Supporting Information

Structure-Activity Relationships of Styrylquinoline and Styrylquinoxaline Derivatives as α-Synuclein Imaging Probes

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Synthesis method for known compounds

1. Materials and Methods

General Remarks

All reagents were commercial products used without further purification unless indicated otherwise. All compounds were purified by Smart Flash EPCLC W-Prep 2XY (Yamazen Corporation, Osaka, Japan) unless otherwise stated. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-ECS400 and JEOL JNM-ECA500 (JEOL, Tokyo, Japan) with tetramethylsilane as an internal standard. Coupling constants are reported in Hertz. Multiplicity was defined as singlet (s), doublet (d), triplet (t), quartet (q), or multiplet (m). ESI mass spectrometry was conducted with a Shimadzu LCMS-2020 EV (Shimadzu, Kyoto, Japan). High-resolution mass spectrometry (HRMS) was carried out with a JEOL JMS-700 (JEOL). HPLC was performed with a Shimadzu system (an LC-20AD pump with SPD-20A UV detector, λ = 254 nm) using a Cosmosil C_{18} column ($5C_{18}$-AR-II 4.6 mm I.D. × 150 mm, Nacalai Tesque, Kyoto, Japan) and MeCN/H_2O (with 0.1% TFA) or MeCN/H_2O as the mobile phase at a flow rate of 1.0 mL/min. All key compounds were proven by this method to show > 95% purity. No unexpected or unusually high safety hazards were encountered.

Chemistry

7-Bromo-2-methylquinoxaline (1)/ 6-Bromo-2-methylquinoxaline (1') [1]

To a stirred solution of 4-bromo-1,2-benzenediamine (600 mg, 3.21 mmol) in EtOH (6.00 mL) was added pyruvic aldehyde (35-45%, w/w aq. soln) (2.40 mL, 11.7-15.0 mmol) at 25 °C. After being stirred for 10 min, the mixture was diluted with H_2O. The whole solution was extracted with AcOEt. The extract was washed with brine, and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by flash chromatography over silica gel with *n*-hexane-EtOAc (2:1) to give mixture of **1** and **1'** as a yellow solid (621 mg, 87%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.70−2.79 (m, 3H), 7.69−7.96 (m, 2H), 8.11−8.27 (m, 1H), 8.64−8.78 (m, 1H); LC-MS *m/z*: $[M + H]^+$ calcd for $C_9H_8BrN_2$, 223.0, 225.0; found, 223.0, 225.0.

(E)-N,N-Dimethyl-4-(2-(7-(tributylstannyl)quinoxalin-2-yl)vinyl)aniline (**2**)

To a stirred solution of a mixture of **1** and **1'** (408 mg, 1.83 mmol, 1.00 eq.), *p*-dimethylaminobenzaldehyde (1030 mg, 7.31 mmol), and piperidine (4.10 mL) in dry toluene (15.0 mL) was added AcOH (4.10 mL) dropwisely at 25 °C under Ar. After being stirred for 24 h at 120 °C, the mixture was diluted with saturated aqueous $NaHCO_3$. The whole solution was extracted with AcOEt. The extract was washed with brine, and dried

over Na_2SO_4. After concentration *in vacuo*, the residue was purified by flash chromatography over silica gel with *n*-hexane-AcOEt (6:1) to give a crude styryl compound as a red solid (1.12 g). To a stirred solution of the crude styryl compound (48.1 mg, 0.136 mmol) and Bu_4Sn (323 mg, 0.557 mmol) in dry toluene (3.30 mL) was added $Pd(PPh_3)_4$ (15.7 mg, 0.0136 mmol) under Ar. After being stirred for 8 h at 110 °C, the mixture was diluted with H_2O. The whole solution was extracted with $CHCl_3$. After concentration *in vacuo*, the residue was purified by flash chromatography over silica gel with *n*-hexane-AcOEt (6:1) to give **2** as a red solid (19.0 mg, 3.4% yield, 2 steps): ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (m, 9H), 1.16 (m, 6H), 1.36 (m, 6H), 1.59 (m, 6H), 3.03 (s, 6H), 6.74 (d, J = 8.7 Hz, 2H), 7.18 (d, J = 16.0 Hz, 1H), 7.56 (d, J = 8.7 Hz, 2H), 7.72−7.82 (m, 2H), 7.97 (d, J = 8.2 Hz, 2H), 8.14 (s, 1H), 8.99 (s, 1H); LC-MS *m/z*: $[M + H]^+$ calcd for $C_{30}H_{44}N_3Sn$, 566.3; found, 566.2.

(E)-4-(2-(7-Iodoquinoxalin-2-yl)vinyl)-N,N-dimethylaniline (**3, ISQ**)

To a stirred solution of **2** (55.4 mg, 0.0981 mmol) in $CHCl_3$ (0.750 mL) was added I_2 (24.9 mg, 0.0981 mmol) in $CHCl_3$ (0.750 mL). After being stirred for 2 h at 25 °C, the mixture was quenched with saturated aqueous $NaHSO_3$. The whole solution was extracted with $CHCl_3$. The extract was washed with brine and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by flash chromatography over silica gel with *n*-hexane-AcOEt (6:1) to give **3** (ISQ) as a red solid (20.8 mg, 53% yield). The structure of **3** was confirmed by X-ray crystallography: ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.03 (s, 6H), 6.72 (d, J = 8.2 Hz, 2H), 7.11 (d, J = 16.0 Hz, 1H), 7.54 (d, J = 8.2 Hz, 2H), 7.71 (d, J = 8.7 Hz, 1H), 7.80 (d, J = 16.0 Hz, 1H), 7.84−7.89 (m, 1H), 8.41−8.44 (m, 1H), 8.94 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 40.2 (2C), 96.0, 112.0 (2C), 119.8, 123.7, 129.1 (2C), 130.3, 137.1, 137.7, 137.8, 140.2, 143.4, 145.1, 151.2, 152.1; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{17}N_3I$, 402.0467; found, 402.0463.

(E)-4-(2-(7-(2-Fluoroethoxy)quinoxalin-2-yl)vinyl)-N,N-dimethylaniline (**4**, **SQ1**)
(E)-4-(2-(6-(2-Fluoroethoxy)quinoxalin-2-yl)vinyl)-N,N-dimethylaniline (**5**, **SQ2**)

The same reaction as described above to prepare the crude styryl compound (synthesis of **2**) was used. To a stirred solution of the crude styryl compound (1.12 g), $Cu(acac)_2$ (79.1 mg, 0.302 mmol), $LiOH·H_2O$ (436 mg, 10.4 mmol), and N^1, N^2-bis(4-hydroxy-2,6-dimethylphenyl)oxalamide (99.2 mg, 0.302 mmol) in dry DMSO (6.00 mL) was added sonicated H_2O (1.50 mL) under Ar. After being stirred for 24 h at 80 °C under Ar, the mixture was dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by flash chromatography over silica gel with *n*-hexane-AcOEt (6:1) and $CHCl_3$-MeOH

(10:1) following flash chromatography over amino silica gel with *n*-hexane-AcOEt (6:1) and $CHCl_3$-MeOH (10:1) to give a crude phenol compound as a red liquid (224 mg). To a stirred solution of the crude phenol compound (169 mg) and Cs_2CO_3 (860 mg, 2.64 mmol) in dry DMF (6.00 mL) was added 2-fluoroethyl *p*-toluenesulfonate (444 μL, 2.60 mmol) under Ar. After being stirred overnight at 95 °C under Ar, the mixture was diluted with H_2O. The whole solution was extracted with AcOEt. The extract was washed with brine, and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by flash chromatography over amino silica gel with *n*-hexane-AcOEt 4:1 to 2:1 to give **4** (SQ1) as an orange solid (45.0 mg, 6.2% yield, 3 steps) and **5** (SQ2) as an orange solid (38.0 mg, 7.3% yield, 3 steps). The structures of **4** and **5** were confirmed by X-ray crystallography. [**4**]: ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.01 (s, 6H), 4.33 (t, J = 4.1 Hz, 1H), 4.40 (t, J = 4.1 Hz, 1H), 4.78 (t, J = 4.1 Hz, 1H), 4.90 (t, J = 4.1 Hz, 1H), 6.71 (d, J = 8.7 Hz, 2H), 7.11 (d, J = 16.2 Hz, 1H), 7.28 (d, J = 2.3 Hz, 1H), 7.33 (dd, J = 9.3, 2.3 Hz, 1H), 7.53 (d, J = 8.7 Hz, 2H), 7.76 (d, J = 16.2 Hz, 1H), 7.91 (d, J = 9.3 Hz, 1H), 8.83 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 40.2 (2C), 67.3, 67.5, 80.7, 82.4, 107.1, 112.1 (2C), 120.4, 121.6, 124.0, 128.9 (2C), 130.2, 136.6, 137.3, 142.3, 143.9, 151.0, 151.6, 159.6; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{21}FN_3O$, 338.1669; found, 338.1670. [**5**]: ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.00 (s, 6H), 4.29−4.34 (m, 1H), 4.36−4.42 (m, 1H), 4.73−4.79 (m, 1H), 4.85−4.91 (m, 1H), 6.71 (d, J = 8.7 Hz, 2H), 7.11−7.20 (m, 2H), 7.32−7.36 (m, 1H), 7.45−7.54 (m, 3H), 7.55−7.65 (m, 2H), 7.96 (d, J = 8.1, 3.5 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 40.2 (2C), 67.0, 67.2, 80.8, 82.5, 107.7, 112.1 (2C), 117.2.5, 118.7. 122.4, 124.3, 124.6, 128.5 (2C), 128.6, 134.6, 135.6, 149.7, 150.7, 157.2, 159.5; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{21}FN_3O$, 338.1669; found, 338.1670.

7-Bromo-2-methylquinoline (6) [2]

To a stirred solution of 3-bromoaniline (1170 μL, 10.7 mmol) in AcOH (10.0 mL) was added ethyl vinyl ether (3.08 mL, 32.0 mmol). After being stirred for 5 h at 25 °C, the temperature was increased to 100 °C. After being stirred for 4 h at 100 °C, the mixture was quenched with aqueous NaOH. The whole solution was extracted with EtOAc. The extract was washed with brine, and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by flash chromatography over silica gel with *n*-hexane-EtOAc (8:1) to give **6** as a yellow solid (431 mg, 18% yield): ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.70 (s, 3H), 7.23 (d, J = 8.7 Hz, 1H), 7.49 (dd, J = 8.7, 1.2 Hz, 1H), 7.55 (d, J = 8.7 Hz, 1H), 7.92 (dd, J = 8.7, 2.9 Hz, 2H), 8.17 (d, J = 1.2 Hz, 1H); LC-MS *m/z*: $[M + H]^+$ calcd for $C_{10}H_9NBr$, 221.0, 223.0; found, 221.1, 223.1.

6-Bromo-2-methylquinoline (7) [2]

By a procedure identical to that described for synthesis of **6,** 4-bromoaniline (860 mg, 5.00 mmol) and ethyl vinyl ether (1.44 mL, 15.0 mmol) were converted into **7** as a yellow solid (432 mg, 39% yield): ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.67 (s, 3H), 7.17 (d, J = 8.7 Hz, 1H), 7.66 (dd, J = 8.7, 1.7 Hz, 1H), 7.75−7.85 (m, 3H); LC-MS *m/z*: $[M + H]^+$ calcd for $C_{10}H_9NBr$, 221.0, 223.0; found, 221.1, 223.1.

5-Bromo-2-methylquinoline (8) [3]

To a stirred solution of 2-methylquinoline (2.19 g, 15.3 mmol) in conc. H_2SO_4 (15.0 mL) was added NBS (2.72 g, 15.3 mmol) under Ar. After being stirred overnight at 25 °C, the mixture was diluted with iced H_2O. After being quenched with saturated aqueous Na_2SO_3, the whole solution was extracted with $CHCl_3$. The extract was washed with brine, and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by flash chromatography over silica gel with *n*-hexane-EtOAc (10:1) to give **8** as a yellow solid (195 mg, 6% yield): ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.73 (s, 3H), 7.29 (d, J = 8.7 Hz, 1H), 7.48 (d, J = 8.1 Hz, 1H), 7.70 (dd, J = 8.1, 8.1 Hz, 1H), 7.96 (d, J = 8.7 Hz, 1H), 8.33 (d, J = 8.1 Hz, 1H), 7.92 (d, J = 8.7 Hz, 1H); LC-MS *m/z*: $[M + H]^+$ calcd for $C_{10}H_9NBr$, 221.0, 223.0; found, 221.1, 223.1.

8-Bromo-2-methylquinoline (9) [3]

By a procedure identical to that described for synthesis of **8**, 2-methylquinoline (2.19 g, 15.3 mmol) and NBS (2.72 g, 15.3 mmol) were converted into **9** as a yellow solid (493 mg, 15% yield): ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.73 (s, 3H), 7.15−7.23 (m, 2H), 7.56−7.61 (m, 1H), 7.86 (d, J = 8.7 Hz, 1H), 7.92 (d, J = 8.7 Hz, 1H); LC-MS *m/z*: $[M + H]^+$ calcd for $C_{10}H_9NBr$, 221.0, 223.0; found, 221.1, 223.1.

6-(Dimethylamino)nicotinaldehyde (10) [4]

To a stirred solution of $NHMe_2$ in H_2O (abt. 50%, 10.0 mL) was added 2-chloro-5-pyridinecarbaldehyde (1040 mg, 7.34 mmol). After being stirred for 4 h at 90 °C, the mixture was diluted with H_2O. The whole solution was extracted with EtOAc. The extract was washed with brine, and dried over Na_2SO_4. Evaporate the solvent *in vacuo* to give **10** as a white solid (1170 mg, quant.): ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.21 (s, 6H), 6.55 (d, J = 8.7 Hz, 1H), 7.89 (dd, J = 2.3, 8.7 Hz, 1H), 8.55 (d, J = 2.3 Hz, 1H), 9.76 (s, 1H); LC-MS *m/z*: $[M + H]^+$ calcd for $C_8H_{11}N_2O$, 151.1; found, 151.1.

4-(1H-1,2,3-Triazol-1-yl)benzaldehyde (11) [5]

To a stirred solution of 4-fluorobenzaldehyde (2.00 g, 16.0 mmol) and 1, 2, 3 triazole (1.32 g, 19.0 mmol) in DMF (50.0 mL) was added K_2CO_3 (3.30g, 23.9 mmol). After being stirred for 5 h at 100 °C, the mixture was diluted with H_2O. The whole solution was extracted with EtOAc. The extract was washed with brine, and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by flash chromatography over silica gel with *n*-hexane-EtOAc (1:1) to give crude phenol compound as a yellow solid (792 mg, 29% yield): ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.21 (s, 6H), 6.55 (d, J = 8.7 Hz, 1H), 7.89 (dd, J = 2.3, 8.7 Hz, 1H), 8.55 (d, J = 2.3 Hz, 1H), 9.76 (s, 1H).

2-(2-(2-(Tosyloxy)ethoxy)ethoxy)ethyl hypofluorite (12) [6]

To a stirred solution of triethylene glycol bis(*p*-toluenesulfonate) (608 mg, 1.21 mmol) in dry THF (5.00 mL) was added TBAF in THF (1.0 M, 2.42 mL) under Ar. The mixture was stirred for 15 min at 70 °C. After concentration *in vacuo*, the residue was purified by flash chromatography over silica gel with *n*-hexane-EtOAc 4:1 to EtOAc only to give **12** as a colorless liquid (350 mg, 90% yield): ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.46 (s, 3H), 3.50−3.80 (m, 8H), 4.09−4.21 (m, 2H), 4.49 (t, J = 4.1 Hz, 1H), 4.61 (t, J = 4.1 Hz, 1H), 7.36 (d, J = 7.5 Hz, 2H), 7.80 (d, J = 7.5 Hz, 2H); LC-MS *m/z*: $[M + H]^+$ calcd for $C_{13}H_{19}FO_6SNa$, 345.1; found, 345.1.

