Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Supporting Information

Visible Light-Induced three-component 1,2-Difluoroalkylarylation of Styrenes with α-Carbonyl Difluoroalkyl Bromides and Indoles

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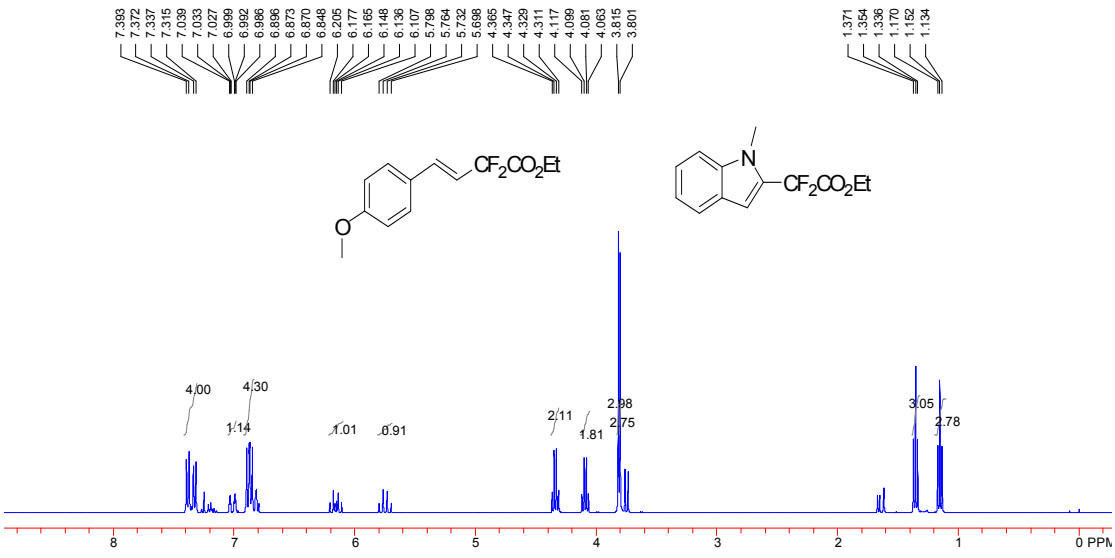
1. General Information

All reactions were carried out under an atmosphere of Ar with dry solvents in flame-dried glassware unless otherwise noted. Anhydrous DMF and DMSO were purchased from J&K® and used as received. CH_3CN and CH_2Cl_2 were distilled from CaH_2. N-substituent indoles (**1a-1v**)[1], bromodifluoroacyl arenes (**2b, 2c**)[2] and difluoro amides **2d** [3]were prepared according to the literature, respectively. [2][3] Reactions were monitored by TLC on silica gel plates (GF254), and the analytical thin-layer chromatography (TLC) was performed on precoated, glass-backed silica gel plates. ^{1}H NMR, ^{13}C NMR spectra and ^{19}F NMR spectra were recorded on a Bruker AVANCE Ⅲ–400 spectrometer at room temperature. Chemical shifts (δ) are reported in ppm downfield from tetramethylsilane. Abbreviations for signal couplings are: s, singlet; d, doublet; dd, double doublet; t, triplet; m, multiplet. High resolution mass spectra were obtained on a high–resolution mass spectrometer in the ESI mode. The 36W fluorescent light bulb was directly got from the supermarket.

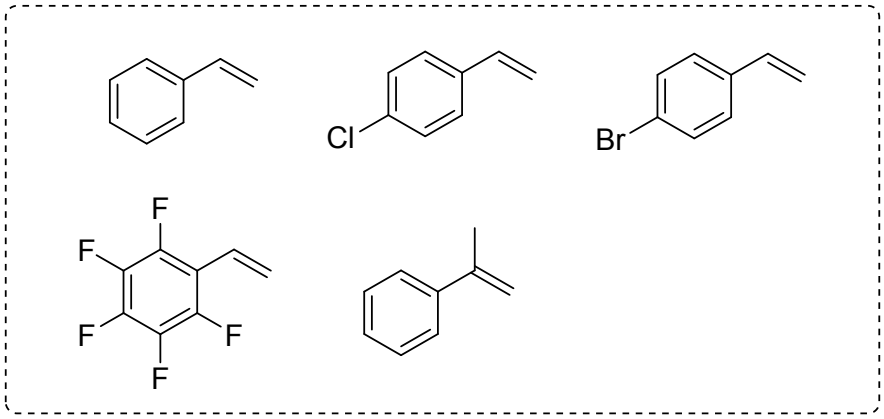
2. General Procedure for Three-Component 1,2-Difluoroalkylarylation of styrenes

An oven-dried Schlenk tube (10 mL) was equipped with a magnetic stir bar, **1** (0.2 mmol), **2** (0.4 mmol), **3** (0.4 mmol), *fac*-Ir(ppy)$_3$ (0.002mmol, 2.6 mg), AgOAc (0.4mmol). The flask was evacuated and backfilled with Ar for 3 times. 2 ml DCM was then added with syringe under Ar. The tube was placed at a distance (app.5 cm) from 36W white LEDs lamb, and the resulting solution was stirred at ambient temperature under visible-light irradiation and monitored by TLC. After the reaction was finished, the mixture was concentrated under vacuum, and the residue was purified by chromatography on silica gel to afford the **4a-4ac**.

Optimization studies show that the base was crucial for this successful transformation. The aromatic C-H difluoroalkylation product and alkene C-H difluoroalkylation product were detected from the reaction without base, as determined by ^{1}HNMR analysis of the crude reaction mixture.



Some alkenes were not suitable for this reaction:



3. References:

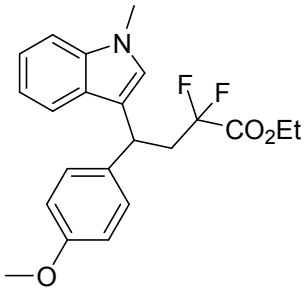
[1] J. M. Fraile, K.L. Jeune, J. A. Mayoral, N. Ravasio and F. Zaccheria, *Org. Biomol. Chem.*, **2013**,*11*, 4327–4332;

[2] T. Nihei, N.Iwai, T. Matsuda and T. Kitazume, *J. Org. Chem.*, **2005**, *70*, 5912-5915;

[3] P. Xu, G. Wang, Y. Zhu, W. Li, Y. Cheng, S. Li, and C. Zhu, *Angew. Chem. Int. Ed.* **2016**, *55*, 2939 –2943.

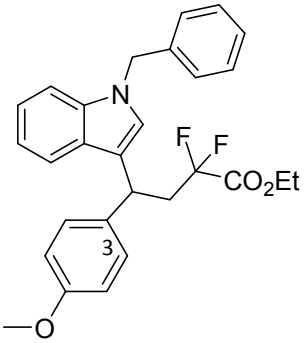
4. Characterization data of compounds

ethyl 2,2-difluoro-4-(4-methoxyphenyl)-4-(1-methyl-1H-indol-3-yl)butanoate **4a**



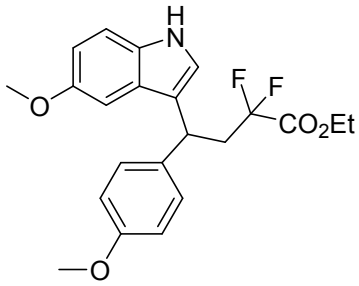
Reaction time 36h,Yield 70%, yellow oil.^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.46 (d, *J* = 8.0 Hz, 1H), 7.26-7.24 (m, 3H), 7.20-7.17 (m, 1H), 7.06-7.04 (m, 1H), 6.82 – 6.78 (m, 3H), 4.49 (dd *J*=8.2, 6.8 Hz, 1H), 3.76-3.72 (m, 8H), 3.06-2.84 (m, 2H), 1.07 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (100MHz, Chloroform-*d*): δ 163.9 (t, *J*=32.4Hz), 158.4 , 137.4 , 134.9 , 129.0 , 126.7 , 126.5 , 121.9 , 119.4 , 119.1 , 117.1 , 116.0 (t, 248.6) , 113.8 , 109.4 , 62.6 , 56.3, 40.8 (t, *J*=23.0 Hz) , 36.0 (t, *J*=5.4 Hz), 32.7, 21.0 , 13.6 ppm. ^{19}F NMR (376 MHz, Chloroform-*d*): δ -102.3(d, *J* = 267.7Hz), -104.0 (d, *J* = 257.6 Hz) ppm. HRMS (ESI) m/z calcd for $C_{22}H_{23}F_2NO_3Na^+$ [M+Na]$^+$:410.1541; found: 410.1541.

ethyl 4-(1-benzyl-1H-indol-3-yl)-2,2-difluoro-4-(4-methoxyphenyl)butanoate **4b**



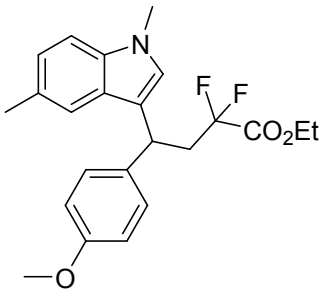
Reaction time 48h,Yield 68%, yellow oil.^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.46 (d, *J* = 8.0 Hz, 1H), 7.29 – 7.18 (m, 6H), 7.13 – 7.08 (m, 3H), 7.02 (t, *J* = 7.6 Hz, 1H), 6.90 (s, 1H), 6.80 (d, *J* = 8.8 Hz, 2H), 5.24 (s, 2H), 4.52 (d, *J* = 7.6 Hz, 1H), 3.74 (s, 2H), 3.71 – 3.69 (m, 2H), 3.06 – 2.83 (m, 2H), 1.04 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (100 MHz, Chloroform-*d*): δ 163.9 (t, *J* = 32.6 Hz), 158.3 , 137.5 , 137.0 , 134.8 , 129.0 , 128.8 , 127.6 , 126.9 , 126.8 , 125.8 , 122.1 , 119.6 , 119.3 , 117.8 , 115.9(t, *J* = 248.9 Hz) , 113.8 , 109.9 , 62.6 , 55.3 , 50.1 , 40.8(t, *J* = 23.7 Hz) , 36.0(t, *J* = 6.3 Hz) , 13.6 ppm. ^{19}F NMR (376 MHz, Chloroform-*d*): δ -102.2(d, *J* = 260.2Hz), -104.3 (d, *J* = 259.8 Hz) ppm. HRMS (ESI) m/z calcd for $C_{28}H_{27}F_2NO_3Na^+$ [M+Na]$^+$ 486.1851; found: 486.1853.

ethyl 2,2-difluoro-4-(5-methoxy-1H-indol-3-yl)-4-(4-methoxyphenyl)butanoate **4e**



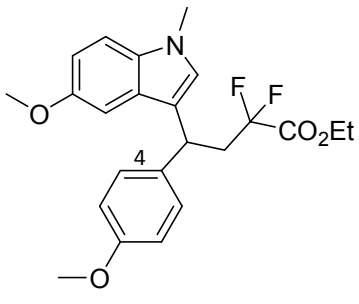
Reaction time 48h,Yield 46%, yellow oil.^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.90 (s, 1H), 7.25-7.18 (m, 3H), 6.92 – 6.87 (m, 2H), 6.82-6.80 (m, 3H), 4.45 (t, *J* = 7.2 Hz, 1H), 3.76 – 3.72 (m, 8H), 3.06 – 2.83 (m, 2H), 1.07 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (100 MHz, Chloroform-*d*): δ 163.9 (t, *J* = 32.3 Hz), 158.2 , 153.9 , 134.6 , 131.7 , 129.0 , 126.6 , 122.4 , 118.2 , 115.9 (t, *J* = 249.6 Hz), 113.8 , 112.2 , 111.9 , 101.3 , 62.6 , 55.8 , 55.2 , 40.5 (t, *J* = 22.6 Hz) , 35.9 (t, *J* = 5.4 Hz), 13.5 ppm . ^{19}F NMR (376 MHz, Chloroform-*d*): δ -102.6(d, *J* = 258.3Hz), -104.1 (d, *J* = 260.2 Hz) ppm. HRMS (ESI) m/z calcd for $C_{22}H_{23}F_2NO_4Na^+$ [M+Na]$^+$ 426.1487; found: 426.1490.

ethyl 4-(1,5-dimethyl-1H-indol-3-yl)-2,2-difluoro-4-(4-methoxyphenyl)butanoate **4f**



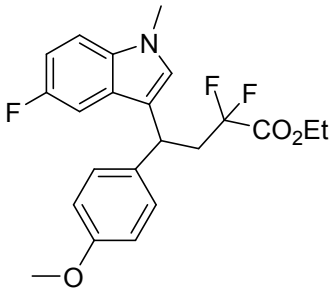
Reaction time 48h,Yield 57%, yellow oil.^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.25-7.23 (m, 3H), 7.13 (d, *J* = 8.4 Hz, 1H), 7.01-6.99 (m, 1H), 6.81 (d, *J* = 8.8 Hz, 2H), 6.71 (s, 1H), 4.47-4.44 (m, 1H), 3.75 (s, 3H), 3.74 – 3.70 (m, 2H), 3.66 (s, 3H), 3.05 – 2.80 (m, 2H), 2.40 (s, 3H), 1.06 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (100 MHz, Chloroform-*d*): δ 163.9 (t, *J* = 32.6 Hz), 158.2 , 135.7 , 134.9 , 128.9 , 128.2 , 126.8 , 126.5 , 123.4 , 118.9 , 116.4 , 115.9 (t, *J* = 249.5 Hz) , 113.7 , 109.0 , 62.5 , 55.2 , 40.9 (t, *J* = 22.9 Hz) , 35.8 (t, *J* = 6 Hz) , 32.7 , 21.5 , 13.5 ppm. ^{19}F NMR (376 MHz, Chloroform-*d*): δ -102.5 (d, *J* = 259.1Hz), -104.2 (d, *J* = 257.9 Hz) ppm. HRMS (ESI) m/z calcd for $C_{23}H_{25}F_2NO_3Na^+$ [M+Na]$^+$ 424.1695; found: 424.1698.

ethyl 2,2-difluoro-4-(5-methoxy-1-methyl-1H-indol-3-yl)-4-(4-methoxyphenyl)butanoate **4g**



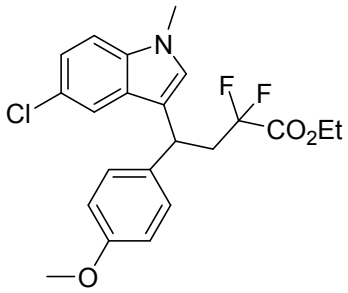
Reaction time 48h,Yield 59%, yellow oil.^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.25-7.23 (m, 2H), 7.13 (d, *J* = 8.8 Hz, 1H), 6.88 (d, *J* = 2.4 Hz, 1H), 6.85-6.80 (m, 3H), 6.74 (s, 1H), 4.43 (dd, *J* = 8.0, 6.0 Hz, 1H), 3.78 (s, 3H), 3.76 (s, 3H), 3.74 – 3.72 (m, 2H), 3.68 (s, 3H), 3.05 – 2.80 (m, 2H), 1.07 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (100 MHz, Chloroform-*d*): δ 163.9 (t, *J* = 32.4 Hz), 158.3 , 153.7 , 134.8 , 132.7 , 129.0 , 127.0 , 126.9 , 116.5 , 115.9 (t, *J* = 222.4 Hz) , 113.8 , 111.8 , 110.0, 101.4, 62.6 , 55.9 , 55.3 , 40.7 (t, *J* = 23.7 Hz) , 35.9 (t, *J* = 4.8 Hz) , 32.9 , 13.6 ppm. ^{19}F NMR (376 MHz, Chloroform-*d*): δ -102.5 (d, *J* = 259.8Hz), -104.3 (d, *J* = 257.6 Hz) ppm. HRMS (ESI) m/z calcd for $C_{23}H_{25}F_2NO_4Na^+$ [M+Na]$^+$ 440.1644; found: 440.1648.

ethyl 2,2-difluoro-4-(5-fluoro-1-methyl-1H-indol-3-yl)-4-(4-methoxyphenyl)butanoate **4h**



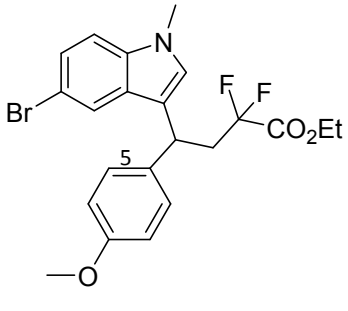
Reaction time 48h,Yield 78%, yellow oil.^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.24-7.20 (m, 2H), 7.14 (dd, *J* = 9.0,4.0 Hz, 1H), 7.06 (dd, *J* = 9.6,2.4 Hz, 1H), 6.94-6.91 (m, 1H), 6.85 (s, 1H), 6.82-6.80 (m, 2H), 4.41 (t, *J* = 7.6 Hz, 1H), 3.76-3.73 (m, 5H), 3.70 (s, 3H), 3.02-2.79 (m, 2H), 1.08 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (100 MHz, Chloroform-*d*): δ 163.8 (t, *J* = 32.5 Hz), 158.7 , 158.3 , 156.3 , 134.5 , 134.0 , 128.9 , 128.0 , 126.8 (d, *J* = 9.2 Hz) , 116.9 (d, *J* = 4.3 Hz) , 115.9 (t, *J* = 249.7 Hz) , 113.9 , 110.3, 110.0 (d, *J* = 3.5 Hz) , 109.9 , 104.4 , 104.2, 62.6 , 55.3 , 40.6 (t, *J* = 22.5 Hz) , 35.8 (t, *J* = 4.6 Hz) , 33.0 , 13.6 ppm. ^{19}F NMR (376 MHz, Chloroform-*d*): δ -102.6 (d, *J* = 260.2 Hz), -104.1 (d, *J* = 259.4 Hz), -124.9 ppm. HRMS (ESI) m/z calcd for $C_{22}H_{22}F_3NO_3Na^+$ [M+Na]$^+$ 428.1444; found: 428.1448.

ethyl 4-(5-chloro-1-methyl-1H-indol-3-yl)-2,2-difluoro-4-(4-methoxyphenyl)butanoate **4i**



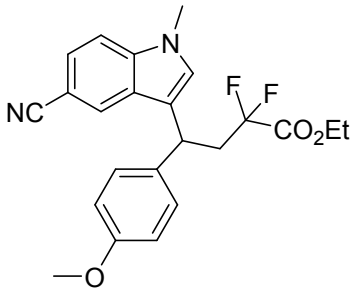
Reaction time 48h,Yield 84%, yellow oil.^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.40 (d, *J* = 1.6 Hz, 1H), 7.22-7.19 (m, 2H), 7.13-7.09 (m, 2H), 6.82 – 6.80 (m, 3H), 4.42 (t, *J*=7.2 Hz, 1H), 3.78-3.73 (m, 5H), 3.68 (s, 3H), 3.02-2.79 (m, 2H), 1.08 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (100MHz, Chloroform-*d*): δ 163.8 (t, *J* = 38.3 Hz), 158.3 , 135.7 , 134.4 , 128.8 , 127.7 , 127.5 , 124.9 , 122.1 ,118.7 , 116.7 , 115.7 (t, *J* = 248.8 Hz) , 113.8 , 110.4 , 62.6 , 55.2, 40.6 (t, *J* = 21.9 Hz) , 35.7 (t, *J* = 5.3 Hz), 32.9, 13.6 ppm. ^{19}F NMR (376 MHz, Chloroform-*d*): δ -102.6(d, *J* = 259.8Hz), -104.0 (d, *J* = 259.4 Hz) ppm. HRMS (ESI) m/z calcd for $C_{22}H_{22}ClF_2NO_3Na^+$ [M+Na]$^+$ 444.1148; found: 444.1150.

ethyl 4-(5-bromo-1-methyl-1H-indol-3-yl)-2,2-difluoro-4-(4-methoxyphenyl)butanoate **4j**



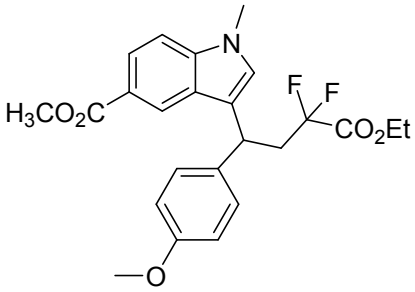
Reaction time 48h,Yield 90%, yellow oil.^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.56 (d, *J* = 2.0 Hz, 1H), 7.26-7.19 (m, 3H), 7.10 (d, *J* = 8.4 Hz, 1H), 6.83 – 6.81 (m, 3H), 4.42 (t, *J*=7.2 Hz, 1H), 3.76-3.71 (m, 5H), 3.68 (s, 3H), 3.01-2.79 (m, 2H), 1.09 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (100MHz, Chloroform-*d*): δ 163.8 (t, *J* = 32.3 Hz), 158.3 , 135.9 , 134.4 , 128.8 , 128.2 , 127.6 , 124.7 , 121.8 , 116.6 , 115.7 (t, *J* = 249.5 Hz) , 113.9 , 112.5 , 110.8 , 62.6 , 55.2, 40.7 (t, *J* = 23.1 Hz) , 35.7 (t, *J* = 4.5 Hz), 32.9, 13.6 ppm. ^{19}F NMR (376 MHz, Chloroform-*d*): δ -102.7(d, *J* = 259.4Hz), -104.0 (d, *J* = 259.4 Hz) ppm. HRMS (ESI) m/z calcd for $C_{22}H_{22}BrF_2NO_3Na^+$ [M+Na]$^+$ 488.0643; found: 488.0644.

ethyl 4-(5-cyano-1-methyl-1H-indol-3-yl)-2,2-difluoro-4-(4-methoxyphenyl)butanoate **4k**



