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Supporting Information

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Palladium-catalyzed oxidative cyclization of *N*-aryl enamines - from anilines to indoles

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CONTENTS:

1. General information

All reactions were carried out in flame dried reaction vessels with Teflon screw caps under argon. All new compounds were fully characterized, starting materials **1u** and **1w** are commercially available.

NMR-spectra were recorded on a Bruker ARX-300, AV-300, AV-400 MHz or on a Varian Associated, Varian 600 unity plus. Chemical shifts (δ) are quoted in ppm downfield of tetramethylsilane. Coupling constants (*J*) are quoted in Hz.

Infrared spectra were recorded on a Varian Associated FT-IR 3100 Excalibur. The wave numbers (ν) of recorded IR-signals are quoted in cm^{-1}. ESI mass spectra were recorded on a Bruker Daltonics MicroTof.

GC/MS Spectra were recorded on a Agilent Technologies 7890A GC-system with Agilent 5975C VL MSD or 5975 inert Mass Selective Detector (EI) and a HP-5MS column (0.25 mm x 30 m, Film: 0.25 µm). For control of the conversion and characterization of the products, 4 different methods were used (table 1.1). The methods used start with the injection temperature T_0, after holding this temperature for 3 min, the column is heated to the temperature T_1 (ramp) and hold for additional 3 min.

Table 1.1: GC/MS methods.

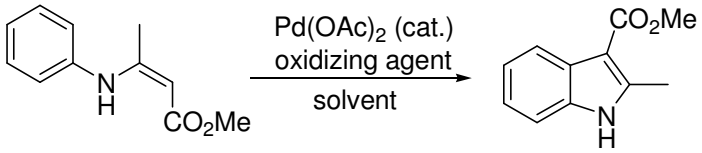
method	T_0[°C]	ramp/K·min^{-1}	T_1[°C]
A	**50**	**20**	**280**
B	**50**	**40**	**290**
C	**70**	**20**	**280**
D	**70**	**40**	**290**

2. Optimization study

Our investigation started with the search for the right oxidizing agent, in order to reoxidize the palladium(0) species formed at the end of one catalytic cycle. Early on, silver carbonate is found to be an efficient oxidizing agent, being mild enough not to decompose the substrate (table 2.1, entry 1). Other silver salts lead to greatly reduced yields. The commonly used oxidizing agents benzoquinone and potassium peroxodisulfate[1] failed to provide substantial amounts of product (table 2.1, entries 5, 6). Among the copper salts tested, anhydrous copper(II) acetate is found to be optimal. The role of the base is essential, since K_2CO_3 is needed for full conversion (when toluene is used as a solvent). The use of Cs_2CO_3 instead of

K_2CO_3 leads to a greatly reduced yield (table 2.1, entries 12-14). The effect of the base is remarkable, especially since C-H-activations of electron-rich aromatics often run in acidic media in order to increase the electrophilicity of the palladium catalyst.[2] The addition of AcOH, however, results in the rapid decomposition of the starting material (table 1 of manuscript, entry 16).

Table 2.1: Optimization of reaction conditions.



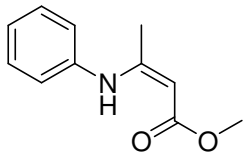
1a **2a**

entry	oxidizing agent	base	yield [%][a]
1	Ag_2CO_3	-	38[b]
2	$AgNO_3$	K_2CO_3	11
3	AgOTf	K_2CO_3	7
4	AgOTf	-	0
5	Benzoquinone	K_2CO_3	0
6	$K_2S_2O_8$	K_2CO_3	0
7	NMO	K_2CO_3	17
8	$CuCl_2 \cdot 2H_2O$	-	0
9	$CuBr_2$		0
10	$Cu(OAc)_2 \cdot H_2O$	-	18
11	$CuCO_3 \cdot Cu(OH)_2$	-	18
12	$Cu(OAc)_2$	-	25
13	$Cu(OAc)_2$	Cs_2CO_3[b]	7
14	$Cu(OAc)_2$	K_2CO_3[b]	32
15[c]	$Cu(OAc)_2$	K_2CO_3[b]	80 (72)[d]

Reaction conditions: **1a** (0.25 mmol), $Pd(OAc)_2$ (10 mol%), oxidizing agent (0.5 mmol), base (0.5 mmol), toluene (3mL), 110°C 12-16 h; a) GC yield determined using internal standard; b) 0.75 mmol base; c) **1a** (0.25 mmol), $Pd(OAc)_2$ (10 mol%), $Cu(OAc)_2$ (0.75 mmol), K_2CO_3 (0.75 mmol) in DMF, 80 °C, 12 h; d) isolated yield in brackets.

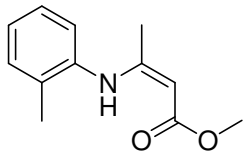
3. N-aryl enaminecarboxylate substrates

(Z)-Methyl-3-(phenylamino)but-2-enoate (1a)[3]



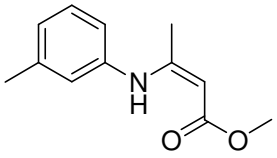
Following a modified procedure of C. A. Brandt,[3] a mixture of methyl acetoacetate (0.22 mL, 2 mmol, 1 eq), aniline (0.18 mL, 2 mmol, 1 eq) and acetic acid (0.01 mL, 0.2 mmol, 0.1 eq) is stirred at room temperature for 18 h. At the end of the reaction, EtOH (5 mL) is added, the solution is dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue is purified by flash chromatography (silica, pentane/EtOAc/NEt_3 97:2:1). The pure product is obtained as a yellow solid (313 mg, 1.64 mmol, 82%). **R_F** (pentane/EtOAc/NEt_3 95:4:1): 0.24; **^{1}H NMR ($CDCl_3$, 300 MHz):** 1.99 (d, *J* = 0.5 Hz, 3H), 3.68 (s, 3H, CH_3), 4.69 (d, *J* = 0.5 Hz, 1H, CH), 7.07-7.18 (m, 3H, CH_{ar}), 7.30-7.35 (m, 2H, CH_{ar}), 10.36 (br s, 1H, NH); **^{13}C NMR (CDCl3, 75 MHz):** 20.3 (CH_3), 50.2 (CH_3), 85.5 (CH), 124.5 (CH_{ar}), 124.9 (CH_{ar}), 129.0 (CH_{ar}), 139.2 (CH_{ar}), 159.1 (C_q), 170.7 (CO); **GC-MS R_t (method B):** 11.0 min, **(EI) m/z (%):** 192.1 (13), 191.1 (86), 176 (10), 160.1 (62), 159 (37), 144 (46), 132.1(60), 131.1 (45), 130.1 (72), 119.0 (13), 118.0 (100), 117.0 (20), 93.0 (10), 77.0 (63), 65.0 (14), 51.0 (18).

(Z)-Methyl-3-(*o*-tolylamino)but-2-enoate (1b)[4]



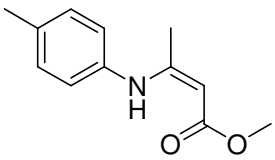
Following a modified procedure by G. Bartoli,[5] a mixture of methyl acetoacetate (7.43 mL, 69 mmol, 1.5 eq), *o*-toluidine (4.82 g, 45 mmol, 1.0 eq), $Zn(ClO_4)_2{\cdot}6H_2O$ (1.08 g, 2.9 mmol, 6.4 mol%) and $MgSO_4{\cdot}xH_2O$ (5.40 g, 45 mmol, 1.0 eq) in CH_2Cl_2 (40 mL) is stirred at room temperature for 10 h. The crude mixture is filtered, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue is purified by flash chromatography (silica, pentane/EtOAc/NEt_3 97:2:1). The pure product is obtained as a pale yellow solid (7.83 g, 38.3 mmol, 85%). **R_F** (pentane/EtOAc/NEt_3 89:10:1): 0.58; **^{1}H NMR ($CDCl_3$, 300 MHz):** 1.85 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 3.68 (s, 3H, CH_3), 4.71 (s, 1H, CH), 7.05-7.24 (m, 4H), 10.13 (s, 1H, NH); **^{13}C NMR ($CDCl_3$, 75 MHz):** 18.0 (CH_3), 20.0 (CH_3), 50.2 (CH_3), 84.7 (CH), 126.0 (CH_{ar}), 126.3 (CH_{ar}), 126.4 (CH_{ar}), 130.7 (CH_{ar}), 133.9 (CH_{ar}), 137.9 (CH_{ar}), 159.9 (C_q), 170.9 (CO); **GC-MS R_t (method B):** 10.29 min, **(EI) m/z (%):** 205.1 (56), 190.0 (14), 174.0 (29), 173.0 (16), 158.0 (14), 146.1 (18), 145.0 (15), 144.0 (32), 132.0 (100), 131.0 (19), 130.0 (36), 91.0 (23).

***(Z)*-Methyl-3-(*m*-tolylamino)but-2-enoate (1c)**



Following a modified procedure by G. Bartoli,[5] a mixture of methyl acetoacetate (7.43 mL, 69 mmol, 1.5 eq), *m*-toluidine (4.82 g, 45 mmol, 1.0 eq), $Zn(ClO_4)_2 \cdot 6H_2O$ (1.08 g, 2.9 mmol, 6.4 mol%) and $MgSO_4 \cdot xH_2O$ (5.40 g, 45 mmol, 1.0 eq) in CH_2Cl_2 (40 mL) is stirred at room temperature for 10 h. The crude mixture is filtered, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue is purified by flash chromatography (silica, pentane/EtOAc/NEt_3 97:2:1). The pure product is obtained as a red oil (6.56 g, 32.0 mmol, 71%). $\mathbf{R_F}$ (pentane/EtOAc/NEt_3 89:10:1): 0.57; **^{1}H NMR (300 MHz, $CDCl_3$):** 1.99 (d, J = 0.30 Hz, 3H, CH_3), 2.34 (s, 3H, CH_3), 3.68 (s, 3H, CH_3), 4.68 (d, J = 0.30 Hz, 1H, CH), 6.89-6.91 (m, 2H, CH_{ar}), 6.97 (d, J = 7.80 Hz, 1H, CH_{ar}), 7.21 (m, 1H, CH_{ar}), 10.32 (s, 1H, NH); **^{13}C NMR (75 MHz, $CDCl_3$):** 20.2 (CH_3), 21.2 (CH_3), 50.1 (CH_3), 85.2 (CH), 121.3 (CH_{ar}), 124.9 (CH_{ar}), 125.6 (CH_{ar}), 128.7 (CH_{ar}), 138.7 (C_{ar}), 139.0 (C_{ar}), 159.0 (C_q), 170.0 (CO); **GC-MS $\mathbf{R_t}$ (method B):** 11.6 min, **(EI) m/z (%):** 206.1 (14), 205.1 (100), 174.1 (54), 173.0 (30), 172.1 (11), 158.1 (33), 146.1 (65), 145.1 (53), 144.1 (70), 133.0 (11), 132.1 (78), 131.1 (19), 130.1 (26), 91.0 (42), 77.1 (11), 65.0 (18); **ESI-MS:** calculated $[C_{12}H_{15}NNaO_2]^+$: 228.0995 and $[C_{12}H_{16}NO_2]^+$: 206.1176, found: $[C_{12}H_{15}NNaO_2]^+$: 228.0994 and $[C_{12}H_{16}NO_2]^+$: 206.1176. **ATR-FTIR (cm-1):** 2948, 1654, 1584, 1491, 1437, 1383, 1358, 1270, 1246, 1153, 1090, 786, 697, 651.

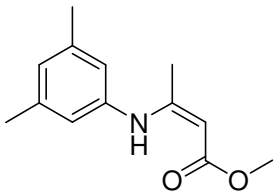
***(Z)*-Methyl-3-(*p*-tolylamino)but-2-enoate (1d)**[4]



Following a modified procedure by G. Bartoli,[5] a mixture of methyl acetoacetate (7.43 mL, 69 mmol, 1.5 eq), *p*-toluidine (4.82 g, 45 mmol, 1.0 eq), $Zn(ClO_4)_2 \cdot 6H_2O$ (0.54 g, 1.45 mmol, 3 mol%), molecular sieves (4 Å, 5 g) and $MgSO_4 \cdot xH_2O$ (5.40 g, 45 mmol, 1.0 eq) in CH_2Cl_2 is stirred at 40 °C for 10 h. The crude mixture is filtered, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue is purified by flash chromatography (silica, pentane/EtOAc/NEt_3 97:2:1). The pure product is obtained as a yellow solid (7.01 g, 34.2 mmol, 76%). $\mathbf{R_F}$ (pentane/EtOAc/NEt_3 89:10:1): 0.53; **^{1}H NMR ($CDCl_3$, 300 MHz):** 1.95 (d, J = 0.4 Hz, 3H, CH_3), 2.33 (s, 3H, CH_3), 3.68 (s, 3H, CH_3), 4.67 (d, J = 0.5 Hz, 1H, CH), 6.98 (d, J = 8.3 Hz, 2H, CH_{ar}), 7.12 (d, J = 8.1 Hz, 2H, CH_{ar}), 10.26 (s, 1H, NH); **^{13}C NMR ($CDCl_3$, 75 MHz):** 20.1 (CH_3), 20.8 (CH_3), 50.2 (CH_3), 84.8 (CH), 124.7 (CH_{ar}), 129.6 (CH_{ar}), 134.9 (CH_{ar}), 136.5 (CH_{ar}), 159.4 (C_q), 170.7 (CO); **GC-MS $\mathbf{R_t}$**

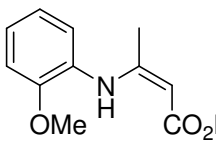
(method B): 11.7 min, **(EI) m/z (%):** 206.1 (12), 205.1 (100), 174.1 (53), 173.1 (67), 172.0 (13), 158.1 (46), 146.1 (28), 145.0 (28), 144.1 (60), 132.1 (76), 130.1 (27), 91.0 (34), 77.0 (13), 65.0 (14).

***(Z)*-Methyl-3-(3,5-dimethylphenylamino)but-2-enoate (1e)**



Following a modified procedure of C. A. Brandt,[3] a mixture of methyl acetoacetate (4.42 mL, 41 mmol, 1.0 eq), 3,5-dimethylaniline (5.12 mL, 41 mmol, 1.0 eq) and acetic acid (0.5 mL, 8.2 mmol, 0.2 eq) is stirred at room temperature for 18 h. At the end of the reaction, EtOH (40 mL) is added, the solution is dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue is purified by flash chromatography (silica, pentane/EtOAc/NEt_3 96:3:1). The pure product is obtained as yellow oil (4.4 g, 20.1 mmol, 49%). $\mathbf{R_F}$ (pentane/EtOAc/NEt_3 89:10:1): 0.61; **^{1}H NMR (300 MHz, $CDCl_3$):** 1.99 (s, 3H, CH_3), 2.29 (s, 6H, 2xCH_3), 3.68 (s, 3H, CH_3), 4.66 (s, 1H, CH), 6.71 (s, 2H, CH_{ar}), 6.80 (s, 1H, CH_{ar}), 10.28 (s, 1H, NH); **^{13}C NMR (75 MHz, $CDCl_3$):** 20.3 (CH_3), 21.2 (CH_3), 50.1 (CH_3), 85.0 (CH), 122.2 (CH_{ar}), 126.7 (CH_{ar}), 138.7 (CH_{ar}), 139.0 (C_{ar}), 159.3 (C_q), 170.6 (CO); **GC-MS $\mathbf{R_t}$ (method A):** 12.2 min, **(EI) m/z (%):** 219.1 (90), 206.8 (16), 188.1 (53), 187.0 (43), 186.1 (30), 172.2 (36), 160.1 (100), 159.0 (78), 158.1 (53), 146.0 (90), 145.0 (38), 144 (75),105.0 (36), 91.0 (16), 77.0 (30); **ESI-MS:** calculated $[C_{12}H_{15}NNaO_2]$+: 242.1151, found: $[C_{12}H_{15}NNaO_2]$+: 242.1144. **ATR-FTIR (cm-1):** 2949, 2919, 1652, 1589, 1495, 1433, 1383, 1358, 1270, 1247, 1184, 1154, 1056, 1001, 929, 849, 787, 671, 609.

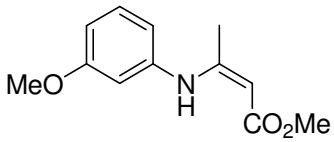
***(Z)*-Methyl 3-(2-methoxyphenylamino)but-2-enoate (1f)**



Following a modified procedure by G. Bartoli,[5] *o*-anisidine (4.23 mL, 37.5 mmol, 1.5 eq), methyl acetoacetate (2.70 mL, 25 mmol, 1 eq), $Zn(ClO_4)_2{\cdot}6H_2O$ (465 mg, 1.25 mmol, 5 mol %), $MgSO_4{\cdot}xH_2O$ (903 mg, 7.5 mmol, 30 mol%) are stirred in CH_2Cl_2 (10 mL) at rt for 16 h. After addition of molecular sieves (4 Å, 5 g) the mixture is stirred for additional 1.5 h at 60 °C. The mixture is cooled to rt, filtered and the solvents are evaporated. After rapid flash chromatography (silica, pentane/EtOAc/NEt_3 10:1:0.1), the product is obtained as a nearly colorless oil (1.88 g, 34%). $\mathbf{R_F}$ (Pentane/EtOAc 5:1): 0.38; **^{1}H NMR (400 MHz, $CDCl_3$):** 2.01 (s, 3 H, CH_3), 3.69 (s, 3H, CH_3), 3.87 (s, 3H, CH_3), 4.72 (s, 1H, CH), 6.88-6.92 (m, 2H, CH_{ar}), 7.09-7.14 (m, 2 H, CH_{ar}), 10.26 (s, 1 H, NH); **^{13}C NMR (100 MHz, $CDCl_3$):** 20.4 (CH_3), 50.2 (CH_3), 55.7 (CH_3), 85.9 (CH); 111.1 (CH_{ar}), 120.3 (CH_{ar}), 124.5 (CH_{ar}), 125.5 (CH_{ar}), 128.8 (C_{ar}), 152.7 (C_{ar}), 159.1

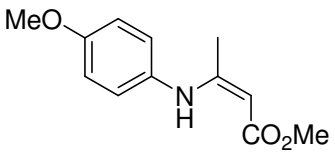
(C_q), 170.6 (CO); **GC/MS: R_t (method B):** 12.3 min, **(EI) m/z (%):** 221 (100), 189 (56), 175 (47), 160 (43), 148 (95), 77 (34); **ESI-MS:** calculated $[C_{12}H_{15}NNaO_3]^+$: 244.0944, found: 244.0951; **ATR-FTIR [cm^{-1}]:** 2948, 1657, 1615, 1507, 1478, 1271, 1160, 1027, 788, 749.

***(Z)*-Methyl 3-(phenylamino)but-2-enoate (1g)**



Following a modified procedure by G. Bartoli,[5] *m*-anisidine (4.5 mL, 37.5 mmol, 1.5 eq), methyl acetoacetate (2.7 mL, 25 mmol, 1.0 eq), $Zn(ClO_4)_2{\cdot}6H_2O$ (465 mg, 1.25 mmol, 5 mol %), $MgSO_4{\cdot}xH_2O$ (903 mg, 7.5 mmol, 30 mol%) are stirred in CH_2Cl_2 (10 mL) at rt for 13.5 h. After addition of molecular sieves (4 Å, 5 g) the mixture is stirred for additional 5 h at 60 °C. The mixture is cooled to rt, filtered and the solvents are evaporated. After rapid flash chromatography (silica, pentane/EtOAc/NEt_3 10:1:0.1), the product is obtained as a nearly colorless oil (4.78 g, 86%). **R_F** (Pentane/EtOAc 10:1): 0.29; **^{1}H NMR (400 MHz, $CDCl_3$):** 2.02 (s, 3 H, CH_3), 3.68 (s, 3H, CH_3), 3.79 (s, 3H, CH_3), 4.69 (s, 1H, CH), 6.62 (t, *J* = 2.18 Hz, 1H, CH_{ar}), 6.67-6.72 (m, 2H, CH_{ar}), 7.22 (t, *J* = 8.1 Hz, 2H, CH_{ar}), 10.35 (s, 1 H, NH); **^{13}C NMR (100 MHz, $CDCl_3$):** 20.4 (CH_3), 50.25 (CH_3), 55.3 (CH_3), 85.8 (CH), 110.1 (CH_{ar}), 110.5 (CH_{ar}), 116.6 (CH_{ar}), 129.7 (CH_{ar}), 140.5 (C_{ar}), 159.0 (C_{ar}), 160.2 (C_q), 170.7 (CO); **GC/MS: R_t (method A):** 12.5 min, **(EI) m/z (%):** 221 (27), 162 (28), 148 (46) 44 (100); **ESI-MS:** calculated $[C_{12}H_{15}NNaO_3]^+$: 244.0944, found: 244.0954; **ATR-FTIR [cm^{-1}]:** 3001, 2949, 1655, 1587, 1277, 1252, 1154.

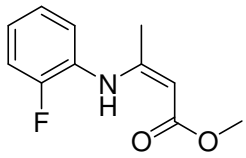
***(Z)*-Methyl 3-(4-methoxyphenylamino)but-2-enoate (1h)**[4]



Following a modified procedure by G. Bartoli,[5] *p*-anisidine (3.33 g, 27.0 mmol, 1.5 eq), methyl acetoacetate (1.94 mL, 18 mmol, 1.0 eq), $Zn(ClO_4)_2{\cdot}6H_2O$ (465 mg, 1.25 mmol, 7 mol%), $MgSO_4{\cdot}xH_2O$ (903 mg, 7.5 mmol, 42 mol%) and molecular sieves (4 Å, 5 g) are stirred in CH_2Cl_2 (10 mL) at rt for 23 h. The mixture is filtered and the solvents are evaporated. After rapid flash chromatography (silica, pentane/EtOAc/NEt_3 10:1:0.1), the product is obtained as a yellow solid (3.64 g, 92%). **R_F** (pentane/EtOAc 10:1): 0.38; **^{1}H NMR (400 MHz, $CDCl_3$):** 1.88 (s, 3H, CH_3), 3.67 (s, 3H, CH_3), 3.79 (s, 3H, CH_3), 4.65 (s, 1H, CH), 6.84 (d, *J* = 8.9 Hz, 2 H, CH_{ar}), 7.01 (d, *J* = 8.8 Hz, 2H, CH_{ar}), 10.13 (s, 1H, NH); **^{13}C NMR (100 MHz, $CDCl_3$):** 20.0 (CH_3), 50.1 (CH_3), 55.4 (CH_3), 84.3 (CH), 114.1 (CH_{ar}), 126.8 (CH_{ar}), 132.0 (C_{ar}), 157.5 (C_{ar}), 160.1 (C_q), 170.7 (CO); **ESI-MS:** calculated $[C_{12}H_{15}NNaO_3]^+$: 244.0944, found: 244.0924; **EI-MS:** m/z (%) = 221 (M^+, 95), 189 (100),

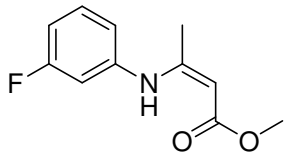
174 (74), 148 (82); **ATR-FTIR [cm^{-1}]:** 3263, 3001, 1647, 1595, 1510, 1240, 1155, 1031, 786.

(*Z*)-Methyl-3-(2-fluorophenylamino)but-2-enoate (1i)



Following a modified procedure of G. Bartoli,[5] methyl acetoacetate (2.6 mL, 24 mmol, 1.2 eq), 2-fluoroaniline (2.22 g, 20 mmol, 1.0 eq), $Zn(ClO_4)_2 \cdot 6H_2O$ (2.40 g, 6.4 mmol, 32 mol%) and $MgSO_4 \cdot xH_2O$ (2.41 g, 20 mmol, 1.0 eq) in CH_2Cl_2 (20 ml) is stirred at room temperature for 10 h. The crude mixture is filtered, dried over Na_2SO_4, filtered and concentrated in vacuum. The residue is purified by flash chromatography (silica, pentane/EtOAc/NEt_3 95:4:1) and the pure product is obtained as a white solid (1.714 g, 8.2 mmol, 41 %). $\mathbf{R_F}$ (pentane/EtOAc/NEt_3 79:20:1): 0.72; **^{1}H NMR (300 MHz, $CDCl_3$):** 1.95 (s, 3H, CH_3), 3.68 (s, 3H, CH_3), 4.77 (s, 1H, CH), 7.07-7.18 (m, 4H, CH_{ar}), 10.18 (s, 1H, NH); **^{13}C NMR (75 MHz, $CDCl_3$):** 19.87 (CH_3), 50.3 (CH_3), 86.6 (CH), 116.0 (d, $J_{(C,F)}$ = 20.3 Hz, C_{ar}), 124.1 (d, $J_{(C,F)}$ = 4.0 Hz, C_{ar}), 126.4 (d, $J_{(C,F)}$ = 7.6 Hz, C_{ar}), 126.5 (C_{ar}), 127.3 (d, $J_{(C,F)}$ = 12.1 Hz, C_{ar}), 156.5 (d, $J_{(C,F)}$ = 246.9 Hz, C_{ar}), 158.9 (C_q), 170.6 (CO); **ESI-MS:** calculated $[C_{11}H_{12}FNNaO_2]^+$: 232.0744, found: 232.0743. **ATR-FTIR [cm^{-1}]:** 3272, 3000, 2950, 1650, 1596, 1476, 1430, 1349, 1241, 1191, 1185, 1101, 1057, 1004, 960, 913, 832, 768, 658, 615.

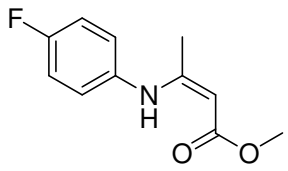
***(Z)*-Methyl-3-(3-fluorophenylamino)but-2-enoate (1j)**



Following a modified procedure of Y. Wang,[4] methyl acetoacetate (2.6 mL, 24 mmol, 1.2 eq), 3-fluoroaniline (2.22 g, 20 mmol, 1 eq), $InBr_3$ (354 mg, 1.0 mmol, 5 mol%) and $MgSO_4 \cdot xH_2O$ (2.41 g, 20 mmol, 1 eq) in CH_2Cl_2 (20 ml) is stirred at room temperature for 10 h. The crude mixture is filtered, dried over Na_2SO_4, filtered and concentrated in vacuum. The residue is purified by flash chromatography (silica, pentane/EtOAc/NEt_3 95:3:1) and the pure product is obtained as a colorless oil (3.81 g, 18.4 mmol, 92 %). $\mathbf{R_F}$ (pentane/EtOAc/NEt_3 89:10:1): 0.60; **^{1}H-NMR (300 MHz, $CDCl_3$):** 2.07 (d, J = 0.6Hz, 3H, CH_3), 3.72 (s, 3H, CH_3), 4.77 (d, J = 0.6 Hz, 1H, CH), 6.81-6.90 (m, 3H, CH_{ar}), 7.28-7.34 (m, 1H, CH_{ar}), 10.46 (s, 1H, NH); **^{13}C-NMR (75 MHz, $CDCl_3$):** 20.4 (CH_3), 50.4 (CH_3), 86.9 (CH), 110.9 (d, $J_{(C,F)}$ = 23.5 Hz, CH_{ar}), 111.4 (d, $J_{(C,F)}$ = 21.4 Hz, CH_{ar}), 119.4 (d, $J_{(C,F)}$ = 2.9 Hz, CH_{ar}), 130.2 (d, $J_{(C,F)}$ = 9.5 Hz, CH_{ar}), 140.9 (s, C_{ar}), 158.2 (C_q), 162.9 (d, $J_{(C,F)}$ = 246.4 Hz, C_{ar}), 170.7 (CO); **ESI-MS:** calculated $[C_{11}H_{12}FNNaO_2]^+$: 232.0744, found: 232.0749. **ATR-FTIR [cm^{-1}]:**

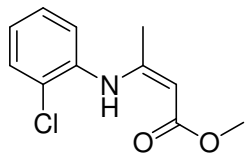
2949, 1656, 1584, 1491, 1440, 1384, 1360, 1240, 1178, 1140, 1057, 1013, 931, 861, 788, 690, 653.

***(Z)*-Methyl-3-(4-fluorophenylamino)but-2-enoate (1k)**



Following a modified procedure of Y. Wang,[4] methyl acetoacetate (2.6 mL, 24 mmol, 1.2 eq), 4-fluoroaniline (2.22 g, 20 mmol, 1.0 eq), $InBr_3$ (354 mg, 1.0 mmol, 5 mol%) and $MgSO_4 \cdot xH_2O$ (2.41 g, 20 mmol, 1 eq) in CH_2Cl_2 (20 ml) is stirred at room temperature for 10 h. The crude mixture is filtered, dried over Na_2SO_4, filtered and concentrated in vacuum. The residue is purified by flash chromatography (silica, pentane/EtOAc/NEt_3 95:3:1) and the pure product is obtained as a white solid (3.23 g, 15.6 mmol, 78 %). **R_F** (pentane/EtOAc/NEt_3 89:10:1): 0.68; **^{1}H-NMR (300 MHz, $CDCl_3$):** 1.91 (s, 3H, CH_3), 3.68 (s, 3H, CH_3), 4.69 (s, 1H, CH), 7.02-7.05 (m, 4H, CH_{ar}), 10.21 (s, 1H, NH); **^{13}C-NMR (75 MHz, $CDCl_3$):** 20.1 (s, CH_3), 50.3 (s, CH_3), 85.4 (s, CH), 115.8 (d, $J_{(C,F)}$ = 22.6 Hz, CH_{ar}), 126.8 (d, $J_{(C,F)}$ = 8.3 Hz, CH_{ar}), 135.2 (s, C_{ar}), 160.4 (d, $J_{(C,F)}$ = 244.9 Hz, C_{ar}), 159.3 (s, C_q), 170.8 (s, CO); **GC-MS R_t (method B):** 12.5 min, **(EI) m/z (%):** 207.1 (77), 206.9 (100); **ESI-MS:** calculated $[C_{11}H_{12}FNNaO_2]^+$: 232.0744, found: 232.0740. **ATR-FTIR [cm^{-1}]:** 3281, 3077, 3010, 2958, 1646, 1606, 1591, 1510, 1483, 1433, 1385, 1351, 1261, 1231, 1209, 1164, 1095, 1060, 1008, 946, 855, 824, 782, 666.

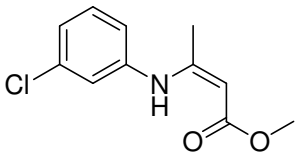
***(Z)*-Methyl-3-(2-chlorophenylamino)but-2-enoate (1l)**



Following a modified procedure of Y. Wang,[4] a mixture of methyl acetoacetate (2.6 mL, 24 mmol, 1.2 eq), 2-chloroaniline (2.55 g, 20 mmol, 1.0 eq), $InBr_3$ (351 mg, 1.0 mmol, 5 mol%) and $MgSO_4 \cdot xH_2O$ (2.41 g, 20 mmol, 1 eq) in CH_2Cl_2 (10 mL) is stirred at room temperature for 10 h. The crude mixture is filtered, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue is purified by flash chromatography (silica, pentane/EtOAc/NEt_3 95:4:1). The pure product is obtained as a white solid (3.74 g, 16.6 mmol, 83%). **R_F** (pentane/EtOAc/NEt_3 89:10:1): 0.68; **^{1}H NMR (300 MHz, $CDCl_3$):** 1.97 (d, J = 0.6 Hz, 3H, CH_3), 3.71 (s, 3H, CH_3), 4.79 (s, 1H, CH), 7.08-7.14 (m, 1H, CH_{ar}), 7.18-7.24 (m, 2H, CH_{ar}), 7.43 (dd, J = 7.9 Hz, J = 1.3 Hz, 1H, CH_{ar}), 10.36 (s, 1H, NH); **^{13}C NMR (75 MHz, $CDCl_3$):** 20.2 (CH_3), 50.4 (CH_3), 87.3 (CH), 125.9 (CH_{ar}), 126.0 (CH_{ar}), 127.1 (CH_{ar}), 129.2 (C_{ar}), 130.0 (CH_{ar}), 136.6 (C_{ar}), 158.2 (C_q), 170.5 (CO); **ESI-MS:** calculated $[C_{11}H_{12}ClNNaO_2]^+$: 248.0449, found:

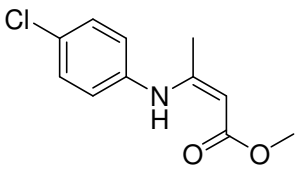
248.0440. **ATR-FTIR [cm^{-1}]:** 3474, 3373, 2948, 1656, 1611, 1487, 1464, 1443, 1385, 1360, 1269, 1224, 1164, 1056, 1056, 1005, 918, 790, 741, 678, 639.

***(Z)*-Methyl-3-(2-chlorophenylamino)but-2-enoate (1m)**



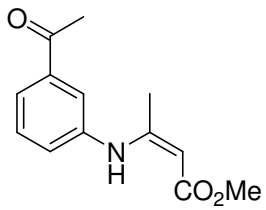
Following a modified procedure of Y. Wang,[4] a mixture of methyl acetoacetate (2.6 mL, 24 mmol, 1.2 eq), 3-chloroaniline (2.55 g, 20 mmol, 1 eq), $InBr_3$ (351 mg, 1.0 mmol, 5 mol%) and $MgSO_4 \cdot xH_2O$ (2.41 g, 20 mmol, 1 eq) in CH_2Cl_2 (10 mL) is stirred at room temperature for 10 h. The crude mixture is filtered, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue is purified by flash chromatography (silica, pentane/EtOAc/NEt_3 95:4:1). The pure product is obtained as a white solid (3.60 g, 16.0 mmol, 80%). $\mathbf{R_F}$ (pentane/EtOAc/NEt_3 89:10:1): 0.63; **^{1}H NMR (300 MHz, $CDCl_3$):** 2.07 (s, 3H, CH_3), 3.73 (s, 3H, CH_3), 4.79 (s, 1H, CH), 7.01 (d, *J* = 8.7 Hz, 1H, CH_{ar}), 7.14-7.17 (m, 2H, CH_{ar}), 7.28-7.32 (d, *J* = 8.10 Hz, 1H, CH_{ar}), 10.47 (s, 1H, NH); **^{13}C NMR (75 MHz, $CDCl_3$):** 20.2 (CH_3), 50.2 (CH_3), 86.9 (CH), 121.9, 123.8 (CH_{ar}), 124.6 (CH_{ar}), 129.9 (CH_{ar}), 134.4 (C_{ar}), 140.5 (C_{ar}), 157.9 (C_q), 170.4 (CO); **ESI-MS:** calculated $[C_{11}H_{12}ClNNaO_2]$+: 248.0449, found: 248.0457. **ATR-FTIR [cm^{-1}]:** 3274, 1645, 1608, 1575, 1474, 1433, 1347, 1255, 1219, 1161, 1060, 1008, 959, 971, 882, 786, 737, 713, 681, 644.

***(Z)*-Methyl-3-(2-chlorophenylamino)but-2-enoate (1n)**[4]



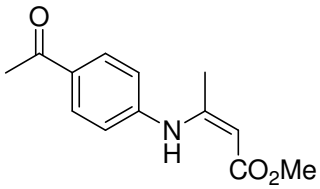
Following a modified procedure of Y. Wang,[4] a mixture of methyl acetoacetate (2.6 mL, 24 mmol, 1.2 eq), 4-chloroaniline (2.55 g, 20 mmol, 1.0 eq), $InBr_3$ (351 mg, 1.0 mmol, 5 mol%) and $MgSO_4 \cdot xH_2O$ (2.41 g, 20 mmol) in CH_2Cl_2 (10 mL) is stirred at room temperature for 10 h. The crude mixture is filtered, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue is purified by flash chromatography (silica, pentane/EtOAc/NEt_3 95:3:1). The pure product is obtained as a yellow solid (3.42, 15.2 mmol, 76%). **^{1}H NMR (300 MHz, $CDCl_3$):** 1.97 (d, *J* = 0.5 Hz, 3 H, CH_3), 3.67 (s, 3H, CH_3), 4.71 (d, *J* = 0.5 Hz, 1H, CH), 6.98-7.03 (m, 2H, CH_{ar}), 7.25-7.30 (m, 2H, CH_{ar}), 10.32 (s, 1H, NH); **^{13}C NMR (75 MHz, $CDCl_3$):** 20.2 (CH_3), 50.3 (CH_3), 86.3 (CH), 125.6 (CH_{ar}), 129.1 (CH_{ar}), 130.4 (C_{ar}), 137.9 (C_{ar}), 158.5 (C_q), 170.7 (CO).

***(Z)*-Methyl 3-(3-acetylphenylamino)but-2-enoate (1o)**



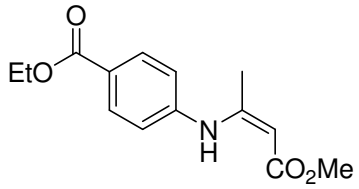
Following a modified procedure by G. Bartoli,[5] 3-aminoacetophenone (5.41 g, 40 mmol, 1.0 eq), methyl acetoacetate (4.31 mL, 40 mmol, 1 eq), $Zn(ClO_4)_2 \cdot 6H_2O$ (745 mg, 2 mmol, 5 mol %), $MgSO_4 \cdot xH_2O$ (2.4 g, 20 mmol, 0.5 eq) are stirred in CH_2Cl_2 (10 mL) at 60 °C for 17 h. The mixture is cooled to rt, filtered and the solvents are evaporated. After rapid flash chromatography (silica, pentane/EtOAc/NEt_3 5:1:0.5), the product is obtained as a yellow solid (6.86 g, 74%). **R_F** (pentane/EtOAc/NEt_3 5:1:0.1): 0.62; **^{1}H NMR (400 MHz, $CDCl_3$):** 1.87 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 3.53 (s, 3H, CH_3), 4.59 (s, 1H, CH), 7.10-7.12 (m, 1H, CH_{ar}), 7.26 (t, *J* = 7.8 Hz, 1H, CH_{ar}), 7.51 (t, *J* = 1.8 Hz, CH_{ar}), 7.56 (dt, *J* = 7.8 Hz, *J* = 1.2 Hz, 1H, CH_{ar}), 10.31 (s, 1H, NH); **^{13}C NMR (100 MHz, $CDCl_3$):** 20.2 (CH_3), 26.6 (CH_3), 50.3 (CH_3), 86.8 (CH), 123.4 (CH_{ar}), 124.6 (CH_{ar}), 128.4 (CH_{ar}), 129.3 (CH_{ar}), 138.0 (C_{ar}), 139.8 (C_{ar}), 158.2 (C_q), 170.6 (CO), 197.3 (CO); **ESI-MS:** calculated $[C_{13}H_{15}NNaO_3]^+$: 256.0944, found: 256.0984; **ATR-FTIR [cm^{-1}]:** 3126, 2956, 1682, 1629, 1585, 1512, 1465, 1272, 1212, 1157, 780, 729, 679.

***(Z)*-Methyl 3-(4-acetylphenylamino)but-2-enoate (1p)**



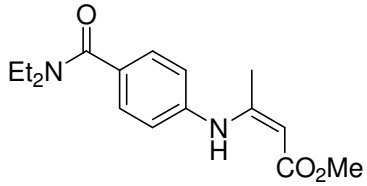
Following a modified procedure by G. Bartoli,[5] 4-aminoacetophenone (5.41 g, 40 mmol, 1.0 eq), methyl acetoacetate (4.31 mL, 40 mmol, 1 eq), $Zn(ClO_4)_2 \cdot 6H_2O$ (745 mg, 2 mmol, 5 mol %), $MgSO_4 \cdot xH_2O$ (2.4 g, 20 mmol, 0.5 eq) are stirred in CH_2Cl_2 (10 mL) at 60 °C for 17 h. The mixture is cooled to rt, filtered and the solvents are evaporated. After rapid flash chromatography (silica, pentane/EtOAc/NEt_3 5:1:0.5), the product is obtained as a yellow solid (3.04 g, 30%). **R_F** (pentane/EtOAc/NEt_3 5:1:0.1): 0.54; **^{1}H NMR (400 MHz, $CDCl_3$):** 2.14 (d, *J* = 0.5 Hz, 3H, CH_3), 2.55 (s, 3H, CH_3), 3.68 (s, 3H, CH_3), 4.79 (d, *J* = 0.6 Hz, 1H, CH), 7.09 (d, *J* = 8.4 Hz, 2H, CH_{ar}), 7.90 (d, *J* = 8.4 Hz, 2H, CH_{ar}), 10.67 (s, 1H, NH); **^{13}C NMR (100 MHz, $CDCl_3$):** 20.8 (CH_3), 26.3 (CH_3), 50.5 (CH_3), 88.9 (CH), 121.5 (CH_{ar}), 129.7 (CH_{ar}), 132.4 (C_{ar}), 144.0 (C_{ar}), 157.0 (C_q), 170.5 (CO), 196.6 (CO); **ESI-MS:** calculated $[C_{13}H_{15}NNaO_3]^+$: 256.0944, found: 256.0954; **ATR-FTIR [cm^{-1}]:** 3180, 3118, 2950, 1640, 1594, 1351, 1264, 1163, 785.

***(Z)*-Ethyl 4-(4-methoxy-4-oxobut-2-en-2-ylamino) benzoate (1q)**



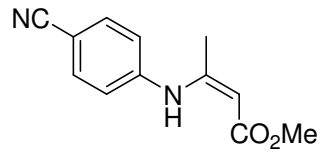
Following a modified procedure by G. Bartoli,[5] ethyl-4-aminobenzoate (6.61 g, 40 mmol, 1.0 eq), methyl acetoacetate (4.31 mL, 40 mmol, 1.0 eq), $Zn(ClO_4)_2 \cdot 6H_2O$ (745 mg, 2 mmol, 5 mol%), $MgSO_4 \cdot xH_2O$ (2.4 g, 20 mmol, 0.5 eq) are stirred in CH_2Cl_2 (10 mL) at 60 °C for 14 h. The mixture is cooled to rt, filtered and the solvents are evaporated. After rapid flash chromatography (silica, pentane/EtOAc/NEt_3 5:1:0.5), the product is obtained as a yellow solid (5.20 g, 49%). **R_F** (pentane/EtOAc/NEt_3 10:3:0.1): 0.53; **^{1}H NMR (400 MHz, $CDCl_3$):** 1.38 (t, *J* = 7.1 Hz, 3H, CH_3), 2.12 (s, 3H, CH_3), 3.69 (s, 3H, CH_3), 4.35 (q, *J* = 7.1 Hz, 2H, CH_2), 4.78 (s, 1H, CH), 7.08 (d, *J* = 8.7 Hz, 1H, CH_{ar}), 7.98 (d, *J* = 8.7 Hz, CH_{ar}), 10.63 (s, 1H, NH); **^{13}C NMR (100 MHz, $CDCl_3$):** 14.3 (CH_3), 20.7 (CH_2), 50.4 (CH_3), 60.8 (CH_3), 88.4 (CH), 121.8 (CH_{ar}), 125.6 (C_{ar}), 130.8 (CH_{ar}), 143.7 (C_{ar}), 157.3 (C_q), 166.0 (CO), 170.5 (CO); **ESI-MS:** calculated $[C_{14}H_{17}NNaO_4]^+$: 286.1050, found: 286.1042; **ATR-FTIR [cm^{-1}]:** 3001, 1707, 1637, 1601, 1362, 1263, 1162, 1104, 918, 763.

***(Z)*-Methyl 3-(4-(diethylcarbamoyl)phenylamino)but-2-enoate (1r)**



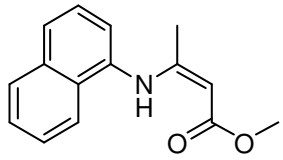
Following a modified procedure of Y. Wang,[4] a mixture of methyl acetoacetate (0.54 mL, 5 mmol, 1.0 eq), 4-amino-*N*,*N*-diethylbenzamide (961 mg, 5 mmol, 1.0 eq) and $InBr_3$ (18 mg, 0.05 mmol, 1 mol%) in CH_2Cl_2 (5 mL) is stirred at 80 °C for 24 h. After completion of the reaction, the solvent is removed under reduced pressure. Purification by flash chromatography (silica, pentane/EtOAc/NEt_3 4/1/0.05) afforded the product as an off-white solid (1.16 g, 3.99 mmol, 80%). **R_F** (pentane/EtOAc/NEt_3 1:1:0.02): 0.30; **^{1}H NMR (400 MHz, $CDCl_3$):** 1.15 (br s, 6H, 2xCH_3), 2.01 (s, 3H, CH_3), 3.27 (br s, 2H, CH_2), 3.49 (br s, 2H, CH_2) 3.65 (s, 3H, CH_3), 4.70 (s, 1H, CH), 7.04-7.07 (m, 2H, CH_{ar}), 7.321-7.33 (m, 2H, CH_{ar}), 10.43 (s, 1H, NH); **^{13}C NMR (100 MHz, $CDCl_3$):** 13.0 (CH_3), 14.3 (CH_3), 20.5 (CH_3), 39.4 (CH_2), 43.5 (CH_2), 50.4 (CH_3), 86.9 (CH), 123.5 (CH_{ar}), 127.6 (CH_{ar}), 133.4 (C_{ar}), 140.3 (C_{ar}), 158.4 (C), 170.6 (CO), 170.8 (CO); **GC-MS, R_t (method A):** 14.8 min, **(EI) m/z (%):** 289.1 (41), 218.0 (100), 186 (15), 130 (12); **ESI-MS:** calculated $[C_{16}H_{22}N_2NaO_3]^+$: 313.1523, found: 313.1508; **ATR-FTIR [cm^{-1}]:** 3193, 2974, 2946, 1655, 1598, 1568, 1522, 1472, 1433, 1388, 1365, 1271, 1230, 1161, 1099, 1061, 1012, 942, 917, 866, 848, 796, 760, 718, 648, 612.

***(Z)*-Methyl 3-(4-cyanophenylamino)but-2-enoate (1s)**[6]



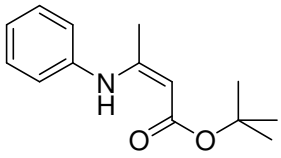
Following a modified procedure of Y. Wang,[4] a mixture of methyl acetoacetate (0.54 mL, 5 mmol, 1.0 eq), 4-aminobenzonitrile (591 mg, 5 mmol, 1.0 eq) and $InCl_3$ (11 mg, 0.05 mmol, 1 mol%) is stirred at 50 °C for 3 h. After purification by flash chromatography (silica, pentane/EtOAc/NEt_3 7:3:0.1) the product is obtained as white needles (615 mg, 2.84 mmol, 28%). **R_F** (pentane/EtOAc/NEt_3 5:1:0.06): 0.15; **^{1}H NMR (400 MHz, $CDCl_3$):** 2.16 (s, 3H, CH_3), 3.70 (s, 3H, CH_3), 4.84 (d, *J* = 0.7 Hz, 1H, CH,), 7.09-7.12 (m, 2H, CH_{ar}), 7.57-7.60 (m, 2H, CH_{ar}), 10.72 (s, 1H, NH); **^{13}C NMR (100 MHz, $CDCl_3$):** 21.0 (CH_3), 50.8 (CH_3), 90.13 (CH), 106.6 (C_{ar}), 119.0 (CN), 122.0 (CH_{ar}), 133.5 (CH_{ar}), 143.5 (C_{ar}), 156.5 (C), 170.6 (CO); **GC-MS, R_t (method B):** 8.8 min, **(EI) m/z (%):** 216.1 (41), 185.1 (25), 168.9 (19), 143.0 (100), 101.9 (35); **ESI-MS:** calculated $[C_{12}H_{12}N_2NaO_2]^+$: 239.0791, found: 239.0788; **ATR-FTIR [cm^{-1}]:** 3280, 3130, 3009, 2954, 2219, 1641, 1602, 1569, 1520, 1434, 1386, 1280, 1234, 1169, 1057, 958, 919, 825, 784, 720, 649, 597, 542, 477, 439.

***(Z)*-Methyl-3-(1-naphthylamino)but-2-enoate (1t)**



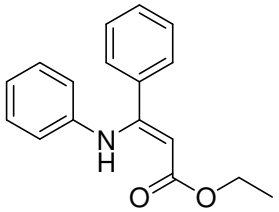
Following a modified procedure of Y. Wang,[4] a mixture of methyl acetoacetate (2.6 mL, 24 mmol, 1.2 eq), 1-naphthylamine (2.86 g, 20 mmol, 1 eq), $InBr_3$ (354 mg, 1.0 mmol, 5 mol%) and $MgSO_4$ (2.41 g, 20 mmol, 1 eq) in CH_2Cl_2 (20 mL) is stirred at room temperature for 3 h. The crude mixture is filtered, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue is purified by flash chromatography (silica, pentane/EtOAc/NEt_3 96:2:1). The pure product is obtained as a white solid (4.97, 17.0 mmol, 85%). **R_F** (pentane/EtOAc/NEt_3 89:10:1): 0.55; **^{1}H NMR (300 MHz, $CDCl_3$):** 1.59 (s, 3H, CH_3), 3.48 (s, 3H, CH_3), 4.56 (s, 1H, CH), 7.00 (d, *J* = 7.2 Hz, 1H, CH_{ar}), 7.17 (t, *J* = 8.1 Hz, 1H, CH_{ar}), 7.22-7.31 (m, 2H, CH_{ar}), 7.48 (d, *J* = 8.3 Hz, 1H, CH_{ar}), 7.59-7.62 (m, 1H, CH_{ar}), 7.78-7.81 (m, 1H, CH_{ar}), 10.30 (s, 1H, NH); **^{13}C NMR (75 MHz, $CDCl_3$):** 19.9 (CH_3), 50.3 (CH_3), 85.2 (CH), 122.6 (CH_{ar}), 123.6 (CH_{ar}), 125.2 (CH_{ar}), 126.4 (CH_{ar}), 126.6 (CH_{ar}), 126.7 (CH_{ar}), 128.1 (CH_{ar}), 130.4 (C_{ar}), 134.2 (C_{ar}), 135.2 (C_{ar}), 160.6 (C_q), 171.0 (CO); **ESI-MS:** calculated $[C_{15}H_{15}NNaO_2]^+$: 264.0995, found: 264.0960. **ATR-FTIR [cm^{-1}]:** 3224, 3047, 2998, 2952, 1642, 1590, 1507, 1488, 1459, 1432, 1376, 1328, 1253, 1189, 1156, 1083, 1051, 999, 940, 864, 779, 738, 738, 696, 663.

(*Z*)-*tert*-butyl-3-(phenylamino)-but-2-enoate (1v)[5]



Following a modified procedure by G. Bartoli[5], aniline (6.99 g, 6.84 mL, 75.0 mmol, 1.5 eq), *tert*-butyl acetoacetate (7.91 g, 8.29 mL, 50.0 mmol, 1.0 eq), $Zn(ClO_4)_2 \cdot 6H_2O$ (931 mg, 2.50 mmol, 5 mol%) and $MgSO_4$ (1.81 g, 15.0 mmol, 0.3 eq) were stirred in CH_2Cl_2 (20 mL) at rt for 24 h. The mixture is diluted with CH_2Cl_2 (100 mL), filtered through Celite and the solvents were evaporated. After rapid flash column chromatography (silica, pentane/EtOAc gradient 99/1-90/10, 1% NEt_3), the product is obtained as a slightly yellow solid (11.35 g, 48.7 mmol, 97%). **^{1}H NMR (400 MHz, $CDCl_3$):** 1.51 (s, 9H, $C(CH_3)_3$), 1.88 (s, 3 H, CH_3), 4.64 (s, 1 H, CH), 7.07-7.14 (m, 3H, CH_{ar}), 7.28-7.32 (m, 3H, CH_{ar}), 10.37 (s, 1H, NH); **^{13}C NMR (100 MHz, $CDCl_3$):** 20.3 (CH_3), 28.7 ($C(CH_3)_3$), 78.6 ($C(CH_3)_3$), 88.0 (CH), 124.4 (CH_{ar}), 124.7 (CH_{ar}), 129.1 (CH_{ar}), 139.7 (C_{ar}), 158.1 (C_q), 170.5 (CO); **ESI-MS:** calculated $[C_{14}H_{19}NNaO_2]^+$: 256.1308, found: 256.1305.

(*Z*)-Ethyl-3-(phenylamino)-3-phenylpropenoate (1x)[7]



Following a modified procedure by Wentrup,[7a] aniline (11.64 g, 11.4 mL, 125 mmol, 5.0 eq), ethyl benzoylacetate (4.81 g, 4.3 mL, 25 mmol, 1.0 eq) and AcOH (7.2 mL, 125 mmol, 5.0 eq.) were stirred at 80 °C for 5 h. The mixture is diluted with water (50 mL), extracted with CH_2Cl_2 (3 x 100 mL), the combined organic phase is washed with brine, dried and concentrated. After flash column chromatography (silica, pentane/EtOAc gradient 85/15-0/100), the product is obtained as a slightly yellow solid (5.82 g, 21.8 mmol, 87%). **^{1}H NMR (400 MHz, $CDCl_3$):** 1.31 (t, J = 7.1 Hz, 3H, CH_3), 4.21 (q, J = 7.1 Hz, 2 H, CH_2), 5.00 (s, 1 H, CH), 6.66 (d, J = 8.0 Hz, 2H, CH_{ar}), 6.89 (t, J = 7.2 Hz, 1H, CH_{ar}), 7.04-7.08 (m, 2H, CH_{ar}), 7.24-7.36 (m, 5H, CH_{ar}), 10.31 (s, 1H, NH); **^{13}C NMR (100 MHz, $CDCl_3$):** 14.6 (CH_3), 59.4 (CH_2), 91.3 (CH), 122.3 (CH_{ar}), 123.0 (CH_{ar}), 128.3 (CH_{ar}), 128.5 (CH_{ar}), 128.7 (CH_{ar}), 129.5 (CH_{ar}), 136.1 (C_{ar}), 140.5 (C_{ar}), 159.2 (C_q), 170.2 (CO; **ESI-MS:** calculated $[C_{17}H_{17}NNaO_2]^+$: 290.1151, found: 290.1149.

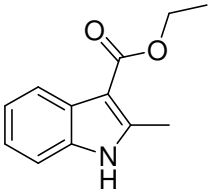
4. Typical procedure for the palladium-catalyzed cyclization

a. General procedure

The enaminecarboxylate **1** (1 mmol) is stirred with $Pd(OAc)_2$ (0.1 mmol), $Cu(OAc)_2$ (3 mmol) and K_2CO_3 (3 mmol) in DMF (12 mL) at the indicated temperature. When all starting material is consumed (TLC, GC, GC/MS-analysis) the mixture is cooled to rt and filtered through celite. The filter residue is washed with ethylacetate (100 mL) and the organic phase is washed with aqueous ammonia (5-10%, 100 mL). After extraction of the aqueous layer with ethylacetate (3x 100 mL), the organic layers were combined, washed with brine (100 mL) and dried with $MgSO_4$. The solvents were removed under reduced pressure and the crude product **2** is purified by flash chromatography.

b. Modified procedure with $Cu(OAc)_2 \cdot H_2O$

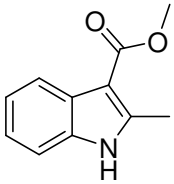
Ethyl 2-methyl-indole-3-carboxylate (2u)



$Pd(OAc)_2$ (11.2 mg, 0.05 mmol, 5 mol%), $Cu(OAc)_2 \cdot H_2O$ (599 mg, 3.0 mmol, 3.0 eq), K_2CO_3 (415 mg, 3.0 mmol, 3.0 eq) are weighed on the bench under air into a not specially dried reaction vessel. Ethyl 3-anilinocrotonate (205 mg, 1.00 mmol) in DMF (12 mL) is added, the reaction vessel is evacuated and backfilled with Argon, closed and placed into a preheated oil bath at 140 °C for 15 min. After standard workup and purification by flash column chromatography (silica, pentane/EtOAc 4:1) the product is obtained as a light brown solid. (143 mg, 0.70 mmol, 70%). The product is of the same analytical purity as the one obtained under water-free conditions.

c. One-pot procedure

Methyl 2-methyl-indole-3-carboxylate (2a)[8]

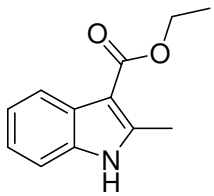


In a glovebox, $InBr_3$ (17.7 mg, 0.05 mmol, 0.01 eq) is weighed into a flame-dried 3 mL reaction tube. Aniline (466 mg, 456 µl, 5.00 mmol, 1.00 eq) and methyl acetoacetate were added subsequently under argon, the Teflon screw cap is closed and the mixture is stirred vigorously for 20 min at rt. Reaction

control via GC and GC/MS showed clean conversion to the enamine and only traces of aniline left. In the case of methyl 3-(phenylamino)but-2-enoate, the reaction mixture became solid and 3 mL DMF were added to allow efficient stirring. The mixture was transferred with a syringe into a 150 mL reaction flask containing $Pd(OAc)_2$ (56.1 mg, 0.25 mmol, 5 mol%), $Cu(OAc)_2$ (2.72 g, 15.0 mmol, 3.0 eq), K_2CO_3 (2.07 g, 15.0 mmol, 3.0 eq) and DMF (50 mL), product residues were rinsed into the bigger flask with DMF (2 x 3mL). The reaction vessel was evacuated and backfilled with Argon three times, closed and placed into a preheated oil bath at 140 °C. The reaction mixture was stirred for 20 min (no more enamine substrate detectable by GC, GC/MS and TLC), cooled to rt, diluted with EtOAc (100 mL) and filtered through a short pad of silica and sea sand. The red-brown solid was washed with EtOAc (2 x 50 mL) and the combined filtrates were concentrated on a rotary evaporator and in high vacuum to yield 1.11 g of a black tar. The crude product was adsorbed on silica from a CH_2Cl_2-solution and purified by flash column chromatography (silica, pentane/EtOAc gradient, 95/5 – 60/40) to yield 680 mg (3.59 mmol, 72%) methyl 2-methyl-indole-3-carboxylate (**2a)** as a light brown solid. The product is of the same analytical purity as the one obtained from the isolated methyl 3-(phenylamino)-but-2-enoate (**1a**).

d. Large-Scale Indole Synthesis with reduced catalyst amount

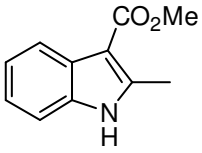
Ethyl 2-methyl-indole-3-carboxylate (2u)



Following the general procedure, ethyl 3-anilinocrotonate (2.05 g, 10.0 mmol) is stirred with $Pd(OAc)_2$ (44.8 mg, 0.20 mmol, 2 mol%), $Cu(OAc)_2 \cdot H_2O$ (5.99 g, 30.0 mmol, 3.0 eq), K_2CO_3 (4.15 g, 30.0 mmol, 3.0 eq) and DMF (120 mL) under Argon in a preheated oil bath at 140 °C for 17 h. The reaction mixture is diluted with EtOAc (300 mL) and filtered through a short pad of silica. The solid is washed with EtOAc (2 x 100 mL), the combined filtrates are evaporated to dryness. After purification by flash column chromatography (silica, pentane/EtOAc 4:1) the product is obtained as a light brown solid (1.26 g, 6.20 mmol, 62%). The product is of the same analytical purity as the one obtained on a 1.0 mmol scale.

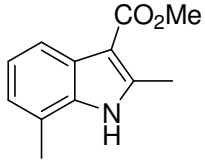
5. Characterization of indole products

Methyl 2-methyl-indole-3-carboxylate (2a)[8]



Following the general procedure, the mixture is stirred in a preheated oil bath at 80°C for 12 h. After purification by flash chromatography (silica, pentane/EtOAc 5:1) the product is obtained as an orange solid (136 mg, 0.72 mmol, 72%). **R_F** (pentane/EtOAc 10:3): 0.20; **^{1}H NMR (300 MHz, $CDCl_3$):** 2.79 (s, 3H, CH_3), 3.99 (s, 3H, CH_3), 7.24-7.36 (m, 3H, CH_{ar}), 8.16 (d, *J* = 7.4 Hz, 1H, CH_{ar}), 8.53 (bs, 1H, NH); **^{13}C NMR (75 MHz, $CDCl_3$):** 14.1 (CH_3), 50.8 (CH_3), 104.4 (C_{ar}), 110.5, 121.2, 121.7, 122.3 (CH_{ar}), 127.1 134.5, 144.1 (C_{ar}), 166.6 (CO).

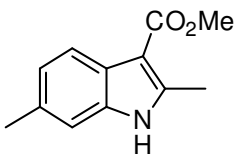
Methyl-2,7-dimethyl-3-indolecarboxylate (2b)

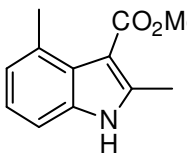


Following the general procedure, the mixture is stirred in a preheated oil bath at 110 °C for 14 h. After purification by flash chromatography (silica, pentane/EtOAc 4:1) the product is obtained as a brown solid (166 mg, 0.82 mmol, 82%). **R_F** (pentane/EtOAc 7:3): 0.51; **^{1}H NMR (300 MHz, $CDCl_3$):** 2.48 (s, 3H, CH_3), 2.75 (s, 3H, CH_3), 3.94 (s, 3H, CH_3), 7.00 (d, *J* = 7.2 Hz, 1H, CH_{ar}), 7.15 (t, *J* = 7.5 Hz, 1H, CH_{ar}), 7.95 (d, *J* = 8.0 Hz, 1H, CH_{ar}), 8.57 (s, 1H, NH); **^{13}C NMR (75 MHz, $CDCl_3$):** 13.2 (CH_3), 15.4 (CH_3), 49.8 (CH_3), 103.8 (C_{ar}), 117.9 (C_{ar}), 118.7 (CH_{ar}), 120.8 (CH_{ar}), 122.0 (CH_{ar}), 125.7 (C_{ar}), 132.9 (C_{ar}), 142.7 (C_{ar}), 165.7 (CO); **GC-MS R_t (method B):** 9.1 min, **(EI) m/z (%):** 204.0 (14), 203.0 (84), 188.0 (14), 173.0(13), 172.0 (100), 171.1 (13), 144.1 (23), 143.0 (26), 142.0 (14), 115.0 (24); **ESI-MS:** calculated $[C_{12}H_{13}NNaO_2]$+: 226.0838, found: 226.0822; **ATR-FTIR [cm^{-1}]:** 3299, 3026, 2952, 1658, 1547, 1442, 1201, 1091, 809, 677, 596.

