Electronic Supplementary Information

Development of a Continuous Flow Synthesis of FGIN-1-27 Enabled by in-line ^{19}F NMR Analyses and Optimization Algorithms

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1. General information

All commercially available chemicals were used as received unless otherwise noted. High-field ^{1}H and ^{13}C NMR spectra were recorded at 300 or 400 and 75 or 100 MHz, respectively. ^{1}H and ^{13}C NMR spectra were referenced to the residual signal of the internal deuterated solvent ($CDCl_3$) at 7.26 and 77.16 ppm, respectively, and coupling constants were measured in Hertz. ^{19}F spectra were recorded at 40.88 MHz with a 1T-benchtop spectrometer (Spinsolve, Magritek) equipped with a flow cell (4 mm id). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. FT-IR spectra were recorded in the ATR mode. Wavelengths of maximum absorbance (ν_{max}) are quoted in wave numbers (cm^{-1}). Flash column chromatography was performed using silica gel 60 (40−63 μm). In order to remove any trace of waste (Pd particles, inorganic salts…) which progressively deposits on the wall of the reactor coil, the tubbing was washed every 100 hours of use with an aqueous solution of nitric acid (1M, 50 mL) followed by a thorough washing with water (100 mL) and CH_3CN (100 mL).

2. Optimization algorithm

The optimization algorithm here used has been described in our previous reports.[1, 2]

3. Details of the experimental setup

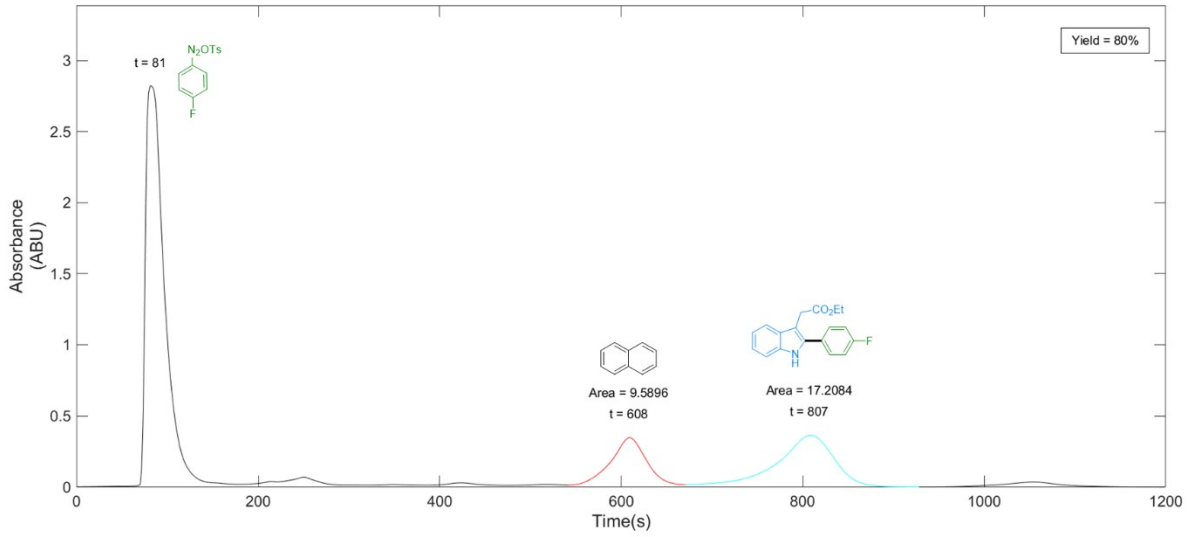
HPLC pumps (JASCO PU4185) were employed to flow the solution through the system. The reactor coil was heated with a heating plate (Heidolph, MR Hei-Connect). The reaction yields were determined by HPLC using the following method: Agela Promosil C18 column (3.5 mm × 150mm, 5 μm), solvent: MeOH/H_2O (70/30), isocratic mode, flow rate 0.5 mL/min, UV detection (254 nm).