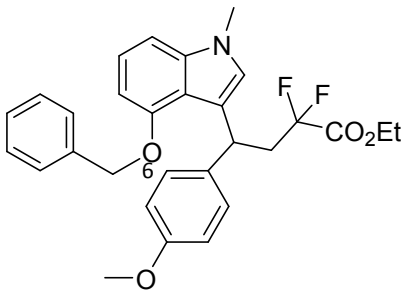
Reaction time 48h,Yield 52%, yellow oil.^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.75-7.74 (m, 1H), 7.40 (dd, *J* = 8.6,1.6 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 1H), 7.19 (d, *J* = 8.8 Hz, 1H), 6.98 (s, 1H), 6.83 (d, *J* = 8.8 Hz, 2H), 4.47 (t, *J*=8.4 Hz, 1H), 3.87-3.80 (m, 2H), 3.78 (m, 6H), 3.01-2.82 (m, 2H), 1.12 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (100MHz, Chloroform-*d*): δ 163.8 (t, *J* = 32.0 Hz), 158.5 , 138.7 , 134.0 , 128.8 , 128.4 , 126.4, 125.1 , 124.8 , 120.7 , 118.4 , 115.6 (t, *J* = 250.4 Hz) , 114.0 , 110.2 , 102.1 , 62.7 , 55.3, 40.5 (t, *J* = 23.1 Hz) , 35.6 (t, *J* = 5.2 Hz), 33.0 , 13.6 ppm. ^{19}F NMR (376 MHz, Chloroform-*d*): δ -102.3(d, *J* = 262.1Hz), -104.6 (d, *J* = 261.7 Hz) ppm. HRMS (ESI) m/z calcd for $C_{23}H_{22}F_2N_2O_3Na^+$ [M+Na]$^+$ 435.1491; found: 435.1492.

ethyl2,2-difluoro-4-(4-methoxyphenyl)-4-(1-methyl-5-((methylperoxy)carbonyl)-1H-indol-3-yl)butanoate **4l**



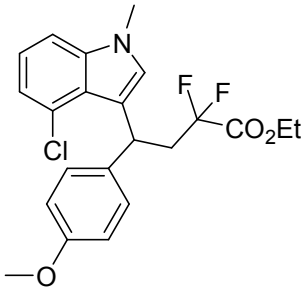
Reaction time 48h,Yield 77%, yellow oil.^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.25 (d, *J* = 0.8 Hz, 1H), 7.89 (dd, *J* = 8.8,1.6 Hz, 1H), 7.25-7.22 (m, 3H), 6.88 (s, 1H), 6.83-6.80 (m, 2H), 4.53 (t, *J*=7.2 Hz, 1H), 3.90 (s, 3H), 3.78-3.76 (m, 2H), 3.74 (s, 3H), 3.72 (s, 3H), 3.05-2.83 (m, 2H), 1.07 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (100MHz, Chloroform-*d*): δ 168.1 , 163.9 (t, *J* = 32.6 Hz), 158.4 , 139.7 , 134.5 , 128.8 , 127.7 , 126.2 , 123.3 , 122.3 , 121.2 , 118.6 , 115.8 (t, *J* = 249.2 Hz) , 113.9 , 109.0 , 62.6 , 55.2, 51.9, 40.9 (t, *J* = 23.3 Hz) , 35.7 (t, *J* = 5.8 Hz), 32.9, 13.6 ppm. ^{19}F NMR (376 MHz, Chloroform-*d*): δ -102.5 (d, *J* = 259.4Hz), -104.1 (d, *J* = 260.2 Hz) ppm. HRMS (ESI) m/z calcd for $C_{24}H_{25}F_2NO_5Na^+$ [M+Na]$^+$ 468.1593; found: 468.1596.

ethyl 4-(4-(benzyloxy)-1-methyl-1H-indol-3-yl)-2,2-difluoro-4-(4-methoxyphenyl)butanoate **4m**



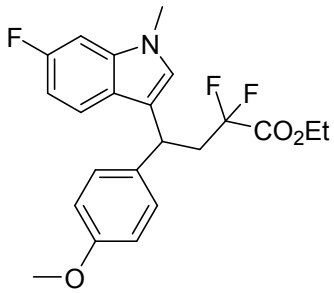
Reaction time 48h,Yield 54%, yellow oil.^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.36 – 7.30 (m, 5H), 7.05 – 7.01 (m, 3H), 6.83 (d, *J* = 8.0 Hz, 1H), 6.71 – 6.68 (m, 3H), 6.46 (d, *J* = 8.0 Hz, 1H), 5.14 (dd, *J* = 21.6,12.0 Hz, 2H), 4.90 (t, *J* = 7.6 Hz, 1H), 3.72 (s, 3H), 3.68 – 3.62 (m, 5H), 3.13-3.02 (m, 1H), 2.81-2.68 (m, 1H), 1.02 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (100 MHz, Chloroform-*d*): δ 164.2 (t, *J* = 32.4Hz), 157.8 , 153.5 , 138.9 , 137.3 , 136.0 , 129.1 , 128.4 , 127.8 , 125.5 , 122.5 , 117.6 , 116.8 , 116.0 (t, *J* = 249.1Hz) , 113.3 , 102.6 , 100.6 , 69.8 , 62.3 , 55.2 , 41.7 (t, *J* = 22.5Hz), 36.1(t, *J* = 4.7Hz) , 32.9 , 13.5 ppm. ^{19}F NMR (376 MHz, Chloroform-*d*): δ -102.5(d, *J* = 257.2Hz), -104.3 (d, *J* = 258.7 Hz) ppm. HRMS (ESI) m/z calcd for $C_{29}H_{29}F_2NO_3Na^+$ $[M+Na]^+$ 516.1957; found: 516.1960.

ethyl 4-(4-chloro-1-methyl-1H-indol-3-yl)-2,2-difluoro-4-(4-methoxyphenyl)butanoate **4n**



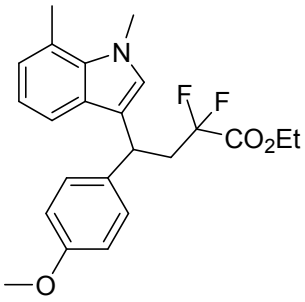
Reaction time 48h,Yield 58%, yellow oil.^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.26-7.24 (m, 2H), 7.14 (dd, *J* = 9.4,1.2 Hz, 1H), 7.09-7.02 (m, 2H), 6.83-6.81 (m, 3H), 5.20 (t, *J*=7.6 Hz, 1H), 3.83-3.74 (m, 5H), 3.70 (s, 3H), 3.04-2.77 (m, 2H), 1.12 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (100MHz, Chloroform-*d*): δ 164.2 (t, *J* = 32.7 Hz), 158.1 , 138.5 , 135.2 , 129.2 , 128.2 , 126.3 , 123.3 , 122.3 , 120.5 , 117.7 , 115.7 (t, *J* = 249.4 Hz) , 113.7 , 118.2 , 62.6 , 55.2, 42.1 (t, *J* = 22.7 Hz) , 35.2 (t, *J* = 5.0 Hz), 33.1, 13.6 ppm. ^{19}F NMR (376 MHz, Chloroform-*d*): δ -101.6 (d, *J* = 261.3Hz), -104.3 (d, *J* = 259.4 Hz) ppm. HRMS (ESI) m/z calcd for $C_{22}H_{22}ClF_2NO_3Na^+$ $[M+Na]^+$ 444.1148; found: 444.1150.

ethyl 2,2-difluoro-4-(6-fluoro-1-methyl-1H-indol-3-yl)-4-(4-methoxyphenyl)butanoate **4o**



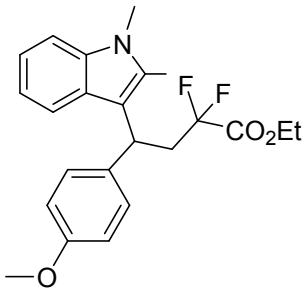
Reaction time 48h,Yield 88%, yellow oil.^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.32 (dd, *J* = 8.6,5.6 Hz, 1H), 7.22-7.20 (m, 2H), 6.90 (dd, *J* = 9.8,2.4 Hz, 1H), 6.82 – 6.76 (m, 4H), 4.45 (t, *J*=8.0 Hz, 1H), 3.78-3.73 (m, 5H), 3.65 (s, 3H), 3.02-2.80 (m, 2H), 1.08 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (100MHz, Chloroform-*d*): δ 163.8 (t, *J* = 32.3 Hz), 161.1 , 158.8 , 158.3 , 137.4 , 137.3 , 134.6 , 128.9 , 126.6 (d, *J* = 3.2 Hz), 123.1 , 120.2 (d, *J* = 9.7 Hz), 117.4 , 115.8 (t, *J* = 249.6 Hz) , 113.8 , 107.7 (d, *J* = 24.4 Hz), 95.6 (d, *J* = 24.9 Hz), 62.6 , 55.2 , 40.7 (t, *J* = 23.1 Hz) , 35.8 (t, *J* = 6.0 Hz) , 32.8 , 13.6 ppm. ^{19}F NMR (376 MHz, Chloroform-*d*): δ -102.4(d, *J* = 259.8Hz), -104.4 (d, *J* = 259.8 Hz), -120.7 ppm. HRMS (ESI) m/z calcd for $C_{22}H_{22}F_3NO_3Na^+$ $[M+Na]^+$ 428.1444; found: 428.1447.

ethyl 4-(1,7-dimethyl-1H-indol-3-yl)-2,2-difluoro-4-(4-methoxyphenyl)butanoate **4p**



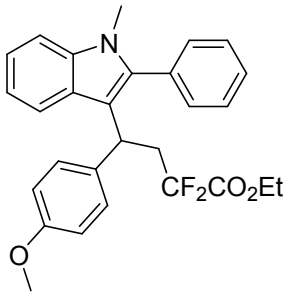
Reaction time 48h,Yield 70%, yellow oil.^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.29 (d, *J* = 6.8 Hz, 1H), 7.22(d, *J* = 8.4 Hz, 2H), 6.91-6.85 (m, 2H), 6.80 (d, *J* = 8.8 Hz, 3H), 6.65 (s, 1H), 4.45 (dd, *J* = 8.4, 6.0 Hz, 1H), 3.98 (s, 3H), 3.80 – 3.75 (m, 5H), 3.02 – 2.79 (m, 2H), 2.71 (s, 3H), 1.09 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (100 MHz, Chloroform-*d*): δ 163.9 (t, *J* = 32.5 Hz), 158.2 , 136.0 , 134.7 , 129.0 , 128.0 , 127.6 , 124.5 , 121.3 , 119.3 , 117.4 , 116.8, 115.9 (t, *J* = 249.7 Hz) , 113.7 , 62.6 , 55.2 , 40.7 (t, *J* = 23.1 Hz) , 36.7 , 35.7 (t, *J* = 5.3 Hz) , 19.7 , 13.6 ppm. ^{19}F NMR (376 MHz, Chloroform-*d*): δ -102.1 (d, *J* = 259.8Hz), -104.6 (d, *J* = 259.1 Hz) ppm. HRMS (ESI) m/z calcd for $C_{23}H_{25}F_2NO_3Na^+$ [M+Na]$^+$ 424.1695; found: 424.1697.

ethyl 4-(1,2-dimethyl-1H-indol-3-yl)-2,2-difluoro-4-(4-methoxyphenyl)butanoate **4q**



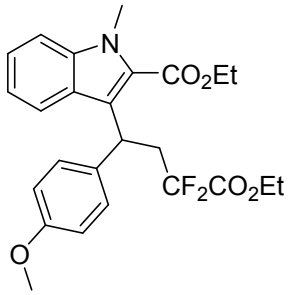
Reaction time 48h,Yield 62%, yellow oil.^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.34 (d, *J* = 8.0 Hz, 1H), 7.24-7.19 (m, 3H), 7.08 (t, *J* = 7.6 Hz, 1H), 6.95 (s, *J* = 7.6 Hz, 1H), 6.79-6.78 (m, 2H), 4.49 (dd, *J*=11.0,4.0 Hz, 1H), 3.72 (s, 3H), 3.61 (s, 3H), 3.56-3.48 (m, 1H), 3.35-3.20 (m, 1H), 3.01-2.83 (m, 2H), 2.37 (s, 3H), 0.76 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (100MHz, Chloroform-*d*): δ 163.1 (dd, *J* = 35.0,30.8 Hz), 157.8 , 136.9 , 135.3 , 134.7 , 128.2 , 126.2 , 120.5 , 119.4 , 118.9 , 116.2 (dd, *J* = 249.2,245.6 Hz) , 113.7 , 110.6 , 108.7 , 62.0 , 55.2, 39.1 (t, *J* = 22.7 Hz) , 34.6 (dd, *J* = 32.2,12.4 Hz), 29.6, 13.2 , 10.4 ppm. ^{19}F NMR (376 MHz, Chloroform-*d*): δ -98.8 (d, *J* = 259.1Hz), -108.6 (d, *J* = 262.1 Hz) ppm. HRMS (ESI) m/z calcd for $C_{23}H_{25}F_2NO_3Na^+$ [M+Na]$^+$ 424.1695; found: 424.1697.

ethyl 2,2-difluoro-4-(4-methoxyphenyl)-4-(1-methyl-2-phenyl-1H-indol-3-yl)butanoate **4r**



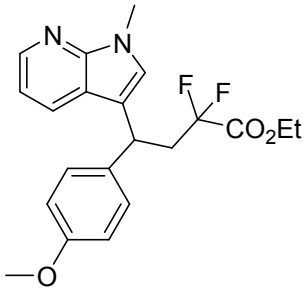
Reaction time 48h,Yield 68%, yellow oil.^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.60 (d, *J* = 7.6 Hz, 1H), 7.44-7.30 (m, 6H), 7.20-7.18 (m, 3H), 7.11-7.07 (m, 1H), 6.78-6.74 (m, 2H), 4.35 (dd, *J*=10.2,5.2 Hz, 1H), 3.72 (s, 3H), 3.64-3.56 (m, 1H), 3.50 (s, 3H), 3.34-3.20 (m, 1H), 3.10-3.02 (m, 1H), 2.94-2.82 (m, 1H), 0.92 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (100MHz, Chloroform-*d*): δ 163.4 (dd, *J* = 34.7,31.7 Hz), 157.8 , 139.2 , 137.3 , 135.8 , 131.5 , 130.9 , 128.5 , 128.4 , 128.3 , 125.0 , 121.4 , 120.5 , 119.4 , 116.0 (dd, *J* = 250.1,246.2 Hz) , 113.7 , 112.5 , 109.6 , 62.1 , 55.2, 39.7 (t, *J* = 22.1 Hz) , 35.2 (dd, *J* = 6.2,3.9 Hz), 30.7, 13.4 ppm. ^{19}F NMR (376 MHz, Chloroform-*d*): δ -99.7 (d, *J* = 260.2Hz), -107.0 (d, *J* = 259.8 Hz) ppm. HRMS (ESI) m/z calcd for $C_{28}H_{27}F_2NO_3Na^+$ [M+Na]$^+$ 486.1851; found: 486.1853.

ethyl 2,2-difluoro-4-(4-methoxyphenyl)-4-(1-methyl-2-phenyl-1H-indol-3-yl)butanoate **4s**



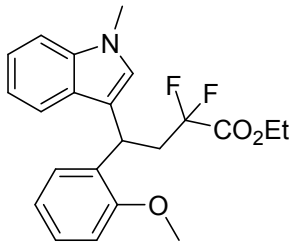
Reaction time 48h,Yield 51%, yellow oil.[1]H NMR (400 MHz, Chloroform-*d*): δ 7.60 (d, *J* = 8.4 Hz, 1H), 7.33-7.27 (m, 4H), 7.07-7.03 (m, 1H), 6.81-6.79 (m, 2H), 5.52 (dd, *J*=9.4,5.2 Hz, 1H), 4.53-4.38 (m, 2H), 3.97 (s, 3H), 3.79-3.74 (m, 4H), 3.50-3.42 (m, 1H), 3.31-3.02 (m, 2H), 1.44 (t, *J* = 7.2 Hz, 3H), 0.97 (t, *J* = 7.2 Hz, 3H) ppm. [13]C NMR (100MHz, Chloroform-*d*): δ 163.5 (t, *J* = 32.5 Hz), 162.5 , 157.9 , 138.9 , 135.1 , 128.4 , 126.0 , 125.0 , 124.9 , 123.6 , 122.2 , 120.1 , 116.0 (dd, *J* = 250.2,247.4 Hz) , 113.7 , 110.4 , 62.4 , 61.1 , 55.2, 39.1 (t, *J* = 23.1 Hz) , 33.9 (dd, *J* = 6.0,3.1 Hz), 32.3 , 14.3, 13.4 ppm. [19]F NMR (376 MHz, Chloroform-*d*): δ -101.2 (d, *J* = 259.4Hz), -106.7 (d, *J* = 259.1 Hz) ppm. HRMS (ESI) m/z calcd for $C_{25}H_{27}F_2NO_5Na^+$ [M+Na]$^+$ 482.1750; found: 482.1753.

ethyl 2,2-difluoro-4-(4-methoxyphenyl)-4-(1-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)butanoate **4u**



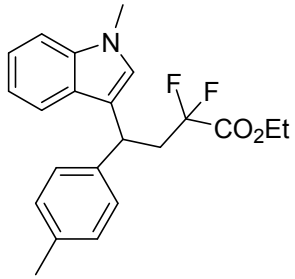
Reaction time 48h,Yield 53%, yellow oil.[1]H NMR (400 MHz, Chloroform-*d*): δ 8.28 (dd, *J*= 4.6,1.6Hz, 1H), 7.69 (dd, *J* = 8.0,1.6 Hz, 1H), 7.22-7.20 (m, 2H), 6.98-6.95 (m, 2H), 6.83-6.81 (m, 2H), 4.46 (t, *J*= 7.2Hz, 1H), 3.83 (s, 3H), 3.81 – 3.77 (m, 5H), 3.04 – 2.81 (m, 2H), 1.08 (t, *J* = 7.2 Hz, 3H) ppm. [13]C NMR (100 MHz, Chloroform-*d*): δ 163.8 (t, *J* = 31.3 Hz), 158.4 , 148.1 , 143.1 , 134.4 , 128.9 , 127.6 , 126.3 , 119.1 , 115.7 (t, *J* = 248.4 Hz) , 115.6 , 115.2 , 113.9 , 62.6 , 55.3 , 40.5 (t, *J* = 22.7 Hz) , 36.0 (t, *J* = 4.0 Hz) , 31.1 , 13.6 ppm. [19]F NMR (376 MHz, Chloroform-*d*): δ -102.6 (d, *J* = 259.4Hz), -104.3 (d, *J* = 259.1 Hz) ppm. HRMS (ESI) m/z calcd for $C_{21}H_{24}F_2N_2O_3^+$ [M+H]$^+$ 389.1669; found: 389.1669.

ethyl 2,2-difluoro-4-(2-methoxyphenyl)-4-(1-methyl-1H-indol-3-yl)butanoate **4v**



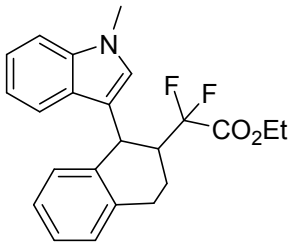
Reaction time 48h,Yield 75%, yellow oil.[1]H NMR (400 MHz, Chloroform-*d*): δ 7.56 (d, *J*= 7.6Hz, 1H), 7.24-7.21 (m, 2H), 7.18-7.12 (m, 2H),7.06-7.03 (m, 1H), 6.86-6.82 (m, 3H), 5.01 (t, *J*= 7.2Hz, 1H), 3.85 (s, 3H), 3.73 – 3.66 (m, 5H), 3.04 – 2.84 (m, 2H), 1.04 (t, *J* = 7.2 Hz, 3H) ppm. [13]C NMR (100 MHz, Chloroform-*d*): δ 164.2 (t, *J* = 32.5 Hz), 156.8 , 137.1 , 131.3 , 128.6 , 127.7 , 127.1 , 126.9 , 121.7 , 120.4 , 119.5 , 118.9 , 116.3 , 116.1 (t, *J* = 249.7 Hz) , 110.8 , 109.2 , 62.4 , 55.5 , 39.9 (t, *J* = 23.3 Hz) , 32.7 , 29.5 (t, *J* = 5.8 Hz) , 13.6 ppm. [19]F NMR (376 MHz, Chloroform-*d*): δ -103.3, -103.4 ppm. HRMS (ESI) m/z calcd for $C_{22}H_{23}F_2NO_3Na^+$ [M+Na]$^+$ 410.1538; found: 410.1539.

ethyl 2,2-difluoro-4-(1-methyl-1H-indol-3-yl)-4-(p-tolyl)butanoate **4w**



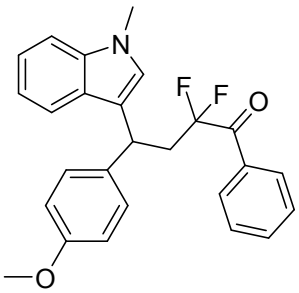
Reaction time 48h,Yield 58%, yellow oil.^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.48 (d, *J*= 8.0Hz, 1H), 7.26-7.16 (m, 4H), 7.09-7.02 (m, 3H), 6.79 (s, 1H), 4.50 (t, *J*= 7.2Hz, 1H), 3.75 – 3.66 (m, 5H), 3.08 – 2.83 (m, 2H), 2.29(s, 3H), 1.05 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (100 MHz, Chloroform-*d*): δ 163.9 (t, *J* = 32.1 Hz), 139.8 , 137.3 , 136.1 , 129.1 , 127.8 , 126.6 , 126.5 , 121.8 , 119.4 , 119.0 , 116.9 , 115.9 (t, *J* = 249.7 Hz) , 109.2 , 62.5 , 40.7 (t, *J* = 23.2 Hz) , 36.3 (t, *J* = 5.2 Hz) , 32.7 , 21.0 , 13.5 ppm. ^{19}F NMR (376 MHz, Chloroform-*d*): δ -102.8 (d, *J* = 257.6Hz), -104.0 (d, *J* = 258.3 Hz) ppm. HRMS (ESI) m/z calcd for $C_{22}H_{23}F_2NO_2Na^+$ [M+Na]$^+$ 394.1589; found: 394.1590.

ethyl 2,2-difluoro-2-(1-(1-methyl-1H-indol-3-yl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetate **4x**



Reaction time 48h,Yield 65%, yellow oil.^{1}H NMR (400 MHz, Chloroform-*d*): δ7.28-7.26 (m, 2H), 7.19-7.10 (m, 3H), 7.02-6.96 (m, 3H), 6.72 (s, 1H), 4.50 (d, *J*= 8.4Hz, 1H), 3.73 – 3.68 (m, 4H), 3.22 – 3.06 (m, 2H), 3.02 (t, *J*= 6.4Hz, 2H), 2.34-2.27(m, 1H), 1.90-1.81 (m, 1H), 0.84 (t, *J* = 7.6 Hz, 3H) ppm. ^{13}C NMR (100 MHz, Chloroform-*d*): δ 163.9 (dd, *J* = 33.6, 32.2 Hz), 137.8 , 137.4 , 135.8 , 129.7 , 128.3 , 126.3 , 126.0 , 125.9 , 121.6 , 119.8 , 119.1 , 117.0 (dd, *J* = 253.0, 247.9 Hz) , 116.1 , 109.2 , 62.1 , 44.0 (t, *J* = 21.3 Hz) , 36.3 (dd, *J* = 5.4, 2.2 Hz) , 32.7 , 27.9 , 20.5 (dd, *J* = 5.8, 3.8 Hz) , 13.3 ppm. ^{19}F NMR (376 MHz, Chloroform-*d*): δ -106.3 (d, *J* = 257.6Hz), -116.1 (d, *J* = 257.2 Hz) ppm. HRMS (ESI) m/z calcd for $C_{23}H_{23}F_2NO_3Na^+$ [M+Na]$^+$ 406.1589; found: 406.1590.

