Supporting Information

Development of [^{18}F]Maleimide-Based Glycogen Synthase Kinase-3β Ligands for Positron Emission Tomography Imaging

Kongzhen Hu,[a] Debasis Patnaik,[b] Thomas Lee Collier,[c] Katarzyna N. Lee,[a] Han Gao,[a] Matthew Swoyer,[a] Benjamin H. Rotstein,[c] Hema S. Krishnan,[c] Steven H. Liang,[c] Jin Wang,[a] pZhiqiang Yan,[e] Jacob Hooker,[d] Neil Vasdev,[c] Stephen J. Haggarty,[b] Ming-Yu Ngai*[a]

[a] Department of Chemistry, Stony Brook University, Stony Brook, NY 11794-3400, Institute of Chemical Biology and Drug Discovery, Stony Brook University, Stony Brook, New York 11794-3400

[b] Chemical Neurobiology Laboratory, Center for Human Genetic Research, Departments of Neurology & Psychiatry, Massachusetts General Hospital and Harvard Medical School, Boston MA 02114 USA

[c] Gordon Center for Medical Imaging & Nuclear Medicine and Molecular Imaging, Massachusetts General Hospital & Department of Radiology, Harvard Medical School, Boston, MA, 02114, USA

[d] Division of Nuclear Medicine and Molecular Imaging, Department of Radiology, Massachusetts General Hospital, Boston, Massachusetts 02114, USA. Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital and Harvard Medical School, Charlestown, Massachusetts 02129, USA

[e] State Key Laboratory of Electroanalytical Chemistry Changchun Institute of Applied Chemistry, Chinese Academy of Sciences, Changchun 130022, Jilin, China

E-mail: ming-yu.ngai@stonybrook.edu

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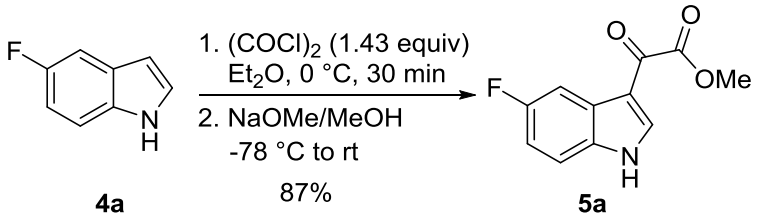
Materials and Methods

All air- and moisture-insensitive reactions were carried out under an ambient atmosphere, magnetically stirred, and monitored by thin layer chromatography (TLC) using Agela Technologies TLC plates pre-coated with 250 μm thickness silica gel 60 F254 plates and visualized by fluorescence quenching under UV light. Flash chromatography was performed on SiliaFlash® Silica Gel 40-63μm 60Å particle size using a forced flow of eluent at 0.3–0.5 bar pressure.[1] All air- and moisture-sensitive manipulations were performed using oven-dried glassware, including standard Schlenk and glovebox techniques under an atmosphere of nitrogen. Diethyl ether and THF were distilled from deep purple sodium benzophenone ketyl. Methylene chloride, chloroform and acetonitrile were dried over CaH_2 and distilled. Methylene chloride was degassed *via* three freeze-pump-thaw cycles. All other chemicals were used as received. All deuterated solvents were purchased from Cambridge Isotope Laboratories. NMR spectra were recorded on either a Bruker Ascend 700 spectrometer operating at 700 MHz for ^{1}H acquisitions and 175 MHz for ^{13}C acquisitions, a Bruker 500 Advance spectrometer operating at 500 MHz and 125 MHz for ^{1}H and ^{13}C acquisitions, respectively, a Bruker 400 Nanobay spectrometer operating at 400 MHz, 100 MHz, and 376 MHz for ^{1}H, ^{13}C, and ^{19}F acquisitions, respectively. Chemical shifts were referenced to the residual proton solvent peaks (^{1}H: $CDCl_3$, δ 7.26; $(CD_3)_2SO$, δ 2.50; CD_3OD, δ 3.31; CD_3CN, δ 1.94), solvent ^{13}C signals ($CDCl_3$, δ 77.16; $(CD_3)_2SO$, δ 39.52; CD_3OD, δ 49.00),[2] dissolved or external neat $PhCF_3$ (^{19}F, δ –63.3 relative to $CFCl_3$).[3] Signals are listed in ppm, and multiplicity identified as s = singlet, br = broad, d = doublet, t = triplet, q = quartet, m = multiplet; coupling constants in Hz; integration. High-resolution mass spectra were performed at Mass Spectrometry Services at the Univ. of Illinois at Urbana-Champaign and were obtained using Waters Q-TOF Ultima ESI mass spectrometer. Concentration under reduced pressure was performed by rotary evaporation at 25–30 °C at appropriate pressure. Purified compounds were further dried under high vacuum (0.01–0.05 Torr). Yields refer to purified and spectroscopically pure compounds. GE Tracerlab FX_{FN} synthesis module and Waters QMA cartridge were used for the radiosynthesis of **[^{18}F]10a**.

Experimental data

Methyl 2-(5-fluoro-1*H*-indol-3-yl)-2-oxoacetate (5a)

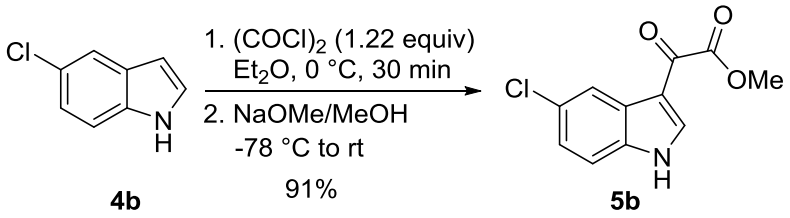


4a **5a**

To a solution of 5-fluoro-1*H*-indole (2.00 g, 14.8 mmol, 1.00 equiv) in Et_2O (20.0 mL, 0.740 M) was added oxalyl chloride (1.80 mL, 21.1 mmol, 1.43 equiv) dropwise at 0 °C. The yellow slurry was stirred at 0 °C for 30 min and then cooled to −78 °C. A solution of NaOMe in MeOH (25%, 8.00 mL) was added to this slurry at the same temperature. The reaction mixture was then allowed to warm up to room temperature, and was quenched by addition of water (10.0 mL). The precipitate was collected by filtration, washed with water and dried to afford the title compound as a yellow solid (2.85 g, 12.9 mmol, 87% yield).

NMR Spectroscopy: ^{1}H NMR (700 MHz, $(CD_3)_2SO$, 25 °C, δ): 12.54 (s,1H), 8.51 (s, 1H), 7.82 (s, 1H), 7.56 (s, 1H), 7.12–7.20 (m, 1H), 3.89 (s, 3H). ^{13}C NMR (175 MHz, $(CD_3)_2SO$, 25 °C, δ): 178.4, 163.6, 159.2 (d, J = 232.8 Hz), 139.7, 133.3, 126.3 (d, J = 10.5 Hz), 114.2 (d, J = 10.5 Hz), 112.5 (d, J = 5.3 Hz), 112.0 (d, J = 26.3 Hz), 106.2 (d, J = 24.5 Hz), 52.6. The ^{1}H NMR data were in good agreement with values reported in the literature.[4]

Methyl 2-(5-chloro-1*H*-indol-3-yl)-2-oxoacetate (5b)

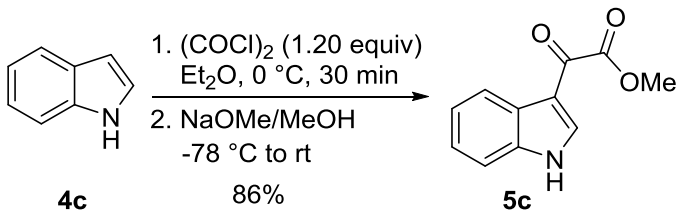


4b **5b**

To a solution of 5-chloro-1*H*-indole (2.80 g, 18.5 mmol, 1.00 equiv) in Et_2O (25.0 mL, 0.740 M) was added oxalyl chloride (1.89 mL, 22.2 mmol, 1.22 equiv) dropwise at 0 °C. The yellow slurry was stirred at 0 °C for 30 min and then cooled to −78 °C. A solution of NaOMe in MeOH (25%, 8.50 mL) was added to this slurry at the same temperature. The reaction mixture was then allowed to warm up to room temperature, and was quenched by addition of water (10.0 mL). The precipitate was collected by filtration, washed with water and dried to afford the title compound as a gray solid (4.00 g, 16.8 mmol, 91% yield).

NMR Spectroscopy: ^{1}H NMR (500 MHz, $(CD_3)_2SO$, 25 °C, δ): 12.71 (s, 1H), 8.52 (d, J = 3.3 Hz, 1H), 8.13 (d, J = 2.1 Hz, 1H), 7.58 (d, J = 8.6 Hz, 1H), 7.32 (dd, J = 2.1, 8.6 Hz, 1H), 3.89 (s, 3H). ^{13}C NMR (125 MHz, $(CD_3)_2SO$, 25 °C, δ): 178.4, 163.4, 139.5, 135.2, 127.5, 126.8, 123.9, 120.2, 114.5, 112.0, 52.6. The ^{1}H NMR data were in good agreement with values reported in the literature.[4]

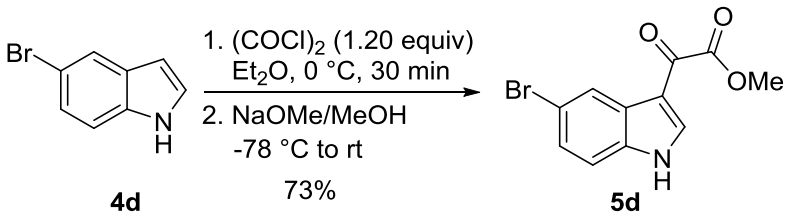
Methyl 2-(1*H*-indol-3-yl)-2-oxoacetate (5c)



To a solution of 1*H*-indole (6.00 g, 51.2 mmol, 1.00 equiv) in Et_2O (60.0 mL, 0.850 M) was added oxalyl chloride (5.27 mL, 61.4 mmol, 1.20 equiv) dropwise at 0 °C. The yellow slurry was stirred at 0 °C for 30 min and then cooled to −78 °C. A solution of NaOMe in MeOH (25%, 23.0 mL) was added to this slurry at the same temperature. The reaction mixture was then allowed to warm up to room temperature, and was quenched by addition of water (40.0 mL). The precipitate was collected by filtration, washed with water and dried to afford the title compound as a gray solid (8.96 g, 44.0 mmol, 86% yield).

NMR Spectroscopy: ^{1}H NMR (700 MHz, $(CD_3)_2SO$, 25 °C, δ): 12.50 (s, 1H), 8.44 (d, J = 3.2 Hz, 1H), 8.16 (d, J = 7.6 Hz, 1H), 7.55 (d, J = 7.7 Hz, 1H), 7.25 – 7.33 (m, 2H), 3.89 (s, 3H). ^{13}C NMR (175 MHz, $(CD_3)_2SO$, 25 °C, δ): 178.7, 164.0, 138.4, 136.7, 125.5, 123.8, 122.9, 121.1, 112.8, 112.4, 52.5. The ^{1}H NMR data were in good agreement with values reported in the literature.[4]

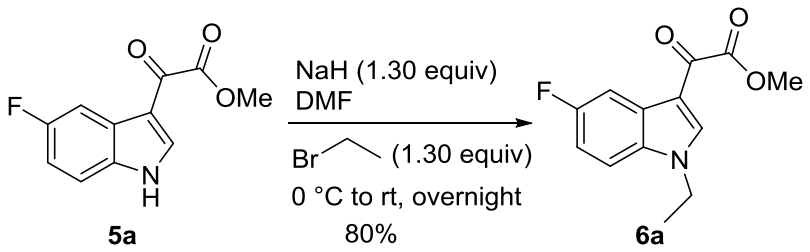
Methyl 2-(5-bromo-1*H*-indol-3-yl)-2-oxoacetate (5d)



To a solution of 5-bromo-1*H*-indole (1. 00 g, 5.10 mmol, 1.00 equiv) in Et_2O (6.00 mL, 0.850 M) was added oxalyl chloride (0.524 mL, 6.12 mmol, 1.20 equiv) dropwise at 0 °C. The yellow slurry was stirred at 0 °C for 30 min and then cooled to −78 °C. A solution of NaOMe in MeOH (25%, 2.34 mL) was added to this slurry at the same temperature. The reaction mixture was then allowed to warm up to room temperature, and was quenched by addition of water (10.0 mL). The precipitate was collected by filtration, washed with water and dried to afford the title compound as a gray solid (1.05 g, 3.72 mmol, 73% yield).

NMR Spectroscopy: ^{1}H NMR (700 MHz, $(CD_3)_2SO$, 25 °C, δ): 12.62 (s, 1H), 8.51 (d, J = 2.2 Hz, 1H), 8.29 (s, 1H), 7.53 (d, J = 8.5 Hz, 1H), 7.43 (d, J = 7.9 Hz, 1H), 3.89 (s, 3H). ^{13}C NMR (175 MHz, $(CD_3)_2SO$, 25 °C, δ): 178.4, 163.4, 139.4, 135.5, 127.4, 126.5, 123.3, 115.6, 114.9, 111.9, 52.6. The ^{1}H NMR data were in good agreement with values reported in the literature.[5]

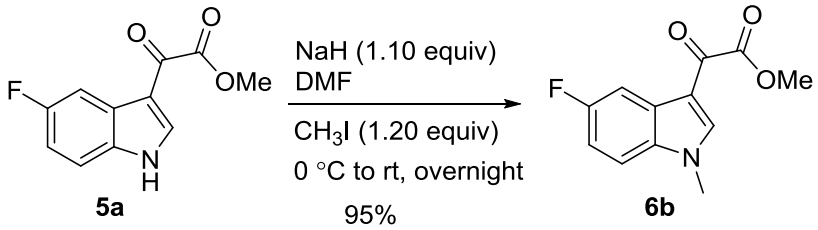
Methyl 2-(1-ethyl-5-fluoro-1*H*-indol-3-yl)-2-oxoacetate (6a)



To a solution of methyl 2-(5-fluoro-1*H*-indol-3-yl)-2-oxoacetate (1.23 g, 5.55 mmol, 1.00 equiv) in anhydrous DMF (20.0 mL, 0.278 M) was added sodium hydride (57-63% suspension in mineral oil, 289 mg, 7.22 mmol, 1.30 equiv) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min before bromoethane (786 mg, 7.22 mmol, 1.30 equiv) was added. The reaction mixture was stirred overnight at room temperature. The reaction was quenched with ice water (60.0 mL) and the aqueous layer was extracted with EtOAc (6 × 20.0 mL). The organic extracts were combined, washed with 5% LiCl(aq) (5.00 mL), and then dried over Na_2SO_4. After being concentrated *in vacuo*, the residue was purified by flash chromatography on silica gel (EtOAc:hexanes = 1:2) to afford the title compound as a yellow solid (1.10 g, 4.41 mmol, 80% yield).

NMR Spectroscopy: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, δ): 8.43 (s, 1H), 8.12 (dd, *J* = 2.6, 9.4 Hz, 1H), 7.32 (dd, *J* = 4.2, 8.9 Hz, 1H), 7.08 (dt, *J* = 2.6, 9.0 Hz, 1H), 4.23 (q, *J* = 7.3 Hz, 2H), 3.97 (s, 3H), 1.58 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, δ): 176.7, 163.3, 160.3 (d, *J* = 238.2 Hz), 139.7, 133.0, 128.3 (d, *J* = 27.3 Hz), 113.0, 112.5 (d, *J* = 26.3 Hz), 111.0 (d, *J* = 9.5 Hz), 108.6 (d, *J* = 25.1 Hz), 52.9, 42.5, 15.1.

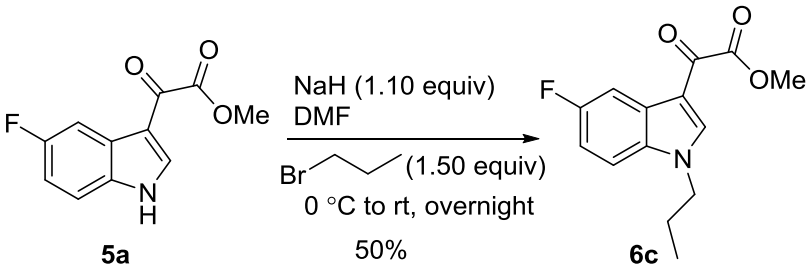
Methyl 2-(5-fluoro-1-methyl-1*H*-indol-3-yl)-2-oxoacetate (6b)



To a solution of methyl 2-(5-fluoro-1*H*-indol-3-yl)-2-oxoacetate (850 mg, 3.83 mmol, 1.00 equiv) in anhydrous DMF (10.0 mL, 0.383 M) was added sodium hydride (57-63% suspension in mineral oil, 169 mg, 4.20 mmol, 1.10 equiv) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min before iodomethane (653 mg, 4.60 mmol, 1.20 equiv) was added. The reaction mixture was stirred overnight at room temperature. The reaction was quenched with ice water (30.0 mL) and the aqueous layer was extracted with EtOAc (4 × 30.0 mL). The organic extracts were combined, washed with 5% LiCl(aq) (5.00 mL), and then dried over Na_2SO_4. After being concentrated *in vacuo*, the residue was purified by flash chromatography on silica gel (EtOAc:hexanes = 1:2) to afford the title compound as a white solid (860 mg, 3.66 mmol, 95% yield).

NMR Spectroscopy: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, δ): 8.28 (s, 1H), 8.04 (dd, *J* = 2.4, 9.4 Hz, 1H), 7.23 (dd, *J* = 4.2, 8.9 Hz, 1H), 7.03 (dt, *J* = 2.5, 9.0 Hz, 1H), 3.94 (s, 3H), 3.82 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, δ): 176.7, 163.2, 160.4 (d, *J* = 238.1 Hz), 141.4, 133.9, 128.0 (d, *J* = 11.2 Hz), 112.7 (d, *J* = 4.4 Hz), 112.5 (d, *J* = 26.3 Hz), 111.0 (d, *J* = 10.0 Hz), 108.2 (d, *J* = 25.2 Hz), 52.9, 34.2. The ^{1}H NMR data were in good agreement with values reported in the literature.[4]

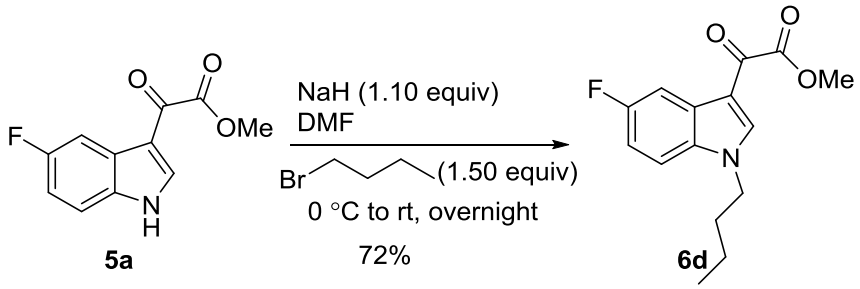
Methyl 2-(5-fluoro-1-propyl-1*H*-indol-3-yl)-2-oxoacetate (6c)



To a solution of methyl 2-(5-fluoro-1*H*-indol-3-yl)-2-oxoacetate (0.210 g, 0.949 mmol, 1.00 equiv) in anhydrous DMF (10.0 mL, 0.095 M) was added sodium hydride (57-63% suspension in mineral oil, 41.0 mg, 1.04 mmol, 1.10 equiv) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min before 1-bromopropane (174 mg, 1.42 mmol, 1.50 equiv) was added. The reaction mixture was stirred overnight at room temperature. The reaction was quenched with ice water (40.0 mL) and the aqueous layer was extracted with EtOAc (4 × 30.0 mL). The organic extracts were combined, washed with 5% LiCl(aq) (5.00 mL), and then dried over Na_2SO_4. After being concentrated *in vacuo*, the residue was purified by flash chromatography on silica gel (EtOAc:hexanes = 1:2) to afford the title compound as a yellow solid (124 mg, 0.471 mmol, 50% yield).

NMR Spectroscopy: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, δ): 8.41 (s, 1H), 8.13 (dd, J = 2.6, 9.4 Hz, 1H), 7.32 (dd, J = 4.2, 8.9 Hz, 1H), 7.08 (dt, J = 2.6, 9.0 Hz, 1H), 4.15 (t, J = 7.2 Hz, 2H), 3.96 (s, 3H), 1.90–2.00 (m, 2H), 0.99 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, δ): 176.8, 163.3, 160.4 (d, J = 237.9 Hz), 140.6, 133.3, 128.3 (d, J = 11.3 Hz), 112.9 (d, J = 4.3 Hz), 112.6 (d, J = 26.3 Hz), 111.2 (d, J = 9.6 Hz), 108.6 (d, J = 25.0 Hz), 53.0, 49.5, 23.3, 11.5.

Methyl 2-(1-butyl-5-fluoro-1*H*-indol-3-yl)-2-oxoacetate (6d)

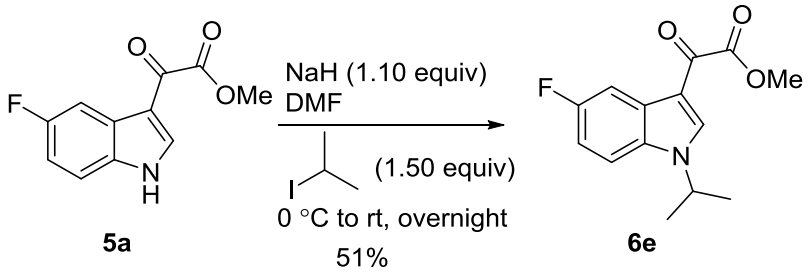


To a solution of methyl 2-(5-fluoro-1*H*-indol-3-yl)-2-oxoacetate (221 mg, 1.00 mmol, 1.00 equiv) in anhydrous DMF (10.0 mL, 0.100 M) was added sodium hydride (57-63% suspension in mineral oil, 44.0 mg, 1.10 mmol, 1.10 equiv) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min before 1-bromobutane (206 mg, 1.50 mmol, 1.50 equiv) was added. The reaction mixture was stirred overnight at room temperature. The reaction was quenched with ice water (30.0 mL) and the aqueous layer was extracted with EtOAc (4 × 30.0 mL). The organic organic extracts were combined, washed with 5% LiCl(aq) (5.00 mL), and then dried over Na_2SO_4. After being concentrated *in vacuo*, the residue was purified by flash chromatography on silica gel (EtOAc:hexanes = 1:2) to afford the title compound as a white solid (200 mg, 0.721 mmol, 72% yield).

NMR Spectroscopy: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, δ): 8.39 (s, 1H), 8.10 (dd, J = 2.5, 9.4 Hz, 1H), 7.29 (dd, J = 4.2, 8.9 Hz, 1H), 7.06 (dt, J = 2.6, 9.0 Hz, 1H), 4.15 (t, J = 7.2 Hz, 2H), 3.95 (s, 3H), 1.88 (q, J = 7.4 Hz, 2H), 1.31–1.46 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, δ): 176.7, 163.3, 160.3 (d, J = 238.2 Hz), 140.4, 133.2, 128.2 (d, J = 11.2 Hz), 113.0

(d, J = 4.3 Hz), 112.5 (d, J = 26.3 Hz), 111.1 (d, J = 9.8 Hz), 108.5 (d, J = 24.9 Hz), 52.9, 47.6, 31.8, 20.1, 13.7.

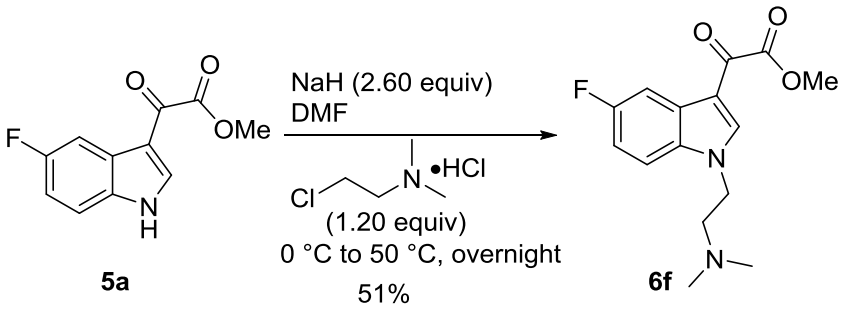
Methyl 2-(5-fluoro-1-isopropyl-1*H*-indol-3-yl)-2-oxoacetate (6e)



To a solution of methyl 2-(5-fluoro-1*H*-indol-3-yl)-2-oxoacetate (245 mg, 1.11 mmol, 1.00 equiv) in anhydrous DMF (5.00 mL, 0.222 M) was added sodium hydride (57-63% suspension in mineral oil, 48.8 mg, 1.22 mmol, 1.10 equiv) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min before 2-bromopropane (283 mg, 1.66 mmol, 1.50 equiv) was added. The reaction mixture was stirred overnight at room temperature. The reaction was quenched with ice water (20.0 mL) and the aqueous layer was extracted with EtOAc (4 × 20.0 mL). The organic extracts were combined, washed with 5% LiCl(aq) (5.00 mL), and then dried over Na_2SO_4. After being concentrated *in vacuo*, the residue was purified by flash chromatography on silica gel (EtOAc:hexanes = 1:2) to afford the title compound as a white solid (150 mg, 0.570 mmol, 51% yield).

NMR Spectroscopy: ^{1}H NMR (700 MHz, $CDCl_3$, 25 °C, δ): 8.48 (s, 1H), 8.10 (d, J = 7.0 Hz, 1H), 7.33 (t, J = 7.0 Hz, 1H), 7.05 (s, 1H), 4.66 (t, J = 7.3 Hz, 2H), 3.94 (s, 3H), 1.60 (d, J = 6.7 Hz, 6H). ^{13}C NMR (175 MHz, $CDCl_3$, 25 °C, δ): 176.7, 163.3, 160.2 (d, J = 238.1 Hz), 136.9, 132.9, 128.2 (d, J = 11.1 Hz), 113.1 (d, J = 4.2 Hz), 112.3 (d, J = 26.2 Hz), 111.2 (d, J = 9.7 Hz), 108.5 (d, J = 25.0 Hz), 52.9, 49.0, 22.6.

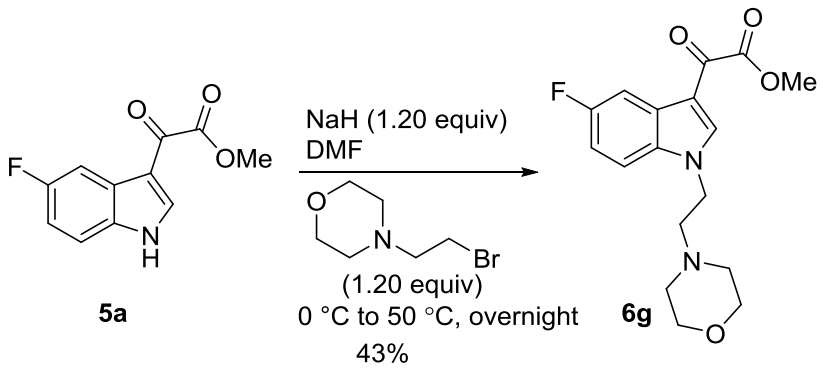
Methyl 2-(1-(2-(dimethylamino)ethyl)-5-fluoro-1*H*-indol-3-yl)-2-oxoacetate (6f)



To a solution of methyl 2-(5-fluoro-1*H*-indol-3-yl)-2-oxoacetate (613 mg, 2.77 mmol, 1.00 equiv) in anhydrous DMF (15.0 mL, 0.185 M) was added sodium hydride (57-63% suspension in mineral oil, 288 mg, 7.2 mmol, 2.60 equiv) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min before 2-chloro-*N*,*N*-dimethylethan-1-amine hydrochloride (479 mg, 3.32 mmol, 1.20 equiv) was added. The reaction mixture was heated to 50 °C and stirred overnight. The reaction was quenched with ice water (30.0 mL) and the aqueous layer was extracted with EtOAc (4 × 30.0 mL). The organic extracts were combined, washed with 5% LiCl(aq) (5.00 mL), and then dried over Na_2SO_4. After being concentrated *in vacuo*, the residue was purified by flash chromatography on silica gel (CH_2Cl_2:MeOH = 20:1) to afford the title compound as a colorless oil (410 mg, 1.40 mmol, 51% yield).

NMR Spectroscopy: ^{1}H NMR (700 MHz, $CDCl_3$, 25 °C, δ): 8.42 (s, 1H), 8.05 (dd, *J* = 2.1, 9.4 Hz, 1H), 7.28 (dd, *J* = 4.0, 8.8 Hz, 1H), 7.02 (dt, *J* = 2.1, 8.8 Hz, 1H), 4.21 (t, *J* = 6.7 Hz, 2H), 3.92 (s, 3H), 2.73 (t, *J* = 6.7 Hz, 2H), 2.28 (s, 6H). ^{13}C NMR (175 MHz, $CDCl_3$, 25 °C, δ): 176.8, 163.1, 160.2 (d, *J* = 237.7 Hz), 141.0, 133.2, 128.0 (d, *J* = 11.0 Hz), 112.9 (d, *J* = 3.9 Hz), 112.4 (d, *J* = 26.4 Hz), 111.0 (d, *J* = 9.9 Hz), 108.3 (d, *J* = 24.7 Hz), 58.3, 52.8, 45.7, 45.6.

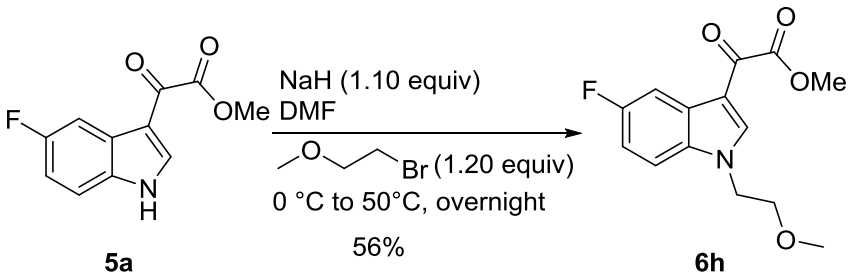
Methyl 2-(5-fluoro-1-(2-morpholinoethyl)-1*H*-indol-3-yl)-2-oxoacetate (6g)



To a solution of methyl 2-(5-fluoro-1*H*-indol-3-yl)-2-oxoacetate (715 mg, 3.23 mmol, 1.00 equiv) in anhydrous DMF (15.0 mL, 0.215 M) was added sodium hydride (57-63% suspension in mineral oil, 155 mg, 3.88 mmol, 1.20 equiv) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min before 4-(2-bromoethyl)morpholine (894 mg, 3.88 mmol, 1.20 equiv) was added. The reaction mixture was heated to 50 °C and stirred overnight. The reaction was quenched with ice water (30 mL) and the aqueous layer was extracted with EtOAc (4 × 30.0 mL). The organic extracts were combined, washed with 5% LiCl(aq) (5.00 mL), and then dried over Na_2SO_4. After being concentrated *in vacuo*, the residue was purified by flash chromatography on silica gel (CH_2Cl_2:MeOH = 10:1) to afford the title compound as a colorless oil (460 mg, 1.38 mmol, 43% yield).

NMR Spectroscopy: ^{1}H NMR (700 MHz, $CDCl_3$, 25 °C, δ): 8.47 (s, 1H), 8.06 (dd, *J* = 2.4, 9.3 Hz, 1H), 7.29 (dd, *J* = 4.0, 8.8 Hz, 1H), 7.04 (dd, *J* = 2.5, 8.8 Hz, 1H), 4.24 (t, *J* = 6.1 Hz, 2H), 3.93 (s, 3H), 3.68 (d, *J* = 3.9 Hz, 4H), 2.78 (t, *J* = 6.1 Hz, 2H), 2.49 (s, 4H). ^{13}C NMR (175 MHz, $CDCl_3$, 25 °C, δ): 176.8, 163.1, 160.3 (d, *J* = 238 Hz), 141.3, 133.2, 128.0 (d, *J* = 11.3 Hz), 112.9 (d, *J* = 4.1 Hz), 112.4 (d, *J* = 26.3 Hz), 111.0 (d, *J* = 9.9 Hz), 108.4 (d, *J* = 24.6 Hz), 67.0, 57.5, 53.8, 52.9, 44.9.

Methyl 2-(5-fluoro-1-(2-methoxyethyl)-1*H*-indol-3-yl)-2-oxoacetate (6h)

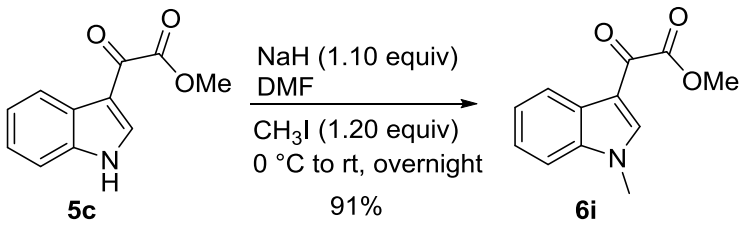


To a solution of methyl 2-(5-fluoro-1*H*-indol-3-yl)-2-oxoacetate (570 mg, 2.58 mmol, 1.00 equiv) in anhydrous DMF (15.0 mL, 0.172 M) was added sodium hydride (57-63% suspension in mineral oil, 114 mg, 2.84 mmol, 1.10 equiv) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min

before 1-bromo-2-methoxyethane (430 mg, 3.09 mmol, 1.20 equiv) was added. The reaction mixture was stirred overnight at room temperature. The reaction was quenched with ice water (30.0 mL) and the aqueous layer was extracted with EtOAc (4 × 30.0 mL). The organic extracts were combined, washed with 5% LiCl(aq) (5.00 mL), and then dried over Na_2SO_4. After being concentrated *in vacuo*, the residue was purified by flash chromatography on silica gel (EtOAc:hexanes = 1:1) to afford the title compound as a colorless oil (401 mg, 1.44 mmol, 56% yield).

NMR Spectroscopy: ^{1}H NMR (700 MHz, $CDCl_3$, 25 °C, δ): 8.33 (s, 1H), 7.80–8.06 (m, 1H), 7.10–7.28 (m, 1H), 6.82–7.03 (m, 1H), 4.22 (s, 2H), 3.88 (s, 3H), 3.66 (s, 2H), 3.24 (s, 3H). ^{13}C NMR (175 MHz, $CDCl_3$, 25 °C, δ): 176.8, 163.0, 160.0 (d, J = 237.4 Hz), 141.3, 133.1, 127.6 (d, J = 10.4 Hz), 112.6, 112.0 (d, J = 26.1 Hz), 111.2 (d, J = 8.4 Hz), 107.8 (d, J = 24.9 Hz), 70.3, 58.8, 52.6, 47.0.

Methyl 2-(1-methyl-1*H*-indol-3-yl)-2-oxoacetate (6i)

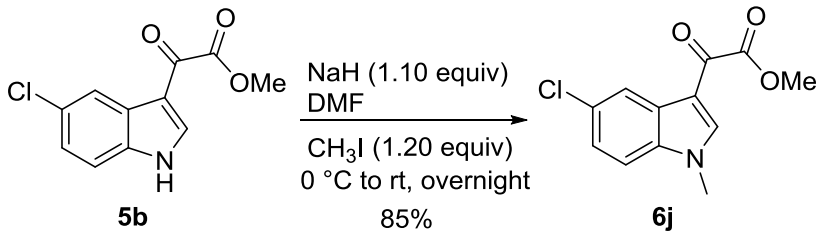


5c **6i**

To a solution of methyl 2-(1*H*-indol-3-yl)-2-oxoacetate (1.04 g, 5.12 mmol, 1.00 equiv) in anhydrous DMF (25.0 mL, 0.205 M) was added sodium hydride (57-63% suspension in mineral oil, 225 mg, 5.63 mmol, 1.10 equiv) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min before iodomethane (872 mg, 6.14 mmol, 1.20 equiv) was added. The reaction mixture was stirred overnight at room temperature. The reaction was quenched with ice water (50.0 mL) and the aqueous layer was extracted with EtOAc (6 × 30.0 mL). The organic extracts were combined, washed with 5% LiCl(aq) (5.00 mL), and then dried over Na_2SO_4. After being concentrated *in vacuo*, the residue was purified by flash chromatography on silica gel (EtOAc:hexanes = 1:1) to afford the title compound as a white solid (1.01 g, 4.65 mmol, 91% yield).

NMR Spectroscopy: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, δ): 8.40–8.46 (m, 1H), 8.29 (s, 1H), 7.31–7.40 (m, 3H), 3.95 (s, 3H), 3.84 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, δ): 177.0, 163.5, 140.6, 137.5, 127.1, 124.3, 123.7, 122.8, 112.9, 110.1, 52.8, 33.9. The ^{1}H NMR data were in good agreement with values reported in the literature.[6]

Methyl 2-(5-chloro-1-methyl-1*H*-indol-3-yl)-2-oxoacetate (6j)



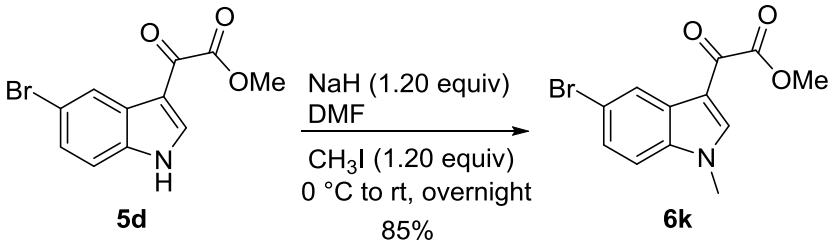
5b **6j**

To a solution of methyl 2-(5-chloro-1*H*-indol-3-yl)-2-oxoacetate (1.00 g, 4.20 mmol, 1.00 equiv) in anhydrous DMF (15.0 mL, 0.280 M) was added sodium hydride (57-63% suspension in mineral oil, 185 mg, 4.62 mmol, 1.10 equiv) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min before iodomethane (715 mg, 5.04 mmol, 1.20 equiv) was added. The reaction mixture was stirred

overnight at room temperature. The reaction was quenched with ice water (30.0 mL) and the aqueous layer was extracted with EtOAc (5 × 30.0 mL). The organic extracts were combined, washed with 5% LiCl(aq) (5.00 mL), and then dried over Na_2SO_4. After being concentrated *in vacuo*, the residue was purified by flash chromatography on silica gel (EtOAc:hexanes = 1:1) to afford the title compound as a white solid (900 mg, 3.58 mmol, 85% yield).

NMR Spectroscopy: ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, δ): 8.27 (d, J = 1.9 Hz, 1H), 8.21 (s, 1H), 7.13–7.20 (m, 2H), 3.93 (s, 3H), 3.79 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C, δ): 176.6, 163.0, 141.1, 135.6, 129.4, 127.9, 124.2, 121.9, 112.2, 111.1, 52.9, 34.0. The ^{1}H NMR data were in good agreement with values reported in the literature.[4]

Methyl 2-(5-bromo-1-methyl-1*H*-indol-3-yl)-2-oxoacetate (6k)

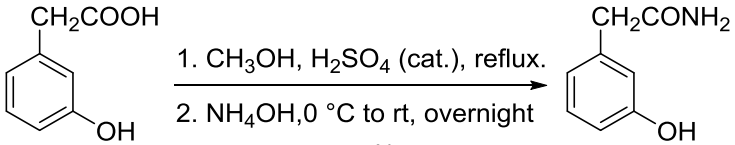


5d **6k**

To a solution of methyl 2-(5-bromo-1*H*-indol-3-yl)-2-oxoacetate (984 mg, 3.49 mmol, 1.00 equiv) in anhydrous DMF (12.0 mL, 0.291 M) was added sodium hydride (57-63% suspension in mineral oil, 168 mg, 4.19 mmol, 1.20 equiv) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min before iodomethane (595 mg, 4.19 mmol, 1.20 equiv) was added. The reaction mixture was stirred overnight at room temperature. The reaction was quenched with ice water (30.0 mL) and the aqueous layer was extracted with EtOAc (5 × 30.0 mL). The organic extracts were combined, washed with 5% LiCl(aq) (5.00 mL), and then dried over Na_2SO_4. After being concentrated *in vacuo*, the residue was purified by flash chromatography on silica gel (EtOAc:hexanes = 1:1) to afford the title compound as a white solid (739 mg, 2.50 mmol, 72% yield).

NMR Spectroscopy: ^{1}H NMR (700 MHz, $CDCl_3$, 25 °C, δ): 8.34 (s, 1H), 8.11 (s, 1H), 7.25 (d, J = 7.7 Hz, 1 H), 7.03 (d, J = 8.1 Hz, 1 H), 3.91 (s, 3H), 3.74 (s, 3H). ^{13}C NMR (175 MHz, $CDCl_3$, 25 °C, δ): 176.5, 162.9, 141.0, 135.8, 128.3, 126.9, 124.8, 117.1, 112.0, 111.5, 52.9, 34.0. The ^{1}H NMR data were in good agreement with values reported in the literature. [4]

2-(3-Hydroxyphenyl)acetamide (8)

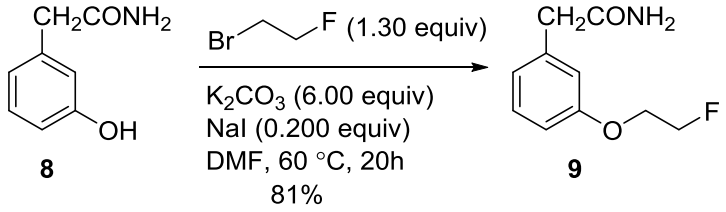


7 **8**

To a solution of 2-(3-hydroxyphenyl)acetic acid (20.0 g, 130 mmol, 1.00 equiv) in MeOH (300 mL, 0.433 M) was added concentrated sulphuric acid (1.00 mL). The solution was heated to reflux for 5 h. The solvent was evaporated and the residue was dissolved in CH_2Cl_2 (300 mL) and washed with water (3 × 20.0 mL). The organic layer was dried over Na_2SO_4 and evaporated to dryness to afford an ester. To the residue was added 28-30% $NH_3 \cdot H_2O$ (110 mL) at 0 °C, then the mixture was stirred overnight at room temperature. The resulting solution was evaporated and the residue neutralized with acetic acid. The crude product was recrystallized from EtOAc to afford the title compound as a white crystalline solid (10.8 g, 71.4 mmol, 55% yield).

NMR Spectroscopy: ^{1}H NMR (400 MHz, $(CD_3)_2SO$, 25 °C, δ): 9.27 (s, 1H), 7.39 (s, 1H), 7.06 (t, J = 7.8 Hz, 1H), 6.83 (s, 1H), 6.50-6.72 (m, 3H), 3.26 (s, 2H). ^{13}C NMR (100 MHz, $(CD_3)_2SO$, 25 °C, δ): 172.2, 157.2, 137.7, 129.0, 119.7, 115.9, 113.2, 42.3. All the analytical data were in good agreement with values reported in the literature.[7]

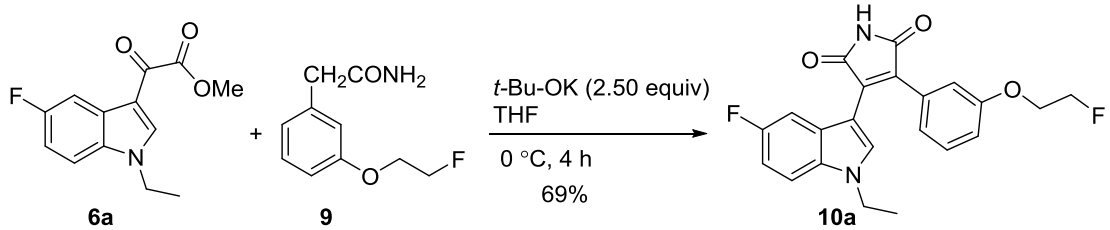
2-(3-(2-Fluoroethoxy)phenyl)acetamide (9)



To a solution of 2-(3-hydroxyphenyl)acetamide (466 mg, 3.09 mmol, 1.00 equiv) in DMF (20.0 mL, 0.155 M) was added K_2CO_3 (2.56 g, 18.5 mmol, 6.00 equiv), NaI (93.0 mg, 0.62 mmol, 0.200 equiv), and 1-bromo-2-fluoroethane (510 mg, 4.01 mmol, 1.30 equiv) under nitrogen atmosphere at room temperature. The reaction mixture was heated to 60 °C and stirred for 20 h. The reaction was cooled to 0 °C and quenched with water (50.0 mL) and the aqueous layer was extracted with EtOAc (6 × 30.0 mL). The organic extracts were combined, washed with 5% LiCl(aq) (5.00 mL), and then dried over Na_2SO_4. After being concentrated *in vacuo*, the residue was purified by flash chromatography on silica gel (EtOAc) to afford the title compound as a white solid (494 mg, 2.50 mmol, 81% yield).

NMR Spectroscopy: ^{1}H NMR (400 MHz, $(CD_3)_2SO$, 25 °C, δ): 7.44 (s, 1H), 7.21 (t, J = 7.8 Hz, 1H), 6.75–6.91 (m, 4H), 4.73 (td, J = 3.9, 47.8 Hz, 2H), 4.20 (td, J = 3.9, 30.1 Hz, 2H), 3.36 (s, 2H). ^{13}C NMR (100 MHz, $(CD_3)_2SO$, 25 °C, δ): 172.1, 158.0, 138.1, 129.2, 121.7, 115.5, 112.2, 82.2 (d, J = 165.7 Hz), 66.9 (d, J = 18.8 Hz), 42.3.

3-(1-Ethyl-5-fluoro-1*H*-indol-3-yl)-4-(3-methoxyphenyl)-1*H*-pyrrole-2,5-dione (10a)

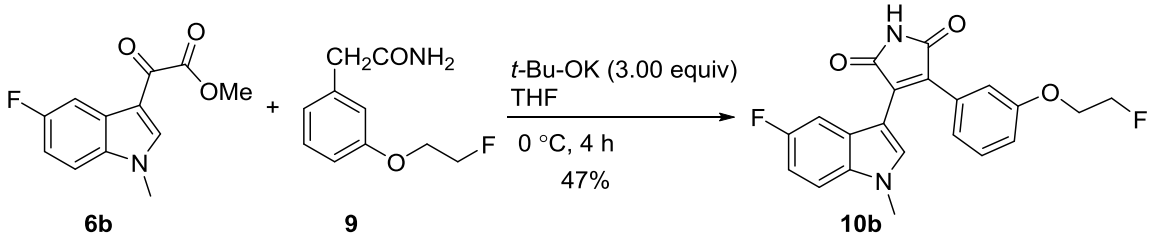


Under N_2 atmosphere, to a suspension of methyl 2-(1-ethyl-5-fluoro-1*H*-indol-3-yl)-2-oxoacetate (410 mg, 1.65 mmol, 1.00 equiv) and 2-(3-(2-fluoroethoxy)phenyl)acetamide (357 mg, 1.81 mmol, 1.10 equiv) in THF (10.0 mL, 0.165 M) was slowly added (dropwise) *t*-BuOK solution (463 mg in 20.0 mL THF, 4.13 mmol, 2.5 mmol) at 0 °C for 30 min. The reaction mixture was stirred at 0 °C for another 4 h. The reaction was quenched with HCl (1N, 5.0 mL) at 0 °C and the aqueous layer was extracted with EtOAc (4 × 20.0 mL). The organic extracts were combined, washed with saturated NaCl (aq) (5.00 mL), and then dried over Na_2SO_4. After being concentrated *in vacuo*, the residue was purified by flash chromatography on silica gel (EtOAc:hexanes = 1:1) to afford the title compound as a red solid (450 mg, 1.14 mmol, 69% yield).

NMR Spectroscopy: ^{1}H NMR (400 MHz, $(CD_3)_2SO$, 25 °C, δ): 11.10 (s, 1H), 8.13 (s, 1H), 7.56 (dd, J = 4.6, 9.0 Hz, 1H), 7.20–7.31 (m, 1H), 6.90–7.05 (m, 4H), 5.98 (dd, J = 2.5, 10.6 Hz, 1H), 4.62–4.70 (m, 1H), 4.51–4.58 (m, 1H), 4.32 (q, J = 7.2 Hz, 2H), 4.00–4.15 (m, 2 H), 1.41 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $(CD_3)_2SO$, 25 °C, δ): 172.2, 172.0, 157.7, 156.9 (d, J = 232.6

Hz), 134.8, 132.7, 132.0, 131.7, 129.3, 128.5, 125.1 (d, J = 10.5 Hz), 122.5, 116.0, 115.0, 111.8 (d, J = 9.8 Hz), 110.1 (d, J = 25.7 Hz), 106.5 (d, J = 25.0 Hz), 103.3 (d, J = 4.1 Hz), 81.9 (d, J = 165.9 Hz), 67.1 (d, J = 19.1 Hz), 41.2, 15.2. ^{19}F NMR (376 MHz, $(CD_3)_2SO$, 25 °C, δ): –124.6 (m), –224.5 (m). HRMS (ESI-TOF) (m/z): calcd for $C_{22}H_{19}F_2N_2O_3$ ([M + H]$^+$), 397.1364, found, 397.1357.

3-(5-Fluoro-1-methyl-1*H*-indol-3-yl)-4-(3-(2-fluoroethoxy)phenyl)-1*H*-pyrrole-2,5-dione (10b)

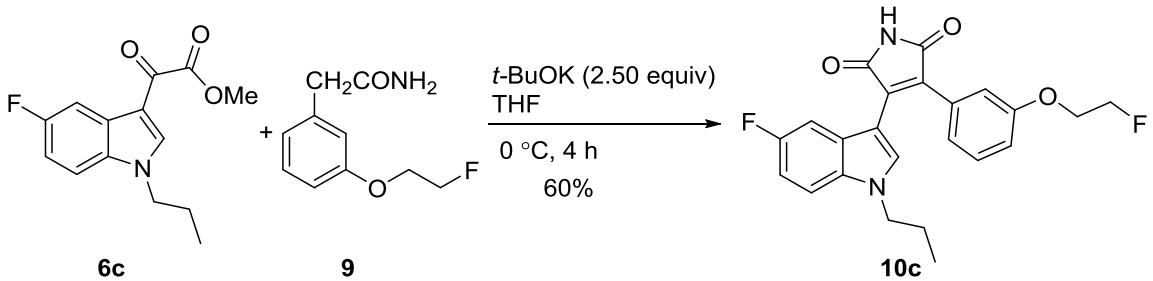


6b 9 10b

Under N_2 atmosphere, to a suspension of methyl methyl 2-(5-fluoro-1-methyl-1*H*-indol-3-yl)-2-oxoacetate (316 mg, 1.34 mmol, 1.00 equiv) and 2-(3-(2-fluoroethoxy)phenyl)acetamide (318 mg, 1.61 mmol, 1.20 equiv) in THF (15.0 mL, 0.089 M) was slowly added (dropwise) *t*-BuOK solution (451 mg, 4.02 mmol in 15 mL THF, 3.00 equiv) at 0 °C for 30 min. The reaction mixture was stirred at 0 °C for another 4 h. The reaction was quenched with HCl (1 N, 5.00 mL) at 0 °C and the aqueous layer was extracted with EtOAc (4 × 10.0 mL). The organic extracts were combined, washed with saturated NaCl (aq) (5.00 mL), and then dried over Na_2SO_4. After being concentrated *in vacuo*, the residue was purified by flash chromatography on silica gel (EtOAc:hexanes = 1:1) to afford the title compound as a red solid (240 mg, 0.628 mmol, 47% yield).

NMR Spectroscopy: ^{1}H NMR (400 MHz, $(CD_3)_2SO$, 25 °C, δ): 11.09 (s, 1H), 8.10 (s, 1H), 7.51 (dd, J = 4.6, 9.0 Hz, 1H), 7.26 (t, J = 7.8 Hz, 1H), 6.97–7.04 (m, 3H), 6.95 (d, J = 7.7 Hz, 1H), 5.94 (dd, J = 2.4, 10.6 Hz, 1H), 4.63 (td, J = 3.7, 47.9 Hz, 2H), 4.09 (td, J = 3.7, 30.0 Hz, 2H), 3.90 (s, 3H). ^{13}C NMR (175 MHz, $(CD_3)_2SO$, 25 °C, δ): 172.2, 172.1, 157.7, 157.0 (d, J = 233.7 Hz), 136.4, 133.7, 131.9, 131.8, 129.4, 128.4, 124.9, 122.5, 116.0, 115.0, 111.8 (d, J = 10.0 Hz), 110.1 (d, J = 25.8 Hz), 106.4 (d, J = 25.1 Hz), 103.1, 81.9 (d, J = 165.6 Hz), 67.1 (d, J = 18.9 Hz), 33.3. ^{19}F NMR (376 MHz, $(CD_3)_2SO$, 25 °C, δ): –124.5 (m), –224.4 (m). HRMS (ESI-TOF) (m/z): calcd for $C_{21}H_{17}F_2N_2O_3$ ([M + H]$^+$), 383.1207, found, 383.1202.

3-(5-Fluoro-1-propyl-1*H*-indol-3-yl)-4-(3-(2-fluoroethoxy)phenyl)-1*H*-pyrrole-2,5-dione (10c)



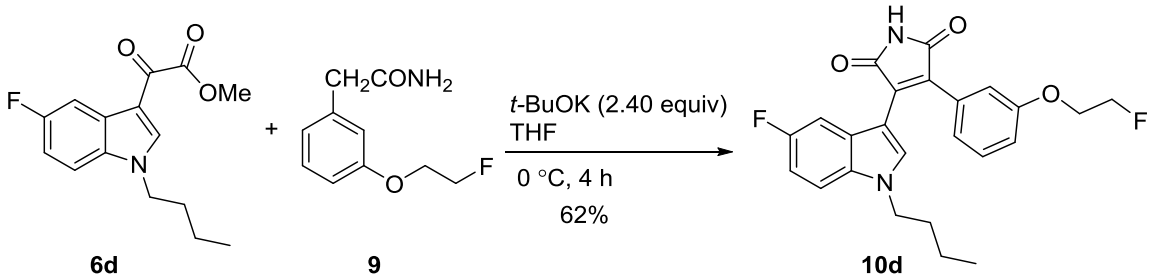
6c 9 10c

Under N_2 atmosphere, to a suspension of methyl methyl 2-(5-fluoro-1-propyl-1*H*-indol-3-yl)-2-oxoacetate (60.0 mg, 0.228 mmol, 1.00 equiv) and 2-(3-(2-fluoroethoxy)phenyl)acetamide (54.0 mg, 0.274 mmol, 1.20 equiv) in THF (5.00 mL) was added *t*-BuOK solution (64.0 mg, 0.570 mmol

in 10.0 mL THF, 2.50 equiv) at 0 °C for 30 min. The reaction mixture was stirred at 0 °C for another 4 h. The reaction was quenched with HCl (1N, 5.00 mL) at 0 °C and the aqueous layer was extracted with EtOAc (4 × 10.0 mL). The organic extracts were combined, washed with saturated NaCl (aq) (5 mL), and then dried over Na_2SO_4. After being concentrated *in vacuo*, the residue was purified by flash chromatography on silica gel (EtOAc:hexanes = 1:1) to afford the title compound as a red solid (56.1 mg, 0.134 mmol, 60% yield).

NMR Spectroscopy: ^{1}H NMR (700 MHz, ($(CD_3)_2SO$, 25 °C, δ): 11.10 (s, 1H), 8.10 (s, 1H), 7.57 (t, J = 4.4 Hz, 1H), 7.27 (t, J = 7.9 Hz, 1H), 6.90–7.04 (m, 4H), 6.01 (dd, J = 2.1, 10.4 Hz, 1H), 4.61 (td, J = 3.5, 47.9 Hz, 2H), 4.25 (t, J = 7.0 Hz, 2H), 4.06 (td, J = 3.5, 30.0 Hz, 2H), 1.80 (q, J = 7.1 Hz, 2H), 0.85 (t, J = 7.3 Hz, 3H). ^{13}C NMR (175 MHz, $(CD_3)_2SO$, 25 °C, δ): 172.1, 172.0, 157.7, 157.0 (d, J = 232.6 Hz), 135.5, 133.0, 132.0, 131.7, 129.4, 128.6, 125.1 (d, J = 10.7 Hz), 122.4, 115.9, 115.1, 111.9 (d, J = 9.8 Hz), 110.1 (d, J = 25.6 Hz), 106.5 (d, J = 25.0 Hz), 103.2 (d, J = 4.1 Hz), 81.9 (d, J = 165.7 Hz), 67.0 (d, J = 18.9 Hz), 47.8, 23.0, 11.0. ^{19}F NMR (376 MHz, $(CD_3)_2SO$, 25 °C, δ): –124.5 (m), –224.6 (m). HRMS (ESI-TOF) (m/z): calcd for $C_{23}H_{21}F_2N_2O_3$ ($[M + H]^+$), 411.1520, found, 411.1534.

3-(1-Butyl-5-fluoro-1*H*-indol-3-yl)-4-(3-(2-fluoroethoxy)phenyl)-1*H*-pyrrole-2,5-dione (10d)

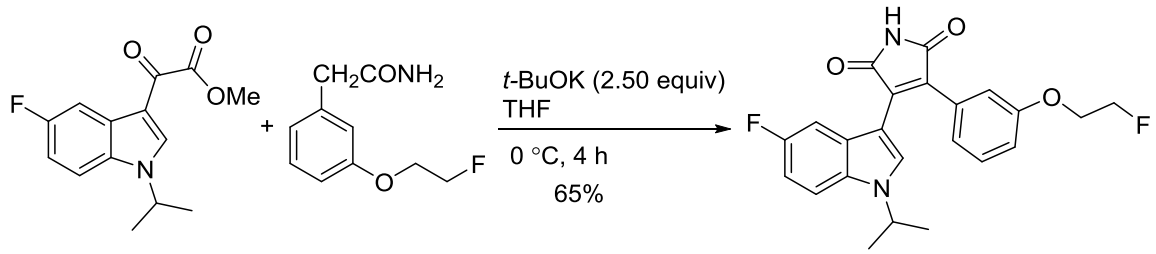


6d **9** **10d**

Under N_2 atmosphere, to a suspension of methyl methyl 2-(1-butyl-5-fluoro-1*H*-indol-3-yl)-2-oxoacetate (106 mg, 0.380 mmol, 1.00 equiv) and 2-(3-(2-fluoroethoxy)phenyl)acetamide (90.5 mg, 0.459 mmol, 1.20 equiv) in THF (10.0 mL) was slowly added (dropwise) *t*-BuOK solution (102 mg, 0.912 mmol in 10 mL THF, 2.40 equiv) at 0 °C for 30 min. The reaction mixture was stirred at 0 °C for another 4 h. The reaction was quenched with HCl (1N, 5.00 mL) at 0 °C and the aqueous layer was extracted with EtOAc (4 × 10.0 mL). The organic extracts were combined, washed with saturated NaCl aqueous (5.00 mL), and then dried over Na_2SO_4. After being concentrated *in vacuo*, the residue was purified by flash chromatography on silica gel (EtOAc:hexanes = 1/3) to afford the title compound as a red solid (100 mg, 0.236 mmol, 62% yield).