4. Optimization studies for the direct C-H arylation

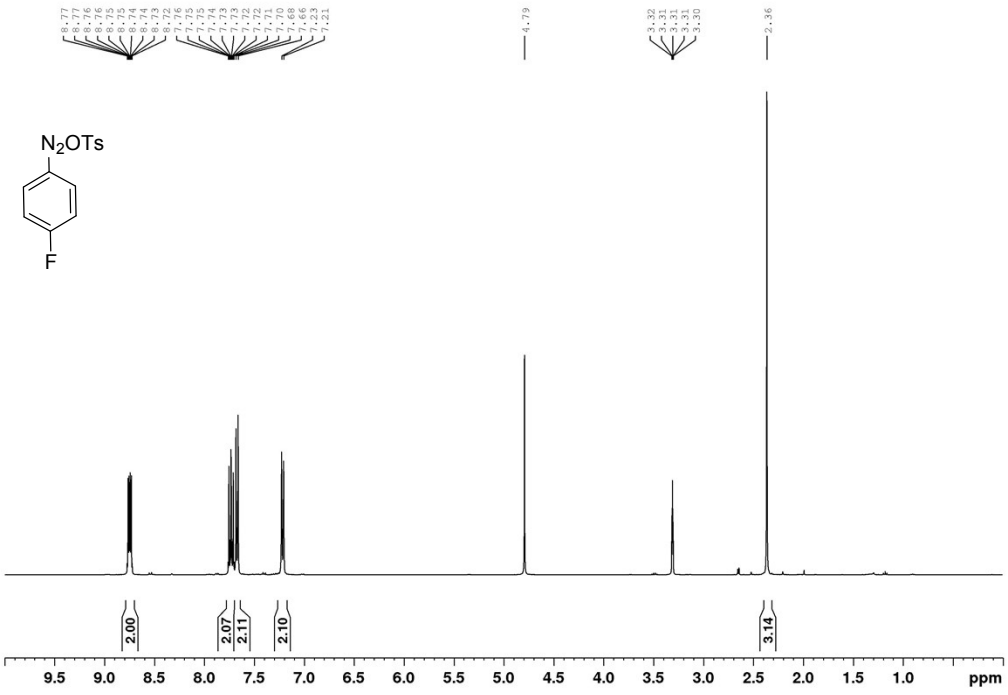
a. Table S1. Maximization of the reaction yield of compound **6**

