Supporting information

α-C–H functionalization of Glycine Derivatives Under Mechanochemical Accelerated Aging en Route to the Synthesis of 1,4-Dihydropyridines and α-Substituted Glycine Esters

Keyu Xiang,[a] Ying Ping,[a,b] Tao Ying,[a] Weike Su,[a] Jingbo Yu[a,*]

[a] *National Engineering Research Center for Process Development of Active Pharmaceutical Ingredients, Collaborative Innovation Center of Yangtze River Delta Region Green Pharmaceuticals, Zhejiang University of Technology. Hangzhou, 310014, P.R. China. E-mail: yjb@zjut.edu.cn*

[b] *College of Ecology, Lishui University, Lishui, 323000, P.R. China*

Table of Contents

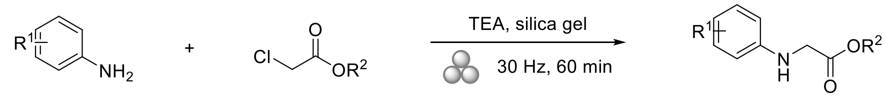
1. General information

Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification. All of the ball-milling reactions were conducted in a Mix miller (MM 400 RetschGmbh, Hann, Germany) with 25/50 mL stainless-steel grinding jars with stainless-steel balls (d_{MB} = 1.4 cm), if not mentioned otherwise. Reactions were monitored by Thin Layer Chromatography (TLC) using UV light (254/365 nm) for detection. Flash chromatography was carried out using silica gel (200-300 mesh). ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on Bruker 400, 500 or 600 MHz spectrometer in $CDCl_3$ or d_6-DMSO with tetramethylsilane (TMS) as internal standard. The following abbreviations were used to explain multiplicities: s = singlet, brs = broad singlet, d = doublet, t = triplet, dd = doublet of doublets, m = multiplet and the *J* coupling constants were reported in Hertz unit (Hz). Melting points were measured using an SRS OptiMelt MPA100 apparatus and were uncorrected. High Resolution Mass spectra (HRMS) was recorded on micrOTOF-Q II 10366, Agilent 6210 LC/TOFMS or Waters GCT Premier TOFMS. Particle size was measured by Malvern Mastersizer 2000. BET experiments were recorded with Micromeritics ASPS 2010.

2. General procedures for the synthesis of substrates

The *N*-arylglycine esters/amides were synthesized under solvent-free ball-milling conditions.

2.1 The synthesis of *N*-arylglycine esters



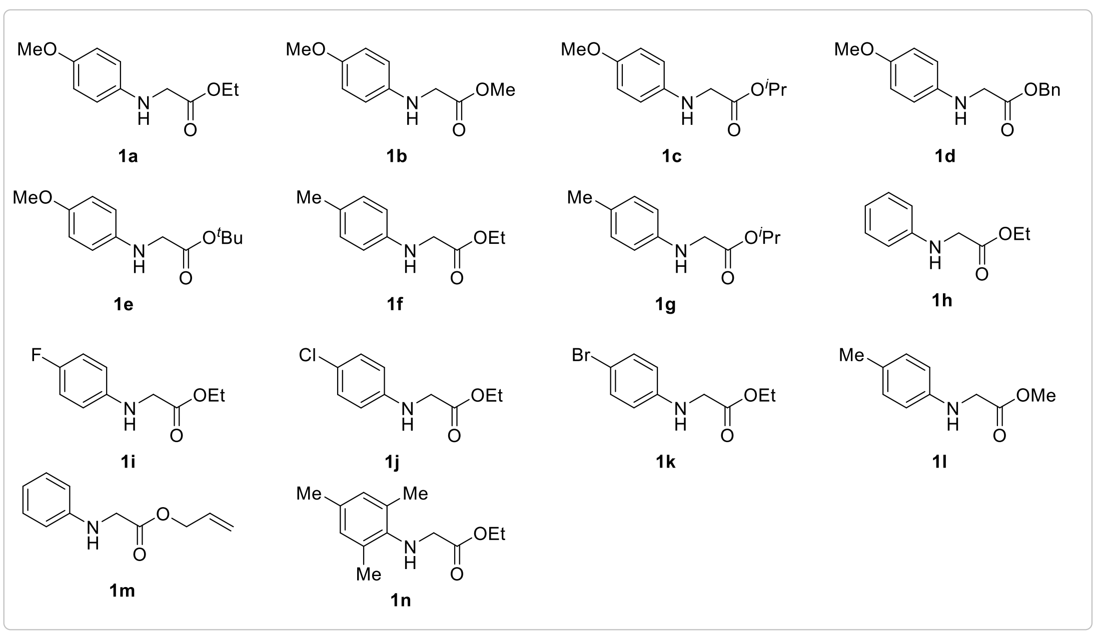
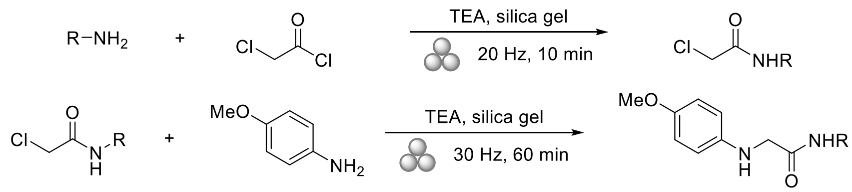


