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Potassium Carbonate-Mediated Tandem C-S and C-N Coupling Reaction for the Synthesis of Phenothiazines under Transition-Metal-Free and Ligand-Free Condition

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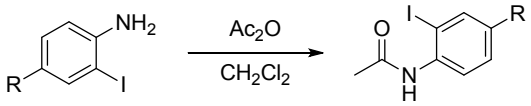
General details

All chemicals were purchased from J&K，Aldrich, Adamas, Acros, Energy chemical and Alfa Asia company and used without further purification. Solvents were purchased from commercial source, without further purification before use. Petroleum ether (PE) used refers to the 60-90 °C boiling point fraction of petroleum. All reactions were conducted under a nitrogen atmosphere. The flash column chromatography was carried out on Merck silica gel (200-300 mesh). ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 or $CDCl_3$ on a Bruker 400 MHz spectrometer. Chemical shifts in ^{1}H NMR spectra are reported in parts per million (ppm, δ) downfield from the internal standard Me_4Si (TMS, δ = 0.00 ppm) or DMSO (2.50 ppm). Chemical shifts in ^{13}C NMR spectra are reported relative to the central line of the chloroform signal (δ = 77.00 ppm) or DMSO signal (δ = 40.00 ppm).

General experimental procedure

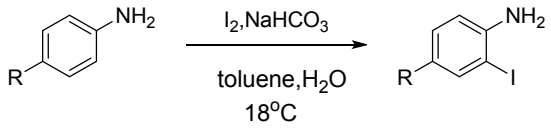
Synthesis and Characterization of Starting Materials **1a-1f**

General Procedure A:



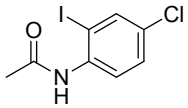
To a solution of the desired 2-iodoaniline (10 mmol scale, 1.0 equiv) in CH_2Cl_2 (25 ml) at room temperature was added acetic anhydride (15 mmol, 1.5 equiv) dropwise. The resulting mixture was stirred at room temperature until the reaction was judged to be completed by TLC (2-16 hours). Water was added and the crude product was extracted with CH_2Cl_2. The combined organic phases were washed with saturated solutions of $NaHCO_3$ and H_2O, dried over Na_2SO_4 and concentrated under reduce pressure. The product was purified by silica gel chromatography.

General Procedure B



Following protocols reported by Sturino et al., [1] a magnetically stirred emulsion of desired aniline (37.9 mmol) in water (100 mL) and toluene (3 mL) maintained at 18 °C was treated with $NaHCO_3$ (60 mmol) and iodine (29.8 mmol) over a period of 0.5 h. The resulting mixture was stirred at room temperature until the reaction was judged to be completed by TLC .The reaction mixture was then poured into water (500 mL) and the pH was adjusted to 6-7 with HCl (ca. 30 mL of a 2M aqueous solution). The aqueous layer was extracted with diethyl ether (2 × 30 mL) and the combined organic phases washed with $Na_2S_2O_3$ (2 × 5 mL of a 5% aqueous solution) then brine (1 × 5 mL). The organic phase thus obtained was dried over Na_2SO_4, and concentrated under reduced pressure. The product was purified by silica gel chromatography.

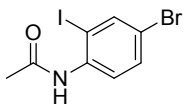
Synthesis of N-(4-chloro-2-iodophenyl)acetamide [2] (**1a**):



1a

According to general procedure B, the desired 4-chloro-2-iodoaniline was obtained from 4-chloroaniline (97%). Then N-(4-chloro-2-iodophenyl)acetamide was prepared according to general procedure A (85%). white solid; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 8.16 (d, *J*=8.0 Hz, 1H), 7.76 (s, 1H), 7.38 (s, 1H) , 7.32 (d, *J*=8.8 Hz, 1H), 2.24 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.21, 137.75, 136.94, 129.85, 129.22, 122.38, 89.68, 24.76 ppm; LC-MS: $[M+H]^+$ m/z = 295.9

Synthesis of N-(4-bromo-2-iodophenyl)acetamide [3] (**1b**):

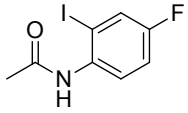


1b

According to general procedure B, the desired 4-bromo-2-iodoaniline was obtained from 4-bromoaniline (77%). Then N-(4-bromo-2-iodophenyl)acetamide was prepared according to general procedure A (89%). white solid; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 8.09 (d, *J*=8.4 Hz, 1H), 7.89 (d, *J*=2.0 Hz, 1H), 7.44 (dd, *J*=8.8 and 2.0Hz, 1H),

7.41 (s, 1H), 2.23 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.17, 140.40, 137.41, 132.15, 122.77, 117.32, 90.08, 24.77 ppm ; LC-MS: $[M+H]^+$ m/z = 339.9 and 341.9

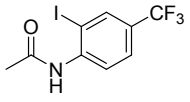
Synthesis of N-(4-fluoro-2-iodophenyl)acetamide [4] (**1c**):



1c

According to general procedure B, the desired 4-Fluoro-2-iodoaniline was obtained from 4-chloroaniline (30%). Then N-(4-fiuoro-2-iodophenyl)acetamide was prepared according to general procedure A (81%). white solid; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 8.11-8.07 (m, 1H), 7.50 (dd, *J*=8.0 and 2.8Hz, 1H), 7.32 (s, 1H), 7.11-7.06 (m, 1H), 2.23(s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.26, 158.63 (^1J(C,F)=248Hz), 134.71 (^4J(C,F)=3Hz), 125.27 (^2J(C,F)=24Hz), 123.39 (^3J(C,F)=8Hz), 115.91 (^2J(C,F)=22Hz), 90.00 (^3J(C,F)=8Hz), 24.47 ppm ; LC-MS: $[M+H]^+$ m/z = 280.0

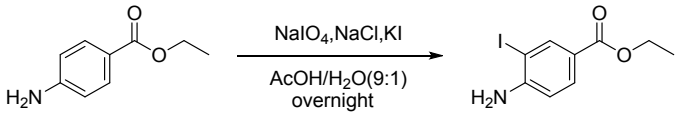
Synthesis of N-(2-iodo-4-(trifluoromethyl)phenyl)acetamide [5] (**1d**):



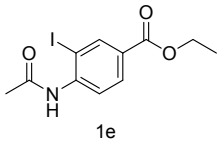
1d

According to general procedure B, the desired 2-iodo-4-(trifluoromethyl)aniline was obtained from 4-(trifluoromethyl)aniline (49%). Then N-(2-iodo-4-(trifluoromethyl)phenyl)acetamide was prepared according to general procedure A (71%). white solid; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 8.40 (d, *J*=8.4Hz, 1H), 8.01 (d, *J*=1.2Hz, 1H), 7.60-7.58 (m, 2H) , 2.28 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.39, 141.22, 135.67, 126.43, 124.16, 122.80 (*J*=271Hz), 120.09, 88.45, 24.88 ppm; LC-MS: $[M+H]^+$ m/z = 330.0

Synthesis of ethyl 4-acetamido-3-iodobenzoate (new) (**1e**):



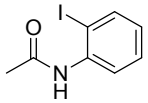
Ethyl 4-amino-3-iodobenzoate was prepared following protocols reported by Shabat et al.,[6] Ethyl-4-aminobenzoate (47 mmol) was dissolved in 100 ml mixture of AcOH : H2O (9:1). $NaIO_4$ (47 mmol), NaCl (93 mmol) and KI (47 mmol) were added sequentially. The reaction mixture was stirred at room temperature over night, then diluted with EtOAc and washed with brine, then with a saturated solution of $Na_2O_3S_2$ and finally, with a saturated solution of $NaHCO_3$. The organic layer was dried over Na_2SO_4, the solvent removed under reduced pressure, and the crude product purified by column chromatography on silica gel (95%).



1e

Prepared according to general procedure A, from Ethyl 4-amino-3-iodobenzoate (81%); white solid; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 8.45 (d, *J*=2.0 Hz, 1H), 8.38 (d, *J*=8.4Hz, 1H), 8.01 (dd, *J*=8.4 and 2.0Hz, 1H), 7.63 (s, 1H), 4.39-4.34 (m, 2H), 2.28 (s, 3H), 1.39 (t, *J*=6.8Hz 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.31, 164.67, 141.89, 140.09, 127.35, 120.11, 61.22, 25.02, 14.29 ppm; HRMS (ESI/micrOTOF-Q III) *m/z* Calcd for $C_{11}H_{12}INO_3H$ 333.99346, found 333.99341.

Synthesis of N-(2-iodophenyl)acetamide [7] (**1f**):

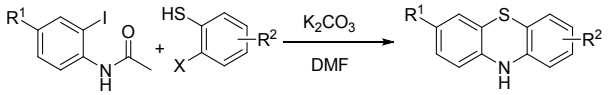


1f

Prepared according to general procedure A, from 2-iodoaniline (87%); white solid; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 8.18 (d, *J*=8.0 Hz, 1H), 7.77 (d, *J*=7.6 Hz, 1H), 7.45 (s,1H), 7.35-7.31 (m, 1H), 6.84 (t, *J*=7.6 Hz, 1H), 2.23 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.19, 138.71, 138.15, 129.18, 125.97, 122.14, 90.03, 24.74 ppm; LC-MS: $[M+H]^+$ m/z = 262.0

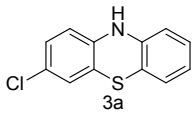
Synthesis and Characterization of substituted phenothiazines (**3a-3p**)

General Procedure C



An oven-dried Schlenk tube was charged with N-(2-iodophenyl)acetamide (0.5 mmol), K_2CO_3 (278 mg, 2.0 mmol). The tube was evacuated and backfilled with nitrogen (3 times), and then 2-halo-benzenethiol (0.55 mmol) and DMF (3.0 ml) were added. The reaction mixture was stirred at 135 °C for 48 h. Water and 0.5 ml NEt_3 was added and the crude product was extracted with ethyl acetate. The combined organic phases were washed with saturated solutions of NaCl and H_2O, dried over Na_2SO_4 and concentrated under reduced pressure. The product was purified by silica gel chromatography to give the desired phenothiazines.

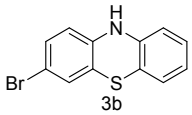
3-chloro-10H-phenothiazine [8] (**3a**):



3a

Pale yellow solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.71 (s, 1H), 7.01-6.97 (m, 3H), 6.89 (dd, J =7.6 and 1.2 Hz, 1H), 6.77-6.73 (m, 1H), 6.69-6.54 (m, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 142.07, 141.57, 128.26, 127.65, 126.74, 125.85, 125.44, 122.53, 119.07, 116.01, 115.85, 115.04 ppm; LC-MS: $[M]^+$ m/z = 233.0

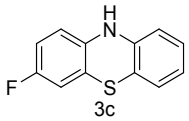
3-bromo-10H-phenothiazine [9] (**3b**):



3b

Pale yellow solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.71 (s, 1H), 7.12-7.07 (m, 2H), 6.98 (t, J =7.6, 1H), 6.88 (d, J =7.2, 1H), 6.76-6.60 (m, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 141.99, 141.96, 130.47, 128.48, 128.21, 126.73, 122.51, 119.48, 116.30, 116.08, 115.04, 112.83 ppm ; LC-MS: $[M]^+$ m/z = 277.0

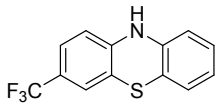
3-fluoro-10H-phenothiazine [10] (**3c**):



3c

White Solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 (s, 1H), 7.01-6.98 (m, 1H), 6.92-6.90 (m, 1H), 6.85-6.81 (m, 2H), 6.77-6.73(m, 1H), 6.70-6.66(m, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.02（*J*=236Hz）, 142.66, 139.18（*J*=2Hz）, 128.28, 126.72, 122.31, 118.73(*J*=8Hz), 115.81, 115.42(*J*=8Hz), 114.92, 114.33(*J*=22Hz), 113.56 (*J*=25Hz) ppm; LC-MS: $[M]^+$ m/z = 217.0

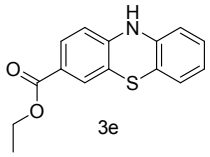
3-(trifluoromethyl)-10H-phenothiazine [8] (**3d**):



3d

Pale yellow solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.02 (s, 1H), 7.30-7.27 (m, 1H), 7.21(s, 1H), 7.0 (td, *J*=8.4 and 1.2Hz, 1H), 6.91 (dd, *J*=8.0 and 1.2 Hz, 1H), 6.81-6.75 (m, 2H), 6.69 (dd, *J*=8.0 and 1.2 Hz, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 145.91, 141.07, 128.39, 126.78, 126.10, 124.44 (*J*=191 and 4 Hz), 123.40, 123.20, 122.40(*J*=32), 117.83, 116.10, 115.33, 114.54 ppm; LC-MS: $[M]^+$ m/z = 267.0

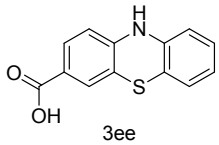
ethyl 10H-phenothiazine-3-carboxylate [10] (**3e**):



3e

Yellow solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.07 (s, 1H), 7.56 (dd, J =8.4 and 2.0 Hz,1H), 7.39 (d, J =1.6 Hz, 1H), 7.01-6.97 (m, 1H), 6.90-6.88 (m, 1H), 6.80-6.76 (m, 1H), 6.70-6.67 (m, 2H), 4.25-4.19 (m, 2H), 1.27 (t, J =7.2, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.29, 146.56, 140.72, 129.92, 128.27, 127.44, 126.73, 123.29, 123.22, 116.67, 116.32, 115.38, 114.22, 60.75, 14.67 ppm; LC-MS: $[M]^+$ m/z = 271.0

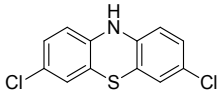
10H-phenothiazine-3-carboxylic acid [8] (**3ee**):



3ee

Yellow solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.55 (s, 1H), 9.03 (s, 1H), 7.54 (dd, J =8.4 and 2.0 Hz, 1H), 7.38 (d, J =2.0 Hz, 1H), 7.01-6.97 (m, 1H), 6.91-6.89 (m, 1H), 6.80-6.76 (m, 1H), 6.69-6.67 (m, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.92, 146.33, 140.91, 130.11, 128.29, 127.76, 126.78, 124.26, 123.18, 116.51, 116.41, 115.36, 114.22 ppm ; LC-MS: $[M]^+$ m/z = 243.0

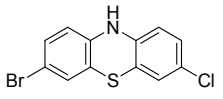
3, 7-dichloro-10H-phenothiazine [11] (**3f**)



3f

Pale yellow solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.83 (s, 1H), 7.03-7.02 (m, 4H), 6.64 (d, J =8.4 Hz, 2H), ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 141.04, 127.87, 125.88, 125.75, 118.22, 115.97 ppm; LC-MS: $[M]^+$ m/z = 267.0

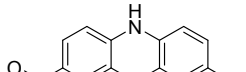
3-bromo-7-chloro-10H-phenothiazine [12] (**3g**)



3g

Pale yellow solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.82 (s, 1H), 7.12-7.09 (m, 1H), 7.05 (d, J =2.0, 1H), 7.0-6.97 (m, 1H), 6.94 (d, J =2.0, 1H), 6.64-6.57 (m, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 141.44, 140.96, 130.72, 128.48, 127.86, 125.89, 125.77, 118.61, 118.30, 116.43, 115.98, 113.14 ppm; LC-MS: $[M]^+$ m/z = 310.9

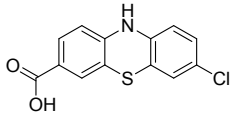
ethyl 7-chloro-10H-phenothiazine-3-carboxylate [10] (**3j)**



3j

Yellow solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.16 (s, 1H), 7.55 (dd, J =8.0 and 1.2 Hz,1H), 7.38 (s, 1H), 7.02-6.96 (m, 2H), 6.50 (t, J =8.8 Hz, 2H), 4.24-4.19 (m, 2H), 1.26 (t, J =7.2, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.18, 146.01, 139.75, 130.10, 127.89, 127.47, 126.44, 125.89, 123.59, 118.62, 116.34, 115.91, 114.38, 60.79, 14.65 ppm; LC-MS: $[M]^+$ m/z = 305.0.

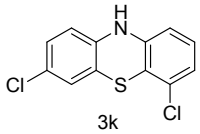
7-chloro-10H-phenothiazine-3-carboxylic acid (**3jj**)



3jj

Yellow solid; mp: 252.0-253.1 ° C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.56 (s, 1H), 9.14(s, 1H), 7.55 (dd, J =8.4 and 2.0 Hz, 1H), 7.38(d, J = 2.0 Hz, 1H), 7.03-6.99 (m, 2H), 6.68-6.64 (m, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.82, 145.78, 139.96, 130.32, 127.93, 127.80, 126.38, 125.95, 124.61, 118.72, 116.34, 115.76, 114.39 ppm; IR: 3440.57, 2924.31, 1681.74, 1629.65, 1476.46, 1384.42, 1291.09; HRMS (ESI/TOF-Q) m/z: [M+Na]+ calcd for $C_{13}H_8ClNO_2SNa$ 299.9862; found 299.9868.

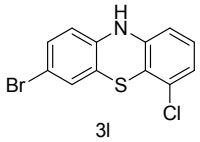
3, 6-dichloro-10H-phenothiazine (**3k**)



3k

Pale yellow solid; mp: 106.7-107.2 ° C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16 (s, 1H), 7.13-7.11 (m, 2H), 7.05-7.02 (m, 2H), 6.89 (d, J =7.6, 1H), 6.76 (t, J =8.0, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 140.44, 138.17, 128.67, 127.74, 126.74, 125.71, 123.06, 119.50, 118.93, 118.81, 117.71 ppm; IR: 3439.81, 3390.10, 1629.54, 1483.51, 1456.61, 1426.26, 1384.67, 1301.58 cm^{-1}; HRMS (ESI/TOF-Q) m/z: [M]+ calcd for $C_{12}H_7Cl_2NS$ 266.9676; found 276.9683.

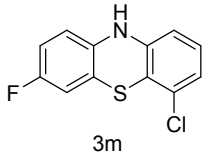
3-bromo-6-chloro-10H-phenothiazine (**3l**)



3l

Pale yellow solid; mp: 91.1-92.5 ° C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.19 (s, 1H), 7.20-7.14 (m, 3H), 7.07 (d, J =8.4, 1H), 6.94-6.92 (m, 1H), 6.79 (t, J =8.0, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 140.85, 138.10, 130.60, 128.66, 128.38, 125.71, 123.07, 119.89, 118.95, 118.88, 118.14, 114.26 ppm; IR: 3454.66, 3391.72, 1576.63, 1491.60, 1479.22, 1452.41, 1421.21, 1384.79, 1297.68 cm^{-1}; HRMS (ESI/TOF-Q) m/z: [M]+ calcd for $C_{12}H_7BrClNS$ 310.9171 and 312.9151; found 310.9178 and 312.9153.

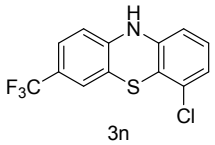
6-chloro-3-fluoro-10H-phenothiazine (**3m**)



3m

Pale yellow solid; mp: 105.4-106.1 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 807 (s, 1H), 7.16-7.12 (m, 2H), 6.91-6.85 (m, 3H), 6.77 (t, J =8.0, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.65 (*J*=238Hz）, 138.67, 137.98（*J*=3Hz）, 128.68, 125.71, 122.88, 119.21 (*J*=8Hz), 118.78, 118.59, 117.43 (*J*=8Hz), 114.49 (*J*=22Hz), 113.33 (*J*=26Hz) ppm; IR: 3439.84, 3395.92, 1602.04, 1493.20, 1453.73, 1431.33, 1421.21, 1384.60, 1300.51 cm^{-1}; HRMS (ESI/TOF-Q) m/z: [M]+ calcd for $C_{12}H_7ClFNS$ 250.9972; found 250.9970.

