

Structural Assignment of Enol-Keto Tautomerization of One-Pot Synthesized 4-Hydroxyquinolines / 4-Quinolones

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General method

Analytical thin layer chromatography (TLC) was performed on Kieselgel 60 F₂₅₄ glass plates precoated with a 0.2 mm thickness of silica gel. The TLC plates were visualized by shortwave (254 nm). Flash chromatography on Kieselgel 60 (230–400 mesh) silica gel was performed. ¹H NMR and spectra were obtained at 300 MHz or 500 MHz using CDCl₃ as solvent. ¹H NMR assignment abbreviations are the following; singlet (s), doublet (d), triplet (t), quartet (q), broad singlet (bs), doublet of doublets (dd), doublet of triplets (dt), and multiplet (m). ¹³C NMR spectra were measured at 75.5 MHz or 125 MHz using CDCl₃ as an internal reference. IR spectra were recorded using a Bruker FT/IR-300E spectrometer. High-resolution mass spectra (HRMS) were recorded with an electron scattering ionization (ESI) using a sector field mass analyzer. The melting points were determined in capillary tubes on Buchi 510 melting point apparatus without corrections. All DFT calculations were performed with the Jaguar Tool (Jaguar version 9.9, release 11, Schrödinger, LLC, New York, USA). Geometry optimization was carried out at the B3LYP level of theory and the 6-31+G** basis set was used.

General Procedure for synthesis of 4-Hydroxyquinolines / 4-Quinolones

Dimethyl 2-(bis(methylthio)methylene)malonate was prepared by following the reported procedure.¹ To a stirred solution of the dimethyl 2-(bis(methylthio)methylene)malonate (2.0 mmol) in solvent (5 ml) was added reagent (0.1-1.0 eq) diluted in solvent at -20 °C. The solution was stirred for 10 min and then aniline (1.0 mmol) was added to above the solution. The resulting mixture was heated at 75 °C for 24 hours. The solvent was evaporated and then, *o*-Dichlorobenzene (5 mL) was added to the mixture. The resulting mixture was heated at 190 °C for 20 min. After the reaction was completed, the solvent was removed. The crude product was purified by column chromatography on silica gel using Hexane/Ethyl acetate.

General Procedure of cyclization reaction

To a stirred solution of the mono-amination product **3a** in solvent (5 ml) was added reagent and the resulting solution was heated at corresponding temperature. After the reaction was completed, the solvent was removed. The crude product was purified by column chromatography on silica gel using Hexane/Ethyl acetate.

¹ Junjappa, H; Ila, H; Asokan, C. V. *Tetrahedron* **1990**, *46*, 5423.

Optimized Procedure for synthesis of 4-Hydroxyquinolines / 4-Quinolones (Table S1, Entry 11)

To a stirred solution of the dimethyl 2-(bis(methylthio)methylene)malonate (2.0 mmol) in THF (5 ml) was added NIS (0.1 mmol) diluted in THF at -20 °C. The solution was stirred for 10 min and then aniline (1.0 mmol) was added to above the solution. The resulting mixture was heated at 75 °C for 24 hours. The solvent was evaporated and then, *o*-Dichlorobenzene (5 mL) was added to the mixture. The resulting mixture was heated at 190 °C for 20 min. After the reaction was completed, the solvent was removed. The crude product was purified by column chromatography on silica gel using Hexane/Ethyl acetate.

General Procedure for Time dependent ¹H NMR study of cyclization and decarboxylation

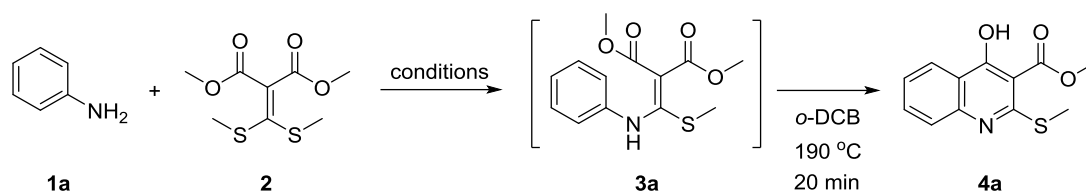
To a stirred solution of the dimethyl 2-(bis(methylthio)methylene)malonate (2.3 g, 9.75 mmol) in THF (5 ml) was added NIS (108 mg, 0.48 mmol) diluted in THF at -20 °C. The solution was stirred for 10 min and then *o*-anisidine (600 mg, 4.87 mmol) was added to above the solution. The resulting mixture was heated at 75 °C for 24 hours. After the reaction was completed, the solvent was removed *in vacuo*. The crude product was purified by column chromatography on silica gel using Hexane/Ethyl acetate 0% → 3%, v:v) **3d** was obtained (1.22 g, 3.918 mmol, 80%) as a brown oil. And then, **3d** was dissolved in *o*-Dichlorobenzene (10 ml). And the solution was heated at 190 °C. The solution was analyzed by ¹H NMR over time (5 min, 10 min, 15 min, 20 min, 30min, 40 min, 60 min, 80 min, 120 min, 160 min, 200 min, 240 min, 10 h, 24 h, 56 h).

Optimized procedure for the decarboxylation of the 4-quinolones

4-Hydroxyquinolines / 4-Quinolones (**4**) (1.0 mmol) was dissolved in *o*-Dichlorobenzene (5 mL) and the resulting solution was heated at 190 °C for 56 h. After the reaction was completed, the solvent was removed. The crude product was purified by column chromatography on silica gel using Hexane/Ethyl acetate.

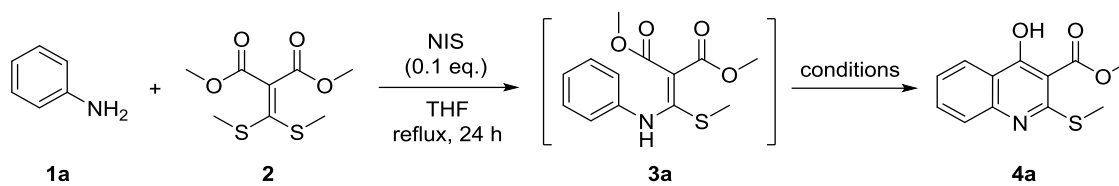
Optimized procedure for the oxidation of the thiomethyl groups

To a stirred solution of 4-Hydroxyquinolines / 4-Quinolones (**4**) (1.0 mmol) in CH₂Cl₂ (5 mL) was added *m*-CPBA (1.1 eq) at 0 °C. The resulting mixture was stirred at r.t for 6 h. After the reaction was completed, a saturated aqueous Na₂S₂O₃ solution was added. The mixture was extracted with CH₂Cl₂ and the organic layer was dried over MgSO₄. The crude product was purified by column chromatography on silica gel using Hexane/Ethyl acetate.

Table S1. Optimization of mono-amination condition^[a]

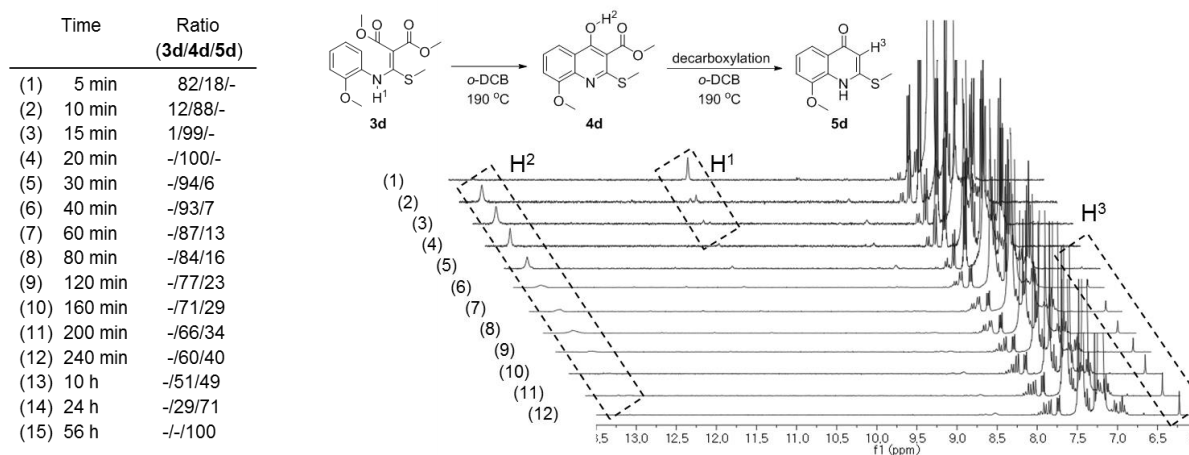
Entry	Reagent	Solvent	Yield (%) ^[b]
1	None	THF	N.R.
2	None	EtOH	< 5
3	<i>p</i> -TsOH	Toluene	18
4	BF ₃ ·OEt ₂	THF	17
5	FeCl ₃	THF	17
6	AlCl ₃	THF	N.R.
7 ^[c]	PhI(OAc) ₂	THF	N.R.
8 ^[c]	NFSI	THF	N.R.
9	NCS	THF	12
10	NBS	THF	< 5
11	NIS	THF	60
12 ^[d]	NIS	THF	16
13	NIS	1,4-Dioxane	36
14	NIS	DMF	N.R.

[a] Reaction conditions: **1a** (1 mmol), **2** (2 mmol), Reagent (0.1 eq), 75 °C, 24 h, Solvent (5 ml); *o*-DCB (5 mL), 190 °C, 20 min; [b] Isolated yields of final product (**4a**); [c] N-fluorobenzenesulfonimide (NFSI) 0.5 eq. used; [d] 1.0 eq. used.

Table S2. Optimization of cyclization condition^[a]

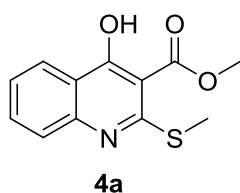
Entry	Reagent	Solvent	Temp. (°C)	Time	Yield (%) ^[b]
1	None	<i>o</i> -DCB	190	20 min	60
2	None	Xylene	120	4 h	39
3	PPA ^[c]	DMF	120	5 h	23
4	P ₂ O ₅ ^[d]	Toluene	120	3 h	26
5	MeSO ₃ H ^[d]	Toluene	120	1 h	28
6	<i>p</i> -TsOH ^[d]	Toluene	120	1 h	5

[a] Reaction conditions: **1a** (1 mmol), **2** (2 mmol), NIS (0.1 eq), 75 °C, 24 h, THF; Solvent (5 mL), Reagent, Corresponding temperature and time; [b] Isolated yields of final product (**4a**); [c] Polyphosphoric acid (PPA) xg/mmol used; [d] 1.0 eq. used.

Figure S1. Time dependent ¹H NMR studies of cyclization and decarboxylation^[a]

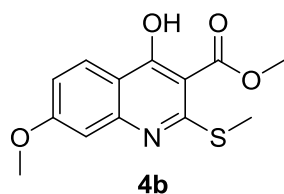
[a] ¹H NMR was measured in CDCl₃

Synthesis of Methyl 4-hydroxy-2-(methylthio)quinoline-3-carboxylate (**4a**)

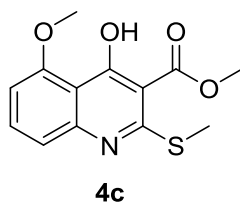


Using the optimized condition (Table S1, entry 11), **4a** was obtained as white solid (60%); m.p. 103-104 °C; ¹H NMR (300 MHz, CDCl₃) δ 13.14 (s, 1H), 8.18 (d, *J* = 8.2 Hz, 1H), 7.78 (d, *J* = 8.3 Hz, 1H), 7.69 (t, *J* = 7.4 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 1H), 4.05 (s, 3H), 2.59 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 171.5, 168.6, 160.1, 148.9, 133.0, 127.8, 125.0, 123.8, 118.0, 102.5, 52.6, 14.8; IR (neat) 3444br, 3064, 2992, 2952, 2920, 1660, 1621, 1584, 1558, 1446, 1348, 1228, 1158, 1000, 807, 751 cm⁻¹; HRMS (ESI) calcd for C₁₂H₁₁NO₃S [M]⁺ 249.0460 found: 249.0465.

Synthesis of Methyl 4-hydroxy-7-methoxy-2-(methylthio)quinoline-3-carboxylate (**4b**) and Methyl 4-hydroxy-5-methoxy-2-(methylthio)quinoline-3-carboxylate (**4c**)

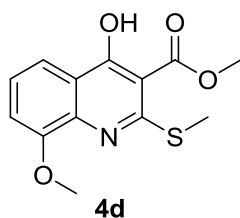


Using the optimized condition (Table S1, entry 11), **4b** and **4c** were obtained as white solid (53%, **4b/4c** = 10:1); **4b** : m.p. 156-157 °C; ¹H NMR (300 MHz, CDCl₃) δ 13.08 (s, 1H), 8.08 (d, *J* = 9.0 Hz, 1H), 7.13 (d, *J* = 2.5 Hz, 1H), 7.02 (dd, *J* = 9.0, 2.5 Hz, 1H), 4.05 (s, 3H), 3.95 (s, 3H), 2.60 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ : 171.5, 168.2, 163.7, 160.9, 151.1, 125.2, 117.2, 112.2, 106.7, 101.2, 55.7, 52.5, 14.8; IR (neat) 3443br, 3011, 2945, 2916, 1656, 1615, 1586, 1440, 1346, 1214, 1166, 1106, 997, 837 cm⁻¹; HRMS (ESI) calcd for C₁₃H₁₃NO₄S₁ [M]⁺ 279.0565 found: 279.0566.



4c : m.p. 120-121 °C; ¹H NMR (300 MHz, CDCl₃) δ 12.12 (s, 1H), 7.57 (t, *J* = 8.2 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 1H), 6.78 (d, *J* = 7.8 Hz, 1H), 4.03 (s, 3H), 4.02 (s, 3H), 2.60 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 169.1, 165.6, 160.2, 157.6, 150.6, 132.2, 121.3, 108.9, 106.4, 104.9, 56.6, 52.5, 14.3; IR (neat) 3424br, 3301, 2921, 1722, 1657, 1620, 1577, 1437, 1402, 1352, 1245, 1224, 1090, 923, 861 cm⁻¹; HRMS (ESI) calcd for C₁₃H₁₃NO₄S₁ [M]⁺ 279.0565 found: 279.0563.

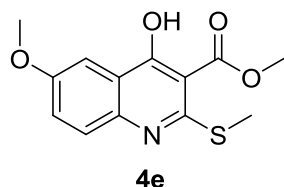
Synthesis of Methyl 4-hydroxy-8-methoxy-2-(methylthio)quinoline-3-carboxylate (**4d**)



Using the optimized condition (Table S1, entry 11), **4d** was obtained as White solid, 41%; m.p. 118-119 °C; ¹H NMR (300 MHz, CDCl₃) (Enol-form) δ 13.15 (s, 1H), 7.81 (d, *J* = 8.3 Hz, 1H), 7.35 (t, *J* = 8.0 Hz, 1H), 7.13 (d, *J* = 7.8 Hz, 1H), 4.08 (s, 3H), 4.04 (s, 3H), 2.68 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 171.5, 168.5, 159.2, 154.4, 140.5, 125.0, 119.0, 115.4, 112.5, 103.0, 56.5, 52.6, 14.6; ¹H NMR (300 MHz, CDCl₃) (Keto-form) δ 8.65 (bs, 1H), 7.90 (d, *J* = 8.1 Hz, 1H), 7.23 (t, *J* = 8.0 Hz, 1H), 7.06 (d, *J* = 7.0 Hz, 1H), 4.03 (s, 3H), 3.95 (s, 3H), 2.61 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 173.9, 167.2, 153.3, 146.9, 129.4, 126.0, 124.3, 118.1, 113.5, 111.4, 56.4, 52.3 14.8; IR (neat) 3424br,

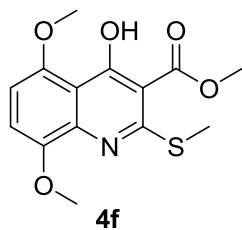
2957, 2917, 1660, 1617, 1565, 1480, 1437, 1396, 1346, 1260, 1157, 1076, 1001, 738 cm^{-1} ; IR (neat) (crystal-keto) 3468, 3213, 3140, 3013, 2954, 2845, 1715, 1624, 1547, 1496, 1452, 1355, 1316, 1269, 1241, 1190, 1143, 1072, 1000, 977, 752, 730 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{13}\text{NO}_4\text{S}_1$ $[\text{M}]^+$ 279.0565 found: 279.0571.

Synthesis of Methyl 4-hydroxy-6-methoxy-2-(methylthio)quinoline-3-carboxylate (4e)



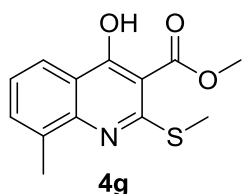
Using the optimized condition (Table S1, entry 11), **4e** was obtained as White solid, 46%; m.p. 140-141 $^{\circ}\text{C}$; ^1H NMR (300 MHz, CDCl_3) δ 13.09 (s, 1H), 7.73 (d, $J = 9.1$ Hz, 1H), 7.46 (d, $J = 2.9$ Hz, 1H), 7.35 (dd, $J = 9.1, 2.9$ Hz, 1H), 4.07 (s, 3H), 3.93 (s, 3H), 2.59 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.7, 167.6, 157.2, 156.9, 145.0, 129.4, 125.1, 118.4, 102.6, 101.5, 55.8, 52.6; IR (neat) 3435br, 2945, 2917, 1657, 1617, 1588, 1486, 1467, 1437, 1409, 1347, 1312, 1215, 1167, 1107, 999, 840 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{13}\text{NO}_4\text{S}_1$ $[\text{M}]^+$ 279.0565 found: 279.0565.

Synthesis of Methyl 4-hydroxy-5,8-dimethoxy-2-(methylthio)quinoline-3-carboxylate (4f)



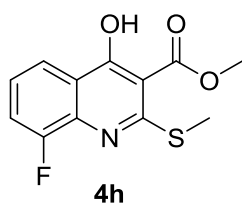
Using the optimized condition (Table S1, entry 11), **4f** was obtained as White solid, 43%; m.p. 130-131 $^{\circ}\text{C}$; ^1H NMR (300 MHz, CDCl_3) (Enol-form) δ 11.61 (s, 1H), 6.95 (d, $J = 8.7$ Hz, 1H), 6.64 (d, $J = 8.7$ Hz, 1H), 3.97 (s, 3H), 3.95 (s, 6H), 2.66 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 168.0, 163.6, 159.1, 150.4, 149.1, 141.4, 111.5, 109.4, 108.2, 104.0, 56.8, 56.5, 52.4, 13.8; ^{13}C NMR (125 MHz, CDCl_3) δ 168.0, 163.6, 159.1, 150.4, 149.1, 141.4, 111.5, 109.4, 108.2, 104.0, 56.8, 56.5, 52.4, 13.8; ^1H NMR (300 MHz, CDCl_3) (Keto-form) δ 11.61 (s, 1H), 6.95 (d, $J = 8.7$ Hz, 1H), 6.64 (d, $J = 8.7$ Hz, 1H), 3.97 (s, 3H), 3.95 (s, 6H), 2.66 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 174.6, 167.2, 158.7, 153.6, 141.9, 129.6, 117.8, 112.6, 106.9, 102.9, 56.6, 56.2; IR (neat) 3417br, 3268, 3000, 2951, 2918, 2840, 1717, 1618, 1573, 1486, 1372, 1258, 1217, 1179, 1143, 1095, 1063, 1007, 947, 796; HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{15}\text{NO}_5\text{S}_1$ $[\text{M}]^+$ 309.0671 found: 309.0670.

Synthesis of Methyl 4-hydroxy-8-methyl-2-(methylthio)quinoline-3-carboxylate (4g)



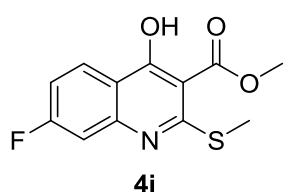
Using the optimized condition (Table S1, entry 11), **4g** was obtained as White solid, 44%; m.p. 98-99 $^{\circ}\text{C}$; ^1H NMR (300 MHz, CDCl_3) δ 13.09 (s, 1H), 8.08 (dd, $J = 8.5, 1.0$ Hz, 1H), 7.58 (d, $J = 7.0$ Hz, 1H), 7.36-7.29 (m, 1H), 4.08 (s, 3H), 2.70 (s, 3H), 2.61 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ : 171.5, 168.8, 158.7, 147.4, 136.0, 133.1, 124.6, 121.4, 117.6, 105.6, 102.1, 52.4, 17.8, 14.9; IR (neat) 3450br, 2955, 2915, 1654, 1618, 1572, 1355, 1243, 1194, 1161, 822 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{13}\text{NO}_3\text{S}_1$ $[\text{M}]^+$ 263.0616 found 263.0612.

Synthesis of Methyl 8-fluoro-4-hydroxy-2-(methylthio)quinoline-3-carboxylate (**4h**)



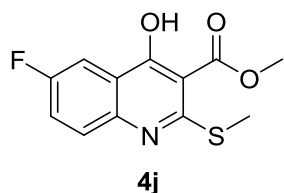
Using the optimized condition (Table S1, entry 11), **4h** was obtained as White solid, 26%; m.p. 113-114 °C; $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 13.25 (s, 1H), 7.99 (dt, $J = 8.1, 1.2$ Hz, 1H), 7.42 (ddd, $J = 10.4, 7.8, 1.5$ Hz, 1H), 7.33 (td, $J = 8.0, 4.8$ Hz, 1H), 4.09 (s, 3H), 2.64 (s, 3H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 171.4, 168.4, 161.1, 158.1, 156.1, 138.9, 124.6, 119.9, 119.4, 117.5, 117.4, 103.2, 100.1, 52.8, 14.9; IR (neat) 3443br, 2924, 2854, 1654, 1630, 1584, 1565, 1481, 1460, 1400, 1361, 1254, 982, 934, 786, 748 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{10}\text{F}_1\text{N}_1\text{O}_3\text{S}_1$ $[\text{M}]^+$ 267.0365 found 267.0364.

Synthesis of Methyl 7-fluoro-4-hydroxy-2-(methylthio)quinoline-3-carboxylate (**4i**)



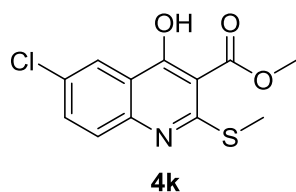
Using the optimized condition (Table S1, entry 11), **4i** was obtained as white solid, 79%; m.p. 160-161 °C; $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 13.21 (s, 1H), 8.20 (dd, $J = 9.1, 6.2$ Hz, 1H), 7.42 (dd, $J = 10.2, 2.5$ Hz, 1H), 7.16 (ddd, $J = 9.1, 8.2, 2.5$ Hz, 1H), 4.07 (s, 3H), 2.58 (s, 3H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 171.4, 168.3, 166.7, 164.7, 161.9, 150.4, 150.3, 126.4, 114.9, 114.8, 114.7, 112.1, 111.9, 102.1, 52.7, 14.9; IR (neat) 3433br, 3100, 2954, 2926, 1644, 1626, 1574, 1446, 1352, 1310, 1229, 1206,

Synthesis of Methyl 6-fluoro-4-hydroxy-2-(methylthio)quinoline-3-carboxylate (**4j**)



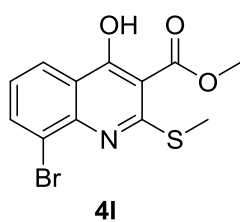
Using the optimized condition (Table S1, entry 11), **4j** was obtained as white solid, 53%; m.p. 139-140 °C; $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 13.09 (s, 1H), 7.78-7.74 (m, 1H), 7.45 (ddd, $J = 9.3, 8.2, 3.0$ Hz, 1H), 4.07 (s, 3H), 2.58 (s, 3H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 171.3, 167.8, 160.5, 159.3, 158.5, 145.9, 130.1, 130.0, 122.6, 122.4, 118.5, 118.4, 107.7, 107.5, 102.7, 52.7, 14.8; IR (neat) 3435br, 3093, 2959, 2916, 1660, 1593, 1563, 1490, 1435, 1210, 1179, 825 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{10}\text{F}_1\text{N}_1\text{O}_3\text{S}_1$ $[\text{M}]^+$ 267.0365 found 267.0364.

Synthesis of Methyl 6-chloro-4-hydroxy-2-(methylthio)quinoline-3-carboxylate (**4k**)



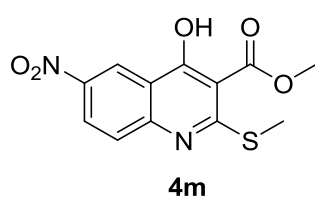
Using the optimized condition (Table S1, entry 11), **4k** was obtained as white solid, 77%; m.p. 158-159 °C; $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 13.09 (s, 1H), 8.10 (d, $J = 2.4$ Hz, 1H), 7.68 (d, $J = 8.9$ Hz, 1H), 7.58 (dd, $J = 8.9, 2.4$ Hz, 1H), 4.06 (s, 3H), 2.55 (s, 3H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 171.3, 167.6, 160.7, 147.3, 133.6, 130.6, 129.4, 122.8, 118.7, 103.0, 52.7, 14.8; IR (neat) 3451br, 2956, 2918, 1739, 1656, 1579, 1557, 1438, 1393, 1347, 1219, 1010, 828 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{10}\text{Cl}_1\text{N}_1\text{O}_3\text{S}_1$ $[\text{M}]^+$ 283.0070 found 283.0071.

Synthesis of Methyl 8-bromo-4-hydroxy-2-(methylthio)quinoline-3-carboxylate (**4l**)



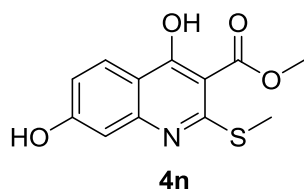
Using the optimized condition (Table S1, entry 11), **4l** was obtained as white solid, 38%; m.p. 136-137 °C; ¹H NMR (300 MHz, CDCl₃) δ 13.14 (s, 1H), 8.07 (d, *J* = 8.1 Hz, 1H), 7.96 (d, *J* = 7.4 Hz, 1H), 7.18 (t, *J* = 7.9 Hz, 1H), 4.06 (s, 3H), 2.63 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 171.3, 168.5, 161.6, 145.3, 136.3, 125.1, 123.8, 123.4, 119.1, 102.7, 52.7, 15.4; IR (neat) 3435br, 2989, 2950, 2917, 2849, 1656, 1610, 1579, 1546, 1469, 1445, 1391, 1347, 1228, 1205, 1162, 1118, 1002, 950, 842, 783 cm⁻¹; HRMS (ESI) calcd for C₁₂H₁₀BrN₁O₃S₁ [M]⁺ 326.9565 found 326.9567.

Synthesis of Methyl 4-hydroxy-2-(methylthio)-6-nitroquinoline-3-carboxylate (**4m**)



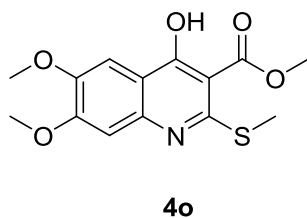
Using the optimized condition (Table S1, entry 11), **4m** was obtained as white solid, 84%; m.p. 292-293 °C; ¹H NMR (300 MHz, CDCl₃) δ 13.36 (s, 1H), 9.10 (s, 1H), 8.44 (dd, *J* = 9.1, 2.9 Hz, 1H), 7.85 (d, *J* = 9.1 Hz, 1H), 4.10 (s, 3H), 2.61 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 171.0, 169.0, 165.5, 150.8, 144.1, 129.1, 126.5, 121.4, 117.2, 103.7, 53.1, 15.1; IR (neat) 3433br, 2923, 1658, 1618, 1597, 1562, 1478, 1432, 1339, 1234, 1205, 840 cm⁻¹; HRMS (ESI) calcd for C₁₂H₁₀N₂O₅S₁ [M]⁺ 294.0310 found 294.0303.

Synthesis of Methyl 4,7-dihydroxy-2-(methylthio)quinoline-3-carboxylate (**4n**)



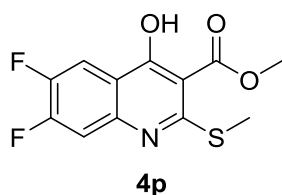
Using the optimized condition (Table S1, entry 11), **4n** was obtained as white solid, 25%; m.p. 225-226 °C; ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.43 (s, 1H), 10.45 (s, 1H), 7.88 (d, *J* = 8.8 Hz, 1H), 6.98 (s, 1H), 6.84 (d, *J* = 8.8 Hz, 1H), 3.76 (s, 3H), 2.62 (s, 3H); ¹³C NMR (125 MHz, DMSO-*d*₆) δ 172.6, 166.9, 161.5, 148.0, 142.5, 127.4, 118.0, 117.4, 115.0, 101.8, 52.3, 16.6; IR (neat) 3360br, 3211, 3091, 3065, 2955, 2391, 1714, 1626, 1524, 1467, 1438, 1354, 1320, 1187, 1139, 831 cm⁻¹; HRMS (ESI) calcd for C₁₂H₁₁N₁O₄S₁ [M]⁺ 265.0409 found 265.0404.

Synthesis of Methyl 4-hydroxy-6,7-dimethoxy-2-(methylthio)quinoline-3-carboxylate (**4o**)



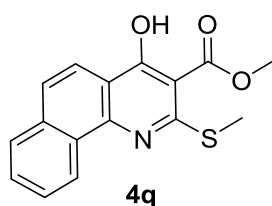
Using the optimized condition (Table S1, entry 11), **4o** was obtained as white solid, 46%; m.p. 162-163 °C; ¹H NMR (300 MHz, CDCl₃) δ 13.03 (s, 1H), 7.40 (s, 1H), 7.15 (s, 1H), 4.05 (s, 3H), 4.03 (s, 3H), 4.00 (s, 3H), 2.58 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 171.7, 167.0, 158.2, 154.9, 148.4, 146.5, 111.8, 107.4, 101.6, 56.3, 52.4, 14.7; IR (neat) 3426br, 3296, 3001, 2960, 2927, 1657, 1596, 1508, 1454, 1407, 1232, 993, 838 cm⁻¹; HRMS (ESI) calcd for C₁₄H₁₅N₁O₅S₁ [M]⁺ 309.0671 found 309.0665.

Synthesis of Methyl 6,7-difluoro-2-(methylthio)-4-oxo-1,4-dihydroquinoline-3-carboxylate (**4p**)



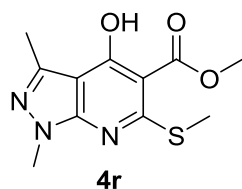
Using the optimized condition (Table S1, entry 11), **4p** was obtained as white solid, 59%; m.p. 175-176 °C; $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 13.17 (s, 1H), 7.93 (dd, $J = 10.4, 8.7$ Hz, 1H), 7.56 (dd, $J = 11.2, 7.3$ Hz, 1H), 4.08 (s, 3H), 2.57 (s, 3H); $^{13}\text{C NMR}$ (CDCl_3) δ : 171.3, 167.7, 161.3, 155.6, 153.7, 150.1, 150.0, 148.1, 148.0, 146.6, 114.7, 114.5, 110.3, 110.2, 102.7, 52.8, 14.9; IR (neat) 3425br, 3016, 2962, 2923, 1655m 1598, 1569, 1510, 1445, 1361, 1229, 1186, 1000, 874 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{12}\text{H}_9\text{F}_2\text{N}_1\text{O}_3\text{S}_1$ $[\text{M}]^+$ 285.0271 found 285.0270.

Synthesis of Methyl 4-hydroxy-2-(methylthio)benzo[*h*]quinoline-3-carboxylate (**4q**)



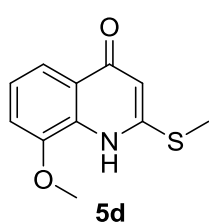
Using the optimized condition (Table S1, entry 11), **4q** was obtained as brown solid, 75%; m.p. 163-164 °C; $^1\text{H NMR}$ (CDCl_3) δ : 12.93(s, 1H), 9.11-9.08(d, $J = 5.7$ Hz, 1H), 8.03-8.00(d, $J = 9.0$ Hz, 1H), 7.84-7.82(d, $J = 5.4$ Hz, 1H), 7.66-7.64(d, $J = 5.9$ Hz, 1H), 4.07(s, 3H), 2.73(s, 3H); $^{13}\text{C NMR}$ (CDCl_3) δ : 171.4, 167.8, 160.0, 147.2, 135.1, 130.5, 129.1, 127.9, 126.8, 125.6, 125.4, 119.8, 114.2, 103.6, 52.6, 15.2; IR (neat) 3448br, 3048, 2953, 2919, 1664, 1611, 1582, 1346, 1233, 1153, 804 cm^{-1} ; HRMS (EI+) m/z : calcd for $\text{C}_{16}\text{H}_{13}\text{N}_1\text{O}_3\text{S}_1$ 299.0616; found 299.0615.

Synthesis of Methyl 4-hydroxy-1,3-dimethyl-6-(methylthio)-1H-pyrazolo[3,4-*b*]pyridine-5-carboxylate (**4r**)



Using the optimized condition (Table S1, entry 11), **4r** was obtained as white solid, 5%; m.p. 138-139 °C; $^1\text{H NMR}$ (300 MHz, CDCl_3) (Enol-form) δ 13.18 (s, 1H), 4.02 (s, 3H), 3.94 (s, 3H), 2.61 (s, 3H), 2.55 (s, 3H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 171.8, 167.4, 164.0, 152.5, 143.1, 102.3, 99.8, 52.3, 33.3, 15.3, 14.3; $^1\text{H NMR}$ (300 MHz, CDCl_3) (Keto-form) δ 12.57 (s, 1H), 4.13 (s, 3H), 4.05 (s, 3H), 2.83 (s, 3H), 2.68 (s, 3H); IR (neat) 3432br, 3002, 2946, 2922, 2852, 1656, 1611, 1554, 1454, 1435, 1375, 1348, 1329, 1303, 1219, 1138, 995, 972, 833, 803, 757 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{11}\text{H}_{13}\text{N}_3\text{O}_3\text{S}_1$ $[\text{M}]^+$ 267.0678; found 267.0673.

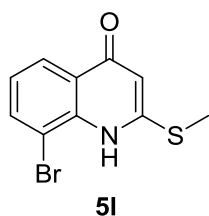
Synthesis of 8-methoxy-2-(methylthio)quinolin-4(1H)-one (**5d**)



Using the optimized condition of decarboxylation, **5d** was obtained as light brown solid (95%); m.p. 220-221 °C; $^1\text{H NMR}$ (300 MHz, CDCl_3) δ : 8.49 (br s, 1H), 7.88-7.84 (dd, $J = 8.3, 1.2$ Hz, 1H), 7.25-7.20 (t, $J = 8.0$ Hz, 1H), 7.04-7.01 (dd, $J = 7.8, 1.2$ Hz, 1H), 6.20 (s, 1H), 4.00 (s, 3H), 2.58 (s, 3H); $^{13}\text{C NMR}$ (CDCl_3) δ 177.3, 151.2, 147.1, 131.2, 125.6, 123.2, 117.6, 110.9, 107.3, 56.3, 15.2; IR (neat) 3409,

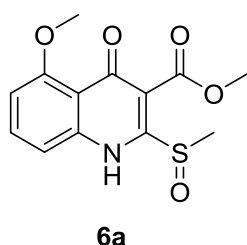
3063, 2988, 2810, 2230, 1554, 1519, 1497, 1446, 1412, 1367, 1266, 1189, 1154, 1106, 1060, 983, 953, 876, 826, 791, 938; HRMS (EI+) m/z : calcd for $C_{11}HN_1O_2S_1$ 221.0511; found 221.2772.