Methyl-2,6-dimethyl-3-indolecarboxylate (2c)

Following the general procedure, the mixture is stirred in a preheated oil bath at 80 °C for 16 h. After purification by flash chromatography (silica, pentane/EtOAc 4:1) the product is obtained as a brown solid (138 mg, 0.68 mmol, 68%) as a mixture of 4- and 6-substituted isomers (6-Me/4-Me 88:12). **R_F** (pentane/EtOAc 7:3): 0.56; **^{1}H NMR (400 MHz, $CDCl_3$):**

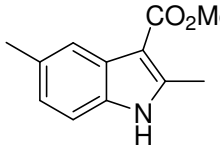




2.44 (s, 3H, CH_3 of 6-Me), 2.64 (s, 3H, CH_3 of 4-Me), 2.70 (s, 3H, CH_3 of 4-Me), 2.71 (s, 3H, CH_3 of 6-Me), 3.90 (s, 3H, CH_3 of 4-Me), 3.92 (s, 3H, CH_3 of 6-Me), 7.05 (d, *J* = 8.00 Hz, 1H, CH_{ar} of 6-Me), 7.08 (s, 1H, CH_{ar} of 6-Me), 7.95 (d, *J* = 8.00 Hz, 1H, CH_{ar} of 6-Me), 8.28 (s, 1H, NH); **^{13}C NMR (100 MHz, $CDCl_3$):** 14.1 (CH_3), 21.6 (CH_3), 50.7

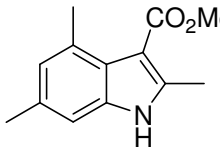
(CH_3), 50.9 (CH_3), 104.3 (C_{ar}), 110.5 (CH_{ar}), 120.9 (CH_{ar}), 123.3 (CH_{ar}), 124.8 (C_{ar}), 132.1 (C_{ar}), 134.8 (C_{ar}), 143.4 (C_{ar}), 166.6 (CO); Signals of the minor isomer are too weak to be detected! **GC-MS R_t (method C):** 12.1 (for 4-Me) and 12.2 (for 6-Me), **(EI) m/z (%):** 203.9 (14), 203.1 (65), 202.9 (15), 172.2 (61), 171.0 (100), 144.0 (34), 143.0 (79), 142.7 (11), 142.0 (11), 114.9 (24) [for b] and 204.0 (13), 203.1 (100), 188.0 (19), 173.0 (11), 172.0 (81), 171.0 (15), 144.0 (20), 144.1 (24), 142.0 (13), 115.0 (15) [for 6-Me]; **ESI-MS:** calculated $[C_{12}H_{13}NNaO_2]^+$: 226.0838, found: 226.0841. **ATR-FTIR [cm-1]:** 3299, 3026, 2952, 1658, 1547, 1442, 1201, 1091, 809, 677, 596.

Methyl-2,5-dimethyl-3-indolecarboxylate (2d)[9]



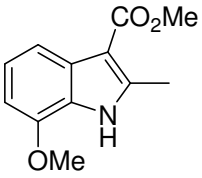
Following the general procedure, the mixture is stirred in a preheated oil bath at 80 °C for 12 h. After purification by flash chromatography (silica, pentane/EtOAc 4:1) the product is obtained as a pale brown solid (145 mg, 0.72 mmol, 72%). **GC-MS R_t (method C):** 12.2 min, **(EI) m/z (%):** 204 (20), 188 (12), 173 (19), 172 (89), 171 (19), 144 (19), 143 (20), 115 (15), 85 (11), 203 (100), 204 (20). **^{1}H NMR (300 MHz, $CDCl_3$):** 2.48 (s, 3H, CH_3), 2.70 (s, 3H, CH_3), 3.95 (s, 3H, CH_3), 7.02 (dd, *J* = 8.1 Hz, *J* = 1.2 Hz, CH_{ar}), 7.14 (d, *J* = 8.1 Hz, 1H, CH_{ar}), 7.91 (s, 1H, CH_{ar}), 8.62 (s, 1H, NH); **^{13}C NMR (75 MHz, $CDCl_3$):** 14.2 (CH_3), 21.6 (CH_3), 50.8 (CH_3), 103.7 (C_{ar}), 110.2 (CH_{ar}), 120.9 (CH_{ar}), 123.7 (C_{ar}), 127.3 (C_{ar}), 131.1 (C_{ar}), 132.8 (C_{ar}), 144.2 (C_{ar}), 166.8 (CO).

Methyl-2,4,6-trimethyl-3-indolecarboxylate (2e)



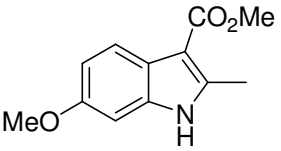
Following the general procedure, the mixture is stirred in a preheated oil bath at 110 °C for 12 h. After purification by flash chromatography (silica, pentane/EtOAc 4:1) the product is obtained as a pale orange solid (135 mg, 0.62 mmol, 62%). **R_F** (pentane/EtOAc 7:3): 0.55; **^{1}H NMR (300 MHz, $CDCl_3$):** 2.37 (s, 3H, CH_3), 2.57 (s, 3H, CH_3), 2.68 (s, 3H, CH_3), 3.89 (s, 3H, CH_3), 6.82 (s, 1H, CH_{ar}), 6.84 (s, 1H, CH_{ar}), 8.45 (s, 1H, NH); **^{13}C NMR (75 MHz, $CDCl_3$):** 14.4 (CH_3), 21.2 (CH_3), 22.1 (CH_3), 50.8 (CH_3), 105.5 (C_{ar}), 108.4 (CH_{ar}), 123.2 (C_{ar}), 125.6 (CH_{ar}), 130.7 (C_{ar}), 132.1 (C_{ar}), 135.5 (C_{ar}), 141.9 (C_{ar}), 166.8 (CO); **GC-MS R_t (method B):** 9.4 min, **(EI) m/z (%):** 218.0 (17), 217.1 (100), 206.0 (10), 186.1 (72), 185.0 (65), 158.1 (28), 157.1 (94), 156.1 (25), 143.9 (13), 130.0 (13), 127.9 (12), 115.0 (26); **ESI-MS:** calculated $[C_{13}H_{15}NNaO_2]$+: 240.0995, found: 240.0997; **ATR-FTIR [cm^{-1}]:** 3306, 3230, 2951, 2920, 1664, 1442, 1418, 1334, 1199, 1151, 1099, 1024.

Methyl 7-methoxy-2-methyl-indole-3-carboxylate (2f)



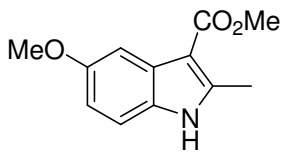
Following the general procedure, the mixture is stirred in a preheated oil bath at 140 °C for 30 min. After purification by flash chromatography (silica, pentane/EtOAc 5:1) the product is obtained as an orange solid. (140 mg, 0.64 mmol, 64%). **R_F** (pentane/EtOAc 10:3): 0.50; **^{1}H NMR (400 MHz, $CDCl_3$):** 2.74 (s, 3H, CH_3), 3.93 (s, 3H, CH_3), 3.94 (s, 3H, CH_3), 6.66 (d, *J* = 7.5 Hz, 1H, CH_{ar}), 7.13 (t, *J* = 8.0 Hz, 1H, CH_{ar}) 7.67 (d, *J* = 8.1 Hz, 1H, CH_{ar}), 8.62 (s, 1H, NH); **^{13}C NMR (100 MHz, $CDCl_3$):** 14.1 (CH_3), 50.7 (CH_3), 55.3 (CH_3), 102.5 (CH_{ar}), 104.9 (C_{ar}), 113.9 (CH_{ar}), 122.1 (CH_{ar}), 124.7 (C_{ar}), 128.4 (C_{ar}), 143.3 (C_{ar}), 145.3 (C_{ar}), 166.6 (CO); **GC/MS R_t (method B):** 9.3 min, **(EI) m/z (%):** 219.1 (100), 204.1 (18), 188 (85), 173 (32); **ESI-MS:** calculated $[C_{12}H_{13}NNaO_3]^+$: 242.0788, found: 242.0789. **ATR-FTIR [cm^{-1}]:** 3342, 3317, 1670, 1452, 1277, 1083, 1026, 792, 737, 682, 646.

Methyl 6-methoxy-2-methyl-indole-3-carboxylate (2g)



Following the general procedure, the mixture is stirred in a preheated oil bath at 140 °C for 30 min. After purification by flash chromatography (silica, pentane/EtOAc 5:1) the product is obtained as an orange solid. (141 mg, 0.64 mmol, 64%). **R_F** (pentane/EtOAc 10:3): 0.56; **^{1}H NMR (300 MHz, d^6-DMSO):** 2.61 (s, 3H, CH_3), 3.76 (s, 3H, CH_3), 3.78 (s, 3H, CH_3), 6.76(dd, *J* = 8.7 Hz, *J* = 2.3, 1H, CH_{ar}), 6.85 (d, *J* = 2.2 Hz, 1 H, CH_{ar}) 7.76 (d, *J* = 8.7 Hz, CH_{ar}), 11.63 (s, 1H, NH); **^{13}C NMR (75 MHz, d^6-DMSO):** 13.5 (CH_3), 50.3 (CH_3), 55.1 (CH_3), 94.6, 102.4, 110.3, 120.6, 120.9, 135.4, 143.4, 155.5 (C_{ar}), 165.4 (CO); **GC/MS R_t (method A):** 14.1 min, **(EI) m/z (%):** 219 (100), 204 (42), 188 (27), 172 (24), 159 (13), 144 (11); **ESI-MS:** calculated $[C_{12}H_{13}NNaO_3]^+$: 242.0788, found: 242.0791; **ATR-FTIR [cm^{-1}]:** 3278, 1660, 1627, 1552, 1454, 1337, 1198, 1158, 1092, 812.

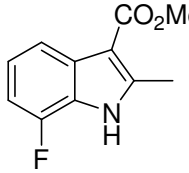
Methyl 5-methoxy-2-methyl-indole-3-carboxylate (2h)



Following the general procedure, the mixture is stirred in a preheated oil bath at 140 °C for 30 min. After purification by flash chromatography (silica, pentane/EtOAc 5:1) the product is obtained as an orange solid. (149 mg, 0.68 mmol, 68%). **R_F** (pentane/EtOAc 10:3): 0.52; **^{1}H NMR (400 MHz, $CDCl_3$):** 2.71 (s, 3H, CH_3), 3.88 (s, 3H, CH_3), 3.93 (s, 3H, CH_3), 6.83 (dd, *J* = 8.7 Hz, *J* = 2.5 Hz, 1H, CH_{ar}), 7.18 (d, *J* = 8.7 Hz, 1 H, CH_{ar}) 7.61 (d, *J* = 2.5 Hz, CH_{ar}), 8.38 (s, 1H,

NH); **^{13}C NMR (100 MHz, $CDCl_3$):** 14.4 (CH_3), 50.8 (CH_3), 55.8 (CH_3), 103.4 (CH_{ar}), 104.3 (C_{ar}), 111.2 (CH_{ar}), 112.1 (CH_{ar}), 128.0 (C_{ar}), 129.3 (C_{ar}), 144.2 (C_{ar}), 155.6 (C_{ar}), 166.5 (CO); **GC/MS R_t (method B):** 9.5 min; **(EI) m/z (%):** 219 (100), 204 (28), 188 (48), 176 (10); **ESI-MS:** calculated $[C_{12}H_{13}NNaO_3]^+$: 242.0788, found: 242.0798; **ATR-FTIR [cm^{-1}]:** 3271, 1656, 1587, 1452, 1194, 1162, 1087, 1027, 850, 702.

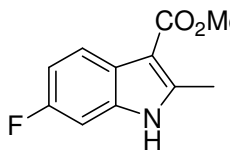
Methyl-7-fluoro-2-methyl-indole-3-carboxylate (2i)[10]



Following the general procedure, the mixture is stirred in a preheated oil bath at 110 °C for 5 h. After purification by flash chromatography (silica, pentane/EtOAc 4:1) the product is obtained as a yellow solid (161 mg, 0.78 mmol, 78 %). **R_F** (pentane/EtOAc 7:3): 0.70; **^{1}H NMR (300 MHz, $CDCl_3$):** 2.77 (s, 3H, CH_3), 3.93 (s, 3H, CH_3), 6.91 (ddd, J = 10.8 Hz, J = 8.1 Hz, J = 0.6 Hz, 1H, CH_{ar}), 7.11 (dt, J = 8.1 Hz, , J = 5.1 Hz, 1H, CH_{ar}), 7.84 (d, J = 8.1 Hz, 1H, CH_{ar}), 8.56 (s, 1H, NH); **^{13}C NMR (100 MHz, $CDCl_3$):** 14.2 (CH_3), 50.9 (CH_3), 105.3 (C_{ar}), 107.3 (d, $J_{(C,F)}$ = 15.7 Hz, C_{ar}), 116.9 (d, $J_{(C,F)}$ = 3.5 Hz, CH_{ar}), 121.9 (d, $J_{(C,F)}$ = 6.2 Hz, CH_{ar}), 122.7 (d, $J_{(C,F)}$ = 13.3 Hz, C_{ar}), 130.4 (d, $J_{(C,F)}$ = 4.5 Hz, C_{ar}), 144.6 (C_{ar}), 148.7 (d, $J_{(C,F)}$ = 243.6 Hz, C_{ar}), 166.2 (CO). **GC-MS R_t (method B):** 8.6 min, **(EI) m/z (%):** 207.0 (69), 177.0 (11), 176.0 (100), 175.0 (12), 148.0 (16), 147.0 (15), 146.0 (12), 101.0 (13); **ESI-MS:** calculated $[C_{11}H_{10}FNNaO_2]^+$: 230.0588, found: 230.0592; **ATR-FTIR [cm^{-1}]:** 3271, 3008, 2949, 1660, 1581, 1474, 1452, 1372, 1309, 1275, 1217, 1157, 1106, 1064, 1040, 998, 874, 827, 792, 767, 710, 629, 600.

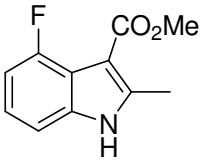
Methyl-6-fluoro-2-methyl-3-indolecarboxylate & Methyl-4-fluoro-2-methyl-3-indolecarboxylate (2j)

Following the general procedure, the mixture was stirred in a preheated oil bath at 110 °C for 14 h. After purification by flash chromatography (silica, pentane/EtOAc 4:1), the 4- and 6-substituted isomers are obtained as pale brown solids (153 mg, 0.74 mmol, 74 %) (6-F/4-F = 53:47).



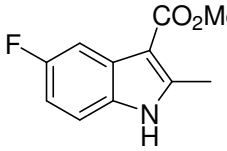
R_F (pentane/EtOAc 7:3): 0.63; **^{1}H NMR (300 MHz, $CDCl_3$):** 2.74 (s, 3H, CH_3), 3.93 (s, 3H, CH_3), 7.18 (dd, J = 8.4 Hz, J = 1.8 Hz, 1H, CH_{ar}), 7.29 (d, J = 1.2 Hz, 1H, CH_{ar}), 7.99 (d, J = 8.7 Hz, 1H), 8.27 (s, 1H, NH); **^{13}C NMR (75 MHz, d^6-DMSO):** 13.8 (CH_3), 50.7 (CH_3), 101.7 (C_{ar}), 106.9 (d, $J_{(C,F)}$ = 21.5 Hz, CH_{ar}), 107.7 (d, $J_{(C,F)}$ = 3.6 Hz, CH_{ar}), 114.2 (d, $J_{(C,F)}$ = 18.7 Hz, C_{ar}), 122.5 (d, $J_{(C,F)}$ = 8.0 Hz, CH_{ar}), 137.7 (d, $J_{(C,F)}$ = 10.8 Hz, C_{ar}), 144.8 (C_{ar}), 154.7 (d,

$J_{(C,F)}$ = 248.9 Hz, C_{ar}), 164.6 (CO). **GC-MS R_t (method B):** 9.0 min, **(EI) m/z (%):** 207.0 (65), 177.0 (10), 176.0 (100), 175.0 (10), 147.9 (16), 145.9 (14), 101.0 (15); **ESI-MS:** calculated $[C_{11}H_{10}FNNaO_2]^+$: 230.0588, found: 230.0597; **ATR-FTIR [cm^{-1}]:** 3309, 3010, 2954, 1678, 1630, 1582, 1538, 1444, 1364, 1371, 1261, 1205, 1096, 1024, 984, 807, 762, 723, 692, 636, 591.



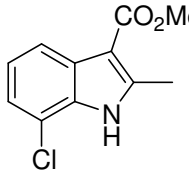
R_F (pentane/EtOAc 7:3): 0.54; **^{1}H NMR (300 MHz, $CDCl_3$):** 2.71 (s, 3H, CH_3), 3.93 (s, 3H, CH_3), 6.93-7.00 (m, 2H, CH_{ar}), 8.01 (dd, *J* = 5.4 Hz, *J* = 9.5 Hz, 1H, CH_{ar}), 8.75 (s, 1H, NH); **^{13}C NMR (75 MHz, $CDCl_3$):** 14.1 (CH_3), 50.9 (CH_3), 97.2 (d, $J_{(C,F)}$ = 26.3 Hz, CH_{ar}), 104.3 (C_{ar}), 110. (d, $J_{(C,F)}$ = 23.6 Hz, CH_{ar}), 122.0 (d, $J_{(C,F)}$ = 9.6 Hz, CH_{ar}), 123.5 (C_{ar}), 134.4 (d, $J_{(C,F)}$ = 12.3 Hz, C_{ar}), 144.5 (C_{ar}), 159.7 (d, $J_{(C,F)}$ = 238.6 Hz, C_{ar}), 166.4 (CO). **GC-MS R_t (method B):** 8.9 min, **(EI) m/z (%):** 208.0 (11), 207.0 (88), 192 (19), 177 (11), 176 (100), 174.9 (18), 174 (12) 147.9(28), 147.0 (23), 146.0 (18), 120.0 (13), 101.0 (17); **ESI-MS:** calculated $[C_{11}H_{10}FNNaO_2]^+$: 230.0588, found: 230.0590; **ATR-FTIR [cm^{-1}]:** 3256, 3011, 2946, 1652, 1599, 1549, 1467, 1448, 1382, 1344, 1280, 1204, 1138, 1107, 1090, 1025, 984, 956, 838, 810, 786, 727, 686, 611.

Methyl-5-fluoro-2-methyl-indole-3-carboxylate (2k)



Following the general procedure, the mixture is stirred in a preheated oil bath at 110 °C for 5 h. After purification by flash chromatography (silica, pentane/EtOAc 4:1) the product is obtained as a brown solid (153 mg, 0.74 mmol, 74 %). **R_F** (pentane/EtOAc 7:3): 0.42; **^{1}H NMR (300 MHz, $CDCl_3$):** 2.74 (s, 3H, CH_3), 3.93 (s, 3H, CH_3), 6.92 (dt, *J* = 9.0 Hz, *J* = 2.6 Hz, 1H, CH_{ar}), 7.21 (dd, *J* = 8.8 Hz, *J* = 4.4 Hz, 1H, CH_{ar}), 7.75 (dd , *J* = 10.4 Hz, *J* = 2.6 Hz , 1H, CH_{ar}), 8.47 (s, 1H, NH); **^{13}C NMR (75 MHz, $CDCl_3$):** 14.3 (CH_3), 50.9 (CH_3), 104.8 (C_{ar}), 106.8 (d, $J_{(C,F)}$ = 25.3 Hz, CH_{ar}), 110.5 (d, $J_{(C,F)}$ = 26.3 Hz, CH_{ar}), 111.1 (d, $J_{(C,F)}$ = 9.8 Hz, CH_{ar}), 127.9 (d, $J_{(C,F)}$ = 11.7 Hz, C_{ar}), 130.8 (C_{ar}), 145.5 (C_{ar}), 159.1 (d, $J_{(C,F)}$ = 235.9 Hz, C_{ar}), 166.2 (CO). **GC-MS R_t (method B):** 8.9 min, **(EI) m/z (%):** 207.0 (76), 177.0 (11), 176.0 (100), 175.0 (17), 174.0 (10), 148.0 (16), 147.0 (12), 146.0 (10), 101.1 (11); **ESI-MS:** calculated $[C_{11}H_{10}FNNaO_2]^+$: 230.0588, found: 230.0581; **ATR-FTIR [cm^{-1}]:** 3272, 2951, 1983, 1846, 1548, 1441, 1337, 1296, 1189, 1156, 1109, 1087, 1008, 974, 877, 826, 804, 776, 709, 631, 600.

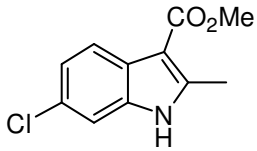
Methyl-7-chloro-2-methyl-indole-3-carboxylate (2l)



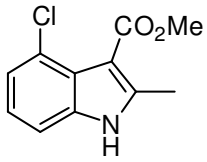
Following the general procedure, the mixture is stirred in a preheated oil bath at 80 °C for 12 h. After purification by flash chromatography (silica, pentane/EtOAc 4:1) the product is obtained as an orange solid (119 mg, 0.53 mmol, 53%). **R_F** (pentane/EtOAc 7:3): 0.59; **^{1}H NMR (400 MHz, $CDCl_3$):** 2.78 (s, 3H, CH_3), 3.93 (s, 3H, CH_3), 7.13-7.21 (m, 2H, CH_{ar}), 7.98 (d, *J* = 7.7 Hz, 1H, CH_{ar}), 8.51 (s, 1H, NH); **^{13}C NMR (100 MHz, $CDCl_3$):** 14.2 (CH_3), 50.9 (CH_3), 105.7 (C_{ar}), 115.9 (C_{ar}), 119.9 (CH_{ar}), 121.8(CH_{ar}), 122.5 (CH_{ar}), 128.5 (C_{ar}), 131.7 (C_{ar}), 144.4 (C_{ar}), 166.0 (CO). **GC-MS R_t (method B):** 9.0 min, **(EI) m/z (%):** 225.0 (25), 223.0 (68), 208.0 (11), 194.0 (37), 193 (19), 192.0 (100), 191.0 (14), 164.0 (16), 162.9 (10), 128.0 (18), 102.0 (14), 101.1 (23), 75.0 (13); **ESI-MS:** calculated $[C_{11}H_{10}ClNNaO_2]^+$: 246.0292, found: 246.0287; **ATR-FTIR [cm^{-1}]:** 3280, 2960, 1656, 1436, 1364, 1301, 1266, 1228, 1185, 1139, 1094, 1031, 981, 945, 867, 792, 734, 701, 589, 476.

Methyl-6-chloro-2-methyl-indole-3-carboxylate & Methyl-4-chloro-2-methyl-indole-3-carboxylate (2m)[10]

Following the general procedure, the mixture is stirred in a preheated oil bath at 80 °C for 14 h. After purification by flash chromatography (silica, pentane/EtOAc 4:1), two products are obtained as brown solids (168 mg, 0.75 mmol, 75%) (6-Cl/4-Cl = 88:12).



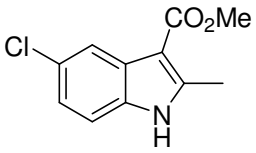
R_F (pentane/EtOAc 7:3): 0.50; **^{1}H NMR (300 MHz, d^6-DMSO):** 2.67 (s, 3H, CH_3), 3.84 (s, 3H, CH_3), 7.17 (d, *J* = 8.5 Hz, 1H, CH_{ar}), 7.44 (s, 1H, CH_{ar}), 7.91 (d, *J* = 8.5 Hz, 1H, CH_{ar}), 12.01 (s, 1H, NH); **^{13}C NMR (75 MHz, d^6-DMSO):** 14.6 (CH_3), 51.5 (CH_3), 103.7 (C_{ar}), 111.9 (CH_{ar}), 122.1 (CH_{ar}), 122.5 (CH_{ar}), 126.4 (C_{ar}), 127.2 (C_{ar}), 136.2 (C_{ar}), 146.7 (C_{ar}), 166.1 (CO). **GC-MS R_t (method B):** 9.5 min, **(EI) m/z (%):** 225.0 (35), 224.0 (11), 223.1 (87), 208.0 (14), 194.0 (36), 193.0 (16), 192.0 (100), 191.0 (22), 165.0 (10), 164.0 (22), 163.0 (17), 128.0 (14), 102.0 (113), 101.0 (15); **ESI-MS:** calculated $[C_{11}H_{10}ClNNaO_2]^+$: 246.0292, found: 246.0302; **ATR-FTIR [cm^{-1}]:** 3319, 3003, 2954, 2909, 1659, 1546, 1495, 1458, 1435, 1411, 1346, 1272, 1199, 1132, 1097, 1065, 1009, 908, 807, 779, 736, 709, 670.



R_F (pentane/EtOAc 7:3): 0.38; **^{1}H NMR (300 MHz, d^6-DMSO):** 2.57 (s, 3H, CH_3), 3.82 (s, 3H, CH_3), 7.11-7.18 (m, 2H, CH_{ar}), 7.34-7.39 (m, 1H, CH_{ar}), 12.07 (s, 1H, NH); **^{13}C NMR (75 MHz, d^6-DMSO):** 14.2 (CH_3), 51.7 (CH_3), 105.0 (C_{ar}), 111.3 (CH_{ar}), 123.1 (CH_{ar}), 123.4 (CH_{ar}), 124.2

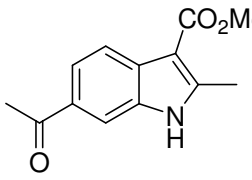
(C_{ar}), 124.9 (C_{ar}), 137.5 , 144.2 (C_{ar}), 165.9 (CO). **GC-MS R_t (method B):** 9.6 min, **(EI) m/z (%):** 281.0 (26), 225 (18), 223.0 (40), 207.9 (29), 207.0 (91), 194.0 (19), 191.9 (20), 78.0 (20), 73.0 (18), 44 (100), 39.9 (27); **ESI-MS:** calculated $[C_{11}H_{10}ClNNaO_2]$+: 246.0292, found: 246.0302; **ATR-FTIR [cm^{-1}]:** 3268, 3010, 2854, 1657, 1542, 1487, 1459, 1450, 1411, 1346, 1251, 1199, 1120, 1112, 1065, 1019, 909, 821, 732, 673, 625, 591.

Methyl-5-chloro-2-methyl-indole-3-carboxylate (2n)



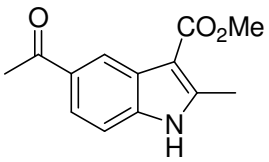
Following the general procedure, the mixture is stirred in a preheated oil bath at 80 °C for 12 h. After purification by flash chromatography (silica, pentane/EtOAc 4:1) the product is obtained as a pale brown solid (143 mg, 0.64 mmol, 64%). **R_F** (pentane/EtOAc 7:3): 0.51; **^{1}H NMR (300 MHz, $CDCl_3$):** 2.74 (s, 3H, CH_3), 3.94 (s, 3H, CH_3), 7.13-7.22 (m, 2H, CH_{ar}), 8.06 (d, *J* = 2.0 Hz, 1H, CH_{ar}), 8.46 (s, 1H, NH); **^{13}C NMR (75 MHz, $CDCl_3$):** 14.2 (CH_3), 50.9 (CH_3), 104.4 (C_{ar}), 111.4 (CH_{ar}), 120.9 (CH_{ar}), 122.7 (CH_{ar}), 127.6 (C_{ar}), 128.2(C_{ar}), 132.8 (C_{ar}), 145.2 (C_{ar}), 166.0 (CO). **GC-MS R_t (method B):** 9.4 min, **(EI) m/z (%):** 225.0 (37), 223.1 (81), 208.1 (14), 194.0 (31), 193.1 (11), 192.1 (100), 191.0 (29), 165.1 (9), 164.0 (20), 163.0 (15), 128.0 (11), 102.0 (11), 73.1 (12); **ESI-MS:** calculated $[C_{11}H_{10}ClNNaO_2]^+$: 246.0292, found: 246.0252; **ATR-FTIR [cm^{-1}]:** 3310, 3000, 2944, 2902, 1649, 1547, 1491, 1432, 1411, 1382, 1273, 1199, 1132, 1091, 1063, 1009, 921, 802, 771, 726, 709, 671, 624.

Methyl 6-acetyl-2-methyl-indole-3-carboxylate (2o)



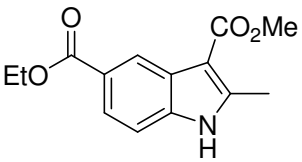
Following the general procedure, the mixture is stirred in a preheated oil bath at 140 °C for 30 min. After purification by flash chromatography (silica, CH_2Cl_2/EtOAc 10:1) the product is obtained as an orange/red solid (125 mg, 0.54 mmol, 54%). **R_F** (CH_2Cl_2/EtOAc 10:1): 0.20; **^{1}H NMR (300 MHz, d^6-DMSO):** 2.60 (s, 3H, CH_3), 2.69 (s, 3H, CH_3), 3.83 (s, 3H, CH_3), 7.75 (dd, *J* = 8.4 Hz, *J* = 1.6 Hz, 1H, CH_{ar}), 7.94-7.98 (m, 2H, CH_{ar}), 12.20 (s, 1H, NH); **^{1}H NMR (400 MHz, $CDCl_3$):** 2.67 (s, 3H, CH_3), 2.80 (s, 3H, CH_3), 3.95 (s, 3 H, CH_3), 7.82 (dd, *J* = 8.4 Hz, *J* = 1.5 Hz, 1H, CH_{ar}), 8.06 (d, *J* = 1.0 Hz, 1H, CH_{ar}), 8.12 (d, *J* = 8.4 Hz, 1H, CH_{ar}); **^{13}C NMR (75 MHz, d^6-DMSO):** 13.9 (CH_3), 26.6 (CH_3), 50.6 (CH_3), 103.1, 111.9, 119.8, 121.0, 130.4, 130.8, 134.2, 148.2 (C_{ar}), 165.0 (CO), 197.3 (CO); **GC/MS R_t (method A):** 15.2 min, **(EI) m/z (%):** 231 (67), 261 (100), 200 (19), 156 (41); **ESI-MS:** calculated $[C_{13}H_{13}NNaO_3]^+$: 254.0788, found: 254.0779; **ATR-FTIR [cm^{-1}]:** 3266, 2951, 1698, 1663, 1613, 1544, 1357, 1291, 1199, 1097, 821, 785, 724.

Methyl 5-acetyl-2-methyl-indole-3-carboxylate (2p)



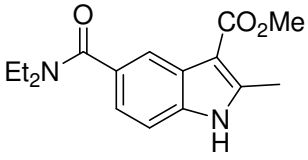
Following the general procedure, the mixture is stirred in a preheated oil bath at 140 °C for 30 min. After purification by flash chromatography (silica, pentane/EtOAc 2:1 – 1:1.5) the product is obtained as an orange solid. (120 mg, 0.52 mmol, 52%). **R_F** (pentane/EtOAc 2:1): 0.21; **^{1}H NMR (300 MHz, d^6-DMSO):** 2.61 (s, 3H, CH_3), 2.67 (s, 3H, CH_3), 3.85 (s, 3H, CH_3), 7.44 (d, *J* = 8.5 Hz, 1H, CH_{ar}), 7.77 (dd, *J* = 8.5 Hz, *J* = 1.6 Hz, 1 H, CH_{ar}) 8.56 (s, 1H, CH_{ar}), 12.16 (s, 1H, NH); **^{13}C NMR (75 MHz, d^6-DMSO):** 13.7 (CH_3), 26.6 (CH_3), 50.6 (CH_3), 103.7, 111.7, 121.7, 122.2, 126.2, 130.4, 137.5, 148.2 (C_{ar}), 165.1 (CO), 197.4 (CO); **GC/MS R_t (method B):** 10.2 min, **(EI) m/z (%):** 231 (50), 216 (100), 200 (18), 156 (46); **ESI-MS:** calculated $[C_{13}H_{13}NNaO_3]^+$: 254.0788, found: 254.0777; **ATR-FTIR [cm^{-1}]:** 3223, 1689, 1663, 1609, 1445, 1356, 1278, 1234, 1184, 951, 915, 812, 747.

5-Ethyl 3-methyl 2-methyl-indole-3,5-dicarboxylate (2q)



Following the general procedure, the mixture is stirred in a preheated oil bath at 140 °C for 30 min. After purification by flash chromatography (silica, CH_2Cl_2/EtOAc 20:1) the product is obtained as an yellow solid (166 mg, 0.64 mmol, 64%). **R_F** (CH_2Cl_2/EtOAc 10:1): 0.39; **^{1}H NMR (300 MHz, d^6-DMSO):** 1.34 (t, *J* = 7.1 Hz, 3H, CH_3), 2.67 (s, 3H, CH_3), 3.84 (s, 3H, CH_3), 4.32 (q, *J* = 7.1 Hz, 2H, CH_2), 7.44 (dd, *J* = 8.5 Hz, *J* = 0.5 Hz, 1H, CH_{ar}), 7.77 (dd, *J* = 8.5 Hz, *J* = 1.7 Hz, 1H, CH_{ar}), 8.60 (d, *J* = 1.3 Hz, 1H, CH_{ar}), 12.17 (s, 1H, NH); **^{13}C NMR (75 MHz, d^6-DMSO):** 13.7 (CH_3), 14.23 (CH_3), 50.6 (CH_3), 60.2 (CH_2), 103.5, 111.1, 122.4, 122.6, 122.7, 126.3, 137.4, 146.4 (C_{ar}), 165.0 (CO), 166.5 (CO); **GC/MS R_t (method B):** 10.5 min, **(EI) m/z (%):** 261 (100), 246 (9), 230 (34), 216 (72), 202 (23), 156 (39); **ESI-MS:** calculated $[C_{14}H_{15}NNaO_4]^+$: 284.0893, found: 284.0879; **ATR-FTIR [cm^{-1}]:** 3261, 2983, 1684, 1615, 1450, 1279, 1189, 1075, 765, 720.

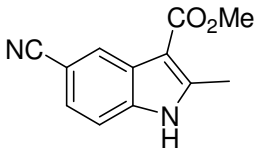
Methyl 5-(diethylcarbamoyl)-2-methyl-indole-carboxylate (2r)



Following the general procedure, the mixture is stirred in a preheated oil bath at 140 °C for 30 min. After purification by flash chromatography (silica, CH_2Cl_2/MeOH 24:1) the product is obtained as an orange solid (203 mg, 0.70 mmol, 70 %). **R_F** (CH_2Cl_2/MeOH 10:1): 0.47; **^{1}H-NMR (400 MHz, d$_6$-DMSO):** 1.12 (s, 6H, 2xCH_3), 2.66 (s, 3H, CH_3), 3.31 (br s, 4H, 2xCH_2), 3.81 (s, 3H, CH_3), 7.12 (dd, *J* = 8.3 Hz, *J* = 1.5 Hz, 1H,

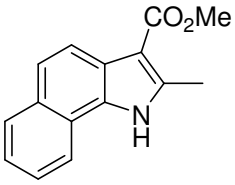
CH_{ar},), 7.39 (d, *J* = 8.3 Hz, 1H, CH_{ar}), 7.91 (s, *J* = 1.5 Hz, 1H, CH_{ar}), 12.01 (s, 1H, NH); **^{13}C-NMR (100 MHz, d_6-DMSO):** 13.7 (CH_3), 43.0 (CH_2), 50.6 (CH_3), 103.0 (C_{ar}), 111.1 (CH_{ar}), 118.5 (C_{ar}), 120.4 (CH_{ar}), 126.1 (CH_{ar}), 130.0 (C_{ar}), 135.0 (C_{ar}), 145.9 (C_{ar}), 165.3 (CO), 171.1 (CO); **GC-MS, R_t (method B):** 10.2 min, **(EI) m/z (%):** 287.1 (36), 257.1 (8), 216.0 (100), 156 (36); **ESI-MS:** calculated $[C_{16}H_{20}N_2NaO_3]^+$: 311.1366, found: 311.1361; **ATR-FTIR (cm^{-1}):** 2982, 2928, 2749, 1685, 1579, 1446, 1388, 1361, 1325, 1288, 1248, 1167, 1125, 1098, 1079, 1025, 951, 913, 862, 819, 766, 715, 676, 645, 586.

Methyl 5-cyano-2-methyl-indole-carboxylate (2s)



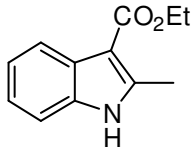
Following the general procedure, the mixture is stirred in a preheated oil bath at 140 °C for 30 min. After purification by flash chromatography (silica, pentane/EtOAc 7:3) the product is obtained as a white solid (139 mg, 0.65 mmol, 65%). **R_F** (pentane/EtOAc 7:3): 0.14; **^{1}H NMR (300 MHz, d_6-DMSO):** 2.65 (s, 3H, CH_3), 3.83 (s, 3H, CH_3), 7.46-7.52 (m, 2H, CH_{ar}), 8.22 (s, 1H, CH_{ar}), 12.33 (s, 1H, NH); **^{13}C NMR (75 MHz, d_6-DMSO):** 13.6 (CH_3), 50.8 (CH_3), 103.2 (C_{ar}), 103.2 (C_{ar}), 112.6 (CH_{ar}), 120.4 (CN), 124.7 (C_{ar}), 125.1 (CH_{ar}), 126.5 (CH_{ar}), 136.7 (C_{ar}), 147.4 (C_{ar}), 164.8 (CO); **GC-MS, R_t (method B):** 10.2 min, **(EI) m/z (%):** 214.0 (60), 183.0 (100), 155.0 (12); **ESI-MS:** calculated $[C_{12}H_{10}N_2NaO_2]^+$: 237.0634, found: 237.0625; **ATR-FTIR (cm^{-1}):** 3272, 3009, 2955, 2217, 1665, 1619, 1469, 1435, 1302, 1280, 1206, 1188, 1153, 1126, 1092, 1009, 959, 889, 809, 781, 716.

Methyl 2-methyl-benz[g]indole-3-carboxylate (2t)[11]



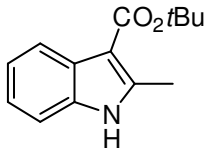
Following the general procedure, the mixture is stirred in a preheated oil bath at 80 °C for 14 h. After purification by flash chromatography (silica, pentane/EtOAc 4:1) the product is obtained as a yellow solid (203 mg, 0.85 mmol, 85%). **^{1}H NMR (300 MHz, d^6-DMSO):** 2.76 (s, 3H, CH_3), 3.85 (s, 3H, CH_3), 7.40-7.46 (m, 1H, CH_{ar}), 7.55-7.61 (m, 2H, CH_{ar}), 7.93 (d, *J* = 8.0 Hz, 1H, CH_{ar}), 8.09 (d, *J* = 8.7 Hz, 1H, CH_{ar}), 8.37 (d, *J* = 8.3 Hz, 1H, CH_{ar}), 12.57 (s, 1H, NH); **^{13}C NMR (75 MHz, d^6-DMSO):** 13.7 (CH_3), 50.5 (CH_3), 104.4 120.5, 120.6, 121.3, 121.5, 122.9, 123.9, 125.8, 128.4, 129.3, 129.7, 142.3 (C_{ar}), 165.6 (CO). **GC-MS R_t (method B):** 10.6 min, **(EI) m/z (%):** 240.0 (16), 239.0 (100), 224.0 (33), 208.0 (43), 207.0 (12), 206.0 (10), 180.0 (22), 179.0 (27), 178.0 (20), 153.0 (16), 152.0 (27), 151.0 (16).

Ethyl 2-methyl-indole-3-carboxylate (2u)[12]



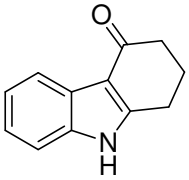
Following the general procedure, ethyl 3-anilinocrotonate (205 mg, 1.0 mmol) is stirred with $Pd(OAc)_2$ (11.2 mg, 0.05 mmol, 5 mol%), $Cu(OAc)_2$ (545 mg, 3.0 mmol, 3.0 eq), K_2CO_3 (415 mg, 3.0 mmol, 3.0 eq) and DMF (12 mL) under Argon in a preheated oil bath at 140 °C for 15 min. After standard workup and purification by flash column chromatography (silica, pentane/EtOAc 4:1) the product is obtained as a light brown solid. (144 mg, 0.71 mmol, 71 %). **R_F** (pentane/EtOAc 4:1): 0.34. **^{1}H NMR (300 MHz, $CDCl_3$):** 1.46 (t, *J* = 7.1 Hz, 3H, CH_3), 2.71 (s, 3H, CH_3), 4.43 (q, *J* = 7.1 Hz, 2H, CH_2), 7.17-7.31 (m, 3H, CH_{ar}), 8.12-8.15 (m, 1H, CH_{ar}), 8.69 (s, 1H, NH); **^{13}C NMR (75 MHz, $CDCl_3$):** 14.3 (CH_3), 14.7 (CH_3), 59.7 (CH_2), 104.6 (C_{ar}), 110.7 (CH_{ar}), 121.4 (CH_{ar}), 121.8 (CH_{ar}), 122.4 (CH_{ar}), 127.3 (C_{ar}), 134.7 (C_{ar}), 144.3 (C_{ar}), 166.4 (CO). **GC-MS, R_t (method B):** 9.1 min, **(EI) m/z (%):** 203 (100), 188 (5), 174 (37), 158 (80), 130 (24), 103 (9); **ESI-MS:** calculated $[C_{12}H_{13}NNaO_2]^+$: 226.0838, found: 226.0849. **ATR-FTIR [cm^{-1}]**: 3298, 2983, 1635, 1620, 1581, 1548, 1494, 1455, 1438, 1370, 1333, 1269, 1195, 1113, 1091, 1010, 783, 732, 689, 673, 580.

***tert*-butyl 2-methyl-indole-3-carboxylate (2v)**



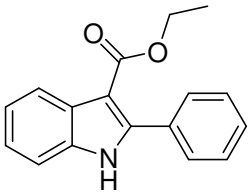
Following the general procedure, (*Z*)-*tert*-butyl-3-(phenylamino)but-2-enoate (233 mg, 1.00 mmol) is stirred with $Pd(OAc)_2$ (11.2 mg, 0.05 mmol, 5 mol%), $Cu(OAc)_2$ (545 mg, 3.0 mmol, 3.0 eq.), K_2CO_3 (415 mg, 3.0 mmol, 3.0 eq.) and DMF (12 mL) under Argon in a preheated oil bath at 140 °C for 15 min. After purification by flash column chromatography (silica, pentane/EtOAc 4:1) the product is obtained as an orange-brown solid. (183 mg, 0.79 mmol, 79%). **R_F** (pentane/EtOAc 4:1): 0.48. **^{1}H NMR (300 MHz, $CDCl_3$):** 1.67 (s, 9H, $C(CH_3)_3$), 2.71 (s, 3H, CH_3), 7.15-7.24 (m, 2H, CH_{ar}), 7.25-7.30 (m, 1H, CH_{ar}), 8.08-8.11 (m, 1H, CH_{ar}), 8.38 (s, 1H, NH); **^{13}C NMR (75 MHz, $CDCl_3$):** 14.4 (CH_3), 28.8 ($C(CH_3)_3$), 80.0 ($C(CH_3)_3$), 106.0 (C_{ar}), 110.6 (CH_{ar}), 121.4 (CH_{ar}), 121.6 (CH_{ar}), 122.3 (CH_{ar}), 127.3 (C_{ar}), 134.5 (C_{ar}), 143.6 (C_{ar}), 165.7 (CO). **GC-MS, R_t (method B):** 9.2 min, **(EI) m/z (%):** 231 (24), 175 (100), 158 (41), 130 (35); **ESI-MS:** calculated $[C_{14}H_{17}NNaO_2]^+$: 254.1151, found: 254.1139. **ATR-FTIR [cm^{-1}]:** 3292, 2978, 2934, 1652, 1582, 1548, 1458, 1439, 1388, 1366 1314, 1274, 1215, 1166, 1114, 1095, 1007, 847, 789, 741, 695, 583.

1,2-Dihydrocarbazol-4(3-H)-one (2w)[13]



Following the general procedure, the mixture is stirred in a preheated oil bath at 140 °C for 24 h. After purification by flash chromatography (silica, pentane/EtOAc 7:3) the product is obtained as a white solid (157 mg, 0.85 mmol, 85%). **R_F** (pentane/EtOAc 7:3): 0.23; **^{1}H-NMR (300 MHz, d^6-DMSO):** 2.08-2.14 (m, 2H, CH_2), 2.42 (t, *J* = 6.6 Hz, 2H, CH_2), 2.95 (t, *J* = 6.2 Hz, 2HH, CH_2), 7.12-7.19 (m, 2H, CH_{ar}), 7.39-7.42 (m, 1H, CH_{ar}), 7.97-7.99 (m, 1H, CH_{ar}), 11.85 (s, 1H, NH); **^{13}C-NMR (75 MHz, d^6-DMSO):** 22.7 (CH_2), 23.4 (CH_2), 37.8 (CH_2), 111.5 (CH_{ar}), 111.8 (C_{ar}), 120.2 (CH_{ar}), 121.5 (C_{ar}), 122.4 (CH_{ar}), 124.6 (C_{ar}), 135.9 (C_{ar}), 152.3 (C_{ar}), 192.9 (CO); **GC-MS R_t (method B):** 9.9 min, **(EI) m/z (%):** 186.1 (13), 185.0 (100), 158.0 (10), 157.0 (100), 129.0 (67), 128.0 (16), 102.0 (15).

Ethyl 2-phenyl-1H-indole-3-carboxylate (2x)[14]



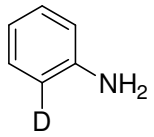
(*Z*)-ethyl 3-phenyl-3-(phenylamino)acrylate (267 mg, 1.00 mmol), $Pd(OAc)_2$ (22.4 mg, 0.10 mmol, 0.10 eq.), $Cu(OAc)_2$ (545 mg, 3.0 mmol, 3.0 eq.) and K_2CO_3 (415 mg, 3.0 mmol, 3.0 eq.) were weighed into a flame-dried microwave reaction vessel and suspended in DMF (12 mL). The reaction tube is closed, a temperature sensor is installed and the reaction mixture is exposed to microwave irradiation to maintain the temperature at 180 °C (short pulses of 300-850 W). Following standard work-up of the general procedure, an orange oil is obtained. After purification by flash column chromatography (silica, pentane/EtOAc 98/2-0/100) the product is obtained as a yellow solid. (182 mg, 0.68 mmol, 68 %). **R_F** (pentane/EtOAc 4:1): 0.58; **^{1}H NMR (300 MHz, $CDCl_3$):** 1.32 (t, *J* = 7.1 Hz, 3H, CH_3), 4.29 (q, *J* = 7.1 Hz, 2H, CH_2), 7.24-7.42 (m, 6H, CH_{ar}), 7.62-7.65 (m, 2H, CH_{ar}), 8.23-8.26 (m, 1H, CH_{ar}), 8.74 (s, 1H, NH); **^{13}C NMR (75 MHz, $CDCl_3$):** 14.4 (CH_3), 59.8 (CH_2), 104.7 (C_{ar}), 111.2 (CH_{ar}), 122.1 (CH_{ar}), 122.2 (CH_{ar}), 123.3 (CH_{ar}), 127.7(C_{ar}), 128.2 (CH_{ar}), 129.3 (CH_{ar}), 129.7 (CH_{ar}), 132.1 (C_{ar}), 135.3 (C_{ar}), 144.7 (C_{ar}), 165.6 (CO); **GC/MS, R_t (method A):** 15.7 min, **(EI) m/z (%):** 265 (95), 237 (13), 220 (100), 193 (45), 165 (31), 95 (7); **ESI-MS:** calculated $[C_{17}H_{15}NNaO_2]^+$: 288.0995, found: 288.0985; **ATR-FTIR [cm^{-1}]:** 3248, 2981, 1659, 1544, 1488, 1451, 1428, 1375, 1333, 1269, 1210, 1170, 1126, 1045, 1027, 934, 871, 834, 788, 765, 742, 722, 687, 609.

6. Mechanistic Experiments

a. Determination of Intramolecular Kinetic Isotope Effect

Synthesis of deuterated substrates

2-Deuterio-aniline[15]



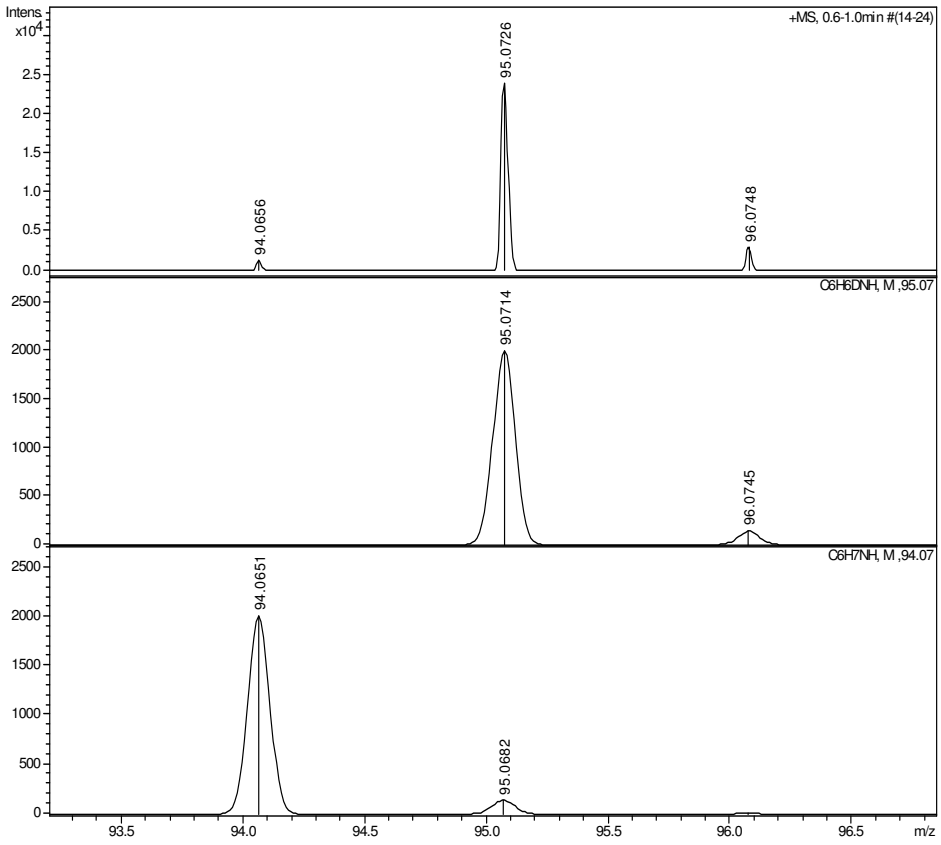
Following a modified procedure by Witkop et al.,[16] 2-deuterio-aniline is synthesised by catalytic hydrogenolysis of 2-bromoaniline. 2-Bromoaniline (4.30 g, 25.0 mmol) is dissolved in diethylether (25 mL) and washed with deuterium oxide (3 x 15 mL) to replace most of the amine protons by deuterium. The ethereal solution is dried ($MgSO_4$) and concentrated. The yellowish liquid is dissolved in dry THF (25 mL) in a 100 mL-two-necked round-bottom flask equipped with a tee-branch connected to a vacuo/Argon line and to a Schlenk flask. Dry triethylamine (2.78 g, 3.82 mL, 27.5 mmol, 1.10 eq.), 10% Pd/C (215 mg, 5 w% relative to bromoaniline) and deuterium oxide (1.38 g, 1.25 mL, 68.7 mmol, 2.75 eq.) were added to the solution with stirring. Deuterium gas is generated in the separate Schlenk flask connected to the reaction flask by slow addition of deuterium oxide (approx. 8 mL) with a syringe through a septum to a suspension of sodium (approx. 5 g) in dry THF (120 mL). The reaction flask is evacuated and backfilled with the generated deuterium gas five times and stirred at rt under D_2 atmosphere for 10 h. Since reaction control by GCMS analysis still showed remaining 2-bromoaniline, the generation and purging with D_2 is repeated and the mixture is stirred at rt for further 5 h. The reaction mixture is diluted with diethylether (50 mL), filtered through Celite and concentrated to give a brown liquid. The crude product is solved in diethylether (20 mL), washed with water (5 mL) to replace most of the nitrogen-bound deuterium by protons, dried ($MgSO_4$) and concentrated. Bulb-to-bulb distillation (30 mbar, 85-95 °C) yielded the desired product as a clear and colorless liquid (1.85 g, 19.7 mmol, 79%). ^{1}H NMR and ESI-MS showed deuterium incorporation > 95%. **^{1}H NMR (500 MHz, $CDCl_3$):** 3.65 (s, 2H, NH_2), 6.72 (dd, 1H, J = 8.4 Hz, J = 1.1 Hz, 6-CH), 6.82 (dt, 1H, J = 7.4 Hz, J = 1.1 Hz, 4-CH), 7.20-7.24 (m, 2H, 3-CH, 5-CH); **^{13}C NMR (125 MHz, $CDCl_3$):** 114.8 (t, J_{CD} = 23.8 Hz, 2-CD), 115.1 (6-CH), 118.5 (4-CH), 129.2 (CH_{ar}), 129.3 (CH_{ar}), 146.4 (1-CNH_2); **^{2}H NMR (77 MHz, $CHCl_3$):** 6.76 (s), 3.65 (s). **GC/MS, R_t (method B):** 5.5 min; **(EI) m/z (%):** 94 (100), 67 (37) 52 (12), 39 (18); **ESI-MS:** calculated $[C_6H_7DN]^+$: 95.0714, found: 95.0726; **ATR-FTIR [cm^{-1}]:** 3356, 1620, 1596, 1482, 1455, 1307, 1264, 762.

ESI-MS spectra of 2-deuterio-aniline

Experiment:

Simulation of C_6H_6DNH:

Simulation of C_6H_7NH:



Measured:

#	m/z		Res.	S/N	I	FWHM
2	94.0656	3875	45.5	1314	0.0243	
3	95.0726	2892	825.7	23864	0.0329	
4	96.0748	3869	106.1	3066	0.0248	

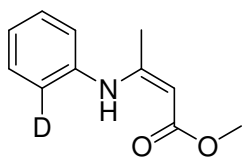
simulated for C_6H_6DNH:

#	m/z		Res.	S/N	I	FWHM
1	95.0714	951			2000	0.1000
2	96.0745	961			139	0.1000
3	97.0774	971			4	0.1000

simulated for C_6H_7NH:

#	m/z		Res.	S/N	I	FWHM
1	94.0651	941			2000	0.1000
2	95.0682	951			139	0.1000
3	96.0712	961			4	0.1000

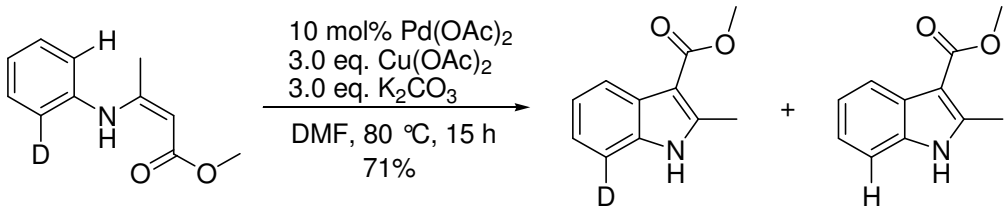
(*Z*)-Methyl 3-(2'-deuterio-phenylamino)but-2-enoate



Following a modified procedure by Wang et al.,[4] 2-deuterio-aniline (492 mg, 5.23 mmol, 1.00 eq.) and methyl acetoacetate (646 mg, 600 µL, 5.56 mmol, 1.06 eq.) are stirred with $InBr_3$ (17.7 mg, 0.05 mmol, 1 mol%) at rt for 3 h. The reaction mixture is loaded directly onto a column with silica pretreated with pentane/EtOAc/NEt_3 19/1/0.2 and purified by rapid column chromatography to yield the desired product as a white solid (879 mg, 4.57 mmol, 87%). **^{1}H**

NMR (500 MHz, $CDCl_3$): 1.99 (s, 3H, CH_3), 3.68 (s, 3H, CH_3), 4.70 (s, 1H, CH), 7.08 (d, 1H, J = 7.9 Hz, CH_{ar}), 7.15 (dt, 1H, J = 7.4 Hz, J = 1.0 Hz, CH_{ar}), 7.30-7.34 (m, 2H, CH_{ar}); **^{13}C NMR (125 MHz, $CDCl_3$):** 20.4 (CH_3), 50.4 (CH_3), 85.7 (CH), 124.3 (t, J_{CD} = 24.4 Hz, CD), 124.5 (CH_{ar}), 125.1 (CH_{ar}), 129.1 (CH_{ar}), 129.2 (CH_{ar}), 139.3 (C_{ar}), 159.2 (C_q) 170.8 (CO); **^{2}H NMR (77 MHz, $CHCl_3$):** 7.14 (s); **GC/MS, R_t (method A):** 11.2 min; **(EI) m/z (%):** 192 (75), 177 (8), 161 (63), 145 (48), 131 (77), 119 (100), 104 (4), 94 (13), 78 (69), 66 (19), 52 (15), 39 (11); **ESI-MS:** calculated $[C_{11}H_{12}DNNaO_2]^+$: 215.0901, found: 215.0894; **ATR-FTIR [cm^{-1}]:** 3251, 2995, 1645, 1602, 1585, 1494, 1470, 1434, 1383, 1357, 1252, 1190, 1160, 1117, 1056, 1007, 989, 914, 855, 824, 779, 666.

Determination of Intramolecular Kinetic Isotope Effect (KIE)



Following the general procedure, (*Z*)-Methyl 3-(2'-deuterio-phenylamino)but-2-enoate (96 mg, 0.50 mmol) is stirred with $Pd(OAc)_2$ (11.2 mg, 0.05 mmol, 10 mol%), $Cu(OAc)_2$ (272 mg, 1.5 mmol, 3.0 eq.), K_2CO_3 (207 mg, 1.5 mmol, 3.0 eq.) and DMF (6 mL) under Argon in a preheated oil bath at 80 °C for 15 h. The mixture was diluted with EtOAc (20 mL), filtered through a short pad of silica, the red-brown solid is washed with EtOAc (3 x 20 mL) and the combined filtrates were concentrated. After purification by flash column chromatography (silica, pentane/EtOAc 4:1) the product is obtained as a light brown solid. (67 mg, 0.35 mmol, 71 %). **R_F** (pentane/EtOAc 4:1): 0.32. **^{1}H NMR (600 MHz, C_6D_6):** 2.36 (s, 3H, CH_3), 3.64 (s, 3H, CH_3), 6.78 (s, 1H, NH), 6.96 (d, J = 8.1 Hz, 0.17H, 7-CH), 7.19-7.21 (m, 1H, CH_{ar}), 7.30 (t, J = 8.1 Hz, 1H, CH_{ar}), 8.49 (d, J = 8.0 Hz, CH_{ar}); **GC-MS, R_t (method A):** 12.8 min, **(EI) m/z (%):** 191 (14), 190 (78), 189 (16), 175 (12), 159 (100), 131 (23), 103 (13), 78 (12); **ESI-MS:** calculated $[C_{11}H_{11}NNaO_2]^+$: 212.0682, found: 212.0681; calculated $[C_{11}H_{10}DNNaO_2]^+$: 213.0745, found: 213.0744.

Intramolecular KIE determined by ESI-MS: k_H/k_D = 4.54.

Intramolecular KIE determined by ^{1}H NMR: k_H/k_D = 4.56.

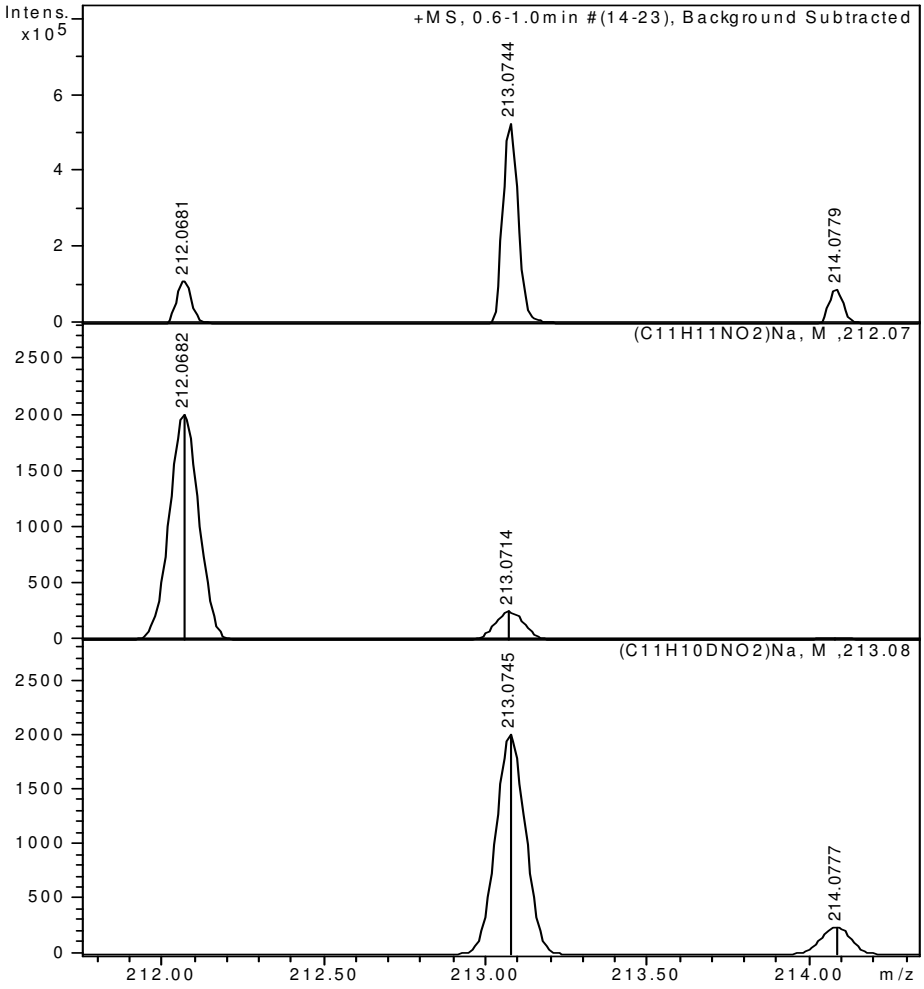
→ Averaged Intramolecular KIE: k_H/k_D = 4.6.

ESI-MS spectra of Intramolecular Kinetic Isotope Effect:

Experiment:

Simulation of $C_{11}H_{11}NNaO_2$:

Simulation of $C_{11}H_{10}DNNaO_2$



measured:

#	m/z		Res.	S/N		I		FWHM	Area
3	212.0681	4326	1762.7		112520	0.0490	6021		
4	213.0744	4164	8267.4		525224	0.0512	28950		
5	214.0779	4423	1428.0		90291		0.0484	4759	

simulated for $C_{11}H_{11}NNaO_2$:

#	m/z		Res.	S/N		I		FWHM	Area
1	212.0682	2121			2000		0.1000	0	
2	213.0714	2131			249		0.1000	0	
3	214.0738	2141			22		0.1000	0	

simulated for $C_{11}H_{10}DNNaO_2$:

#	m/z		Res.	S/N		I		FWHM	Area
1	213.0745	2131			2000		0.1000	0	
2	214.0777	2141			249		0.1000	0	
3	215.0801	2151			22		0.1000	0	

Determination of Intramolecular Kinetic Isotope Effect by ESI-MS:

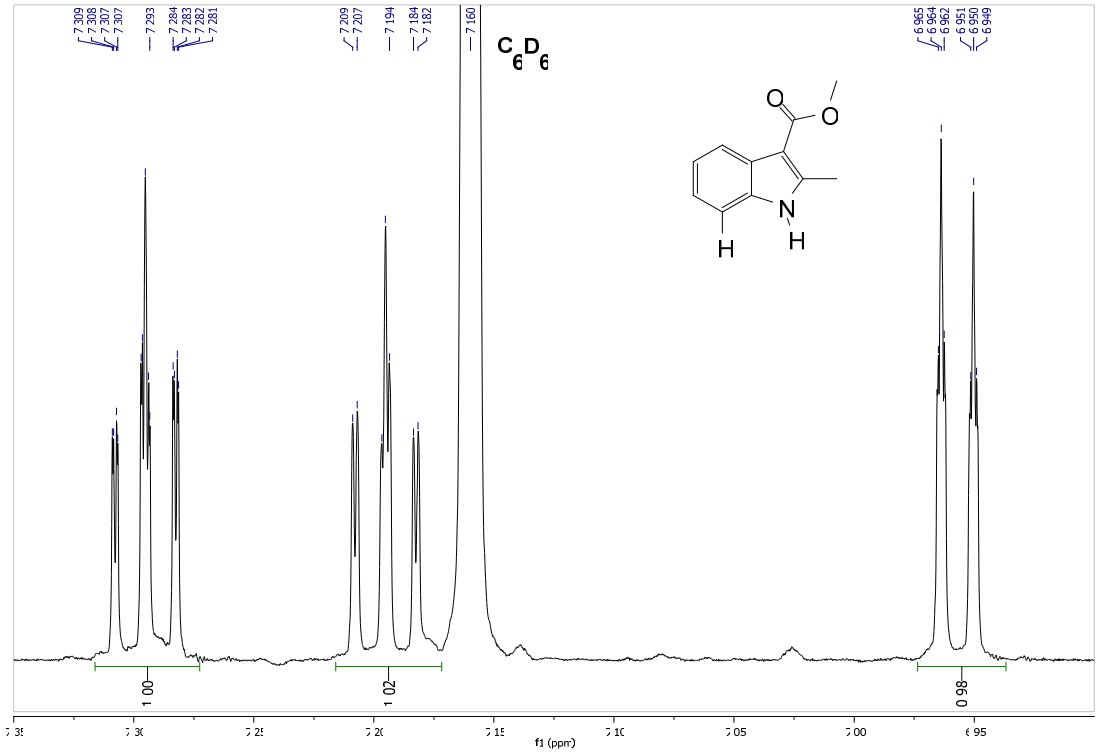
calculated for non-deuterated product: $[C_{11}H_{11}NNaO_2]^+$: 212.0682, found: 212.0681 (intensity: 112520).

calculated for deuterated product: $[C_{11}H_{10}DNNaO_2]^+$: 213.0745, found: 213.0744 (intensity: 525224, corrected intensity (reduced by carbon-isotope signal of $C_{11}H_{11}NNaO_2$): 511215.