NMR Spectroscopy: ^{1}H NMR (400 MHz, $(CD_3)_2SO$, 25 °C, δ): 11.11 (s, 1H), 8.08 (s, 1H), 7.54 (dd, J = 4.6, 9.0 Hz, 1H), 7.22–7.30 (m, 1H), 6.90–7.03 (m, 4H), 6.03 (dd, J = 2.4, 10.6 Hz, 1H), 4.61 (td, J = 3.7, 47.9 Hz, 2H), 4.26 (t, J = 7.0 Hz, 2H), 4.06 (td, J = 3.7, 30.0 Hz, 2H), 1.70–1.79 (m, 2H), 1.22–1.32 (m, 2H), 0.88 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $(CD_3)_2SO$, 25 °C, δ): 172.2, 172.0, 157.7, 157.0 (d, J = 232.6 Hz), 135.3, 132.9, 132.0, 131.7, 129.3, 128.6, 125.1 (d, J = 10.7 Hz), 122.5, 115.9, 115.1, 111.8 (d, J = 9.7 Hz), 110.1 (d, J = 25.8 Hz), 106.5 (d, J = 24.9 Hz), 103.3 (d, J = 4.2 Hz), 81.9 (d, J = 166.1 Hz), 67.0 (d, J = 19.0 Hz), 64.9, 46.0, 31.6, 19.4, 13.5. ^{19}F NMR (376 MHz, $(CD_3)_2SO$, 25 °C, δ): –121.6 (m), –223.2 (m). HRMS (ESI-TOF) (m/z): calcd for $C_{24}H_{23}F_2N_2O_3$ ($[M + H]^+$), 425.1677, found, 425.1679.

3-(5-Fluoro-1-isopropyl-1*H*-indol-3-yl)-4-(3-(2-fluoroethoxy)phenyl)-1*H*-pyrrole-2,5-dione (10e)

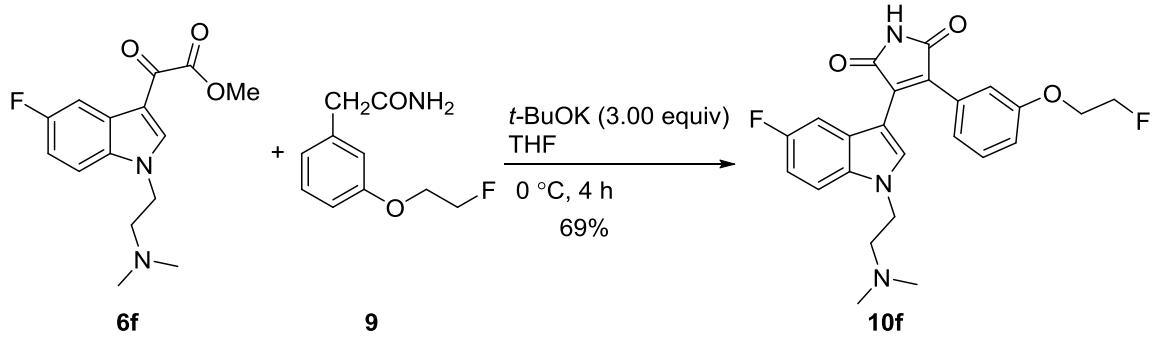


6e **9** **10e**

Under N_2 atmosphere, to a suspension of methyl methyl 2-(5-fluoro-1-isopropyl-1*H*-indol-3-yl)-2-oxoacetate (90.0 mg, 0.342 mmol, 1.00 equiv) and 2-(3-(2-fluoroethoxy)phenyl)acetamide (80.5 mg, 0.408 mmol, 1.19 equiv) in THF (5.00 mL, 0.068 M) was added *t*-BuOK solution (95.9 mg, 0.855 mmol in 10 mL THF, 2.50 equiv) at 0 °C for 30 min. The reaction mixture was stirred at 0 °C for another 4 h. The reaction was quenched with HCl (1N, 5.00 mL) at 0 °C and the aqueous layer was extracted with EtOAc (4 × 10.0 mL). The organic extracts were combined, washed with saturated NaCl (aq) (5.00 mL), and then dried over Na_2SO_4. After being concentrated *in vacuo*, the residue was purified by flash chromatography on silica gel (EtOAc:hexanes = 1:2) to afford the title compound as a red solid (91.0 mg, 0.223 mmol, 65% yield).

NMR Spectroscopy: ^{1}H NMR (400 MHz, $(CD_3)_2SO$, 25 °C, δ): 11.11 (s, 1H), 8.13 (s, 1H), 7.61 (dd, J = 4.6, 9.0 Hz, 1H), 7.22–7.31 (m, 1H), 6.90–7.04 (m, 4H), 6.04 (dd, J = 2.5, 10.6 Hz, 1H), 4.85 (q, J = 6.7 Hz, 1H), 4.62 (td, J =3.8, 51.4 Hz, 2H), 4.09 (td, J = 3.8, 30.0 Hz, 2H), 1.50 (d, J = 6.7 Hz, 6H). ^{13}C NMR (100 MHz, $(CD_3)_2SO$, 25 °C, δ): 172.1, 172.0, 157.7, 157.0 (d, J = 233.0 Hz), 132.5, 132.0, 131.7, 131.5, 129.4, 128.6, 125.1 (d, J = 10.4 Hz), 122.4, 115.9, 115.0, 111.9 (d, J = 8.6 Hz),, 110.1 (d, J = 24.1 Hz),, 106.6 (d, J = 22.6 Hz), 103.7, 81.9 (d, J = 165.8 Hz), 67.1 (d, J = 18.8 Hz), 47.7, 22.3. ^{19}F NMR (376 MHz, $(CD_3)_2SO$, 25 °C, δ): –124.4 (m), –224.4 (m). HRMS (ESI-TOF) (m/z): calcd for $C_{23}H_{21}F_2N_2O_3$ ($[M + H]^+$), 411.1520, found, 411.1534.

3-(1-(2-(Dimethylamino)ethyl)-5-fluoro-1*H*-indol-3-yl)-4-(3-(2-fluoroethoxy)phenyl)-1*H*-pyrrole-2,5-dione (10f)



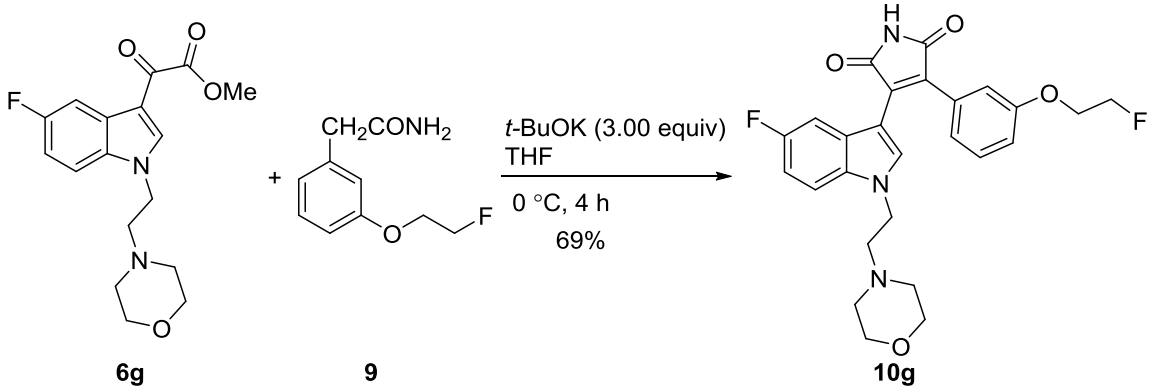
6f **9** **10f**

Under N_2 atmosphere, to a suspension of methyl 2-(1-(2-(dimethylamino)ethyl)-5-fluoro-1*H*-indol-3-yl)-2-oxoacetate (318 mg, 1.09 mmol, 1.00 equiv) and 2-(3-(2-fluoroethoxy)phenyl)acetamide (257 mg, 1.31 mmol, 1.20 equiv) in THF (20.0 mL, 0.055 M) was slowly added (dropwise) *t*-BuOK solution (367 mg, 3.27 mmol in 15 mL THF, 3.00 equiv) at 0 °C for 30 min. The reaction mixture was stirred at 0 °C for another 4 h. The reaction was quenched with ice water (5.00 mL) at 0 °C and the aqueous layer was extracted with EtOAc (4 × 20.0 mL). The organic extracts were combined, washed with saturated NaCl (aq) (5.00 mL), and then dried over Na_2SO_4. After being

concentrated *in vacuo*, the residue was purified by flash chromatography on silica gel (CH_2Cl_2:MeOH = 20:1) to afford the title compound as a yellow solid (330 mg, 0.751 mmol, 69% yield).

NMR Spectroscopy: ^{1}H NMR (700 MHz, $(CD_3)_2SO$, 25 °C, δ): 11.10 (s, 1H), 8.13 (s, 1H), 7.57 (t, *J* = 4.4 Hz, 1H), 7.28 (t, *J* = 7.9 Hz, 1H), 6.90–7.10 (m, 4H), 6.02 (dd, *J* = 2.5, 10.5 Hz, 1H), 4.61 (td, *J* = 3.8, 47.8 Hz, 2H), 4.37 (t, *J* = 6.4 Hz, 2H), 4.06 (td, *J* = 3.8, 30.0 Hz, 2H), 2.65 (t, *J* = 6.3 Hz, 2H), 2.19 (s, 6H). ^{13}C NMR (175 MHz, $(CD_3)_2SO$, 25 °C, δ): 172.2, 172.0, 157.7, 157.0 (d, *J* = 232.5 Hz), 156.3, 135.8, 133.1, 132.0, 131.7, 129.4, 128.6, 125.0 (d, *J* = 10.3 Hz), 122.4, 115.8, 115.1, 111.8 (d, *J* = 9.9 Hz), 110.1 (d, *J* = 25.6 Hz), 106.5 (d, *J* = 24.8 Hz), 103.3 (d, *J* = 3.8 Hz), 81.9 (d, *J* = 165.8 Hz), 67.0 (d, *J* = 19.0 Hz), 58.3, 45.2, 44.3. ^{19}F NMR (376 MHz, $(CD_3)_2SO$, 25 °C, δ): –124.7 (m), –224.4 (m). HRMS (ESI-TOF) (m/z): calcd for $C_{24}H_{24}F_2N_3O_3$ ($[M + H]^+$), 440.1786, found, 440.1785.

3-(5-Fluoro-1-(2-morpholinoethyl)-1*H*-indol-3-yl)-4-(3-(2-fluoroethoxy)phenyl)-1*H*-pyrrole-2,5-dione (10g)

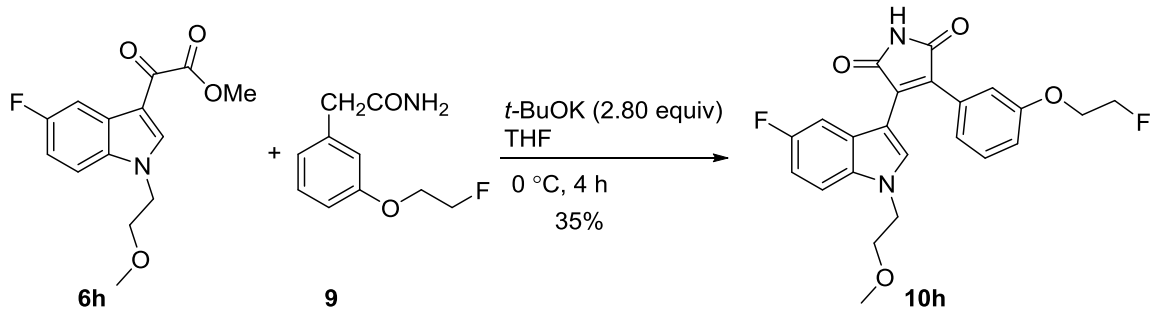


6g **9** **10g**

Under N_2 atmosphere, to a suspension of methyl 2-(5-fluoro-1-(2-morpholinoethyl)-1*H*-indol-3-yl)-2-oxoacetate (360 mg, 1.08 mmol, 1.00 equiv) and 2-(3-(2-fluoroethoxy)phenyl)acetamide (255 mg, 1.30 mmol, 1.20 equiv) in THF (20 mL, 0.054 M) was slowly added (dropwise) *t*-BuOK solution (364 mg, 3.24 mmol in 15 mL THF, 3.00 equiv) at 0 °C for 30 min. The reaction mixture was stirred at 0 °C for another 4 h. The reaction was quenched with ice water (5.00 mL) at 0°C and the aqueous layer was extracted with EtOAc (4 × 20.0 mL). The organic extracts were combined, washed with saturated NaCl (aq) (5 mL), and then dried over Na_2SO_4. After being concentrated *in vacuo*, the residue was purified by flash chromatography on silica gel (CH_2Cl_2:MeOH = 20:1) to afford the title compound as a yellow solid (360 mg, 0.748 mmol, 69% yield).

NMR Spectroscopy: ^{1}H NMR (700 MHz, $(CD_3)_2SO$, 25 °C, δ): 11.10 (s, 1H), 8.18 (s, 1H), 7.57 (t, *J* = 4.4 Hz, 1H), 7.27 (t, *J* = 7.9 Hz, 1H), 6.90–7.04 (m, 4H), 5.99 (dd, *J* = 2.2, 10.4 Hz, 1H), 4.61 (td, *J* = 3.5, 47.9 Hz, 2H), 4.38 (t, *J* = 6.3 Hz, 2H), 4.07 (td, *J* = 3.5, 30.0 Hz, 2H), 3.54 (s, 4H), 2.68 (t, *J* = 6.2 Hz, 2H), 2.42 (s, 4H). ^{13}C NMR (100 MHz, $(CD_3)_2SO$, 25 °C, δ): 172.2, 172.0, 157.7, 157.0 (d, *J* = 232.5 Hz), 136.1, 133.1, 132.0, 131.8, 129.4, 128.5, 125.0 (d, *J* = 10.3 Hz), 122.5, 116.0, 115.0, 111.8 (d, *J* = 9.8 Hz), 110.0 (d, *J* = 25.9 Hz), 106.4 (d, *J* = 25.1 Hz), 103.3 (d, *J* = 4.3 Hz), 81.9 (d, *J* = 165.7 Hz), 67.1 (d, *J* = 18.9 Hz), 66.2, 57.3, 53.2, 43.5. ^{19}F NMR (376 MHz, $(CD_3)_2SO$, 25 °C, δ): –124.7 (m), –224.4 (m). HRMS (ESI-TOF) (m/z): calcd for $C_{26}H_{26}F_2N_3O_4$ ($[M + H]^+$), 482.1891, found, 482.1883.

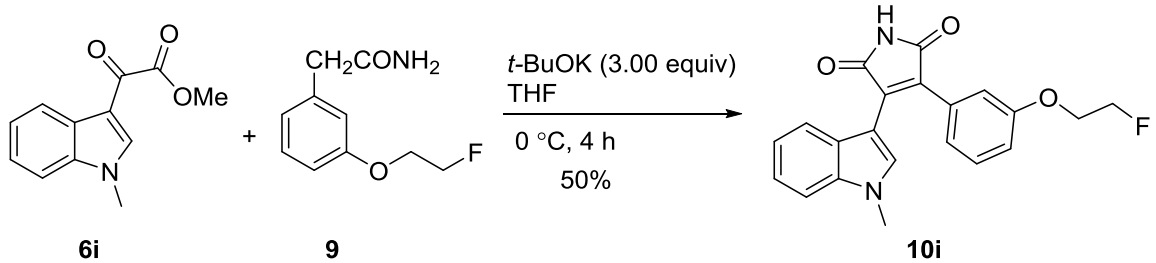
3-(5-Fluoro-1-(2-methoxyethyl)-1*H*-indol-3-yl)-4-(3-(2-fluoroethoxy)phenyl)-1*H*-pyrrole-2,5-dione (10h)



Under N_2 atmosphere, to a suspension of methyl 2-(5-fluoro-1-(2-methoxyethyl)-1*H*-indol-3-yl)-2-oxoacetate (370 mg, 1.32 mmol, 1.00 equiv) and 2-(3-(2-fluoroethoxy)phenyl)acetamide (312 mg, 1.58 mmol, 1.20 equiv) in THF (20 mL, 0.066 M) was slowly added (dropwise) *t*-BuOK solution (415 mg, 3.70 mmol in 15 mL THF, 2.80 equiv) at 0 °C for 30 min. The reaction mixture was stirred at 0 °C for another 4 h. The reaction was quenched with ice water (5.00 mL) at 0 °C and the aqueous layer was extracted with EtOAc (4 × 20.0 mL). The organic extracts were combined, washed with saturated NaCl (aq) (5.00 mL), and then dried over Na_2SO_4. After being concentrated *in vacuo*, the residue was purified by flash chromatography on silica gel (EtOAc:hexanes = 1:2) to afford the title compound as a red fluffy solid (197 mg, 0.462 mmol, 35% yield).

NMR Spectroscopy: ^{1}H NMR (700 MHz, $(CD_3)_2SO$, 25 °C, δ): 11.10 (s, 1H), 8.10 (s, 1H), 7.58 (t, J = 4.4 Hz, 1H), 7.28 (t, J = 7.9 Hz, 1H), 6.90–7.05 (m, 4H), 6.01 (dd, J = 1.8, 10.4 Hz, 1H), 4.62 (td, J = 3.3, 51.1 Hz, 2H), 4.45 (t, J = 4.9 Hz, 2H), 4.07 (td, J = 3.3, 30.0 Hz, 2H), 3.69 (t, J = 4.9 Hz, 2H), 3.23 (s, 3H). ^{13}C NMR (175 MHz, $(CD_3)_2SO$, 25 °C, δ): 172.2, 172.0, 157.7, 157.0 (d, J = 232.5 Hz), 156.3, 135.8, 133.2, 131.9, 131.7, 129.4, 128.6, 125.0 (d, J = 10.9 Hz), 122.5, 115.9, 115.1, 112.0 (d, J = 9.7 Hz), 110.1 (d, J = 25.6 Hz), 106.4 (d, J = 25.1 Hz), 103.4 (d, J = 4.3 Hz), 81.9 (d, J = 165.7 Hz), 70.7, 67.0 (d, J = 19.0 Hz), 58.1, 46.2. ^{19}F NMR (376 MHz, $(CD_3)_2SO$, 25 °C, δ): –124.6 (m), –224.4 (m). HRMS (ESI-TOF) (m/z): calcd for $C_{23}H_{21}F_2N_2O_4$ ($[M + H]^+$), 427.1469, found, 427.1463.

3-(3-(2-Fluoroethoxy)phenyl)-4-(1-methyl-1*H*-indol-3-yl)-1*H*-pyrrole-2,5-dione (10i)

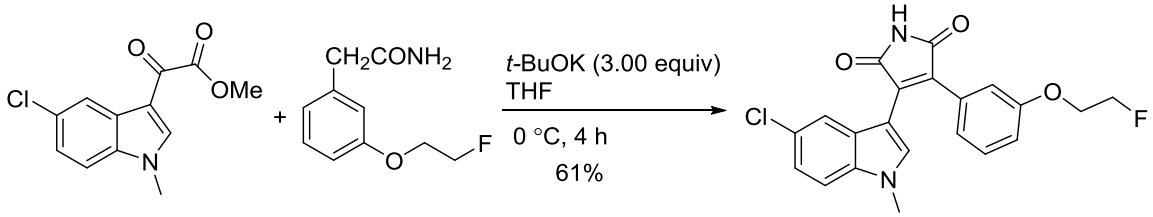


Under N_2 atmosphere, to a suspension of methyl 2-(1-methyl-1*H*-indol-3-yl)-2-oxoacetate (333 mg, 1.53 mmol, 1.00 equiv) and 2-(3-(2-fluoroethoxy)phenyl)acetamide (333 mg, 1.69 mmol, 1.10 quiv) in THF (10.0 mL, 0.153 M) was slowly added (dropwise) *t*-BuOK solution (516 mg, 4.60 mmol in 25 mL THF, 3.00 equiv) at 0 °C for 30 min. The reaction mixture was stirred at 0 °C for another 4 h. The reaction was quenched with HCl (1N, 10.0 mL) at 0 °C and the aqueous layer was extracted with EtOAc (4 × 20.0 mL). The organic extracts were combined, washed with saturated NaCl (aq) (5 mL), and then dried over Na_2SO_4. After being concentrated *in vacuo*, the

residue was purified by flash chromatography on silica gel (EtOAc:hexanes = 1:2) to afford the title compound as a red solid (280 mg, 0.768 mmol, 50% yield).

NMR Spectroscopy: ^{1}H NMR (700 MHz, $(CD_3)_2SO$, 25 °C, δ): 11.08 (s, 1H), 8.04 (s, 1H), 7.49 (d, J = 8.2 Hz, 1H), 7.22 (t, J = 7.6 Hz, 1H), 7.00 (s, 1H), 6.90–6.98 (m, 2H), 6.76 (t, J = 7.6 Hz, 1H), 6.34 (d, J = 8.1 Hz, 1H), 4.60 (td, J = 3.7, 47.8 Hz, 2H), 4.04 (td, J = 3.7, 30.1 Hz, 2H), 3.90 (s, 3H). ^{13}C NMR (175 MHz, $(CD_3)_2SO$, 25 °C, δ): 172.4, 172.2, 157.6, 137.1, 134.9, 132.2, 131.9, 129.2, 128.0, 124.4, 122.5, 122.1, 120.1, 115.9, 114.9, 110.6, 103.1, 81.9 (d, J = 165.6), 67.0 (d, J = 18.9), 33.1. ^{19}F NMR (376 MHz, $(CD_3)_2SO$, 25 °C, δ): –224.4 (m). HRMS (ESI-TOF) (m/z): calcd for $C_{21}H_{18}FN_2O_3$ ([M + H]$^+$), 365.1301, found, 365.1289.

3-(5-Chloro-1-methyl-1*H*-indol-3-yl)-4-(3-(2-fluoroethoxy)phenyl)-1*H*-pyrrole-2,5-dione (10j)

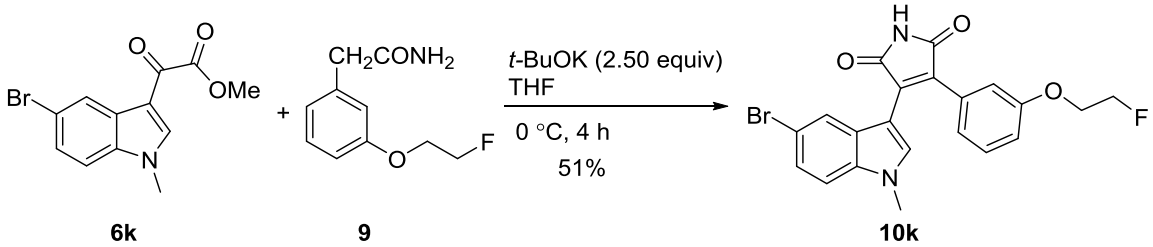


6j **9** **10j**

Under N_2 atmosphere, to a suspension of methyl 2-(5-chloro-1-methyl-1*H*-indol-3-yl)-2-oxoacetate (279 mg, 1.11 mmol, 1.00 equiv) and 2-(3-(2-fluoroethoxy)phenyl)acetamide (262 mg, 1.33 mmol, 1.20 equiv) in THF (20 mL, 0.056 M) was slowly added (dropwise) *t*-BuOK solution (374 mg, 3.33 mmol in 15 mL THF, 3.00 equiv) at 0 °C for 30 min. The reaction mixture was stirred at 0 °C for another 4 h. The reaction was quenched with ice water (5.00 mL) at 0 °C and the aqueous layer was extracted with EtOAc (4 × 20.0 mL). The organic extracts were combined, washed with saturated NaCl (aq) (5.00 mL), and then dried over Na_2SO_4. After being concentrated *in vacuo*, the residue was purified by flash chromatography on silica gel (EtOAc:hexanes = 1:2) to afford the title compound as a yellow solid (270 mg, 0.677 mmol, 61% yield).

NMR Spectroscopy: ^{1}H NMR (700 MHz, $(CD_3)_2SO$, 25 °C, δ): 11.11 (s, 1H), 8.10 (s, 1H), 7.52 (d, J = 8.6 Hz, 1H), 7.28 (t, J = 7.9 Hz, 1H), 7.14 (dd, J = 1.8, 8.6 Hz, 1H), 7.03 (dd, J = 2.3, 8.3 Hz, 1H), 6.98 (s, 1H), 6.94 (d, J = 7.6 Hz, 1H), 6.21 (d, J = 1.8 Hz, 1H), 4.62 (td, J = 3.8, 47.8 Hz, 2H), 4.08 (td, J = 3.8, 30.0 Hz, 2H), 3.90 (s, 3H). ^{13}C NMR (175 MHz, $(CD_3)_2SO$, 25 °C, δ): 172.2, 172.0, 157.8, 136.1, 135.5, 131.8, 129.3, 128.8, 125.5, 124.9, 122.6, 121.9, 121.0, 116.2, 115.1, 112.0, 102.9, 81.9 (d, J = 166.1 Hz), 67.2 (d, J = 19.0 Hz), 20.8. ^{19}F NMR (376 MHz, $(CD_3)_2SO$, 25 °C, δ): –224.4 (m). HRMS (ESI-TOF) (m/z): calcd for $C_{21}H_{17}ClFN_2O_3$ ([M + H]$^+$), 399.0912, found, 399.0900.

3-(5-Bromo-1-methyl-1*H*-indol-3-yl)-4-(3-(2-fluoroethoxy)phenyl)-1*H*-pyrrole-2,5-dione (10k)

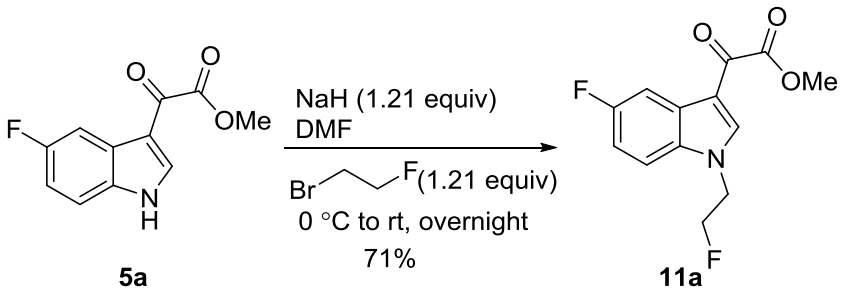


6k **9** **10k**

Under N_2 atmosphere, to a suspension of methyl 2-(5-bromo-1-methyl-1*H*-indol-3-yl)-2-oxoacetate (120 mg, 0.405 mmol, 1.00 equiv) and 2-(3-(2-fluoroethoxy)phenyl)acetamide (87.9 mg, 0.446 mmol, 1.10 equiv) in THF (10 mL, 0.041 M) was slowly added (dropwise) *t*-BuOK solution (114 mg, 1.01 mmol in 10 mL THF, 2.50 equiv) at 0 °C for 30 min. The reaction mixture was stirred at 0 °C for another 4 h. The reaction was quenched with ice water (5.00 mL) at 0 °C and the aqueous layer was extracted with EtOAc (4 × 20.0 mL). The organic extracts were combined, washed with saturated NaCl (aq) (5.00 mL), and then dried over Na_2SO_4. After being concentrated *in vacuo*, the residue was purified by flash chromatography on silica gel (EtOAc:hexanes = 1:2) to afford the title compound as a yellow solid (91.6 mg, 0.207 mmol, 51% yield).

^{1}H NMR (700 MHz, DMSO) δ 11.11 (s, 1H), 8.09 (s, 1H), 7.46 (d, J = 8.6 Hz, 1H), 7.31–7.22 (m, 2H), 7.07–7.02 (m, 1H), 6.97 (s, 1H), 6.93 (d, J = 7.5 Hz, 1H), 6.35 (s, 1H), 4.68–4.64 (m, 1H), 4.61–4.57 (m, 1H), 4.13–4.09 (m, 1H), 4.08–4.05 (m, 1H), 3.89 (s, 3H). ^{13}C NMR (175 MHz, $(CD_3)_2SO$, 25 °C, δ): 172.1, 172.0, 157.8, 136.0, 135.7, 128.9, 124.5, 122.6, 116.2, 112.9, 112.5, 102.7, 82.4, 81.9 (d, J = 166.3 Hz), 67.2 (d, J = 19.3 Hz), 33.2. ^{19}F NMR (376 MHz, $(CD_3)_2SO$, 25 °C, δ): –224.3 (s). HRMS (ESI-TOF) (m/z): calcd for $C_{21}H_{17}BrFN_2O_3$ ([M + H]$^+$), 433.0407, found, 433.0421.

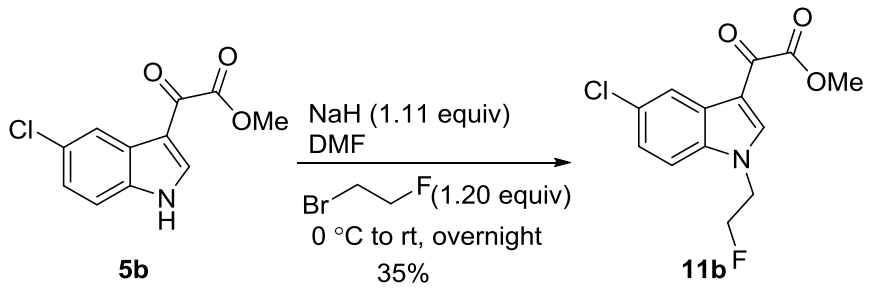
Methyl 2-(5-fluoro-1-(2-fluoroethyl)-1*H*-indol-3-yl)-2-oxoacetate (11a)



To a solution of methyl 2-(5-fluoro-1*H*-indol-3-yl)-2-oxoacetate (0.55 g, 2.48 mmol, 1.00 equiv) in anhydrous DMF (10.0 mL, 0.248 M) was added sodium hydride (57-63% suspension in mineral oil, 119 mg, 3.00 mmol, 1.21 equiv) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min before 1-bromo-2-fluoroethane (378 mg, 3.00 mmol, 1.21 equiv) was added. The reaction mixture was stirred overnight at room temperature. The reaction was quenched with ice water (40.0 mL) and the aqueous layer was extracted with EtOAc (4 × 30.0 mL). The organic extracts were combined, washed with 5% LiCl(aq) (5.00 mL), and then dried over Na_2SO_4. After being concentrated *in vacuo*, the residue was purified by flash chromatography on silica gel (EtOAc:hexanes = 1:1) to afford the title compound as a yellow solid (0.47 g, 1.76 mmol, 71% yield).

NMR Spectroscopy: ^{1}H NMR (700 MHz, CD_3Cl, 25 °C, δ): 8.44 (d, J = 4.3 Hz, 1H), 8.08–8.12 (m, 1H), 7.27–7.32 (m, 1H), 7.04–7.09 (m, 1H), 4.79 (td, J = 4.6, 46.8 Hz, 2H), 4.42–4.51 (m, 2H), 3.95 (d, J = 2.0 Hz, 3H). ^{13}C NMR (175 MHz, CD_3Cl, 25 °C, δ): 177.0, 163.0, 160.4 (d, J = 238 Hz), 140.9, 133.2, 128.1 (d, J = 11.0 Hz), 113.5 (d, J = 3.4 Hz), 112.8 (d, J = 26.3 Hz), 111.0 (d, J = 9.8 Hz), 108.5 (dd, J = 4.0, 25.0 Hz), 81.5 (d, J = 172.6 Hz), 53.0, 48.0.

Methyl 2-(5-chloro-1-(2-fluoroethyl)-1*H*-indol-3-yl)-2-oxoacetate (11b)

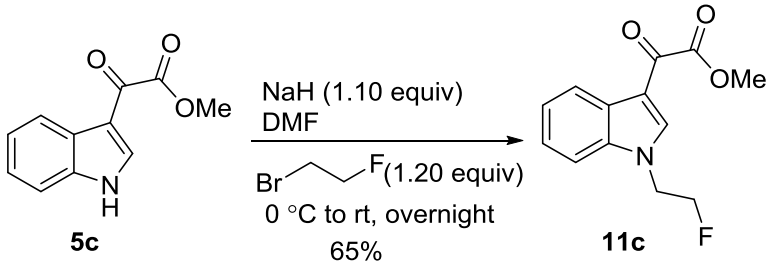


5b **11b**

To a solution of 2-(5-chloro-1*H*-indol-3-yl)-2-oxoacetate (1.70 g, 7.14 mmol, 1.00 equiv) in anhydrous DMF (30.0 mL, 0.238 M) was added sodium hydride (57-63% suspension in mineral oil, 316 mg, 7.90 mmol, 1.11 equiv) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min before 1-bromo-2-fluoroethane (1.09 g, 8.57 mmol, 1.20 equiv) was added. The reaction mixture was stirred overnight at room temperature. The reaction was quenched with ice water (60.0 mL) and the aqueous layer was extracted with EtOAc (6 × 30.0 mL). The organic extracts were combined, washed with 5% LiCl(aq) (5.00 mL), and then dried over Na_2SO_4. After being concentrated *in vacuo*, the residue was purified by flash chromatography on silica gel (EtOAc:hexanes = 1:1) to afford the title compound as a white solid (700 mg, 2.47 mmol, 35% yield).

NMR Spectroscopy: ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, δ): 8.47 (s, 1H), 8.45 (d, J = 1.7 Hz, 1H), 7.28–7.35 (m, 2H), 4.81 (td, J = 4.8, 46.8 Hz, 2H), 4.49 (td, J = 4.8, 26.2 Hz, 2H), 3.98 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C, δ): 177.0, 163.0, 140.6, 135.1,130.0, 128.3, 124.9, 122.6, 113.2, 111.0, 81.4 (d, J = 173.2 Hz), 53.0, 47.9 (d, J = 21.3 Hz).

Methyl 2-(5-fluoro-1-(2-fluoroethyl)-1*H*-indol-3-yl)-2-oxoacetate (11c)

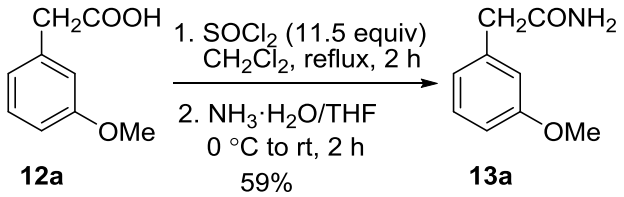


5c **11c**

To a solution of methyl 2-(1*H*-indol-3-yl)-2-oxoacetate (983 mg, 4.84 mmol, 1.00 equiv) in anhydrous DMF (20.0 mL, 0.242 M) was added sodium hydride (57-63% suspension in mineral oil, 213 mg, 5.32 mmol, 1.10 equiv) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min before 1-bromo-2-fluoroethane (737 mg, 5.81 mmol, 1.20 equiv) was added. The reaction mixture was stirred overnight at room temperature. The reaction was quenched with ice water (40.0 mL) and the aqueous layer was extracted with EtOAc (6 × 30.0 mL). The organic extracts were combined, washed with 5% LiCl(aq) (5.00 mL), and then dried over Na_2SO_4. After being concentrated *in vacuo*, the residue was purified by flash chromatography on silica gel (EtOAc:hexanes = 1:1) to afford the title compound as a white solid (780 mg, 3.13 mmol, 65% yield).

NMR Spectroscopy: ^{1}H NMR (700 MHz, $CDCl_3$, 25 °C, δ): 8.46–8.50 (m, 1H), 8.44 (s, 1H), 7.32–7.42 (m, 3H), 4.80 (td, J = 4.8, 46.8 Hz, 2H), 4.49 (td, J = 4.8, 26.0 Hz, 2H), 3.97 (s, 3H). ^{13}C NMR (175 MHz, $CDCl_3$, 25 °C, δ): 177.3, 163.3, 140.1, 136.8, 127.3, 124.6, 123.9, 123.2, 113.7, 110.0, 81.5 (J = 172 Hz), 53.0, 47.7 (J = 21.0 Hz).

2-(3-Methoxyphenyl)acetamide (13a)

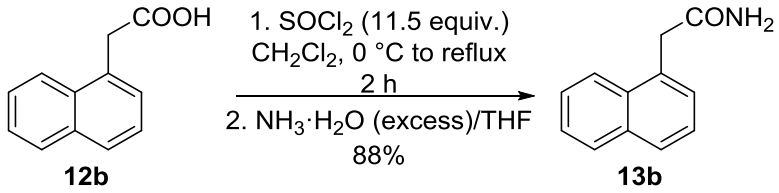


12a 13a

To a solution of 2-(3-methoxyphenyl)acetic acid (1.00 g, 6.00 mmol, 1.00 equiv) in dry CH_2Cl_2 (20.0 mL, 0.300 M) was added thionyl chloride (5 mL, 69.0 mmol, 11.5 equiv) at 0 °C. The reaction mixture was refluxed for 2 h. The solvent was evaporated and the residue was azeotroped with toluene (2 × 10.0 mL. THF (30.0 mL) was added to the residue followed by a slow addition of $NH_3 \cdot H_2O$ (7.00 mL, 28-30%) under vigorous stirring at 0 °C. After stirring at room temperature for 2 h, the solvent was removed, Water (10.0 mL) was added and the mixture was heated for 10 min while stirring. The suspension was cooled to 0 °C, filtered and the residue was washed with ice water. The product was dried overnight to afford the title compound as a white solid (580 mg, 3.51 mmol, 59% yield).

NMR Spectroscopy: ^{1}H NMR (700 MHz, $(CD_3)_2SO$, 25 °C, δ): 7.46 (s, 1H), 7.20 (t, J = 7.8 Hz, 1H), 6.87 (s, 1H), 6.83 (s, 1H), 6.82 (s, 1H), 6.79 (dd, J = 1.9, 8.2 Hz, 1H), 3.72 (s, 3H), 3.32 (s, 2H). ^{13}C NMR (175 MHz, $(CD_3)_2SO$, 25 °C, δ): 172.1, 159.1, 138.0, 129.1, 121.3, 114.8, 111.7, 54.9, 42.3. All the analytical data were in good agreement with values reported in the literature.[8]

2-(Naphthalen-1-yl)acetamide (13b)

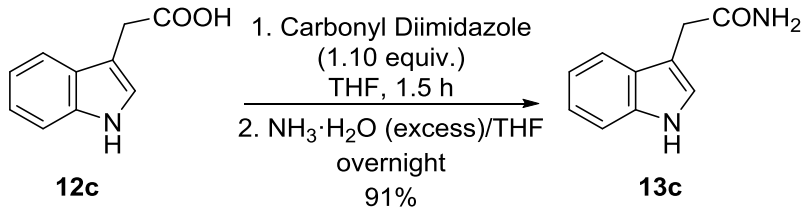


12b 13b

To a solution of 2-(naphthalen-1-yl)acetic acid (1.50 g, 8.01 mmol, 1.00 equiv.) in dry CH_2Cl_2 (10.0 mL, 0.801 M) was added thionyl chloride (6.73 mL, 92.6 mmol, 11.5 equiv.) at 0 °C, then the reaction was refluxed for 2 h. The solvent was evaporated and the residue was azeotroped with toluene (2 × 10.0 mL). To the crude acyl chloride was added THF (30.0 mL) and $NH_3 \cdot H_2O$ (30.0 mL) under vigorous stirring at 0 °C. After the reaction mixture was stirred at room temperature for overnight, the solvent was removed. The residue was purified by column chromatography using with EtOAc:hexane (1 :2 (v/v)) to afford the title compound as a white solid (1.31 g, 7.07 mmol, 88% yield).

NMR Spectroscopy: ^{1}H NMR (700 MHz, $(CD_3)_2SO$, 25 °C, δ): 8.08 (d, J = 8.3 Hz, 1H), 7.92 (d, J = 7.7 Hz, 1H), 7.81 (d, J = 7.7 Hz, 1H), 7.56–7.49 (m, 3H), 7.45–7.41 (m, 2H), 6.99 (s, 1H), 3.86 (s, 2H). ^{13}C NMR (175 MHz, $(CD_3)_2SO$, 25 °C, δ): 172.1, 133.3, 132.9, 132.0, 128.3, 127.8, 126.9, 125.9, 125.5, 125.5, 124.2. The ^{1}H NMR data were in good agreement with values reported in the literature.[9]

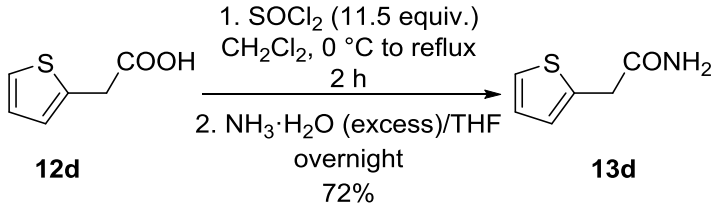
2-(1*H*-Indol-3-yl)acetamide (13c)



To a solution of indole-3-acetic acid (1.00 g, 5.70 mmol, 1.00 equiv.) in THF (15.0 mL, 0.380 M) was added carbonyl diimidazole (1.02 g, 6.28 mmol, 1.10 equiv.). The resulting solution was stirred at room temperature for 1.5 h. Then $NH_3 \cdot H_2O$ (20.0 mL) was added, and the reaction was stirred at room temperature for 18 h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography using EtOAc:hexane (2:1 (v/v)). The purification gave the title compound as a white solid (0.902 g, 5.12 mmol, 91% yield).

NMR Spectroscopy: ^{1}H NMR (500 MHz, $(CD_3)_2SO$, 25 °C, δ): 10.84 (s, 1H), 7.54 (d, J = 7.9 Hz, 1H), 7.33 (d, J = 8.1 Hz, 1H), 7.26 (s, 1H), 7.17 (d, J = 2.3 Hz, 1H), 7.06–7.03 (m, 1H), 6.97–6.94 (m, 1H), 6.80 (s, 1H), 3.45 (s, 2H). ^{13}C NMR (125 MHz, $(CD_3)_2SO$, 25 °C, δ): 172.8, 136.0, 127.2, 123.7, 120.8, 118.6, 118.2, 111.2, 109.0, 32.4. All the analytical data were in good agreement with values reported in the literature.[10]

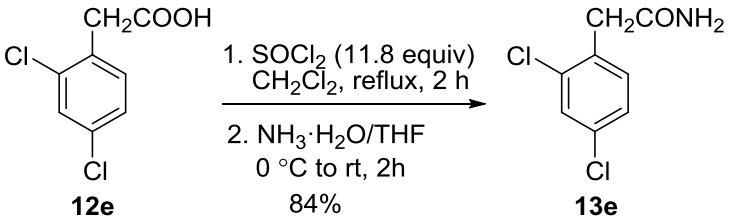
2-(Thiophen-2-yl)acetamide (13d)



To a solution of 2-thiopheneacetic acid (500 mg, 3.52 mmol, 1.00 equiv.) in dry CH_2Cl_2 (10.0 mL) was added thionyl chloride (2.94 mL, 40.4 mmol, 11.5 equiv.) at 0 °C, then the reaction was refluxed for 2 h. The solvent was removed under reduced pressure and the residue was azeotroped with toluene (2 × 5.00 mL). $NH_3 \cdot H_2O$ (10.0 mL) was added to the crude acyl chloride residue in THF (10.0 mL) at 0 °C. After the reaction mixture was stirred at room temperature for overnight, the organic solvent was removed under reduced pressure, and the aqueous mixture was extracted with CH_2Cl_2 (20.0 mL × 3), the organic extracts were dried with $MgSO_4$ and concentrated to afford the title compound as a white solid (0.356 g, 2.52 mmol, 72% yield).

NMR Spectroscopy: ^{1}H NMR (700 MHz, $(CD_3)_2SO$, 25 °C, δ): 7.49 (s, 1H), 7.33–7.27 (m, 1H), 6.96 (s, 1H), 6.93 (t, J = 2.2 Hz, 1H), 6.88 (s, 1H), 3.58 (s, 2H). ^{13}C NMR (175 MHz, $(CD_3)_2SO$, 25 °C, δ): 171.1, 137.7, 126.5, 126.0, 124.7, 36.3. The ^{1}H NMR data were in good agreement with values reported in the literature.[11]

2-(2,4-Dichlorophenyl)acetamide (13e)

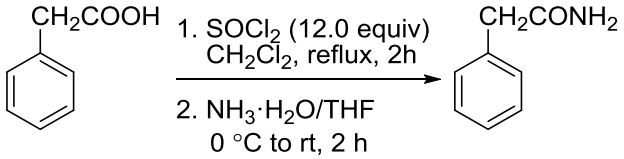


12e **13e**

To a solution of 2-(2,4-dichlorophenyl)acetic acid (3.60 g, 17.6 mmol, 1.00 equiv) in dry CH_2Cl_2 (60.0 mL, 0.293 M) was added thionyl chloride (15.0 mL, 207 mmol, 11.8 equiv) at 0 °C. The reaction mixture was refluxed for 2 h. The solvent was evaporated and the residue was azeotroped with toluene (2 × 5.00 mL). The residue was dissolved in THF (30.0 mL) and the resulting solution was cooled to 0 °C. $NH_3 \cdot H_2O$ (30.0 mL, 28-30%) was added slowly under vigorous stirring. The mixture was warmed to room temperature and stirred for 2 h. The solvent was removed, water (10.0 mL) was added and the resulting mixture was heated for 10 min while stirring. The suspension was cooled to 0 °C and filtered. The residue was washed with ice water (20.0 mL). The product was dried under vacuum for overnight to afford the title compound as a white solid (3.00 g, 14.7 mmol, 84% yield).

NMR Spectroscopy: ^{1}H NMR (700 MHz, $(CD_3)_2SO$, 25 °C, δ): 7.55 (s, 1H), 7.50 (s, 1H), 7.30–7.40 (m, 2H), 7.02 (s, 1H), 3.56 (s, 2H). ^{13}C NMR (175 MHz, $(CD_3)_2SO$, 25 °C, δ): 170.6, 134.6, 133.6, 133.4, 131.9, 128.3, 127.1. The ^{1}H NMR data was in good agreement with values reported in the literature.[6]

2-Phenylacetamide (13f)

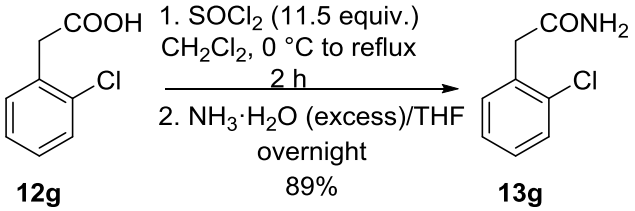


12f **13f**

To a solution of 2-phenylacetic acid (3.00 g, 22.0 mmol, 1.00 equiv) in dry CH_2Cl_2 (70.0 mL, 0.314 M) was added thionyl chloride (19.2 mL, 264 mmol, 12.0 equiv) at 0 °C. The reaction mixture was refluxed for 2 h. The solvent was evaporated and the residue was azeotroped with toluene (2 × 5 mL). The residue was dissolved in THF (30.0 mL) and the resulting solution was cooled to 0 °C. $NH_3 \cdot H_2O$ (40.0 mL, 28-30%) was added slowly under vigorous stirring. The mixture was warmed to room temperature and stirred for 2 h. The solvent was removed, water (20.0 mL) was added and the resulting mixture was heated for 10 min while stirring. The suspension was cooled to 0 °C and filtered. The residue was washed with ice water (20.0 mL). The product was dried under vacuum overnight to afford the title compound as a white solid (2.66 g, 19.6 mmol, 89% yield).

NMR Spectroscopy: ^{1}H NMR (700 MHz, $(CD_3)_2SO$, 25 °C, δ): 7.49 (s, 1H), 7.24–7.36 (m, 4H), 7.20–7.24 (m, 1H), 6.91 (s, 1H), 3.38 (d, J = 2.4 Hz, 1H). ^{13}C NMR (175 MHz, $(CD_3)_2SO$, 25 °C, δ): 172.3, 136.5, 129.1, 128.2, 126.3, 42.3. All the analytical data were in good agreement with values reported in the literature.[12]

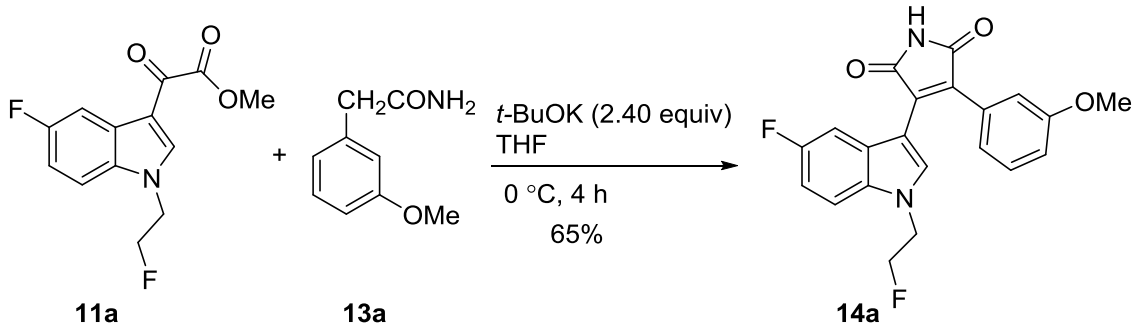
2-(2-Chlorophenyl)acetamide (13g)



To a solution of 2-chlorophenylacetic acid **12g** (2.00 g, 11.80 mmol, 1.00 equiv.) in dry CH_2Cl_2 (30.0 mL) was added thionyl chloride (9.80 mL, 135.3 mmol, 11.5 equiv.) at 0 °C. The reaction was refluxed for 2 h. The solvent was removed under reduced pressure and the residue was azeotroped with toluene (2 × 5.00 mL). To a solution of crude acyl chloride in THF (30.0 mL) was added $NH_3 \cdot H_2O$ (60.0 mL), and the reaction was stirred at room temperature for overnight. The solvent was removed under reduced pressure, and the precipitate was filtered, washed with water, and dried under vacuum to afford the title compound as a white solid (1.77 g, 10.5 mmol, 89% yield).

NMR Spectroscopy: ^{1}H NMR (500 MHz, $(CD_3)_2SO$, 25 °C, δ): 7.44 (s, 1H), 7.41–7.38 (m, 1H), 7.35–7.33 (m, 1H), 7.28–7.24 (m, 2H), 6.96 (s, 1H), 3.54 (s, 2H). ^{13}C NMR (125 MHz, $(CD_3)_2SO$, 25 °C, δ): 170.8, 134.3, 133.5, 132.0, 128.8, 128.2, 126.9. The ^{1}H NMR data was in good agreement with values reported in the literature.[13]

3-(5-Fluoro-1-(2-fluoroethyl)-1*H*-indol-3-yl)-4-(3-methoxyphenyl)-1*H*-pyrrole-2,5-dione (14a)

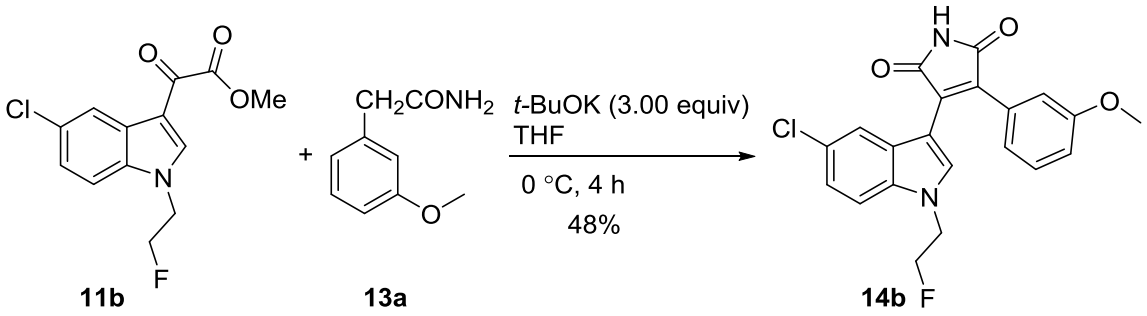


Under N_2 atmosphere, to a suspension of methyl 2-(5-fluoro-1-(2-fluoroethyl)-1*H*-indol-3-yl)-2-oxoacetate (153 mg, 0.57 mmol, 1.00 equiv) and 2-(3-methoxyphenyl)acetamide (104 mg, 0.627 mmol, 1.10 equiv) in THF (10.0 mL, 0.057 M) was slowly added (dropwise) *t*-BuOK solution (154 mg, 1.37 mmol in 15 mL THF, 2.40 equiv) at 0 °C for 30 min. The reaction mixture was stirred at 0 °C for another 4 h. The reaction was quenched with ice water (5.00 mL) at 0 °C. The reaction was quenched with HCl (1N, 4 mL) at 0 °C and the aqueous layer was extracted with EtOAc (4 × 10.0 mL). The organic extracts were combined, washed with saturated NaCl (aq) (5.00 mL), and then dried over Na_2SO_4. After being concentrated *in vacuo*, the residue was purified by flash chromatography on silica gel (EtOAc:hexanes = 1:2) to afford the title compound as a red solid (142 mg, 0.371 mmol, 65% yield).

NMR Spectroscopy: ^{1}H NMR (400 MHz, $(CD_3)_2SO$, 25 °C, δ): 11.11 (s, 1H), 8.13 (s, 1H), 7.59 (dd, J = 4.5, 9.0 Hz, 1H), 7.24–7.30 (m, 1H), 6.90–7.00 (m, 4H), 5.99 (dd, J = 2.5, 10.6 Hz, 1H), 4.58–4.86 (m, 4H), 3.58 (s, 3H). ^{13}C NMR (100 MHz, $(CD_3)_2SO$, 25 °C, δ): 172.1, 172.0, 158.8, 157.0 (d, J = 232.6 Hz), 135.6, 133.2, 131.7, 131.5, 129.3, 129.2, 125.1 (d, J = 10.6 Hz), 122.1, 115.2, 114.5, 112.0 (d, J = 9.5 Hz), 110.2 (d, J = 25.9 Hz), 106.5 (d, J = 25.1 Hz), 103.8 (d, J = 4.3

Hz), 82.6 (d, J = 166.9 Hz), 55.0, 46.7 (d, J = 19.4 Hz). ^{19}F NMR (376 MHz, $(CD_3)_2SO$, 25 °C, δ): –124.4 (m), –221.9 (m). HRMS (ESI-TOF) (m/z): calcd for $C_{21}H_{17}F_2N_2O_3$ ([M + H]$^+$), 383.1207, found, 383.1211.

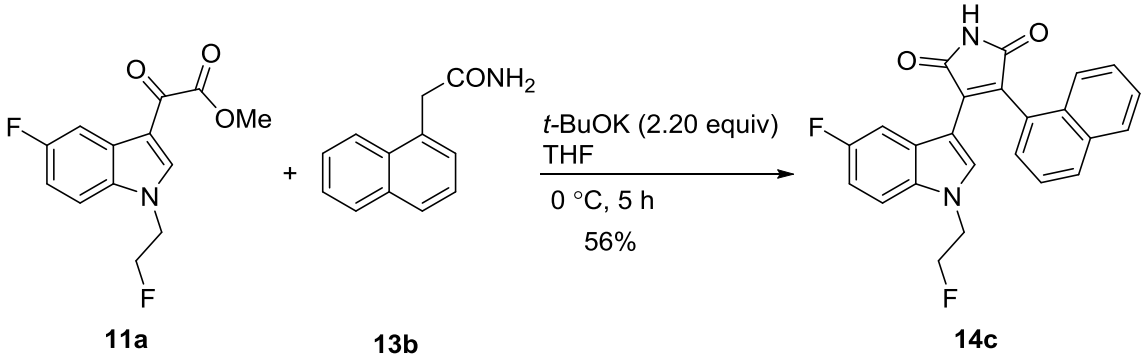
3-(5-Chloro-1-(2-fluoroethyl)-1*H*-indol-3-yl)-4-(3-methoxyphenyl)-1*H*-pyrrole-2,5-dione (14b)



Under N_2 atmosphere, to a suspension of methyl 2-(5-chloro-1-(2-fluoroethyl)-1*H*-indol-3-yl)-2-oxoacetate (281 mg, 0.99 mmol, 1.00 equiv) and 2-(3-methoxyphenyl)acetamide (196 mg, 1.19 mmol, 1.20 equiv) in THF (10.0 mL, 0.099 M) was slowly added (dropwise) *t*-BuOK solution (333 mg, 2.97 mmol in 15 mL THF, 3.00 equiv) at 0 °C for 30 min. The reaction mixture was stirred at 0 °C for another 4 h. The reaction was quenched with ice water (5.00 mL) at 0 °C and the aqueous layer was extracted with EtOAc (4 × 20 mL). The organic extracts were combined, washed with saturated NaCl (aq) (5.00 mL), and then dried over Na_2SO_4. After being concentrated *in vacuo*, the residue was purified by flash chromatography on silica gel (EtOAc:hexanes = 1:2) to afford the title compound as a yellow solid (190 mg, 0.476 mmol, 48% yield).

NMR Spectroscopy: ^{1}H NMR (700 MHz, $(CD_3)_2SO$, 25 °C, δ): 11.13 (s, 1H), 8.14 (s, 1H), 7.60 (d, J = 8.6 Hz, 1H), 7.28 (t, J = 7.9 Hz, 1H), 7.14 (d, J = 8.6 Hz, 1H), 7.00 (d, J = 8.2 Hz, 1H), 6.96 (d, J = 7.6 Hz, 1H), 6.92 (s, 1H), 6.25 (d, J = 1.4 Hz, 1H), 4.77 (td, J = 4.4, 47.3 Hz, 2H), 4.65 (td, J = 4.2, 28.0 Hz, 2H), 3.58 (s, 3H). ^{13}C NMR (175 MHz, $(CD_3)_2SO$, 25 °C, δ): 172.1, 171.9, 158.9, 135.3, 135.0,131.6, 131.5, 129.6, 129.3, 125.6., 124.8, 122.1, 122.0, 121.0, 115.3, 114.6, 112.3, 103.5, 82.7 (d, J = 166.8 Hz), 55.0 (d, J = 20.8 Hz), 46.6 (d, J = 19.4 Hz). ^{19}F NMR (376 MHz, $(CD_3)_2SO$, 25 °C, δ): –222.0 (m). HRMS (ESI-TOF) (m/z): calcd for $C_{21}H_{17}ClFN_2O_3$ ([M + H]$^+$), 399.0912, found, 399.0909.