Synthesis of 8-bromo-2-(methylthio)quinolin-4(1H)-one (**5l**)



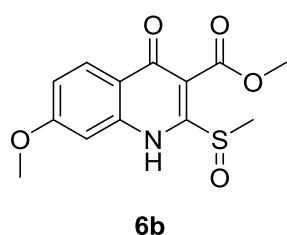
Using the optimized condition of decarboxylation, **5l** was obtained as white solid (98%); m.p. 184-185 °C; 1H NMR (300 MHz, $CDCl_3$) δ 8.47 (s, 1H), 8.24 (d, $J = 8.0$ Hz, 1H), 7.79 (d, $J = 7.5$ Hz, 1H), 7.19 (t, $J = 7.8$ Hz, 1H), 6.25 (s, 1H), 2.60 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 176.6, 152.6, 137.4, 135.2, 126.3, 126.2, 124.4, 110.6, 107.2, 15.1; IR (neat) 3363, 3068, 2922, 2852, 1725, 1615, 1584, 1550, 1495, 1429, 1349, 1095, 950, 929, 798, 748; HRMS (EI+) m/z : calcd for $C_{10}H_8Br_1N_1O_1S_1$ 268.9510; found 268.9531.

Synthesis of Methyl 5-methoxy-2-(methylsulfinyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (**6a**)



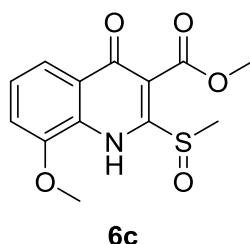
Using the optimized condition for the oxidation, **6a** was obtained as white solid (75%); m.p. 200-201 °C; 1H NMR (300 MHz, $CDCl_3$) (Keto-form) δ 10.01 (s, 1H), 7.57 (t, $J = 8.2$ Hz, 1H), 7.04 (dd, $J = 8.3, 1.0$ Hz, 1H), 6.85 (d, $J = 8.3$ Hz, 1H), 3.97 (s, 3H), 3.91 (s, 3H), 3.01 (s, 3H); (Enol-form) δ 11.58 (s, 1H), 7.83 (d, $J = 8.6$ Hz, 1H), 7.72 (t, $J = 8.2$ Hz, 1H), 6.98 (d, $J = 8.1$ Hz, 1H), 4.10 (s, 3H), 4.01 (s, 3H), 2.93 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.9, 167.3, 165.8, 161.0, 158.9, 139.6, 133.8, 123.7, 117.4, 110.1, 108.2, 107.6, 56.4, 52.6, 43.2; IR (neat) 3466, 3136, 3118, 3091, 1669, 1643, 1609, 1532, 1438, 1320, 1198, 1104, 815 cm^{-1} . HRMS (ESI) calcd for $C_{13}H_{13}NO_5S_1$ $[M]^+$ 295.0514; found 295.0536.

Synthesis of Methyl 7-methoxy-2-(methylsulfinyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (**6b**)



Using the optimized condition for the oxidation, **6b** was obtained as white solid, 87%; m.p. 208-209 °C; 1H NMR (300 MHz, $CDCl_3$) (Keto-form) δ 10.25 (s, 1H), 8.34 (d, $J = 9.0$ Hz, 1H), 7.06 (dd, $J = 9.0, 2.3$ Hz, 1H), 6.90 (d, $J = 2.3$ Hz, 1H), 3.96 (s, 3H), 3.93 (s, 3H), 3.02 (s, 3H); (Enol-form) δ 12.58 (s, 1H), 8.22 (d, $J = 9.0$ Hz, 1H), 7.62 (d, $J = 1.3$ Hz, 1H), 7.25-7.20 (m, 1H), 4.08 (s, 3H), 3.96 (s, 3H), 2.85 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.3, 167.3, 163.8, 160.6, 138.9, 129.2, 121.5, 115.9, 106.9, 100.1, 55.9, 52.8, 43.5; IR (neat) 3448, 3117, 3049, 1729, 1665, 1624, 1595, 1479, 1440, 1332, 1206, 1141, 1037, 957 cm^{-1} . HRMS (ESI) calcd for $C_{13}H_{13}NO_5S_1$ $[M]^+$ 295.0514; found 295.0510.

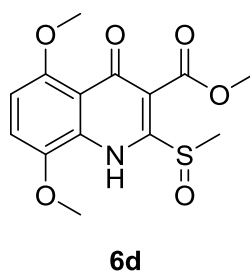
Synthesis of Methyl 8-methoxy-2-(methylsulfinyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (**6c**)



Using the optimized condition for the oxidation, **6c** was obtained as white solid, 72%; m.p. 210-211 °C; ¹H NMR (300 MHz, CDCl₃) δ 10.81 (s, 1H), 7.98 (d, *J* = 8.2 Hz, 1H), 7.41 (t, *J* = 8.1 Hz, 1H), 7.16 (dd, *J* = 7.9, 1.1 Hz, 1H), 4.05 (s, 3H), 3.97 (s, 3H), 3.03 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 174.8, 167.4, 160.4, 148.9, 128.4, 128.1, 126.3, 118.3, 112.4, 106.9, 56.4, 52.8, 43.6; IR (neat) 3435, 3175, 2954, 1666, 1638, 1600, 1443, 1329, 1265, 1150, 974, 785 cm⁻¹.

HRMS (ESI) calcd for C₁₃H₁₃NO₅S₁ [M]⁺ 295.0514; found 295.0538.

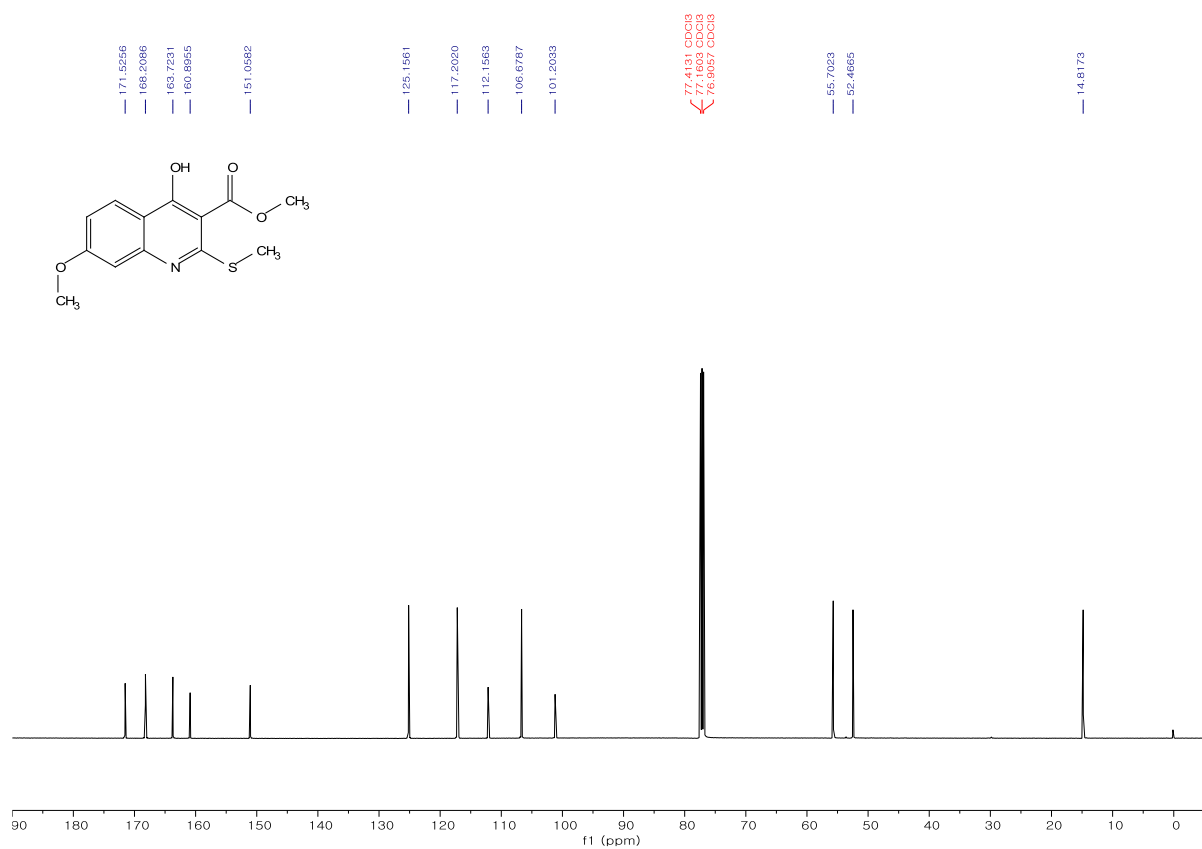
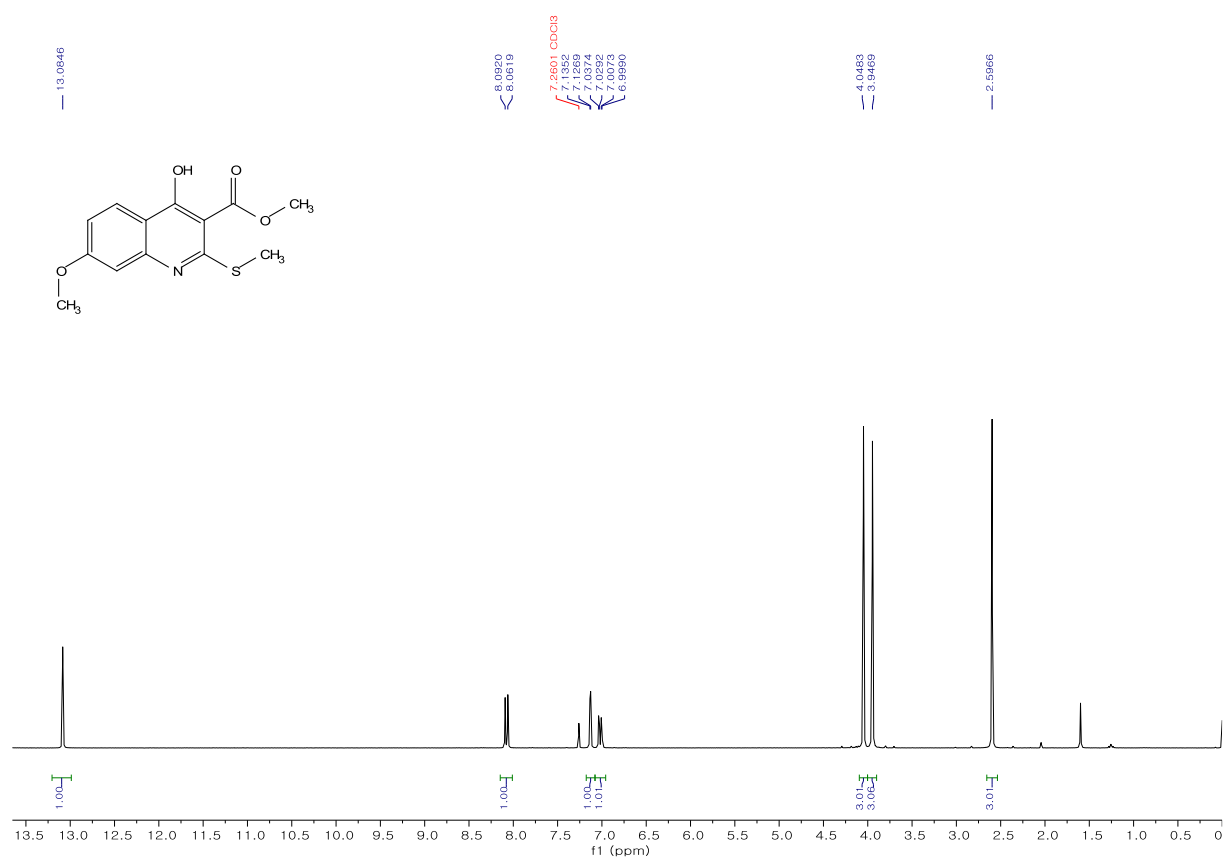
Synthesis of Methyl 5,8-dimethoxy-2-(methylsulfinyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (**6d**)



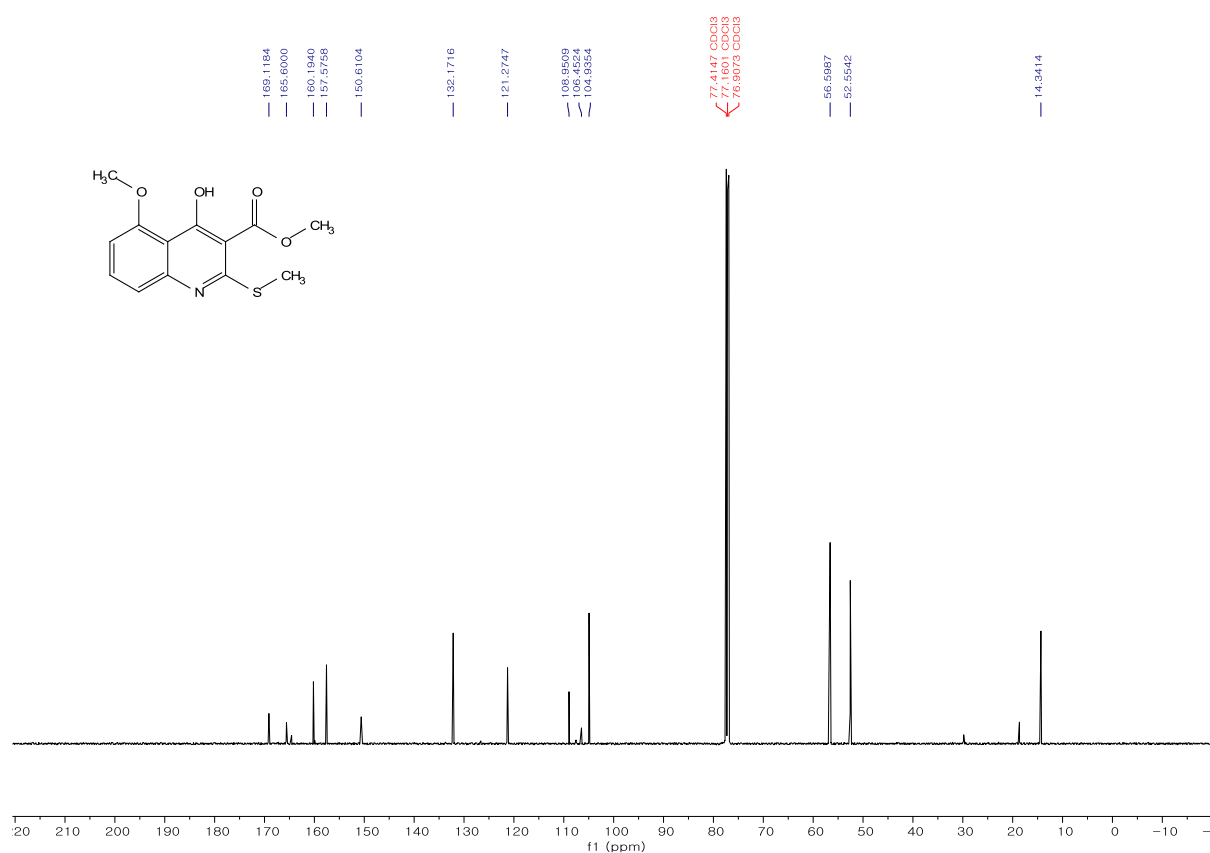
Using the optimized condition for the oxidation, **6d** was obtained as white solid, 67%; m.p. 186-187 °C; ¹H NMR (300MHz, CDCl₃) δ 10.56 (s, 1H), 7.04 (d, *J* = 8.9 Hz, 1H), 6.75 (d, *J* = 8.9 Hz, 1H), 3.97 (s, 3H), 3.91 (s, 6H), 3.01 (s, 3H); ¹³C NMR (125 Mz, CDCl₃) δ 174.78, 167.34, 158.90, 153.94, 142.12, 129.89, 118.09, 112.74, 108.38, 107.15, 56.88, 56.41, 52.52, 43.29; IR (neat) 3442, 3179, 3038, 2968, 2841, 1666, 1640, 1615, 1550, 1526, 1443, 1320, 1275, 1252,

1145, 1103, 1030, 811, 774 cm⁻¹. HRMS (ESI) calcd for C₁₄H₁₅NO₆S₁ [M]⁺ 325.0620; found 325.0642.

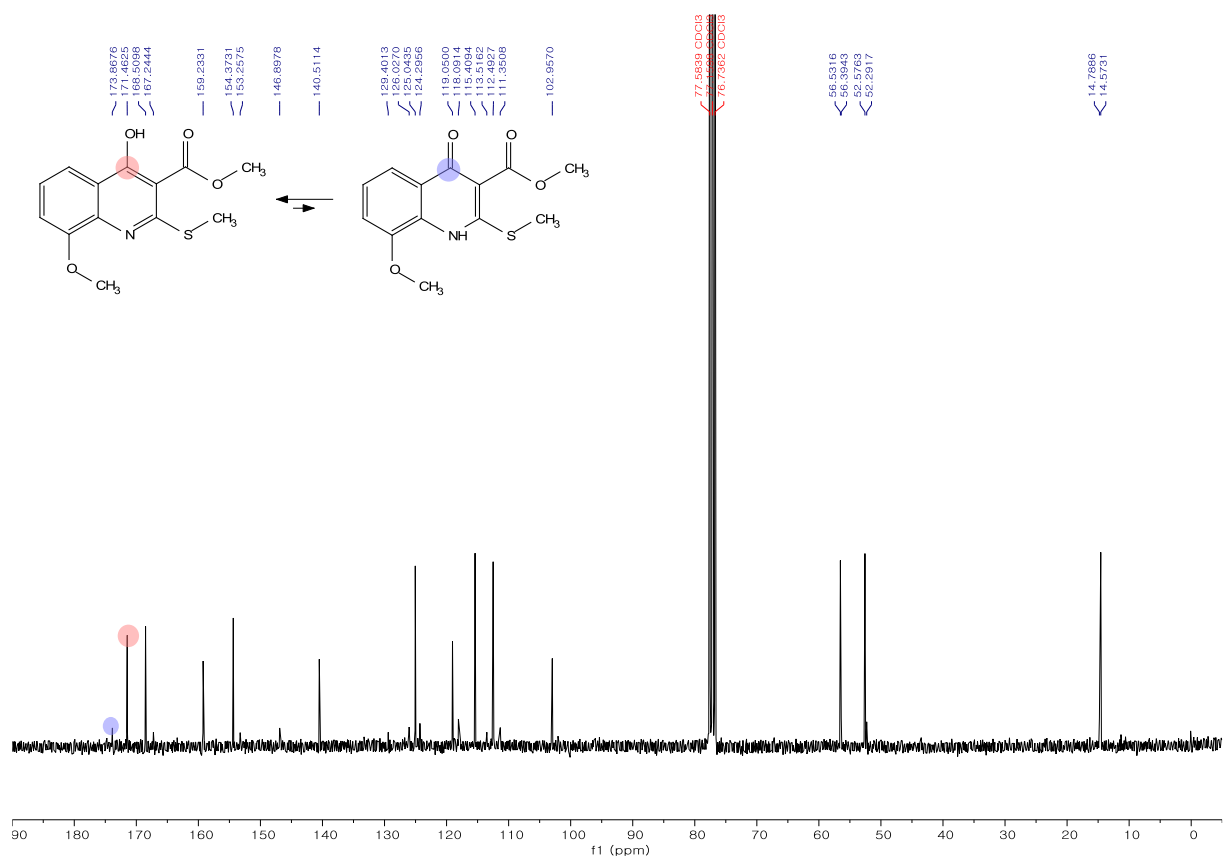
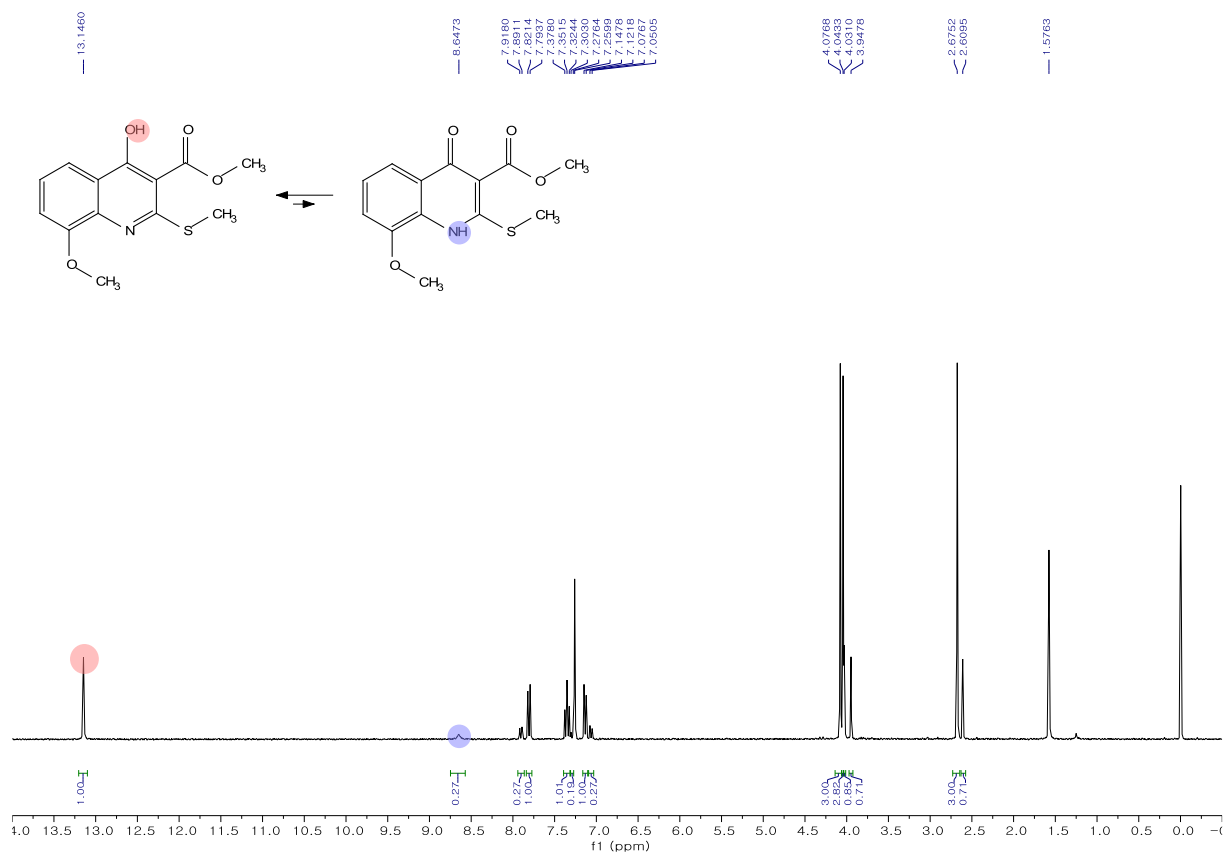
¹H and ¹³C NMR data of methyl 4-hydroxy-7-methoxy-2-(methylthio)quinoline-3-carboxylate (4b)



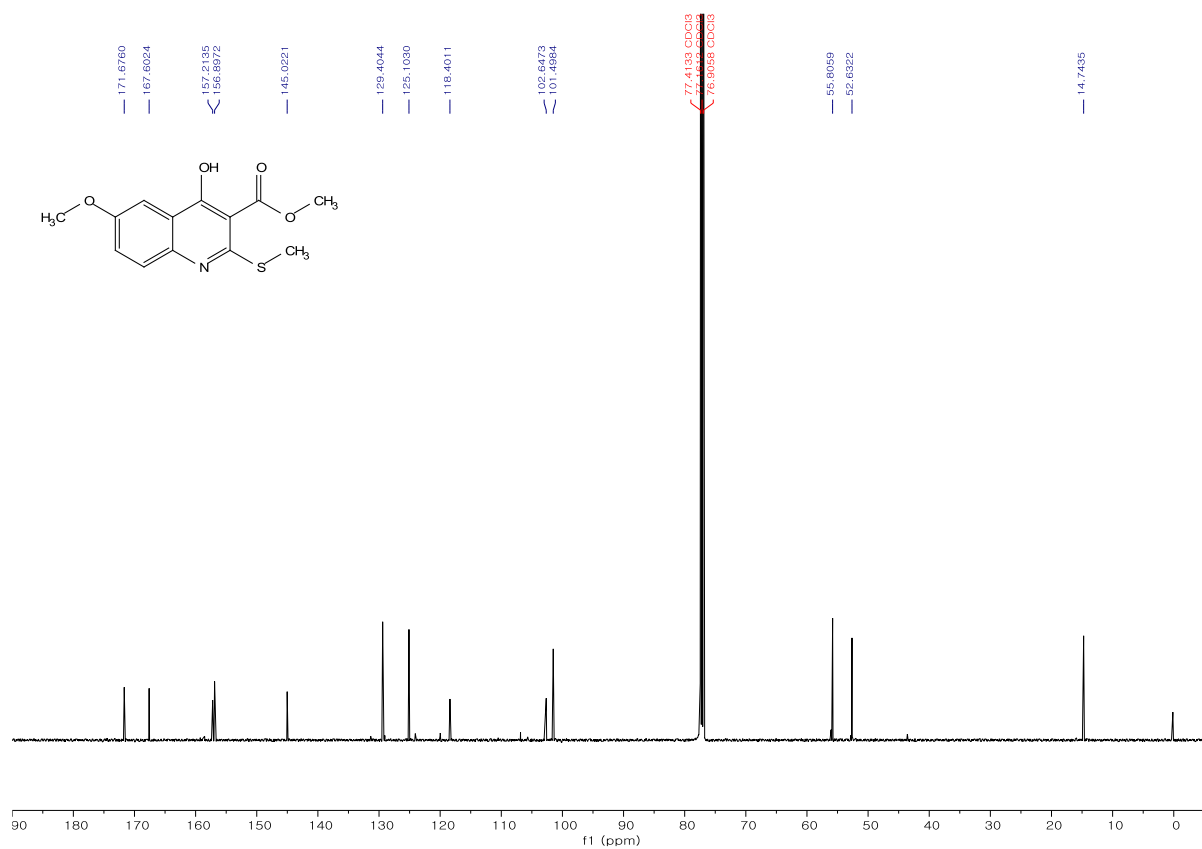
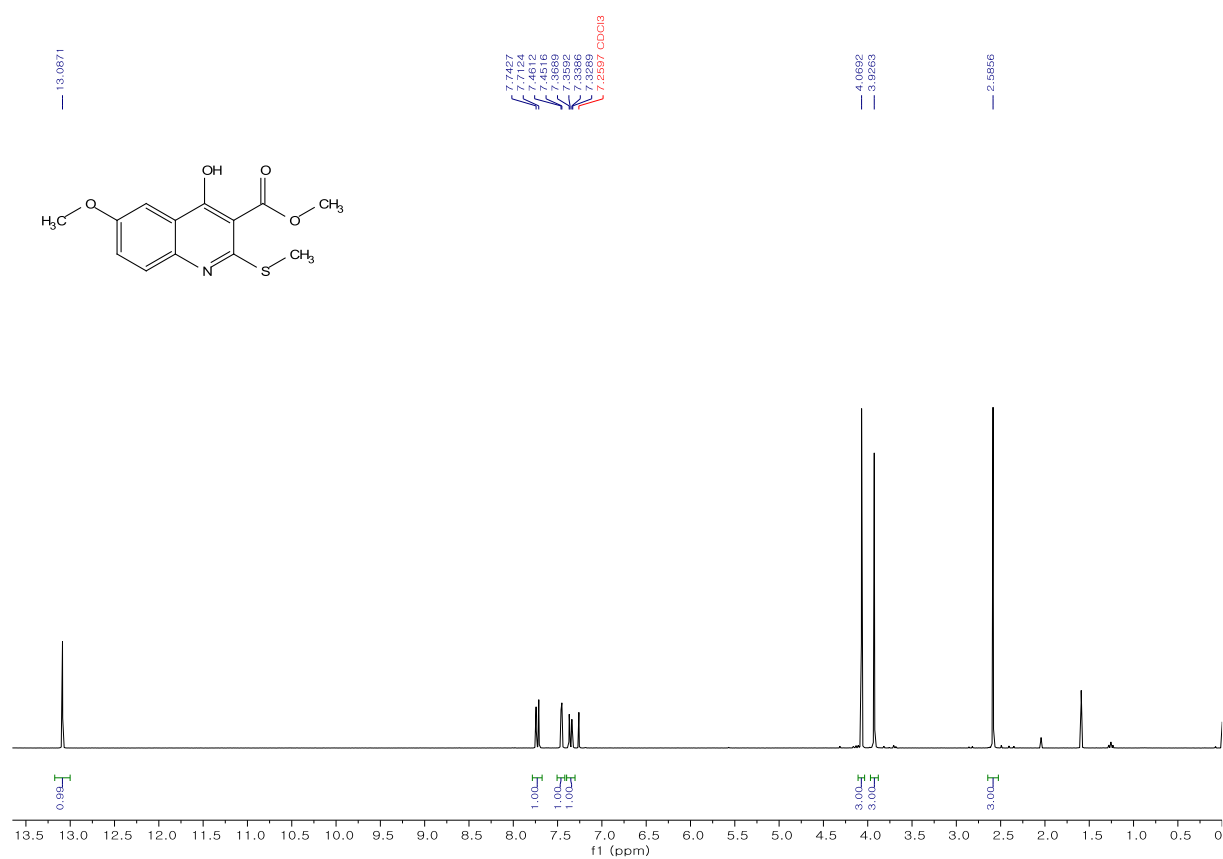
¹H and ¹³C NMR data of methyl 4-hydroxy-5-methoxy-2-(methylthio)quinoline-3-carboxylate (4c)



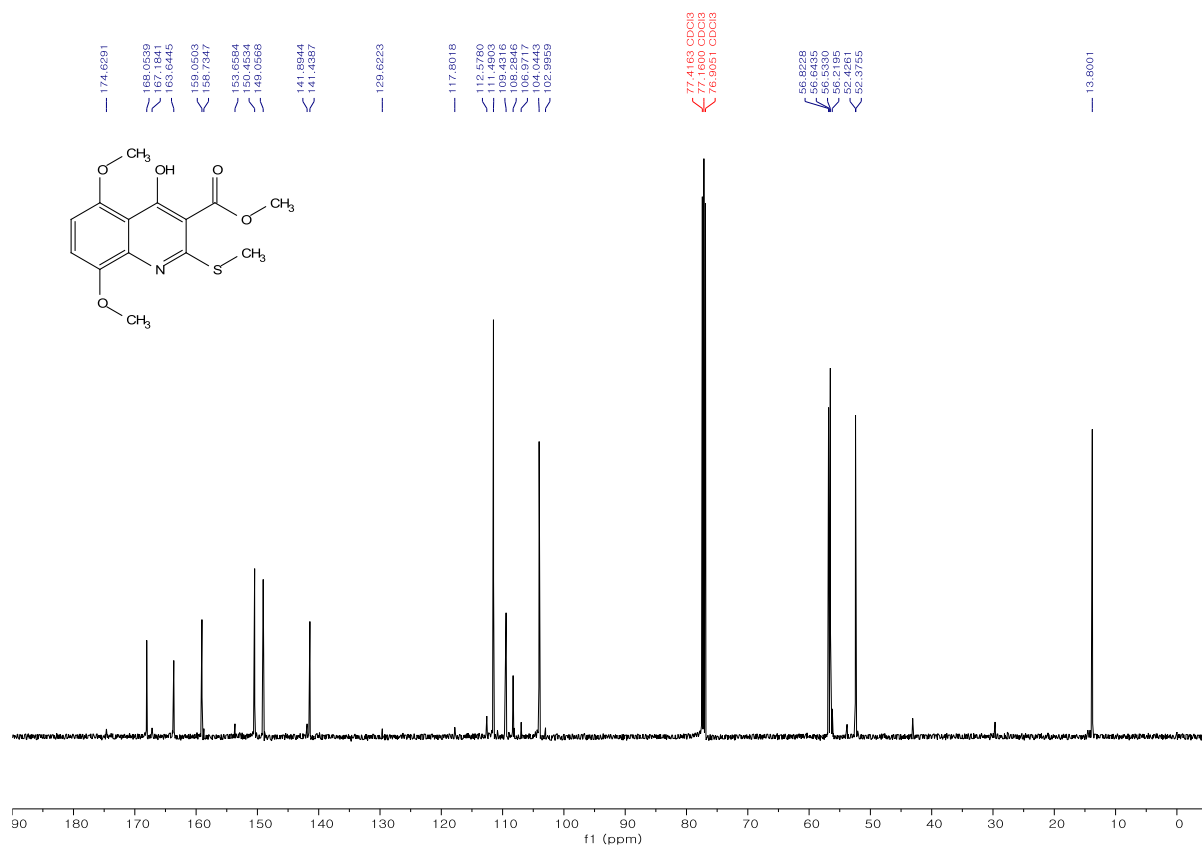
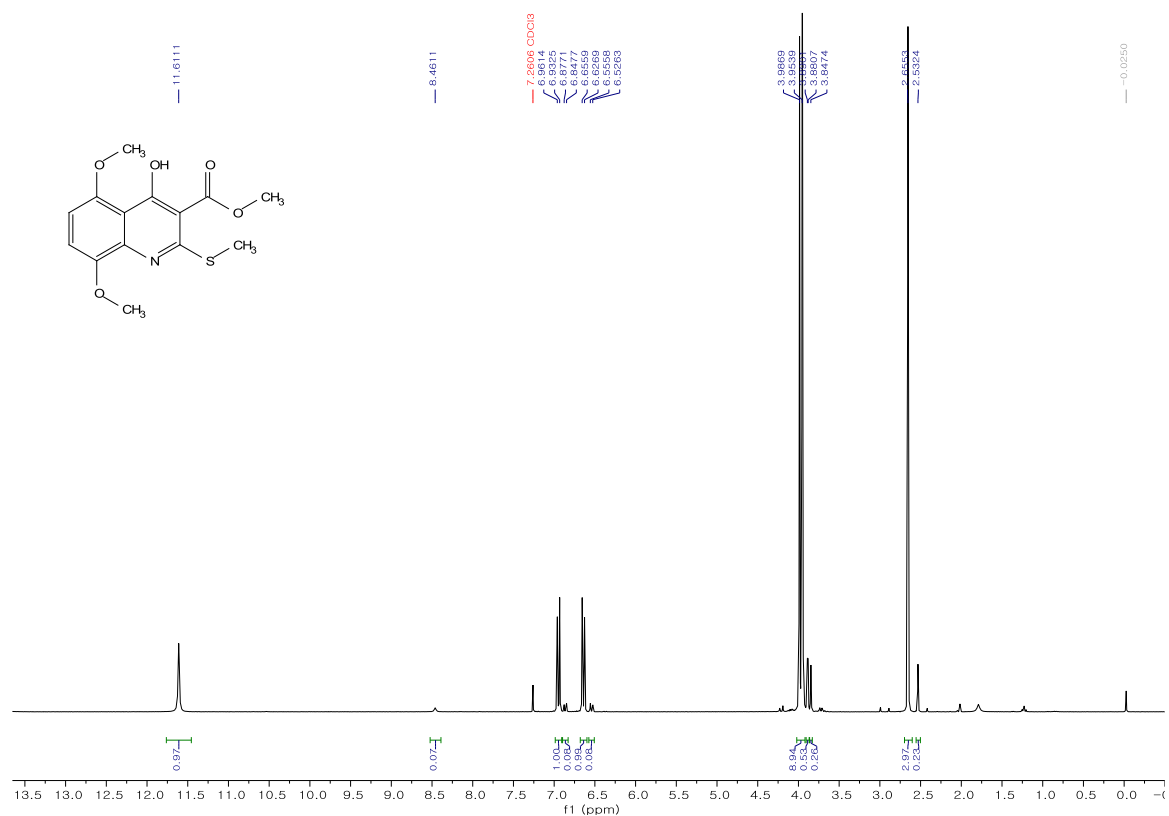
¹H and ¹³C NMR data of methyl 4-hydroxy-8-methoxy-2-(methylthio)quinoline-3-carboxylate (4d)



