Copper (II)-catalyzed and Oxidant promoted regioselective C-2 difluoromethylation of indoles and pyrroles

Dong Zhang, [a] Zheng Fang, [a] Jinlin Cai, [a] Chengkou Liu, [a] Wei He, [a] Jindian Duan, [a] Ning Qin, [a] Zhao Yang, [b] and Kai Guo [a, *]

[a] College of Biotechnology and Pharmaceutical Engineering Nanjing Tech University, 30 Puzhu Rd S., Nanjing, 211816, China Email: guok@njtech.edu.cn, Tel +86 25 5813 9901, Fax +86 25 5813 9935.

[b] College of Engineering China Pharmaceutical University, 24 Tongjiaxiang, Nanjing, 210003, China

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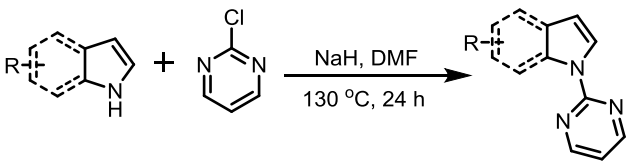
1. General Information

All reactions were carried out with magnetic stirring and in dried glassware. Standard syringe techniques were applied for transfer of dry solvents. All reagents and solvents were commercially available and used without any further purification unless specified. Proton (^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded at 400 MHz and 100 MHz respectively. The chemical shifts are given in parts per million (ppm) on the delta (δ) scale. ^{1}H NMR chemical shifts were determined relative to internal TMS at δ 0.0 ppm. ^{13}C NMR chemical shifts were determined relative to CDCl3 at δ 77.00 ppm. The following abbreviations were used to explain multiplicities: s =singlet, d =doublet, dd = doublet of doublet, t = triplet, td = triplet of doublet, q = quartet, m = multiplet, and br = broad. Analytical TLC was performed on precoated silica gel plates. High-resolution mass spectra (HRMS) were obtained on an Agilent mass spectrometer using ESI-TOF (electrospray ionization-time of flight).

2. Experimental Section

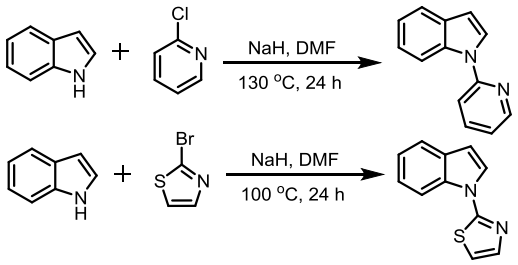
2.1 General Procedure for the synthesis of starting materials [1]



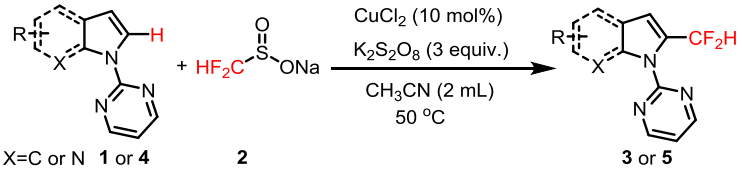
In an oven-dried flask (100 mL), NaH (60% dispersion in mineral oil, 11 mmol) was added in portions at 0 °C to a stirred solution of the corresponding indoles or pyrroles (10 mmol) in DMF

(25 mL). After stirring for 30min at 0 °C, 2-chloropyrimidine (12 mmol) was added and the mixture was stirred at 130 °C for 24 h. Then, the reaction mixture was cooled to room temperature, poured into H_2O (300 mL) and extracted with EtOAc (4×75 mL). The combined organic phase was dried over Na_2SO_4. After filtration and evaporation of the solvents under reduced pressure, the crude product was purified by column chromatography on silica gel (n-hexane/EtOAc) to give the desired product.

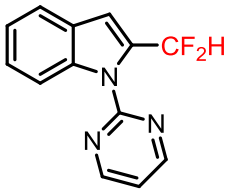
2-Chloropyridine is also suitable for above condition and 2-bromothiazole can replace 2-chloropyrimidine at lower temperature.



2.2 General Procedure for C-2 difluoromethylation of indoles or pyrroles

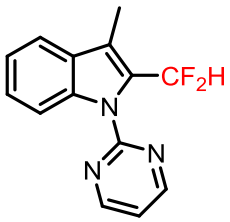


In a 15 mL sealed tube the corresponding indoles or pyrroles **1** or **4** (0.2 mmol, 1.0 equiv.), CF_2HSO_2Na (0.3mmol, 1.5 equiv.), $CuCl_2$ (2.7 mg, 10 mol %), $K_2S_2O_8$ (162.2 mg, 0.6 mmol, 3 equiv.) and 2 mL CH_3CN were added under air. The tube was capped and submerged into a pre-heated 50 °C oil bath. The reaction was stirred for 24h and cooled down to room temperature. Then the reaction mixture was diluted with EtOAc (5 mL) and filtered through a pad of silica gel. The sealed tube and silica gel were washed with an additional of EtOAc (20 mL). The filtrate was concentrated *in vacuo*, and the resulting residue was purified by flash column chromatography using EtOAc/*n*-hexane (1:15) as the eluent to afford the product.



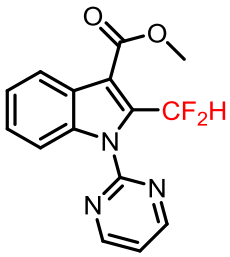
2-(Difluoromethyl)-1-(pyrimidin-2-yl)-1*H*-indole (**3a**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (d, *J* = 4.8 Hz, 2H), 8.66 (d, *J* = 8.5 Hz, 1H), 7.79 (t, *J* = 56 Hz, 1H), δ 7.66 (d, *J* = 8.6 Hz, 1H), 7.39 (t, *J* = 7.8 Hz, 1H), 7.27 (t, *J* = 7.0 Hz, 1H), 7.13 (s, 1H), 7.11 (t, *J* = 4.8 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.72 (s, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.02, 157.57, 137.29, 133.14 (t, *J* = 28.9 Hz), 128.04, 125.21, 122.68, 121.62, 116.99, 115.76, 110.63 (t, *J* = 236.5 Hz), 109.13 (t, *J* = 6.8 Hz). HRMS (ESI-TOF) m/z Calcd for $C_{13}H_9F_2N_3$ $[M+H]^+$: 246.0837, found: 246.0825.



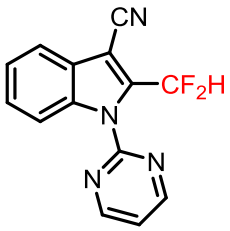
2-(Difluoromethyl)-3-methyl-1-(pyrimidin-2-yl)-1*H*-indole (**3b**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (d, *J* = 4.8 Hz, 2H), 8.51 (d, *J* = 8.4 Hz, 1H), 7.80 (t, *J* = 54.3 Hz, 1H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.38 (t, *J* = 7.7 Hz, 1H), 7.29 (t, *J* = 7.4 Hz, 1H), 7.12 (t, *J* = 4.8 Hz, 1H), 2.55 (t, *J* = 3.3 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -110.61 (s, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.13, 157.72, 136.37, 129.80, 127.58 (d, *J* = 27.7 Hz), 125.49, 122.31, 119.75 (t, *J* = 2.8 Hz), 119.49, 116.84, 115.10, 111.93 (t, *J* = 234.7 Hz), 9.24. HRMS (ESI-TOF) m/z Calcd for $C_{14}H_{11}F_2N_3$ $[M+H]^+$: 260.0994, found: 260.0984.



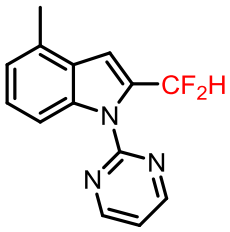
Methyl 2-(difluoromethyl)-1-(pyrimidin-2-yl)-1*H*-indole-3-carboxylate (**3c**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (d, *J* = 4.8 Hz, 2H), 8.22 (d, *J* = 7.3 Hz, 1H), 7.93 – 7.59 (m, 2H), 7.46 – 7.31 (m, 3H), 4.01 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -112.71 (s, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.55, 158.74, 156.85, 136.75, 135.09 (t, *J* = 23.6 Hz), 125.87, 125.36, 123.58, 122.48, 119.80, 112.69, 112.24 (t, *J* = 5.8 Hz), 108.87 (t, *J* = 238.3 Hz), 51.78. HRMS (ESI-TOF) m/z Calcd for $C_{15}H_{11}F_2N_3O_2$ $[M+H]^+$: 304.0892, found: 304.0871.



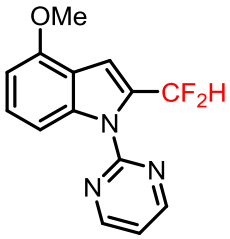
2-(Difluoromethyl)-1-(pyrimidin-2-yl)-1*H*-indole-3-carbonitrile (**3d**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (d, *J* = 4.8 Hz, 2H), 8.53 (d, *J* = 8.5 Hz, 1H), 8.02 – 7.66 (m, 2H), 7.56 – 7.46 (m, 1H), 7.46 – 7.39 (m, 1H), 7.34 (t, *J* = 4.8 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.84 (s, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.55, 156.58, 137.73, 136.75 – 134.87 (m), 127.28, 127.06, 124.45, 120.12, 118.97, 115.82, 113.19, 109.52 (t, *J* = 240.4 Hz), 93.25. HRMS (ESI-TOF) m/z Calcd for $C_{14}H_8F_2N_4$ $[M+H]^+$: 271.0790, found: 271.0779.



2-(Difluoromethyl)-4-methyl-1-(pyrimidin-2-yl)-1*H*-indole (**3e**)

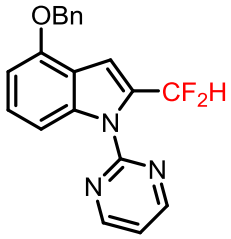
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (d, *J* = 4.8 Hz, 2H), 8.48 (d, *J* = 8.5 Hz, 1H), 7.80 (t, *J* = 56.2 Hz, 1H), 7.33 – 7.26 (m, 1H), 7.17 (s, 1H), 7.12 (t, *J* = 4.8 Hz, 1H), 7.07 (d, *J* = 7.2 Hz, 1H), 2.58 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.49 (s, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.10, 157.69, 137.20, 132.58 (t, *J* = 28.8 Hz), 131.14, 127.83, 125.38, 123.05, 117.04, 113.29, 110.78 (t, *J* = 236.4 Hz), 107.61 (t, *J* = 6.8 Hz), 18.53. HRMS (ESI-TOF) m/z Calcd for $C_{14}H_{11}F_2N_3$ $[M+H]^+$: 260.0994, found: 260.0985.



2-(Difluoromethyl)-4-methoxy-1-(pyrimidin-2-yl)-1*H*-indole (**3f**)

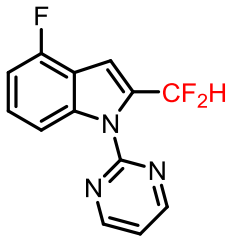
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (d, *J* = 4.8 Hz, 2H), 8.23 (d, *J* = 8.5 Hz, 1H), 7.76 (t, *J* = 56.2 Hz, 1H), 7.30 (t, *J* = 8.2 Hz, 1H), 7.26 (d, *J* = 4.9 Hz, 1H), 7.12 (t, *J* = 4.8 Hz, 1H), 6.68 (d, *J* = 7.9 Hz, 1H), 3.96 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.48 (s, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ

158.03, 157.63, 153.48, 138.53, 131.62 (t, *J* = 28.6 Hz), 126.11, 118.68, 117.07, 110.61 (t, *J* = 236.5 Hz), 108.63, 106.28 (t, *J* = 7.1 Hz), 102.58, 55.40. HRMS (ESI-TOF) m/z Calcd for $C_{14}H_{11}F_2N_3O$ $[M+H]^+$: 276.0943, found: 260.0935.



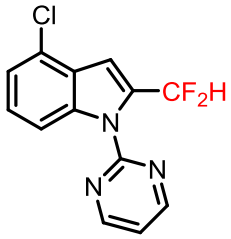
4-(Benzyloxy)-2-(difluoromethyl)-1-(pyrimidin-2-yl)-1*H*-indole (**3g**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (d, *J* = 4.8 Hz, 2H), 8.24 (d, *J* = 8.5 Hz, 1H), 7.76 (t, *J* = 56.2 Hz, 1H), 7.50 (d, *J* = 8.7 Hz, 2H), 7.41 (t, *J* = 7.3 Hz, 2H), 7.35 (d, *J* = 7.3 Hz, 1H), 7.32 (s, 1H), 7.28 (t, *J* = 8.2 Hz, 1H), 7.11 (t, *J* = 4.8 Hz, 1H), 6.74 (d, *J* = 7.9 Hz, 1H), 5.22 (s, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.40 (s, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.03, 157.64, 152.59, 138.64, 137.03, 131.70 (t, *J* = 29.0 Hz), 128.54, 127.89, 127.32, 126.08, 119.05, 117.06, 110.63 (t, *J* = 236.4 Hz), 108.92, 106.50 (t, *J* = 7.1 Hz), 104.02, 69.96. HRMS (ESI-TOF) m/z Calcd for $C_{20}H_{15}F_2N_3O$ $[M+H]^+$: 352.1256, found: 352.1247.



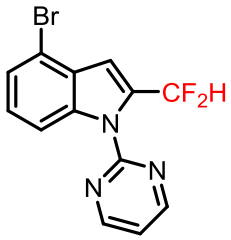
2-(Difluoromethyl)-4-fluoro-1-(pyrimidin-2-yl)-1*H*-indole (**3h**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (d, *J* = 4.8 Hz, 2H), 8.43 (d, *J* = 8.5 Hz, 1H), 7.77 (t, *J* = 55.9 Hz, 1H), 7.31 (td, *J* = 8.3, 5.6 Hz, 1H), 7.23 (s, 1H), 7.18 (t, *J* = 4.8 Hz, 1H), 6.99 – 6.91 (m, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -114.12 (s, 2F), -121.69 (s, 1F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.14 , 157.48 (d, *J* = 5.1 Hz), 155.03 , 139.31 (d, *J* = 9.4 Hz), 133.21 (t, *J* = 29.1 Hz), 125.85 (d, *J* = 7.5 Hz), 117.44 , 117.18 , 111.97 – 111.69 (m), 110.32 (t, *J* = 237.0 Hz), 107.74 , 107.56 , 104.78 – 104.52 (m). HRMS (ESI-TOF) m/z Calcd for $C_{13}H_8F_3N_3$ $[M+H]^+$: 264.0743, found: 264.0731.



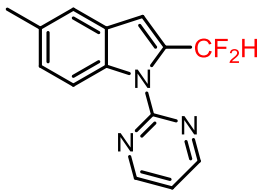
4-Chloro-2-(difluoromethyl)-1-(pyrimidin-2-yl)-1*H*-indole (**3i**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (d, *J* = 4.8 Hz, 2H), 8.55 (d, *J* = 7.7 Hz, 1H), 7.77 (t, *J* = 55.8 Hz, 1H), 7.32 – 7.26 (m, 2H), 7.24 (s, 1H), 7.16 (t, *J* = 4.8 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -114.14 (s, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.13, 157.33, 137.86, 133.72 (t, *J* = 29.1 Hz), 126.89, 126.79, 125.77, 122.41, 117.47, 114.42, 110.32 (t, *J* = 237.1 Hz), 107.20 (t, *J* = 7.0 Hz). HRMS (ESI-TOF) m/z Calcd for $C_{13}H_8ClF_2N_3$ $[M+H]^+$: 280.0448, found: 280.0436.



4-Bromo-2-(difluoromethyl)-1-(pyrimidin-2-yl)-1*H*-indole (**3j**)

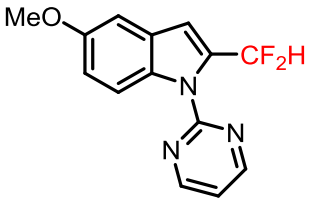
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (d, *J* = 4.8 Hz, 2H), 8.61 (d, *J* = 8.5 Hz, 1H), 7.77 (t, *J* = 55.8 Hz, 1H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.24 – 7.15 (m, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -114.20 (s, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.16, 157.41, 137.53, 133.77 (t, *J* = 29.1 Hz), 128.77, 126.05, 125.63, 117.50, 115.43, 114.95, 110.34 (t, *J* = 237.2 Hz), 108.98 (t, *J* = 7.1 Hz). HRMS (ESI-TOF) m/z Calcd for $C_{13}H_8BrF_2N_3$ $[M+H]^+$: 323.9942, found: 323.9932.



2-(Difluoromethyl)-5-methyl-1-(pyrimidin-2-yl)-1*H*-indole (**3k**)

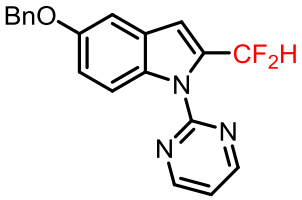
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (d, *J* = 4.8 Hz, 2H), 8.55 (d, *J* = 8.6 Hz, 1H), 7.78 (t, *J* = 56.0 Hz, 1H), 7.44 (s, 1H), 7.20 (d, *J* = 8.6 Hz, 1H), 7.10 (t, *J* = 4.8 Hz, 1H), 7.05 (s, 1H), 2.46 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.54 (s, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.98, 157.68, 135.64, 133.19 (t, *J* = 28.9 Hz), 132.16, 128.34, 126.74, 121.34, 116.75, 115.58, 110.68 (t, *J* = 236.3 Hz), 108.95 (t, *J* = 6.9 Hz), 21.25. HRMS (ESI-TOF) m/z Calcd for $C_{14}H_{11}F_2N_3$ $[M+H]^+$: 260.0994, found:

260.0989.



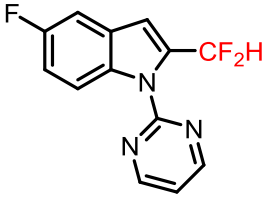
2-(Difluoromethyl)-5-methoxy-1-(pyrimidin-2-yl)-1*H*-indole (**3l**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (d, *J* = 4.8 Hz, 2H), 8.60 (d, *J* = 9.2 Hz, 1H), 7.78 (t, *J* = 55.9 Hz, 1H), 7.13 – 7.08 (m, 2H), 7.06 (s, 1H), 7.01 (dd, *J* = 9.2, 2.5 Hz, 1H), 3.87 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.54 (s, 2F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.98, 157.54, 155.78, 133.62 (t, *J* = 28.9 Hz), 132.19, 128.83, 116.97, 116.75, 114.74, 110.58 (t, *J* = 236.4 Hz), 108.99 (t, *J* = 6.9 Hz), 103.16. HRMS (ESI-TOF) m/z Calcd for $C_{14}H_{11}F_2N_3O$ $[M+H]^+$: 276.0943, found: 260.0933.



5-(Benzyloxy)-2-(difluoromethyl)-1-(pyrimidin-2-yl)-1*H*-indole (**3m**)

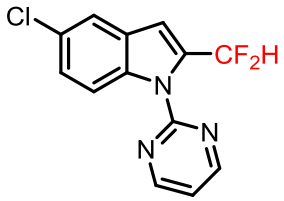
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (d, *J* = 4.8 Hz, 2H), 8.61 (d, *J* = 9.2 Hz, 1H), 7.78 (t, *J* = 56.0 Hz, 1H), 7.48 (d, *J* = 8.7 Hz, 2H), 7.39 (t, *J* = 7.3 Hz, 2H), 7.36 – 7.29 (m, 1H), 7.17 (d, *J* = 2.5 Hz, 1H), 7.12 – 7.07 (m, 2H), 7.05 (s, 1H), 5.13 (s, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.57 (s, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.99, 157.54, 154.92, 137.19, 133.67 (t, *J* = 29.0 Hz), 132.35, 128.56, 127.89, 127.52, 116.99, 116.77, 115.43, 110.57 (t, *J* = 236.3 Hz), 109.03 (t, *J* = 6.9 Hz), 104.70, 70.52. HRMS (ESI-TOF) m/z Calcd for $C_{20}H_{15}F_2N_3O$ $[M+H]^+$: 352.1256, found: 352.1245.



2-(Difluoromethyl)-5-fluoro-1-(pyrimidin-2-yl)-1*H*-indole (**3n**)

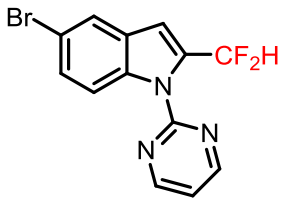
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (d, *J* = 4.8 Hz, 2H), 8.66 (dd, *J* = 9.2, 4.7 Hz, 1H), 7.78 (t, *J* = 55.8 Hz, 1H), 7.31 (dd, *J* = 8.6, 2.6 Hz, 1H), 7.16 (t, *J* = 4.8 Hz, 1H), 7.14 – 7.10 (m, 1H), 7.09 (s, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -114.03 (s, 2F), -120.83 (s, 1F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.27, 158.09, 157.89, 157.42, 134.66 (t, *J* = 29.2 Hz), 133.74, 128.78 (d, *J* = 10.1 Hz), 117.18, 117.10,

113.29 (d, *J* = 25.2 Hz), 110.39 (t, *J* = 236.8 Hz), 108.81 (td, *J* = 6.9, 4.5 Hz), 106.63 (d, *J* = 23.6 Hz). HRMS (ESI-TOF) m/z Calcd for $C_{13}H_8F_3N_3$ $[M+H]^+$: 264.0743, found: 264.0735.



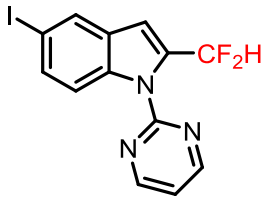
5-Chloro-2-(difluoromethyl)-1-(pyrimidin-2-yl)-1*H*-indole (**3o**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (d, *J* = 4.8 Hz, 2H), 8.63 (d, *J* = 9.0 Hz, 1H), 7.78 (t, *J* = 55.8 Hz, 1H), 7.63 (d, *J* = 2.1 Hz, 1H), 7.33 (dd, *J* = 9.0, 2.1 Hz, 1H), 7.18 (t, *J* = 4.8 Hz, 1H), 7.07 (s, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -114.11 (s, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.13, 157.37, 135.66, 134.29 (d, *J* = 29.4 Hz), 129.19, 128.24, 125.43, 121.00, 117.31, 117.12, 110.34 (t, *J* = 236.9 Hz), 108.41 (t, *J* = 6.9 Hz). HRMS (ESI-TOF) m/z Calcd for $C_{13}H_8ClF_2N_3$ $[M+H]^+$: 280.0448, found: 280.0434.



5-Bromo-2-(difluoromethyl)-1-(pyrimidin-2-yl)-1*H*-indole (**3p**)

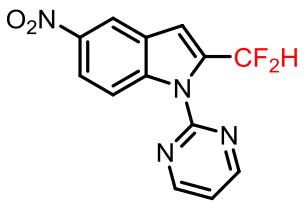
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (d, *J* = 4.8 Hz, 2H), 8.57 (d, *J* = 9.0 Hz, 1H), 7.93 – 7.61 (m, 2H), 7.46 (dd, *J* = 9.0, 1.9 Hz, 1H), 7.18 (t, *J* = 4.8 Hz, 1H), 7.06 (s, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -114.13 (s, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.12, 157.31, 135.95, 134.63 – 133.55 (m), 129.71, 128.03, 124.08, 117.47, 117.33, 115.86, 110.30 (t, *J* = 236.9 Hz), 108.26 (t, *J* = 6.9 Hz). HRMS (ESI-TOF) m/z Calcd for $C_{13}H_8BrF_2N_3$ $[M+H]^+$: 323.9942, found: 323.9935.



2-(Difluoromethyl)-5-iodo-1-(pyrimidin-2-yl)-1*H*-indole (**3q**)

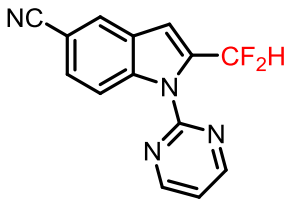
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (d, *J* = 4.8 Hz, 2H), 8.46 (d, *J* = 8.9 Hz, 1H), 8.00 (s, 1H), 7.92 – 7.64 (m, 1H), 7.63 (d, *J* = 4.1 Hz, 1H), 7.18 (t, *J* = 4.8 Hz, 1H), 7.04 (s, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -114.12 (s, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.12, 157.32, 136.49, 134.23 –

133.60 (m), 133.58, 130.34, 128.77, 117.86, 117.33, 110.27 (t, *J* = 236 Hz), 108.00 (t, *J* = 7.1 Hz), 86.50. HRMS (ESI-TOF) m/z Calcd for $C_{13}H_8IF_2N_3$ $[M+H]^+$: 371.9804, found: 371.9796.



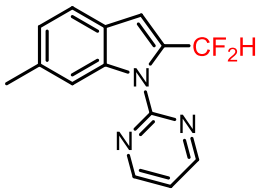
2-(Difluoromethyl)-5-nitro-1-(pyrimidin-2-yl)-1*H*-indole (**3r**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (d, *J* = 4.8 Hz, 2H), 8.79 (d, *J* = 9.3 Hz, 1H), 8.62 (d, *J* = 2.2 Hz, 1H), 8.28 (dd, *J* = 9.3, 2.3 Hz, 1H), 7.80 (t, *J* = 55.5 Hz, 1H), 7.32 – 7.27 (m, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -114.78 (s, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.41, 157.00, 143.58, 140.10, 136.28, 127.65, 120.27, 118.27, 118.16, 116.18, 109.99 (t, *J* = 237.7 Hz), 109.76 (t, *J* = 6.9 Hz). HRMS (ESI-TOF) m/z Calcd for $C_{13}H_8F_2N_4O_2$ $[M+H]^+$: 291.0688, found: 291.0679.



2-(Difluoromethyl)-1-(pyrimidin-2-yl)-1*H*-indole-5-carbonitrile (**3s**)

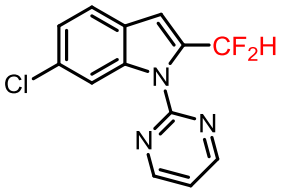
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (d, *J* = 4.8 Hz, 2H), 8.78 (d, *J* = 8.8 Hz, 1H), 8.03 (s, 1H), 7.79 (t, *J* = 55.6 Hz, 1H), 7.63 (d, *J* = 10.3 Hz, 1H), 7.27 (t, *J* = 4.8 Hz, 1H), 7.19 (s, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -114.66 (s, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.34, 157.05, 138.87, 136.18 – 135.09 (m), 127.96, 127.89, 126.73, 119.71, 118.06, 116.79, 110.06 (t, *J* = 236 Hz),108.74 (t, *J* = 6.9 Hz), 106.04. HRMS (ESI-TOF) m/z Calcd for $C_{14}H_8F_2N_4$ $[M+H]^+$: 271.0790, found: 271.0781.



2-(Difluoromethyl)-6-methyl-1-(pyrimidin-2-yl)-1*H*-indole (**3t**)

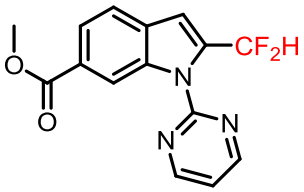
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (d, *J* = 4.8 Hz, 2H), 8.47 (s, 1H), 7.77 (t, *J* = 56.2 Hz, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.16 – 7.03 (m, 3H), 2.52 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.55 (s, 2F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.03, 157.62, 137.67, 135.32, 132.52 (t, *J* = 28.9 Hz), 125.82, 124.32, 121.20, 116.88, 115.56, 110.71 (t, *J* = 236.4 Hz), 109.07 (t, *J* = 6.9 Hz), 22.19. HRMS

(ESI-TOF) m/z Calcd for $C_{14}H_{11}F_2N_3$ [M+H] $^+$: 260.0994, found: 260.0987.



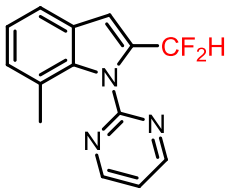
6-Chloro-2-(difluoromethyl)-1-(pyrimidin-2-yl)-1*H*-indole (**3u**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (d, *J* = 4.8 Hz, 2H), 8.75 (d, *J* = 1.6 Hz, 1H), 7.77 (t, *J* = 55.9 Hz, 1H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.26 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.18 (t, *J* = 4.8 Hz, 1H), 7.09 (s, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.95 (s, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.14, 157.30, 137.52, 133.82 (t, *J* = 29.1 Hz), 131.11, 126.53, 123.39, 122.33, 117.34, 116.07, 110.37 (t, *J* = 236.7 Hz), 108.89 (t, *J* = 6.9 Hz). HRMS (ESI-TOF) m/z Calcd for $C_{13}H_8ClF_2N_3$ [M+H] $^+$: 280.0448, found: 280.0437.



Methyl 2-(difluoromethyl)-1-(pyrimidin-2-yl)-1*H*-indole-6-carboxylate (**3v**)

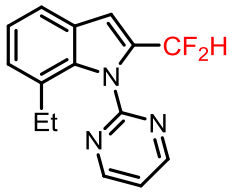
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.35 (s, 1H), 8.82 (d, *J* = 4.8 Hz, 2H), 7.97 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.95 – 7.64 (m, 2H), 7.21 (t, *J* = 4.8 Hz, 1H), 7.16 (s, 1H), 3.97 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -114.51 (s, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.74, 158.30, 157.26, 136.69, 135.94 (t, *J* = 29.1 Hz), 131.58, 126.83, 123.64, 121.36, 117.92, 117.55, 110.26 (t, *J* = 237.0 Hz), 108.70 (t, *J* = 6.8 Hz), 52.19. HRMS (ESI-TOF) m/z Calcd for $C_{15}H_{11}F_2N_3O_2$ [M+H] $^+$: 304.0892, found: 304.0873.



2-(Difluoromethyl)-7-methyl-1-(pyrimidin-2-yl)-1*H*-indole (**3w**)

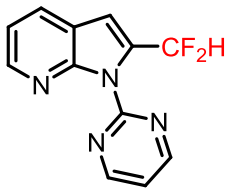
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (d, *J* = 4.8 Hz, 2H), 7.55 (d, *J* = 7.7 Hz, 1H), 7.39 – 7.30 (m, 1H), 7.24 – 7.07 (m, 3H), 7.04 (s, 1H), 2.09 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -114.65 (s, 2F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.50, 157.63, 136.89, 133.02, 128.24, 127.70, 123.12, 122.29, 119.76, 119.16, 110.16 (t, *J* = 236.2 Hz), 107.21 (t, *J* = 5.9 Hz), 20.72. HRMS (ESI-TOF) m/z Calcd for

$C_{14}H_{11}F_2N_3$ [M+H] $^+$: 260.0994, found: 260.0985.



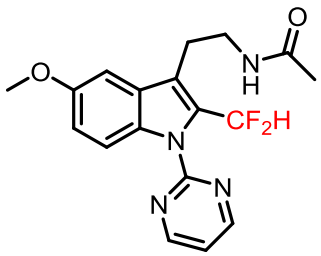
2-(Difluoromethyl)-7-ethyl-1-(pyrimidin-2-yl)-1*H*-indole (**3x**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (d, *J* = 4.8 Hz, 2H), 7.56 (dd, *J* = 6.7, 2.2 Hz, 1H), 7.34 (d, *J* = 4.7 Hz, 1H), 7.32 – 7.17 (m, 3H), 7.05 (s, 1H), 2.47 (q, *J* = 7.5 Hz, 2H), 0.98 (t, *J* = 7.5 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -114.71 (s, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.53, 158.02, 136.16, 133.18 (t, *J* = 28.0 Hz), 129.33, 128.47, 125.52, 122.43, 119.80, 119.26, 110.19 (t, *J* = 236.1 Hz), 107.33 (t, *J* = 5.9 Hz), 26.30, 13.64. HRMS (ESI-TOF) m/z Calcd for $C_{15}H_{13}F_2N_3$ [M+H] $^+$: 274.1150, found: 274.1141.



2-(Difluoromethyl)-1-(pyrimidin-2-yl)-1*H*-pyrrolo[2,3-b] pyridine (**3y**)

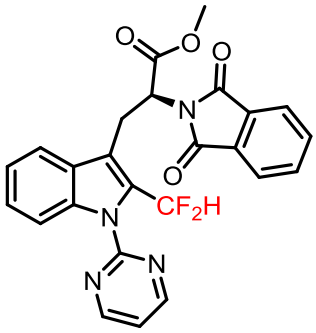
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.95 (d, *J* = 4.8 Hz, 2H), 8.68 (d, *J* = 4.1 Hz, 1H), 8.12 (d, *J* = 8.7 Hz, 1H), 7.66 (t, *J* = 14 Hz, 1H), 7.37 – 7.29 (m, 2H), 7.09 (s, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -116.03 (s, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.89, 156.09, 147.80, 145.48, 133.60 (t, *J* = 29.4 Hz), 131.33, 120.83, 118.88, 118.66, 109.98 (t, *J* = 237.8 Hz), 105.25 (t, *J* = 6.7 Hz). HRMS (ESI-TOF) m/z Calcd for $C_{12}H_8F_2N_4$ [M+H] $^+$: 247.0790, found: 247.0782.



N-(2-(2-(difluoromethyl)-5-methoxy-1-(pyrimidin-2-yl)-1*H*-indol-3-yl) ethyl) acetamide (**3z**)

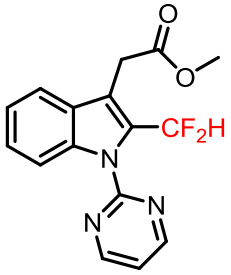
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (d, *J* = 4.8 Hz, 2H), 8.44 (d, *J* = 9.2 Hz, 1H), 7.85 (t, *J* = 54.2 Hz, 1H), 7.20 – 7.12 (m, 2H), 7.03 (dd, *J* = 9.2, 2.4 Hz, 1H), 5.69 (s, 1H), 3.91 (s, 3H), 3.61 (q, *J* = 6.5 Hz, 2H), 3.23 (t, *J* = 6.7 Hz, 2H), 1.93 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -109.40 (s, 2F). ^{13}C

NMR (101 MHz, $CDCl_3$) δ 170.30, 158.21, 157.49, 155.96, 131.18, 129.77, 128.73 (t, *J* = 27.9 Hz), 120.59 (t, *J* = 2.2 Hz), 117.02, 116.44, 115.69, 111.71 (t, *J* = 234.6 Hz), 100.85, 55.73, 39.93, 24.29, 23.36. HRMS (ESI-TOF) m/z Calcd for $C_{18}H_{18}F_2N_4O_2$ $[M+H]^+$: 361.1471, found: 361.1462.



Methyl (*S*)-3-(2-(difluoromethyl)-1-(pyrimidin-2-yl)-1*H*-indol-3-yl)-2-(1,3-dioxoisoindolin-2-yl) propanoate (**3za**)

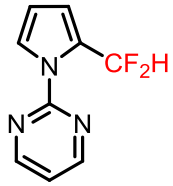
^1H NMR (400 MHz, $CDCl_3$) δ 8.75 (d, *J* = 4.8 Hz, 2H), 8.41 (d, *J* = 8.5 Hz, 1H), 8.00 – 7.69 (m, 3H), 7.65 – 7.55 (m, 3H), 7.26 (t, *J* = 7.5 Hz, 1H), 7.15 (t, *J* = 4.8 Hz, 1H), 7.10 (t, *J* = 7.5 Hz, 1H), 5.32 (dd, *J* = 11.3, 4.3 Hz, 1H), 4.08 – 3.98 (m, 1H), 3.94 – 3.84 (m, 1H), 3.81 (s, 3H), 1.59 (s, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -108.89 – -114.12 (m, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.33, 167.48, 158.11, 157.45, 136.19, 133.87, 131.70, 128.86, 128.79, 125.52, 123.32, 122.50, 119.11, 118.61 – 118.23 (m), 117.24, 115.06, 111.70 (t, *J* = 236.0 Hz), 52.92, 52.76 (t, *J* = 2.8 Hz), 24.15, 14.18. HRMS (ESI-TOF) m/z Calcd for $C_{26}H_{19}F_2N_3O_4$ $[M+H]^+$: 476.1416, found: 476.1407.



Methyl 2-(2-(difluoromethyl)-1-(pyrimidin-2-yl)-1*H*-indol-3-yl) acetate (**3zb**)

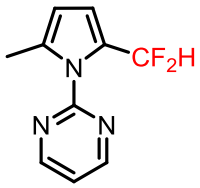
^1H NMR (400 MHz, $CDCl_3$) δ 8.76 (d, *J* = 4.8 Hz, 2H), 8.52 (d, *J* = 8.5 Hz, 1H), 7.85 (t, *J* = 54.4 Hz, 1H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.40 (t, *J* = 8.3 Hz, 1H), 7.30 (t, *J* = 8.0 Hz, 1H), 7.15 (t, *J* = 4.8 Hz, 1H), 4.08 (t, *J* = 2.1 Hz, 2H), 3.71 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.33 (s, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.31, 158.16, 157.48, 136.27, 129.03 (t, *J* = 27.7 Hz), 128.82, 125.66, 122.69, 119.37, 117.28, 115.65 (t, *J* = 2.5 Hz), 115.20, 111.71 (t, *J* = 235.9 Hz), 52.15, 30.06. HRMS (ESI-TOF)

m/z Calcd for $C_{16}H_{13}F_2N_3O_2$ $[M+H]^+$: 318.1049, found: 318.1038.



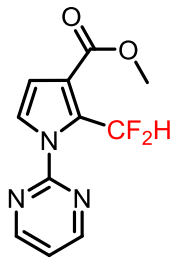
2-(2-(Difluoromethyl)-1*H*-pyrrol-1-yl) pyrimidine (**5a**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, *J* = 4.8 Hz, 2H), 7.91 (dd, *J* = 3.1, 2.0 Hz, 1H), 7.66 (t, *J* = 56.0 Hz, 1H), 7.13 (t, *J* = 4.8 Hz, 1H), 6.76 (d, *J* = 3.2 Hz, 1H), 6.32 (t, *J* = 3.4 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.60 (s, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.29, 156.37, 127.34, 123.19 (t, *J* = 2.8 Hz), 117.69, 114.29 (t, *J* = 5.6 Hz), 110.31 (t, *J* = 232Hz), 110.30. HRMS (ESI-TOF) m/z Calcd for $C_9H_7F_2N_3$ $[M+H]^+$: 196.0681, found: 196.0673.



2-(2-(Difluoromethyl)-5-methyl-1*H*-pyrrol-1-yl) pyrimidine (**5b**)

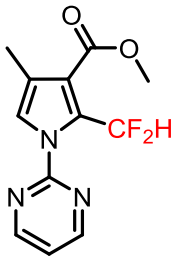
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (d, *J* = 4.8 Hz, 2H), 7.32 (t, *J* = 4.9 Hz, 1H), 6.96 (t, *J* = 58.6 Hz, 1H), 6.66 (d, *J* = 3.5 Hz, 1H), 6.09 (d, *J* = 3.4 Hz, 1H), 2.35 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -94.94 (s, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.24, 156.82, 135.93, 123.35, 122.26 (t, *J* = 276.0 Hz), 119.20, 112.18 (d, *J* = 4.9 Hz), 110.08, 14.43. HRMS (ESI-TOF) m/z Calcd for $C_{10}H_9F_2N_3$ $[M+H]^+$: 210.0837, found: 210.0825.



Methyl 2-(difluoromethyl)-1-(pyrimidin-2-yl)-1*H*-pyrrole-3-carboxylate (**5c**)

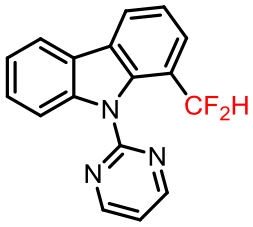
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (d, *J* = 4.8 Hz, 2H), 7.76 (t, *J* = 53.3 Hz, 1H), 7.69 (d, *J* = 3.3 Hz, 1H), 7.29 (t, *J* = 4.8 Hz, 1H), 6.74 (d, *J* = 3.3 Hz, 1H), 3.90 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -112.10 (s, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.12, 158.55, 156.45, 128.12 (t, *J* = 25.8 Hz), 124.14, 121.17 (t, *J* = 4.9 Hz), 119.31, 111.79, 108.11 (t, *J* = 235.9 Hz), 51.87. HRMS (ESI-TOF) m/z Calcd

for $C_{11}H_9F_2N_3O_2$ [M+H] $^+$: 254.0736, found: 254.0728.



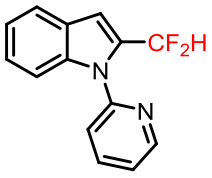
Methyl 2-(difluoromethyl)-4-methyl-1-(pyrimidin-2-yl)-1*H*-pyrrole-3-carboxylate (**5d**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (d, *J* = 4.8 Hz, 2H), 7.69 (t, *J* = 53.5 Hz, 1H), 7.50 (s, 1H), 7.23 (t, *J* = 4.8 Hz, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 2.25 (s, 3H), 1.40 (t, *J* = 7.1 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.46 (s, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.63, 158.43, 156.34, 127.66 (t, *J* = 26.6 Hz), 122.29, 121.89, 121.07 (t, *J* = 4.2 Hz), 118.79, 108.69 (t, *J* = 235.6 Hz), 60.67, 14.17, 11.72. HRMS (ESI-TOF) m/z Calcd for $C_{12}H_{11}F_2N_3O_2$ [M+H] $^+$: 268.0892, found: 268.0883.



1-(Difluoromethyl)-9-(pyrimidin-2-yl)-9*H*-carbazole (**5e**)

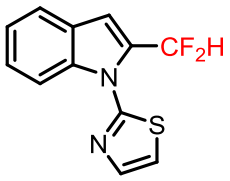
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.95 (d, *J* = 7.5 Hz, 1H), 8.86 (d, *J* = 4.8 Hz, 2H), 8.82 (d, *J* = 8.5 Hz, 1H), 8.25 (d, *J* = 8.0 Hz, 1H), 7.55 (q, *J* = 7.2 Hz, 3H), 7.45 – 7.29 (m, 2H), 7.21 – 7.14 (m, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -112.42 (s, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.66, 158.03, 139.65, 139.41, 127.10, 125.82, 123.34, 122.94 (t, *J* = 4.0 Hz), 122.65, 122.51 (t, *J* = 3.8 Hz), 119.97 (t, *J* = 8.7 Hz), 118.18, 116.73, 115.51, 114.78 (t, *J* = 238.2 Hz). HRMS (ESI-TOF) m/z Calcd for $C_{17}H_{11}F_2N_3$ [M+H] $^+$: 296.0994, found: 296.0983.



2-(Difluoromethyl)-1-(pyridin-2-yl)-1*H*-indole (**6a**)

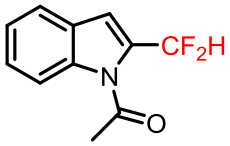
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, *J* = 3.4 Hz, 1H), 8.47 – 8.25 (m, 1H), 7.86 (td, *J* = 8.1, 1.9 Hz, 1H), 7.79 (d, *J* = 3.5 Hz, 1H), 7.50 (d, *J* = 8.2 Hz, 1H), 7.34 (m, 2H), 7.23 (dd, *J* = 7.1, 5.1

Hz, 1H), 7.11 – 6.80 (m, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -110.43 (s, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.10, 148.93, 138.75, 135.60, 127.21, 126.01 (t, *J* = 22.4 Hz), 122.63, 121.43, 120.62, 119.11 (t, *J* = 7 Hz), 115.70, 115.45 (t, *J* = 237.5 Hz), 114.94, 103.75. HRMS (ESI-TOF) m/z Calcd for $C_{14}H_{10}F_2N_2$ $[M+H]^+$: 245.0885, found: 245.0879.



2-(2-(Difluoromethyl)-1*H*-indol-1-yl) thiazole (**7a**)

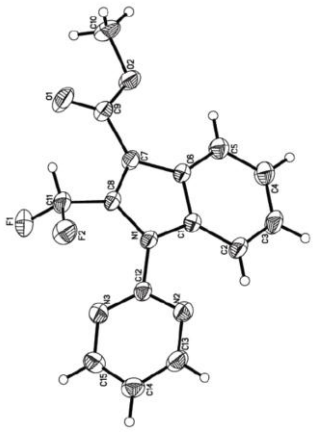
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.4 Hz, 1H), 7.73 – 7.68 (m, 2H), 7.55 – 7.32 (m, 3H), 7.30 – 7.25 (m, 1H), 7.08 (s, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -114.28 (s, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.52, 140.18, 137.41, 133.08 (t, *J* = 28.9 Hz), 127.40, 125.21, 122.55, 122.24, 117.55, 111.29, 109.82 (t, *J* = 236.2 Hz), 107.17 (t, *J* = 5.7 Hz). HRMS (ESI-TOF) m/z Calcd for $C_{12}H_8F_2N_2S$ $[M+H]^+$: 251.0449, found: 251.0444.



