Supporting Information

Autocatalytic One Pot Orchestration for the Synthesis of α-Arylated α-Amino Esters.

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I. GENERAL INFORMATION

A. Instrumentation and methods

Infrared spectra were recorded on a Nicolet IS5 FT-IR spectrophotometer. ^{1}H NMR spectra were recorded on a Varian Mercury400 (400 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.26 ppm, CD_3CN at 1.94 ppm and DMSO-d_6 at 2.50 ppm). **Quantitative ^{1}H NMR spectra were performed using standard parameter (Pw = 90, at = 5, d1 = 15) and recorded on a Varian Mercury400; careful treatment of the NMR signal is required to proceed to quantification.** Data are reported as: (b = broad, s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet; coupling constant(s) in Hz, integration). ^{13}C NMR spectra were recorded on Varian Mercury400 (100 MHz) spectrometer. Chemical shifts are reported in ppm, with solvent resonance employed as the internal standard ($CDCl_3$ at 77.0 ppm, CD_3CN at 1.9 ppm, 118.7 ppm and DMSO-d_6 at 39.5 ppm). Positive ion MALDI-TOF mass spectrometry was carried out on an Applied Biosystems Voyager-DE STR spectrometer. Samples were dissolved in 0.1% TFA, 60% acetonitrile, and applied on α-cyano-4-hydroxycinnamic acid matrix. Spectra were obtained in the linear and reflector mode using Calmix 1 and Calmix 2 (Applied Biosystems) as external calibration standards. The low resolution ES-API mass spectra performed on FTICR mass spectrometer. Accurate mass (High resolution HRMS) was obtained from University of Florida using Agilent 6210 TOF instrument.

Reactions were performed in flame-dried glassware under a positive pressure of argon. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise noted. Analytical TLC was performed on 0.25 mm glass backed 60Å F-254 TLC plates. Flash chromatography was performed using 200-400 mesh silica gels (Silicycle, Inc.) or 60-325 mesh neutral alumina (Fisher, Inc.). Neutralized silica gel was prepared by adding 5 wt % of triethylamine in methylene chloride solution to normal-phase silica gel and mixed 1h at room temperature. The plates were visualized by exposure to UV light (254 nm) and developed by a solution of phosphomolybdic acid in ethanol, or vanillin/sulfuric acid in ethanol, or ninhydrin in ethanol, or potassium permanganate in water/potassium carbonate/sodium hydroxide or cerium-ammonium-molybdate in water/sulfuric acid and heat.

B. Reagents and solvents

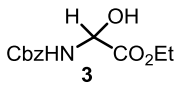
All reagents used in the present paper were acquired from Alfa Aesar or Sigma Aldrich. All bulk solvents were acquired from Fischer Scientific. Freshly distillated solvents were used in the reactions presented herein.

Chloroform was dried over $CaCl_2$ overnight prior to distillation (B.P. 61°C) and transferred under argon to a dark glass bottle with 3Å molecular sieves for storage. Tetrahydrofuran was purified by refluxing with and distilling from sodium with benzophenone and transferred under argon to a dark glass bottle for storage. Dichloromethane was dried over $CaCl_2$ overnight, prior to distillation (B.P. 40°C) and transferred under argon to a dark glass bottle with 3Å molecular

sieves for storage. Toluene was dried over CaH_2 and molecular sieves and transferred under argon to a dark glass bottle for storage. Full procedures can be found in Purification of Laboratory Chemicals by Armarego, W. L.F.; and Chai C. L. L., Elsevier (Sixth Edition).

II. Optimization for the Autocatalytic Synthesis of α-Amino Esters

A. Experimental Procedures and ^{1}H NMR overlay of hydroxy-, acetoxy-, and chloroaminals 3, SI-1 and 5:



3
$C_{12}H_{15}NO_5$
MW = 253.3 g.mol^{-1}

N-Cbz-Gly(α-OH)-OEt 3: To a solution of benzyl carbamate **1** (76 mg, 0.50 mmol, 1.0 equiv.) in ethyl acetate (5.0 mL) under argon atmosphere were added successively ethyl glyoxylate **2 (**132 µL**,** 0.65 mmol, 1.3 equiv.), and acetic acid (3 µL, 10 mol %, 0.1 equiv.) at 60 °C and stirred for 14 h. After completion of reaction (observed by ^{1}H NMR), the solvent was concentrated under vacuum and the crude reaction mixture was purified by flash chromatography using a gradient elution of ethyl acetate and hexanes (from 20:80 to 40:60) to deliver the desired product **3** as a white solid (102 mg, 0.40 mmol, 81% yield)

M.P. = 79-81 °C

R$_f$ = 0.25 (EtOAc/hexanes 30:70; UV Active, stains green yellow in vanillin)

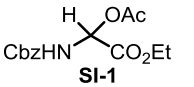
IR (Neat): ν_{max} = 695, 719, 734, 753, 867, 982, 1009, 1023, 1080, 1108, 1211, 1242, 1352, 1535, 1696, 1751, 3334 cm^{-1}.

^{1}H NMR (400 MHz, CD_3CN): δ (ppm) 7.51–7.23 (m, 5H), 6.63 (s, 1H), 5.31 (d, *J* = 8.5 Hz, 1H), 5.10 (s, 2H), 4.42 (s, 1H), 4.18 (dd, *J* = 14.1, 7.0 Hz, 2H), 1.24 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 169.4 (C), 155.7 (C_{quat}), 135.8 (C), 128.7(2 CH), 128.5 (CH), 128.3 (2 CH), 73.7 (CH), 67.5 (CH_2), 62.7 (CH_2), 14.1 (CH_3).

HR-MS (ESI): m/z Calcd. for $[C_{12}H_{15}NO_5+Na]^+$ = 276.0842, Found 276.0848 (+2.2 ppm).

SMILES: OC([H])(C(OCC)=O)NC(OCC1=CC=CC=C1)=O



SI-1
$C_{14}H_{17}NO_6$
MW = 295.1 g.mol^{-1}

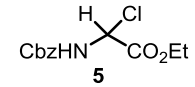
N-Cbz-Gly(α-OAc)-OEt SI-1: In a flame dried round bottom flask, a mixture of hemiaminal **3** (253 mg, 1.0 mmol, 1.0 equiv.) and pyridine (24 mg**,** 0.3 mmol, 0.13 equiv.) in acetic anhydride (3.0 mL) were stirred for 20 h under argon at RT. The orange solution was concentrated under vacuum and co-evaporated with toluene (3 x 5.0 mL). The crude product was purified by flash chromatography using a gradient elution of EtOAc/hexanes (20:80 to 50:40) to obtain the desired product **SI-1** as colorless liquid (260 mg, 0.88 mmol, 88% yield).

R$_f$ = 0.49 (EtOAc/hexanes 30:70; UV Active; stains white in $KMnO_4$)

IR (Neat) ν_{max} = 696, 738, 777, 848, 975, 1019, 1210, 1326, 1371, 1455, 1514, 1727, 3340 cm^{-1}.

^{1}H NMR (400 MHz, CD_3CN): δ (ppm) 7.46–7.30 (m, 5H), 6.98 (bs, 1H), 6.28 (d, *J* = 9.3 Hz, 1H), 5.13 (s, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 2.06 (s, 3H), 1.23 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, CD_3CN): δ (ppm) 170.8, 167.0, 156.2, 137.3, 129.5 (2 C), 129.2, 129.0 (2 C), 75.3, 68.0, 63.2, 20.9, 14.3.
HR-MS (ESI): m/z Calcd. for $[C_{14}H_{17}NO_6+NH_4]^+$ = 313.1394, Found 313.1398 (+1.3 ppm)
SMILES: [H]C(OC(C)=O)(C(OCC)=O)NC(OCC1=CC=CC=C1)=O



5
$C_{12}H_{14}ClNO_4$
MW = 271.1 g.mol^{-1}

N-Cbz-Gly(α-Cl)-OEt 5: Chloroaminal **5** was synthesized using two different procedures.

Procedure A: In a flame dried vial, a mixture of benzyl carbamate **1** (76 mg, 0.50 mmol, 1.0 equiv.), ethyl glyoxylate **2 (**132 µL**,** 0.65 mmol, 1.3 equiv.), acetyl chloride **(**95 µL**,** 1.25 mmol, 2.5 equiv.) and catalytic acetic acid (3 µL, 10 mol %, 0.1 equiv.) in chloroform (5.0 mL) were stirred for 12 h under argon at 60 °C. The reaction mixture was then evaporated under vacuum to obtain the desired product **5** as a white solid (135 mg, 0.50 mmol, and quantitative yield).

Procedure B: In a flame dried vial, a mixture of hemiaminal **3** (506 mg, 2.00 mmol, 1.0 equiv.) and thionyl chloride (720 µL, 10 mmol, 5.0 equiv.) in CH_2Cl_2 (10.0 mL) were stirred for 4 h under argon at 40 °C. The reaction mixture was then evaporated under vacuum to obtain the desired product **5** as a white solid (541 mg, 2.00 mmol, and quantitative yield).

R_f = ***Caution!!*** (The chloroaminal **5** is not stable on silica; it hydrolyses back to hemiaminal **3** to give a spot on TLC at the exact same R_f).
M.P. = 117-119 °C
IR (Neat) ν_{max} = 660, 694, 753, 778, 976, 1023, 1056, 1204, 1240, 1337, 1529, 1700, 1742 cm^{-1}.
^{1}H NMR (400 MHz, CD_3CN): δ (ppm) 7.48–7.22 (m, 5H), 7.03 (bs, NH), 6.18 (d, *J* = 10.4 Hz, 1H), 5.16 (s, 2H), 4.26 (q, *J* = 7.1, 2H), 1.27 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 169.6 (C), 168.0 (C), 156.0 (C), 135.9 (C), 128.6 (2 CH), 128.4 (CH), 128.3 (2 CH), 73.6 (CH), 67.4 (CH_2), 62.7 (CH_2), 14.0 (CH_3).
HR-MS (ESI): Not compatible with the experiment condition found hemiaminal **3** calcd. m/z for $[C_{12}H_{15}NO_5+Na]^+$ = 276.0842, Found 276.0848 (+2.2 ppm).
SMILES: ClC([H])(C(OCC)=O)NC(OCC1=CC=CC=C1)=O

Below is presented an NMR overlay of the plausible reaction intermediates **SI-1**, **3** and **5**:

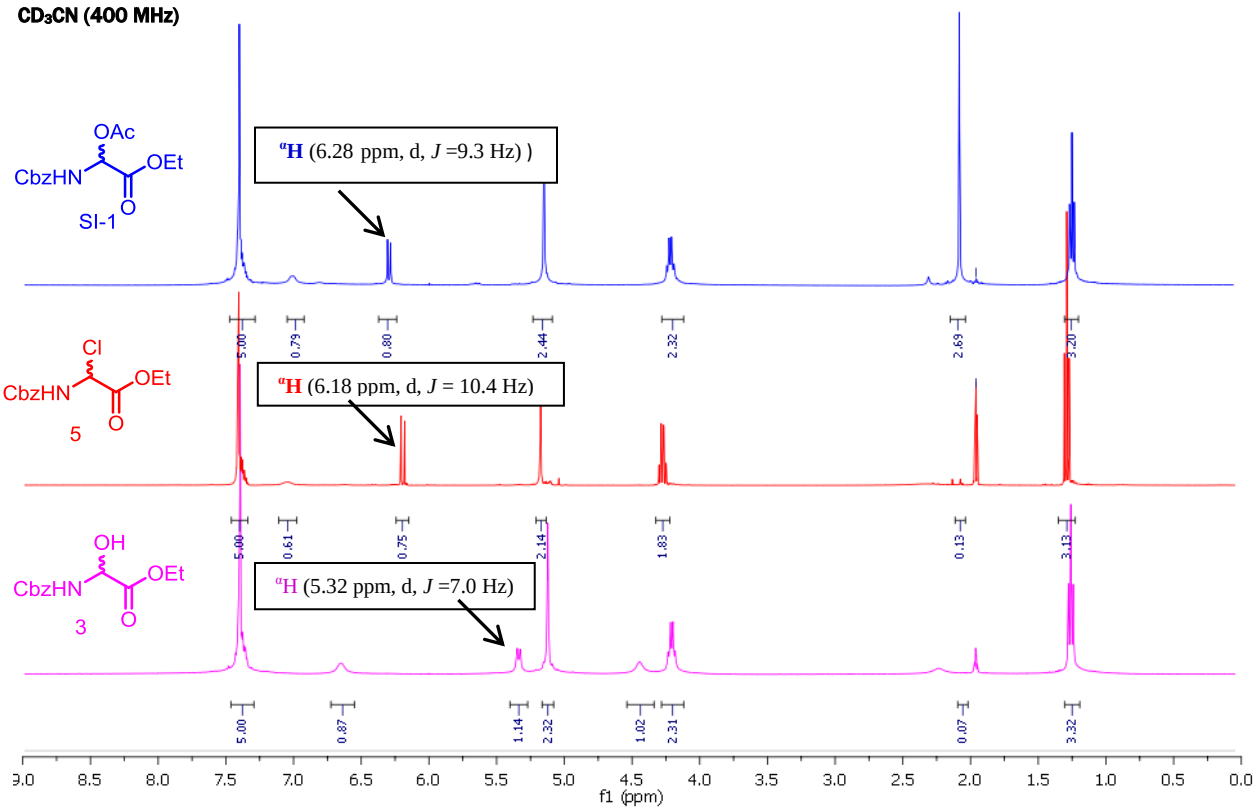


Figure SI-1. ^{1}H NMR Overlay of hemiaminal **3**, acetoxyaminal **SI-1** and chloroaminal **5**.

B. Reaction Optimization:

*1) The synthesis of chloroaminal **5**:*

In a flame dried vial under argon, a mixture of benzyl carbamate **1** (76 mg, 0.50 mmol, 1.0 equiv.), ethyl glyoxylate **2 (**132 µL, 0.65 mmol, and 1.3 equiv), acetyl chloride (95 µL**,** 1.25 mmol, and 2.5 equiv.) and acetic acid (3 µL, 10 mol %, 0.1 equiv.) in the appropriate solvent ($CHCl_3$ or EtOAc; 5.0 mL) was stirred for 12 hours at 60 °C. Every 3 hours, a reaction aliquot was taken (1.0 mL of the reaction mixture corresponding ~0.1 mmol of **1**) and solvent was evaporated under vacuum. In the dry aliquot, mesitylene (12 mg, 0.10 mmol, 1.0 equiv.) was added as an internal standard. ^{1}H NMR was determined using quantitative protocol with the appropriate acquisition parameters (*see section instrumentation and methods*). The advancement of both reactions are presented below in the **Table SI-1** and **Figures SI-2 and SI-3** showing percentile conversion based on the mesitylene peaks (2.24 ppm, 6.80 ppm) and ratio between reaction intermediates present in the reaction mixture.

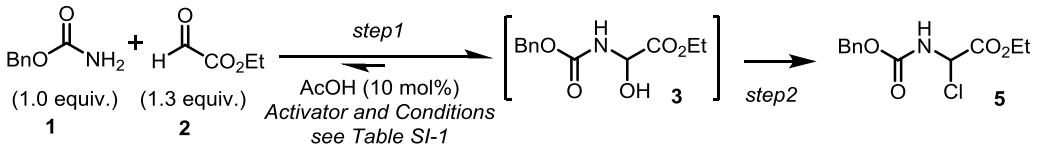
After 3 hours in ethyl acetate (**Table SI-1**, entry 1) the reaction mixture at 60 °C presents majorly product hemiaminal **3** (82% conv.) along with a small amount of chloroaminal **5** (28% conv.). Allowing the reaction mixture for longer time (6 hours) produces mostly chloroaminal **5**

(92% conv.). Finally after 9 hours, the reaction in ethyl acetate reaches full conversion to the chloro-aminal **5** (100% conv.; **Table SI-1**, entry 1).

After 3 hours at 60 °C in chloroform (**Table SI-1**, entry 2), the reaction mixture produces hemi-aminal **3** (67% conv.) as major product with small amount of chloroaminal **5** (33% conv.). The advancement of reaction after 6 hours was observed with slow formation of chloroaminal **5** (55% conv.). Allowing the reaction to proceed for 9 hours gives mainly chloro-aminal **5** (73% conv.) with some hemiaminal **3** (27% conv.). The reaction was completed after 12 hours affording chloroaminal **5 (**100% conv.; **Table SI-1,** entry 2**).**

Note: It was also found that the reaction was not compatible with the use of molecular sieves. Also the Friedel−Crafts reaction seems to slow down in presence of molecular sieves. We observed that addition of MS 3Å (1 g/mol) to the reaction mixture drastically decreases the reaction's rate, probably due to sequestration of HCl.

Conclusion: Both of the above reactions proceed smoothly and very cleanly to the desired chloroaminal **5** and the reaction in ethyl acetate was found to be slightly faster than the one in chloroform.



entry	solvent, temp.	activator	time (h)	^{1}H NMR conversion (%) in the aliquots
1	Ethyl acetate, 60 ^{o}C	AcCl	3	**3** (82); **5** (28)
			6	**3** (8); **5** (92)
			9	**5** (100)
2	$CHCl_3$, 60 ^{o}C	AcCl	3	**3** (67); **5** (33)
			6	**3** (45); **5** (55)
			9	**3** (27); **5** (73)
			12	**5** (100)

Table SI-1. Reaction optimization to access the key reactive intermediate chloroaminal **5**

2) ^{1}H NMR overlay following the cascade reaction advancement:

^{1}H NMR overlays presented below in **Figure-SI-2** and **Figure-SI-3** were done using MestReNova software for each reaction mixture for ethyl acetate and chloroform respectively.

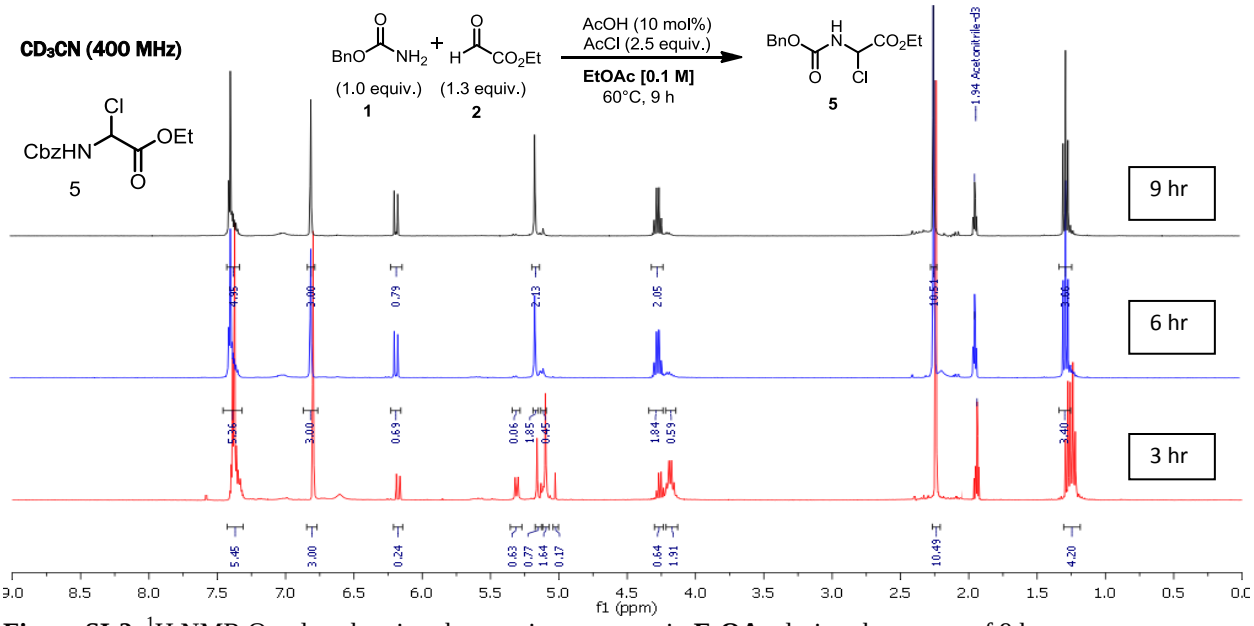


Figure SI-2. ^{1}H NMR Overlay showing the reaction progress in **EtOAc** during the course of 9 hours

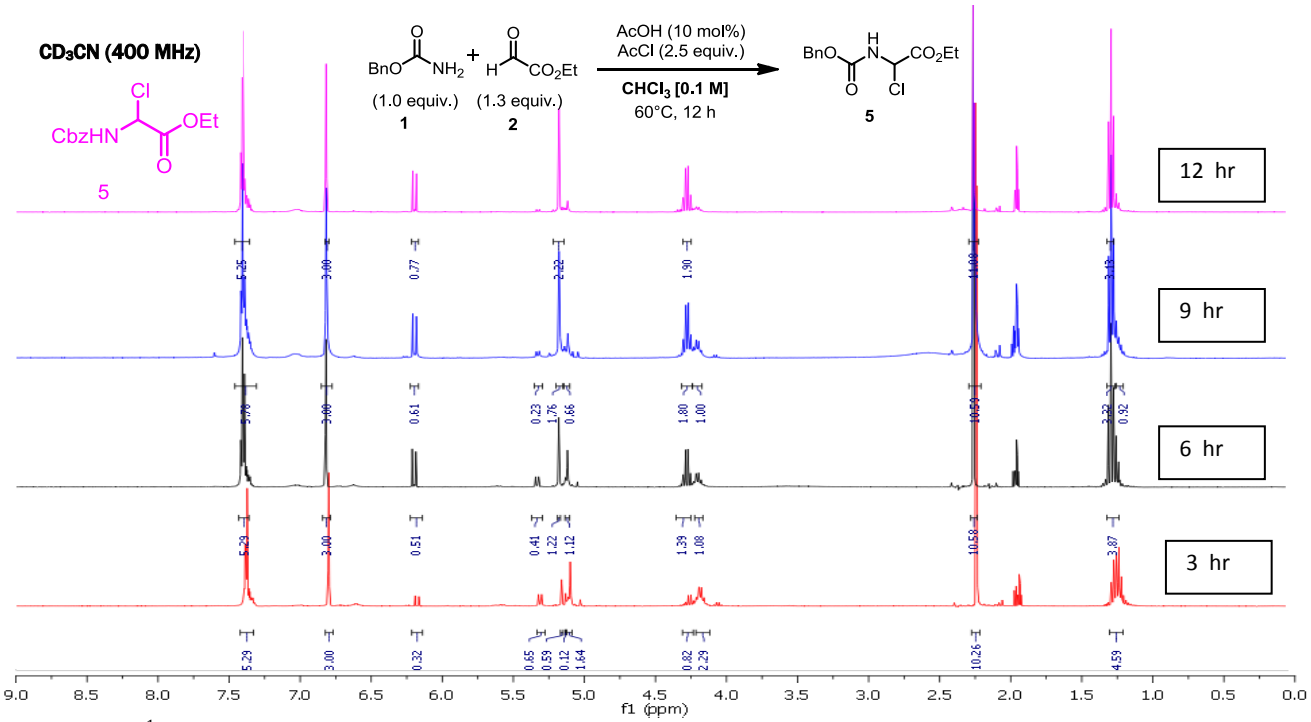
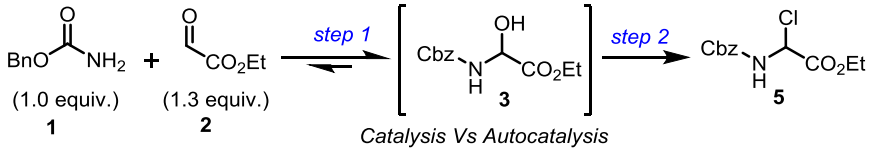


Figure SI-3. ^{1}H NMR Overlay showing the reaction progress in **chloroform** during the course of 12 hours

C. Experimental evidence for the autocatalysis with a AcOH/AcCl system :



Scheme SI- 1

Table SI-2: ^{1}H NMR Data for the reaction conversion with time

Entry	solvent, temp.	activator	time (hours)	Conversion were calculated based on signal integrations		Avg	conversion (%) [c]
				(αH) [a]	(CH_2) [b]		
1	$CHCl_3$, RT ***CATALYSIS***	-	0.5	-	-	-	Not detectable
			1	-	-	-	Not detectable
			1.5	8	9	9	9 **(3)**, 91 **(1)**
			3	16	19	18	18 **(3),** 82 **(1)**
			6	26	29	28	28 **(3),** 72 **(1)**
			9	45	50	48	48 **(3),** 52 **(1)**
			12	62	70	66	66 **(3),** 34 **(1)**
			15	70	63	67	67 **(3),** 33 **(1)**
			18	70	67	69	69 **(3),** 21 **(1)**
			21	72	72	72	72 **(3),** 28 **(1)**
2	$CHCl_3$, RT ***AUTOCATALYSIS***	AcCl	0.5	18	18	18	18 **(3+5),**82 **(1)**
			1	33	34	34	34 **(3+5),** 66 **(1)**
			1.5	56	46	51	51 **(3+5),** 49 **(1)**
			3	73	78	76	76 **(3+5),** 24 **(1)**
			6	78	80	79	79 **(3+5),** 21 **(1)**
			9	86	87	87	87 **(3+5),** 13 **(1)**
			12	93	88	91	91 **(3+5),** 9 **(1)**

All data reported in **Table SI-2** are collected using a quantitative ^{1}H NMR technique with mesitylene (1.0 equiv.) as internal standard. For each collected spectrum, the percentage of error was calculated based on the ratio between the two peaks of the mesitylene internal standard (at 2.23 ppm, 9H and 6.79 ppm, 3H).

