.2 mmol) and PDC (1.67 g, 4.4 mmol) in dichloromethane (10 mL) was stirred at room temperature to afford the title compound as off-white solid (611 mg, 68%); mp 238-240℃; ^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm) δ: 10.71 (s, 1H), 9.20 (s, 1H), 7.58 (s, 1H), 7.44 (m, 2H), 6.85 (d, *J* = 8.4 Hz, 1H), 4.67 (q, *J* = 7.2 Hz, 1H), 1.20 (d, *J* = 7.6 Hz, 3H); HRMS (ESI): *m/z*, calcd. for $C_{14}H_{11}Cl_2N_2O_4S_2$ [M + H^+]: 404.9532, found 404.9530.

6-Chloro-3-methyl-4-(2-((thiazol-2-ylimino)methyl)thiophen-3-ylsulfonyl)-3,4-dihydroquinoxalin-2(1*H*)-one (6a).

The mixture of compound **5a** (370 mg, 1.0 mmol), 2-aminothiazole (300 mg, 3.0 mmol) and 9 drops HCOOH in methanol (5 mL) was refluxed for 20 h. The cooled mixture was concentrated and the residue was dissolved in EtOAc (50 mL). The organic layer was washed with water (50 mL x 3) and dried over anhydrous $MgSO_4$. After concentration, the crude product was purified by column chromatograph on silica gel with DCM-MeOH (v/v = 80:1) to afford the title compound as yellow solid (298 mg, 66%); mp 226-227℃; ^{1}H-NMR(400 MHz, Acetone-d_6, δ ppm) δ: 9.45 (s, 1H), 8.90 (s, 1H), 7.88 (d, *J* = 4.8 Hz, 1H), 7.69 (d, *J* = 2.8 Hz, 1H), 7.65 (d, *J* = 2.0 Hz, 1H), 7.57 (d, *J* = 3.2 Hz, 1H), 7.31 (d, *J* = 5.2 Hz, 1H), 7.03 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1H), 6.88 (d, *J* = 8.4 Hz, 1H), 4.70 (q, *J* = 7.2 Hz, 1H), 1.28 (d, *J* = 7.2 Hz, 3H); ^{13}C-NMR(100 MHz, Acetone-d_6, δ ppm) δ: 171.71, 167.56, 153.05, 144.77, 142.83, 138.92, 133.48, 133.18, 130.10, 129.97, 129.71, 128.46, 122.55, 121.01, 118.04, 117.97, 55.79, 17.11; HRMS (ESI): *m/z*, calcd. for $C_{17}H_{14}ClN_4O_3S_3$ [M + H^+]: 452.9911, found 452.9918.

6-Chloro-3-methyl-4-(5-chloro-(2-((thiazol-2-ylimino)methyl)thiophen-3-ylsulfonyl)-3,4-dihydroquinoxalin-2(1*H*)-one (6b).

Following the procedure of 5.1.20, the mixture of compound **5b** (305 mg, 0.75 mmol), 2-aminothiazole (226 mg, 2.25 mmol) and HCOOH (0.1 mL) in methanol (5 mL) and THF (1 mL) was refluxed to afford the title compound as yellow solid (323 mg, 56%); mp 231-232℃; ^{1}H-NMR(400 MHz, DMSO-d_6, δ ppm) δ: 10.73 (s, 1H), 8.53 (s, 1H), 7.73 (d, *J* = 2.8 Hz, 2H), 7.56 (d, *J* = 2.0 Hz, 1H), 7.44 (s, 1H), 7.02 (dd, J_1 = 8.8 Hz, J_2 = 2.0 Hz,1H), 6.77 (d, *J* = 8.4 Hz,

1H), 4.61 (q, *J* = 7.2 Hz, 1H), 1.18 (d, *J* = 7.2 Hz, 3H); ^{13}C-NMR(100 MHz, DMSO-d_6, δ ppm) δ: 169.68, 166.65, 150.66, 142.09, 141.93, 136.59, 135.90, 132.48, 129.44, 128.42, 126.76, 121.44, 120.59, 117.39, 54.39, 16.42; HRMS (ESI): *m/z*, calcd. for $C_{17}H_{13}Cl_2N_4O_3S_3$ [M + H^+]: 486.9521, found 486.9526.

6-Chloro-3-methyl-4-(5-chloro-2-(oxazol-5-yl)thiophen-3-ylsulfonyl)-3,4-dihydroquinoxanlin-2 (1*H*)-one (6c).

The mixture of compound **5b** (101 mg, 0.25 mmol) and 1-(isocyanomethylsulfonyl)-4-methylbenzene (58 mg, 0.3 mmol) in methanol (5 mL) was stirred at 0℃ for 20 min. Then K_2CO_3 (52 mg, 0.375 mmol) was added and stirred for further 30 min. The reaction mixture was warmed to room temperature and stirred for 4 h. Dichloromethane (50 mL) was added to the mixture and then washed with water and brine, and dried over anhydrous $MgSO_4$. After concentration, the crude product was obtained and purified by column chromatography on silica gel with petroleum ether-EtOAc (v/v = 4:1, v/v = 2.5:1). Compound **6c** was obtained as white solid (55 mg, 50%); mp 264-265℃; ^{1}H-NMR(400 MHz, DMSO-d_6, δ ppm) δ: 10.72 (s, 1H), 8.37 (s, 1H), 7.39 (s, 1H), 7.31 (s, 1H), 7.23 (d, *J* = 9.2 Hz, 1H), 7.20 (s, 1H), 6.80 (d, *J* = 8.8 Hz, 1H), 4.54 (q, *J* = 7.2 Hz, 1H), 1.14 (d, *J* = 7.2 Hz, 3H); ^{13}C-NMR(100 MHz, DMSO-d_6, δ ppm) δ: 166.95, 152.99, 140.61, 132.12, 131.36, 130.61, 130.55, 128.76, 128.00, 127.45, 127.32, 126.16, 121.35, 117.19, 54.20, 16.31; HRMS (ESI): *m/z*, calcd. for $C_{16}H_{12}Cl_2N_3O_4S_2$ [M + H^+]: 443.9641, found 443.9646.

6-Chloro-3-methyl-4-(2-((thiazol-2-ylamino)methyl)thiophen-3-ylsulfonyl)-3,4-dihydroquinoxalin-2(1*H*)-one (7a).

The mixture of compound **6a** (189 mg, 0.42 mmol) and sodium triacetoxyborohydride (177 mg, 0.84 mmol) in dichloromethane (3 mL) was stirred at room temperature for 20 h. The reaction mixture was diluted with dichloromethane (30 mL) and quenched with cold water (20 mL). The organic layer was separated and washed with water (20 mL x 2), dried over anhydrous $MgSO_4$. After concentration, the crude product was purified by column chromatograph on silica gel with DCM-MeOH (v/v = 50:1) to afford the title compound as yellow solid (180 mg, 94%); mp 116-118℃; ^{1}H-NMR(400 MHz, Acetone-d_6, δ ppm) δ: 10.00 (s, 1H), 7.62 (d, *J* = 1.6 Hz, 1H), 7.51 (d, *J* = 5.2 Hz, 1H), 7.41 (d, *J* = 4.0 Hz, 1H), 7.32 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1H), 7.18 (d, *J* = 8.4 Hz, 1H), 7.00 (d, *J* = 4.4 Hz, 1H), 6.96 (d, *J* = 5.2 Hz, 1H), 4.88 (d, *J* = 16.4 Hz, 1H), 4.75 (q, *J* = 7.2 Hz, 1H), 4.60 (d, *J* = 16.4 Hz, 1H), 1.29 (d, *J* = 7.2 Hz, 3H); ^{13}C-NMR(100 MHz, Acetone-d_6, δ ppm) δ: 170.80, 168.06, 146.71, 133.79, 133.21, 130.60, 129.31, 128.87, 128.52, 127.98, 127.29, 123.64, 118.79, 118.71, 108.84, 55.53, 44.17, 16.97; HRMS (ESI): *m/z*, calcd. for $C_{17}H_{16}ClN_4O_3S_3$ [M + H^+]: 455.0068, found 455.0075.

6-Chloro -4-(5-chloro-(2-((thiazol-2-ylamino)methyl)thiophen-3-ylsulfonyl)-3-methyl-3,4-dihydroquinoxalin-2(1*H*)-one (7b).

Following the procedure of 5.1.25, the mixture of compound **6b** (283 mg, 0.58 mmol), and sodium triacetoxyborohydride (246 mg, 1.16 mmol) in dichloromethane (3 mL) was stirred at room temperature to afford the title compound as white solid (185 mg, 65%); mp 174-175℃; ^{1}H-NMR(400 MHz, Acetone-d_6, δ ppm) δ: 9.71 (s, 1H), 7.61 (d, *J* = 2.4 Hz, 1H), 7.38 (dd, J_1 = 9.6 Hz, J_2 = 2.4 Hz, 1H), 7.10 (s, 1H), 7.08 (d, *J* = 4.4 Hz, 1H), 6.70 (s, 1H), 6.69 (d, *J* = 3.6 Hz, 1H), 4.69 ~ 4.75 (m, 2H), 4.44 (d, *J* = 16.8 Hz, 1H), 1.29 (d, *J* = 7.2 Hz, 3H); ^{13}C-NMR(100 MHz, Acetone-d_6, δ ppm) δ: 169.19, 168.09, 150.97, 138.55, 133.33, 131.56, 129.63, 128.96, 128.06, 126.66, 123.42, 118.39, 108.81, 55.61, 42.92, 16.95; HRMS (ESI): *m/z*, calcd. for

$C_{17}H_{15}Cl_2N_4O_3S_3$ [M + H^+]: 488.9678, found 488.9686.

Anti-HIV activity assay

The anti-HIV-1 activity assay was performed according to the procedure as described in the literature. [15]

Table 1s. Inhibitory effects of seven compounds on wild-type and NNRTI-resistant HIV-1 replication

Compound	IC_{50} (μM)[a]		
	VSVG/HIV_{wt}	VSVG/$HIV_{RT\text{-}K103N}$	VSVG/$HIV_{RT\text{-}Y181C}$
1a	0.2	2.6 (13)[b]	> 10 (>50)
1b	0.07	7.94 (113)	> 10 (>143)
1c	0.13	6.39 (49)	> 10 (>77)
1d	0.075	6.68 (89)	> 10 (>133)
1h	1.97	> 10 (>5)	> 10 (>5)
3a	1.09	> 10 (>9)	> 10 (>9)
3b	0.77	> 10 (>13)	> 10 (>13)
Nevirapine	0.04	1.29 (32)	> 10 (>250)

a. Compound dose (μM) required to inhibit the HIV replication activity by 50 %.

b. Folds of IC_{50} value compared to wt IC_{50}

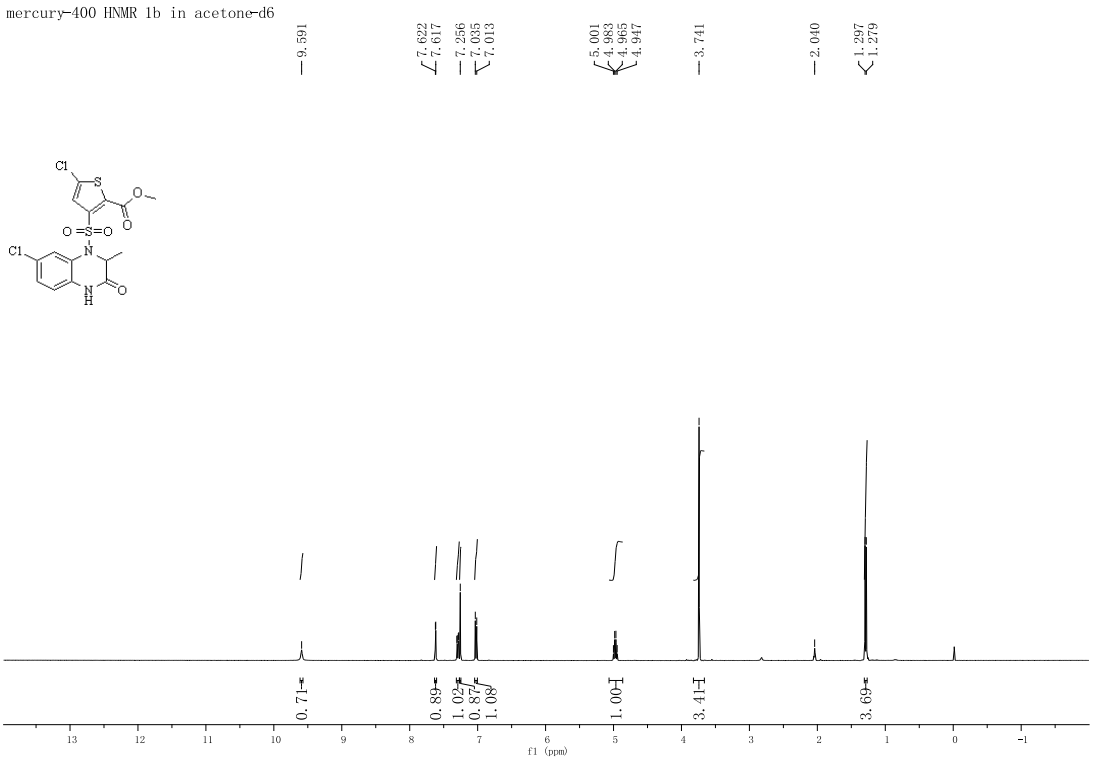
c. The highest final concentration of tested compounds is 10μM.

