Electronic Supplementary Material (ESI) for MedChemComm.

Supporting Information

Synthesis and evaluation of 6-Heteroarylamino-2,4,5-trimethylpyridin-3-ols as inhibitors of TNF-α-induced cell adhesion and inflammatory bowel disease

Sang Won Park,[a,#] Suhrid Banskota,[b,#] Pallavi Gurung,[b] You Jin Jin,[a] Han-eol Kang,[a] Chhabi Lal Chaudhary,[b] Sang Yeul Lee,[a] Byeong-Seon Jeong,*[,b] Jung-Ae Kim,*[,b] and Tae-gyu Nam*[,a]

[a]Department of Pharmacy and Institute of Pharmaceutical Science and Technology, Hanyang University, Ansan, Gyeonggi-do 15588, Republic of Korea.

[b]College of Pharmacy and Institute for Drug Research, Yeungnam University, Gyeongsan 38541, Republic of Korea.

[#]These authors contributed equally to this work.

Experimental procedures

Synthesis

Unless noted otherwise, materials were purchased from commercial suppliers and used without further purification. Air- or moisture-sensitive reactions were carried out under an inert gas atmosphere. Progress of reaction was monitored by thin layer chromatography (TLC) using silica gel F_{254} plates. Purification of the products was performed by flash column chromatography using silica gel 60 (70–230 mesh) or by Biotage 'Isolera One' system with indicated solvents. Melting points were determined using a Kruss melting pointer meter and were not corrected. NMR spectra were obtained using a Bruker spectrometer 400 MHz, 600 MHz or 700 MHz for ^{1}H-NMR, 100 MHz, 150 MHz, or 175 MHz for ^{13}C-NMR, respectively. Chemical shifts (δ) were expressed in ppm using solvent as an internal standard and coupling constant (*J*) in hertz. Low-resolution mass spectra (LRMS) were obtained using an Advion Expression CMS, and recorded in a positive ion mode with an electrospray (ESI) source. High-resolution mass spectra (HRMS) were obtained using a Thermo Scientific LTQ Orbitrap XL mass spectrometer, and recorded in positive ion mode with an electrospray (ESI) source.

General synthetic procedure for compounds (5)

To a solution of **3** (1 eq.), heteroarylamine **4** (2 eq.) in toluene (0.1 M) were added Cs_2CO_3 (1.5 eq.), $Pd(OAc)_2$ (0.1 eq.) and BINAP (0.1 eq.) at room temperature. After stirring for 3 h at 100 °C, the reaction mixture was filtered through a filter paper and rinsed with EtOAc. The filtrate was washed with water and brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The obtained residue was purified using flash column chromatography (SiO_2) to afford the corresponding desired products **5**.

General synthetic procedure for compounds (6)

For **6a – 6f**, **6j** and **6l**: to a solution of **5** (1.0 eq.) in EtOH (0.01 M) was added Pd/C (10% wt%) and stirred at room temperature for 1 h under H_2. The reaction mixture was filtered through celite and the filtrate was concentrated under reduced pressure. The obtained residue was purified using flash chromatography (SiO_2) to afford the corresponding desired products **6a – 6f**, **6j** and **6l**.

For **6g – 6i**, .**6k** and **6m** – **6q**: BCl_3 (2.0 eq.) was added to a suspension of **5** (1.0 eq.) and pentamethylbenzene (3.0 eq.) in DCM at 0 °C and stirred at 0 °C for 1~4 h. The reaction mixture was quenched by 10% MeOH/DCM

solution. The residue was purified by silica gel column chromatography (SiO_2) to give desired products **6g – 6i**, .**6k** and **6m** – **6q**.

General synthetic procedure for compounds (13)

To a solution of **10** (1.0 eq.) and **11** (1.1 eq.) in CH_2Cl_2 (0.2 M) was stirred at room temperature for 5 ~ 18 h. The reaction mixture was directly applied to flash column chromatography (SiO_2) to afford the corresponding desired product **12**. To a stirred solution of **12** (1.0 eq.) in DMSO was added EDCI (1.2 eq.) and stirring at 60 °C. After 3 h, the reaction mixture was diluted with EtOAC, washed with water four times and brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The obtained residue was purified using flash column chromatography (SiO_2) to afford the corresponding desired products **13**.

General synthetic procedure for compounds (14)

12 (1.0 eq.) in *N*-methylpyrrolidine (NMP, 0.1 M) was treated with Et_3N (2.4 eq.), *p*-TsCl (1.2 eq.). The reaction mixture was stirred at room temperature for 1 h in a capped vial and then, diluted with EtOAC, washed with water four times and brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The obtained residue was purified using flash column chromatography (SiO_2) to afford the corresponding desired products **14**.

General synthetic procedure for compounds (15) and (16)

To a solution of **13** or **14** (1.0 eq.) in THF was added TBAF at 0 °C. After 10 min, the reaction mixture was quenched with brine and diluted with EtOAc and washed with water and brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The obtained residue was purified using flash column chromatography (SiO_2) to afford the corresponding desired products **15** or **16**.

5-(benzyloxy)-3,4,6-trimethyl-*N*-(pyridin-2-yl)pyridin-2-amine (5a)

2-Aminopyridine (**4a**, 105 mg, 1.11 mmol) was added to a mixture of **3** (310 mg, 1.01 mmol), $Pd_2(dba)_3$ (46 mg, 0.05 mmol), BINAP (63 mg, 0.10 mmol), NaO^tBu (136 mg, 1.41 mmol) in toluene (4 mL) and the resulting mixture was refluxed for 4 h. The mixture was cooled down to room temperature, and then diluted with EtOAc (70 mL) and water. The organic layer was washed with brine (40 mL × 3) and dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography (SiO_2, EtOAc:Hexane = 1:8) to give **5a** (310 mg, 96%) as yellow solid. m.p. 108.8 - 110.1 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.32 (s, 1H), 8.12 (dt, *J* = 4.9, 1.5 Hz, 1H), 7.59 – 7.55 (m, 2H), 7.53 – 7.47 (m, 2H), 7.46 – 7.35 (m, 3H), 6.80 – 6.74 (m, 1H), 4.77 (s, 2H), 2.34 (s, 3H), 2.20 (s, 3H), 2.12 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 154.63, 147.50, 147.45, 146.91, 146.15, 140.45, 137.89, 137.18, 128.65, 128.24, 128.01, 117.55, 116.23, 111.37, 75.08, 19.28, 13.43, 13.16; MS (ESI) *m/z* $[M+H]^+$ 320.3.

5-(benzyloxy)-3,4,6-trimethyl-N-(4-(trifluoromethyl)pyridin-2-yl)pyridin-2-amine (5b)

Prepared according to the general procedure using **3** (306 mg, 1.0 mmol) and corresponding arylamine **4**(324 mg, 2. 0 mmol)**.** Flash column chromatography (SiO_2, 5% -> 20% EtOAc in hexanes) yielded brown solid (280 mg, 72%). R_f = 0.20 (20% EtOAC in hexanes); m.p.: 135~137 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.98 (s, 1H), 8.37 (d, J = 5.2 Hz, 1H), 7.88–7.84 (m, 1H), 7.52–7.48 (m, 2H), 7.46–7.36 (m, 3H), 7.06 (dd, J = 5.2, 1.1 Hz, 1H), 4.79 (s, 2H), 2.34 (s, 3H), 2.22 (s, 3H), 2.14 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 155.3, 148.7, 147.4, 146.7, 146.5, 140.8, 139.7 (q, $J_{C\text{-}F}$ = 33 Hz), 137.1, 128.7, 128.3, 128.0, 123.2 (q, $J_{C\text{-}F}$ = 271.5 Hz), 117.5, 111.5 (q, $J_{C\text{-}F}$ = 5.1 Hz) 107.4 (q, $J_{C\text{-}F}$ = 4.2 Hz) 75.1, 19.2, 13.2, 13.1 ppm; MS (ESI) *m/z* 388.4 $[M+H]^+$; HRMS (ESI): Calcd for $C_{21}H_{20}F_3N_3O$ $[M+H]^+$ 388.1631, Found 388.1628.

5-(benzyloxy)-3,4,6-trimethyl-N-(5-(trifluoromethyl)pyridin-2-yl)pyridin-2-amine (5c)

Prepared according to the general procedure using **3** (306 mg, 1.0 mmol) and corresponding arylamine **4** (324 mg, 2.0 mmol)**.** Flash column chromatography (SiO_2, 5% to 10% EtOAc in hexanes) yielded pale yellow solid (255 mg, 66%). R_f = 0.20 (20% EtOAC in hexanes); m.p.: 131~134 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 9.19 (s, 1H), 8.43 (dd, J = 1.6, 0.9 Hz, 1H), 7.86 (dd, J = 9.0, 2.5 Hz, 1H), 7.51 (dd, J = 8.1, 1.4 Hz, 2H), 7.41 (ddd, J = 11.7, 8.8, 5.8 Hz, 4H), 4.80 (s, 2H), 2.36 (s, 3H), 2.22 (s, 3H), 2.11 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 156.9, 147.7, 146.4, 146.2, 145.1 (q, $J_{C\text{-}F}$ = 4.1 Hz), 141.4, 136.9, 135.2 (q, $J_{C\text{-}F}$ = 3.2 Hz), 128.7, 128.4, 128.3, 125.6, 122.9, 118.8 (q, $J_{C\text{-}F}$ = 32.9 Hz), 118.6, 110.6, 75.2, 19.1, 13.5, 13.3 ppm; MS (ESI) *m/z* 384.4 $[M+H]^+$; HRMS (ESI) Calcd for $C_{14}H_{14}F_3N_3O$ $[M+H]^+$ 388.1631, Found 388.1626.

5-(benzyloxy)-3,4,6-trimethyl-N-(6-(trifluoromethyl)pyridin-3-yl)pyridin-2-amine (5d)

Prepared according to the general procedure using **3** (306 mg, 1.0 mmol) and corresponding arylamine **4** (582 mg, 2.0 mmol)**.** Flash column chromatography (SiO_2, 5% to 20% EtOAc in hexanes) yielded pale yellow solid (184 mg, 48%). R_f = 0.20 (20% EtOAC in hexanes); m.p.: 155~158 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.89 (d, J = 2.5 Hz, 1H), 8.50 (s, 1H), 8.18 (dd, J = 8.6, 2.3 Hz, 1H), 7.70 (d, J = 8.7 Hz, 1H), 7.49 (dd, J = 8.1, 1.4 Hz, 2H), 7.45–7.35 (m, 3H), 4.76 (s, 2H), 2.34 (s, 3H), 2.20 (d, J = 7.9 Hz, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 147.6, 147.0, 146.7, 141.3, 141.0, 139.6, 139.4 (q, $J_{C\text{-}F}$ = 36.4 Hz), 136.9, 128.7, 128.3, 128.0, 123.7, 122.1 (q, $J_{C\text{-}F}$ = 270.9 Hz), 120.8 (q, $J_{C\text{-}F}$ = 2.7 Hz), 117.7, 75.2, 19.1, 13.4, 13.2 ppm; MS (ESI) *m/z* 388.3 $[M+H]^+$; HRMS (ESI): Calcd for $C_{21}H_{20}F_3N_3O$ $[M+H]^+$ 388.1631, Found 388.1632.

5-(benzyloxy)-N-(5-chloropyridin-2-yl)-3,4,6-trimethylpyridin-2-amine (5e)

Prepared according to the general procedure using **3** (306 mg, 1.0 mmol) and corresponding arylamine **4** (257 mg, 2.0 mmol)**.** Flash column chromatography (SiO_2, 5% to 20% EtOAc in hexanes) yielded pale yellow solid

(269 mg, 76%). R_f = 0.20 (20% EtOAC in hexanes); m.p.: 135~136 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.63 (s, 1H), 8.13 (dd, *J* = 2.7, 0.6 Hz, 1H), 7.66 (dd, *J* = 9.0, 2.7 Hz, 1H), 7.55–7.48 (m, 3H), 7.46–7.34 (m, 3H), 4.77 (s, 2H), 2.34 (s, 3H), 2.20 (s, 3H), 2.11 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 153.0, 147.0, 146.1, 140.6, 137.4, 137.1, 128.7, 128.3, 128.0, 122.9, 117.3, 112.2, 77.4, 77.1, 76.8, 75.1, 19.2, 13.2 ppm; MS (ESI) *m/z* 354.3 $[M+H]^+$; HRMS (ESI): Calcd for $C_{20}H_{20}Cl_3N_3O$ $[M+H]^+$ 354.1367, Found 354.1368.

5-(benzyloxy)-3,4,6-trimethyl-*N*-(6-chloropyridin-3-yl)pyridin-2-amine (5f)

Prepared according to the general procedure using **3** (306 mg, 1.00 mmol) and corresponding arylamine **4** (257 mg, 2.00 mmol)**.** Flash column chromatography (SiO_2, 5% to 20% EtOAc in hexanes) yielded pale yellow solid (200 mg, 57%). R_f = 0.20 (30% EtOAC in hexanes); m.p.: 132~134 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.65 (dd, *J* = 2.9, 0.4 Hz, 1H), 8.12 (s, 1H), 8.09 (dd, *J* = 8.8, 2.9 Hz, 1H), 7.49 (dd, *J* = 8.1, 1.5 Hz, 2H), 7.45–7.31 (m, 4H), 4.74 (s, 2H), 2.31 (s, 3H), 2.18 (d, *J* = 12.0 Hz, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 147.7, 147.0, 146.4, 142.1, 140.8, 139.5, 137.8, 137.1, 128.7, 128.3, 128.1, 128.0, 123.7, 116.7, 75.1, 19.1, 13.3, 13.1 ppm; MS (ESI) *m/z* 354.2 $[M+H]^+$; HRMS (ESI): Calcd for $C_{20}H_{20}Cl_3N_3O$ $[M+H]^+$ 354.1367, Found 354.1383.

***N*-(5-(benzyloxy)-3,4,6-trimethylpyridin-2-yl)quinolin-4-amine (5g)**

5-Aminoquinoline (**4g**, 71 mg, 0.49 mmol) was added to a mixture of **3** (150 mg, 0.49 mmol), $Pd(OAc)_2$ (22 mg, 0.10 mmol), Xantphos (57 mg, 0.10 mmol), Cs_2CO_3 (239 mg, 0.74 mmol) in toluene (4 mL) and the resulting mixture was refluxed for 3 h. The mixture was cooled down to room temperature, and then diluted with EtOAc (70 mL) and water. The organic layer was washed with brine (40 mL × 3) and dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography (SiO_2, EtOAc:Hexane = 1:6) to give **5g** (129 mg, 71%) as yellow solid. m.p. 181.3 - 182.4 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.87 (dd, *J* = 4.1, 1.6 Hz, 2H), 8.51 (dd, *J* = 8.6, 1.5 Hz, 2H), 8.11 (s, 2H), 7.66 – 7.60 (m, 4H), 7.53 – 7.36 (m, 13H), 7.18 (dd, *J* = 5.4, 3.3 Hz, 2H), 4.78 (s, 4H), 2.25 (s, 6H), 2.21 (s, 6H), 2.16 (s, 6H); ^{13}C-NMR (150 MHz, DMSO-d_6) δ 149.91, 149.66, 148.46, 146.55, 145.75, 140.19, 139.97, 137.24, 132.18, 129.48, 128.42, 128.15, 128.02, 122.12, 121.89, 119.83, 119.16, 115.60, 74.37, 18.84, 13.69, 12.79; MS (ESI) *m/z* $[M+H]^+$ 370.3.

***N*-(5-(benzyloxy)-3,4,6-trimethylpyridin-2-yl)isoquinolin-4-amine (5h)**

4-Aminoisoquinoline (**4h**, 144 mg, 0.98 mmol) was added to a mixture of **3** (300 mg, 0.98 mmol), $Pd(OAc)_2$ (44 mg, 0.20 mmol), Xantphos (113 mg, 0.20 mmol), Cs_2CO_3 (479 mg, 1.47 mmol) in toluene (8 mL) and the resulting mixture was refluxed for 3 h. The mixture was cooled down to room temperature, and then diluted with EtOAc (70 mL) and water. The organic layer was washed with brine (40 mL × 3) and dried over $MgSO_4$ and

concentrated. The residue was purified by silica gel column chromatography (SiO_2, MeOH:DCM = 0:100~2:98) to give **5h** (268 mg, 74%) as yellow foam. m.p. 61.3 - 62.1 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.96 (s, 4H), 8.35 (s, 4H), 8.11 – 8.08 (m, 4H), 8.07 – 8.03 (m, 4H), 7.97 (s, 4H), 7.69 (dddd, *J* = 20.4, 8.0, 6.9, 1.3 Hz, 9H), 7.50 (dd, *J* = 8.1, 1.4 Hz, 8H), 7.46 – 7.36 (m, 14H), 4.77 (s, 8H), 2.25 (s, 12H), 2.22 (s, 12H), 2.17 (s, 12H); ^{13}C-NMR (150 MHz, DMSO-d_6) δ 149.75, 146.19, 145.67, 145.52, 139.88, 137.27, 134.63, 133.90, 129.92, 129.03, 128.58, 128.39, 128.12, 127.98, 127.36, 127.00, 122.63, 118.06, 74.36, 18.89, 13.50, 12.73; MS (ESI) *m/z* $[M+H]^+$ 370.3.

***N*-(5-(benzyloxy)-3,4,6-trimethylpyridin-2-yl)quinolin-8-amine (5i)**

8-Aminoquinoline (**4i**, 72 mg, 0.49 mmol) was added to a mixture of **3** (150 mg, 0.49 mmol), $Pd(OAc)_2$ (22 mg, 0.10 mmol), Xantphos (57 mg, 0.10 mmol), Cs_2CO_3 (239 mg, 0.74 mmol) in toluene (4 mL) and the resulting mixture was refluxed for 5 h. The mixture was cooled down to room temperature, and then diluted with EtOAc (70 mL) and water. The organic layer was washed with brine (40 mL × 3) and dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography (SiO_2, EtOAc:Hexane = 0:100~20:80) to give **5i** (137 mg, 76%) as yellow solid. m.p. 144.3 - 144.6 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 9.29 (s, 1H), 8.98 (dd, *J* = 7.8, 1.2 Hz, 1H), 8.92 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.38 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.63 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.59 – 7.50 (m, 3H), 7.48 – 7.37 (m, 4H), 4.79 (s, 2H), 2.46 (s, 3H), 2.32 (s, 3H), 2.27 (s, 3H); ^{13}C-NMR (150 MHz, DMSO-d_6) δ 148.33, 147.99, 145.37, 145.11, 139.64, 137.90, 137.29, 137.24, 136.64, 128.44, 128.17, 128.03, 127.91, 127.54, 121.86, 117.45, 116.27, 111.91, 74.48, 19.21, 12.80, 12.78; MS (ESI) *m/z* $[M+H]^+$ 370.3.

***N*-(5-(benzyloxy)-3,4,6-trimethylpyridin-2-yl)isoquinolin-5-amine (5j)**

5-Aminoisoquinoline (**4j**, 71 mg, 0.49 mmol) was added to a mixture of **3** (150 mg, 0.49 mmol), $Pd(OAc)_2$ (22 mg, 0.10 mmol), Xantphos (57 mg, 0.10 mmol), Cs_2CO_3 (239 mg, 0.74 mmol) in toluene (4 mL) and the resulting mixture was refluxed for 3 h. The mixture was cooled down to room temperature, and then diluted with EtOAc (70 mL) and water. The organic layer was washed with brine (40 mL × 3) and dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography (SiO_2, EtOAc:Hexane = 0:100~65:35) to give **5j** (156 mg, 86%) as yellow solid. m.p. 120.1 - 121.7 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 9.26 (s, 3H), 8.45 (d, *J* = 6.0 Hz, 3H), 8.08 (s, 3H), 7.97 (d, *J* = 6.0 Hz, 3H), 7.68 (d, *J* = 8.1 Hz, 3H), 7.58 – 7.49 (m, 10H), 7.47 – 7.36 (m, 14H), 4.79 (s, 6H), 2.25 (s, 9H), 2.23 (s, 9H), 2.17 (s, 9H); ^{13}C-NMR (150 MHz,

DMSO-d_6) δ 152.29, 149.31, 146.67, 145.86, 141.73, 140.06, 138.79, 137.23, 129.17, 129.01, 128.40, 128.14, 128.00, 127.47, 120.03, 119.37, 118.32, 116.16, 74.35, 18.92, 13.65, 12.77; MS (ESI) *m/z* $[M+H]^+$ 370.3.

***N*-(5-(benzyloxy)-3,4,6-trimethylpyridin-2-yl)quinolin-3-amine (5k)**

3-Aminoquinoline (**4k**, 173 mg, 1.78 mmol) was added to a mixture of **3** (300 mg, 0.98 mmol), $Pd(OAc)_2$ (44 mg, 0.20 mmol), Xantphos (113 mg, 0.20 mmol), Cs_2CO_3 (479 mg, 1.47 mmol) in toluene (10 mL) and the resulting mixture was refluxed for 1 h. The mixture was cooled down to room temperature, and then diluted with EtOAc (70 mL) and water. The organic layer was washed with brine (40 mL × 3) and dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography (SiO_2, MeOH:DCM = 0:100~2:98 and then, EtOAc:Hexane=0:100~40:60) to give **5k** (308 mg, 85%) as yellow solid. m.p. 167.2 - 168.3 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 9.09 (d, *J* = 2.6 Hz, 1H), 8.56 (d, *J* = 2.4 Hz, 1H), 8.28 (s, 1H), 7.93 – 7.87 (m, 1H), 7.80 (dt, *J* = 6.5, 2.7 Hz, 1H), 7.55 – 7.49 (m, 4H), 7.47 – 7.37 (m, 3H), 4.78 (s, 2H), 2.39 (s, 3H), 2.24 (s, 6H); ^{13}C-NMR (150 MHz, DMSO-d_6) δ 148.45, 146.06, 145.97, 145.03, 142.59, 139.99, 137.28, 136.66, 128.53, 128.44, 128.39, 128.17, 128.03, 126.92, 126.53, 125.88, 118.11, 117.15, 74.43, 19.04, 13.23, 12.79; MS (ESI) *m/z* $[M+H]^+$ 370.3.

***N*-(5-(benzyloxy)-3,4,6-trimethylpyridin-2-yl)quinolin-6-amine (5l)**

6-Aminoquinoline (**4l**, 144 mg, 0.98 mmol) was added to a mixture of **3** (300 mg, 0.98 mmol), $Pd(OAc)_2$ (44 mg, 0.20 mmol), Xantphos (113 mg, 0.20 mmol), Cs_2CO_3 (479 mg, 1.47 mmol) in toluene (8 mL) and the resulting mixture was refluxed for 3 h. The mixture was cooled down to room temperature, and then diluted with EtOAc (70 mL) and water. The organic layer was washed with brine (40 mL × 3) and dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography (SiO_2, MeOH:DCM = 0:100~2:98 and then, EtOAc:Hexane=0:100~40:60) to give **5l** (267 mg, 74%) as yellow solid. m.p. 105.5 - 106.0 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.66 (dd, *J* = 4.1, 1.5 Hz, 1H), 8.19 (s, 1H), 8.14 (t, *J* = 5.5 Hz, 2H), 7.92 (dd, *J* = 9.2, 2.3 Hz, 1H), 7.87 (d, *J* = 9.1 Hz, 1H), 7.52 (d, *J* = 6.9 Hz, 2H), 7.42 (ddd, *J* = 12.5, 8.2, 3.3 Hz, 4H), 4.78 (s, 2H), 2.40 (s, 3H), 2.23 (s, 3H), 2.22 (s, 3H); ^{13}C-NMR (150 MHz, DMSO-d_6) δ 148.53, 146.98, 146.04, 145.12, 143.59, 141.17, 139.85, 137.29, 134.40, 128.87, 128.65, 128.41, 128.13, 128.00, 124.18, 121.30, 117.77, 110.86, 74.39, 19.05, 13.38, 12.78; MS (ESI) *m/z* $[M+H]^+$ 370.3.

***N*-(5-(benzyloxy)-3,4,6-trimethylpyridin-2-yl)-1H-indol-4-amine (5m)**

4-Aminoindole (**4m**, 129 mg, 0.98 mmol) was added to a mixture of **3** (300 mg, 0.98 mmol), $Pd(OAc)_2$ (44 mg, 0.20 mmol), Xantphos (113 mg, 0.20 mmol), Cs_2CO_3 (479 mg, 1.47 mmol) in toluene (8 mL) and the resulting

mixture was refluxed for 4 h. The mixture was cooled down to room temperature, and then diluted with EtOAc (70 mL) and water. The organic layer was washed with brine (40 mL × 3) and dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography (SiO_2, EtOAc:Hexane = 1:4) to give **5m** (216 mg, 62%) as yellow solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.96 (s, 1H), 7.51 (dd, *J* = 8.1, 1.4 Hz, 2H), 7.47 – 7.36 (m, 4H), 7.23 – 7.19 (m, 1H), 7.06 (dd, *J* = 5.8, 2.7 Hz, 1H), 6.97 – 6.92 (m, 2H), 6.58 – 6.53 (m, 1H), 4.78 (s, 2H), 2.30 (s, 3H), 2.23 (s, 3H), 2.17 (s, 3H); ^{13}C-NMR (150 MHz, DMSO-d_6) δ 149.27, 145.91, 145.34, 139.45, 137.32, 136.71, 135.60, 128.39, 128.12, 127.97, 122.90, 121.37, 119.48, 118.51, 106.21, 104.09, 99.27, 74.36, 18.98, 13.57, 12.75; MS (ESI) *m/z* $[M+H]^+$ 358.3.

Methyl 3-((5-(benzyloxy)-3,4,6-trimethylpyridin-2-yl)amino)thiophene-2-carboxylate (5n)

Methyl 3-aminothiophene-2-carboxylate (**4n**, 77 mg, 0.49 mmol) was added to a mixture of **3** (150 mg, 0.49 mmol), $Pd_2(dba)_3$ (90 mg, 0.10 mmol), Xantphos (57 mg, 0.10 mmol), Cs_2CO_3 (239 mg, 0.74 mmol) in toluene (4 mL) and the resulting mixture was refluxed for 4 h. The mixture was cooled down to room temperature, and then diluted with EtOAc (70 mL) and water. The organic layer was washed with brine (40 mL × 3) and dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography (SiO_2, EtOAc:Hexane = 0:100~5:95) to give **5n** (341 mg, 91%) as yellow solid. m.p. 139.2 - 143.7 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 9.73 (s, 1H), 8.45 (d, *J* = 5.5 Hz, 1H), 7.86 (d, *J* = 5.5 Hz, 1H), 7.49 (dd, *J* = 8.1, 1.5 Hz, 2H), 7.45 – 7.34 (m, 3H), 4.76 (s, 2H), 3.85 (s, 3H), 2.39 (s, 3H), 2.24 (s, 3H), 2.20 (s, 3H); ^{13}C-NMR (150 MHz, DMSO-d_6) δ 164.95, 148.82, 146.60, 146.07, 145.61, 140.24, 137.16, 132.82, 128.41, 128.16, 128.03, 121.30, 115.62, 103.51, 74.44, 51.70, 19.09, 12.77, 12.49; MS (ESI) *m/z* $[M+Na]^+$ 404.3.

***N*-(5-(benzyloxy)-3,4,6-trimethylpyridin-2-yl)thiazol-2-amine (5o)**

2-Aminothiazle (**4o**, 59 mg, 0.59 mmol) was added to a mixture of **3** (150 mg, 0.49 mmol), $Pd(OAc)_2$ (22 mg, 0.10 mmol), Xantphos (57 mg, 0.10 mmol), Cs_2CO_3 (239 mg, 0.74 mmol) in toluene (4 mL) and the resulting mixture was refluxed for 4 h. The mixture was cooled down to room temperature, and then diluted with EtOAc (70 mL) and water. The organic layer was washed with brine (40 mL × 3) and dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography (SiO_2, EtOAc:Hexane = 1:9~1:1) to give **5o** (85 mg, 53%) as yellow solid. m.p. 132.2 - 132.6 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 12.33 (s, 1H), 7.45 – 7.37 (m, 5H), 7.33 (d, *J* = 4.4 Hz, 1H), 6.79 (d, *J* = 4.4 Hz, 1H), 4.80 (s, 2H), 2.50 (s, 3H), 2.46 (s, 3H), 2.28 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 163.22, 148.87, 145.99, 142.85, 141.68, 136.73, 128.91, 128.67, 128.23, 124.73, 119.21, 111.08, 75.54, 18.36, 13.54, 13.45; MS (ESI) *m/z* $[M+H]^+$ 326.5.

Ethyl 2-((5-(benzyloxy)-3,4,6-trimethylpyridin-2-yl)amino)oxazole-4-carboxylate (5p)

Ethyl 2-aminooxazole-4-carboxylate (**4p**, 765 mg, 4.90 mmol) was added to a mixture of **3** (500 mg, 1.63 mmol), $Pd(OAc)_2$ (74 mg, 0.33 mmol), Xantphos (191 mg, 0.33 mmol), Cs_2CO_3 (798 mg, 2.45 mmol) in toluene (6.5 mL) and the resulting mixture was refluxed for 4 h. The mixture was cooled down to room temperature, and then diluted with EtOAc (70 mL) and water. The organic layer was washed with brine (40 mL × 3) and dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography (SiO_2, MeOH:DCM = 1:99) to give **5p** (515 mg, 83%) as yellow solid. m.p. 135.0 - 135.5 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 9.72 (s, 2H), 8.35 (s, 2H), 7.50 (d, *J* = 6.8 Hz, 6H), 7.46 – 7.35 (m, 9H), 4.79 (s, 5H), 4.23 (q, *J* = 7.1 Hz, 5H), 2.31 (s, 7H), 2.21 (s, 7H), 2.08 (s, 7H), 1.26 (t, *J* = 7.1 Hz, 8H); ^{13}C-NMR (150 MHz, DMSO-d_6) δ 161.11, 158.38, 148.75, 146.85, 145.45, 140.65, 139.78, 137.07, 131.87, 128.45, 128.18, 128.09, 122.69, 74.33, 60.17, 18.94, 14.16, 13.79, 12.79; MS (ESI) *m/z* $[M+Na]^+$ 404.4.

***N*-(5-(benzyloxy)-3,4,6-trimethylpyridin-2-yl)-1H-benzo[d]imidazol-2-amine (5q)**

2-Aminobenzimidazole (**4q**, 81 mg, 0.590 mmol) was added to a mixture of **3** (150 mg, 0.49 mmol), $Pd(OAc)_2$ (22 mg, 0.10 mmol), Xantphos (57 mg, 0.10 mmol), Cs_2CO_3 (239 mg, 0.74 mmol) in toluene (4 mL) and the resulting mixture was refluxed for 1 d. The mixture was cooled down to room temperature, and then diluted with EtOAc (70 mL) and water. The organic layer was washed with brine (40 mL × 3) and dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography (SiO_2, MeOH:DCM = 0:100~3:97) to give **5q** (85 mg, 53%) as yellow solid. m.p. 133.1 - 133.5 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.56 – 7.51 (m, 2H), 7.48 – 7.37 (m, 5H), 7.10 – 7.01 (m, 2H), 4.80 (s, 2H), 2.53 (s, 3H), 2.24 (s, 6H); ^{13}C-NMR (150 MHz, DMSO-d_6) δ 172.02, 150.38, 147.18, 147.12, 146.22, 145.35, 140.78, 137.16, 128.44, 128.21, 128.07, 120.21, 112.83, 74.41, 18.90, 13.10, 12.87; MS (ESI) *m/z* $[M+H]^+$ 359.3.

2,4,5-Trimethyl-6-(pyridin-2-ylamino)pyridin-3-ol (6a)

A suspension of **5a** (150 mg, 0.47 mmol), Pd/C (15 mg) in MeOH (9 mL) was stirred at r.t. for 12 h. The reaction mixture was filtered with celite pad and concentrated. The residue was purified by silica gel column chromatography (SiO_2, MeOH:DCM = 3:97) to give **6a** (88 mg, 82%) as yellow solid. m.p. 230.0 - 230.6 °C; ^{1}H-NMR (600 MHz, DMSO-d_6) δ 8.22 (s, 1H), 8.16 (s, 1H), 8.04 (s, 1H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.16 (d, *J* = 8.1 Hz, 1H), 6.67 (d, *J* = 4.1 Hz, 1H), 2.29 (s, 3H), 2.14 (s, 3H), 2.06 (s, 3H); ^{13}C-NMR (150 MHz, DMSO-d_6) δ 156.57, 147.47, 145.53, 143.80, 140.43, 136.95, 134.31, 121.93, 114.06, 109.31, 19.33, 13.91, 12.66; MS (ESI) *m/z* $[M+H]^+$ 230.4; HRMS (ESI): Calcd for $C_{13}H_{16}ON_3$ $[M+H]^+$ 230.1288, Found 230.1288.

2,4,5-trimethyl-6-((4-(trifluoromethyl)pyridin-2-yl)amino)-pyridin-3-ol (6b)

Prepared according to the general procedure using **5b** (174 mg, 0.45 mmol) and Pd/C (20 mg)**.** Flash column chromatography (SiO_2, 50% EtOAc in hexanes) yielded white solid (71 mg, 53%). R_f = 0.50 (60% EtOAc in hexanes); m.p.: 232~235 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.83 (s, 1H), 8.37 (s, 1H), 8.28 (s, 1H), 7.49 (s, 1H), 6.94 (s, 1H), 2.31 (s, 3H), 2.15 (s, 3H), 2.07 (s, 3H); ^{13}C-NMR (150 MHz, DMSO-d_6) δ 157.7, 149.9, 146.6, 143.3, 141.1, 138.0 (q, $J_{C\text{-}F}$ = 32.3 Hz), 135.0, 126.4, 124.6, 123.7 (q, $J_{C\text{-}F}$ = 271.3 Hz), 109.1 (q, $J_{C\text{-}F}$ = 3.4 Hz), 105.0 (q, $J_{C\text{-}F}$ = 4.1 Hz), 19.7, 14.3, 13.1 ppm; MS (ESI) *m/z* 298.1 $[M+H]^+$; HRMS (ESI): Calcd for $C_{14}H_{14}F_3N_3O$ $[M+H]^+$ 298.1161, Found 298.1164.

2,4,5-trimethyl-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-pyridin-3-ol (6c)

Prepared according to the general procedure using **5c** (223 mg, 0.58 mmol) and Pd/C (25 mg)**.** Flash column chromatography (SiO_2, 3% to 5% MeOH in CH_2Cl_2) yielded yellow solid (137 mg, 80%). R_f = 0.20 (30% EtOAc in hexanes); m.p.: 200~203 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 9.06 (s, 1H), 8.45 (s, 1H), 8.35 (dd, *J* = 1.6, 0.9 Hz, 1H), 7.77 (dd, *J* = 9.0, 2.5 Hz, 1H), 7.03 (d, *J* = 8.9 Hz, 1H), 2.30 (s, 3H), 2.15 (s, 3H), 2.05 (s, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 159.9, 147.2, 145.8 (q, $J_{C\text{-}F}$ = 4.2 Hz), 142.7, 141.6, 134.8, 134.5 (q, $J_{C\text{-}F}$ = 3.0 Hz), 125.3 (q, $J_{C\text{-}F}$ = 268.6 Hz), 124.4, 115.0 (q, $J_{C\text{-}F}$ = 31.9 Hz), 108.8, 19.8, 14.5, 13.1 ppm; MS (ESI) *m/z* 298.1 $[M+H]^+$; HRMS (ESI): calcd for $C_{14}H_{14}F_3N_3O$ $[M+H]^+$ 298.1161, Found 298.1178.

2,4,5-trimethyl-6-((6-(trifluoromethyl)pyridin-3-yl)amino)-pyridin-3-ol (6d)

Prepared according to the general procedure using **5d** (138 mg, 0.36 mmol) and Pd/C (14 mg)**.** Flash column chromatography (SiO_2, 50% EtOAc in hexanes) yielded light brown solid (68mg, 64%). R_f = 0.50 (60% EtOAc in hexanes); m.p.: 216~218 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.71 (s, 1H), 8.38 (s, 1H), 8.25 (s, 1H), 7.92 (d, *J* = 6.6 Hz, 1H), 7.61 (d, *J* = 6.8 Hz, 1H), 2.31 (s, 3H), 2.14 (d, *J* = 4.4 Hz, 6H); ^{13}C-NMR (150 MHz DMSO-d_6) δ 145.5, 144.2, 143.8, 140.6, 139.0, 135.9 (q, $J_{C\text{-}F}$ = 33.7 Hz), 135.4, 122.9 (q, $J_{C\text{-}F}$ = 244.8 Hz), 122.2, 121.2 (q, $J_{C\text{-}F}$ = 4.1 Hz), 119.7, 19.8, 13.8, 13.1 ppm; MS (ESI) *m/z* 298.1 $[M+H]^+$; HRMS (ESI): Calcd for $C_{14}H_{14}F_3N_3O$ $[M+H]^+$ 298.1161, Found 298.1164.

6-((5-chloropyridin-2-yl)amino)-2,4,5-trimethylpyridin-3-ol (6e)

Prepared according to the general procedure using **5e** (160 mg, 0.45 mmol) and Pd/C (16 mg)**.** Flash column chromatography (SiO_2 60% EtOAc in hexanes) yielded yellow solid (53 mg, 45%). R_f = 0.50 (60% EtOAc in hexanes); m.p.: 148~150 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.47 (s, 1H), 8.30 (s, 1H), 8.04 (s, 1H), 7.56 (d, *J* = 6.9 Hz, 1H), 7.16 (d, *J* = 8.4 Hz, 1H), 2.30 (s, 3H), 2.13 (s, 3H), 2.05 (s, 3H); ^{13}C-NMR (150 MHz, DMSO-d_6)

δ 155.8, 146.4, 146.0, 143.8, 141.1, 137.2, 134.9, 122.8, 120.0, 111.0, 19.8, 14.4, 13.1 ppm; MS (ESI) *m/z* 264.0 $[M+H]^+$; HRMS (ESI): Calcd for $C_{13}H_{14}ClN_3O$ $[M+H]^+$ 264.0898, Found 264.0896.

6-((6-chloropyridin-3-yl)amino)-2,4,5-trimethylpyridin-3-ol (6f)

Prepared according to the general procedure using **5f** (155 mg, 0.44 mmol) and Pd/C (16 mg)**.** Flash column chromatography (SiO_2, 50% EtOAc in hexanes) yielded light pinky solid (74 mg, 64%). R_f = 0.20 (40% EtOAC in hexanes); m.p.: 185~186 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.50 (s, 1H), 8.09 (s, 1H), 7.94 (s, 1H), 7.93 – 7.87 (m, 1H), 7.25 (d, *J* = 6.7 Hz, 1H), 2.28 (s, 3H), 2.13 (d, *J* = 9.4 Hz, 6H); ^{13}C-NMR (150 MHz, DMSO-d_6) δ 145.1, 144.6, 140.4, 140.2, 139.2, 138.9, 135.4, 127.4, 123.8, 118.2, 19.8, 13.7, 13.1 ppm; MS (ESI) *m/z* 264.9 $[M+H]^+$; HRMS (ESI): Calcd for $C_{13}H_{14}ClN_3O$ $[M+H]^+$ 264.0898, Found 264.0895.

2,4,5-Trimethyl-6-(quinolin-4-ylamino)pyridin-3-ol (6g)

BCl_3 (0.42 mL, 0.42 mmol) was added to a suspension of **5g** (80 mg, 0.21 mmol) and pentamethylbenzene (94 mg, 0.63 mmol) in DCM (5 mL) at 0 °C and stirred at 0 °C for 4 h. The reaction mixture was quenched by 10% MeOH/DCM solution. The residue was purified by silica gel column chromatography (SiO_2, MeOH:DCM = 0:100~10:90) to give **6g** (35 mg, 59%) as yellow solid. m.p. 224.4 - 226.1 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.85 (dd, *J* = 4.1, 1.6 Hz, 1H), 8.66 (dd, *J* = 8.6, 0.8 Hz, 1H), 8.28 (s, 1H), 8.05 (s, 1H), 7.54 – 7.42 (m, 3H), 6.71 (dd, *J* = 7.4, 1.2 Hz, 1H), 2.27 (s, 3H), 2.19 (s, 3H), 2.07 (s, 3H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 149.91, 148.79, 145.62, 145.39, 141.72, 141.23, 134.59, 131.40, 129.59, 121.95, 120.16, 119.74, 119.50, 110.80, 19.29, 13.94, 12.66; MS (ESI) *m/z* $[M+H]^+$ 280.5; HRMS (ESI): Calcd for $C_{17}H_{18}ON_3$ $[M+H]^+$ 280.1444, Found 280.1444.

6-(Isoquinolin-4-ylamino)-2,4,5-trimethylpyridin-3-ol (6h)

BCl_3 (0.42 mL, 0.42 mmol) was added to a suspension of **5h** (80 mg, 0.21 mmol) and pentamethylbenzene (94 mg, 0.63 mmol) in DCM (5 mL) at 0 °C and stirred at 0 °C for 1 h. The reaction mixture was quenched by 10% MeOH/DCM solution. The residue was purified by silica gel column chromatography (SiO_2, MeOH:DCM = 0:100~15:85) to give **6h** (29 mg, 48%) as yellow solid. m.p. 199.0 - 201.5 °C; ^{1}H-NMR (600 MHz, DMSO-d_6) δ 8.77 (s, 1H), 8.19 (s, 1H), 8.17 (d, *J* = 8.0 Hz, 1H), 8.02 (d, *J* = 7.5 Hz, 1H), 7.96 (s, 1H), 7.84 (s, 1H), 7.68 (d, *J* = 7.5 Hz, 1H), 7.63 (d, *J* = 6.2 Hz, 1H), 2.21 (s, 3H), 2.18 (s, 3H), 2.12 (s, 3H); ^{13}C-NMR (150 MHz, DMSO-d_6) δ 145.45, 145.23, 143.47, 140.95, 135.42, 134.66, 130.45, 128.73, 128.52, 127.90, 127.29, 126.97, 122.15, 120.85, 19.30, 13.78, 12.66; MS (ESI) *m/z* $[M+H]^+$ 280.4; HRMS (ESI): Calcd for $C_{17}H_{18}ON_3$ $[M+H]^+$ 280.1444, Found 280.1446.

2,4,5-Trimethyl-6-(quinolin-8-ylamino)pyridin-3-ol (6i)

BCl_3 (0.42 mL, 0.42 mmol) was added to a suspension of **5i** (80 mg, 0.21 mmol) and pentamethylbenzene (94 mg, 0.63 mmol) in DCM (5 mL) at 0 °C and stirred at 0 °C for 1 h. The reaction mixture was quenched by 10% MeOH/DCM solution. The residue was purified by silica gel column chromatography (SiO_2, MeOH:DCM = 0.5:95.5) to give **6i** (15 mg, 25%) as yellow solid. m.p. 148.5 - 153.0 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.89 (s, 1H), 8.71 (dd, *J* = 4.1, 1.4 Hz, 1H), 8.50 (d, *J* = 7.7 Hz, 1H), 8.03 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.40 (t, *J* = 8.0 Hz, 1H), 7.32 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.17 (d, *J* = 8.3 Hz, 1H), 2.43 (s, 3H), 2.25 (s, 3H), 2.17 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 147.16, 146.57, 143.14, 138.83, 138.79, 138.53, 136.18, 133.72, 128.40, 127.78, 121.17, 118.34, 116.68, 111.01, 18.88, 13.37, 12.45; MS (ESI) *m/z* $[M+H]^+$ 280.5; HRMS (ESI): Calcd for $C_{17}H_{18}ON_3$ $[M+H]^+$ 280.1444, Found 280.1446.

6-(Isoquinolin-5-ylamino)-2,4,5-trimethylpyridin-3-ol (6j)

A suspension of **5j** (44 mg, 0.12 mmol), Pd/C (9 mg) in MeOH (10 mL) was stirred at r.t. for 3 h under H_2 atmosphere. The reaction mixture was filtered with celite pad and concentrated. The residue was purified by silica gel column chromatography (SiO_2, MeOH:DCM = 1:100~10:90) to give **6j** (14 mg, 42%) as brown film. m.p. 208.0 - 209.5 °C (dec.); ^{1}H-NMR (400 MHz, DMSO-d_6) δ 9.21 (s, 1H), 8.44 (d, *J* = 6.0 Hz, 1H), 8.30 (s, 1H), 8.11 (d, *J* = 6.0 Hz, 1H), 8.01 (s, 1H), 7.50 (d, *J* = 8.1 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 1H), 6.93 (dd, *J* = 7.5, 0.8 Hz, 1H), 2.28 (s, 3H), 2.20 (s, 3H), 2.08 (s, 3H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 152.20, 145.76, 144.98, 141.51, 141.27, 140.46, 134.62, 129.22, 127.71, 127.21, 122.23, 117.72, 115.73, 113.62, 19.31, 13.92, 12.68; MS (ESI) *m/z* $[M+H]^+$ 280.0; HRMS (ESI): Calcd for $C_{17}H_{18}ON_3$ $[M+H]^+$ 280.1444, Found 280.1447.

2,4,5-Trimethyl-6-(quinolin-3-ylamino)pyridin-3-ol (6k)

BCl_3 (1.5 mL, 1.5 mmol) was added to a suspension of **5k** (277 mg, 0.75 mmol) and pentamethylbenzene (333 mg, 2.25 mmol) in DCM (30 mL) at 0 °C and stirred at 0 °C for 2 h. The reaction mixture was quenched by 10% MeOH/DCM solution. The residue was purified by silica gel column chromatography (SiO_2, MeOH:DCM = 0:100~10:90) to give **6k** (195 mg, 93%) as yellow solid. m.p. 215 - 220 °C (dec); ^{1}H-NMR (400 MHz, DMSO-d_6) δ 9.51 (s, 1H), 9.18 (s, 1H), 8.35 (s, 1H), 8.14 (d, *J* = 8.3 Hz, 1H), 8.02 (d, *J* = 8.0 Hz, 1H), 7.75 (ddd, *J* = 20.7, 11.1, 4.1 Hz, 2H), 2.48 (s, 3H), 2.34 (s, 3H), 2.27 (s, 3H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 145.48, 145.07, 144.23, 142.16, 139.86, 137.72, 134.88, 128.74, 128.36, 126.62, 126.43, 125.29, 118.04, 115.93, 19.42, 13.38, 12.68; MS (ESI) *m/z* $[M+H]^+$ 280.3; HRMS (ESI): Calcd for $C_{17}H_{18}ON_3$ $[M+H]^+$ 280.1444, Found 280.1445.

2,4,5-Trimethyl-6-(quinolin-6-ylamino)pyridin-3-ol (6l)

A suspension of **5l** (200 mg, 0.54 mmol), Pd/C (40 mg) in MeOH (6 mL) was stirred at r.t. for 6 h under H_2 atmosphere. The reaction mixture was filtered with celite pad and concentrated. The residue was purified by silica gel column chromatography (SiO_2, MeOH:DCM = 0:100~3:97) to give **6l** (88 mg, 58%) as brown solid. m.p. 75.7 - 76.5 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.60 (dd, *J* = 4.1, 1.6 Hz, 1H), 8.17 (s, 1H), 8.09 – 8.02 (m, 2H), 7.85 – 7.79 (m, 1H), 7.72 (dd, *J* = 7.2, 2.5 Hz, 2H), 7.35 (dd, *J* = 8.3, 4.2 Hz, 1H), 2.35 (s, 3H), 2.18 (s, 3H), 2.16 (s, 3H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 146.37, 145.06, 144.57, 143.17, 142.50, 140.20, 134.69, 134.02, 129.11, 128.78, 123.32, 121.24, 119.31, 108.49, 19.43, 13.62, 12.70; MS (ESI) *m/z* $[M+H]^+$ 280.4; HRMS (ESI): Calcd for $C_{17}H_{18}ON_3$ $[M+H]^+$ 280.1444, Found 280.1445.