1-Chloro-3-fluoropropan-2-ol (13) [7]

The solution of epichlorohydrin (1.00 g, 10.8 mmol) in TREAT HF (1.77 mL, 10.8 mmol) was stirred for 2 h at 130 °C in a sealed tube. The mixture was stirred for 15 min at 70 °C. After being quenched with iced H_2O, the whole solution was extracted with AcOEt. The extract was washed with brine, and dried over Na_2SO_4. Evaporate the solvent *in vacuo* to give crude **13** as a colorless liquid (1000 mg).

(E)-4-(2-(7-(2-Fluoroethoxy)quinolin-2-yl)vinyl)-N,N-dimethylaniline (**14**, **SQ3**)

To a stirred solution of **6** (353 mg, 1.59 mmol, 1.00 eq.), *p*-dimethylaminobenzaldehyde (949 mg, 6.36 mmol), and piperidine (4.10 mL) in dry toluene (15.9 mL) was added AcOH (4.10 mL) dropwisely at 25 °C under Ar. After being stirred for 24 h at 120 °C, the mixture was diluted with saturated aqueous $NaHCO_3$. The whole solution was extracted with AcOEt. The extract was washed with brine, and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by flash chromatography over silica gel with *n*-hexane-AcOEt (6:1) to give a crude styryl compound as a yellow solid (920 mg). To a stirred solution of the crude styryl compound

(920 mg), $Cu(acac)_2$ (65.0 mg, 0.248 mmol), $LiOH·H_2O$ (359 mg, 8.56 mmol), and N^1, N^2-bis(4-hydroxy-2,6-dimethylphenyl)oxalamide (81.5 mg, 0.248 mmol) in dry DMSO (6.00 mL) was added sonicated H_2O (1.50 mL). After being stirred for 24 h at 80 °C under Ar, the mixture was dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by flash chromatography over silica gel with *n*-hexane-AcOEt (6:1) and $CHCl_3$-MeOH (10:1) following flash chromatography over amino silica gel with *n*-hexane-AcOEt (6:1) and $CHCl_3$-MeOH (10:1) to give a crude phenol compound as a black liquid (127 mg). To a stirred solution of the crude phenol compound (126 mg), and NaH (31.0 mg, 1.30 mmol) in dry DMF (6.00 mL) was added 2-fluoroethyl *p*-toluenesulfonate (222 μL, 1.30 mmol). After being stirred overnight at 95 °C, the mixture was diluted with H_2O. The whole solution was extracted with AcOEt. The extract was washed with brine, and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by flash chromatography over silica gel with *n*-hexane-AcOEt (6:1) and $CHCl_3$-MeOH (10:1) following flash chromatography over amino silica gel with *n*-hexane-AcOEt (6:1) and $CHCl_3$-MeOH (10:1) to give **14** as a yellow solid (92.4 mg, 17% yield): ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.01 (s, 6H), 4.32 (t, J = 4.1 Hz, 1H), 4.39 (t, J = 4.1 Hz, 1H), 4.77 (t, J = 4.1 Hz, 1H), 4.89 (t, J = 4.1 Hz, 1H), 6.72 (d, J = 8.7 Hz, 2H), 7.12 (d, J = 16.2 Hz, 2H), 7.32 (d, J = 2.3 Hz, 1H), 7.42 (dd, J = 9.3, 2.3 Hz, 1H), 7.53 (d, J = 8.7 Hz, 2H), 7.72 (d, J = 16.2 Hz, 1H), 7.92 (d, J = 9.3 Hz, 1H), 8.91 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 40.2 (2C), 67.3, 67.5, 80.7, 82.4, 107.6, 112.1 (2C), 120.5, 123.1, 124.2, 128.7 (2C), 130.0, 135.5, 138.7, 142.3, 144.5, 149.7, 150.9, 158.5; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{22}FN_2O$, 337.1716; found, 337.1718.

(E)-4-(2-(6-(2-Fluoroethoxy)quinolin-2-yl)vinyl)-N,N-dimethylaniline (**15**, **SQ4**)

To a stirred solution of a mixture of **7** (432 mg, 1.95 mmol, 1.00 eq.), *p*-dimethylaminobenzaldehyde (1370 mg, 9.72 mmol), and piperidine (4.31 mL) in dry toluene (16.0 mL) was added AcOH (4.31 mL) dropwisely at 25 °C under Ar. After being stirred for 24 h at 120 °C, the mixture was diluted with saturated aqueous $NaHCO_3$. The whole solution was extracted with AcOEt. The extract was washed with brine, and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by flash chromatography over silica gel with *n*-hexane-AcOEt (6:1) to give a crude styryl compound as a yellow solid (622 mg). To a stirred solution of the crude styryl compound (622 mg), $Cu(acac)_2$ (46.0 mg, 0.176 mmol), $LiOH·H_2O$ (359 mg, 9.13 mmol), and N^1, N^2-bis(4-hydroxy-2,6-dimethylphenyl)oxalamide (57.4 mg, 0.175 mmol) in dry DMSO (6.00 mL) was added sonicated H_2O (1.50 mL). After being stirred for 24 h at 80 °C under Ar, the mixture was dried over Na_2SO_4. After concentration *in vacuo*, the residue was

purified by flash chromatography over silica gel with *n*-hexane-AcOEt (6:1) and $CHCl_3$-MeOH (10:1) following flash chromatography over amino silica gel with *n*-hexane-AcOEt (6:1) and $CHCl_3$-MeOH (10:1) to give a crude phenol compound as a black liquid (394 mg). To a stirred solution of the crude phenol compound (394 mg), Cs_2CO_3 (1330 mg, 4.07 mmol) in dry DMF (6.00 mL) was added 2-fluoroethyl *p*-toluenesulfonate (347 μL, 2.04 mmol). After being stirred overnight at 95 °C, the mixture was diluted with H_2O. The whole solution was extracted with AcOEt. The extract was washed with brine, and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by flash chromatography over amino silica gel with *n*-hexane-AcOEt 4:1 to 1:1 and silica gel with *n*-hexane-AcOEt 3:1 to 2:1 to give **15** as a yellow solid (92.4 mg, 17% yield): ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.00 (s, 6H), 4.29 (t, J = 4.1 Hz, 1H), 4.36 (t, J = 4.1 Hz, 1H), 4.76 (t, J = 4.1 Hz, 1H), 4.88 (t, J = 4.1 Hz, 1H), 6.72 (d, J = 8.7 Hz, 2H), 7.04 (d, J = 2.9 Hz, 1H), 7.18 (d, J = 16.2 Hz, 1H), 7.37 (dd, J = 8.7, 2.9 Hz, 1H), 7.47−7.57 (m, 3H), 7.60 (d, J = 8.7 Hz, 1H), 7.93−7.98 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 40.3 (2C), 67.2, 67.4, 81.0, 82.7, 106.4, 112.2 (2C), 119.4. 122.0, 124.4, 124.8, 127.7, 128.4 (2C), 130.5, 133.8, 134.9, 144.4, 150.6, 155.0, 156.0; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{22}FN_2O$, 337.1716; found, 337.1711.

(E)-4-(2-(5-(2-Fluoroethoxy)quinolin-2-yl)vinyl)-N,N-dimethylaniline (**16**, **SQ5**)

By a procedure identical to that described for synthesis of **15,** quinolone **8** (195 mg, 0.882 mmol, 1.00 eq.), *p*-dimethylaminobenzaldehyde (896 mg, 6.01 mmol), and 2-fluoroethyl *p*-toluenesulfonate (347 μL, 2.04 mmol) were converted into **16** as a red solid (8.90 mg, 3.0% yield, 3 steps): ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.01 (s, 6H), 4.33 (t, J = 4.1 Hz, 1H), 4.40 (t, J = 4.1 Hz, 1H), 4.77 (t, J = 4.1 Hz, 1H), 4.89 (t, J = 4.1 Hz, 1H), 6.66 (d, J = 8.72 Hz, 2H), 6.89 (d, J = 8.1 Hz, 1H), 7.37 (t, J = 16.2 Hz, 1H), 7.52 (t, J = 8.7 Hz, 2H), 7.66−7.83 (m, 5H), 8.75 (d, J = 8.7 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 40.3 (2C), 68.1, 68.3, 80.5, 82.2, 107.4, 112.4 (2C), 112.6, 113.2, 116.6, 118.4, 122.6, 131.3 (2C), 134.6, 137.7, 139.1, 145.7, 152.5, 154.0, 154.2; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{22}FN_2O$, 337.1716; found, 337.1718.

(E)-4-(2-(8-(2-Fluoroethoxy)quinolin-2-yl)vinyl)-N,N-dimethylaniline (**17**, **SQ6**)

By a procedure identical to that described for synthesis of **15**, quinoline **9** (493 mg, 2.22 mmol, 1.00 eq.), *p*-dimethylaminobenzaldehyde (1260 mg, 8.45 mmol), and 2-fluoroethyl *p*-toluenesulfonate (347 μL, 2.04 mmol) were converted into **17** as a red solid (3.06 mg, 0.4% yield, 3 steps): ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.02 (s, 6H), 4.53 (t, J = 4.6 Hz, 1H), 4.60 (t, J = 4.6 Hz, 1H), 4.93 (t, J = 4.6 Hz, 1H), 5.05 (t, J = 4.6 Hz, 1H),

6.73 (d, *J* = 8.7 Hz, 2H), 7.11 (d, *J* = 8.7 Hz, 1H), 7.29 (d, *J* = 16.8 Hz, 1H), 7.34−7.40 (m, 2H), 7.51−7.61 (m, 3H), 7.70 (d, *J* = 8.7 Hz, 1H), 8.05 (d, *J* = 8.7 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 40.4 (2C), 68.5, 68.7, 81.3, 83.0, 110.9, 112.2 (2C), 119.2, 120.6, 124.8, 125.1, 125.5, 128.3, 128.6 (2C), 134.4, 136.0, 140.5, 150.7, 154.0, 156.2; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{22}FN_2O$, 337.1716; found, 337.1714.

(E)-2-(4-(1H-1,2,3-Triazol-1-yl)styryl)-7-(2-fluoroethoxy)quinolone (**18**, **SQ7**)

By a procedure identical to that described for synthesis of **15**, quinoline **6** (300 mg, 1.35 mmol, 1.00 eq.), aldehyde **11** (792 mg, 4.57 mmol), and 2-fluoroethyl *p*-toluenesulfonate (338 μL, 1.98 mmol) were converted into **18** as a colorless solid (27.3 mg, 5.6% yield): ^{1}H NMR (400 MHz, DMSO-d^6): δ 4.40 (t, *J* = 4.1 Hz, 1H), 4.47 (t, *J* = 4.1 Hz, 1H), 4.77 (t, *J* = 4.1 Hz, 1H), 4.89 (t, *J* = 4.1 Hz, 1H), 7.25 (dd, *J* = 8.7, 2.9 Hz, 2H), 7.40 (d, *J* = 2.9 Hz, 1H), 7.55 (d, *J* = 16.2 Hz, 1H), 7.71 (d, *J* = 8.7 Hz, 1H), 7.85−7.92 (m, 3H), 7.93−8.01 (m, 5H), 8.29 (d, J = 8.7 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d^6): δ 107.9, 118.3, 119.0, 120.4 (2C), 122.5, 123.8, 128.6, 129.1, 129.9, 132.3, 134.5, 136.27, 136.32, 136.5, 149.3, 155.4, 159.3; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{18}FN_4O$, 361.1465; found, 361.1465.

(E)-2-(4-(1H-1,2,3-Triazol-1-yl)styryl)-6-(2-fluoroethoxy)quinolone (**19**, **SQ8**)

By a procedure identical to that described for synthesis of **15**, quinoline **7** (323 mg, 1.46 mmol, 1.00 eq.), aldehyde **11** (756 mg, 4.36 mmol), and 2-fluoroethyl *p*-toluenesulfonate (338 μL, 1.98 mmol) were converted into **19** as a colorless solid (3.9 mg, 0.7% yield): ^{1}H NMR (400 MHz, DMSO-d^6): δ 4.42 (t, *J* = 3.7 Hz, 1H), 4.50 (t, *J* = 3.7 Hz, 1H), 4.84 (t, *J* = 3.7 Hz, 1H), 4.95 (t, *J* = 3.7 Hz, 1H), 7.47 (d, *J* = 2.7 Hz, 1H), 7.51 (dd, *J* = 9.2, 2.7 Hz, 1H), 7.62 (d, *J* = 16.0 Hz, 1H), 7.85−7.94 (m, 2H), 7.97−8.08 (m, 6H), 8.32 (d, *J* = 9.2 Hz, 1H), 8.95 (d, *J* = 1.4 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d^6): δ 67.3, 67.5, 81.2, 82.9, 106.8, 120.3 (2C), 122.3, 123.0, 128.1, 128.4 (2C), 130.0, 130.3, 131.5, 134.5, 135.4, 136.2, 136.7, 143.7, 153.1, 156.1; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{17}FN_4O$, 361.1465; found, 361.1465.

(E)-5-(2-(7-(2-Fluoroethoxy)quinolin-2-yl)vinyl)-N,N-dimethylpyridin-2-amine (**20**, **SQ9**)

By a procedure identical to that described for synthesis of **15**, quinoline **6** (432 mg, 1.96 mmol, 1.00 eq.), aldehyde **10** (1020 mg, 6.79 mmol), and 2-fluoroethyl *p*-toluenesulfonate (304 μL, 1.78 mmol) were converted into **20** as a yellow solid (79.3 mg, 12% yield, 3steps): ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.14 (s, 6H), 4.34 (t, *J* = 4.6 Hz, 1H),

4.41 (t, J = 4.6 Hz, 1H), 4.78 (t, J = 4.6 Hz, 1H), 4.90 (t, J = 4.6 Hz, 1H), 6.56 (d, J = 8.7 Hz, 1H), 7.09−7.19 (m, 2H), 7.36 (d, J = 2.3 Hz, 1H), 7.49 (d, J = 8.7 Hz, 1H), 7.57 (d, J = 16.2 Hz, 1H) 7.65 (d, J = 8.7 Hz, 1H), 7.80 (dd, J = 8.7, 2.3 Hz, 1H), 8.00 (d, J = 8.7 Hz, 1H), 8.35 (d, J = 2.3 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 38.1 (2C), 67.0, 67.2, 80.9, 82.6, 106.0, 107.7, 117.4, 119.0, 120.5, 122.6, 124.9, 128.7, 131.6, 134.3, 135.9, 148.8, 149.8, 156.8, 159.1, 159.6; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{21}FN_3O$, 338.1669; found, 338.1672.