Computational Studies

All molecular computation studies were performed on a Dell 2.83 GHz Core 2 running Windows XP. The X-ray crystal structure of reverse transcriptase complexed with efavirenz was retrieved from PDB (PDB code: 1FK9).[17] The CDOCKER protocol in Discovery Studio 2.5.5 (Accelrys Software Inc., San Diego, CA) was used in this study to investigate the binding mode of compound **1b** in the crystal structure HIV-1 reverse transcriptase.[16] CDOCKER uses molecular dynamics (MD) with CHARMm force field scheme to dock ligands into a binding site of targeted protein. The water molecules in protein were removed and the protein was prepared by adding hydrogen and correcting incomplete residues using Clean Protein tool of DS, then the protein was refined with CHARMm. The binding site was constructed within 7 Å with efavirenz set as the center. Compound **1b** was built and minimized using Clean Geometry tool of DS and refined with CHARMm force field. Docking of compound **1b** into the reverse transcriptase with CDOCKER was done using the default parameters except that Pose Cluster Radius was defined as 0.5 Å for increasing the diversity of the docked poses. The pose with the top –CDOCKER_INTERACTION_ENERGY was chosen for analyzing the binding features of compound 1b and HIV-1 reverse transcriptase

Copies of 1H NMR and 13C NMR spectra

mercury-400 HNMR 1b in acetone-d6



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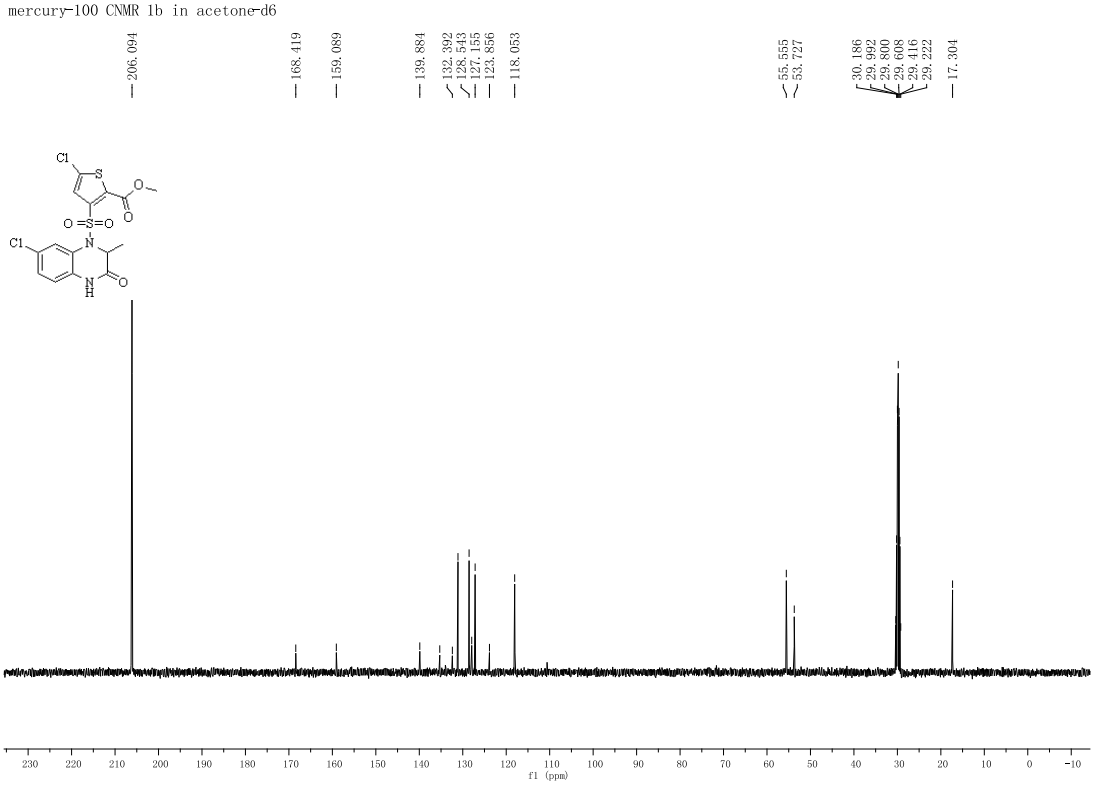
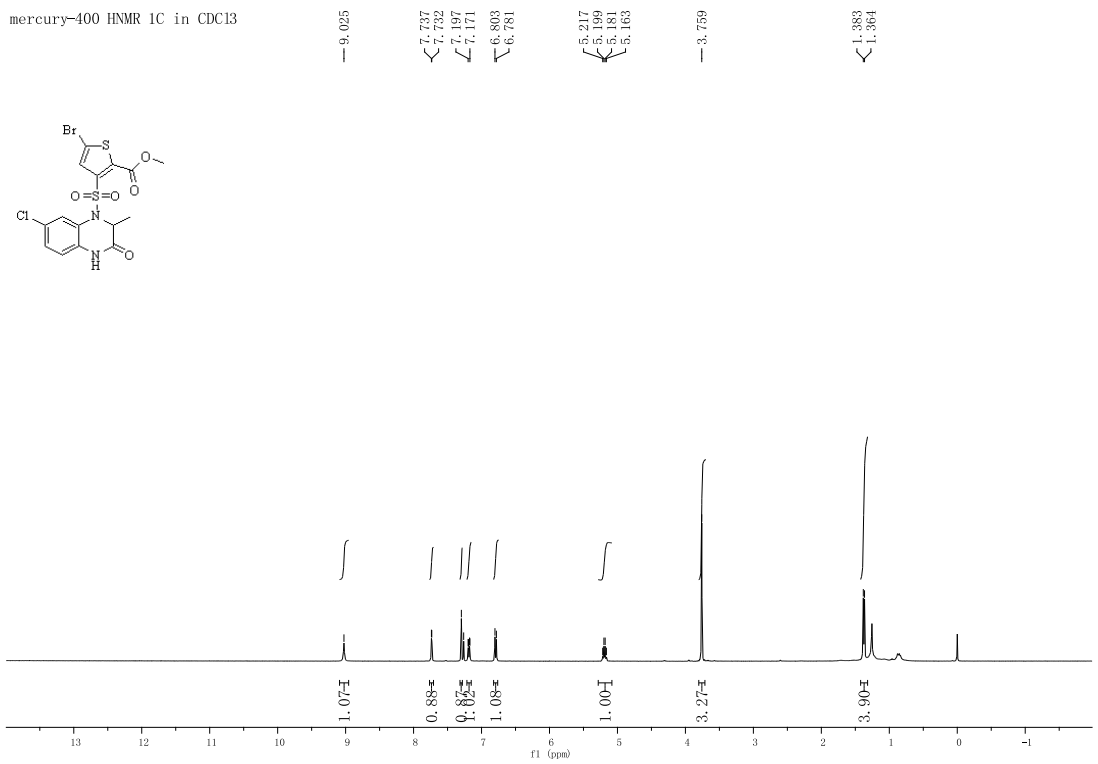


mercury-400 HNMR 1C in CDCl3



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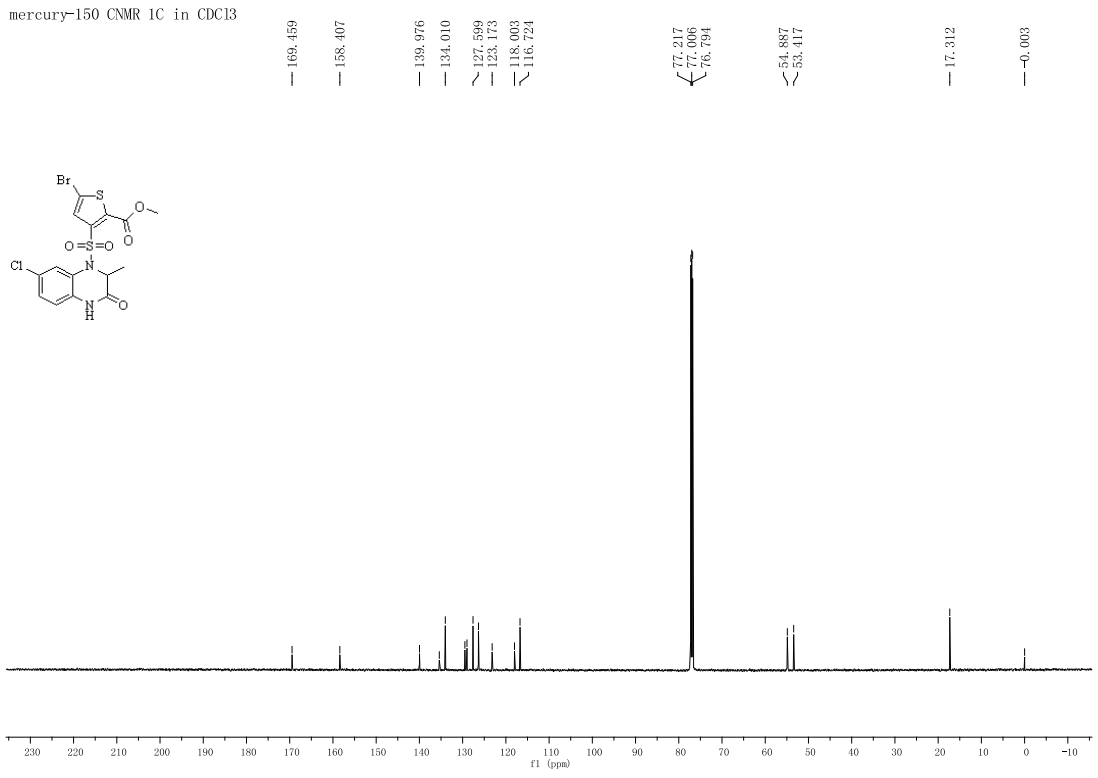

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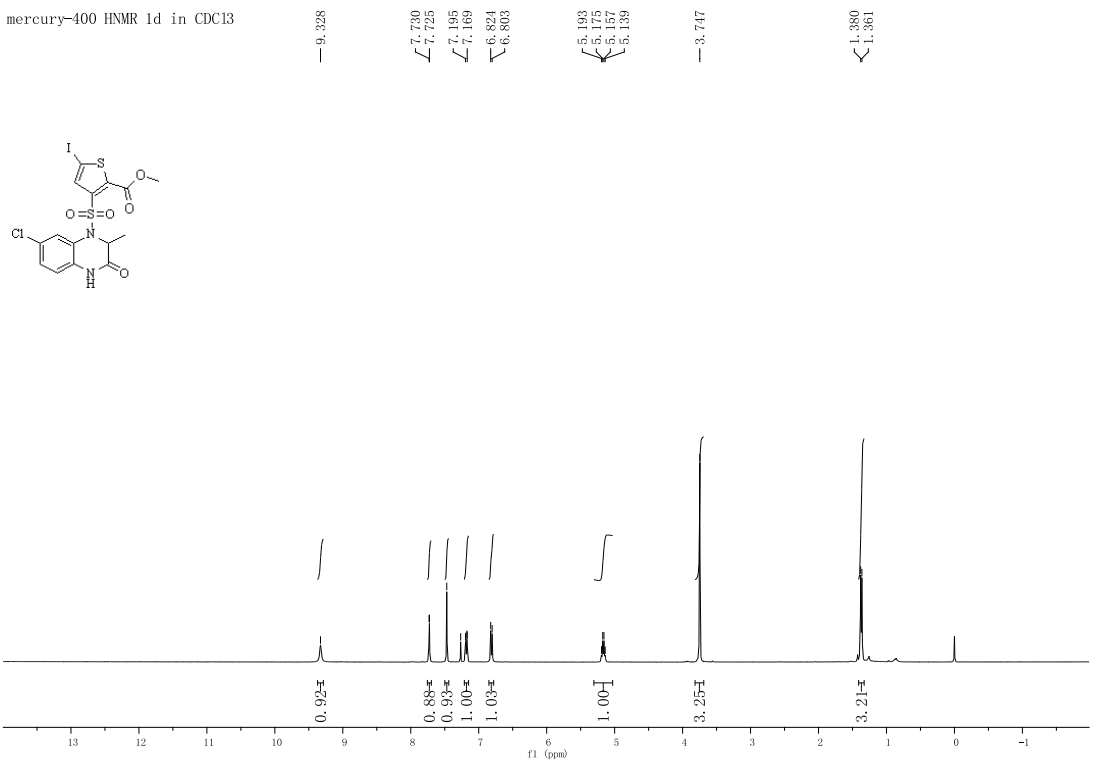

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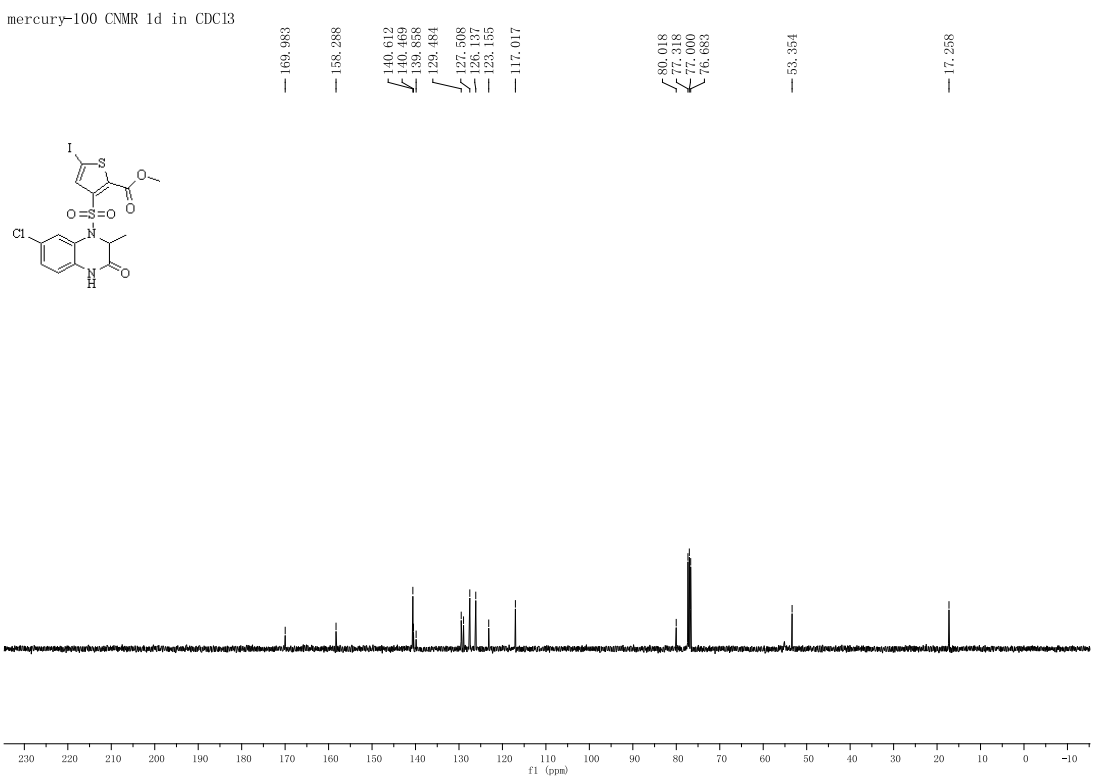

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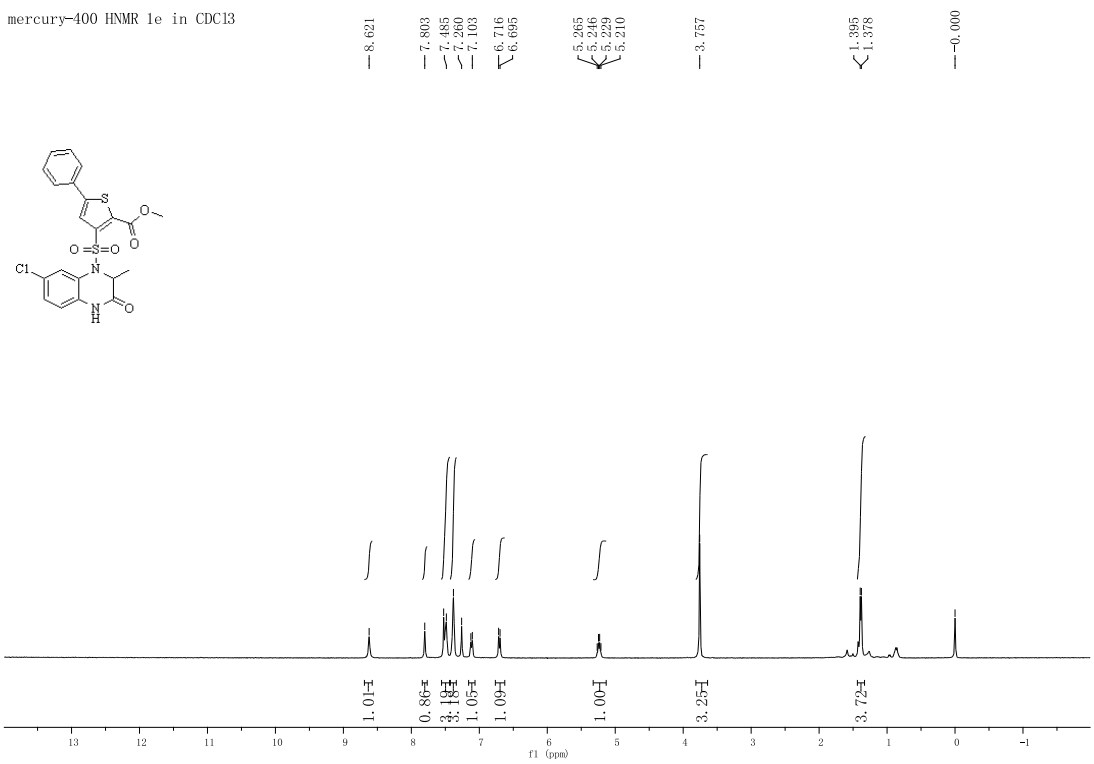