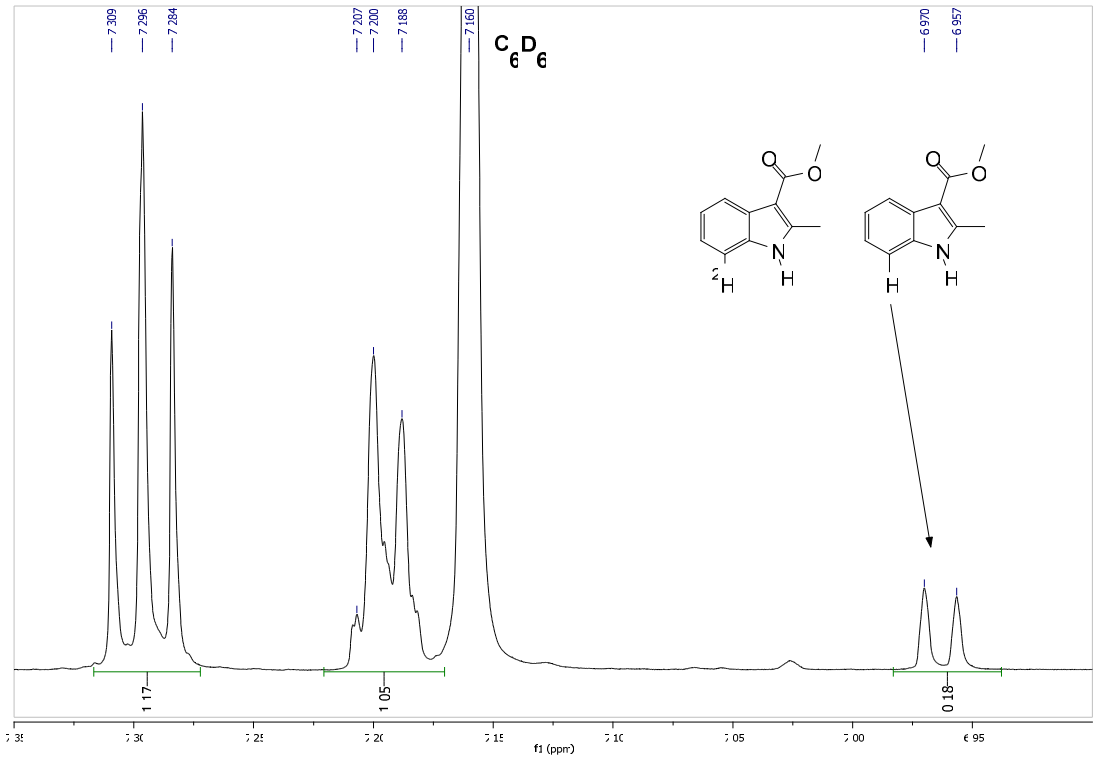
→ ESI-MS-ratio: $[C_{11}H_{11}NNaO_2]^+/[C_{11}H_{10}DNNaO_2]^+ = k_H/k_D = 4.54$.

Determination of Intramolecular Kinetic Isotope Effect by ^{1}H NMR:

^{1}H NMR of the product obtained from (*Z*)-Methyl 3-(phenylamino)-but-2-enoate

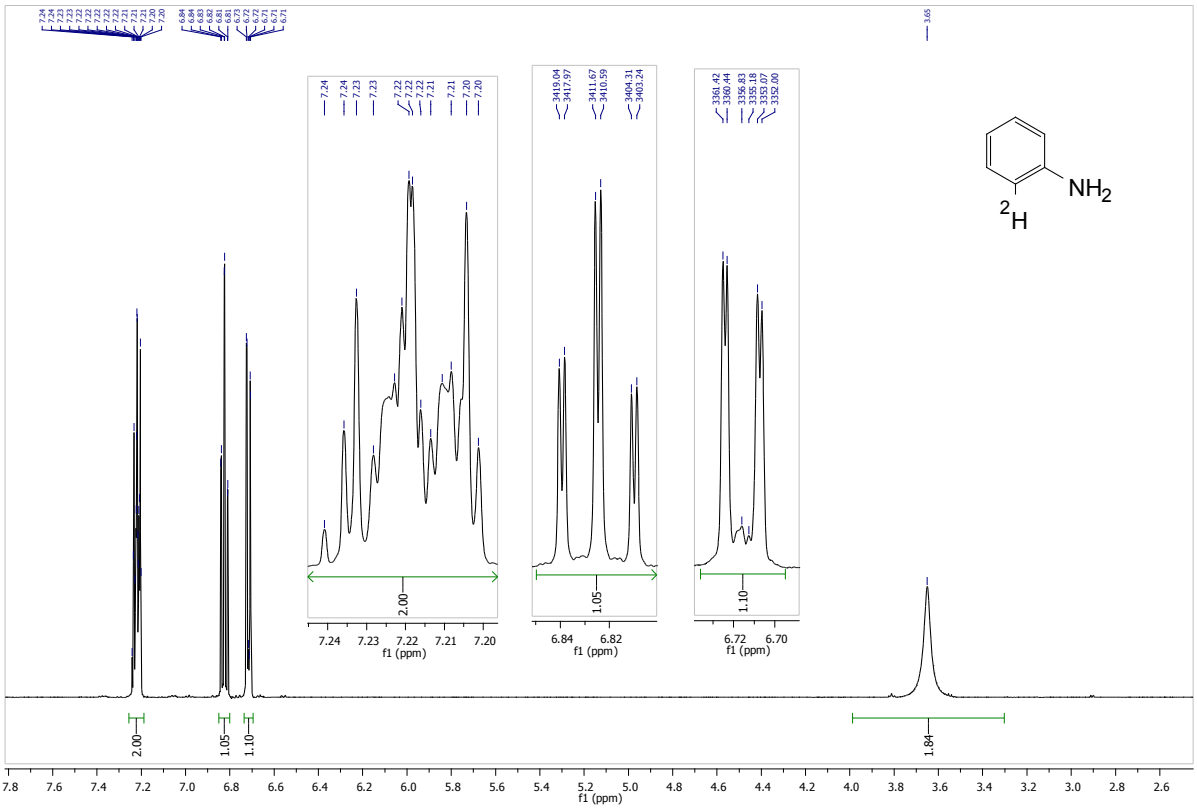


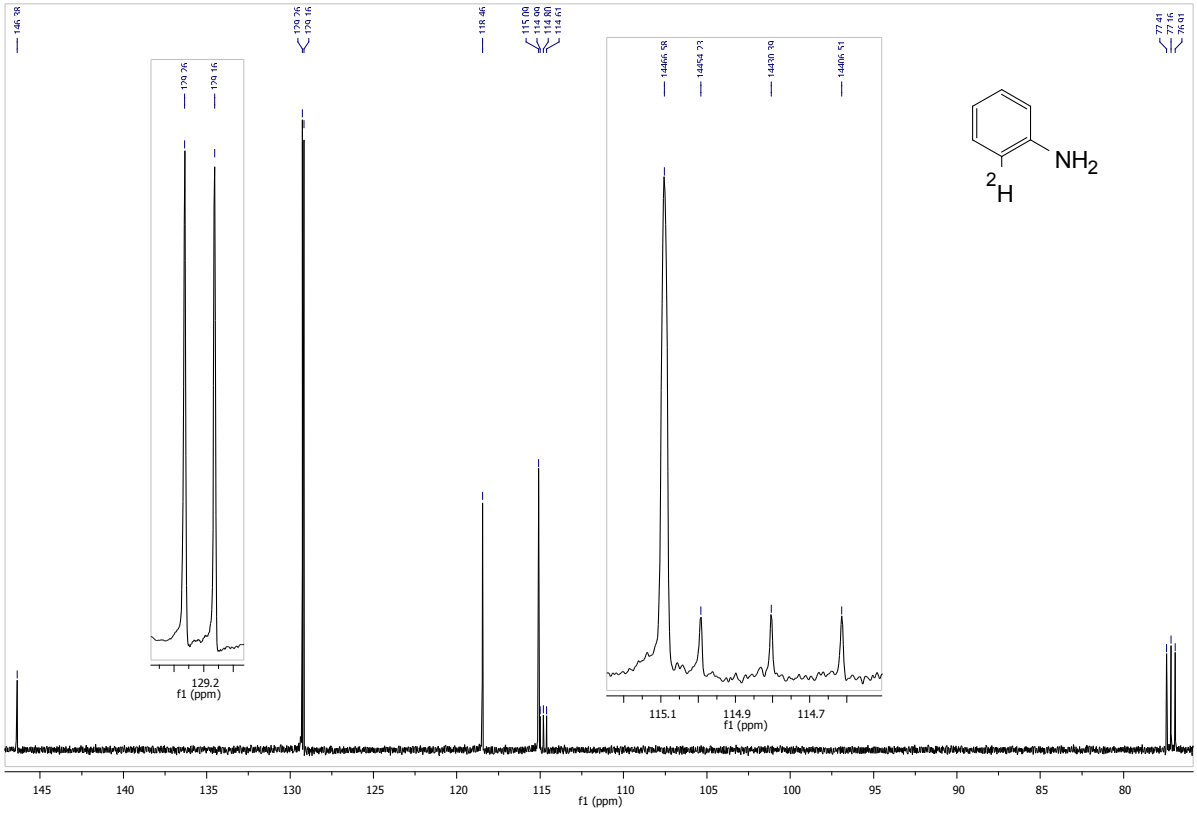
^{1}H NMR of the product obtained from (*Z*)-Methyl 3-(2'-deuterio-phenylamino)-but-2-enoate

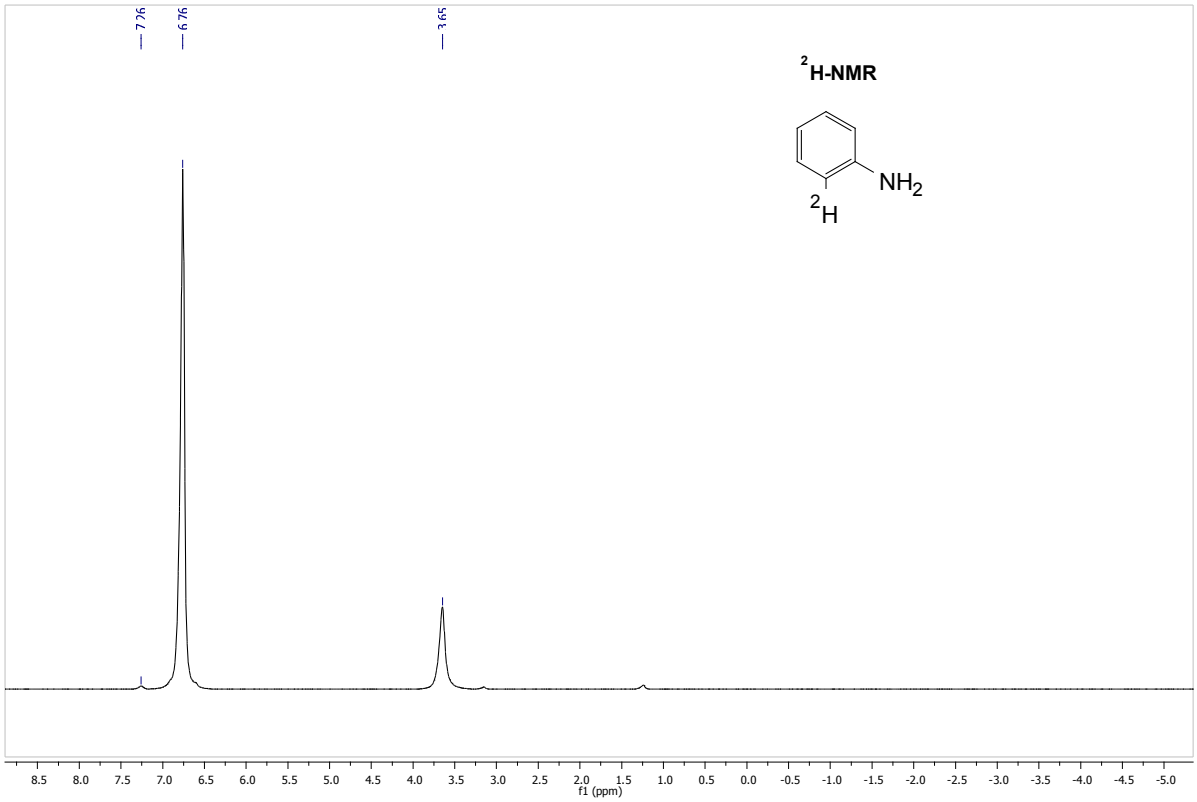


→ $k_H/k_D = (1.00-0.18)/0.18 = 4.56$

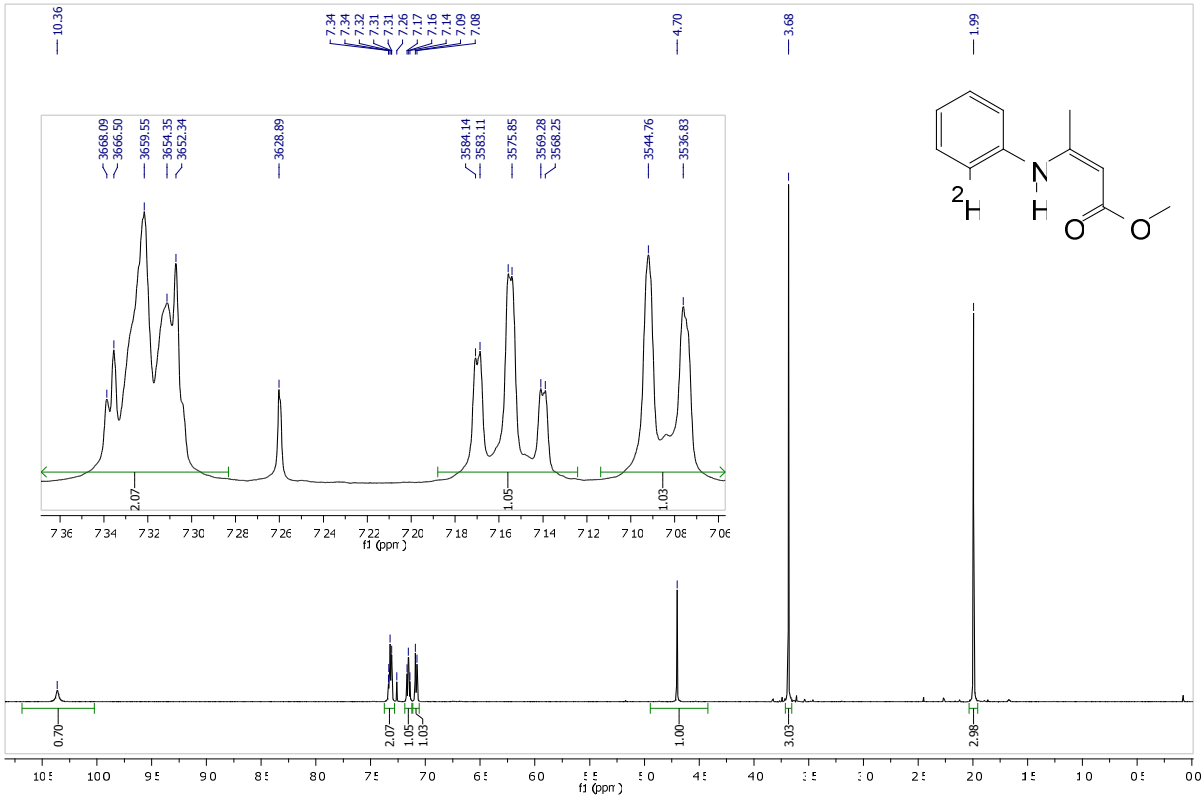
2-Deuterio-aniline

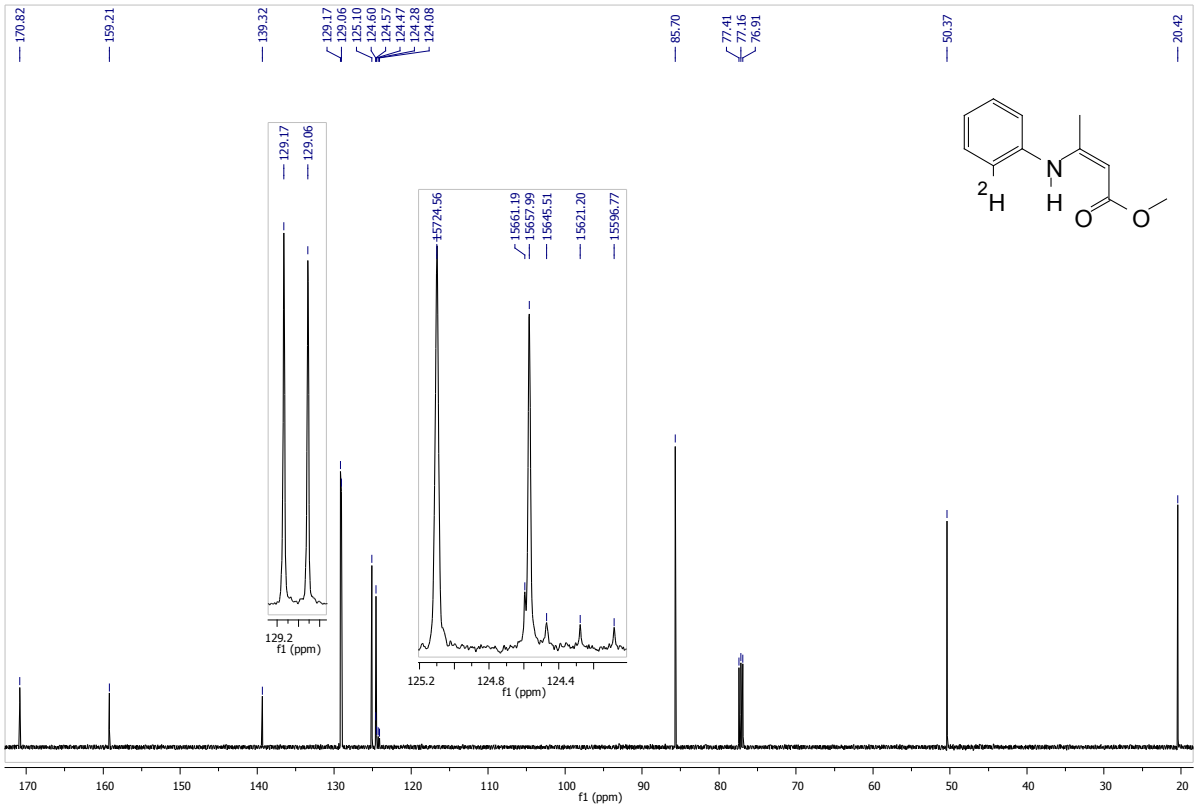






Methyl 3-(2'-deuterio-phenylamino)but-2-enoate

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159.21
139.32
129.17
129.06
125.10
124.60
124.57
124.47
124.28
124.08
85.70
77.41
77.16
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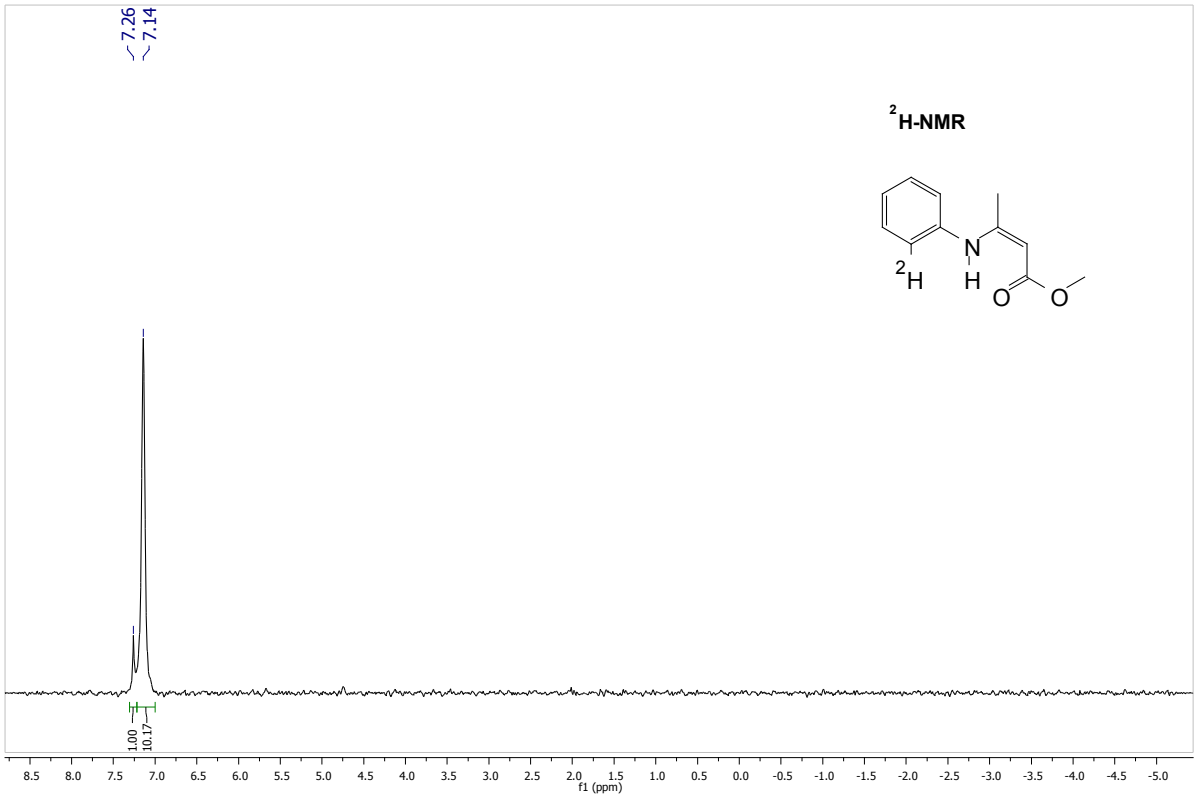
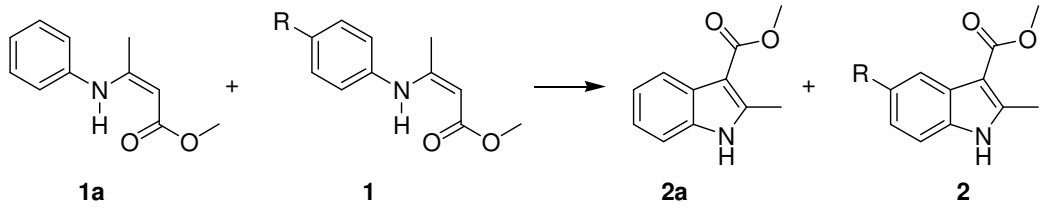
f1 (ppm)
125.2
124.8
124.4
f1 (ppm)
f1 (ppm)


7.26
7.14
1.00
10.17
f1 (ppm)

^{2}H-NMR

b. Competition Experiments

General Procedure for the Competition Experiments



47.8 mg (0.25 mmol) (*Z*)-Methyl 3-(phenylamino)-but-2-enoate as the standard substrate **1a** and 0.25 mmol of a para-substituted competing substrate (**1**, R = Me, Cl, OMe) were weighed into a flame-dried reaction flask containing $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 5 mol%), $Cu(OAc)_2$ (273 mg, 1.5 mmol, 3.00 eq.) and K_2CO_3 (207 mg, 1.5 mmol, 3.0 eq). The flask is evacuated and backfilled with Argon three times, DMF (6 mL) and *n*-decane as an internal standard (25 µL) were added under Argon. The mixture is placed into a preheated oil bath and stirred at 80 °C under Argon. Every 10 minutes, an aliquot of 60 µl from the reaction solution is taken under standard Schlenk technique with sufficient Argon flow without cooling of the solution. The aliquot is diluted with CH_2Cl_2 and filtered over a short pad of silica with additional CH_2Cl_2 (2 mL). The sample is analysed by GC and GCMS as ratios of substrates and products to the internal standard *n*-decane. After the indicated time period, the reaction flask is cooled to rt by running tab water, diluted with diethylether (20 mL), filtered through a short pad of silica and sea sand, pretreated with diethylether. The solid residue is washed thoroughly with diethylether (2 x 20 mL), the combined filtrates were evaporated to dryness and analyzed by ^1H NMR to confirm the GC analysis.

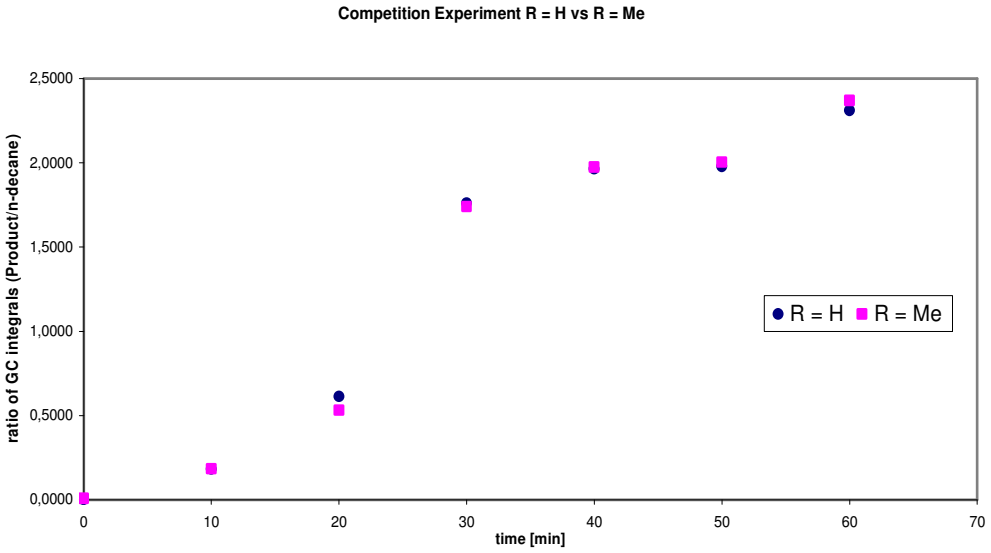


Figure 6.1: Product formation versus time for **2a** (R = H) and **2d** (R = Me)

R=H vs. R=Me

Time (min)	Standard	Substrate1 (R_{para}=H)	Substrate2 (R_{para}=Me)	Product1 (R_{para}=H)	Product2 (R_{para}=Me)	Substrate1/ Standard	Substrate2/ Standard	Product1/ Standard	Product2/ Standard
0	23,631	37,270	35,202	0,071	0,184	1,5772	1,4897	0,0030	0,0078
10	21,222	34,487	27,476	3,849	3,915	1,6251	1,2947	0,1814	0,1845
20	22,138	24,773	23,863	13,591	11,783	1,1190	1,0779	0,6139	0,5323
30	17,704	8,842	9,955	31,169	30,819	0,4994	0,5623	1,7606	1,7408
40	17,837	5,876	5,876	35,036	35,218	0,3294	0,3294	1,9642	1,9744
50	17,743	5,217	5,377	35,123	35,553	0,2940	0,3030	1,9795	2,0038
60	15,589	4,315	4,546	36,034	36,946	0,2768	0,2916	2,3115	2,3700

Table 6.1: GC-integrals for **2a** (R = H) and **2d** (R = Me)

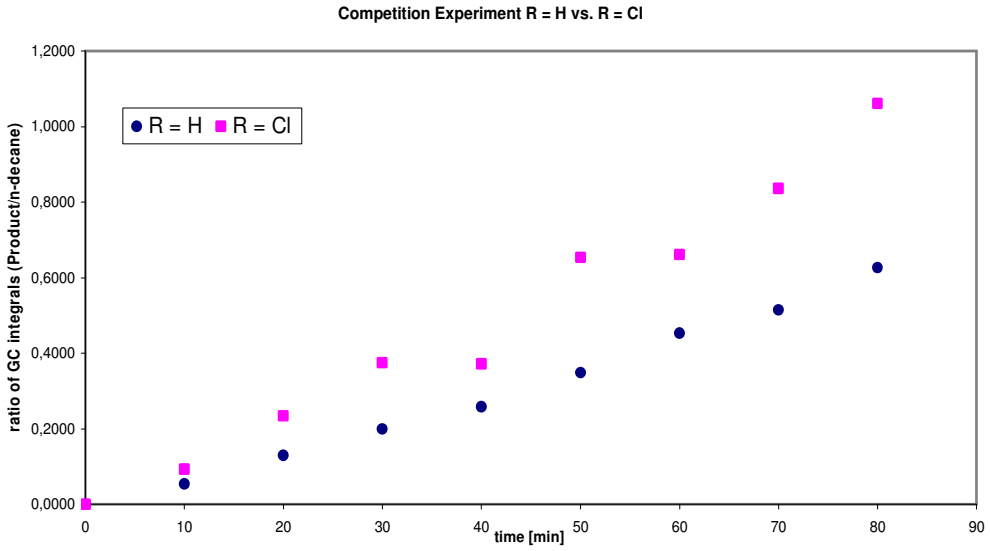


Figure 6.2: Product formation versus time for **2a** (R = H) and **2n** (R = Cl)

R=H vs. R=Cl

Time (min)	Standard	Substrate1 (R_{para}=H)	Substrate2 (R_{para}=Cl)	Product1 (R_{para}=H)	Product2 (R_{para}=Cl)	Substrate1/ Standard	Substrate2/ Standard	Product1/ Standard	Product2/ Standard
0	22,035	40,483	37,323	0,000	0,000	1,8372	1,6938	0,0000	0,0000
10	21,607	36,235	33,579	1,166	2,011	1,6770	1,5541	0,0540	0,0931
20	23,166	35,428	29,022	2,993	5,432	1,5293	1,2528	0,1292	0,2345
30	22,485	30,442	25,791	4,491	8,433	1,3539	1,1470	0,1997	0,3751
40	25,484	28,749	25,345	6,591	9,488	1,1281	0,9945	0,2586	0,3723
50	18,889	25,028	19,286	6,595	12,350	1,3250	1,0210	0,3491	0,6538
60	22,722	27,465	20,590	10,287	15,012	1,2087	0,9062	0,4527	0,6607
70	22,619	25,473	19,607	11,634	18,910	1,1262	0,8668	0,5143	0,8360
80	21,370	21,187	16,437	13,397	22,669	0,9914	0,7692	0,6269	1,0608

Table 6.2: GC-integrals for **2a** (R = H) and **2n** (R = Cl)

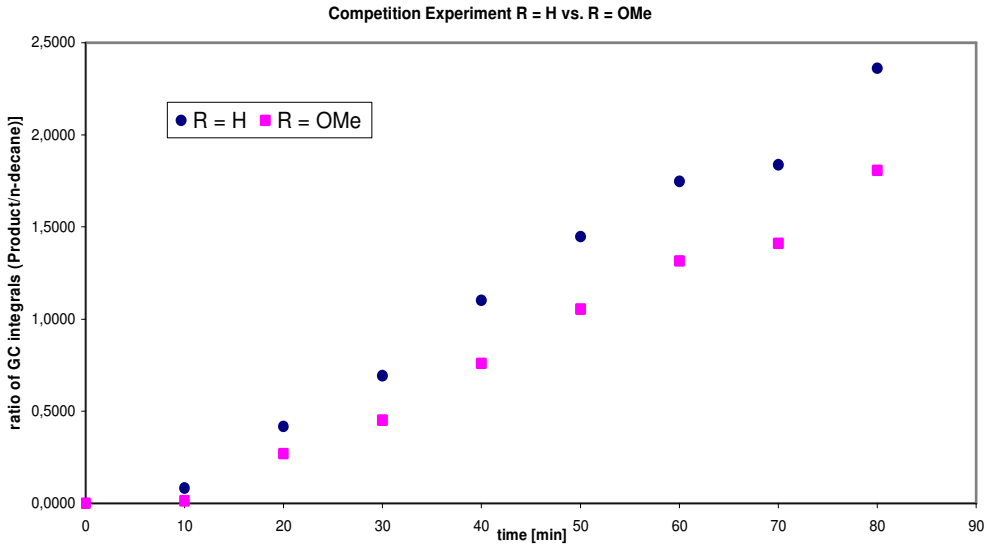


Figure 6.3: Product formation versus time for **2a** (R = H) and **2h** (R = OMe)

R=H vs. R=OMe

Time (min)	Standard	Substrate1 (R_{para}=H)	Substrate2 (R_{para}=OMe)	Product1 (R_{para}=H)	Product2 (R_{para}=OMe)	Substrate1/ Standard	Substrate2/ Standard	Product1/ Standard	Product2/ Standard
0	25,588	41,430	30,414	0,000	0,000	1,6191	1,1886	0,0000	0,0000
10	26,851	40,251	25,780	2,190	0,376	1,4991	0,9601	0,0816	0,0140
20	24,839	31,935	18,189	10,340	6,677	1,2857	0,7323	0,4163	0,2688
30	19,789	20,212	14,783	13,686	8,928	1,0214	0,7470	0,6916	0,4512
40	22,470	20,842	12,545	24,717	17,065	0,9275	0,5583	1,1000	0,7595
50	19,762	14,006	10,459	28,603	20,800	0,7087	0,5292	1,4474	1,0525
60	19,442	10,594	7,193	33,961	25,567	0,5449	0,3700	1,7468	1,3150
70	18,230	8,260	5,239	33,494	25,728	0,4531	0,2874	1,8373	1,4113
80	16,919	6,045	4,529	39,934	30,550	0,3573	0,2677	2,3603	1,8057

Table 6.3: GC-integrals for **2a** (R = H) and **2h** (R = OMe)

As shown in Figures 6.1-3, there is no big difference in the rate of product formation of the standard substrate **1a** (R = H) and the *para*-methyl-substituted enaminecarboxylate **1d**, whereas the electron-withdrawing substituted substrate **1n** (R = Cl) seems to react faster and the electron-donating substituted substrate **1h** (R = OMe) seems to react slower compared to the standard substrate. Deviations from expected curve progression (linearity for very low conversions, exponential in principle) are presumably caused by inhomogeneties of the oil bath temperature and/or inadequate stirring.

These results were confirmed by proton NMR of the crude products (see below).

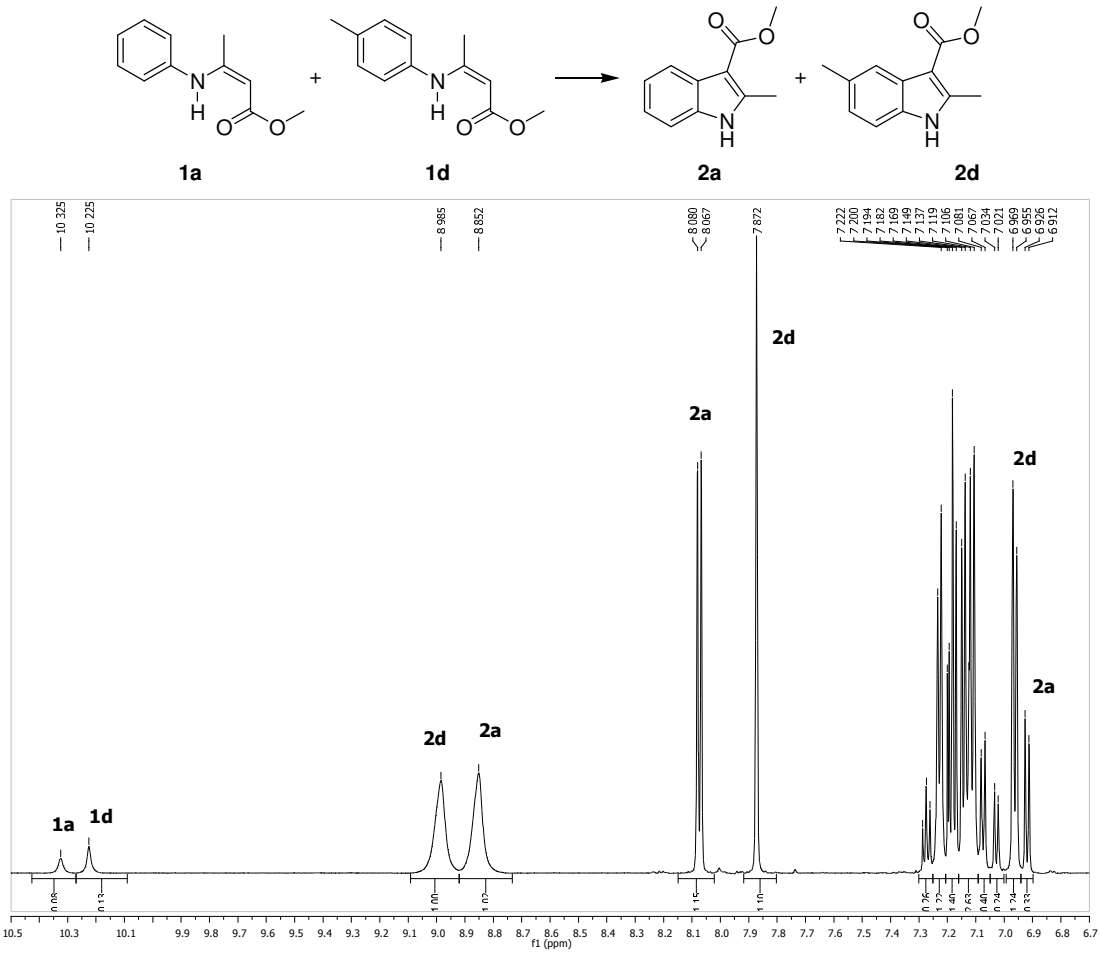


Fig. 6.4: Downfield-region of the ^{1}H NMR from the mixture of **1a**, **1d**, **2a** and **2d**

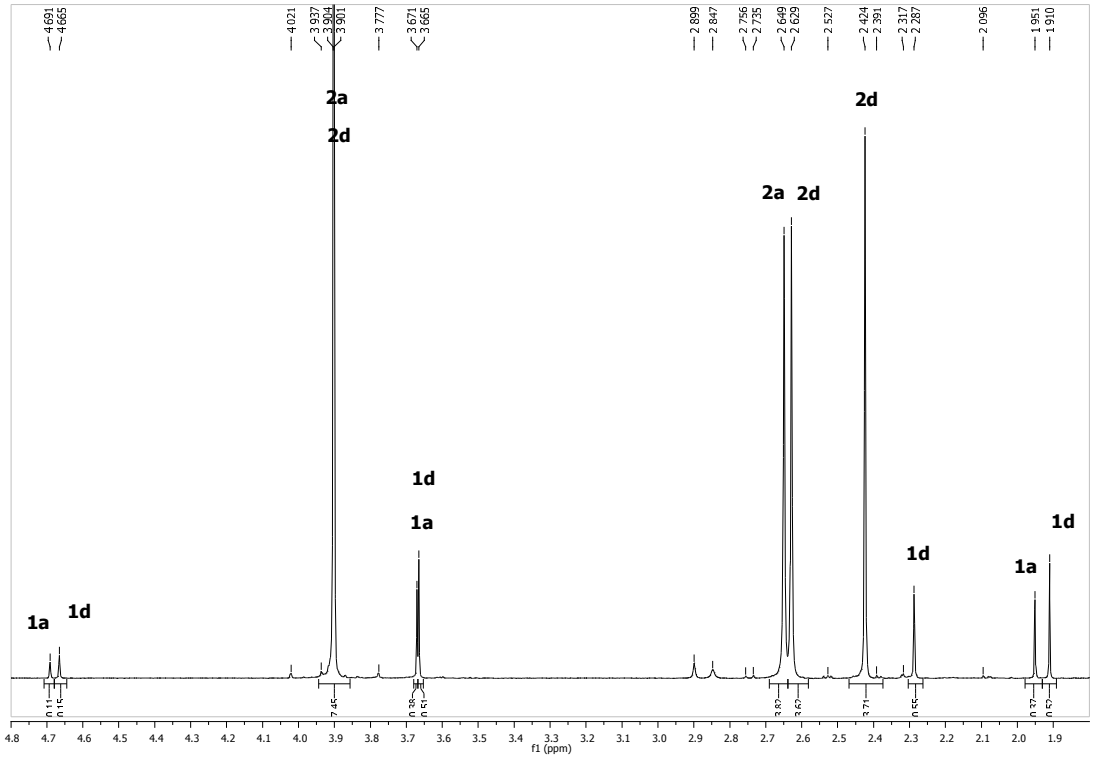


Fig. 6.5: Upfield-region of the ^{1}H NMR from the mixture of **1a**, **1d**, **2a** and **2d**

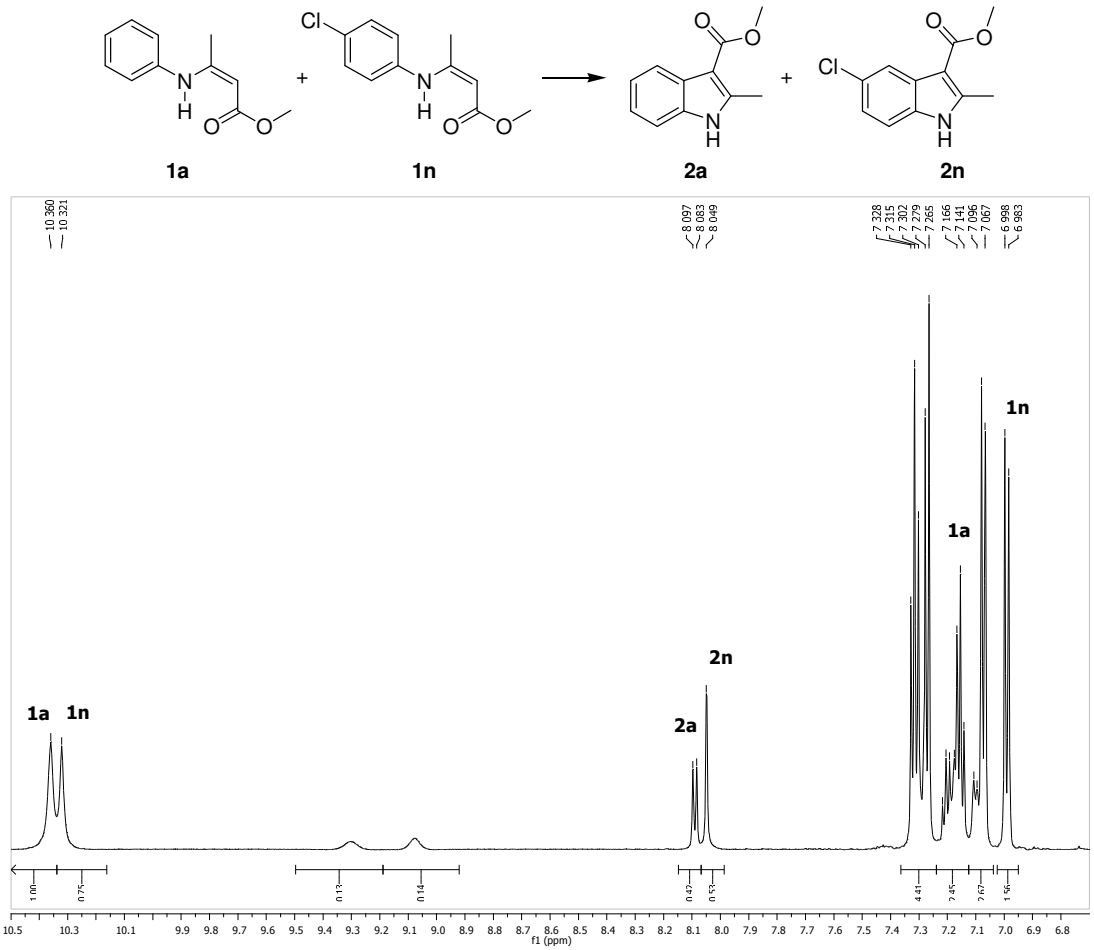


Fig. 6.6: Downfield-region of the ^{1}H NMR from the mixture of **1a**, **1n**, **2a** and **2n**

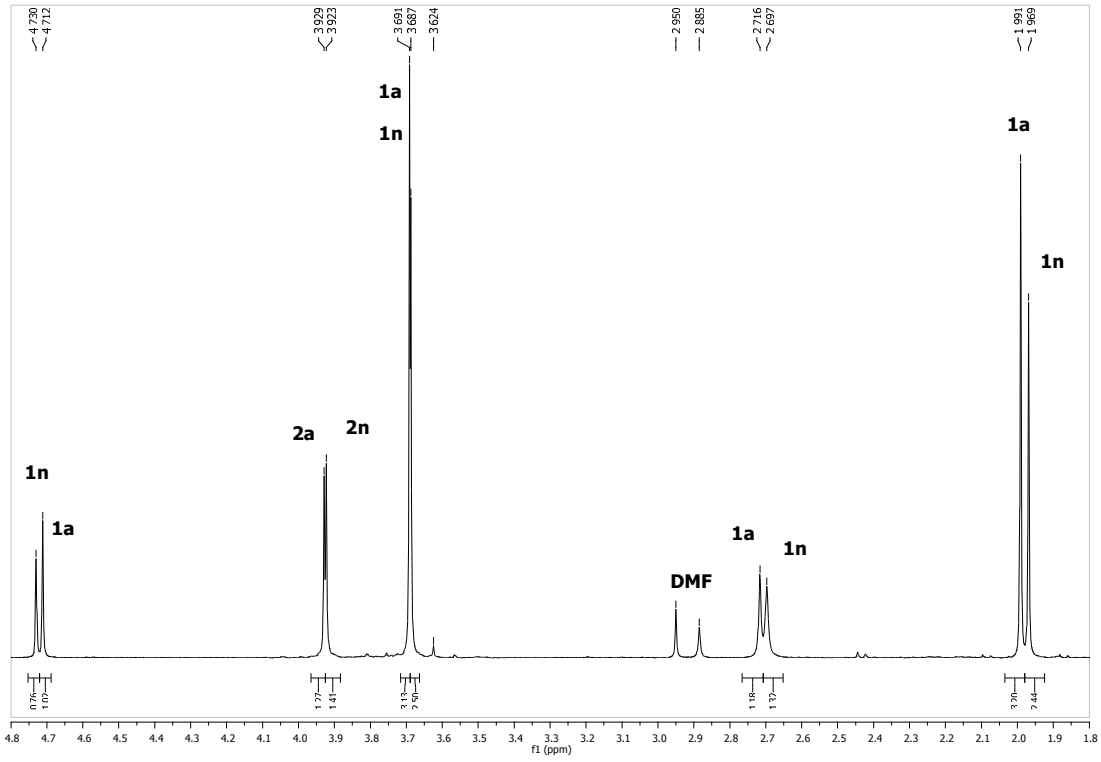


Fig. 6.7: Upfield-region of the ^{1}H NMR from the mixture of **1a**, **1n**, **2a** and **2n**

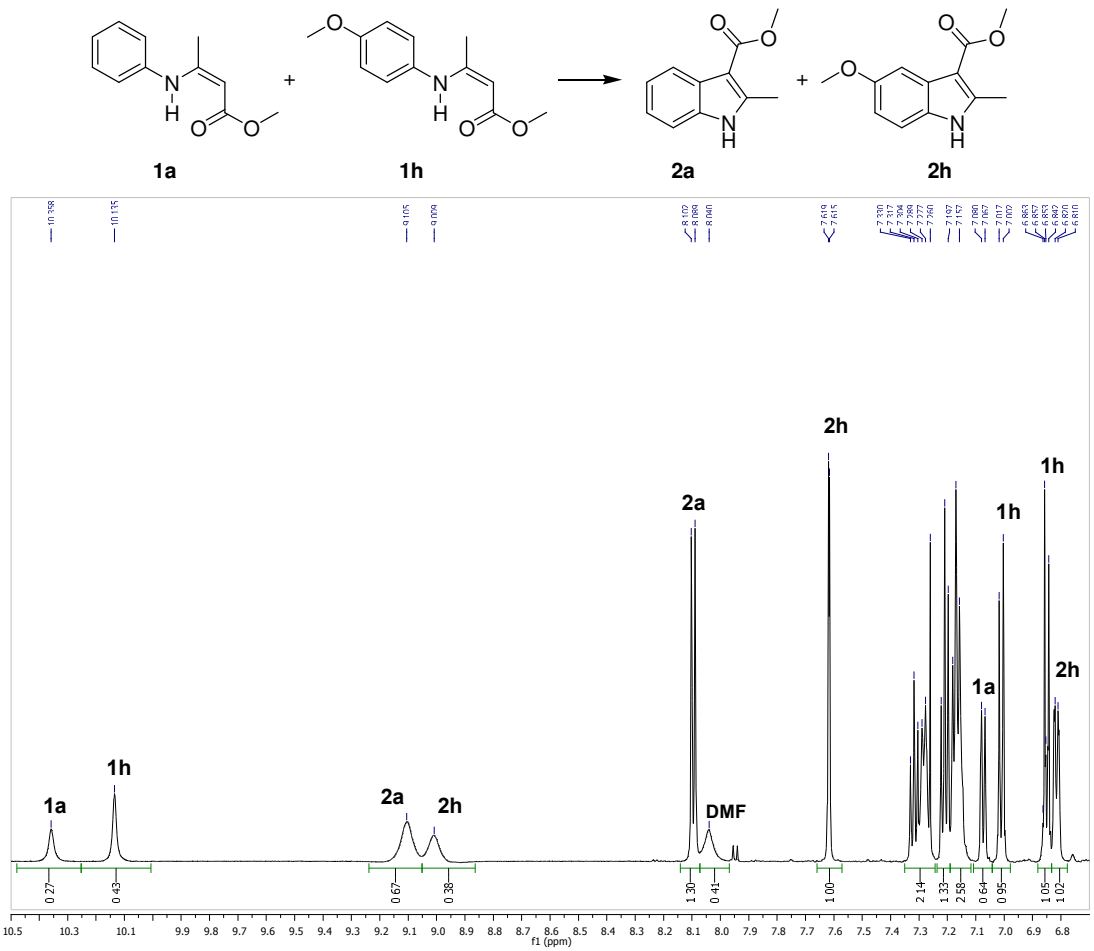


Fig. 6.8: Downfield-region of the ^{1}H NMR from the mixture of **1a**, **1h**, **2a** and **2h**

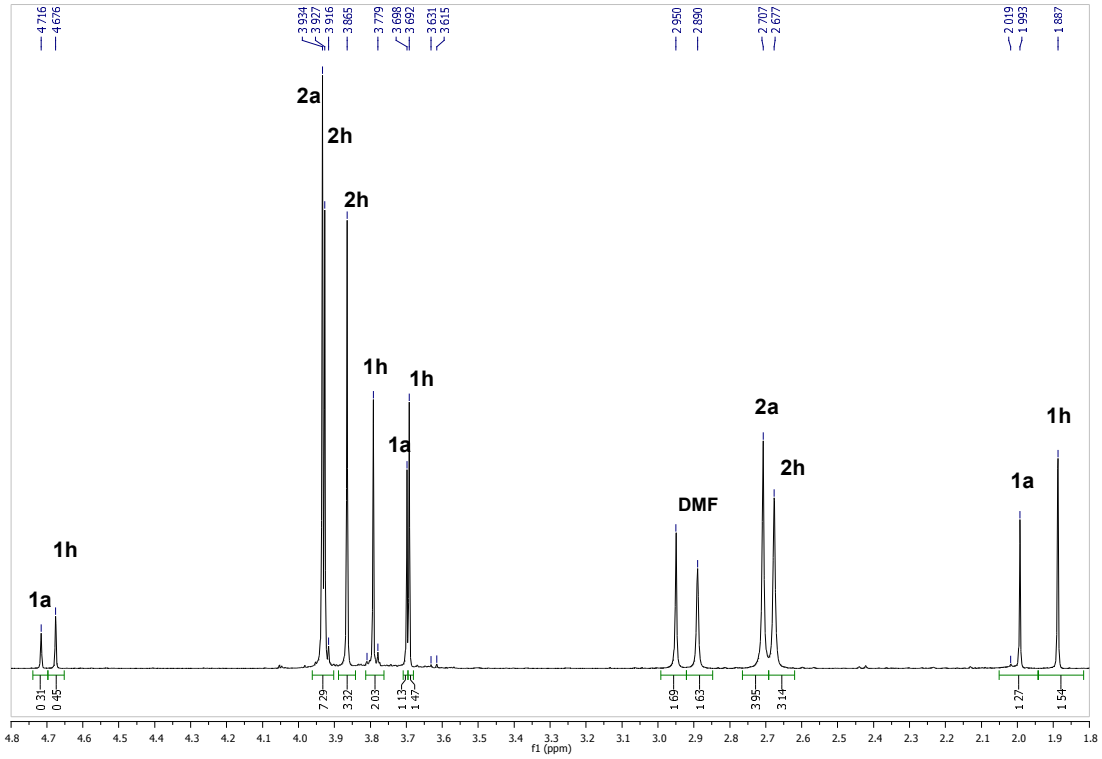


Fig. 6.9: Upfield-region of the ^{1}H NMR from the mixture of **1a**, **1h**, **2a** and **2h**

Careful examination and comparison of the ^{1}H NMR spectra of the crude mixture from the competition experiment **1a** vs. **1d** (Figures 6.4 and 6.5) showed that there is almost no difference in the amount of product formed in the competition experiment of **1a** (R = H) and **1d** (R = Me). Comparing the separate product signals at 8.07 and 7.87 ppm, respectively, shows a product ratio **2a/2d** = 1.15/1.10 = 1.04. This is in accordance with the approximate equal amount of remaining substrate (e. g. signals at 4.69 and 4.67 ppm, respectively indicate a ratio 1a/1d = 0.11/0.15 = 0.73).

Figure 6.6 shows that more indole product from the electron-withdrawing substrate **1n** (R = Cl) is formed than from the standard substrate **1a** (R = H). The product signals at 8.09 and 8.05 ppm suggest a ratio **2n/2a** = 0.53/0.42 = 1.26. The faster substrate consumption of the chloro-compounds as can be seen from the signals around 4.7 ppm (**1n/1a** = 0.76/1.02 = 0.75) or around 1.98 ppm (**1n/1a** = 2.44/3.20 = 0.76) is consistent with this result.

In agreement with this electronic influence on the reaction course, the product formation of the methoxy-substituted substrate **1h** is slowed down compared to the unsubstituted (*Z*)-Methyl 3-(phenylamino)-but-2-enoate **1a**. Both the signal pair at 8.10, 7.62 ppm as well as the one around 2.7 ppm prove a product ratio **2a/2h** = 1.30/1.00 = 1.30 or **2a/2h** = 3.95/3.14 = 1.26. The remaining substrate proportion of **1a/1h** = 1.27/1.54 = 0.82 is in accordance with this finding.