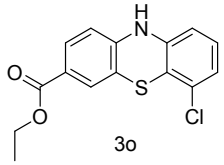
6-chloro-3-(trifluoromethyl)-10H-phenothiazine (**3n**)



3n

Pale yellow solid; mp: 91.7-93.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.46 (s, 1H), 7.34 (d, *J*=8.4 Hz, 1H), 7.26 (t, *J*=8.4 Hz, 2H), 7.16 (dd, *J*=8.0 and 1.2 Hz, 1H), 6.93 (d, *J*=7.2 Hz, 1H), 6.81(t, *J*=8.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 144.93, 137.36, 129.51, 128.85, 125.94, 125.79, 124.42 (*J*=193 and 3 Hz), 123.76, 123.24, 119.27, 118.99, 118.43, 116.48 ppm; IR: 3431.71, 1629.57, 1492.96, 1455.38, 1433.76, 1384.77, 1325.09 cm^{-1}; HRMS (ESI/TOF-Q) m/z: [M]+ calcd for $C_{13}H_7ClF_3NS$ 300.9940; found 300.9938.

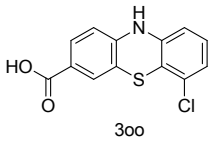
ethyl 6-chloro-10H-phenothiazine-3-carboxylate (**3o**)



3o

Yellow solid; mp: 112.1-113.1 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49 (s, 1H), 7.59 (dd, J =8.4 and 2.0 Hz,1H), 7.45 (d, J =2.0 Hz, 1H), 7.15-7.20 (m, 2H), 6.93 (d, J =8.4 Hz, 1H), 6.81 (t, J =8.0 Hz, 1H), 4.26-4.21 (m, 2H), 1.28 (t, J =7.2, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.21, 145.62, 137.11, 129.77, 128.80, 127.33, 125.79, 124.57, 123.82, 119.32, 119.25, 117.37, 116.18, 60.93, 14.66 ppm; IR: 3434.65, 3351.97, 1699.97; 1606.10, 1503.80, 1455.60, 1384.63, 1300.89 cm^{-1}; HRMS (ESI/TOF-Q) m/z: [M+Na]+ calcd for $C_{15}H_{12}ClNO_2SNa$ 328.0175; found 328.0172.

6-chloro-10H-phenothiazine-3-carboxylic acid (**3oo**)

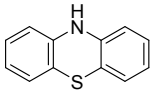


3oo

Yellow solid; mp: 272.1-274.0 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.68 (s, 1H), 8.45(s, 1H), 7.58 (dd, J =8.4 and 2.0 Hz,1H), 7.44 (d, J =2.0 Hz, 1H), 7.18-7.15 (m, 2H), 6.93 (dd, J =7.6 and 1.6 Hz, 1H), 6.81 (t, J =8.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.81, 145.34, 137.26, 129.95, 128.77, 127.62, 125.81, 125.56,

123.75, 119.35, 119.28, 117.19, 116.13 ppm; IR: 3440.51, 2920.84, 1679.65; 1636.64, 1577.25, 1492.79, 1384.41, 1290.07 cm^{-1}; HRMS (ESI/TOF-Q) m/z: [M+Na]+ calcd for $C_{13}H_8ClNO_2SNa$ 299.9862; found 299.9861.

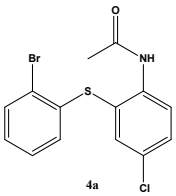
10H-phenothiazine [8] (**3p**)



3p

Pale yellow solid; ^1H NMR (400 MHz, DMSO-d_6) δ 8.58 (s, 1H), 7.00-6.90 (m, 4H), 6.76-6.68 (m, 4H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 142.58, 128.01, 126.71, 122.24, 116.81, 114.90 ppm; LC-MS: LC-MS: $[M]^+$ m/z = 199.0.

N-(2-((2-bromophenyl)thio)-4-chlorophenyl)acetamide (**4a**)

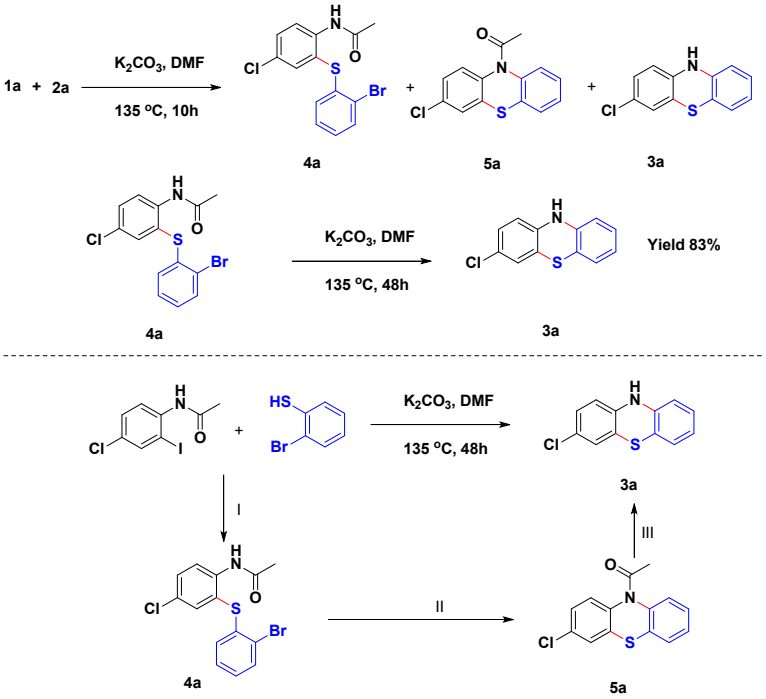


4a

White solid; mp: 128.5-139.7; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 8.44 (d, *J*=8.8 Hz, 1H), 8.08 (s, 1H), 7.58-7.56 (m, 2H), 7.43 (dd, *J* = 8.8 and 2.4 Hz, 1H), 7.18-7.14 (m, 1H), 7.09-7.05 (m, 1H), 6.70 (dd, *J* = 8.0 and 1.6 Hz, 1H), 2.08 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.39, 138.73, 136.05, 135.82, 133.13, 131.35, 129.01, 128.37, 128.25, 127.84, 122.05, 121.03, 99.94, 24.77 ppm; IR: 3440.45, 3327.40, 1676.72; 1628.96, 1573.56, 1507.64, 1445.72, 1384.13, 1290.02 cm^{-1}; HRMS (ESI/TOF-Q) m/z: [M+H]+ calcd for $C_{14}H_{11}BrClNOSH$ 355.9512 and 357.9491; found 355.9510 and 357.9485

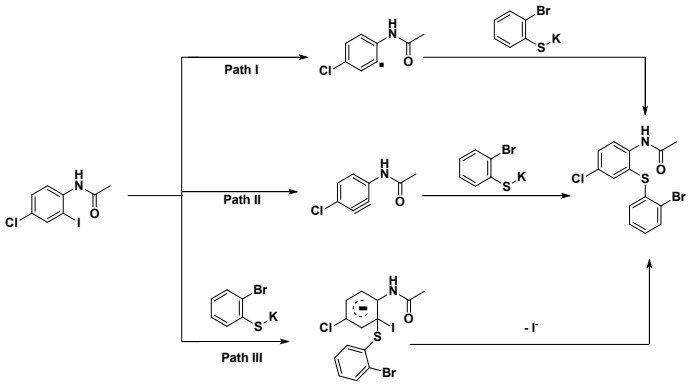
Investigations into the mechanism

Several control experiments were performed to investigate the reaction mechanism. When the reaction time was reduced to 10 h, the intermediate **4a** was separated and **5a** was detected by LC-MS. Then the intermediate **4a** was employed instead of the reactants under the optimized condition and the product **3a** was obtained in 83%. Based on these results, we proposed a plausible pathway for the reaction, which was shown in Scheme S1.



Scheme S1 Plausible pathway for the reaction

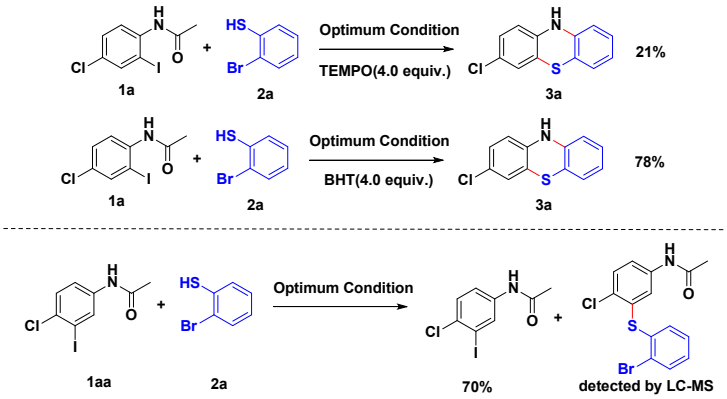
Based on previous reports of 'Typical Transition-Metal-Free Coupling Reactions through Various Pathways', [13] three different mechanisms for C-S coupling were proposed in Scheme S2.



Scheme S2 three proposed mechanism for C-S coupling

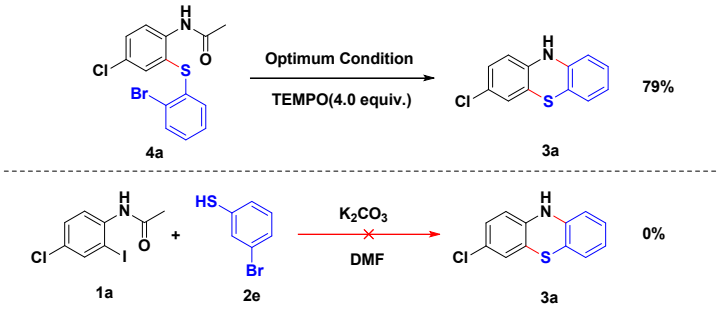
When we performed the reaction under the optimum condition in the presence of 4.0 equiv. radical scavenger 2,2,6,6-Tetramethylpiperidine-1-oxyl (TEMPO), the title compound was obtained in 21% because the reactant 2-bromo-benzenethiol (**2a**) was decomposed by TEMPO. And another radical scavenger 2,6-di-tert-butyl-4-methylphenol (BHT) cannot inhibit the reaction. The results indicated that a radical pathway (I) was not occurred for this reaction. To investigate whether a benzyne intermediate was formed during C-S coupling process, N-(4-chloro-3-iodophenyl)acetamide (**1aa**) was employed instead of **(1a)** (Scheme S3). The corresponding product **(3a)** was not observed and it was difficult to realize this C-S coupling which means the benzyne intermediate was impossible (II). According to the above results, a nucleophilic addition-elimination pathway (III) was plausible for

this reaction (Scheme S2).



Scheme S3 Investigations into the mechanism for C-S coupling

According to Bolm·s research, [14] control experiments were performed to investigate the intramolecular C-N coupling reaction. The intermediate **4a** was also employed under the optimum condition in the presence of 4.0 equiv. TEMPO, the product **3a** was obtained in 79% yield. The results indicated the reaction might be completed without a radical pathway. To investigate whether a benzyne intermediate was formed during coupling progress, 3-bromo-benzenethiol was employed as the substrate instead of 2-bromo-benzenethio under the optimum condition (Scheme S4). And the corresponding product **3a** was not observed. The results were consistent to previous research.



Scheme S4 Investigations into the mechanism for C-N coupling

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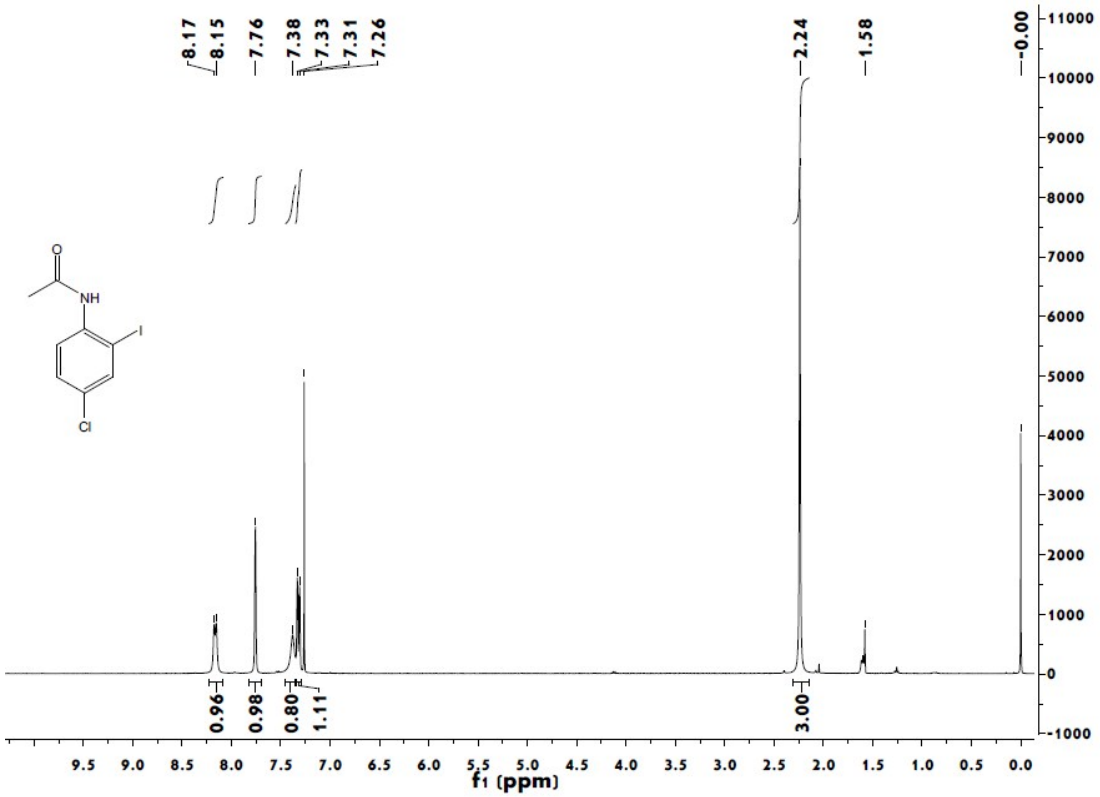
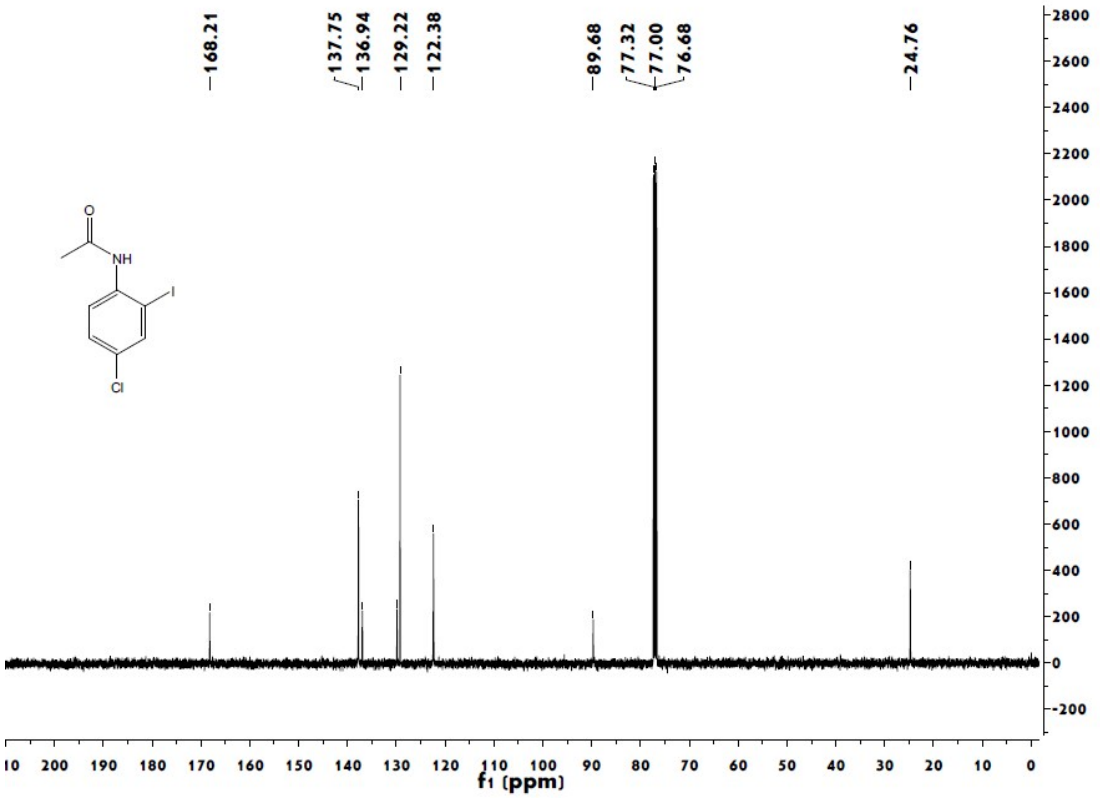
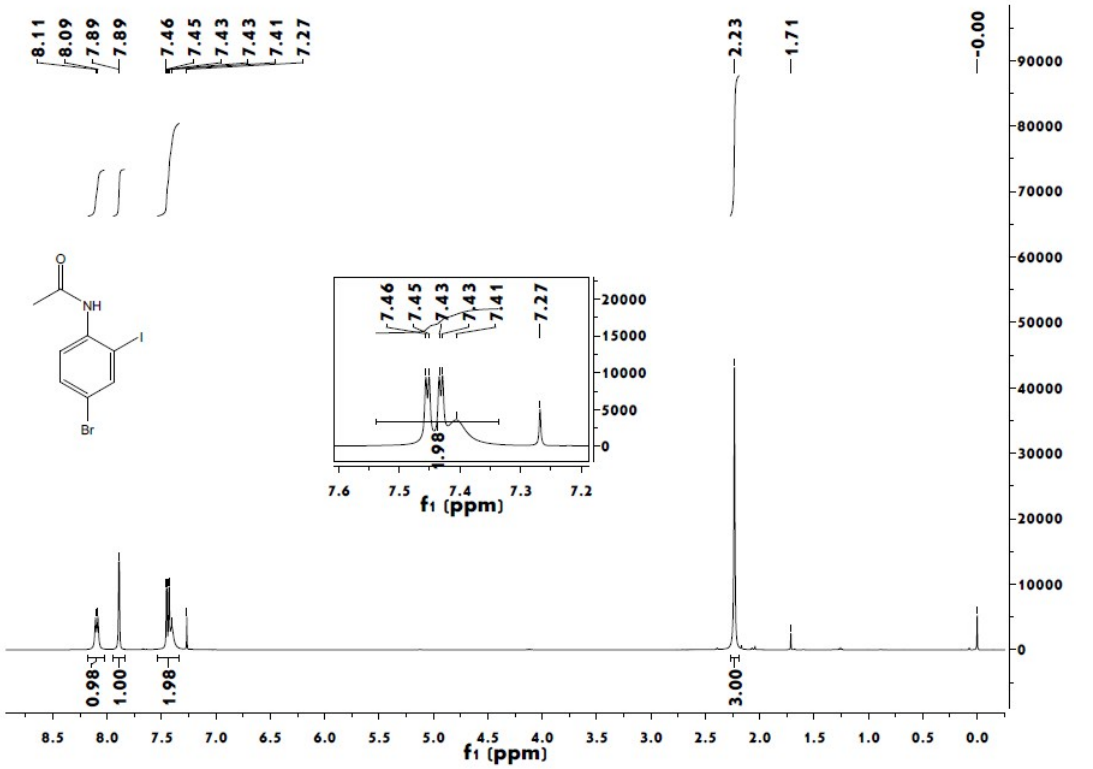
[1]HNMR and [13]CNMR spectra of the compounds



