# Sustainable access to benzothiophene derivatives bearing trifluoromethyl group via three-component domino reaction in water

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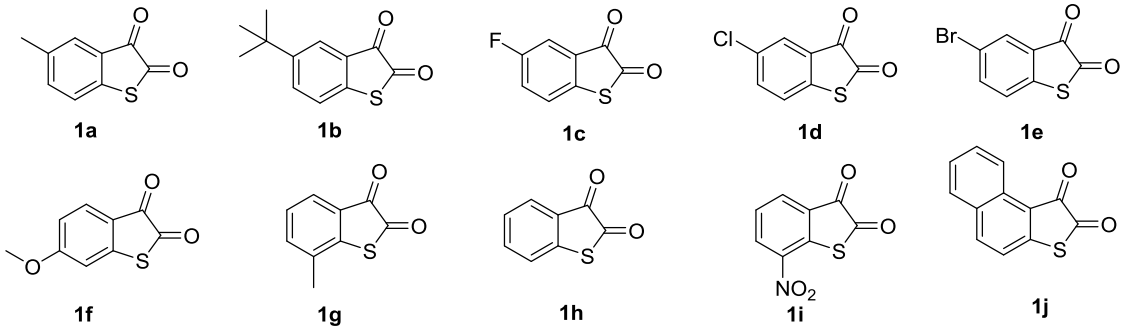
## 1. General information and materials

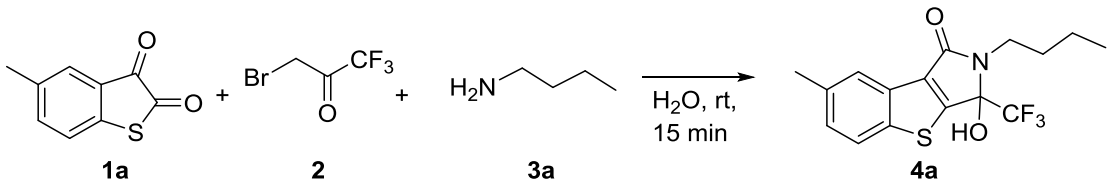
All reactions were performed under Ar atmospheres in oven-dried glassware with magnetic stirring. The heating source is oil bath. Unless otherwise stated, all reagents were purchased from commercial suppliers (Aldrich, TCI or Alfa Aesar) and used without further purification. All solvents were purified and dried according to standard methods prior to use. TLC monitored all reactions with silica gel-coated plates. Flash column chromatography was performed using 200-300 mesh silica gel. $^{1}$H- and $^{13}$C NMR spectra were recorded at ambient temperature on Bruker 400 or 600 instruments. All spectra were referenced to $CDCl_3$ ($^{1}$H δ 7.26 ppm and $^{13}$C NMR δ 77.00 ppm). $^{19}$F NMR spectrum was recorded on Bruker 400 (376 MHz) spectrometers with $CFCl_3$ as external standard. HRMS were obtained on Waters Xevo Q-TOF MS with ESI resource. Melting points were measured on a RY-I apparatus and are reported uncorrected. IR were measured on a Perkin-Elmer 983G apparatus. Compound **1a-1j** was synthesized according to the reported method[1].

## 2. The structure of thioisatin 1




## 3. General procedure for the synthesis of 4

**4a** as an example



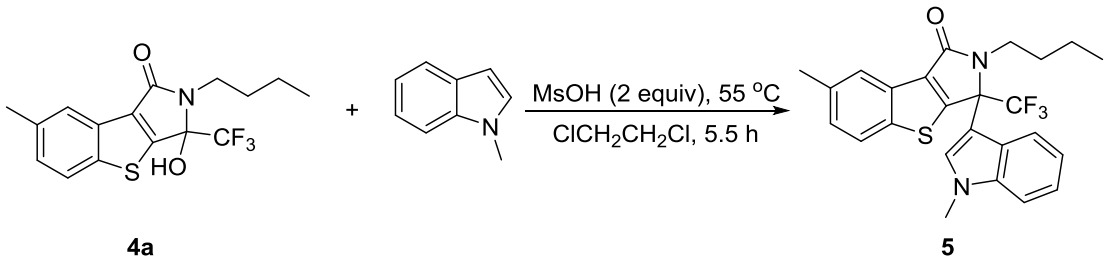

To a solution of **1a** (134 mg, 0.75 mmol) in water 5 mL was added **2** (286 mg, 1.5 mmol), and **3a** (165 mg, 2.25 mmol). The reaction mixture was stirred at room temperature for 15 min. The reaction mixture was extracted with DCM (15 mL×4). The combined organic layers were dried over $MgSO_4$ and concentrated. The reside was purified by column chromatography (ethyl acetate: petroleum ether = 1:5) to give **4a** (186 mg, 72%) as a white solid.

## 4. Procedure for gram-scale reaction of 4a

To a solution of **1a** (1 g, 5.615 mmol) in water 37 mL was added **2** (2.14 g, 11.22 mmol), and **3a** (1.23 mg, 16.83 mmol). The reaction mixture was stirred at room temperature for 15 min. The reaction mixture was extracted with DCM (15 mL×4). The combined organic layers were dried over $MgSO_4$ and

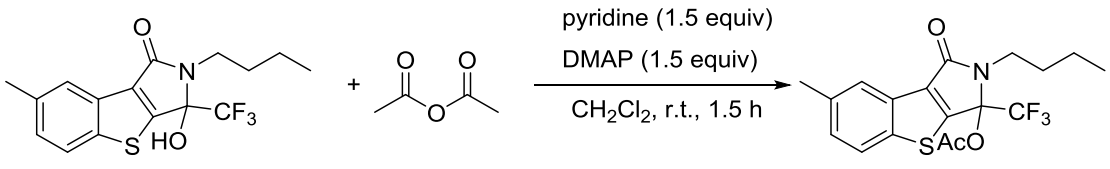
concentrated. The reside was purified by column chromatography (ethyl acetate: petroleum ether = 1:5) to give **4a** (1.02 g, 53%) as a white solid.

## 5. Synthetic procedure for 5, 6 and 7



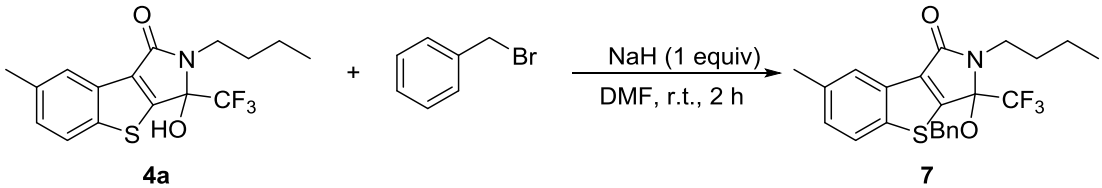

**4a** **5**

To a DCE (5 mL) solution of **4a** (258 mg, 0.75 mmol) was added MsOH (144 mg, 1.5 mmol), *N*-methylindole (98 mg, 0.75 mmol) The resulting mixture was stirred at 55 ℃ for 5.5 h. After the reaction completed (monitored by TLC). The crude product was purified by column chromatography (ethyl acetate: petroleum ether = 1:5) to give **5** (254 mg, 74%) as a white solid.




**4a** **6**

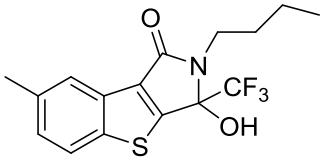
To a DCE (5 mL) solution of **4a** (258 mg, 0.75 mmol) was added pyridine (89 mg, 1.13 mmol), DMAP (9.2 mg, 0.075 mmol), acetic anhydride (115 mg, 1.13 mmol), The resulting mixture was stirred at room temperature for 1.5 h. After the reaction completed (monitored by TLC). The crude product was purified by column chromatography (ethyl acetate: petroleum ether = 1:5) to give **6** (215 mg, 74%) as a yellow oil.




**4a** **7**

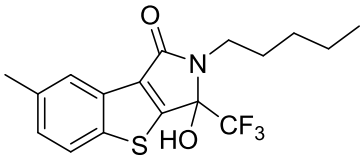
To a dry DMF (5 mL) solution of **4a** (258 mg, 0.75 mmol) was added NaH (18 mg, 0.75 mmol), benzyl bromide (141 mg, 0.825 mmol) The resulting mixture was stirred at room temperature for 2 h. After the reaction completed (monitored by TLC). The crude product was purified by column chromatography (ethyl acetate: petroleum ether = 1:5) to give **7** (294 mg, 90%) as a white solid.

## 6. Characterization of all new compounds



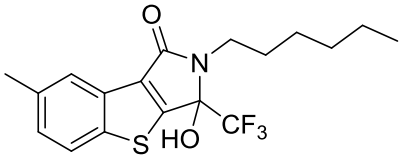
**2-butyl-3-hydroxy-7-methyl-3-(trifluoromethyl)-2,3-dihydro-1*H*-benzo[4,5]thieno[2,3-*c*]pyrrol-1-one (4a)**

Purified by chromatography on silica gel, eluting with petroleum ether/ethyl acetate 5:1 (v/v). White solid: 186 mg (yield 72%); mp 150-152 °C; IR (KBr) 3226, 2963, 2859, 1670, 1467, 1371, 1253, 1183, 1126, 809, 729, 671 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.54 (d, *J* = 8.4 Hz, 1H), 7.13 (dd, *J* = 8.4, 1.2 Hz, 1H), 5.39 (s, 1H), 3.20 (ddd, *J* = 15.4, 10.8, 4.9 Hz, 1H), 3.05 (td, *J* = 14.6, 12.5, 8.3 Hz, 1H), 2.44 (s, 3H), 1.66 – 1.55 (m, 1H), 1.49 – 1.38 (m, 1H), 1.26 – 1.14 (m, 2H), 0.86 (t, *J* = 7.4 Hz, 3H) ppm. $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ 165.9, 151.3, 142.4, 136.2, 134.3, 130.7, 128.3, 123.0, 122.7, 122.2 (q, *J* = 316.0 Hz), 87.2 (q, *J* = 34.7 Hz), 40.1, 30.4, 21.5, 20.3, 13.7 ppm. $^{19}F$ NMR (376 MHz, $CDCl_3$) δ -79.34 ppm. HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{17}F_3NO_2S^+$ 344.0927, found 344.0935.



**3-hydroxy-7-methyl-2-pentyl-3-(trifluoromethyl)-2,3-dihydro-1*H*-benzo[4,5]thieno[2,3-*c*]pyrrol-1-one (4b)**

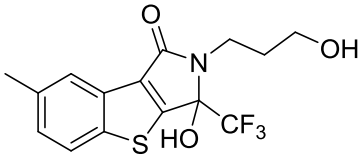
Purified by chromatography on silica gel, eluting with petroleum ether/ethyl acetate 5:1 (v/v). White solid: 184 mg (yield 69%); mp 132-134 °C; IR (KBr) 3123, 2959, 2928, 2870, 1675, 1469, 1379, 1318, 1269, 1188, 1127, 868, 799, 642 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.54 (d, *J* = 8.4 Hz, 1H), 7.17 – 7.07 (m, 1H), 5.73 (d, *J* = 5.4 Hz, 1H), 3.17 (ddd, *J* = 15.5, 11.0, 4.9 Hz, 1H), 2.99 (ddd, *J* = 14.5, 10.8, 5.9 Hz, 1H), 2.43 (s, 3H), 1.60 (ddt, *J* = 16.9, 12.7, 6.3 Hz, 1H), 1.44 (tq, *J* = 12.5, 7.6 Hz, 1H), 1.27 – 1.06 (m, 4H), 0.86 (t, *J* = 7.2 Hz, 3H) ppm. $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ 165.8, 151.4, 142.3, 136.1, 134.1, 130.5, 128.1, 122.8, 122.6, 122.1 (q, *J* = 283.6 Hz), 87.1 (q, J = 34.5 Hz), 40.2, 29.0, 27.8, 22.1, 21.4, 14.0 ppm. $^{19}F$ NMR (376 MHz, $CDCl_3$) δ -79.31 ppm. HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{19}F_3NO_2S^+$ 358.1083, found 358.1093.



**2-hexyl-3-hydroxy-7-methyl-3-(trifluoromethyl)-2,3-dihydro-1*H*-benzo[4,5]thieno[2,3-*c*]pyrrol-1-one (4c)**

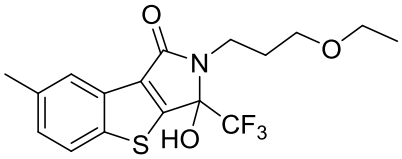
Purified by chromatography on silica gel, eluting with petroleum ether/ethyl acetate 5:1 (v/v). White solid: 142 mg (yield 51%); mp 159-161 °C; IR (KBr) 3115, 2936, 2858, 1670,1539, 1468, 1373, 1320, 1190, 1176, 1128, 879, 799, 729 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 4.4 Hz, 1H), 7.56 (dd, *J* = 8.0, 2.4 Hz, 1H), 7.14 (d, *J* = 8.4 Hz, 1H), 5.70 – 5.49 (m, 1H), 3.18 (tt, *J* = 10.8, 4.9 Hz, 1H), 3.01 (dt, *J* = 13.9, 7.4 Hz, 1H), 2.44 (s, 3H), 1.74 – 1.68 (m, 1H), 1.60 (dq, *J* = 10.1, 6.7, 6.1 Hz, 1H), 1.52 – 1.38 (m, 1H), 1.31 – 1.09 (m, 6H), 0.87 (t, *J* = 7.1 Hz, 3H) ppm. $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ 165.7, 151.2, 142.3, 136.1, 134.3, 130.6, 128.1, 122.9, 122.63 (q, *J* = 308.3

Hz), 122.57, 87.2 (q, $J$ = 43.7 Hz), 40.3, 31.2, 28.1, 26.6, 22.5, 21.4, 14.0 ppm. $^{19}$F NMR (376 MHz, $CDCl_3$) δ -79.35 ppm. HRMS (ESI-TOF) $m/z$ $[M + H]^+$ calcd for $C_{18}H_{21}F_3NO_2S^+$ 372.1240, found 372.1244.



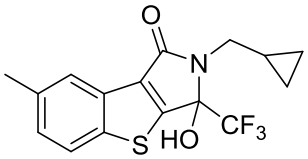

**3-hydroxy-2-(3-hydroxypropyl)-7-methyl-3-(trifluoromethyl)-2,3-dihydro-1*H*-benzo[4,5]thieno[2,3-*c*]pyrrol-1-one (4d)**

Purified by chromatography on silica gel, eluting with petroleum ether/ethyl acetate 1:1 (v/v). White solid: 152 mg (yield 59%); mp 138-140 °C; IR (KBr) 3361, 3055, 2945, 2884, 1695, 1471, 1375, 1348, 1315, 1272, 1183, 1056, 970, 812, 729 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.65 (d, $J$ = 8.4 Hz, 1H), 7.43 (s, 1H), 7.26 – 7.21 (m, 1H), 4.37 (s, 1H), 3.80 – 3.46 (m, 4H), 2.46 (s, 3H), 1.87 (ddq, $J$ = 14.2, 9.3, 4.9 Hz, 1H), 1.79 – 1.64 (m, 1H) ppm. $^{13}$C{H} NMR (100 MHz, $CDCl_3$) δ 166.2, 152.3, 142.3, 136.3, 133.8, 130.7, 128.1, 122.9, 122.9, 122.1 (q, $J$ = 303.4 Hz), 87.5 (q, $J$ = 34.0 Hz), 60.2, 37.2, 30.6, 21.4 ppm. $^{19}$F NMR (376 MHz, $CDCl_3$) δ -79.67 ppm. HRMS (ESI-TOF) $m/z$ $[M + H]^+$ calcd for $C_{15}H_{15}F_3NO_3S^+$ 346.0719, found 346.0726.




**2-(3-ethoxypropyl)-3-hydroxy-7-methyl-3-(trifluoromethyl)-2,3-dihydro-1*H*-benzo[4,5]thieno[2,3-*c*]pyrrol-1-one (4e)**

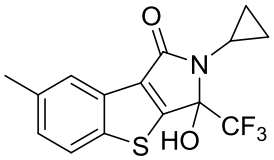
Purified by chromatography on silica gel, eluting with petroleum ether/ethyl acetate 5:1 (v/v). White solid: 148 mg (yield 53%); mp 126-128 °C; IR (KBr) 3078, 2978, 2935, 2874, 2800, 1667, 1535, 1470, 1419, 1344, 1279, 1190, 1119, 1049, 974, 867, 799 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.76 (d, $J$ = 8.4 Hz, 1H), 7.28 (dd, $J$ = 8.4, 1.2 Hz, 1H), 7.08 (s, 1H), 4.20 (ddt, $J$ = 14.8, 8.1, 4.8 Hz, 1H), 3.70 – 3.56 (m, 2H), 3.47 (dt, $J$ = 14.9, 5.2 Hz, 1H), 3.42 – 3.22 (m, 2H), 2.21 – 2.03 (m, 2H), 0.81 (t, $J$ = 7.0 Hz, 3H) ppm. $^{13}$C{H} NMR (100 MHz, $CDCl_3$) δ 164.8, 152.6, 142.4, 136.1, 134.3, 131.2, 128.0, 123.3, 123.0, 122.9 (q, J = 270.8 Hz), 87.9 (q, $J$ = 34.2 Hz), 69.6, 66.6, 38.4, 27.5, 21.4, 14.3 ppm. $^{19}$F NMR (376 MHz, $CDCl_3$) δ -78.05. HRMS (ESI-TOF) $m/z$ $[M + H]^+$ calcd for $C_{17}H_{19}F_3NO_3S^+$ 374.1032, found 374.1038.




**2-(cyclopropylmethyl)-3-hydroxy-7-methyl-3-(trifluoromethyl)-2,3-dihydro-1*H*-benzo[4,5]thieno[2,3-*c*]pyrrol-1-one (4f)**

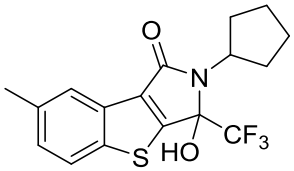
Purified by chromatography on silica gel, eluting with petroleum ether/ethyl acetate 5:1 (v/v). White solid: 181 mg (yield 71%); mp 122-124 °C; IR (KBr) 3166, 2926, 1667, 1538, 1471, 1383, 1328, 1268, 1186, 1128, 1044, 876, 799, 729 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.57 (d, $J$ = 8.4 Hz, 1H), 7.15 (dd, $J$ = 8.4, 1.2 Hz, 1H), 5.58 (s, 1H), 3.50 (dd, $J$ = 14.8, 5.6 Hz, 1H), 2.75 (dd, $J$ = 14.8, 8.8 Hz, 1H), 2.45 (s, 3H), 1.02-1.12 (m, 1H), 0.45 (t, $J$ = 9.3 Hz, 2H), 0.41 – 0.33 (m, 1H), 0.20 – 0.09 (m, 1H) ppm. $^{13}$C{H} NMR (100 MHz, $CDCl_3$) δ 165.7, 151.2, 142.3, 136.1, 134.2,

130.6, 128.1, 122.9, 122.5, 122.2 (q, $J$ = 284.2 Hz), 87.2 (q, $J$ = 34.6 Hz), 44.8, 21.3, 10.3, 4.5, 3.8 ppm. $^{19}$F NMR (376 MHz, $CDCl_3$) δ -79.09 ppm. HRMS (ESI-TOF) $m/z$ $[M + H]^+$ calcd for $C_{16}H_{15}F_3NO_2S^+$ 342.0770, found 342.0776.



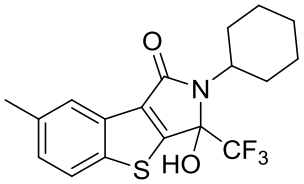
**2-cyclopropyl-3-hydroxy-7-methyl-3-(trifluoromethyl)-2,3-dihydro-1*H*-benzo[4,5]thieno[2,3-*c*]pyrrol-1-one (4g)**

Purified by chromatography on silica gel, eluting with petroleum ether/ethyl acetate 5:1 (v/v). White solid: 171 mg (yield 70%); mp 202-204 °C; IR (KBr) 3210, 3023, 1675, 1537, 1408, 1369, 1254, 1204, 1138, 1101, 1035, 968, 888, 836, 809 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.63 (s, 1H), 8.08 (d, $J$ = 8.4 Hz, 1H), 7.90 (s, 1H), 7.39 (d, $J$ = 8.4 Hz, 1H), 2.53 (dd, $J$ = 7.0, 3.6 Hz, 1H), 2.47 (s, 3H), 1.38 – 1.25 (m, 1H), 0.90 (dtd, $J$ = 9.3, 7.1, 4.9 Hz, 1H), 0.82 – 0.67 (m, 2H) ppm. $^{13}$C{H} NMR (100 MHz, DMSO) δ 164.6, 152.4, 142.2, 136.4, 134.3, 131.1, 128.6, 124.4, 123.2 (q, $J$ = 285.5 Hz), 122.6, 88.5 (q, $J$ = 34.4 Hz), 22.9, 21.4, 6.6, 4.3. $^{19}$F NMR (376 MHz, DMSO) δ -78.10 ppm. HRMS (ESI-TOF) $m/z$ $[M + H]^+$ calcd for $C_{15}H_{13}F_3NO_2S^+$ 328.0614, found 328.0620.



**2-cyclopentyl-3-hydroxy-7-methyl-3-(trifluoromethyl)-2,3-dihydro-1*H*-benzo[4,5]thieno[2,3-*c*]pyrrol-1-one (4h)**

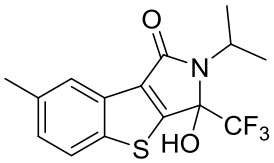
Purified by chromatography on silica gel, eluting with petroleum ether/ethyl acetate 5:1 (v/v). White solid: 133 mg (yield 50%); mp 179-181 °C; IR (KBr) 3077, 2959, 2870, 1675, 1538, 1470, 1373, 1265, 1109, 970, 887, 729 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.87 (s, 1H), 8.07 (d, $J$ = 8.4 Hz, 1H), 7.91 (s, 1H), 7.38 (dd, $J$ = 8.4, 0.8 Hz, 1H), 4.00 (p, $J$ = 8.4 Hz, 1H), 2.47 (s, 3H), 1.90 – 1.74 (m, 4H), 1.62 – 1.48 (m, 2H) ppm. $^{13}$C{H} NMR (100 MHz, $CDCl_3$) δ 168.1, 155.9, 147.0, 141.2, 140.3, 135.8, 133.4, 129.2, 128.1 (q, $J$ = 284.9 Hz), 127.4, 91.7 (q, $J$ = 32.6 Hz), 58.4, 34.3, 34.1, 29.87, 29.7, 26.2 ppm. $^{19}$F NMR (376 MHz, DMSO) δ -79.45 ppm. HRMS (ESI-TOF) $m/z$ $[M + H]^+$ calcd for $C_{17}H_{17}F_3NO_2S^+$ 356.0927, found 356.0934.



**2-cyclohexyl-3-hydroxy-7-methyl-3-(trifluoromethyl)-2,3-dihydro-1*H*-benzo[4,5]thieno[2,3-*c*]pyrrol-1-one (4i)**

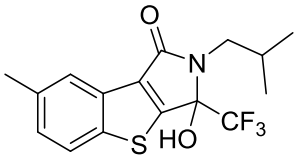
Purified by chromatography on silica gel, eluting with petroleum ether/ethyl acetate 5:1 (v/v). White solid: 124 mg (yield 72%); mp 165-167 °C; IR (KBr) 3434, 2933, 2858, 1671, 1462, 1370, 1263, 1190, 798, 651 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.64 (d, $J$ = 8.4 Hz, 1H), 7.23 (d, $J$ = 8.4 Hz, 1H), 4.96 (s, 1H), 3.63 – 3.38 (m, 1H), 2.47 (s, 3H), 2.33 – 2.12 (m, 2H), 1.69 (td, $J$ = 31.8, 30.3, 10.1 Hz, 5H), 1.31 – 1.03 (m, 3H) ppm. $^{13}$C{H} NMR (100 MHz, $CDCl_3$) δ 164.6, 149.6,

142.4, 136.4, 136.1, 131.3, 128.3, 123.5, 122.9, 122.4 (q, $J$ = 296.6 Hz), 87.2 (q, $J$ = 33.9 Hz), 54.3, 30.7, 29.7, 26.5, 26.5, 25.2, 21.5 ppm. $^{19}$F NMR (376 MHz, $CDCl_3$) δ -79.37 ppm. HRMS (ESI-TOF) $m/z$ $[M + H]^+$ calcd for $C_{18}H_{19}F_3NO_2S^+$ 370.1083, found 370.1091.



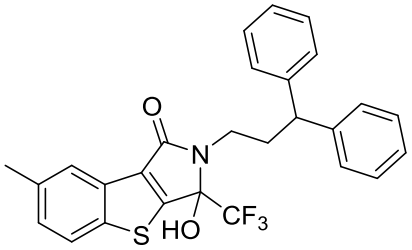

**3-hydroxy-2-isopropyl-7-methyl-3-(trifluoromethyl)-2,3-dihydro-1*H*-benzo[4,5]thieno[2,3-*c*]pyrrol-1-one (4j)**

Purified by chromatography on silica gel, eluting with petroleum ether/ethyl acetate 5:1 (v/v). White solid: 170 mg (yield 69%); mp 142-144 °C; IR (KBr) 3210, 2997, 2974, 2938, 1686, 1671, 1474, 1384, 1325, 1264, 1203, 1114, 964, 799 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.73 (d, $J$ = 8.4 Hz, 1H), 7.30 (s, 1H), 4.23 (s, 1H), 4.02 (hept, $J$ = 7.3, 6.8 Hz, 1H), 2.51 (s, 3H), 1.52 (t, $J$ = 6.6 Hz, 6H) ppm. $^{13}$C{H} NMR (100 MHz, $CDCl_3$) δ 164.3, 149.3, 142.3, 136.3, 136.3, 131.2, 128.3, 123.5, 122.9, 122.4 (q, $J$ = 284.7 Hz), 86.9 (q, $J$ = 31.5 Hz), 46.0, 21.4, 21.0, 19.9 ppm. $^{19}$F NMR (376 MHz, $CDCl_3$) δ -70.45 ppm. HRMS (ESI-TOF) $m/z$ $[M + H]^+$ calcd for $C_{15}H_{15}F_3NO_2S^+$ 330.0770, found 330.0775.




**3-hydroxy-2-isobutyl-7-methyl-3-(trifluoromethyl)-2,3-dihydro-1*H*-benzo[4,5]thieno[2,3-*c*]pyrrol-1-one (4k)**

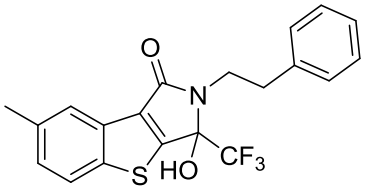
Purified by chromatography on silica gel, eluting with petroleum ether/ethyl acetate 5:1 (v/v). White solid: 157 mg (yield 61%); mp 176-178 °C; IR (KBr) 3240, 2982, 2950, 1679, 1537, 1468, 1384, 1335, 1187, 973, 875, 811, 727 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.57 (d, $J$ = 8.4 Hz, 1H), 7.15 (dd, $J$ = 8.4, 1.2 Hz, 1H), 5.61 (s, 1H), 3.14 (dd, $J$ = 14.2, 6.0 Hz, 1H), 2.84 (dd, $J$ = 14.3, 9.7 Hz, 1H), 2.44 (s, 3H), 2.11 – 1.84 (m, 1H), 0.80 (d, $J$ = 6.4 Hz, 3H), 0.76 (d, $J$ = 6.8 Hz, 3H) ppm. $^{13}$C{H} NMR (100 MHz, $CDCl_3$) δ 166.2, 151.2, 142.3, 136.2, 134.3, 130.7, 128.2, 123.0, 122.7, 122.2 (q, $J$ = 284.6 Hz), 87.4 (q, $J$ = 34.5 Hz), 47.4, 27.6, 21.4, 20.2, 20.2 ppm. $^{19}$F NMR (376 MHz, $CDCl_3$) δ -79.10 ppm. HRMS (ESI-TOF) $m/z$ $[M + H]^+$ calcd for $C_{16}H_{17}F_3NO_2S^+$ 344.0927, found 344.0932.




**2-(3,3-diphenylpropyl)-3-hydroxy-7-methyl-3-(trifluoromethyl)-2,3-dihydro-1*H*-benzo[4,5]thieno[2,3-*c*]pyrrol-1-one (4l)**

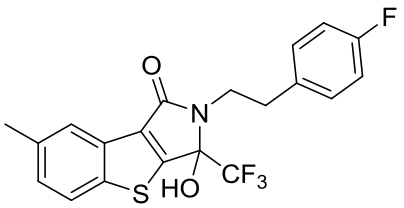
Purified by chromatography on silica gel, eluting with petroleum ether/ethyl acetate 5:1 (v/v). White solid: 216 mg (yield 60%); mp 206-208°C; IR (KBr) 3163, 3956, 1673, 1494, 1465, 1397, 1322, 1164, 963, 747 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.60 (s, 1H), 7.50 (d, $J$ = 8.4 Hz, 1H), 7.35 –

7.28 (m, 4H), 7.27 – 7.15 (m, 6H), 7.10 (d, $J$ = 8.4 Hz, 1H), 5.51 – 5.26 (m, 1H), 3.73 (t, $J$ = 7.3 Hz, 1H), 3.12 – 2.88 (m, 2H), 2.41 (s, 1H), 2.52 – 2.31 (m, 3H) , 2.17 (tt, $J$ = 12.8, 7.2 Hz, 1H) ppm. $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ 165.6, 151.2, 144.0, 143.7, 142.2, 136.1, 134.0, 133.6, 130.4, 128.6, 128.6, 128.2, 127.8, 127.7, 126.4, 122.6, 122.51, 122.5 (q, $J$ = 275.4 Hz), 86.9 (q, $J$ = 34.4 Hz), 49.2, 39.3, 33.6, 21.4 ppm. $^{19}F$ NMR (376 MHz, $CDCl_3$) δ -79.33 ppm. HRMS (ESI-TOF) $m/z$ $[M + H]^+$ calcd for $C_{27}H_{22}F_3NO_2S^+$ 482.1396, found 482.1403.



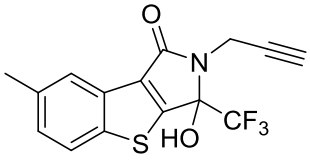

**3-hydroxy-7-methyl-2-phenethyl-3-(trifluoromethyl)-2,3-dihydro-1*H*-benzo[4,5]thieno[2,3-*c*]pyrrol-1-one (4m)**

Purified by chromatography on silica gel, eluting with petroleum ether/ethyl acetate 5:1 (v/v). White solid: 190 mg (yield 65%); mp 145-147 °C; IR (KBr) 3146, 3025, 1667, 1538, 1469, 1294, 1190, 1128, 999, 881, 729, 699 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.50 (d, $J$ = 8.4 Hz, 1H), 7.26 – 7.18 (m, 3H), 7.11 – 7.06 (m, 1H), 7.06 – 6.98 (m, 2H), 5.18 (s, 1H), 3.38 (ddd, $J$ = 14.5, 11.3, 4.8 Hz, 1H), 3.18 – 3.04 (m, 1H), 2.93 (td, $J$ = 12.1, 11.4, 6.0 Hz, 1H), 2.76 – 2.65 (m, 1H), 2.40 (s, 3H) ppm. $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ 165.6, 151.4, 142.3, 138.5, 136.3, 134.1, 130.6, 128.6, 128.6, 128.3, 126.5, 122.9, 122.7, 122.2 (q, $J$ = 279.4 Hz), 87.0 (q, $J$ = 34.5 Hz), 41.9, 34.4, 21.4 ppm. $^{19}F$ NMR (376 MHz, $CDCl_3$) δ -79.31 ppm. HRMS (ESI-TOF) $m/z$ $[M + H]^+$ calcd for $C_{20}H_{17}F_3NO_2S^+$ 392.0927, found 392.0934.



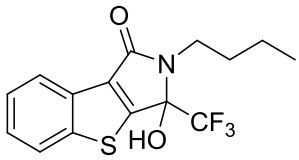

**2-(4-fluorophenethyl)-3-hydroxy-7-methyl-3-(trifluoromethyl)-2,3-dihydro-1*H*-benzo[4,5]thieno[2,3-*c*]pyrrol-1-one (4n)**

Purified by chromatography on silica gel, eluting with petroleum ether/ethyl acetate 3:1 (v/v). White solid: 193 mg (yield 63%); mp 164-166 °C; IR (KBr) 3220, 2963, 1680, 1509, 1398, 1364, 1297, 1194, 1121, 802, 728 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.52 (d, $J$ = 8.4 Hz, 1H), 7.16 – 7.06 (m, 1H), 7.02 – 6.87 (m, 4H), 5.83 (d, $J$ = 2.7 Hz, 1H), 3.25 (ddd, $J$ = 14.3, 11.9, 5.0 Hz, 1H), 2.98 (td, $J$ = 14.2, 12.9, 5.5 Hz, 1H), 2.84 (td, $J$ = 12.3, 5.5 Hz, 1H), 2.65 (td, $J$ = 12.3, 5.0 Hz, 1H), 2.40 (s, 3H) ppm. $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ 165.7, 161.6 (d, $J$ = 242.9 Hz), 151.5, 142.2, 136.3, 134.0, 133.9 (d, $J$ = 3.1 Hz), 130.5, 130.0 (d, $J$ = 7.8 Hz), 128.3, 122.8, 122.7, 122.2 (q, $J$ = 34.5 Hz), 115.3 (d, $J$ = 21 Hz), 87.0 (q, $J$ = 34.6 Hz) 41.8, 33.6, 21.3 ppm. $^{19}F$ NMR (376 MHz, $CDCl_3$) δ -79.40, -116.63 ppm. HRMS (ESI-TOF) $m/z$ $[M + H]^+$ calcd for $C_{20}H_{16}F_4NO_2S^+$ 410.0832, found 410.0837.



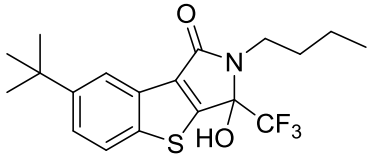
**3-hydroxy-7-methyl-2-(prop-2-yn-1-yl)-3-(trifluoromethyl)-2,3-dihydro-1*H*-benzo[4,5]thieno[2,3-*c*]pyrrol-1-one (4o)**

Purified by chromatography on silica gel, eluting with petroleum ether/ethyl acetate 5:1 (v/v). White solid: 143 mg (yield 59%); mp 141-143 °C; IR (KBr) 3312, 2999, 2926, 1701, 1473, 1438, 1341, 1263, 1183, 1059, 948, 818, 732, 650 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.50 (s, 1H), 7.24 – 7.15 (m, 2H), 4.48 (s, 1H), 4.42 (s, 1H), 4.20 (d, *J* = 1.8 Hz, 2H), 3.88 (s, 1H), 2.34 (s, 3H), 2.23 (t, *J* = 2.5 Hz, 1H) ppm. $^{13}C\{H\}$ NMR (101 MHz, $CDCl_3$) δ 171.9, 137.1, 136.8, 135.1, 132.7, 126.4, 122.5 (q, *J* = 284.8 Hz), 122.3, 86.0, 85.0 (q, *J* = 33.4 Hz), 76.8, 71.8, 58.6, 30.8, 21.0 ppm. $^{19}F$ NMR (376 MHz, $CDCl_3$) δ -80.51 ppm. HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{10}F_3NO_2S^+$ 326.0457, found 326.0462.



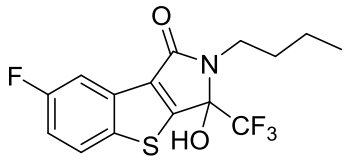

**2-butyl-3-hydroxy-3-(trifluoromethyl)-2,3-dihydro-1*H*-benzo[4,5]thieno[2,3-*c*]pyrrol-1-one (4p)**

Purified by chromatography on silica gel, eluting with petroleum ether/ethyl acetate 5:1 (v/v). White solid: 178 mg (yield 72%); mp 152-154 °C; IR (KBr) 3146, 2965, 2875, 1663, 1473, 1432, 1354, 1190, 1126, 965, 783 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.89 (dp, *J* = 7.1, 3.8, 3.2 Hz, 1H), 7.79 – 7.70 (m, 1H), 7.44 – 7.31 (m, 2H), 6.10 – 5.90 (m, 1H), 3.01 (ddd, *J* = 15.5, 11.1, 4.9 Hz, 1H), 2.68 (ddd, *J* = 14.6, 10.9, 5.7 Hz, 1H), 1.50 (qt, *J* = 12.6, 6.7 Hz, 1H), 1.32 (ddt, *J* = 19.6, 12.6, 7.6 Hz, 1H), 1.11 – 0.97 (m, *J* = 6.1 Hz, 2H), 0.77 (t, *J* = 7.4 Hz, 3H) ppm. $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ 165.8, 151.6, 145.1, 134.4, 130.4, 126.4, 126.1, 123.3, 123.1, 122.1 (q, *J* = 283.8 Hz), 87.2 (q, *J* = 34.5 Hz), 39.9, 30.1, 20.0, 13.4 ppm. $^{19}F$ NMR (376 MHz, $CDCl_3$) δ -79.37 ppm. HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{15}F_3NO_2S^+$ 330.0770, found 330.0780.



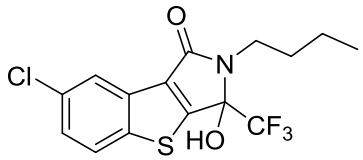

**7-(*tert*-butyl)-2-butyl-3-hydroxy-3-(trifluoromethyl)-2,3-dihydro-1*H*-benzo[4,5]thieno[2,3-*c*]pyrrol-1-one (4q)**

Purified by chromatography on silica gel, eluting with petroleum ether/ethyl acetate 5:1 (v/v). White solid: 196 mg (yield 68%); mp 146-148 °C; IR (KBr) 3473, 2965, 2875, 1664, 1530, 1467, 1368, 1279, 1258, 1193, 1138, 973, 815 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 1.5 Hz, 1H), 7.71 (d, *J* = 8.7 Hz, 1H), 7.52 (dd, *J* = 8.7, 1.9 Hz, 1H), 5.94 (s, 1H), 2.88 (ddd, *J* = 15.4, 11.1, 4.8 Hz, 1H), 2.55 (ddd, *J* = 14.7, 11.0, 5.7 Hz, 1H), 1.55 – 1.44 (m, 2H), 1.44 (s, 9H), 1.32 (ddd, *J* = 11.8, 7.5, 3.6 Hz, 1H), 1.03 (h, *J* = 7.4 Hz, 2H), 0.77 (t, *J* = 7.3 Hz, 3H) ppm. $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ 166.1, 151.7, 149.7, 142.4, 134.3, 130.5, 124.9, 122.8, 122.1 (q, *J* = 283.6 Hz), 87.1 (q, *J* = 34.6 Hz), 119.6, 39.7, 35.0, 31.4, 30.1, 20.0, 13.4 ppm. $^{19}F$ NMR (376 MHz, $CDCl_3$) δ -79.46 ppm. HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{23}F_3NO_2S^+$ 386.1396, found 386.1399.