6-((1*H*-indol-4-yl)amino)-2,4,5-trimethylpyridin-3-ol (6m)

BCl_3 (0.35 mL, 0.35 mmol) was added to a suspension of **5m** (62 mg, 0.17 mmol) and pentamethylbenzene (76 mg, 0.52 mmol) in DCM (4 mL) at 0 °C and stirred at 0 °C for 4h. The reaction mixture was quenched by 10% MeOH/DCM solution. The residue was purified by silica gel column chromatography (SiO_2, MeOH:DCM = 0:100~3:97) to give **6m** (14 mg, 31%) as green film. m.p. 80.2 - 80.9 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.90 (s, 1H), 8.14 (s, 1H), 7.29 (s, 1H), 7.19 – 7.15 (m, 1H), 6.88 – 6.82 (m, 2H), 6.62 – 6.58 (m, 1H), 6.55 (dd, *J* = 6.1, 2.3 Hz, 1H), 2.30 (s, 3H), 2.18 (s, 3H), 2.10 (s, 3H); ^{13}C-NMR (150 MHz, DMSO-d_6) δ 145.73, 144.77, 140.63, 137.44, 136.72, 134.31, 122.50, 121.56, 120.95, 118.28, 103.33, 102.72, 99.20, 19.36, 13.95, 12.67; MS (ESI) *m/z* $[M+H]^+$ 267.9; HRMS (ESI): Calcd for $C_{16}H_{18}ON_3$ $[M+H]^+$ 268.1444, Found 268.1443.

Methyl 3-((5-hydroxy-3,4,6-trimethylpyridin-2-yl)amino)-thiophene-2-carboxylate (6n)

BCl_3 (0.77 mL, 0.77 mmol) was added to a suspension of **5n** (147 mg, 0.38 mmol) and pentamethylbenzene (171 mg, 1.15 mmol) in DCM (4 mL) at 0 °C and stirred at 0 °C for 1h. The reaction mixture was quenched by 10% MeOH/DCM solution. The residue was purified by silica gel column chromatography (SiO_2, MeOH:DCM = 2:98) to give **6n** (18 mg, 17%) as yellow solid. m.p. 170.7 - 171.9 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 9.54 (s, 1H), 8.33 (d, *J* = 5.5 Hz, 1H), 8.17 (s, 1H), 7.81 (d, *J* = 5.5 Hz, 1H), 3.83 (s, 3H), 2.34 (s, 3H), 2.17 (s, 3H), 2.16 (s, 3H); ^{13}C-NMR (150 MHz, DMSO-d_6) δ 164.97, 149.58, 144.03, 143.72, 140.08, 135.08, 132.71, 121.00, 115.53, 102.20, 51.58, 19.48, 12.67, 12.59; MS (ESI) *m/z* $[M+H]^+$ 293.4; HRMS (ESI): Calcd for $C_{14}H_{17}O_3N_2S$ $[M+H]^+$ 293.0954, Found 293.0962.

2,4,5-Trimethyl-6-(thiazol-2-ylamino)pyridin-3-ol (6o)

BCl_3 (0.43 mL, 0.43 mmol) was added to a suspension of **5o** (70 mg, 0.22 mmol) and pentamethylbenzene (96 mg, 0.65 mmol) in DCM (4 mL) at 0 °C and stirred at 0 °C for 3h. The reaction mixture was quenched by 10% MeOH/DCM solution. The residue was purified by silica gel column chromatography (SiO_2, MeOH:DCM = 0:100~3:97) to give **6o** (41 mg, 80%) as yellow solid. m.p. 236 - 240 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 9.92 (s, 1H), 8.14 (s, 1H), 7.35 (d, *J* = 3.6 Hz, 1H), 6.87 (d, *J* = 3.6 Hz, 1H), 2.38 (s, 3H), 2.19 (s, 3H), 2.16 (s, 3H); ^{13}C-NMR (150 MHz, DMSO-d_6) δ 161.32, 143.59, 142.17, 138.50, 136.94, 135.38, 115.45, 109.69, 18.51, 12.64, 12.60; MS (ESI) *m/z* $[M+H]^+$ 236.1; HRMS (ESI): Calcd for $C_{11}H_{14}ON_3S$ $[M+H]^+$ 236.0852, Found 236.0853.

Ethyl 2-((5-hydroxy-3,4,6-trimethylpyridin-2-yl)amino)-oxazole-4-carboxylate (6p)

BCl_3 (0.32 mL, 0.32 mmol) was added to a suspension of **5p** (60 mg, 0.16 mmol) and pentamethylbenzene (70 mg, 0.47 mmol) in DCM (2 mL) at 0 °C and stirred at 0 °C for 1h. The reaction mixture was quenched by 10% MeOH/DCM solution. The residue was purified by silica gel column chromatography (SiO_2, EtOAc:Hexane = 0:100~50:50 and then MeOH:DCM = 3:97) to give **6p** (24 mg, 51%) as brown solid. m.p. 130 °C (dec.); ^{1}H-NMR (400 MHz, DMSO-d_6) δ 9.49 (s, 1H), 8.49 (s, 1H), 8.27 (s, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 2.29 (s, 3H), 2.16 (s, 3H), 2.05 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (150 MHz, DMSO-d_6) δ 161.22, 159.20, 147.14, 141.46, 141.41, 139.20, 134.28, 131.95, 123.78, 60.09, 19.28, 14.16, 13.91, 12.60; MS (ESI) *m/z* $[M+H]^+$ 292.5; HRMS (ESI): Calcd for $C_{14}H_{18}O_4N_3$ $[M+H]^+$ 292.1292, Found 292.1296.

6-((1*H*-benzo[*d*]imidazol-2-yl)amino)-2,4,5-trimethylpyridin-3-ol (6q)

BCl_3 (0.13 mL, 0.13 mmol) was added to a suspension of **5q** (26 mg, 0.07 mmol) and pentamethylbenzene (29 mg, 0.20 mmol) in DCM (1 mL) at 0 °C and stirred at 0 °C for 1h. The reaction mixture was quenched by 10% MeOH/DCM solution. The residue was purified by silica gel column chromatography (SiO_2, MeOH:DCM = 5:95) to give **6q** (18 mg, 100%) as yellow solid. m.p. 262 °C (dec.); ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.91 (s, 1H), 9.16 (s, 1H), 8.24 (s, 1H), 7.34 (s, 2H), 6.98 (dd, *J* = 5.8, 3.1 Hz, 2H), 2.45 (s, 3H), 2.18 (s, 3H), 2.16 (s, 3H); ^{13}C-NMR (150 MHz, DMSO-d_6) δ 171.83, 151.06, 144.29, 143.83, 139.82, 135.60, 119.92, 117.56, 112.62, 19.30, 13.14, 12.74; MS (ESI) *m/z* $[M+H]^+$ 269.4; HRMS (ESI): Calcd for $C_{15}H_{17}ON_4$ $[M+H]^+$ 269.1397, Found 269.1396.

2-bromo-5-((tert-butyldiphenylsilyl)oxy)-3,4,6-trimethylpyridine (7)

To a solution of **2** (5.11 g, 23.7 mmol) in DMF (34 mL) was added imidazole (3.54 g 52.0 mmol) and TBDPSCl (9.1 mL, 35.5 mmol)**.** After 16 h, the reaction mixture was quenched with water and extracted with CH_2Cl_2 (40 mL × 4). The combined extracts were washed with water and brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified using flash column chromatography (SiO_2, 1% EtOAc in

hexanes) to afford **7** (9.73 g, 91%) as white solid. R_f = 0.80 (20% EtOAC in hexanes); m.p.: 123~126 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.67–7.62 (m, 4H), 7.44–7.31 (m, 6H), 2.21 (s, 3H), 2.16 (s, 3H), 1.98 (s, 3H), 1.10 (s, 9H).; MS (ESI) *m/z* 454.1 $[M+H]^+$; HRMS (ESI): Calcd for $C_{24}H_{28}BrNOSi$ $[M+H]^+$ 454.1196, Found 454.1212.

N-(5-((tert-butyldiphenylsilyl)oxy)-3,4,6-trimethylpyridin-2-yl)-1,1-diphenylmethanimine (8)

A solution of **7** (3.70 g, 8.14 mmol) in toluene (32 mL) was treated with $Pd_2(dba)_3$ (375 mg 0.05 mmol), BINAP (504 mg, 0.10 mmol)**,** NaO^{t}Bu (860 mg, 1.10 mmol) and benzopheoneimine (1.37 mL, 8.14 mmol). The reaction mixture was refluxed for 3 h under Ar and diluted with EtOAc, washed with water three times and brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified using flash column chromatography (SiO_2, 3% to 5% EtOAc in hexanes) to afford **8** (3.72 g, 82%) as yellow solid. R_f = 0.50 (20% EtOAC in hexanes); m.p.: 143~145 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.85–7.75 (m, 2H), 7.66–7.61 (m, 4H), 7.48–7.28 (m, 11H), 7.25–7.10 (m, 3H), 2.09 (s, 3H), 1.84 (d, *J* = 9.1 Hz, 6H), 1.10 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 169.64, 154.58, 145.50, 143.81, 139.29, 137.08, 135.23, 133.90, 130.78, 129.80, 129.58, 128.93, 128.49, 127.97, 127.79, 127.66, 127.54, 119.430, 26.01, 21.42, 20.24, 14.83, 14.02 ppm; MS (ESI) *m/z* 555.1 $[M+H]^+$; HRMS (ESI) Calcd for $C_{37}H_{38}N_2OSi$ $[M+H]^+$ 555.2826, Found 555.2820.

5-((tert-butyldiphenylsilyl)oxy)-3,4,6-trimethylpyridin-2-amine (9)

A solution of **8** (6.78 g, 12.2 mmol) in MeOH (61 mL) and THF (6.1 mL) (10:1) was added AcCl (1.92 mL, 26. 9 mmol) at 0 °C stirring for 20 min and allowed to warm to room temperature. After stirring for 28 h, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in EtOAc, washed with 2 N NaOH to make pH 7 and washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified using flash column chromatography (SiO_2, 2.5% MeOH in CH_2Cl_2) to afford **9** (2.52 g, 96%) as brown solid. R_f = 0.2 (3% MeOH in CH_2Cl_2); m.p.: 121~130 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.65 (d, *J* = 1.4 Hz, 4H), 7.48–7.36 (m, 6H), 5.02 (s, 2H), 1.92 (s, 3H), 1.86 (d, *J* = 2.4 Hz, 6H), 1.04 (s, 9H).; ^{13}CNMR (100 MHz, $CDCl_3$) δ 151.63, 140.97, 140.79, 135.68, 134.77, 133.67, 129.88, 127.74, 112.53, 26.72, 21.17, 19.63, 14.37, 13.09 ppm; MS (ESI) *m/z* 391.5 $[M+H]^+$; HRMS (ESI): Calcd for $C_{24}H_{30}N_2OSi$ $[M+H]^+$ 391.2200, Found 391.2220.

3-((tert-butyldiphenylsilyl)oxy)-6-isothiocyanato-2,4,5-trimethylpyridine (10)

To a solution of **9** (4.27 g, 10.9 mmol) in CH_2Cl_2 (55 mL) at 0 °C under Ar was treated with DIPEA (5.7 mL, 32.8 mmol), thiophosgene (0.88 mL, 11.5 mmol). The reaction mixture was stirred same temperature for 10 min

and allowed to warm to room temperature for 1 h and then, poured onto a SiO_2 packed column. The reaction mixture was purified using flash chromatography (2.5% to 5% Et_2O in hexanes) to afford **10** (4.26 g, 90%) as brown solid. R_f = 0.4 (5% Et_2O in hexanes); m.p.: 119~123 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.68–7.63 (m, 4H), 7.47–7.41 (m, 2H), 7.39–7.34 (m, 4H), 2.20 (s, 3H), 2.16 (s, 3H), 1.95 (s, 3H), 1.14–1.10 (m, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 148.50, 146.81, 137.93, 136.28, 136.28, 136.18, 135.11, 133.12, 130.18, 127.87, 126.86, 26.81, 21.64, 20.24, 15.17, 14.74 ppm; MS (ESI) *m/z* 433.7 $[M+H]^+$; HRMS (ESI): Calcd for $C_{25}H_{28}N_2OSSi$ $[M+H]^+$ 433.1764, Found 433.1767.

***N*-(5-((tert-butyldiphenylsilyl)oxy)-3,4,6-trimethylpyridin-2-yl)-5-methyl-1,3,4-oxadiazol-2-amine (13a)**

Prepared according to the general procedure using **10** (198 mg, 0.45 mmol)**.** Flash column chromatography (SiO_2, 35% EtOAc in hexanes) yielded **13a** as white form (93 mg, 43%, 2 steps). R_f = 0.50 (40% EtOAC in hexanes); m.p.: 150~151 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 9.48 (s, 1H), 7.66 (d, J = 6.6 Hz, 4H), 7.46 (dd, J = 15.4, 7.2 Hz, 6H), 2.33 (s, 3H), 2.12 (s, 1H), 2.04–1.94 (m, 8H), 1.07 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 166.6, 157.4, 149.4, 143.7, 140.3, 135.2, 132.8, 130.3, 128.6, 128.0, 125.9, 26.8, 20.2, 17.3, 15.9, 13.8, 11.2 ppm; MS (ESI) *m/z* 473.5 $[M+H]^+$; HRMS (ESI): Calcd for $C_{27}H_{32}N_4O_2SSi$ $[M+H]^+$ 473.2367, Found 473.2364.

***N*-(5-((tert-butyldiphenylsilyl)oxy)-3,4,6-trimethylpyridin-2-yl)-5-(trifluoromethyl)-1,3,4-oxadiazol-2-amine (13b)**

Prepared according to the general procedure using **10** (610 mg, 1.41 mmol)**.** Flash column chromatography (SiO_2, 5% EtOAc in hexanes) yielded **13b** as white solid (160 mg, 19%, 2 steps). R_f = 0.10 (10% EtOAC in hexanes); m.p.: 140~142 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.67 (dd, J = 8.0, 1.4 Hz, 4H), 7.52–7.41 (m, 6H), 2.08 (s, 6H), 2.00 (s, 3H), 1.08 (s, 9H); ^{13}C-NMR (175 MHz, $CDCl_3$) δ 167.1, 149.1, 148.2 (q, $J_{C\text{-}F}$ = 43.2 Hz), 145.3, 141.4, 135.1, 132.5, 130.5, 129.2, 128.0, 126.8, 116.7 (q, $J_{C\text{-}F}$ = 268.5 Hz), 26.7, 20.2, 17.3, 16.0, 13.8 ppm; MS (ESI) *m/z* 527.5 $[M+H]^+$; HRMS (ESI): Calcd for $C_{27}H_{29}F_3N_4O_2Si$ $[M+H]^+$ 527.2084, Found 527.2124.

***N*-(5-((tert-butyldiphenylsilyl)oxy)-3,4,6-trimethylpyridin-2-yl)-5-phenyl-1,3,4-oxadiazol-2-amine (13c)**

Prepared according to the general procedure using **10** (340 mg, 0.78 mmol)**.** Flash column chromatography (SiO_2, 15% EtOAc in hexanes) yielded **13c** as yellow solid (235 mg, 50%, 2 steps). R_f = 0.10 (20% EtOAC in hexanes); m.p.: 169~172 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 7.80 (d, J = 3.2 Hz, 2H), 7.68 (d, J = 6.8 Hz, 4H), 7.57–7.40 (m, 9H), 2.20–1.94 (m, 9H), 1.08 (s, 9H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 161.5, 158.9, 146.3, 143.3, 142.8, 137.3, 134.8, 133.0, 130.8, 130.2, 129.2, 127.9, 125.3, 124.1, 122.4, 26.5, 21.3, 19.6,

14.6, 13.9 ppm; MS (ESI) *m/z* 535.8 $[M+H]^+$; HRMS (ESI): Calcd for $C_{32}H_{34}N_4O_2Si$ $[M+H]^+$ 535.2523, Found 527.2519.

***N*-(5-((tert-butyldiphenylsilyl)oxy)-3,4,6-trimethylpyridin-2-yl)-5-(4-(trifluoromethyl)phenyl)-1,3,4-oxadiazol-2-amine (13d)**

Prepared according to the general procedure using **10** (500 mg, 1.16 mmol)**.** Flash column chromatography (SiO_2, 12% EtOAc in hexanes) yielded **13d** as light yellow solid (430 mg, 56%, 2 steps). R_f = 0.40 (20% EtOAC in hexanes); m.p.: 215~217 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.06 (s, 1H), 7.99 (s, 2H), 7.91 (d, J = 8.4 Hz, 2H), 7.68 (d, J = 6.7 Hz, 4H), 7.46 (dt, J = 14.1, 7.0 Hz, 6H), 2.06 (d, J = 10.5 Hz, 9H), 1.08 (s, 9H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 166.3, 157.3, 148.9, 144.9, 141.0, 135.2, 132.5, 132.1 (q, $J_{C\text{-}F}$ = 32.4 Hz), 130.4, 129.2, 128.2, 128.0, 127.9, 126.3, 125.9 (q, $J_{C\text{-}F}$ = 3.7 Hz), 123.8 (q, $J_{C\text{-}F}$ = 270.6 Hz), 20.2, 17.3, 16.0, 14.0 ppm; MS (ESI) *m/z* 603.2 $[M+H]^+$; HRMS (ESI): Calcd for $C_{32}H_{34}N_4O_2Si$ $[M+H]^+$ 603.2397, Found 603.2402.

***N*-(5-((tert-butyldiphenylsilyl)oxy)-3,4,6-trimethylpyridin-2-yl)-5-phenyl-1,3,4-thiadiazol-2-amine (14a)**

Prepared according to the general procedure using **10** (338 mg, 0.78 mmol)**.** Flash column chromatography (SiO_2, 10% to 15% EtOAc in hexanes) yielded **14a** as yellow solid (173 mg, 36%, 2 steps). R_f = 0.30 (40% EtOAC in hexanes); m.p.: 241~243 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.65 (s, 1H), 7.87 (dd, J = 7.9, 1.4 Hz, 2H), 7.69–7.65 (m, 4H), 7.49–7.40 (m, 9H), 2.19 (s, 3H), 2.10 (s, 3H), 2.06 (s, 3H), 1.08 (s, 9H).; ^{13}C-NMR (100 MHz, DMSO-d_6) δ 144.3, 138.6, 137.6, 137.4, 135.3, 133.6, 131.6, 130.7, 130.1, 129.8, 129.6, 128.9, 128.4, 128.2, 126.8, 27.1, 21.0, 20.2, 15.2, 13.3 ppm; MS (ESI) *m/z* 551.6 $[M+H]^+$; HRMS (ESI): Calcd for $C_{32}H_{34}N_4OSSi$ $[M+H]^+$ 551.2295, Found 551.2313.

5-(4-bromophenyl)-N-(5-((tert-butyldiphenylsilyl)oxy)-3,4,6-trimethylpyridin-2-yl)-1,3,4-thiadiazol-2-amine (14b)

Prepared according to the general procedure using **10** (260 mg, 0.60 mmol)**.** Flash column chromatography (SiO_2, 20% to 30% EtOAc in hexanes) yielded **14b** as yellow solid (158 mg, 42%, 2 steps). R_f = 0.2 (20% EtOAC in hexanes); m.p.: 241~243 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.73 (s, 1H), 7.82 (d, J = 8.5 Hz, 2H), 7.69–7.65 (m, 6H), 7.50–7.41 (m, 6H), 2.18 (s, 3H), 2.10 (s, 3H), 2.06 (s, 3H), 1.08 (s, 9H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 145.2, 135.4, 135.3, 135.2, 133.30, 132.3, 132.2, 130.3, 130.2, 129.5, 128.3, 128.0, 127.9, 127.7, 124.6, 29.7, 26.9, 20.2, 15.3, 13.2 ppm; MS (ESI) *m/z* 631.0 $[M+H]^+$; HRMS (ESI): Calcd for $C_{32}H_{33}BrN_4OSSi$ $[M+H]^+$: 631.1385, Found 631.1377.

***N*-(5-((tert-butyldiphenylsilyl)oxy)-3,4,6-trimethylpyridin-2-yl)-5-(4-methoxyphenyl)-1,3,4-thiadiazol-2-amine (14c)**

Prepared according to the general procedure using **10** (836 mg, 1.41 mmol)**.** Flash column chromatography (SiO_2, 20% to 40% EtOAc in hexanes) yielded **14c** as yellow solid (143 mg, 18%, 2 steps). R_f = 0.2 (20% EtOAC in hexanes); m.p.: 220~222 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.56 (s, 1H), 7.80 (d, J = 8.7 Hz, 2H), 7.69–7.66 (m, 4H), 7.50–7.41 (m, 6H), 7.05–7.00 (m, 2H), 3.80 (s, 3H), 2.18 (s, 3H), 2.10 (s, 3H), 2.05 (s, 3H), 1.08 (s, 9H); ^{13}C-NMR (150 MHz, DMSO-d_6) δ 160.9, 144.2, 141.0, 138.5, 135.2, 133.6, 130.6, 128.4, 128.3, 124.2, 115.0, 55.8, 27.1, 21.0, 20.1, 15.1, 13.2 ppm; MS (ESI) *m/z* 581.4 $[M+H]^+$; HRMS (ESI): Calcd for $C_{33}H_{36}N_4O_2SSi$ $[M+H]^+$ 581.2401, Found 581.2405.

***N*-(5-((tert-butyldiphenylsilyl)oxy)-3,4,6-trimethylpyridin-2-yl)-5-(p-tolyl)-1,3,4-thiadiazol-2-amine (14d)**

Prepared according to the general procedure using **10** (302 mg, 0.70 mmol)**.** Flash column chromatography (SiO_2, 20% to 30% EtOAc in hexanes) yielded **14d** as yellow solid (75 mg, 24%, 2 steps). R_f = 0.2 (20% EtOAC in hexanes); m.p.: 152~156 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.61 (s, 1H), 7.75 (d, J = 8.1 Hz, 2H), 7.69–7.66 (m, 4H), 7.50–7.41 (m, 6H), 7.28 (d, J = 7.9 Hz, 2H), 2.34 (s, 3H), 2.18 (s, 3H), 2.10 (s, 3H), 2.06 (s, 3H), 1.08 (s, 9H); MS (ESI) *m/z* 565.8 $[M+H]^+$; HRMS (ESI): Calcd for $C_{33}H_{36}N_4OSSi$ $[M+H]^+$ 565.2452, Found 565.2523.

***N*-(5-((tert-butyldiphenylsilyl)oxy)-3,4,6-trimethylpyridin-2-yl)-5-(4-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-amine (14e)**

Prepared according to the general procedure using **10** (240 mg, 0.55 mmol)**.** Flash column chromatography (SiO_2, 10% to 20% EtOAc in hexanes) yielded **14e** as yellow solid (183 mg, 53%, 2 steps). R_f = 0.25 (20% EtOAC in hexanes); m.p.: 233~235 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.85 (s, 1H), 8.10 (d, J = 7.5 Hz, 2H), 7.83 (d, J = 8.3 Hz, 2H), 7.68 (dd, J = 8.0, 1.5 Hz, 4H), 7.52 – 7.41 (m, 6H), 2.20 (s, 3H), 2.12 (s, 3H), 2.07 (s, 3H), 1.08 (s, 9H); ^{13}C-NMR (150 MHz, DMSO-d_6) δ 161.9, 157.4, 143.9, 140.6, 138.3, 134.9, 134.8, 133.1, 130.2, 129.4 (q, $J_{C\text{-}F}$ = 31.8 Hz), 129.3, 127.9, 126.9, 126.1 (q, $J_{C\text{-}F}$ = 3.6 Hz), 124.0 (q, $J_{C\text{-}F}$ = 270.5 Hz), 116.9, 26.6, 20.5, 20.2, 19.7, 14.7, 12.7 ppm; MS (ESI) *m/z* 619.9 $[M+H]^+$; HRMS (ESI): Calcd for $C_{33}H_{33}F_3N_4OSSi$ $[M+H]^+$ 619.2169, Found 565.2166.

2,4,5-trimethyl-6-((5-methyl-1,3,4-oxadiazol-2-yl)amino)pyridin-3-ol (15a)

Prepared according to the general procedure using **13a** (148 mg, 0.31 mmol)**.** Flash column chromatography (SiO_2, 2% to 5% MeOH in CH_2Cl_2) yielded **15a** as yellow solid (38 mg, 52%). R_f = 0.50 (7.5% MeOH in CH_2Cl_2); m.p.: 205~207 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 9.38 (s, 1H), 8.44 (s, 1H), 2.33 (s, 3H), 2.28 (s, 3H), 2.10 (d, J = 34.2 Hz, 6H); ^{13}C-

NMR (100 MHz, DMSO-d_6) δ 161.7, 157.8, 146.85, 141.7, 141.3, 134.4, 123.0, 19.2, 13.8, 12.6, 10.6 ppm; MS (ESI) *m/z* 235.9 $[M+H]^+$; HRMS (ESI): Calcd for $C_{11}H_{14}N_4O_2$ $[M+H]^+$ 235.1189, Found 235.1187.

2,4,5-trimethyl-6-((5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl)amino)pyridin-3-ol (15b)

Prepared according to the general procedure using **13b** (122 mg, 0.23 mmol)**.** Flash column chromatography (SiO_2, 0.5% to 1% MeOH in CH_2Cl_2) yielded **15b** as pale yellow solid (50 mg, 75%). R_f = 0.30 (5% MeOH in CH_2Cl_2); m.p.: 213~215 ^oC; ^1H NMR (400 MHz, DMSO-d_6) δ 10.44 (s, 1H), 8.67 (s, 1H), 2.33 (s, 3H), 2.17 (d, J = 21.1 Hz, 6H); MS (ESI) *m/z* 289.0 $[M+H]^+$; HRMS (ESI): Calcd for $C_{11}H_{11}F_3N_4O_2$ $[M+H]^+$ 289.0906, Found 289.0964.

2,4,5-trimethyl-6-((5-phenyl-1,3,4-oxadiazol-2-yl)amino)pyridin-3-ol (15c)

Prepared according to the general procedure using **13c** (183 mg, 0.34 mmol)**.** Flash column chromatography (SiO_2, 1% to 2.5% MeOH in CH_2Cl_2) yielded **15c** as yellow solid (88 mg, 87%). R_f = 0.30 (5% MeOH in CH_2Cl_2); m.p.: 249~250 ^oC; ^1H-NMR (400 MHz, DMSO-d_6) δ 9.79 (s, 1H), 8.53 (s, 1H), 7.91 (d, J = 57.9 Hz, 2H), 7.58–7.51 (m, 3H), 2.45–2.06 (m, 9H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 161.9, 158.6, 148.7, 147.0, 141.4, 134.5, 130.7, 129.3, 125.3, 124.3, 123.1, 19.3, 13.8, 12.6 ppm; MS (ESI) *m/z* 297.1 $[M+H]^+$; HRMS (ESI): Calcd for $C_{16}H_{16}N_4O_2$ $[M+H]^+$ 297.1346, Found 297.1343.

2,4,5-trimethyl-6-((5-(4-(trifluoromethyl)phenyl)-1,3,4-oxadiazol-2-yl)amino)pyridin-3-ol (15d)

Prepared according to the general procedure using **13d** (372 mg, 0.62 mmol)**.** Flash column chromatography (SiO_2, 1% to 2% MeOH in CH_2Cl_2) yielded **15d** as yellow solid (151 mg, 67%). R_f = 0.30 (5% MeOH in CH_2Cl_2); m.p.: 265 ^oC (dec.); ^1H-NMR (400 MHz, DMSO-d_6) δ 9.99 (s, 1H), 8.60 (s, 1H), 8.05 (s, 2H), 7.91 (d, J = 8.3 Hz, 2H), 2.34 (s, 3H), 2.18 (d, J = 16.9 Hz, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.6, 162.4, 157.3, 147.2, 141.6, 141.0, 134.7, 130.3 (q, $J_{C\text{-}F}$ = 31.2 Hz), 126.2, 126.0, 123.9 (q, $J_{C\text{-}F}$ = 270.5 Hz), 123.3, 19.3, 13.7, 12.8 ppm; MS (ESI) *m/z* 365.4 $[M+H]^+$; HRMS (ESI): Calcd for $C_{17}H_{15}F_3N_4O_2$ $[M+H]^+$ 365.1219, Found 365.1238.

2,4,5-trimethyl-6-((5-phenyl-1,3,4-thiadiazol-2-yl)amino)pyridin-3-ol (16a)

Prepared according to the general procedure using **14a** (132 mg, 0.24 mmol)**.** Flash column chromatography (SiO_2, 1% to 2% MeOH in CH_2Cl_2) yielded **16a** as yellow solid (54 mg, 72%). R_f = 0.30 (5% MeOH in CH_2Cl_2); m.p.: 256~266 ^oC; ^1H-NMR (400 MHz, DMSO-d_6) δ 10.55 (s, 1H), 8.29 (s, 1H), 7.96–7.87 (m, 2H), 7.56–7.43 (m, 3H), 2.43 (s, 3H), 2.23 (s, 3H), 2.17 (s, 3H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 161.3, 158.2, 144.4, 140.8, 138.8, 135.9, 131.2, 129.6, 129.2, 126.3, 116.5, 18.5, 12.7, 12.6 ppm; MS (ESI) *m/z* 313.2 $[M+H]^+$; HRMS (ESI): Calcd for $C_{16}H_{16}N_4OS$ $[M+H]^+$ 313.1117, Found 313.1138.

6-((5-(4-bromophenyl)-1,3,4-thiadiazol-2-yl)amino)-2,4,5-trimethylpyridin-3-ol (16b)

Prepared according to the general procedure using **14b** (105 mg, 0.17 mmol)**.** Flash column chromatography (SiO_2, 1% to 2% MeOH in CH_2Cl_2) yielded **16b** as yellow solid (36 mg, 54%). R_f = 0.30 (5% MeOH in CH_2Cl_2); m.p.: 285~287 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.61 (s, 1H), 8.31 (s, 1H), 7.86 (d, J = 8.5 Hz, 2H), 7.73–7.68 (m, 2H), 2.43 (s, 3H), 2.23 (s, 3H), 2.17 (s, 3H); ^{13}C-NMR (175 MHz, DMSO-d_6) δ 162.0, 157.8, 145.0, 141.0, 139.3, 136.4, 132.6, 130.9, 128.6, 123.1, 166.9, 19.0, 13.2, 13.1 ppm; MS (ESI) *m/z* 391.3 $[M+H]^+$; HRMS (ESI): Calcd for $C_{16}H_{15}BrN_4OS$ $[M+H]^+$ 391.0222, Found 391.0276.

6-((5-(4-methoxyphenyl)-1,3,4-thiadiazol-2-yl)amino)-2,4,5-trimethylpyridin-3-ol (16c)

Prepared according to the general procedure using **14c** (112 mg, 0.19 mmol)**.** Flash column chromatography (SiO_2, 1% to 2% MeOH in CH_2Cl_2) yielded **16c** as yellow solid (38 mg, 58%). R_f = 0.30 (5% MeOH in CH_2Cl_2); m.p.: 275~278 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.44 (s, 1H), 8.26 (s, 1H), 7.83 (d, J = 8.8 Hz, 2H), 7.09–7.03 (m, 2H), 3.82 (s, 3H), 2.42 (s, 3H), 2.22 (s, 3H), 2.16 (s, 3H); ^{13}C-NMR (175 MHz, DMSO-d_6) δ 161.3, 160.8, 158.9, 144.8, 141.2, 139.3, 129.1, 128.6, 128.3, 124.3, 116.8, 115.1, 55.8, 19.0, 13.2, 13.1 ppm; MS (ESI) *m/z* 343.3 $[M+H]^+$; HRMS (ESI): Calcd for $C_{17}H_{18}N_4O_2S$ $[M+H]^+$ 343.1223, Found 343.1288.

2,4,5-trimethyl-6-((5-(p-tolyl)-1,3,4-thiadiazol-2-yl)amino)pyridin-3-ol (16d)

Prepared according to the general procedure using **14d** (154 mg, 0.27 mmol)**.** Flash column chromatography (SiO_2, 1% to 2% MeOH in CH_2Cl_2) yielded **16d** as yellow solid (77 mg, 87%). R_f = 0.30 (5% MeOH in CH_2Cl_2); m.p.: 288~290 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.50 (s, 1H), 8.28 (s, 1H), 7.79 (d, J = 8.1 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 2.42 (s, 3H), 2.36 (s, 3H), 2.22 (s, 3H), 2.16 (s, 3H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 161.5, 157.2, 144.5, 140.6, 138.8, 135.9, 132.1, 130.5, 128.1, 122.6, 116.6, 18.5, 12.7, 12.6 ppm; MS (ESI) *m/z* 327.6 $[M+H]^+$; HRMS (ESI): Calcd for $C_{17}H_{18}N_4OS$ $[M+H]^+$ 327.1274, Found 327.1309.

2,4,5-trimethyl-6-((5-(4-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)amino)pyridin-3-ol (16e)

Prepared according to the general procedure using **14e** (154 mg, 0.27 mmol)**.** Flash column chromatography (SiO_2, 1% to 2% MeOH in CH_2Cl_2) yielded **16e** as yellow solid (77 mg, 87%). R_f = 0.30 (5% MeOH in CH_2Cl_2); m.p.: 282~283 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.73 (s, 1H), 8.33 (s, 1H), 8.12 (d, J = 8.1 Hz, 2H), 7.85 (d, J = 8.2 Hz, 2H), 2.44 (s, 3H), 2.23 (s, 3H), 2.19–2.14 (m, 3H); ^{13}C-NMR (150 MHz, DMSO-d_6) δ 162.2, 157.1, 144.6, 140.4, 138.9, 136.0, 135.1, 129.3 (q, $J_{C\text{-}F}$ = 25.4 Hz), 126.4, 126.1 (q, $J_{C\text{-}F}$ = 3.0 Hz), 124.1 (q, $J_{C\text{-}F}$ = 216.2 Hz) ppm; MS (ESI) *m/z* 381.7 $[M+H]^+$; HRMS (ESI): Calcd for $C_{17}H_{15}F_3N_4OS$ $[M+H]^+$ 381.0990, Found 381.0990.

Evaluation of in vitro and in vivo efficacy

Cell lines and culture

HT-29 (human colon cancer cell line) and U937 (monocytic leukemic cell line), were obtained from American Type Culture Collection (ATCC, USA). They were cultured in RPMI 1640 supplemented with 10% fetal bovine serum (FBS), 1% penicillin/streptomycin and incubated at 37 °C in 5% CO_2 atmosphere.

TNF-α-induced adhesion of monocytes to colon epithelial cells

Adhesion of U937 cells to HT-29 cells was evaluated as evaluated as described previously.[1] Briefly, U937 cells were pre-labeled with BCECF-AM (2′,7′-Bis(2-carboxyethyl)-5(6)-carboxyfluorescein acetoxymethyl ester, 10 μg/mL) for 1 h at 37 °C. HT-29 cells in 48-well plates were pretreated with drug or 5-ASA for 1 h. The cells were then co-incubated with BCECF-AM-pre-labeled U937 cells ($5x10^5$ cells/well) in the presence of TNF-α for 3 h at 37 °C. The plates were gently washed twice with PBS for removal of non-adherent U937 cells. Cells in three sets were lysed with 0.1 % Triton X-100 in 0.1 M Tris, and analysis of BCECF fluorescence was performed using Fluostar Optima microplate reader (BMG Labtech GmbH, Offenburg, Germany) with excitation at 485 nm and emission at 520 nm.

Inhibitory effects of 5-aminosalicylic acid (5-ASA) and aminopyridinol **16a** on TNF-α-induced adhesion of U937 cells to HT-29 cells. Confluent monolayers of HT-29 cells were pretreated with drugs for 1 h, and then stimulated by 10 ng/mL of TNF-α. After 3 h, HT-29 cells were co-cultured with U937 cells that were already labeled with BCECF-AM (10 μg/mL). Images of the adhesion of BCECF fluorescence-labeled U937 cells to HT-29 colon epithelial cells were captured by light microscopy (phase contrast) and fluorescent microscopy. Fluorescent images were then merged over the corresponding light microscopy images to show the adhering position of U937 cells (magnification, 200×).

TNBS-induced experimental colitis

Sprague–Dawley rats (7 weeks old) were purchased from Orient-Bio Korea Co. Ltd., Korea. Rats were divided into six different groups (six rats/group) and fasted (but allowed to drink water ad libitum) for 24 h before induction of colitis. Rats were then lightly anesthetized using diethyl ether, and received slow injections of 0.8 mL 5% TNBS in 50v/v% ethanol into the lumen of the colon (8 cm proximal to the anus through the rectum) using a polyethylene catheter fitted onto a 1 mL syringe; they were then kept in vertical position for 60 s before being returned to their cages. Rats in the control group were handled similarly but were administered 50 v/v% ethanol alone. SSZ (300 mg/kg/day) or compounds **6f** or **16a** (1 mg/kg/day) was administered by oral gavage for 5 days starting 1-day after

administration of TNBS. SSZ was directly dissolved in saline solution, and compounds were first dissolved in DMSO and then diluted with saline solution. The administration volume of drugs and compounds was 1 mL/200 g body weight. On 7th day of TNBS the rats were sacrificed and the colon tissues were cut out for morphological examination and determining protein expressions of various cytokines and inflammatory markers by ELISA or western blot. The study protocol of the animal experiment was reviewed and approved beforehand by the Institutional Animal Care and Use Committee of Yeungnam University (Approval number 2017-015) and were performed following the institutional and national ethical guidelines for working with laboratory animals (Institutional guidelines of the Institute of Laboratory Animal Resources and Yeungnam University for the care and use of laboratory animals)

Myeloperoxidase measurement

Myeloperoxidase (MPO), an indicator of tissue neutrophil infiltration, was assessed using MPO Detection Kit (Hycult Biotechnology, Uden, Netherlands). Rat colon tissue was homogenized in 2 mL of ice cold lysis buffer using a tissue homogenizer (Biospec Products Inc., Basel, Switzerland). The homogenized tissues were centrifuged twice at 1,000 g for 15 min. The level of MPO in the supernatant was determined and measured by performing ELISA assay using Rat MPO assay kit (Hycult Biotech, Uden, Netherlands) according to the manufacturer's instructions.

Enzyme- linked immunosorbent assay (ELISA)

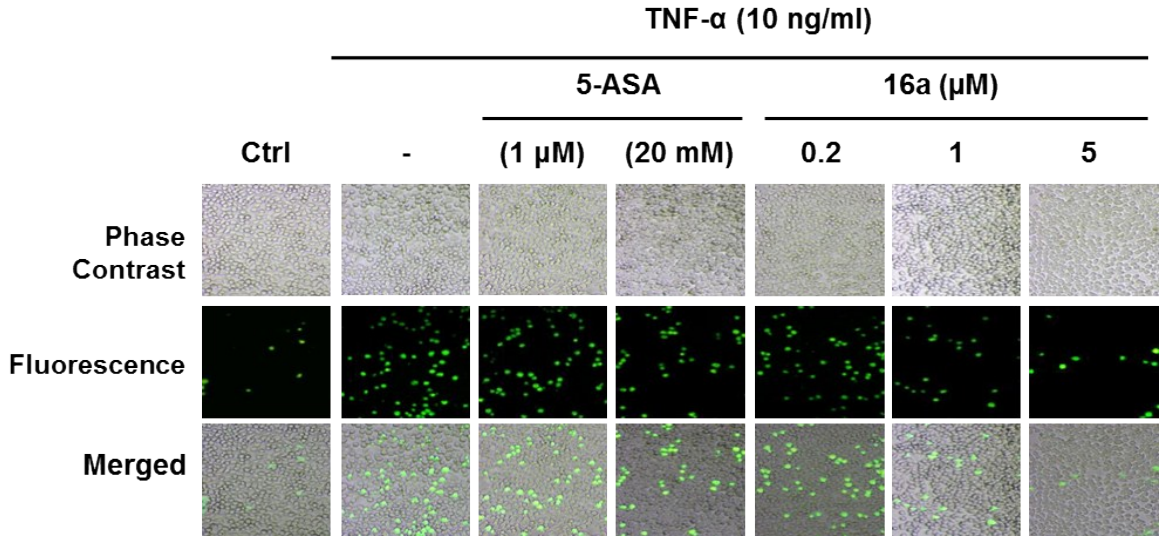
MCP-1 ELISA from rat colon tissue was measured using Quantikine ELISA (MJE00, R&D Systems). Fifty milligram of tissue was homogenized in 2 mL of ice cold PBS containing protease inhibitor cocktail. The homogenized tissue was centrifuged at 900 g for 10 min at 4 °C, and MCP-1 level was measured from the supernatant according to the instruction provided by the manufacturer.

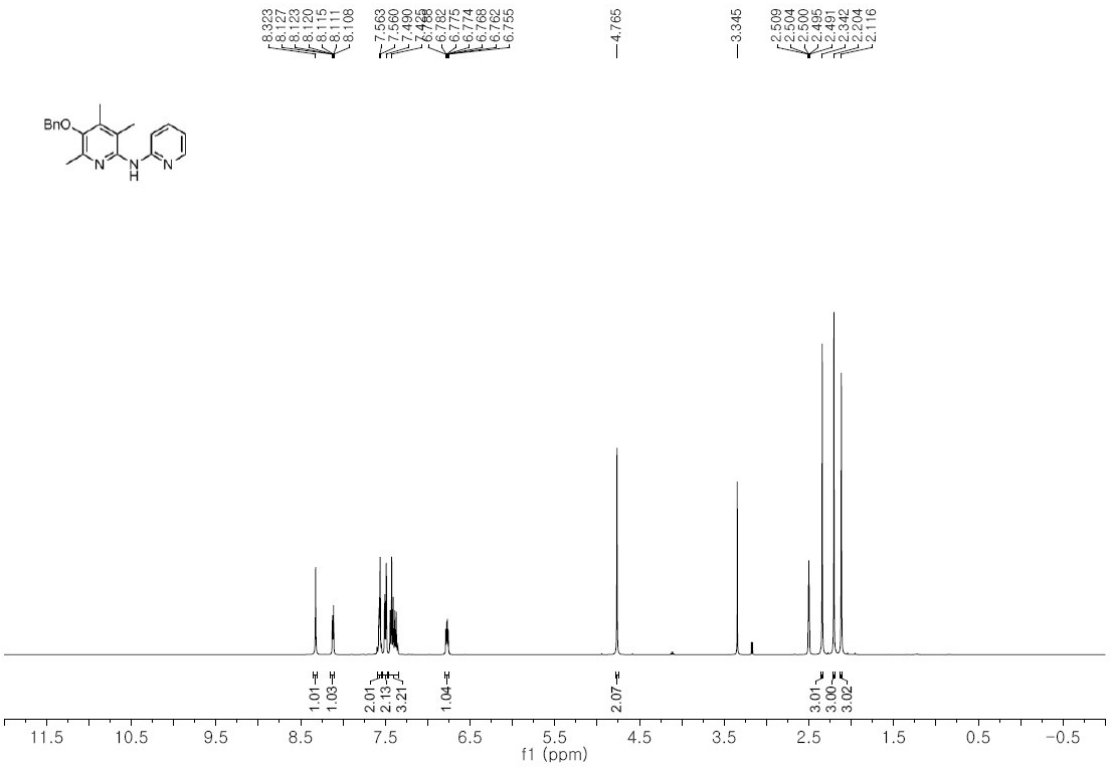
Western Blot Analysis

Total protein was extracted from rat colon tissues using RIPA buffer containing protease inhibitor cocktail and phosphatase inhibitor in ice. The tissue lysates were centrifuged at 17,000 g for 10 min and the supernatant were collected. Protein concentration was measured using BCA protein assay kit (Pierce-Thermo, Logan, UT, U.S.). Equal amount of protein was loaded and resolved by SDS-polyacrylamide gel electrophoresis (PAGE) and transferred to a nitrocellulose transfer membrane (Whatman GmbH, Dassel, Germany). The membrane was subjected for blocking in 5% skimmed milk in 1X TBST for 1 h. After incubation with primary antibody for overnight in a shaker membrane was washed thrice with 1X TBST at 10 min interval and then incubated for 1 h at room temperature with horseradish peroxidase-conjugated secondary antibody in skim milk-TBS. Then the membrane was again washed thrice with 1 X TBST at 10 min interval. The protein was detected and quantitated using a LAS 4000 mini luminescent image analyzer (Fujifilm, Tokyo, Japan)

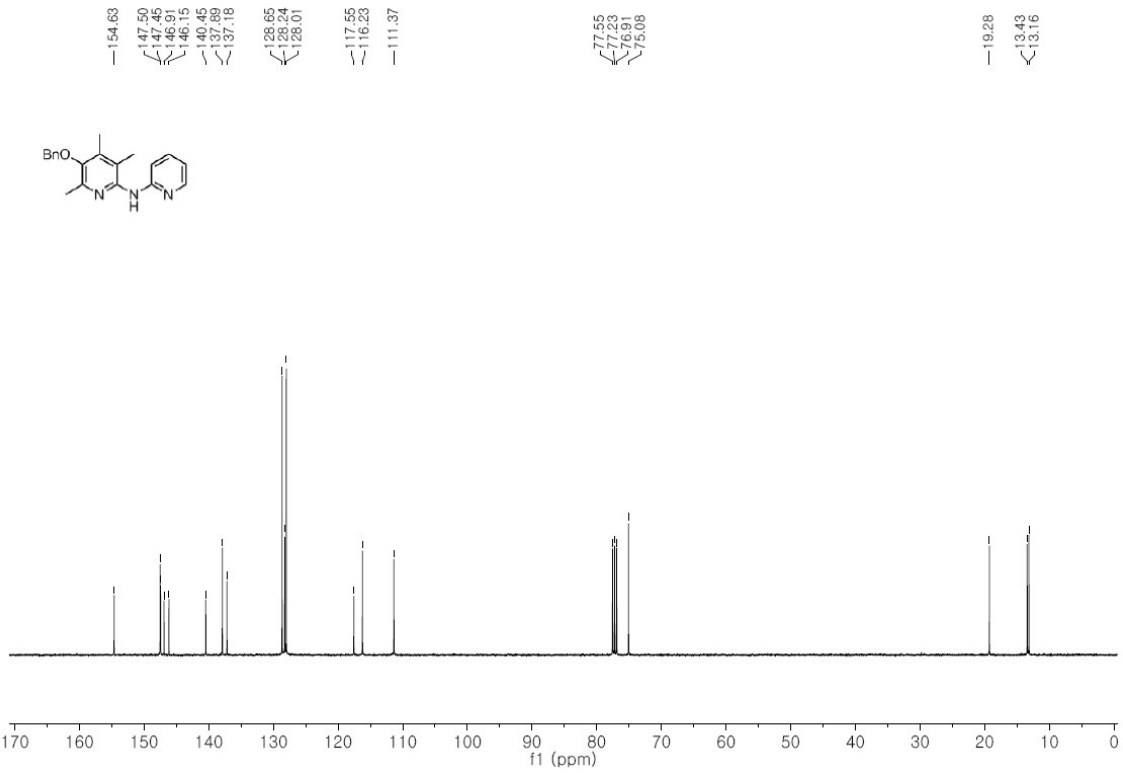
Cell adhesion assay

Inhibitory effects of 5-aminosalicylic acid (5-ASA) and aminopyridinol **16a** on TNF-α-induced adhesion of U937 cells to HT-29 cells. Confluent monolayers of HT-29 cells were pretreated with drugs for 1 h, and then stimulated by 10 ng/mL of TNF-α. After 3 h, HT-29 cells were co-cultured with U937 cells that were already labeled with BCECF-AM (10 μg/mL). Images of the adhesion of BCECF fluorescence-labeled U937 cells to HT-29 colon epithelial cells were captured by light microscopy (phase contrast) and fluorescent microscopy. Fluorescent images were then merged over the corresponding light microscopy images to show the adhering position of U937 cells (magnification, 200×).