7. References

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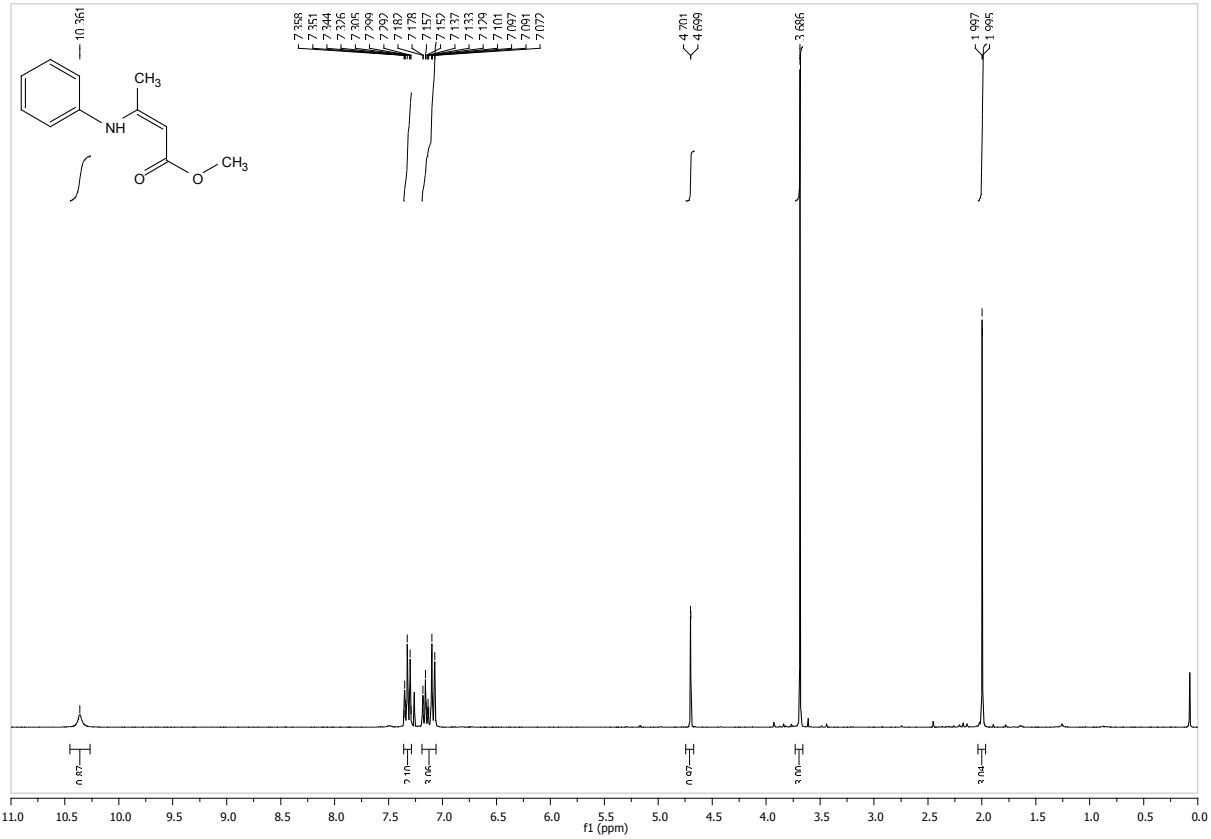
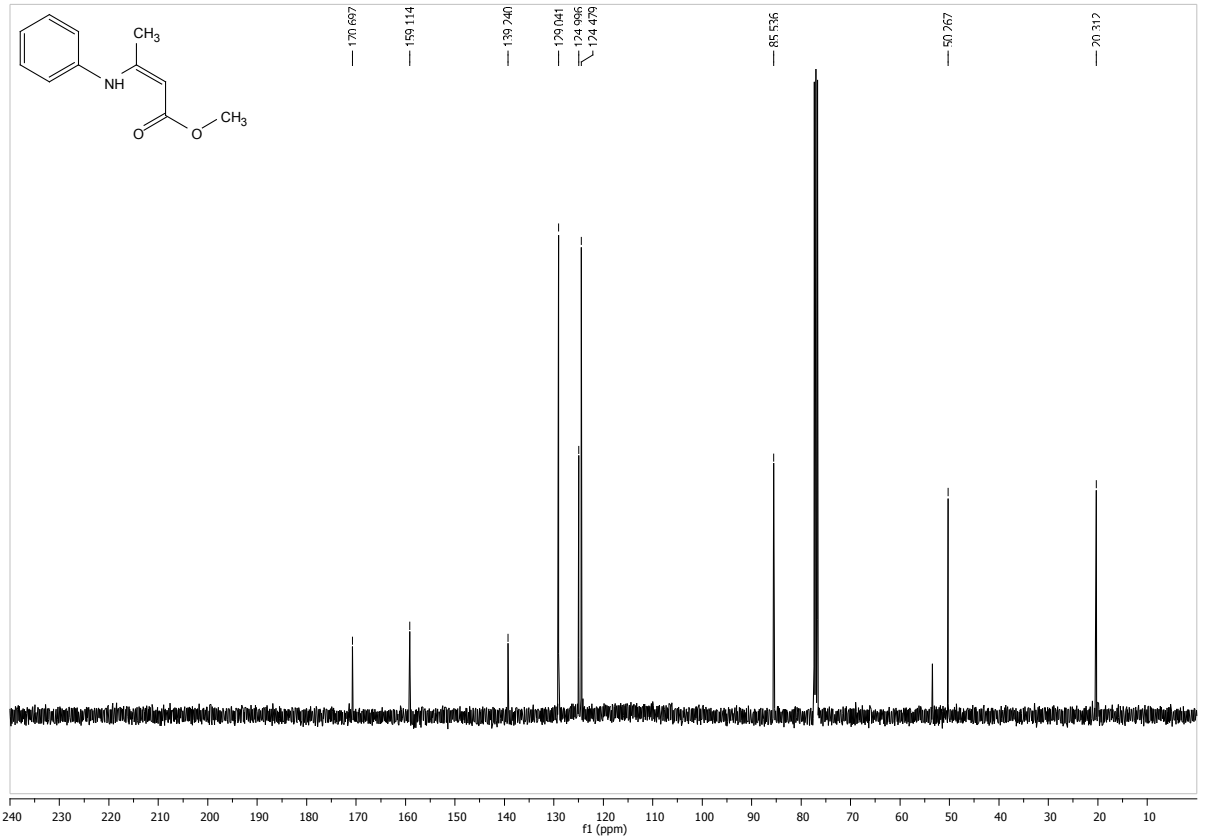
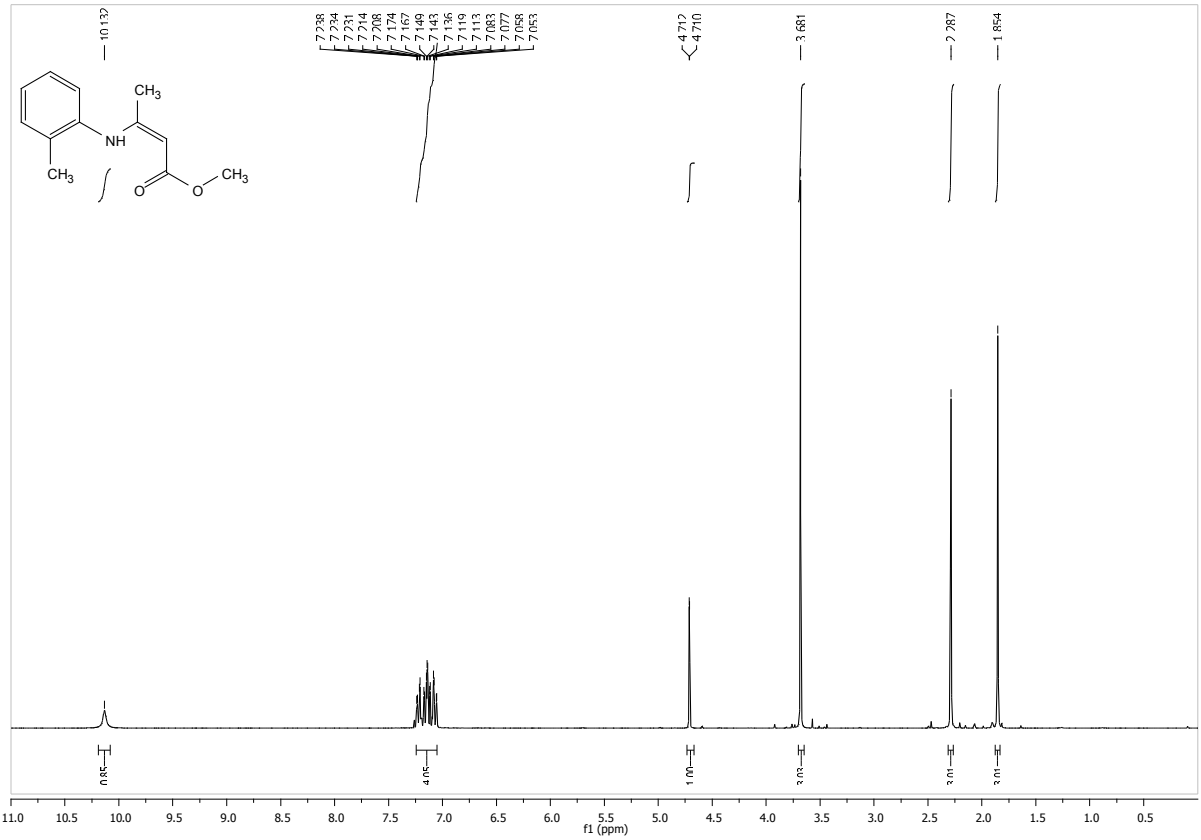
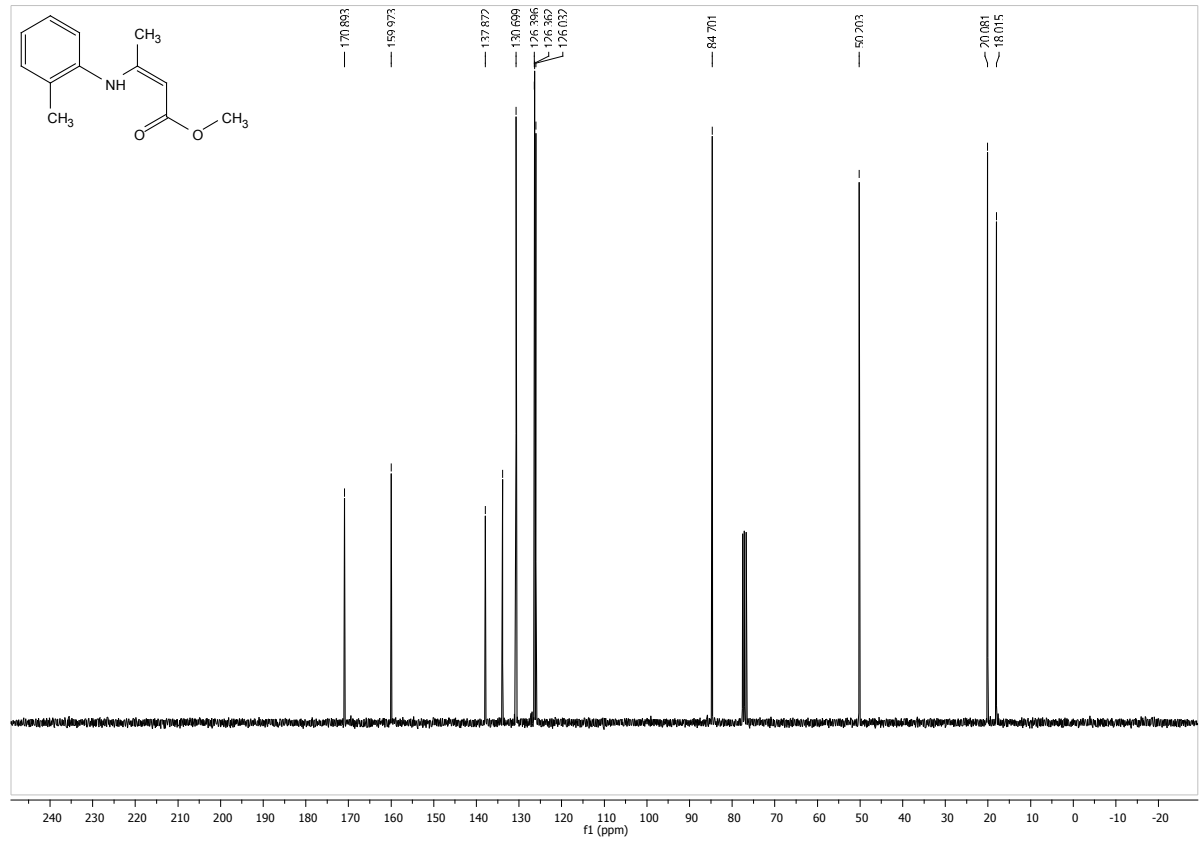
8. Scans of ^{1}H and ^{13}C spectra

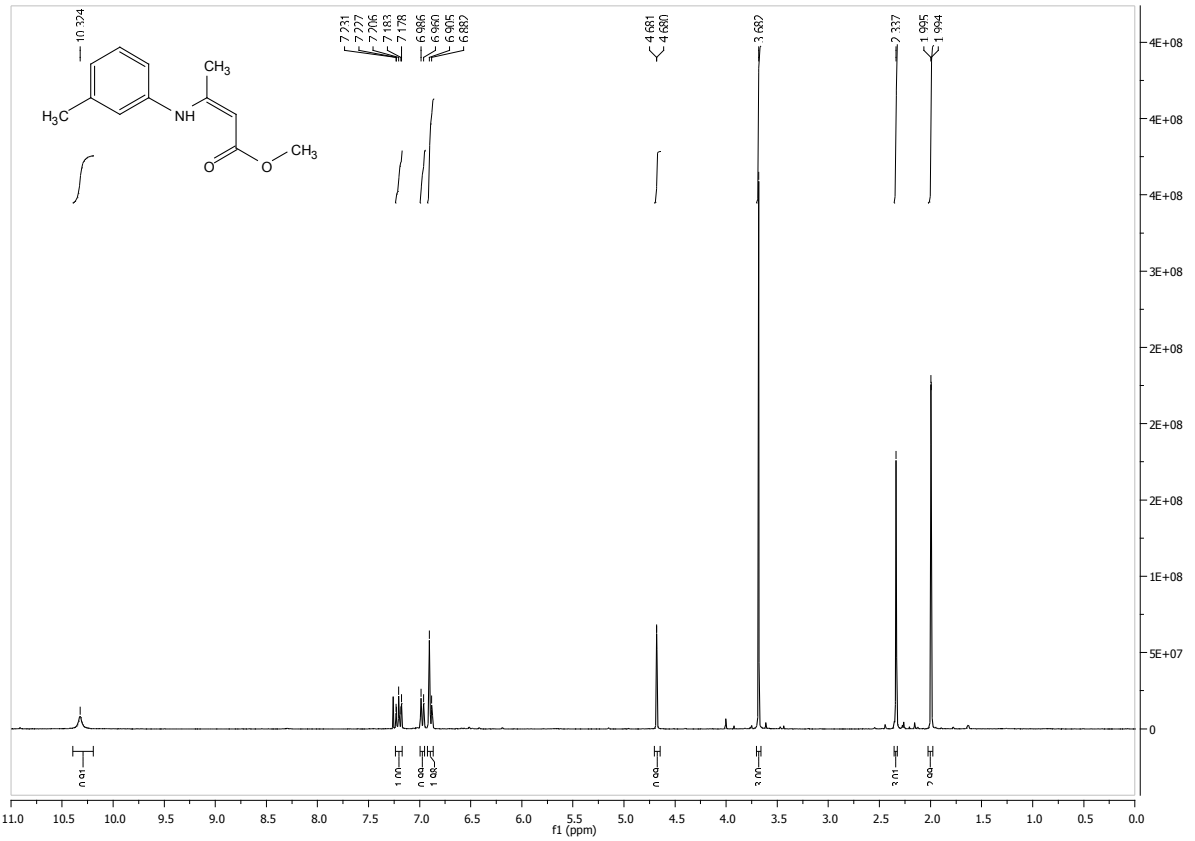
a. Substrates

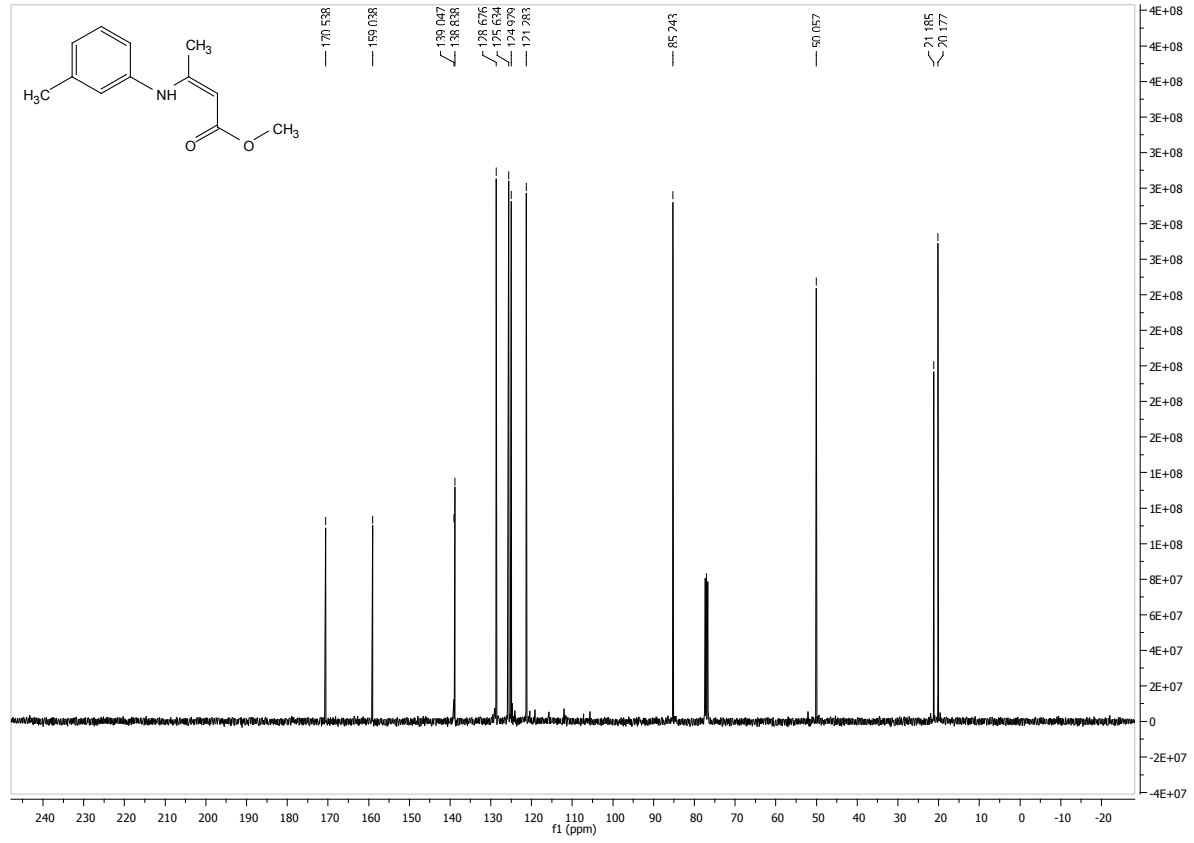


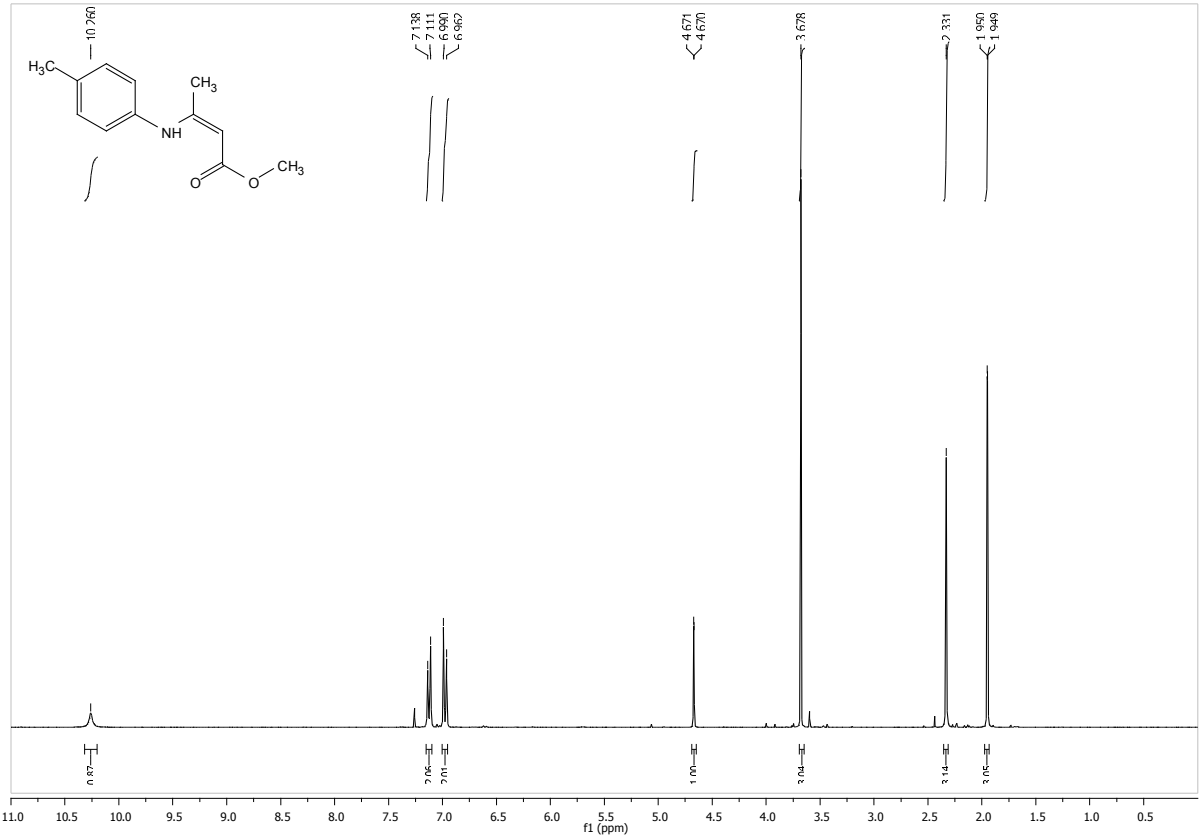


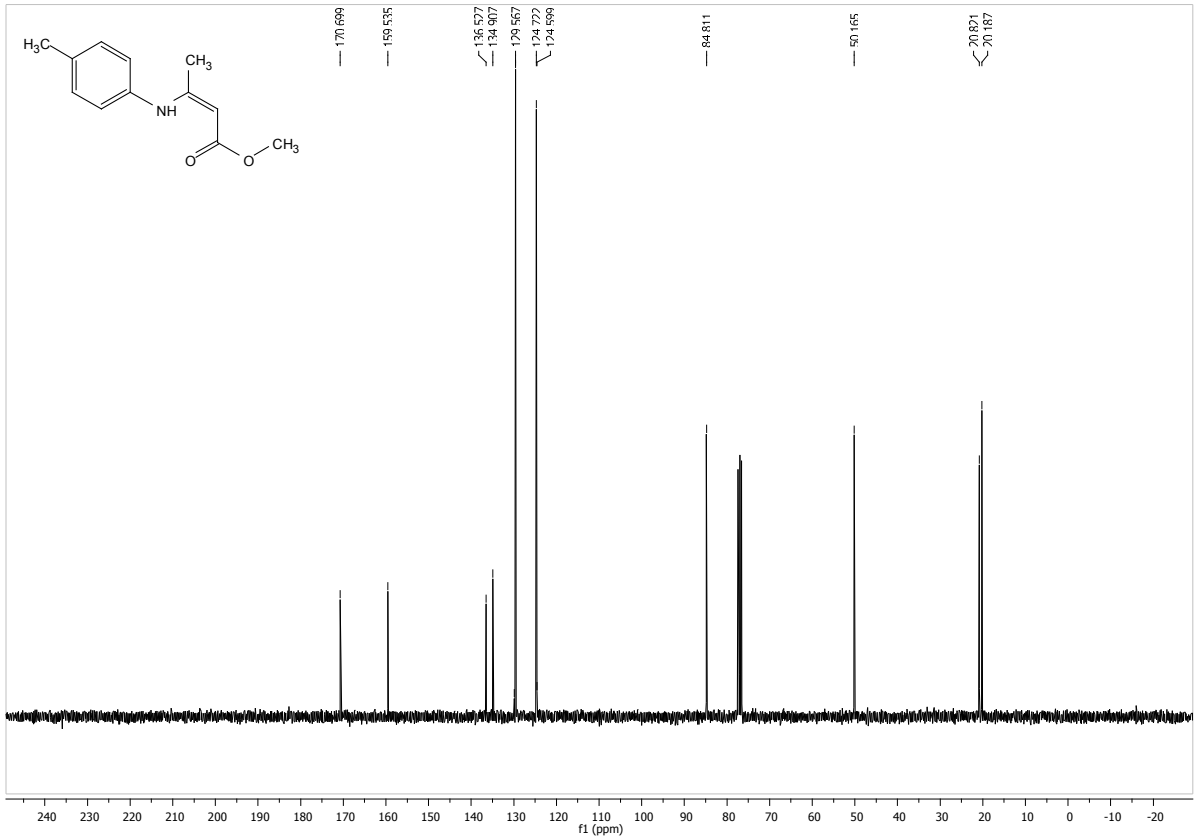

10.132
7.238
7.234
7.231
7.214
7.208
7.174
7.167
7.149
7.143
7.136
7.119
7.113
7.083
7.077
7.058
7.053
4.712
4.710
3.681
2.287
1.854
NH
CH3
CH3
O
O
CH3
0.98
4.05
1.00
3.03
3.01
3.01
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

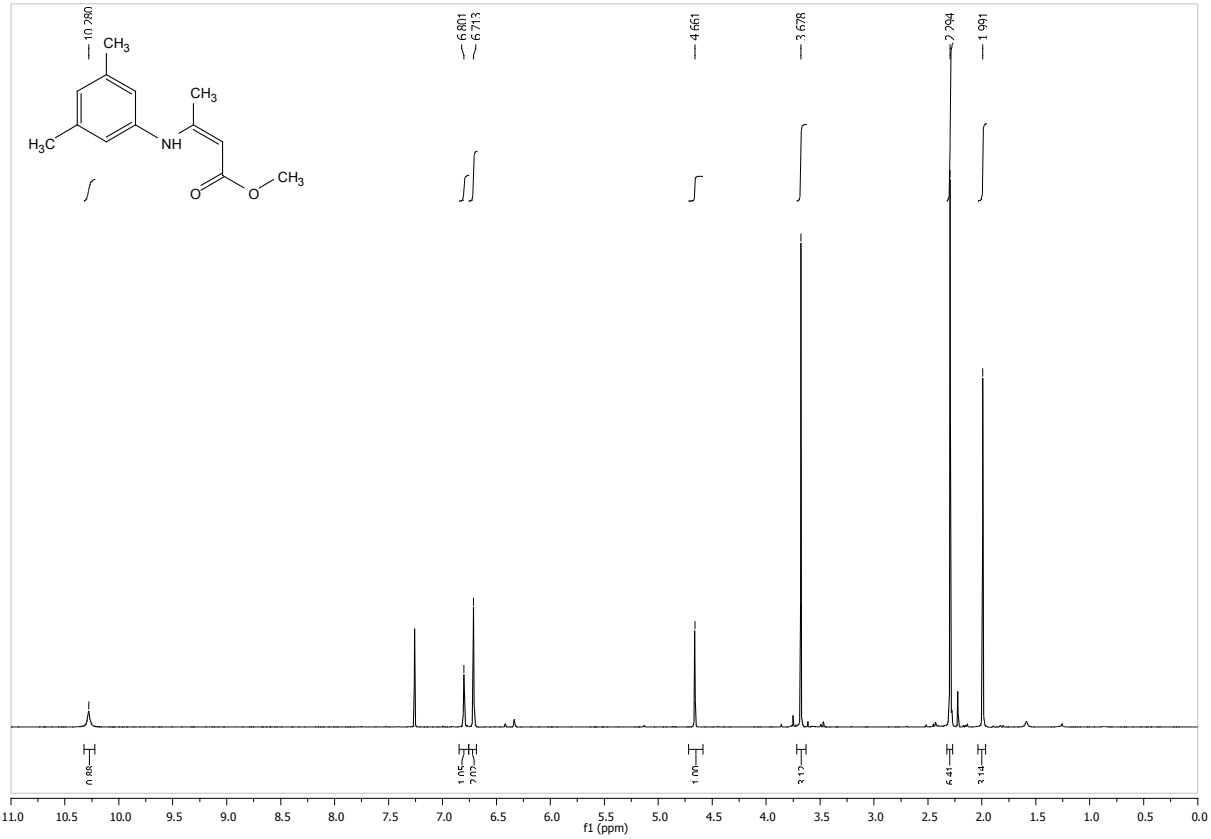

170.893
159.973
137.877
130.699
126.396
126.362
126.032
84.701
50.203
20.081
18.015
NH
CH3
CH3
O
O
CH3
240
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

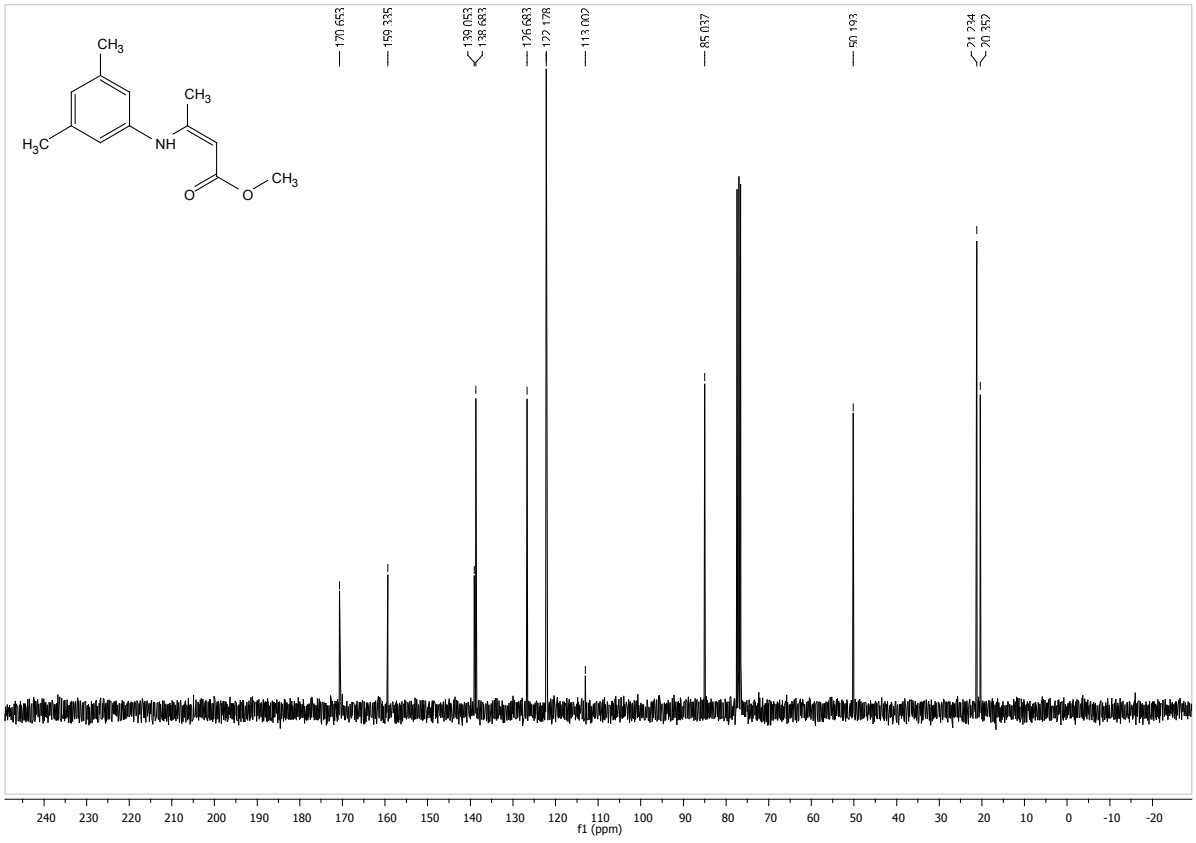

10.334
7.231
7.227
7.206
7.183
7.178
6.986
6.960
6.905
6.882
4.681
4.680
3.682
2.337
1.995
1.994
CH3
H3C
NH
O
O
CH3
f1 (ppm)

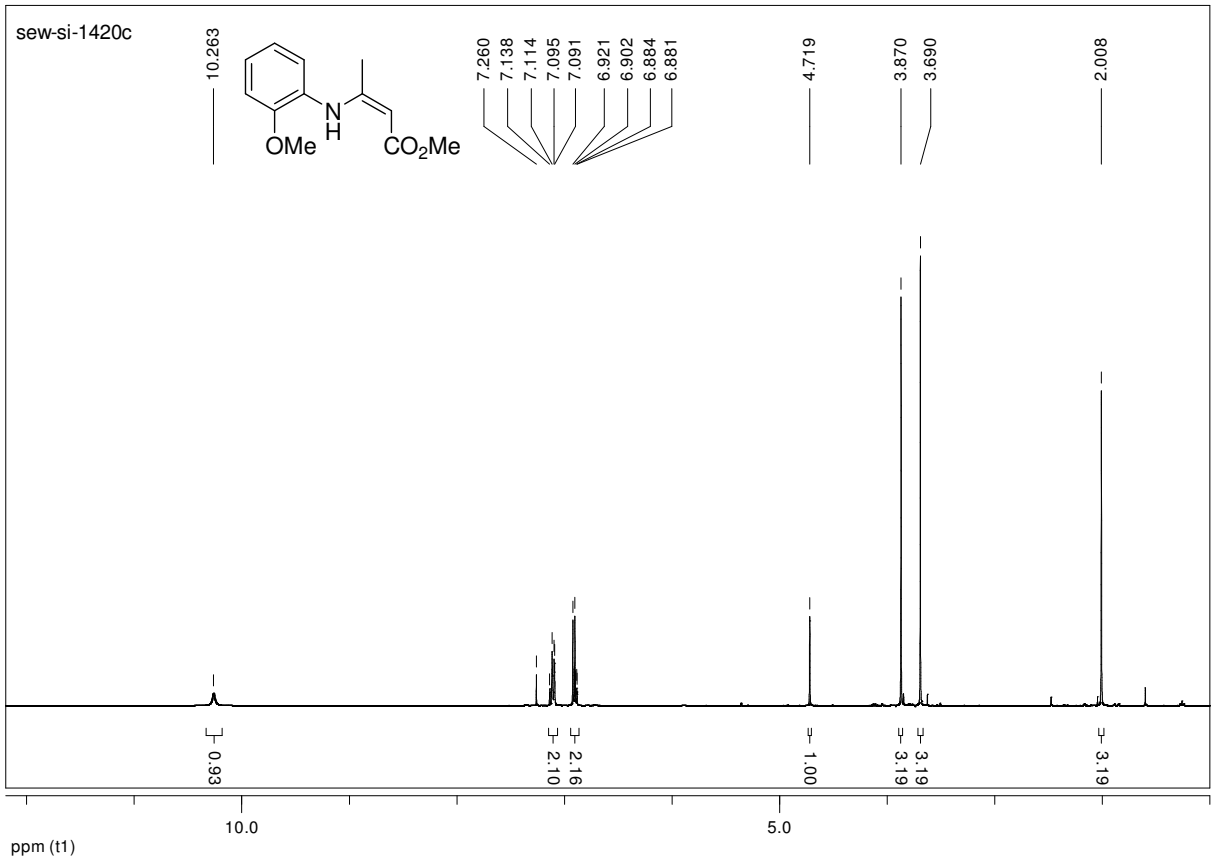

170.538
159.038
139.047
138.838
128.676
125.634
124.979
121.283
85.243
50.057
21.185
20.177
CH3
H3C
NH
O
O
CH3
f1 (ppm)

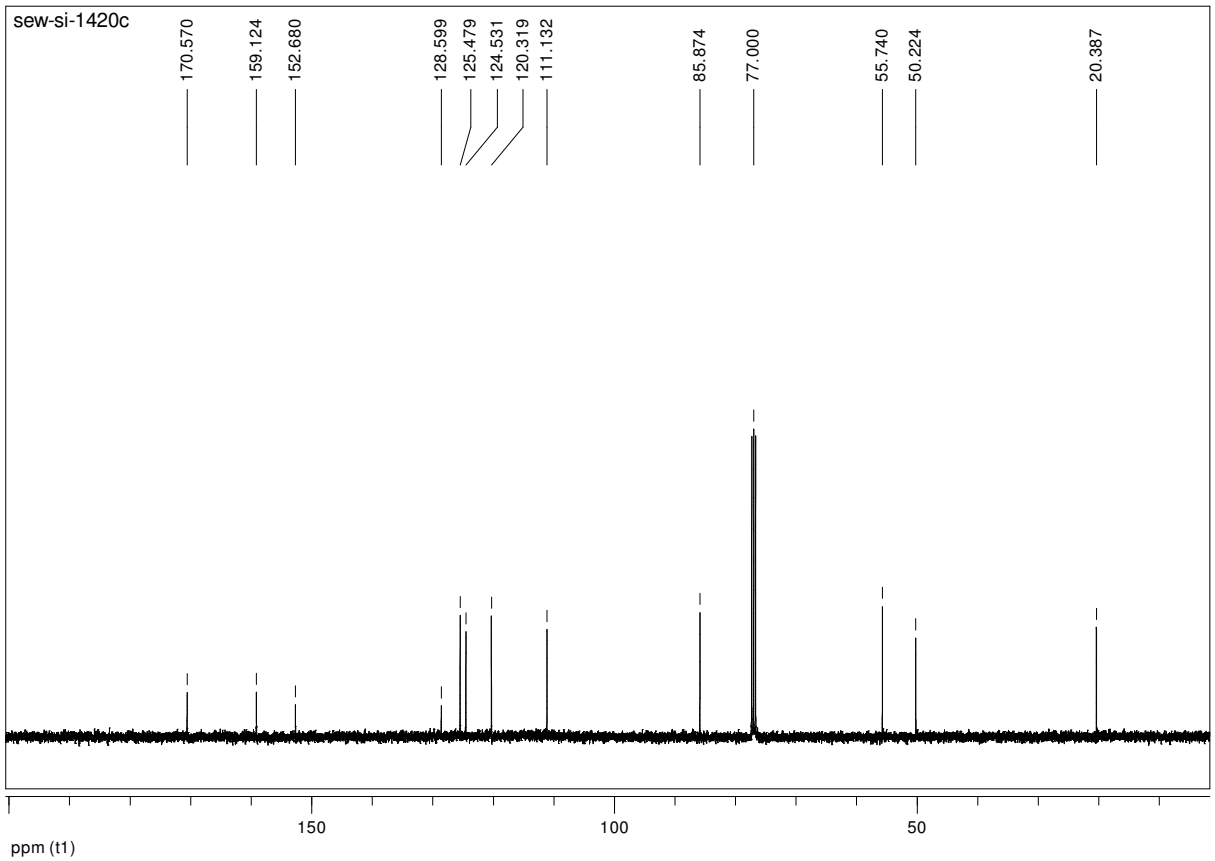

10.760
7.138
7.111
6.990
6.967
4.671
4.670
3.678
2.331
1.950
1.949
f1 (ppm)

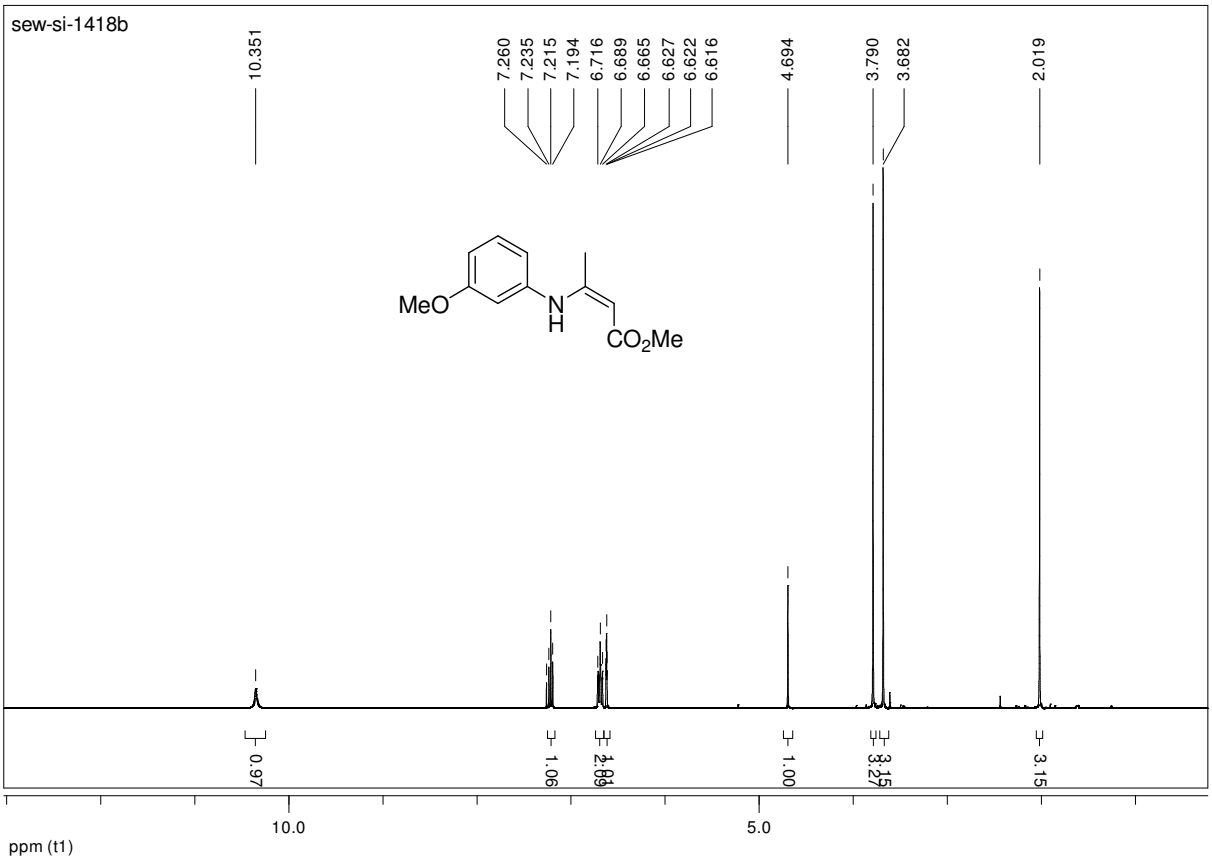

170.699
159.535
136.527
134.907
129.567
124.772
124.599
84.811
50.165
20.871
20.187
f1 (ppm)

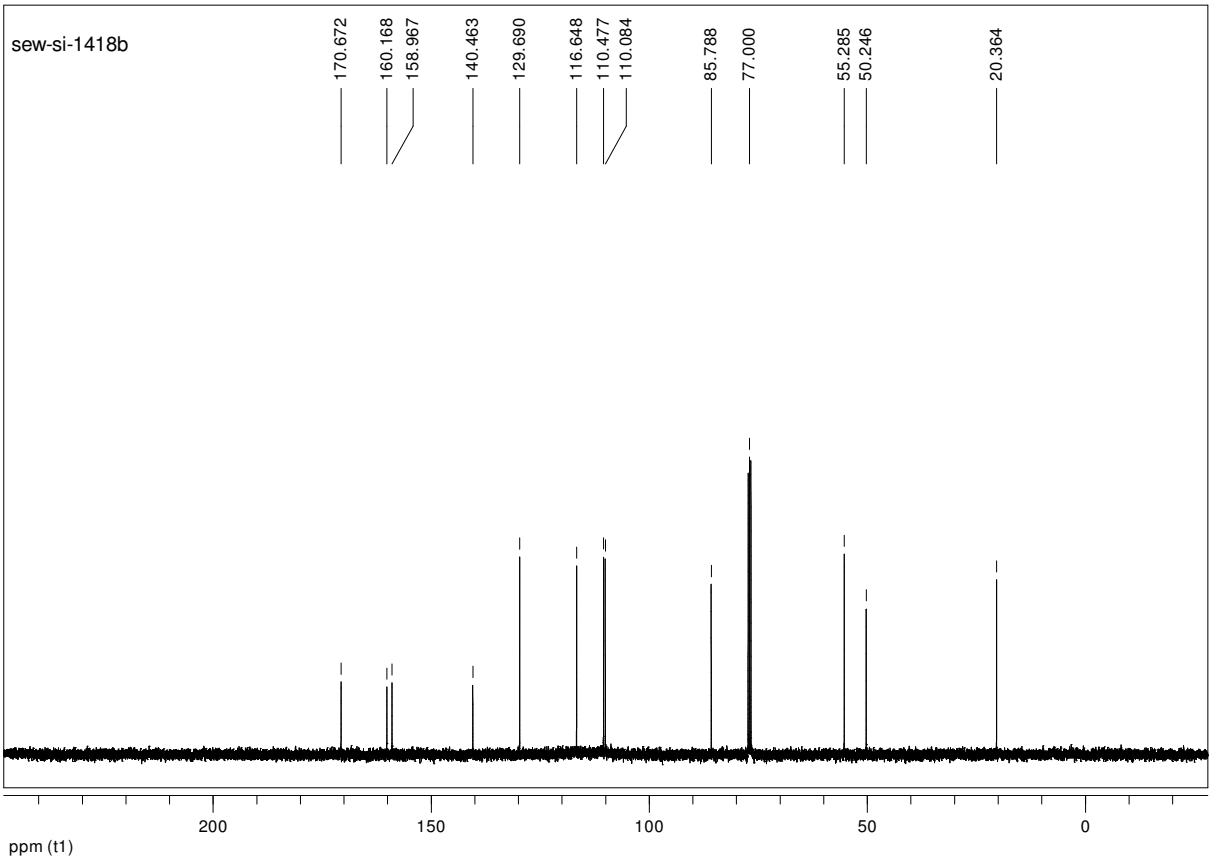

10.280
6.801
6.713
4.661
3.678
2.794
1.991
CH3
H3C
NH
O
O
CH3
f1 (ppm)

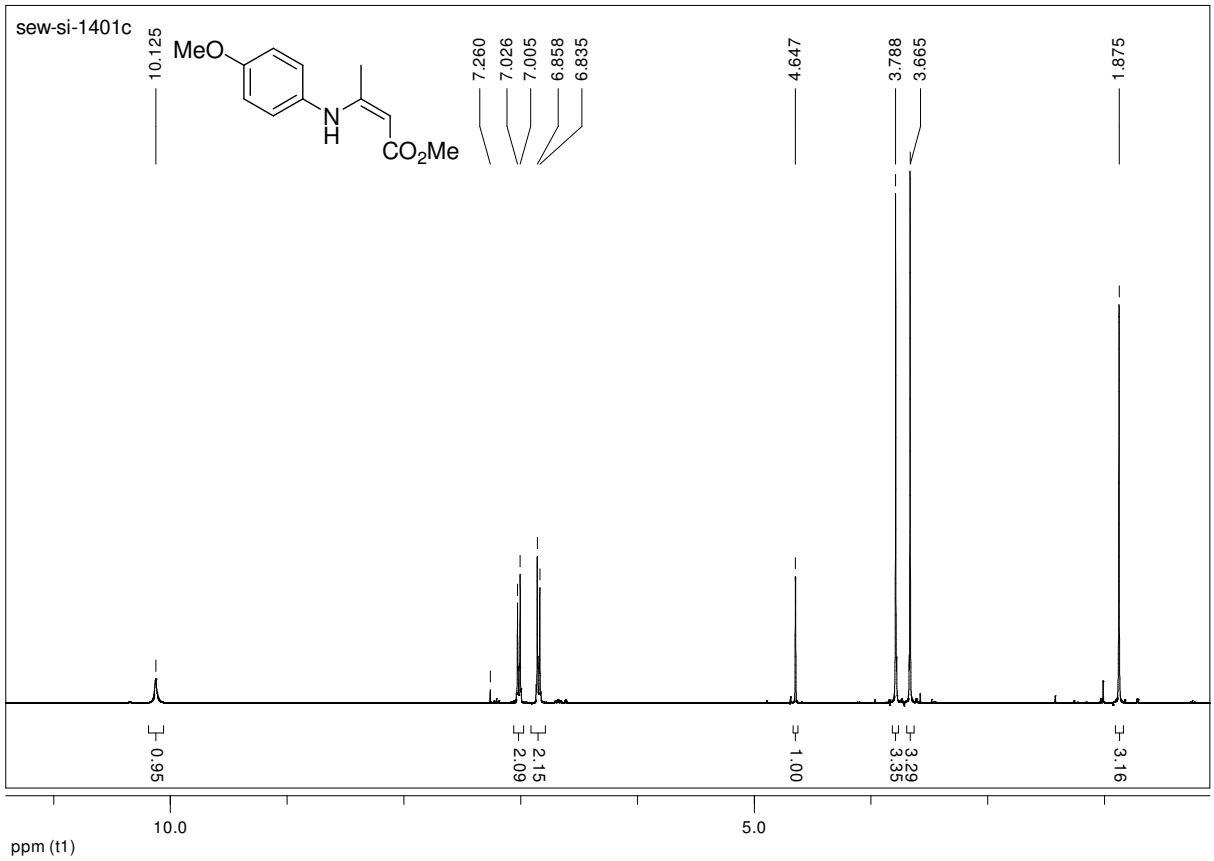

170.653
159.335
139.053
138.683
126.683
123.178
113.002
85.037
50.193
21.734
20.352
CH3
H3C
NH
O
O
CH3
f1 (ppm)

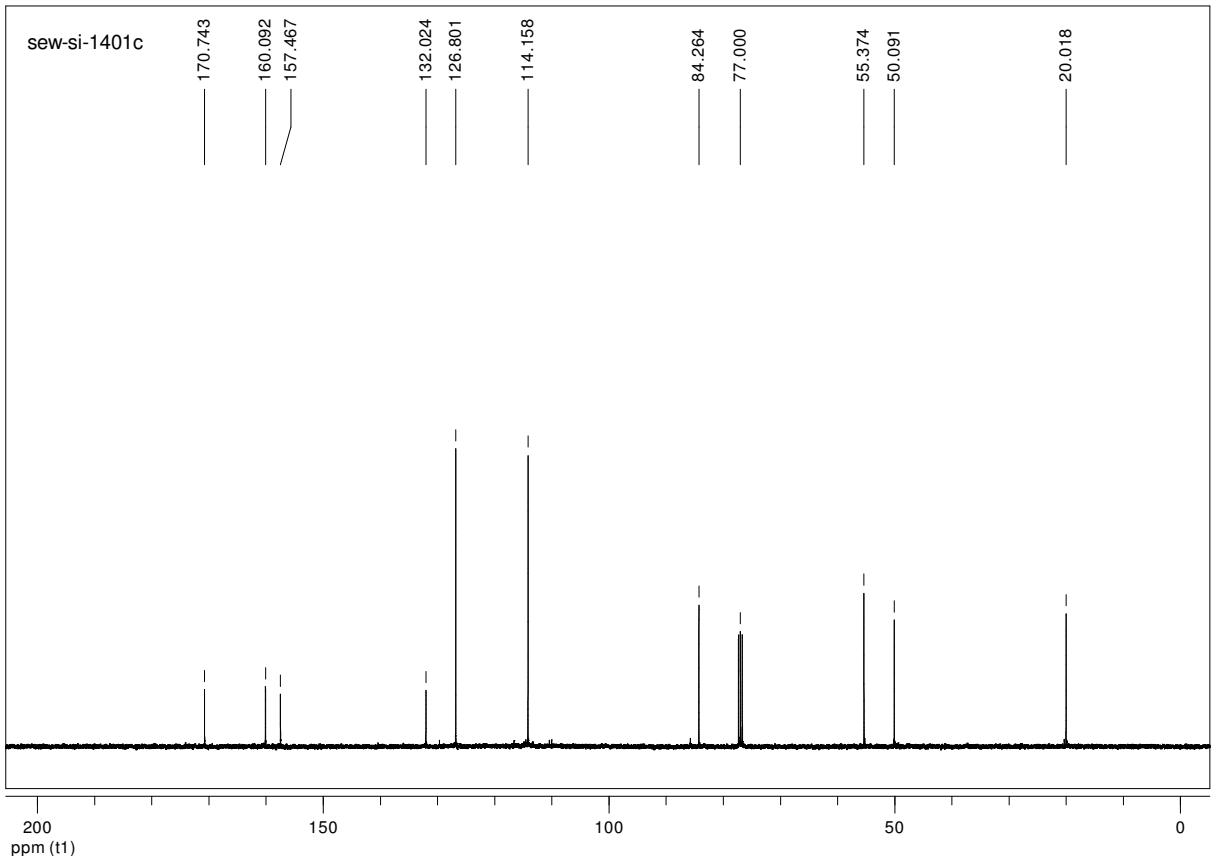

sew-si-1420c
10.263
7.260
7.138
7.114
7.095
7.091
6.921
6.902
6.884
6.881
4.719
3.870
3.690
2.008
OMe
N
H
CO2Me
0.93
2.10
2.16
1.00
3.19
3.19
3.19
10.0
5.0
ppm (t1)

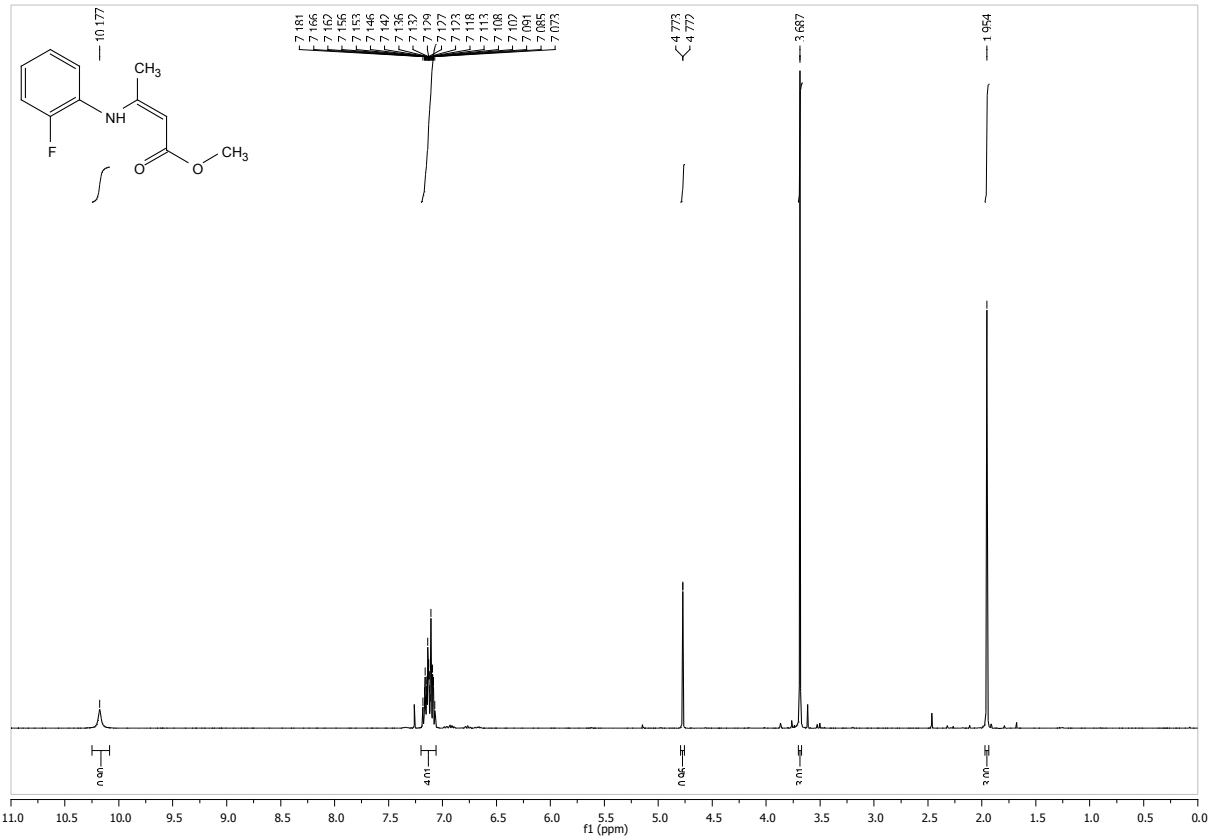

sew-si-1420c
170.570
159.124
152.680
128.599
125.479
124.531
120.319
111.132
85.874
77.000
55.740
50.224
20.387
150
100
50
ppm (t1)

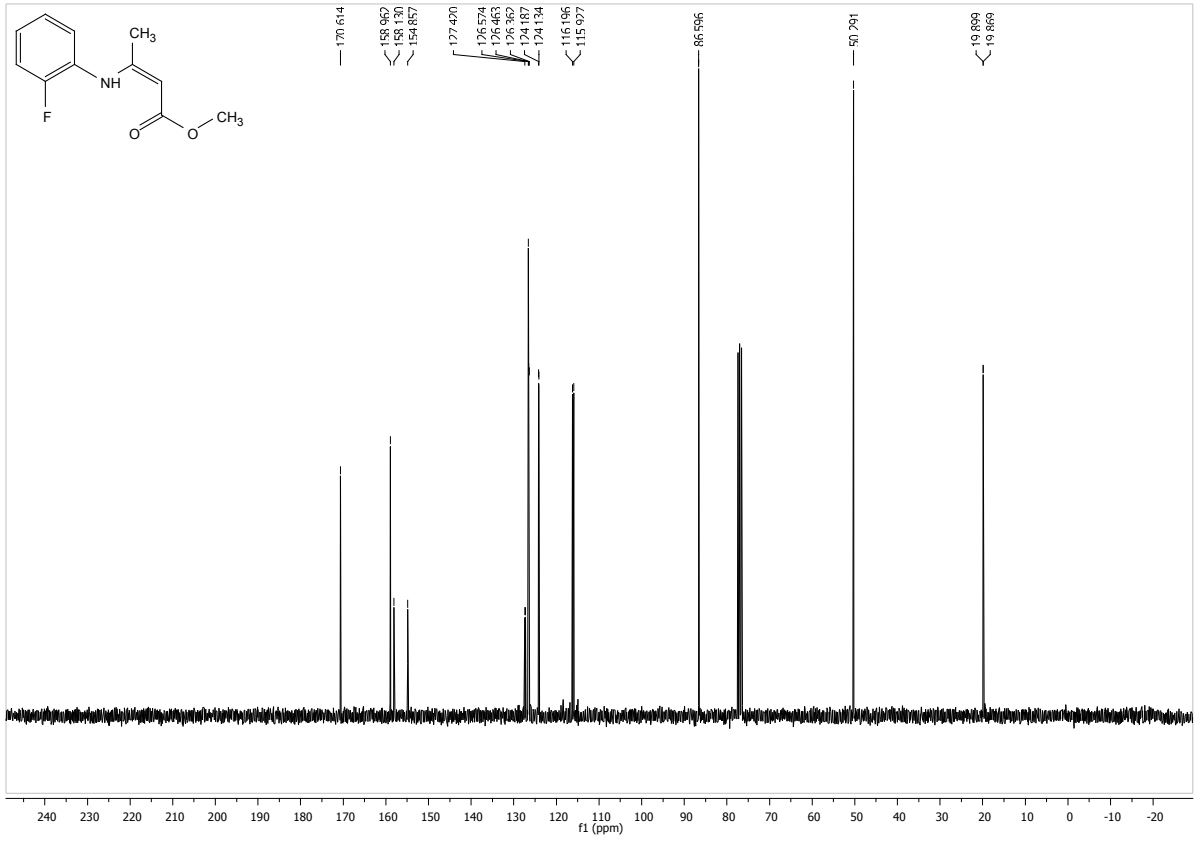

sew-si-1418b
10.351
7.260
7.235
7.215
7.194
6.716
6.689
6.665
6.627
6.622
6.616
4.694
3.790
3.682
2.019
MeO
N
H
CO2Me
0.97
1.96
2.09
1.00
3.27
3.15
10.0
5.0
ppm (t1)

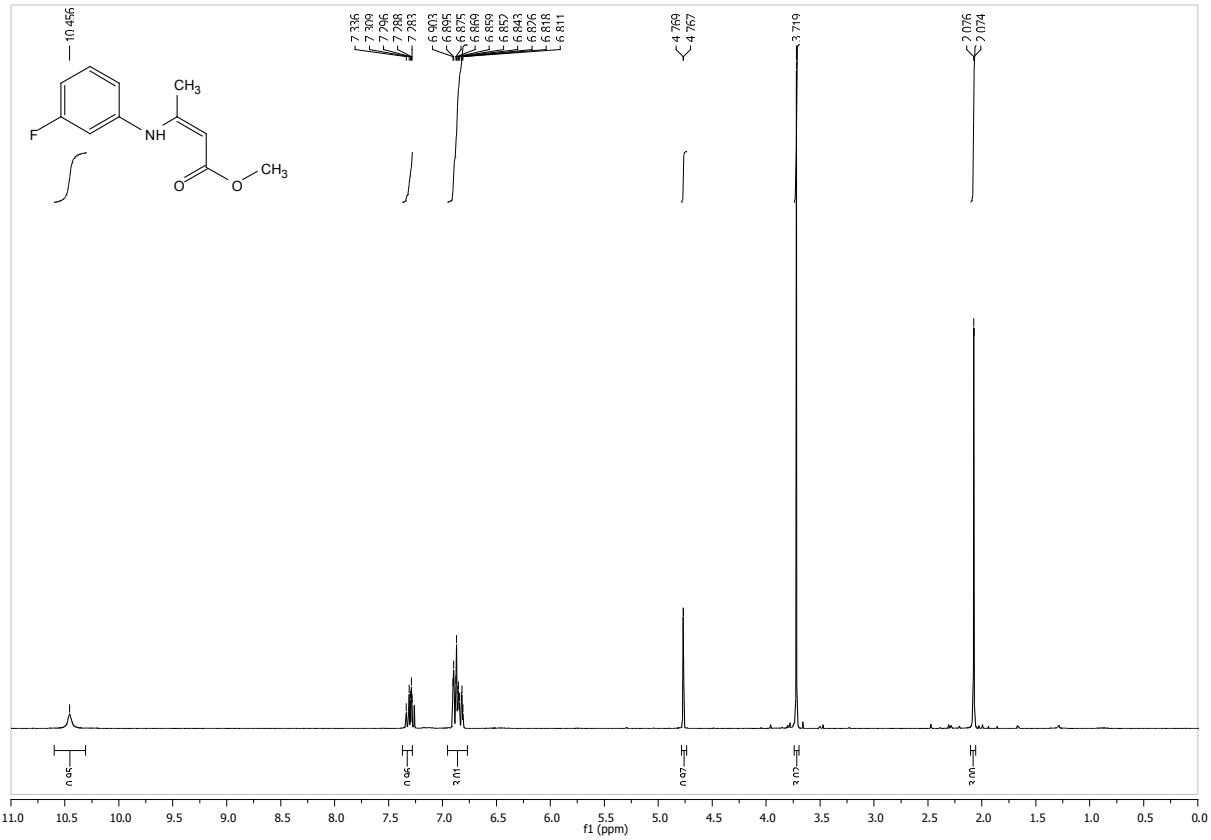

sew-si-1418b
170.672
160.168
158.967
140.463
129.690
116.648
110.477
110.084
85.788
77.000
55.285
50.246
20.364
200
150
100
50
0
ppm (t1)

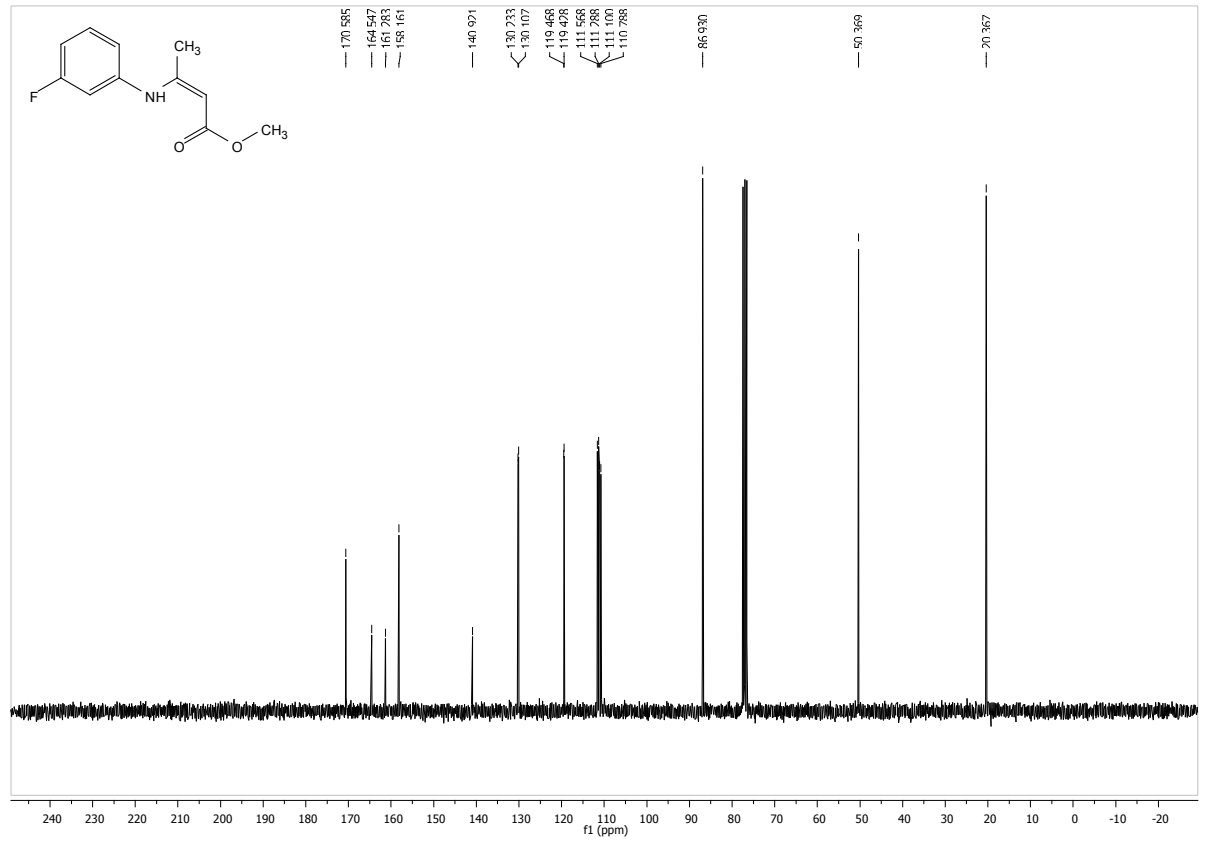

sew-si-1401c
MeO
N
H
CO2Me
10.125
7.260
7.026
7.005
6.858
6.835
4.647
3.788
3.665
1.875
0.95
2.09
2.15
1.00
3.35
3.29
3.16
10.0
5.0
ppm (t1)

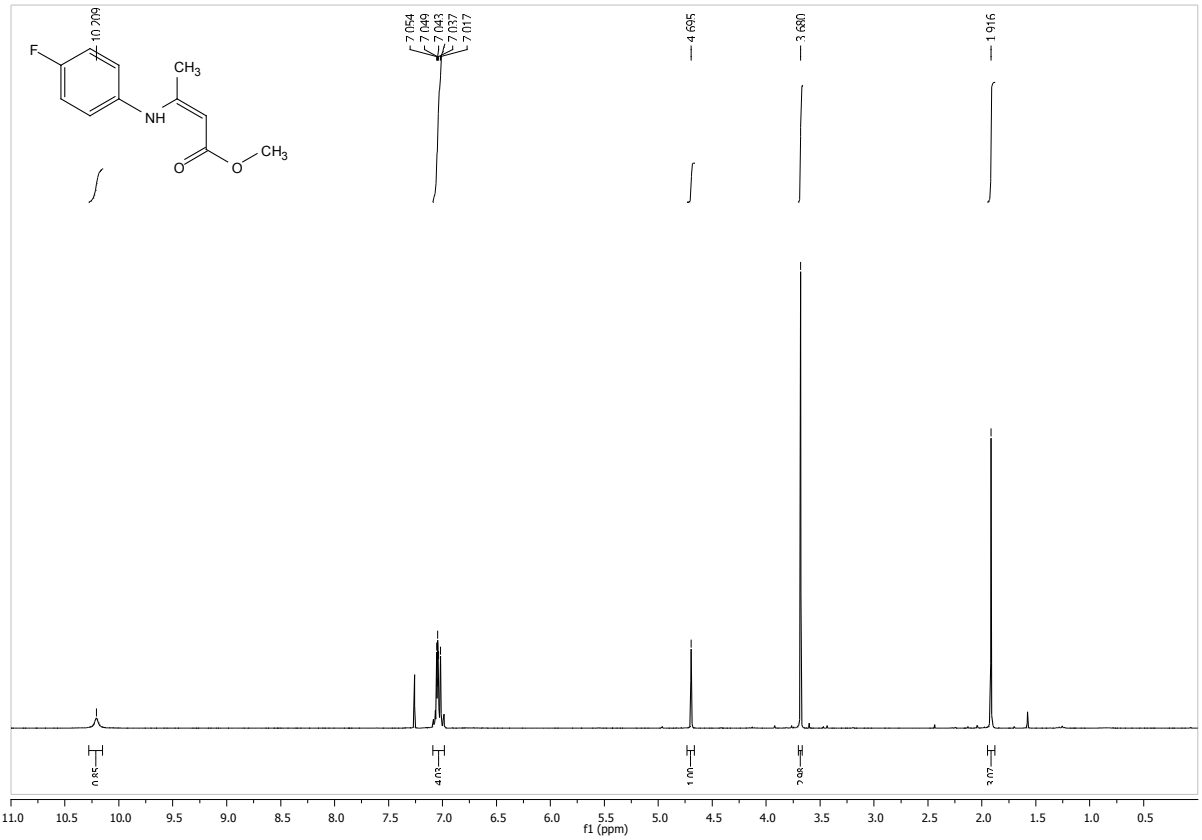

sew-si-1401c
170.743
160.092
157.467
132.024
126.801
114.158
84.264
77.000
55.374
50.091
20.018
200
150
100
50
0
ppm (t1)