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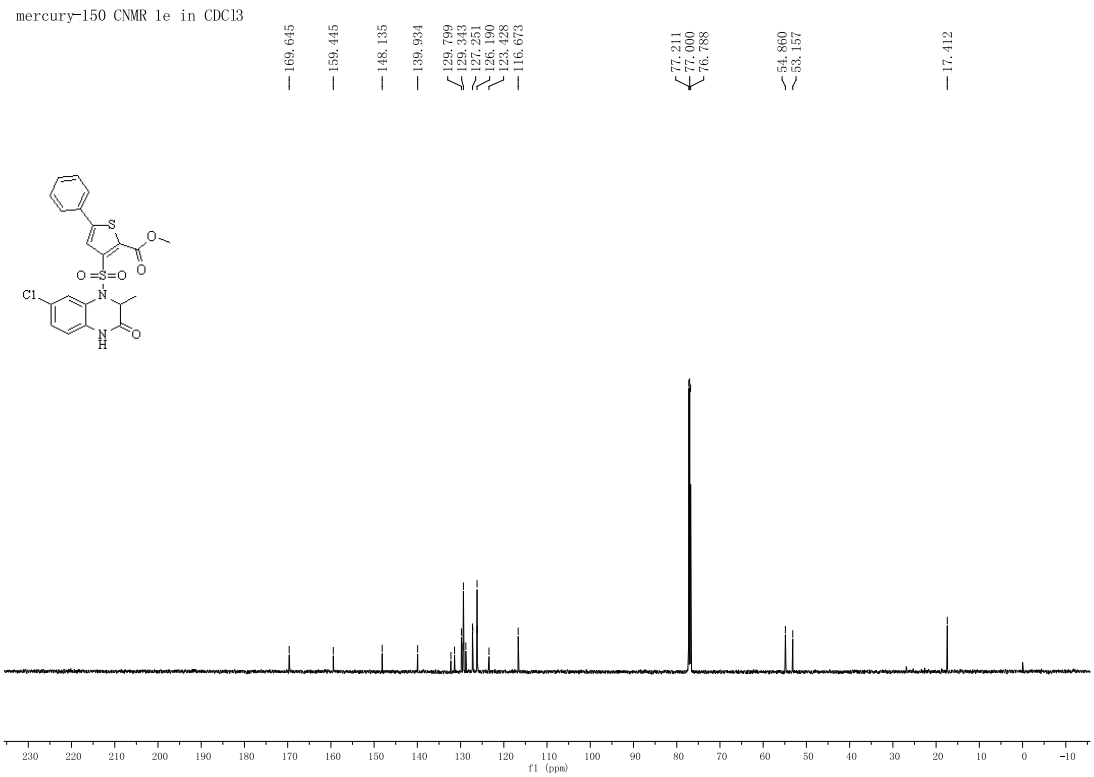

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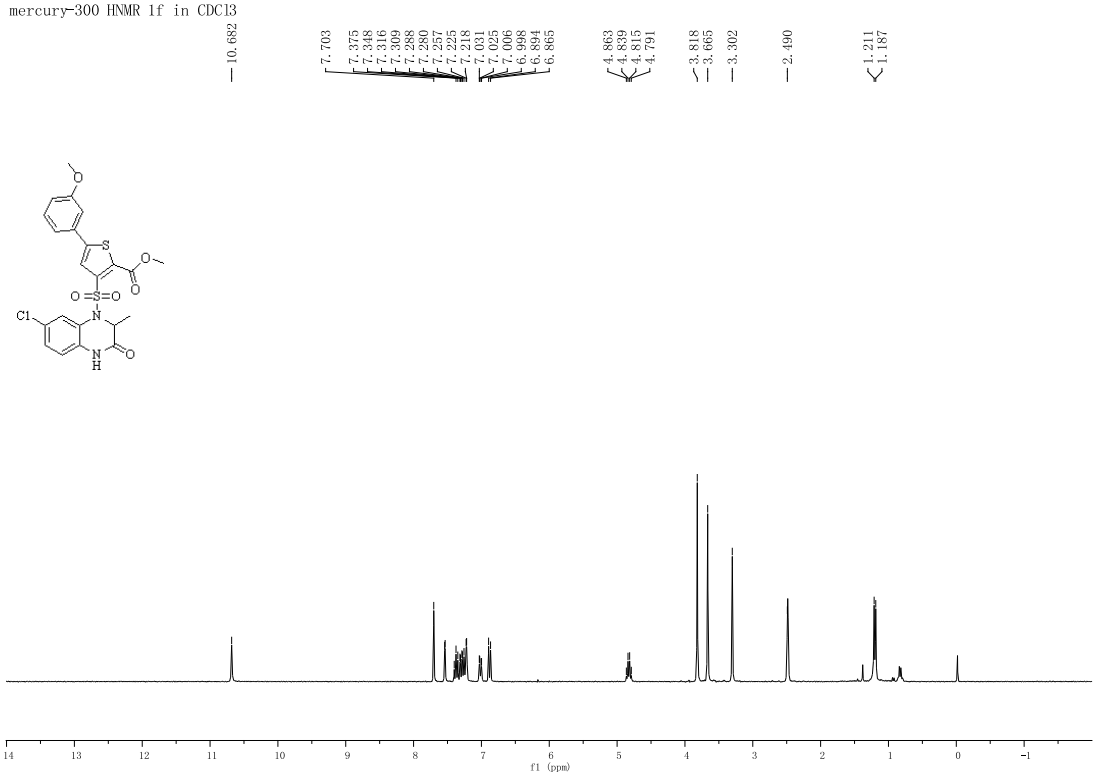

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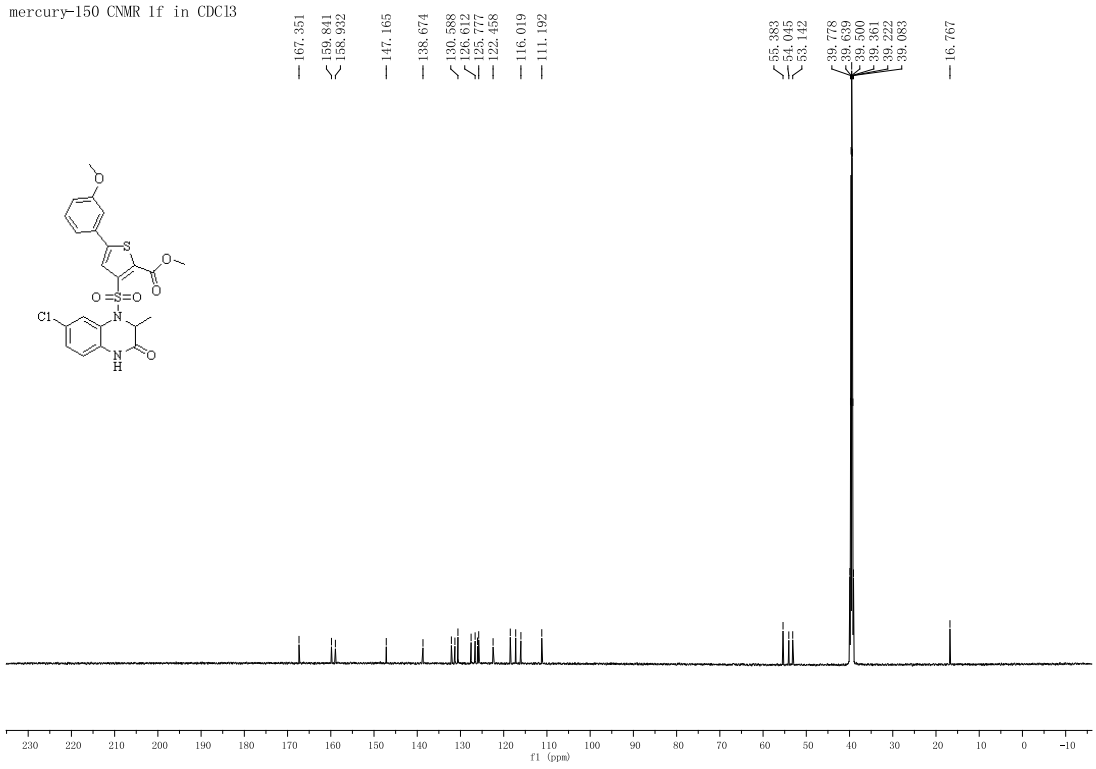

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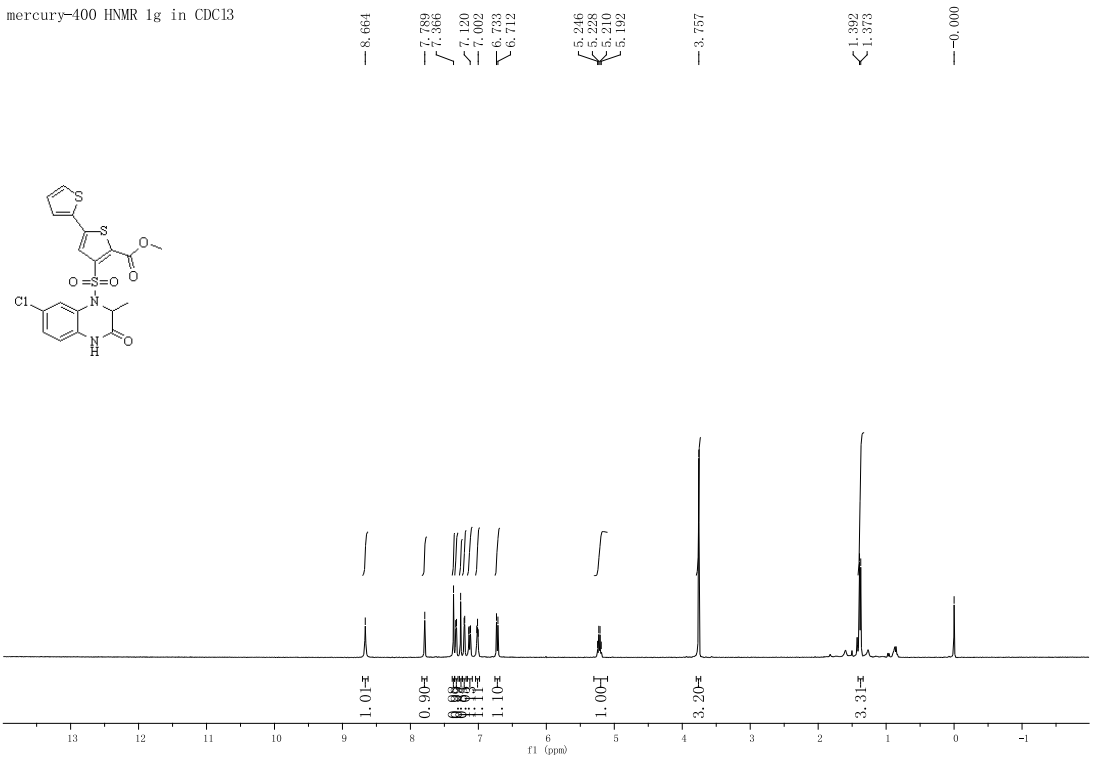
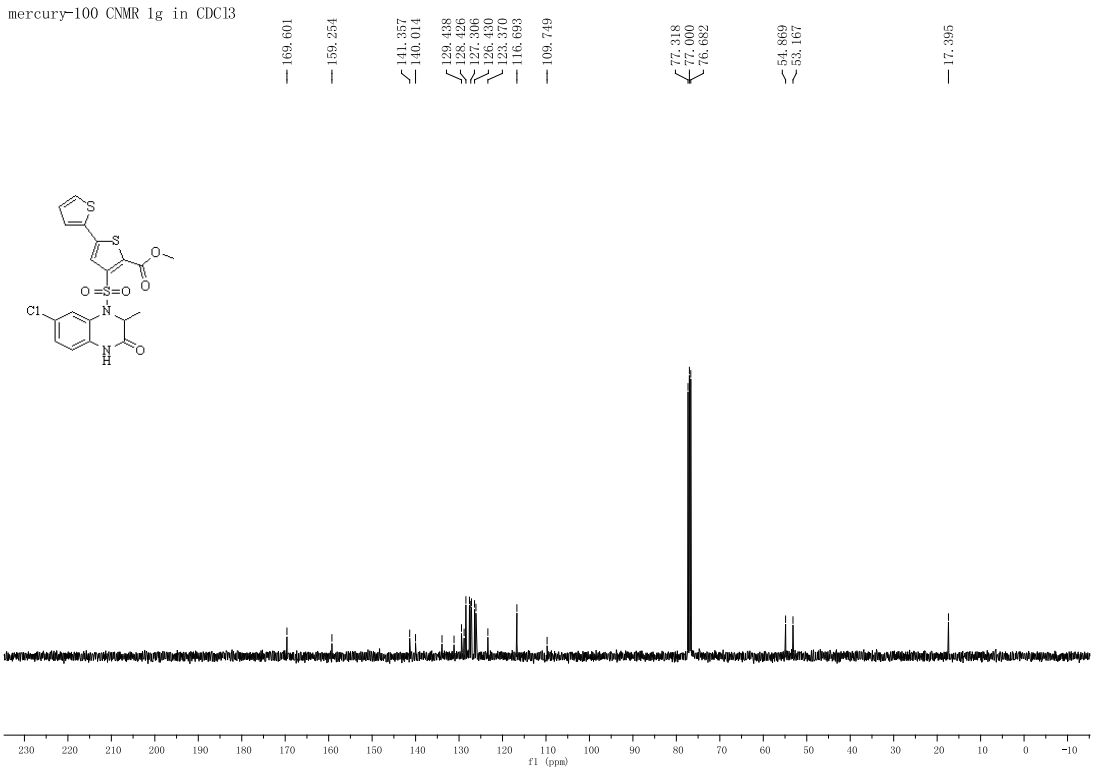


mercury-100 CNMR 1g in CDCl3



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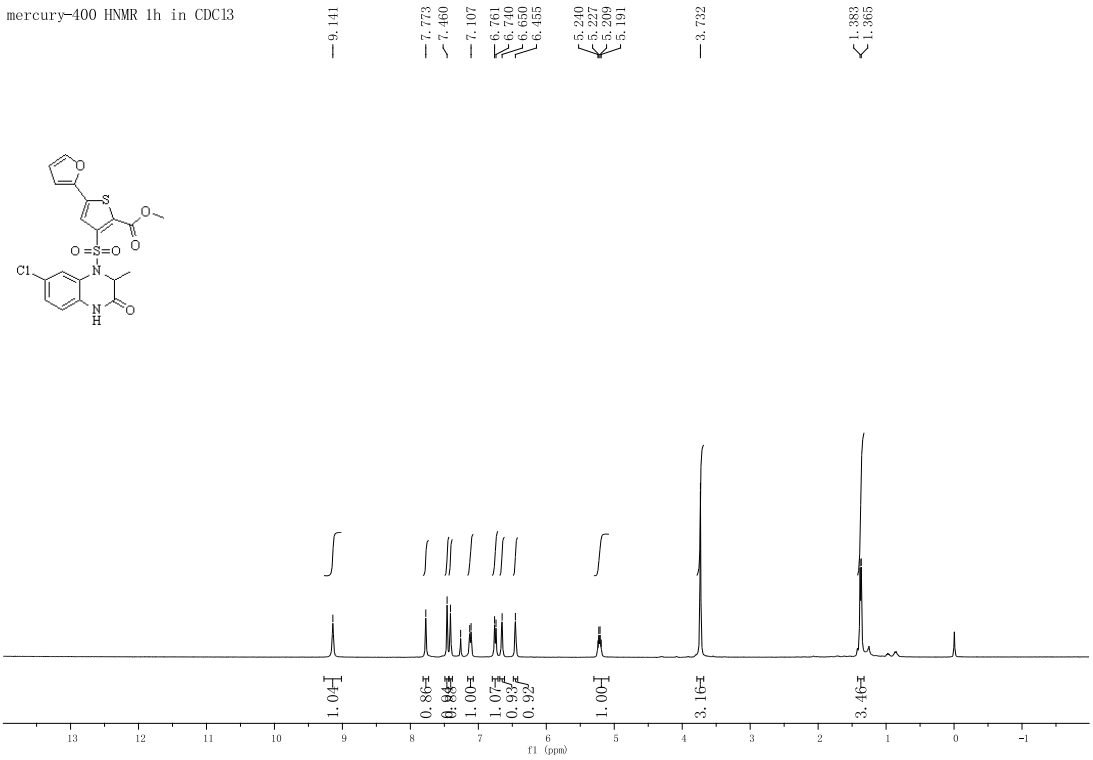