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7.89
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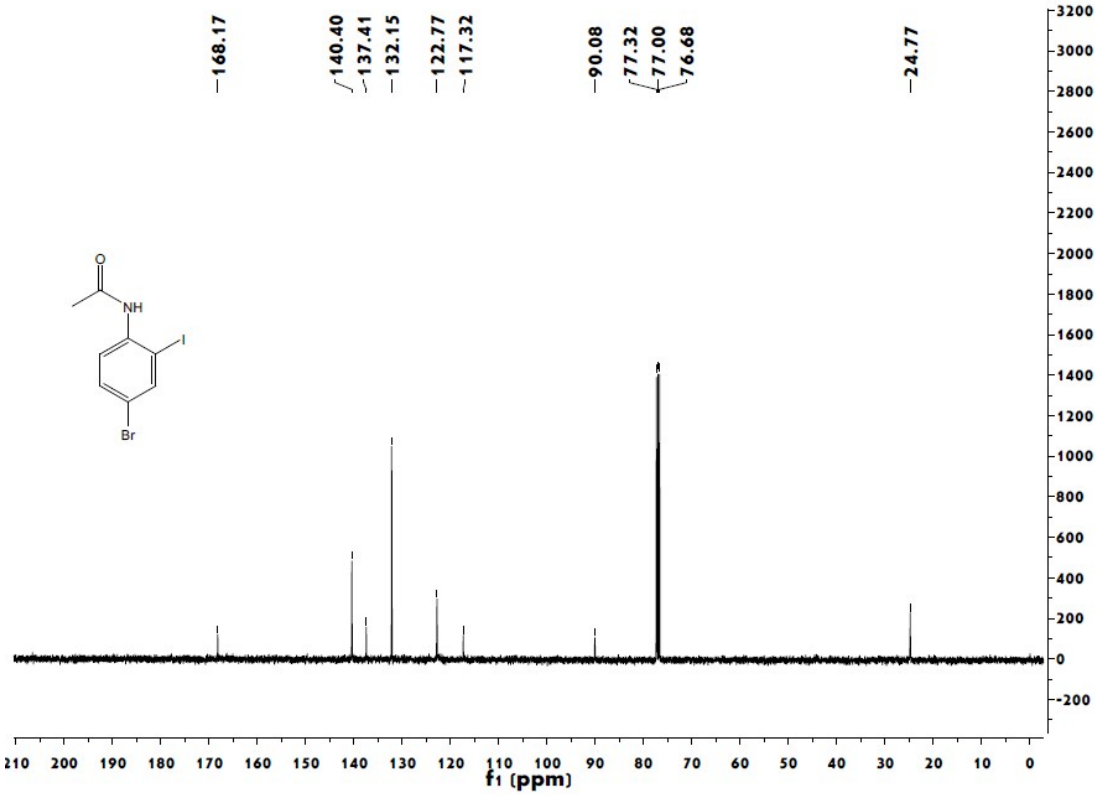
7.45
7.43
7.43
7.41
7.27
2.23
1.71
0.00
O
NH
I
Br
0.98
1.00
1.98
3.00
f1 (ppm)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77.00
76.68
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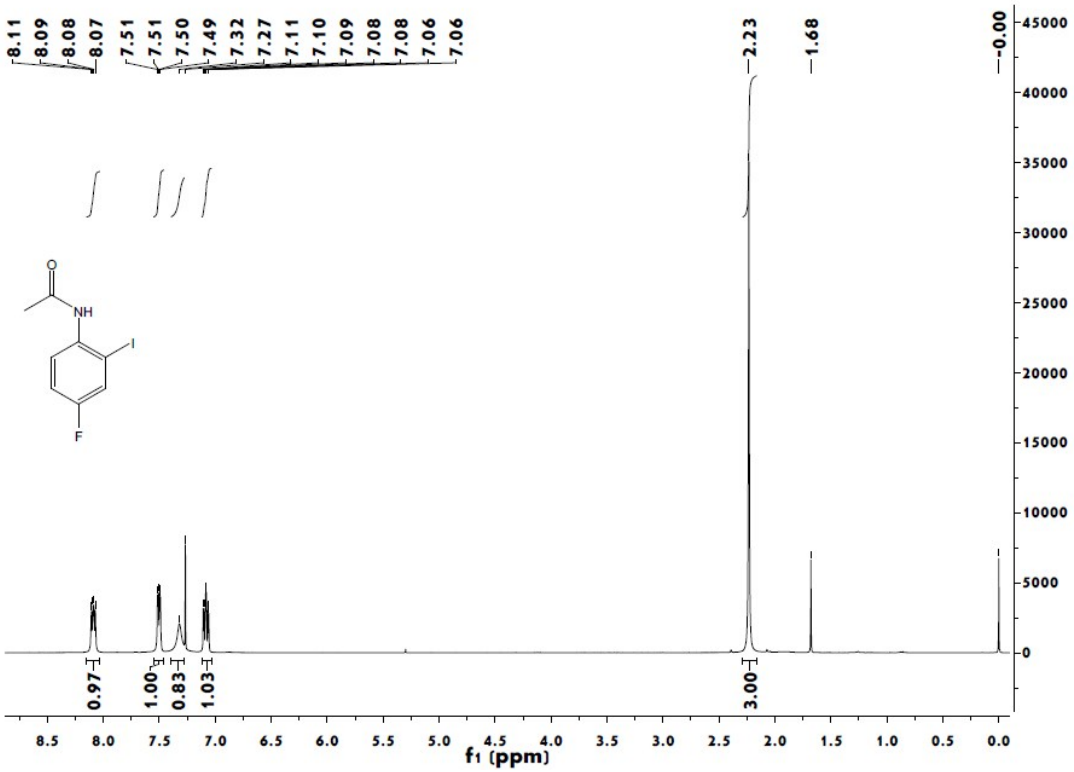
O
NH
I
Br
f1 (ppm)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7.09
7.08
7.08
7.06
7.06
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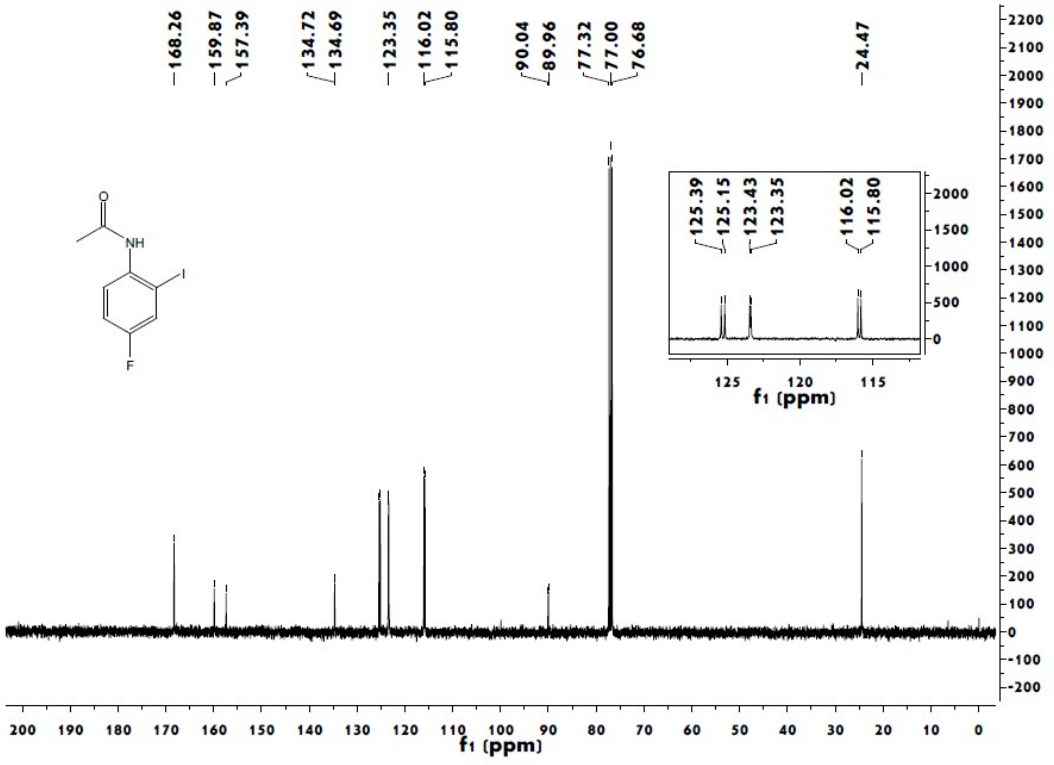
f1 (ppm)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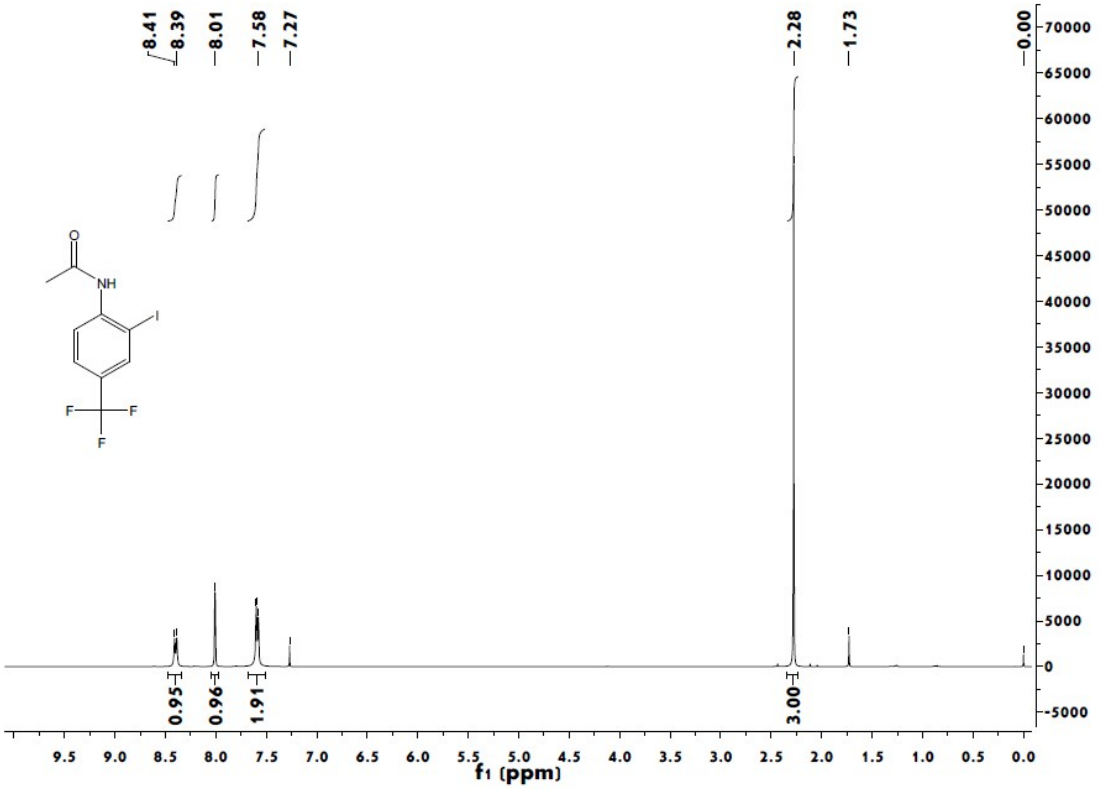
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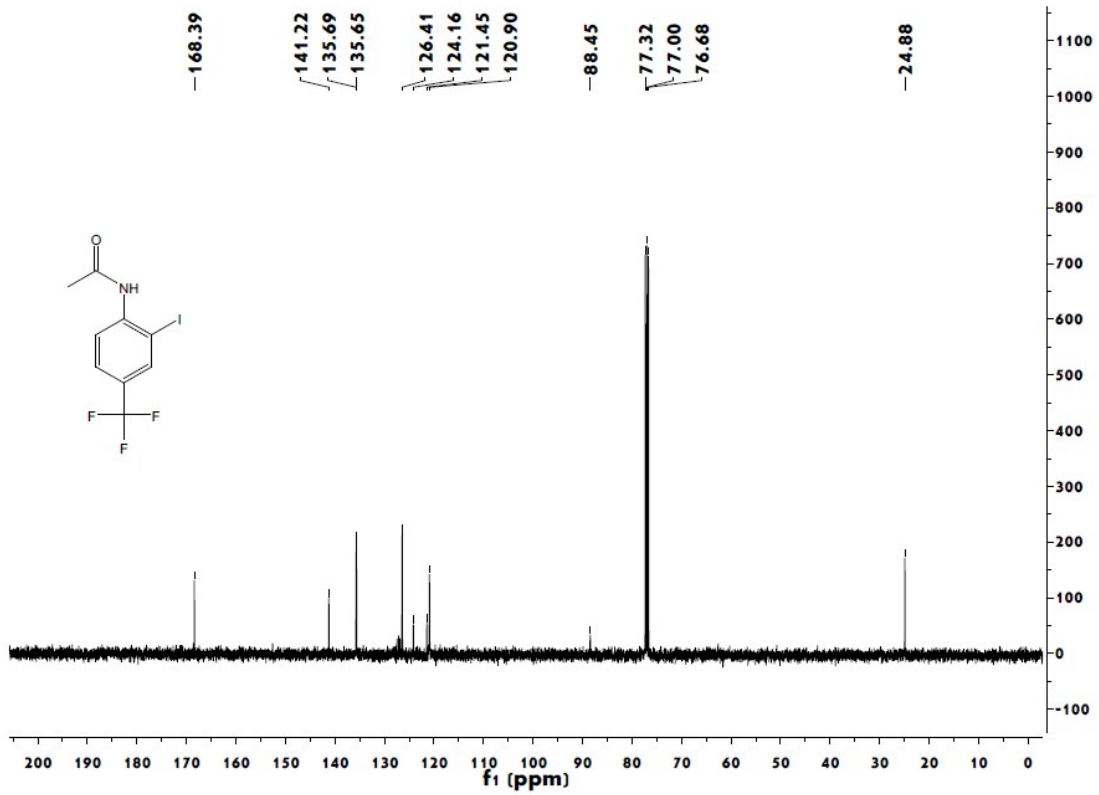
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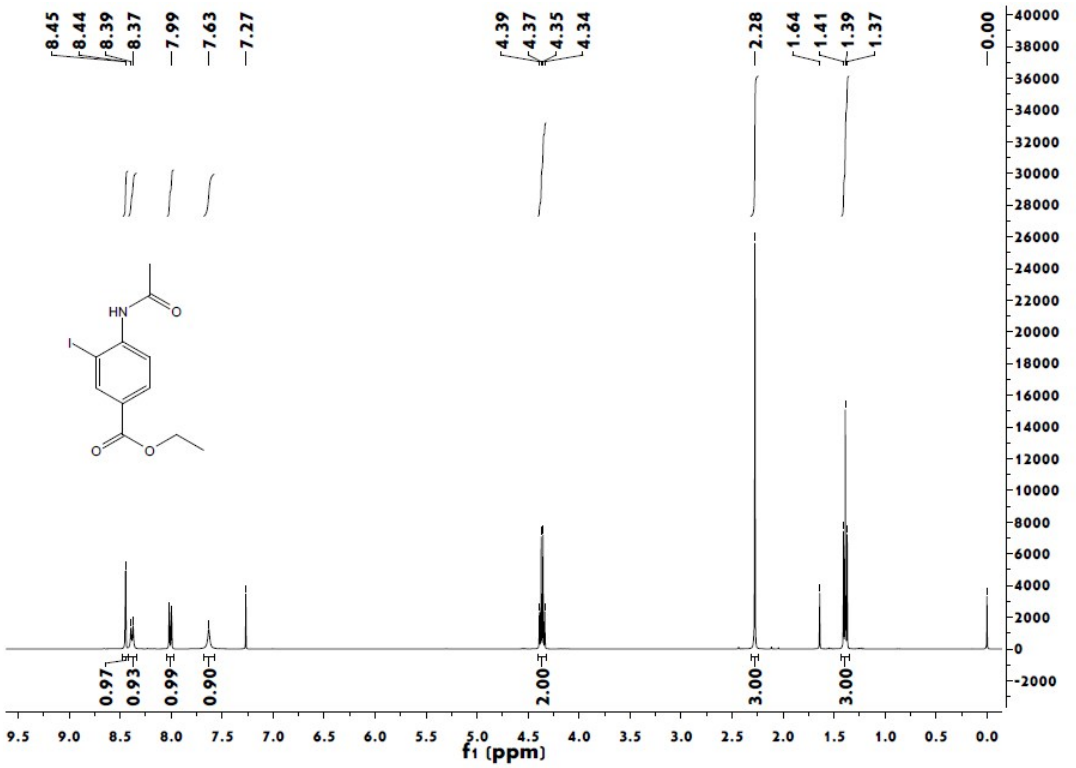
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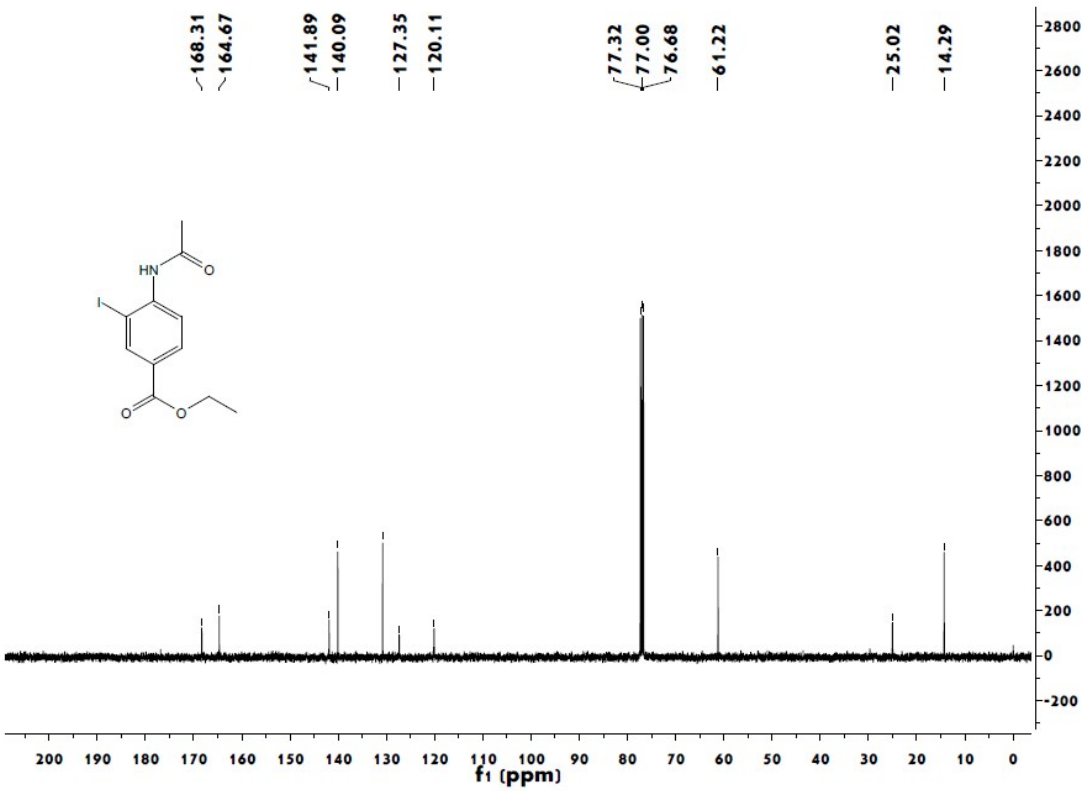
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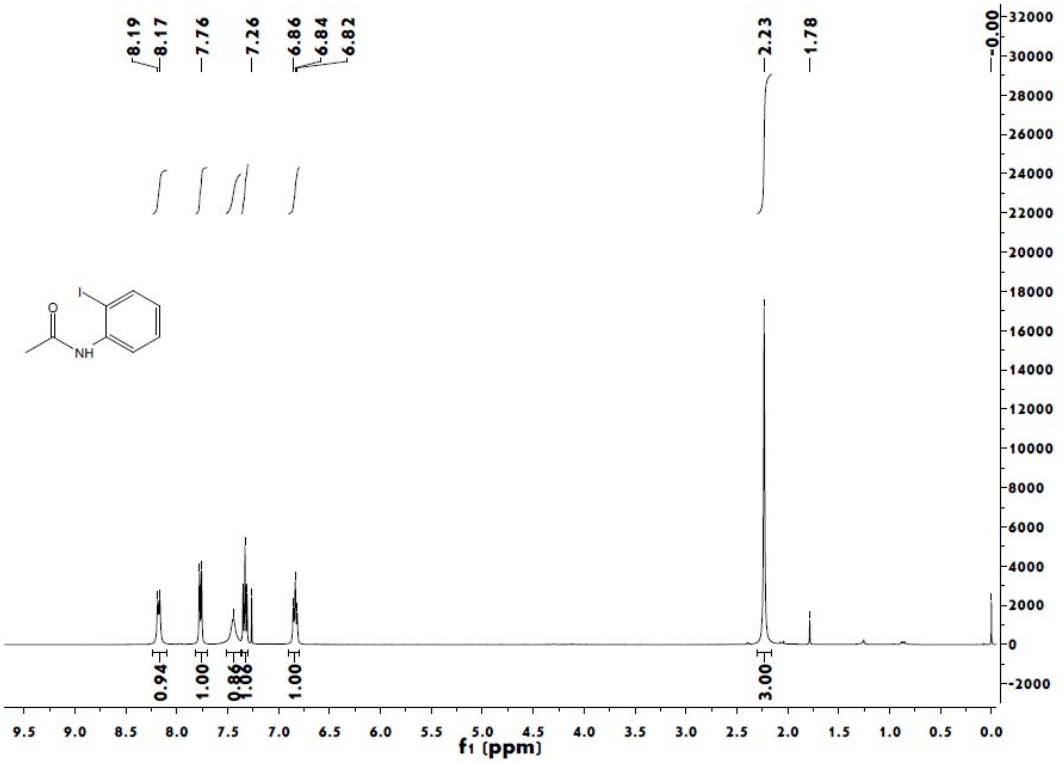
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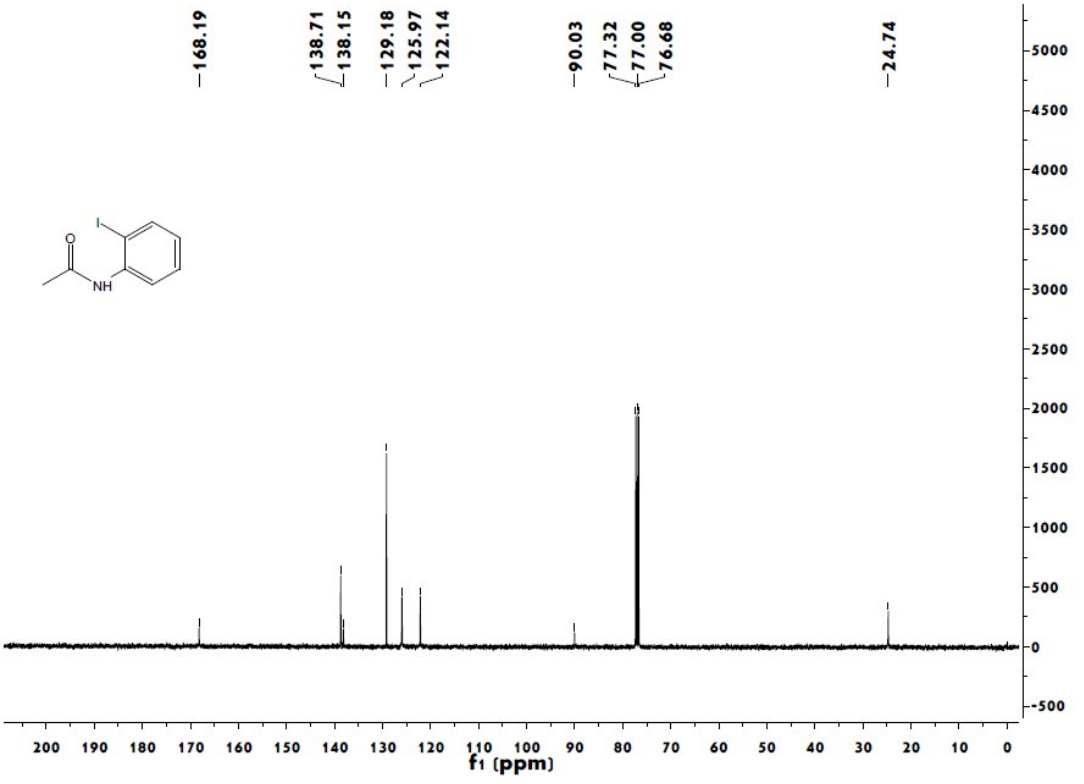
f1 (ppm)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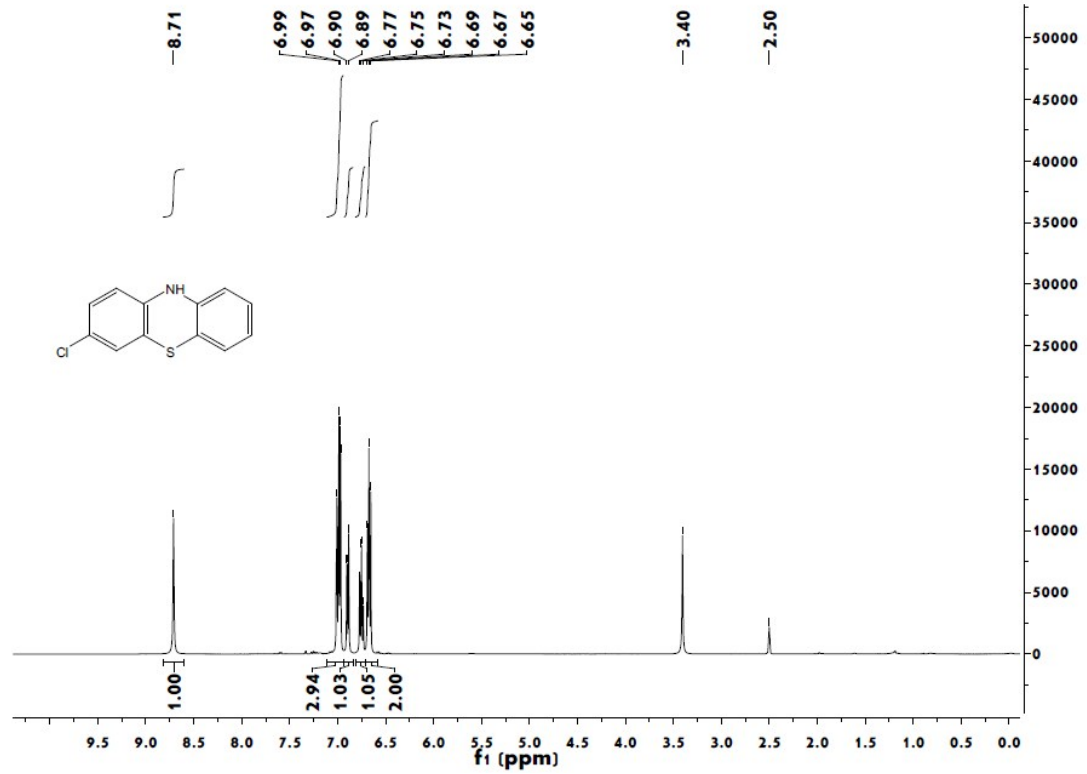