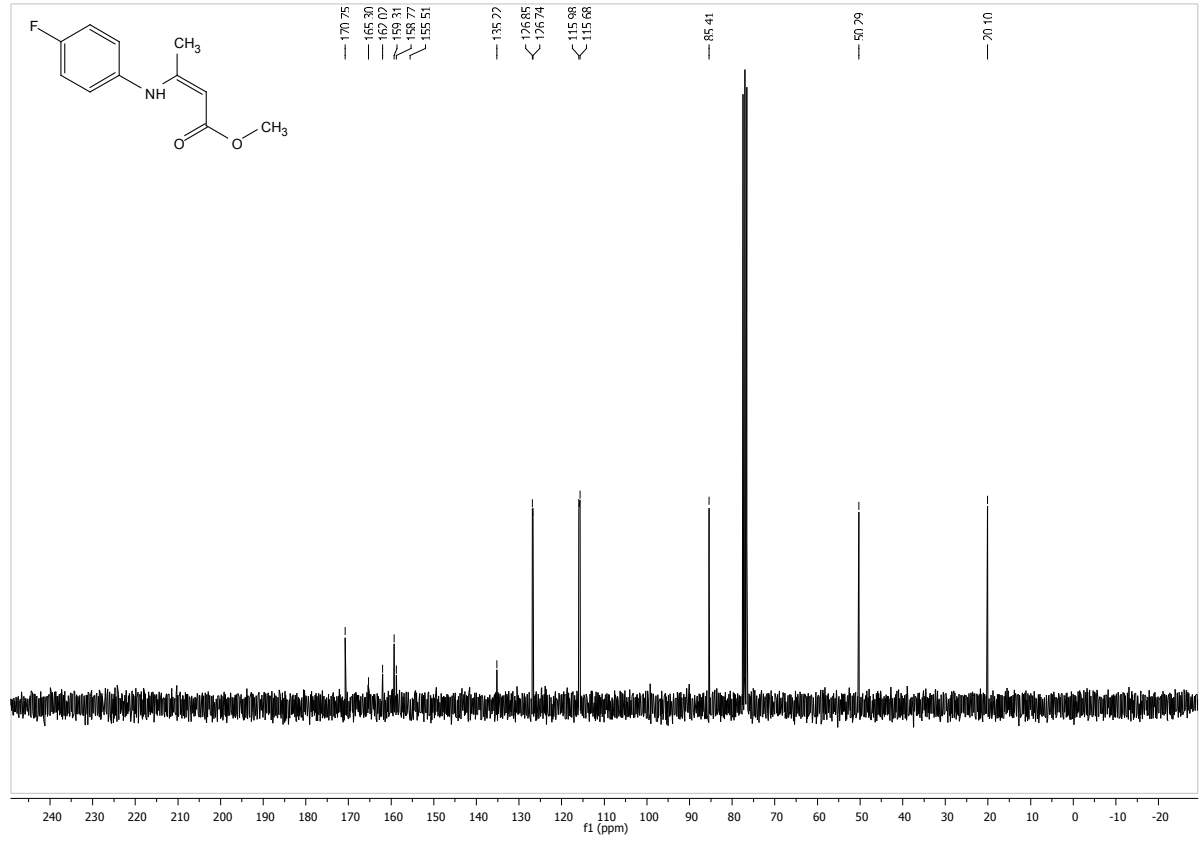

10.177
7.181
7.166
7.162
7.155
7.153
7.146
7.142
7.136
7.132
7.129
7.127
7.123
7.118
7.113
7.108
7.102
7.091
7.085
7.073
4.773
4.772
3.687
1.954
NH
F
O
O
CH3
CH3
f1 (ppm)

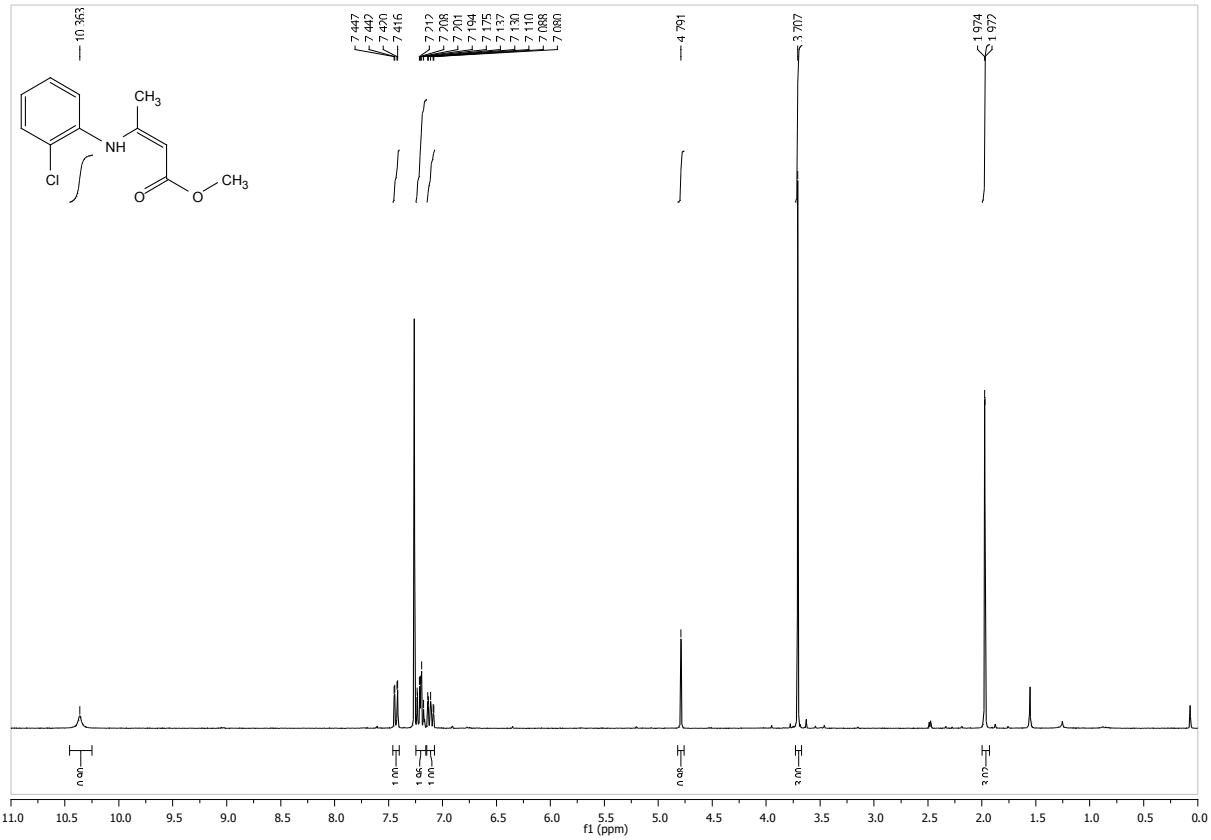

170.614
158.962
158.130
154.857
127.420
126.574
126.463
126.362
124.187
124.134
116.196
115.977
86.596
50.791
19.899
19.869
NH
F
O
O
CH3
CH3
f1 (ppm)

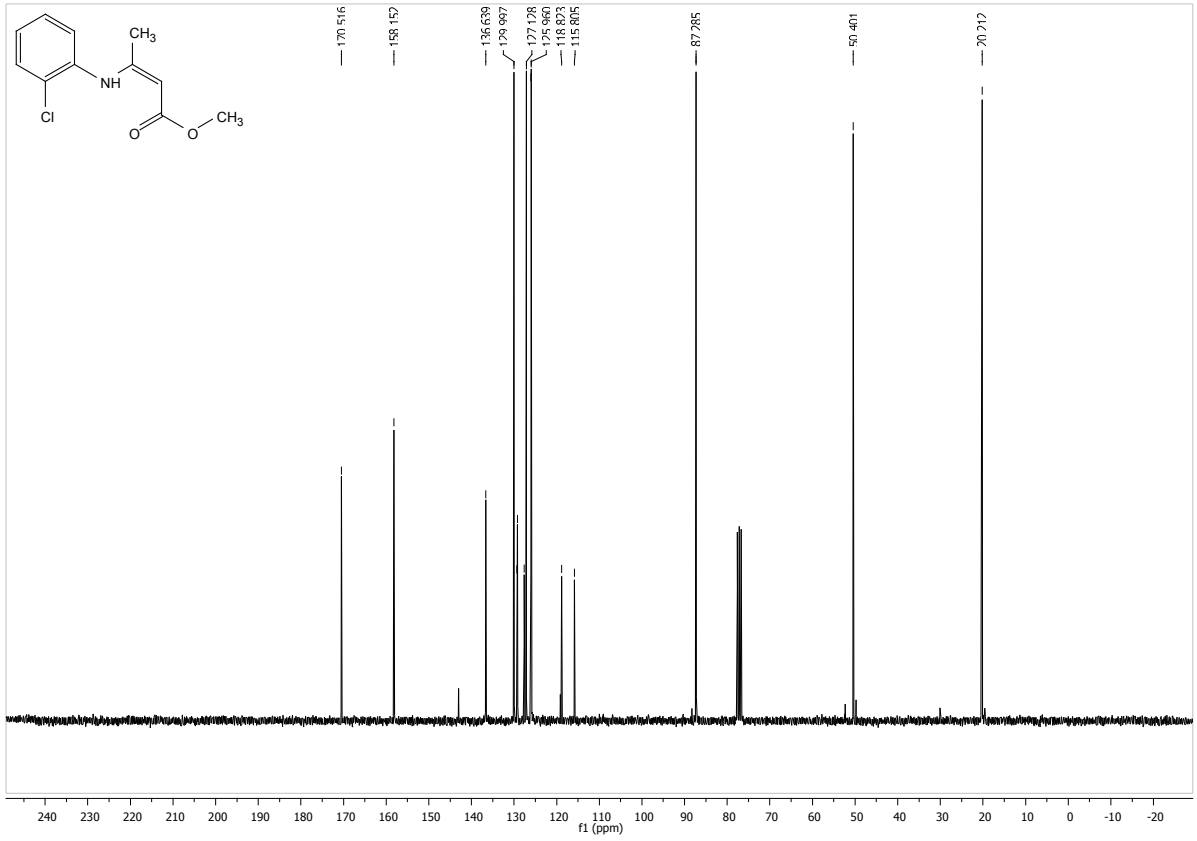

10.456
7.336
7.309
7.296
7.288
7.283
6.903
6.895
6.875
6.869
6.859
6.852
6.843
6.826
6.818
6.811
4.769
4.767
3.719
2.076
2.074
F
NH
CH3
O
O
CH3
f1 (ppm)

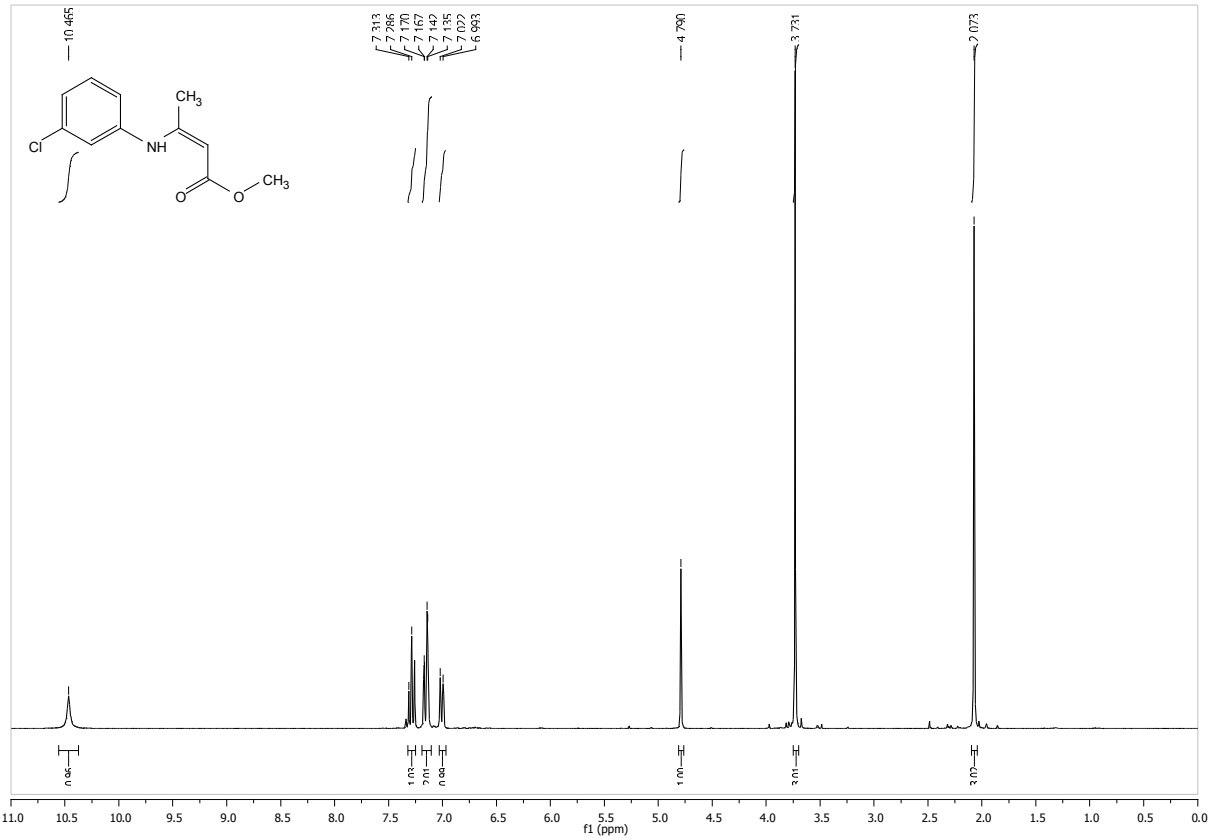

170.585
164.547
161.283
158.161
140.971
130.233
130.107
119.468
119.428
111.568
111.388
111.100
110.788
86.930
50.369
20.367
F
NH
CH3
O
O
CH3
f1 (ppm)

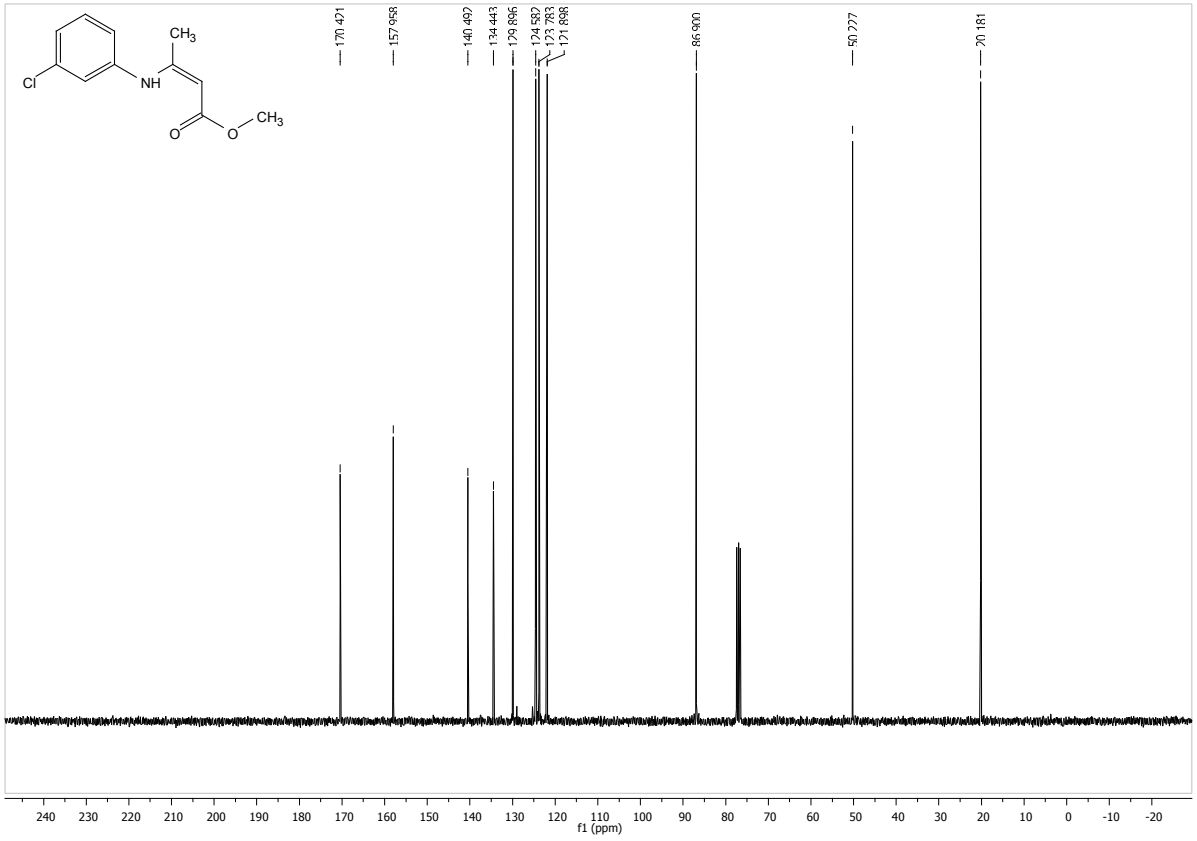

F
CH3
NH
O
O
CH3
10.209
7.054
7.049
7.043
7.037
7.017
4.695
3.680
1.916
f1 (ppm)

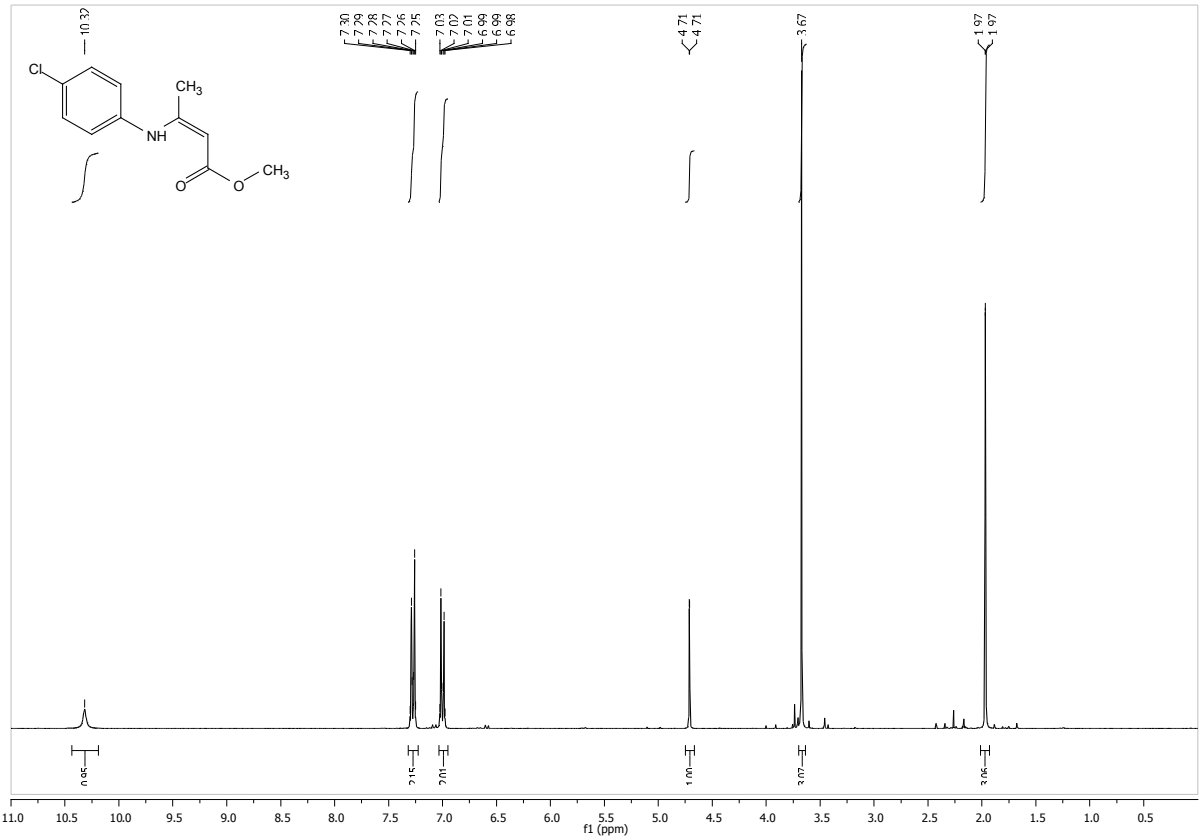

F
CH3
NH
O
O
CH3
170.75
165.30
162.02
159.31
158.77
155.51
135.22
126.85
126.74
115.98
115.68
85.41
50.79
20.10
f1 (ppm)

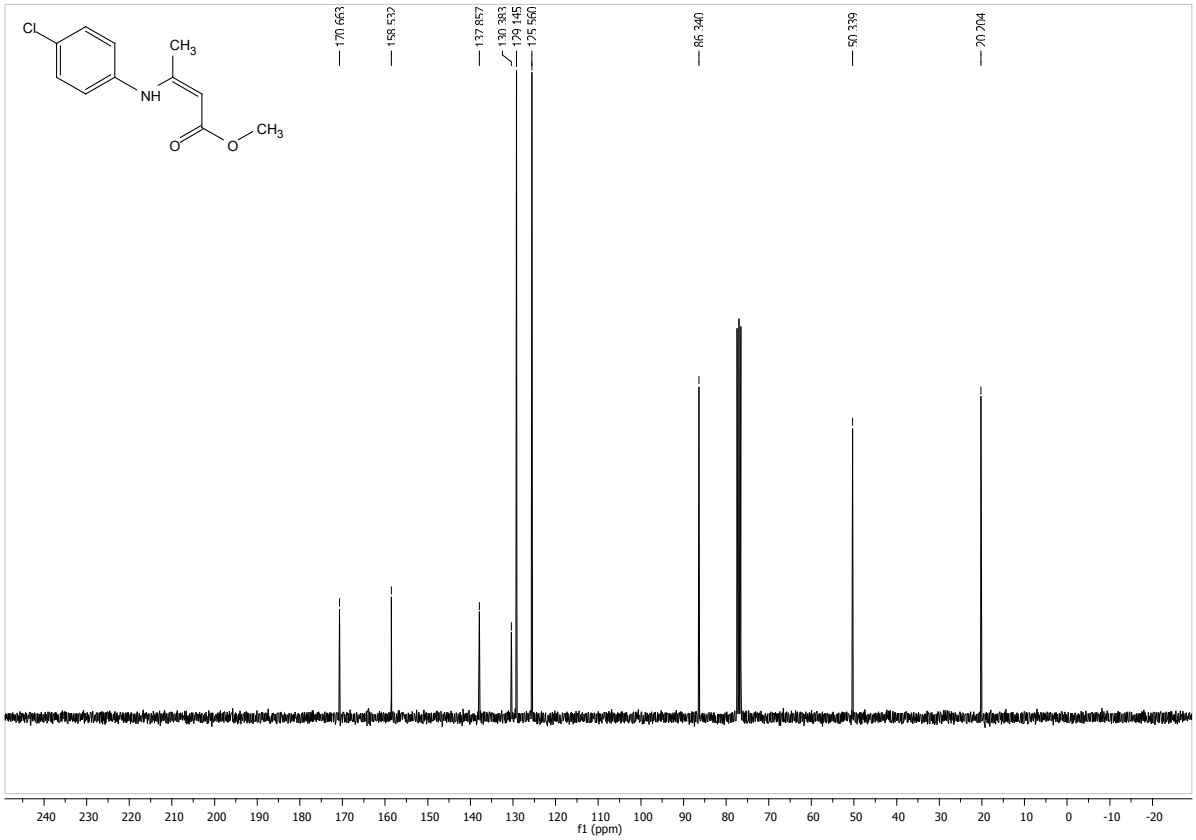

10.363
7.447
7.442
7.430
7.416
7.212
7.208
7.201
7.194
7.175
7.137
7.130
7.110
7.088
7.080
4.791
3.707
1.974
1.972
CH3
NH
Cl
O
O
CH3
f1 (ppm)

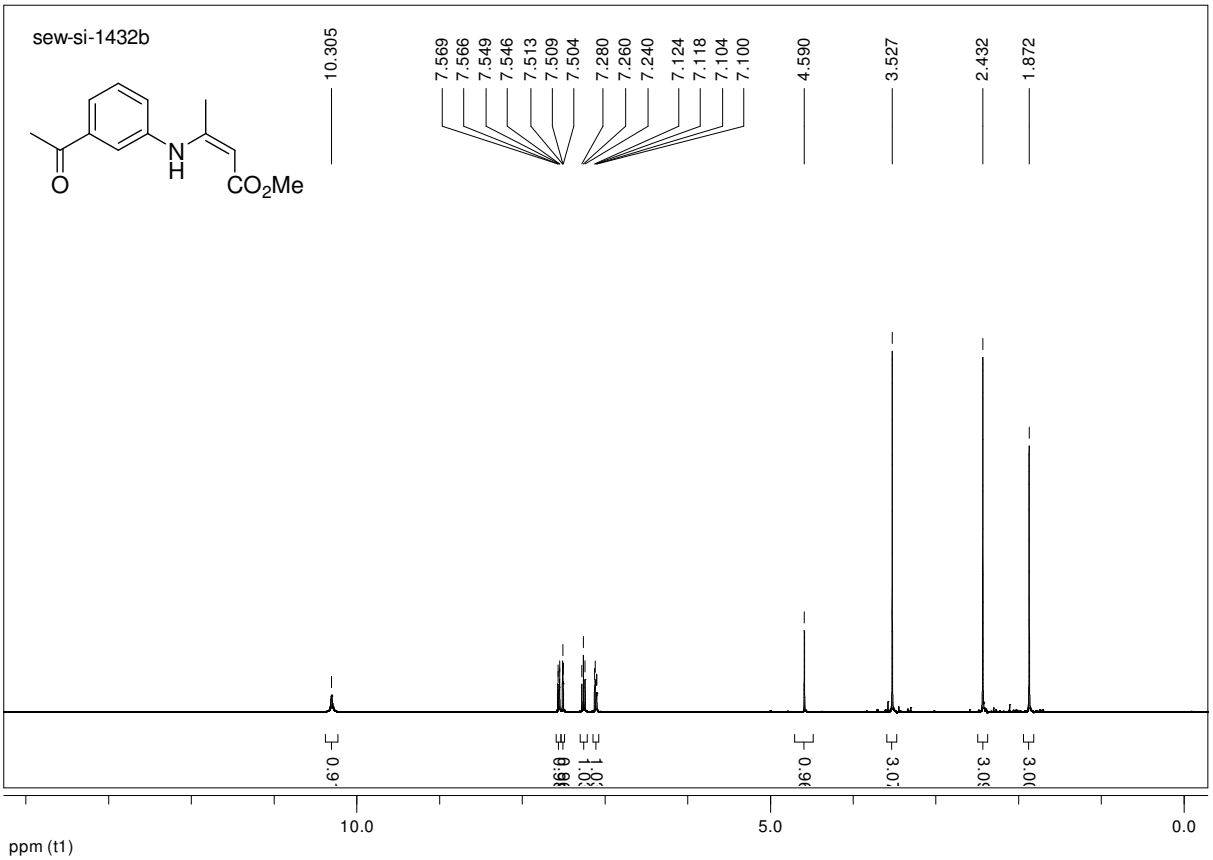

170.516
158.152
136.639
129.997
127.128
125.960
118.823
115.805
87.285
50.401
20.212
CH3
NH
Cl
O
O
CH3
f1 (ppm)

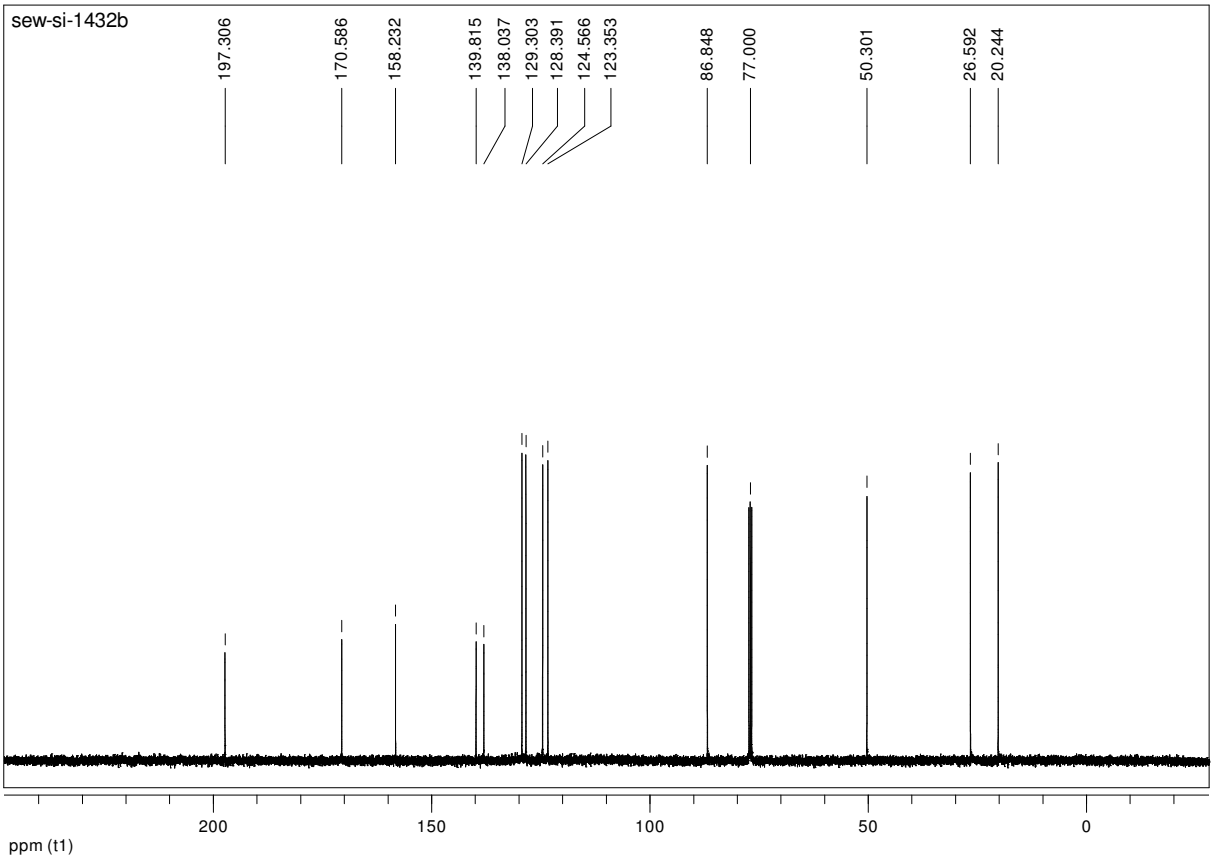

10.465
7.313
7.286
7.170
7.167
7.142
7.135
7.022
6.993
4.790
3.731
2.073
Cl
NH
CH3
O
O
CH3
f1 (ppm)


170.471
157.958
140.492
134.443
129.896
124.582
123.783
121.898
86.900
50.727
20.181
Cl
NH
CH3
O
O
CH3
f1 (ppm)


10.32
7.80
7.79
7.78
7.77
7.76
7.75
7.03
7.02
7.01
6.99
6.99
6.98
4.71
4.71
3.67
1.97
1.97
Cl
CH3
NH
O
O
CH3
f1 (ppm)


170.663
158.532
137.857
130.383
129.145
125.560
86.340
50.339
20.204
Cl
CH3
NH
O
O
CH3
f1 (ppm)


sew-si-1432b
10.305
7.569
7.566
7.549
7.546
7.513
7.509
7.504
7.280
7.260
7.240
7.124
7.118
7.104
7.100
4.590
3.527
2.432
1.872
O
N
H
CO2Me
10.0
5.0
0.0
ppm (t1)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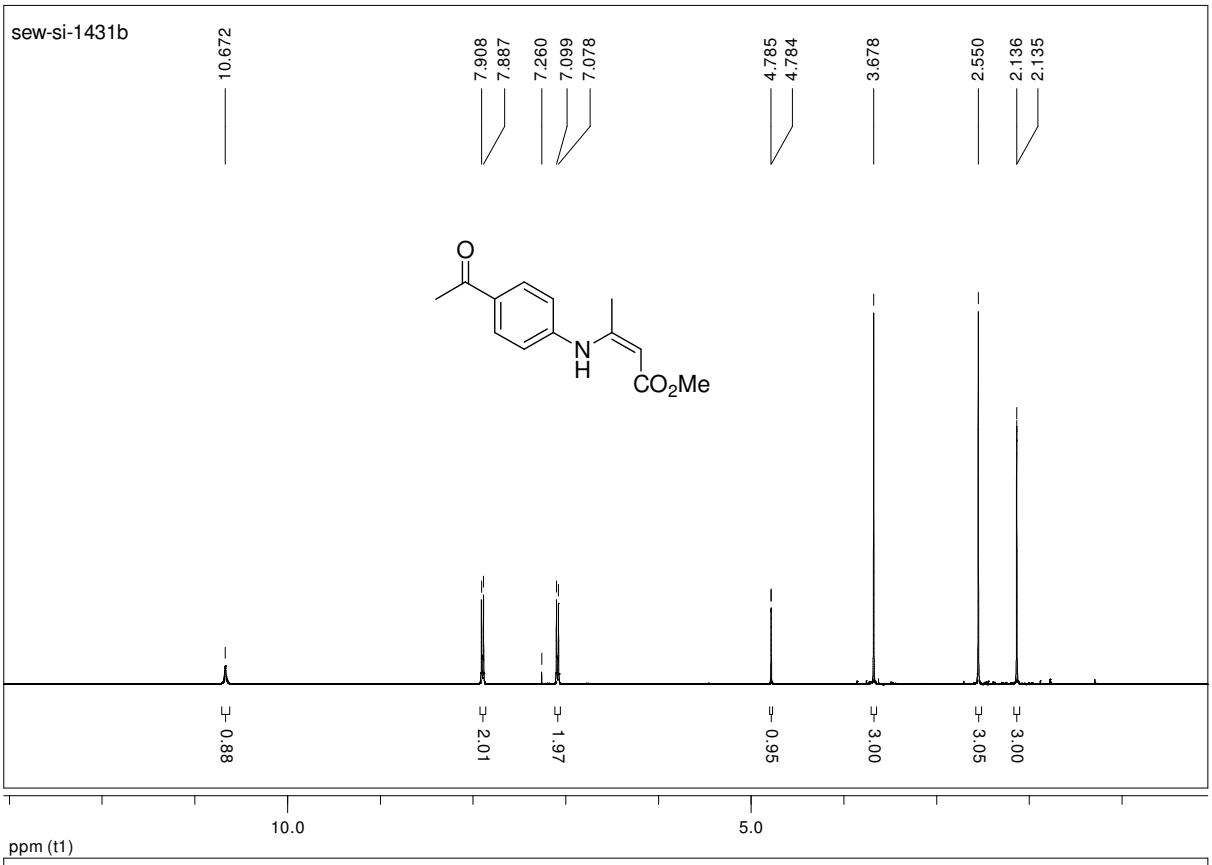
197.306
170.586
158.232
139.815
138.037
129.303
128.391
124.566
123.353
86.848
77.000
50.301
26.592
20.244
200
150
100
50
0
ppm (t1)


sew-si-1431b
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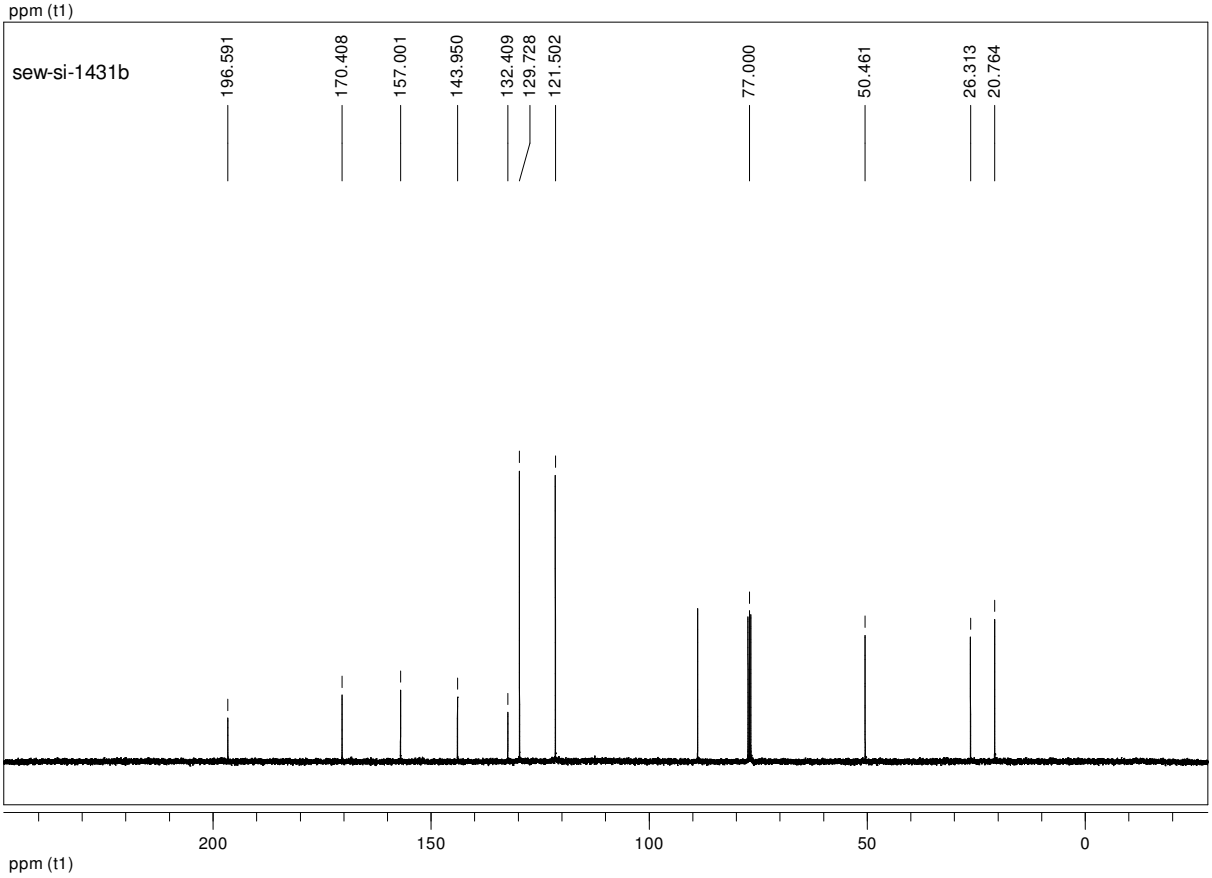
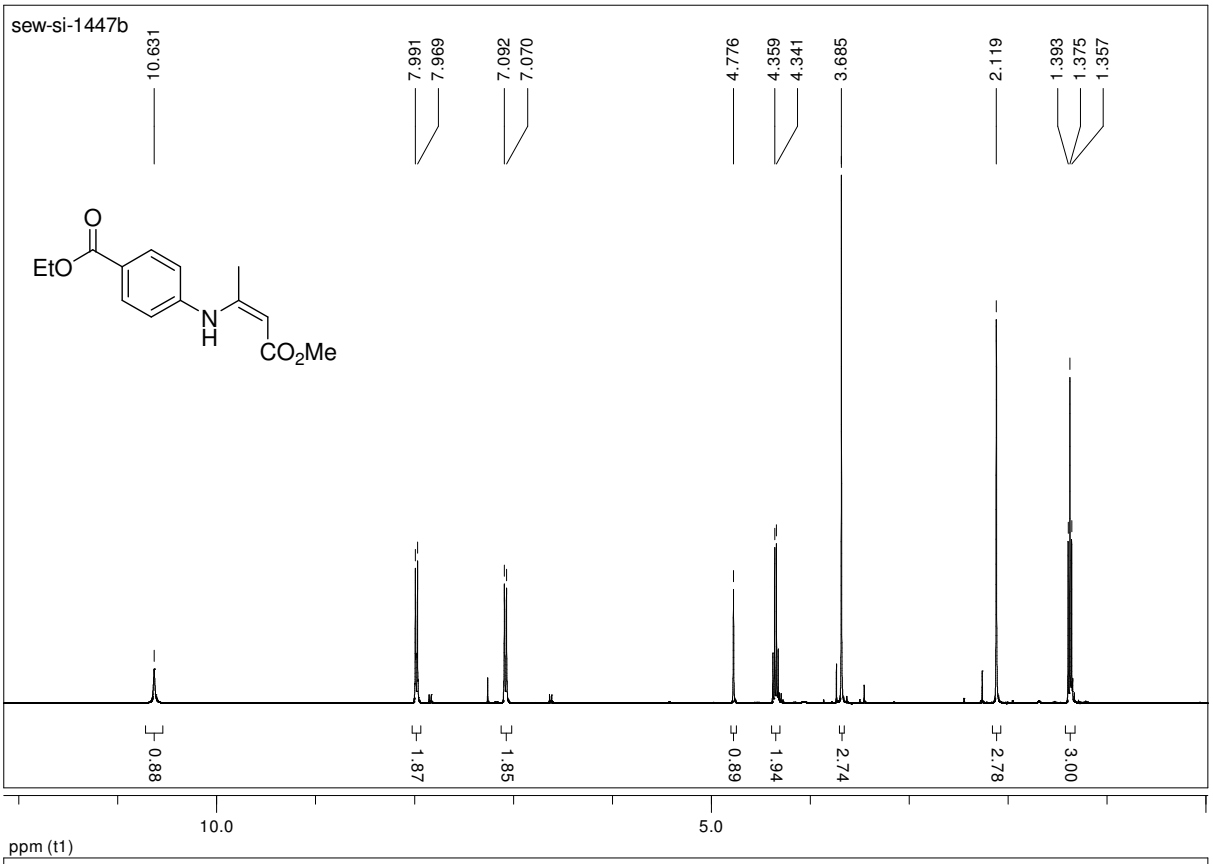
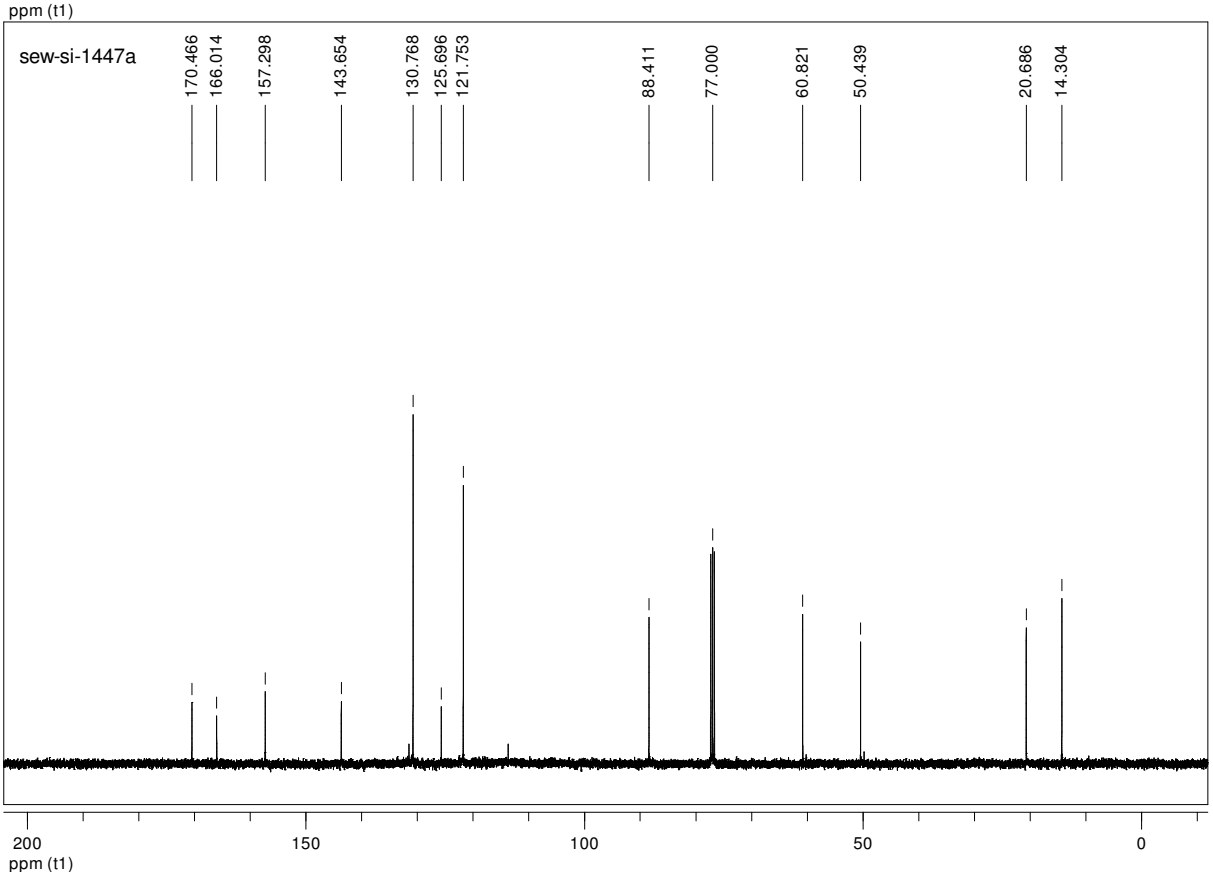
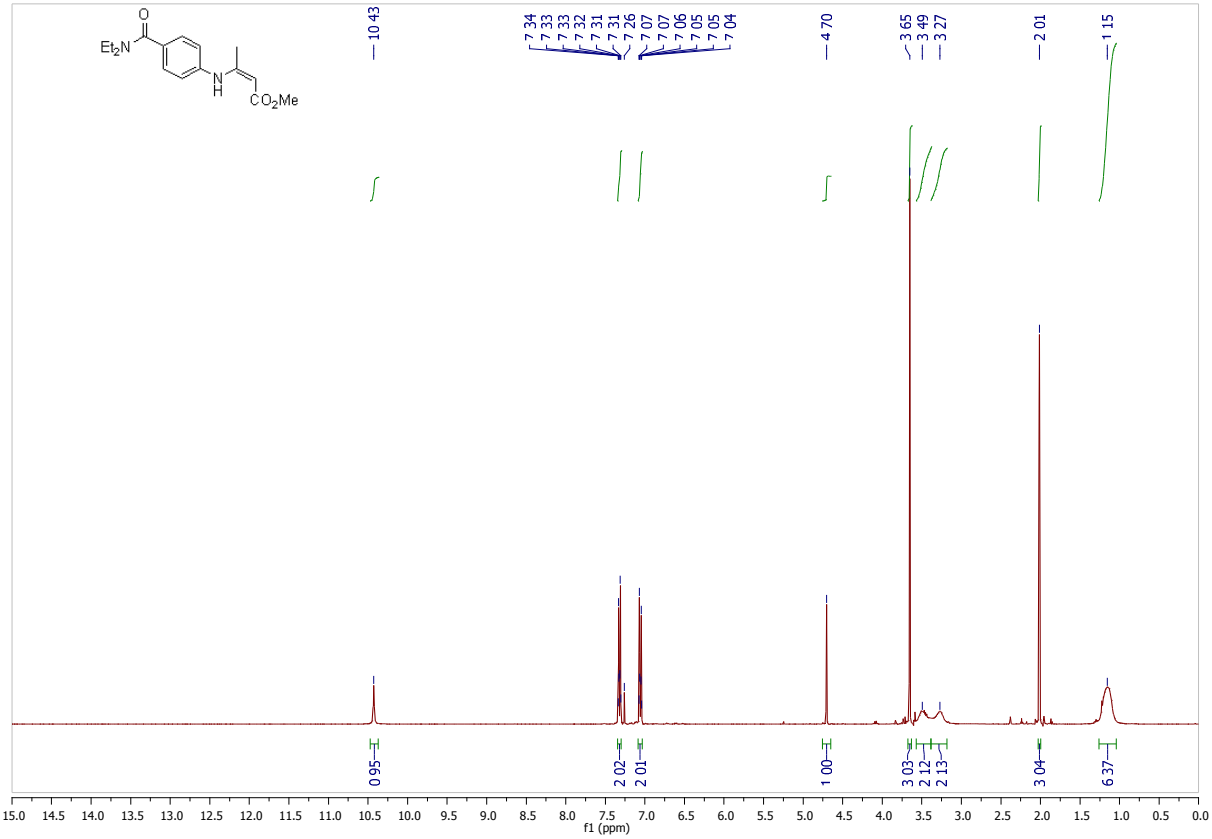
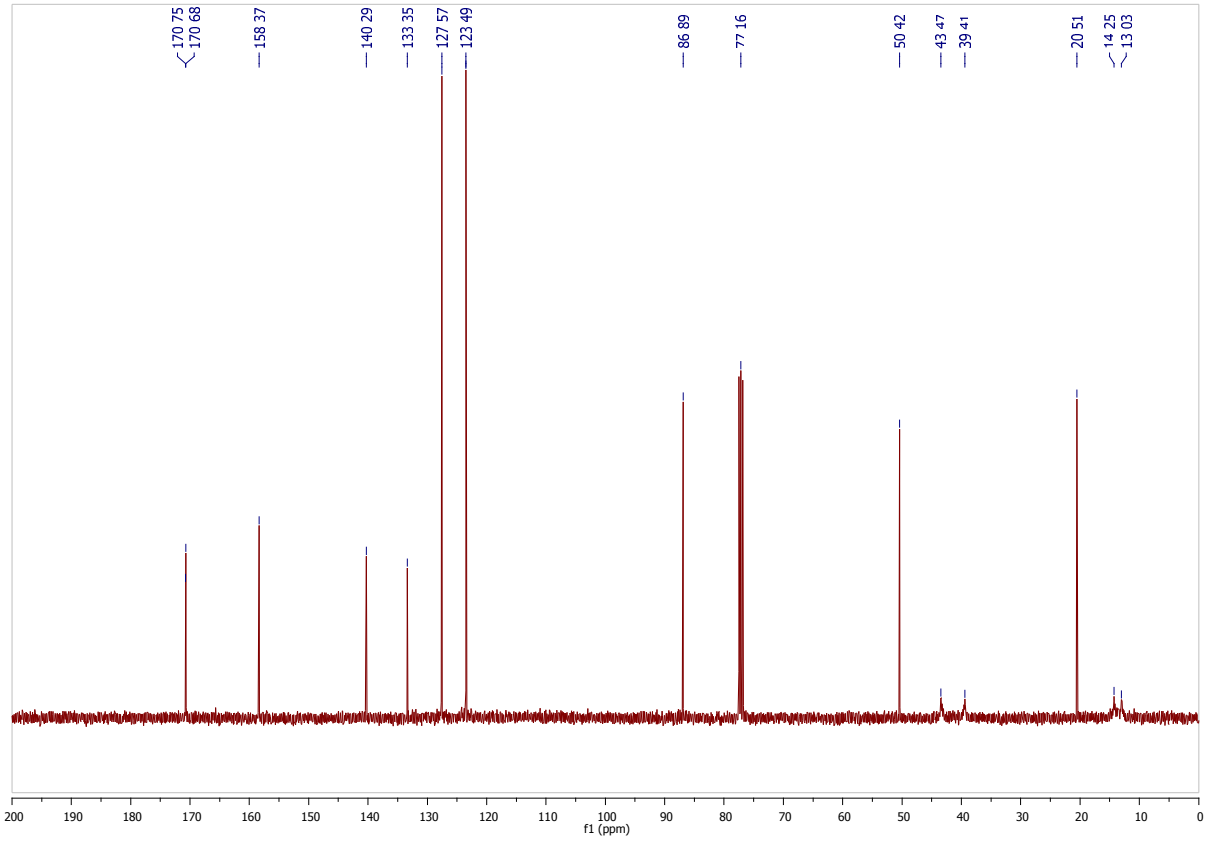
7.908
7.887
7.260
7.099
7.078
4.785
4.784
3.678
2.550
2.136
2.135
O
N
H
CO2Me
0.88
2.01
1.97
0.95
3.00
3.05
3.00
10.0
5.0
ppm (t1)

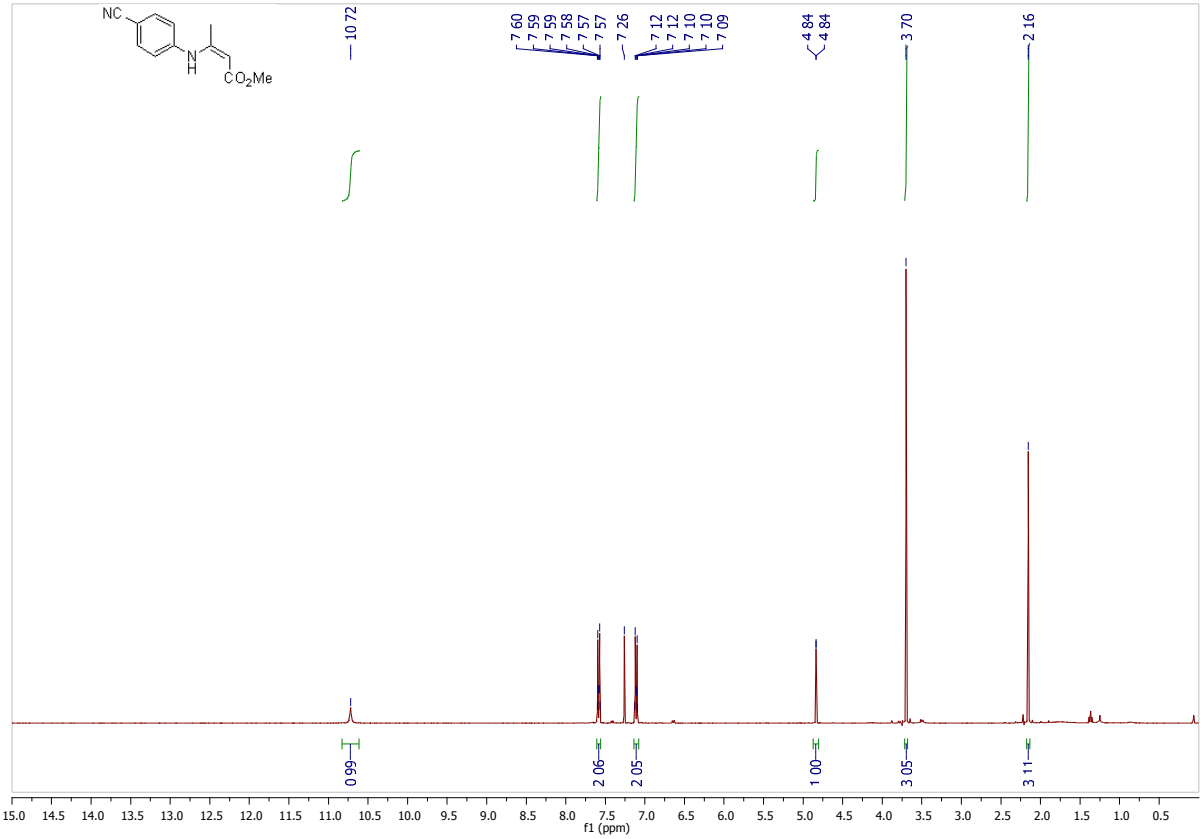

sew-si-1431b
196.591
170.408
157.001
143.950
132.409
129.728
121.502
77.000
50.461
26.313
20.764
200
150
100
50
0
ppm (t1)

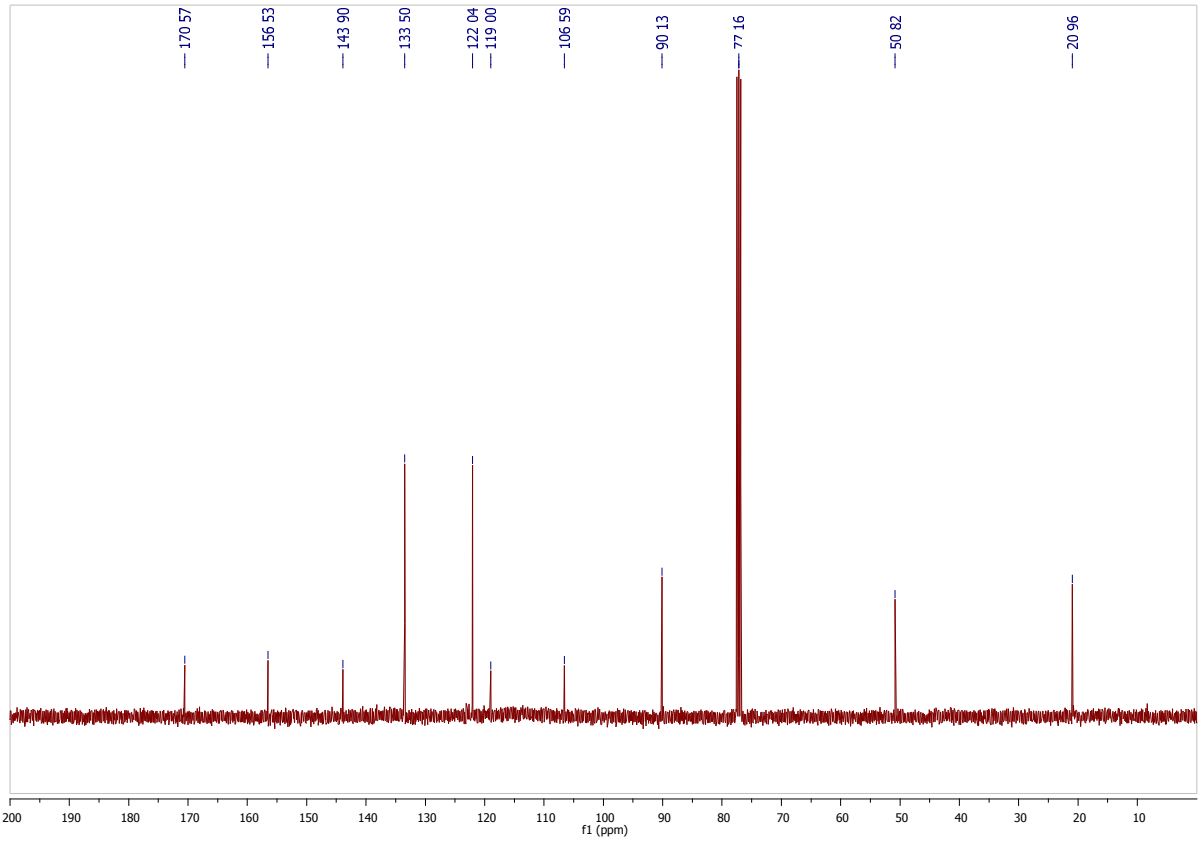

sew-si-1447b
10.631
7.991
7.969
7.092
7.070
4.776
4.359
4.341
3.685
2.119
1.393
1.375
1.357
EtO
O
N
H
CO2Me
0.88
1.87
1.85
0.89
1.94
2.74
2.78
3.00
10.0
5.0
ppm (t1)

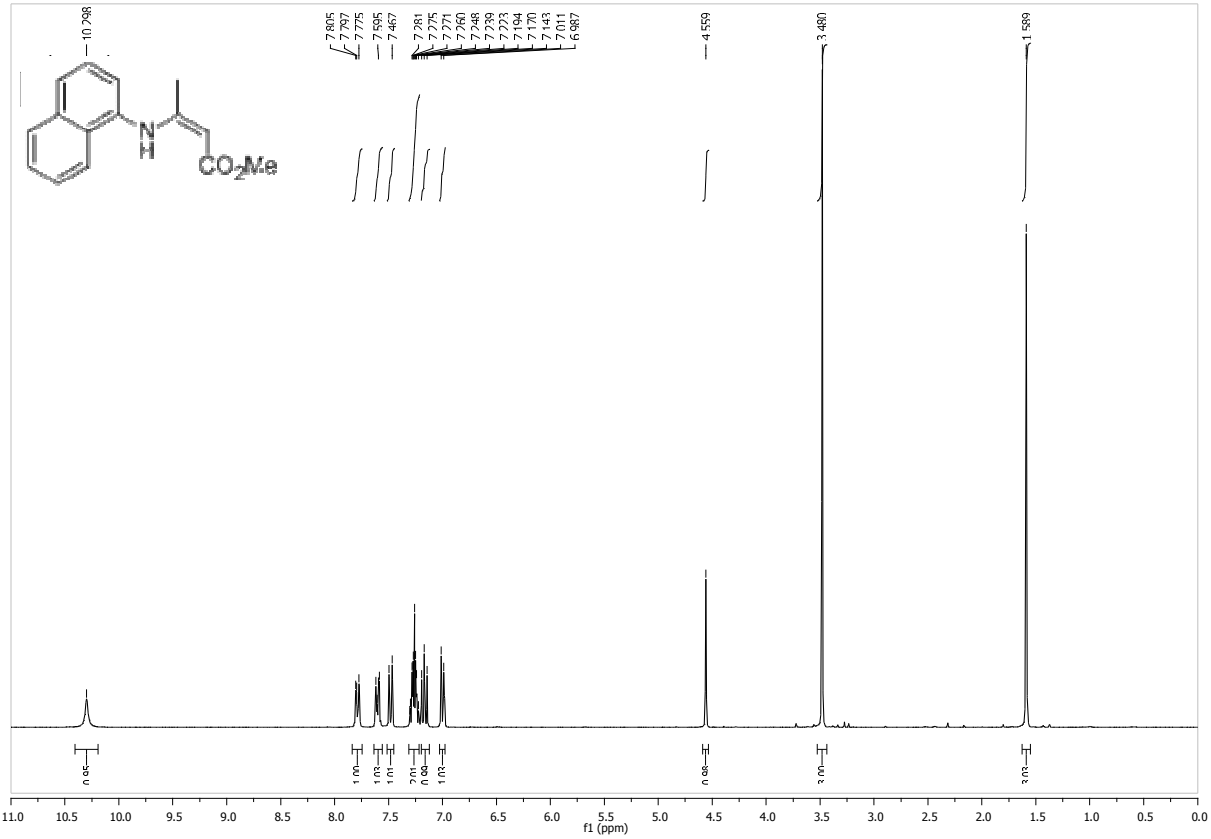

sew-si-1447a
170.466
166.014
157.298
143.654
130.768
125.696
121.753
88.411
77.000
60.821
50.439
20.686
14.304
200
150
100
50
0
ppm (t1)

