Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.
This journal is © The Royal Society of Chemistry 2019

Table of contents

Supporting Information

1. General

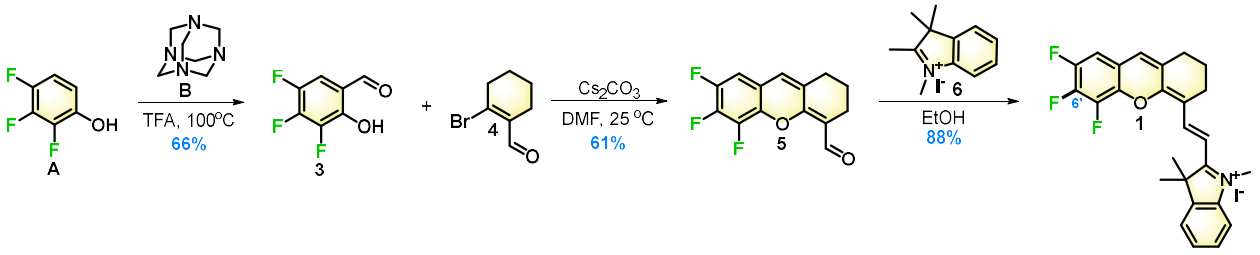
Chemicals, reagents and solvents were purchased from commercial vendors and used without further purification. Trifluoroacetic acid (TFA), dichloromethane (DCM), dimethylformamide (DMF), ethyl acetate (EtOAc), petroleum ether (b.p. 40-60 ºC), acetonitrile (MeCN), dimethyl sulfoxide (DMSO), methanol (MeOH), ethanol (EtOH), and pyridine used in this work were reagent grade. Bovine serum albumin (BSA, heat shock fraction, pH 7, ≥ 98%) was provided by Sigma-Aldrich. The HPLC-gradient grade CH_3CN used for HPLC-MS analyses was obtained from Carlo Erba. Formic acid (FA, puriss p.a., ACS reagent, reag. Ph. Eur., ≥ 98%) was provided by Sigma-Aldrich. All aq. buffers used in this work (PBS and aq. mobile-phases for HPLC were prepared using water purified with a PURELAB Ultra system from ELGA (purified to 18.2 MΩ.cm). Thin-layer chromatography (TLC) was carried on pre-coated glass plates with 0.2 mm silica gel and visualized under UV (254 nm) and/or potassium permanganate ($KMnO_4$) stain. Flash-column chromatography was performed using Silica gel 60 (200–400 mesh) with specified eluents.

2. Instruments and methods

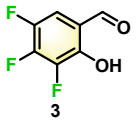
^1H, ^{13}C and ^{19}F NMR spectra were recorded on Brüker Avance 400 MHz or 600 MHz spectrometers. Chemical shifts (δ) are reported in parts per million (ppm) and residual non-deuterated solvent peaks were used as internal reference (proton δ 7.26 and carbon δ 77. 16 for $CDCl_3$ and proton δ 2.50 and carbon δ 39.5 for DMSO-d_6). ^1H NMR coupling constants (*J*) are reported in Hertz (Hz). The following abbreviations were used in reporting multiplicities: s (singlet), d (doublet), t (triplet), m (multiplet), dd (doublet of doublets), ddd (doublet of doublet of doublets) and br (broad). High-resolution mass spectra (HRMS) were recorded on either a Q-ToF micro (Bruker Compass Data Analysis 4.0) spectrometer or a Thermo LTQ Orbitrap XL apparatus, both equipped with an ESI analytical source. HPLC-MS analyses were performed on a Thermo-Dionex Ultimate 3000 instrument (pump + autosampler at 20 °C + column oven at 25 °C) equipped with a diode array detector (Thermo-Dionex DAD 3000-RS) and a MSQ Plus single quadrupole mass spectrometer (low-resolution mass (LRMS) analyses through electrospray ionization (ESI) source).

3. Experimental Section

3.1 Preparation of Intermediate 1

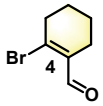


Scheme S1 Synthetic route towards Intermediate **1**

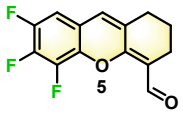


3

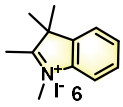
2-Hydroxyl-3,4,5-trifluoro-benzaldehyde 3. To 2,3,4-trifluorophenol **A** (148 mg, 1 mmol, 1 equiv.) in TFA (2 mL) was added hexamethylenetetramine **B** (350 mg, 2.5 mmol, 2.5 equiv.). The mixture was stirred at room temperature (r.t.) for ~10 min until observation of a clear solution. The resulting solution was refluxed at 100 °C for 13 h and cooled down to r.t. Deionized water (2 mL) and conc. H_2SO_4 (370 µL) were added and the mixture was further stirred at r.t. for 18 h. The reaction mixture was extracted with DCM (3 x 20 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash-column chromatography on silica gel (100% Petroleum ether) afforded 2-hydroxyl-3,4,5-trifluoro-benzaldehyde **3** as a white solid (117 mg, 66%). ^{1}H NMR (400.0 MHz, $CDCl_3$): δ = 11.05 (s, 1H), 9.83 (s, 1H), 7.27 (m, 1H) ppm; ^{19}F NMR (376.5 MHz, $CDCl_3$): δ = -144.4 (dd, J = 9.0, 21.1 Hz, 1F), -145.2 (m, 1F), -155.3 (d, J = 18.3 Hz, 1F) ppm; ^{13}C NMR (100.0 MHz, $CDCl_3$): δ = 194.7, 148.2 (m), 145.7 (ddd, $J_{C\text{-}FC}$ = 12.3 Hz, $J_{C\text{-}F}$ = 16.2 Hz, $^1J_{C\text{-}F}$ = 262.0 Hz), 144.4 (ddd, $J_{C\text{-}F}$ = 1.2 Hz, $J_{C\text{-}F}$ = 10.8 Hz, $^1J_{C\text{-}F}$ = 245.4 Hz), 140.4 (ddd, $J_{C\text{-}F}$ = 2.6 Hz, $J_{C\text{-}F}$ = 11.8 Hz, $^1J_{C\text{-}F}$ = 254.5 Hz), 115.7 (m), 114.0 (ddd, $J_{C\text{-}F}$ = 1.9 Hz, $J_{C\text{-}F}$ = 3.7 Hz, $J_{C\text{-}F}$ = 18.1 Hz) ppm; MS (EI+): m/z calcd for $C_7H_3F_3O_2$ [M]+ 176.0085, found 176.0000.



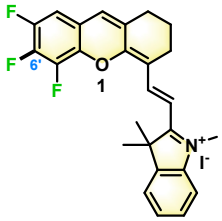
6-Bromocyclohex-1-ene-1-carbaldehyde 4. To a mixture of DMF (23.5 mL, 306 mmol, 3 equiv.) and $CHCl_3$ (100 mL) at 0 °C was added PBr_3 (24.2 mL, 255 mmol, 2.5 equiv.) portionwise under an atmosphere of N_2. After 1.5 h, cyclohexanone (10.5 mL, 102 mmol, 1 equiv.) was added and the mixture was stirred at r.t. overnight. The resulting solution was poured onto ice and then solid $NaHCO_3$ was slowly added until pH ~ 7. The aqueous layer was extracted with CH_2Cl_2 and the organic layer was washed with water. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The yellow mixture was purified by flash-column chromatography on silica gel (100% Petroleum ether) and 6-Bromocyclohex-1-ene-1-carbaldehyde **4** was obtained as a pale yellow liquid (13.6 g, 72%). ^{1}H NMR (400.0 MHz, $CDCl_3$): δ = 10.01 (s, 1H), 2.74 (m, 2H), 2.26 (m, 2H), 1.75 (m, 2H), 1.68 (m, 2H). The spectral data matched with the reference.[1]



5',6',7'-Trifluoro-2,3-dihydro-1H-xanthene-4-carbaldehyde 5. To 2-hydroxyl-3,4,5-trifluoro-benzaldehyde **3** (528 mg, 3 mmol, 1 equiv.) and Cs_2CO_3 (978 mg, 3 mmol, 1 equiv.) in DMF (15 mL) was added 6-bromocyclohex-1-ene-1-carbaldehyde **4** (2.26 g, 12 mmol, 4 equiv.) and the mixture was stirred at 25 °C for 56 h. The reaction mixture was filtered and concentrated *in vacuo*. Purification by flash-column chromatography on silica gel (10% EtOAc in petroleum ether) afforded 5,6,7-Trifluoro-2,3-dihydro-1H-xanthene-4-carbaldehyde **5** as a yellow solid (483 mg, 61%). ^{1}H NMR (400.0 MHz, $CDCl_3$): δ = 10.35 (s, 1H), 6.78 (m, 1H), 6.53 (s, 1H), 2.59 (t, J = 5.8 Hz, 2H), 2.45 (t, J = 6.1 Hz, 2H), 1.73 (m, 2H) ppm; ^{19}F NMR (376.5 MHz, $CDCl_3$): δ = -140.7 (m, 1F), -155.2 (m, 1F), -155.8 (m, 1F) ppm; ^{13}C NMR (100.0 MHz, $CDCl_3$): δ = 188.1, 157.9, 146.9 (ddd, $J_{C\text{-}F}$ = 2.1 Hz, $J_{C\text{-}F}$ = 11.1 Hz, $^1J_{C\text{-}F}$ = 246.6 Hz), 140.6 (ddd, $J_{C\text{-}F}$ = 12.1 Hz, $J_{C\text{-}F}$ = 16.9 Hz, $^1J_{C\text{-}F}$ = 254.2 Hz), 139.8 (ddd, $J_{C\text{-}F}$ = 4.0 Hz, $J_{C\text{-}F}$ = 12.5 Hz, $^1J_{C\text{-}F}$ = 253.8 Hz), 137.4 (m), 131.5 (d, $J_{C\text{-}F}$ = 2.9 Hz), 123.6 (dd, $J_{C\text{-}F}$ = 3.1 Hz, $J_{C\text{-}F}$ = 5.7 Hz), 117.1 (m), 115.2 (d, $J_{C\text{-}F}$ = 0.9 Hz), 107.8 (dd, $J_{C\text{-}F}$ = 3.7 Hz, $J_{C\text{-}F}$ = 19.6 Hz), 30.1, 21.5, 20.0 ppm; HRMS (ESI+): m/z calcd for $C_{14}H_9F_3O_2$ $[M + Na]^+$ 289.0447, found 289.0450.

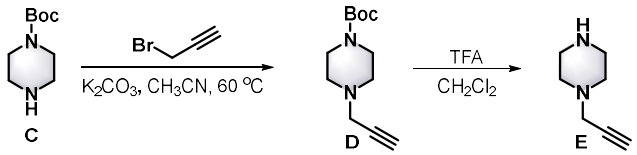


1,2,3,3-tetramethyl-3H-indol-1-ium iodide 6. To 2,3,3-trimethyl-3H-idole (32 mL, 200 mmol, 1 equiv.) in CH_3CN (200 mL) was added iodomethane (14 mL, 228 mmol, 2.28 equiv.) portion-wise and the solution was refluxed overnight. The precipitate was filtered and washed with Et_2O and dried *in vacuo* to afford 1,2,3,3-tetramethyl-3H-indol-1-ium iodide **6** as a light pink solid (56.5 g, 94%). ^{1}H NMR (400.0 MHz, DMSO-d_6): δ = 7.91 (m, 1H), 7.82 (m, 1H), 7.62 (m, 2H), 3.97 (s, 3H), 2.76 (s, 3H), 1.53 (s, 3H) ppm; ^{13}C NMR (100.0 MHz, DMSO-d_6): δ = 196.5, 142.6, 142.1, 129.8, 129.3, 123.8, 115.6, 54.4, 35.1, 22.2, 14.5 ppm. The spectral data matched with the reference.[2]



5',6',7'-trifluoro DHX-hemicyanine fused dye precursor 1. To 5',6',7'-Trifluoro-2,3-dihydro-1H-xanthene-4-carbaldehyde **5** (265 mg, 0.99 mmol, 1 equiv.) in EtOH (2 mL) was added 1,2,3,3-tetramethyl-3H-indol-1-ium iodide **6** (300 mg, 0.99 mmol, 1 equiv.) and the solution was refluxed at 80 °C for 4 h. The reaction mixture was concentrated and the crude product was purified by flash-column chromatography on silica gel (1% MeOH in CH_2Cl_2) to afford compound **1** as a dark blue solid (483 mg, 88%). ^{1}H NMR (400.0 MHz, DMSO-d_6): δ = 8.50 (d, J = 15.6 Hz, 1H), 7.82 (m, 2H), 7.56 (m, 3H), 7.18 (s, 1H), 6.83 (d, J = 15.6 Hz, 1H), 4.01 (s, 3H), 2.70 (m, 4H),1.82 (m, 2H), 1.74 (s, 6H) ppm; ^{19}F NMR (376.5 MHz, DMSO-d_6): δ = -140.2 (m, 1F), -156.1 (m, 1F), -157.6 (d, J_{F-F} = 19.4 Hz, 1F) ppm; ^{13}C NMR (100.0 MHz, DMSO-d_6): δ = 180.0, 156.0, 146.8 (dd, J_{C-F} = 10.2 Hz, $^1J_{C-F}$ = 244.2 Hz), 145.3, 143.1, 142.5, 140.6 (m), 140.4 (ddd, J_{C-F} = 11.9 Hz, J_{C-F} = 17.1 Hz, $^1J_{C-F}$ = 253.0 Hz), 138. 0 (m), 131.9, 129.4, 128.8, 127.2, 123.3, 118.5 (dd, J_{C-F} = 3.1 Hz, J_{C-F} = 9.2 Hz), 115.5, 114.8, 109.6 (d, J_{C-F} = 2.8 Hz), 109.4, 51.6, 34.1, 29.2, 27.1, 23.9, 20.1 ppm; HRMS (ESI+): m/z calcd for $C_{26}H_{23}F_3NO^+$ $[M]^{+\circ}$ 422.1763, found 422.1707; HPLC (system A): t_R = 4.8 min (purity >99% at 600 nm); LRMS (ESI+, recorded during RP-HPLC analysis): *m/z* 422.2 $[M]^{+\circ}$ (100), calcd for $C_{26}H_{23}F_3NO^+$ 422.2; UV-vis (recorded during the HPLC analysis): λ_{max} = 541 nm (broad peak).

3.2. Preparation of Substrate E

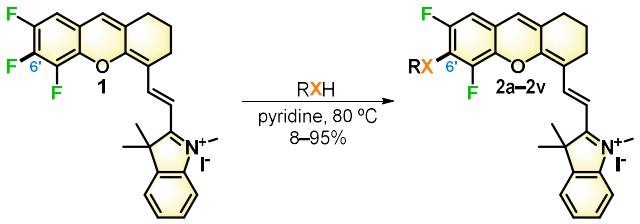


Scheme S2 Synthesis of substrate **E**

To 1-(tert-Butyloxycarbonyl)piperazine **C** (3.7 g, 20 mmol, 1 equiv.) in CH_3CN (80 mL) were added 3-bromopropyne (1.9 mL, 22 mmol, 1.1 equiv.) and K_2CO_3 (4.1 g, 30 mmol, 1.5 equiv.) and the mixture was stirred at 60 °C for 2 h. After cooling down to r.t., the solvent was removed under reduced pressure. The residue was washed with water and extracted

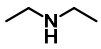
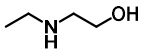
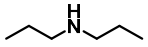
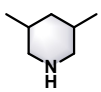
in DCM. Purification by flash-column chromatography on silica gel (20% EtOAc in petroleum ether) afforded tert-butyl 4-(prop-2-yn-1-yl)piperazine-1-carboxylate **D**. The latter was dissolved in DCM (25 mL), TFA (25 mL) was added and the mixture was stirred at r.t. for 3 h. The reaction mixture was washed with sat. aqueous $NaHCO_3$ solution and extracted with EtOAc. After concentration *in vacuo*, 1-(prop-2-yn-1-yl)piperazine **E** was obtained as a yellow solid (1.2 g, 48%). ^{1}H NMR (400.0 MHz, DMSO-d_6): δ = 3.20 (d, J = 2.2 Hz, 2H), 3.09 (t, J = 2.4 Hz, 1H), 2.71 (brs, 4H), 2.36 (brs, 4H) ppm. The spectrum matched with the corresponding reference.[3]

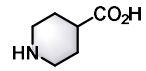
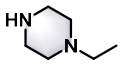
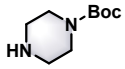
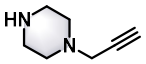
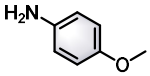
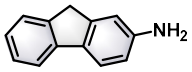
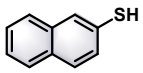
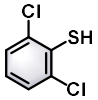
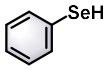
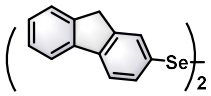
3.3 General procedure for the S_NAr reaction

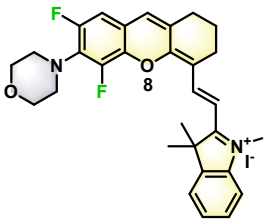


General procedure for the synthesis of NIR DHX-hemicyanine fused dyes 8 and 2a–2u. To intermediate **1** (220 mg, 0.4 mmol, 1 equiv.) in pyridine (1 mL) was added the respective nucleophile (2 mmol, 5 equiv.) and the mixture was heated at 80 °C for 12 h in a sealed tube. After cooling down to r.t., the reaction mixture was concentrated in *vacuo* and directly purified by flash-column chromatography on silica gel (1% MeOH in CH_2Cl_2) to afford the corresponding blue products **2a–2u**.

Table 1 The product and corresponding nucleophiles

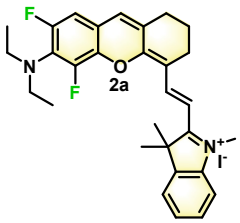
Nucleophiles (RXH)	**Product**	**Yields**
	**8**	61%
	**2a**	25%
	**2b**	34%
	**2c**	16%
NaN_3	**2d**	44%
	**2e**	61%
	**2f**	65%
	**2g**	8%
	**2h**	45%

	**2i**	35%
	**2j**	29%
	**2k**	76%
	**2l**	81%
	**2m**	39%
	**2n**	35%
	**2o**	43%
	**2p**	45%
	**2q**	86%
	**2r**	71%
	**2s**	92%
	**2t**	95%
	**2u**	66%

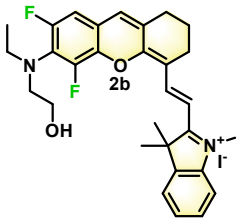


8: 61% yield; Dark green solid; ^{1}H NMR (400.0 MHz, DMSO-d_6): δ = 8.54 (d, J = 15.4 Hz, 1H), 7.83 (d, J = 7.3 Hz, 1H), 7.74 (d, J = 7.9 Hz, 1H), 7.57 (dd, J = 7.3, 7.5 Hz, 1H), 7.50 (t, J = 7.4 Hz, 1H), 7.26 (m, 2H), 6.71 (d, J = 15.4 Hz, 1H), 3.95 (s, 3H), 3.73 (t, J = 4.2 Hz, 4H),3.26 (brs, 4H), 2.70 (m, 4H), 1.82 (m, 2H), 1.74 (s, 6H) ppm; ^{19}F NMR (376.5 MHz, DMSO-d_6): δ = -124.3 (m, 1F), -146.5 (s, 1F) ppm; ^{13}C NMR (100.0 MHz, DMSO-d_6): δ = 179.2, 157.9, 153.3 (dd, $J_{C\text{-}F}$ = 5.9 Hz, $^{1}J_{C\text{-}F}$ = 243.8 Hz), 144.3 (dd, $J_{C\text{-}F}$ = 7,6 Hz, $^{1}J_{C\text{-}F}$ = 247.9 Hz), 145.2, 142.8, 142.6, 138.6 (dd, $J_{C\text{-}F}$ = 1.6 Hz, $J_{C\text{-}F}$ = 10.1 Hz), 130.3 (dd, $J_{C\text{-}F}$ = 9.0 Hz, $J_{C\text{-}F}$ = 14,5 Hz), 130.0, 129.7, 129.4, 128.3, 123.3, 117.0 (d, $J_{C\text{-}F}$ = 11.0

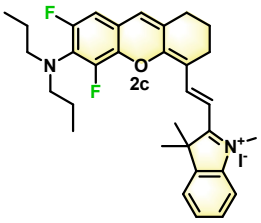
Hz), 115.0, 114.3, 109.1 (dd, $J_{C\text{-}F}$ = 2.2 Hz, $J_{C\text{-}F}$ = 24.3 Hz), 107.6, 67.1, 51.4, 51.2, 33.7, 29.1, 27.4, 23.9, 20.2 ppm; HRMS (ESI+): m/z calcd for $C_{30}H_{31}F_2N_2O_2^+$ $[M]^{+\circ}$ 489.2348, found 489.2343; HPLC (system A): t_R = 4.8 min (purity 100% at 600 nm); LRMS (ESI+, recorded during RP-HPLC analysis): *m/z* 489.2 $[M]^{+\circ}$ (100), calcd for $C_{30}H_{31}F_2N_2O_2^+$ 489.2; UV-vis (recorded during the HPLC analysis): λ_{max} = 602 nm (broad peak).



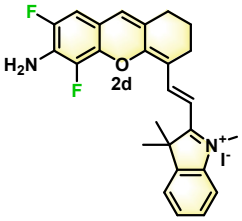
2a: 25% yield; Dark green solid; ^{1}H NMR (400.0 MHz, DMSO-d_6): δ = 8.58 (d, J = 15.3 Hz, 1H), 7.82 (d, J = 7.3 Hz, 1H), 7.73 (d, J = 7.9 Hz, 1H), 7.57 (dd, J = 7.5, 7.7 Hz, 1H), 7.50 (t, J = 7.4 Hz, 1H), 7.26 (m, 2H), 6.70 (d, J = 15.3 Hz, 1H), 3.94 (s, 3H), 3.26 (q, J = 7.0 Hz, 4H), 2.70 (m, 4H), 1.82 (m, 2H), 1.74 (s, 6H), 1.05 (t, J = 7.0Hz, 6H) ppm; ^{19}F NMR (376.5 MHz, DMSO-d_6): δ = -123.2 (m, 1F), -145.0 (s, 1F) ppm; ^{13}C NMR (100.0 MHz, DMSO-d_6): δ = 178.7, 157.5, 154.4 (dd, $J_{C\text{-}F}$ = 5.8 Hz, $^1J_{C\text{-}F}$ = 244.3 Hz), 145.4 (dd, $J_{C\text{-}F}$ = 9.2 Hz, $^1J_{C\text{-}F}$ = 248.1 Hz), 144.8, 142.3, 142.1, 138.0 (dd, $J_{C\text{-}F}$ = 1.3 Hz, $J_{C\text{-}F}$ = 10.5 Hz), 129.6, 129.4, 128.9 - 128.6 (m), 128.8, 127.7, 122.7, 116.8 (d, $J_{C\text{-}F}$ = 11.6 Hz), 114.4, 113.7, 108.3 (dd, $J_{C\text{-}F}$ = 2.0 Hz, $J_{C\text{-}F}$ = 24.5 Hz), 106.9, 50.7, 46.4, 33.1, 28.6, 26.9, 23.4, 19.8, 13.2 ppm; HRMS (ESI+): m/z calcd for $C_{30}H_{33}F_2N_2O^+$ $[M]^{+\circ}$ 475.2555, found 475.2552; HPLC (system A): t_R = 5.4 min (purity 99% at 600 nm); LRMS (ESI+, recorded during RP-HPLC analysis): *m/z* 474.9 $[M]^{+\circ}$ (100), calcd for $C_{30}H_{33}F_2N_2O^+$ 475.3; UV-vis (recorded during the HPLC analysis): λ_{max} = 598 nm (broad peak).



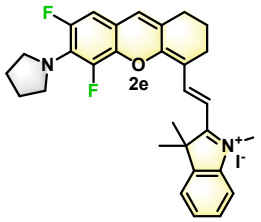
2b: 34% yield; Dark green solid; ^{1}H NMR (400.0 MHz, CD_3OD): δ = 8.80 (d, J = 15.2 Hz, 1H), 7.69 (d, J = 7.3 Hz, 1H), 7.62 (d, J = 7.9 Hz, 1H), 7.56 (dd, J = 7.1, 7.6 Hz, 1H), 7.50 (t, J = 7.3 Hz, 1H), 7.21 (s, 1H), 7.06 (dd, $J_{H\text{-}F}$= 1.1 Hz, $J_{H\text{-}F}$= 11.6 Hz, 1H), 6.66 (d, J = 15.2 Hz, 1H), 3.93 (s, 3H), 3.68 (t, J = 6.0 Hz, 2H), 3.42 (m, 4H), 2.76 (m, 4H), 1.94 (m, 2H), 1.83 (s, 6H), 1.14 (t, J = 7.1 Hz, 3H) ppm; ^{19}F NMR (376.5 MHz, CD_3OD): δ = -123.7 (m, 1F), -145.3 (s, 1F) ppm; ^{13}C NMR (100.0 MHz, CD_3OD): δ = 180.8, 160.5, 156.7 (dd, $J_{C\text{-}F}$ = 5.9 Hz, $^1J_{C\text{-}F}$ = 245.3 Hz), 147.6, 147.4 (dd, $J_{C\text{-}F}$ = 8.0 Hz, $^1J_{C\text{-}F}$ = 248.2 Hz), 143.8, 143.7, 140.1 (dd, $J_{C\text{-}F}$ = 2.1 Hz, $J_{C\text{-}F}$ = 10.9 Hz), 131.7 (t, $J_{C\text{-}F}$ = 2.9 Hz), 131.5 (dd, $J_{C\text{-}F}$ = 10.1 Hz, $J_{C\text{-}F}$ = 15.6 Hz), 131.3, 130.4, 129.2, 123.9, 118.6 (d, $J_{C\text{-}F}$ = 11.3 Hz), 116.4, 114.4, 109.4 (dd, $J_{C\text{-}F}$ = 3.1 Hz, $J_{C\text{-}F}$ = 24.9 Hz), 107.2, 61.4, 55.9 (t, $J_{C\text{-}F}$ = 3.3 Hz), 52.5, 33.4, 30.4, 28.1, 25.1, 21.7, 14.0 ppm; HRMS (ESI+): m/z calcd for $C_{30}H_{33}F_2N_2O_2^+$ $[M]^{+\circ}$ 491.2505, found 491.2488; HPLC (system A): t_R = 4.7 min (purity >99% at 600 nm); LRMS (ESI+, recorded during RP-HPLC analysis): *m/z* 491.0 $[M]^{+\circ}$ (100), calcd for $C_{30}H_{33}F_2N_2O_2^+$ 491.2; UV-vis (recorded during the HPLC analysis): λ_{max} = 598 nm (broad peak).



2c: 16% yield; Dark green solid; ^{1}H NMR (400.0 MHz, CD_3OD): δ = 8.78 (d, J = 15.1 Hz, 1H), 7.69 (d, J = 7.3 Hz, 1H), 7.62 (d, J = 7.9 Hz, 1H), 7.56 (dd, J = 7.4, 7.8 Hz, 1H), 7.49 (t, J = 7.4 Hz, 1H), 7.22 (s, 1H), 7.06 (dd, $J_{H\text{-}F}$= 1.0 Hz, $J_{H\text{-}F}$= 11.6 Hz, 1H), 6.66 (d, J = 15.2 Hz, 1H), 3.94 (s, 3H), 3.27 (t, J = 7.0 Hz, 4H), 2.75 (m, 4H), 1.94 (brs, 2H), 1.83 (s, 6H), 1.56 (m, 4H), 0.91 (t, J = 7.3 Hz, 6H) ppm; ^{19}F NMR (376.5 MHz, CD_3OD): δ = -123.8 (m, 1F), -145.9 (s, 1F) ppm; ^{13}C NMR (100.0 MHz, CD_3OD): δ = 180.7, 160.5, 156.5 (dd, $J_{C\text{-}F}$ = 6.0 Hz, $^{1}J_{C\text{-}F}$ = 245.2 Hz), 147.5, 147.1 (dd, $J_{C\text{-}F}$ = 7.9 Hz, $^{1}J_{C\text{-}F}$ = 247.8 Hz), 143.8, 143.7, 140.1 (dd, $J_{C\text{-}F}$ = 1.7 Hz, $J_{C\text{-}F}$ = 10.6 Hz), 131.8 (m), 131.8, 130.4, 129.1, 123.9, 118.2 (d, $J_{C\text{-}F}$ = 1.3 Hz), 116.4, 114.5, 109.5 (d, $J_{C\text{-}F}$ = 24.6 Hz), 107.2, 56.1 (t, $J_{C\text{-}F}$ = 3.3 Hz), 52.4, 33.7, 30.4, 28.1, 25.1, 22.7, 21.6, 11.8 ppm; HRMS (ESI+): m/z calcd for $C_{32}H_{37}F_2N_2O^+$ $[M]^{+\circ}$ 503.2868, found 503.2868; HPLC (system A): t_R = 5.7 min (purity >99% at 600 nm); LRMS (ESI+, recorded during RP-HPLC analysis): *m/z* 503.1 $[M]^{+\circ}$ (100), calcd for $C_{32}H_{37}F_2N_2O^+$ 503.3; UV-vis (recorded during the HPLC analysis): λ_{max} = 615 nm (broad peak).

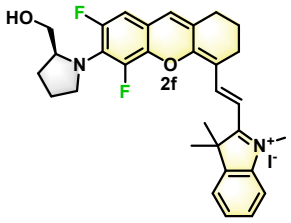


2d: 44% yield; Dark green solid; ^{1}H NMR (600.0 MHz, DMSO-d_6): δ = 8.58 (d, J = 14.9 Hz, 1H), 7.76 (d, J = 7.4 Hz, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.53 (dd, J = 7.5, 7.9 Hz, 1H), 7.43 (t, J = 7.5 Hz, 1H), 7.41 (s, 1H), 7.26 (d, $J_{H\text{-}F}$ = 10.5 Hz, 1H), 6.60 (brs, 2H), 6.54 (d, J = 15.0 Hz, 1H), 3.84 (s, 3H), 2.71 (t, J = 5.8 Hz, 2H), 2.67 (t, J = 6.0 Hz, 2H), 1.82 (m, 2H), 1.72 (s, 6H) ppm; ^{19}F NMR (376.5 MHz, DMSO-d_6): δ = -133.2 (m, 1F), -157.4 (d, $J_{F\text{-}F}$ = 11.4 Hz, 1F) ppm; ^{13}C NMR (100.0 MHz, DMSO-d_6): δ = 177.0, 159.4, 147.6 (dd, $J_{C\text{-}F}$ = 7.4 Hz, $^{1}J_{C\text{-}F}$ = 239.5 Hz), 144.0, 142.3, 141.7, 138.6 (d, $J_{C\text{-}F}$ = 8.0 Hz), 137.1 (dd, $J_{C\text{-}F}$ = 8.7 Hz, $^{1}J_{C\text{-}F}$ = 240.4 Hz), 133.0, 130.4 (dd, $J_{C\text{-}F}$ = 12.7 Hz, $J_{C\text{-}F}$ = 18.5 Hz), 128.7, 126.7, 125.4, 122.6, 113.9, 112.9, 109.6 (d, $J_{C\text{-}F}$ = 10.2 Hz), 107.8 (d, $J_{C\text{-}F}$ = 20.9 Hz), 104.3, 50.0, 32.4, 28.2, 27.2, 23.4, 19.9 ppm; HRMS (ESI+): m/z calcd for $C_{26}H_{25}F_2N_2O^+$ $[M]^{+\circ}$ 419.1929, found 419.1916; HPLC (system A): t_R = 4.6 min (purity 99% at 600 nm); LRMS (ESI+, recorded during RP-HPLC analysis): *m/z* 419.0 $[M]^{+\circ}$ (100), calcd for $C_{26}H_{25}F_2N_2O^+$ 419.2; UV-vis (recorded during the HPLC analysis): λ_{max} = 620 and 671 nm (broad peak).

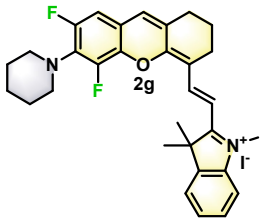


2e: 61% yield; Dark green solid; ^{1}H NMR (400.0 MHz, CD_3OD): δ = 8.72 (d, J = 14.9 Hz, 1H), 7.64 (d, J = 7.4 Hz, 1H), 7.52 (m, 2H), 7.43 (m, 1H), 7.27 (s, 1H), 7.02 (d, $J_{H\text{-}F}$ = 13.6 Hz, 1H), 6.50 (d, J = 14.9 Hz, 1H), 3.84 (s, 3H), 3.74 (brs, 4H), 2.74 (m, 4H), 1.95 (m, 6H), 1.79 (s, 6H) ppm; ^{19}F NMR (376.5 MHz, CD_3OD): δ = -126.0 (m, 1F), -153.1 (s, 1F) ppm; ^{13}C NMR (100.0 MHz, CD_3OD): δ = 179.3, 162.0, 151.6 (dd, $J_{C\text{-}F}$ = 8.1 Hz, $^{1}J_{C\text{-}F}$ = 243.5 Hz), 146.6, 143.9, 143.4, 141.4 (d, $J_{C\text{-}F}$ = 11.0 Hz), 141.3 (dd, $J_{C\text{-}F}$ = 9.4 Hz, $^{1}J_{C\text{-}F}$ = 243.2 Hz), 134.2, 131.9 (dd, $J_{C\text{-}F}$ = 8.3 Hz, $J_{C\text{-}F}$ = 14.4 Hz),

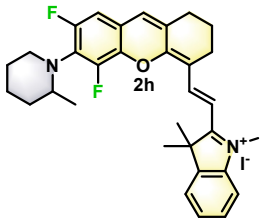
130.3, 128.4, 128.1, 123.8, 116.2, 113.7, 113.4 (d, $J_{C\text{-}F}$ = 11.3 Hz), 110.0 (d, $J_{C\text{-}F}$ =25.3 Hz), 105.1, 53.1 (t, $J_{C\text{-}F}$ = 6.4 Hz), 51.9, 33.0, 30.9, 30.1, 28.4, 26.9, 21.8 ppm; HRMS (ESI+): m/z calcd for $C_{30}H_{31}F_2N_2O^+$ $[M]^{+\circ}$ 473.2399, found 473.2386; HPLC (system A): t_R = 5.5 min (purity 98% at 600 nm); LRMS (ESI+, recorded during RP-HPLC analysis): *m/z* 473.2 $[M]^{+\circ}$ (100), calcd for $C_{30}H_{31}F_2N_2O^+$ 473.2; UV-vis (recorded during the HPLC analysis): λ_{max} = 647 and 701 nm (broad peak).



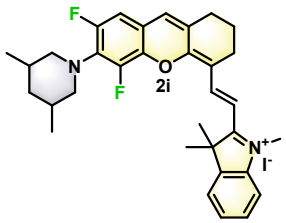
2f: 10% yield; Dark blue solid; Purification using semi-preparative RP-HPLC; ^{1}H NMR (400.0 MHz, CD_3OD): δ = 8.79 (d, *J* = 15.0 Hz, 1H), 7.65 (d, *J* = 7.4 Hz, 1H), 7.59–7.48 (m, 2H), 7.48–7.43 (m, 1H), 7.26 (d, *J* = 1.6 Hz, 1H), 7.05 (dd, *J* = 13.0, 2.0 Hz, 1H), 6.55 (d, *J* = 15.0 Hz, 1H), 4.38 (m, *J* = 7.5 Hz, 1H), 4.00–3.90 (m, 1H), 3.86 (s, 3H), 3.65–3.42 (m, 3H), 2.75 (dt, *J* = 20.5, 6.4 Hz, 4H), 2.23–2.17 (m, *J* = 7.3, 3.9 Hz, 1H), 2.10–2.02 (m, 1H), 1.98–1.88 (m, *J* = 12.5, 4.9 Hz, 4H), 1.81 (d, *J* = 3.2 Hz, 6H); ^{13}C NMR (100.0 MHz, CD_3OD): δ = 179.8, 161.5, 147.0, 143.7, 143.4, 133.3, 130.2, 129.0, 128.5, 123.6, 116.0, 115.1, 115.0, 113.8, 109.6, 109.4, 105.5, 64.7, 63.0, 54.2, 52.0, 32.8, 30.1, 29.5, 28.1, 26.0, 24.9, 21.6 pm; IR (film) ν_{max} = 3386, 2925, 2861, 1686, 1636, 1600, 1565, 1536, 1503, 1459, 1402, 1366, 1307, 1292, 1270, 1237, 1202, 1171, 1114, 1065, 1043, 1020, 929, 837 cm^{-1}; HRMS (ESI+): *m/z* calcd for $C_{31}H_{33}F_2N_2O_2^+$ $[M]^{+\circ}$ 503.2505, found 503.2500; HPLC (system A): t_R = 4.8 min (purity 98% at 600 nm); LRMS (ESI+, recorded during RP-HPLC analysis): *m/z* 503.3 $[M]^{+\circ}$ (100), calcd for $C_{31}H_{33}F_2N_2O_2^+$ 503.3; UV-vis (recorded during the HPLC analysis): λ_{max} = 637 and 691 nm (broad peak).



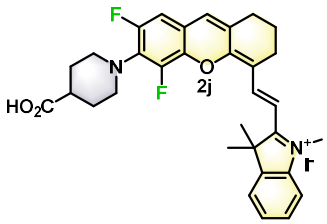
2g: 65% yield; Dark green solid; ^{1}H NMR (400.0 MHz, $CDCl_3$): δ = 8.69 (d, *J* = 15.1 Hz, 1H), 7.46 (m, 4H) 6.97 (s, 1H), 6.82 (m, 2H), 4.16 (s, 3H), 3.31 (brs, 4H), 2.90 (t, *J* = 6.0 Hz, 2H), 2.72 (t, *J* = 5.4 Hz, 2H), 1.96 (m, 2H), 1.81 (s, 6H), 1.72 (m, 4H), 1.66 (m, 2H) ppm; ^{19}F NMR (376.5 MHz, CD_3OD): δ = -125.1 (d, $J_{H\text{-}F}$ = 6.4 Hz, 1F), -147.1 (s, 1F) ppm; ^{13}C NMR (100.0 MHz, CD_3OD): δ = 180.7, 160.7, 155.3 (dd, $J_{C\text{-}F}$ = 6.8 Hz, $^1J_{C\text{-}F}$ = 245.0 Hz), 147.5, 145.8 (dd, $J_{C\text{-}F}$ = 7.0 Hz, $^1J_{C\text{-}F}$ = 247.2 Hz), 143.8, 143.7, 140.4 (m), 133.6 (dd, $J_{C\text{-}F}$ = 9.1 Hz, $J_{C\text{-}F}$ = 14.7 Hz), 132.0, 130.8, 130.4, 129.1, 123.9, 117.6 (d, $J_{C\text{-}F}$ = 11.0 Hz), 116.4, 114.4, 109.6 (dd, $J_{C\text{-}F}$ =2.8 Hz, $J_{C\text{-}F}$ =24.4 Hz), 106.9, 53.7 (t, $J_{C\text{-}F}$ = 3.8 Hz), 52.4, 33.4, 30.3, 28.1, 27.9, 25.4, 25.1, 21.7 ppm; HRMS (ESI+): m/z calcd for $C_{31}H_{33}F_2N_2O^+$ $[M]^{+\circ}$ 487.2555, found 487.2524; HPLC (system A): t_R = 5.5 min (purity 100% at 600 nm); LRMS (ESI+, recorded during RP-HPLC analysis): *m/z* 487.2 $[M]^{+\circ}$ (100), calcd for $C_{31}H_{33}F_2N_2O^+$ 487.3; UV-vis (recorded during the HPLC analysis): λ_{max} = 613 nm (broad peak).



2h: 8% yield; Dark green solid; ^{1}H NMR (400.0 MHz, CD_3OD): δ = 8.80 (d, *J* = 15.2 Hz, 1H), 7.70 (d, *J* = 7.3 Hz, 1H), 7.64 (d, *J* = 7.9 Hz, 1H), 7.57 (dd, *J* = 7.3, 7.9 Hz, 1H), 7.51 (t, *J* = 7.5 Hz, 1H), 7.19 (s, 1H), 7.06 (d, $J_{H\text{-}F}$= 11.0 Hz, 1H), 6.69 (d, *J* = 15.3 Hz, 1H), 3.95 (s, 3H), 3.42 (m, 1H), 3.26 (m, 1H), 3.08 (m, 1H), 2.76 (m, 4H), 1.94 (m, 2H), 1.84 (s, 7H), 1.70 (m, 3H), 1.56 (m, 2H), 1.04 (d, *J* = 6.3 Hz, 3H) ppm; ^{19}F NMR (376.5 MHz, CD_3OD): δ = -123.7 (m, 1F), -145.3 (s, 1F) ppm; ^{13}C NMR (100.0 MHz, CD_3OD): δ = 181.1, 160.0, 157.9 (d, $^{1}J_{C\text{-}F}$ = 245.2 Hz), 148.7 (d, $^{1}J_{C\text{-}F}$ = 251.5 Hz), 147.7, 143.9, 143.7, 139.8 (d, $J_{C\text{-}F}$ = 10.5 Hz), 132.3 (dd, $J_{C\text{-}F}$ = 16.6 Hz, $J_{C\text{-}F}$ = 27.1 Hz), 132.1, 131.0, 130.4, 129.3, 120.1 (d, $J_{C\text{-}F}$ = 10.2 Hz) 116.6, 114.7, 109.4 (d, $J_{C\text{-}F}$ = 25.3 Hz), 107.9, 56.0, 52.6, 35.2, 30.9, 30.4, 28.1, 27.9, 25.1, 24.0, 21.6, 19.5 ppm; HRMS (ESI+): m/z calcd for $C_{32}H_{35}F_2N_2O^+$ $[M]^{+\circ}$ 501.2712, found 501.2707; HPLC (system A): t_R = 5.6 min (purity >99% at 600 nm); LRMS (ESI+, recorded during RP-HPLC analysis): *m/z* 501.1 $[M]^{+\circ}$ (100), calcd for $C_{32}H_{35}F_2N_2O^+$ 501.3; UV-vis (recorded during the HPLC analysis): λ_{max} = 589 nm (broad peak).