Conversions were calculated as follow:

[a] **Entry 1/2:** Integration of the $^{\alpha}$H peaks of hemiaminal **3** and chloroaminal **5** were obtained from the crude ^{1}H NMR. The percentage conversion was directly obtained from these integrations.

[b] **Entry 1/2:** Integration of the CH_2 peak of the hemiaminal **3** and chloroaminal **5** were obtained from the crude ^{1}H NMR. These integration of the CH_2 peaks were converted to the equivalent $^{\alpha}$H peaks (divided by two) to calculate the percentage conversion with respect to CH_2 peaks.

[c] **Entry 1/2:** The percentage of reaction conversion were calculated from the average of $^{\alpha}$H peaks and CH_2 peaks of hemiaminal **3** and chloroaminal **5.**

[1]H NMR overlay following the AcOH/AcCl autocatalytic reaction advancement:

[1]H NMR overlays presented below in **Figure SI-4** was done using MestReNova software taking crude of AcOH/AcCl corresponding to **Table SI-2 entry 2**.

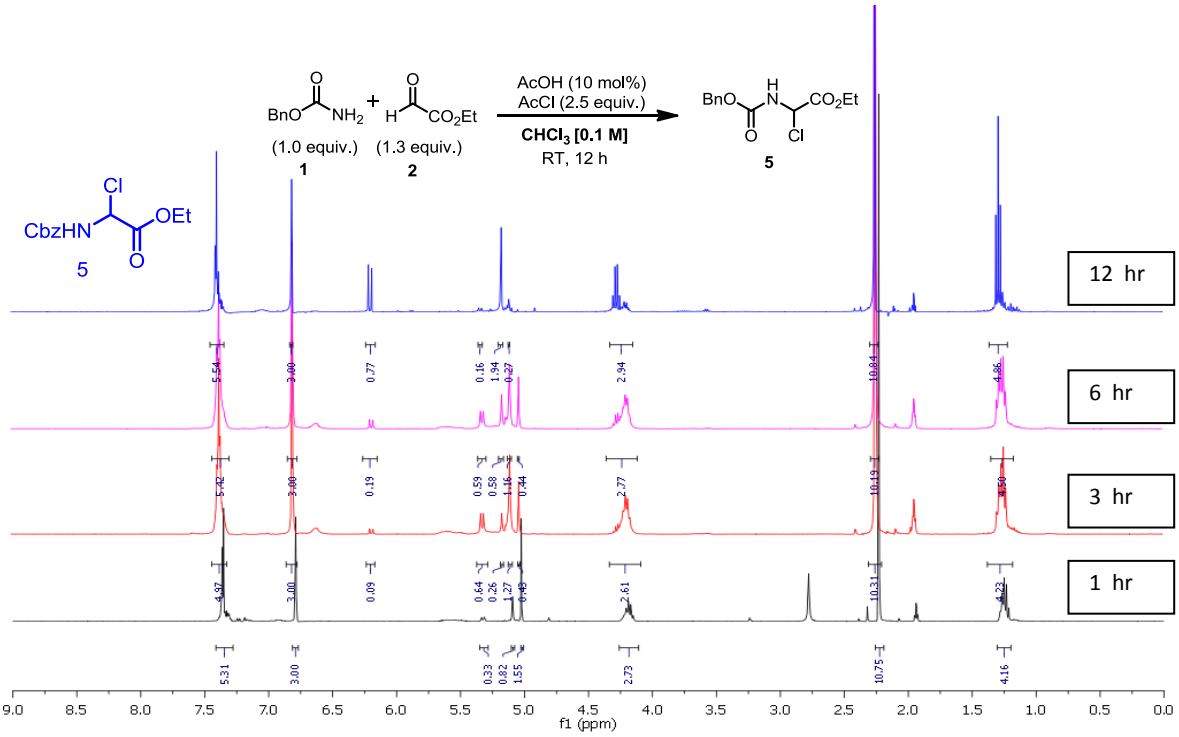
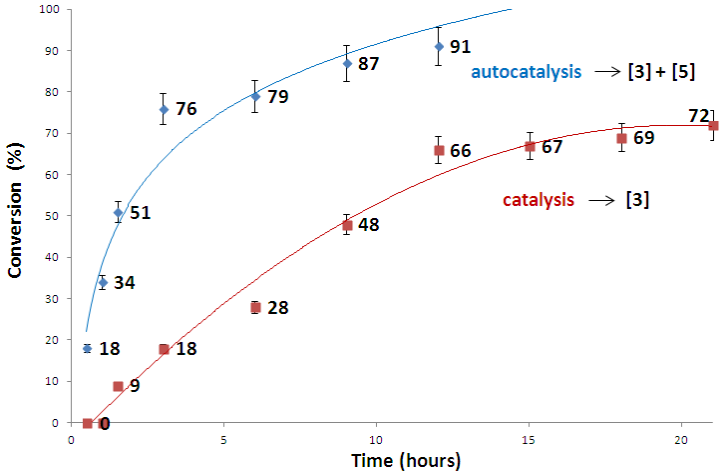


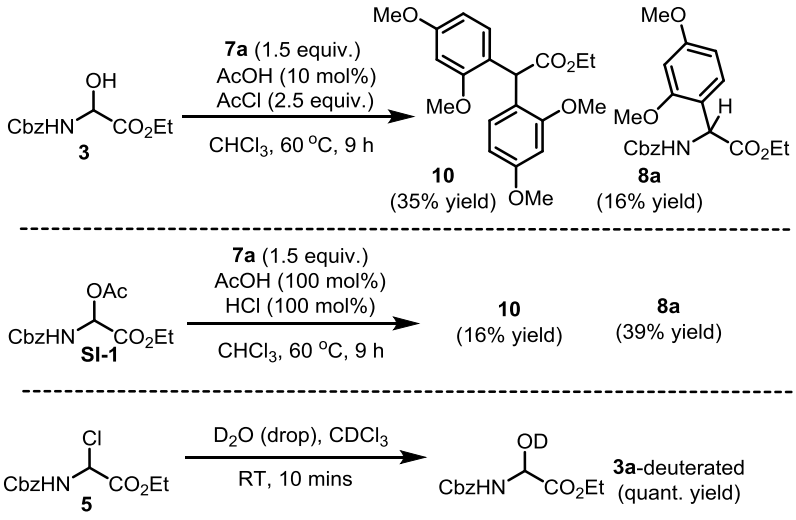
Figure SI-4. [1]H NMR Overlay showing the reaction progress in chloroform with a AcOH/AcCl autocatalytic system at room temperature

Figure SI-5. Catalysis Vs Autocatalysis



We proceeded to examine the condensation and activation steps in more details (**Scheme SI-1**, steps 1/2). The two kinetic curves have been plotted using the %conv. Vs time from **Table SI-2**. Upon addition of acetyl chloride the reactions preceded faster to full conversion into hemiaminal **3** and further afforded the desired chloroaminal **5** (**Fig. SI-5**; **autocatalysis**). These kinetic experiments support that acetyl chloride displaces the reaction equilibrium towards hemiaminal **3**, by further advancing to the chlorination step and autocatalyzing the production of acetic acid.

D. Control experiments to examine the reactivity of the various plausible reaction intermediates :

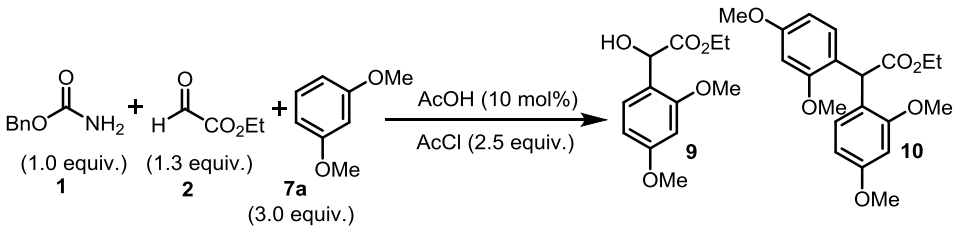


Scheme SI-2

To gain more insight into the reaction mechanism, we decided to run control experiments starting from hemiaminal **3** and the other plausible reaction intermediates acetoxy- and chloroaminal **SI-1** and **5** (**Scheme SI-2**). Interestingly, addition of arene **7a** to hemiaminal **3** afforded a bis-arylated product **10** along with the desired α-amino ester **8a** in 35% and 16% yield respectively. This result strongly supports that hemiaminal **3** has a tendency to fragment (retro-condensation) before undergoing several arylations leading to **10**.[SI-1] Reaction of α-acetoxyglycinate **SI-1** proceeded only in presence of HCl and not surprisingly delivered the same products **10** and **8a** in 16% and 39% yield respectively showing similar reactivity as hemiaminal **3**. Finally, treatment of chloroaminal **5** with D_2O regenerates the hemiaminal **3** quantitatively, demonstrating that water should be entirely excluded from the reaction media.

Ref (SI-1) Treatment of hemiaminal **3** without nucleophile, in presence of acids such as acetic acid, thioureas, boron trifluoride or scandium triflate results in a quantitative fragmentation (retro-condensation).

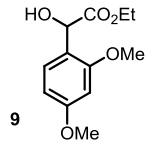
III. Experimental Procedures and Compounds Characterization:



In a flame dried round bottom flask under argon, a mixture of benzyl carbamate **1** (76 mg, 0.50 mmol, 1.0 equiv.), ethyl glyoxylate **2** (132 µL**,** 0.65 mmol, and 1.3 equiv.), acetyl chloride (95 µL, 1.25 mmol, 2.5 equiv.), acetic acid (3 µL, 10 mol %, 0.1 equiv.), and 1,3-dimethoxybenzene **7a** (207 mg, 1.50 mmol, 3.0 equiv.) in chloroform (5.0 mL) were stirred for 12 h at RT. After consumption of all the starting material (observed by TLC), the reaction mixture was quenched with a saturated sodium bicarbonate solution (20.0 mL) and extracted with CH_2Cl_2 (3 x 10.0 mL). The combined organic layers were then dried over sodium sulfate, filtered and concentrated under vacuum to afford yellowish liquid crude.

The crude reaction mixture was purified by flash chromatography using a gradient elution of EtOAc/hexanes (from 20:80 to 40:60) to deliver the desired products as a colorless liquid **9** (68 mg, 0.28 mmol, 57% yield) and colorless oil **10** (39 mg, 0.11 mmol, 22% yield) respectively.

Ethyl 2-(2,4-dimethoxyphenyl)-2-hydroxyacetate 9: **R_f** = 0.31 (EtOAc/hexanes 30:70; UV Active, stains pink in vanillin)



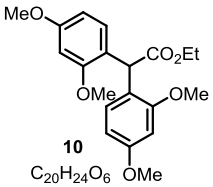
$C_{12}H_{16}O_5$
MW= 240.26 g.mol^{-1}

IR (Neat) ν_{max} = 832, 1032, 1068, 1119, 1132, 1159, 1209, 1267, 1297, 1466, 1508, 1612, 1733, 2261 cm^{-1}.

^{1}H NMR (400 MHz, CD_3CN): δ (ppm) 7.17 (d, *J* = 8.3 Hz, 1H), 6.57–6.47 (m, 2H), 5.17 (d, *J* = 6.6 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.79 (d, *J* = 2.2 Hz, 6H), 3.72 (d, *J* = 6.5 Hz, 1H), 1.16 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, CD_3CN): δ (ppm) 174.5, 162.2, 159.2, 130.7, 121.4, 105.6, 99.5, 69.7, 61.9, 56.3, 56.0, 14.5. **HR-MS (ESI):** m/z Calcd. for $[C_{12}H_{16}O_5+Na]^+$ = 263.0890, Found 263.0903(+4.9 ppm). **SMILES:** OC(C(OCC)=O)C1=CC=C(OC)C=C1OC

Ethyl 2,2-bis(2,4-dimethoxyphenyl)acetate 10: **R_f** = 0.34 (EtOAc/hexanes 30:70; UV Active, stains pink in vanillin)



$C_{20}H_{24}O_6$
MW = 360.4 g.mol^{-1}

IR (Neat) ν_{max} = 792, 832, 935, 1031, 1117, 1156, 1191, 1208, 1259, 1294, 1338, 1336, 1418, 1440, 1464, 1505, 1586, 1611, 1730, 2260, 2941 cm^{-1}.

^{1}H NMR (400 MHz, CD_3CN): δ (ppm) 6.86 – 6.77 (m, 2H), 6.55 (d, *J* = 2.5 Hz, 2H), 6.45 (dd, *J* = 8.5, 2.5 Hz, 2H), 5.30 (s, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.77 (s, 12H), 1.17 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, CD_3CN): δ (ppm) 174.3, 161.3 (2 C), 159.1 (2 C), 130.4 (2 C), 120.3 (2 C), 105.4 (2 C), 99.4 (2 C), 61.4, 56.3 (2 C), 56.0 (2 C), 44.5, 14.6.

HR-MS (ESI): m/z Calcd. for $[C_{14}H_{17}NO_6+H]^+$ = 361.1643, Found 361.1641(-0.5 ppm)

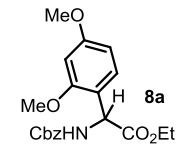
SMILES: O=C(C(C1=CC=C(OC)C=C1OC)C2=CC=C(OC)C=C2OC)OCC

A. General procedure for the One pot preparation of α-Amino Ester:

In a flame dried round bottom flask under argon, a mixture of benzyl carbamate **1** (76 mg, 0.50 mmol, 1.0 equiv.), ethyl glyoxylate **2** (108 µL**,** 0.05 mmol, and 1.05 equiv.), acetyl chloride (95 µL, 1.25 mmol, and 2.5 equiv.), and acetic acid (3 µL, 10 mol %, 0.1 equiv.), in CH_3CN or $CHCl_3$ solvent (5.0 mL; [0.1 M]) were stirred for 24 h or 12 h respectively (steps 1/2) at 60 °C. After that point, the reaction mixture was cooled down to RT then the arene nucleophile (1.5 equiv.) was added (step 3) in the reaction mixture and stirred at the indicated temperature for the appropriate time (x h). After full consumption of the chloroaminal intermediate **5** (observed by TLC *caution*: same R_f value as the hydroxyaminal **3**), the reaction mixture was quenched with a saturated solution of sodium bicarbonate (20.0 mL) and extracted with CH_2Cl_2 (3 x 10.0 mL). The combined organic layers were then dried over sodium sulfate, filtered and concentrated under vacuum to afford the crude reaction mixture. The crude mixture was then purified by flash chromatography using an appropriate elution.

B. Compounds Characterization

Ethyl *N*-benzyloxycarbonyl-α-(2,4-dimethoxyphenyl)glycinate 8a:



$C_{20}H_{23}NO_6$
MW = 373.4 g.mol^{-1}

Product **8a** was synthesized following the ***general procedure***
Steps 1/2: Solvent: chloroform (5.0 mL) at 60 °C for 12 h.
Step 3: Dimethoxy benzene (104 mg**,** 0.75 mmol, 1. 5 equiv.) as nucleophile and stirred for 9 h at 60 °C.
The crude reaction mixture was purified by flash chromatography using an isocratic solvent system of EtOAc/hexanes (20:80) to deliver the desired product **8a** as a colorless liquid (152 mg, 0.41 mmol, 82% yield).

R_f = 0.30 (EtOAc/hexanes 30:70; UV Active, stains pink red in vanillin)

IR (Neat) ν_{max} = 699, 747, 756, 968, 1028, 1045, 1207, 1237, 1251, 1329, 1524, 1715, 1730, 3395 cm^{-1}.

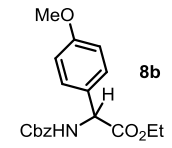
^{1}H NMR (400 MHz, CD_3CN): δ (ppm) 7.41 – 7.26 (m, 5H), 7.16 (d, *J* = 8.3 Hz, 1H), 6.53 (d, *J* = 2.3 Hz, 1H), 6.49 (dd, *J* = 8.3, 2.3 Hz, 1H), 6.22 (d, *J* = 7.4 Hz, 1H), 5.37 (d, *J* = 8.4 Hz, 1H), 5.07 (q, *J* = 12.4 Hz, 2H), 4.11 (q, *J* = 7.0 Hz, 2H), 3.78 (d, *J* = 3.8 Hz, 6H), 1.70 – 1.10 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 171.4 (C), 161.2 (C), 158.1 (C), 156.0 (C), 136.5 (CH), 131.1 (CH), 128.7 (2CH), 128.4 (2CH), 128.3 (CH), 118.5 (C), 104.4 (CH), 99.1 (CH), 67.1 (CH_2), 61.7 (CH_2), 55.6 (CH_3), 55.0 (CH_3), 29.9 (CH_2), 14.3 (CH_3).

HRMS (ESI): m/z Calcd. for $[C_{20}H_{23}NO_6+Na]^+$ = 396.1418, Found 396.1429 (+2.8 ppm)

SMILES: [H][C@](C1=CC=C(OC)C=C1OC)(C(OCC)=O)NC(OCC2=CC=CC=C2)=O

Ethyl *N*-benzyloxycarbonyl-α-(4-methoxyphenyl)glycinate *8b:*



$C_{19}H_{21}NO_5$
MW = 343.4 g.mol^{-1}

Product **8b** was synthesized following the ***general procedure***
Steps 1/2: Solvent: acetonitrile (5.0 mL) at 60 °C for 24 h.
Step 3: Anisole (82 µL**,** 0.75 mmol, 1. 5 equiv.) as nucleophile at 60 °C for 24 h.
The crude reaction mixture was purified by flash chromatography using an isocratic solvent system of EtOAc/hexanes (20:80) to deliver the desired product **8b** as a colorless liquid (81 mg, 0.42 mmol, 48% yield).

R_f = 0.37 (EtOAc/hexanes 25:75; UV Active, stains yellow white in vanillin)

IR (Neat) ν_{max} = 697, 752, 775, 835, 1027, 1046, 1177, 1208, 1245, 1304, 1454, 1510, 1714, 3349 cm^{-1}.

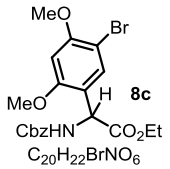
^{1}H NMR (400 MHz, CD_3CN): δ (ppm) 7.37 (d, *J* = 7.2 Hz, 5H), 7.33 (dd, *J* = 12.0, 8.7 Hz, 2H), 6.94 (d, *J* = 8.7 Hz, 2H), 6.43 (d, *J* = 5.5 Hz, 1H), 5.23 (d, *J* = 7.4 Hz, 1H), 5.10 (d, *J* = 2.9 Hz, 2H), 4.21 – 4.08 (m, 2H), 3.80 (s, *J* = 6.1 Hz, 3H), 1.17 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, CD_3CN): δ (ppm) 171.9 (C), 160.7 (C_{quat}), 156.7 (C), 138.0(C_{quat}), 129.8 (3 CH), 129.6 (C), 129.4 (2 CH), 128.9 (CH), 128.7 (CH), 115.1 (2 CH), 67.2 (CH_2), 62.4 (CH_2), 58.7 (CH), 55.9 (CH_3), 14.4 (CH_3).