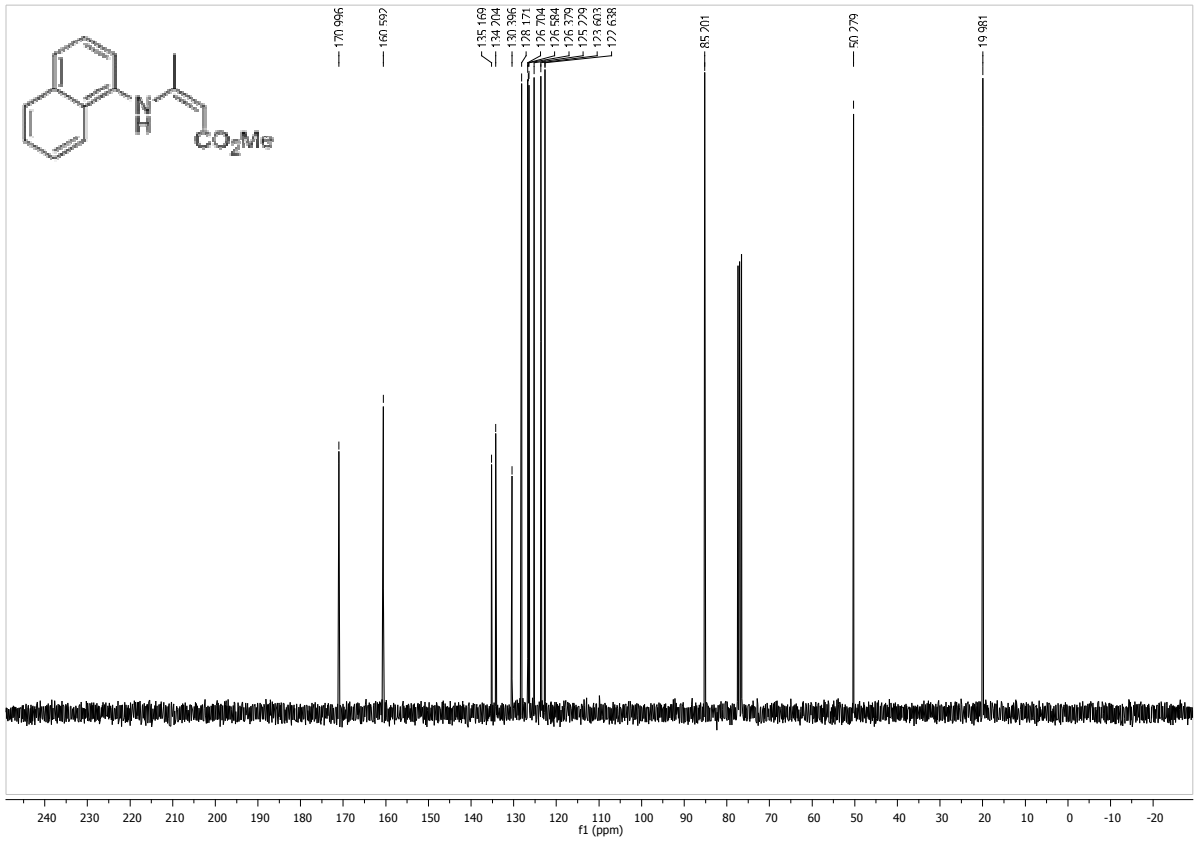

Et2N
O
N
H
CO2Me
10.43
7.34
7.33
7.33
7.32
7.31
7.31
7.26
7.07
7.07
7.06
7.05
7.05
7.04
4.70
3.65
3.49
3.27
2.01
1.15
0.95
2.02
2.01
1.00
3.03
2.12
2.13
3.04
6.37
f1 (ppm)

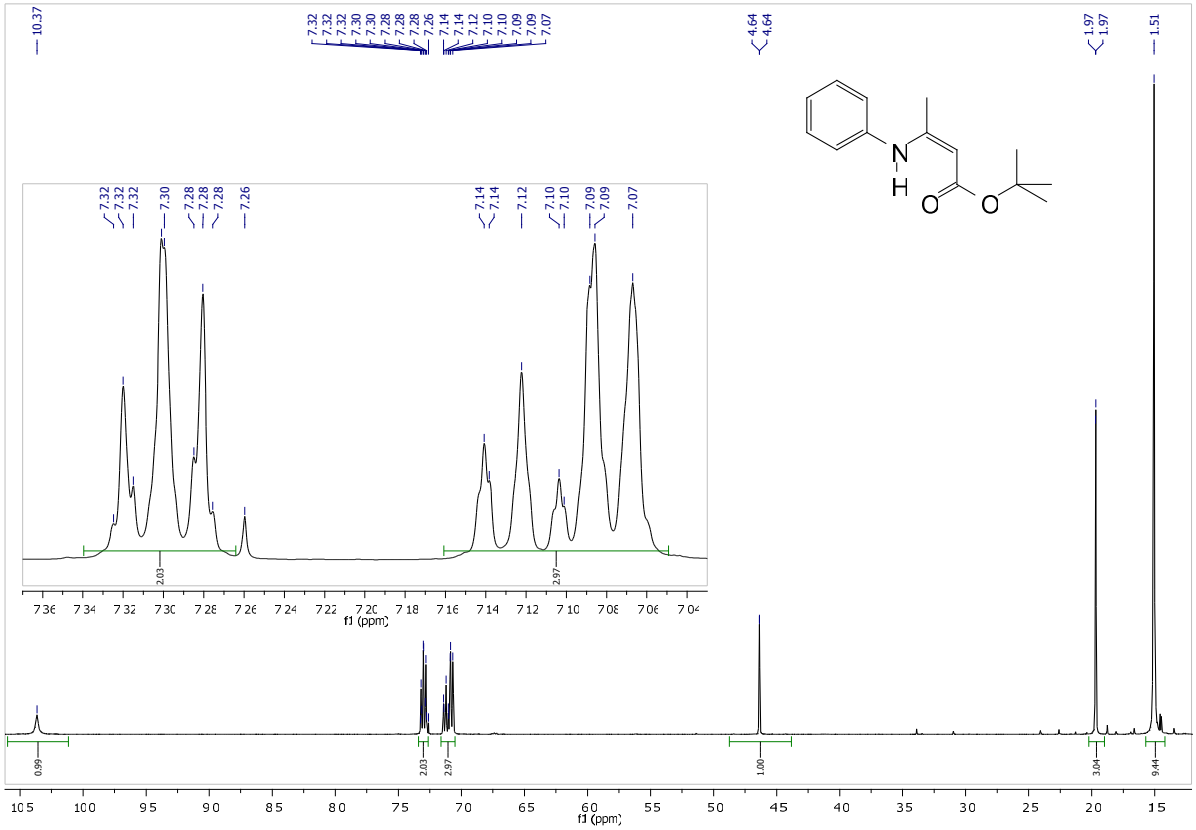

170.75
170.68
158.37
140.29
133.35
127.57
123.49
86.89
77.16
50.42
43.47
39.41
20.51
14.25
13.03
f1 (ppm)

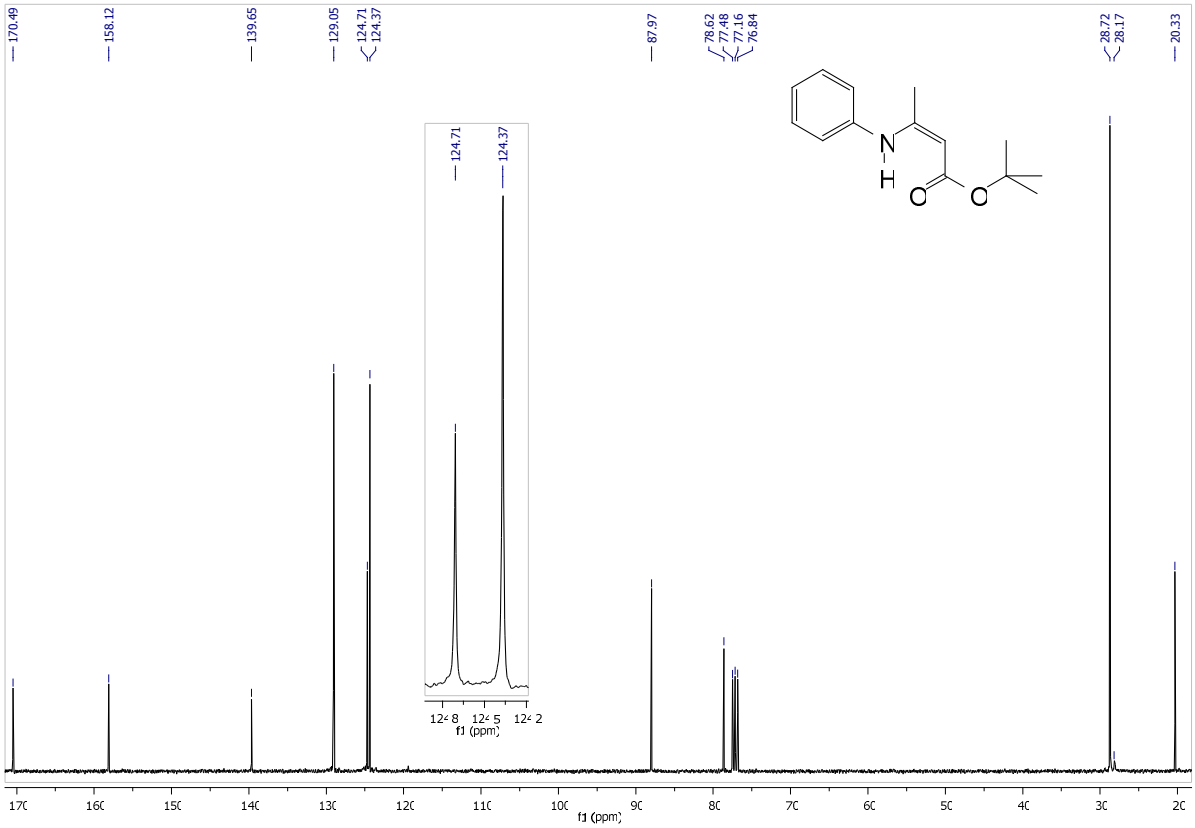

NC
N
H
CO2Me
10.72
7.60
7.59
7.59
7.58
7.57
7.57
7.26
7.12
7.12
7.10
7.10
7.09
4.84
4.84
3.70
2.16
0.99
2.06
2.05
1.00
3.05
3.11
f1 (ppm)

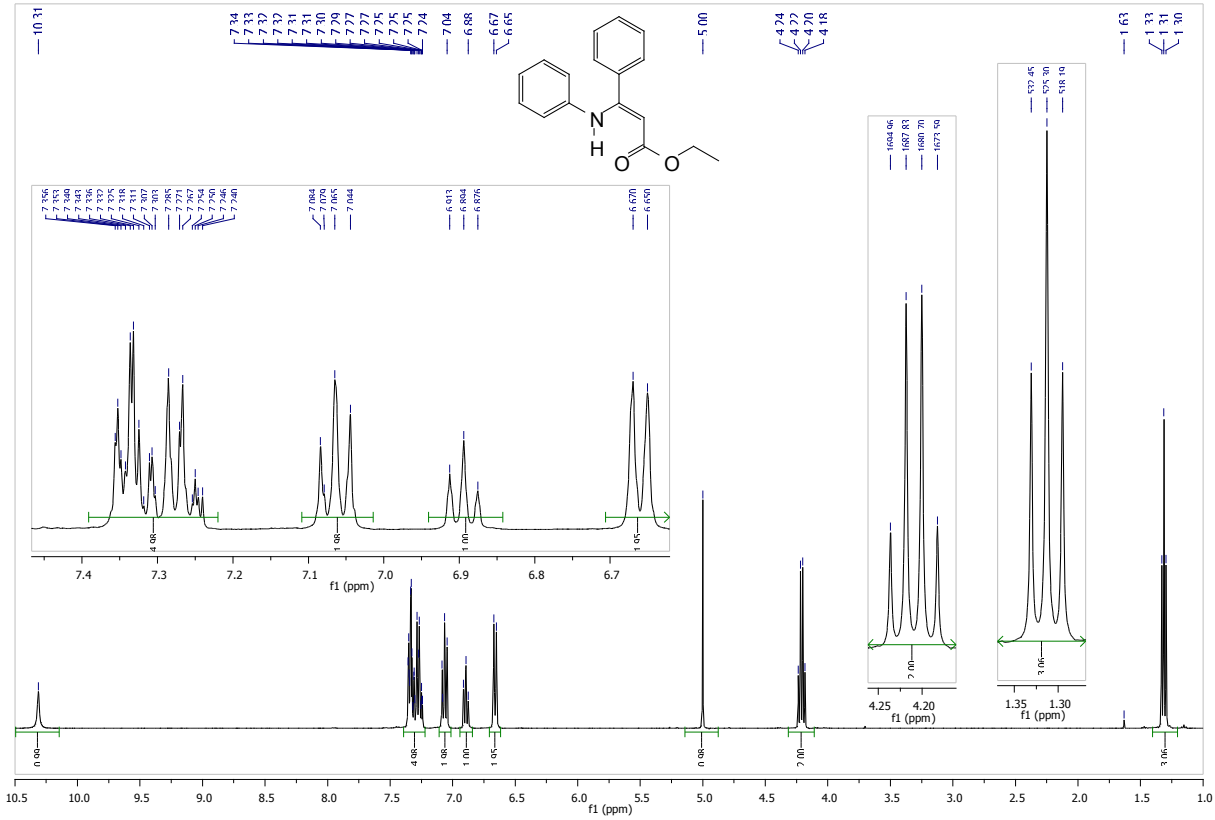

170.57
156.53
143.90
133.50
122.04
119.00
106.59
90.13
77.16
50.82
20.96
f1 (ppm)

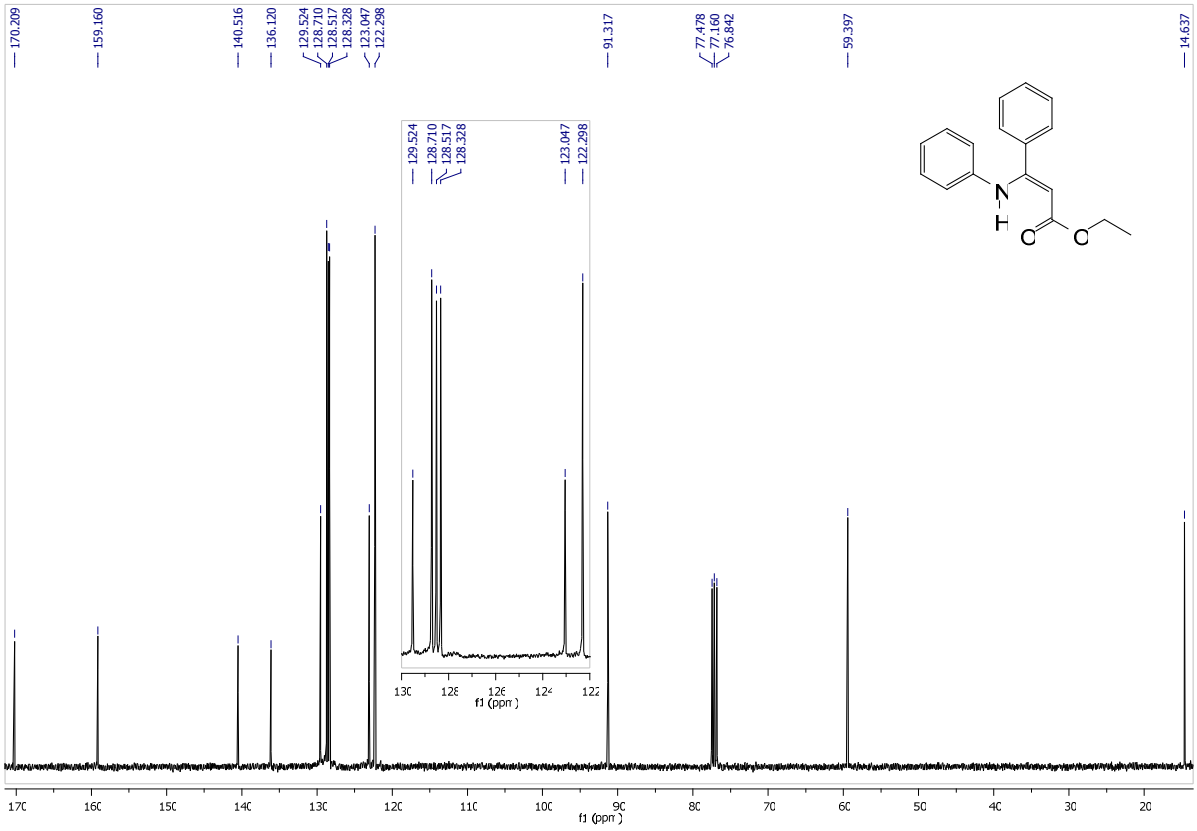

10.298
7.805
7.797
7.775
7.595
7.467
7.281
7.275
7.271
7.260
7.248
7.239
7.223
7.194
7.170
7.143
7.011
6.987
4.559
3.480
1.589
CO2Me
f1 (ppm)


170.996
160.597
135.169
134.204
130.396
128.171
126.704
126.584
126.379
125.229
123.603
122.638
85.201
50.779
19.981
CO2Me
f1 (ppm)

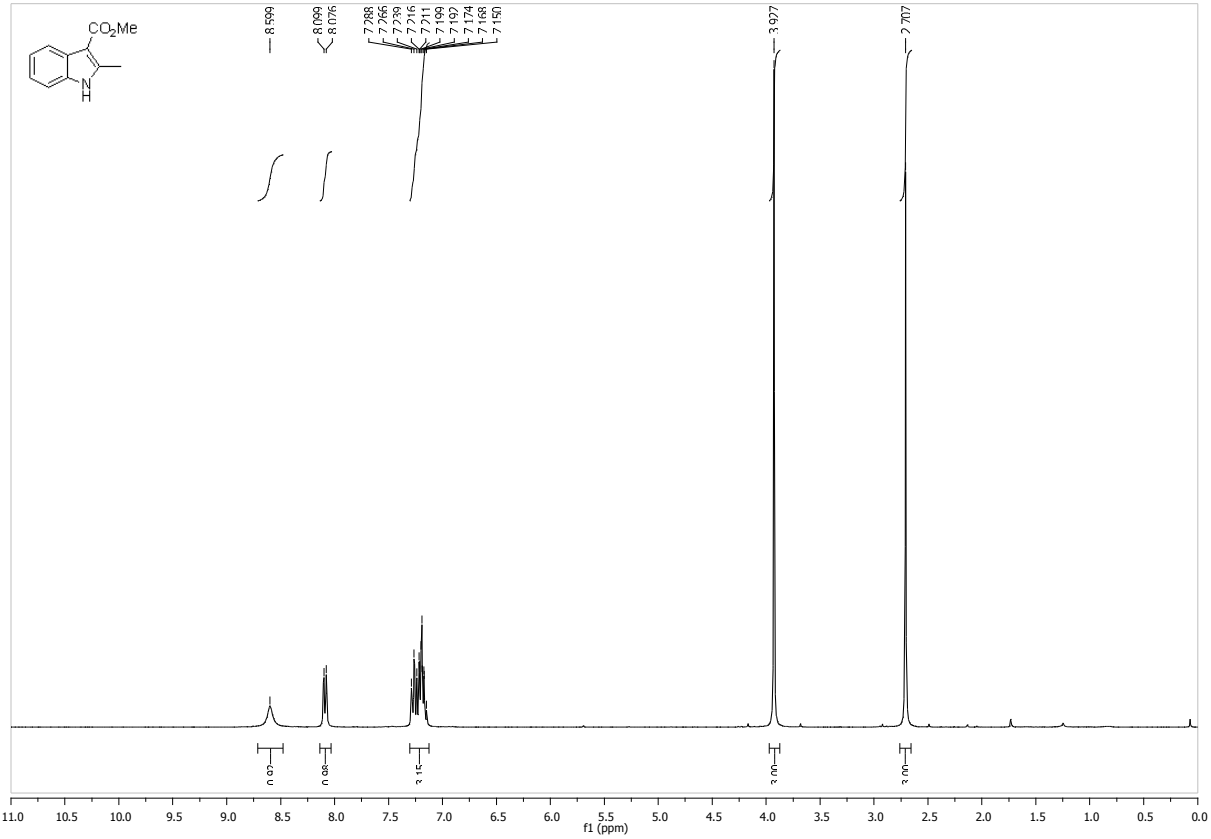

10.37
7.32
7.32
7.32
7.30
7.28
7.28
7.28
7.26
7.14
7.14
7.12
7.10
7.10
7.09
7.09
7.07
4.64
4.64
1.97
1.97
1.51
N
H
O
O
f1 (ppm)

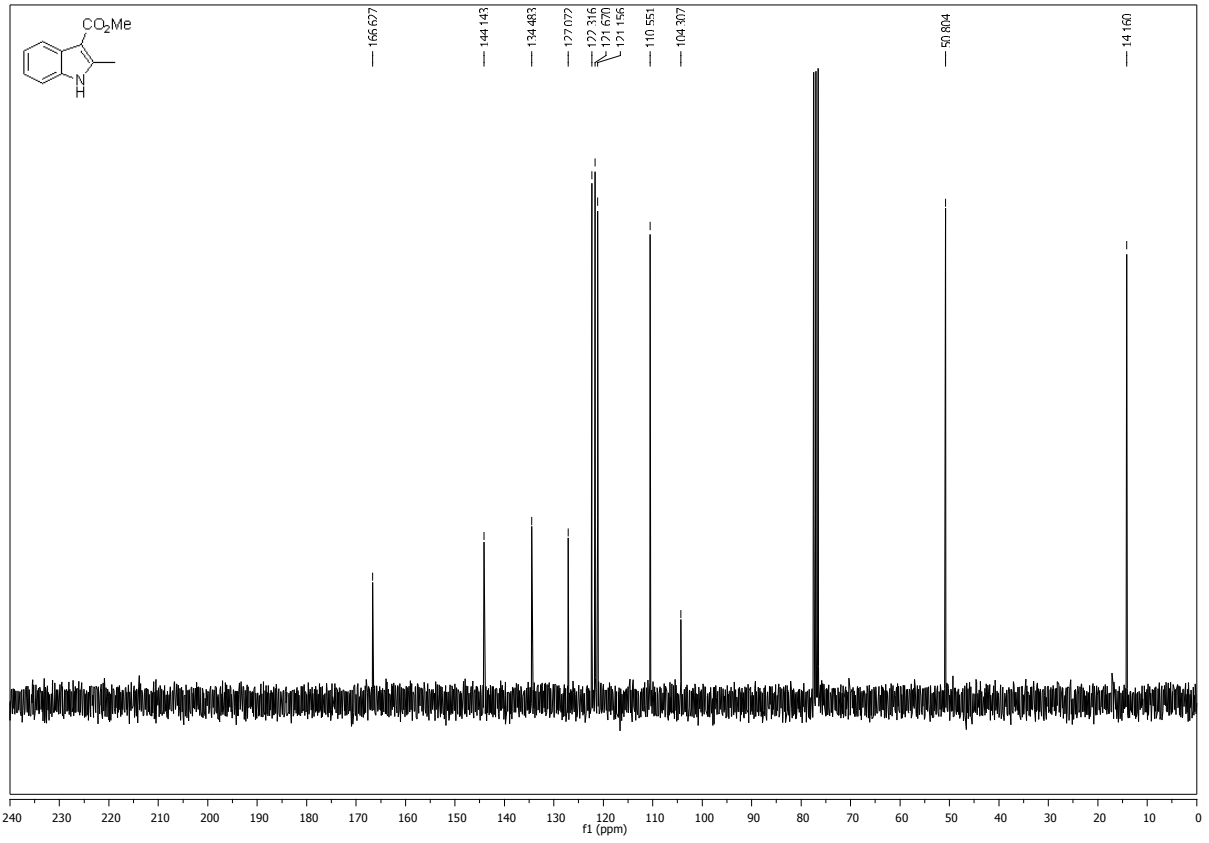

170.49
158.12
139.65
129.05
124.71
124.37
87.97
78.62
77.48
77.16
76.84
28.72
28.17
20.33
N
H
O
O
f1 (ppm)

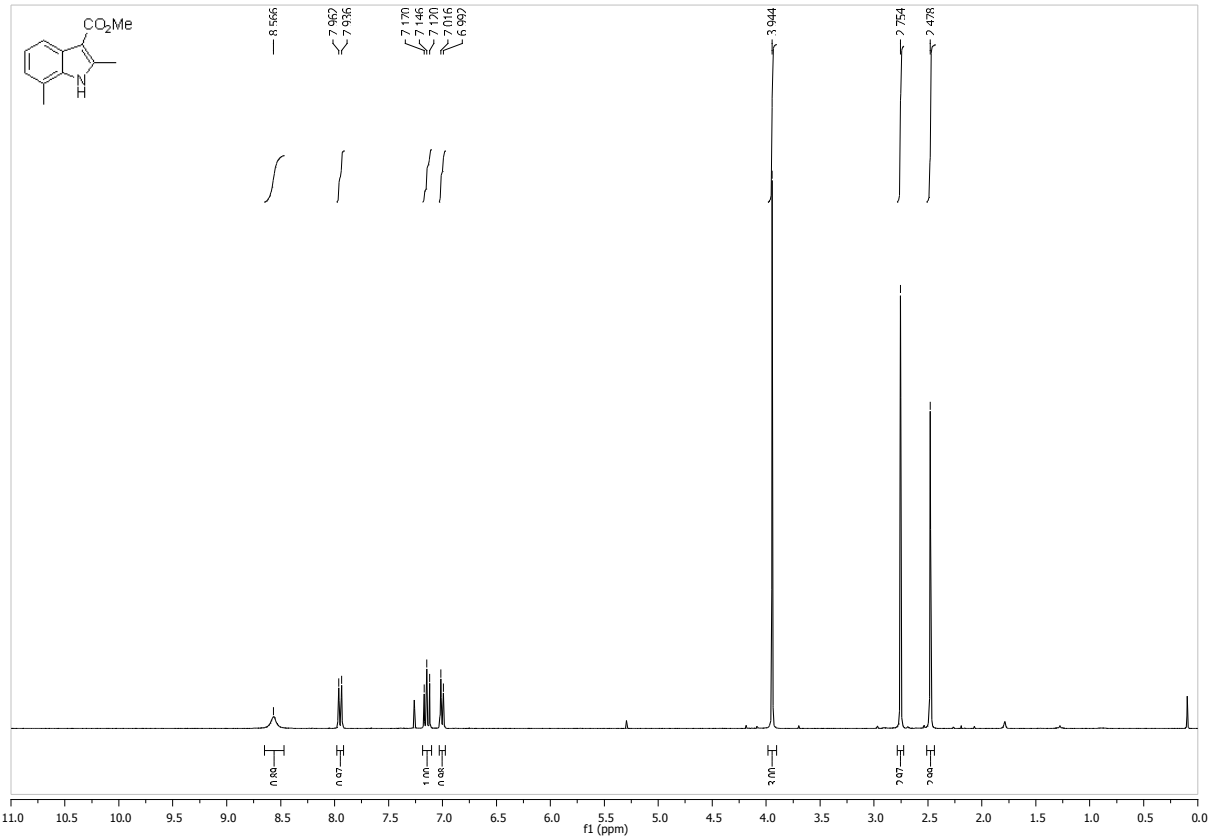


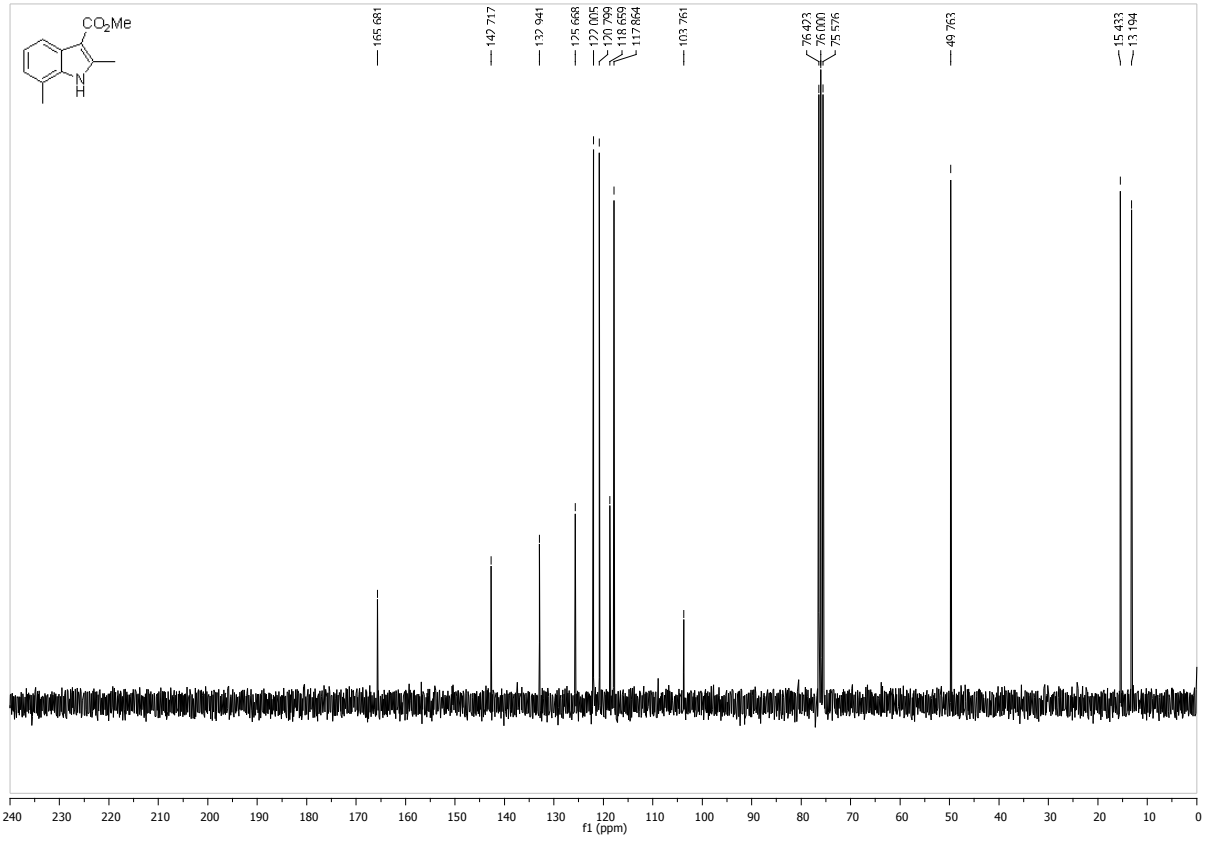


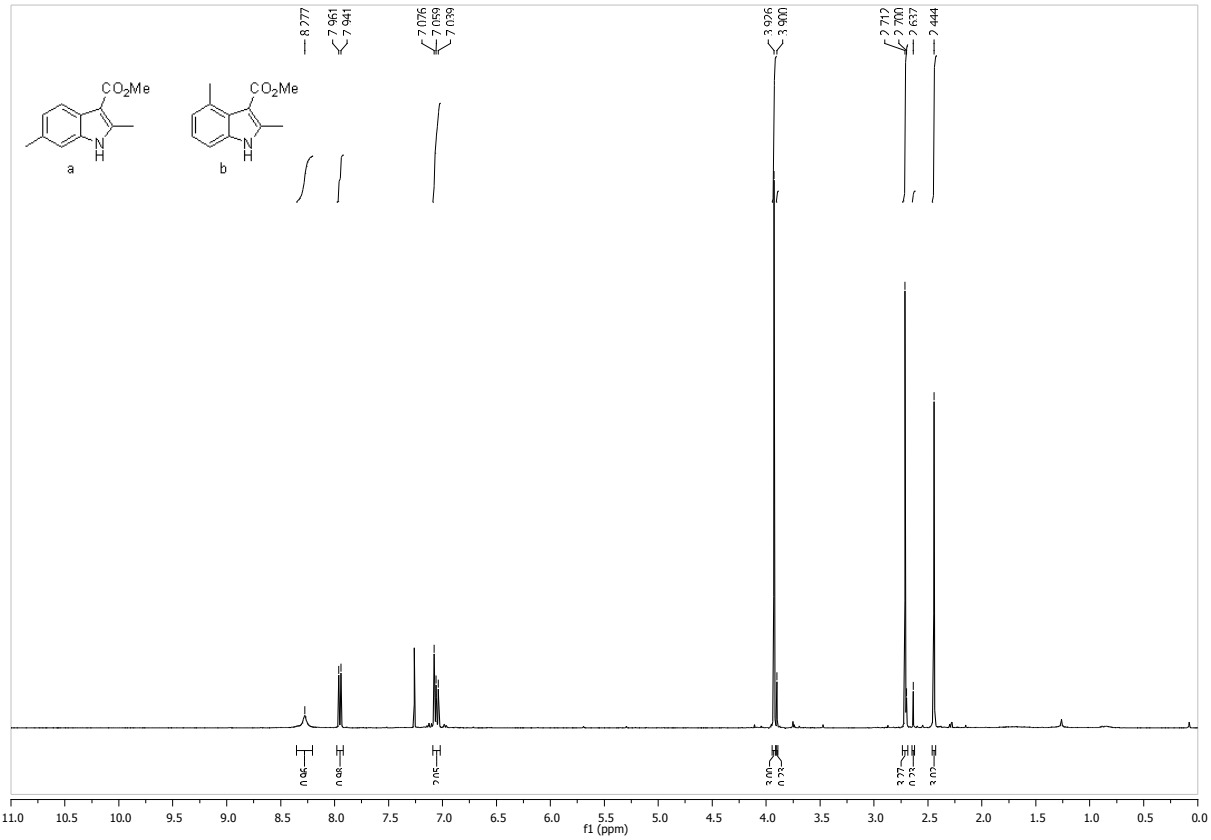
a. Products

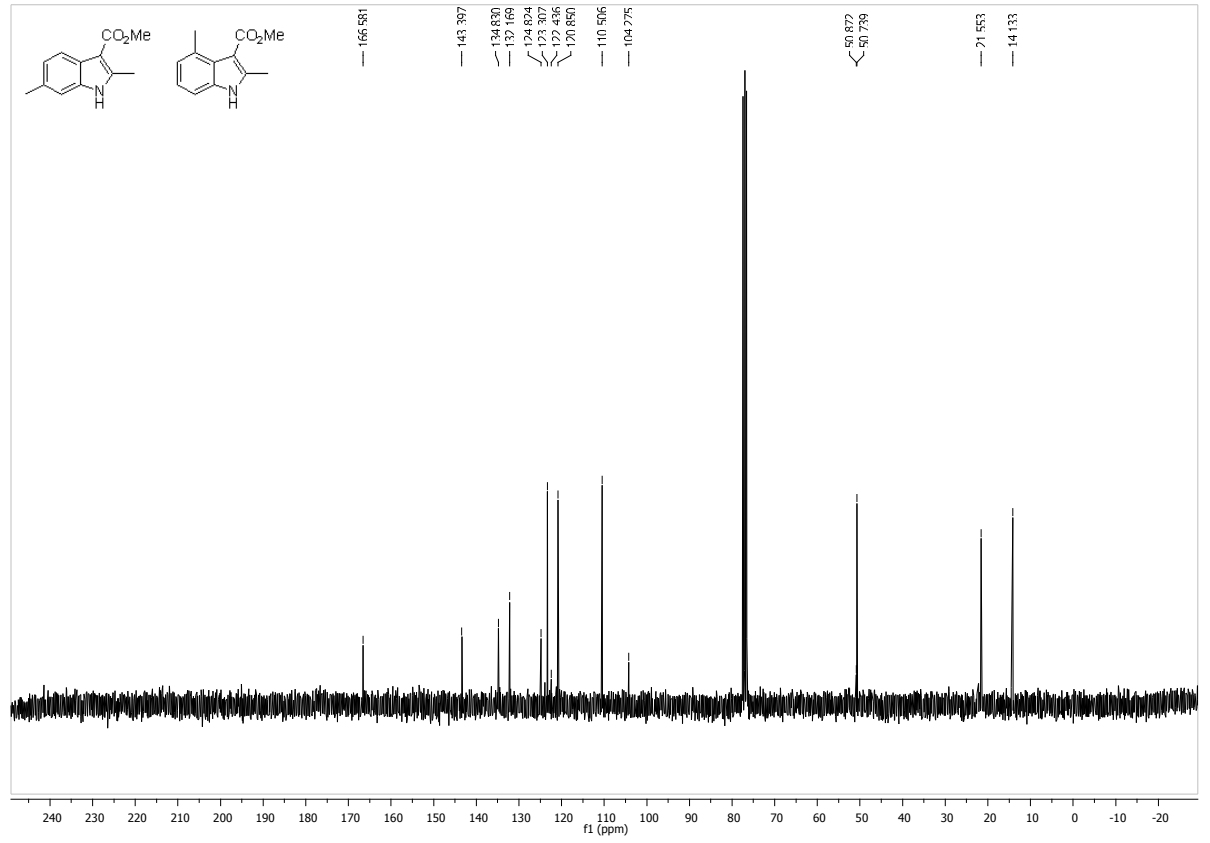

CO2Me
N
H
8.599
8.099
8.076
7.288
7.266
7.239
7.216
7.211
7.190
7.192
7.174
7.168
7.150
3.927
2.707
0.93
0.98
3.15
3.00
3.00
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

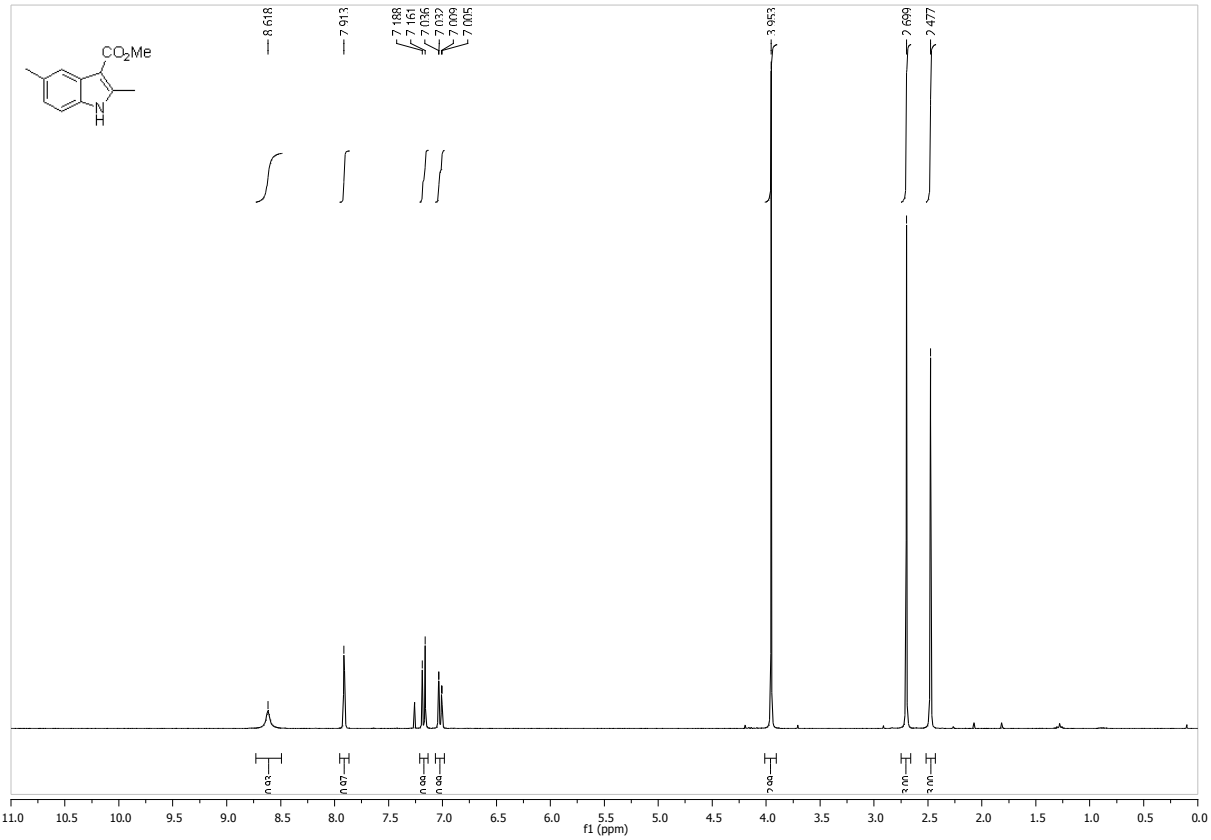

CO2Me
N
H
166.677
144.143
134.483
127.072
122.316
121.670
121.156
110.551
104.307
50.804
14.160
240
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

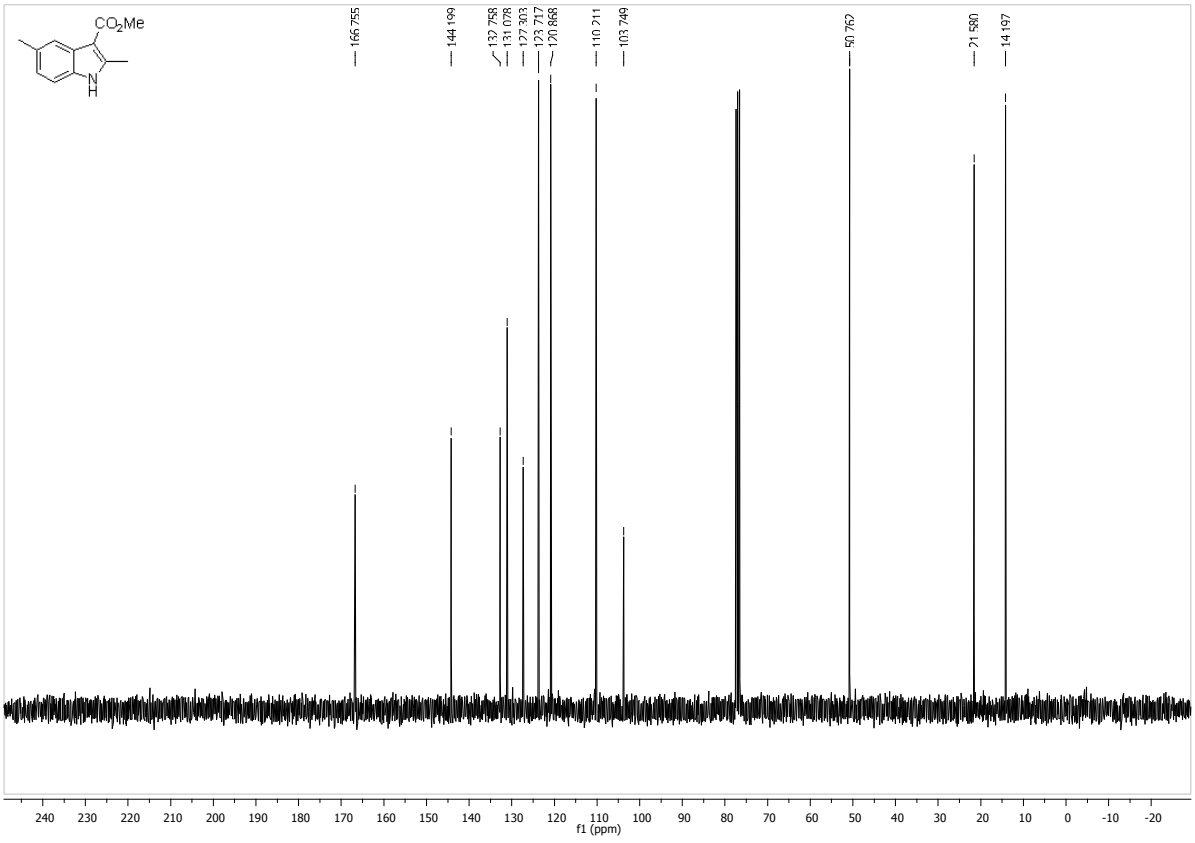

CO2Me
N
H
8.566
7.967
7.936
7.170
7.146
7.120
7.016
6.992
3.944
2.754
2.478
f1 (ppm)

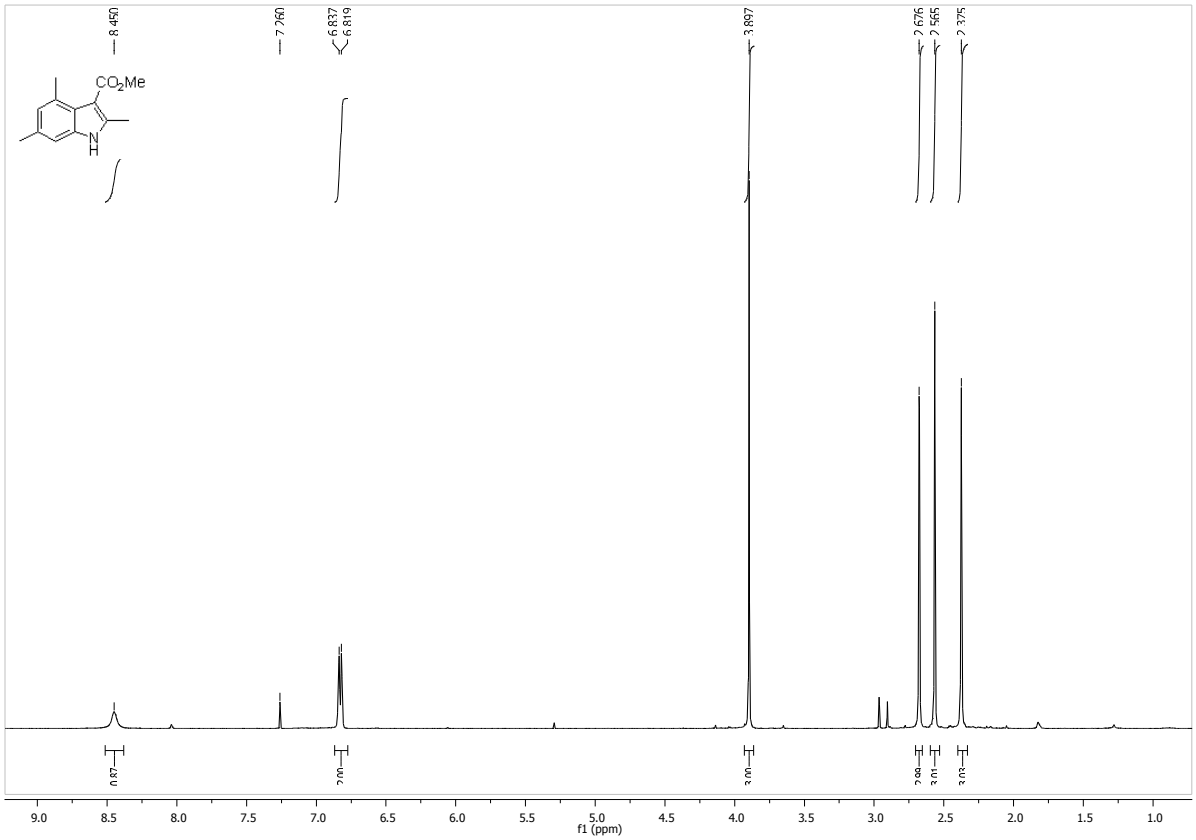

CO2Me
N
H
166.681
142.717
137.941
125.668
122.005
120.799
118.659
117.864
103.761
76.473
76.000
75.576
49.763
15.433
13.194
f1 (ppm)

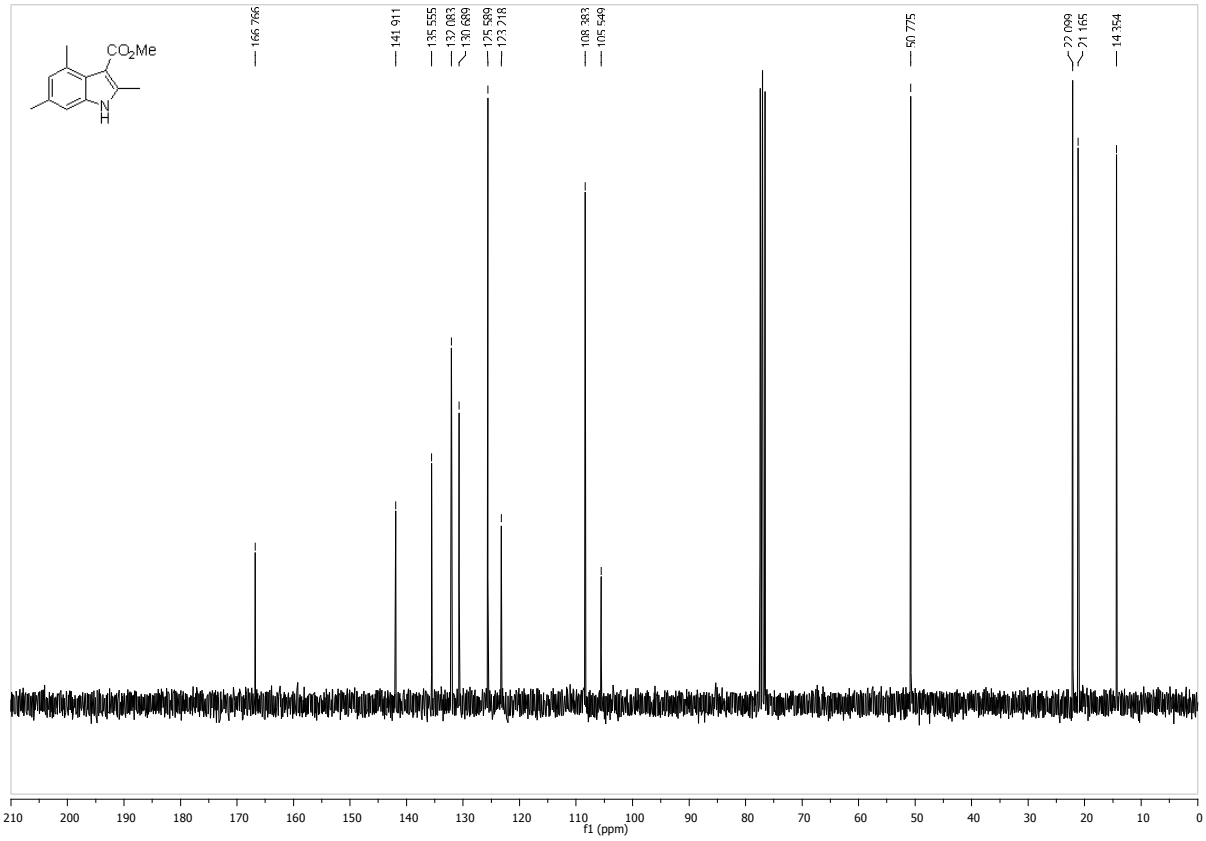

8.777
7.961
7.941
7.076
7.059
7.039
3.926
3.900
2.712
2.700
2.637
2.444
CO2Me
N
H
a
b
f1 (ppm)

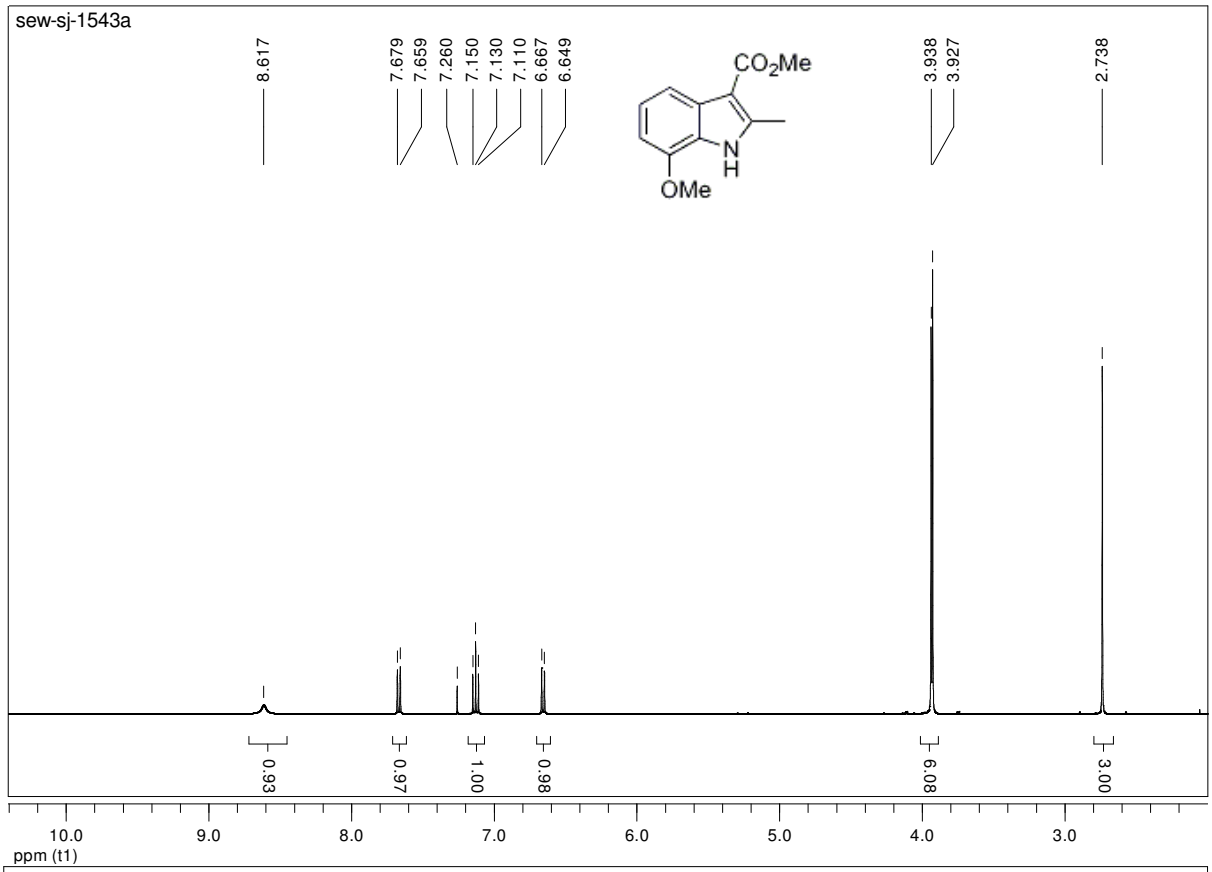

166.581
143.397
134.830
133.169
124.624
123.307
122.436
120.850
110.506
104.775
50.877
50.739
21.553
14.133
CO2Me
N
H
f1 (ppm)

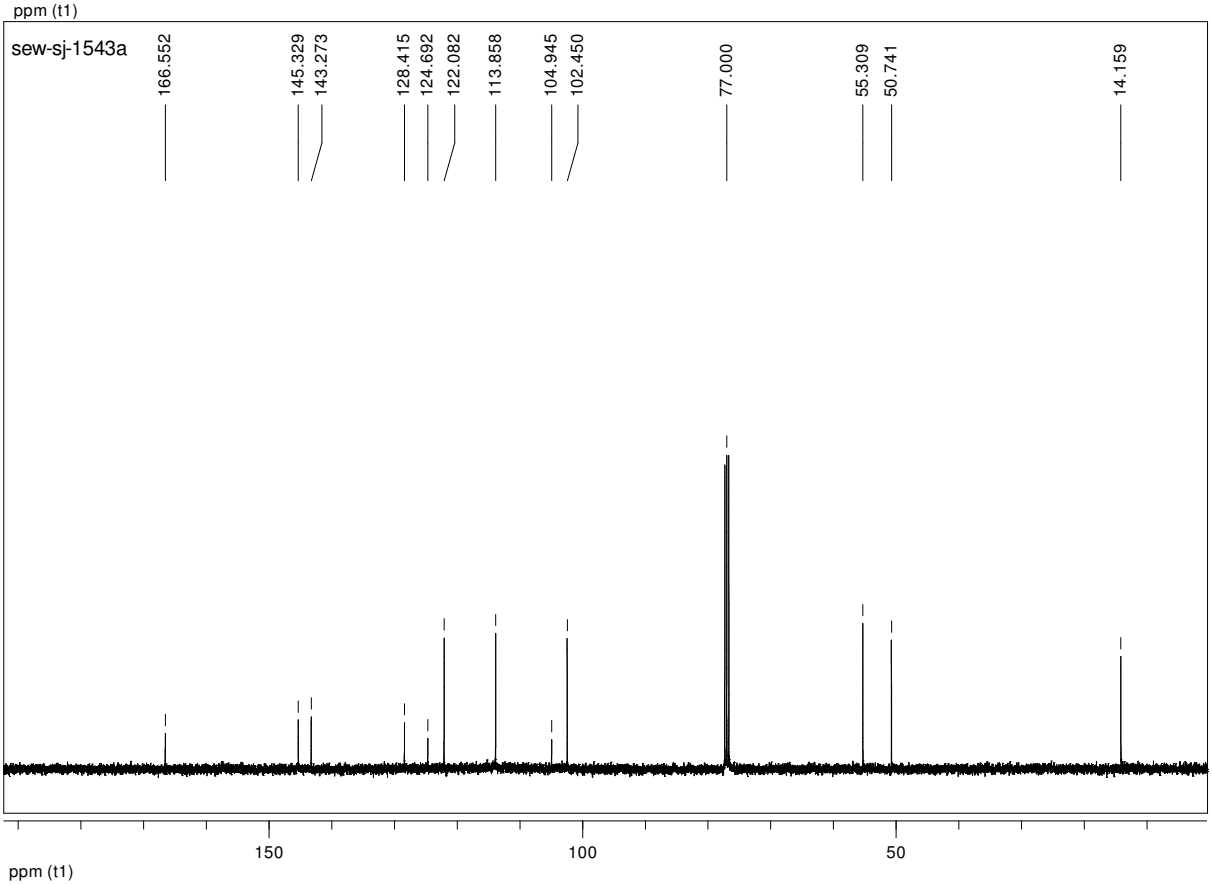

CO2Me
N
H
8.618
7.913
7.188
7.161
7.036
7.032
7.009
7.005
3.953
2.699
2.477
f1 (ppm)

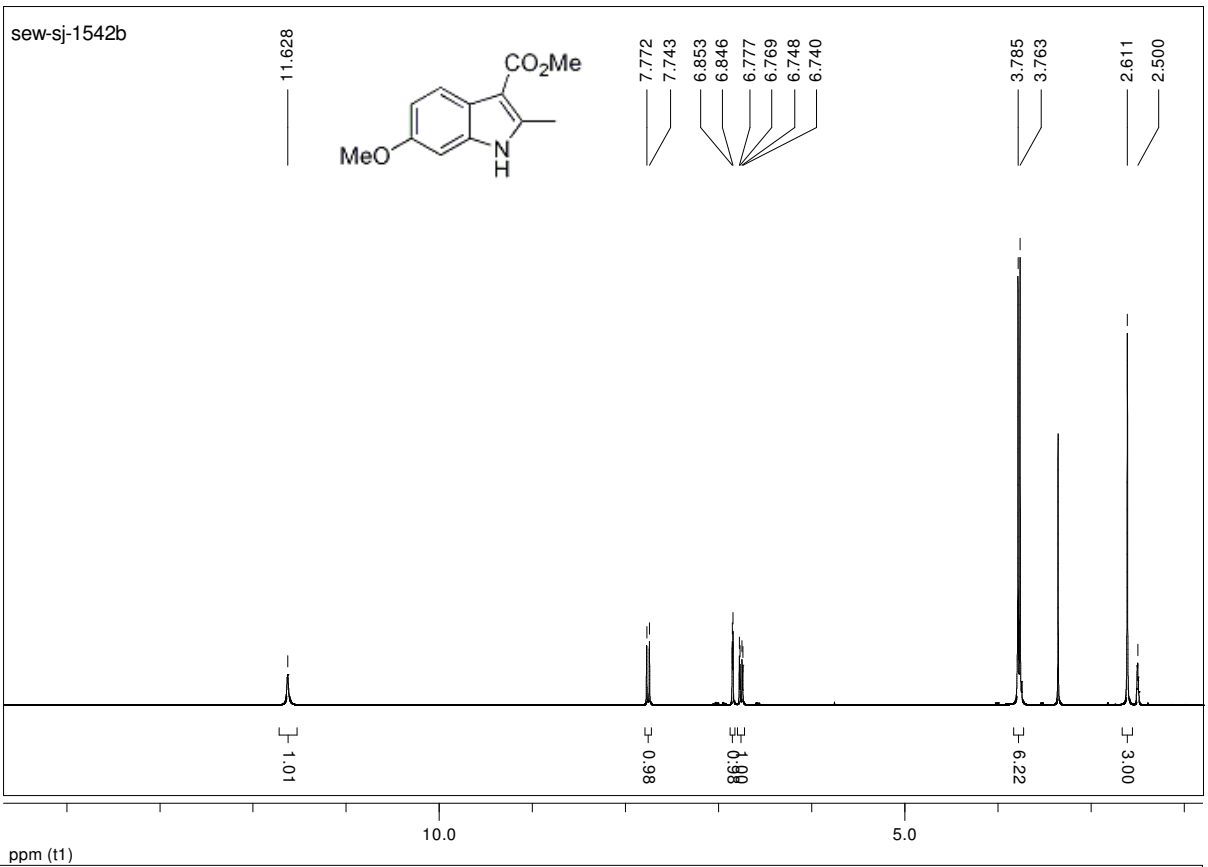

CO2Me
N
H
166.755
144.199
132.758
131.078
127.303
123.717
120.868
110.711
103.749
50.762
21.580
14.197
f1 (ppm)

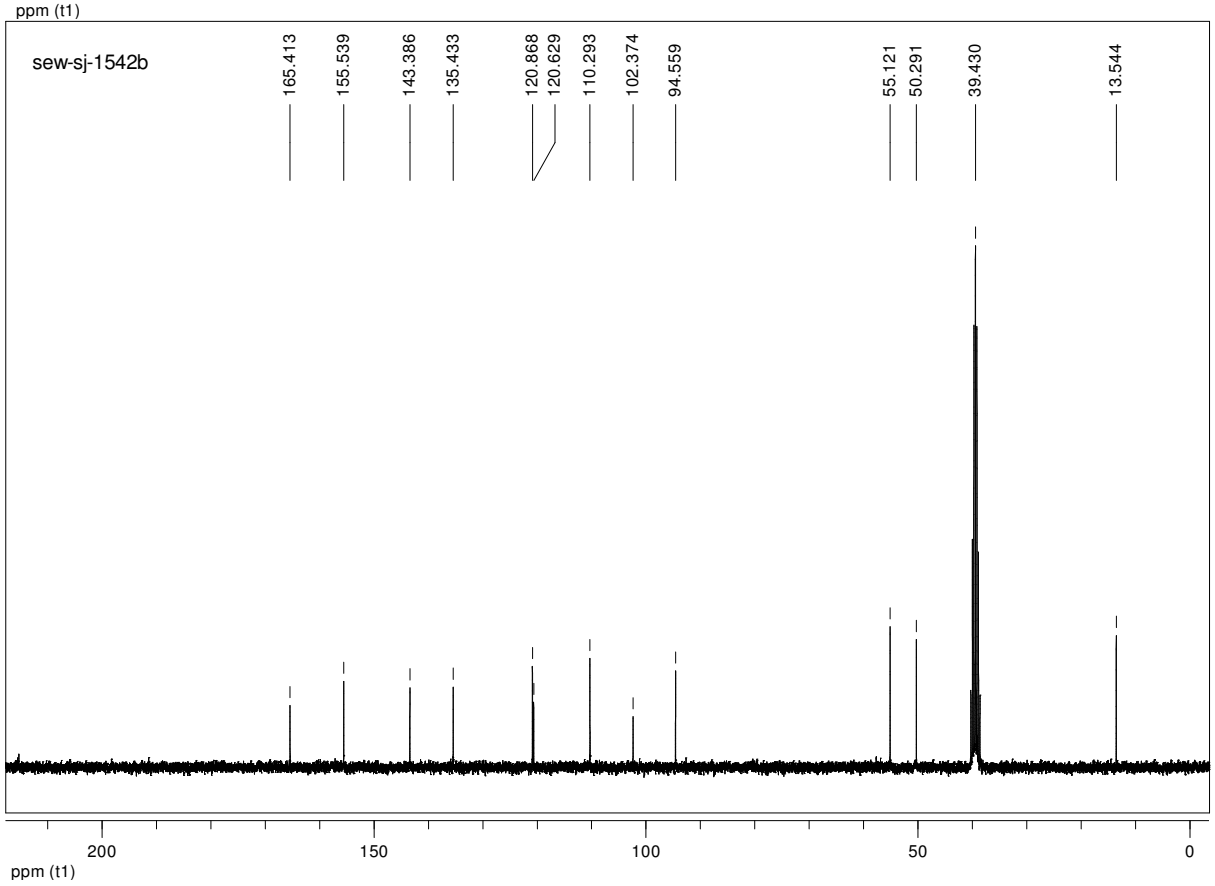

8.450
7.260
6.837
6.819
3.897
2.676
2.565
2.375
CO2Me
N
H
f1 (ppm)