(E)-5-(2-(6-(2-Fluoroethoxy)quinolin-2-yl)vinyl)-N,N-dimethylpyridin-2-amine (**21**, **SQ10**)

By a procedure identical to that described for synthesis of **15**, quinoline **7** (430 mg, 1.94 mmol, 1.00 eq.), aldehyde **10** (1170 mg, 7.76 mmol), and 2-fluoroethyl *p*-toluenesulfonate (338 μL, 1.98 mmol) were converted into **21** as a colorless solid (12.2 mg, 1.9% yield, 3 steps): ^1H NMR (400 MHz, $CDCl_3$): δ 3.06 (s, 6H), 4.22 (t, J = 4.1 Hz, 1H), 4.29 (t, J = 4.1 Hz, 1H), 4.69 (t, J = 4.1 Hz, 1H), 4.80 (t, J = 4.1 Hz, 1H), 6.49 (d , J = 9.2 Hz, 1H), 6.97 (d , J = 2.7 Hz, 1H), 6.97 (d , J = 16.5 Hz, 1H), 7.31 (dd , J = 9.2, 2.7 Hz, 1H), 7.44 (d , J = 16.5 Hz, 1H), 7.52 (d , J = 8.7 Hz, 1H), 7.73 (dd , J = 8.7, 2.7 Hz, 1H), 7.88 (d , J = 2.3 Hz, 1H), 7.91 (d , J = 2.7 Hz, 1H), 8.26 (d , J = 2.3 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 38.1 (2C), 67.2, 67.4, 81.0, 82.7, 106.0 106.4, 119.4, 120.5, 122.2, 124.8, 127.8, 130.5, 130.8, 134.2, 135.1, 144.3, 148.6, 154.5, 156.1, 159.0; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{21}FN_3O$, 338.1669; found, 338.1672.

(E)-7-(2-Fluoroethoxy)-2-(4-nitrostyryl)quinolone (**22**, **SQ11**)

By a procedure identical to that described for synthesis of **15**, quinoline **6** (294 mg, 1.32 mmol, 1.00 eq.), *p*-nitrobenzaldehyde (999 mg, 6.61 mmol), and 2-fluoroethyl *p*-toluenesulfonate (147 μL, 0.861 mmol) were converted into **22** as a colorless solid (25.0 mg, 5.6% yield, 3 steps): ^1H NMR (400 MHz, $CDCl_3$): δ 4.37 (t, J = 4.6 Hz, 1H), 4.44 (t, J = 4.6 Hz, 1H), 4.80 (t, J = 4.6 Hz, 1H), 4.92 (t, J = 4.6 Hz, 1H), 7.23−7.26 (m, 1H), 7.40 (d, J = 2.3 Hz, 1H), 7.48 (d, J = 16.2 Hz, 1H), 7.54 (d, J = 8.7 Hz, 1H), 7.68−7.79 (m, 4H), 8.11 (d, J = 8.7 Hz, 1H), 8.26 (d, J = 8.7 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 67.1, 67.3, 80.8, 82.5, 107.9, 118.1, 120.2, 123.3, 124.2 (2C), 127.7 (2C), 128.8, 131.5, 133.2, 136.4, 143.0, 147.4, 149.9, 154.9, 160.0; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{16}FN_2O_3$, 339.1145; found, 339.1148

(E)-6-(2-Fluoroethoxy)-2-(4-nitrostyryl)quinolone (**23**, **SQ12**)

By a procedure identical to that described for synthesis of **15**, quinoline **7** (377 mg, 1.71 mmol, 1.00 eq.), *p*-nitrobenzaldehyde (1040 mg, 6.86 mmol), and 2-fluoroethyl *p*-toluenesulfonate (196 μL, 1.15 mmol) were converted into **23** as a colorless solid (38.6 mg, 8.3% yield, 3 steps): ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.31 (t, J = 4.6 Hz, 1H), 4.38 (t, J = 4.6 Hz, 1H), 4.78 (t, J = 4.6 Hz, 1H), 4.90 (t, J = 4.6 Hz, 1H), 7.08 (d, J = 2.3 Hz, 1H), 7.40−7.51 (m, 2H), 7.60 (d, J = 8.7 Hz, 1H), 7.64−7.75 (m, 3H), 7.98−8.07 (m, 2H), 8.22 (d, J = 8.7 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 67.3, 67.5, 80.9, 82.6, 106.2, 120.2, 122.8, 124.1 (2C), 127.5, 128.6, 130.6, 131.1, 133.1, 135.4, 143.1, 144.5, 147.2, 152.6, 156.9; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{16}FN_2O_3$, 339.1145; found, 339.1142.

(E)-4-(2-(7-(2-(2-(2-Fluoroethoxy)ethoxy)ethoxy)quinolin-2-yl)vinyl)-N,N-dimethylaniline (**24**, **SQ13**)

By a procedure identical to that described for synthesis of **15**, quinoline **6** (252 mg, 1.14 mmol, 1.00 eq.), *p*-dimethylaminobenzaldehyde (677 mg, 4.54 mmol), and fluorine **12 (**171 mg, 0.558 mmol) were converted into **25** as a yellow solid (2.7 mg, 0.6% yield): ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.02 (s, 6H), 3.64−3.76 (m, 6H), 3.89 (t, J = 4.1 Hz, 2H), 4.29 (t, J = 4.1 Hz, 2H), 4.44 (t, J = 4.1 Hz, 1H), 4.56 (t, J = 4.1 Hz, 1H), 6.65 (d, J = 8.7 Hz, 2H), 7.21(dd, J = 8.7, 2.3 Hz, 1H), 7.28 (d, J = 16.2 Hz, 1H), 7.51 (d, J = 8.7 Hz, 2H), 7.63 (d, J = 8.7 Hz, 1H), 7.67 (d, J = 8.7 Hz, 1H), 7.70−7.77 (m, 2H), 8.23 (d, J = 8.7 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 40.3 (2C), 68.5, 69.2, 70.3, 70.5, 70.8(2C), 82.3, 84.0, 100.4, 112.3 (2C), 112.8, 121.45, 121.55, 122.6, 129.1, 131.0 (2C), 140.9, 142.0 (2C), 144.4, 152.3, 153.0, 163.6; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{25}H_{30}FN_2O_3$, 425.2240; found, 425.2237.

(E)-4-(2-(6-(2-(2-(2-Fluoroethoxy)ethoxy)ethoxy)quinolin-2-yl)vinyl)-N,N-dimethylaniline (**25**, **SQ14**)

By a procedure identical to that described for synthesis of **15**, quinoline **7** (333 mg, 1.50 mmol, 1.00 eq.), *p*-dimethylaminobenzaldehyde (895 mg, 6.00 mmol), and fluorine **12 (**138 mg**,** 0.394 mmol) were converted into **25** as a yellow solid (40.0 mg, 6.3% yield, 3 steps): ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.91 (s, 6H), 3.60−3.73 (m, 6H), 3.84 (t, J = 4.6 Hz, 2H), 4.16 (t, J = 4.6 Hz, 2H), 4.42 (t, J = 4.6 Hz, 1H), 4.54 (t, J = 4.6 Hz, 1H), 6.64 (d , J = 8.7 Hz, 2H), 6.95 (d , J = 2.9 Hz, 1H), 7.10 (d , J = 16.2 Hz, 1H), 7.28 (dd , J = 8.7, 2.9 Hz, 1H), 7.40−7.48 (m, 3H), 7.50 (d , J = 8.7 Hz, 1H), 7.85 (d , J = 4.6 Hz, 1H), 7.87 (d , J = 4.6 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 40.2 (2C), 67.6, 69.7, 70.3, 70.5, 70.80, 70.84, 82.2, 83.9, 106.3, 112.2 (2C), 119.2, 122.2, 124.4, 124.8, 127.7, 128.4

(2C), 130.2, 133.7, 134.9, 144.2, 150.6, 154.7, 156.3; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{25}H_{30}FN_2O_3$, 425.2240; found, 425.2237.

(E)-1-((2-(4-(Dimethylamino)styryl)quinolin-7-yl)oxy)-3-fluoropropan-2-ol (**26**, **SQ15**)

By a procedure identical to that described for synthesis of **15**, quinoline **6** (500 mg, 2.25 mmol, 1.00 eq.), *p*-dimethylaminobenzaldehyde (1340 mg, 9.00 mmol), and crude fluorine **13** (1.00 g) were converted into **26** as a red solid (65.2 mg, 6.8% yield, 3 steps): ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.92 (s, 6H), 4.16 (d, J = 4.6 Hz, 2H), 4.22−4.32 (m, 1H), 4.48−4.53 (m, 1H), 4.60−4.65 (m, 1H), 6.64 (d, J = 8.7 Hz, 2H), 7.00 (dd, J = 8.7, 2.3 Hz, 1H), 7.10 (d, J = 16.2 Hz, 1H), 7.33 (d, J = 2.3 Hz, 1H), 7.39−7.55 (m, 5H), 7.88 (d, J = 8.7 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 40.2 (2C), 67.96, 68.03, 68.5, 68.7, 83.0, 84.7, 107.8, 112.2 (2C), 117.1, 118.4, 122.4, 124.0, 124.5, 128.6 (2C), 134.9, 135.8 (2C), 149.5, 150.7, 157.2, 159.4; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{22}H_{24}FN_2O_2$, 367.1822; found, 367.1821.

(E)-1-((2-(4-(Dimethylamino)styryl)quinolin-6-yl)oxy)-3-fluoropropan-2-ol (**27**, **SQ16**)

By a procedure identical to that described for synthesis of **15**, quinoline **7** (474 mg, 2.13 mmol, 1.00 eq.), *p*-dimethylaminobenzaldehyde (1270 mg, 8.52 mmol), and crude fluorine **13** (1.00 g) were converted into **27** as a red solid (35.0 mg, 3.9% yield, 3 steps): ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.08 (s, 6H), 4.20 (d, J = 4.6 Hz, 2H), 4.26−4.37 (m, 1H), 4.55−4.58 (m, 1H), 4.66−4.70 (m, 1H), 6.79 (d, J = 8.7 Hz, 2H), 7.17−7.21 (m, 1H), 7.41 (d, J = 16.2 Hz, 1H), 7.50 (d, J = 8.7 Hz, 1H), 7.53−7.59 (m, 2H), 7.71 (d, J = 8.7 Hz, 1H), 7.83−7.91 (m, 1H), 8.24 (d, J = 8.7 Hz, 1H), 8.27−8.34 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 40.2 (2C), 68.54, 68.57, 68.77, 69.8, 82.5, 84.2, 107.4, 112.2 (2C), 112.8, 118.2, 122.5, 122.7, 125.7, 127.4, 130.9 (2C), 134.1, 141.2, 144.0, 151.6, 152.5, 157.8; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{22}H_{24}FN_2O_2$, 367.1822; found, 367.1819.

(*E*)-2-((2-(4-(Dimethylamino)styryl)quinolin-7-yl)oxy)ethyl 4-methylbenzenesulfonate (**28**)

The same reaction described above to prepare crude phenol compound (synthesis of **14**) was used. To a stirred solution of crude phenol compound (54.6 mg), and NaH (13.5 mg, 0.564 mmol) in dry DMF (1.88 mL) was added 1,2-bis(tosyloxy)ethane (348 mg, 0.939 mmol). After being stirred for 2 h at 100 °C, the mixture was diluted with H_2O. The whole solution was extracted with AcOEt. The extract was washed with brine, and dried

over Na_2SO_4. After concentration *in vacuo*, the residue was purified by flash chromatography over amino silica gel with *n*-hexane-AcOEt 2:1 to 1:1 to give **28** as an orange solid (58.3 mg, 18% yield, 3 steps): ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.42 (s, 3H), 3.01 (s, 6H), 4.25−4.30 (m, 2H), 4.43−4.48 (m, 2H), 6.72 (d, J = 8.7 Hz, 2H), 6.97 (dd, J = 8.7, 1.7 Hz, 1H), 7.15 (d, J = 15.7 Hz, 1H), 7.22 (d, J = 1.7 Hz, 1H), 7.32 (d, J = 8.2 Hz, 2H), 7.47−7.63 (m, 5H), 7.83 (d, J = 8.2 Hz, 2H), 7.96 (d, J = 8.7 Hz, 1H); LC-MS *m/z*: $[M + H]^+$ calcd for $C_{28}H_{29}N_2O_4S$, 489.2; found, 489.2.

(*E*)-2-((2-(4-(Dimethylamino)styryl)quinolin-6-yl)oxy)ethyl 4-methylbenzenesulfonate (29)

The same reaction described above to prepare crude phenol compound (synthesis of **15**) was used. To a stirred solution of crude phenol compound (131 mg), and Cs_2CO_3 (1000 mg, 3.07 mmol) in dry DMF (9.00 mL) was added 1,2-bis(tosyloxy)ethane (1420 mg, 3.84 mmol). After being stirred for 2.5 h at 90 °C, the mixture was diluted with H_2O. The whole solution was extracted with AcOEt. The extract was washed with brine, and dried over Na_2SO_4. After concentration in vacuo, the residue was purified by flash chromatography over amino silica gel with *n*-hexane-AcOEt 2:1 to 1:1 to give **29** as an orange solid (25.0 mg, 5% yield, 3 steps): ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.94 (s, 3H), 3.01 (s, 6H), 4.18−4.21 (m, 2H), 4.36−4.39 (m, 2H), 6.66 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 2.9 Hz, 1H), 7.10 (d, J = 2.9 Hz, 1H), 7.12 (d, J = 2.9 Hz, 1H), 7.26 (d, J = 8.6 Hz, 2H), 7.43−7.56 (m, 4H), 7.76 (d, J = 8.6 Hz, 2H), 7.86 (d, J = 8.6 Hz, 2H); LC-MS *m/z*: $[M + H]^+$ calcd for $C_{28}H_{29}N_2O_4S$, 489.2; found, 489.2.

(E)-2-(2-(2-((2-(4-(Dimethylamino)styryl)quinolin-6-yl)oxy)ethoxy)ethoxy)ethyl 4-methylbenzenesulfonate (30)

The same reaction described above to prepare crude phenol compound (synthesis of **15**) was used. To a stirred solution of crude phenol compound (157 mg) and Cs_2CO_3 (1000 mg, 3.07 mmol) in dry DMF (4.00 mL) was added triethylene glycol bis(*p*-toluenesulfonate) (962 mg, 2.10 mmol). After being stirred for 3 h at 95 °C, the mixture was diluted with H_2O. The whole solution was extracted with AcOEt. The extract was washed with brine, and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by flash chromatography over amino silica gel with *n*-hexane-AcOEt 2:1 to 1:1 to give **28** as an orange solid (7.6 mg, 1.3% yield, 3 steps): ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.48 (s, 3H), 3.15 (s, 6H), 3.68−3.78 (m, 6H), 3.95−4.01 (m, 2H), 4.18−4.23 (m, 2H) 4.30−4.35 (m, 2H), 6.91 (d, J = 8.7 Hz, 2H), 7.38 (d, J = 8.2 Hz, 2H), 7.50 (d, J = 16.2 Hz, 1H), 7.60 (dd, J = 2.9, 8.7 Hz, 1H), 7.64 (d, J = 8.7 Hz, 2H), 7.74−7.86 (m, 4H), 7.94

(d, J = 8.7 Hz, 1H), 8.26 (d, J = 8.7 Hz, 1H), 8.42 (d, J = 8.7 Hz, 1H); LC-MS *m/z*: $[M + H]^+$ calcd for $C_{32}H_{37}N_2O_6S$, 577.2; found, 577.2.

^{125}I-labeling reaction

Total of 100 μL of 3% H_2O_2 aq. and 100 μL of 1 N HCl aq. were added to a mixture of tributyltin precursor **2** (150 μg/150 μL EtOH) and [^{125}I]NaI (1.85-7.40 MBq, specific activity: 81.4 TBq/mmol) in 150 μL EtOH in a sealed vial. The reaction was allowed to proceed at 25 °C for 10 min and terminated by the addition of saturated $NaHSO_3$ aq. (200 μL). After neutralization with saturated $NaHCO_3$ aq. (200 μL) and extraction with ethyl acetate (600 μL ×3), the organic phase was dried by passing through a column filled with anhydrous Na_2SO_4. The solution was gas-dried with a stream of nitrogen gas. The crude ligands were purified by HPLC on a Cosmosil C_{18} column (Nacalai Tesque) with an isocratic solvent of acetonitrile/H_2O = 85/15 at a flow rate of 1.0 mL/min.