1-(2-(Difluoromethyl)-1*H*-indol-1-yl) ethan-1-one (**8a**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.5 Hz, 1H), 7.66 (d, *J* = 7.7 Hz, 1H), 7.42 (t, *J* = 7.8 Hz, 1H), 7.37 (t, *J* = 55.4 Hz, 1H), 7.32 (t, *J* = 7.9 Hz, 1H), 7.12 (s, 1H), 2.85 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.63 (s, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.21, 136.03, 134.15 (t, *J* = 28.9 Hz), 128.80, 126.07, 123.65, 122.72, 114.23, 111.57 (t, *J* = 7.3 Hz), 110.00 (t, *J* = 236.8 Hz), 26.89. HRMS (ESI-TOF) m/z Calcd for $C_{11}H_9F_2NO$ $[M+H]^+$: 210.0725, found: 210.0716.

2.3 The single crystal X-ray diffraction study of 3c



X-ray structure of **3c**

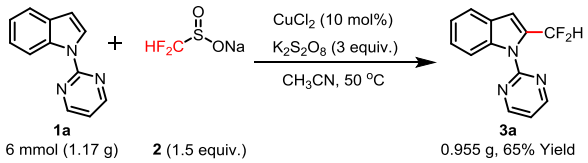
CCDC 1982943 (**3c**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via https://www.ccdc.cam.ac.uk/structures/.

Crystal Data and Structure Refinement for **3c**

Compound	**3c**
Formula	$C_{15}H_{11}F_2N_3O_2$
Formula weight	303.27
Crystal system	Triclinic
Space group	P -1
a (Å)	7.7930(16)
b (Å)	9.7180(19)
c (Å)	10.297(2)
α (Å)	99.54(3)
β (Å)	107.52(3)
γ (Å)	109.15(3)
Volume(Å3)	671.5(3)
Z	2
T (K)	293(2)
*D*calcd (g/m3)	1.500
F (000)	312
Reflections collected	2474
Unique reflections	1868

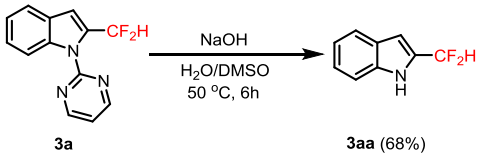
Goodness-of-fit on F2	1.009
*R*1[I> 2σ(I)]	0.0571
*wR*2[I>2σ(I)]	0.1569

2.4 Gram scale synthesis of 3a

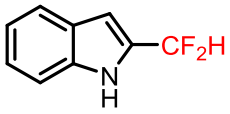


In a 100 mL sealed flask the substrate **1a** (6 mmol, 1.0 equiv.), HCF_2SO_2Na (9 mmol, 1.5 equiv.), $CuCl_2$ (10 mol %), $K_2S_2O_8$ (18 mmol, 3 equiv.) and 15 mL CH_3CN were added under air. The tube was capped and submerged into a pre-heated 50 ^oC oil bath. The reaction was stirred for 24h and cooled down to room temperature quenched with 20 mL water. Then the reaction mixture was extracted with EtOAc (3×20 mL). Combined organic phase dried over anhydrous Na_2SO_4 and concentrated *in vacuo*, and the resulting residue was purified by flash column chromatography using EtOAc/*n*-hexane (1:15) as the eluent to afford the product **3a** in 65% yield.

2.5 Procedure for removal of the directing Group [2], [3]



To a solution of 2-(difluoromethyl)-1-(pyrimidin-2-yl)-1*H*-indole **3a** (1 mmol, 1.0 eq) in DMSO (5.0 mL) was added NaOH (3 mmol, 3.0 eq) (20% wt. in H_2O) at room temperature under Ar atmosphere. After the mixture was stirred at 50 °C for 6 h, saturated NH_4Cl aq. was added at room temperature. Then, the reaction mixture was diluted with EtOAc (10 mL) and washed with H_2O (2 × 10 mL). The aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography using EtOAc/hexanes (1:8) as eluent to afford the desired product **3aa** in 68% yield.

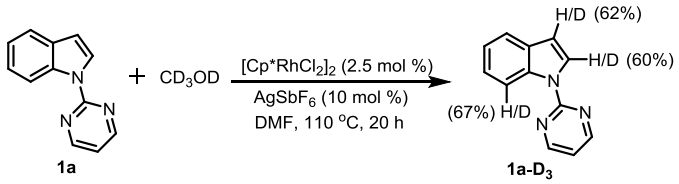


2-(Difluoromethyl)-1*H*-indole (**3aa**)

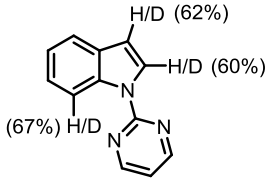
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.49 – 7.18 (m, 4H), 7.14 (t, *J* = 7.5 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.81 (s, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.46, 131.30 (t, *J* = 23.2 Hz), 128.45, 124.91, 121.35, 120.11, 112.01, 109.13 (t, *J* = 234.6 Hz), 107.62 – 107.36 (m).

2.6 Kinetic isotope effect studies

2.6.1 Synthesis of 1a-D_3

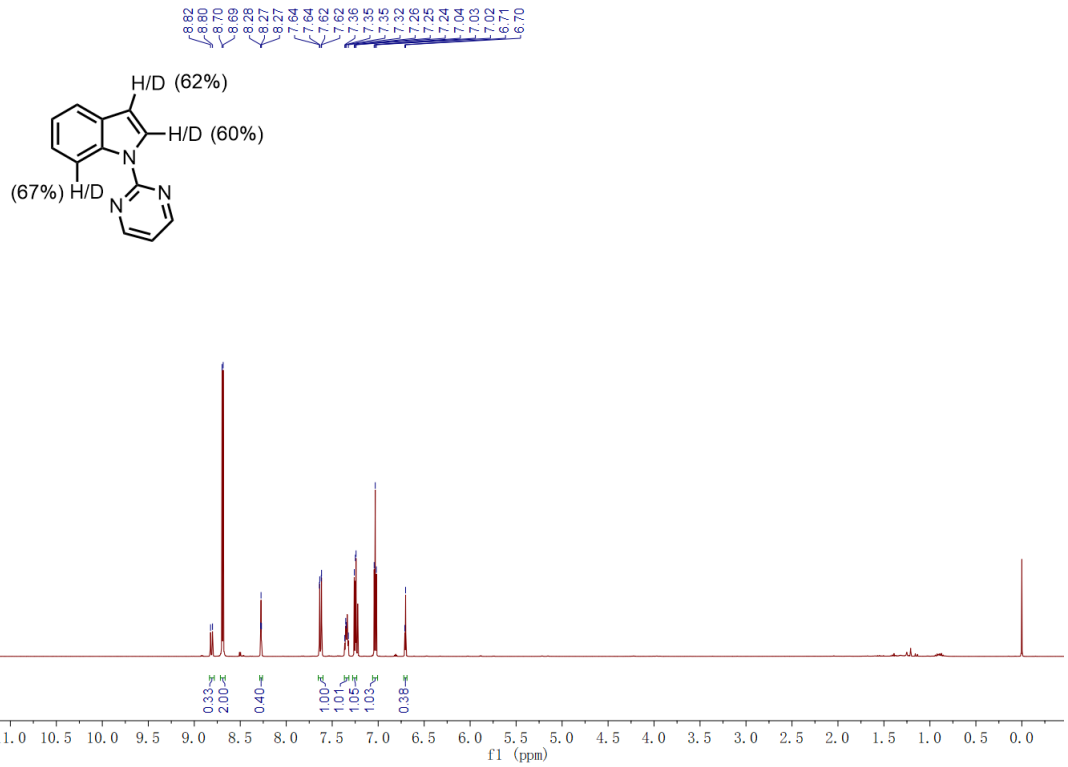


To an oven-dried sealed tube charged with 1-(pyrimidin-2-yl)-1*H*-indole **1a** (117.1 mg, 0.6 mmol, 100 mol %), $[RhCp^*Cl_2]_2$ (18.5 mg, 0.03 mmol, 5 mol %), and $AgSbF_6$ (41.2 mg, 0.12 mmol, 20 mol %), in DCE (3 mL) was added CD_3OD (0.48 mL, 12 mmol, 20 equiv.) under N_2-atmosphere. The reaction mixture stired at 110 °C for 20 h and cooled to room temperature. The reaction mixture was diluted with EtOAc (3 mL) and concentrated in vacuo. The residue was purified by flash column chromatography using EtOAc/hexanes (1:6) as eluent to afford the desired product **1a-D_3**.

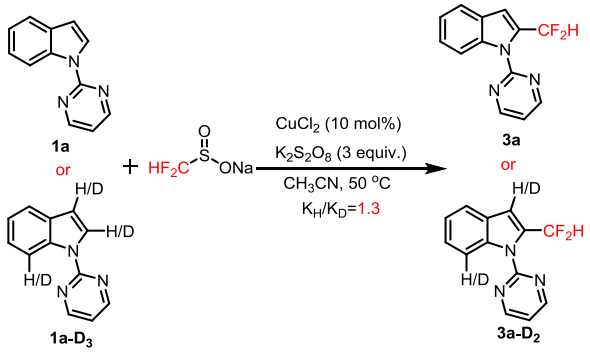


1-(Pyrimidin-2-yl)-1*H*-2,3,7-trideuterioindole (**1a-D_3**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (d, *J* = 8.4 Hz, 0.33H), 8.69 (d, *J* = 4.8 Hz, 2H), 8.27 (t, *J* = 1.8 Hz, 0.4H), 7.63 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.39 – 7.32 (m, 1H), 7.29 – 7.23 (m, 1H), 7.03 (t, *J* = 4.8 Hz, 1H), 6.71 (d, *J* = 3.4 Hz, 0.38H).

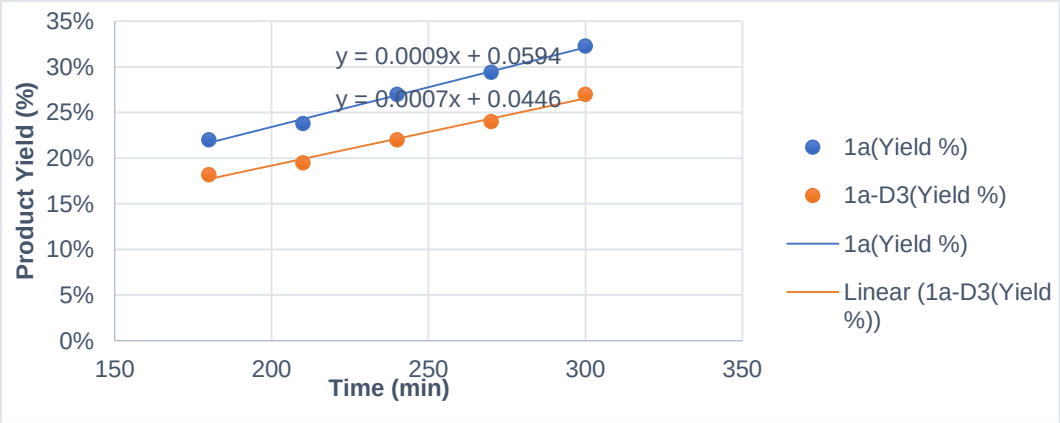


2.6.2 Kinetic isotope effect studies between 1a and 1a-D_3



In a 15 mL sealed tube substrate **1a** (0.2 mmol) or **1a-D_3** (0.2 mmol), CF_2HSO_2Na (0.3mmol, 1.5 equiv.), $CuCl_2$ (2.7 mg, 10 mol %), $K_2S_2O_8$ (162.2 mg, 0.6 mmol, 3 equiv.) and 2 mL CH_3CN were added under air. The tubes were capped with rubber plugs and submerged into a pre-heated 50 ^oC oil bath. A periodic aliquot (100 μl) was removed by a syringe and concentrated, ^1H NMR analysis using dibromomethane as an internal standard to provide the following conversions:

Time /(min)	180	210	240	270	300
Yield of **1a**/(%)	22.0	23.8	27	29.4	32.3
Yield of **1a-D_3**/(%)	18.2	19.5	22	24	27



The KIE value was calculated as k_H/k_D = 1.3.

3. References

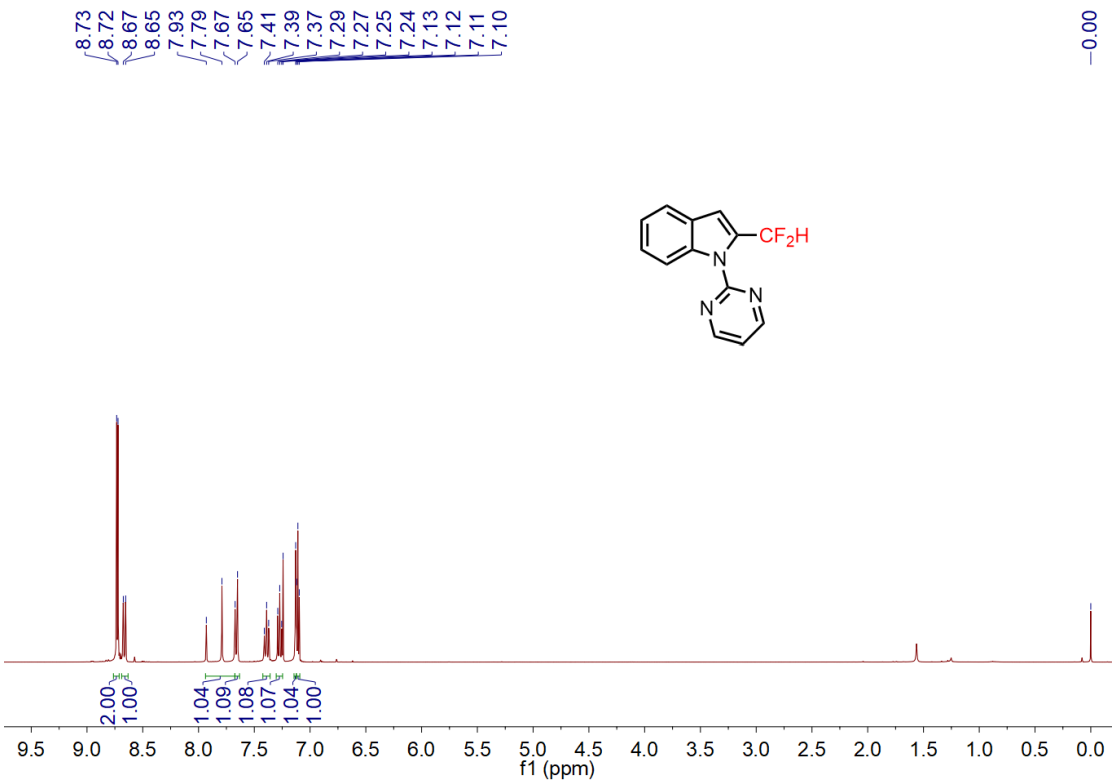
[1] L. Ackermann and A. V. Lygin, *Org. Lett.*, 2011, **13**, 3332-3335.

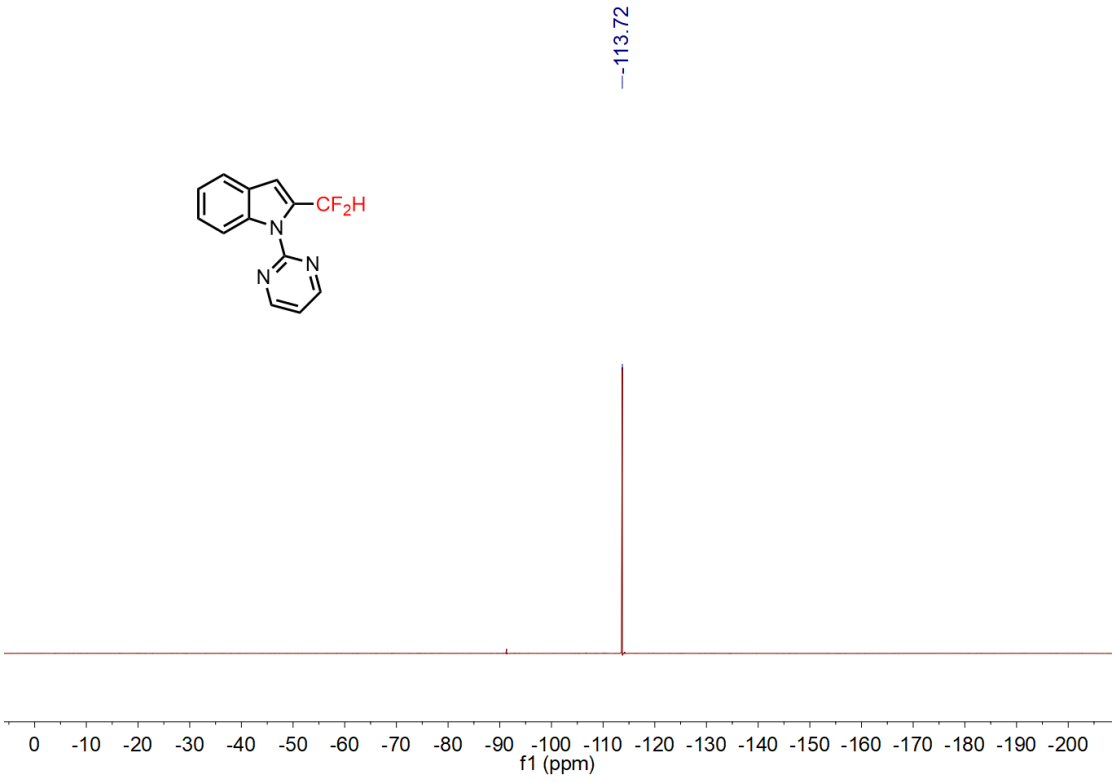
[2] T. Jeong, S. Han, N. K. Mishra, S. Sharma, S.-Y. Lee, J. S. Oh, J. H. Kwak, Y. H. Jung and I. S. Kim, *J. Org. Chem.*, 2015, **80**, 7243-7250.

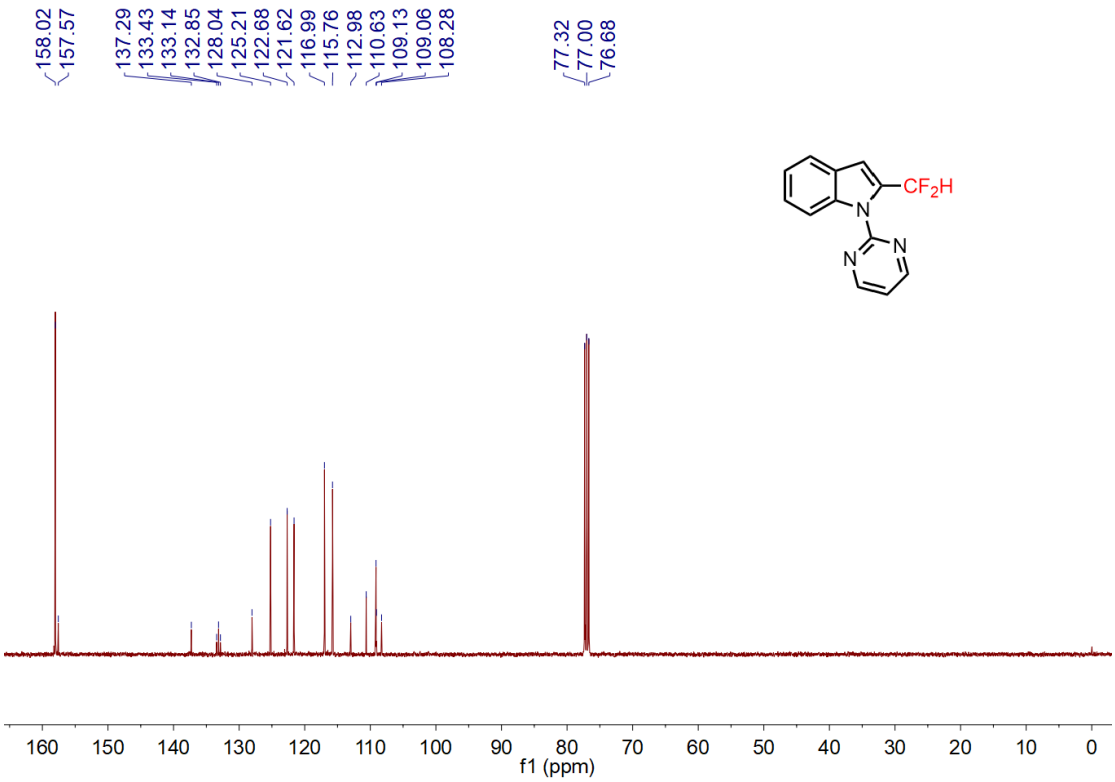
[3] T. Yoshino, H. Ikemoto, S. Matsunaga and M. Kanai, *Chem. Eur. J.*, 2013, **19**, 9142-9146.

4. ^{1}H NMR, ^{19}F NMR and ^{13}C NMR spectra

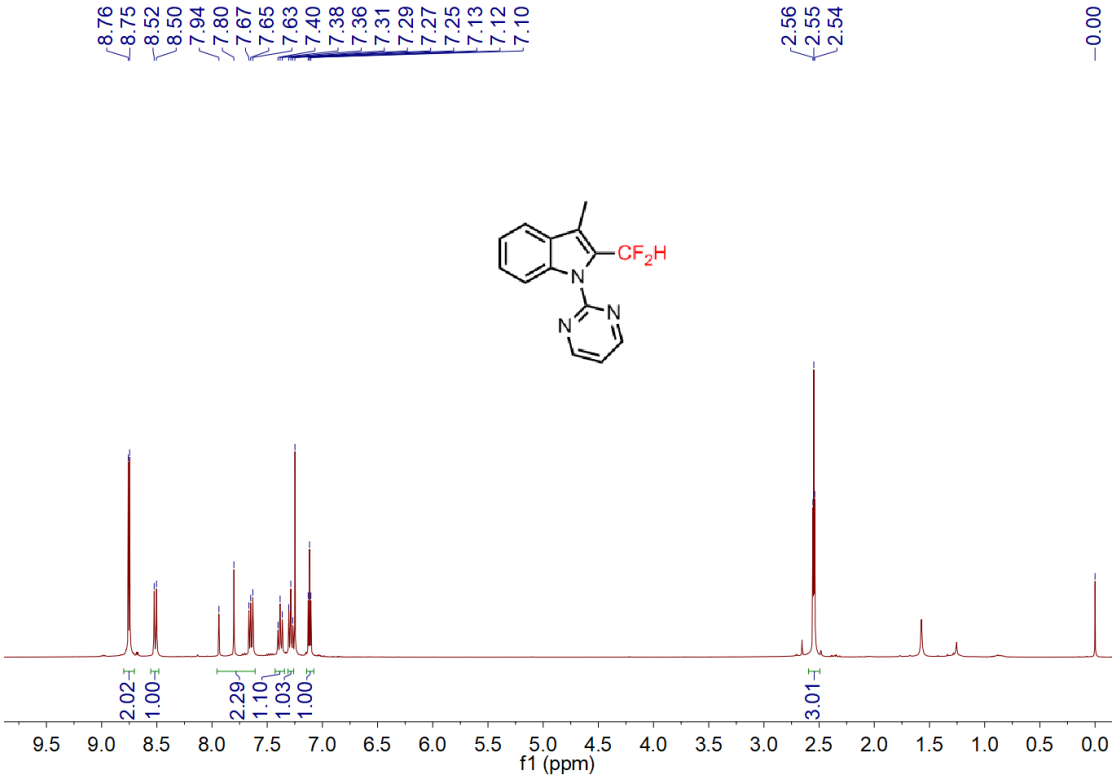
2-(Difluoromethyl)-1-(pyrimidin-2-yl)-1*H*-indole (**3a**)

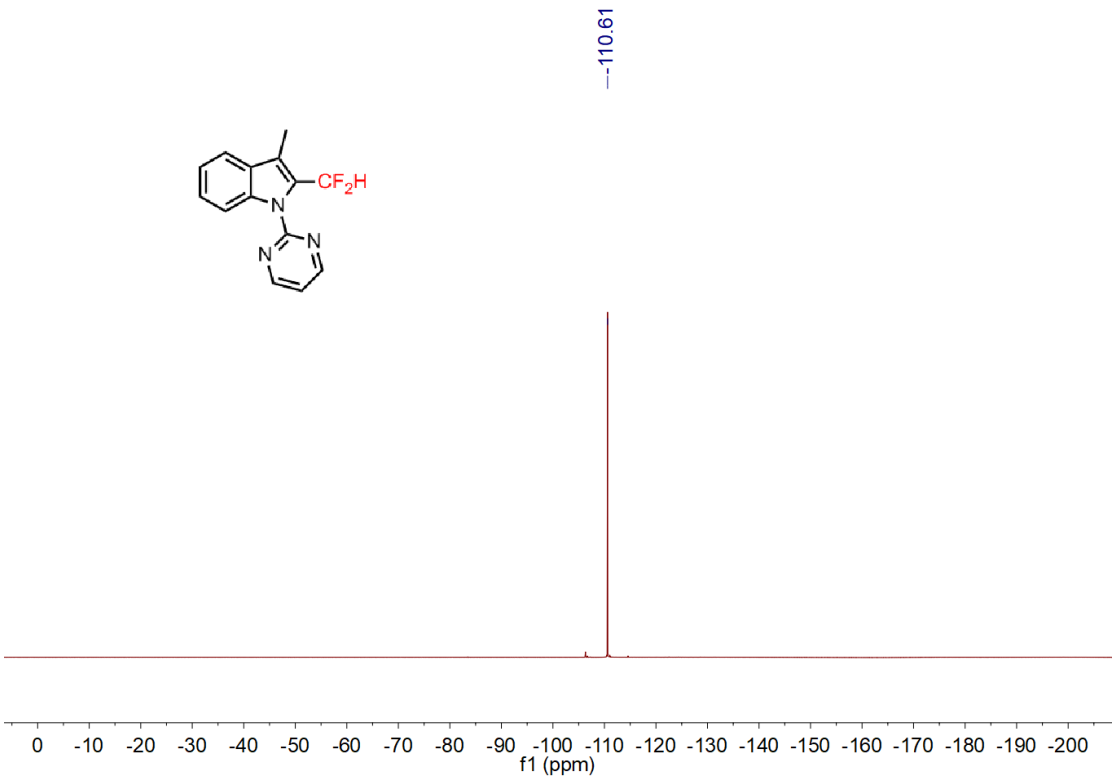

8.73
8.72
8.67
8.65
7.93
7.79
7.67
7.65
7.41
7.39
7.37
7.29
7.27
7.25
7.24
7.13
7.12
7.11
7.10
0.00
CF2H
N
N
N
2.00
1.00
1.04
1.09
1.08
1.07
1.04
1.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

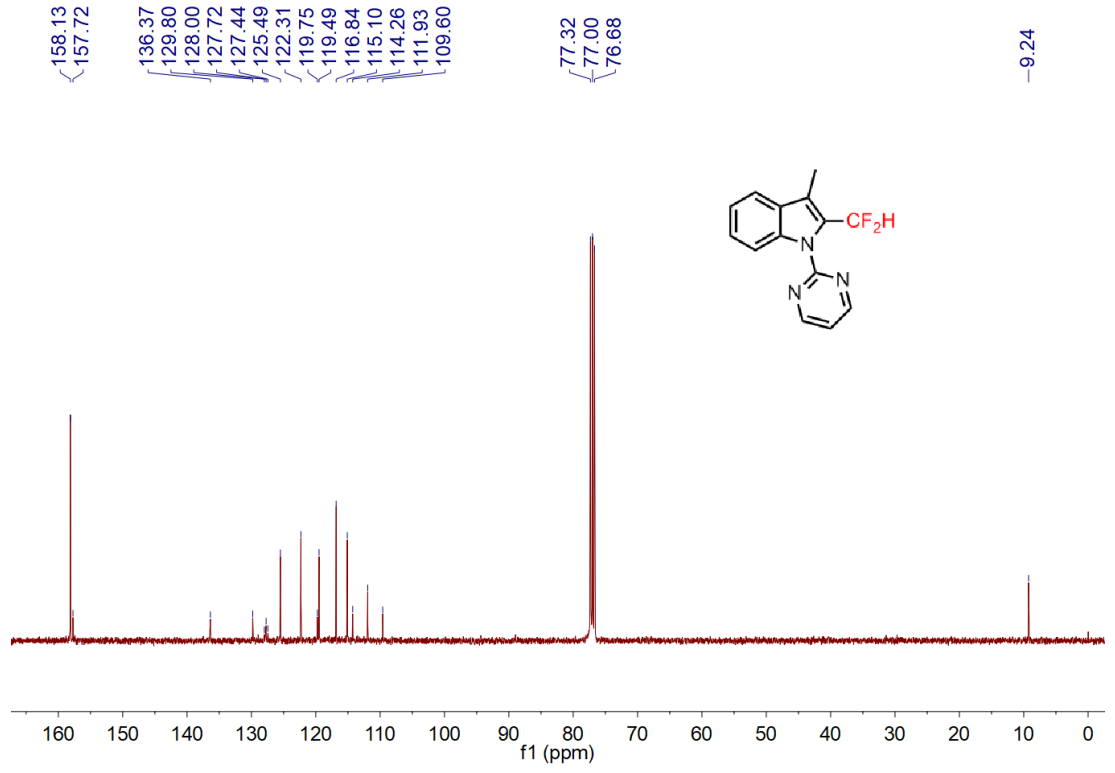

-113.72
CF2H
N
N
N
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)



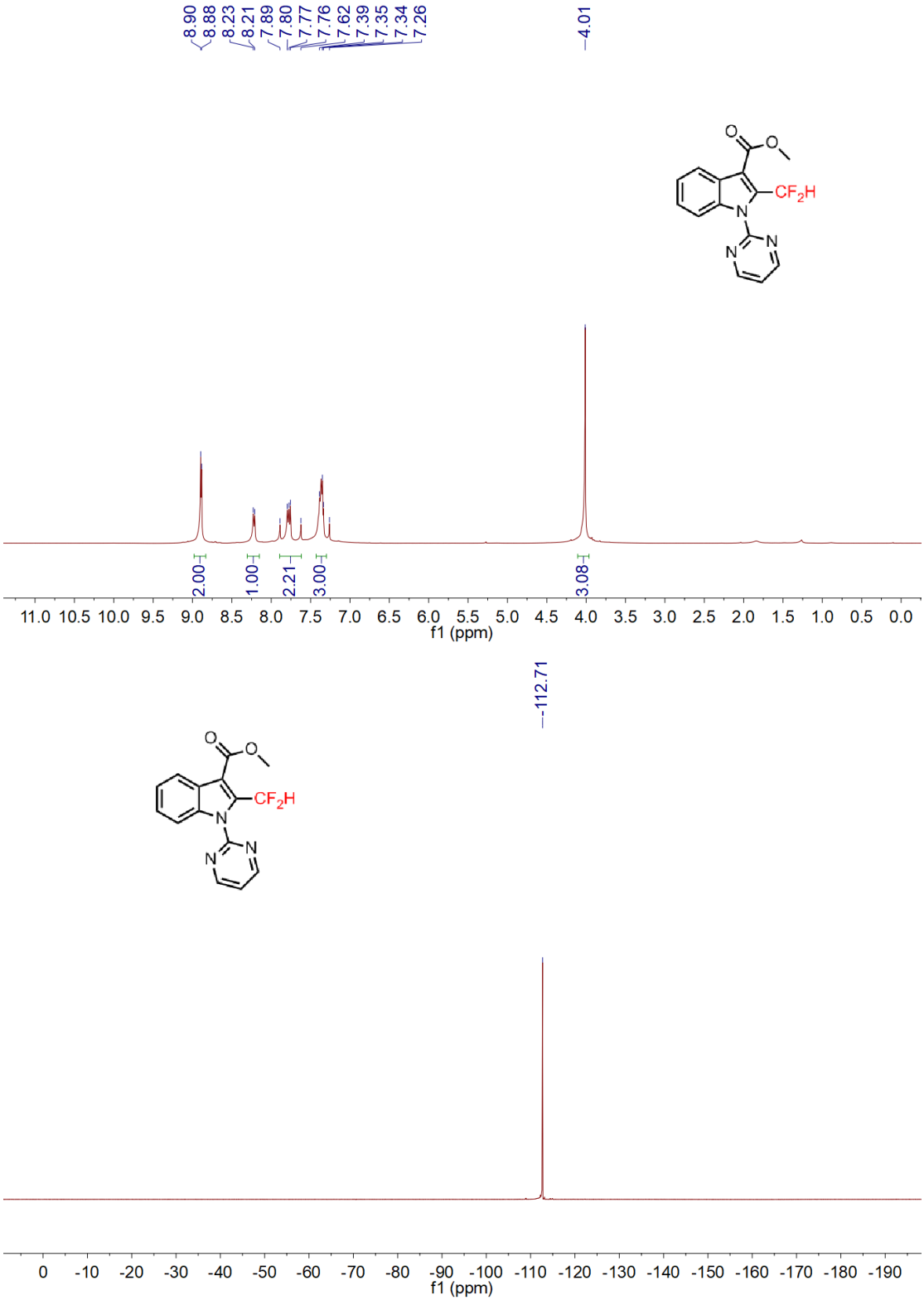
2-(Difluoromethyl)-3-methyl-1-(pyrimidin-2-yl)-1*H*-indole (**3b**)

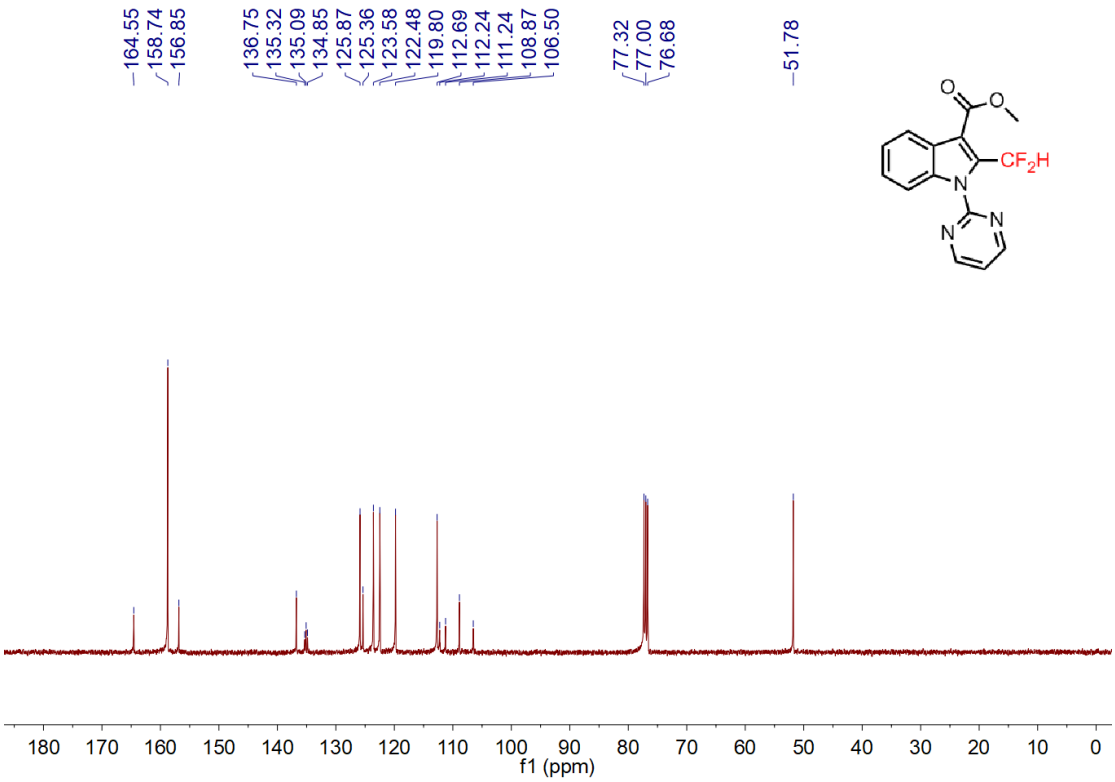



-110.61
CF2H
N
N
N
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

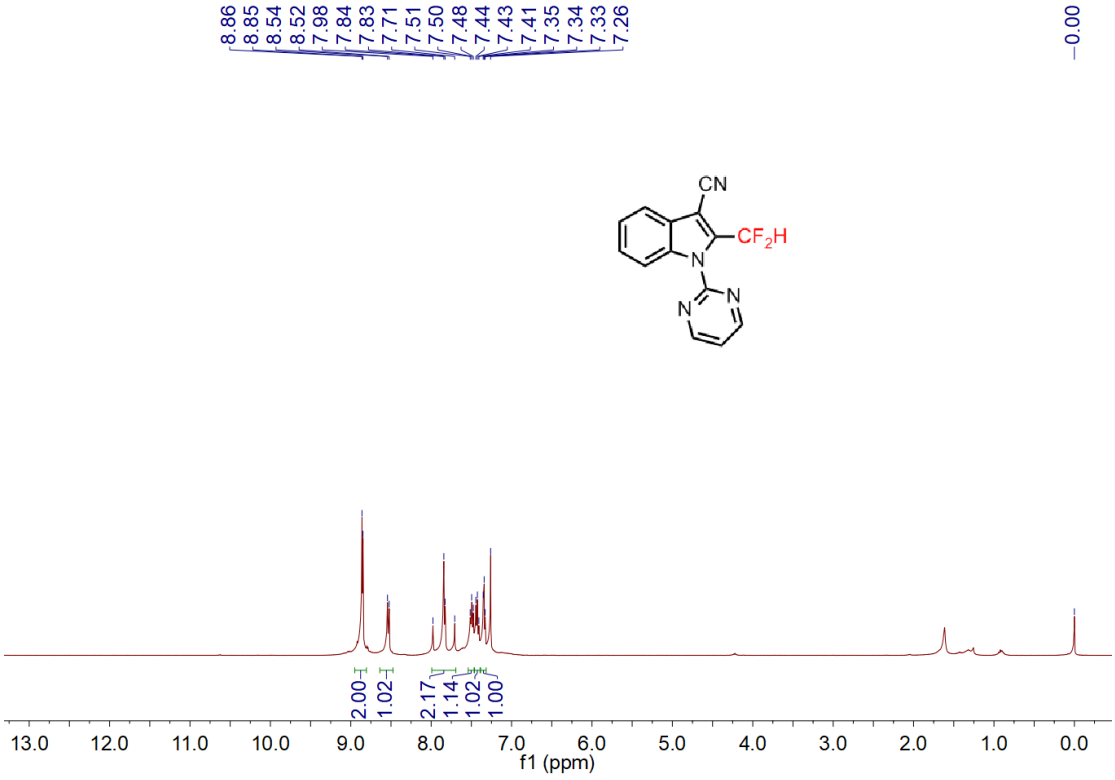

158.13
157.72
136.37
129.80
128.00
127.72
127.44
125.49
122.31
119.75
119.49
116.84
115.10
114.26
111.93
109.60
77.32
77.00
76.68
-9.24
CF2H
N
N
N
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

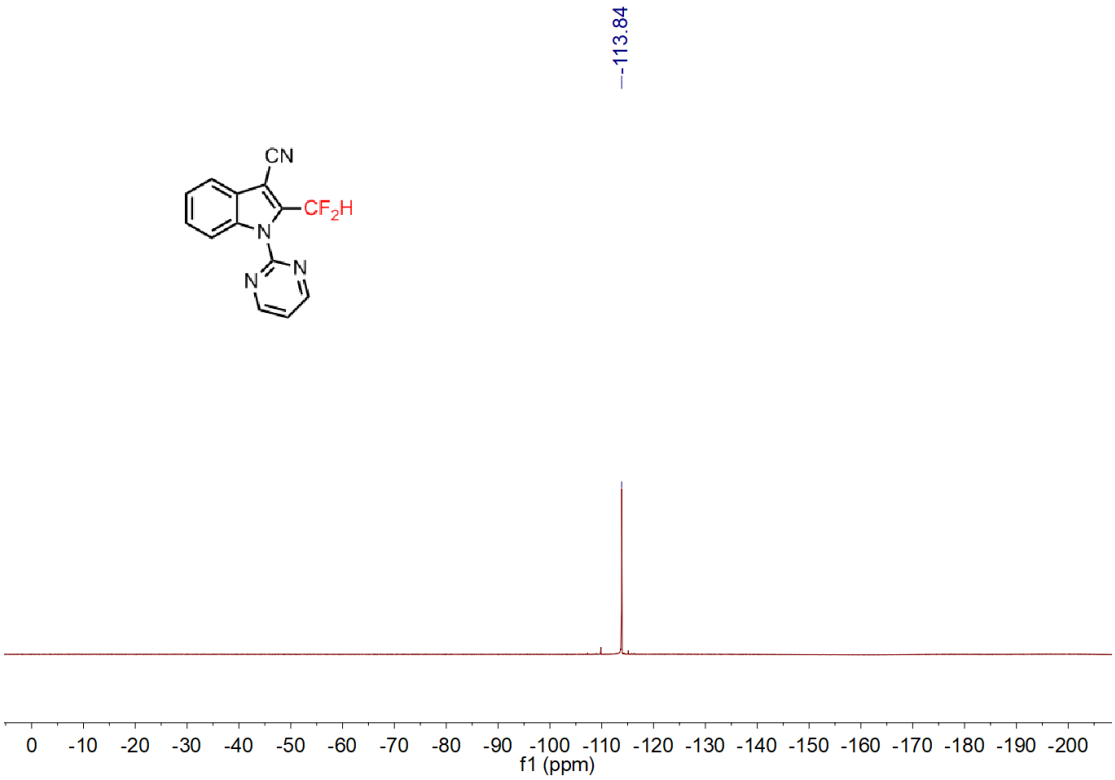
Methyl 2-(difluoromethyl)-1-(pyrimidin-2-yl)-1*H*-indole-3-carboxylate (**3c**)