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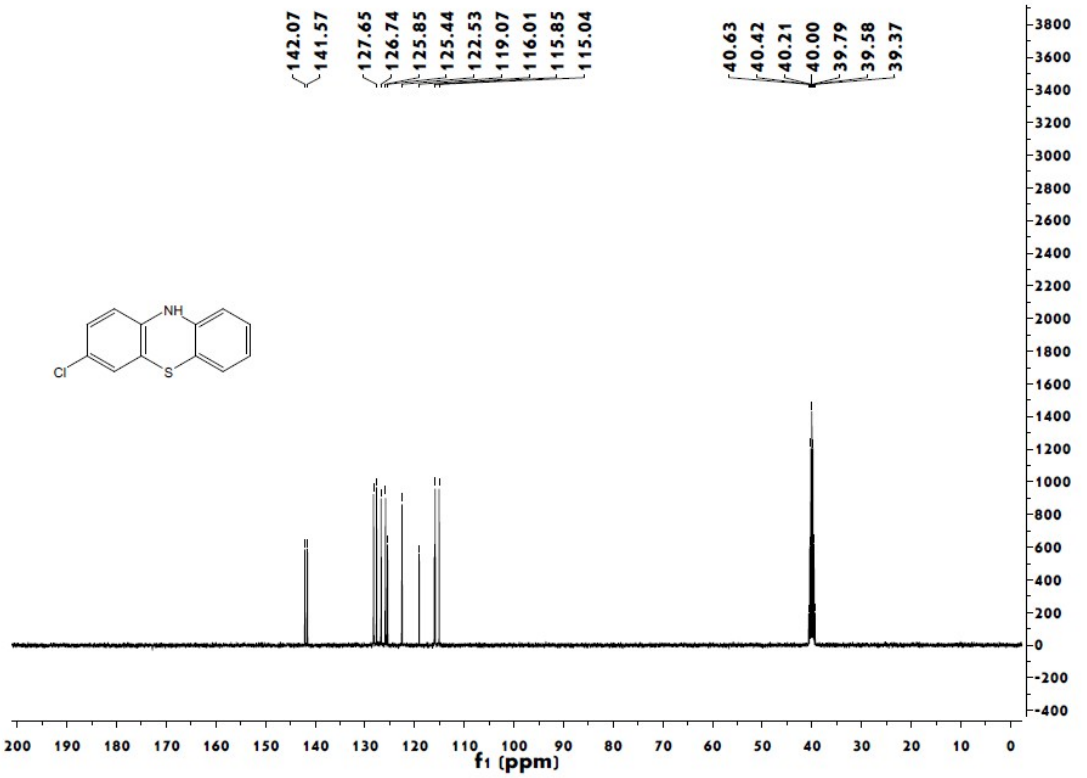
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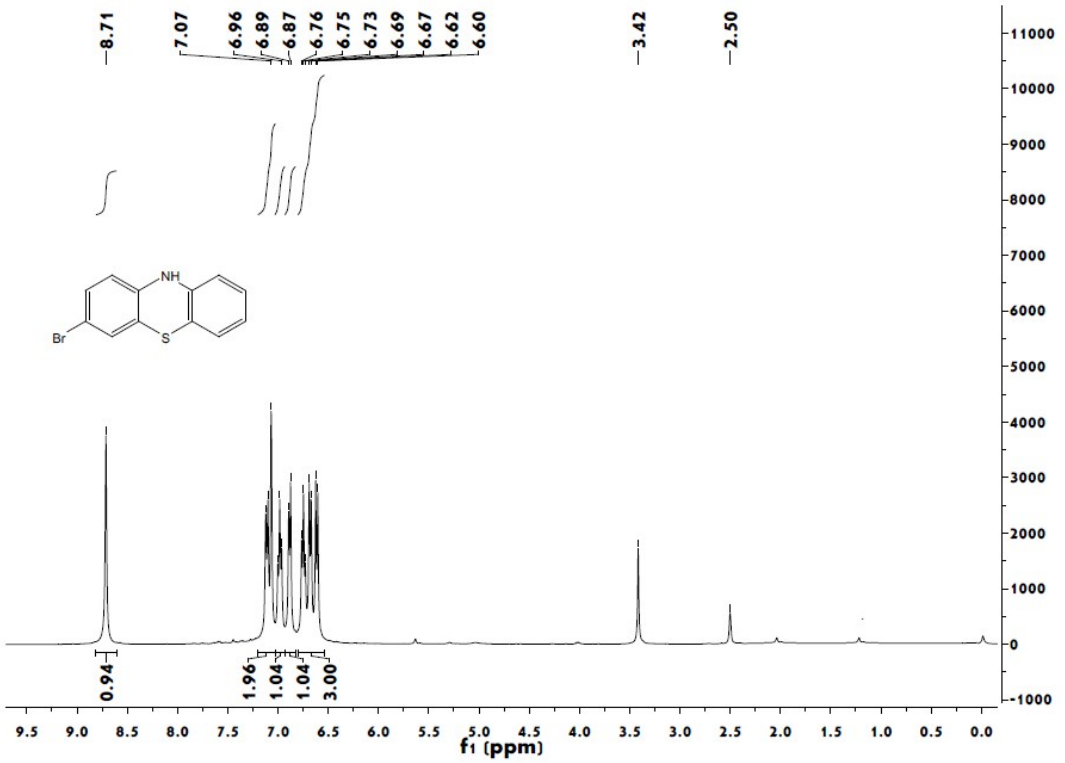
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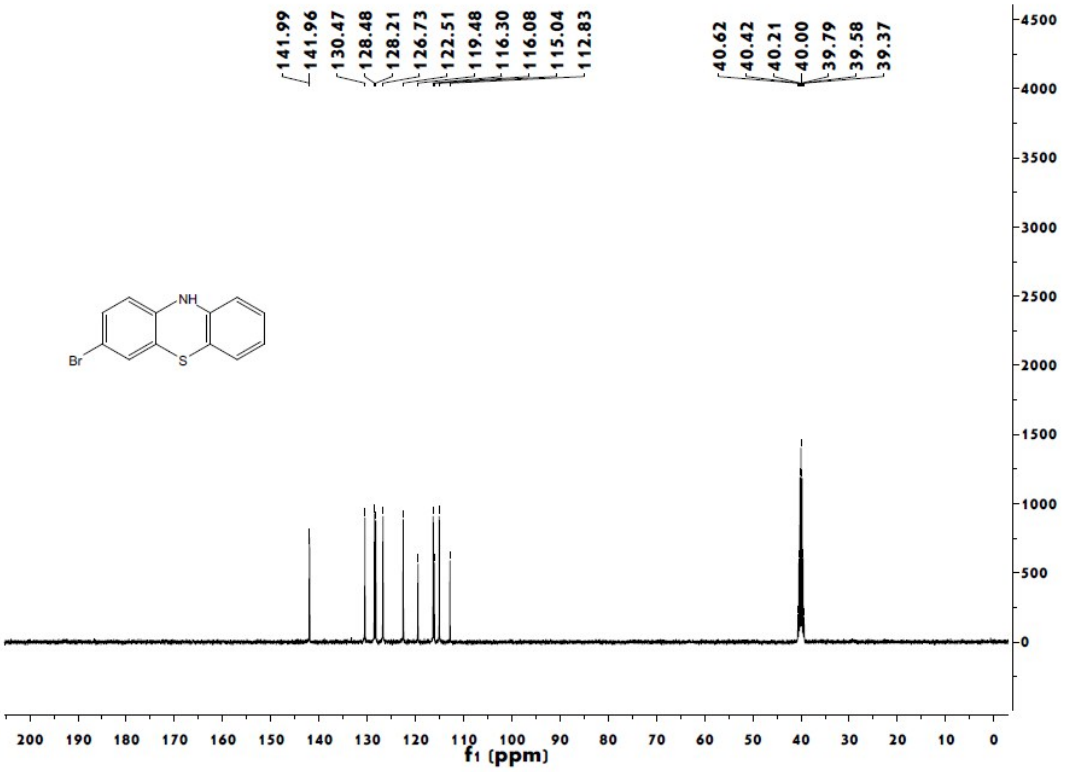
1.04
3.00
f1 (ppm)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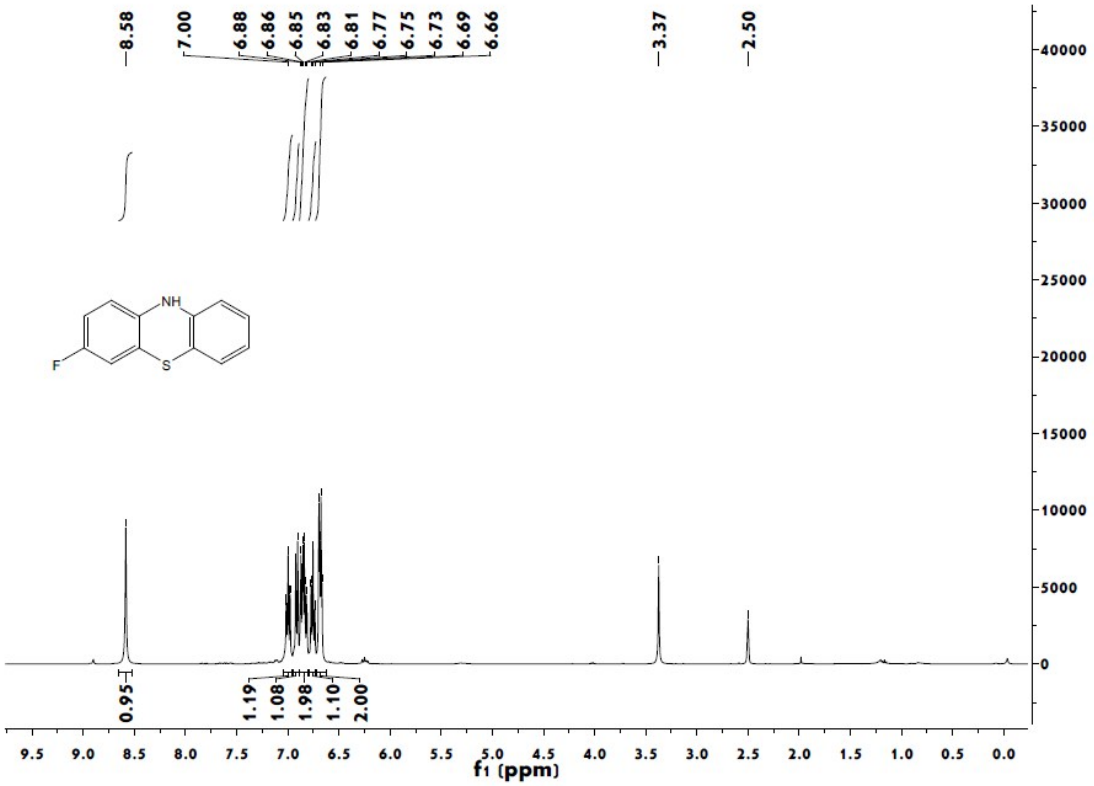
NH
Br
S
f1 (ppm)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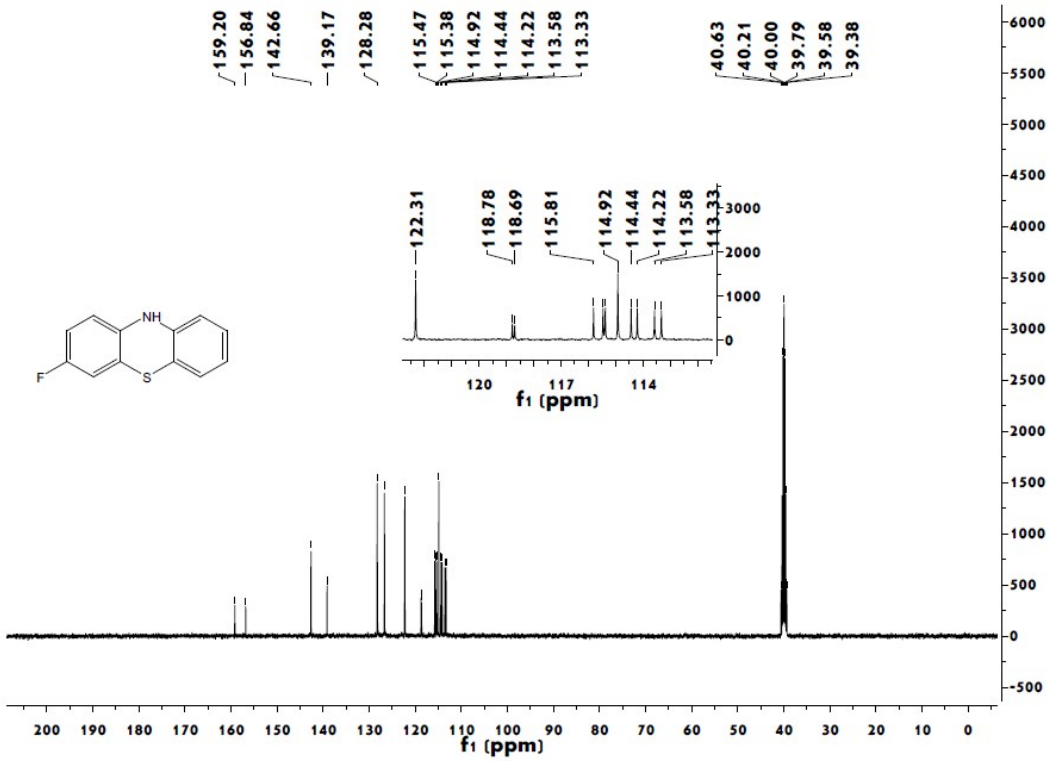
2.00
f1 (ppm)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39.38
122.31
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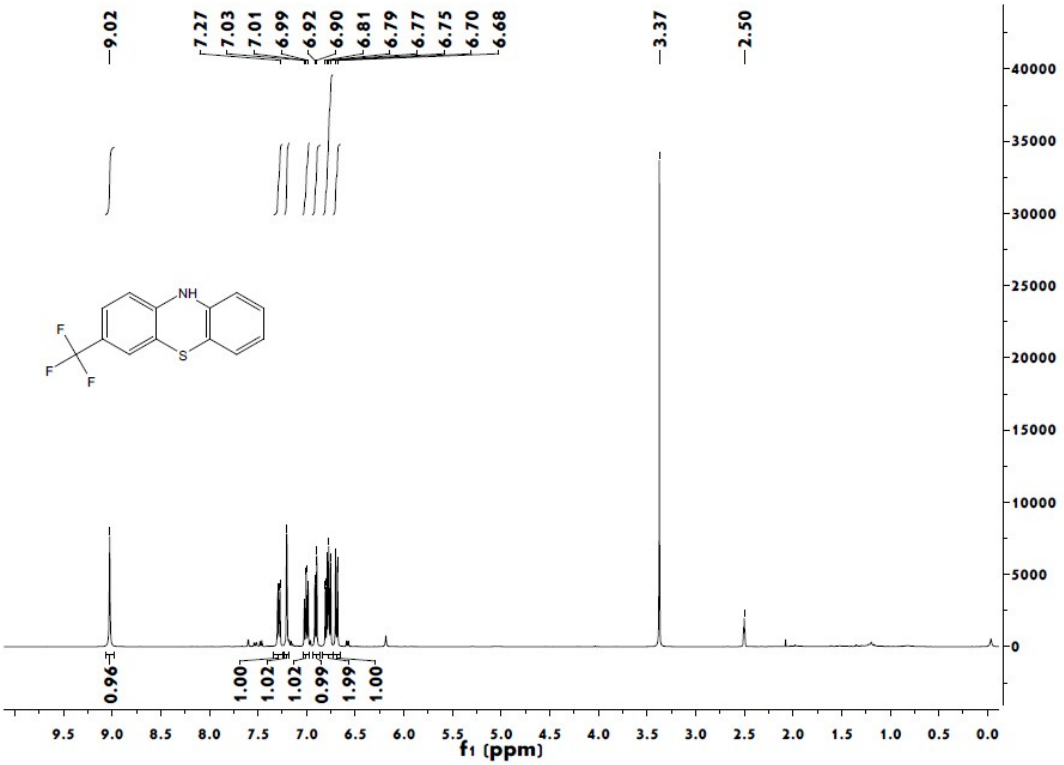
NH
F
S
f1 (ppm)
f1 (ppm)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3.37
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F
F
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0.99
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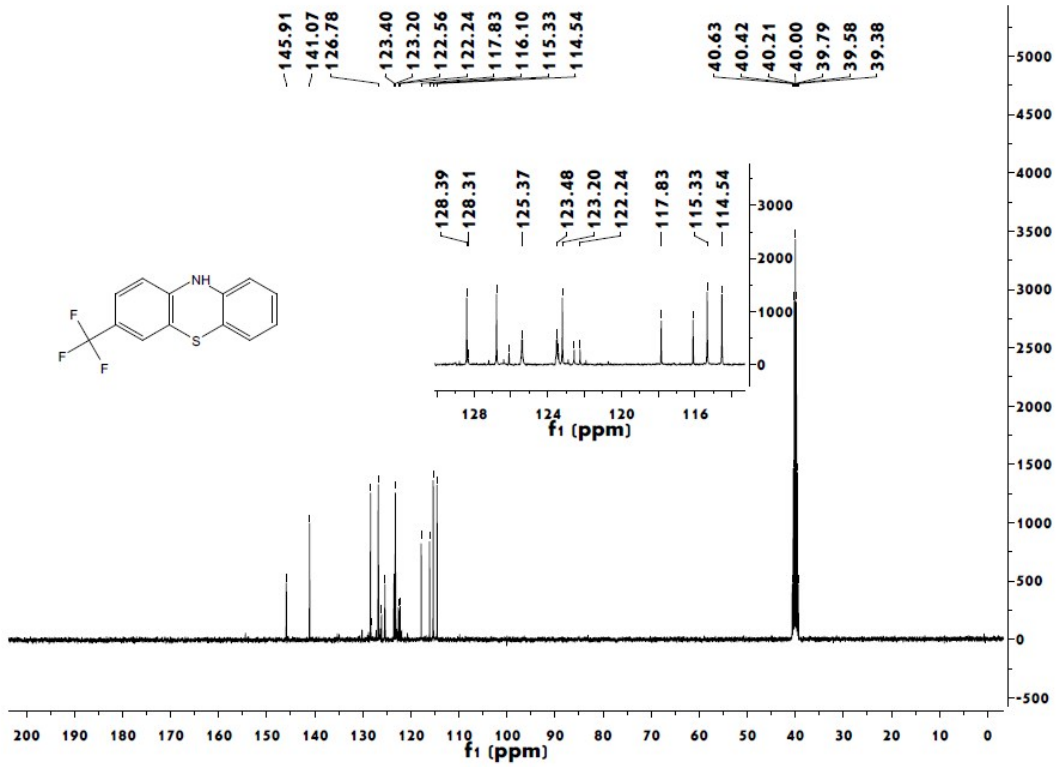
1.00
f1 (ppm)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39.58
39.38
128.39
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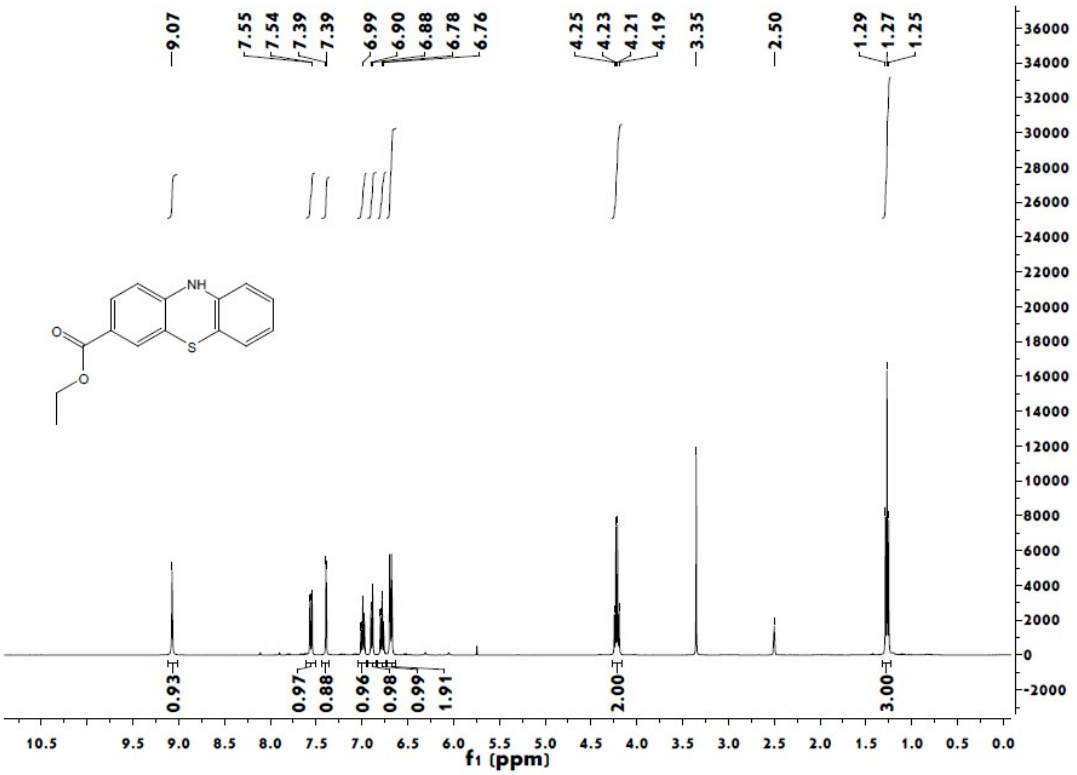
F
F
F
f1 (ppm)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3.35
2.50
1.29
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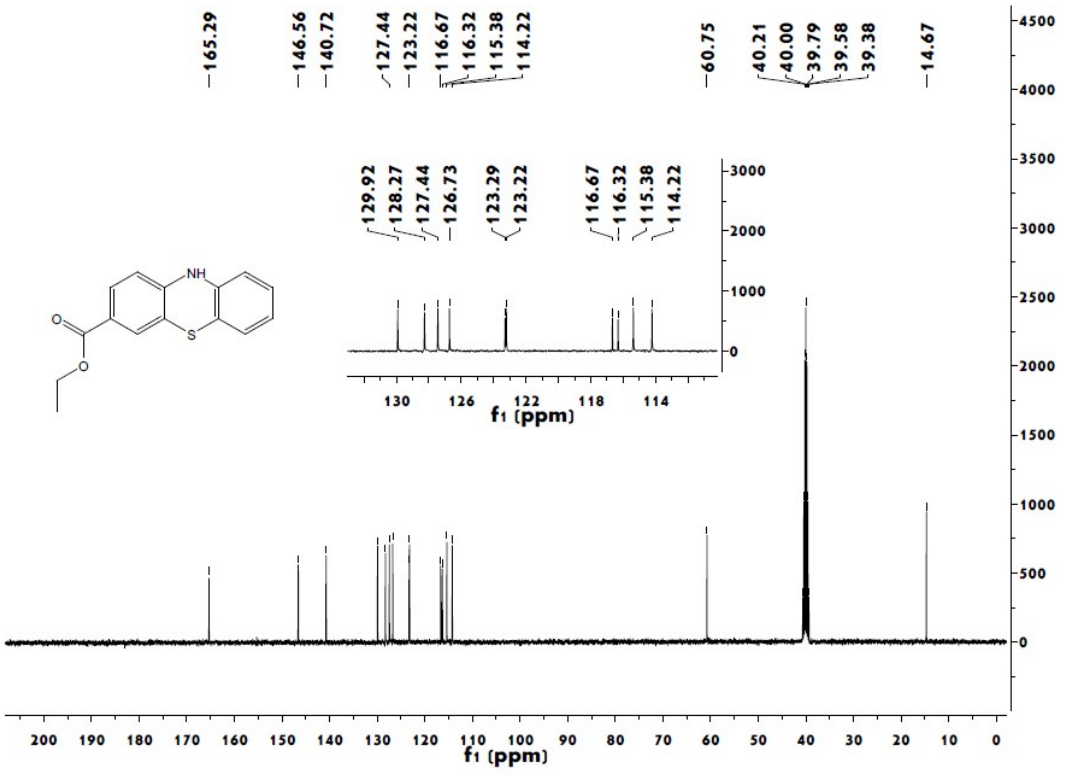