Figure S1 *N*-arylglycine esters used in this study

All *N*-arylglycine esters were synthesized from the corresponding anilines and alkyl 2-chloroacetate according to the **typical procedure 1**.

Typical procedure 1: ethyl (4-methoxyphenyl)glycinate (**1a**): A mixture of 4-methoxyaniline (0.246 g, 2.0 mmol), ethyl 2-chloroacetate (0.244 g, 2.2 mmol), triethylamine (0.222 g, 2.2 mmol) and silica gel (2.0 g) were placed in a 50 mL stainless-steel jar with two stainless-steel balls (d_{MB} = 1.4 cm). Then, the milling jar was placed in a mixer mill (30 Hz, 60 min). After the reaction was finished, the contents were scratched off the jar and *purified directly by rinsing with cyclohexane in a Buchner funnel to give desired products **1a~1n***.

2.2 The synthesis of *N*-arylglycine amides



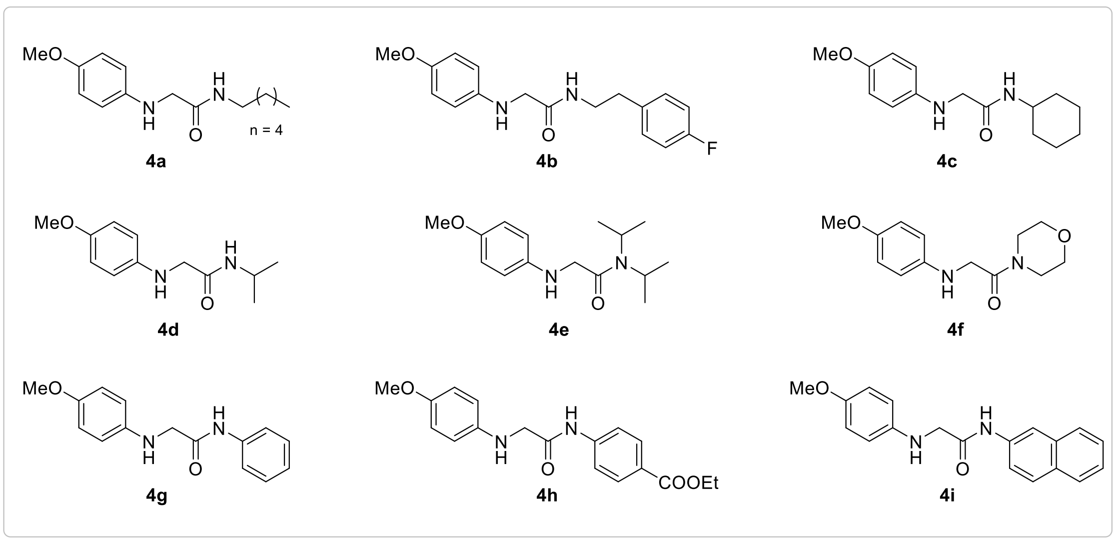
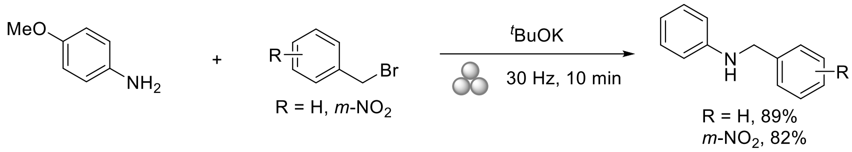