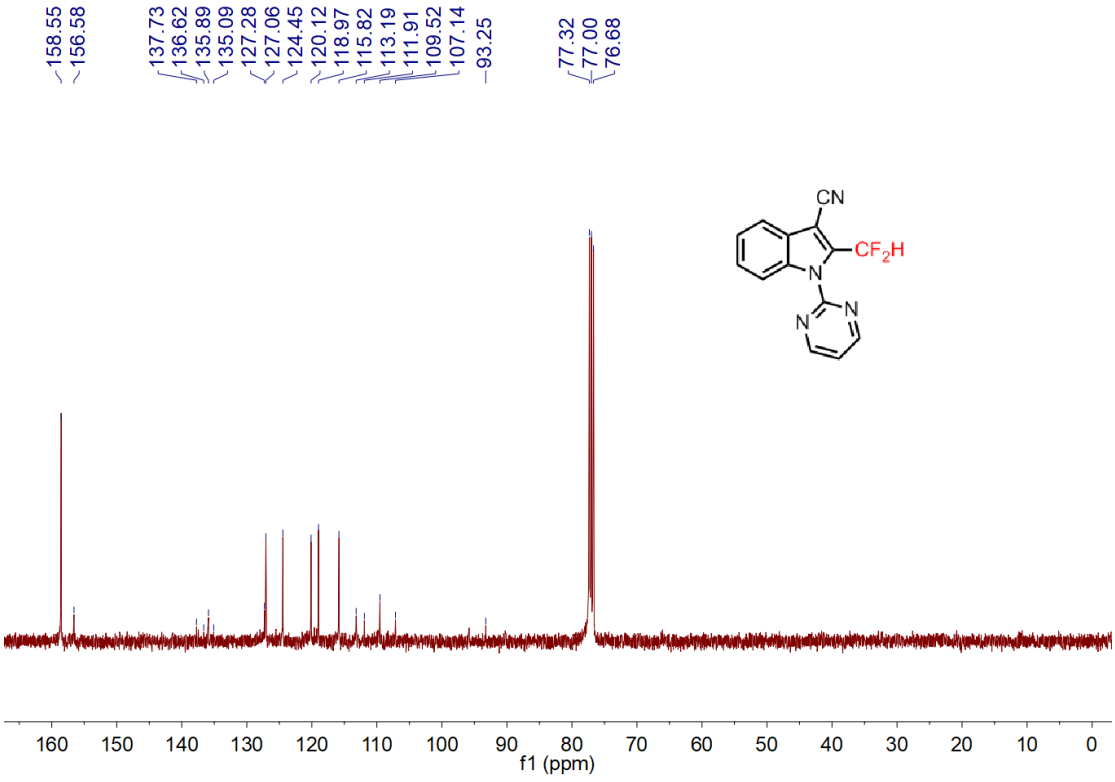




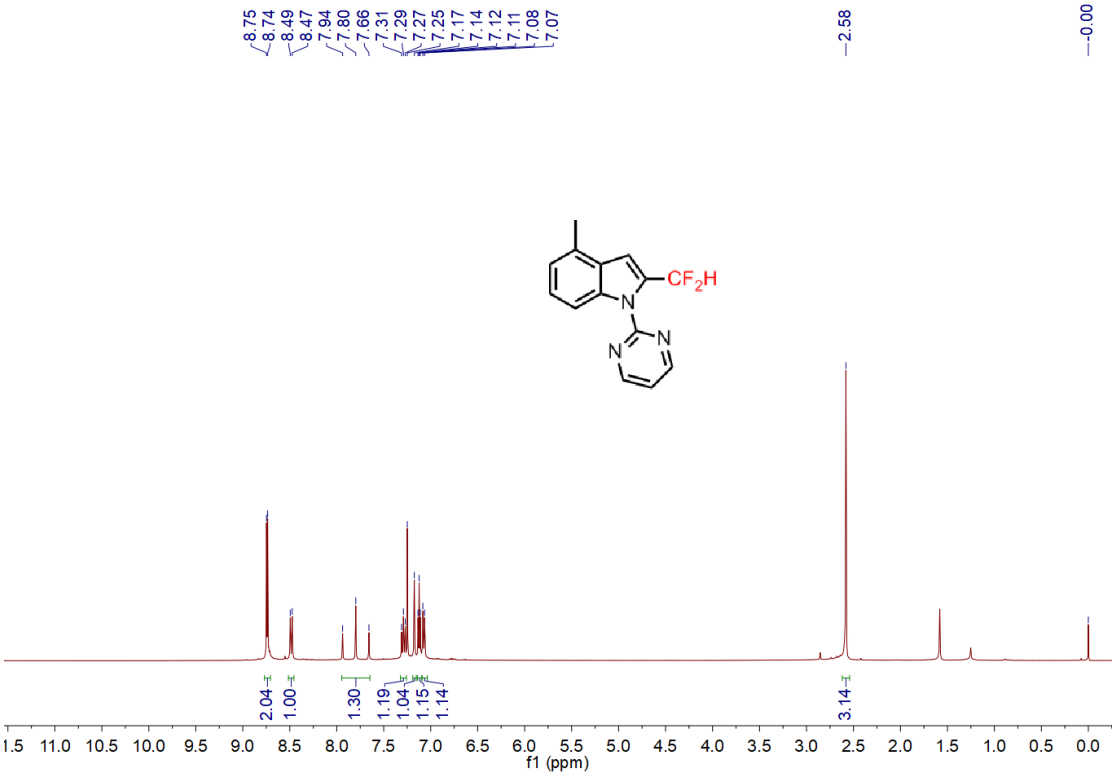
2-(Difluoromethyl)-1-(pyrimidin-2-yl)-1*H*-indole-3-carbonitrile (**3d**)

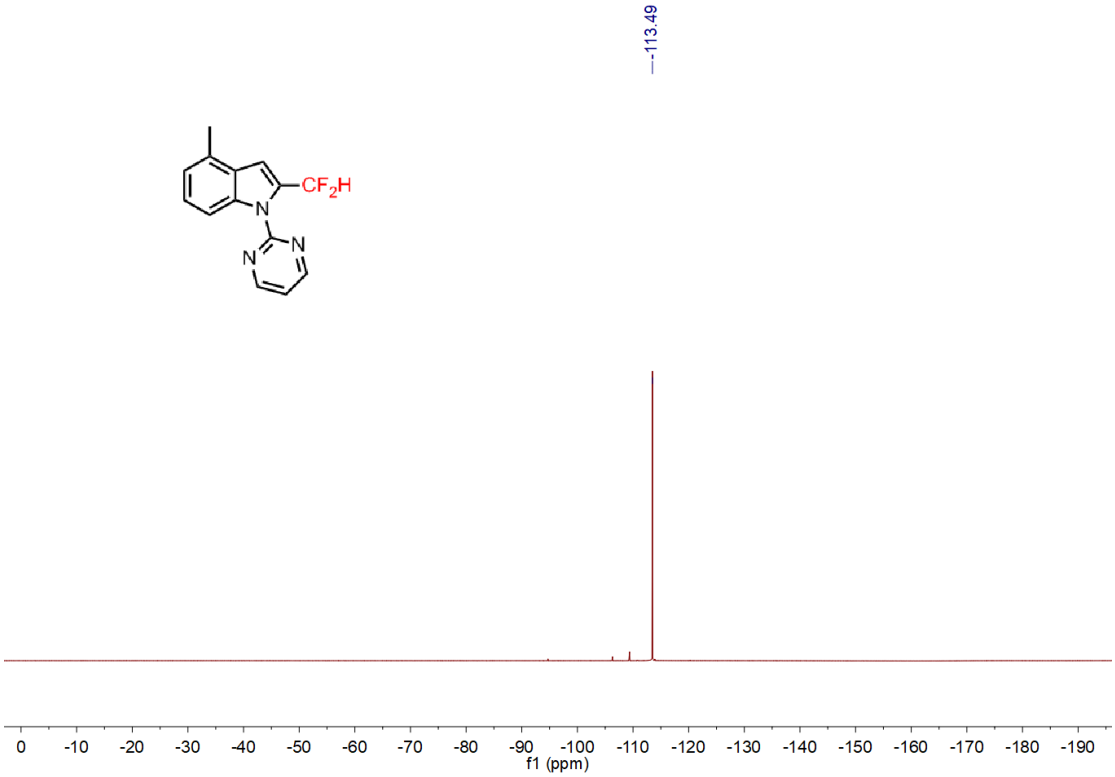


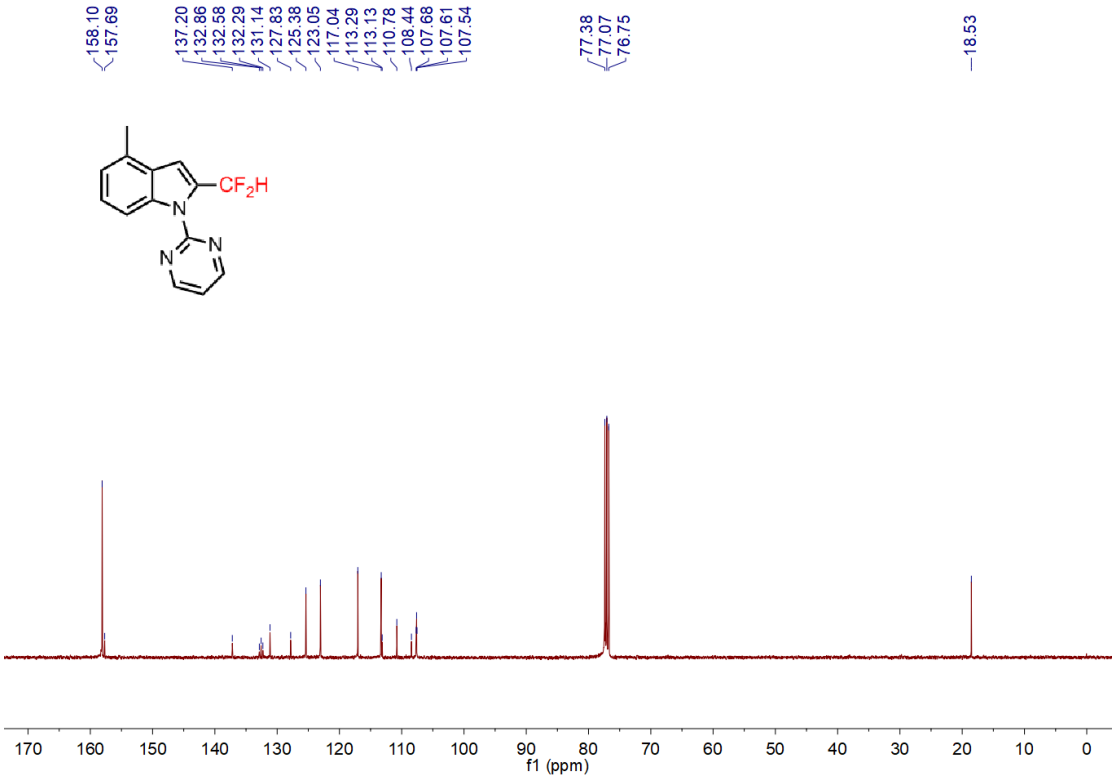

-113.84
CN
CF2H
N
N
N
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)


158.55
156.58
137.73
136.62
135.89
135.09
127.28
127.06
124.45
120.12
118.97
115.82
113.19
111.91
109.52
107.14
93.25
77.32
77.00
76.68
CN
CF2H
N
N
N
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

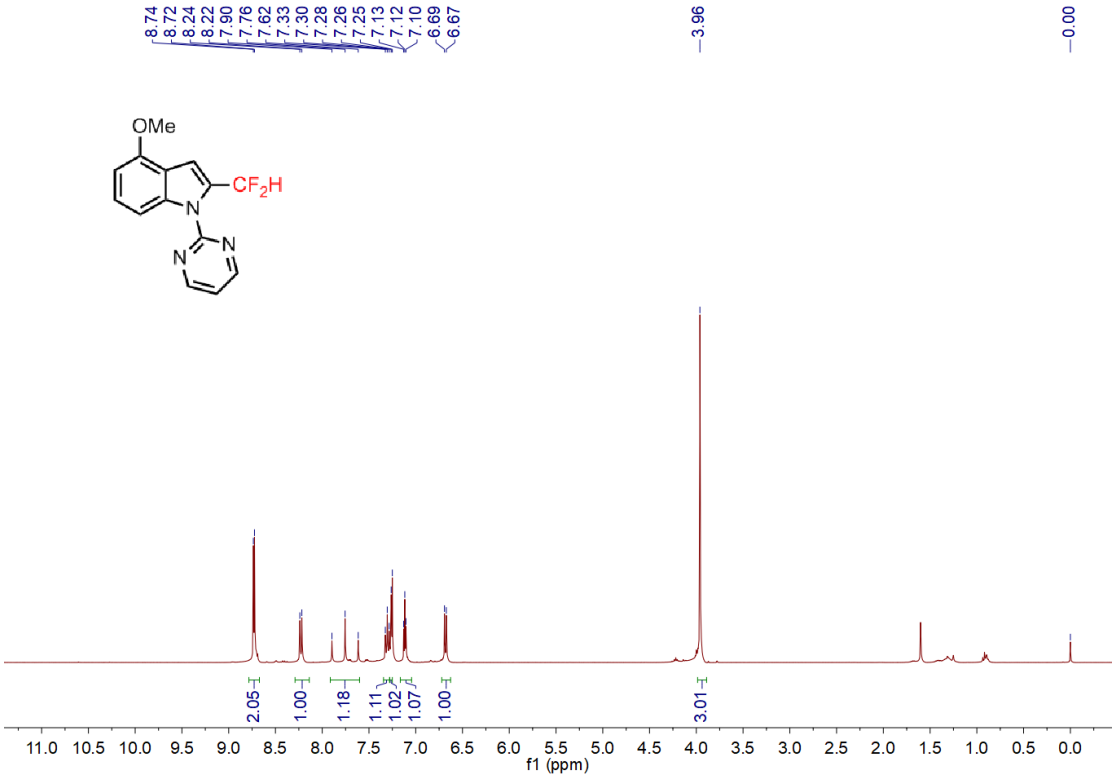
2-(Difluoromethyl)-4-methyl-1-(pyrimidin-2-yl)-1*H*-indole (**3e**)

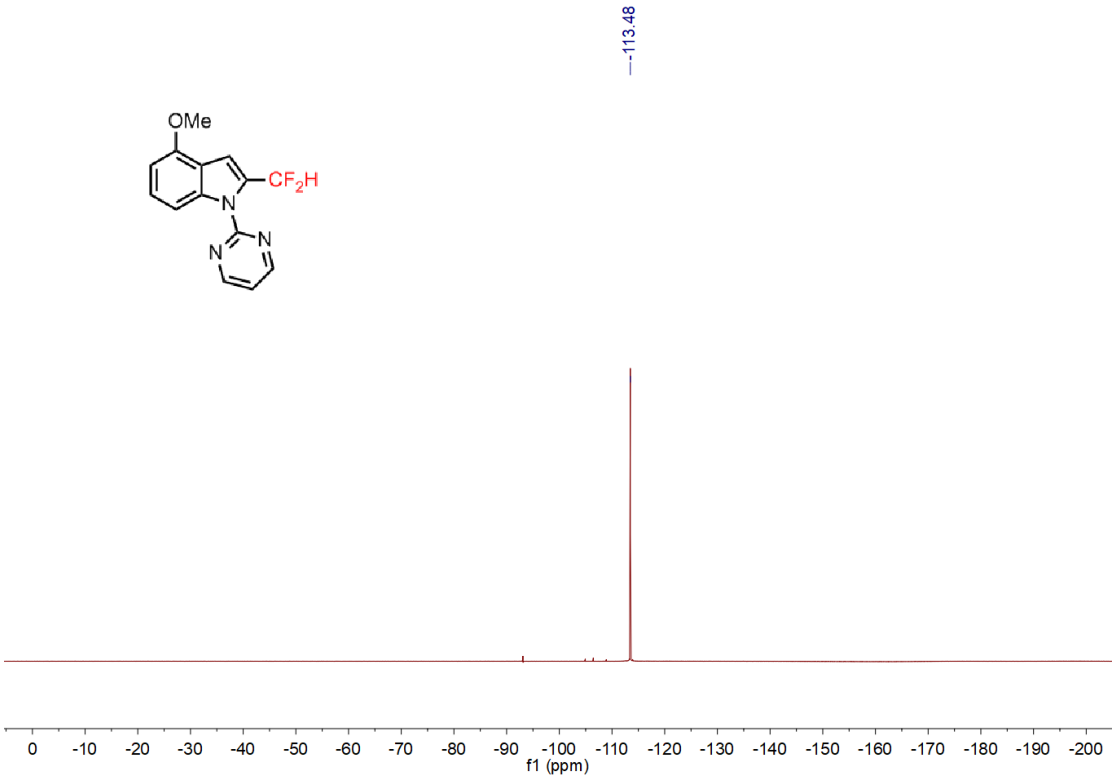


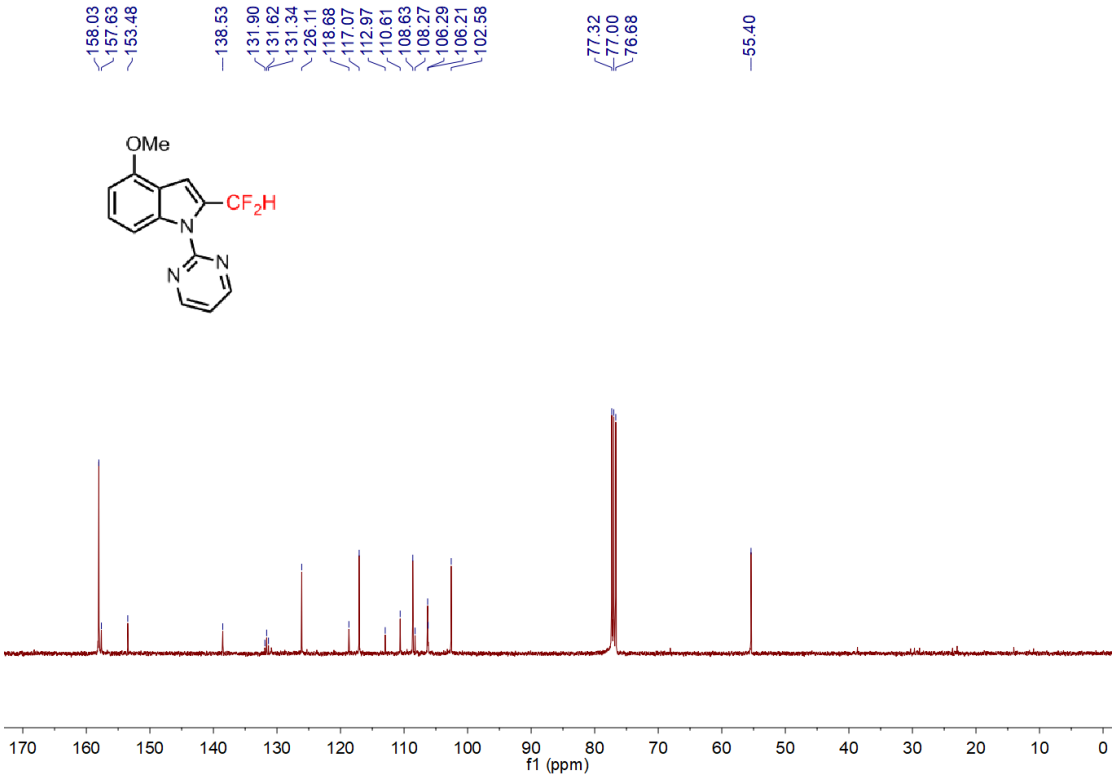




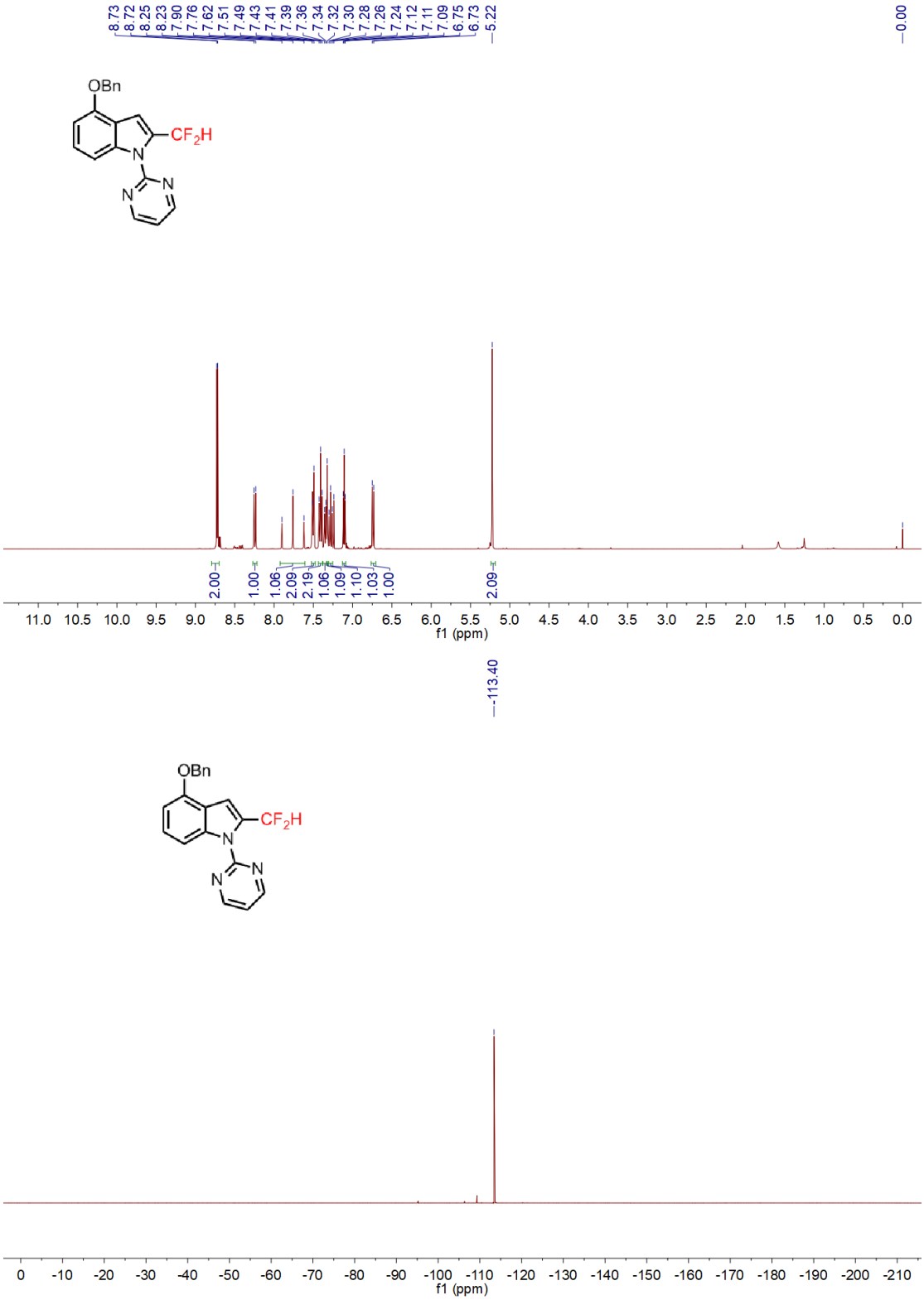
2-(Difluoromethyl)-4-methoxy-1-(pyrimidin-2-yl)-1*H*-indole (**3f**)

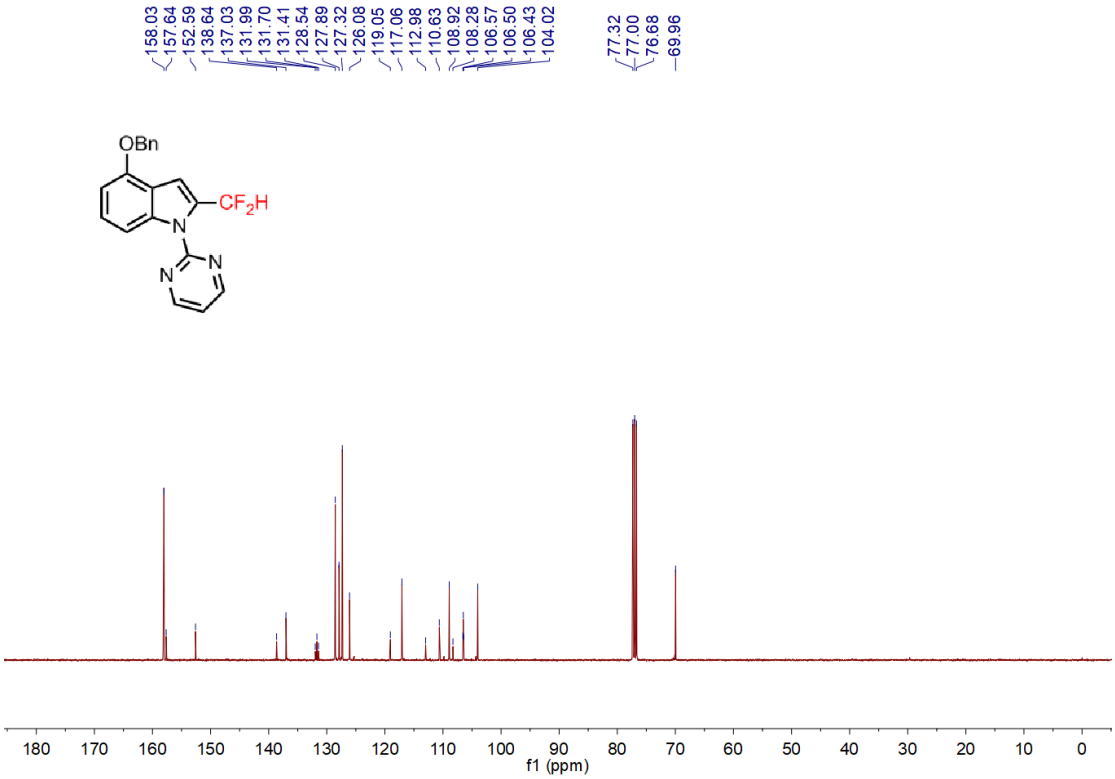



-113.48
OMe
CF2H
N
N
N
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

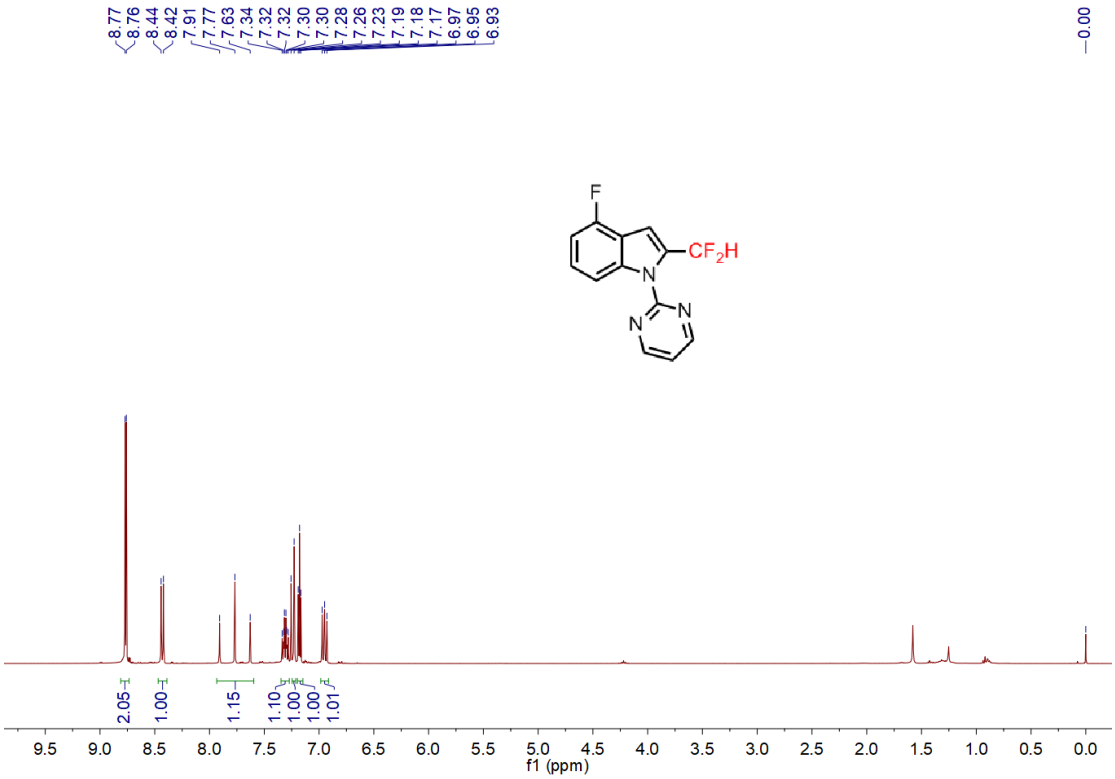

158.03
157.63
153.48
138.53
131.90
131.62
131.34
126.11
118.68
117.07
112.97
110.61
108.63
108.27
106.29
106.21
102.58
77.32
77.00
76.68
55.40
OMe
CF2H
N
N
N
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

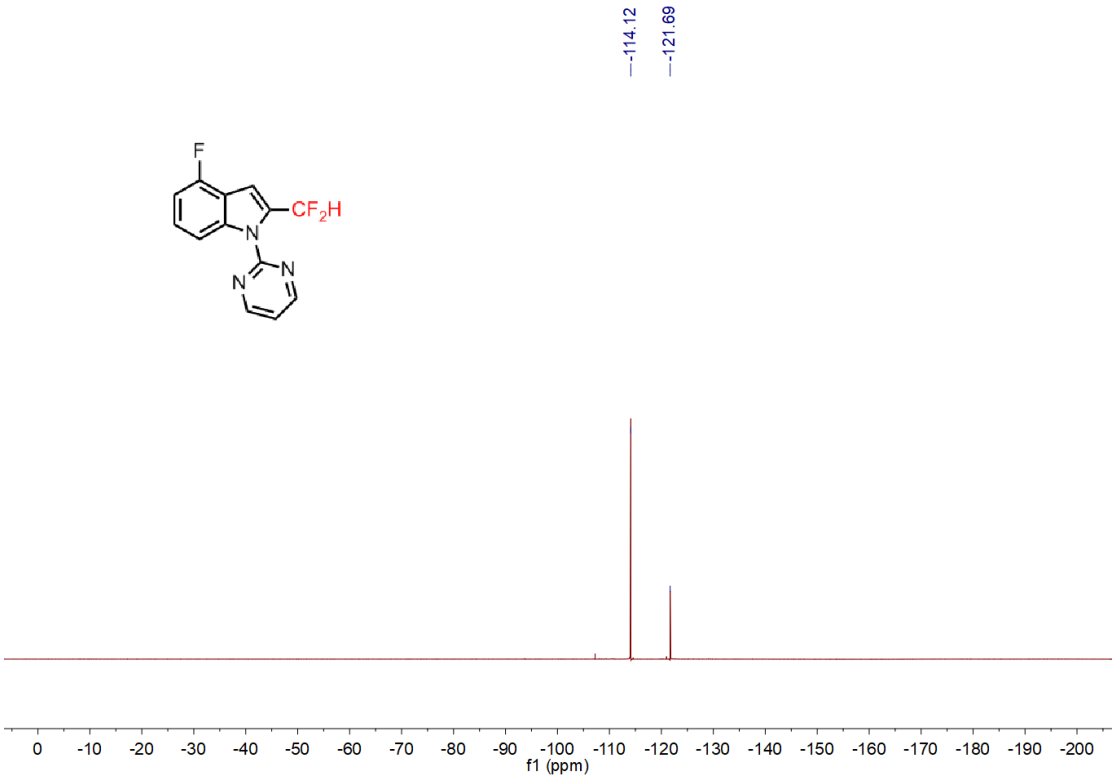
4-(Benzyloxy)-2-(difluoromethyl)-1-(pyrimidin-2-yl)-1*H*-indole (**3g**)

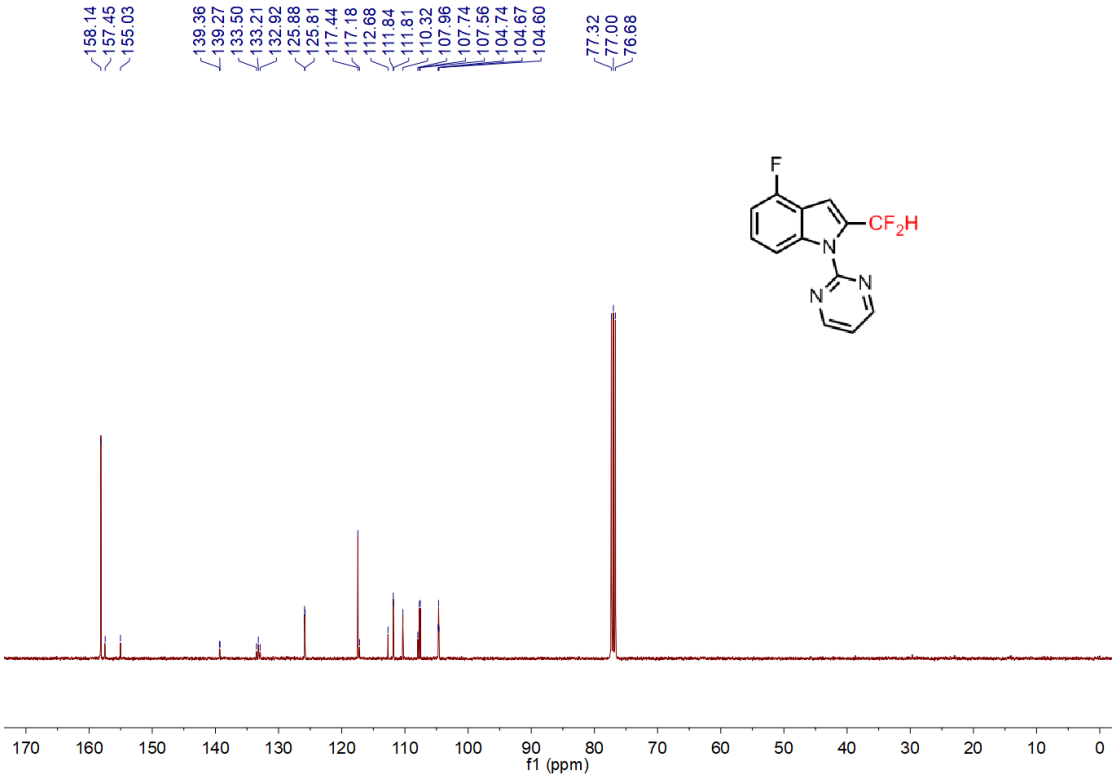




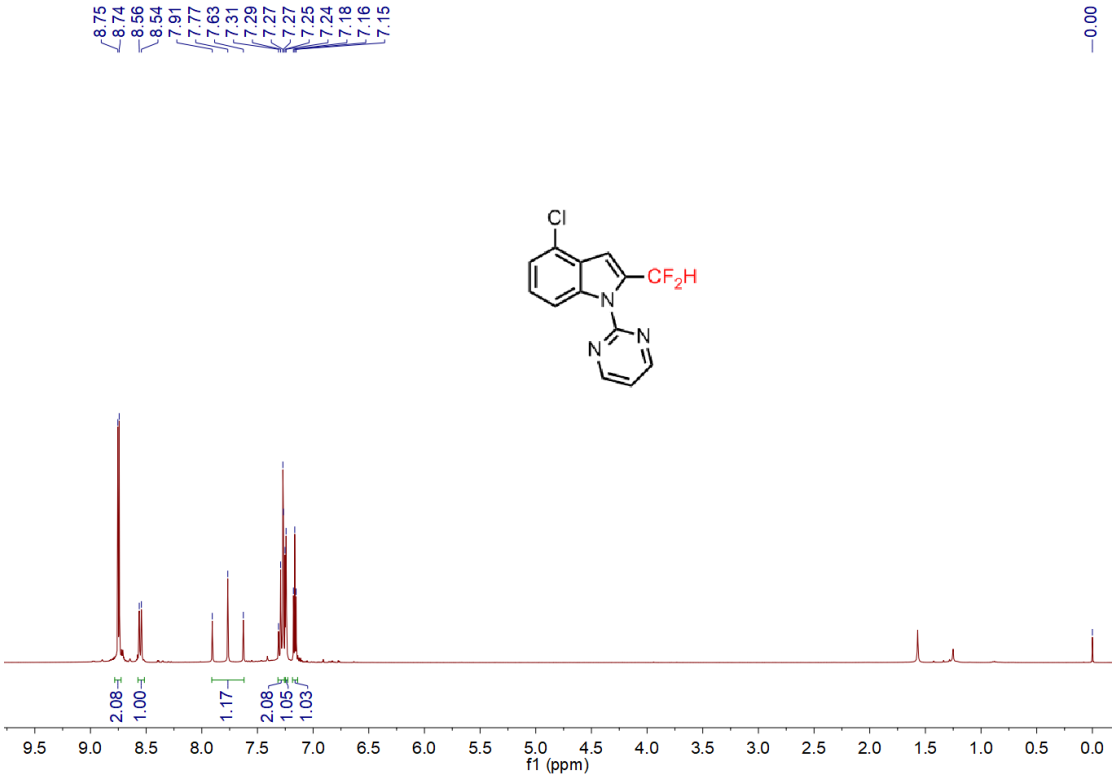
2-(Difluoromethyl)-4-fluoro-1-(pyrimidin-2-yl)-1*H*-indole (**3h**)

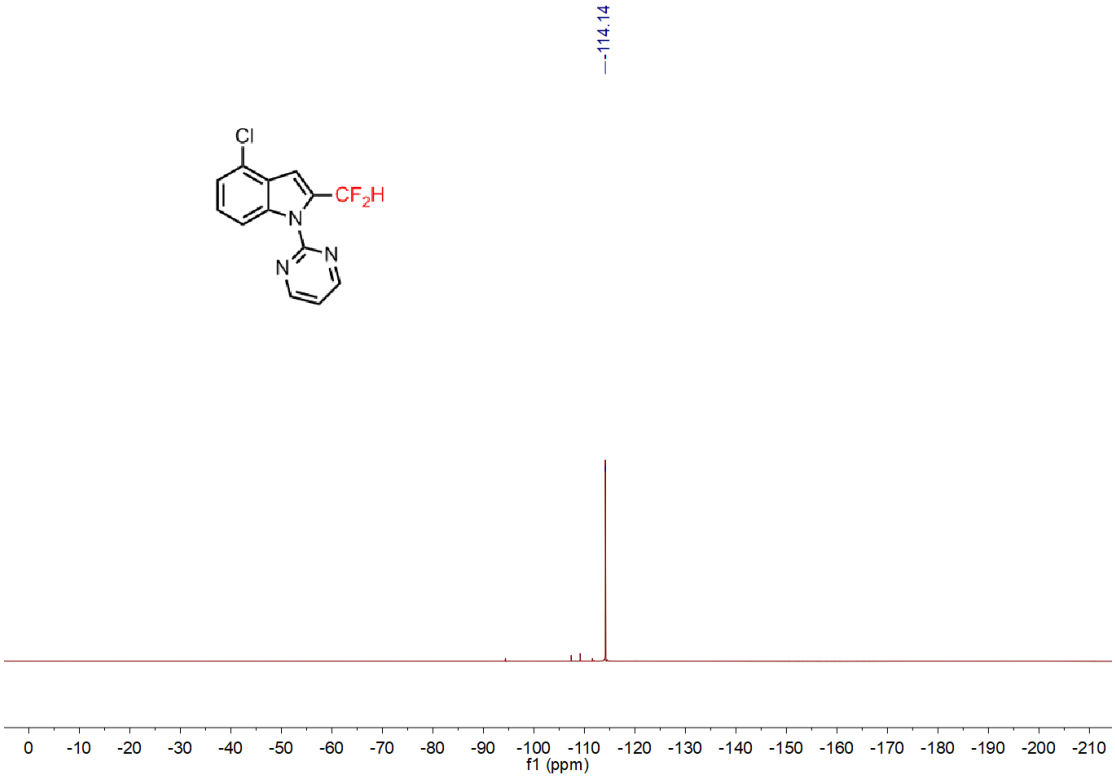


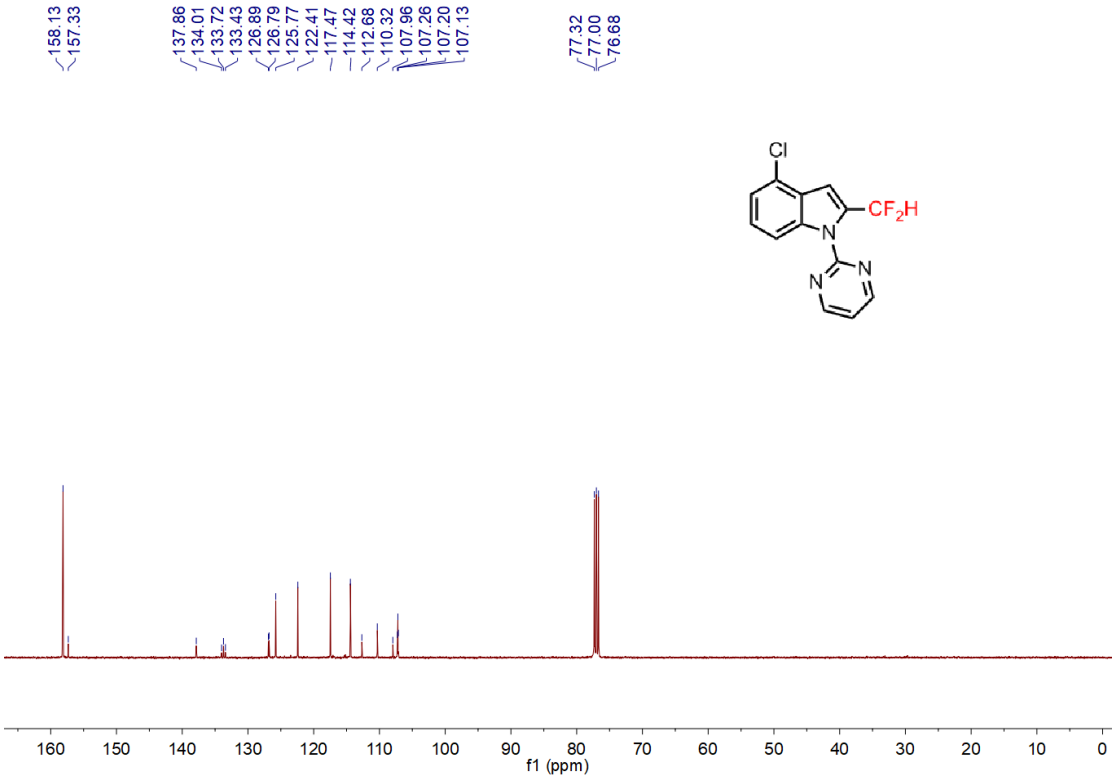

-114.12
-121.69
F
CF2H
N
N
N
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)


158.14
157.45
155.03
139.36
139.27
133.50
133.21
132.92
125.88
125.81
117.44
117.18
112.68
111.84
111.81
110.32
107.96
107.74
107.56
104.74
104.67
104.60
77.32
77.00
76.68
F
CF2H
N
N
N
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

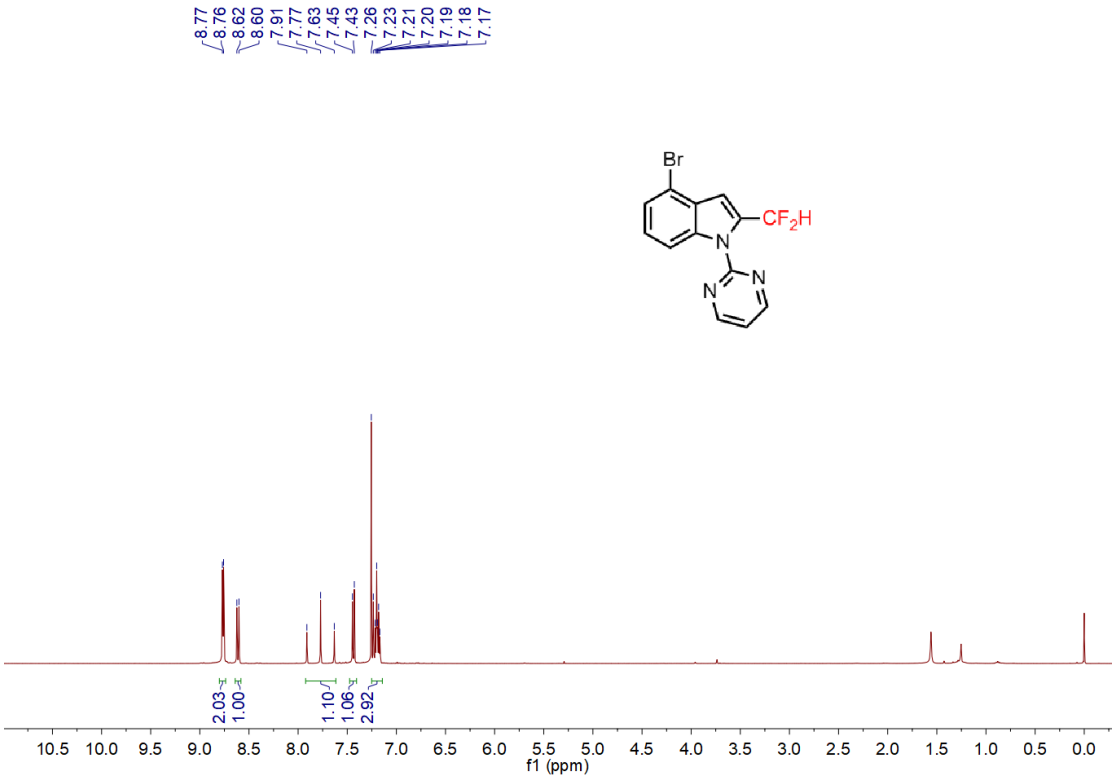
4-Chloro-2-(difluoromethyl)-1-(pyrimidin-2-yl)-1*H*-indole (**3i**)