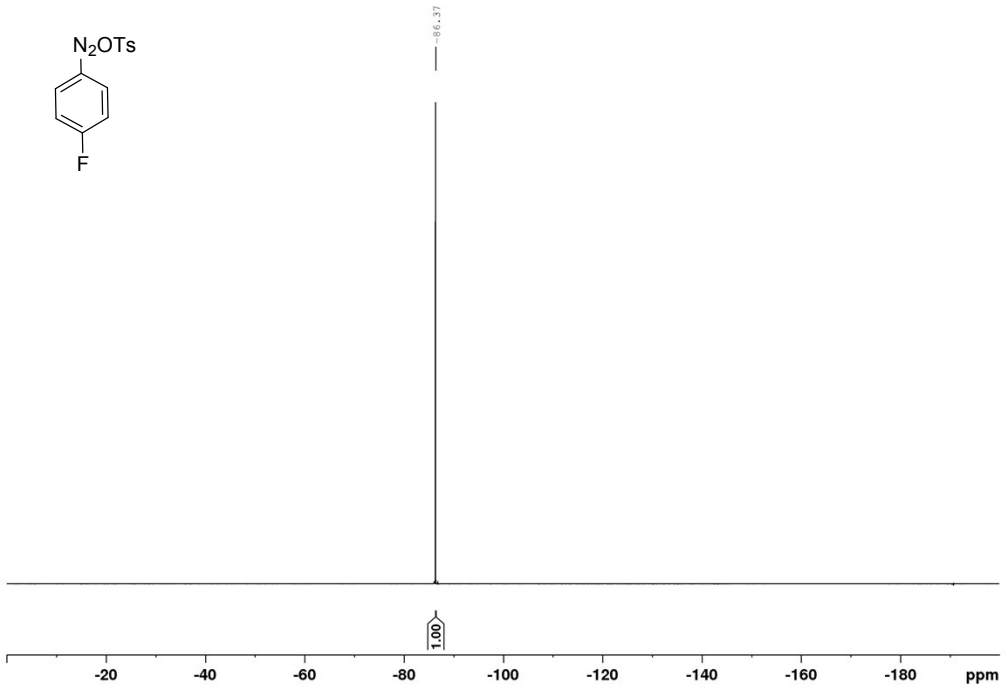
Run	Diazonium (equiv.)	Palladium (mol%)	Residence time (min)	Temperature (° C)	HPLC Yield (%)
1	1.0	1.0	10	25	0
2	1.2	1.0	10	25	0
3	1.0	1.8	10	25	0
4	1.0	1.0	14	25	0
5	1.0	1.0	10	32	0
6	1.7	4.0	25	39	32
7	1.9	4.0	25	39	28
8	1.7	4.8	25	39	32
9	1.7	4.0	29	39	31
10	1.7	4.0	25	46	48
11	1.5	4.4	27	43	39
12	1.6	4.6	22	44	36
13	1.6	4.9	25	47	53
14	1.5	5.0	24	48	52
15	1.5	4.2	24	51	50
16	1.5	4.1	28	49	45
17	1.6	4.2	24	54	65
18	1.7	4.1	23	59	80
19	1.7	4.4	20	53	57
20	1.5	4.8	21	59	78
21	1.7	5.0	19	58	69
22	1.7	4.5	20	60	77
23	1.6	4.6	21	60	75

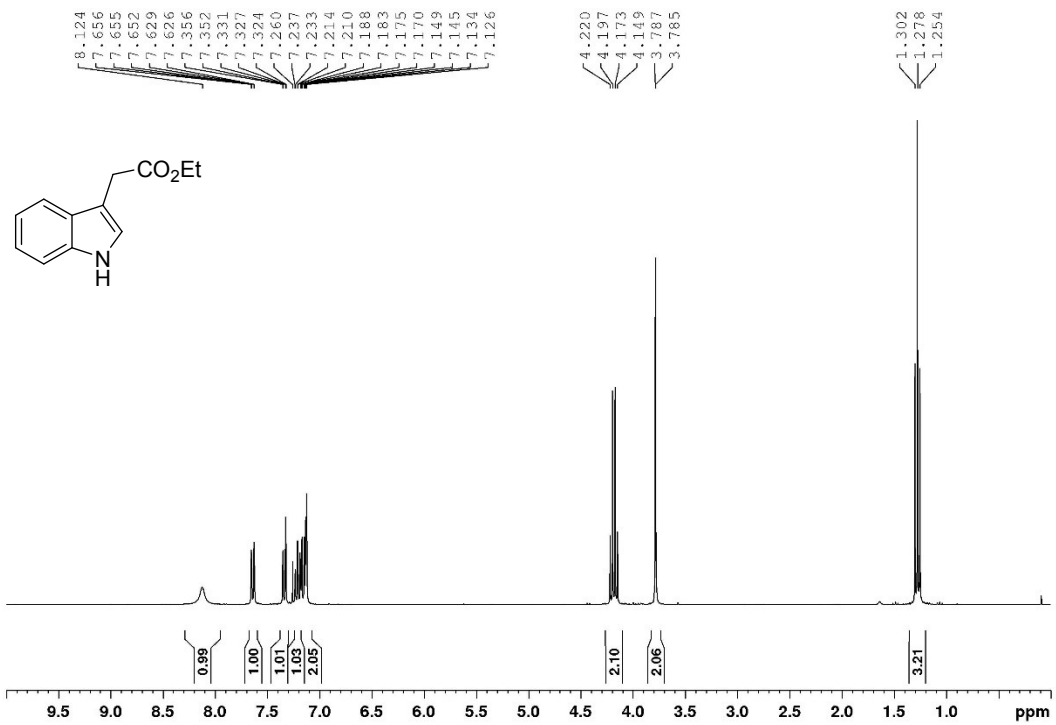
b. Figure S1. HPLC chromatogram of the crude mixture of experiment 18