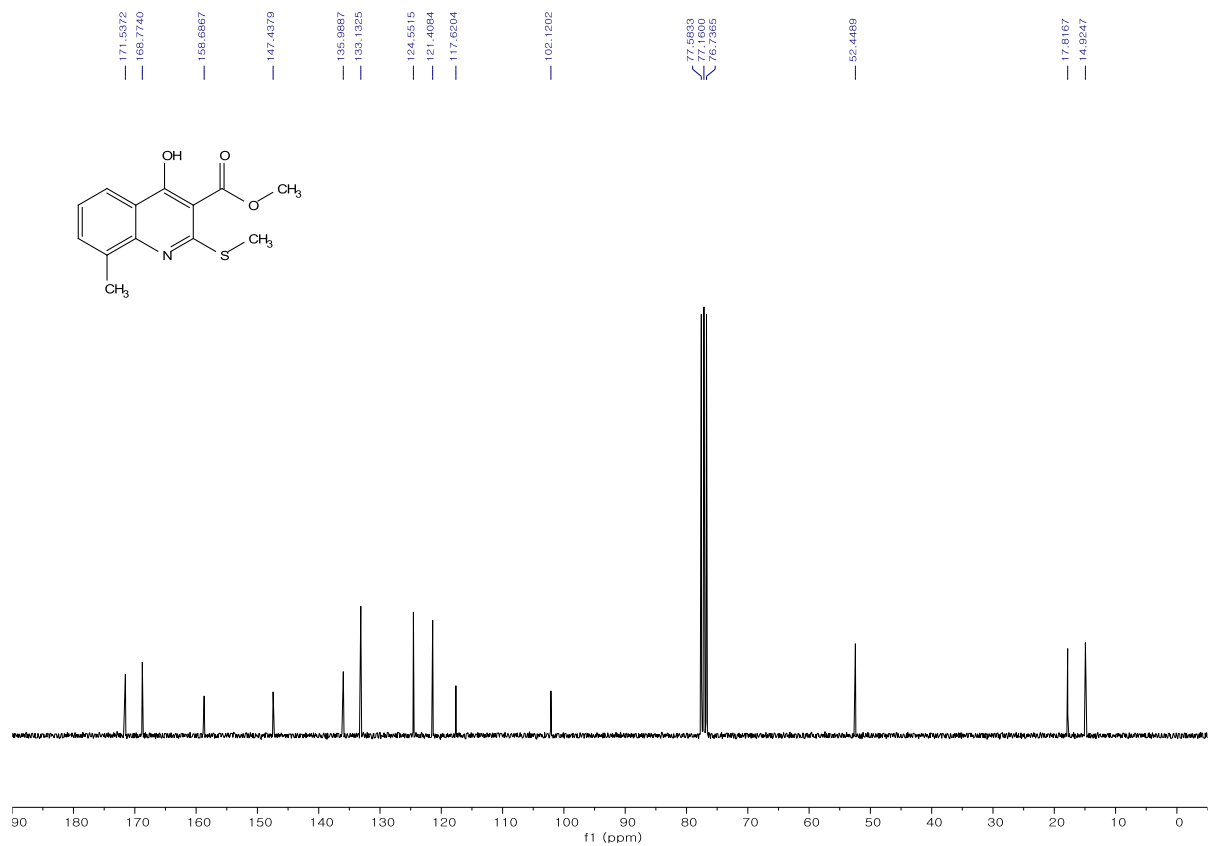
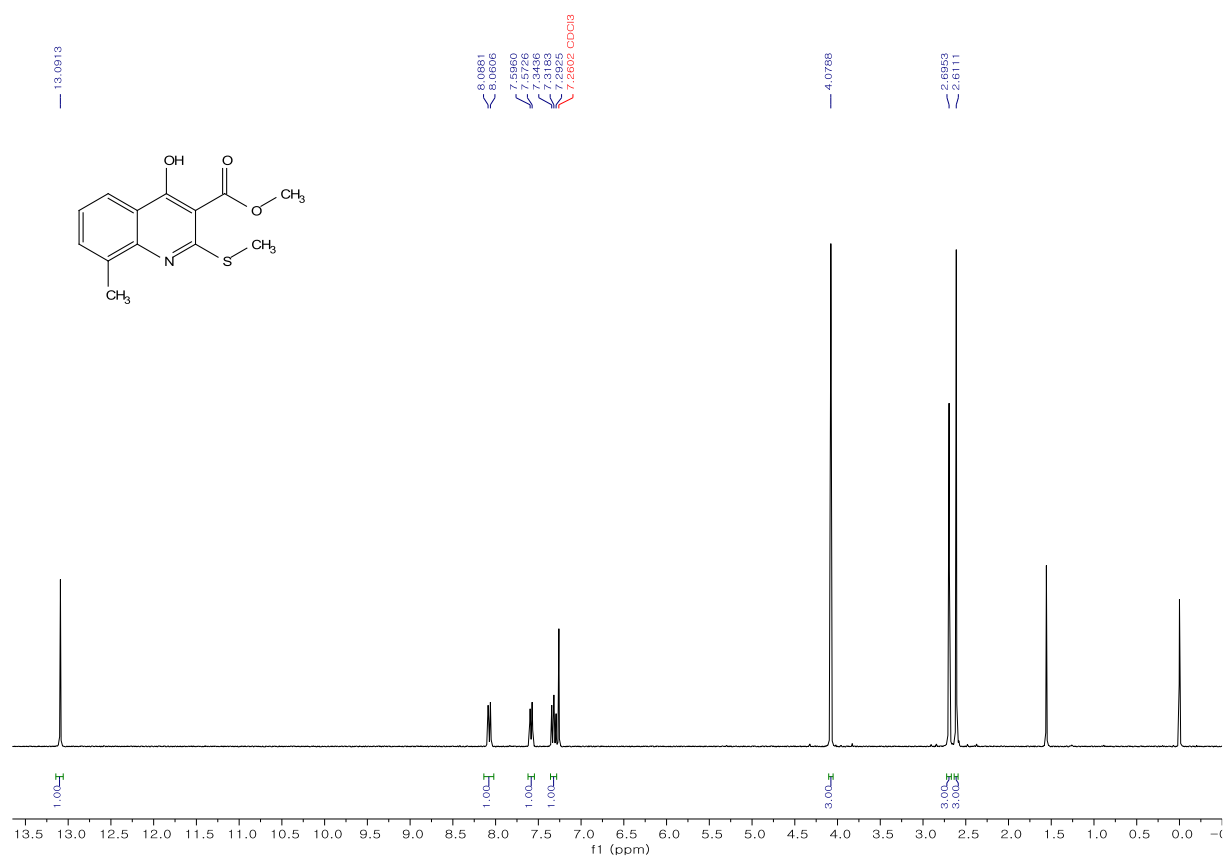
¹H and ¹³C NMR data of methyl 4-hydroxy-6-methoxy-2-(methylthio)quinoline-3-carboxylate (4e)



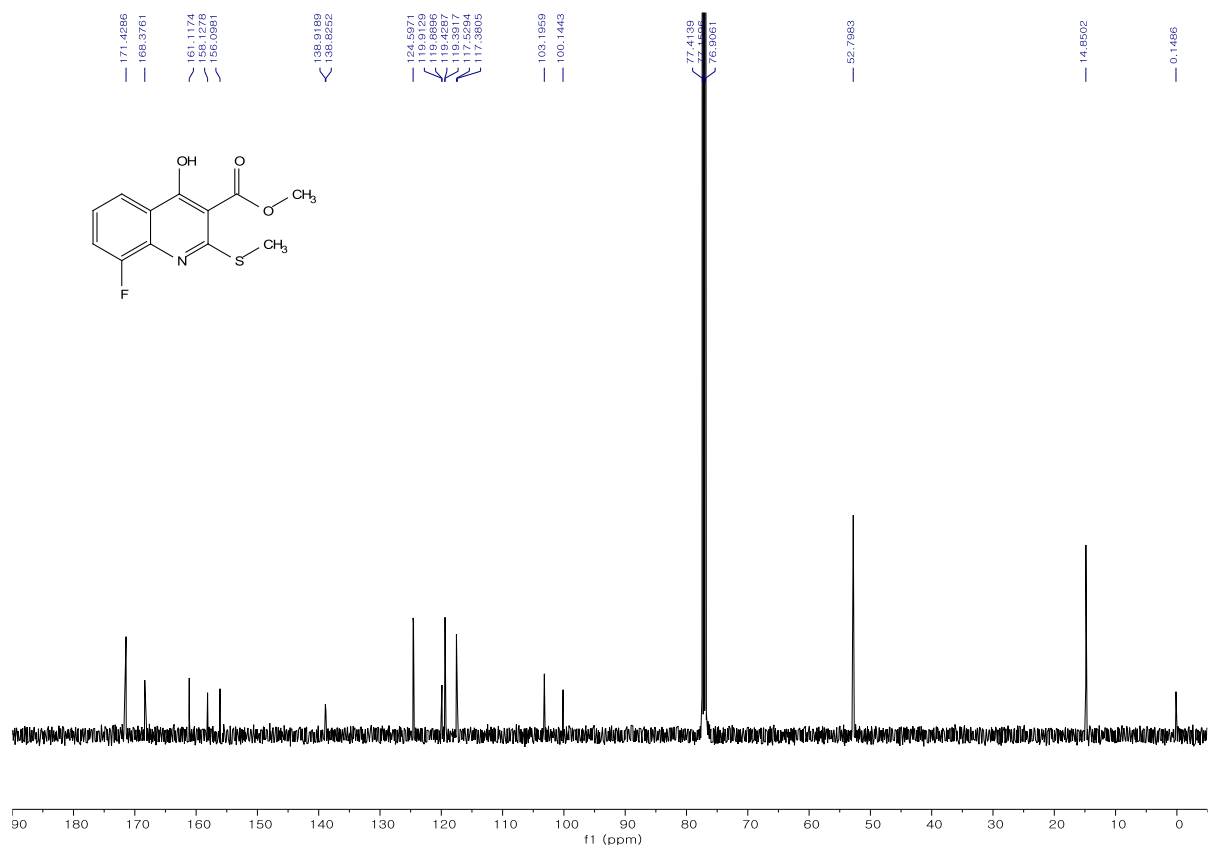
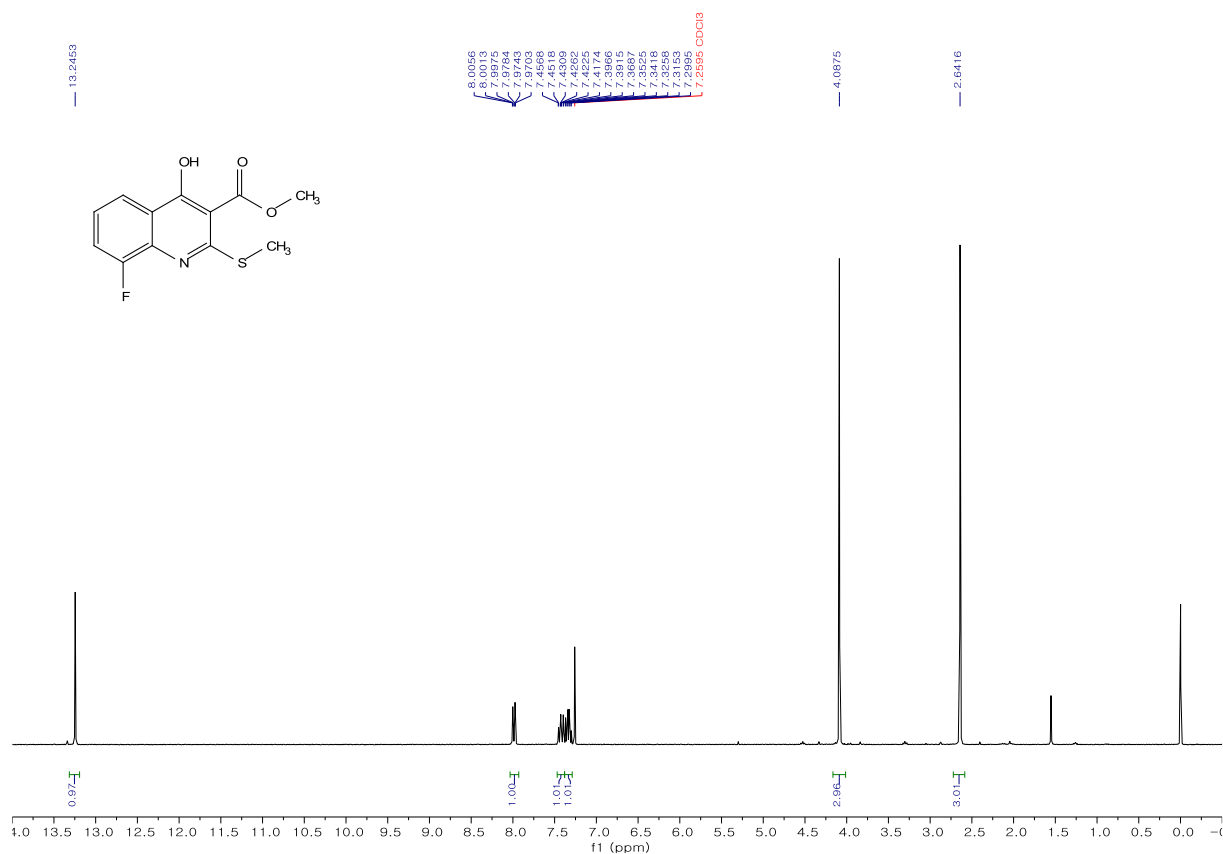
¹H and ¹³C NMR data of methyl 4-hydroxy-5,8-dimethoxy-2-(methylthio)quinoline-3-carboxylate (4f)



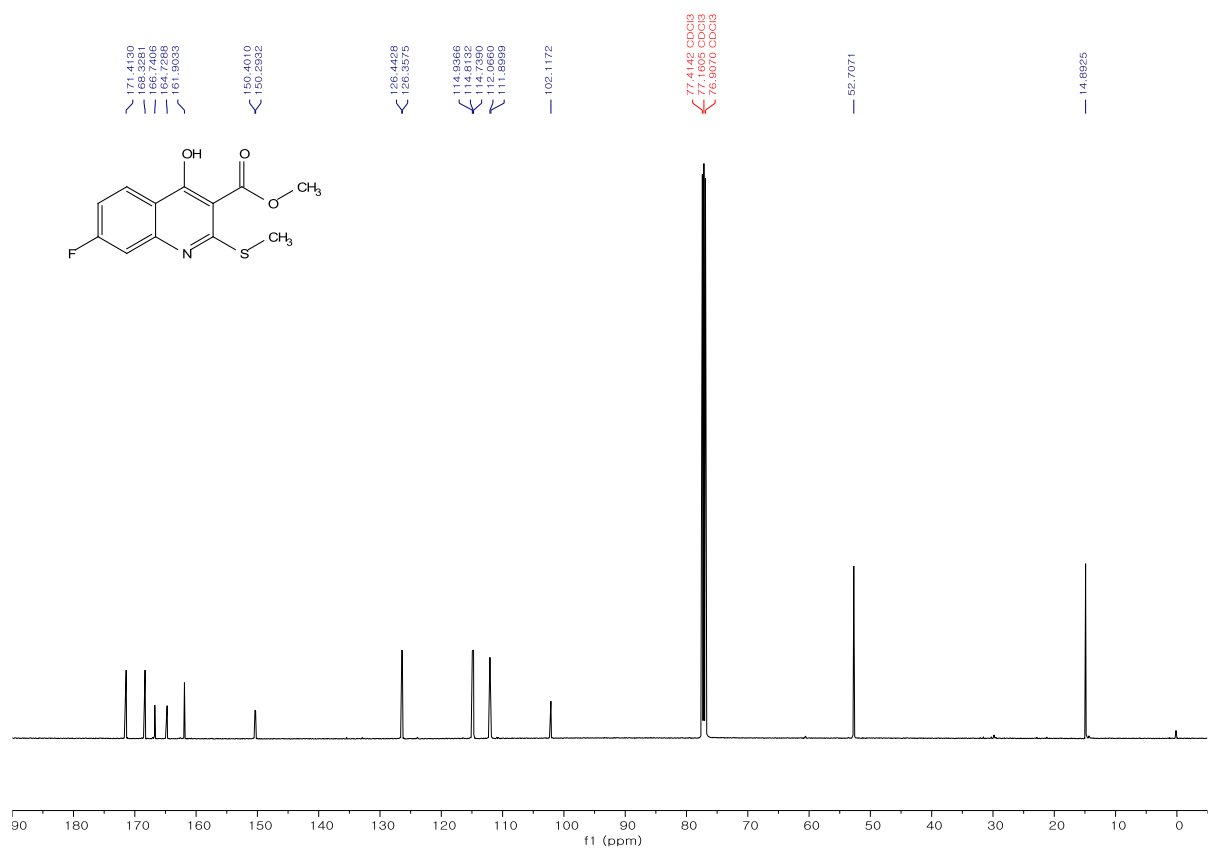
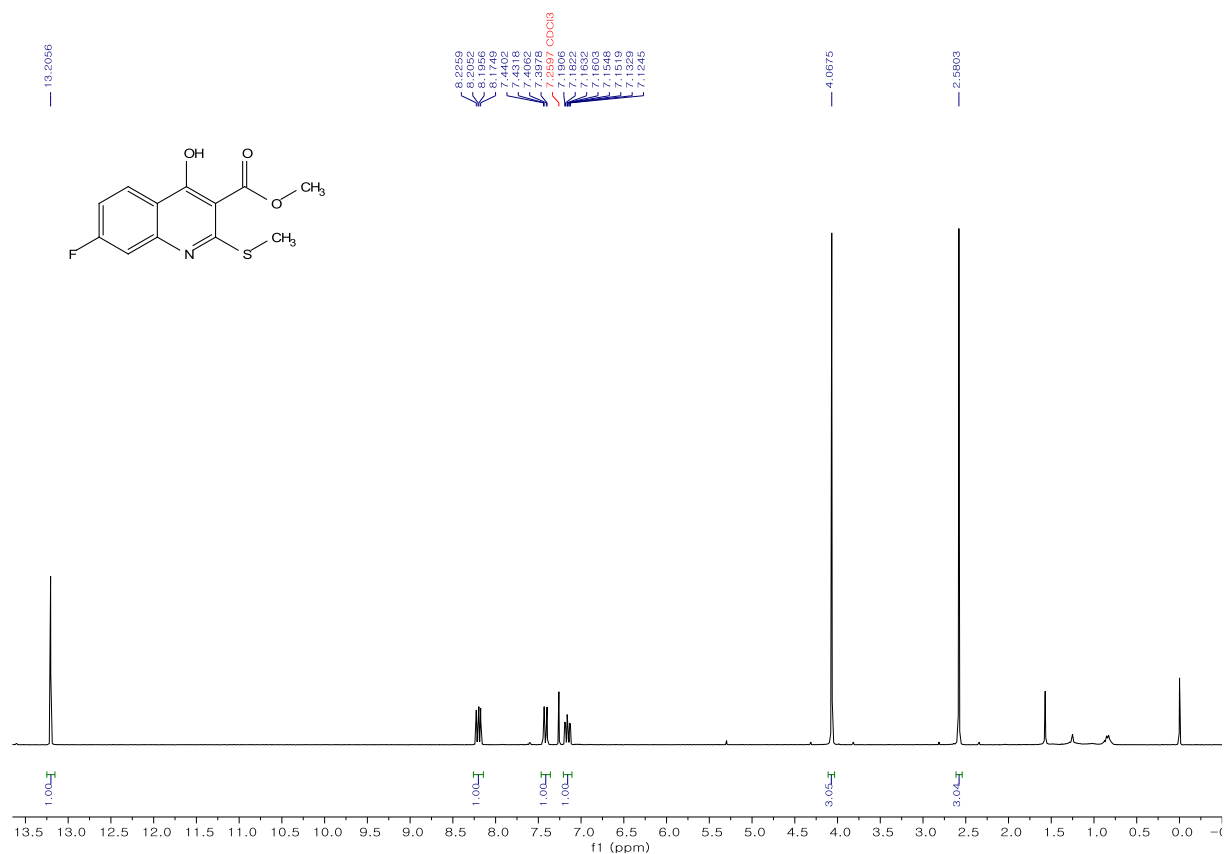
¹H and ¹³C NMR data of methyl 4-hydroxy-8-methyl-2-(methylthio)quinoline-3-carboxylate (4g)



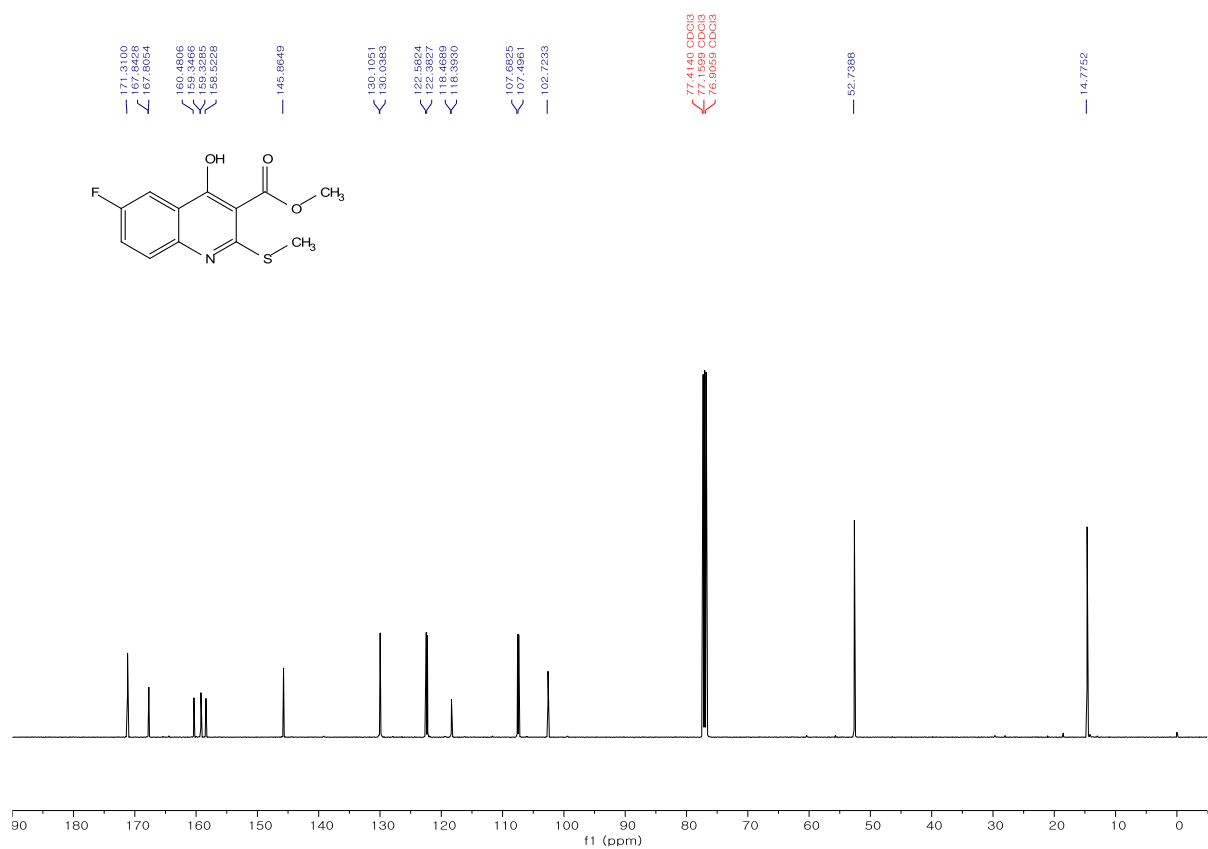
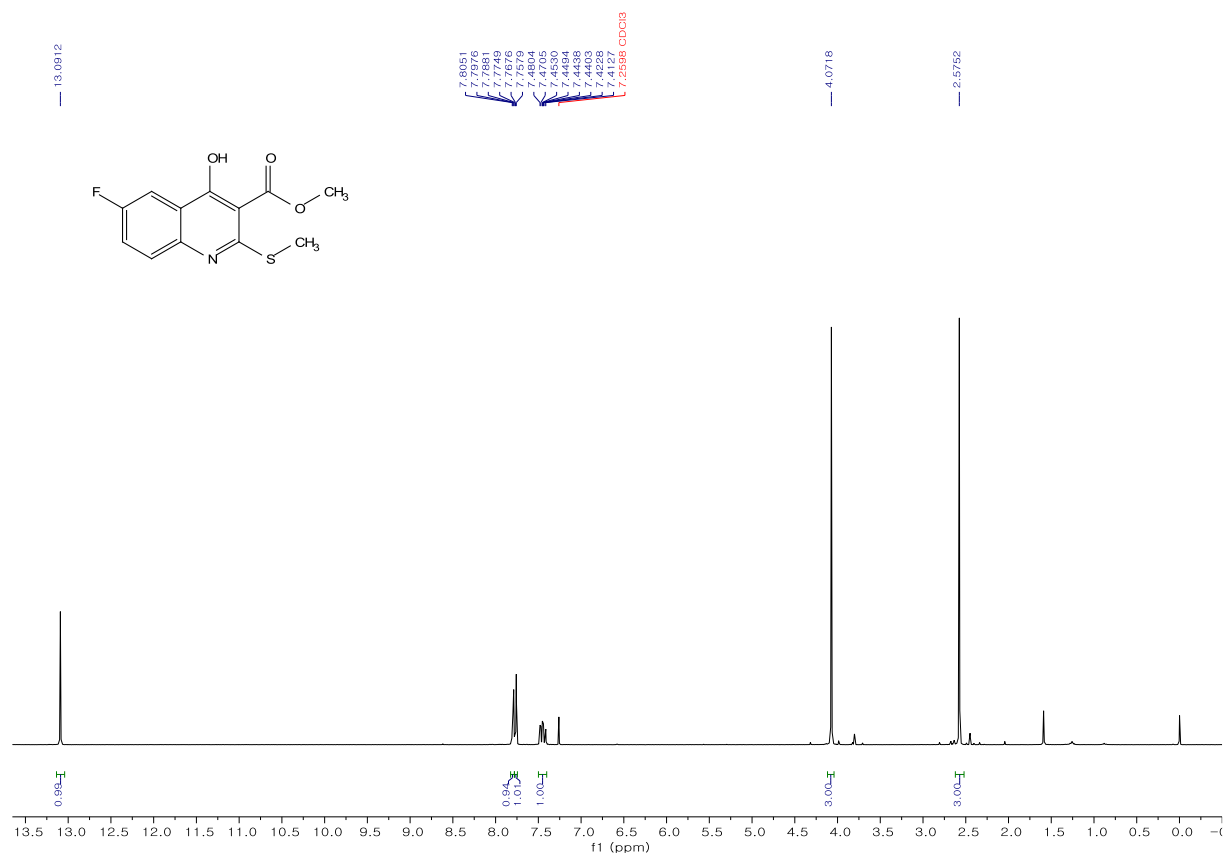
¹H and ¹³C NMR data of methyl 8-fluoro-4-hydroxy-2-(methylthio)quinoline-3-carboxylate (4h)



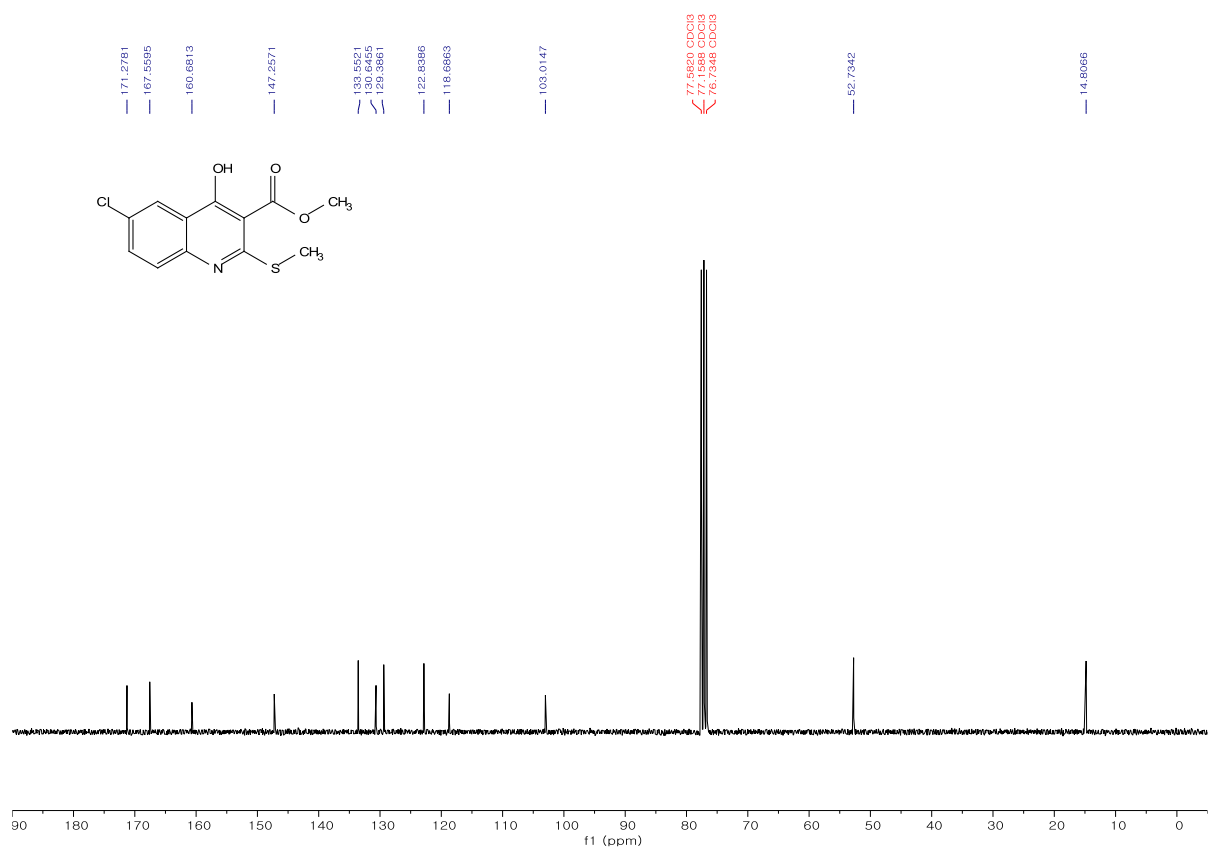
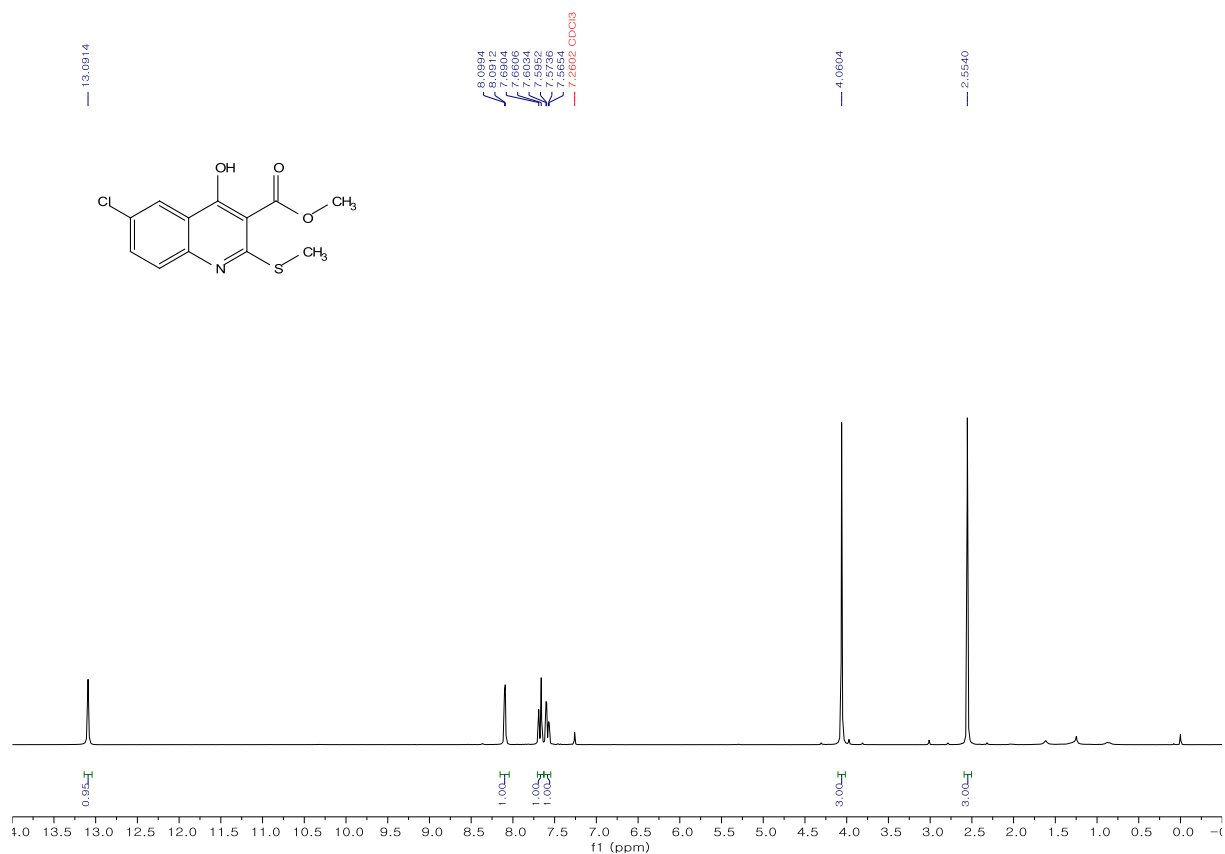
¹H and ¹³C NMR data of methyl 7-fluoro-4-hydroxy-2-(methylthio)quinoline-3-carboxylate (4i)