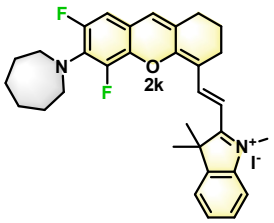


2i: 45% yield; Dark green solid; ^{1}H NMR (400.0 MHz, DMSO-d_6): δ = 8.52 (d, *J* = 15.3 Hz, 1H), 7.82 (d, *J* = 7.3 Hz, 1H), 7.74 (d, *J* = 7.9 Hz, 1H), 7.56 (dd, *J* = 7.1, 7.5 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 1H), 7.27 (s, 1H), 7.22 (m, 1H), 6.68 (d, *J* = 15.3 Hz, 1H), 3.94 (s, 3H), 3.26 (d, *J* = 10.8 Hz, 2H), 2.64 (m, 6H), 1.78 (m, 12H), 0.86 (d, *J* = 6.5 Hz, 6H) ppm; ^{19}F NMR (376.5 MHz, DMSO-d_6): δ = -124.2 (m, 1F), -146.9 (s, 1F) ppm; ^{13}C NMR (100.0 MHz, DMSO-d_6): δ = 178.4, 157.6, 152.7 (dd, $J_{C\text{-}F}$ = 6.1 Hz, $^{1}J_{C\text{-}F}$ = 243.4 Hz), 144.5, 143.6 (dd, $J_{C\text{-}F}$ = 7,5 Hz, $^{1}J_{C\text{-}F}$ = 247.1 Hz), 142.2, 142.1, 138.1 (dd, $J_{C\text{-}F}$ = 1.5 Hz, $J_{C\text{-}F}$ = 10.2 Hz), 130.7 (dd, $J_{C\text{-}F}$ = 9.4 Hz, $J_{C\text{-}F}$ = 14.7 Hz), 129.6, 129.0, 128.8, 127.6, 122.7, 115.7 (d, $J_{C\text{-}F}$ = 11.3 Hz), 114.4, 113.7, 108.4 (dd, $J_{C\text{-}F}$ = 1.7 Hz, $J_{C\text{-}F}$ = 24.3 Hz), 106.7, 58.0, 50.6, 41.3, 33.1, 31.4, 28.5, 26.9, 23.5, 19.7, 18.9 ppm; HRMS (ESI+): m/z calcd for $C_{33}H_{37}F_2N_2O^+$ $[M]^{+\circ}$ 515.2868, found 515.2853; HPLC (system A): t_R = 5.9 min (purity 98% at 600 nm); LRMS (ESI+, recorded during RP-HPLC analysis): *m/z* 514.9 $[M]^{+\circ}$ (100), calcd for $C_{33}H_{37}F_2N_2O^+$ 515.3; UV-vis (recorded during the HPLC analysis): λ_{max} = 515 nm (broad peak).

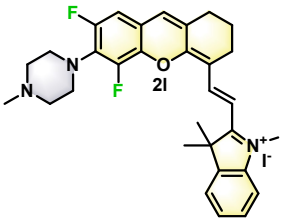


2j: 35% yield; Dark green solid; ^{1}H NMR (400.0 MHz, CD_3OD): δ = 8.80 (d, *J* = 15.3 Hz, 1H), 7.69 (d, *J* = 7.3 Hz, 1H), 7.62 (d, *J* = 7.8 Hz, 1H), 7.56 (dd, *J* = 7.2, 8.0 Hz, 1H), 7.50 (t, *J* = 7.4 Hz, 1H), 7.20 (s, 1H), 7.06 (d, $J_{H\text{-}F}$= 11.6 Hz, 1H), 6.65 (d, *J* = 15.2 Hz, 1H), 3.92 (s, 3H), 3.51 (d, *J* = 12.6 Hz, 2H), 3.25 (t, *J* = 11.7 Hz, 2H), 2.76 (m, 4H), 2.54 (m, 1H), 2.03 (m, 2H), 1.94 (m, 2H), 1.85 (m, 8H) ppm; ^{19}F NMR (376.5 MHz, CD_3OD): δ = -125.4 (m, 1F), -147.6 (s, 1F) ppm; ^{13}C NMR (100.0 MHz, CD_3OD): δ = 180.8, 178.7, 160.6, 155.3 (dd, $J_{C\text{-}F}$ = 6.1 Hz, $^{1}J_{C\text{-}F}$ = 244.7 Hz), 147.6, 146.0 (dd,

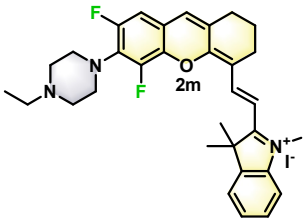
$J_{C\text{-}F}$ = 7.6 Hz, $^{1}J_{C\text{-}F}$ = 247.4 Hz), 143.8, 143.7, 140.2 (dd, $J_{C\text{-}F}$ = 2.2 Hz, $J_{C\text{-}F}$ = 10.7 Hz), 133.0 (dd, $J_{C\text{-}F}$ = 9.5 Hz, $J_{C\text{-}F}$ = 14.9 Hz), 131.8, 131.1, 130.4, 129.2, 123.9, 118.0 (d, $J_{C\text{-}F}$ = 11.4 Hz), 116.4, 114.4, 109.6 (dd, $J_{C\text{-}F}$ = 2.0 Hz, $J_{C\text{-}F}$ = 24.5 Hz), 107.1, 52.5, 52.1 (t, $J_{C\text{-}F}$ = 3.6 Hz), 42.0, 33.4, 30.4, 30.3, 28.1, 25.1, 21.7 ppm; HRMS (ESI+): m/z calcd for $C_{32}H_{33}F_2N_2O_3^+$ $[M]^{+\circ}$ 531.2454, found 531.2461; HPLC (system A): t_R = 4.8 min (purity >99% at 600 nm); LRMS (ESI+, recorded during RP-HPLC analysis): *m/z* 530.8 $[M]^{+\circ}$ (100), calcd for $C_{32}H_{33}F_2N_2O_3^+$ 531.3; UV-vis (recorded during the HPLC analysis): λ_{max} = 608 nm (broad peak).



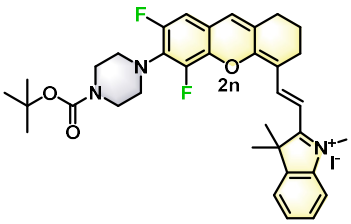
2k: 29% yield; Dark green solid; ^{1}H NMR (400.0 MHz, CD_3OD): δ = 8.79 (d, *J* = 15.1 Hz, 1H), 7.68 (d, *J* = 7.2 Hz, 1H), 7.60 (d, *J* = 7.5 Hz, 1H), 7.55 (ddd, *J* = 1.2, 7.3, 7.9 Hz, 1H), 7.48 (dt, *J* = 1.2, 7.2 Hz, 1H), 7.23 (s, 1H), 7.05 (dd, $J_{H\text{-}F}$ = 1.7 Hz, $J_{H\text{-}F}$ = 12.3 Hz, 1H), 6.62 (d, *J* = 15.1 Hz, 1H), 3.91 (s, 3H), 3.51 (t, *J* = 5.6 Hz, 4H), 2.76 (m, 4H), 1.94 (m, 2H), 1.83 (m, 10H), 1.74 (m, 4H) ppm; ^{19}F NMR (376.5 MHz, CD_3OD): δ = -125.3 (t, $J_{H\text{-}F}$ = 9.0 Hz, 1F), -146.5 (s, 1F) ppm; ^{13}C NMR (100.0 MHz, CD_3OD): δ = 180.4, 161.0, 154.9 (d, $^{1}J_{C\text{-}F}$ = 242.7 Hz), 147.4, 145.3 (d, $^{1}J_{C\text{-}F}$ = 246.5 Hz), 143.8, 143.7, 140.6 (m), 134.4 (dd, $J_{C\text{-}F}$ = 9.9 Hz, $J_{C\text{-}F}$ = 15.0 Hz), 132.4, 130.4, 130.2, 128.9, 123.9, 116.6 (d, $J_{C\text{-}F}$ = 11.1 Hz), 116.3, 114.2, 109.7 (d, $J_{C\text{-}F}$ =25.3 Hz), 106.6, 55.1 (t, $J_{C\text{-}F}$ = 4.1 Hz), 52.3, 33.4, 31.0, 30.3, 28.8, 28.2, 25.1, 21.7 ppm; HRMS (ESI+): m/z calcd for $C_{32}H_{35}F_2N_2O^+$ $[M]^{+\circ}$ 501.2712, found 501.2713; HPLC (system A): t_R = 5.7 min (purity 98% at 600 nm); LRMS (ESI+, recorded during RP-HPLC analysis): *m/z* 501.1 $[M]^{+\circ}$ (100), calcd for $C_{32}H_{35}F_2N_2O^+$ 501.3; UV-vis (recorded during the HPLC analysis): λ_{max} = 598 nm (broad peak).



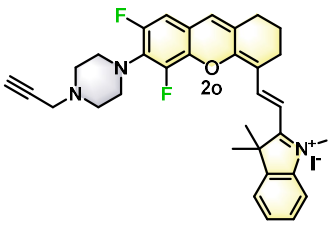
2l: 76% yield; Dark green solid; ^{1}H NMR (400.0 MHz, CD_3OD): δ = 8.77 (d, *J* = 15.4 Hz, 1H), 7.70 (d, *J* = 7.2 Hz, 1H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.57 (dd, *J* = 7.2, 7.6 Hz, 1H), 7.51 (dd, *J* = 7.3, 7.2 Hz, 1H), 7.17 (s, 1H), 7.12 (d, $J_{H\text{-}F}$ = 10.6 Hz, 1H), 6.71 (d, *J* = 15.3 Hz, 1H), 3.95 (s, 3H), 3.63 (brs, 4H), 3.42 (brs, 4H), 2.96 (s, 3H), 2.76 (m, 4H), 1.94 (m, 2H), 1.82 (s, 6H) ppm; ^{19}F NMR (376.5 MHz, CD_3OD): δ = -125.9 (m, 1F), -146.5 (s, 1F) ppm; ^{13}C NMR (100.0 MHz, CD_3OD): δ = 179.7, 158.2, 153.8 (dd, $J_{C\text{-}F}$ = 5.2 Hz, $^{1}J_{C\text{-}F}$ = 245.3 Hz), 146.2, 144.9 (m), 142.4, 142.2, 138.4 (dd, $J_{C\text{-}F}$ = 2.3 Hz, $J_{C\text{-}F}$ = 10.7 Hz), 130.7, 129.1, 128.9, 128.6 (dd, $J_{C\text{-}F}$ = 10.5 Hz, $J_{C\text{-}F}$ = 15.5 Hz), 127.9, 122.4, 118.2 (d, $J_{C\text{-}F}$ =10.9 Hz), 115.1, 113.2, 108.3 (dd, $J_{C\text{-}F}$ = 3.0 Hz, $J_{C\text{-}F}$ = 24.3 Hz), 106.5, 54.0, 51.1, 48.1, 42.8, 32.2, 28.9, 26.5, 23.5, 20.0 ppm; MS (ESI+): m/z calcd for $C_{31}H_{34}F_2N_3O^+$ $[M]^{+\circ}$ 502.2670, found 502.2658; HPLC (system A): t_R = 3.6 min (purity >99% at 600 nm); LRMS (ESI+, recorded during RP-HPLC analysis): *m/z* 272.3 $[2M + H + CH_3CN]^{2+}$ (100) and 502.1 $[M]^{+\circ}$ (45), calcd for $C_{31}H_{34}F_2N_3O^+$ 502.3; UV-vis (recorded during the HPLC analysis): λ_{max} = 591 nm (broad peak).



2m: 81% yield; Dark green solid; ^{1}H NMR (400.0 MHz, CD_3OD): δ = 8.78 (d, *J* = 15.3 Hz, 1H), 7.69 (d, *J* = 7.4 Hz, 1H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.56 (ddd, *J* = 0.9, 7.4, 8.0 Hz, 1H), 7.50 (dt, *J* = 0.7, 7.4 Hz, 1H), 7.17 (s, 1H), 7.10 (dd, $J_{H\text{-}F}$= 1,8 Hz, $J_{H\text{-}F}$= 11.6 Hz, 1H), 6.68 (d, *J* = 15.3 Hz, 1H), 3.94 (s, 3H), 3.55 (t, *J* = 4.4 Hz, 4H), 3.12 (brs, 4H), 2.98 (m, 2H), 2.76 (m, 4H), 1.94 (m, 2H), 1.82 (s, 6H), 1.31 (t, *J* = 7.3 Hz, 3H) ppm; ^{19}F NMR (376.5 MHz, CD_3OD): δ = -125.7 (m, 1F), -146.9 (s, 1F) ppm; ^{13}C NMR (100.0 MHz, DMSO-d_6): δ = 179.2, 157.8, 153.3 (dd, $J_{C\text{-}F}$ = 4.6 Hz, $^{1}J_{C\text{-}F}$ = 243.7 Hz), 144.4 (dd, $J_{C\text{-}F}$ = 7,6 Hz, $^{1}J_{C\text{-}F}$ = 247.7 Hz), 145.2, 142.8, 142.6, 138.6 (m), 130.1, 129.9 (m), 129.6, 129.4, 128.3, 123.3, 117.1 (d, $J_{C\text{-}F}$ =12.1 Hz), 115.0, 114.3, 109.1 (d, $J_{C\text{-}F}$ = 24.6 Hz), 107.7, 52.6, 51.9, 51.2, 49.9, 33.7, 29.1, 27.4, 23.9, 20.2, 11.2 ppm; MS (ESI+): m/z calcd for $C_{32}H_{36}F_2N_3O^+$ $[M]^{+\circ}$ 516.2826, found 516.2890; HPLC (system A): t_R = 3.7 min (purity >99% at 600 nm); LRMS (ESI+, recorded during RP-HPLC analysis): *m/z* 279.3 [2M + H + $CH_3CN]^{2+}$ (100) and 516.1 $[M]^{+\circ}$ (30), calcd for $C_{32}H_{36}F_2N_3O^+$ 516.3; UV-vis (recorded during the HPLC analysis): λ_{max} = 592 nm (broad peak).

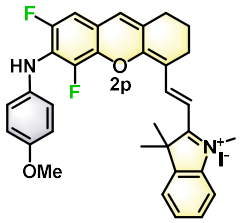


2n: 39% yield; Dark green solid; ^{1}H NMR (400.0 MHz, DMSO-d_6): δ = 8.56 (d, *J* = 15.2 Hz, 1H), 7.80 (d, *J* = 7.2 Hz, 1H), 7.74 (d, *J* = 7.9 Hz, 1H), 7.57 (dd, *J* = 7.5, 7.6 Hz, 1H), 7.50 (dd, *J* = 7.3, 7.4 Hz, 1H), 7.26 (m, 2H), 6.71 (d, *J* = 15.4 Hz, 1H), 3.94 (s, 3H), 3.47 (brs, 4H), 3.21 (brs, 4H), 2.70 (m, 4H), 1.82 (m, 2H), 1.75 (s, 6H), 1.43 (s, 9H) ppm; ^{19}F NMR (376.5 MHz, DMSO-d_6): δ = -124.1 (m, 1F), -146.0 (s, 1F) ppm; ^{13}C NMR (100.0 MHz, DMSO-d_6): δ = 178.7, 157.3, 153.7, 152.7 (d, $^{1}J_{C\text{-}F}$ = 244.3 Hz), 144.8, 143.9 (d, $^{1}J_{C\text{-}F}$ = 247.8 Hz), 142.3, 142.0, 138.0 (d, $J_{C\text{-}F}$ = 10.0 Hz), 129.9 - 129.8 (m), 129.6, 129.0, 128.8, 127.7, 122.6, 116.6 (d, $J_{C\text{-}F}$ = 11.2 Hz), 114.5, 113.7, 108.5 (d, $J_{C\text{-}F}$ = 23.7 Hz), 107.1, 79.0, 50.6, 50.4, 33.1, 28.9, 28.5, 28.0, 26.9, 23.4, 19.7 ppm; HRMS (ESI+): m/z calcd for $C_{35}H_{40}F_2N_3O_3^+$ $[M]^{+\circ}$ 588.3032, found 588.3021; HPLC (system A): t_R = 5.4 min (purity 97% at 600 nm); LRMS (ESI+, recorded during RP-HPLC analysis): *m/z* 588.3 $[M]^{+\circ}$ (100), calcd for $C_{35}H_{40}F_2N_3O_3^+$ 588.3; UV-vis (recorded during the HPLC analysis): λ_{max} = 602 nm (broad peak).

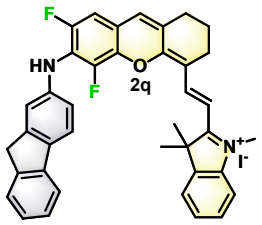


2o: 35% yield; Dark green solid; ^{1}H NMR (600.0 MHz, DMSO-d_6): δ = 8.56 (d, *J* = 14.9 Hz, 1H), 7.82 (d, *J* = 7.4 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.57 (dd, *J* = 7.6, 7.8 Hz, 1H), 7.50 (t, *J* = 7.4 Hz, 1H), 7.25 (m, 2H), 6.70 (d, *J* = 15.3 Hz, 1H), 3.94 (s, 3H), 3.38 (brs, 2H), 3.30 (brs, 4H), 3.21 (brs, 1H), 2.71 (brs, 2H), 2.68 (brs, 2H), 2.61 (brs, 4H), 1.82 (m, 2H), 1.75 (s, 6H) ppm; ^{19}F NMR (376.5 MHz, DMSO-d_6): δ = -124.2 (s, 1F), -146.3 (s, 1F) ppm; ^{13}C NMR (100.0 MHz,

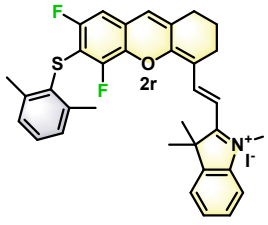
DMSO-d_6): δ = 178.7, 157.5, 152.7 (d, $^1J_{C\text{-}F}$ = 243.7 Hz), 144.7, 143.7 (dd, $J_{C\text{-}F}$ = 7.8 Hz, $^1J_{C\text{-}F}$ = 247.0 Hz), 142.2, 142.0, 138.0 (d, $J_{C\text{-}F}$ = 9.2 Hz), 130.0 (dd, $J_{C\text{-}F}$ = 8.4 Hz, $J_{C\text{-}F}$ = 11.3 Hz), 129.3(br), 128.8, 127.6, 122.6, 116.2 (d, $J_{C\text{-}F}$ = 11.0 Hz), 114.4, 113.6, 108.5 (d, $J_{C\text{-}F}$ = 24.5 Hz), 106.9, 78.9, 75.9, 51.5, 50.6, 50.3, 46.1, 33.0, 28.5, 26.9, 23.4, 19.7 ppm; HRMS (ESI+): m/z calcd for $C_{33}H_{34}F_2N_3O^+$ $[M]^{+\circ}$ 526.2664, found 526.2644; HPLC (system A): t_R = 3.9 min (purity 99% at 600 nm); LRMS (ESI+, recorded during RP-HPLC analysis): *m/z* 284.3 $[2M + H + CH_3CN]^{+\circ}$ (100) and 526.0 $[M]^{+\circ}$ (55), calcd for $C_{33}H_{34}F_2N_3O^+$ 526.3; UV-vis (recorded during the HPLC analysis): λ_{max} = 591 nm (broad peak).



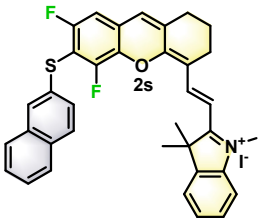
2p: 43% yield; Dark green solid; ^{1}H NMR (600.0 MHz, $CDCl_3$): δ = 8.67 (d, *J* = 15.3 Hz, 1H), 7.52 (m, 1H), 7.44 (m, 3H), 7.00 (m, 3H), 6.92 (d, $J_{H\text{-}F}$ = 10.0 Hz,1H), 6.89 (m, 2H), 6.84 (d, *J* = 14.9 Hz, 1H), 5.89 (brs, 1H), 4.15 (s, 3H), 3.83 (s, 3H), 2.91 (t, *J* = 6.1 Hz, 2H), 2.74 (t, *J* = 5.7 Hz, 2H), 1.96 (m, 2H), 1.74 (s, 6H) ppm; ^{19}F NMR (376.5 MHz, CD_3OD): δ = -128.0 (m, 1F), -147.3 (s, 1F) ppm; ^{13}C NMR (100.0 MHz, CD_3OD): δ = 180.1, 161.1, 157.2, 152.4 (dd, $J_{C\text{-}F}$ = 6.5 Hz, $^1J_{C\text{-}F}$ = 244.1 Hz), 147.1, 143.6, 143.5, 140.5 (dd, $J_{C\text{-}F}$ = 2.0 Hz, $J_{C\text{-}F}$ = 9.2 Hz), 136.4, 132.9, 130.2, 129.6, 128.7, 126.9 (dd, $J_{C\text{-}F}$ = 10.1 Hz, $J_{C\text{-}F}$ = 16.5 Hz), 123.7, 121.9, 116.1, 115.4 (d, $J_{C\text{-}F}$ = 10.3 Hz), 115.1, 113.9, 109.2 (dd, $J_{C\text{-}F}$ = 2.5 Hz, $J_{C\text{-}F}$ = 22.7 Hz), 106.0, 56.0, 52.1, 32.9, 30.1, 27.9, 25.0, 21.6 ppm; HRMS (ESI+): m/z calcd for $C_{33}H_{31}F_2N_2O_2^+$ $[M]^{+\circ}$ 525.2348, found 525.2348; HPLC (system A): t_R = 5.1 min (purity 99% at 600 nm); LRMS (ESI+, recorded during RP-HPLC analysis): *m/z* 525.0 $[M]^{+\circ}$ (100), calcd for $C_{33}H_{31}F_2N_2O_2^+$ 525.2; UV-vis (recorded during the HPLC analysis): λ_{max} = 626 nm (broad peak).



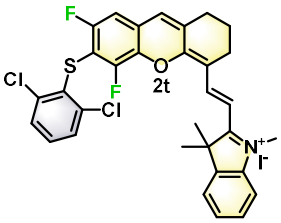
2q: 45% yield; Dark green solid; ^{1}H NMR (400.0 MHz, CD_3OD): δ = 8.74 (d, *J* = 15.2 Hz, 1H), 7.68 (dd, *J* = 8.1, 8.5 Hz, 2H), 7.56 (d, *J* = 7.9 Hz, 2H), 7.50 (m, 2H), 7.40 (m, 1H), 7.32 (t, *J* = 7.4 Hz, 1H), 7.19 (m, 4H), 6.98 (d, $J_{H\text{-}F}$= 8.0 Hz, 1H), 6.60 (d, *J* = 15.1 Hz, 1H), 3.88 (s, 3H), 3.82 (s, 2H), 2.77 (t, *J* = 5.8 Hz, 2H), 2.71 (t, *J* = 5.9 Hz, 2H), 1.94 (m, 2H), 1.73 (s, 6H) ppm; ^{19}F NMR (376.5 MHz, CD_3OD): δ = -126.7 (m, 1F), -144.9 (s, 1F) ppm; ^{13}C NMR (100.0 MHz, CD_3OD): δ = 180.5, 160.8, 153.4 (dd, $J_{C\text{-}F}$ = 5.7 Hz, $^1J_{C\text{-}F}$ = 244.5 Hz), 147.4, 145.7, 144.8 (d, $J_{C\text{-}F}$ = 6.2 Hz), 144.2, 143.7, 143.1, 143.0, 140.4 (d, $J_{C\text{-}F}$ = 9.9 Hz), 137.3, 130.5, 130.3, 129.0, 128.0, 127.0, 126.0, 125.3 (dd, $J_{C\text{-}F}$ = 11.0 Hz, $J_{C\text{-}F}$ = 16.9 Hz), 123.9, 121.1, 120.0, 118.1, 117.1 (d, $J_{C\text{-}F}$ = 10.3 Hz), 116.3, 115.7, 114.2, 109.5 (d, $J_{C\text{-}F}$ = 22.8 Hz), 106.7, 52.3, 37.8, 33.2, 30.3, 28.0, 25.0, 21.7 ppm; HRMS (ESI+): m/z calcd for $C_{39}H_{33}F_2N_2O^+$ $[M]^{+\circ}$ 583.2555 found 583.2541.



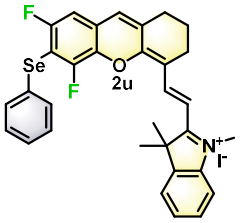
2r: 86% yield; Dark green solid; ^{1}H NMR (600.0 MHz, CD_3OD): δ = 8.72 (d, *J* = 15.5 Hz, 1H), 7.72 (d, *J* = 7.2 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.59 (dt, *J* = 1.0, 7.6 Hz, 1H), 7.54 (dt, *J* = 0.7, 7.5 Hz, 1H), 7.20 (m, 1H), 7.15 (s, 1H), 7.13 (d, *J* = 11.7 Hz, 2H), 7.05 (dd, $J_{H\text{-}F}$= 1.4, 9.1 Hz, 1H), 6.76 (d, *J* = 15.4 Hz, 1H), 3.96 (s, 3H), 2.77 (t, *J* = 5.7 Hz, 2H), 2.73 (t, *J* = 6.0 Hz, 2H), 2.47 (s, 6H), 1.94 (m, 2H), 1.79 (s, 6H) ppm; ^{19}F NMR (376.5 MHz, DMSO-d_6): δ = -112.7 (d, $J_{H\text{-}F}$ = 9.1 Hz, 1F), -131.3 (s, 1F) ppm; ^{13}C NMR (100.0 MHz, DMSO-d_6): δ = 179.4,, 156.8 (dd, $J_{C\text{-}F}$ = 3.6 Hz, $^{1}J_{C\text{-}F}$ = 244.0 Hz), 156.1, 148.1 (dd, $J_{C\text{-}F}$ = 6.5 Hz, $^{1}J_{C\text{-}F}$ = 248.0 Hz), 145.0, 142.6, 142.1, 142.0, 137.0 (dd, $J_{C\text{-}F}$ = 2.5 Hz, $J_{C\text{-}F}$ = 11.9 Hz), 132.5, 129.6, 129.3, 129.0, 128.6, 128.2, 127.5, 122.8, 122.6 (dd, $J_{C\text{-}F}$ = 1.6 Hz, $J_{C\text{-}F}$ = 10.8 Hz), 115.0, 114.2, 113.7 (dd, $J_{C\text{-}F}$ = 17.4 Hz, $J_{C\text{-}F}$ = 23.3 Hz), 108.6, 108.5 (m), 51.0, 33.5, 28.8, 26.7, 23.4, 21.3, 19.7 ppm; HRMS (ESI+): m/z calcd for $C_{34}H_{32}F_2NOS^+$ $[M]^{+\circ}$ 540.2167, found 540.2158.



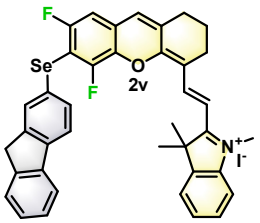
2s: 71% yield; Dark green solid; ^{1}H NMR (400.0 MHz, DMSO-d_6): δ = 8.51 (d, *J* = 15.5 Hz, 1H), 7.88 (d, *J* = 8.5 Hz, 2H), 7.82 (m, 2H), 7.77 (dd, *J* = 8.1, 8.5 Hz, 2H), 7.58 (t, *J* = 7.3 Hz, 1H), 7.46 (m, 3H), 7.42 (d, *J* = 8.5 Hz, 1H), 7.36 (dd, $J_{H\text{-}F}$ = 1.8 Hz, $J_{H\text{-}F}$ = 8.7 Hz, 1H), 7.25 (s, 1H), 6.82 (d, *J* = 15.6 Hz, 1H), 3.99 (s, 3H), 2.70 (m, 4H), 1.83 (m, 2H), 1.69 (s, 6H) ppm; ^{19}F NMR (376.5 MHz, DMSO-d_6): δ = -110.6 (m, 1F), -128.4 (s, 1F) ppm; ^{13}C NMR (100.0 MHz, DMSO-d_6): δ = 179.5, 157.6 (dd, $J_{C\text{-}F}$ = 2.4 Hz, $^{1}J_{C\text{-}F}$ = 244.4 Hz), 155.7, 149.4 (dd, $J_{C\text{-}F}$ = 4.7 Hz, $^{1}J_{C\text{-}F}$ = 248.5 Hz), 144.9, 142.6, 142.0, 137.2 (dd, $J_{C\text{-}F}$ = 2.6 Hz, $J_{C\text{-}F}$ = 12.1 Hz), 133.4, 133.2, 131.6, 131.3, 129.2, 128.9, 128.3, 127.7, 127.1, 127.0, 126.4, 126.2, 125.7, 124.8 (dd, $J_{C\text{-}F}$ = 2.2 Hz, $J_{C\text{-}F}$ = 11.1 Hz), 122.7, 115.2, 114.3, 110.1 (dd, $J_{C\text{-}F}$ = 18.6Hz, $J_{C\text{-}F}$ = 24.8 Hz), 108.9, 108.6 (m), 51.0, 33.6, 28.8, 26.6, 23.3, 19.6 ppm; HRMS (ESI+): m/z calcd for $C_{36}H_{30}F_2NOS^+$ $[M]^{+\circ}$ 562.2011, found 562.1994.



2t: 92% yield; Dark green solid; ^{1}H NMR (400.0 MHz, DMSO-d_6): δ = 8.50 (d, *J* = 15.6 Hz, 1H), 7.84 (d, *J* = 7.1 Hz, 1H), 7.79 (d, *J* = 7.8 Hz, 1H), 7.60 (m, 3H), 7.54 (dd, *J* = 7.3, 7.4 Hz, 1H), 7.47 (dd, *J* = 7.7, 8.5 Hz, 1H), 7.30 (d, $J_{H\text{-}F}$ = 9.0 Hz, 1H), 7.19 (s, 1H), 6.82 (d, *J* = 15.6 Hz, 1H), 3.98 (s, 3H), 2.71 (m, 4H), 1.82 (m, 2H), 1.73 (s, 6H) ppm; ^{19}F NMR (376.5 MHz, DMSO-d_6): δ = -112.4 (d, $J_{H\text{-}F}$ = 9.3 Hz, 1F), -130.2 (s, 1F) ppm; ^{13}C NMR (100.0 MHz, DMSO-d_6): δ = 179.5, 156.5 (dd, $J_{C\text{-}F}$ = 2.5 Hz, $^{1}J_{C\text{-}F}$ = 244.9 Hz), 155.9, 148.2 (dd, $J_{C\text{-}F}$ = 5.3 Hz, $^{1}J_{C\text{-}F}$ = 249.2 Hz), 145.0, 142.6, 142.1, 138.9, 137.0 (dd, $J_{C\text{-}F}$ = 2.0 Hz, $J_{C\text{-}F}$ = 10.8 Hz), 133.0, 131.9, 129.4, 128.9, 128.8, 128.3, 127.1, 123.4 (dd, $J_{C\text{-}F}$ = 2.2 Hz, $J_{C\text{-}F}$ = 11.0 Hz), 122.8, 115.2, 114.2, 111.8 (dd, $J_{C\text{-}F}$ = 16.9 Hz, $J_{C\text{-}F}$ = 22.9 Hz), 108.8, 108.6 (dd, $J_{C\text{-}F}$ = 2.7 Hz, $J_{C\text{-}F}$ = 24.7 Hz), 51.1, 33.5, 28.8, 26.6, 23.4, 19.6 ppm; HRMS (ESI+): m/z calcd for $C_{32}H_{26}Cl_2F_2NOS^+$ $[M]^{+\circ}$ 580.1075, found 580.1072.



2u: 95% yield; Dark green solid; ^{1}H NMR (400.0 MHz, DMSO-d_6): δ = 8.52 (d, J = 15.5 Hz, 1H), 7.81 (dd, J = 6.1, 6.8 Hz, 2H), 7.58 (dd, J = 7.3, 7.8 Hz, 1H), 7.53 (dd, J = 7.2, 7.4 Hz, 1H), 7.40 (m, 3H), 7.30 (m, 3H), 7.25 (s, 1H), 6.83 (d, J = 15.6 Hz, 1H), 4.00 (s, 3H), 2.70 (m, 4H), 1.82 (brs, 2H), 1.72 (s, 6H) ppm; ^{19}F NMR (376.5 MHz, DMSO-d_6): δ = -105.1 (d, $J_{H\text{-}F}$ = 7.8 Hz, 1F), -122.6 (s, 1F) ppm; ^{13}C NMR (100.0 MHz, DMSO-d_6): δ = 179.5, 157.4 (dd, $J_{C\text{-}F}$ = 4.3 Hz, $^{1}J_{C\text{-}F}$ = 241.5 Hz), 155.9, 149.2 (dd, $J_{C\text{-}F}$ = 6.6 Hz, $^{1}J_{C\text{-}F}$ = 245.5 Hz), 144.9, 142.6, 142.0, 136.8 (dd, $J_{C\text{-}F}$ = 2.9 Hz, $J_{C\text{-}F}$ = 13.1 Hz), 133.1, 130.7, 129.7, 129.6, 128.9, 128.3, 127.5, 127.3, 124.8 (dd, $J_{C\text{-}F}$ = 2.2 Hz, $J_{C\text{-}F}$ = 10.9 Hz), 122.8, 115.1, 114.3, 108.8, 108.4 (dd, $J_{C\text{-}F}$ = 2.9 Hz, $J_{C\text{-}F}$ = 27.3 Hz), 106.8 (dd, $J_{C\text{-}F}$ = 23.01 Hz, $J_{C\text{-}F}$ = 29.5 Hz), 51.0, 33.5, 28.8, 26.7, 23.3, 19.6 ppm; HRMS (ESI+): m/z calcd for $C_{32}H_{28}F_2NOSe^+$ $[M]^{+\circ}$ 560.1301, found 560.1290; HPLC (system A): t_R = 5.3 min (purity 97% at 600 nm); LRMS (ESI+, recorded during RP-HPLC analysis): *m/z* 558.1 (60) and 560.1 (100) $[M]^{+\circ}$ (two major Se isotopes), calcd for $C_{32}H_{28}F_2NOSe^+$ 560.1; UV-vis (recorded during the HPLC analysis): λ_{max} = 553 nm (broad peak).



2v: 66% yield; Dark green solid; ^{1}H NMR (400.0 MHz, $CDCl_3$): δ = 8.35 (d, J = 15.5 Hz, 1H), 7.76 (d, J = 7.5 Hz, 1H), 7.73 (s, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.58 (d, J = 7.9 Hz, 1H), 7.52 (m, 2H), 7.46 (m, 2H), 7.39 (m, 2H), 7.32 (dt, J = 1.0, 7.5 Hz, 1H), 7.04 (d, J = 15.4 Hz, 1H), 6.87 (m, 2H), 4.25 (s, 3H), 3.88 (s, 2H), 2.95 (t, J = 6.0 Hz, 2H), 2.72 (t, J = 5.7 Hz, 2H), 1.94 (m, 2H), 1.76 (s, 6H) ppm; ^{19}F NMR (376.5 MHz, DMSO-d_6): δ = -105.1 (s, 1F), -122.7 (s, 1F) ppm; ^{13}C NMR (100.0 MHz, DMSO-d_6): δ = 179.3, 157.3 (dd, $J_{C\text{-}F}$ = 3.8 Hz, $^{1}J_{C\text{-}F}$ = 241.8 Hz), 155.8, 149.0 (dd, $J_{C\text{-}F}$ = 6.3 Hz, $^{1}J_{C\text{-}F}$ = 245.7 Hz), 144.8, 144.4, 142.8, 142.5, 142.0, 140.8, 140.0, 136.7 (dd, $J_{C\text{-}F}$ = 2.5 Hz, $J_{C\text{-}F}$ = 12.9 Hz), 132.8, 130.0, 128.9, 128.2, 128.1, 127.3, 127.2, 126.8, 125.0, 124.4 (d, $J_{C\text{-}F}$ = 10.8 Hz), 122.7, 120.9, 120.1, 115.0, 114.2, 108.7, 108.3 (d, $J_{C\text{-}F}$ = 27.5 Hz), 107.3 (dd, $J_{C\text{-}F}$ = 22.9 Hz, $J_{C\text{-}F}$ = 29.5 Hz), 50.9, 36.3, 33.6, 28.7, 26.7, 23.3, 19.5 ppm; HRMS (ESI+): m/z calcd for $C_{39}H_{32}F_2NOSe^+$ $[M]^{+\circ}$ 648.1615, found 648.1643.

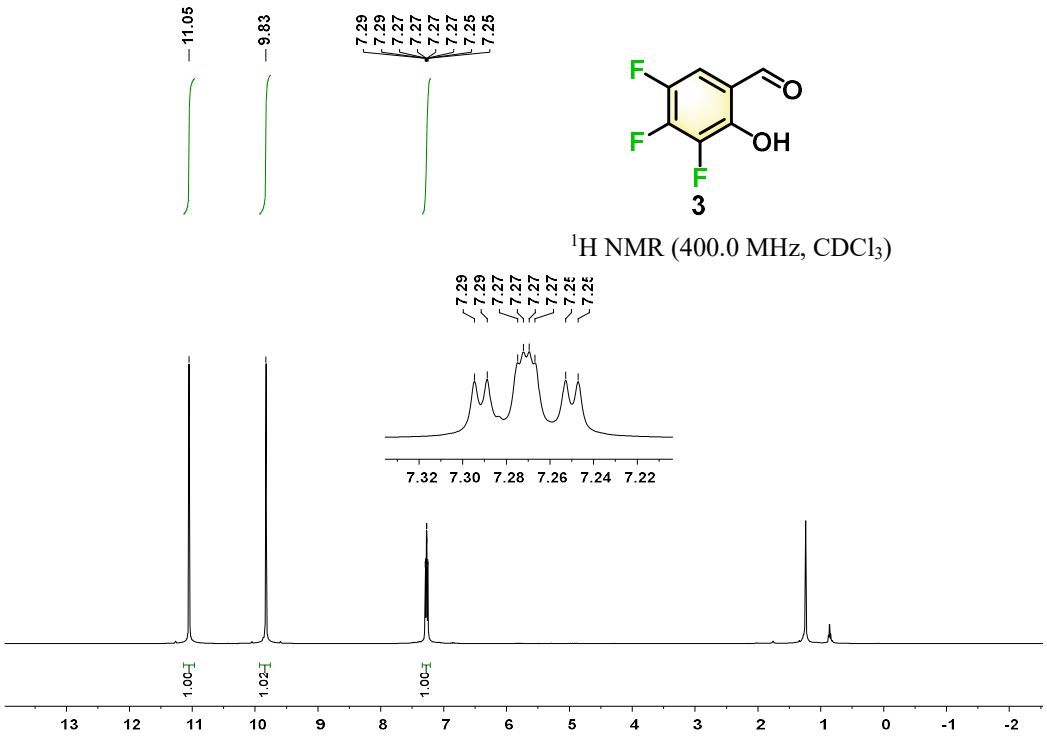
4. References

1. X. Zou, L. Yang, X. Liu, H. Sun, H. Lu, *Adv. Synth. Catal.* **2015**, 357, 3040 - 3046.

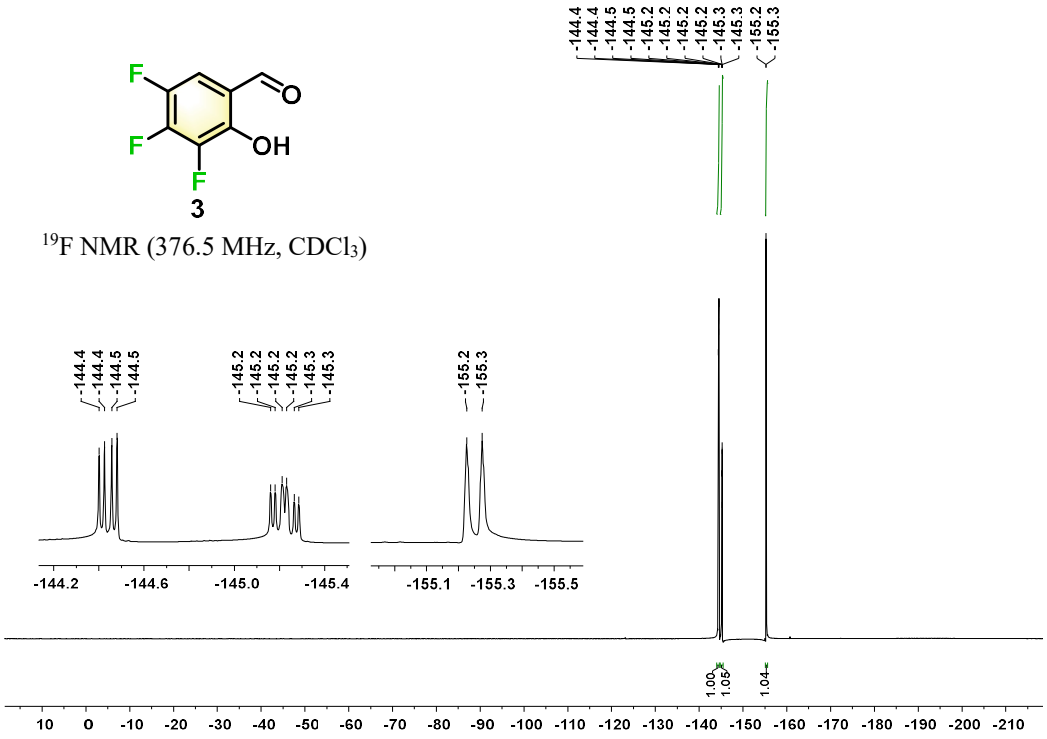
2. M. J. H. Ong, R. Srinivasan, A. Romieu, J. A. Richard, *Org. Lett*. **2016**, 18, 5122-5125.