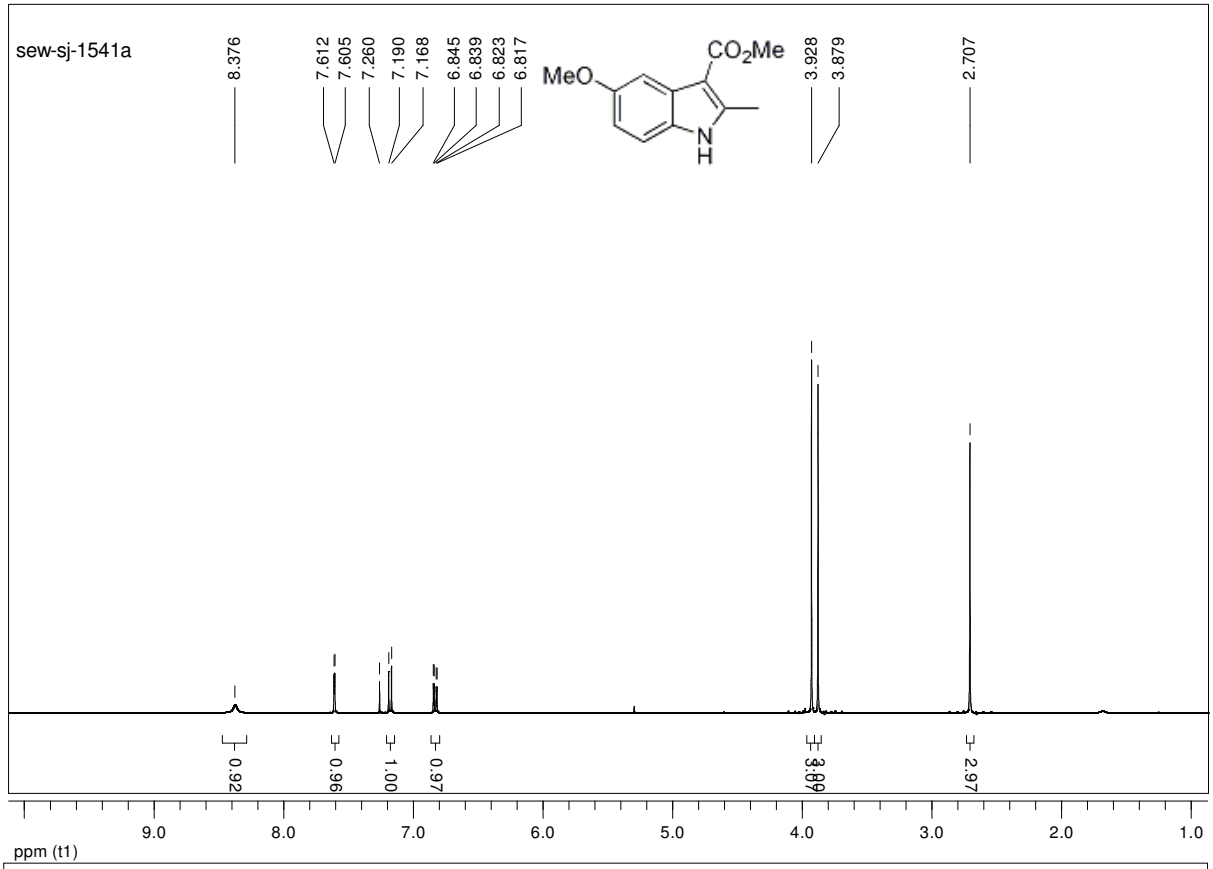

166.766
141.911
135.555
132.083
130.689
125.589
123.718
108.383
105.549
50.775
22.099
21.165
14.354
CO2Me
N
H
f1 (ppm)

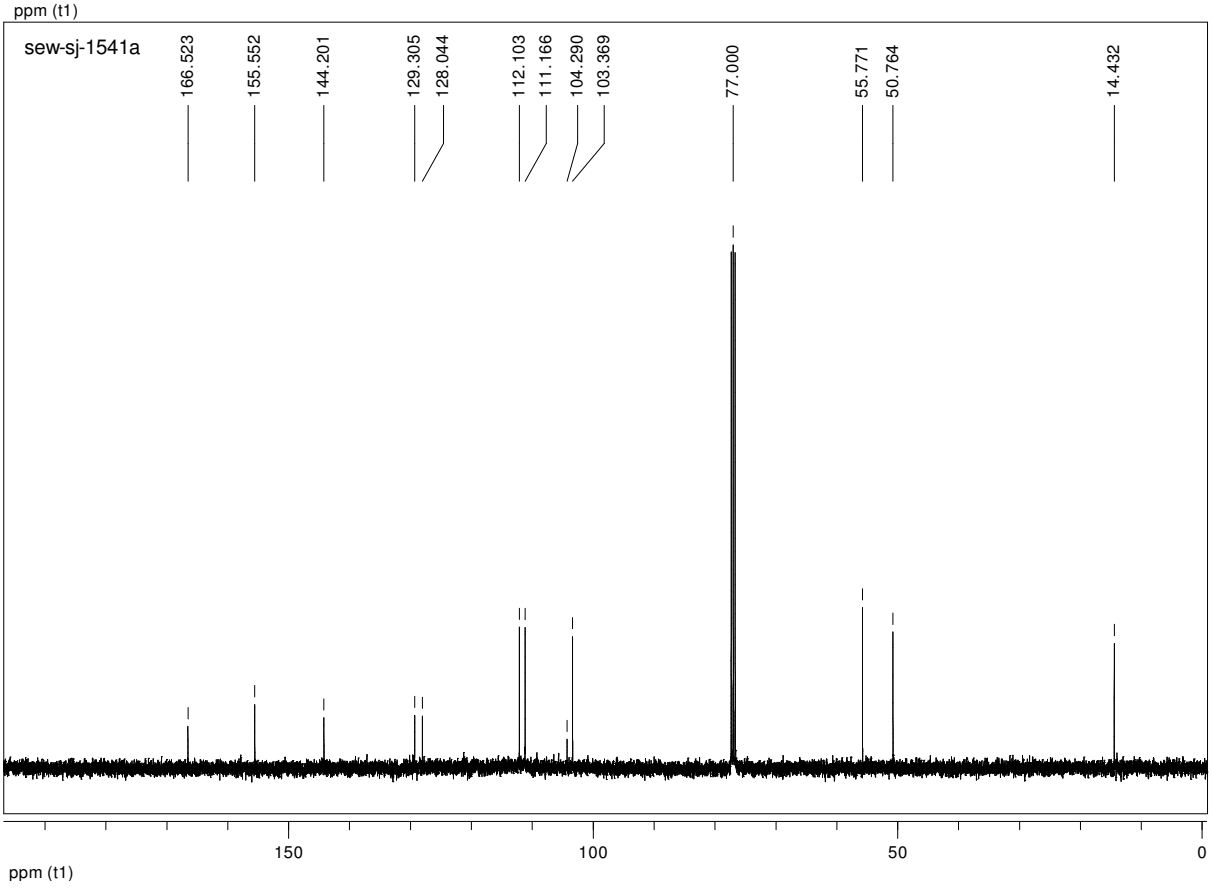

sew-sj-1543a
8.617
7.679
7.659
7.260
7.150
7.130
7.110
6.667
6.649
3.938
3.927
2.738
CO2Me
N
H
OMe
0.93
0.97
1.00
0.98
6.08
3.00
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
ppm (t1)

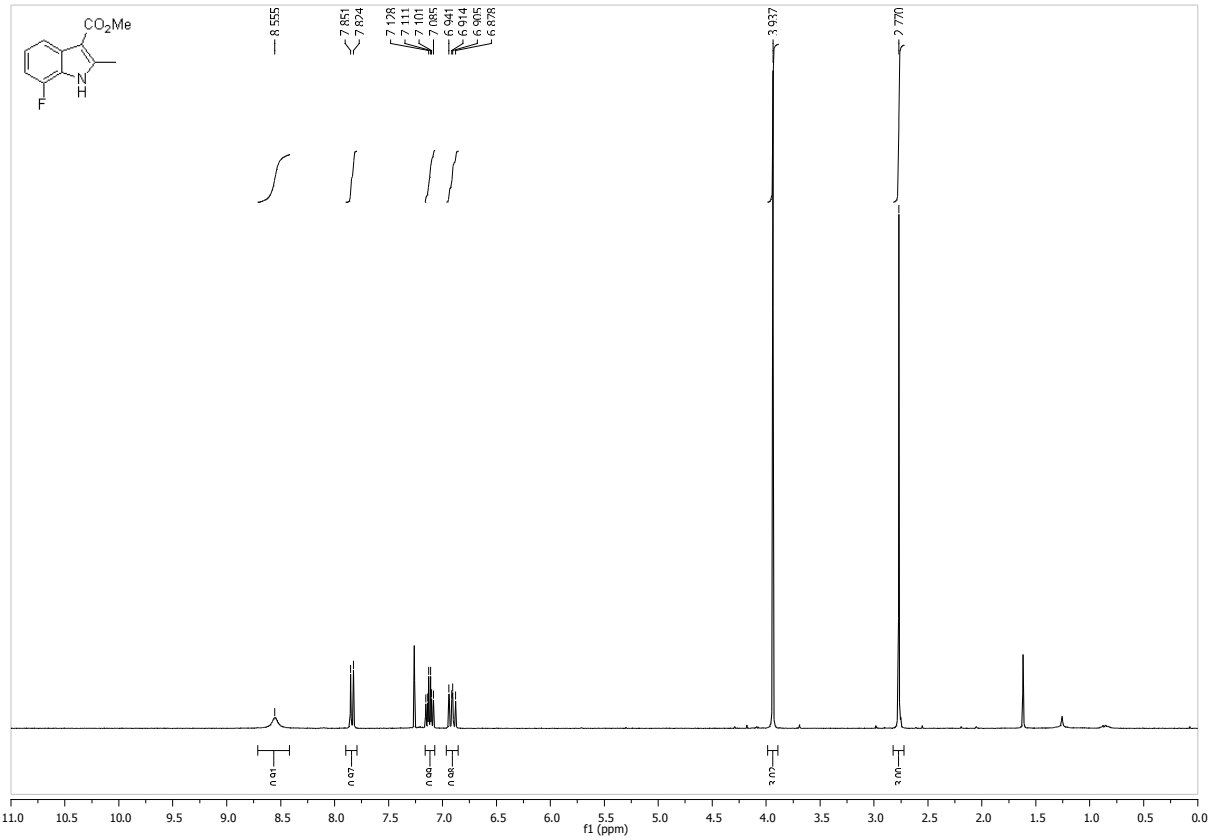

sew-sj-1543a
166.552
145.329
143.273
128.415
124.692
122.082
113.858
104.945
102.450
77.000
55.309
50.741
14.159
150
100
50
ppm (t1)

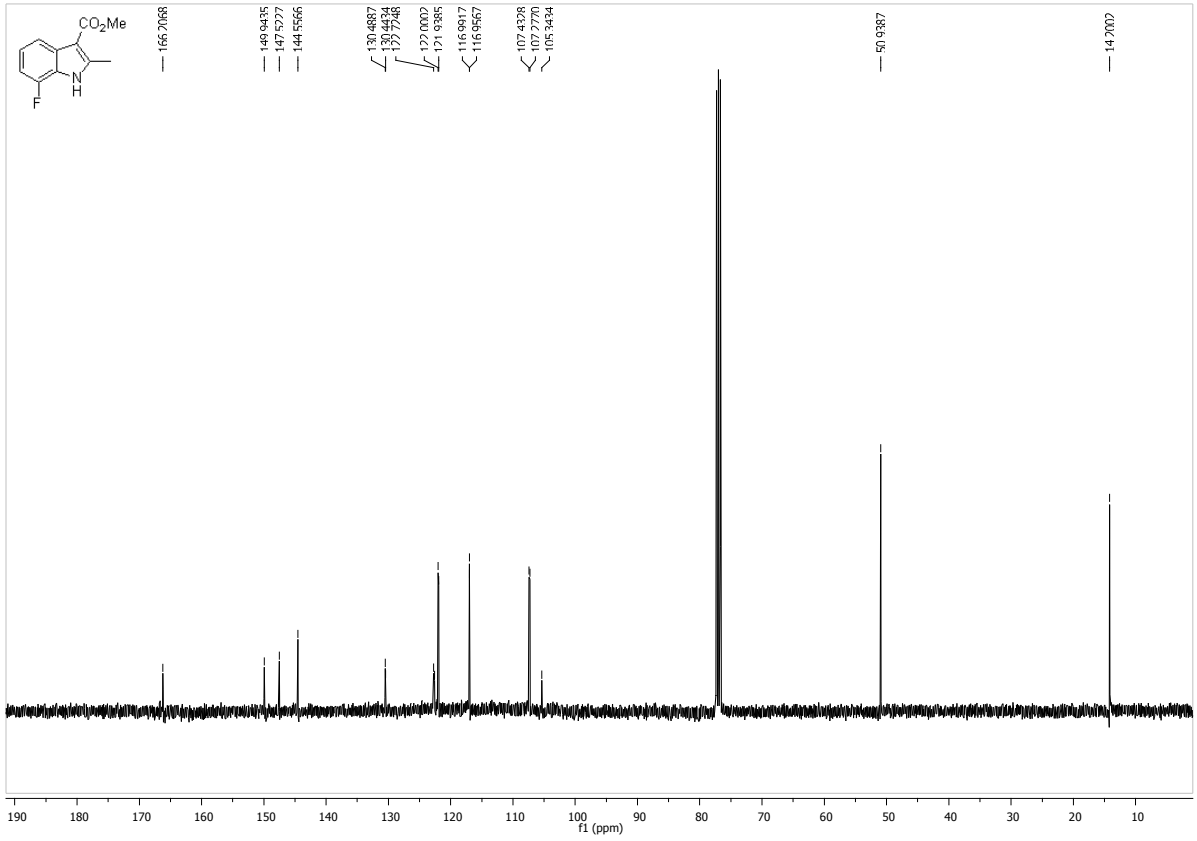

sew-sj-1542b
11.628
7.772
7.743
6.853
6.846
6.777
6.769
6.748
6.740
3.785
3.763
2.611
2.500
CO2Me
MeO
N
H
1.01
0.98
1.00
6.22
3.00
10.0
5.0
ppm (t1)

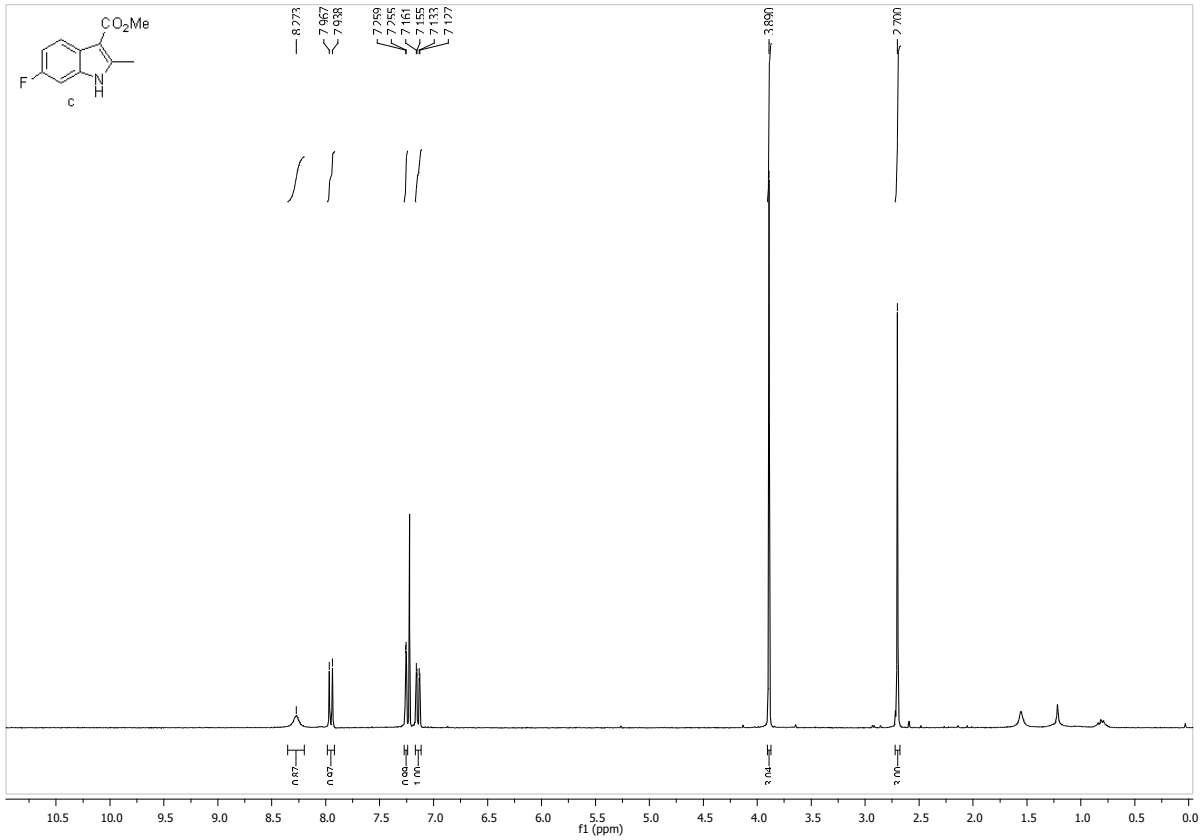

sew-sj-1542b
165.413
155.539
143.386
135.433
120.868
120.629
110.293
102.374
94.559
55.121
50.291
39.430
13.544
200
150
100
50
0
ppm (t1)

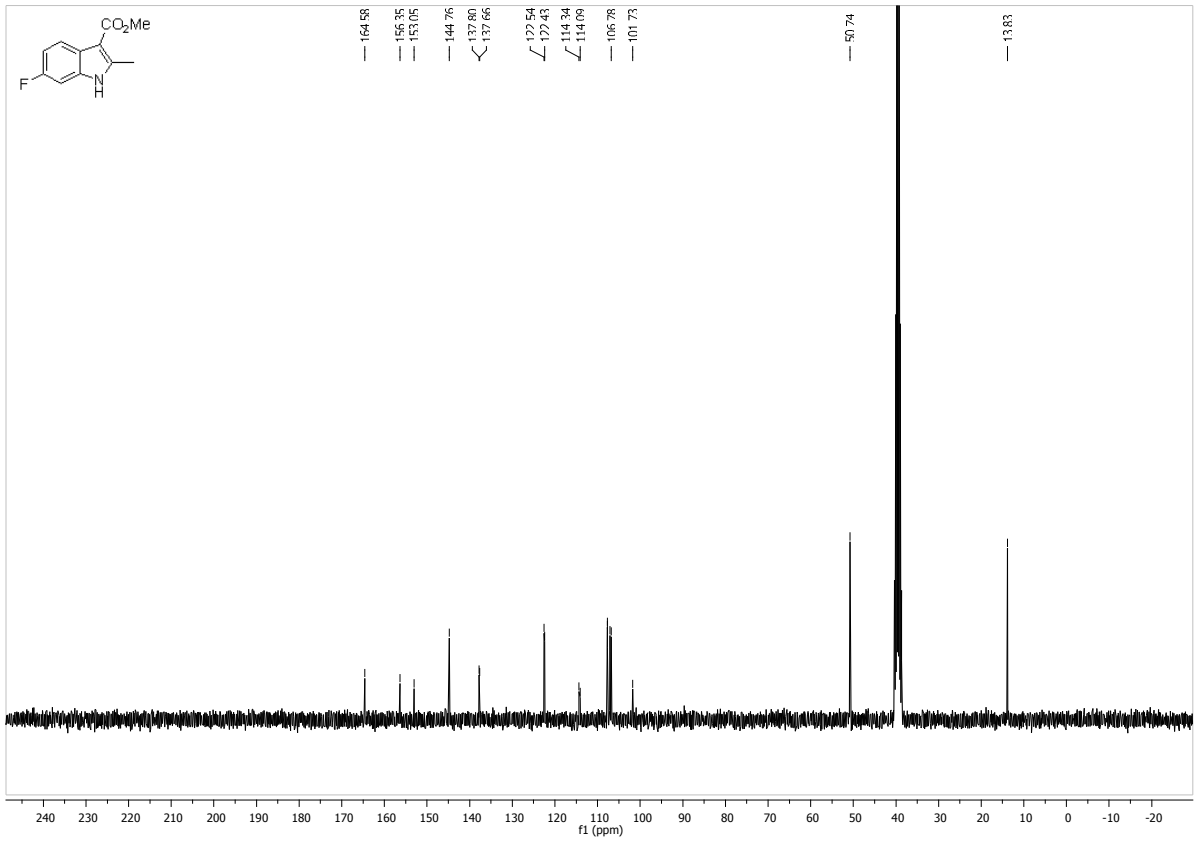

sew-sj-1541a
8.376
7.612
7.605
7.260
7.190
7.168
6.845
6.839
6.823
6.817
MeO
CO2Me
N
H
3.928
3.879
2.707
0.92
0.96
1.00
0.97
3.09
2.97
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)

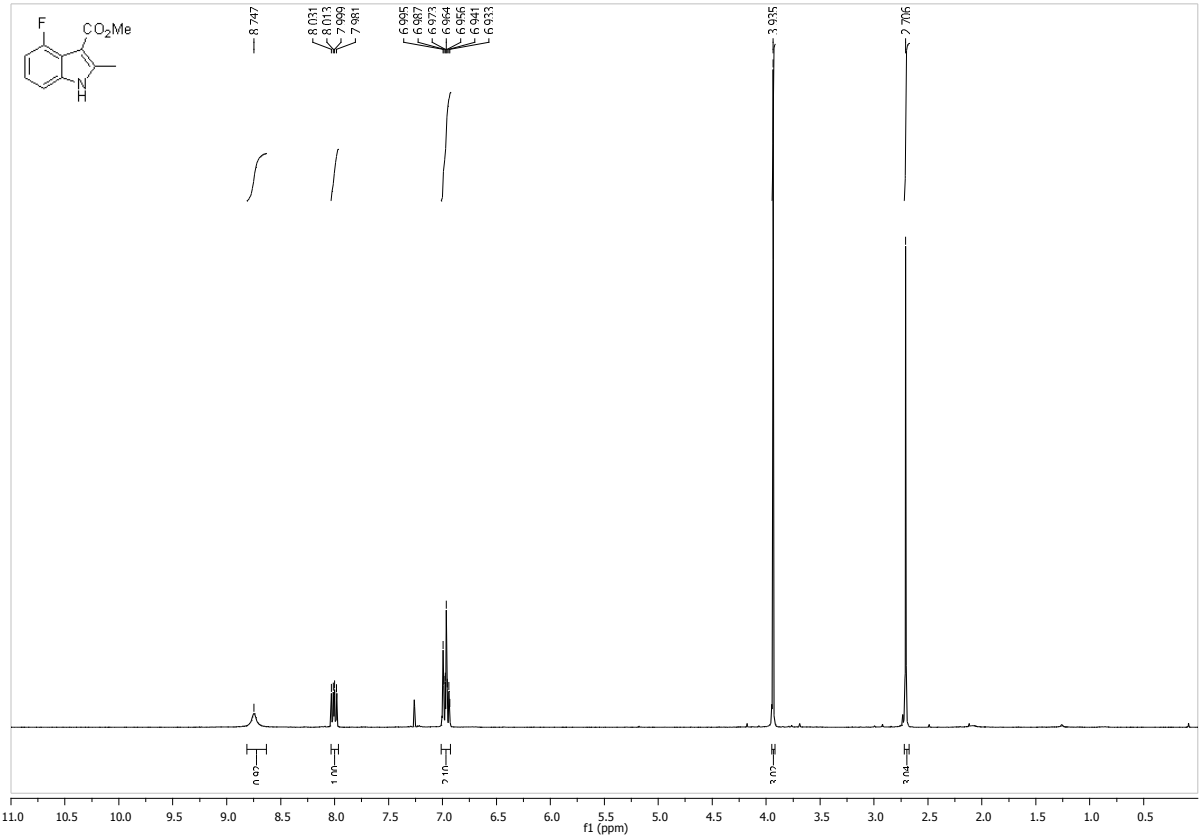

sew-sj-1541a
166.523
155.552
144.201
129.305
128.044
112.103
111.166
104.290
103.369
77.000
55.771
50.764
14.432
150
100
50
0
ppm (t1)

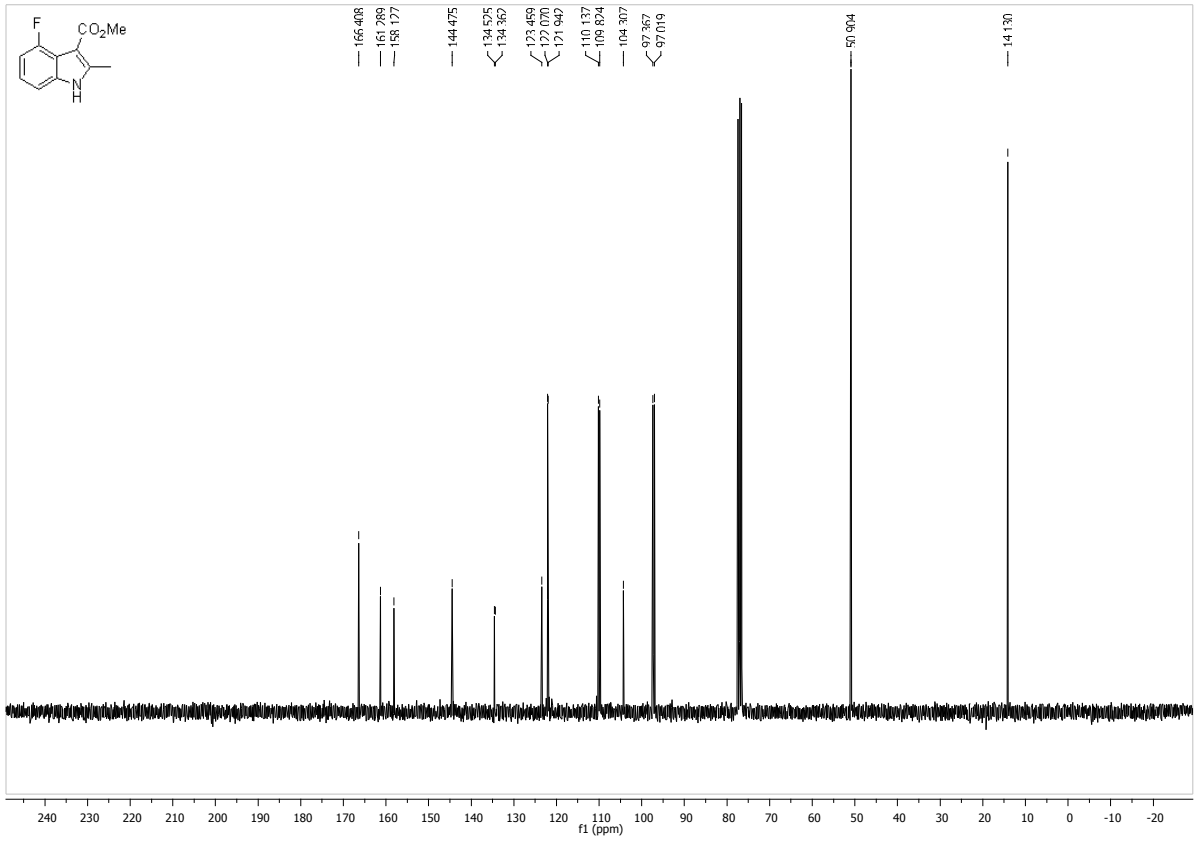

CO2Me
N
H
F
8.555
7.851
7.824
7.128
7.111
7.101
7.085
6.941
6.914
6.905
6.878
3.937
2.770
0.91
0.97
0.98
0.98
3.07
3.00
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

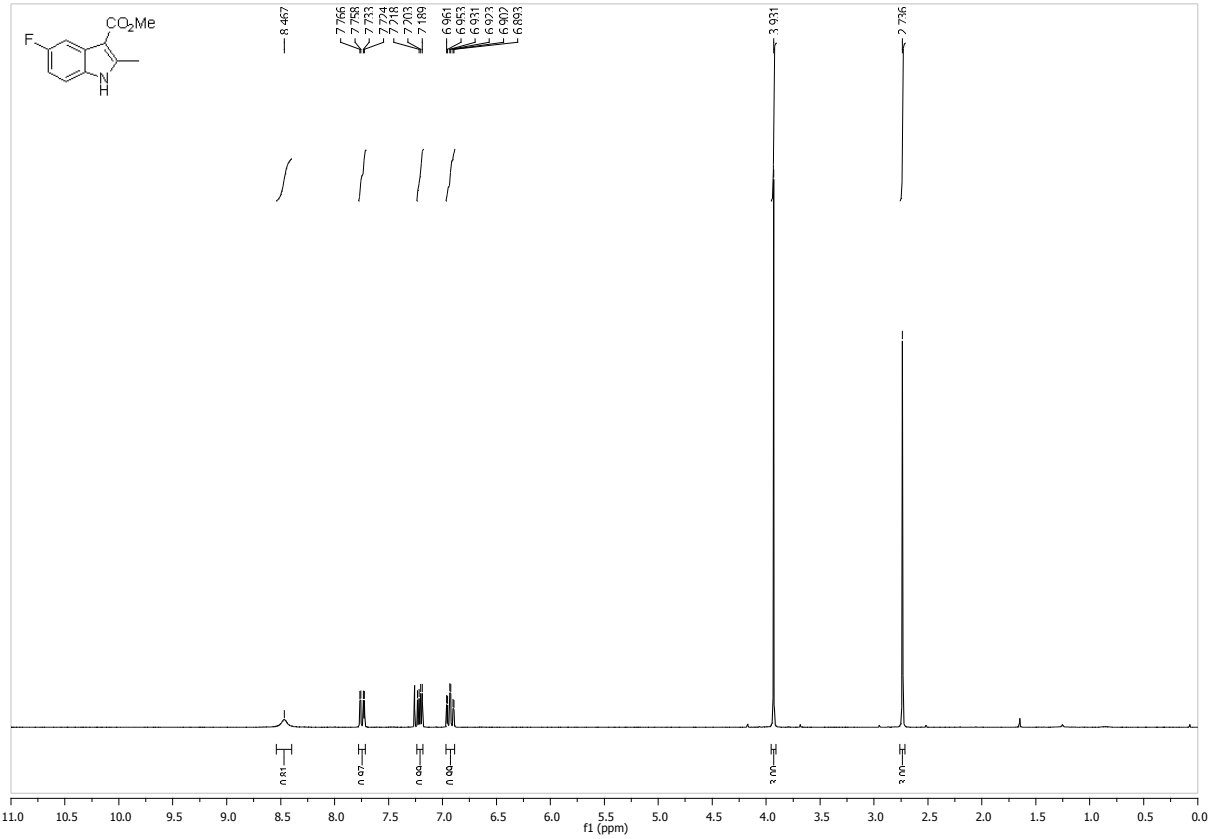

CO2Me
N
H
F
166.2068
149.9435
147.5277
144.5566
130.4887
130.4434
129.7748
122.0002
121.9385
116.9917
116.9567
107.4328
107.2770
105.3434
50.9387
14.2002
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

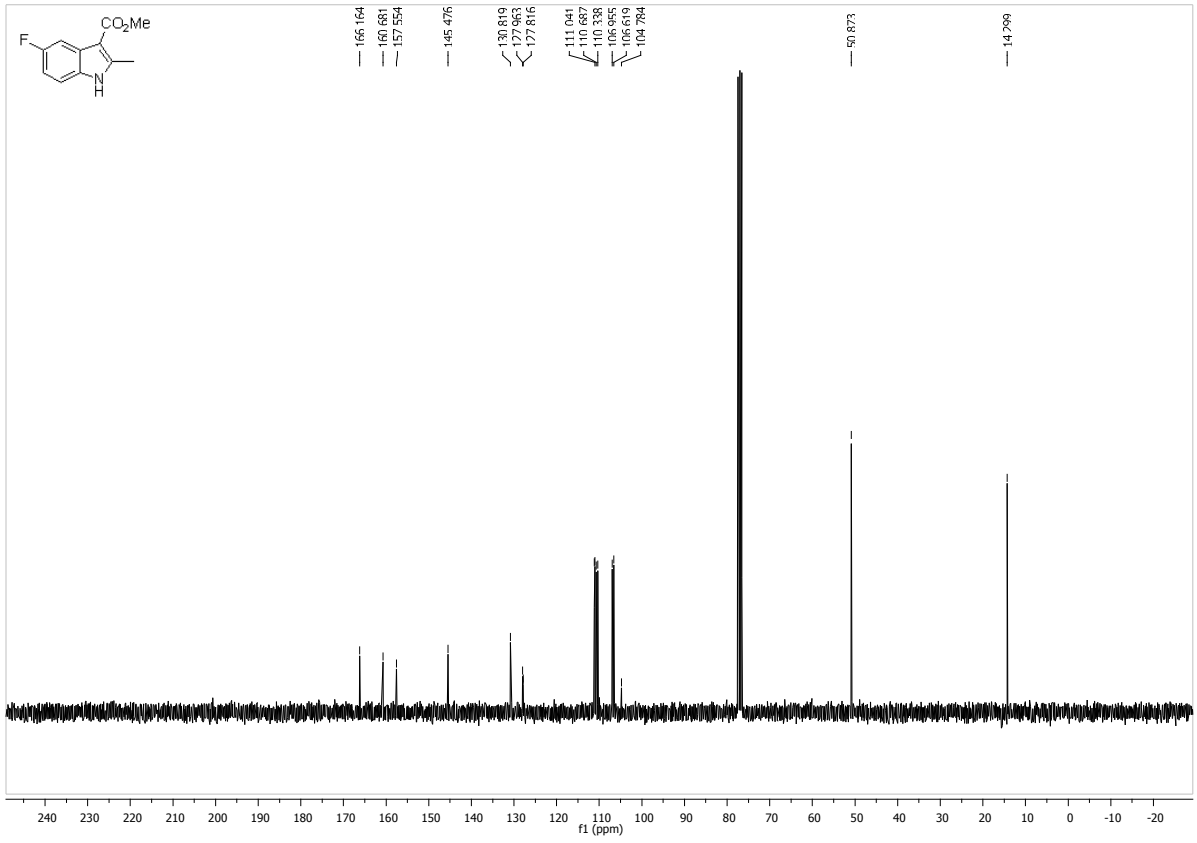

CO2Me
F
N
H
c
8.273
7.967
7.938
7.759
7.755
7.161
7.155
7.133
7.127
3.890
2.700
0.87
0.97
0.98
1.00
3.04
3.00
f1 (ppm)

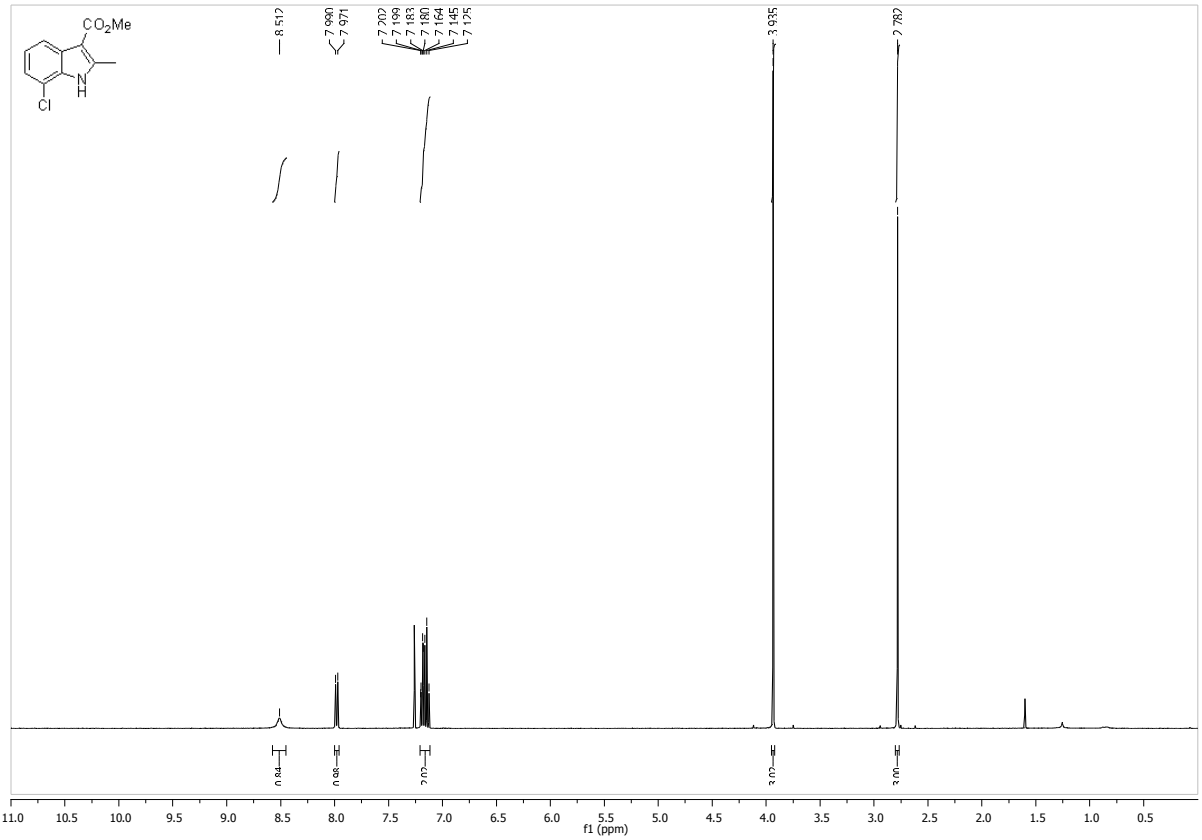

CO2Me
F
N
H
164.58
156.35
153.05
144.76
137.80
137.66
127.54
127.43
114.34
114.09
106.78
101.73
50.74
13.83
f1 (ppm)

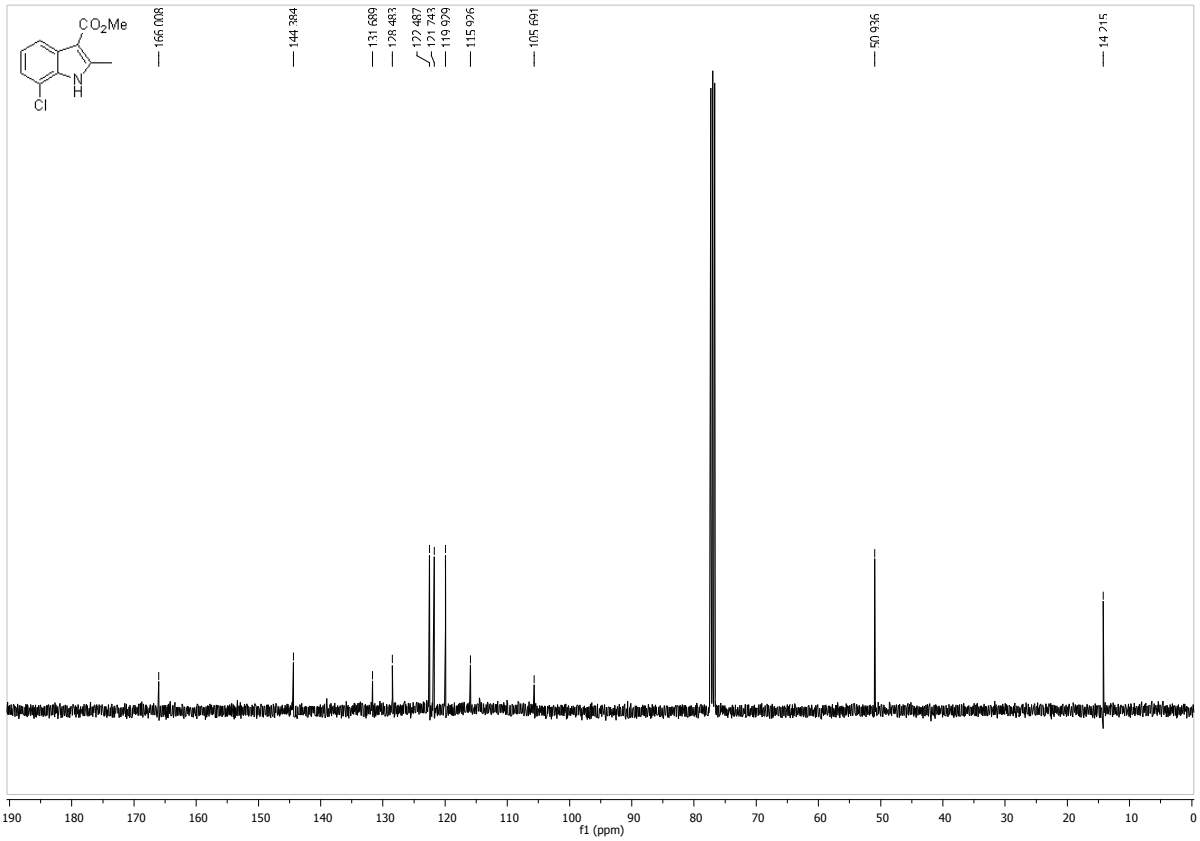

F
CO2Me
N
H
8.747
8.031
8.013
7.999
7.981
6.995
6.987
6.973
6.964
6.956
6.941
6.933
3.935
2.706
0.93
1.00
2.10
3.07
3.04
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

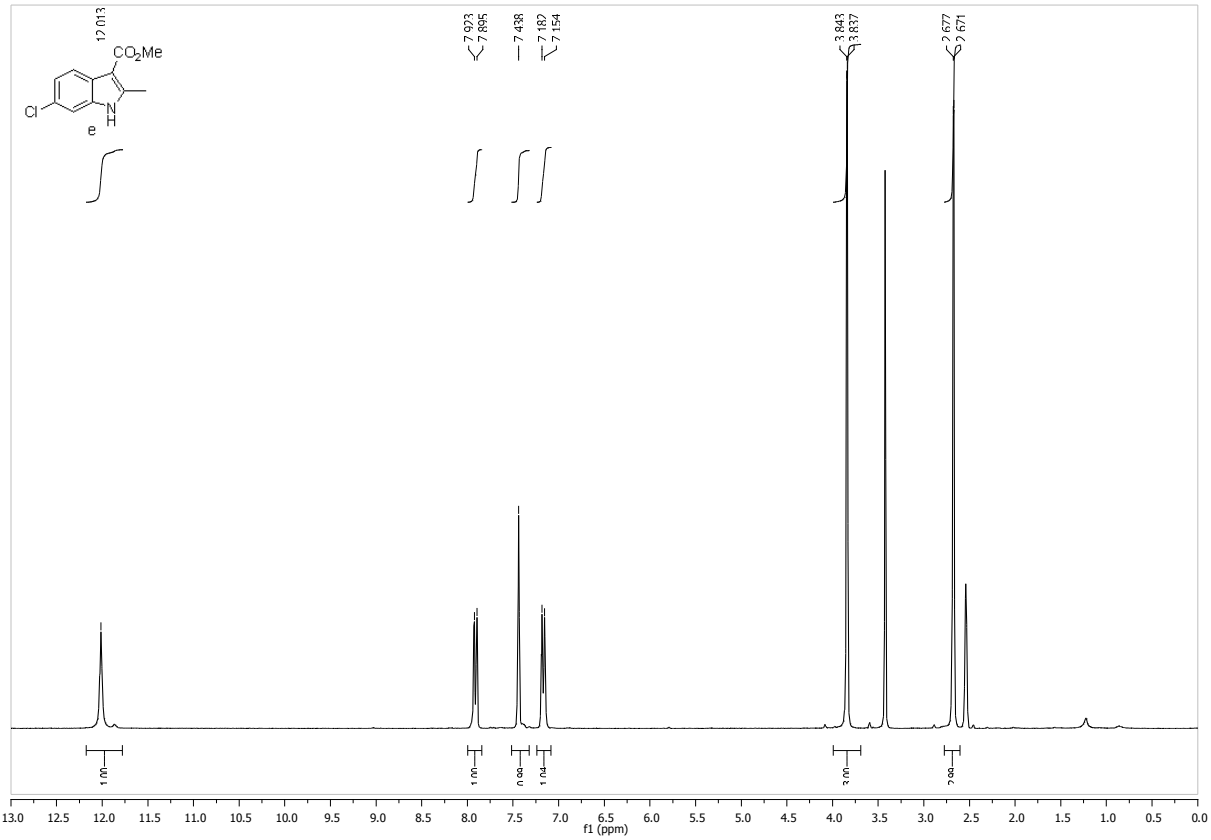

F
CO2Me
N
H
166.408
161.289
158.177
144.475
134.525
134.362
123.459
122.070
121.942
110.137
109.824
104.307
97.367
97.019
50.904
14.130
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

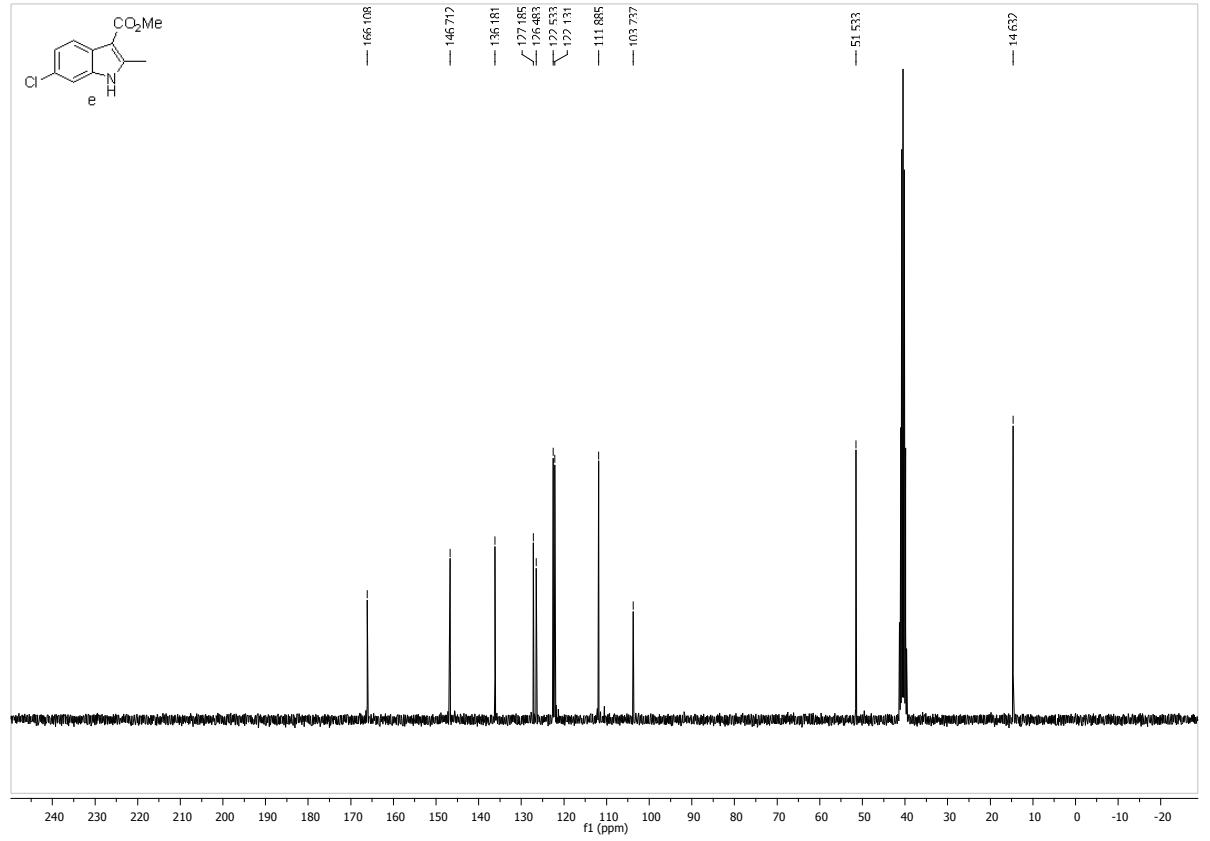

CO2Me
F
N
H
8.467
7.766
7.758
7.733
7.724
7.718
7.703
7.189
6.961
6.953
6.931
6.923
6.902
6.893
3.931
3.736
0.81
0.97
0.99
0.98
3.00
3.00
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

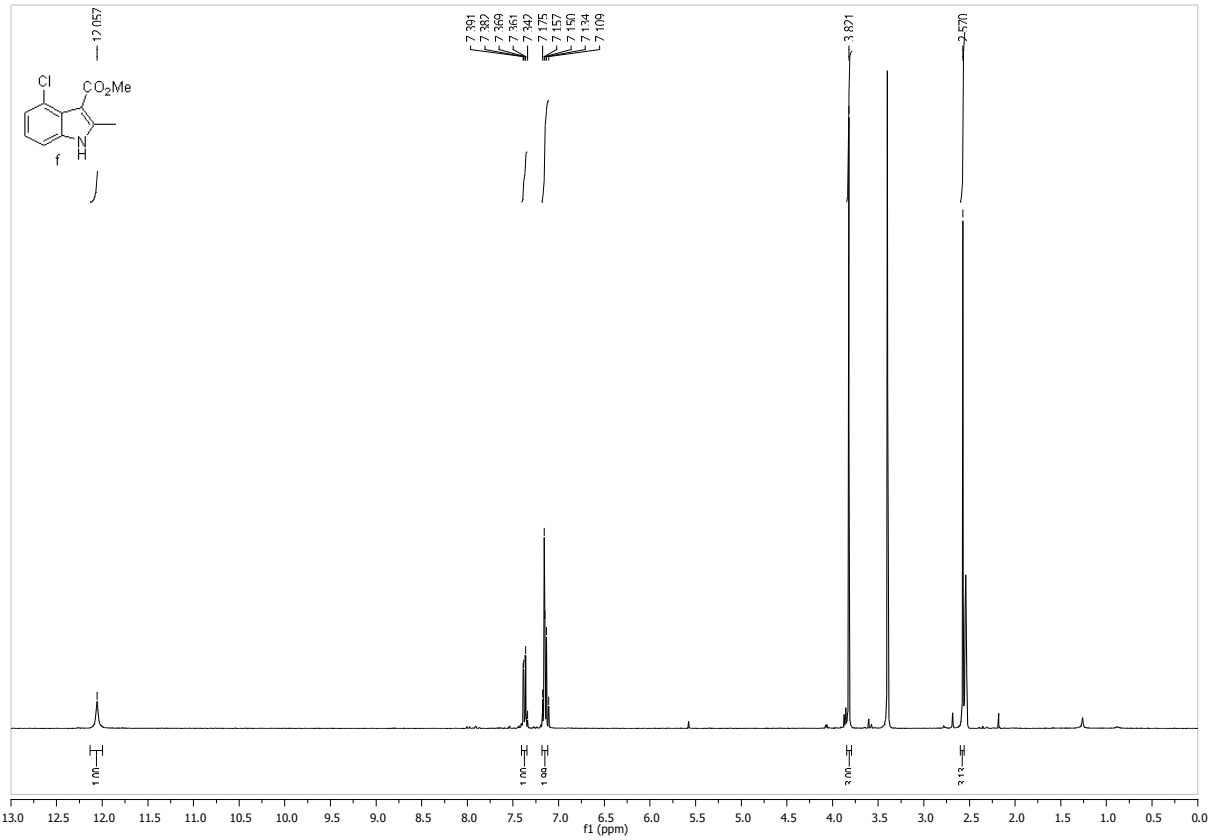

CO2Me
F
N
H
166.164
160.681
157.554
145.476
130.819
127.963
127.816
111.041
110.687
110.338
106.955
106.619
104.784
50.873
14.799
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

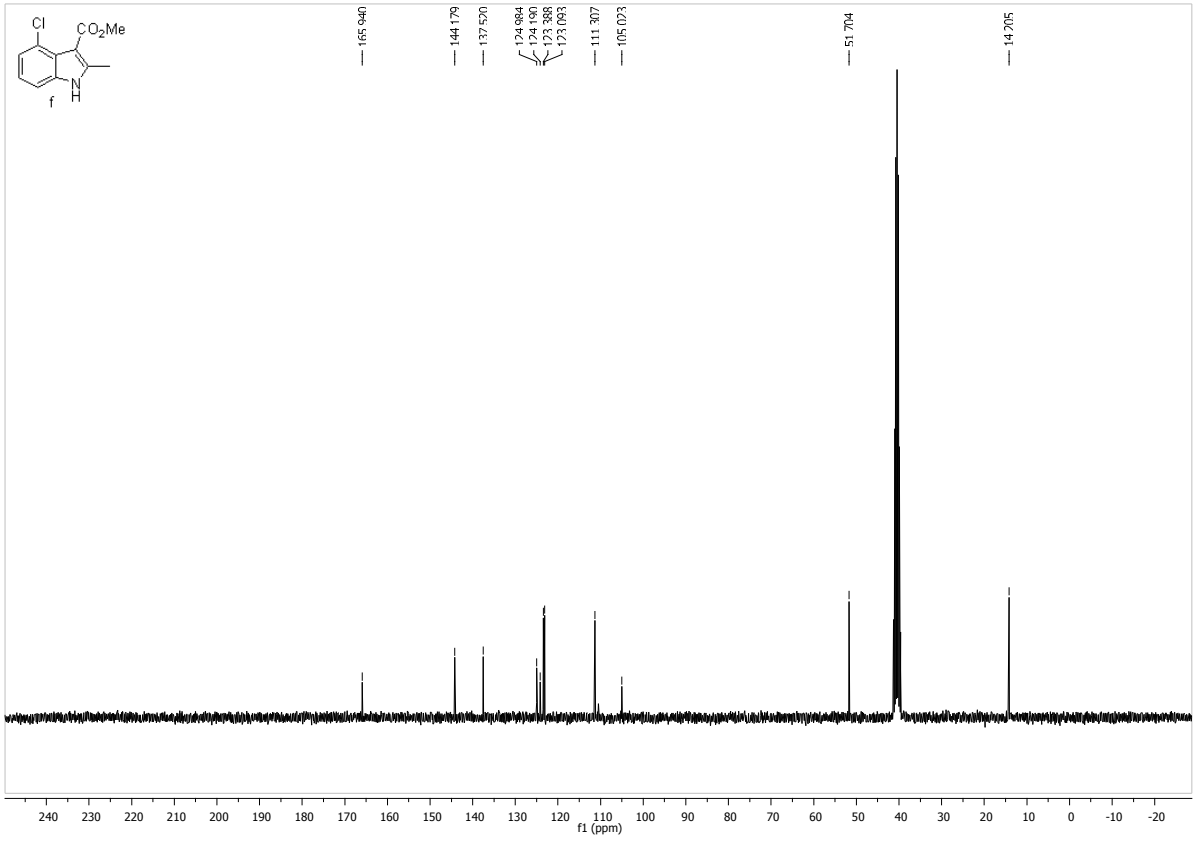

CO2Me
Cl
8.512
7.990
7.971
7.202
7.199
7.183
7.180
7.164
7.145
7.135
3.935
2.782
f1 (ppm)

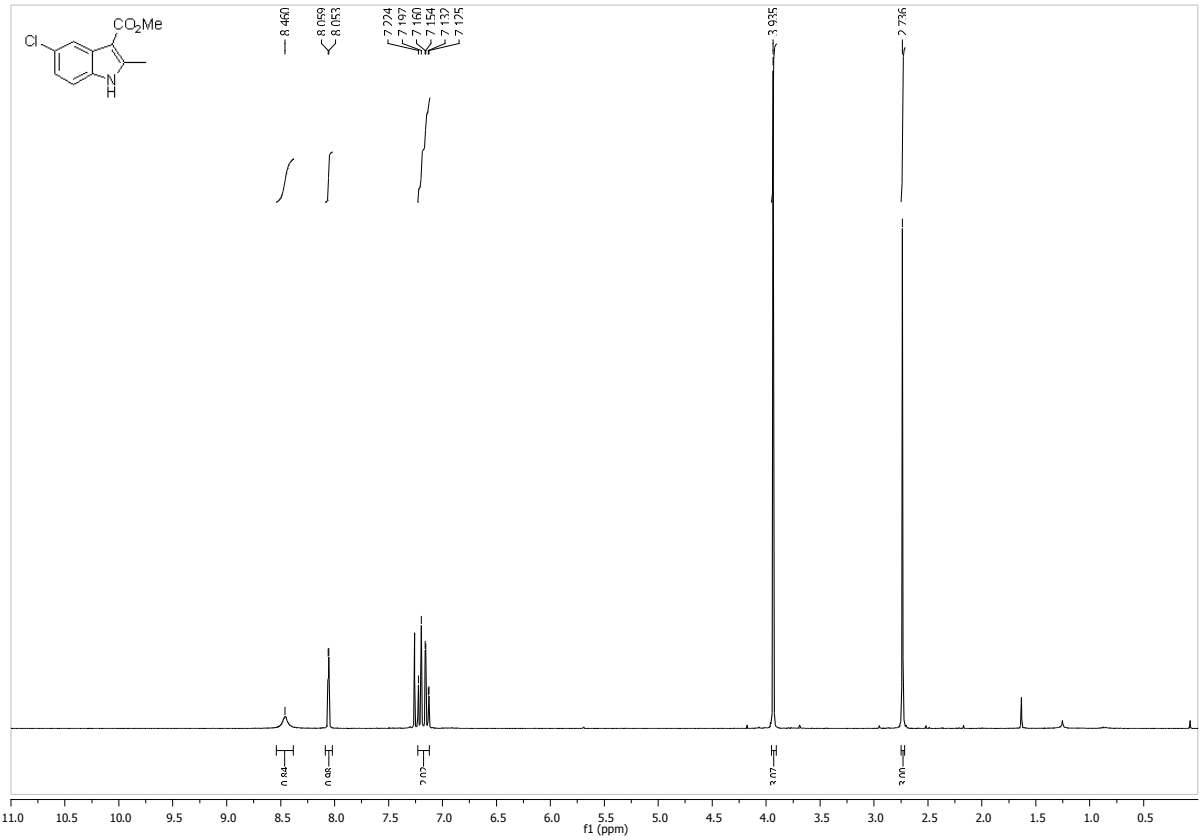

CO2Me
Cl
166.008
144.384
131.689
128.483
122.487
121.743
119.979
115.926
105.691
50.936
14.715
f1 (ppm)

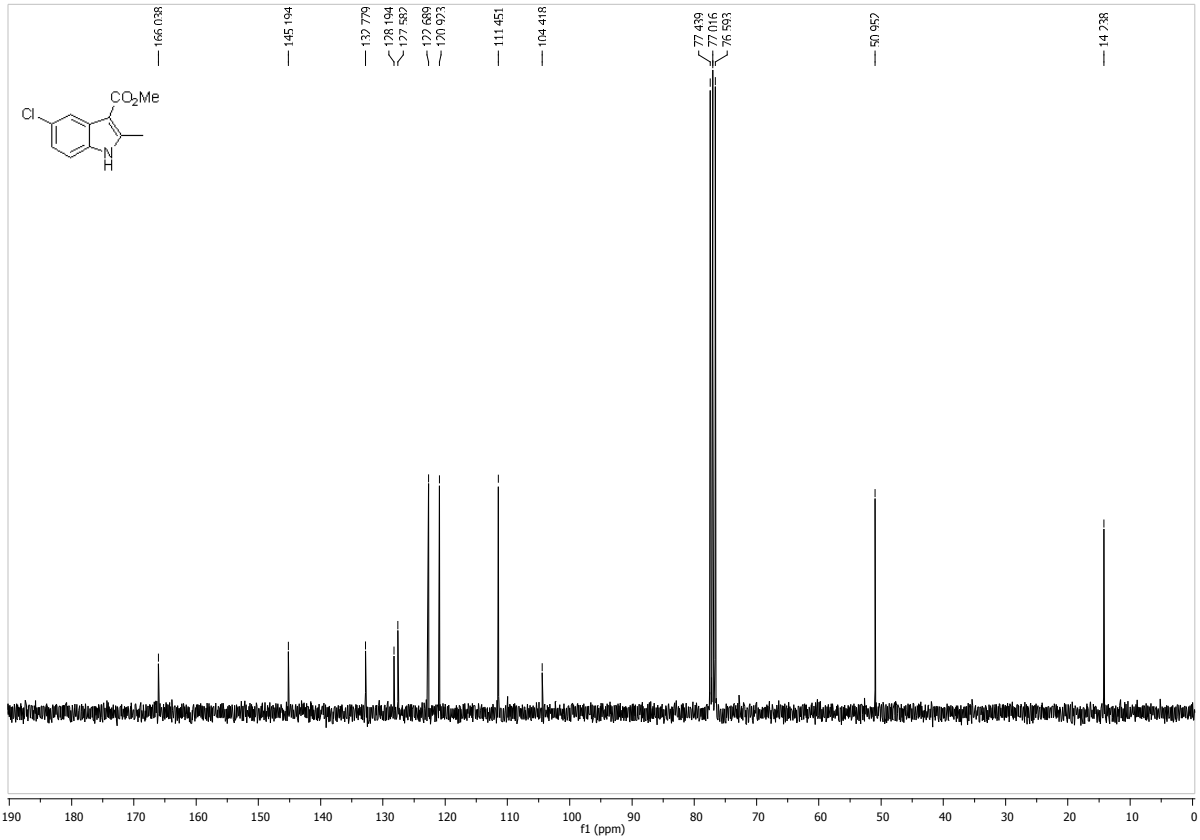

12.013
7.923
7.895
7.438
7.182
7.154
3.843
3.837
2.677
2.671
CO2Me
Cl
N
H
e
f1 (ppm)

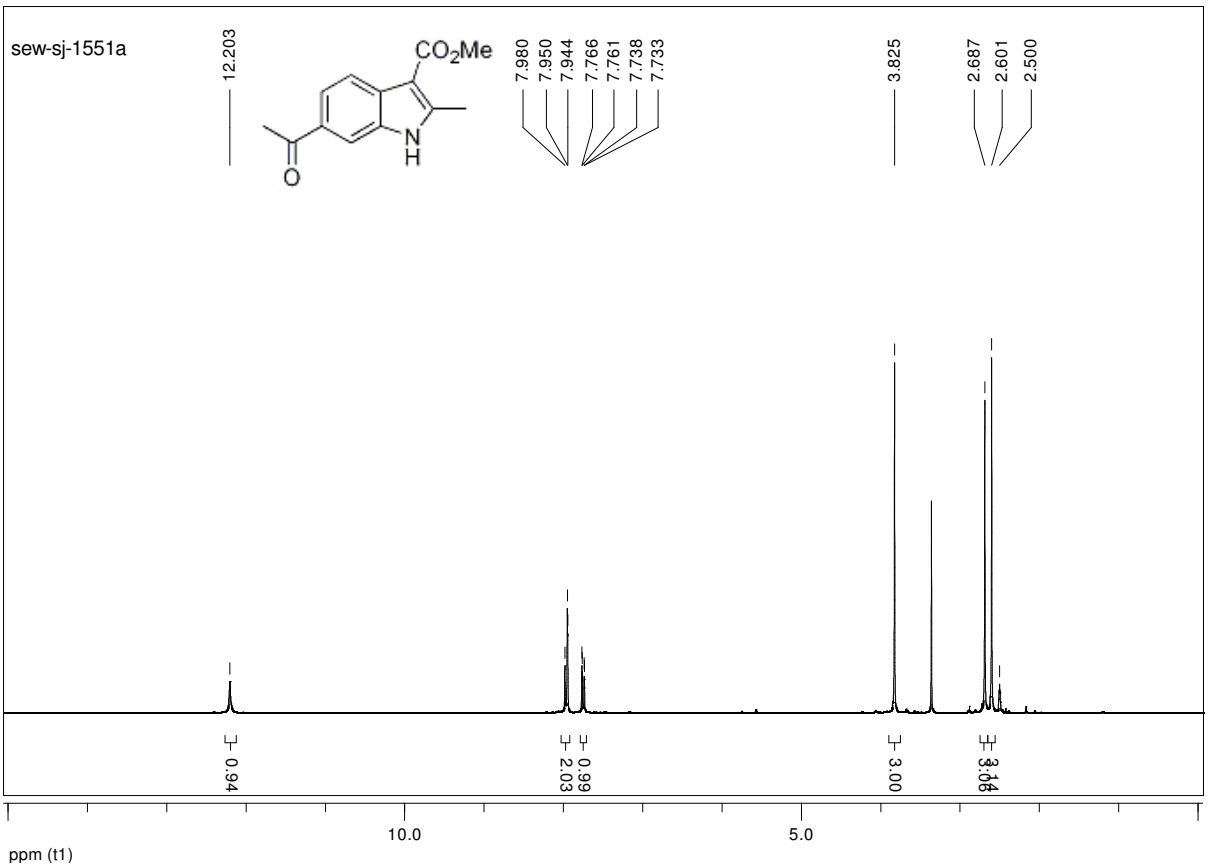

166.108
146.712
136.181
127.185
126.483
123.533
122.131
111.885
103.737
51.533
14.632
CO2Me
Cl
N
H
e
f1 (ppm)