Figure S2 *N*-arylglycine amides used in this study

Chloroacetamides were synthesized from amines and chloracetyl chloride according to **typical procedure 2**, then *N*-arylglycine amides were obtained by **typical procedure 1**.

Typical procedure 2: *N*-hexyl-2-((4-methoxyphenyl)amino)acetamide (**4a**): A mixture of hexylamine (0.102 g, 1.0 mmol), triethylamine (0.111 g, 1.1 mmol) and silica gel (1.5 g) were placed in a 50 mL stainless-steel jar with two stainless-steel balls (d_{MB} = 1.4 cm). After precooling the sealed jar with ice, chloroacetyl chloride (0.124 g, 1.1 mmol) was added, and the milling jar was placed in a mixer mill (20 Hz, 10 min). *4-methoxyaniline (0.123 g, 1.0 mmol) was then added to the mixture, further milling at 30 Hz for 60 min. After the reaction was finished, the contents were scratched off the jar and purified directly by rinsing with cyclohexane in a Buchner funnel to give desired products **4a~4i***. (**typical procedure 1**)

2.3 The synthesis of *N*-benzyl-4-methoxyanilines



Scheme S1 The synthesis of *N*-benzyl-4-methoxyanilines

The *N*-benzyl-4-methoxyanilines were synthesized from 4-methoxyaniline and the corresponding benzyl bromides according to Rathi's report[1].

3. Reaction optimization & typical procedures

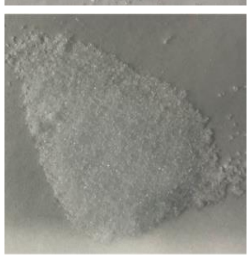
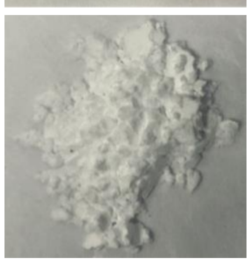
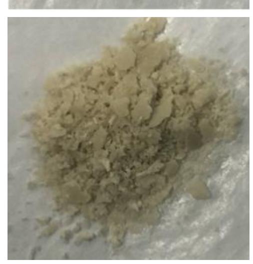
3.1 Influence of the grinding auxiliaries on the cascade CDC reaction

Table S1 Screen of the grinding auxiliaries[a]

Entry	Auxiliaries (g)	Yield (%)
1	**Silica gel (0.60)**	**67**
2	LiCl (1.43)	44
3	NaCl (1.50)	59
4	KCl (1.37)	53
5	NaF (0.71)	n.d.
6	KBr (1.91)	31
7	Na_2SO_4 (1.86)	37
8	$CaCl_2$ (1.49)	41
9	$BaTiO_3$ (4.17)	n.d.
10	Nano ZnO (3.89)	n.d.
11	Kieselguhr (0.60)	n.d.
12	Al_2O_3 (2.42)	n.d.
13	none	n.d.

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1.5 mmol) and grinding auxiliaries (with the same volume) were pre-grinded for 30 min at 30 Hz, using two stainless-steel grinding balls (d_{MB} = 1.4 cm) in a 25 mL stainless jar, then aging in an opened flask for 24 h at 40 °C.