Binding saturation assays using the aggregated α-syn and Aβ in solution

α-Syn and Aβ were purchased from rPeptide (Bogart, GA, USA) and the Peptides Institute, Inc. (Osaka, Japan), respectively. α-Syn aggregates were prepared by incubating recombinant α-syn monomer (1.67 mg/mL in 20 mM Tris–HCl, 100 mM NaCl, pH 7.48) at 37 °C for 144 h with shaking at 1000 rpm. Aggregation of Aβ was carried out by gently dissolving the peptide (0.25 mg/mL) in PBS solution (pH 7.4). The solution was incubated at 37 °C for 42 h with gentle and constant shaking. The reaction mixture contained increasing concentrations of [^{125}I]ISQ (15.6 nM–20 μM, 100 mL, EtOH), a fixed concentration of α-syn aggregates (33.3 μg/mL, 50 μL, 20 mM Tris–HCl, 100 mM NaCl) or Aβ aggregates (5.00 μg/mL, 50 μL, PBS), and 10% EtOH (850 μL). Nonspecific binding was determined in the presence of 1 μM nonradioactive ISQ. After incubating for 3 h at 25 °C, the solution was filtered through GF/B filters using an M-24 cell harvester. The radioactivity of the bound [^{125}I]ISQ was measured with a γ counter (Wizard 2480, PerkinElmer). The dissociation constants (K_d) and Bmax were determined by Scatchard analysis using GraphPad Prism 6 (GraphPad Software, San Diego, CA, USA).

Binding inhibition assays using the aggregated α-syn and Aβ in solution

Aggregated α-syn and Aβ were prepared by the same method as the saturation assay. The reaction mixture contained increasing concentrations of nonradioactive SQ derivative (1.28 nM-100 μM, 50 μL, EtOH or DMSO), a fixed concentration of [^{125}I]ISQ (6.25 pM-12.5 pM, 50 μL, EtOH), α-syn aggregates (33.3 μg/mL, 50 μL, 20 mM Tris–HCl, 100 mM NaCl, pH 7.48) or $A\beta_{1\text{-}42}$ aggregates (5.00 μg/mL, 50 μL, PBS, pH 7.4),

and 10% EtOH (850 μL). After incubating for 3 h at 25 °C, the mixture was then filtered through Whatman GF/B filters using a Brandel M-24 cell harvester, and the radioactivity of the filters containing the bound [^{125}I]ISQ were measured in a γ counter. Values for the half maximal inhibitory concentration (IC50) were determined from displacement curves using GraphPad Prism 5.0, and those for the inhibition constant (K_i) were calculated using the Cheng-Prusoff equation: K_i = IC50/(1 + [L]/K_d), where [L] is the concentration of [^{125}I]ISQ used in the assay and K_d is the dissociation constant of ISQ (α-syn: 25.1 nM, Aβ: 8.53 nM).

Calculation of CNS MPO score

CNS MPO score was calculated using the drug discovery software, StarDrop (Optibrium Ltd., Cambridge, UK).

^{18}F-Labeling reaction

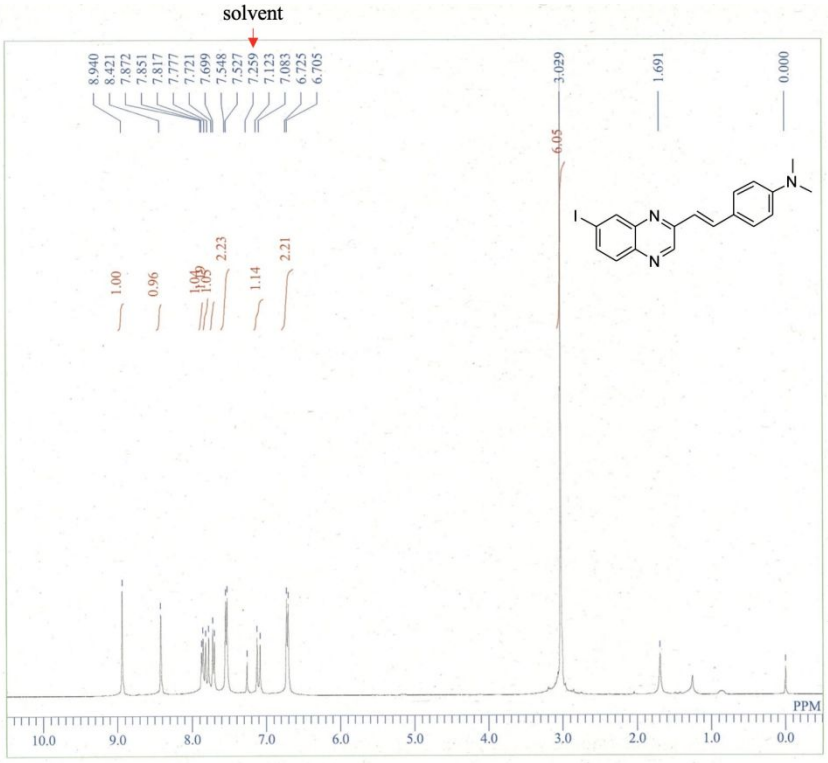
Kryptofix 222 (10.0 mg) was added to the reaction vessel, and the mixture was evaporated azeotropically with dry acetonitrile (300 μL) under a nitrogen gas stream at 120 °C, three times. A solution of Kryptofix 222 (3.00 mg) and tosyl precursor (**28**, **29**, and **30)** (1.00 mg) in anhydrous DMF (200 μL) was added to the reaction vessel. After being heated at 120 °C for 20 min, the mixture was diluted with H_2O (1.00 mL). The whole solution was extracted with AcOEt (600 μL ×3). The organic phase was dried by passing through a column filled with anhydrous Na_2SO_4. The solution was gas-dried with a stream of nitrogen gas. The crude ^{18}F-labeled probes were purified by HPLC on a Cosmosil C_{18} column (Nacalai Tesque) with a gradient solvent of acetonitrile/H_2O (with 0.1% TFA) 25:75 (0 min) to 50:50 (30 min) at a flow rate of 1.0 mL/min.

***In vivo* biodistribution study using normal mice**

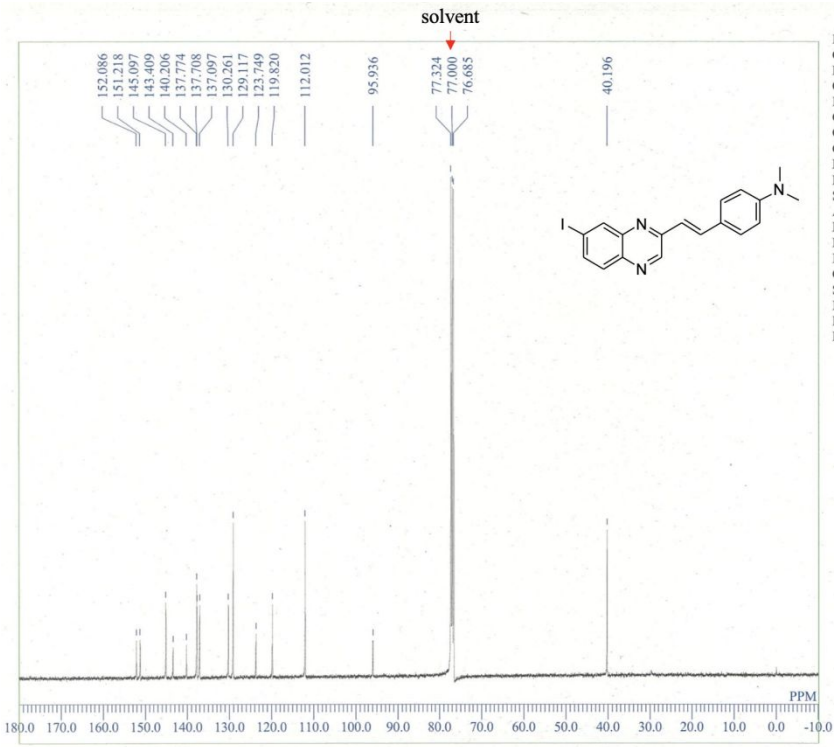
A saline solution (100 μL) of [^{18}F]**SQ3**, **4**, and **14** (10.0, 8.78, and 5.00 kBq) containing EtOH (10.0 μL) and Tween 80 (0.100 μL) was injected intravenously directly into the tails of ddY mice (5 weeks old, male, n = 5). The mice were sacrificed at various time-points post injection. The brains were removed and weighed, and the radioactivity was measured with an automatic γ counter (Wallac WIZARD 1470, PerkinElmer Inc., Massachusetts, USA). The animal experiment was approved by the Animal Experimentation Committee of Graduate School of Pharmaceutical Sciences, Kyoto University.

2. ^{1}H and ^{13}C NMR Spectrum

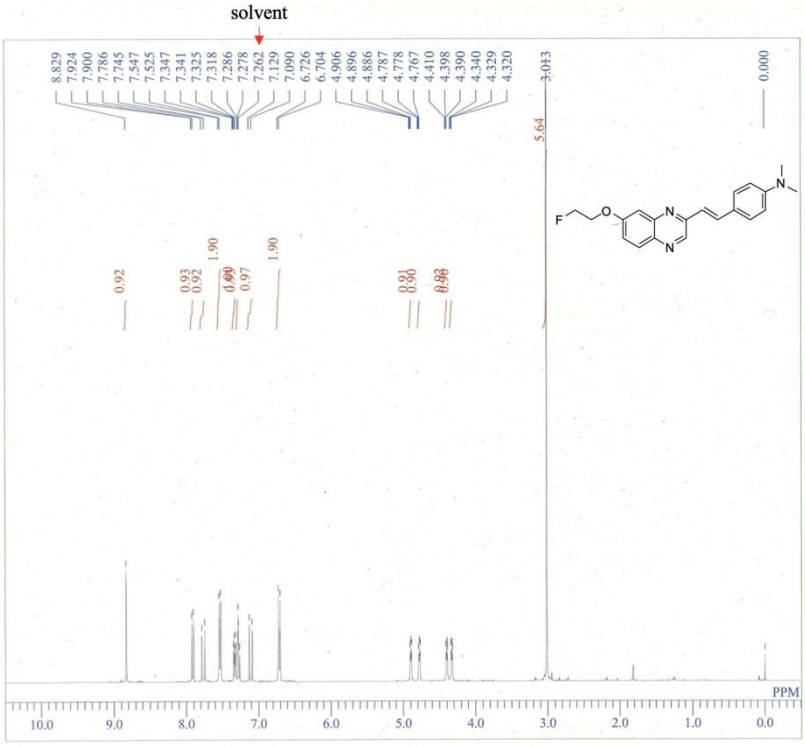
^{1}H NMR Spectrum for Compound **3** (ISQ)



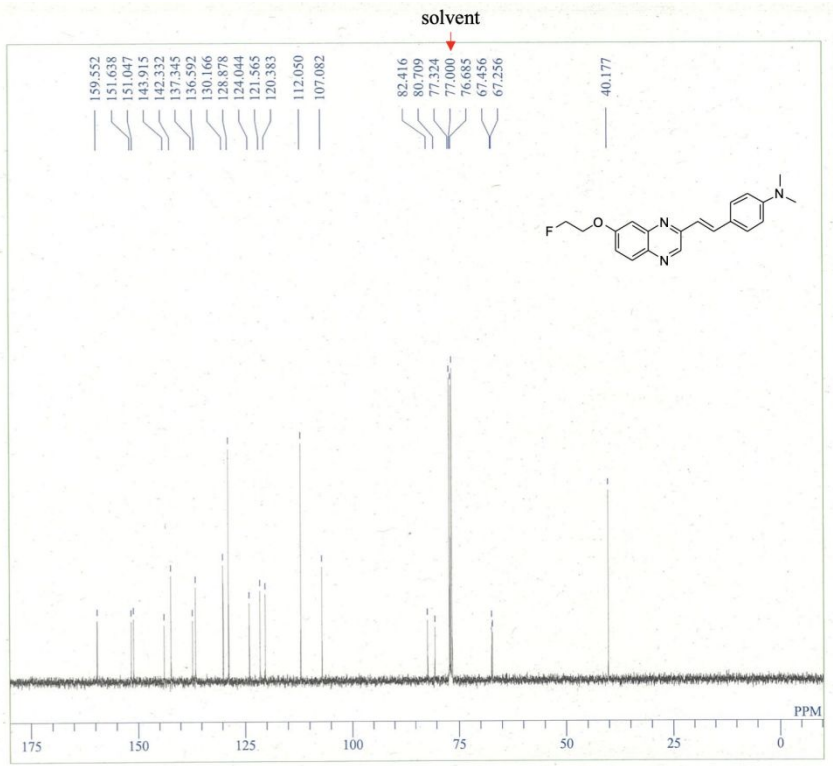
^{13}C NMR Spectrum for Compound **3** (ISQ)



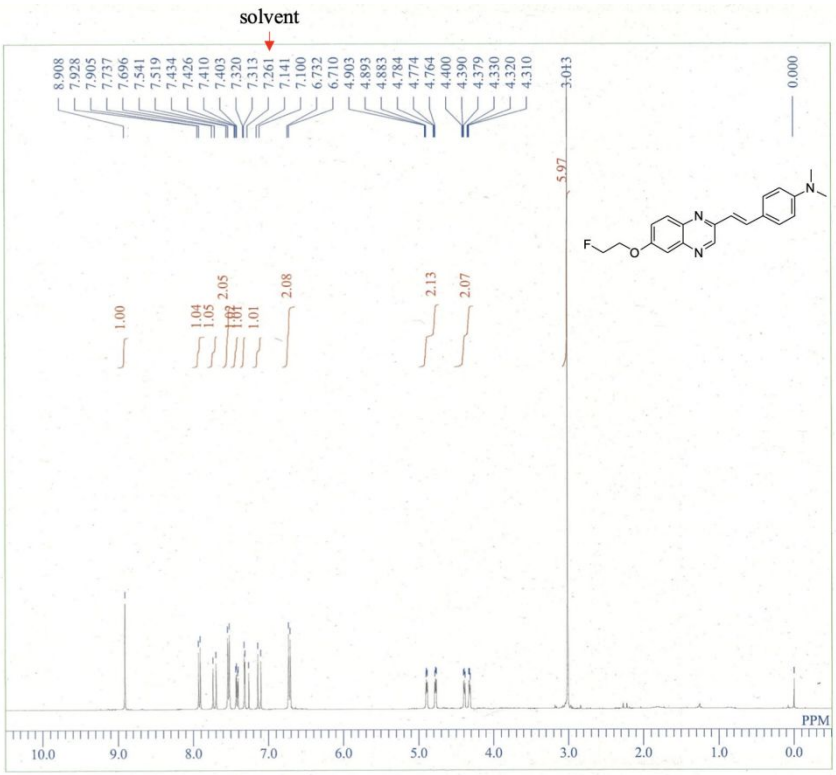
^{1}H NMR Spectrum for Compound **4** (SQ1)