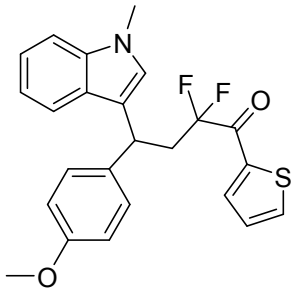
2,2-difluoro-4-(4-methoxyphenyl)-4-(1-methyl-1H-indol-3-yl)-1-phenylbutan-1-one **4aa**



Reaction time 48h,Yield 80%, yellow oil.^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.87 (d, *J*= 7.6Hz, 2H), 7.54-7.50 (m, 1H), 7.38-7.34 (m, 2H), 7.22-7.16 (m, 4H), 7.03-7.00 (m, 1H), 6.76-6.74 (m, 2H), 6.71 (s, 1H), 4.62 (dd, *J*= 8.2, 6.0Hz, 1H), 3.73 (s, 3H), 3.64 (s, 3H),3.22-2.94(m, 2H) ppm. ^{13}C NMR (100 MHz, Chloroform-*d*): δ 189.3 (t, *J* = 30.9 Hz), 158.1 , 137.3 , 135.6 , 133.9 , 129.9 (t, *J* = 4.1 Hz), 128.9 , 128.4 , 126.7 , 126.5 , 121.8 , 119.5 (t, *J* = 251.3 Hz), 119.4 , 119.0 , 117.7 , 113.8 , 109.2 , 55.2 , 40.8 (t, *J* = 23.0 Hz) , 35.8 (t, *J* = 3.9Hz) , 32.7 ppm. ^{19}F NMR (376 MHz,

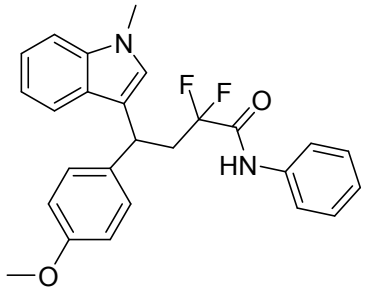
Chloroform-*d*): δ -98.2, -98.3 ppm. HRMS (ESI) m/z calcd for $C_{26}H_{23}F_2NO_3Na^+$ $[M+Na]^+$ 442.1589; found: 442.1591.

2,2-difluoro-4-(4-methoxyphenyl)-4-(1-methyl-1H-indol-3-yl)-1-(thiophen-2-yl)butan-1-one **4ab**



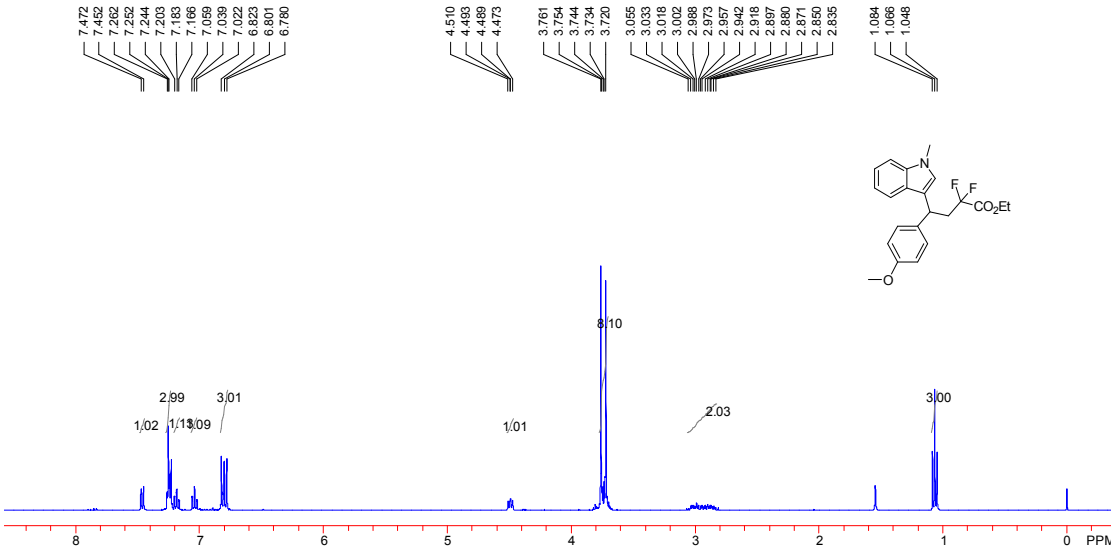
Reaction time 48h,Yield 76%, yellow oil.^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.68 (d, *J*= 2.8Hz, 1H), 7.56-7.54 (m, 1H), 7.38 (d, *J*= 8.0Hz, 1H), 7.14-7.08 (m, 4H), 6.96-6.92 (m, 2H), 6.68-6.60 (m, 2H), 6.63 (s, 1H), 4.52 (t, *J*= 8.0 Hz, 1H), 3.65 (s, 3H), 3.56 (s, 3H), 3.12-2.83 (m, 2H) ppm. ^{13}C NMR (100 MHz, Chloroform-*d*): δ 182.9 (t, *J* = 30.8 Hz), 158.1 , 138.5 , 137.2 , 135.9 , 135.4 (t, *J* = 6.2 Hz), 128.9, 128.4 , 128.0 , 126.7 , 126.6 , 121.8 , 119.3 , 119.5 (t, *J* = 252.7 Hz), 119.0 , 117.4 , 113.8 , 109.2 , 55.2 , 40.9 (t, *J* = 23.0 Hz) , 35.8 (t, *J* = 3.6Hz) , 32.7 ppm. ^{19}F NMR (376 MHz, Chloroform-*d*): δ -98.9 (*J* = 268.8Hz), -100.1 (*J* = 270.3Hz) ppm. HRMS (ESI) m/z calcd for $C_{24}H_{21}F_2NO_3SNa^+$ $[M+Na]^+$ 448.1153; found: 448.1154.

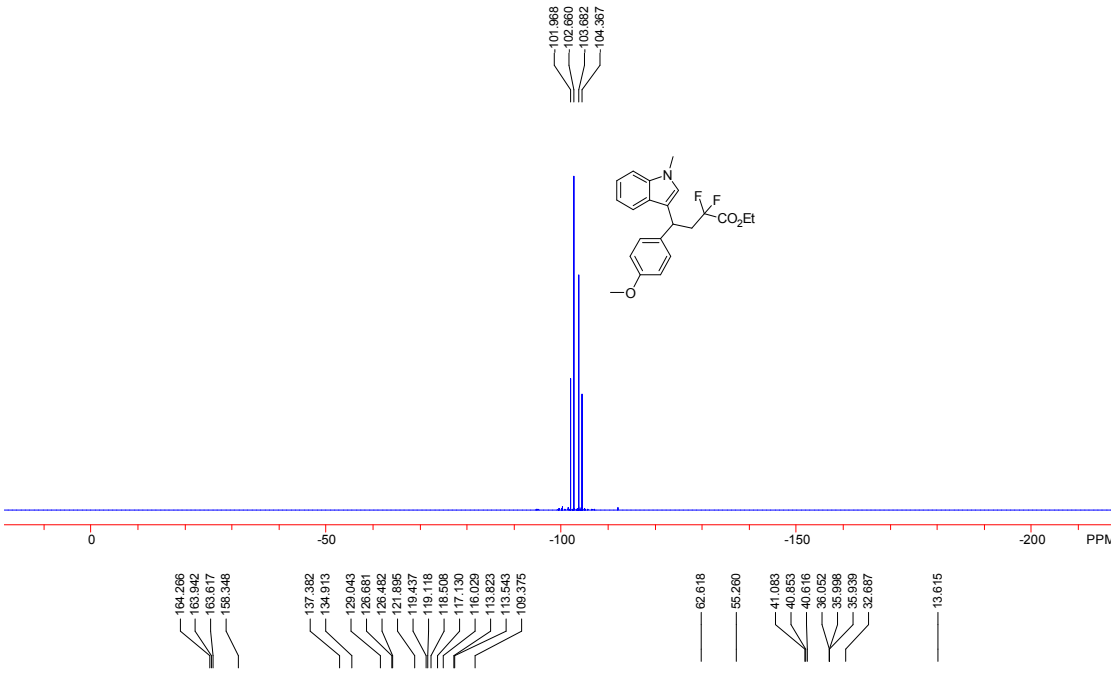
2,2-difluoro-4-(4-methoxyphenyl)-4-(1-methyl-1H-indol-3-yl)-N-phenylbutanamide **4ac**

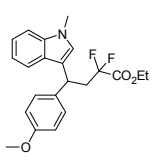


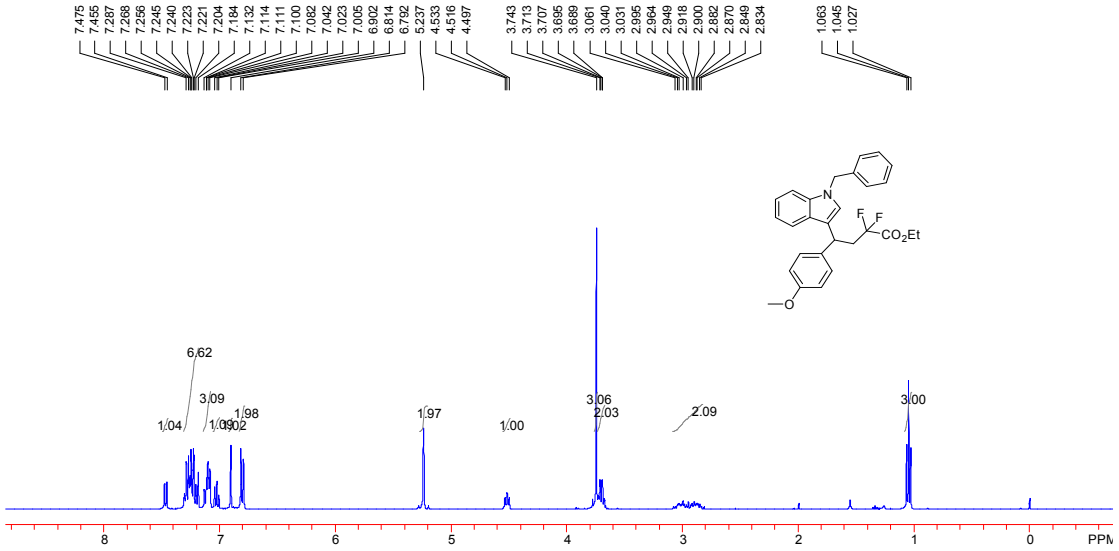
Reaction time 48h,Yield 30%, yellow oil.^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.53 (d, *J*= 8.0Hz, 1H), 7.42 (s, 1H), 7.28-7.24 (m, 4H), 7.19-7.04 (m, 6H), 6.81 (s, 1H), 6.77-6.75 (m, 2H), 4.54 (t, *J*= 7.6 Hz, 1H), 3.67 (s, 3H), 3.54 (s, 3H), 3.22-3.09 (m, 1H), 3.02-2.89 (m, 1H) ppm. ^{13}C NMR (100 MHz, Chloroform-*d*): δ 162.0 (t, *J* = 27.9 Hz), 158.2 , 137.0 , 135.8 , 135.0 , 128.8, 128.7 , 126.8 , 126.4 , 125.2 , 121.8 , 119.8 , 119.1 , 119.0 , 117.9 (t, *J* = 254.0 Hz), 116.5 , 113.9 , 109.4 , 55.1 , 40.2 (t, *J* = 22.4 Hz) , 35.9 (t, *J* = 5.8 Hz) , 32.5 ppm. ^{19}F NMR (376 MHz, Chloroform-*d*): δ -101.8 (*J* = 255.7Hz), -103.8 (*J* =254.9Hz) ppm. HRMS (ESI) m/z calcd for $C_{26}H_{24}F_2N_2O_2Na^+$ $[M+Na]^+$ 457.1698; found: 457.1699.