3. N. B. Yapici, S. Mandalapu, L. Bi, *Bioorg. Med. Chem. Lett.* **2015**, 25, 3476-3480.

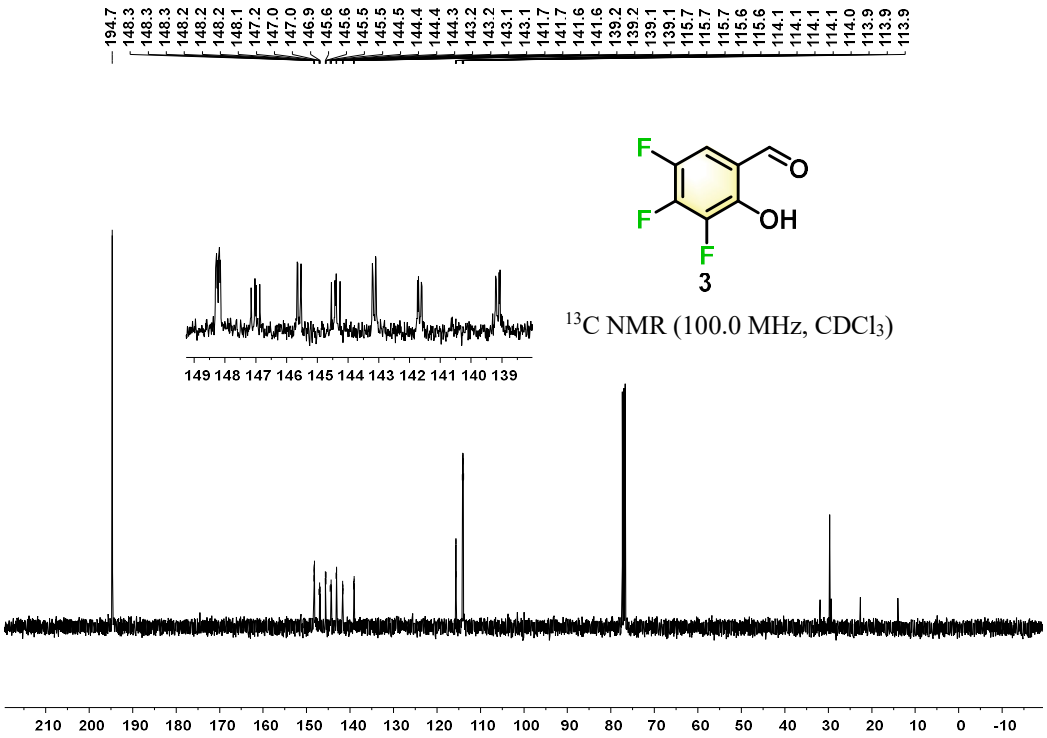
5. ^{1}H, ^{19}F and ^{13}C NMR spectra of synthesized compounds



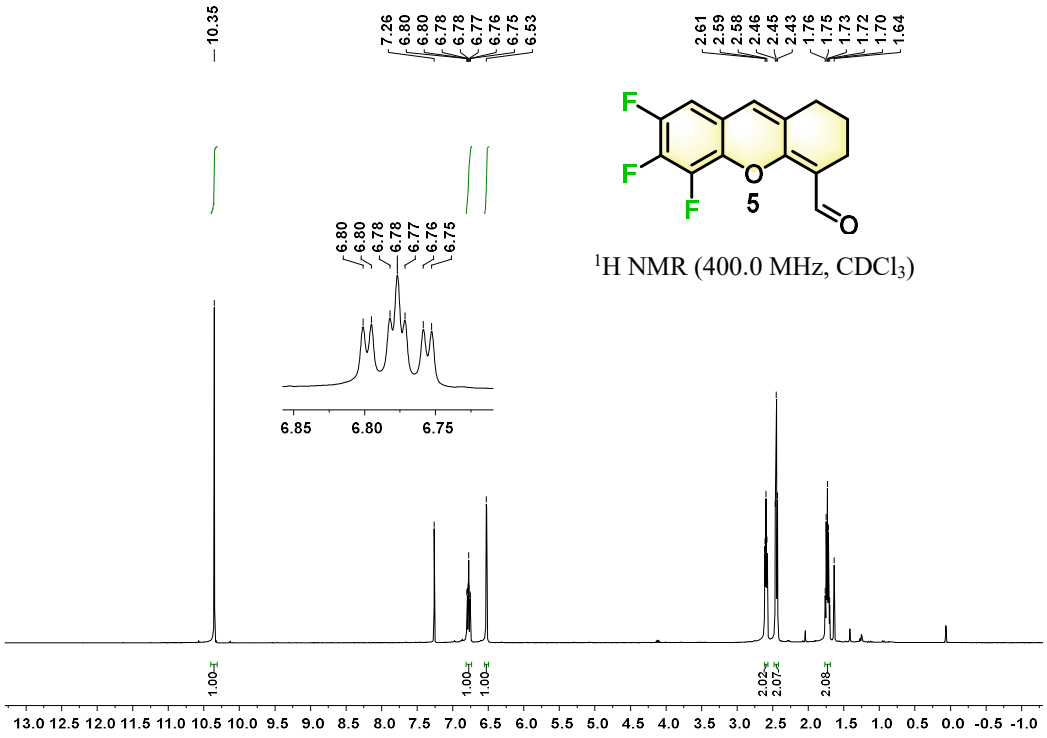
^{1}H NMR (400.0 MHz, $CDCl_3$)



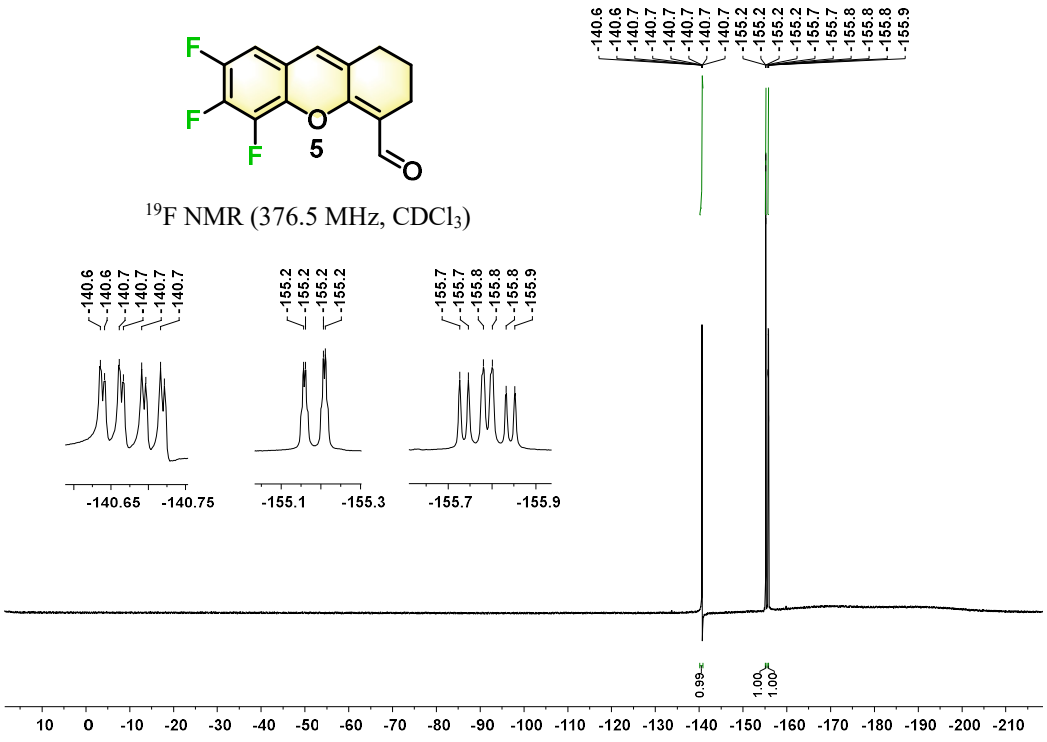
^{19}F NMR (376.5 MHz, $CDCl_3$)



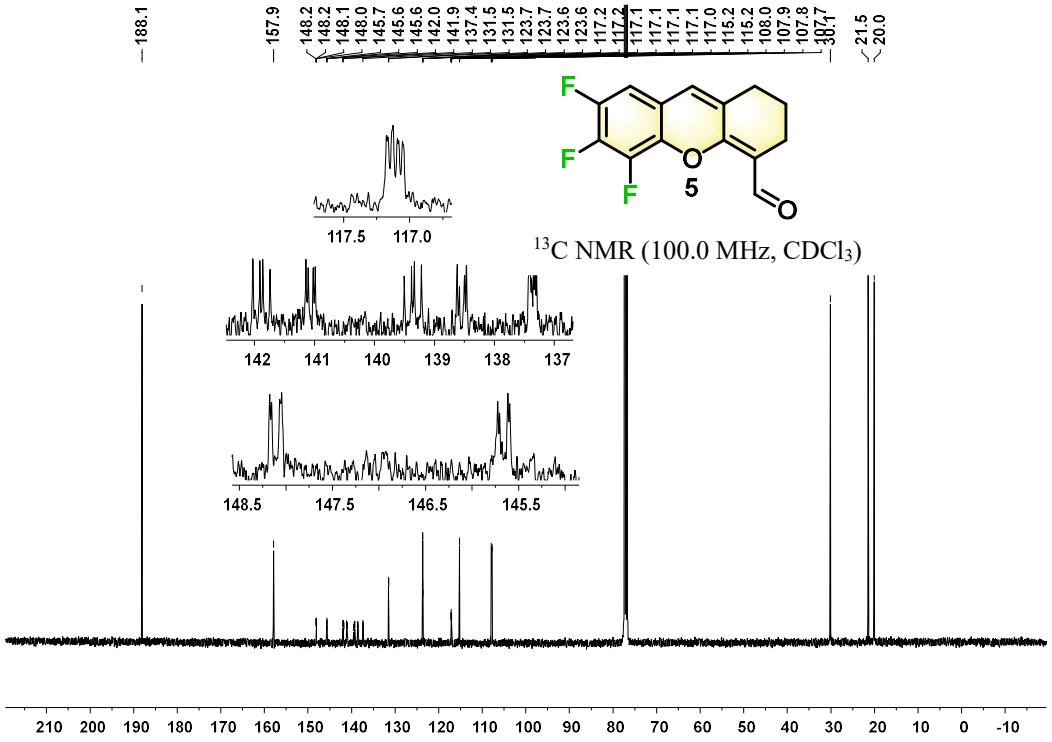
^{13}C NMR (100.0 MHz, $CDCl_3$)



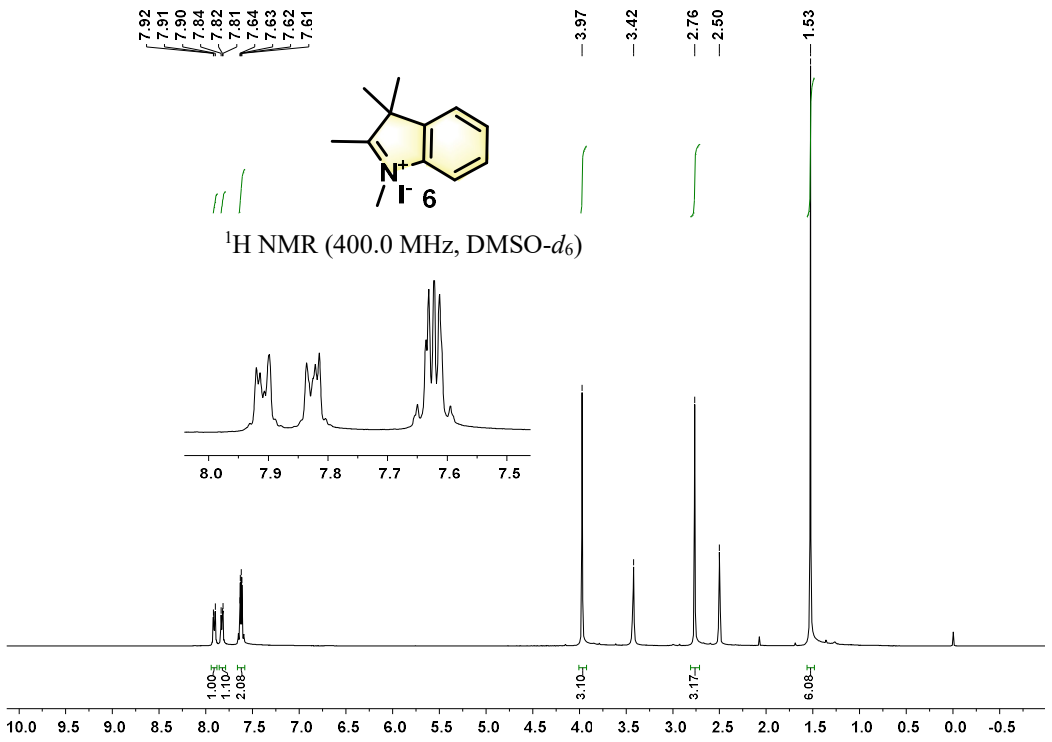
^{1}H NMR (400.0 MHz, $CDCl_3$)



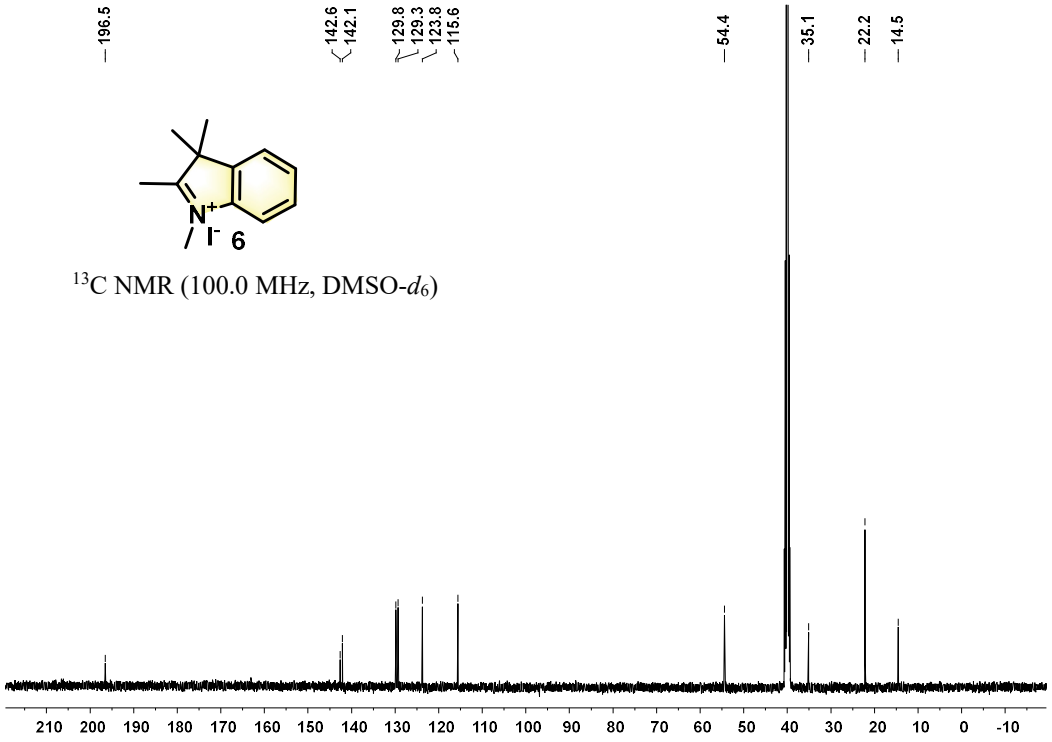
^{19}F NMR (376.5 MHz, $CDCl_3$)



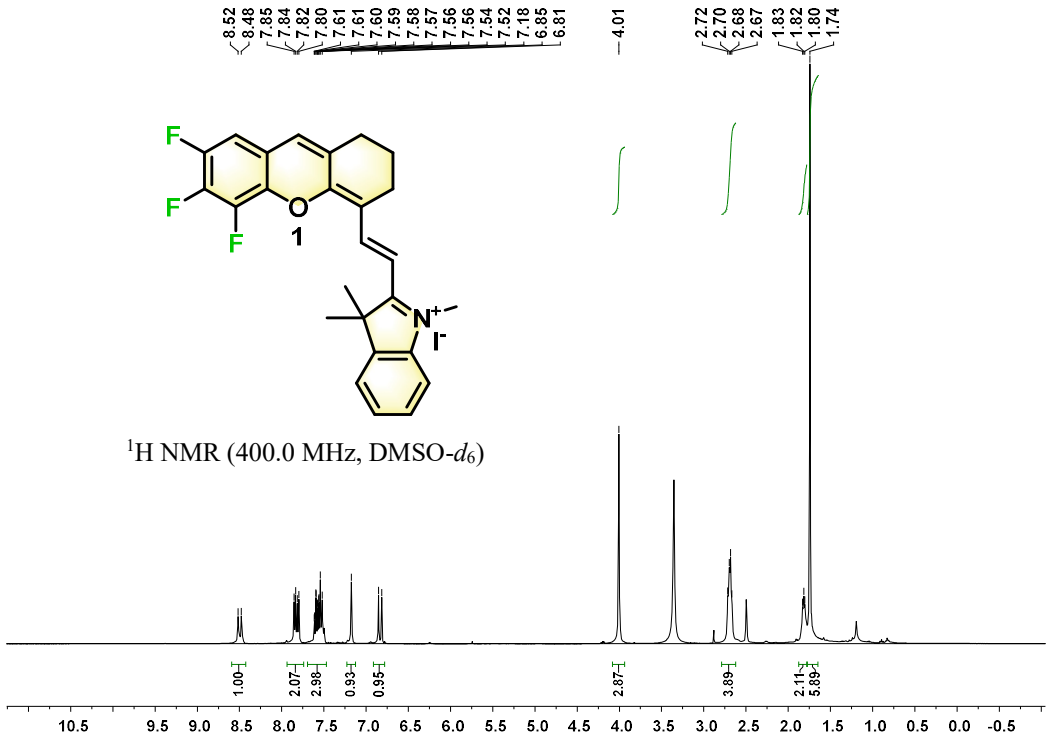
^{13}C NMR (100.0 MHz, $CDCl_3$)



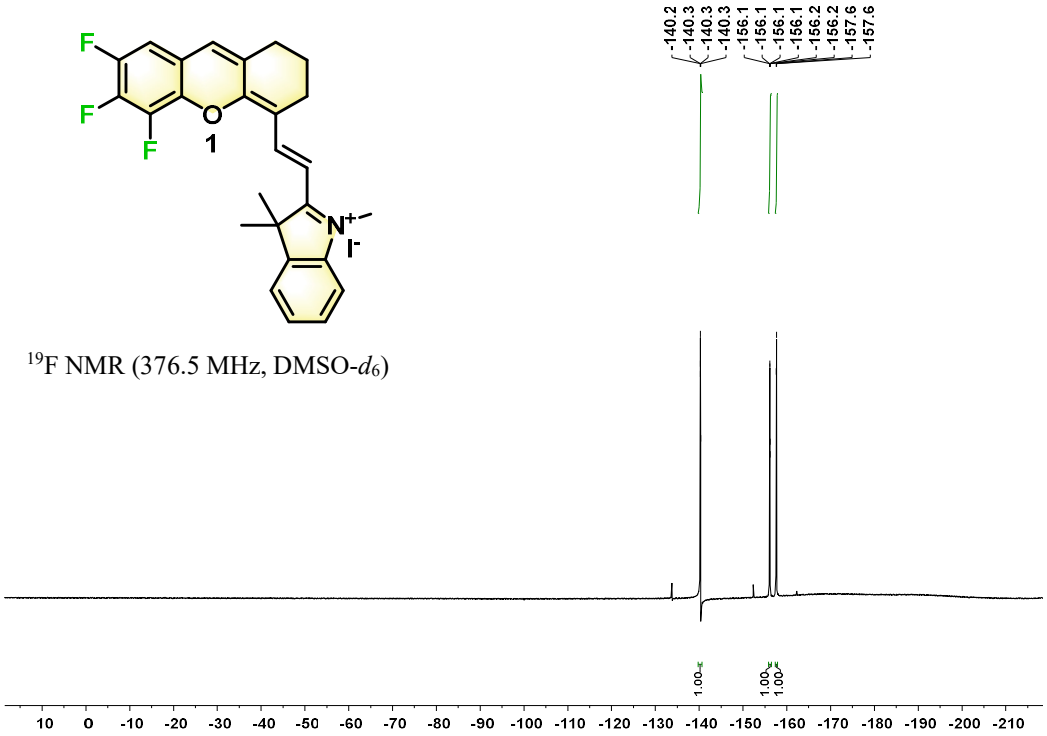
^{1}H NMR (400.0 MHz, DMSO-d_6)



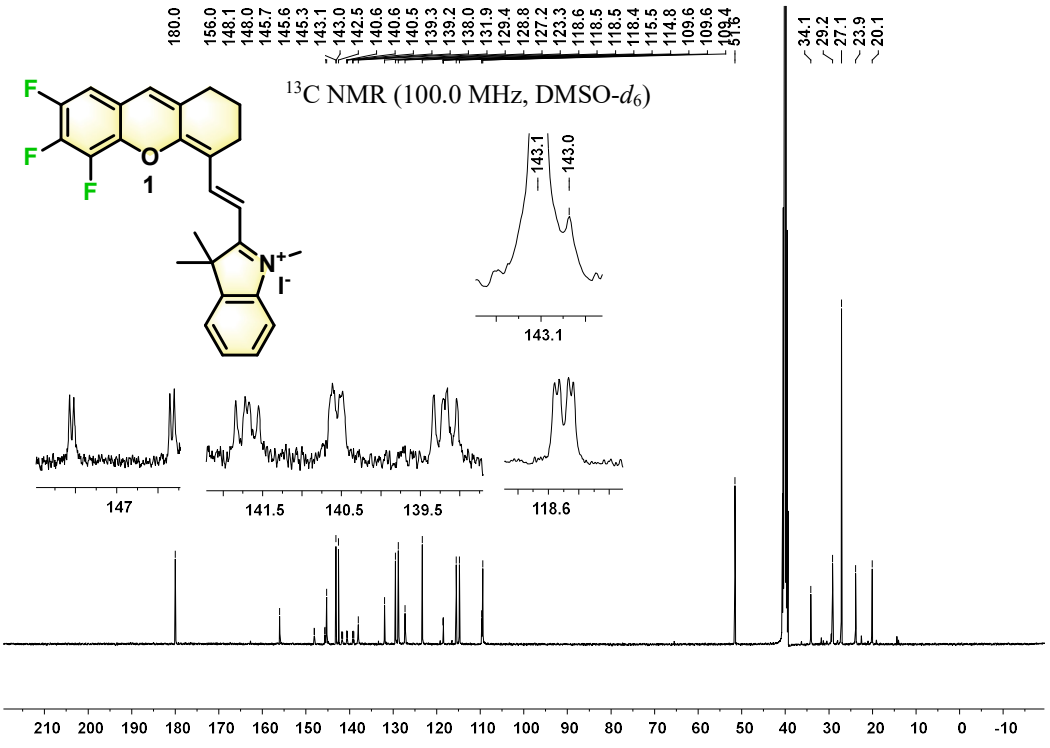
^{13}C NMR (100.0 MHz, DMSO-d_6)



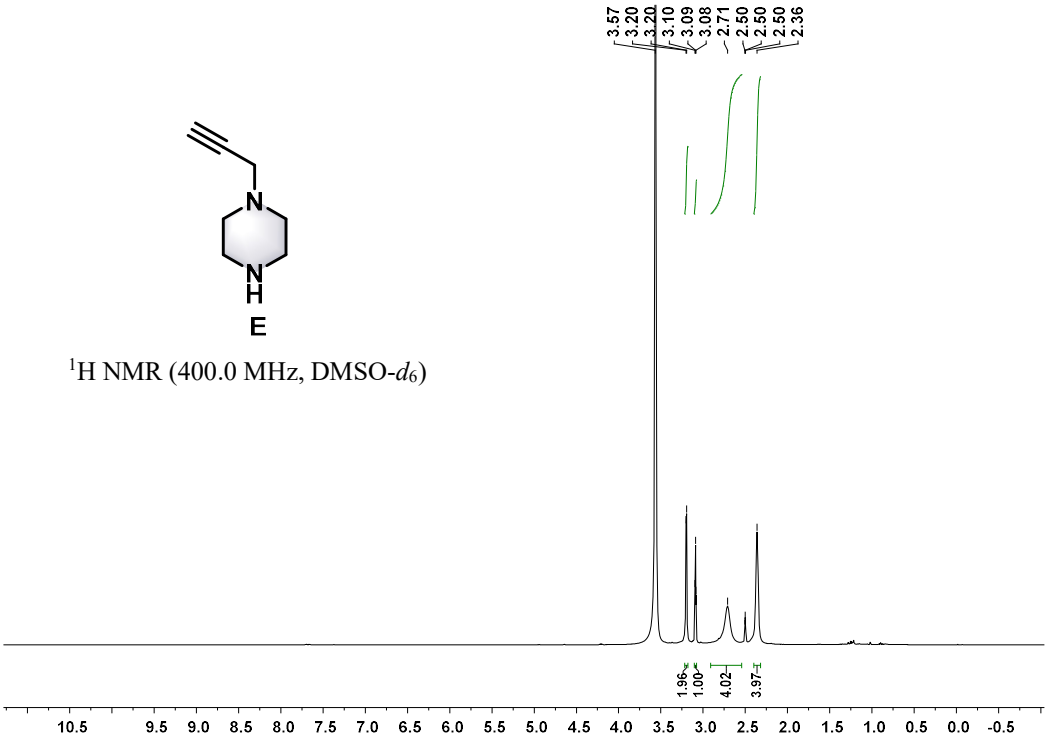
^{1}H NMR (400.0 MHz, DMSO-d_6)

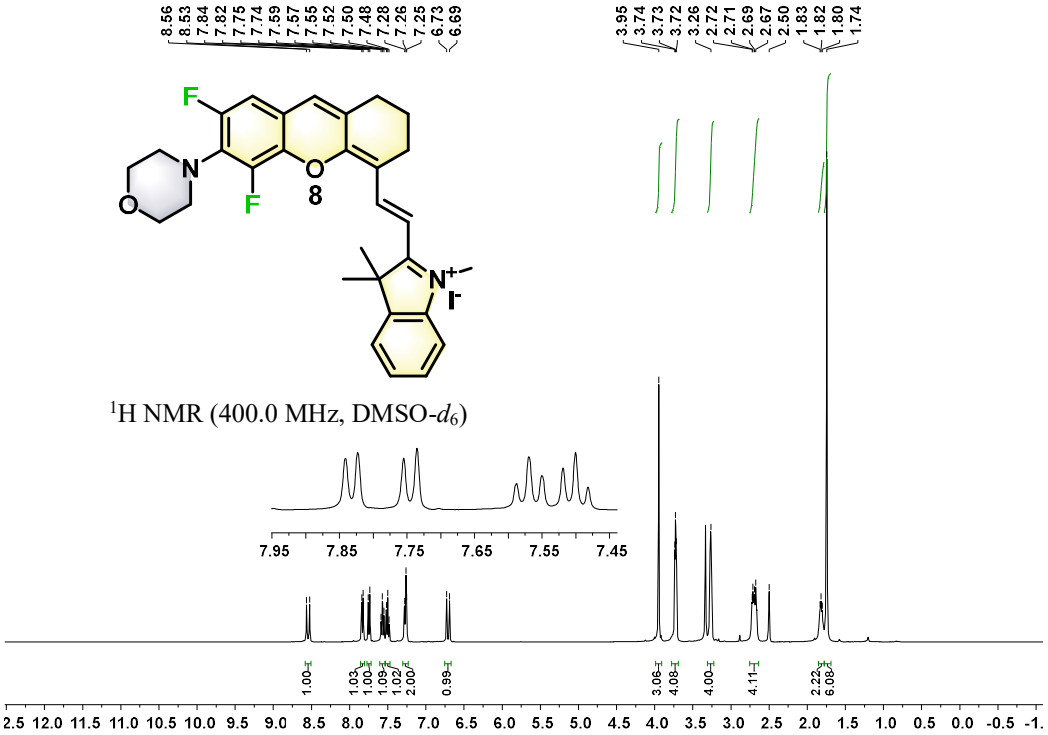


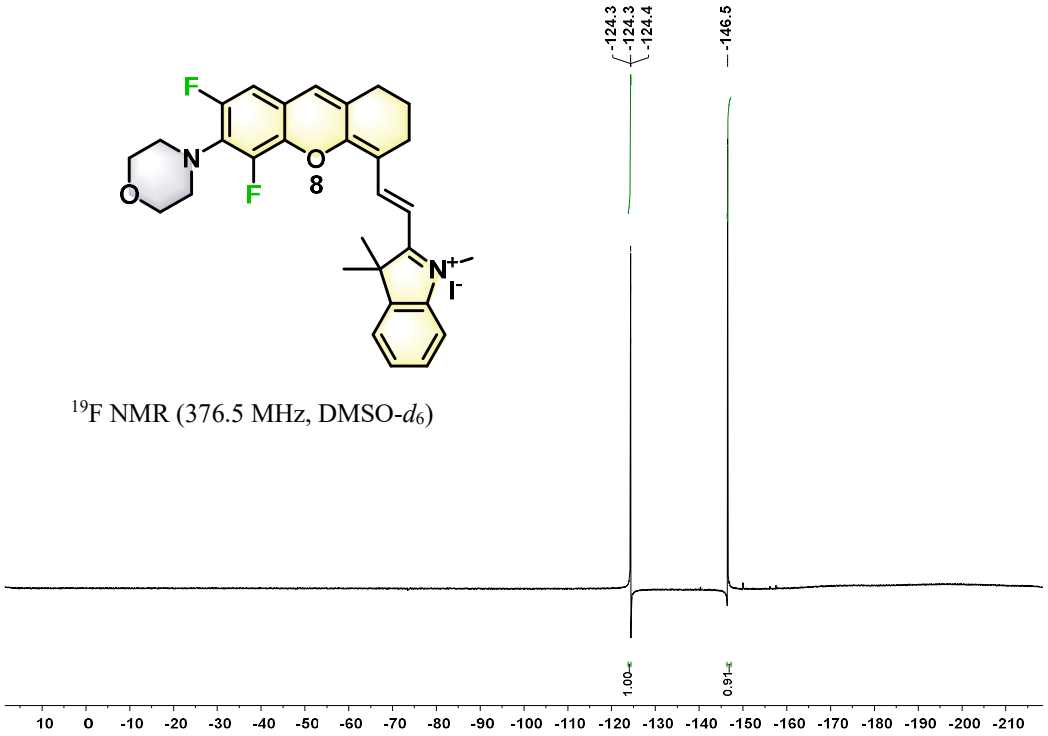
^{19}F NMR (376.5 MHz, DMSO-d_6)



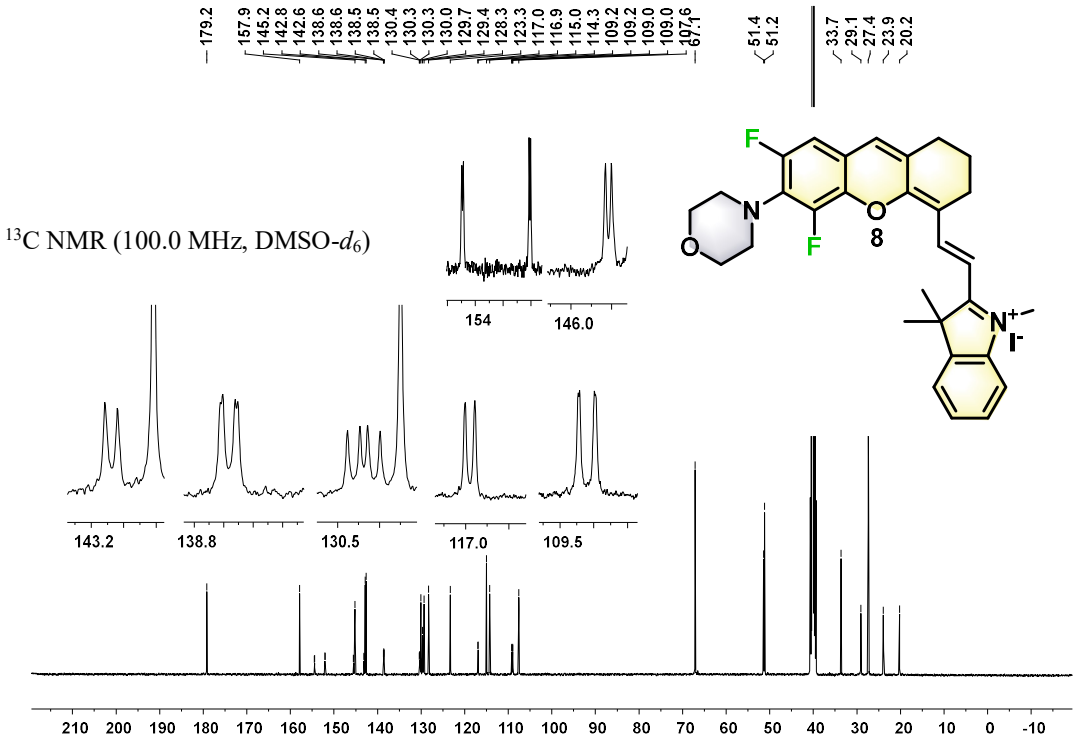
^{13}C NMR (100.0 MHz, DMSO-d_6)


E
^{1}H NMR (400.0 MHz, DMSO-d_6)

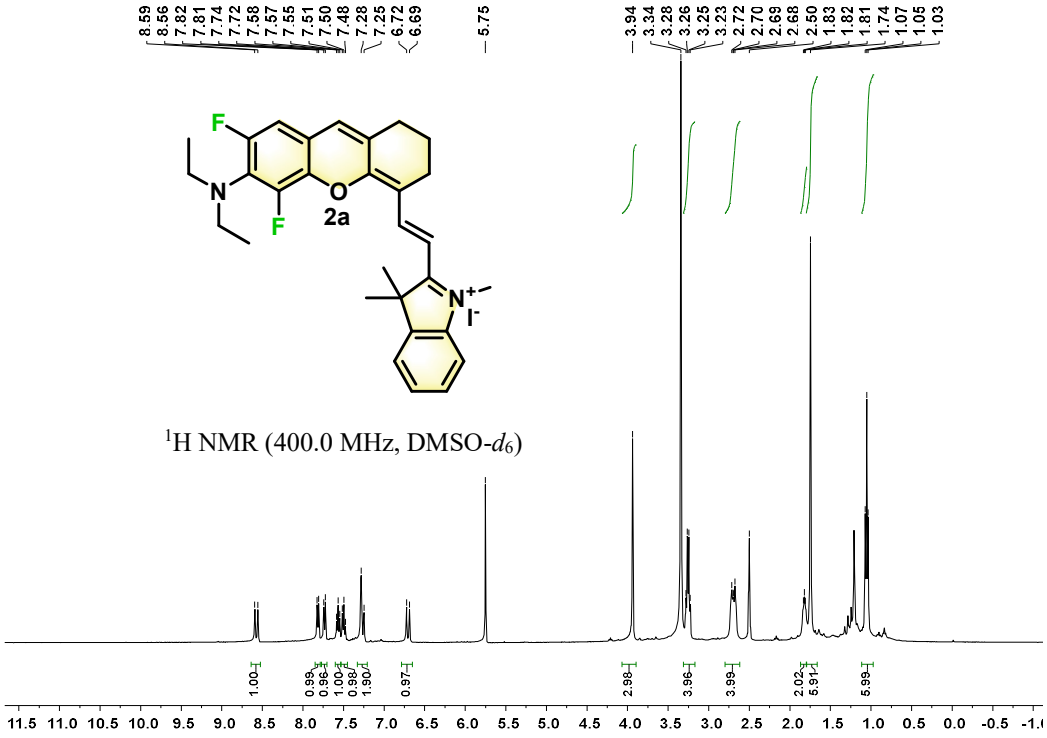

8
^{1}H NMR (400.0 MHz, DMSO-d_6)



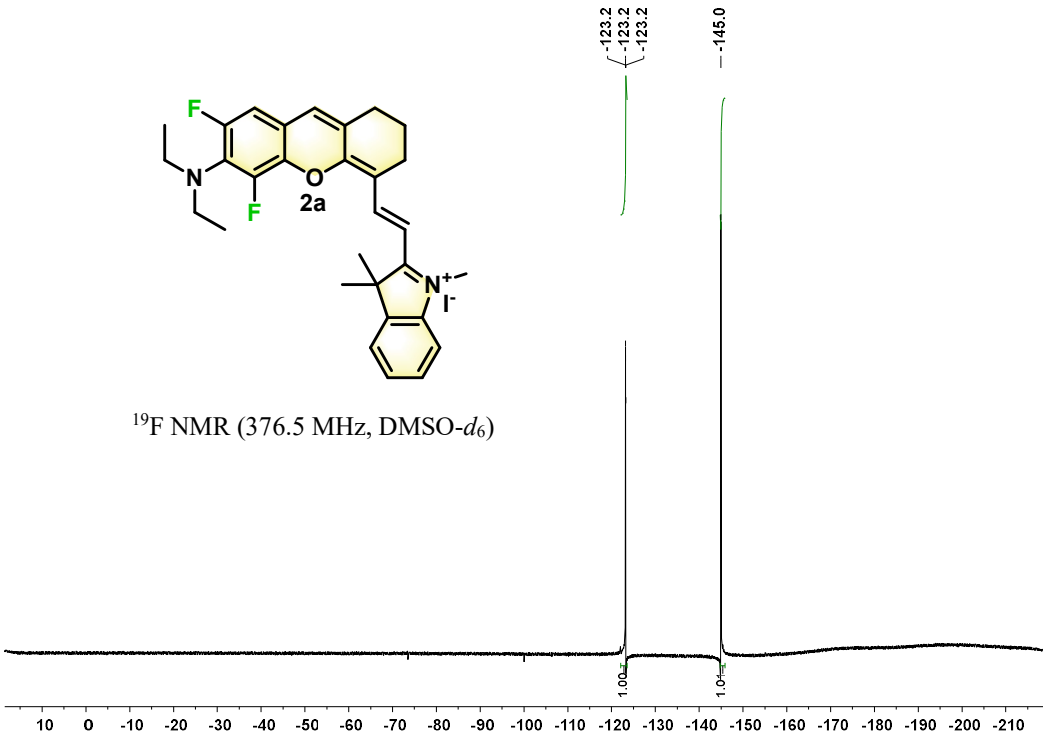
^{19}F NMR (376.5 MHz, DMSO-d_6)



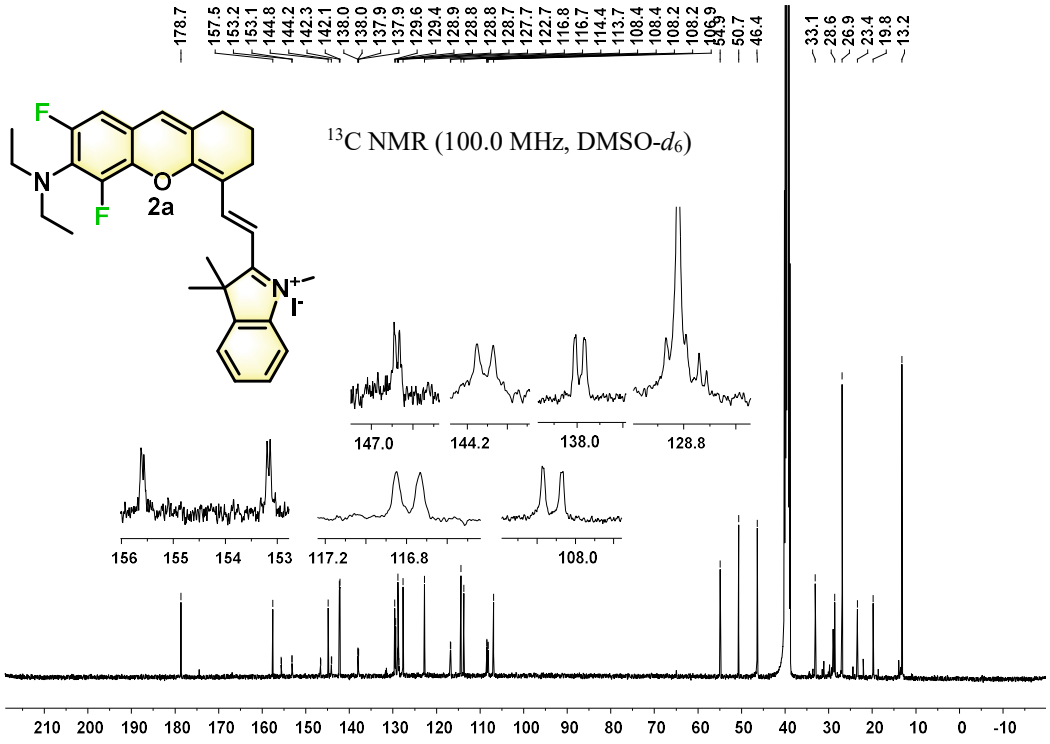
^{13}C NMR (100.0 MHz, DMSO-d_6)