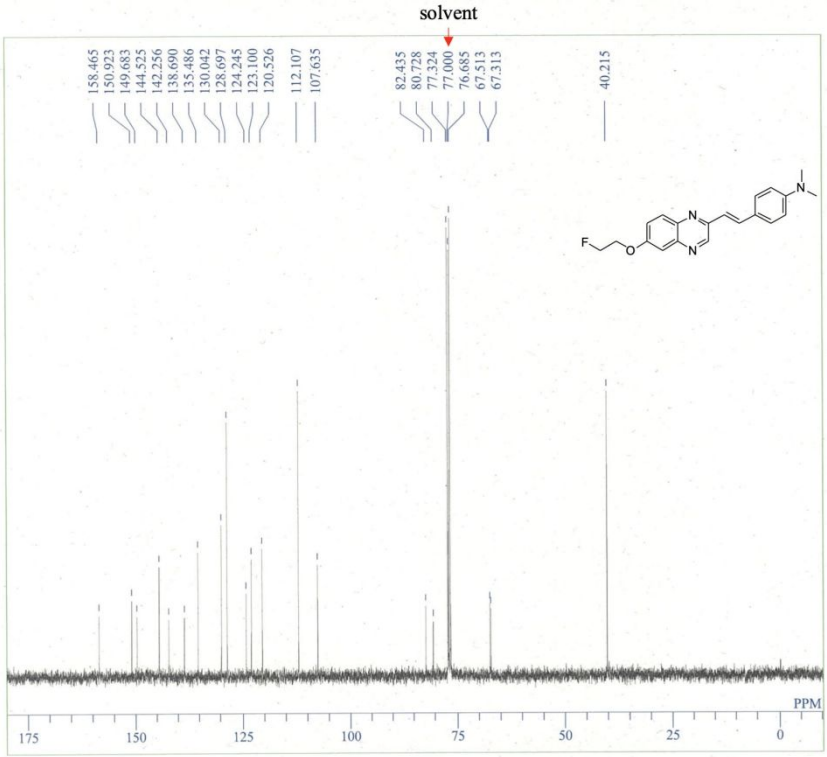
^{13}C NMR Spectrum for Compound **4** (SQ1)



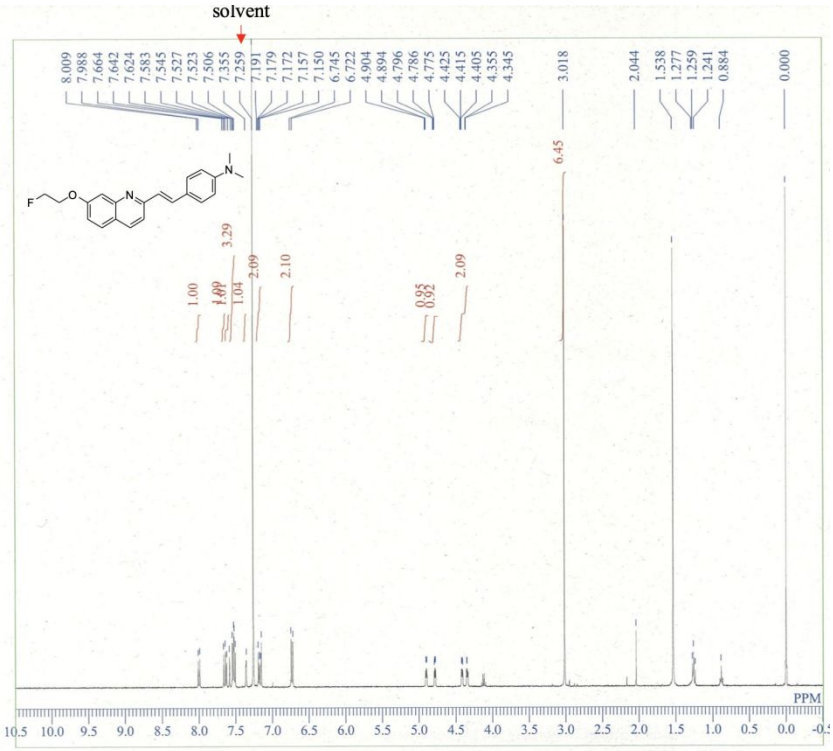
^{1}H NMR Spectrum for Compound **5** (SQ2)



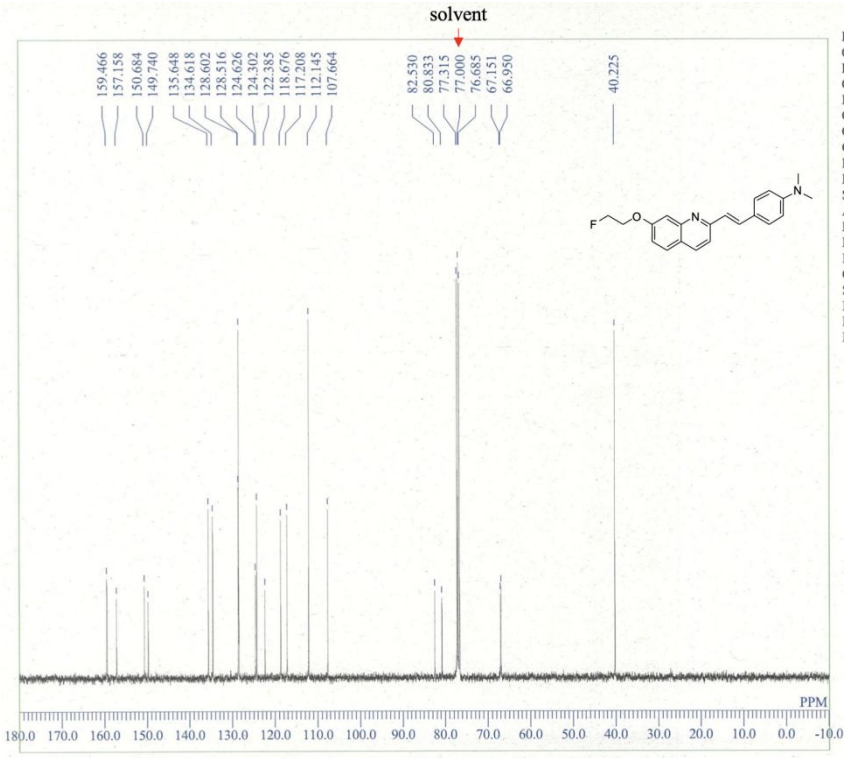
^{13}C NMR Spectrum for Compound **5** (SQ2)



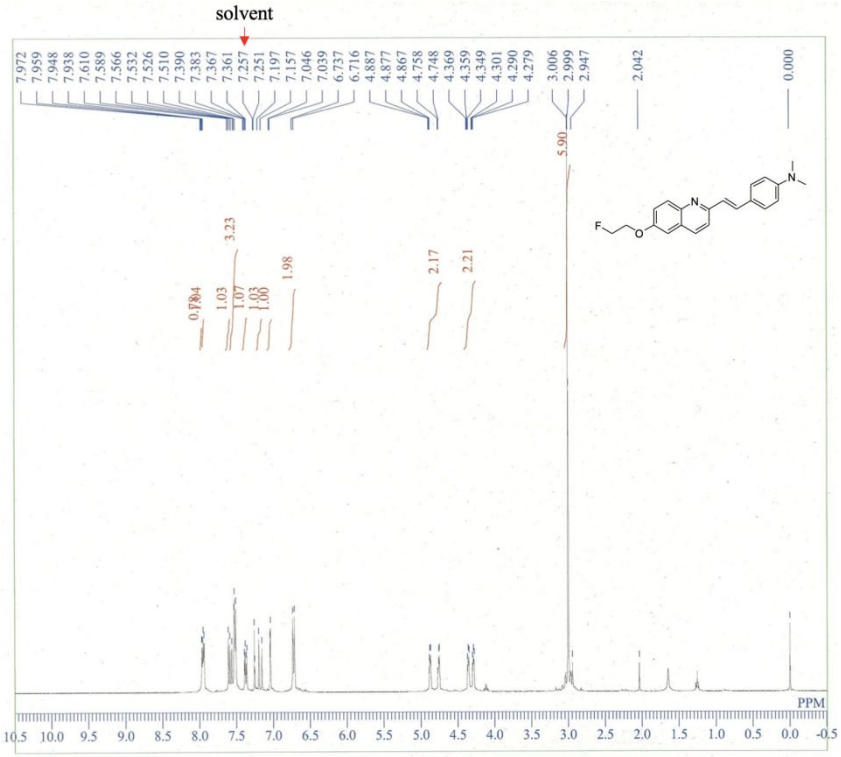
^{1}H NMR Spectrum for Compound **14** (SQ3)



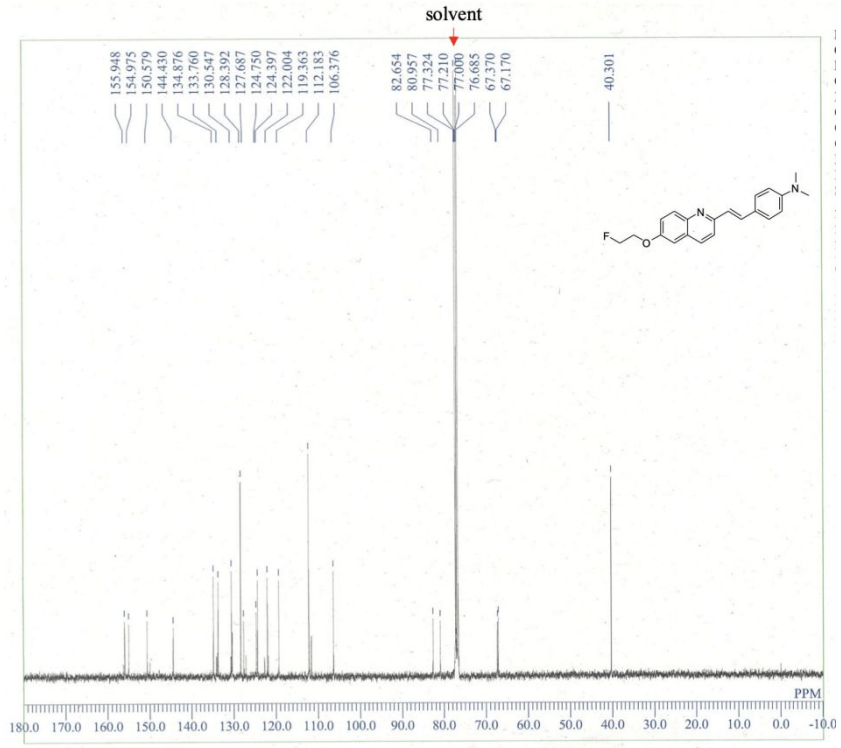
^{13}C NMR Spectrum for Compound **14** (SQ3)



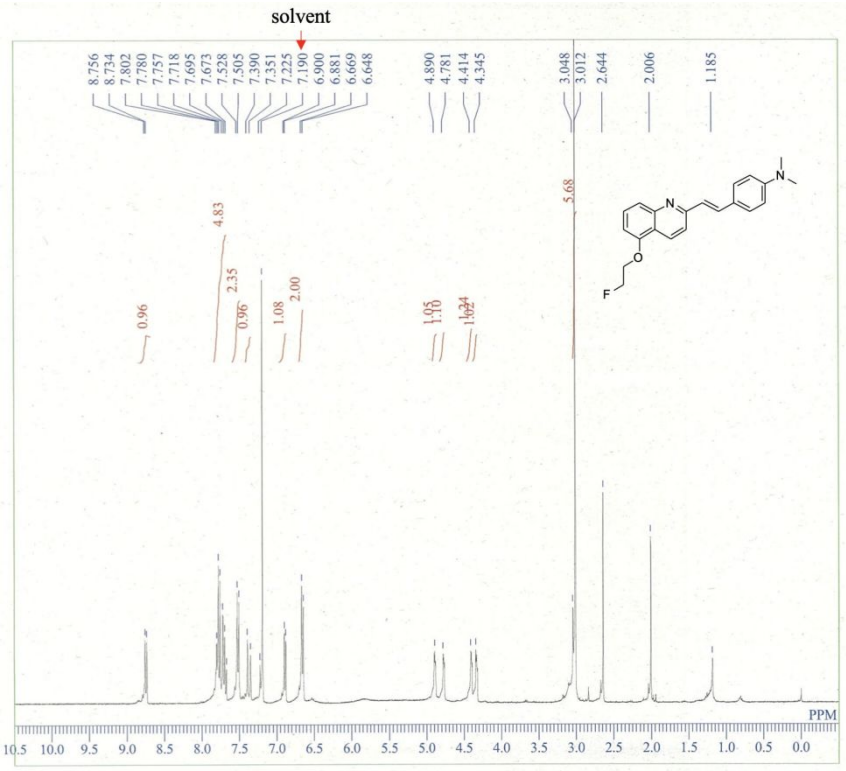
^{1}H NMR Spectrum for Compound **15** (SQ4)



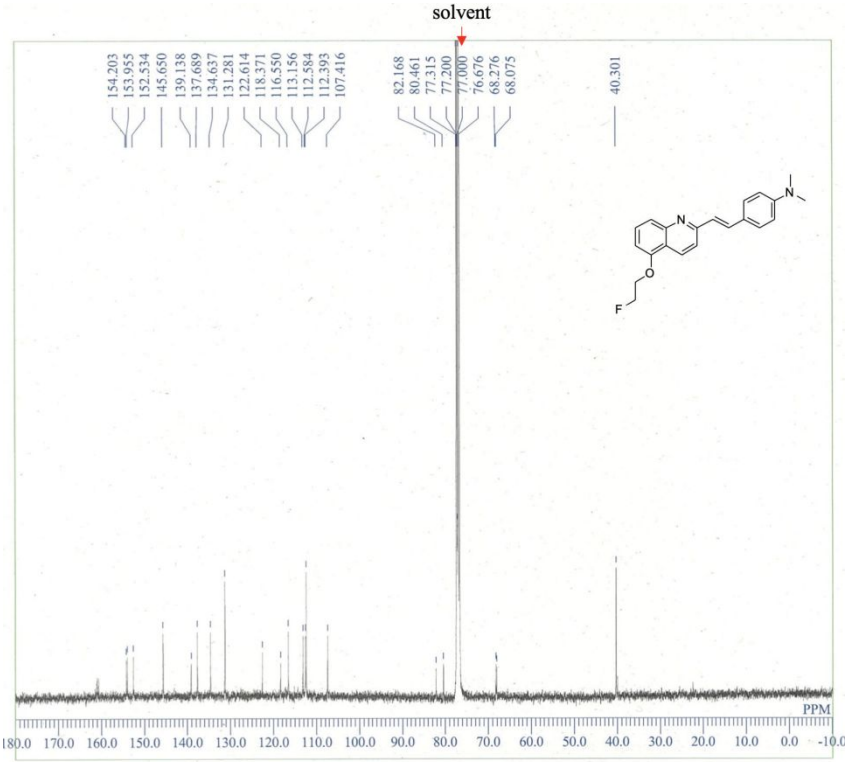
^{13}C NMR Spectrum for Compound **15** (SQ4)