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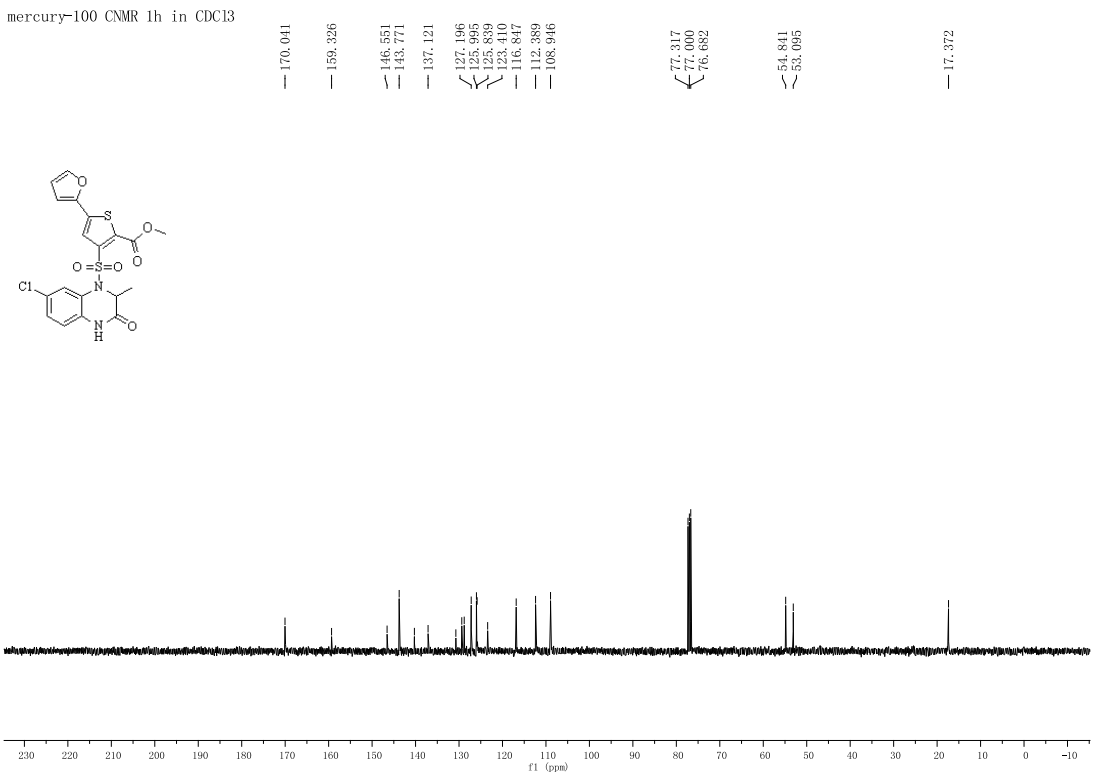
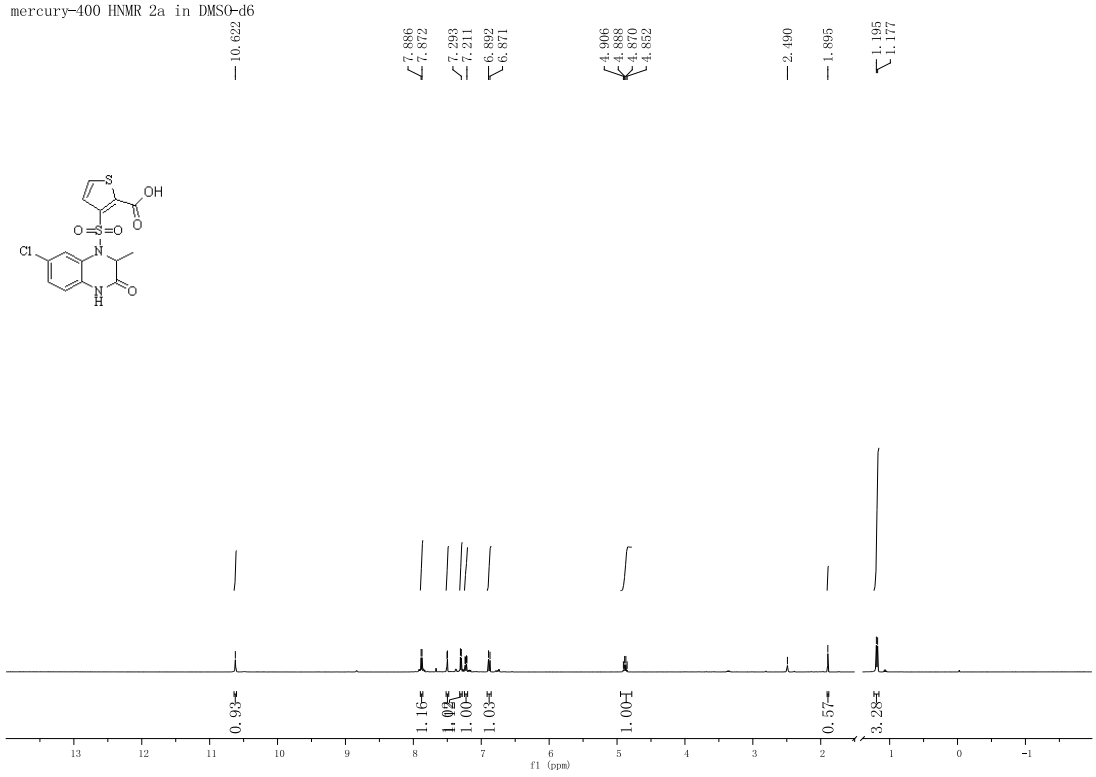
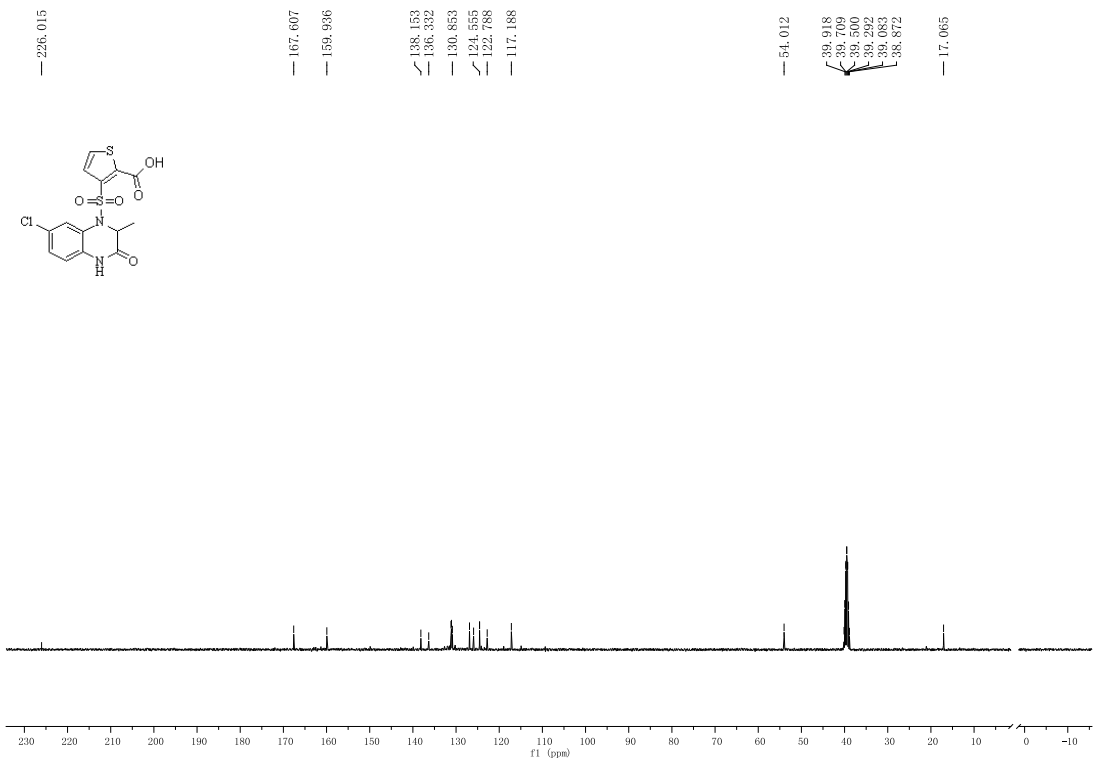