5. Copies of ^{1}H NMR, ^{13}C NMR, ^{19}F NMR





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2.870
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2.834
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1.045
1.027
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F
F
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O
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1.04
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1.02
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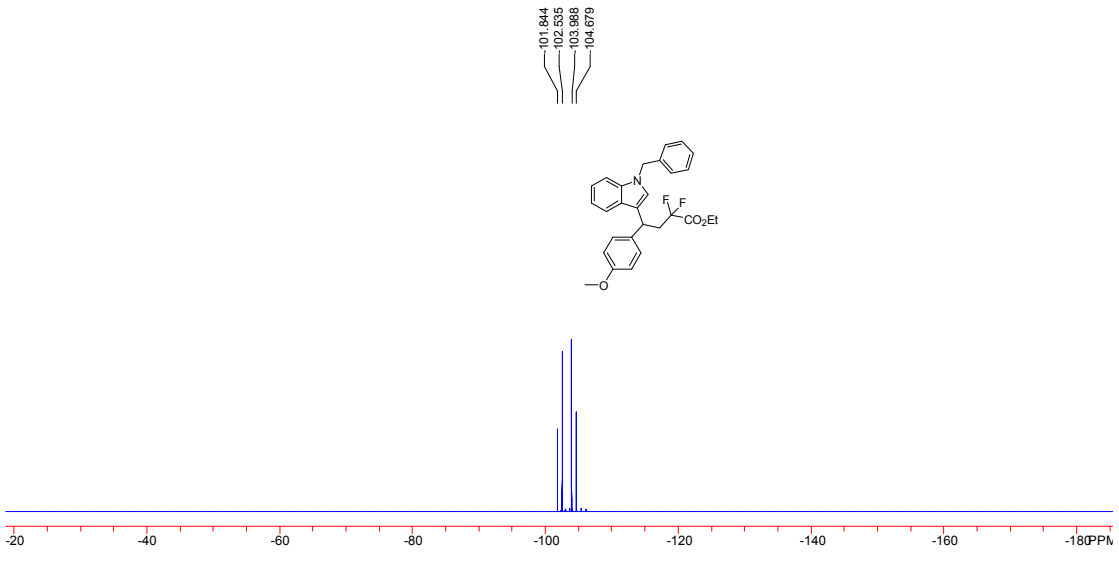
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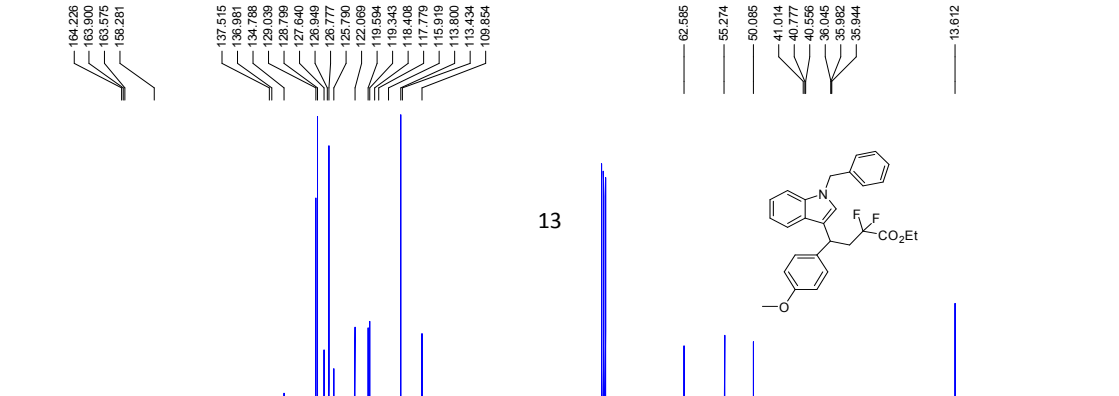
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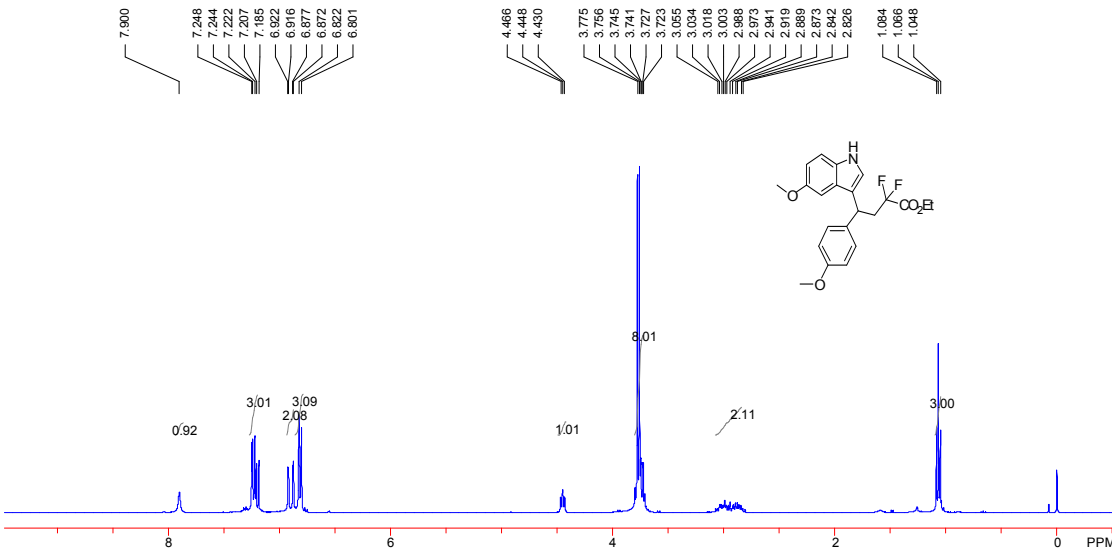
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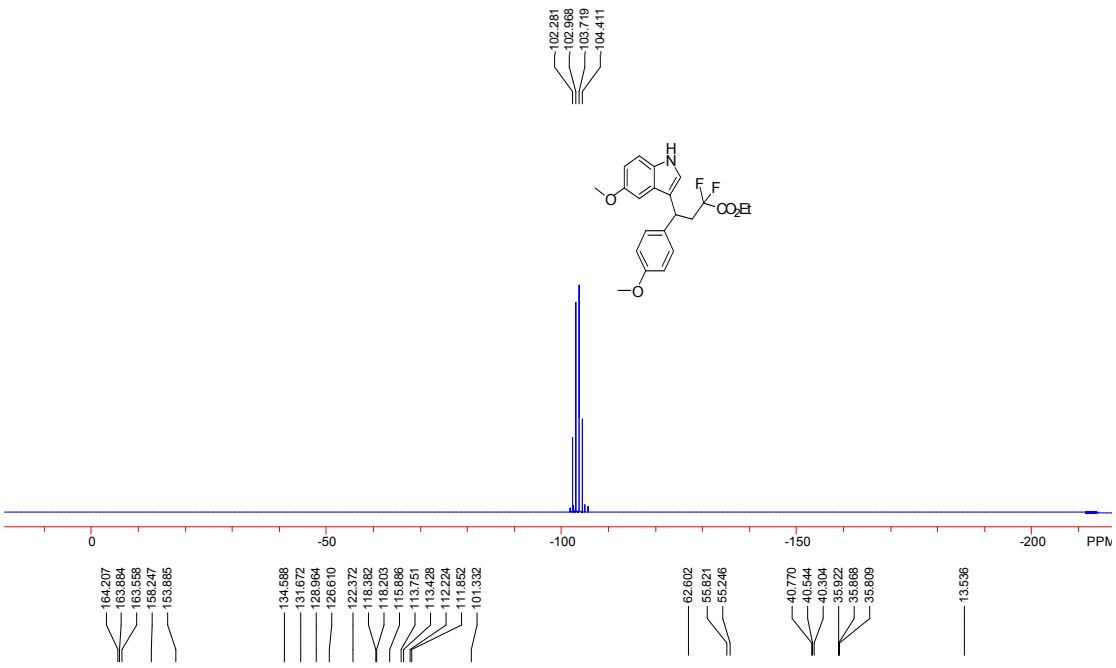
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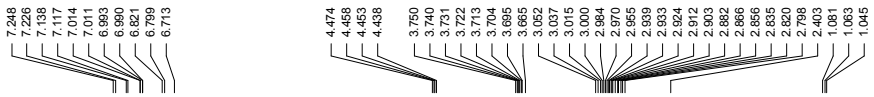
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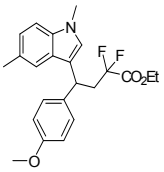
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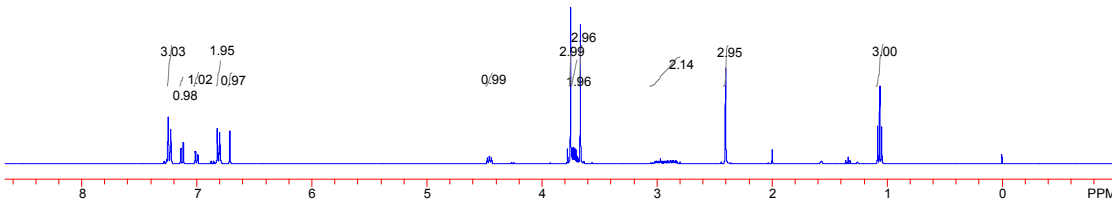
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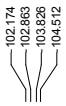
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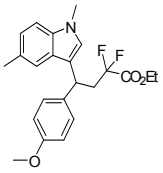