HRMS (ESI): m/z Calcd. for $[C_{19}H_{21}NO_5+Na]^+$ = 366.1312, Found 366.1329(+4.6 ppm)

SMILES: [H]C(C1=CC=C(OC)C=C1)(C(OCC)=O)NC(OCC2=CC=CC=C2)=O

Ethyl *N*-benzyloxycarbonyl-α-(5-bromo-2,4-dimethoxyphenyl)glycinate *8c :*



$C_{20}H_{22}BrNO_6$
MW = 452.3 g.mol^{-1}

Product **8c** was synthesized following the ***general procedure***
Steps 1/2: Solvent: acetonitrile (5.0 mL) at 60 °C for 24 h.
Step 3: 1-Bromo-2,4-dimethoxybenzene (162 mg**,** 0.75 mmol, 1.5 equiv.) as nucleophile at RT for 16 h.
The crude reaction mixture was purified by flash chromatography using an isocratic solvent system of EtOAc/hexanes (20:80) to deliver the desired product **8c** as a colorless liquid (161 mg, 0.36 mmol, 72% yield).

R_f = 0.46 (EtOAc/hexanes 25:75; UV Active, stains yellow in vanillin)

IR (Neat) ν_{max} = 659, 696, 759, 836, 881, 981, 1028, 1044, 1170, 1187, 1210, 1234, 1299, 1317, 1499, 1699, 1734, 3343 cm^{-1}.

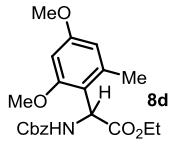
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.46 (s, 1H), 7.32 (dd, *J* = 11.1, 3.8 Hz, 5H), 6.44 (s, 1H), 5.91 (d, *J* = 8.5 Hz, 1H), 5.41 (d, *J* = 8.5 Hz, 1H), 5.09 (q, *J* = 12.3 Hz, 2H), 4.25 – 4.06 (m, 2H), 3.84 (d, *J* = 28.1 Hz, 6H), 1.18 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, CD_3CN): δ (ppm) 170.8 (C), 157.4 (C), 156.9 (C), 155.7 (C), 136.3 (C), 133.9 (CH), 128.6(2 CH), 128.2(2 CH), 119.5 (C), 101.9 (C), 96.7 (2 CH), 67.1(CH_2), 61.8 (CH_2), 56.4 (CH_3), 55.9 (CH_3), 54.1 (CH), 14.2 (CH_3).

HRMS (ESI): m/z Calcd. for $[C_{20}H_{22}BrNO_6+Na]^+$ = 474.0528, Found 474.0540 (+2.5 ppm) and for another isotope m/z Calcd. for $[C_{20}H_{22}BrNO_6+Na]^+$= 476.0508, Found 476.0524 (+3.4 ppm)

SMILES: [H]C(C1=CC(Br)=C(OC)C=C1OC)(C(OCC)=O)NC(OCC2=CC=CC=C2)=O

Ethyl *N*-benzyloxycarbonylamino-α-*(*3,5-dimethoxytoluen-2-yl)glycinate *8d:*

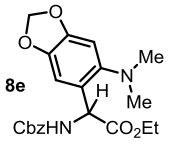


$C_{21}H_{25}NO_6$
MW = 387.4 g.mol^{-1}

Product **8d** was synthesized following the ***general procedure***
Steps 1/2: Solvent: chloroform (5.0 mL) at 60 °C for 12 h.
Step 3: 3, 5-dimethoxytoluene (110 µL**,** 0.75 mmol, 1.5 equiv.) as nucleophile at 60 °C for 1.5 days.
The crude reaction mixture was purified by flash chromatography using an isocratic solvent system of ethyl acetate and hexanes (15:85) to deliver the desired product **8d** as colorless oil (137mg, 0.35 mmol, 71% yield).

R_f = 0.46 (EtOAc/ Hexanes 30/70; UV active; light purple in vanillin). **IR**: (Neat) ν_{max}= 697, 740, 829, 1044, 1090, 1141, 1199, 1318, 1455, 1496, 1604, 1720, 2957, 3463 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.40 – 7.27 (m, 5H), 6.36 (d, *J* = 2.3 Hz, 1H), 6.29 (d, *J* = 2.3 Hz, 1H), 6.00 (d, *J* = 9.5 Hz, 1H), 5.69 (d, *J* = 9.5 Hz, 1H), 5.10 (dd, *J* = 28.8, 12.1 Hz, 2H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.79 (s, 3H), 3.73 (s, 3H), 2.50 (s, 3H), 1.17 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm) 171.7 (C), 160.1 (CH), 158.4 (CH), 156.2 (C), 138.9 (CH), 136.4 (C quat), 128.6 (2 CH), 128.2 (2 CH), 128.2 (CH), 117.9 (C quat), 107.0 (CH), 96.5 (CH), 67.0 (CH_2), 61.4 (CH_2), 55.4 (CH_3), 55.3 (CH3), 51.6 (CH_2), 20.4 (CH_3), 14.2 (CH_3).
HRMS (ESI): m/z Calcd. for $[C_{17}H_{20}N_2O_4+H]^+$ = 317.1496, Found 317.1507(+3.5 ppm).
SMILES: CC(C=C(OC)C=C1OC)=C1C(C(OCC)=O)NC(OCC2=CC=CC=C2)=O

Ethyl *N*-benzyloxycarbonyl-α-*(*4-(dimethylamino)benzo[1,3]dioxol-5-yl)glycinate 8e:



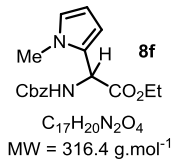
$C_{21}H_{24}N_2O_6$
MW = 400.4 g.mol^{-1}

Product **8e** was synthesized following the ***general procedure***
Step 1/2: Solvent: acetonitrile (5.0 mL) at 60 °C for 24 h.
Step 3: aniline hydrochloride[SI-2] (151 mg**,** 0.75 mmol, 1.5 equiv.) as nucleophile at RT for 12 h.
The crude reaction mixture was purified by flash chromatography using an isocratic solvent system of ethyl acetate and hexanes (15:85) to deliver the desired products as a colorless liquid **8e** (132 mg, 0.33 mmol, 66% yield).

R_f = 0.32 (EtOAc/hexanes 20:80; UV Active, stains deep red in vanillin)
IR (Neat) ν_{max} = 671,753, 1035, 1044, 1052, 1169, 1200, 1252, 1293, 1319, 1342, 1496, 1505, 1531, 1567, 1637, 1692, 1741, 3332 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) 7.40 – 7.25 (m, 5H), 6.80 (s, *J* = 32.0 Hz, 2H), 6.12 (d, *J* = 7.0 Hz, 1H), 5.92 (d, *J* = 1.7 Hz, 2H), 5.68 (d, *J* = 7.6 Hz, 1H), 5.09 (q, *J* = 12.1 Hz, 2H), 4.28 – 4.01 (m, 2H), 2.56 (s, *J* = 23.5 Hz, 6H), 1.19 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 171.5, 155.8, 148.3, 147.4, 145.0, 136.5, 128.6(2 CH), 128.2(2 CH), 127.3, 108.5, 103.5, 101.6 (2 CH), 67.0, 61.7, 54.8, 46.2 (2 CH_3), 14.2. **HRMS (ESI):** m/z Calcd. for $[C_{21}H_{24}N_2O_6+H]^+$ = 401.1707, Found 401.1726 (+4.7ppm).
SMILES:[H][C@](C1=C(N(C)C)C=C(OCO2)C2=C1)(C(OCC)=O)NC(OCC3=CC=CC=C3)=O

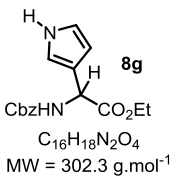
Ref (SI-2) Aniline hydrochloride salt was prepared at O °C using diethyl ether as solvent from *N*,*N*-dimethyl-3,4-(methylenedioxy)aniline treating with Hydrogen chloride solution [4.0 M] in dioxane**.**

Ethyl *N*-benzyloxycarbonyl-α-(*N*-metyl-pyrrol-2-yl)glycinate 8f:



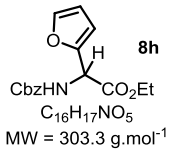
Product **8f** was synthesized following the ***general procedure***
Steps 1/2: Solvent: chloroform (5.0 mL) at 60 °C for 12 h.
Step 3: *N*-methylpyrrole (67 µL**,** 0.75 mmol, 1. 5 equiv.) as nucleophile at 0 °C for 1.5 h.
The crude reaction mixture was purified by flash chromatography using a gradient elution of EtOAc/hexanes (from 10:90 to 20:80) to deliver the desired product **8f** as a white solid (91 mg, 0.29 mmol, 60% yield).
MP: 111-112 °C.
R_f = 0.57 (EtOAc/ Hexanes 30/70; UV active; stains dark red/pink in vanillin)
IR: (Neat) ν_{max}= 700, 7474, 758, 968, 1028, 1045, 1207, 1237, 1251, 1329, 1524, 1701, 1730, 3351 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.44 – 7.29 (m, 5H), 6.60 (s, 1H), 6.05 (dd, *J* = 5.6, 2.8 Hz, 2H), 5.53 (d, *J* = 8.1 Hz, 1H), 5.46 (d, *J* = 8.1 Hz, 1H), 5.12 (s, 2H), 4.23 (dd, *J* = 16.1, 7.2 Hz, 2H), 3.67 (s, 3H), 1.26 (t, *J* = 7.0 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 170.3 (C), 155.6 (C), 136.2 (C quat), 128.6 (2 CH), 128.3 (CH), 128.2 (2 CH), 127.3 (C quat), 123.7 (CH), 107.8 (CH), 107.4 (CH), 67.2 (CH_2), 62.1 (CH_2), 50.6 (CH), 34.1 (CH_3), 14.2 (CH_3).
HRMS (ESI): m/z Calcd. for $[C_{17}H_{20}N_2O_4+Na]^+$ = 339.1315, Found 339.1331 (+4.7 ppm)
SMILES: CN1C=CC=C1C(C(OCC)=O)NC(OCC2=CC=CC=C2)=O

Ethyl *N*-benzyloxycarbonyl-α-(pyrrol-2-yl)glycinate 8g:



Product **8g** was synthesized following the ***general procedure***
Step 1/2: Solvent: Chloroform (5.0 mL) at 60 °C for 12 h.
Step 3: Pyrrole (52 µL**,** 0.75 mmol, 1.5 equiv.) as nucleophile at -60 °C for 35 min.
The crude reaction mixture was purified by flash chromatography using an isocratic solvent system of ethyl acetate and hexanes (15:85) to deliver the desired products as a colorless liquid **8g** (102 mg, 0.34 mmol, 67% yield).
R_f = 0.45 (EtOAc/hexanes 30:70; UV Active, stains black in vanillin)
IR (Neat) ν_{max} = 698, 733, 778, 1028, 1051, 1093, 1186, 1219, 1329, 1370, 1454, 1504, 1712, 3360 cm^{-1}.
^{1}H NMR (400 MHz, CD_3CN): δ (ppm) 9.31 (s, 1H), 7.46 – 7.27 (m, 5H), 6.75 (dt, *J* = 4.4, 2.3 Hz, 1H), 6.34 (s, 1H), 6.07 (t, *J* = 2.5 Hz, 2H), 5.32 (d, *J* = 7.6 Hz, 1H), 5.12 (s, 2H), 4.19 (qd, *J* = 6.7, 3.3 Hz, 2H), 1.23 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (100 MHz, CD_3CN): δ (ppm) 171.2, 156.9, 138.0, 129.5 (2 CH), 129.0 (CH), 128.7 (2 CH), 126.5, 119.7, 108.9, 107.9, 67.3, 62.6, 53.4, 14.4.
HRMS (ESI): m/z Calcd. for $[C_{16}H_{18}N_2O_4+H]^+$ = 303.1339, Found 303.1344 (+1.6 ppm)
SMILES: [H][C@](C1=CN([H])C=C1)(C(OCC)=O)NC(OCC2=CC=CC=C2)=O

Ethyl *N*-benzyloxycarbonyl-α-(furan-2-yl)glycinate *8h:*



Product **8h** was synthesized following the ***general procedure.***
Steps 1/2: Solvent: acetonitrile (5.0 mL) at 60 °C for 24 h.
Step 3: furan (55 μL**,** 0.75 mmol, 1. 5 equiv.) as nucleophile at 60 °C for 17 h.
The crude reaction mixture was purified by flash chromatography using an isocratic solvent system of EtOAc/hexanes (20:80) to deliver the desired product **8h** as a colorless liquid (89 mg, 0.29 mmol, 59% yield).

R_f = 0.34 (EtOAc/hexanes 20:80; UV Active, stains red in vanillin)

IR (Neat) ν_{max} = 667, 698, 753, 776, 1028, 1049, 1179, 1247, 1369, 1393, 1511, 1611, 1720, 2360, 2979, 3359 cm^{-1}.

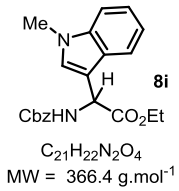
^{1}H NMR (400 MHz, CD_3CN): δ (ppm) 7.47 (d, *J* = 0.8 Hz, 1H), 7.40 – 7.28 (m, 5H), 6.45 (s, 1H), 6.40 (dd, *J* = 6.4, 2.4 Hz, 2H), 5.40 (d, *J* = 7.9 Hz, 1H), 5.09 (s, 2H), 4.25 – 4.09 (m, 2H), 1.19 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, CD_3CN): δ (ppm) 169.7, 156.7, 150.0, 144.1, 137.9, 129.4 (2 CH), 129.0, 128.7 (2 CH), 111.7, 109.6, 67.4, 62.9, 53.2, 14.4.

HRMS (ESI): m/z Calcd. for $[C_{16}H_{17}NO_5+2MeO^-+H]^+$ = 366.1553, Found 366.1326 (-62.0 ppm).

SMILES: [H]C(C1=CC=CO1)(C(OCC)=O)NC(OCC2=CC=CC=C2)=O

Ethyl *N*-benzyloxycarbonyl-α-(1-methyl-indol-3-yl)glycinate 8i:



Product **8i** was synthesized following the ***general procedure.***
Step 1/2: Solvent: chloroform (5.0 mL) at 60 °C for 12 h.
Step 3: *N*-methylindole (94 μL**,** 0.75 mmol, 1.5 equiv.) as nucleophile at -45 °C for 3 h.
The crude reaction mixture was purified by flash chromatography using an isocratic solvent system of ethyl acetate and hexanes (15:75) to deliver the desired products **8i** as a yellowish liquid (145 mg, 0.39 mmol, 79% yield).

R_f = 0.13(EtOAc/hexanes 20:80; UV Active, stains brown in vanillin)

IR (Neat) ν_{max} = 698, 742, 1027, 1048, 1197, 1331, 1475, 1498, 1715, 3343 cm^{-1}.

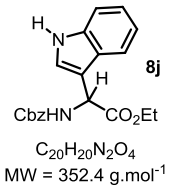
^{1}H NMR (400 MHz, CD_3CN): δ (ppm) δ 7.63 (d, *J* = 8.0 Hz, 1H), 7.41 – 7.29 (m, 6H), 7.23 (ddd, *J* = 8.2, 7.1, 1.1 Hz, 1H), 7.19 (s, 1H), 7.10 (ddd, *J* = 8.0, 7.1, 0.9 Hz, 1H), 6.36 (s, 1H), 5.52 (d, *J* = 7.1 Hz, 1H), 5.09 (s, 2H), 4.15 (dd, *J* = 14.6, 7.3 Hz, 2H), 3.75 (s, 3H), 1.16 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, CD_3CN): δ (ppm) 171.6, 156.1, 137.3, 128.7 (2 CH), 128.6 (CH), 128.2 (2 CH), 128.0 (2 CH), 126.3, 122.2, 119.7, 119.2, 110.1, 109.3, 66.4, 61.5, 51.6, 32.5, 13.7.

HRMS (ESI): m/z Calcd. for $[C_{21}H_{22}N_2O_4+Na]^+$ = 389.1472, Found 389.1491(+4.9 ppm).

SMILES: [H][C@](C1=CN(C)C2=C1C=CC=C2)(C(OCC)=O)NC(OCC3=CC=CC=C3)=O

Ethyl *N*-benzyloxycarbonyl-α-(1H-indol-3-yl)glycinate 8j:



$C_{20}H_{20}N_2O_4$
MW = 352.4 g.mol^{-1}

Product **8j** was synthesized following the ***general procedure.***
Step 1/2: Solvent: chloroform (5.0 mL) at 60 °C for 12 h.
Step 3: Indole (88 mg**,** 0.75 mmol, 1.5 equiv.) as nucleophile at 0 °C for 2 h.
The crude reaction mixture was purified by flash chromatography using an isocratic solvent system of Acetone and hexanes (15:75). Another purification performed by preparative TLC using solvent system of ether and dichloromethane (2: 98) to obtain the pure desired products **8j** as a yellowish liquid (113 mg, 0.32 mmol, 64% yield).

R_f = 0.35 (Acetone/hexanes 25:75; UV Active, stains brown in vanillin)

IR (Neat) ν_{max} = 698, 743, 1027, 1048, 1192, 1218, 1250, 1279, 1327, 1370, 1456, 1500, 1704, 3345 cm^{-1}.

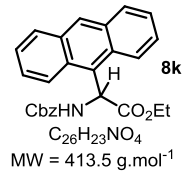
^{1}H NMR (400 MHz, CD_3CN): δ (ppm) 9.39 (s, 1H), 7.62 (dd, *J* = 8.0, 0.7 Hz, 1H), 7.43 (d, *J* = 8.2 Hz, 1H), 7.38 – 7.29 (m, 5H), 7.27 (d, *J* = 2.6 Hz, 1H), 7.17 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H), 7.12 – 7.06 (m, 1H), 6.32 (s, 1H), 5.52 (d, *J* = 7.1 Hz, 1H), 5.09 (s, 2H), 4.24 – 4.01 (m, 2H), 1.15 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, CD_3CN): δ (ppm) 172.4, 156.7, 137.4, 129.4 (2 CH), 128.9 (CH), 128.7 (2 CH), 126.6, 125.1, 123.1, 120.6, 119.8, 112.6, 111.0, 67.2, 62.2, 52.4, 30.9, 14.4.

HRMS (ESI): m/z Calcd. for $[C_{20}H_{20}N_2O_4+Na]^+$ = 375.1315, Found 375.1323(+2.1 ppm).

SMILES: [H][C@](C1=CN([H])C2=C1C=CC=C2)(C(OCC)=O)NC(OCC3=CC=CC=C3)=O

Ethyl N-benzyloxycarbonyl-2-(anthracen-9-yl)glycinate 8k:



$C_{26}H_{23}NO_4$
MW = 413.5 g.mol^{-1}

Product **8k** was synthesized following the ***general procedure.***
Step 1/2: Solvent: acetonitrile (5.0 mL) at 60 °C for 24 h.
Step 3: Anthracene (134 mg**,** 0.75 mmol, 1. 5 equiv.) as nucleophile at 60 °C for 17 h.
The crude reaction mixture was purified by flash chromatography using an isocratic solvent system of ethyl acetate and hexanes (15:85) to deliver the desired products as a white solid **8k** (168 mg, 0.40 mmol, 82% yield).

MP: 195-196 °C

R_f = 0.42 (EtOAc/hexanes 20:80; UV Active, stains yellowish in vanillin)

IR (Neat) ν_{max} = 694, 755, 809, 936, 1026, 1053, 1170, 1214, 1285, 1304, 1318, 1332, 1511, 1590, 1676, 1723, 3366, cm^{-1}.

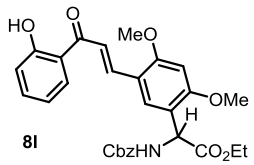
^{1}H NMR (400 MHz, CD_3CN): δ (ppm) 8.60 (s, 1H), 8.39 – 8.20 (m, 3H), 8.14 – 8.04 (m, 2H), 7.64 – 7.46 (m, 4H), 7.31 (s, 4H), 6.85 (d, *J* = 7.1 Hz, 1H), 6.77 (s, 1H), 5.06 (dd, *J* = 35.9, 12.4 Hz, 2H), 4.22 – 4.00 (m, 2H), 0.99 – 0.89 (m, 3H).

^{13}C NMR (100 MHz, CD_3CN): δ (ppm) 173.0, 157.1, 137.9, 132.5 (2 CH), 130.8, 130.3 (2 CH), 129.9 (2 CH), 129.6, 129.4 (2 CH), 128.9, 128.7 (2 CH), 127.9 (2 CH), 126.2 (2 CH), 124.7 (2 CH), 67.4, 62.8, 53.4, 14.2.

HRMS (ESI): m/z Calcd. for $[C_{26}H_{23}NO_4+MeOH+Na]^+$ = 468.1787, Found 468.1424 (-77.5 ppm).

SMILES:[H]C(C1=C(C=CC=C2)C2=CC3=C1C=CC=C3)(C(OCC)=O)NC(OCC4=CC=CC=C4)=O

Ethyl-N-benzyloxycarbonylamino-2-(5-(3-(2-hydroxyphenyl)-3-oxoprop-1-en-1-yl)-2,4-dimethoxyphenyl)glycinate 8l:



8l

$C_{29}H_{29}NO_8$
MW = 519.5 g.mol^{-1}

Product **8l** was synthesized following the ***general procedure***
Step 1/2: Solvent: acetonitrile (5.0 mL) at 60 °C for 24 h.
Step 3: Chalcone[SI-3] (78 mg**,** 0.275 mmol, 1.1 equiv.) as nucleophile at RT for 48 h.
The crude reaction mixture was purified by flash chromatography using an isocratic solvent system of ethyl acetate and hexanes (50:50) to deliver the desired products, which show little impurity which was then purified by preparative TLC using dichloromethane and ether (95:5) solvent system to obtained desired compound as a yellow solid **8l** (46 mg, 0.09 mmol, 35% yield).

MP: 105-106 °C

R_f = 0.50 (EtOAc/hexanes 50:50; UV Active, stains red in vanillin)

IR (Neat) ν_{max} = 667, 750, 1032, 1052, 1163, 1205, 1252, 1293, 1319, 1342, 1505, 1533, 1567, 1637, 1692, 1741 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) δ 13.05 (s, 1H), 8.21 (d, *J* = 15.6 Hz, 1H), 7.94 (d, *J* = 7.9 Hz, 1H), 7.66 (s, 1H), 7.63 (d, *J* = 15.6 Hz, 1H), 7.48 (t, *J* = 7.7 Hz, 1H), 7.33 (dd, *J* = 15.0, 6.7 Hz, 5H), 7.01 (d, *J* = 8.4 Hz, 1H), 6.94 (t, *J* = 7.6 Hz, 1H), 6.43 (s, 1H), 5.95 (d, *J* = 8.5 Hz, 1H), 5.50 (d, *J* = 8.5 Hz, 1H), 5.11 (q, *J* = 12.1 Hz, 2H), 4.26 – 4.07 (m, 2H), 3.91 (d, *J* = 30.5 Hz, 6H), 1.19 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 194.2, 171.1, 163.7, 161.0, 160.6, 156.0, 140.2, 136.4, 136.2 (2 C), 131.0, 130.0, 128.8 (2 CH), 128.5 (2 CH), 120.4, 119.0, 119.0, 118.7, 118.5, 116.5, 95.4, 67.4, 62.0, 56.1, 56.0, 54.8, 14.4.