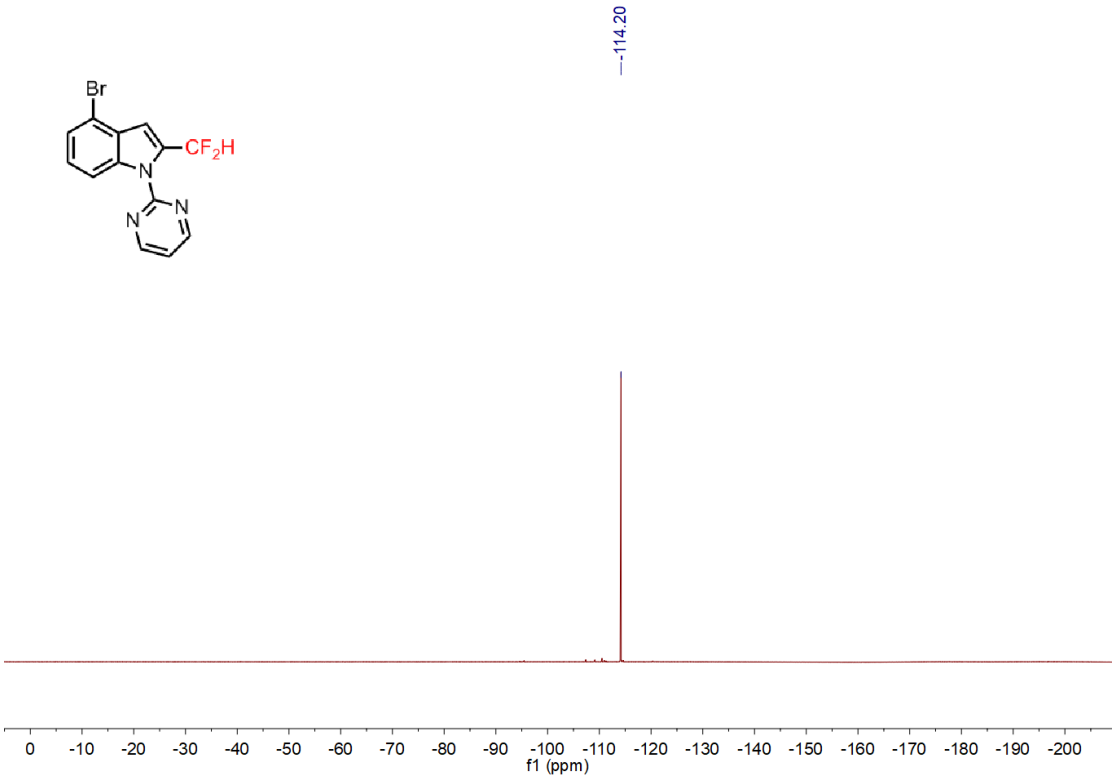


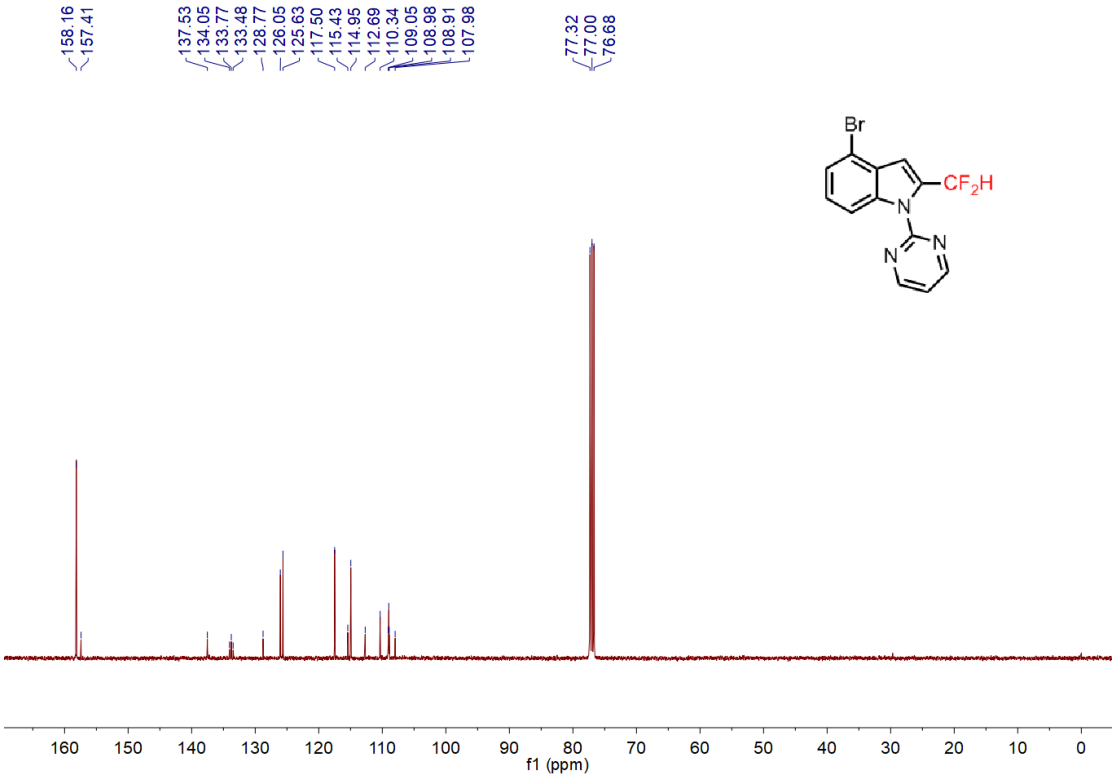




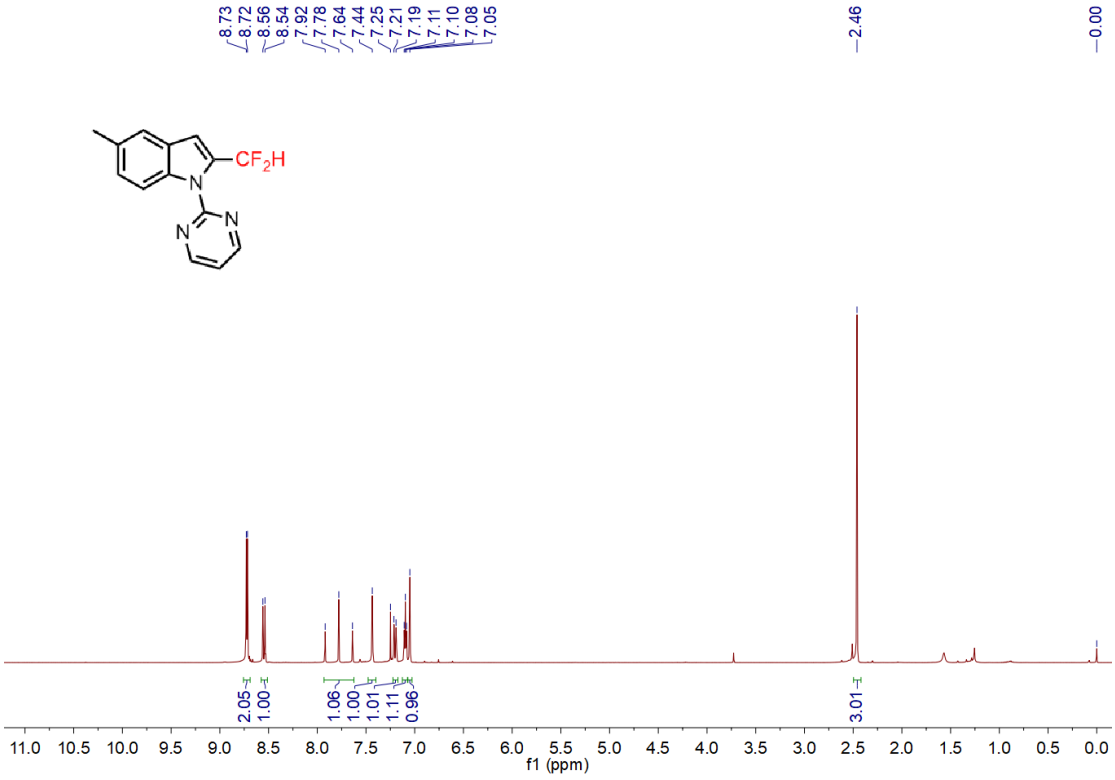
4-Bromo-2-(difluoromethyl)-1-(pyrimidin-2-yl)-1*H*-indole (**3j**)

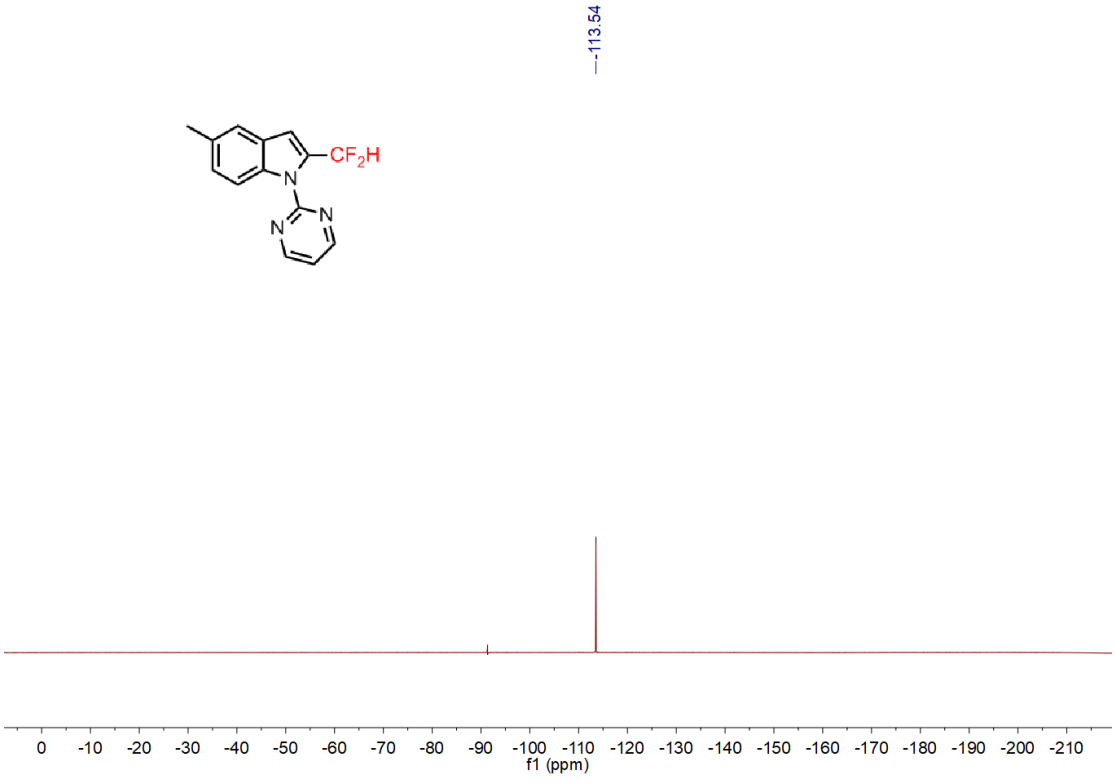


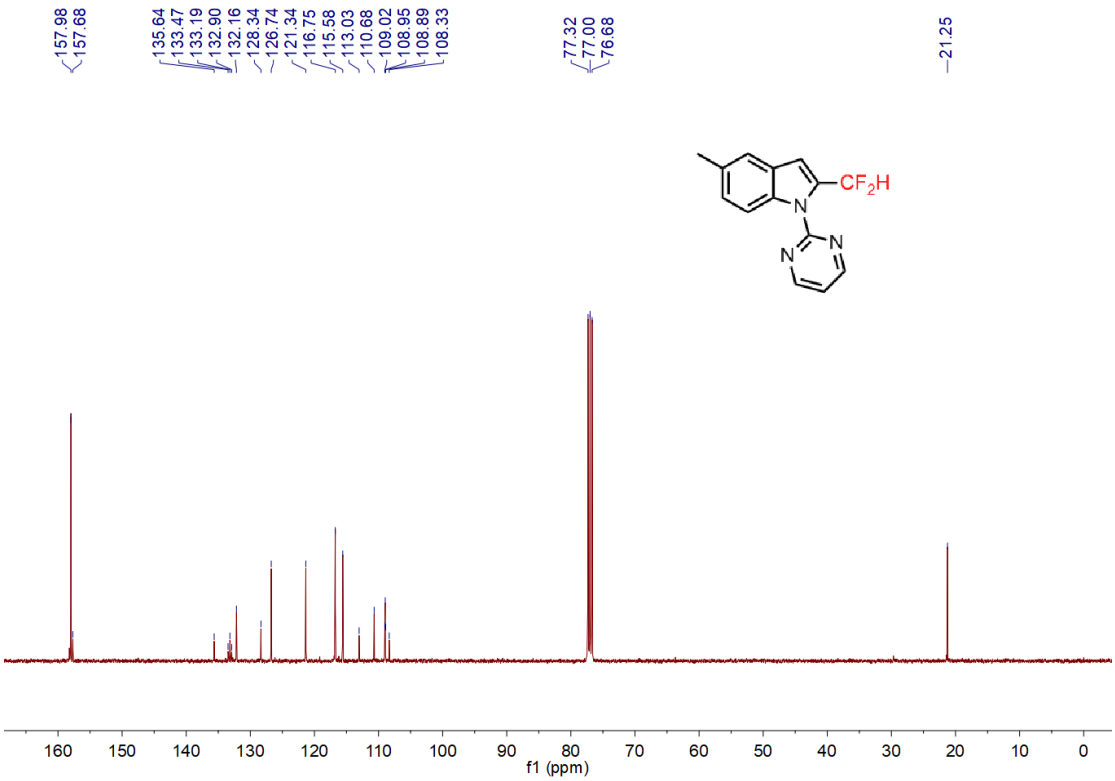

Br
CF2H
N
N
N
-114.20
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)


158.16
157.41
137.53
134.05
133.77
133.48
128.77
126.05
125.63
117.50
115.43
114.95
112.69
110.34
109.05
108.98
108.91
107.98
77.32
77.00
76.68
Br
CF2H
N
N
N
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

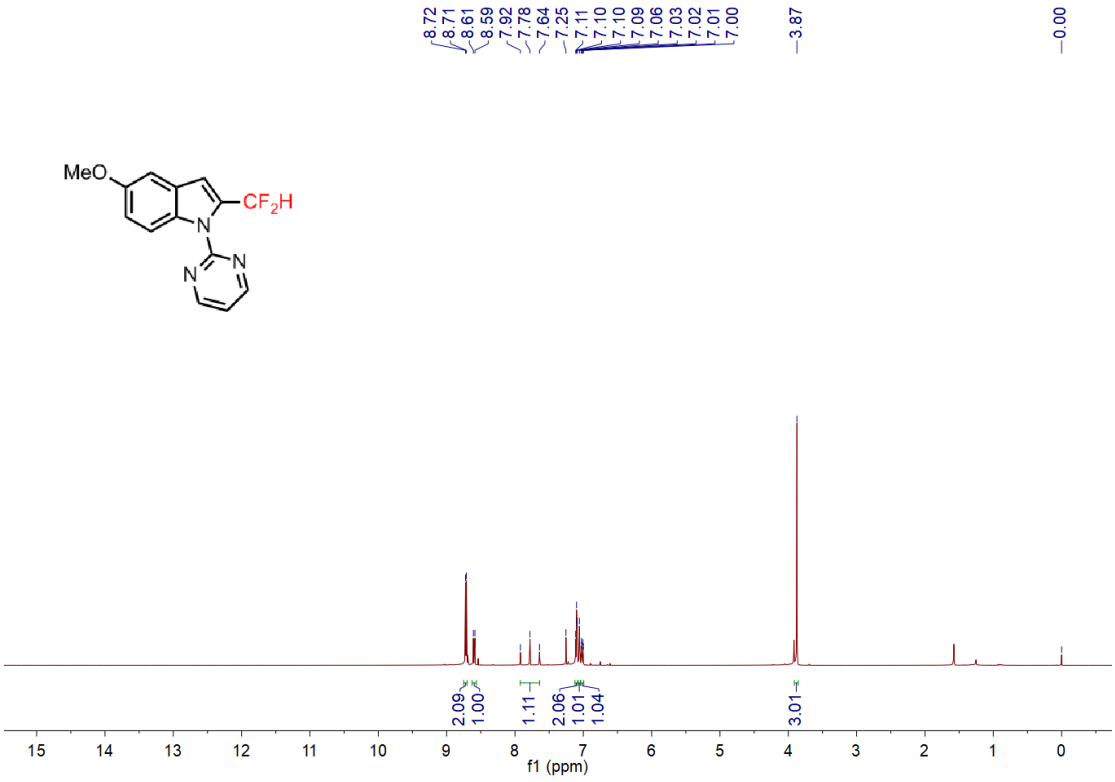
2-(Difluoromethyl)-5-methyl-1-(pyrimidin-2-yl)-1*H*-indole (**3k**)

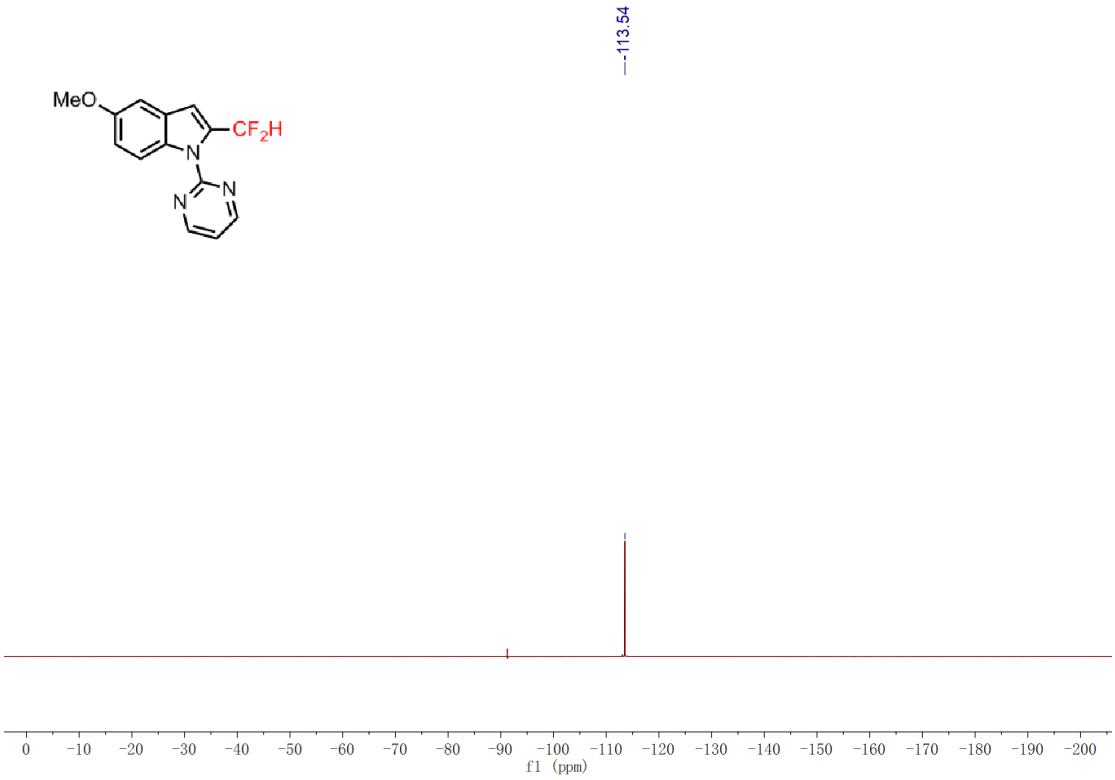




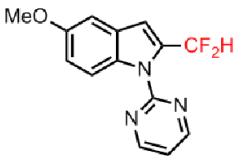


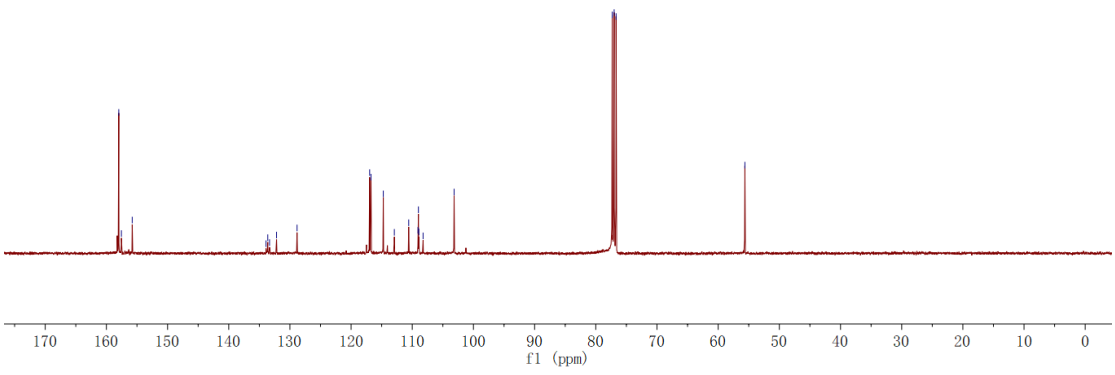
2-(Difluoromethyl)-5-methoxy-1-(pyrimidin-2-yl)-1*H*-indole (**3l**)



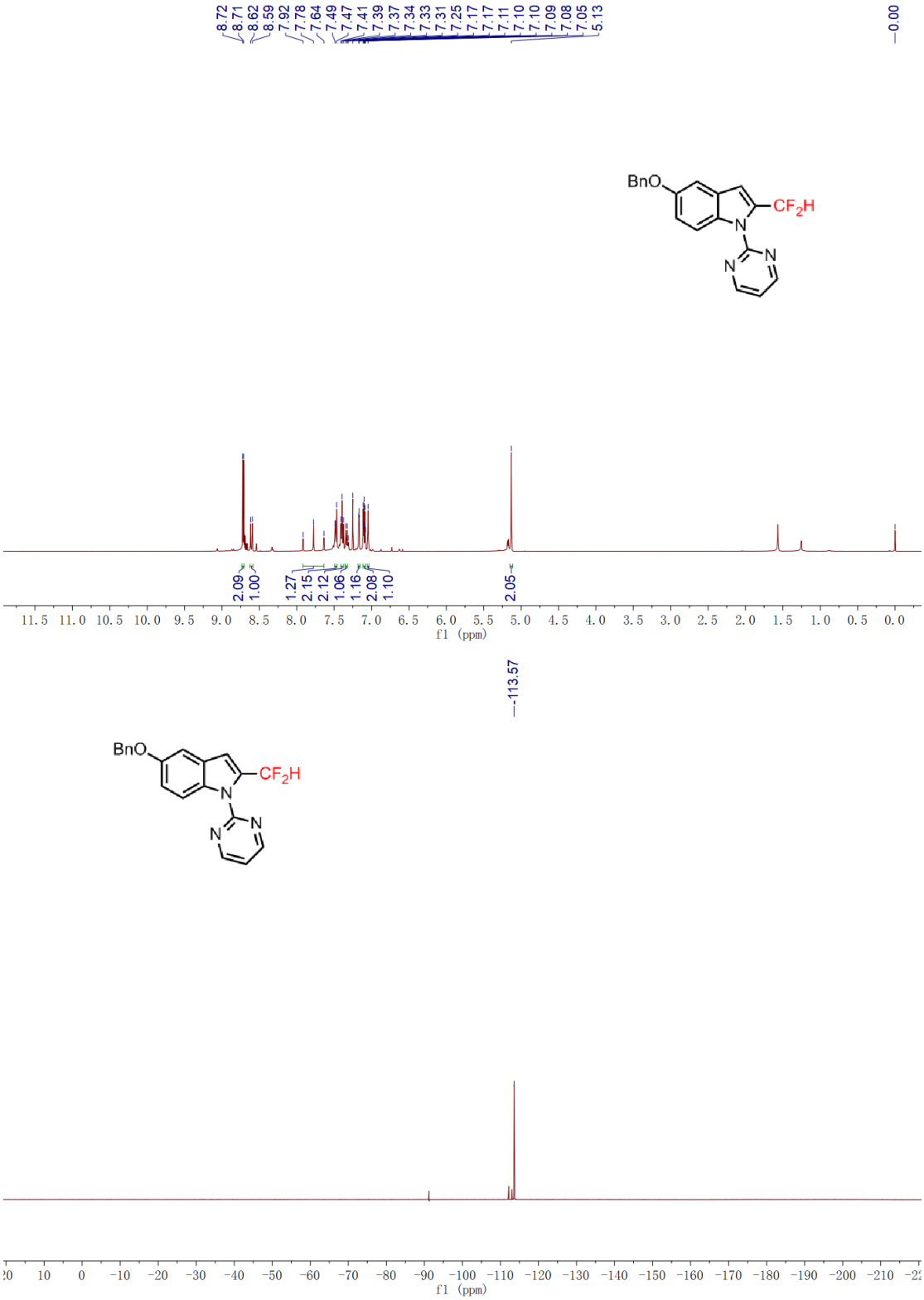


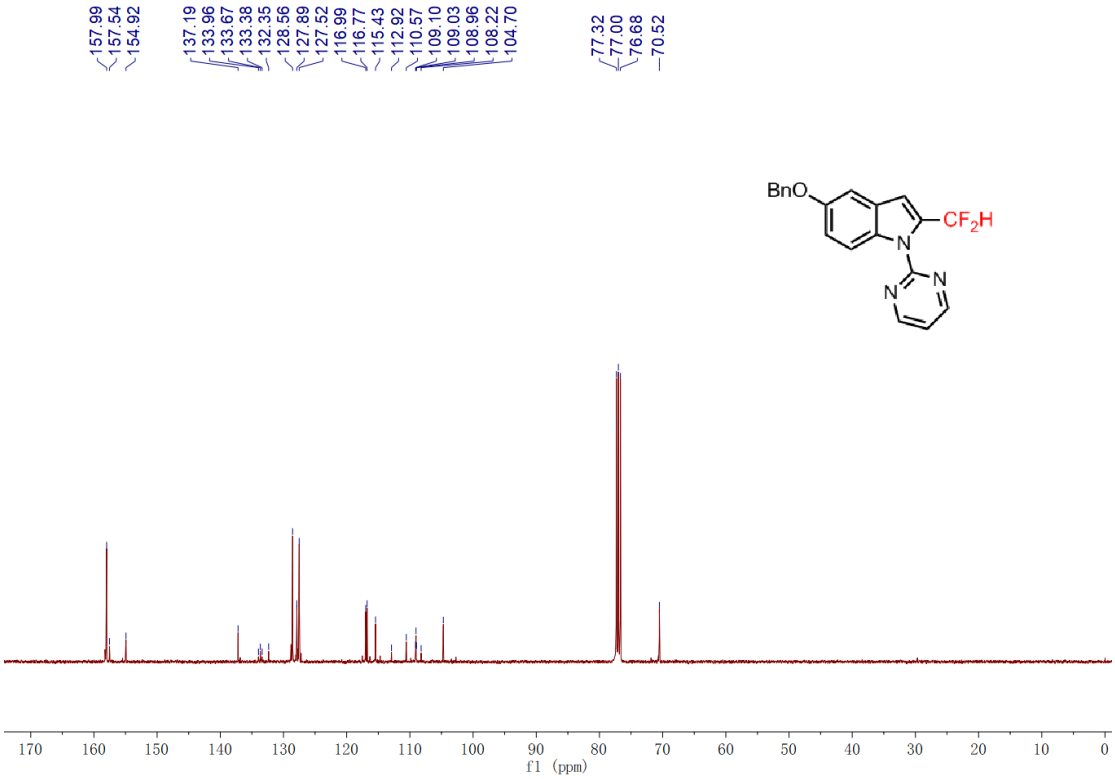
157.98
157.54
155.78
133.91
133.62
133.33
132.19
128.83
116.97
116.75
114.74
112.93
110.58
109.06
109.00
108.93
108.23
103.16
77.32
77.00
76.68
55.63



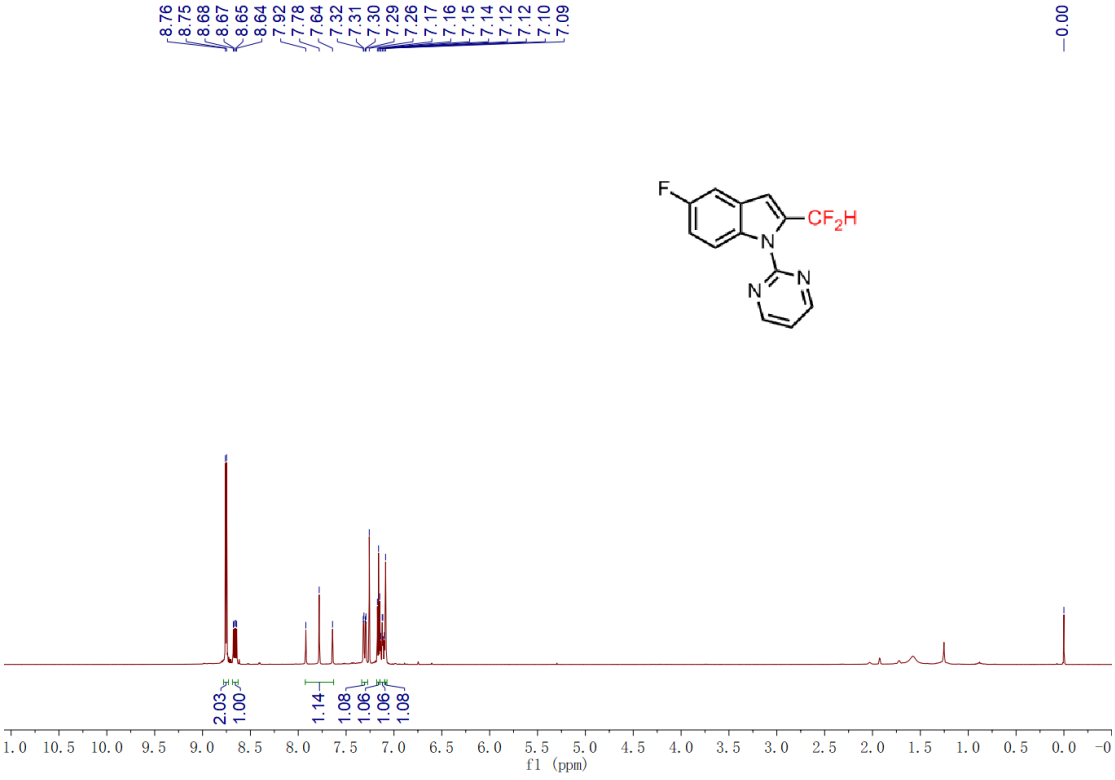


5-(Benzyloxy)-2-(difluoromethyl)-1-(pyrimidin-2-yl)-1*H*-indole (**3m**)

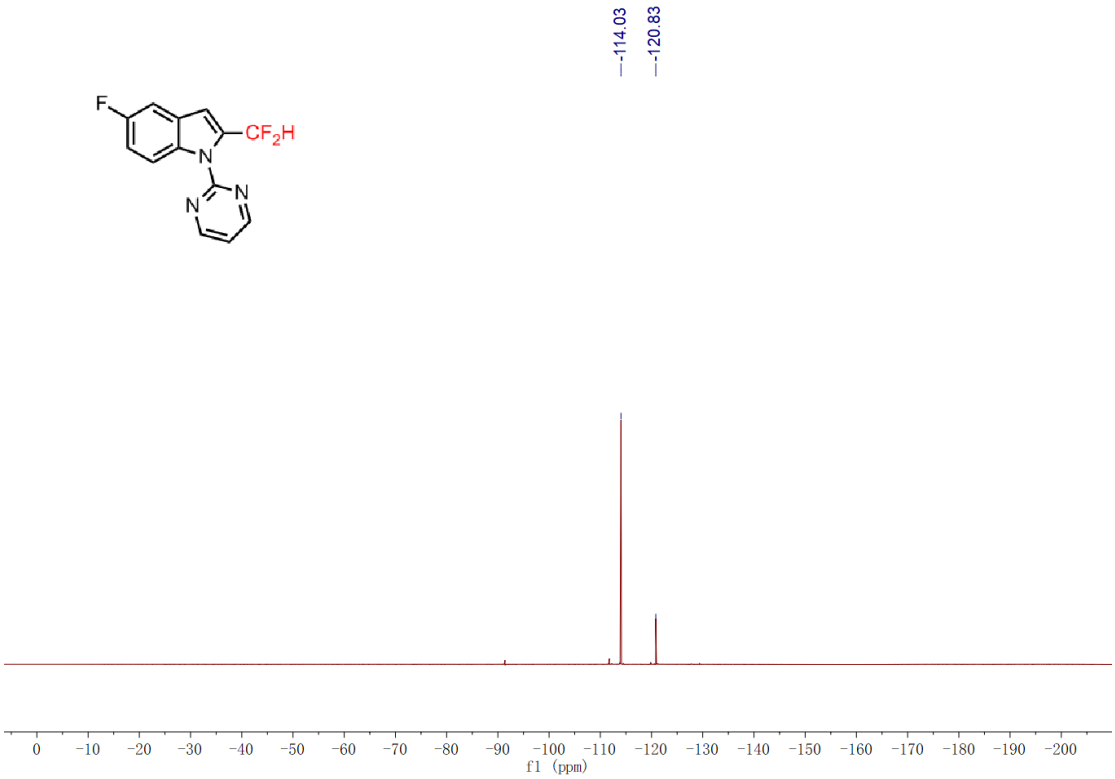


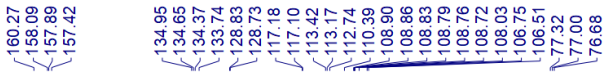


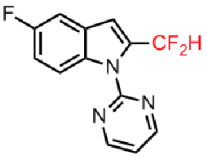
2-(Difluoromethyl)-5-fluoro-1-(pyrimidin-2-yl)-1*H*-indole (**3n**)

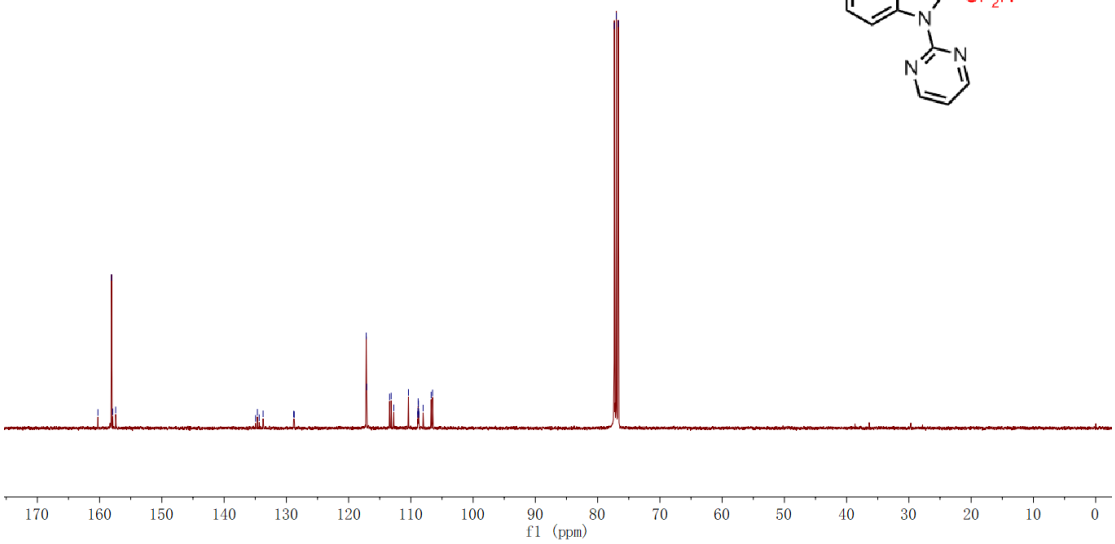


F
CF2H
N
N
N

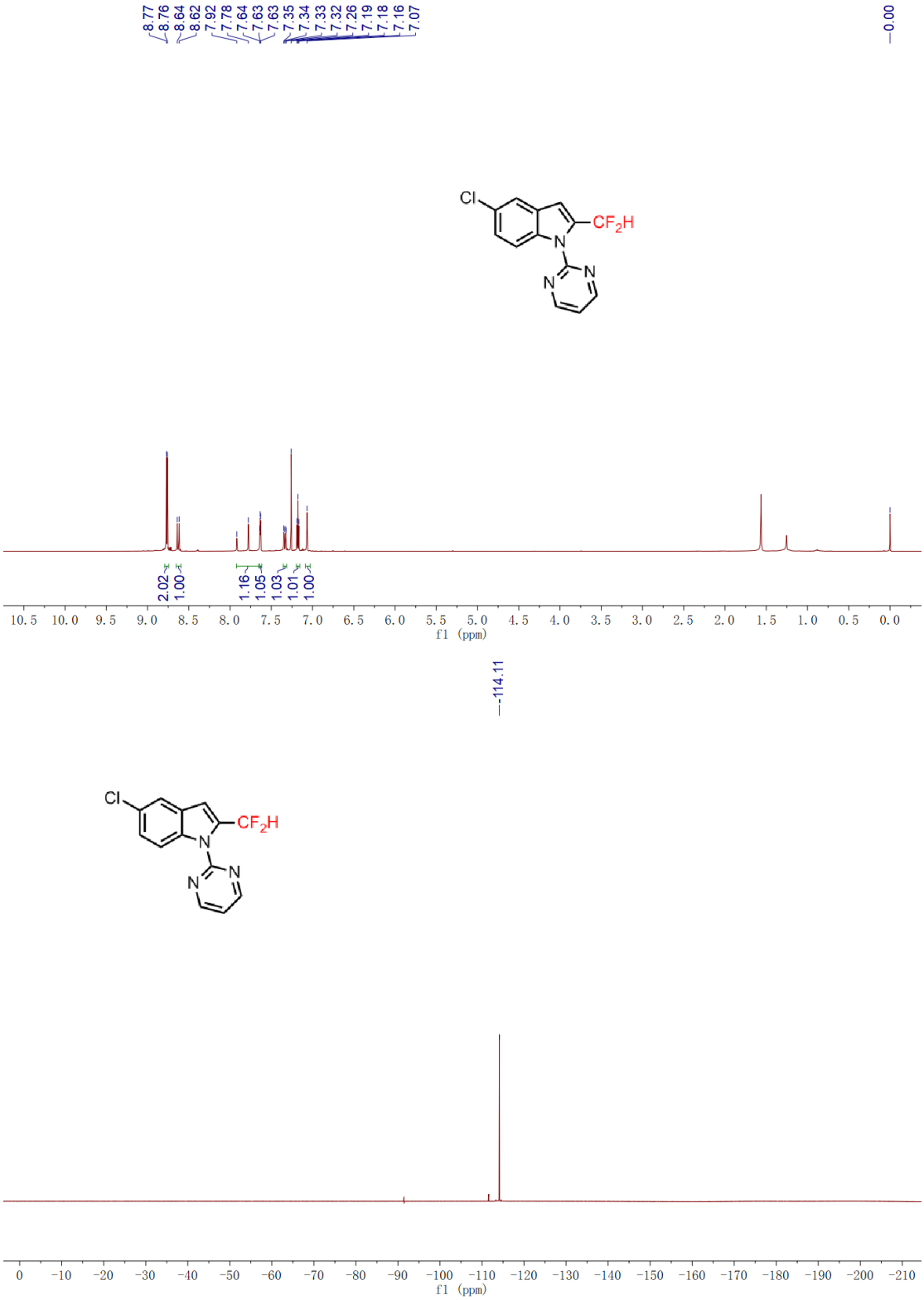

-114.03
-120.83
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

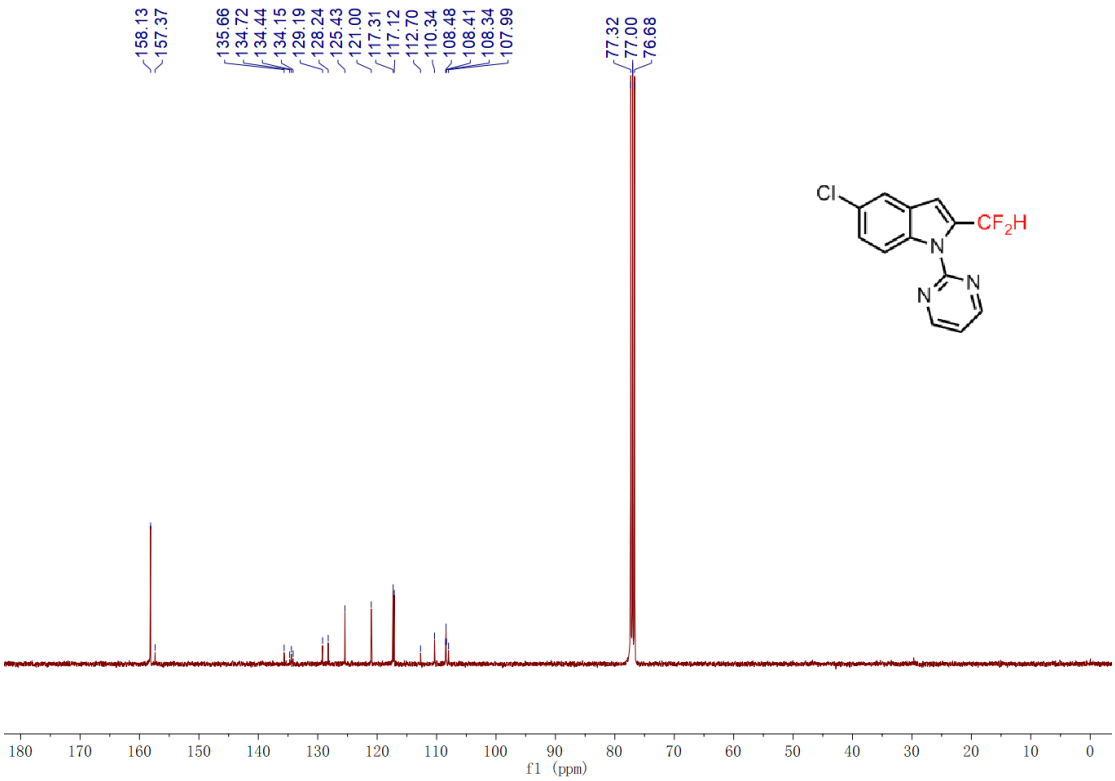

160.27
158.09
157.89
157.42
134.95
134.65
134.37
133.74
128.83
128.73
117.18
117.10
113.42
113.17
112.74
110.39
108.90
108.86
108.83
108.79
108.76
108.72
108.03
106.75
106.51
77.32
77.00
76.68