Table S2 The morphology of the grinding auxiliaries and the reaction mixtures

Entry	Before Milling	After Milling	After Aging
Silica gel			
LiCl			
NaCl			
KCl			
NaF			
KBr			

Na_2SO_4

$CaCl_2$

Nano ZnO

Kieselguhr

$BaTiO_3$

Al_2O_3

None	–		–

In the absence of grinding auxiliary, the substrates were hardly dispersed (Table S2, none), which gave no aging product (Table S1, entry 13). Most of the powdered mixtures give rise to better yields except Al_2O_3 and $BaTiO_3$ (Table S1, entries 9 and 12), while either the pulpy slurry (Table S2, Kieselguhr, Table S1, entry 11) or the nubbly aggregations ([Table S2, NaF, Table S1, entry 5]; [Table S2 Nano ZnO, Table S1, entry 10]) could not give any aging products. Besides, most of the halogen salts diminished the transformation due to the slight agglomeration of the mixtures.

3.2 Influence of amount of silica gel on the cascade CDC reaction

Further investigation of the amount of silica gel showed that 600 mg silica gel gave the best performance. Lower its usage (400 mg, 500 mg) led to a bad dispersion of the substrates which resulted in poor yields. The excess silica gel (700 mg) also resulted in a sharp decrease of yield, which was probably raised by the dilution of reagents. Thus, our investigation was continued with 600 mg silica gel.

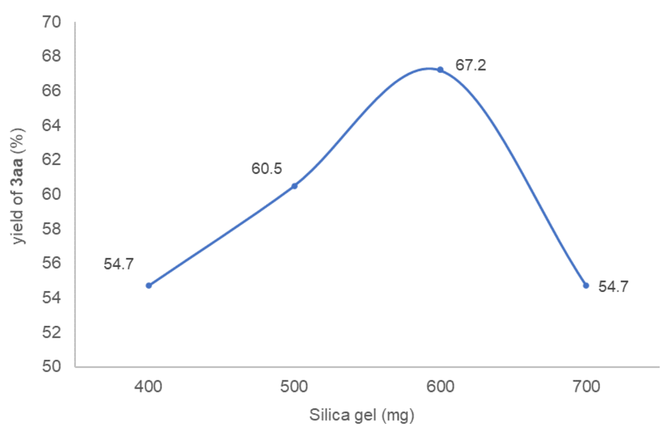
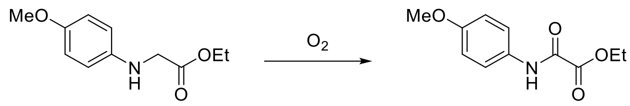


Figure S3 Effect of silica gel amount on the reaction yield. Reaction conditions: **1a** (0.5 mmol), **2a** (1.5 mmol) and silica gel were pre-grinded at 30 Hz for 30 min, using two stainless-steel balls (d_{MB} = 1.4 cm) in a 25 mL stainless jar, then aging in an opened flask for 24 h at 40 ^{o}C.

3.3 Influence of aging temperature on the cascade CDC reaction

The aging temperature after pre-grinding was then examined. As seen the results depicted in Figure S4, proper heating during the aging process can promote the reaction transformation, but overheating depreciated the product yield probably due to the augment of the side-reaction[2] (auto-oxidation of glycine, Scheme S1).