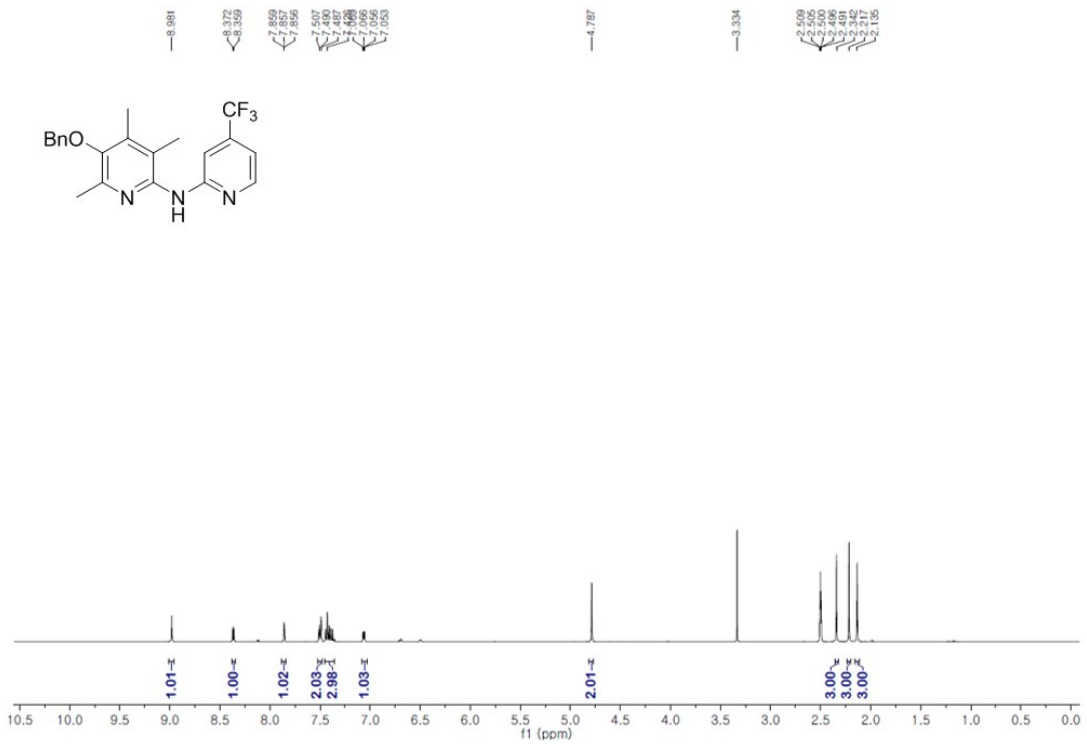




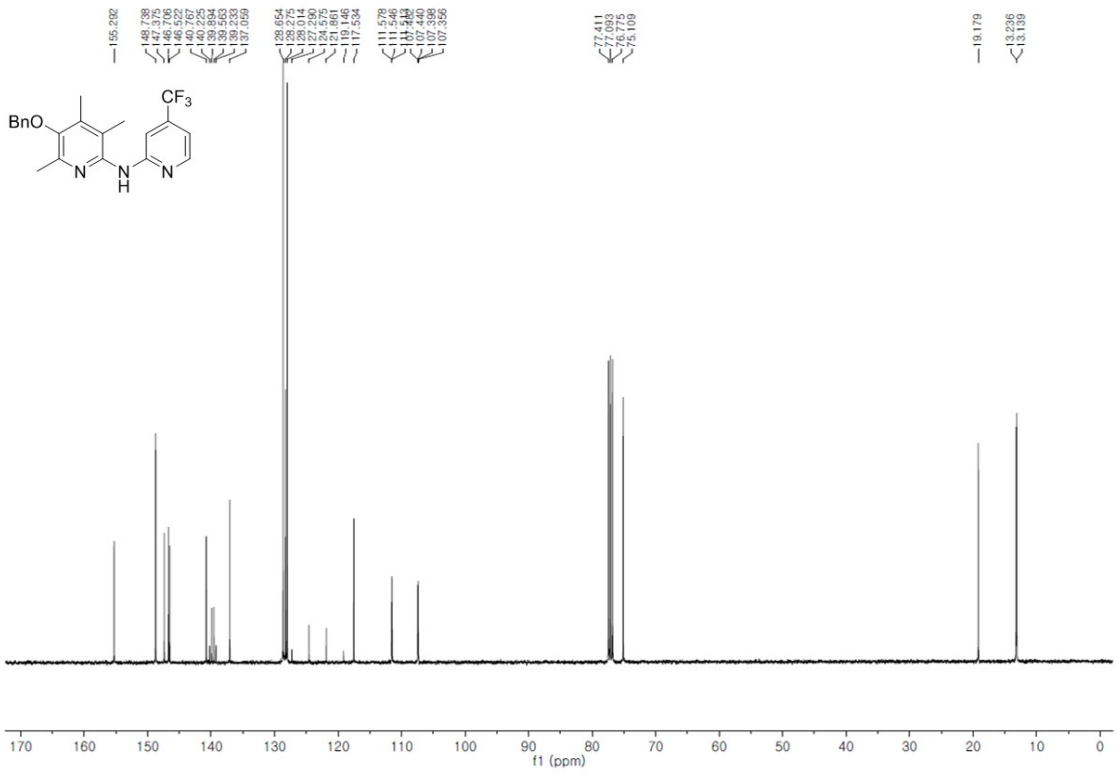
^{1}H-NMR of **5a** (DMSO-d_6)



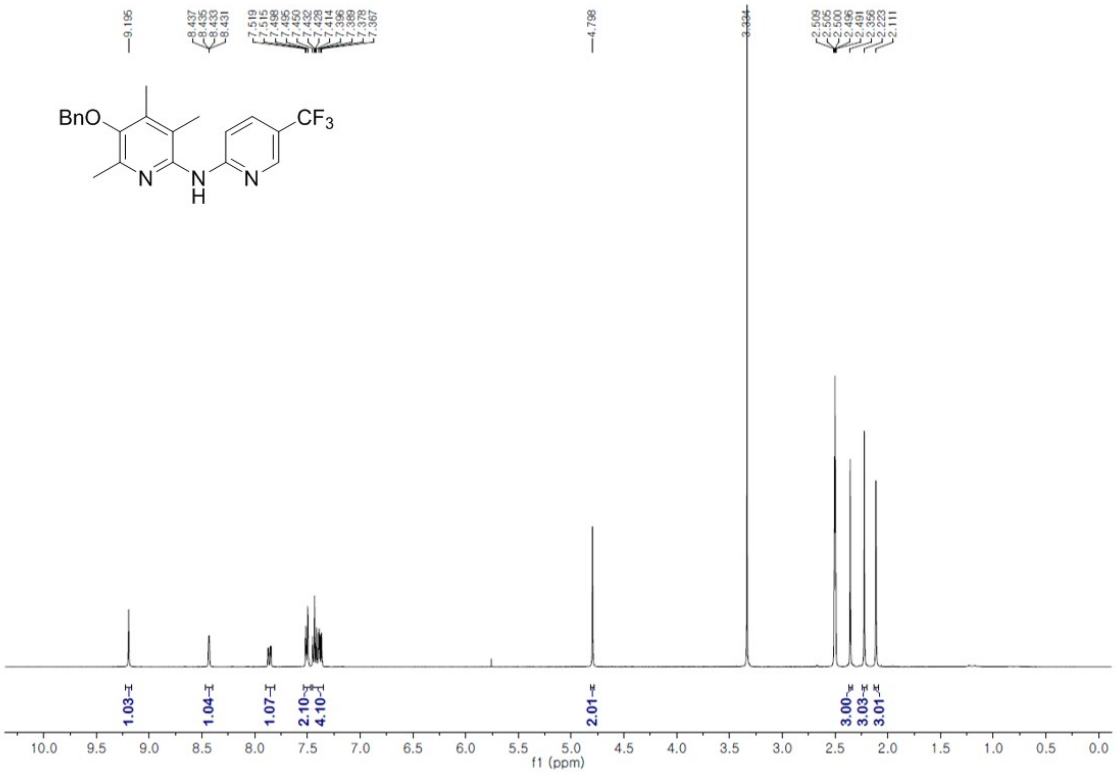
^{13}C-NMR of **5a** ($CDCl_3$)



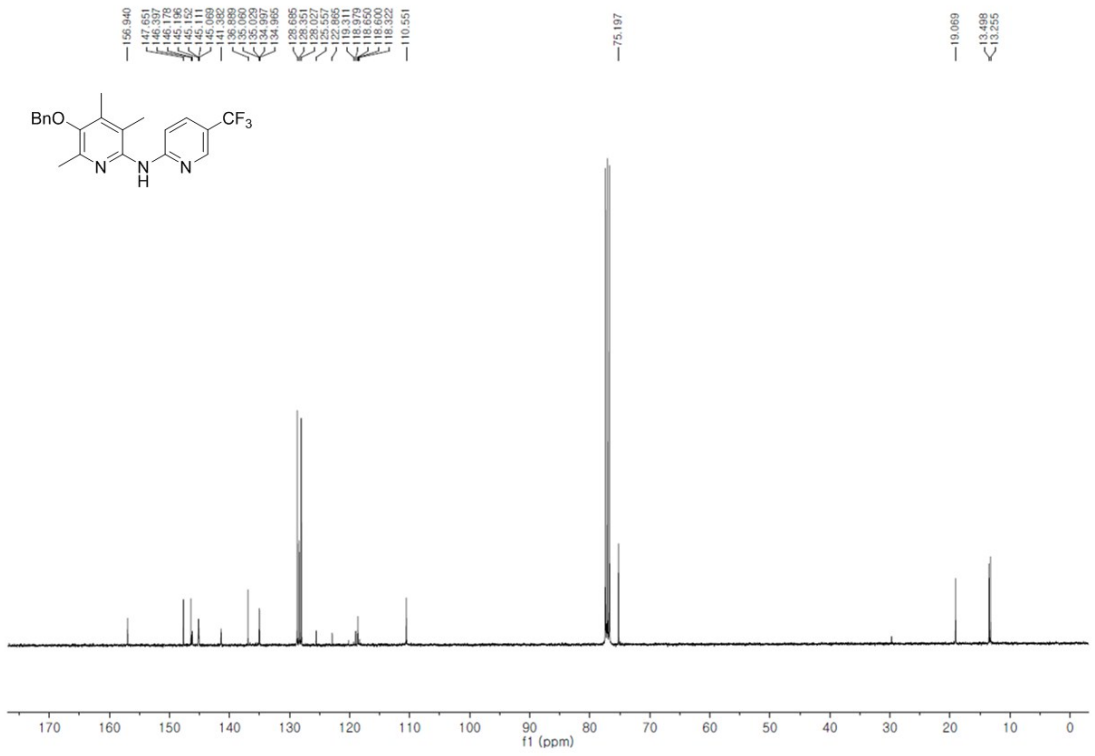
^{1}H-NMR of **5b** (DMSO-d_6)



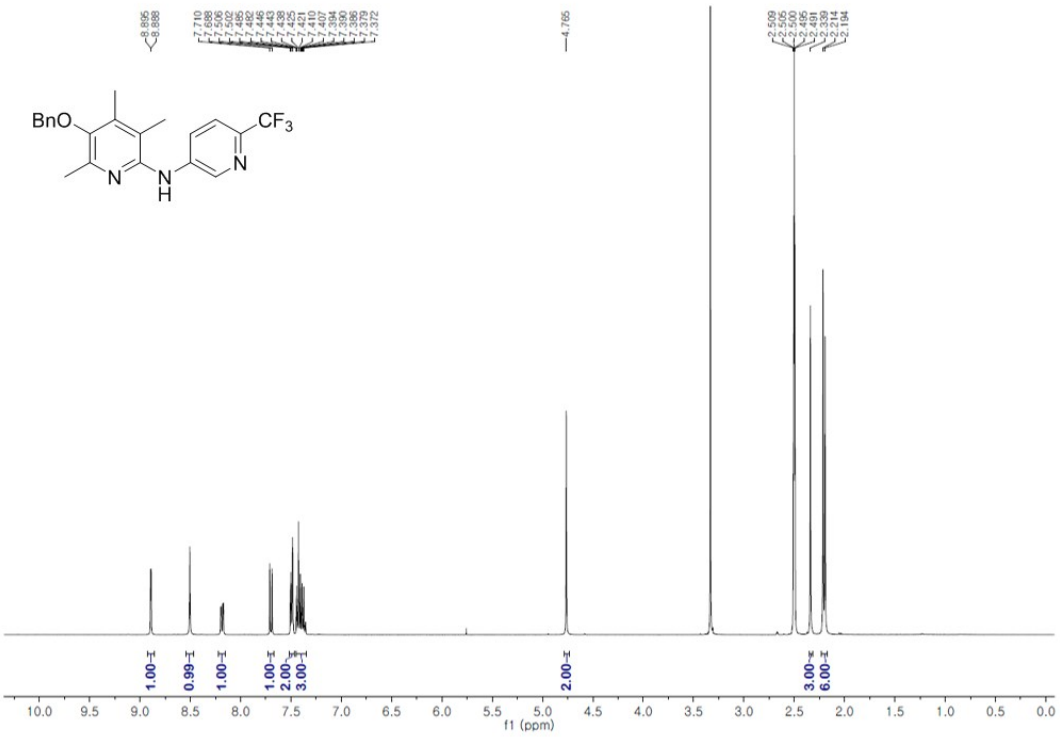
^{13}C-NMR of **5b** ($CDCl_3$)



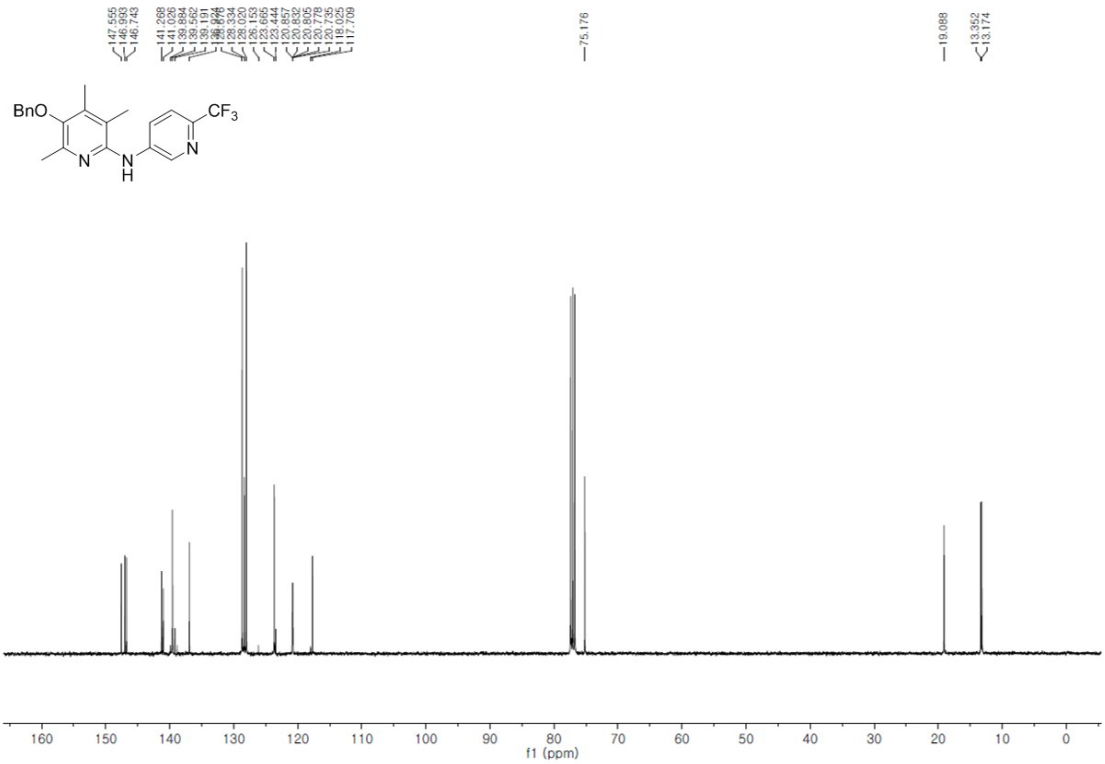
^{1}H-NMR of **5c** (DMSO-d_6)



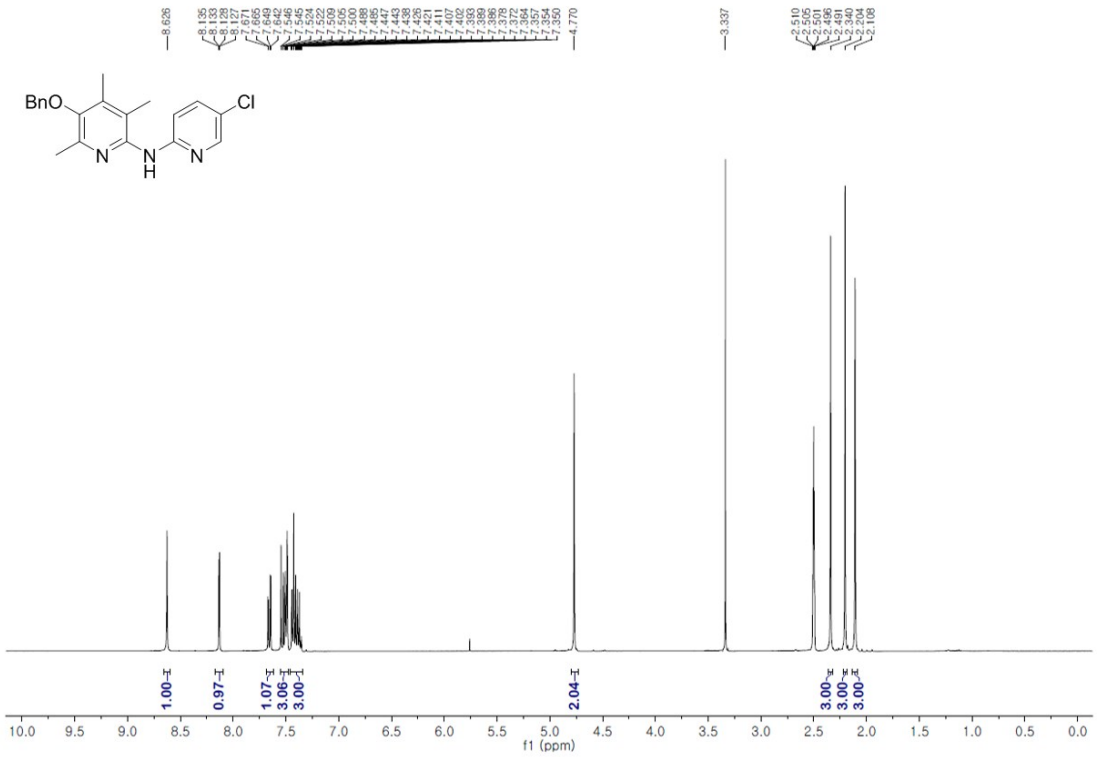
^{13}C-NMR of **5c** ($CDCl_3$)



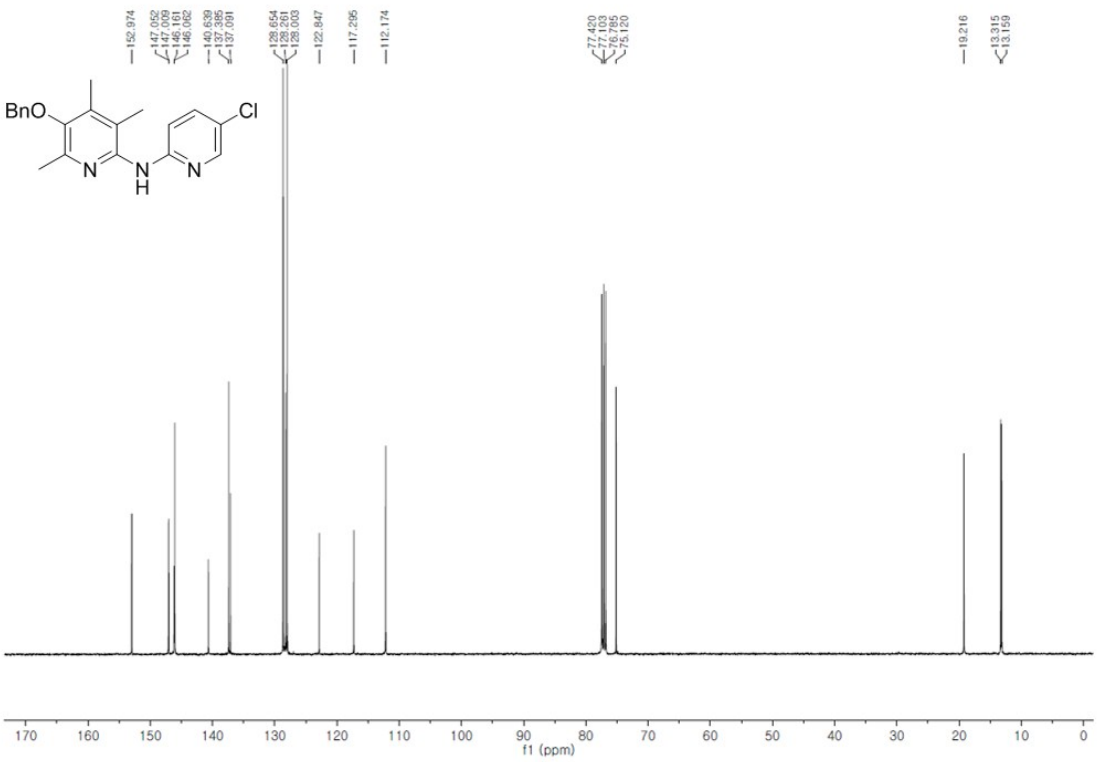
^{1}H-NMR of **5d** (DMSO-d_6)



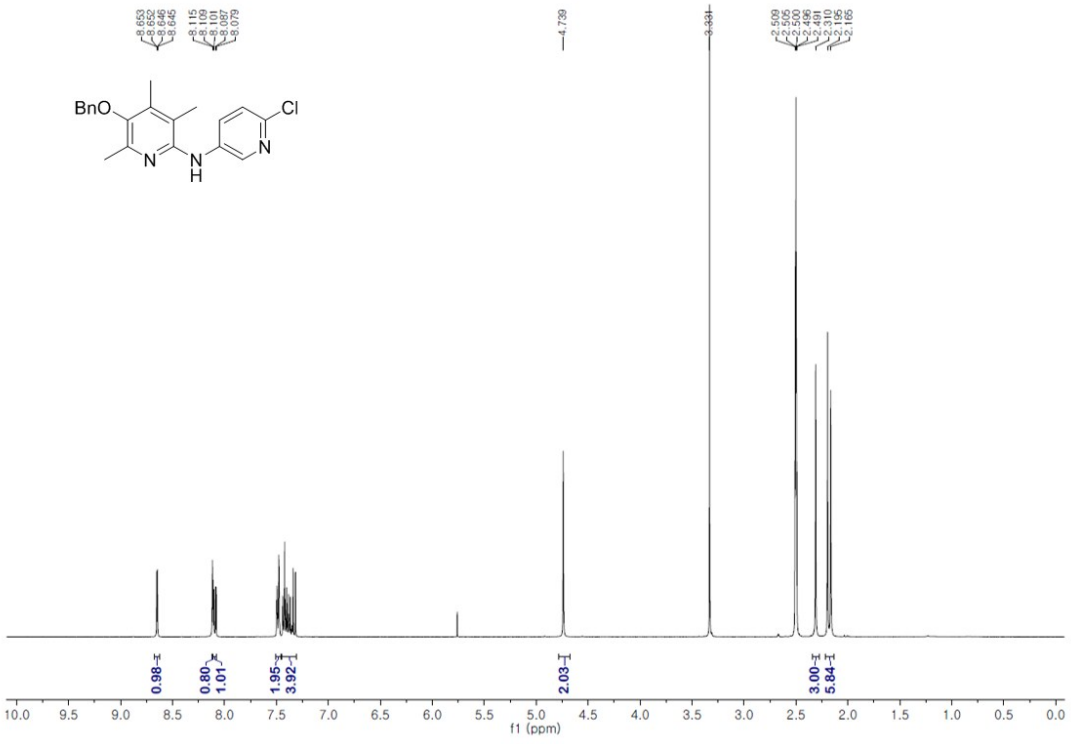
^{13}C-NMR of **5d** ($CDCl_3$)



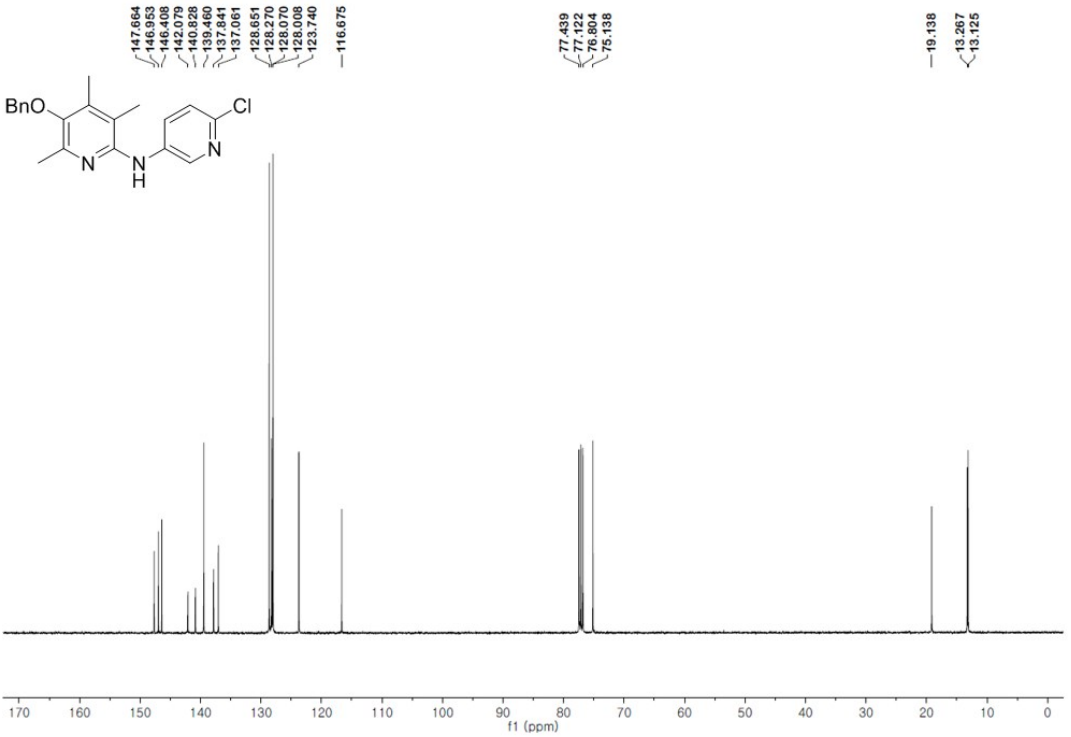
^{1}H-NMR of **5e** (DMSO-d_6)



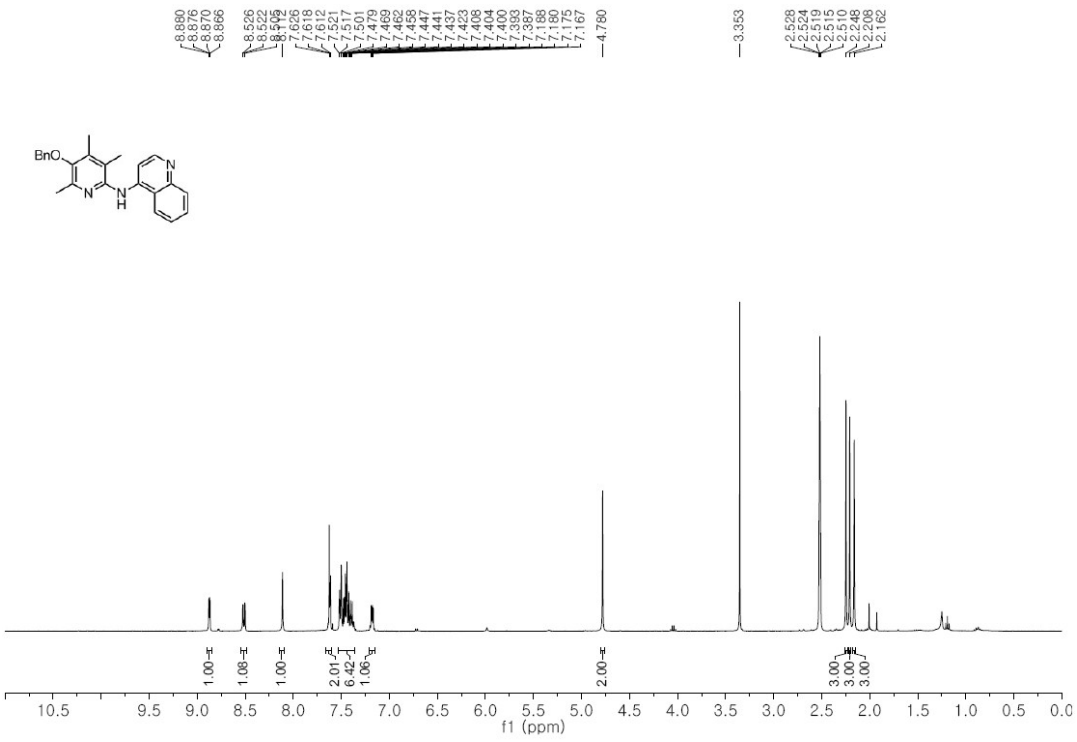
^{13}C-NMR of **5e** ($CDCl_3$)



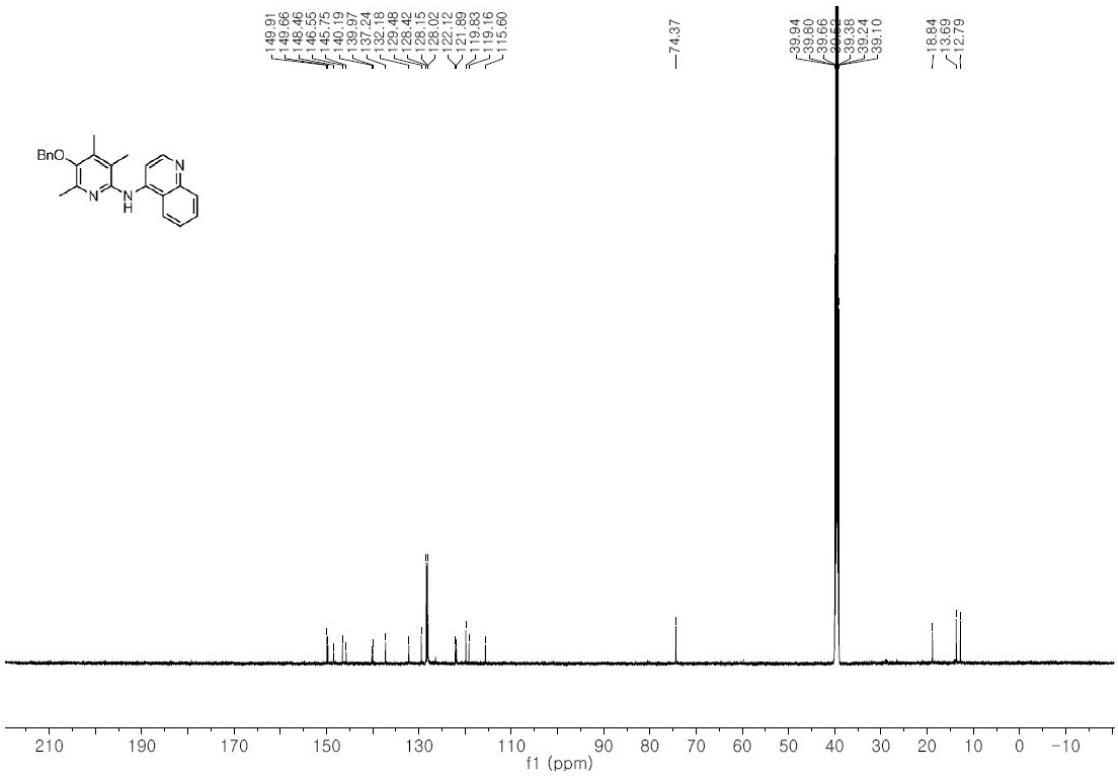
^{1}H-NMR of **5f** (DMSO-d_6)



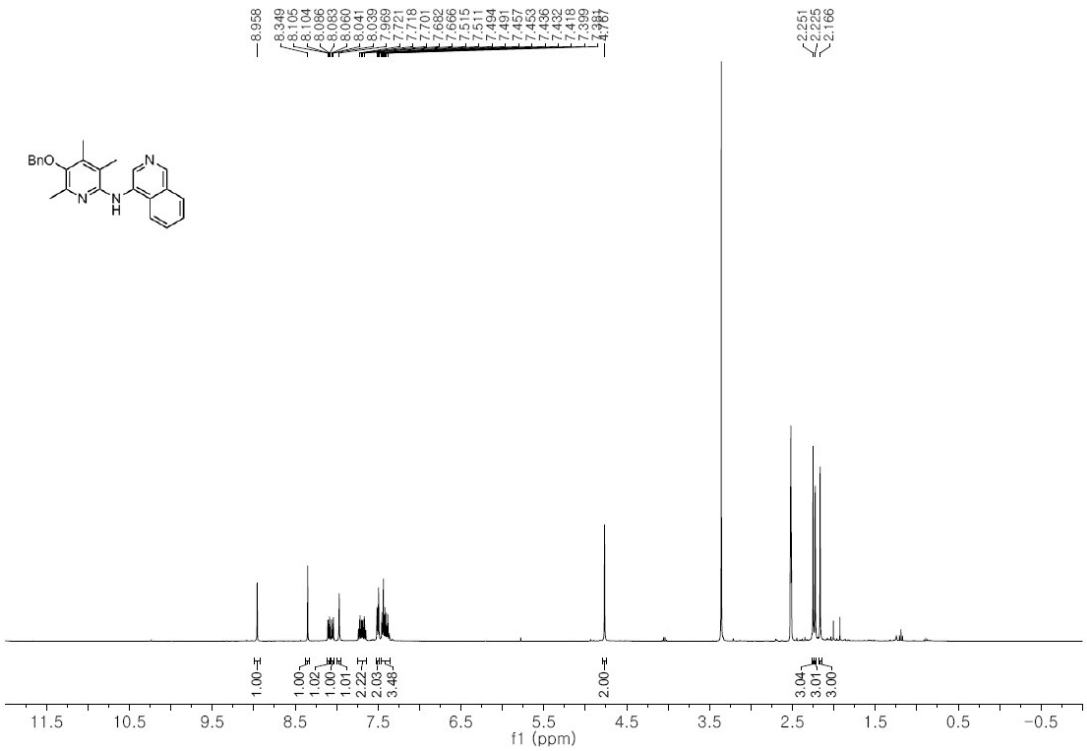
^{13}C-NMR of **5f** ($CDCl_3$)



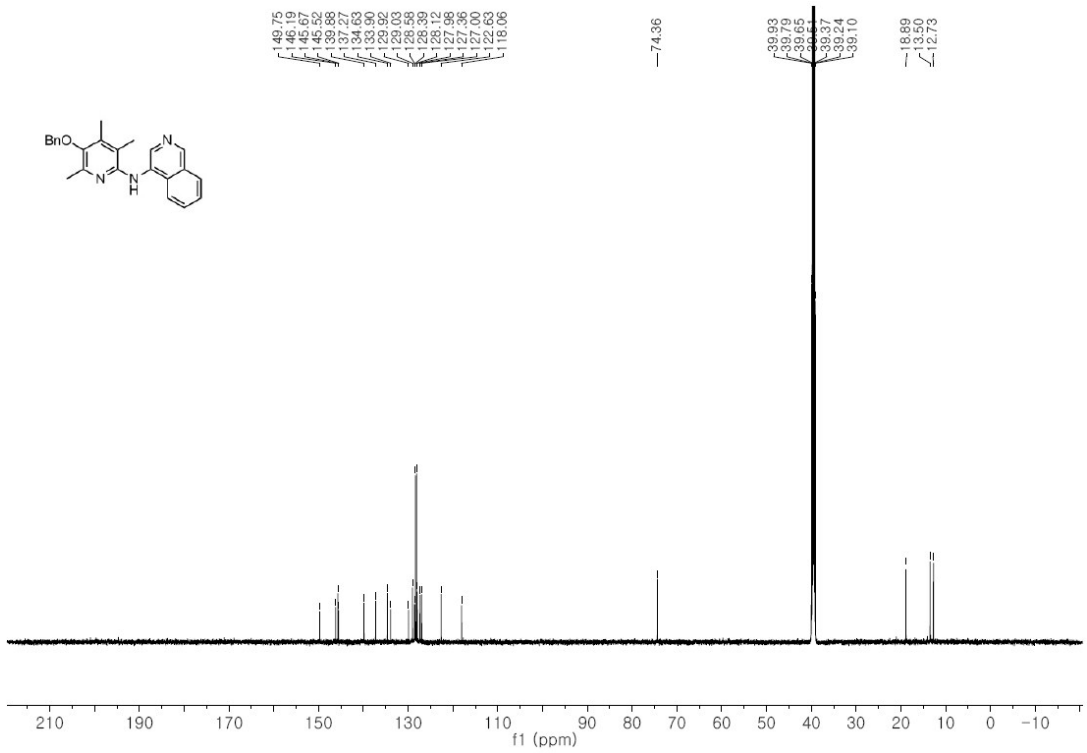
^{1}H-NMR of **5g** (DMSO-d_6)



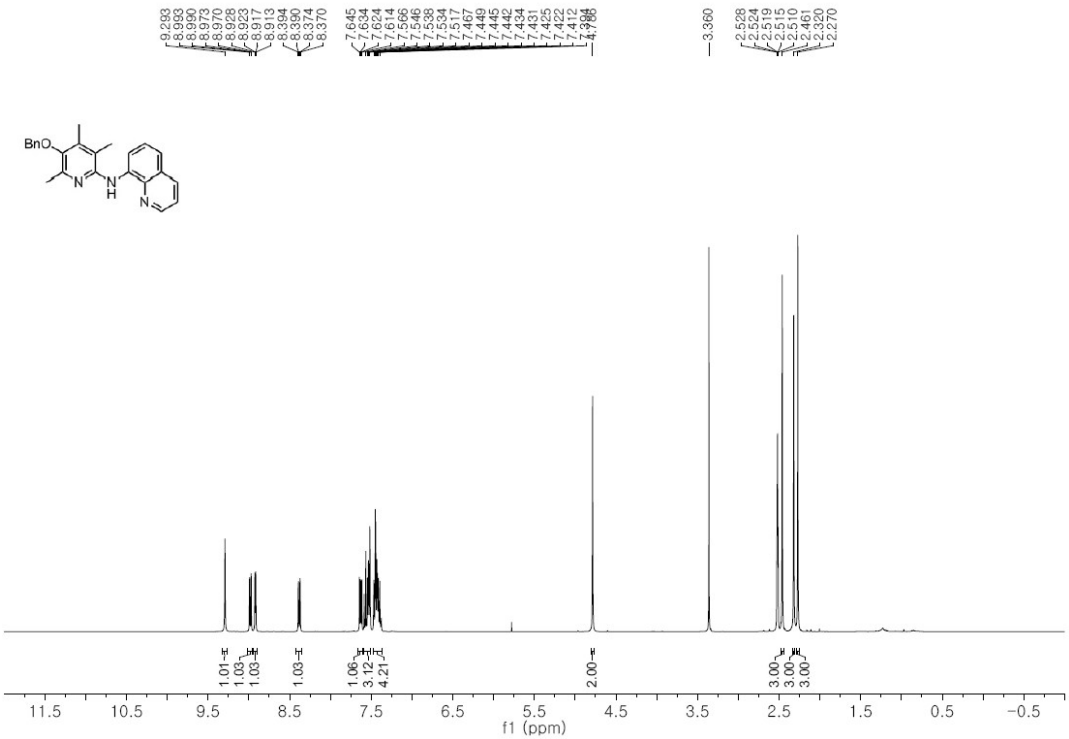
^{13}C-NMR of **5g** (DMSO-d_6)



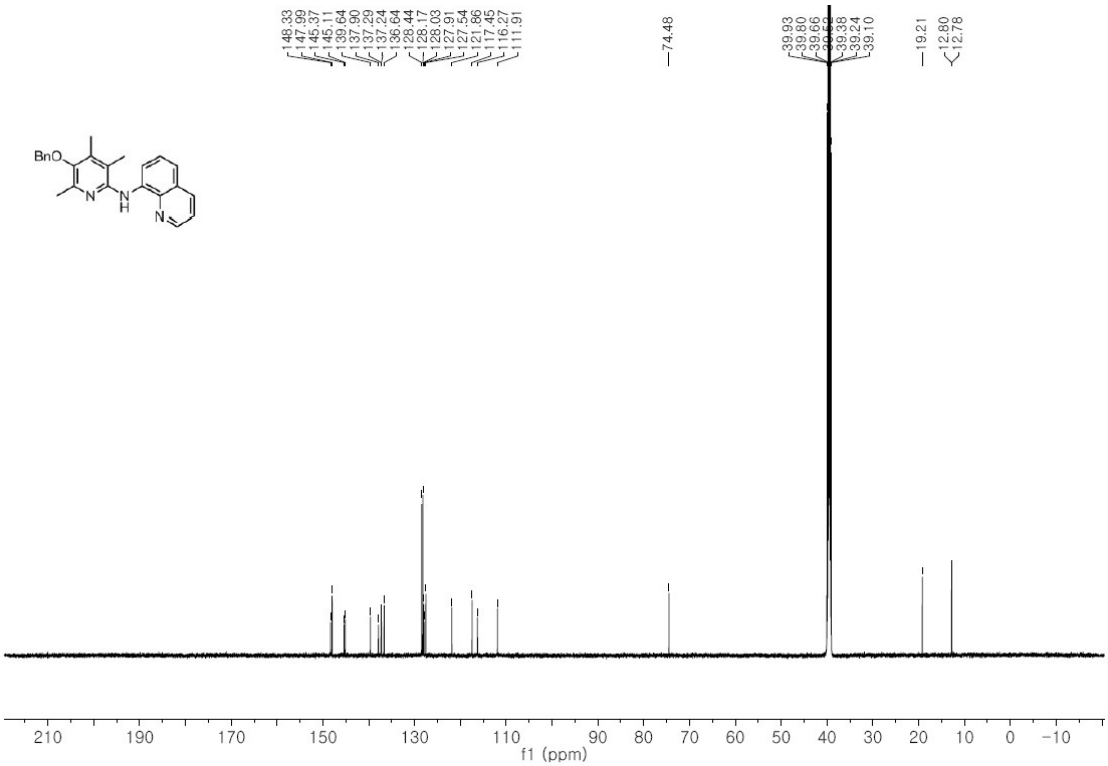
^{1}H-NMR of **5h** (DMSO-d_6)



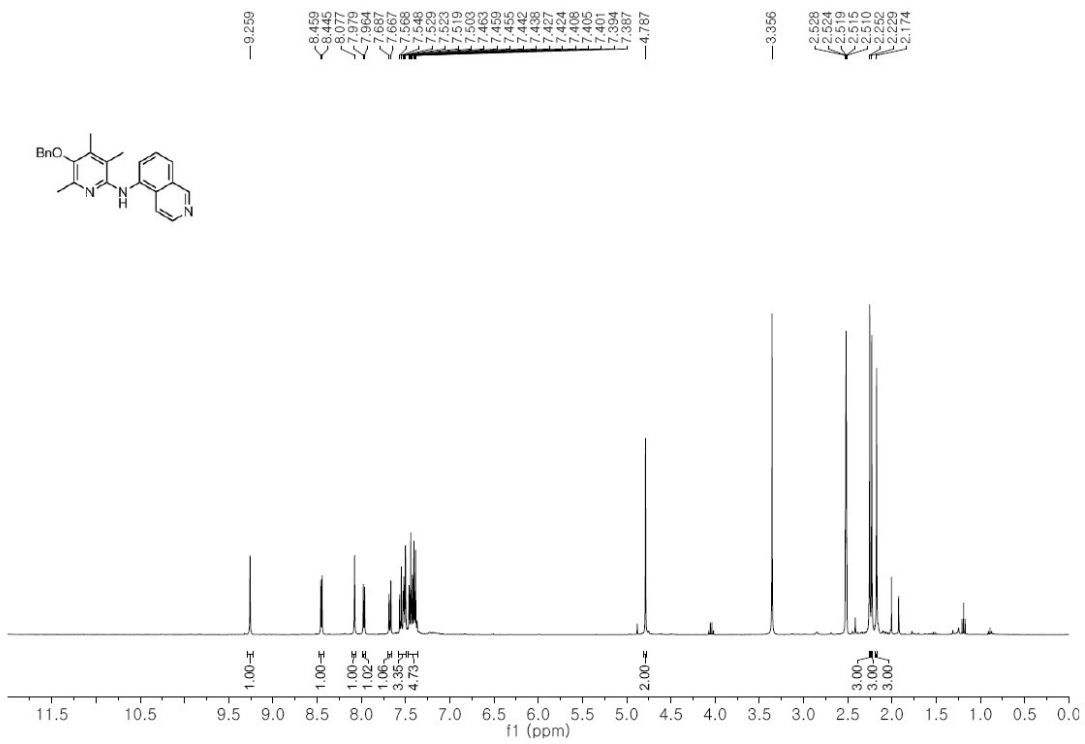
^{13}C-NMR of **5h** (DMSO-d_6)



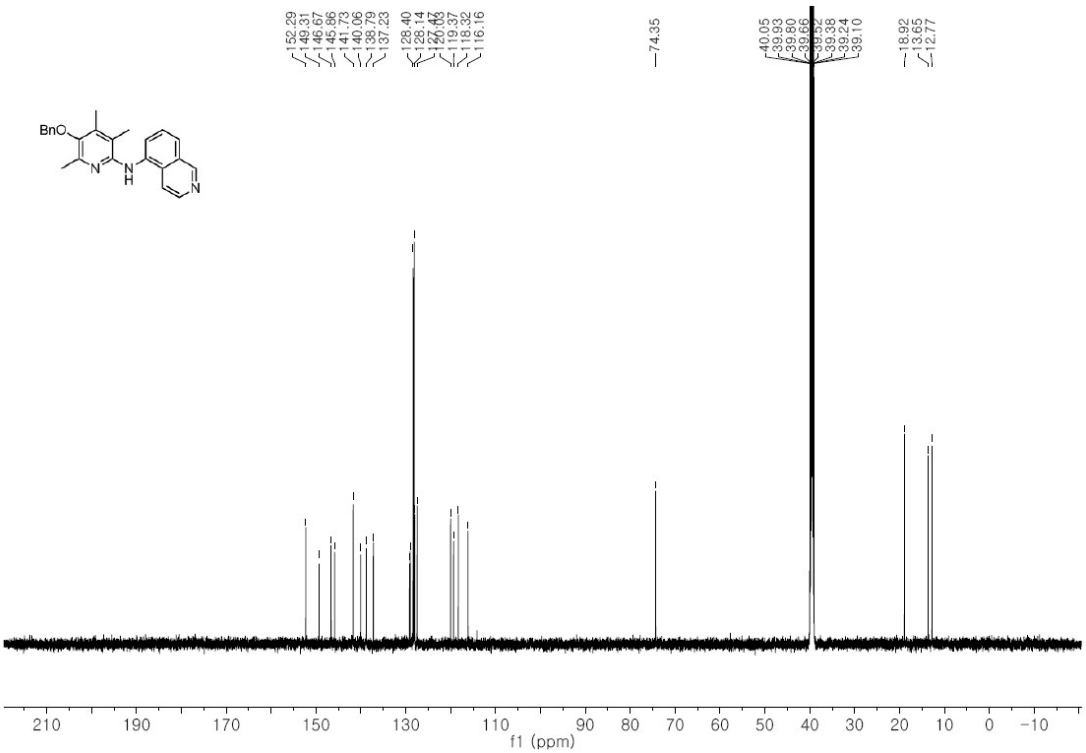
^{1}H-NMR of **5i** (DMSO-d_6)