0.96
0.98
0.99
1.91
2.00
3.00
f1 (ppm)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39.58
39.38
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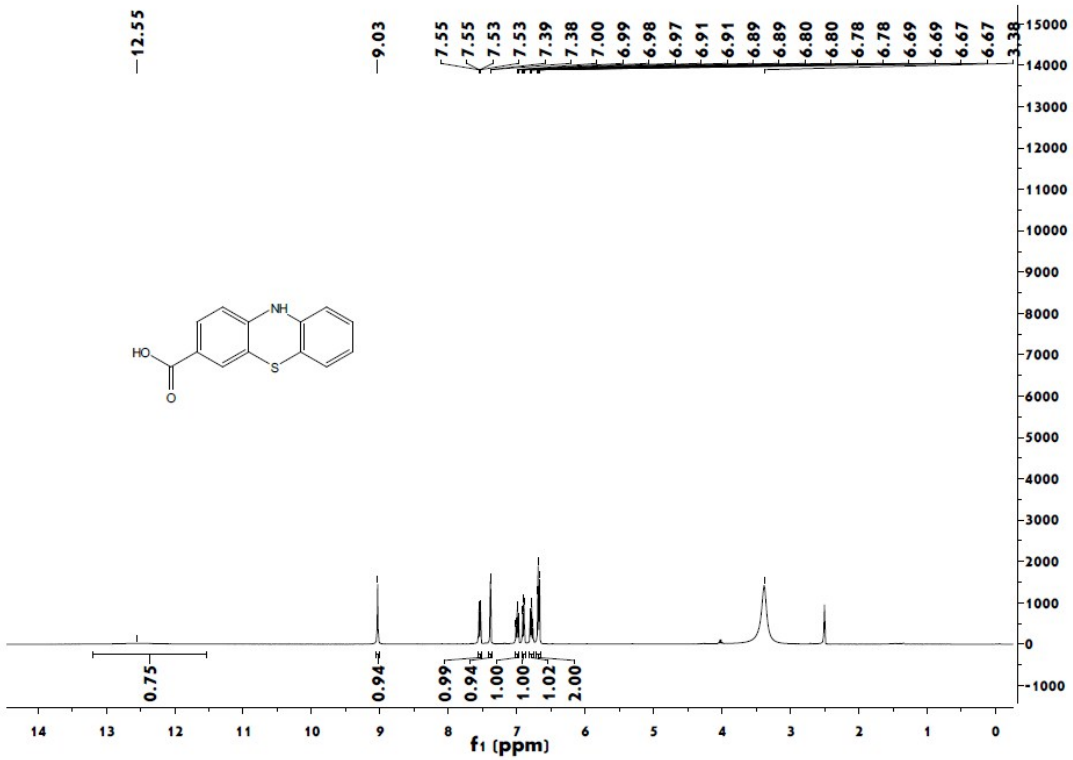
114.22
f1 (ppm)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6.89
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6.80
6.78
6.78
6.69
6.69
6.67
6.67
3.38
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1.00
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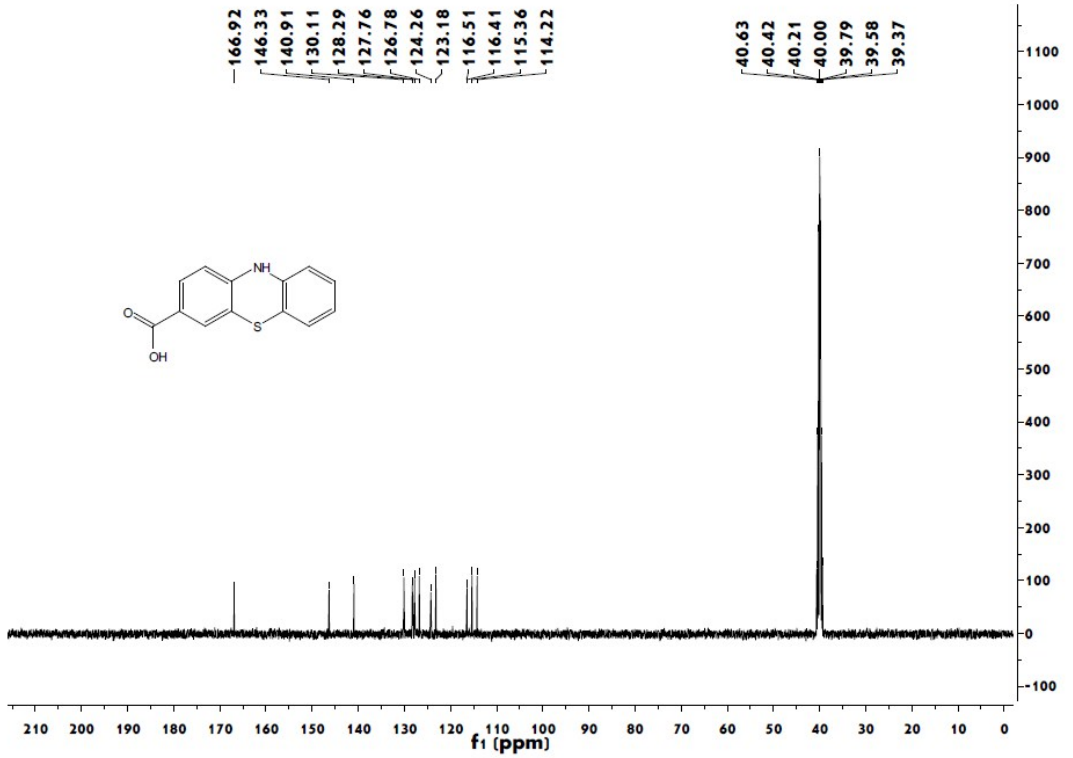
2.00
f1 (ppm)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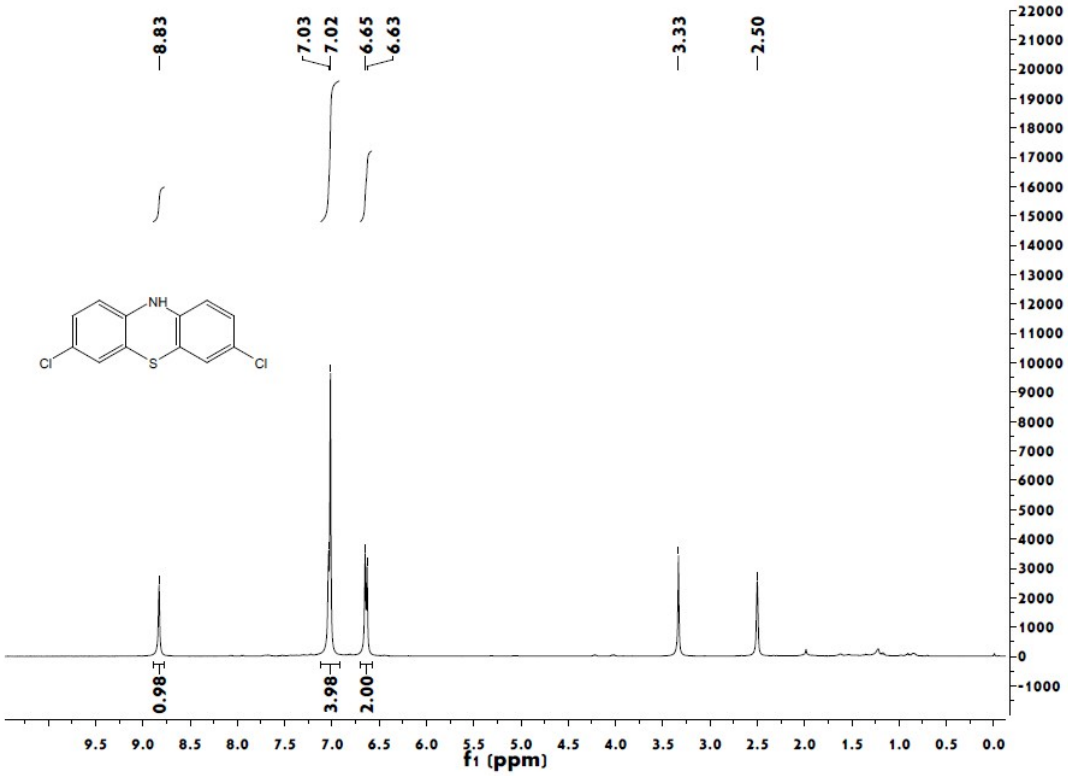
39.37
NH
O
OH
S
f1 (ppm)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6.63
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NH
Cl
S
Cl
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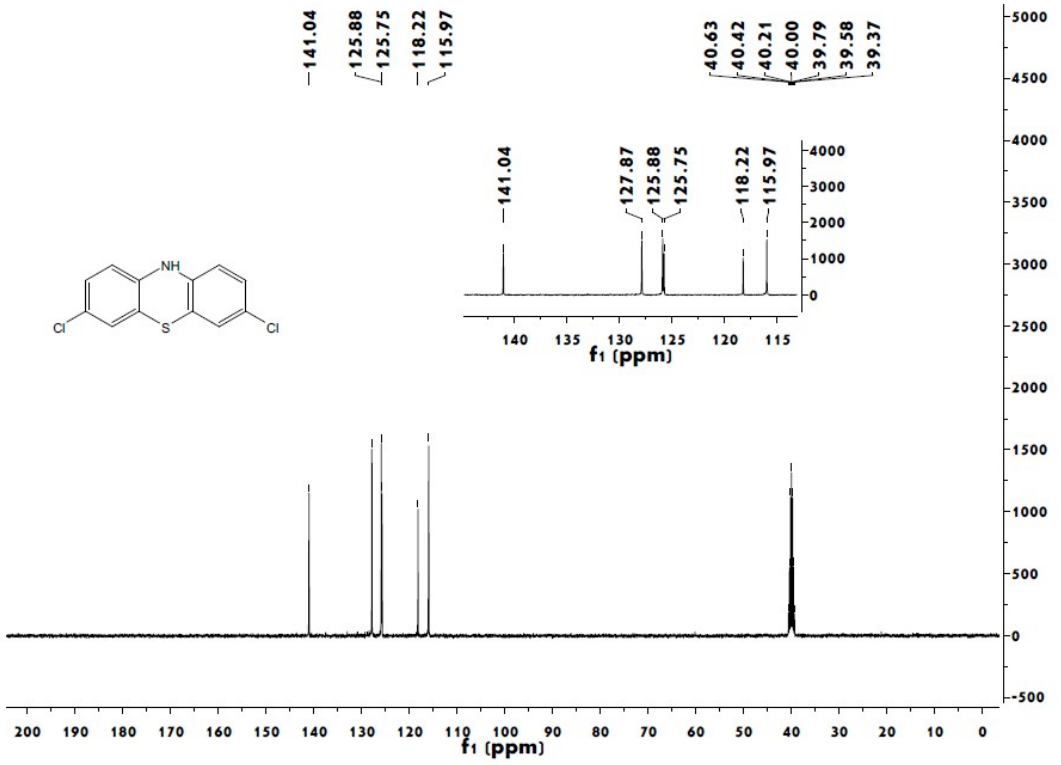
3.98
2.00
f1 (ppm)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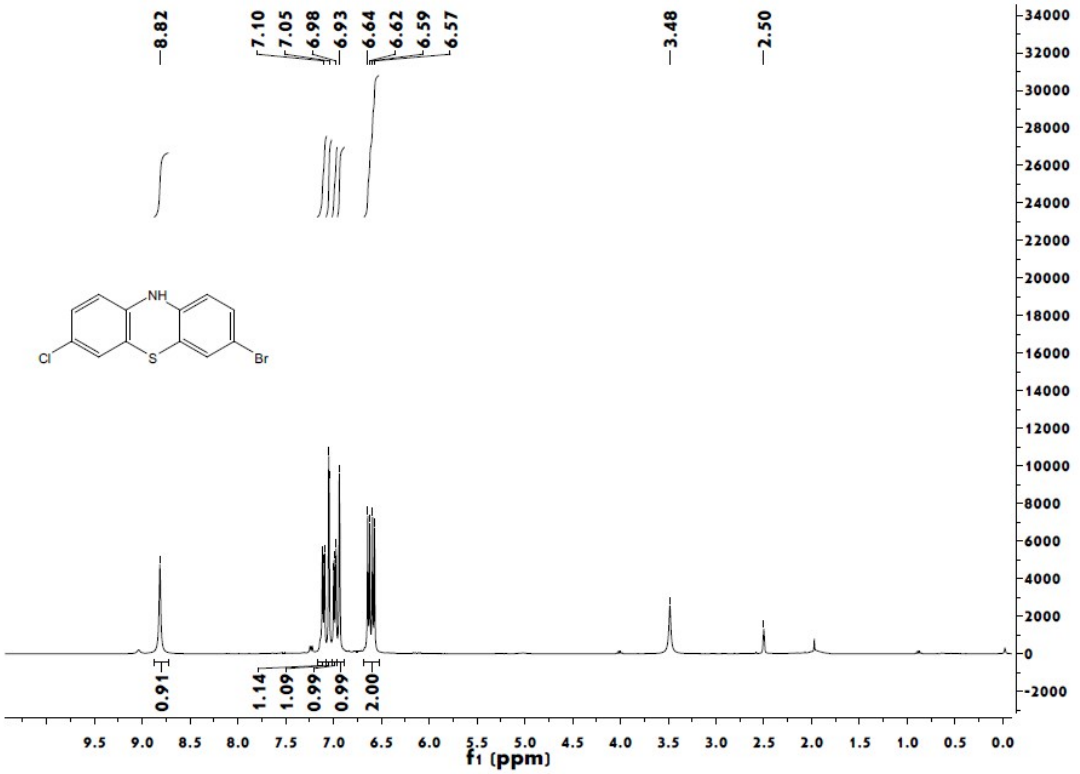
Cl
S
Cl
f1 (ppm)
f1 (ppm)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6.57
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Cl
S
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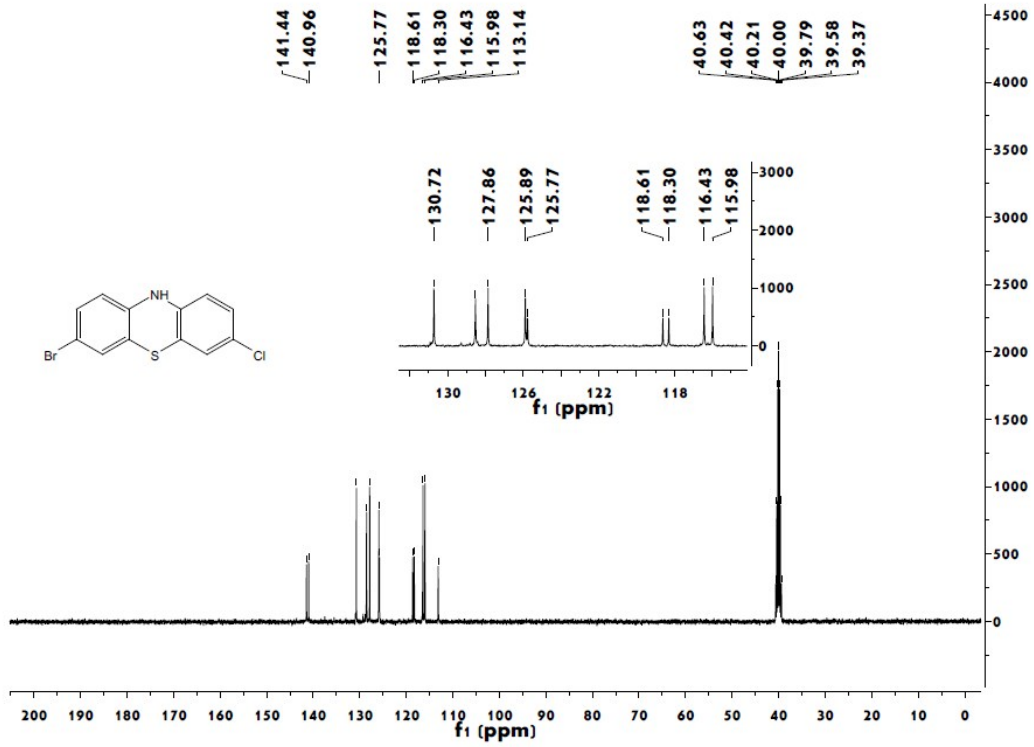
0.99
0.99