3-(5-Fluoro-1-(2-fluoroethyl)-1*H*-indol-3-yl)-4-(naphthalen-1-yl)-1*H*-pyrrole-2,5-dione (14c)

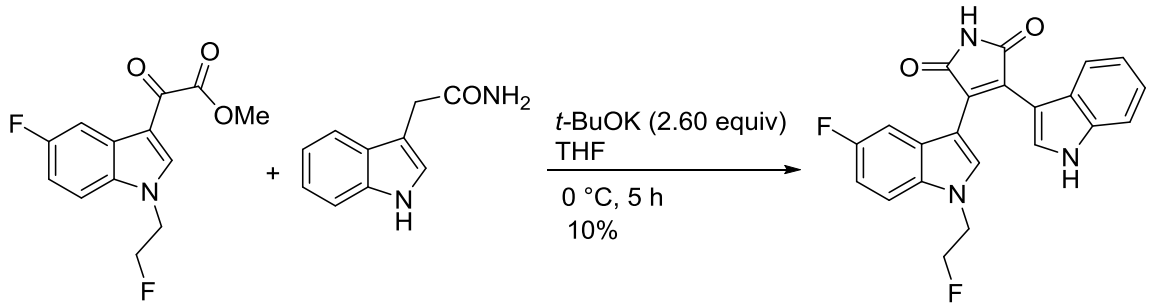


To a solution of compound methyl 2-(5-fluoro-1-(2-fluoroethyl)-1H-indol-3-yl)-2-oxoacetate (27.7 mg, 0.104 mmol, 1.00 equiv.) 2-(naphthalen-1-yl)acetamide (25.0 mg, 0.135 mmol, 1.30

equiv) in THF (5.00 mL, 0.021 M) was added with *t*-BuOK solution (32.6 mg, 0.291 mmol, 2.20 equiv.)/THF (3.00 mL) under nitrogen atmosphere at 0 °C. After the reaction mixture was stirred at 0 °C for another 5 h, it was quenched with 1 N $HCl_{(aq)}$ (5 mL). The excess acid was neutralized by sodium bicarbonate, and the solution was extracted with EtOAc (5.00 mL × 3). The organic layer was washed with water, brine, and dried over Na_2SO_4. The reaction mixture was then concentrated and the residue purified by column chromatography using EtOAc:hexane (1:2 (v/v))) to afford the title compound as a yellow solid (23.3 mg, 0.058 mmol, 56% yield).

NMR Spectroscopy: ^{1}H NMR (700 MHz, $(CD_3)_2SO$, 25 °C, δ): 11.19 (s, 1H), 8.19 (s, 1H), 8.05 (d, *J* = 8.3 Hz, 1H), 7.97 (d, *J* = 8.1 Hz, 1H), 7.71 (d, *J* = 8.3 Hz, 1H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.49–7.43 (m, 3H), 7.35–7.33 (m, *J* = 2.7 Hz, 1H), 6.82 (dt, *J* = 2.5, 13.4 Hz, 1H), 5.63 (dd, *J* = 2.5, 10.9 Hz, 1H), 4.73 (q, *J* = 4.3 Hz, 1H), 4.66 (q, *J* = 4.3 Hz, 1H), 4.61 (t, *J* = 4.6 Hz, 1H), 4.56 (t, *J* = 4.6 Hz, 1H). ^{13}C NMR (175 MHz, $(CD_3)_2SO$, 25 °C, δ): 172.3, 172.1, 135.8), 134.4, 133.0, 132.9, 131.1, 129.3, 128.8, 128.7, 128.6, 128.3, 126.3, 126.1, 125.7, 125.6, 125.2, 111.7 (d, *J* =9.6 Hz), 110.1 (d, *J* = 26.5 Hz), 105.7 (d, *J* = 25.2 Hz), 104.7 (d, *J* = 3.8 Hz), 83.0, 82.0, 46.6 (d, *J* = 19.6 Hz). ^{19}F NMR (376 MHz, $(CD_3)_2SO$, 25 °C, δ): –124.8 (m), –221.9 (m). HRMS (ESI-TOF) (m/z): calcd for $C_{24}H_{17}N_2O_2F_2$ ($[M + H]^+$), 383.1196, found, 383.1196.

3-(5-Fluoro-1-(2-fluoroethyl)-1*H*-indol-3-yl)-4-(1*H*-indol-3-yl)-1*H*-pyrrole-2,5-dione (14d)

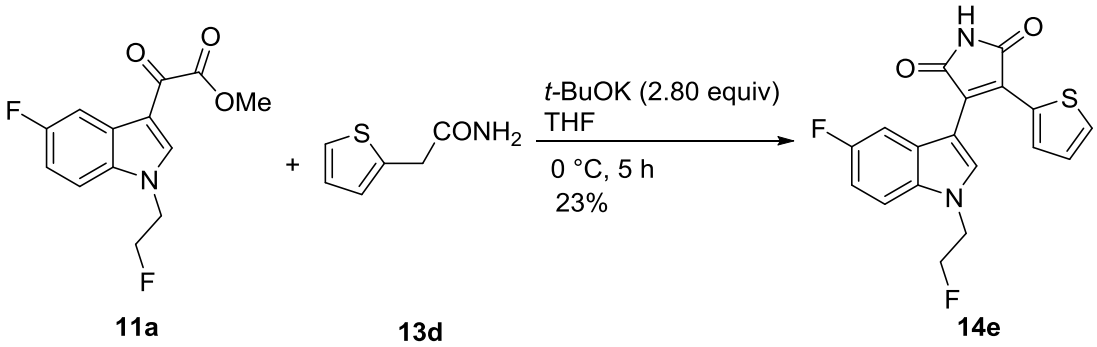


11a **13c** **14d**

To a solution of compound methyl 2-(5-fluoro-1-(2-fluoroethyl)-1H-indol-3-yl)-2-oxoacetate (100.0 mg, 0.370 mmol, 1.00 equiv.) and 2-(1*H*-indol-3-yl)acetamide (78.2 mg, 0.450 mmol, 1.20 equiv.) in THF (5.00 mL, 0.074 M) was added with *t*-BuOK solution (109 mg, 0.970 mmol, 2.60 equiv.)/THF (5.00 mL) under nitrogen atmosphere at 0 °C. After the reaction mixture was stirred at 0 °C for another 5 h, it was quenched with 1 N $HCl_{(aq)}$ (10.0 mL). The excess acid was neutralized by sodium bicarbonate, and the solution was extracted with EtOAc (5 mL × 3). The organic layer was washed with water, brine, and dried over Na_2SO_4. The reaction mixture was concentrated and the residue was purified by column chromatography using EtOAc : hexane (1:1.5 (v/v)) to afford the title compound as an orange solid (15.0 mg, 0.038 mmol, 10% yield).

NMR Spectroscopy: ^{1}H NMR (700 MHz, $(CD_3)_2SO$, 25 °C, δ): 11.73 (d, *J* = 2.2 Hz, 1H), 11.09 (s, 1H), 7.86 (s, 1H), 7.79 (d, *J* = 2.8 Hz, 1H), 7.52 (q, *J* = 4.5 Hz, 1H), 7.39 (d, *J* = 8.1 Hz, 1H), 7.00 (dt, *J* = 1.0, 11.6 Hz, 1H), 6.89 (dt, *J* = 2.6, 9.0 Hz, 1H), 6.72 (d, *J* = 8.1 Hz, 1H), 6.63–6.60 (m, 1H), 6.49 (dd, *J* = 2.5, 10.4 Hz, 1H), 5.75 (s, 1H), 4.71 (t, *J* = 4.6 Hz, 1H), 4.65 (t, *J* = 4.7 Hz, 1H), 4.60 (t, *J* = 4.6 Hz, 1H), 4.55 (t, *J* = 4.7 Hz, 1H). ^{13}C NMR (175 MHz, $(CD_3)_2SO$, 25 °C, δ): 172.8, 157.5, 156.1, 136.0, 133.6, 132.7,129.3, 128.2, 126.4, 125.2, 121.7, 120.7, 119.3, 111.6, 109.9 (d, *J* = 25.7 Hz), 106.0 (d, *J* = 24.3 Hz), 105.5 (d, *J* = 3.8 Hz), 105.3, 83.2, 82.2, 54.9, 46.5 (d, *J* = 19.4 Hz). ^{19}F NMR (376 MHz, $(CD_3)_2SO$, 25 °C, δ): –125.1 (m), –221.5 (m). HRMS (ESI-TOF) (m/z): calcd for $C_{22}H_{16}N_3O_2F_2$ ($[M + H]^+$), 392.1211, found, 392.1207.

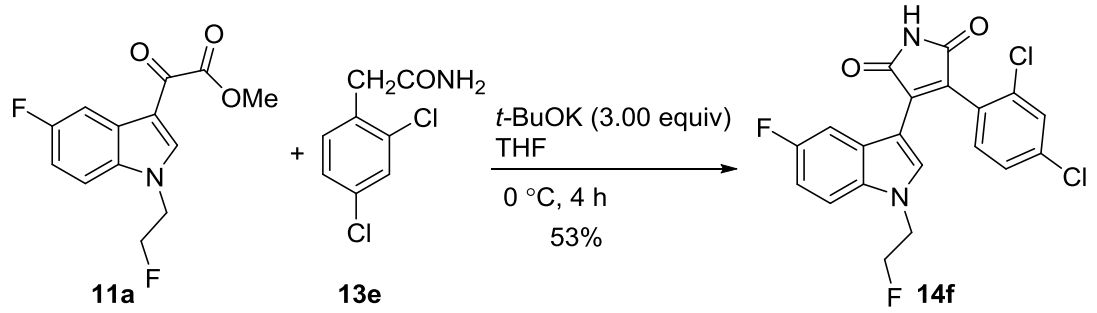
3-(5-Fluoro-1-(2-fluoroethyl)-1*H*-indol-3-yl)-4-(thiophen-2-yl)-1*H*-pyrrole-2,5-dione (14e)



To a solution of compound methyl 2-(5-fluoro-1-(2-fluoroethyl)-1H-indol-3-yl)-2-oxoacetate (100 mg, 0.370 mmol, 1.00 equiv.) and 2-(thiophen-2-yl)acetamide (69.3 mg, 0.490 mmol, 1.30 equiv.) in THF (5.00 mL, 0.074 M) was added with *t*-BuOK solution (116 mg, 1.04 mmol, 2.80 equiv.)/THF (5.00 mL) at 0 °C under nitrogen atmosphere. After the reaction mixture was stirred at 0 °C for another 5 h, it was quenched by 1 N HCl (10.0 mL). The excess acid was neutralized by sodium bicarbonate. The solution was extracted by EtOAc (10 mL x 3), washed with brine, dried with anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography using EtOAc:hexane (1:2 (v/v)) to afford the title compound a red solid (31.4 mg, 0.088 mmol, 23% yield).

NMR Spectroscopy: ^{1}H NMR (300 MHz, $(CD_3)_2SO$, 25 °C, δ): 11.19 (s, 1H), 8.02 (s, 1H), 7.77 (d, J = 5.04 Hz, 1H), 7.67 (q, J = 4.23 Hz, 1H), 7.26 (d, 3,72 Hz, 1H), 7.10–7.06 (m, 2H), 6.47 (dd, J = 2.25, 10.29 Hz, 1H), 4.88 (t, J = 4.47 Hz, 1H), 4.72–4.69 (m, 2H), 4.63 (t, J = 4.56 Hz, 1H). ^{13}C NMR (175 MHz, $(CD_3)_2SO$, 25 °C, δ): 171.7 (d, J = 11.7 Hz), 156.2, 134.8, 133.2, 130.7 (d, J = 5.5 Hz), 130.2, 128.1, 127.1, 125.7, 125.0 (d, J = 10.1 Hz), 112.2, 110.4, 106.4, 103.5, 83.3, 82.0, 46.7 (d, J = 19.7 Hz), 30.6. ^{19}F NMR (376 MHz, $(CD_3)_2SO$, 25 °C, δ): –124.7 (m), –221.9 (m). HRMS (ESI-TOF) (m/z): calcd for $C_{18}H_{13}N_2O_2SF_2$ ($[M + H]^+$), 359.0666, found, 359.0662.

3-(2,4-Dichlorophenyl)-4-(5-fluoro-1-(2-fluoroethyl)-1*H*-indol-3-yl)-1*H*-pyrrole-2,5-dione (14f)

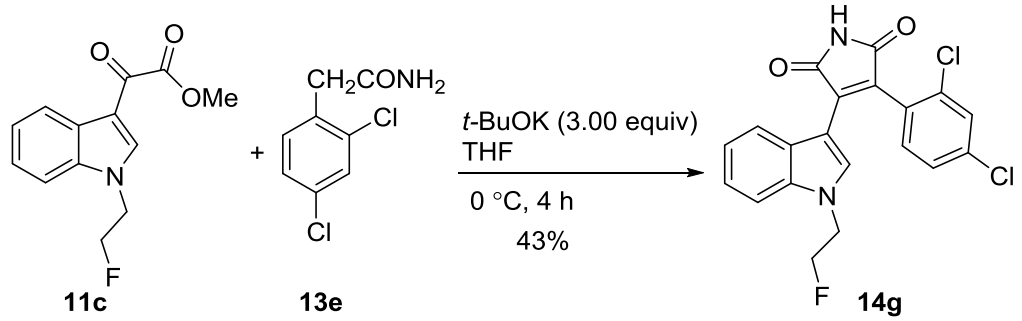


Under N_2 atmosphere, to a suspension of methyl 2-(5-fluoro-1-(2-fluoroethyl)-1*H*-indol-3-yl)-2-oxoacetate (377 mg, 1.41 mmol, 1.00 equiv) and 2-(2,4-dichlorophenyl)acetamide (345 mg, 1.69 mmol, 1.20 equiv) in THF (15.0 mL) was slowly added (dropwise) *t*-BuOK solution (475 mg, 4.23 mmol in 20.0 mL THF) at 0 °C for 30 min. The reaction mixture was stirred at 0°C for another 4 h. The reaction was quenched with ice water (5.00 mL) at 0 °C and the aqueous layer was extracted with EtOAc (4 × 20.0 mL). The organic extracts were combined, washed with saturated NaCl (aq) (5.00 mL), and then dried over Na_2SO_4. After being concentrated *in vacuo*, the residue was purified by flash chromatography on silica gel (EtOAc:hexanes = 1:2) to afford the title

compound as a yellow solid (315 mg, 0.747 mmol, 53% yield).

NMR Spectroscopy: ^{1}H NMR (700 MHz, $(CD_3)_2SO$, 25 °C, δ): 11.26 (s, 1H), 8.18 (s, 1H), 7.76 (d, *J* = 1.8 Hz, 1H), 7.60 (q, *J* = 4.4 Hz, 1H), 7.54 (dd, *J* = 1.9, 8.3 Hz, 1H), 7.47 (d, *J* = 8.3 Hz, 1H), 6.98-7.08 (m, 1H), 6.03 (d, *J* = 10.6 Hz, 1H), 4.71 (td, *J* = 4.5, 47.3 Hz, 2H), 4.64 (td, *J* = 4.5, 28.0 Hz, 2H). ^{13}C NMR (175 MHz, $(CD_3)_2SO$, 25 °C, δ): 171.7, 171.1, 157.4 (d, *J* =232.8 Hz), 136.1, 134.9, 134.7, 134.6, 133.6, 133.3, 129.4, 129.1, 127.4, 126.2, 125.7 (d, *J* = 10.3 Hz), 112.4 (d, *J* = 10.0 Hz), 110.6 (d, *J* = 25.7 Hz), 104.7 (d, *J* = 3.4 Hz), 82.5 (d, *J* = 166.8 Hz), 46.8 (d, *J* = 19.3 Hz). ^{19}F NMR (376 MHz, $(CD_3)_2SO$, 25 °C, δ): –124.3 (m), –222.2 (m). HRMS (ESI-TOF) (m/z): calcd for $C_{20}H_{13}Cl_2F_2N_2O_2$ ($[M + H]^+$), 421.0322, found, 421.0317.

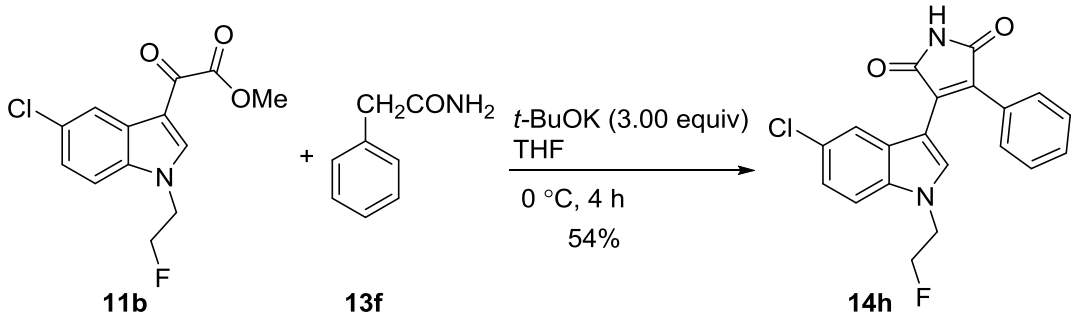
3-(2,4-Dichlorophenyl)-4-(1-(2-fluoroethyl)-1*H*-indol-3-yl)-1*H*-pyrrole-2,5-dione (14g)



Under N_2 atmosphere, to a suspension of methyl 2-(1-(2-fluoroethyl)-1*H*-indol-3-yl)-2-oxoacetate (274 mg, 1.10 mmol, 1.00 equiv) and 2-(2,4-dichlorophenyl)acetamide (269 mg, 1.32 mmol, 1.20 equiv) in THF (15.0 mL) was slowly added (dropwise) *t*-BuOK solution (370 mg, 3.30 mmol in 20.0 mL THF, 3.00 equiv) at 0 °C for 30 min. The reaction mixture was stirred at 0 °C for another 4 h. The reaction was quenched with ice water (5.00 mL) at 0 °C and the aqueous layer was extracted with EtOAc (4 × 20.0 mL). The organic extracts were combined, washed with saturated NaCl (aq) (5.00 mL), and then dried over Na_2SO_4. After being concentrated *in vacuo*, the residue was purified by flash chromatography on silica gel (EtOAc:hexanes = 1:2) to afford the title compound as a yellow solid (190 mg, 0.471 mmol, 43% yield).

NMR Spectroscopy: ^{1}H NMR (700 MHz, $(CD_3)_2SO$, 25 °C, δ): 11.23 (s, 1H), 8.13 (s, 1H), 7.73 (d, *J* = 1.0 Hz, 1H), 7.57 (d, *J* = 8.2 Hz, 1H), 7.48 (d, *J* = 8.3 Hz, 1H), 7.42 (d, *J* = 8.3 Hz, 1H), 7.10–7.16 (m, 1H), 6.70–6.85 (m, 1H), 6.41 (d, *J* = 8.1 Hz, 1H), 4.75 (td, *J* = 4.6, 47.4 Hz, 2H), 4.64 (td, *J* = 4.6, 28.0 Hz, 2H). ^{13}C NMR (175 MHz, $(CD_3)_2SO$, 25 °C, δ): 171.8, 171.1, 136.6, 135.2, 134.7, 134.6, 134.4, 133.5, 129.6, 129.1, 127.3, 126.1, 125.2, 122.5, 120.7, 120.0, 111.0, 104.6, 82.5 (d, *J* = 166.7 Hz), 46.5 (d, *J* = 19.8 Hz). ^{19}F NMR (376 MHz, $(CD_3)_2SO$, 25 °C, δ): –222.2 (m). HRMS (ESI-TOF) (m/z): calcd for $C_{20}H_{14}Cl_2FN_2O_2$ ($[M + H]^+$), 403.0388, found, 403.0399.

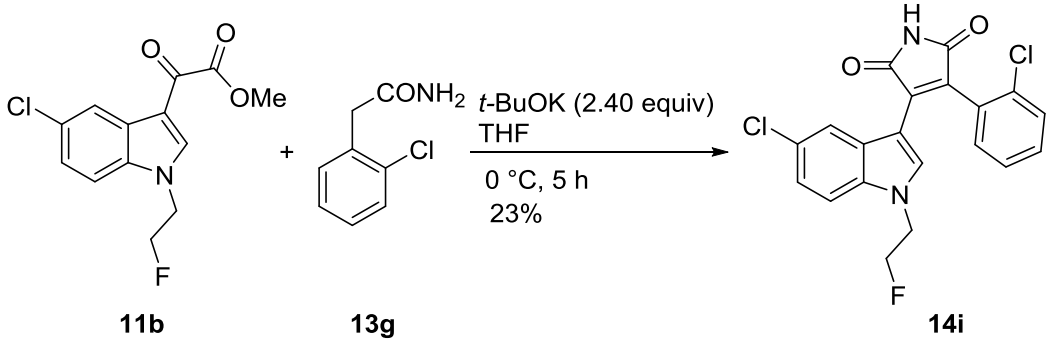
3-(5-Chloro-1-(2-fluoroethyl)-1*H*-indol-3-yl)-4-phenyl-1*H*-pyrrole-2,5-dione (14h)



Under N_2 atmosphere, to a suspension of methyl 2-(5-chloro-1-(2-fluoroethyl)-1*H*-indol-3-yl)-2-oxoacetate (318 mg, 1.12 mmol, 1.00 equiv) and 2-phenylacetamide (182 mg, 1.35 mmol, 1.20 equiv) in THF (10 mL, 0.112 M) was slowly added (dropwise) *t*-BuOK solution (377 mg, 3.36 mmol in 20 mL THF, 3.00 equiv) at 0 °C for 30 min. The reaction mixture was stirred at 0 °C for another 4 h. The reaction was quenched with ice water (5.00 mL) at 0 °C and the aqueous layer was extracted with EtOAc (4 × 20.0 mL). The organic extracts were combined, washed with saturated NaCl (aq) (5.00 mL), and then dried over Na_2SO_4. After being concentrated *in vacuo*, the residue was purified by flash chromatography on silica gel (EtOAc:hexanes = 1:2) to afford the title compound as a yellow solid (220 mg, 0.600 mmol, 54% yield).

NMR Spectroscopy: ^{1}H NMR (700 MHz, $(CD_3)_2SO$, 25 °C, δ): 11.14 (s, 1H), 8.14 (s, 1H), 7.58 (d, J = 8.7 Hz, 1H), 7.32–7.45 (m, 5H), 7.12 (dd, J = 1.6, 8.7 Hz, 1H), 6.19 (d, J = 1.6 Hz, 1H), 4.77 (td, J = 4.5, 40.3 Hz, 2H), 4.64 (td, J = 4.5, 28.1 Hz, 2H). ^{13}C NMR (175 MHz, $(CD_3)_2SO$, 25 °C, δ): 172.2, 172.0, 135.3, 135.1, 131.4, 130.4, 129.9, 129.7, 129.0, 128.2, 125.6, 124.8, 122.1, 120.9, 112.3, 103.5, 82.7 (d, J = 166.7 Hz), 46.7 (d, J = 19.7 Hz). ^{19}F NMR (376 MHz, $(CD_3)_2SO$, 25 °C, δ): –221.9 (m). HRMS (ESI-TOF) (m/z): calcd for $C_{20}H_{15}ClFN_2O_2$ ($[M + H]^+$), 369.0806, found, 369.0790.

3-(5-Chloro-1-(2-fluoroethyl)-1*H*-indol-3-yl)-4-(2-chlorophenyl)-1*H*-pyrrole-2,5-dione (14i)

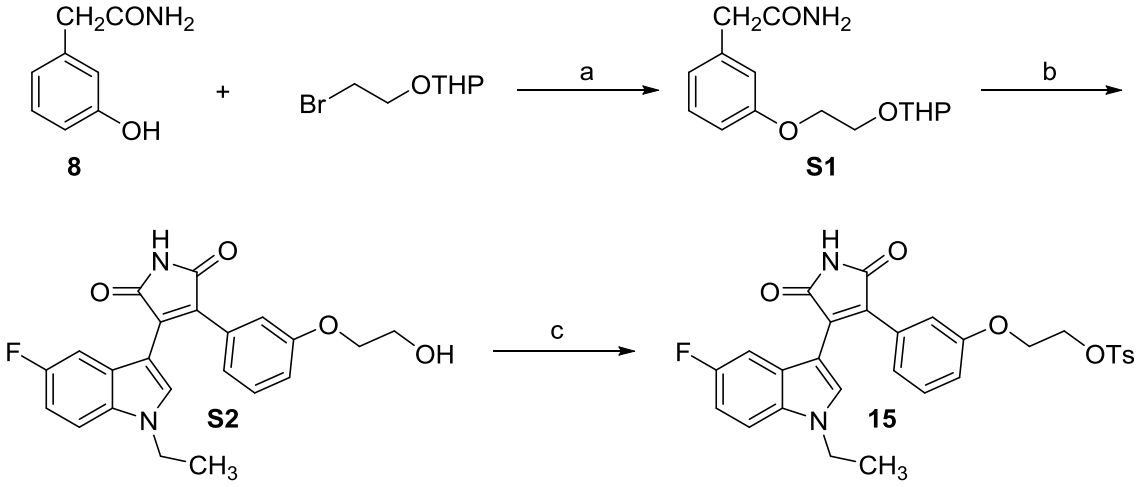


To a solution of compound methyl 2-(5-chloro-1-(2-fluoroethyl)-1*H*-indol-3-yl)-2-oxoacetate (200 mg, 0.710 mmol, 1.00 equiv.) and compound 2-(2-chlorophenyl)acetamide (132 mg, 0.780 mmol, 1.10 equiv.) in THF (10 mL, 0.071 M) was added with *t*-BuOK solution (190 mg, 1.69 mmol, 2.40 equiv.)/THF (5.00 mL) at 0 °C under nitrogen atmosphere. After the reaction mixture was stirred at 0 °C for another 5 h, it was quenched by 1N HCl (10.0 mL). The excess acid was neutralized by sodium bicarbonate. The solution was extracted with EtOAc (10 mL x 3), washed with brine, dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified through column chromatography using EtOAc:hexanes (1 : 1.5 (v/v)) to afford the title compound as a light yellow solid (64.8 mg, 0.161 mm0l, 23% yield).

NMR Spectroscopy: ^{1}H NMR (700 MHz, $(CD_3)_2SO$, 25 °C, δ): 11.22 (s, 1H), 8.21 (s, 1H), 7.58 (d, J = 8.7 Hz, 1H), 7.55 (d, J = 7.9 Hz, 1H), 7.51–7.49 (m, 1H), 7.41–7.40 (m, 2H), 7.13 (dd, J = 2.0, 8.7 Hz, 1H), 6.19 (d, J = 2.0 Hz, 1H), 4.76 (t, J = 4.6 Hz, 1H), 4.70 (t, J = 4.6 Hz, 1H), 4.65 (t, J = 4.6 Hz, 1H), 4.60 (t, J = 4.6 Hz, 1H). ^{13}C NMR (175 MHz, $(CD_3)_2SO$, 25 °C, δ): 171.7, 171.2, 135.7, 135.0, 134.2, 133.5, 132.2, 130.8, 129.4, 127.6, 127.0, 126.2, 125.2, 122.2, 119.8, 112.4, 104.4, 83.0, 82.0, 46.6 (d, J =19.9 Hz). ^{19}F NMR (376 MHz, $(CD_3)_2SO$, 25 °C, δ): –222.1 (m). HRMS (ESI-TOF) (m/z): calcd for $C_{20}H_{14}N_2O_2FCl_2$ ($[M + H]^+$), 403.0416, found, 403.0408.

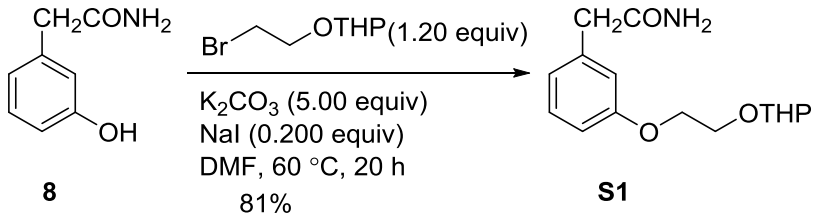
Synthesis of Precursor 15 for ^{18}F-Labeling

Previously available amide **8** was treated with 2-(2-bromoethoxy)tetrahydro-*2H*-pyran in the presence of potassium carbonate and sodium iodide to afford **S1**. Condensation between the amide **S1** with glyoxalate **6a** followed by removal of the tetrahydro-2*H*-pyran (THP) group under acidic conditions gave alcohol **S2** in 58% yield. Finally, *O*-tosylation of **S2** with tosyl chloride in the presence of pyridine at 0 °C afforded the desired precursor **15** in 55% yield (Scheme S1).



Scheme S1. Synthesis of precursor **15**. Reagents and conditions: (a) K_2CO_3, DMF, NaI, 60 °C, overnight; (b) 6a, *t*-BuOK, THF, 0 °C, 4 h; then HCl (37%), rt, 4 h; (c) TsCl, Pyridine, 0 °C, 5 h. THP = tetrahydro-2*H*-pyran.

2-(3-(2-((Tetrahydro-2*H*-pyran-2-yl)oxy)ethoxy)phenyl)acetamide (S1)

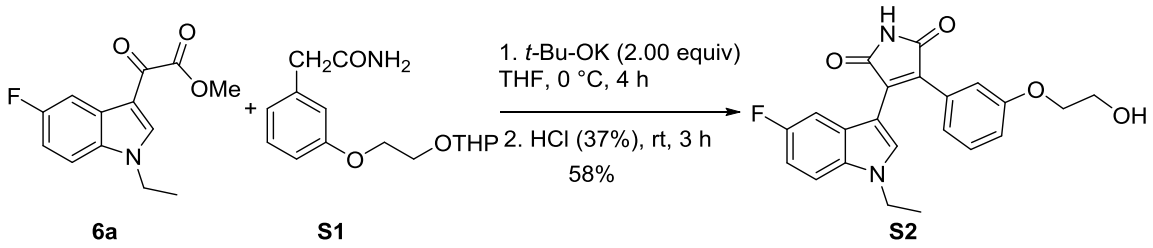


To a solution of 2-(3-hydroxyphenyl) (700 mg, 4.64 mmol, 1.00 equiv) in DMF (10 mL, 0.464 M) was added K_2CO_3 (3.20 g, 23.2 mmol, 5.00 equiv), NaI (139 mg, 0.93 mmol, 0.200 equiv), and 2-(2-bromoethoxy)tetrahydro-2*H*-pyran[14] (1.16 g, 5.56 mmol, 1.20 equiv) under nitrogen atmosphere at room temperature. The reaction mixture was heated to 60 °C and stirred for 20 h. The reaction was cooled to 0 °C and quenched with water (50.0 mL) and the aqueous layer was extracted with EtOAc (4 × 30.0 mL). The organic extracts were combined, washed with 5% LiCl(aq) (5.00 mL), and then dried over Na_2SO_4. After being concentrated *in vacuo*, the residue was purified by flash

chromatography on silica gel (EtOAc) to afford the title compound as a colorless oil (1.05 g, 3.76 mmol, 81% yield).

NMR Spectroscopy: ^{1}H NMR (700 MHz, $(CD_3)_2SO$, 25 °C, δ): 7.45 (s, 1H), 7.12–7.23 (m, 1H), 6.72–6.93 (m, 4H), 4.65 (d, J = 3.2 Hz, 1H), 4.06–4.15 (m, 2H), 3.87–3.93 (m, 1H), 3.75–3.82 (m, 1H), 3.67–3.73 (m, 1H), 3.40–3.47 (m, 1H), 3.32 (s, 2H), 1.71 (d, J = 6.4 Hz, 1H), 1.59–1.65 (m, 1H), 1.38–1.51 (m, 4H). ^{13}C NMR (175 MHz, $(CD_3)_2SO$, 25 °C, δ): 172.1, 158.3, 138.0, 129.1, 121.4, 115.5, 112.2, 98.1, 67.0, 65.3, 61.3, 42.3, 30.2, 25.0, 19.1.

3-(1-Ethyl-5-fluoro-1*H*-indol-3-yl)-4-(3-(2-hydroxyethoxy)phenyl)-1*H*-pyrrole-2,5-dione (S2)

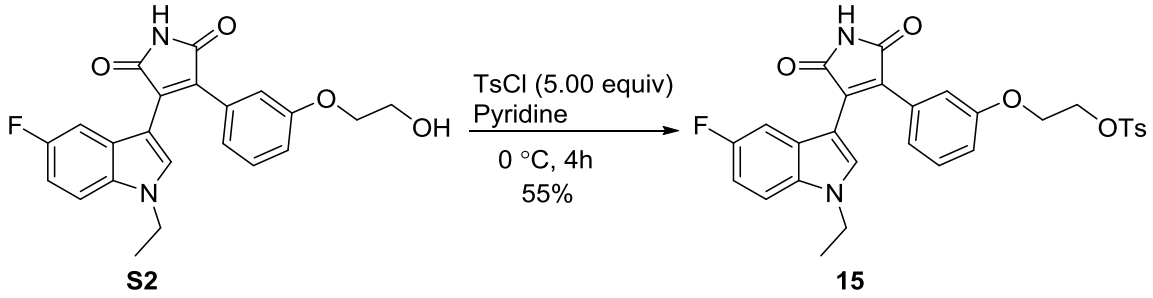


6a S1 S2

Under N_2 atmosphere, to a suspension of methyl 2-(1-ethyl-5-fluoro-1*H*-indol-3-yl)-2-oxoacetate (1.00 g, 4.00 mmol, 1.00 equiv) and 2-(3-(2-((tetrahydro-2*H*-pyran-2-yl)oxy)ethoxy)phenyl)acetamide (1.12 g, 4.00 mmol, 1.00 equiv) in THF (16 mL, 0.250 equiv) was slowly added (dropwise) *t*-BuOK solution (900 mg in 20 mL THF, 8.02 mmol, 2.00 equiv) at 0 °C for 30 min. The reaction mixture was stirred at 0 °C for another 4 h. The reaction was quenched with HCl (1N, 10 mL) at 0 °C and the aqueous layer was extracted with EtOAc (4 × 20 mL). The combined organic phase was concentrated *in vacuo* to get crude THP-protected coupling product, which was dissolved in EtOAc:MeOH (v/v = 1:1, 30 mL) and was added HCl (37%, 3 mL). The reaction mixture was stirred at room temperature for 3h. The solvent was evaporated *in vacuo* and the residue was purified by flash chromatography on silica gel (EtOAc:hexanes = 2:1) to afford the title compound as a red solid (918 mg, 2.33 mmol, 58% yield).

NMR Spectroscopy: ^{1}H NMR (700 MHz, $(CD_3)_2SO$, 25 °C, δ): 11.09 (s, 1H), 8.13 (s, 1H), 7.52 (dd, J = 4.6, 8.9 Hz, 1H), 7.23 (t, J = 7.9 Hz, 1H), 7.00 (s, 1H), 6.93–6.99 (m, 2H), 6.90 (d, J = 7.6 Hz, 1H), 5.99 (dd, J = 2.4, 10.5 Hz, 1H), 4.86 (s, 1H), 4.30 (q, J = 7.2 Hz, 2H), 3.84 (t, J = 5.0 Hz, 2H), 3.63 (d, J = 4.9 Hz, 2H), 1.39 (t, J = 7.2 Hz, 3H). ^{13}C NMR (175 MHz, $(CD_3)_2SO$, 25 °C, δ): 172.3, 172.1, 158.3, 157.0 (d, J = 232.5 Hz), 134.8, 132.7, 131.9, 131.7, 129.3, 128.6, 125.2 (d, J = 10.9 Hz), 122.1, 116.0, 115.0, 111.7 (d, J = 9.5 Hz), 110.1 (d, J = 25.8 Hz), 106.6 (d, J = 25.1 Hz), 103.4 (d, J = 4.5 Hz), 69.6, 59.5, 41.3, 15.3. ^{19}F NMR (376 MHz, $(CD_3)_2SO$, 25 °C, δ): –124.3 (m). HRMS (ESI-TOF) (m/z): calcd for $C_{22}H_{20}FN_2O_4$ ($[M + H]^+$), 395.1407, found, 395.1416.

2-(3-(4-(1-Ethyl-5-fluoro-1*H*-indol-3-yl)-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl)phenoxy)ethyl 4-methylbenzenesulfonate (15)



S2 15

Under N_2 atmosphere, to a suspension of 3-(1-ethyl-5-fluoro-1*H*-indol-3-yl)-4-(3-(2-hydroxyethoxy)phenyl)-1*H*-pyrrole-2,5-dione (750 mg, 1.90 mmol, 1.00 equiv) in pyridine (5.00 mL, 0.380 M) was slowly added (dropwise) 4-methylbenzenesulfonyl chloride (TsCl) solution (1.09 g, 5.70 mmol in 5 mL pyridine, 3.00 equiv) at 0 °C for 30 min. After the reaction mixture was stirred at 0 °C for 2 h, to the reaction was added TsCl solution (726 mg, 3.80 mmol in 3.00 mL pyridine, 2.00 equiv) at 0 °C for 15 min. After the reaction mixture was stirred at 0 °C for another 2 h, the reaction was quenched with water (10.0 mL) and the aqueous layer was extracted with EtOAc (3 × 20.0 mL). The organic extracts were combined, washed with saturated NaCl (aq) (5.00 mL), and then dried over Na_2SO_4. After being concentrated *in vacuo*, the residue was purified by flash chromatography on silica gel (EtOAc:hexanes = 1:2) to afford the title compound as a yellow solid (570 mg, 1.04 mmol, 55% yield).

NMR Spectroscopy: ^{1}H NMR (700 MHz, $(CD_3)_2SO$, 25 °C, δ): 11.11 (s, 1H), 8.14 (s, 1H), 7.75 (d, *J* = 8.3 Hz, 2H), 7.56 (dd, *J* = 4.6, 9.0 Hz, 1H), 7.43 (d, *J* = 8.1 Hz, 2H), 7.22 (t, *J* = 7.9 Hz, 1H), 6.86-7.00 (m, 4H), 5.94 (dt, *J* = 2.5, 10.5 Hz, 1H), 4.32 (q, *J* = 7.2 Hz, 2H), 4.23–4.27 (m, 2H), 4.00–4.03 (m, 2H), 2.39 (s, 3H), 1.40 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (175 MHz, $(CD_3)_2SO$, 25 °C, δ): 172.2, 172.0, 157.4, 156.9 (d, *J* = 232.8 Hz), 145.0, 134.8, 132.7, 132.2, 132.0, 131.7, 130.1, 129.3, 128.4, 127.7, 125.1 (d, *J* = 10.9 Hz), 122.6, 116.1, 114.8, 111.8 (d, *J* = 10.0 Hz), 110.1 (d, *J* = 25.7 Hz), 106.5 (d, *J* = 25.2 Hz), 103.3 (d, *J* = 4.5 Hz), 68.9, 65.5, 41.2, 21.1, 15.3. ^{19}F NMR (376 MHz, $(CD_3)_2SO$, 25 °C, δ): -224.48 (s). HRMS (ESI-TOF) (m/z): calcd for $C_{29}H_{26}FN_2O_6S$ ($[M + H]^+$), 549.1475, found, 549.1481.

In vitro evaluation of GSK-3*β* inhibition by maleimides.

General Procedure: Commercially available human GSK-3*β* (BPS Biosciences) was assayed for its ability to phosphorylate the primed peptide substrate (GSP-2: Tyr-Arg-Arg-Ala-Ala-Val-Pro-Pro-Ser-Pro-Ser-Leu-Ser-Arg-His-Ser-Ser-Pro-His-Gln-Ser(PO_3H_2)-Glu-AspGlu-Glu-Glu). ADP-Glo Kinase assay reagents were purchased from Promega (Cat V9102). Kinase reactions were performed with 9 µM GSP-2), 15 µM ATP, 10 nM GSK3β in reaction buffer (50 mM Tris pH 7.5, 5 mM $MgCl_2$, 0.01% Brij-35, 3 mM DTT) in the presence of 0-30 µM of the maleimides. Test compounds were preincubated with enzyme and substrate for 15 minutes prior to the addition of ATP. Kinase reactions were carried out for a duration of 30 minutes and terminated by addition of ADP-Glo reagent. After 40 minutes incubation with the ADP-Glo reagent, kinase detection reagent was added as per manufacturer's recommendations (Promega). Kinase activity was measured as luminescence resulting due to ADP formation *via* a multilabel plate reader (EnVision, Perkin Elmer). See the Spectroscopic Data section for the dose response curves.

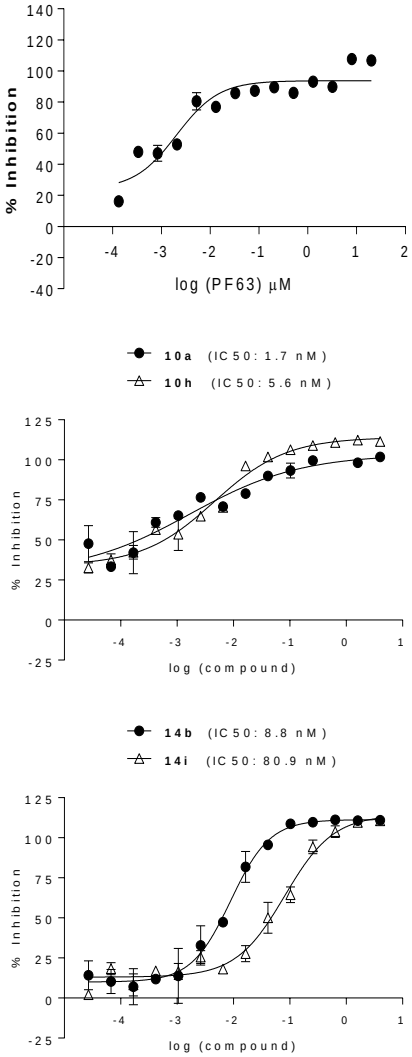
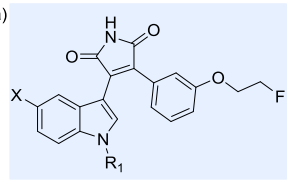
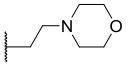


Figure S1. Representative dose response curves of select GSK-3β inhibitors. The top figure shows IC_{50} values for the positive control **Chiron-99021**. Middle and lower figures illustrate dose response curves and IC_{50} values for select maleimides **10a** vs.**10h** and **14b** vs **14i**.

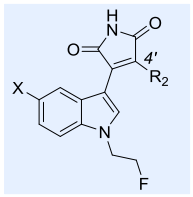
Table S1. Measured IC_{50} and estimated K_i maleimides 10a-k and 14a-i[a]

(a)



Cpd	X	R_1	IC_{50} (nM)	K_i (nM)
CHIR-99021			1.50	0.75
10a	F	$-CH_2CH_3$	1.70	0.85
10b	F	$-CH_3$	45.6	22.8
10c	F	$-CH_2CH_2CH_3$	63.9	32.0
10d	F	$-CH_2CH_2CH_2CH_3$	144	72.0
10e	F	$-CH_2(CH_3)_2$	>10,000	>5,000
10f	F	$-CH_2CH_2N(CH_3)_2$	169	84.5
10g	F		50.0	25.0
10h	F	$-CH_2CH_2OCH_3$	5.60	2.80
10i	H	$-CH_3$	164	82.0
10j	Cl	$-CH_3$	27.0	13.5
10k	Br	$-CH_3$	127	63.5

(b)



Cpd	X	R_2	IC_{50} (nM)	K_i (nM)
14a	F	3-methoxyphenyl	14.7	7.35
14b	Cl	3-methoxyphenyl	8.80	4.40
14c	F	naphthalen-1-yl	> 10,000	> 5,000
14d	F	1*H*-indol-3-yl	> 10,000	> 5,000
14e	F	thiophen-2-yl	36.3	18.2
14f	F	2,4-dichlorophenyl	242	121
14g	H	2,4-dichlorophenyl	1,880	940
14h	Cl	phenyl	6.90	3.45
14i	Cl	2-chlorophenyl	80.9	40.5

[a]Since [S] is equal to K_m under our experimental conditions and most of the compounds mentioned in the manuscript are likely to be ATP-competitive inhibitors, the K_i of our compounds can be estimated using the following equation.[15]

$IC_{50}=K_i(1+[S]/K_m)=K_i(2)$

$K_i=IC_{50}/2$

Estimated K_i value when [S] is equal to K_m would be equal to half of the measured IC_{50} value for competitive inhibitors.

Radiosynthesis of [^{18}F]10a

Fully automated radiosynthesis of [^{18}F]**10a** was performed on a GE Tracerlab FX_{FN} synthesis module. [^{18}F]Fluoride was loaded onto a Waters QMA cartridge and eluted with a solution of K_{222} (10 mg) and K_2CO_3 (1.2 mg) in CH_3CN/H_2O (4/1 v/v, 1 mL) into the reactor. The reactor contents are dried under vacuum with helium flow at 95 °C for 4 min, before the addition of CH_3CN (1 mL) and the drying continued for 3 min, followed by vacuum alone. The dried [^{18}F]K/ K_{222} complex was reacted with **19**, at 90 °C, for 10 minutes, to afford the desired [^{18}F]**10a**. The tracer, [^{18}F]**10a**, was isolated from the automated preparative HPLC in 36% radiochemical yield (non-decay corrected) and formulated for injection. The specific activity was >4 Ci/µmol, and radiochemical purity was >99% at the end of synthesis.

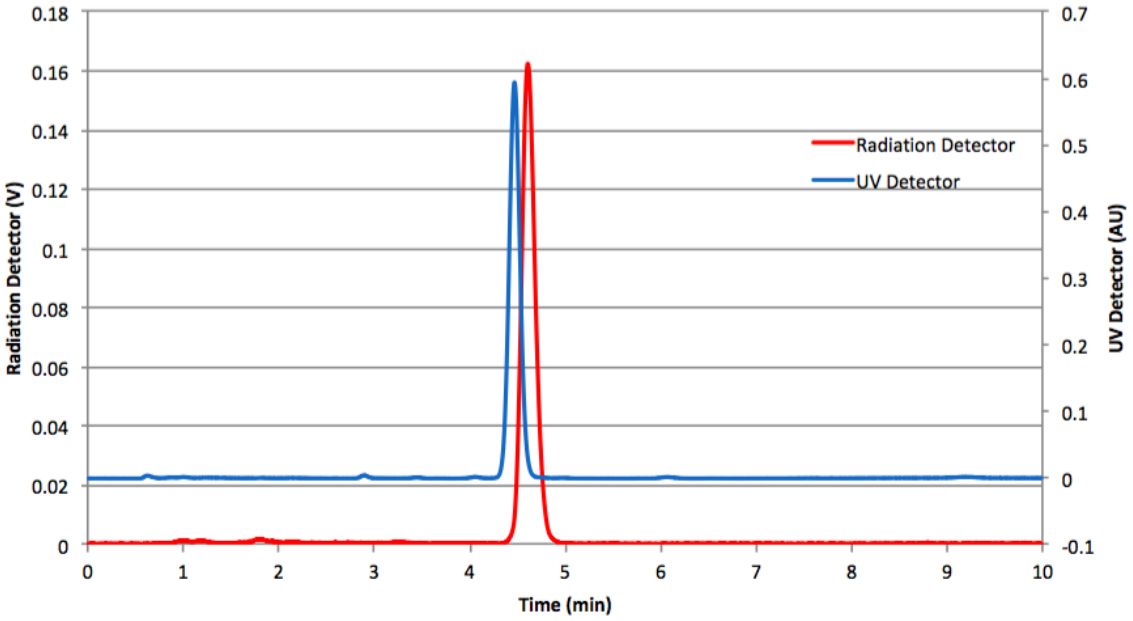


Figure S2. Spiked QC of [^{18}F]**10a.** HPLC column: Eclipse Plus C-18 5 um, 4.6 X 100 mm, Mobile phase: 50% Acetonitrile/Water, Flow rate: 1.5 ml/min, UV: 254 nm.

In Vivo PET-CT Imaging with [^{18}F]10a in Rodents.

All animal studies were performed in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and were approved by the Massachusetts General Hospital Institutional Animal Care and Use Committee.

PET imaging was conducted in Sprague-Dawley rats at baseline (n = 2) and after pretreatment with non-radioactive **10a** (1 mg/kg, iv, n = 2) to determine brain uptake and binding specificity. Animals were anesthetized using isoflurane and positioned in the scanner with their heads in the field-of-view. PET acquisition was initiated at radiotracer administration for 60 minutes, followed by CT. Radiotracer doses were 1.06 and 0.62 μCi and 0.92 and 0.67 μCi for animals at baseline and pretreatment conditions, respectively. Dynamic PET data were binned into 33 timeframes and reconstruction of each frame was performed *via* an iterative MLEM (maximum likelihood expectation maximization) algorithm. Whole brain and regional uptake were quantified using overlaid volumes-of-interest to derive time-activity curves.

In Vitro Metabolic Stability Evaluation of 3-(1-ethyl-5-fluoro-1*H*-indol-3-yl)-4-(3-(2-fluoroethoxy)phenyl)-1*H*- pyrrole-2,5-dione (10a) in Human and Rat Liver Microsomes.

Materials

Pooled human liver microsomes (pool of 50 donors; Cat # 452165) and pooled male rat liver microsomes (cat# 452501) were purchased from BD Gentest, Woburn, MA. Terfenadine (Cat # T9652, 97.5% pure), quinidine (Q3625), NADPH (Cat # N1630), potassium phosphate monobasic (Cat # P5655, >99% pure), potassium phosphate dibasic (Cat # P2222, 99% pure) and DMSO (Cat # D5879, >99.5% pure) were purchased from Sigma, Germany. Albendazole (Cat # A4673) and Glipizide (Cat # 50402G) were purchased from Apin Chemicals, Abingdon, UK. 96 well-plates were procured from Axygen, Union City, California.

Equipment

Refrigerated centrifuge (Kubota, Tokyo, Japan), water bath (Bio-Techniques, India) and LC-MS/MS Waters Acquity ultra performance LC, API-4000 MDS Sciex, Applied Biosystems, Canada).

Preparation of reagents

(i) Potassium phosphate buffer, 50 mM (pH 7.4)
Potassium phosphate buffer (K_{phos}) was prepared by adding 0.647 g potassium phosphate monobasic (KH_2PO_4) and 3.527 g potassium phosphate dibasic (K_2HPO_4) to 400 mL of Milli-Q water. pH of the buffer was adjusted to 7.4 and volume was made up to 500 mL.

(ii) Preparation of microsomes
Microsomes (20 mg/mL) were diluted in K_{phos} buffer to prepare a concentration of 0.178 mg/mL.

(iii) Test compound

Stock solutions of 3-(1-ethyl-5-fluoro-1*H*-indol-3-yl)-4-(3-(2-fluoroethoxy)phenyl)- 1*H*-pyrrole-2,5-dione(**10a**) was prepared in DMSO at a concentration of 1 mM.

(iv) NADPH solution
A stock solution of 3.33 mM NADPH (3.33X) was prepared by dissolving appropriate amount of NADPH in K_{phos} buffer.

Assay Conditions

Total Incubation volume:	100 µL
Compound concentration:	1 µM
Protein:	0.25 mg/mL
Concentration NADPH:	1 mM
Final DMSO contain:	0.1%
Number of replicates:	2
Time points:	0, 5, 15, 30 and 60 minutes

Assay

An 1120 µL aliquot of Kphos buffer (50 mM, pH 7.4) containing liver microsome (0.357 mg/mL) were added to individual 2 mL tubes (final concentration 0.25 mg/mL). Test and positive control compounds (1 mM DMSO stocks) were directly spiked into respective tubes to prepare a concentration of 1.428 µM (final concentration 1 µM). From the above mix, 70 µL was added to individual wells of 96 well reaction plates and pre-incubated in a 37 °C water bath for 5 min. All the reactions were initiated by adding 30 µL of 3.33 mM NADPH (final concentration 1 mM). Reactions without NADPH and heat inactivated microsomes minus NADPH (0 min and 60 min) were also incubated to rule out non-NADPH metabolism or chemical instability in the incubation buffer. All reactions were terminated using 100 µL of ice-cold acetonitrile containing internal standard (glipizide, 1 µM) at 0, 5, 15, 30 and 60 min. The plates were centrifuged at 4000 RPM for 15 min and 100 µL aliquots were submitted for analysis by LC-MS/MS.

Bio-Analysis

Samples were monitored for parent compound disappearance in MRM mode using LC-MS/MS. The LC-MS/MS conditions and representative MRM chromatogram.

LC Conditions	
Mobile Phase	**A:** 0.1 % Formic acid in Acetonitrile **B:** 0.1 % Formic acid in Water
Column	X Select CSH,c18,1.7µ,2.1*500mm
Injection Volume (µL)	5
Column Oven Temperature (°C)	45

LC Gradient Used

Time (min)	Flow (mL/min)	PUMP A (% Conc.)	PUMP B (% Conc.)
Initial	0.8	10	90
0.30	0.8	10	90
0.50	0.8	95	5
1.20	0.8	95	5
1.40	0.8	10	90
1.80	0.8	10	90

Retention time of analyte

Analyte	Retention time (min)
3-(1ethyl-5-floro-1h-indole-3yl)	**0.73**

Mass Conditions
MRM Transitions

Analyte ID / IS ID	Q1	Q3	DP	CE	CXP	Dwell time
Glipizide_pos	446.3	347.0	40	22	12	20
3-(1ethyl-5-floro-1h-	397.000	368.5	107.0	31	18	20
ALBENDAZOLE_POS	266.1	234.0	76	28	12	20
QUINIDINE_307	325.2	307.4	99	31	16	20
TERFIDINE_436	472.2	436.5	137	38	10	20

Data Analysis

The percent remaining of test compounds and positive controls in each sample was determined by considering peak area ratio in the 0 minute sample as 100%. Invitro intrinsic clearance (CL'int) (units in mL/min/kg) was calculated using the formula:

$$CL'_{int} = \frac{0.693}{\text{in vitro T1/2}} \cdot \frac{\text{mL incubation}}{\text{mg microsomes}} \cdot \frac{45\,\text{mg microsomes}}{\text{gm liver}} \cdot \frac{\text{liver weight in gm *}}{\text{Kg b.w}}$$

For liver microsomes, scaling factor used was 45 mg microsomal protein per gm liver.
* Indicates liver weight (gm) which varies species wise. For human and rat the liver weights are 20 gm and 40 gm respectively.

Results and Conclusion

• Metabolic stability of positive control compounds terfenadine (HLM)) and quinidine (RLM) and used in the experiment were consistent with literature values and validation results generated in- house (Tables S2-5).
• Test compound **10a** was unstable in both HLM and RLM, provided in Tables S2-5, while compounds was stable in minus NADPH and buffer control samples.

Table S2. Metabolic stability of positive control and compound **10a** in human liver microsomes.

	Terfenadine	Test Compound
$t_{1/2}$ (minutes)	29.2	22.2
% Remaining at 60 minutes (+ NADPH)	24	15
% Remaining at 60 minutes (- NADPH)	107	116
% Remaining at 60 minutes (Buffer)	100	100
$CL_{h,int}$ (mL/min/kg)	85.5	111

Table S3. Metabolic stability of positive control and compound **10a** in rat liver microsomes.

	Quinidine	Test Compound
$t_{1/2}$ (minutes)	15.1	11.7
% Remaining at 60 minutes (+ NADPH)	6	3
% Remaining at 60 minutes (- NADPH)	100	107
% Remaining at 60 minutes (Buffer)	95	100
$CL_{h,int}$ (mL/min/kg)	330	424

Table S4. Time dependent profile of positive control and **10a** in human liver microsomes.

Time point (min)	Terfenadine	Test compound
Plus NADPH		
0	100	100
5	86	75
15	62	46
30	38	24
60	24	15
Minus NADPH		
0	100	100
60	107	116
Heat inactivated microsomes minus NADPH (buffer control)		
0	100	100
60	100	100

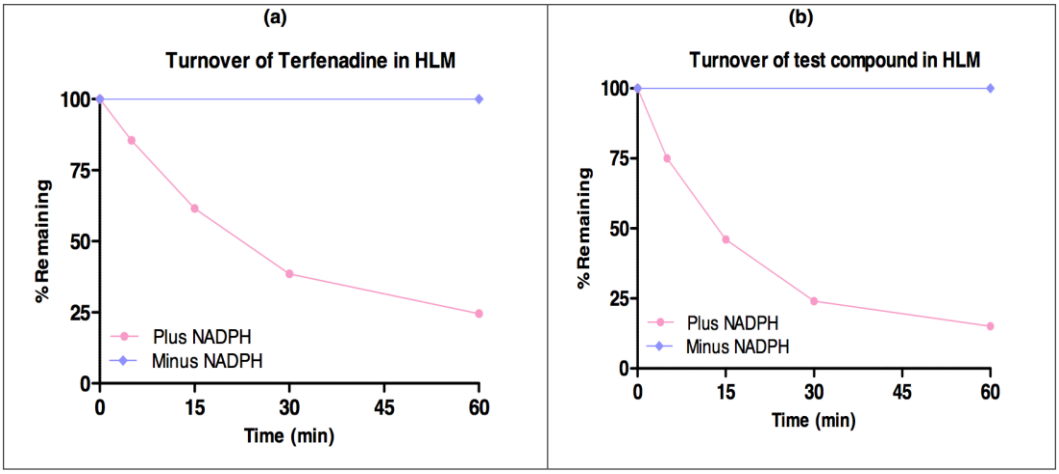


Figure S3. Time-dependent loss of positive control and **10a** in HLM.

Table 5. Time dependent profile of positive control and **10a** in rat liver microsomes.