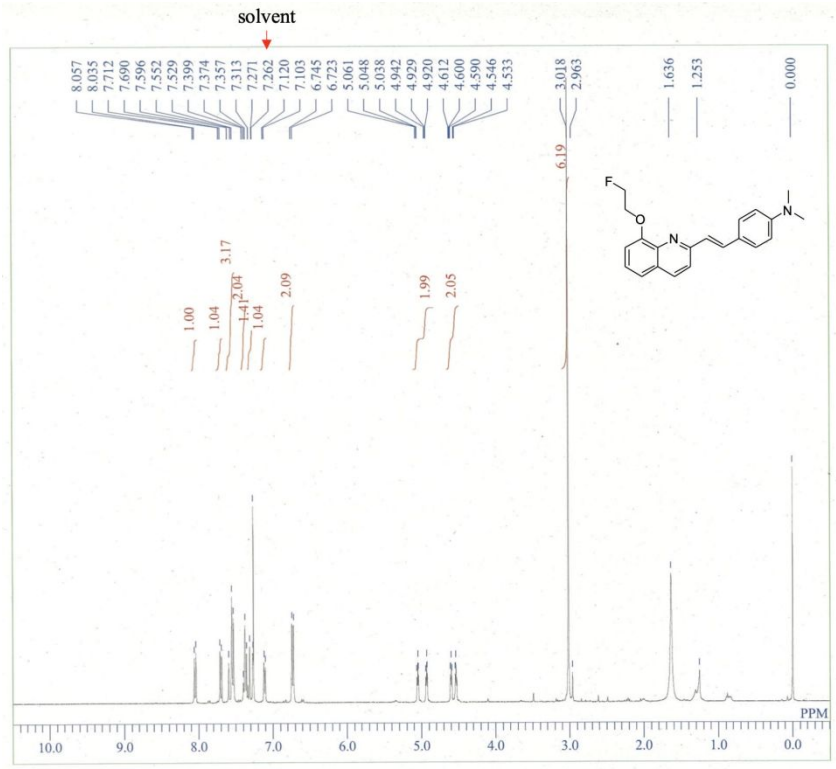
^{1}H NMR Spectrum for Compound **16** (SQ5)



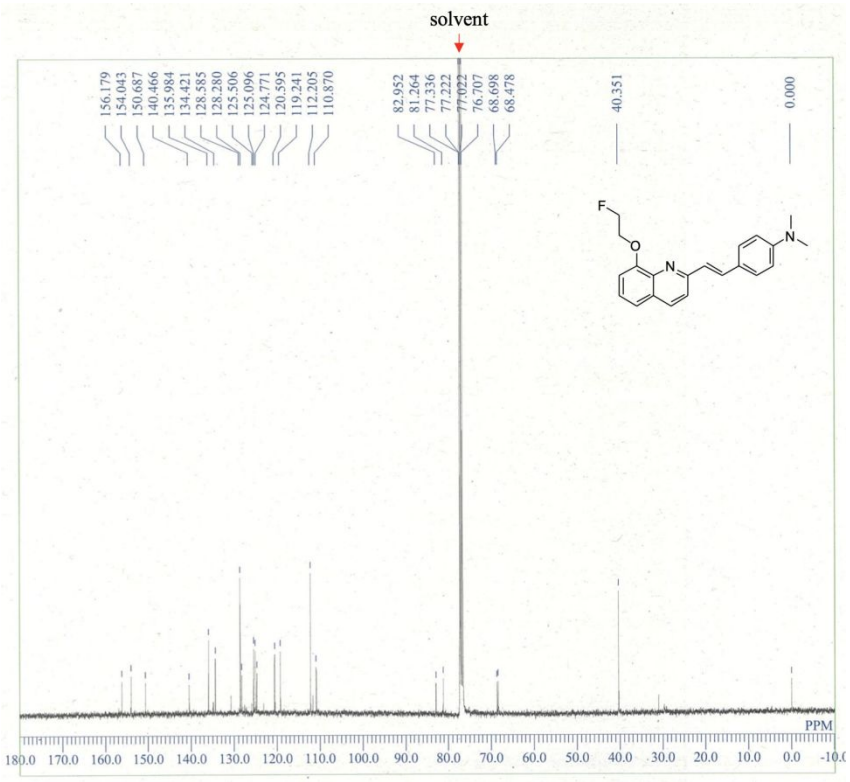
^{13}C NMR Spectrum for Compound **16** (SQ5)



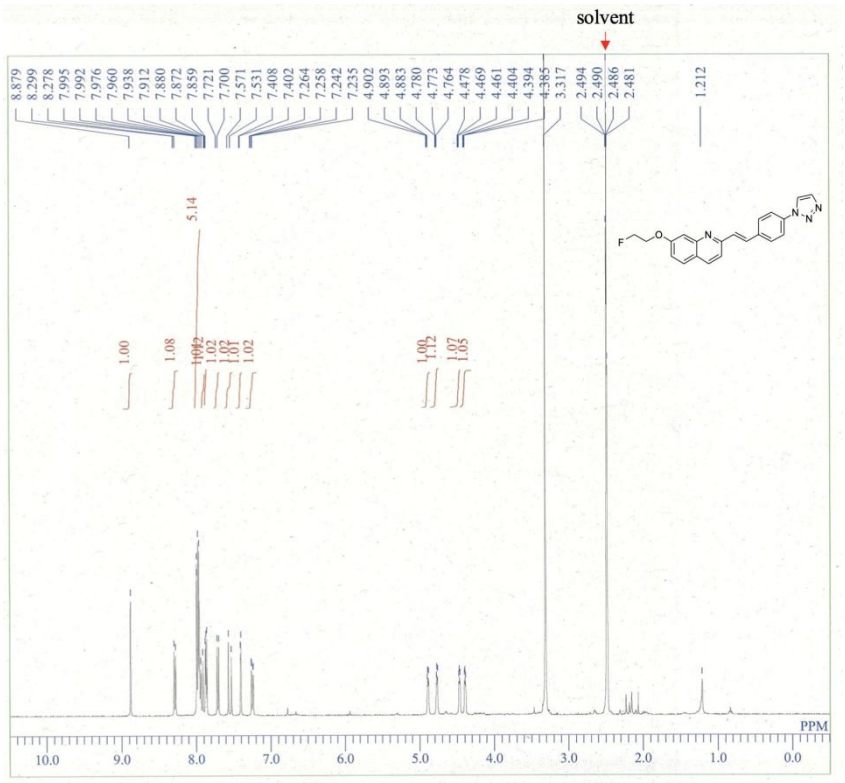
^{1}H NMR Spectrum for Compound **17** (SQ6)



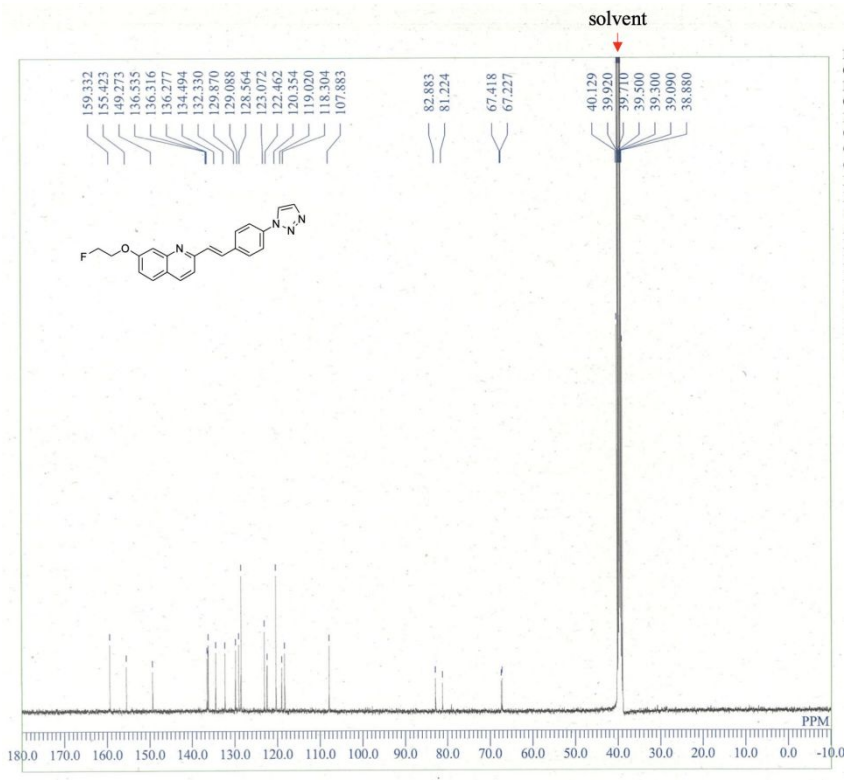
^{13}C NMR Spectrum for Compound **17** (SQ6)



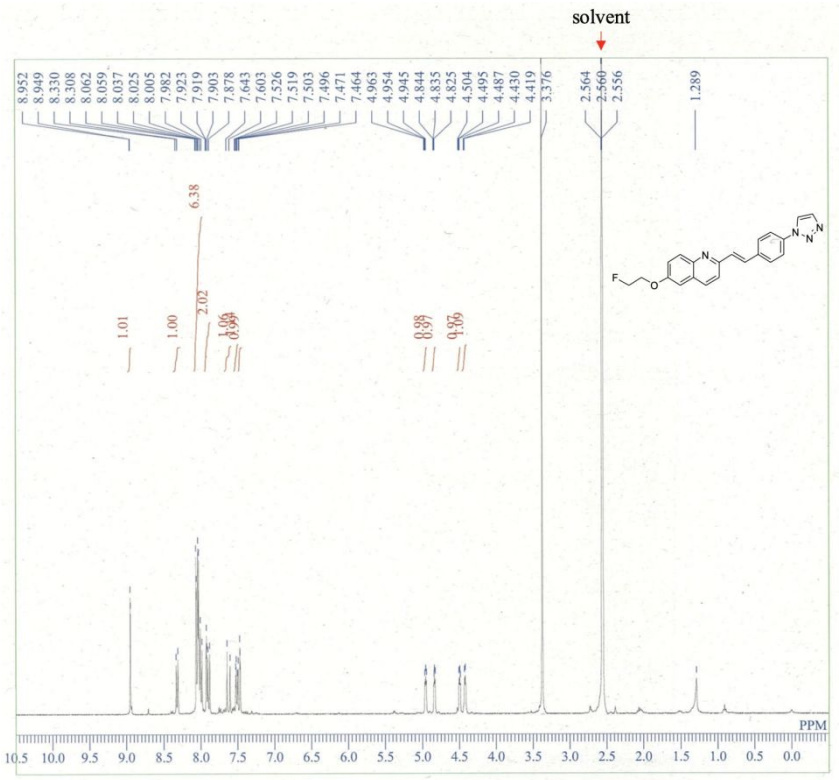
^{1}H NMR Spectrum for Compound **18** (SQ7)



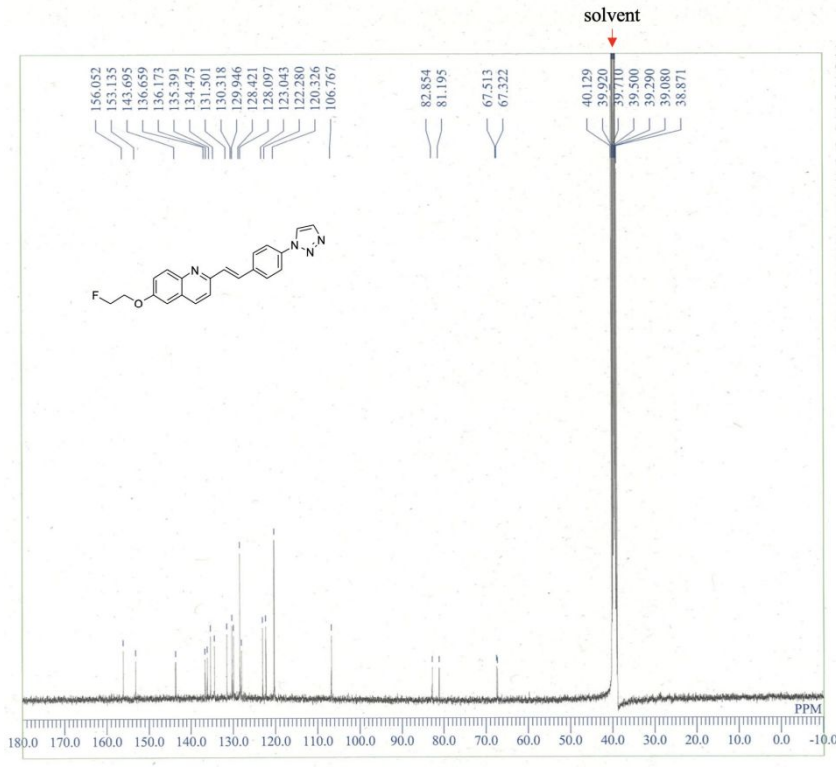
^{13}C NMR Spectrum for Compound **18** (SQ7)



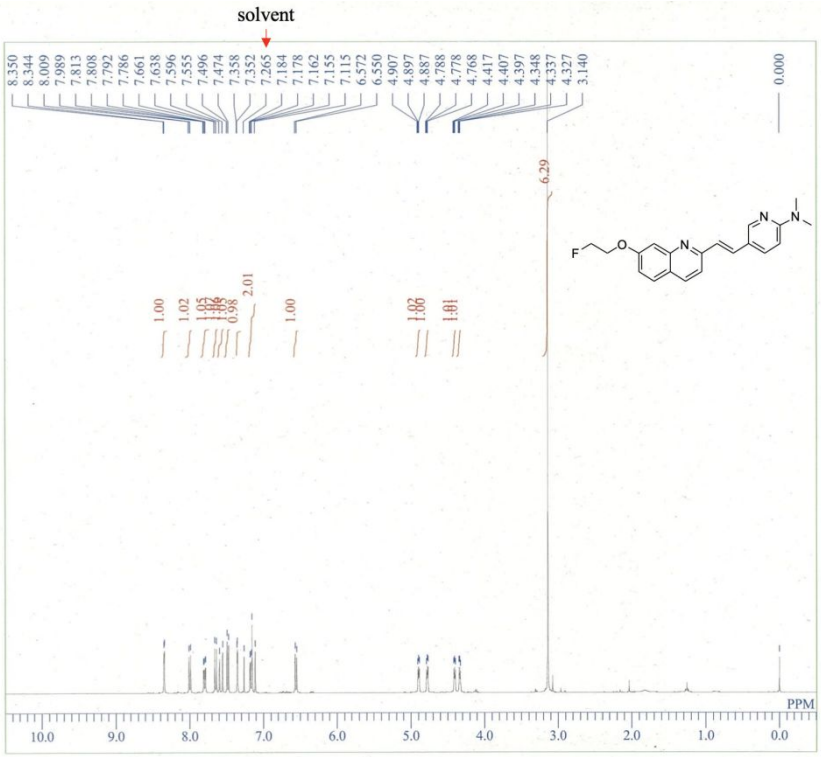
^{1}H NMR Spectrum for Compound **19** (SQ8)



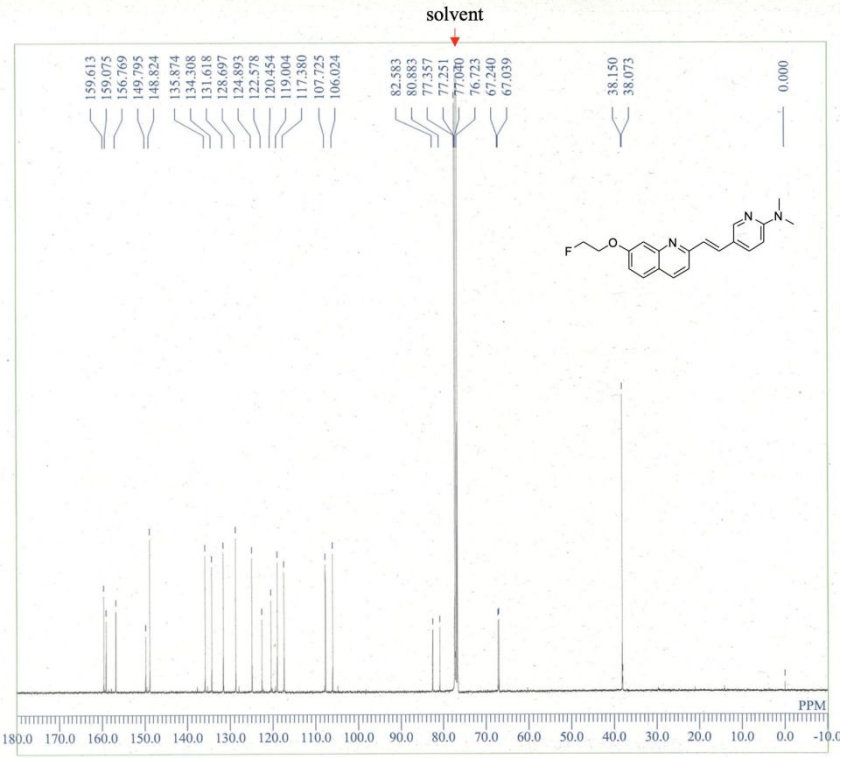
^{13}C NMR Spectrum for Compound **19** (SQ8)