6. NMR spectra



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7.233
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7.183
7.175
7.170
7.149
7.145
7.134
7.126
4.220
4.197
4.173
4.149
3.787
3.785
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1.278
1.254
CO2Et
N
H
0.99
1.00
1.01
1.03
2.05
2.10
2.06
3.21
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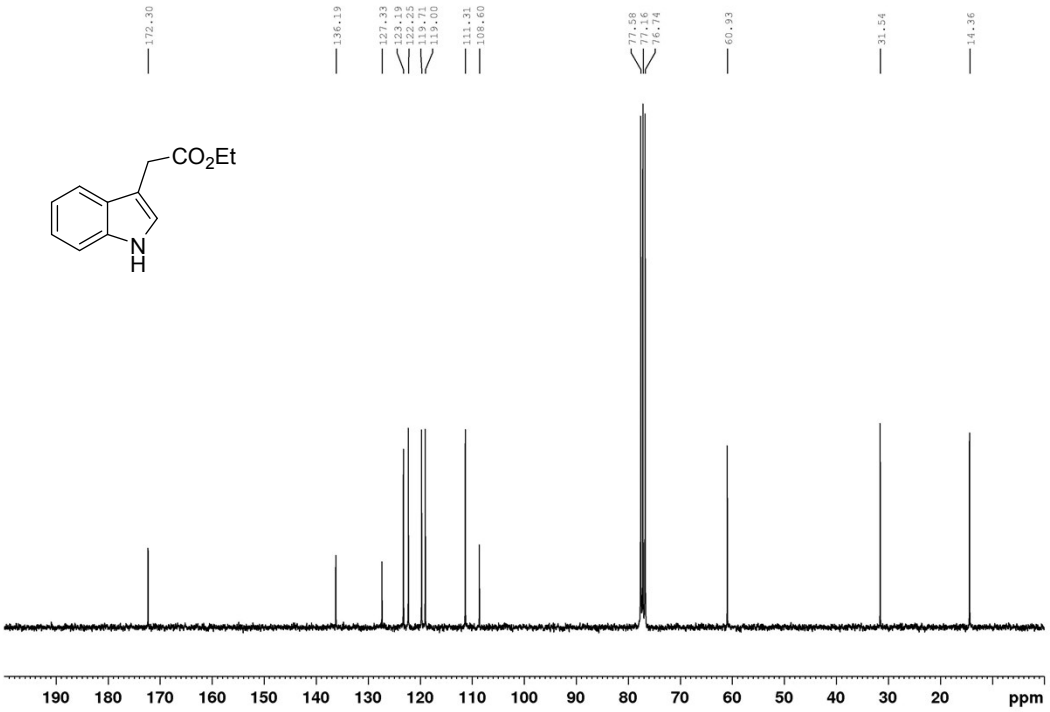
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H
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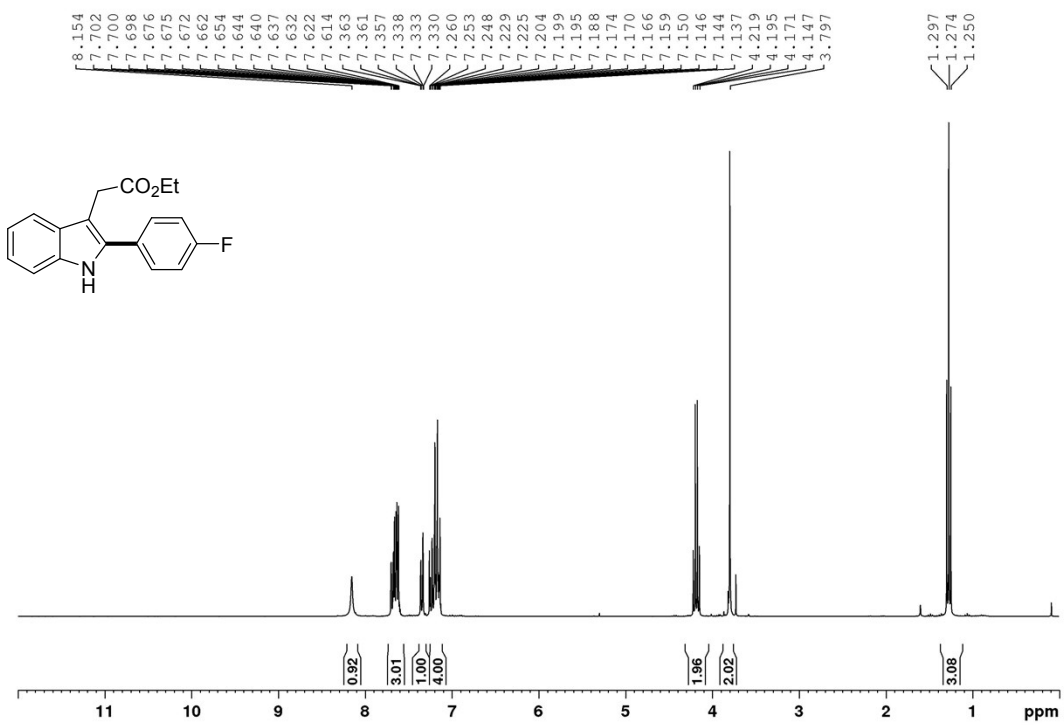
ppm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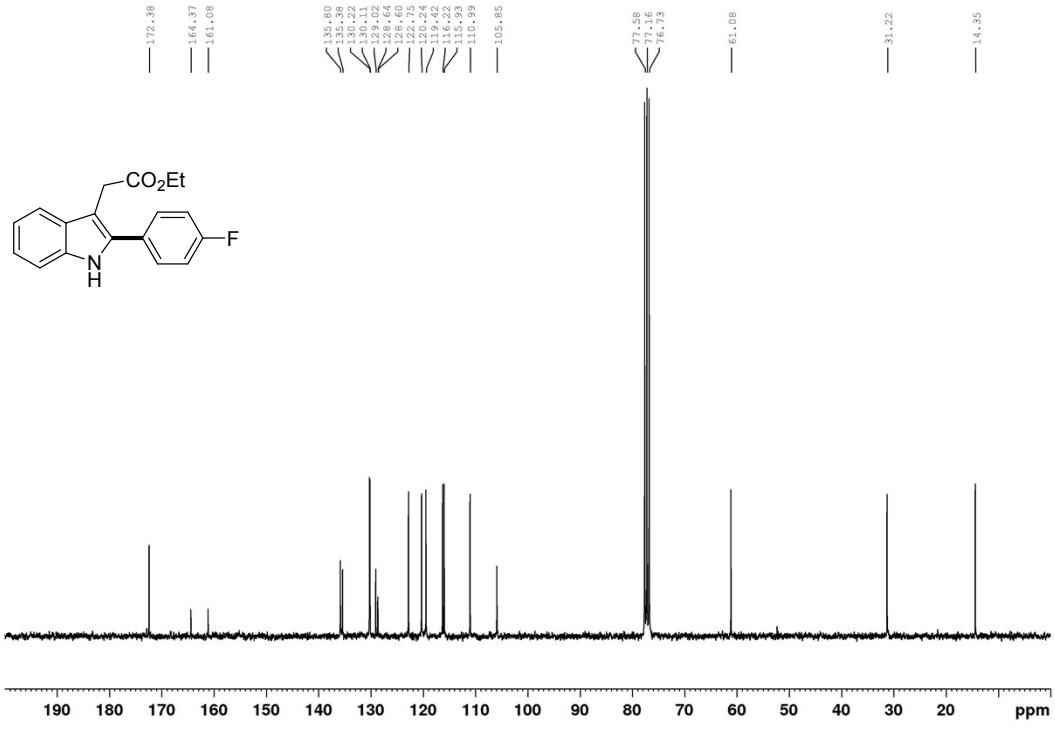