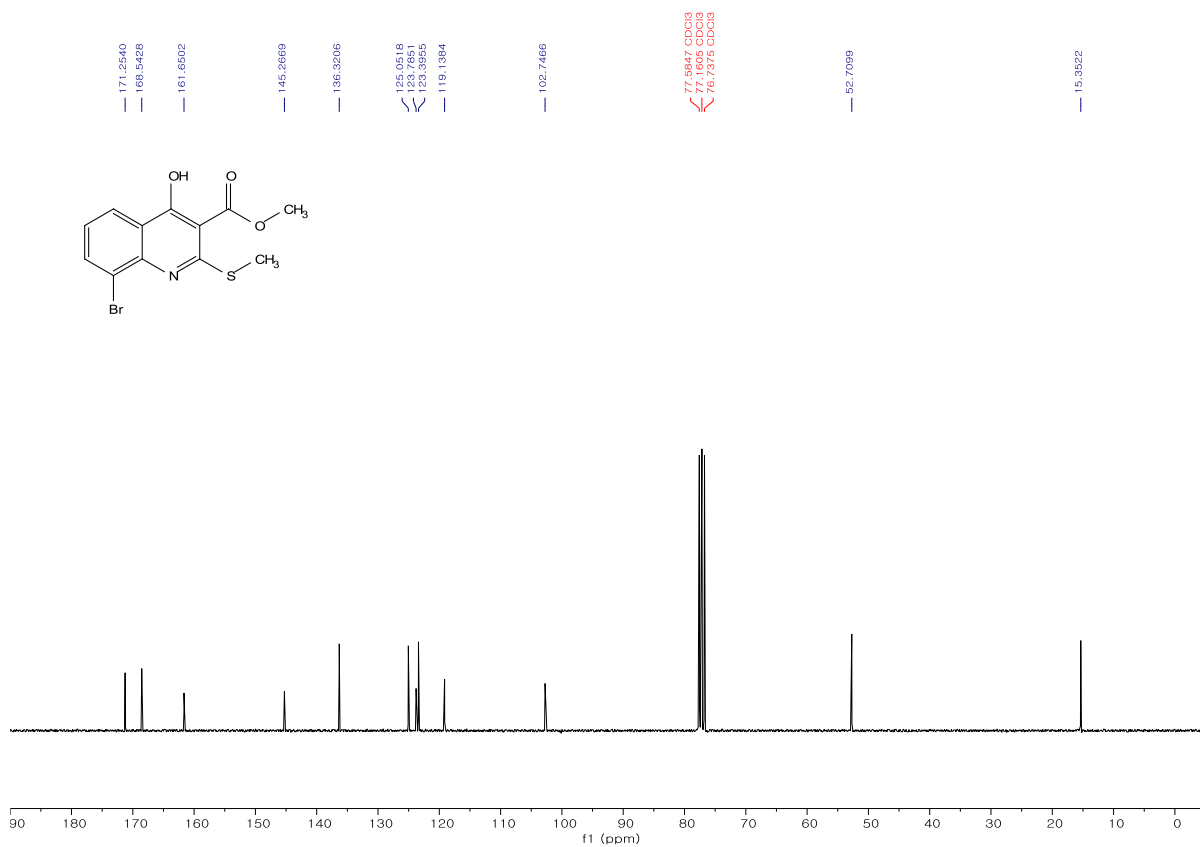
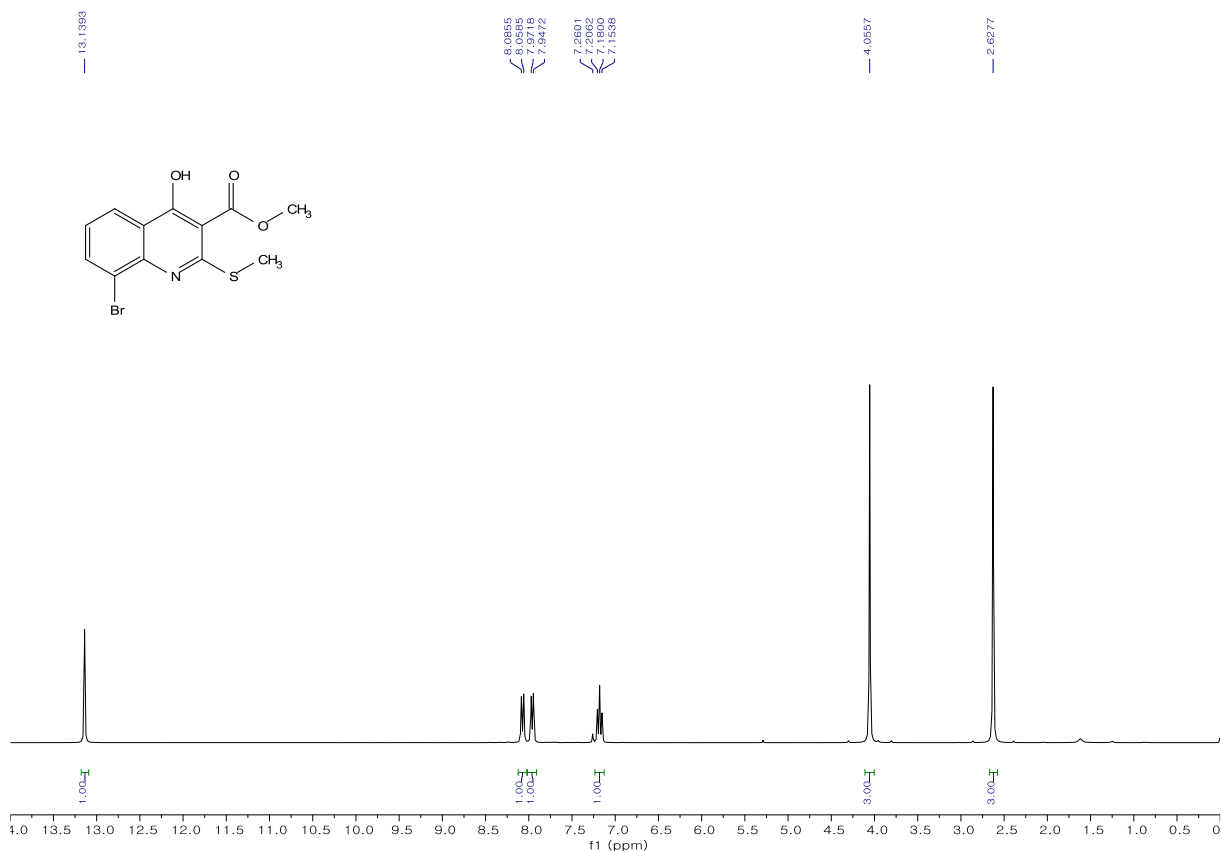
¹H and ¹³C NMR data of methyl 6-fluoro-4-hydroxy-2-(methylthio)quinoline-3-carboxylate (4j)



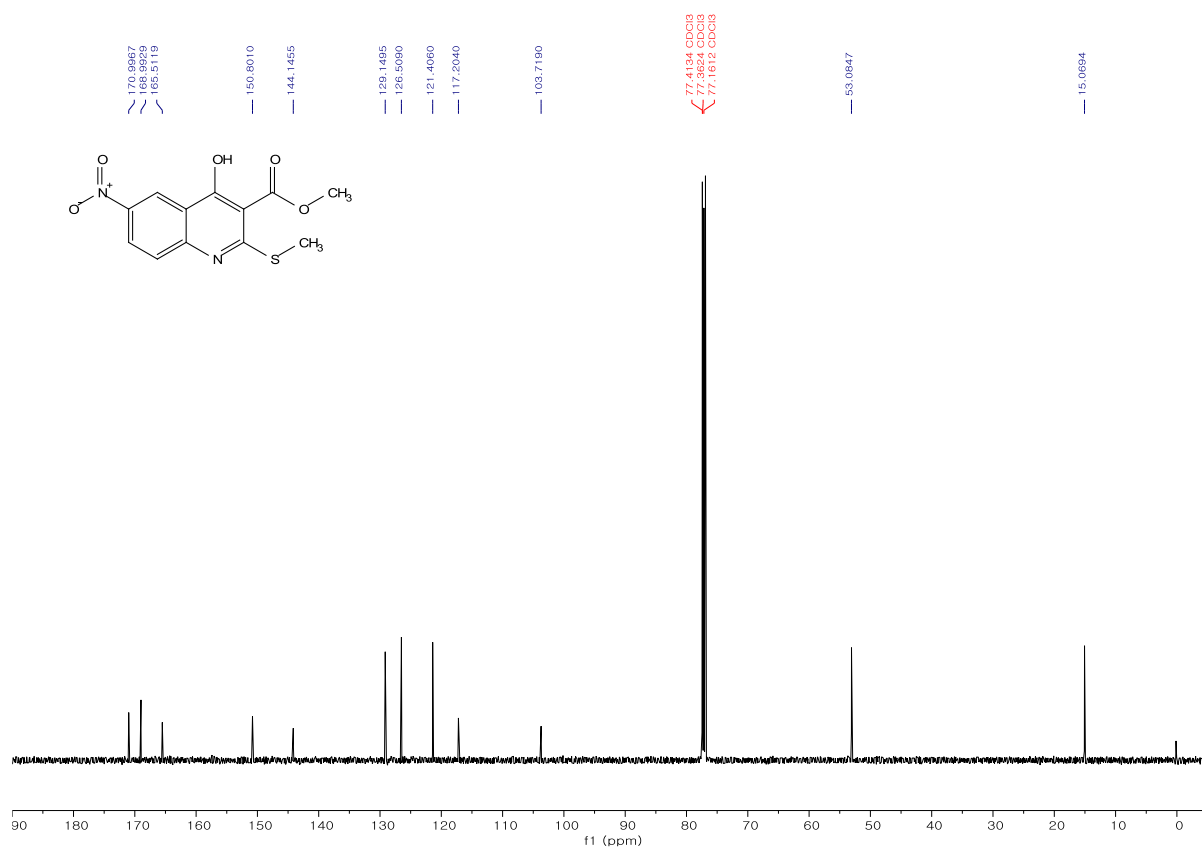
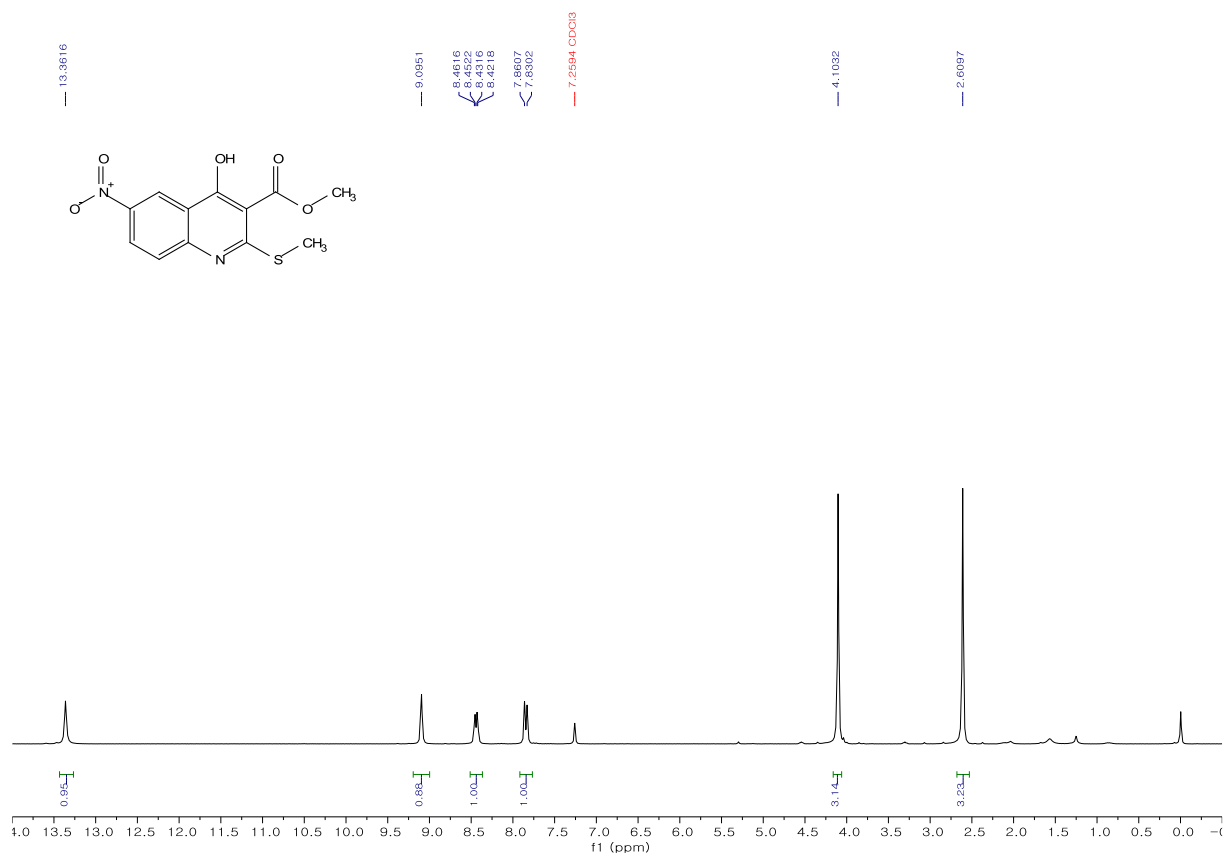
¹H and ¹³C NMR data of methyl 6-chloro-4-hydroxy-2-(methylthio)quinoline-3-carboxylate (4k)



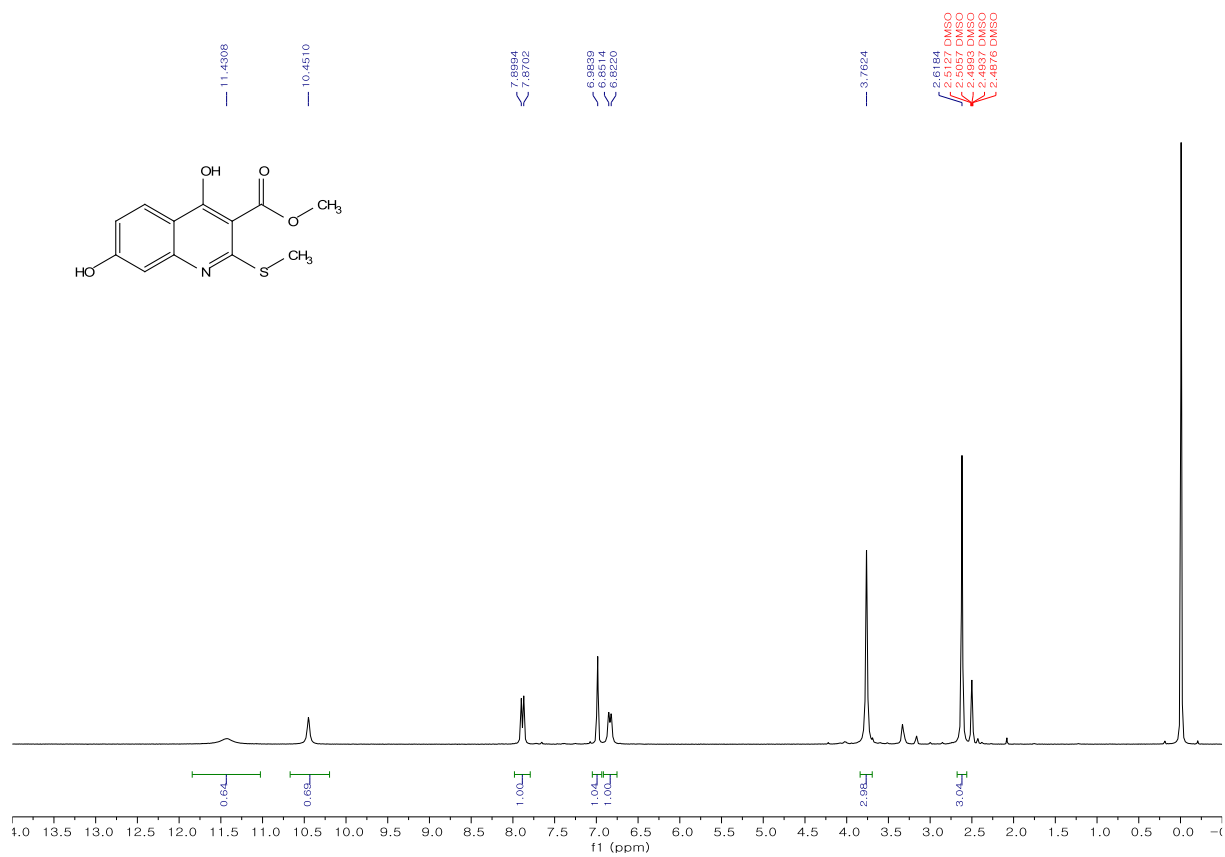
¹H and ¹³C NMR data of methyl 8-bromo-4-hydroxy-2-(methylthio)quinoline-3-carboxylate (4l)

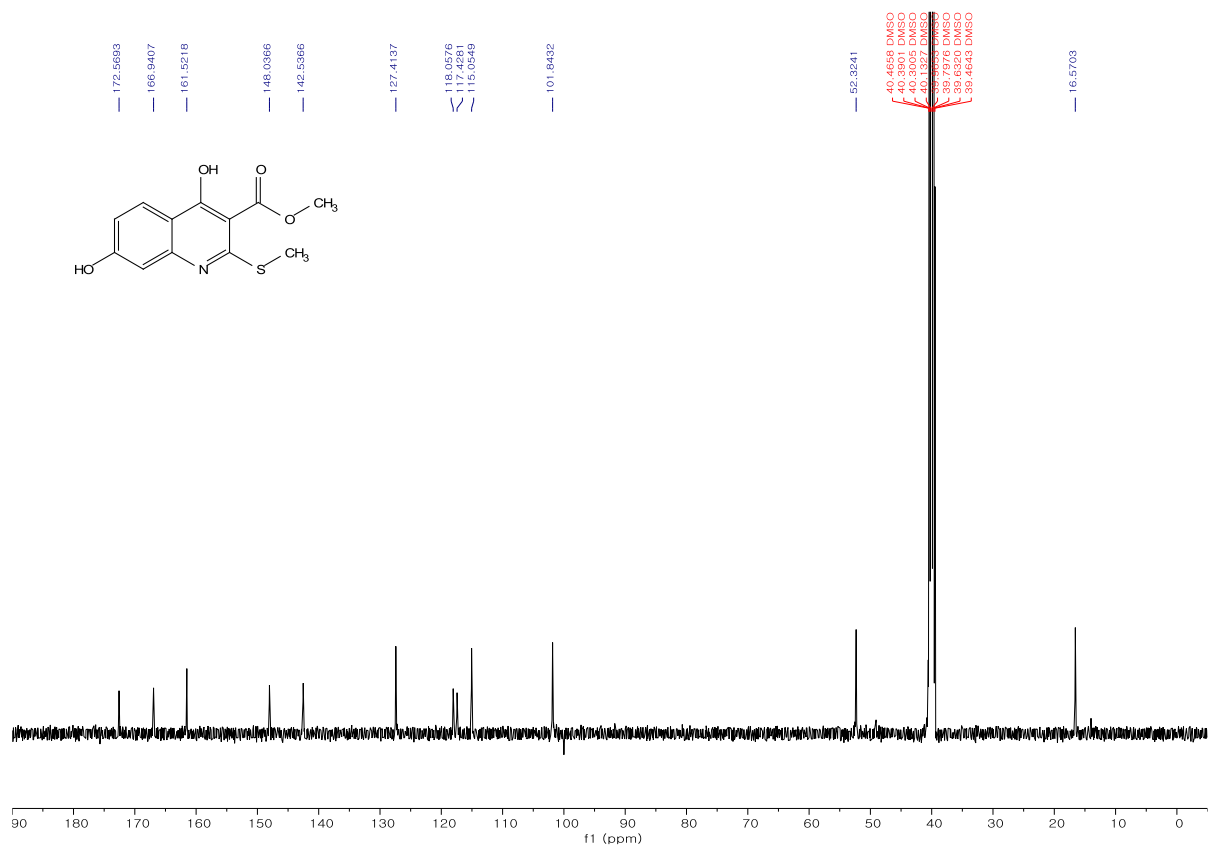


¹H and ¹³C NMR data of methyl 4-hydroxy-2-(methylthio)-6-nitroquinoline-3-carboxylate (4m)

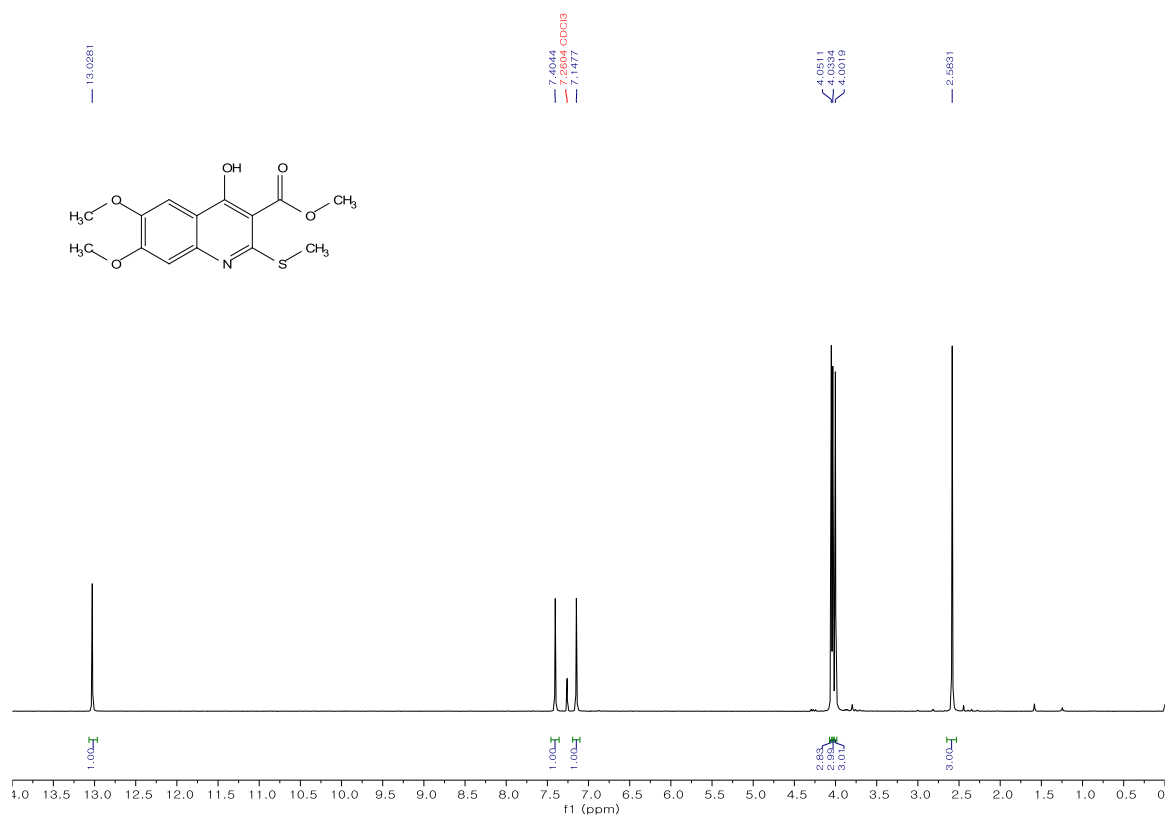


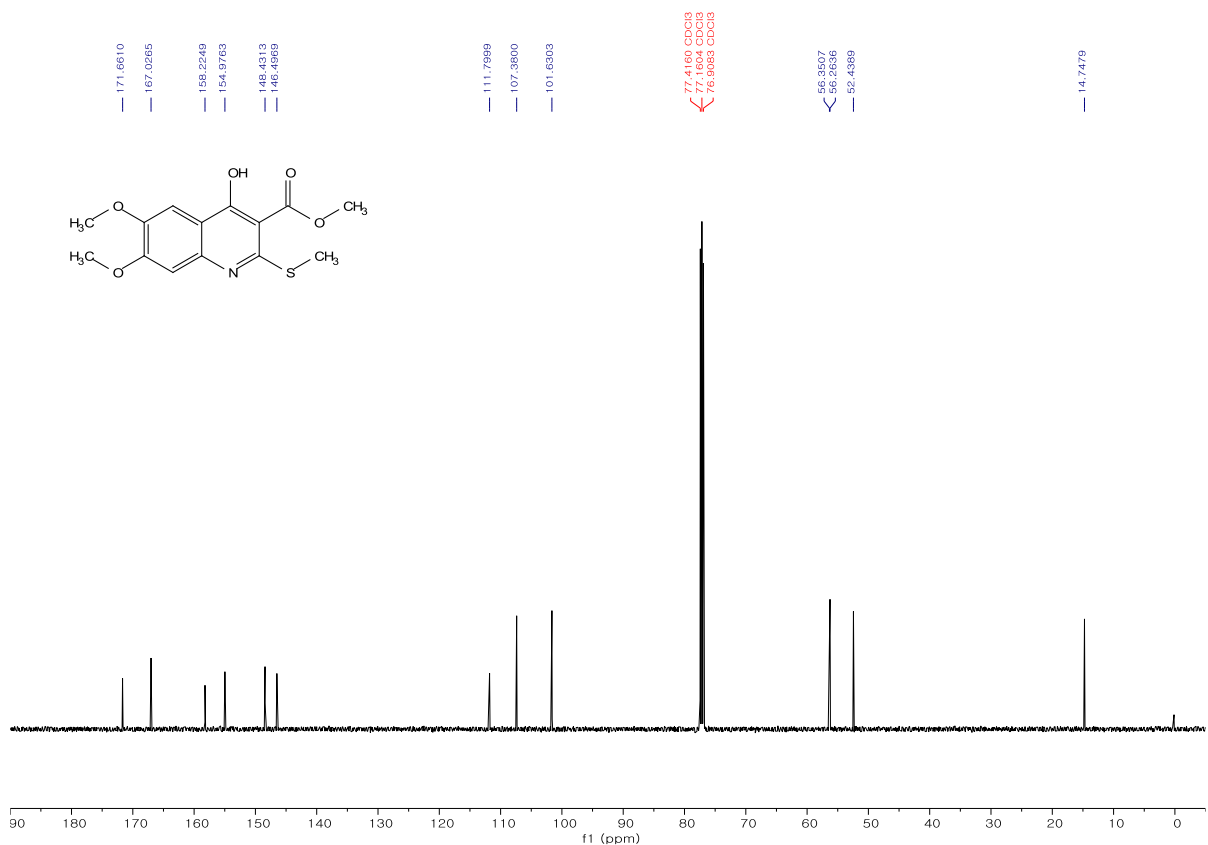
¹H and ¹³C NMR data of methyl 4,7-dihydroxy-2-(methylthio)quinoline-3-carboxylate (4n)



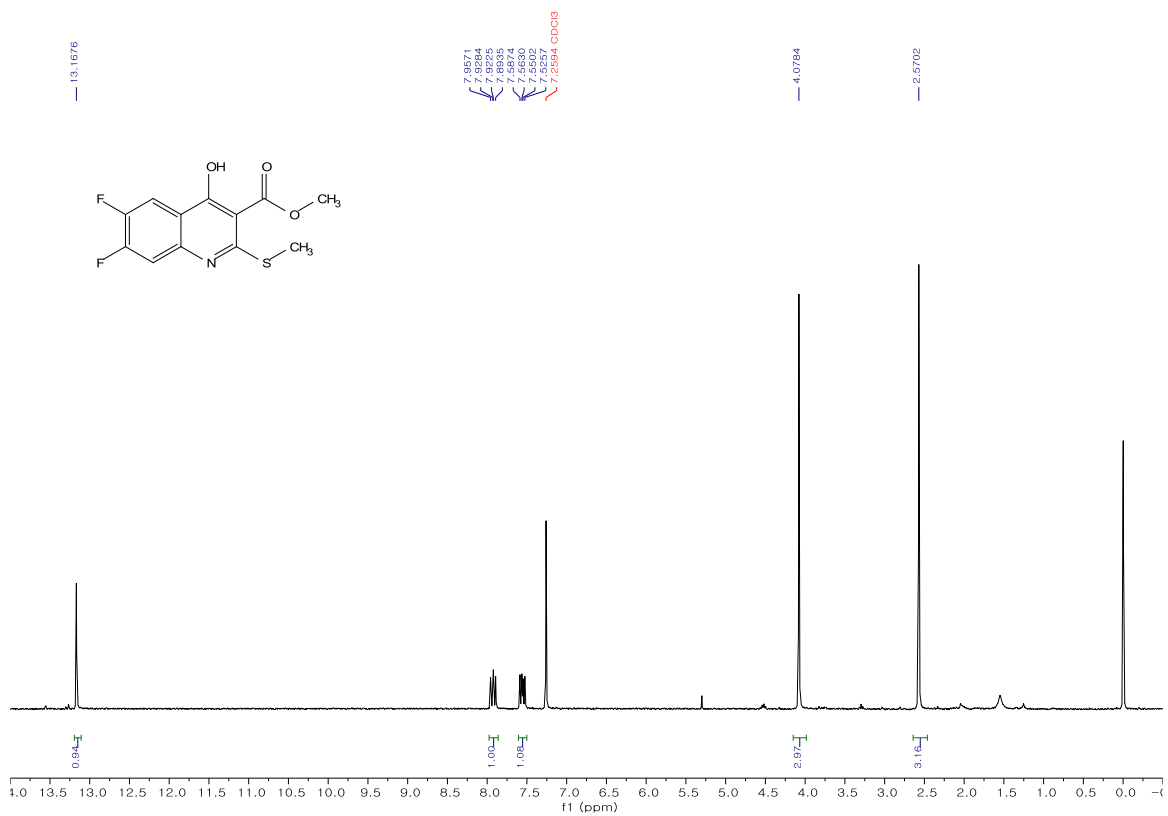


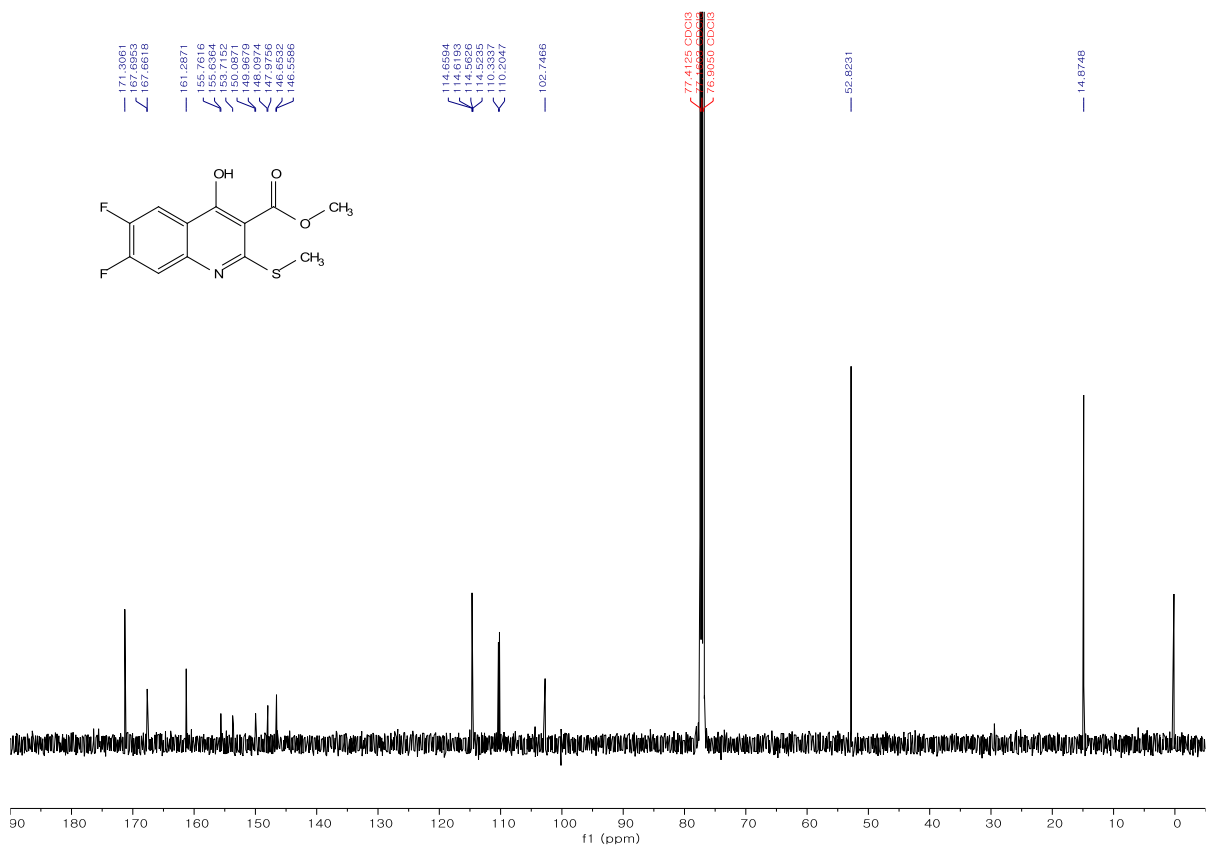
¹H and ¹³C NMR data of methyl 4-hydroxy-6,7-dimethoxy-2-(methylthio)quinoline-3-carboxylate (4o)