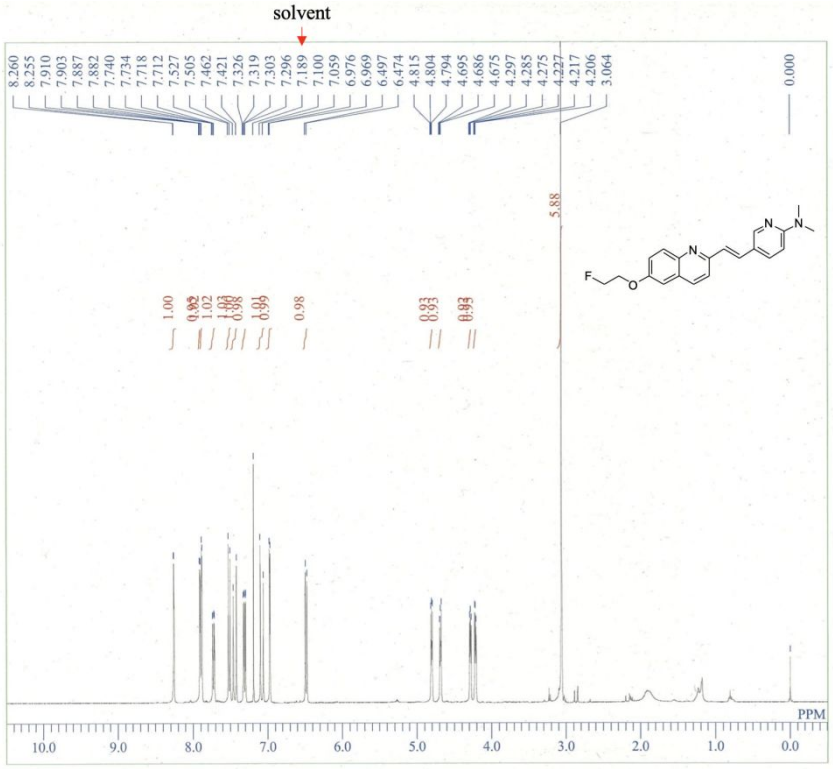
^{1}H NMR Spectrum for Compound **20** (SQ9)



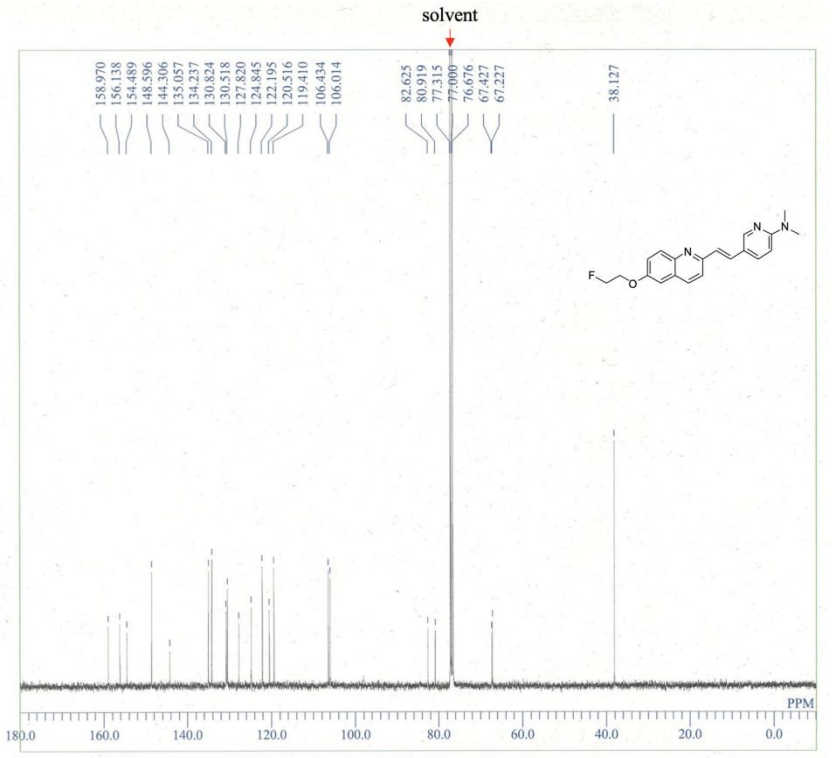
^{13}C NMR Spectrum for Compound **20** (SQ9)



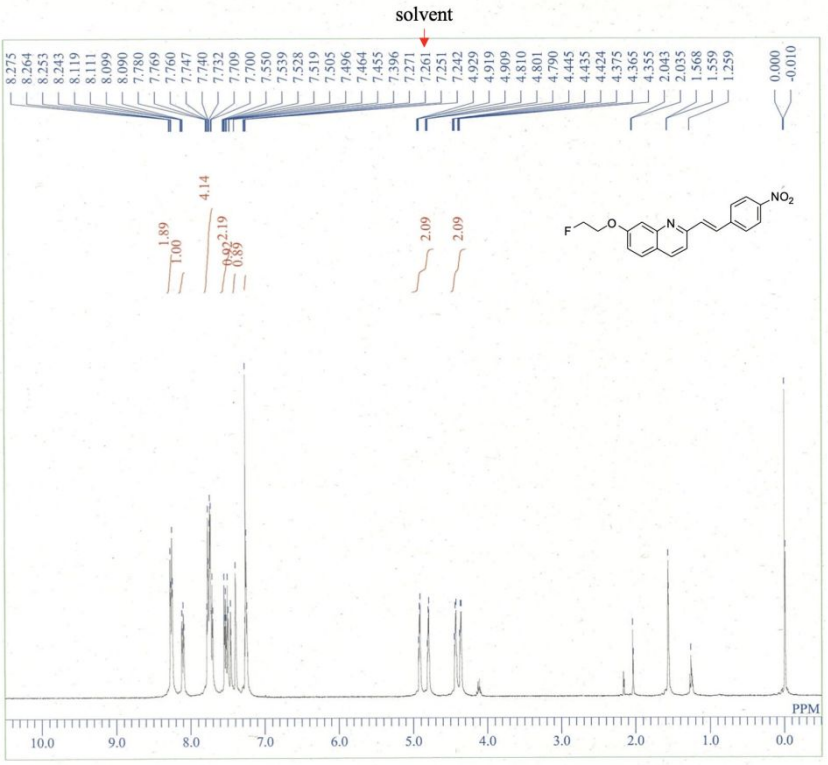
^{1}H NMR Spectrum for Compound **21** (SQ10)



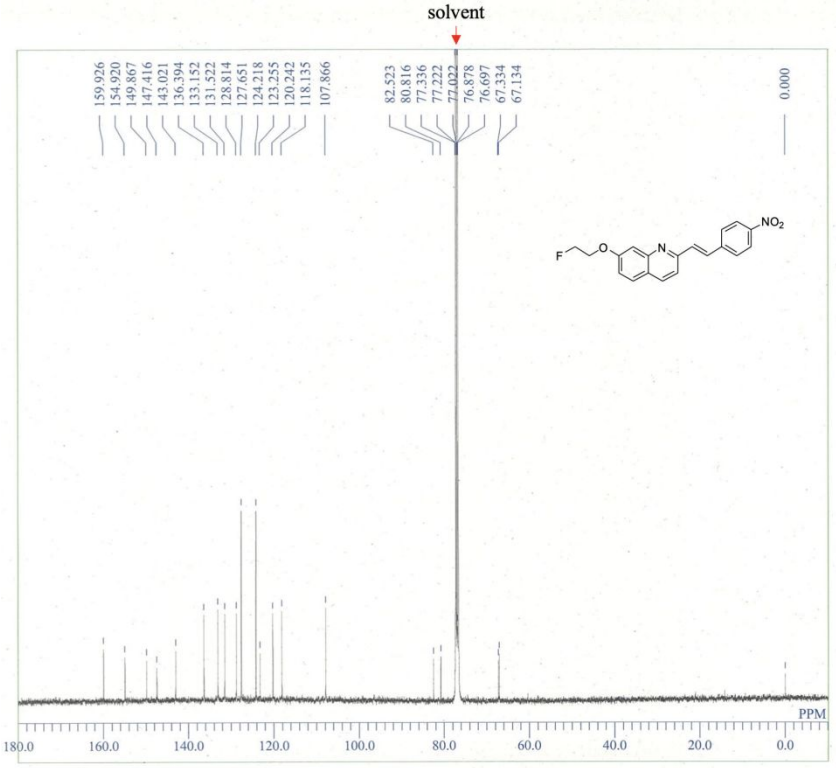
^{13}C NMR Spectrum for Compound **21** (SQ10)



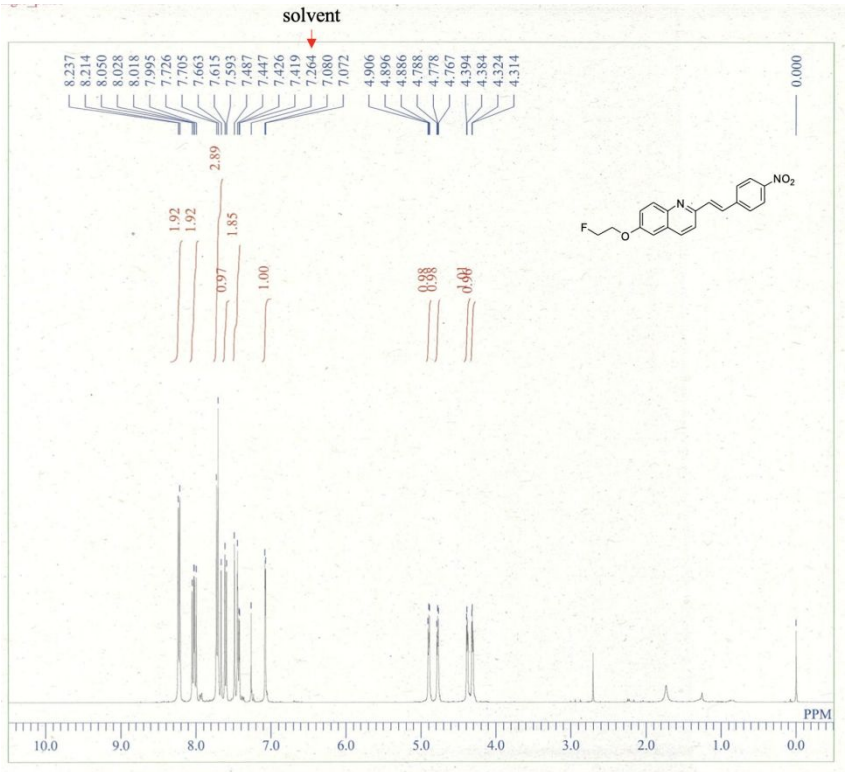
^{1}H NMR Spectrum for Compound **22** (SQ11)



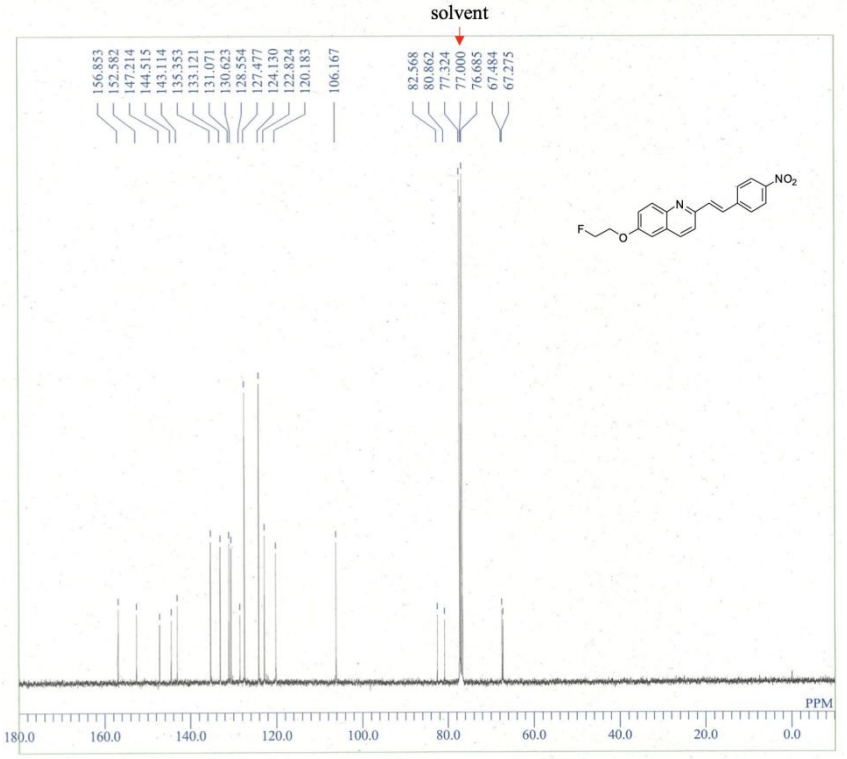
^{13}C NMR Spectrum for Compound **22** (SQ11)



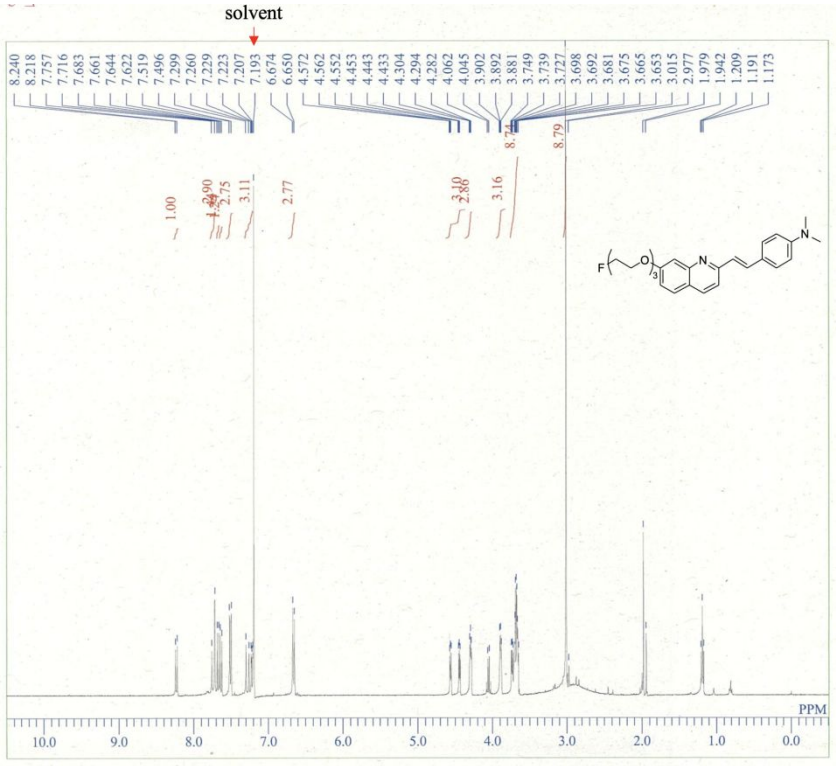
^{1}H NMR Spectrum for Compound **23** (SQ12)