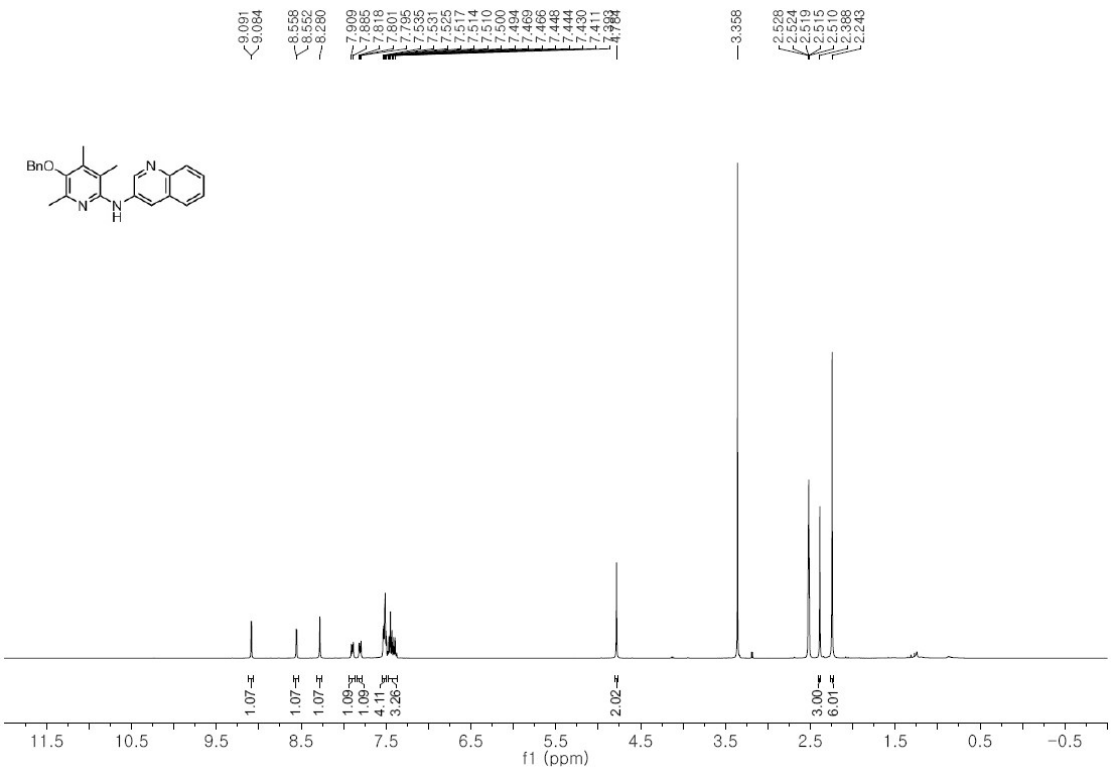
^{13}C-NMR of **5i** (DMSO-d_6)



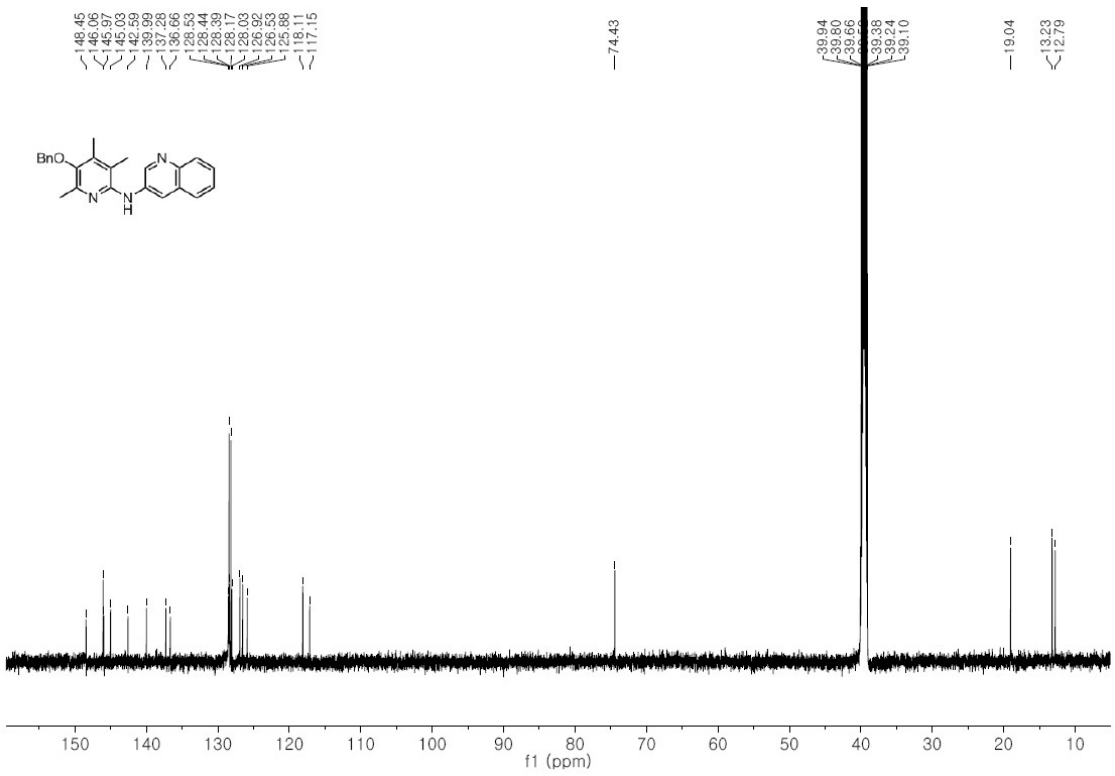
^{1}H-NMR of **5j** (DMSO-d_6)



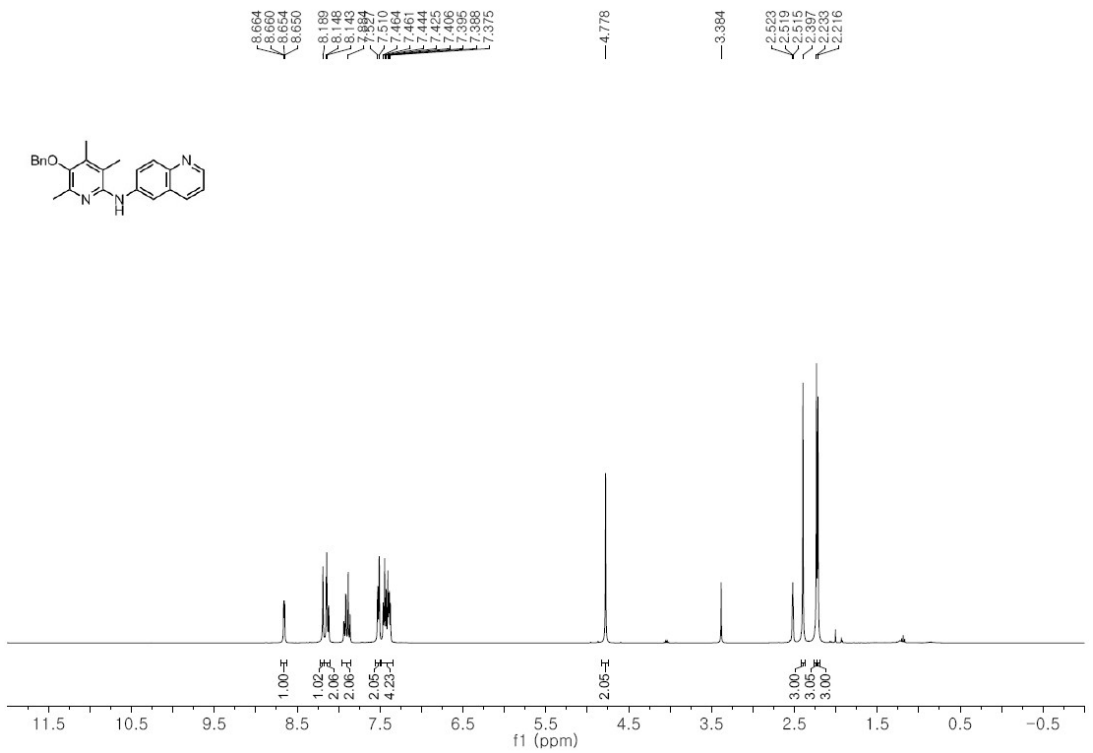
^{13}C-NMR of **5j** (DMSO-d_6)



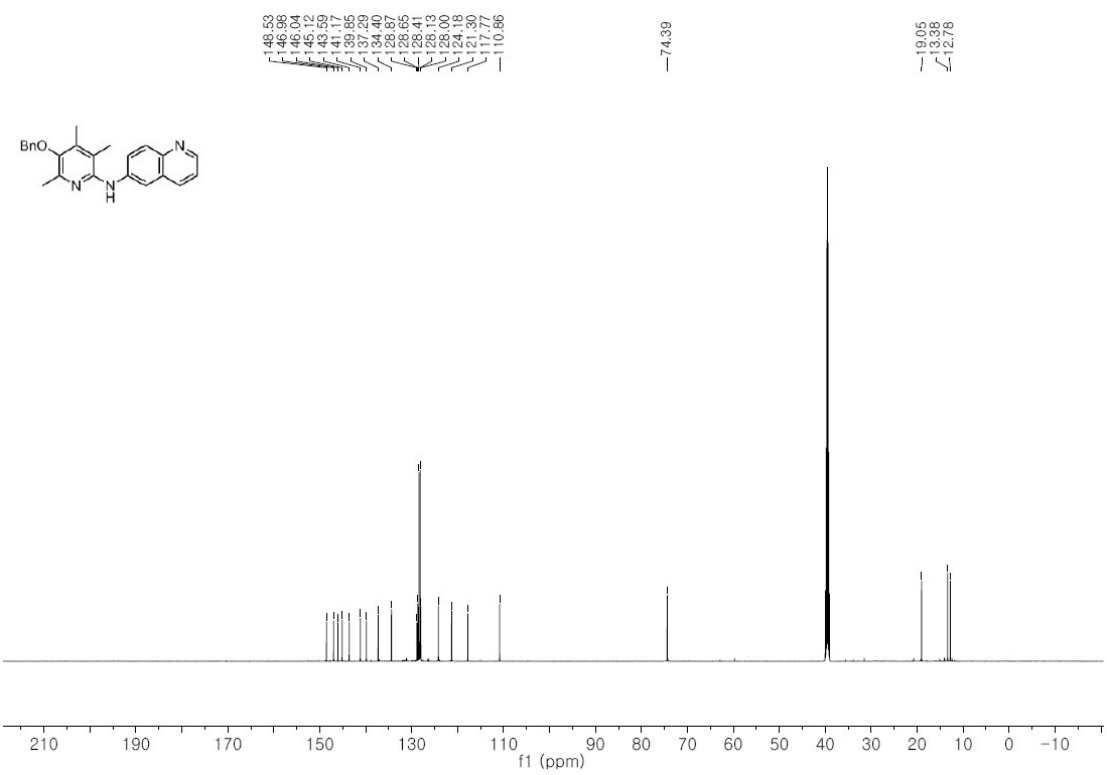
^{1}H-NMR of **5k** (DMSO-d_6)



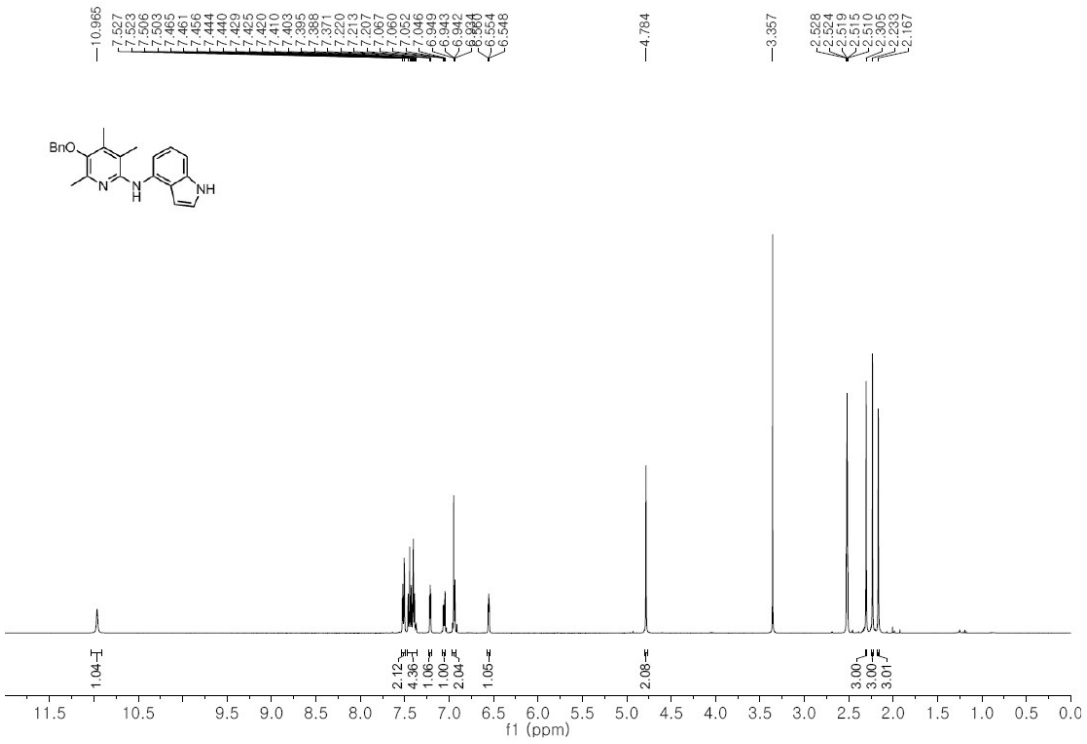
^{13}C-NMR of **5k** (DMSO-d_6)



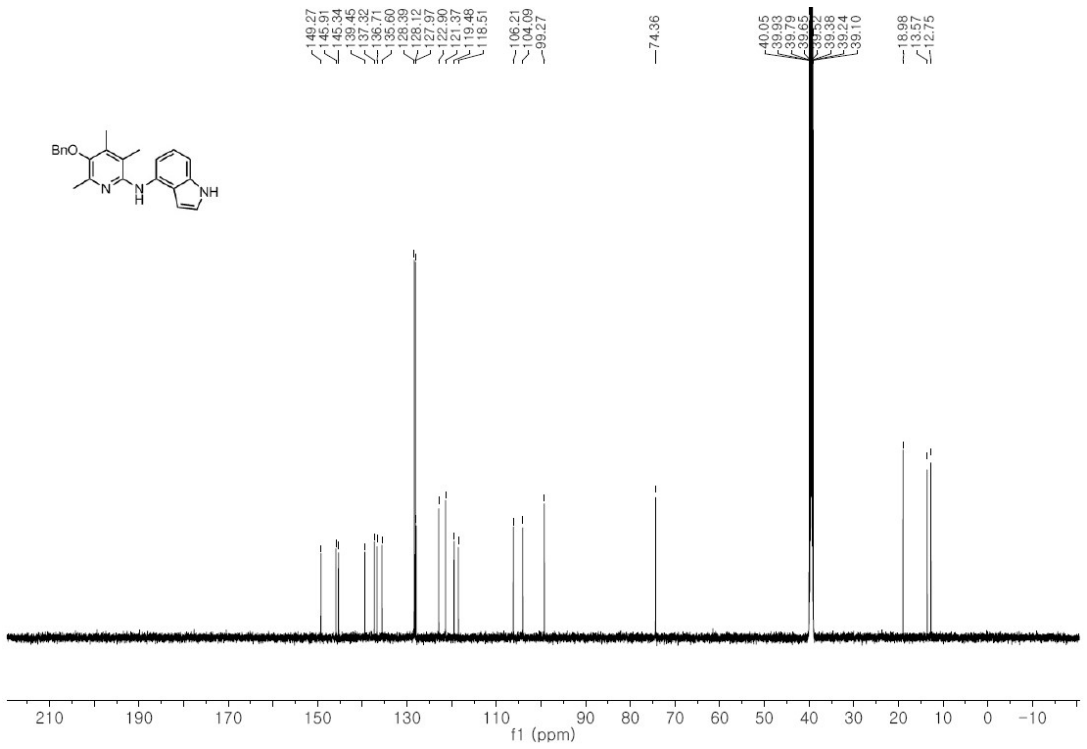
^{1}H-NMR of **5l** (DMSO-d_6)



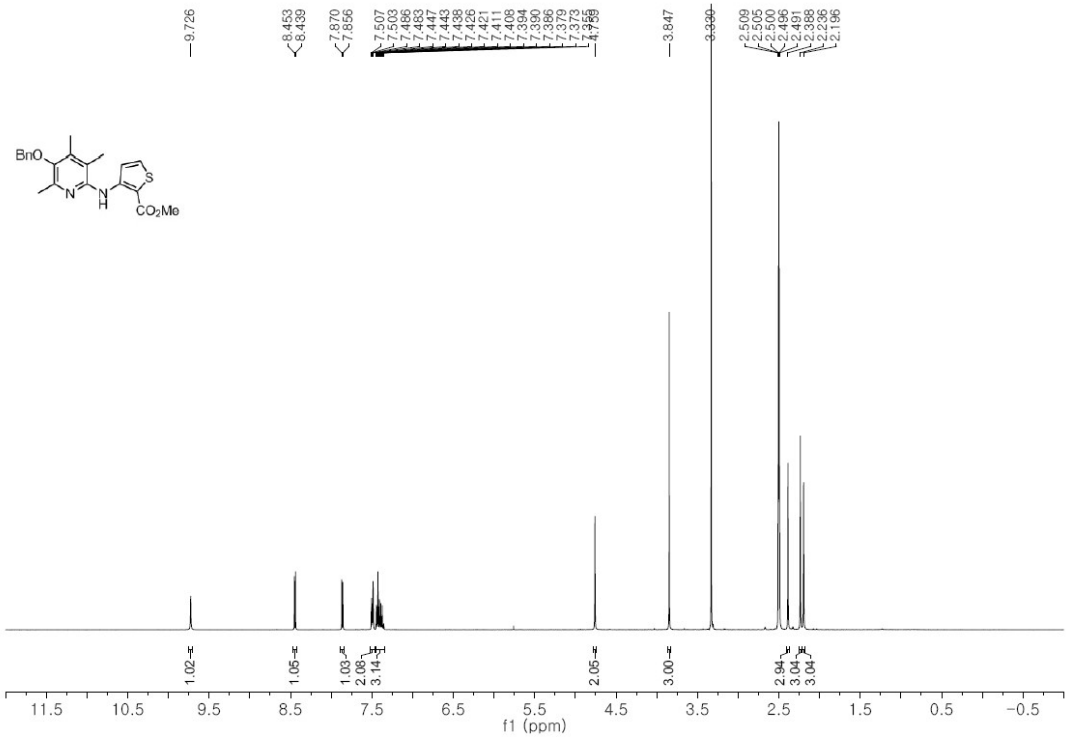
^{13}C-NMR of **5l** (DMSO-d_6)



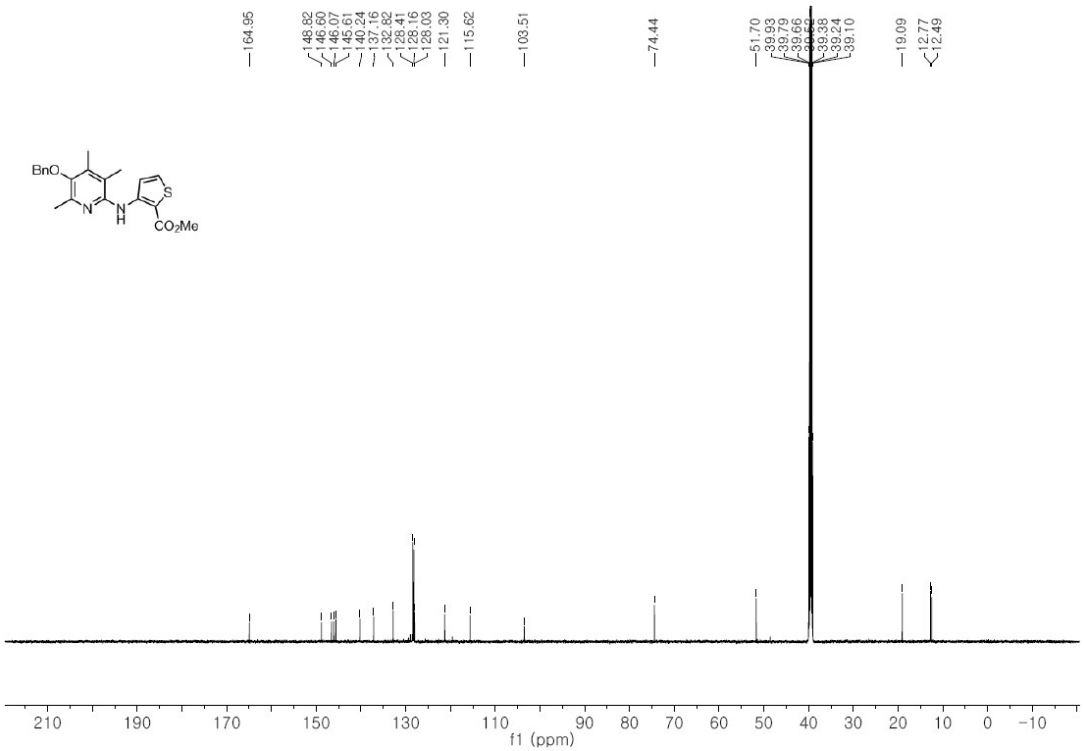
^{1}H-NMR of **5m** (DMSO-d_6)



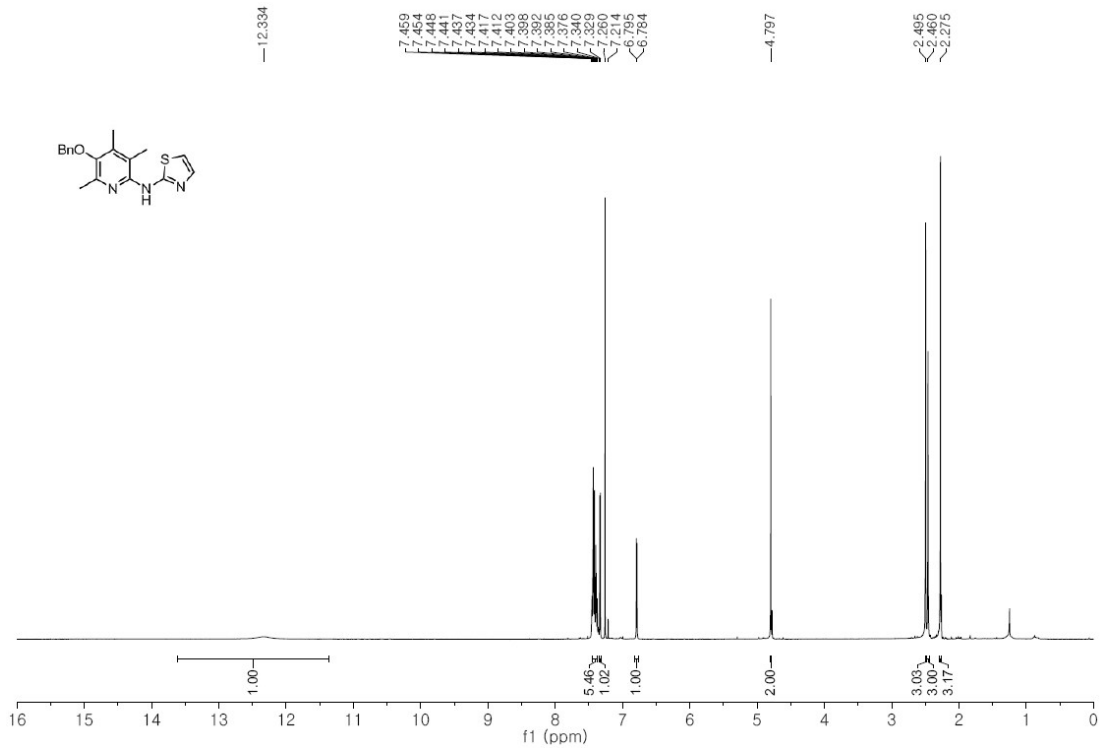
^{13}C-NMR of **5m** (DMSO-d_6)



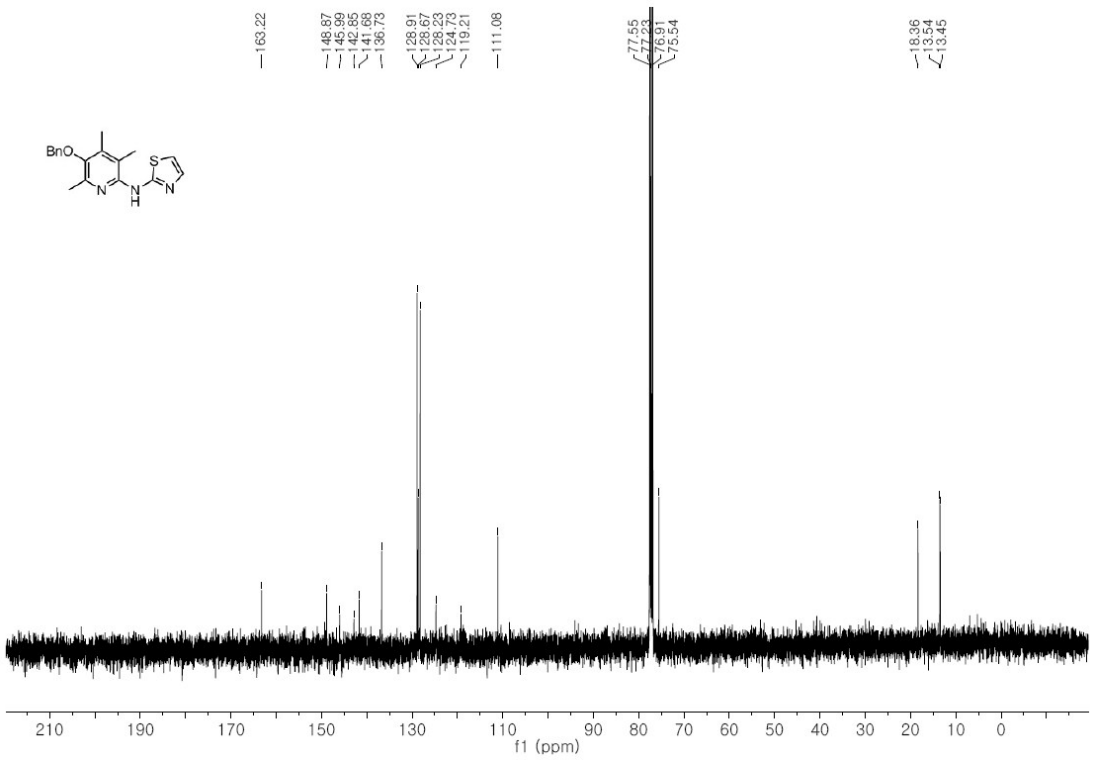
^{1}H-NMR of **5n** (DMSO-d_6)



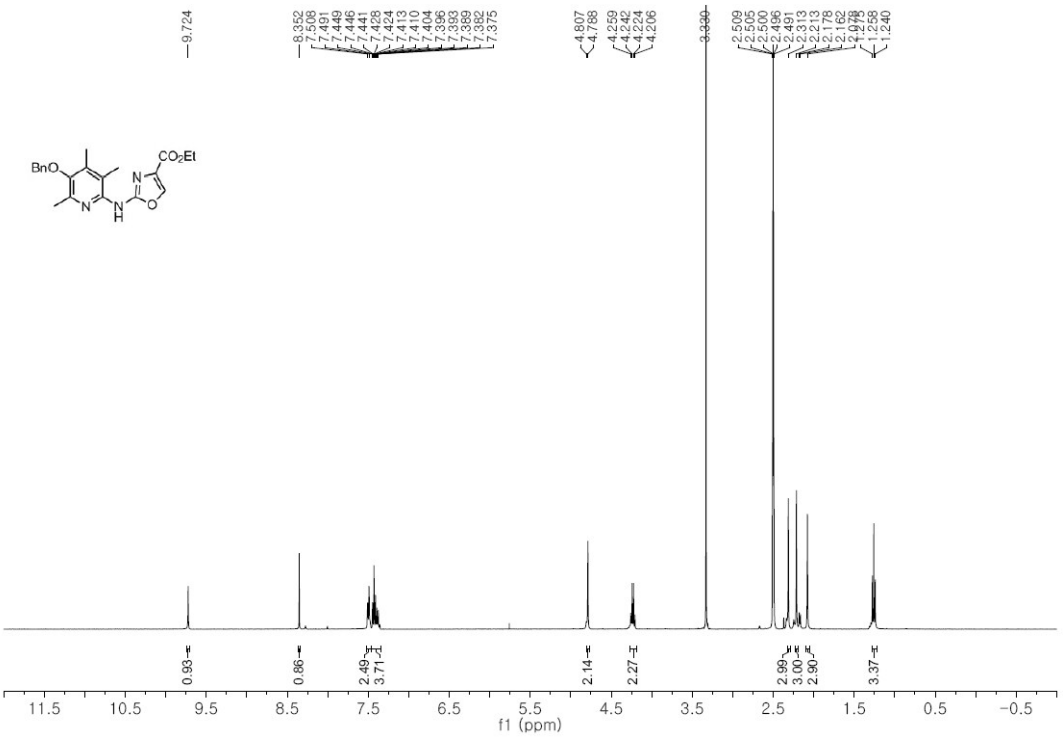
^{13}C-NMR of **5n** (DMSO-d_6)



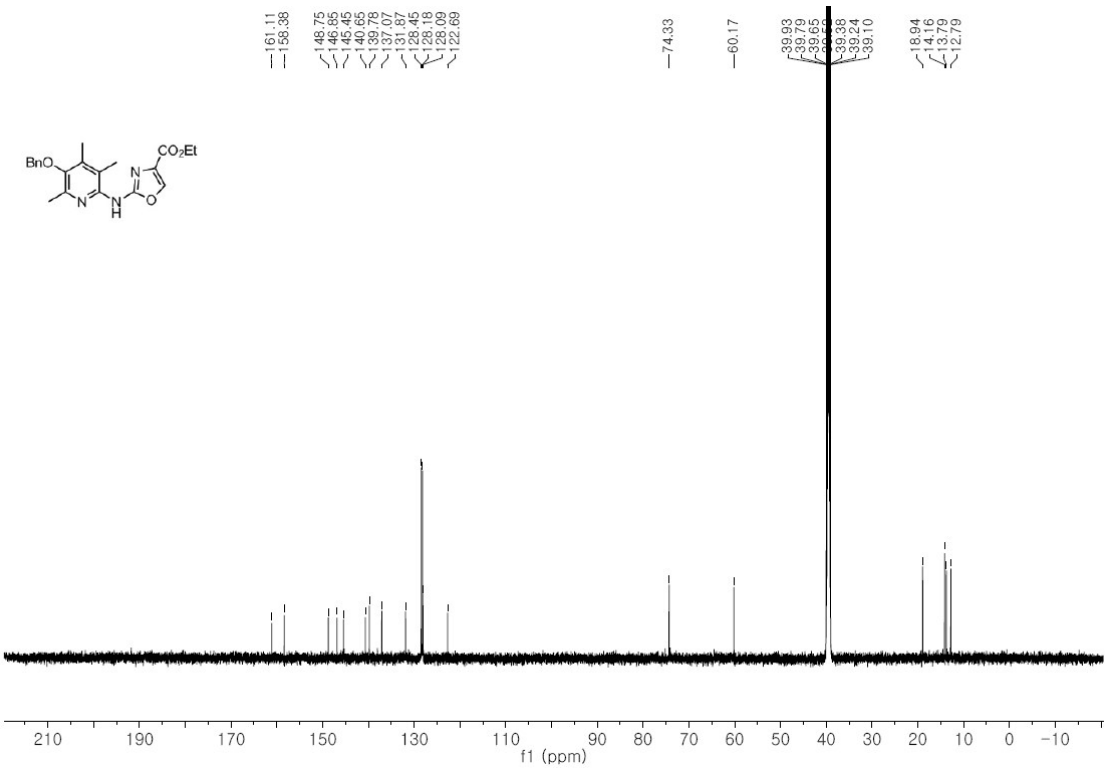
^{1}H-NMR of **5o** ($CDCl_3$)



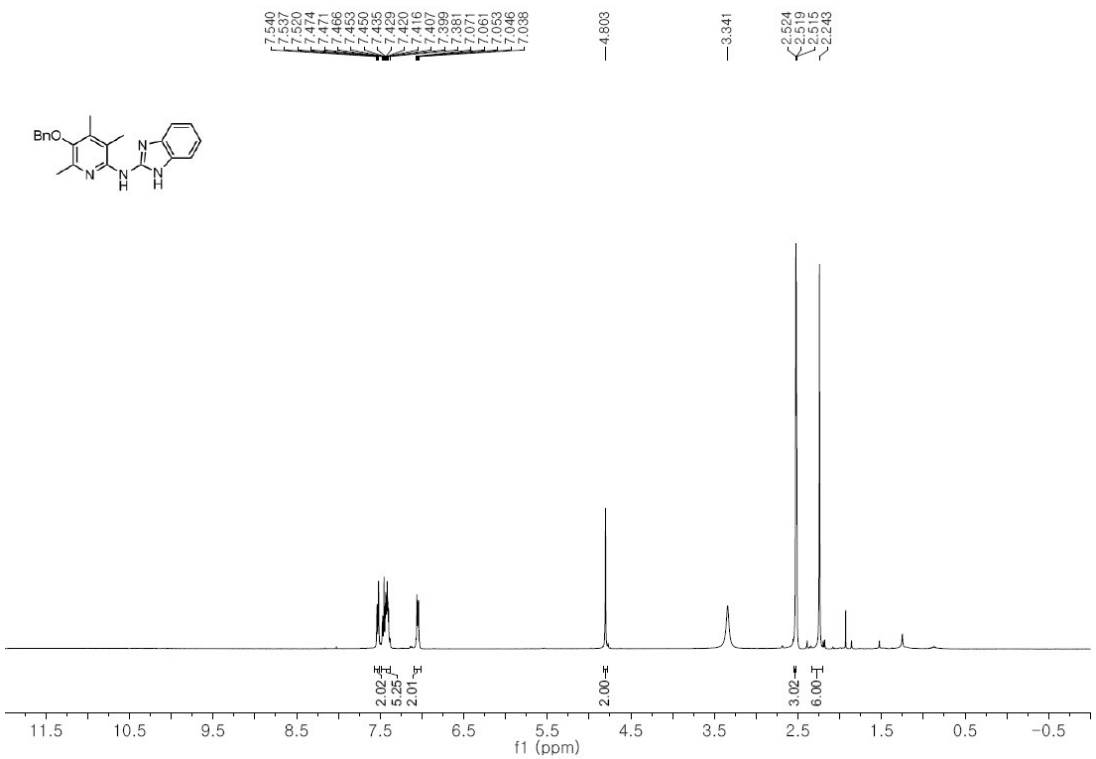
^{13}C-NMR of **5o** ($CDCl_3$)



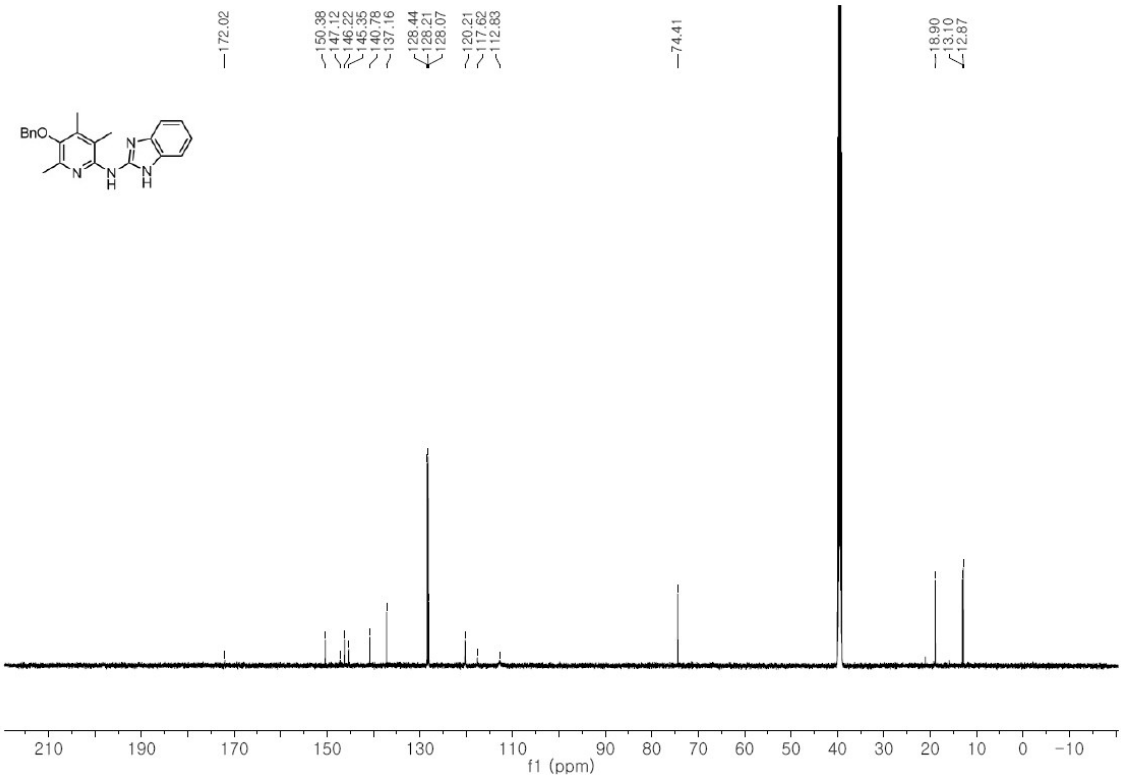
^{1}H-NMR of **5p** (DMSO-d_6)



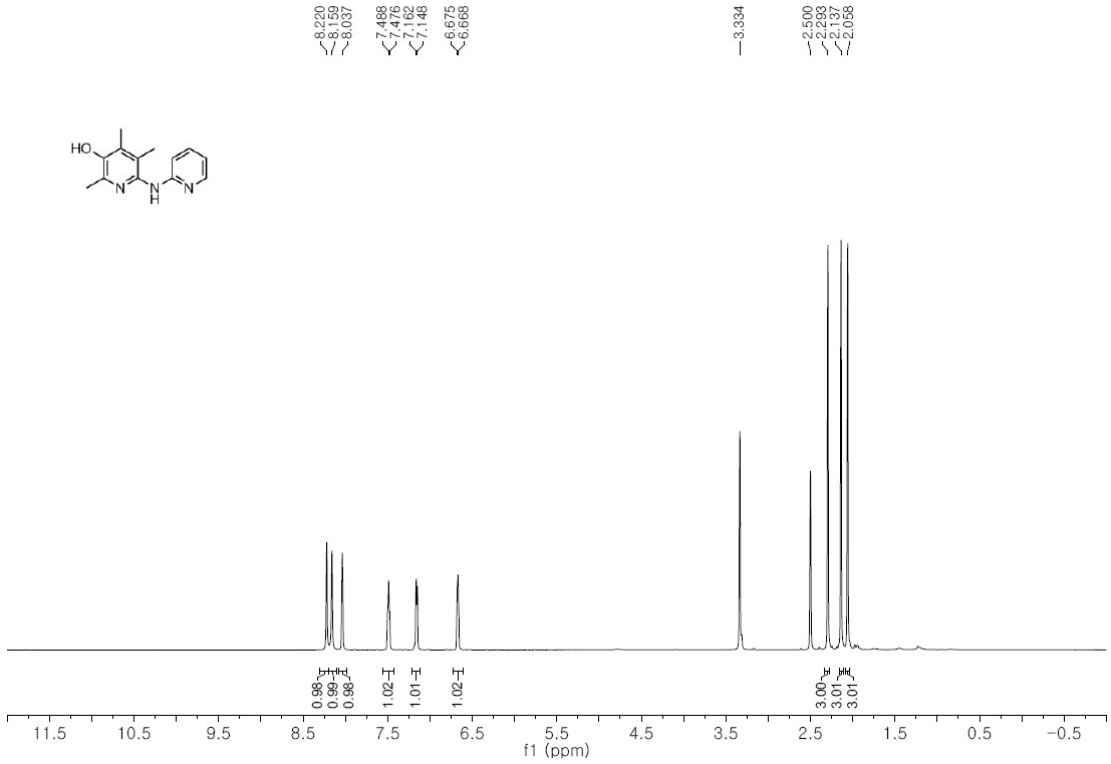
^{13}C-NMR of **5p** (DMSO-d_6)



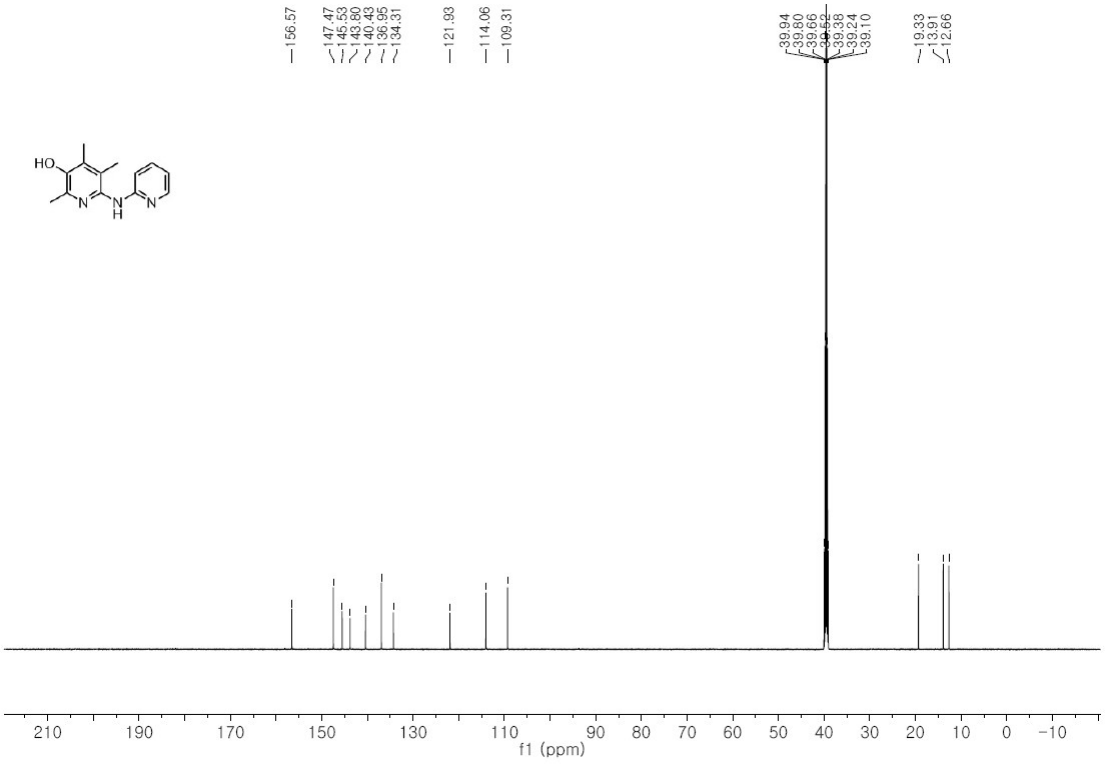
^{1}H-NMR of **5q** (DMSO-d_6)



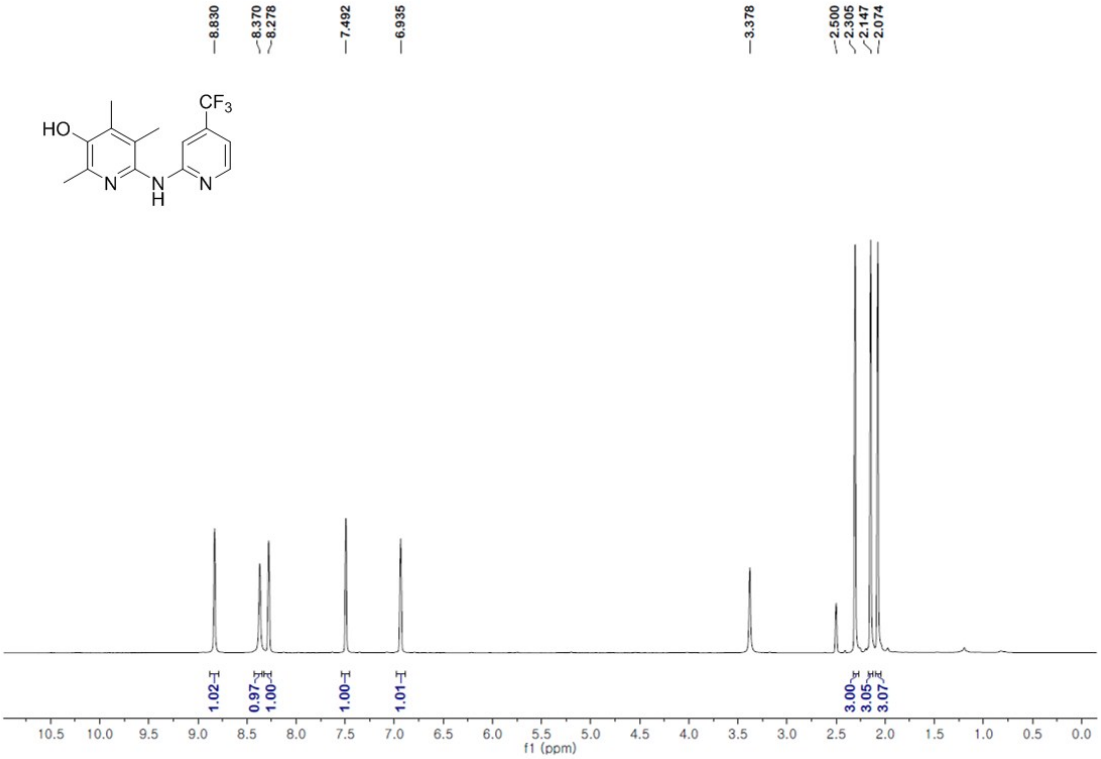
^{13}C-NMR of **5q** (DMSO-d_6)



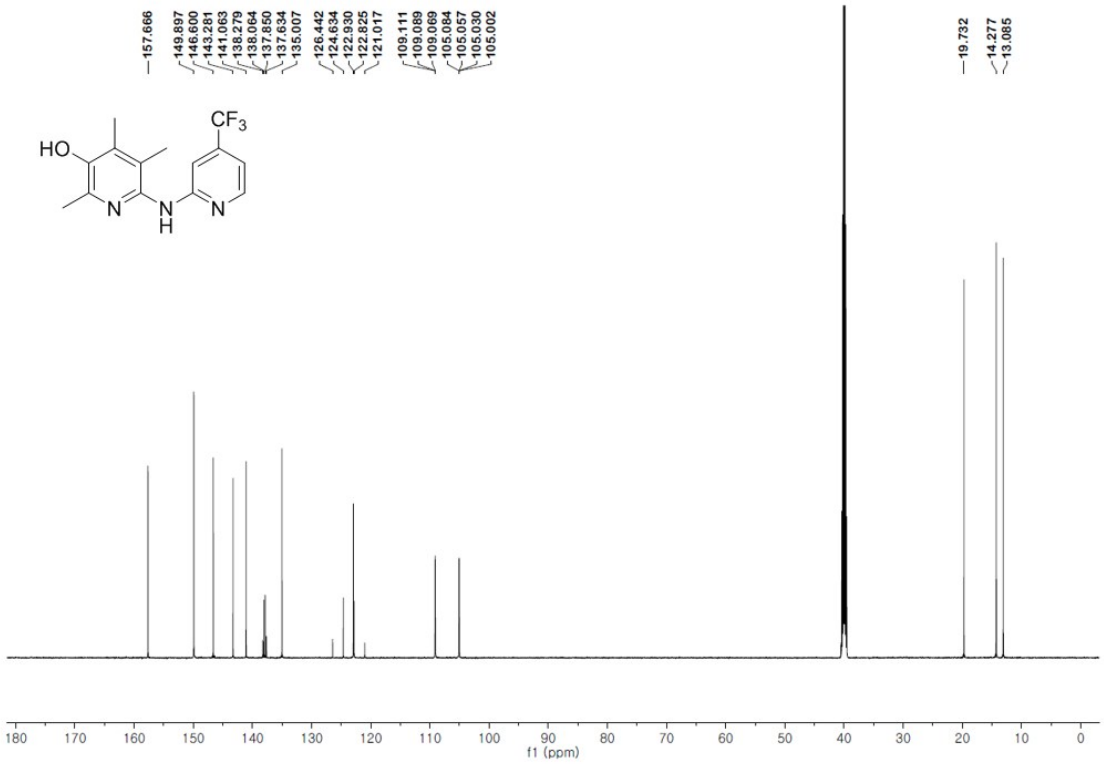
^{1}H-NMR of **6a** (DMSO-d_6)