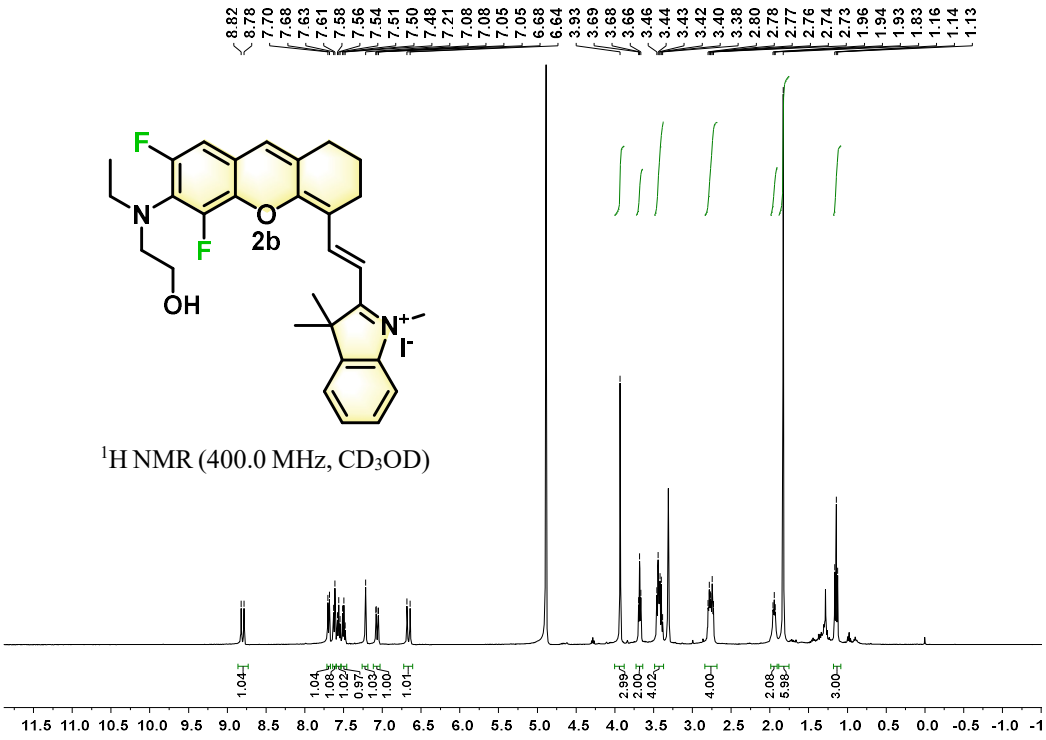


^{1}H NMR (400.0 MHz, DMSO-d_6)

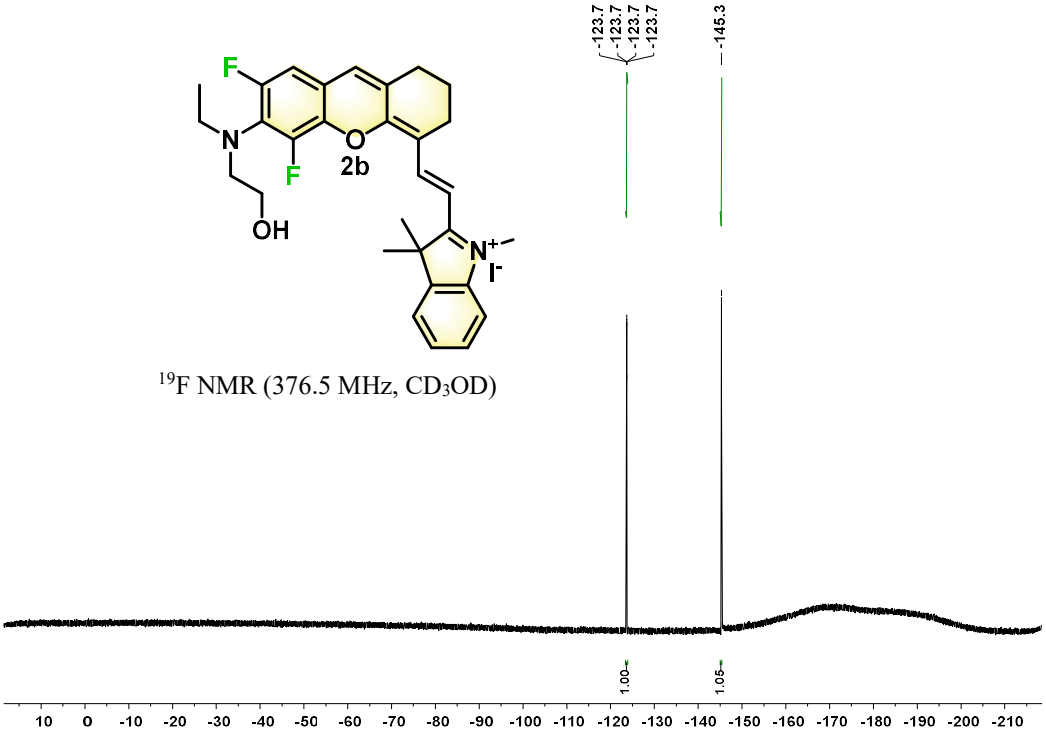


^{19}F NMR (376.5 MHz, DMSO-d_6)

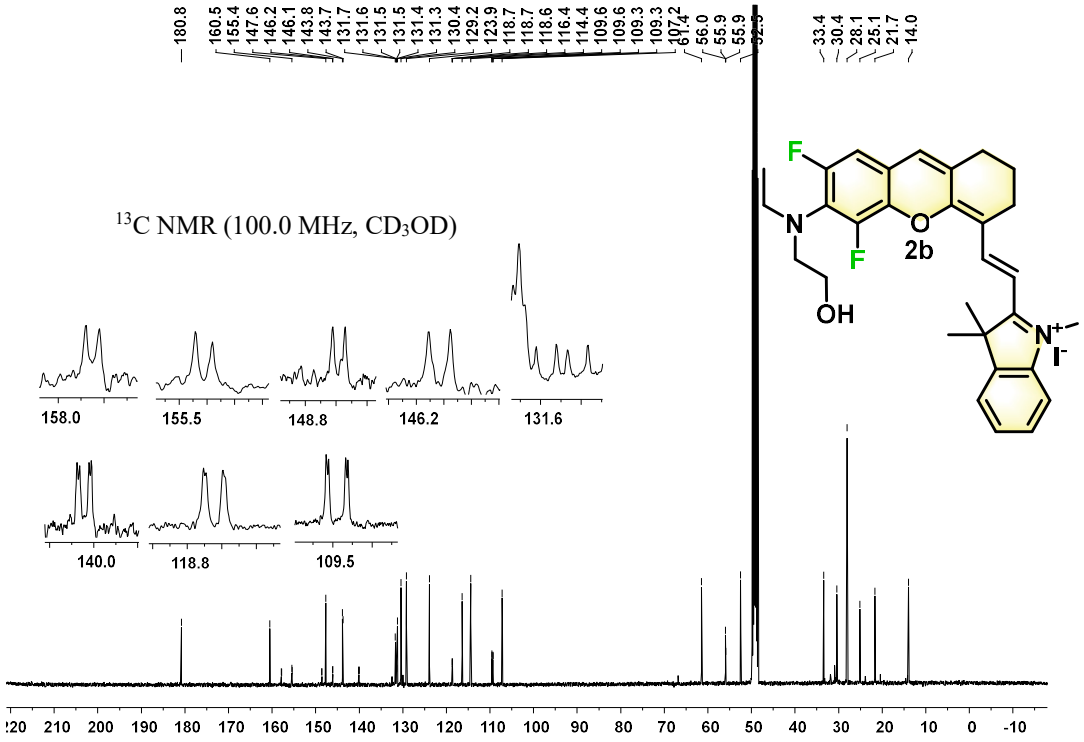

178.7
157.5
153.2
153.1
144.8
144.2
142.3
142.1
138.0
138.0
137.9
137.9
129.6
129.4
128.9
128.8
128.8
128.7
127.7
122.7
116.8
116.7
114.4
113.7
108.4
108.4
108.2
108.2
106.9
54.9
50.7
46.4
33.1
28.6
26.9
23.4
19.8
13.2
F
N
O
F
2a
N+
I-
13C NMR (100.0 MHz, DMSO-d6)
147.0
144.2
138.0
128.8
156
155
154
153
117.2
116.8
108.0
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

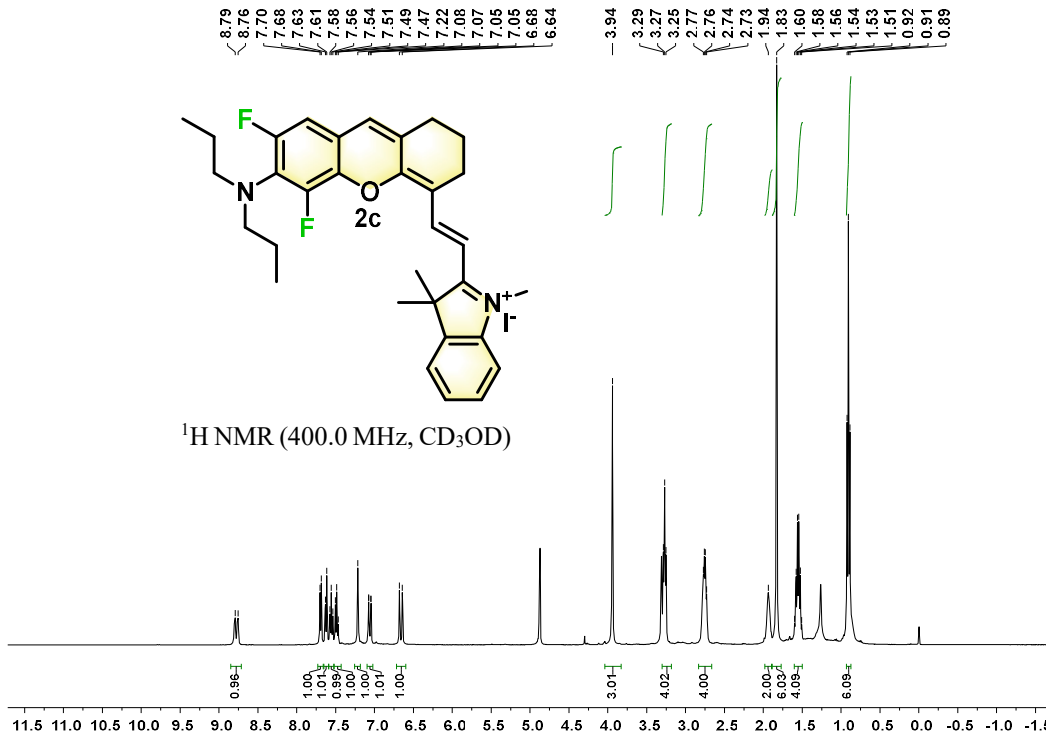


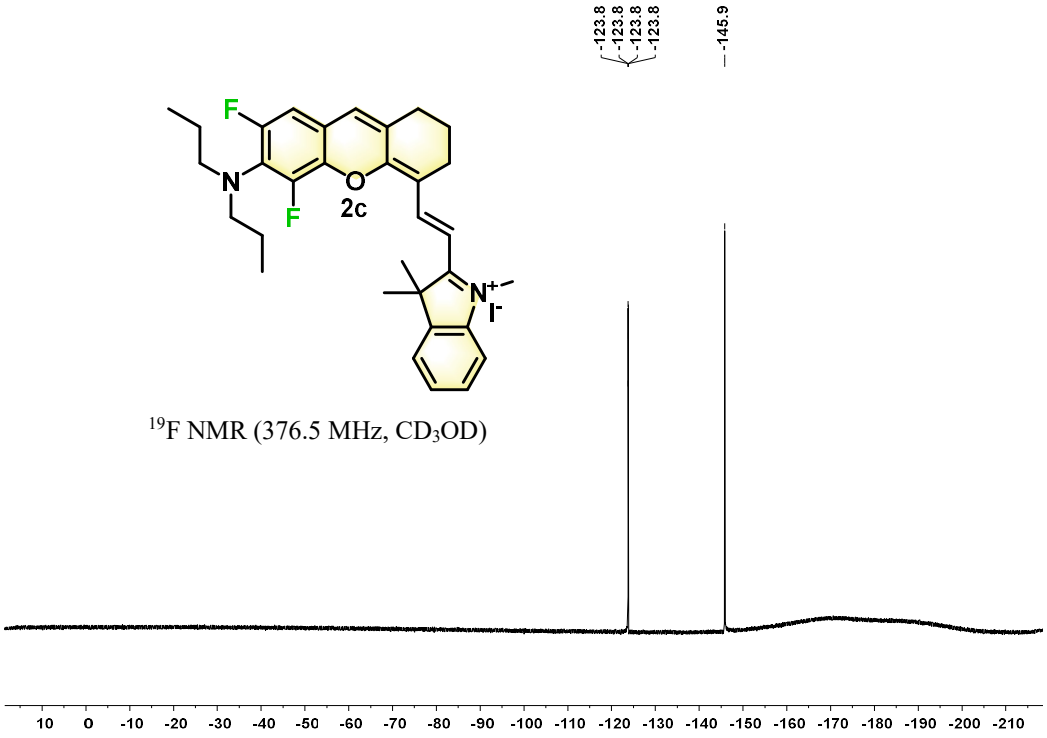
^{1}H NMR (400.0 MHz, CD_3OD)



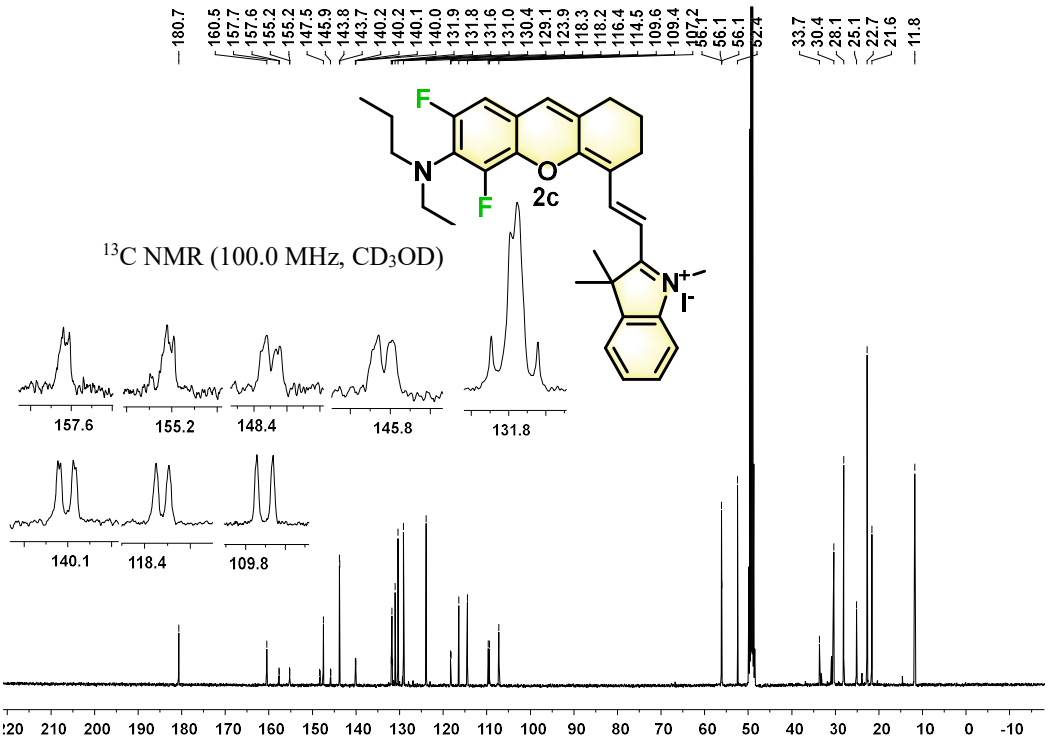
^{19}F NMR (376.5 MHz, CD_3OD)


180.8
160.5
155.4
147.6
146.2
146.1
143.8
143.7
131.7
131.6
131.5
131.5
131.4
131.3
130.4
129.2
123.9
118.7
118.7
118.6
116.4
114.4
109.6
109.6
109.3
109.3
107.2
61.4
56.0
55.9
55.9
52.3
33.4
30.4
28.1
25.1
21.7
14.0
13C NMR (100.0 MHz, CD3OD)
F
N
O
F
2b
OH
N+
I-
158.0
155.5
148.8
146.2
131.6
140.0
118.8
109.5
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

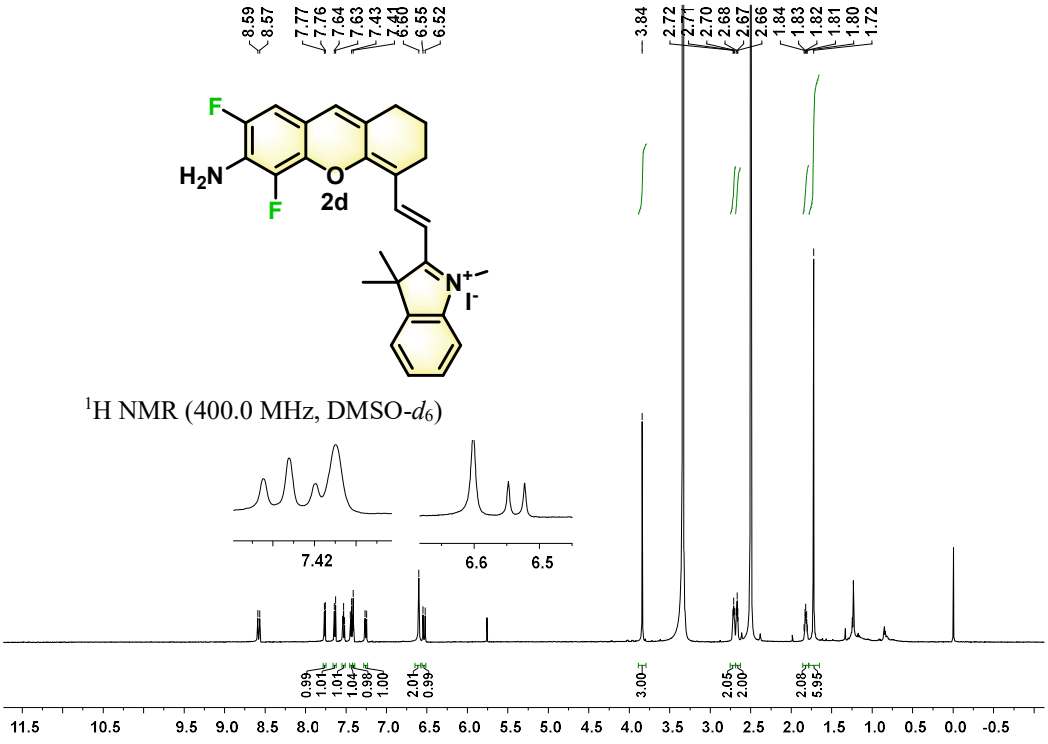

8.79
8.76
7.70
7.68
7.63
7.61
7.58
7.56
7.54
7.51
7.49
7.47
7.22
7.08
7.07
7.05
7.05
6.68
6.64
3.94
3.29
3.27
3.25
2.77
2.76
2.74
2.73
1.94
1.83
1.60
1.58
1.56
1.54
1.53
1.51
0.92
0.91
0.89
F
N
O
F
2c
N+
I-
1H NMR (400.0 MHz, CD3OD)
0.96
1.00
1.01
0.99
1.00
1.00
1.01
1.00
3.01
4.02
4.00
2.00
6.03
4.09
6.09
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0



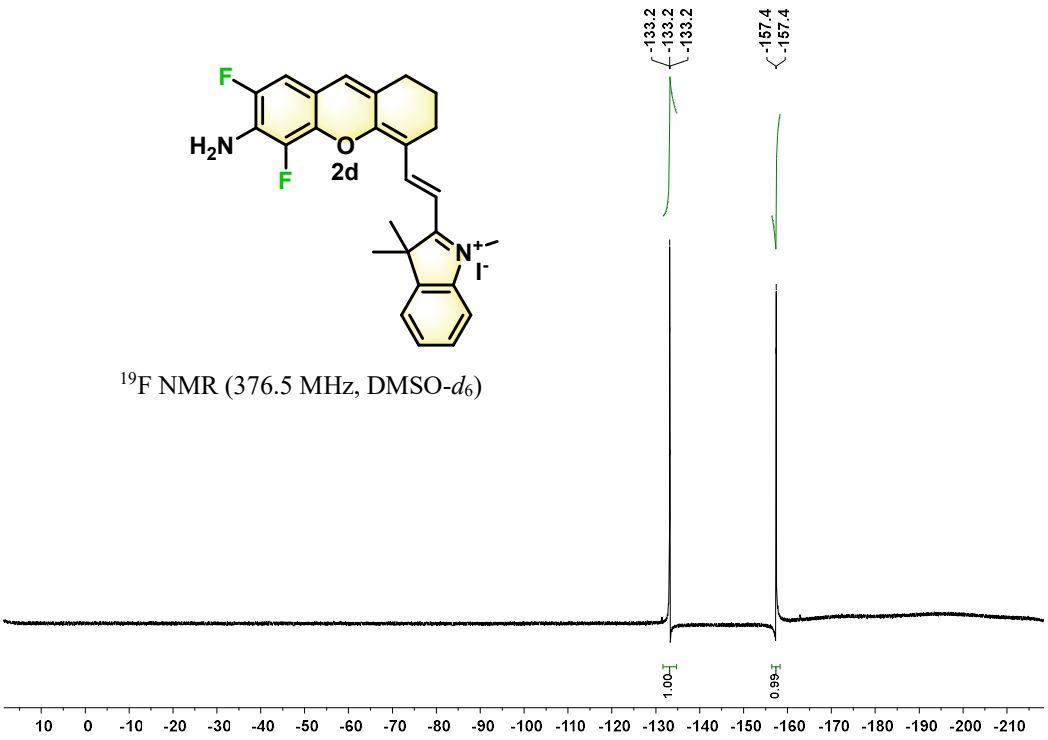
^{19}F NMR (376.5 MHz, CD_3OD)



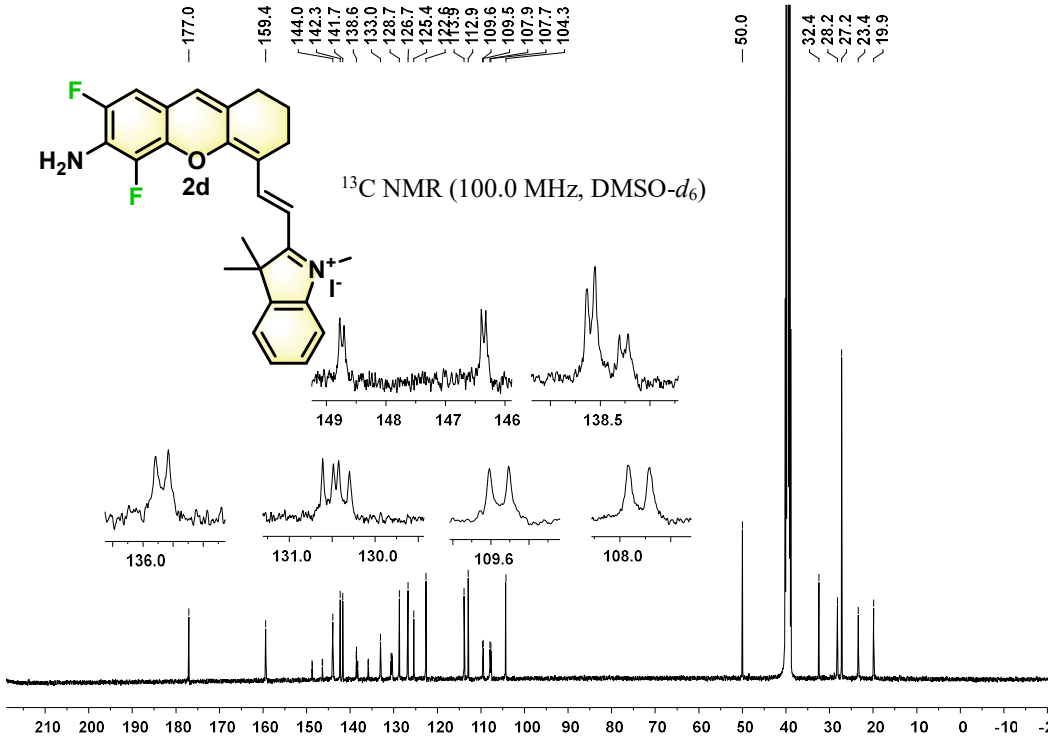
^{13}C NMR (100.0 MHz, CD_3OD)

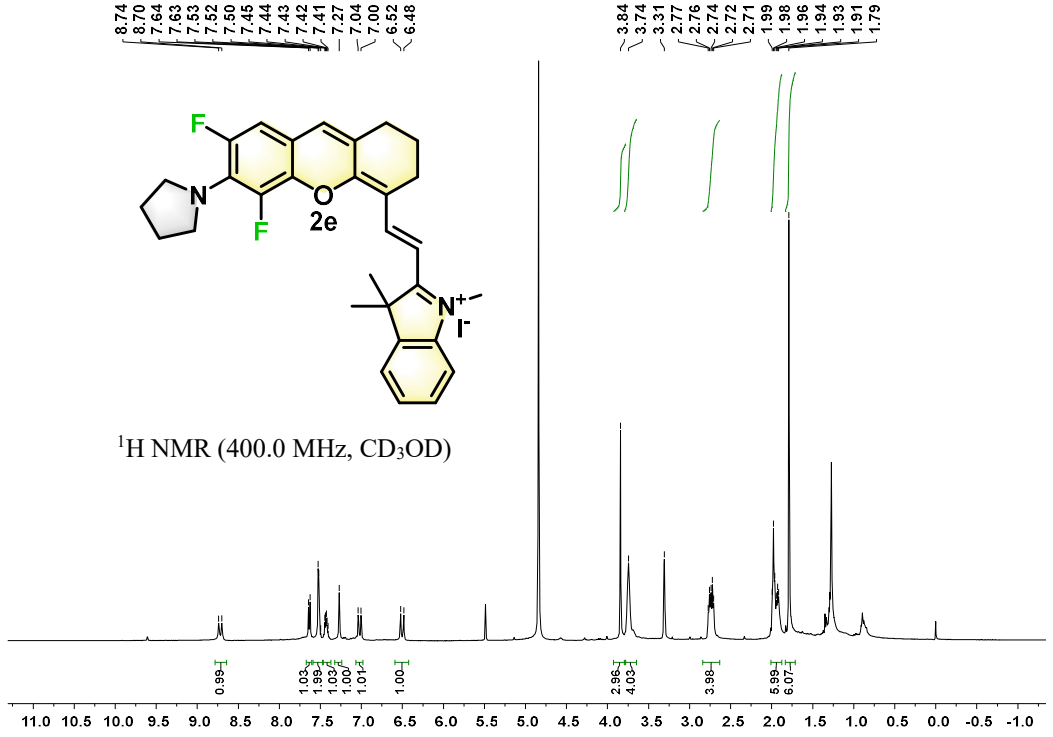


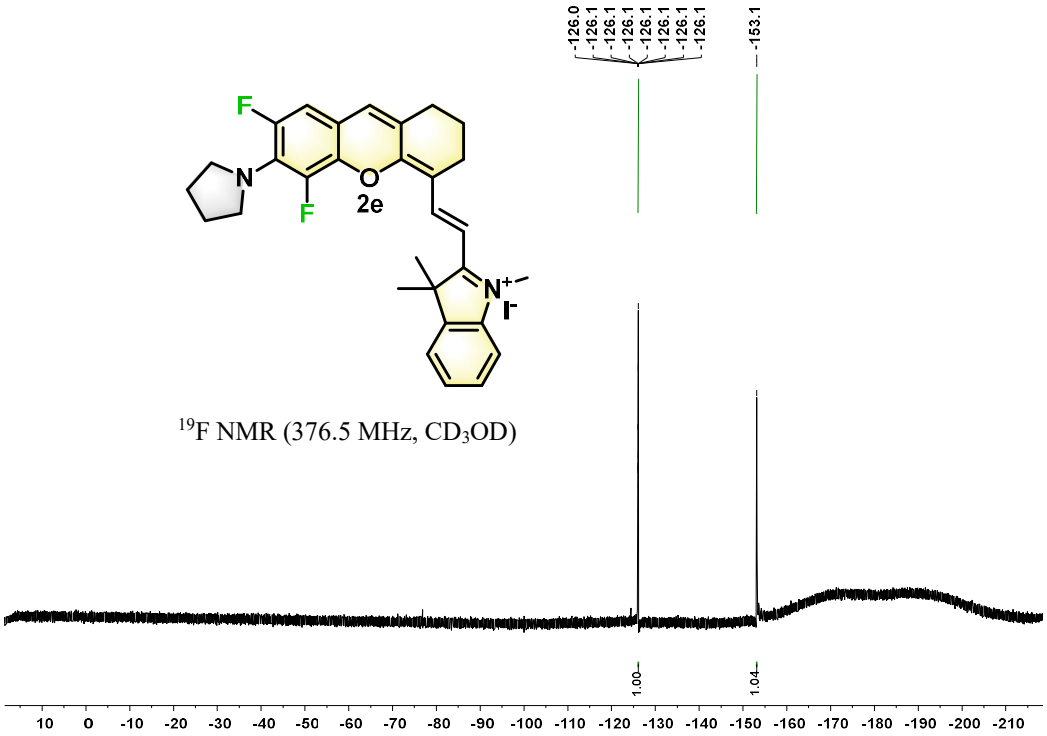
^{1}H NMR (400.0 MHz, DMSO-d_6)



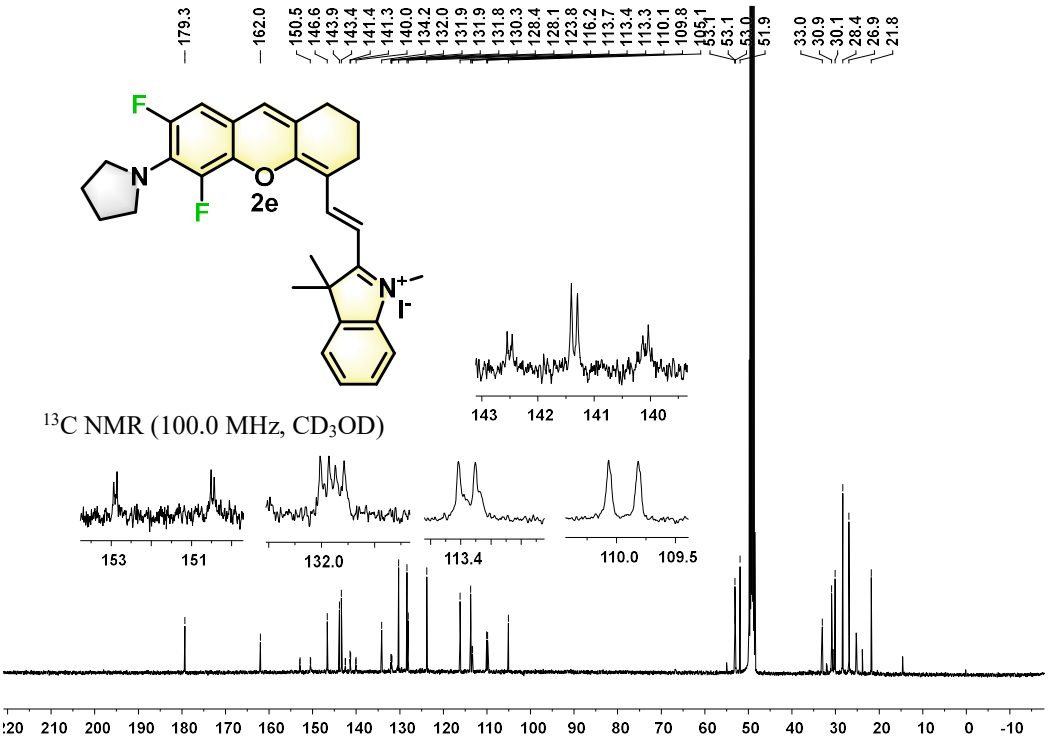
^{19}F NMR (376.5 MHz, DMSO-d_6)


F
H2N
O
F
2d
N+
I-
13C NMR (100.0 MHz, DMSO-d6)

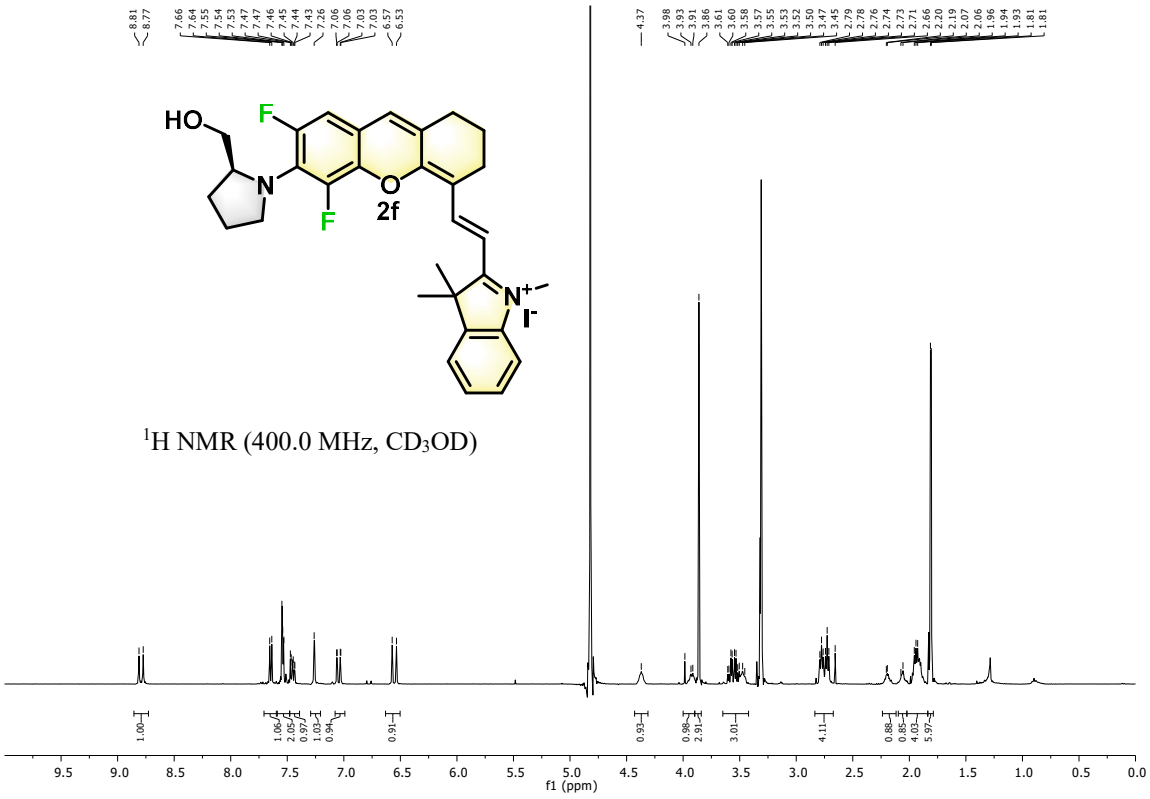

F
N
O
F
2e
N+
I-
1H NMR (400.0 MHz, CD3OD)



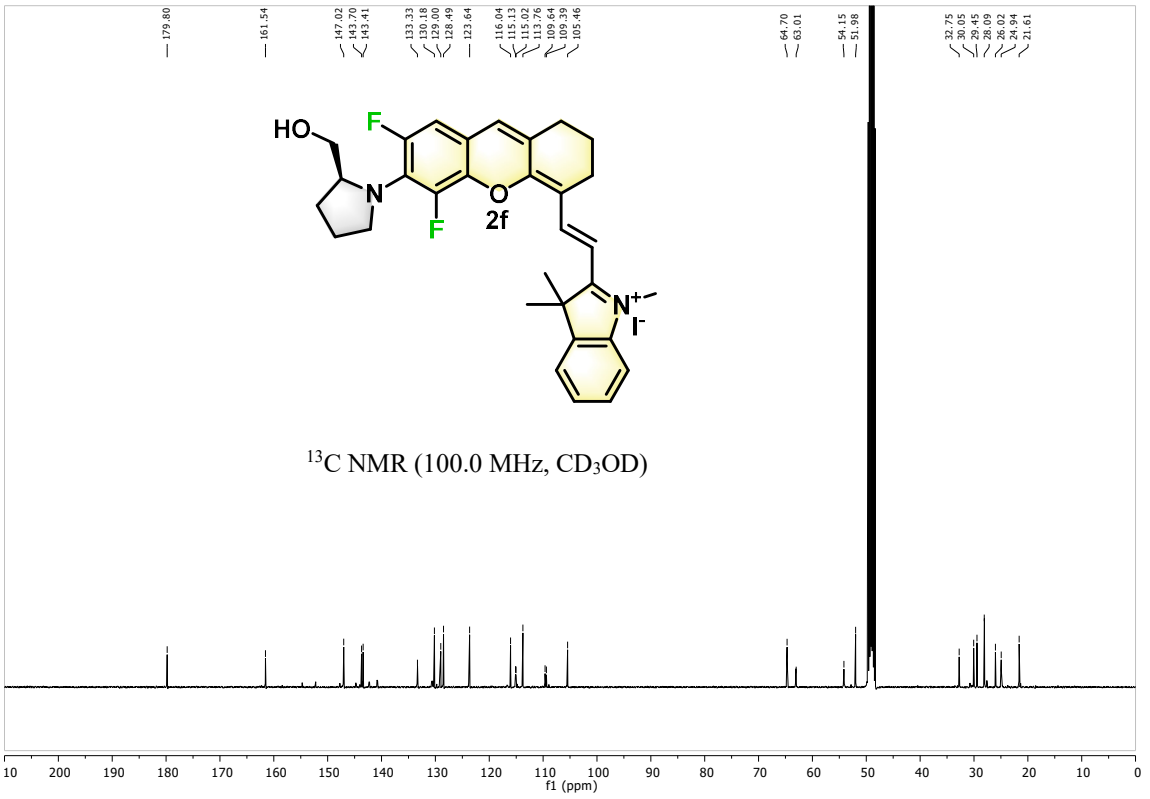
^{19}F NMR (376.5 MHz, CD_3OD)



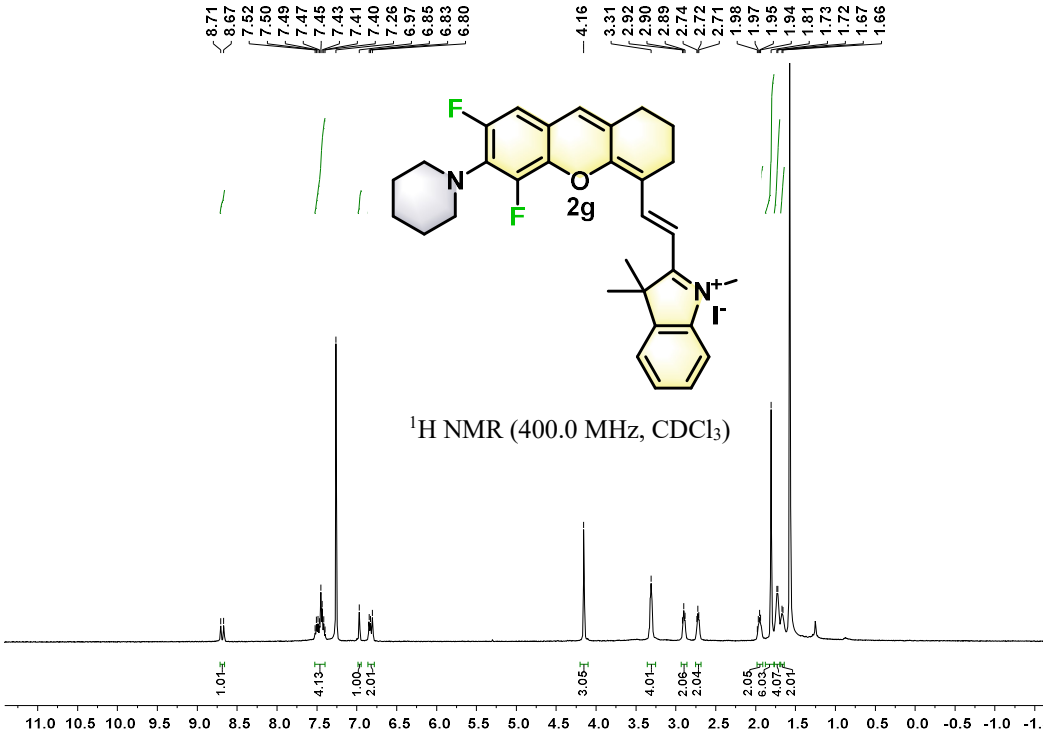
^{13}C NMR (100.0 MHz, CD_3OD)



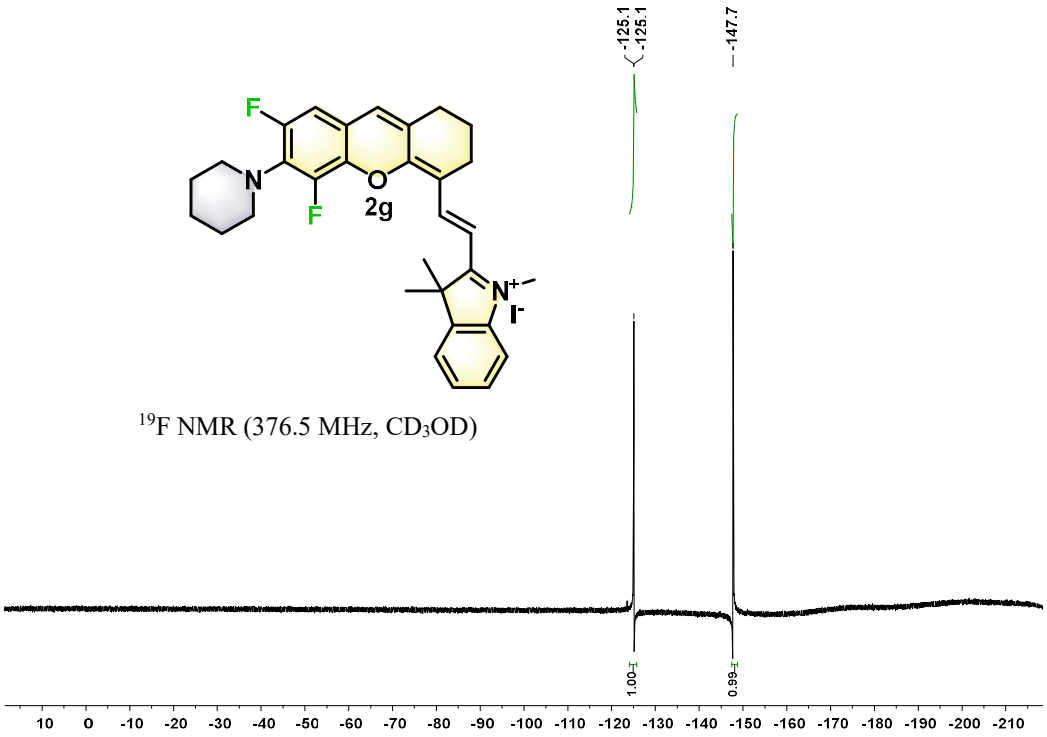
^{1}H NMR (400.0 MHz, CD_3OD)