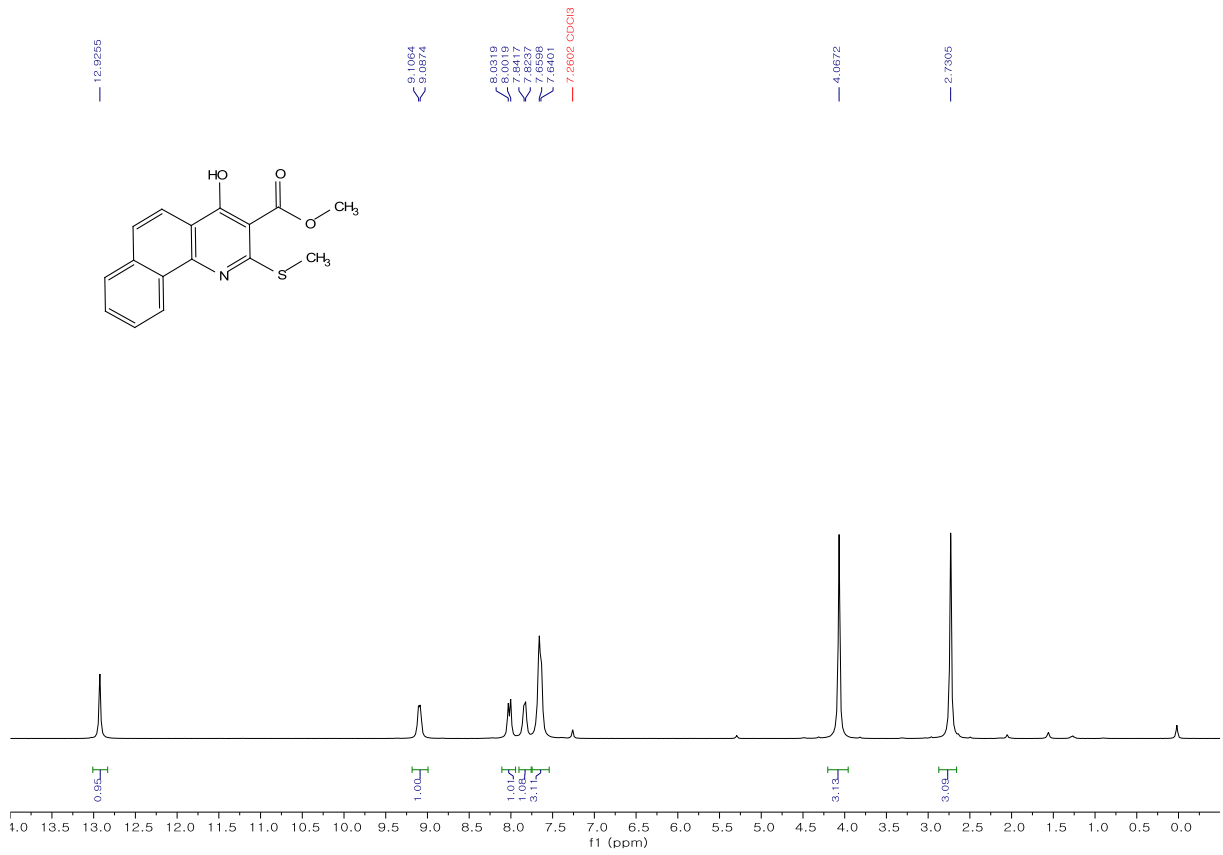


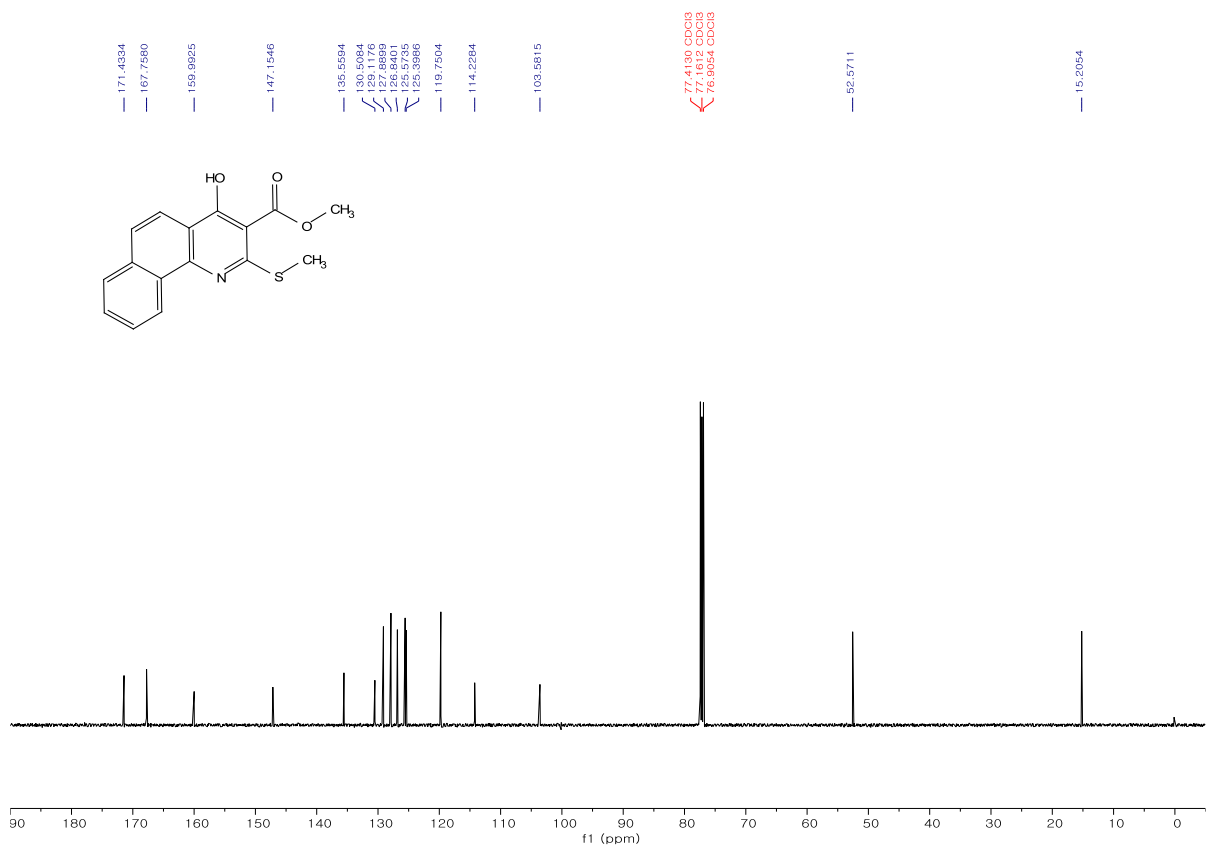
¹H and ¹³C NMR data of methyl 6,7-difluoro-2-(methylthio)-4-oxo-1,4-dihydroquinoline-3-carboxylate (4p)



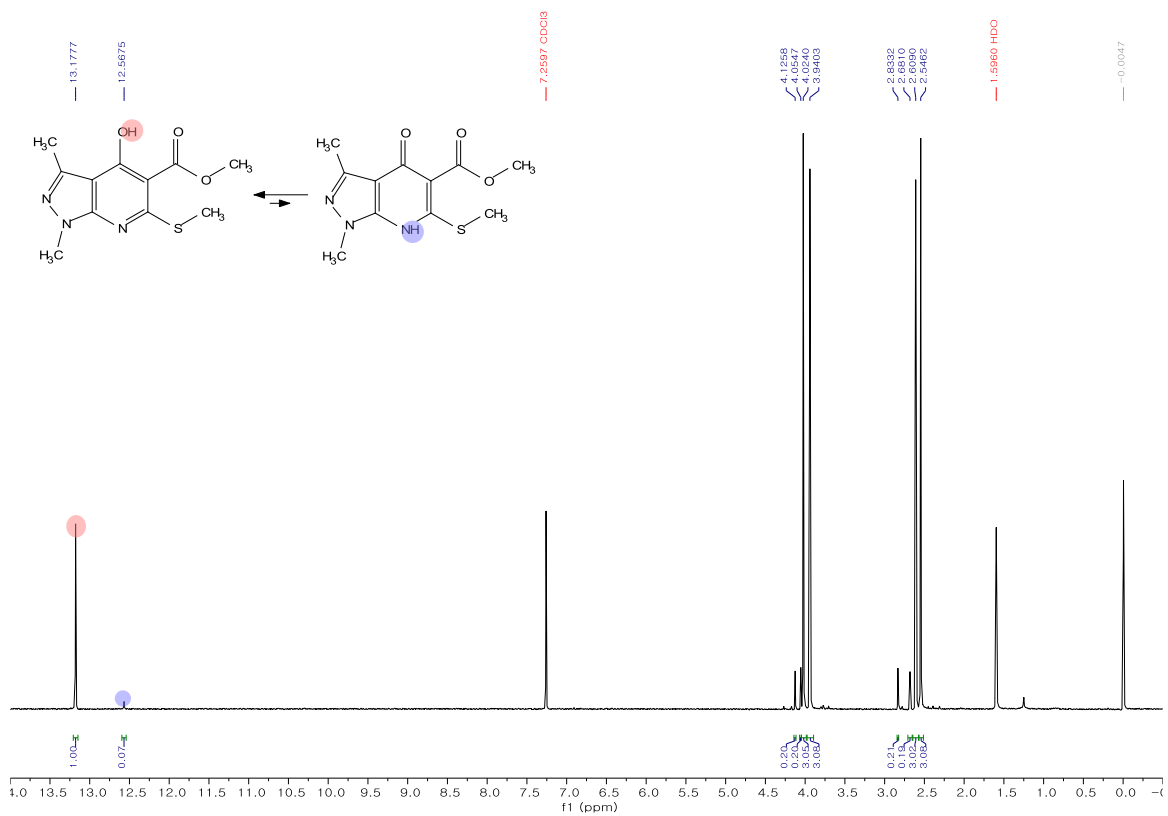


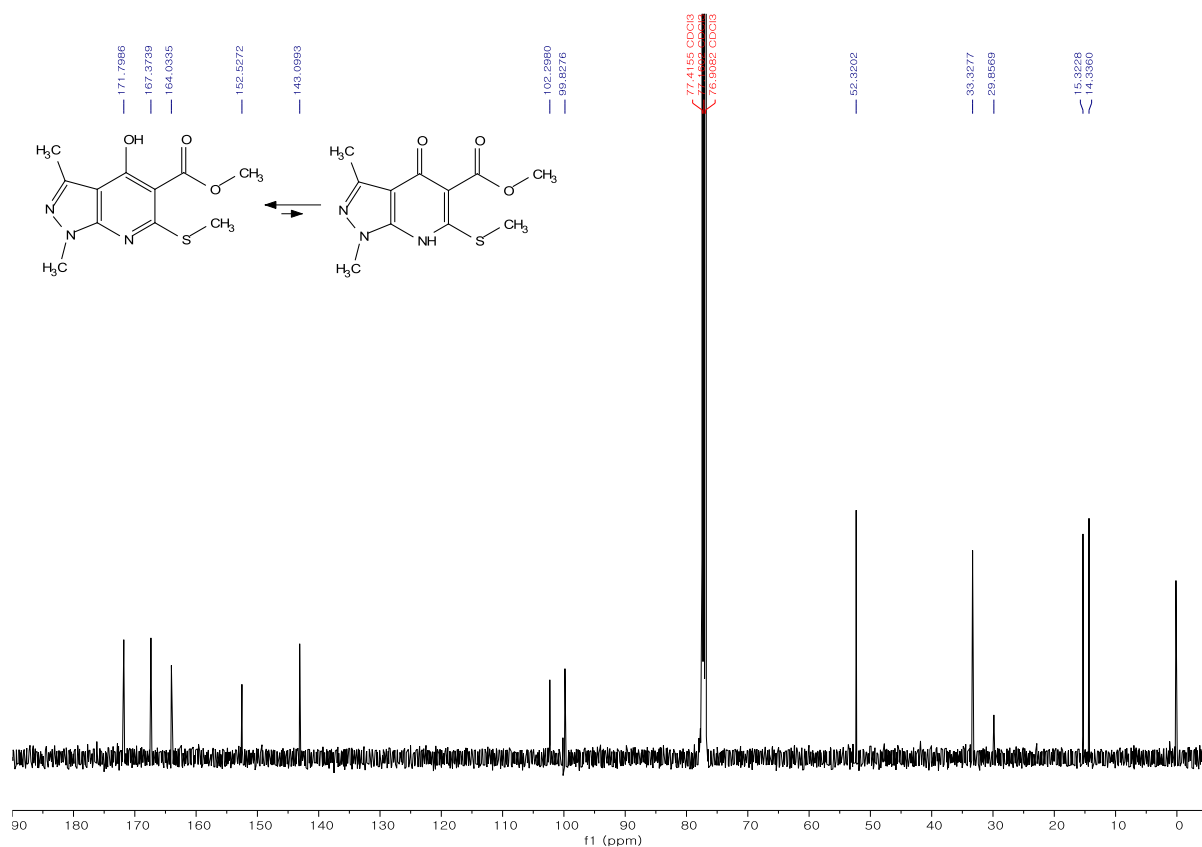
¹H and ¹³C NMR data of methyl 4-hydroxy-2-(methylthio)benzo[h]quinoline-3-carboxylate (4q)



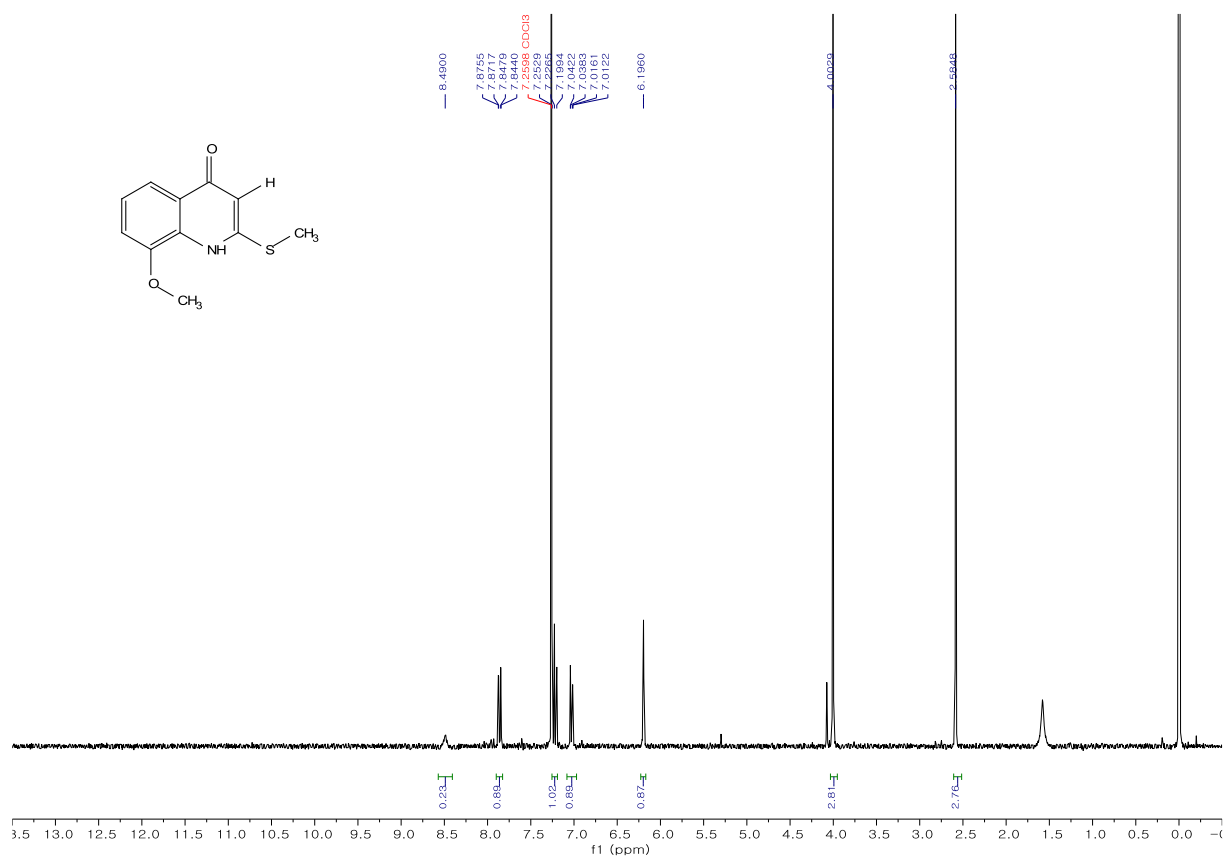


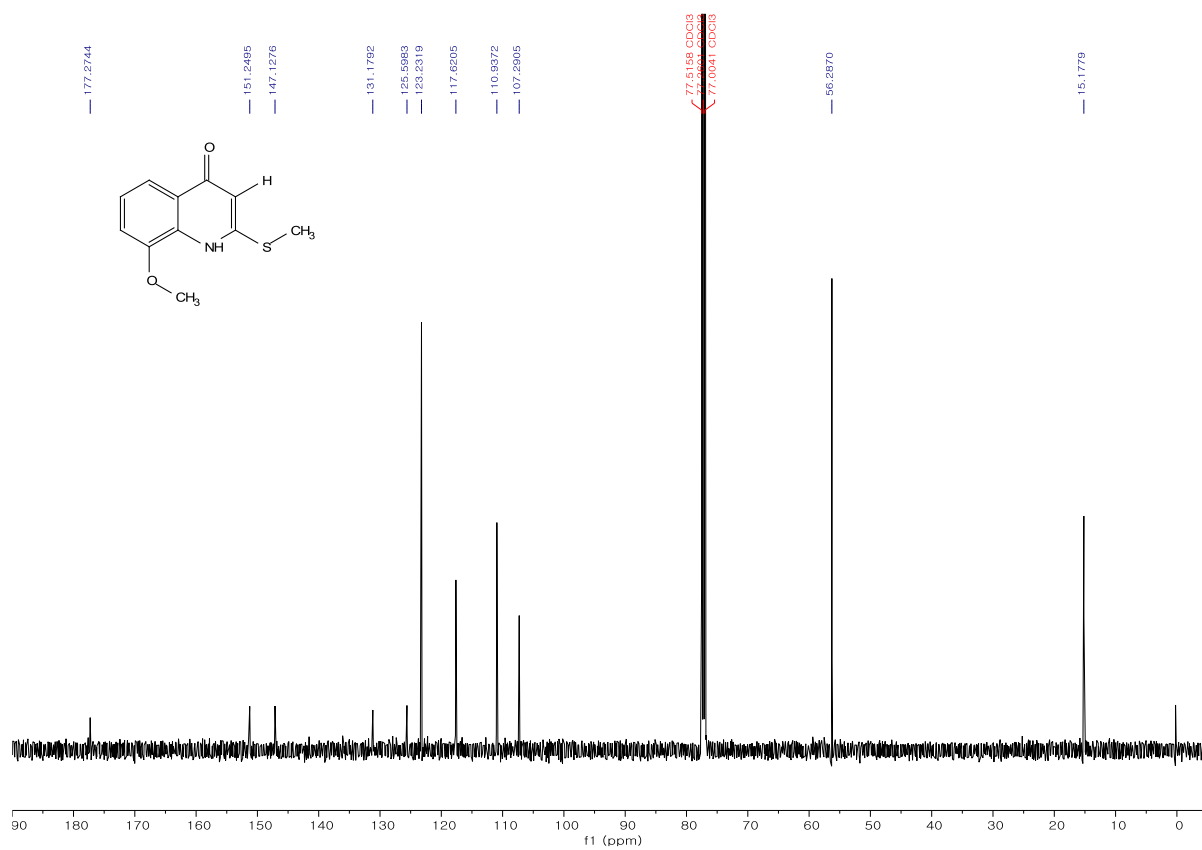
¹H and ¹³C NMR data of methyl 4-hydroxy-1,3-dimethyl-6-(methylthio)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate (4r)



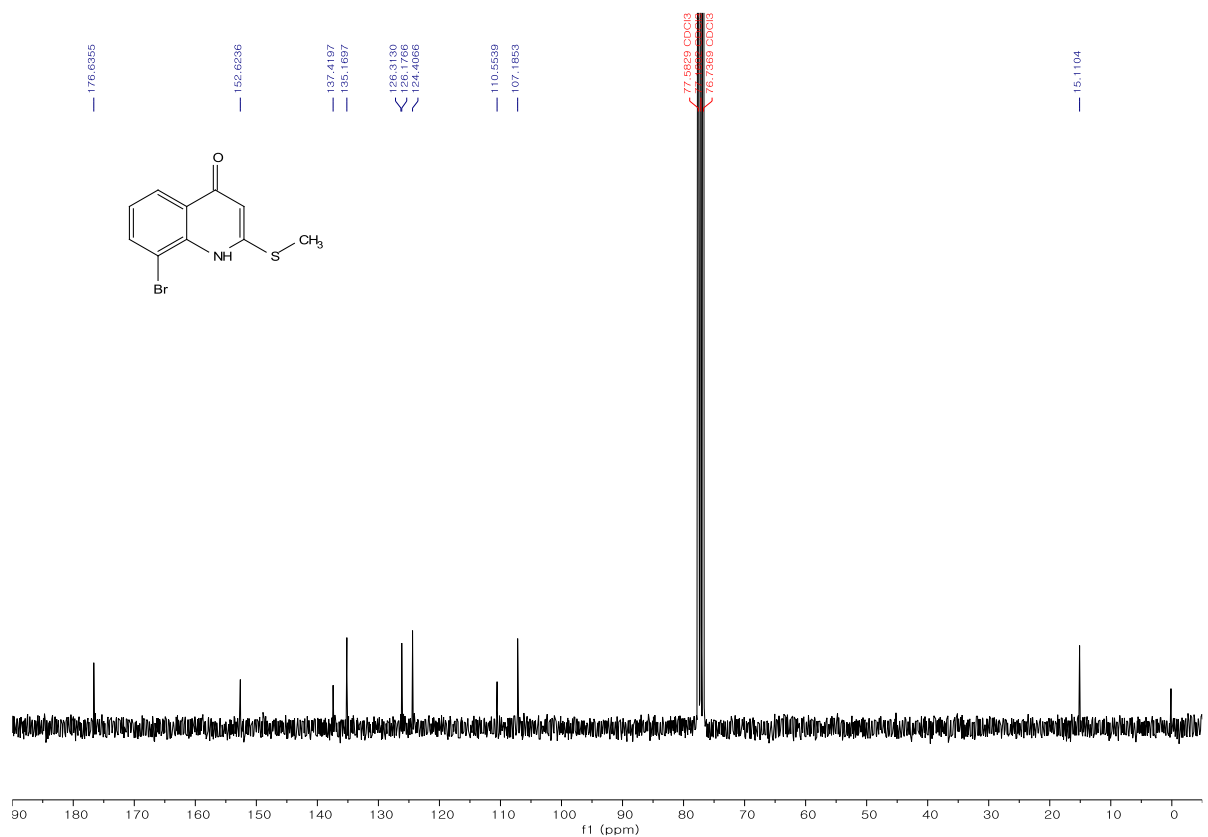


^1H and ^{13}C NMR data of 8-methoxy-2-(methylthio)quinolin-4(1H)-one (5d)

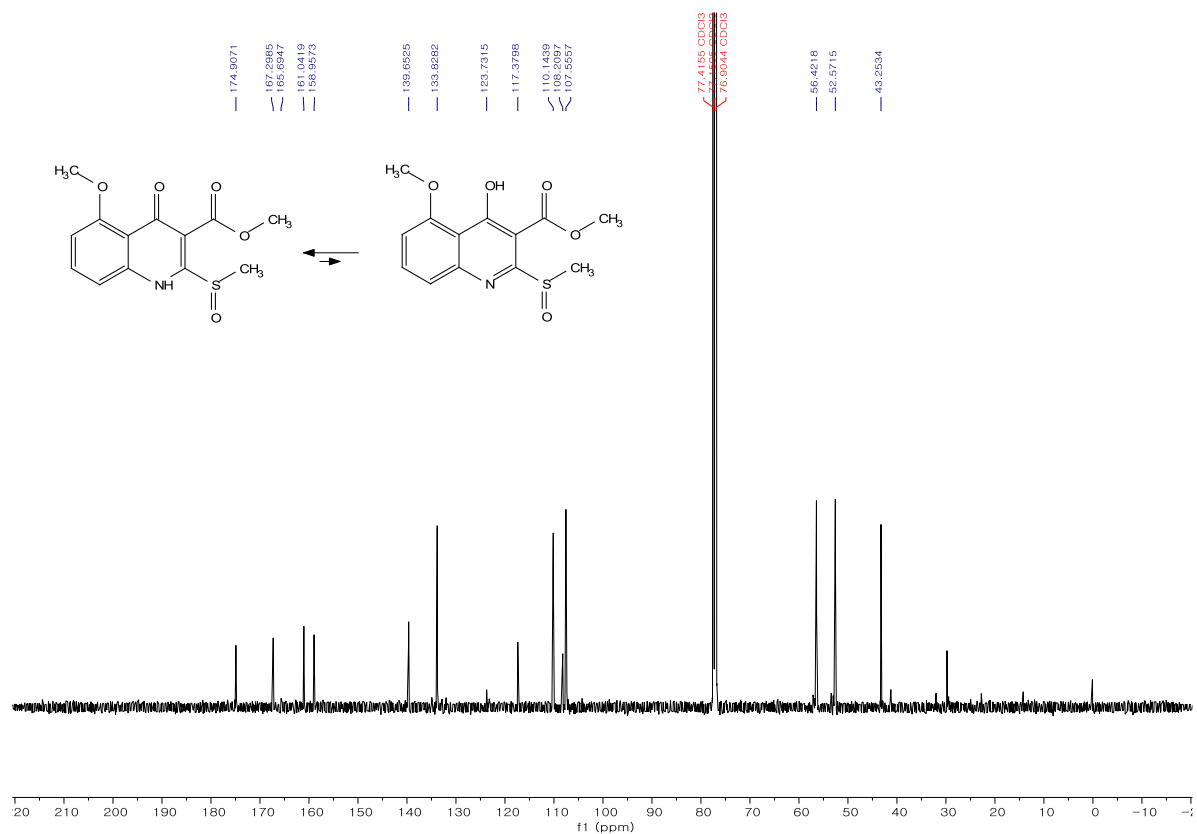
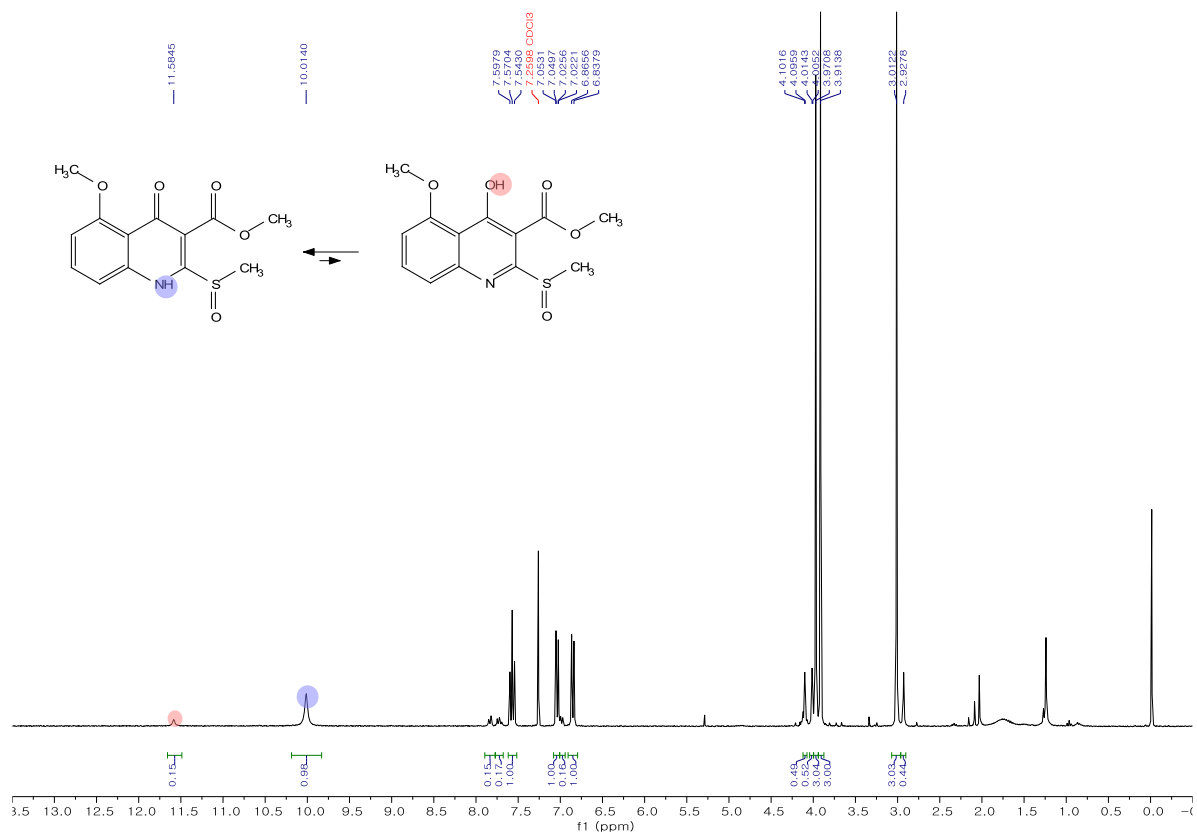




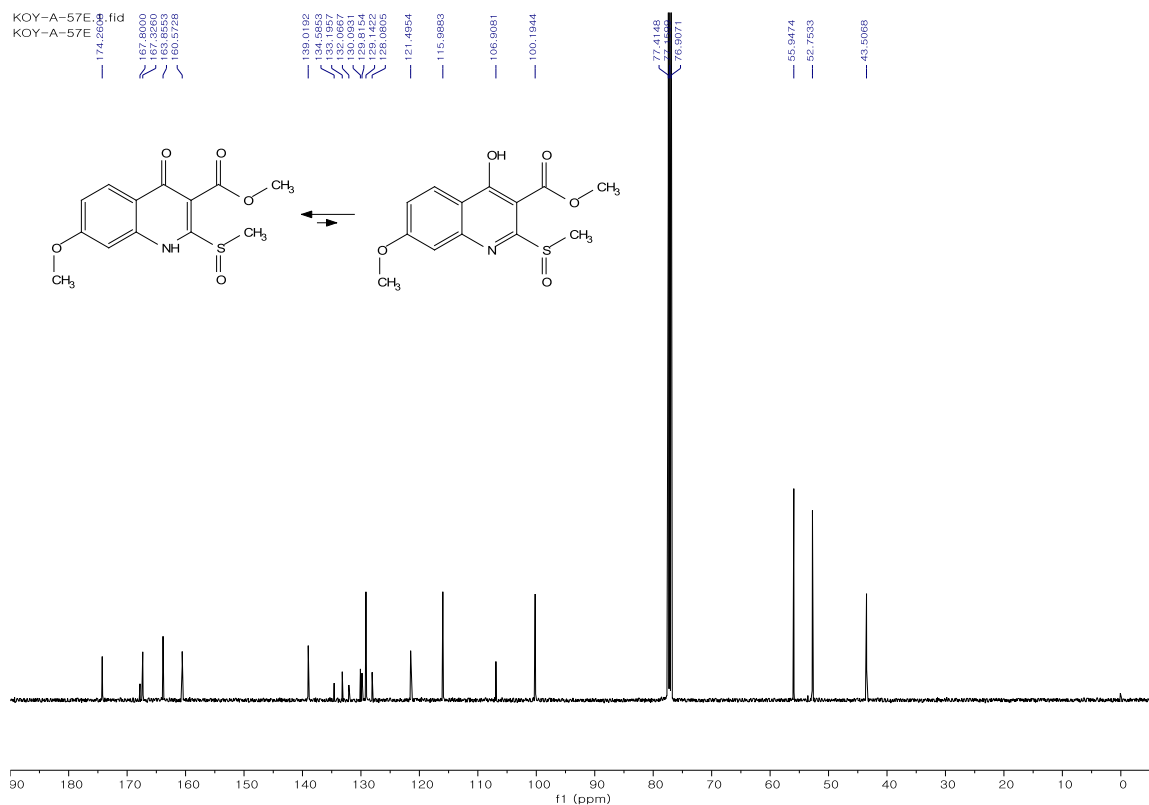
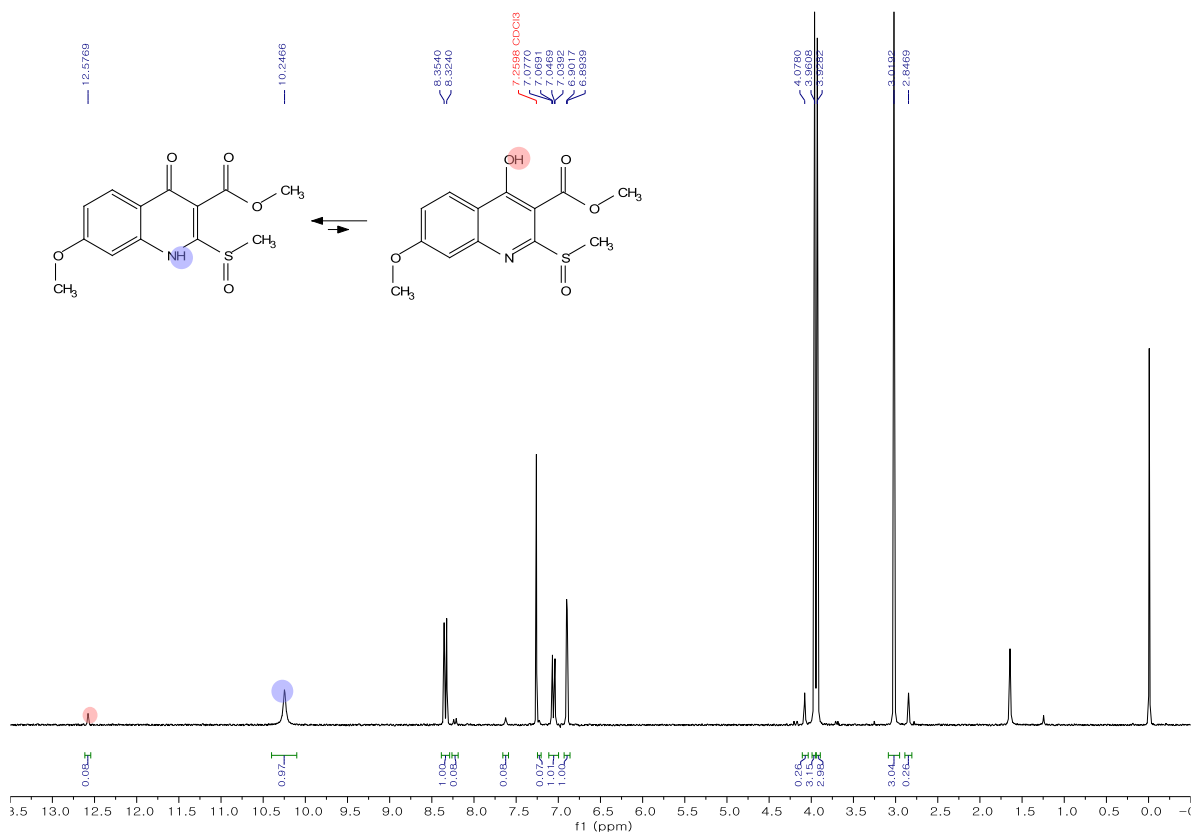
¹H and ¹³C NMR data of 8-bromo-2-(methylthio)quinolin-4(1H)-one (5I)