Scheme S2 Auto-oxidation of **1a**

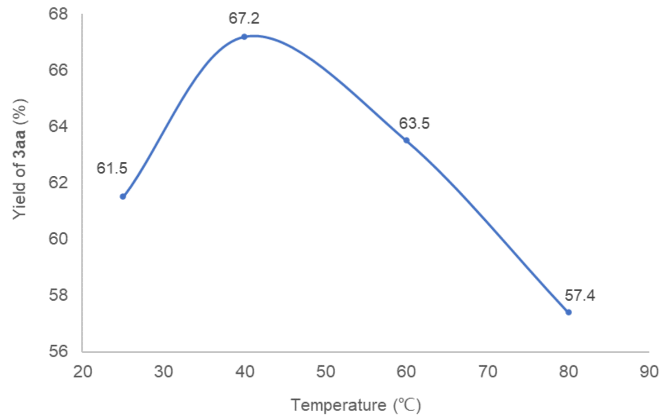
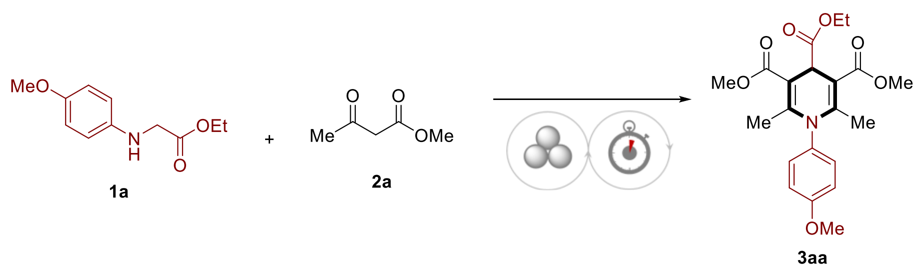


Figure S4 Effect of aging temperature on the reaction yield (pre-grinding at 30 Hz for 30 min). Reaction conditions: **1a** (0.5 mmol), **2a** (1.5 mmol) and silica gel (0.6 g) were pre-grinded at 30 Hz for 30 min, using two stainless-steel balls (d_{MB} = 1.4 cm) in a 25 mL stainless jar, then aging in an opened flask for 24 h.

3.4 Optimization of reaction conditions

Table S3 Optimization of the cascade CDC reaction of **1a** and **2a**



Entry	1a (mmol)	2a (mmol)	Frequency (Hz)	Milling Time (min)	Aging Temp. (°C)	Aging Time (h)	Yield (%)
1	0.5	1.5	30	20	40	24	55
2	0.5	1.5	30	60	40	24	68
3	0.5	1.5	30	30	40	24	67
4	0.5	1.5	25	30	40	24	53
5	0.5	1.5	20	30	40	24	48
6	0.5	1.5	15	30	40	24	35
7	0.5	2	30	30	40	24	68
8	0.5	1.1	30	30	40	24	54

9	0.5	1.1	30	30	rt	24	50
10	0.5	1.1	30	30	rt	36	56
11	0.5	1.1	30	30	rt	48	61
12	0.5	1.1	30	30	rt	60	65
13	0.5	1.1	30	30	rt	72	70
14	**0.5**	**1.1**	**30**	**30**	**rt**	**84**	**71**
15	0.5	1.1	30	30	rt	96	71
16[b]	0.5	1.1	30	30	rt	24	36

[a] Reaction conditions: **1a** (0.5 mmol), **2a** and silica gel (0.6 g) were pre-grinded for a certain time at a certain frequency, using two stainless-steel balls (d_{MB} = 1.4 cm) in a 25 mL stainless jar, then aging in an opened flask. [b] The Teflon jar and balls were used, aging in an opened flask at rt for 24 h. rt = room temperature

The yield of **3aa** rise along the increased milling time (Table S3, entries 1~3) and milling frequency (Table S3, entries 3~6). When the amount of **2a** was increased from 3.0 to 4.0 equiv., nearly the same product yield was obtained (Table S3, entries 3 and 7), while decreased its dosage from 3.0 to 2.2 equiv. led to a lower yield of 54%. Nevertheless, as the "do not require energy" aging time extended to 84 h (Table S3, entries 9~14), the yield of **3aa** could be increased to 71% in the presence of the low amount of **2a** (2.2 equiv.), but further prolonging the aging time to 96 h had no additional benefit on the yield (Table S3, entry 15).