F
CF2H
N
N
N

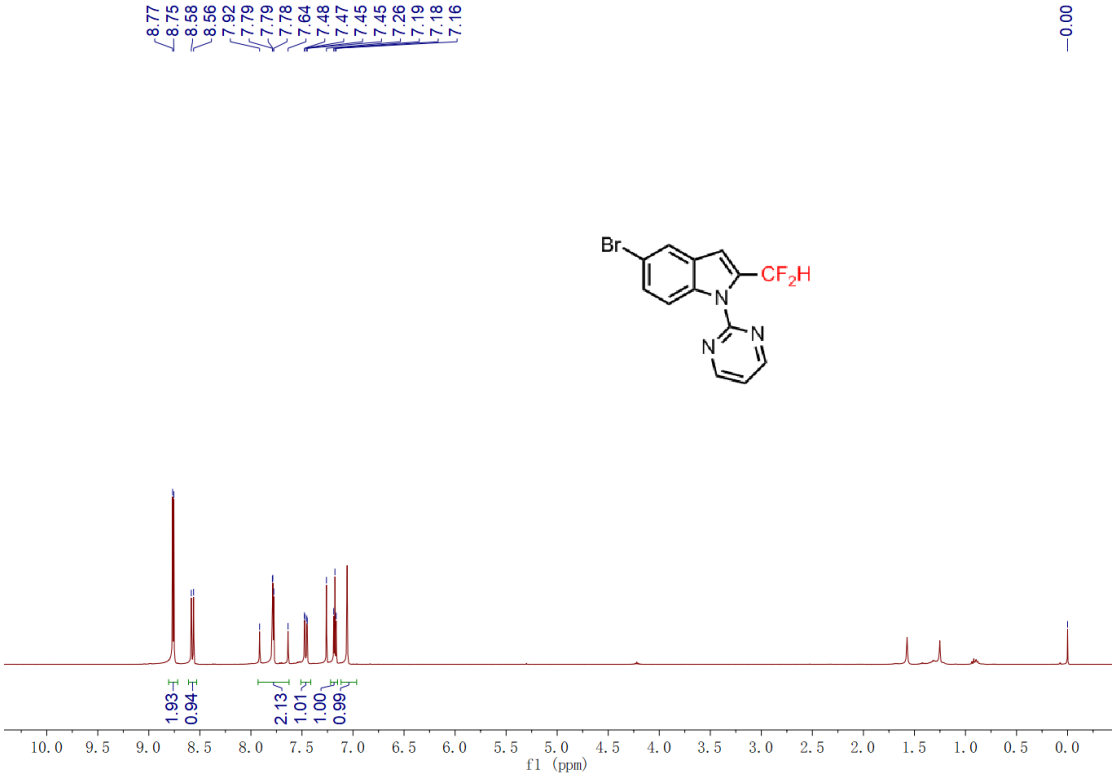

170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

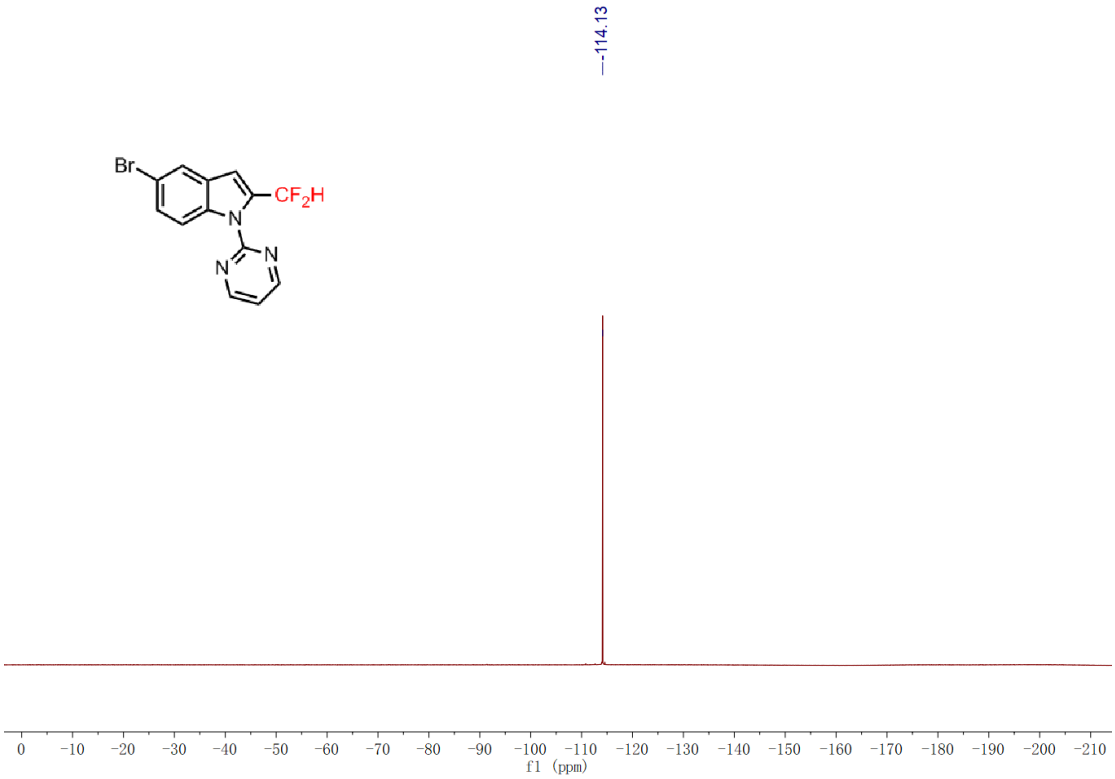
5-Chloro-2-(difluoromethyl)-1-(pyrimidin-2-yl)-1*H*-indole (**3o**)

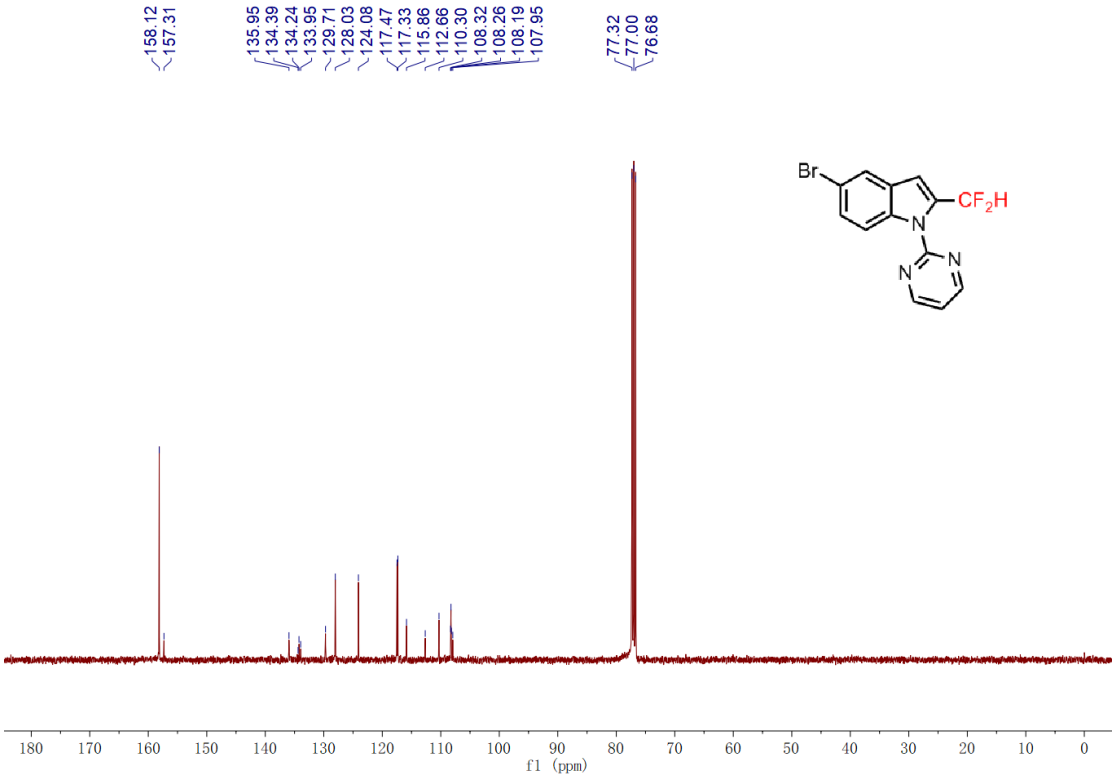




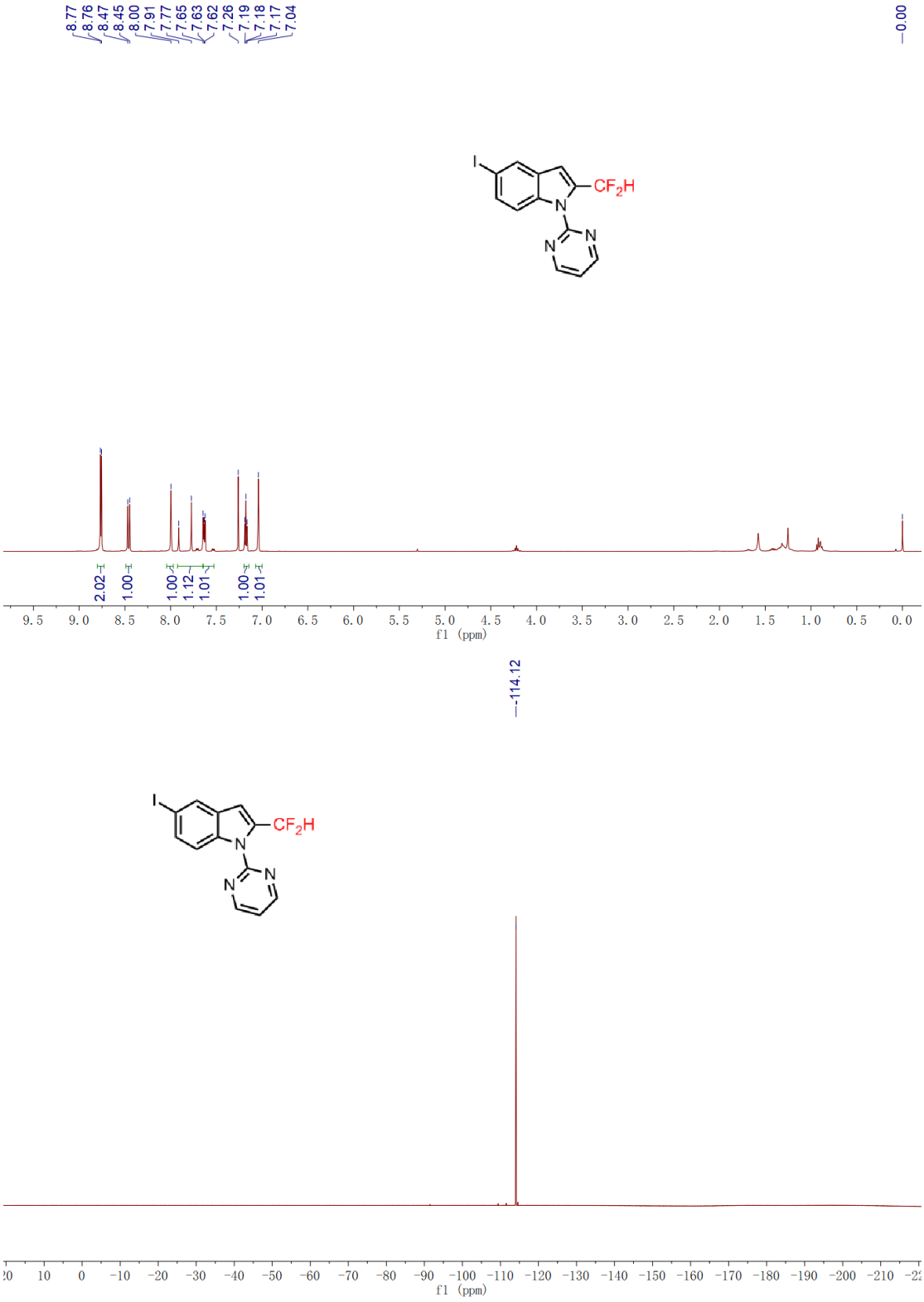
5-Bromo-2-(difluoromethyl)-1-(pyrimidin-2-yl)-1*H*-indole (**3p**)

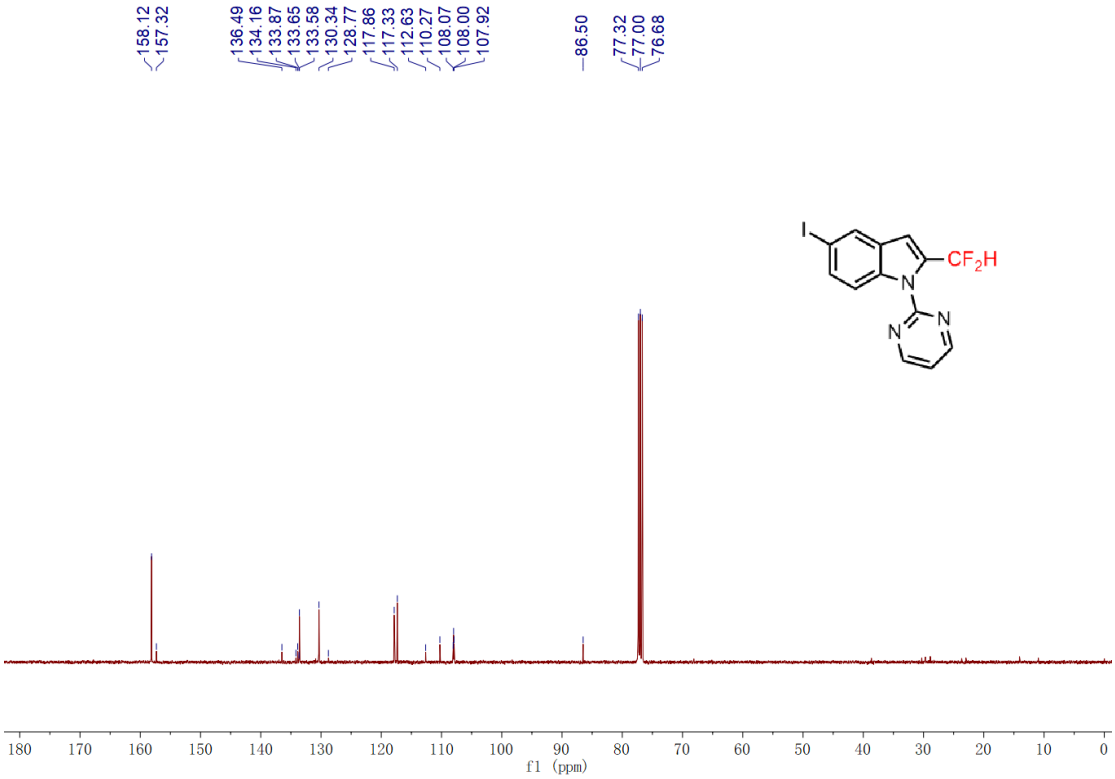



-114.13
Br
CF2H
N
N
N
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

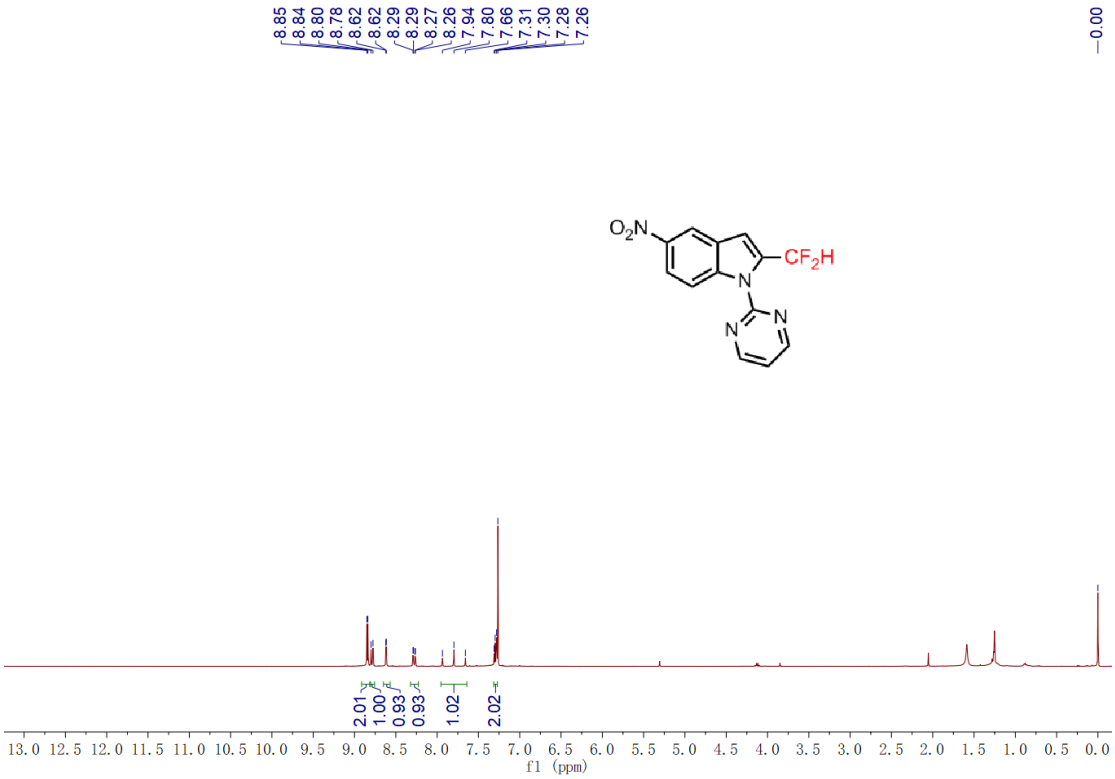

158.12
157.31
135.95
134.39
134.24
133.95
129.71
128.03
124.08
117.47
117.33
115.86
112.66
110.30
108.32
108.26
108.19
107.95
77.32
77.00
76.68
Br
CF2H
N
N
N
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

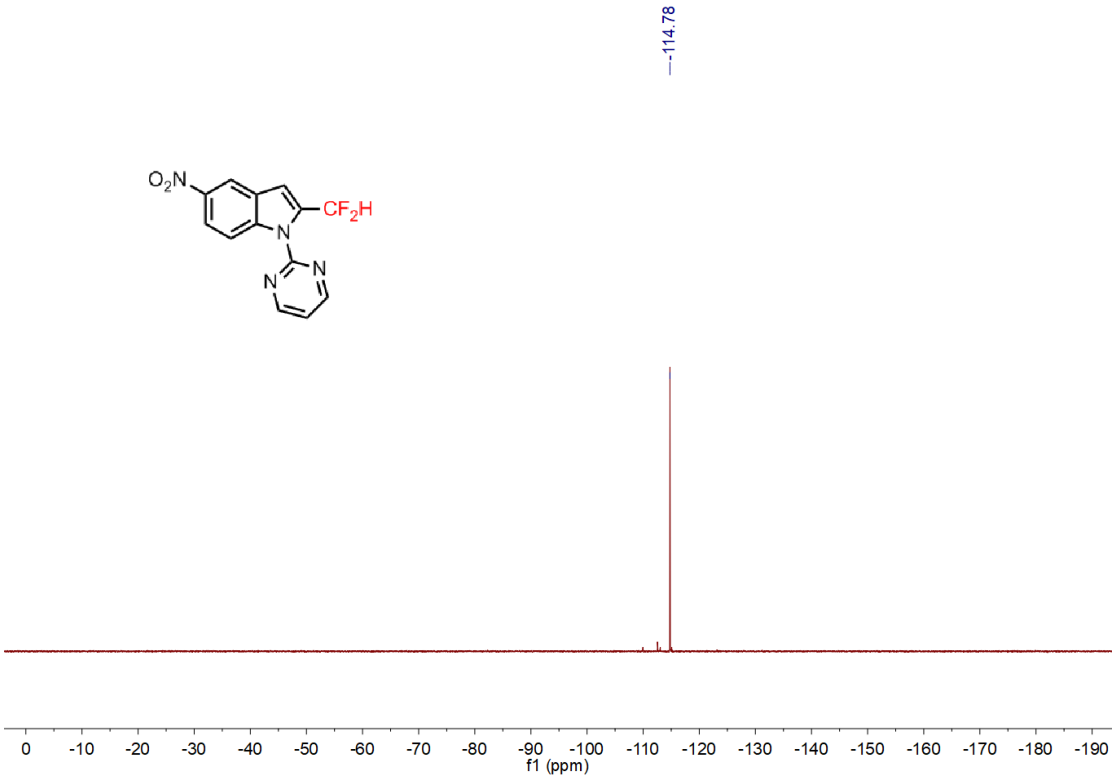
2-(Difluoromethyl)-5-iodo-1-(pyrimidin-2-yl)-1*H*-indole (**3q**)

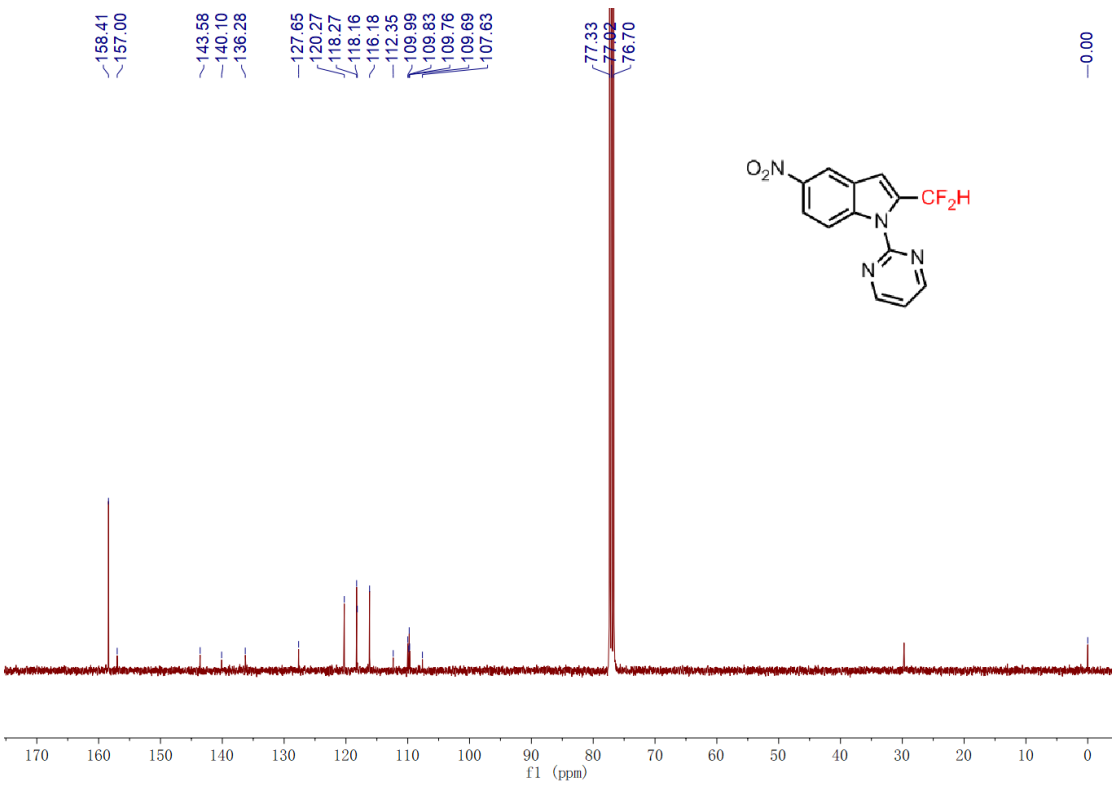




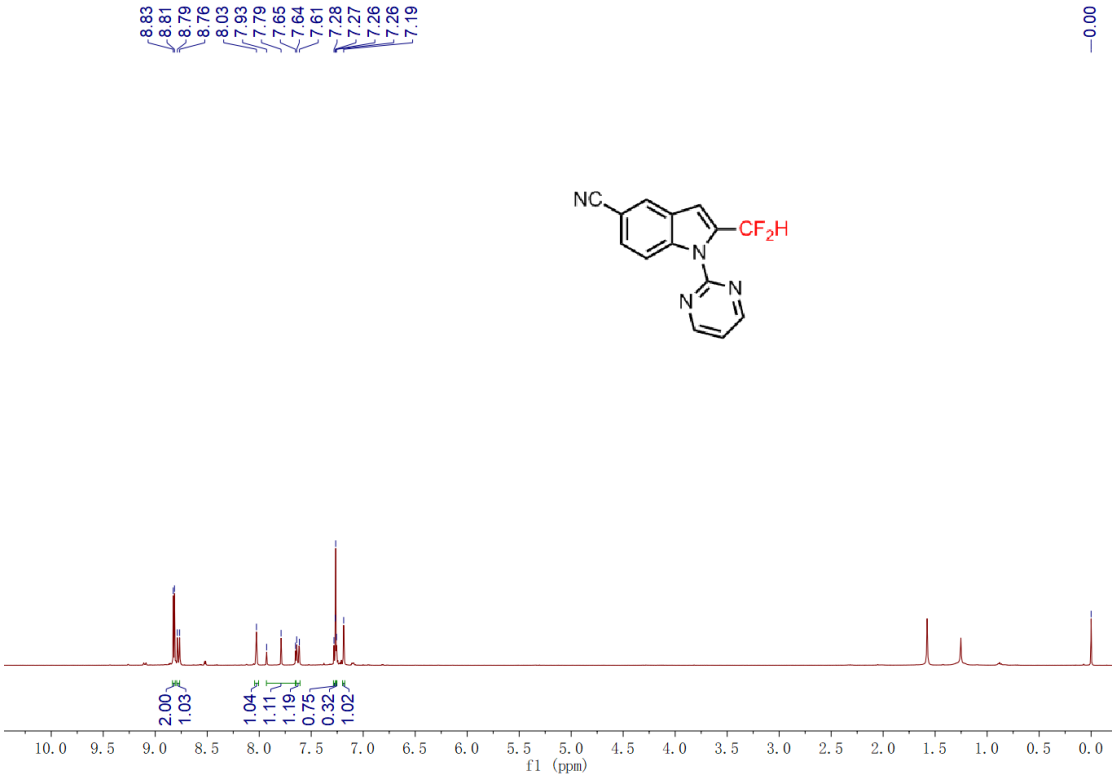
2-(Difluoromethyl)-5-nitro-1-(pyrimidin-2-yl)-1*H*-indole (**3r**)

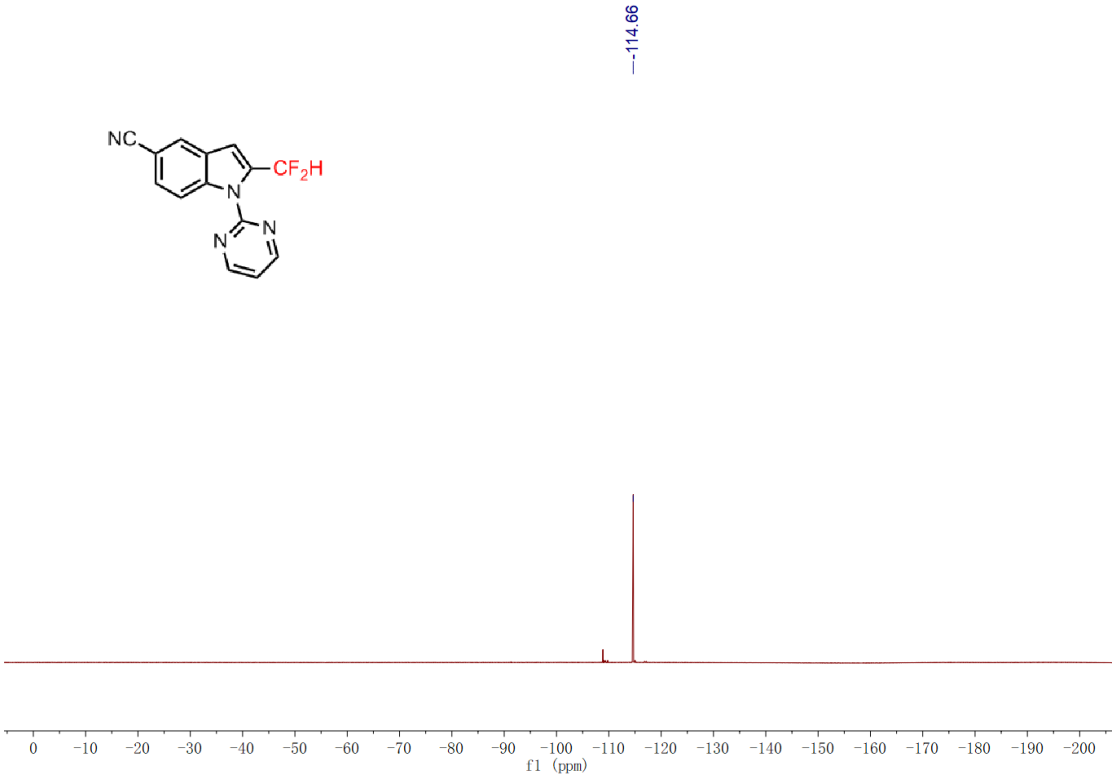


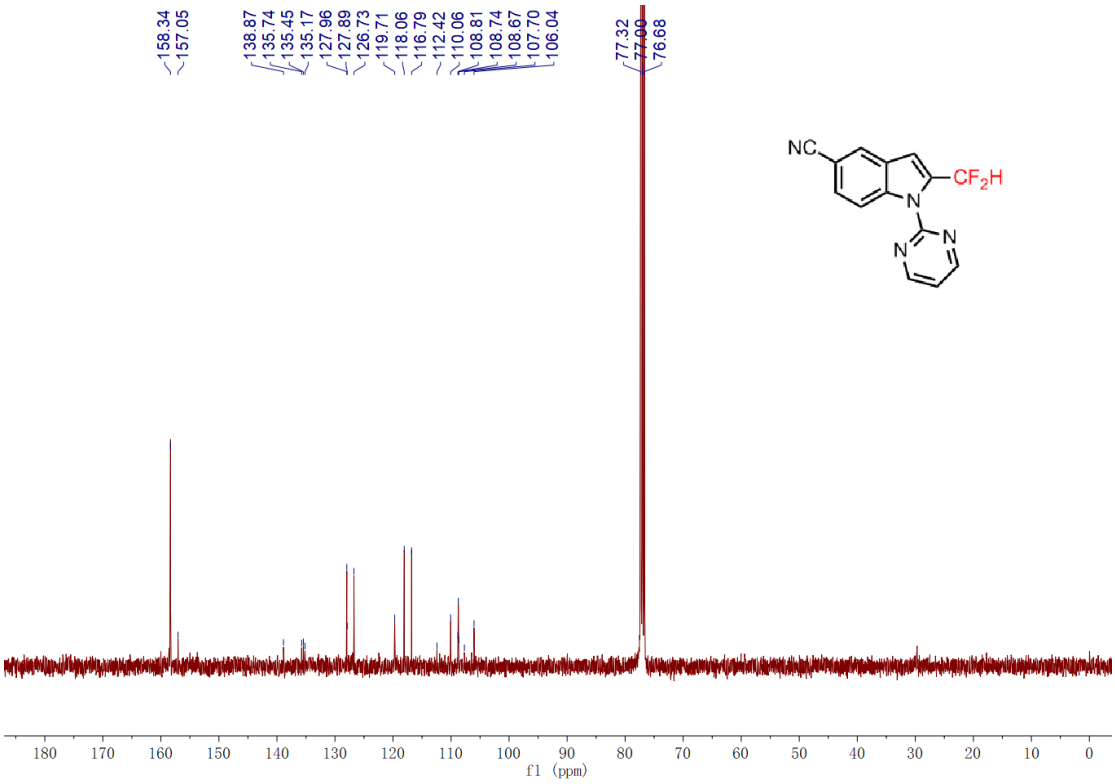

-114.78
O2N
CF2H
N
N
N
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)


158.41
157.00
143.58
140.10
136.28
127.65
120.27
118.27
118.16
116.18
112.35
109.99
109.83
109.76
109.69
107.63
77.33
77.03
76.70
0.00
O2N
CF2H
N
N
N
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

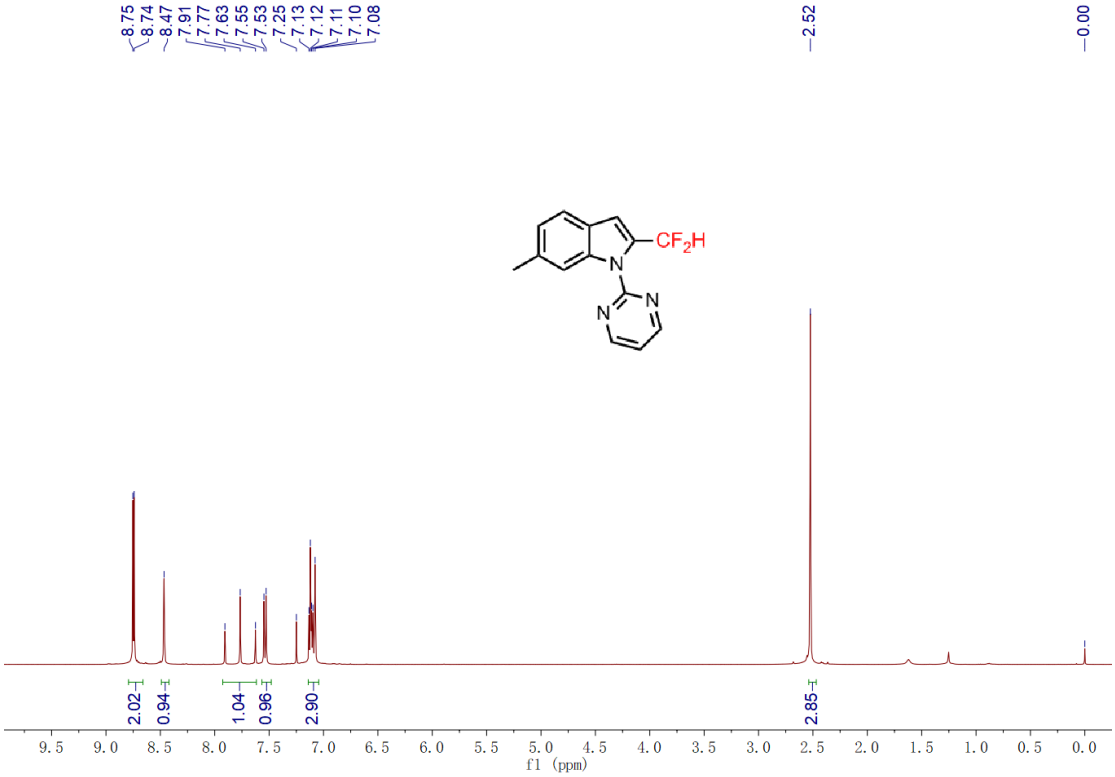
2-(Difluoromethyl)-1-(pyrimidin-2-yl)-1*H*-indole-5-carbonitrile (**3s**)

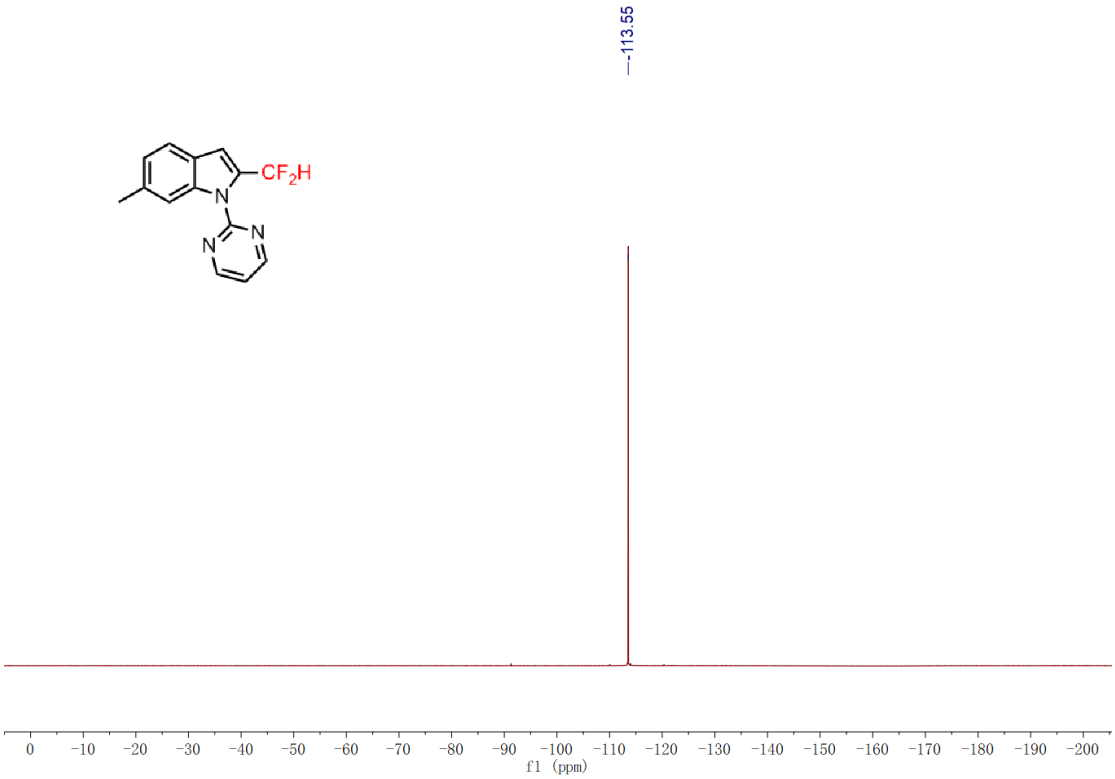


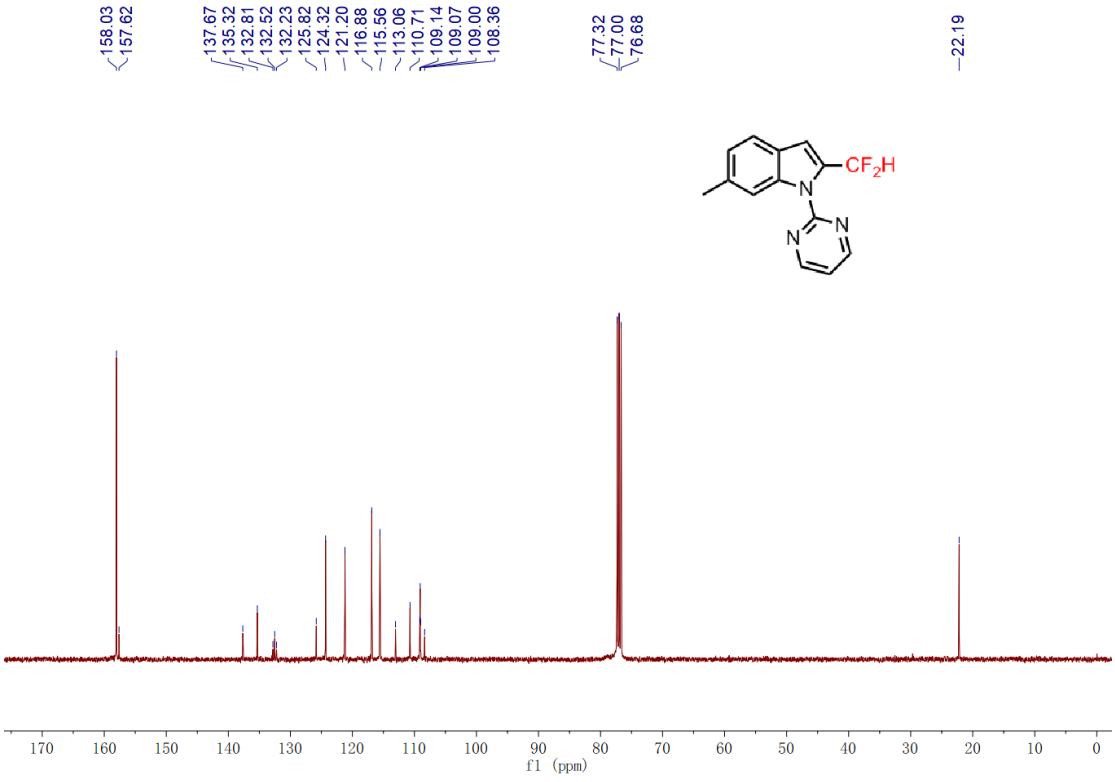




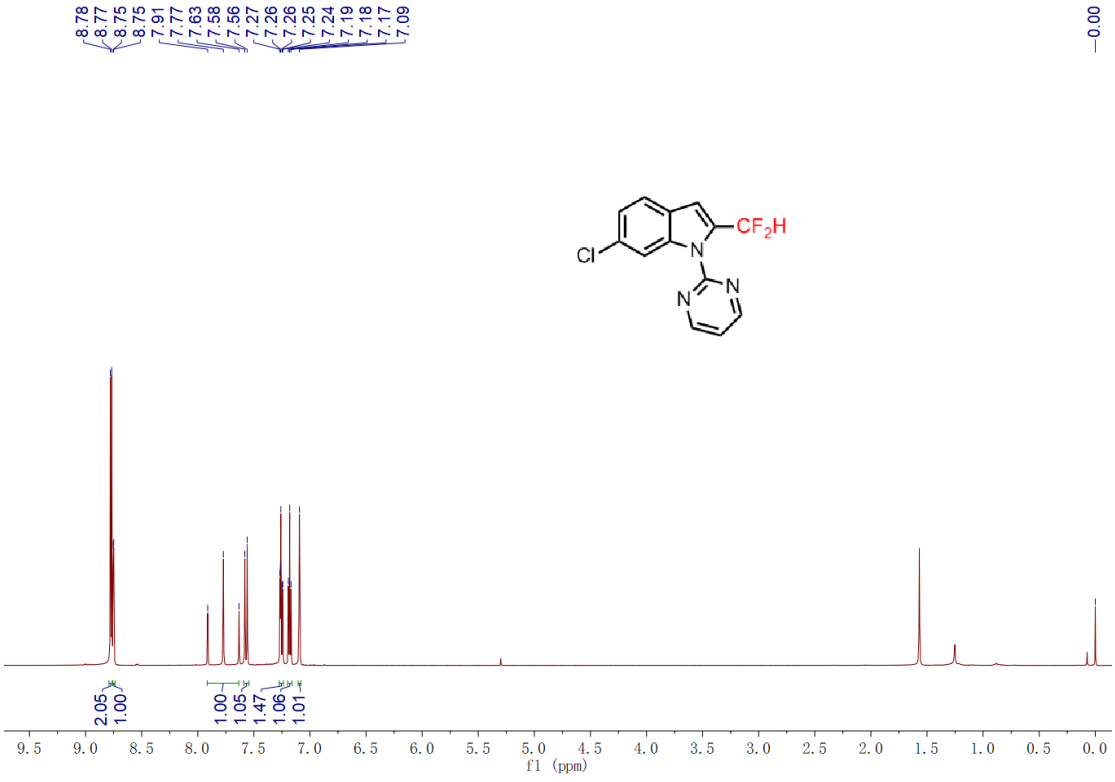
2-(Difluoromethyl)-6-methyl-1-(pyrimidin-2-yl)-1*H*-indole (**3t**)

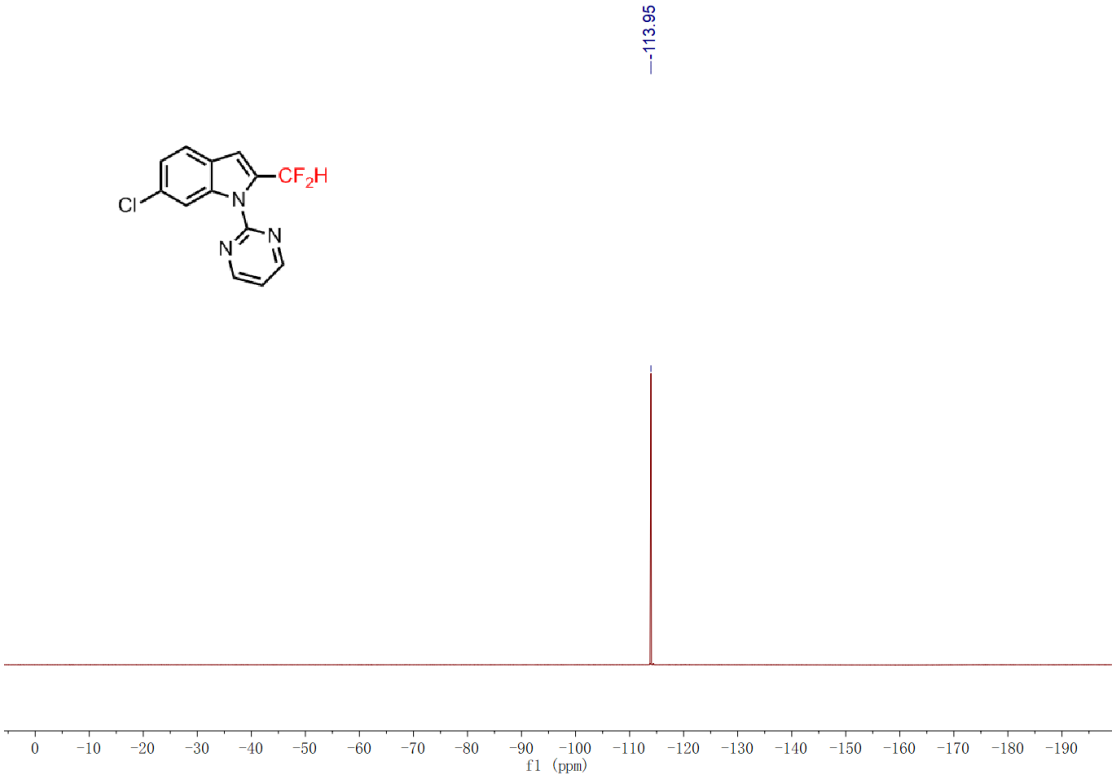


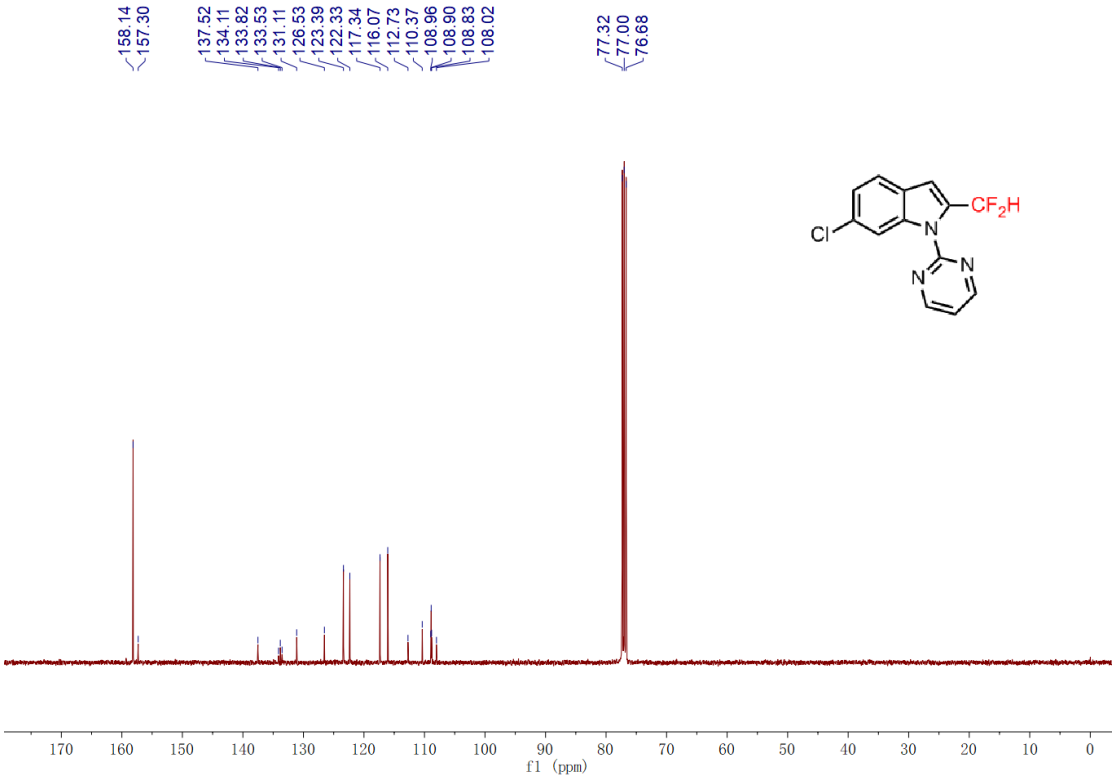

-113.55
CF2H
N
N
N
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)