2.00
f1 (ppm)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130.72
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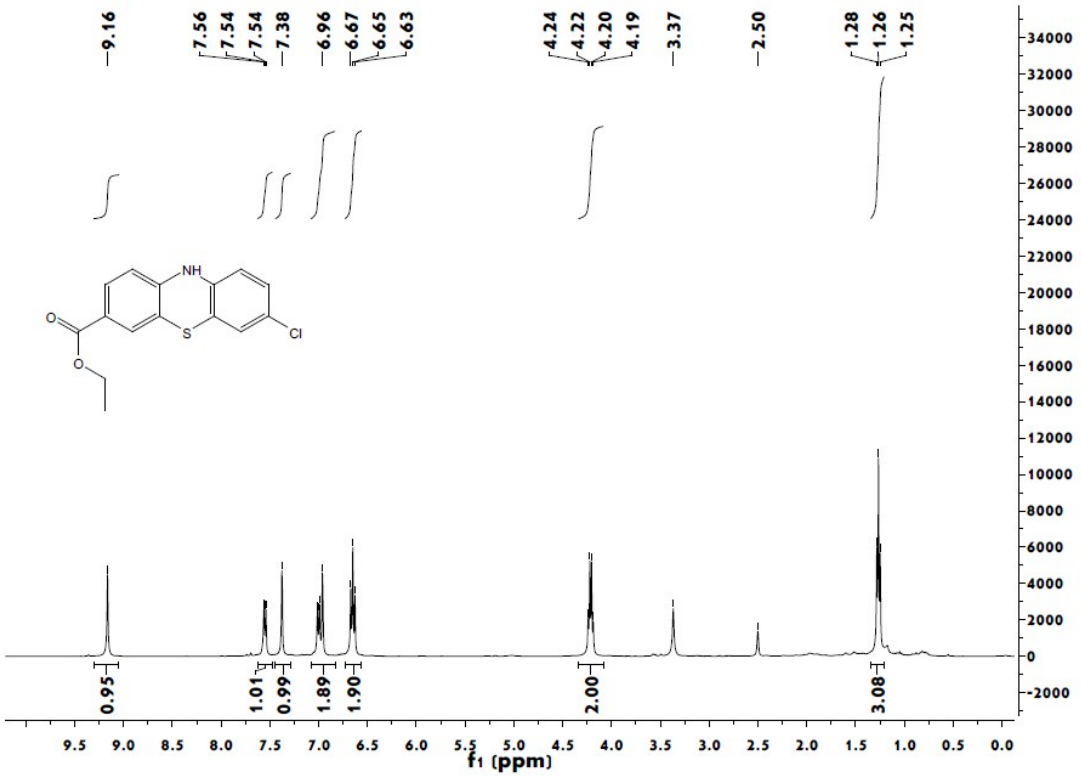
Br
S
Cl
f1 (ppm)
f1 (ppm)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3.37
2.50
1.28
1.26
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O
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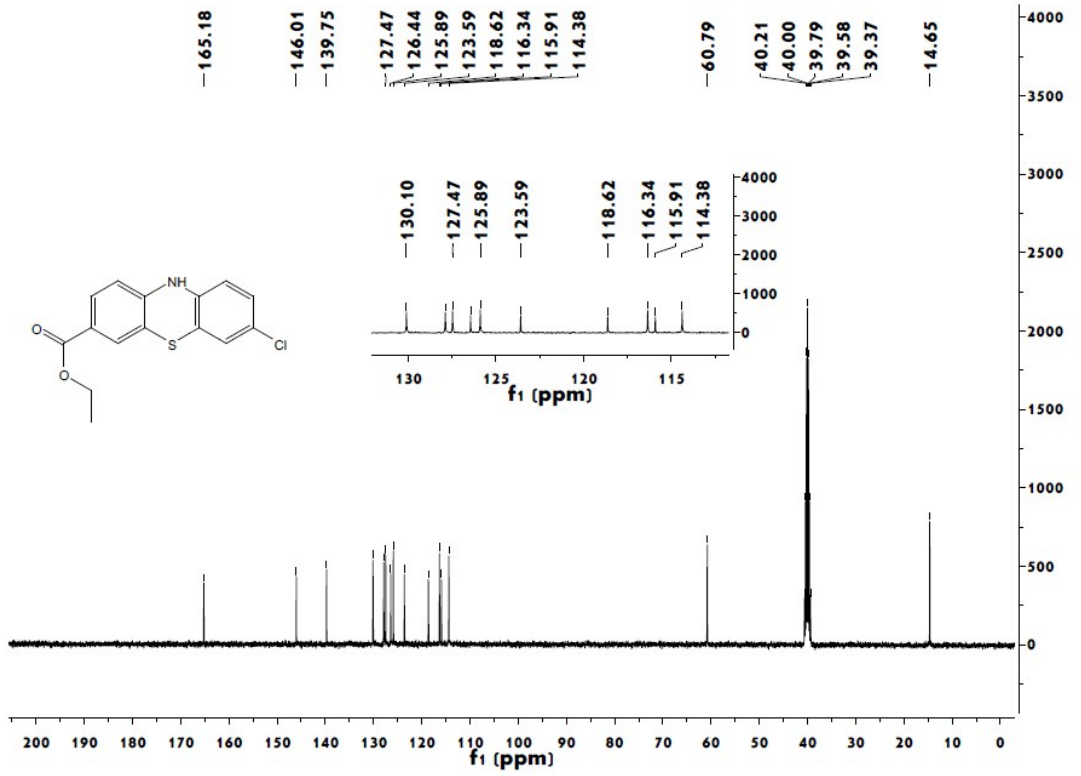
1.90
2.00
3.08
f1 (ppm)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39.58
39.37
14.65
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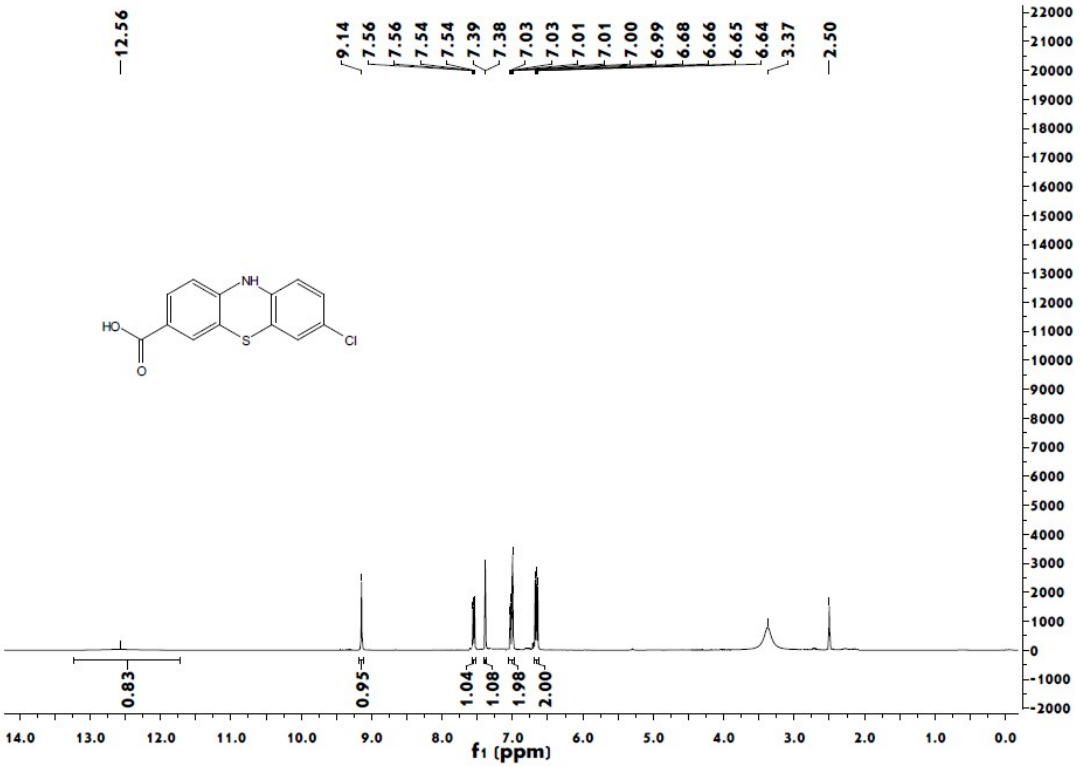
NH
S
Cl
O
O
f1 (ppm)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7.00
6.99
6.68
6.66
6.65
6.64
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HO
O
S
Cl
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1.08
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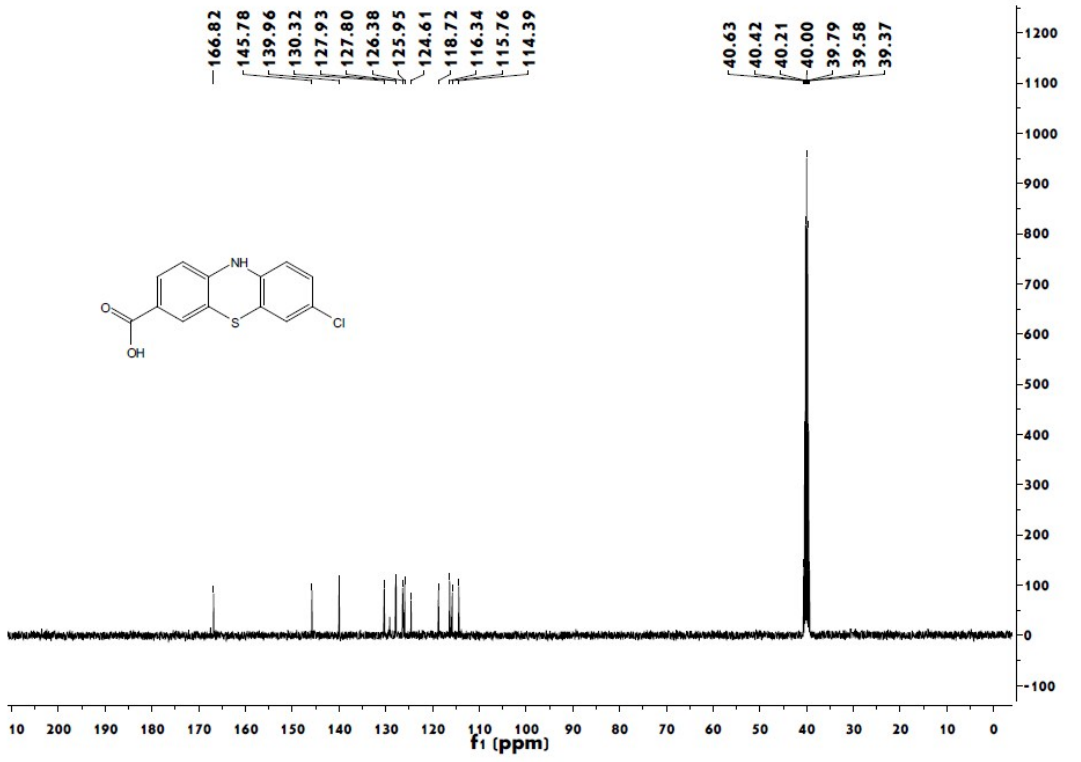
2.00
f1 (ppm)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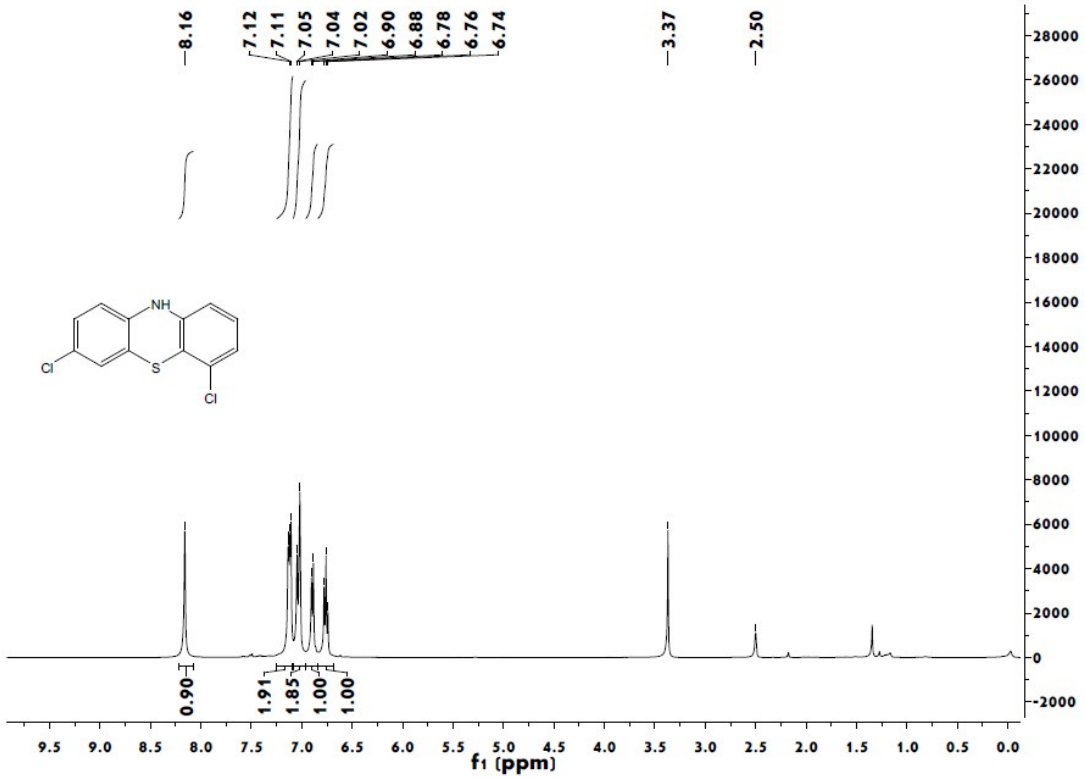
NH
O
OH
S
Cl
f1 (ppm)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Cl
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1.85
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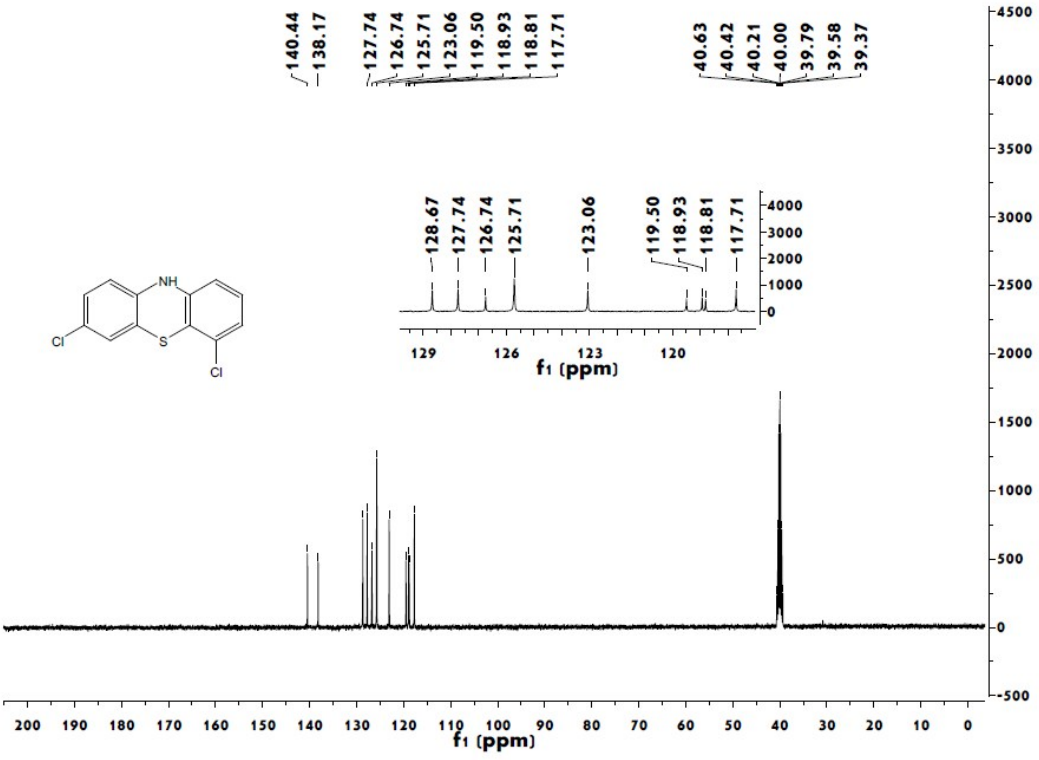
1.00