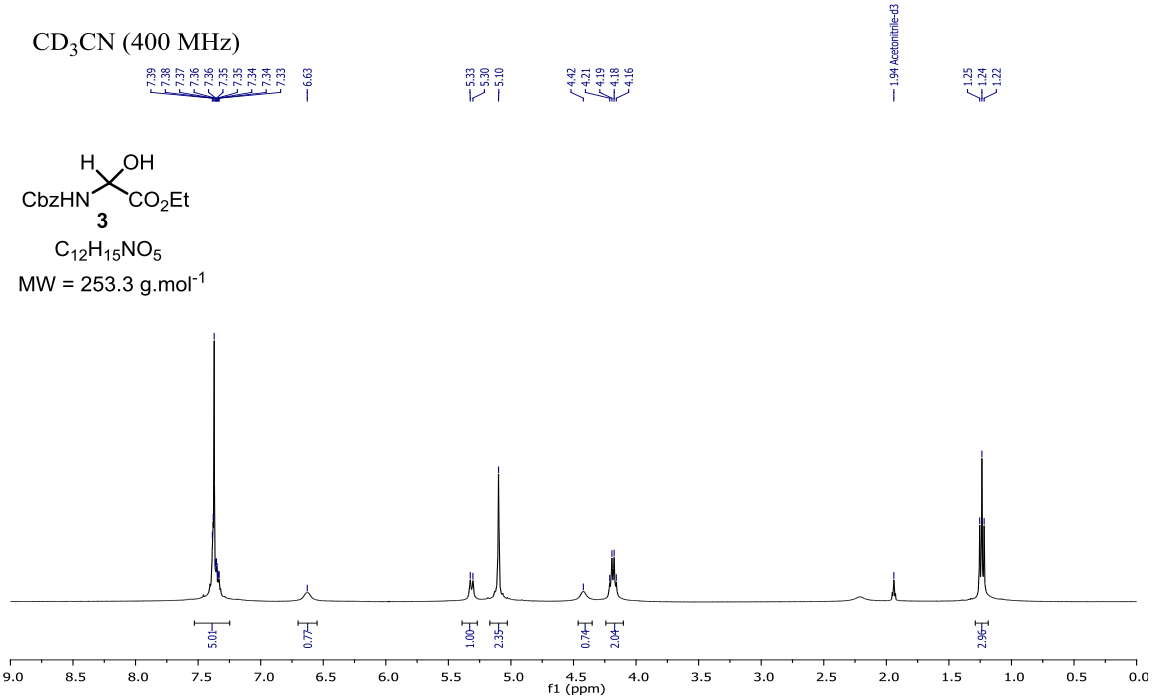
HRMS (ESI): m/z Calcd. for $[C_{29}H_{29}NO_8+H]^+$ = 520.1966, Found 520.1970 (+0.8 ppm).

SMILES:[H]C(C1=C(OC)C=C(OC)C(/C=C/C(C2=C(O)C=CC=C2)=O)=C1)(C(OCC)=O)NC(OCC3=CC=CC=C3)=O

(SI-3) The chalcone was prepared accordingly to the literature protocol: J. Wu, J. Li, Y. Cai, Y. Pan, F. Ye, Y. Zhang, Y. Zhao, S. Yang, X. Li, and G. Liang, *J. Med. Chem.*, 2011, **54**, 8110.

IV. Selected spectra:

CD_3CN (400 MHz)

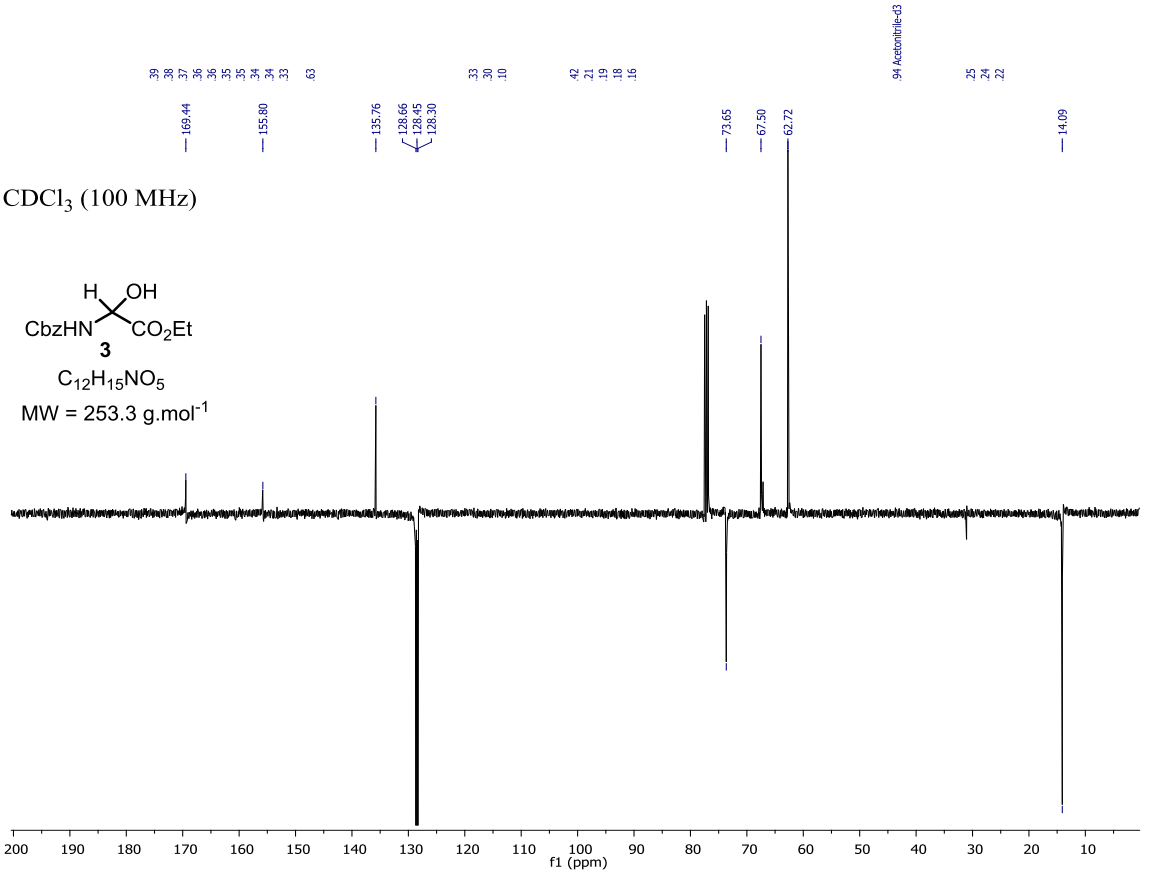


3

$C_{12}H_{15}NO_5$

MW = 253.3 g.mol^{-1}

$CDCl_3$ (100 MHz)

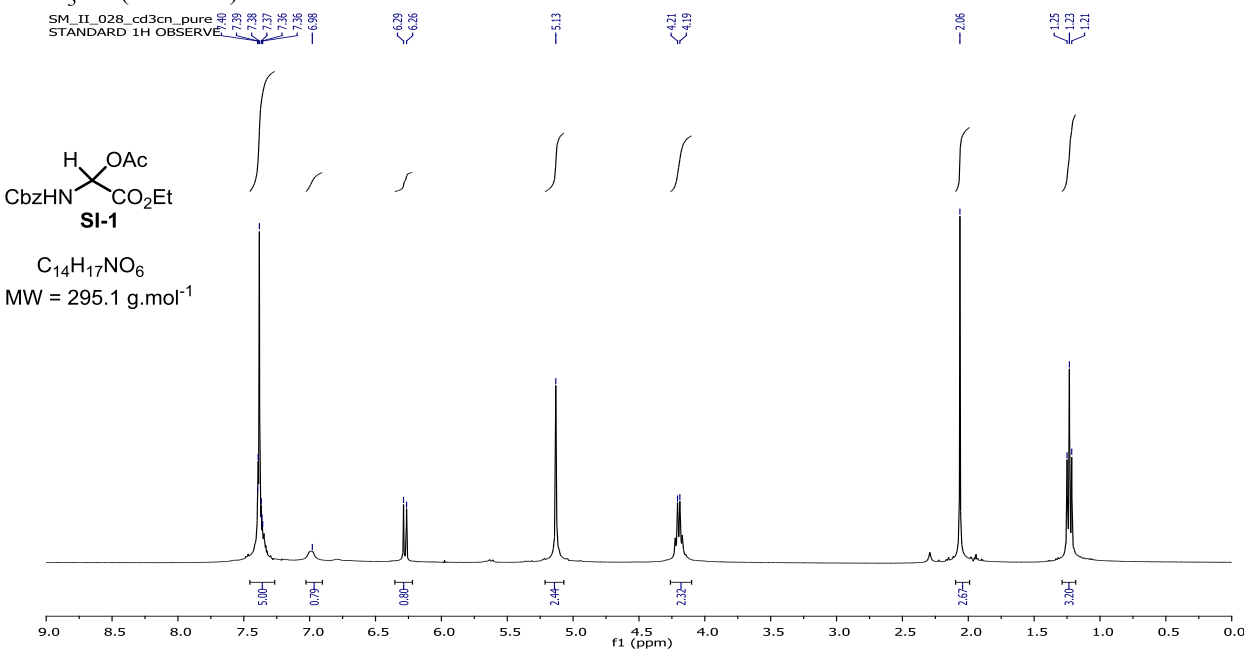


3

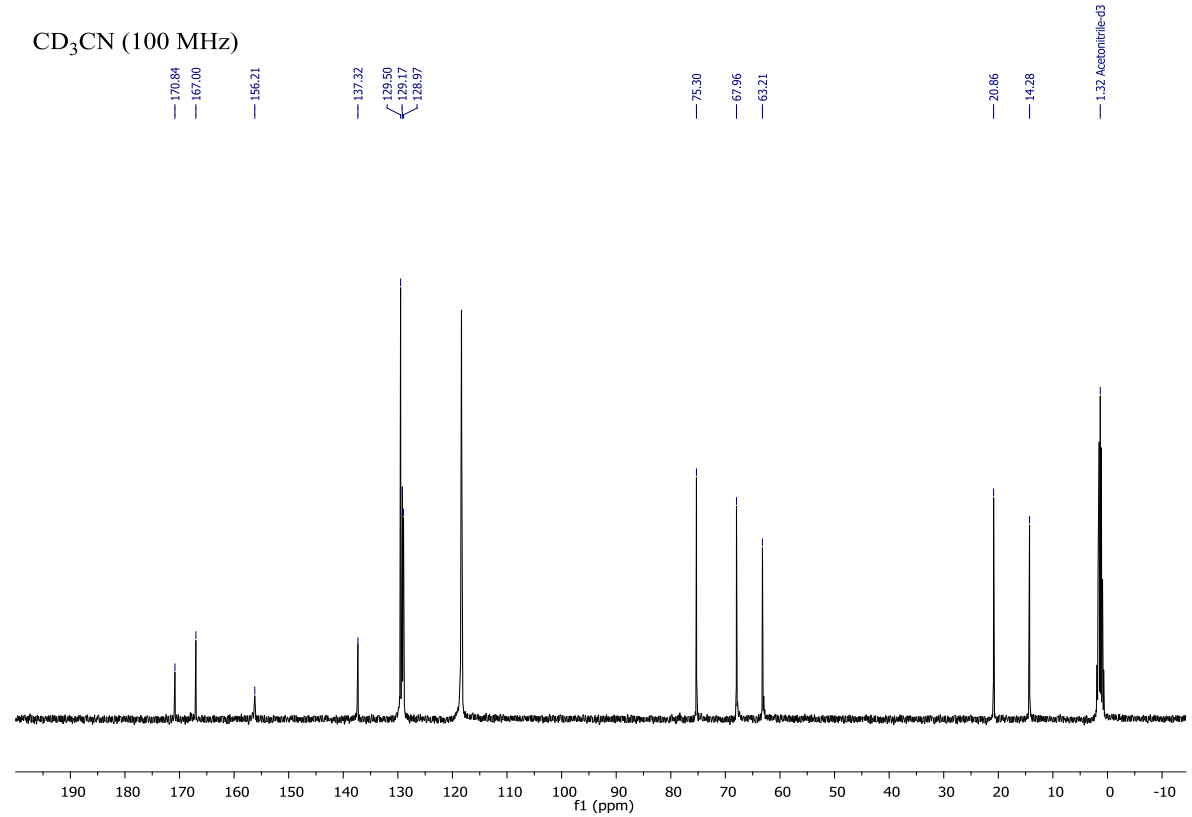
$C_{12}H_{15}NO_5$

MW = 253.3 g.mol^{-1}

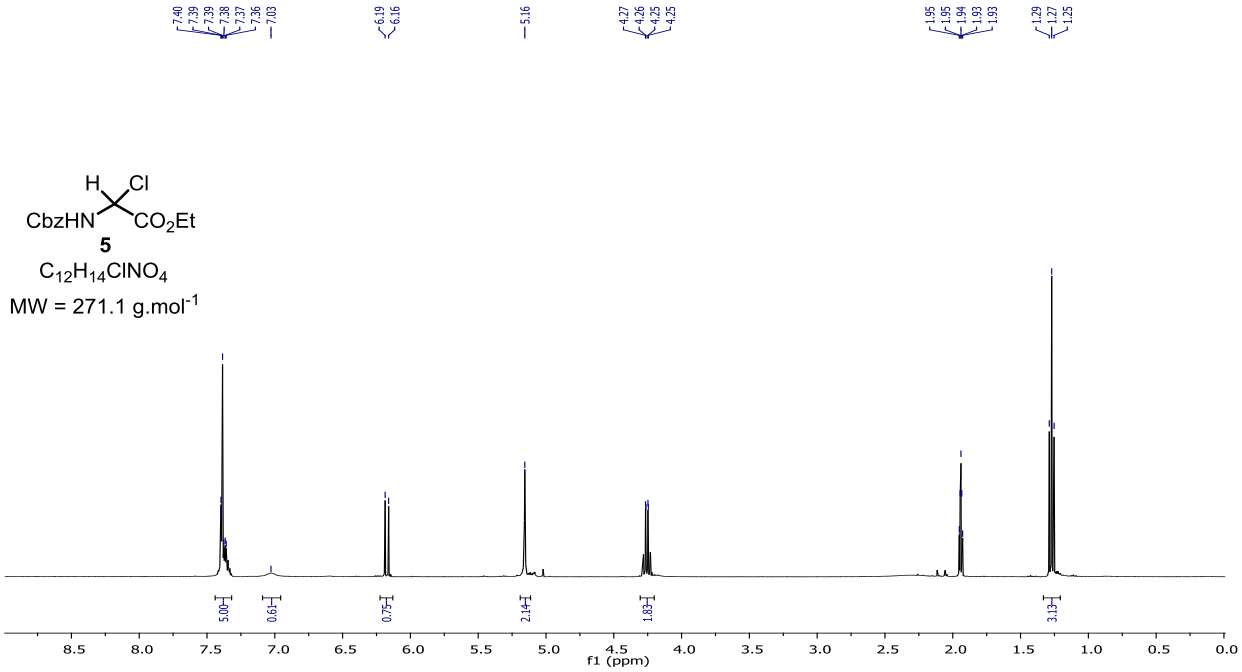
CD_3CN (400 MHz)



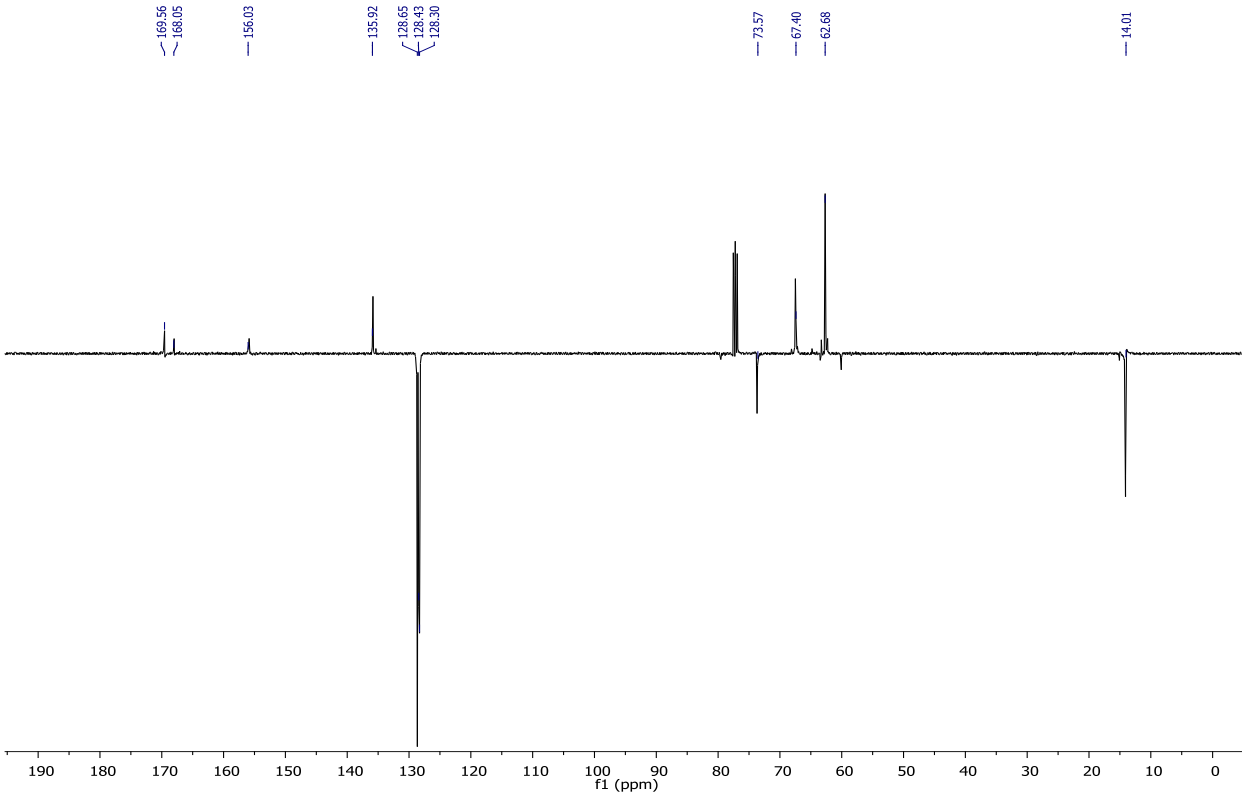
CD_3CN (100 MHz)

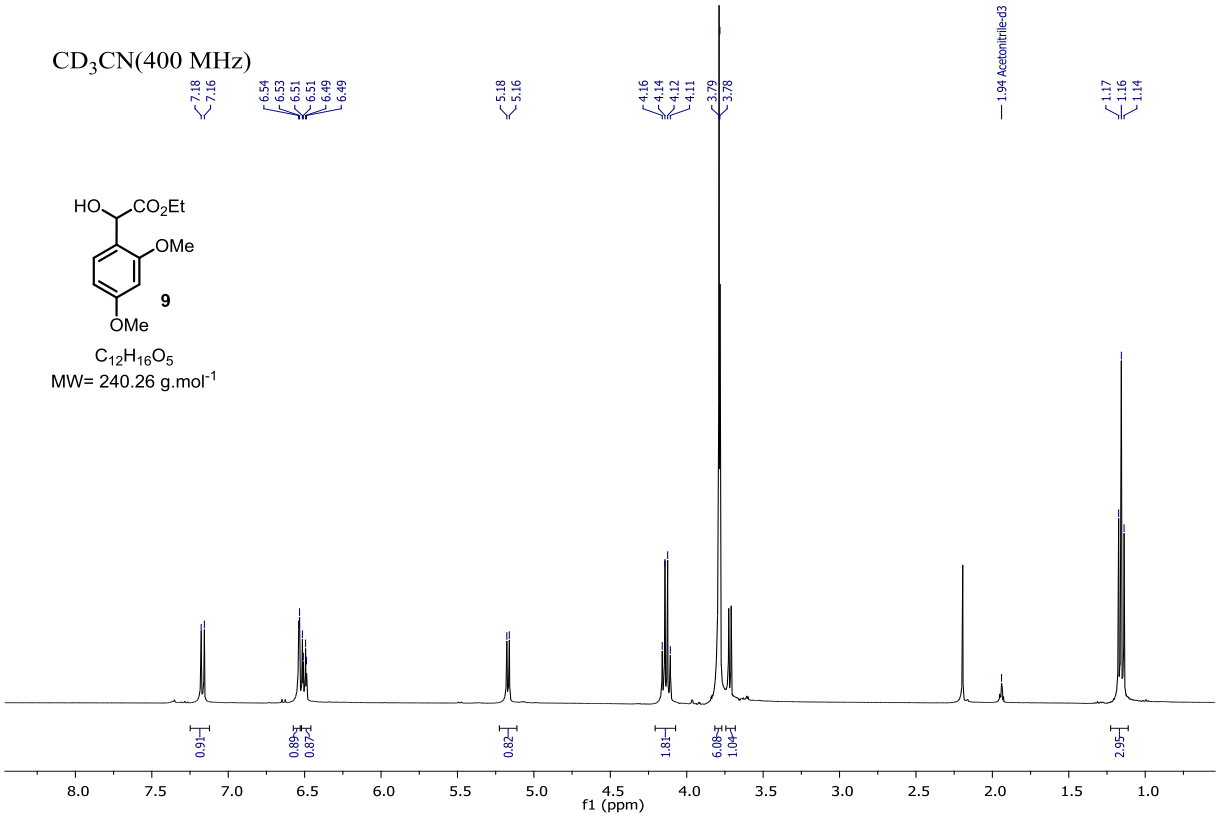


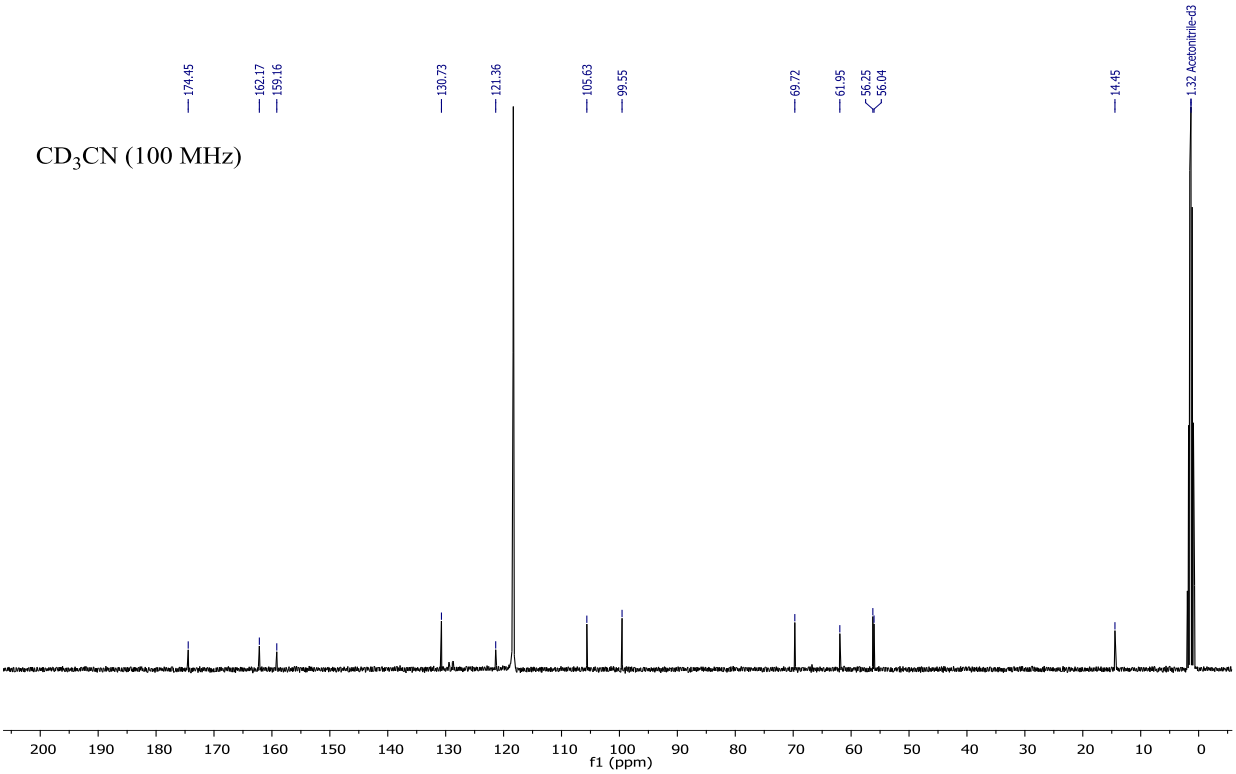
CD_3CN (400 MHz)