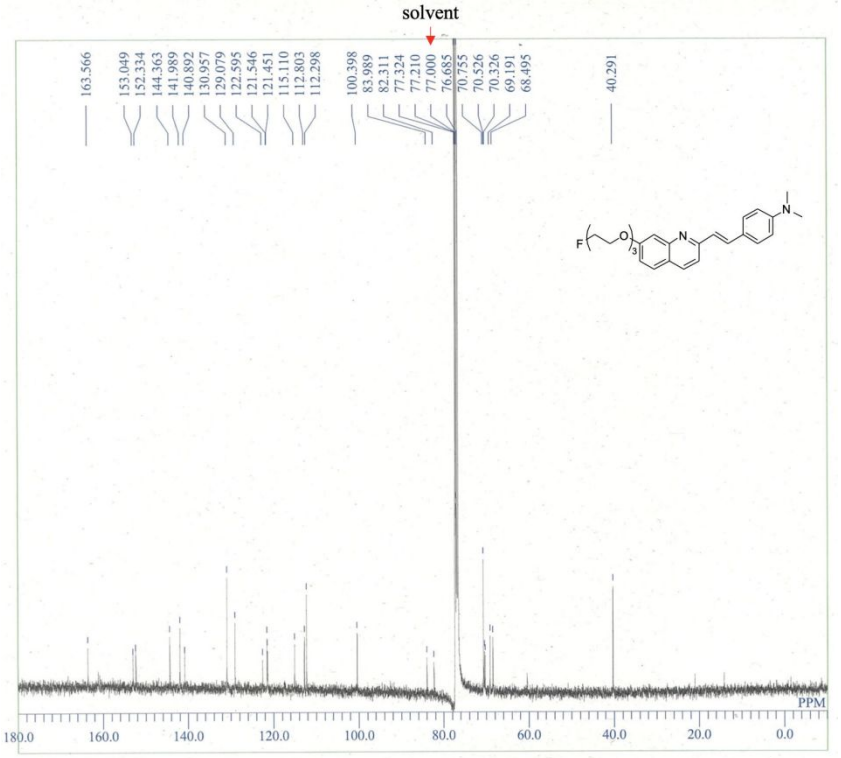
^{13}C NMR Spectrum for Compound **23** (SQ12)



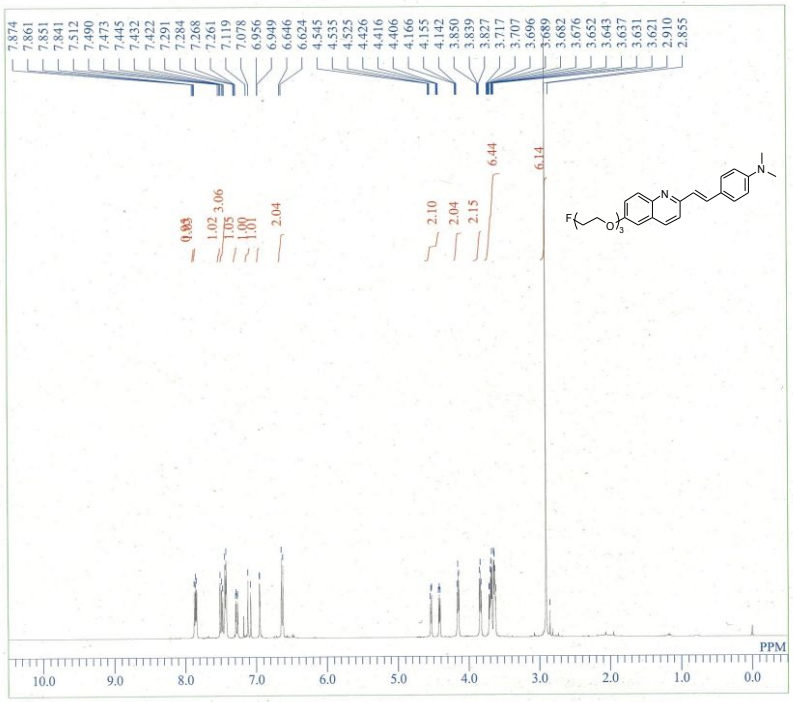
^{1}H NMR Spectrum for Compound **24** (SQ13)



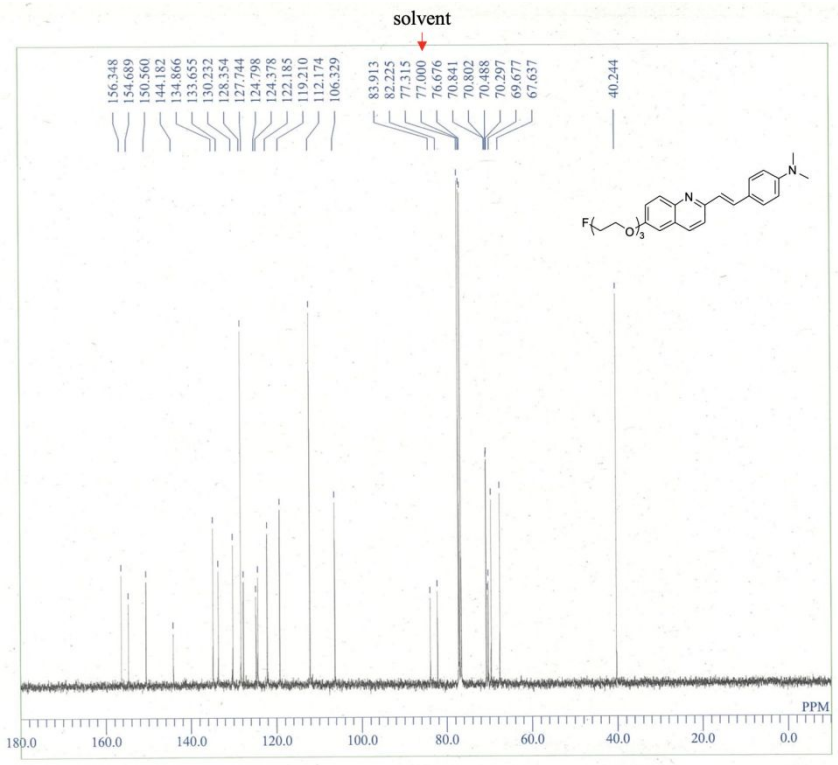
^{13}C NMR Spectrum for Compound **24** (SQ13)



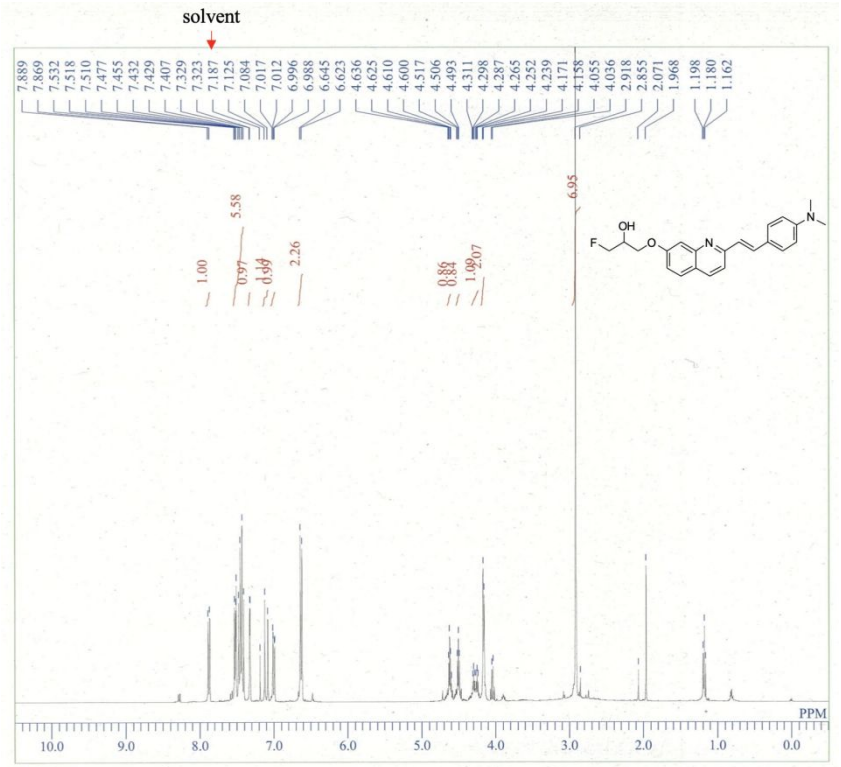
^{1}H NMR Spectrum for Compound **25** (SQ14)



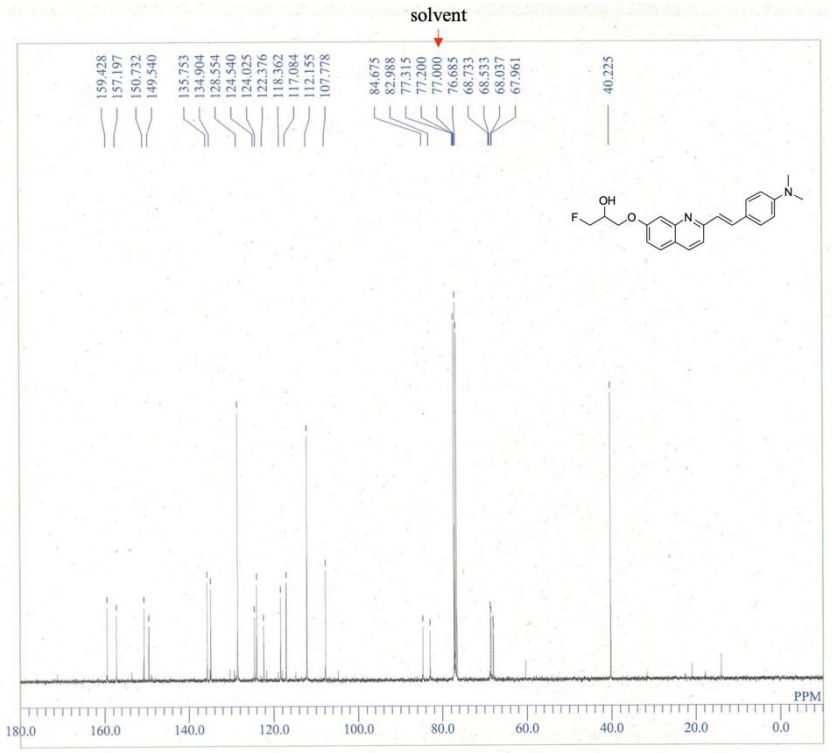
^{13}C NMR Spectrum for Compound **25** (SQ14)



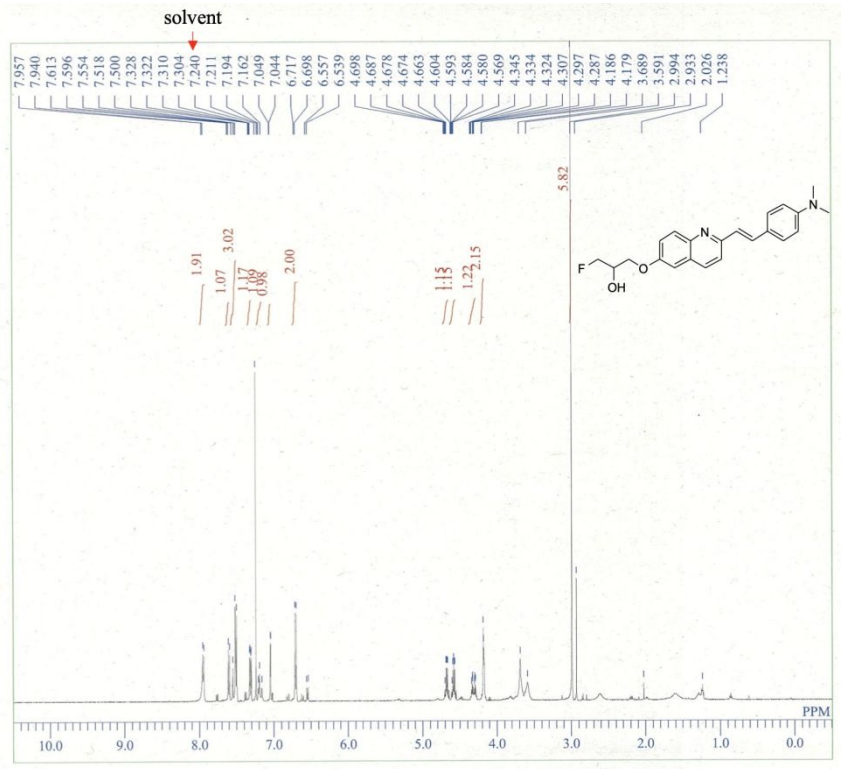
^{1}H NMR Spectrum for Compound **26** (SQ15)



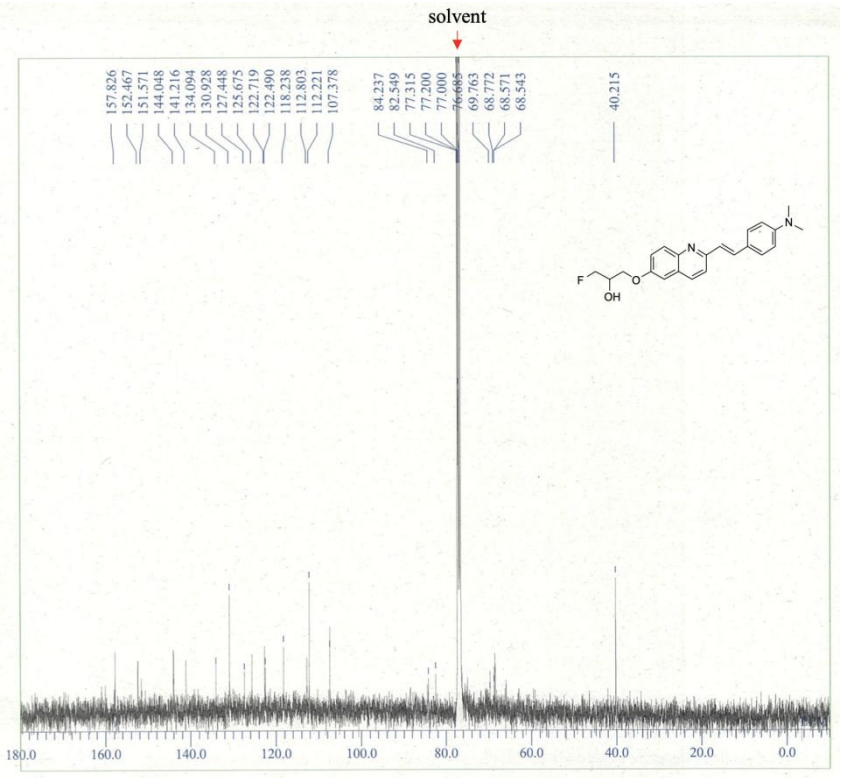
^{13}C NMR Spectrum for Compound **26** (SQ15)



^{1}H NMR Spectrum for Compound **27** (SQ16)



^{13}C NMR Spectrum for Compound **27** (SQ16)



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