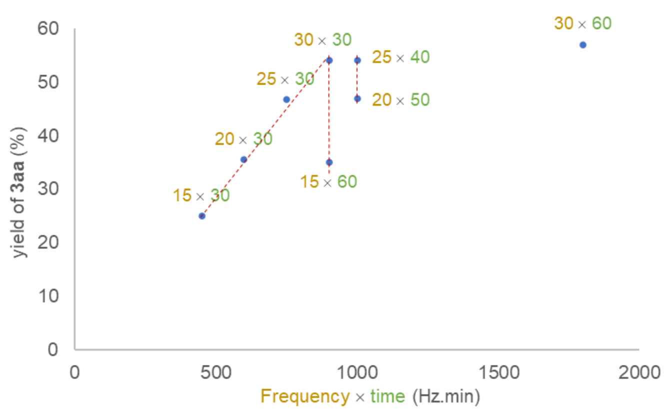


Figure S5 The effect of the product of frequency and milling time on the yield of **3aa.** Reaction conditions: **1a** (0.5 mmol), **2a** (1.1 mmol) and silica gel (0.6 g) were pre-grinded for a certain time at a certain frequency, using two stainless-steel balls (d_{MB} = 1.4 cm) in a 25 mL stainless jar, then aging in an opened flask for 24 h at 40 °C.

Considering the ball-milling frequency can notably affect the rate of molecular collisions and interparticle mixing during the impact[3] while longer milling time means more energy accumulation, we next investigated the relationship between the yield of **3aa** and milling time & frequency detailly under the optimal chemical conditions (Figure S5). As expected, an improved yield was obtained with higher milling frequency, while prolonging the milling time at a specific frequency had a positive effect on the following transformation. It should be noted that the higher frequency gave better results when the products of frequency and milling time were kept in constant (Fig S5, 30 × 30 vs 15 × 60; 25 × 40 vs 20 × 50), yet no significant change was obtained when the milling time was prolonged to 60 min at 30 Hz. The overall evaluation showed that the milling frequency was a key parameter for the following aging transformation.

3.5 Typical procedures for the (cascade) CDC reaction

Typical procedure for the synthesis of products 3 and 5: A mixture of glycine esters **1a~1m** (0.5 mmol, 1.0 equiv.) or amides **4a~4i** (0.5 mmol, 1.0 equiv.), **2a~2g** (1.1 mmol, 2.2 equiv.), LAG (TFA, $\eta = 0.009$, if needed) and silica gel (0.6 g)/NaCl (1.5 g) were placed in a stainless-steel jar (25 mL) with two stainless-steel balls ($d_{MB} = 1.4$ cm) and pre-grinded at 30 Hz for 30 min. After the milling was finished, the contents were scratched off the jars and aging in an opened flask (100 mL) for 84 h at rt. Then, purified by *(a) rinsing with cyclohexane and filtration (details see 3.8)*; (b) column chromatography on silica gel using EtOAc/*n*-hexane to give the desired products.

Typical procedure for the synthesis of unsymmetrical products: A mixture of glycine esters **1a**/**1l** (0.5 mmol, 1.0 equiv.), two different *β*-carbonyl esters/acetylacetone **2a**/**2b**/**2f** (0.55 mmol, 1.1 equiv.) and **2b**/**2g** (0.55 mmol, 1.1 equiv.) as well as silica gel (0.6 g) were placed in a stainless-steel jar (25 mL) with two stainless-steel balls ($d_{MB} = 1.4$ cm) and pre-grinded at 30 Hz for 30 min. After the milling was finished, the contents were scratched off the jars and aging in an opened flask (100 mL) for 84 h at rt. Then, purified directly by column chromatography on silica gel using EtOAc/*n*-hexane to give the desired products **3aab, 3aag**, **3acg**, **3afg** and **3lb**.