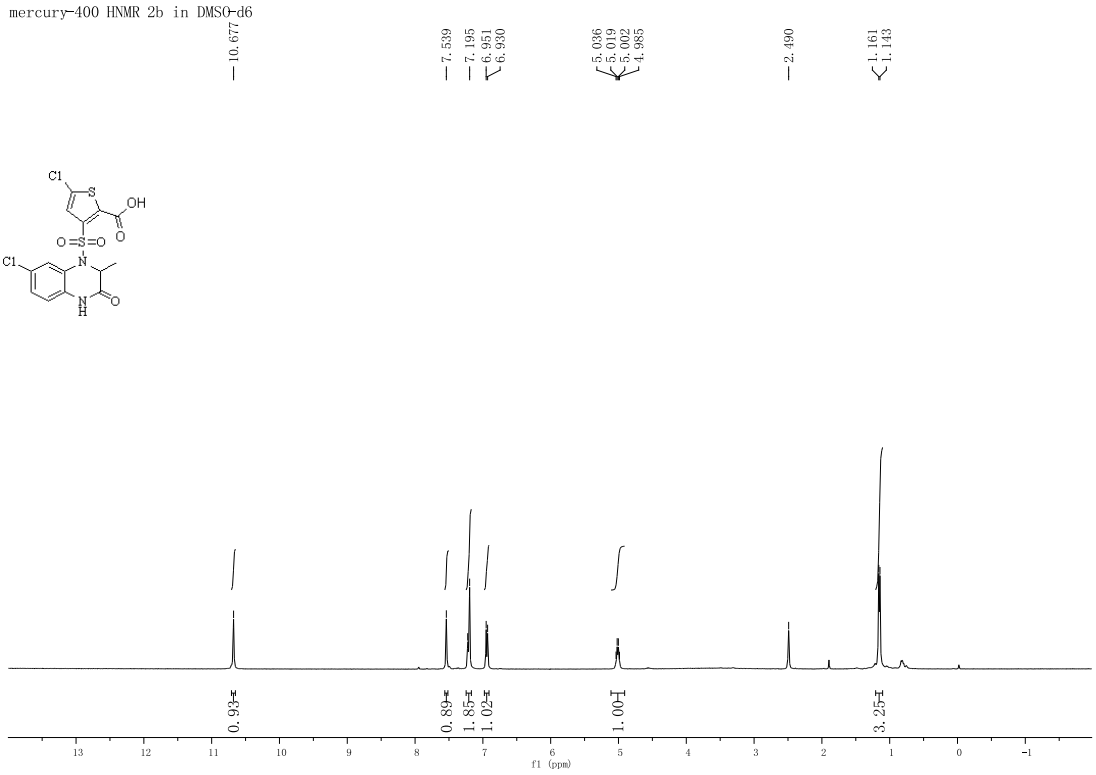
mercury-400 HNMR 2a in DMSO-d6



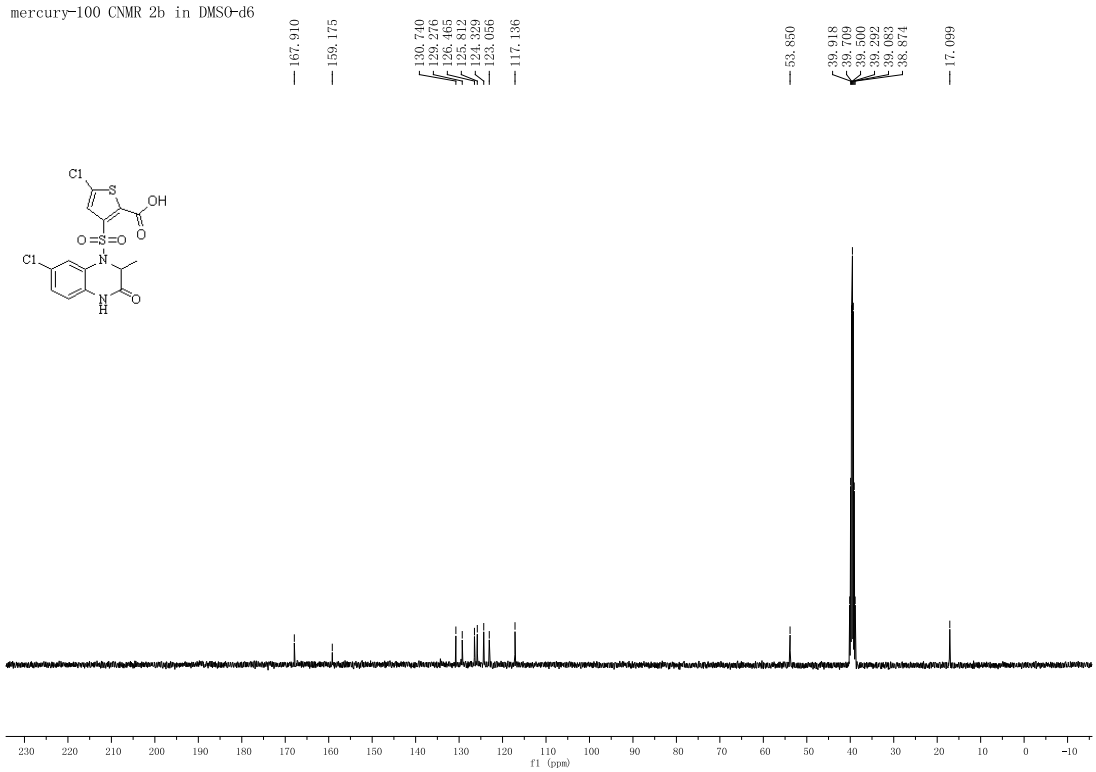
mercury-100 CNMR 2a in DMSO-d6



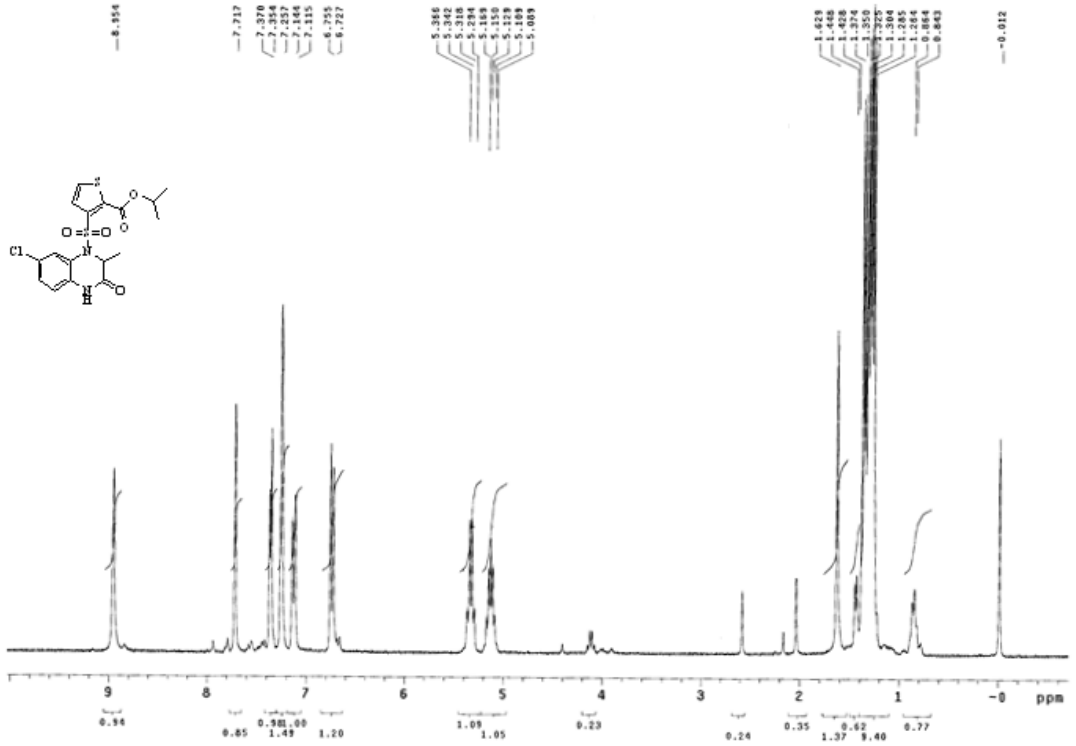
mercury-400 HNMR 2b in DMSO-d6



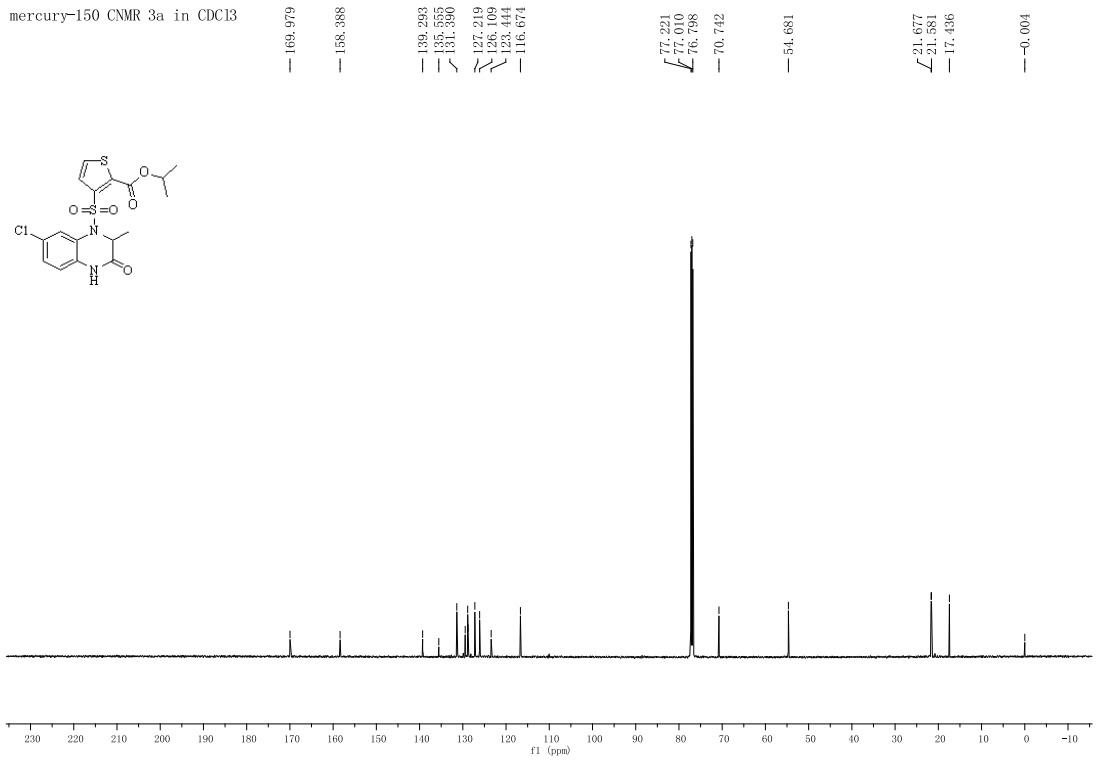
mercury-100 CNMR 2b in DMSO-d6



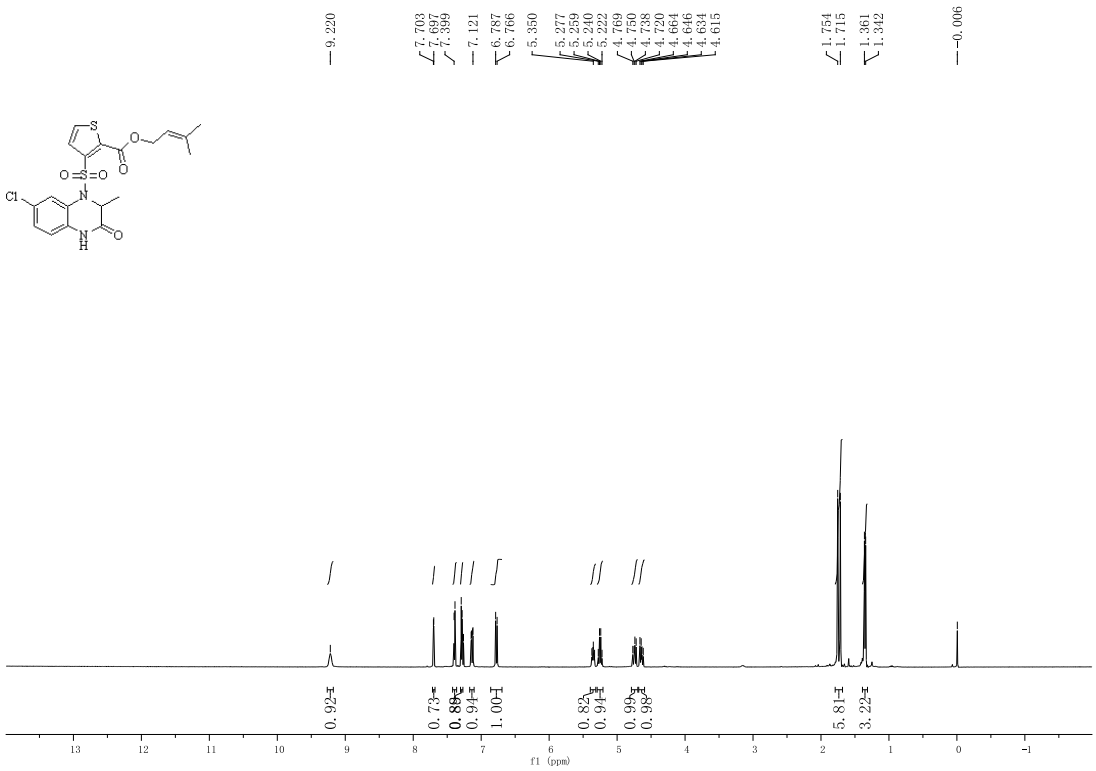
mercury-300 HNMR 3a in CDCl3



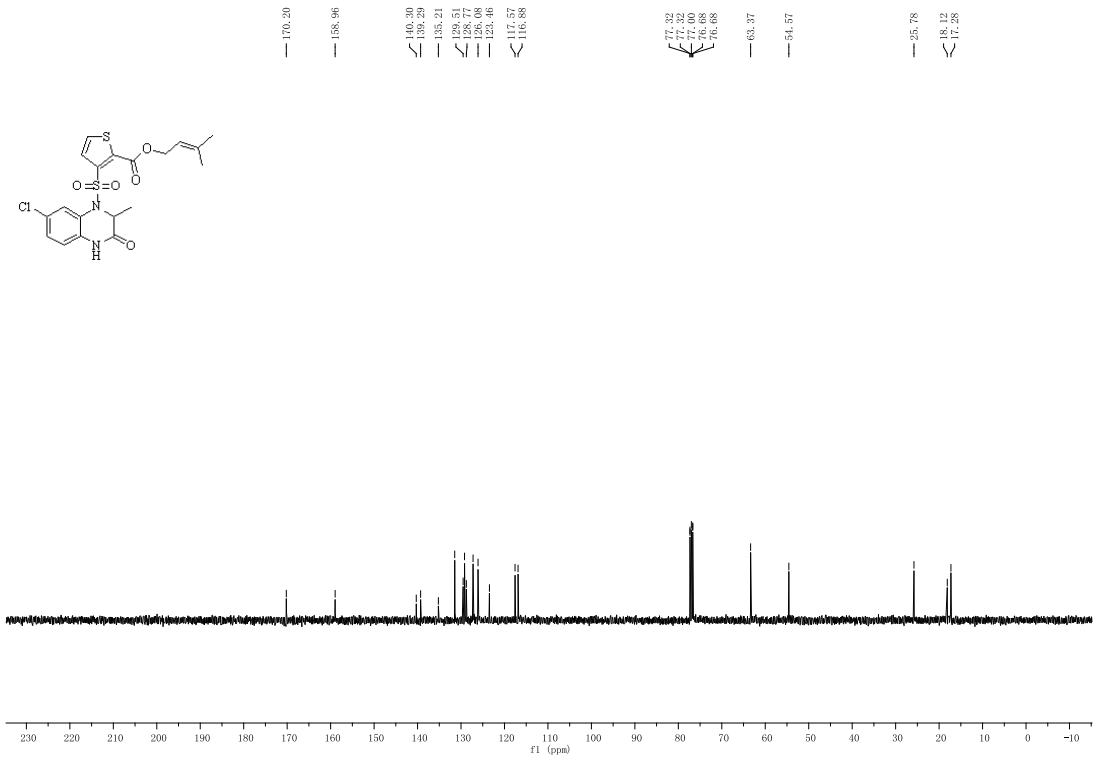
mercury-150 CNMR 3a in CDCl3



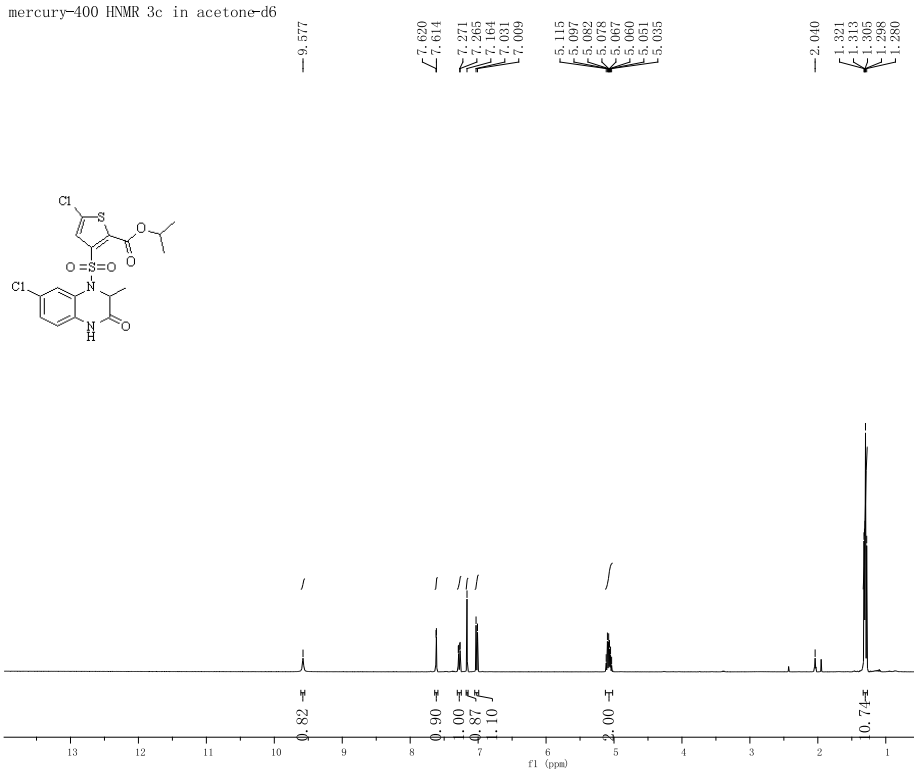
mercury-400 HNMR 3b in CDCl3