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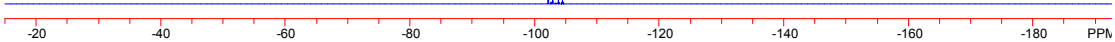
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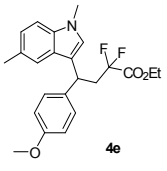
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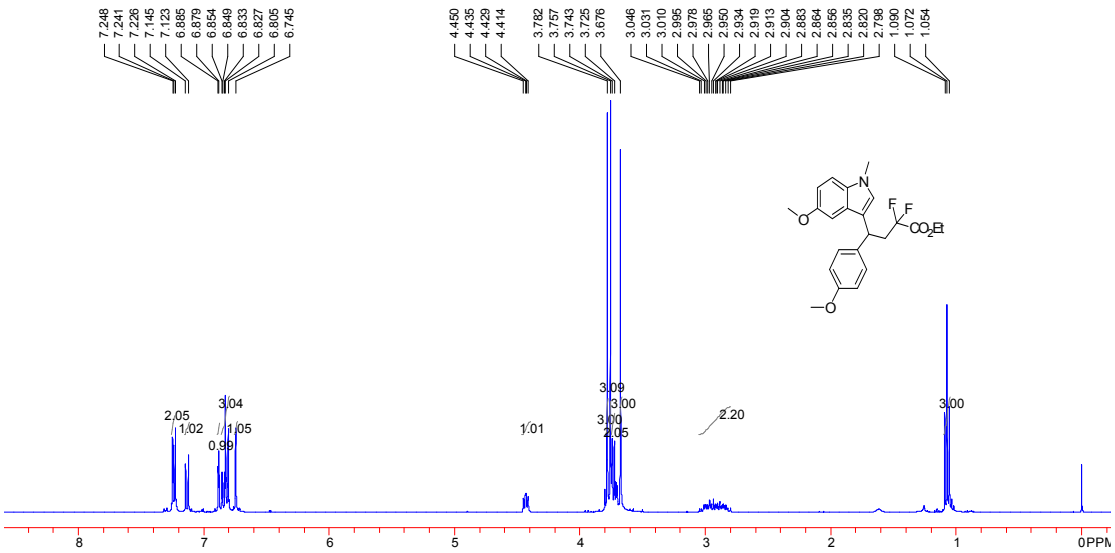
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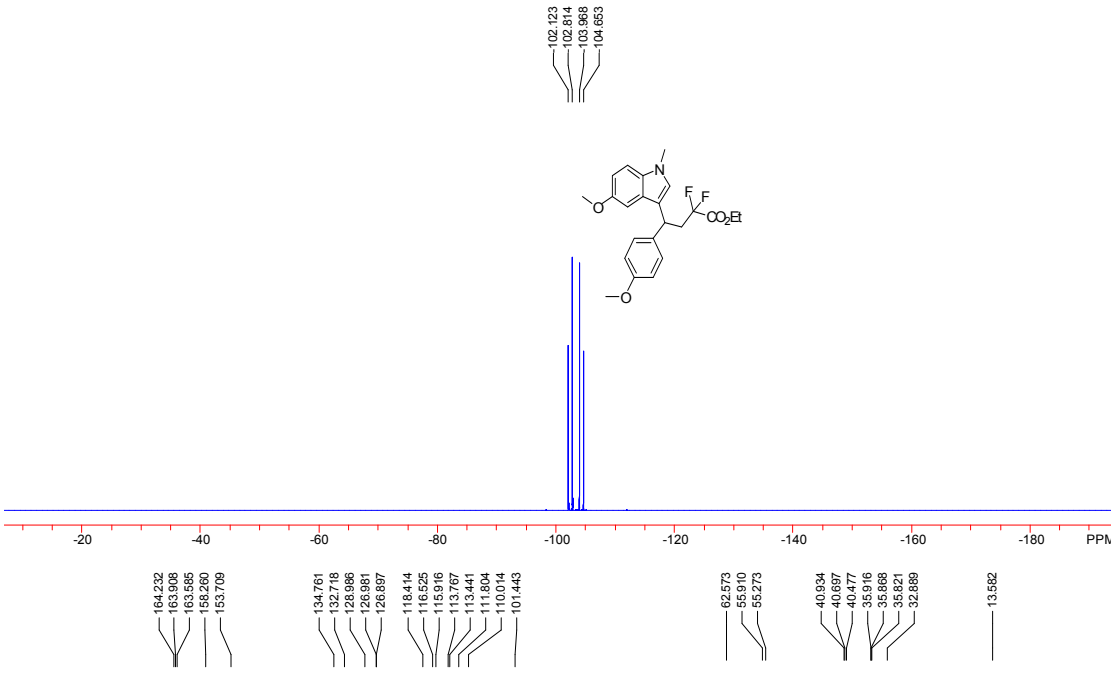
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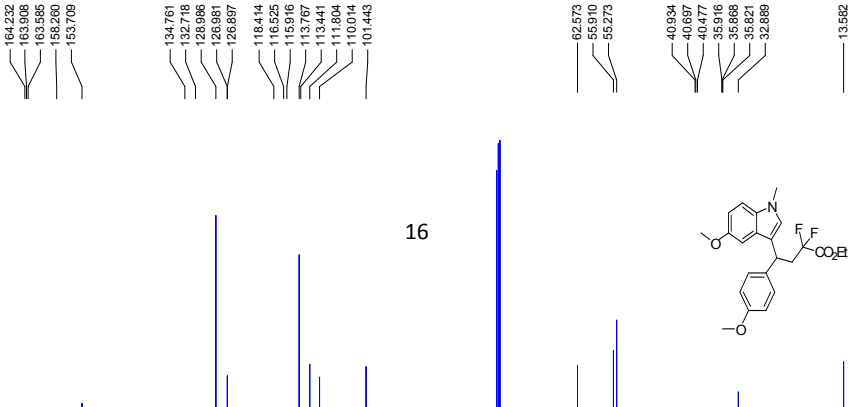
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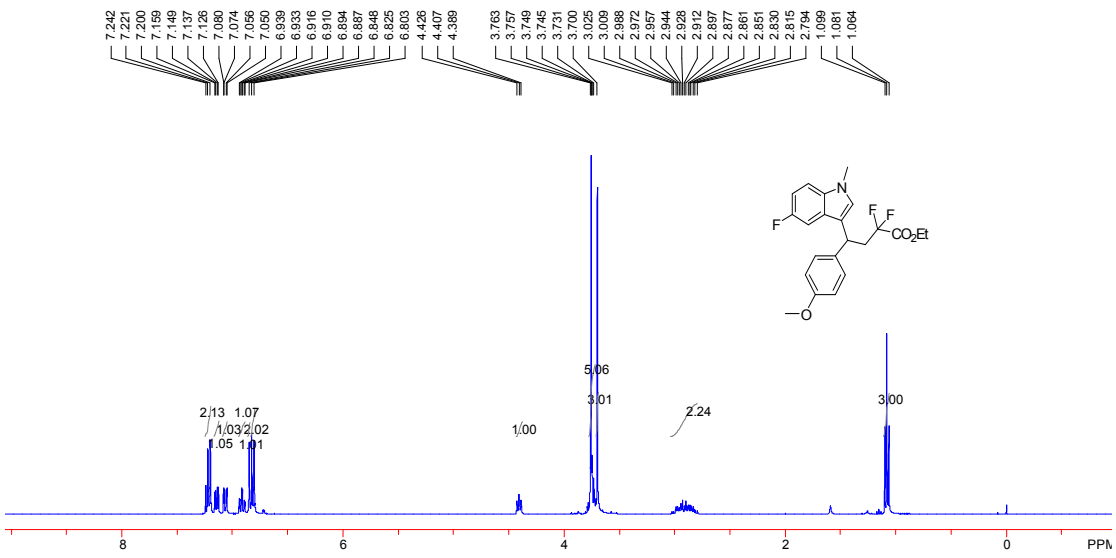
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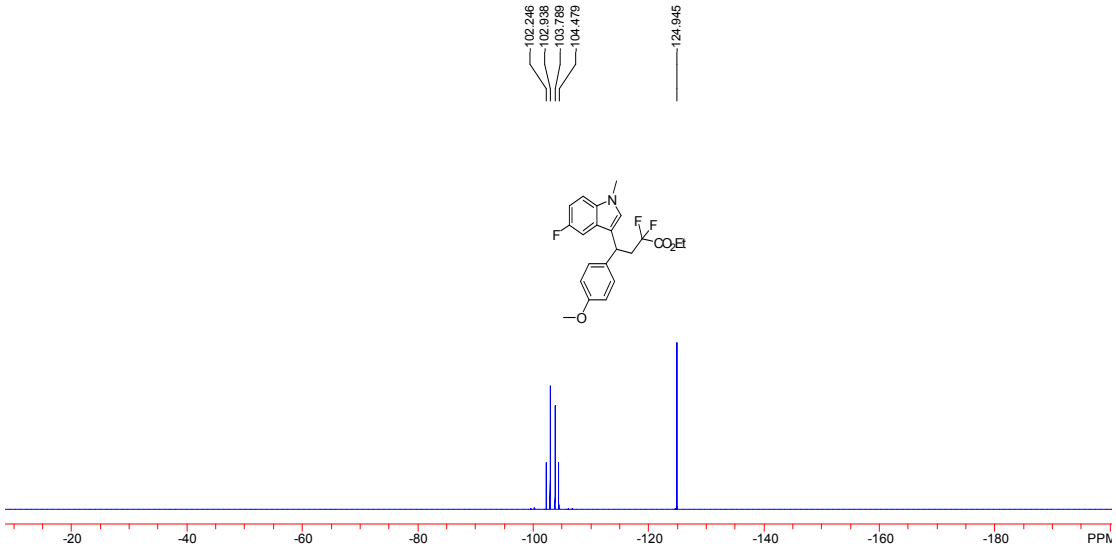
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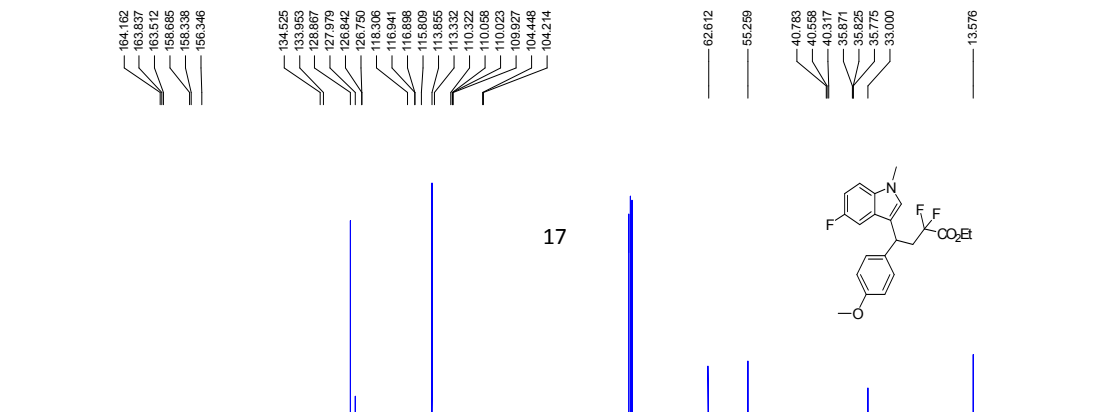
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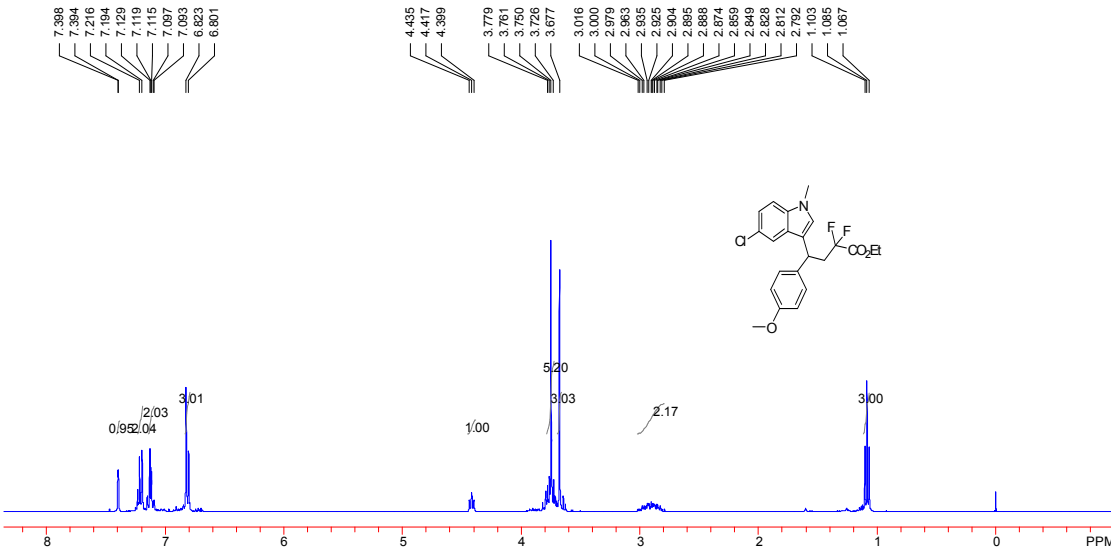
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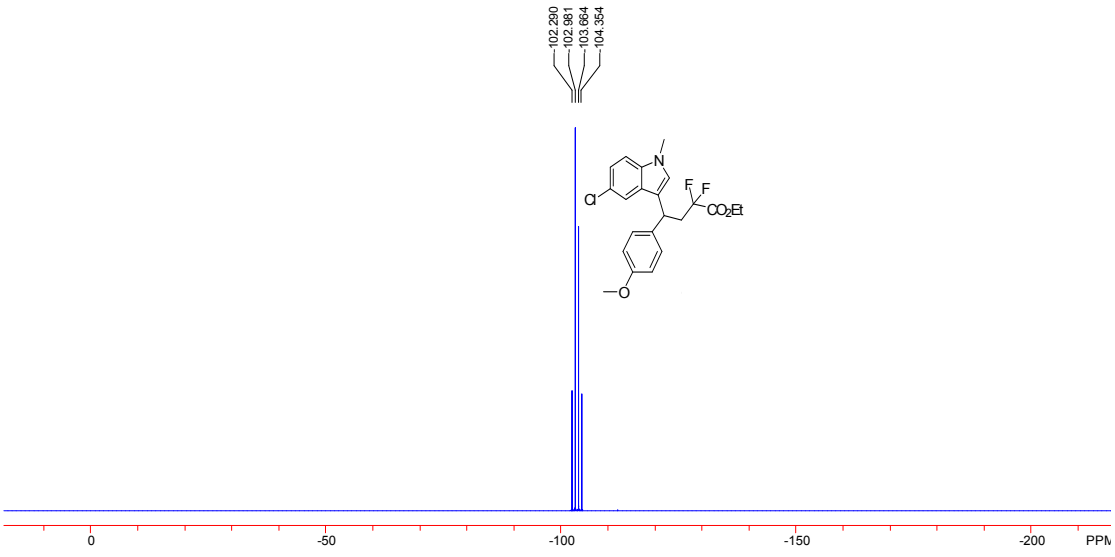
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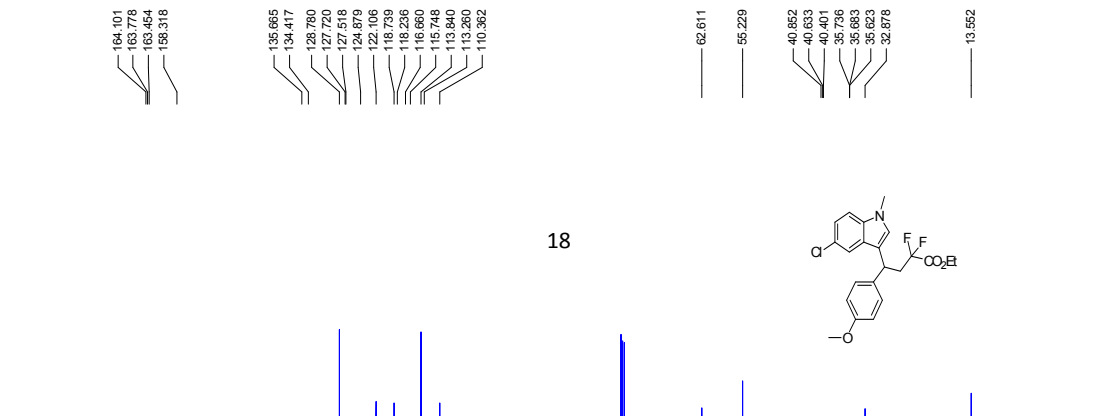
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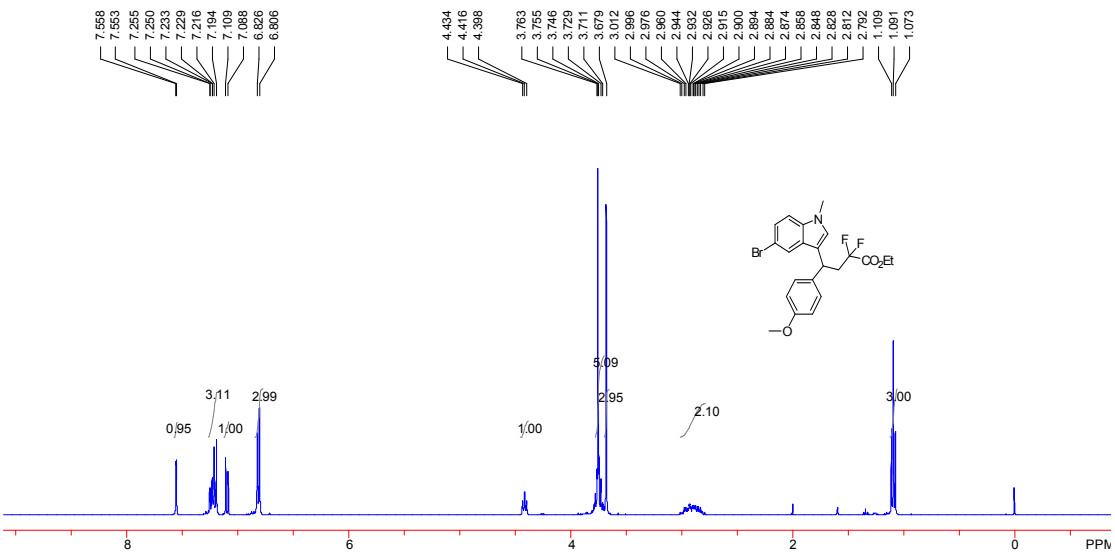
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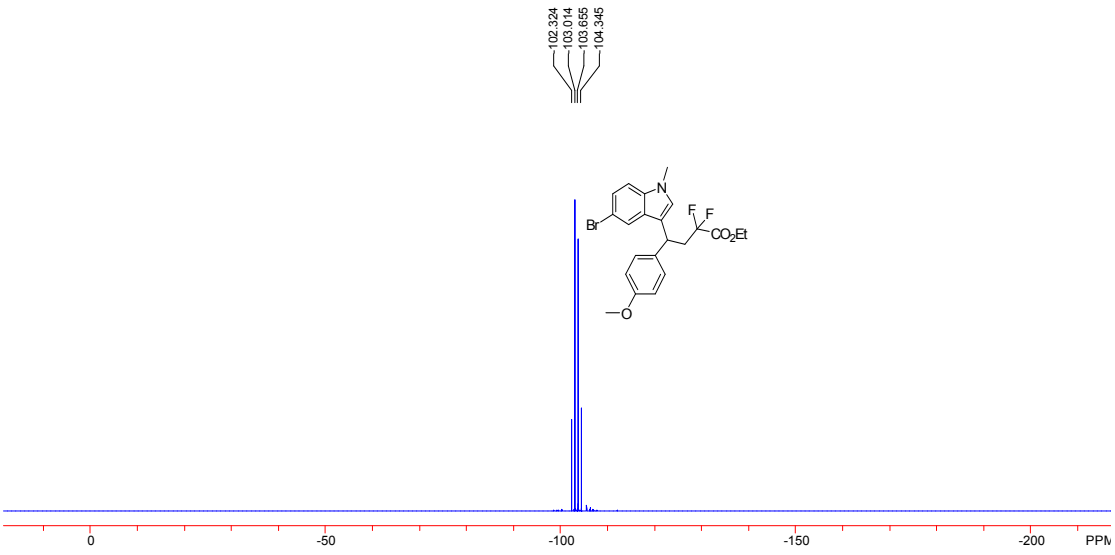
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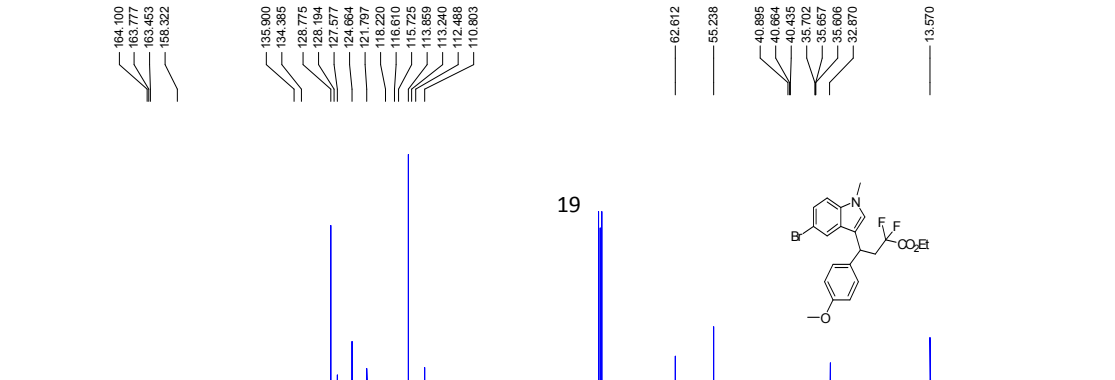