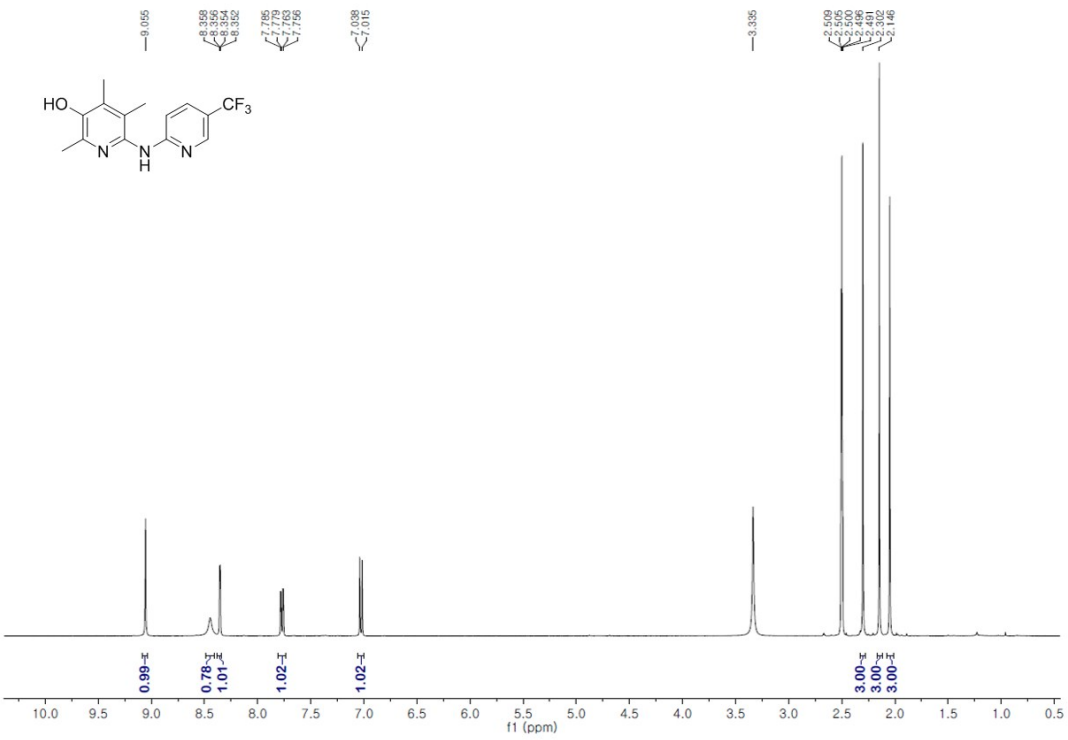
^{13}C-NMR of **6a** (DMSO-d_6)



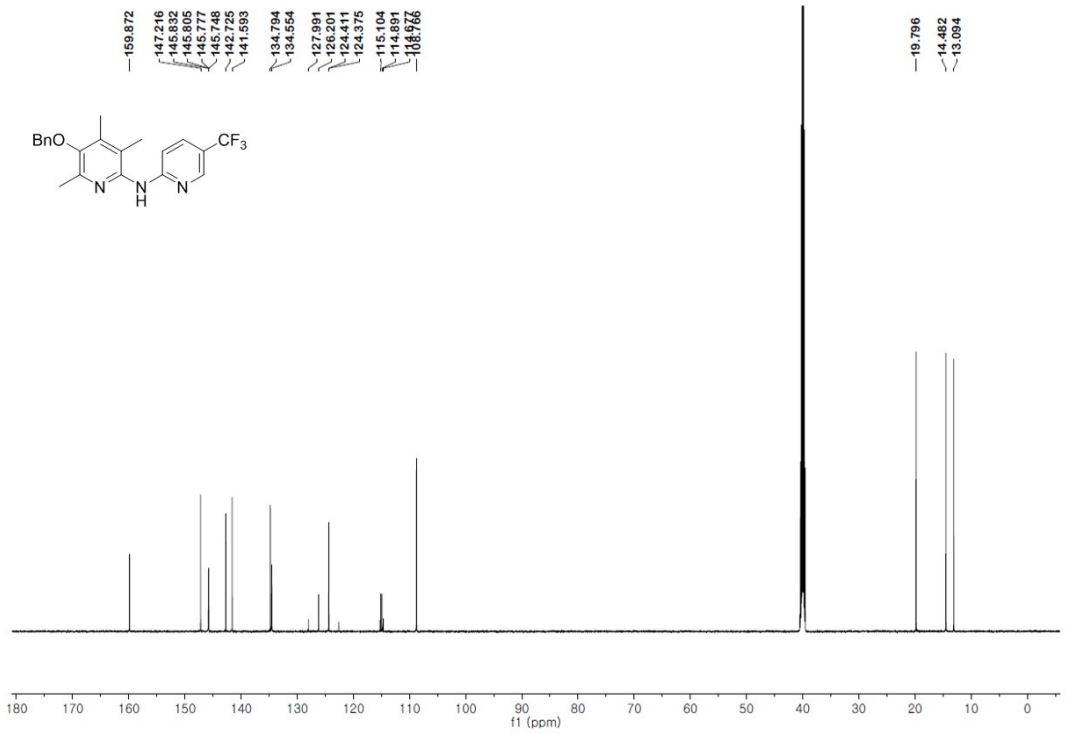
^{1}H-NMR of **6b** (DMSO-d_6)



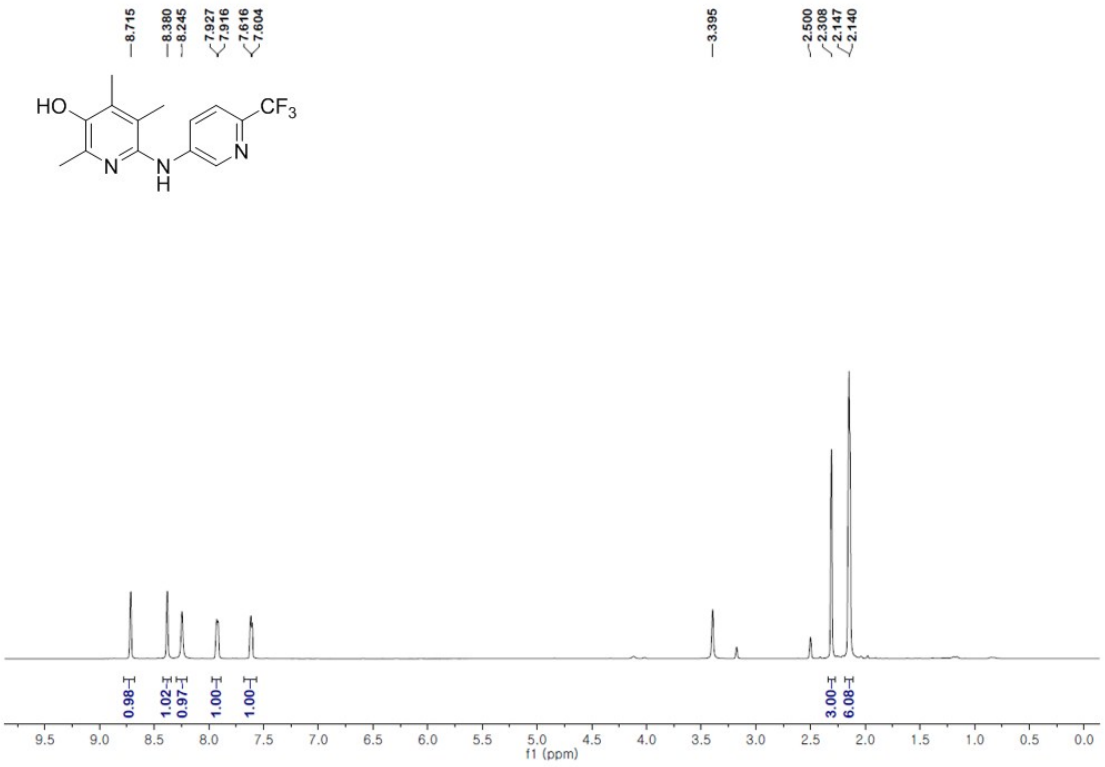
^{13}C-NMR of **6b** (DMSO-d_6)



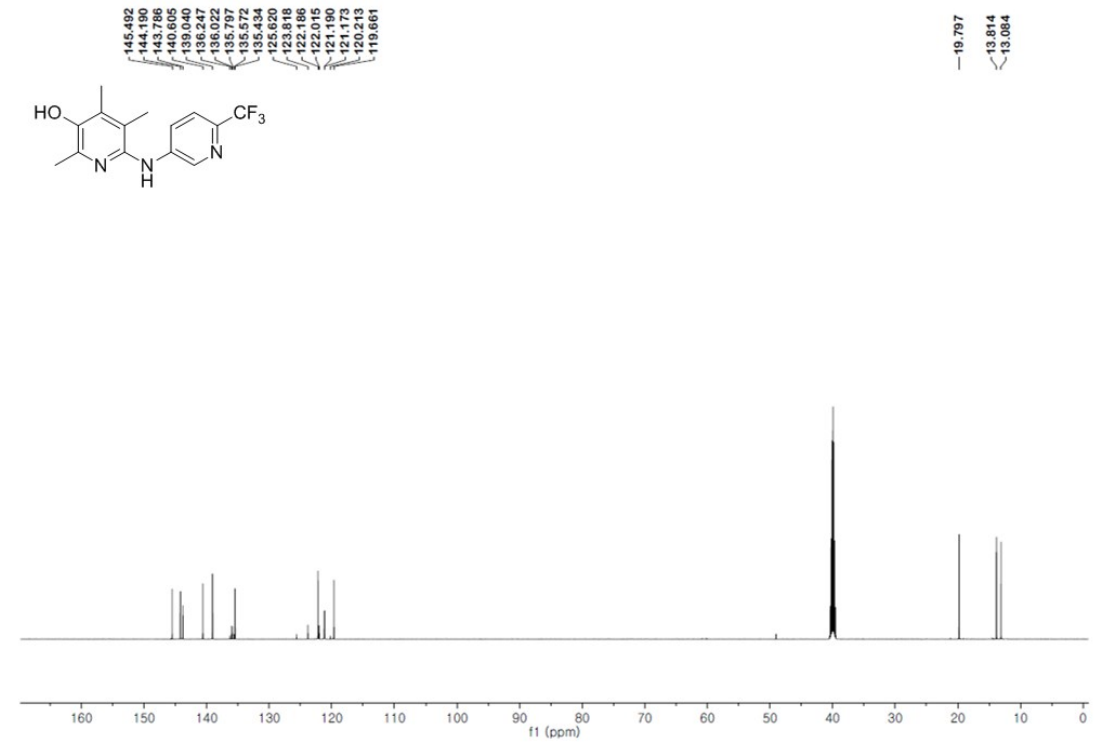
^{1}H-NMR of **6c** (DMSO-d_6)



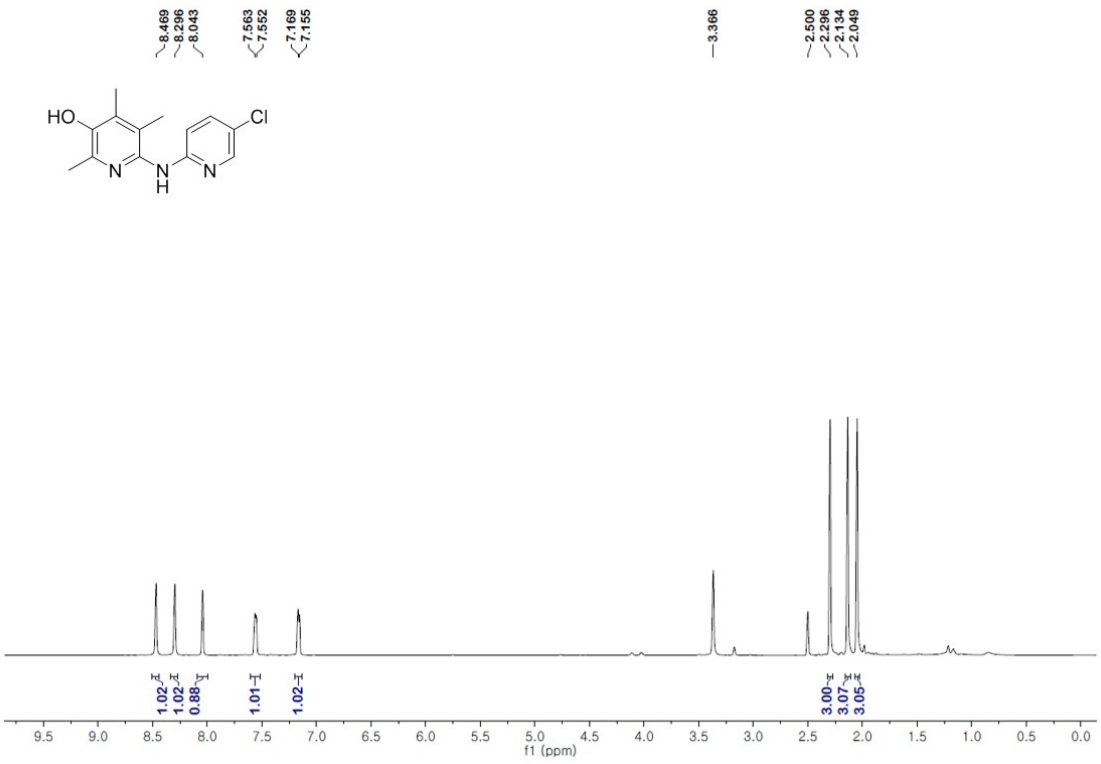
^{13}C-NMR of **6c** (DMSO-d_6)



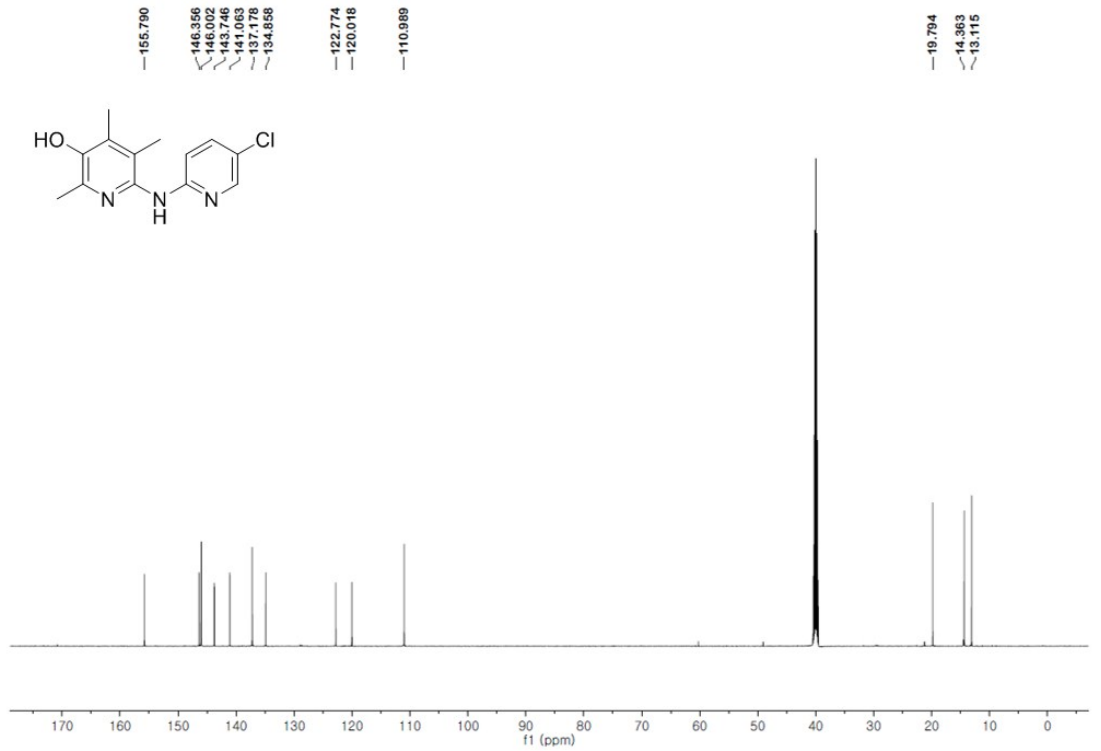
^{1}H-NMR of **6d** (DMSO-d_6)



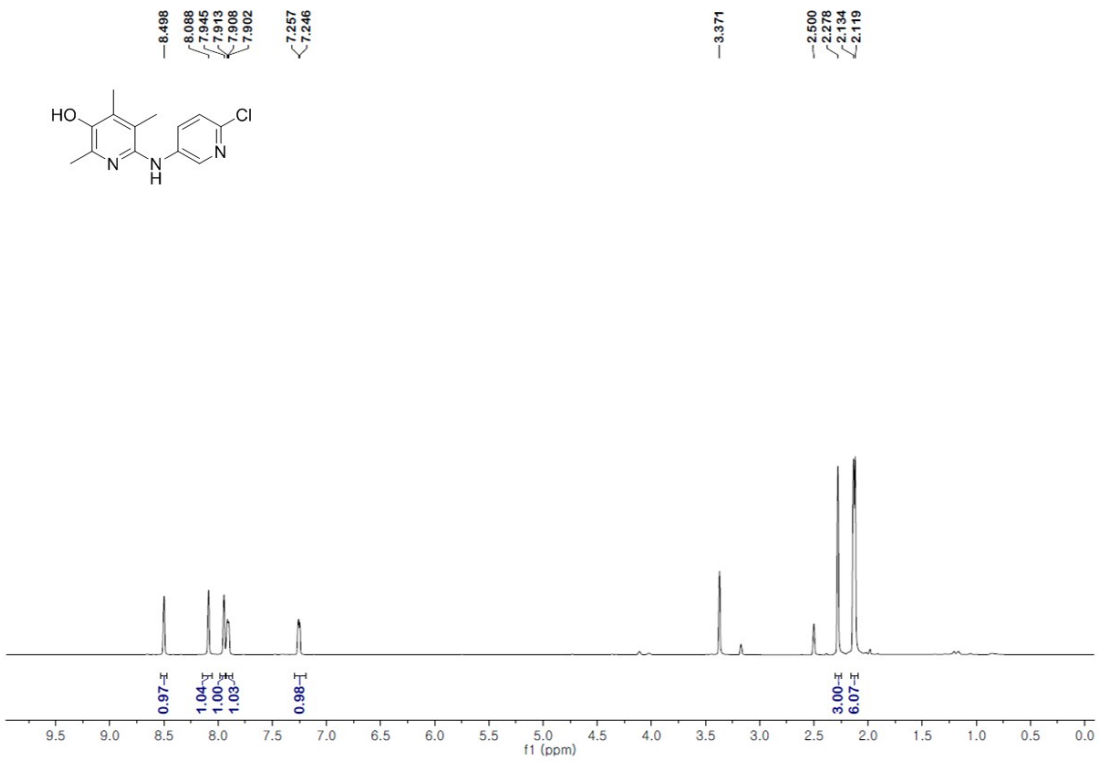
^{13}C-NMR of **6d** (DMSO-d_6)



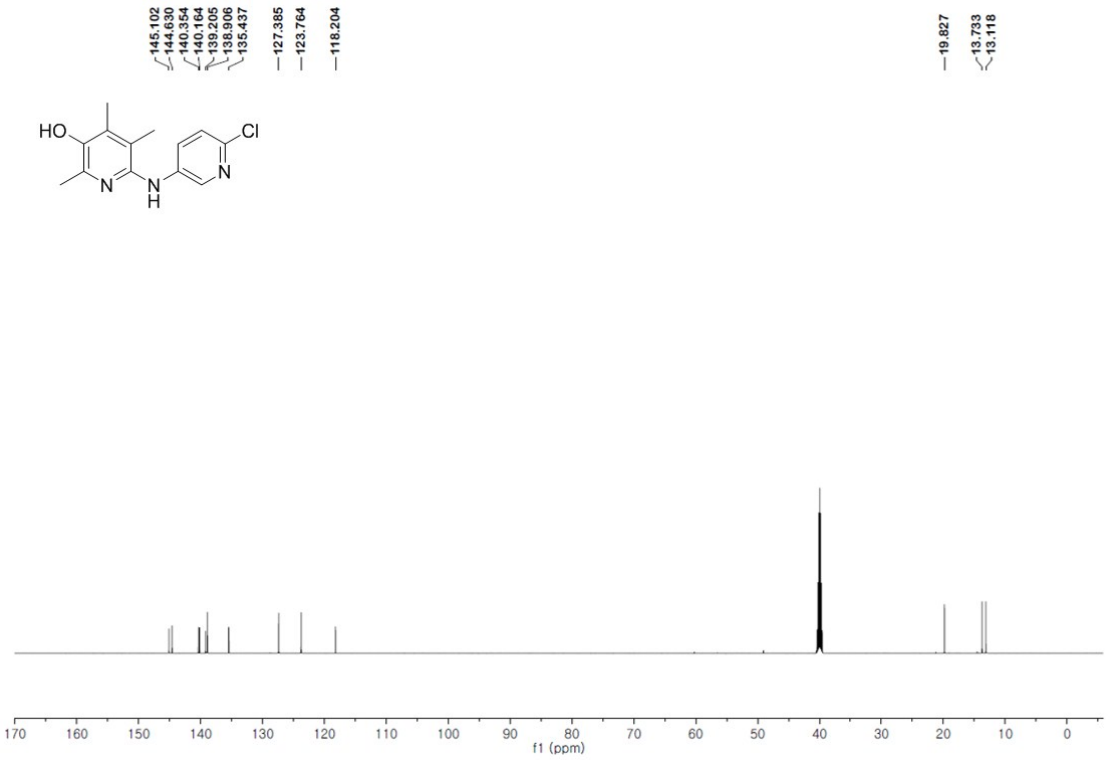
^{1}H-NMR of **6e** (DMSO-d_6)



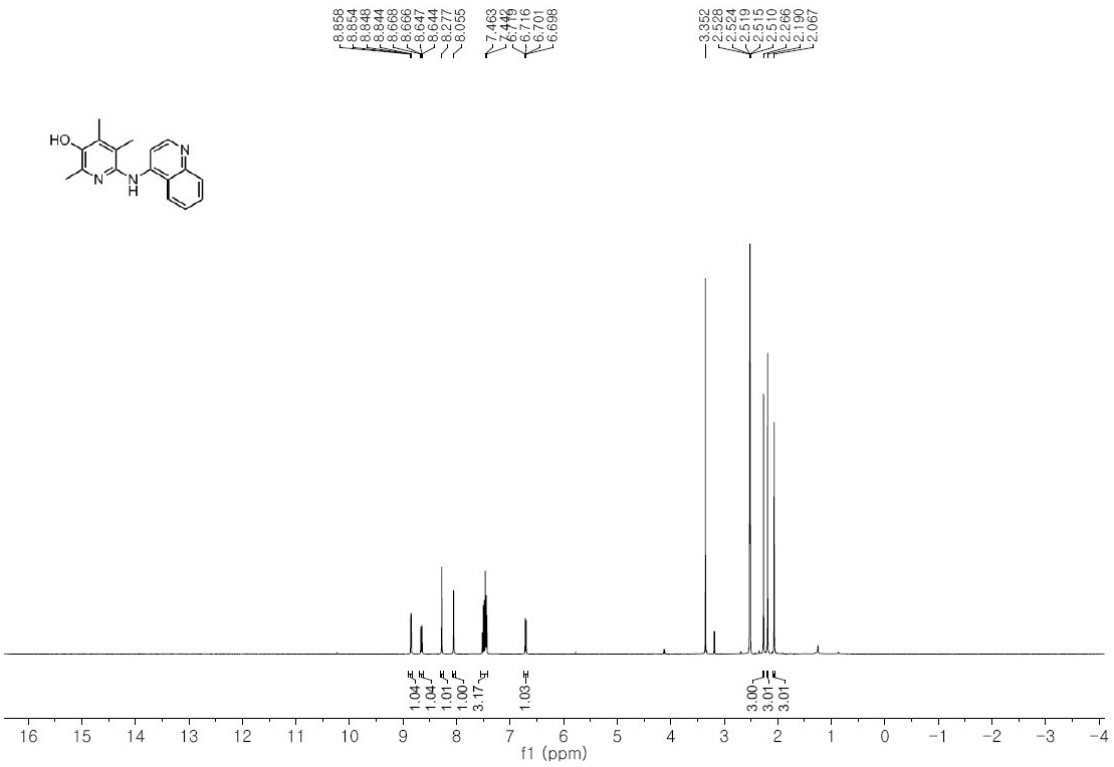
^{13}C-NMR of **6e** (DMSO-d_6)



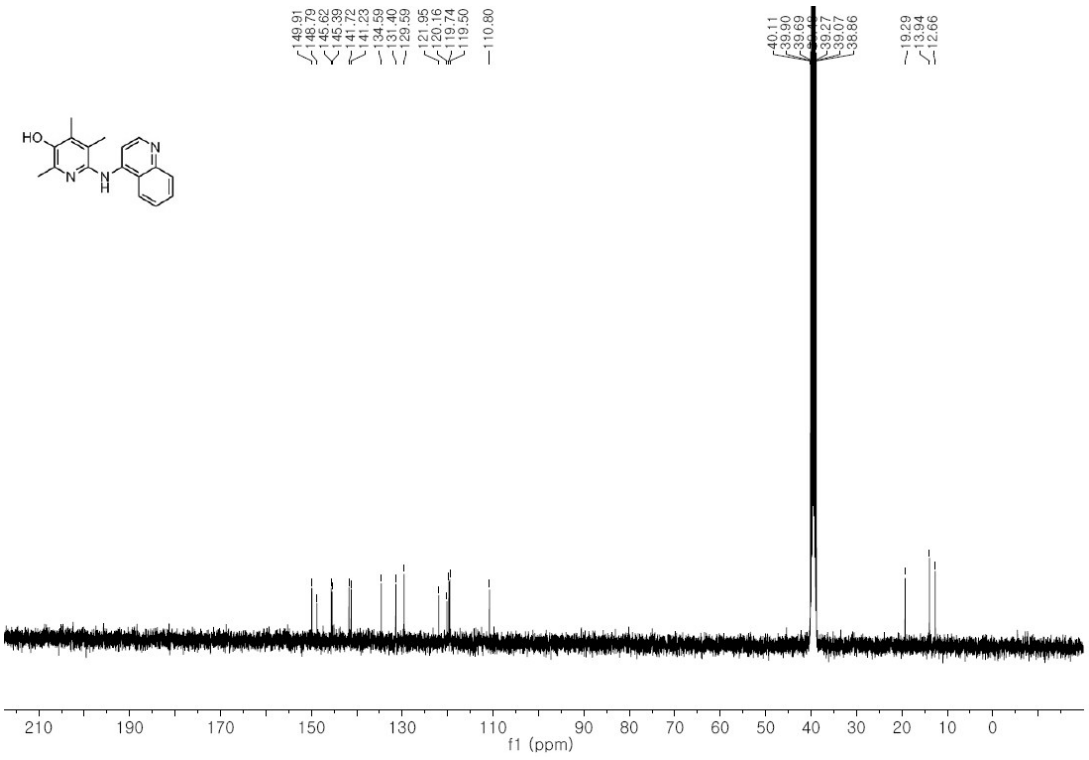
^{1}H-NMR of **6f** (DMSO-d_6)



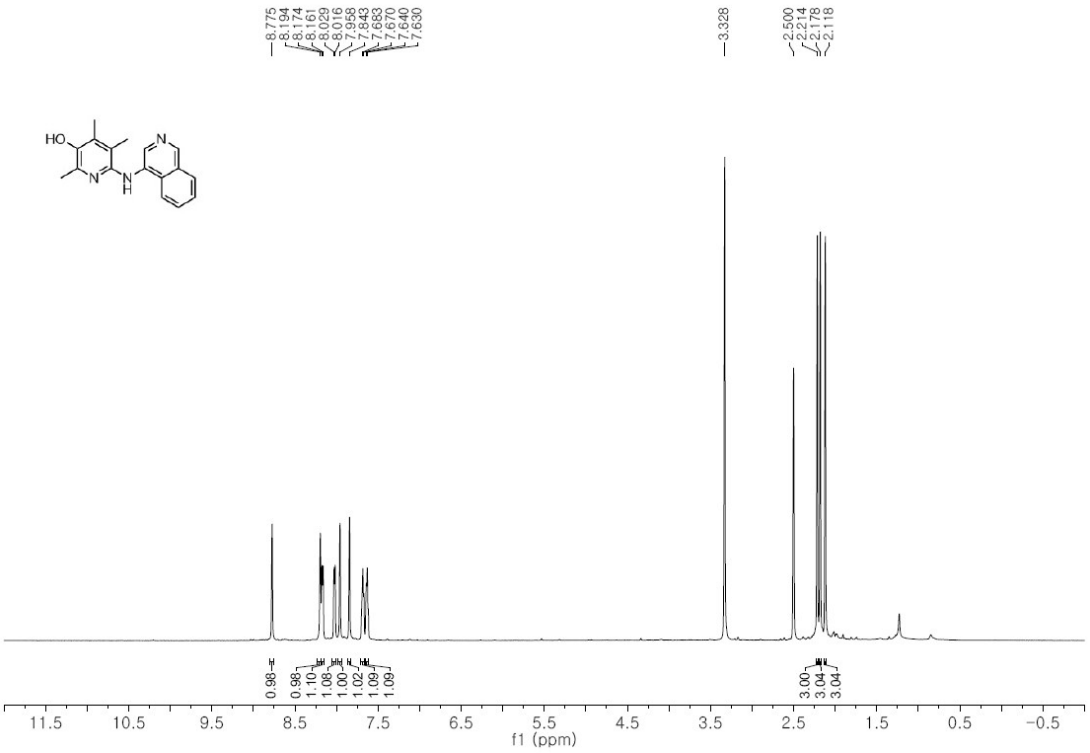
^{13}C-NMR of **6f** (DMSO-d_6)



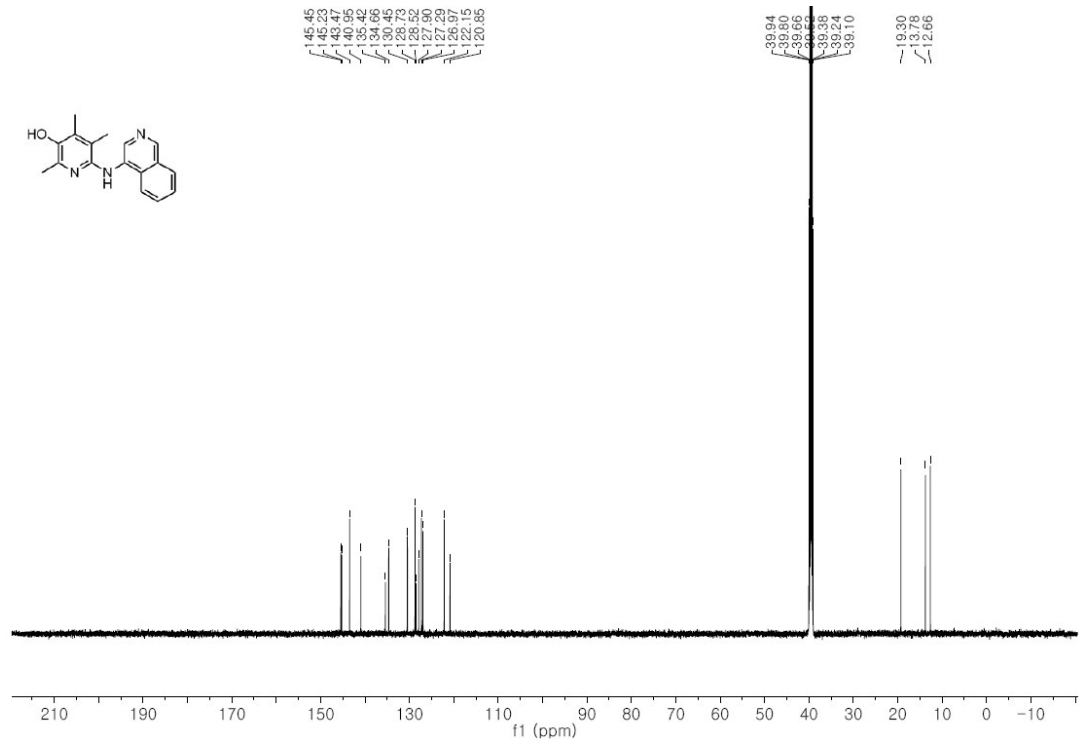
^{1}H-NMR of **6g** (DMSO-d_6)



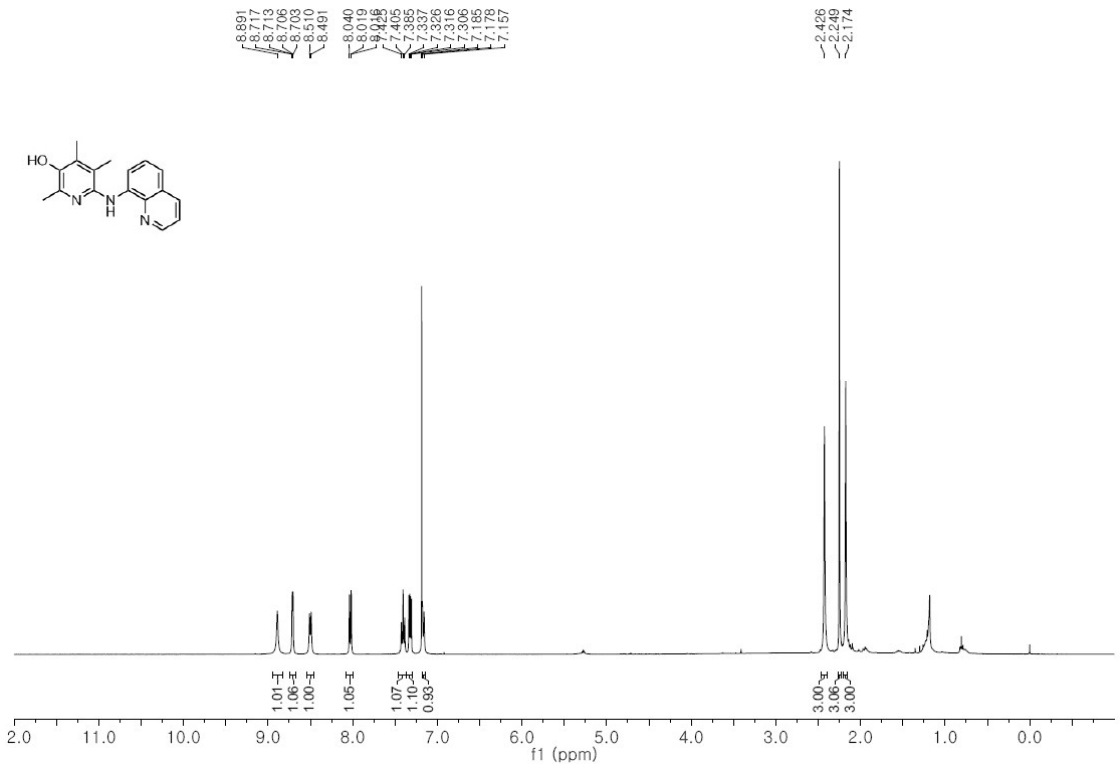
^{13}C-NMR of **6g** (DMSO-d_6)



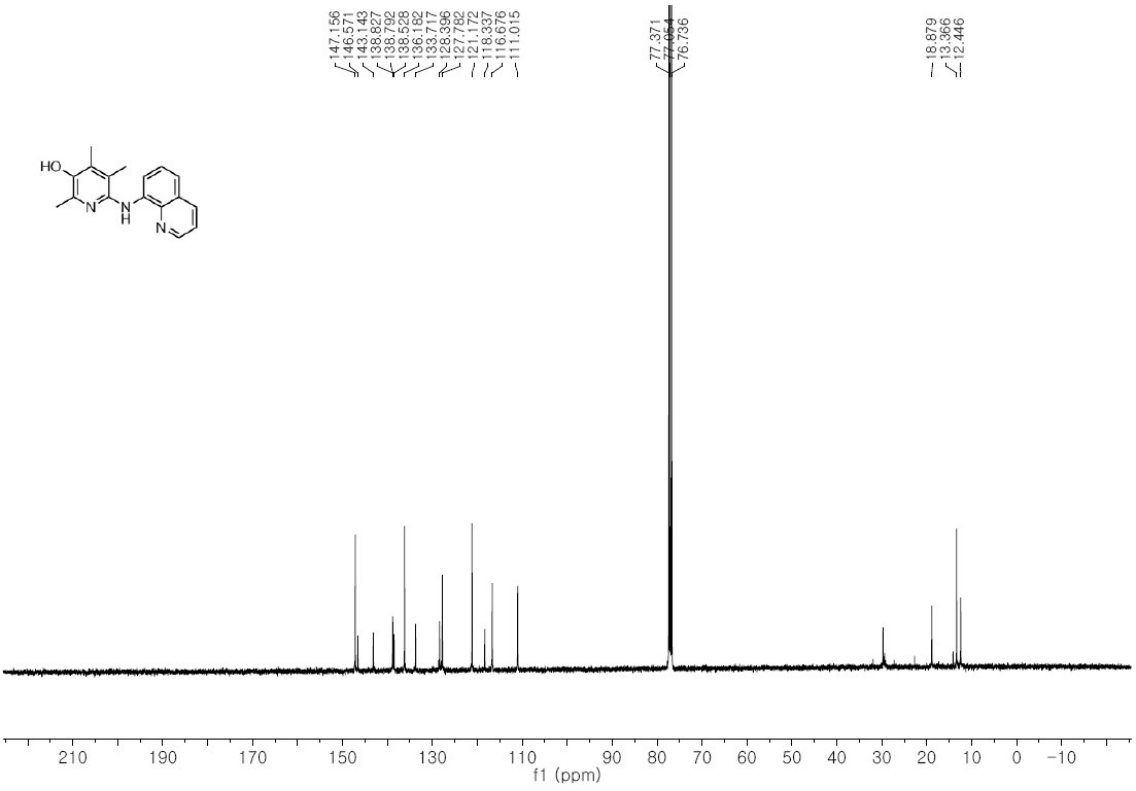
^{1}H-NMR of **6h** (DMSO-d_6)



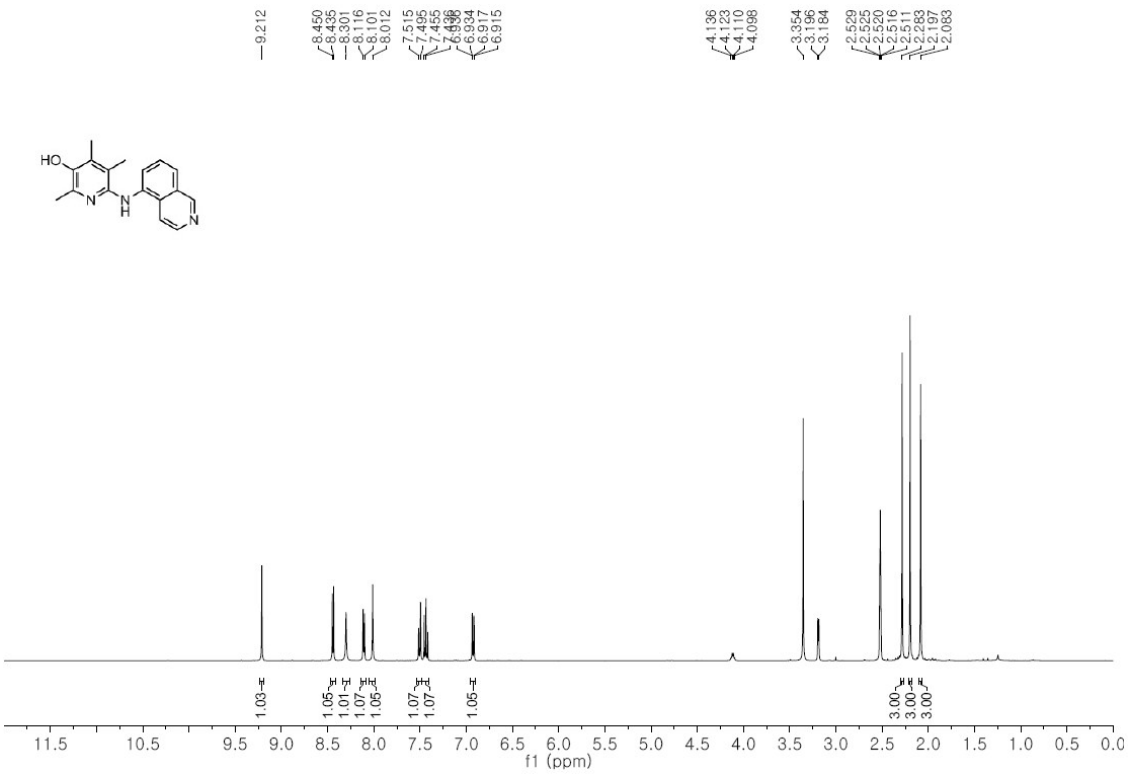
^{13}C-NMR of **6h** (DMSO-d_6)



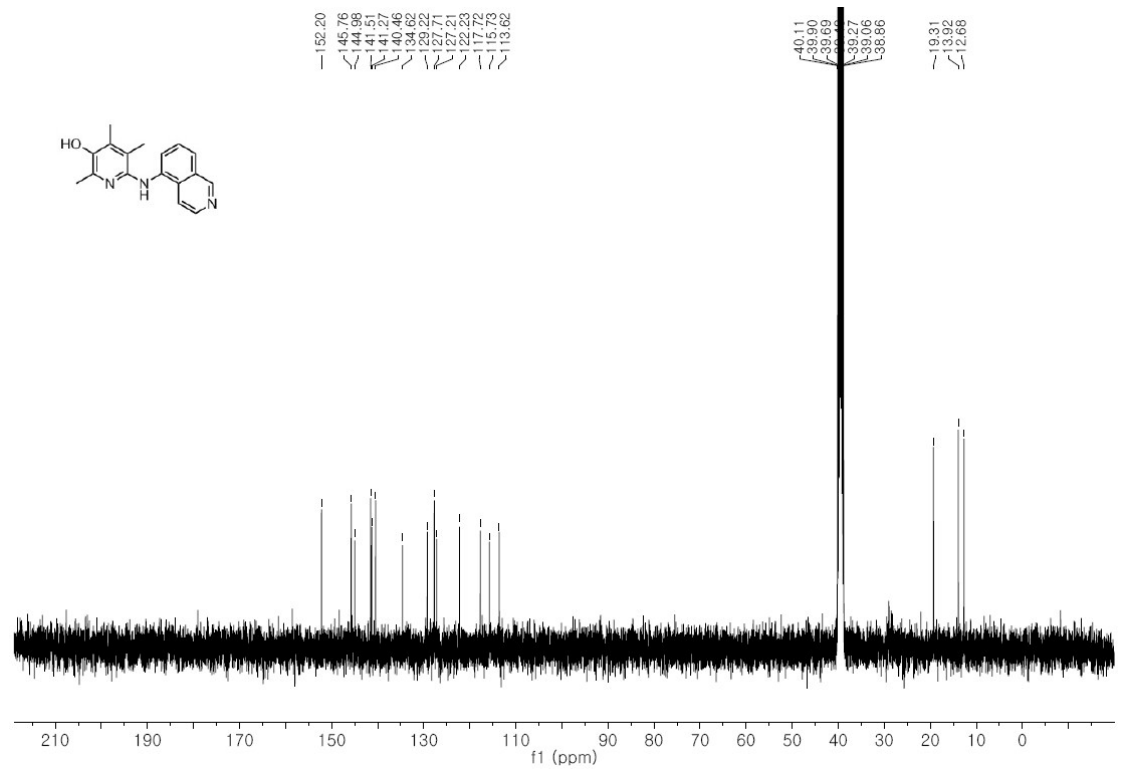
^{1}H-NMR of **6i** ($CDCl_3$)



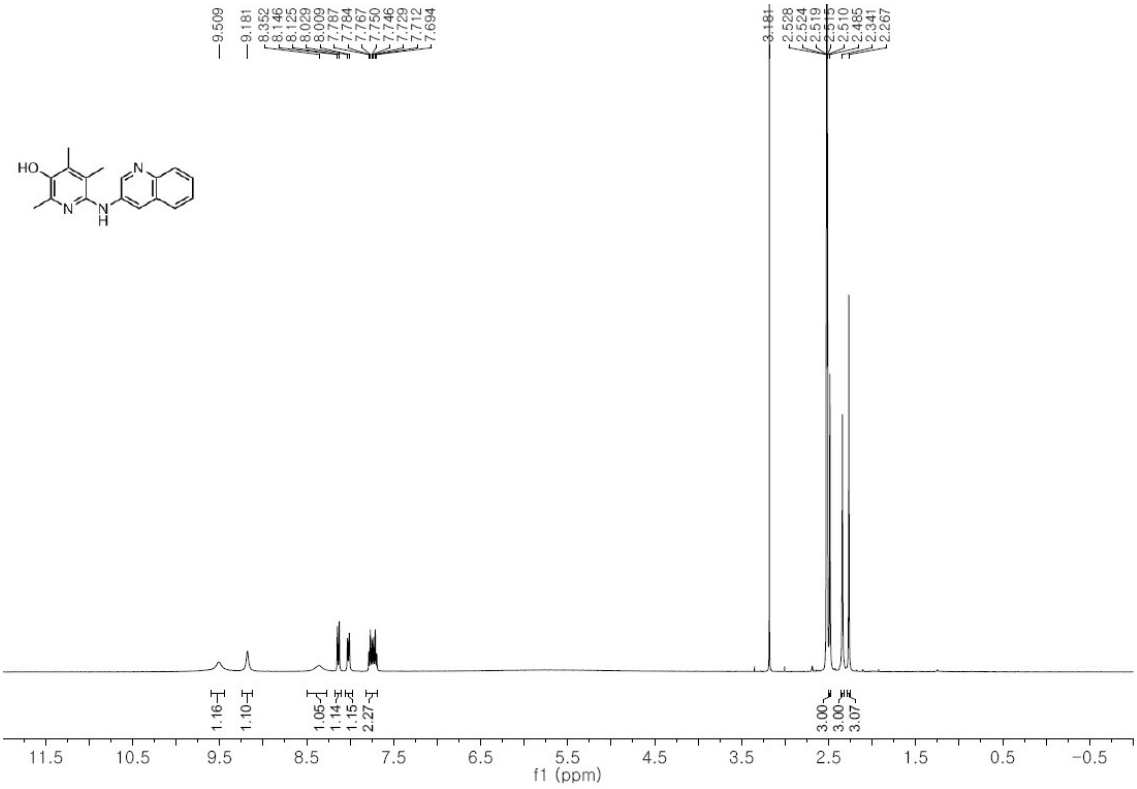
^{13}C-NMR of **6i** ($CDCl_3$)