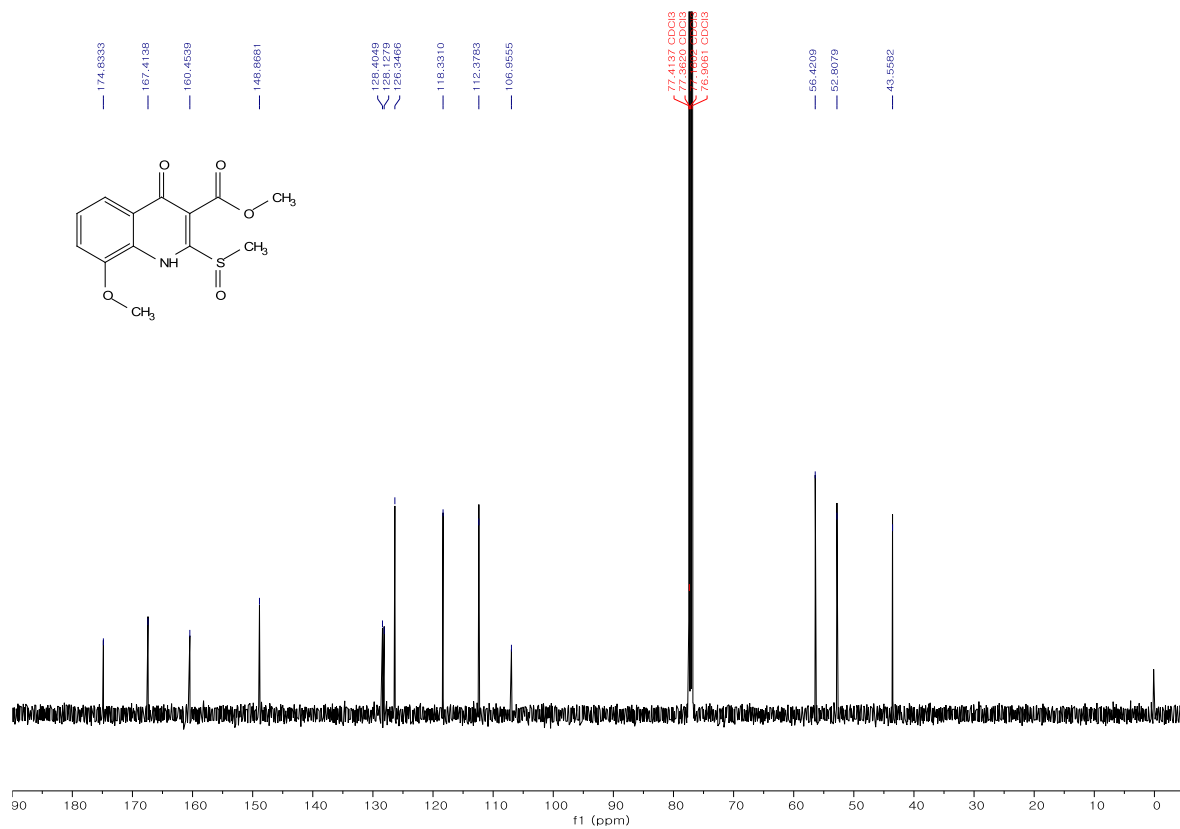
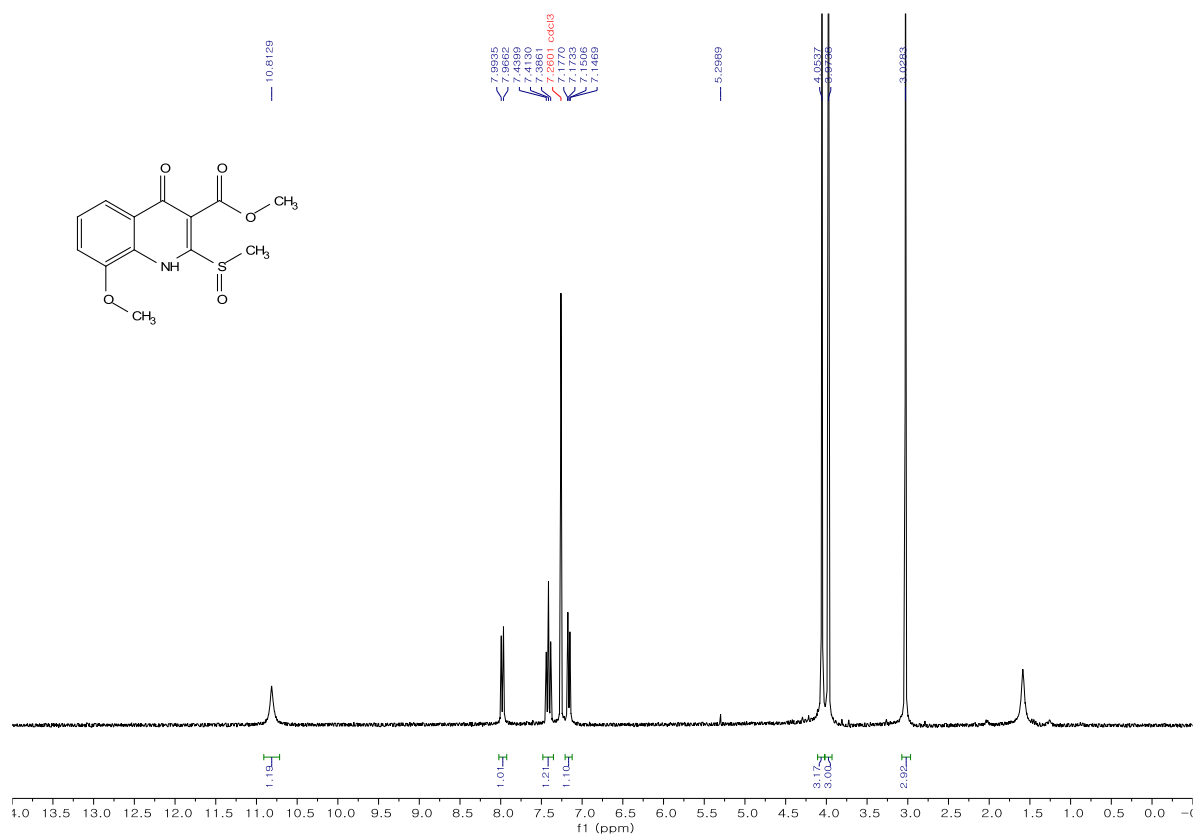
¹H and ¹³C NMR data of methyl 5-methoxy-2-(methylsulfinyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (6a)



¹H and ¹³C NMR data of methyl 7-methoxy-2-(methylsulfinyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (6b)



¹H and ¹³C NMR data of methyl 8-methoxy-2-(methylsulfinyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (6c)



¹H and ¹³C NMR data of methyl 5,8-dimethoxy-2-(methylsulfinyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (6d)

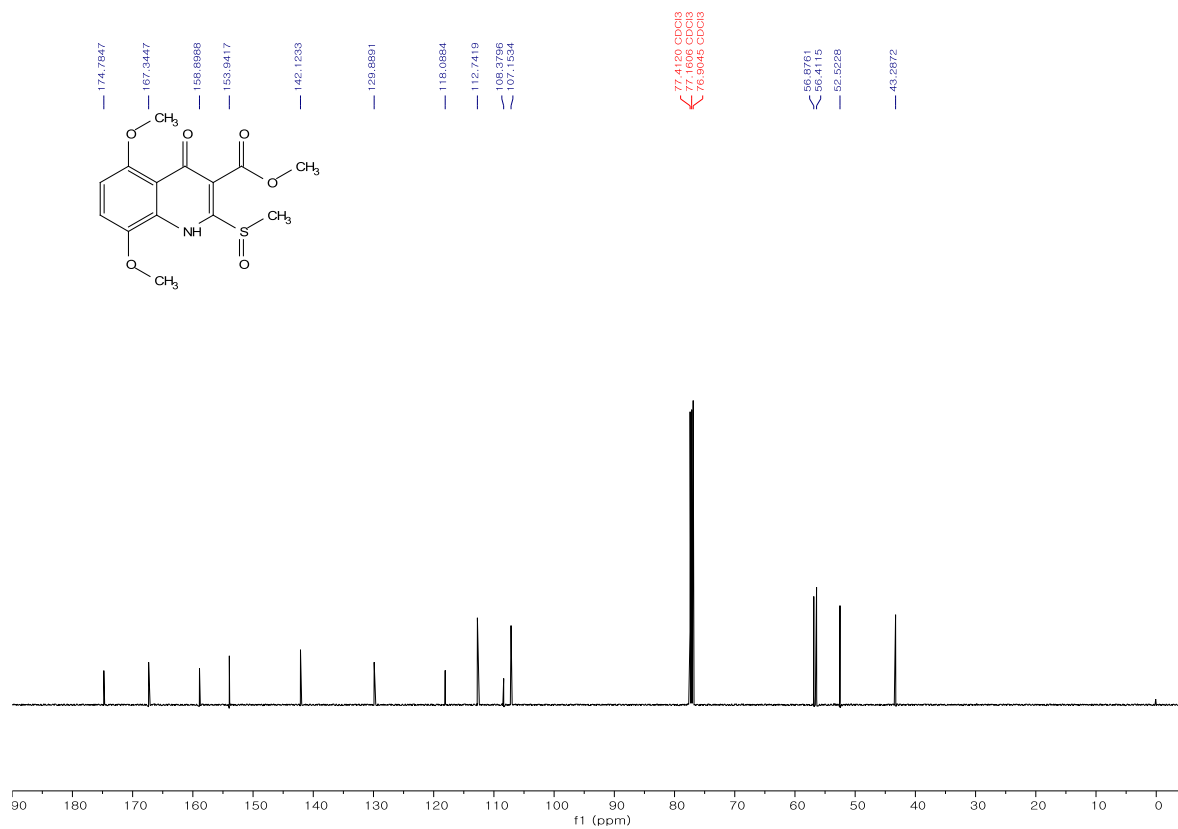
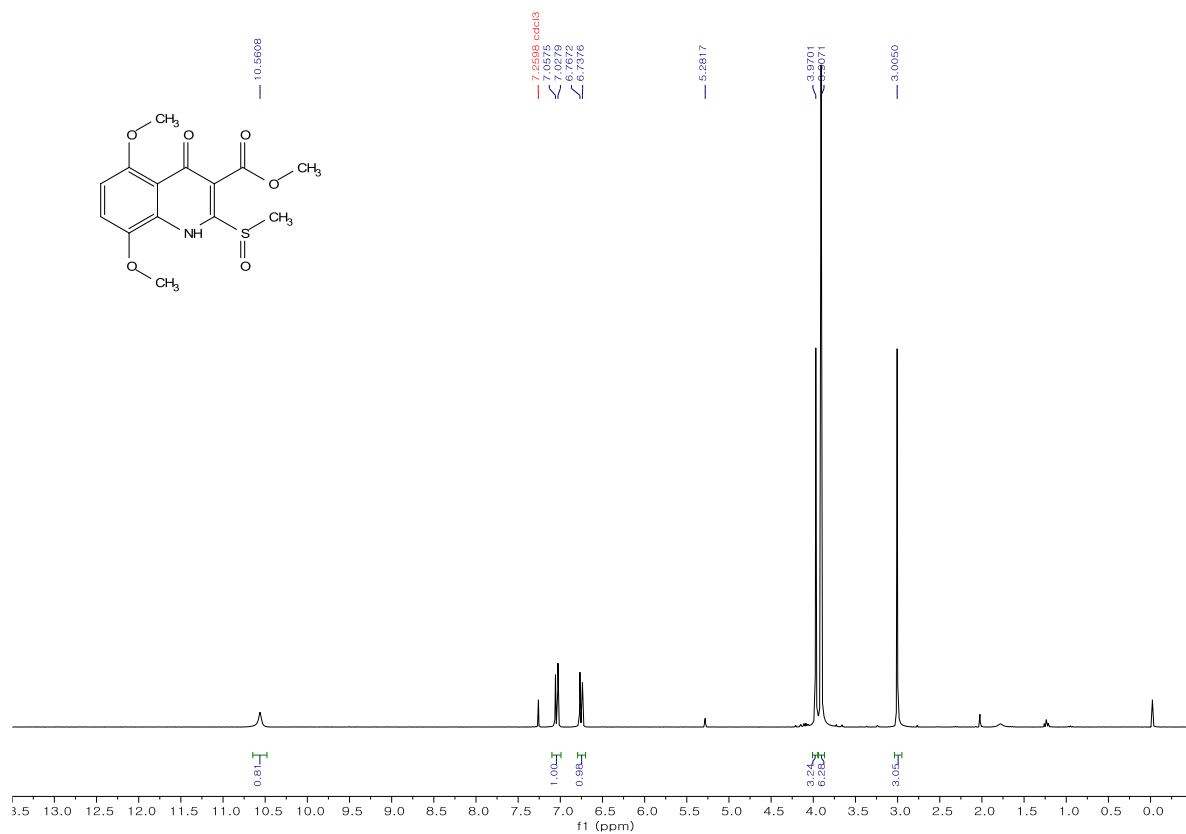


Figure S2. 2D NOESY spectra of **4d** in Chloroform- d_1

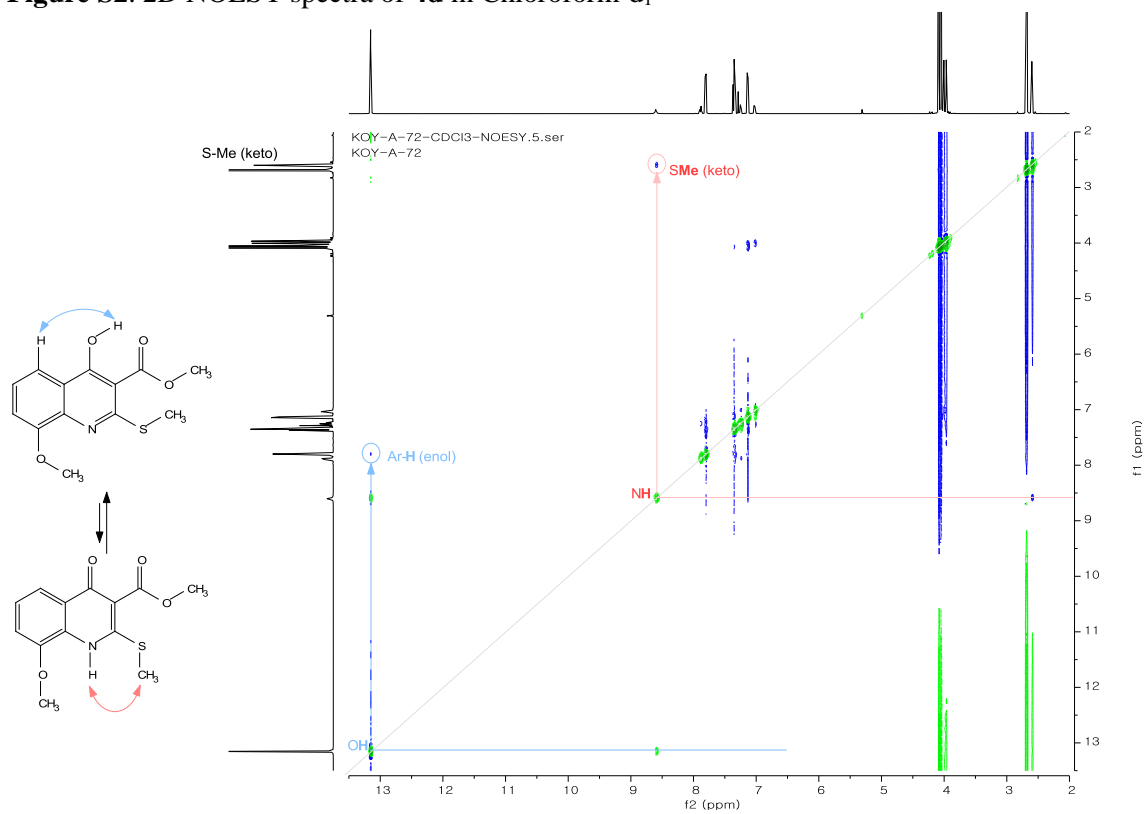


Figure S3. 2D NOESY spectra of **4d** in DMSO- d_6

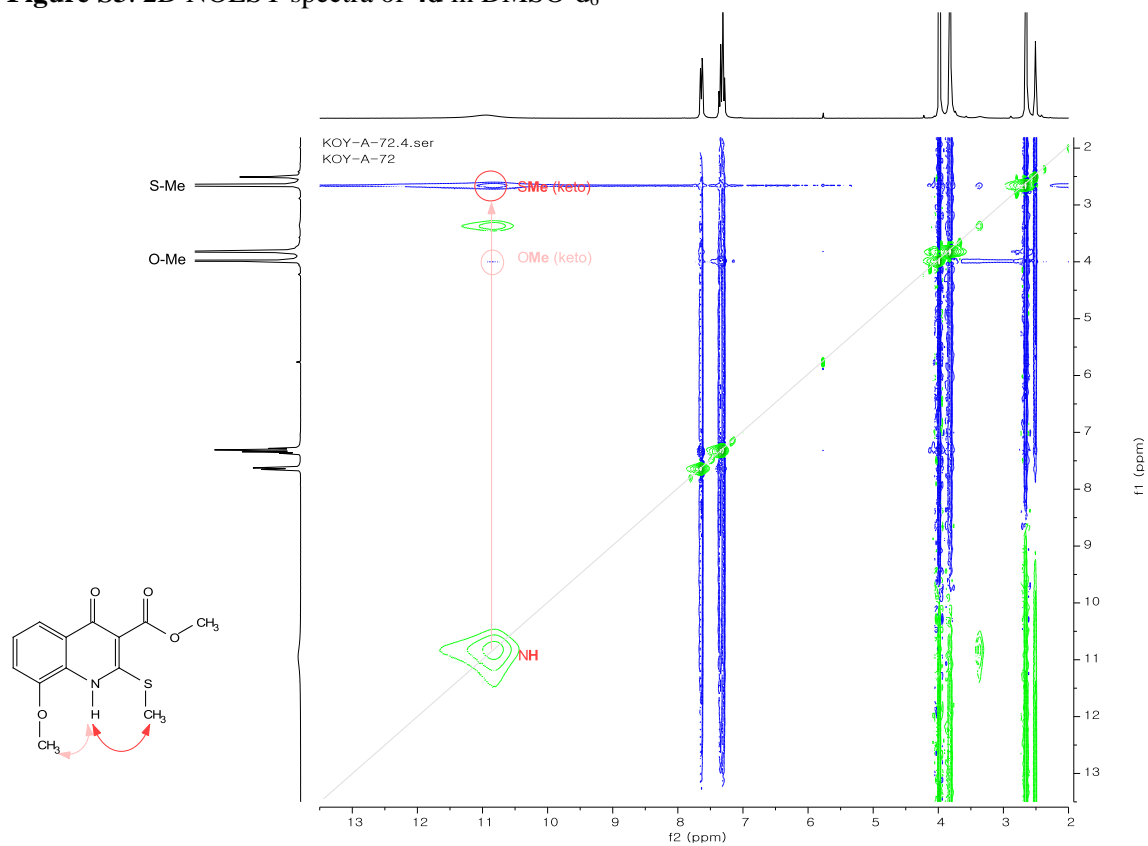


Figure S4. 2D NOESY spectra of **4b** in chloroform- d_1

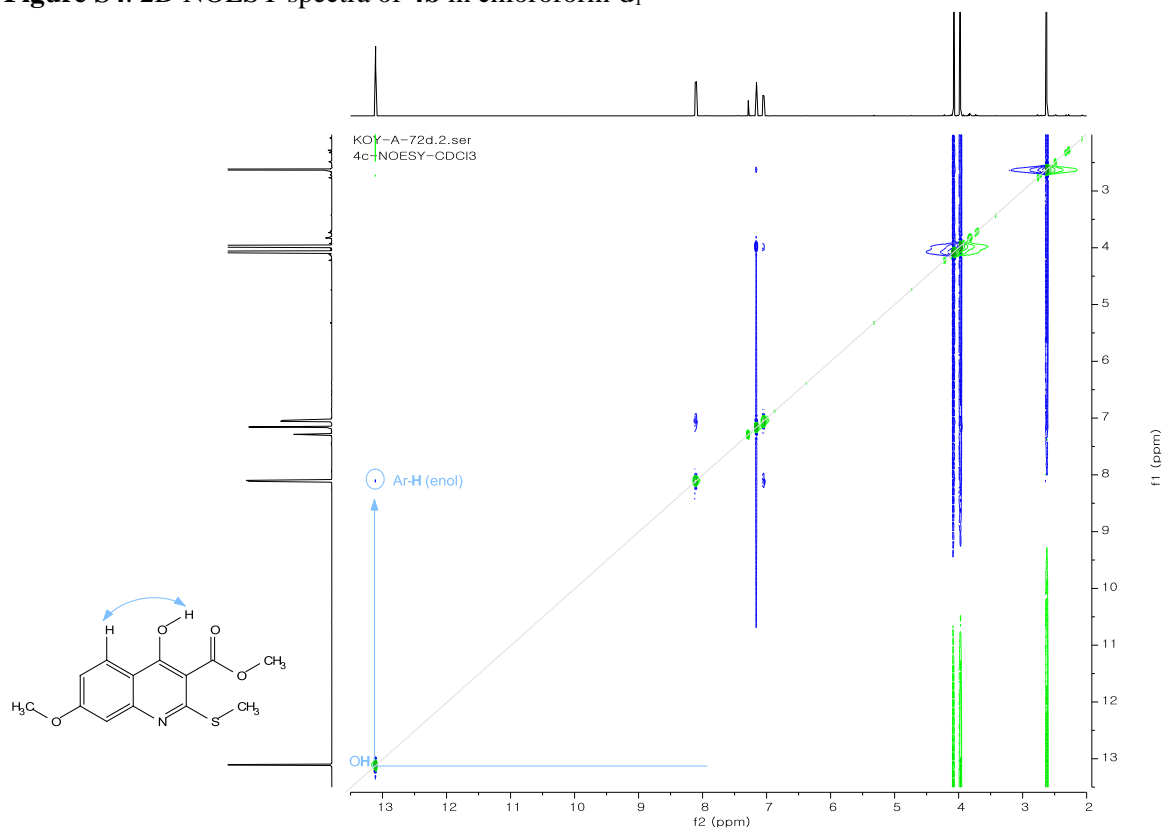


Figure S5. 2D NOESY spectra of **6c** in chloroform- d_1

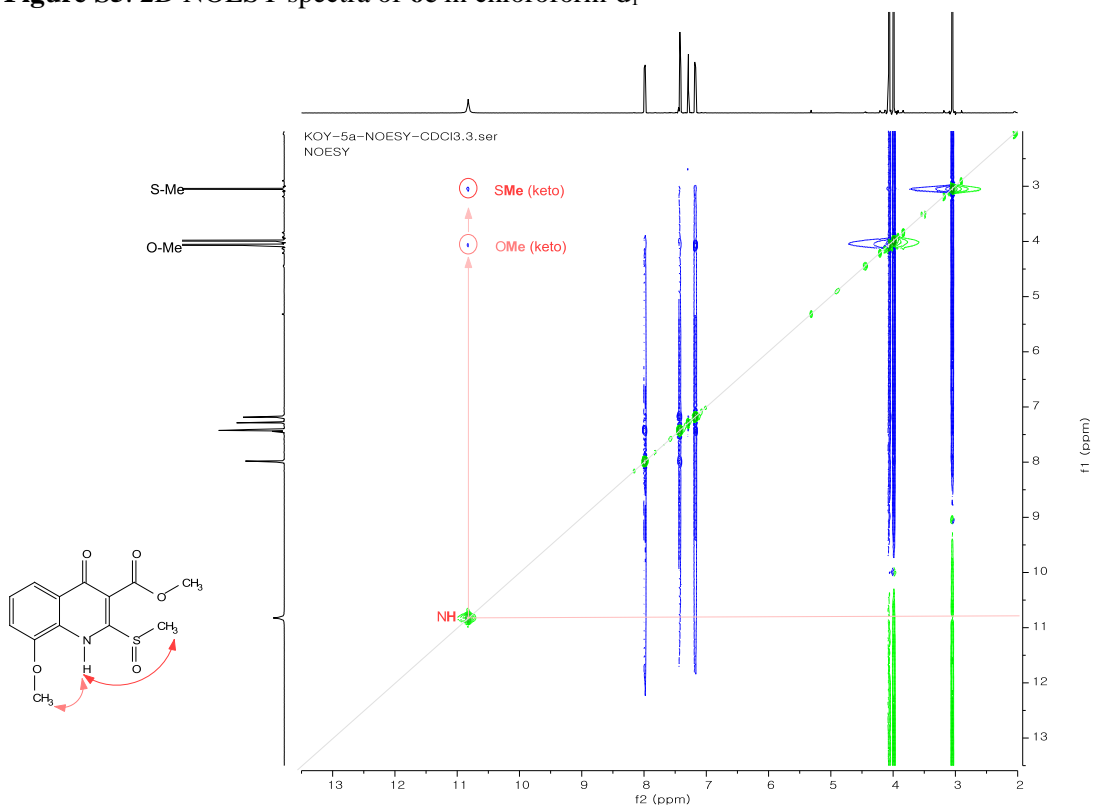
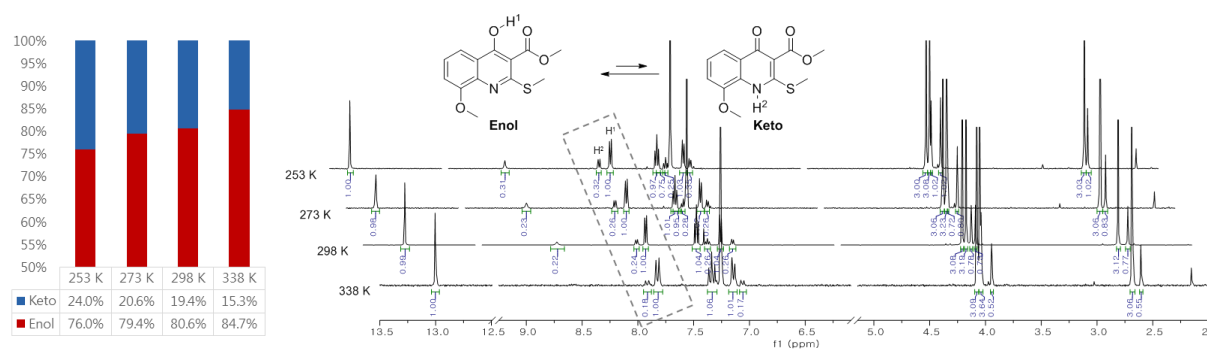


Figure S6. VT NMR studies of **4d**^[a]



[a] ¹H NMR was measured in CDCl₃

Figure S7. IR spectrum of an enol-keto mixture (blue) and crystals (red) of **4d**

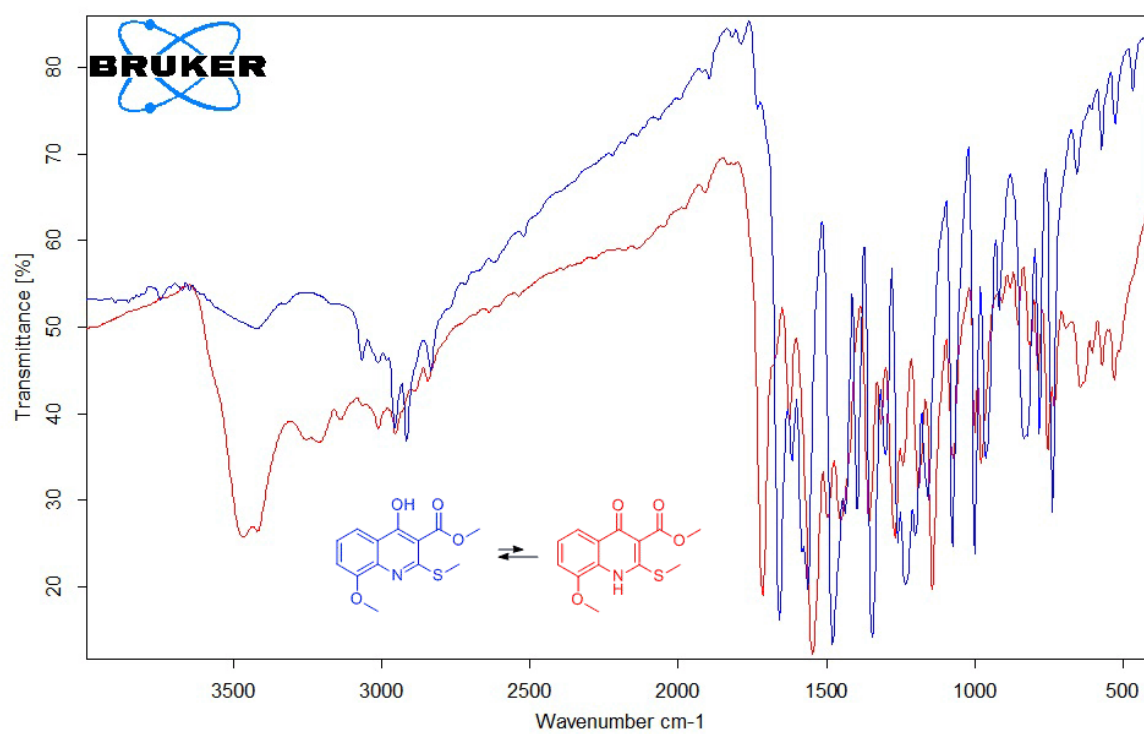
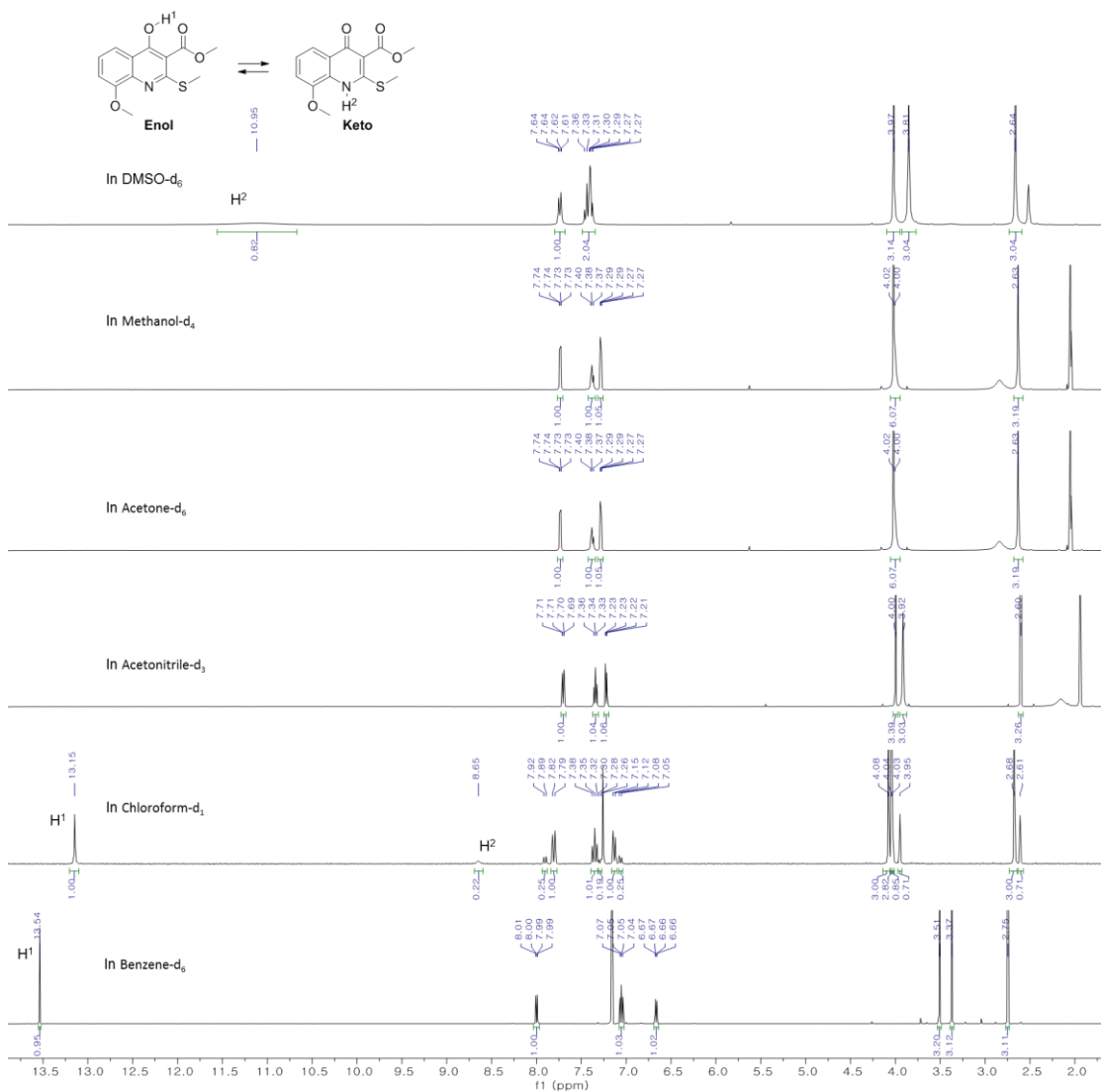


Figure S8. ^1H NMR studies of **4d** in various solvents



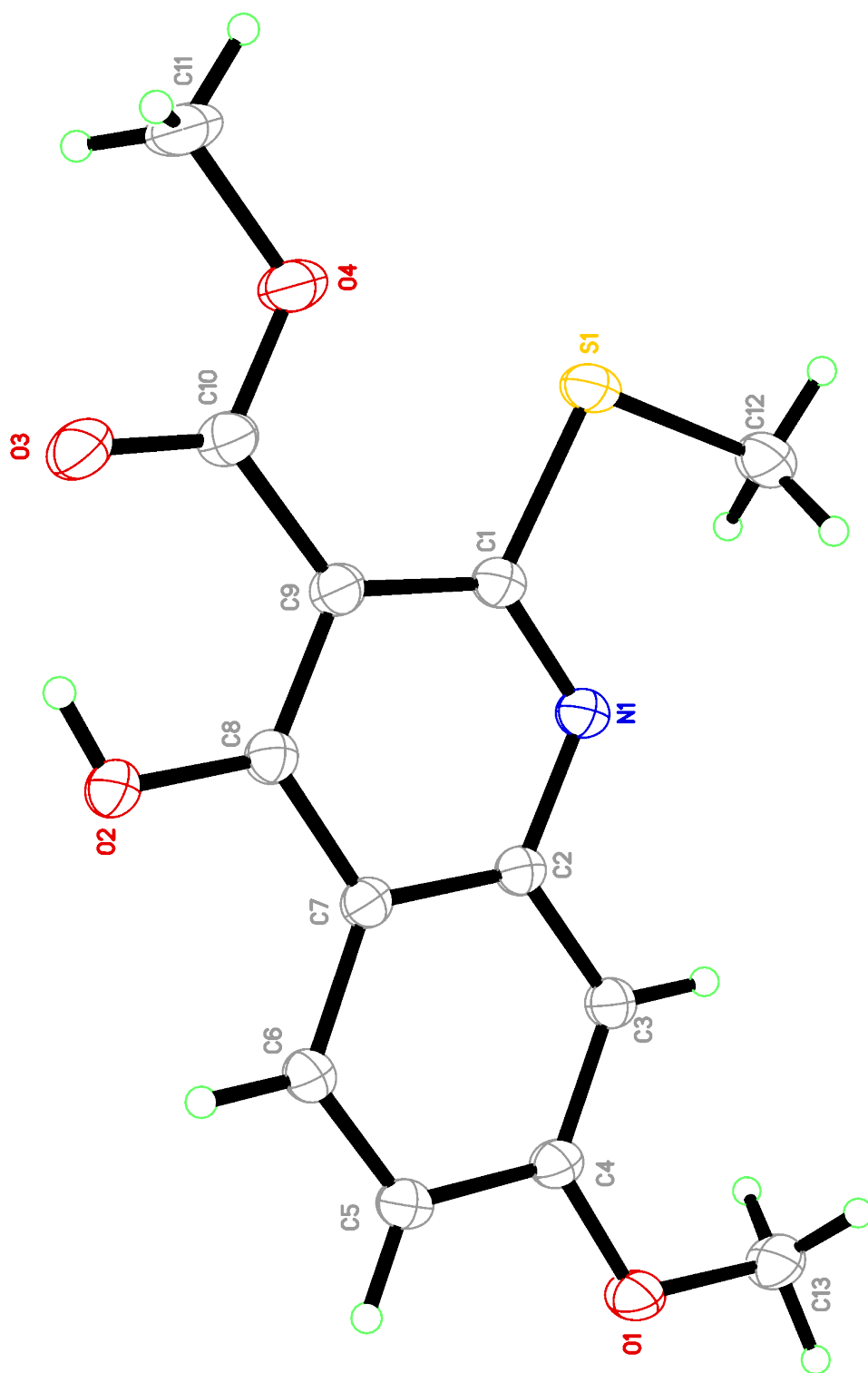


Figure S9. ORTEP plot of **4b** (CCDC# 1534621)

Table S3. Crystal data and structure refinement for **4b**.