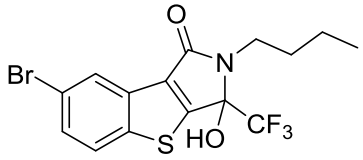
**2-butyl-7-fluoro-3-hydroxy-3-(trifluoromethyl)-2,3-dihydro-1*H*-benzo[4,5]thieno[2,3-*c*]pyrrol-1-one (4r)**

Purified by chromatography on silica gel, eluting with petroleum ether/ethyl acetate 5:1 (v/v). White solid: 172 mg (yield 66%); mp 155-157 °C; IR (KBr) 3086, 2961, 2875, 1675, 1533, 1470, 1369, 1275, 1192, 1128, 976, 879 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.67 (dd, *J* = 9.0, 4.5 Hz, 1H), 7.40 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.07 (td, *J* = 8.8, 2.5 Hz, 1H), 5.87 (s, 1H), 3.28 (ddd, *J* = 15.3, 10.9, 4.9 Hz, 1H), 3.11 (ddd, *J* = 14.5, 10.6, 5.9 Hz, 1H), 1.61 (tdd, *J* = 14.6, 7.5, 3.6 Hz, 1H), 1.50 – 1.38 (m, 1H), 1.28 – 1.14 (m, *J* = 6.7 Hz, 2H), 0.87 (t, *J* = 7.4 Hz, 3H) ppm. $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ 165.3, 161.3 (d, *J* = 244.3 Hz), 153.6, 140.4, 134.1 (d, *J* = 4.7 Hz), 131.3 (d, *J* = 10.5 Hz), 124.5 (d, *J* = 9.5 Hz), 122.0 (q, *J* = 283.7 Hz), 115.4 (d, *J* = 25.4 Hz), 108.6 (d, *J* = 24.2 Hz), 87.1 (q, *J* = 34.7 Hz), 40.2, 30.2, 20.2, 13.5 ppm. $^{19}F$ NMR (376 MHz, $CDCl_3$) δ -79.31, -114.41 ppm. HRMS (ESI-TOF) *m/z* $[M + H]^+$ calcd for $C_{15}H_{14}F_4NO_2S^+$ 348.0676, found 348.0679.



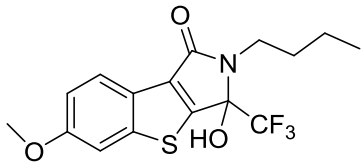

**2-butyl-7-chloro-3-hydroxy-3-(trifluoromethyl)-2,3-dihydro-1*H*-benzo[4,5]thieno[2,3-*c*]pyrrol-1-one (4s)**

Purified by chromatography on silica gel, eluting with petroleum ether/ethyl acetate 5:1 (v/v). White solid: 199 mg (yield 73%); mp 144-146 °C; IR (KBr) 2960, 2874, 1659, 1462, 1371, 1236, 1192, 1124, 971, 881 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.52 (m, 2H), 7.17 (dd, *J* = 8.8, 2.0 Hz, 1H), 5.80 (s, 1H), 3.43 – 3.29 (m, 2H), 1.74 – 1.60 (m, 1H), 1.49 (tt, *J* = 13.2, 7.8 Hz, 1H), 1.31 (tt, *J* = 14.0, 6.7 Hz, 2H), 0.92 (t, *J* = 7.4 Hz, 3H) ppm. $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ 165.2, 153.0, 143.0, 133.7, 132.5, 130.9, 126.9, 123.9, 122.02, 122.0 (q, *J* = 283.5 Hz), 87.2 (q, *J* = 34.7 Hz), 40.2, 30.3, 20.2, 13.6 ppm. $^{19}F$ NMR (376 MHz, $CDCl_3$) δ -79.22 ppm. HRMS (ESI-TOF) *m/z* $[M + H]^+$ calcd for $C_{15}H_{14}ClF_3NO_2S^+$ 364.0380, found 364.0386.



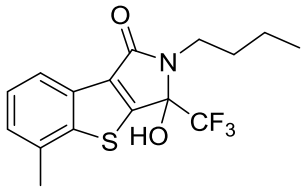

**7-bromo-2-butyl-3-hydroxy-3-(trifluoromethyl)-2,3-dihydro-1*H*-benzo[4,5]thieno[2,3-*c*]pyrrol-1-one (4t)**

Purified by chromatography on silica gel, eluting with petroleum ether/ethyl acetate 5:1 (v/v). White solid: 205 mg (yield 67%); mp 137-139 °C; IR (KBr) 3146, 2957, 2873, 1660, 1469, 1273, 1194, 1125, 969, 880, 816 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 1.6 Hz, 1H), 7.55 (d, *J* = 8.8 Hz, 1H), 7.29 (dd, *J* = 8.8, 2.0 Hz, 1H), 5.98 (s, 1H), 3.37-3.44 (m, 2H), 1.64-1.75 (m, 1H), 1.51 (dp, *J* = 14.5, 7.5 Hz, 1H), 1.34 (h, *J* = 7.2 Hz, 2H), 0.95 (t, *J* = 7.4 Hz, 3H) ppm. $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ 165.3, 152.9, 143.4, 133.5, 131.2, 129.5, 124.9, 124.2, 120.4, 122.0 (q, *J* = 283.7 Hz), 87.1 (q, *J* = 34.7 Hz), 40.2, 30.3, 20.3, 13.6 ppm. $^{19}F$ NMR (376 MHz, $CDCl_3$) δ -79.21 ppm. HRMS (ESI-TOF) *m/z* $[M + H]^+$ calcd for $C_{15}H_{14}BrF_3NO_2S^+$ 407.9875, found 407.9885.



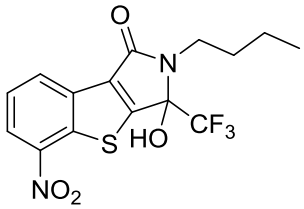
**2-butyl-3-hydroxy-6-methoxy-3-(trifluoromethyl)-2,3-dihydro-1*H*-benzo[4,5]thieno[2,3-*c*]pyrrol-1-one (4u)**

Purified by chromatography on silica gel, eluting with petroleum ether/ethyl acetate 5:1 (v/v). White solid: 175 mg (yield 65%); mp 164-166 °C; IR (KBr) 2965, 2931, 2876, 1664, 1461, 1278, 1193, 1120, 1041, 969, 827 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.8 Hz, 1H), 7.13 (d, *J* = 2.4 Hz, 1H), 6.95 (dd, *J* = 8.8, 2.0 Hz, 1H), 5.68 (s, 1H), 3.85 (s, 3H), 3.16 (ddd, *J* = 15.4, 10.9, 4.9 Hz, 1H), 2.96 (ddd, *J* = 14.6, 10.7, 5.8 Hz, 1H), 1.59 (tdt, *J* = 12.2, 8.9, 6.2 Hz, 1H), 1.48 – 1.34 (m, 1H), 1.19 (tdd, *J* = 14.8, 7.2, 2.7 Hz, 2H), 0.84 (t, *J* = 7.4 Hz, 3H) ppm. $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ 165.9, 158.7, 148.4, 147.1, 134.4, 126.6, 124.3, 123.7, 123.6, 122.4 (q, *J* = 282.8 Hz), 120.9, 118.1, 116.2, 105.6, 87.2 (q, *J* = 34.1 Hz), 55.7, 40.1, 30.4, 20.3, 13.7 ppm. $^{19}F$ NMR (376 MHz, $CDCl_3$) δ -79.34 ppm. HRMS (ESI-TOF) *m/z* $[M + H]^+$ calcd for $C_{16}H_{17}F_3NO_3S^+$ 360.0876, found 360.0879.




**2-butyl-3-hydroxy-5-methyl-3-(trifluoromethyl)-2,3-dihydro-1*H*-benzo[4,5]thieno[2,3-*c*]pyrrol-1-one (4v)**

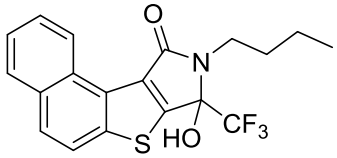
Purified by chromatography on silica gel, eluting with petroleum ether/ethyl acetate 5:1 (v/v). White solid: 188 mg (yield 73%); mp 159-161 °C; IR (KBr) 2966, 1681, 1478, 1422, 1380, 1254, 1185, 1132, 967, 799 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.6 Hz, 1H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.15 (d, *J* = 7.2 Hz, 1H), 5.88 (s, 1H), 3.10 (ddd, *J* = 15.6, 11.1, 4.9 Hz, 1H), 2.85 (ddd, *J* = 14.6, 10.9, 5.7 Hz, 1H), 2.46 (s, 3H), 1.55 (dh, *J* = 19.3, 6.9, 6.4 Hz, 1H), 1.37 (tq, *J* = 12.6, 7.5 Hz, 1H), 1.12 (h, *J* = 7.4 Hz, 2H), 0.81 (t, *J* = 7.4 Hz, 3H) ppm. $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ 166.04, 150.90, 145.38, 135.0, 132.8, 130.1, 126.6, 126.3, 122.1 (q, *J* = 283.7 Hz), 120.7, 87.2 (q, *J* = 34.4 Hz), 39.9, 30.1, 20.1, 20.0, 13.4 ppm. $^{19}F$ NMR (376 MHz, $CDCl_3$) δ -79.37 ppm. HRMS (ESI-TOF) *m/z* $[M + H]^+$ calcd for $C_{16}H_{17}F_3NO_2S^+$ 344.0927, found 344.0933




**2-butyl-3-hydroxy-5-nitro-3-(trifluoromethyl)-2,3-dihydro-1*H*-benzo[4,5]thieno[2,3-*c*]pyrrol-1-one (4w)**

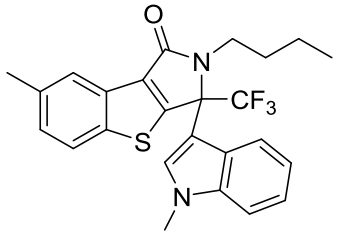
Purified by chromatography on silica gel, eluting with petroleum ether/ethyl acetate 5:1 (v/v). White solid: 196 mg (yield 70%); mp 212-214 °C; IR (KBr) 3094, 2969, 2875, 1695, 1532, 1339, 1324, 1188, 1132, 990, 911, 815, 736 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$) δ 9.03 (s, 1H), 8.62 (d, *J* = 8.0 Hz, 1H), 8.56 (d, *J* = 7.6 Hz, 1H), 7.91 (t, *J* = 7.8 Hz, 1H), 3.45 (dddt, *J* = 17.6, 14.4, 8.5, 4.5 Hz, 2H), 1.72 (dddd, *J* = 16.0, 13.0, 8.4, 3.6 Hz, 1H), 1.56 (tt, *J* = 13.1, 6.9 Hz, 1H), 1.43 – 1.28 (m, *J* = 6.6 Hz, 2H), 0.92 (t, *J* = 7.4 Hz, 3H) ppm. $^{13}C\{H\}$ NMR (100 MHz, DMSO) δ 163.6, 155.1, 143.2, 138.4, 135.3, 133.0, 130.0, 128.3, 124.3, 123.1 (q, *J* = 284.6 Hz), 87.2 (q, *J* = 33.5 Hz), 40.1, 30.8, 20.2, 14.1 ppm. $^{19}F$ NMR (376 MHz, DMSO) δ -78.99 ppm. HRMS (ESI-TOF) *m/z* $[M + H]^+$

calcd for $C_{15}H_{14}F_3N_2O_4S^+$ 375.0621, found 375.0626.



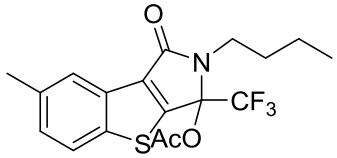

**9-butyl-8-hydroxy-8-(trifluoromethyl)-8,9-dihydro-10*H*-naphtho[1',2':4,5]thieno[2,3-*c*]pyrrol-10-one (4x)**

Purified by chromatography on silica gel, eluting with petroleum ether/ethyl acetate 5:1 (v/v). White solid: 119 mg (yield 42%); mp 195-197 °C; IR (KBr) 2956, 2874, 1662, 1508, 1447, 1363, 1310, 1269, 1186, 1133, 948, 805, 717 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$) δ 9.70 (d, $J$ = 8.0 Hz, 1H), 8.84 (s, 1H), 8.24 (d, $J$ = 8.8 Hz, 1H), 8.11 (d, $J$ = 8.0 Hz, 1H), 8.04 (d, $J$ = 8.8 Hz, 1H), 7.78 – 7.71 (m, 1H), 7.71 – 7.64 (m, 1H), 3.50 (ddtd, $J$ = 20.4, 14.5, 10.0, 5.9 Hz, 2H), 1.89 – 1.71 (m, 1H), 1.69 – 1.53 (m, 1H), 1.39 (h, $J$ = 7.4 Hz, 2H), 0.95 (t, $J$ = 7.4 Hz, 3H) ppm. $^{13}C$ NMR (100 MHz, DMSO) δ 164.6, 151.5, 143.6, 136.7, 131.9, 129.2, 128.92, 128.89, 128.0, 127.6, 127.4, 127.2, 122.9 (q, $J$ = 284.0 Hz), 122.1, 86.3 (q, $J$ = 32.6 Hz), 40.4, 30.8, 20.3, 14.1 ppm. $^{19}F$ NMR (376 MHz, DMSO) δ -79.23 ppm. HRMS (ESI-TOF) $m/z$ $[M + H]^+$ calcd for $C_{19}H_{17}F_3NO_2S^+$ 380.0927, found 380.0936.




**2-butyl-7-methyl-3-(1-methyl-1*H*-indol-3-yl)-3-(trifluoromethyl)-2,3-dihydro-1*H*-benzo[4,5]thieno[2,3-*c*]pyrrol-1-one (5)**

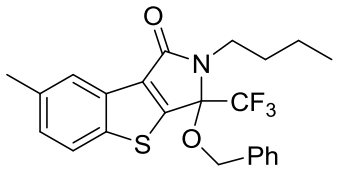
Purified by chromatography on silica gel, eluting with petroleum ether/ethyl acetate 5:1 (v/v). White solid: 254 mg (yield 74%); mp 177-179 °C; IR (KBr) 2964, 2923, 2870, 1697, 1545, 1466, 1340, 1152, 896, 751 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.67 (d, $J$ = 8.4 Hz, 1H), 7.46 – 7.40 (m, 1H), 7.31 (d, $J$ = 8.0 Hz, 1H), 7.28 – 7.23 (m, 1H), 7.18 (t, $J$ = 7.6 Hz, 1H), 6.91 – 6.83 (m, 1H), 6.70 (d, $J$ = 8.0 Hz, 1H), 3.86 (s, 3H), 3.48 (ddd, $J$ = 15.1, 10.6, 5.6 Hz, 1H), 3.05 (ddd, $J$ = 14.6, 10.8, 5.0 Hz, 1H), 2.54 (s, 3H), 1.77 – 1.67 (m, 1H), 1.58 – 1.46 (m, 1H), 1.34 – 1.13 (m, 2H), 0.83 (t, $J$ = 7.4 Hz, 3H) ppm. $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ 166.0, 154.1, 142.2, 137.0, 135.9, 134.6, 131.5, 129.1, 127.6, 125.2, 124.5 (q, $J$ = 284.1 Hz), 123.5, 122.8, 122.6, 120.7, 119.1, 109.7, 103.6, 69.5 (q, $J$ = 30.7 Hz), 42.1, 33.2, 30.4, 21.4, 20.3, 13.7 ppm. $^{19}F$ NMR (376 MHz, $CDCl_3$) δ -72.12 ppm. HRMS (ESI-TOF) $m/z$ $[M + H]^+$ calcd for $C_{25}H_{24}F_3N_2OS^+$ 457.1556, found 457.1560.




**2-butyl-7-methyl-1-oxo-3-(trifluoromethyl)-2,3-dihydro-1*H*-benzo[4,5]thieno[2,3-*c*]pyrrol-3-yl acetate (6)**

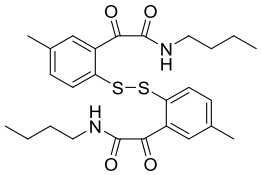
Purified by chromatography on silica gel, eluting with petroleum ether/ethyl acetate 5:1 (v/v). Yellow oil: 215 mg (yield 81%); IR (KBr) 2960, 2933, 2874, 1779, 1727, 1471, 1369, 1304, 1209, 1081, 1032, 984, 801, 735 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.73 (d, $J$ = 8.4 Hz,

1H), 7.28 (d, *J* = 8.4 Hz, 1H), 3.45 (dtq, *J* = 20.0, 10.3, 5.7, 4.9 Hz, 2H), 2.49 (s, 3H), 2.15 (s, 3H), 1.78 (dddt, *J* = 15.6, 9.7, 6.4, 2.9 Hz, 1H), 1.64 – 1.60 (m, 1H), 1.46 – 1.34 (m, 2H), 0.97 (t, *J* = 7.4 Hz, 3H) ppm. $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ 166.6, 165.0, 146.8, 142.7, 136.5, 136.3, 131.2, 128.3, 123.6, 122.8, 121.5 (q, *J* = 284.4 Hz), 89.0 (q, *J* = 34.7 Hz), 40.7, 30.6, 21.5, 21.4, 20.3, 13.8 ppm. $^{19}F$ NMR (376 MHz, $CDCl_3$) δ -78.86 ppm. HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{19}F_3NO_3S^+$ 386.1032, found 386.1038.




**2-butyl-7-methyl-3-phenethoxy-3-(trifluoromethyl)-2,3-dihydro-1*H*-benzo[4,5]thieno[2,3-*c*]pyrrol-1-one (7)**

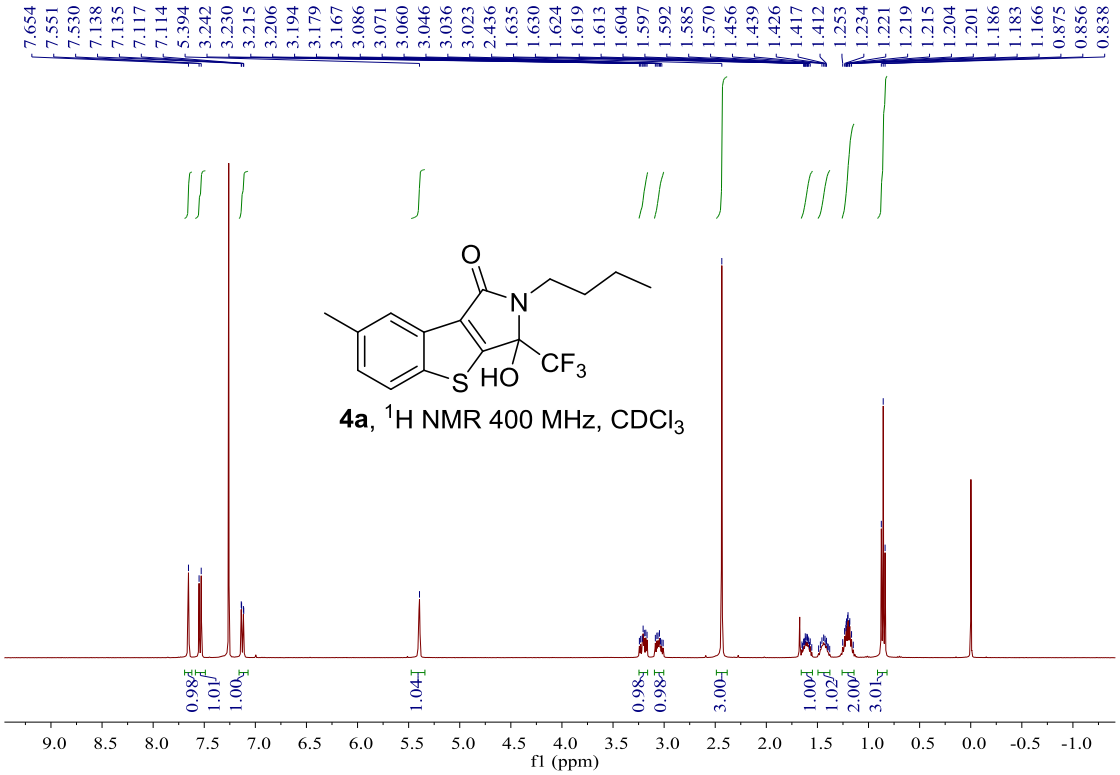
Purified by chromatography on silica gel, eluting with petroleum ether/ethyl acetate 5:1 (v/v). White solid: 294 mg (yield 90%); mp 84-86 °C; IR (KBr) 2967, 2878, 1708, 1466, 1366, 1309, 1194, 94, 882, 815 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.40 – 7.21 (m, 6H), 4.41 – 4.18 (m, 2H), 3.54 (td, *J* = 12.9, 11.3, 5.7 Hz, 1H), 3.39 (td, *J* = 14.5, 13.0, 4.9 Hz, 1H), 2.53 (s, 3H), 1.96 – 1.79 (m, 1H), 1.66 – 1.58 (m, 1H), 1.50 – 1.33 (m, 2H), 0.97 (t, *J* = 7.3 Hz, 3H) ppm. $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ 164.9, 147.3, 143.1, 136.9, 136.4, 135.6, 131.3, 128.6, 128.4, 128.3, 127.6, 123.5, 122.9, 122.1 (q, *J* = 283.9 Hz), 91.3 (q, *J* = 33.7 Hz), 66.3, 40.3, 30.5, 21.4, 20.4, 13.7 ppm. $^{19}F$ NMR (376 MHz, $CDCl_3$) δ -78.29 ppm. HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{22}F_3NO_2S^+$ 434.1396, found 434.1395



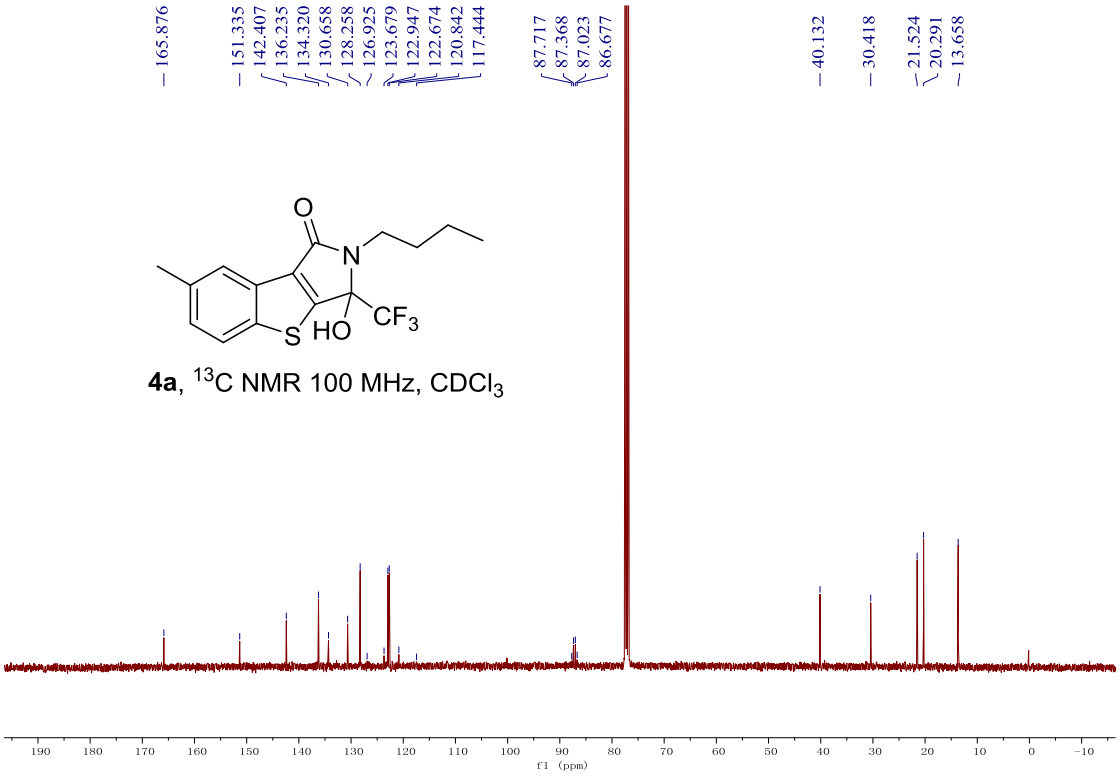

**2,2'-(disulfanediylbis(5-methyl-2,1-phenylene))bis(N-butyl-2-oxoacetamide) (9)**

Purified by chromatography on silica gel, eluting with petroleum ether/ethyl acetate 5:1 (v/v). Yellow solid: 25 mg (yield: 33%); mp 144-146 °C; IR (KBr) 3290, 2936, 2343, 1656, 1543, 1453, 1182, 812 cm-1; $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 2H), 7.66 (d, *J* = 8.0 Hz, 2H), 7.33 – 7.26 (m, 2H), 7.19 – 7.03 (m, 2H), 3.42 (q, *J* = 6.8 Hz, 4H), 2.36 (s, 6H), 1.65 – 1.59 (m, 4H), 1.43 (q, *J* = 7.4 Hz, 4H), 0.97 (t, *J* = 7.4 Hz, 6H) ppm. $^{13}C\{H\}$ NMR (100 MHz, CDCl3) δ 188.4, 161.7, 138.8, 135.7, 135.1, 134.7, 131.3, 127.0, 39.4, 31.3, 20.66, 20.1, 13.7 ppm. HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{26}H_{33}N_2O_4S_2^+$ 501.1876, found 501.1885.