Time point (min)	Quinidine	Test compound
Plus NADPH		
0	100	100
5	71	54
15	25	19
30	11	4
60	**6**	**3**
Minus NADPH		
0	100	100
60	100	107
Heat inactivated microsomes minus NADPH (buffer control)		
0	100	100
60	95	100

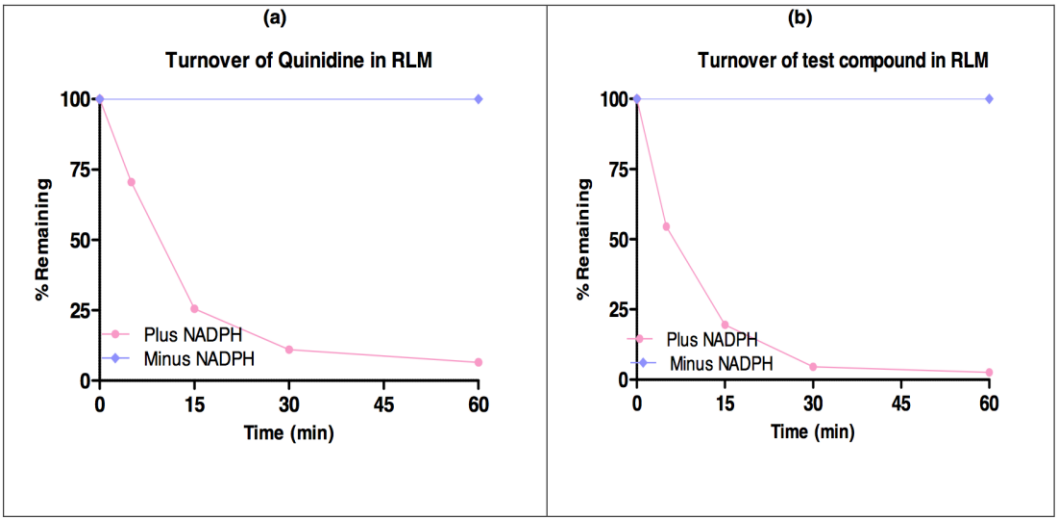


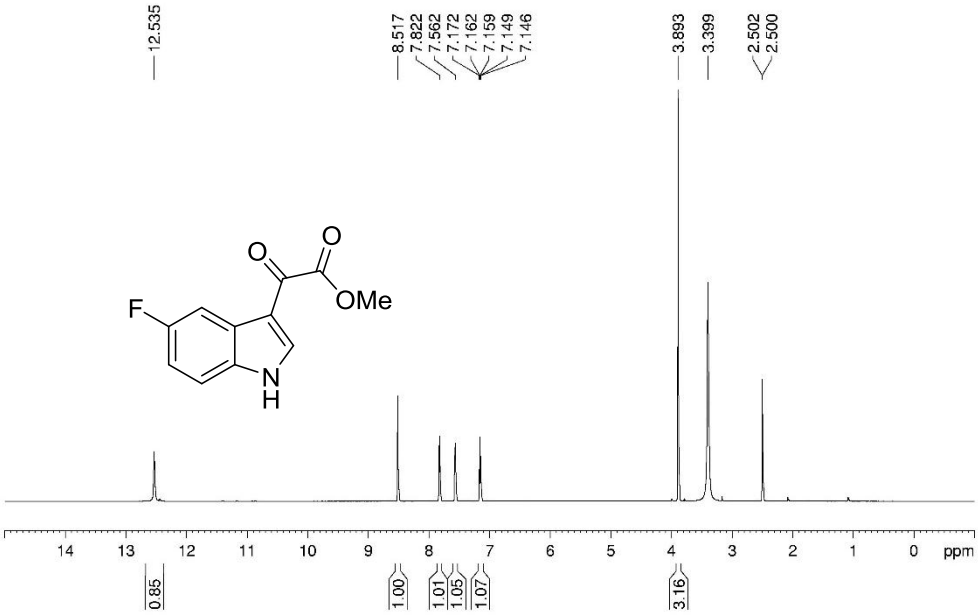
Figure S4. Time-dependent loss of positive control and **10a** in RLM.

References

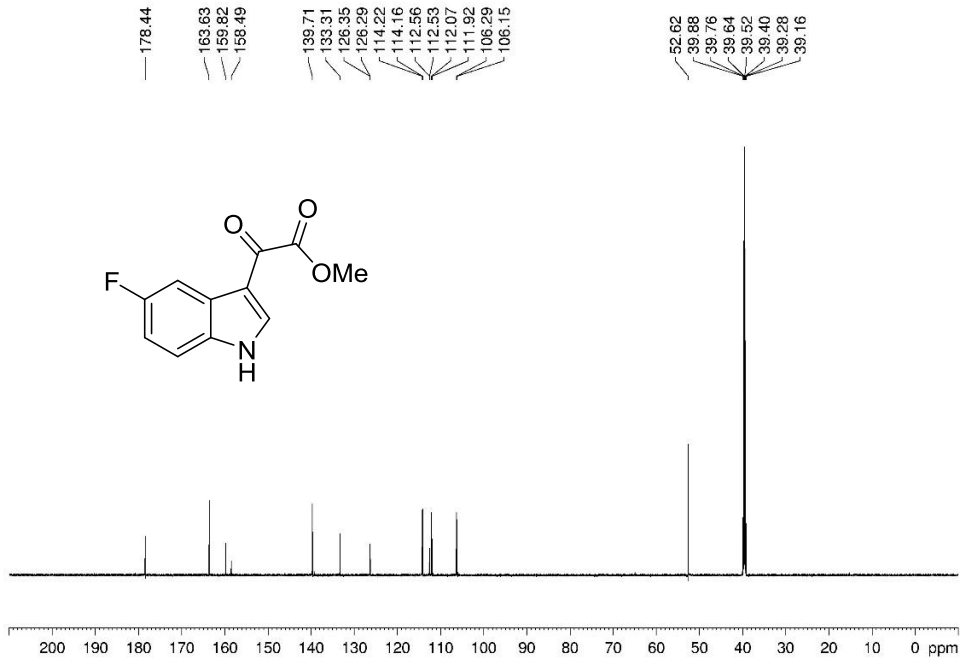
1. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem*. 1978, **43**, 2925–2927.
2. Fulmer, G. R.; Miller, A. J. M.; Sherden, N. H.; Gottlieb, H. E.; Nudelman, A.; Stoltz, B. M.; Bercaw, J. E.; Goldberg, K. I. *Organometallics*. 2010, **29**, 2176–2179.
3. Wang, X.; Xu, Y.; Mo, F.; Ji, G.; Qiu, D.; Feng, J.; Ye, Y.; Zhang, S.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc*. 2013, **135**, 10330–10333.
4. Q. Ye, W. Mao, Y. Zhou, L. Xu, Q. Li, Y. Gao, J. Wang, C. Li, Y. Xu, Y. Xu, H. Liao, L. Zhang, J. Gao, J. Li and T. Pang, *Bioorg. Med. Chem.*, 2015, **23**, 1179-1188.
5. O. Ilovich, H. Billauer, S. Dotan, E. Mishani. *Bioorg. Med. Chem.,* 2010, **18**(2), 612.
6. M. Wang, M. Gao, K. D. Miller, G. W. Sledge, G. D. Hutchins and Q. H. Zheng, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 245.
7. WSS: Spectral data were obtained from Wiley Subscription Services, Inc. (US)
8. B. Kaboudin and Y. Abedi, *Synthesis*, 2009, **12**, 2025.
9. T. Tu, Z. Wang, Z. Liu, X. Feng and Q. Wang, *Green Chem.*, 2012, **14**, 921.
10. Jacques Mauger, Toru Nagasawa and H. Yamada, *Tetrahedron*, 1989, **45**, 1347.
11. M. K. Gupta, Z. Li and T. S. Snowden, *Org. Lett.*, 2014, **16**, 1602.
12. C. Liana Allen, C. Burel, J. M.J. Williams. *Tetrahedron Lett.,* 2010, **51**(20), 2724.
13. J. L. O'Connell, J. S. Simpson, P. G. Dumanski, G. W. Simpson and C. J. Easton, *Org. Biomol. Chem.*, 2006, **4**, 2716-2723.
14. Anzini, M.; Di Capua, A.; Valenti, S.; Brogi, S.; Rovini, M.; Giuliani, G.; Cappelli, A.; Vomero, S.; Chiasserini, L.; Sega, A.; Poce, G.; Giorgi, G.; Calderone, V.; Martelli, A.; Testai, L.; Sautebin, L.; Rossi, A.; Pace, S.; Ghelardini, C.; Di Cesare Mannelli, L.; Benetti, V.; Giordani, A.; Anzellotti, P.; Dovizio, M.; Patrignani, P.; Biava, M. *J. Med. Chem.* 2013, **56**, 3191–3206.
15. Copeland, R. A., *Evaluation of enzyme inhibitors in drug discovery: a guide for medicinal chemists and pharmacologists*. John Wiley & Sons: 2013, page 131.

Spectroscopic Data

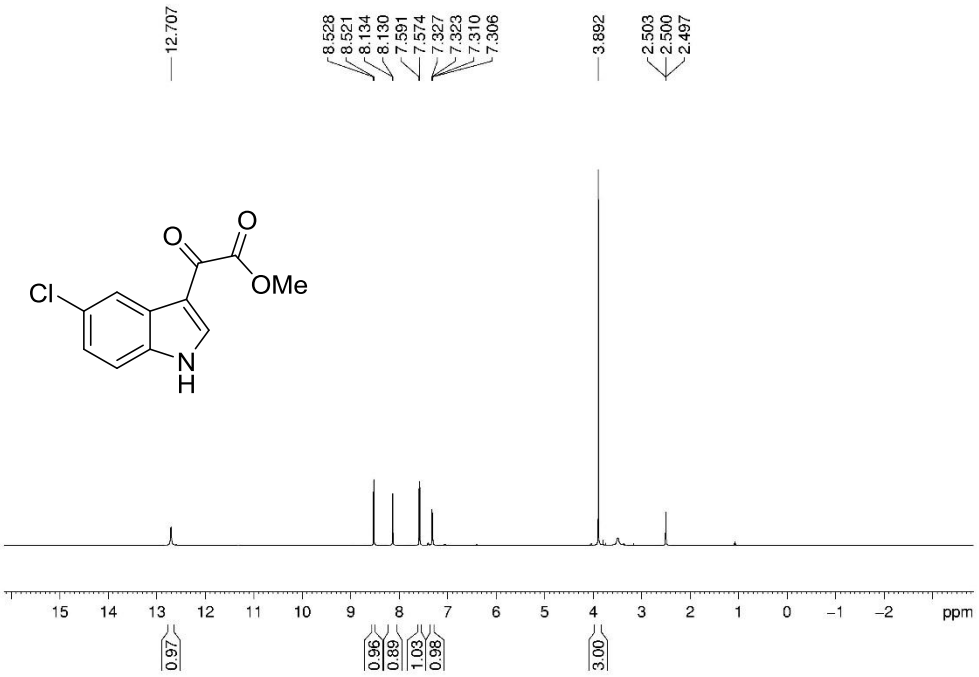
^{1}H NMR ($(CD_3)_2SO$, 25 °C) of **5a**



^{13}C NMR ($(CD_3)_2SO$, 25 °C) of **5a**



^{1}H NMR ($(CD_3)_2SO$, 25 °C) of **5b**



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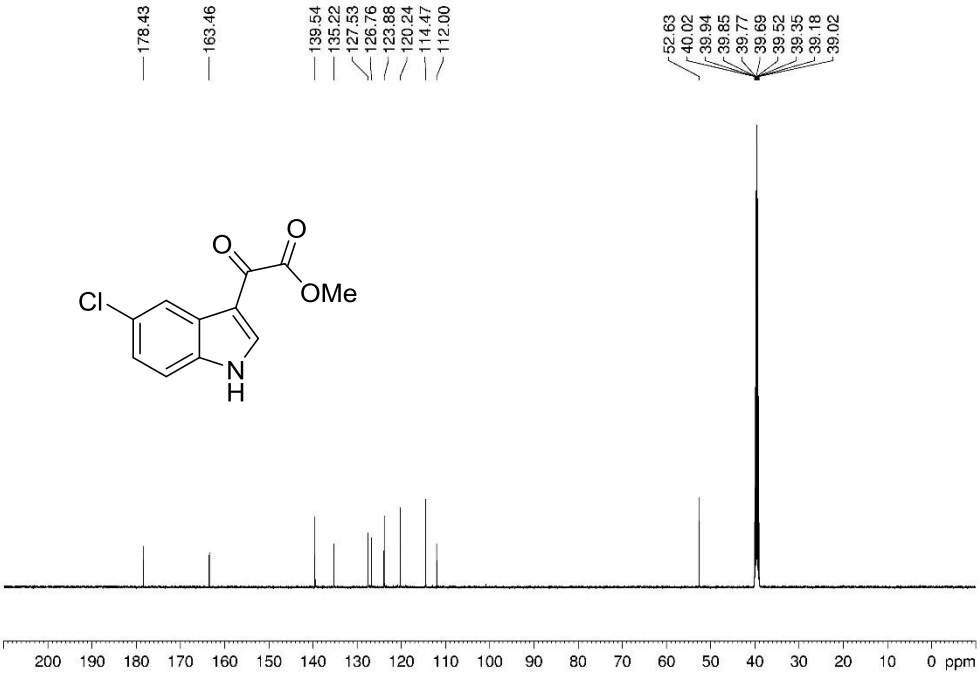

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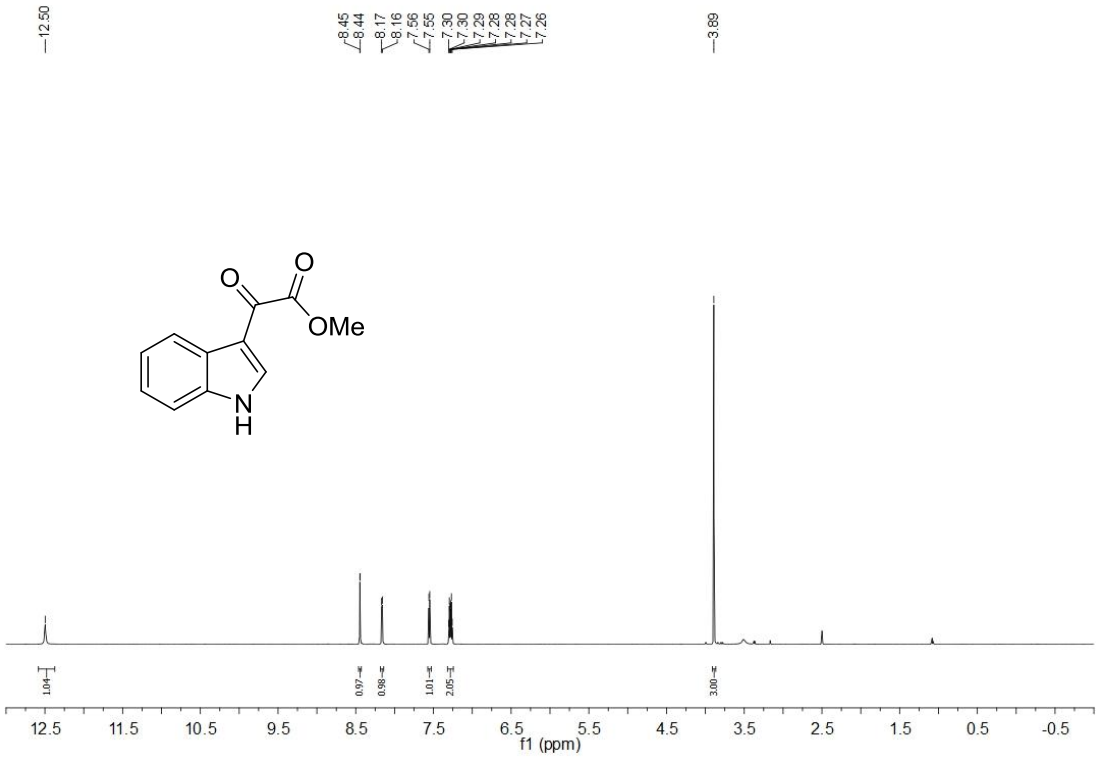

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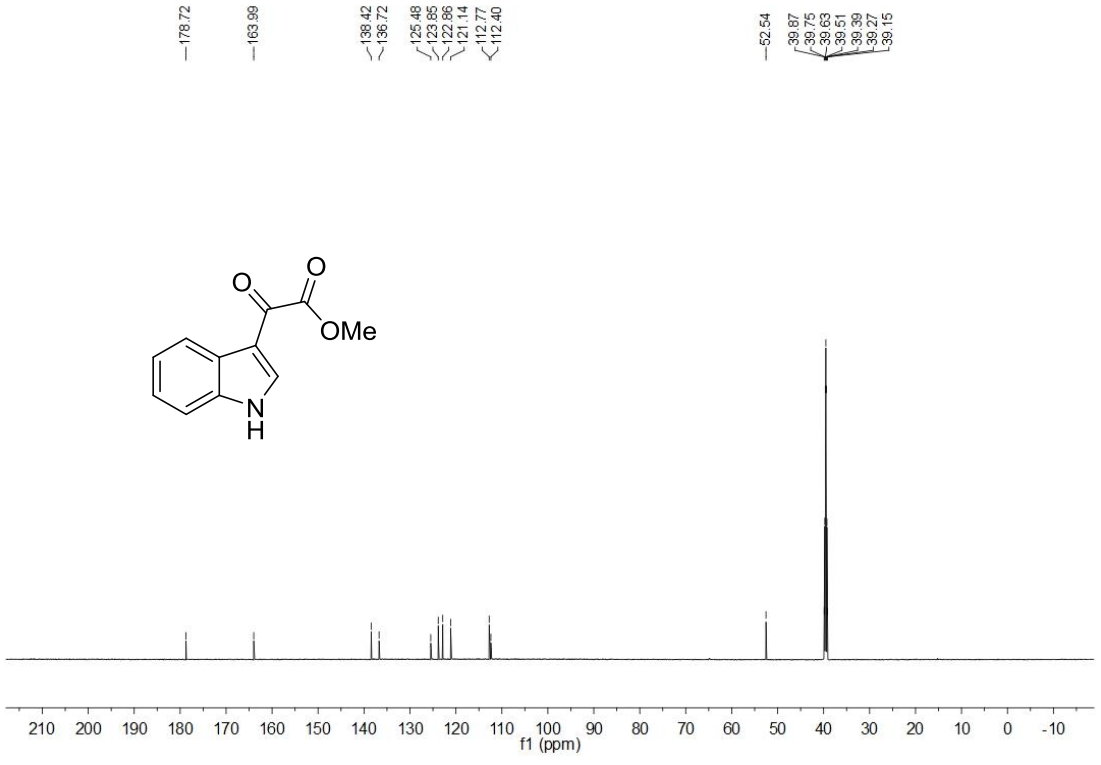
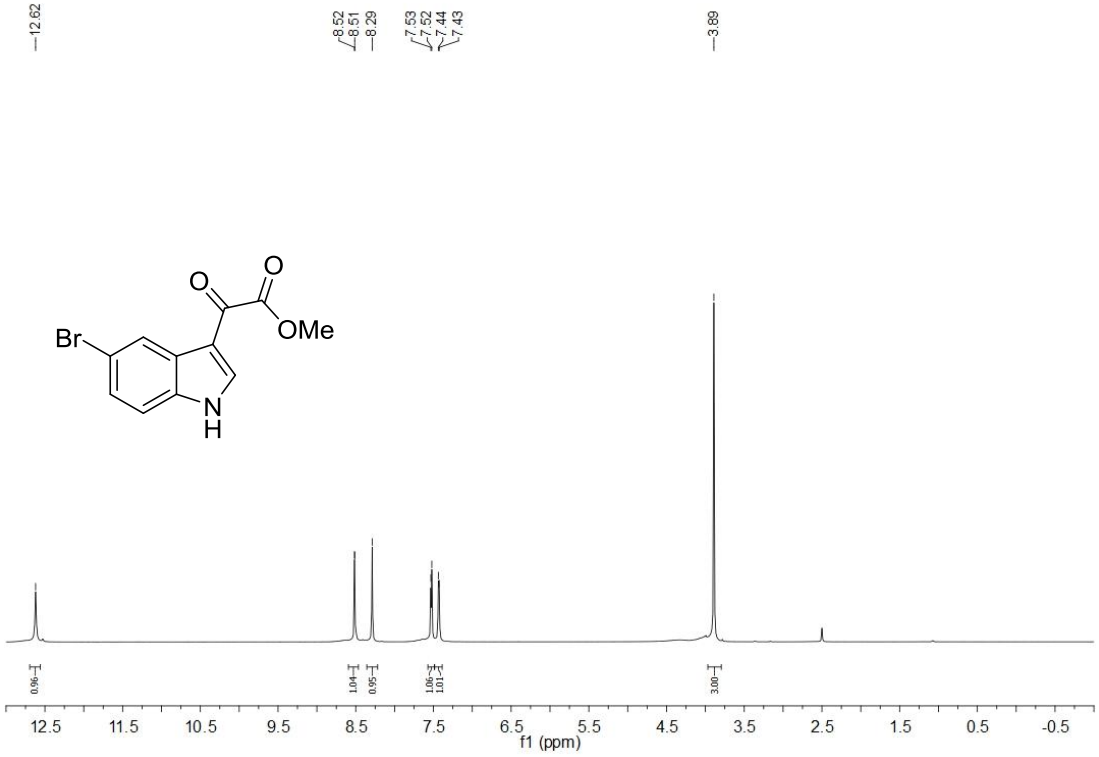
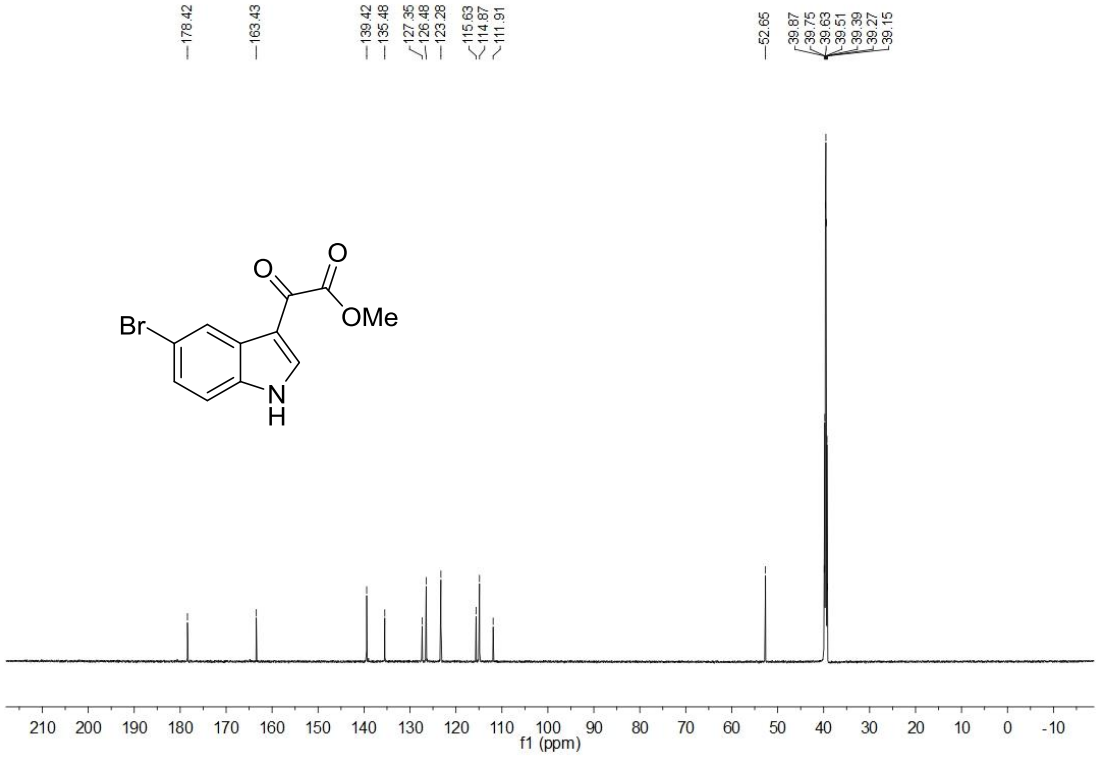


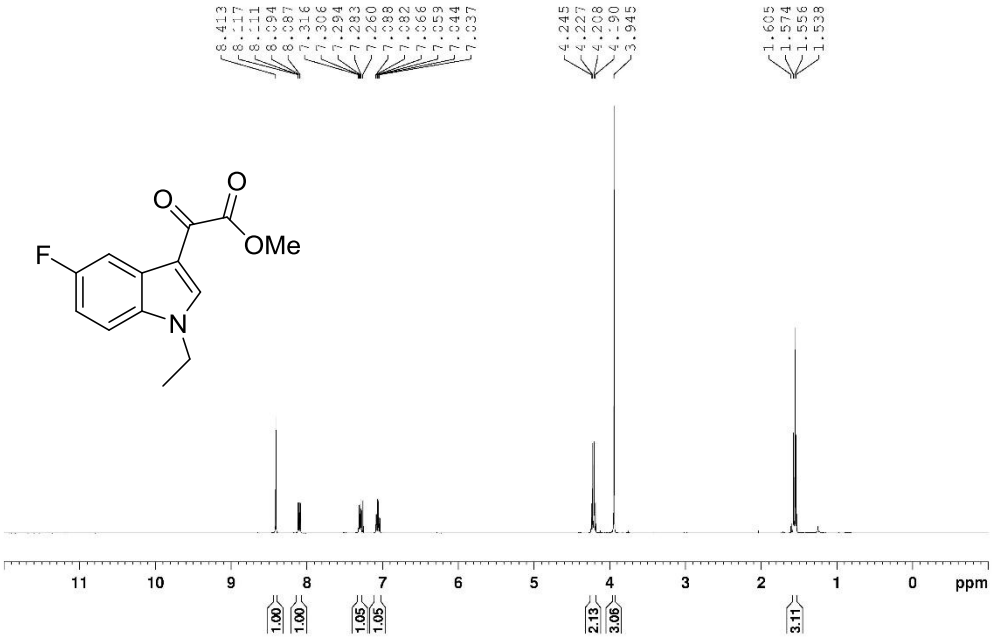
^{1}H NMR ((CD$_3$)$_2$SO, 25 °C) of **5d**



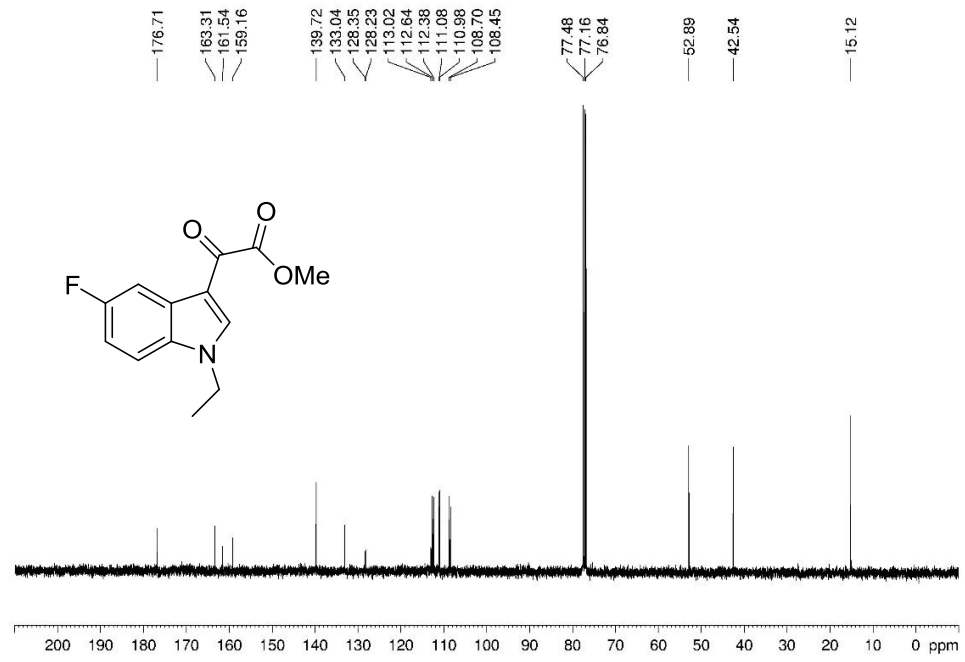
^{13}C NMR ((CD$_3$)$_2$SO, 25 °C) of **5d**



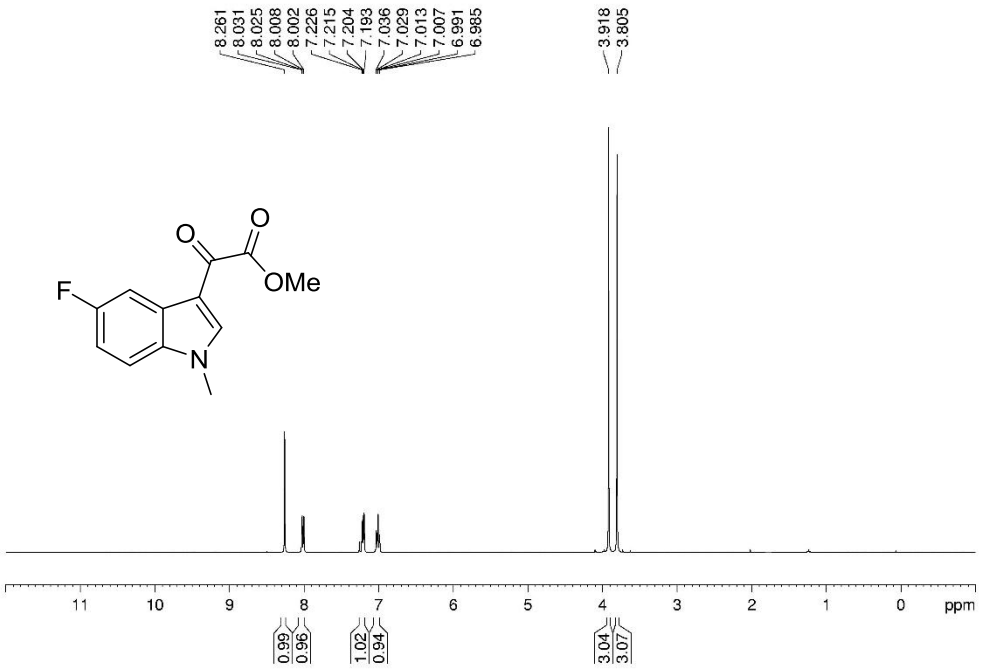
^{1}H NMR ($CDCl_3$, 25 °C) of **6a**



^{13}C NMR ($CDCl_3$, 25 °C) of **6a**



^{1}H NMR ($CDCl_3$, 25 °C) of **6b**



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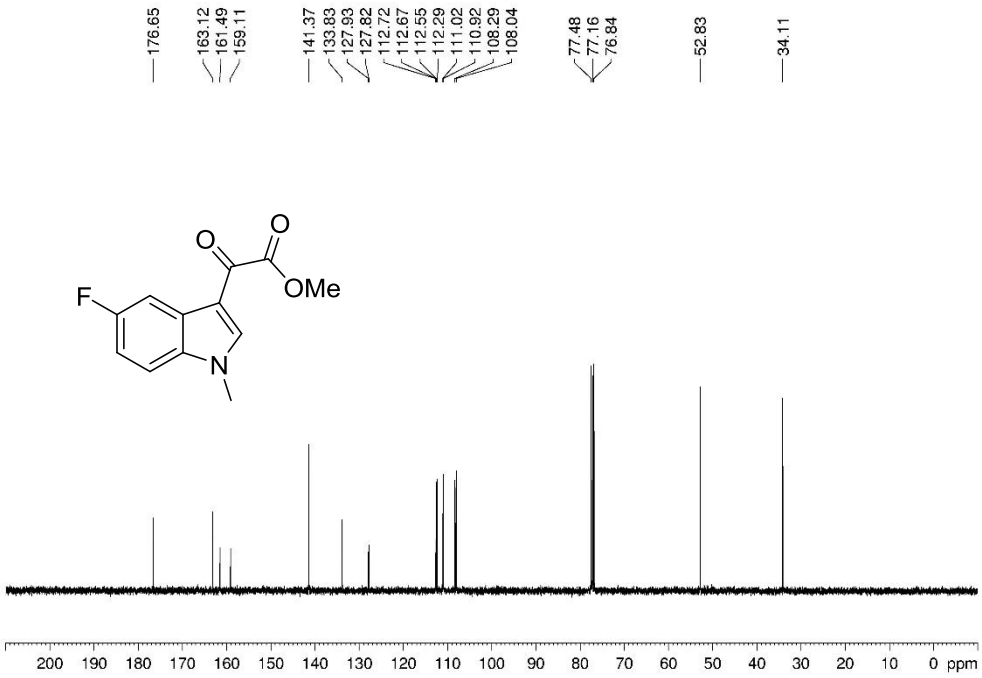

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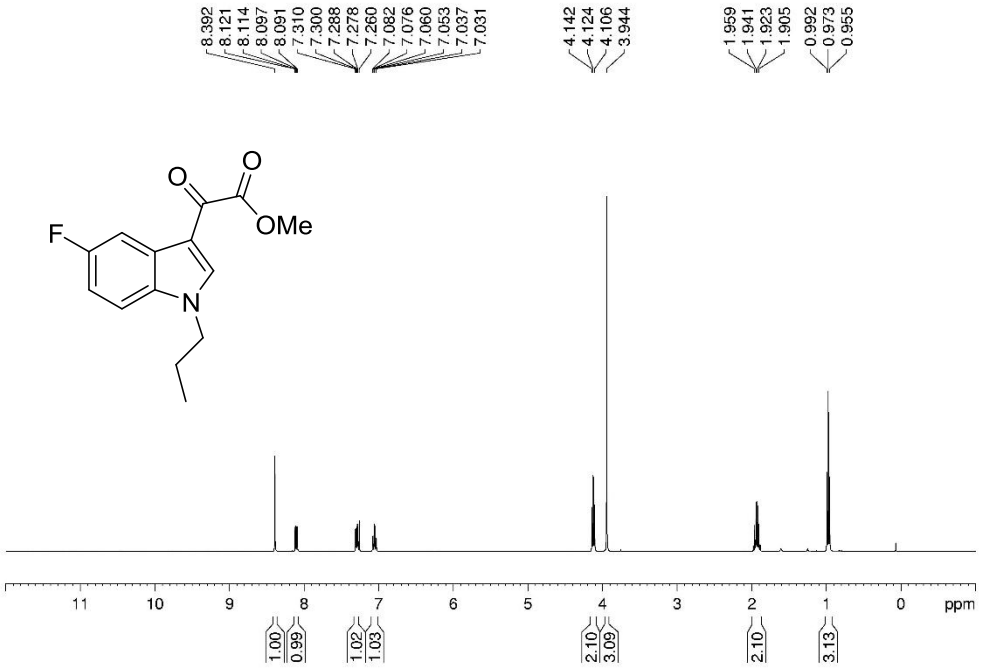

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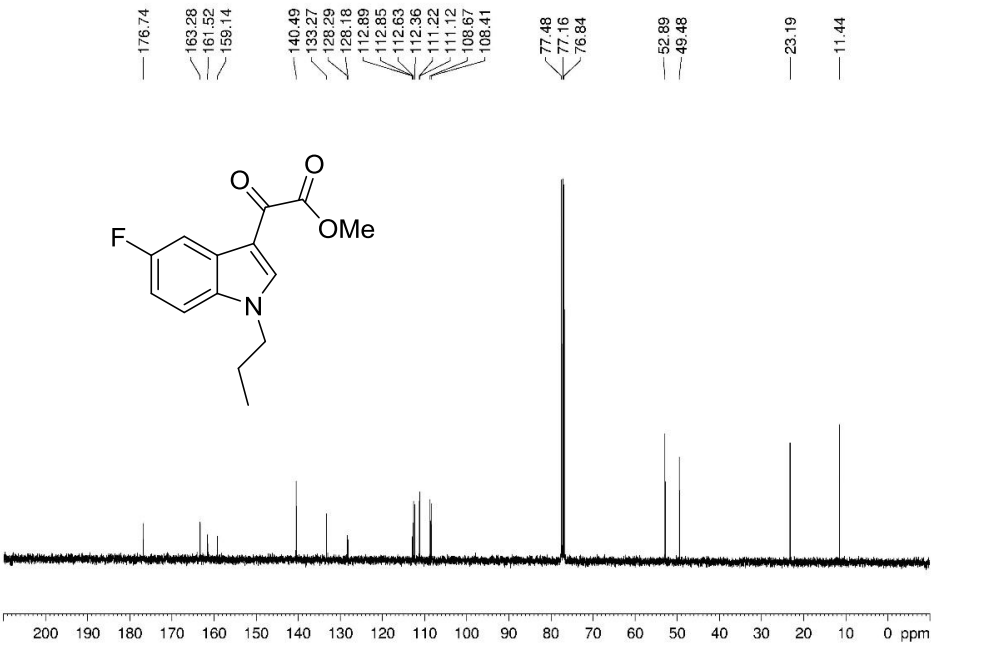
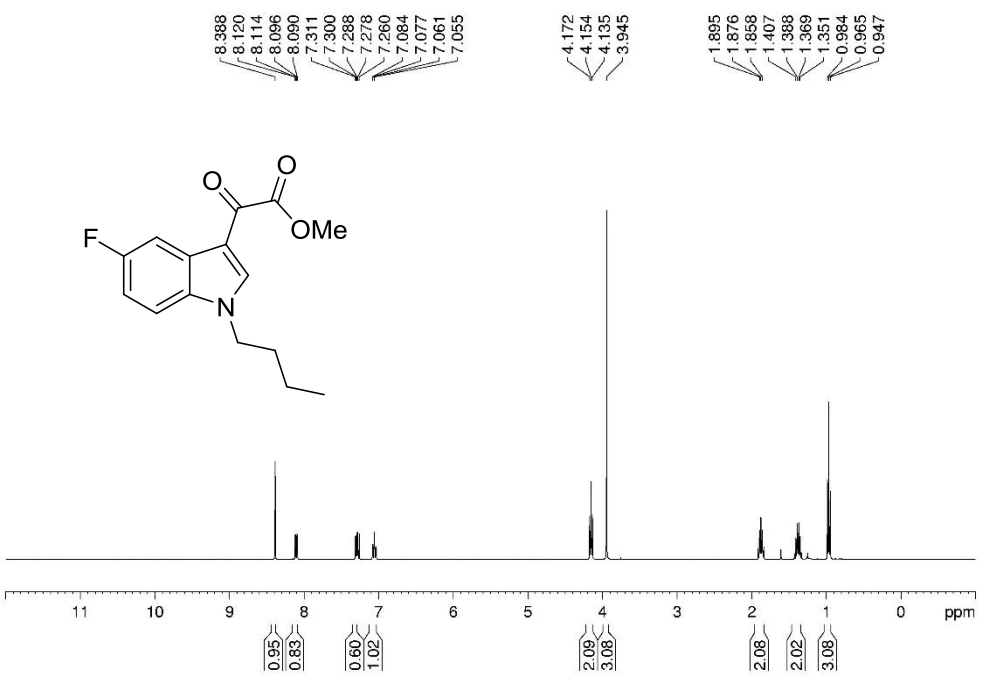


^{1}H NMR ($CDCl_3$, 25 °C) of **6d**



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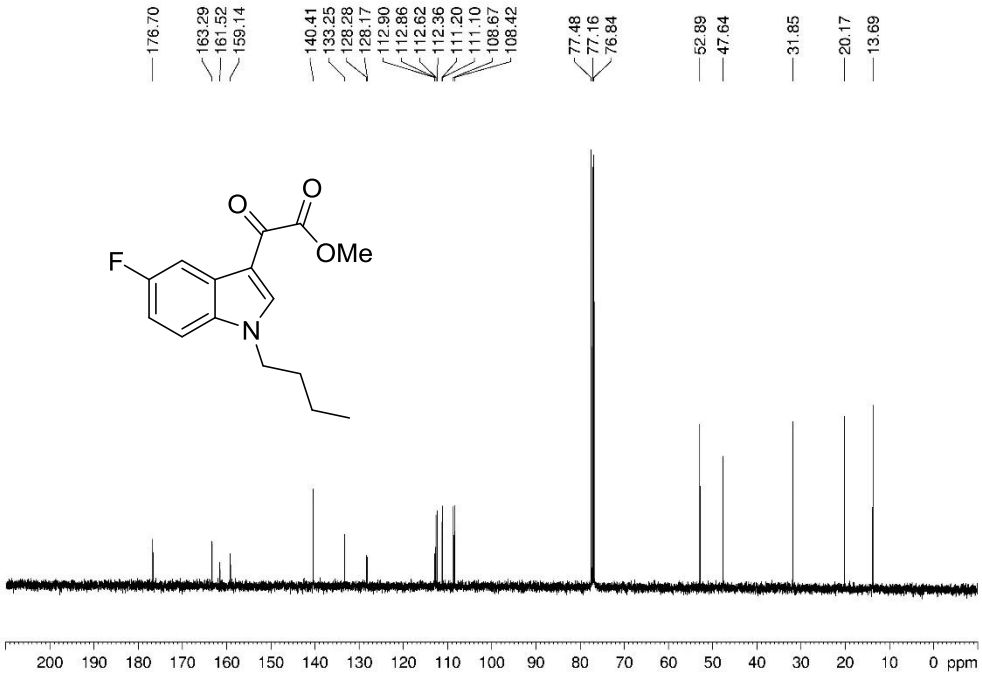

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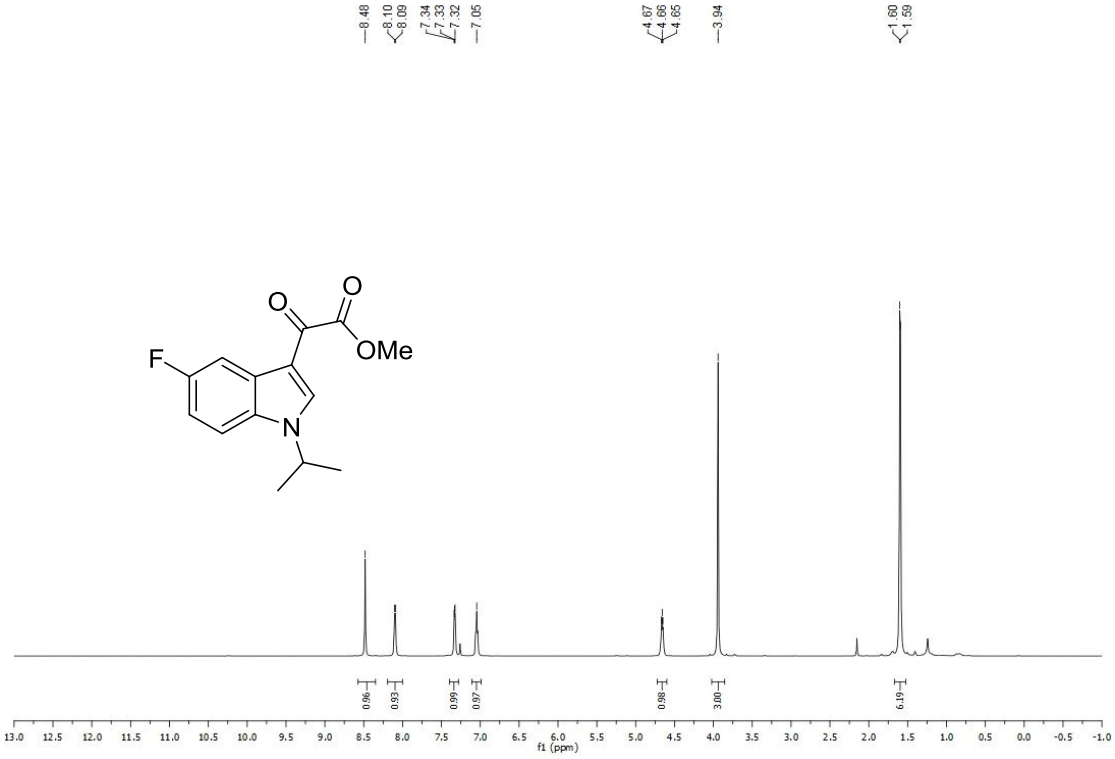

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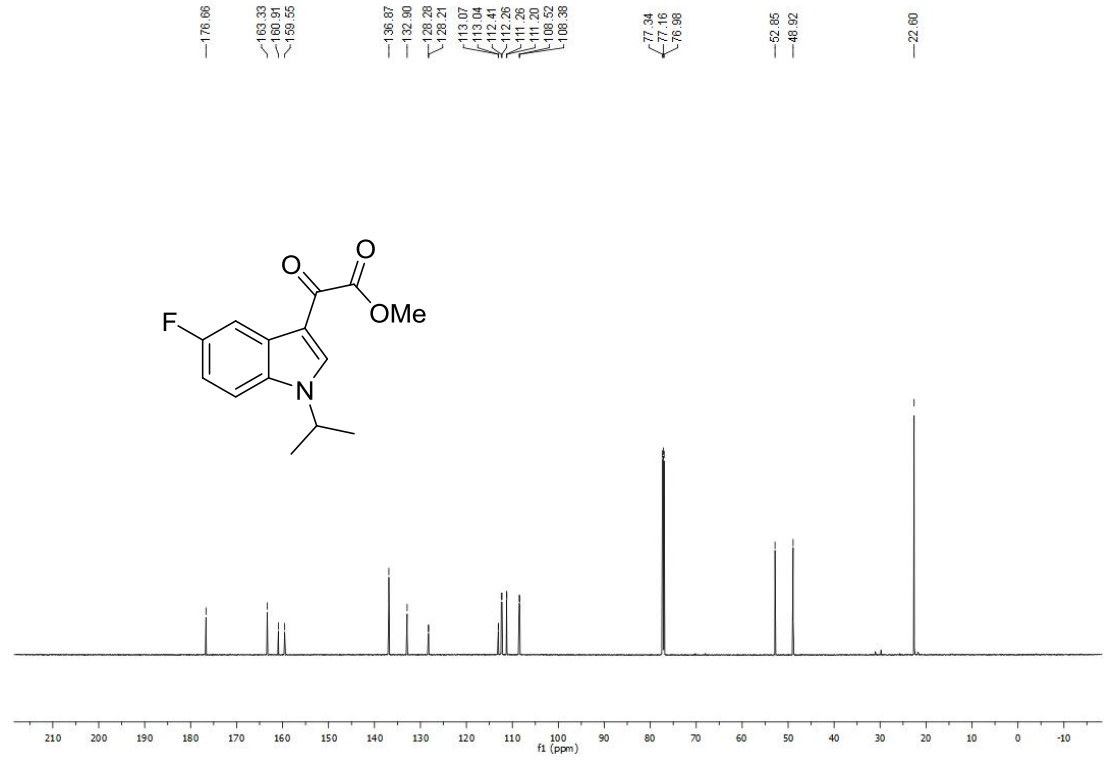

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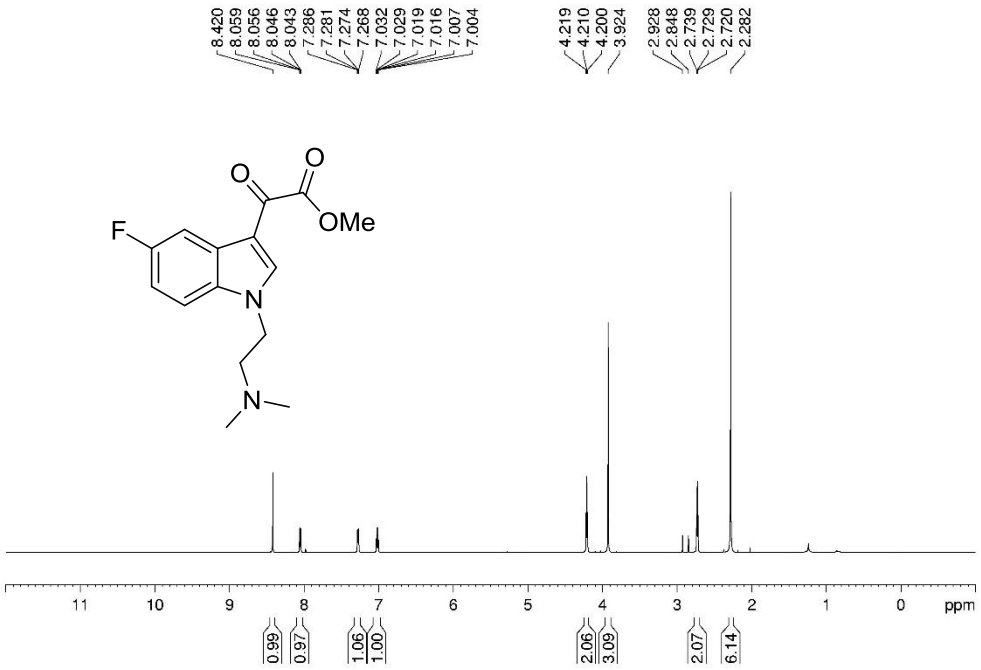

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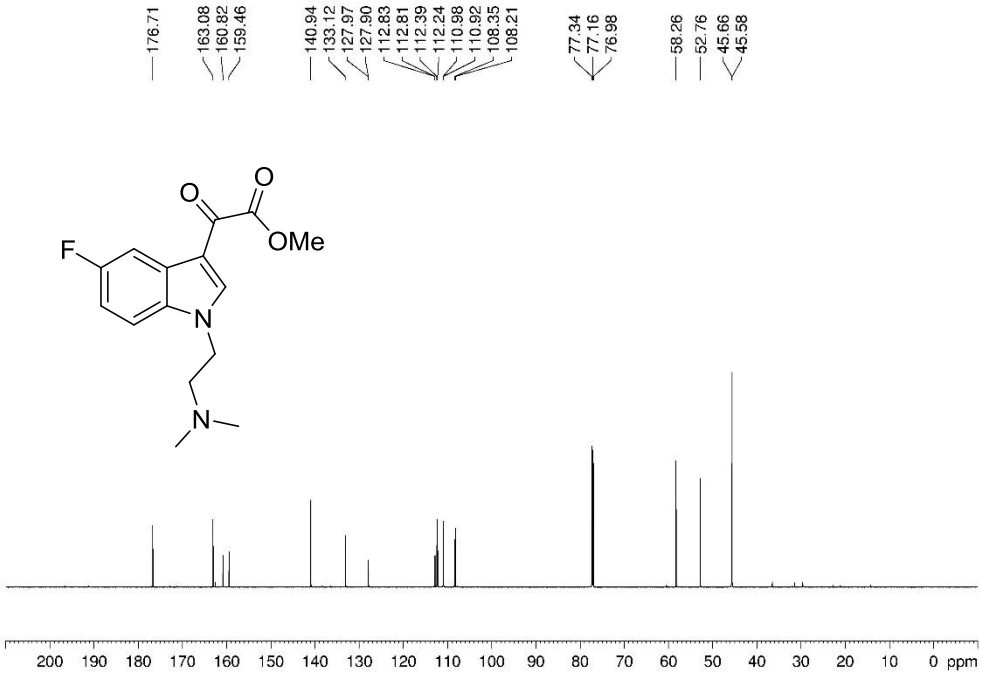

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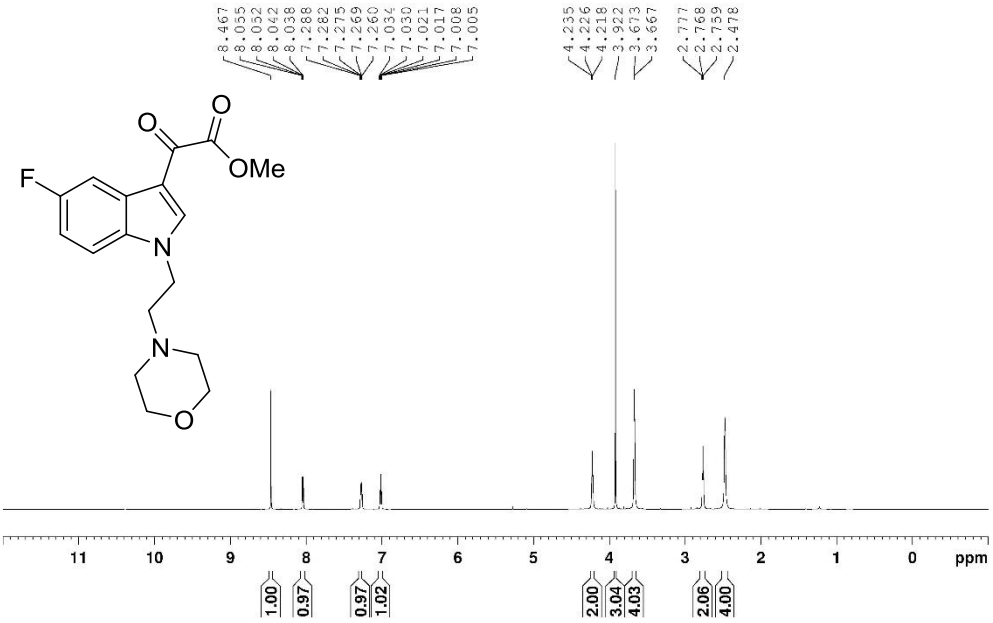

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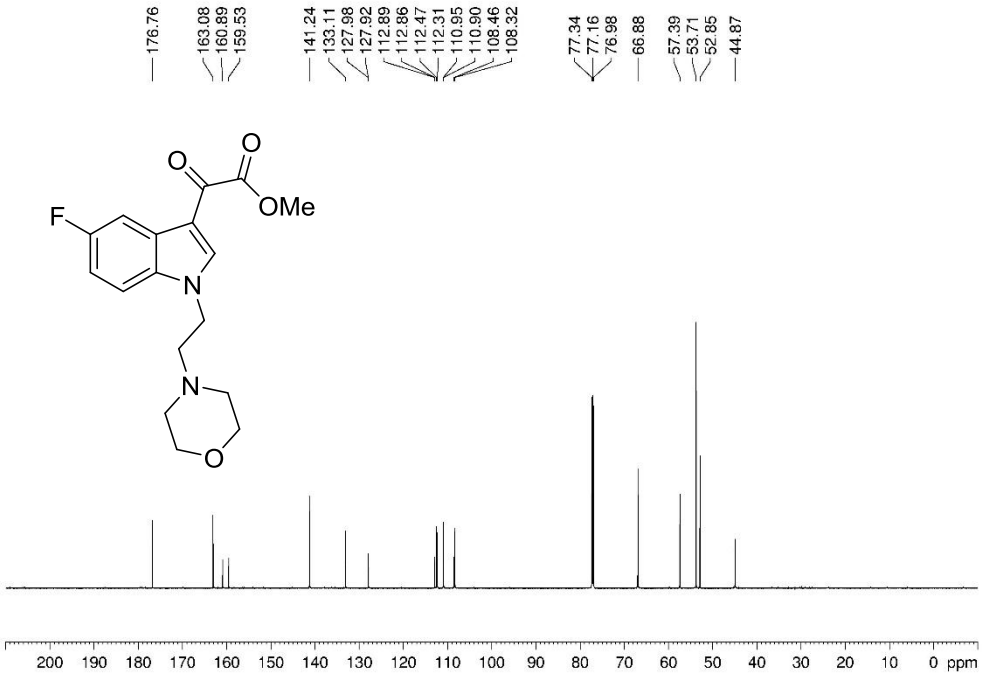

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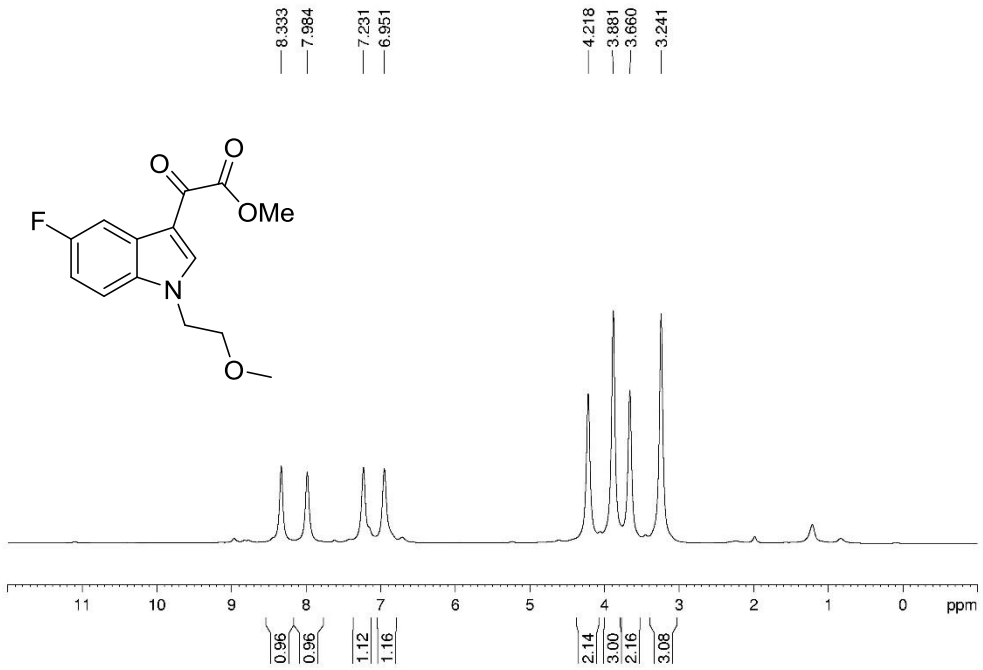

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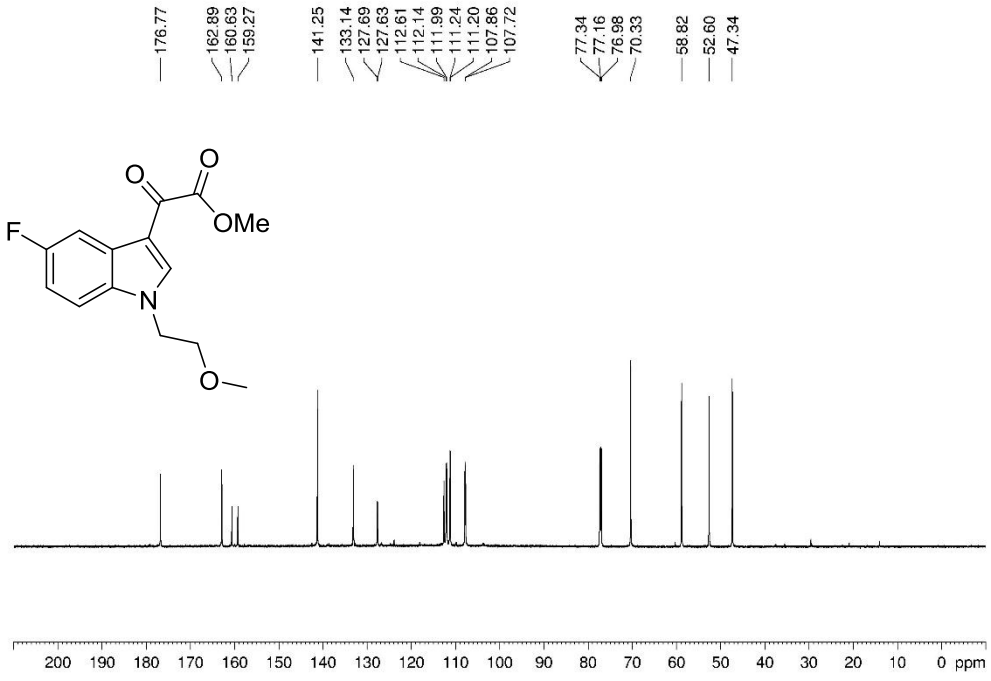