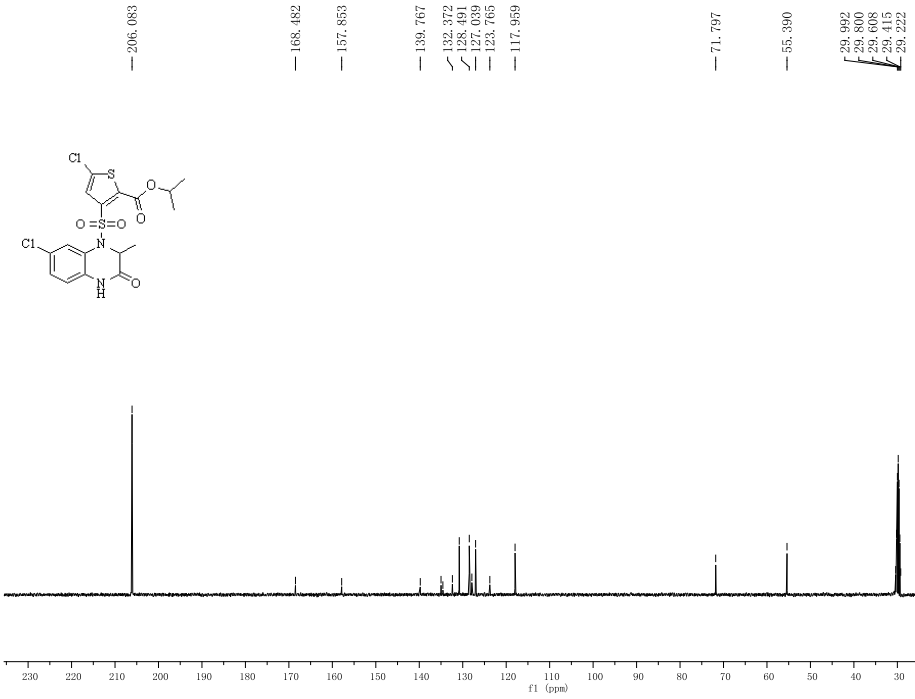
mercury-100 CNMR 3b in CDCl3



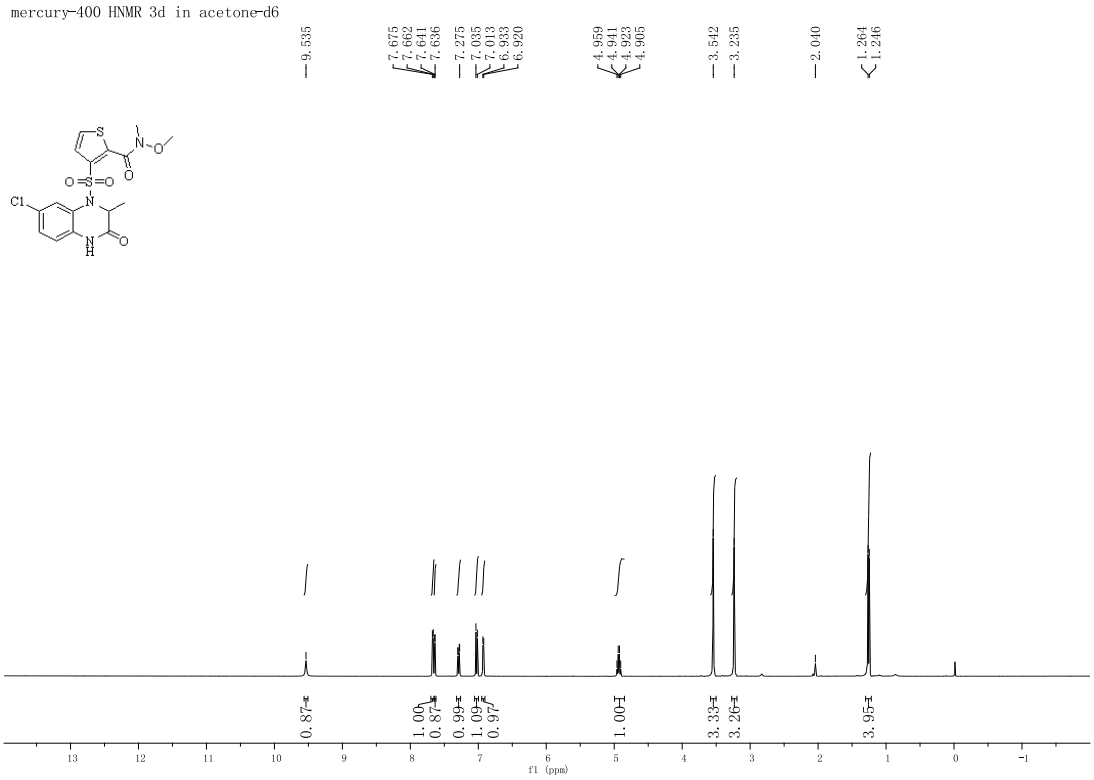
mercury-400 HNMR 3c in acetone-d6



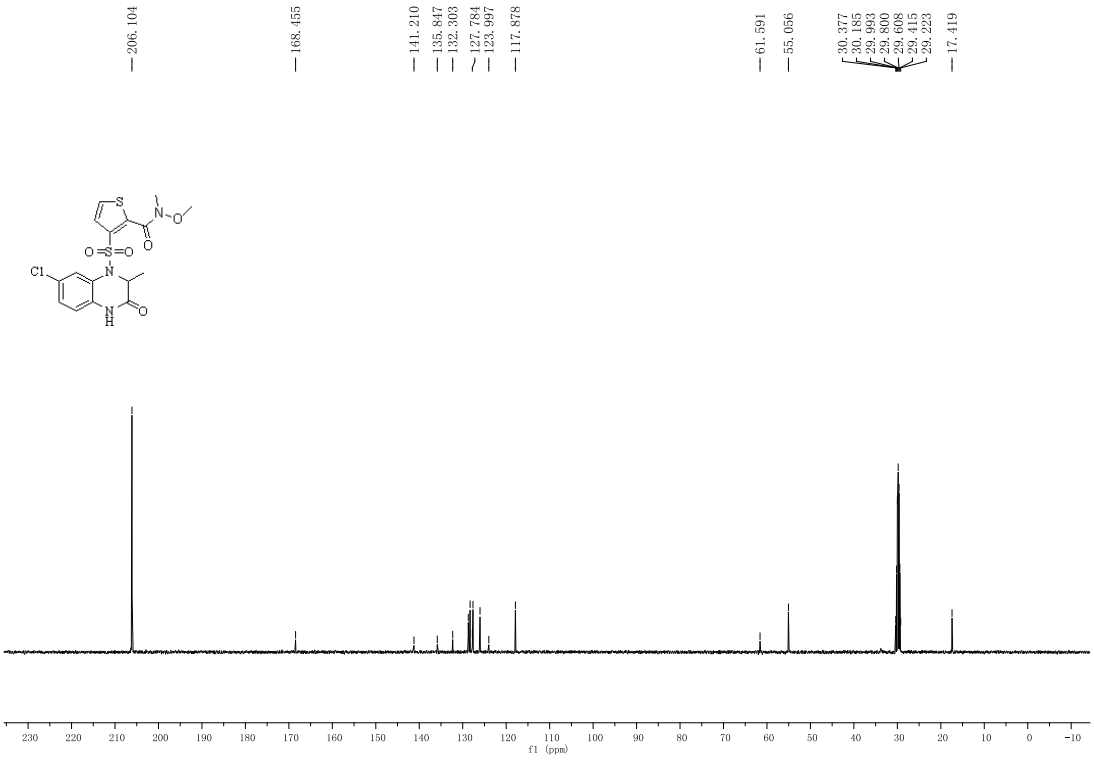
mercury-100 CNMR 3c in acetone-d6



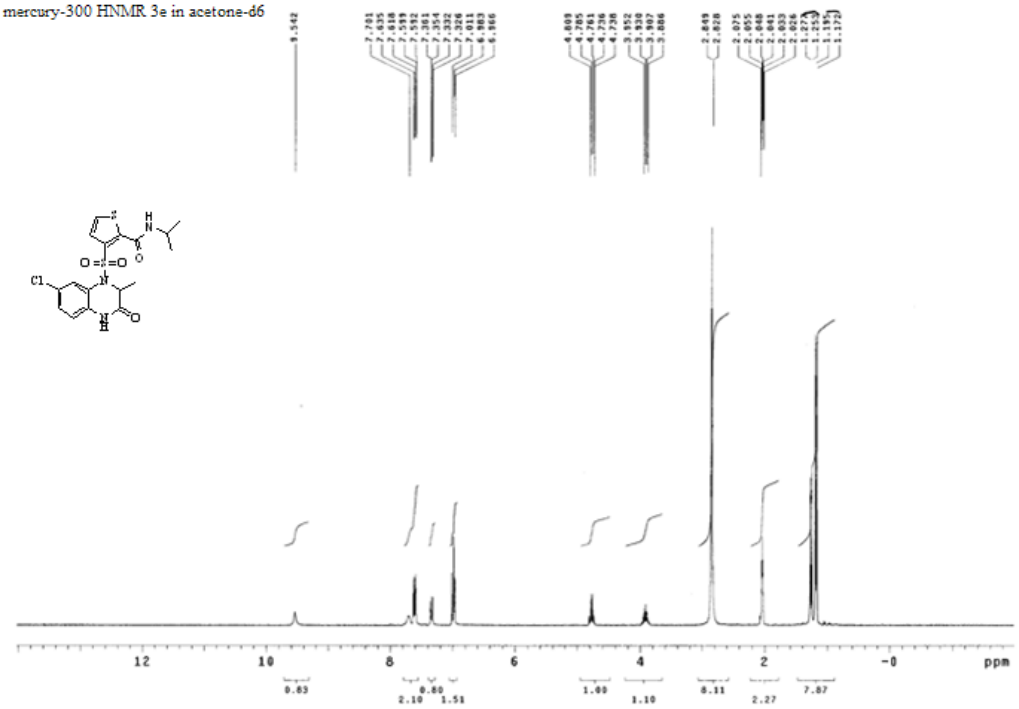
mercury-400 HNMR 3d in acetone-d6



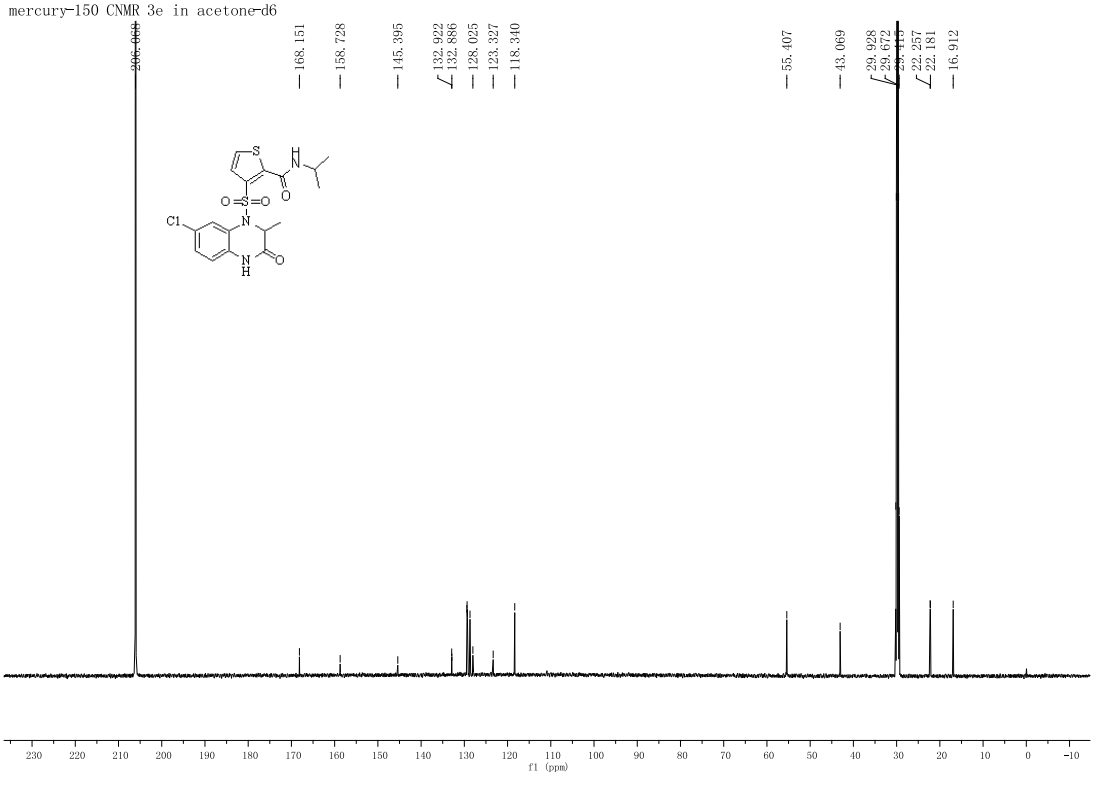
mercury-100 CNMR 3d in acetone-d6



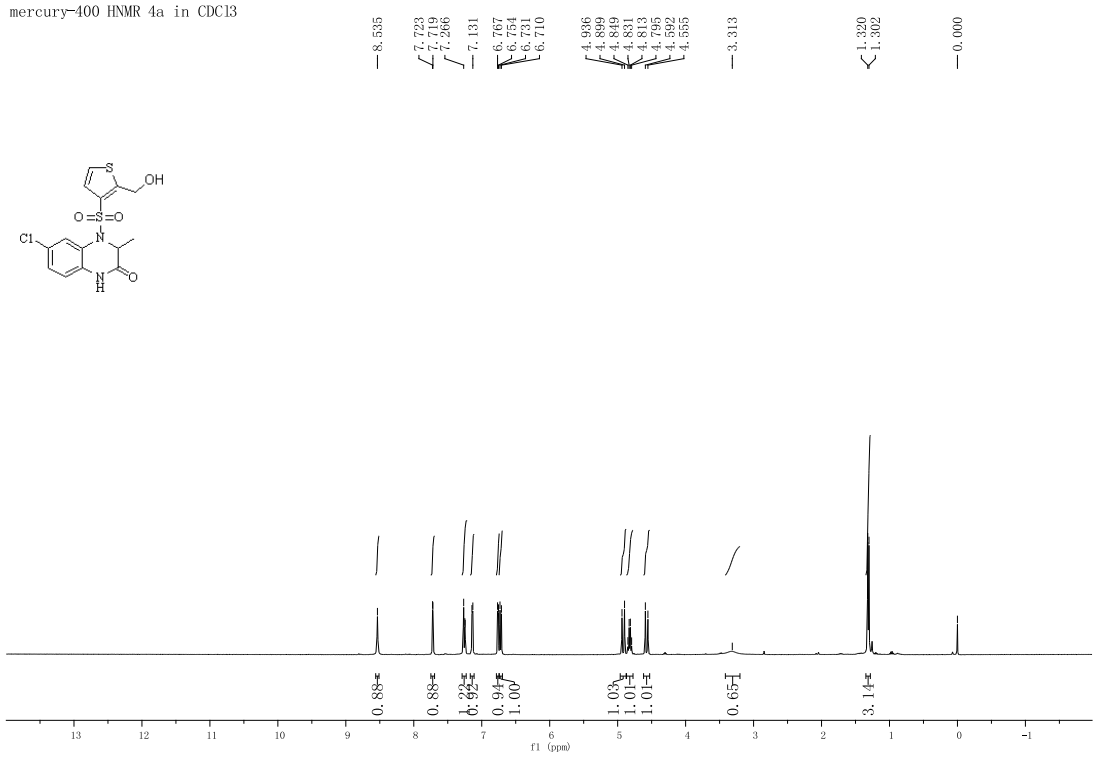
mercury-300 HNMR 3e in acetone-d6



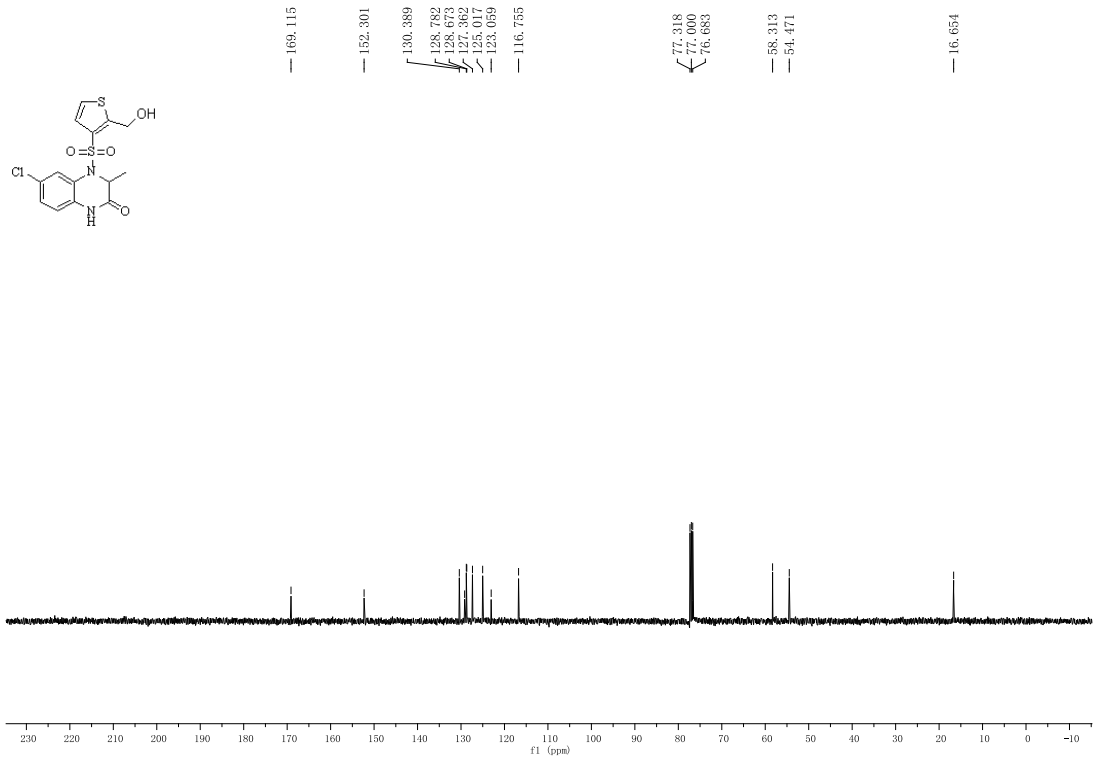