## 7. NMR spectra of all new compounds

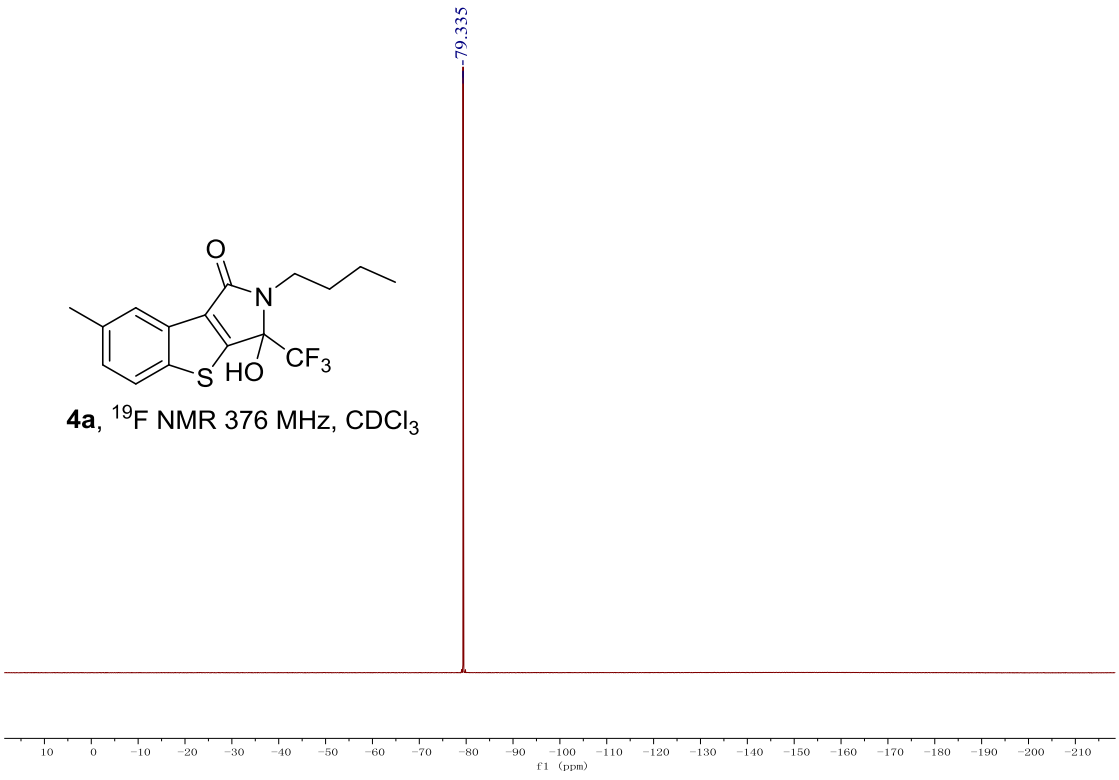


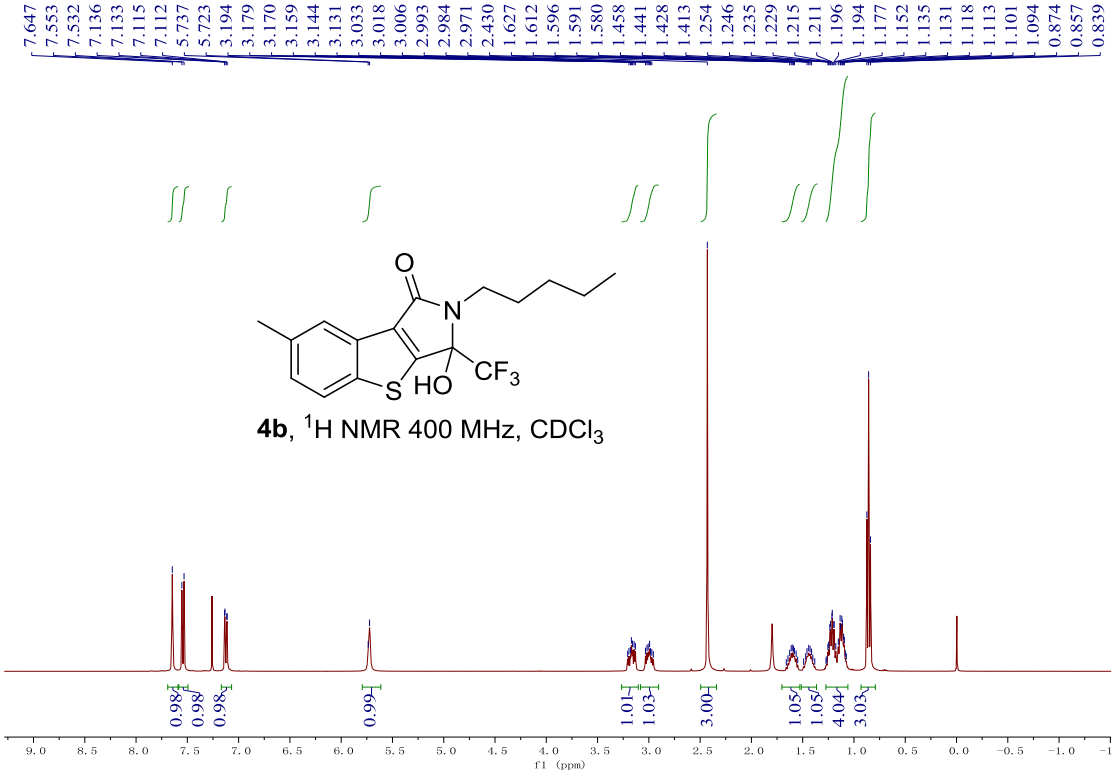

**4a**, $^{1}$H NMR 400 MHz, $CDCl_3$




**4a**, $^{13}$C NMR 100 MHz, $CDCl_3$

**4a**, $^{19}F$ NMR 376 MHz, $CDCl_3$

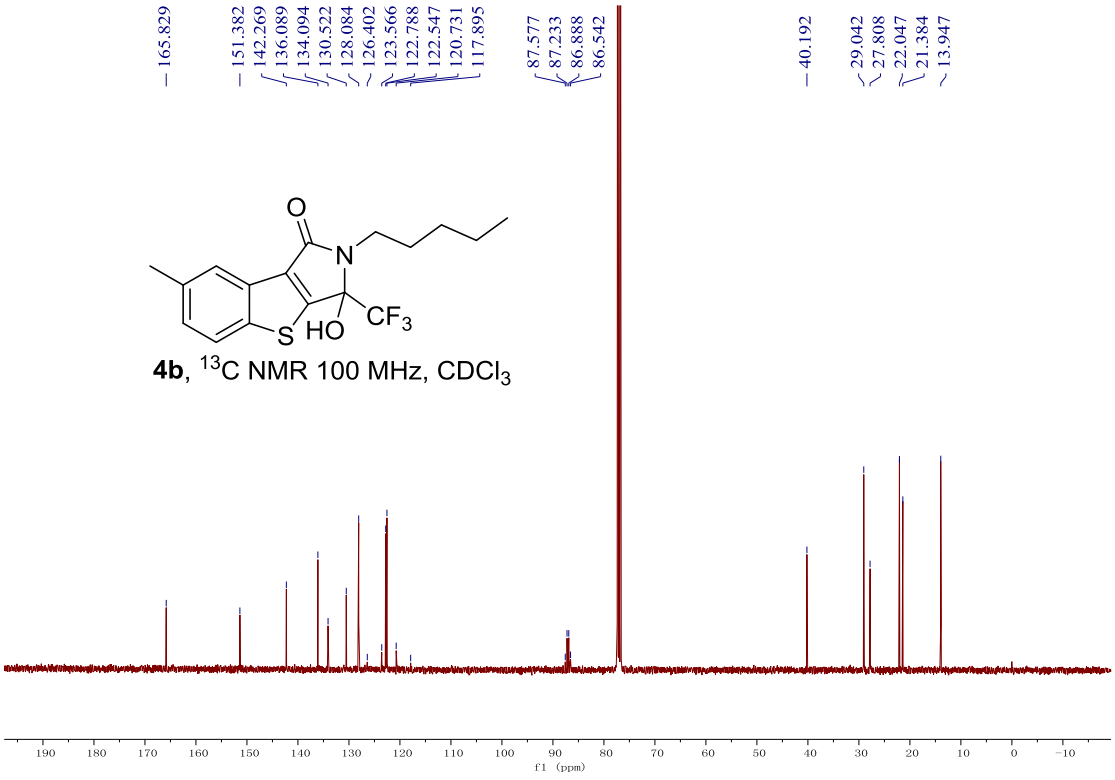


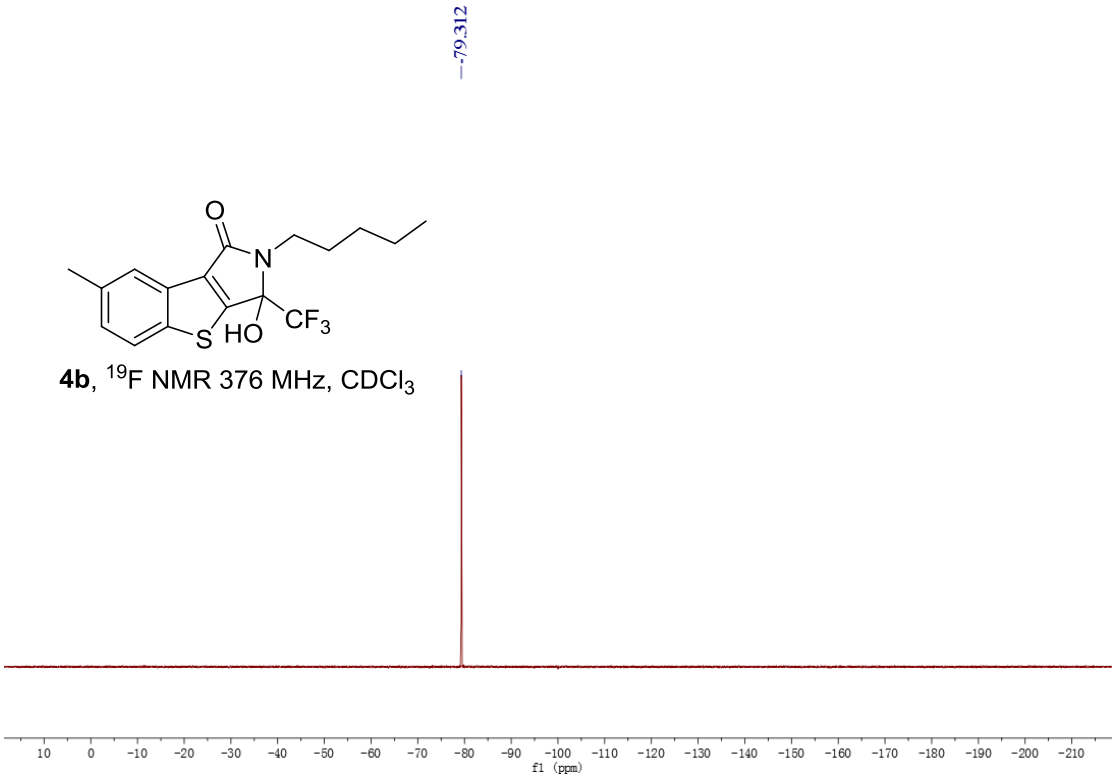




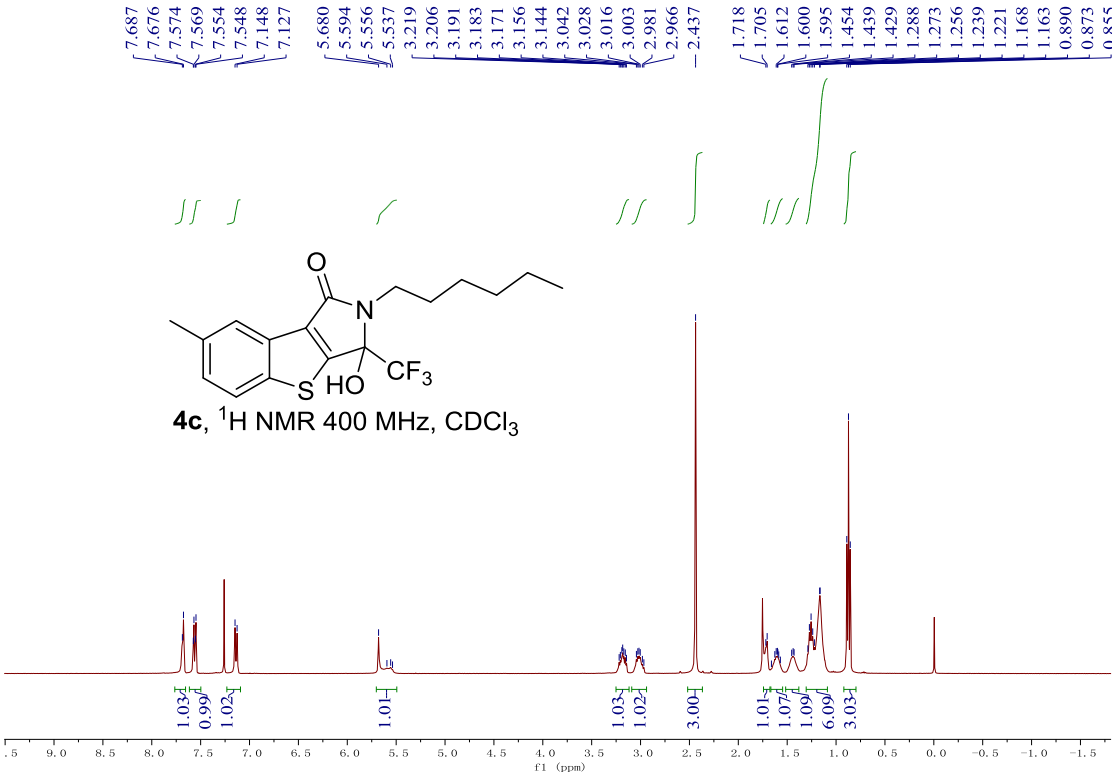
**4b**, $^{1}H$ NMR 400 MHz, $CDCl_3$



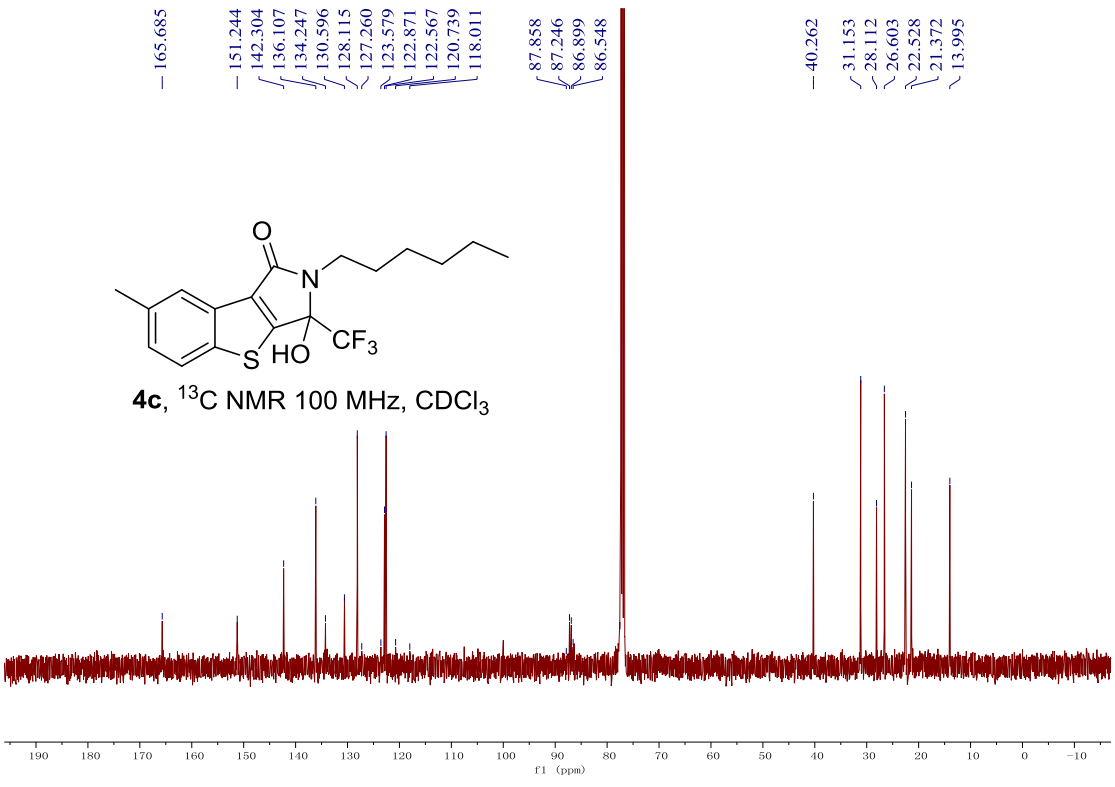

**4b**, $^{13}C$ NMR 100 MHz, $CDCl_3$



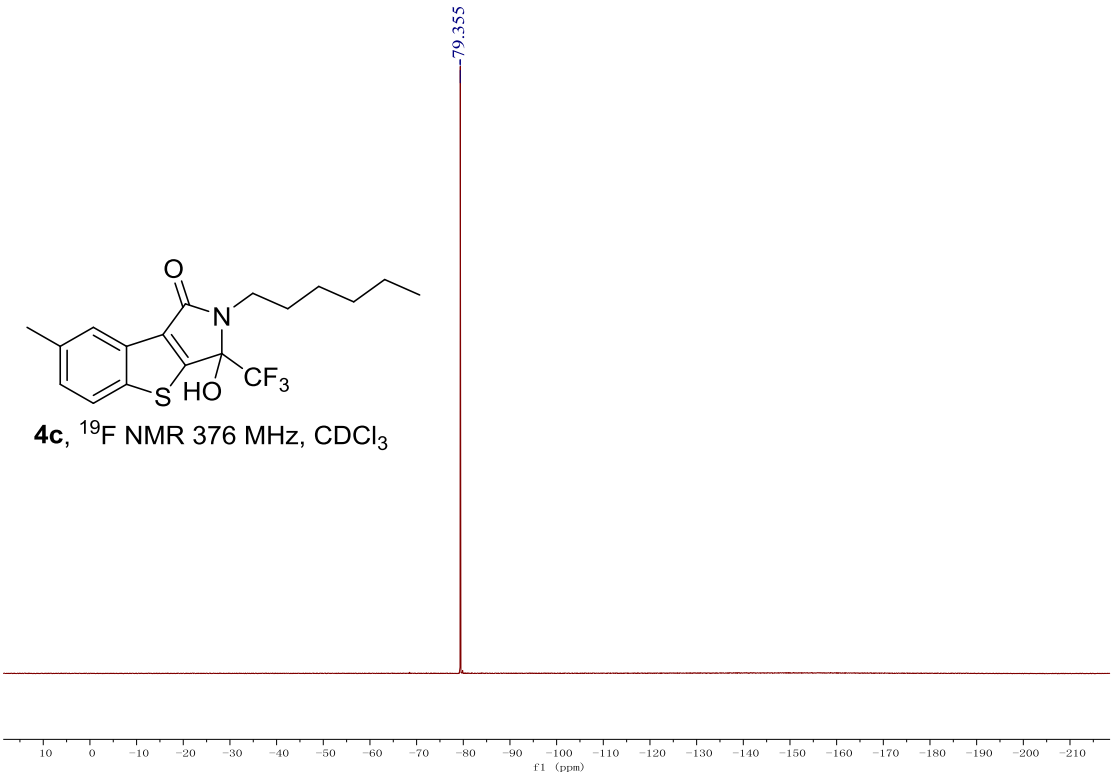

**4b**, $^{19}F$ NMR 376 MHz, $CDCl_3$



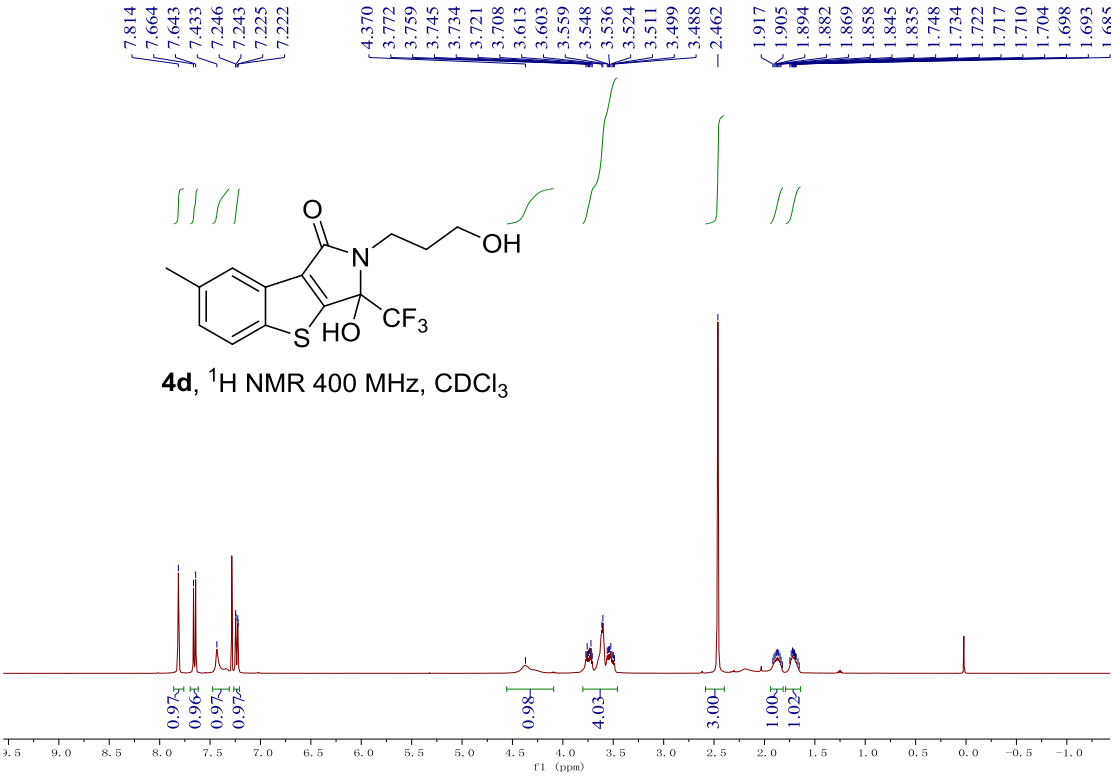

**4c**, $^{1}$H NMR 400 MHz, $CDCl_3$



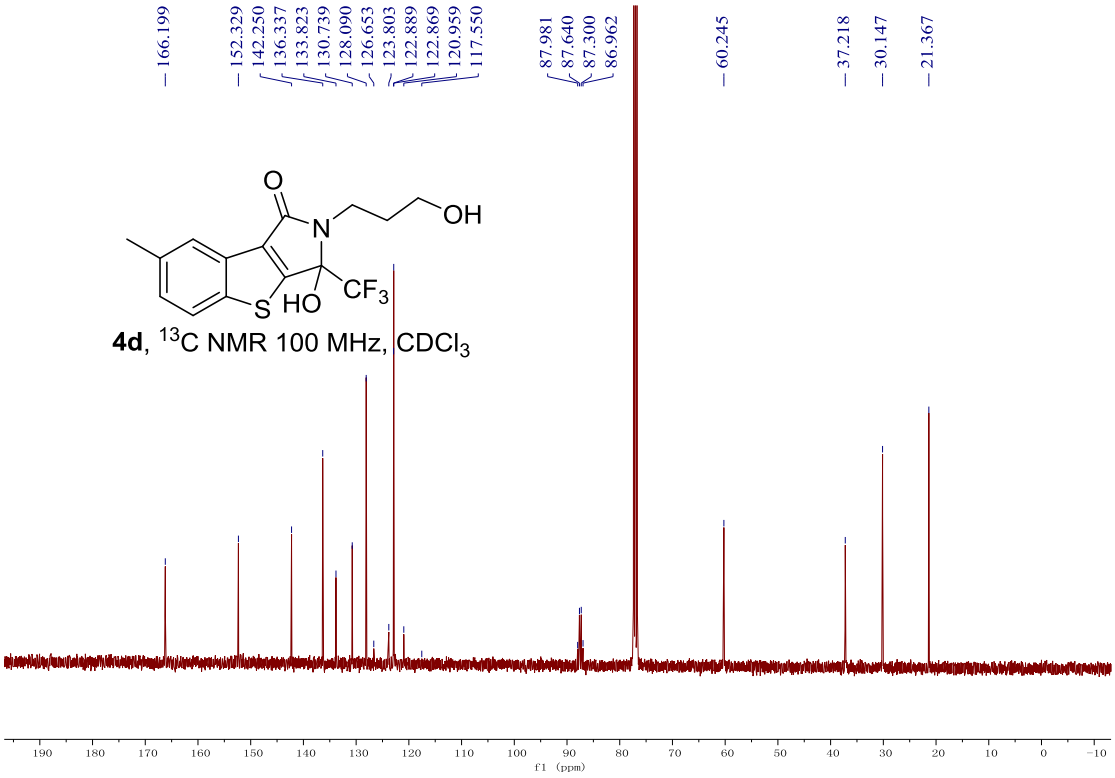

**4c**, $^{13}$C NMR 100 MHz, $CDCl_3$



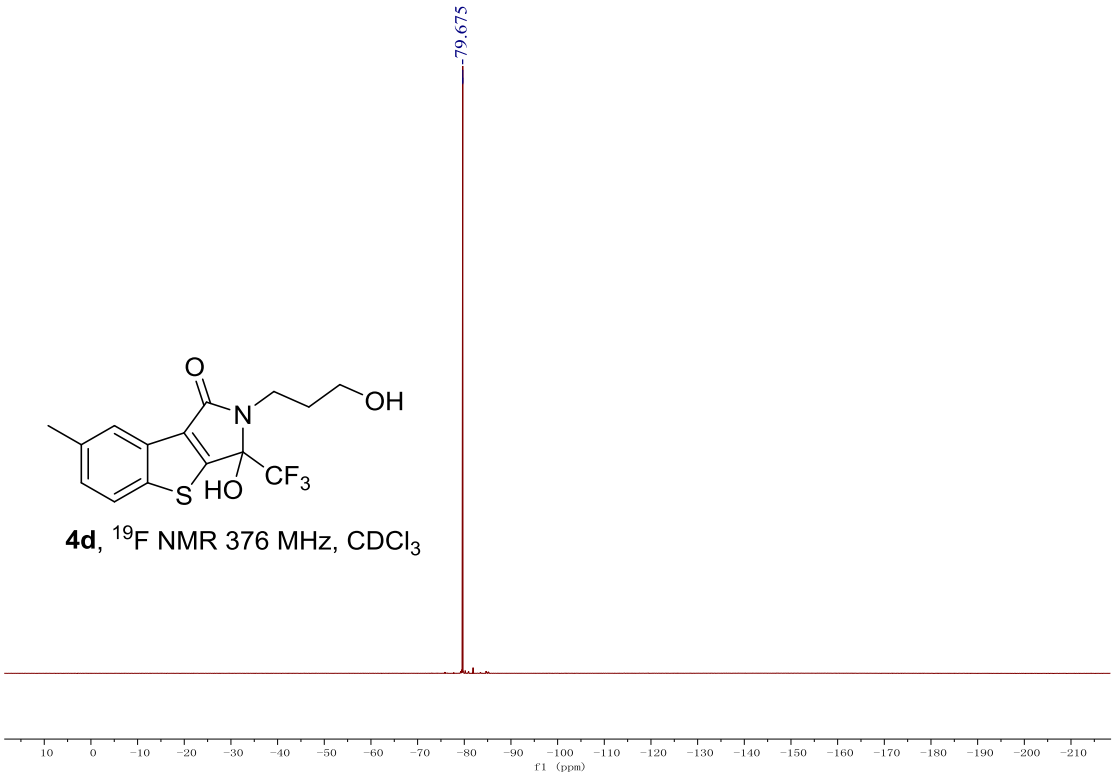

**4c**, $^{19}$F NMR 376 MHz, $CDCl_3$



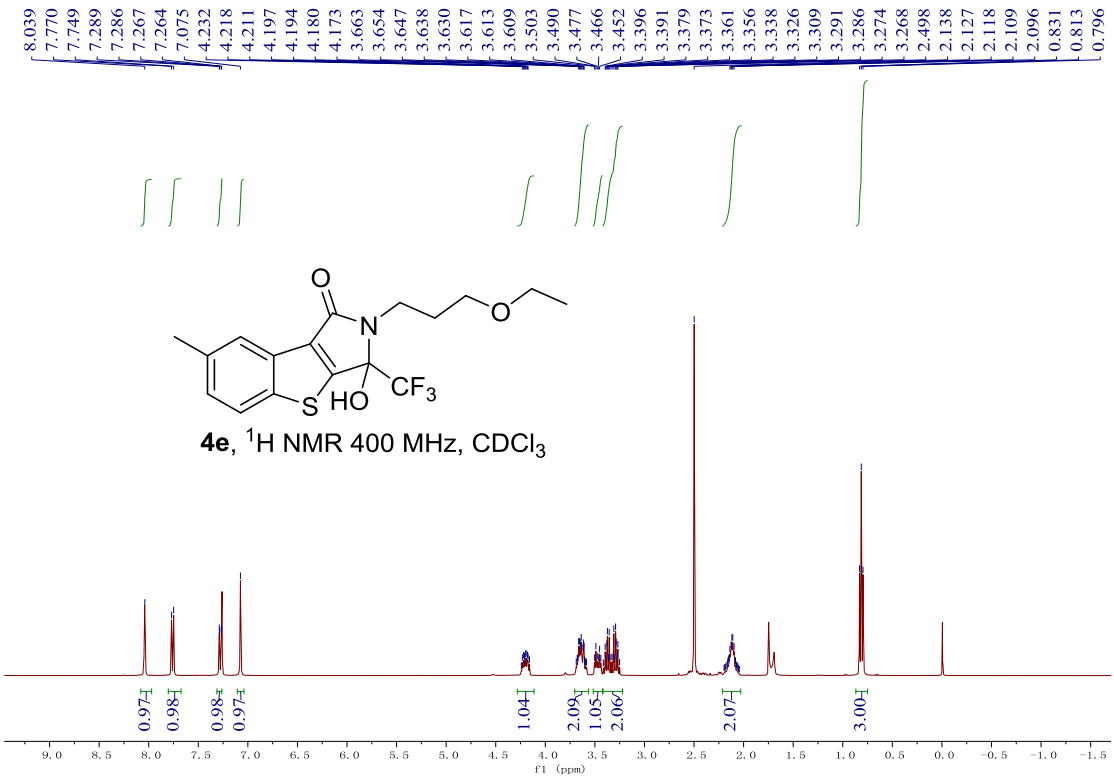

**4d**, $^{1}$H NMR 400 MHz, $CDCl_3$



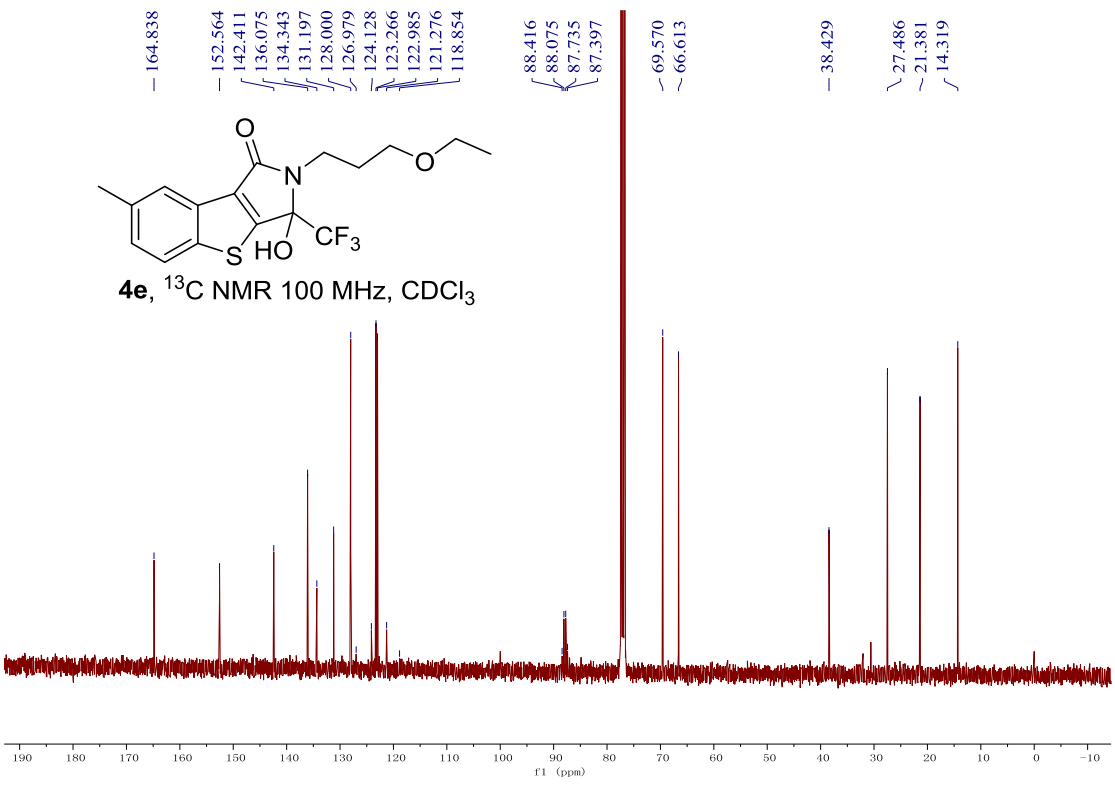

**4d**, $^{13}C$ NMR 100 MHz, $CDCl_3$



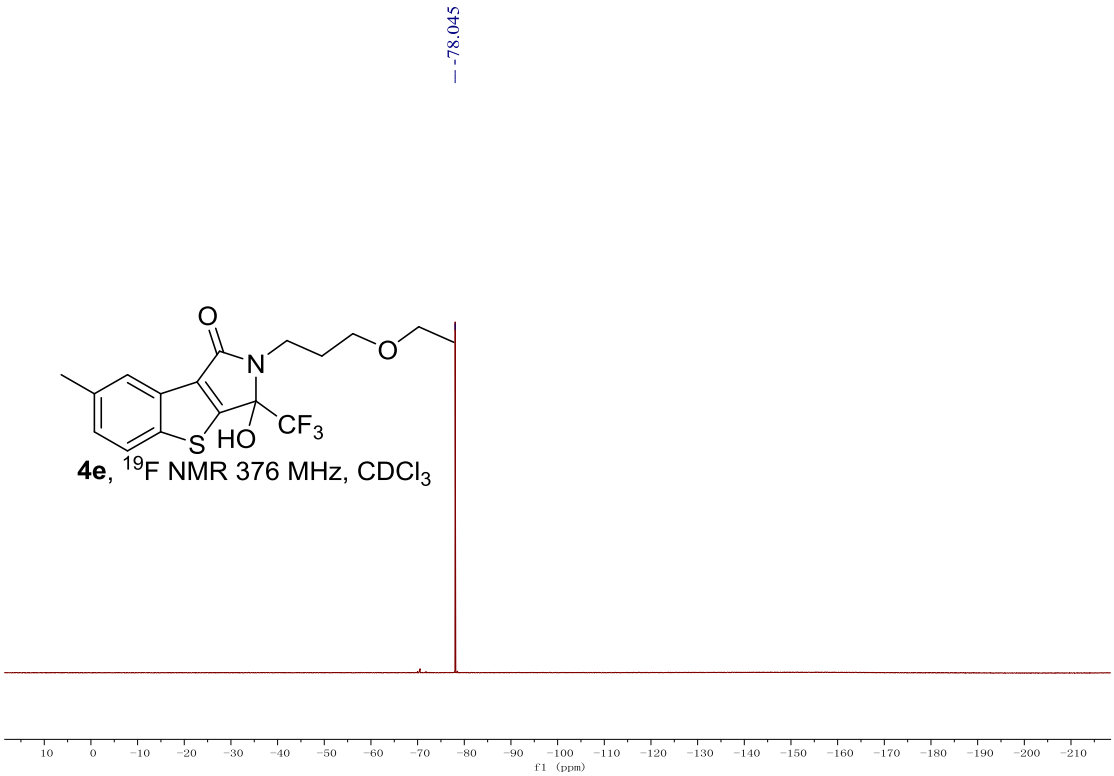

**4d**, $^{19}F$ NMR 376 MHz, $CDCl_3$



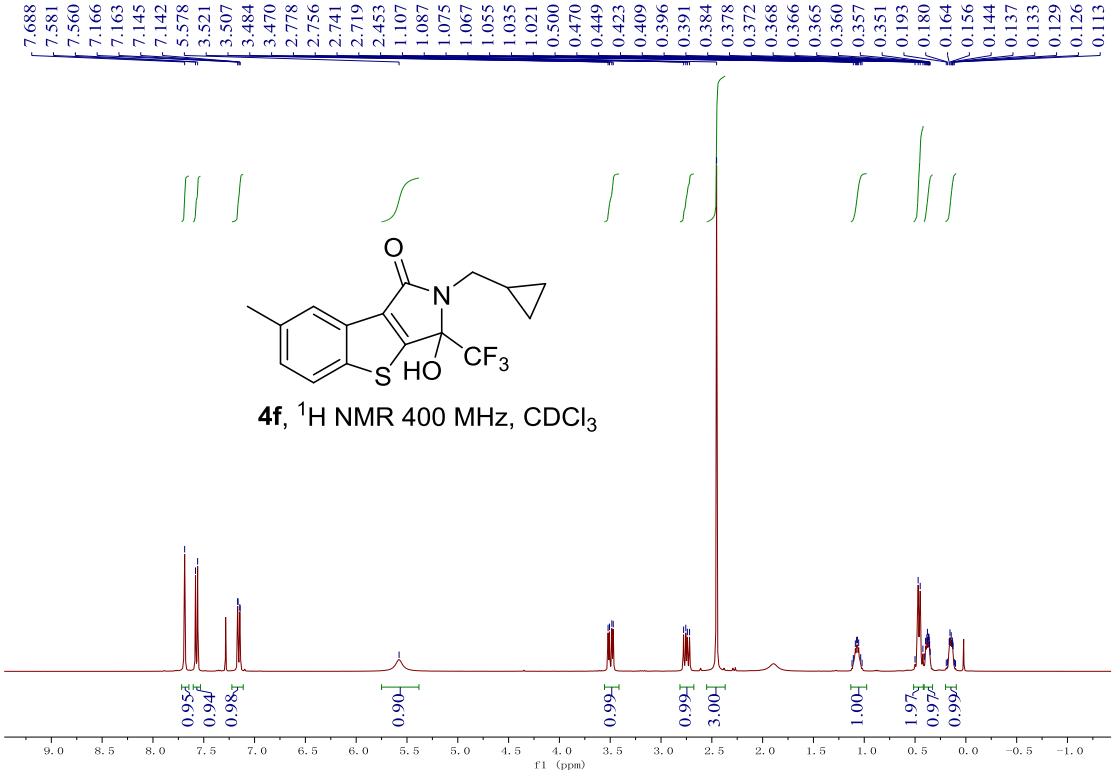

**4e**, $^{1}$H NMR 400 MHz, $CDCl_3$



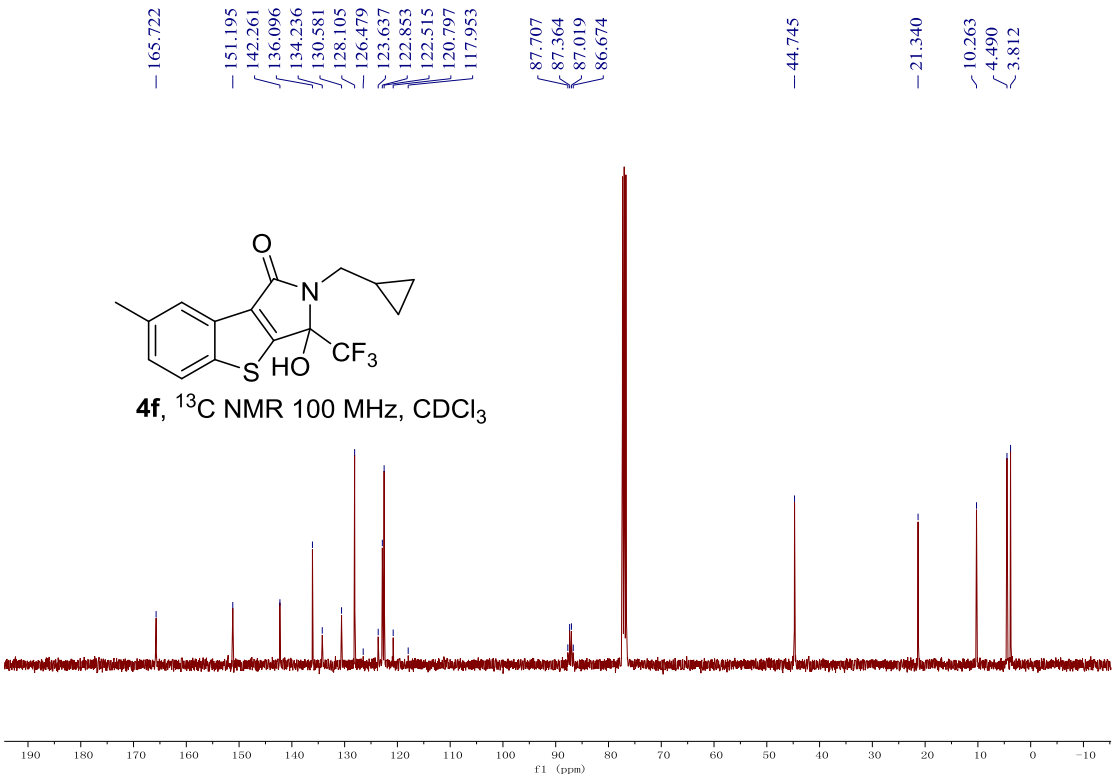

**4e**, $^{13}$C NMR 100 MHz, $CDCl_3$



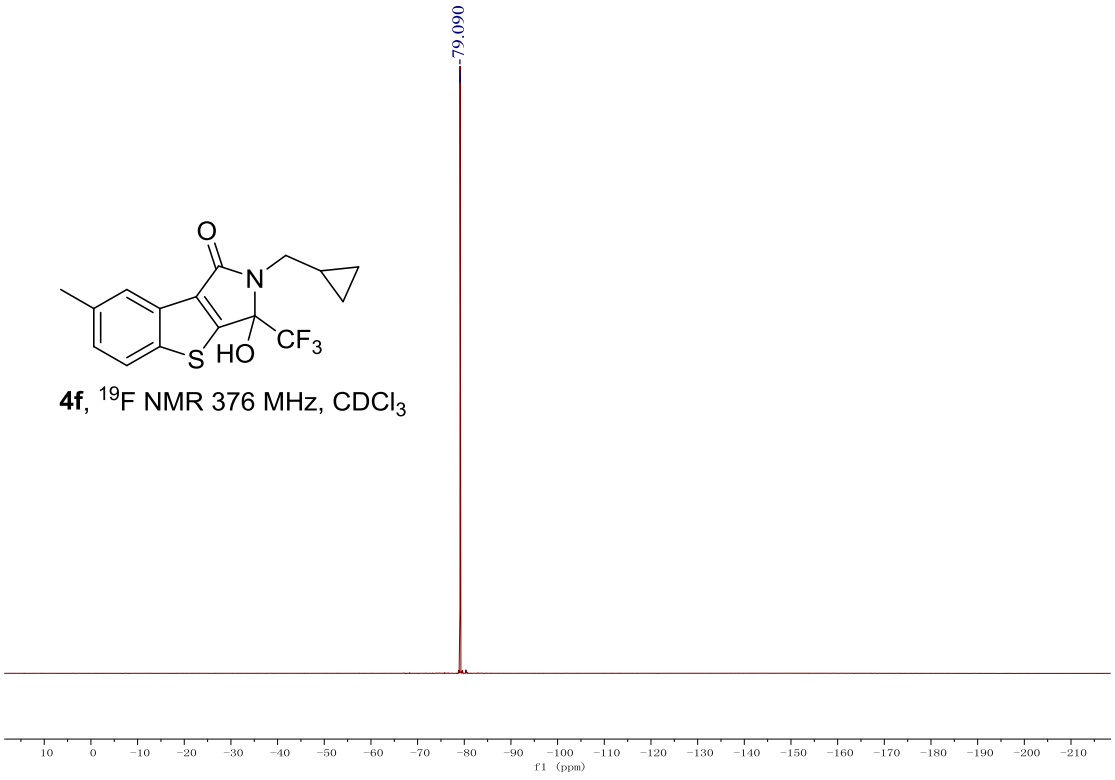

**4e**, $^{19}F$ NMR 376 MHz, $CDCl_3$



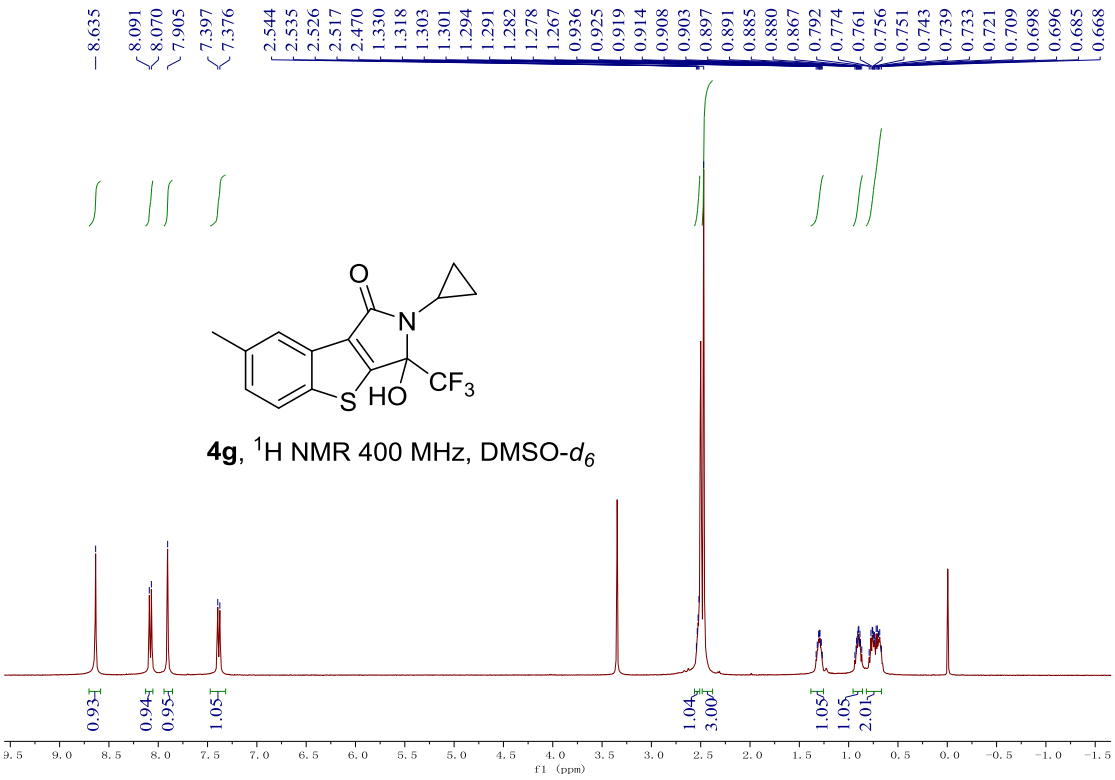

**4f**, $^{1}H$ NMR 400 MHz, $CDCl_3$



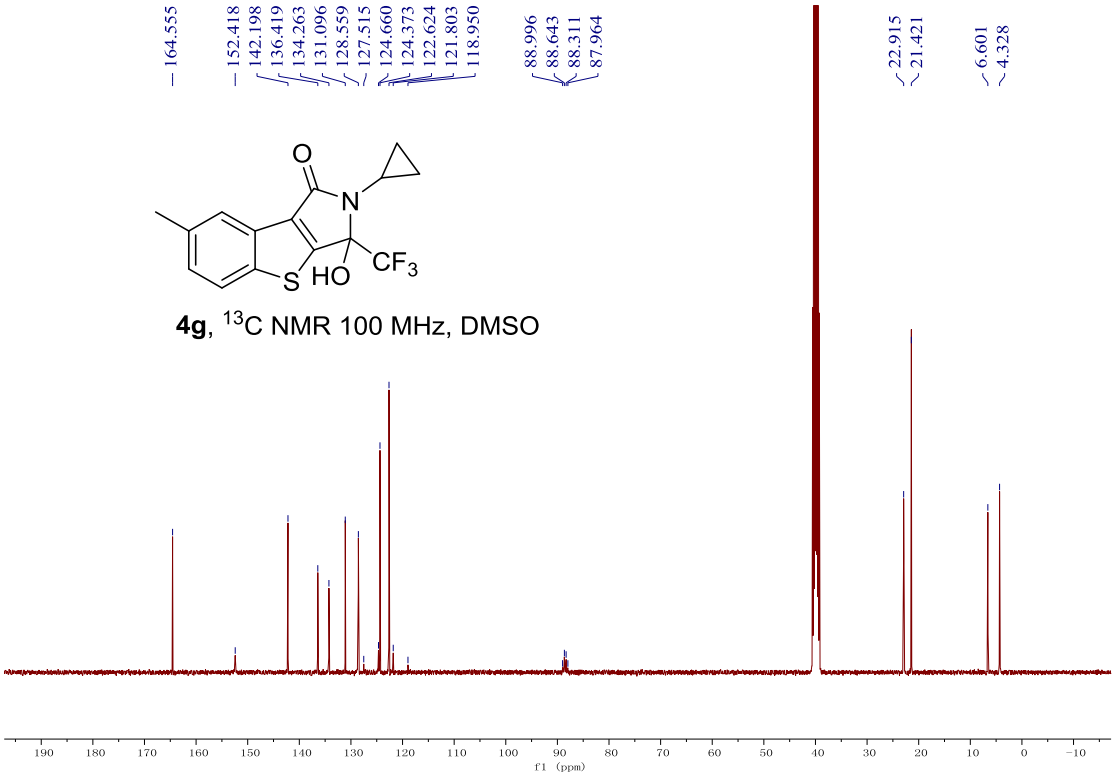

**4f**, $^{13}C$ NMR 100 MHz, $CDCl_3$



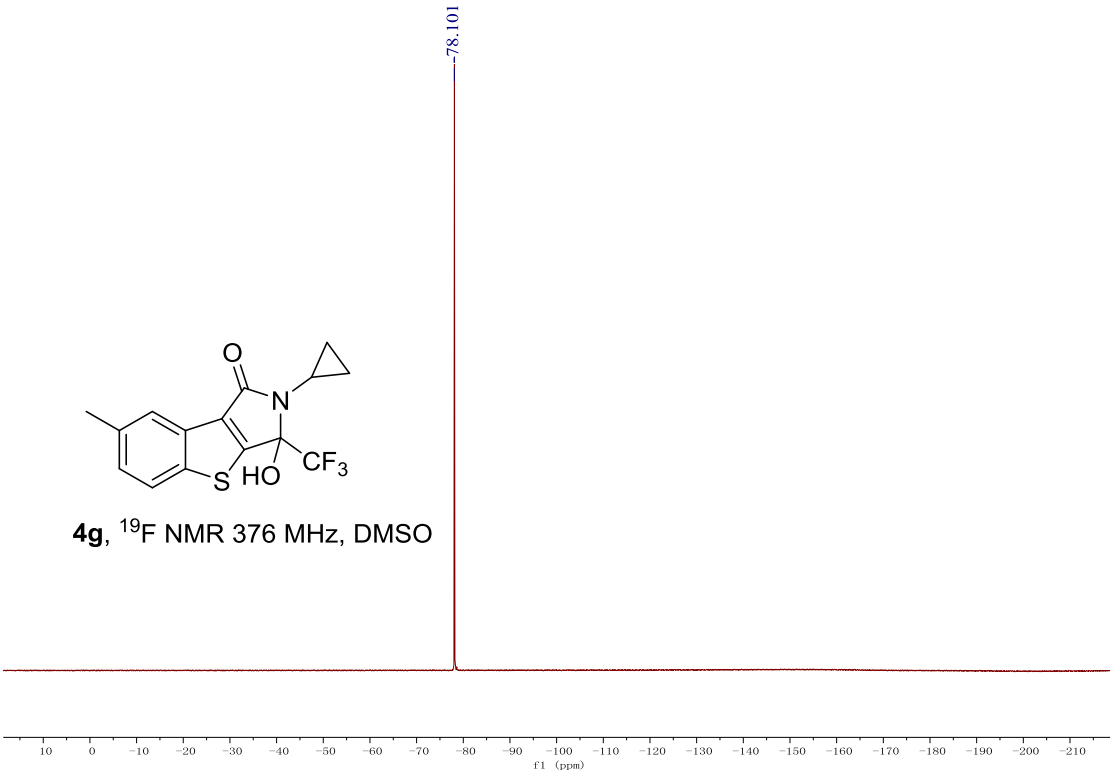

**4f**, $^{19}F$ NMR 376 MHz, $CDCl_3$



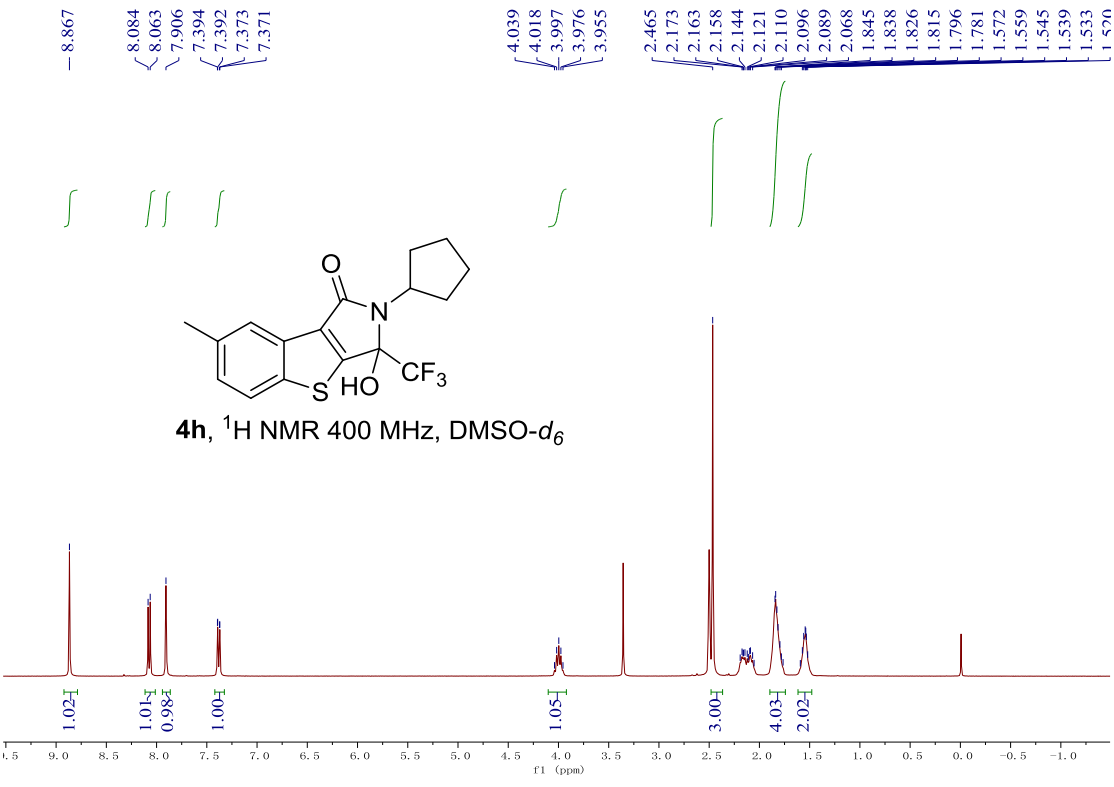

**4g**, $^{1}$H NMR 400 MHz, DMSO-$d_6$



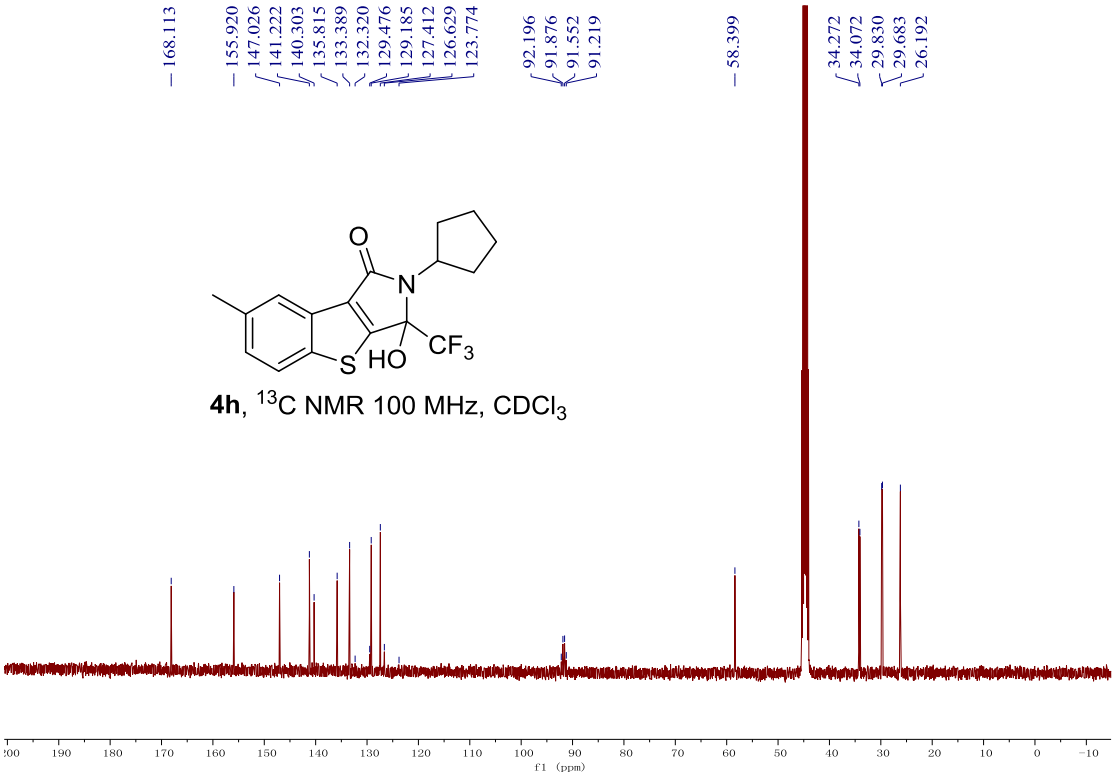