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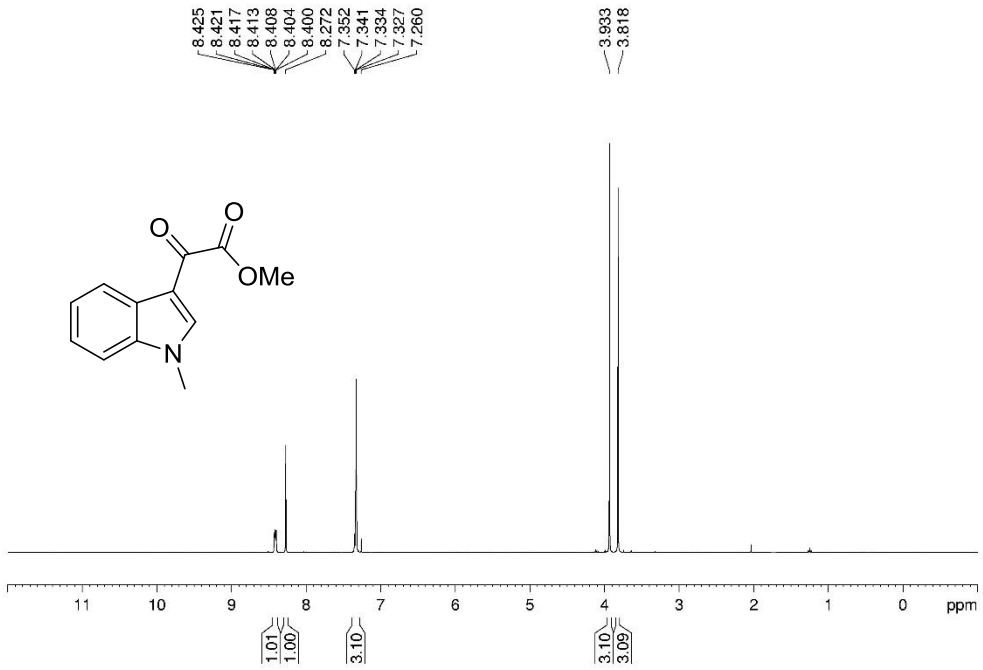

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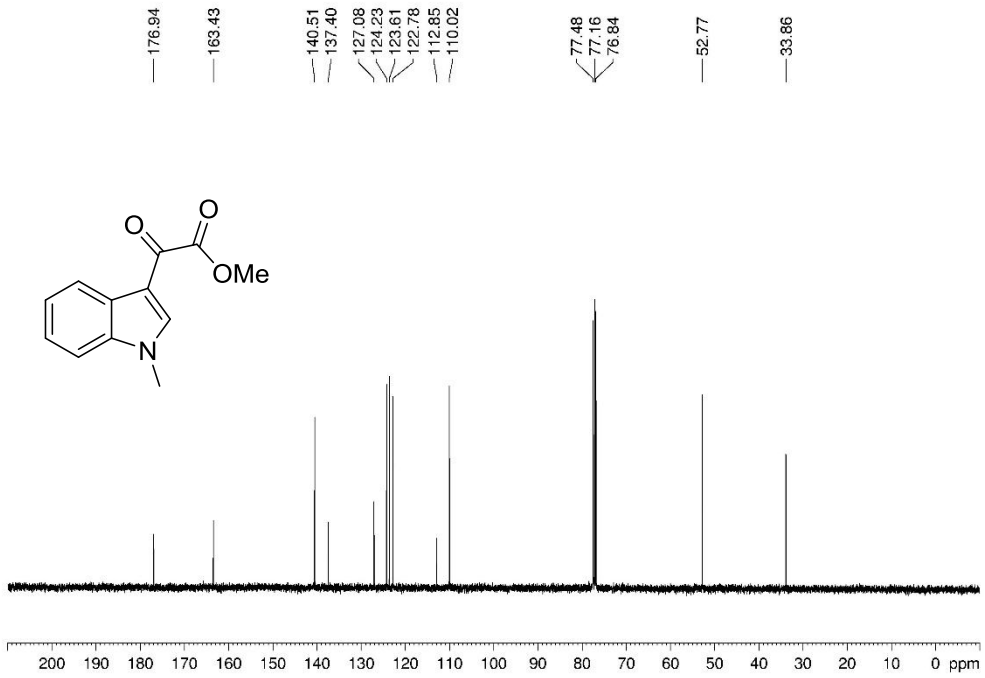

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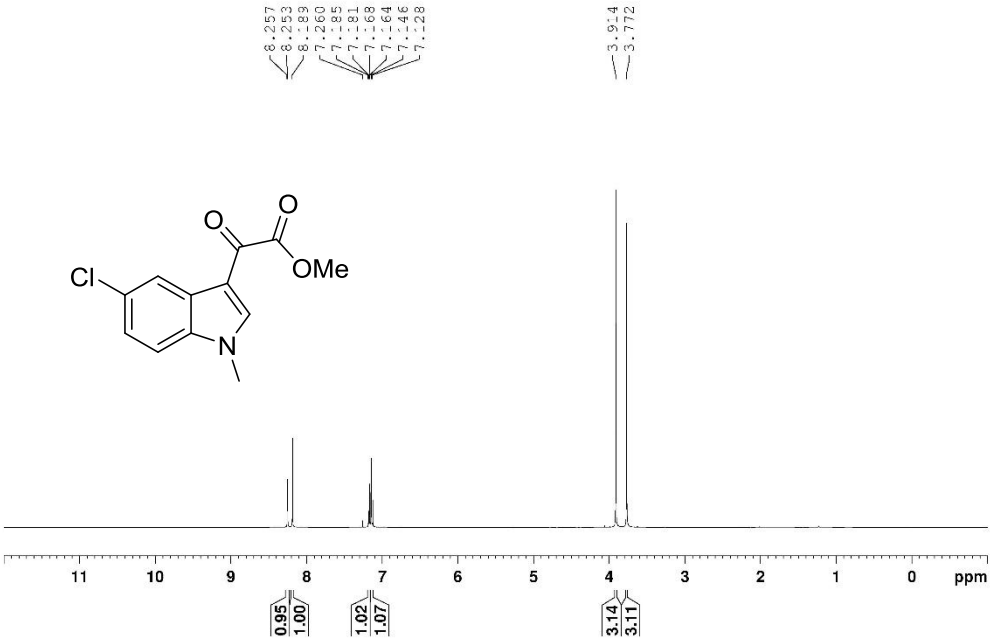

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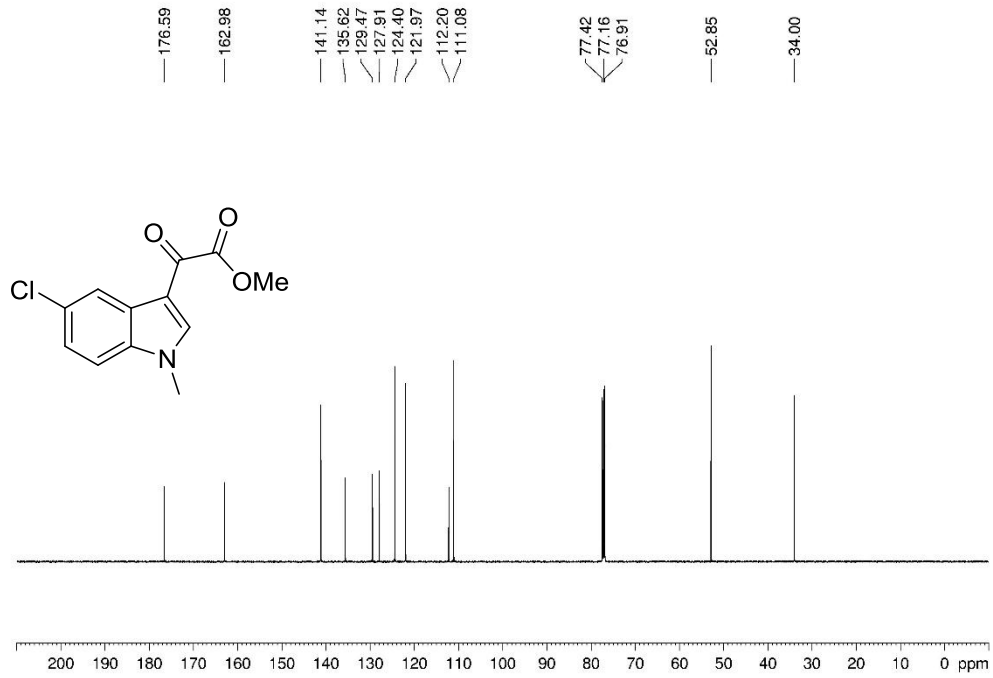

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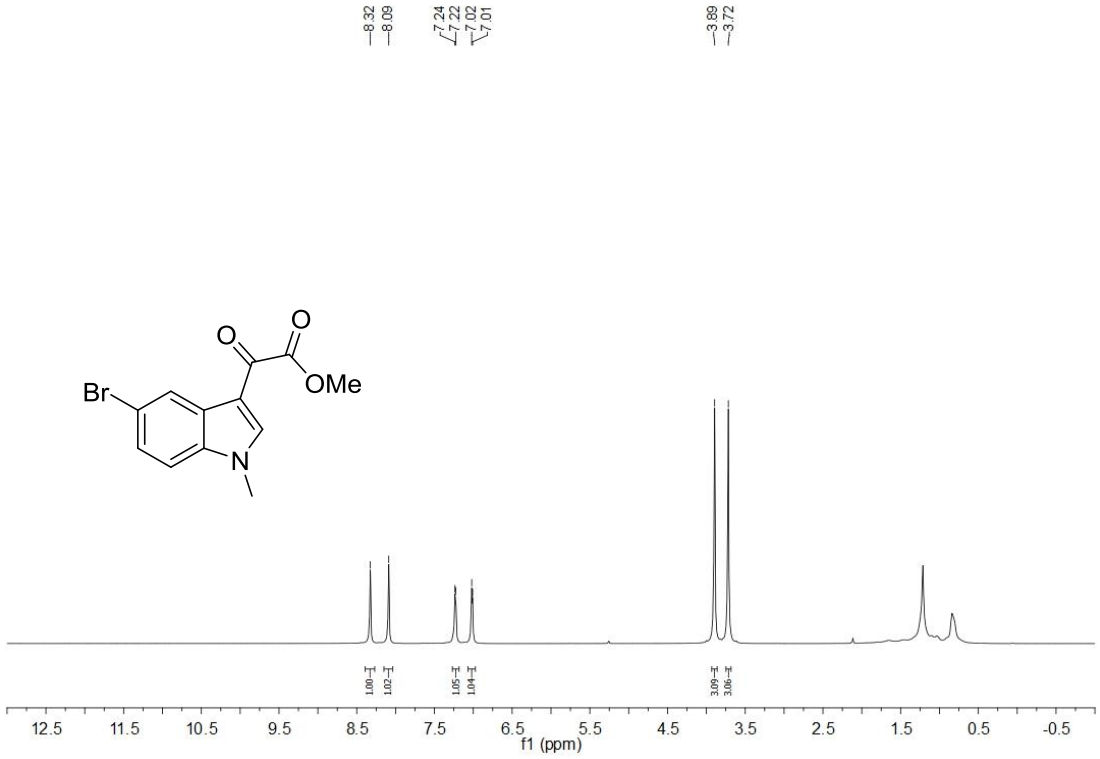

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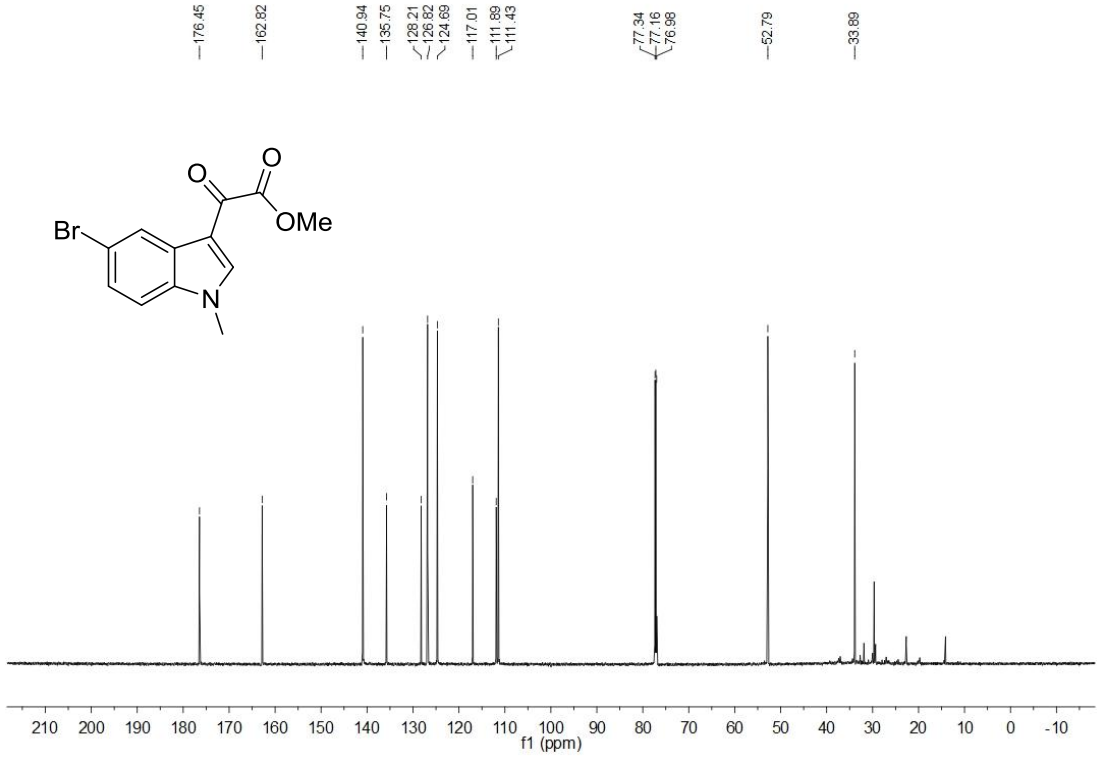
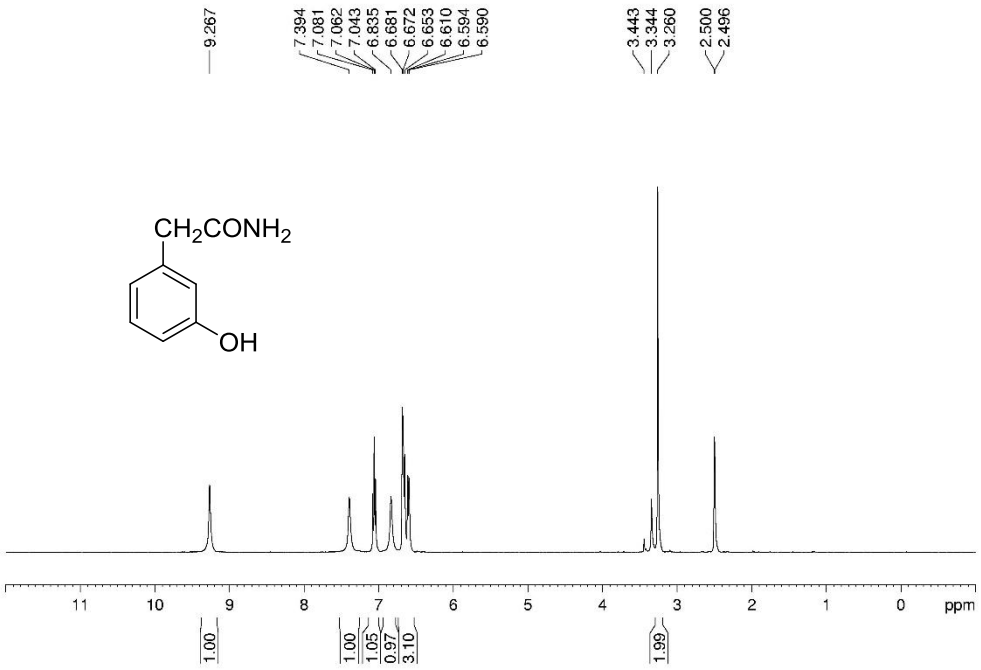
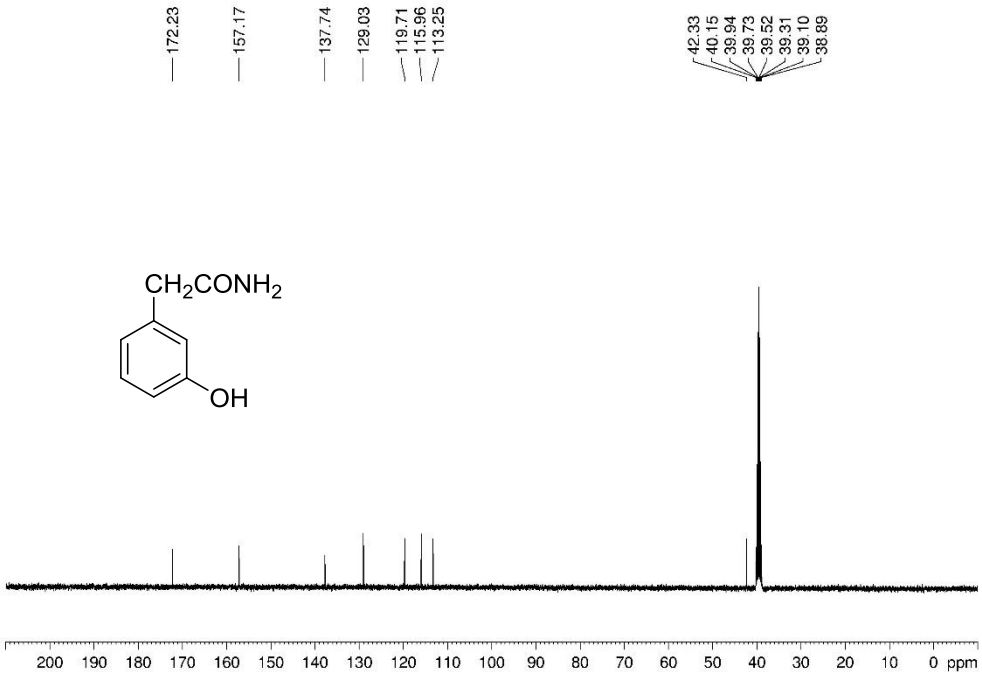


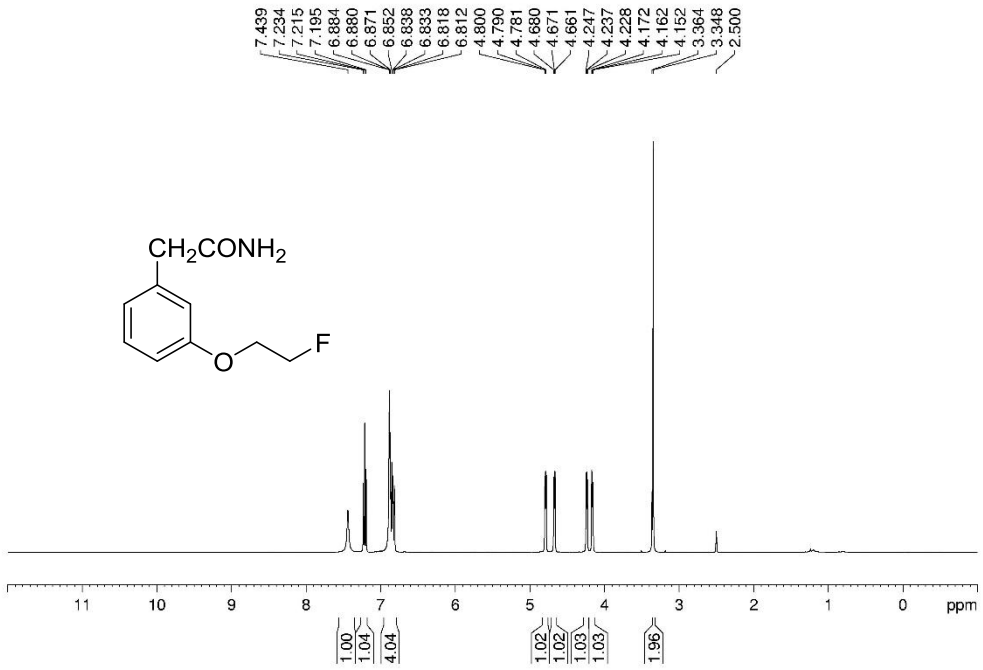
^{1}H NMR ($(CD_3)_2SO$, 25 °C) of **8**



^{13}C NMR ($(CD_3)_2SO$, 25 °C) of **8**



^{1}H NMR ((CD$_3$)$_2$SO, 25 °C) of **9**



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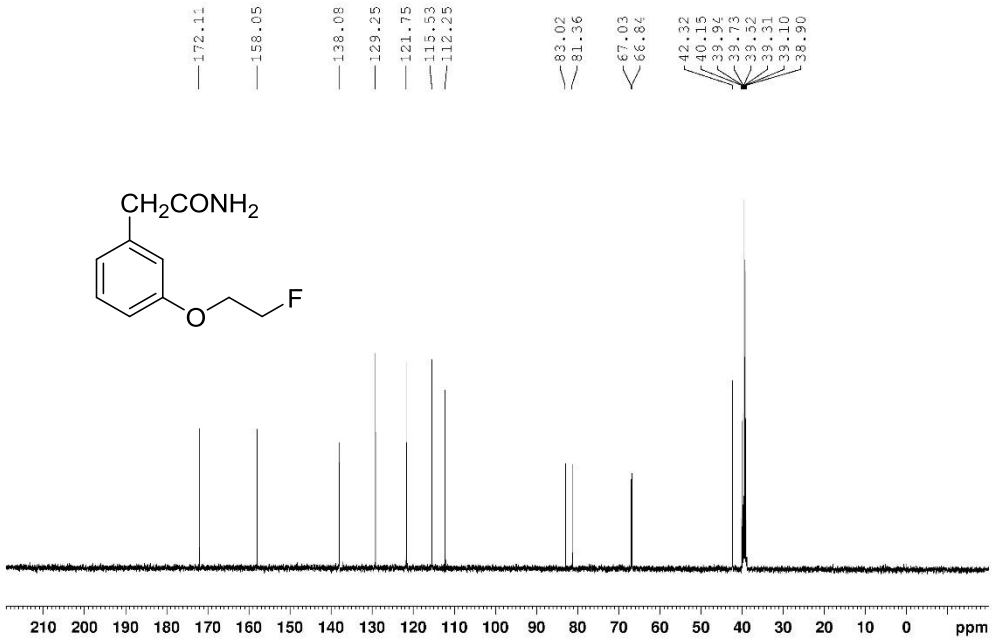

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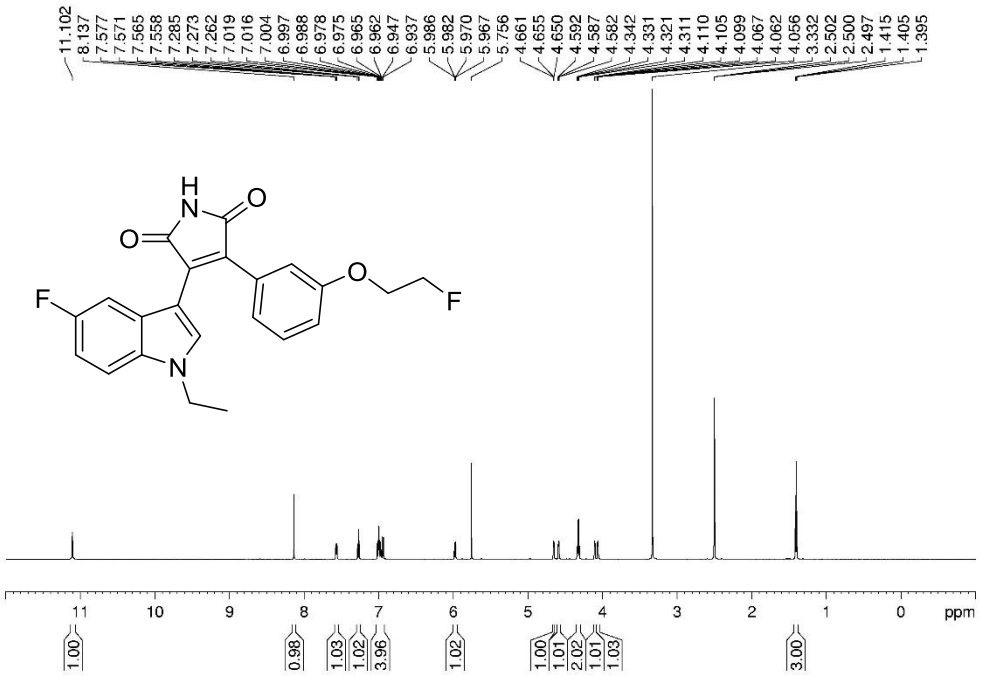

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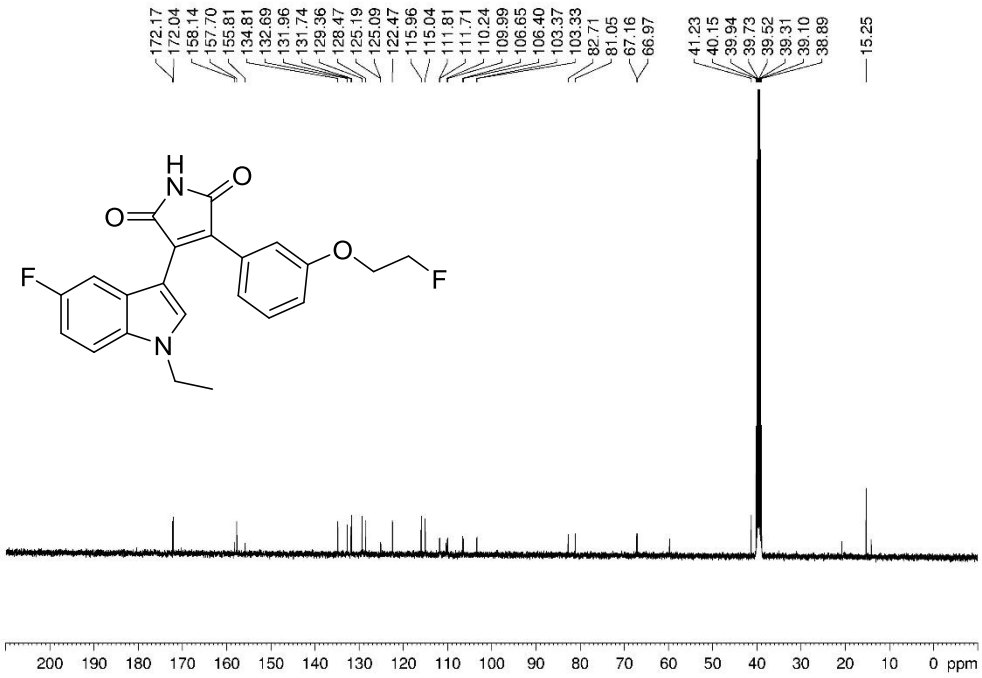
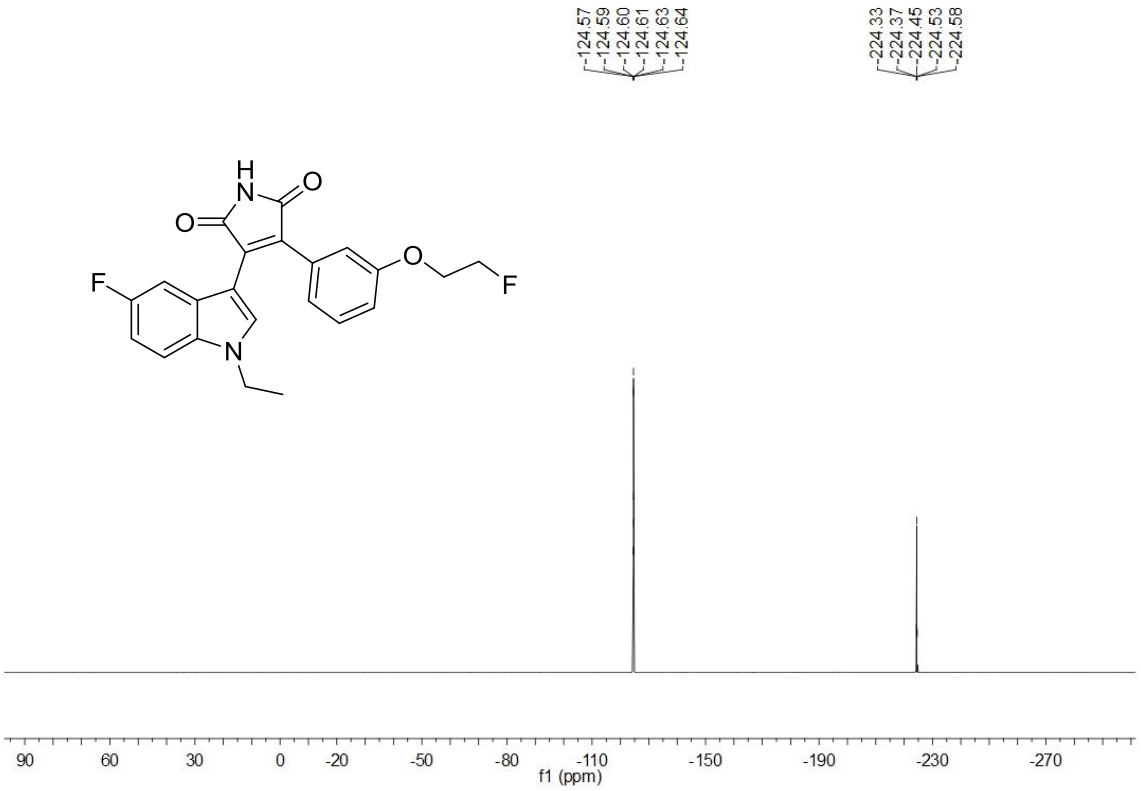


^{19}F NMR ((CD$_3$)$_2$SO, 25 °C) of **10a**



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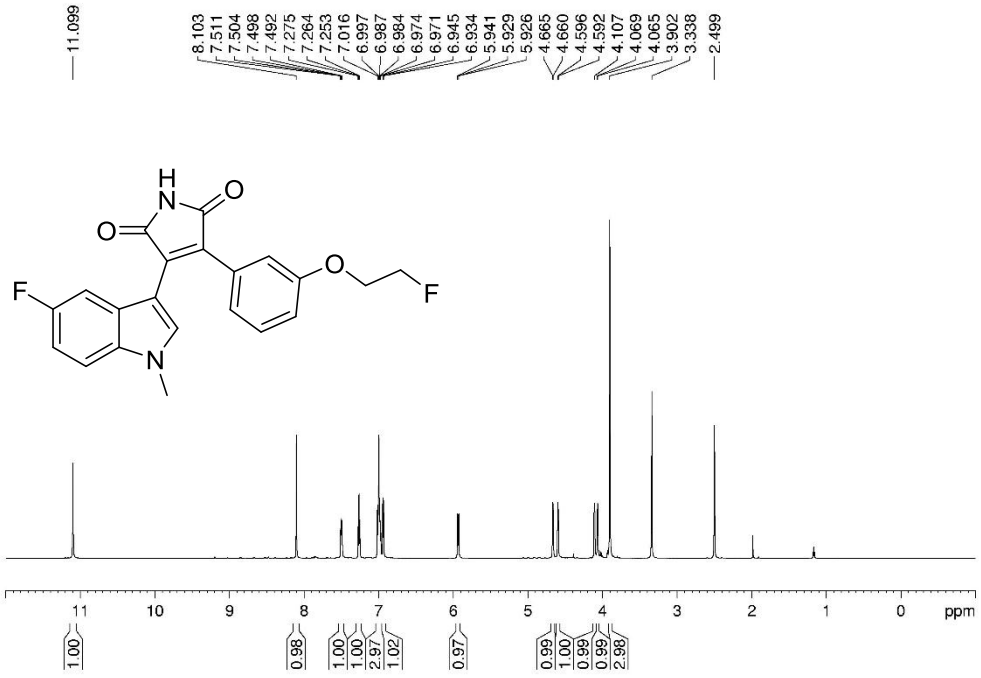

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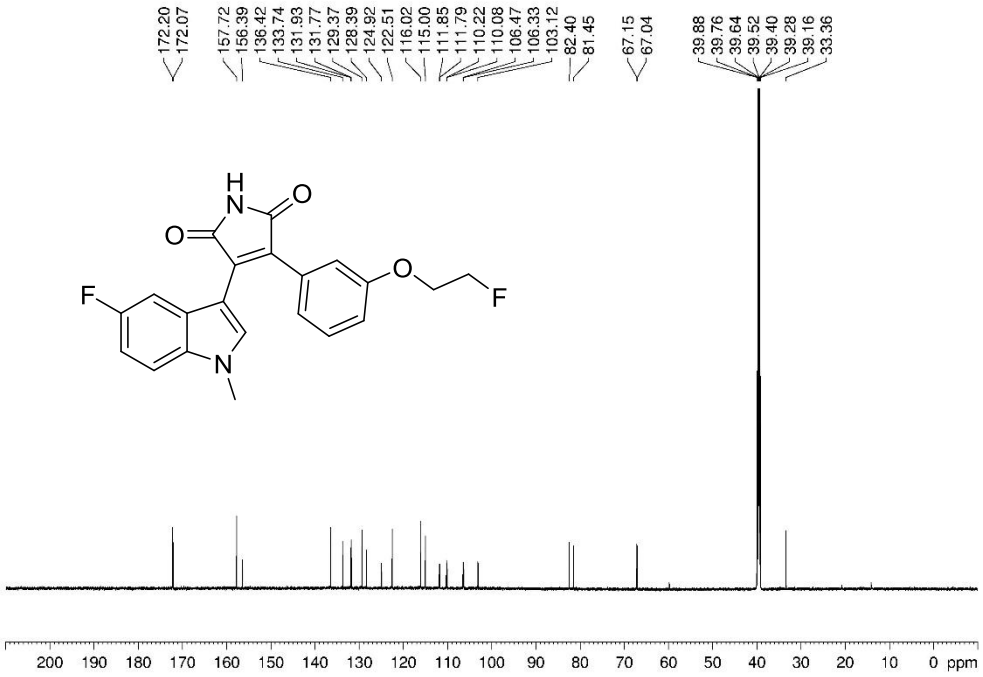

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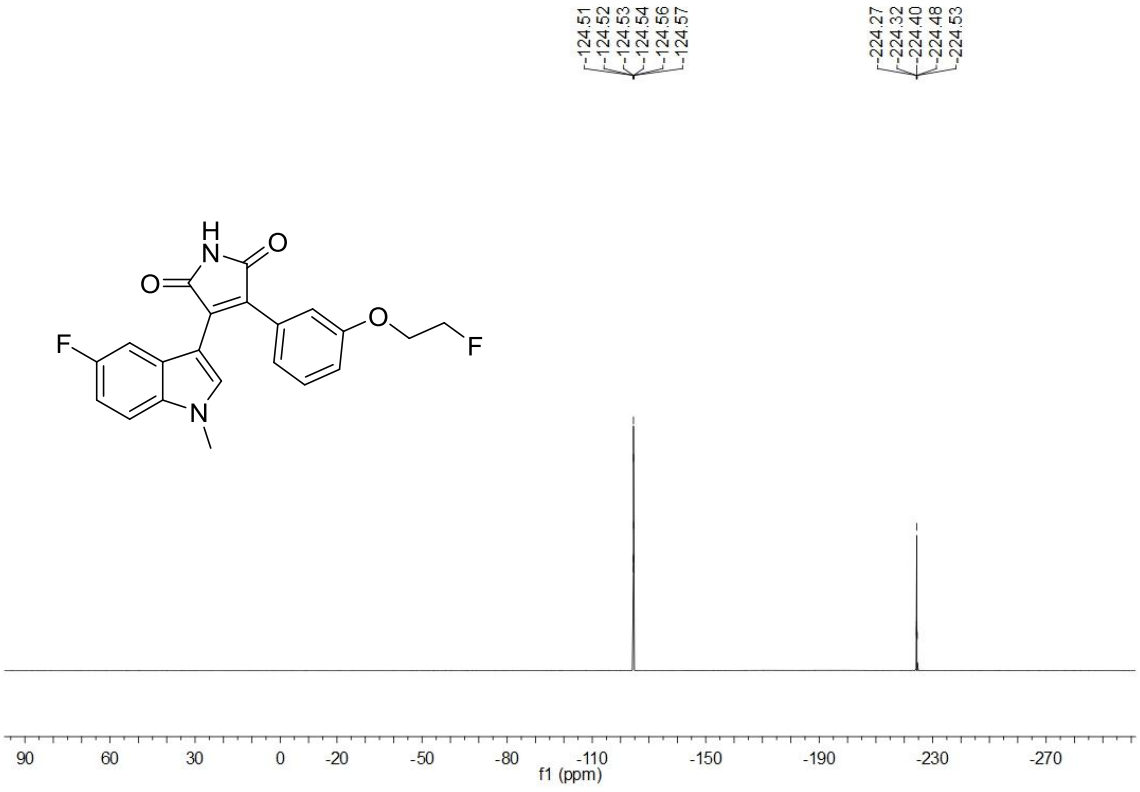

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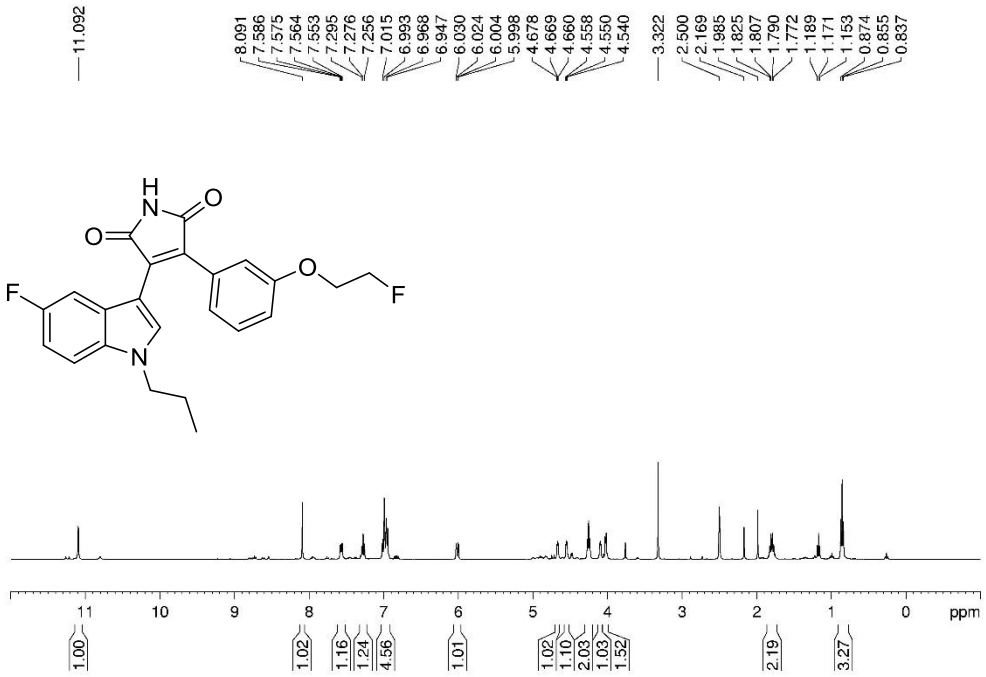

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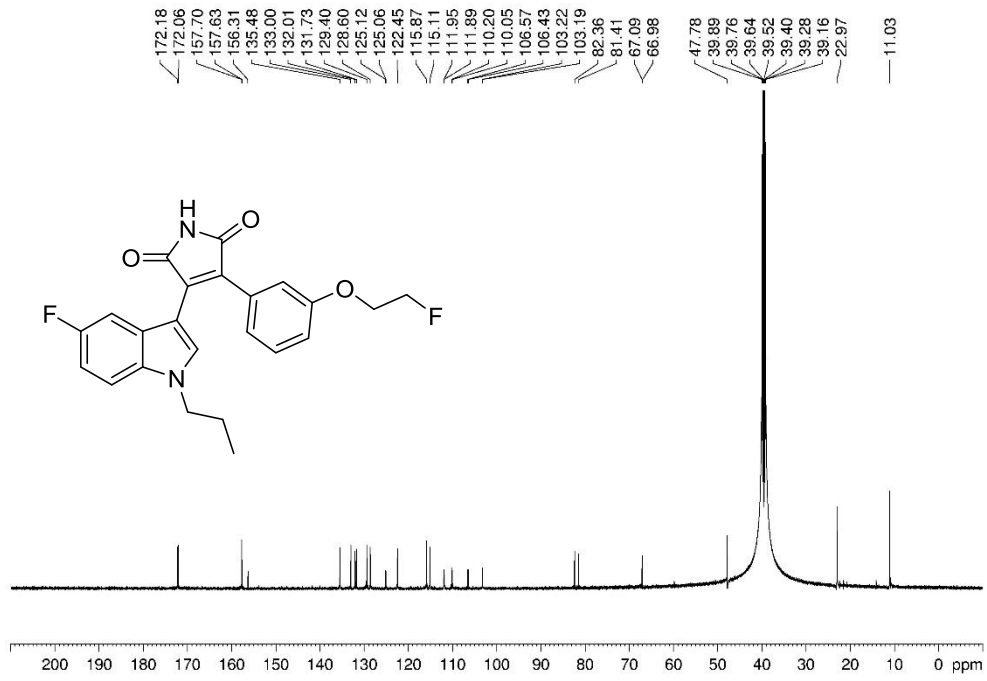

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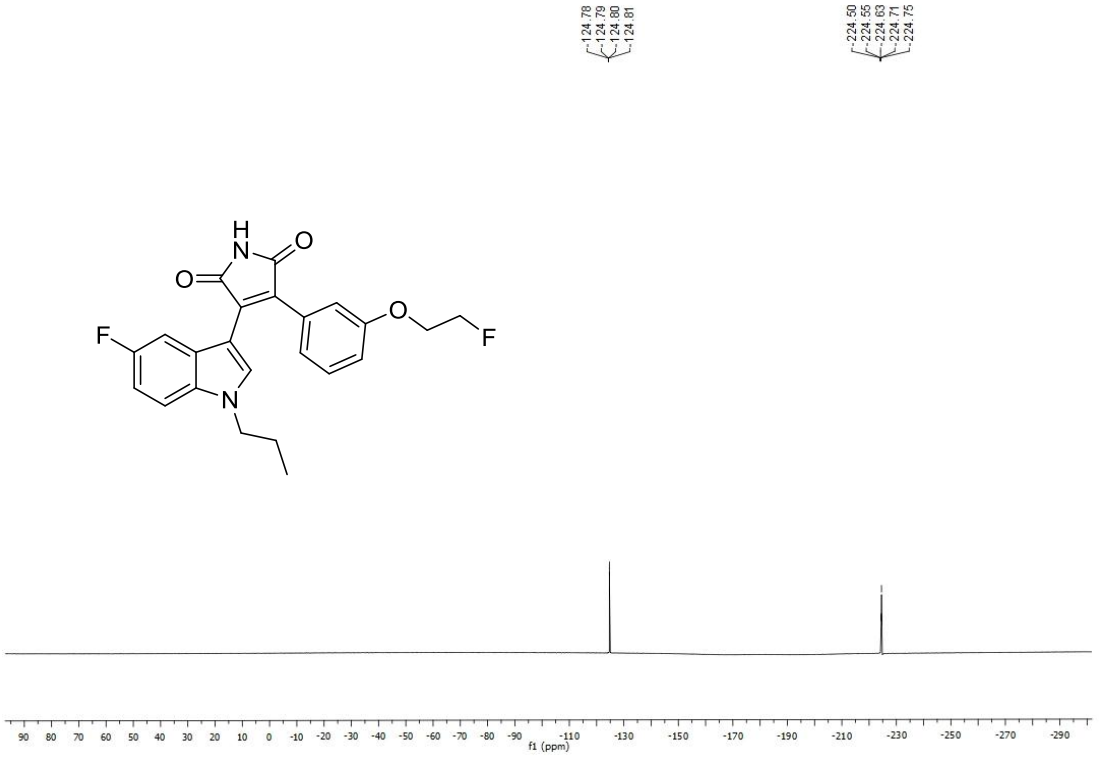

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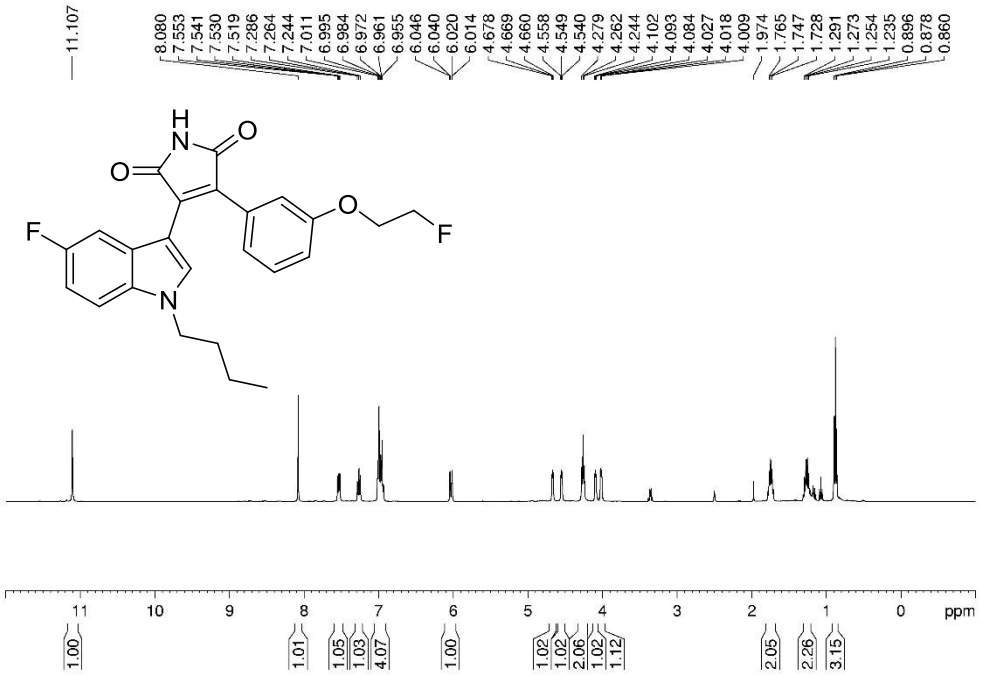

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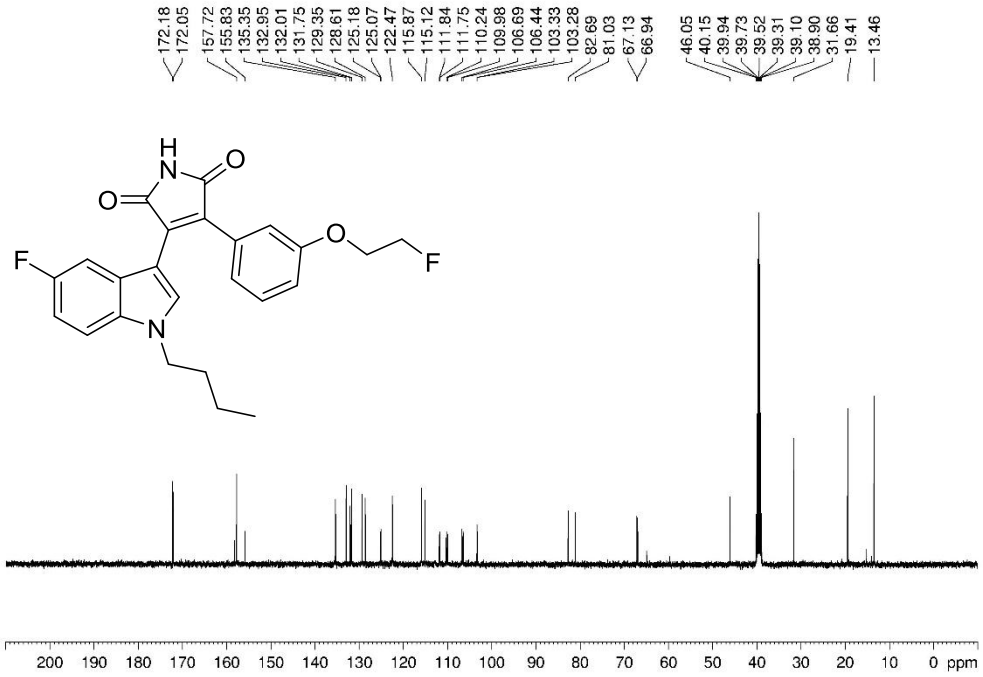

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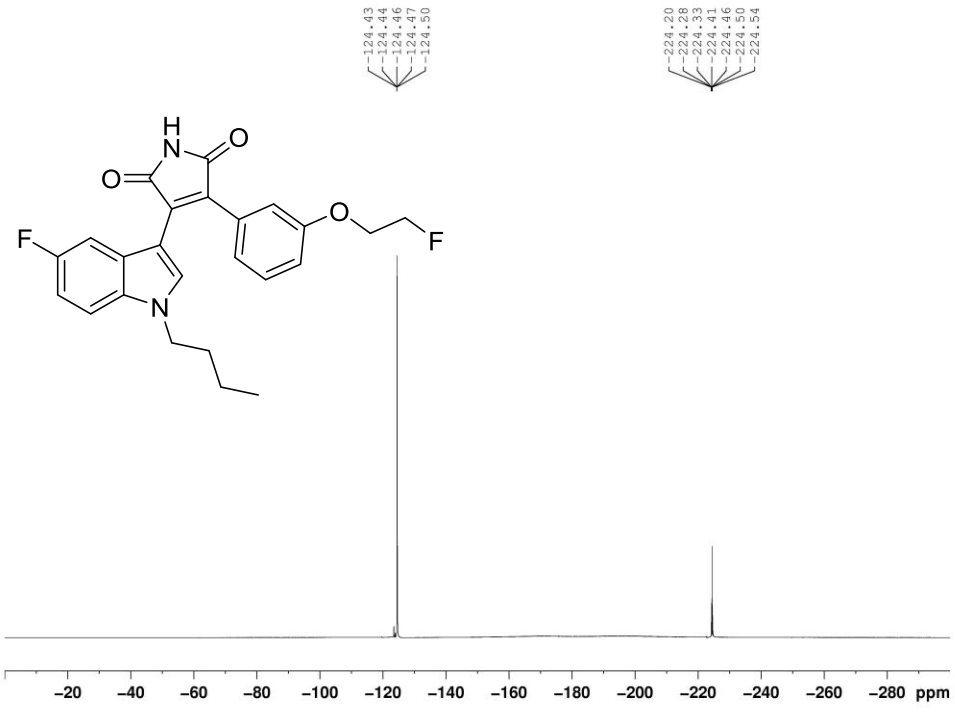

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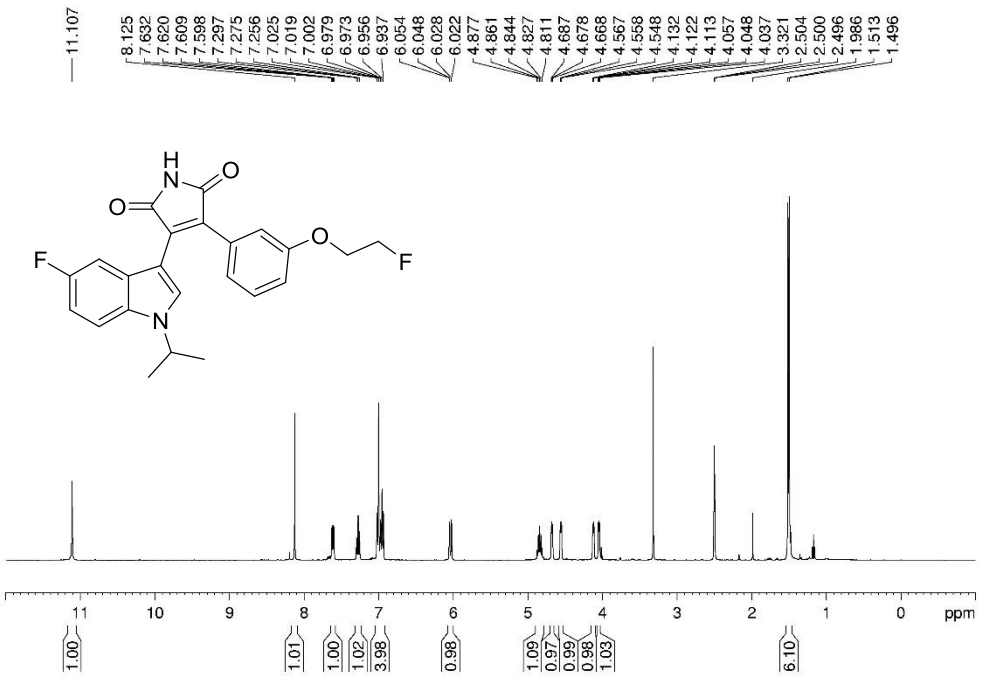

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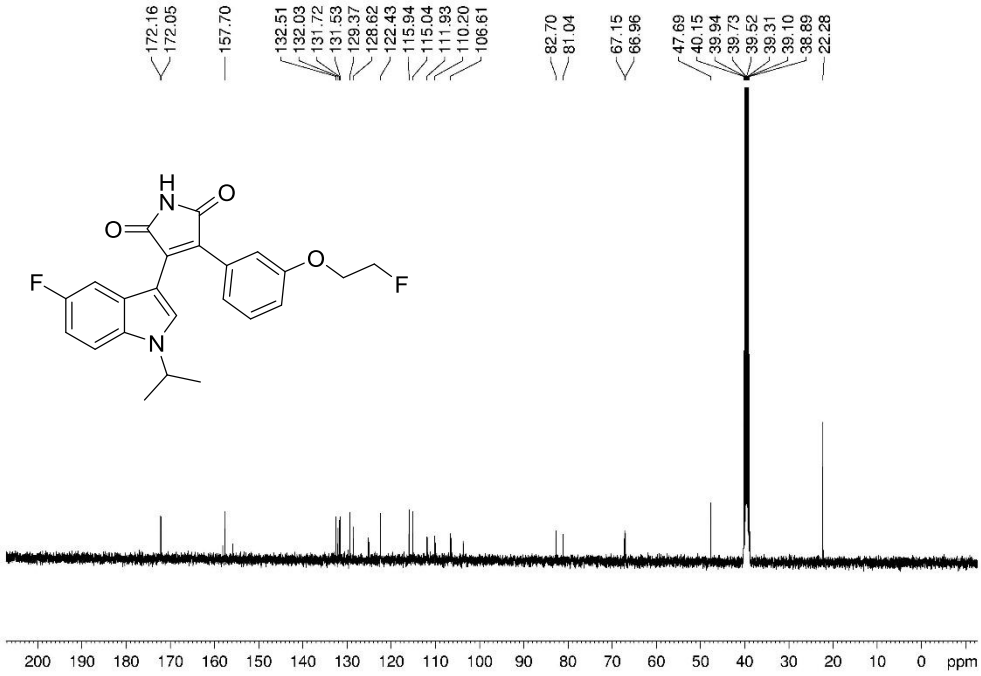
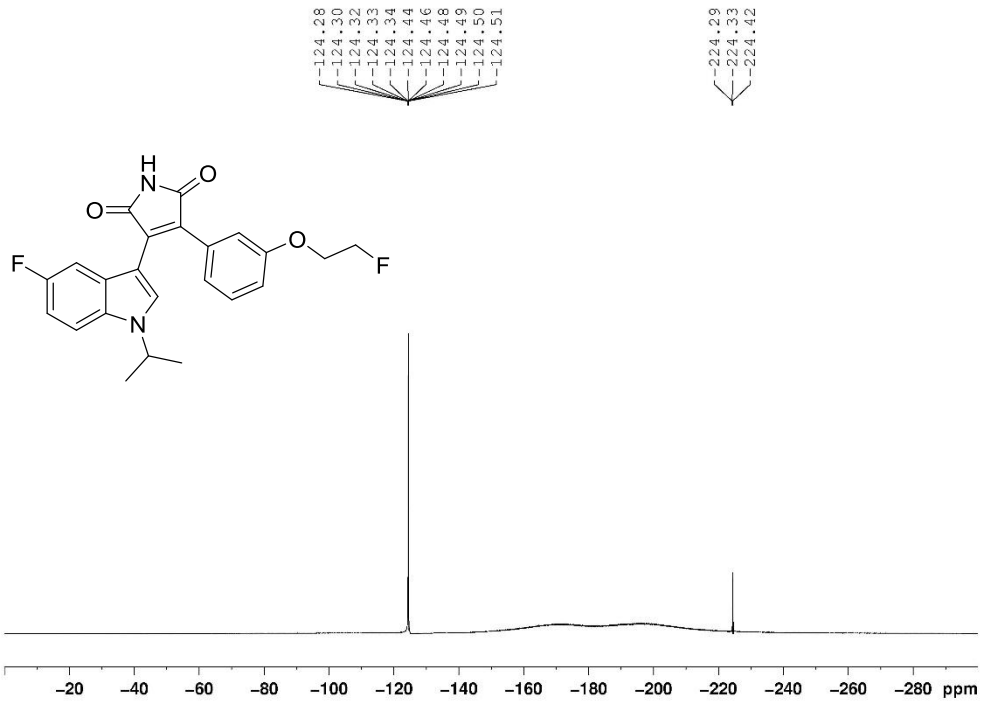
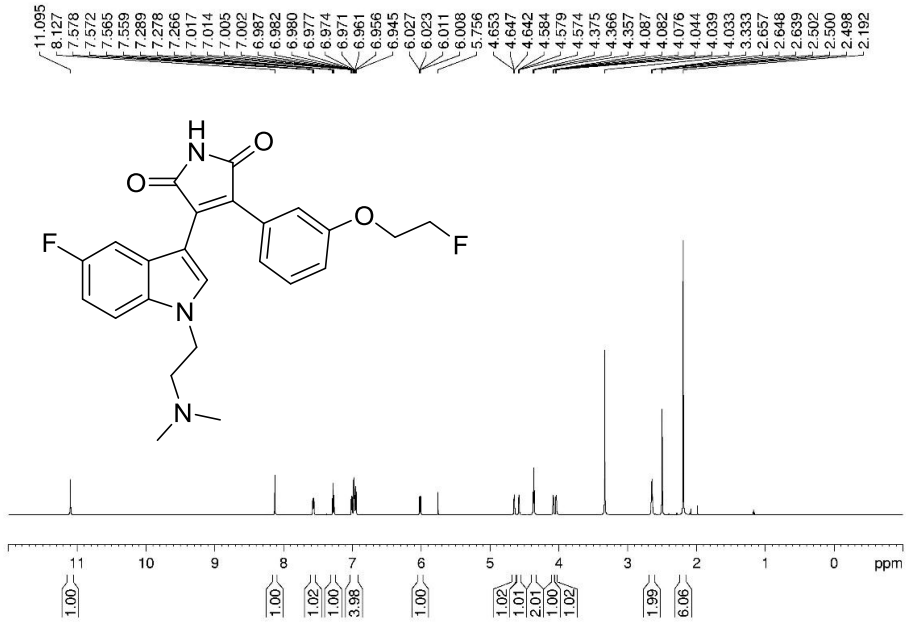