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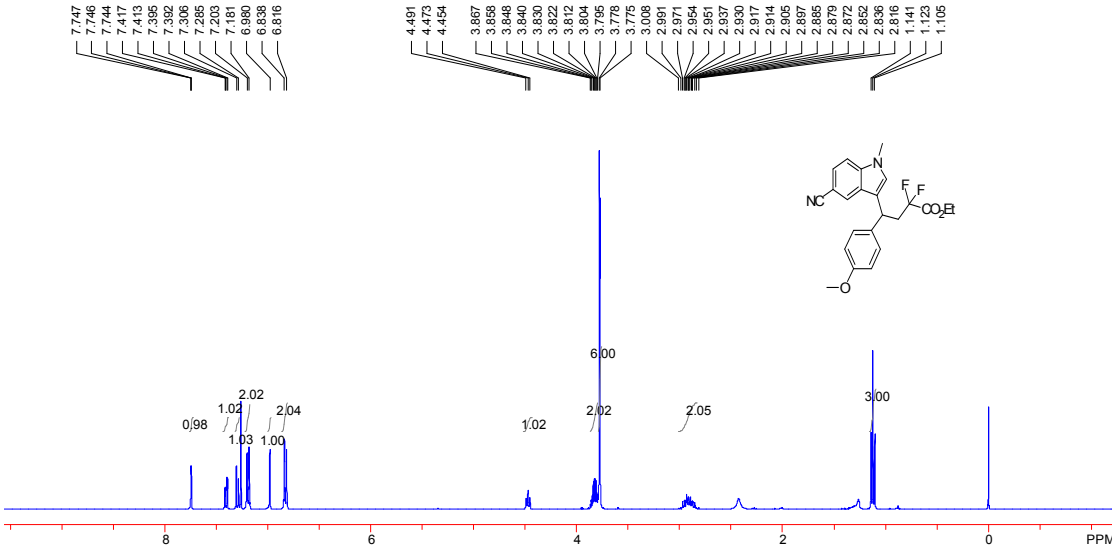
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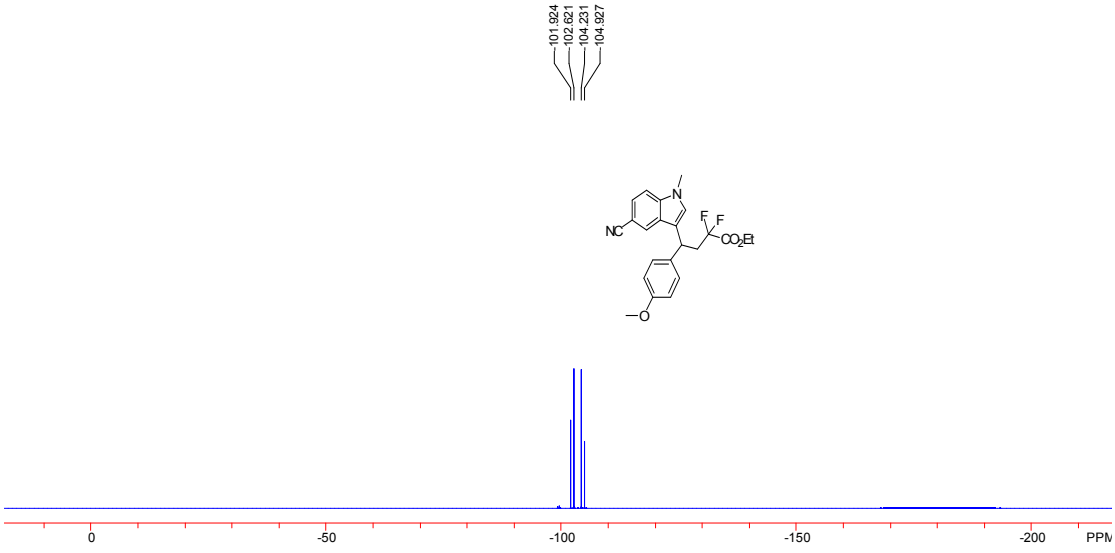
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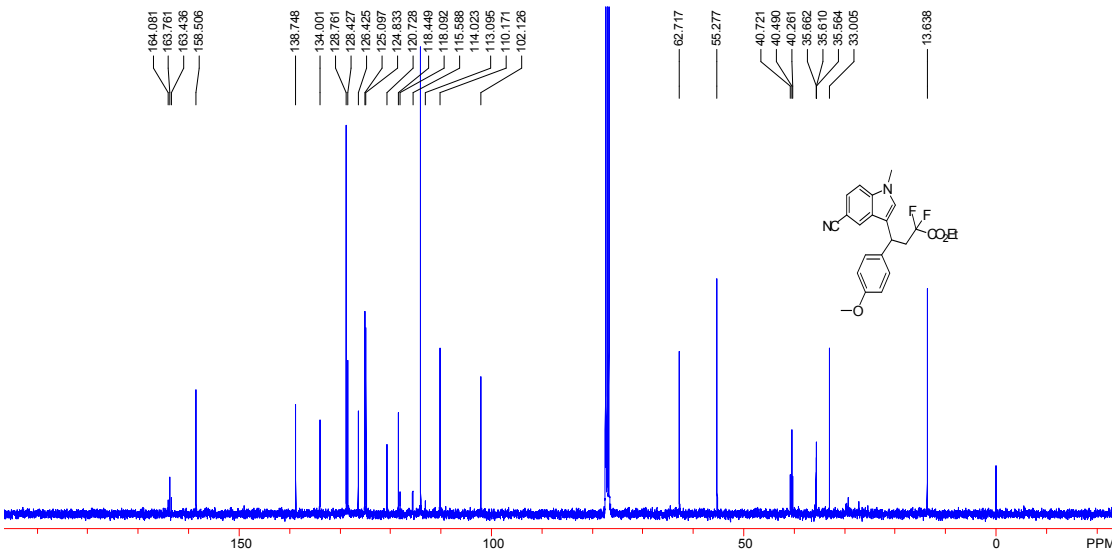
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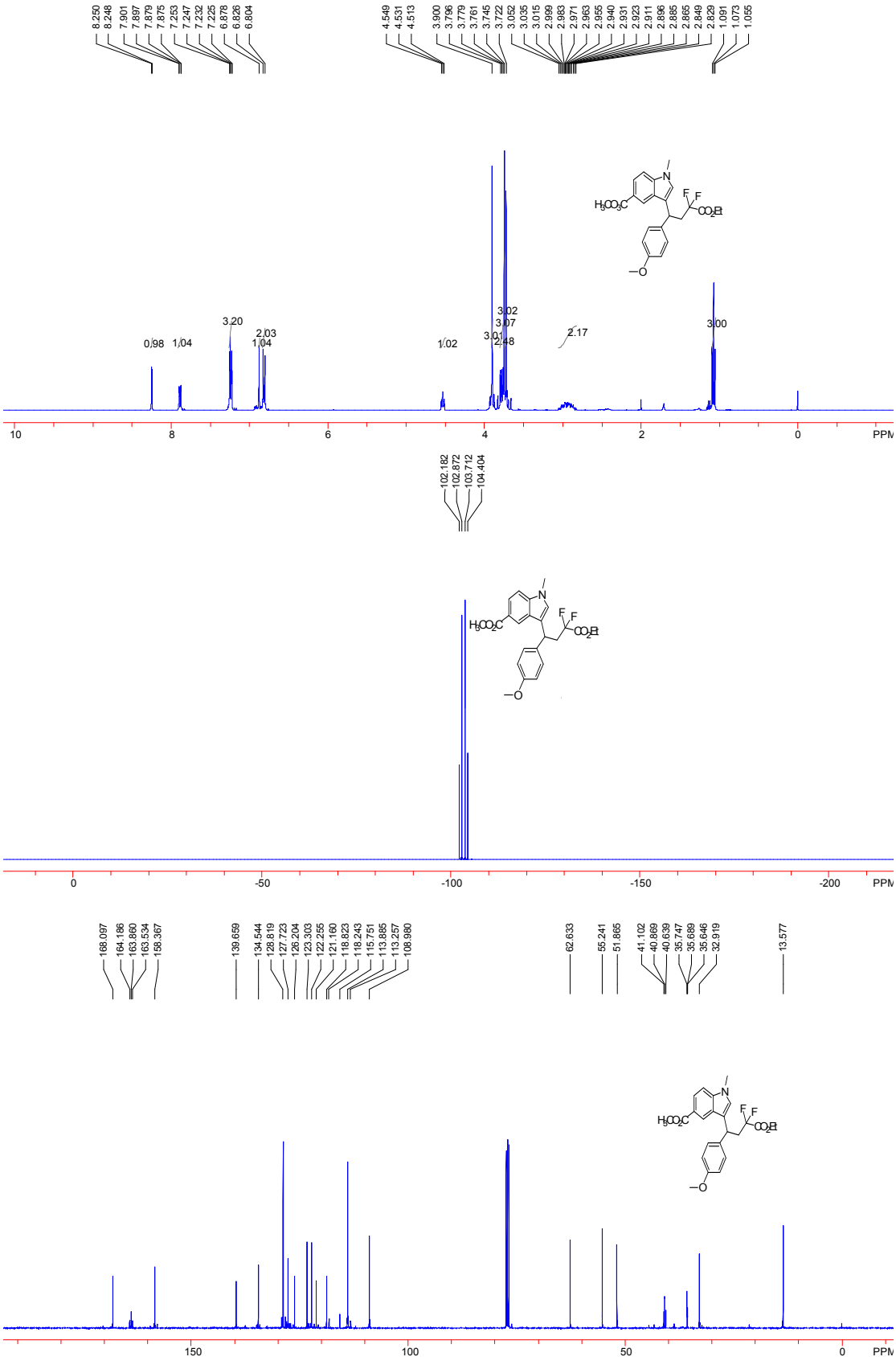
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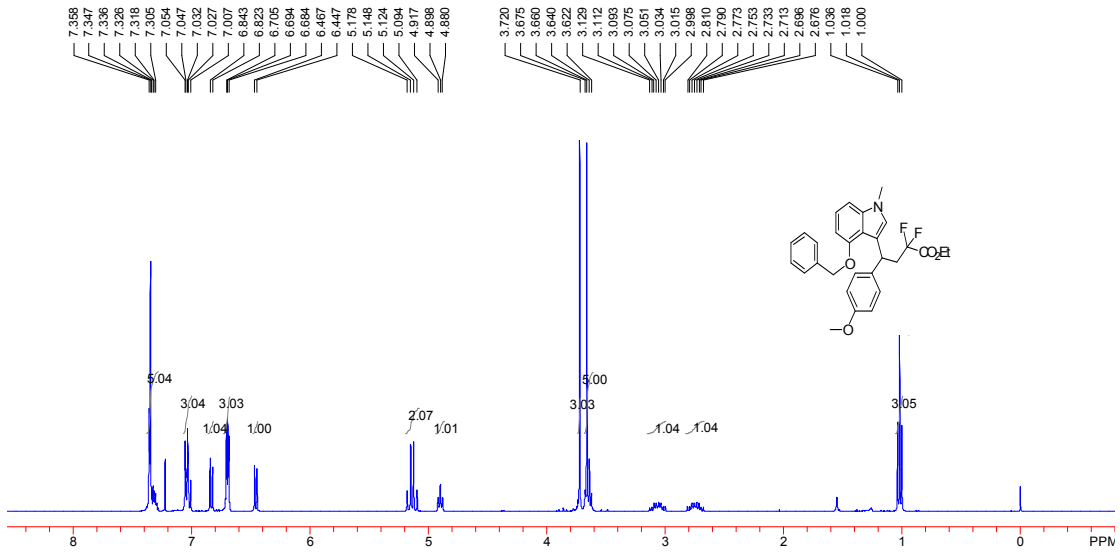
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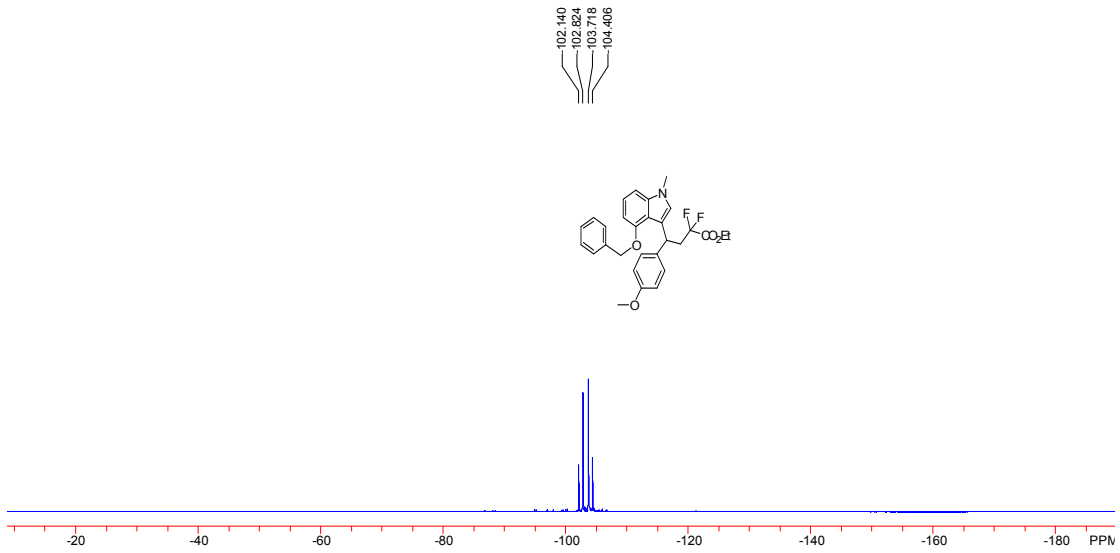
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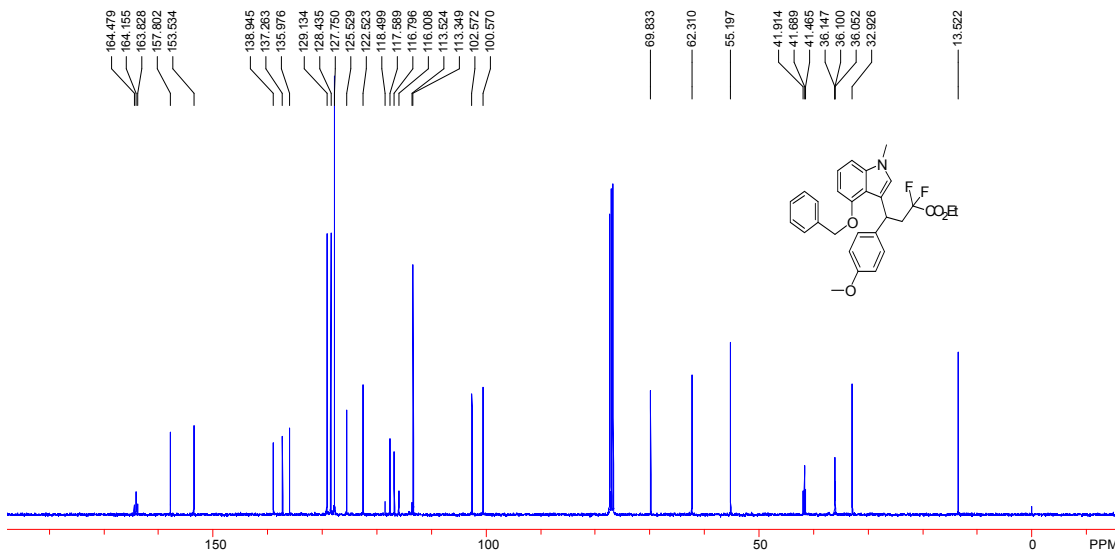
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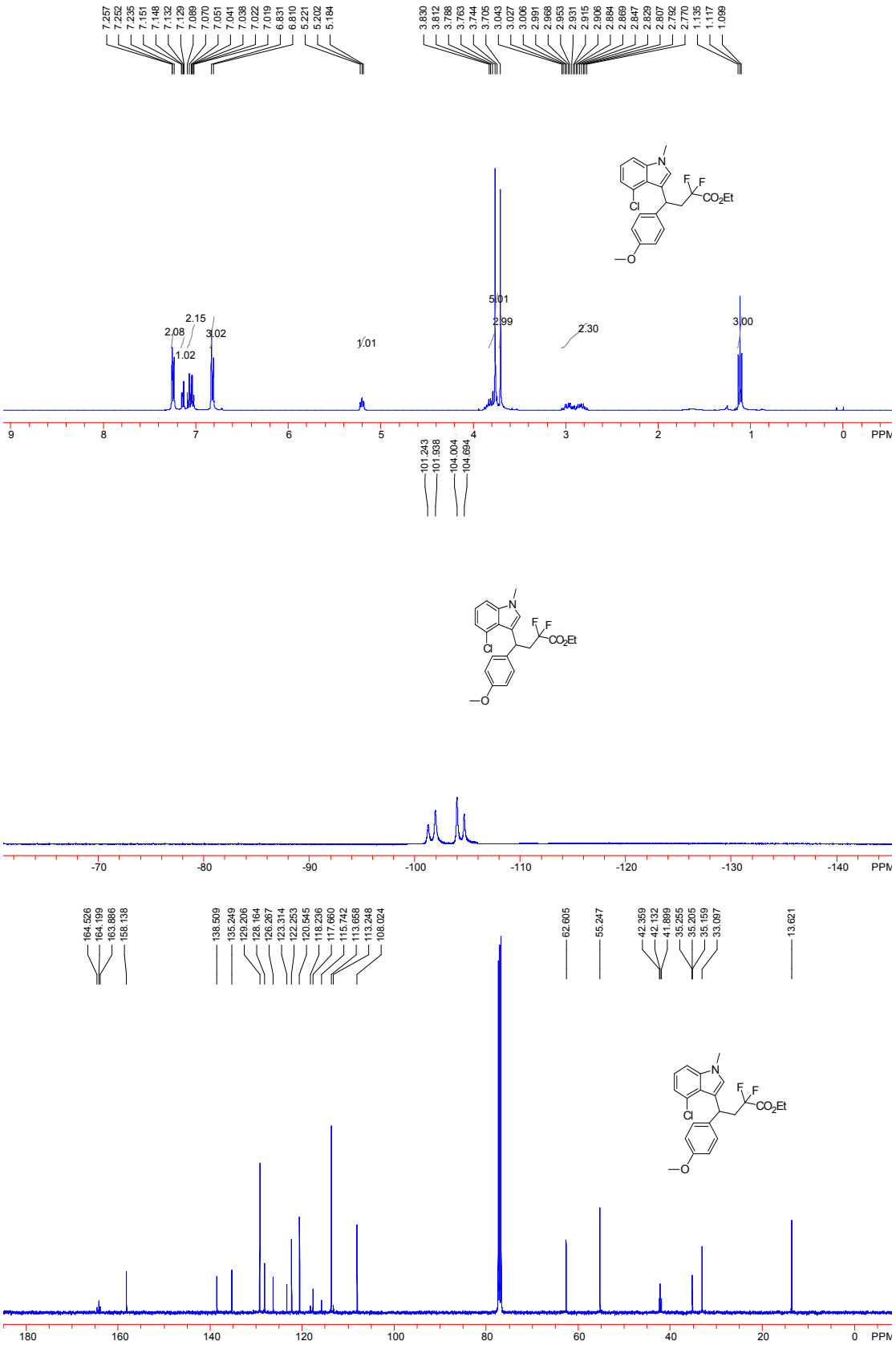
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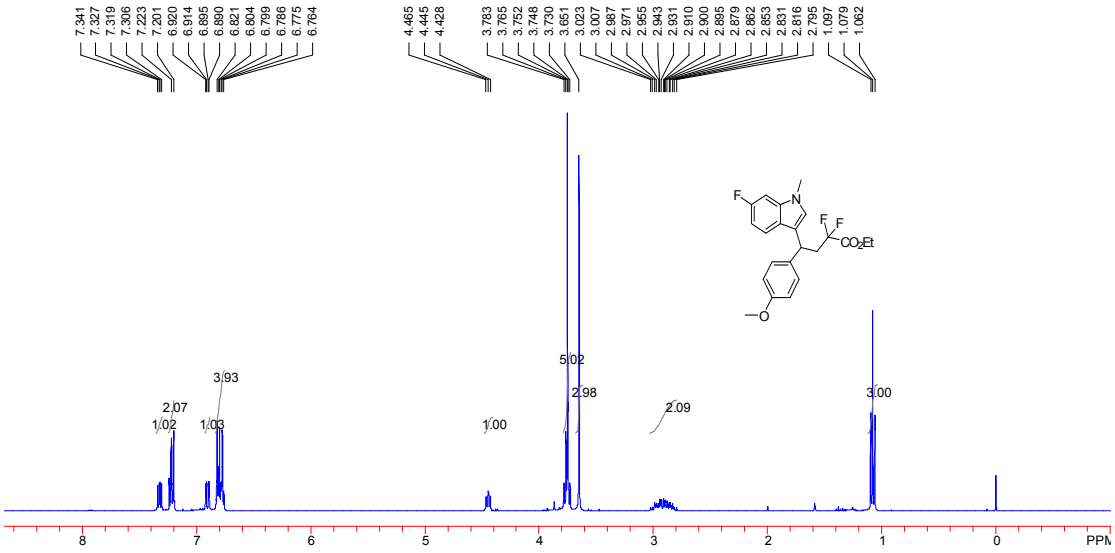
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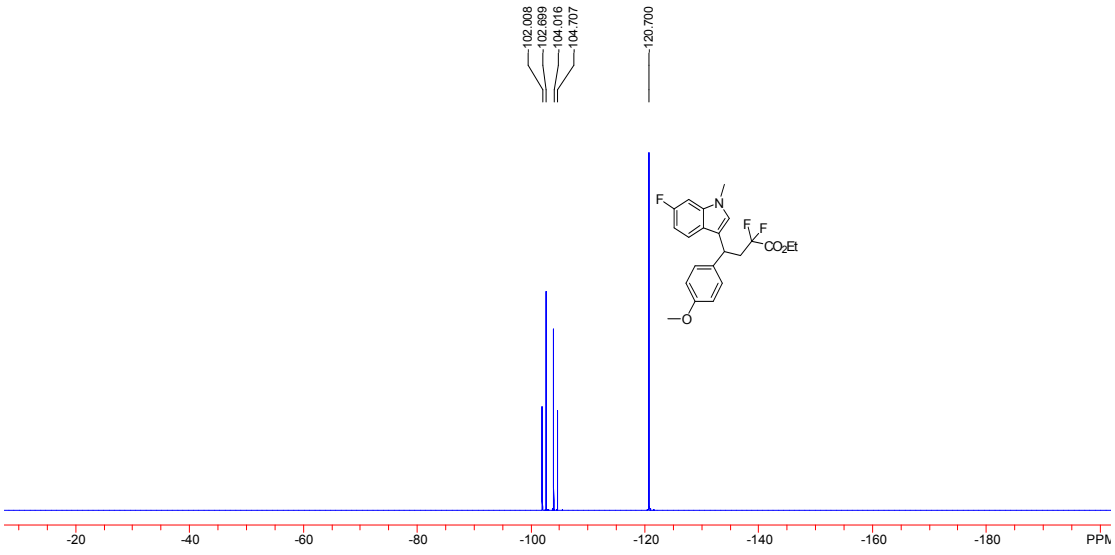
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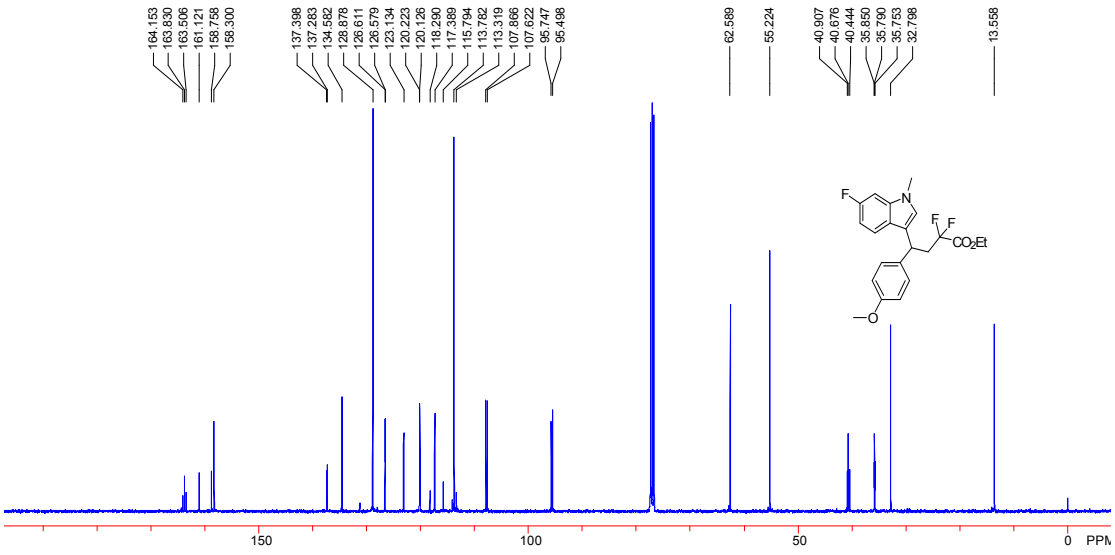
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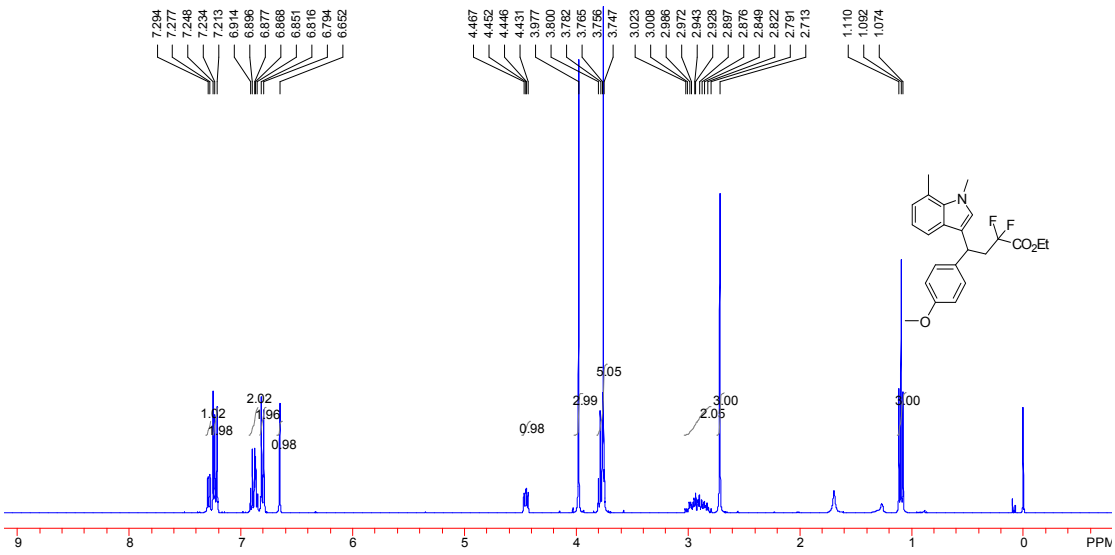
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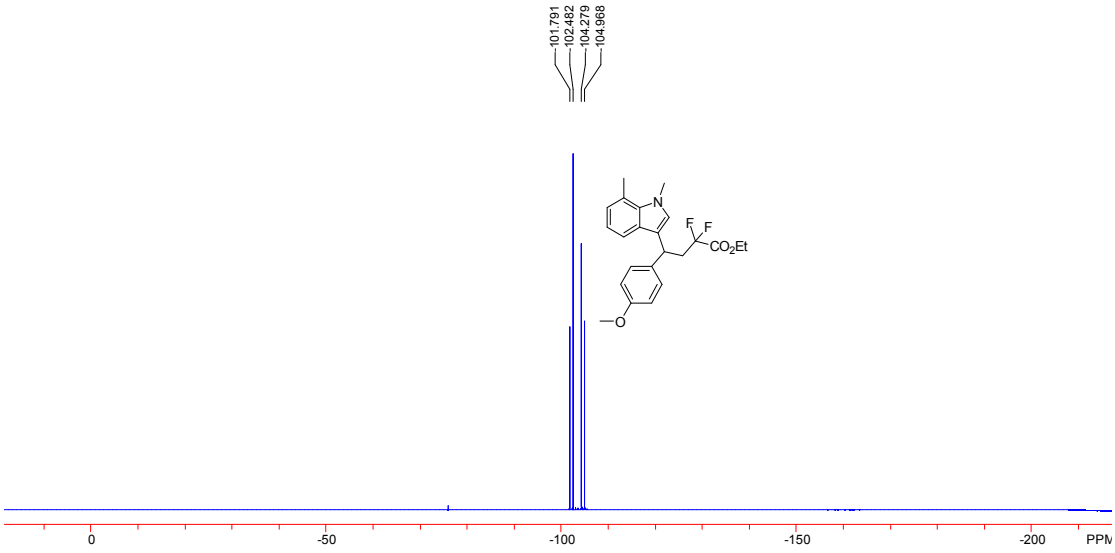
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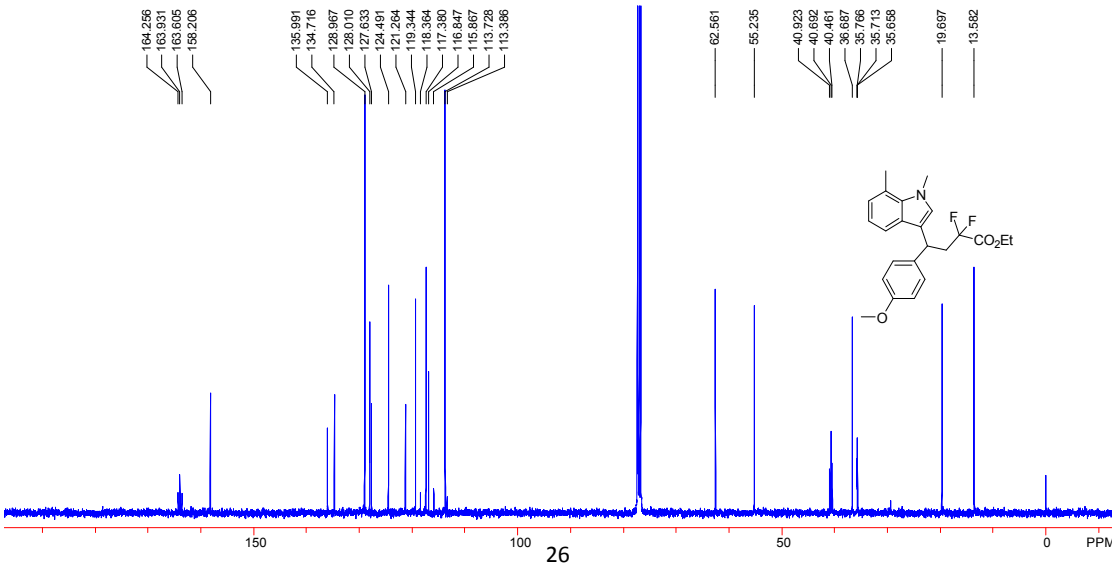