**4g**, $^{13}$C NMR 100 MHz, DMSO



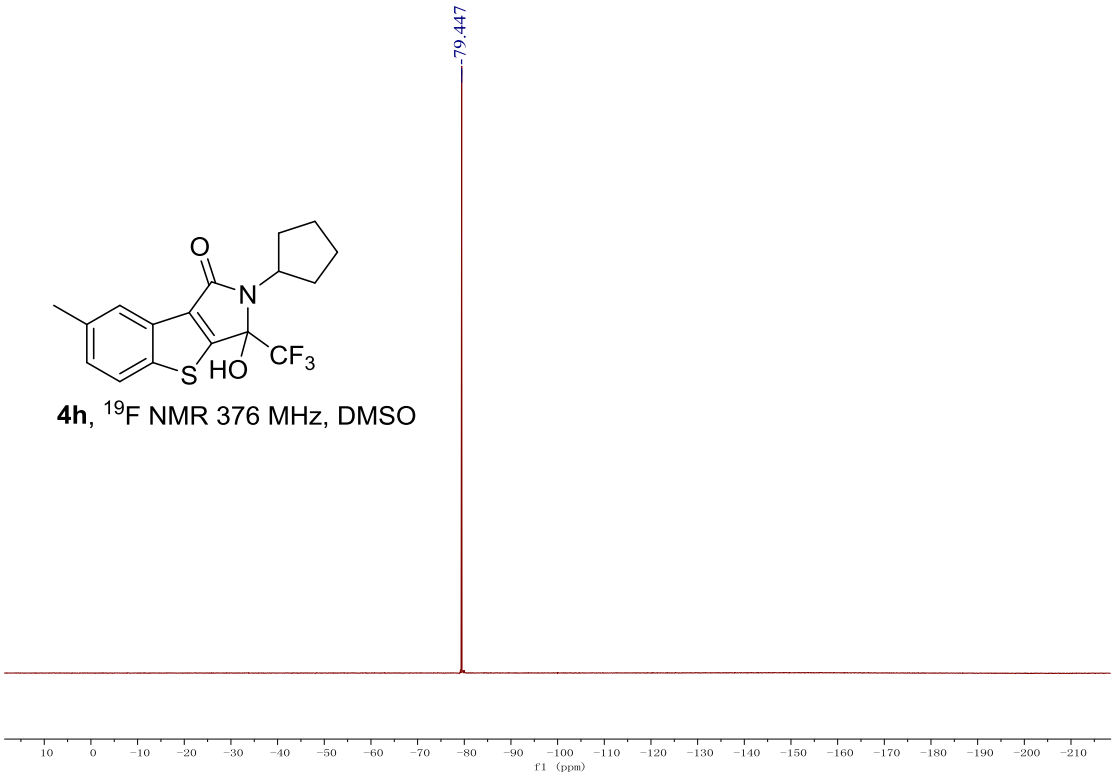

**4g**, $^{19}F$ NMR 376 MHz, DMSO



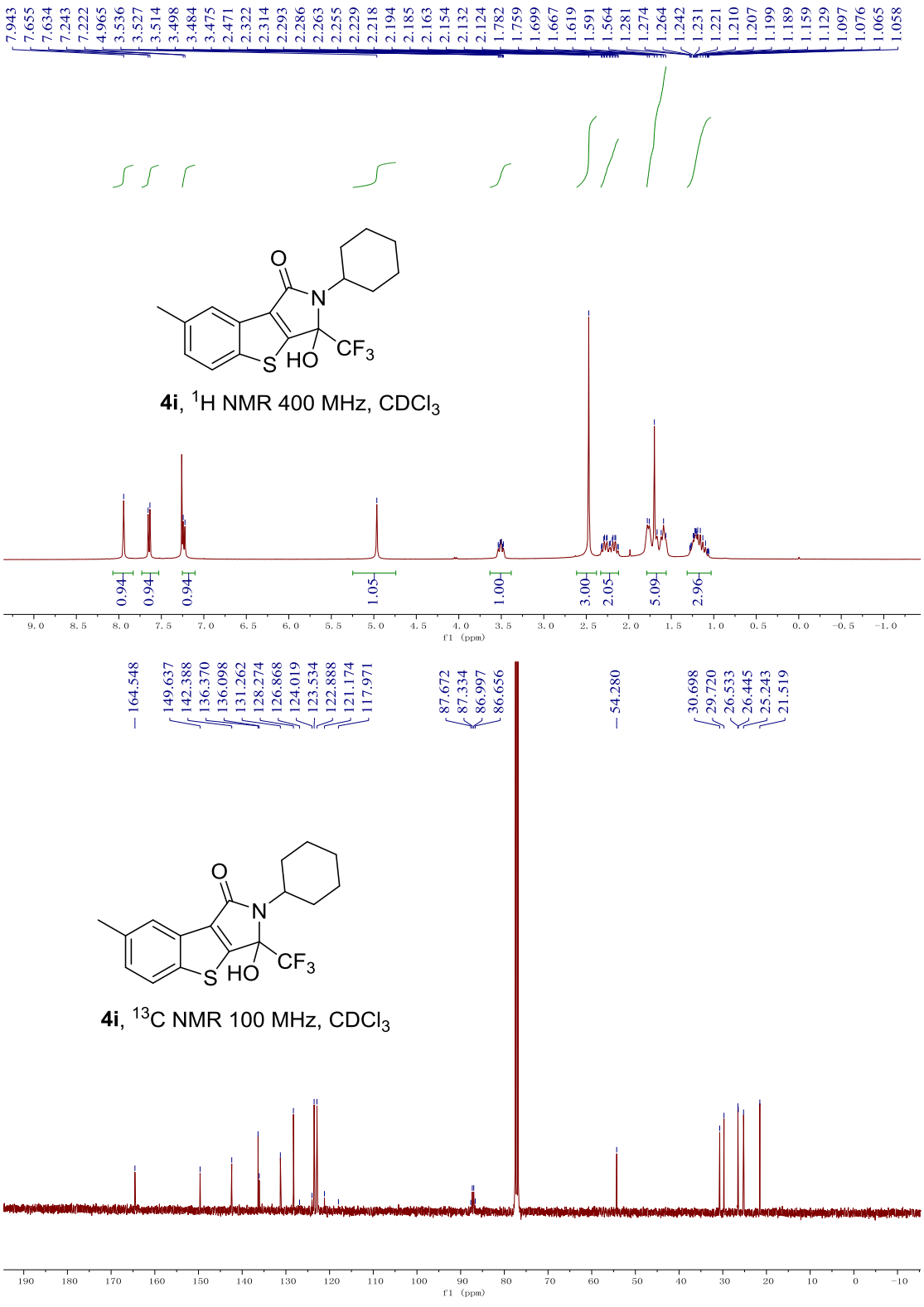

**4h**, $^{1}H$ NMR 400 MHz, DMSO-$d_6$

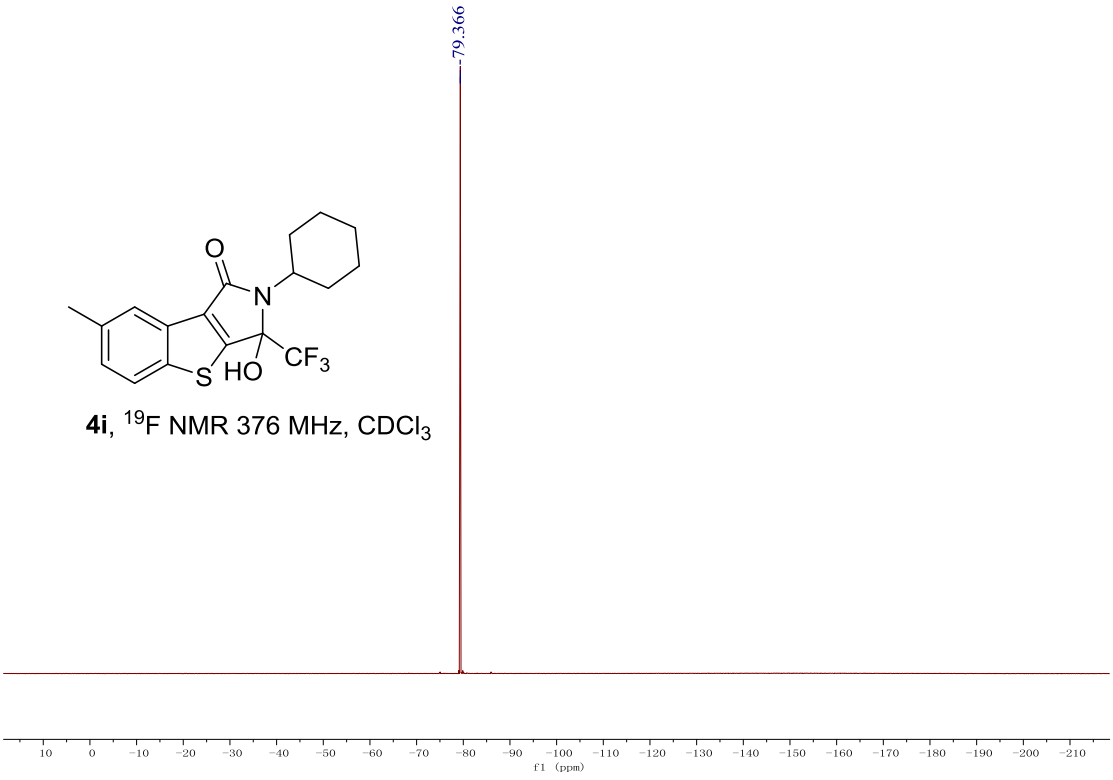



**4h**, $^{13}C$ NMR 100 MHz, $CDCl_3$

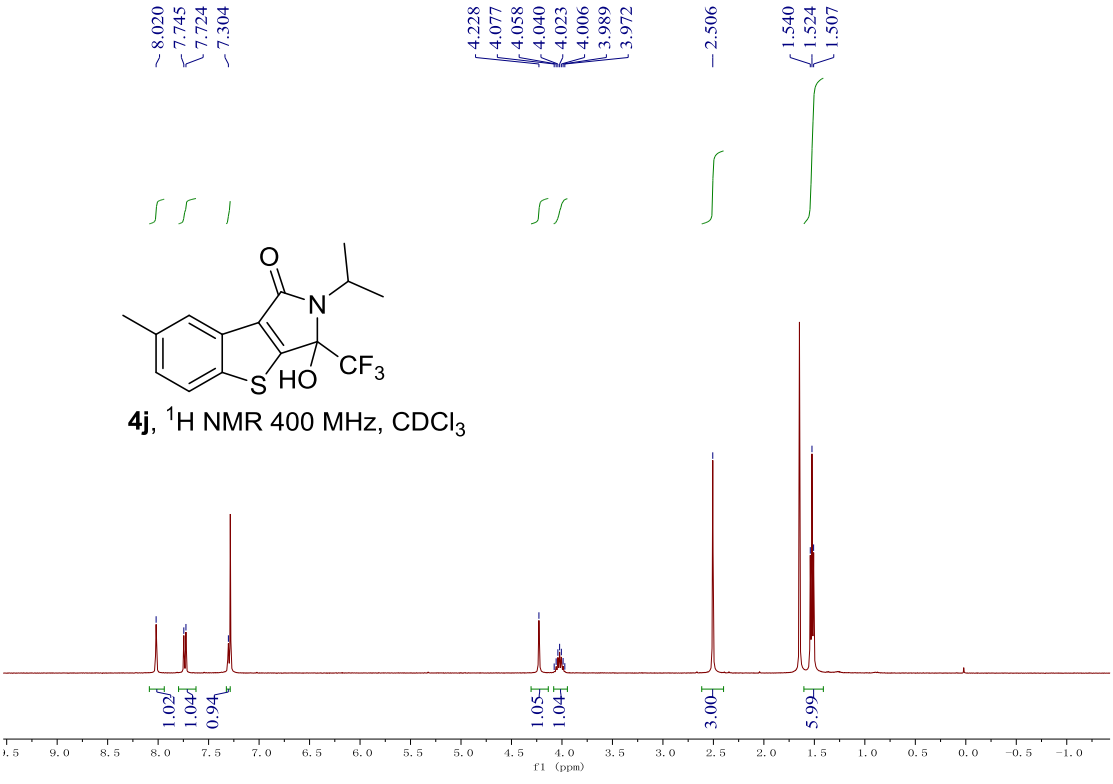



**4h**, $^{19}F$ NMR 376 MHz, DMSO

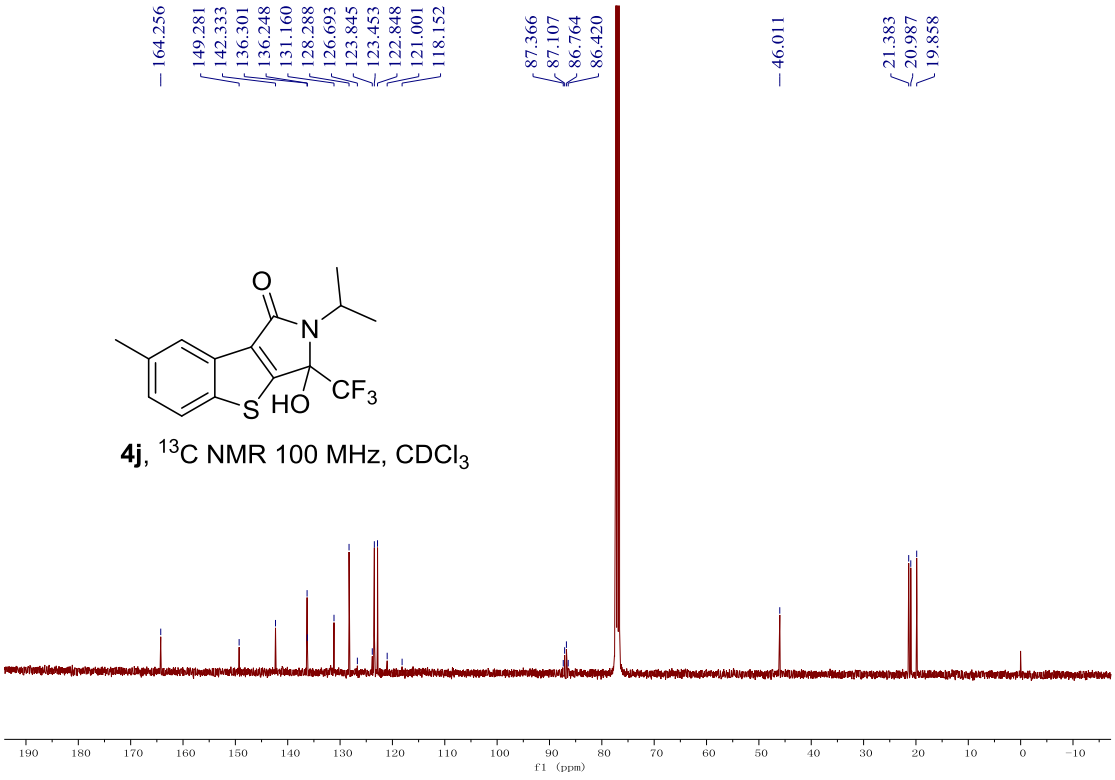

7.943
7.655
7.634
7.243
7.222
4.965
3.536
3.527
3.514
3.498
3.484
3.475
2.471
2.322
2.314
2.293
2.286
2.263
2.255
2.229
2.218
2.194
2.185
2.163
2.154
2.132
2.124
1.782
1.759
1.699
1.667
1.619
1.591
1.564
1.281
1.274
1.264
1.242
1.231
1.221
1.210
1.207
1.199
1.189
1.159
1.129
1.097
1.076
1.065
1.058
O
N
CF3
S HO
4i, 1H NMR 400 MHz, CDCl3
0.94
0.94
0.94
1.05
1.00
3.00
2.05
5.09
2.96
f1 (ppm)
164.548
149.637
142.388
136.370
136.098
131.262
128.274
126.868
124.019
123.534
122.888
121.174
117.971
87.672
87.334
86.997
86.656
54.280
30.698
29.720
26.533
26.445
25.243
21.519
O
N
CF3
S HO
4i, 13C NMR 100 MHz, CDCl3
f1 (ppm)



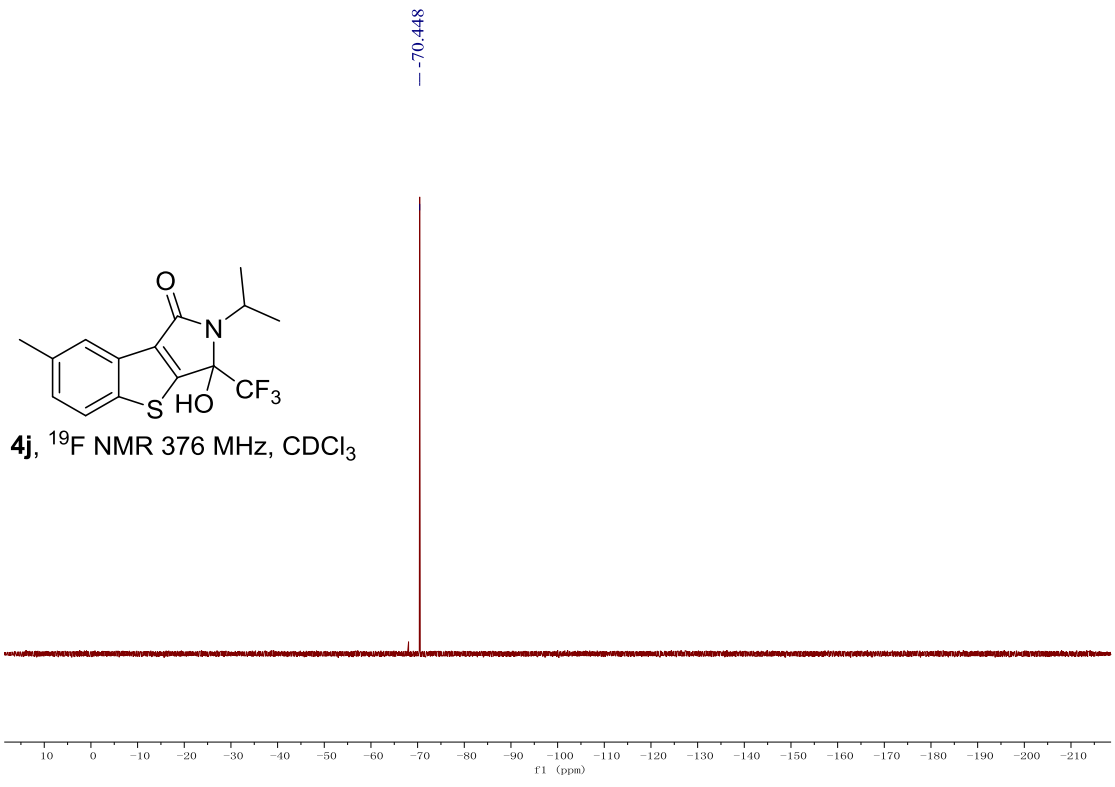

**4i**, $^{19}F$ NMR 376 MHz, $CDCl_3$



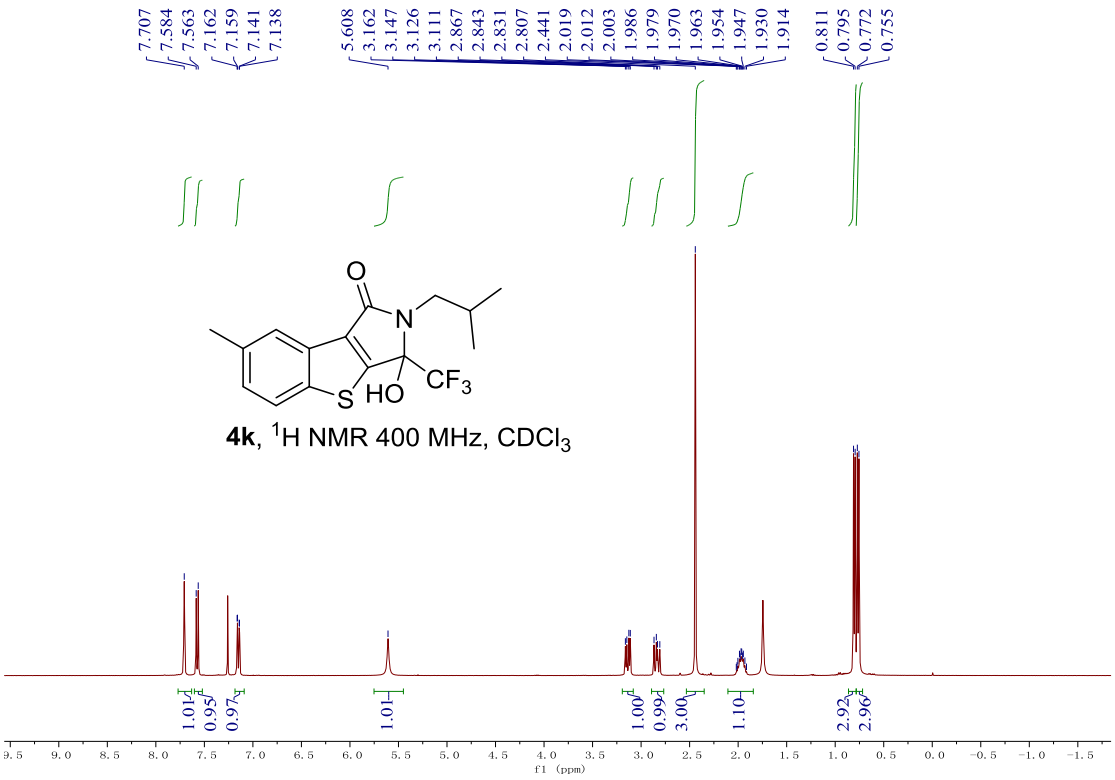

**4j**, $^{1}H$ NMR 400 MHz, $CDCl_3$

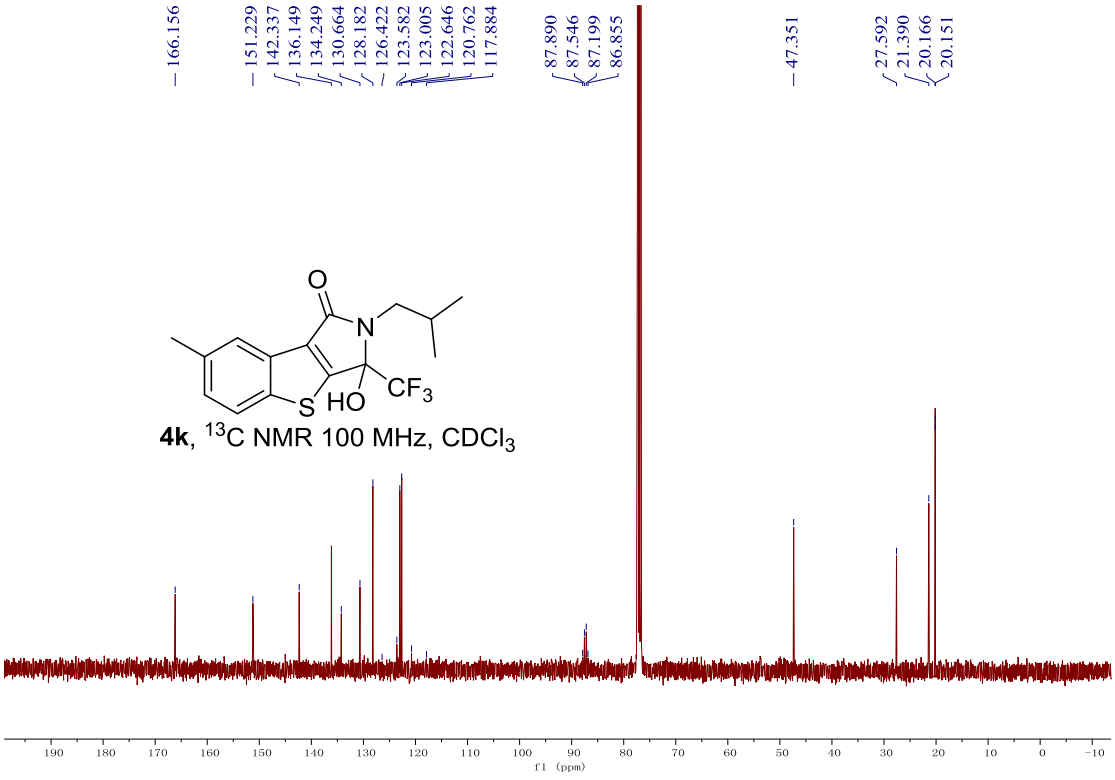


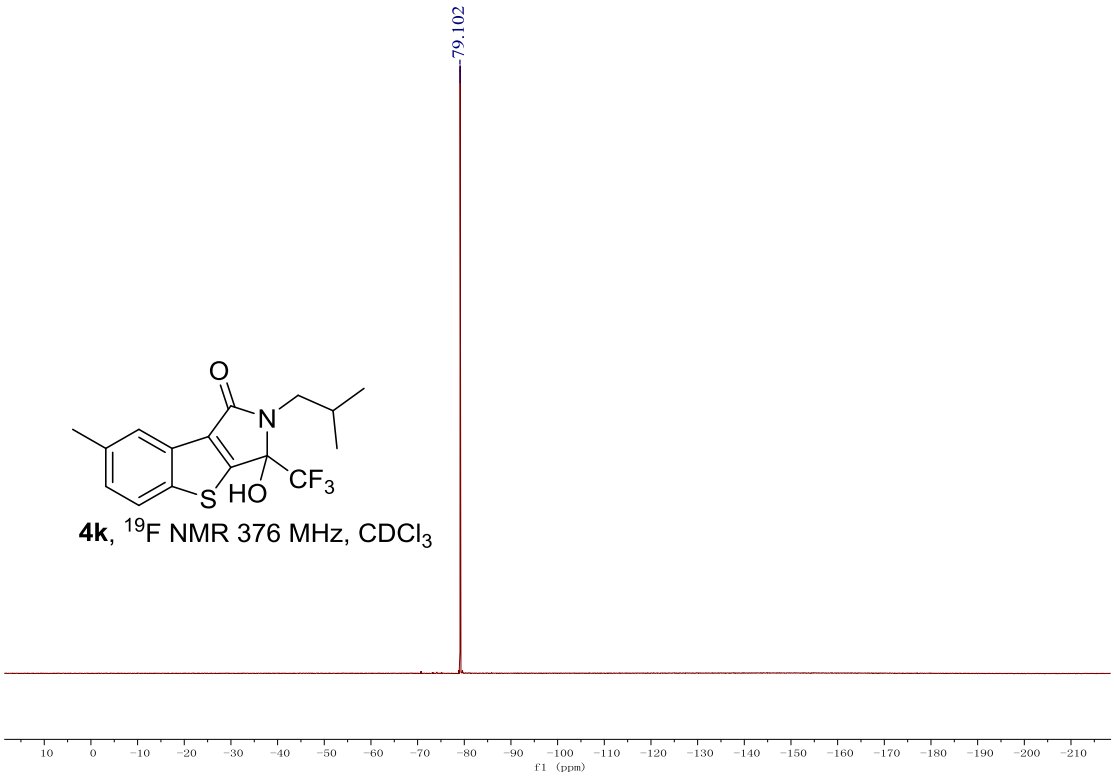

**4j**, $^{13}C$ NMR 100 MHz, $CDCl_3$



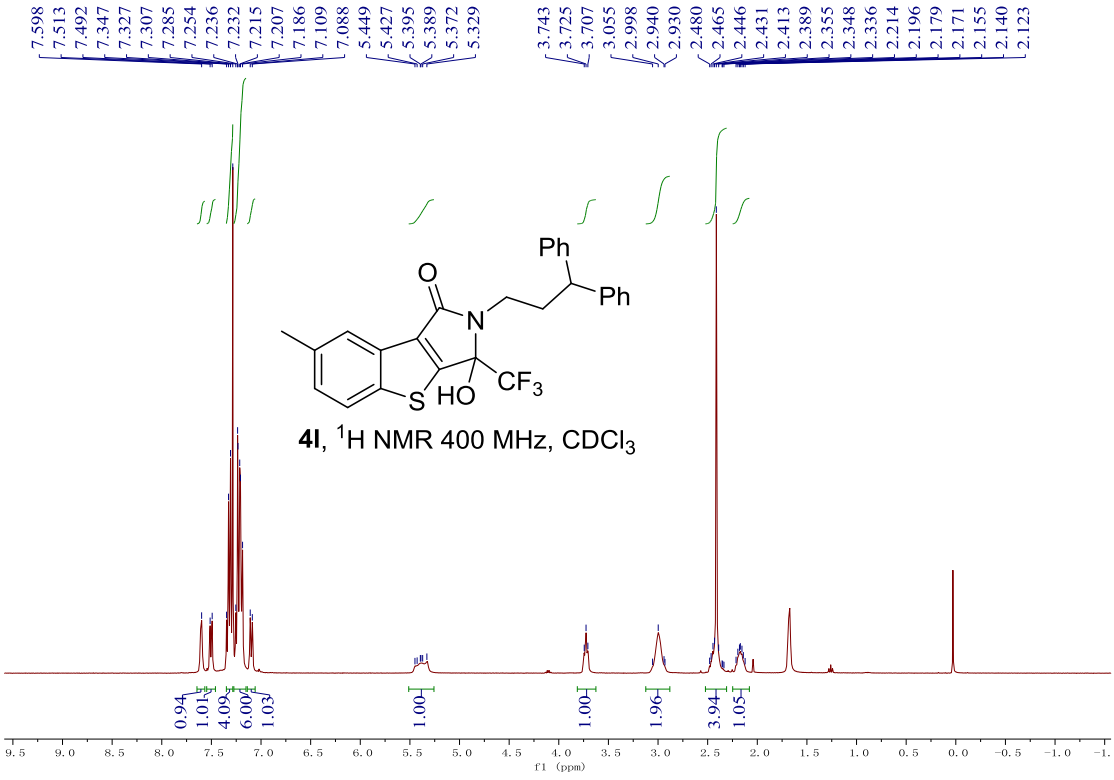

**4j**, $^{19}F$ NMR 376 MHz, $CDCl_3$


7.707
7.584
7.563
7.162
7.159
7.141
7.138
5.608
3.162
3.147
3.126
3.111
2.867
2.843
2.831
2.807
2.441
2.019
2.012
2.003
1.986
1.979
1.970
1.963
1.954
1.947
1.930
1.914
0.811
0.795
0.772
0.755
O
N
CF3
S
HO
4k, 1H NMR 400 MHz, CDCl3
1.01
0.95
0.97
1.01
1.00
0.99
3.00
1.10
2.92
2.96
f1 (ppm)