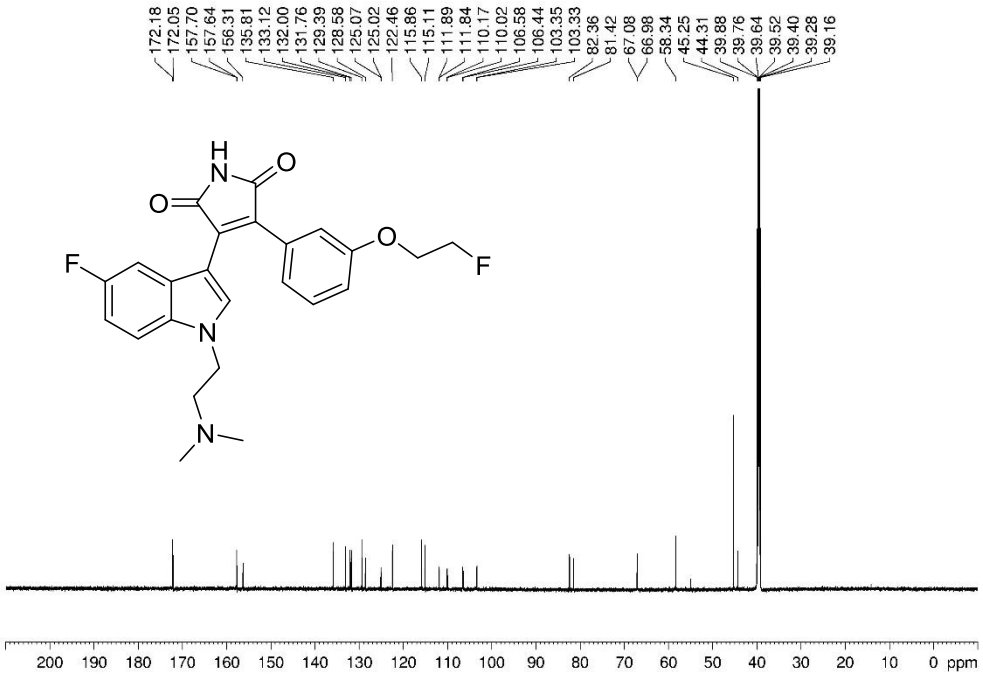
^{19}F NMR ($(CD_3)_2SO$, 25 °C) of **10e**



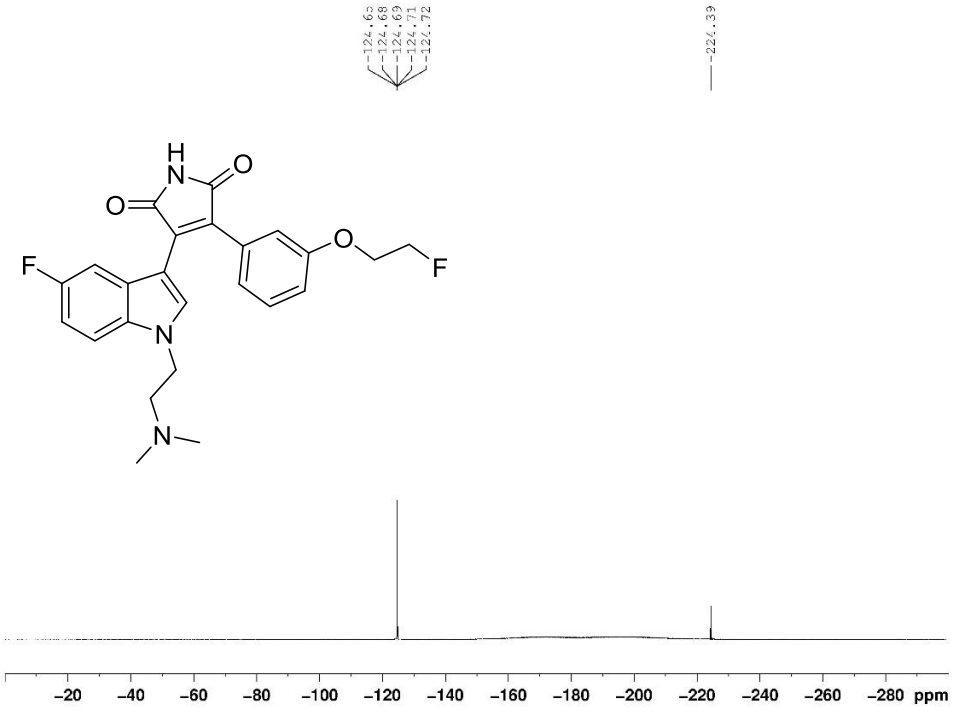
^{1}H NMR ($(CD_3)_2SO$, 25 °C) of **10f**



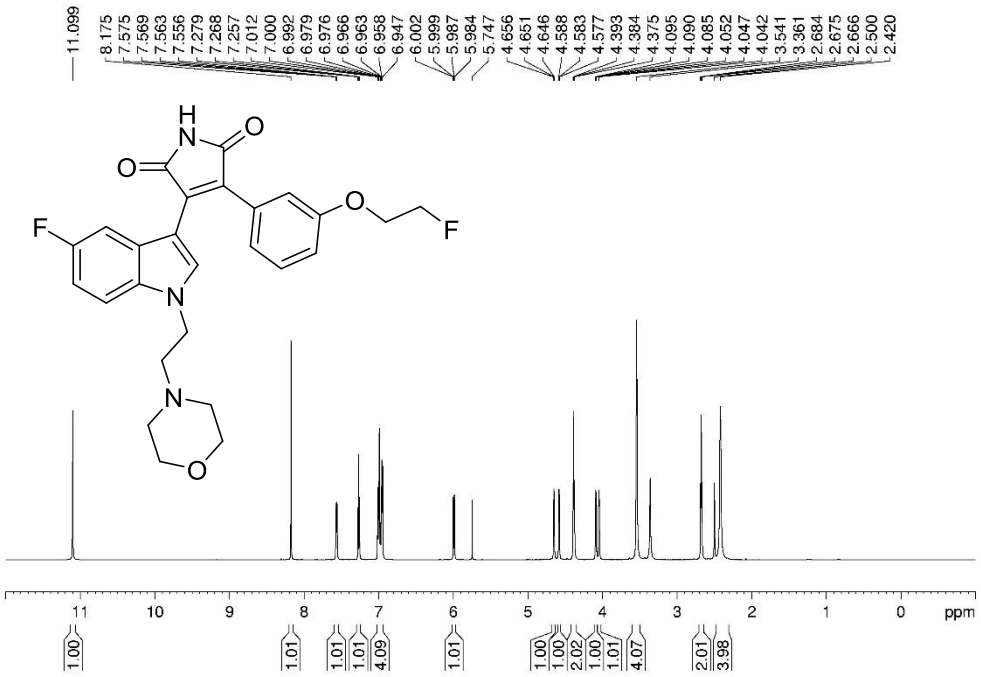
^{13}C NMR ((CD$_3$)$_2$SO, 25 °C) of **10f**



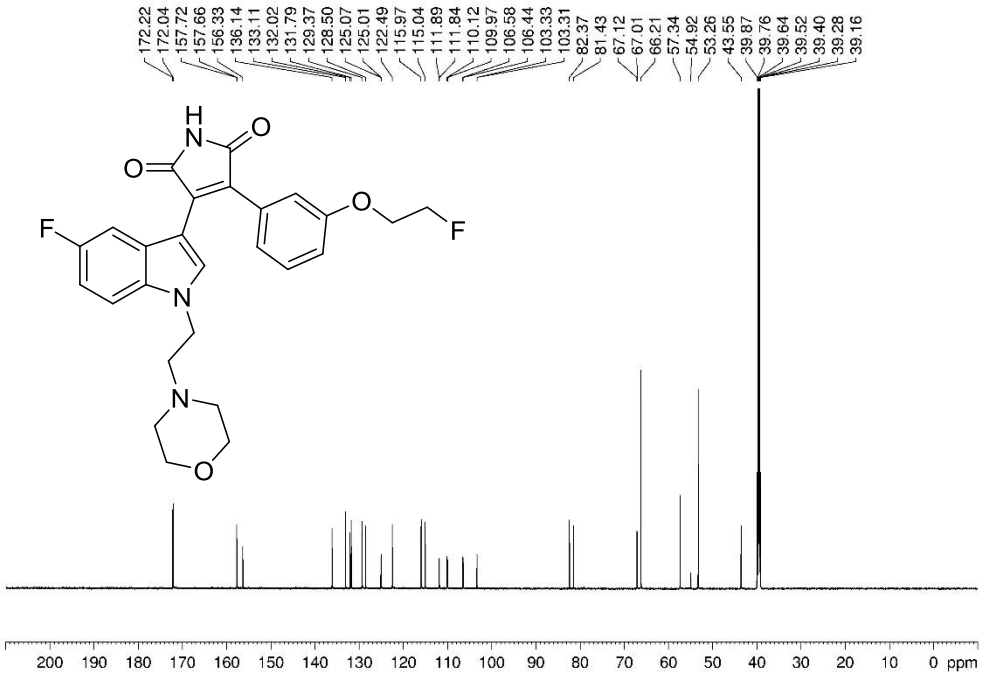
^{19}F NMR ((CD$_3$)$_2$SO, 25 °C) of **10f**



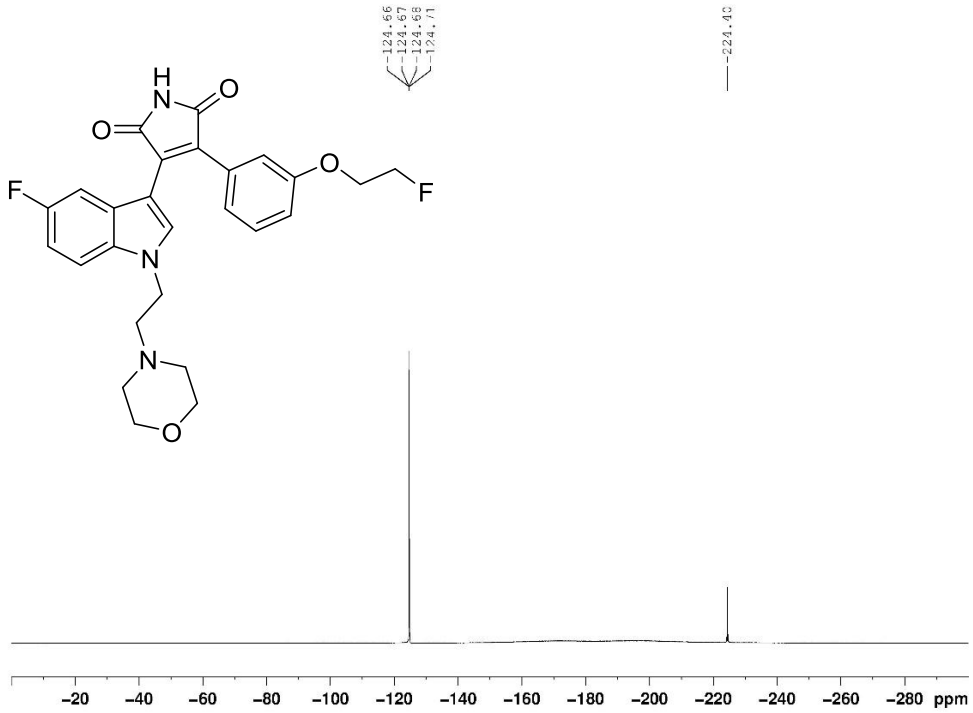
^{1}H NMR ($(CD_3)_2SO$, 25 °C) of **10g**



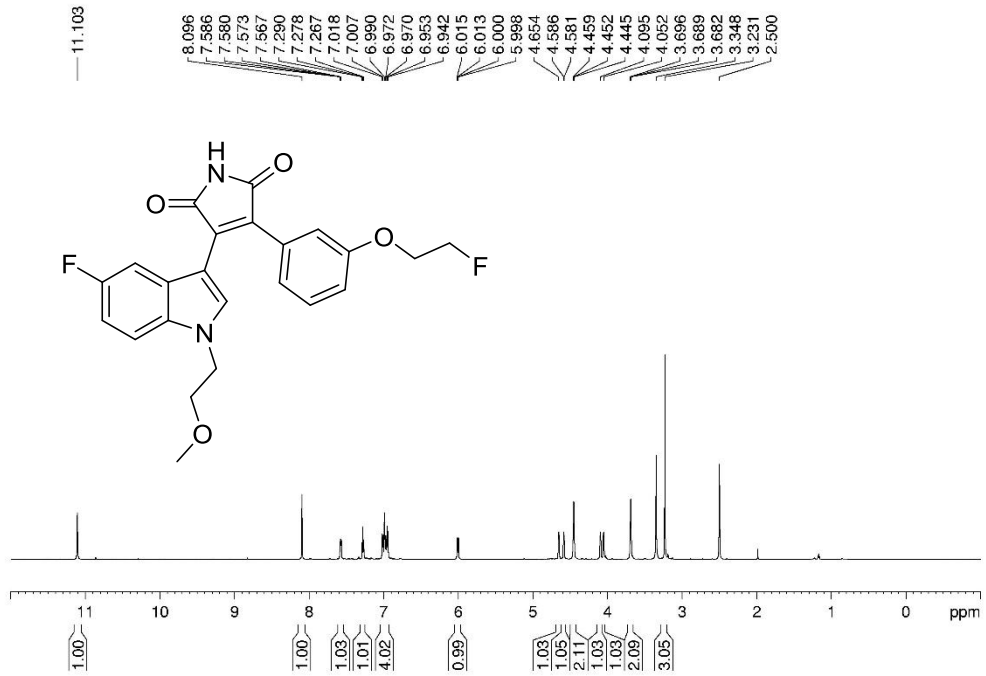
^{13}C NMR ($(CD_3)_2SO$, 25 °C) of **10g**



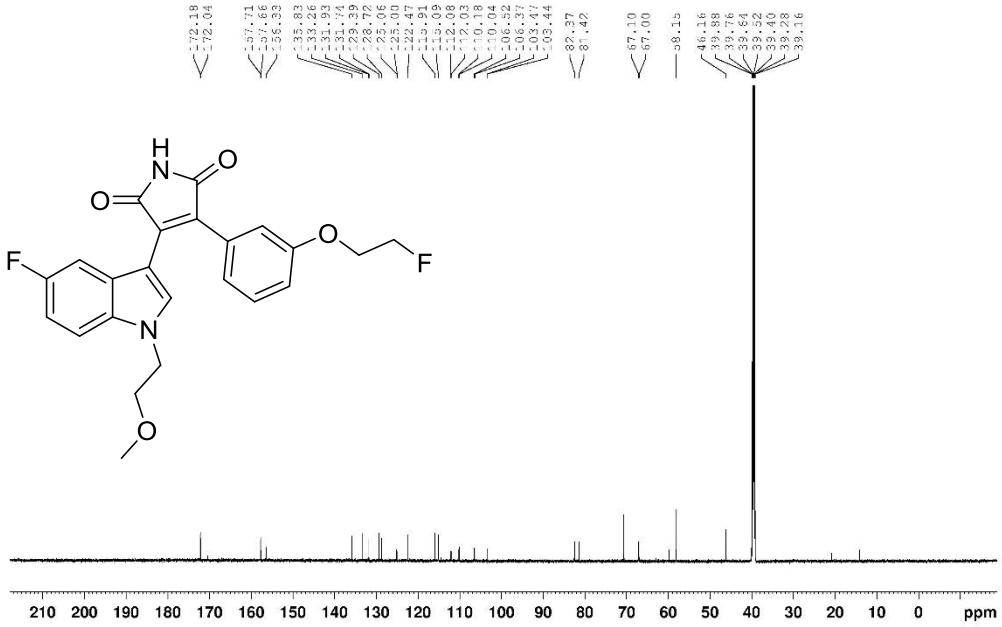
^{19}F NMR ((CD$_3$)$_2$SO, 25 °C) of **10g**



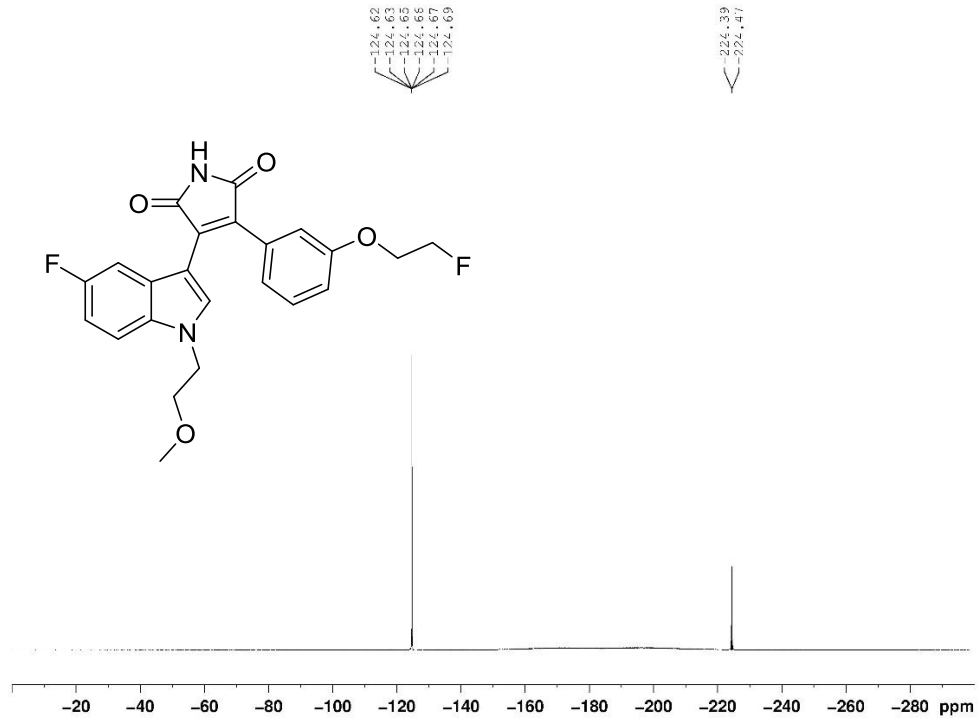
^{1}H NMR ((CD$_3$)$_2$SO, 25 °C) of **10h**



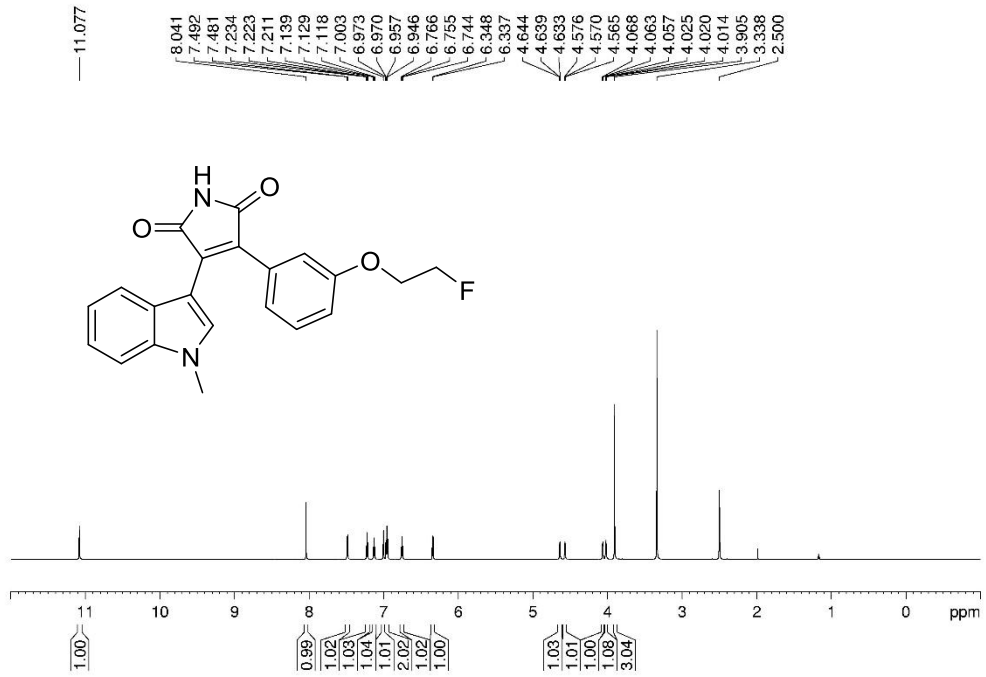
^{13}C NMR ($(CD_3)_2SO$, 25 °C) of **10h**



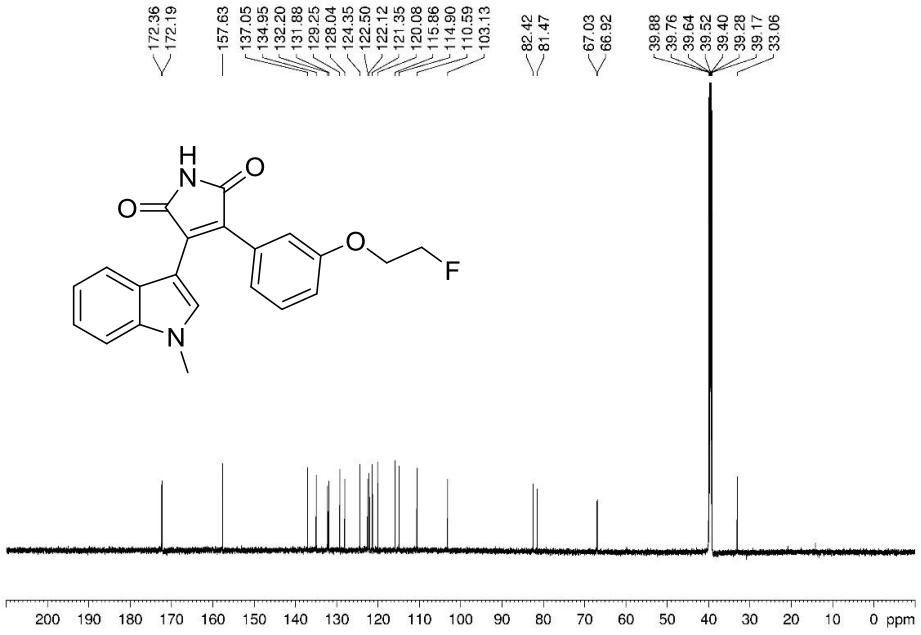
^{19}F NMR ($(CD_3)_2SO$, 25 °C) of **10h**



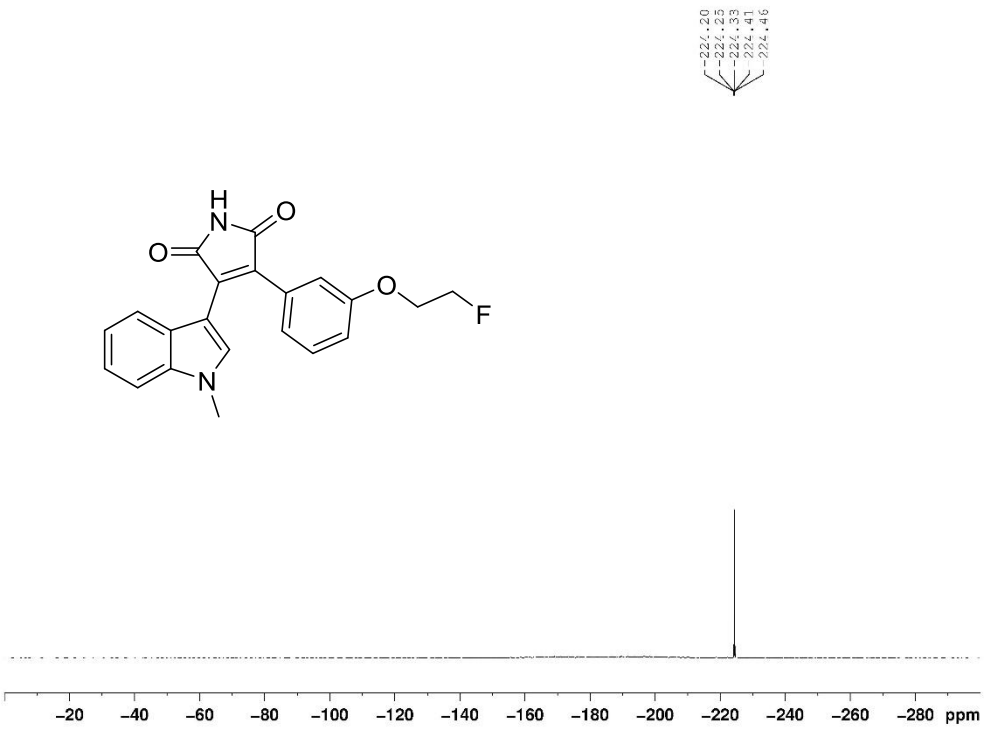
^{1}H NMR ((CD$_3$)$_2$SO, 25 °C) of **10i**



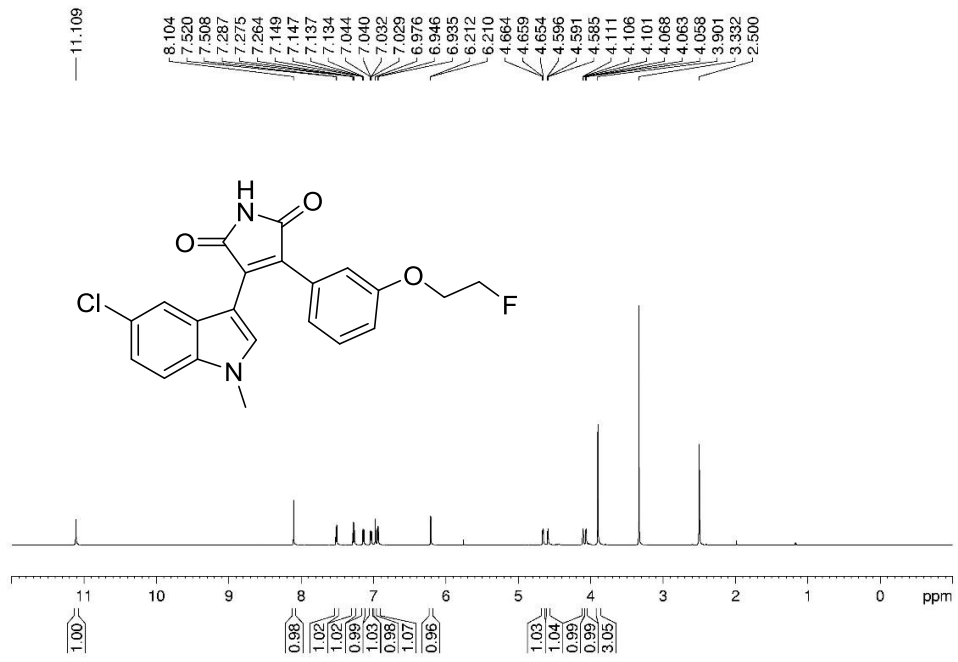
^{13}C NMR ((CD$_3$)$_2$SO, 25 °C) of **10i**



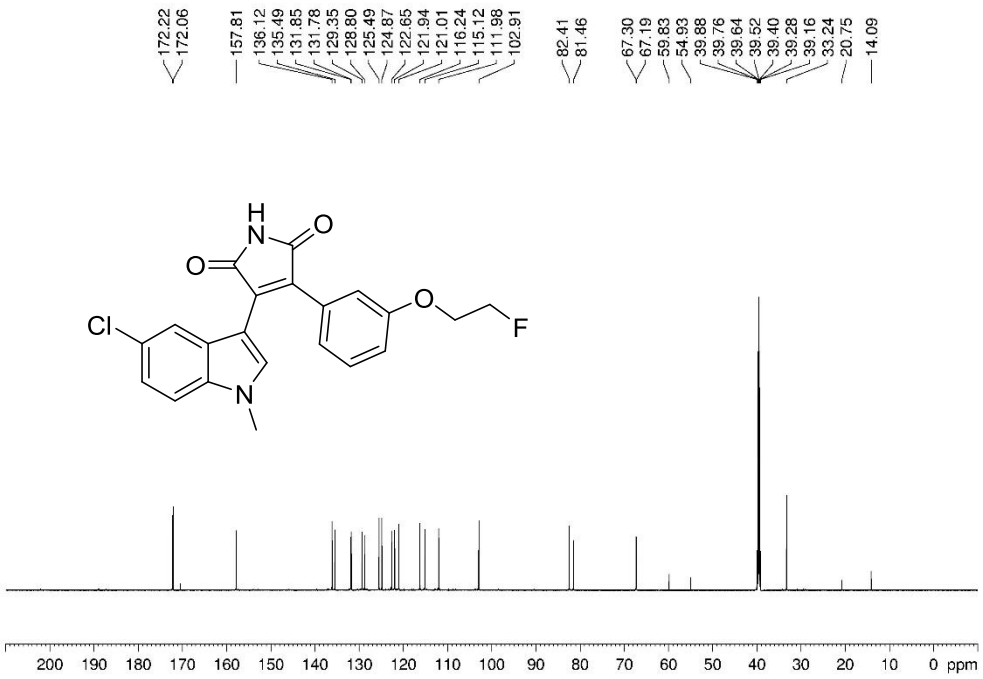
^{19}F NMR ((CD$_3$)$_2$SO, 25 °C) of **10i**



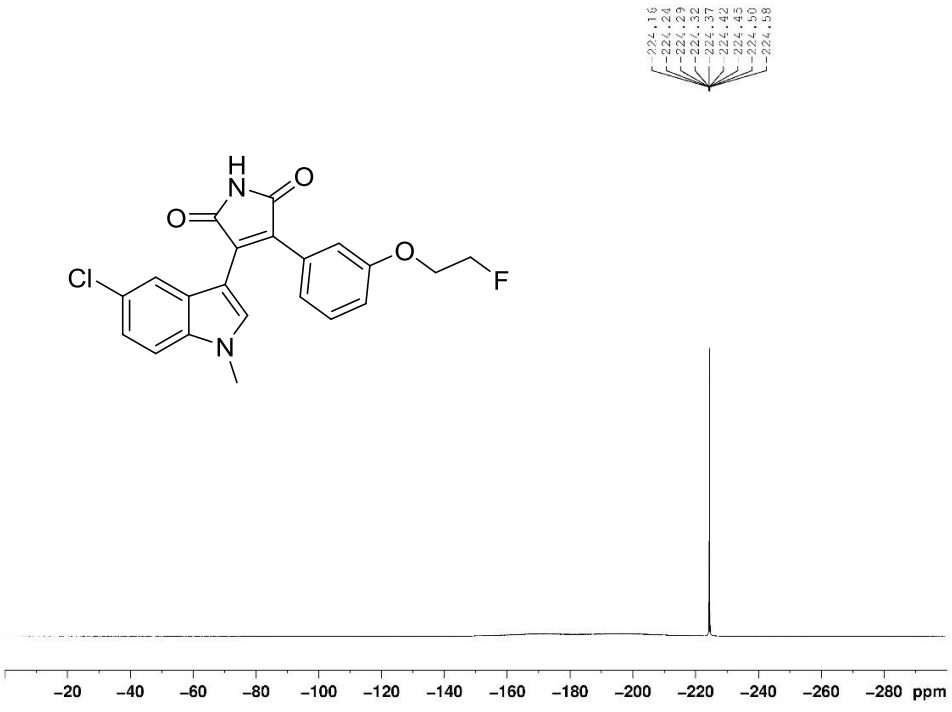
^{1}H NMR ((CD$_3$)$_2$SO, 25 °C) of **10j**



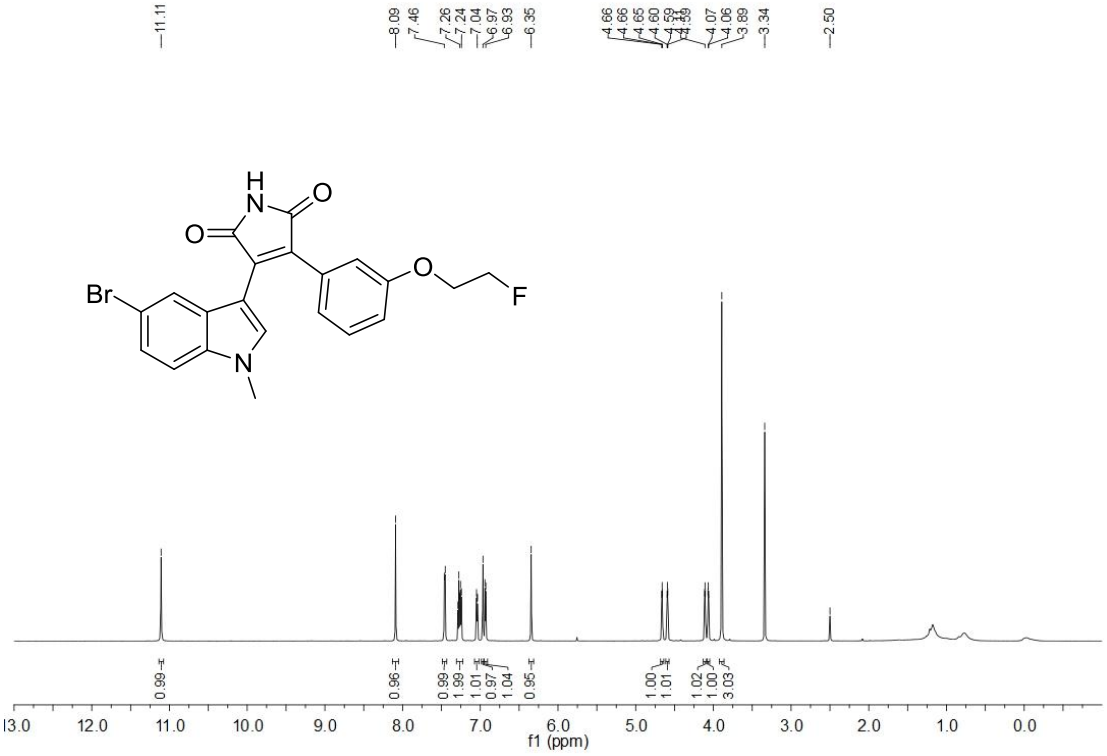
^{13}C NMR ((CD$_3$)$_2$SO, 25 °C) of **10j**



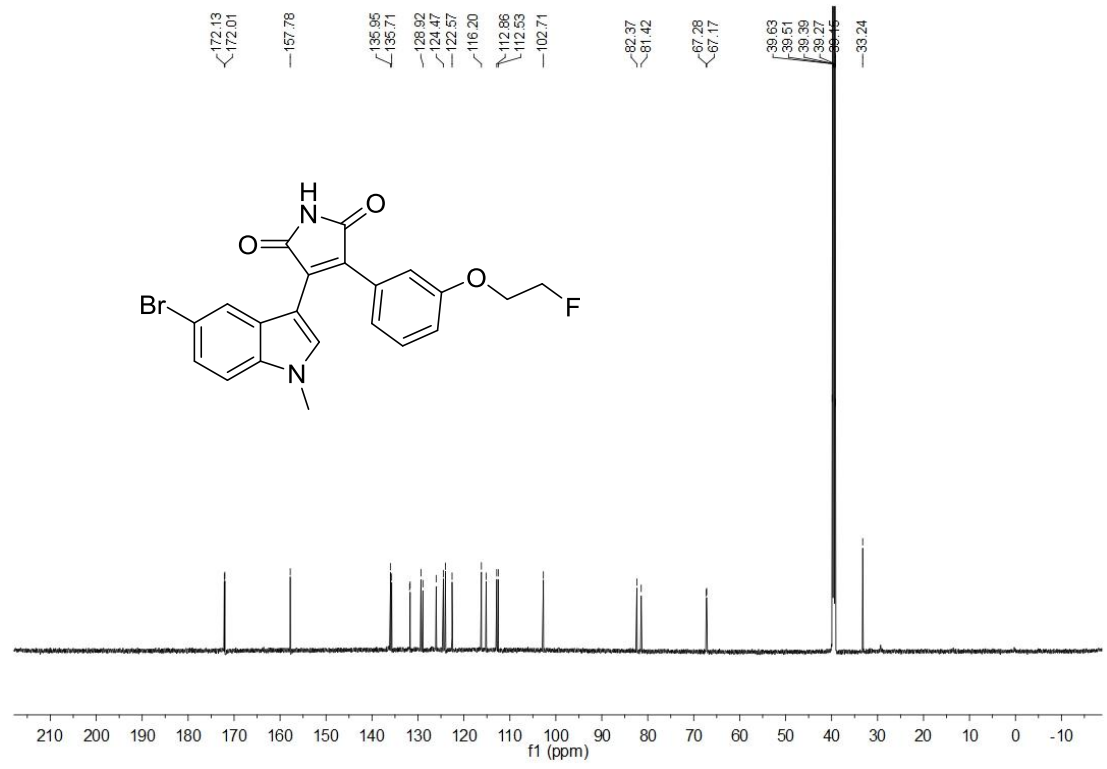
^{19}F NMR ((CD$_3$)$_2$SO, 25 °C) of **10j**



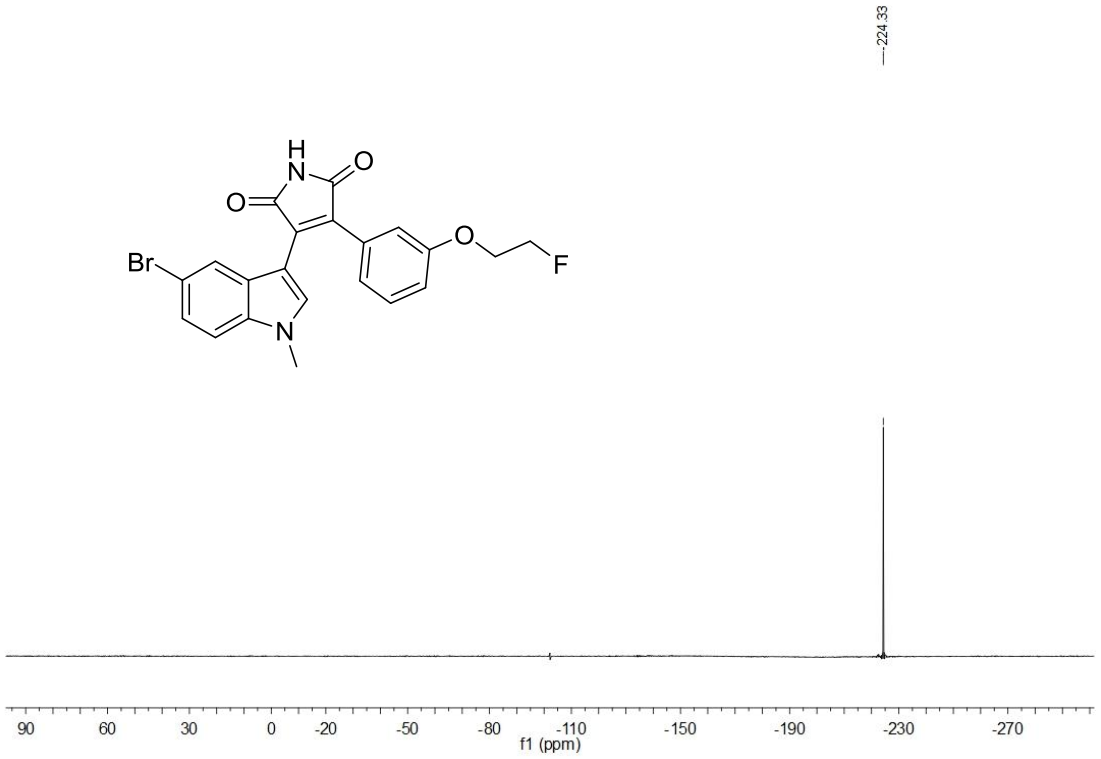
^{1}H NMR ((CD$_3$)$_2$SO, 25 °C) of **10k**



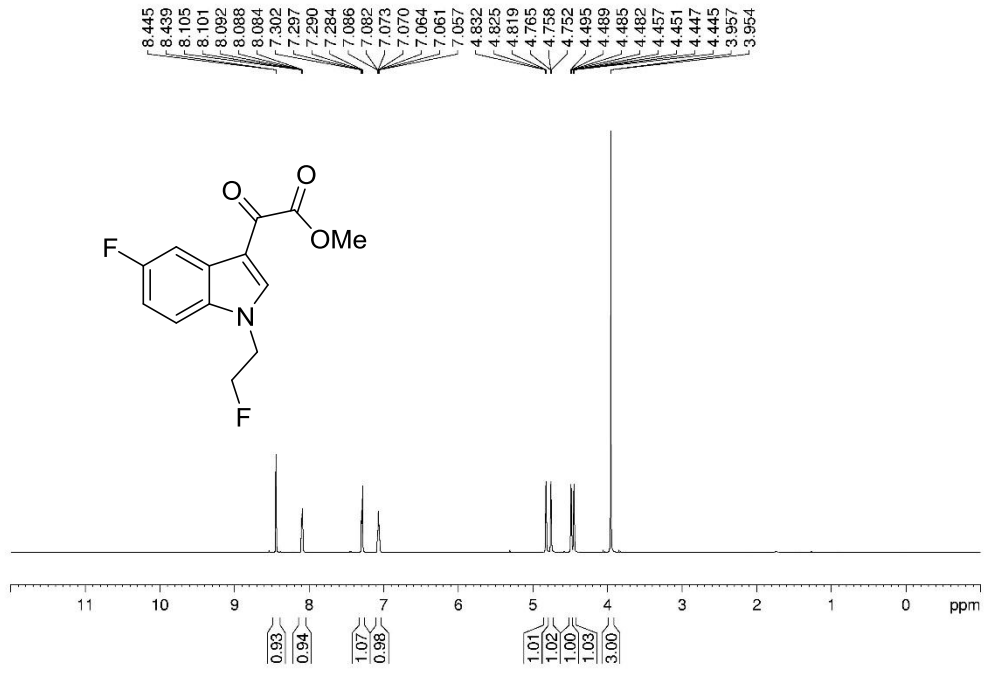
^{13}C NMR ((CD$_3$)$_2$SO, 25 °C) of **10k**



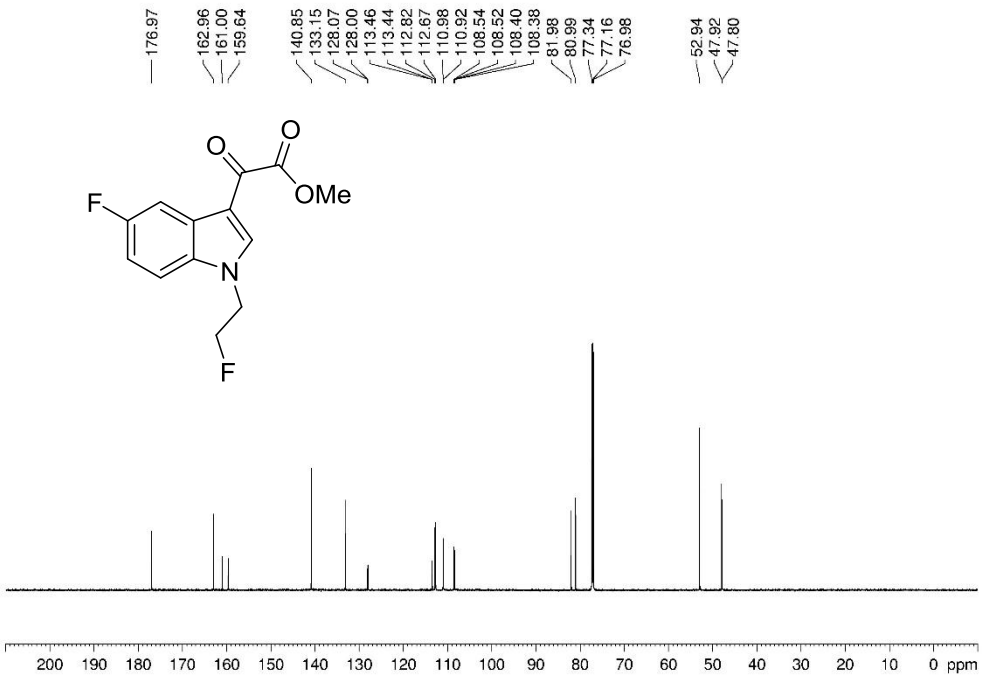
^{19}F NMR ((CD$_3$)$_2$SO, 25 °C) of **10k**



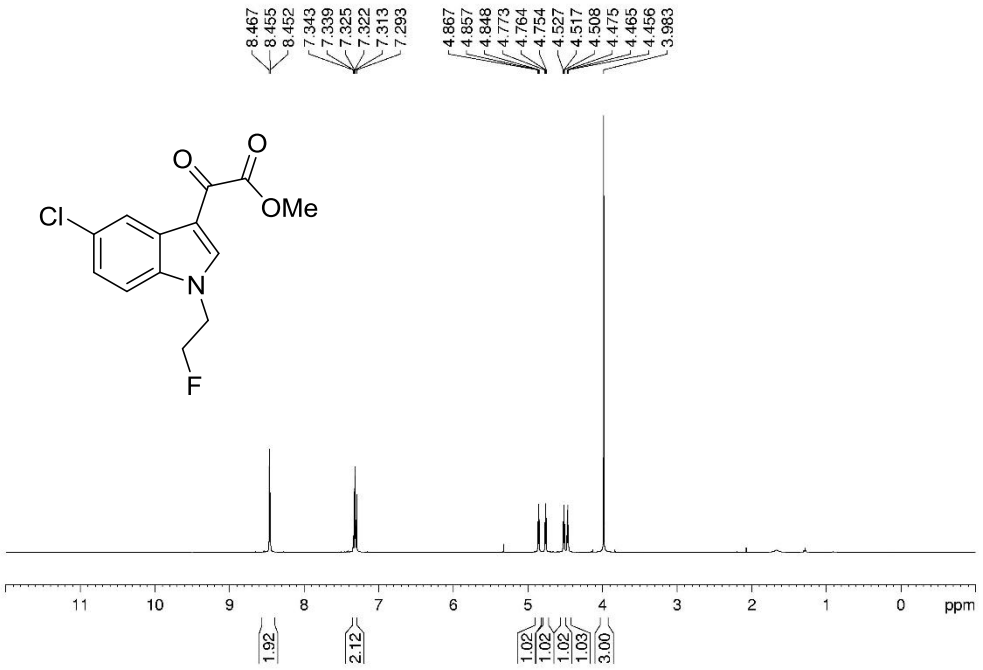
^{1}H NMR (CDCl$_3$, 25 °C) of **11a**



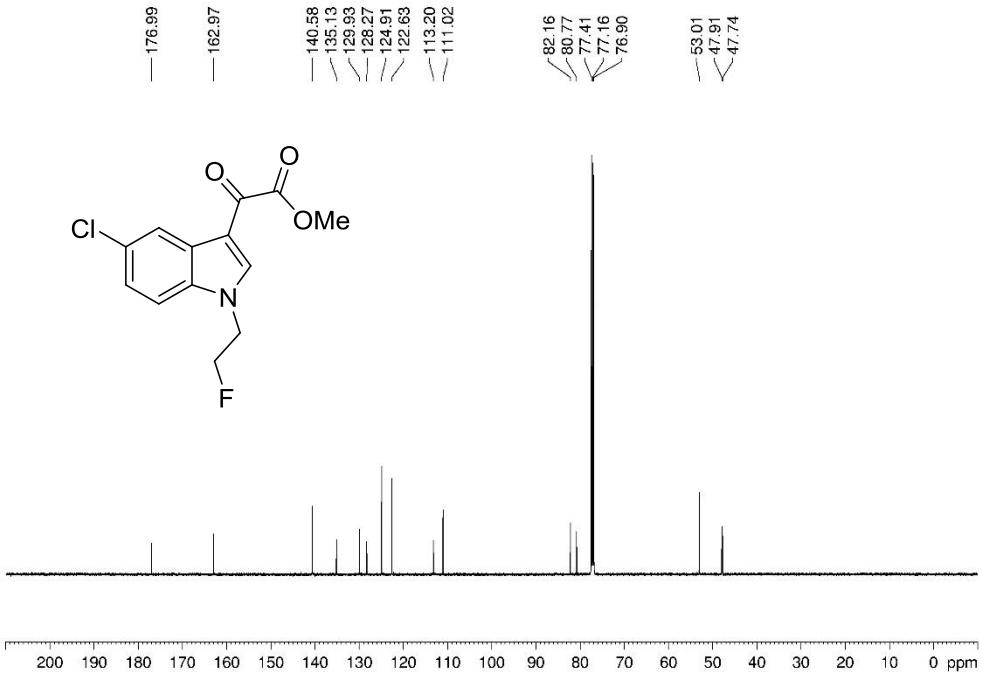
^{13}C NMR ($CDCl_3$, 25 °C) of **11a**



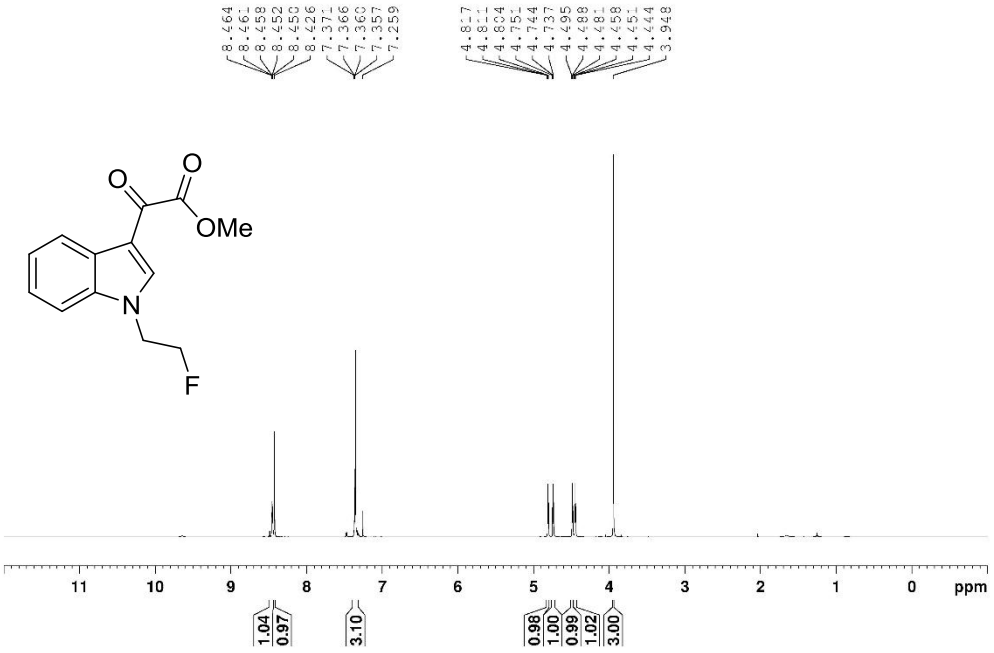
^{1}H NMR ($CDCl_3$, 25 °C) of **11b**



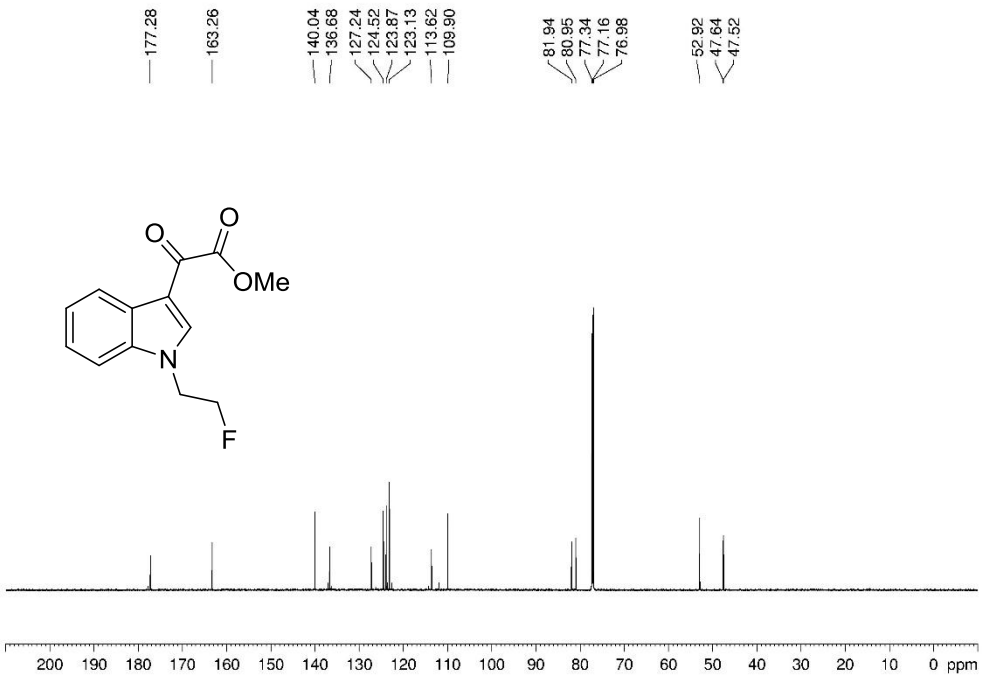
^{13}C NMR ($CDCl_3$, 25 °C) of **11b**



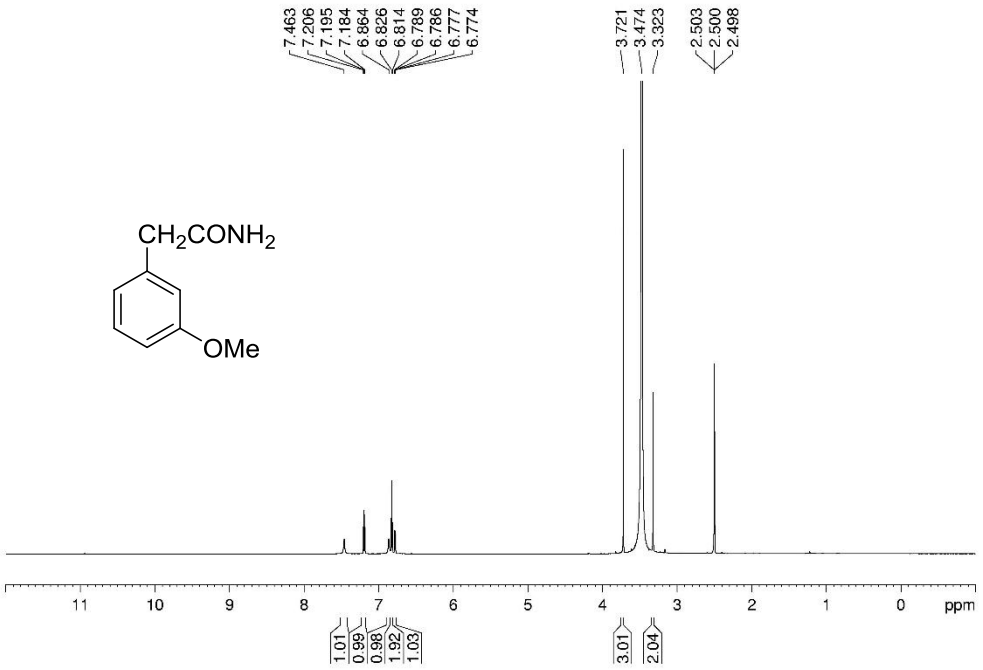
^{1}H NMR ($CDCl_3$, 25 °C) of **11c**



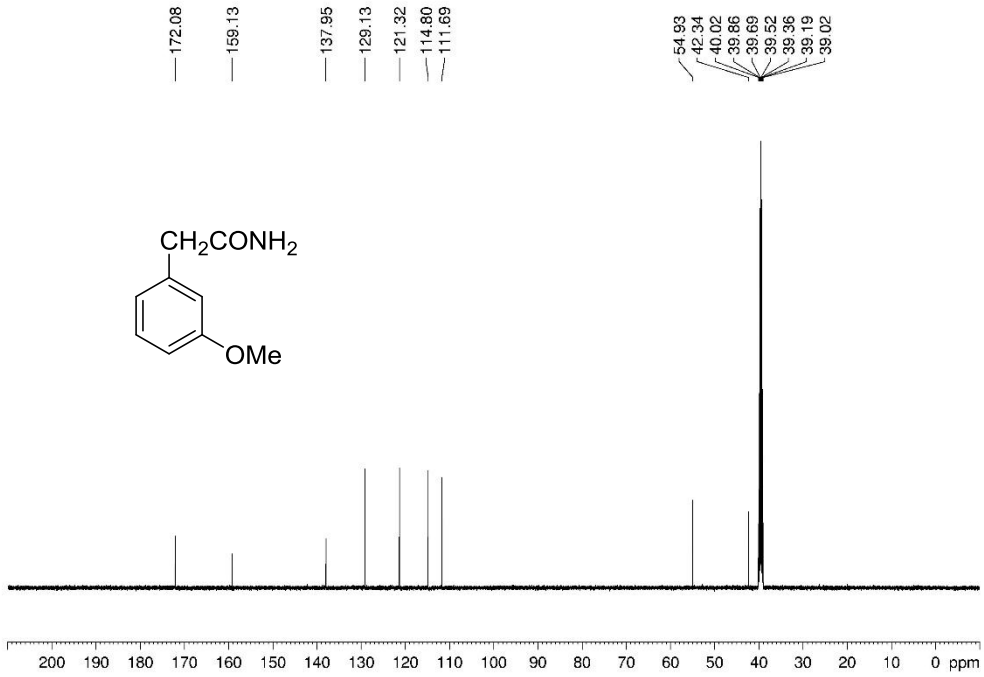
^{13}C NMR ($CDCl_3$, 25 °C) of **11c**



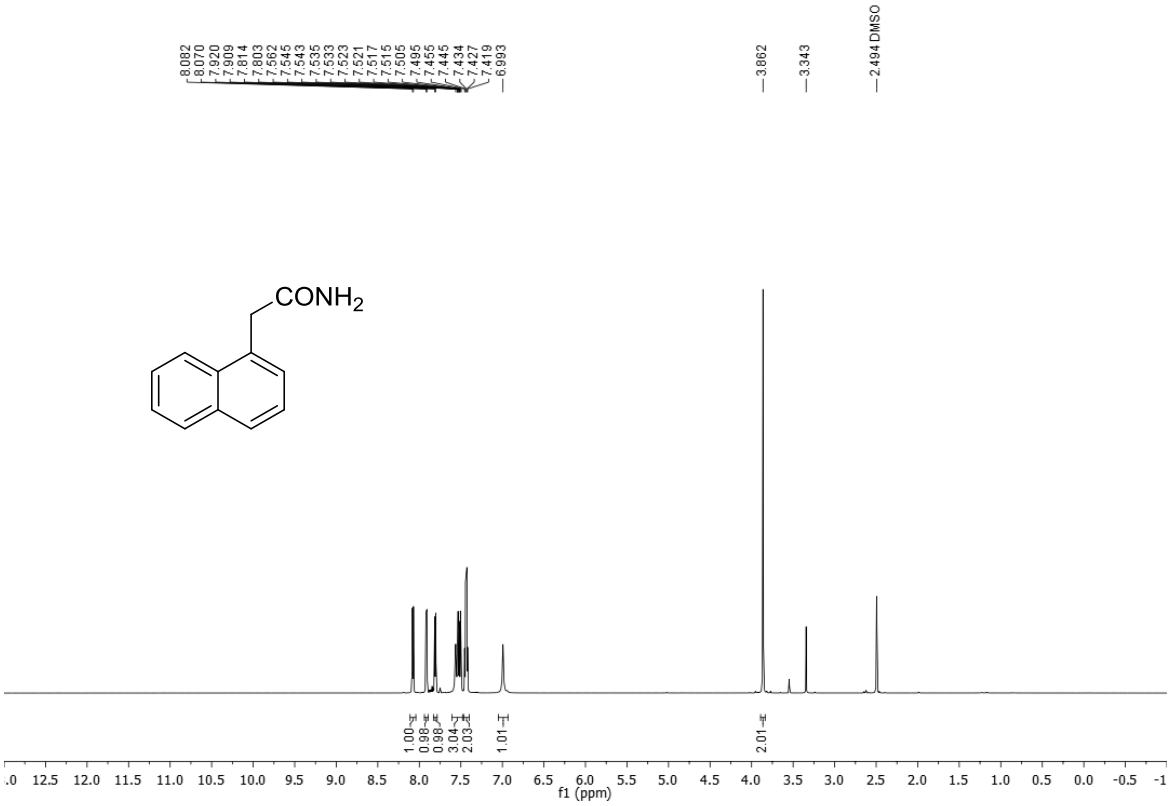
^{1}H NMR ($(CD_3)_2SO$, 25 °C) of **13a**