f1 (ppm)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128.67
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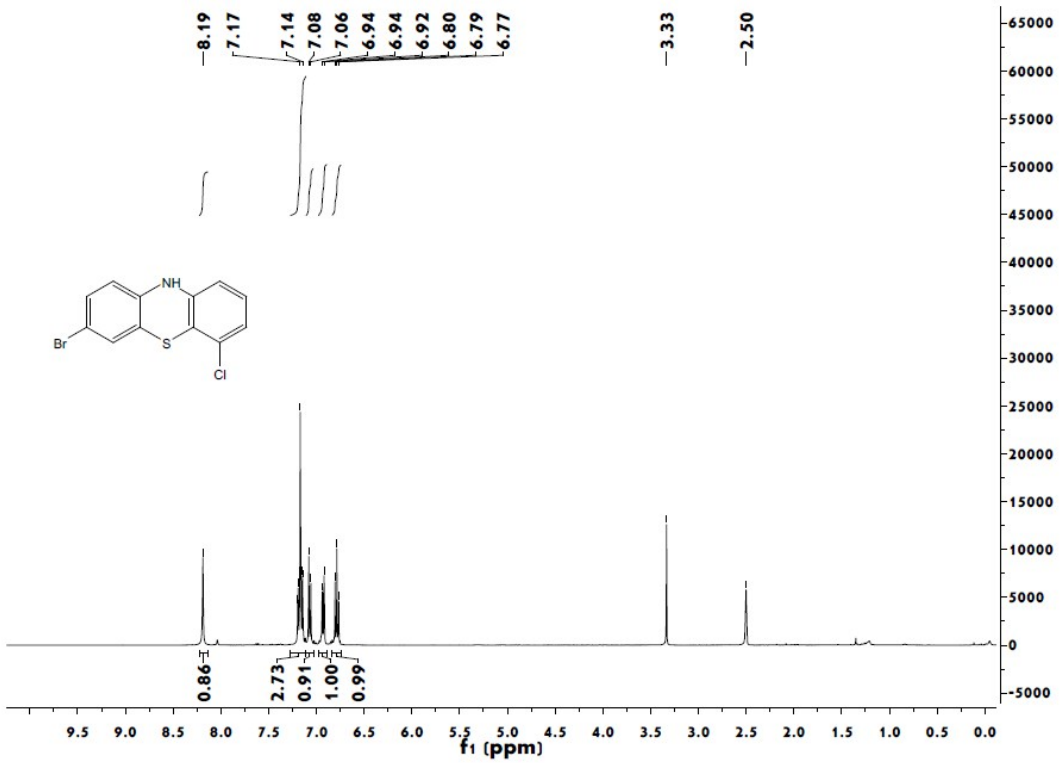
NH
Cl
S
Cl
f1 (ppm)
f1 (ppm)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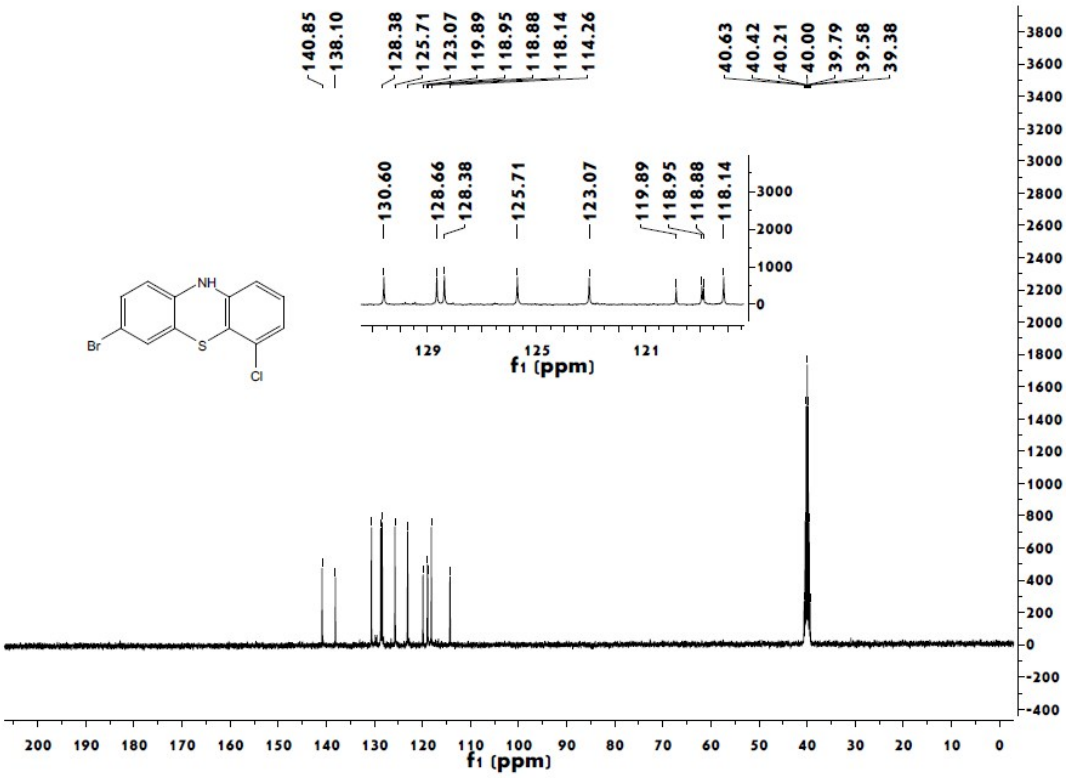
f1 (ppm)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39.58
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130.60
128.66
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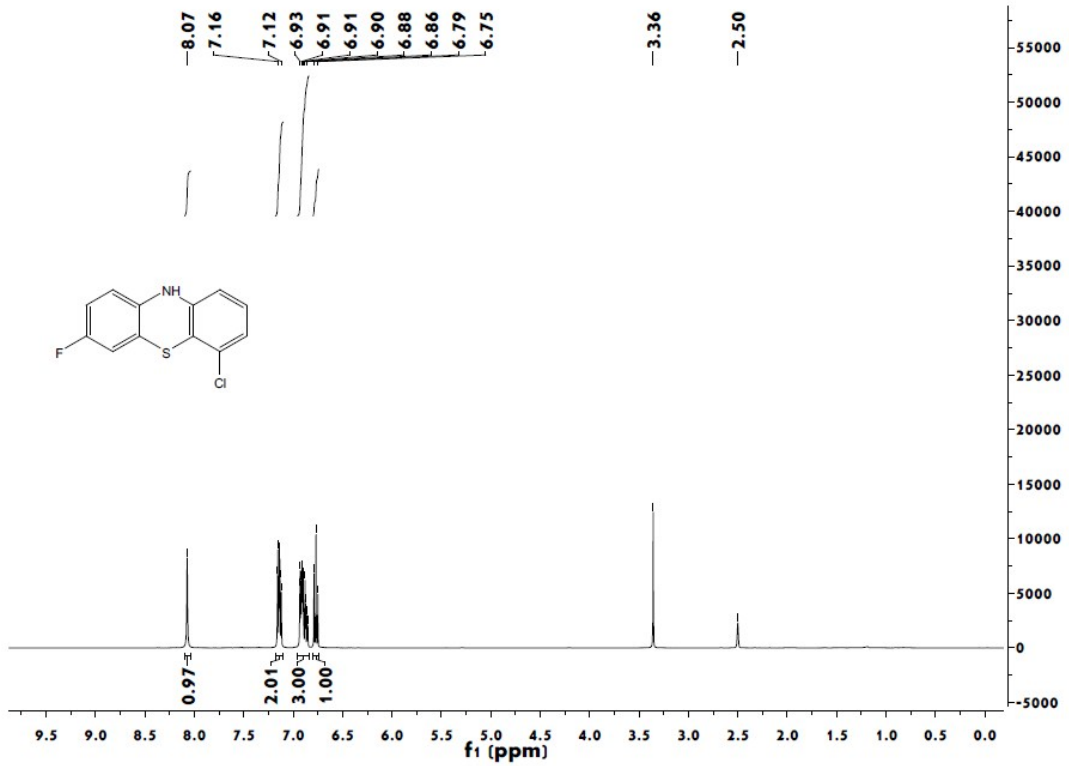
Br
S
Cl
f1 (ppm)
f1 (ppm)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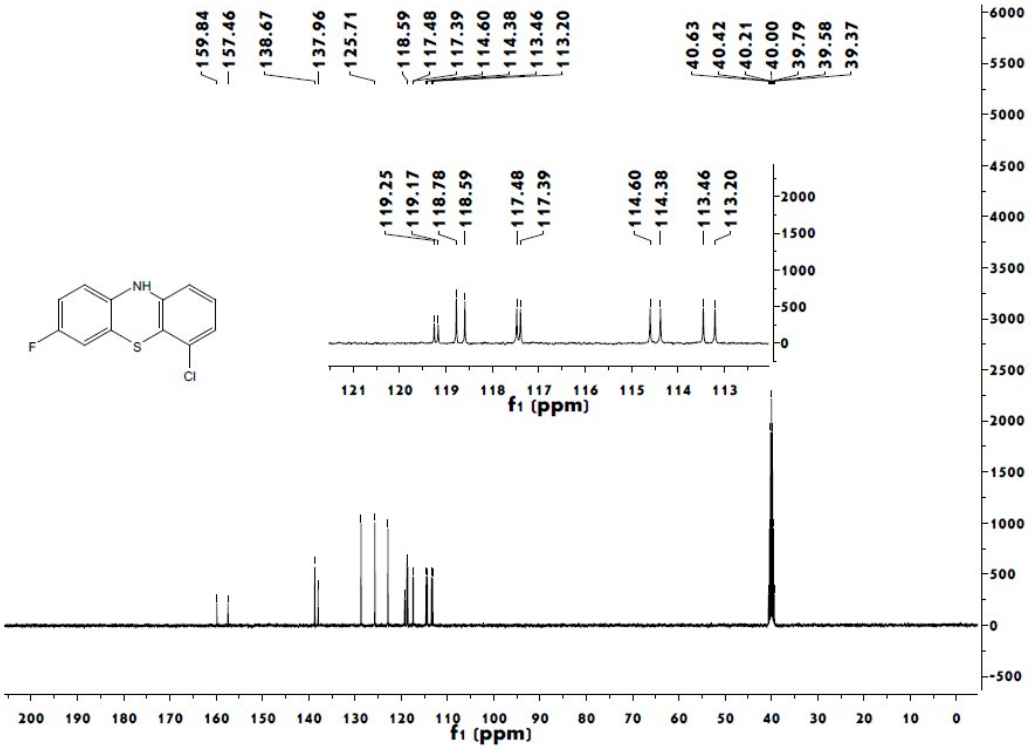
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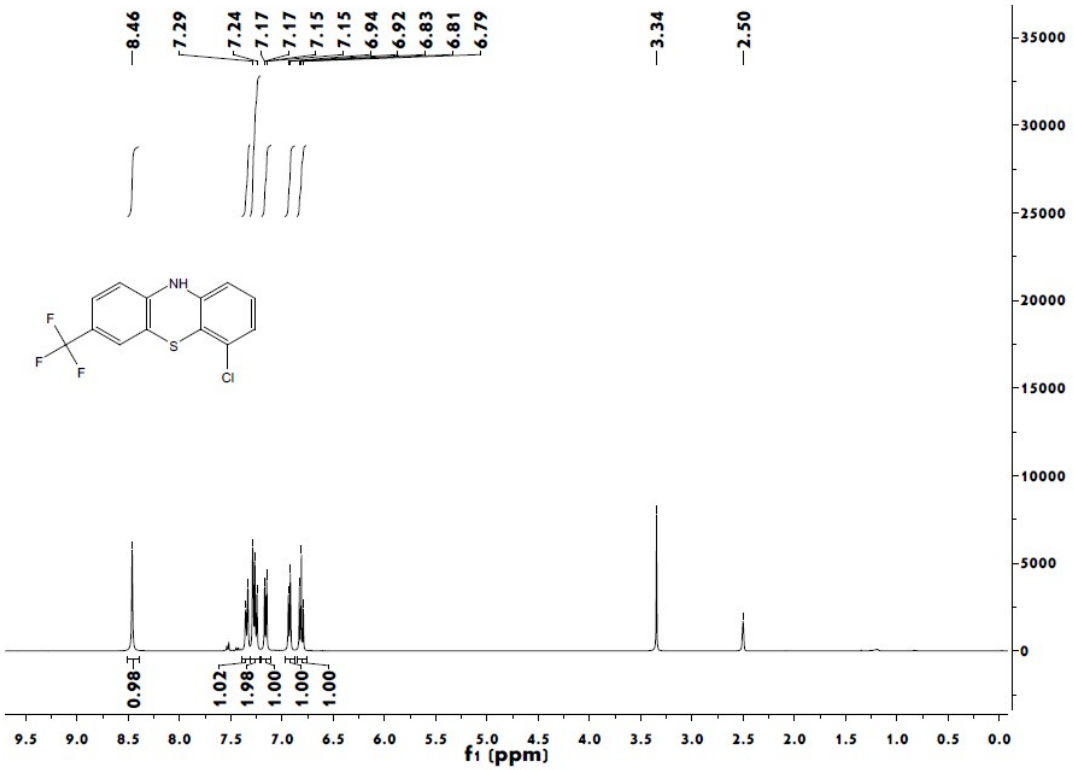
F
S
Cl
f1 (ppm)
f1 (ppm)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F
F
F
Cl
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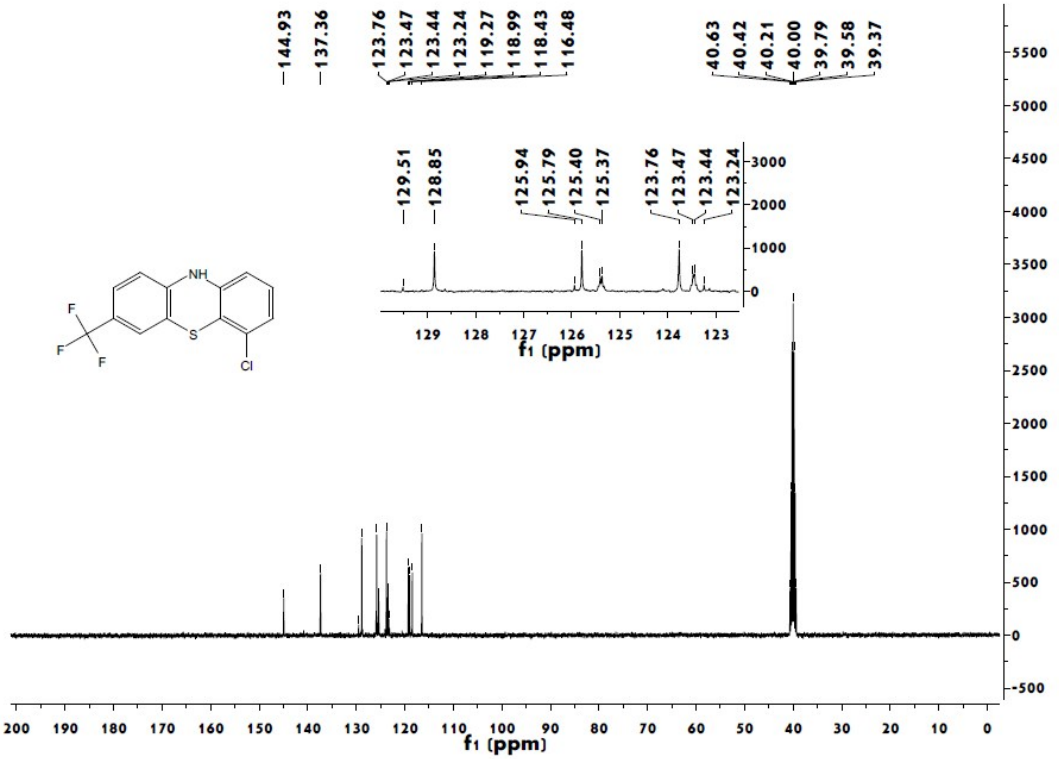
1.00
f1 (ppm)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S
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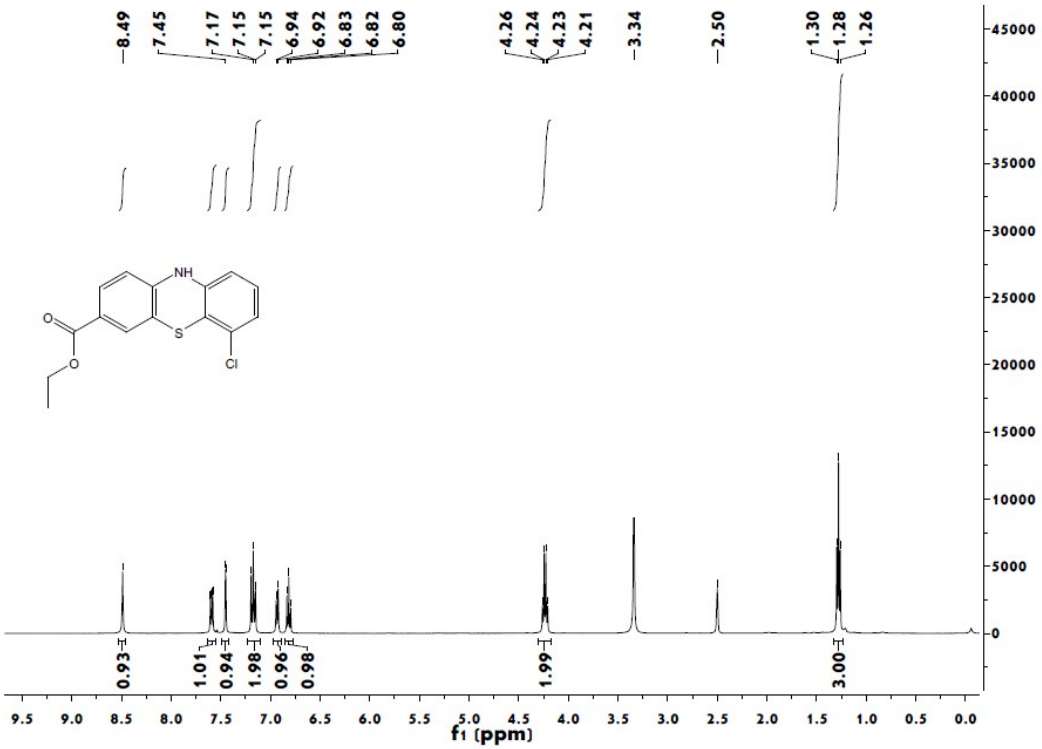
F
Cl
f1 (ppm)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3.34
2.50
1.30
1.28
1.26
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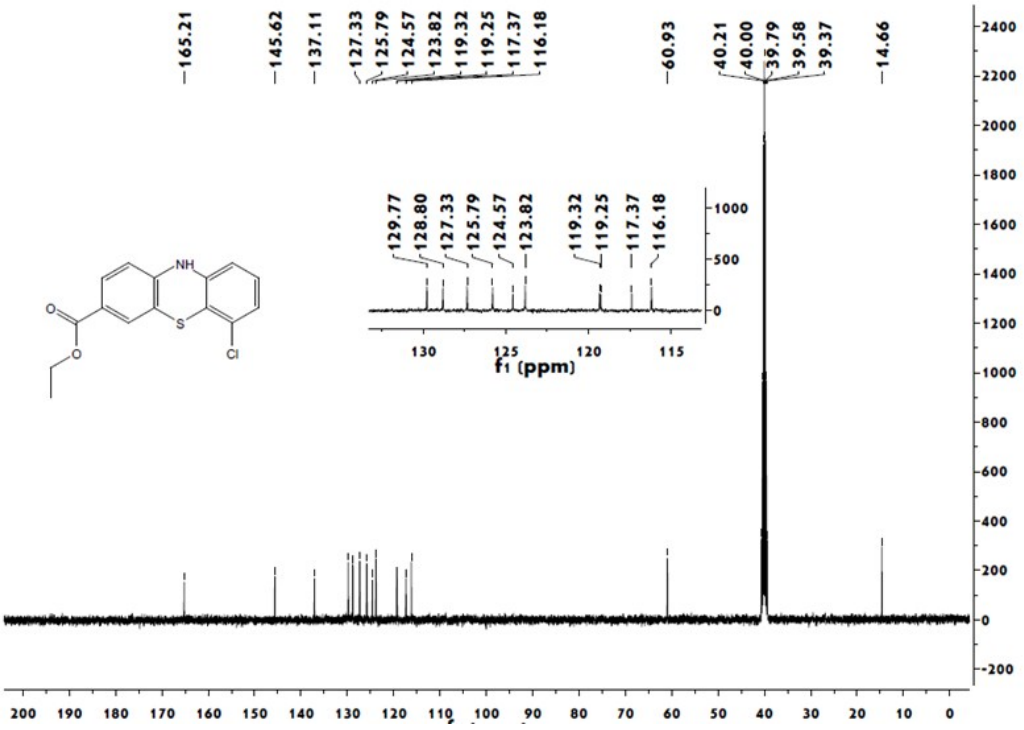
3.00