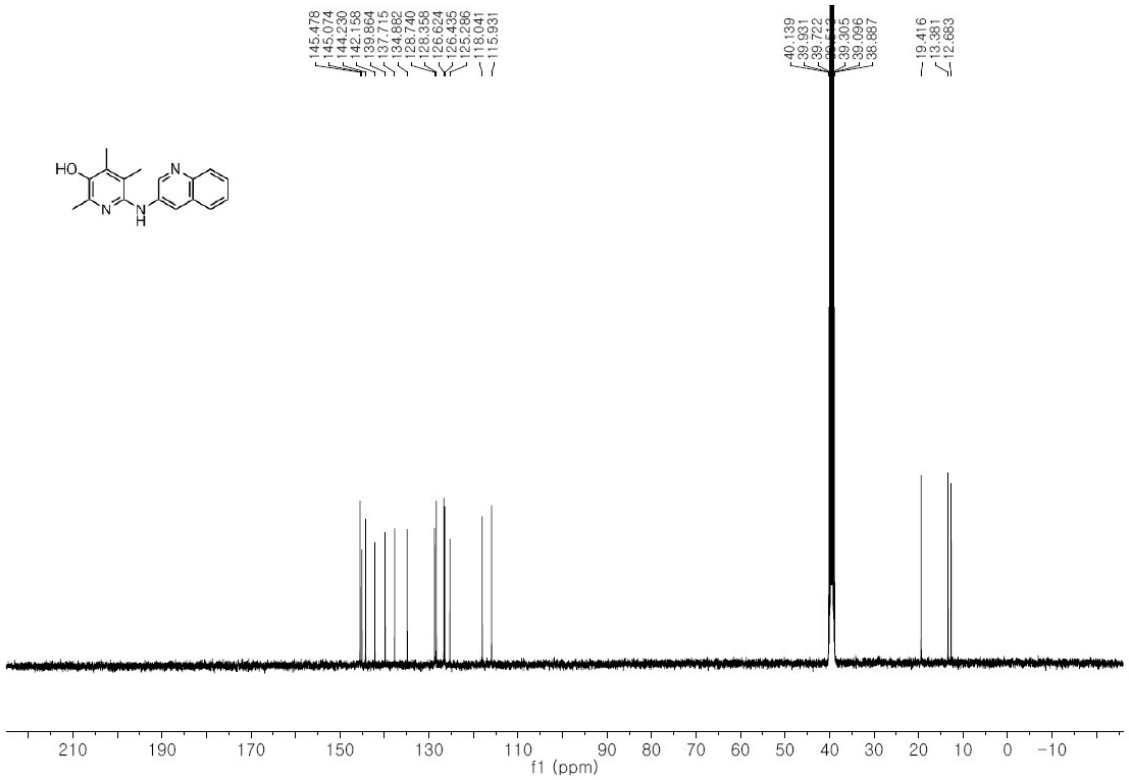
^{1}H-NMR of **6j** (DMSO-d_6)



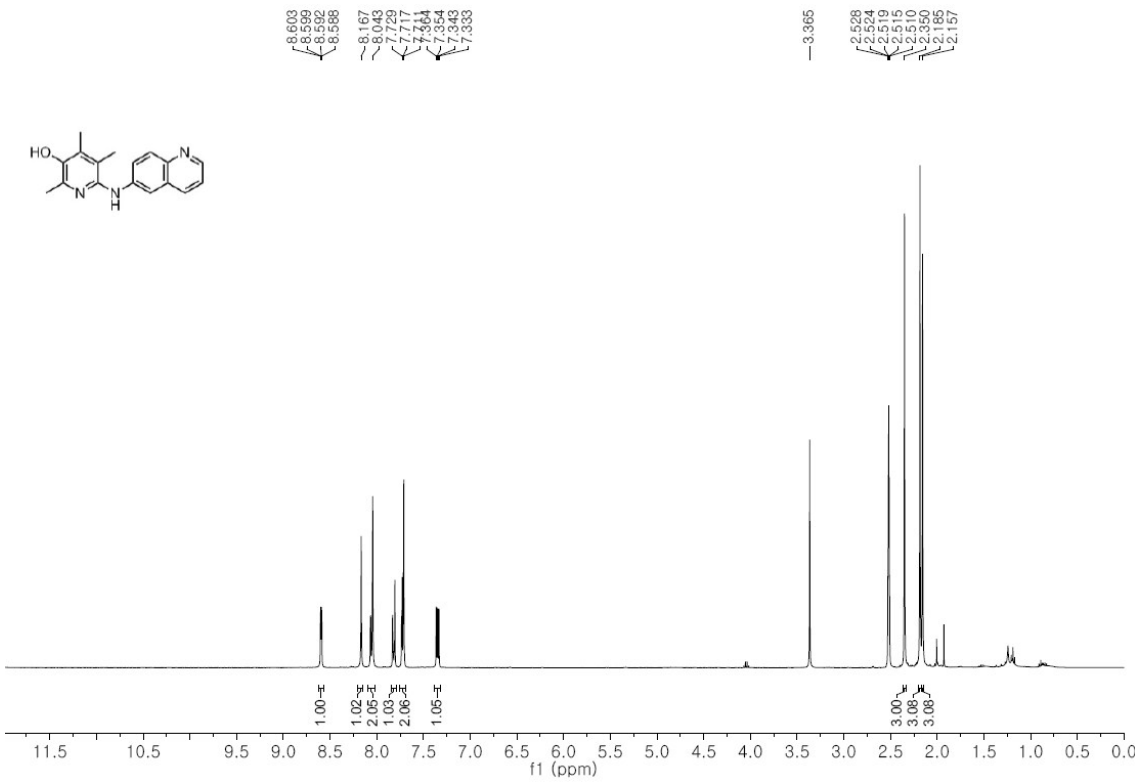
^{13}C-NMR of **6j** (DMSO-d_6)



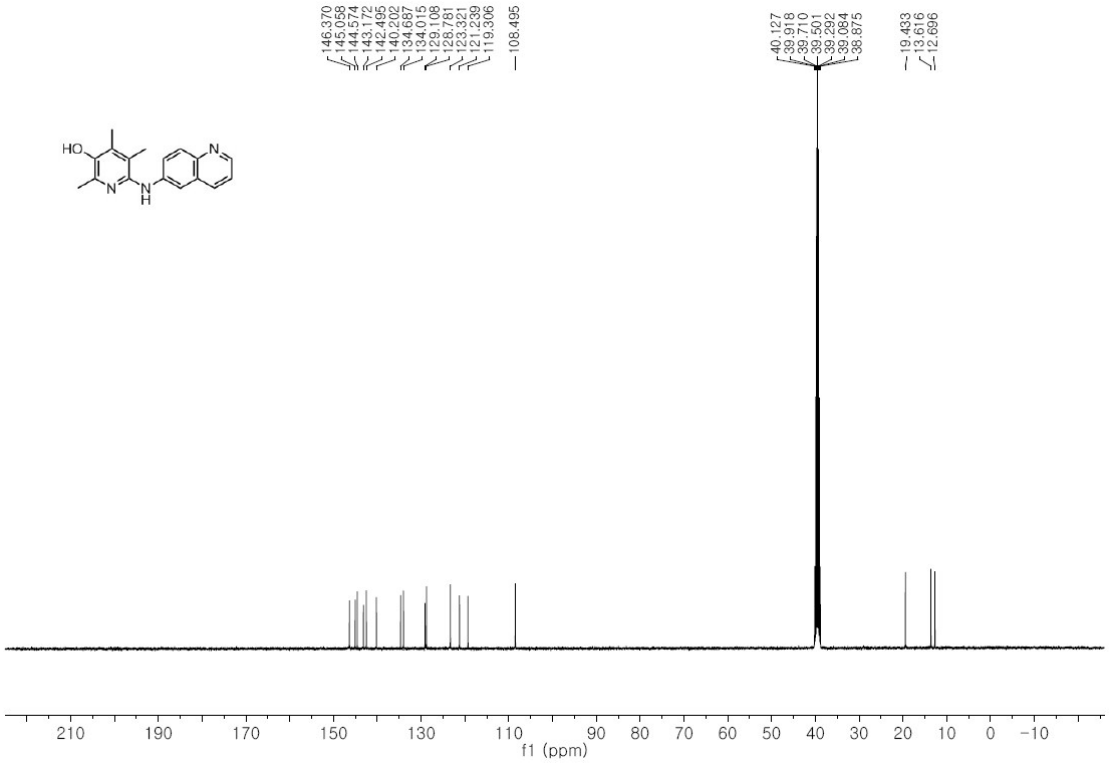
^{1}H-NMR of **6k** (DMSO-d_6)



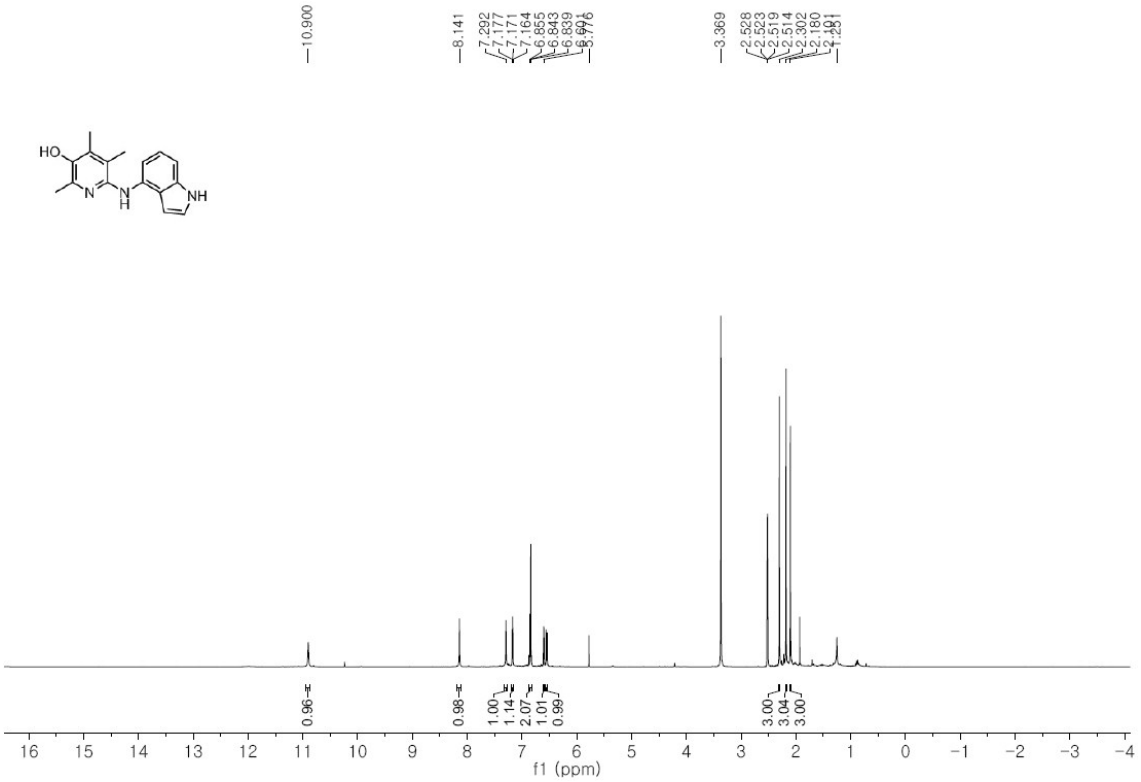
^{13}C-NMR of **6k** (DMSO-d_6)



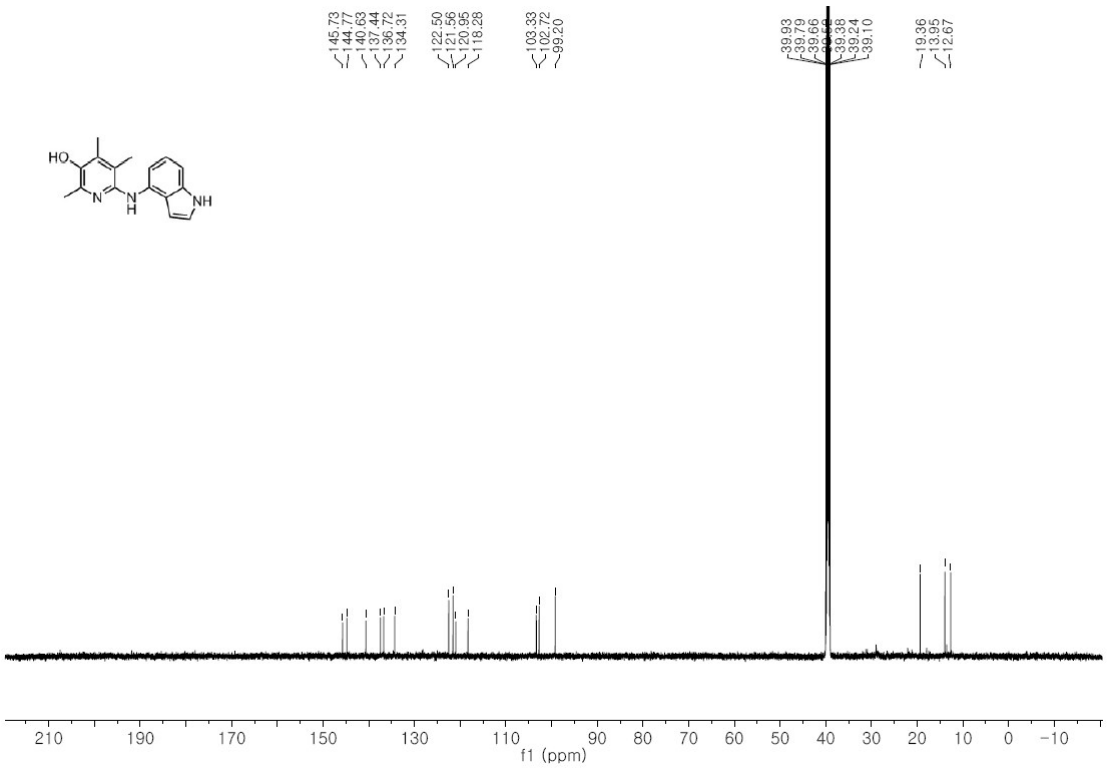
^{1}H-NMR of **6l** (DMSO-d_6)



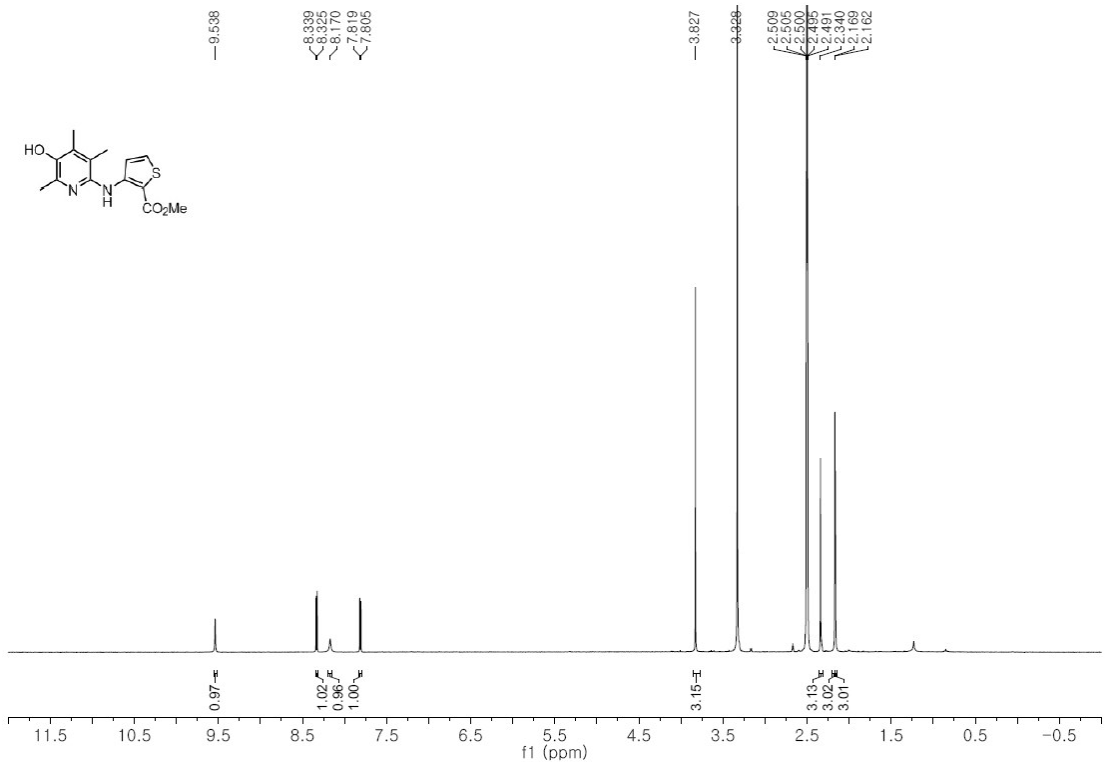
^{13}C-NMR of **6l** (DMSO-d_6)



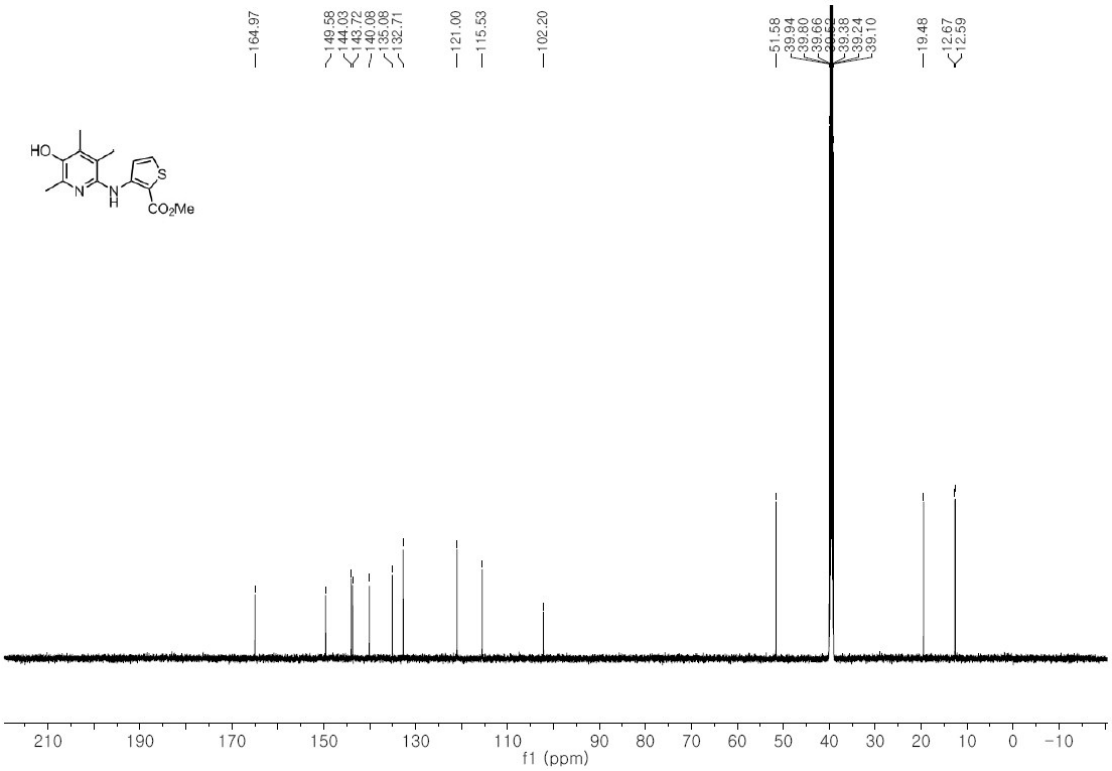
^{1}H-NMR of **6m** (DMSO-d_6)



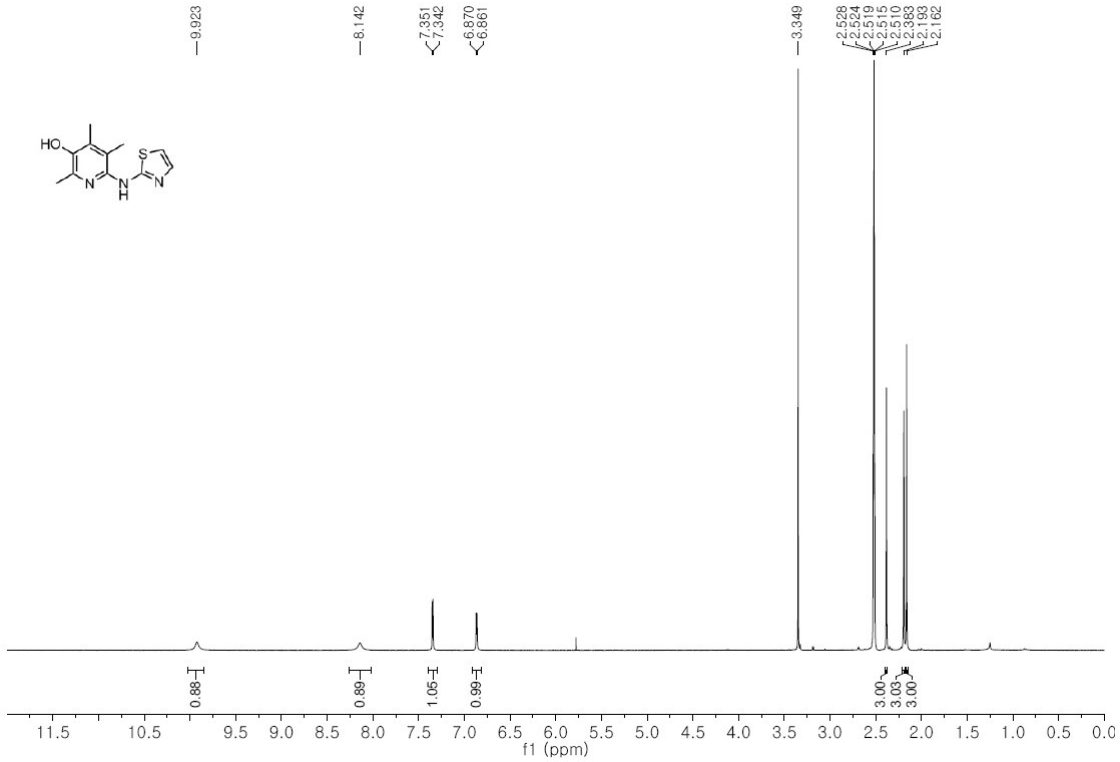
^{13}C-NMR of **6m** (DMSO-d_6)



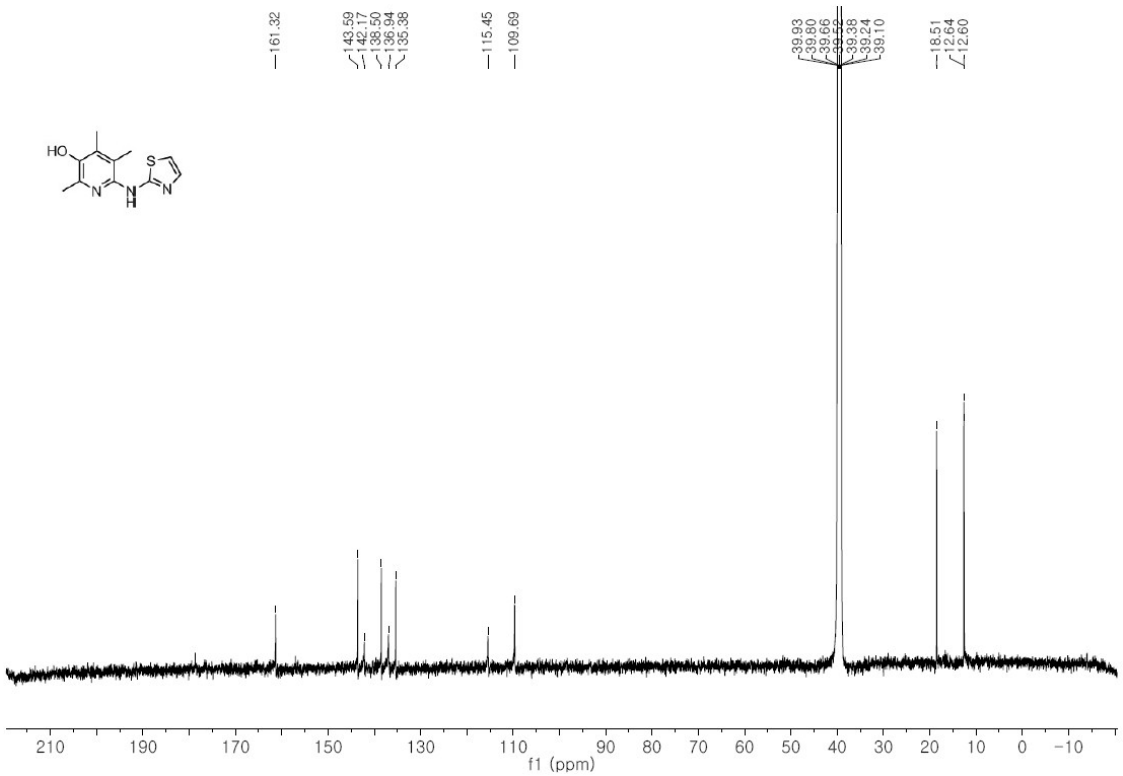
^{1}H-NMR of **6n** (DMSO-d_6)



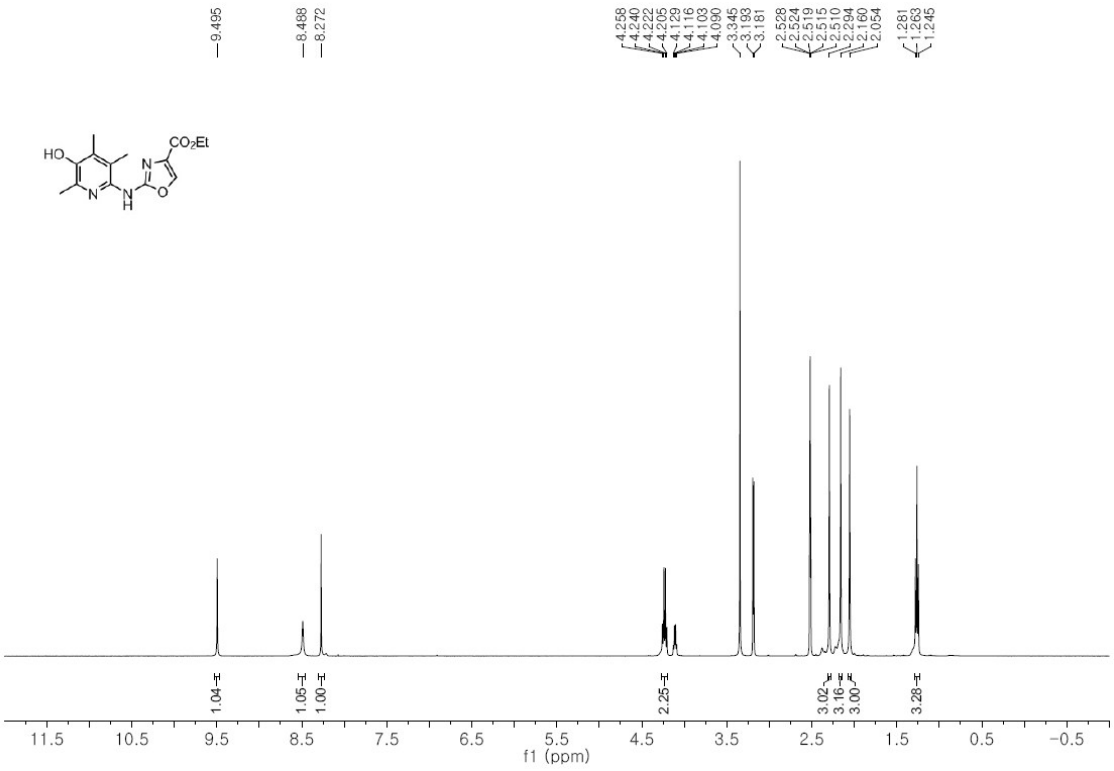
^{13}C-NMR of **6n** (DMSO-d_6)



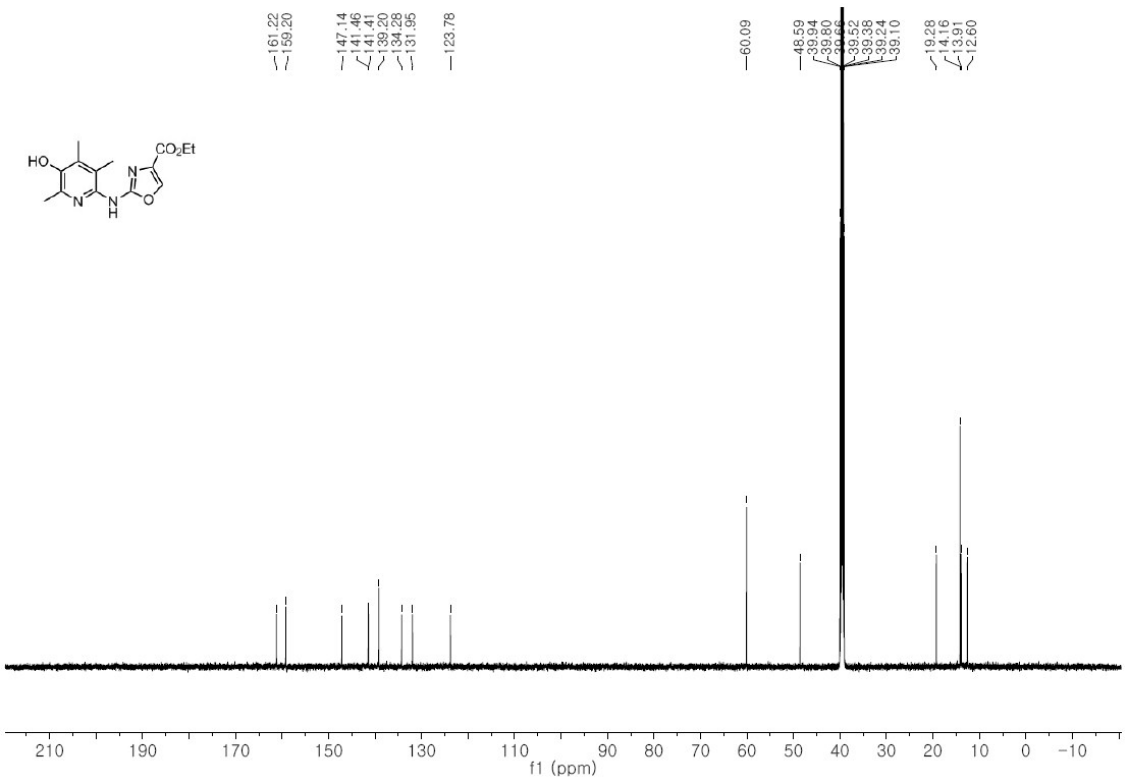
^{1}H-NMR of **6o** (DMSO-d_6)



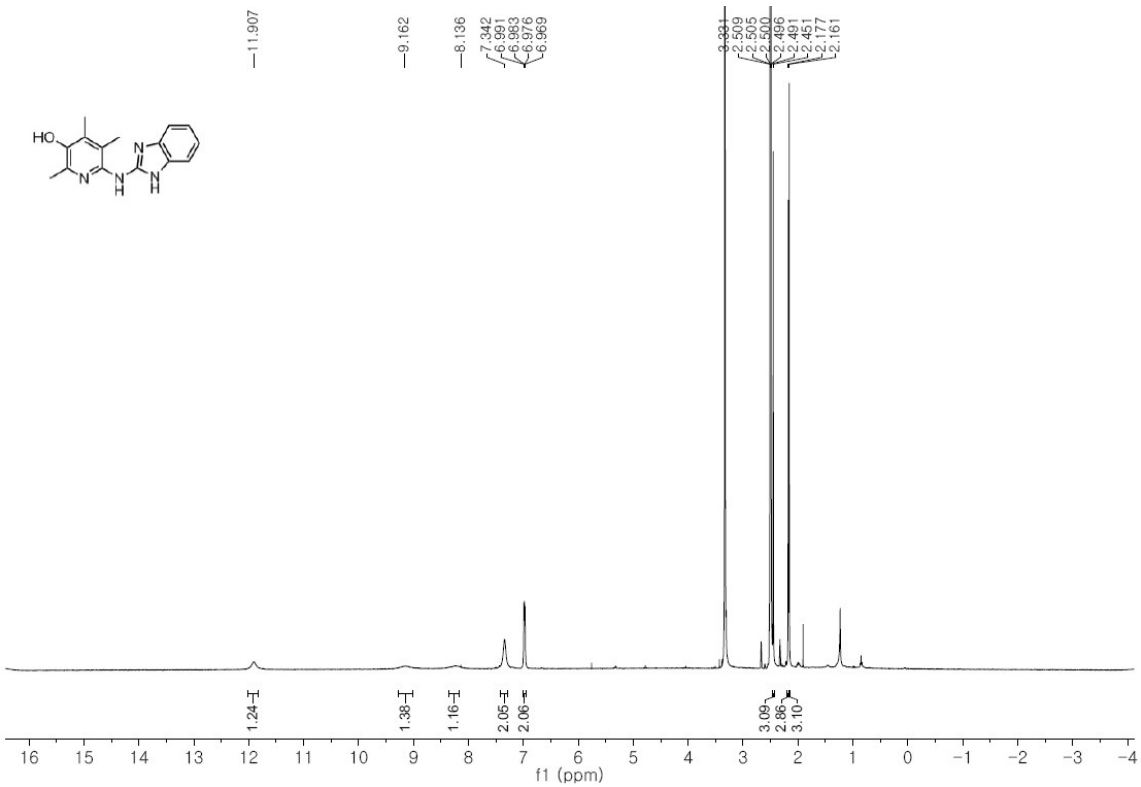
^{13}C-NMR of **6o** (DMSO-d_6)



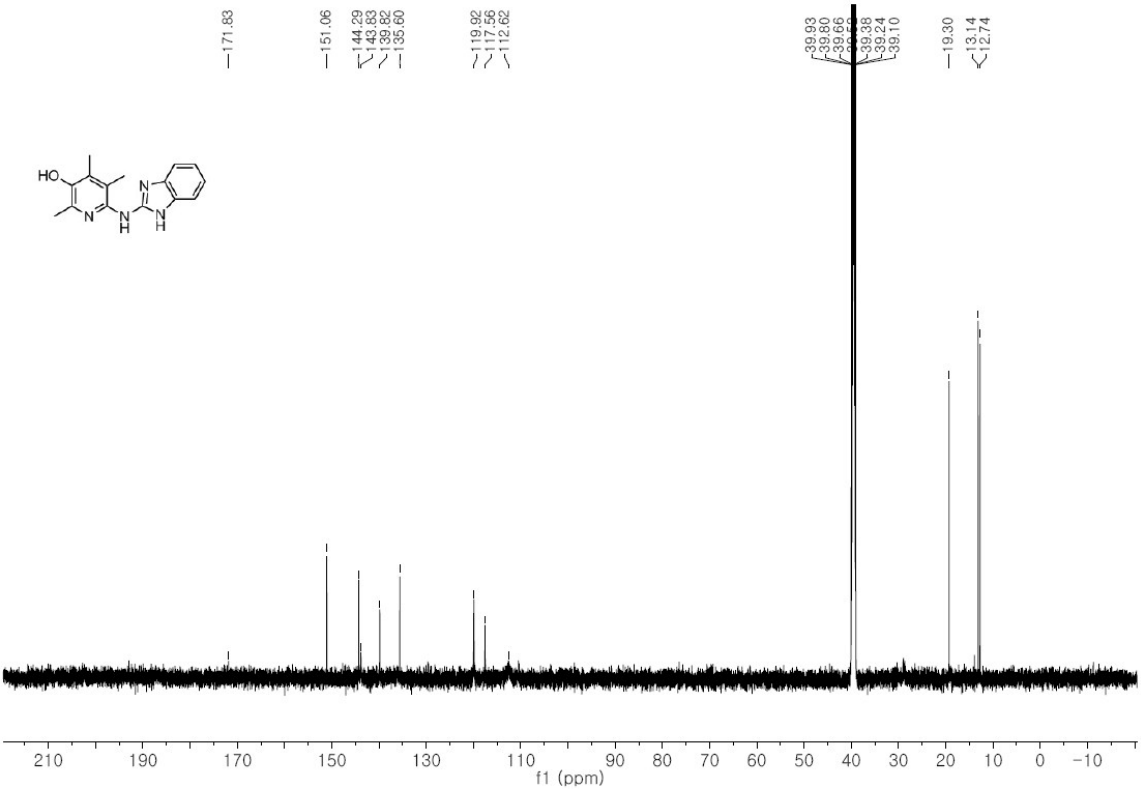
^{1}H-NMR of **6p** (DMSO-d_6)



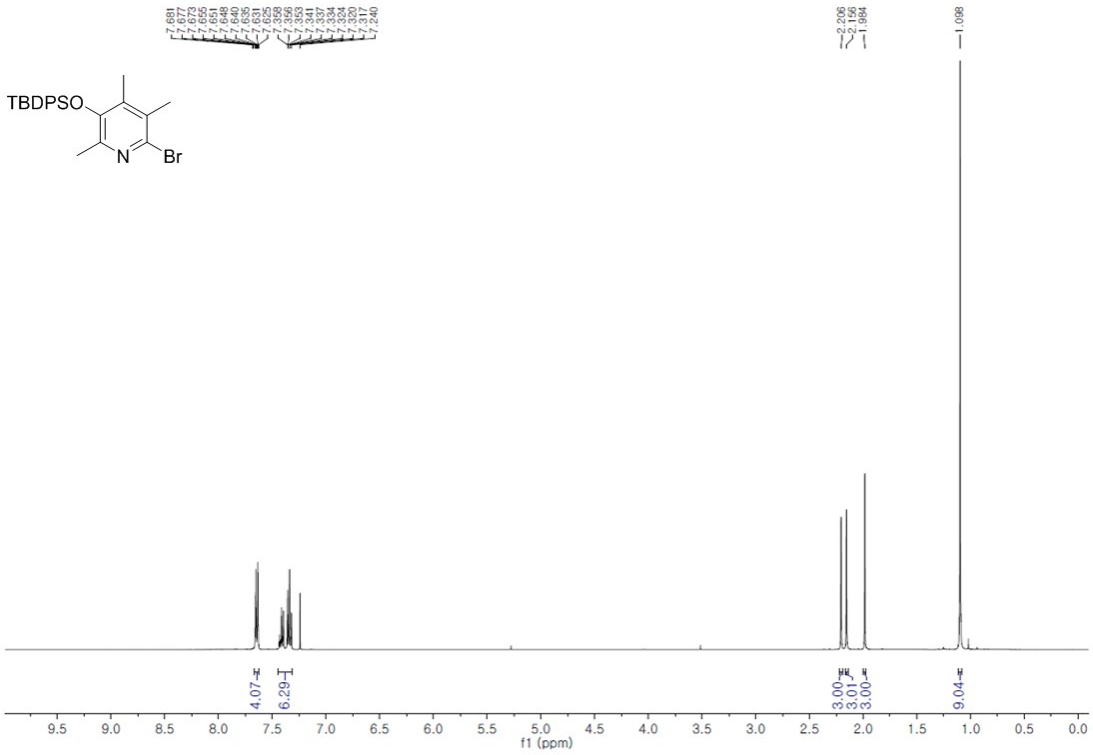
^{13}C-NMR of **6p** (DMSO-d_6)



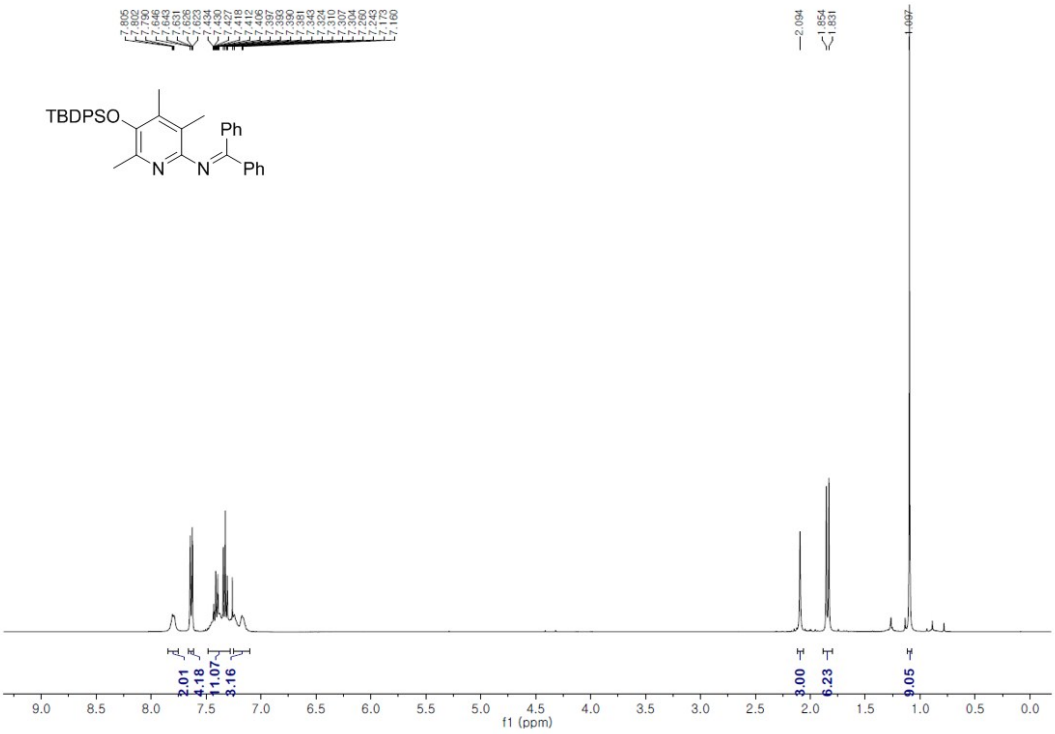
^{1}H-NMR of **6q** (DMSO-d_6)



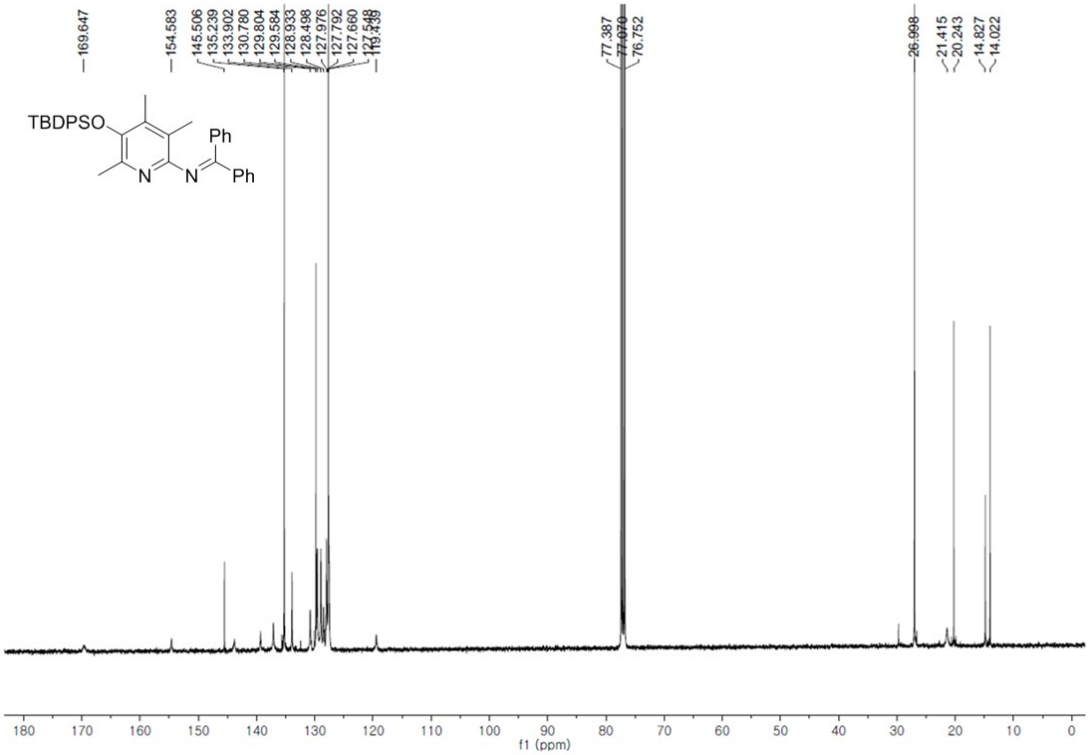
^{13}C-NMR of **6q** (DMSO-d_6)



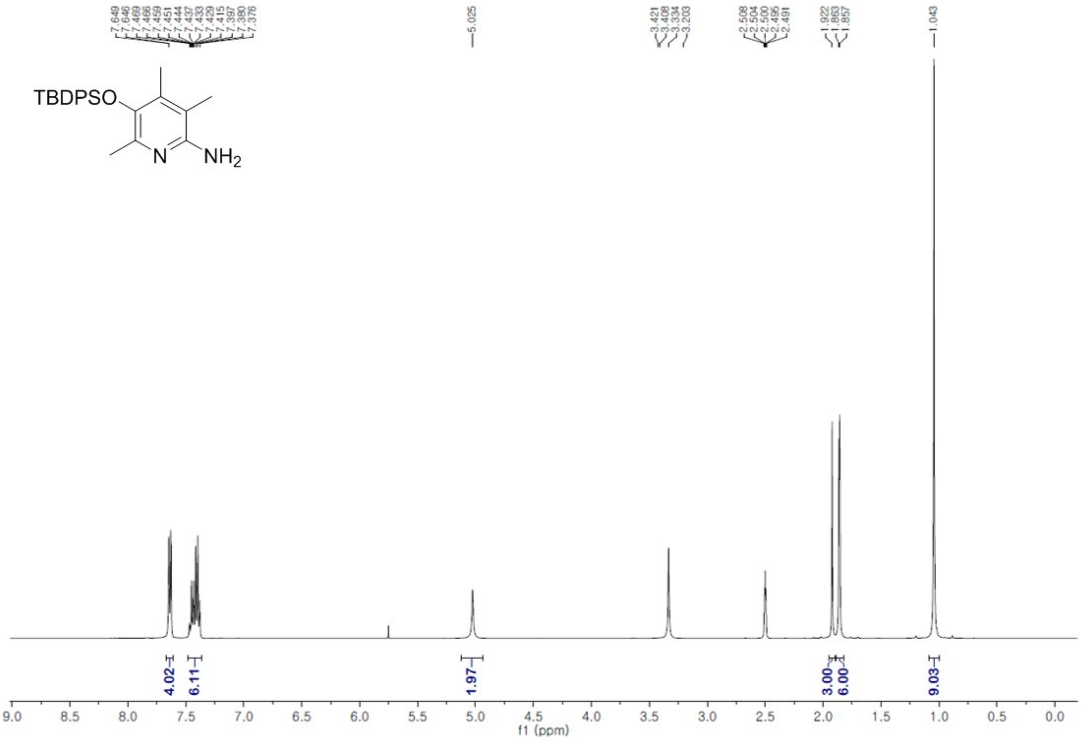
^{1}H-NMR of **7** ($CDCl_3$)



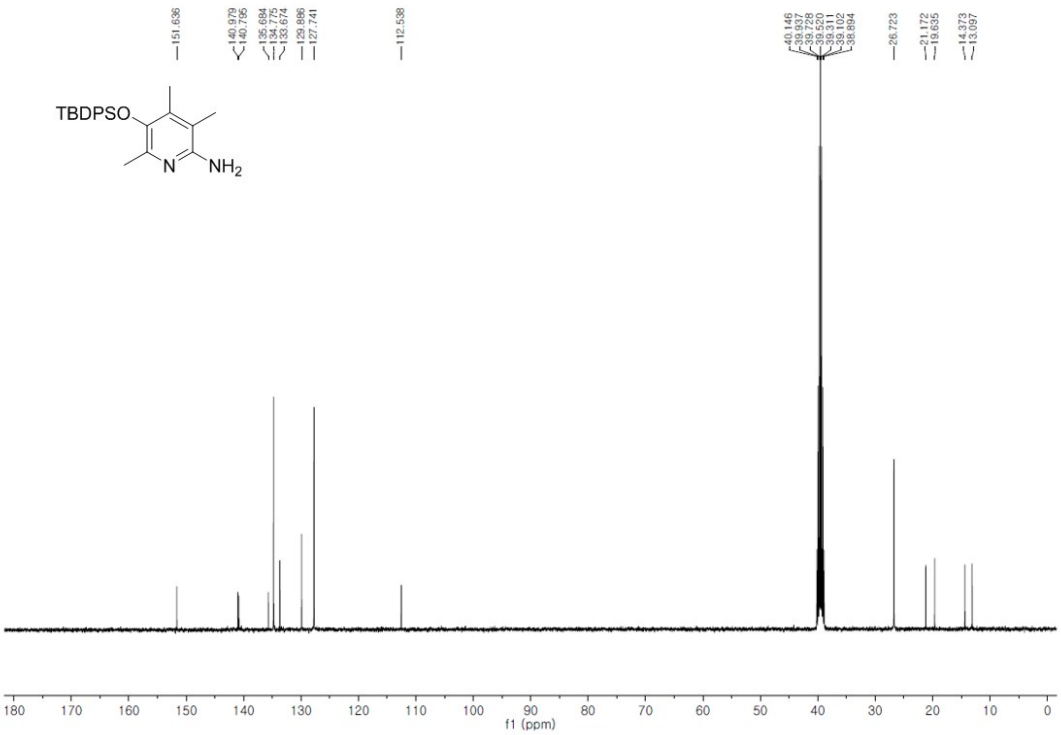
^{1}H-NMR of **8** ($CDCl_3$)