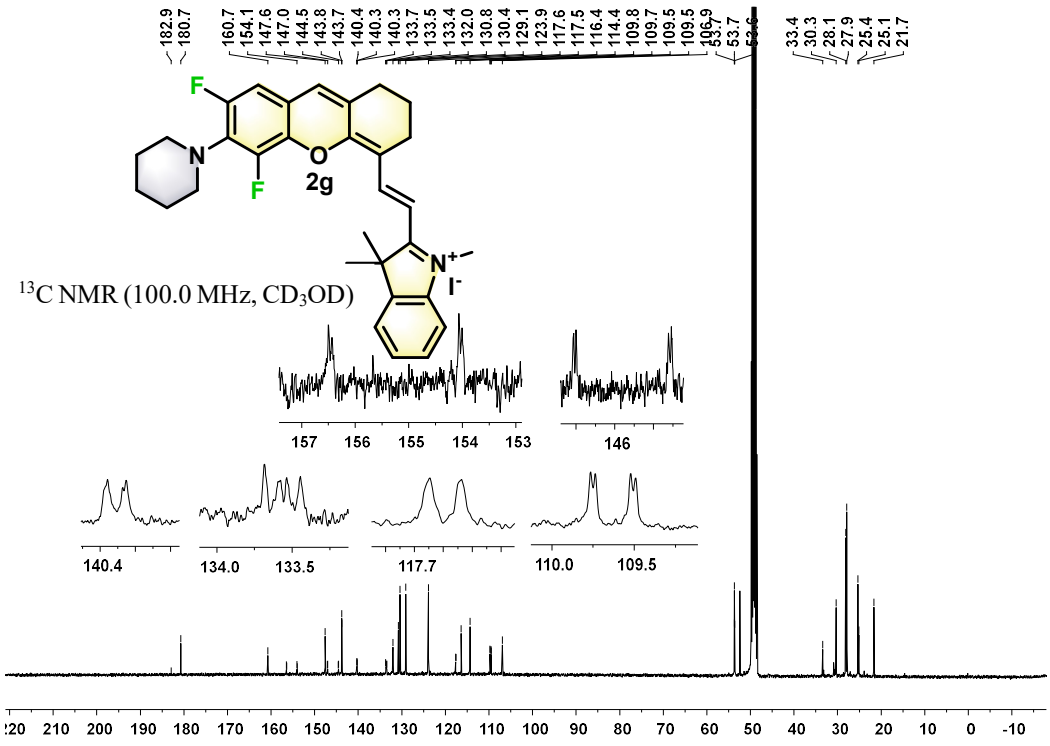
^{13}C NMR (100.0 MHz, CD_3OD)

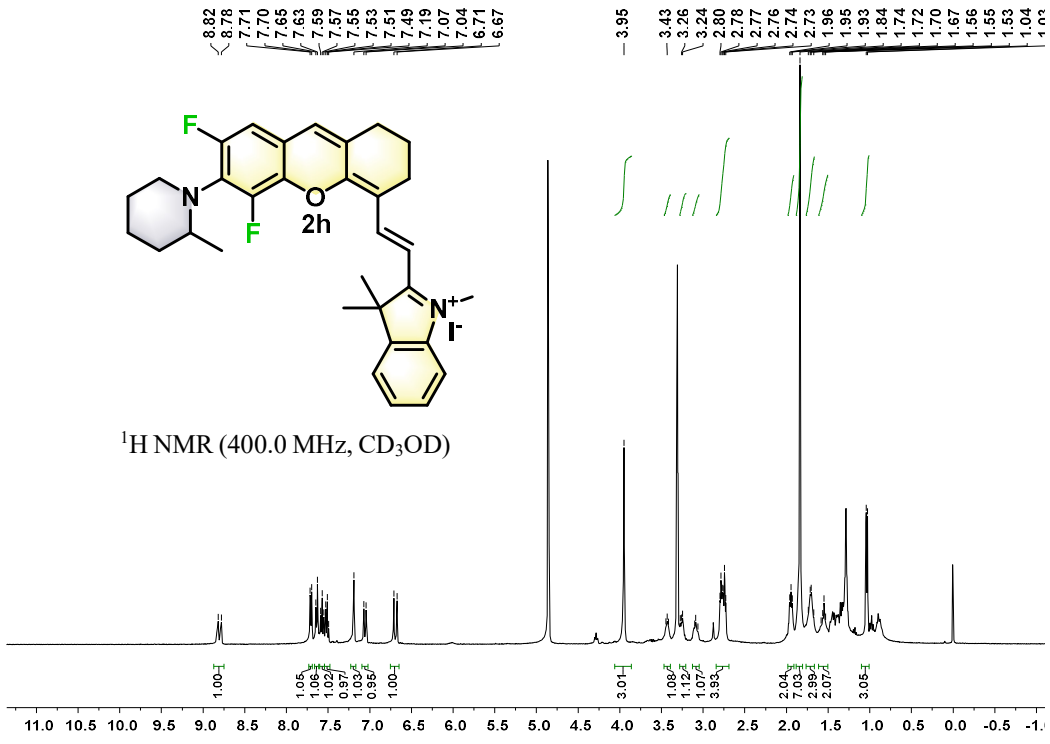


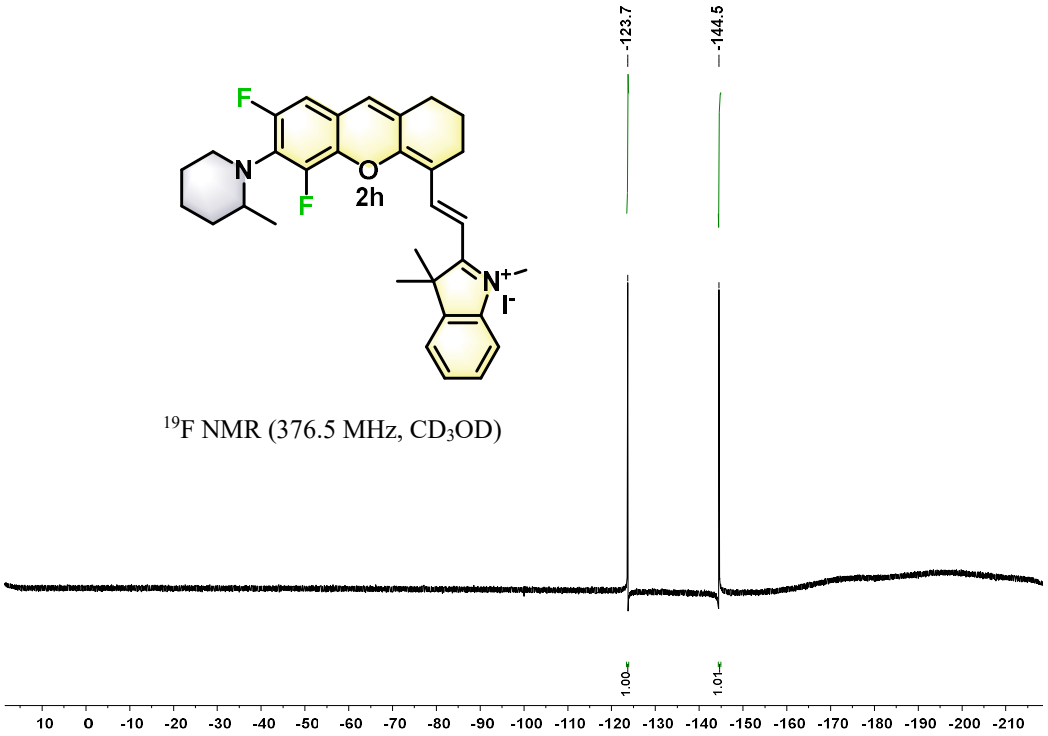
^{1}H NMR (400.0 MHz, $CDCl_3$)



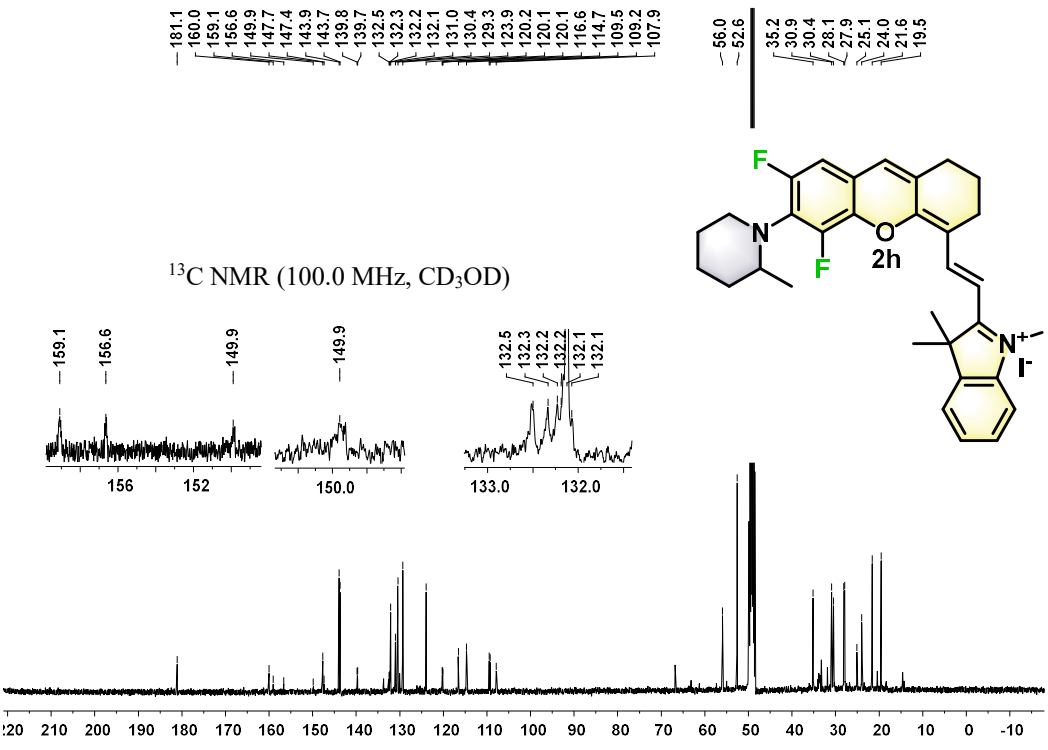
^{19}F NMR (376.5 MHz, CD_3OD)


2g
^{13}C NMR (100.0 MHz, CD$_3$OD)

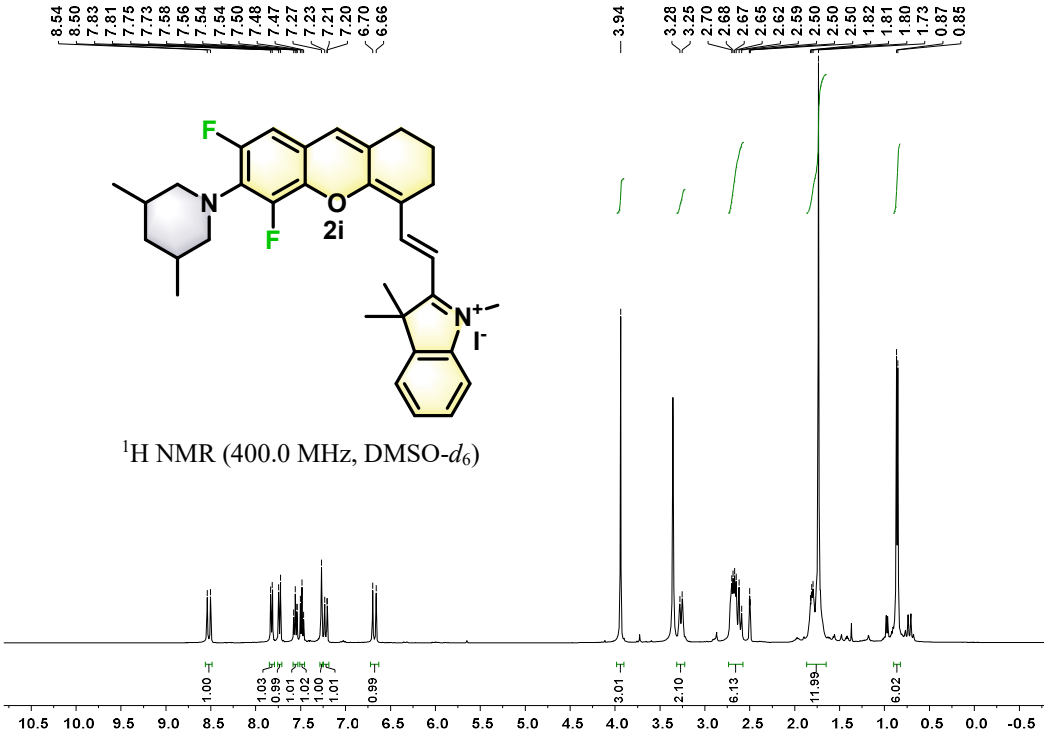

2h
^{1}H NMR (400.0 MHz, CD$_3$OD)



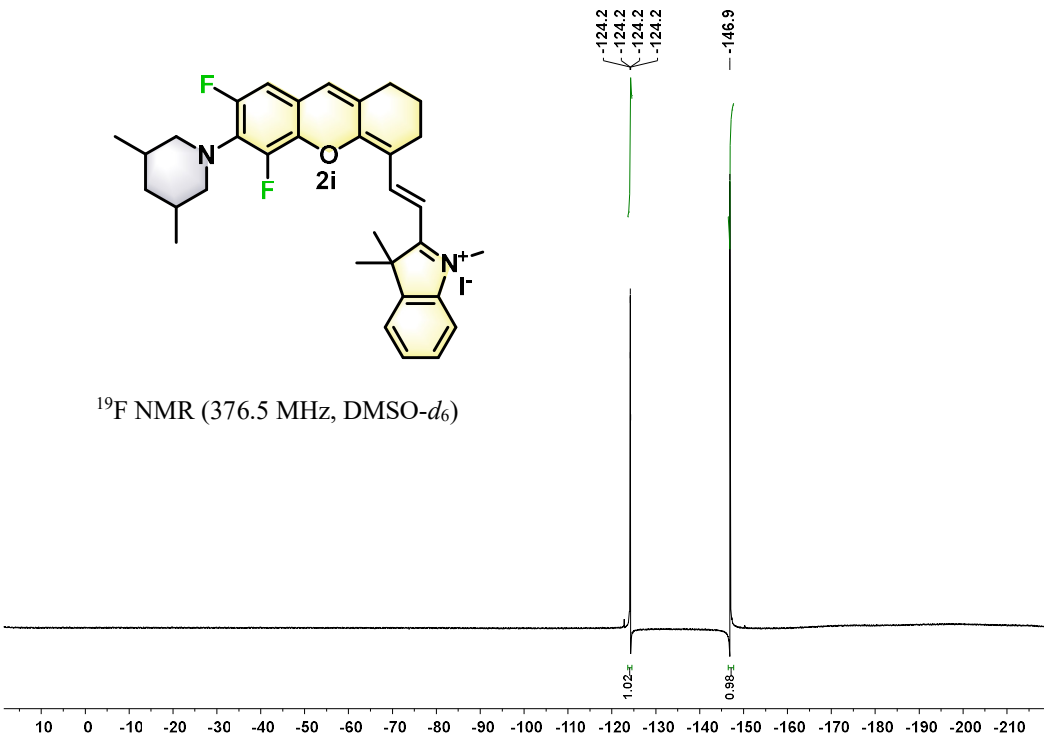
^{19}F NMR (376.5 MHz, CD_3OD)



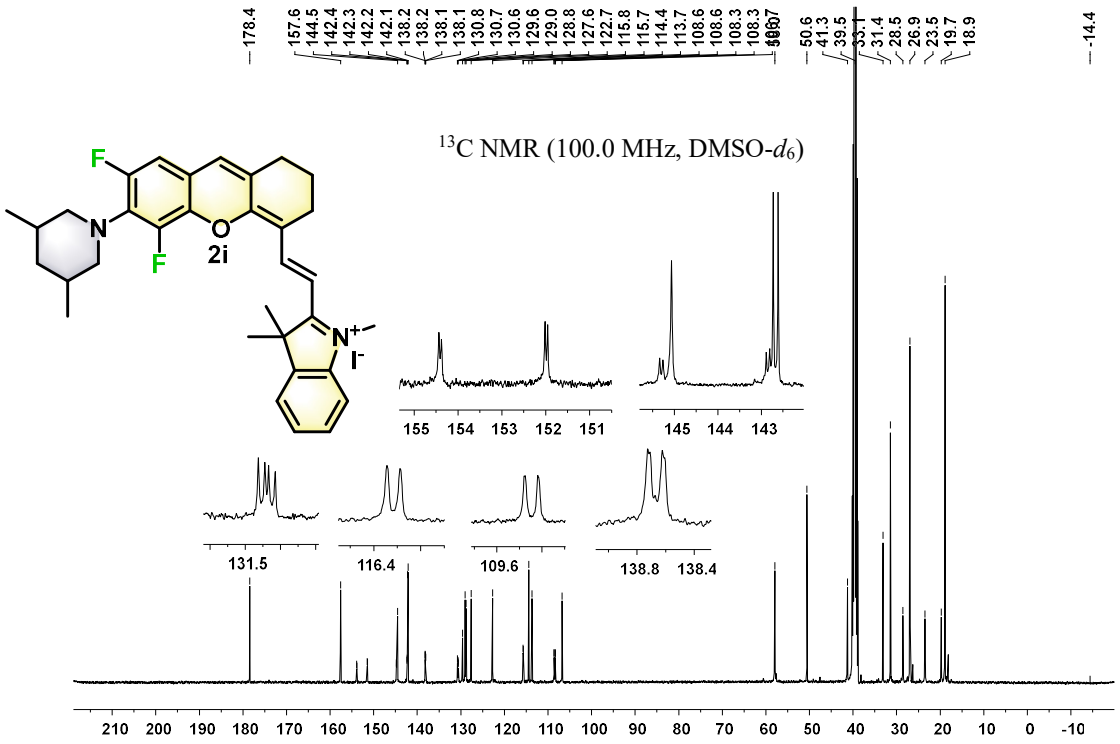
^{13}C NMR (100.0 MHz, CD_3OD)

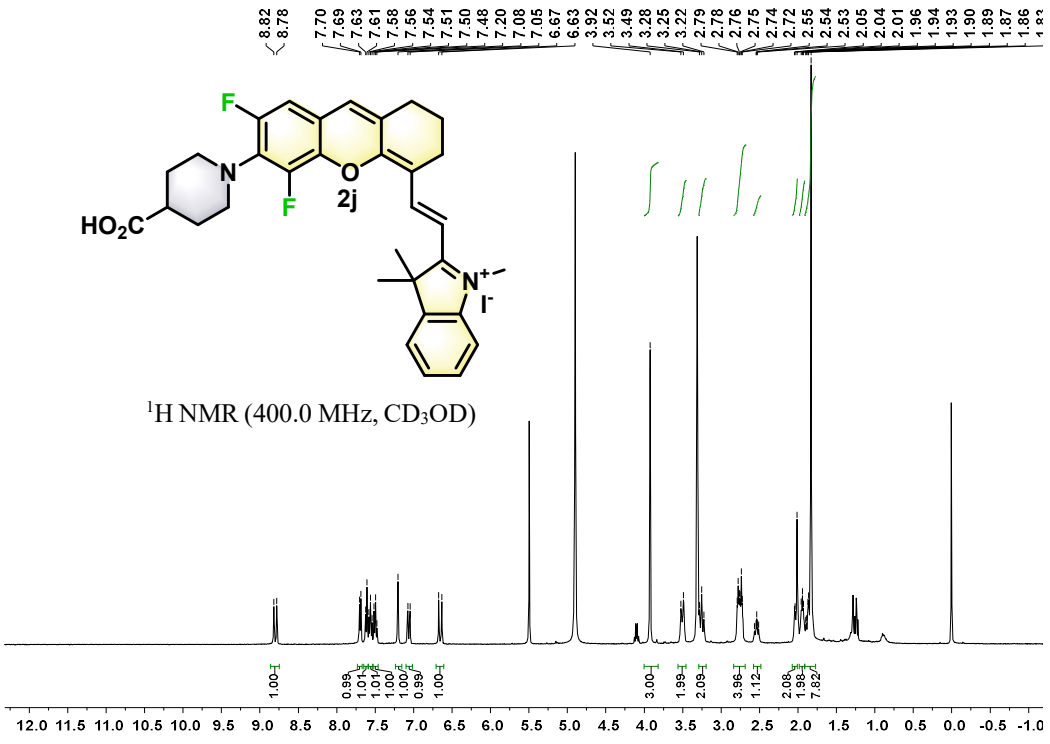


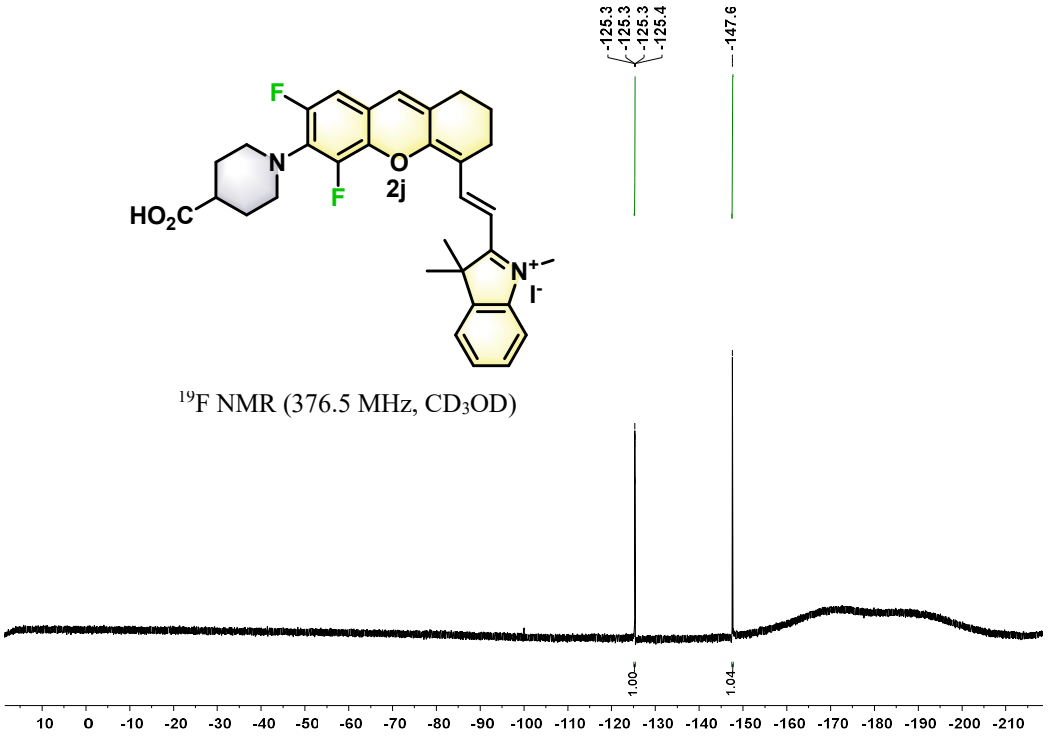
^{1}H NMR (400.0 MHz, DMSO-d_6)



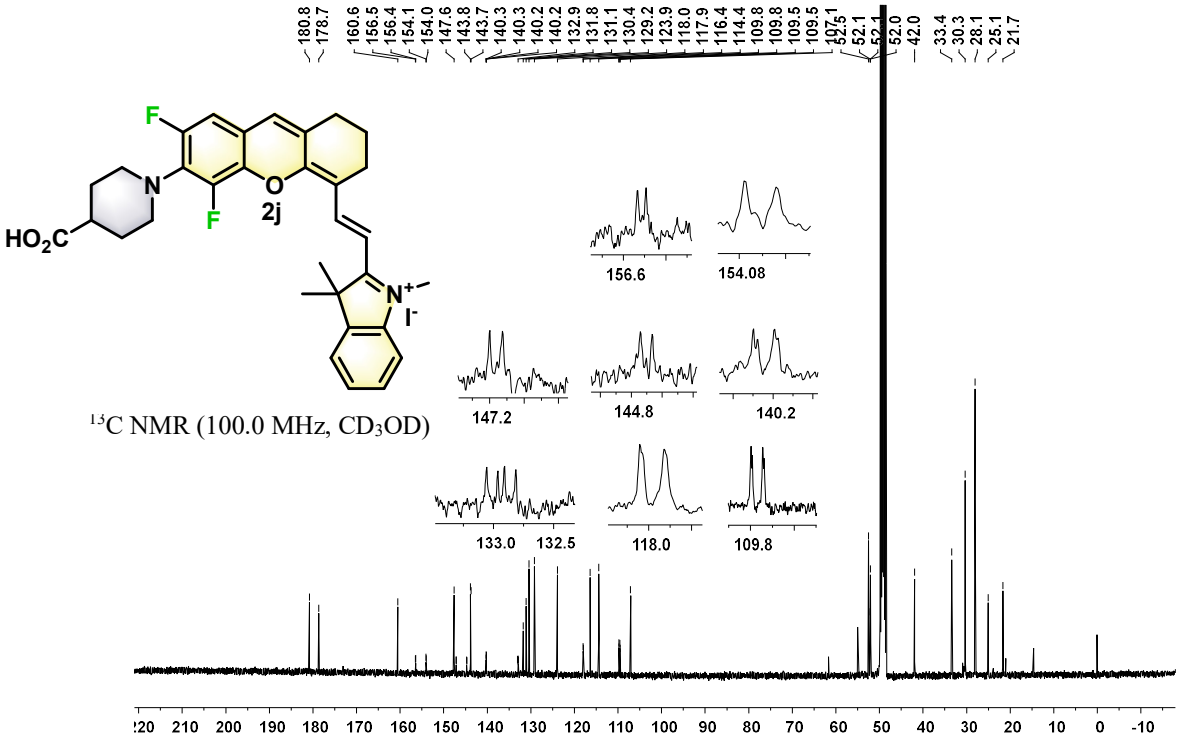
^{19}F NMR (376.5 MHz, DMSO-d_6)


F
N
O
F
2i
N+
I-
^{13}C NMR (100.0 MHz, DMSO-d_6)

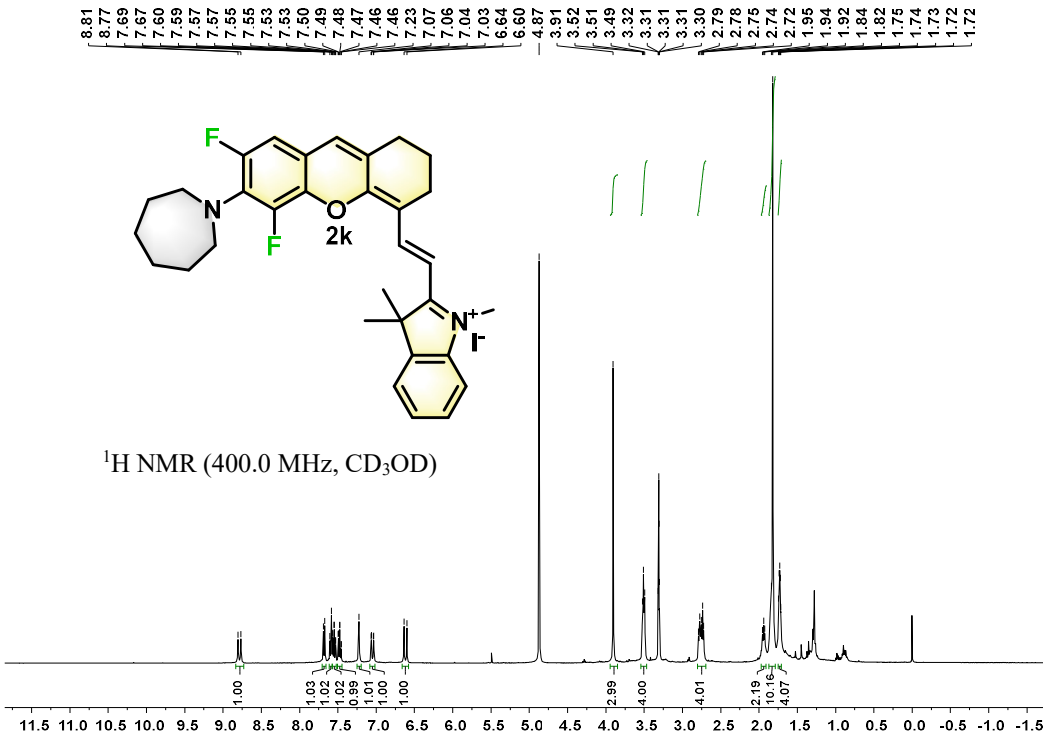

F
N
O
F
2j
HO2C
N+
I-
^{1}H NMR (400.0 MHz, CD3OD)



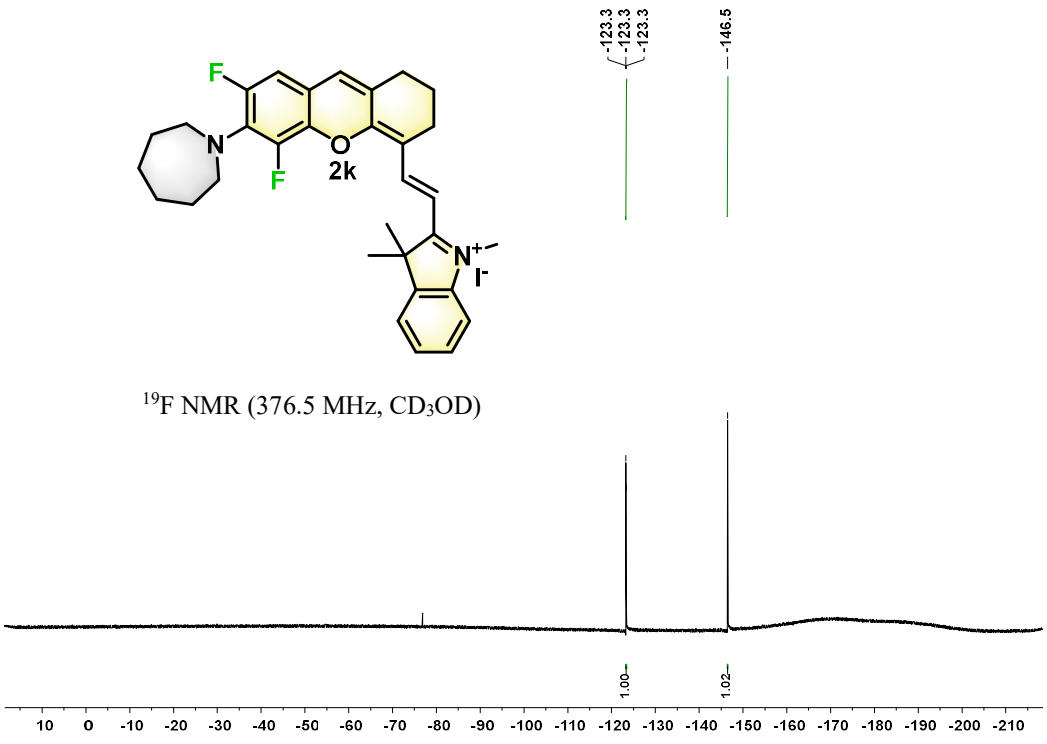
^{19}F NMR (376.5 MHz, CD_3OD)



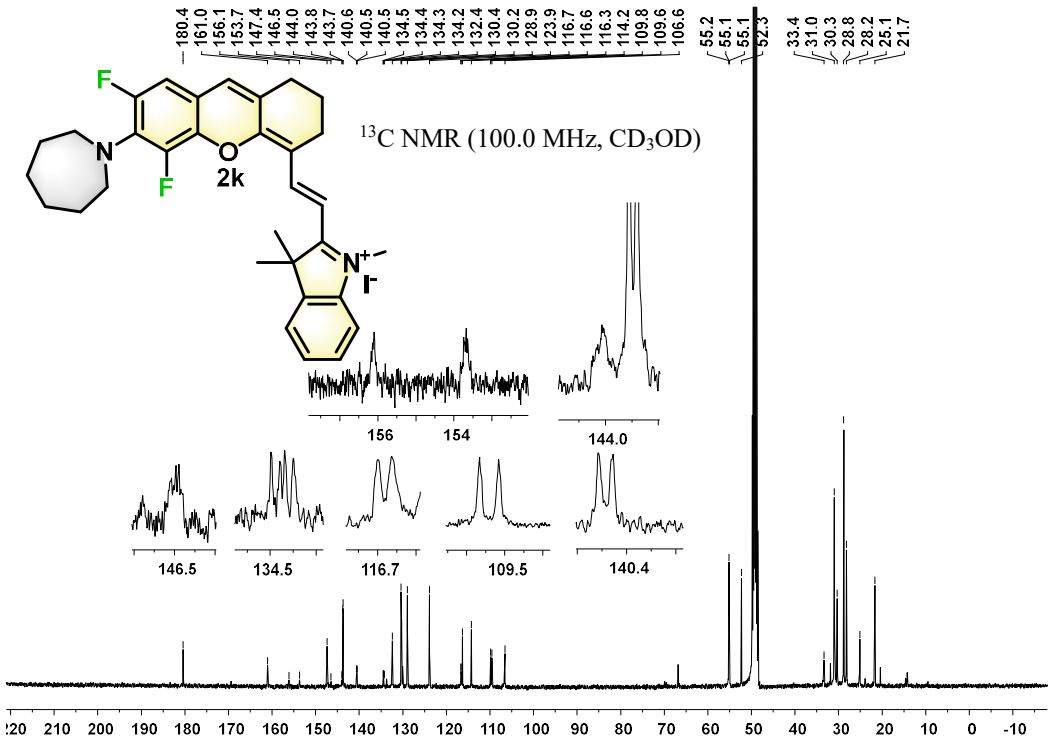
^{13}C NMR (100.0 MHz, CD_3OD)

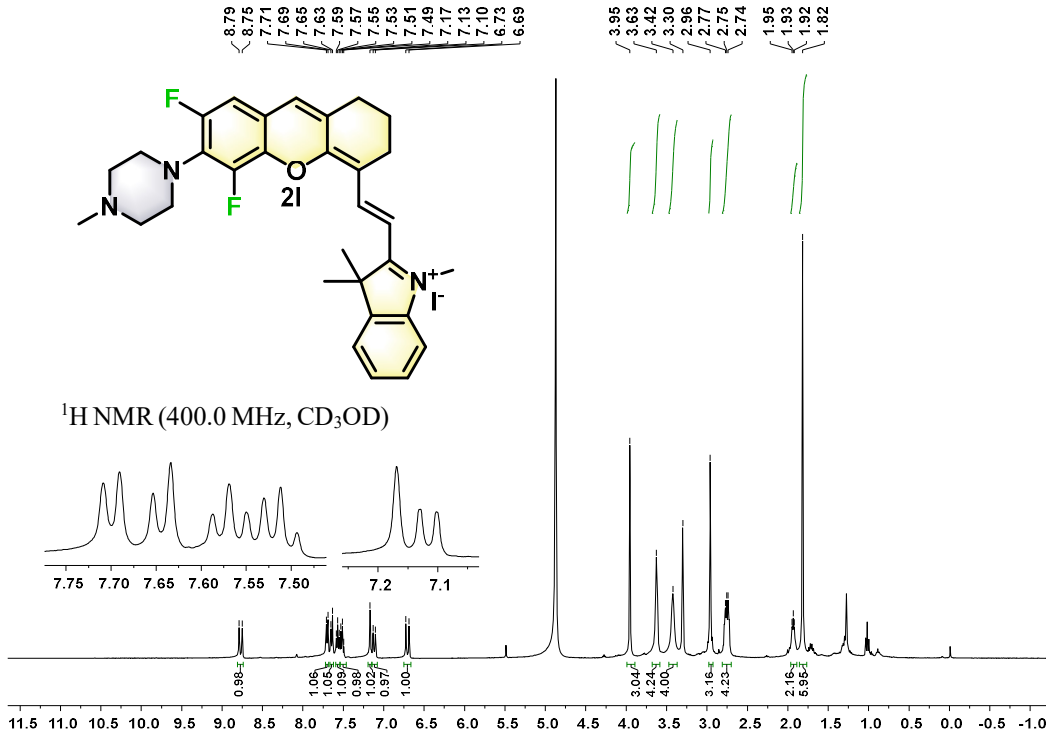


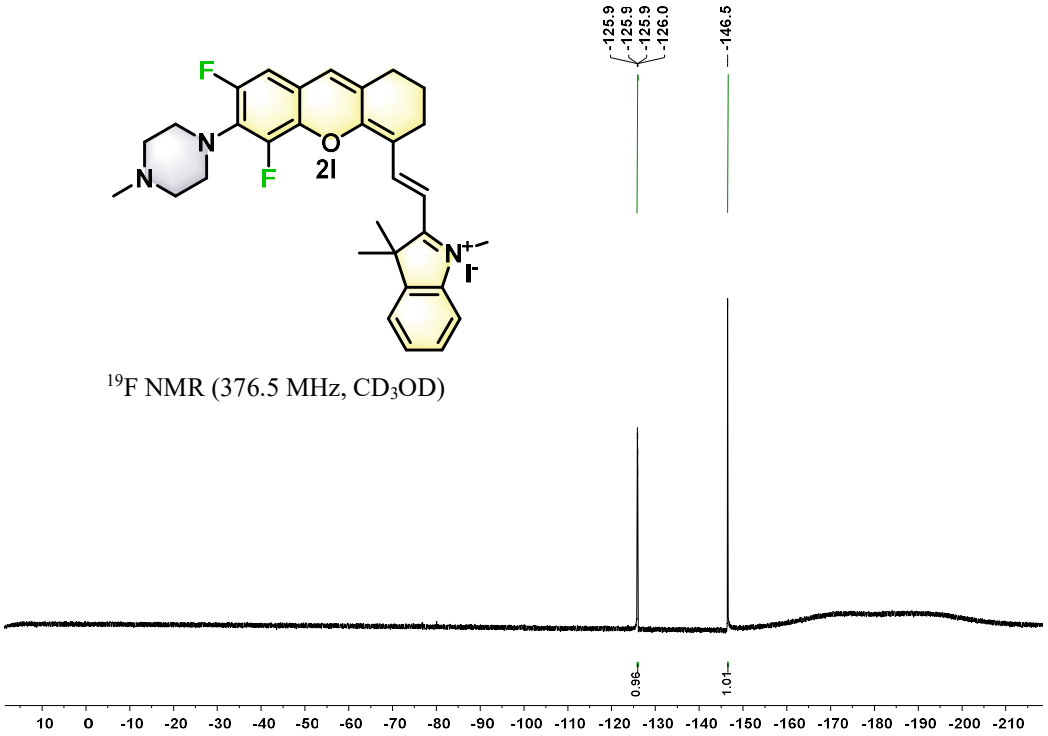
^{1}H NMR (400.0 MHz, CD_3OD)



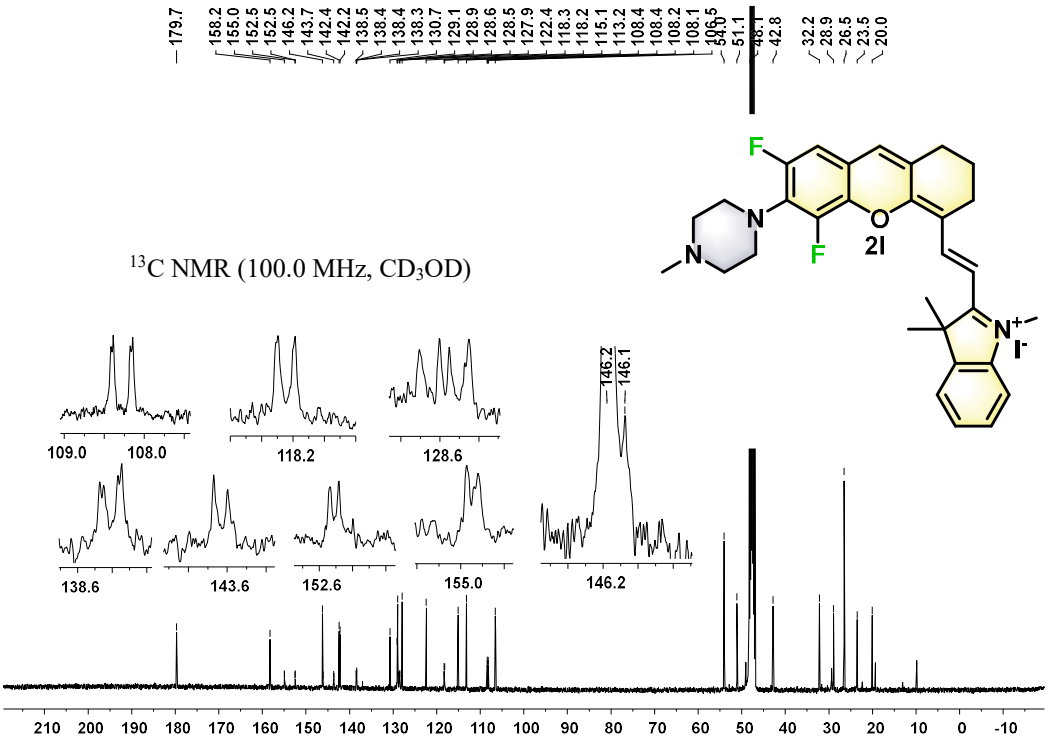
^{19}F NMR (376.5 MHz, CD_3OD)


2k
13C NMR (100.0 MHz, CD3OD)