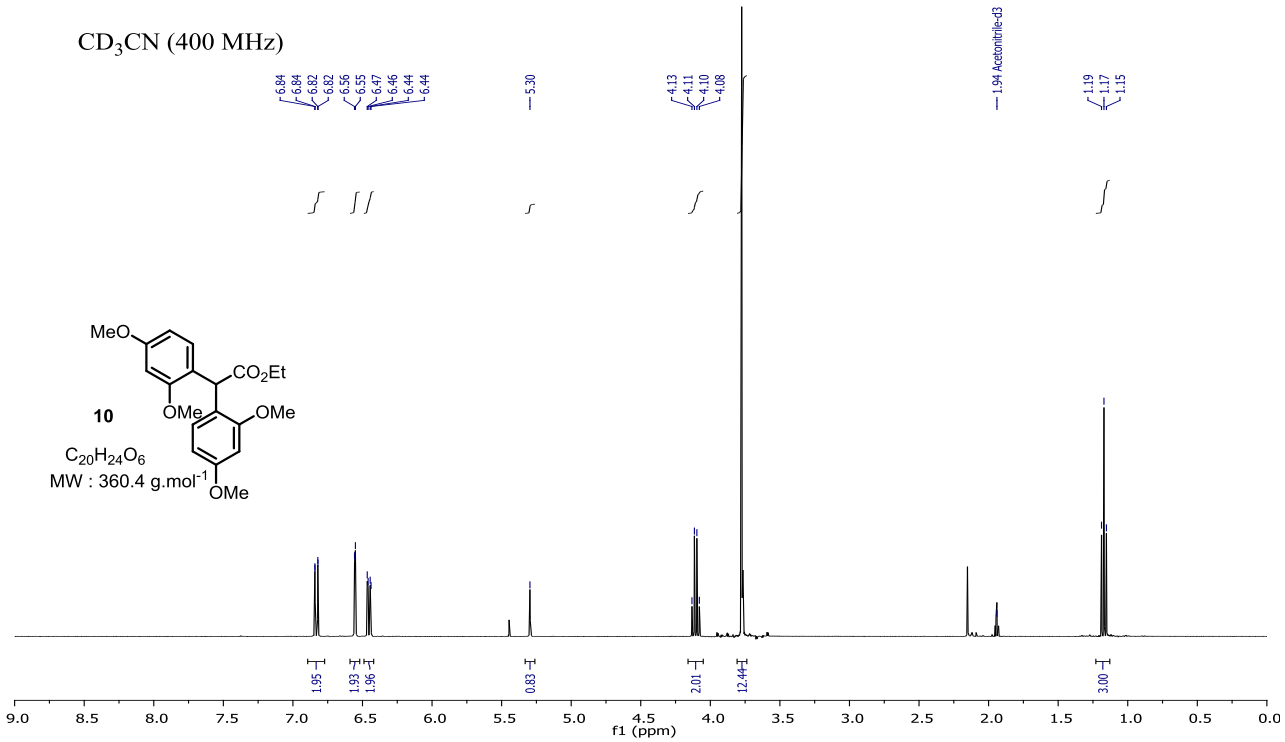


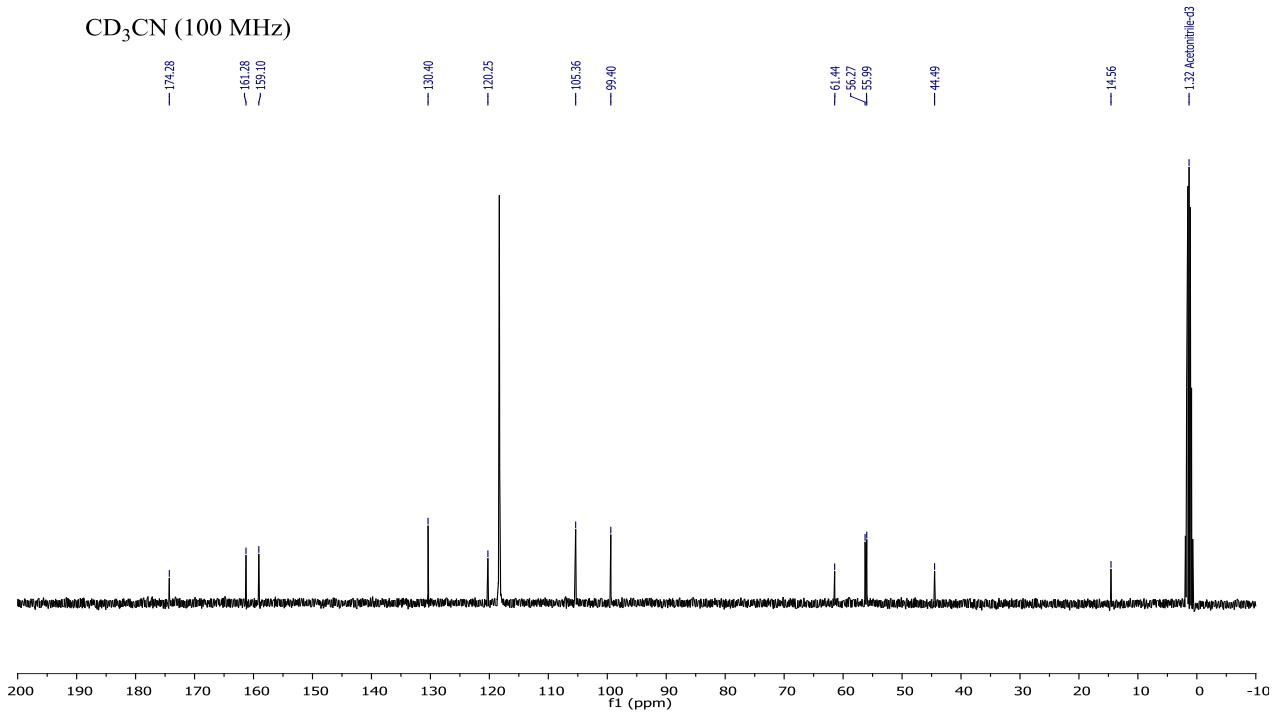
$CDCl_3$ (100 MHz)



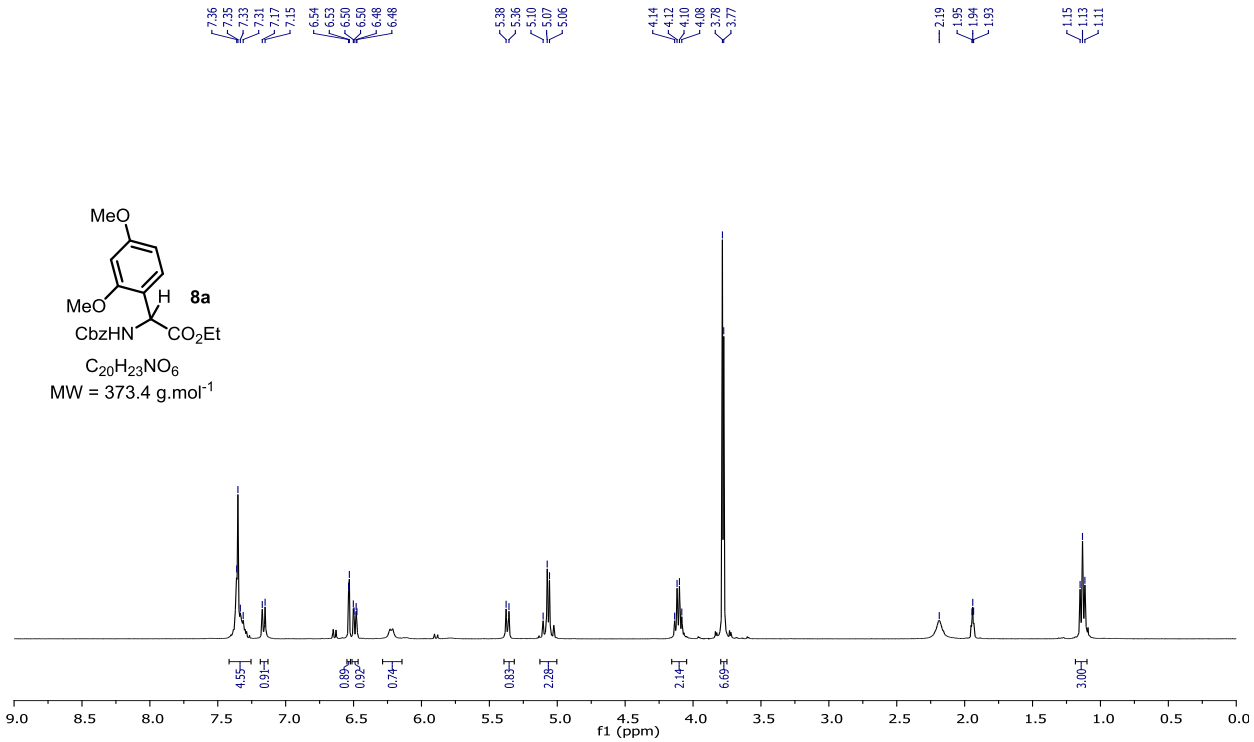

CD3CN(400 MHz)
7.18
7.16
6.54
6.53
6.51
6.51
6.49
6.49
5.18
5.16
4.16
4.14
4.12
4.11
3.79
3.78
1.94 Acetonitrile-d3
1.17
1.16
1.14
HO
CO2Et
OMe
9
OMe
C12H16O5
MW= 240.26 g.mol-1
0.91
0.89
0.87
0.82
1.81
6.08
1.04
2.95
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)


CD3CN (100 MHz)
174.45
162.17
159.16
130.73
121.36
105.63
99.55
69.72
61.95
56.25
56.04
14.45
1.32 Acetonitrile-d3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

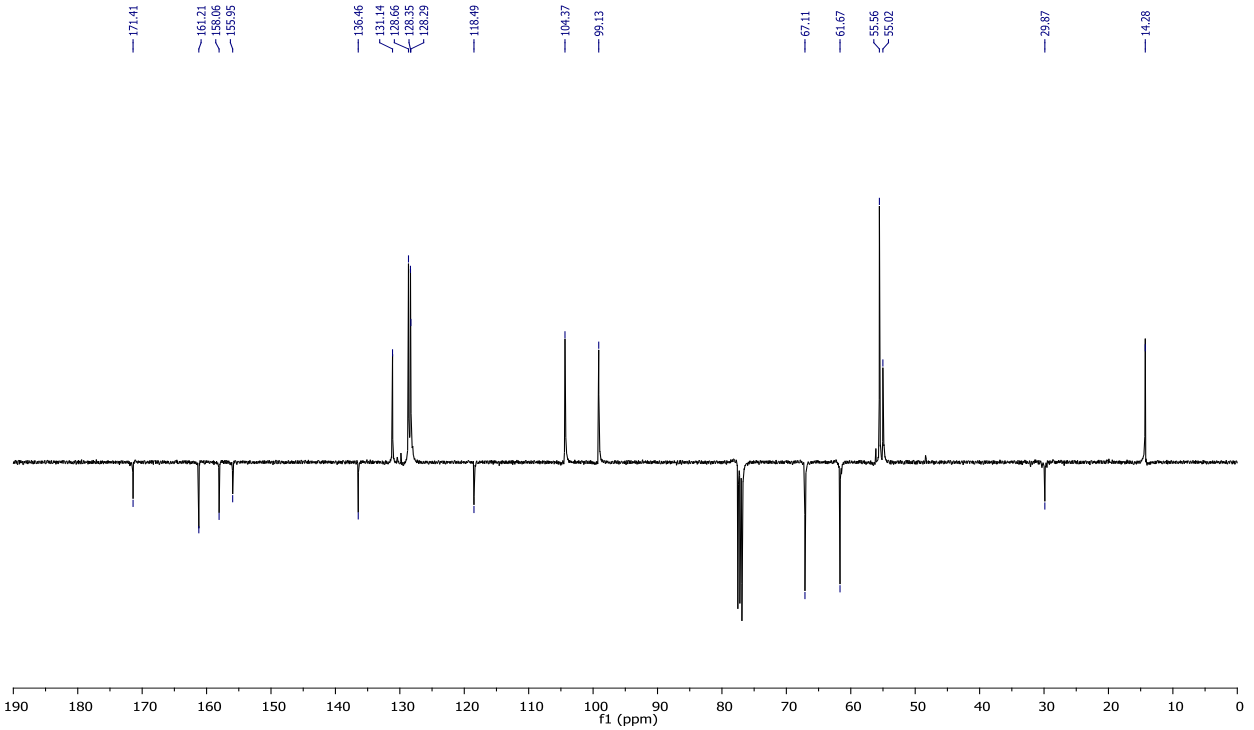

CD3CN (400 MHz)
6.84
6.84
6.82
6.82
6.56
6.55
6.47
6.46
6.44
6.44
5.30
4.13
4.11
4.10
4.08
1.94 Acetonitrile-d3
1.19
1.17
1.15
MeO
CO2Et
OMe
OMe
OMe
10
C20H24O6
MW : 360.4 g.mol-1
1.95
1.93
1.96
0.83
2.01
12.44
3.00
f1 (ppm)


CD3CN (100 MHz)
174.28
161.28
159.10
130.40
120.25
105.36
99.40
61.44
56.27
55.99
44.49
14.56
1.32 Acetonitrile-d3
f1 (ppm)

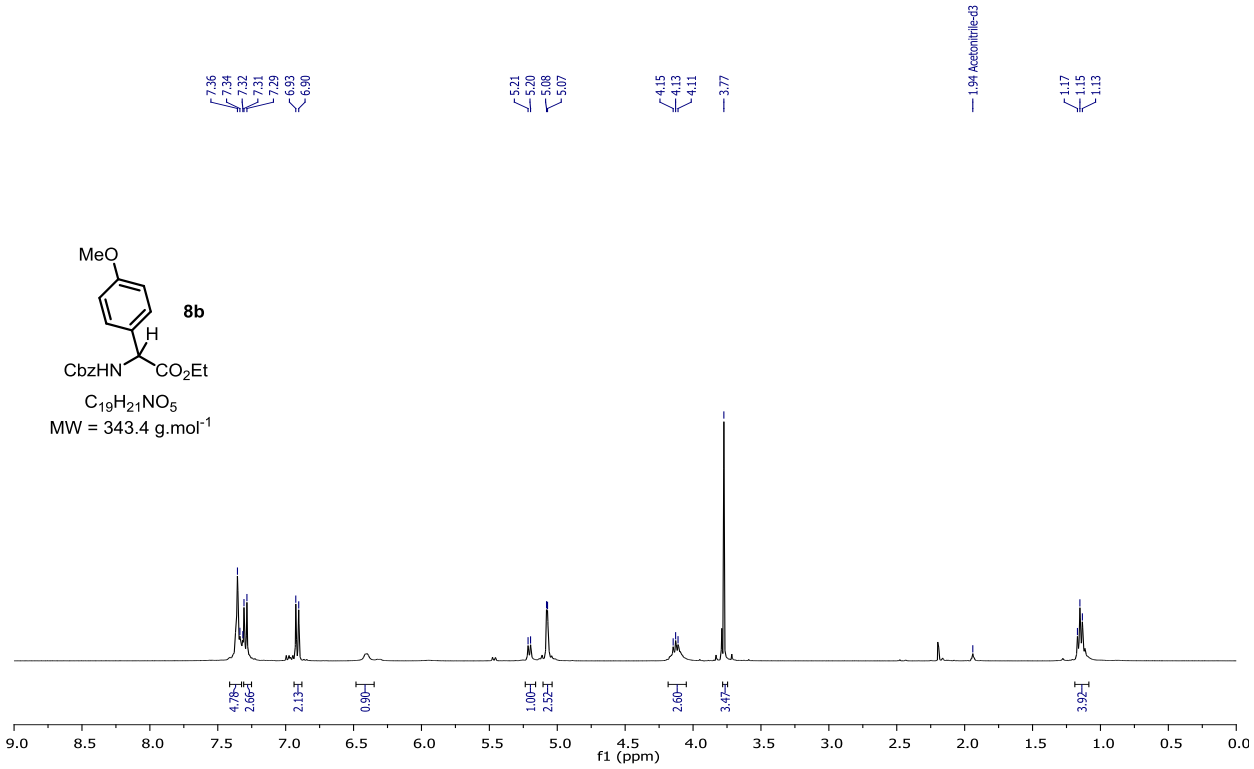
CD_3CN (400 MHz)



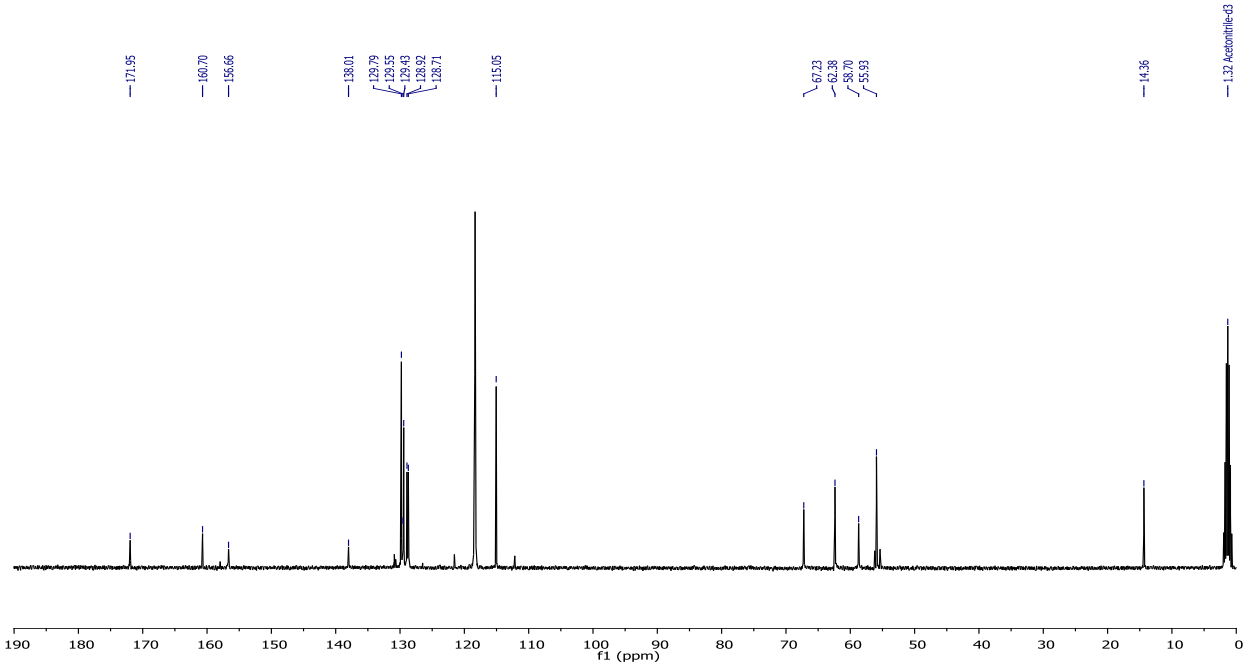
$CDCl_3$ (100 MHz)