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116.22
115.93
110.99
105.85
77.58
77.16
76.73
61.08
31.22
14.35
CO2Et
F
N
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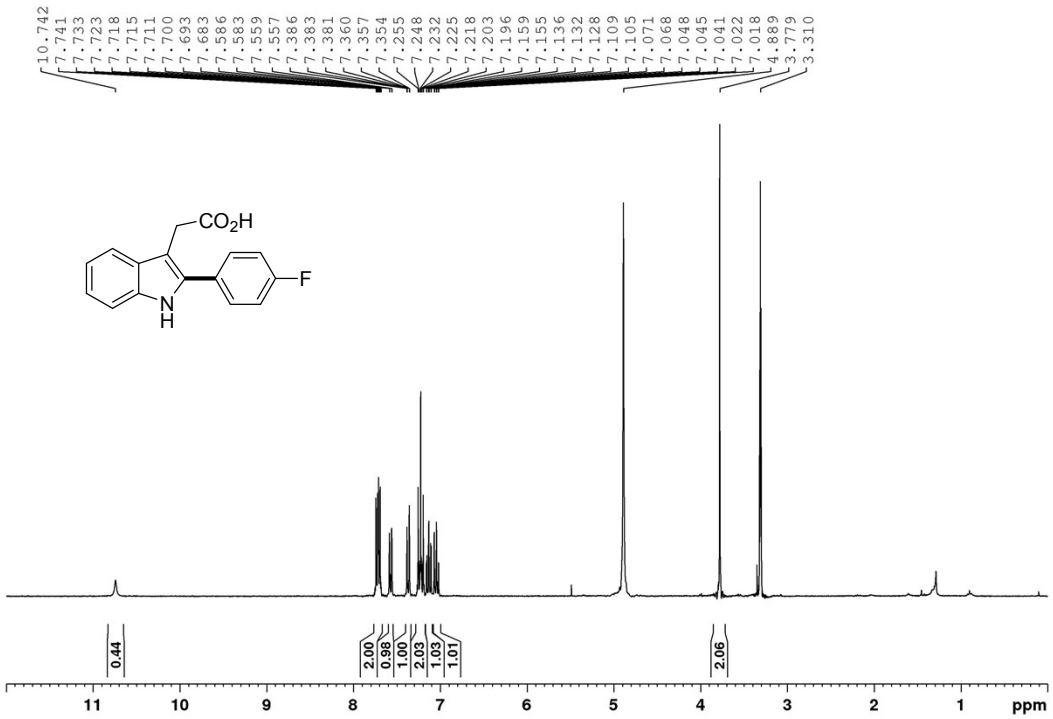
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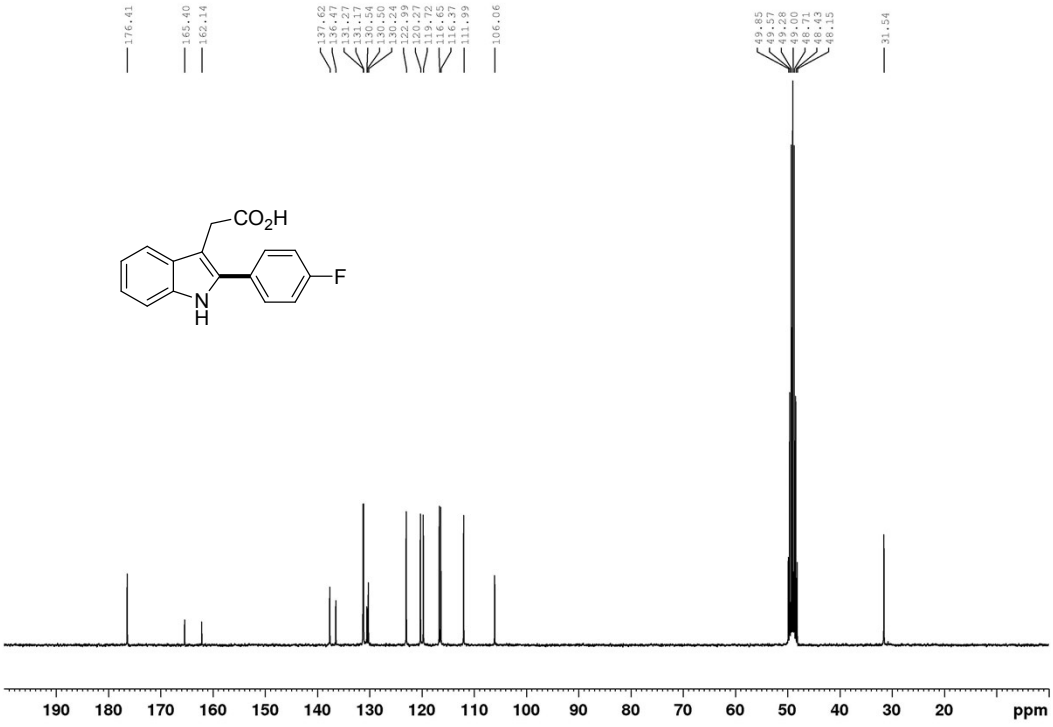