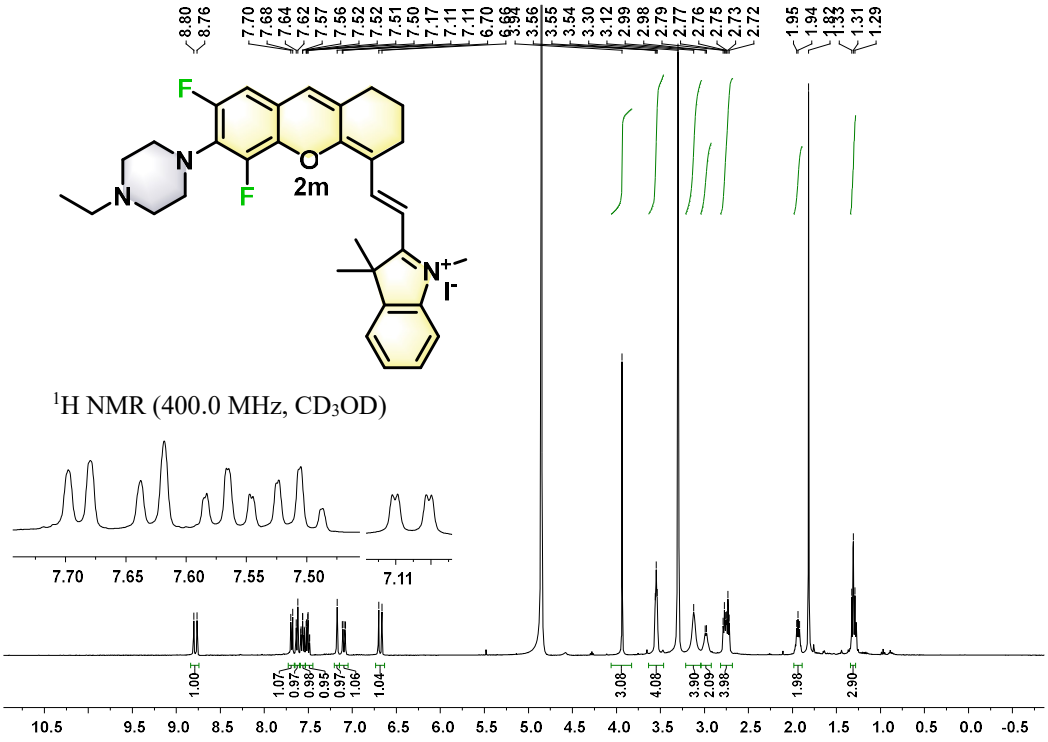

2l
1H NMR (400.0 MHz, CD3OD)



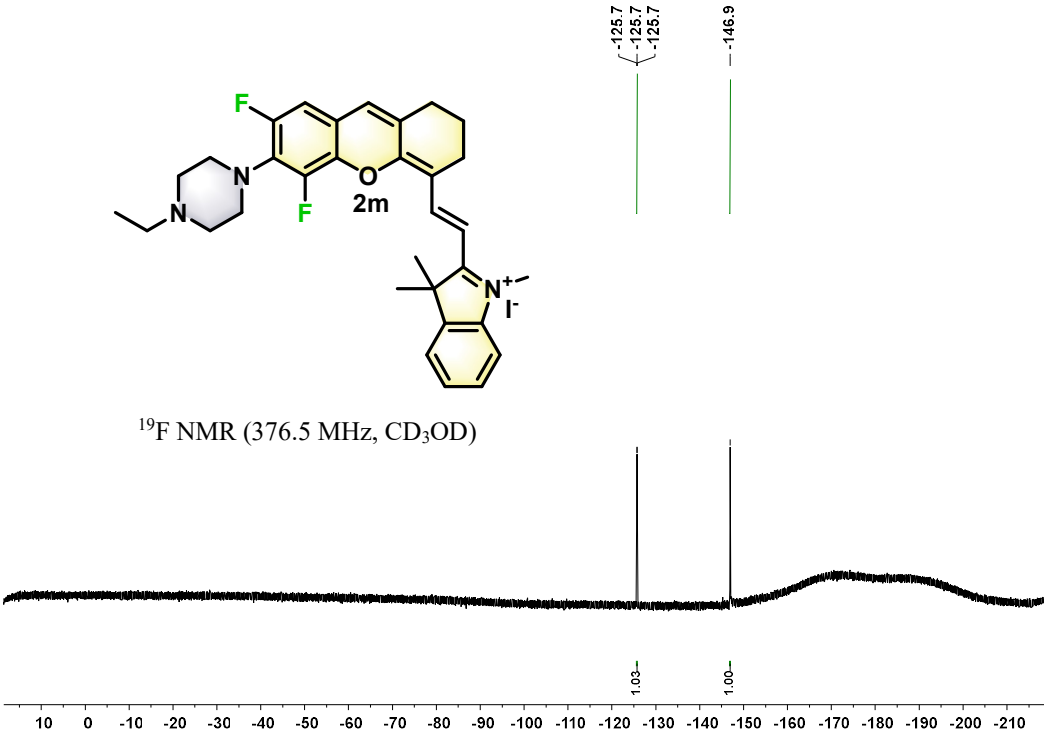
^{19}F NMR (376.5 MHz, CD_3OD)



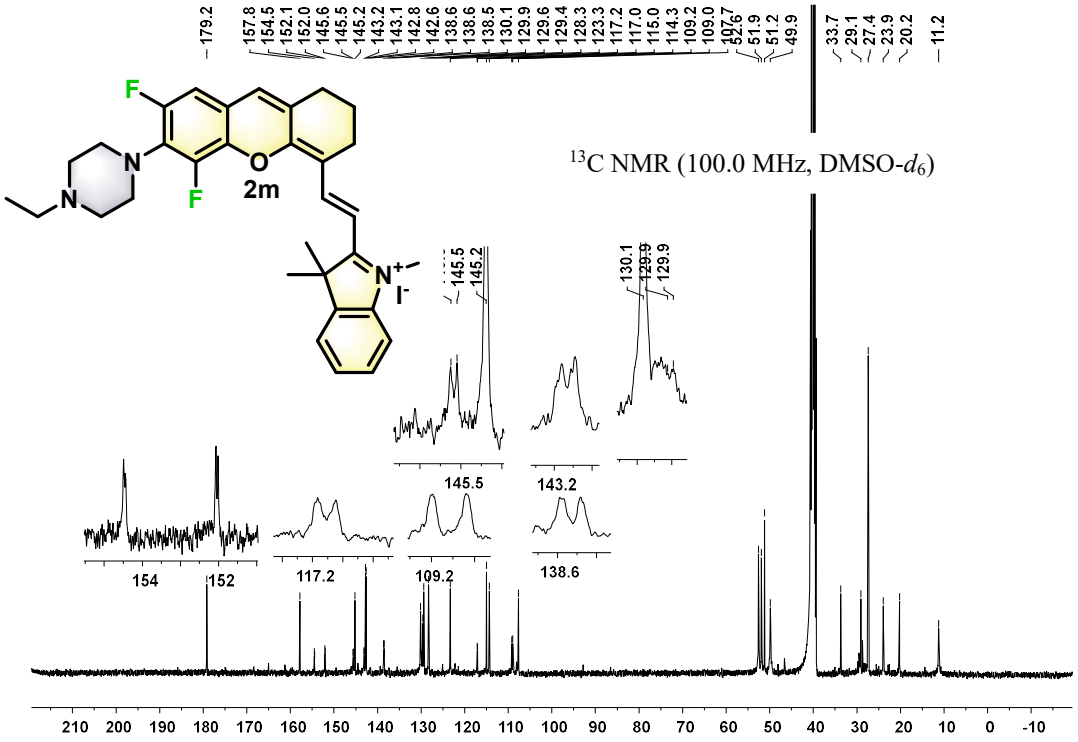
^{13}C NMR (100.0 MHz, CD_3OD)



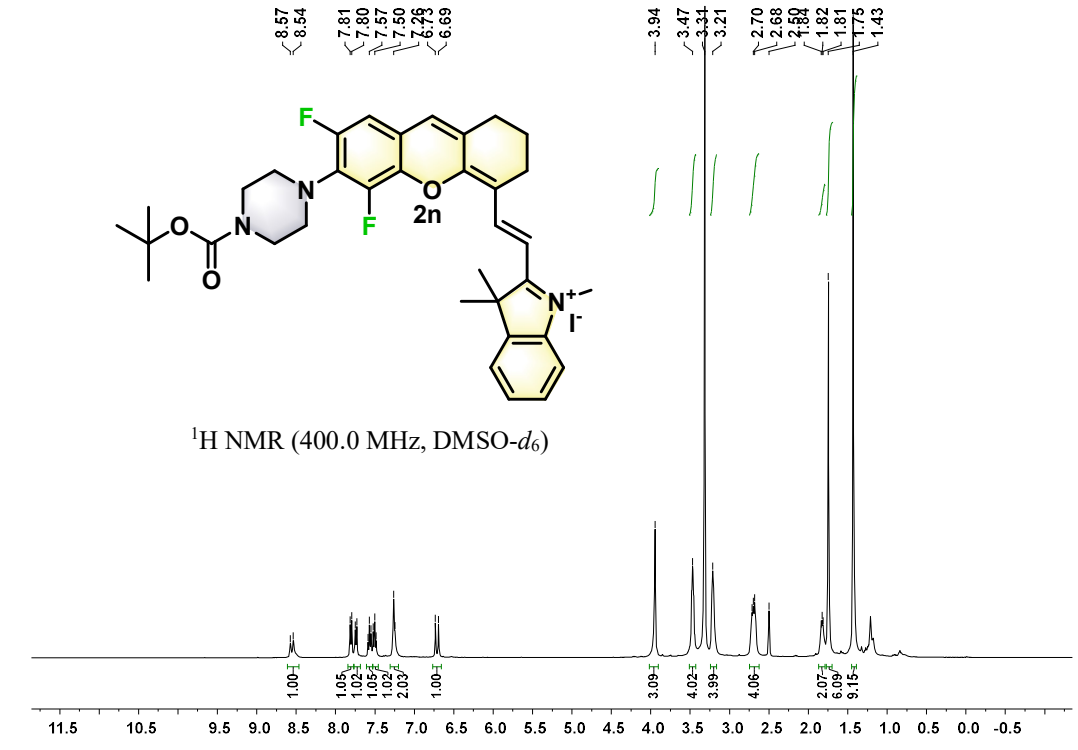
^{1}H NMR (400.0 MHz, CD_3OD)



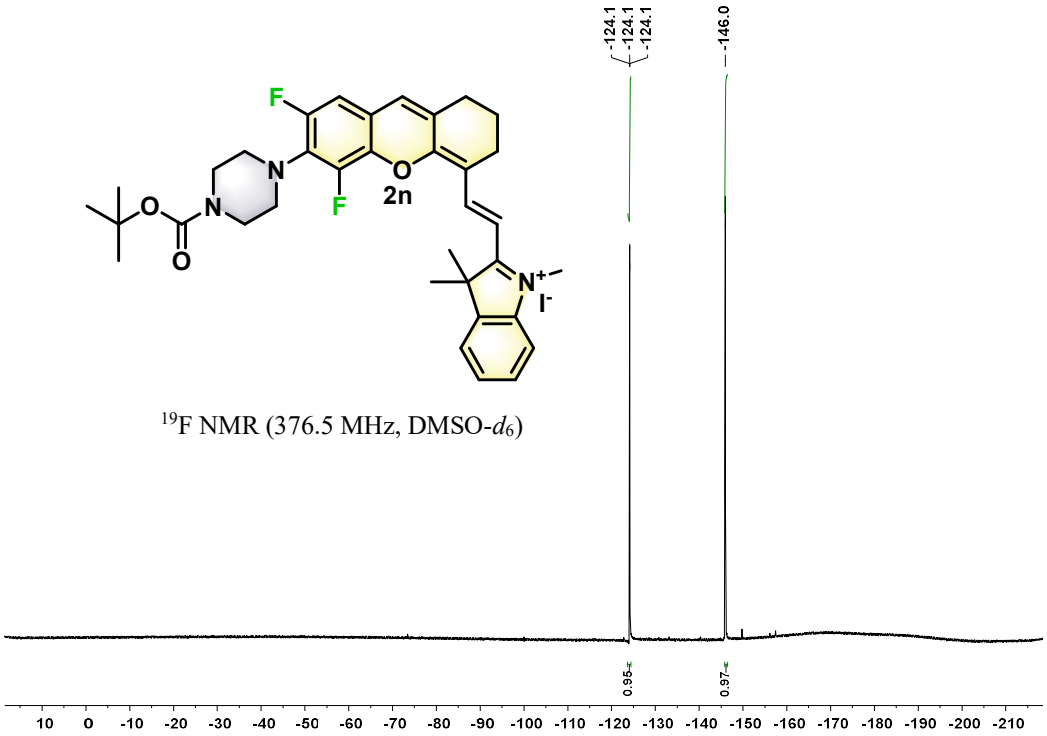
^{19}F NMR (376.5 MHz, CD_3OD)



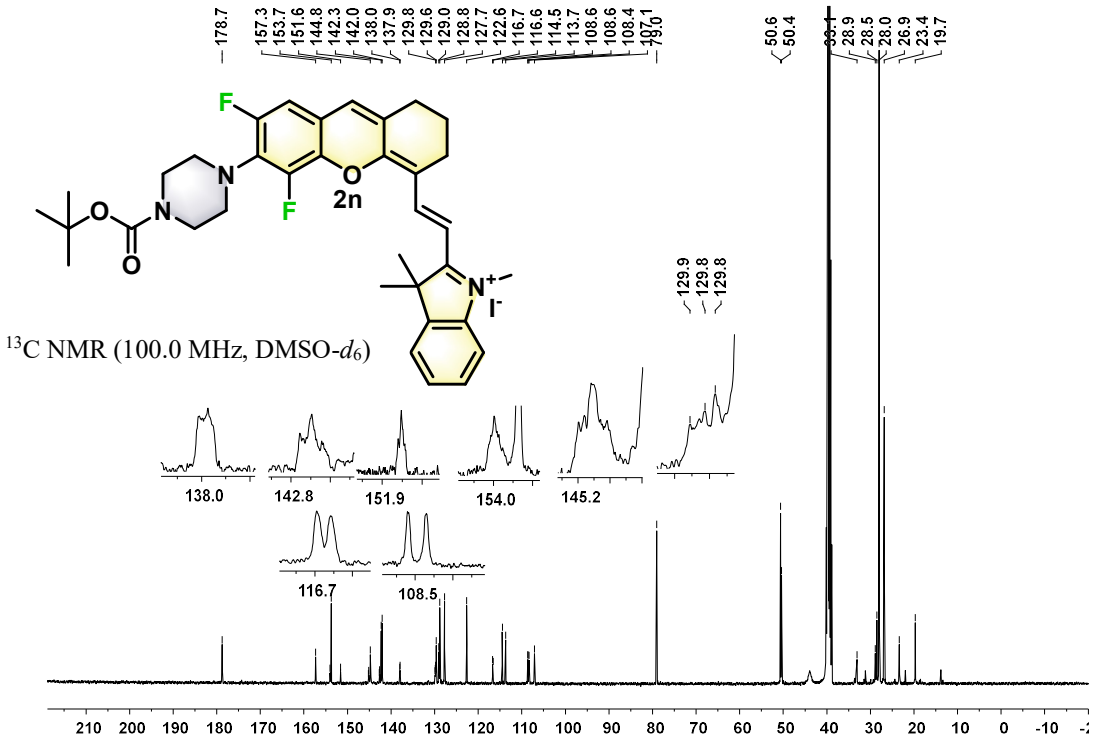
^{13}C NMR (100.0 MHz, DMSO-d_6)



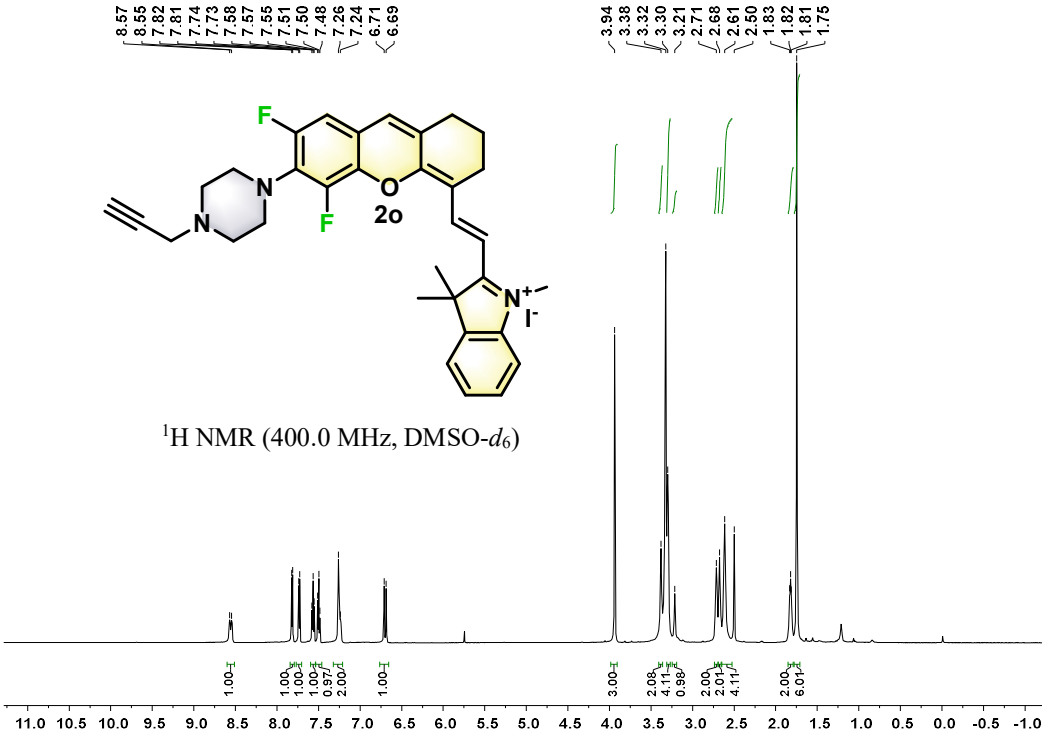
^{1}H NMR (400.0 MHz, DMSO-d_6)



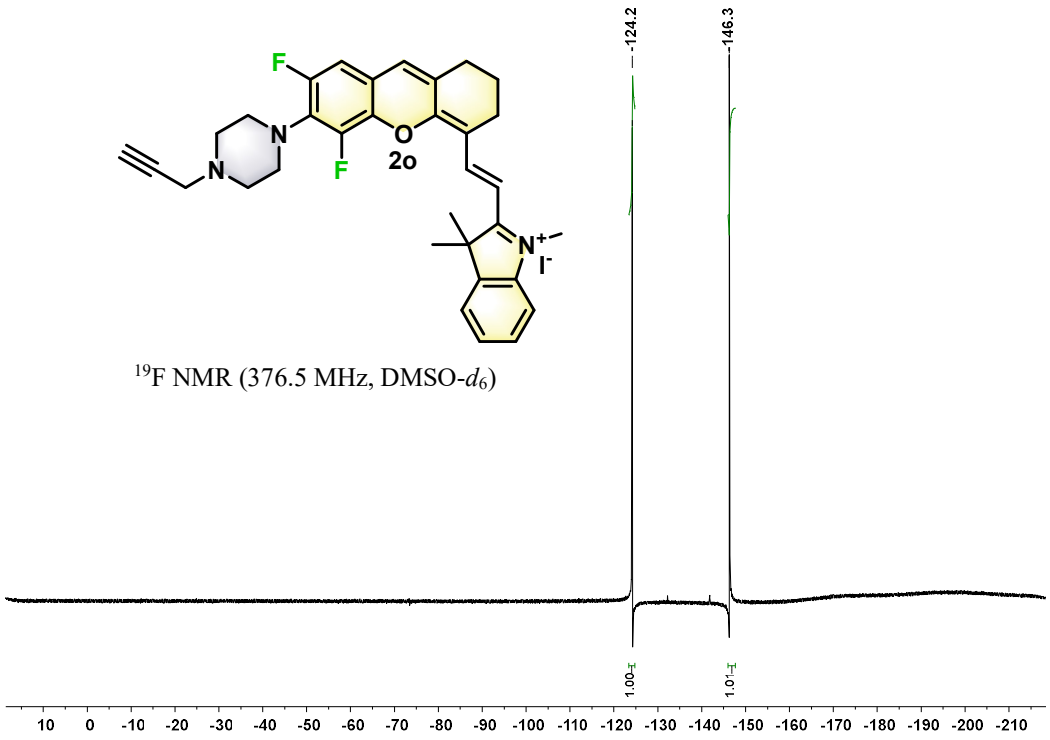
^{19}F NMR (376.5 MHz, DMSO-d_6)



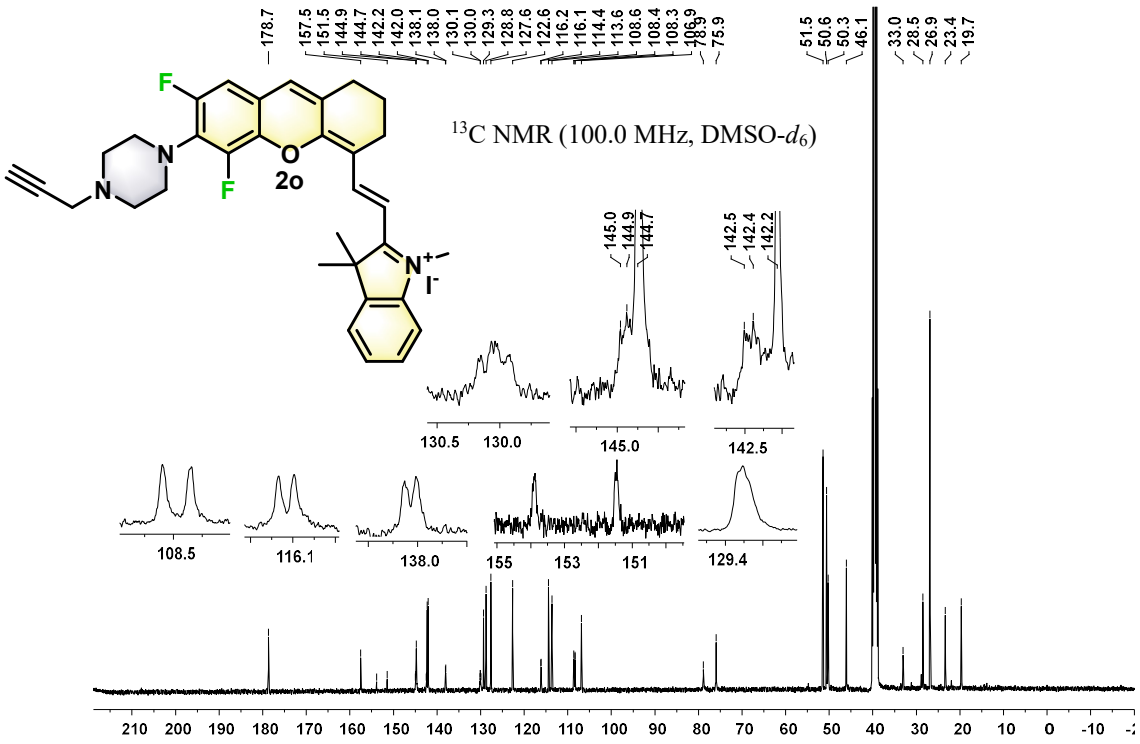
^{13}C NMR (100.0 MHz, DMSO-d_6)

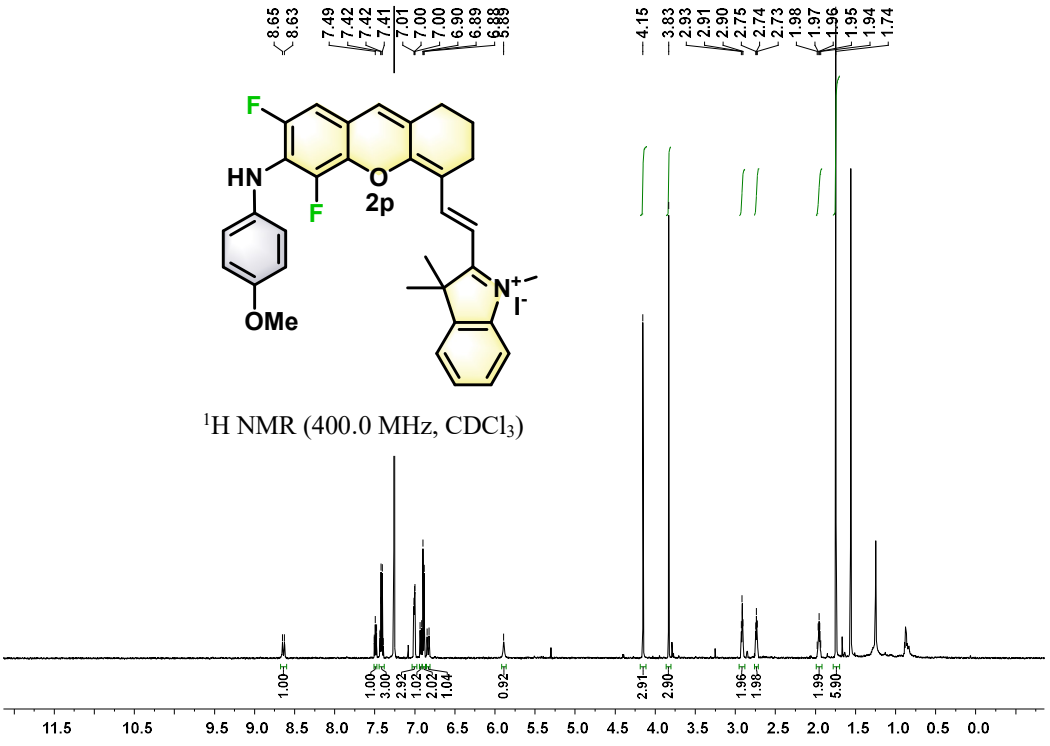


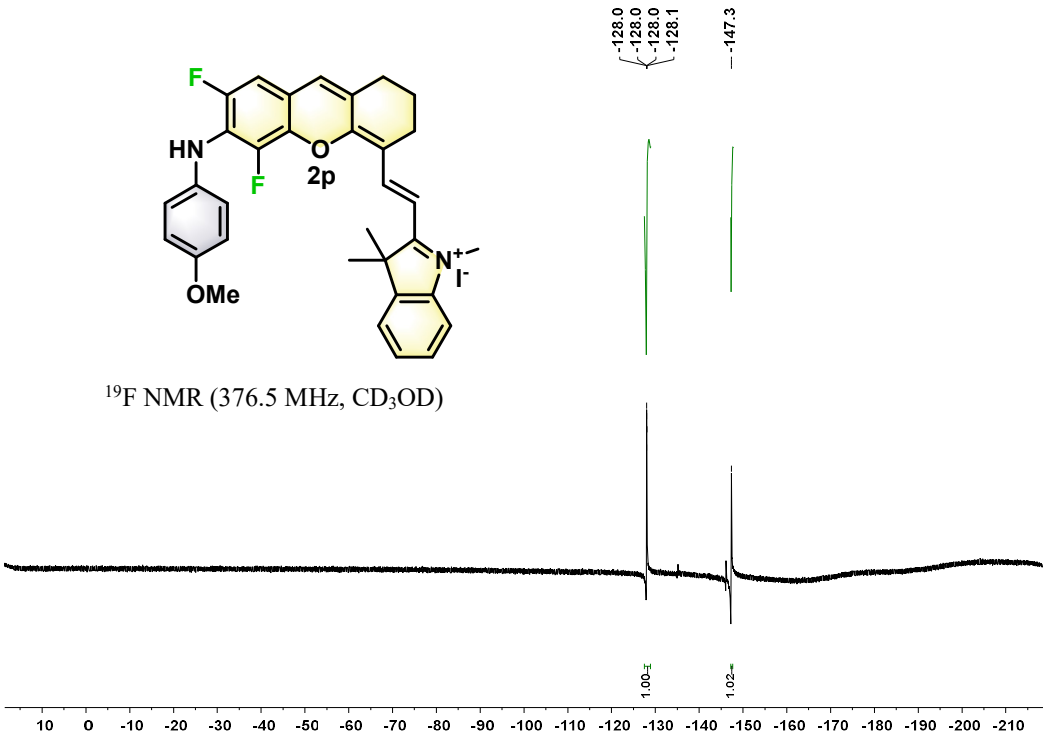
^{1}H NMR (400.0 MHz, DMSO-d_6)



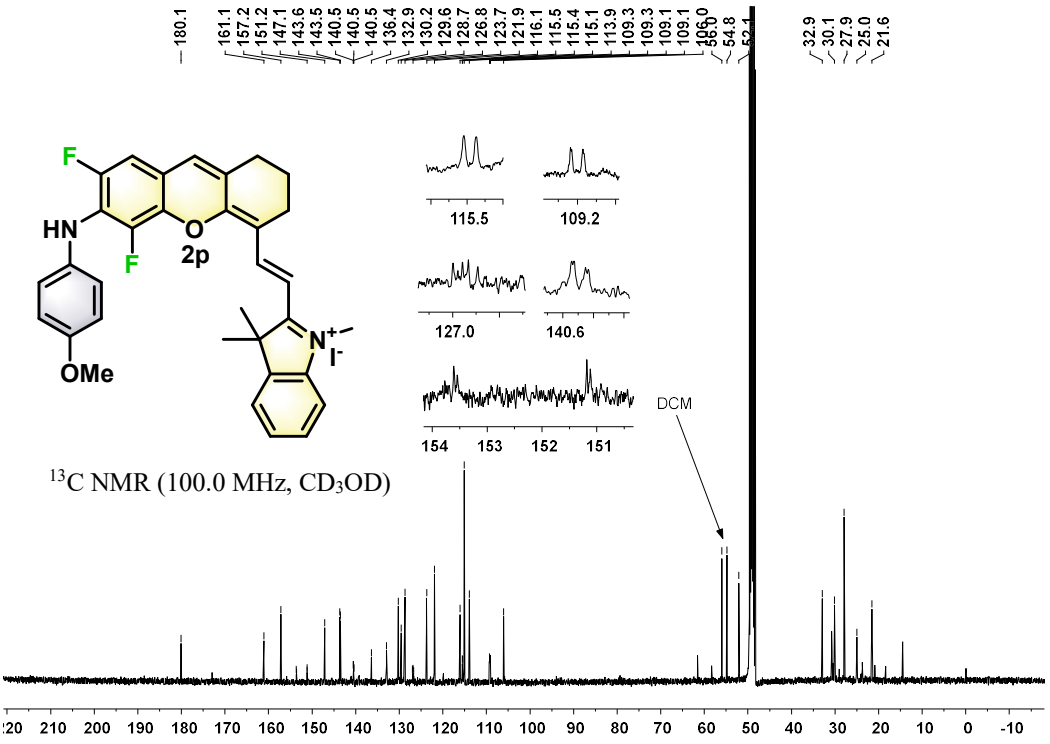
^{19}F NMR (376.5 MHz, DMSO-d_6)


F
N
N
F
O
2o
N+
I-
^{13}C NMR (100.0 MHz, DMSO-d_6)

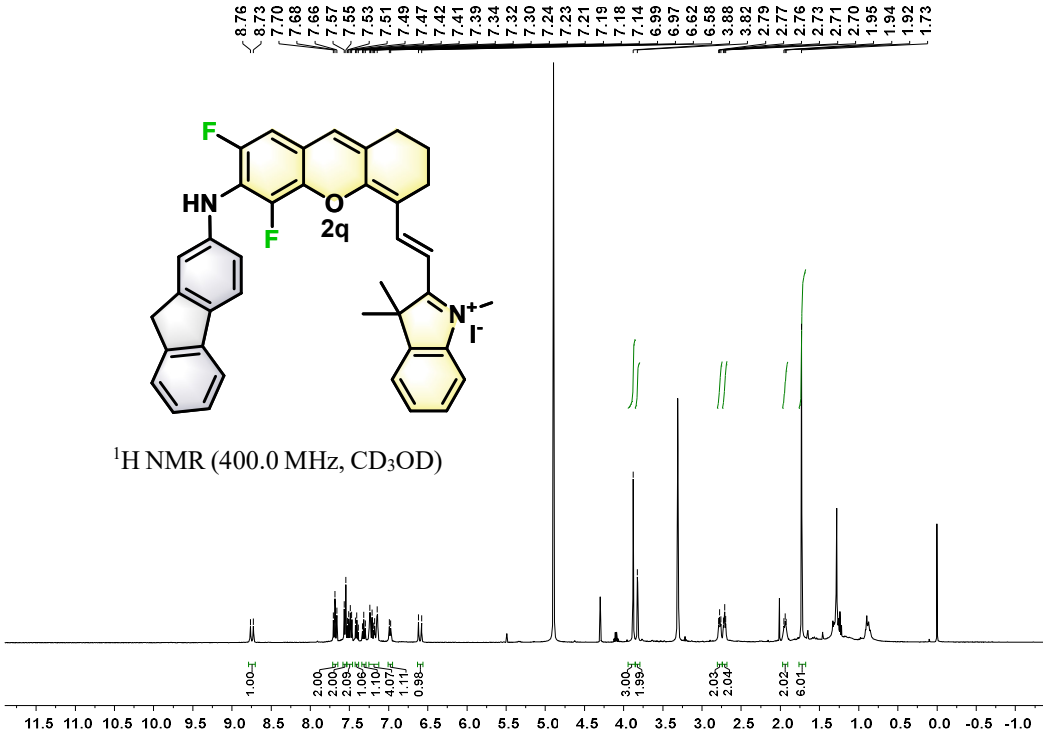

F
HN
O
2p
F
OMe
N+
I-
^{1}H NMR (400.0 MHz, $CDCl_3$)



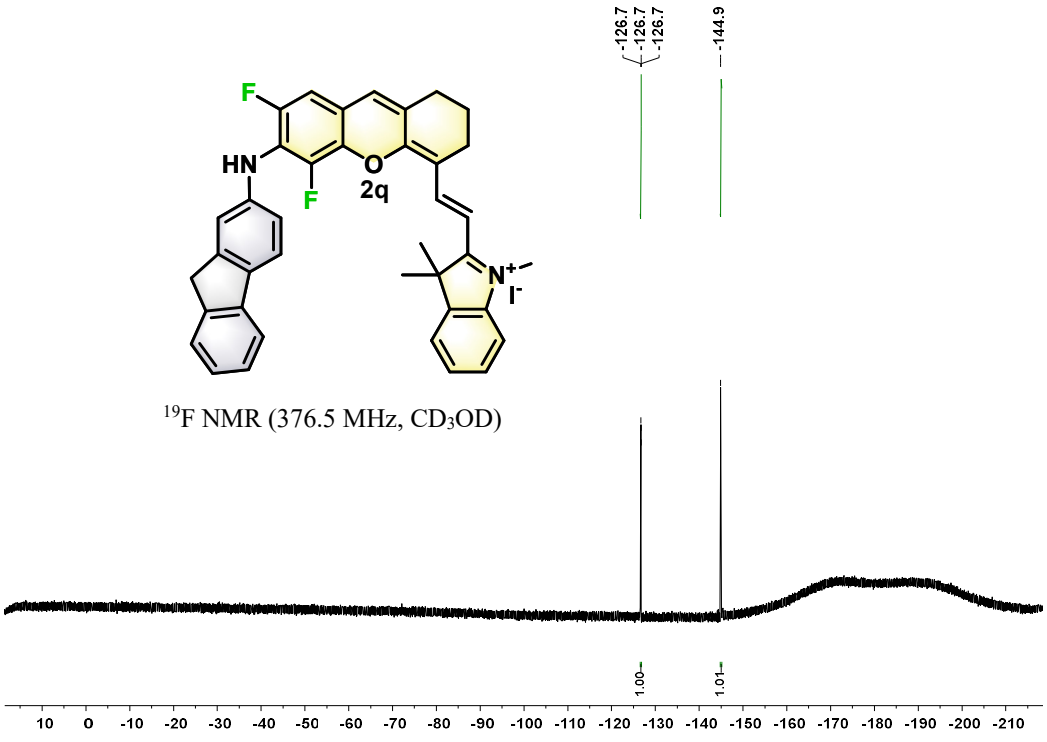
^{19}F NMR (376.5 MHz, CD_3OD)



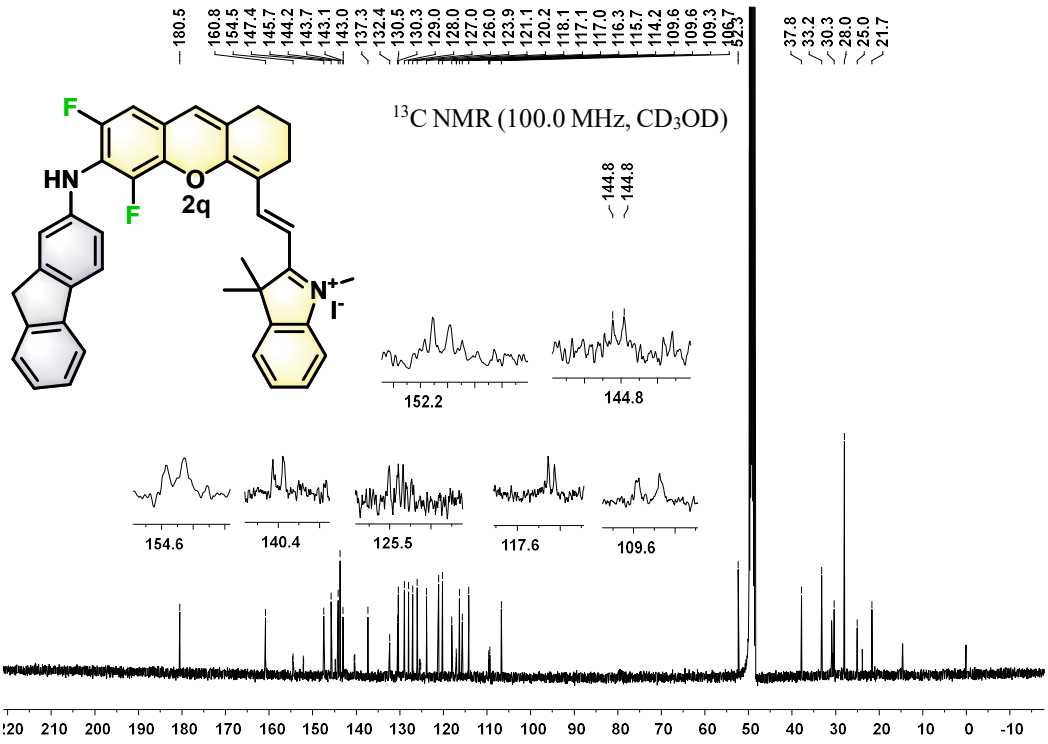
^{13}C NMR (100.0 MHz, CD_3OD)

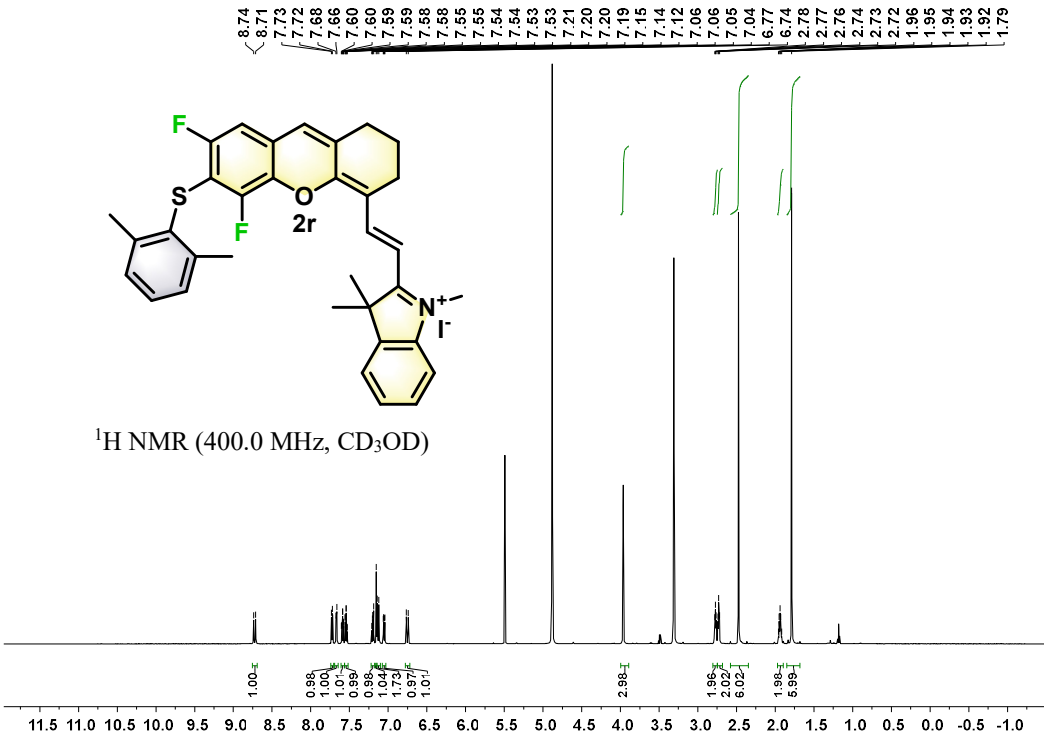


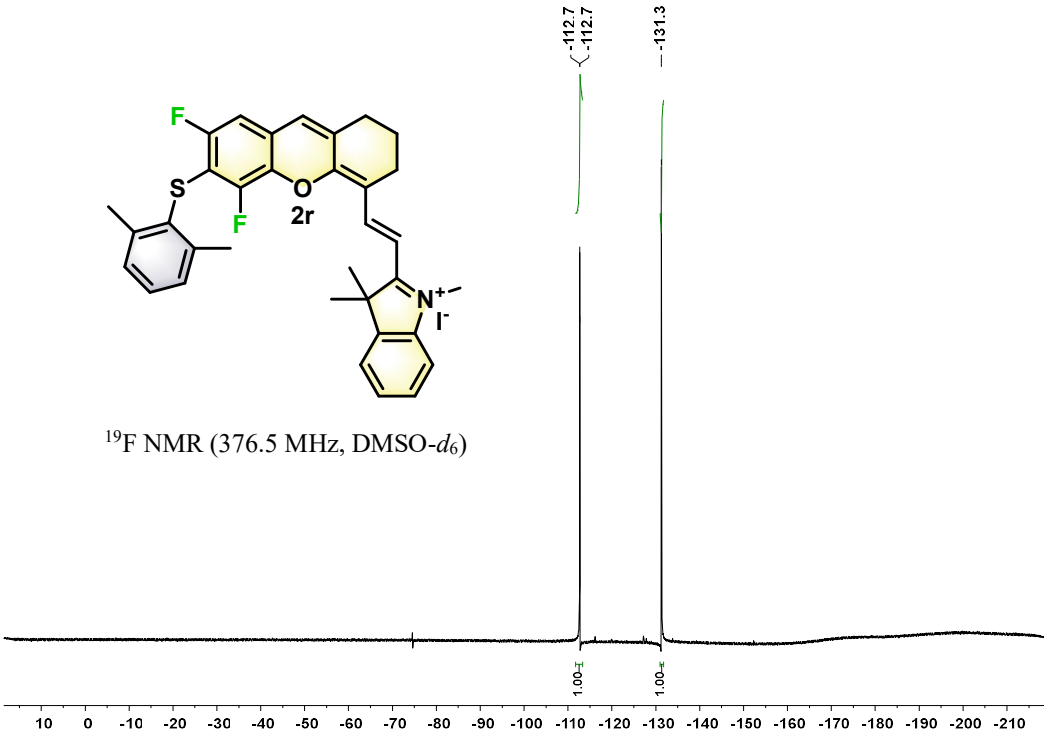
^{1}H NMR (400.0 MHz, CD_3OD)