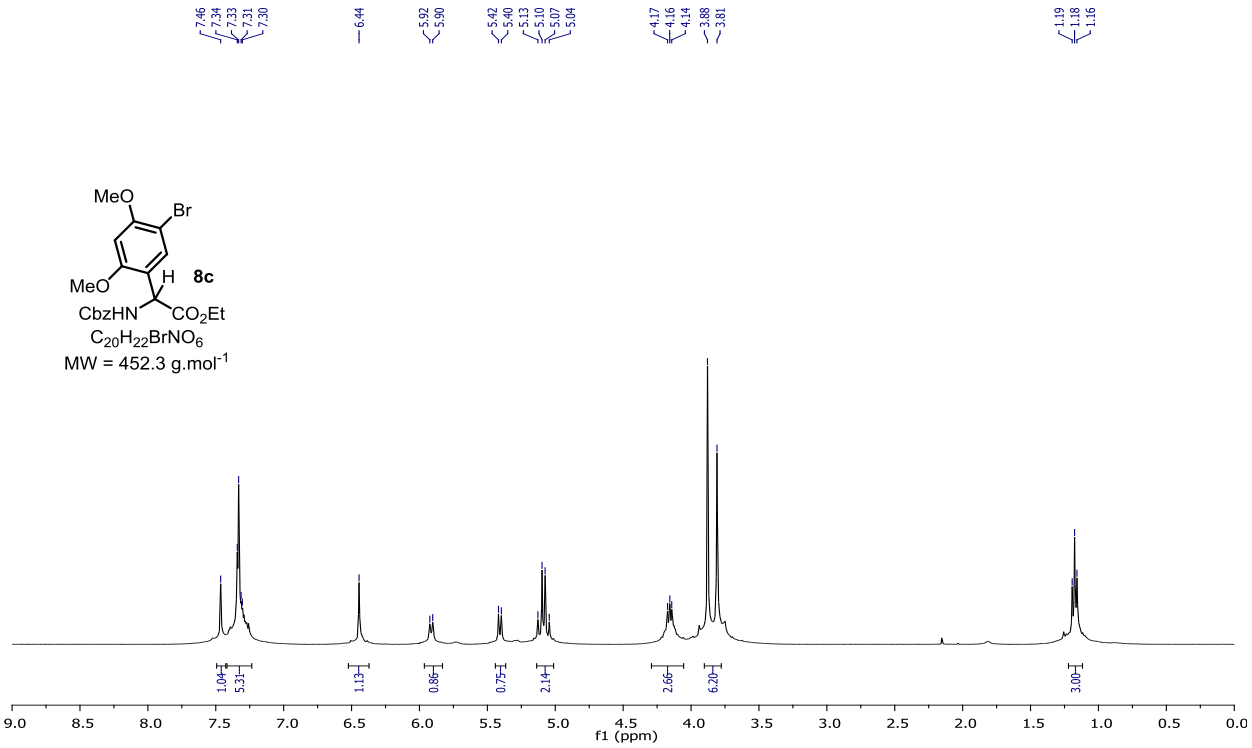
CD_3CN (400 MHz)



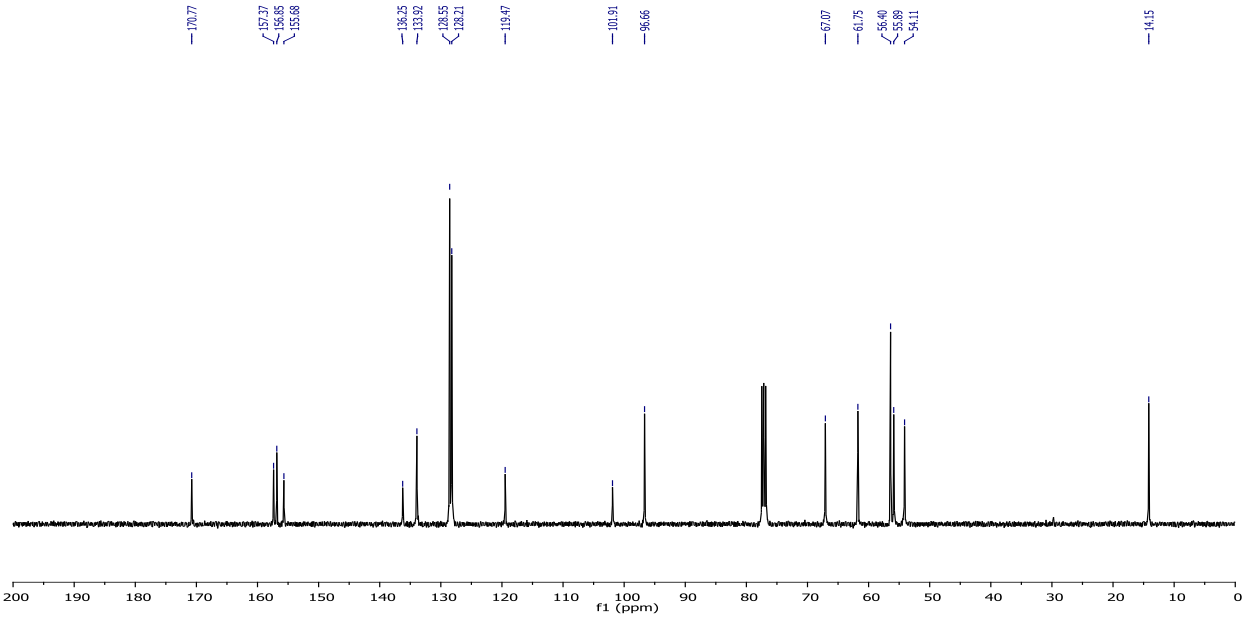
CD_3CN (100 MHz)



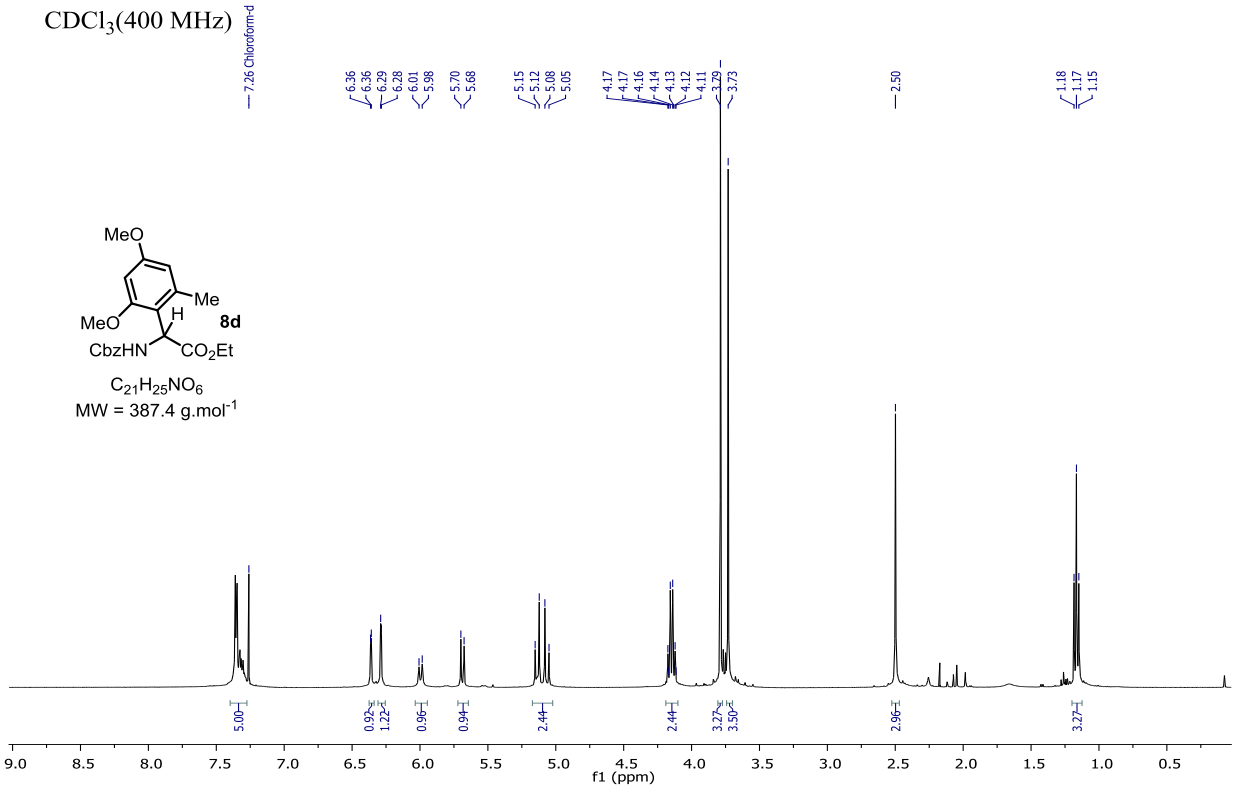
$CDCl_3$ (400 MHz)



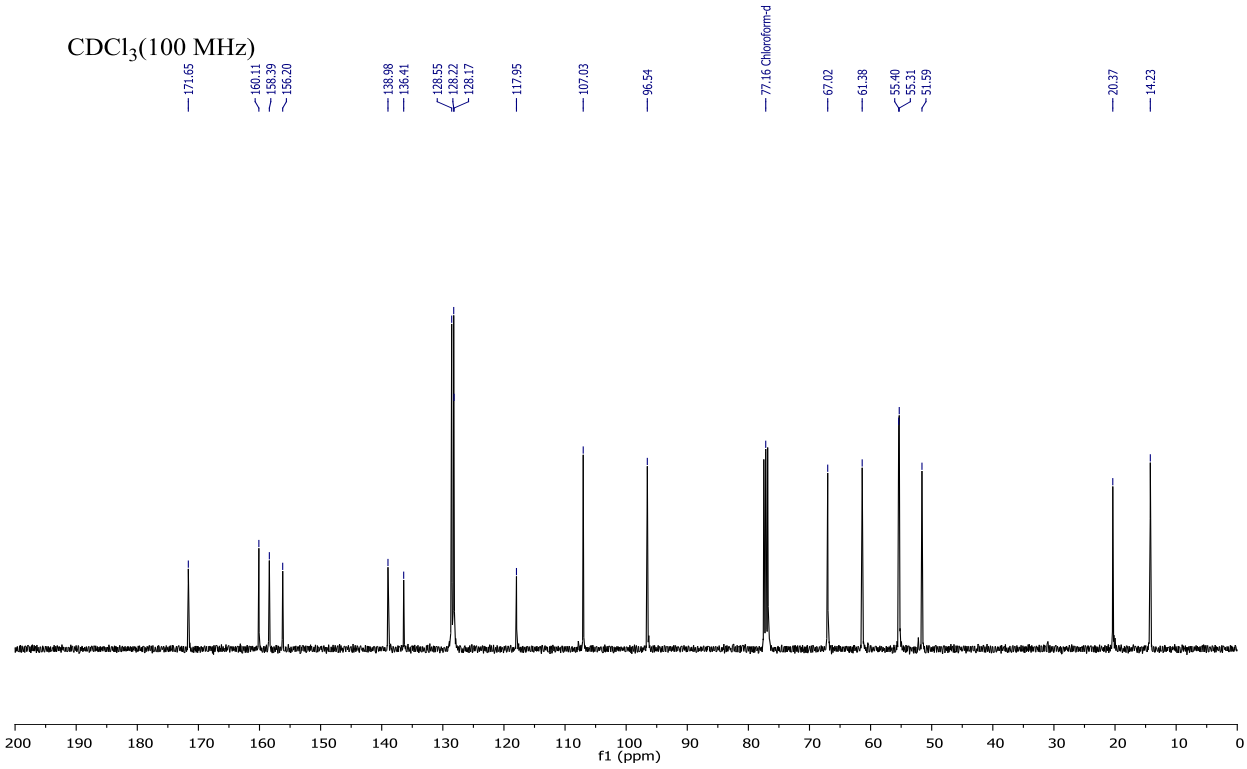
$CDCl_3$ (100 MHz)

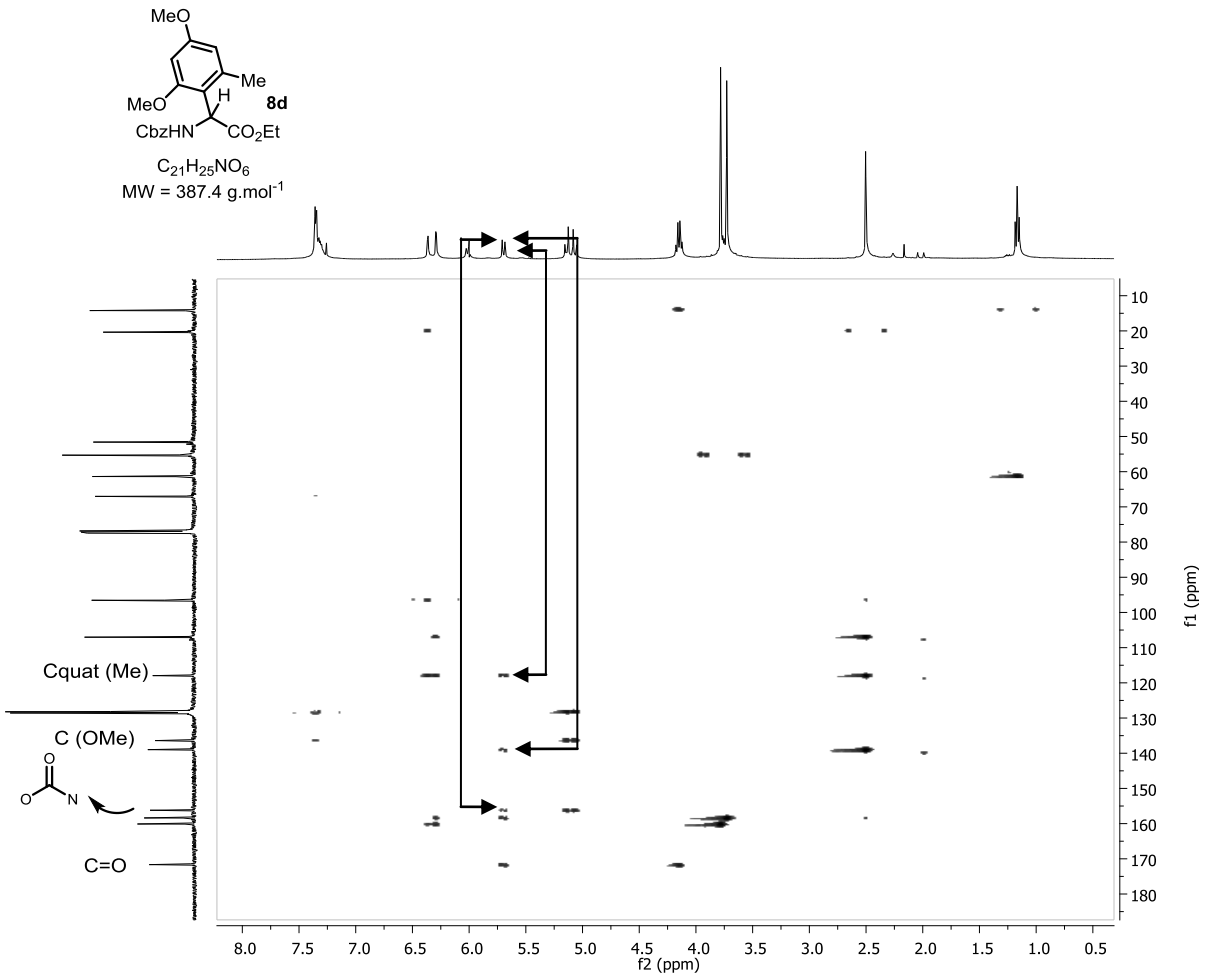


$CDCl_3$(400 MHz)



$CDCl_3$(100 MHz)

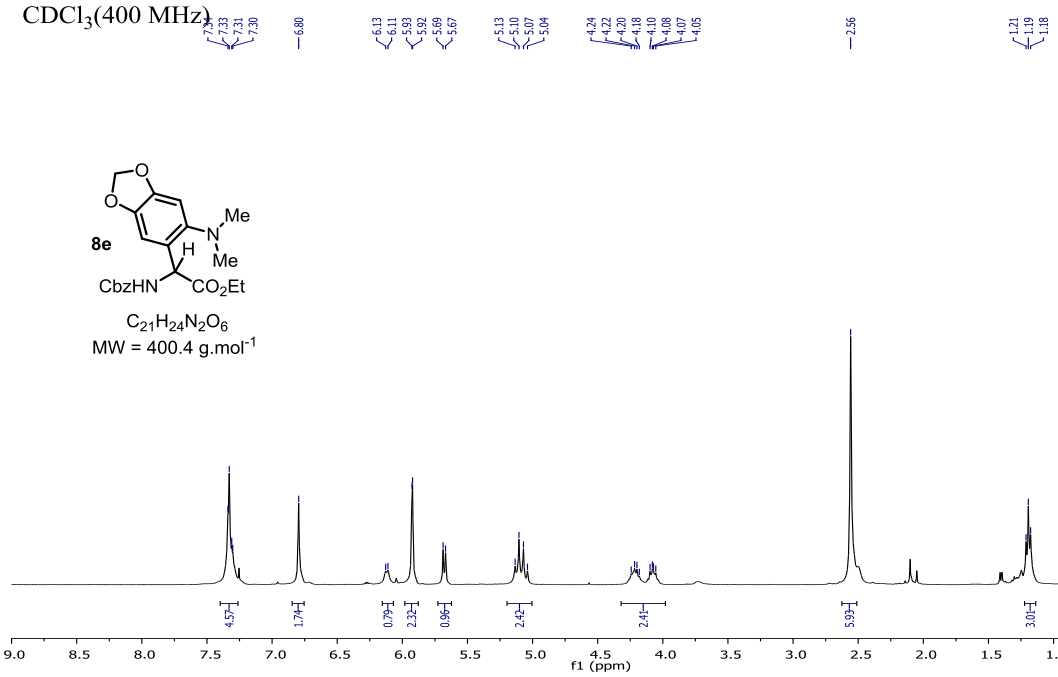




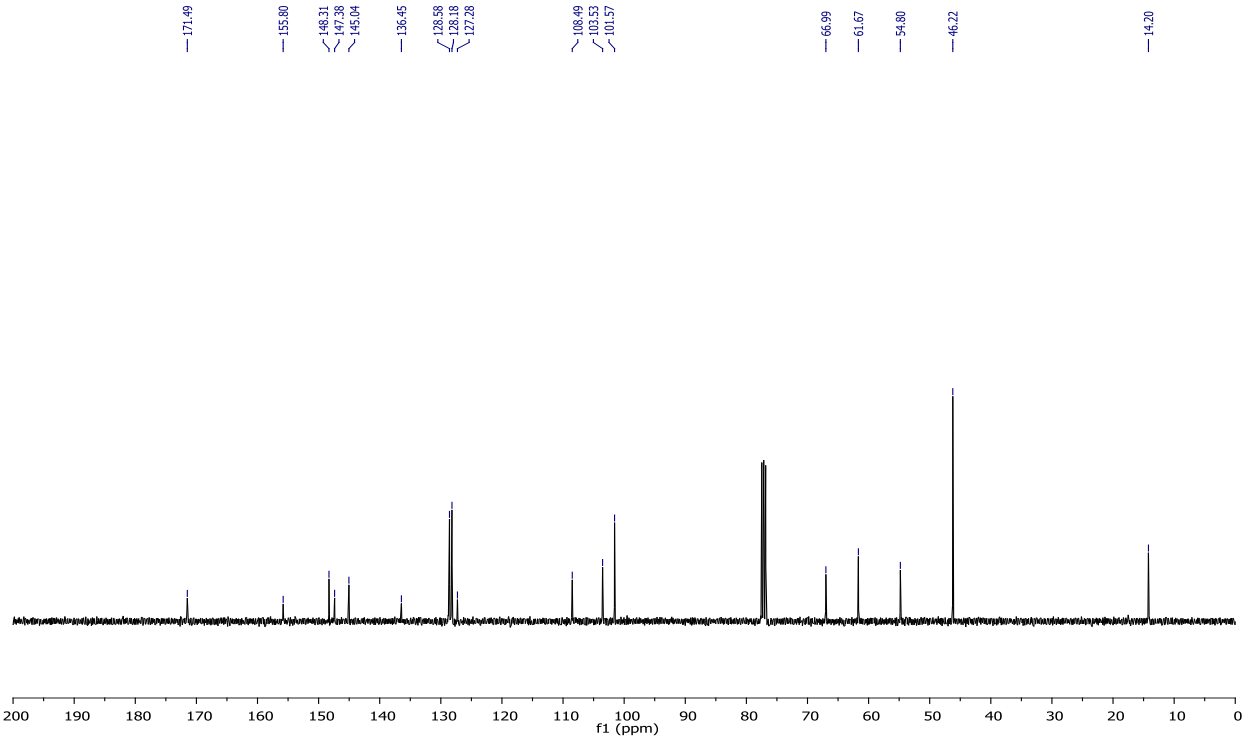
HMBC of compound **8d**

ᵅCH –correlates with: -Carbonyl group of Cbz moiety.
-C_{quat} bearing a methyl group.
- C_{quat} bearing a methoxy group.