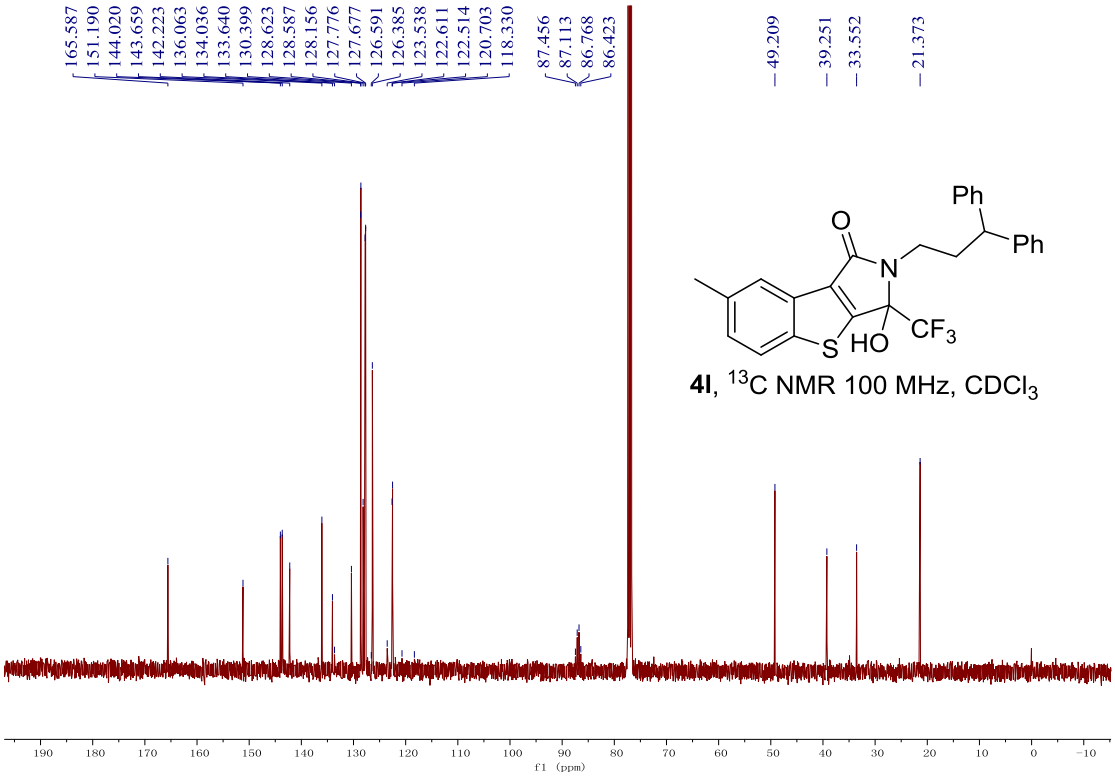

166.156
151.229
142.337
136.149
134.249
130.664
128.182
126.422
123.582
123.005
122.646
120.762
117.884
87.890
87.546
87.199
86.855
47.351
27.592
21.390
20.166
20.151
O
N
CF3
S
HO
4k, 13C NMR 100 MHz, CDCl3
f1 (ppm)