Typical procedure for the synthesis of *α*-glycine derivatives 7: A mixture of glycine esters **1a**/**1f**/**1l** (0.5 mmol, 1.0 equiv.), **6a~6o** (0.5 mmol, 1.0 equiv.), $Cu(OTf)_2$ (1 mol%, for **6j~6o**), LAG (TFA, $\eta = 0.01$, if needed) and silica gel (0.6 g)/NaCl (1.5 g) were placed in a stainless-steel jar (25 mL) with two stainless-steel balls ($d_{MB} = 1.4$ cm) and pre-grinded at 30 Hz for 30 min. After the milling was finished, the contents were scratched off the jars and aging in an opened flask (100 mL) for 96 h/24 h (for **6j~6o**) at rt. Then, purified by *(a) rinsing with cyclohexane and filtration (details see 3.8)*; (b) column chromatography on silica gel using EtOAc/*n*-hexane to give the desired products.

3.6 List of unreactive substrates

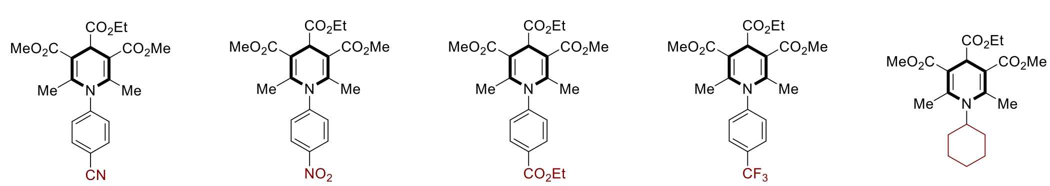


Figure S6 Unreactive substrates

Glycine esters with strong electron-withdrawing groups (nitro-, cyano-, carbonyl and trifluoromethyl) on the benzene rings were tested but failed to give any products, neither did the alkyl substituent, which was probably due to their low reactivity or the formation of less stable intermediates during the C–H activation. (The starting materials for getting these compounds were prepared according to literature methods[4], thus their characterization data were not shown).

3.7 Comparison of the effect of NaCl and silica gel on the yield at different aging time

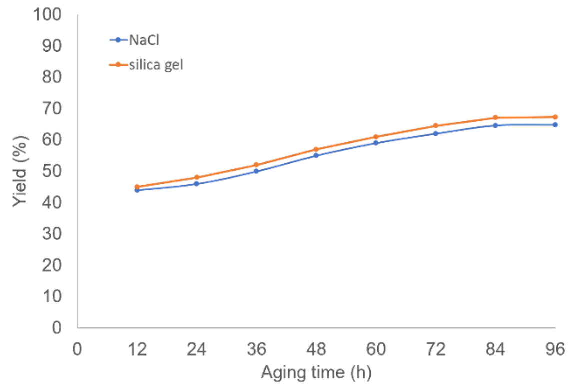


Figure S7 Reaction of **1a** and **2a** with NaCl and silica gel as grinding auxiliary (*isolated yields obtained without column chromatography*). Reaction conditions: **1a** (0.5 mmol), **2a** (1.1 mmol) and NaCl (1.5 g)/silica gel (0.6 g) were pre-grinded for 30 min at 30 Hz, using two stainless-steel balls (d_{MB} = 1.4 cm) in a 25 mL stainless jar, then aging in an opened flask at rt.

3.8 Modified purification method and the recycling of grinding auxiliary

Silica gel as grinding auxiliary: After the reaction was completed, the mixtures were placed to the Buchner funnel, rinsing with cyclohexane, and then concentrated under vacuum to give desired products **3aa**, **3ba**, **3ca**, **3da**, **3ab**, **3lb**, **3ic**, **5fa**, **5ga**, and **5ha**. *The residues (containing mainly silica gel) were directly used for the next reaction after drying under reduced pressure.*

NaCl as grinding auxiliary: After the reaction was completed, the mixtures were dissolved in EtOAc, then filtered to give *the recovered NaCl as offwhite solid which can be directly used for the next reaction after drying under reduced pressure*. The filtrate was concentrated and rinsed with cyclohexane/ EtOAc (5:1) in a Buchner funnel (with a thin layer of SiO_2), and then concentrated under vacuum to give desired products **3aa**, **3ga**, **3gb**, **3af**, **3cg**, **5ea**, **7ac, 7ah** and **11**.