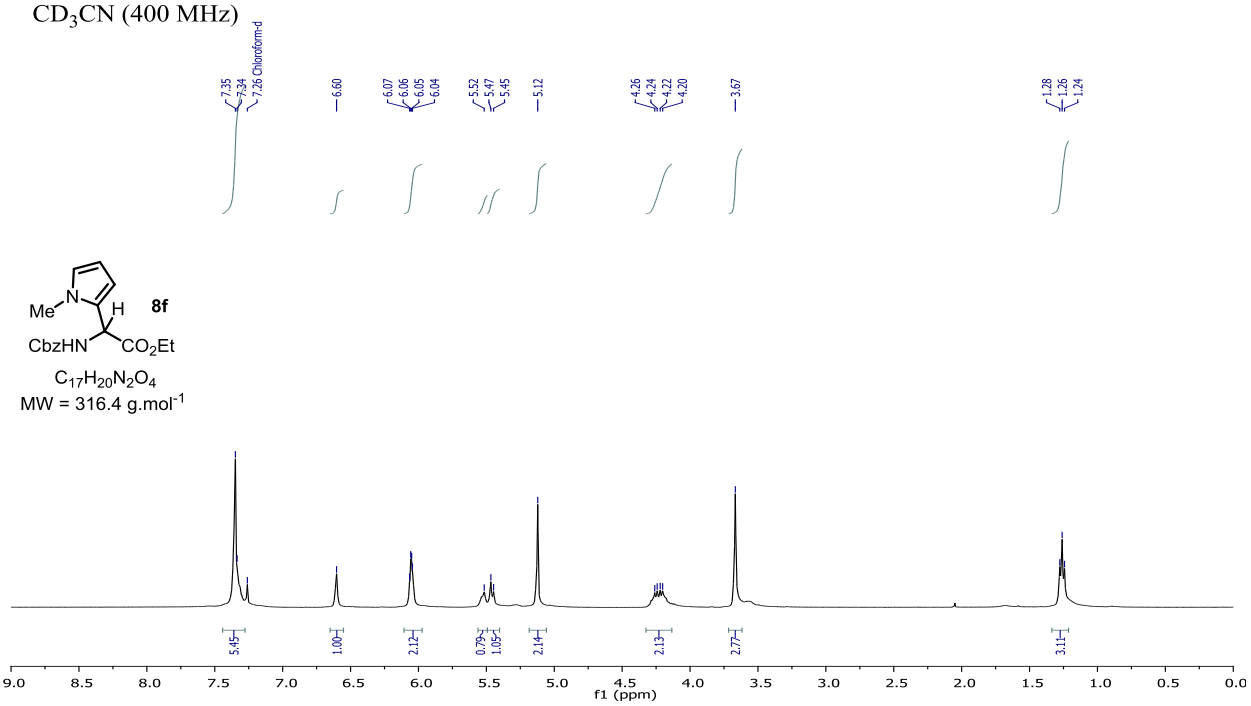
$CDCl_3$(400 MHz)



$CDCl_3$(100 MHz)

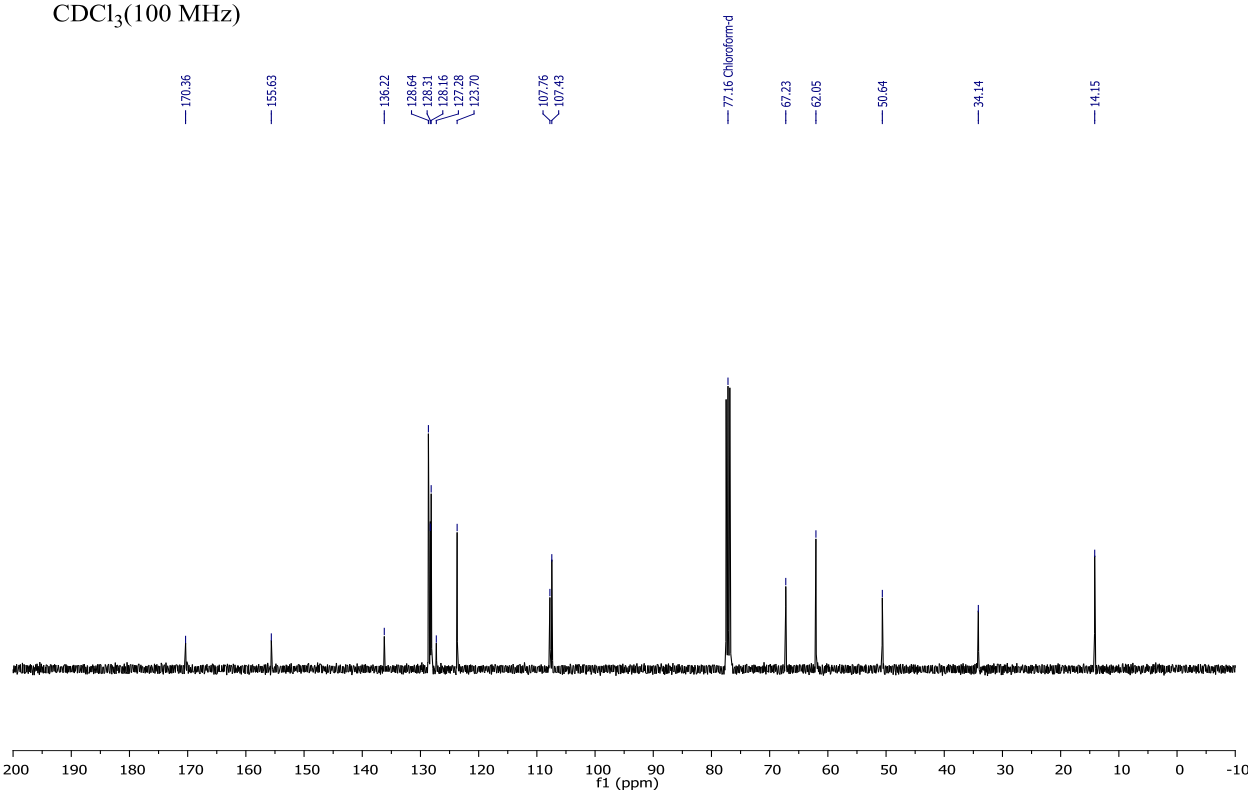


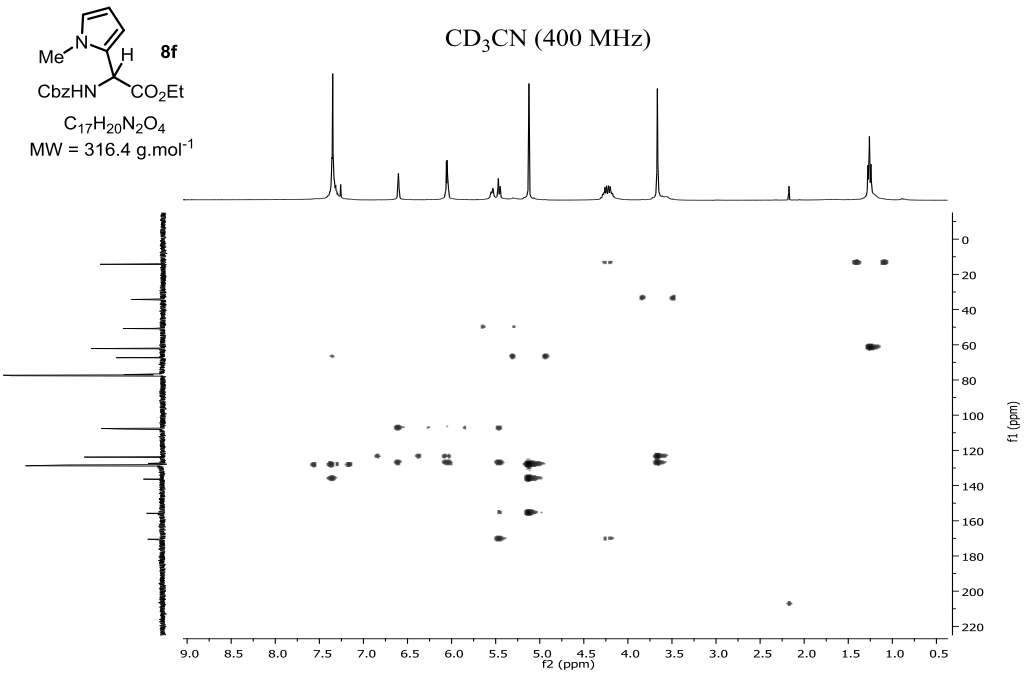
CD_3CN (400 MHz)

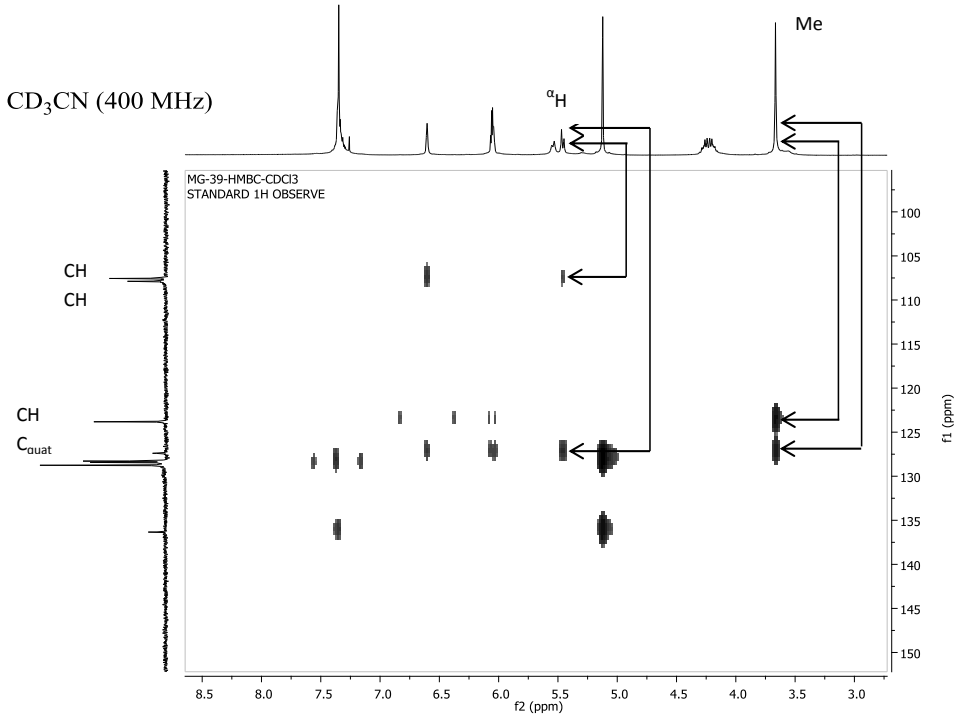


$C_{17}H_{20}N_2O_4$
MW = 316.4 g.mol^{-1}

$CDCl_3$(100 MHz)







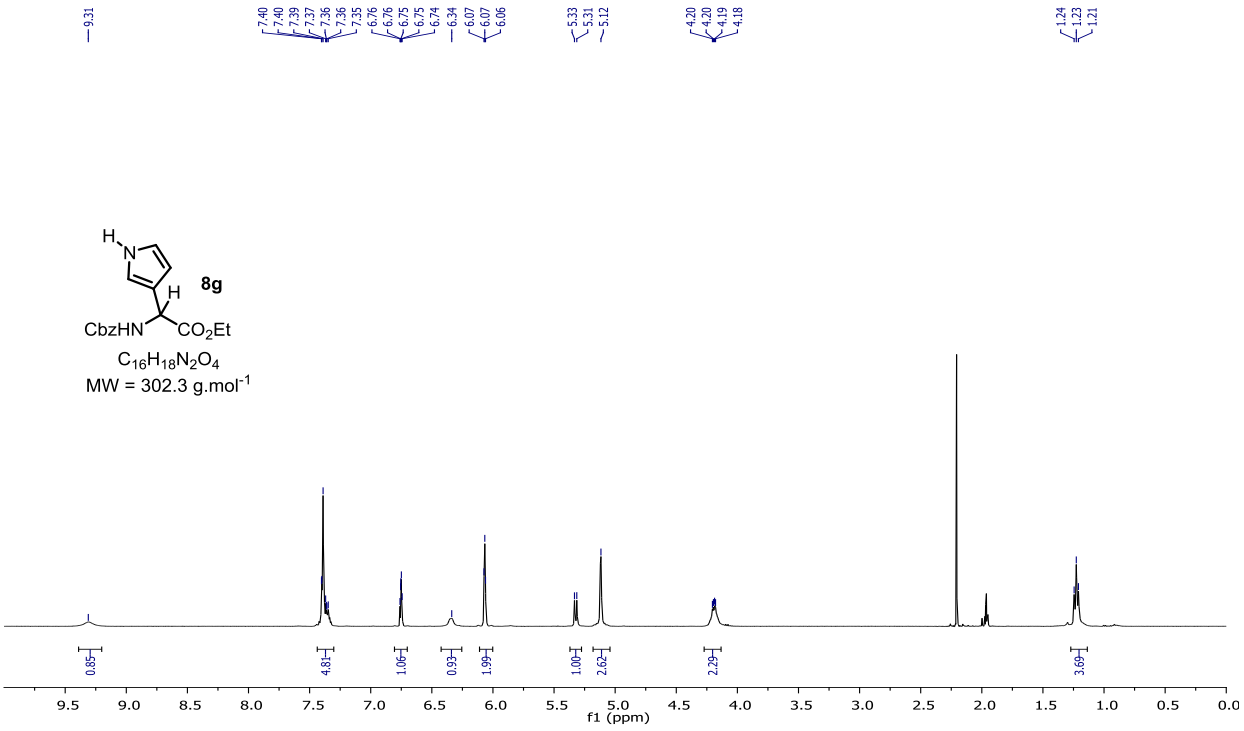
HMBC of compound **8f**

ᵅCH correlates with-

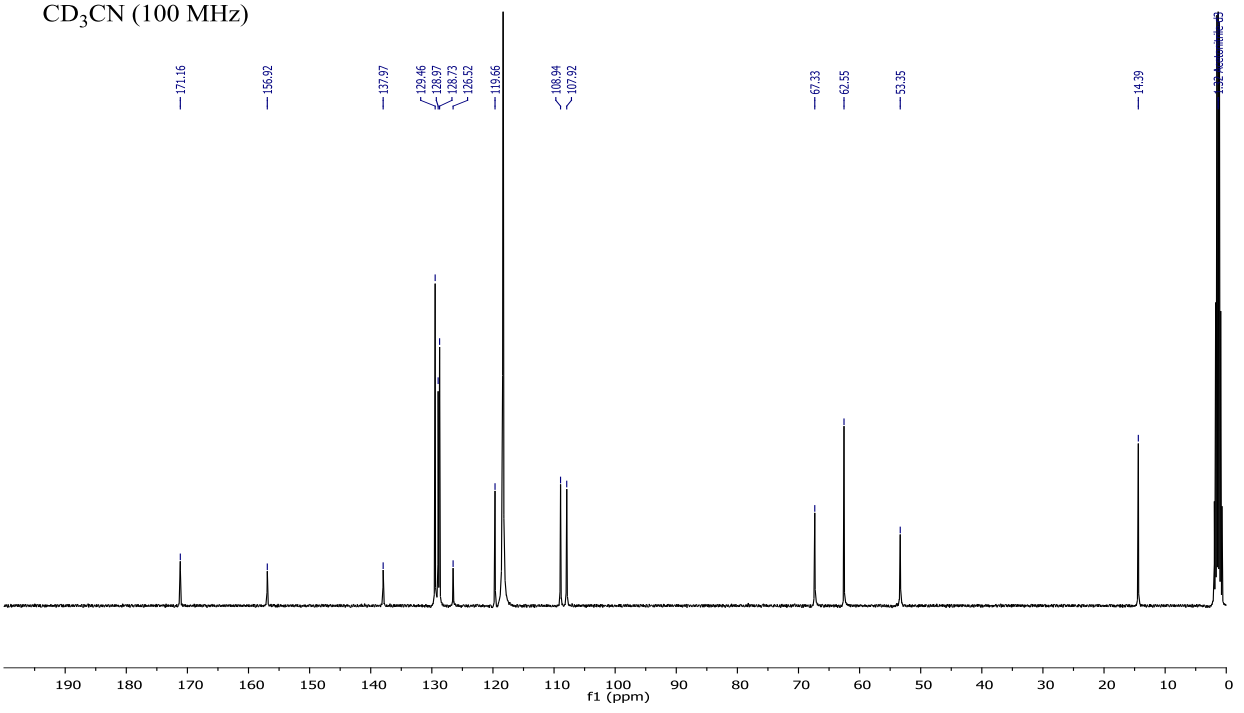
1) One CH (pyrrole ring) and one C_{quat} (pyrrole) and one C_{quat} (pyrrole) and not the other CH (pyrrole).

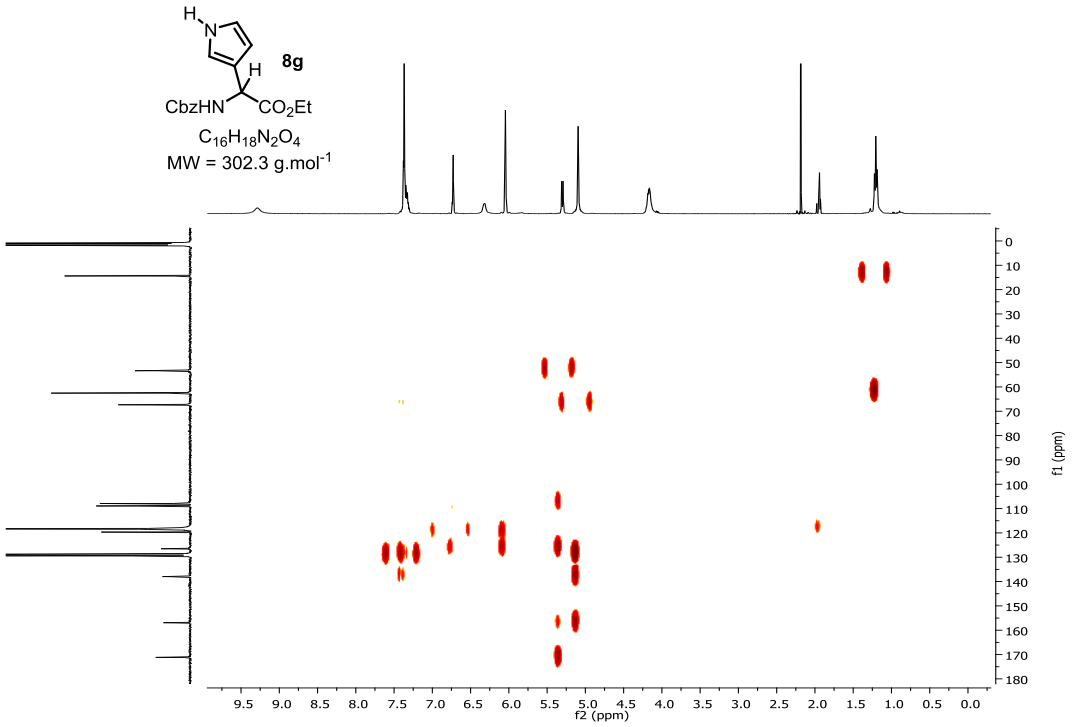
2) Me group correlates to C_{quat} and the second CH (pyrrole ring)

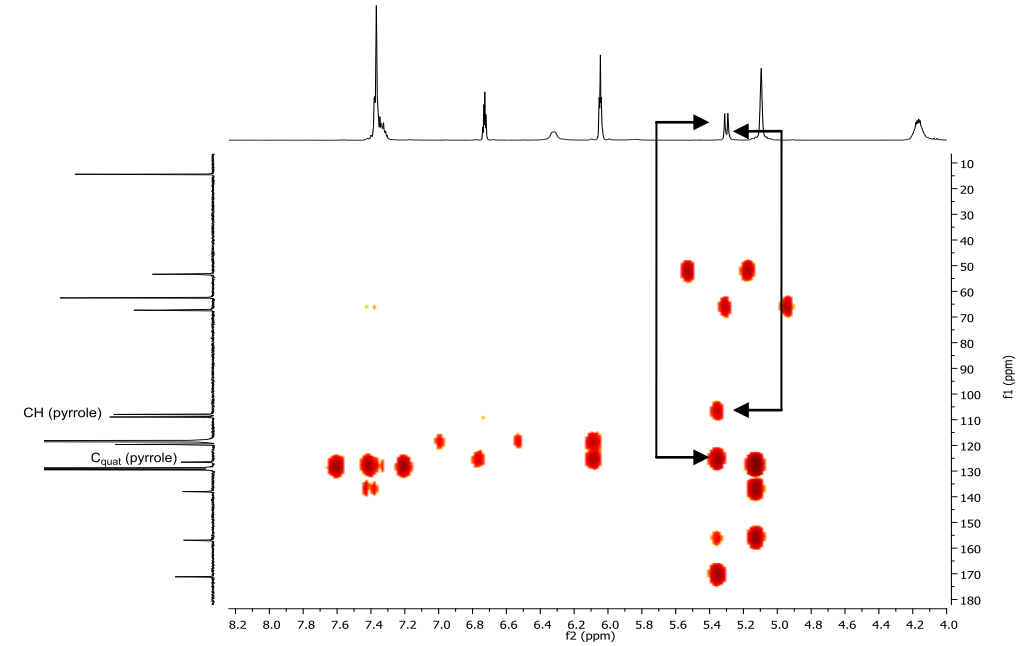
CD_3CN (400 MHz)



CD_3CN (100 MHz)



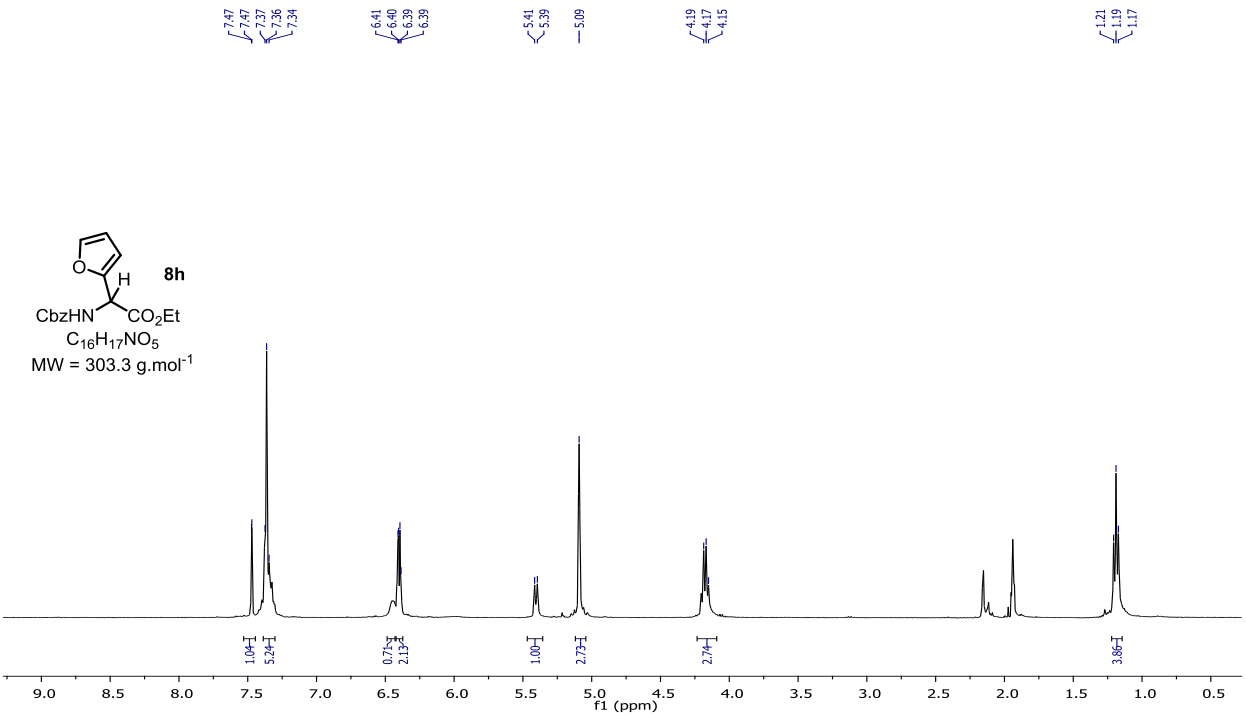




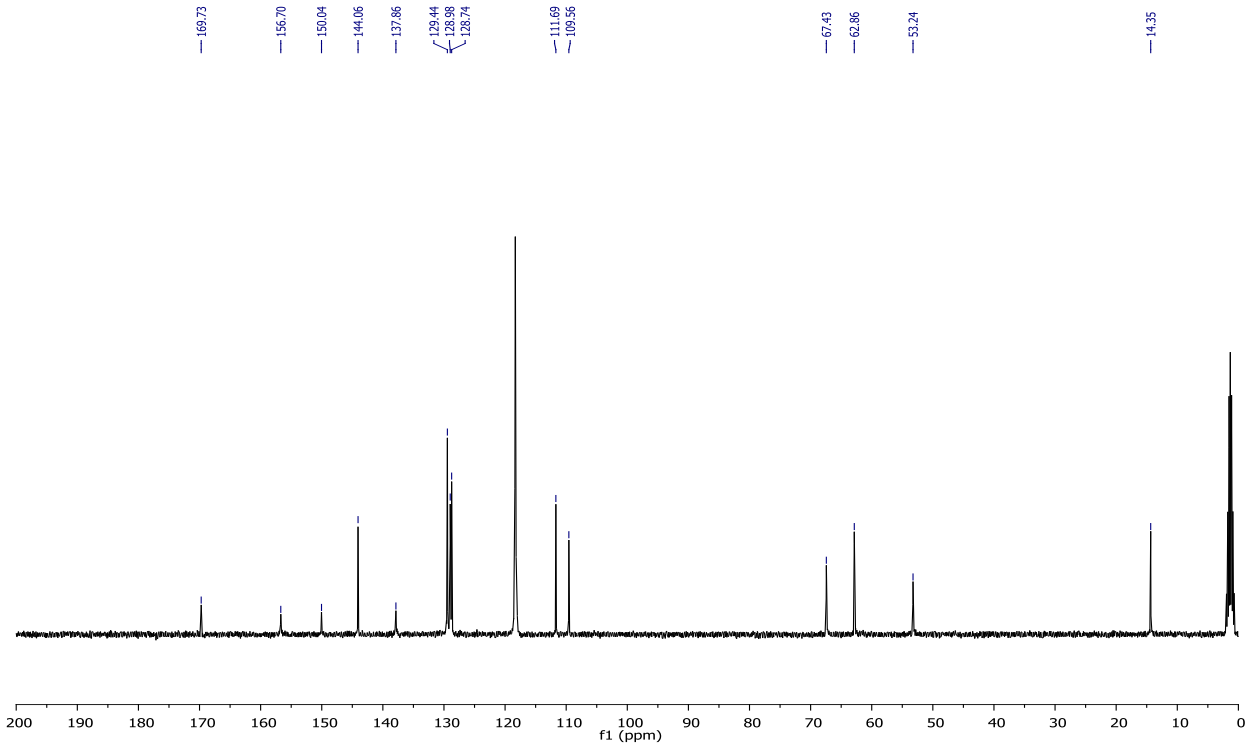
HMBC of compound **8g**

From HMBC, ᵅCH correlates with One CH (pyrrole ring) and one C_{quat} (pyrrole) and not the other CH (pyrrole).