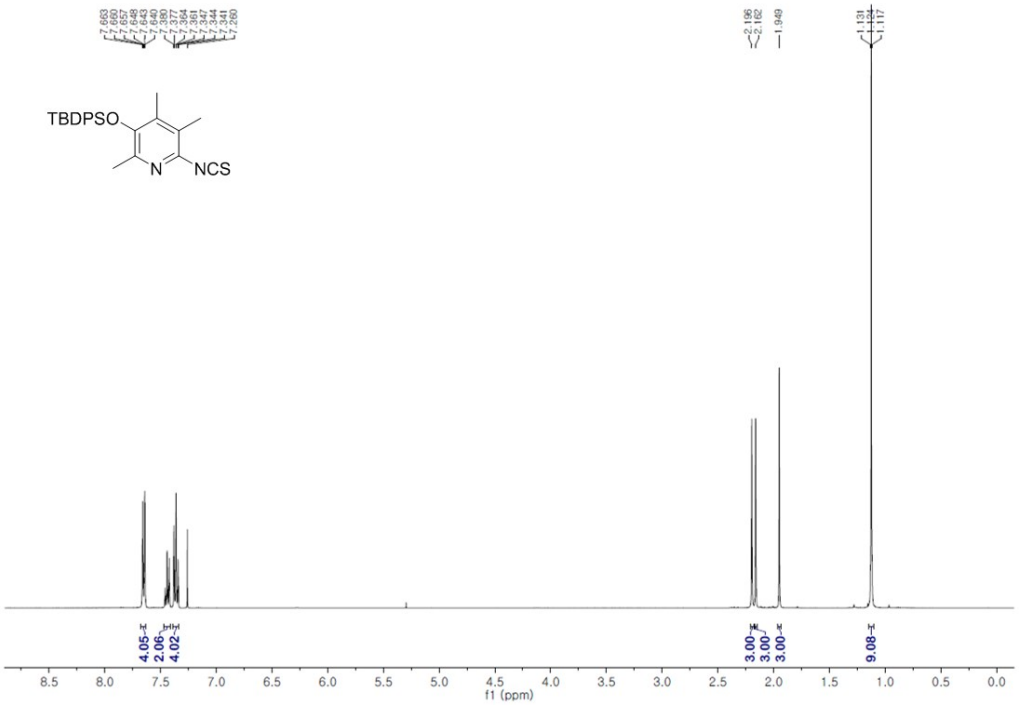
^{13}C-NMR of **8** ($CDCl_3$)



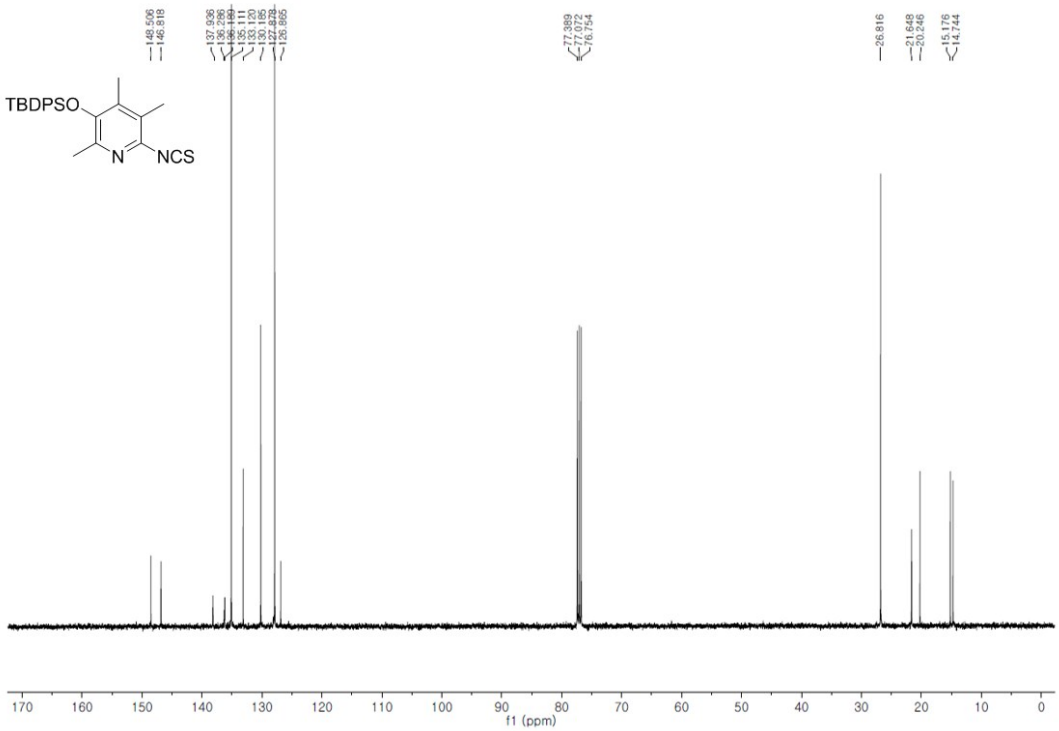
^{1}H-NMR of **9** (DMSO-d_6)



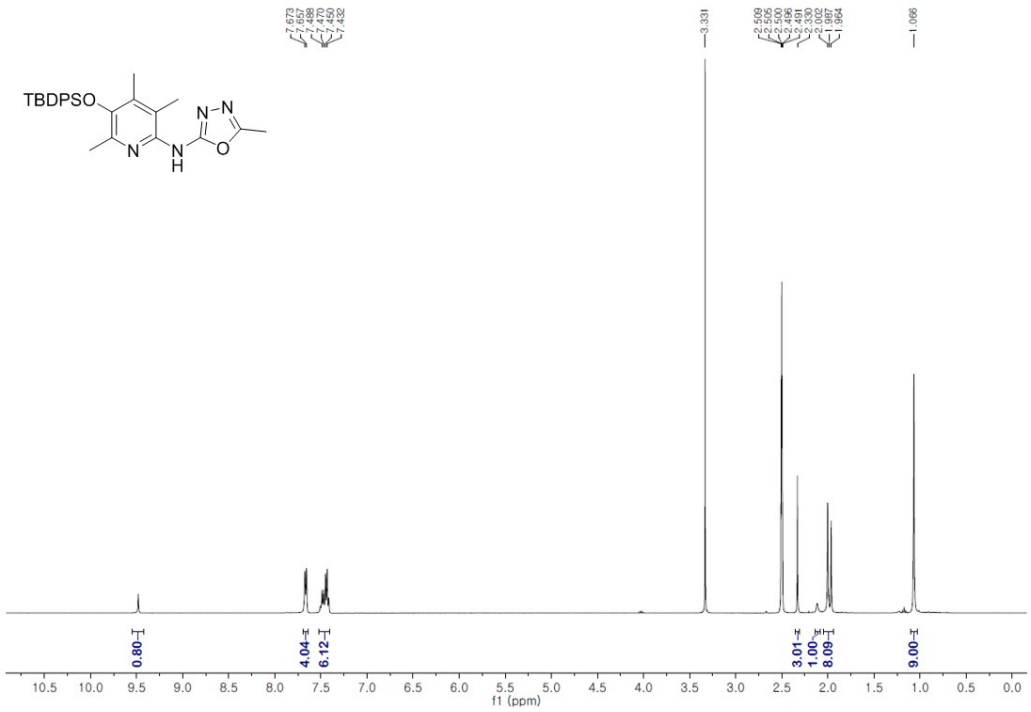
^{13}C-NMR of **9** (DMSO-d_6)



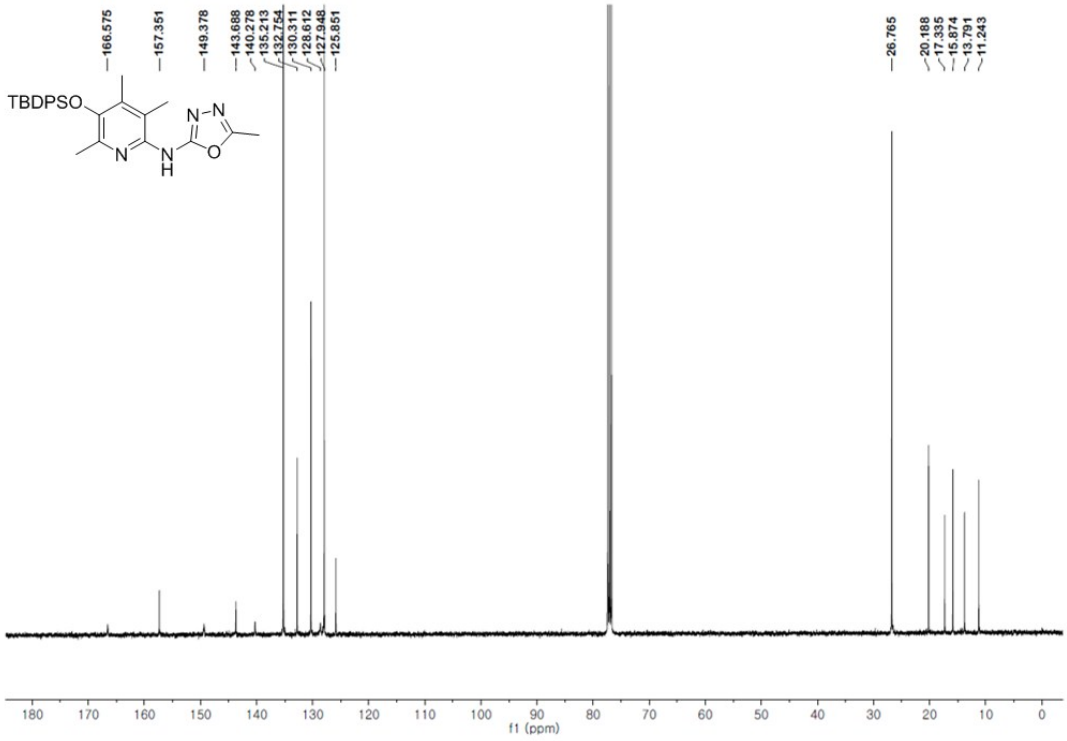
^{1}H-NMR of **10** ($CDCl_3$)



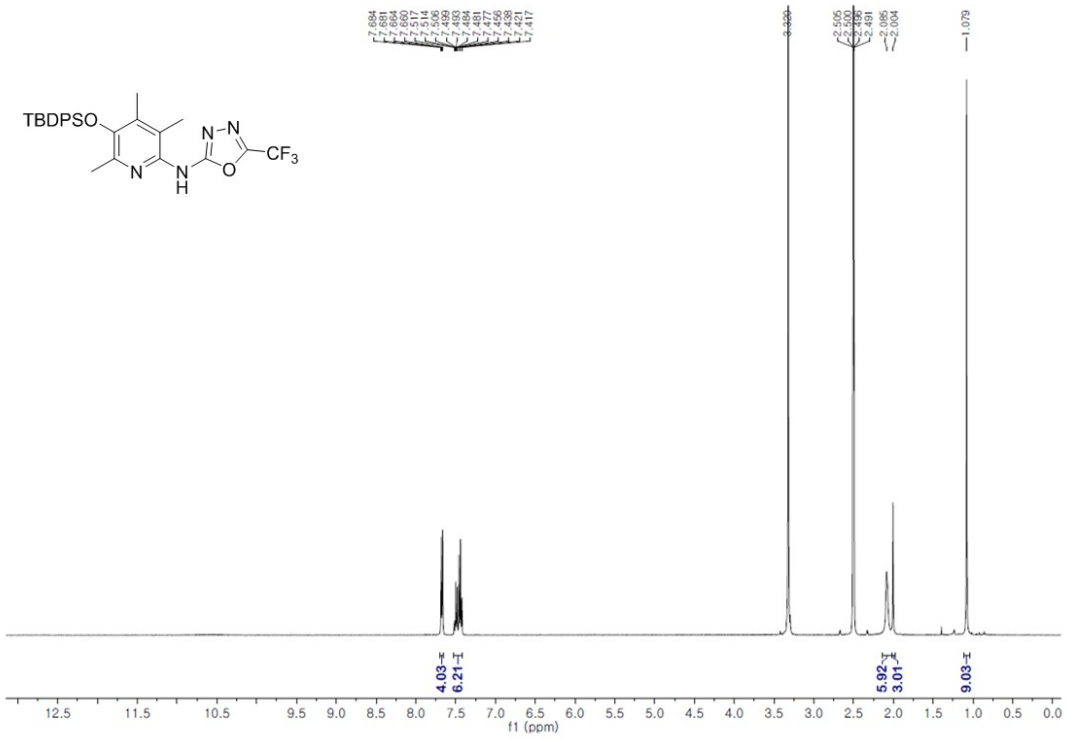
^{13}C-NMR of **10** ($CDCl_3$)



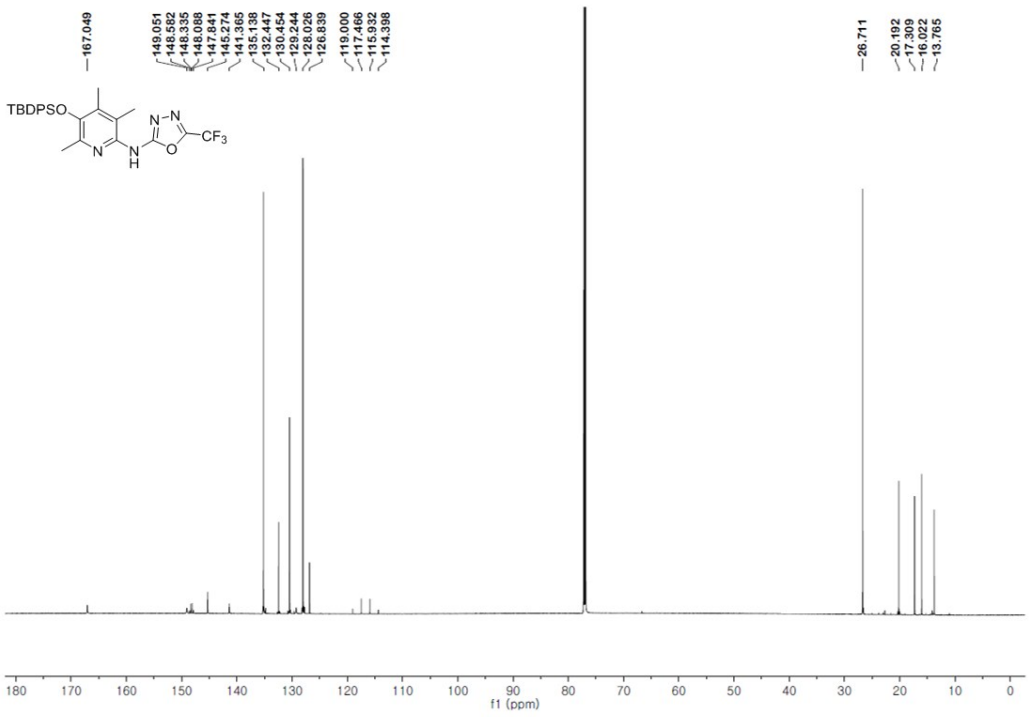
^{1}H-NMR of **13a** (DMSO-d_6)



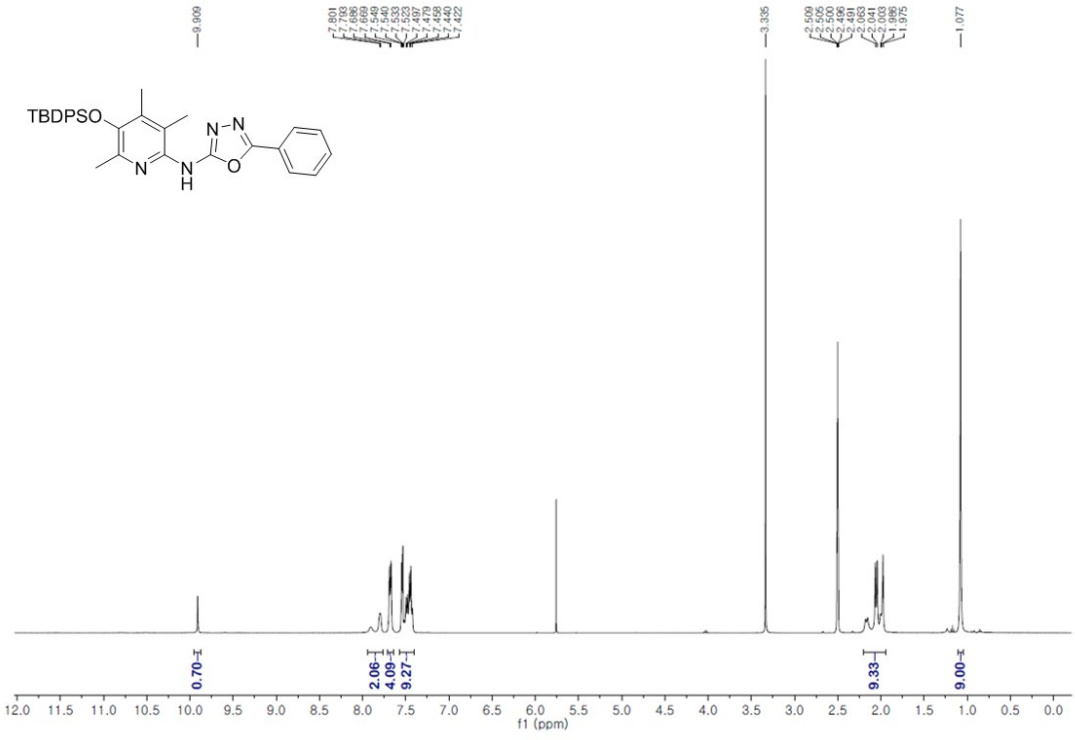
^{13}C-NMR of **13a** ($CDCl_3$)



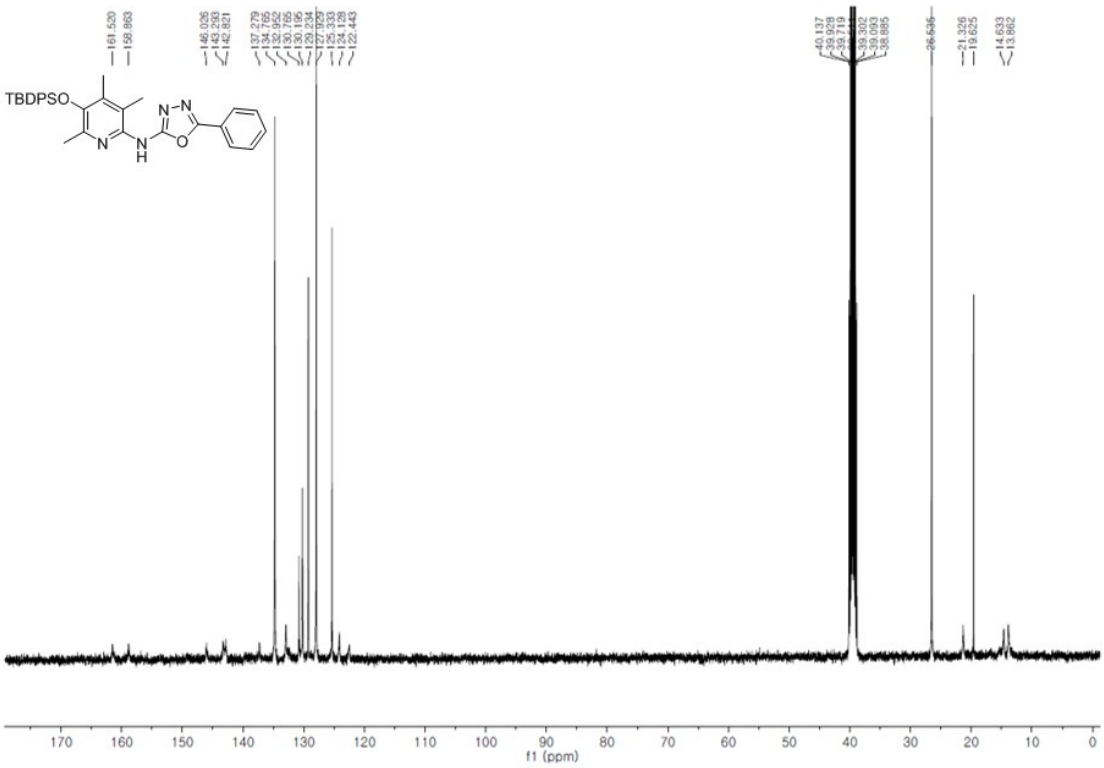
^{1}H-NMR of **13b** (DMSO-d_6)



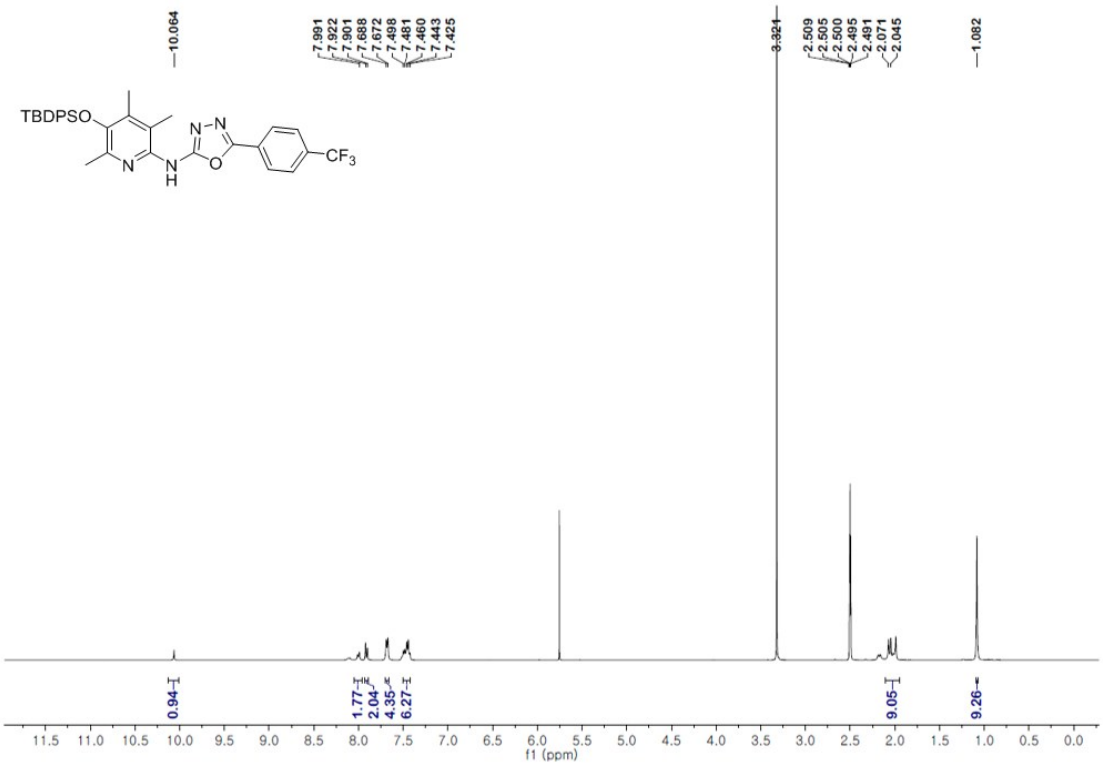
^{13}C-NMR of **13b** ($CDCl_3$)



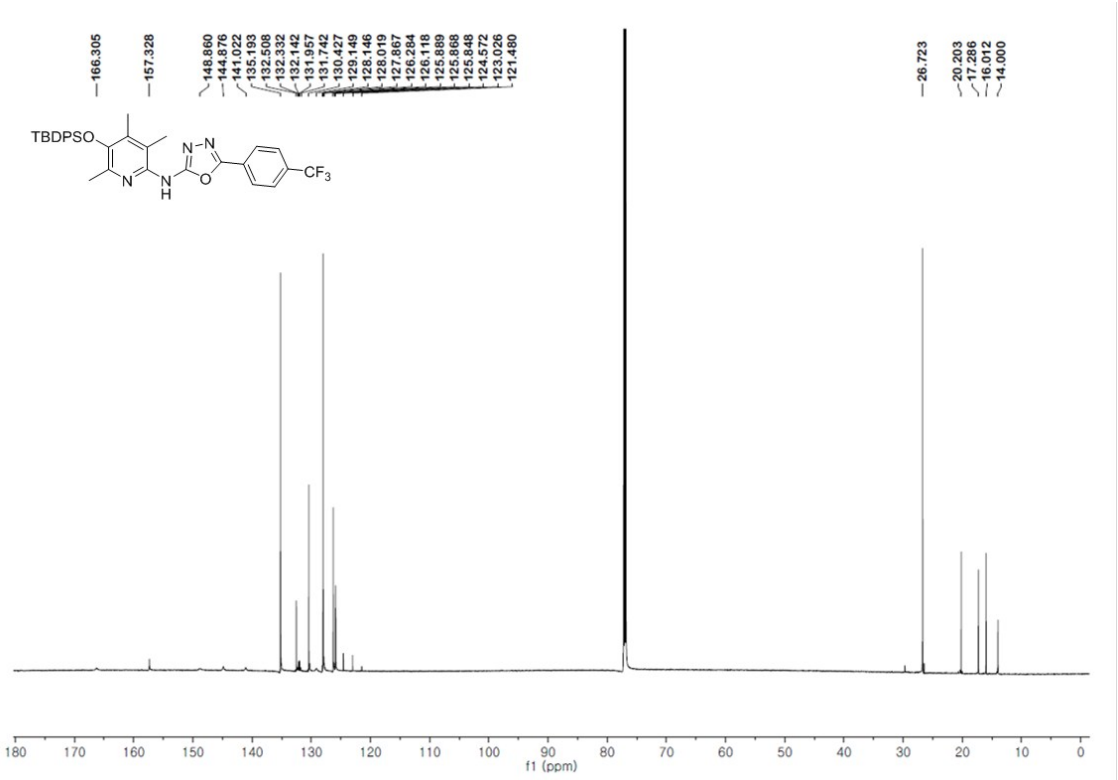
^{1}H-NMR of **13c** (DMSO-d_6)



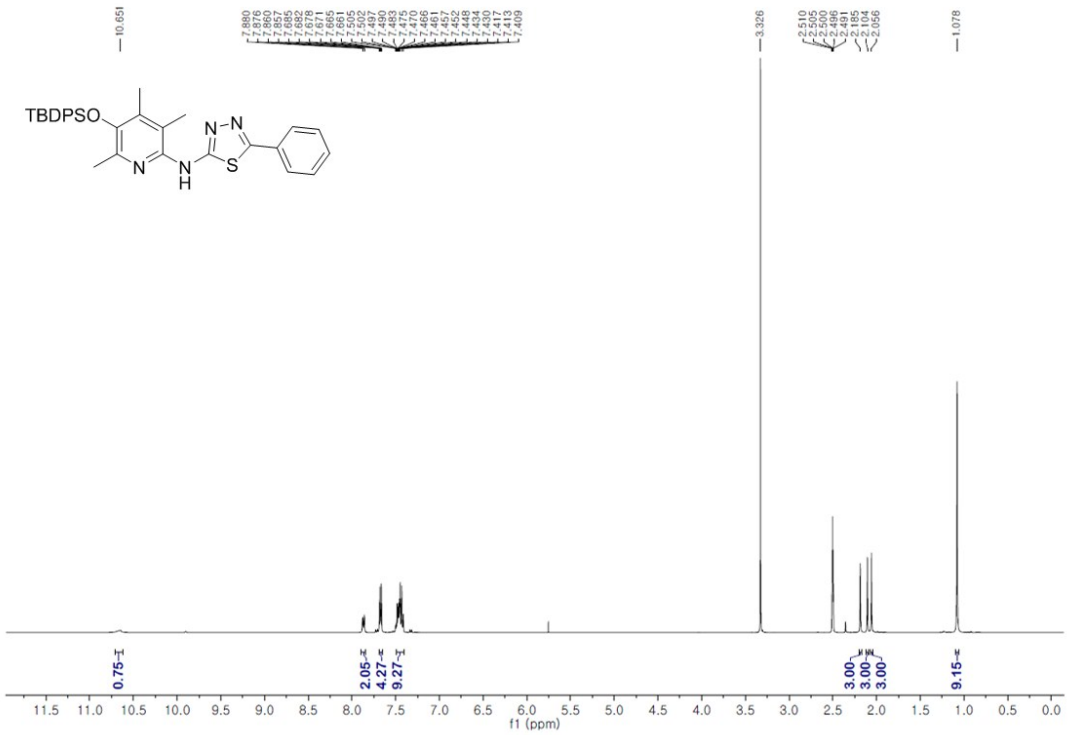
^{13}C-NMR of **13c** (DMSO-d_6)



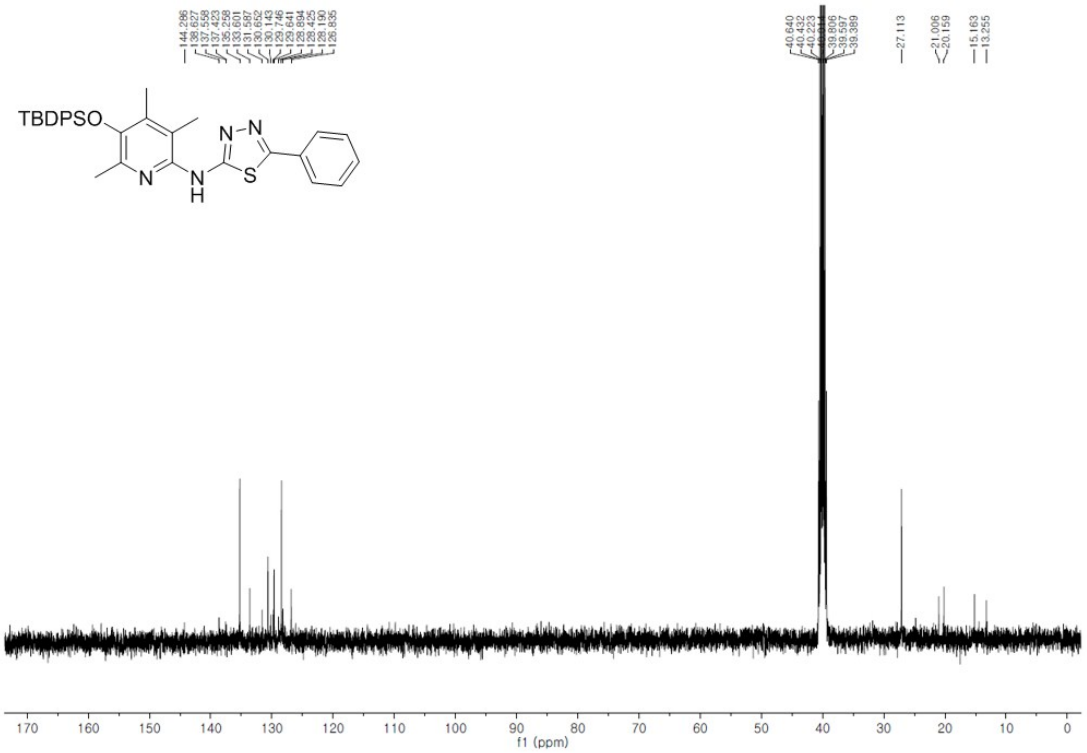
^{1}H-NMR of **13d** (DMSO-d_6)



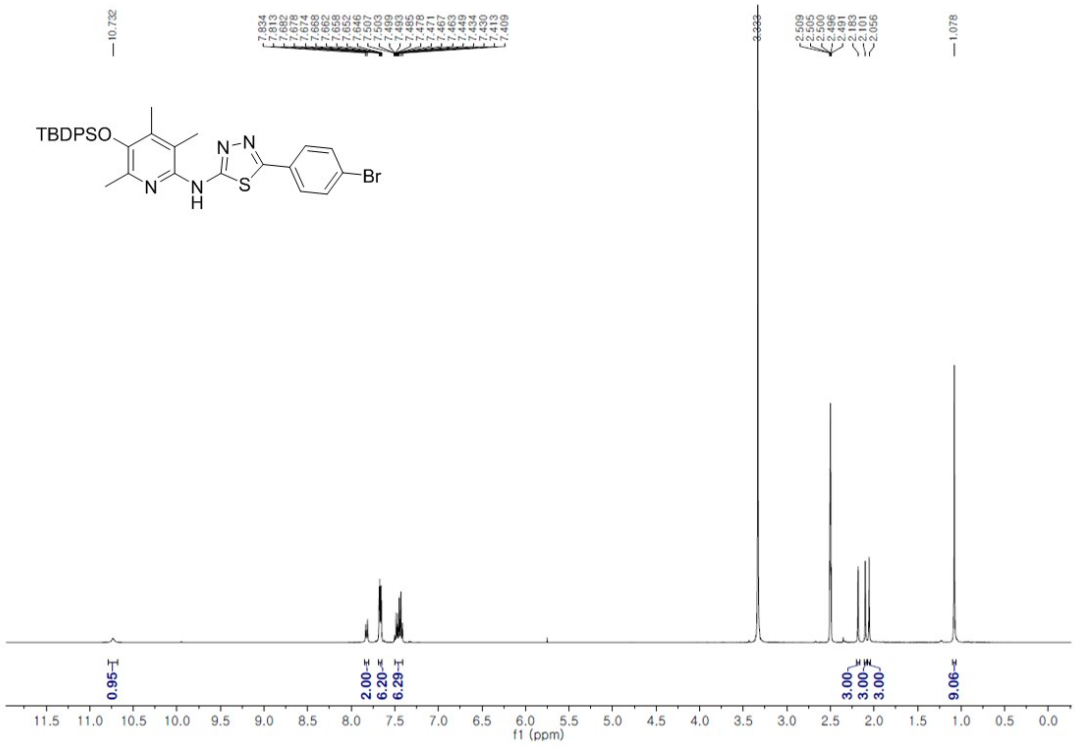
^{13}C-NMR of **13d** ($CDCl_3$)



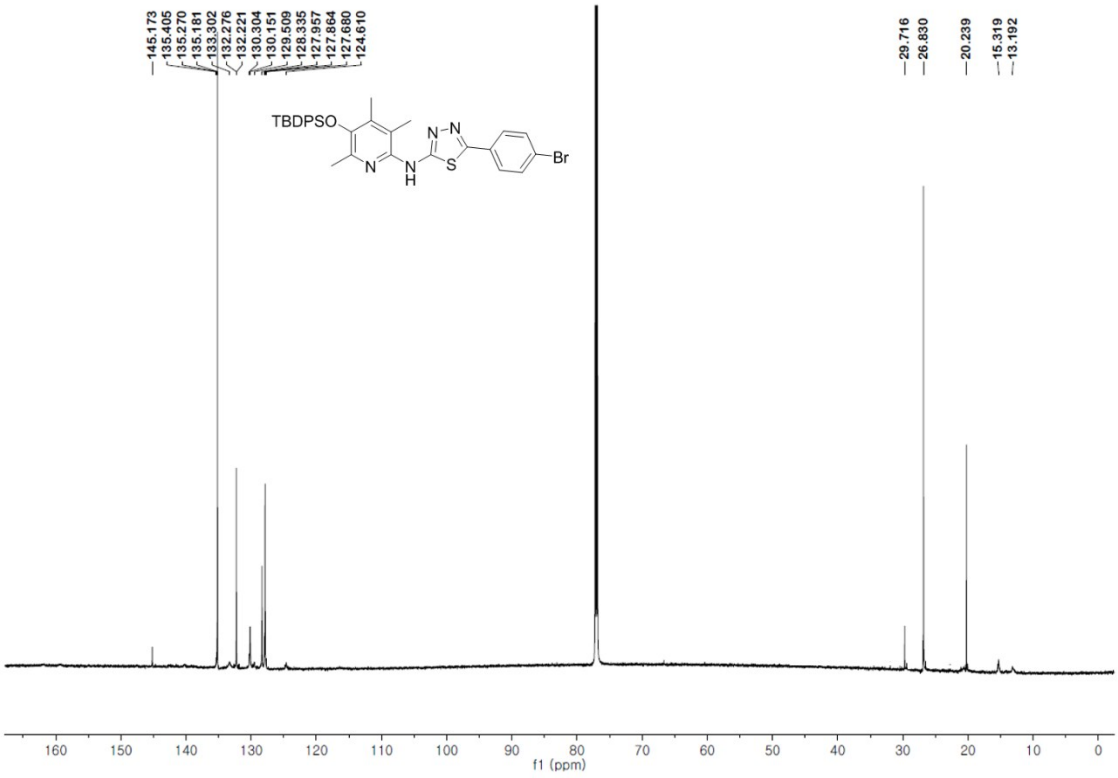
^{1}H-NMR of **14a** (DMSO-d_6)



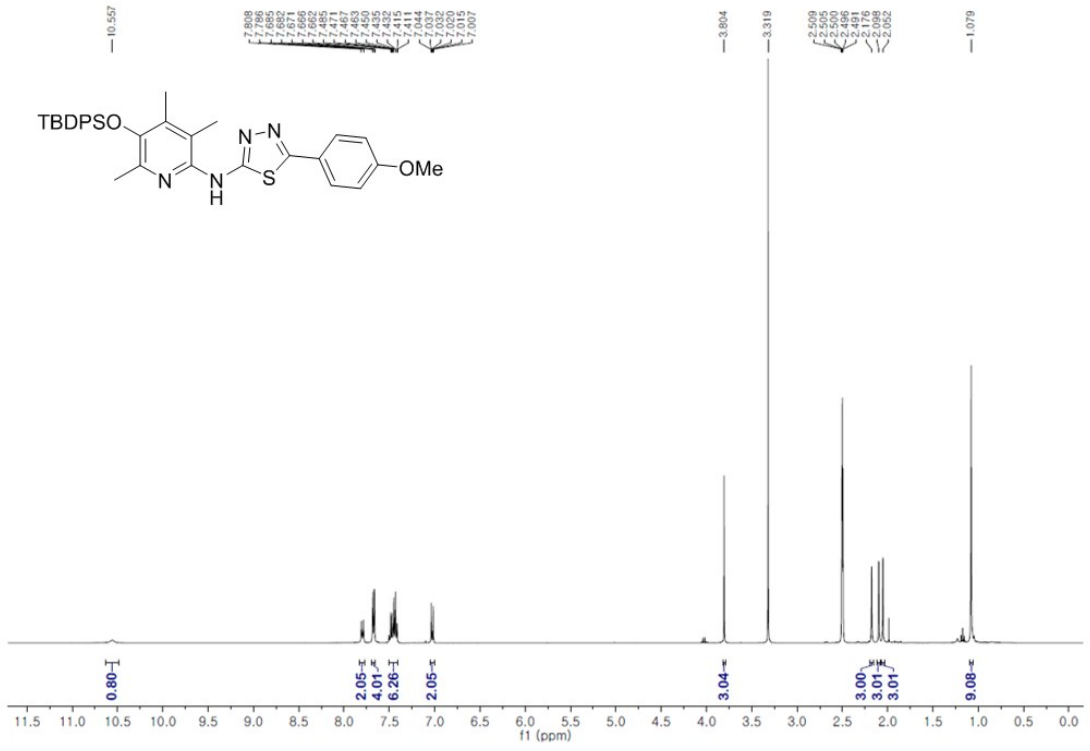
^{13}C-NMR of **14a** (DMSO-d_6)



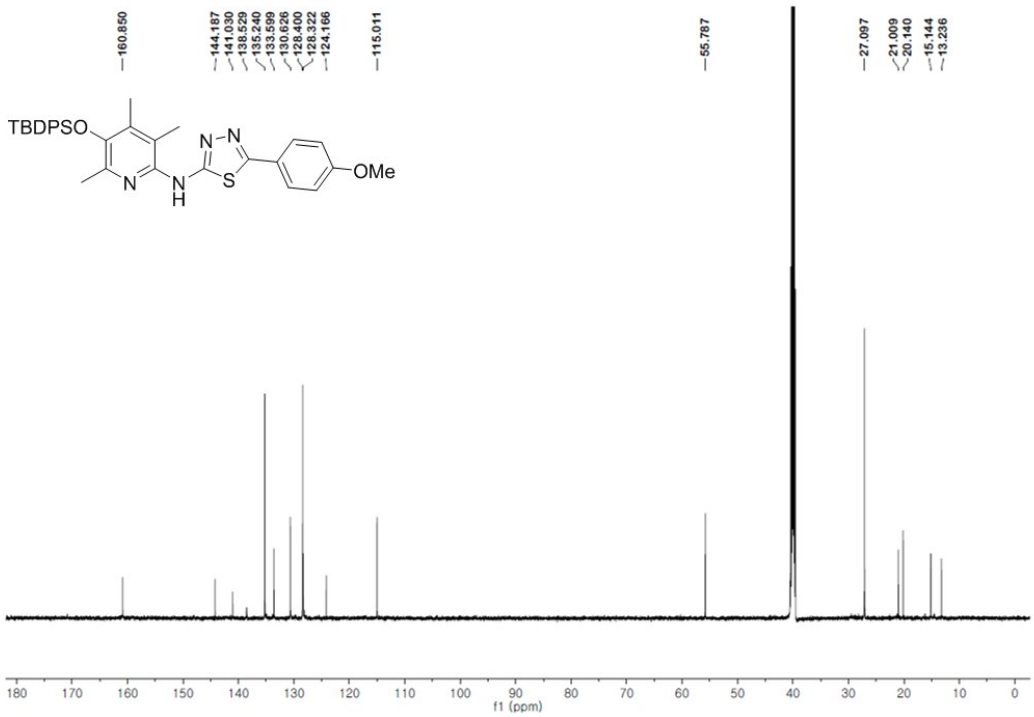
^{1}H-NMR of **14b** (DMSO-d_6)



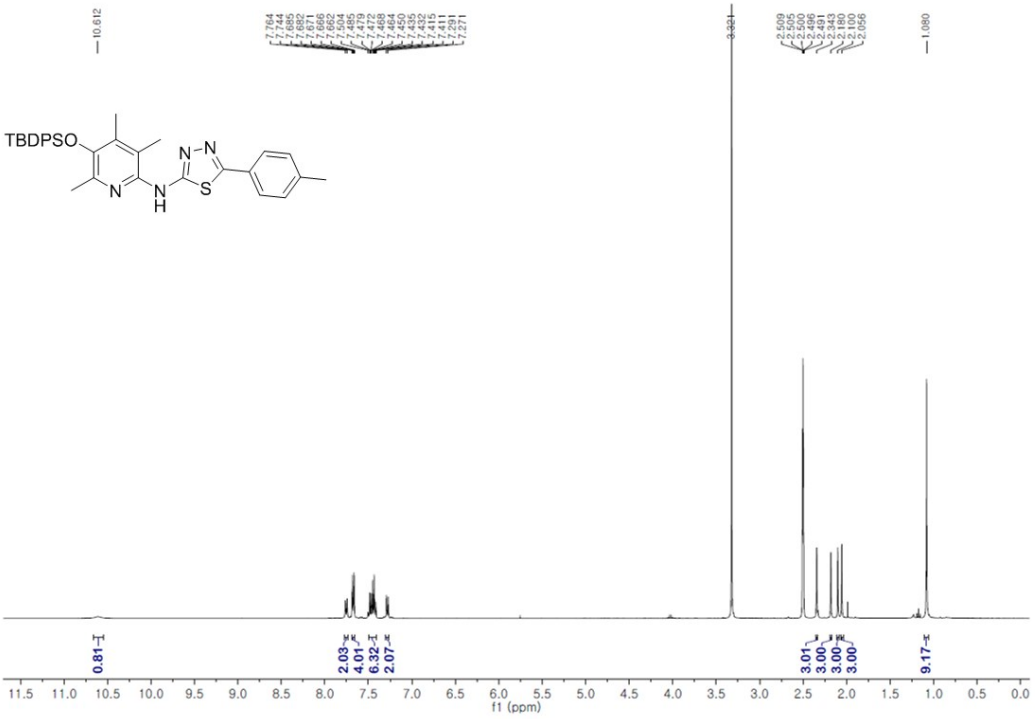
^{13}C-NMR of **14b** ($CDCl_3$)



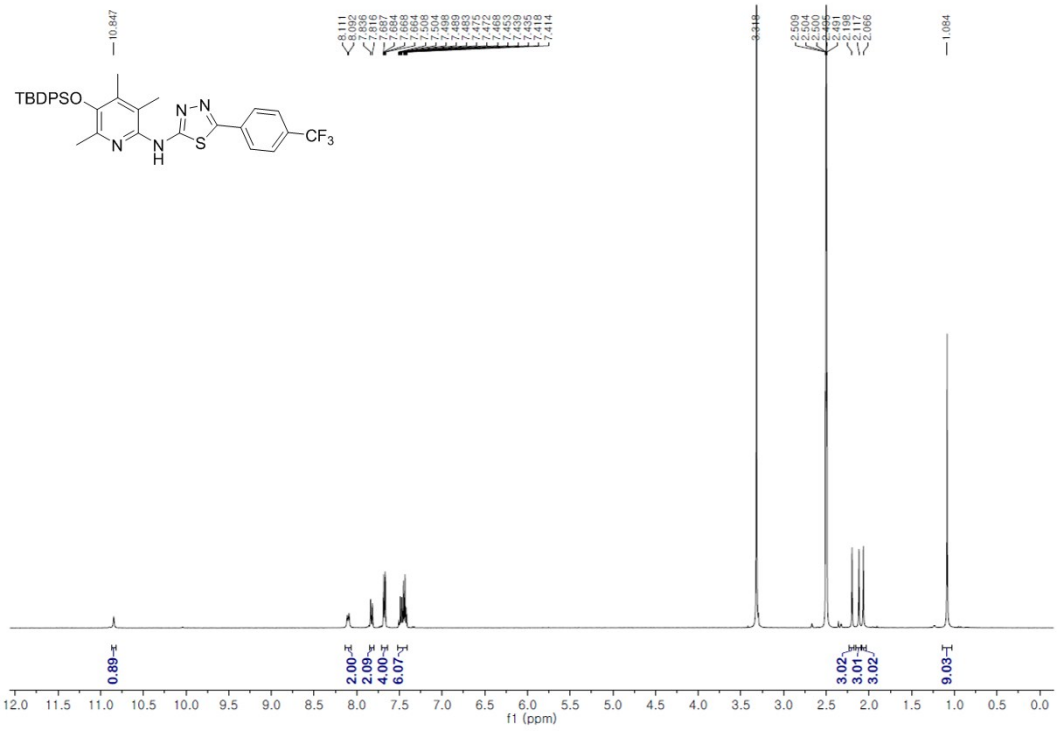
^{1}H-NMR of **14c** (DMSO-d_6)