Identification code	20161124	
Empirical formula	C13 H13 N O4 S	
Formula weight	279.30	
Temperature	296(1) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 9.10090(10) Å	= 90°.
	b = 17.5658(2) Å	= 103.2940(10)°.
	c = 8.18620(10) Å	= 90°.
Volume	1273.61(3) Å ³	
Z	4	
Density (calculated)	1.457 Mg/m ³	
Absorption coefficient	0.264 mm ⁻¹	
F(000)	584	
Crystal size	0.28 x 0.10 x 0.08 mm ³	
Theta range for data collection	2.30 to 28.44°	
Index ranges	0 ≤ h ≤ 12, -23 ≤ k ≤ 0, -10 ≤ l ≤ 10	
Reflections collected	3202	
Independent reflections	3202 [R(int) = 0.0000]	
Completeness to theta = 28.44°	99.7 %	
Absorption correction	Multi-scan	
Max. and min. transmission	0.9792 and 0.9299	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	3202 / 0 / 182	
Goodness-of-fit on F ²	1.079	
Final R indices [I > 2σ(I)]	R1 = 0.0558, wR2 = 0.1285	
R indices (all data)	R1 = 0.0726, wR2 = 0.1368	
Largest diff. peak and hole	0.417 and -0.199 e.Å ⁻³	

Table S4. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **4b**. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
S(1)	-202(1)	6097(1)	2232(1)	48(1)
O(1)	3983(2)	9482(1)	6209(2)	50(1)
O(2)	4709(2)	5932(1)	6959(2)	47(1)
O(3)	3373(2)	4746(1)	5616(2)	58(1)
O(4)	1330(2)	4836(1)	3545(2)	57(1)
N(1)	1446(2)	7216(1)	3774(2)	39(1)
C(1)	1370(2)	6473(1)	3710(2)	37(1)
C(2)	2629(2)	7550(1)	4903(2)	34(1)
C(3)	2693(2)	8350(1)	4936(2)	39(1)
C(4)	3833(2)	8711(1)	6056(2)	38(1)
C(5)	4955(2)	8288(1)	7167(2)	44(1)
C(6)	4908(2)	7515(1)	7135(2)	41(1)
C(7)	3744(2)	7126(1)	6006(2)	34(1)
C(8)	3637(2)	6322(1)	5911(2)	36(1)
C(9)	2446(2)	5974(1)	4755(2)	37(1)
C(10)	2437(2)	5142(1)	4697(2)	41(1)
C(11)	1318(3)	4015(1)	3424(3)	64(1)
C(12)	-1103(3)	6958(1)	1328(3)	59(1)
C(13)	2904(2)	9943(1)	5097(3)	51(1)

Table S5. Bond lengths [Å] and angles [°] for **4b**.

S(1)-C(1)	1.7759(17)
S(1)-C(12)	1.798(2)
O(1)-C(4)	1.363(2)
O(1)-C(13)	1.428(2)
O(2)-C(8)	1.331(2)
O(2)-H(2)	0.8200
O(3)-C(10)	1.216(2)
O(4)-C(10)	1.325(2)
O(4)-C(11)	1.446(2)
N(1)-C(1)	1.306(2)
N(1)-C(2)	1.378(2)
C(1)-C(9)	1.440(2)
C(2)-C(7)	1.406(2)
C(2)-C(3)	1.407(2)
C(3)-C(4)	1.372(2)
C(3)-H(3A)	0.9300
C(4)-C(5)	1.412(2)
C(5)-C(6)	1.359(3)
C(5)-H(5A)	0.9300
C(6)-C(7)	1.412(2)
C(6)-H(6A)	0.9300
C(7)-C(8)	1.417(2)
C(8)-C(9)	1.405(2)
C(9)-C(10)	1.462(2)
C(11)-H(11A)	0.9600
C(11)-H(11B)	0.9600
C(11)-H(11C)	0.9600
C(12)-H(12A)	0.92(3)
C(12)-H(12B)	0.98(3)
C(12)-H(12C)	1.00(3)
C(13)-H(13A)	0.9600
C(13)-H(13B)	0.9600
C(13)-H(13C)	0.9600
C(1)-S(1)-C(12)	100.75(9)

C(4)-O(1)-C(13)	117.73(14)
C(8)-O(2)-H(2)	109.5
C(10)-O(4)-C(11)	116.43(16)
C(1)-N(1)-C(2)	118.55(15)
N(1)-C(1)-C(9)	124.20(15)
N(1)-C(1)-S(1)	115.24(13)
C(9)-C(1)-S(1)	120.55(13)
N(1)-C(2)-C(7)	122.82(15)
N(1)-C(2)-C(3)	117.44(15)
C(7)-C(2)-C(3)	119.74(15)
C(4)-C(3)-C(2)	119.78(16)
C(4)-C(3)-H(3A)	120.1
C(2)-C(3)-H(3A)	120.1
O(1)-C(4)-C(3)	124.39(16)
O(1)-C(4)-C(5)	114.89(15)
C(3)-C(4)-C(5)	120.72(16)
C(6)-C(5)-C(4)	119.89(16)
C(6)-C(5)-H(5A)	120.1
C(4)-C(5)-H(5A)	120.1
C(5)-C(6)-C(7)	120.82(16)
C(5)-C(6)-H(6A)	119.6
C(7)-C(6)-H(6A)	119.6
C(2)-C(7)-C(6)	119.05(15)
C(2)-C(7)-C(8)	117.55(15)
C(6)-C(7)-C(8)	123.40(15)
O(2)-C(8)-C(9)	123.29(16)
O(2)-C(8)-C(7)	116.50(15)
C(9)-C(8)-C(7)	120.21(16)
C(8)-C(9)-C(1)	116.66(15)
C(8)-C(9)-C(10)	117.00(16)
C(1)-C(9)-C(10)	126.32(16)
O(3)-C(10)-O(4)	121.23(16)
O(3)-C(10)-C(9)	123.62(17)
O(4)-C(10)-C(9)	115.14(16)
O(4)-C(11)-H(11A)	109.5
O(4)-C(11)-H(11B)	109.5
H(11A)-C(11)-H(11B)	109.5

O(4)-C(11)-H(11C)	109.5
H(11A)-C(11)-H(11C)	109.5
H(11B)-C(11)-H(11C)	109.5
S(1)-C(12)-H(12A)	107.4(18)
S(1)-C(12)-H(12B)	109.1(17)
H(12A)-C(12)-H(12B)	114(2)
S(1)-C(12)-H(12C)	107.0(16)
H(12A)-C(12)-H(12C)	112(2)
H(12B)-C(12)-H(12C)	108(2)
O(1)-C(13)-H(13A)	109.5
O(1)-C(13)-H(13B)	109.5
H(13A)-C(13)-H(13B)	109.5
O(1)-C(13)-H(13C)	109.5
H(13A)-C(13)-H(13C)	109.5
H(13B)-C(13)-H(13C)	109.5

Symmetry transformations used to generate equivalent atoms:

Table S6. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **4b**. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^*2U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U ¹¹	U ²²	U ³³	U ²³	U ¹³	U ¹²
S(1)	42(1)	41(1)	53(1)	-6(1)	-4(1)	-7(1)
O(1)	52(1)	30(1)	59(1)	-1(1)	-8(1)	-2(1)
O(2)	48(1)	33(1)	51(1)	0(1)	-4(1)	6(1)
O(3)	68(1)	32(1)	63(1)	1(1)	-6(1)	3(1)
O(4)	64(1)	33(1)	64(1)	-5(1)	-7(1)	-5(1)
N(1)	38(1)	36(1)	40(1)	-3(1)	2(1)	-1(1)
C(1)	36(1)	36(1)	36(1)	-2(1)	5(1)	-2(1)
C(2)	35(1)	32(1)	34(1)	-2(1)	5(1)	0(1)
C(3)	39(1)	33(1)	40(1)	1(1)	0(1)	3(1)
C(4)	41(1)	30(1)	42(1)	-2(1)	5(1)	-1(1)
C(5)	42(1)	37(1)	48(1)	-5(1)	-2(1)	-1(1)
C(6)	39(1)	37(1)	42(1)	0(1)	-3(1)	3(1)
C(7)	36(1)	31(1)	35(1)	-1(1)	6(1)	1(1)
C(8)	37(1)	34(1)	36(1)	0(1)	6(1)	2(1)
C(9)	40(1)	33(1)	37(1)	-2(1)	7(1)	-1(1)
C(10)	46(1)	34(1)	43(1)	-2(1)	9(1)	-3(1)
C(11)	76(2)	34(1)	75(2)	-9(1)	3(1)	-12(1)
C(12)	46(1)	52(1)	67(2)	-3(1)	-12(1)	0(1)
C(13)	58(1)	32(1)	57(1)	3(1)	1(1)	3(1)

Table S7. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **4b**.

	x	y	z	U(eq)
H(2)	4609	5477	6743	70
H(3A)	1965	8633	4202	47
H(5A)	5724	8539	7920	53
H(6A)	5652	7239	7865	49
H(11A)	474	3856	2556	96
H(11B)	1234	3799	4476	96
H(11C)	2238	3845	3159	96
H(12A)	-1980(30)	6821(16)	570(40)	88
H(12B)	-400(30)	7246(16)	820(30)	88
H(12C)	-1320(30)	7270(17)	2280(40)	88
H(13A)	3133	10471	5335	76
H(13B)	1911	9834	5251	76
H(13C)	2942	9835	3958	76

Table S8. Torsion angles [°] for **4b**.

C(2)-N(1)-C(1)-C(9)	0.3(3)
C(2)-N(1)-C(1)-S(1)	179.43(12)
C(12)-S(1)-C(1)-N(1)	0.99(18)
C(12)-S(1)-C(1)-C(9)	-179.80(16)
C(1)-N(1)-C(2)-C(7)	-1.0(2)
C(1)-N(1)-C(2)-C(3)	179.41(15)
N(1)-C(2)-C(3)-C(4)	178.94(16)
C(7)-C(2)-C(3)-C(4)	-0.7(3)
C(13)-O(1)-C(4)-C(3)	-1.8(3)
C(13)-O(1)-C(4)-C(5)	178.67(17)
C(2)-C(3)-C(4)-O(1)	-178.87(16)
C(2)-C(3)-C(4)-C(5)	0.7(3)
O(1)-C(4)-C(5)-C(6)	179.42(16)
C(3)-C(4)-C(5)-C(6)	-0.1(3)
C(4)-C(5)-C(6)-C(7)	-0.3(3)
N(1)-C(2)-C(7)-C(6)	-179.37(16)
C(3)-C(2)-C(7)-C(6)	0.3(2)
N(1)-C(2)-C(7)-C(8)	1.0(2)
C(3)-C(2)-C(7)-C(8)	-179.38(16)
C(5)-C(6)-C(7)-C(2)	0.3(3)
C(5)-C(6)-C(7)-C(8)	179.87(17)
C(2)-C(7)-C(8)-O(2)	179.61(15)
C(6)-C(7)-C(8)-O(2)	0.0(3)
C(2)-C(7)-C(8)-C(9)	-0.3(2)
C(6)-C(7)-C(8)-C(9)	-179.95(16)
O(2)-C(8)-C(9)-C(1)	179.76(16)
C(7)-C(8)-C(9)-C(1)	-0.3(2)
O(2)-C(8)-C(9)-C(10)	-1.7(3)
C(7)-C(8)-C(9)-C(10)	178.24(16)
N(1)-C(1)-C(9)-C(8)	0.4(3)
S(1)-C(1)-C(9)-C(8)	-178.78(13)
N(1)-C(1)-C(9)-C(10)	-178.02(17)
S(1)-C(1)-C(9)-C(10)	2.8(2)
C(11)-O(4)-C(10)-O(3)	-1.2(3)
C(11)-O(4)-C(10)-C(9)	178.18(18)

C(8)-C(9)-C(10)-O(3)	1.9(3)
C(1)-C(9)-C(10)-O(3)	-179.70(18)
C(8)-C(9)-C(10)-O(4)	-177.46(16)
C(1)-C(9)-C(10)-O(4)	0.9(3)

Symmetry transformations used to generate equivalent atoms:

Table S9. Hydrogen bonds for **4b** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(2)-H(2)...O(3)	0.82	1.81	2.5331(18)	145.7
O(2)-H(2)...O(1)#1	0.82	2.55	3.0554(18)	120.8

Symmetry transformations used to generate equivalent atoms:

#1 -x+1,y-1/2,-z+3/2

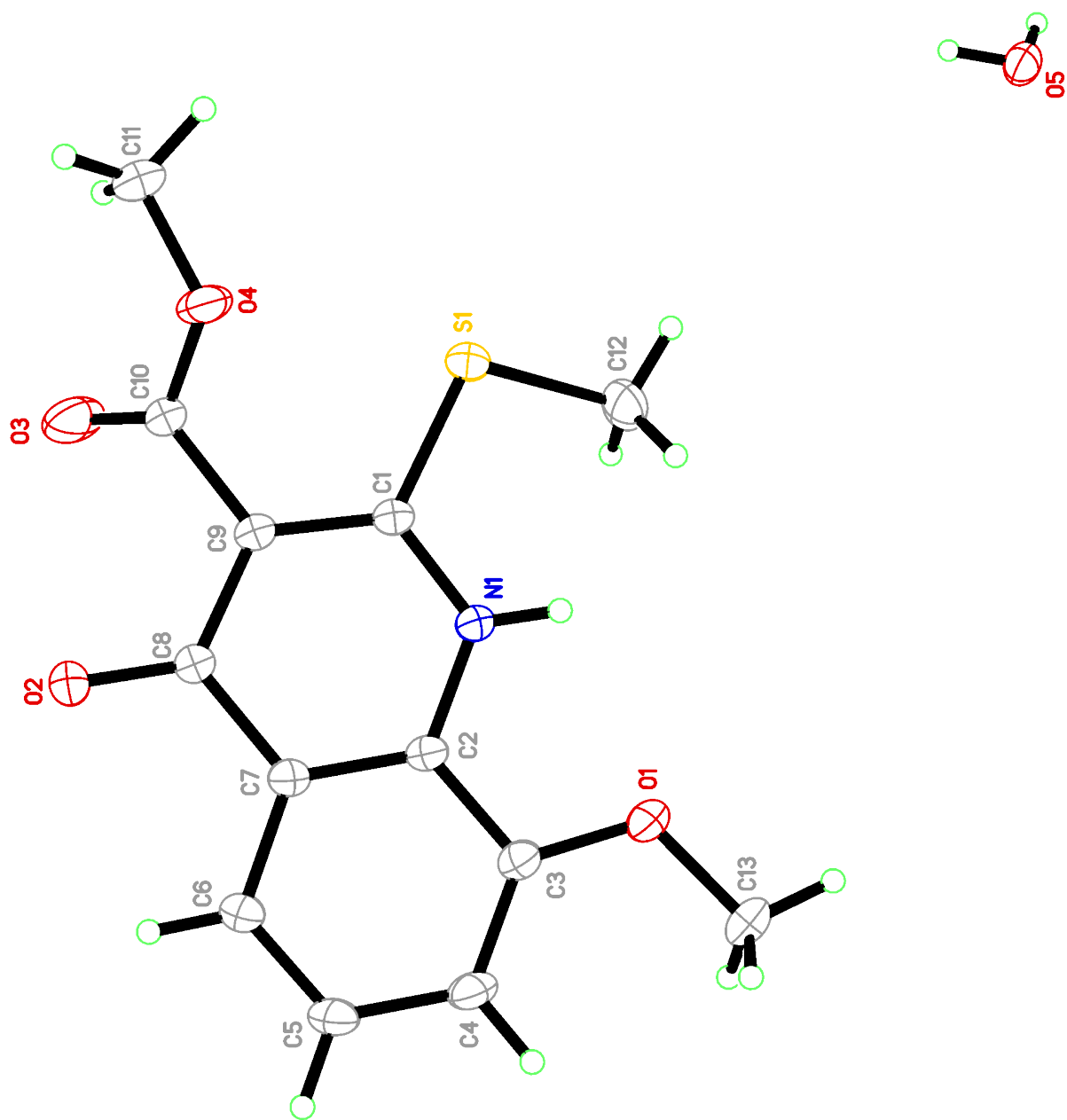


Figure S10. ORTEP of **4d** (CCDC# 1534621)

Table S10. Crystal data and structure refinement for **4d**.

Identification code	20161229_0m
Empirical formula	C ₁₃ H ₁₅ N O ₅ S
Formula weight	297.32
Temperature	296(1) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 7.2268(3) Å = 80.813(2)°. b = 9.0737(4) Å = 84.674(2)°. c = 10.4696(4) Å = 88.958(3)°.
Volume	674.80(5) Å ³
Z	2
Density (calculated)	1.463 Mg/m ³
Absorption coefficient	0.259 mm ⁻¹
F(000)	312
Crystal size	0.34 x 0.28 x 0.14 mm ³
Theta range for data collection	1.98 to 28.48°
Index ranges	-9<=h<=9, -11<=k<=12, 0<=l<=13
Reflections collected	3359
Independent reflections	3359 [R(int) = 0.0000]
Completeness to theta = 28.48°	98.6 %
Absorption correction	Multi-scan
Max. and min. transmission	0.9647 and 0.9172
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	3359 / 0 / 191
Goodness-of-fit on F ²	1.054
Final R indices [I>2sigma(I)]	R1 = 0.0511, wR2 = 0.1476
R indices (all data)	R1 = 0.0589, wR2 = 0.1552
Largest diff. peak and hole	0.471 and -0.295 e.Å ⁻³

Table S11. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **4d**. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S(1)	7357(1)	540(1)	3917(1)	55(1)
O(1)	6553(2)	3292(1)	-497(1)	50(1)
O(2)	8532(2)	-3109(1)	666(1)	50(1)
O(3)	7375(3)	-3856(2)	3420(2)	90(1)
O(4)	9012(2)	-2240(2)	4212(1)	56(1)
N(1)	7346(2)	1097(1)	1348(1)	36(1)
C(1)	7577(2)	19(2)	2365(1)	34(1)
C(2)	7342(2)	794(2)	98(1)	32(1)
C(3)	6943(2)	1970(2)	-902(1)	36(1)
C(4)	6968(2)	1678(2)	-2151(2)	44(1)
C(5)	7369(3)	243(2)	-2421(2)	48(1)
C(6)	7729(2)	-909(2)	-1453(2)	42(1)
C(7)	7716(2)	-640(2)	-167(1)	33(1)
C(8)	8097(2)	-1841(2)	896(1)	34(1)
C(9)	7918(2)	-1447(2)	2187(1)	34(1)
C(10)	8056(2)	-2659(2)	3309(2)	41(1)
C(11)	9032(4)	-3213(2)	5437(2)	64(1)
C(12)	6038(3)	2252(2)	3696(2)	58(1)
C(13)	6275(3)	4562(2)	-1459(2)	57(1)
O(5)	762(2)	6149(2)	8405(1)	54(1)

Table S12. Bond lengths [Å] and angles [°] for **4d**.

S(1)-C(1)	1.7559(15)
S(1)-C(12)	1.802(2)
O(1)-C(3)	1.3516(19)
O(1)-C(13)	1.4294(19)
O(2)-C(8)	1.2421(18)
O(3)-C(10)	1.185(2)
O(4)-C(10)	1.326(2)
O(4)-C(11)	1.438(2)
N(1)-C(1)	1.3461(18)
N(1)-C(2)	1.3803(18)
N(1)-H(1A)	0.8600
C(1)-C(9)	1.387(2)
C(2)-C(7)	1.389(2)
C(2)-C(3)	1.4166(19)
C(3)-C(4)	1.373(2)
C(4)-C(5)	1.396(2)
C(4)-H(4A)	0.9300
C(5)-C(6)	1.374(2)
C(5)-H(5A)	0.9300
C(6)-C(7)	1.405(2)
C(6)-H(6A)	0.9300
C(7)-C(8)	1.4700(19)
C(8)-C(9)	1.446(2)
C(9)-C(10)	1.4853(19)
C(11)-H(11A)	0.9600
C(11)-H(11B)	0.9600
C(11)-H(11C)	0.9600
C(12)-H(12A)	0.9600
C(12)-H(12B)	0.9600
C(12)-H(12C)	0.9600
C(13)-H(13A)	0.9600
C(13)-H(13B)	0.9600
C(13)-H(13C)	0.9600
O(5)-H(5B)	0.87(3)
O(5)-H(5C)	0.89(3)

C(1)-S(1)-C(12)	103.58(8)
C(3)-O(1)-C(13)	117.90(14)
C(10)-O(4)-C(11)	118.28(15)
C(1)-N(1)-C(2)	122.18(12)
C(1)-N(1)-H(1A)	118.9
C(2)-N(1)-H(1A)	118.9
N(1)-C(1)-C(9)	120.90(13)
N(1)-C(1)-S(1)	117.23(11)
C(9)-C(1)-S(1)	121.85(11)
N(1)-C(2)-C(7)	120.38(12)
N(1)-C(2)-C(3)	118.65(13)
C(7)-C(2)-C(3)	120.97(13)
O(1)-C(3)-C(4)	126.73(13)
O(1)-C(3)-C(2)	114.47(13)
C(4)-C(3)-C(2)	118.80(14)
C(3)-C(4)-C(5)	120.27(14)
C(3)-C(4)-H(4A)	119.9
C(5)-C(4)-H(4A)	119.9
C(6)-C(5)-C(4)	121.27(15)
C(6)-C(5)-H(5A)	119.4
C(4)-C(5)-H(5A)	119.4
C(5)-C(6)-C(7)	119.59(15)
C(5)-C(6)-H(6A)	120.2
C(7)-C(6)-H(6A)	120.2
C(2)-C(7)-C(6)	119.09(13)
C(2)-C(7)-C(8)	119.63(13)
C(6)-C(7)-C(8)	121.28(13)
O(2)-C(8)-C(9)	123.53(13)
O(2)-C(8)-C(7)	120.45(13)
C(9)-C(8)-C(7)	116.02(12)
C(1)-C(9)-C(8)	120.56(12)
C(1)-C(9)-C(10)	121.26(13)
C(8)-C(9)-C(10)	118.16(13)
O(3)-C(10)-O(4)	122.87(15)
O(3)-C(10)-C(9)	125.12(15)
O(4)-C(10)-C(9)	111.99(13)

O(4)-C(11)-H(11A)	109.5
O(4)-C(11)-H(11B)	109.5
H(11A)-C(11)-H(11B)	109.5
O(4)-C(11)-H(11C)	109.5
H(11A)-C(11)-H(11C)	109.5
H(11B)-C(11)-H(11C)	109.5
S(1)-C(12)-H(12A)	109.5
S(1)-C(12)-H(12B)	109.5
H(12A)-C(12)-H(12B)	109.5
S(1)-C(12)-H(12C)	109.5
H(12A)-C(12)-H(12C)	109.5
H(12B)-C(12)-H(12C)	109.5
O(1)-C(13)-H(13A)	109.5
O(1)-C(13)-H(13B)	109.5
H(13A)-C(13)-H(13B)	109.5
O(1)-C(13)-H(13C)	109.5
H(13A)-C(13)-H(13C)	109.5
H(13B)-C(13)-H(13C)	109.5
H(5B)-O(5)-H(5C)	103(2)

Symmetry transformations used to generate equivalent atoms:

Table S13. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **4d**. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U ¹¹	U ²²	U ³³	U ²³	U ¹³	U ¹²
S(1)	94(1)	43(1)	26(1)	-6(1)	-3(1)	7(1)
O(1)	73(1)	38(1)	37(1)	1(1)	-9(1)	14(1)
O(2)	77(1)	34(1)	38(1)	-7(1)	-4(1)	8(1)
O(3)	163(2)	50(1)	56(1)	14(1)	-43(1)	-35(1)
O(4)	79(1)	53(1)	36(1)	6(1)	-22(1)	-5(1)
N(1)	50(1)	32(1)	26(1)	-3(1)	-3(1)	6(1)
C(1)	42(1)	35(1)	26(1)	-3(1)	-3(1)	1(1)
C(2)	33(1)	36(1)	26(1)	-2(1)	-4(1)	1(1)
C(3)	38(1)	37(1)	33(1)	0(1)	-6(1)	3(1)
C(4)	51(1)	48(1)	30(1)	4(1)	-12(1)	1(1)
C(5)	64(1)	54(1)	28(1)	-8(1)	-12(1)	-2(1)
C(6)	55(1)	41(1)	32(1)	-9(1)	-9(1)	0(1)
C(7)	34(1)	36(1)	28(1)	-4(1)	-4(1)	-1(1)
C(8)	38(1)	33(1)	31(1)	-4(1)	-5(1)	1(1)
C(9)	39(1)	34(1)	27(1)	-1(1)	-5(1)	1(1)
C(10)	57(1)	35(1)	30(1)	-1(1)	-7(1)	4(1)
C(11)	97(2)	57(1)	36(1)	4(1)	-19(1)	13(1)
C(12)	78(1)	48(1)	48(1)	-15(1)	10(1)	6(1)
C(13)	80(1)	38(1)	50(1)	8(1)	-12(1)	6(1)
O(5)	77(1)	37(1)	44(1)	-1(1)	0(1)	2(1)

Table S14. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **4d**.

	x	y	z	U(eq)
H(1A)	7197	2004	1482	44
H(4A)	6717	2440	-2819	52
H(5A)	7393	63	-3272	57
H(6A)	7980	-1862	-1648	50
H(11A)	7953	-3840	5576	96
H(11B)	9026	-2627	6124	96
H(11C)	10131	-3824	5430	96
H(12A)	5847	2625	4507	88
H(12B)	4857	2066	3403	88
H(12C)	6708	2978	3061	88
H(13A)	7374	4730	-2053	86
H(13B)	6025	5425	-1045	86
H(13C)	5241	4385	-1927	86
H(5B)	1010(40)	5190(30)	8520(30)	82(8)
H(5C)	-60(40)	6250(30)	9080(30)	71(7)

Table S15. Torsion angles [°] for **4d**.

C(2)-N(1)-C(1)-C(9)	3.4(2)
C(2)-N(1)-C(1)-S(1)	-174.78(11)
C(12)-S(1)-C(1)-N(1)	20.78(14)
C(12)-S(1)-C(1)-C(9)	-157.34(14)
C(1)-N(1)-C(2)-C(7)	-4.7(2)
C(1)-N(1)-C(2)-C(3)	175.00(13)
C(13)-O(1)-C(3)-C(4)	-5.3(2)
C(13)-O(1)-C(3)-C(2)	175.27(14)
N(1)-C(2)-C(3)-O(1)	-1.6(2)
C(7)-C(2)-C(3)-O(1)	178.13(13)
N(1)-C(2)-C(3)-C(4)	178.93(13)
C(7)-C(2)-C(3)-C(4)	-1.3(2)
O(1)-C(3)-C(4)-C(5)	-178.96(16)
C(2)-C(3)-C(4)-C(5)	0.4(2)
C(3)-C(4)-C(5)-C(6)	0.6(3)
C(4)-C(5)-C(6)-C(7)	-0.7(3)
N(1)-C(2)-C(7)-C(6)	-179.06(13)
C(3)-C(2)-C(7)-C(6)	1.2(2)
N(1)-C(2)-C(7)-C(8)	0.7(2)
C(3)-C(2)-C(7)-C(8)	-179.06(13)
C(5)-C(6)-C(7)-C(2)	-0.2(2)
C(5)-C(6)-C(7)-C(8)	-179.91(15)
C(2)-C(7)-C(8)-O(2)	-176.08(14)
C(6)-C(7)-C(8)-O(2)	3.7(2)
C(2)-C(7)-C(8)-C(9)	4.3(2)
C(6)-C(7)-C(8)-C(9)	-175.95(13)
N(1)-C(1)-C(9)-C(8)	2.1(2)
S(1)-C(1)-C(9)-C(8)	-179.85(11)
N(1)-C(1)-C(9)-C(10)	-176.09(13)
S(1)-C(1)-C(9)-C(10)	2.0(2)
O(2)-C(8)-C(9)-C(1)	174.68(14)
C(7)-C(8)-C(9)-C(1)	-5.7(2)
O(2)-C(8)-C(9)-C(10)	-7.1(2)
C(7)-C(8)-C(9)-C(10)	172.52(13)
C(11)-O(4)-C(10)-O(3)	-7.6(3)

C(11)-O(4)-C(10)-C(9)	171.02(15)
C(1)-C(9)-C(10)-O(3)	136.8(2)
C(8)-C(9)-C(10)-O(3)	-41.5(3)
C(1)-C(9)-C(10)-O(4)	-41.9(2)
C(8)-C(9)-C(10)-O(4)	139.91(15)

Symmetry transformations used to generate equivalent atoms:

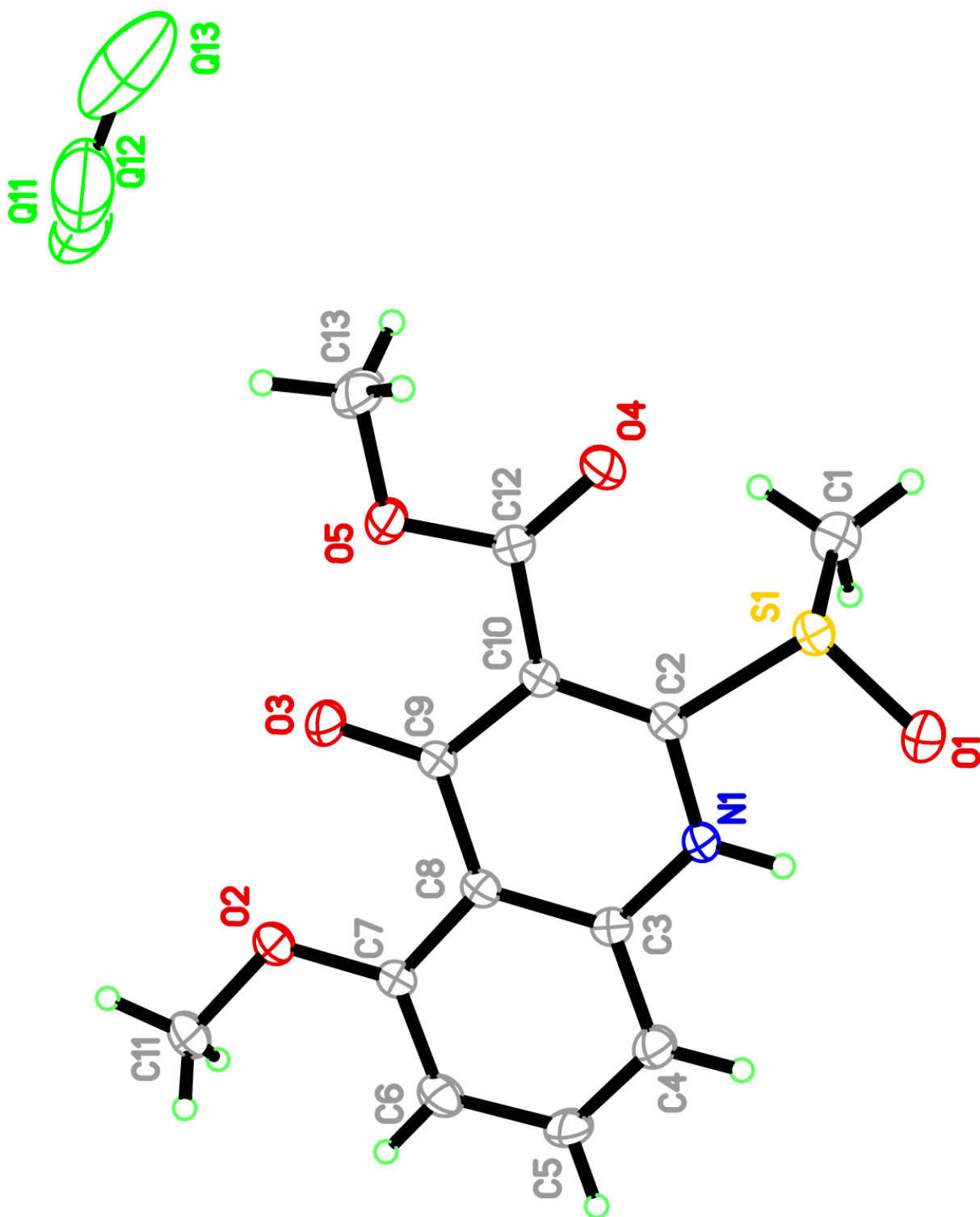


Figure S11. ORTEP of **6a** (CCDC# 1838136).

Table S16. Crystal data and structure refinement for **6a**.

Identification code	20171102_0m
Empirical formula	C ₁₆ H ₁₃ N O ₅ S
Formula weight	331.33
Temperature	296(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)/n
Unit cell dimensions	a = 6.6266(6) Å = 90°. b = 18.2993(15) Å = 99.670(6)°. c = 11.8645(10) Å = 90°.
Volume	1418.3(2) Å ³
Z	4
Density (calculated)	1.552 Mg/m ³
Absorption coefficient	0.256 mm ⁻¹
F(000)	688
Crystal size	0.30 x 0.28 x 0.24 mm ³
Theta range for data collection	2.07 to 26.00°
Index ranges	-8<=h<=8, 0<=k<=22, 0<=l<=14
Reflections collected	2776
Independent reflections	2776 [R(int) = 0.0000]
Completeness to theta = 26.00°	99.8 %
Absorption correction	Multi-scan
Max. and min. transmission	0.9412 and 0.9273
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	2776 / 0 / 208
Goodness-of-fit on F ²	1.103
Final R indices [I>2sigma(I)]	R1 = 0.0785, wR2 = 0.2396
R indices (all data)	R1 = 0.0963, wR2 = 0.2512
Largest diff. peak and hole	0.877 and -0.436 e.Å ⁻³

Table S17. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **6a**. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S(1)	6927(2)	8969(1)	1413(1)	46(1)
O(1)	6436(5)	9713(2)	917(3)	63(1)
O(2)	-1521(4)	6910(2)	-721(3)	48(1)
O(3)	2063(5)	6715(2)	547(3)	59(1)
O(4)	7584(5)	7590(2)	2123(3)	56(1)
O(5)	6035(4)	6580(2)	1358(3)	49(1)
N(1)	3179(5)	8882(2)	259(3)	40(1)
C(1)	6419(9)	9049(3)	2826(4)	61(1)
C(2)	4602(6)	8447(2)	855(3)	36(1)
C(3)	1303(6)	8620(2)	-276(3)	37(1)
C(4)	-86(6)	9108(2)	-894(4)	46(1)
C(5)	-1906(7)	8851(3)	-1446(4)	52(1)
C(6)	-2425(6)	8116(2)	-1405(4)	47(1)
C(7)	-1088(6)	7629(2)	-789(3)	37(1)
C(8)	865(6)	7869(2)	-199(3)	33(1)
C(9)	2403(6)	7368(2)	438(3)	36(1)
C(10)	4351(6)	7710(2)	951(3)	34(1)
C(11)	-3385(7)	6646(3)	-1387(4)	54(1)
C(12)	6140(6)	7294(2)	1547(3)	37(1)
C(13)	7861(8)	6173(3)	1842(5)	62(1)
Q(11)	920(20)	225(7)	4506(16)	150(6)
Q(12)	2450(30)	226(8)	4344(14)	171(6)
Q(13)	4790(40)	304(9)	4895(19)	246(9)

Table S18. Bond lengths [Å] and angles [°] for **6a**.