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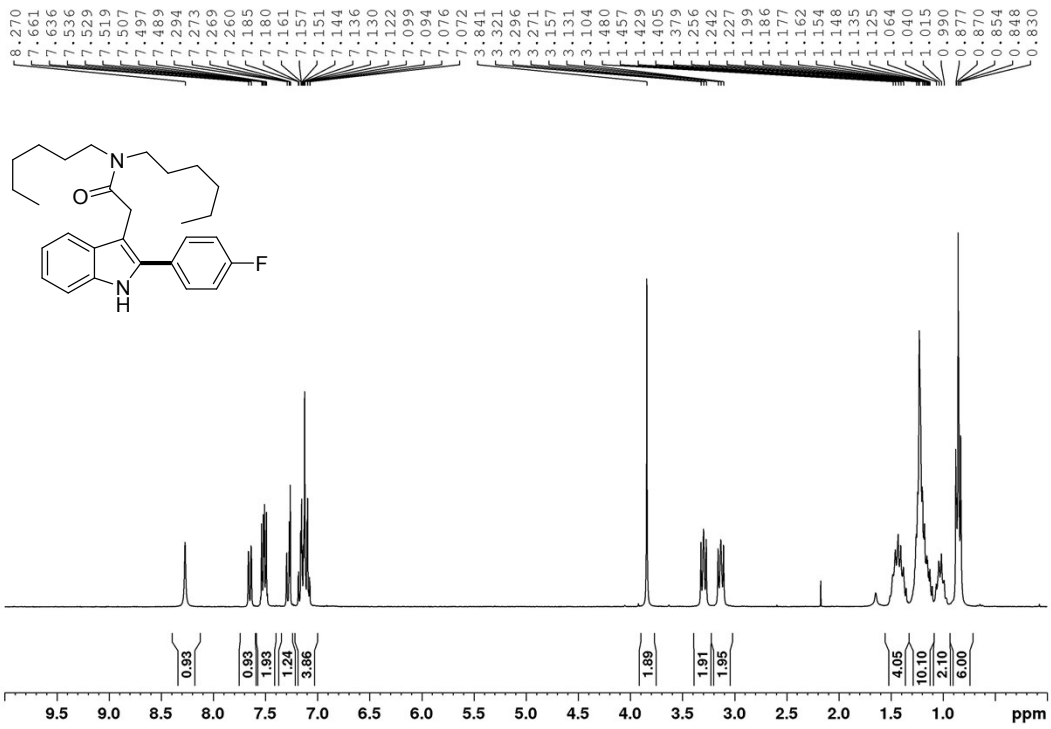
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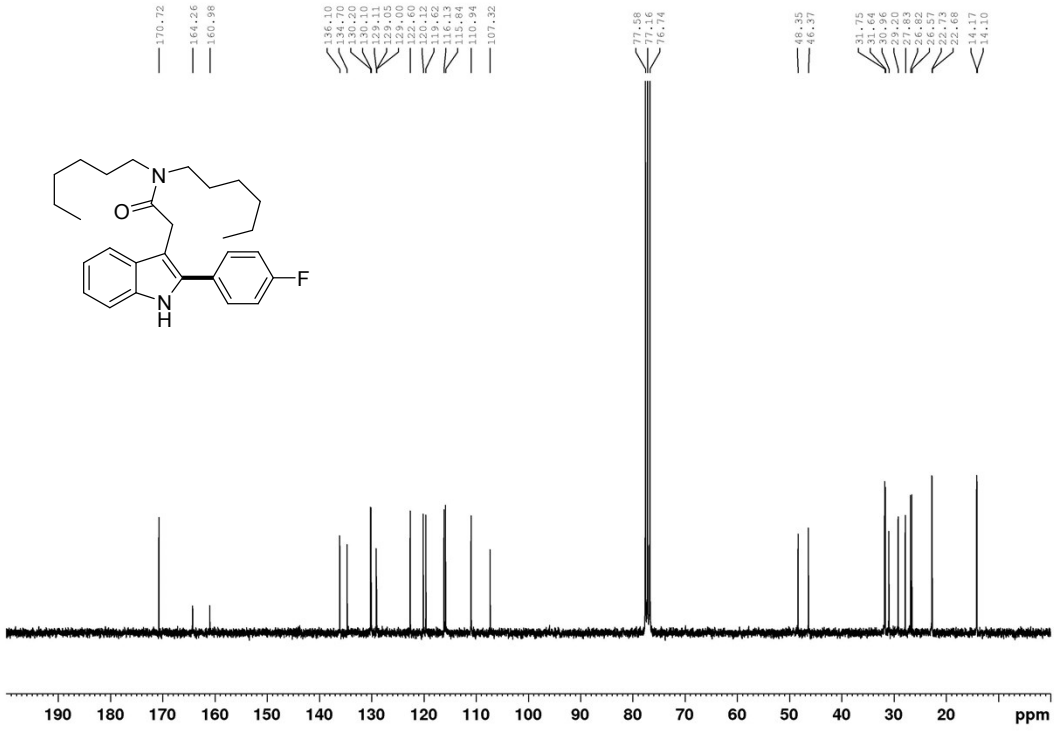
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160
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ppm

6. References

1. D. Cortés-Borda, K. V. Kutonova, C. Jamet, M. E. Trusova, F. Zammattio, C. Truchet, M. Rodriguez-Zubiri and F.-X. Felpin, *Org. Process Res. Dev.*, 2016, **20**, 1979-1987.
2. D. Cortés-Borda, E. Wimmer, B. Gouilleux, E. Barré, N. Oger, L. Goulamaly, L. Peault, B. Charrier, C. Truchet, P. Giraudeau, M. Rodriguez-Zubiri, E. Le Grognec and F.-X. Felpin, *J. Org. Chem.*, 2018, **83**, 14286-14299.