mercury-150 CNMR 3e in acetone-d6



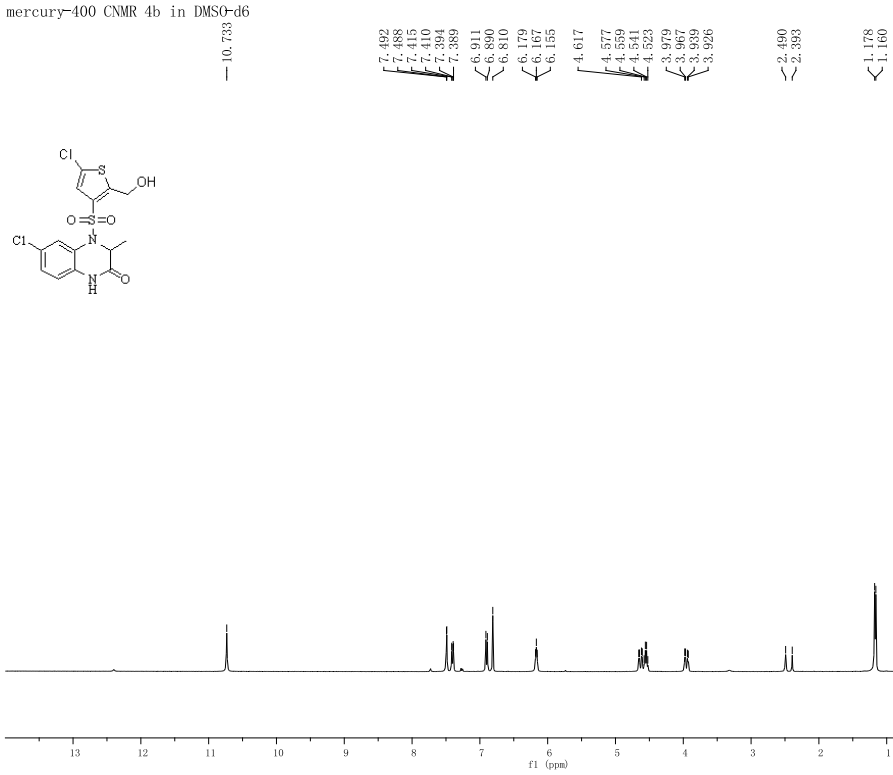
mercury-400 HNMR 4a in CDCl3



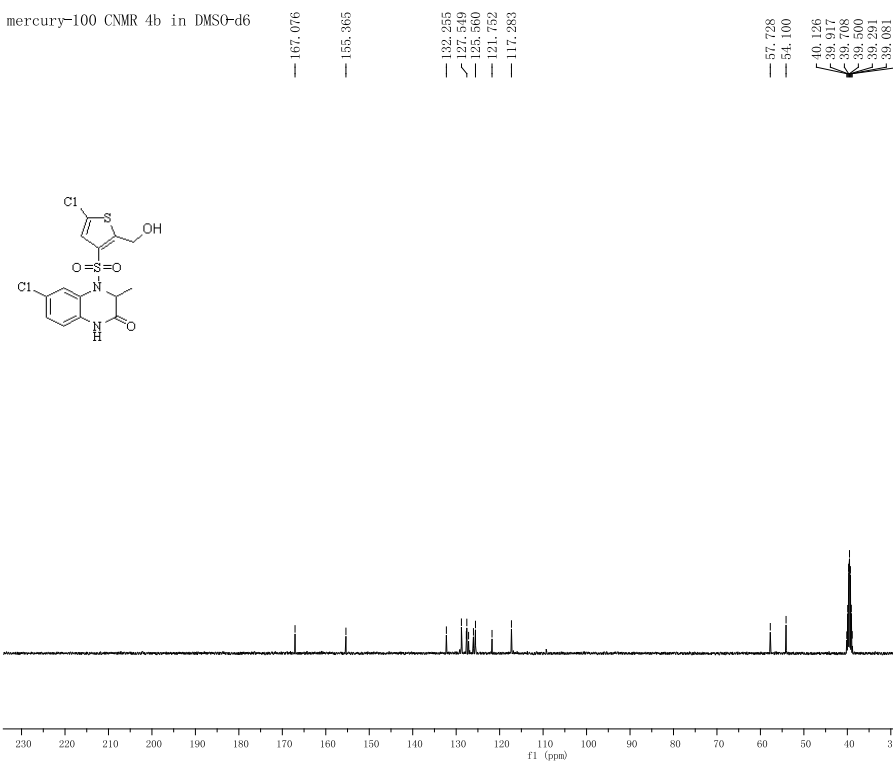
mercury-100 CNMR 4a in CDCl3



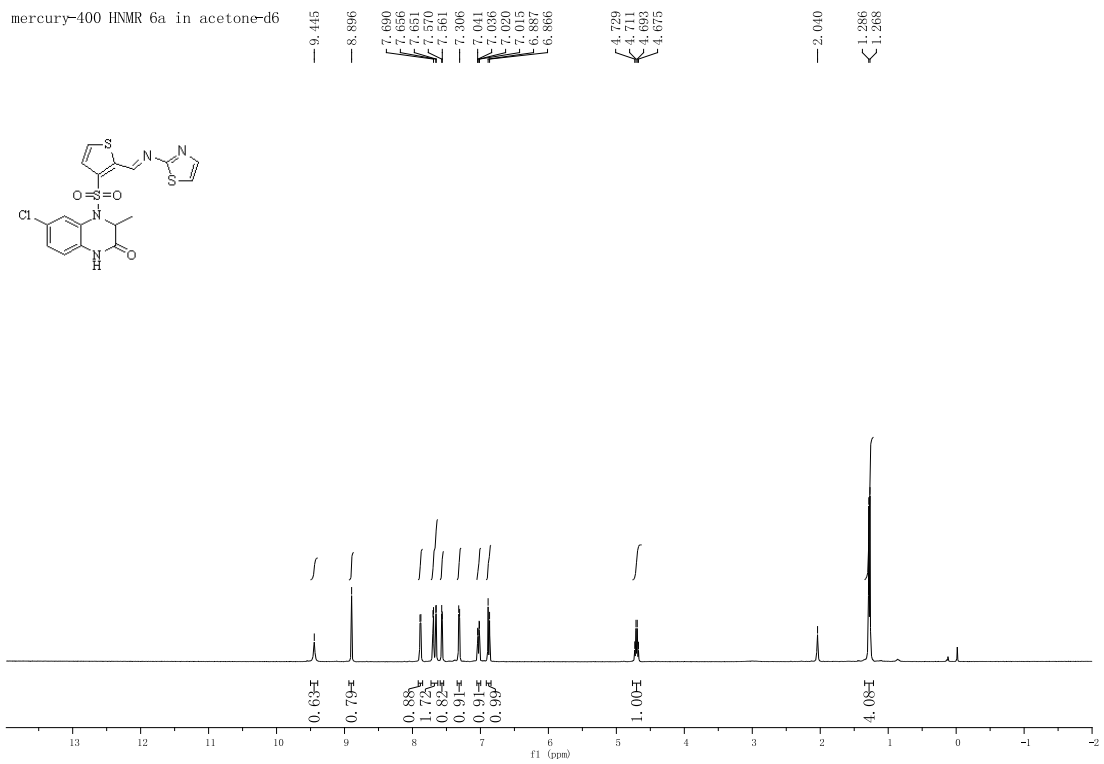
mercury-400 CNMR 4b in DMSO-d6



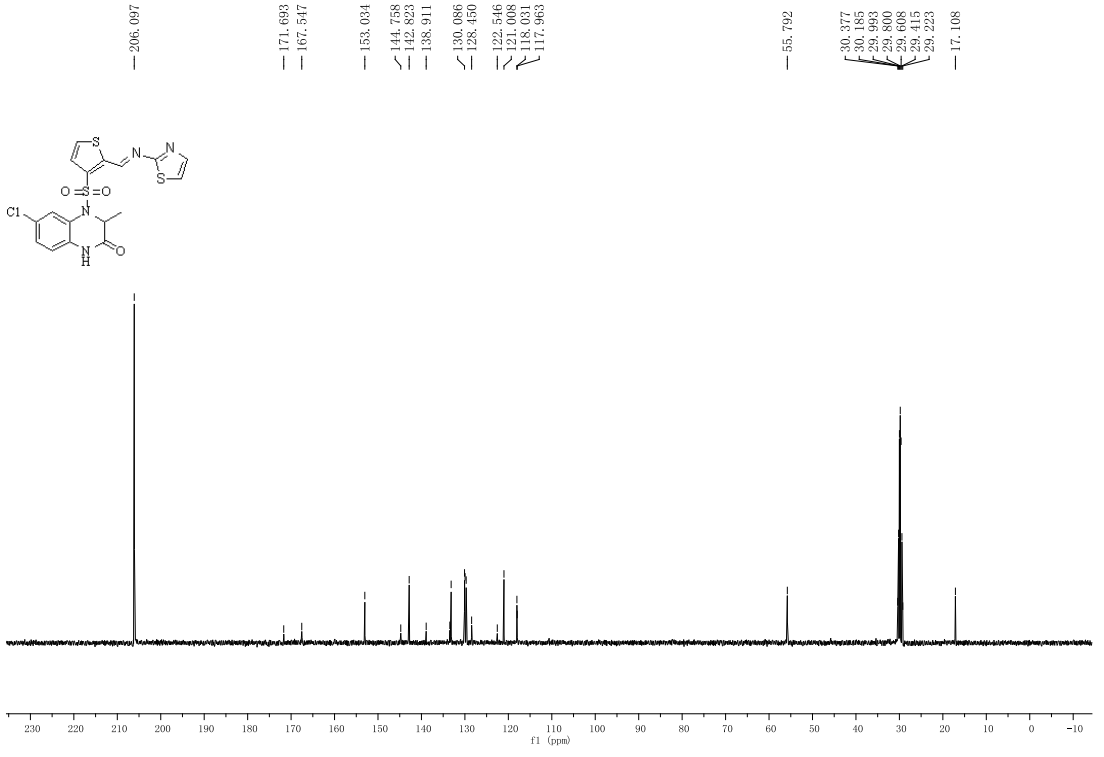
mercury-100 CNMR 4b in DMSO-d6



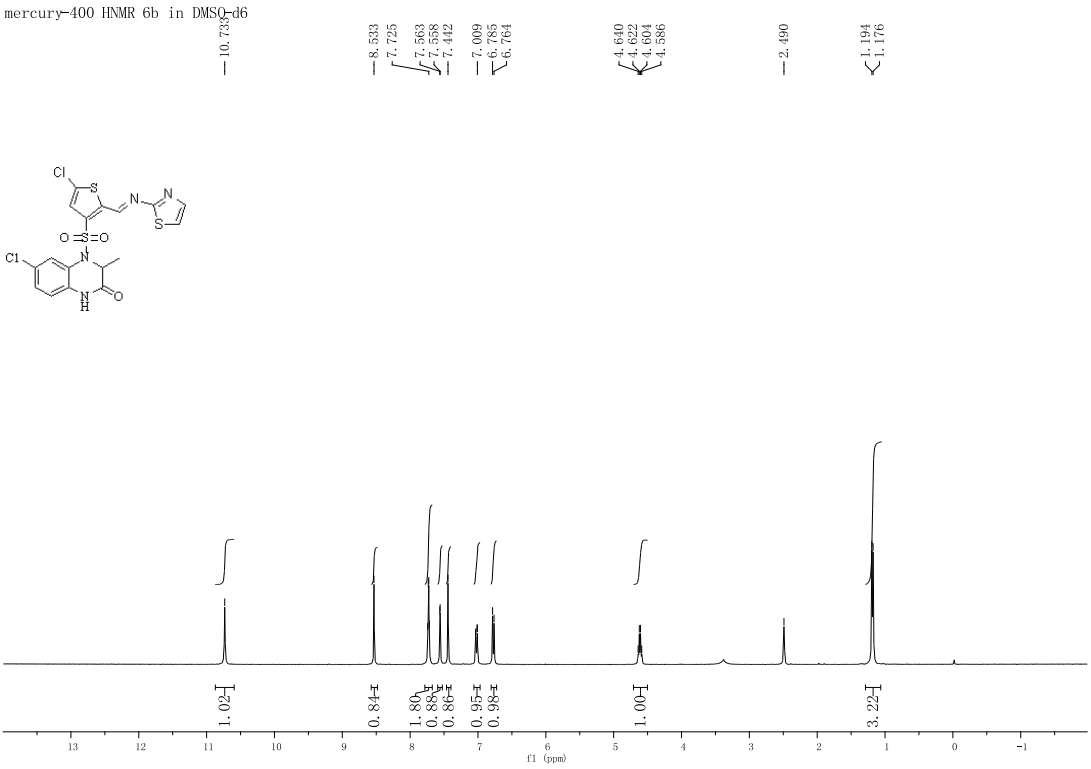
mercury-400 HNMR 6a in acetone-d6



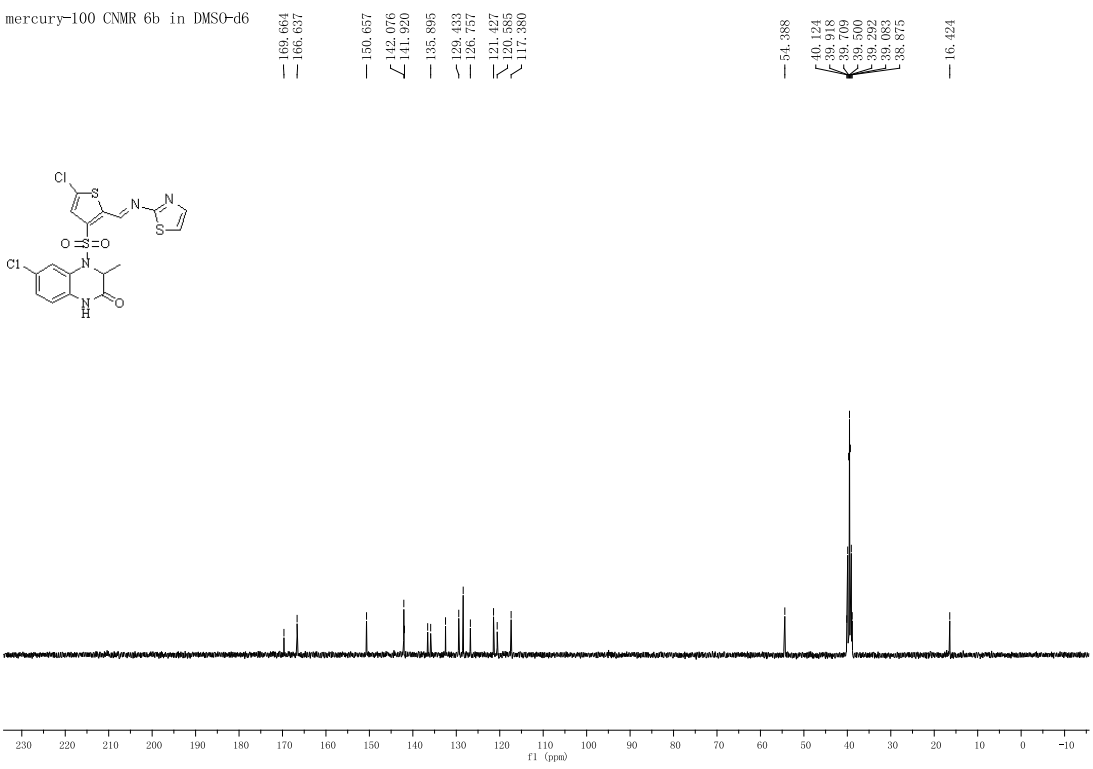
mercury-100 CNMR 6a in acetone-d6