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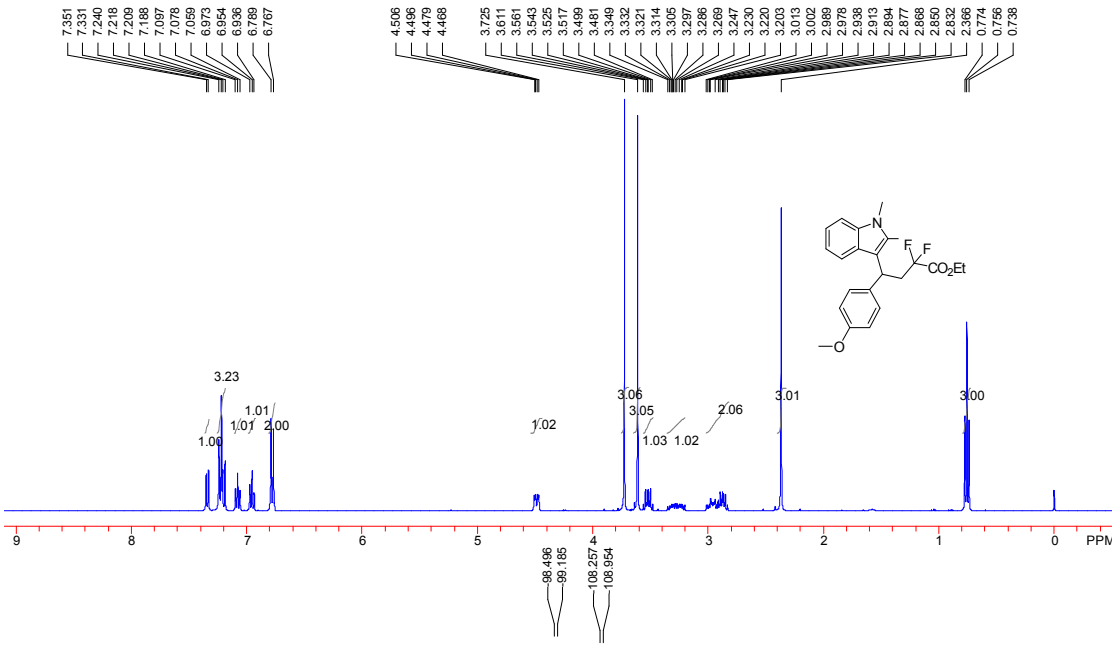
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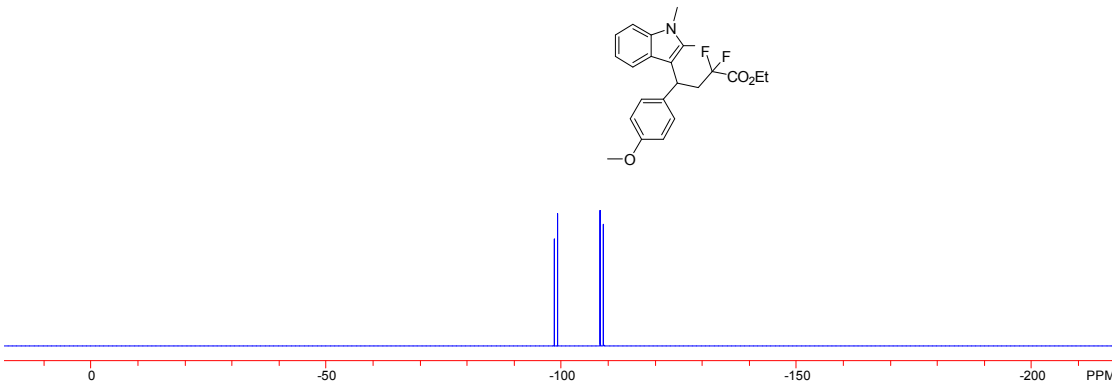
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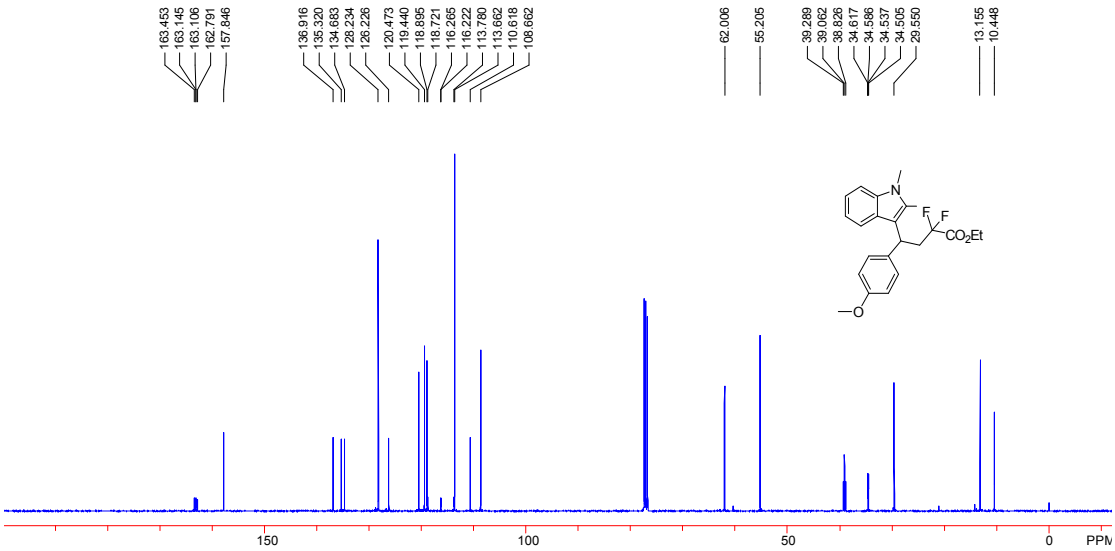
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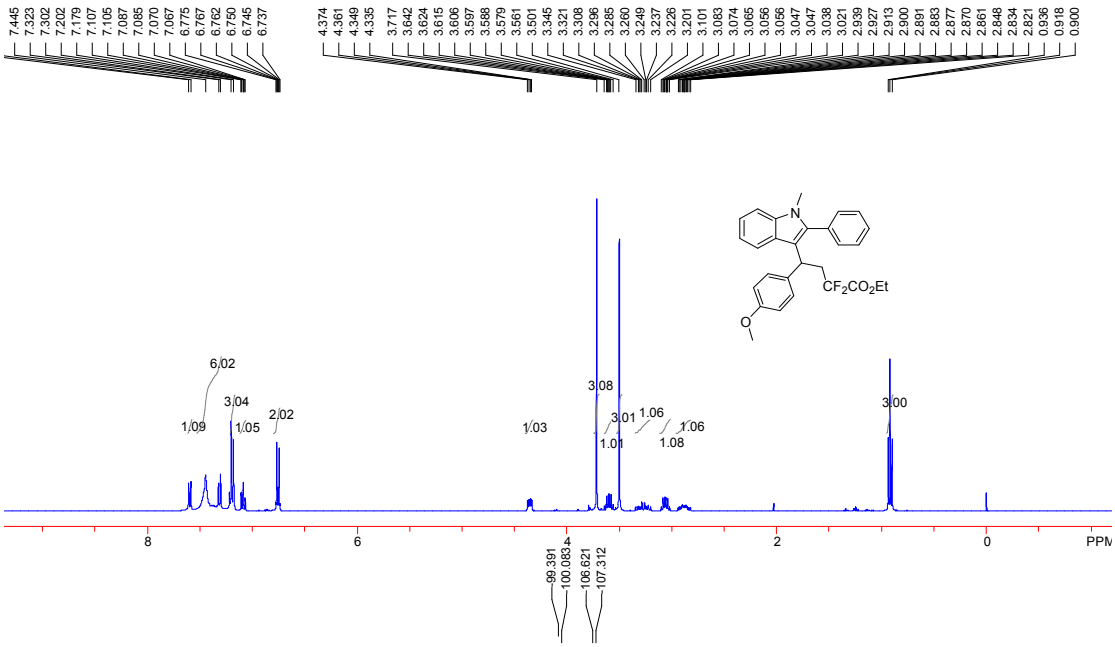
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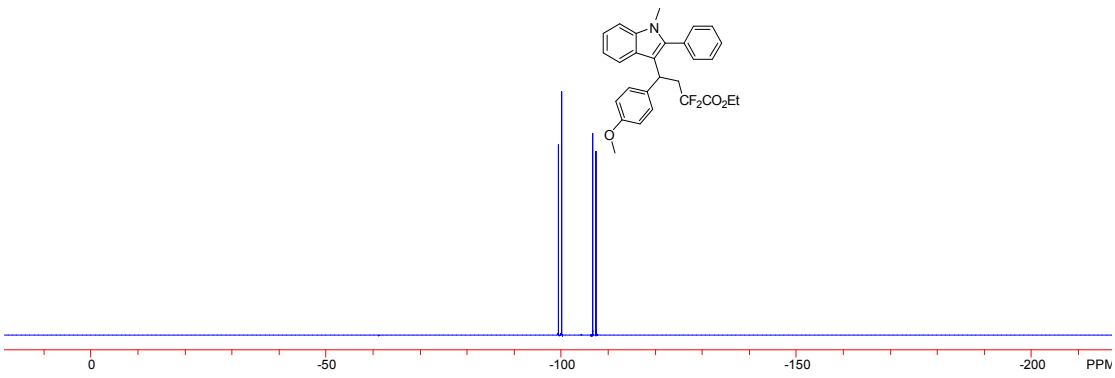
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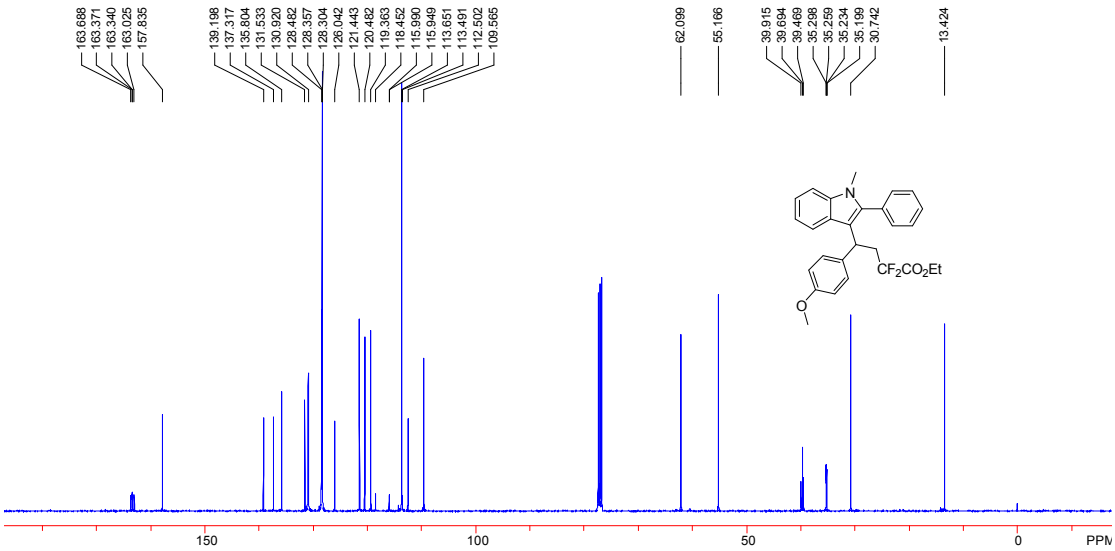
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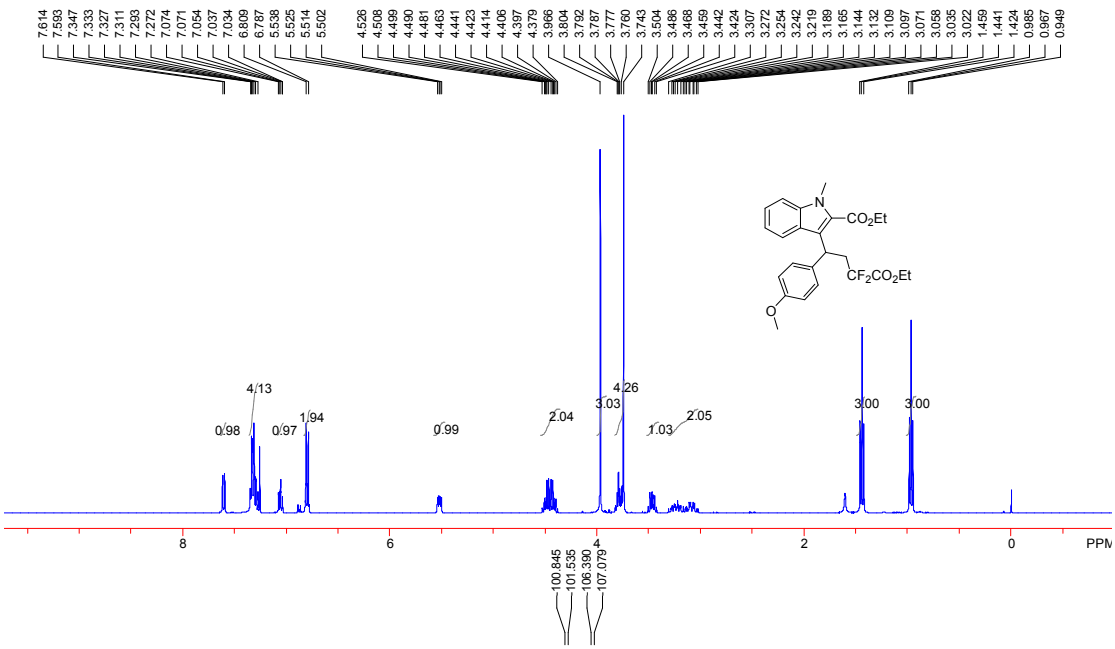
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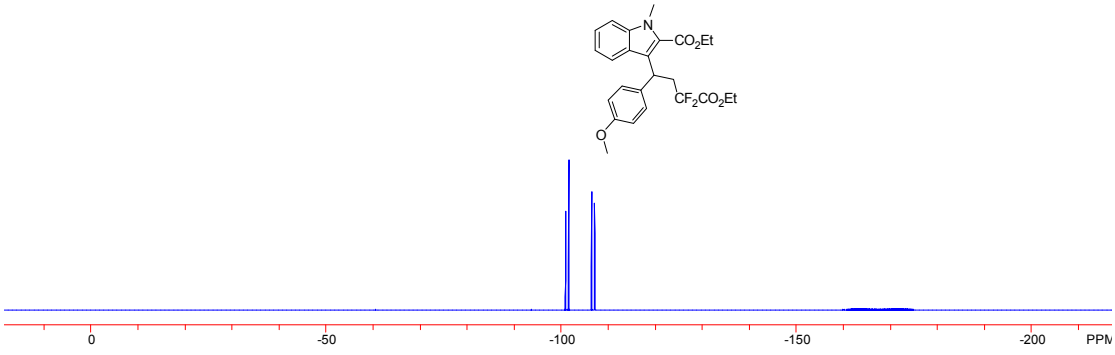
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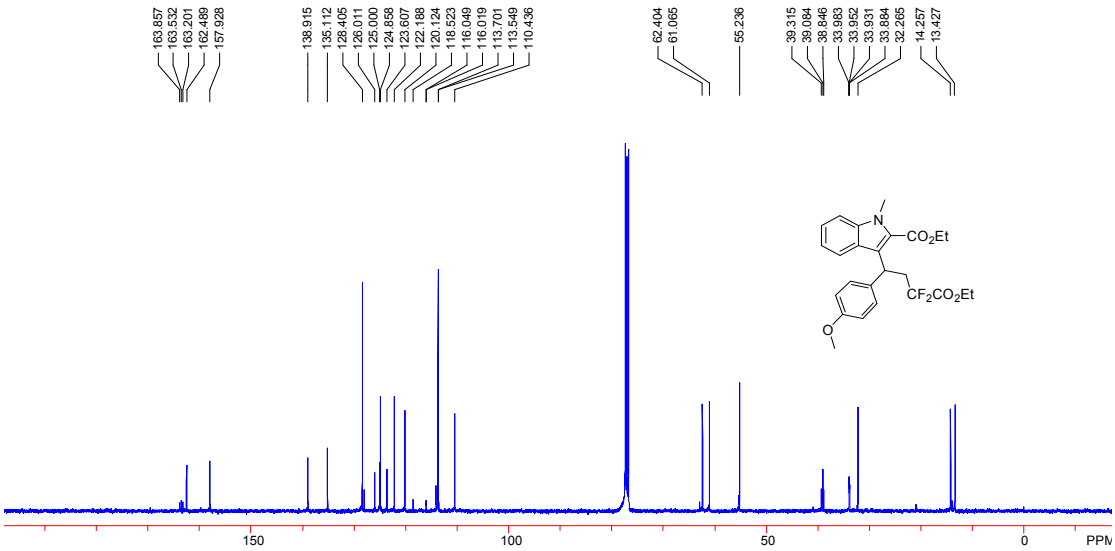
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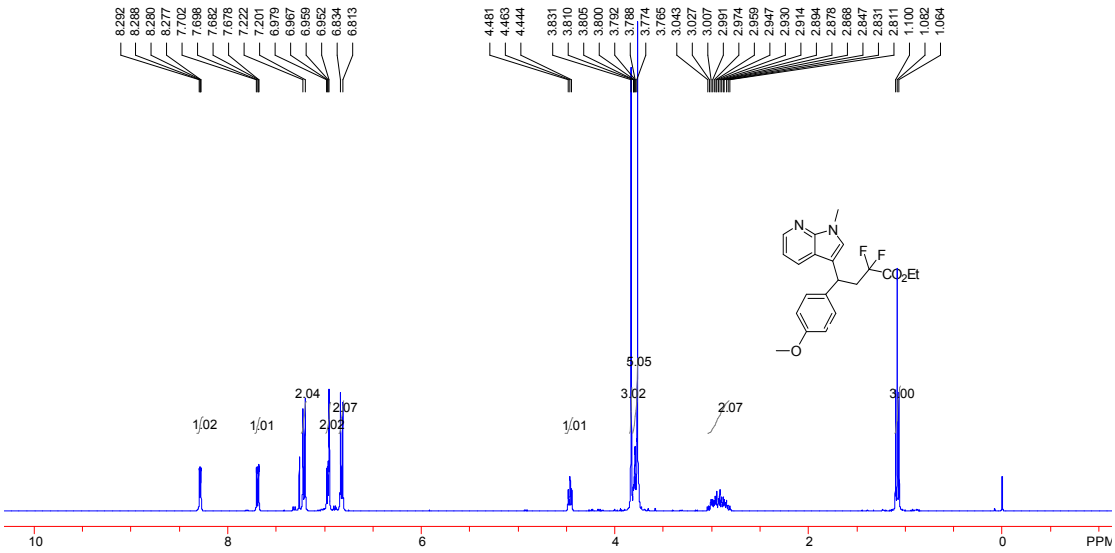
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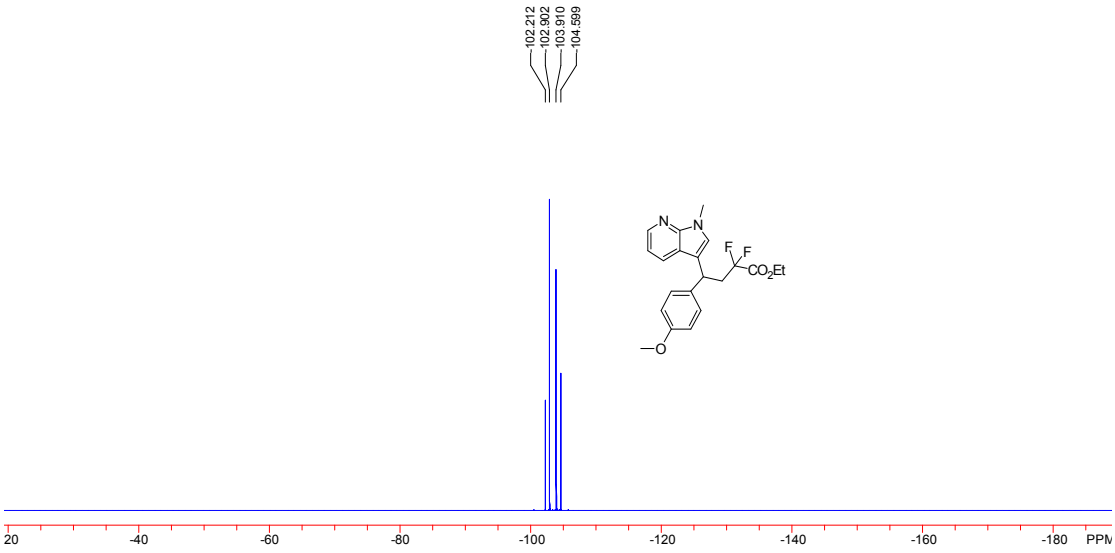
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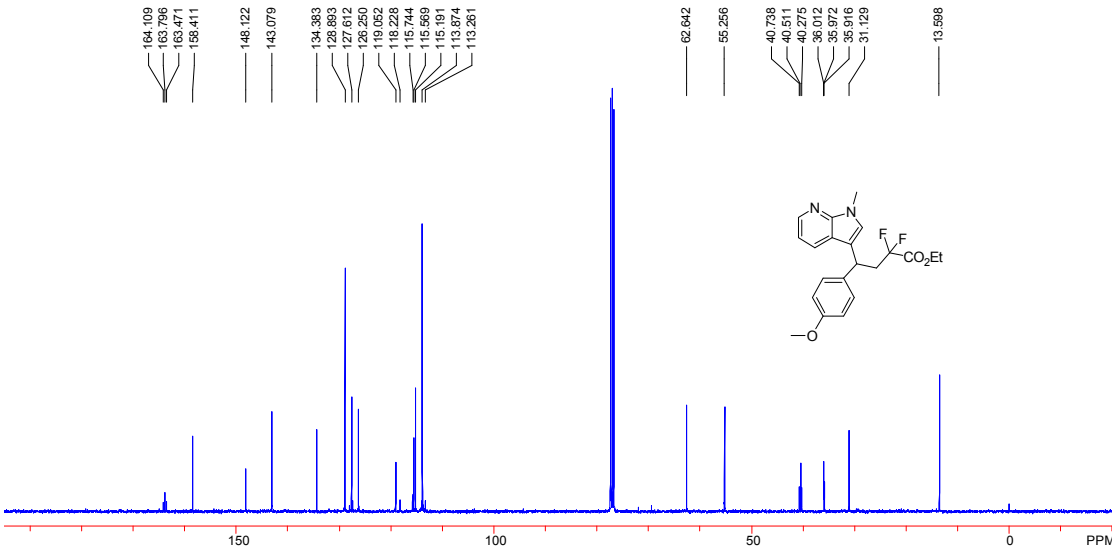
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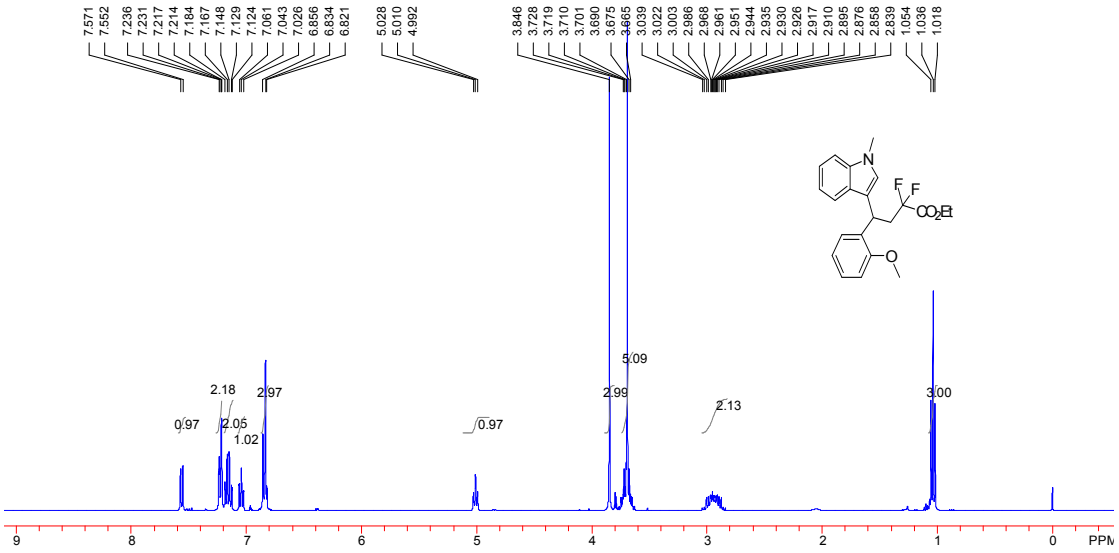
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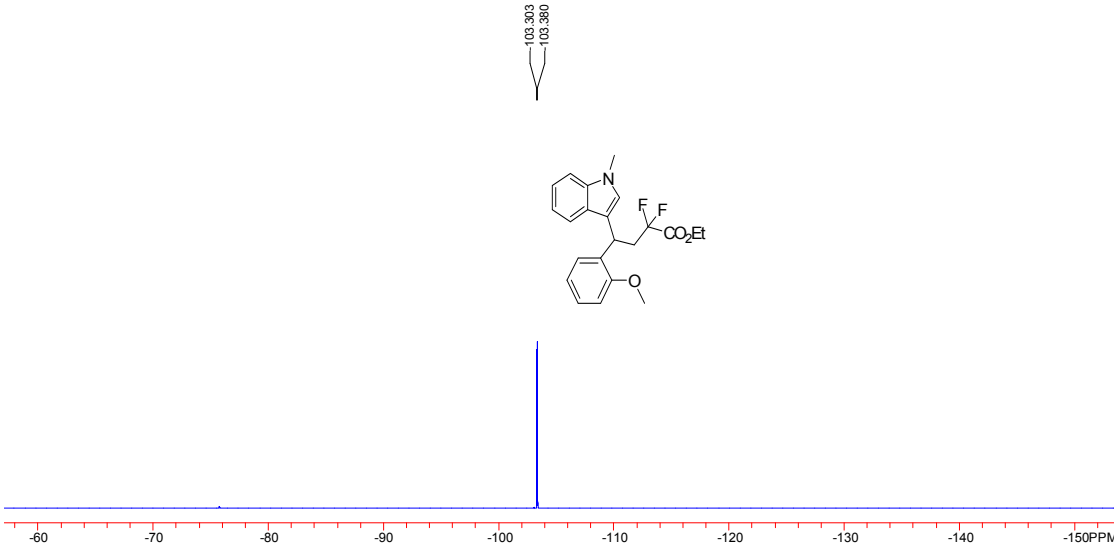