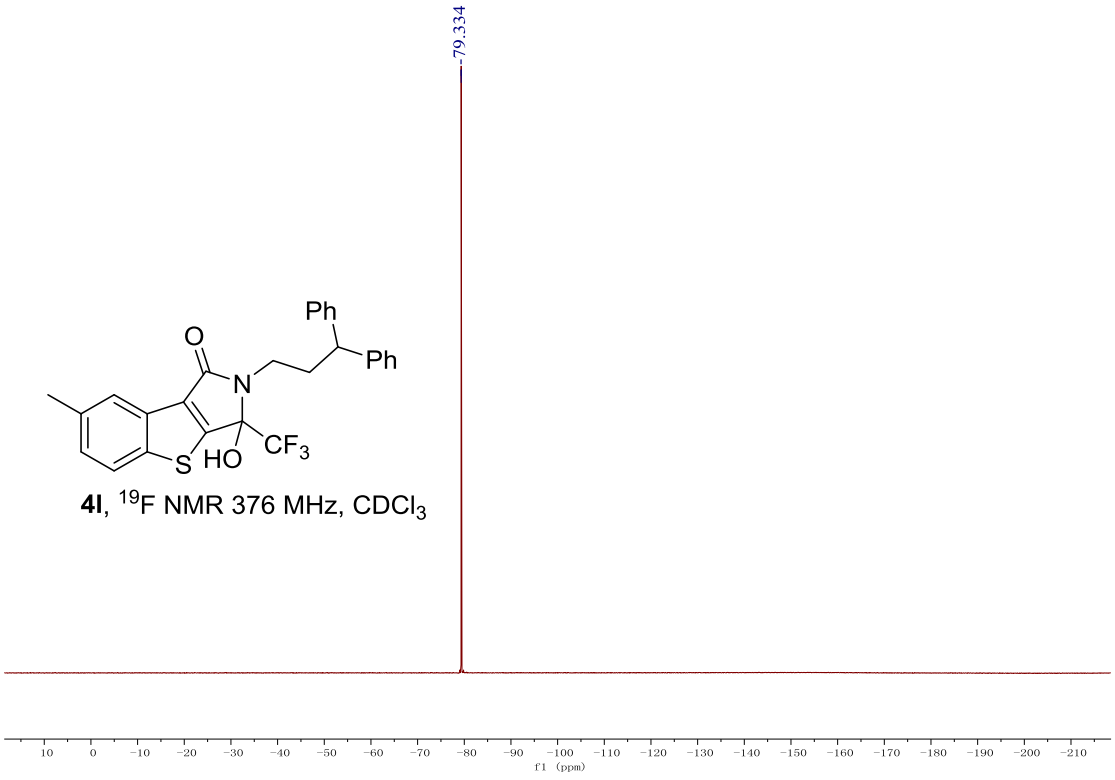

**4k**, $^{19}F$ NMR 376 MHz, $CDCl_3$




**4l**, $^{1}H$ NMR 400 MHz, $CDCl_3$



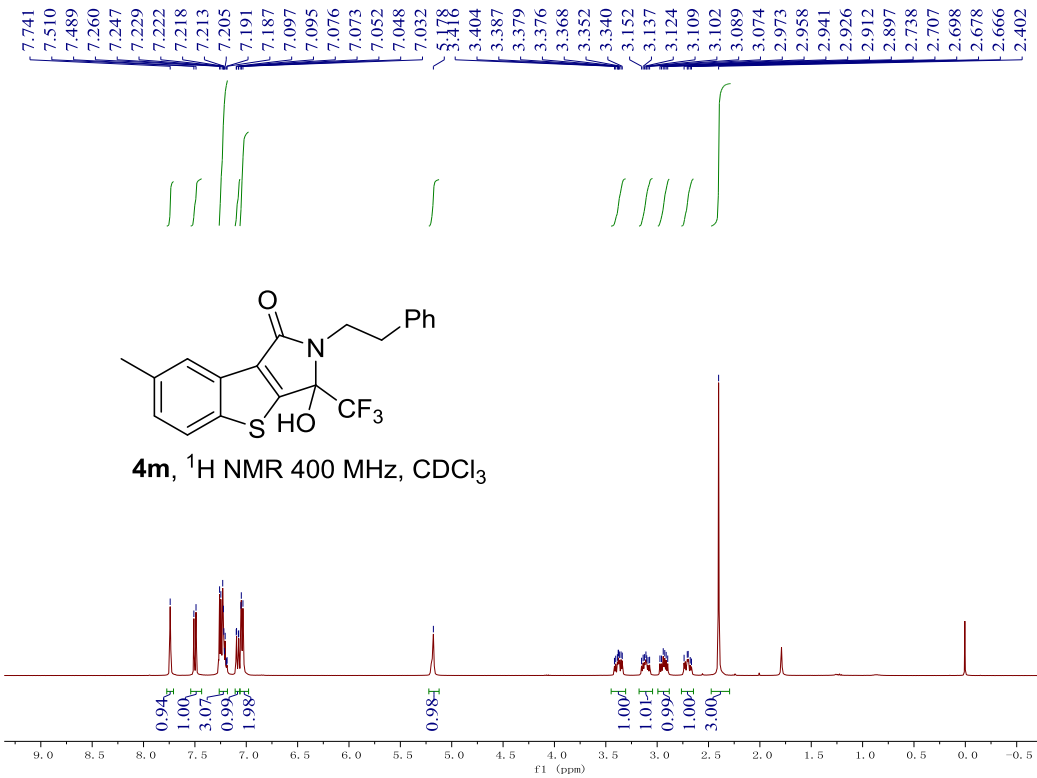

**4l**, $^{13}C$ NMR 100 MHz, $CDCl_3$



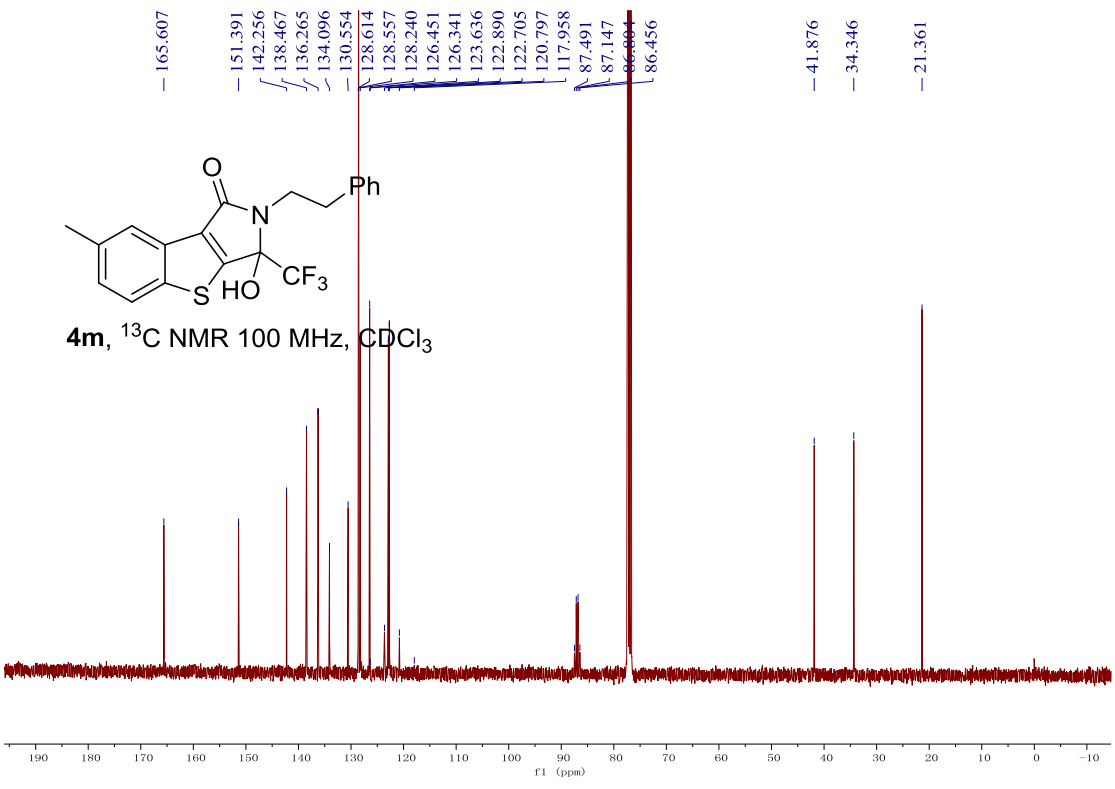




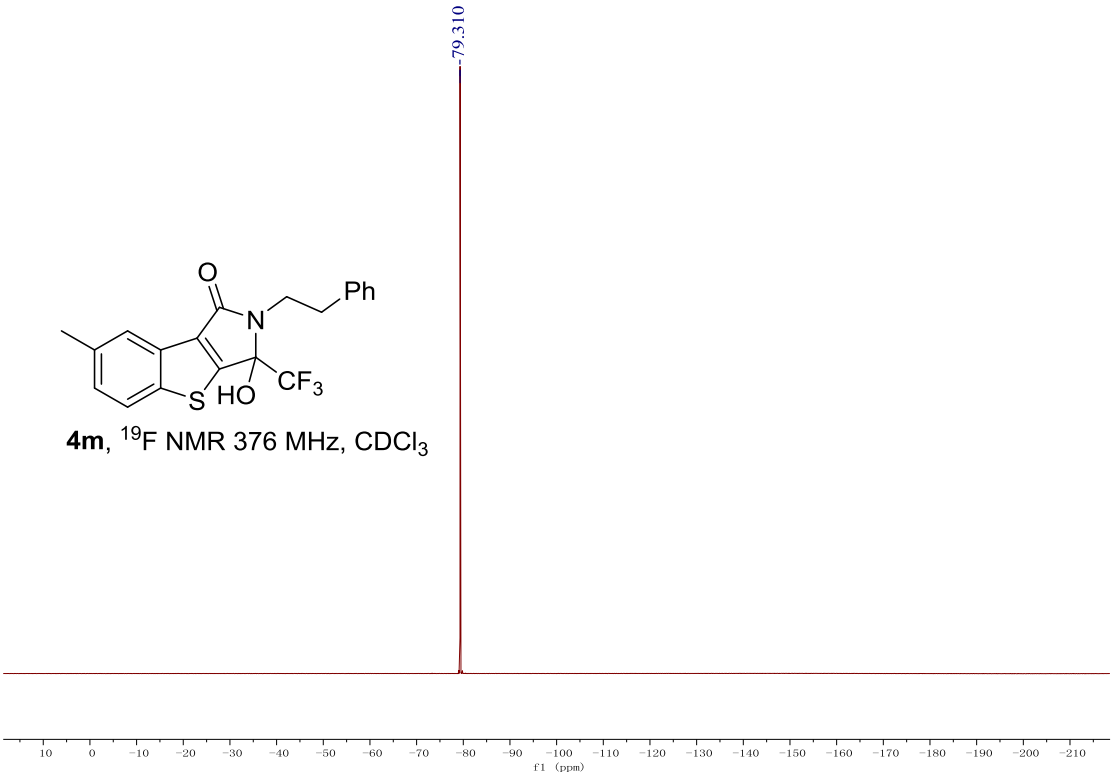
**4l**, $^{19}F$ NMR 376 MHz, $CDCl_3$



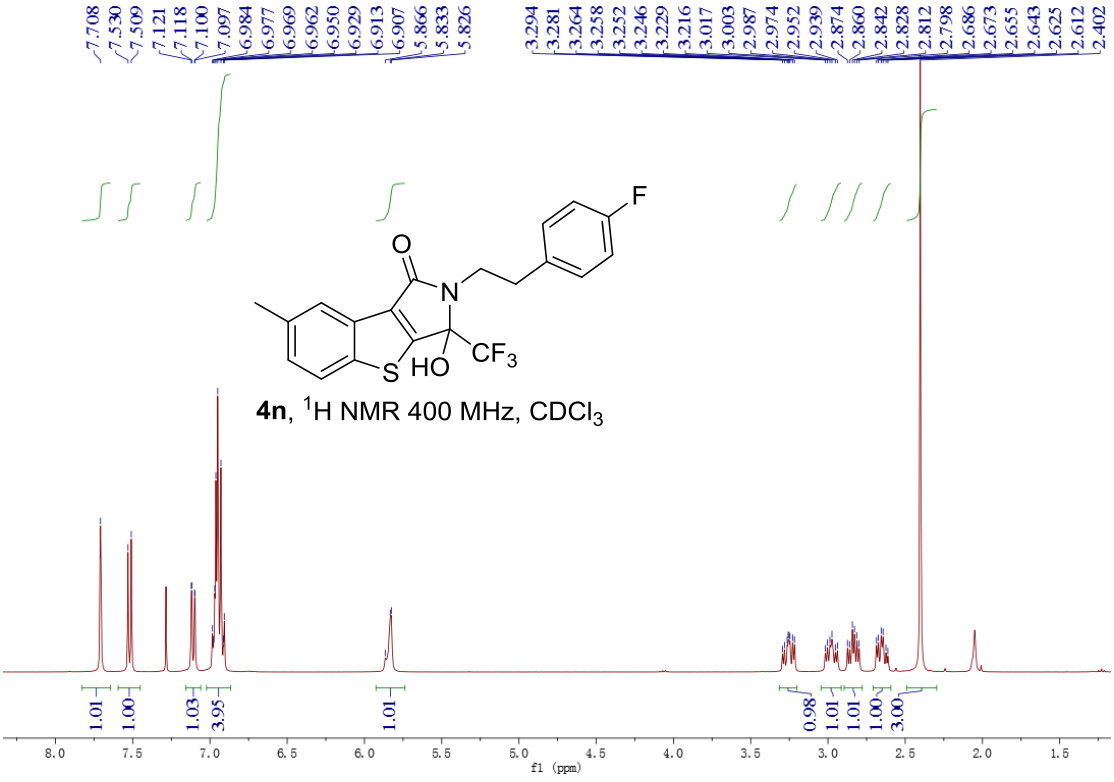

**4m**, $^{1}$H NMR 400 MHz, $CDCl_3$



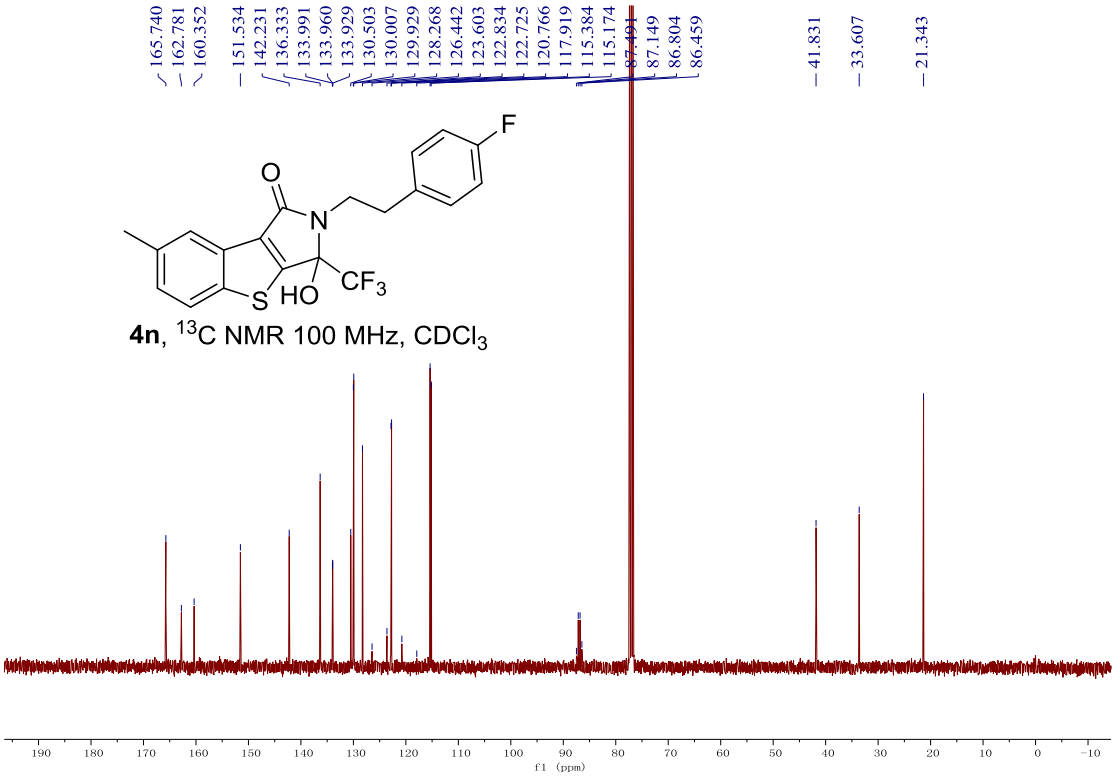

**4m**, $^{13}$C NMR 100 MHz, $CDCl_3$



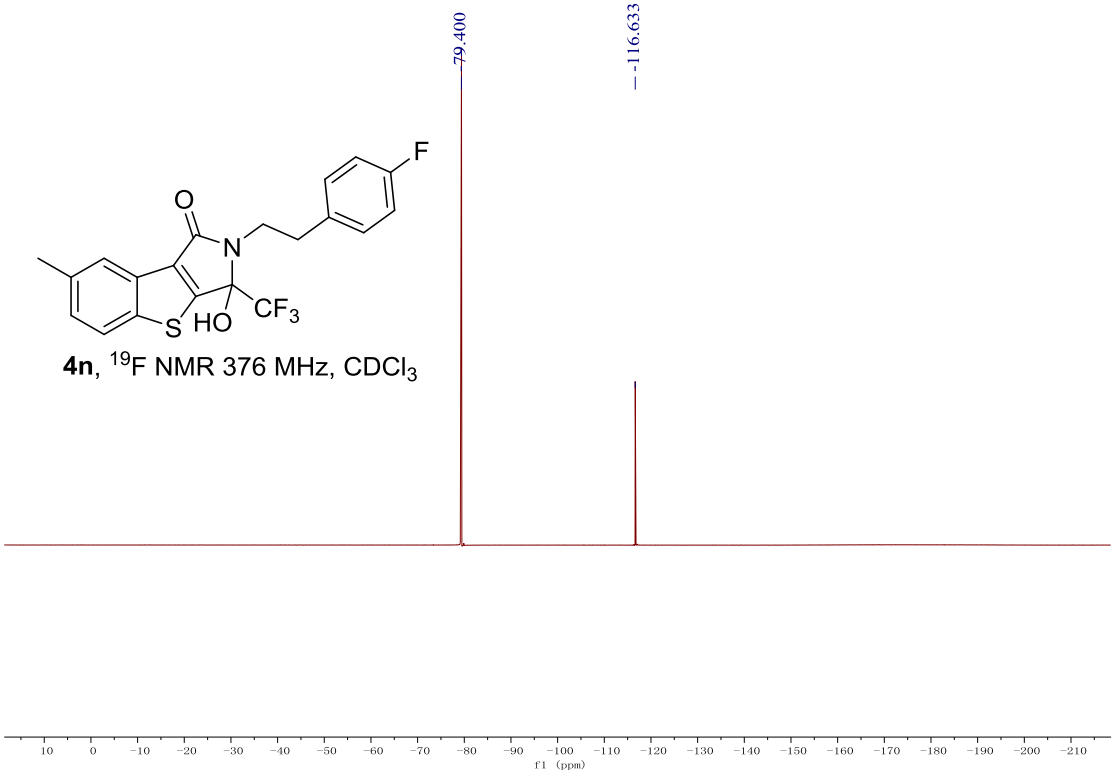

**4m**, $^{19}F$ NMR 376 MHz, $CDCl_3$



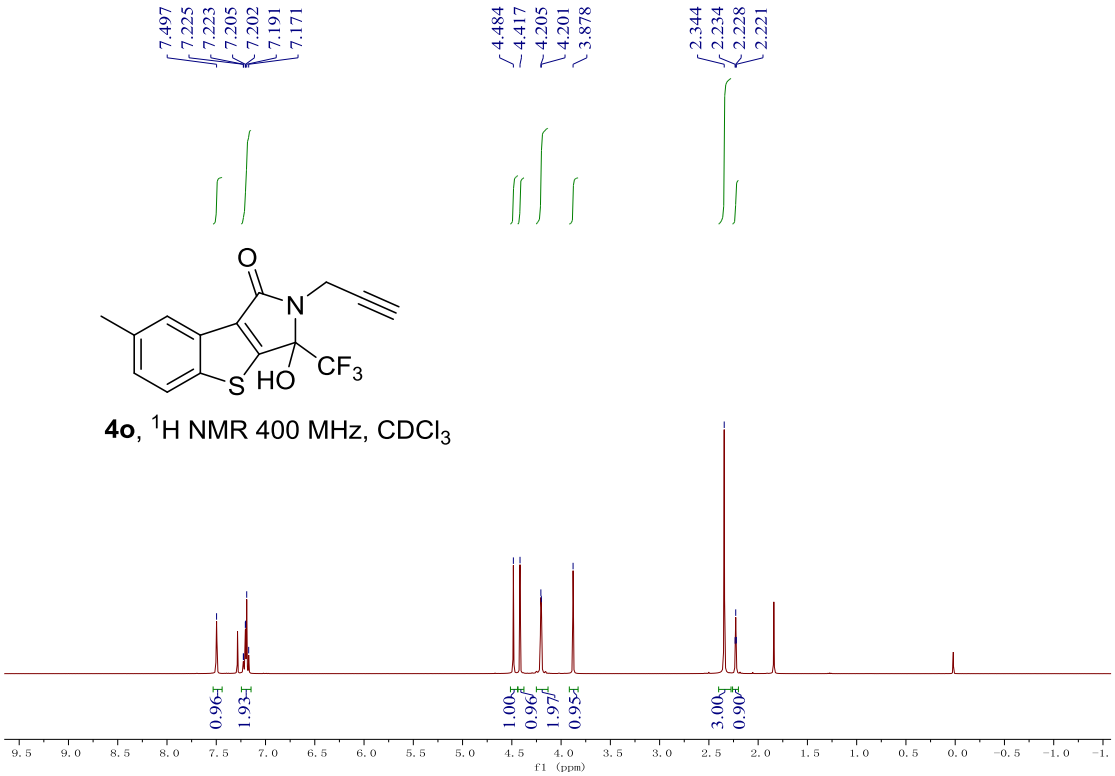

**4n**, $^{1}H$ NMR 400 MHz, $CDCl_3$



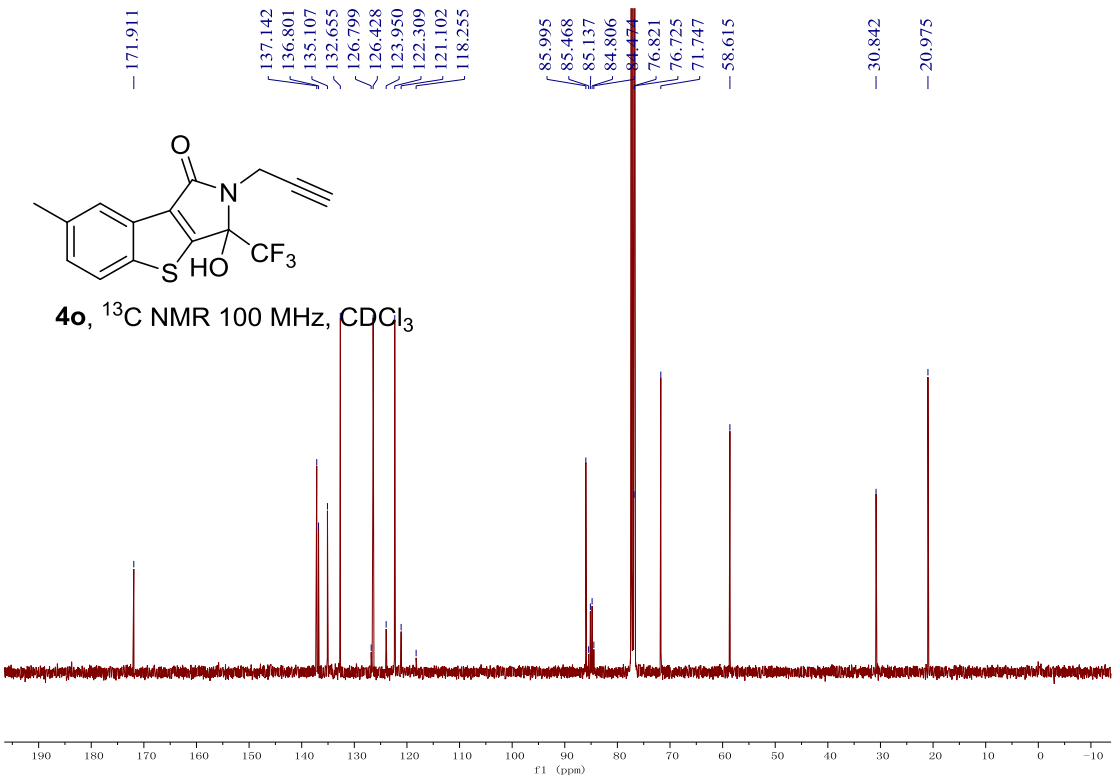

**4n**, $^{13}C$ NMR 100 MHz, $CDCl_3$



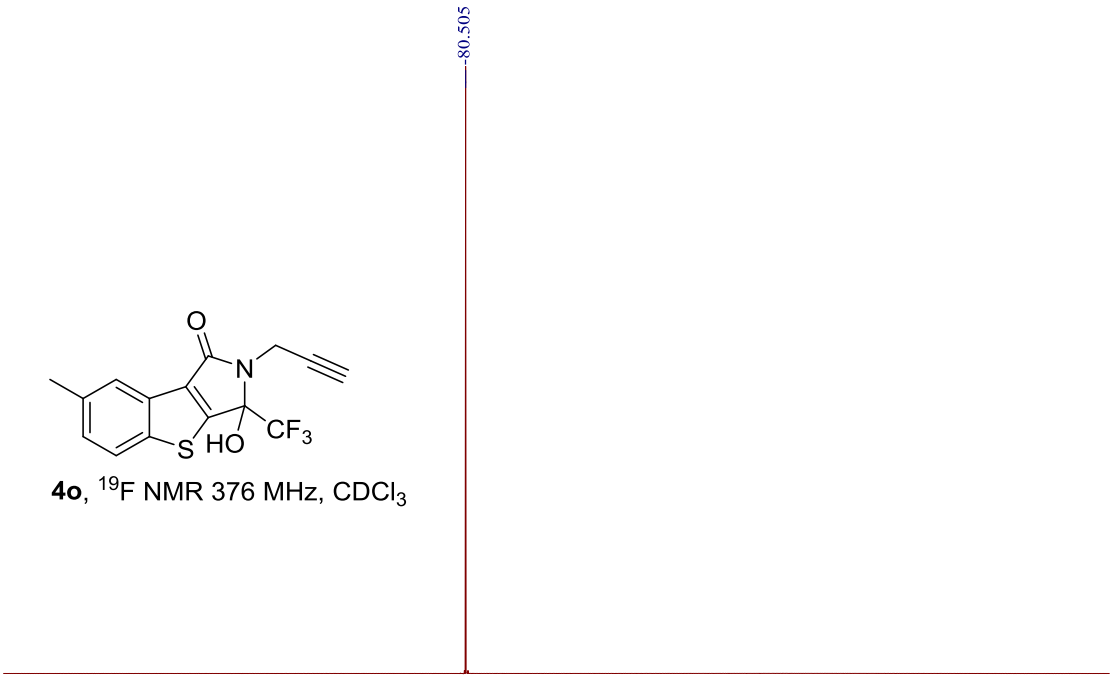

**4n**, $^{19}F$ NMR 376 MHz, $CDCl_3$



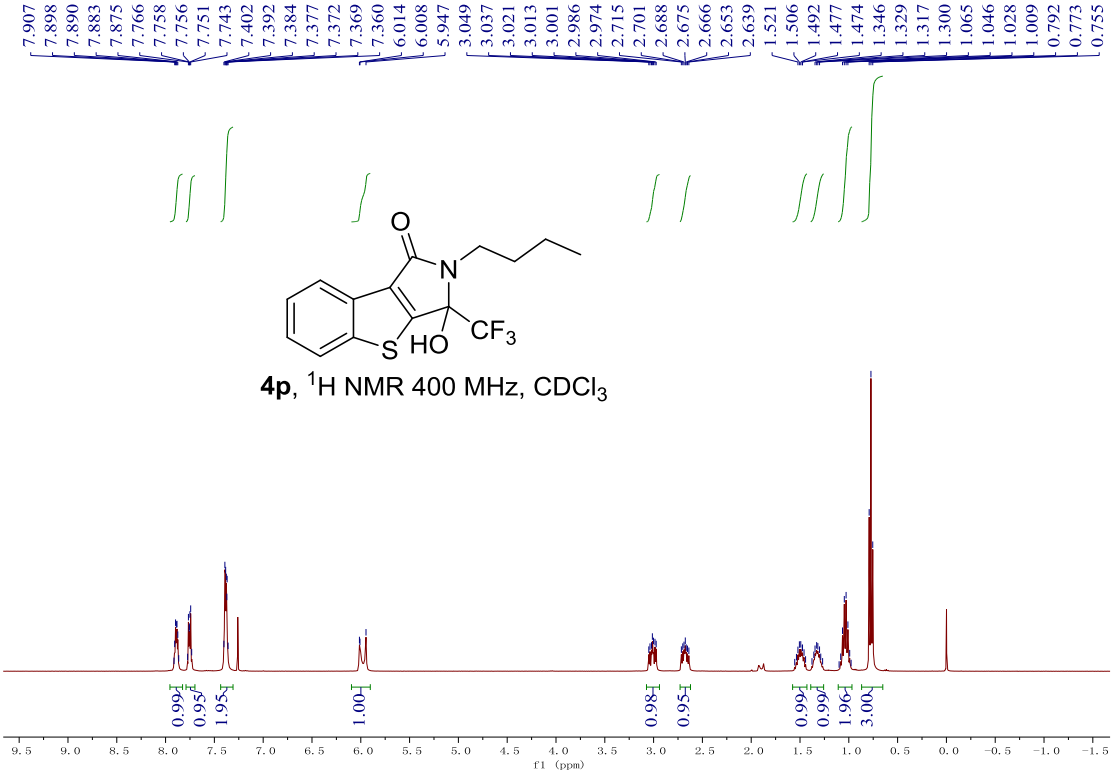

**4o**, $^{1}$H NMR 400 MHz, $CDCl_3$



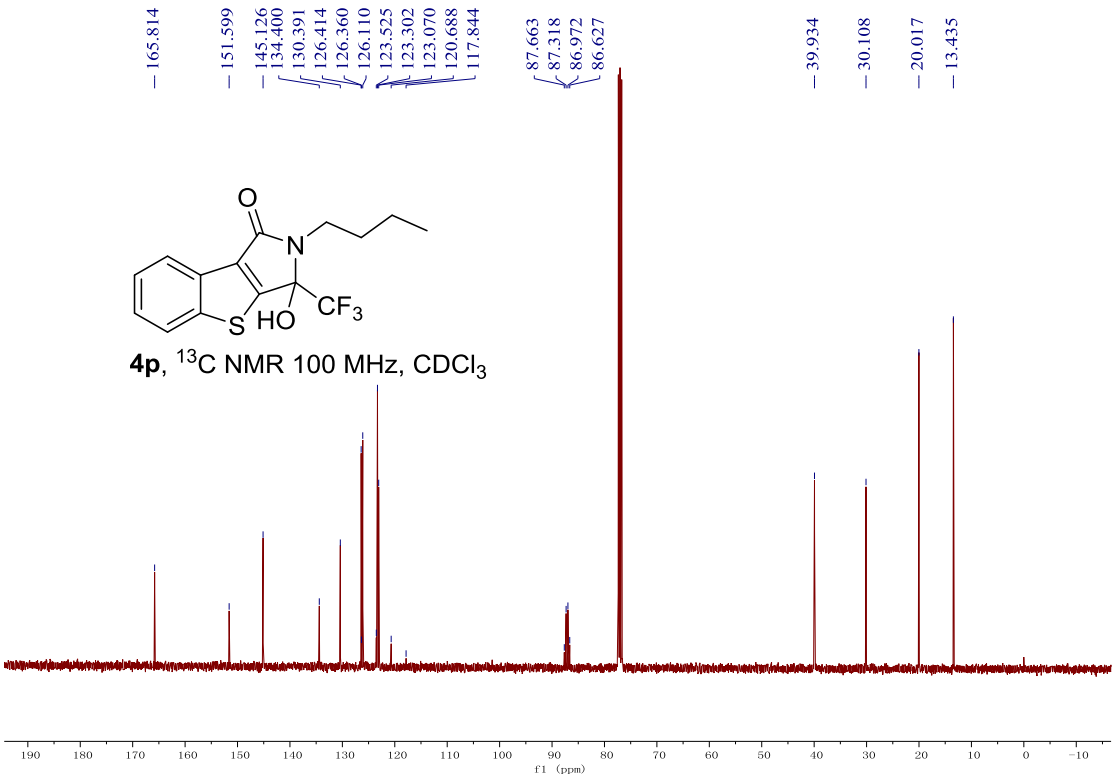

**4o**, $^{13}$C NMR 100 MHz, $CDCl_3$



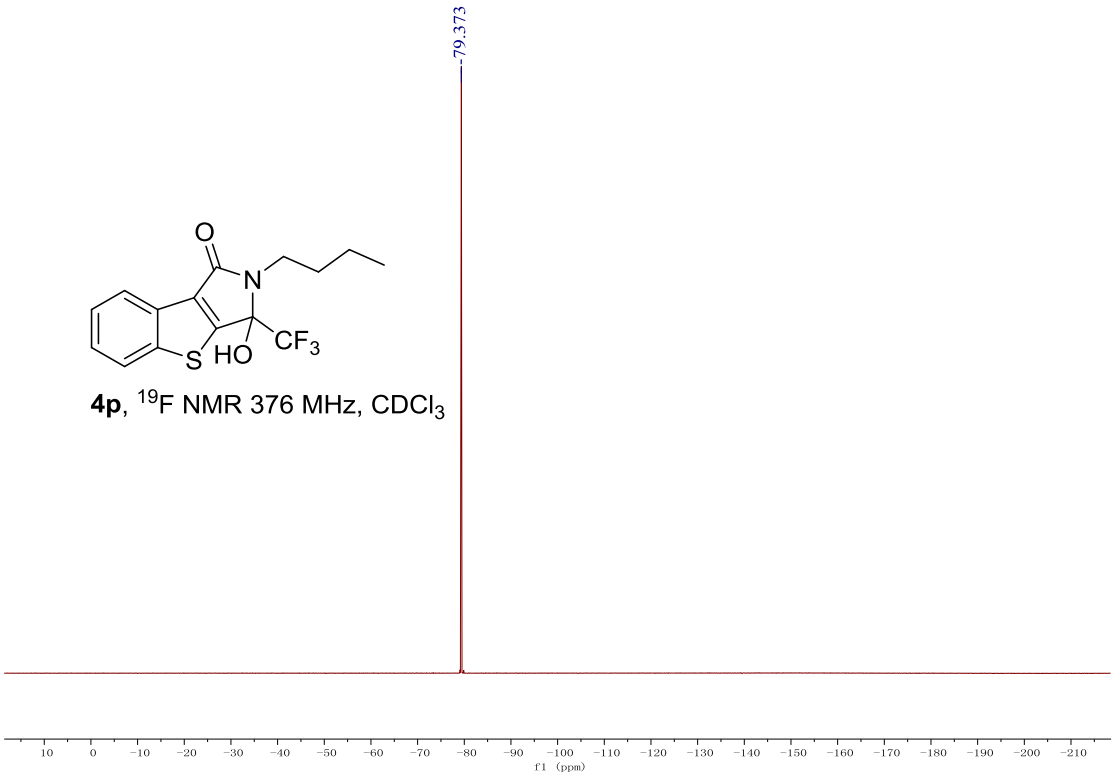

**4o**, $^{19}F$ NMR 376 MHz, $CDCl_3$



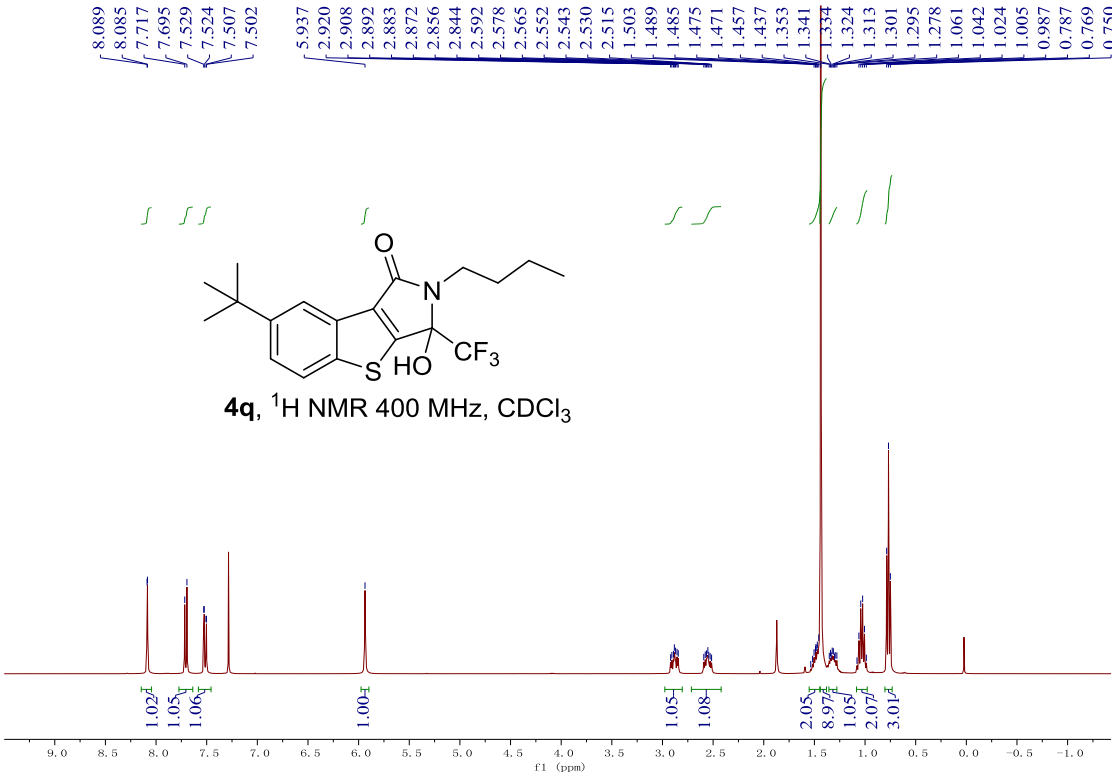

**4p**, $^{1}H$ NMR 400 MHz, $CDCl_3$



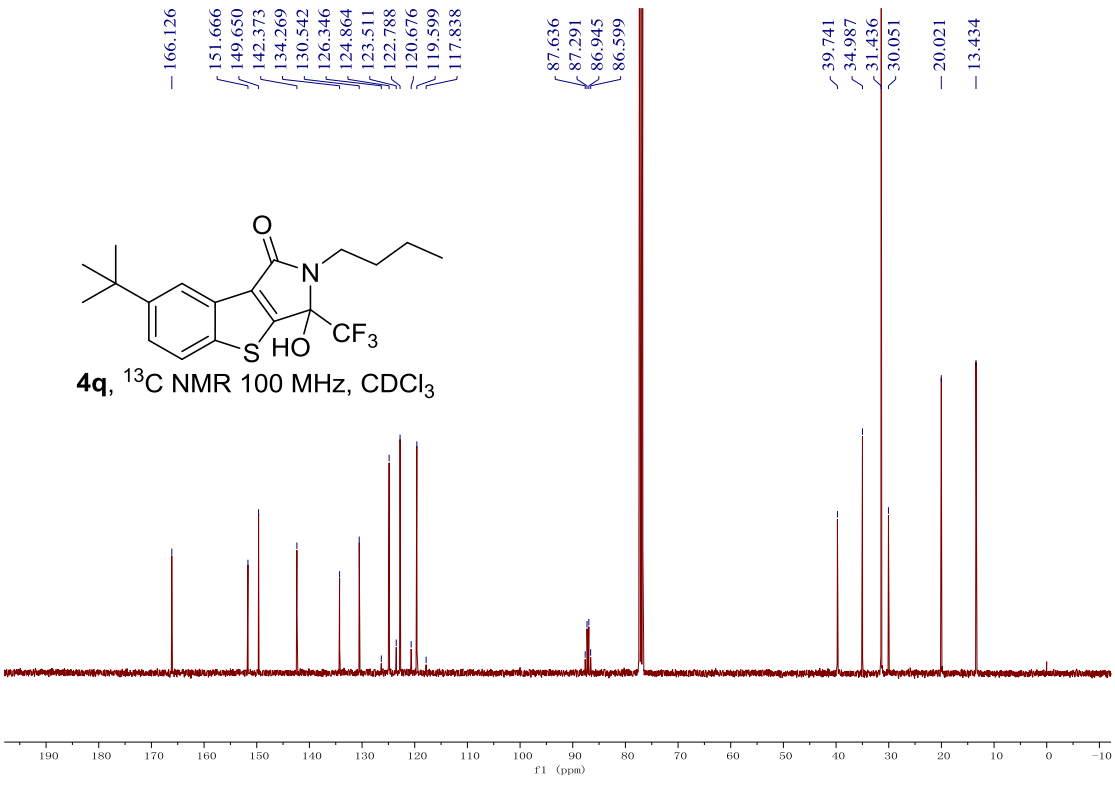

**4p**, $^{13}C$ NMR 100 MHz, $CDCl_3$



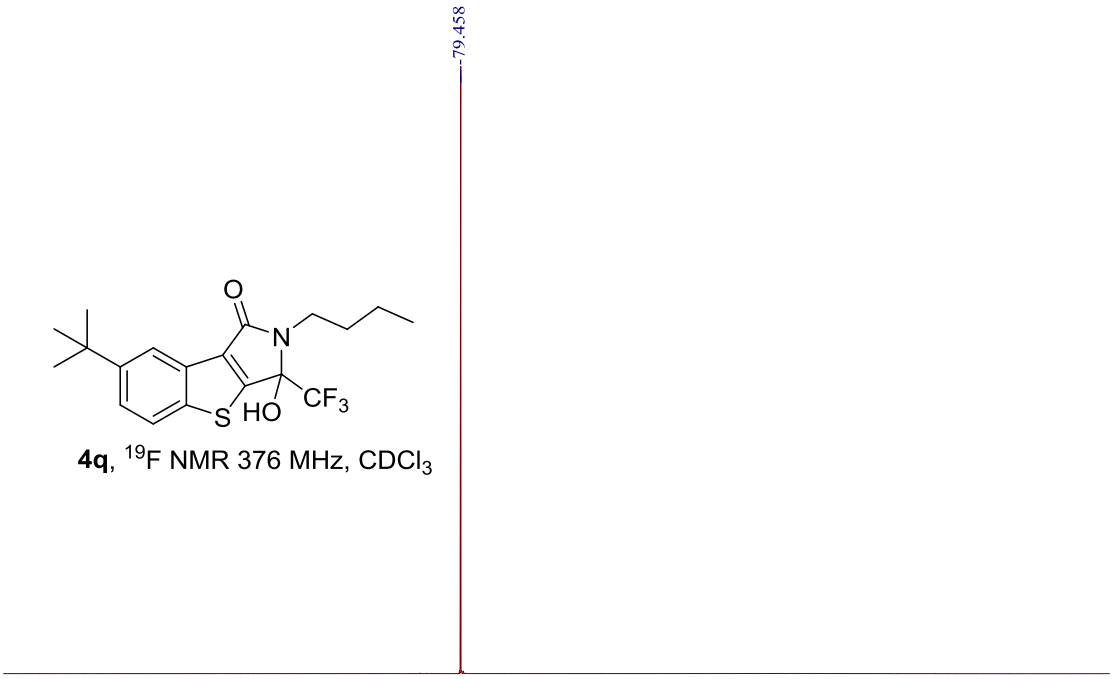

**4p**, $^{19}F$ NMR 376 MHz, $CDCl_3$




**4q**, $^{1}$H NMR 400 MHz, $CDCl_3$



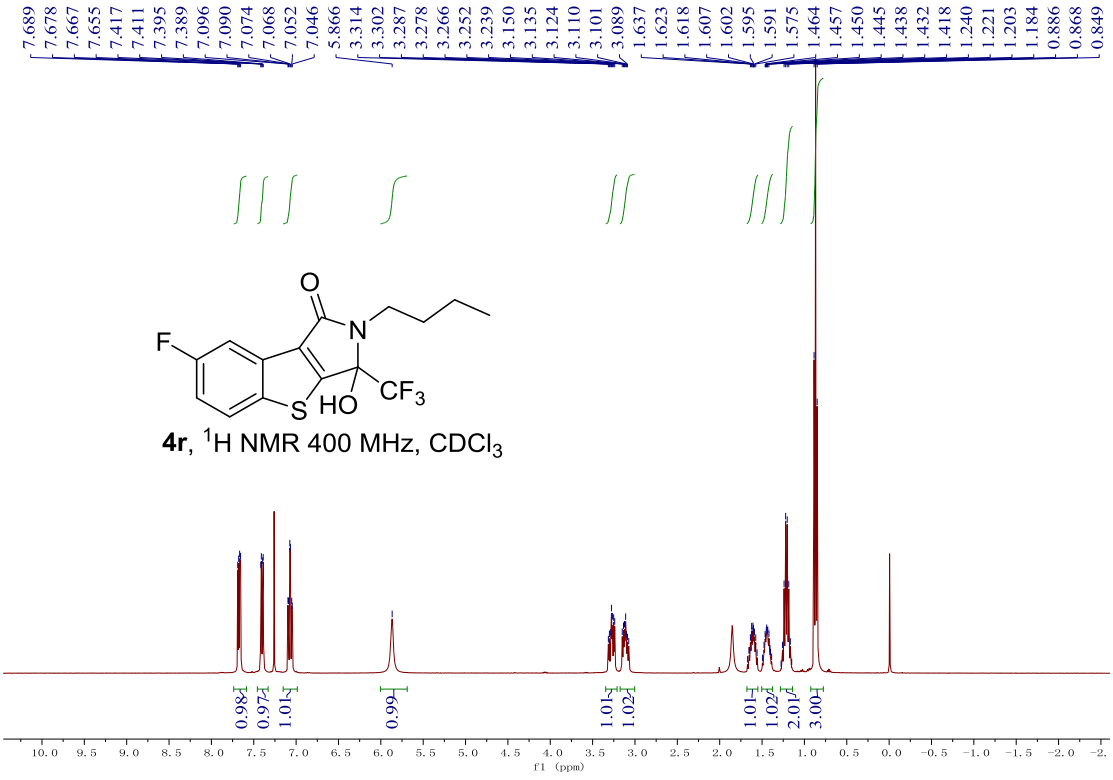

**4q**, $^{13}$C NMR 100 MHz, $CDCl_3$







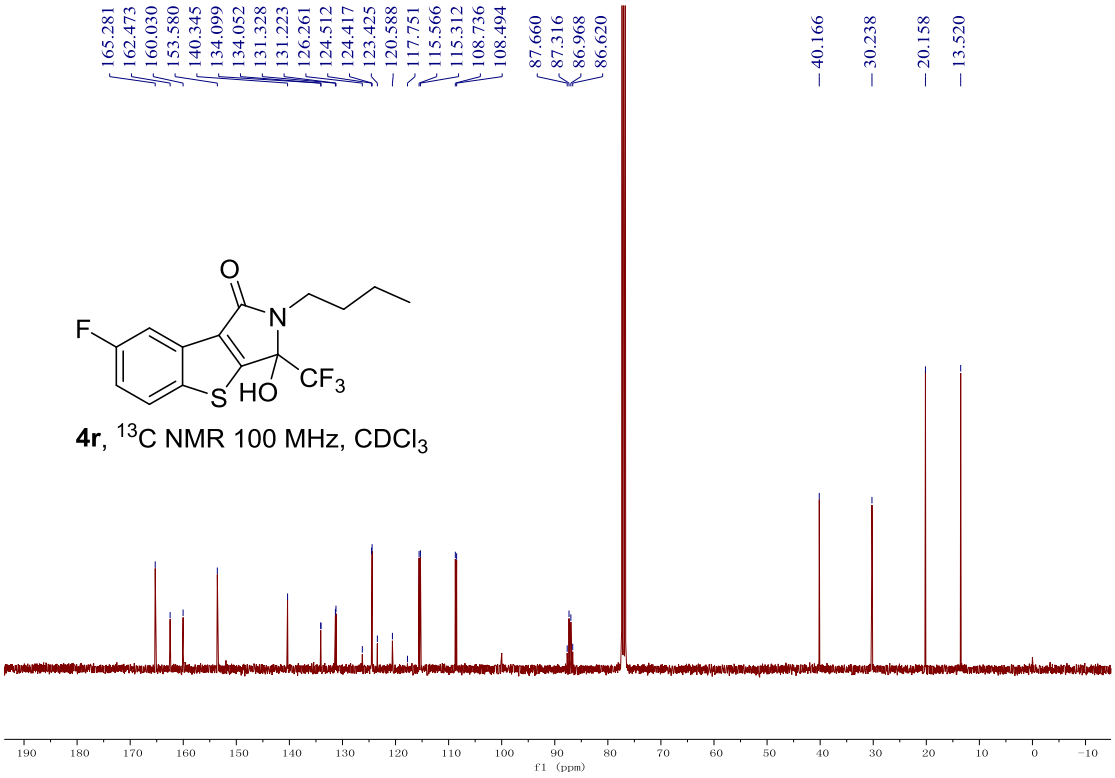
**4q**, $^{19}F$ NMR 376 MHz, $CDCl_3$



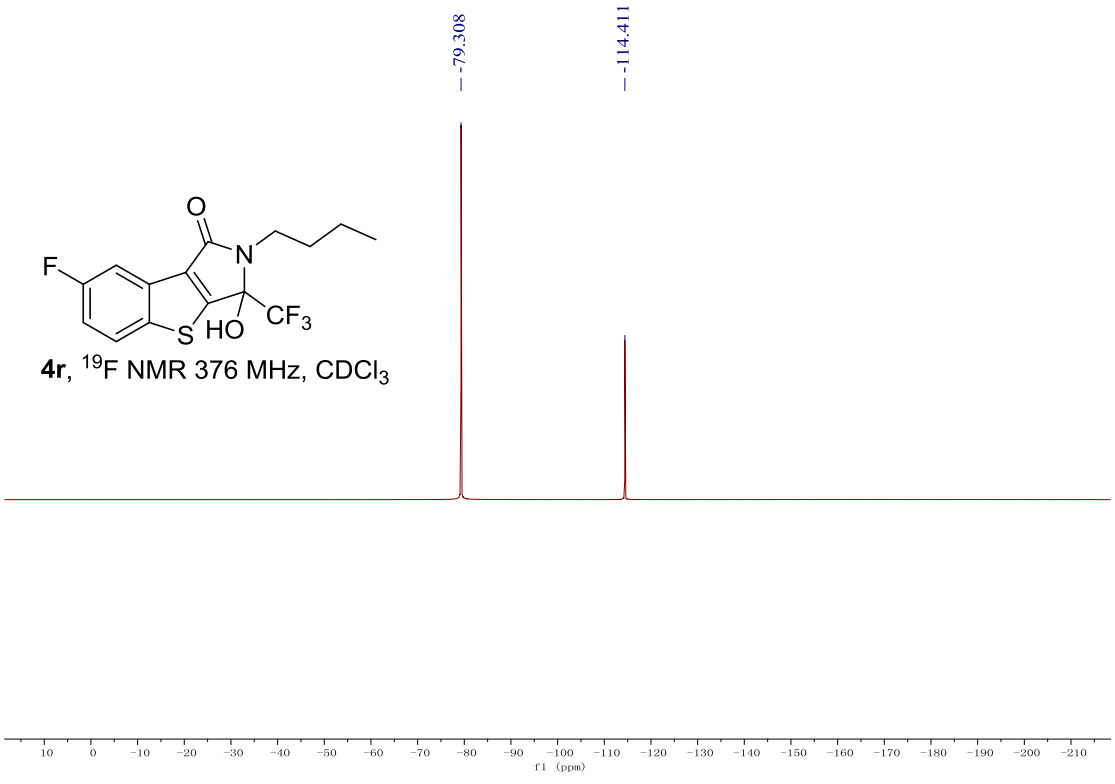




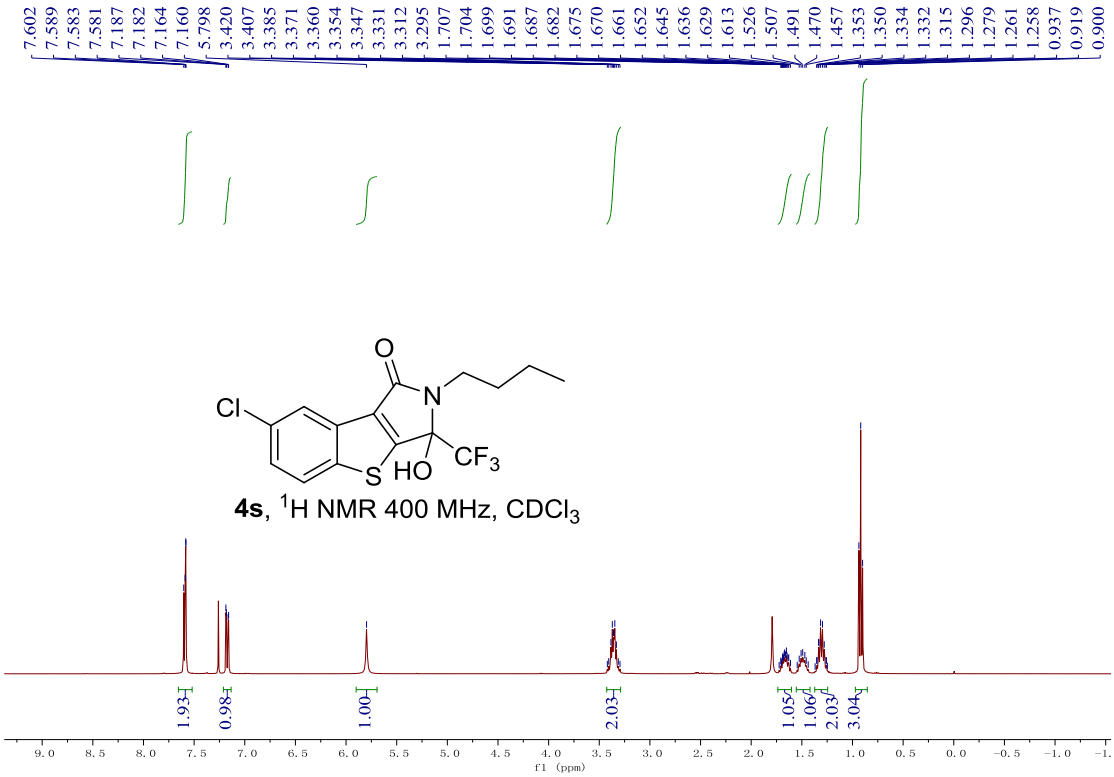
**4r**, $^{1}H$ NMR 400 MHz, $CDCl_3$




**4r**, $^{13}C$ NMR 100 MHz, $CDCl_3$




**4r**, $^{19}F$ NMR 376 MHz, $CDCl_3$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7.160
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3.371
3.360
3.354
3.347
3.331
3.312
3.295
1.707
1.704
1.699
1.691
1.687
1.682
1.675
1.670
1.661
1.652
1.645
1.636
1.629
1.613
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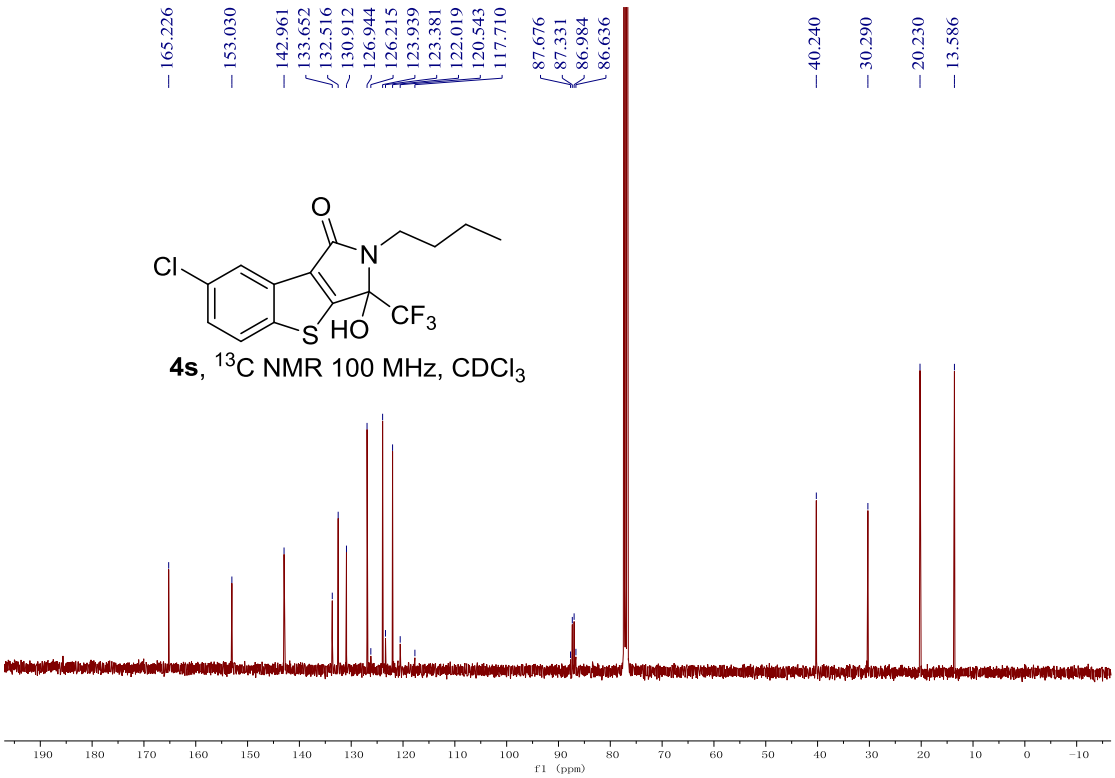
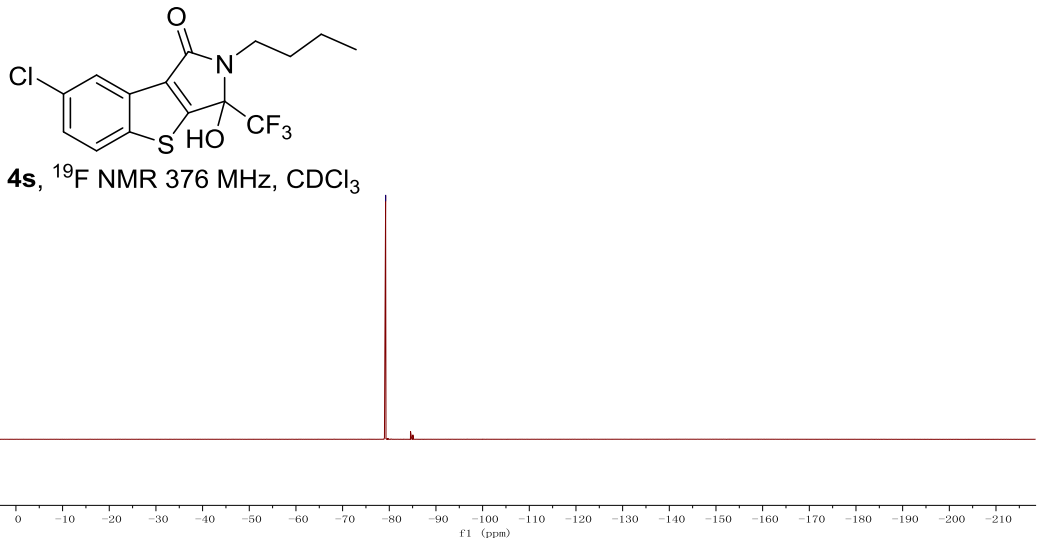
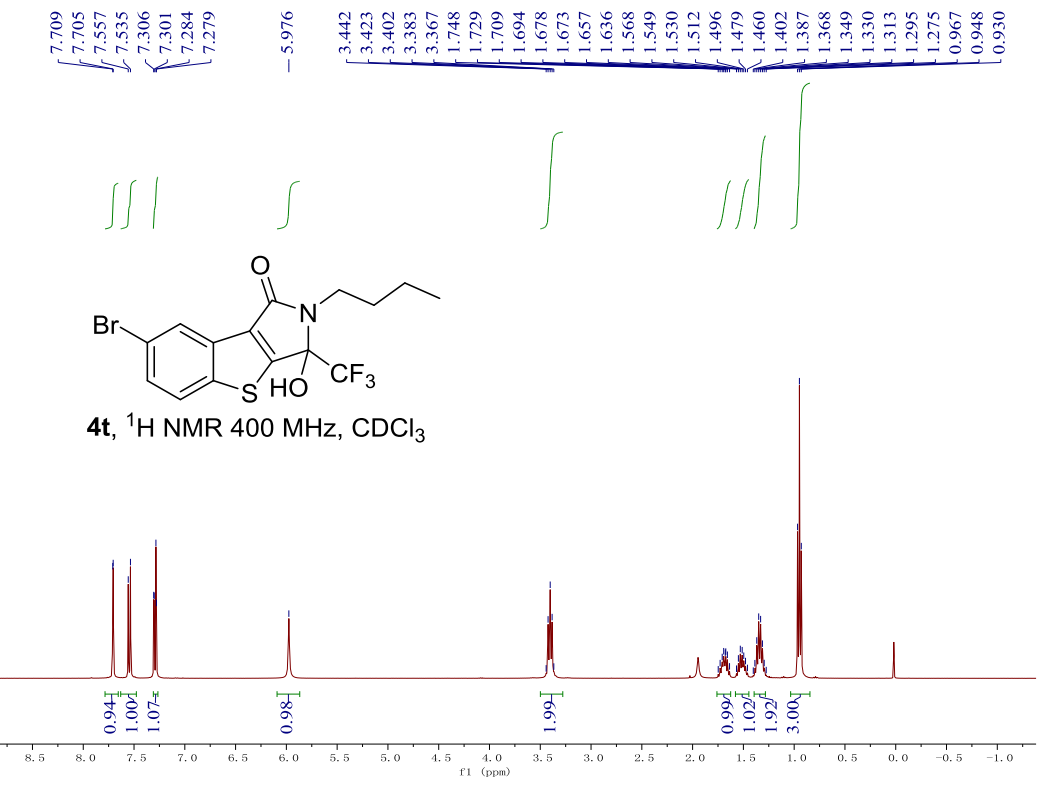
1.457
1.353
1.350
1.334
1.332
1.315
1.296
1.279
1.261
1.258
0.937
0.919
0.900
O
N
Cl
S
HO
CF3
4s, 1H NMR 400 MHz, CDCl3
1.93
0.98
1.00
2.03
1.05
1.06
2.03
3.04
f1 (ppm)

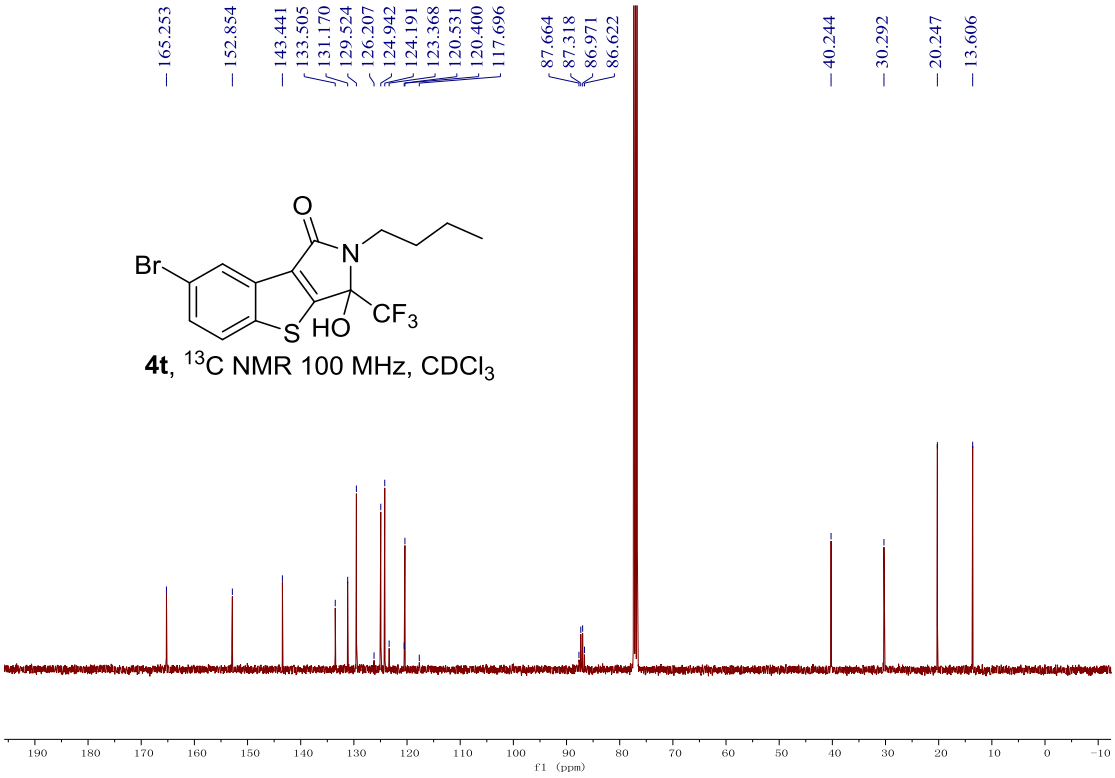

165.226
153.030
142.961
133.652
132.516
130.912
126.944
126.215
123.939
123.381
122.019
120.543
117.710
87.676
87.331
86.984
86.636
40.240
30.290
20.230
13.586
O
N
Cl
S
HO
CF3
4s, 13C NMR 100 MHz, CDCl3
f1 (ppm)