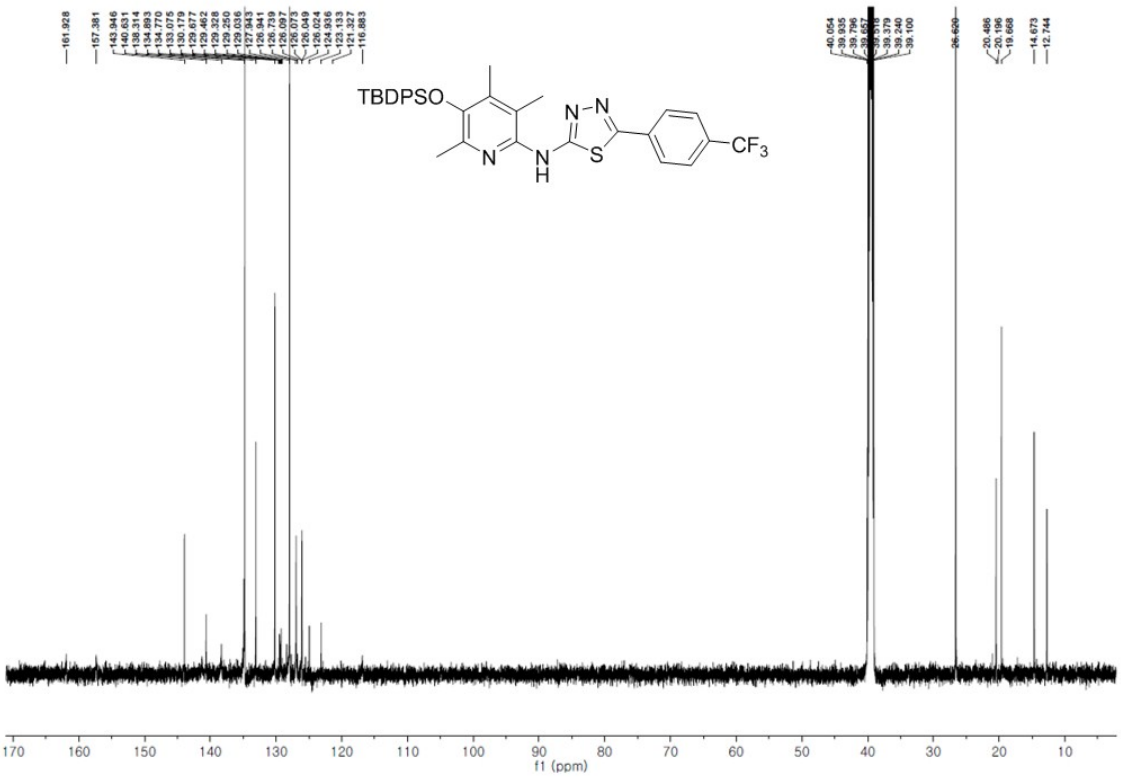
^{13}C-NMR of **14c** (DMSO-d_6)



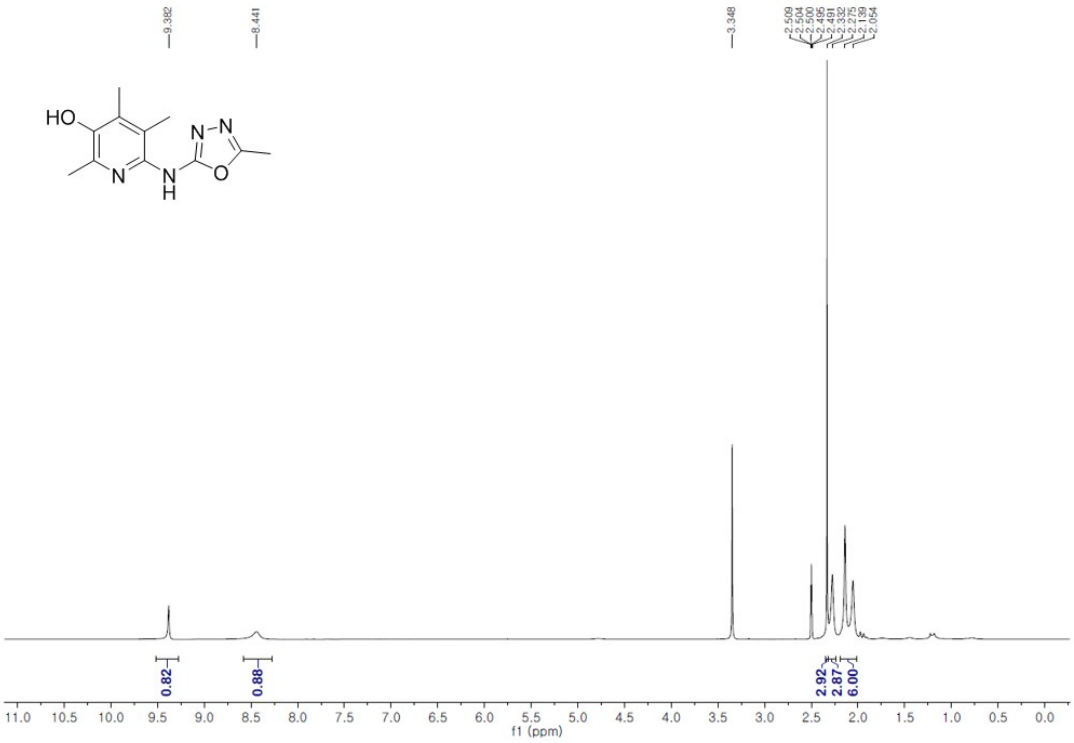
^{1}H-NMR of **14d** (DMSO-d_6)



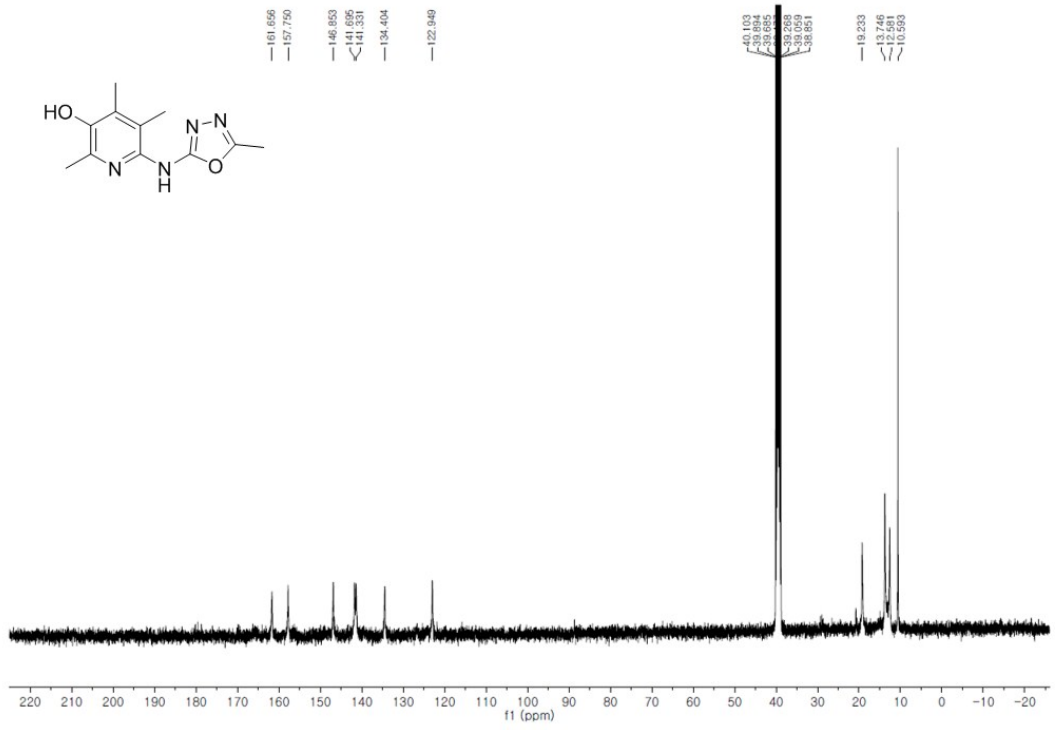
^{1}H-NMR of **14e** (DMSO-d_6)



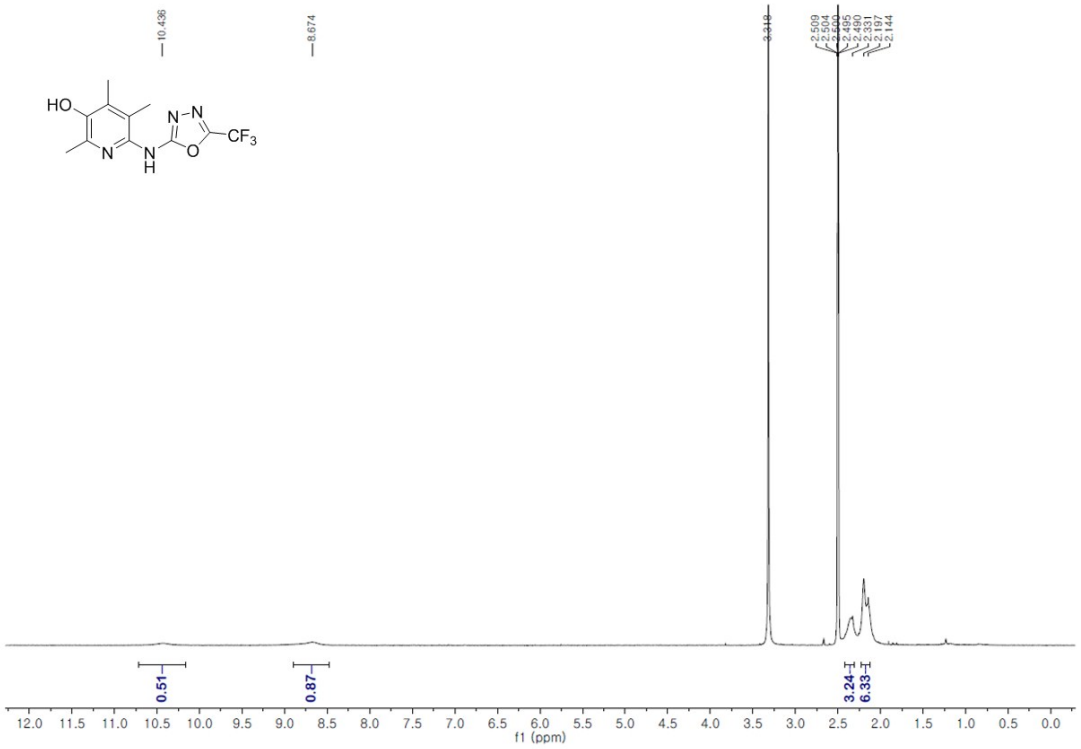
^{13}C-NMR of **14e** (DMSO-d_6)



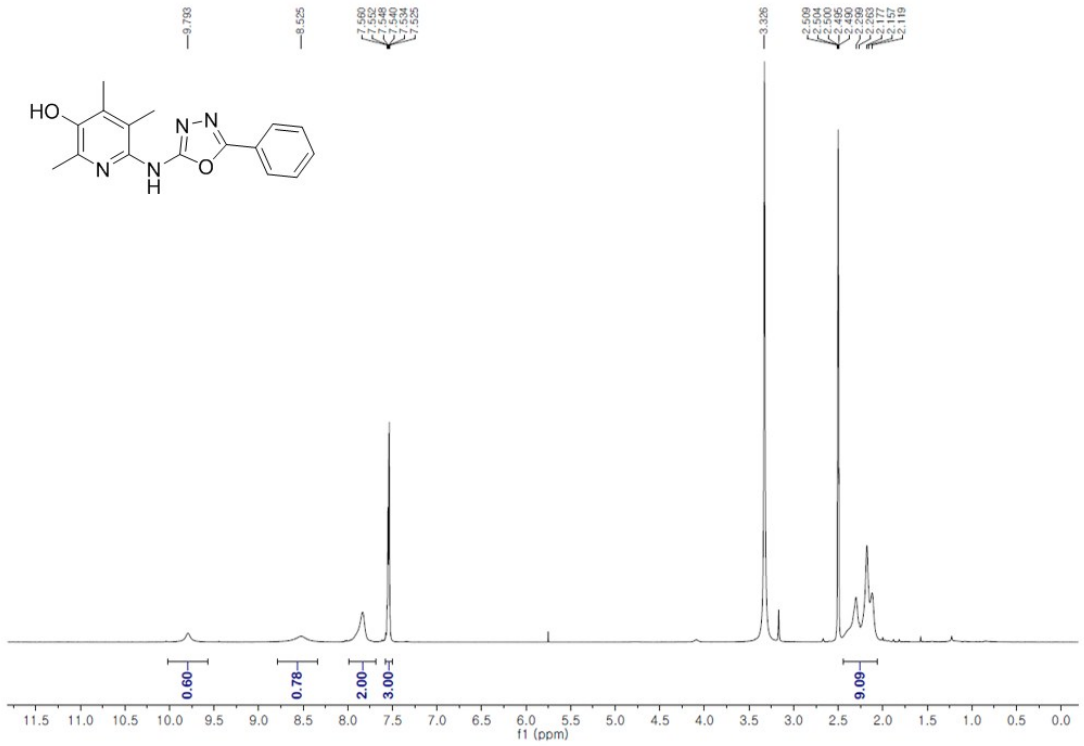
^{1}H-NMR of **15a** (DMSO-d_6)



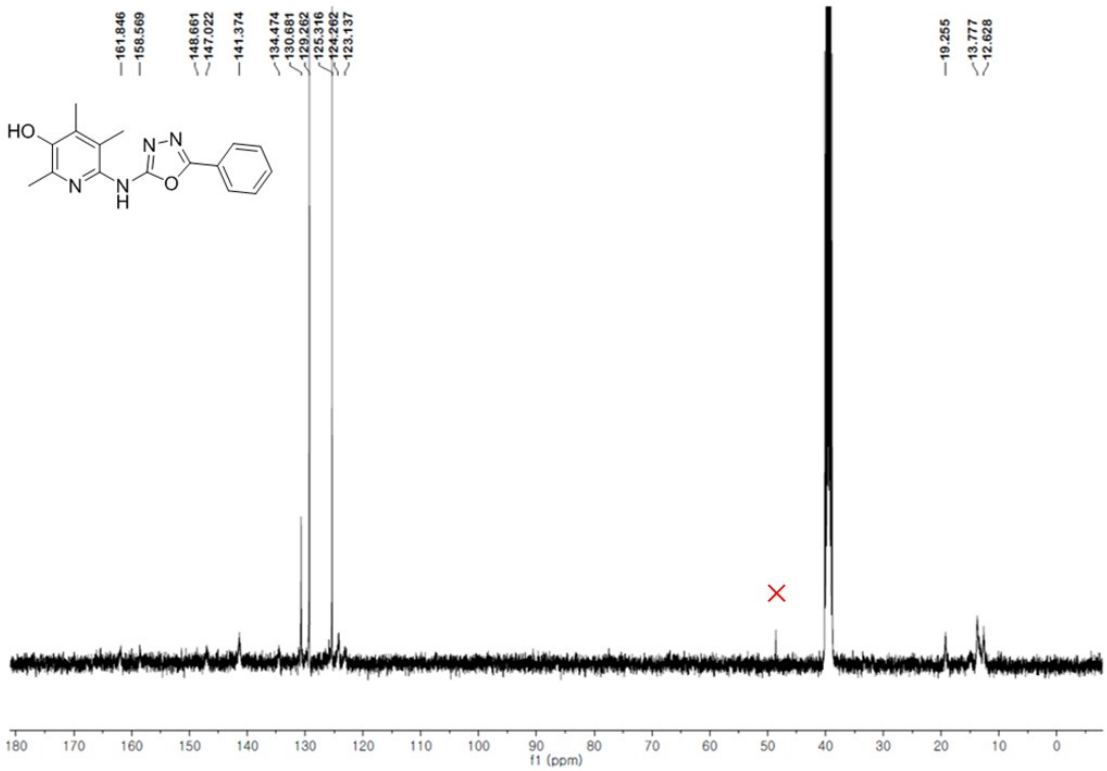
^{13}C-NMR of **15a** (DMSO-d_6)



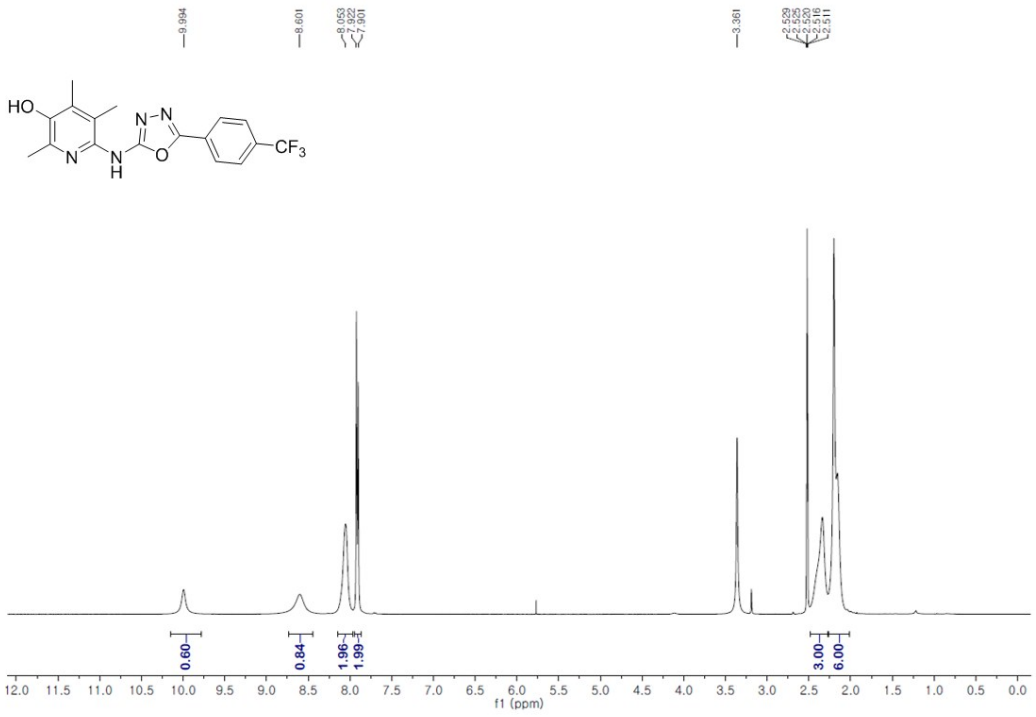
^{1}H-NMR of **15b** (DMSO-d_6)



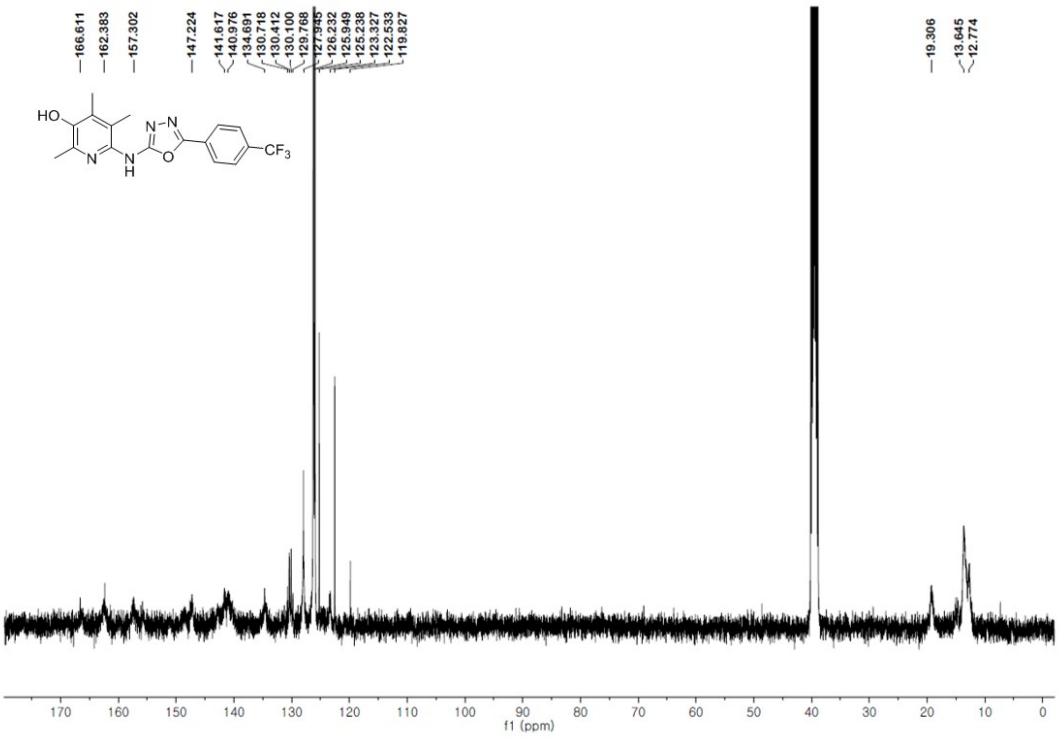
^{1}H-NMR of **15c** (DMSO-d_6)



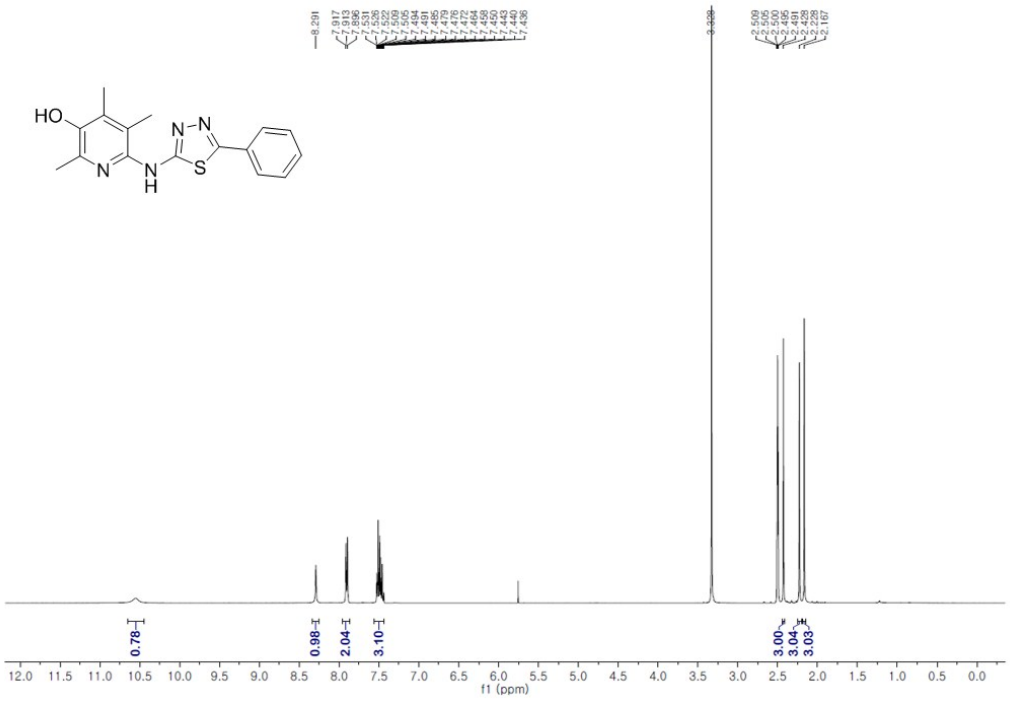
^{13}C-NMR of **15c** (DMSO-d_6)



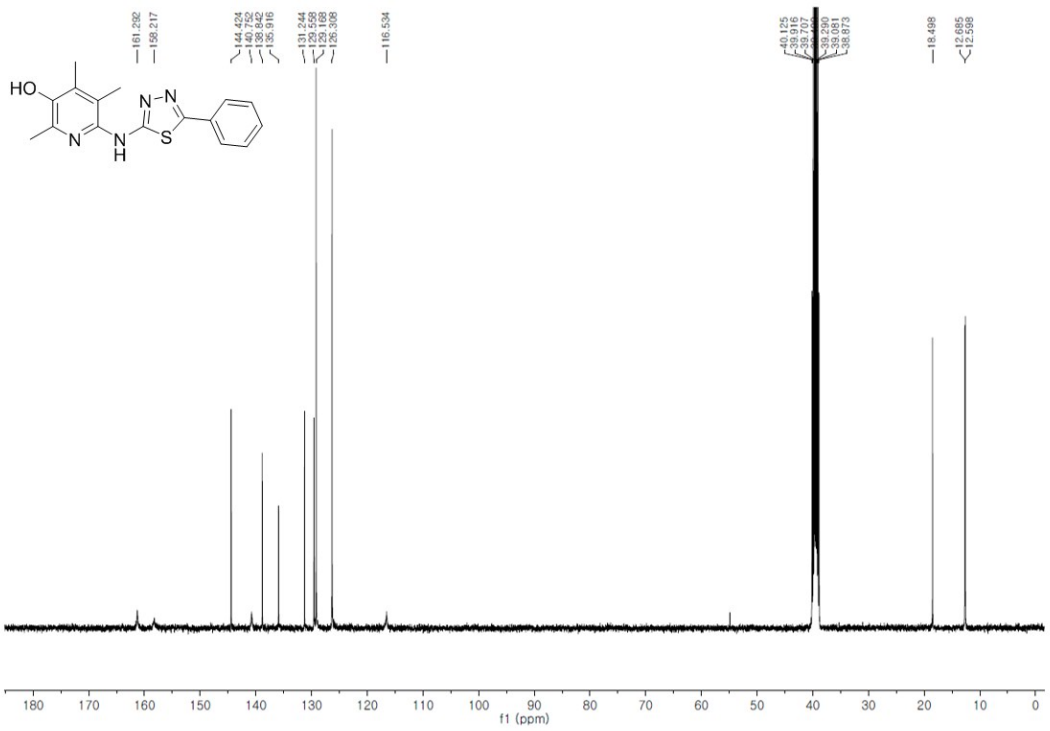
^{1}H-NMR of **15d** (DMSO-d_6)



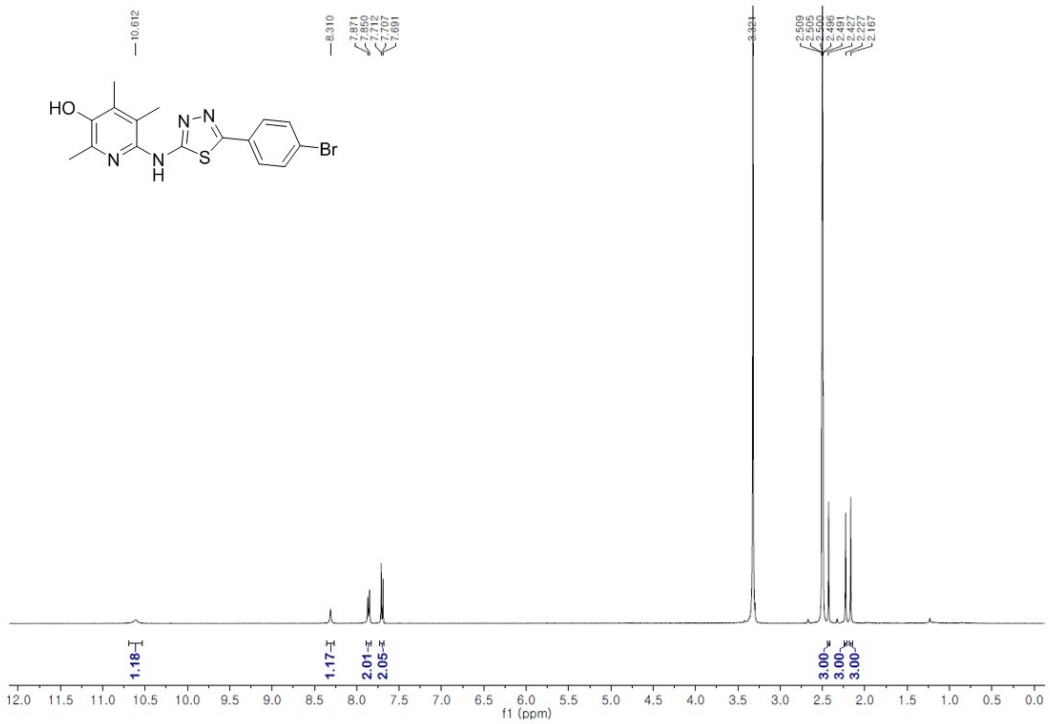
^{13}C-NMR of **15d** (DMSO-d_6)



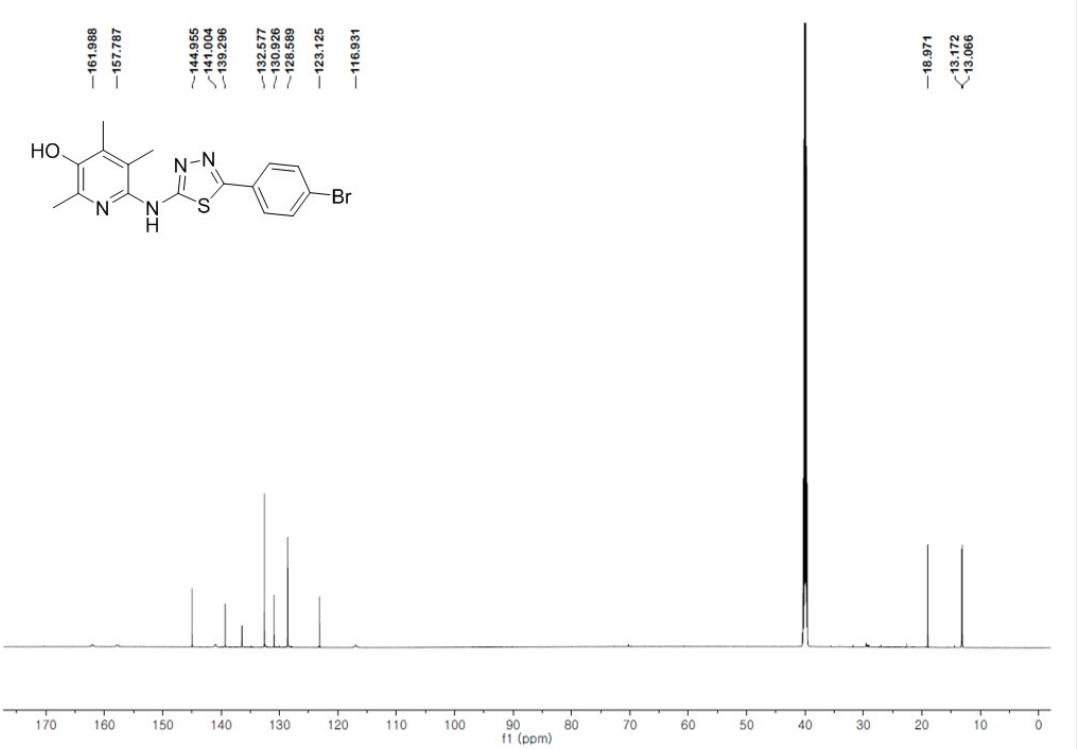
^{1}H-NMR of **16a** (DMSO-d_6)



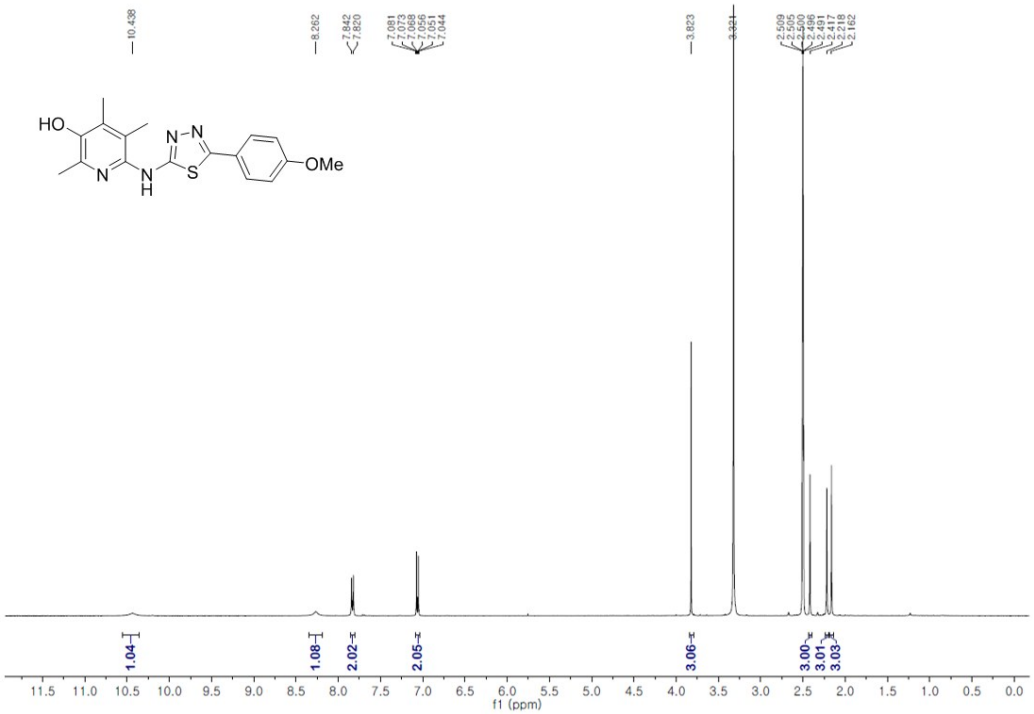
^{13}C-NMR of **16a** (DMSO-d_6)



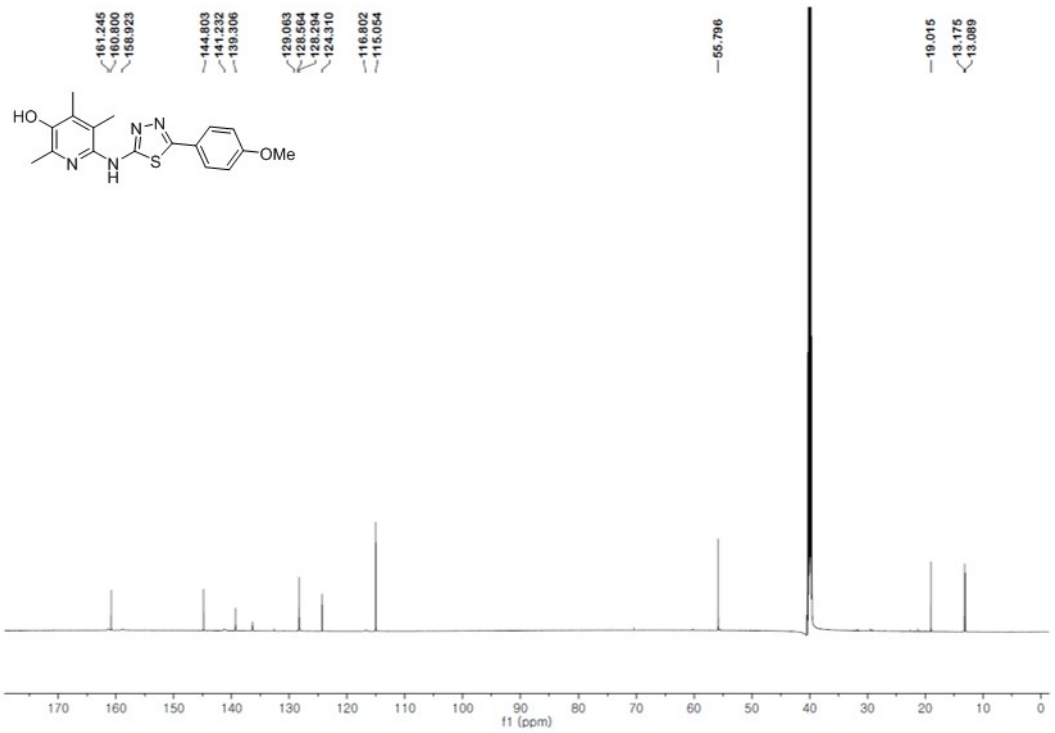
^{1}H-NMR of **16b** (DMSO-d_6)



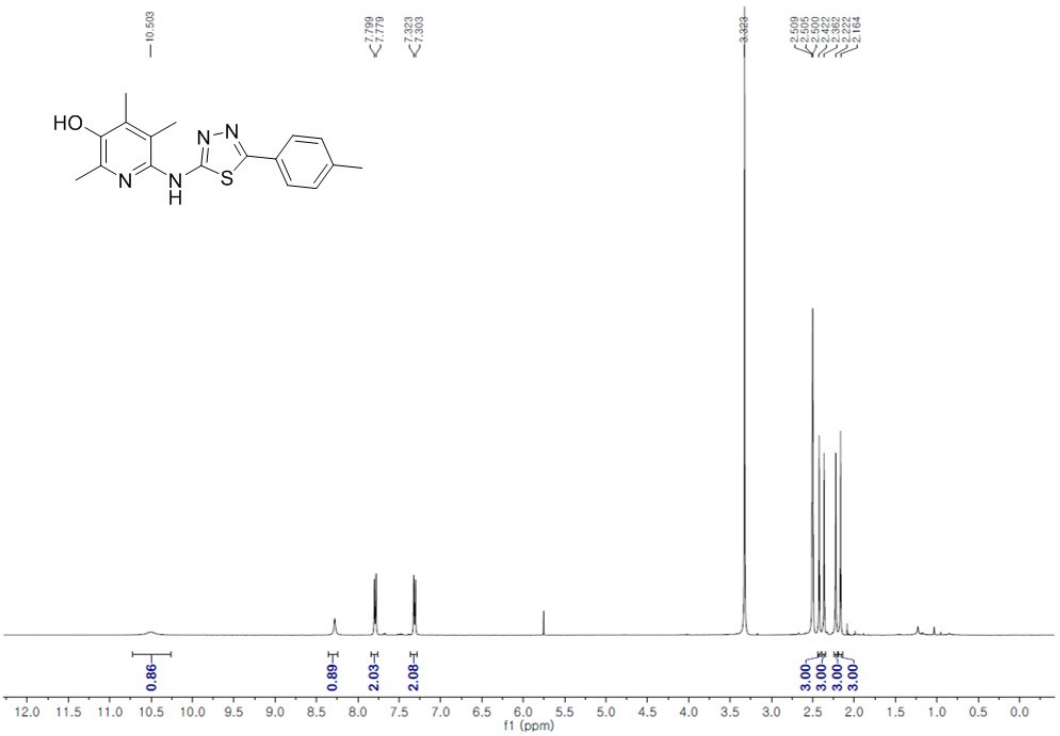
^{13}C-NMR of **16b** (DMSO-d_6)



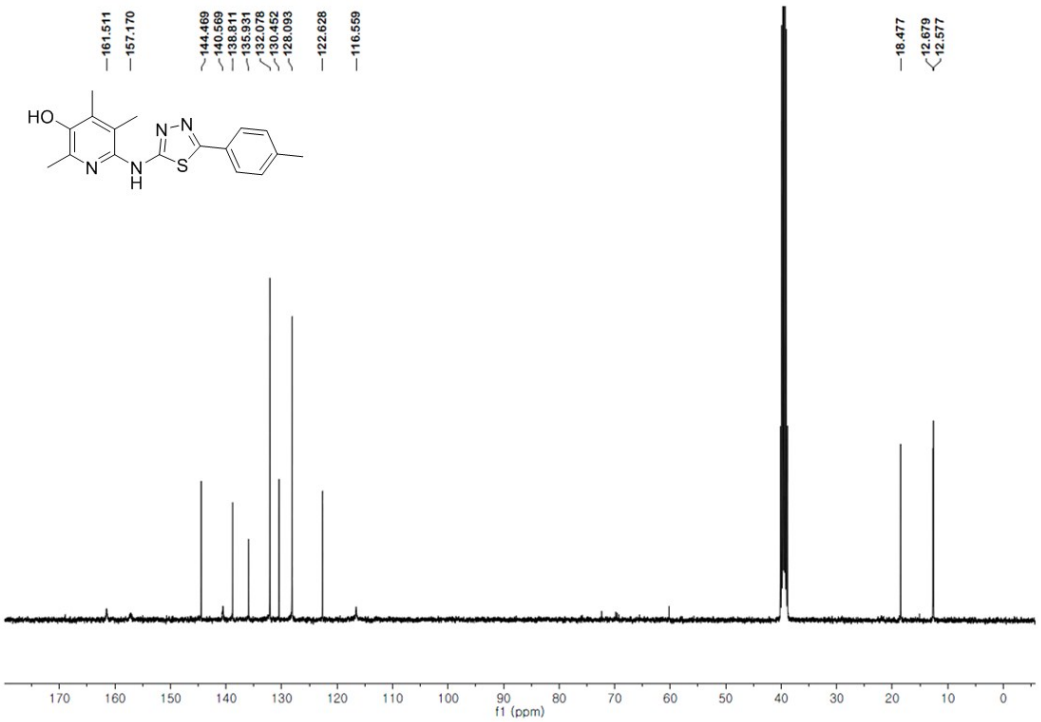
^{1}H-NMR of **16c** (DMSO-d_6)



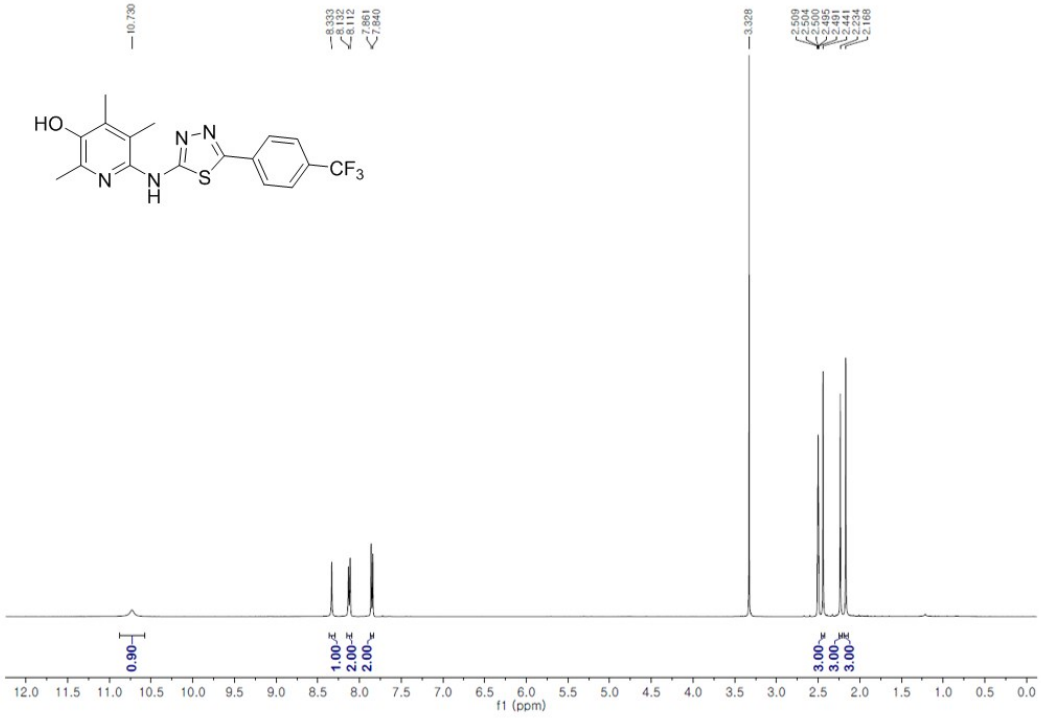
^{13}C-NMR of **16c** (DMSO-d_6)



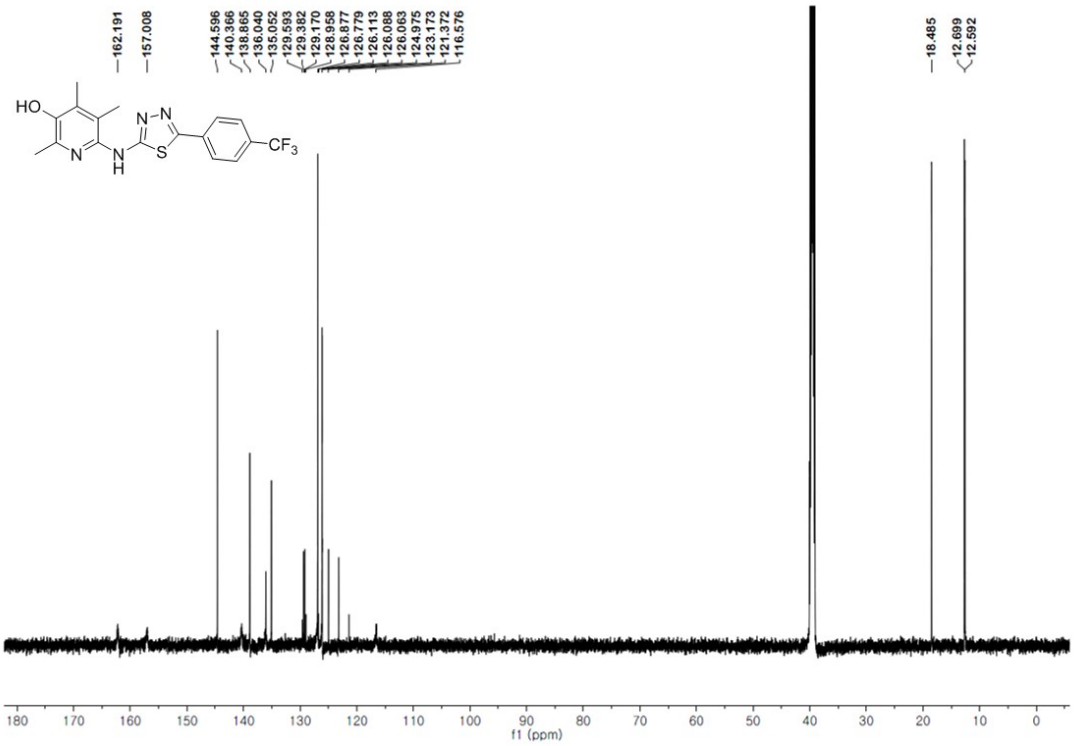
^{1}H-NMR of **16d** (DMSO-d_6)



^{13}C-NMR of **16d** (DMSO-d_6)



^{1}H-NMR of **16e** (DMSO-d_6)



^{13}C-NMR of **16e** (DMSO-d_6)

HPLC traces of compounds 6f and 16a

Mobile Phase A: MeCN (0.1 % Formic acid); Mobile Phase B: H_2O (0.1% Formic acid)

Elution: 10% A → 100% A (0 min → 20 min)

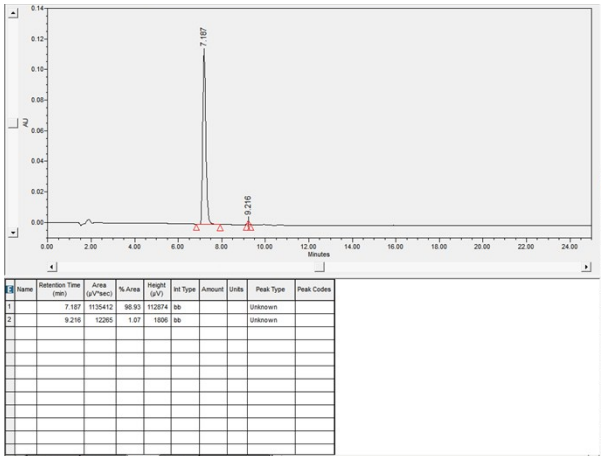
100% A (20 min → 25 min)

100% A → 10% A (25 min → 35 min)

Flow rate: 0.3 mL/min

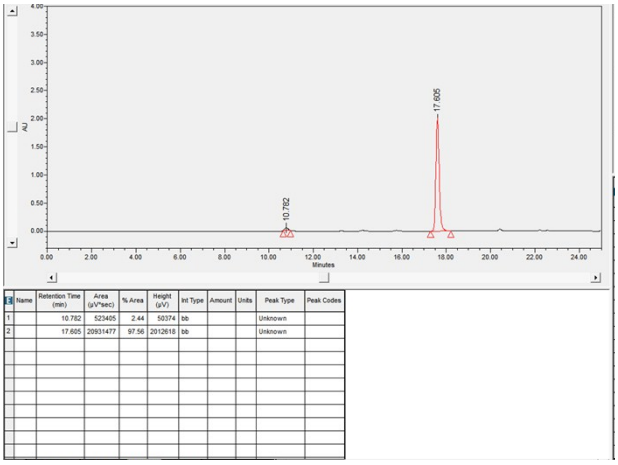
Column: INNO column C18, 3 μM, 120 A, 2.0×100 mm

Detection: UV (254 nm)



	Name	Retention Time (min)	Area (μV*sec)	% Area	Height (μV)	Int Type	Amount	Units	Peak Type	Peak Codes
1		7.187	1135412	98.93	112874	bb			Unknown	
2		9.216	12265	1.07	1806	bb			Unknown	

HPLC chromatogram of compound **6f**



	Name	Retention Time (min)	Area (μV*sec)	% Area	Height (μV)	Int Type	Amount	Units	Peak Type	Peak Codes
1		10.782	523405	2.44	50374	bb			Unknown	
2		17.605	20931477	97.56	2012618	bb			Unknown	

HPLC chromatogram of compound **16a**

References

1. Thapa, D.; Lee, J. S.; Park, M. A.; Cho, M. Y.; Park, Y. J.; Choi, H. G.; Jeong, T. C.; Kim, J.-A. Inhibitory effects of clotrimazole on TNF-alpha-induced adhesion molecule expression and angiogenesis. *Arch. Pharmcal.Res.* **2009**, *32(4)*, 593–603.