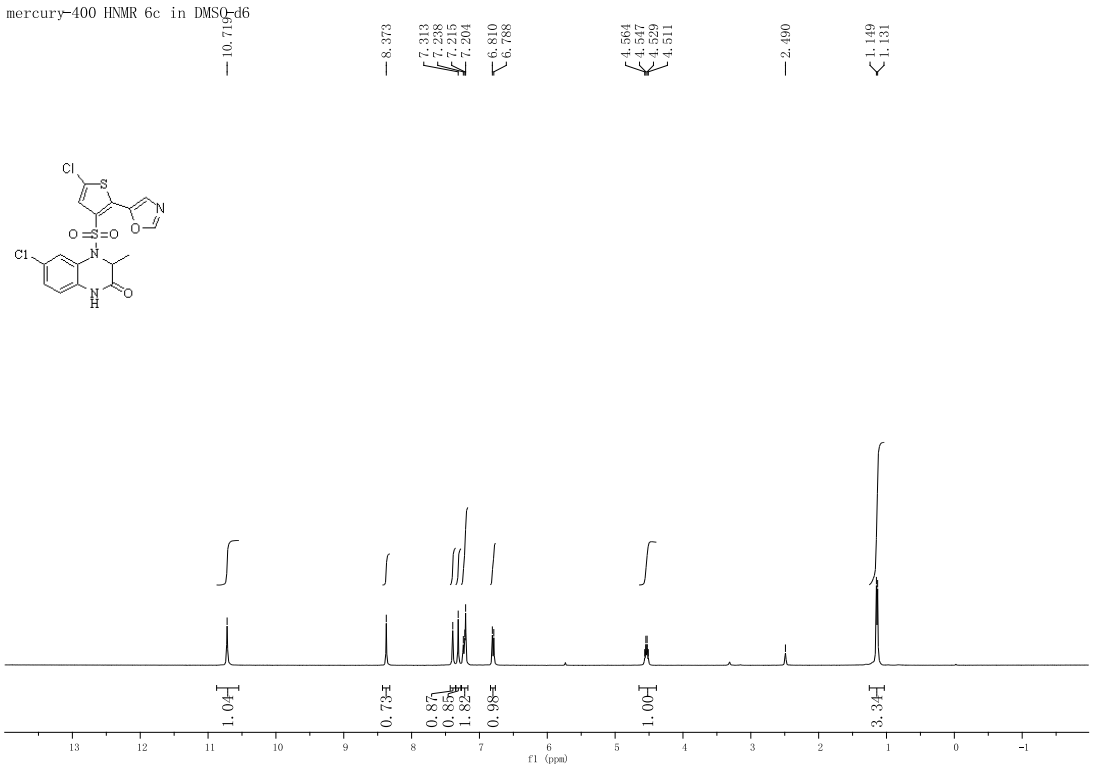
mercury-400 HNMR 6b in DMSO-d6



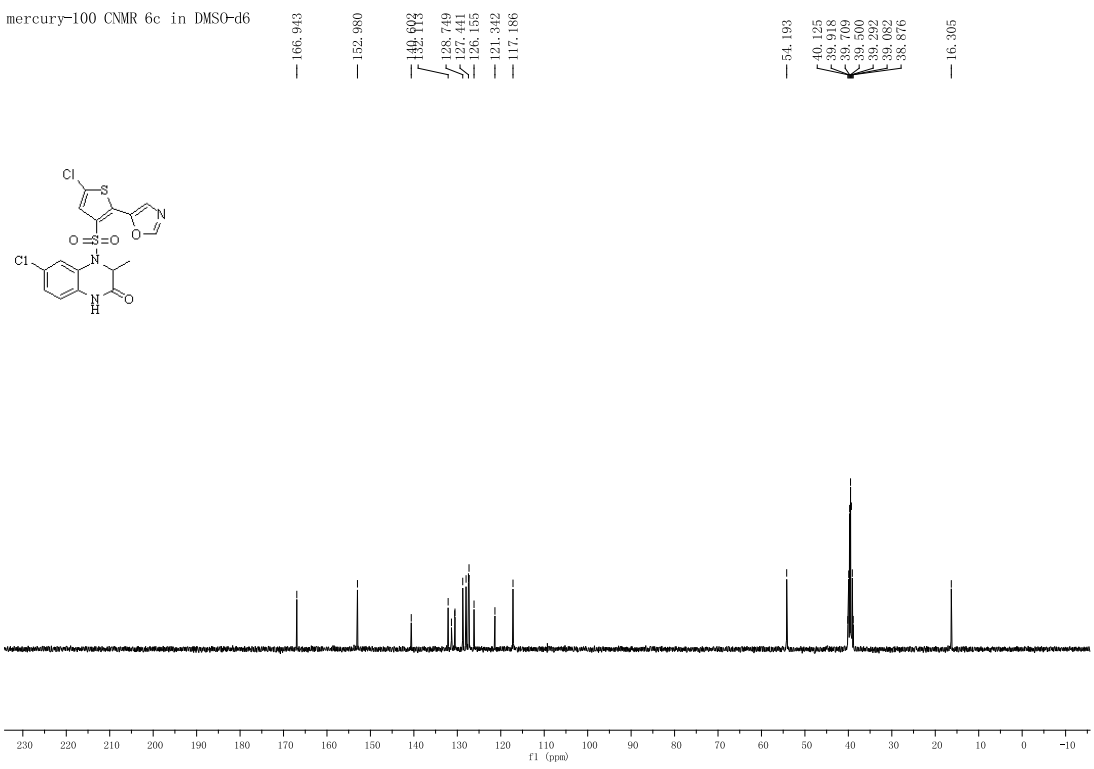
mercury-100 CNMR 6b in DMSO-d6



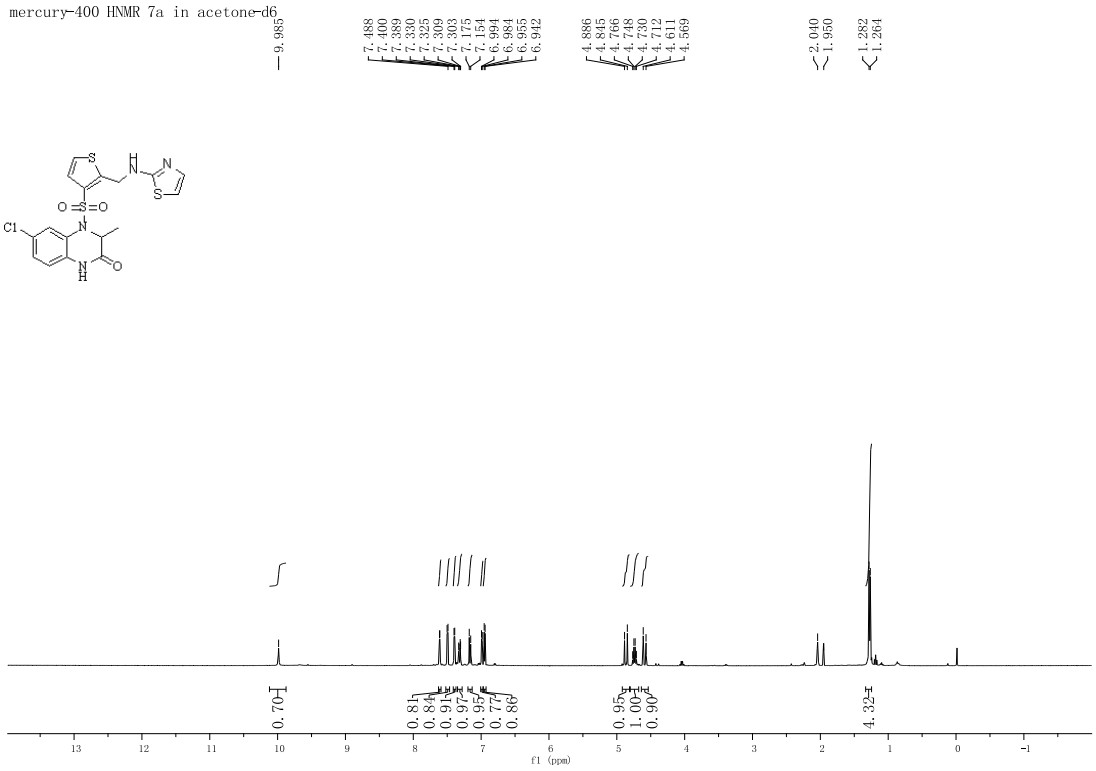
mercury-400 HNMR 6c in DMSO-d6



mercury-100 CNMR 6c in DMSO-d6



mercury-400 HNMR 7a in acetone-d6



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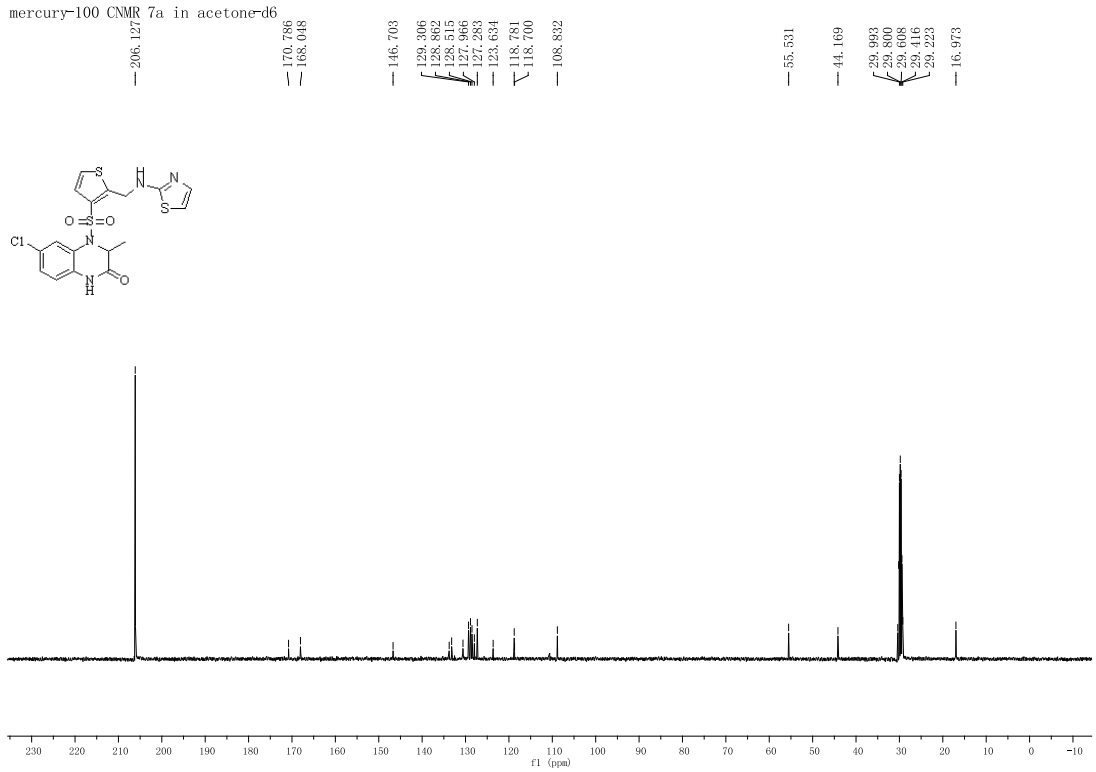
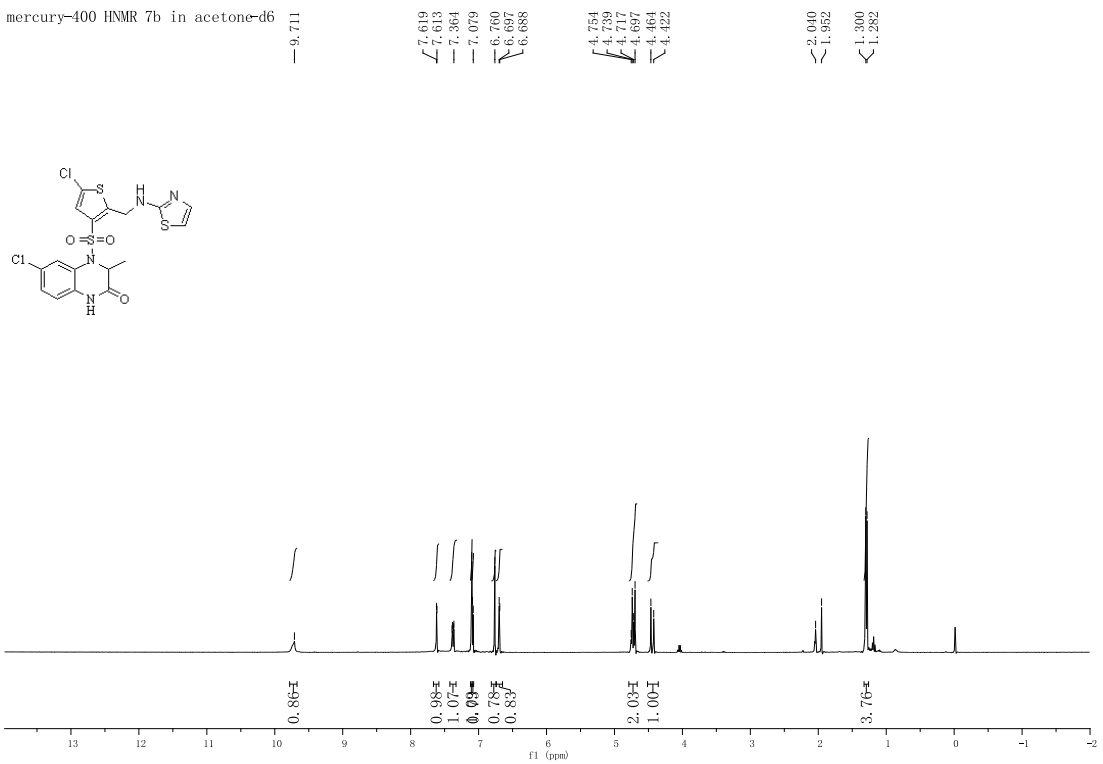


mercury-400 HNMR 7b in acetone-d6



mercury-100 CNMR 7b in acetone-d6