158.03
157.62
137.67
135.32
132.81
132.52
132.23
125.82
124.32
121.20
116.88
115.56
113.06
110.71
109.14
109.07
109.00
108.36
77.32
77.00
76.68
22.19
CF2H
N
N
N
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

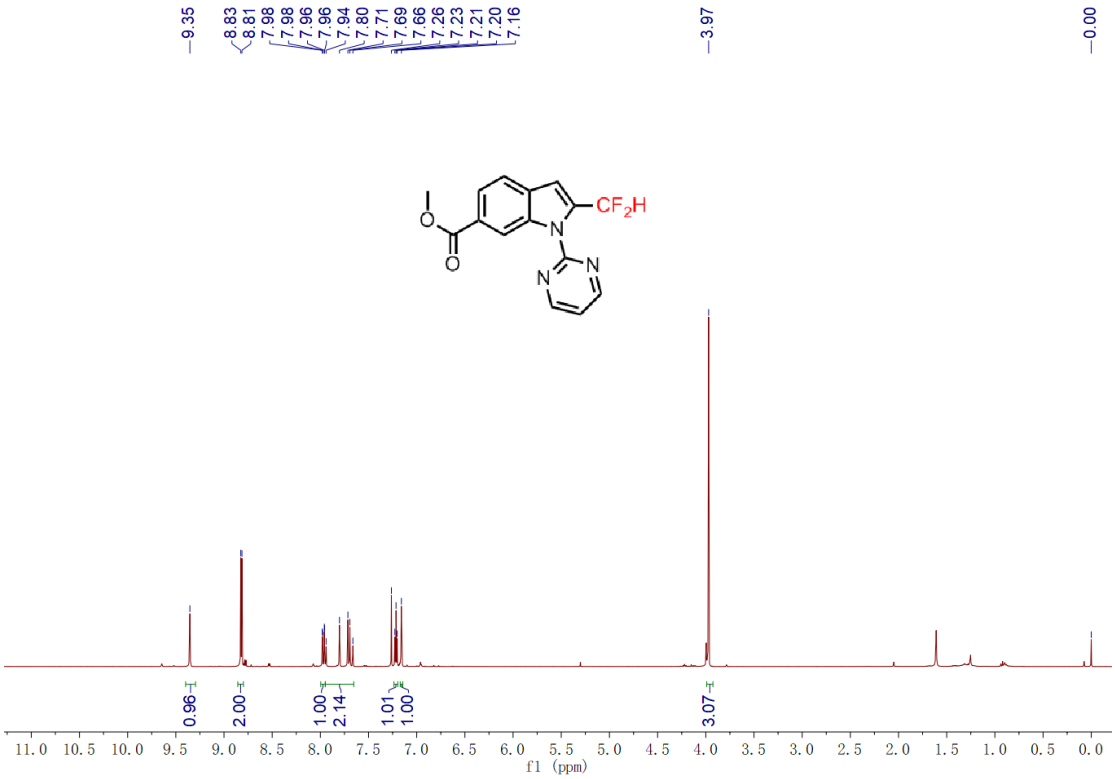
6-Chloro-2-(difluoromethyl)-1-(pyrimidin-2-yl)-1*H*-indole (**3u**)

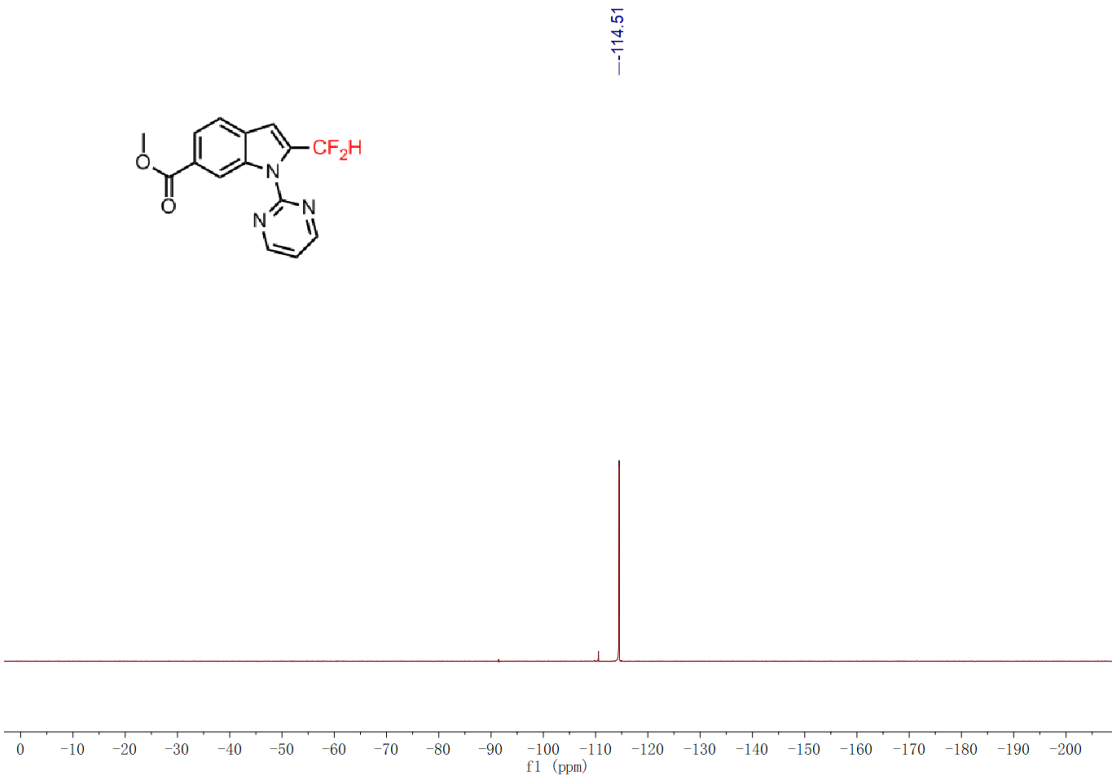


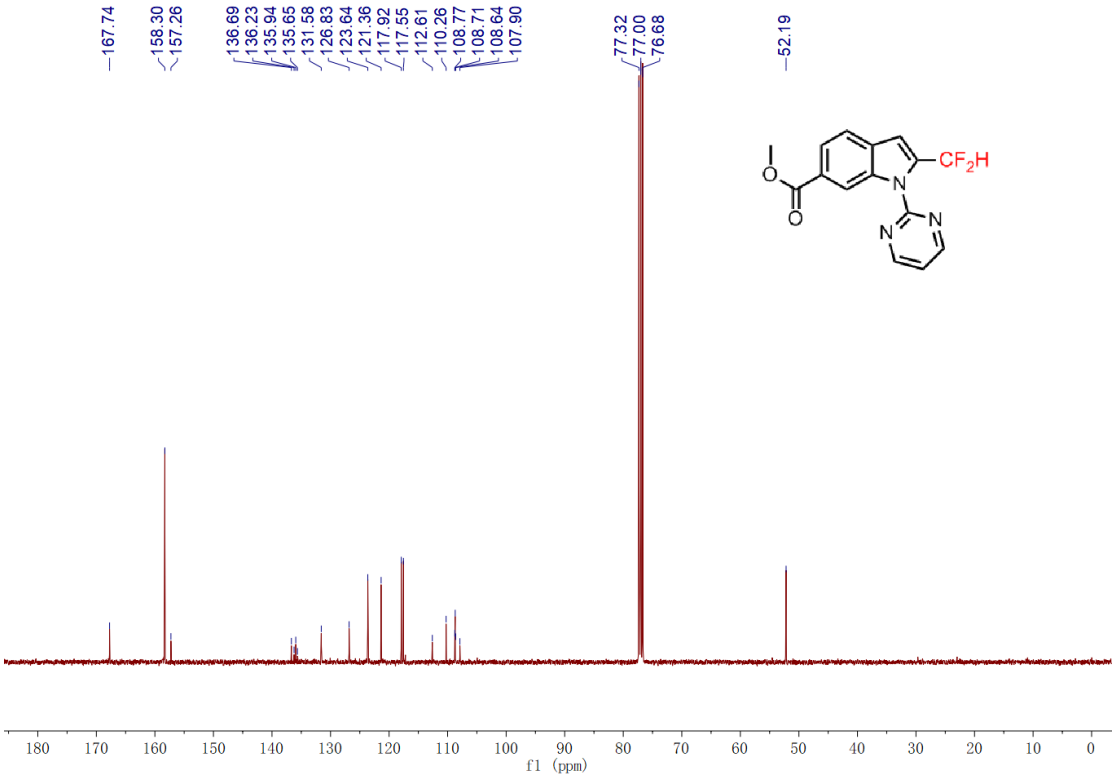




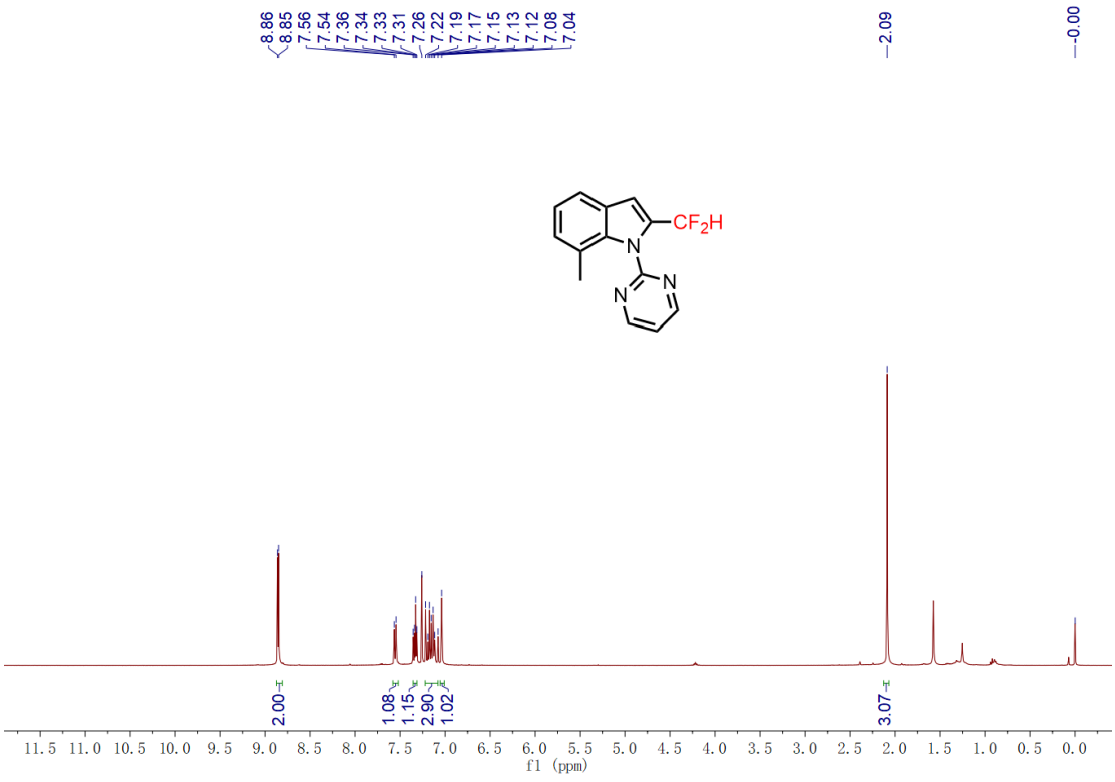
Methyl 2-(difluoromethyl)-1-(pyrimidin-2-yl)-1*H*-indole-6-carboxylate (**3v**)

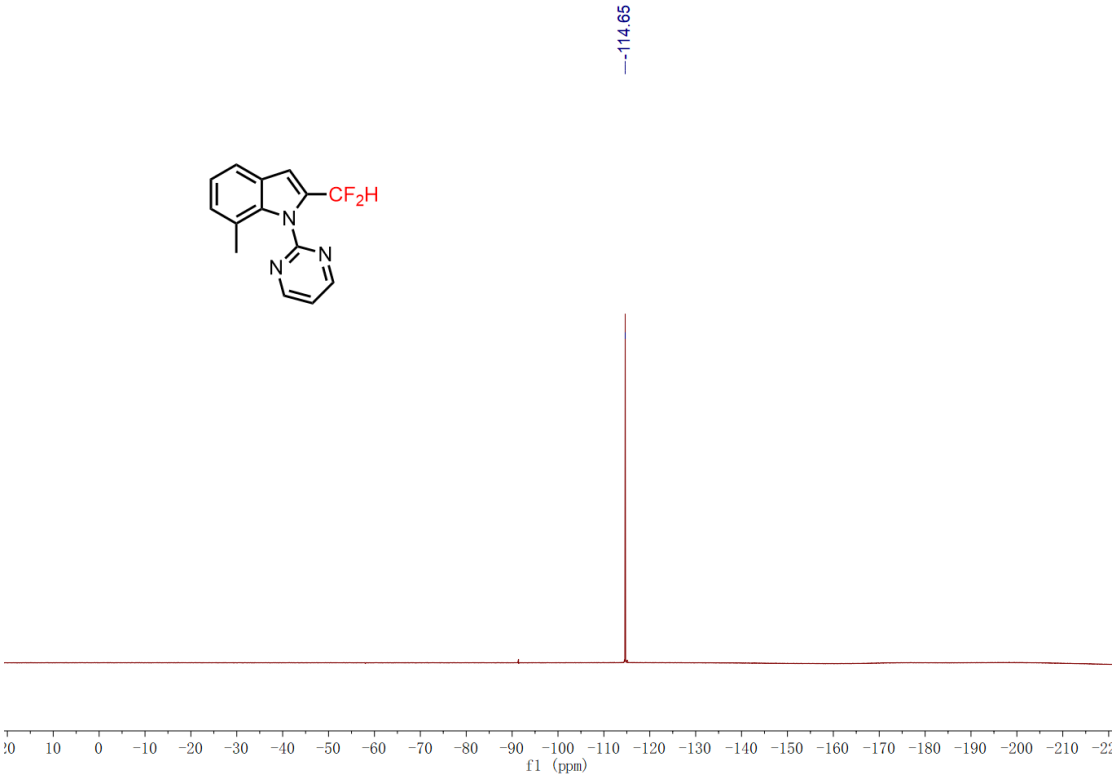


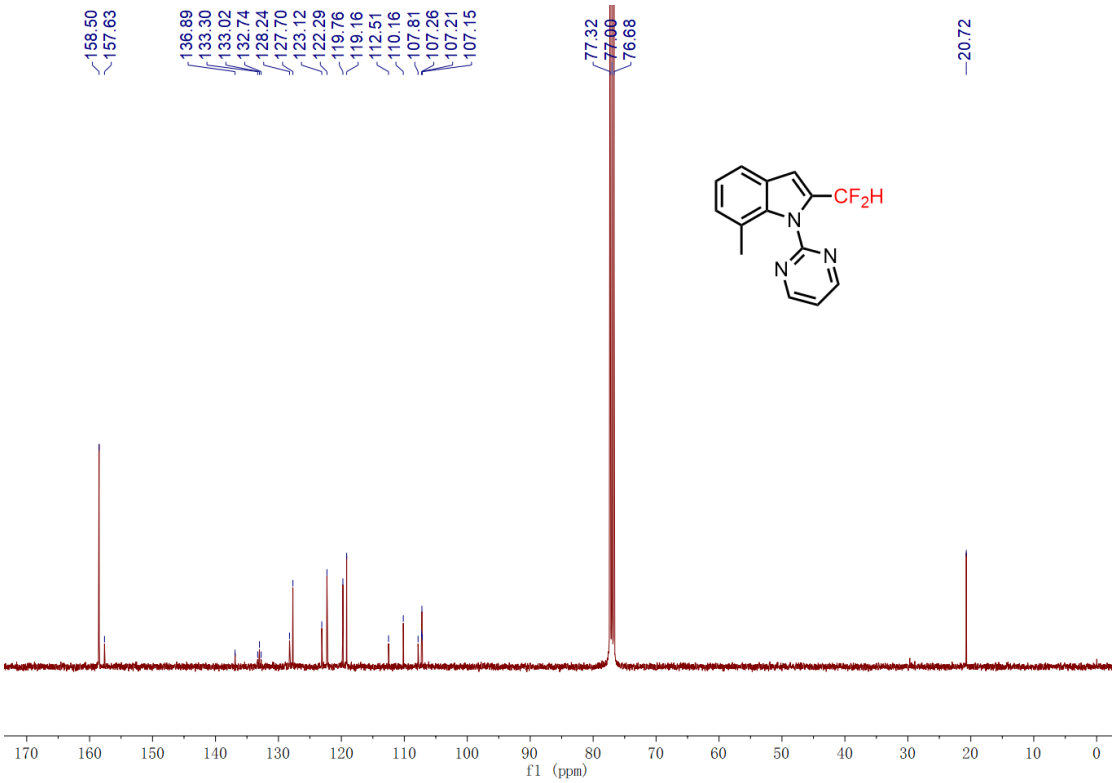

-114.51
CF2H
O
O
N
N
N
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)


167.74
158.30
157.26
136.69
136.23
135.94
135.65
131.58
126.83
123.64
121.36
117.92
117.55
112.61
110.26
108.77
108.71
108.64
107.90
77.32
77.00
76.68
52.19
CF2H
O
O
N
N
N
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

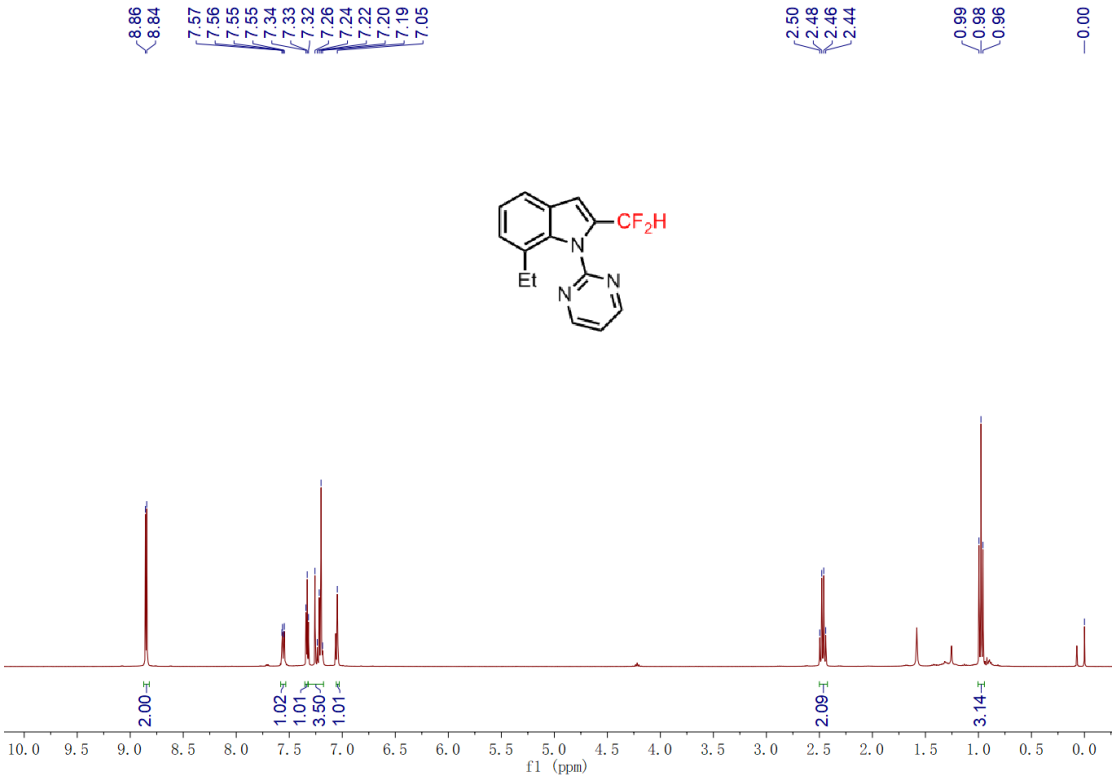
2-(Difluoromethyl)-7-methyl-1-(pyrimidin-2-yl)-1*H*-indole (**3w**)

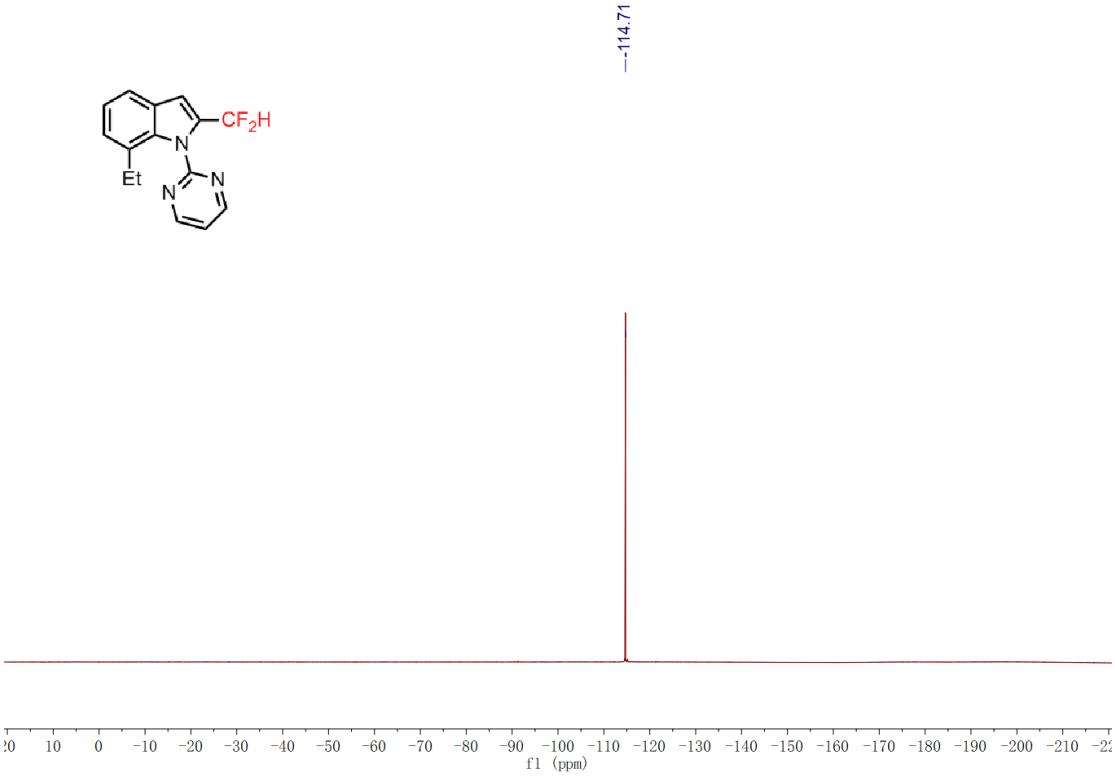


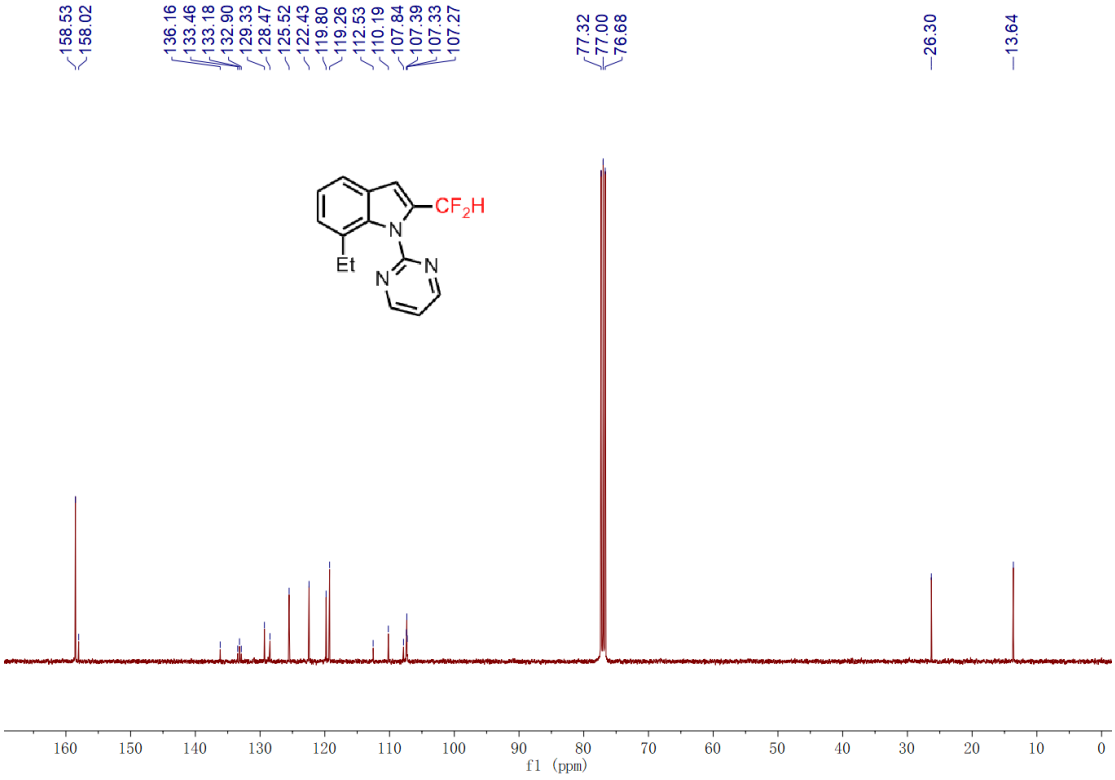




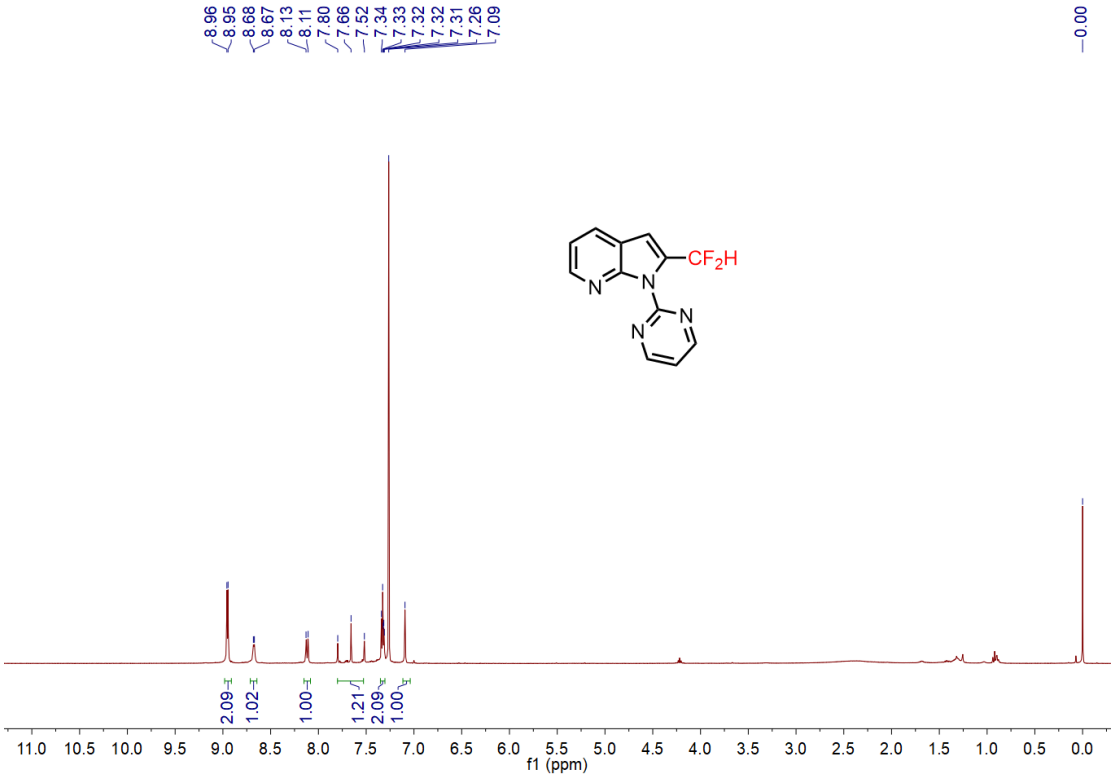
2-(Difluoromethyl)-7-ethyl-1-(pyrimidin-2-yl)-1*H*-indole (**3x**)

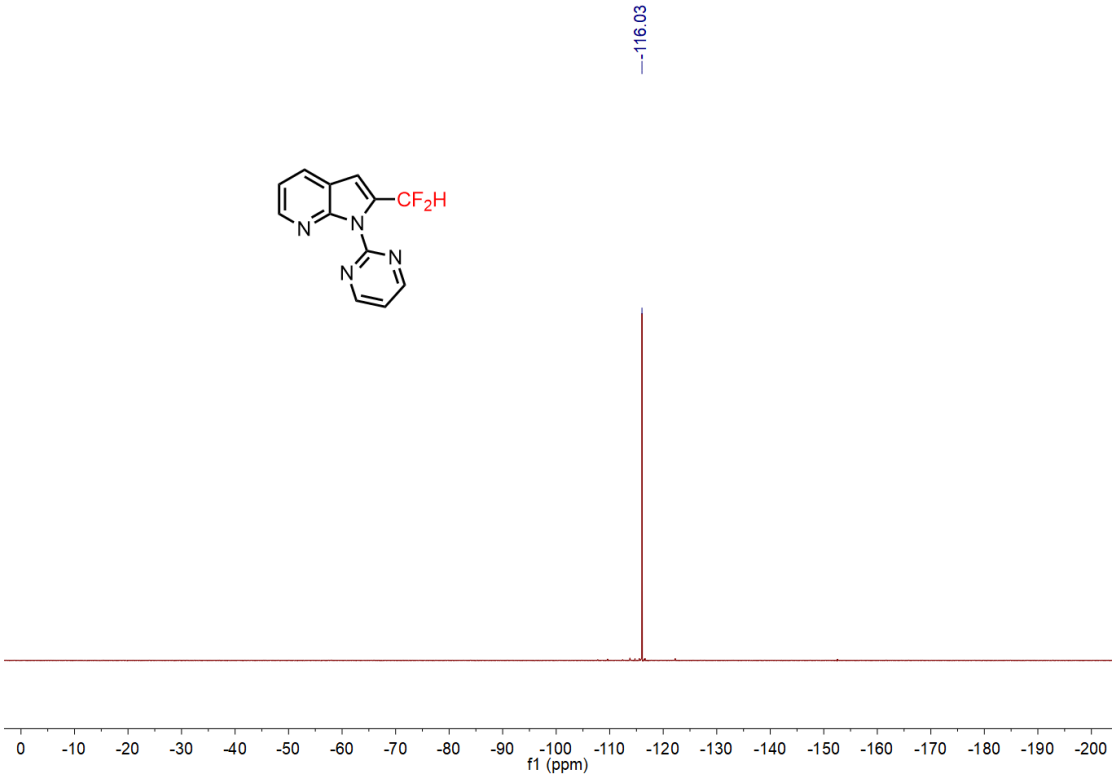


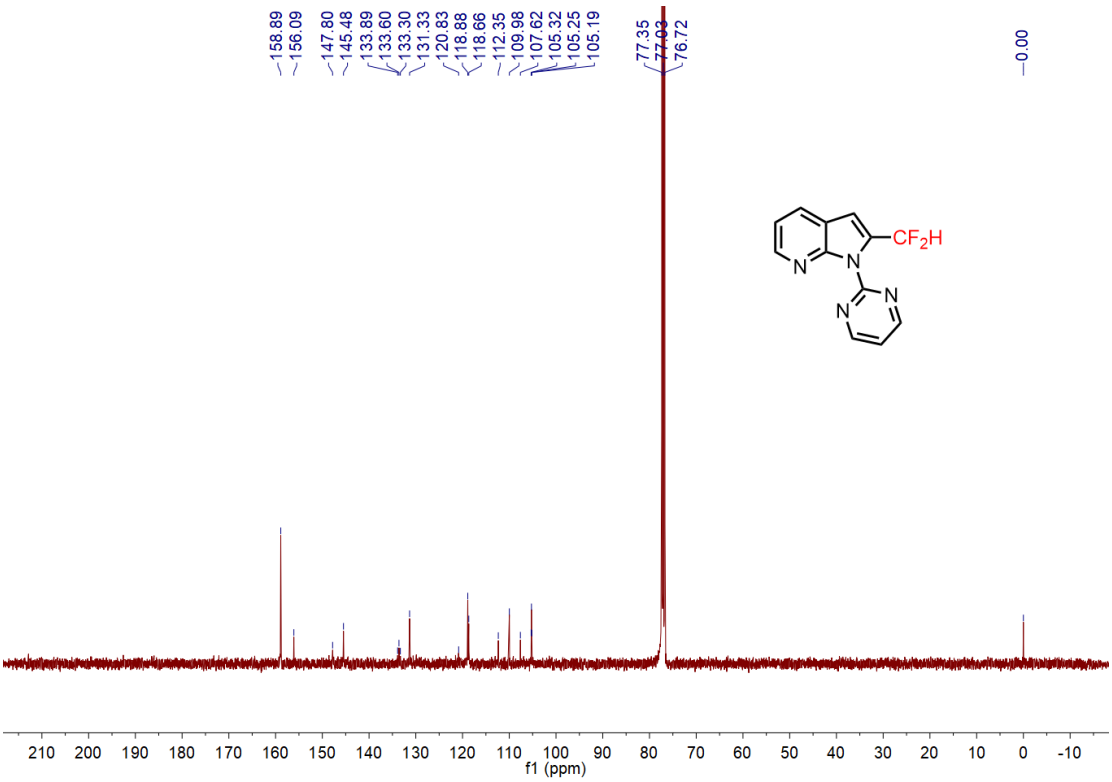

CF2H
Et
N
N
-114.71
f1 (ppm)


158.53
158.02
136.16
133.46
133.18
132.90
129.33
128.47
125.52
122.43
119.80
119.26
112.53
110.19
107.84
107.39
107.33
107.27
77.32
77.00
76.68
26.30
13.64
CF2H
Et
N
N
f1 (ppm)

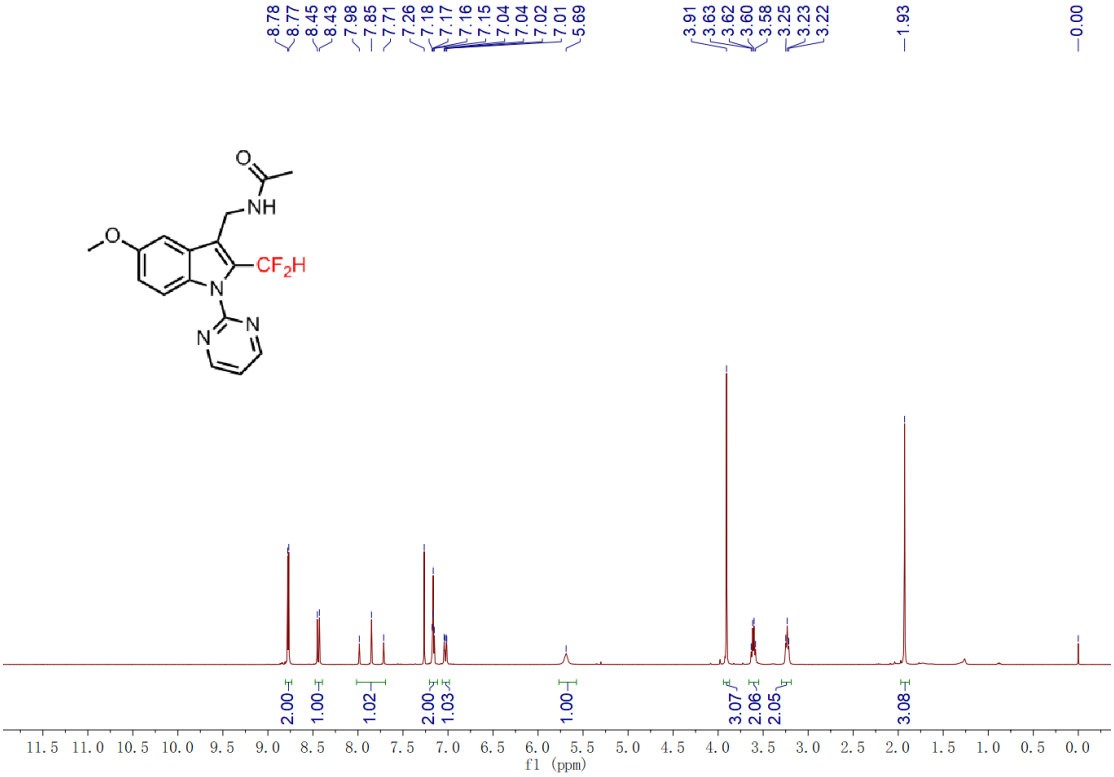
2-(Difluoromethyl)-1-(pyrimidin-2-yl)-1*H*-pyrrolo[2,3-b] pyridine (**3y**)

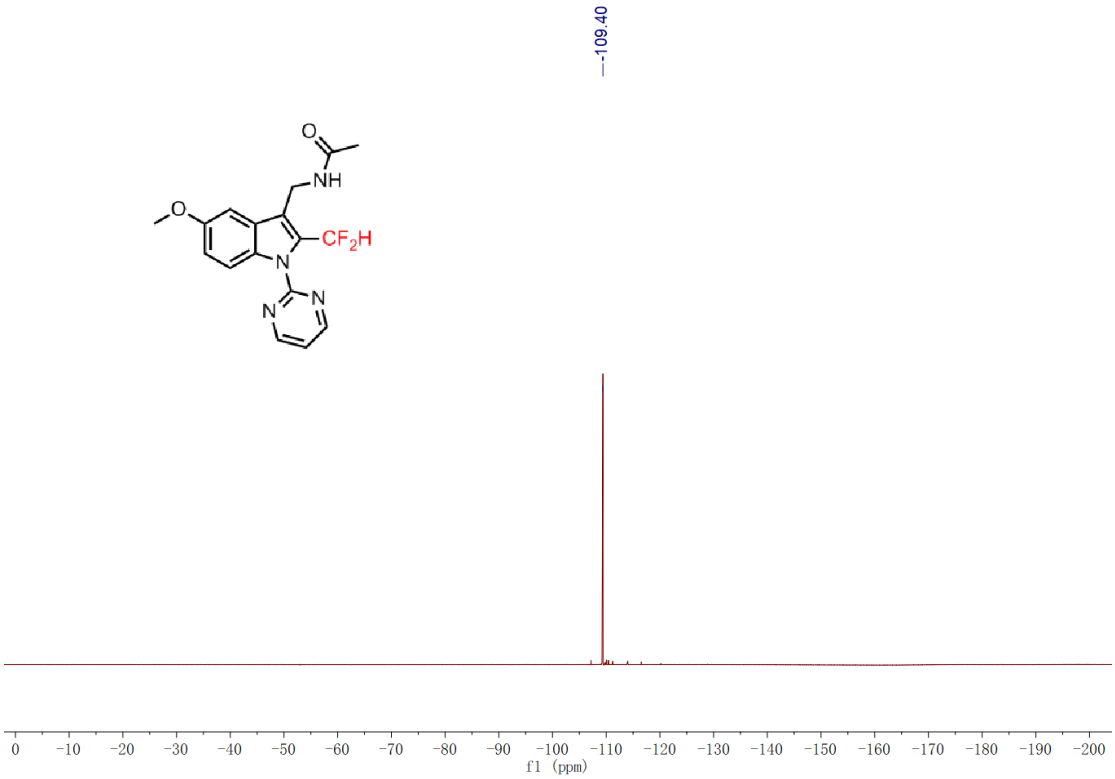


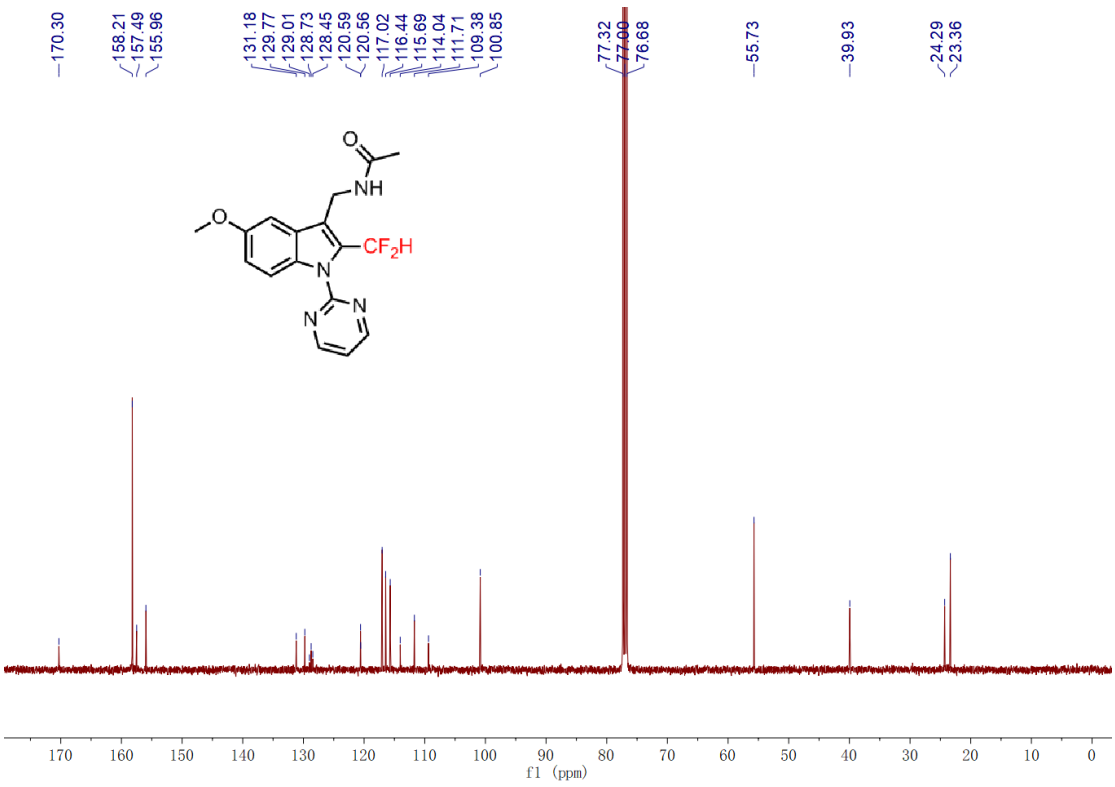




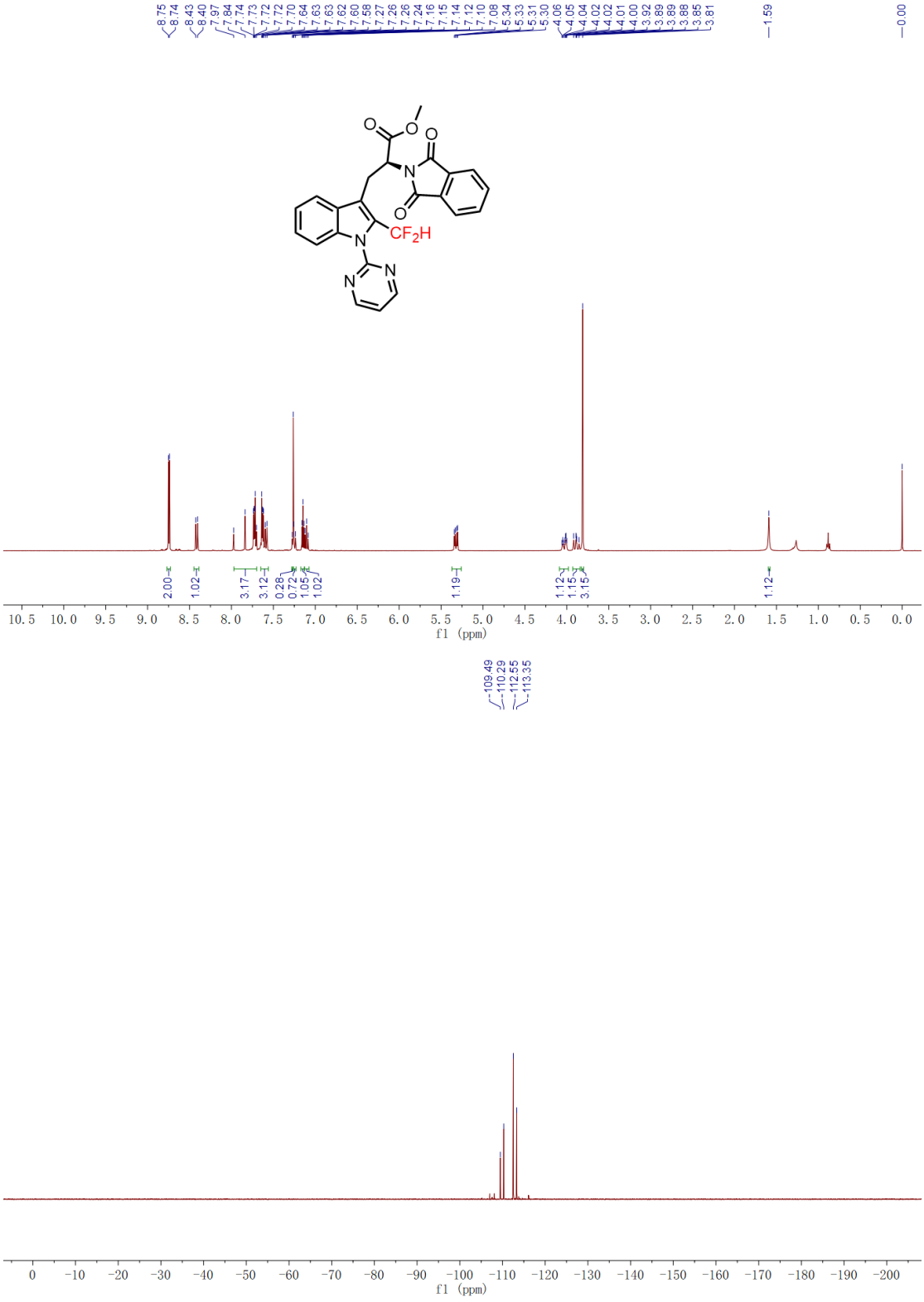
N-(2-(2-(difluoromethyl)-5-methoxy-1-(pyrimidin-2-yl)-1*H*-indol-3-yl) ethyl) acetamide (**3z**)