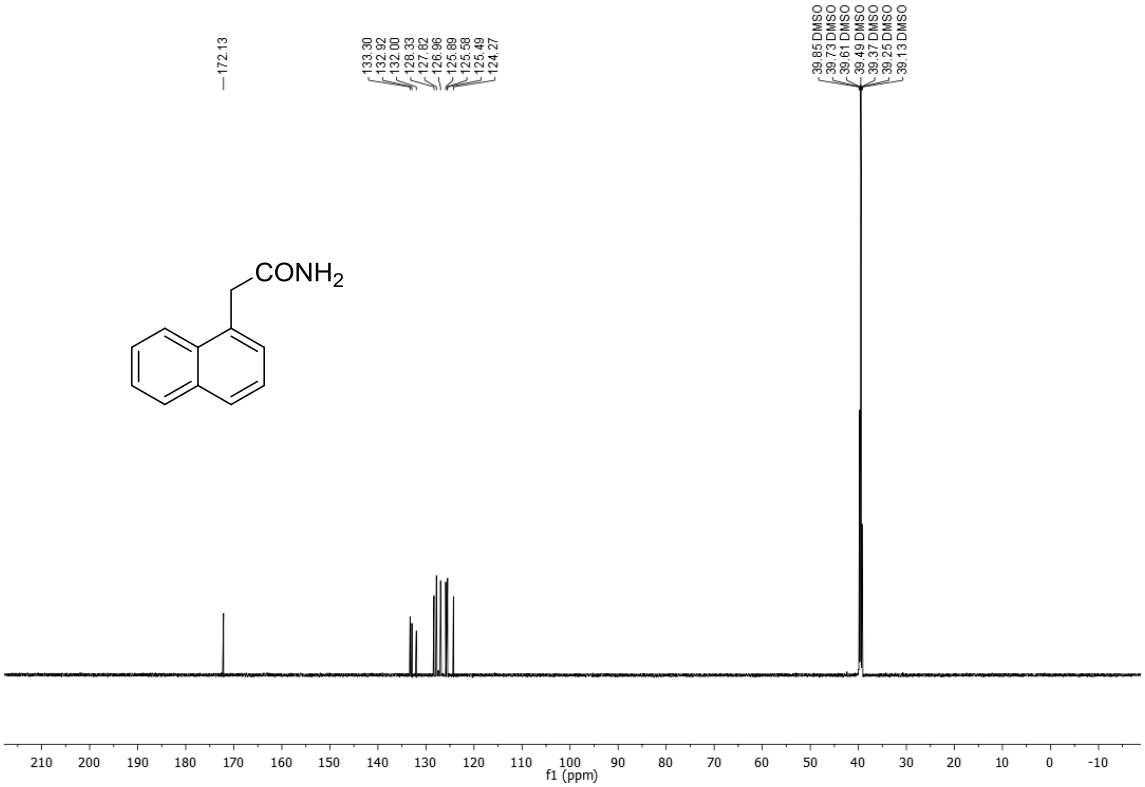
^{13}C NMR ($(CD_3)_2SO$, 25 °C) of **13a**



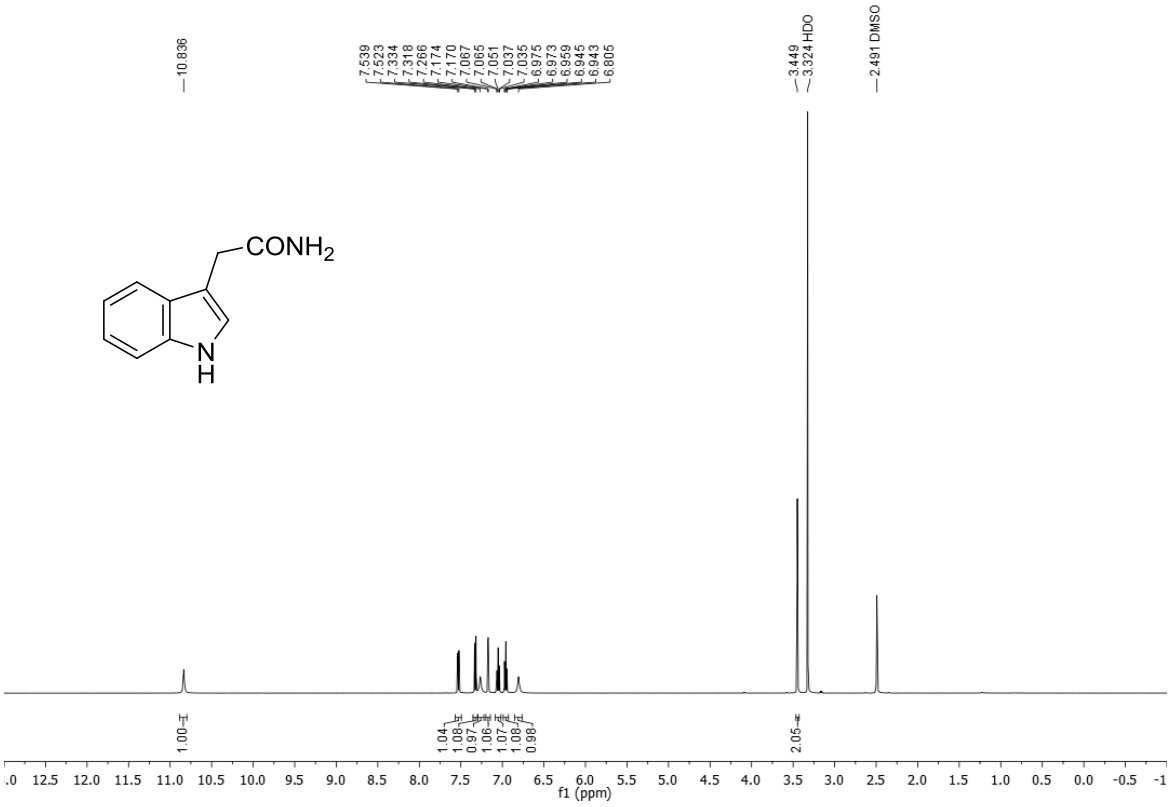
^{1}H NMR ($(CD_3)_2SO$, 25 °C) of **13b**



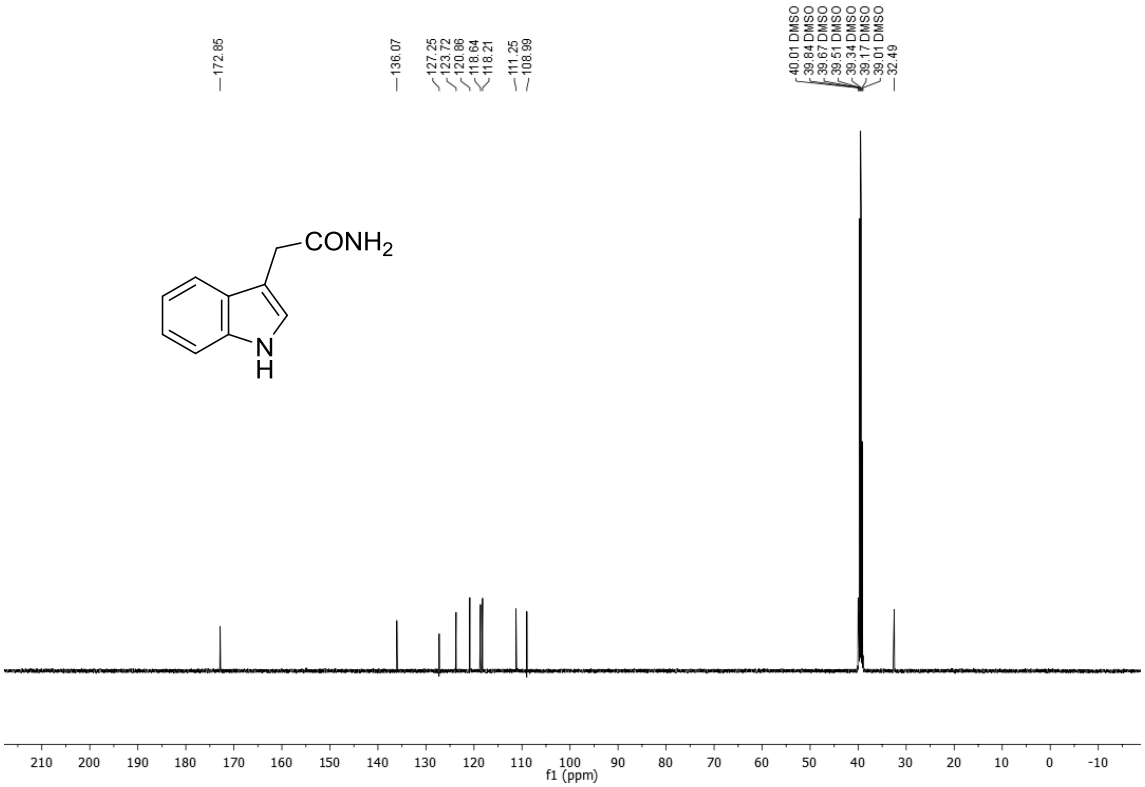
^{13}C NMR ((CD$_3$)$_2$SO, 25 °C) of **13b**



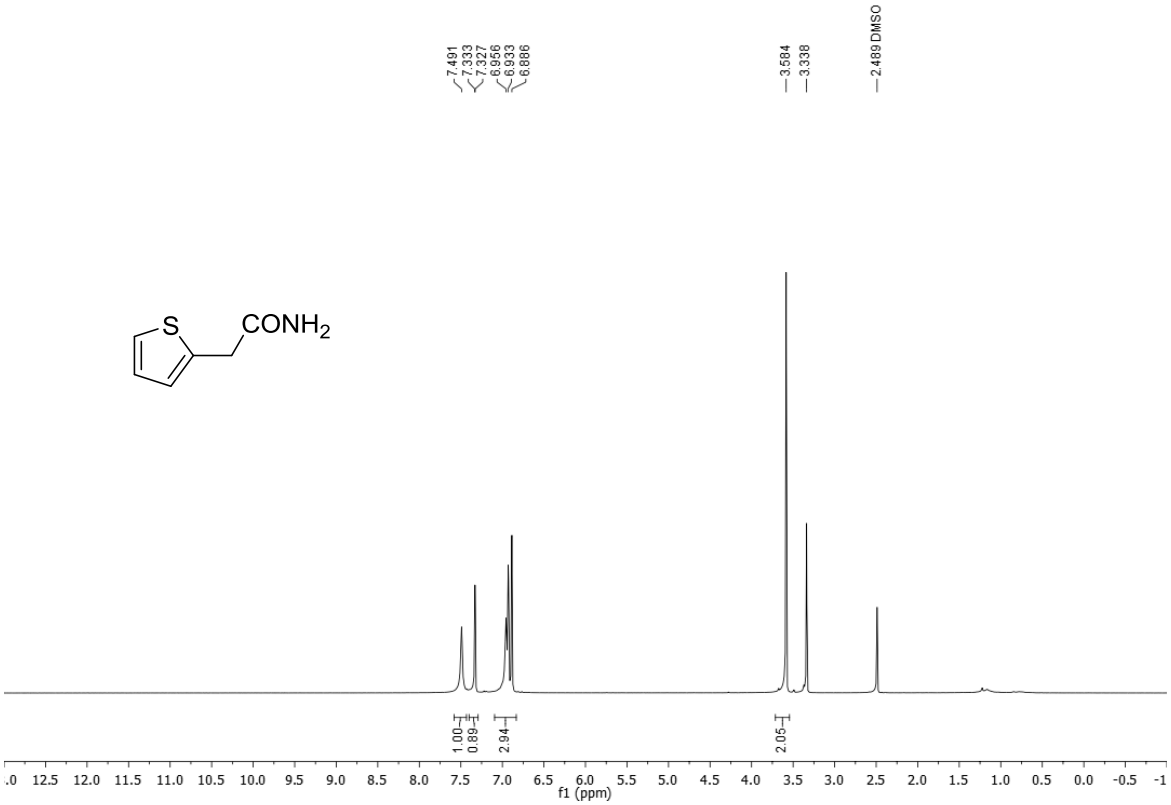
^{1}H NMR ((CD$_3$)$_2$SO, 25 °C) of **13c**



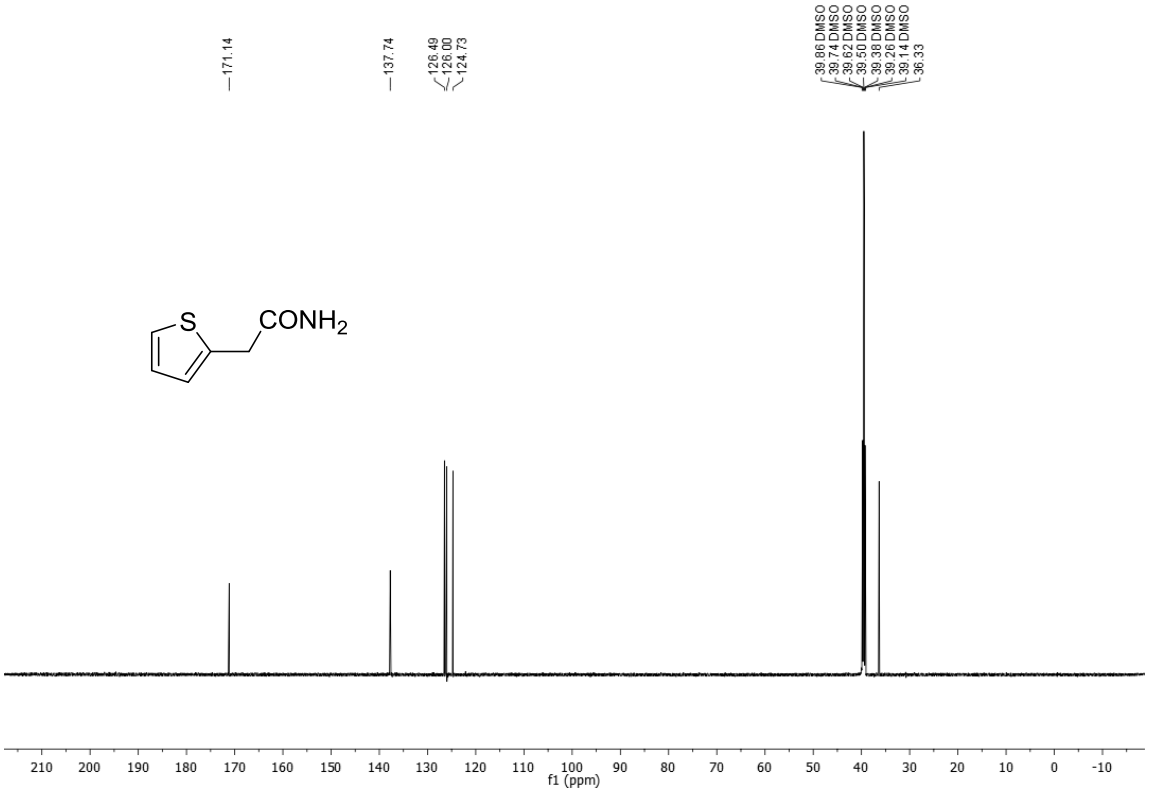
^{13}C NMR ((CD$_3$)$_2$SO, 25 °C) of **13c**



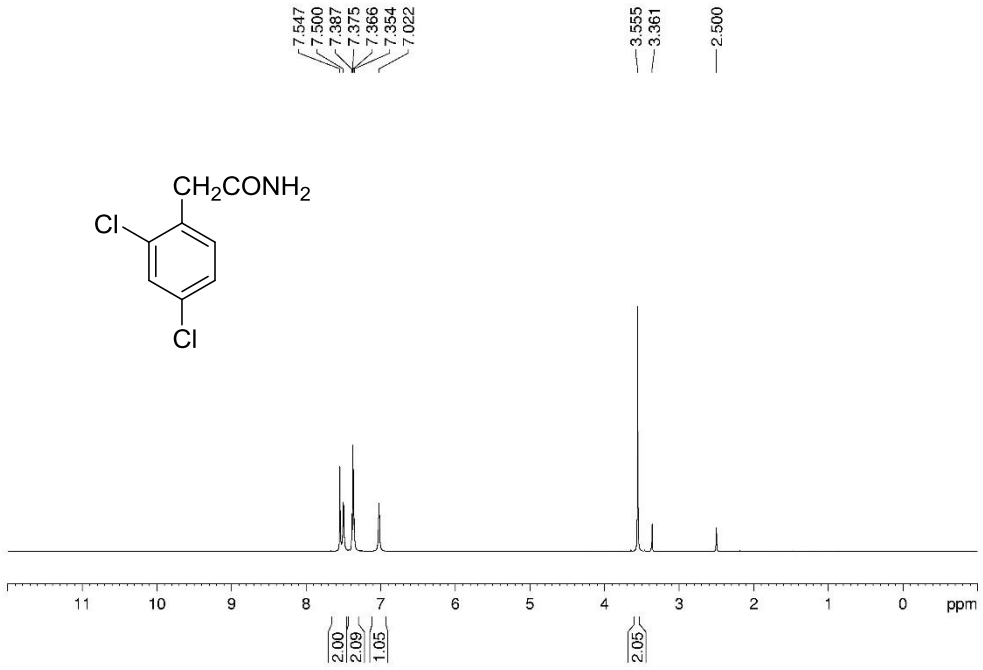
^{1}H NMR ((CD$_3$)$_2$SO, 25 °C) of **13d**



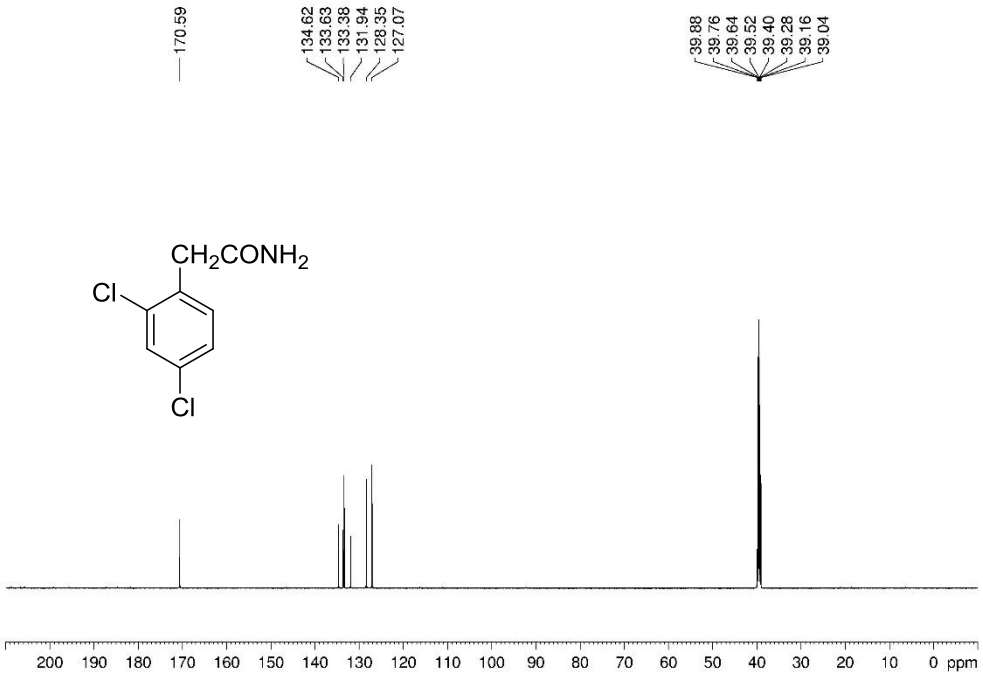
^{13}C NMR ((CD$_3$)$_2$SO, 25 °C) of **13d**



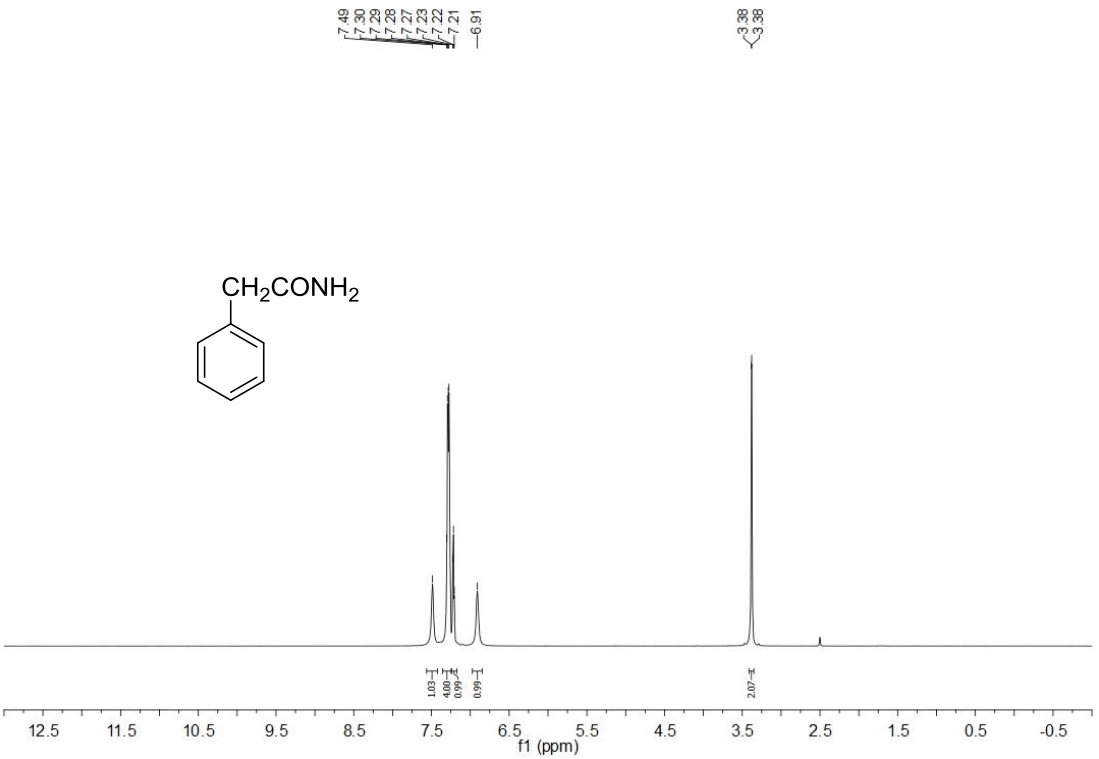
^{1}H NMR ((CD$_3$)$_2$SO, 25 °C) of **13e**



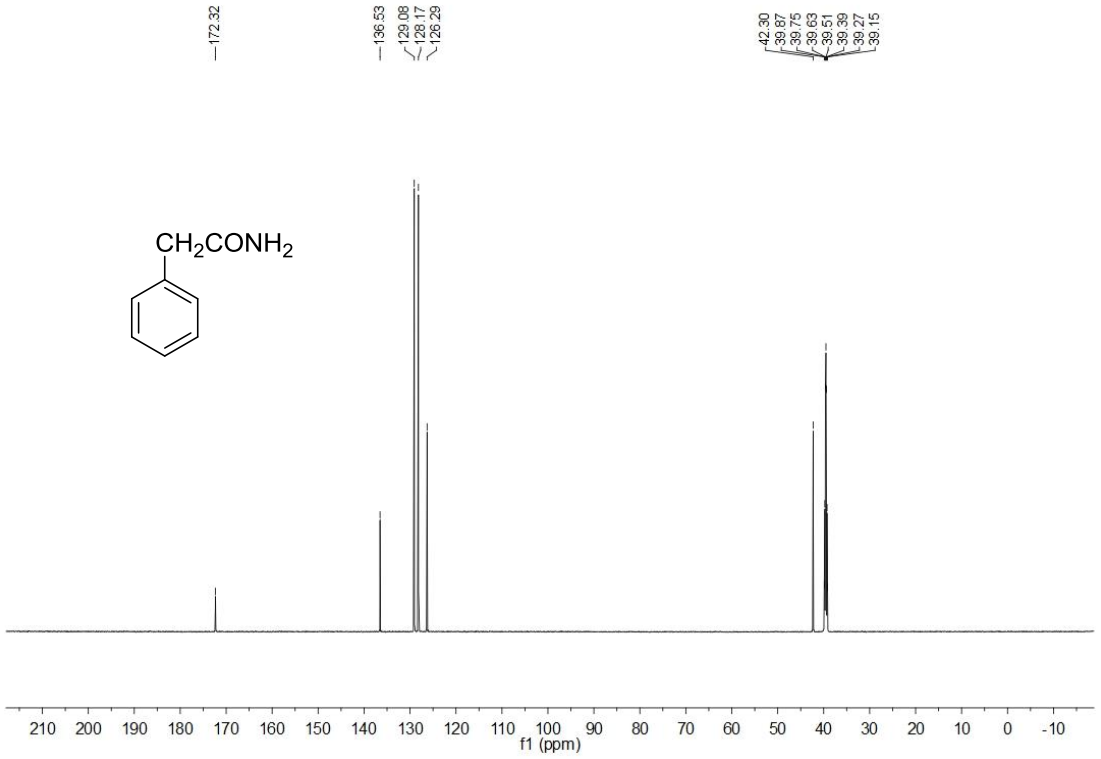
^{13}C NMR ((CD$_3$)$_2$SO, 25 °C) of **13e**



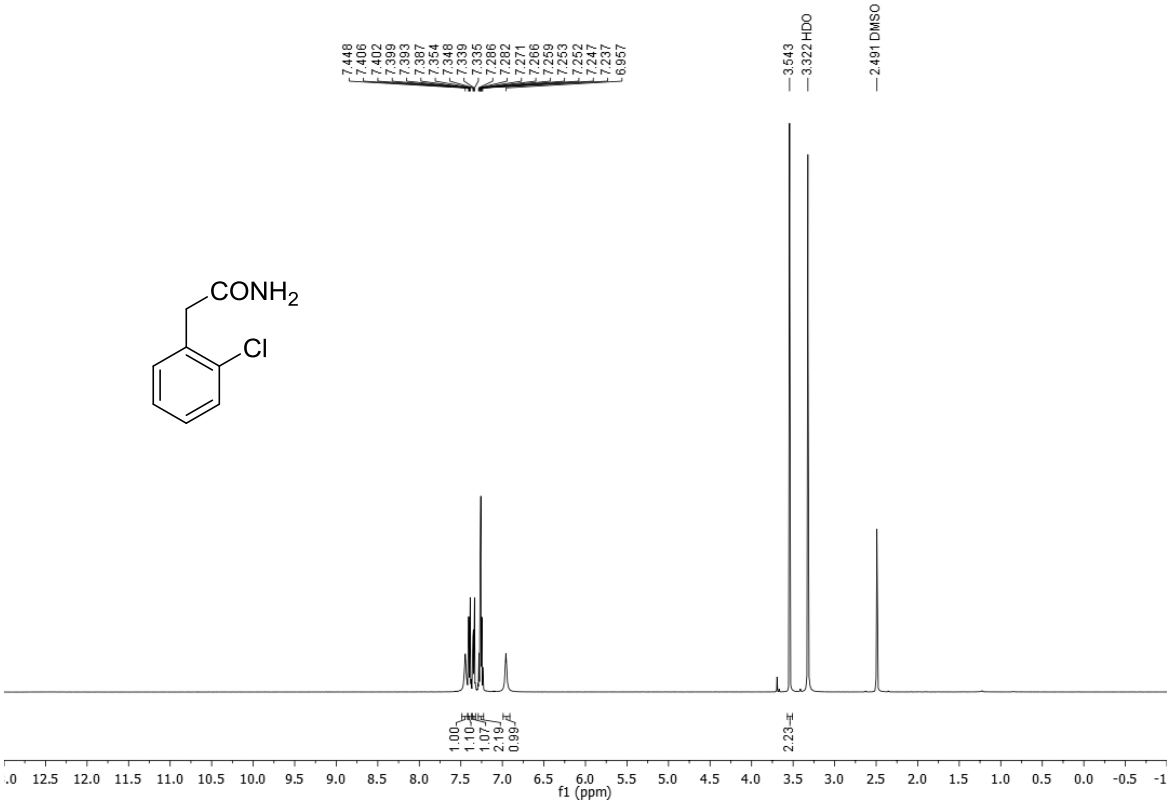
^{1}H NMR ((CD$_3$)$_2$SO, 25 °C) of **13f**



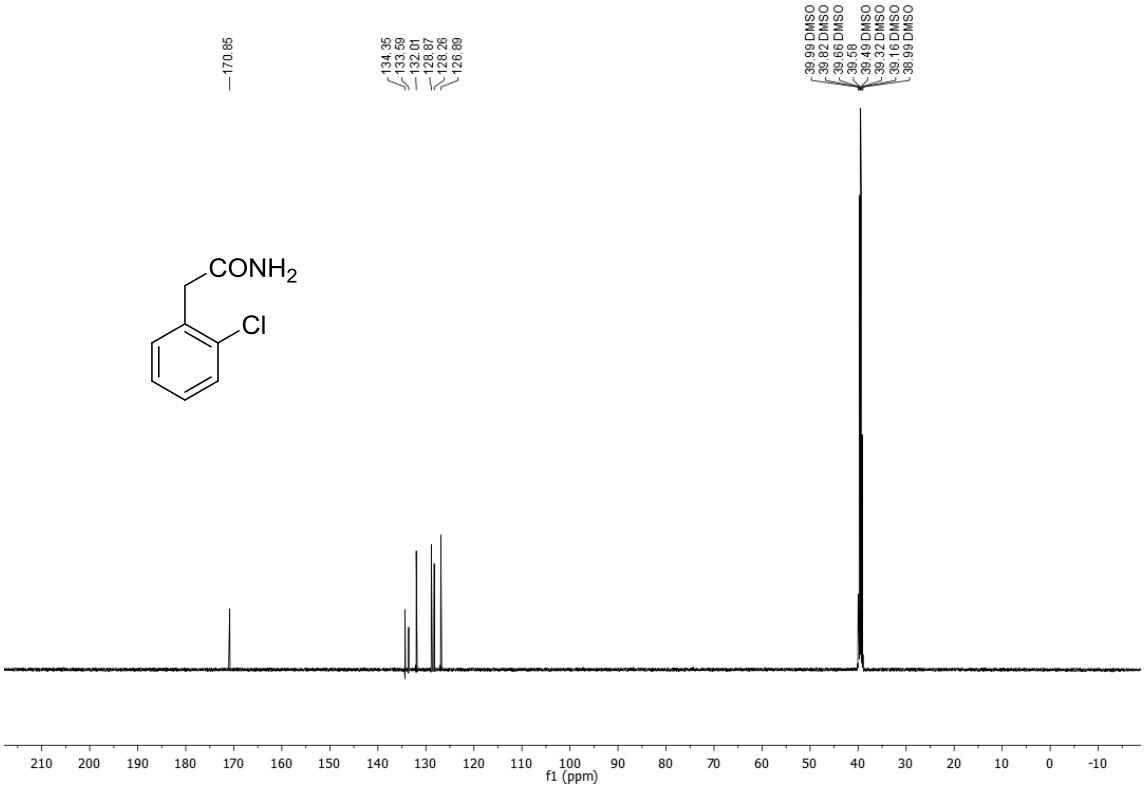
^{13}C NMR ((CD$_3$)$_2$SO, 25 °C) of **13f**



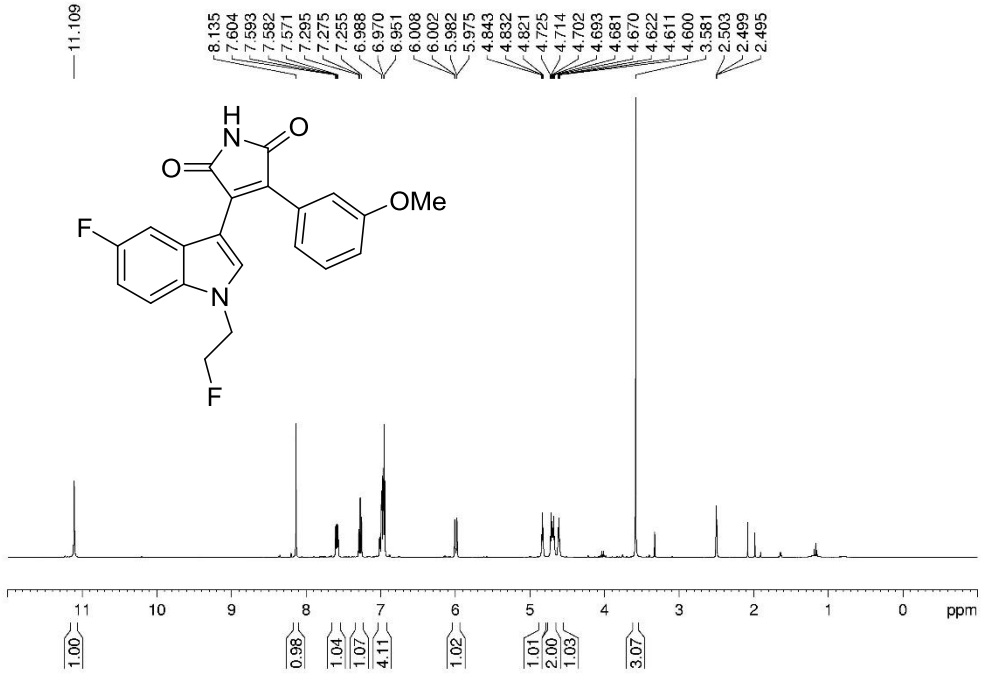
^{1}H NMR ((CD$_3$)$_2$SO, 25 °C) of **13g**



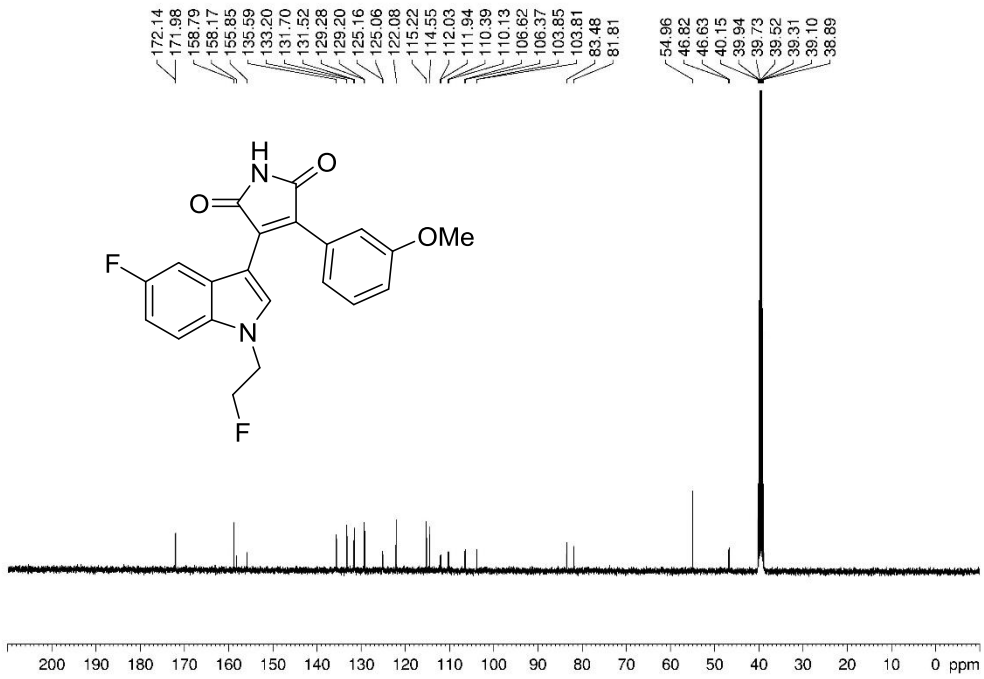
^{13}C NMR ((CD$_3$)$_2$SO, 25 °C) of **13g**



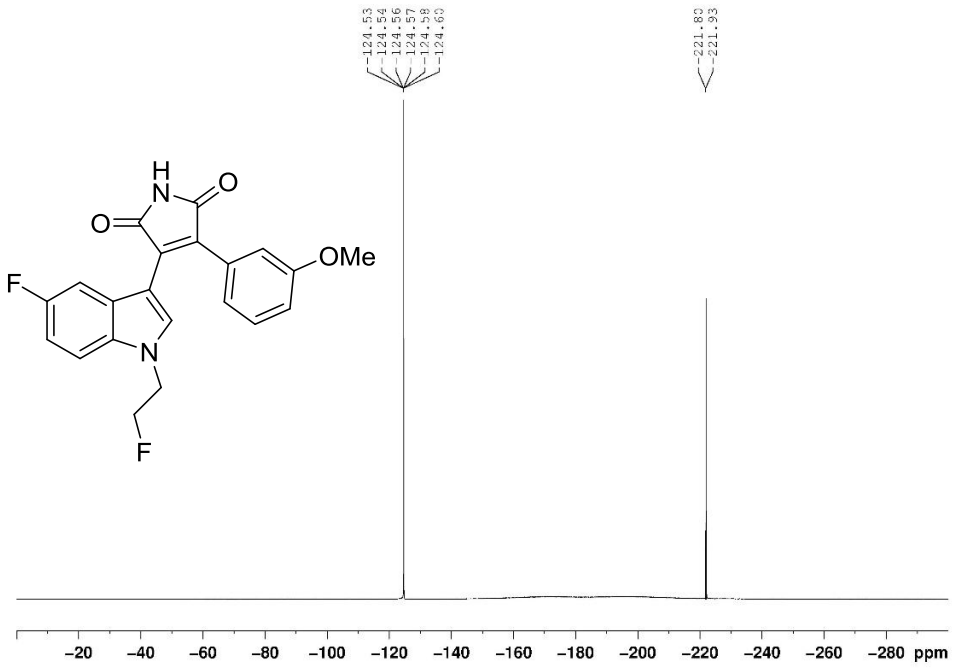
^{1}H NMR ((CD$_3$)$_2$SO, 25 °C) of **14a**



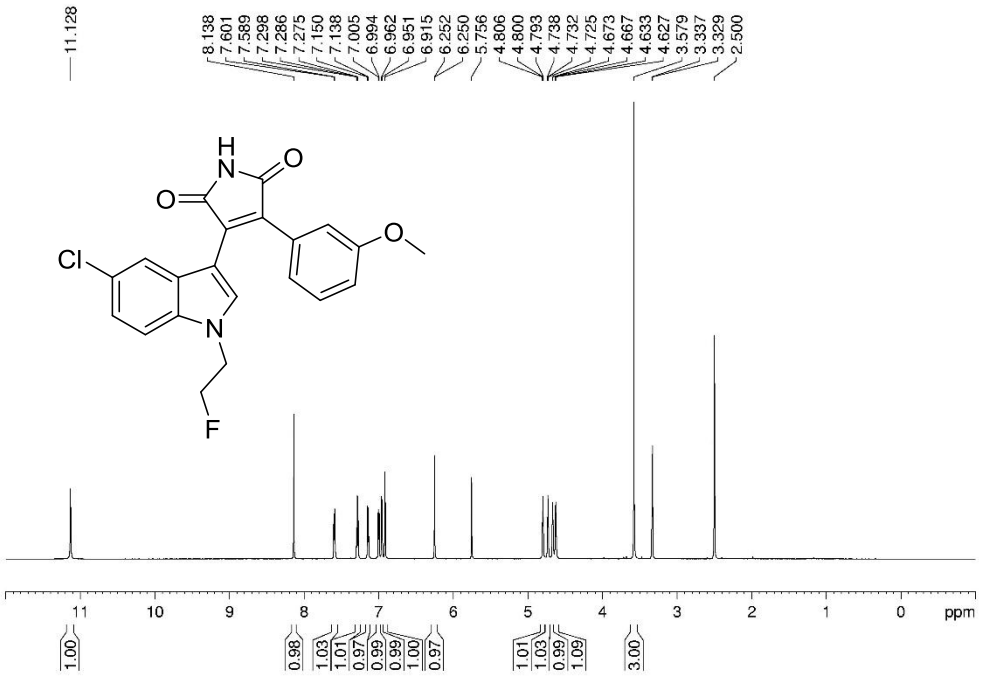
^{13}C NMR ((CD$_3$)$_2$SO, 25 °C) of **14a**



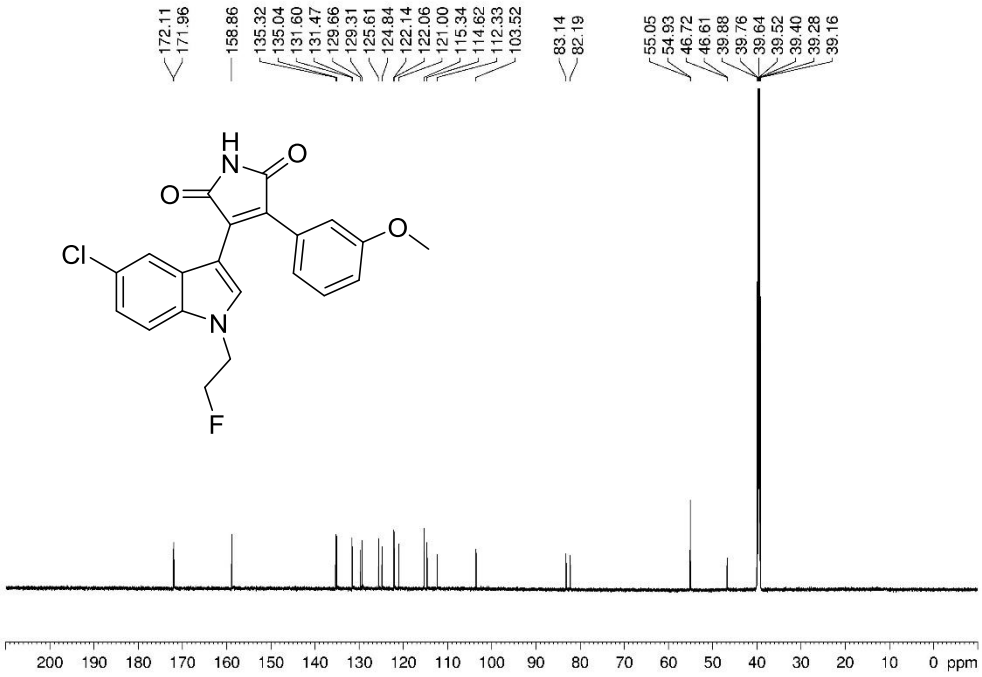
^{19}F NMR ((CD$_3$)$_2$SO, 25 °C) of **14a**



^{1}H NMR ((CD$_3$)$_2$SO, 25 °C) of **14b**

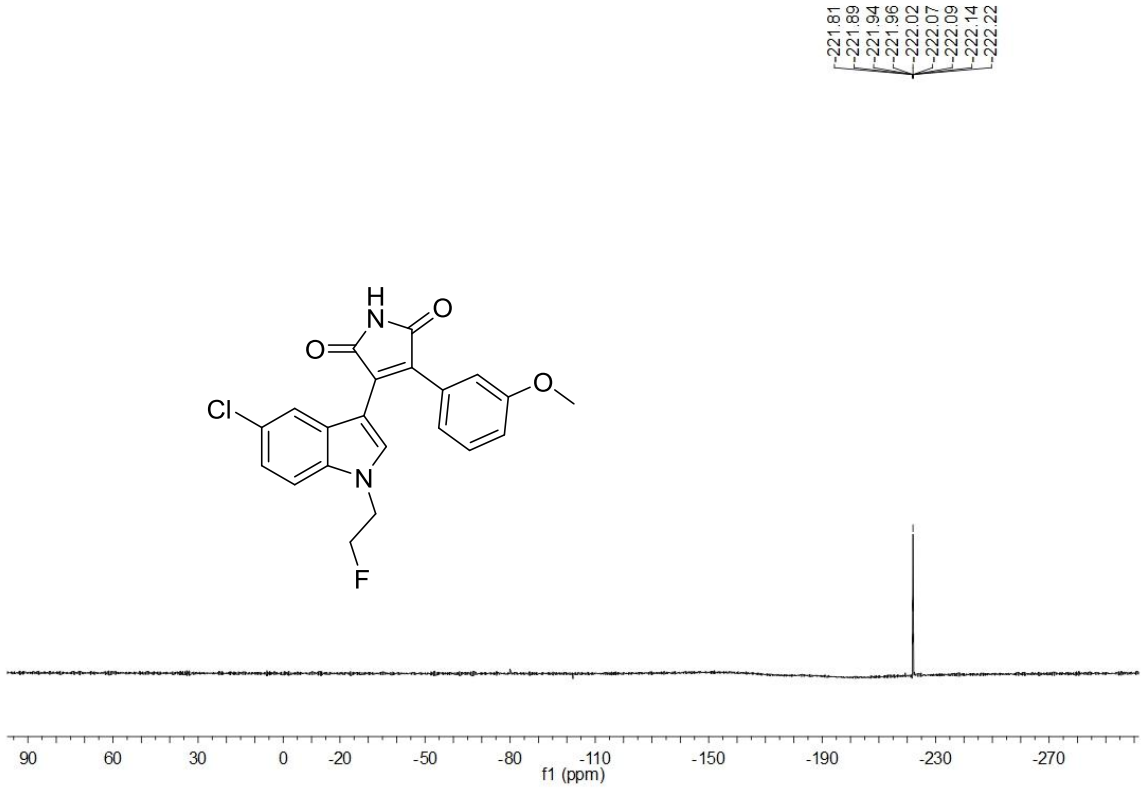


^{13}C NMR ((CD$_3$)$_2$SO, 25 °C) of **14b**

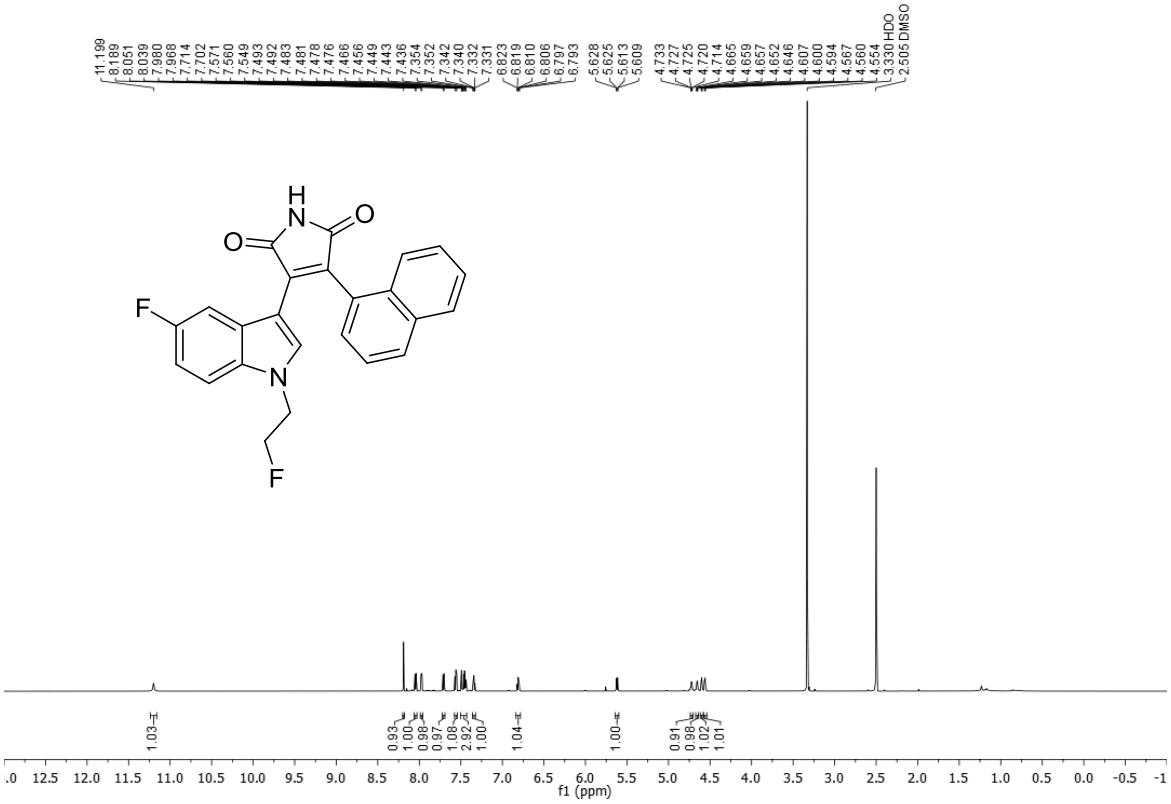


^{19}F

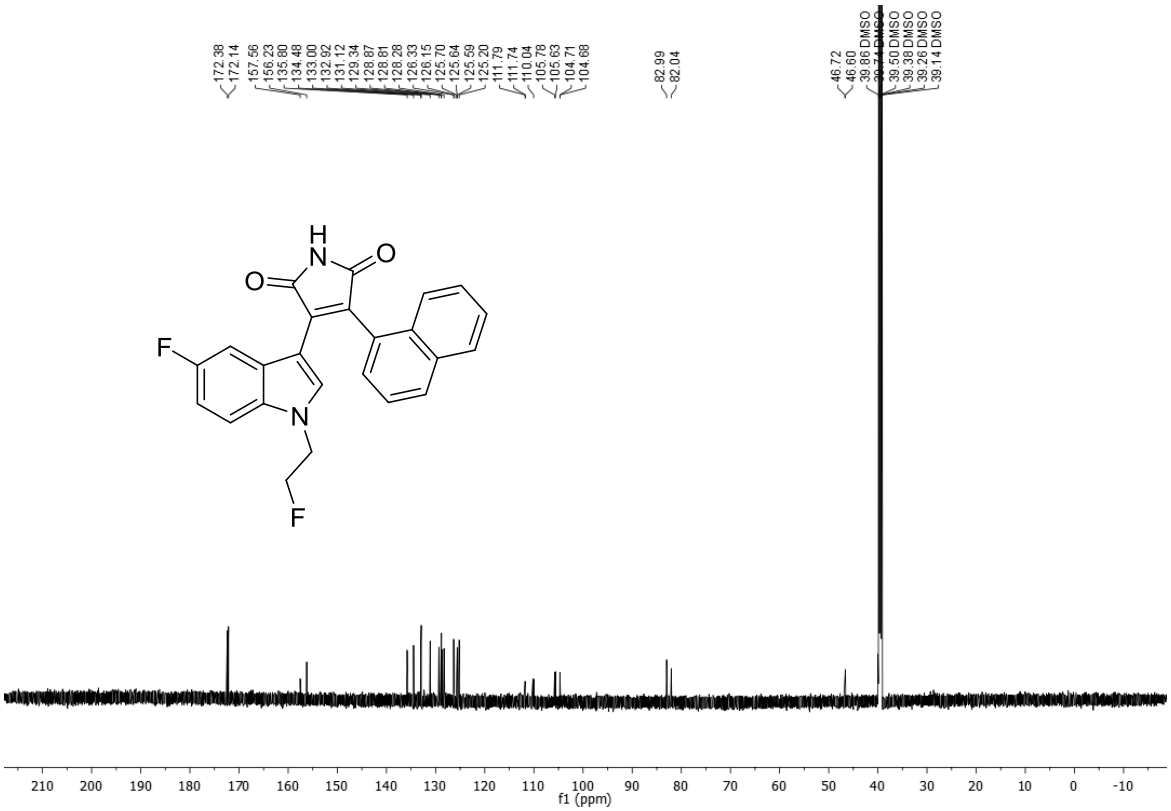
^{19}F NMR ((CD$_3$)$_2$SO, 25 °C) of **14b**



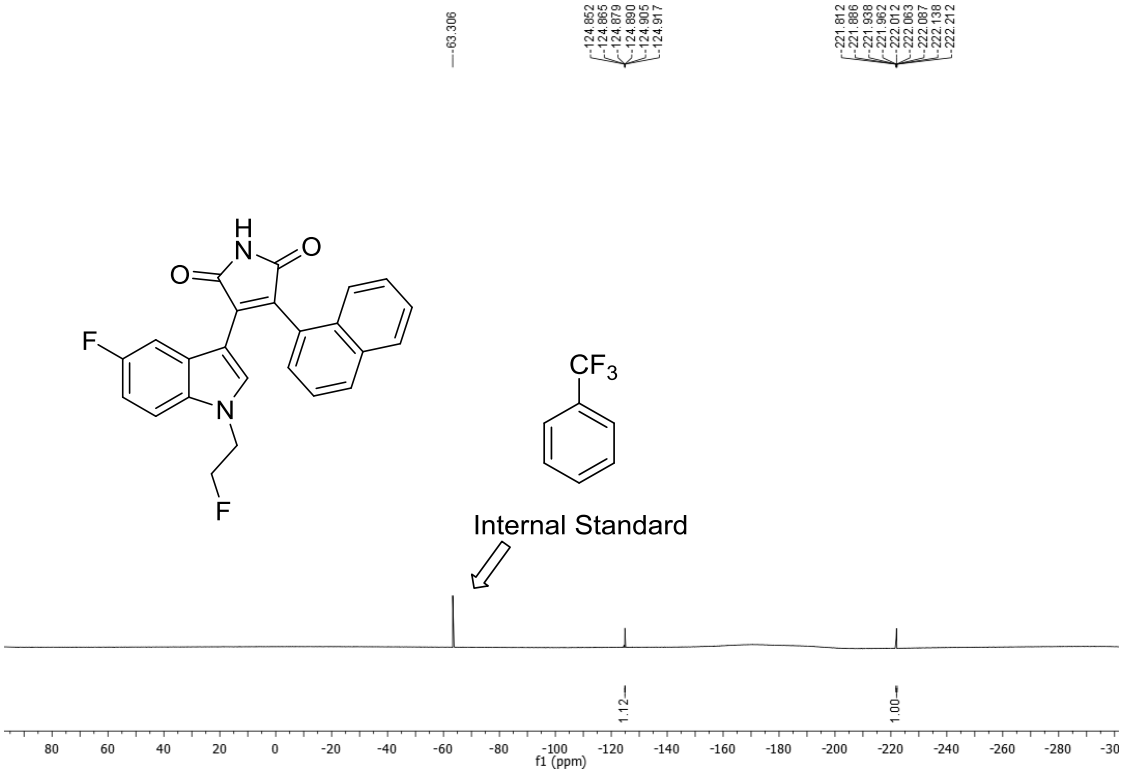
^{1}H NMR ((CD$_3$)$_2$SO, 25 °C) of **14c**



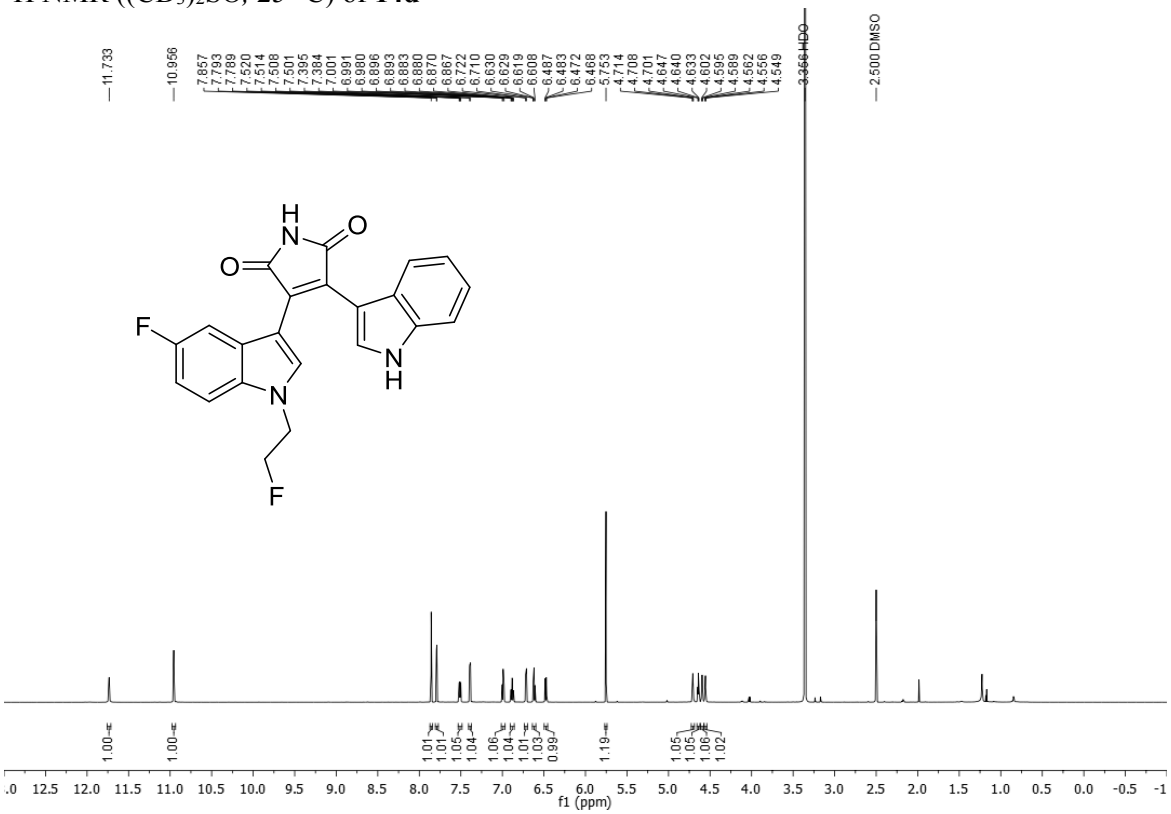
^{13}C NMR ((CD$_3$)$_2$SO, 25 °C) of **14c**