S(1)-O(1)	1.498(3)
S(1)-C(1)	1.771(6)
S(1)-C(2)	1.839(4)
O(2)-C(7)	1.353(5)
O(2)-C(11)	1.433(5)
O(3)-C(9)	1.226(5)
O(4)-C(12)	1.207(5)
O(5)-C(12)	1.324(5)
O(5)-C(13)	1.455(5)
N(1)-C(2)	1.340(5)
N(1)-C(3)	1.383(5)
N(1)-H(1B)	0.8600
C(1)-H(1C)	0.9600
C(1)-H(1D)	0.9600
C(1)-H(1E)	0.9600
C(2)-C(10)	1.366(5)
C(3)-C(4)	1.398(5)
C(3)-C(8)	1.411(5)
C(4)-C(5)	1.355(6)
C(4)-H(4A)	0.9300
C(5)-C(6)	1.391(6)
C(5)-H(5A)	0.9300
C(6)-C(7)	1.377(6)
C(6)-H(6A)	0.9300
C(7)-C(8)	1.433(5)
C(8)-C(9)	1.481(5)
C(9)-C(10)	1.472(5)
C(10)-C(12)	1.484(5)
C(11)-H(11A)	0.9600
C(11)-H(11B)	0.9600
C(11)-H(11C)	0.9600
C(13)-H(13A)	0.9600
C(13)-H(13B)	0.9600
C(13)-H(13C)	0.9600
Q(11)-Q(12)	1.07(2)

Q(11)-Q(11)#1	2.00(3)
Q(12)-Q(13)	1.58(3)
Q(13)-Q(13)#2	1.17(3)
O(1)-S(1)-C(1)	103.5(2)
O(1)-S(1)-C(2)	102.56(18)
C(1)-S(1)-C(2)	95.9(2)
C(7)-O(2)-C(11)	117.8(3)
C(12)-O(5)-C(13)	114.9(3)
C(2)-N(1)-C(3)	122.3(3)
C(2)-N(1)-H(1B)	118.8
C(3)-N(1)-H(1B)	118.8
S(1)-C(1)-H(1C)	109.5
S(1)-C(1)-H(1D)	109.5
H(1C)-C(1)-H(1D)	109.5
S(1)-C(1)-H(1E)	109.5
H(1C)-C(1)-H(1E)	109.5
H(1D)-C(1)-H(1E)	109.5
N(1)-C(2)-C(10)	123.0(3)
N(1)-C(2)-S(1)	110.7(3)
C(10)-C(2)-S(1)	126.1(3)
N(1)-C(3)-C(4)	118.8(4)
N(1)-C(3)-C(8)	119.1(3)
C(4)-C(3)-C(8)	122.1(4)
C(5)-C(4)-C(3)	119.1(4)
C(5)-C(4)-H(4A)	120.5
C(3)-C(4)-H(4A)	120.5
C(4)-C(5)-C(6)	121.6(4)
C(4)-C(5)-H(5A)	119.2
C(6)-C(5)-H(5A)	119.2
C(7)-C(6)-C(5)	120.2(4)
C(7)-C(6)-H(6A)	119.9
C(5)-C(6)-H(6A)	119.9
O(2)-C(7)-C(6)	122.5(3)
O(2)-C(7)-C(8)	116.9(3)
C(6)-C(7)-C(8)	120.6(4)
C(3)-C(8)-C(7)	116.4(3)

C(3)-C(8)-C(9)	120.4(3)
C(7)-C(8)-C(9)	123.2(3)
O(3)-C(9)-C(10)	122.4(3)
O(3)-C(9)-C(8)	122.3(3)
C(10)-C(9)-C(8)	115.4(3)
C(2)-C(10)-C(9)	119.8(3)
C(2)-C(10)-C(12)	116.6(3)
C(9)-C(10)-C(12)	123.6(3)
O(2)-C(11)-H(11A)	109.5
O(2)-C(11)-H(11B)	109.5
H(11A)-C(11)-H(11B)	109.5
O(2)-C(11)-H(11C)	109.5
H(11A)-C(11)-H(11C)	109.5
H(11B)-C(11)-H(11C)	109.5
O(4)-C(12)-O(5)	123.5(4)
O(4)-C(12)-C(10)	122.3(4)
O(5)-C(12)-C(10)	114.2(3)
O(5)-C(13)-H(13A)	109.5
O(5)-C(13)-H(13B)	109.5
H(13A)-C(13)-H(13B)	109.5
O(5)-C(13)-H(13C)	109.5
H(13A)-C(13)-H(13C)	109.5
H(13B)-C(13)-H(13C)	109.5
Q(12)-Q(11)-Q(11)#1	143(2)
Q(11)-Q(12)-Q(13)	145(2)
Q(13)#2-Q(13)-Q(12)	101(3)

Symmetry transformations used to generate equivalent atoms:

#1 -x,-y,-z+1 #2 -x+1,-y,-z+1

Table S19. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **6a**. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U ¹¹	U ²²	U ³³	U ²³	U ¹³	U ¹²
S(1)	40(1)	38(1)	53(1)	5(1)	-6(1)	-9(1)
O(1)	65(2)	41(2)	76(2)	14(2)	-11(2)	-16(2)
O(2)	39(2)	41(2)	58(2)	2(1)	-12(1)	-9(1)
O(3)	50(2)	33(2)	83(2)	10(2)	-22(2)	-11(1)
O(4)	47(2)	41(2)	69(2)	-4(2)	-22(2)	0(1)
O(5)	43(2)	32(2)	67(2)	4(1)	-8(1)	0(1)
N(1)	37(2)	30(2)	46(2)	3(1)	-9(2)	-6(1)
C(1)	68(3)	47(3)	63(3)	0(2)	0(2)	1(2)
C(2)	35(2)	34(2)	36(2)	-1(2)	-4(2)	-5(2)
C(3)	38(2)	35(2)	35(2)	3(2)	0(2)	-1(2)
C(4)	40(2)	37(2)	56(3)	8(2)	-3(2)	-1(2)
C(5)	42(2)	47(3)	59(3)	15(2)	-13(2)	4(2)
C(6)	34(2)	53(3)	50(3)	1(2)	-6(2)	-7(2)
C(7)	39(2)	35(2)	33(2)	0(2)	-3(2)	-2(2)
C(8)	30(2)	35(2)	32(2)	0(2)	0(2)	-2(2)
C(9)	40(2)	32(2)	32(2)	-1(2)	-3(2)	-2(2)
C(10)	34(2)	32(2)	33(2)	0(2)	-1(2)	-2(2)
C(11)	45(2)	49(3)	62(3)	-3(2)	-12(2)	-13(2)
C(12)	37(2)	34(2)	37(2)	3(2)	0(2)	0(2)
C(13)	48(3)	43(3)	87(4)	10(2)	-5(2)	10(2)
Q(11)	133(9)	68(6)	228(16)	16(7)	-29(10)	8(7)
Q(12)	280(20)	94(8)	144(11)	-17(7)	35(16)	-13(15)
Q(13)	320(20)	138(13)	300(20)	52(14)	109(19)	118(17)

Table S20. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **6a**.

	x	y	z	U(eq)
H(1B)	3443	9340	208	48
H(1C)	7505	9318	3282	91
H(1D)	6331	8571	3146	91
H(1E)	5148	9303	2815	91
H(4A)	233	9601	-926	55
H(5A)	-2828	9174	-1861	62
H(6A)	-3680	7953	-1796	56
H(11A)	-3508	6131	-1261	82
H(11B)	-3366	6734	-2183	82
H(11C)	-4528	6896	-1163	82
H(13A)	7654	5663	1669	92
H(13B)	8128	6239	2657	92
H(13C)	9007	6348	1522	92

Table S21. Torsion angles [°] for **6a**.

C(3)-N(1)-C(2)-C(10)	2.3(6)
C(3)-N(1)-C(2)-S(1)	178.4(3)
O(1)-S(1)-C(2)-N(1)	-3.8(3)
C(1)-S(1)-C(2)-N(1)	101.5(3)
O(1)-S(1)-C(2)-C(10)	172.1(4)
C(1)-S(1)-C(2)-C(10)	-82.7(4)
C(2)-N(1)-C(3)-C(4)	-179.1(4)
C(2)-N(1)-C(3)-C(8)	-0.3(6)
N(1)-C(3)-C(4)-C(5)	178.2(4)
C(8)-C(3)-C(4)-C(5)	-0.6(7)
C(3)-C(4)-C(5)-C(6)	0.4(7)
C(4)-C(5)-C(6)-C(7)	0.4(8)
C(11)-O(2)-C(7)-C(6)	4.6(6)
C(11)-O(2)-C(7)-C(8)	-174.5(4)
C(5)-C(6)-C(7)-O(2)	179.9(4)
C(5)-C(6)-C(7)-C(8)	-1.1(7)
N(1)-C(3)-C(8)-C(7)	-178.9(4)
C(4)-C(3)-C(8)-C(7)	-0.1(6)
N(1)-C(3)-C(8)-C(9)	-0.5(6)
C(4)-C(3)-C(8)-C(9)	178.3(4)
O(2)-C(7)-C(8)-C(3)	180.0(3)
C(6)-C(7)-C(8)-C(3)	0.9(6)
O(2)-C(7)-C(8)-C(9)	1.6(6)
C(6)-C(7)-C(8)-C(9)	-177.4(4)
C(3)-C(8)-C(9)-O(3)	178.3(4)
C(7)-C(8)-C(9)-O(3)	-3.5(6)
C(3)-C(8)-C(9)-C(10)	-0.6(5)
C(7)-C(8)-C(9)-C(10)	177.7(4)
N(1)-C(2)-C(10)-C(9)	-3.4(6)
S(1)-C(2)-C(10)-C(9)	-178.8(3)
N(1)-C(2)-C(10)-C(12)	174.4(4)
S(1)-C(2)-C(10)-C(12)	-1.0(5)
O(3)-C(9)-C(10)-C(2)	-176.4(4)
C(8)-C(9)-C(10)-C(2)	2.5(5)
O(3)-C(9)-C(10)-C(12)	5.9(6)

C(8)-C(9)-C(10)-C(12)	-175.2(3)
C(13)-O(5)-C(12)-O(4)	-3.6(6)
C(13)-O(5)-C(12)-C(10)	174.2(4)
C(2)-C(10)-C(12)-O(4)	15.0(6)
C(9)-C(10)-C(12)-O(4)	-167.2(4)
C(2)-C(10)-C(12)-O(5)	-162.8(4)
C(9)-C(10)-C(12)-O(5)	14.9(6)
Q(11)#1-Q(11)-Q(12)-Q(13)	-52(5)
Q(11)-Q(12)-Q(13)-Q(13)#2	91(4)

Symmetry transformations used to generate equivalent atoms:

#1 -x,-y,-z+1 #2 -x+1,-y,-z+1

Table S22. Hydrogen bonds for **6a** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1B)...O(1)#3	0.86	2.20	2.957(4)	147.1
N(1)-H(1B)...O(1)	0.86	2.13	2.649(4)	118.1

Symmetry transformations used to generate equivalent atoms:

#1 -x,-y,-z+1 #2 -x+1,-y,-z+1 #3 -x+1,-y+2,-z

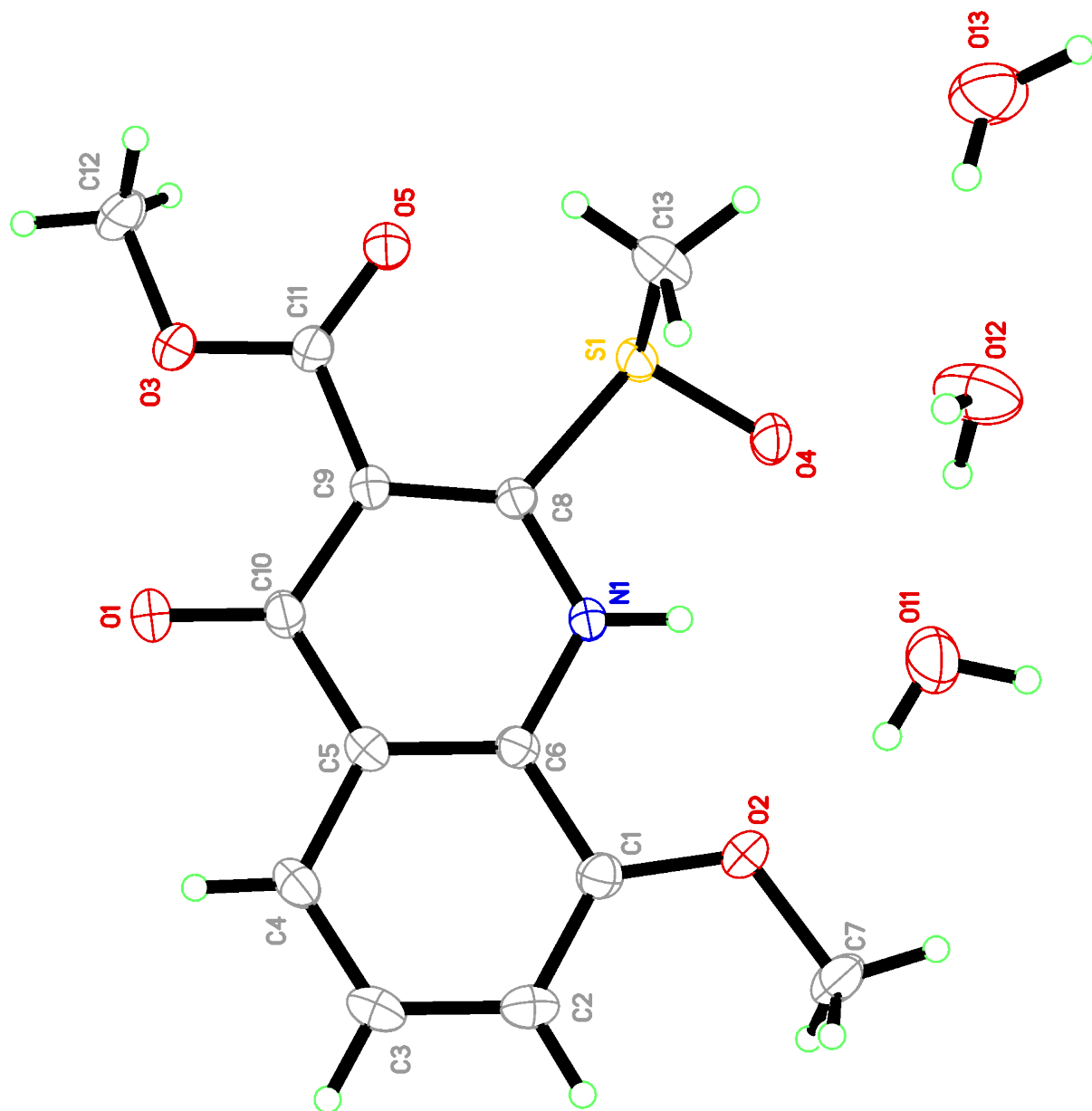


Figure S12. ORTEP of 6c (CCDC# 1838137).

Table S23. Crystal data and structure refinement for **6c**.

Identification code	20170522_0m
Empirical formula	C ₁₃ H ₁₉ N O ₈ S
Formula weight	349.35
Temperature	296(1) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 7.2412(9) Å = 85.640(6)°. b = 9.7236(12) Å = 87.406(6)°. c = 11.4552(15) Å = 77.183(6)°.
Volume	783.86(17) Å ³
Z	2
Density (calculated)	1.480 Mg/m ³
Absorption coefficient	0.248 mm ⁻¹
F(000)	368
Crystal size	0.15 x 0.15 x 0.30 mm ³
Theta range for data collection	1.78 to 26.00°.
Index ranges	-8<=h<=8, -11<=k<=11, -14<=l<=14
Reflections collected	10645
Independent reflections	2965 [R(int) = 0.0349]
Completeness to theta = 26.00°	96.5 %
Absorption correction	Multi-scan
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	2965 / 5 / 232
Goodness-of-fit on F ²	1.077
Final R indices [I>2sigma(I)]	R1 = 0.0429, wR2 = 0.1227
R indices (all data)	R1 = 0.0509, wR2 = 0.1289
Largest diff. peak and hole	0.303 and -0.326 e.Å ⁻³

Table S24. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **6c**. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S(1)	348(1)	1121(1)	3443(1)	37(1)
O(1)	3099(2)	-2913(2)	638(1)	57(1)
O(2)	1824(2)	3283(1)	-343(1)	52(1)
O(3)	1603(2)	-3411(1)	2812(1)	46(1)
O(4)	-185(2)	2648(1)	3009(1)	48(1)
O(5)	1075(2)	-1609(2)	3969(1)	53(1)
N(1)	1583(2)	1248(2)	1266(1)	34(1)
C(1)	2310(3)	1958(2)	-726(2)	37(1)
C(2)	2890(3)	1597(2)	-1838(2)	44(1)
C(3)	3329(3)	167(2)	-2079(2)	46(1)
C(4)	3235(3)	-882(2)	-1234(2)	42(1)
C(5)	2671(2)	-543(2)	-87(2)	34(1)
C(6)	2198(2)	877(2)	151(2)	32(1)
C(7)	1829(4)	4454(2)	-1180(2)	62(1)
C(8)	1413(2)	271(2)	2122(2)	31(1)
C(9)	1864(2)	-1157(2)	1985(2)	34(1)
C(10)	2579(3)	-1657(2)	845(2)	37(1)
C(11)	1500(3)	-2069(2)	3014(2)	37(1)
C(12)	1153(4)	-4295(2)	3814(2)	57(1)
C(13)	2512(3)	987(3)	4194(2)	54(1)
O(11)	3916(3)	4238(2)	1551(2)	72(1)
O(12)	5954(3)	3736(2)	3562(2)	76(1)
O(13)	4247(3)	3328(3)	5829(2)	80(1)

Table S25. Bond lengths [Å] and angles [°] for **6c**.

S(1)-O(4)	1.5002(14)
S(1)-C(13)	1.796(2)
S(1)-C(8)	1.8355(18)
O(1)-C(10)	1.233(2)
O(2)-C(1)	1.359(2)
O(2)-C(7)	1.432(2)
O(3)-C(11)	1.328(2)
O(3)-C(12)	1.450(2)
O(5)-C(11)	1.214(2)
N(1)-C(8)	1.334(2)
N(1)-C(6)	1.380(2)
N(1)-H(1A)	0.8600
C(1)-C(2)	1.370(3)
C(1)-C(6)	1.411(2)
C(2)-C(3)	1.402(3)
C(2)-H(2A)	0.9300
C(3)-C(4)	1.363(3)
C(3)-H(3A)	0.9300
C(4)-C(5)	1.400(3)
C(4)-H(4B)	0.9300
C(5)-C(6)	1.392(3)
C(5)-C(10)	1.472(3)
C(7)-H(7A)	0.9600
C(7)-H(7B)	0.9600
C(7)-H(7C)	0.9600
C(8)-C(9)	1.374(3)
C(9)-C(10)	1.461(3)
C(9)-C(11)	1.470(2)
C(12)-H(12A)	0.9600
C(12)-H(12B)	0.9600
C(12)-H(12C)	0.9600
C(13)-H(13A)	0.9600
C(13)-H(13B)	0.9600
C(13)-H(13C)	0.9600
O(11)-H(11A)	0.822(19)

O(11)-H(11B)	0.88(3)
O(12)-H(12D)	0.875(18)
O(12)-H(12E)	0.819(17)
O(13)-H(13D)	0.835(19)
O(13)-H(13E)	0.880(19)
O(4)-S(1)-C(13)	103.87(10)
O(4)-S(1)-C(8)	102.10(8)
C(13)-S(1)-C(8)	97.17(9)
C(1)-O(2)-C(7)	118.08(17)
C(11)-O(3)-C(12)	115.22(16)
C(8)-N(1)-C(6)	121.35(15)
C(8)-N(1)-H(1A)	119.3
C(6)-N(1)-H(1A)	119.3
O(2)-C(1)-C(2)	126.96(17)
O(2)-C(1)-C(6)	113.99(17)
C(2)-C(1)-C(6)	119.05(18)
C(1)-C(2)-C(3)	119.22(18)
C(1)-C(2)-H(2A)	120.4
C(3)-C(2)-H(2A)	120.4
C(4)-C(3)-C(2)	122.01(19)
C(4)-C(3)-H(3A)	119.0
C(2)-C(3)-H(3A)	119.0
C(3)-C(4)-C(5)	119.88(19)
C(3)-C(4)-H(4B)	120.1
C(5)-C(4)-H(4B)	120.1
C(6)-C(5)-C(4)	118.29(17)
C(6)-C(5)-C(10)	120.80(16)
C(4)-C(5)-C(10)	120.91(17)
N(1)-C(6)-C(5)	119.64(15)
N(1)-C(6)-C(1)	118.82(16)
C(5)-C(6)-C(1)	121.54(17)
O(2)-C(7)-H(7A)	109.5
O(2)-C(7)-H(7B)	109.5
H(7A)-C(7)-H(7B)	109.5
O(2)-C(7)-H(7C)	109.5
H(7A)-C(7)-H(7C)	109.5

H(7B)-C(7)-H(7C)	109.5
N(1)-C(8)-C(9)	123.67(16)
N(1)-C(8)-S(1)	110.21(13)
C(9)-C(8)-S(1)	125.99(13)
C(8)-C(9)-C(10)	119.13(15)
C(8)-C(9)-C(11)	115.89(16)
C(10)-C(9)-C(11)	124.92(17)
O(1)-C(10)-C(9)	124.50(17)
O(1)-C(10)-C(5)	120.17(17)
C(9)-C(10)-C(5)	115.33(16)
O(5)-C(11)-O(3)	122.75(17)
O(5)-C(11)-C(9)	121.99(17)
O(3)-C(11)-C(9)	115.23(17)
O(3)-C(12)-H(12A)	109.5
O(3)-C(12)-H(12B)	109.5
H(12A)-C(12)-H(12B)	109.5
O(3)-C(12)-H(12C)	109.5
H(12A)-C(12)-H(12C)	109.5
H(12B)-C(12)-H(12C)	109.5
S(1)-C(13)-H(13A)	109.5
S(1)-C(13)-H(13B)	109.5
H(13A)-C(13)-H(13B)	109.5
S(1)-C(13)-H(13C)	109.5
H(13A)-C(13)-H(13C)	109.5
H(13B)-C(13)-H(13C)	109.5
H(11A)-O(11)-H(11B)	113(3)
H(12D)-O(12)-H(12E)	113(3)
H(13D)-O(13)-H(13E)	113(4)

Symmetry transformations used to generate equivalent atoms:

Table S26. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **6c**. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U ¹¹	U ²²	U ³³	U ²³	U ¹³	U ¹²
S(1)	43(1)	34(1)	33(1)	-7(1)	7(1)	-8(1)
O(1)	91(1)	30(1)	47(1)	-9(1)	4(1)	-4(1)
O(2)	79(1)	34(1)	42(1)	5(1)	2(1)	-17(1)
O(3)	67(1)	30(1)	42(1)	1(1)	0(1)	-16(1)
O(4)	63(1)	30(1)	48(1)	-8(1)	12(1)	-6(1)
O(5)	82(1)	39(1)	38(1)	-3(1)	11(1)	-14(1)
N(1)	45(1)	26(1)	31(1)	-5(1)	5(1)	-9(1)
C(1)	39(1)	39(1)	37(1)	-2(1)	-1(1)	-14(1)
C(2)	44(1)	56(1)	34(1)	4(1)	1(1)	-16(1)
C(3)	42(1)	64(2)	31(1)	-10(1)	5(1)	-9(1)
C(4)	43(1)	43(1)	37(1)	-14(1)	2(1)	-4(1)
C(5)	34(1)	37(1)	32(1)	-7(1)	-1(1)	-7(1)
C(6)	32(1)	34(1)	30(1)	-4(1)	1(1)	-10(1)
C(7)	94(2)	44(1)	51(1)	15(1)	-9(1)	-28(1)
C(8)	35(1)	30(1)	30(1)	-2(1)	2(1)	-9(1)
C(9)	38(1)	30(1)	34(1)	-4(1)	0(1)	-8(1)
C(10)	41(1)	31(1)	38(1)	-7(1)	-2(1)	-5(1)
C(11)	42(1)	31(1)	39(1)	-1(1)	-3(1)	-9(1)
C(12)	82(2)	39(1)	53(1)	12(1)	-4(1)	-23(1)
C(13)	54(1)	67(2)	43(1)	-18(1)	1(1)	-17(1)
O(11)	104(2)	44(1)	64(1)	-8(1)	-27(1)	-1(1)
O(12)	63(1)	105(2)	47(1)	-7(1)	3(1)	8(1)
O(13)	96(2)	94(2)	57(1)	8(1)	8(1)	-40(1)

Table S27. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **6c**.

	x	y	z	U(eq)
H(1A)	1304	2126	1410	41
H(2A)	2990	2293	-2427	53
H(3A)	3697	-73	-2839	55
H(4B)	3545	-1822	-1419	50
H(7A)	1461	5321	-796	93
H(7B)	952	4446	-1782	93
H(7C)	3079	4379	-1524	93
H(12A)	1269	-5242	3590	86
H(12B)	-121	-3929	4089	86
H(12C)	2014	-4298	4428	86
H(13A)	2954	33	4509	80
H(13B)	2286	1612	4820	80
H(13C)	3451	1245	3654	80
H(11A)	4420(60)	3960(40)	930(20)	147(19)
H(11B)	3480(50)	5160(40)	1530(30)	114(12)
H(12D)	5200(40)	3850(30)	2970(20)	111(13)
H(12E)	7060(30)	3380(30)	3390(30)	94(10)
H(13D)	4770(50)	3280(40)	5160(20)	126(14)
H(13E)	4580(60)	3960(40)	6240(30)	159(19)

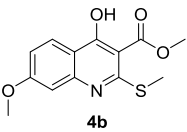
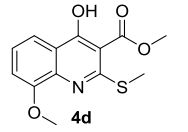
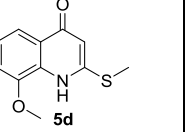
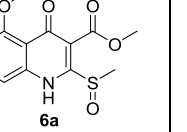
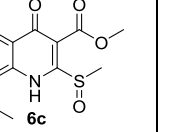
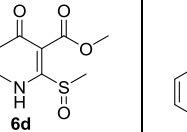
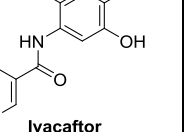
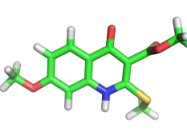
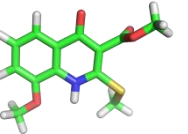
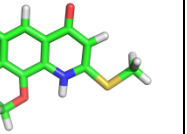
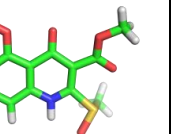
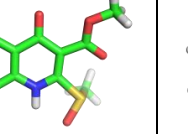
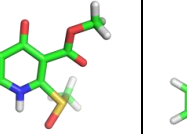
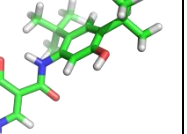
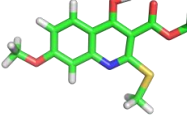
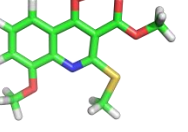
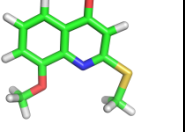
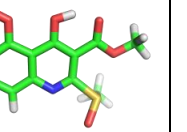
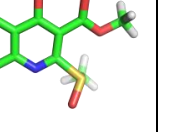
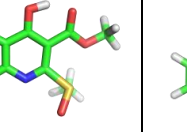
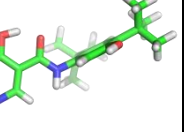
Table S28. Torsion angles [°] for **6c**.

C(7)-O(2)-C(1)-C(2)	2.8(3)
C(7)-O(2)-C(1)-C(6)	-177.85(17)
O(2)-C(1)-C(2)-C(3)	-179.74(18)
C(6)-C(1)-C(2)-C(3)	0.9(3)
C(1)-C(2)-C(3)-C(4)	-1.3(3)
C(2)-C(3)-C(4)-C(5)	0.5(3)
C(3)-C(4)-C(5)-C(6)	0.7(3)
C(3)-C(4)-C(5)-C(10)	-179.28(17)
C(8)-N(1)-C(6)-C(5)	-0.6(3)
C(8)-N(1)-C(6)-C(1)	178.59(15)
C(4)-C(5)-C(6)-N(1)	178.09(16)
C(10)-C(5)-C(6)-N(1)	-1.9(3)
C(4)-C(5)-C(6)-C(1)	-1.1(3)
C(10)-C(5)-C(6)-C(1)	178.88(16)
O(2)-C(1)-C(6)-N(1)	1.7(2)
C(2)-C(1)-C(6)-N(1)	-178.93(16)
O(2)-C(1)-C(6)-C(5)	-179.13(16)
C(2)-C(1)-C(6)-C(5)	0.3(3)
C(6)-N(1)-C(8)-C(9)	1.5(3)
C(6)-N(1)-C(8)-S(1)	-174.48(13)
O(4)-S(1)-C(8)-N(1)	7.21(15)
C(13)-S(1)-C(8)-N(1)	-98.70(15)
O(4)-S(1)-C(8)-C(9)	-168.68(16)
C(13)-S(1)-C(8)-C(9)	85.41(18)
N(1)-C(8)-C(9)-C(10)	0.2(3)
S(1)-C(8)-C(9)-C(10)	175.58(13)
N(1)-C(8)-C(9)-C(11)	-177.27(16)
S(1)-C(8)-C(9)-C(11)	-1.9(2)
C(8)-C(9)-C(10)-O(1)	176.90(18)
C(11)-C(9)-C(10)-O(1)	-5.9(3)
C(8)-C(9)-C(10)-C(5)	-2.6(3)
C(11)-C(9)-C(10)-C(5)	174.67(16)
C(6)-C(5)-C(10)-O(1)	-176.07(18)
C(4)-C(5)-C(10)-O(1)	3.9(3)
C(6)-C(5)-C(10)-C(9)	3.4(3)

C(4)-C(5)-C(10)-C(9)	-176.59(17)
C(12)-O(3)-C(11)-O(5)	0.6(3)
C(12)-O(3)-C(11)-C(9)	-177.13(17)
C(8)-C(9)-C(11)-O(5)	-9.7(3)
C(10)-C(9)-C(11)-O(5)	172.96(18)
C(8)-C(9)-C(11)-O(3)	167.99(16)
C(10)-C(9)-C(11)-O(3)	-9.3(3)

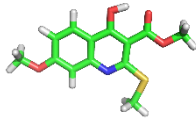
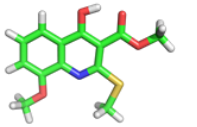
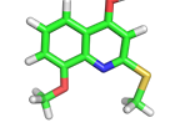
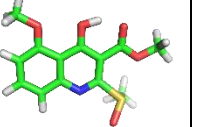
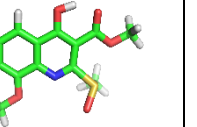
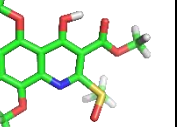
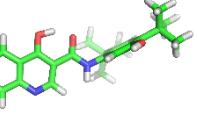
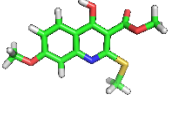
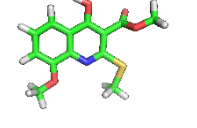
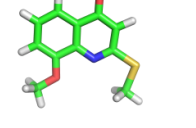
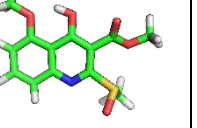
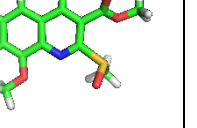
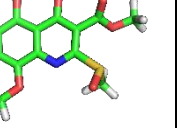
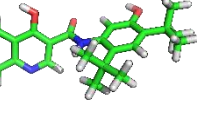
Symmetry transformations used to generate equivalent atoms:

Table S29. DFT Calculations of Enol and Keto forms^[a]

Compounds							
3D Structure (Keto Form)							
3D Structure (Enol Form)							
Total Energy ^{b)} (Keto Form)	-1257.104712	-1257.105067	-1029.223871	-1332.283898	-1332.293932	-1446.809791	-1266.729149
Total Energy (Enol Form)	-1257.121779	-1257.116410	-1029.220480	-1332.281645	-1332.283839	-1446.801635	-1266.724704
Relative Energy ^{c)} (E _{keto} – E _{enol})	10.71	7.12	-2.13	-1.41	-6.33	-5.12	-2.79

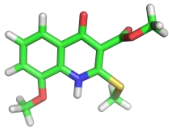
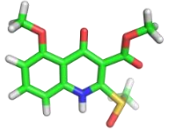
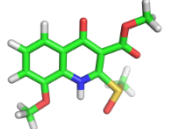
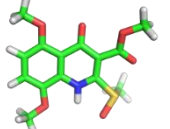
[a] Calculated with DFT methods using Jaguar Tool. (DFT Method; B3LYP, Basis set; 6-31+G**), Jaguar Version 9.9, release 11; [b] Energy unit ; Hartrees (1Hartrees = 627.509 kcal); [c] Energy unit ; kcal/mol, The negative energy value means that keto form is more stable.

Table S30. H-bonding Energy Calculations of Enol forms^[a]

Compounds	4b	4d	5d	6a	6c	6d	Ivacaftor
3D Structure (Hydrogen bond)							
3D Structure (Non-hydrogen bond)							
Total Energy ^{b)} (H-bond)	-1257.121779	-1257.116410	-1029.220480	-1332.281645	-1332.283839	-1446.801635	-1266.724704
Total Energy (Non H-bond)	-1257.098347	-1257.094672	-	-1332.264637	-1332.275750	-1446.797728	-1266.702562
Hydrogen Bond Energy ^{c)} (E _{HB} – E _{NHB})	-14.70	-13.64	-	-3.70	-12.05	-2.45	-13.89

[a] Calculated with DFT methods using Jaguar Tool. (DFT Method; B3LYP, Basis set; 6-31+G**), Jaguar Version 9.9, release 11; [b] Energy unit ; Hartrees (1Hartrees = 627.509 kcal); [c] Energy unit ; kcal/mol, E_{HB}; Hydrogen Bonding, E_{NHB}; Non-hydrogen Bonding.

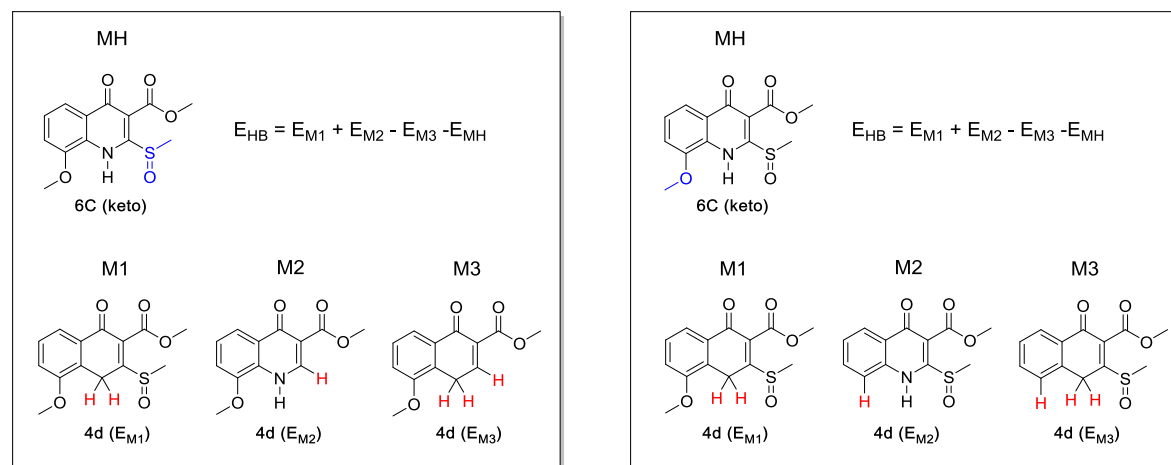
Table S31. H-bonding Energy Calculations of Keto forms^[a]

Compounds	4d	6a	6c	6d
3D Structure (Keto Form)				
Hydrogen Bond Energy	0.26	4.19	2.5	2.61

[a] Calculated with DFT methods using Jaguar Tool. (DFT Method; B3LYP, Basis set; 6-31+G**), Jaguar Version 9.9, release 11; [b] Energy unit ; Hartrees (1Hartrees = 627.509 kcal), kcal/mol, Unit; kcal/mol, The Molecular Tailoring Approach (MTA) for EHB Calculation method was used for calculating H-bonding Energy of Keto forms.

Figure S13. The Molecular Tailoring Approach (MTA) for Hydrogen-bonding Energy Calculation²

The Molecular Tailoring Approach (MTA) for E_{HB} Calculation



² D. Rusinska-Roszak, *Molecules* **2017**, *22*, 481.