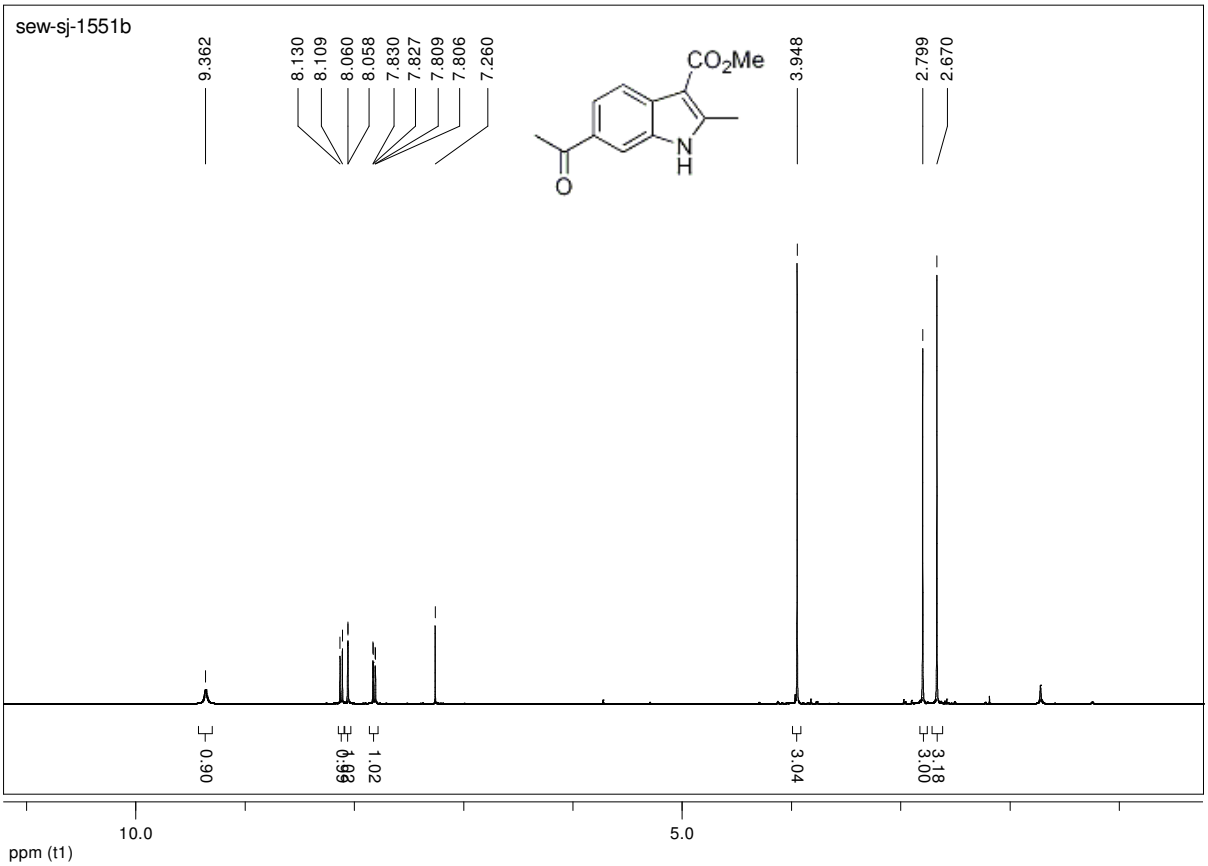

12.057
7.391
7.382
7.369
7.361
7.342
7.175
7.157
7.150
7.134
7.109
3.871
2.570
Cl
CO2Me
N
H
f
1.00
1.00
2.90
3.13
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

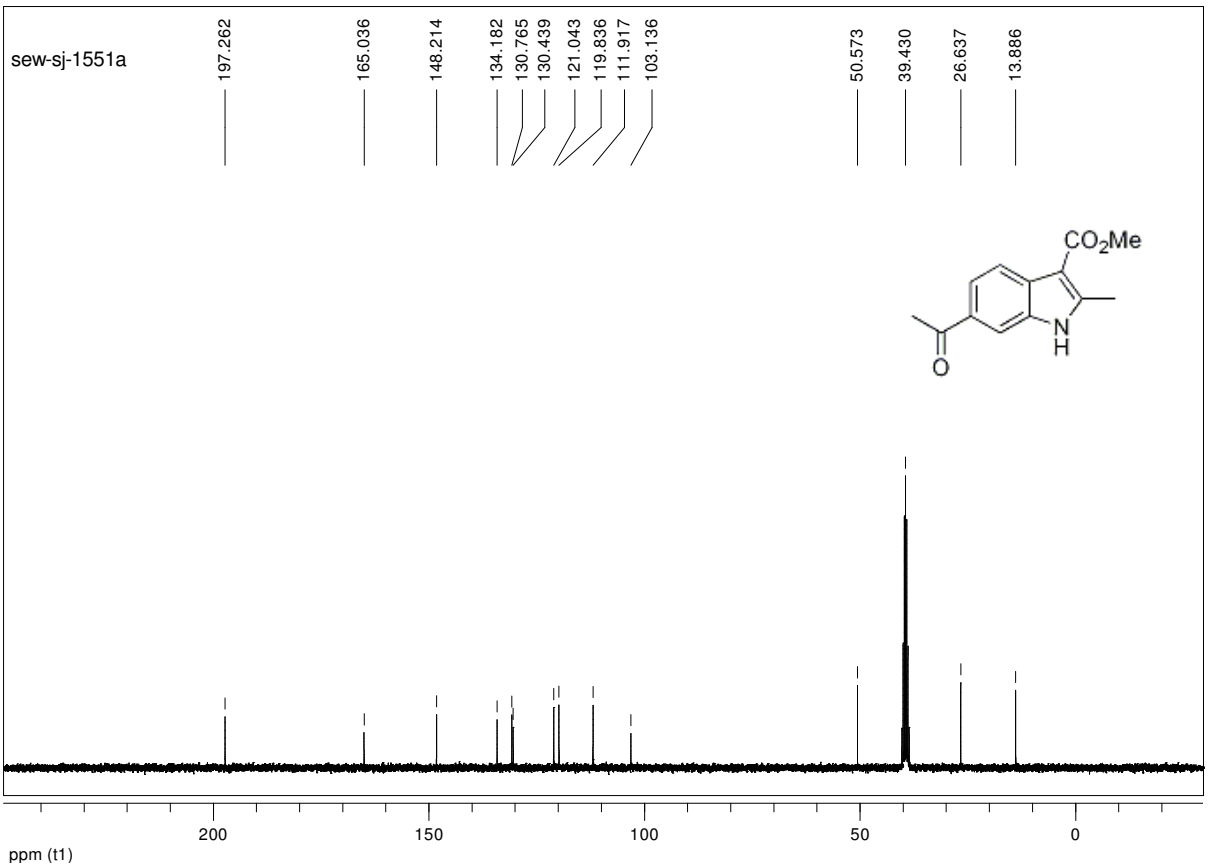

Cl
CO2Me
N
H
f
165.940
144.179
137.520
124.984
124.140
123.388
123.093
111.307
105.093
51.704
14.705
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

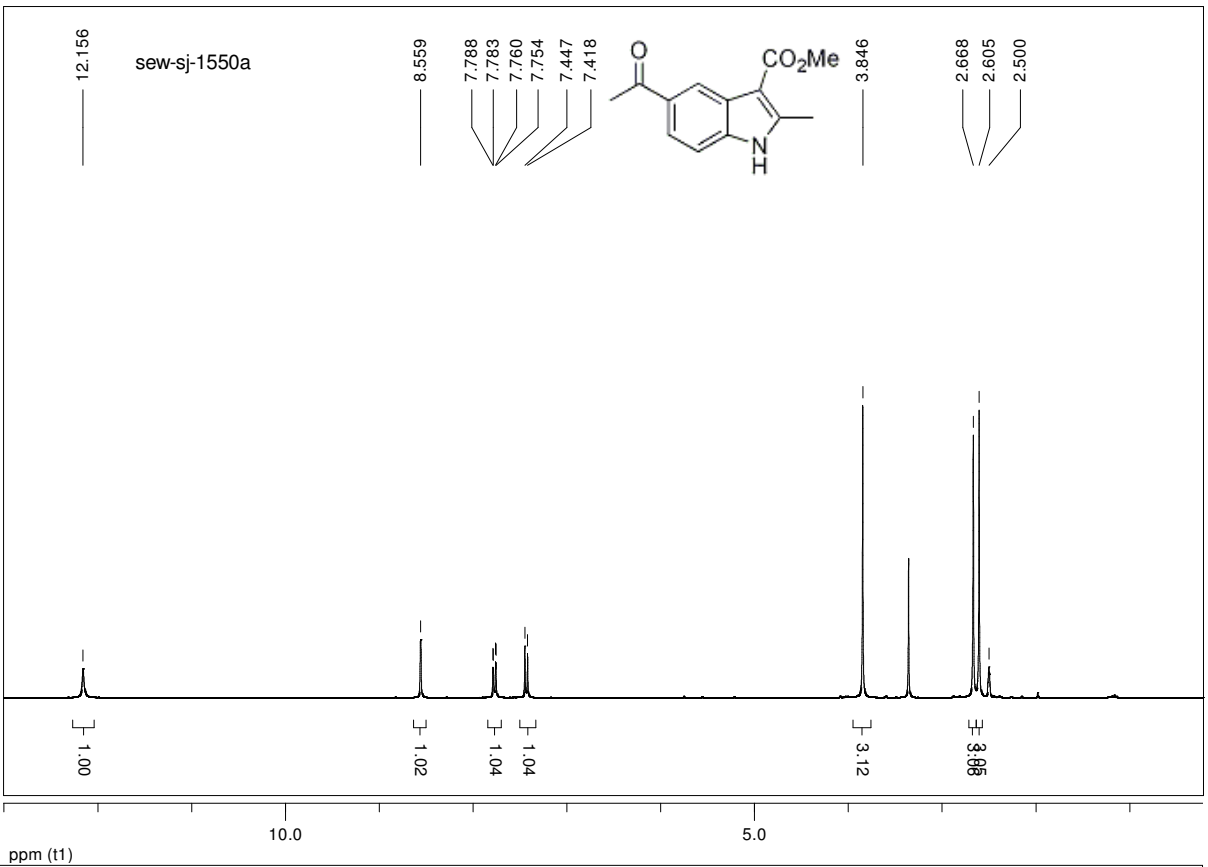

CO2Me
Cl
N
H
8.460
8.059
8.053
7.774
7.197
7.160
7.154
7.132
7.125
3.935
2.736
f1 (ppm)

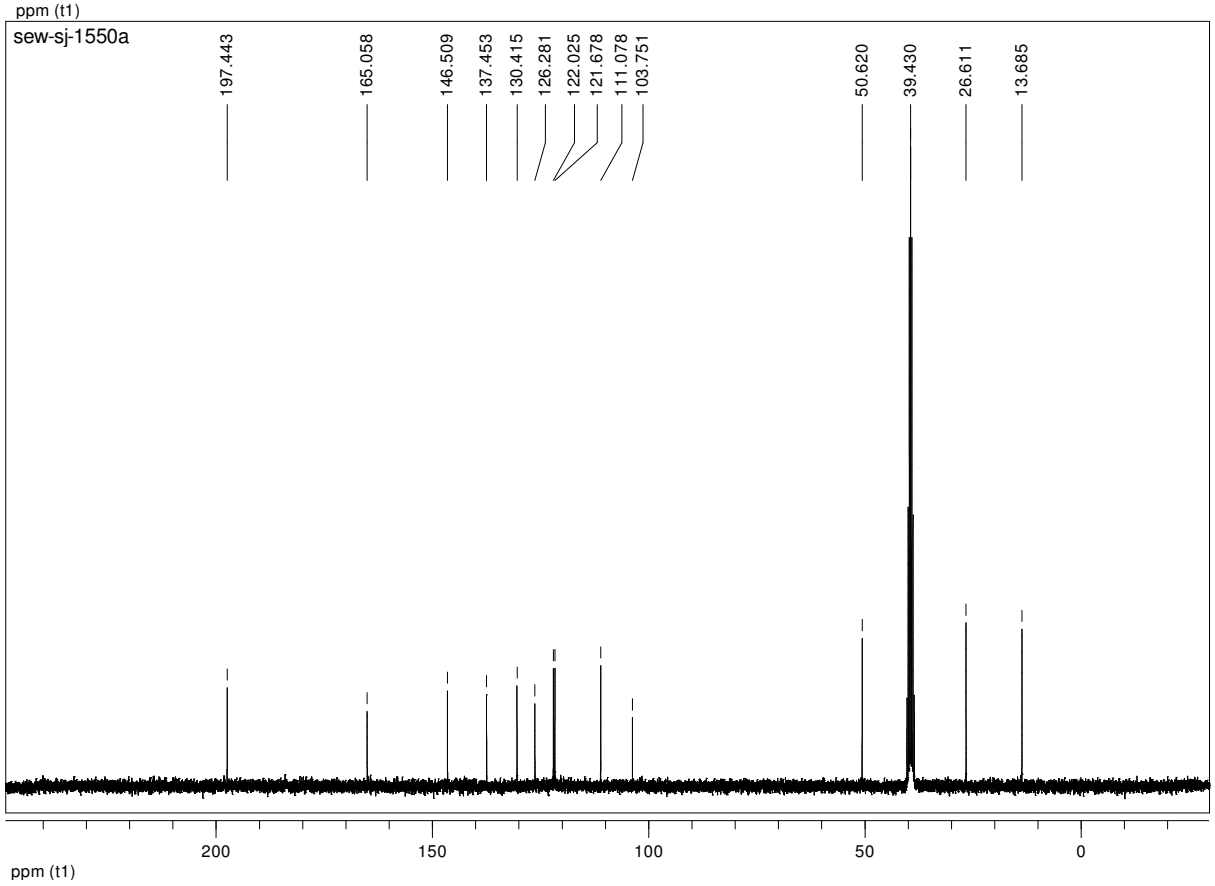

CO2Me
Cl
N
H
166.038
145.194
132.779
128.194
127.582
122.689
120.973
111.451
104.418
77.439
77.016
76.593
50.957
14.238
f1 (ppm)

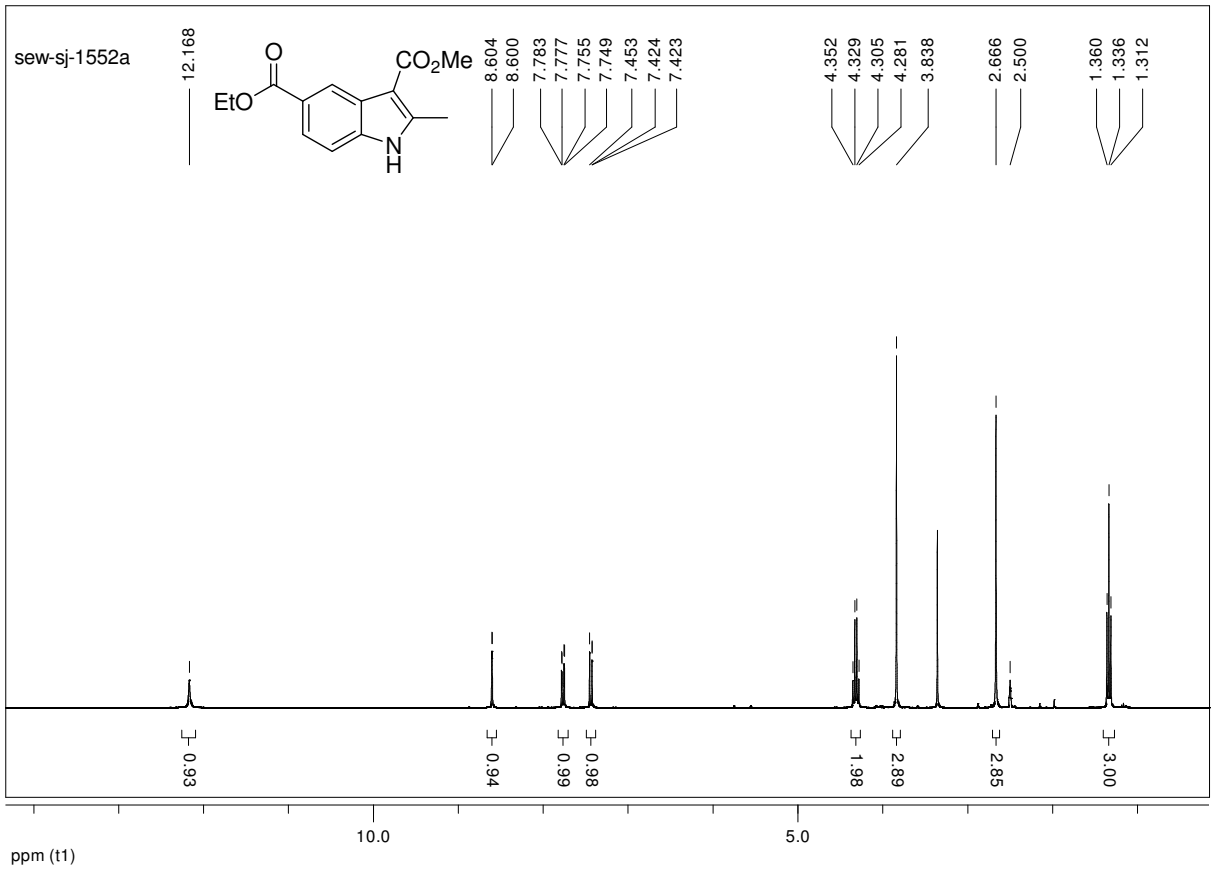

sew-sj-1551a
12.203
7.980
7.950
7.944
7.766
7.761
7.738
7.733
3.825
2.687
2.601
2.500
0.94
2.03
0.99
3.00
3.14
10.0
5.0
ppm (t1)

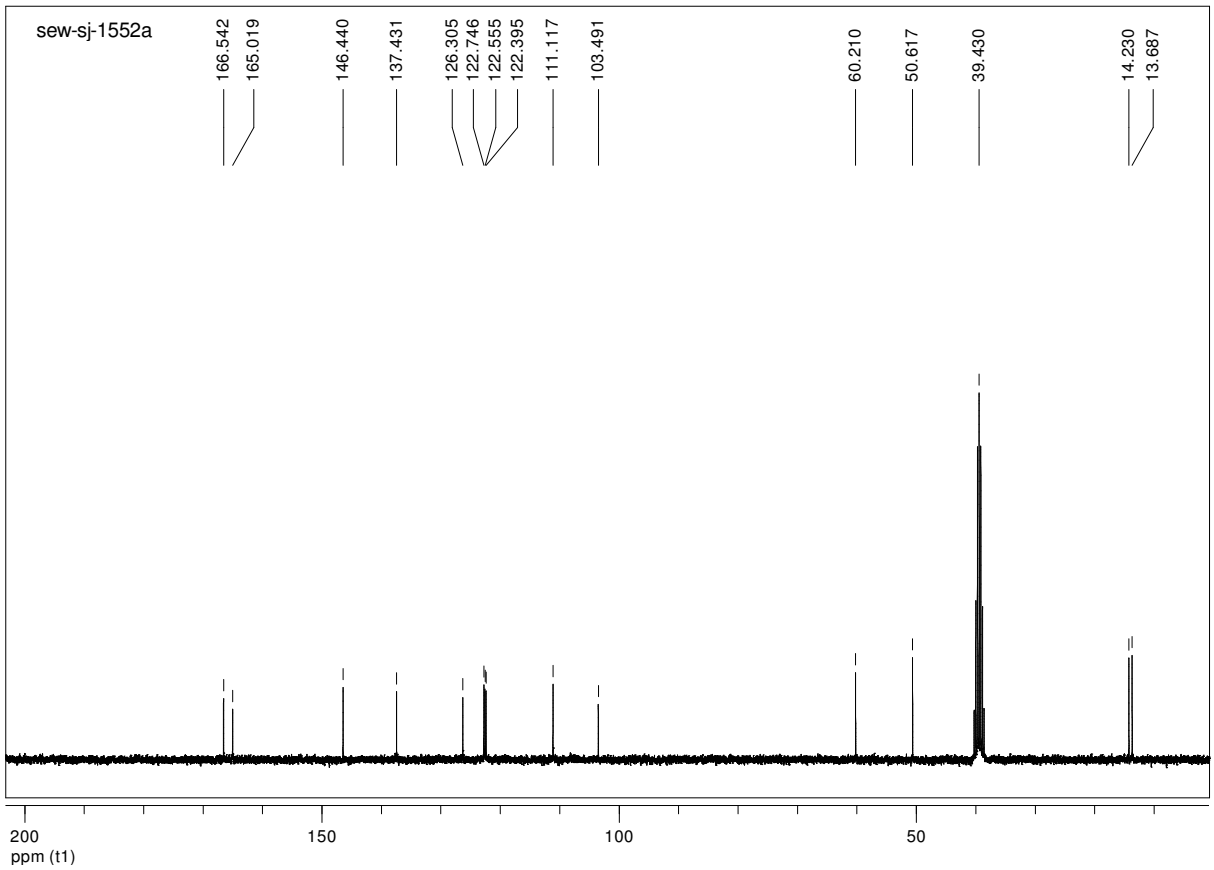

sew-sj-1551b
9.362
8.130
8.109
8.060
8.058
7.830
7.827
7.809
7.806
7.260
3.948
2.799
2.670
0.90
1.02
3.04
3.18
3.00
10.0
5.0
ppm (t1)

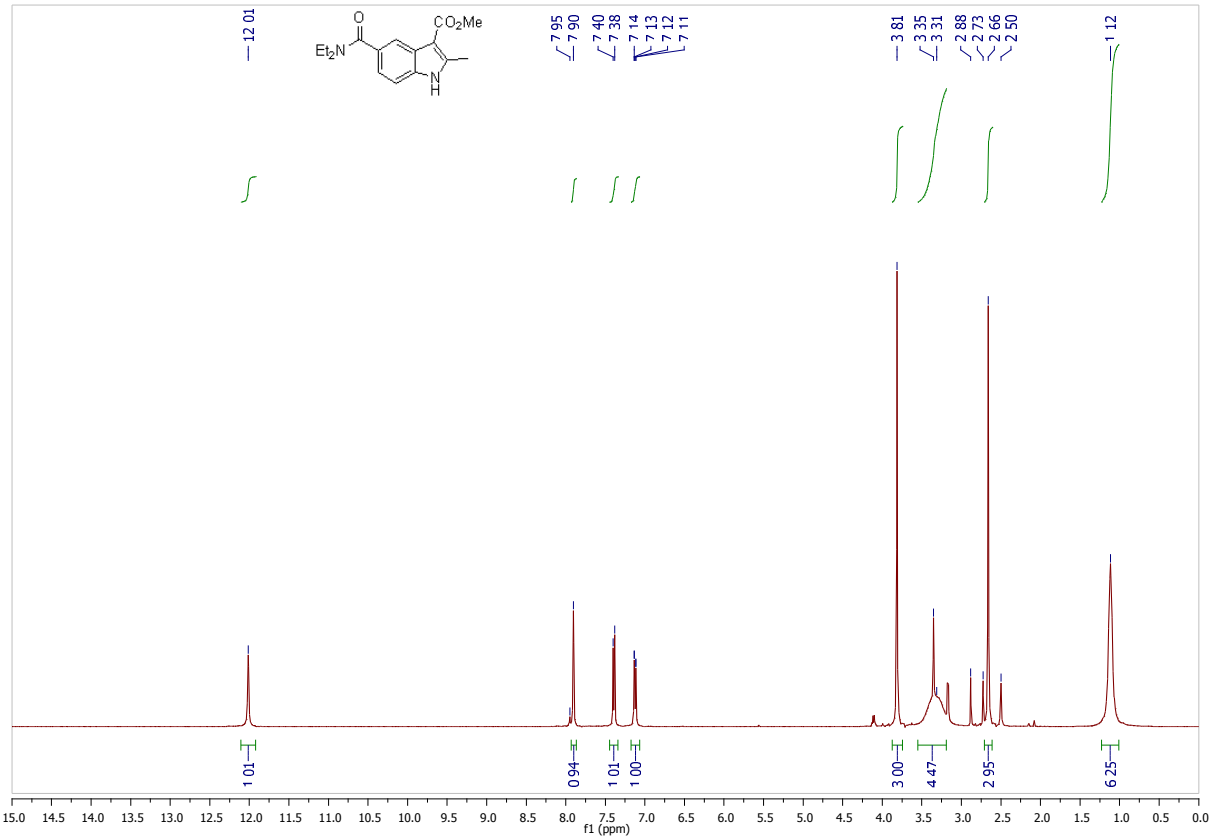

sew-sj-1551a
197.262
165.036
148.214
134.182
130.765
130.439
121.043
119.836
111.917
103.136
50.573
39.430
26.637
13.886
CO2Me
N
H
O
200
150
100
50
0
ppm (t1)

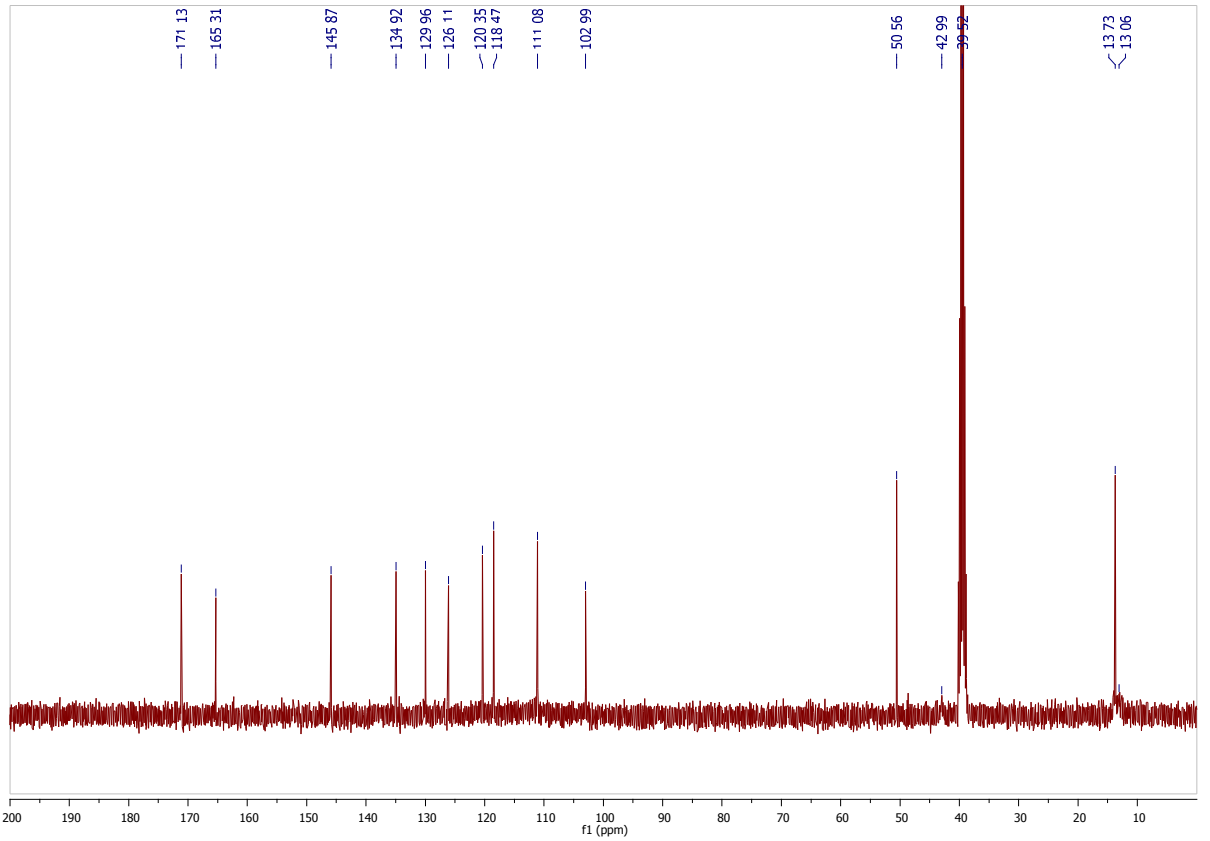

sew-sj-1550a
12.156
8.559
7.788
7.783
7.760
7.754
7.447
7.418
3.846
2.668
2.605
2.500
O
CO2Me
N
H
1.00
1.02
1.04
1.04
3.12
3.05
10.0
5.0
ppm (t1)

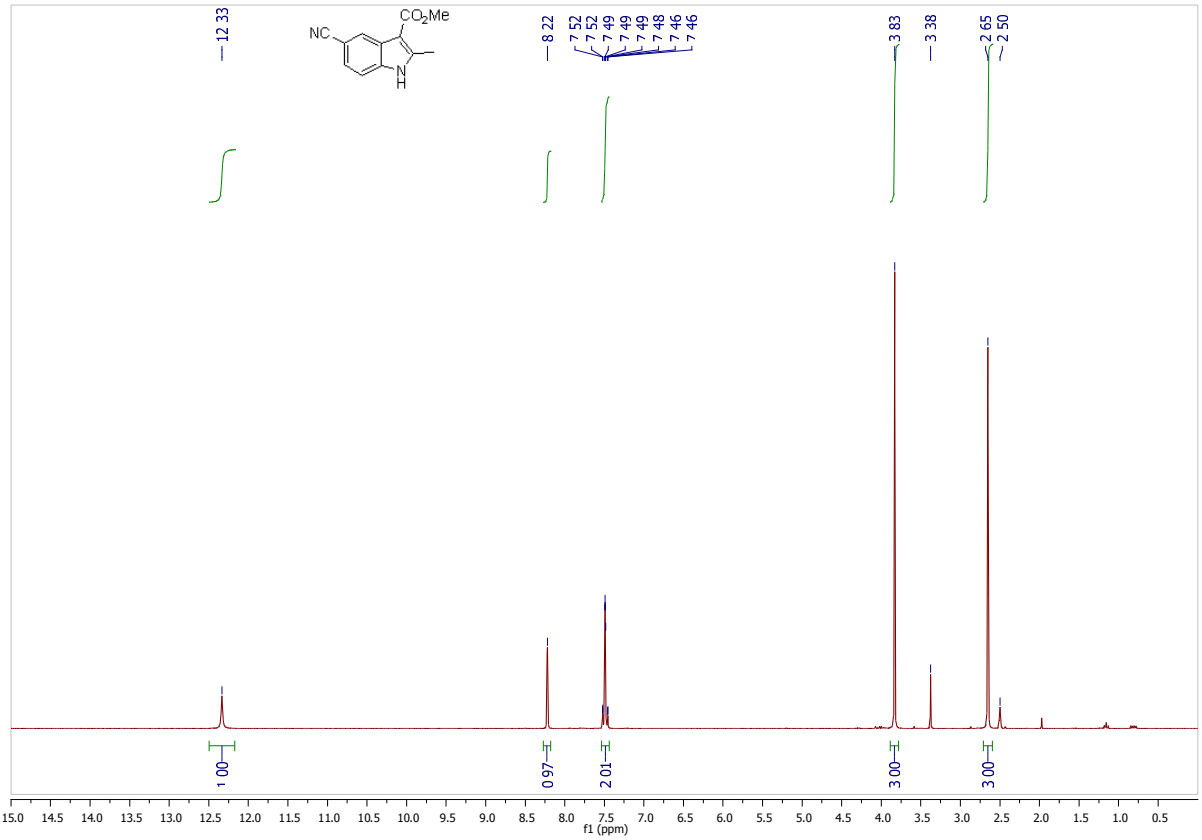

sew-sj-1550a
197.443
165.058
146.509
137.453
130.415
126.281
122.025
121.678
111.078
103.751
50.620
39.430
26.611
13.685
200
150
100
50
0
ppm (t1)

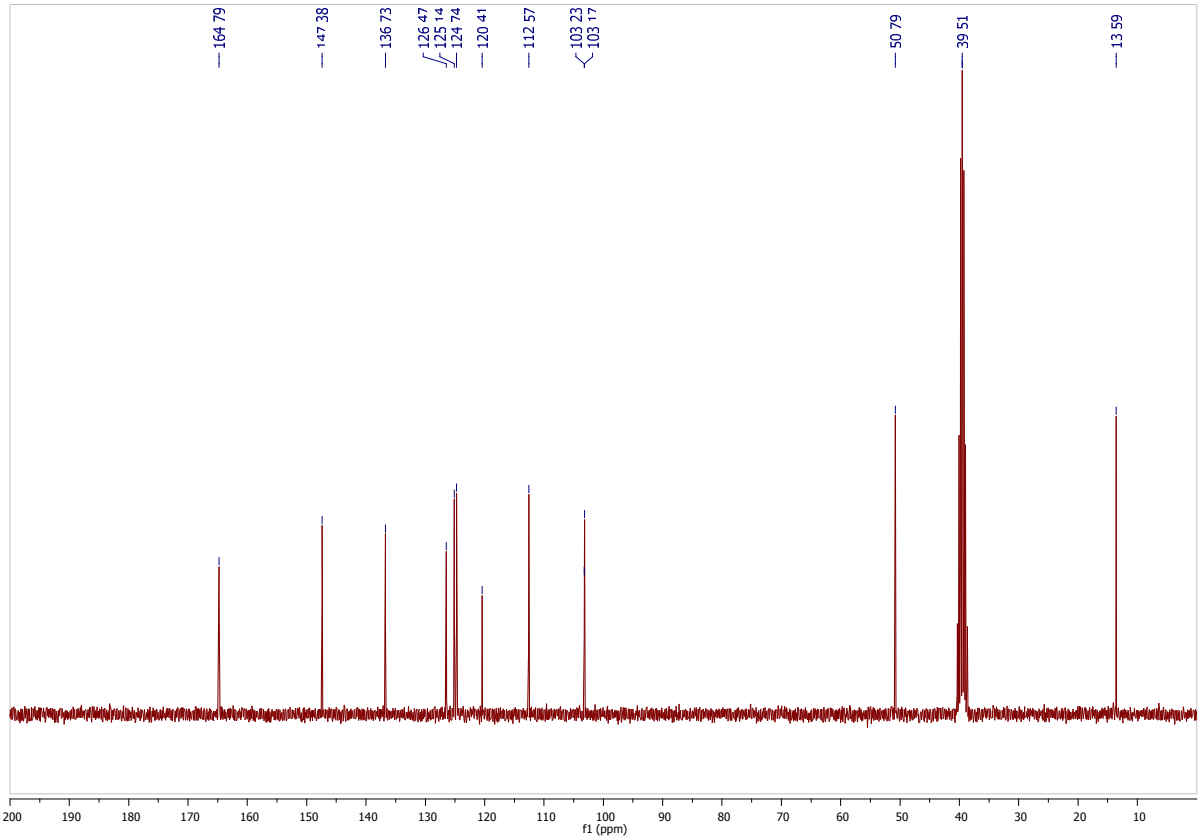

sew-sj-1552a
12.168
8.604
8.600
7.783
7.777
7.755
7.749
7.453
7.424
7.423
4.352
4.329
4.305
4.281
3.838
2.666
2.500
1.360
1.336
1.312
O
EtO
CO2Me
N
H
0.93
0.94
0.99
0.98
1.98
2.89
2.85
3.00
10.0
5.0
ppm (t1)

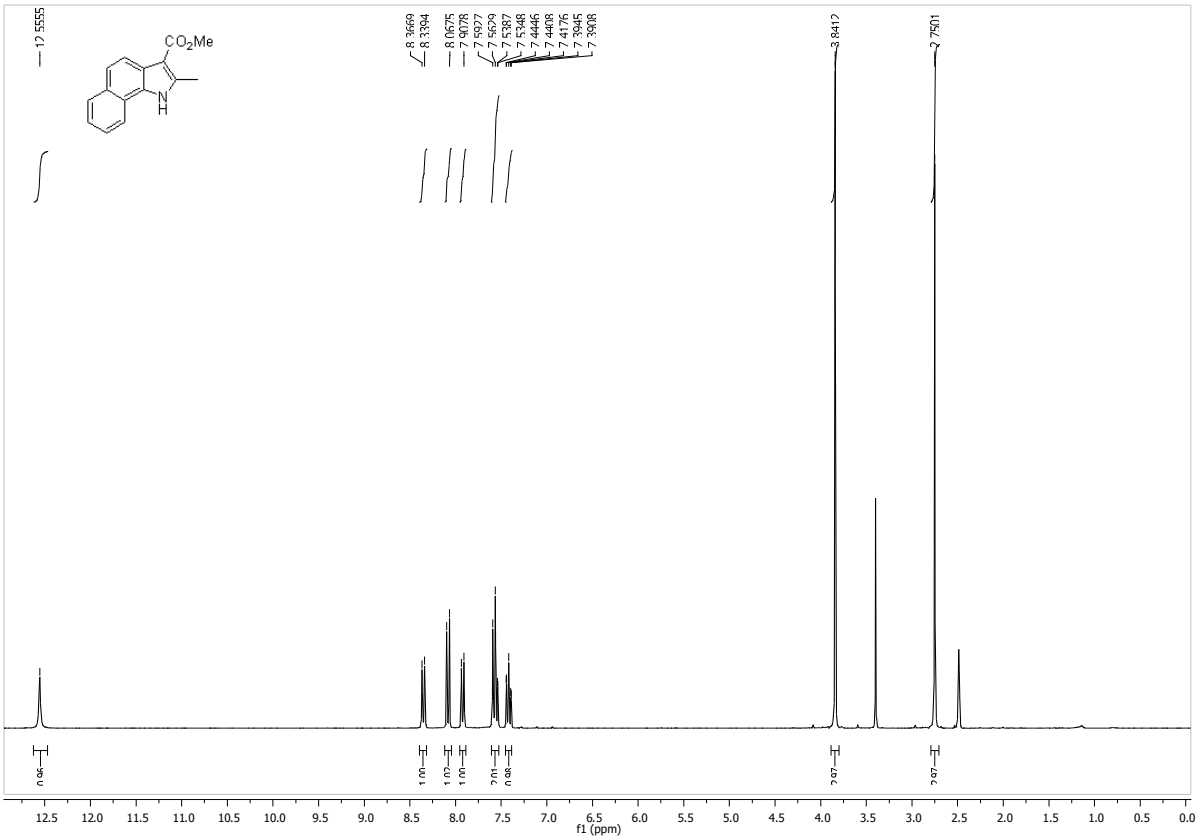

sew-sj-1552a
166.542
165.019
146.440
137.431
126.305
122.746
122.555
122.395
111.117
103.491
60.210
50.617
39.430
14.230
13.687
200
150
100
50
ppm (t1)

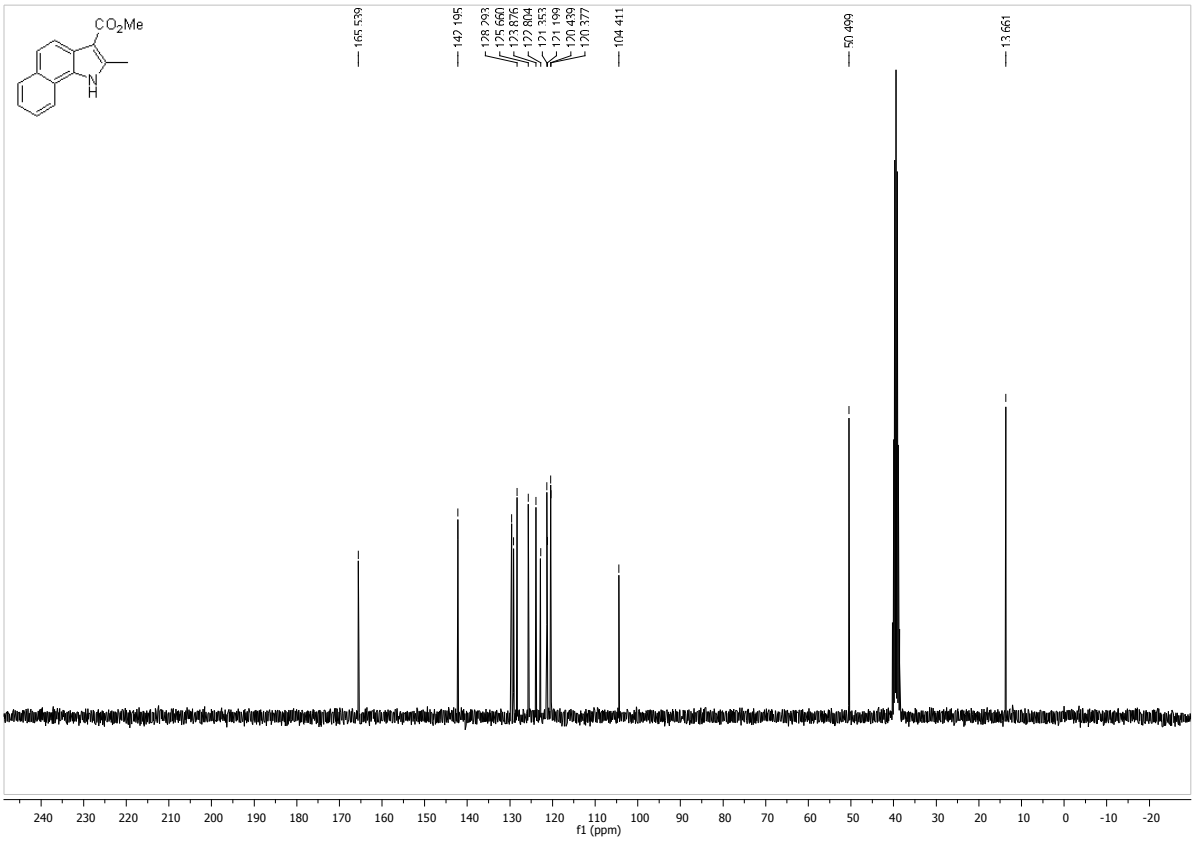

12.01
7.95
7.90
7.40
7.38
7.14
7.13
7.12
7.11
3.81
3.35
3.31
2.88
2.73
2.66
2.50
1.12
1.01
0.94
1.01
1.00
3.00
4.47
2.95
6.25
f1 (ppm)


171.13
165.31
145.87
134.92
129.96
126.11
120.35
118.47
111.08
102.99
50.56
42.99
39.92
13.73
13.06
f1 (ppm)


12.33
8.22
7.52
7.52
7.49
7.49
7.49
7.48
7.46
7.46
3.83
3.38
2.65
2.50
CO2Me
NC
N
H
1.00
0.97
2.01
3.00
3.00
f1 (ppm)


164.79
147.38
136.73
126.47
125.14
124.74
120.41
112.57
103.23
103.17
50.79
39.51
13.59
f1 (ppm)


CO2Me
N
H
12.5555
8.3669
8.3394
8.0675
7.9078
7.5659
7.5387
7.5348
7.4446
7.4176
7.3945
7.3908
3.8417
2.7501
f1 (ppm)


CO2Me
N
H
165.539
142.195
128.293
125.660
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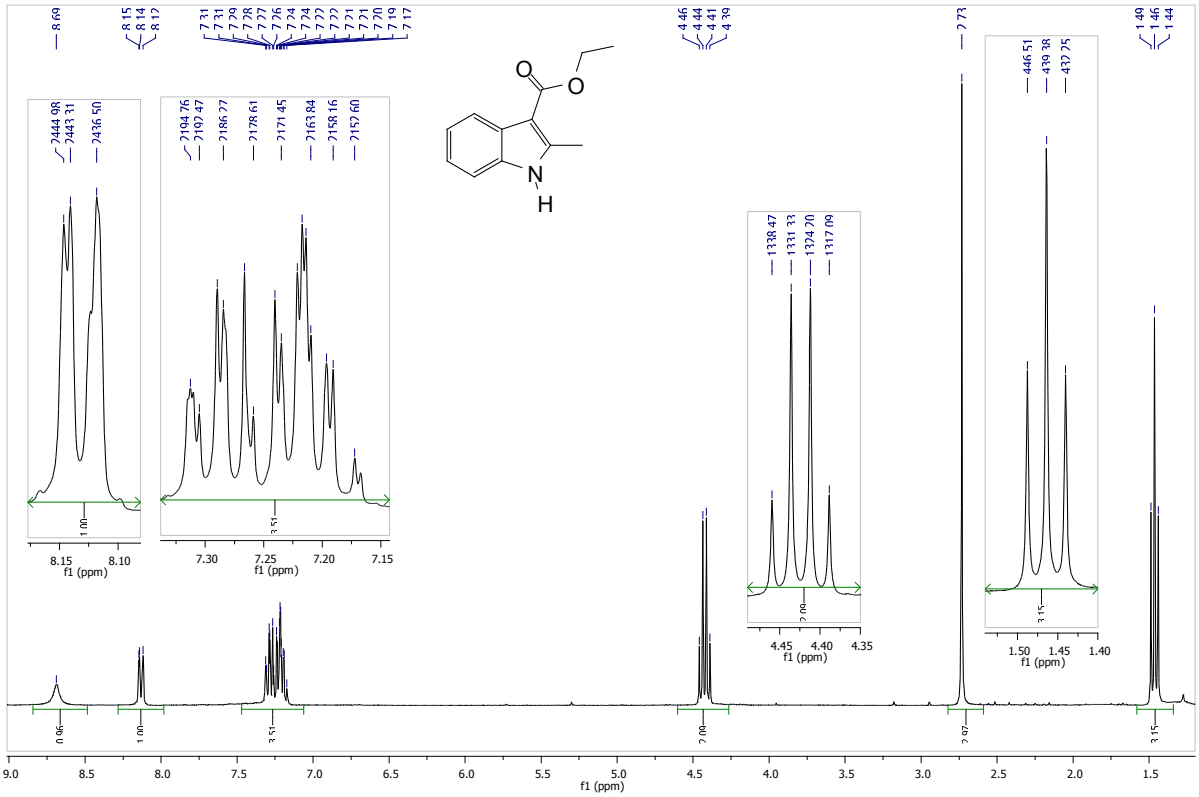
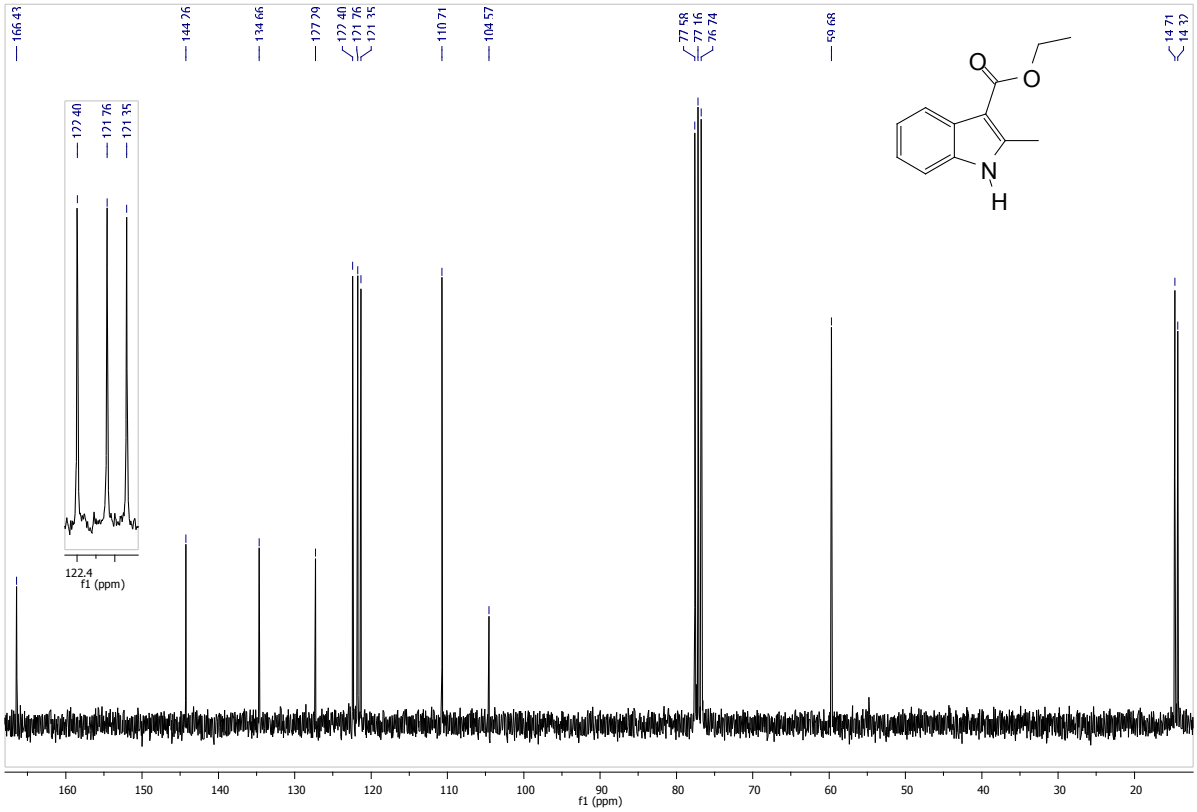
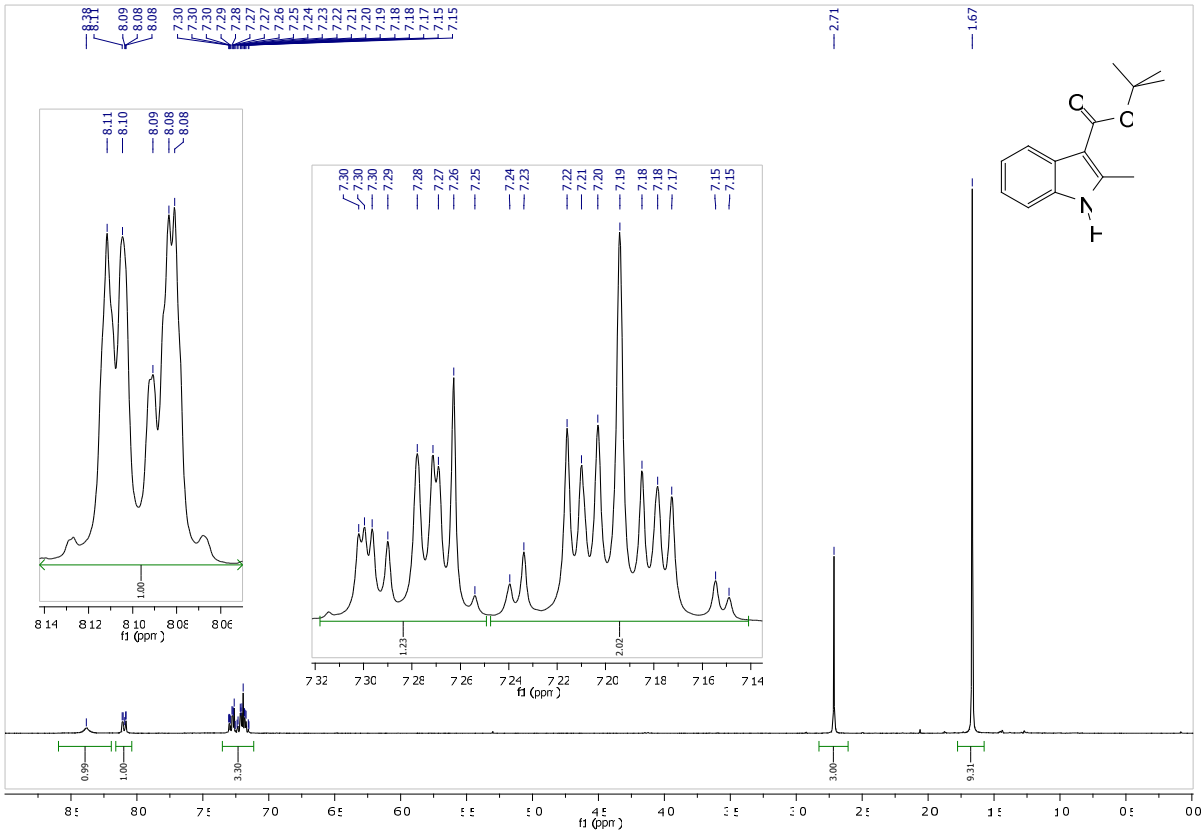
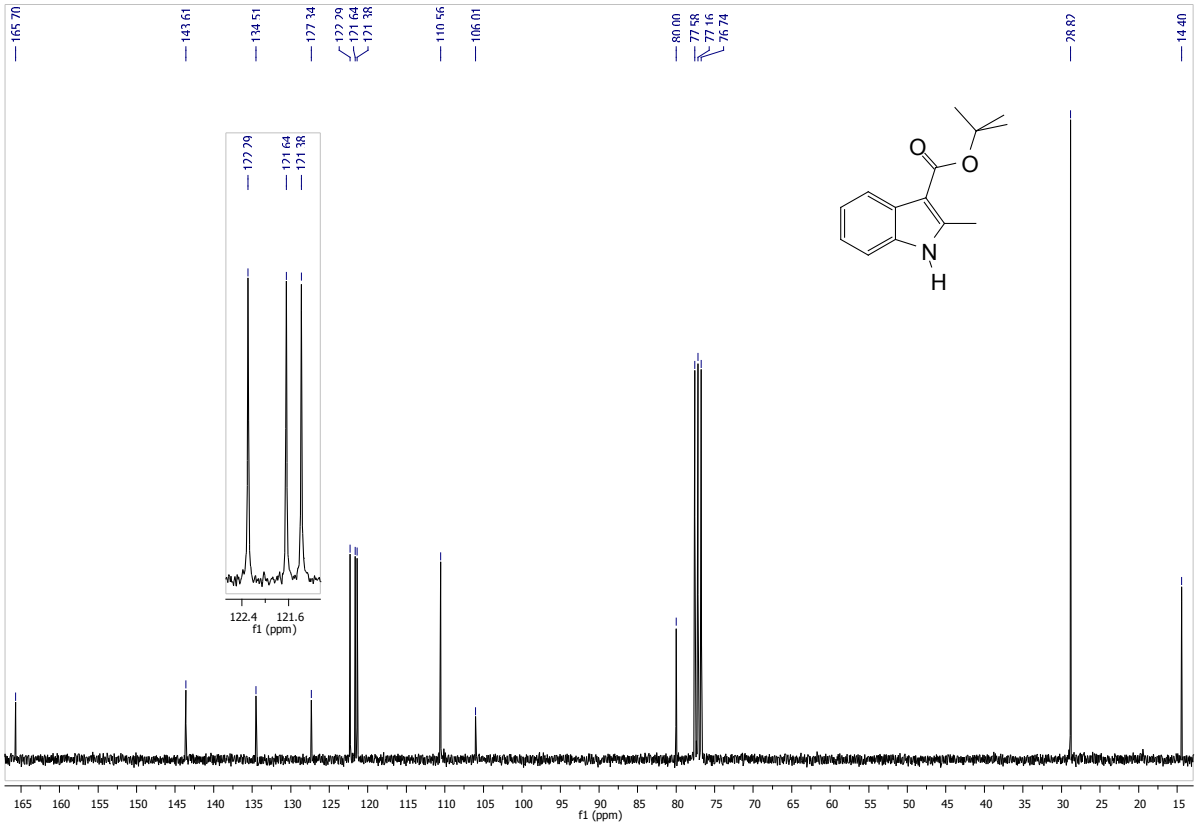
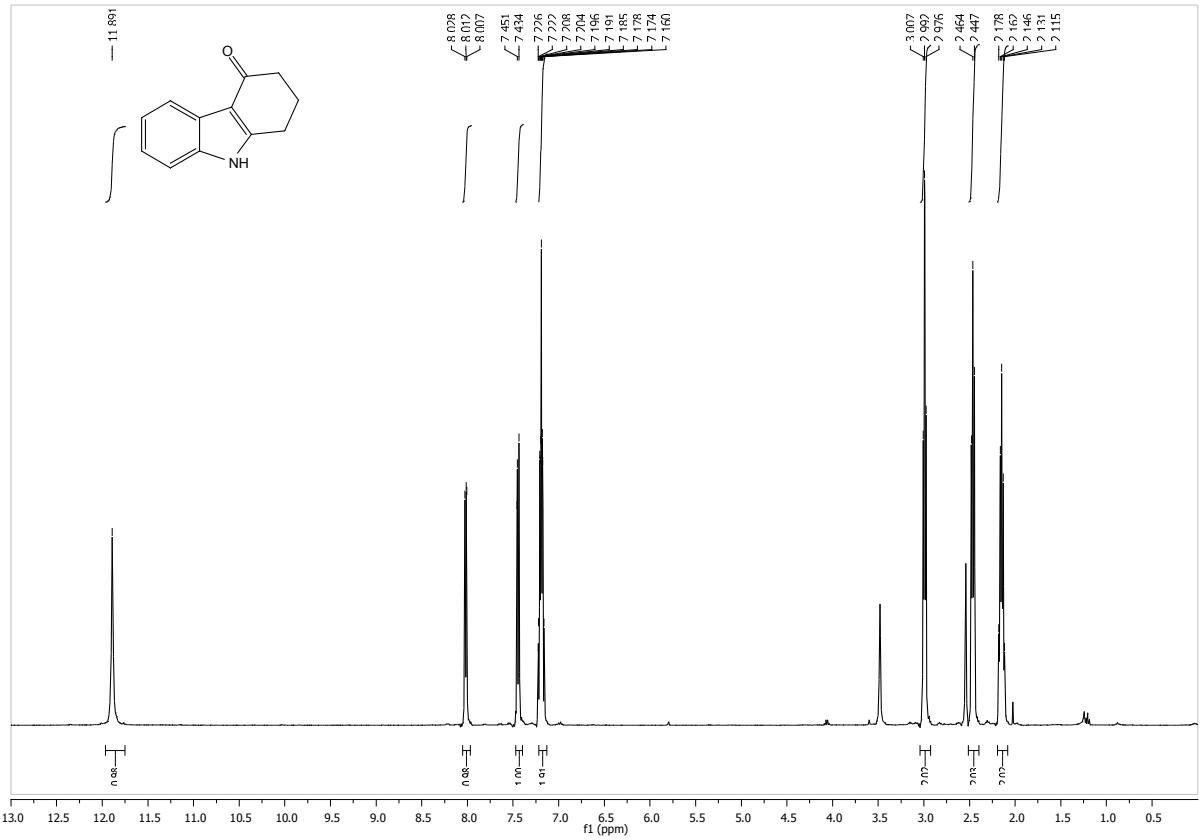
122.804
121.353
121.199
120.439
120.377
104.411
50.499
13.661
f1 (ppm)


f1 (ppm)


f1 (ppm)



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8.017
8.007
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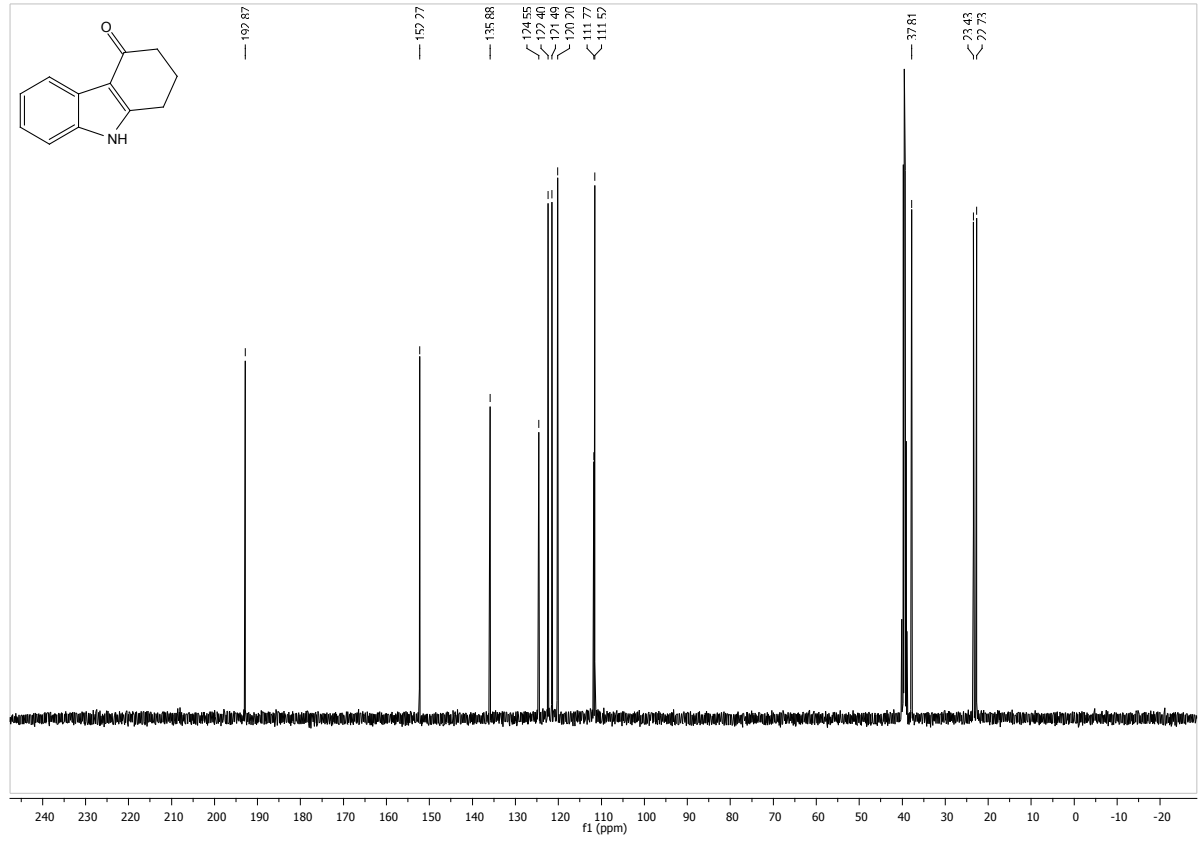
7.434
7.226
7.222
7.208
7.204
7.196
7.191
7.185
7.178
7.174
7.160
3.007
2.992
2.976
2.464
2.447
2.178
2.162
2.146
2.131
2.115
O
NH
f1 (ppm)


192.87
152.77
135.88
124.55
122.40
121.49
120.20
111.77
111.52
37.81
23.43
22.73
O
NH
f1 (ppm)