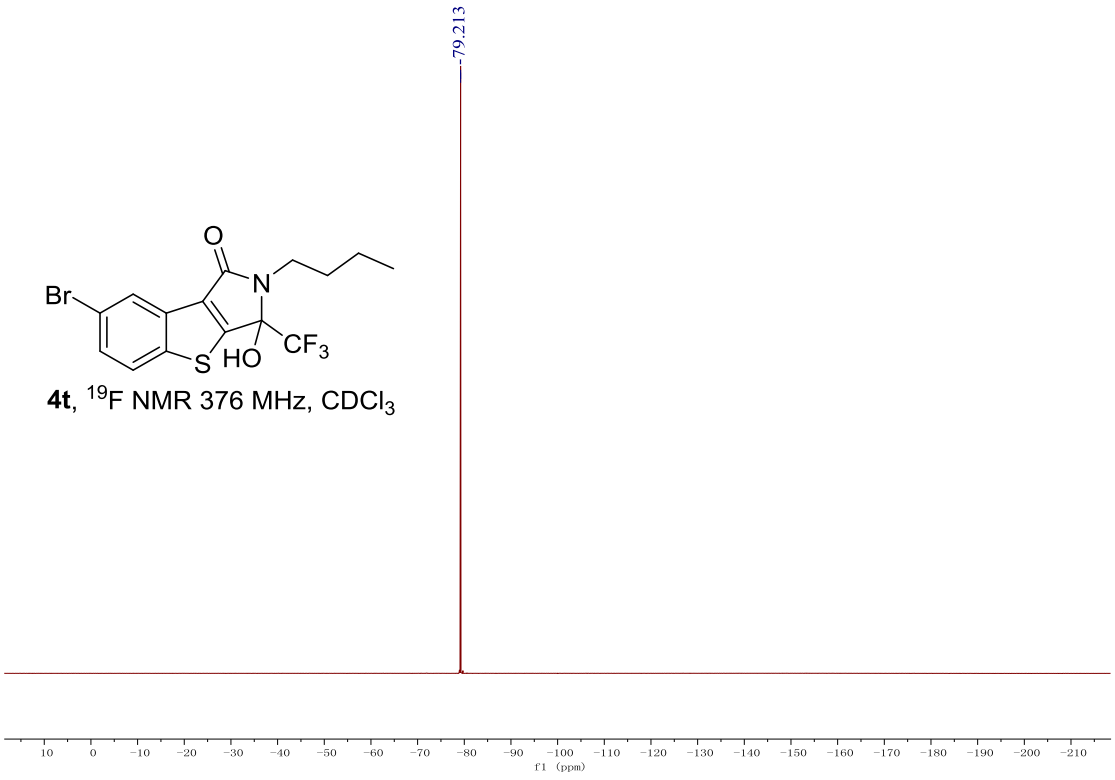

**4s**, $^{19}F$ NMR 376 MHz, $CDCl_3$



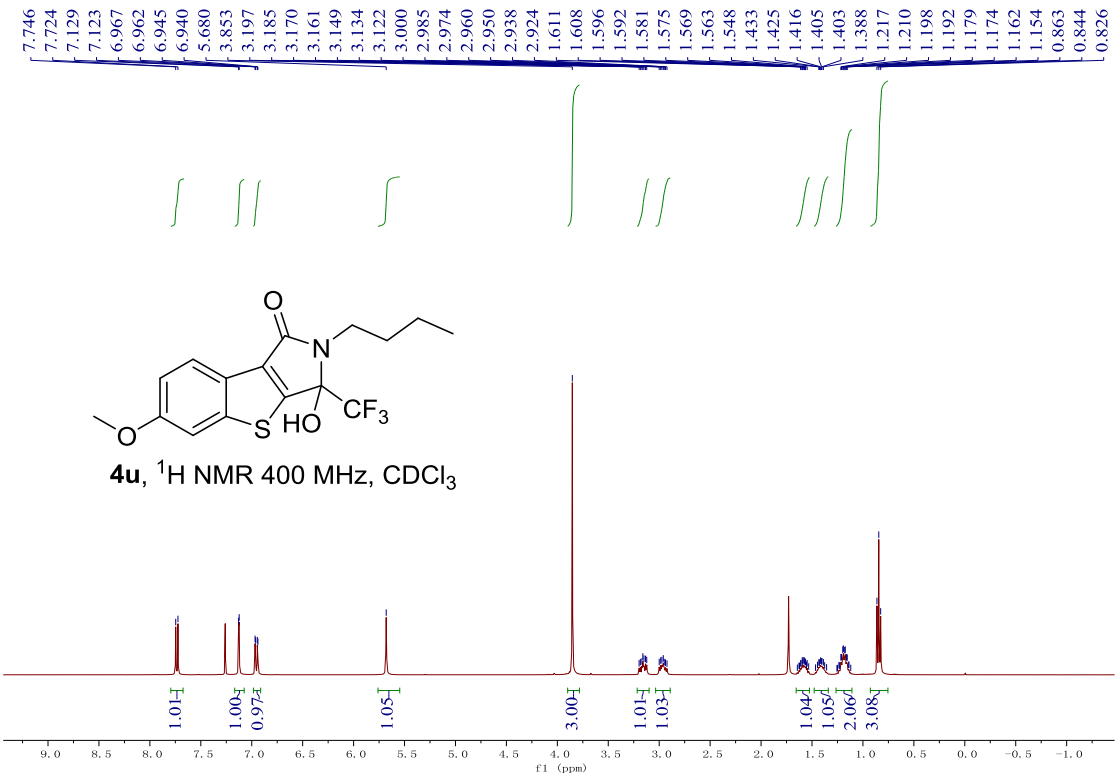

**4t**, $^{1}H$ NMR 400 MHz, $CDCl_3$



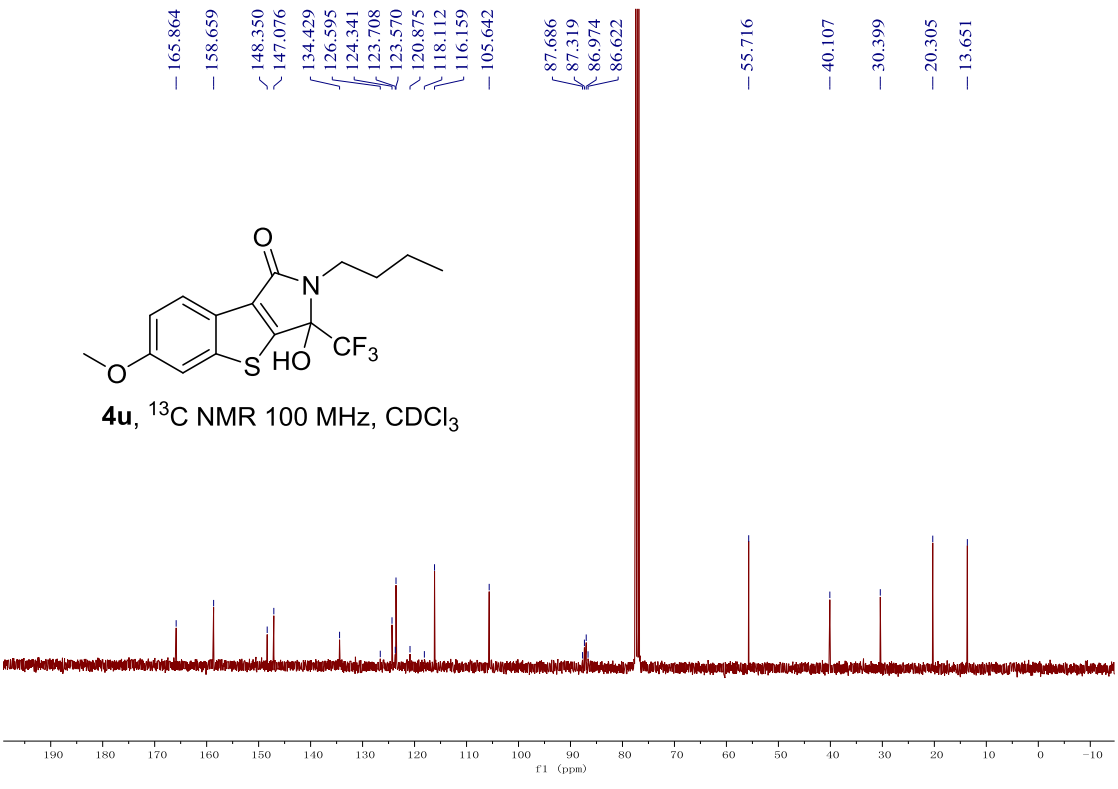

**4t**, $^{13}C$ NMR 100 MHz, $CDCl_3$




**4t**, $^{19}F$ NMR 376 MHz, $CDCl_3$

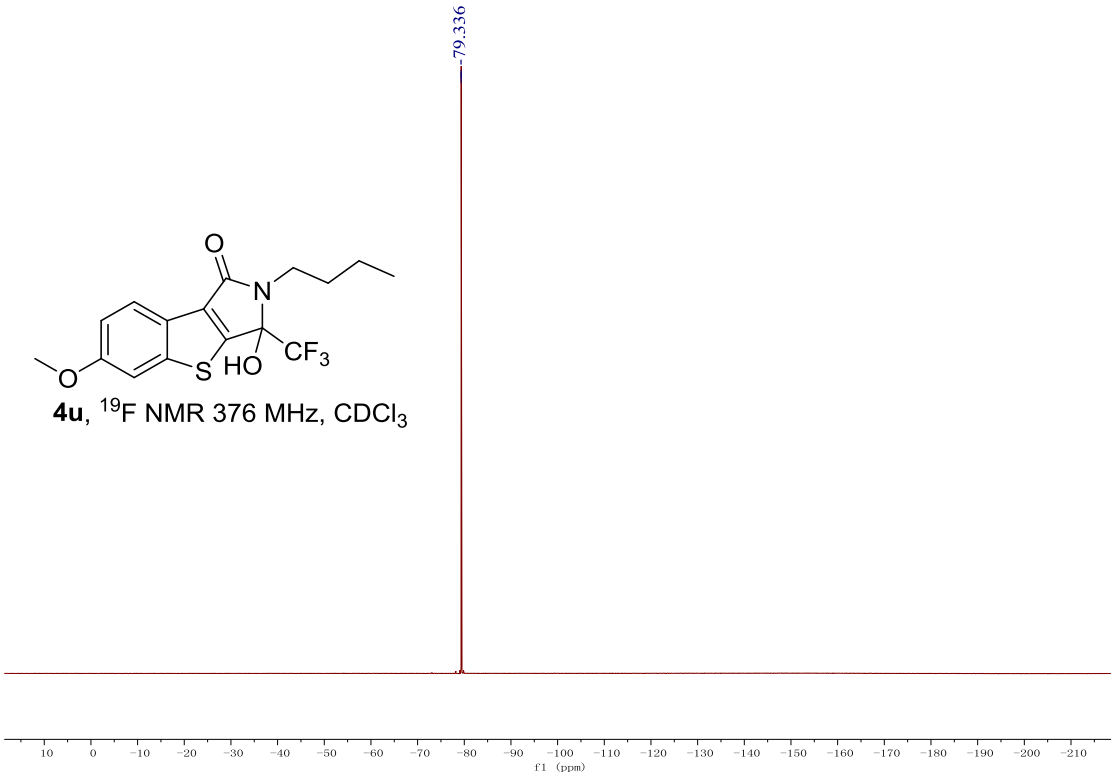


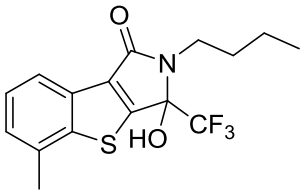

**4u**, $^{1}$H NMR 400 MHz, $CDCl_3$



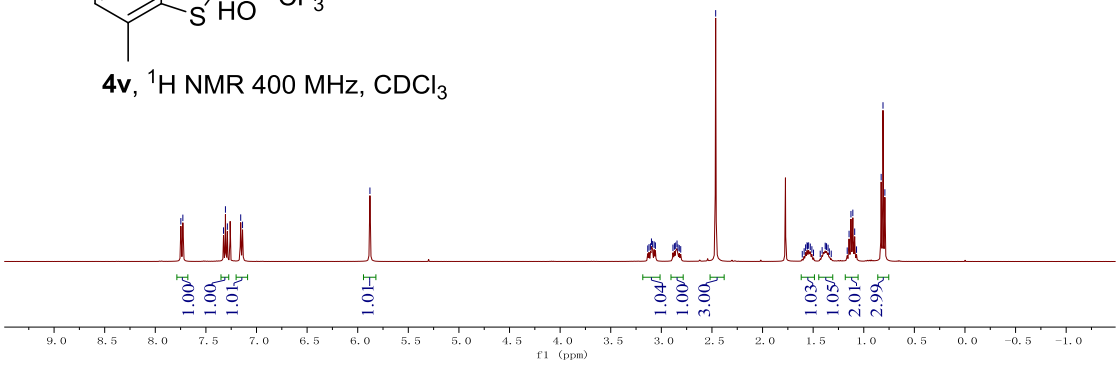

**4u**, $^{13}$C NMR 100 MHz, $CDCl_3$

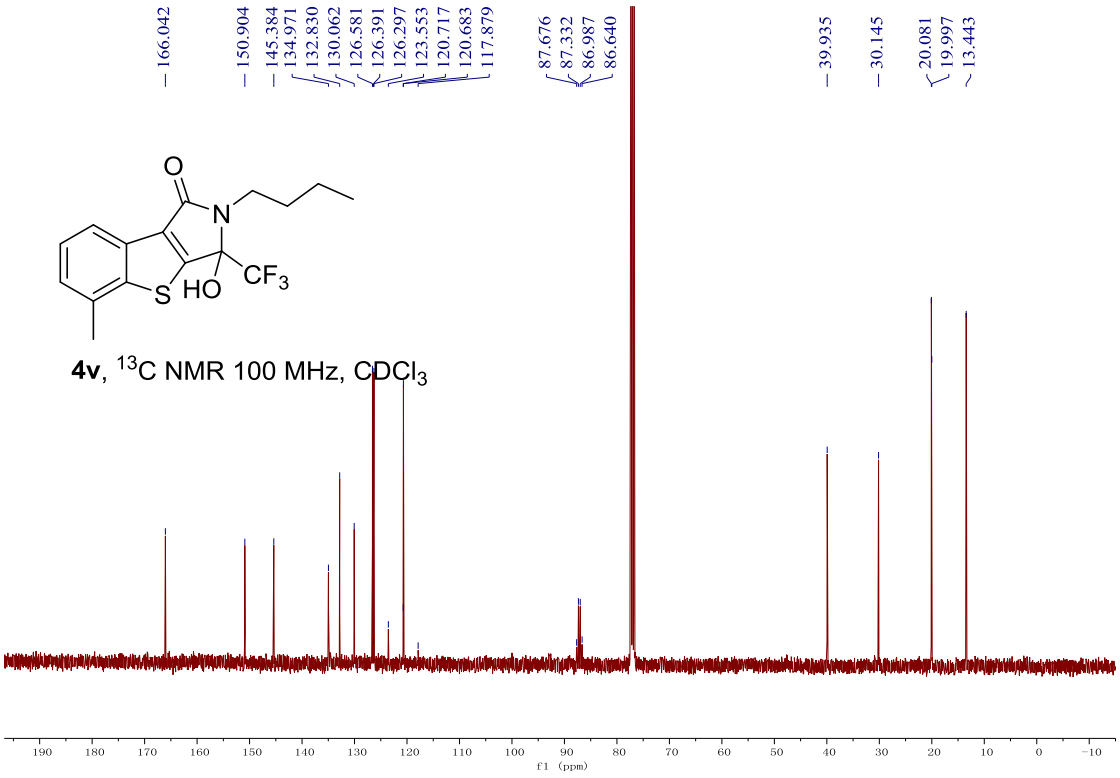
**4u**, $^{19}F$ NMR 376 MHz, $CDCl_3$



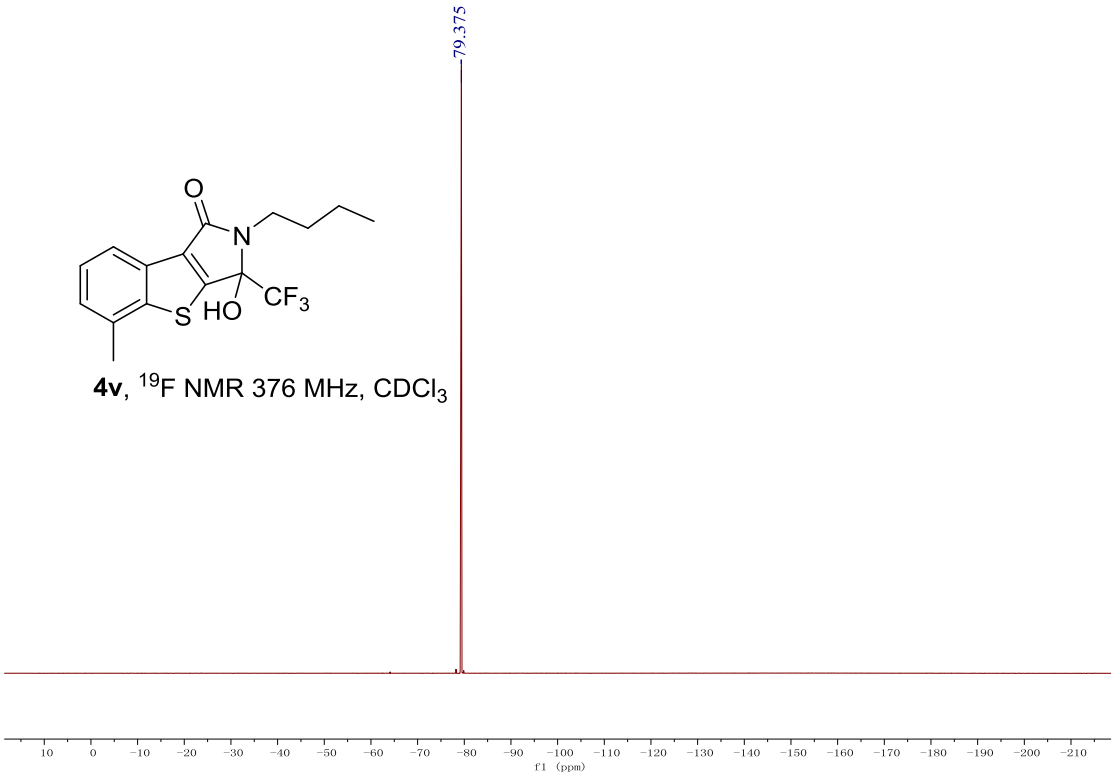




**4v**, $^{1}H$ NMR 400 MHz, $CDCl_3$

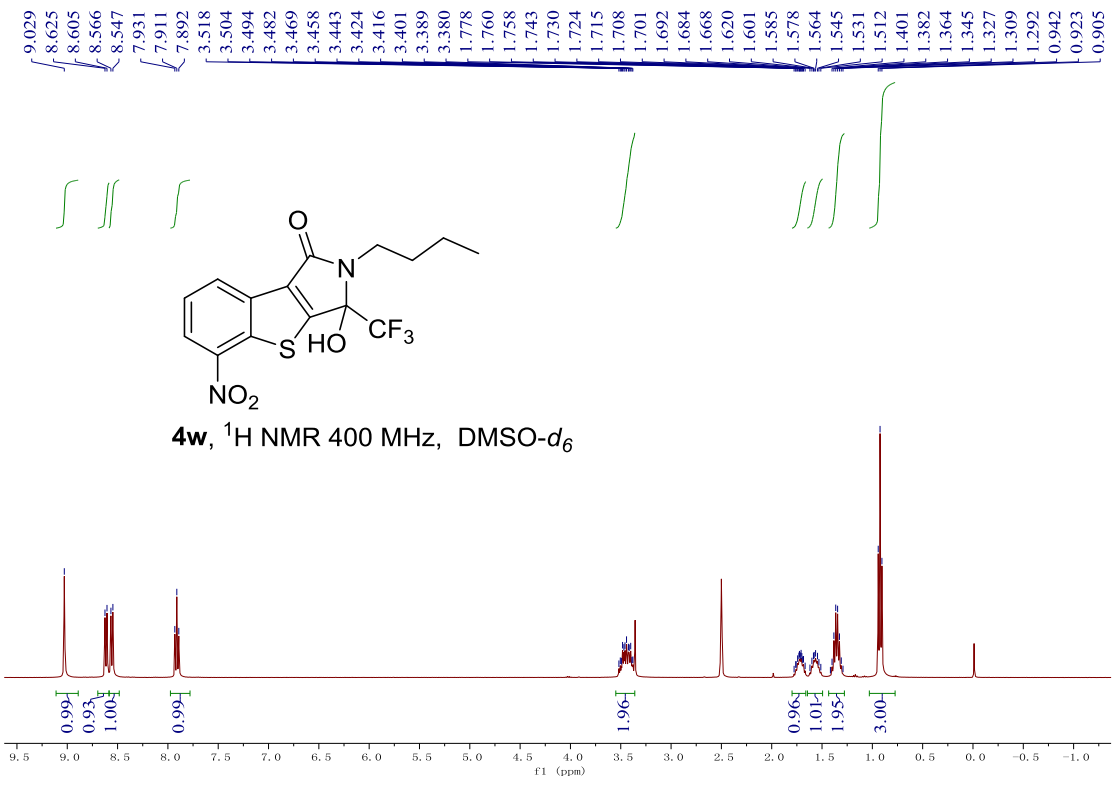




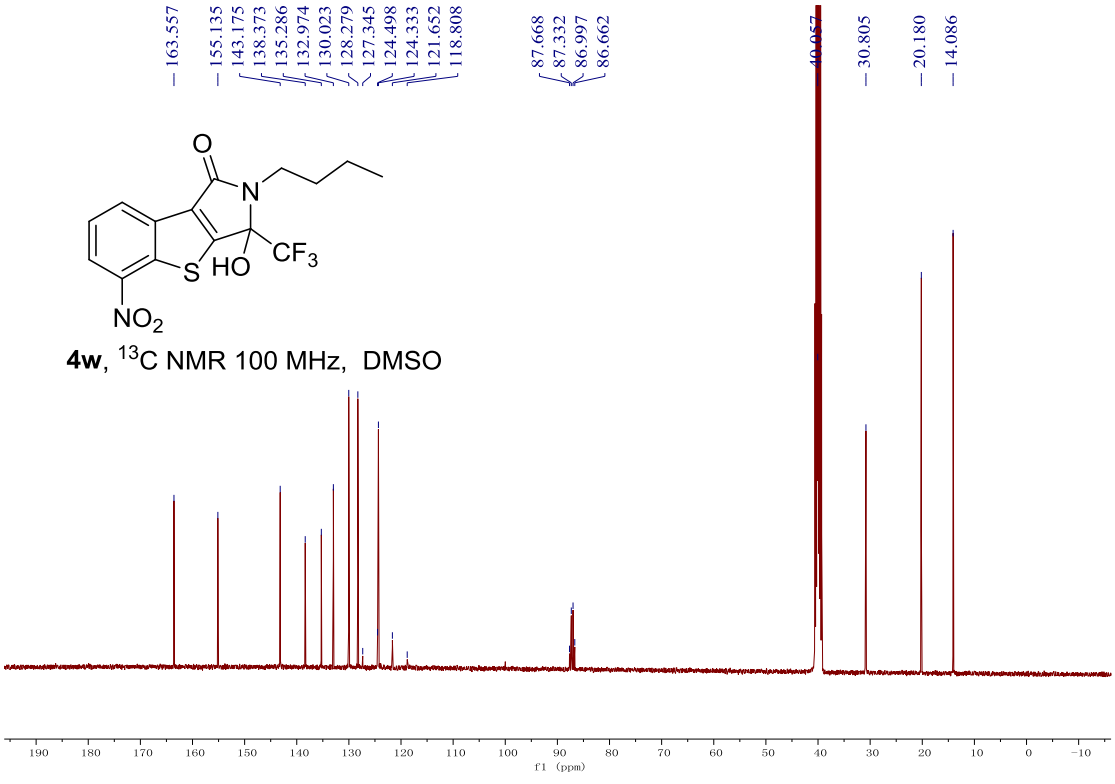

**4v**, $^{13}C$ NMR 100 MHz, $CDCl_3$




**4v**, $^{19}F$ NMR 376 MHz, $CDCl_3$

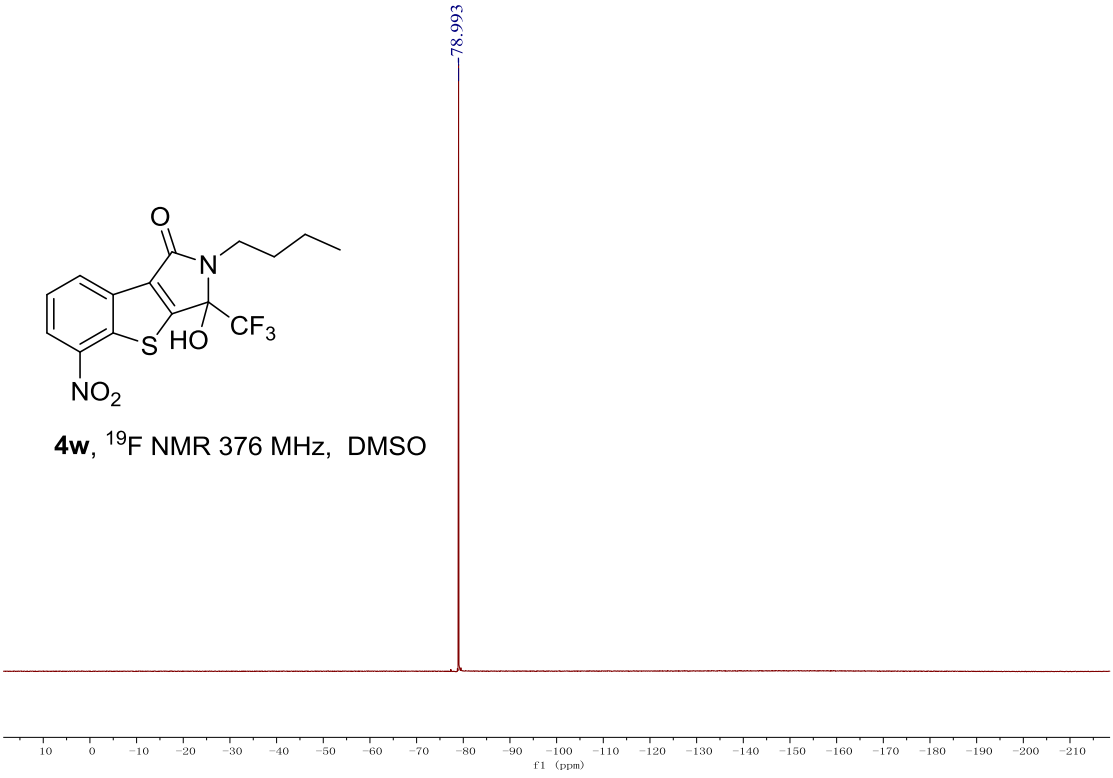



**4w**, $^{1}$H NMR 400 MHz, DMSO-$d_6$



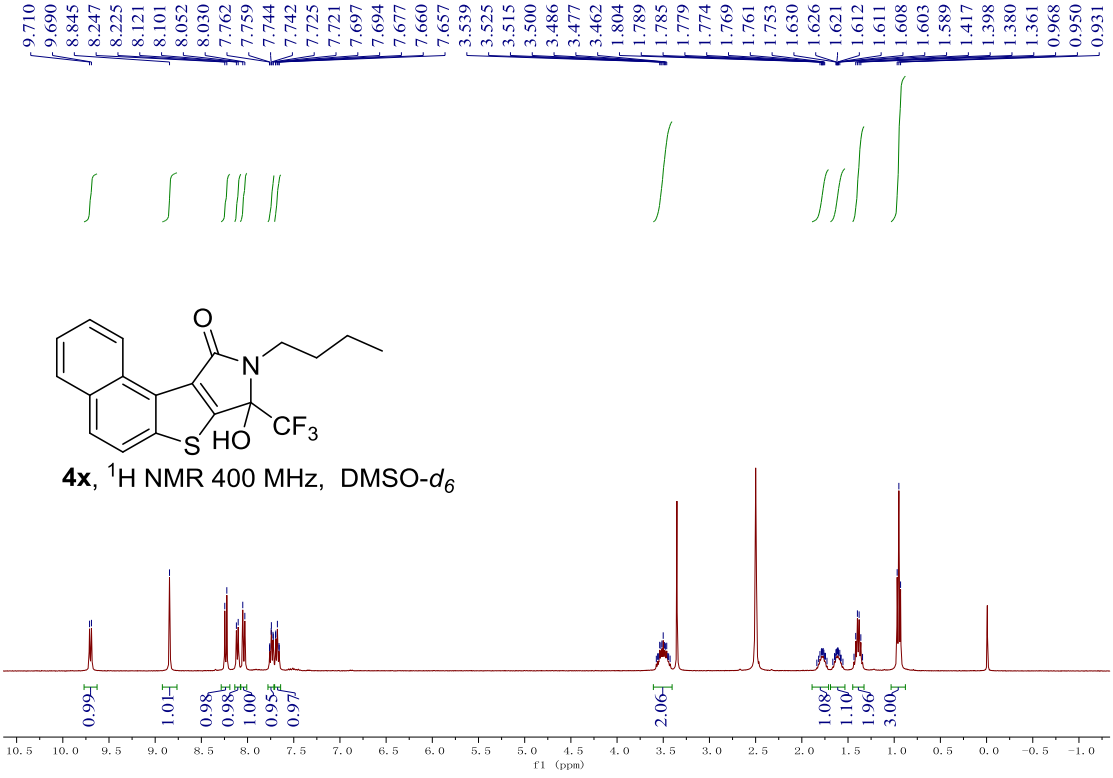

**4w**, $^{13}$C NMR 100 MHz, DMSO

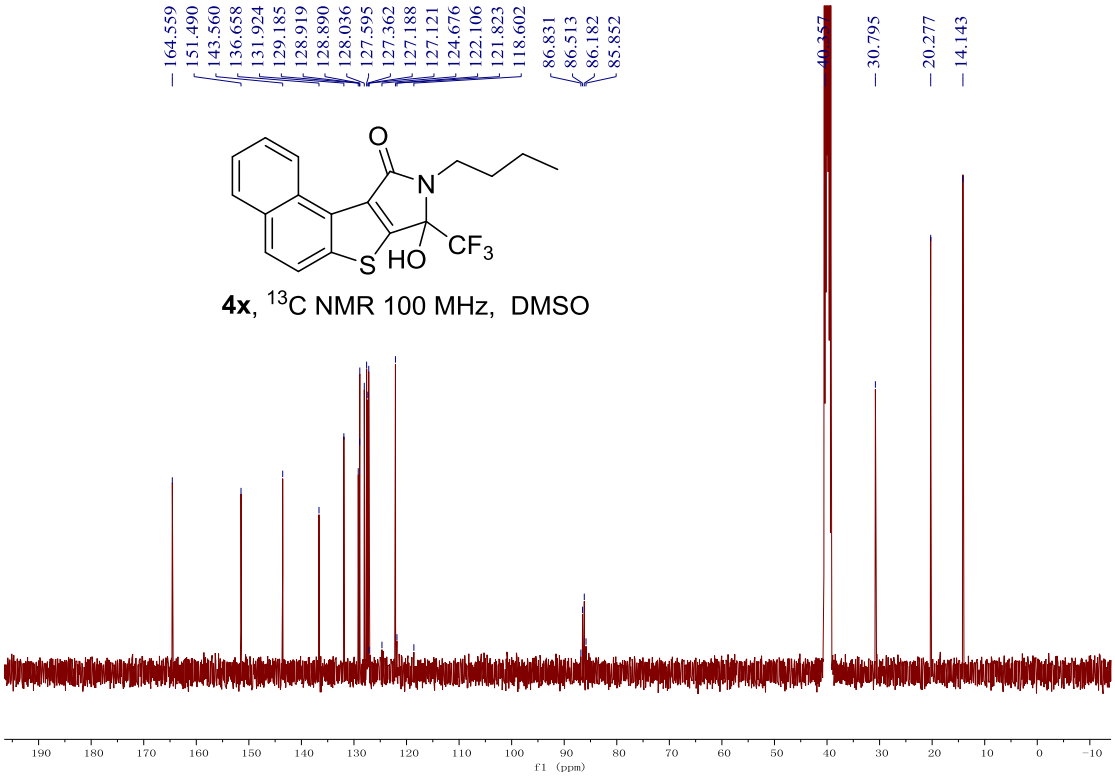
**4w**, $^{19}$F NMR 376 MHz, DMSO



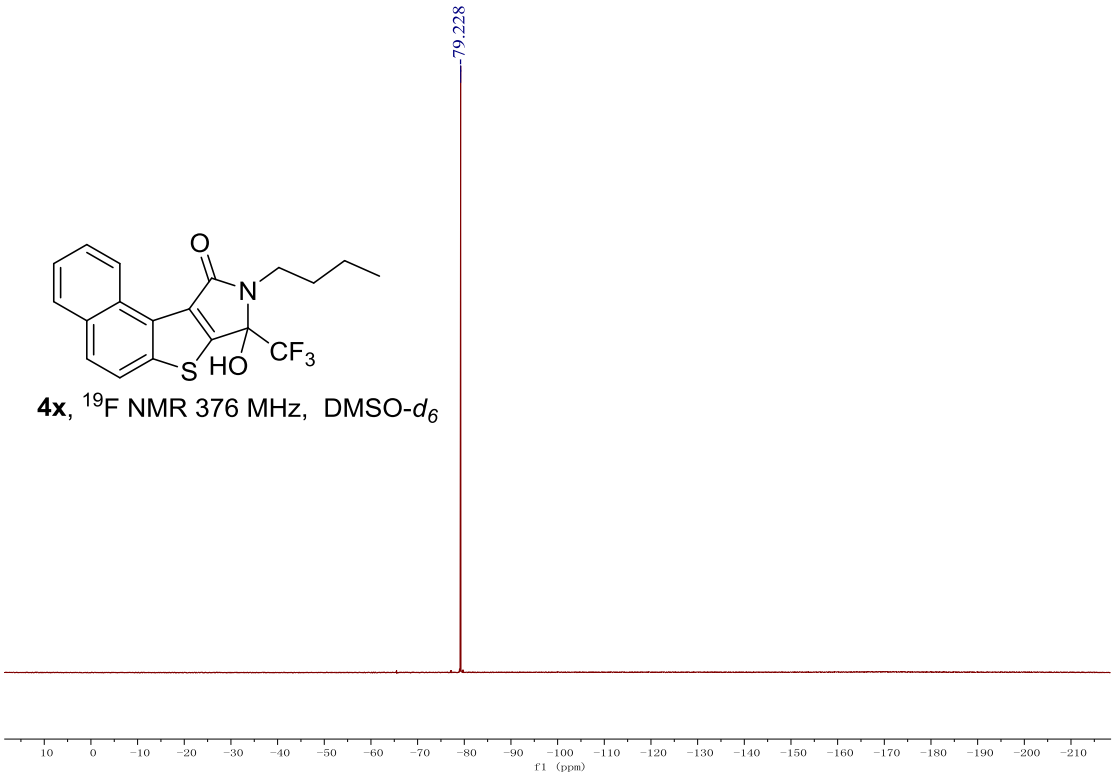



**4x**, $^{1}$H NMR 400 MHz, DMSO-$d_6$

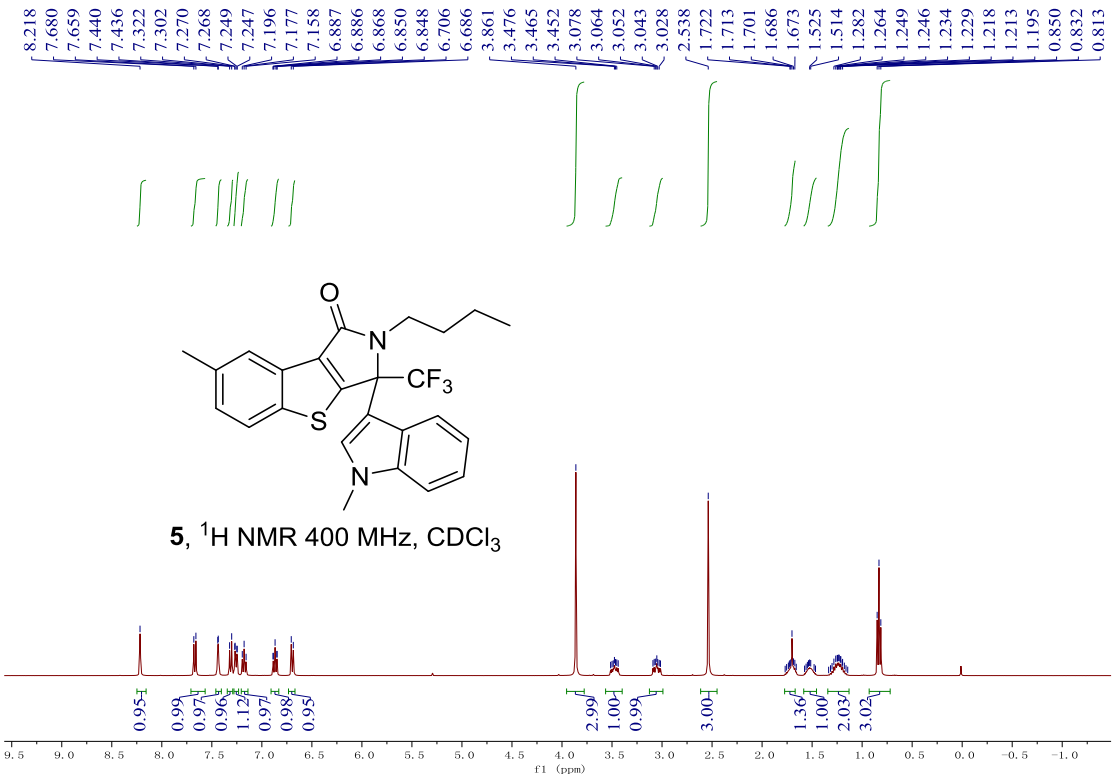




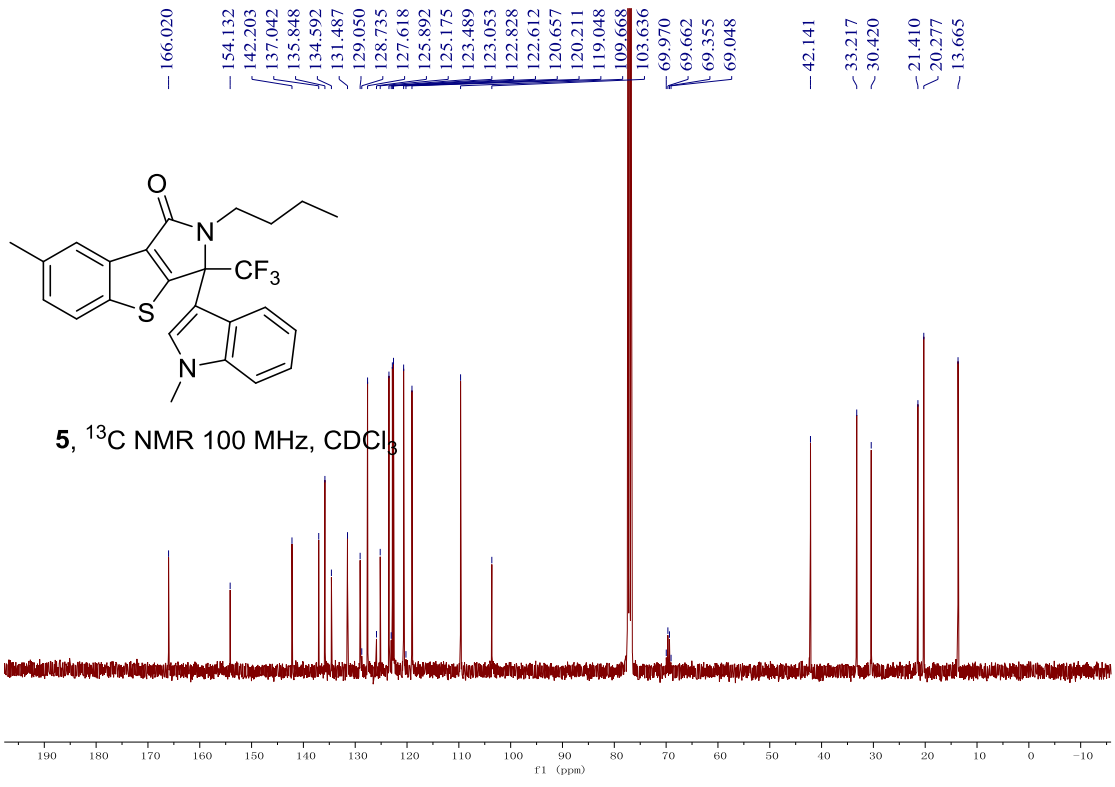

**4x**, $^{13}$C NMR 100 MHz, DMSO



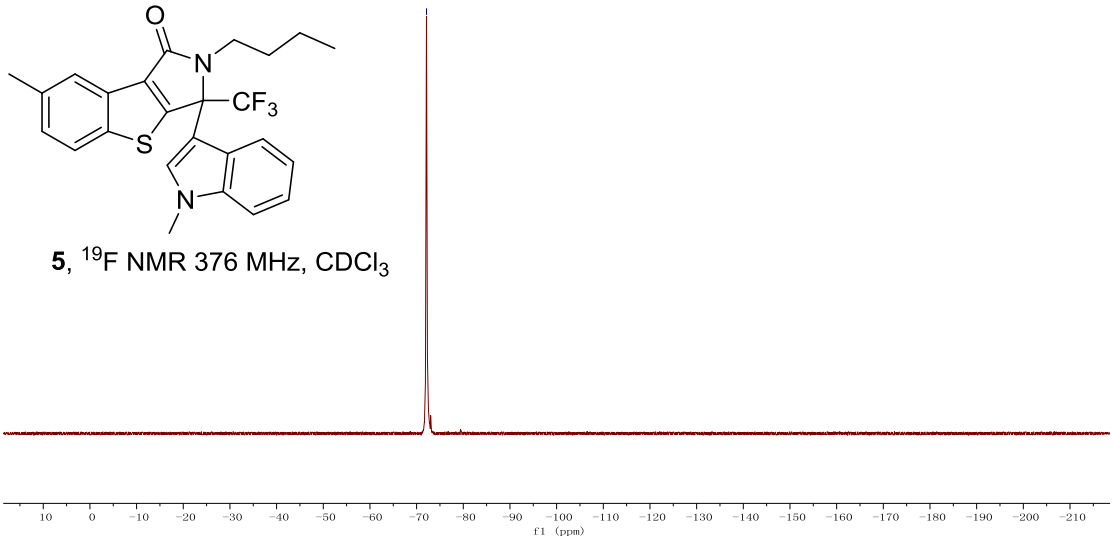

**4x**, $^{19}$F NMR 376 MHz, DMSO-$d_6$



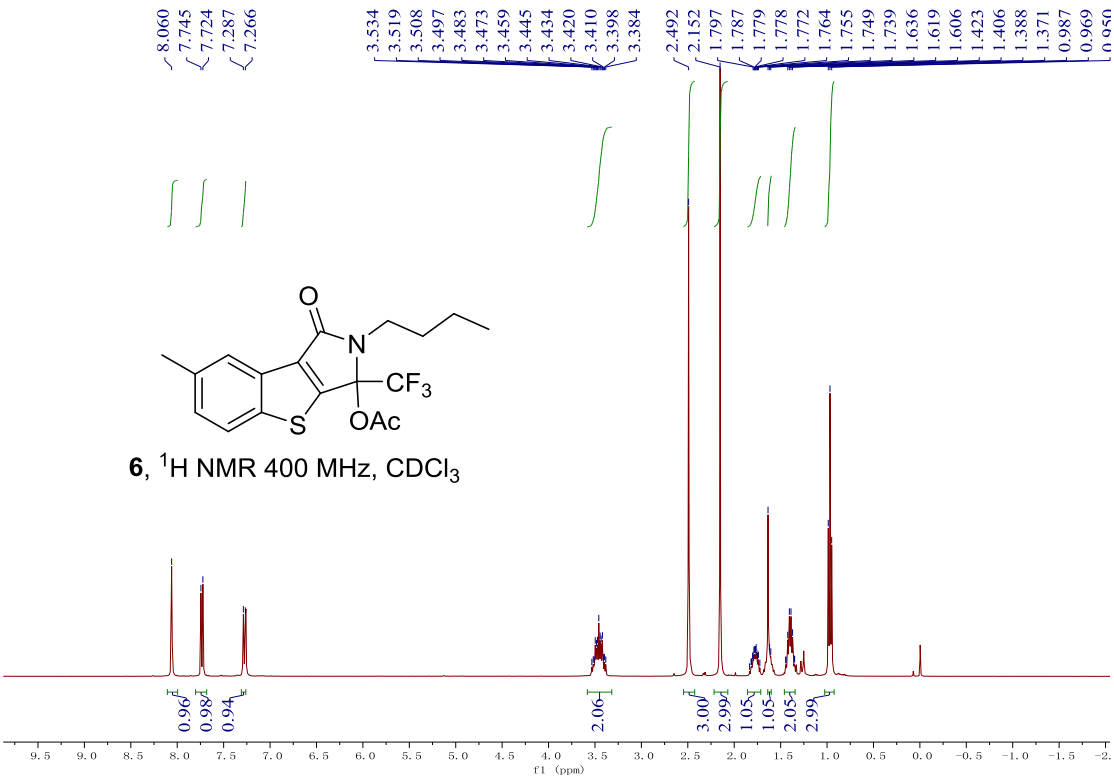

**5**, $^{1}$H NMR 400 MHz, $CDCl_3$



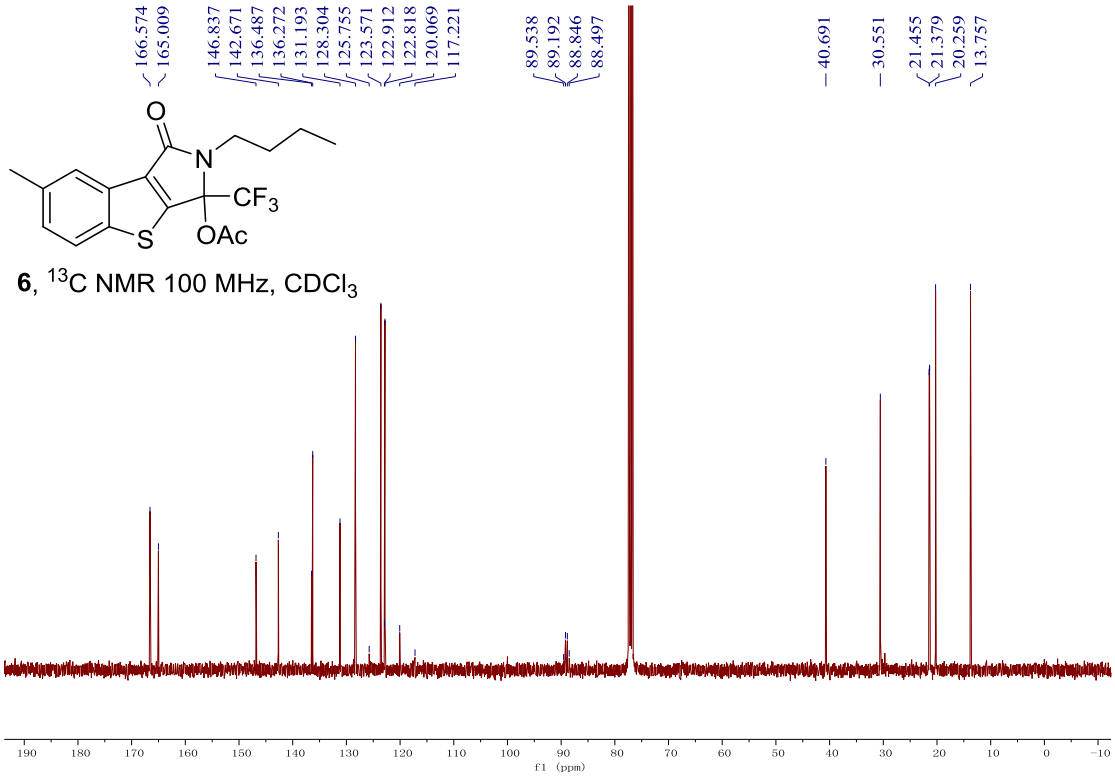

**5**, $^{13}$C NMR 100 MHz, $CDCl_3$



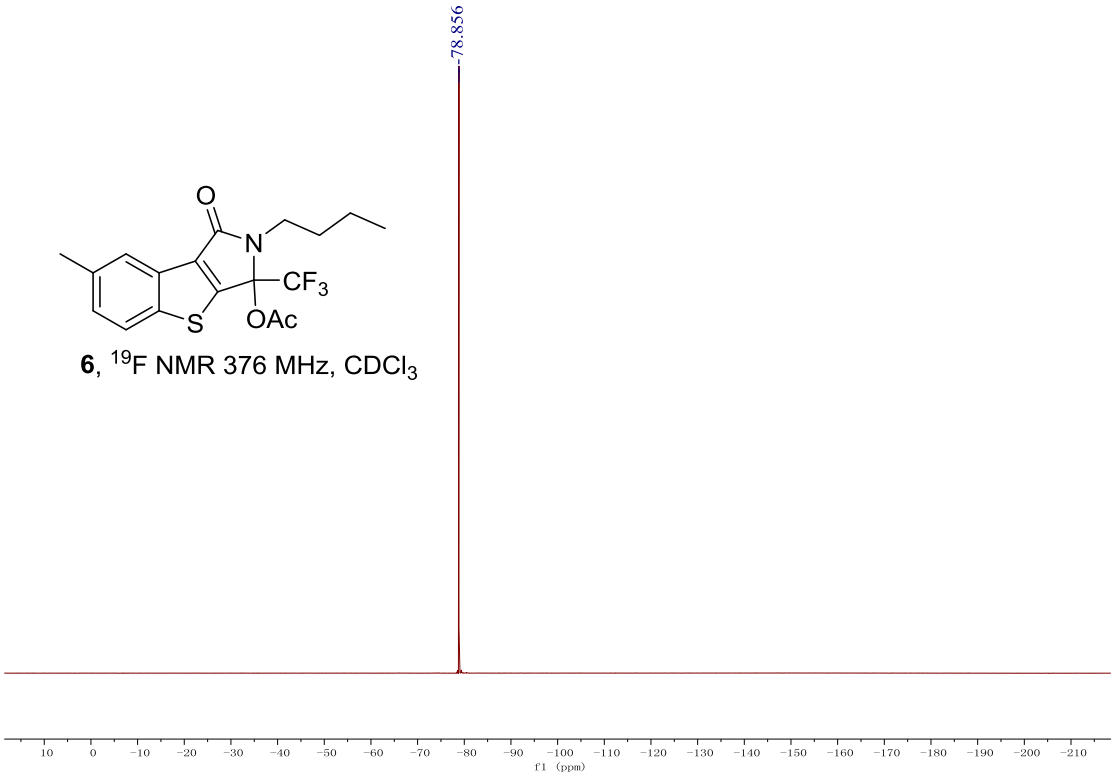

**5**, $^{19}F$ NMR 376 MHz, $CDCl_3$




**6**, $^{1}H$ NMR 400 MHz, $CDCl_3$



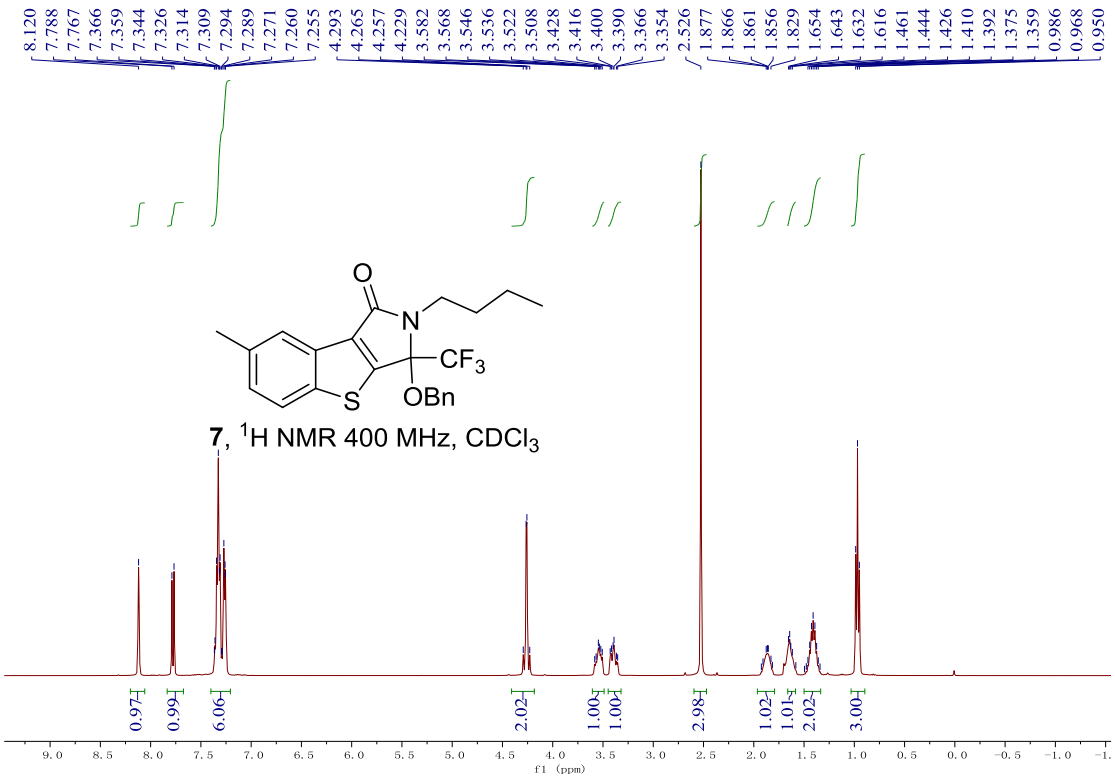

**6**, $^{13}C$ NMR 100 MHz, $CDCl_3$



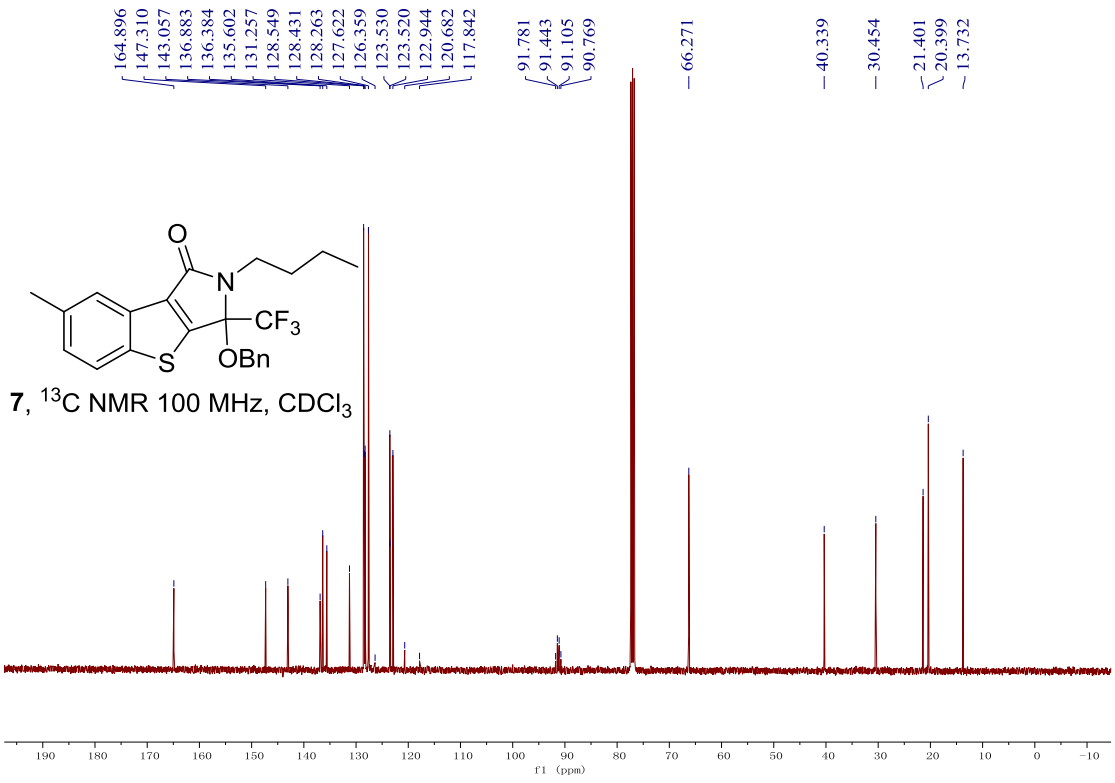




**6**, $^{19}F$ NMR 376 MHz, $CDCl_3$

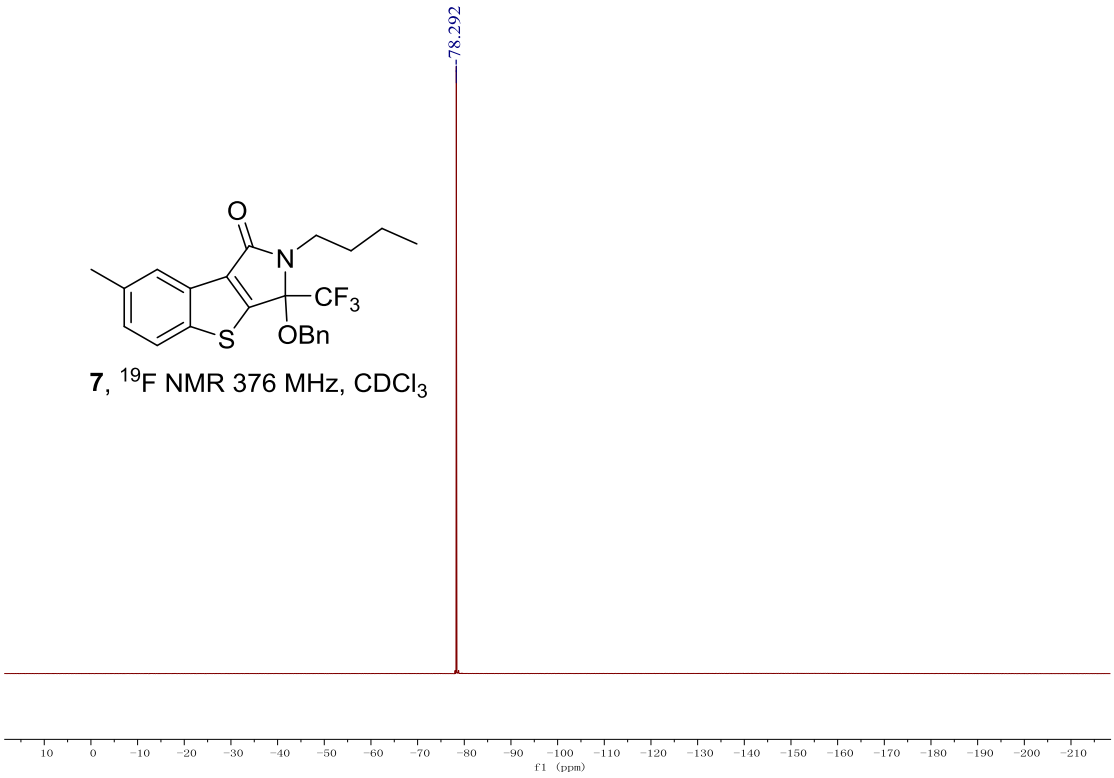



**7**, $^{1}$H NMR 400 MHz, $CDCl_3$

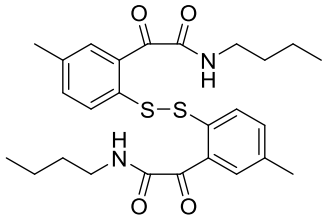



**7**, $^{13}$C NMR 100 MHz, $CDCl_3$

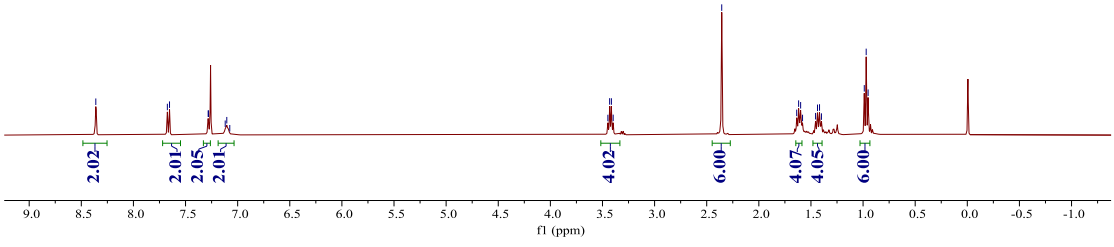
**7**, $^{19}F$ NMR 376 MHz, $CDCl_3$

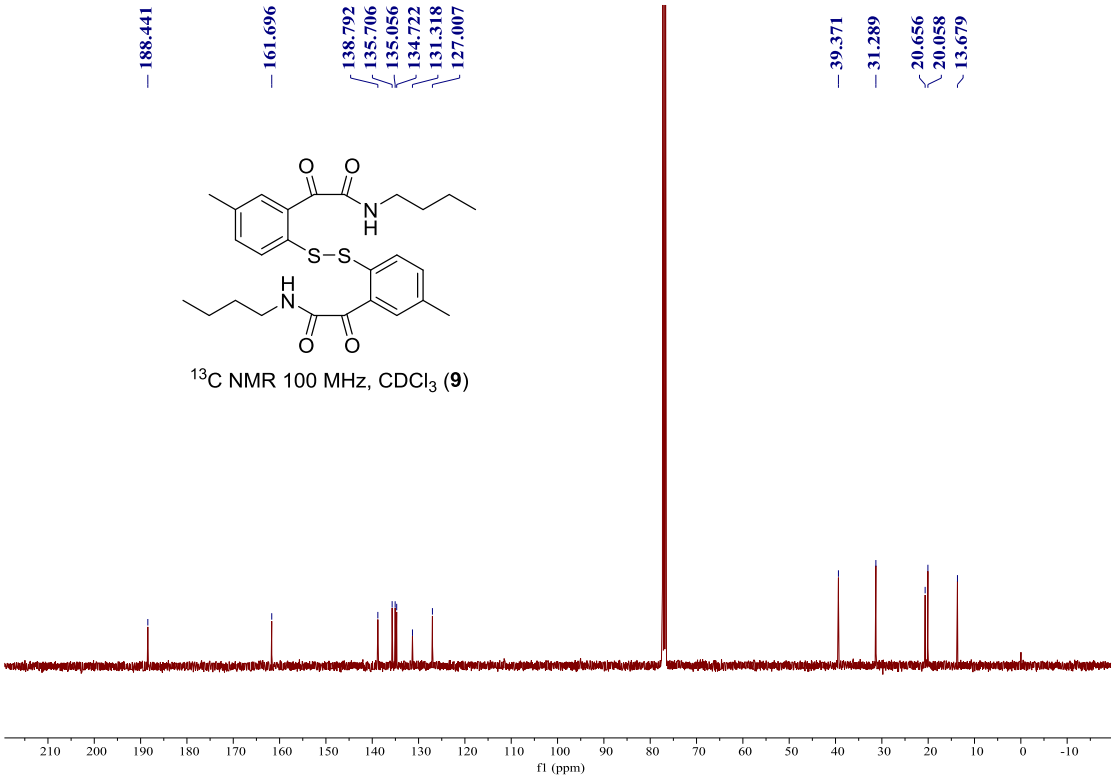







$^1H$ NMR 400 MHz, $CDCl_3$ (**9**)






$^{13}$C NMR 100 MHz, $CDCl_3$ (**9**)

## 8. X-ray data collection and structure determinations

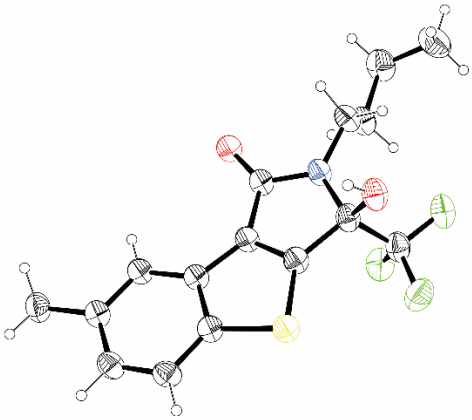
Single crystals of **4a**, **4j** and **5** were grown by slow diffusion of *n*-hexane into a dichloromethane solution. X-ray single-crystal diffraction data was collected on a Rigaku XtaLAB P200 diffractometer at 293(2) K with MoK α radiation ($\lambda$=0.71073 Å) or CuKa ($\lambda$=1.54184 Å) in the $\omega$ scan mode. The program SAINT was used for integration of the diffraction profiles. All of the structures were solved using direct methods using the SHELXS program of the SHELXTL package and refined using full matrix least-squares methods with SHELXL (semi empirical absorption corrections were applied using the SADABS program). Other non-hydrogen atoms were located in successive difference Fourier syntheses and refined with anisotropic thermal parameters on *F*2. The hydrogen atoms were generated theoretically onto the specific atoms and refined isotopically with fixed thermal factors. Detailed crystallographic data were summarized in Table S1

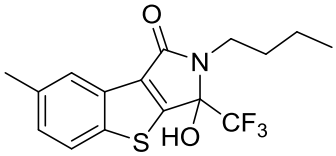
`

**Table S1** Crystal Date and Structure Refinements for **4a**, **4j, 5**

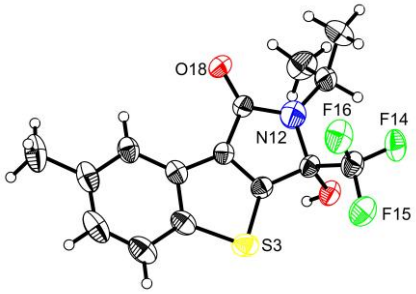
| | **4a** | **4j** | **5** |
|---|---|---|---|
| Chemical formula | $C_{16}H_{16}F_3NO_2S$ | $C_{15}H_{14}F_3NO_2S$ | $C_{25}H_{23}F_3N_2OS$ |
| Formula weight | 343.36 | 329.33 | 456.51 |
| Crystal system | triclinic | triclinic | monoclinic |
| Space group | P 1 21/c 1 | P 1 21/n 1 | P -1 |
| *a* (Å) | 11.9152(6) | 9.0814(2) | 8.9308(9) |
| *b* (Å) | 13.5262(4) | 8.8689(2) | 9.8192(9) |
| *c* (Å) | 10.7286(6) | 19.9409(4) | 14.3606(17) |
| *V* (Å$^3$) | 1618.57(14) | 1583.36(6) | 1116.4(2) |
| α ($^o$) | 90 | 90 | 87.735(8) |
| β ($^o$) | 110.597(6) | 99.649(2) | 77.519(9) |
| γ ($^o$) | 90 | 90 | 65.425(9) |
| *Z* | 4 | 4 | 2 |
| F(000) | 712.0 | 680.0 | 476.0 |
| *GOF* | 1.065 | 1.087 | 0.930 |
| *D*/g cm$^{-3}$ | 1.409 | 1.382 | 1.358 |
| $\mu$ (mm$^{-1}$) | 2.149 | 2.173 | 0.190 |
| *T/K* | 293 | 293 | 293 |
| $R^a/R^b$ | 0.0479/ 0.1462 | 0.0374/0.1126 | 0.0819/0.2791 |
| | $^aR = \Sigma\|\|F_o\| - \|F_c\|\|/\Sigma\|F_o\|$. $^bR_w = [\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma w(Fo^2)^2]^{1/2}$. | | |

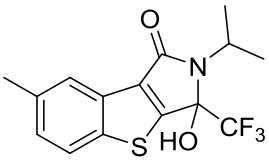
**9. X-ray Crystal Structures** (50% thermal ellipsoid probability levels)



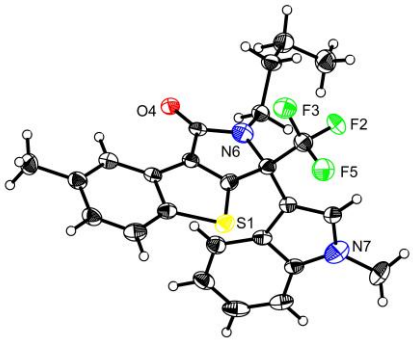


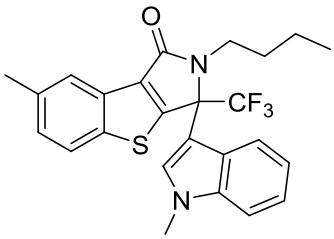

**4a** (CCDC 2035233)



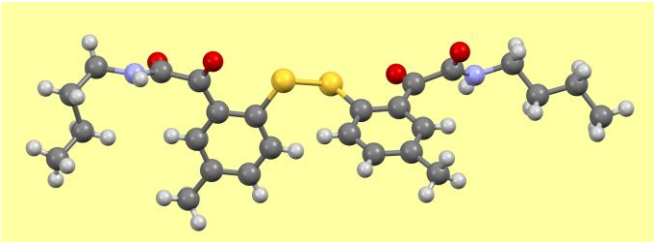




**4j** (CCDC 2035234)




**5** (CCDC 2035235)



**9** (CCDC 2172127)

## 10. Cytotoxicity assay

The cytotoxicity of the product **4a** was detected by a CCK-8 assay. Normal cell line NIH-3T3 cells (Mouse embryonic fibroblast), cancer cell line B16F10 (mouse melanoma cells) and cancer cell line 4T1 (mouse mammary carcinoma cells) used in this study were all purchased from the Institute of Biochemistry and Cell Biology, China Academy of Sciences. The cells were plated in 96-well plates ($5 \times 10^3$ cells/well) in 100 μL of DMEM media containing 10% FBS, 1% L-glutamine, antibiotics penicillin (100 $IUmL^{-1}$) and streptomycin (100 $\mu gmL^{-1}$) for 24 h. A series of concentrations of product **4a** in dimethylsulfoxide (DMSO, Solarbio) were added to sextuplicate wells at doses of 1, 2, 5, 10, 20, 50, 100, 200, 500 μM. The final concentration of DMSO in the culture medium was maintained at 1.0% (v/v) to avoid toxicity of the solvent. After 24 h, the medium was removed and 100 μL of Cell Counting Kit-8 solution (CCK-8, Beyotime, the concentration of CCK-8 in the culture medium was maintained at 10% (v/v)) was added to each well. After treated for 4 h at 37℃, the absorbance was measured at 450 nm. All tests and analyses were run in sextuplicate and averaged.

## 11. Computational details

**Table S2.** Cartesian coordinates of some stationary points, optimized at the B3LYP-PCM/6-31G* level of theory in water.

| Species Name | Cartesian Coordinates | | | |
|---|---|---|---|---|
| **1a** | 6 | -0.523606000 | -0.759730000 | -0.000093000 |
| | 6 | -0.404982000 | 0.641220000 | 0.000149000 |
| | 6 | -1.546956000 | 1.450066000 | 0.000287000 |
| | 6 | -2.803942000 | 0.850656000 | 0.000190000 |
| | 6 | -2.909630000 | -0.546159000 | -0.000030000 |
| | 6 | -1.773483000 | -1.365984000 | -0.000183000 |
| | 6 | 1.963683000 | -0.098060000 | -0.000056000 |
| | 6 | 0.975384000 | 1.117100000 | 0.000220000 |
| | 1 | -1.433607000 | 2.530090000 | 0.000455000 |
| | 1 | -3.700430000 | 1.462014000 | 0.000294000 |
| | 1 | -3.891821000 | -1.009552000 | -0.000108000 |
| | 1 | -1.873906000 | -2.446463000 | -0.000367000 |
| | 16 | 1.035430000 | -1.646980000 | -0.000247000 |
| | 8 | 1.396670000 | 2.256912000 | 0.000364000 |
| | 8 | 3.162589000 | 0.003205000 | -0.000267000 |
| **2a** | 6 | 0.654189000 | 0.894035000 | 0.091793000 |
| | 8 | 0.906767000 | 1.931670000 | -0.472257000 |
| | 6 | -0.564417000 | 0.682046000 | 0.960603000 |
| | 6 | 1.638490000 | -0.299345000 | -0.016460000 |
| | 1 | -0.972709000 | 1.640062000 | 1.273291000 |
| | 1 | -0.375042000 | 0.024895000 | 1.807729000 |
| | 9 | 2.603935000 | -0.049668000 | -0.903354000 |

| | | | | |
|---|---|---|---|---|
| | 9 | 1.003886000 | -1.431065000 | -0.373798000 |
| | 9 | 2.204321000 | -0.507332000 | 1.191583000 |
| | 35 | -1.959578000 | -0.196747000 | -0.135670000 |
| **TS-A** | 6 | 2.055927000 | -0.120966000 | -0.901062000 |
| | 6 | 2.661099000 | 0.281549000 | 0.303672000 |
| | 6 | 3.602460000 | -0.548981000 | 0.920746000 |
| | 6 | 3.920159000 | -1.769879000 | 0.330870000 |
| | 6 | 3.310101000 | -2.153822000 | -0.870213000 |
| | 6 | 2.370530000 | -1.331380000 | -1.503339000 |
| | 6 | 1.229425000 | 2.254823000 | -0.156417000 |
| | 6 | 2.263170000 | 1.593961000 | 0.805395000 |
| | 1 | 4.069007000 | -0.227121000 | 1.846281000 |
| | 1 | 4.646297000 | -2.425289000 | 0.799952000 |
| | 1 | 3.568246000 | -3.104999000 | -1.324584000 |
| | 1 | 1.904931000 | -1.635400000 | -2.434509000 |
| | 16 | 0.904661000 | 1.062108000 | -1.596285000 |
| | 8 | 2.629127000 | 2.187108000 | 1.795372000 |
| | 8 | 0.723368000 | 3.324356000 | -0.069693000 |
| | 6 | -1.003953000 | -0.024125000 | 0.368175000 |
| | 8 | -0.524863000 | 0.576291000 | 1.319696000 |
| | 6 | -1.156045000 | 0.602869000 | -0.979922000 |
| | 6 | -1.123418000 | -1.566856000 | 0.484206000 |
| | 1 | -1.437328000 | 1.648395000 | -0.994727000 |
| | 1 | -1.459630000 | 0.001486000 | -1.826543000 |
| | 9 | -1.820080000 | -1.920374000 | 1.570502000 |