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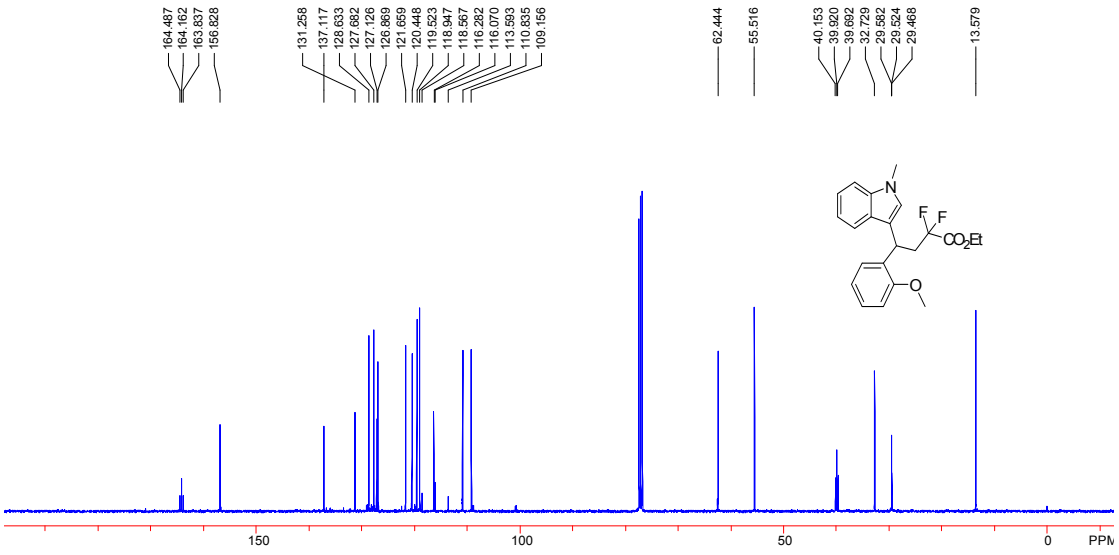
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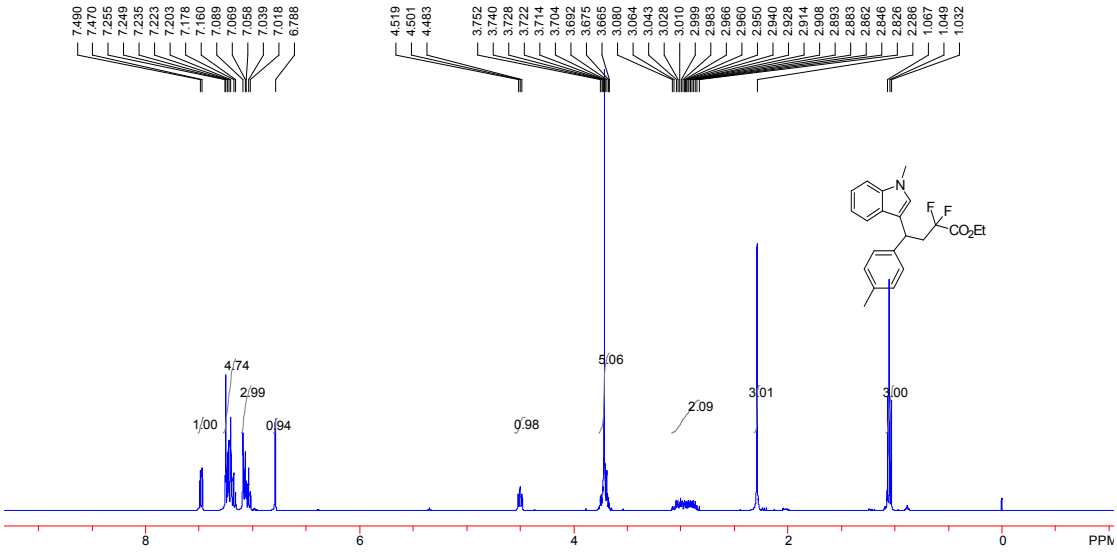
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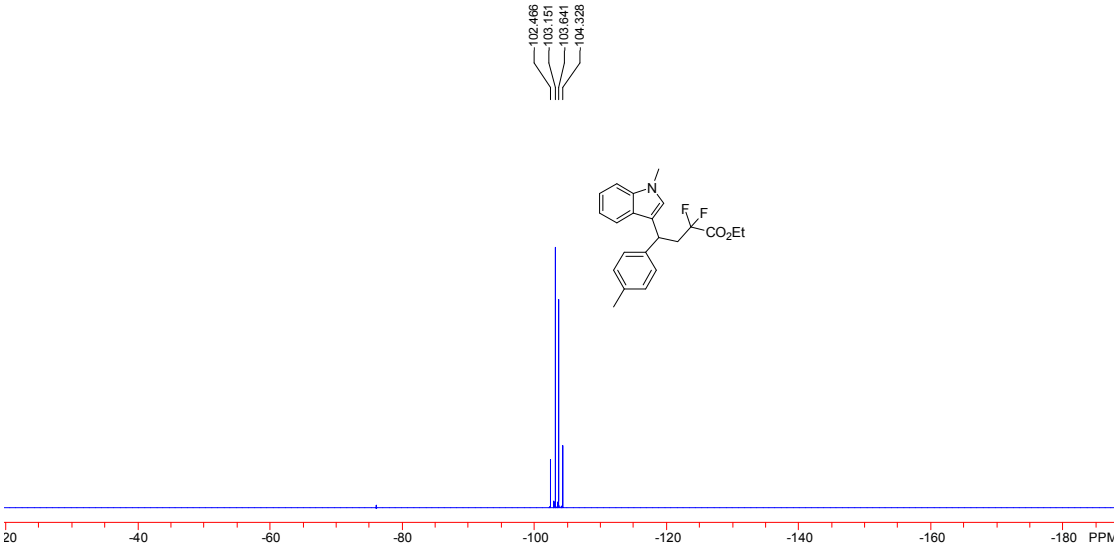
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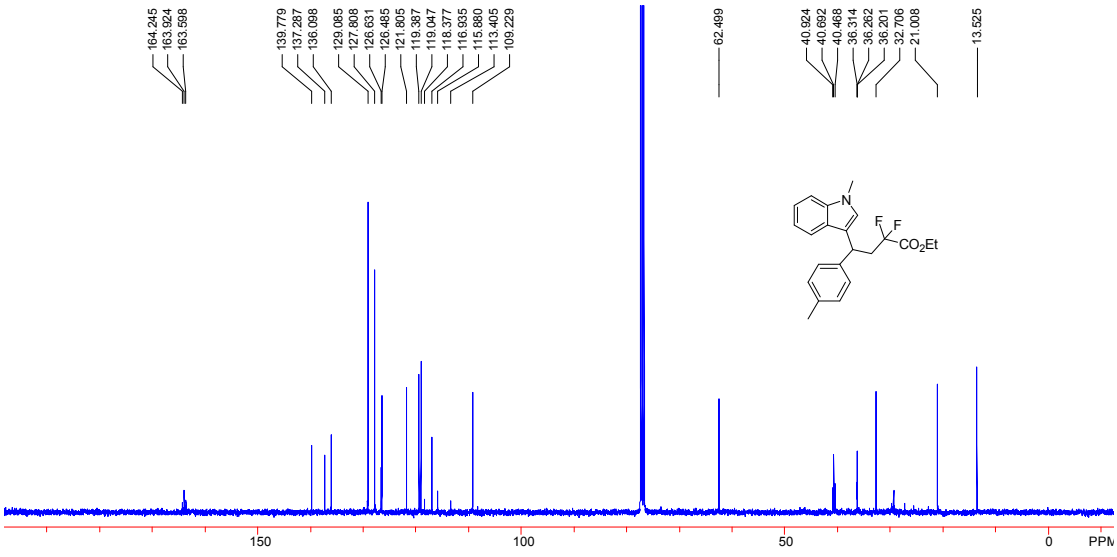
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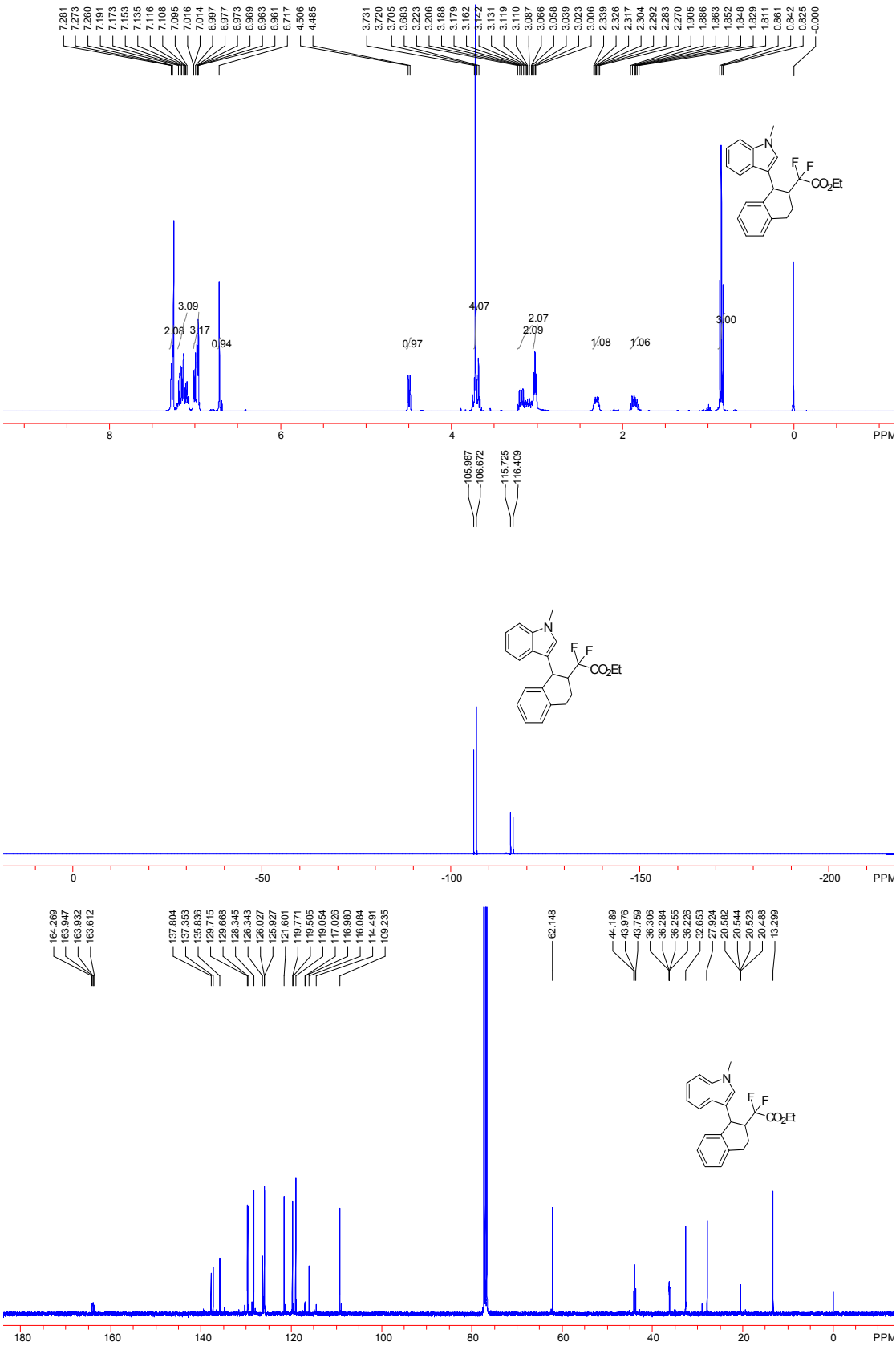
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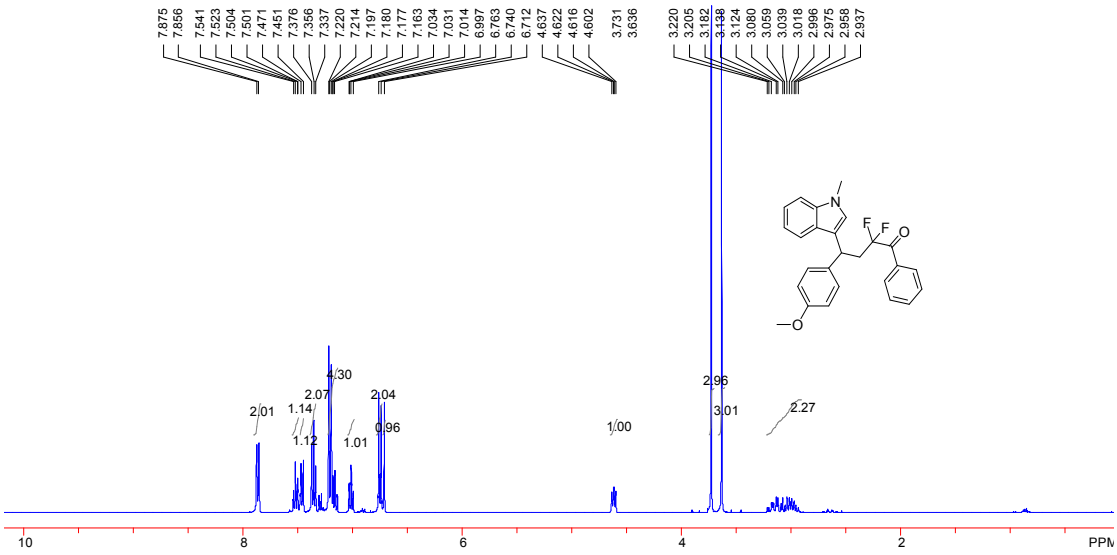
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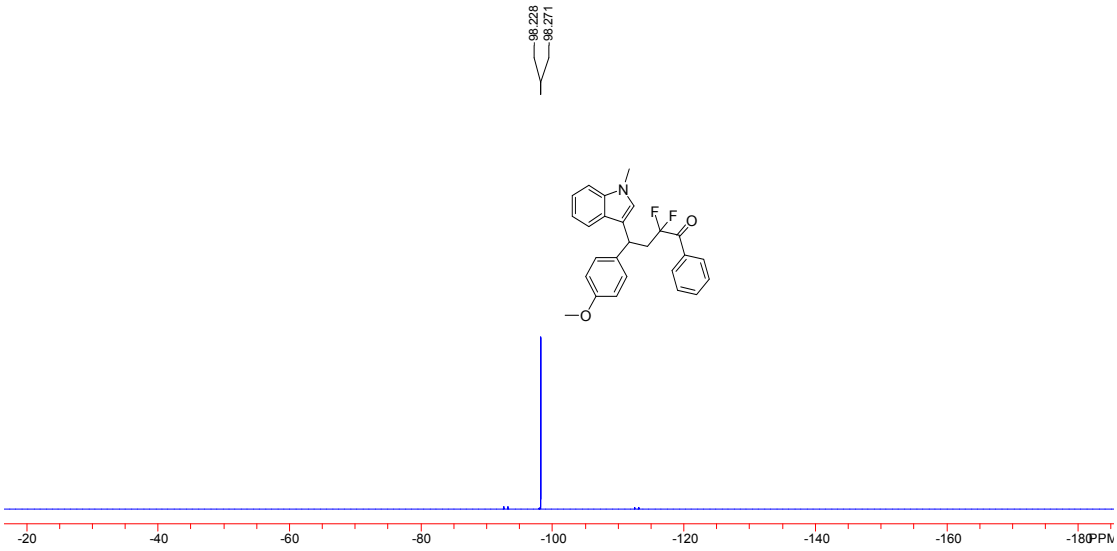
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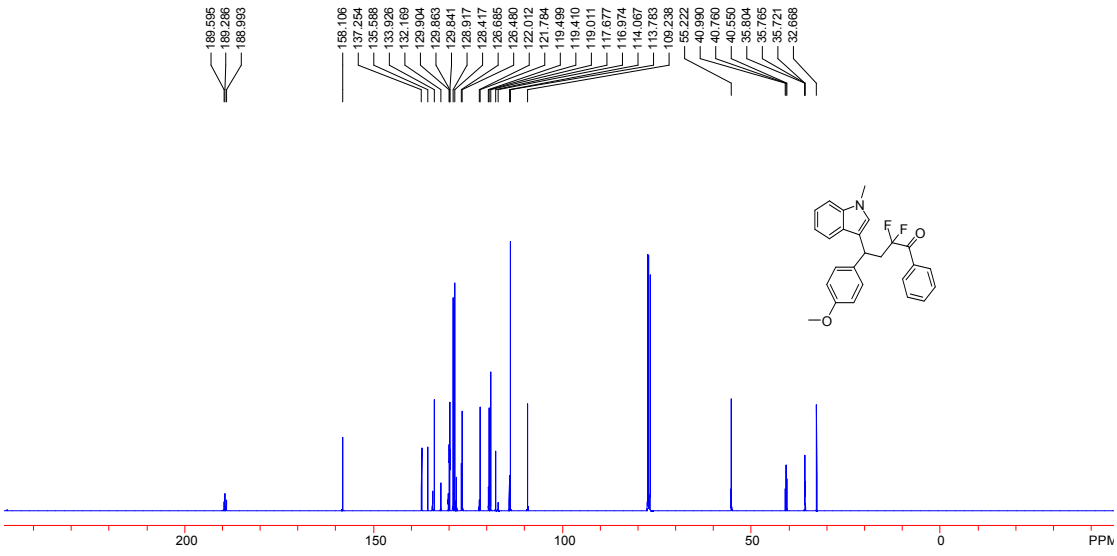
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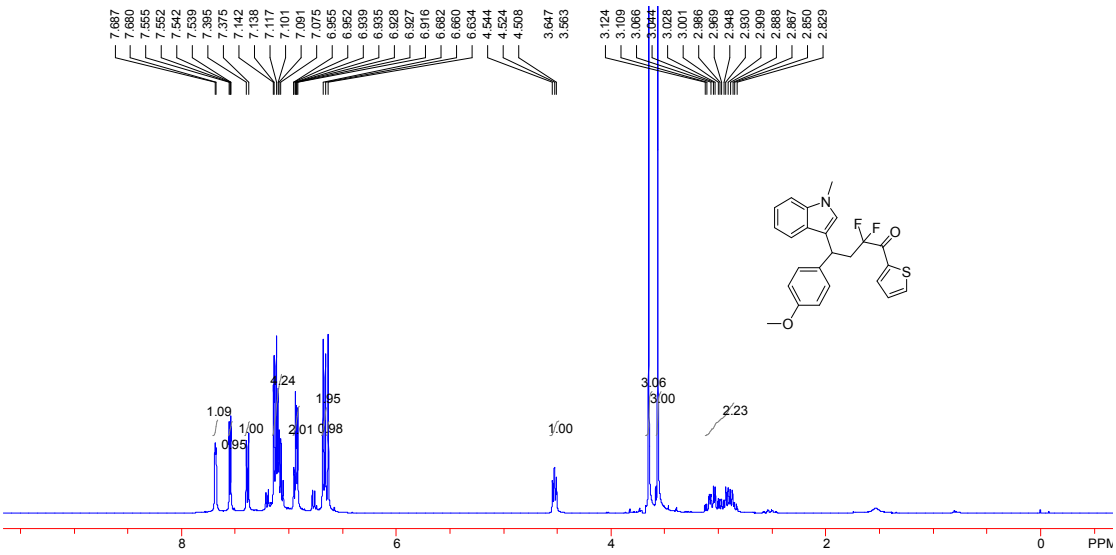
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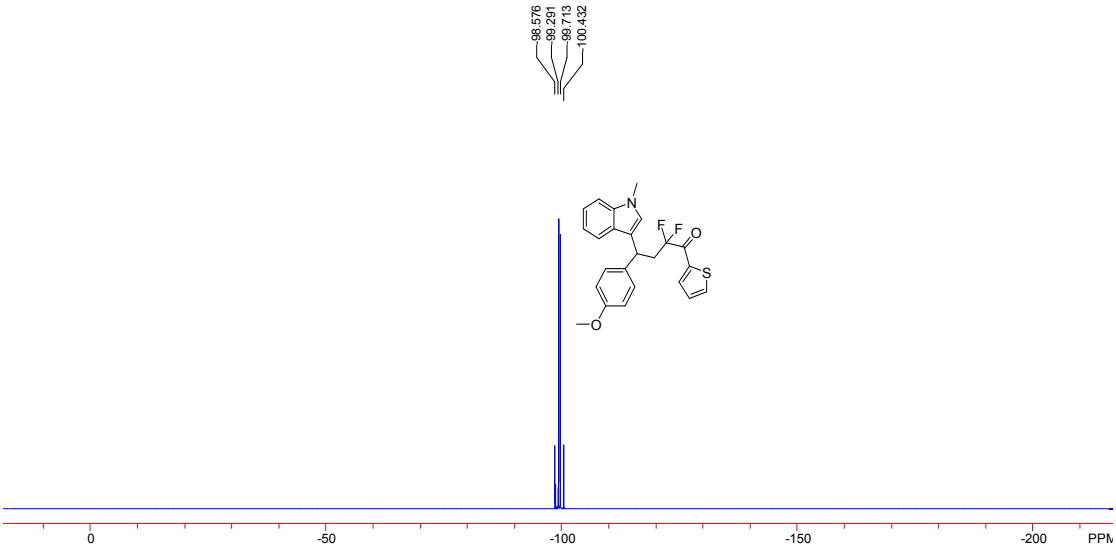
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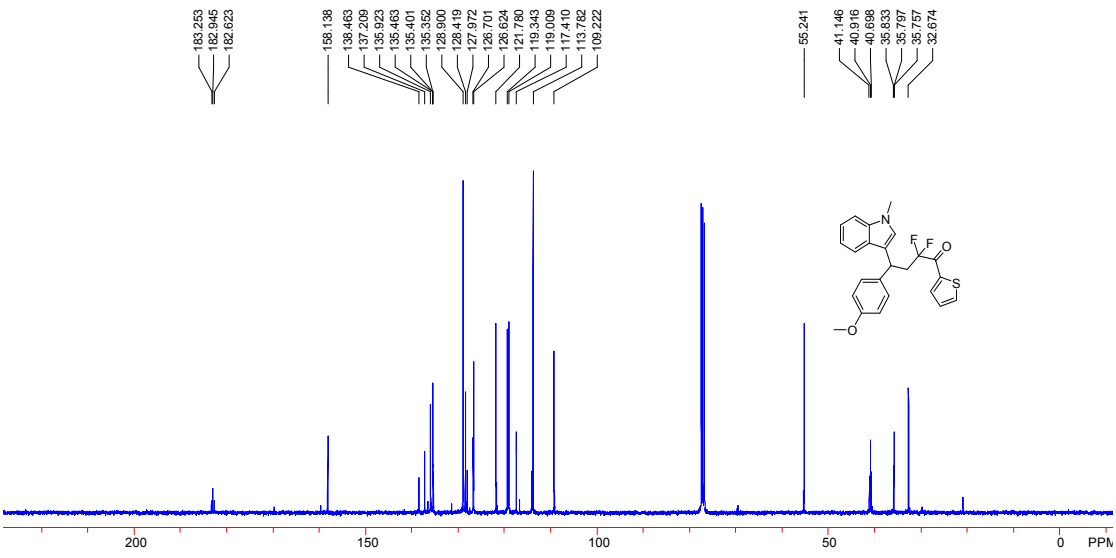
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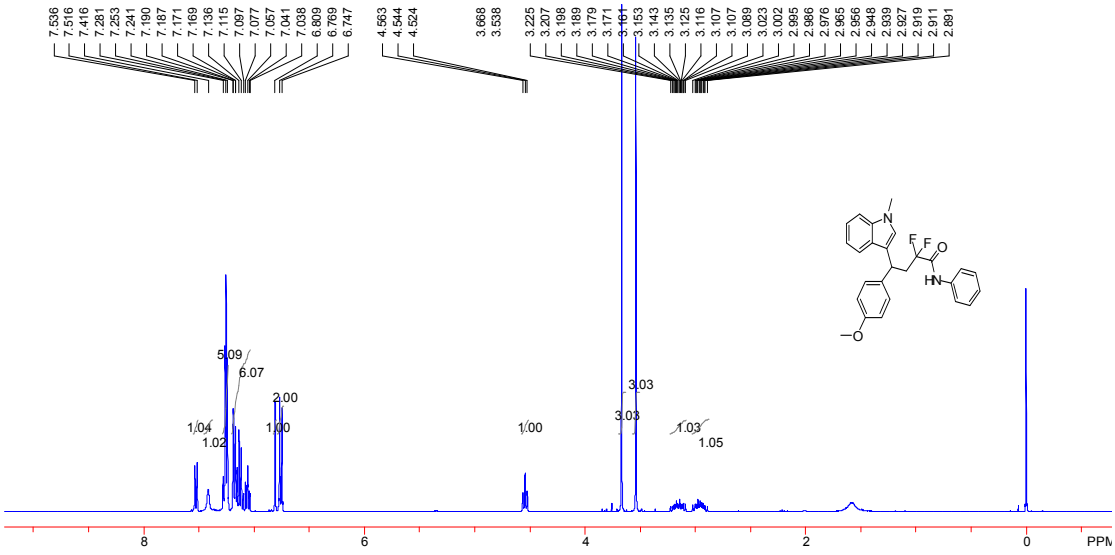
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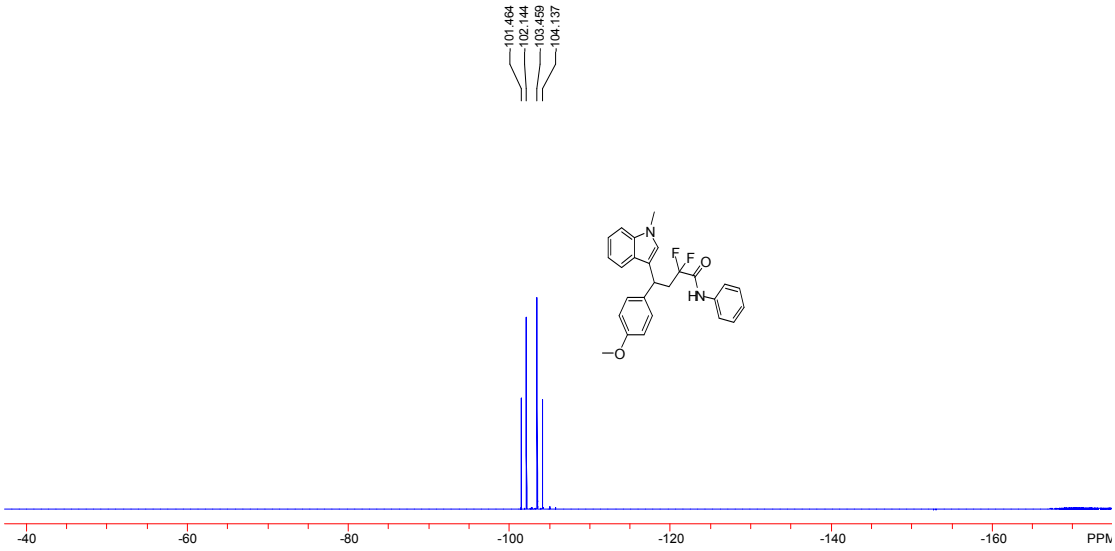
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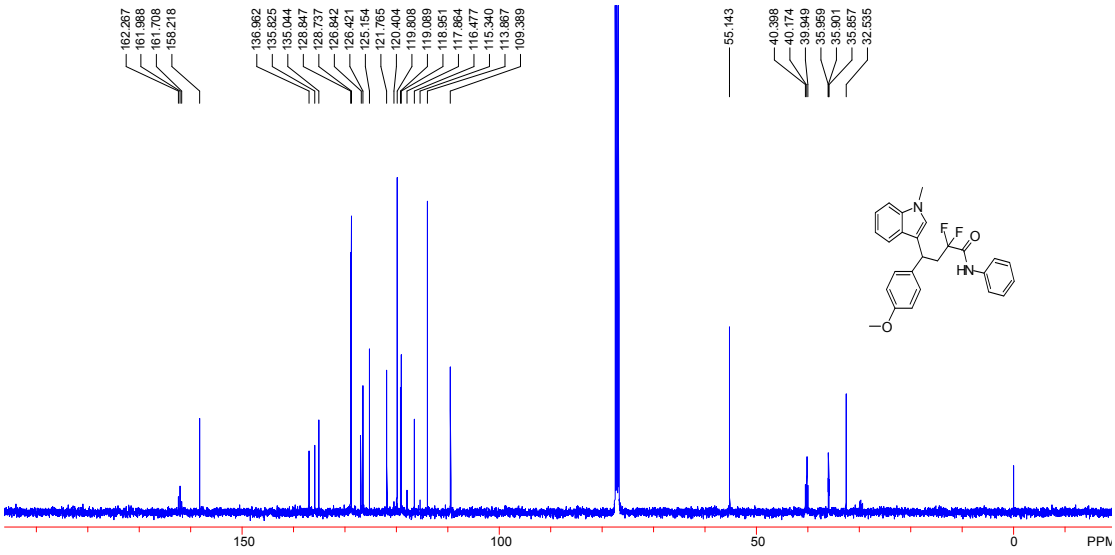
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