f1 (ppm)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128.80
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NH
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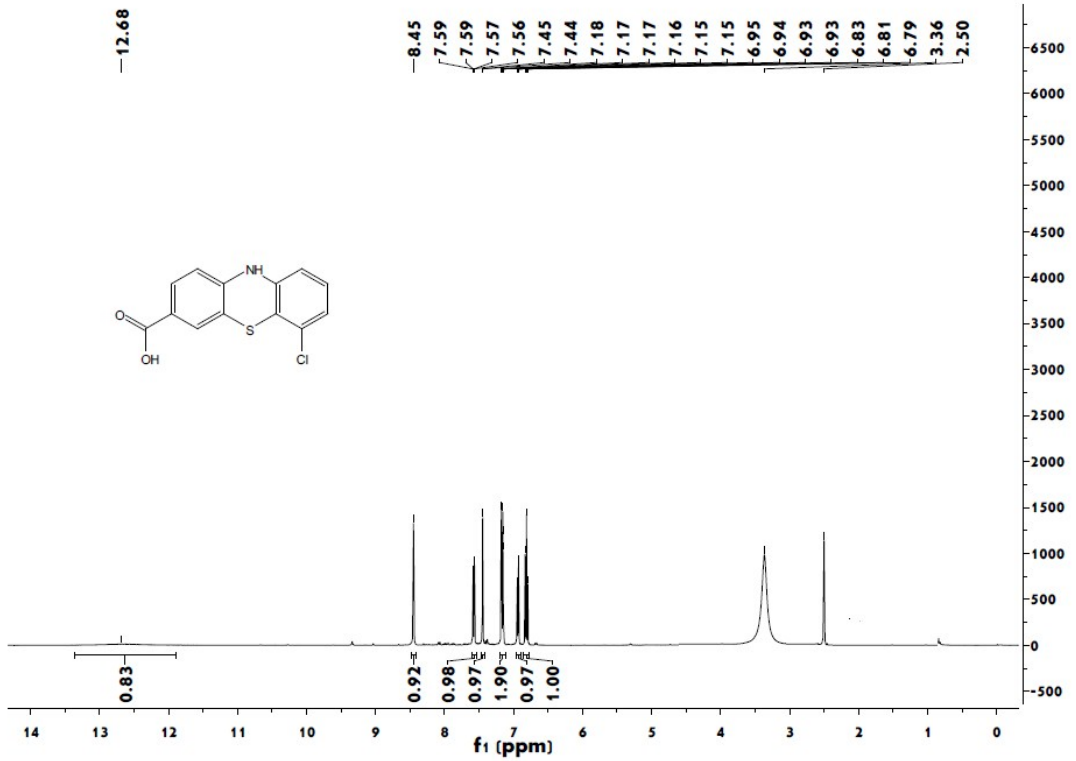
O
O
Cl
f1 (ppm)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7.15
6.95
6.94
6.93
6.93
6.83
6.81
6.79
3.36
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S
Cl
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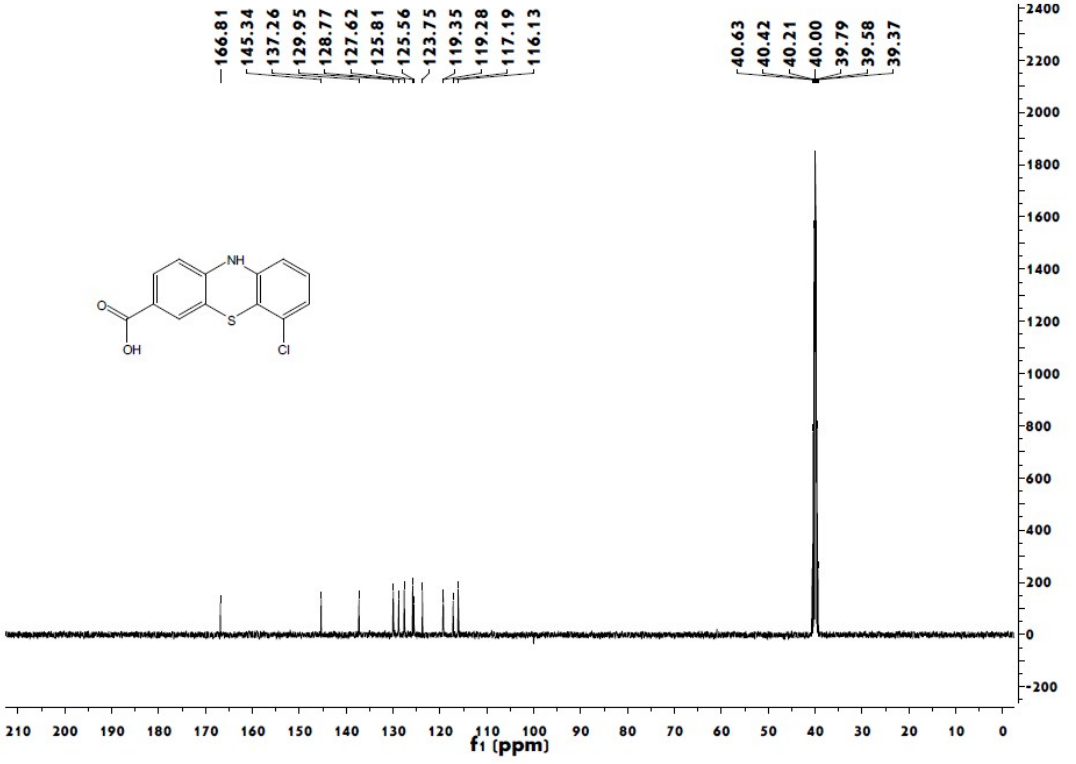
1.00
f1 (ppm)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NH
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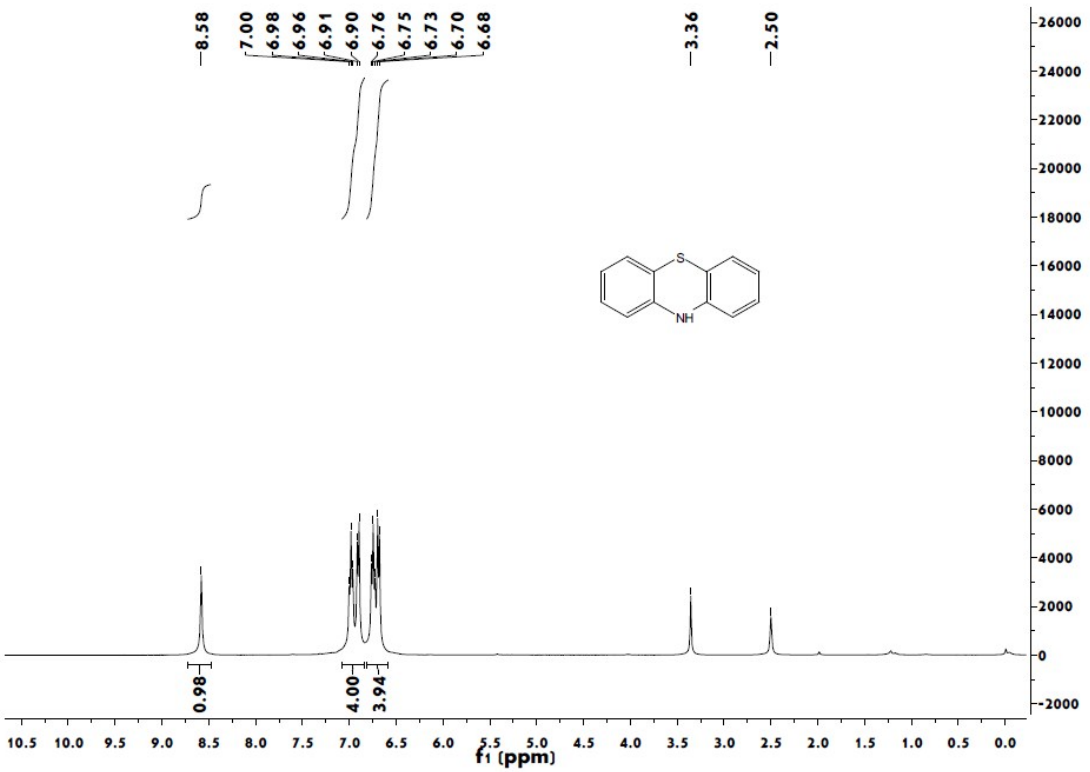
OH
S
Cl
f1 (ppm)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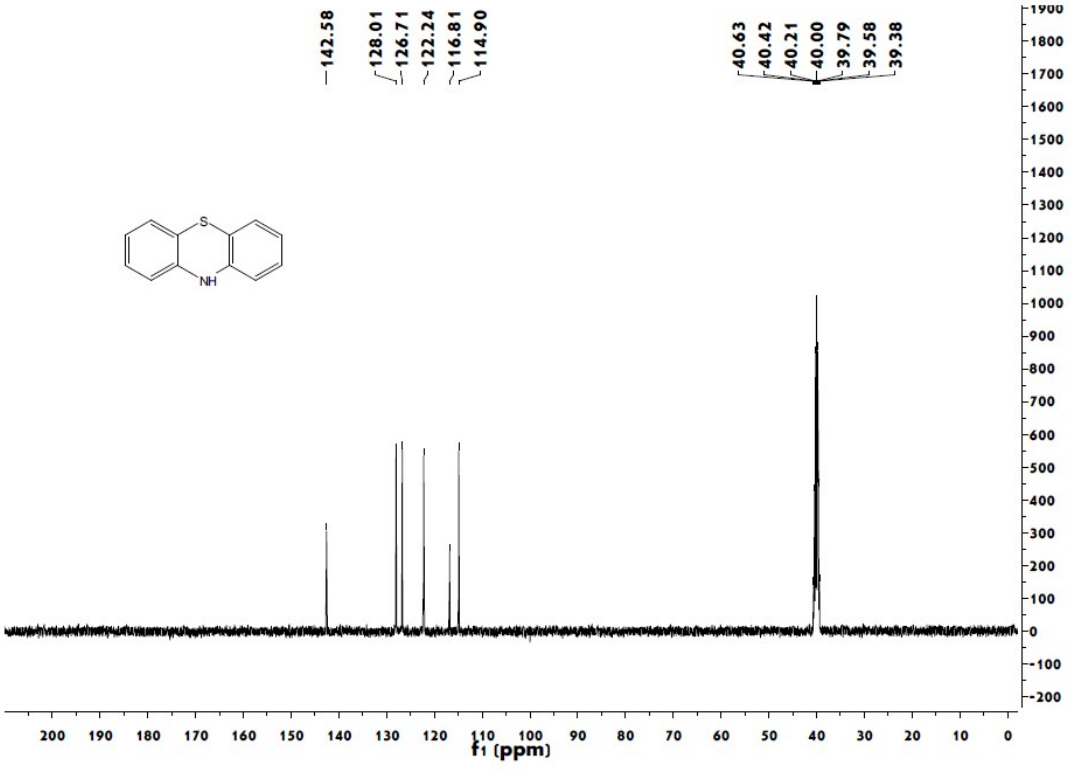
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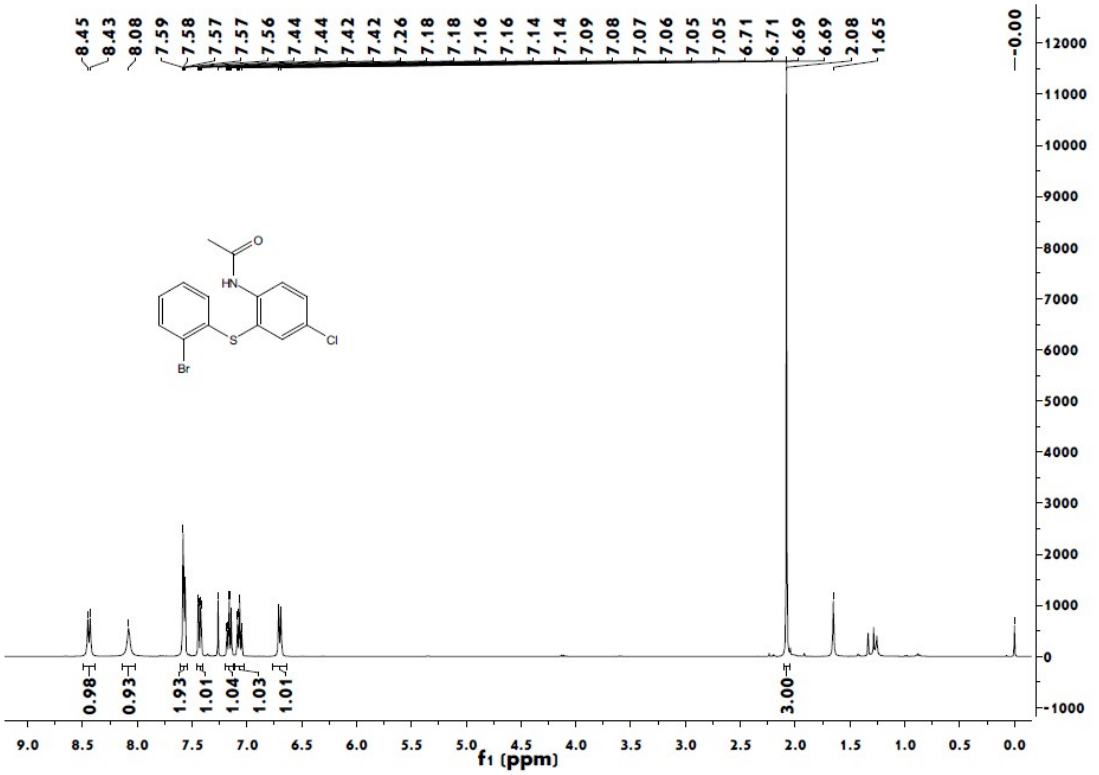
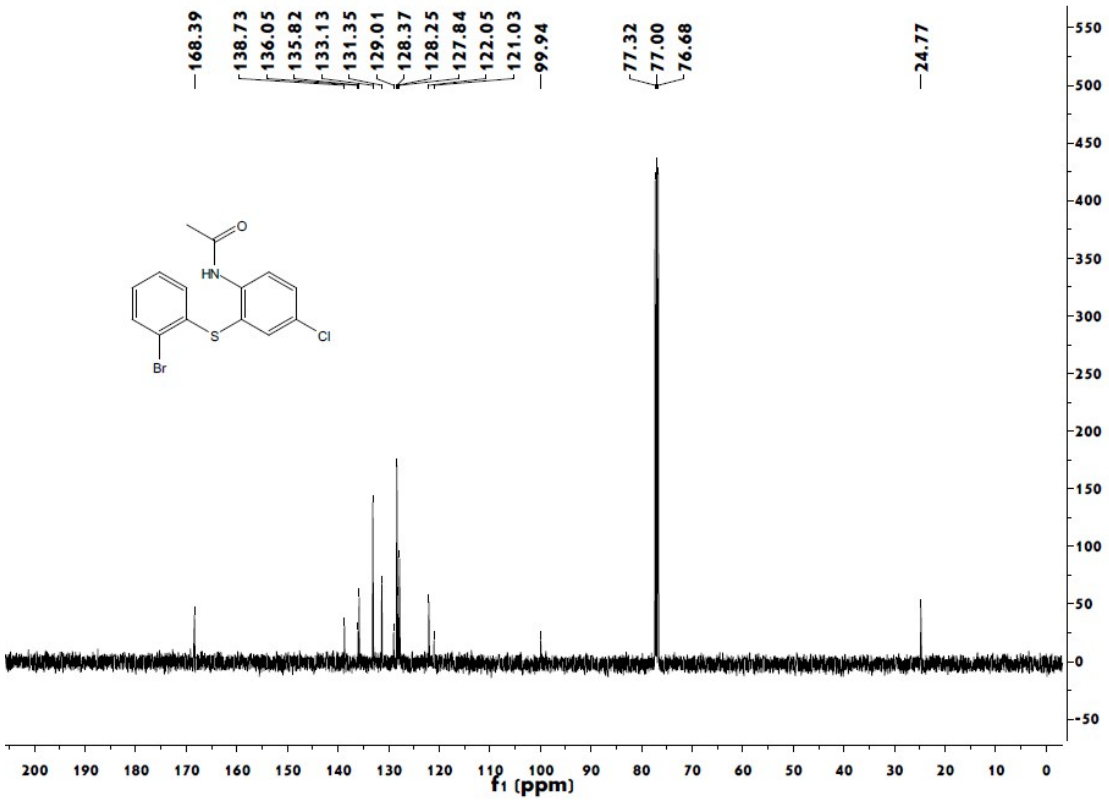
40.42
40.21
40.00
39.79
39.58
39.38
S
NH
f1 (ppm)


8.45
8.43
8.08
7.59
7.58
7.57
7.57
7.56
7.44
7.44
7.42
7.42
7.26
7.18
7.18
7.16
7.16
7.14
7.14
7.09
7.08
7.07
7.06
7.05
7.05
6.71
6.71
6.69
6.69
2.08
1.65
0.00
0.98
0.93
1.93
1.01
1.04
1.03
1.01
3.00
f1 (ppm)


168.39
138.73
136.05
135.82
133.13
131.35
129.01
128.37
128.25
127.84
122.05
121.03
99.94
77.32
77.00
76.68
24.77
f1 (ppm)