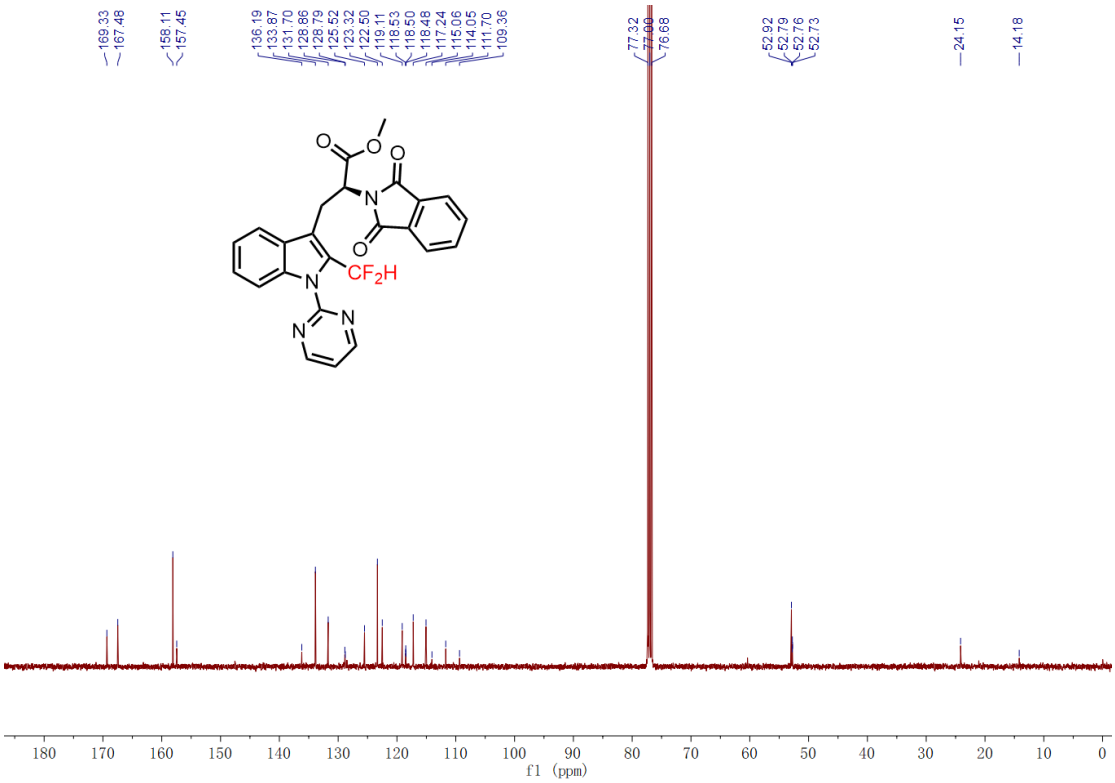



-109.40
O
NH
O
CF2H
N
N
N
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

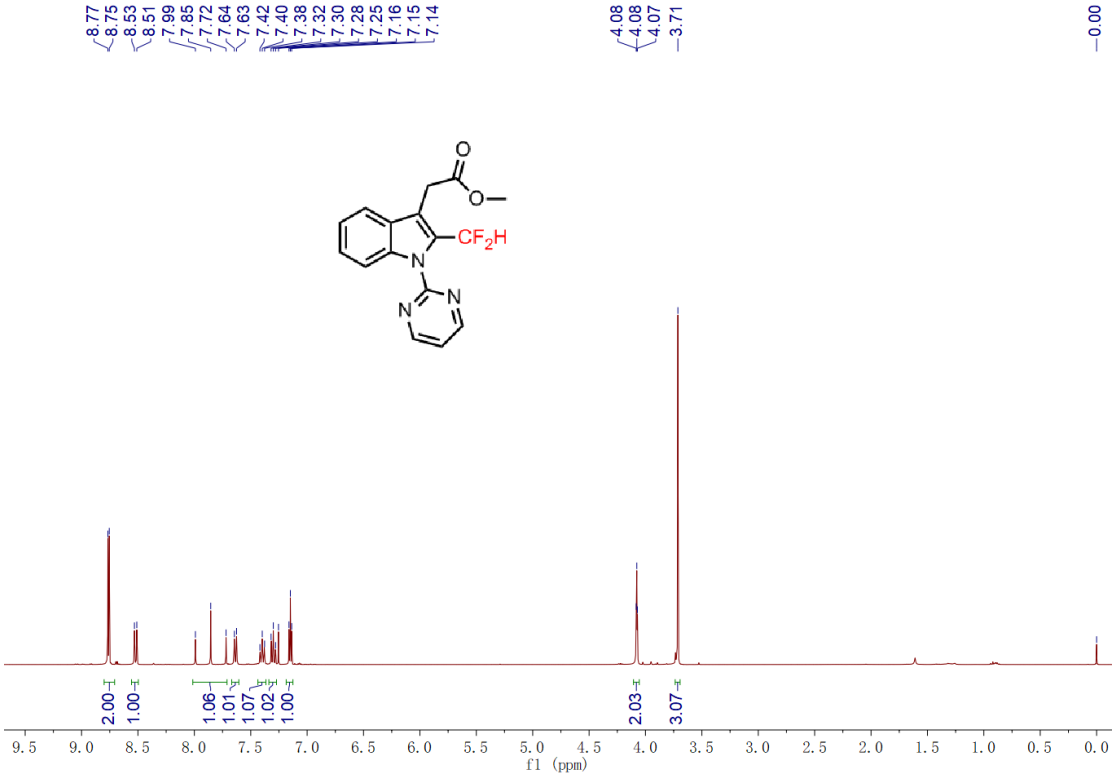

170.30
158.21
157.49
155.96
131.18
129.77
129.01
128.73
128.45
120.59
120.56
117.02
116.44
115.69
114.04
111.71
109.38
100.85
77.32
77.00
76.68
55.73
39.93
24.29
23.36
O
NH
O
CF2H
N
N
N
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

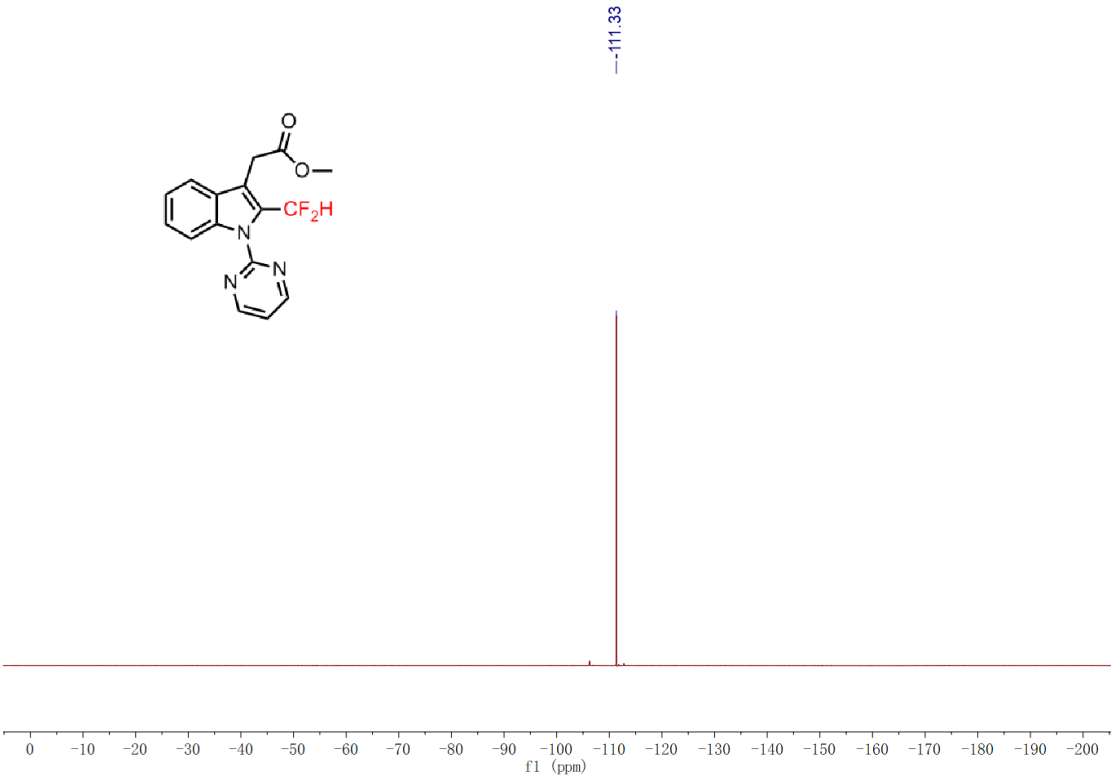
Methyl (*S*)-3-(2-(difluoromethyl)-1-(pyrimidin-2-yl)-1*H*-indol-3-yl)-2-(1,3-dioxoisoindolin-2-yl) propanoate (**3za**)

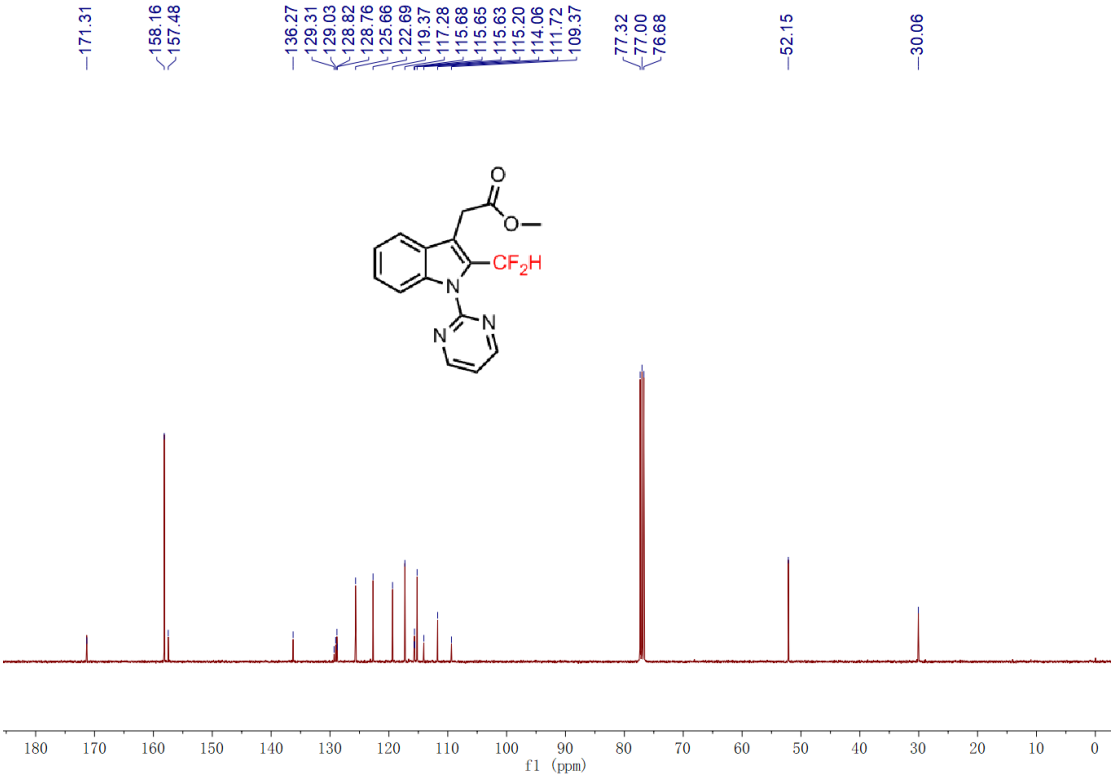




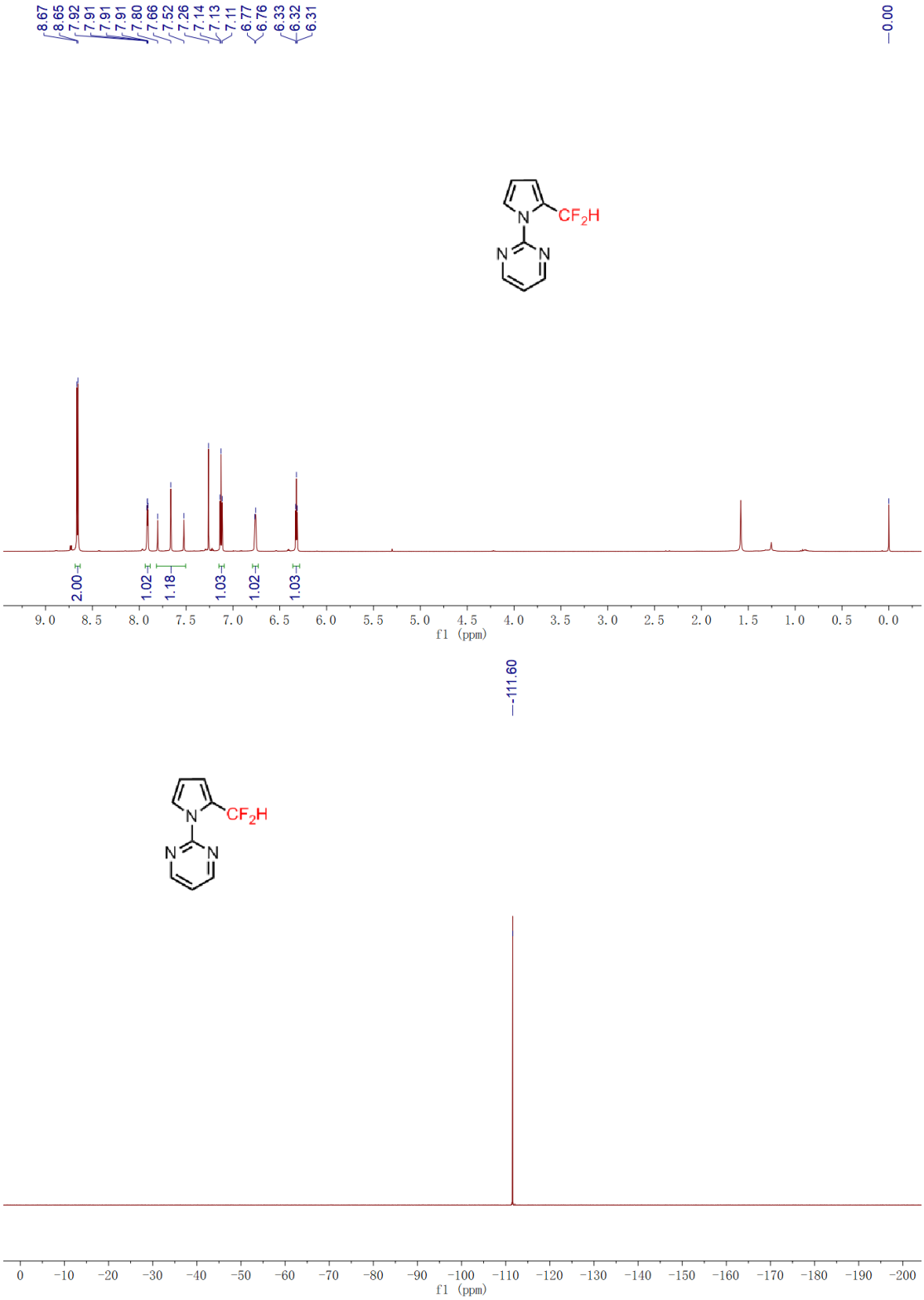
Methyl 2-(2-(difluoromethyl)-1-(pyrimidin-2-yl)-1*H*-indol-3-yl) acetate (**3zb**)

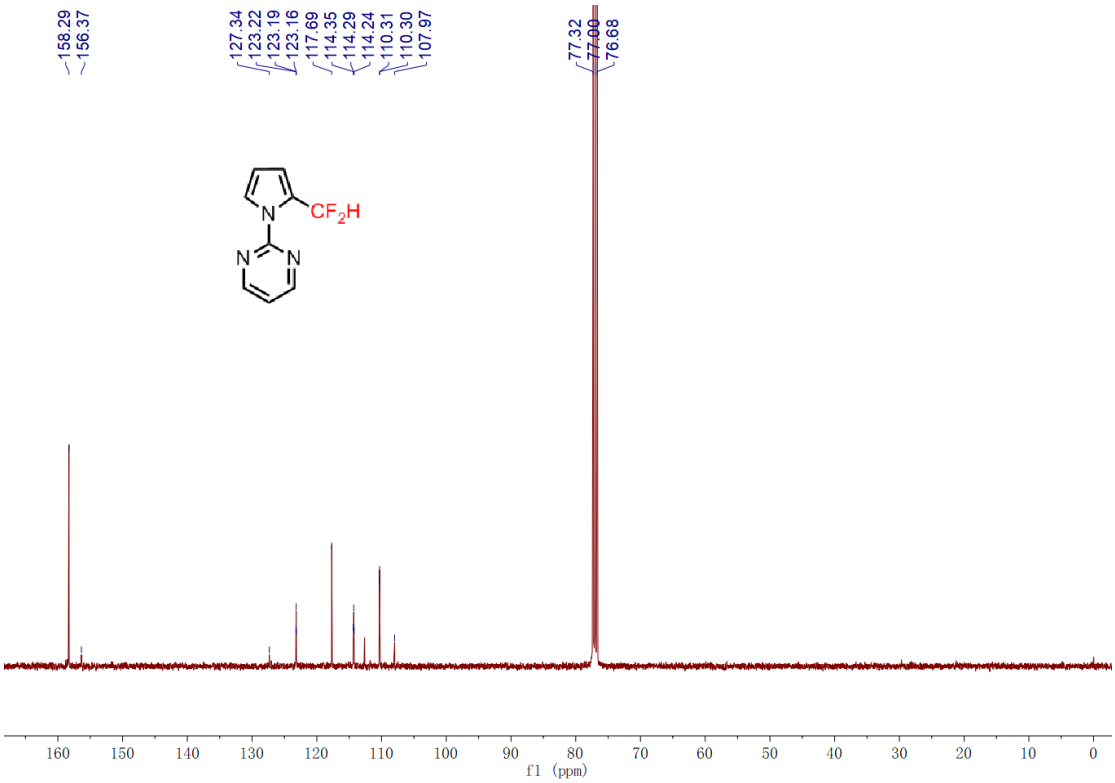



-111.33
O
O
CF2H
N
N
N
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

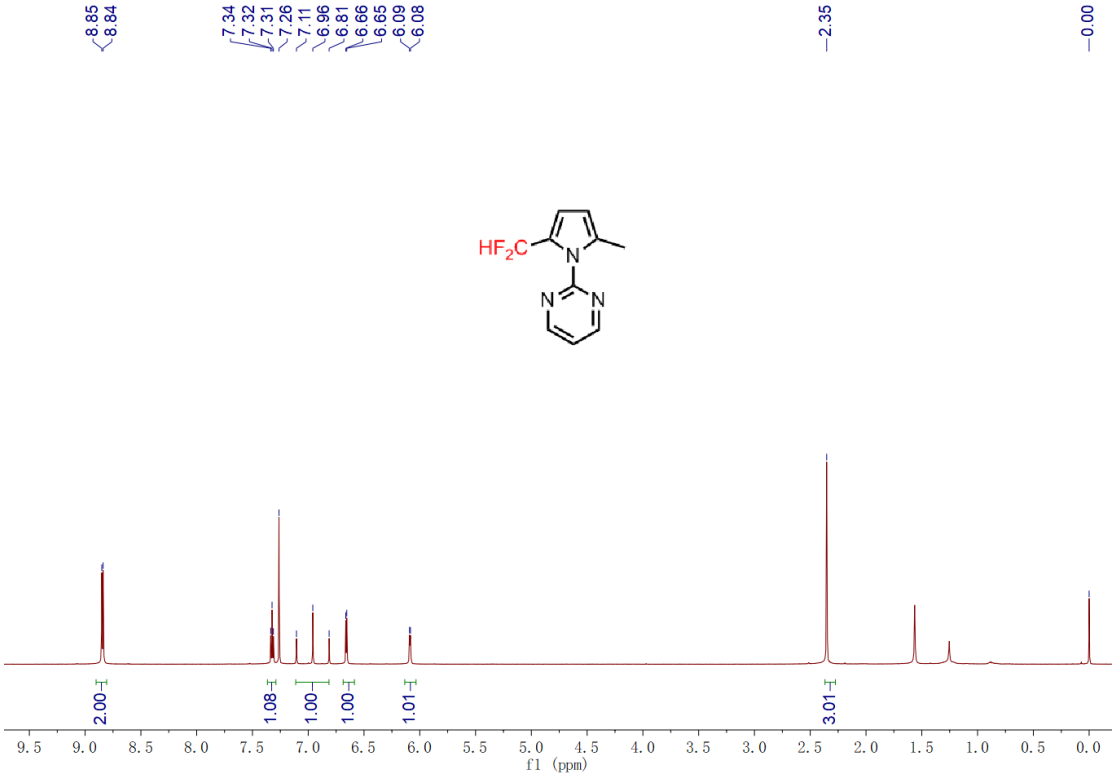

171.31
158.16
157.48
136.27
129.31
129.03
128.82
128.76
125.66
122.69
119.37
117.28
115.68
115.65
115.63
115.20
114.06
111.72
109.37
77.32
77.00
76.68
52.15
30.06
O
O
CF2H
N
N
N
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

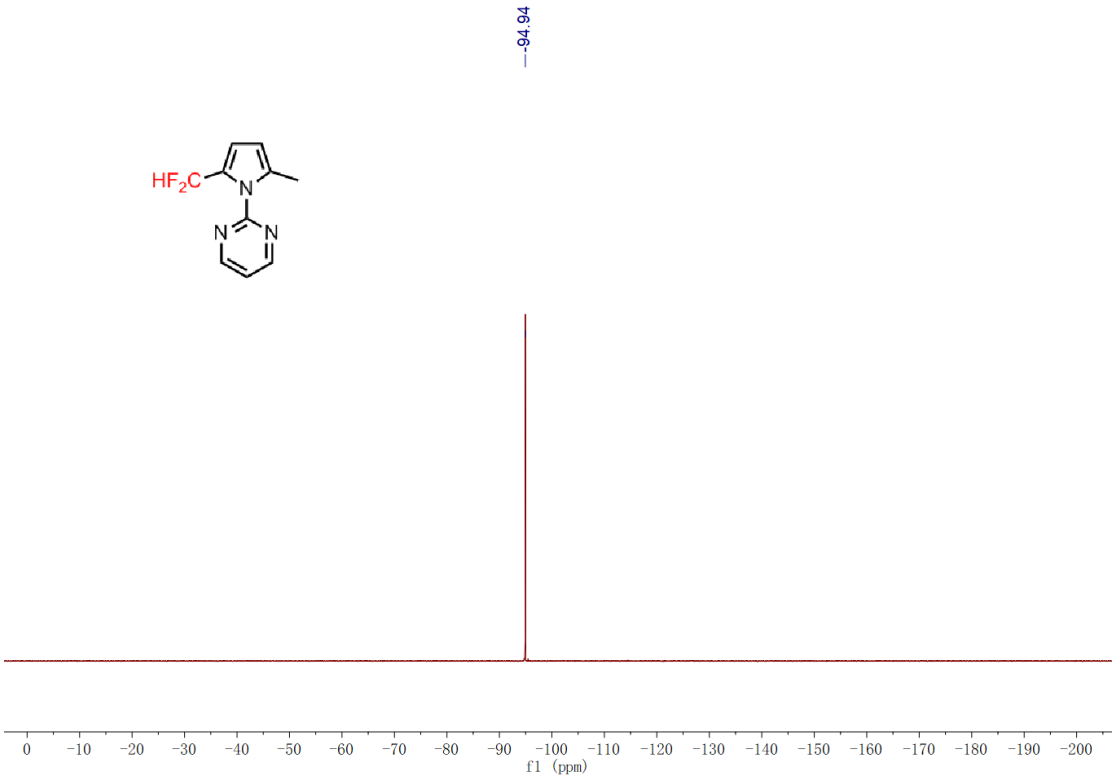
2-(2-(Difluoromethyl)-1*H*-pyrrol-1-yl) pyrimidine (**5a**)

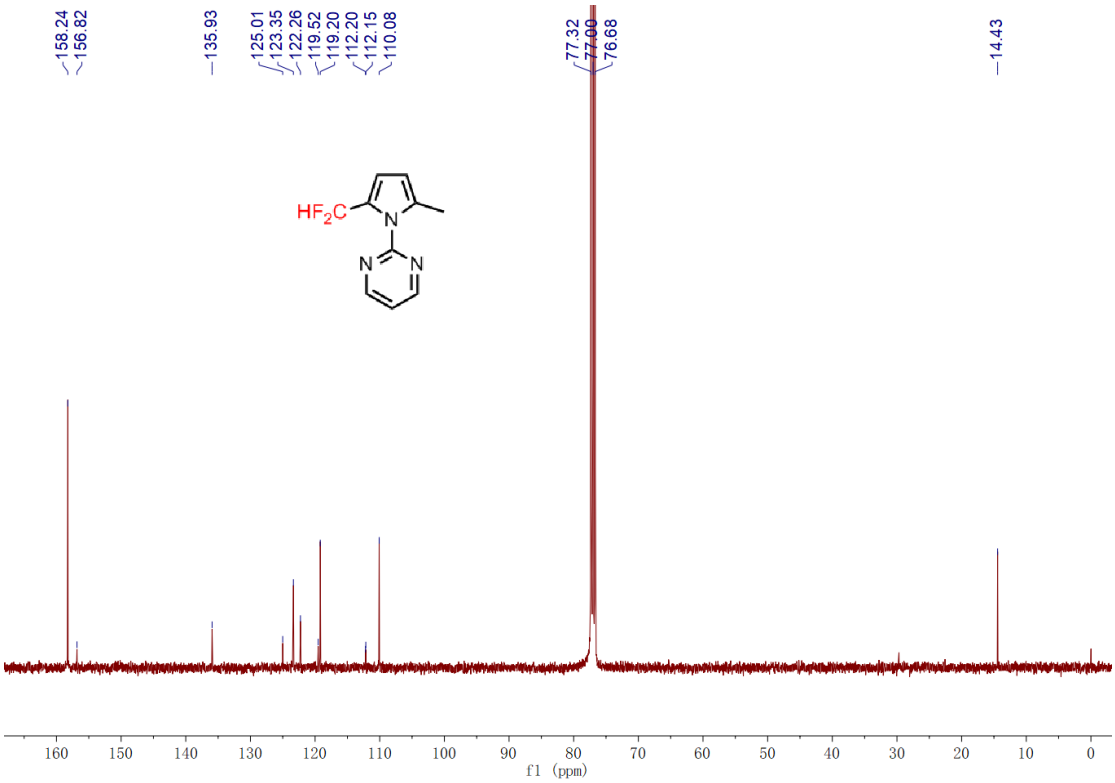




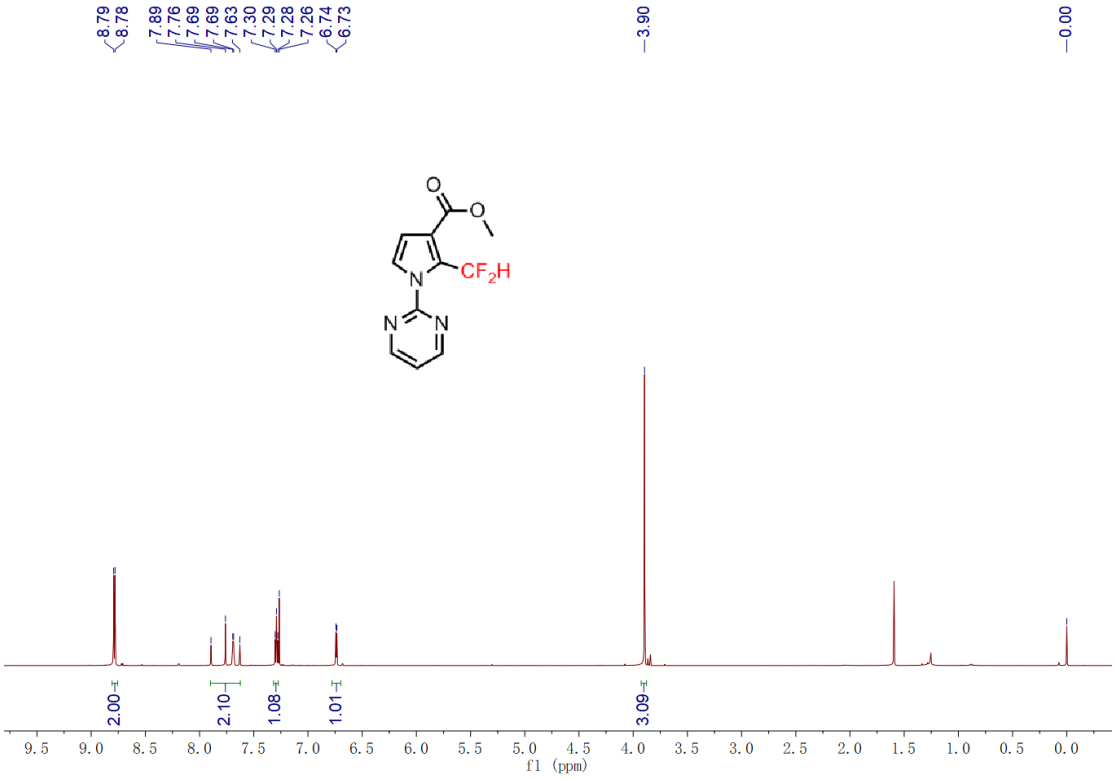
2-(2-(Difluoromethyl)-5-methyl-1*H*-pyrrol-1-yl) pyrimidine (**5b**)

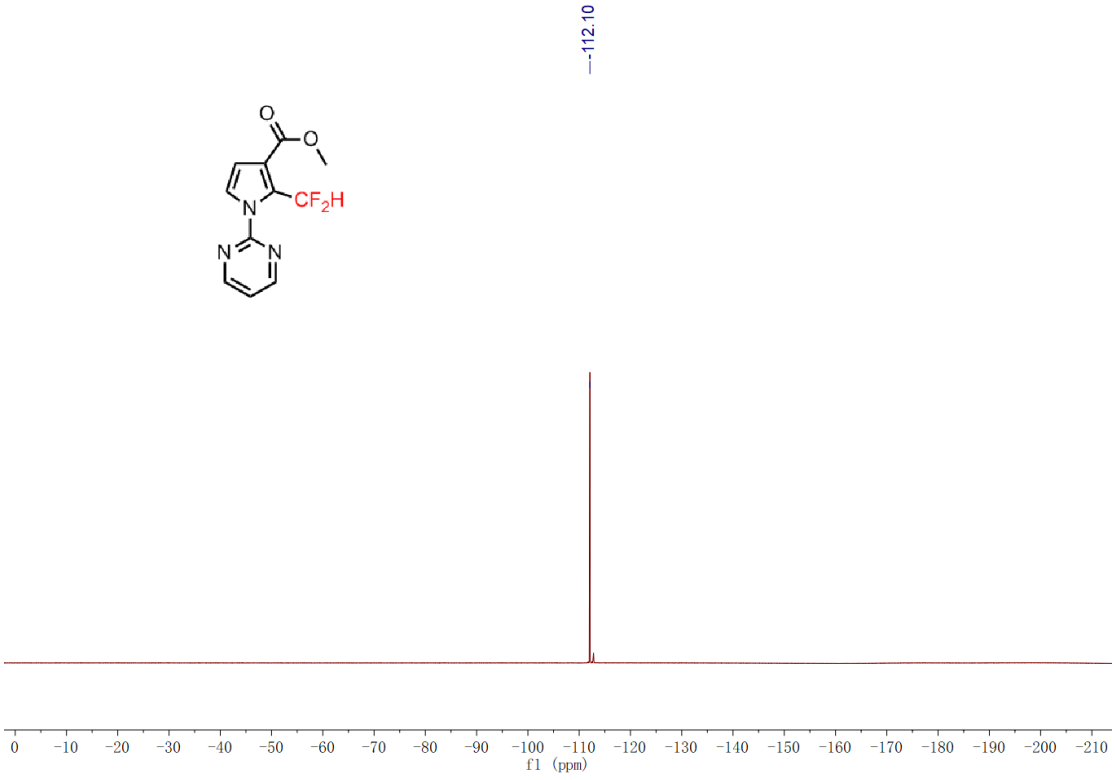


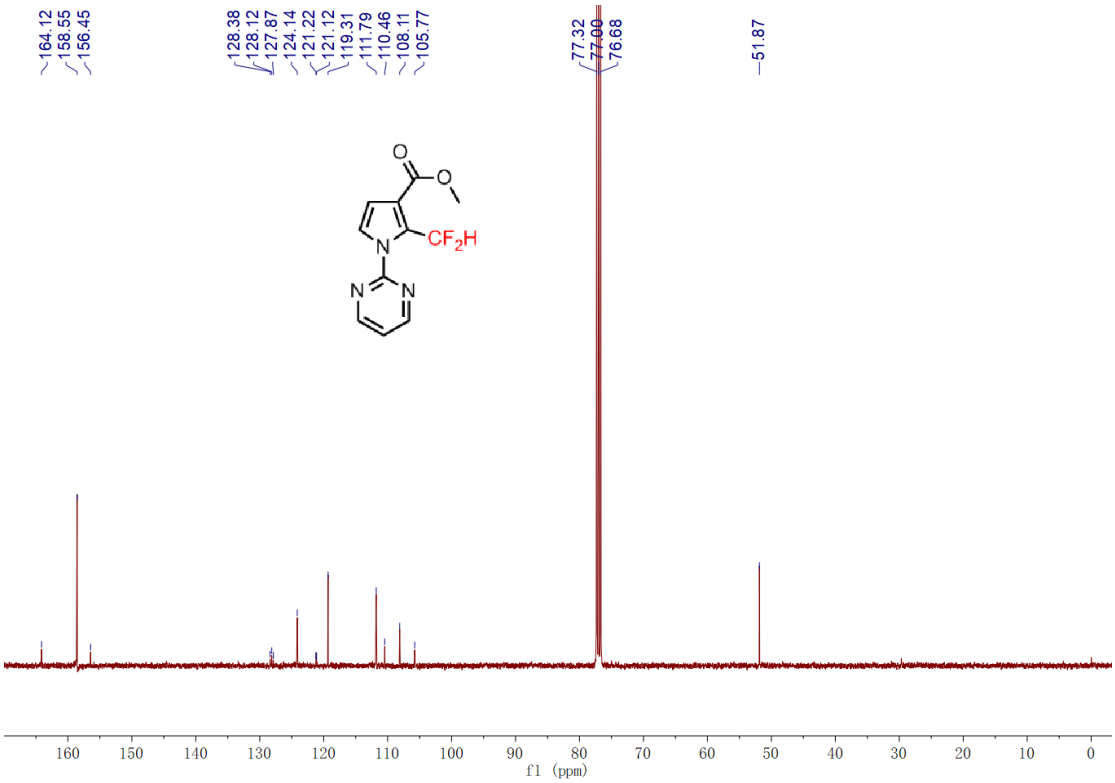

-94.94
HF2C
N
N
N
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)


158.24
156.82
135.93
125.01
123.35
122.26
119.52
119.20
112.20
112.15
110.08
77.32
77.00
76.68
14.43
HF2C
N
N
N
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

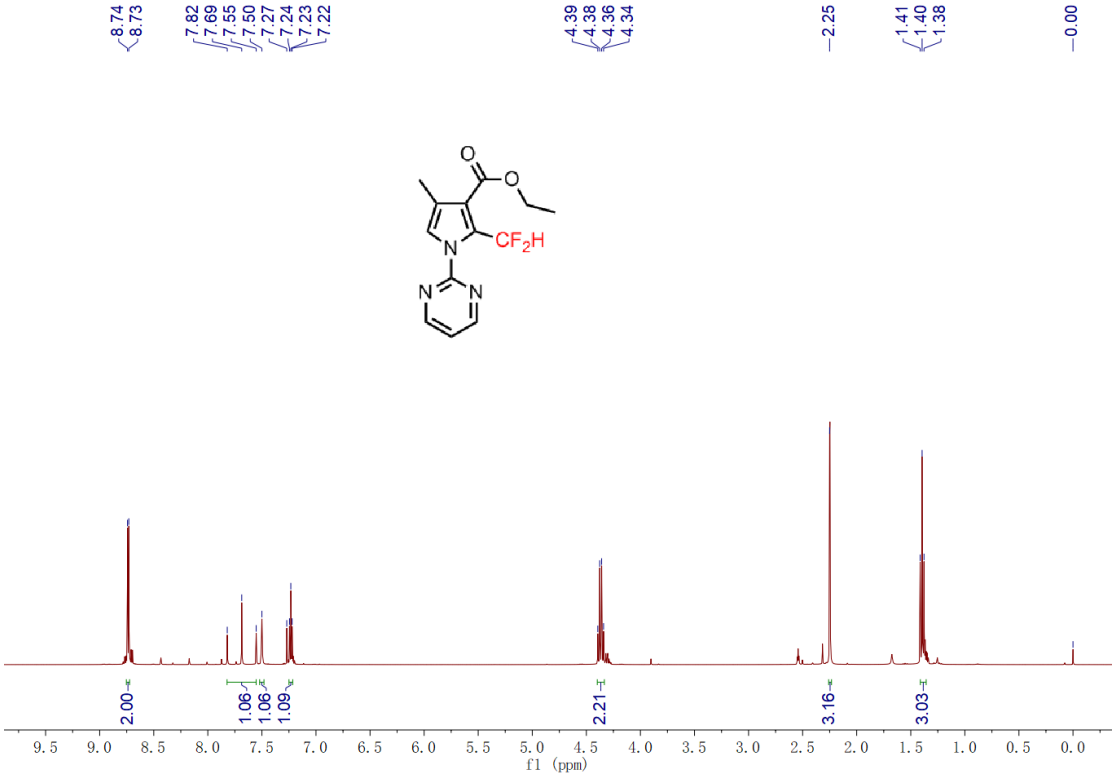
Methyl 2-(difluoromethyl)-1-(pyrimidin-2-yl)-1*H*-pyrrole-3-carboxylate (**5c**)