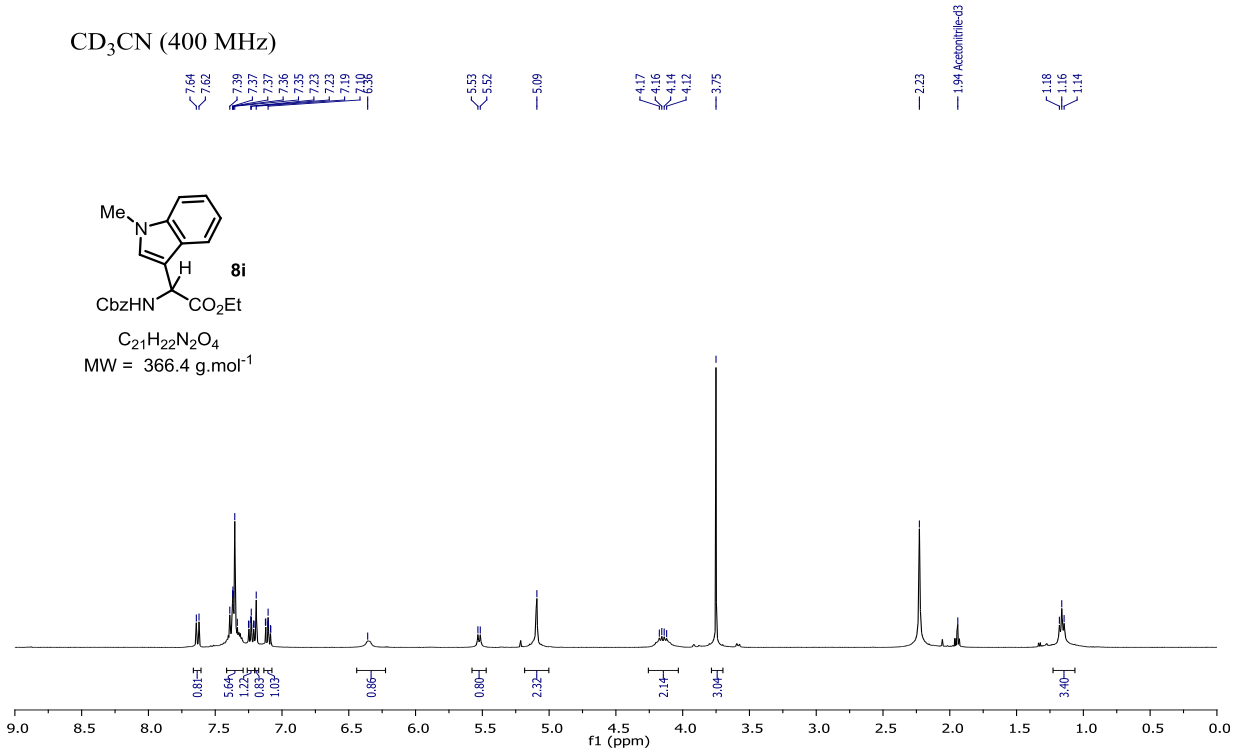
CD_3CN (400 MHz)



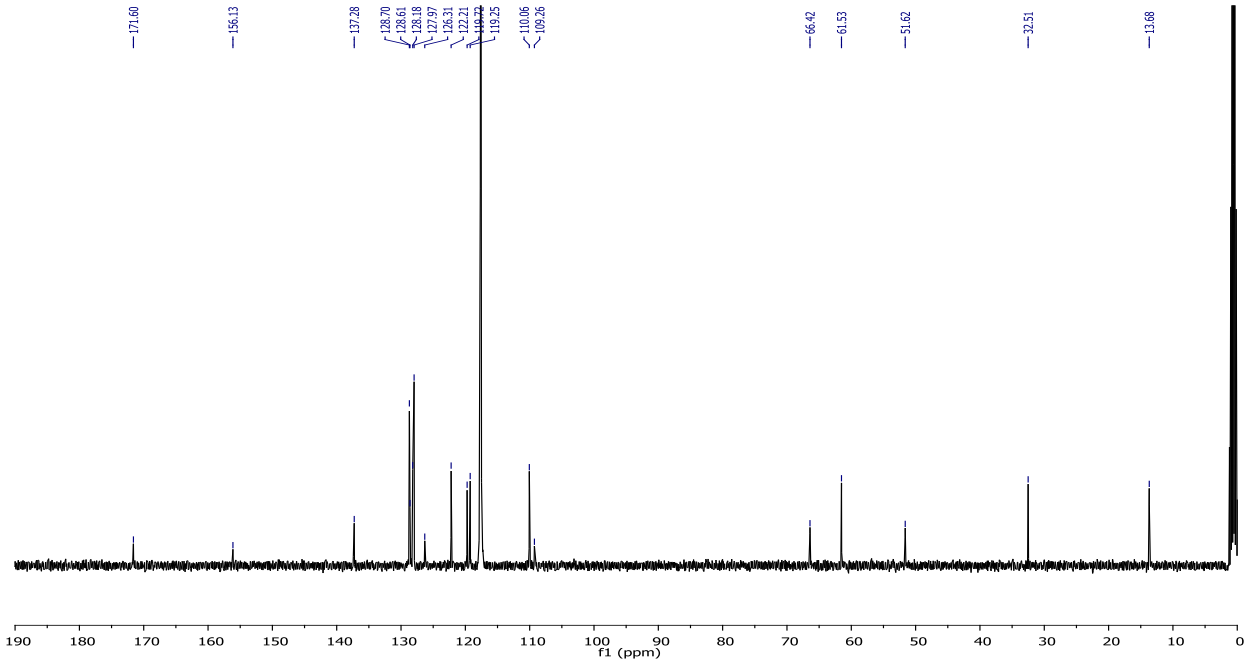
CD_3CN (100 MHz)



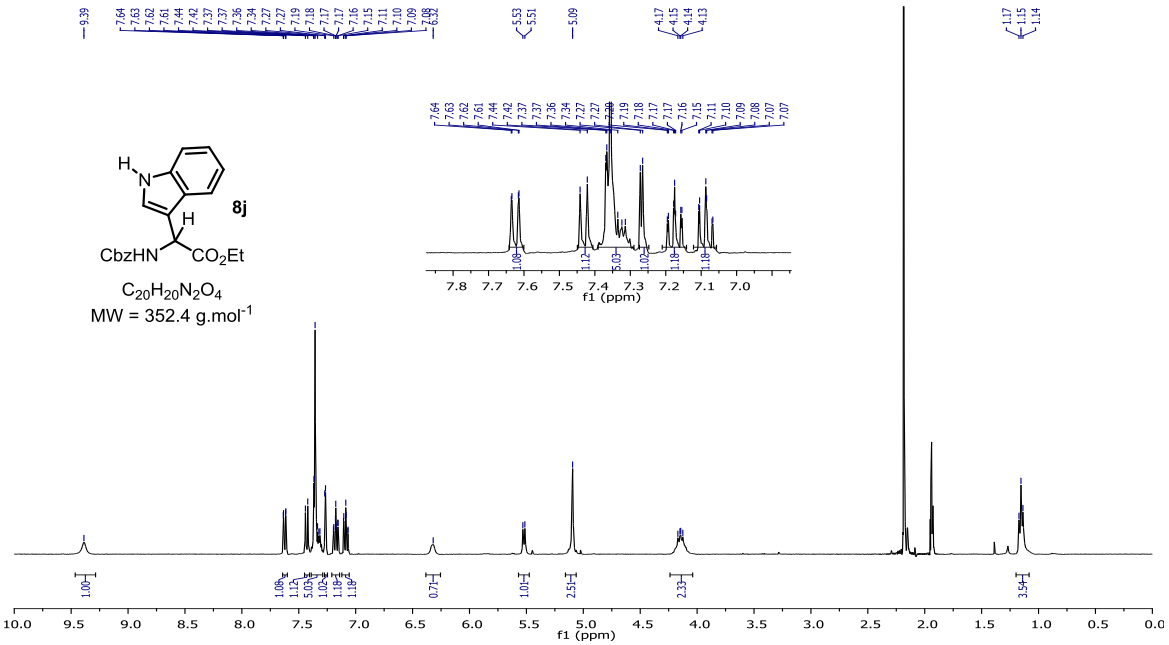
CD_3CN (400 MHz)



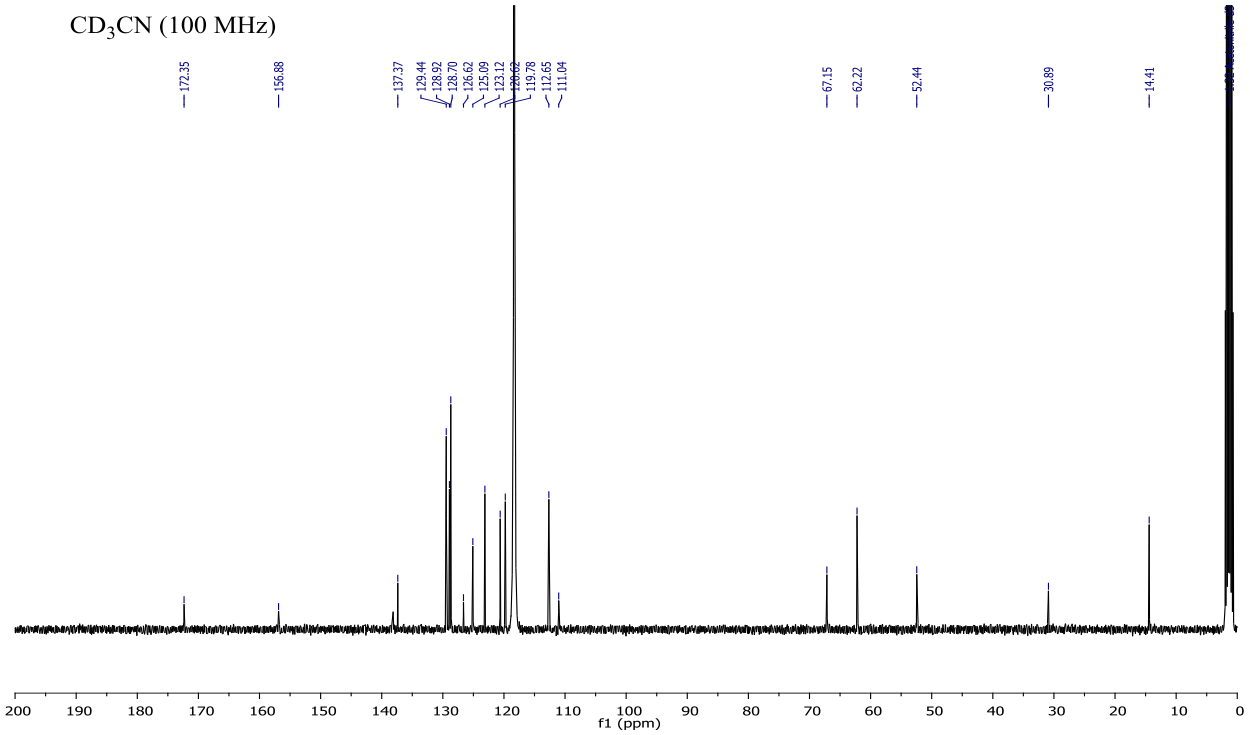
CD_3CN (100 MHz)



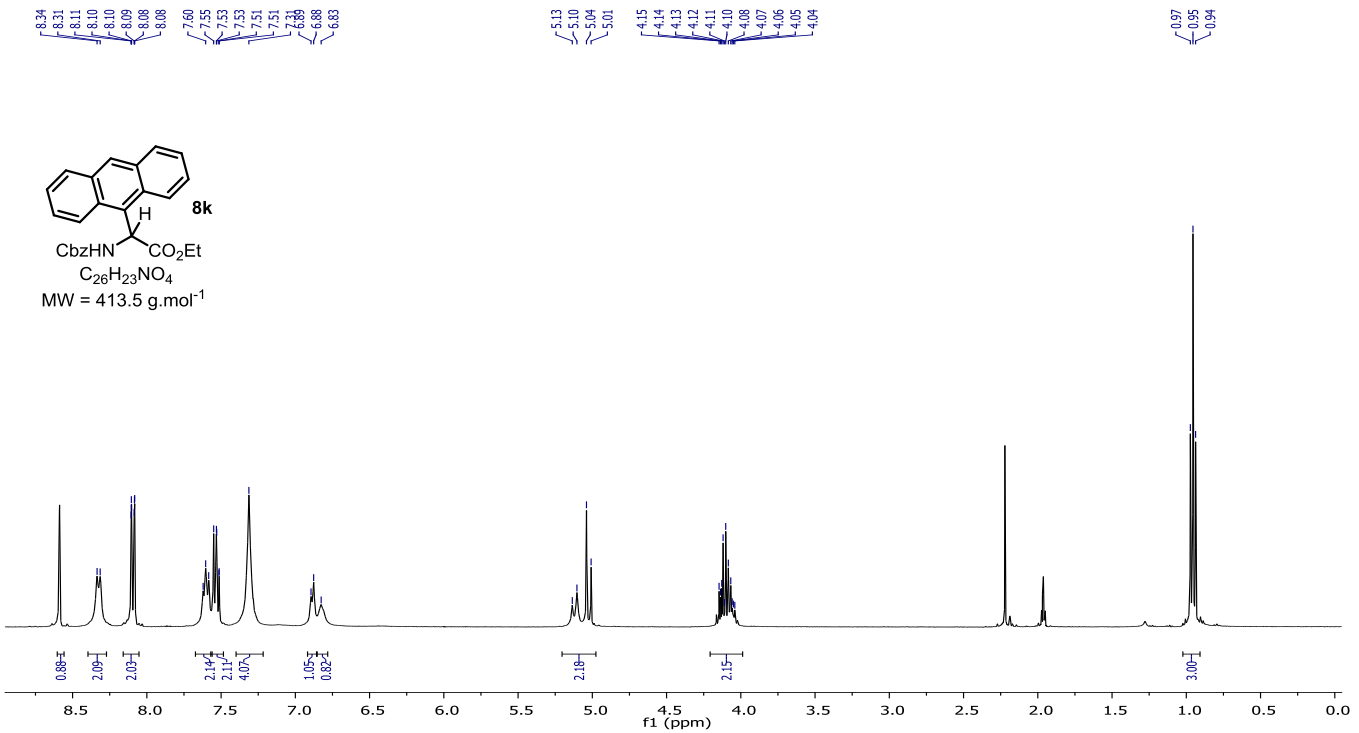
CD_3CN (400 MHz)



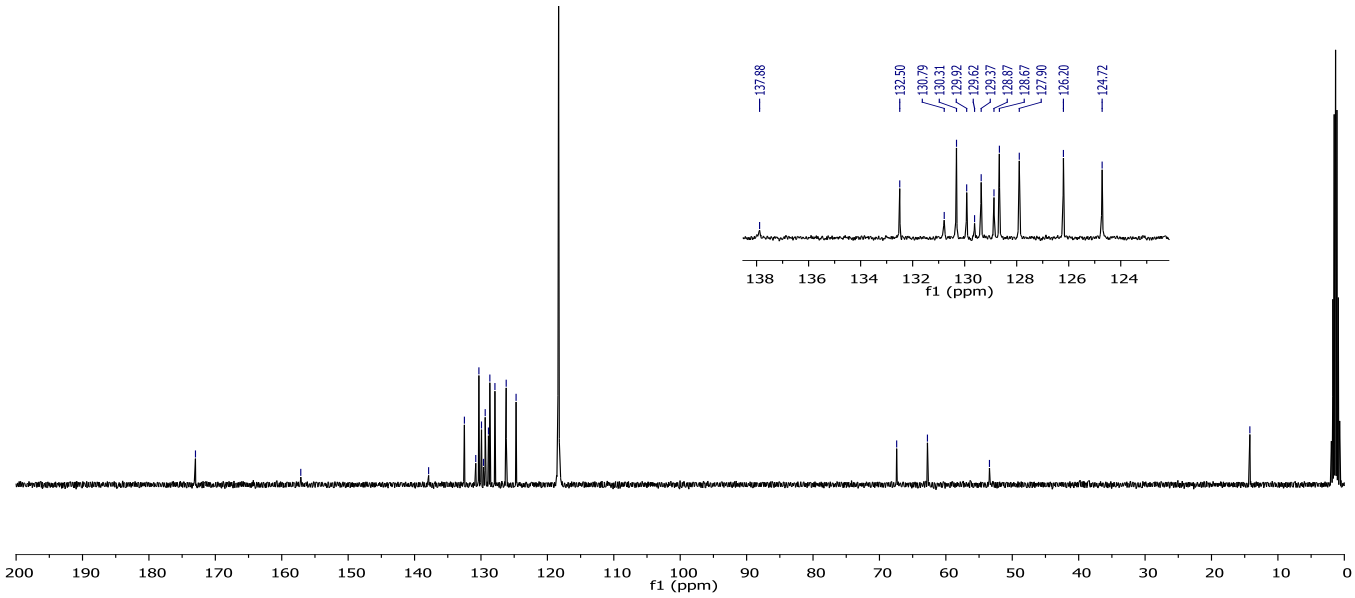
CD_3CN (100 MHz)



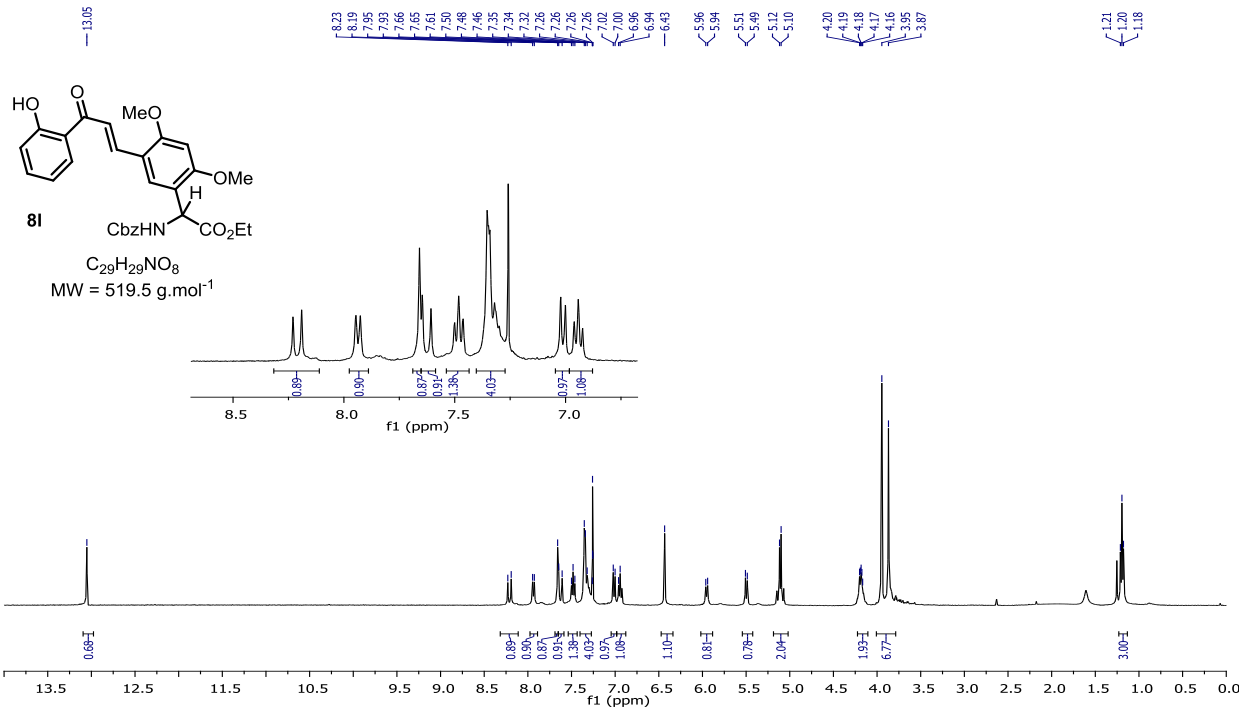
CD_3CN (400 MHz)



CD_3CN (100 MHz)



$CDCl_3$(400 MHz)



$CDCl_3$(100 MHz)