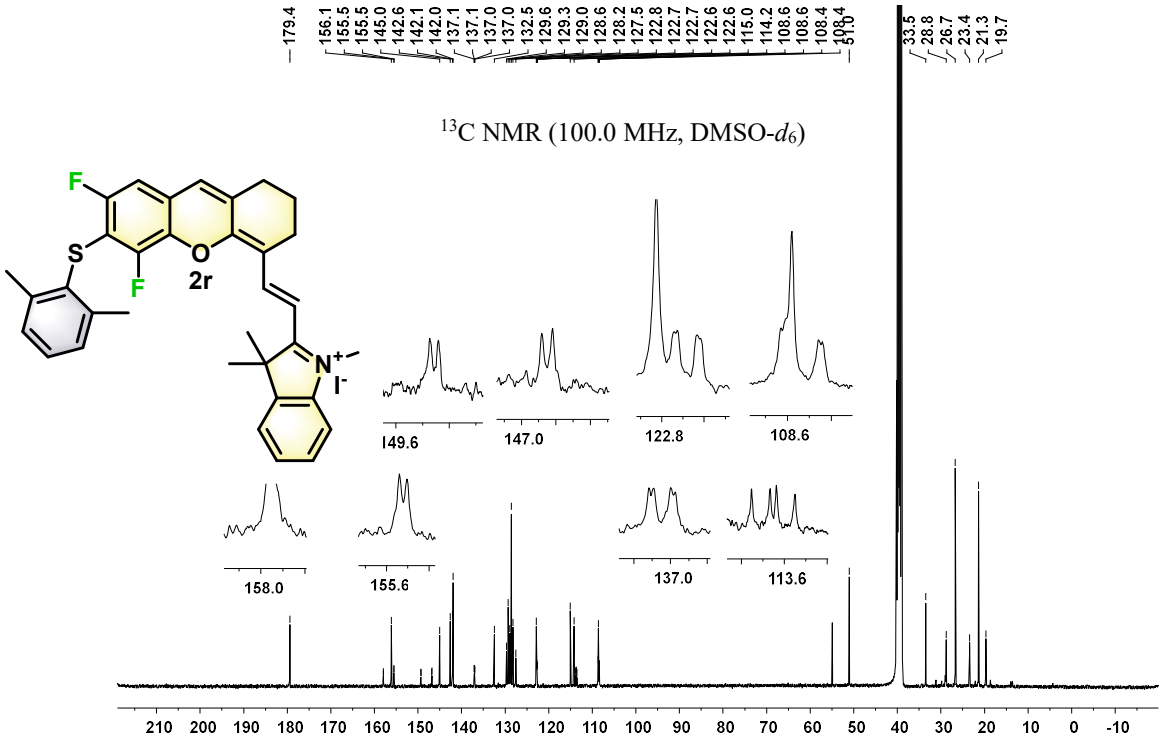
^{19}F NMR (376.5 MHz, CD_3OD)


F
HN
O
2q
F
N+
I-
^{13}C NMR (100.0 MHz, CD$_3$OD)
144.8
144.8
152.2
144.8
154.6
140.4
125.5
117.6
109.6

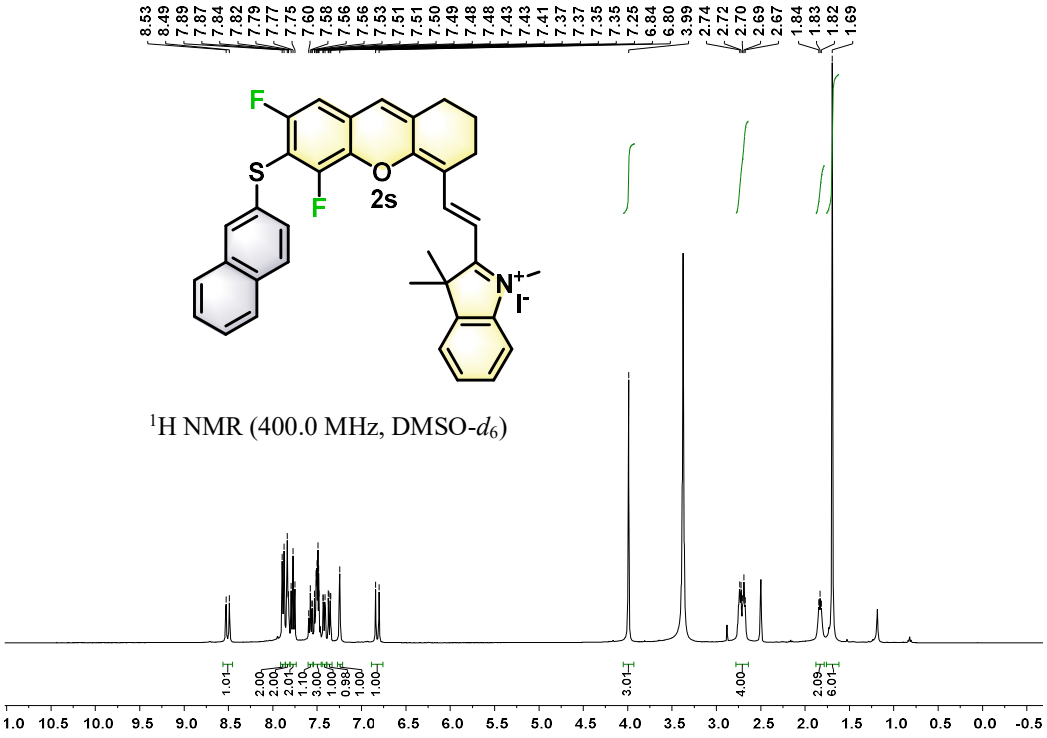

F
S
O
2r
F
N+
I-
^{1}H NMR (400.0 MHz, CD$_3$OD)



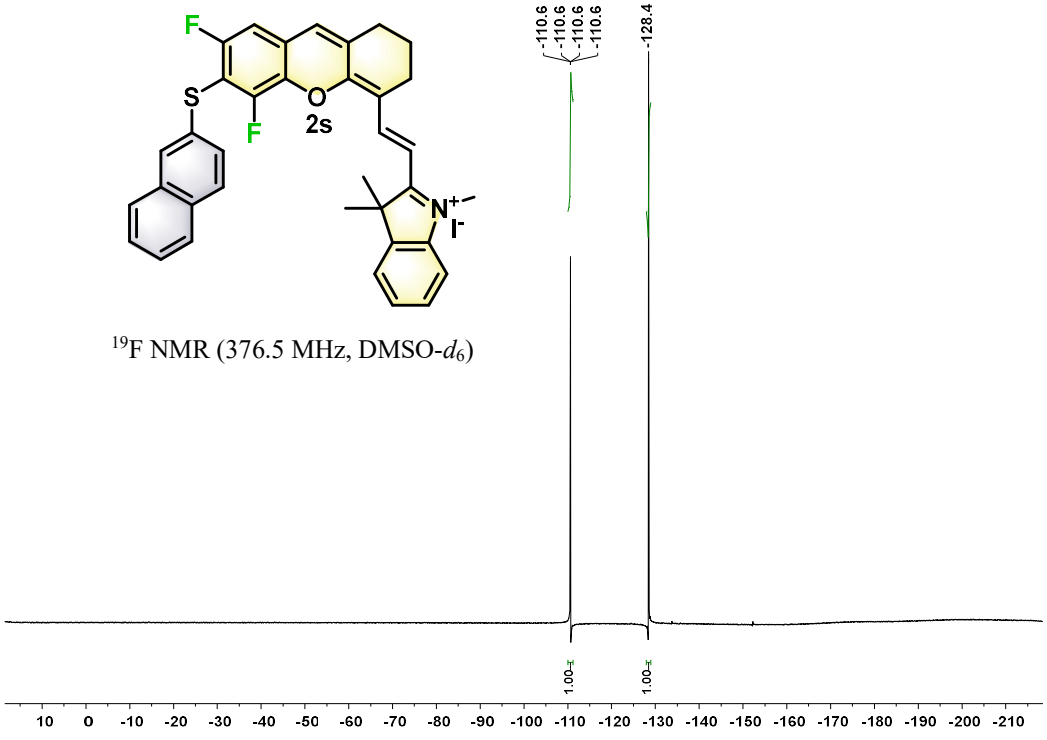
^{19}F NMR (376.5 MHz, DMSO-d_6)



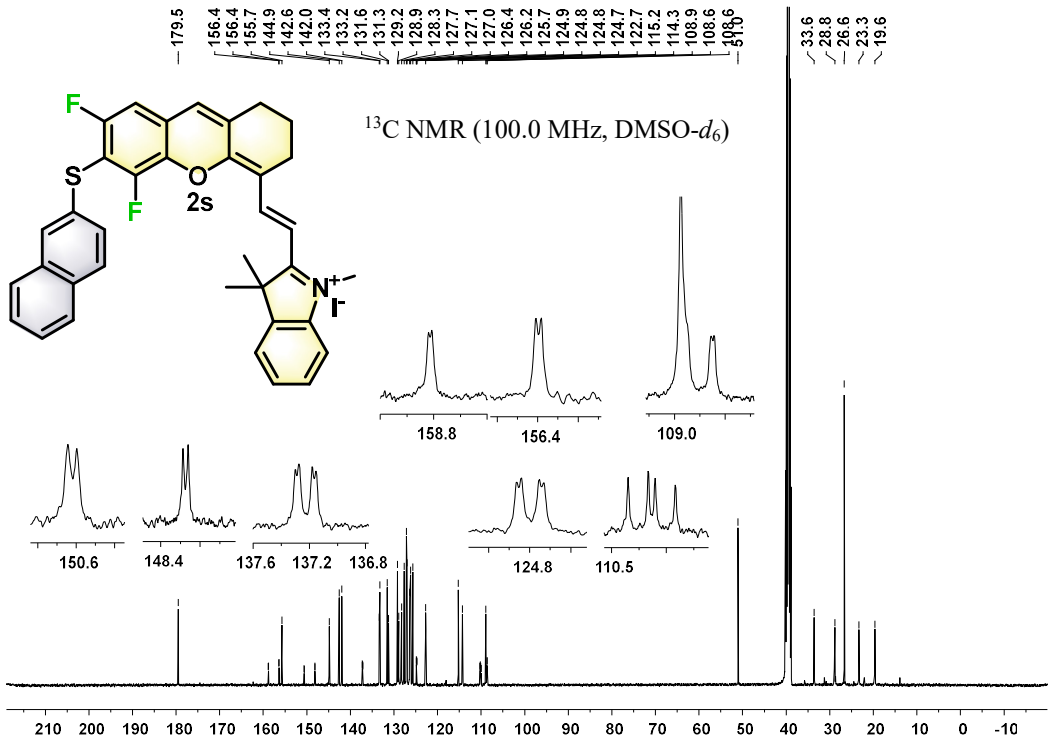
^{13}C NMR (100.0 MHz, DMSO-d_6)



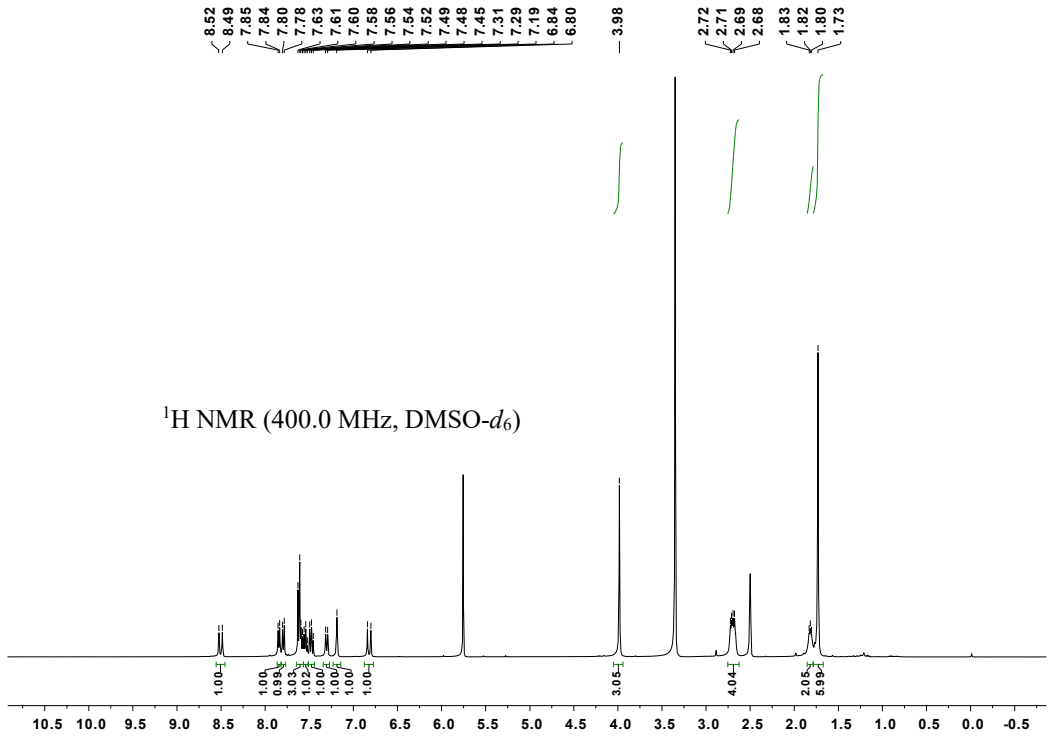
^{1}H NMR (400.0 MHz, DMSO-d_6)



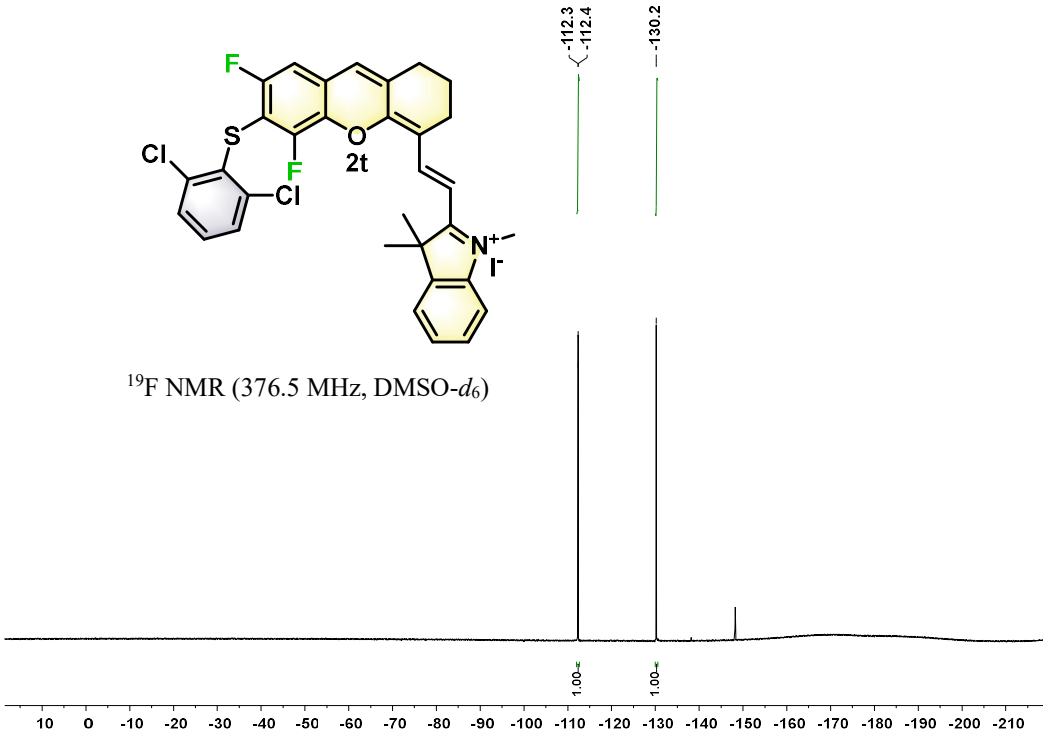
^{19}F NMR (376.5 MHz, DMSO-d_6)



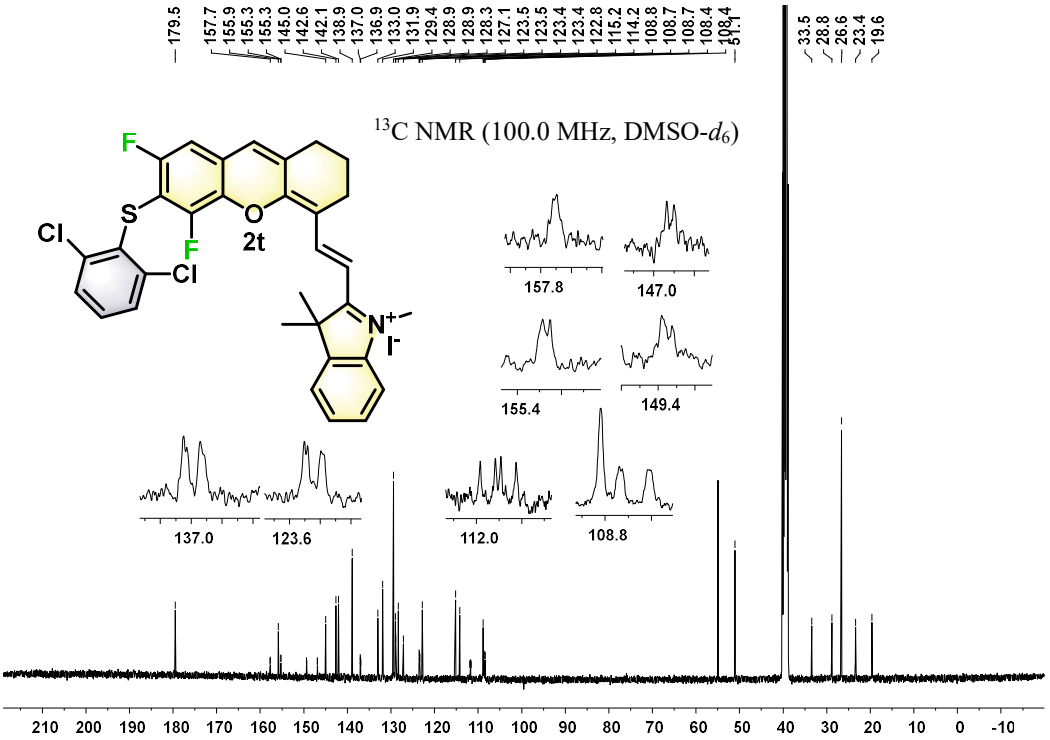
^{13}C NMR (100.0 MHz, DMSO-d_6)



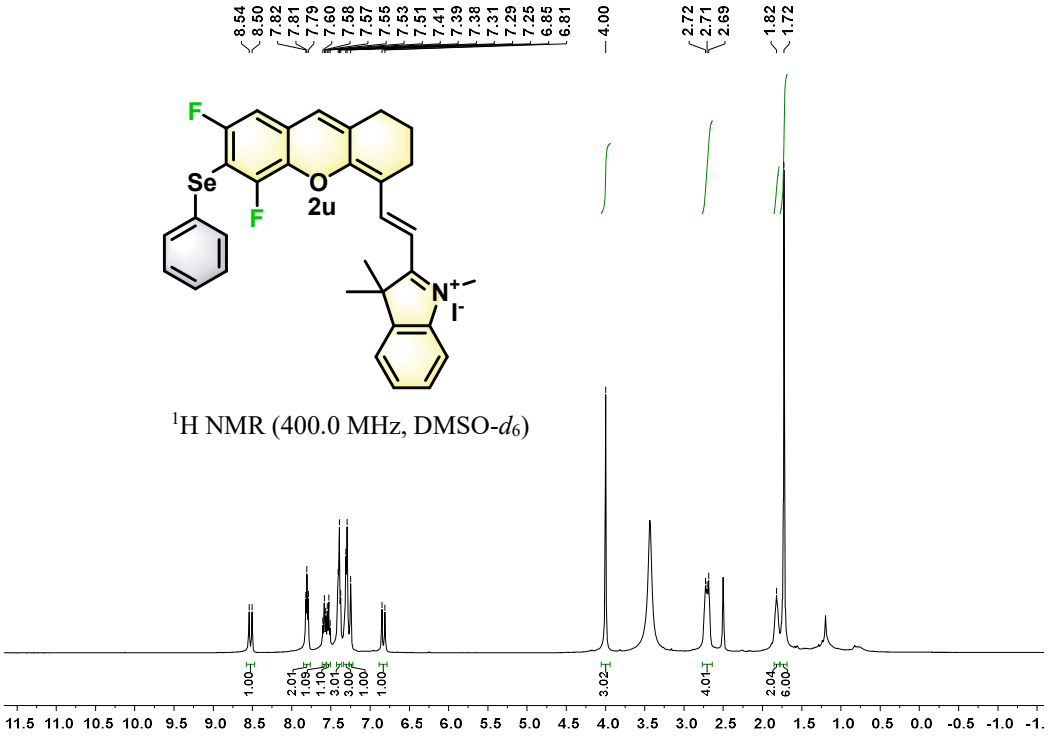
^{1}H NMR (400.0 MHz, DMSO-d_6)



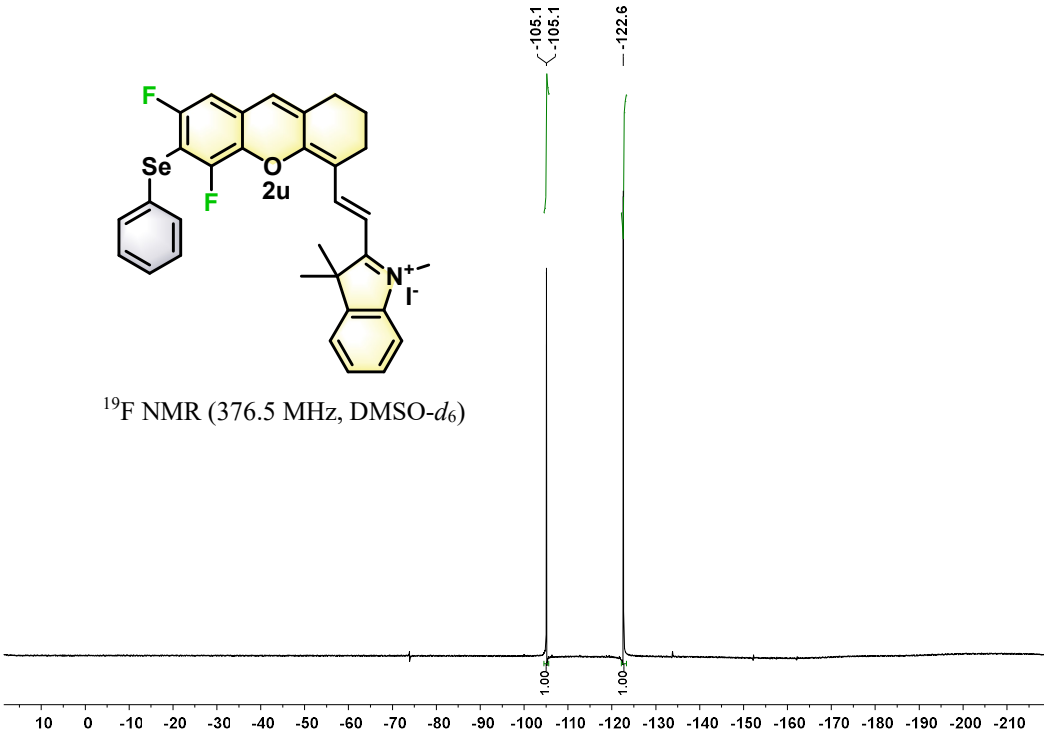
^{19}F NMR (376.5 MHz, DMSO-d_6)



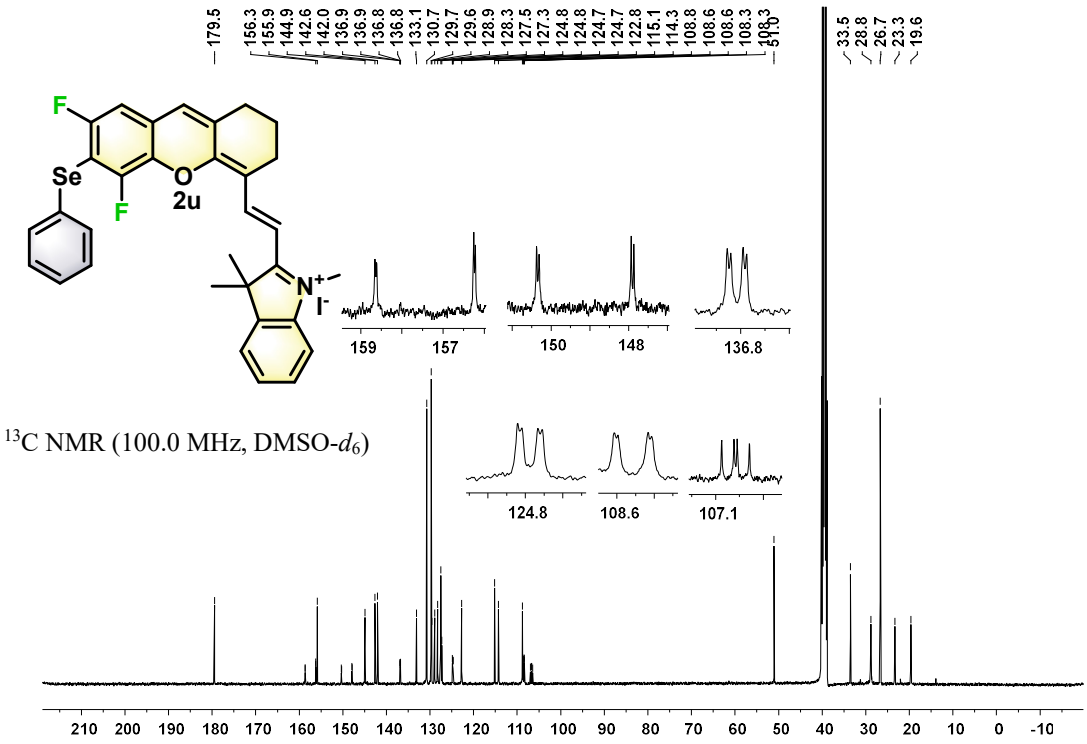
^{13}C NMR (100.0 MHz, DMSO-d_6)



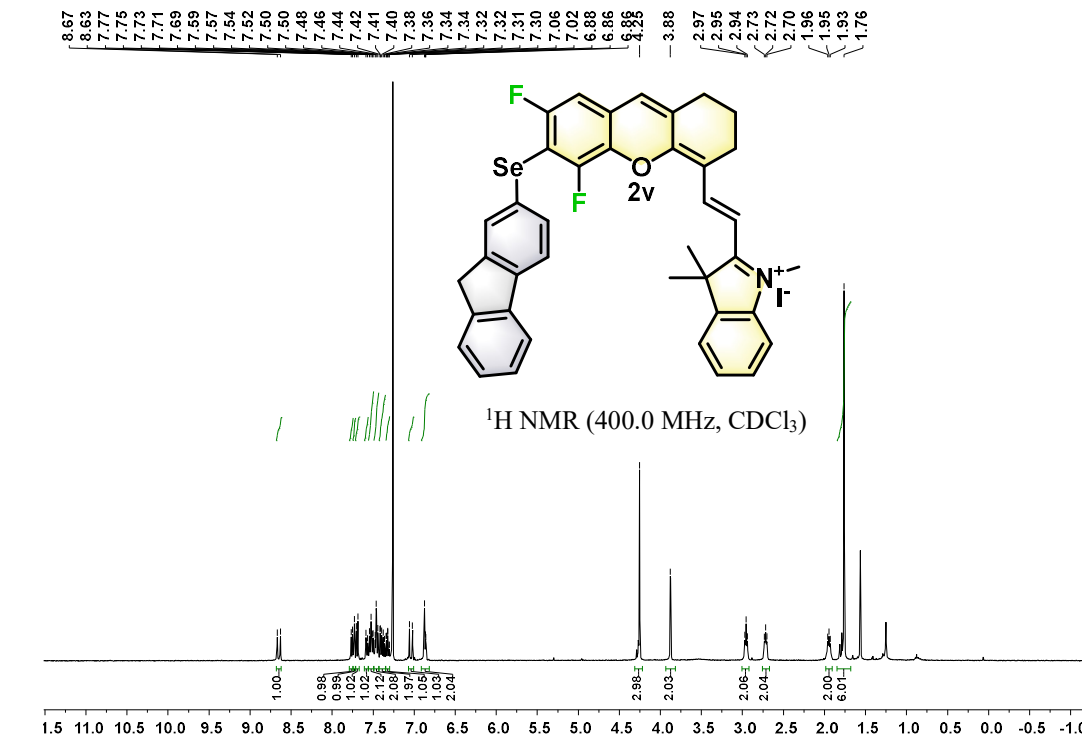
^{1}H NMR (400.0 MHz, DMSO-d_6)



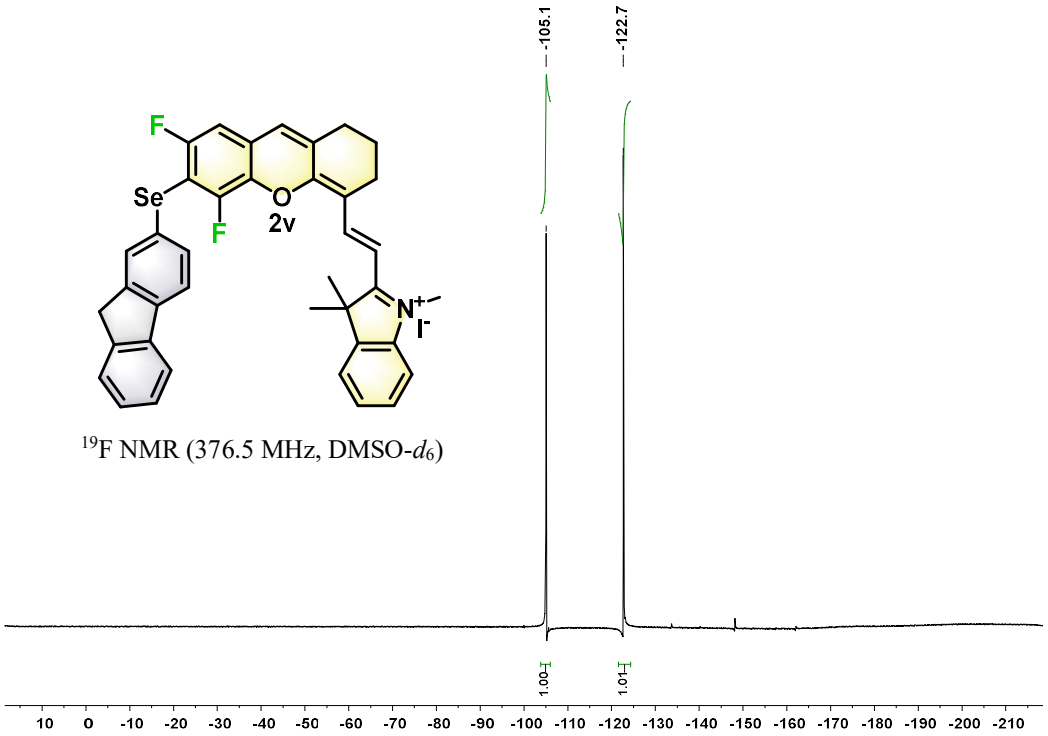
^{19}F NMR (376.5 MHz, DMSO-d_6)



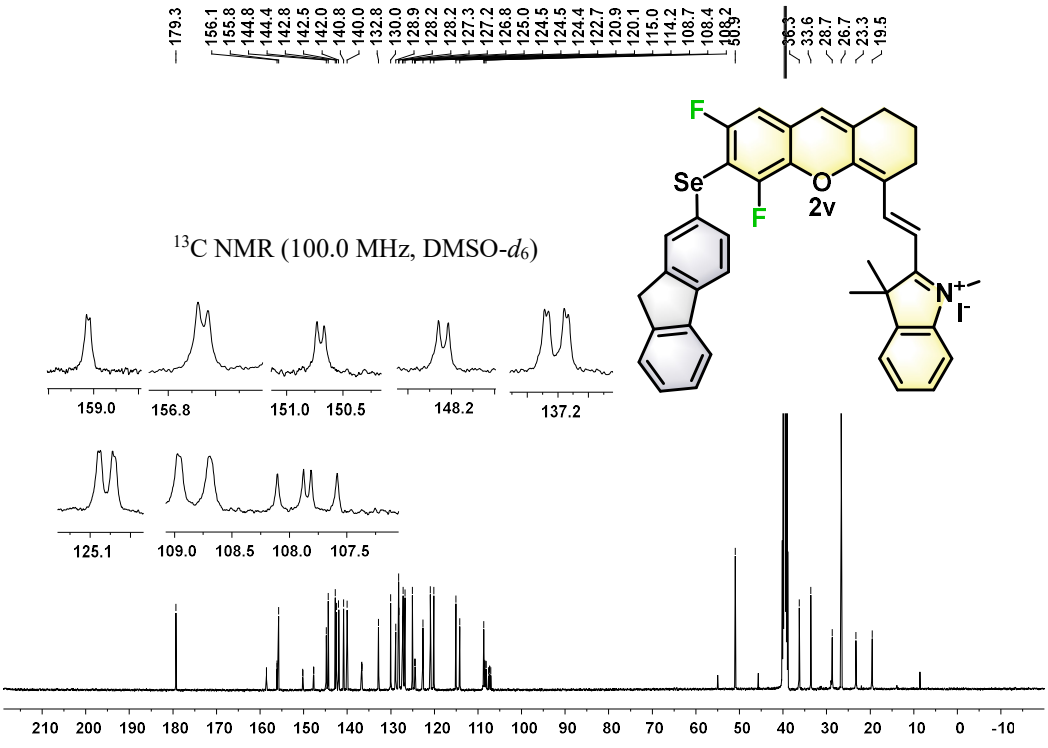
^{13}C NMR (100.0 MHz, DMSO-d_6)



^{1}H NMR (400.0 MHz, $CDCl_3$)



^{19}F NMR (376.5 MHz, DMSO-d_6)

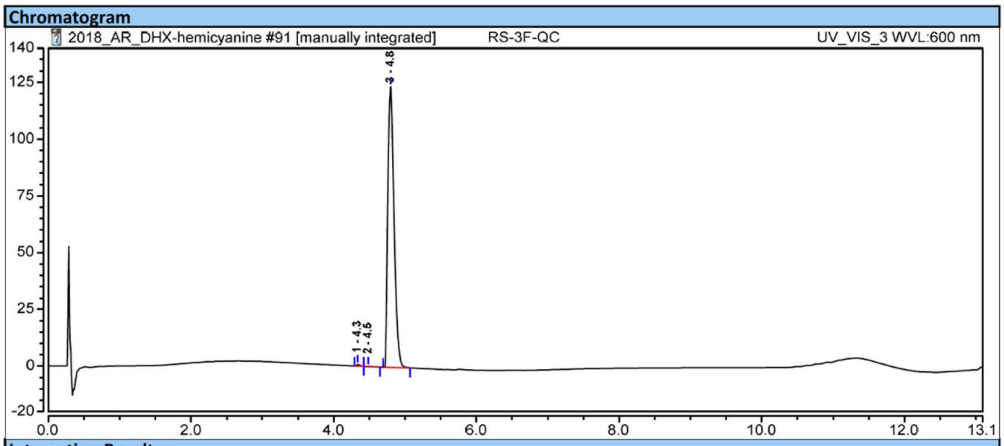


^{13}C NMR (100.0 MHz, DMSO-d_6)

6. High-performance liquid chromatography (HPLC) separations

The following chromatographic system was used for the analytical experiments: *System A*: RP-HPLC (Phenomenex Kinetex C_{18} column, 2.6 µm, 2.1 × 50 mm) with CH_3CN (+ 0.1% FA) and 0.1% aq. formic acid (aq. FA, pH 2.5) as eluents [5% CH_3CN (0.1 min) followed by linear gradient from 5% to 100% CH_3CN (5 min), then 100% CH_3CN (4 min)] at a flow rate of 0.5 mL/min. UV-visible detection was achieved at 220, 260, 600 and 700 nm (+ diode array detection in the range 220-800 nm). Low resolution ESI-MS detection in the positive mode (full scan, 100-1500 a.m.u., data type: centroid, needle voltage: 3.0 kV, probe temperature: 350 °C, cone voltage: 75 V and scan time: 1 s).