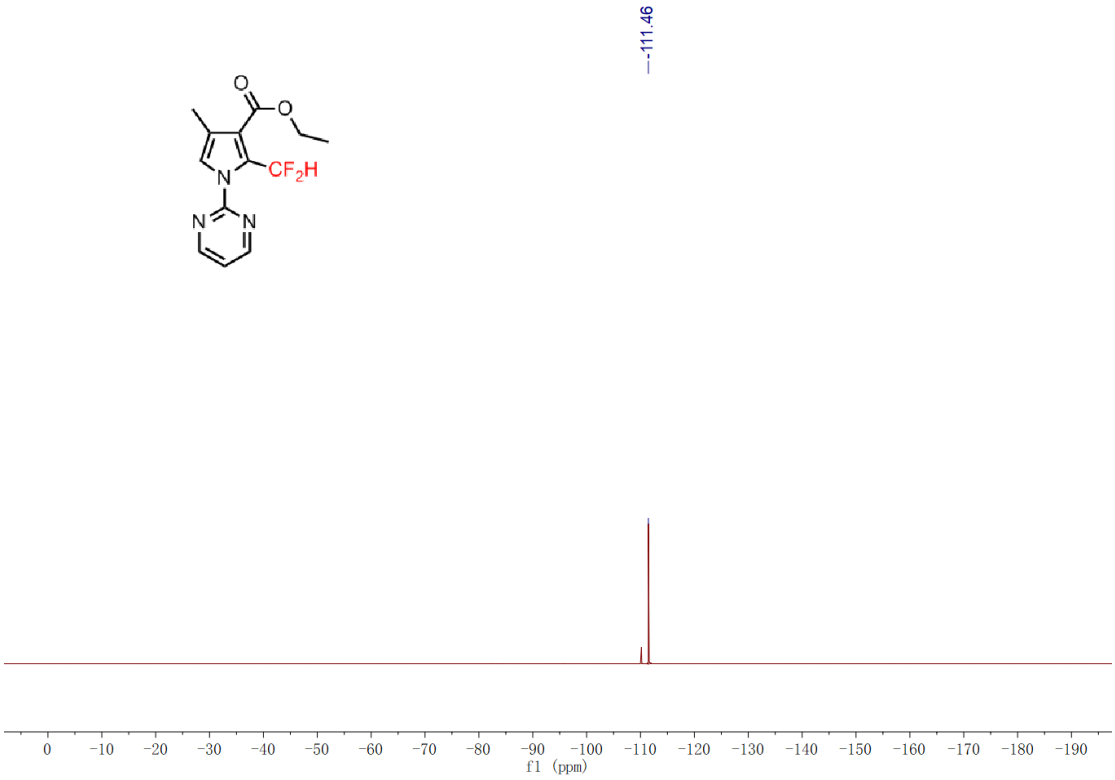


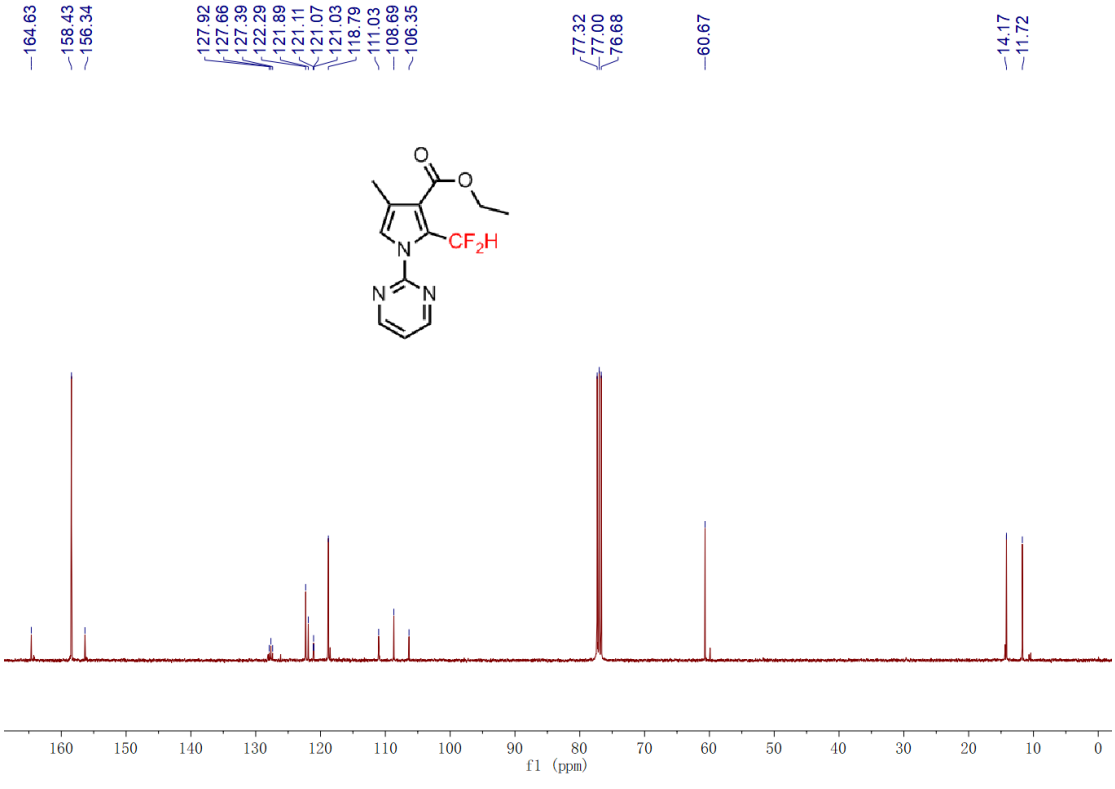


Methyl 2-(difluoromethyl)-4-methyl-1-(pyrimidin-2-yl)-1*H*-pyrrole-3-carboxylate (**5d**)

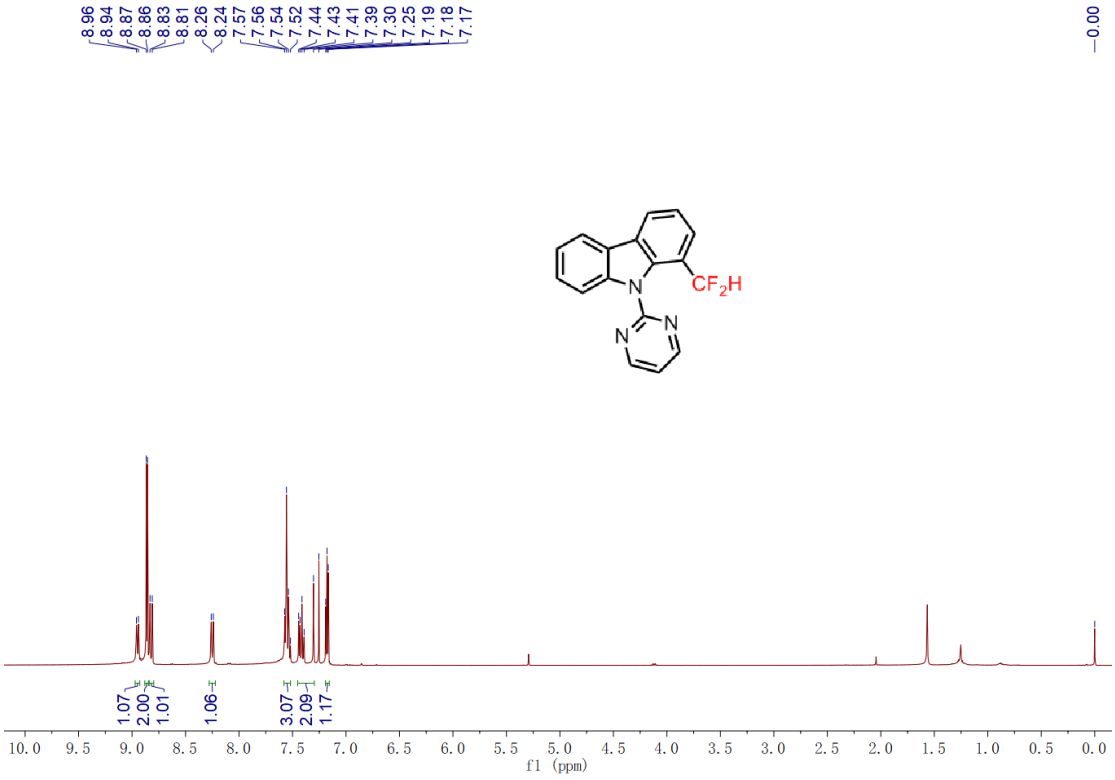


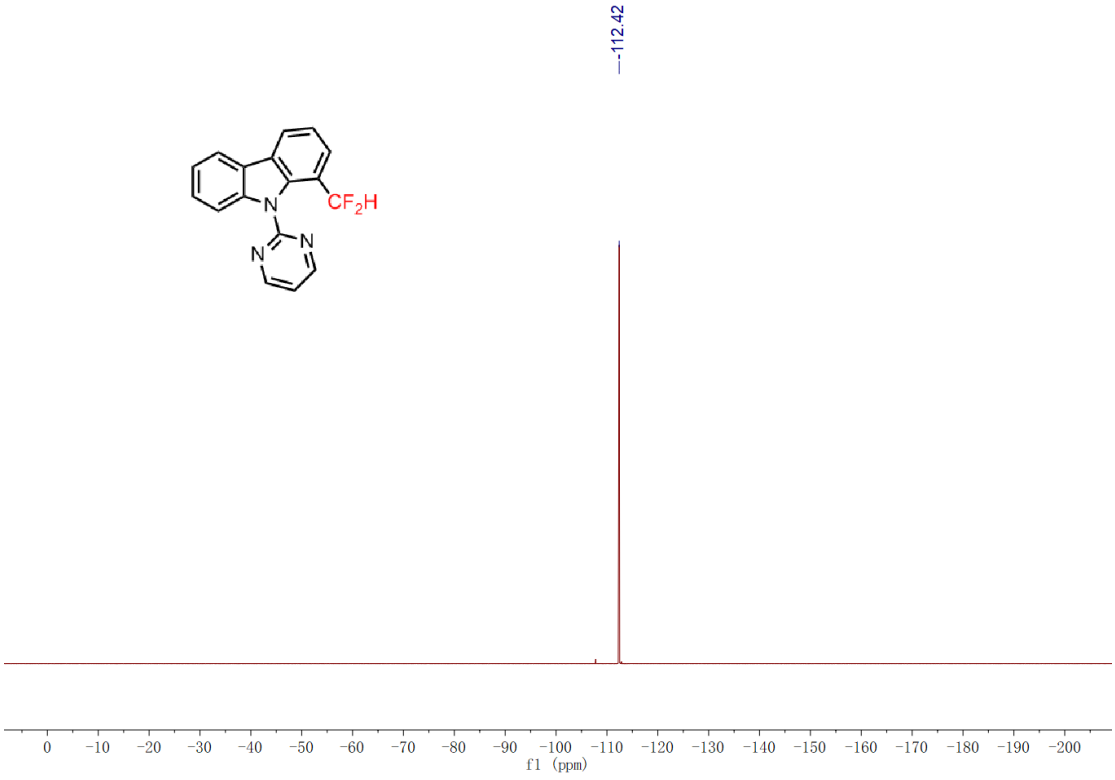
O
O
CF2H
N
N
N

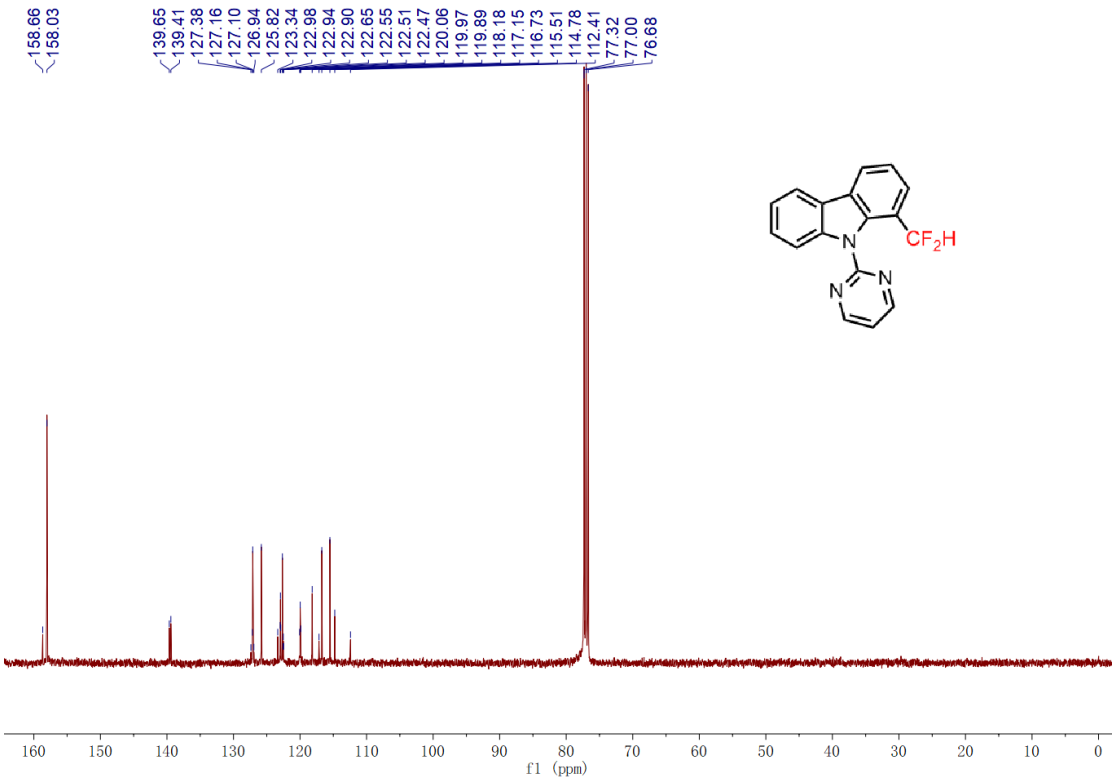

111.46
0
−10
−20
−30
−40
−50
−60
−70
−80
−90
−100
−110
−120
−130
−140
−150
−160
−170
−180
−190
f1 (ppm)


164.63
158.43
156.34
127.92
127.66
127.39
122.29
121.89
121.11
121.07
121.03
118.79
111.03
108.69
106.35
77.32
77.00
76.68
60.67
14.17
11.72
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

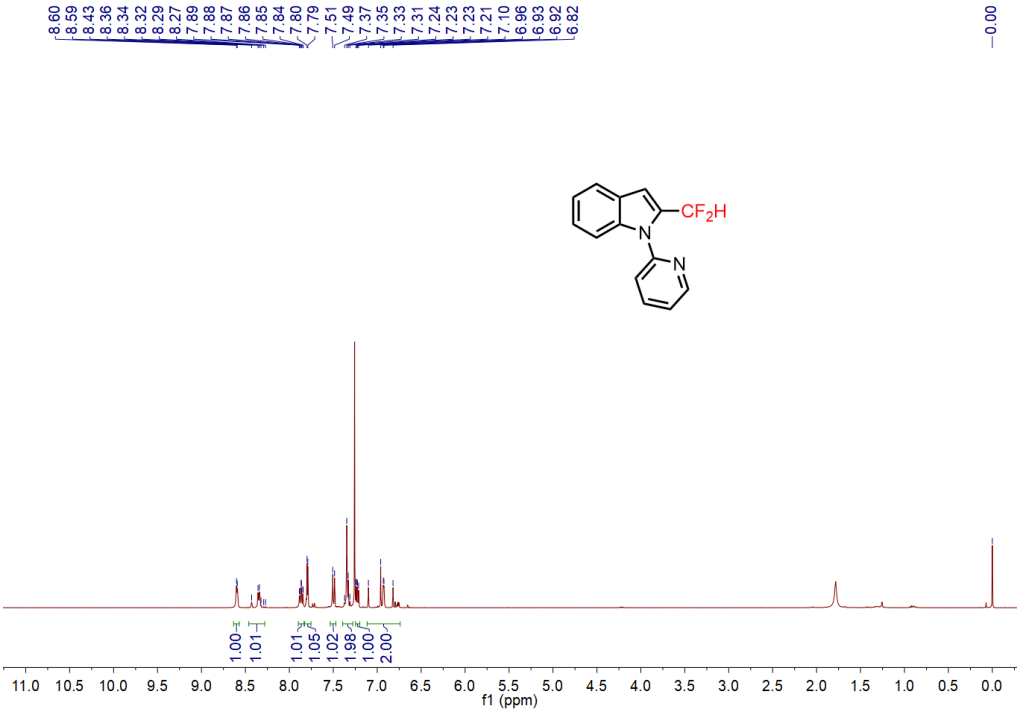
1-(Difluoromethyl)-9-(pyrimidin-2-yl)-9*H*-carbazole (**5e**)

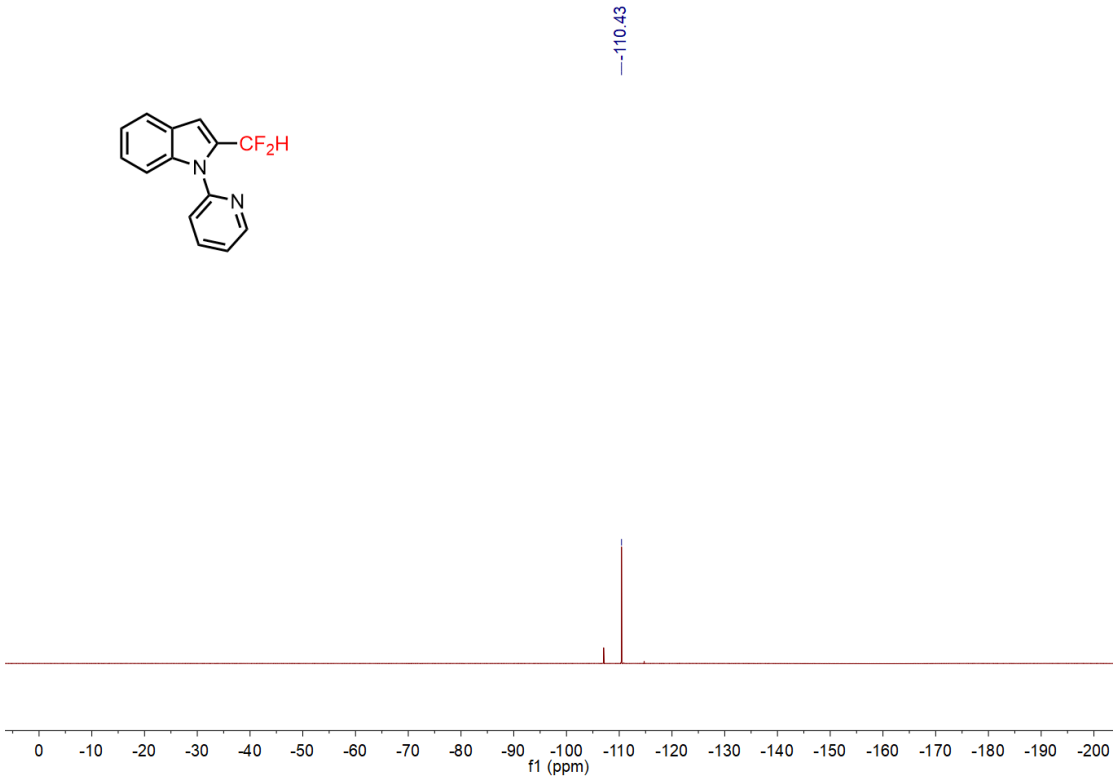


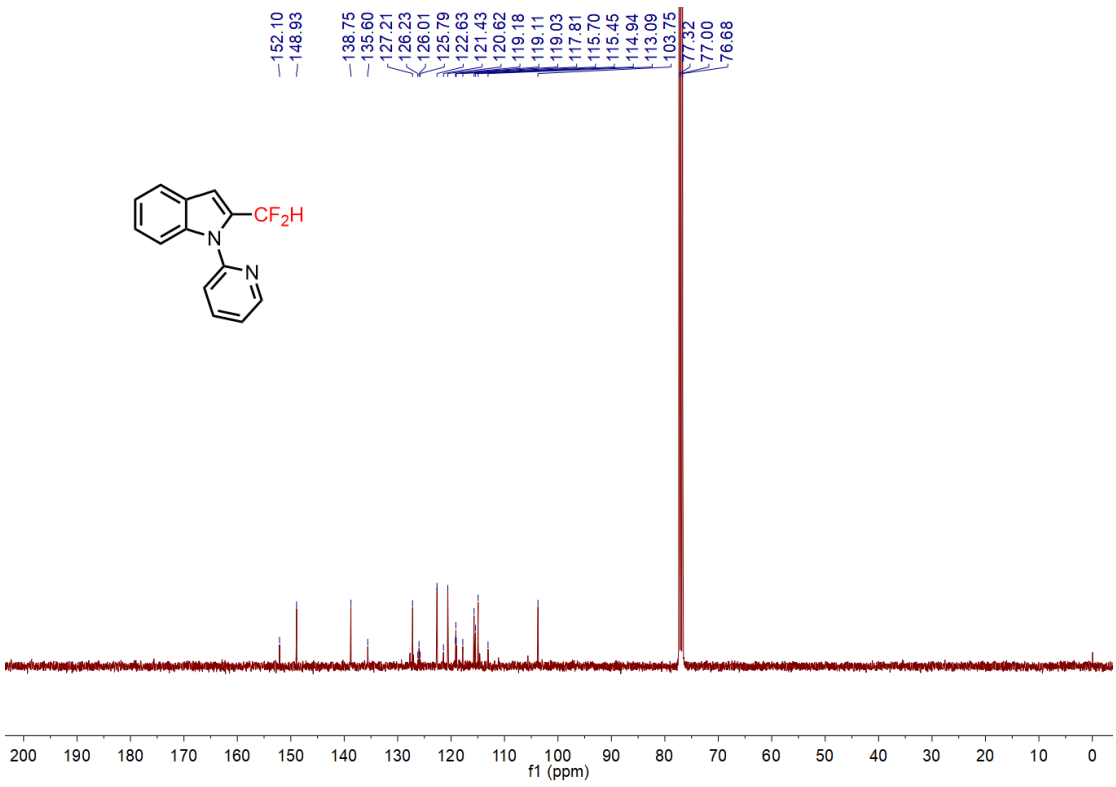




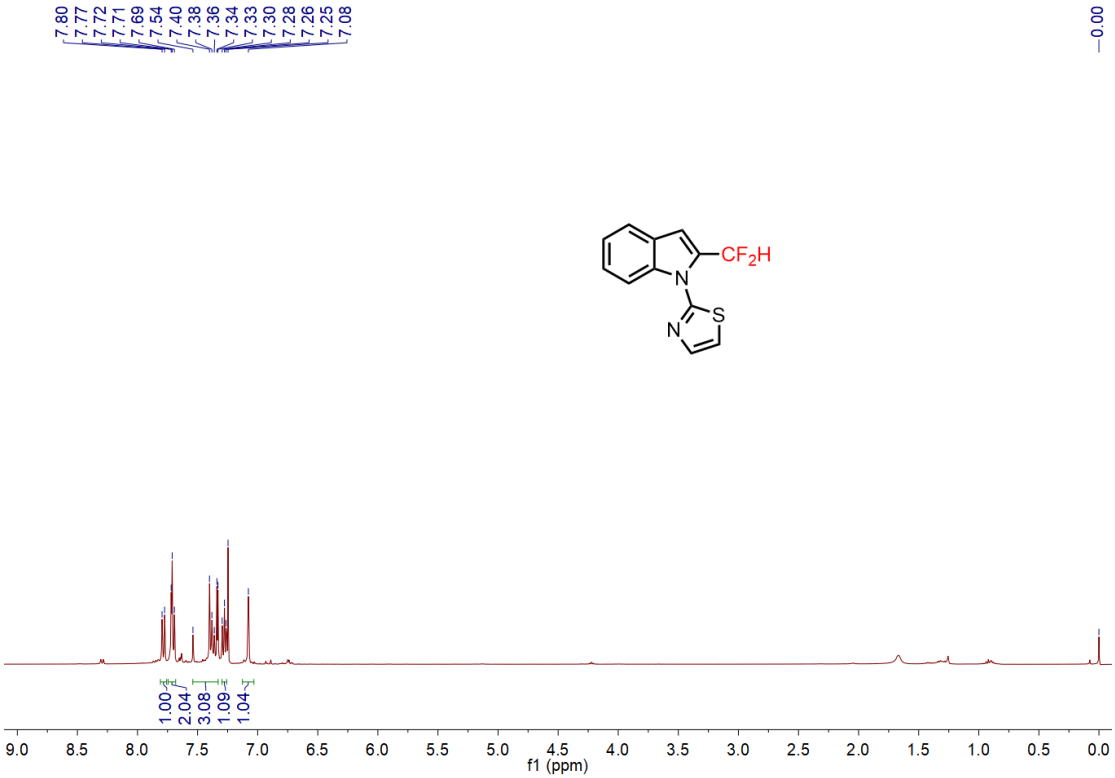
2-(Difluoromethyl)-1-(pyridin-2-yl)-1*H*-indole (**6a**)

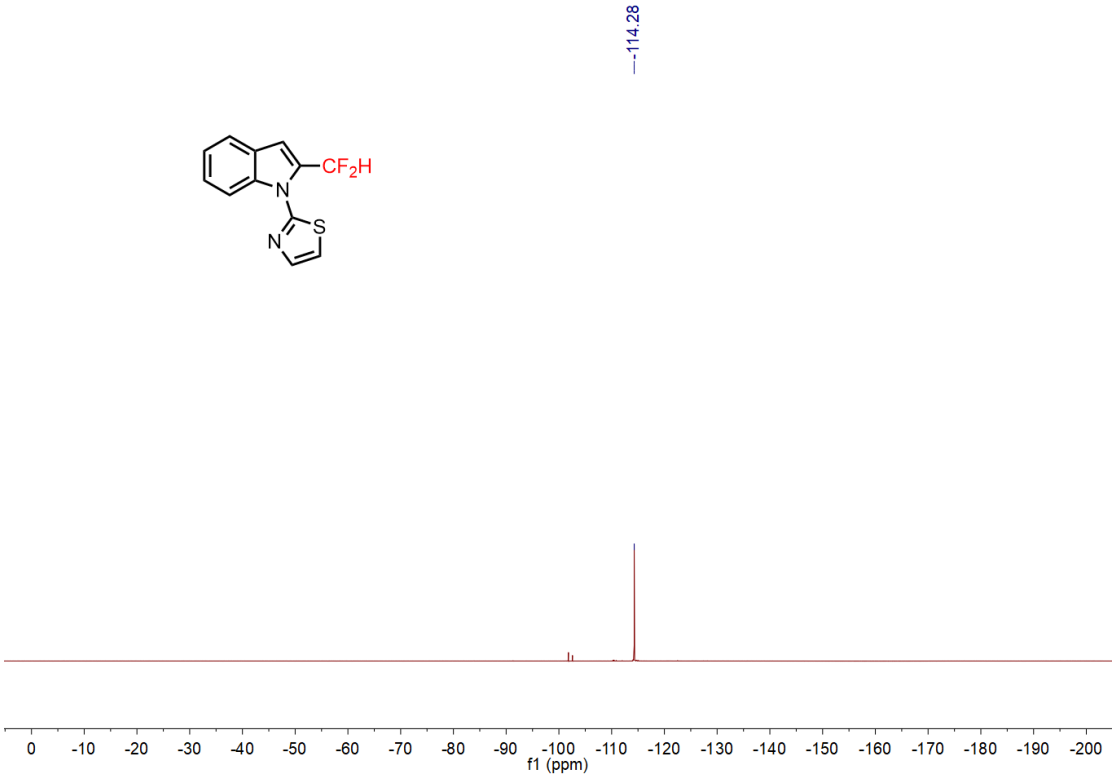


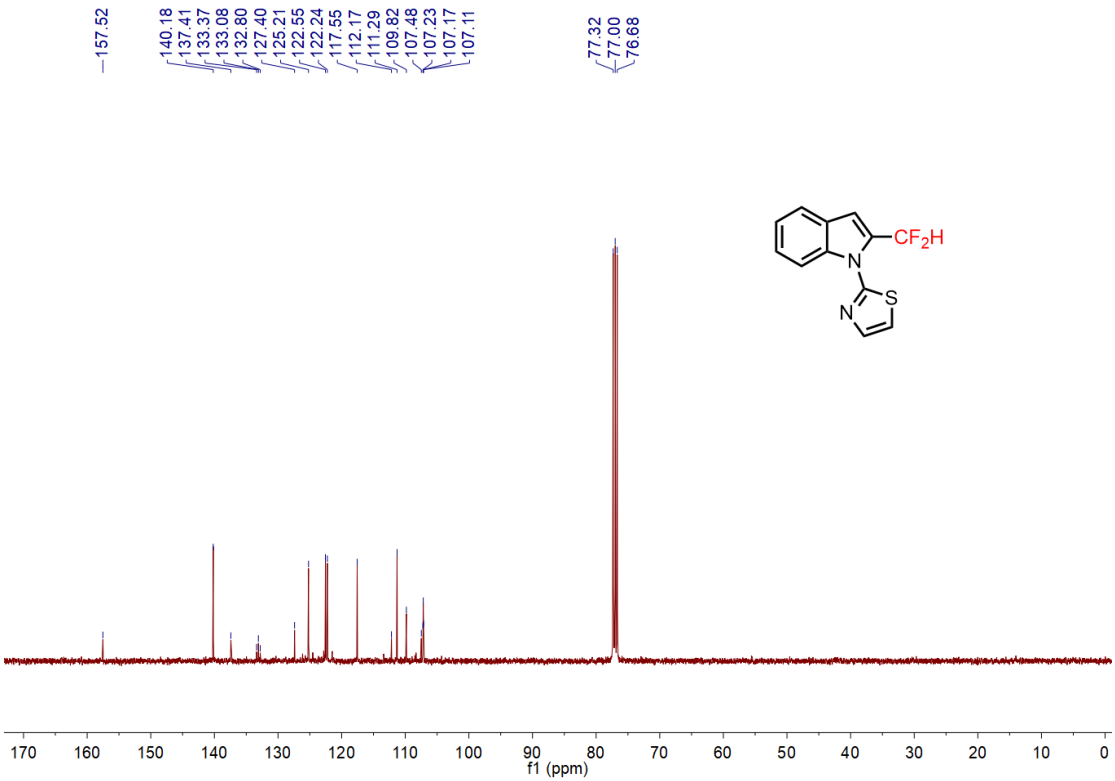

-110.43
CF2H
N
N
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)


152.10
148.93
138.75
135.60
127.21
126.23
126.01
125.79
122.63
121.43
120.62
119.18
119.11
119.03
117.81
115.70
115.45
114.94
113.09
103.75
77.32
77.00
76.68
CF2H
N
N
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

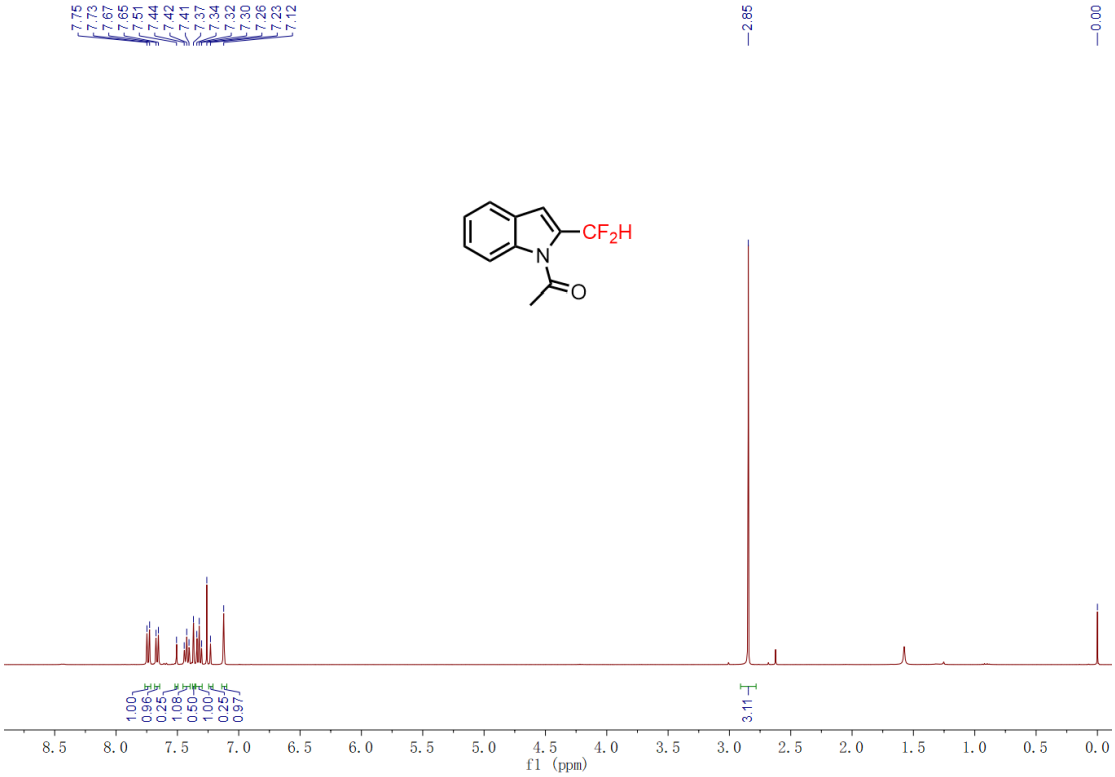
2-(2-(Difluoromethyl)-1*H*-indol-1-yl) thiazole (**7a**)

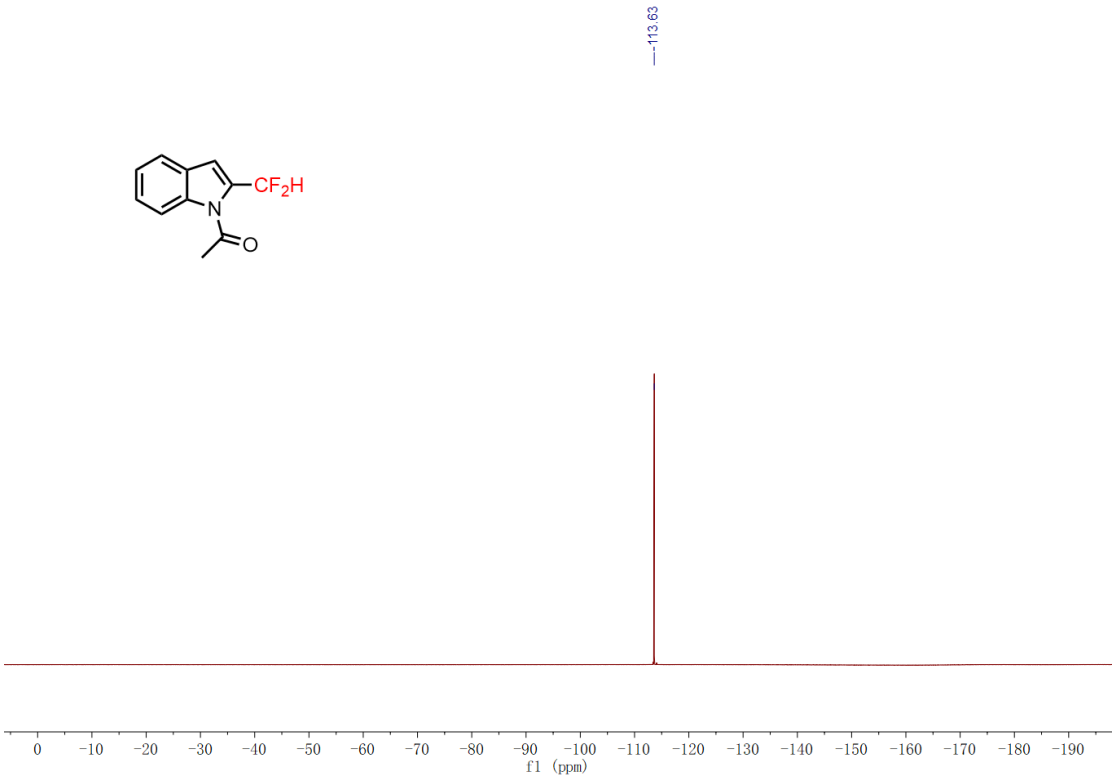


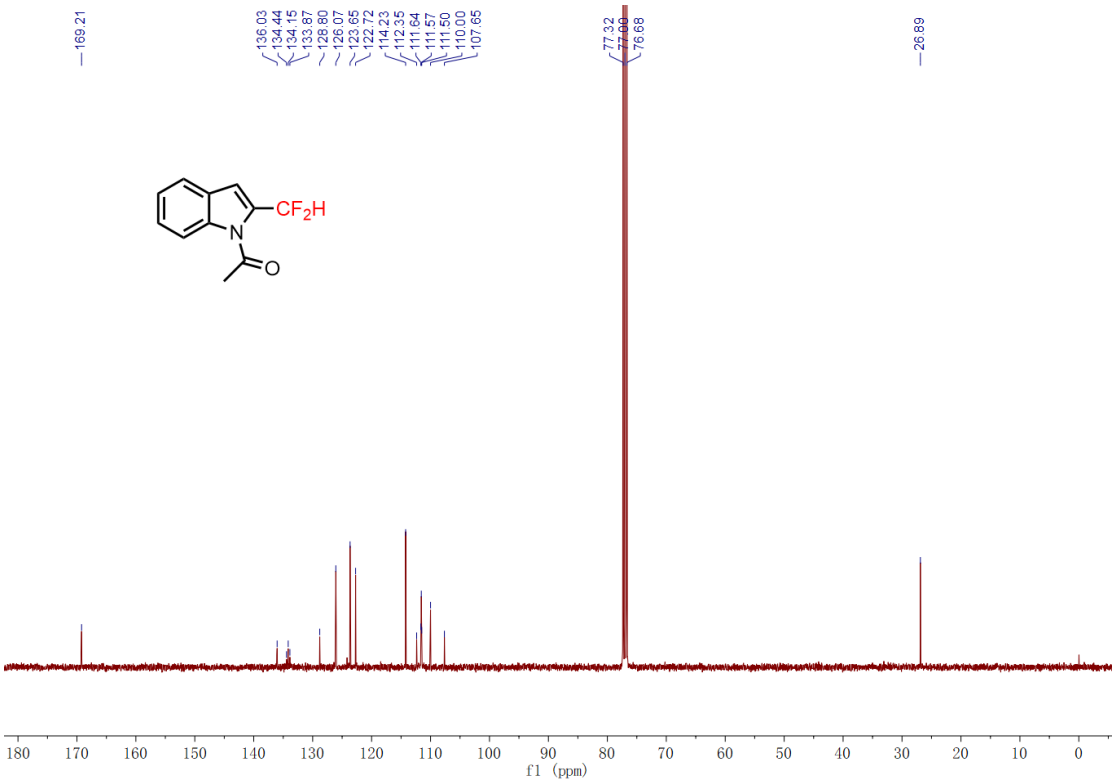




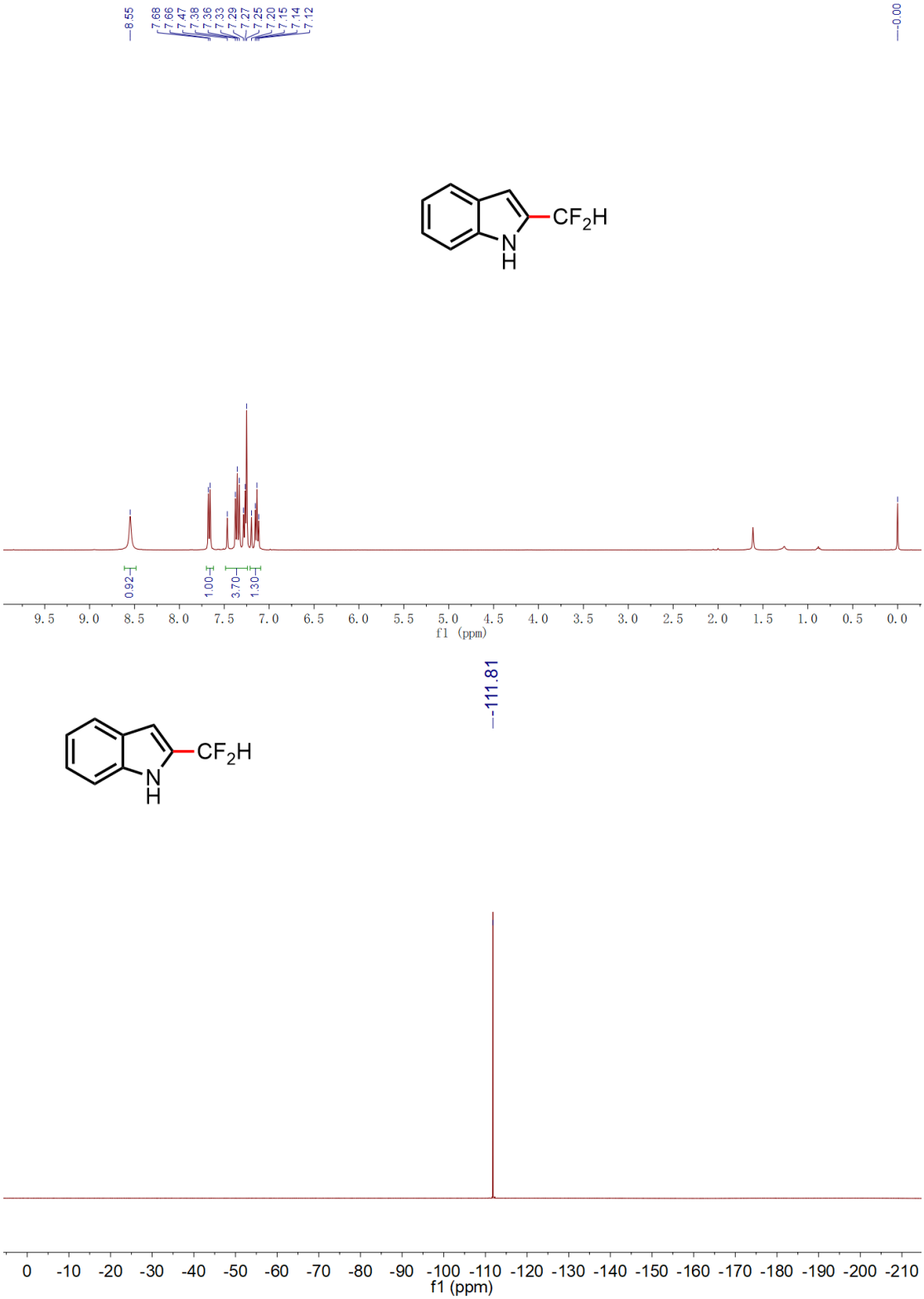
1-(2-(Difluoromethyl)-1*H*-indol-1-yl) ethan-1-one (**8a**)

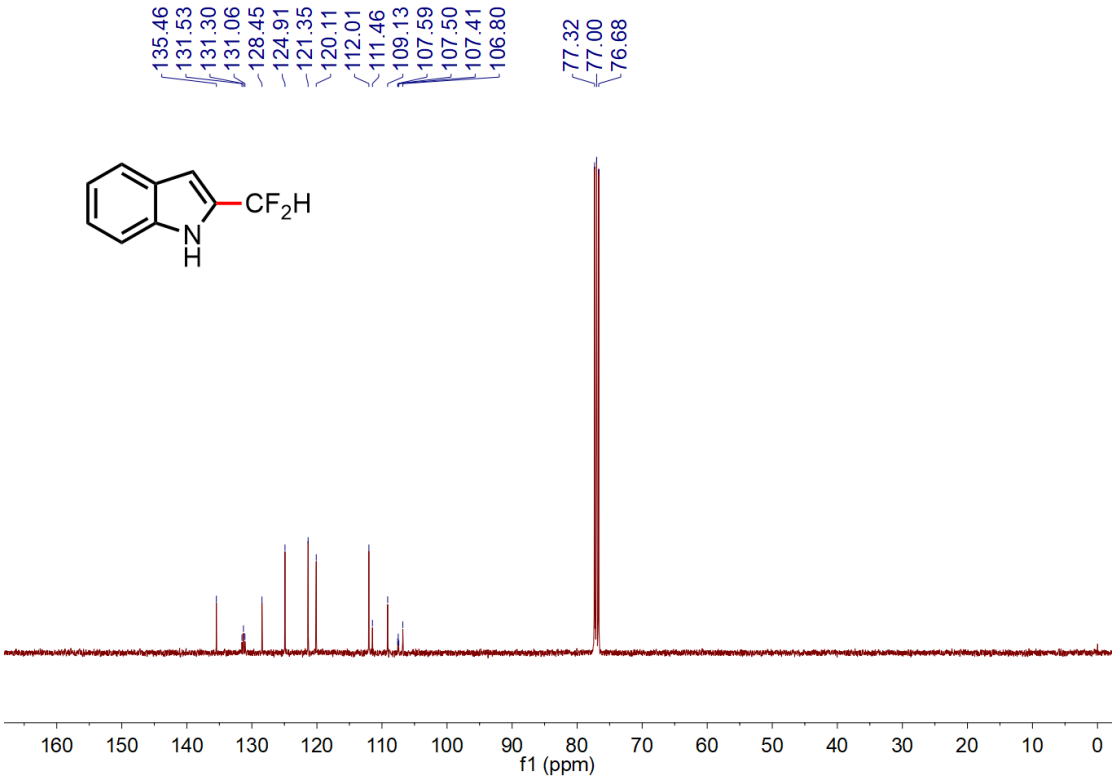



113.63
CF2H
N
O
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)


169.21
136.03
134.44
134.15
133.87
128.80
126.07
123.65
122.72
114.23
112.35
111.64
111.57
111.50
110.00
107.65
77.32
77.00
76.68
26.89
CF2H
N
O
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

2-(Difluoromethyl)-1H-indole (**3aa**)




135.46
131.53
131.30
131.06
128.45
124.91
121.35
120.11
112.01
111.46
109.13
107.59
107.50
107.41
106.80
77.32
77.00
76.68
CF2H
N
H
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)