| | 9 | 0.127134000 | -2.067234000 | 0.622860000 |
| | 9 | -1.669300000 | -2.148755000 | -0.595777000 |
| | 35 | -3.625820000 | 0.342036000 | -0.059407000 |
| **Int-A** | 6 | 2.416295000 | -1.537728000 | -0.035846000 |
| | 6 | 1.089337000 | -1.556111000 | -0.488687000 |
| | 6 | 0.340659000 | -2.729083000 | -0.378042000 |
| | 6 | 0.909762000 | -3.858576000 | 0.218402000 |
| | 6 | 2.229972000 | -3.820318000 | 0.680543000 |
| | 6 | 2.998922000 | -2.660349000 | 0.552064000 |
| | 6 | -0.821079000 | 0.148697000 | -1.080228000 |
| | 6 | 0.670779000 | -0.286178000 | -1.215358000 |
| | 1 | -0.683701000 | -2.759221000 | -0.737276000 |
| | 1 | 0.324268000 | -4.766936000 | 0.320681000 |
| | 1 | 2.665816000 | -4.698918000 | 1.146935000 |
| | 1 | 4.023450000 | -2.634452000 | 0.909481000 |
| | 16 | 3.252002000 | 0.008067000 | -0.345650000 |
| | 8 | 0.876488000 | -0.438130000 | -2.609843000 |
| | 8 | -1.391062000 | 0.681875000 | -2.029464000 |
| | 6 | -2.752205000 | 0.407771000 | 0.407738000 |

| | | | | |
|---|---|---|---|---|
| | 1 | -2.814688000 | 0.603225000 | 1.483389000 |
| | 1 | -2.911142000 | 1.355331000 | -0.115959000 |
| | 7 | -1.385947000 | -0.035000000 | 0.132116000 |
| | 1 | -0.910550000 | -0.549730000 | 0.879342000 |
| | 6 | 1.185568000 | 1.571592000 | 0.584786000 |
| | 8 | 1.173425000 | 1.108910000 | 1.702868000 |
| | 6 | 1.641870000 | 0.850985000 | -0.679826000 |
| | 1 | 1.777434000 | 1.570216000 | -1.487691000 |
| | 6 | 0.748548000 | 3.046187000 | 0.383777000 |
| | 1 | 1.761567000 | -0.822693000 | -2.733630000 |
| | 8 | -0.267966000 | -1.231620000 | 2.561772000 |
| | 1 | 0.499432000 | -0.632572000 | 2.571320000 |
| | 1 | 0.110705000 | -2.099932000 | 2.347512000 |
| | 6 | -3.818895000 | -0.613331000 | -0.009707000 |
| | 1 | -3.720653000 | -0.804072000 | -1.086102000 |
| | 1 | -3.623568000 | -1.565923000 | 0.501812000 |
| | 6 | -5.242377000 | -0.138128000 | 0.306425000 |
| | 1 | -5.426119000 | 0.819975000 | -0.199886000 |
| | 1 | -5.327944000 | 0.063187000 | 1.383621000 |
| | 6 | -6.314704000 | -1.149854000 | -0.110872000 |
| | 1 | -6.178111000 | -2.107143000 | 0.407047000 |
| | 1 | -6.273593000 | -1.347117000 | -1.189143000 |
| | 1 | -7.320608000 | -0.783512000 | 0.123805000 |
| | 9 | -0.256375000 | 3.117337000 | -0.511207000 |
| | 9 | 1.787087000 | 3.758006000 | -0.098687000 |
| | 9 | 0.344377000 | 3.597376000 | 1.528411000 |
| **TS** | 6 | 3.115378000 | 0.238572000 | 0.254207000 |
| | 6 | 2.413767000 | -0.719588000 | -0.485177000 |
| | 6 | 2.999358000 | -1.953217000 | -0.774411000 |
| | 6 | 4.292519000 | -2.220734000 | -0.321240000 |
| | 6 | 4.988908000 | -1.256832000 | 0.416722000 |
| | 6 | 4.409167000 | -0.020304000 | 0.711557000 |
| | 6 | -0.069642000 | -1.098597000 | -0.229488000 |
| | 6 | 1.035787000 | -0.291330000 | -0.949284000 |
| | 1 | 2.445373000 | -2.688805000 | -1.349384000 |
| | 1 | 4.757968000 | -3.175748000 | -0.544653000 |
| | 1 | 5.996267000 | -1.466816000 | 0.764832000 |
| | 1 | 4.957502000 | 0.724188000 | 1.280660000 |
| | 16 | 2.206928000 | 1.739370000 | 0.547821000 |
| | 8 | 0.825309000 | -0.531012000 | -2.331417000 |
| | 8 | -0.276079000 | -2.279822000 | -0.373936000 |
| | 6 | -2.112688000 | -0.733391000 | 1.201433000 |
| | 1 | -1.871517000 | -1.503943000 | 1.940275000 |
| | 1 | -2.516740000 | 0.125444000 | 1.744393000 |

| | | | | |
|---|---|---|---|---|
| | 7 | -0.791968000 | -0.250574000 | 0.659926000 |
| | 1 | -0.174197000 | -0.113024000 | 1.747345000 |
| | 6 | -0.582731000 | 1.325457000 | 0.215716000 |
| | 8 | -0.668741000 | 2.125278000 | 1.245531000 |
| | 6 | 0.802524000 | 1.188359000 | -0.525299000 |
| | 1 | 0.800851000 | 1.826607000 | -1.409407000 |
| | 6 | -1.671745000 | 1.674550000 | -0.834163000 |
| | 1 | 1.634710000 | -0.260873000 | -2.798275000 |
| | 8 | 0.151213000 | 0.448715000 | 2.846915000 |
| | 1 | -0.102993000 | 1.368544000 | 2.379577000 |
| | 1 | 1.123708000 | 0.446184000 | 2.916379000 |
| | 6 | -3.136583000 | -1.286766000 | 0.206288000 |
| | 1 | -3.383508000 | -0.541784000 | -0.552614000 |
| | 1 | -2.715101000 | -2.153013000 | -0.311655000 |
| | 6 | -4.420150000 | -1.703372000 | 0.941441000 |
| | 1 | -4.837911000 | -0.834555000 | 1.468583000 |
| | 1 | -4.176294000 | -2.445624000 | 1.713929000 |
| | 6 | -5.474674000 | -2.281128000 | -0.008104000 |
| | 1 | -5.096361000 | -3.172066000 | -0.523719000 |
| | 1 | -5.760203000 | -1.549404000 | -0.773500000 |
| | 1 | -6.381541000 | -2.568353000 | 0.535649000 |
| | 9 | -1.381529000 | 2.858868000 | -1.411626000 |
| | 9 | -1.756518000 | 0.754980000 | -1.826693000 |
| | 9 | -2.890382000 | 1.789684000 | -0.276233000 |
| **Int-B** | 6 | -3.073447000 | -0.193718000 | 0.286843000 |
| | 6 | -2.437753000 | 0.723326000 | -0.555175000 |
| | 6 | -3.079719000 | 1.910742000 | -0.906997000 |
| | 6 | -4.359255000 | 2.172594000 | -0.410990000 |
| | 6 | -4.986161000 | 1.249628000 | 0.433000000 |
| | 6 | -4.350415000 | 0.057047000 | 0.790438000 |
| | 6 | 0.055459000 | 1.130221000 | -0.321435000 |
| | 6 | -1.060410000 | 0.315304000 | -1.019931000 |
| | 1 | -2.578451000 | 2.616400000 | -1.561819000 |
| | 1 | -4.867812000 | 3.092567000 | -0.683065000 |
| | 1 | -5.982592000 | 1.454830000 | 0.814078000 |
| | 1 | -4.845074000 | -0.659159000 | 1.439568000 |
| | 16 | -2.104921000 | -1.650084000 | 0.629450000 |
| | 8 | -0.853417000 | 0.522623000 | -2.410119000 |
| | 8 | 0.121876000 | 2.351236000 | -0.297796000 |
| | 6 | 2.101312000 | 0.769587000 | 1.015930000 |
| | 1 | 1.727821000 | 1.532558000 | 1.707205000 |
| | 1 | 2.469058000 | -0.067511000 | 1.613061000 |
| | 7 | 0.945001000 | 0.274466000 | 0.254737000 |
| | 1 | -1.208284000 | -0.554416000 | 3.179035000 |

| | | | | |
|---|---|---|---|---|
| | 6 | 0.648169000 | -1.147375000 | 0.082544000 |
| | 8 | 0.796183000 | -1.883952000 | 1.248816000 |
| | 6 | -0.783403000 | -1.145572000 | -0.563421000 |
| | 1 | -0.825388000 | -1.828928000 | -1.411601000 |
| | 6 | 1.645973000 | -1.801544000 | -0.908089000 |
| | 1 | -1.636519000 | 0.181930000 | -2.875647000 |
| | 8 | -0.262021000 | -0.595599000 | 3.398722000 |
| | 1 | 0.359629000 | -1.408694000 | 2.008150000 |
| | 1 | -0.218720000 | -1.213158000 | 4.147882000 |
| | 6 | 3.218263000 | 1.356453000 | 0.143681000 |
| | 1 | 3.564980000 | 0.596343000 | -0.565551000 |
| | 1 | 2.809738000 | 2.186284000 | -0.444670000 |
| | 6 | 4.398697000 | 1.851344000 | 0.989357000 |
| | 1 | 4.794225000 | 1.017209000 | 1.585793000 |
| | 1 | 4.042324000 | 2.601657000 | 1.709023000 |
| | 6 | 5.524445000 | 2.452474000 | 0.141770000 |
| | 1 | 5.165427000 | 3.309013000 | -0.441822000 |
| | 1 | 5.925727000 | 1.714621000 | -0.563786000 |
| | 1 | 6.352776000 | 2.799373000 | 0.769882000 |
| | 9 | 1.306075000 | -3.082214000 | -1.156027000 |
| | 9 | 2.904405000 | -1.802211000 | -0.425332000 |
| | 9 | 1.658783000 | -1.143171000 | -2.083332000 |

**Table S3.** Electronic energies (***E***, a.u.), entropies (***S***, cal/mol·K), and Gibbs free energies (***G***, a.u.) at the B3LYP/6-31G* level of theory, and electronic energies ($E^{m06}$) by the m06/6-311++G** single point computations.

| Species Name | *E* | *S* | *G* | $E^{m06}$ |
|---|---|---|---|---|
| **1a** | -855.8992351 | 90.827 | -855.83325 | -855.7113889 |
| **2a** | -3061.963466 | 94.487 | -3061.947013 | -3064.219484 |
| **TS-A** | -3917.820869 | 141.165 | -3917.717117 | -3919.893024 |
| **C** | -1635.804578 | 179.24 | -1635.542075 | -1635.491434 |
| **TS** | -1635.768532 | 160.377 | -1635.503149 | -1635.452834 |
| **D** | -1635.826456 | 171.378 | -1635.559925 | -1635.516714 |

## Computational Methods

All calculations were finished using the Gaussian 16 computational program.[2] Geometrical optimizations were performed by the B3LYP density functional method [3] with the 6-31g* basis set for all elements. The default self-consistent reaction field polarizable continuum model (PCM) [4] was used to consider the solvation effects of water. All of the resultant stationary point geometries were characterized by vibrational analyses, from which zero point energies and Gibbs free-energies were obtained, in addition to confirming whether all of the structures resided at minima or first-order

saddle points on the potential energy surfaces. Considering the default entropic data obtained from the Gaussian output files are the idea-gas-phase entropies, which would exaggerate the activation entropies for the bimolecular reaction in solution.[5] Hence, the default entropies are scaled by a factor of 0.7 in Gibbs free-energy determinations.
To refined the electronic energies, the m06 density functional method [6] and 6-311++G** basis set for all elements were used in singlet point calculations, in which the SMD solvation method [7] was used.

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