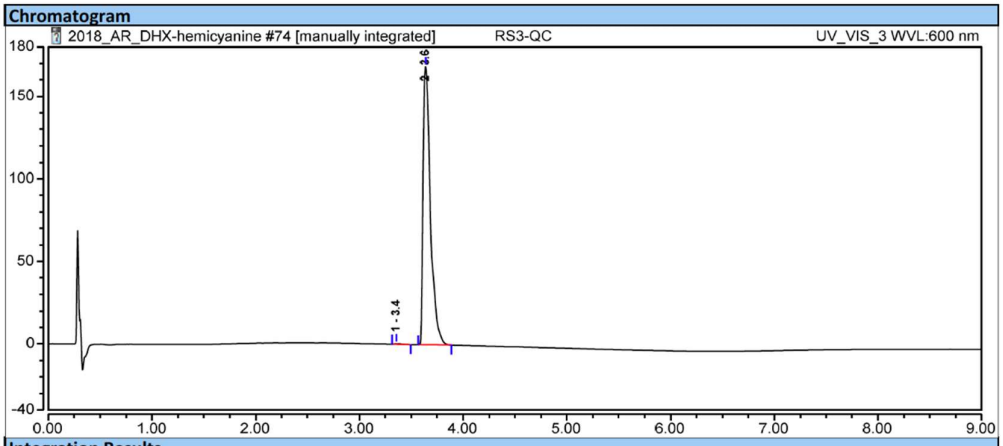
*RP-HPLC elution profile of **1** (system A, detection at 600 nm)*



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		4.3	0.041	0.738	0.32	0.59	n.a.
2		4.5	0.008	0.133	0.07	0.11	n.a.
3		4.8	12.449	123.715	99.61	99.30	n.a.
Total:			**12.498**	**124.586**	**100.00**	**100.00**	

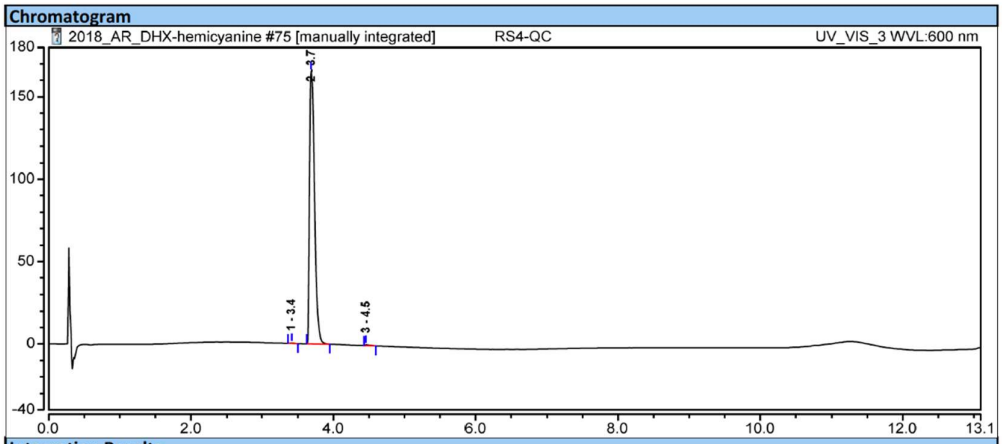
*RP-HPLC elution profile of **2l** (system A, detection at 600 nm)*



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		3.4	0.034	0.395	0.24	0.23	n.a.
2		3.6	13.730	168.507	99.76	99.77	n.a.
Total:			**13.763**	**168.902**	**100.00**	**100.00**	

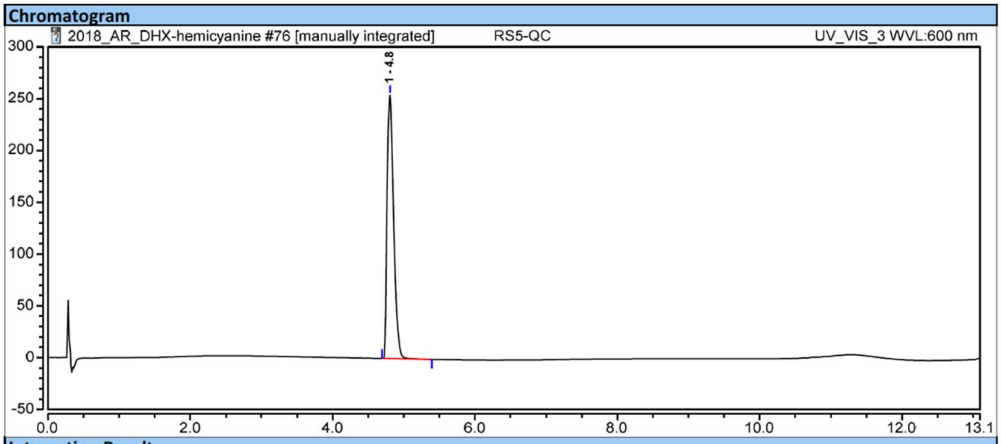
*RP-HPLC elution profile of **2m** (system A, detection at 600 nm)*



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		3.4	0.021	0.301	0.15	0.18	n.a.
2		3.7	13.535	165.649	99.55	99.50	n.a.
3		4.5	0.041	0.523	0.30	0.31	n.a.
Total:			**13.597**	**166.473**	**100.00**	**100.00**	

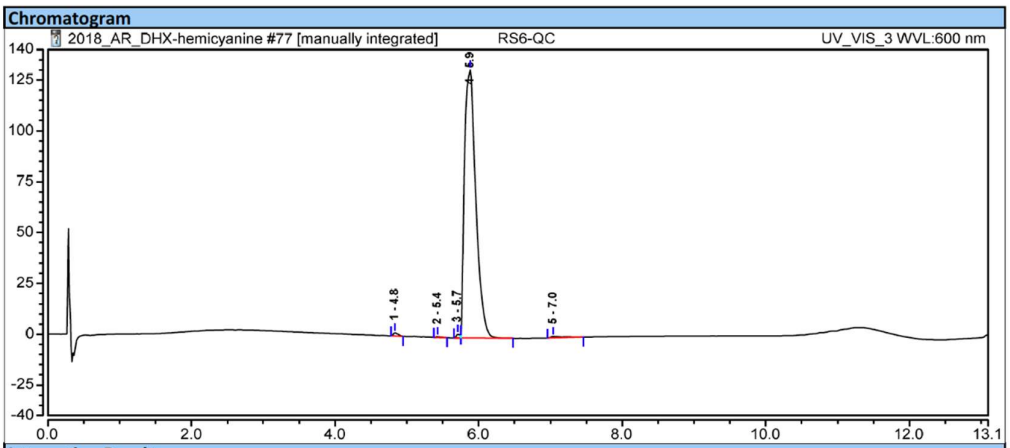
*RP-HPLC elution profile of **8** (system A, detection at 600 nm)*



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		4.8	27.178	254.323	100.00	100.00	n.a.
Total:			**27.178**	**254.323**	**100.00**	**100.00**	

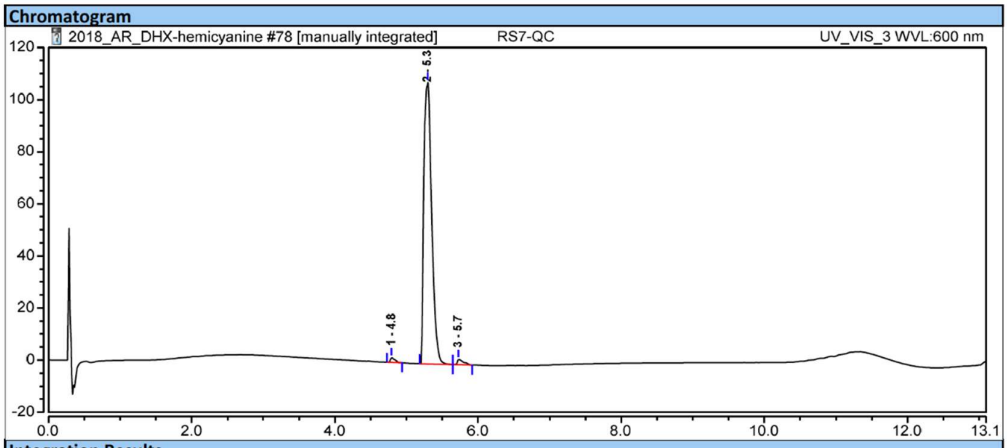
*RP-HPLC elution profile of **2i** (system A, detection at 600 nm)*



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		4.8	0.114	1.662	0.47	1.22	n.a.
2		5.4	0.034	0.431	0.14	0.32	n.a.
3		5.7	0.110	1.836	0.45	1.34	n.a.
4		5.9	23.987	131.854	98.33	96.58	n.a.
5		7.0	0.148	0.744	0.61	0.55	n.a.
Total:			**24.394**	**136.527**	**100.00**	**100.00**	

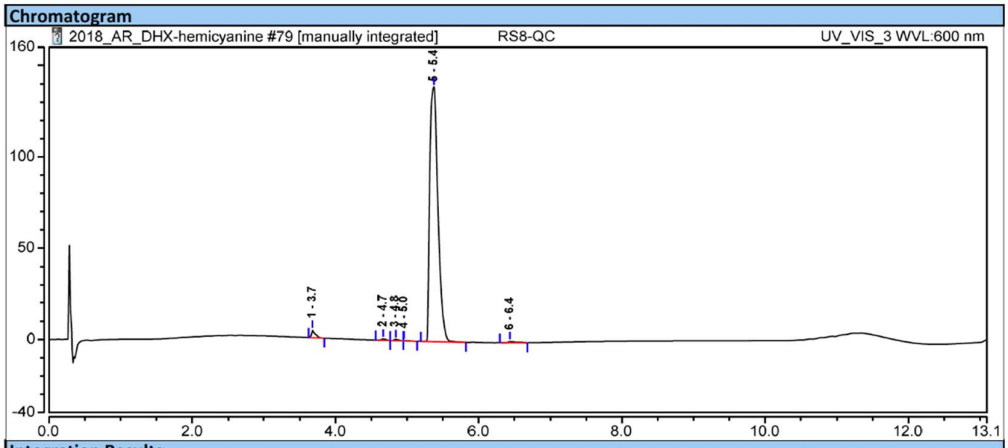
*RP-HPLC elution profile of **2u** (system A, detection at 600 nm)*



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		4.8	0.127	1.876	0.91	1.67	n.a.
2		5.3	13.651	108.165	97.63	96.50	n.a.
3		5.7	0.204	2.043	1.46	1.82	n.a.
Total:			**13.982**	**112.084**	**100.00**	**100.00**	

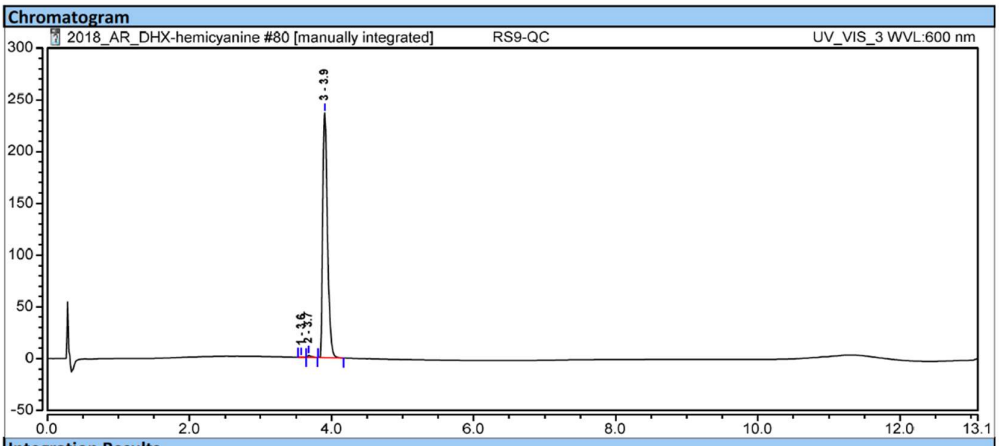
*RP-HPLC elution profile of **2n** (system A, detection at 600 nm)*



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		3.7	0.243	4.096	1.29	2.80	n.a.
2		4.7	0.056	0.814	0.30	0.56	n.a.
3		4.8	0.055	0.760	0.29	0.52	n.a.
4		5.0	0.023	0.324	0.12	0.22	n.a.
5		5.4	18.358	139.664	97.50	95.42	n.a.
6		6.4	0.094	0.706	0.50	0.48	n.a.
Total:			**18.829**	**146.365**	**100.00**	**100.00**	

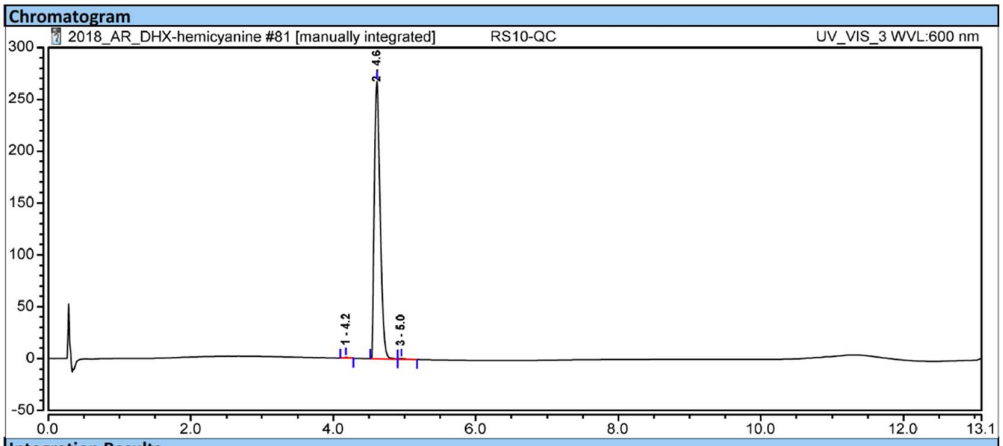
*RP-HPLC elution profile of **2o** (system A, detection at 600 nm)*



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		3.6	0.011	0.198	0.06	0.08	n.a.
2		3.7	0.115	2.132	0.62	0.89	n.a.
3		3.9	18.538	236.713	99.32	99.03	n.a.
Total:			**18.665**	**239.043**	**100.00**	**100.00**	

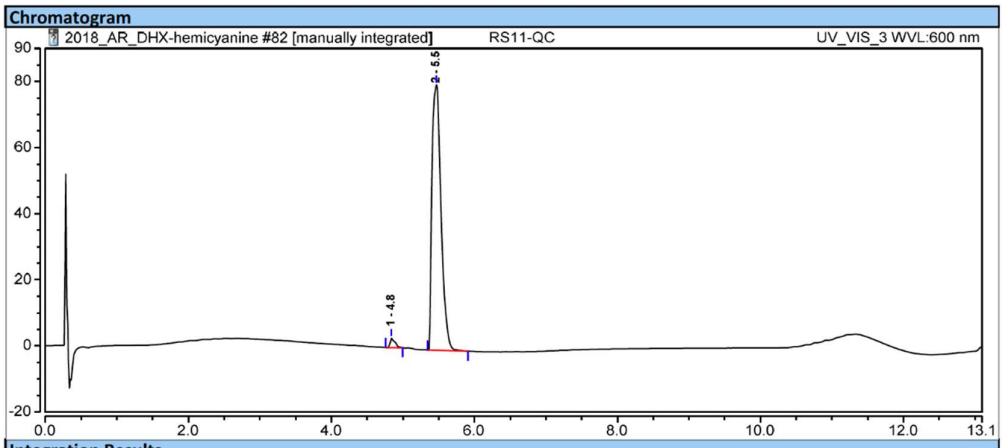
*RP-HPLC elution profile of **2d** (system A, detection at 600 nm)*



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		4.2	0.058	0.795	0.23	0.30	n.a.
2		4.6	25.139	267.624	99.43	99.35	n.a.
3		5.0	0.087	0.949	0.34	0.35	n.a.
Total:			**25.284**	**269.369**	**100.00**	**100.00**	

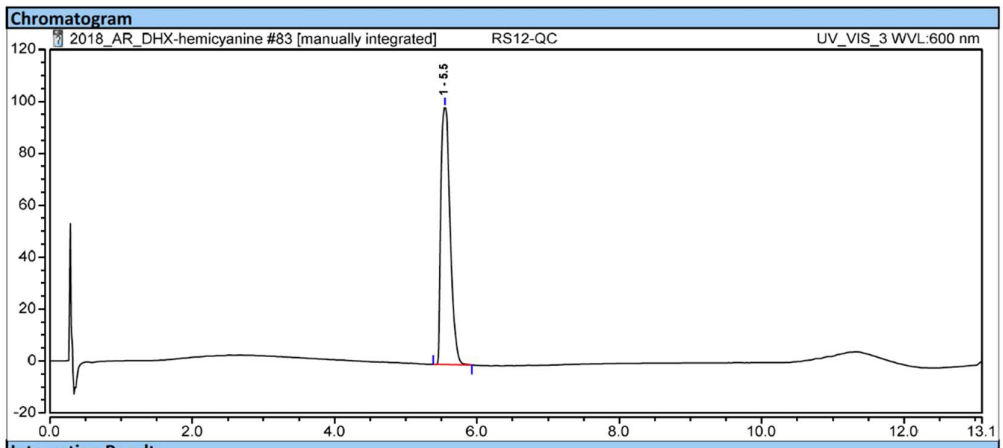
*RP-HPLC elution profile of **2e** (system A, detection at 600 nm)*



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		4.8	0.224	2.856	1.87	3.43	n.a.
2		5.5	11.724	80.331	98.13	96.57	n.a.
Total:			**11.948**	**83.187**	**100.00**	**100.00**	

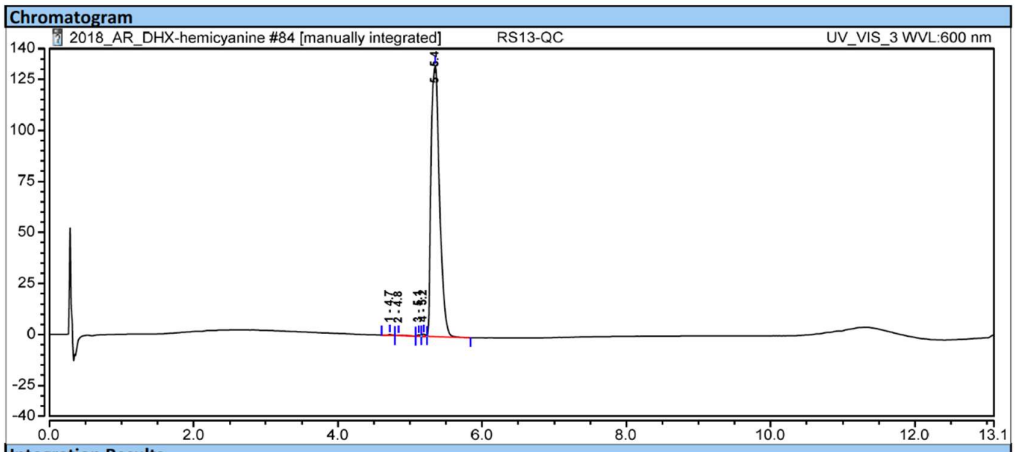
*RP-HPLC elution profile of **2g** (system A, detection at 600 nm)*



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		5.5	14.849	99.092	100.00	100.00	n.a.
Total:			**14.849**	**99.092**	**100.00**	**100.00**	

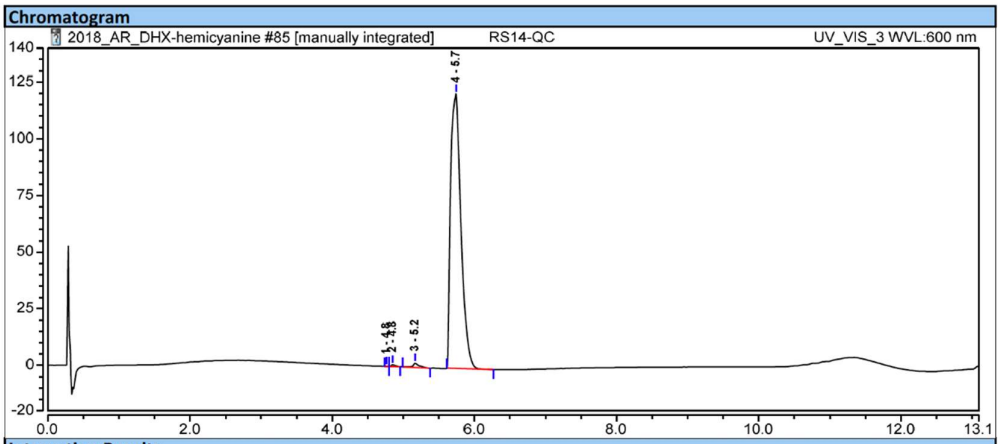
*RP-HPLC elution profile of **2a** (system A, detection at 600 nm)*



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		4.7	0.028	0.478	0.15	0.35	n.a.
2		4.8	0.030	0.165	0.16	0.12	n.a.
3		5.1	0.036	0.704	0.20	0.52	n.a.
4		5.2	0.068	1.156	0.37	0.86	n.a.
5		5.4	18.003	132.650	99.11	98.15	n.a.
Total:			**18.163**	**135.153**	**100.00**	**100.00**	

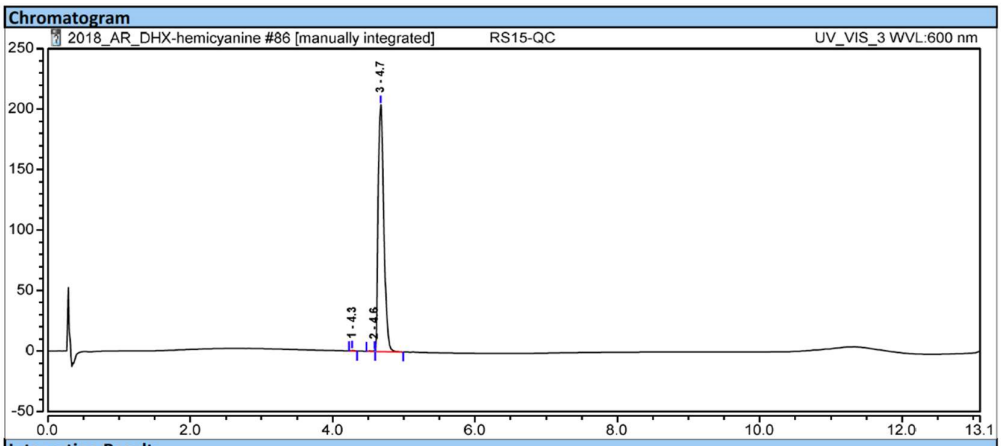
*RP-HPLC elution profile of **2k** (system A, detection at 600 nm)*



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		4.8	0.007	0.178	0.03	0.14	n.a.
2		4.8	0.059	0.832	0.29	0.67	n.a.
3		5.2	0.193	1.826	0.94	1.47	n.a.
4		5.7	20.342	121.196	98.74	97.71	n.a.
Total:			**20.600**	**124.033**	**100.00**	**100.00**	

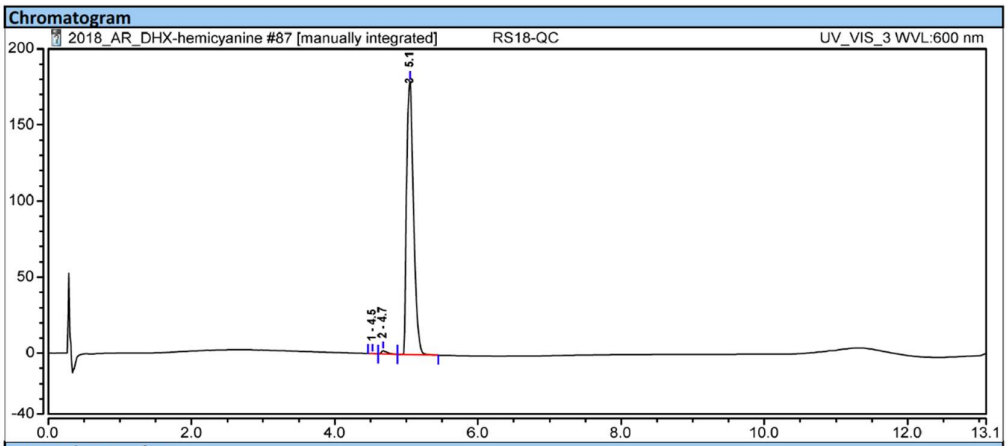
*RP-HPLC elution profile of **2b** (system A, detection at 600 nm)*



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		4.3	0.025	0.436	0.13	0.21	n.a.
2		4.6	0.036	0.534	0.19	0.26	n.a.
3		4.7	18.696	204.097	99.67	99.53	n.a.
Total:			**18.757**	**205.066**	**100.00**	**100.00**	

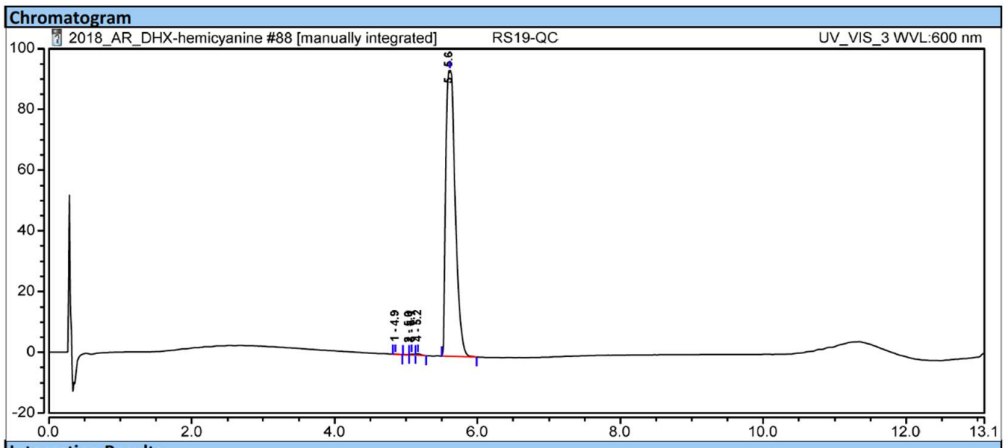
*RP-HPLC elution profile of **2p** (system A, detection at 600 nm)*



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		4.5	0.013	0.242	0.07	0.13	n.a.
2		4.7	0.195	2.195	0.97	1.21	n.a.
3		5.1	19.974	179.701	98.97	98.66	n.a.
Total:			**20.183**	**182.139**	**100.00**	**100.00**	

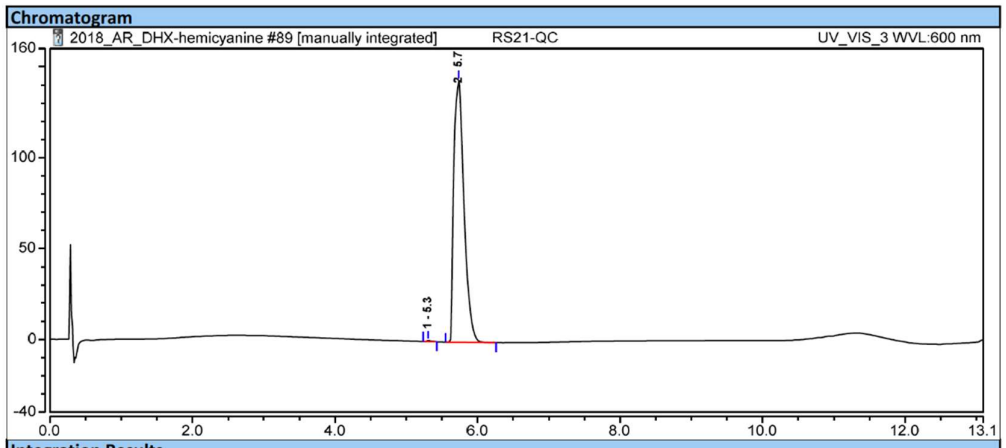
*RP-HPLC elution profile of **2h** (system A, detection at 600 nm)*



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		4.9	0.007	0.119	0.05	0.12	n.a.
2		5.0	0.005	0.122	0.03	0.13	n.a.
3		5.1	0.022	0.324	0.15	0.34	n.a.
4		5.2	0.043	0.545	0.30	0.57	n.a.
5		5.6	14.500	94.327	99.47	98.84	n.a.
Total:			**14.577**	**95.437**	**100.00**	**100.00**	

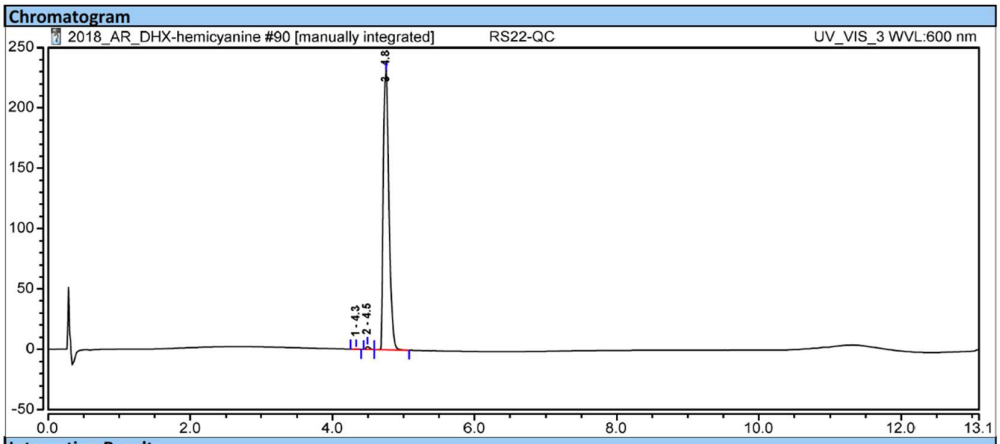
*RP-HPLC elution profile of **2c** (system A, detection at 600 nm)*



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		5.3	0.047	0.598	0.20	0.41	n.a.
2		5.7	23.767	143.876	99.80	99.59	n.a.
Total:			**23.814**	**144.474**	**100.00**	**100.00**	

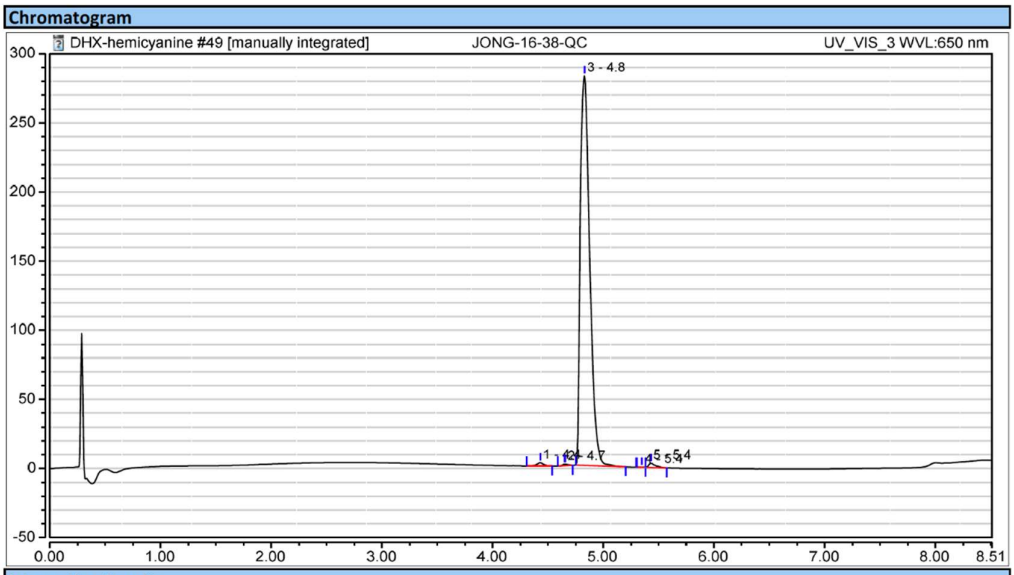
*RP-HPLC elution profile of **2j** (system A, detection at 600 nm)*



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		4.3	0.012	0.242	0.06	0.10	n.a.
2		4.5	0.138	2.437	0.65	1.05	n.a.
3		4.8	21.206	230.417	99.30	98.85	n.a.
Total:			**21.356**	**233.097**	**100.00**	**100.00**	

*RP-HPLC elution profile of **2f** (system A, detection at 600 nm)*

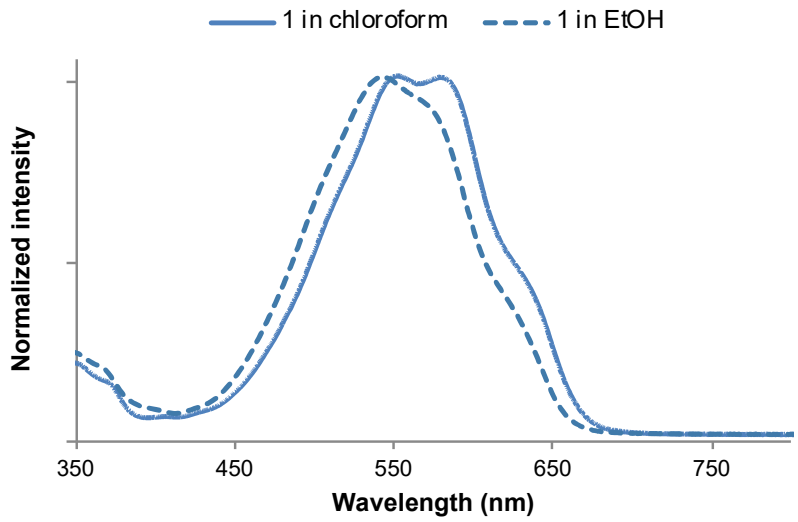


Integration Results

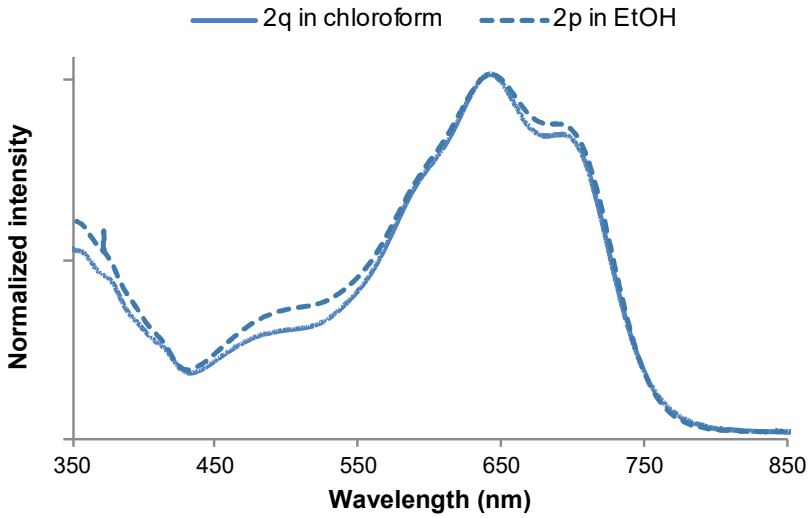
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		4.430	0.180	2.476	0.64	0.86	n.a.
2		4.653	0.063	1.131	0.22	0.39	n.a.
3		4.830	27.706	281.776	98.33	97.60	n.a.
4		5.350	0.009	0.170	0.03	0.06	n.a.
5		5.430	0.218	3.150	0.77	1.09	n.a.
Total:			**28.175**	**288.704**	**100.00**	**100.00**	

7. UV-visible absorption spectra of compound 1 and non-fluorescent 5',7'-difluoro-DHX-hemicyanine fused dyes

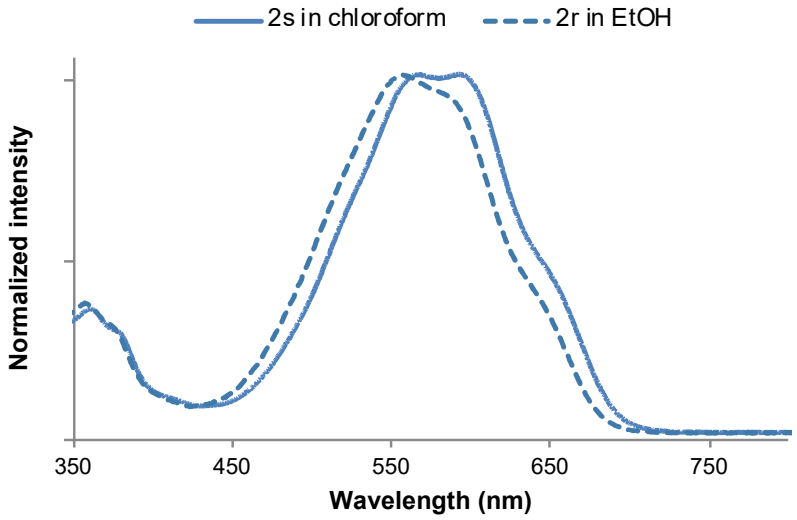
*Compound **1***



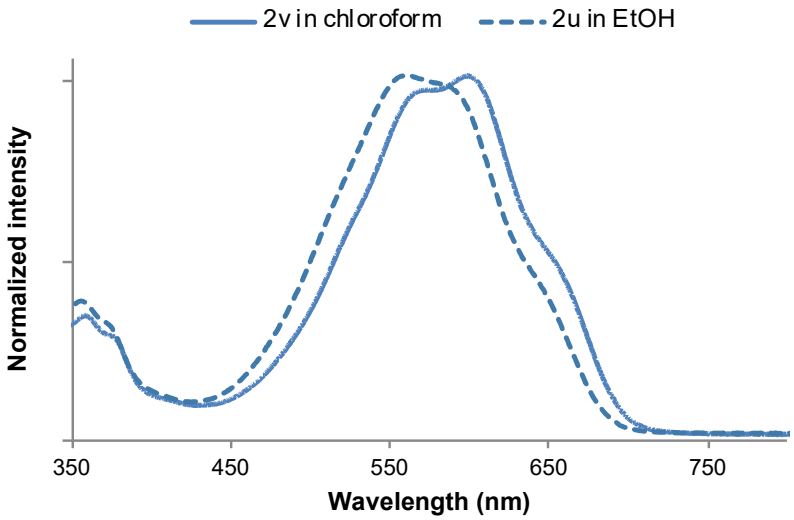
*Compound **2q***



Compound ***2s***



Compound ***2v***

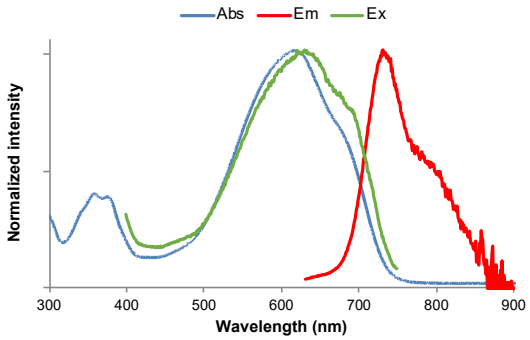


8. Absorption, excitation and emission spectra of selected 5',7'-difluoro-6'-amino-DHX-hemicyanine fused dyes

Please note: All emission spectra are corrected until 850 nm, which explains the artefact observed at this wavelength. Molar extinction coefficients were determined by recording UV-vis spectra using solutions of the fluorophores in the 10^{-6}-10^{-5} M range. More diluted solutions in the range 10^{-7}-10^{-6} M were used for the fluorescence Ex/Em spectra required to determine their quantum yields (QY).

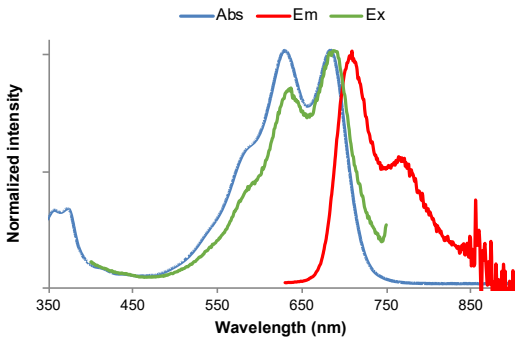
*Compound **2a***

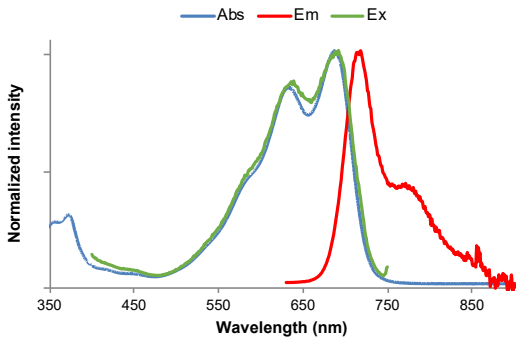
EtOH, 25 °C, excitation at 615 nm, emission at 760 nm.



*Compound **2d***

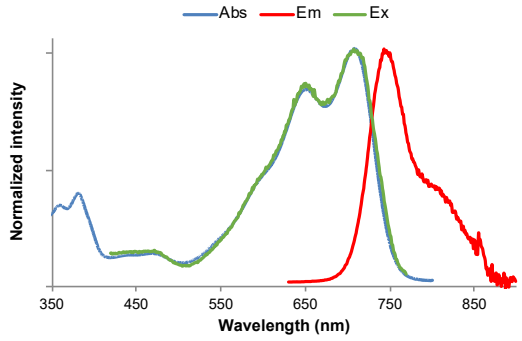
$CHCl_3$ (left) & EtOH (right), 25 °C, excitation at 615 nm, emission at 760 nm.





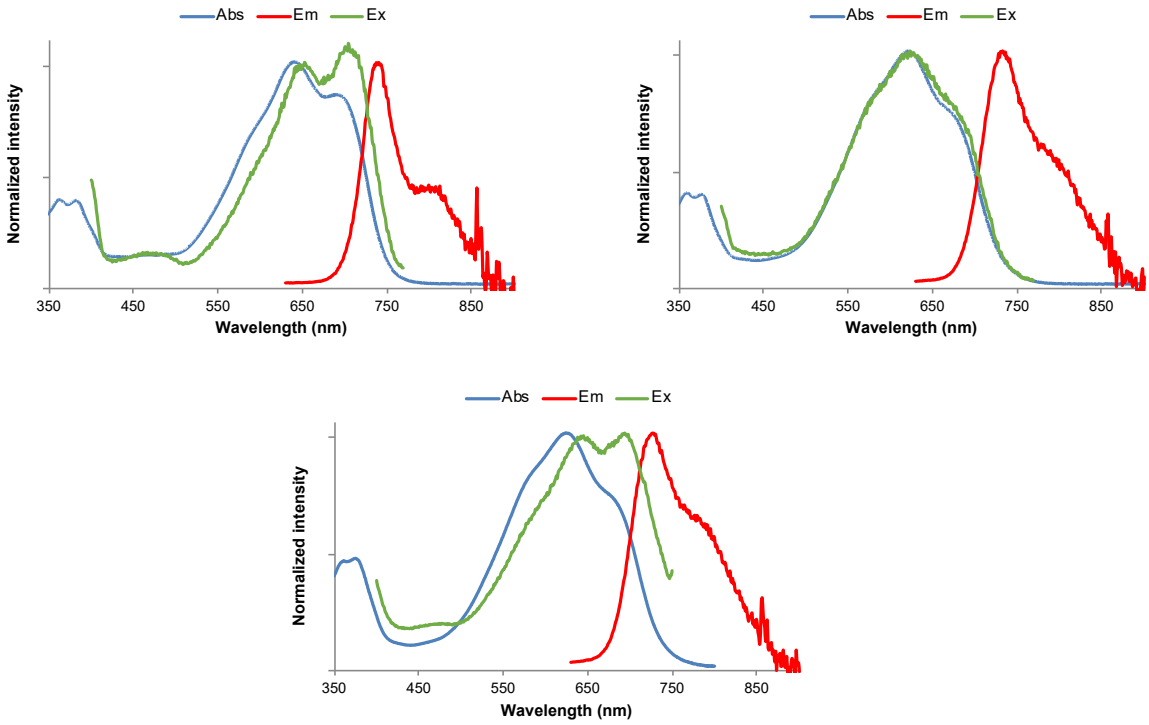
*Compound **2e***

EtOH, 25 °C, excitation at 615 nm, emission at 760 nm.



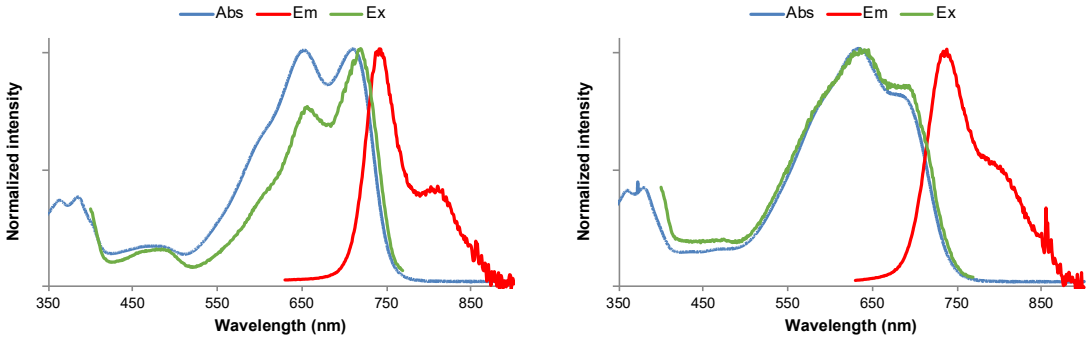
Compound ***2g***

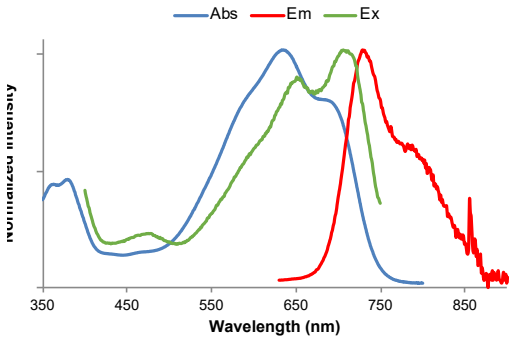
$CHCl_3$ (top left), EtOH (top right) & PBS + 5% BSA (bottom), 25 °C, excitation at 615 nm, emission at 800 nm (for Ex spectra in $CHCl_3$ & EtOH), emission at 760 nm (for Ex spectrum in PBS + 5% BSA).



Compound ***2k***

$CHCl_3$ (top left), EtOH (top right) & PBS + 5% BSA (bottom), 25 °C, excitation at 615 nm, emission at 800 nm (for Ex spectra in $CHCl_3$ & EtOH), emission at 760 nm (for Ex spectrum in PBS + 5% BSA).





*Compound **8***

$CHCl_3$ (left) & EtOH (right), 25 °C, excitation at 615 nm, emission at 760 nm.