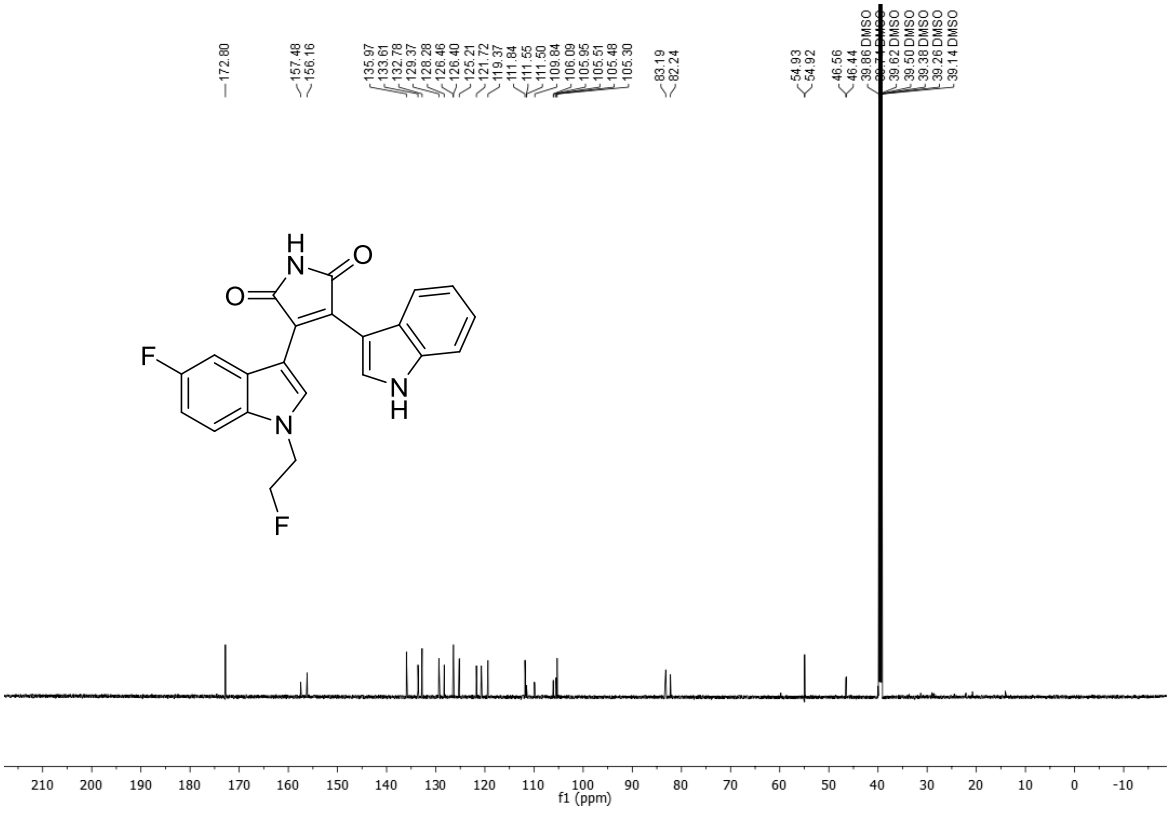
^{19}F NMR ((CD$_3$)$_2$SO, 25 °C) of **14c**



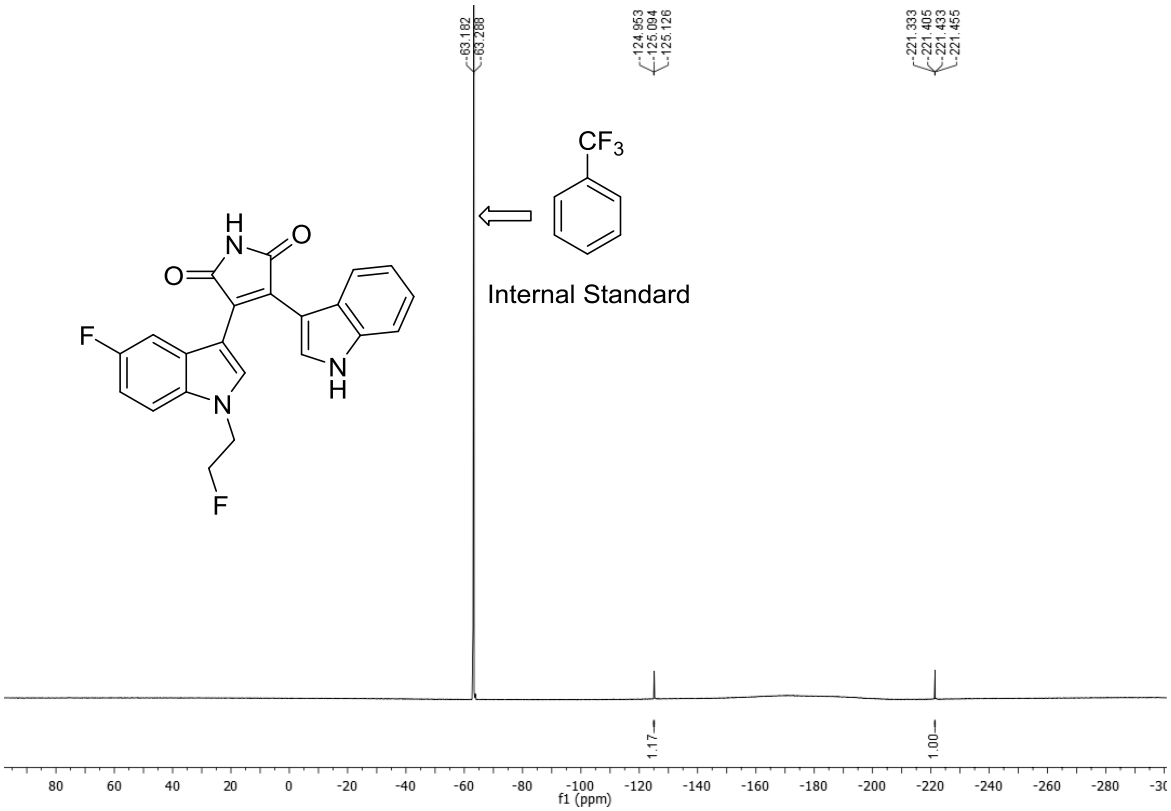
^{1}H NMR ((CD$_3$)$_2$SO, 25 °C) of **14d**



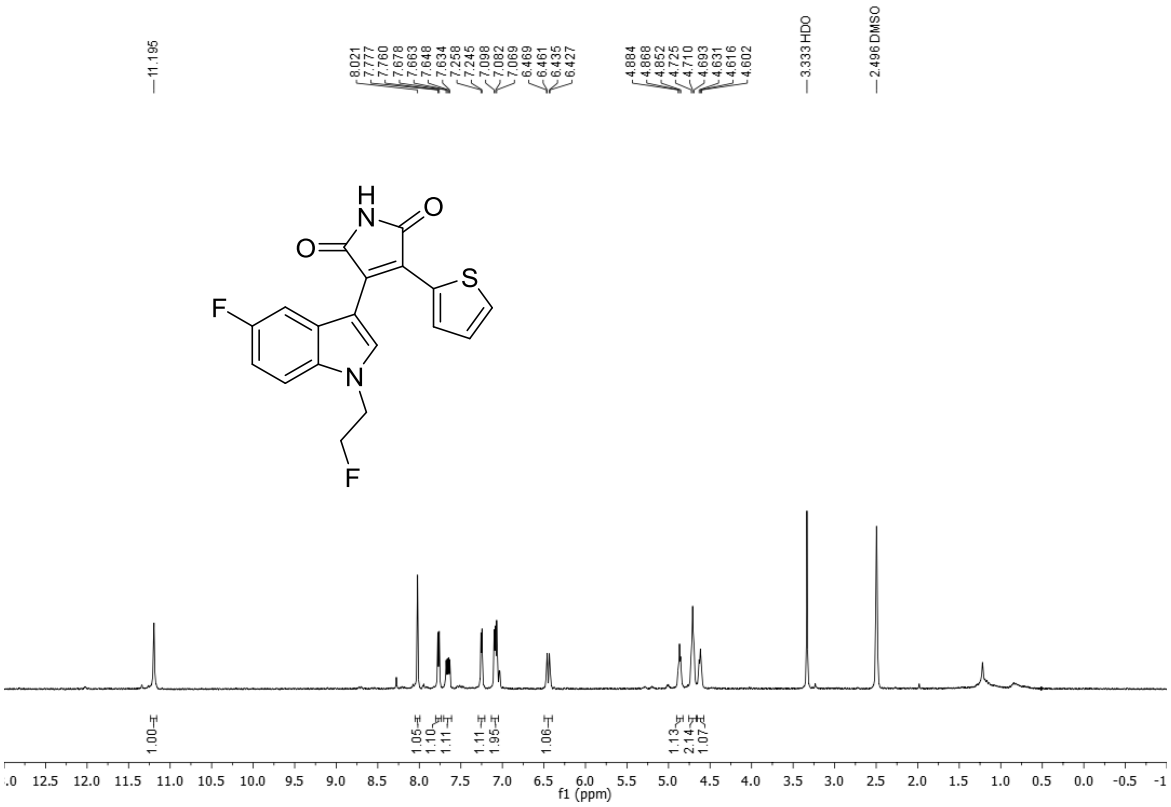
^{13}C NMR ((CD$_3$)$_2$SO, 25 °C) of **14d**



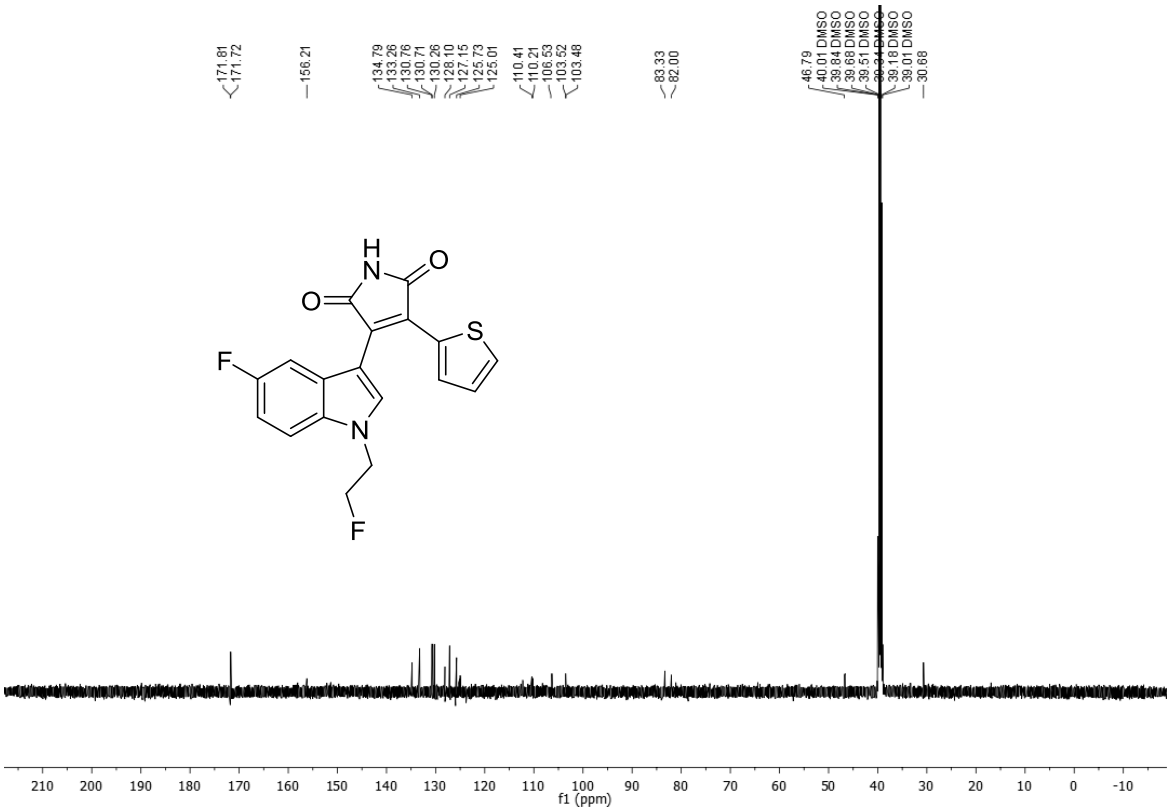
^{19}F NMR ((CD$_3$)$_2$SO, 25 °C) of **14d**



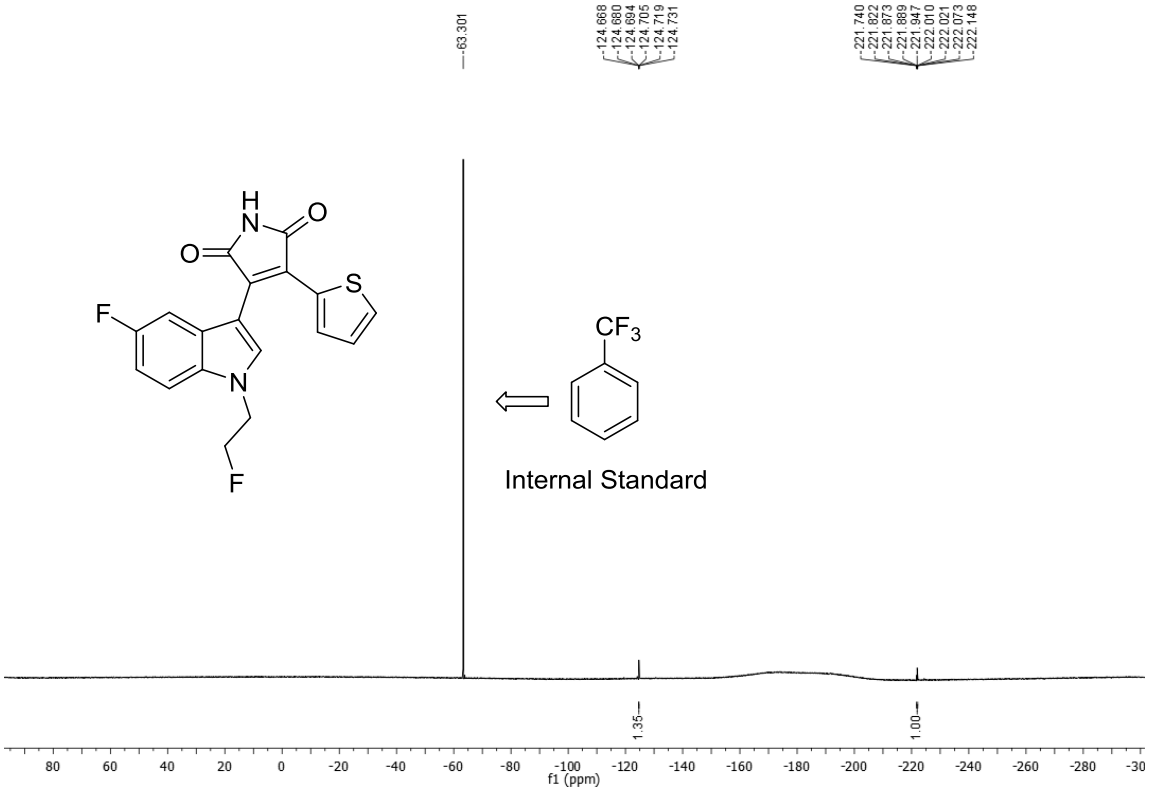
^{1}H NMR ((CD$_3$)$_2$SO, 25 °C) of **14e**



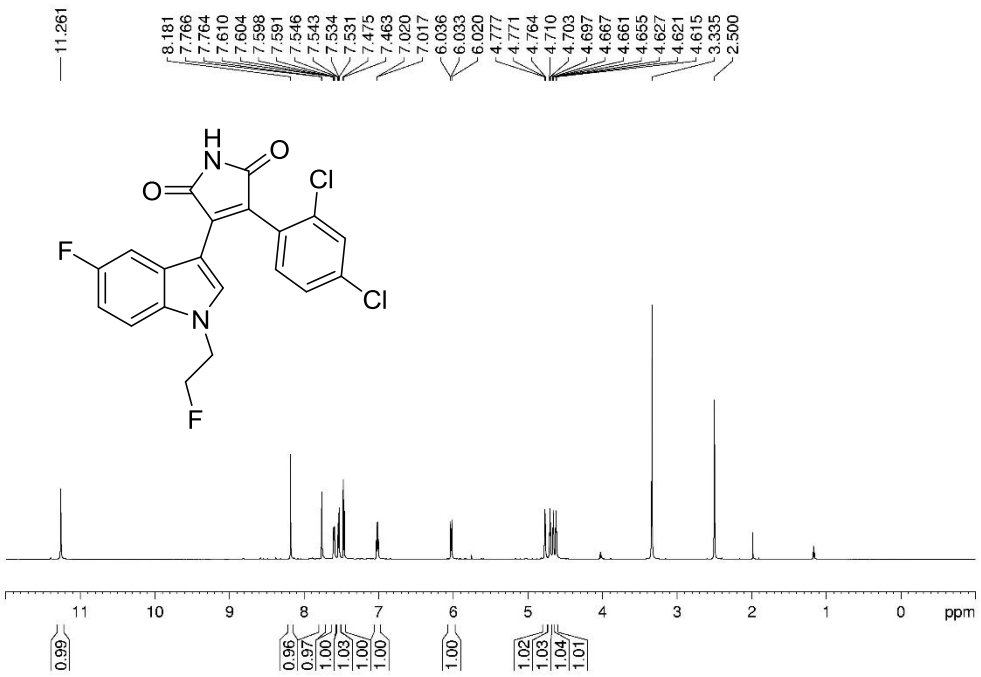
^{13}C NMR ((CD$_3$)$_2$SO, 25 °C) of **14e**



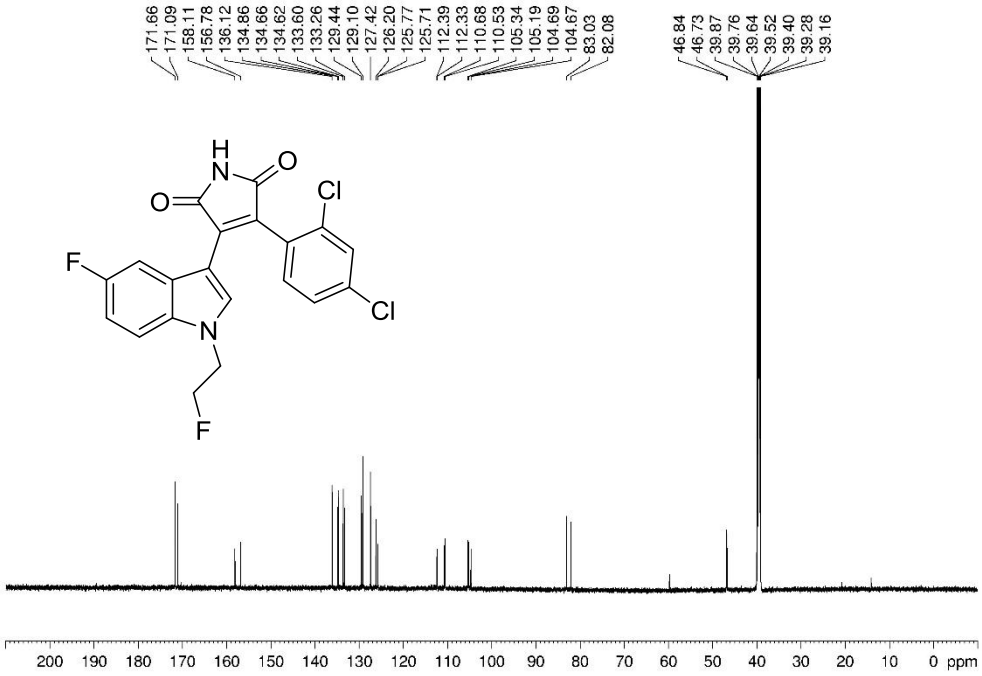
^{19}F NMR ((CD$_3$)$_2$SO, 25 °C) of **14e**



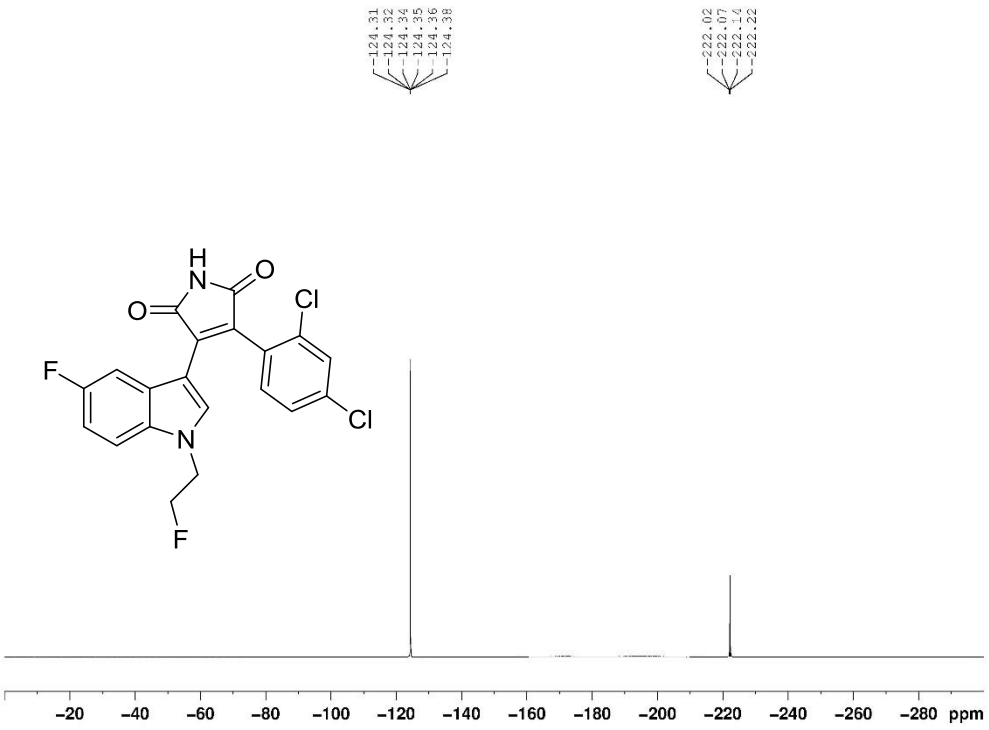
^{1}H NMR ((CD$_3$)$_2$SO, 25 °C) of **14f**



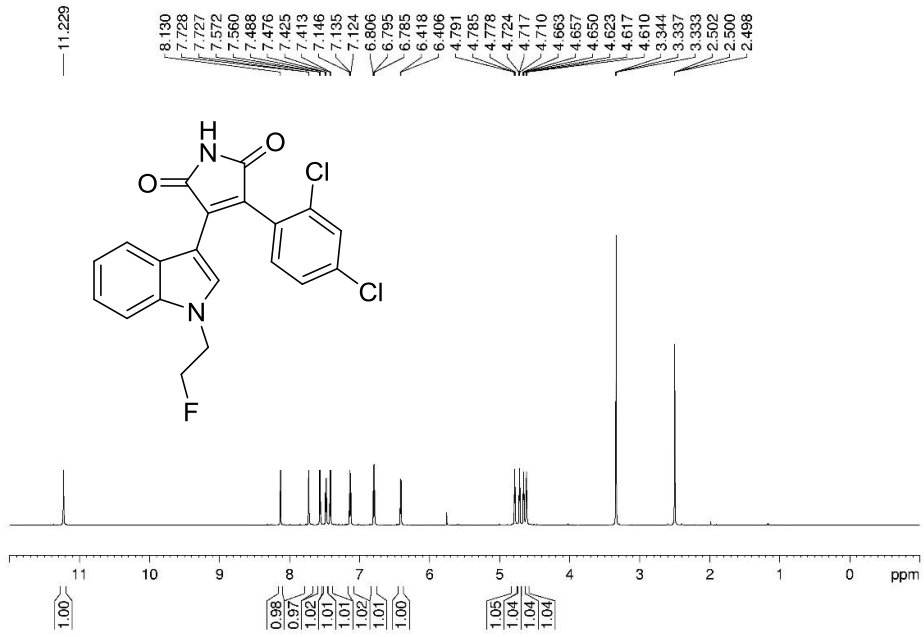
^{13}C NMR ((CD$_3$)$_2$SO, 25 °C) of **14f**



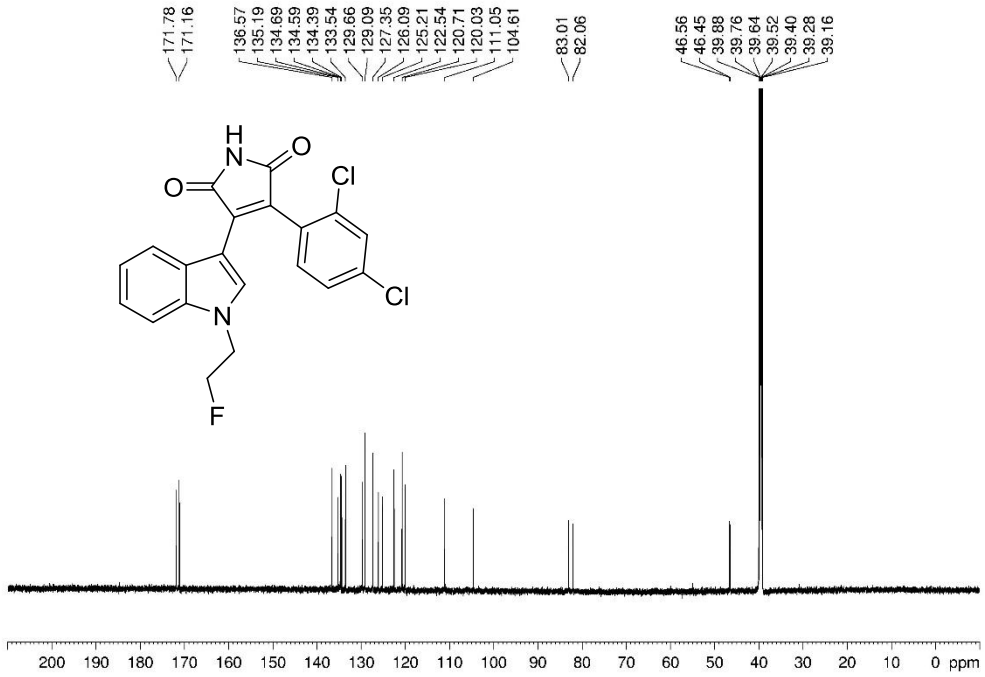
^{19}F NMR ((CD$_3$)$_2$SO, 25 °C) of **14f**



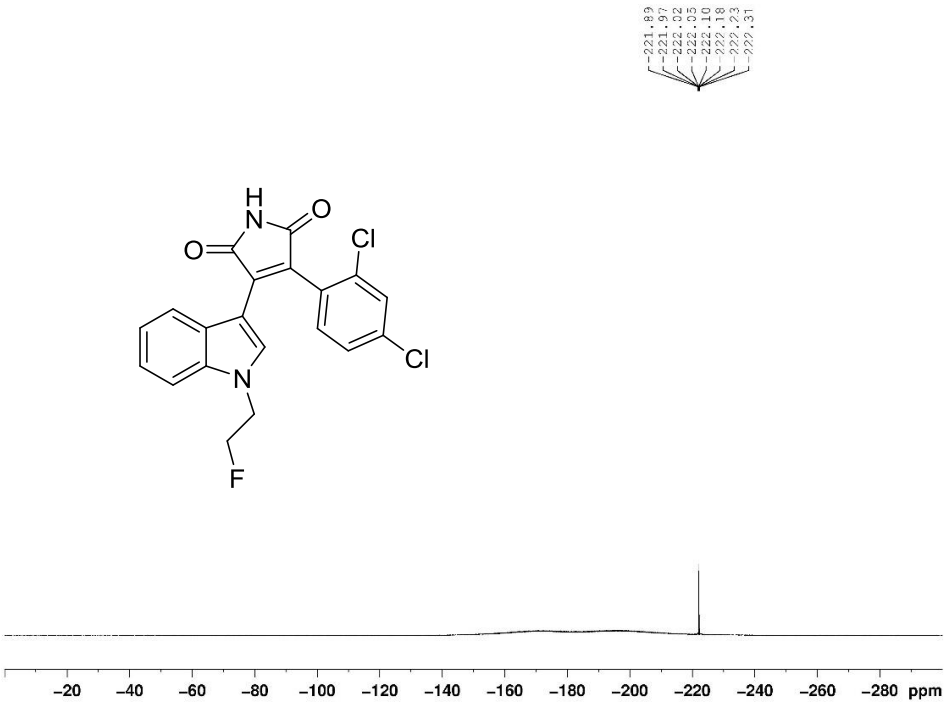
^{1}H NMR ((CD$_3$)$_2$SO, 25 °C) of **14g**



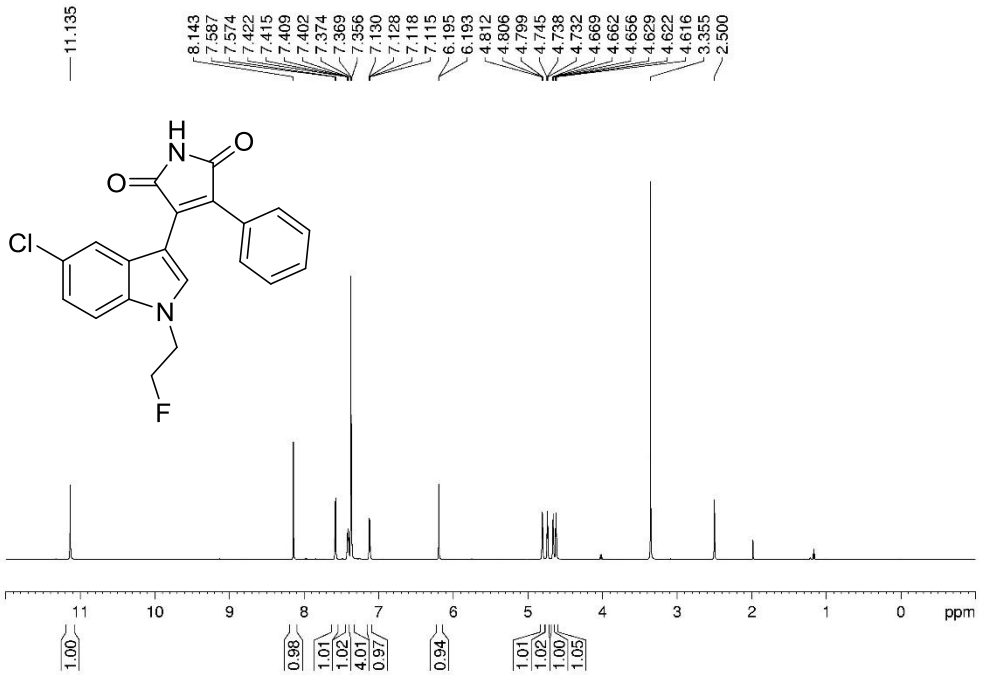
^{13}C NMR ((CD$_3$)$_2$SO, 25 °C) of **14g**



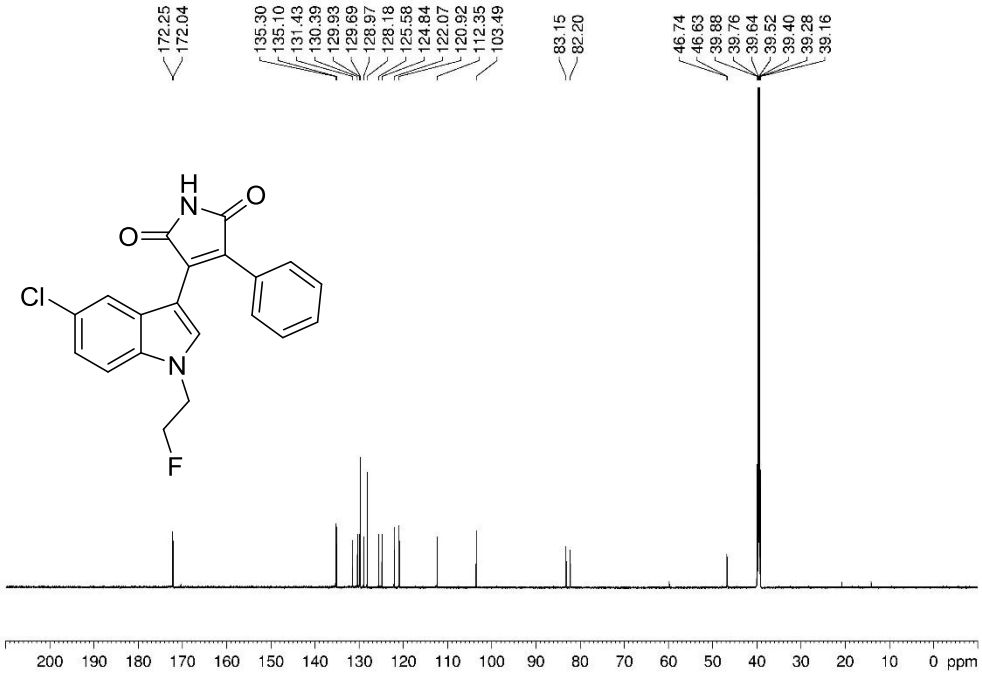
^{19}F NMR ((CD$_3$)$_2$SO, 25 °C) of **14g**



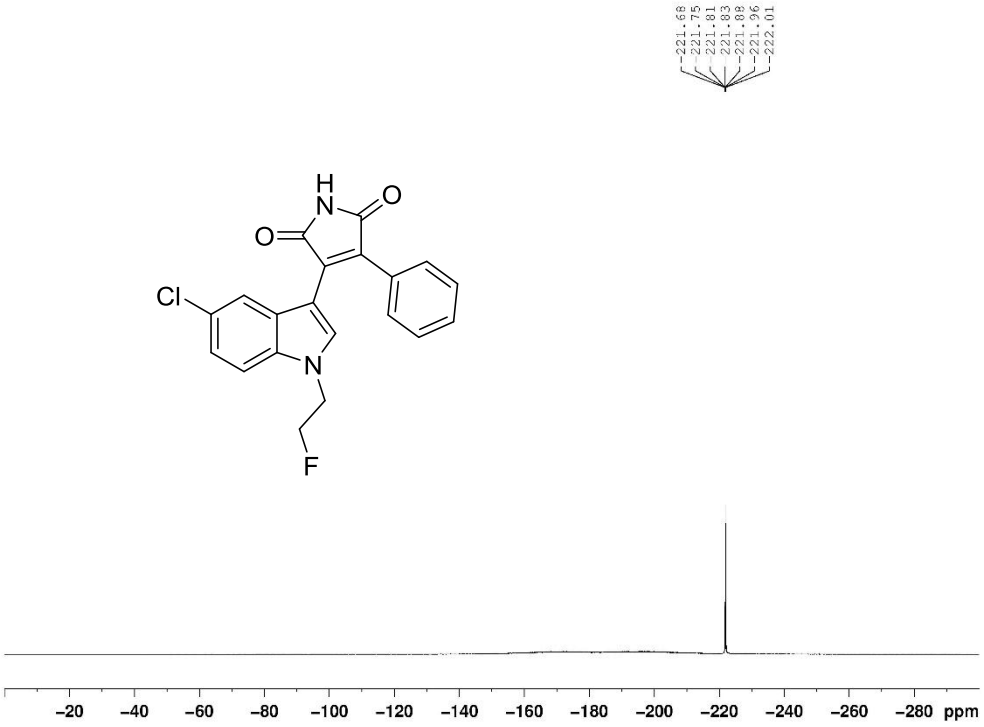
^{1}H NMR ($(CD_3)_2SO$, 25 °C) of **14h**



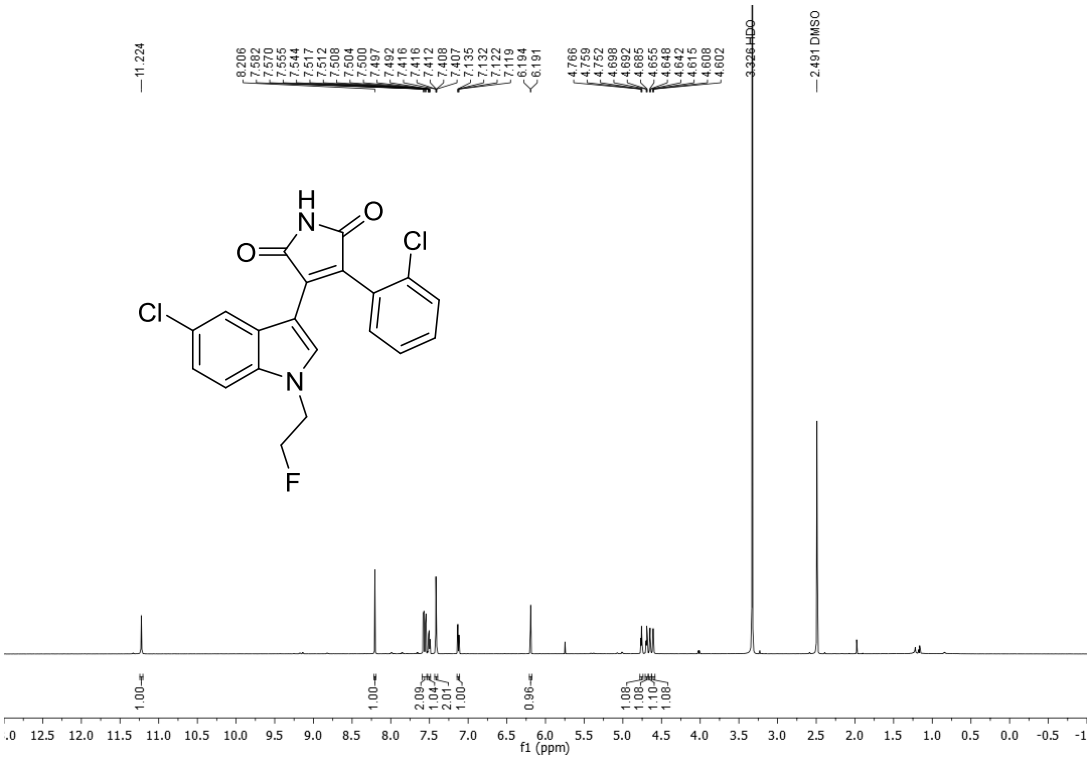
^{13}C NMR ($(CD_3)_2SO$, 25 °C) of **14h**



^{19}F NMR ((CD$_3$)$_2$SO, 25 °C) of **14h**

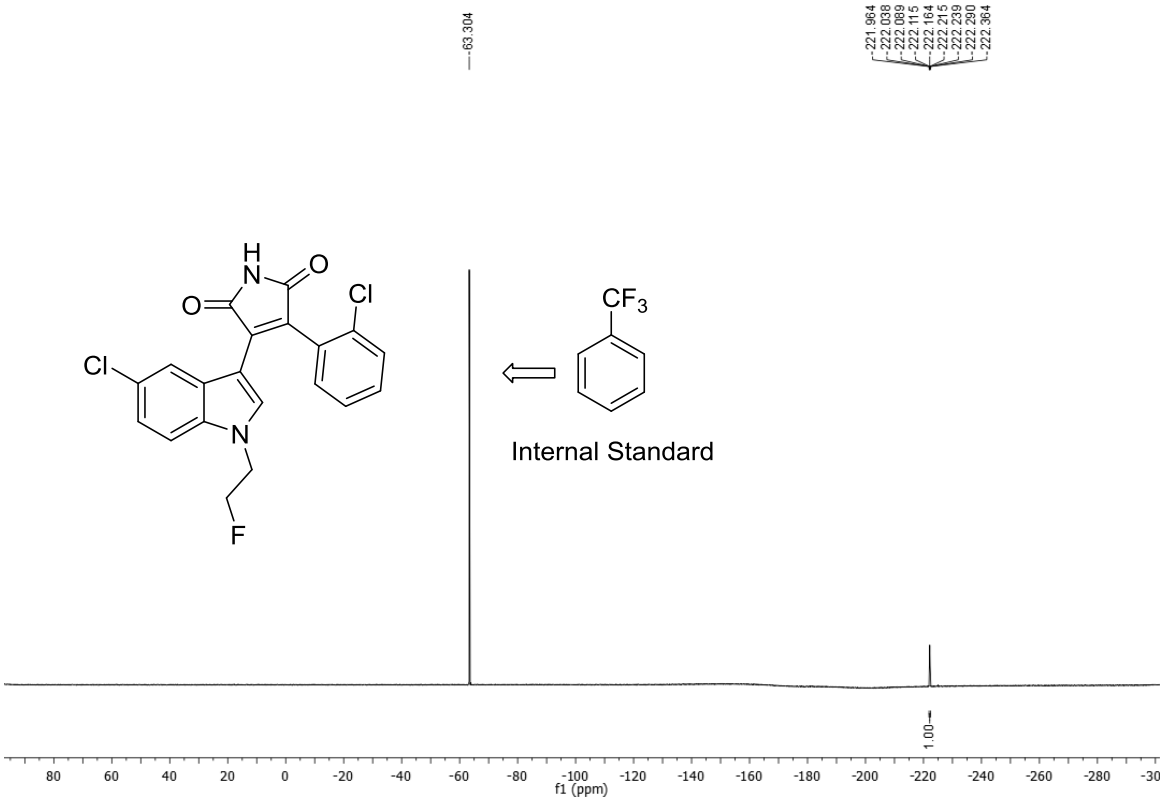


^{1}H NMR ((CD$_3$)$_2$SO, 25 °C) of **14i**

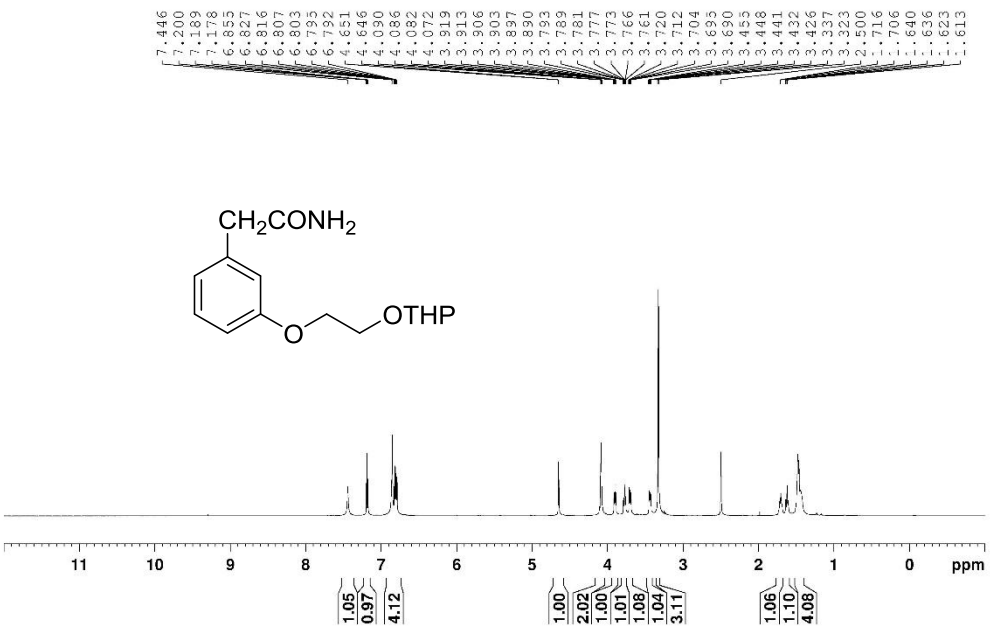


^{13}C NMR ((CD$_3$)$_2$SO, 25 °C) of **14i**

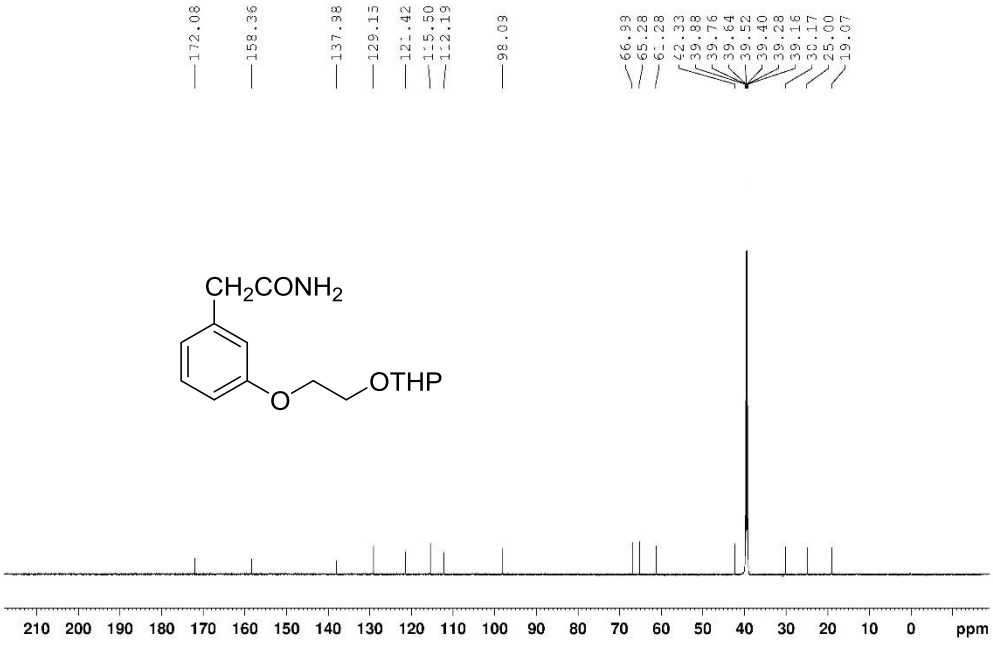
^{19}F NMR ((CD$_3$)$_2$SO, 25 °C) of **14i**



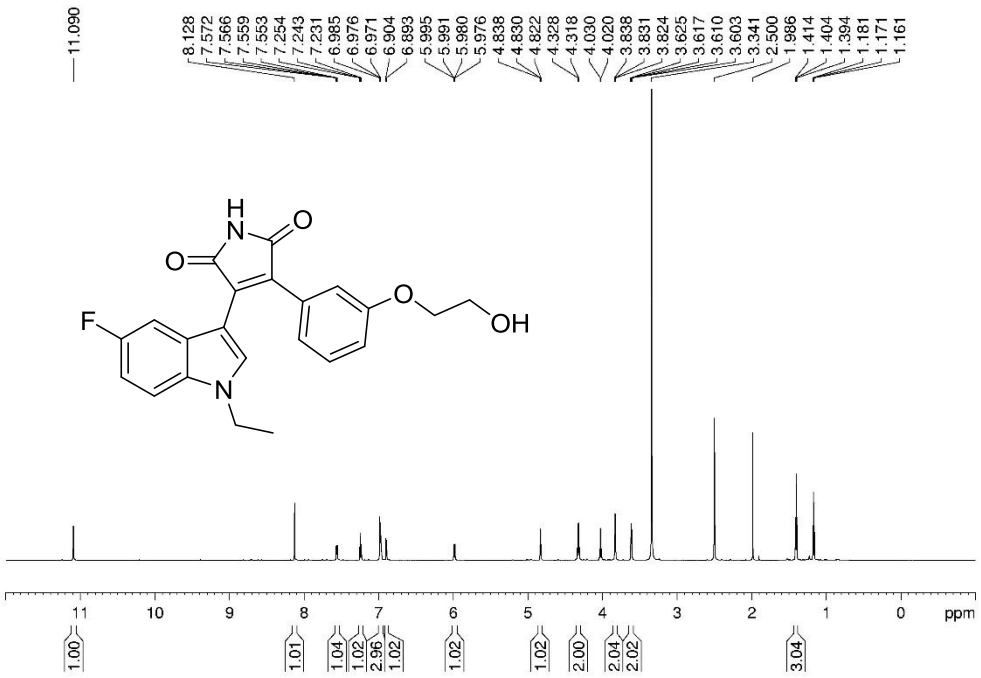
^{1}H NMR ((CD$_3$)$_2$SO, 25 °C) of **S1**



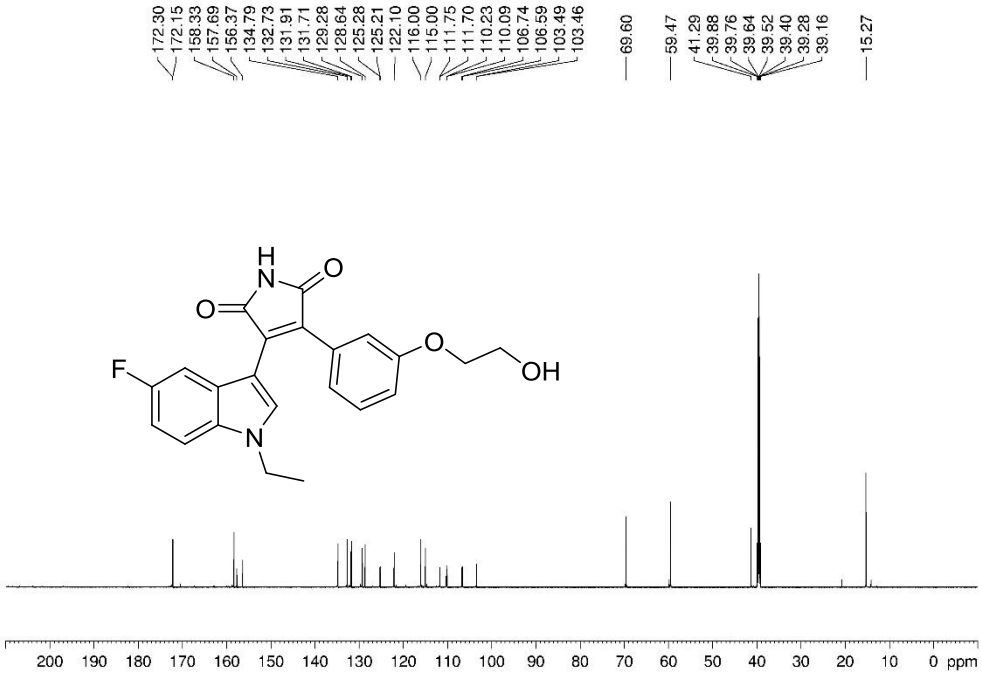
^{13}C NMR ((CD$_3$)$_2$SO, 25 °C) of **S1**



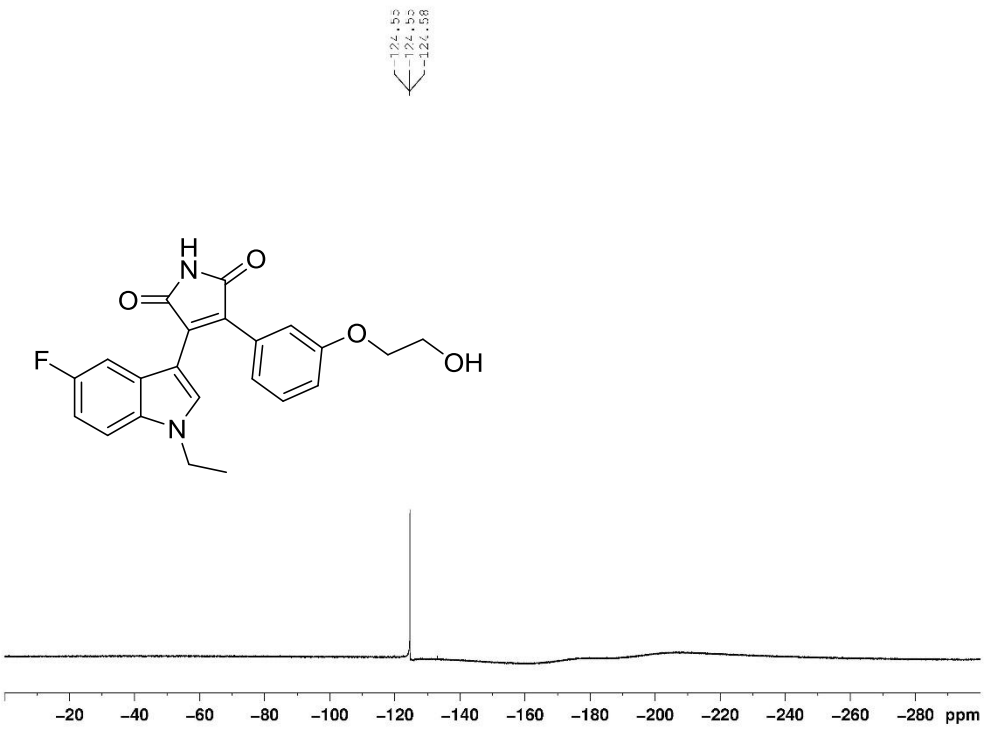
^{1}H NMR ((CD$_3$)$_2$SO, 25 °C) of **S2**



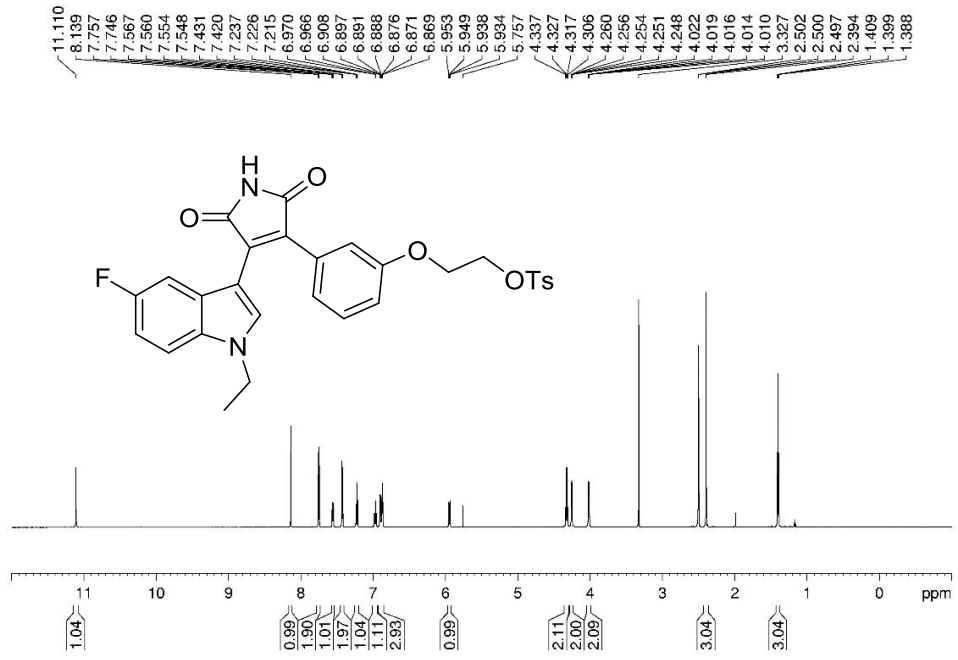
^{13}C NMR ((CD$_3$)$_2$SO, 25 °C) of **S2**



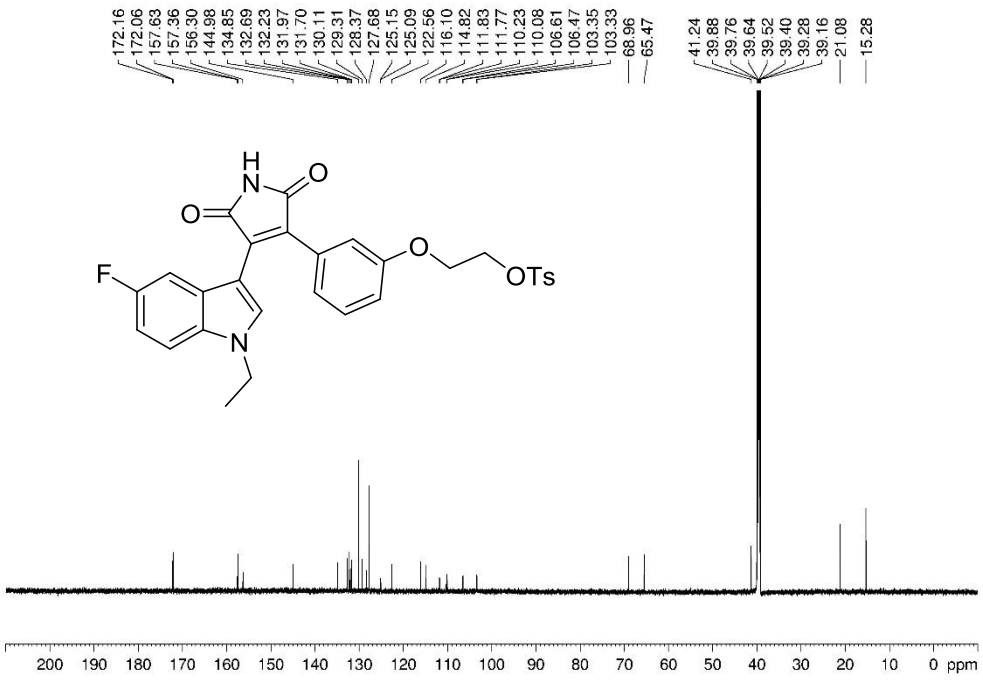
^{19}F NMR ((CD$_3$)$_2$SO, 25 °C) of **S2**



^{1}H NMR ((CD$_3$)$_2$SO, 25 °C) of **15**



^{13}C NMR ((CD$_3$)$_2$SO, 25 °C) of **15**



^{19}F NMR ((CD$_3$)$_2$SO, 25 °C) of **15**