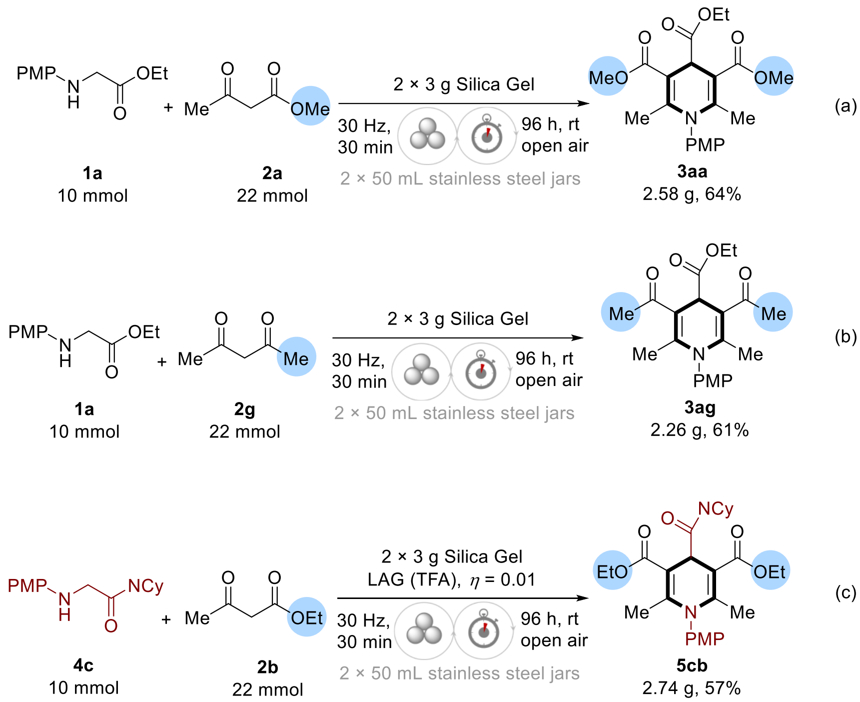
For the synthesis of **3aa**, *NaCl can be recycled and reused for at least 5 times and its recovery yields (mass of recovered solid g/1.5 g) were ranging from 95.3% to 98.6%. The average consumption of NaCl for single reaction is 46 mg.*

For the synthesis of **7ah**, *NaCl can be recycled and reused for at least 5 times and its recovery yields (mass of recovered solid g/1.5 g) were ranging from 96.3% to 96.8%. The average consumption of NaCl for single reaction is 51 mg.*

For the synthesis of **11**, *NaCl can be recycled and reused for at least 5 times and its recovery yields (mass of recovered solid g/1.5 g) were ranging from 96.3% to 97.1%. The average consumption of NaCl for single reaction is 50 mg.*

4. Multigram-scale synthesis and synthetic application

4.1 Multigram-scale synthesis



Scheme S3 Multigram-scale synthesis of **3aa**, **3ag** and **5cb**. Reaction conditions: (a) **1a** (5.0 mmol, 1.0 equiv.), **2a** (11 mmol, 2.2 equiv.) and silica gel (3.0 g) were placed in a stainless-steel jar (50 mL) with two stainless-steel balls (d_{MB} = 1.4 cm) milling at 30 Hz for 30 min (two jars), then the reaction mixture was aging in an opened flask (500 mL) for 96 h. *After the reaction was completed, the contents were rinsed with cyclohexane, the filtrate was concentrated and dried under vacuum to give* **3aa**. (b) **1a** (5.0 mmol, 1.0 equiv.), **2g** (11 mmol, 2.2 equiv.), TFA (η = 0.01) and silica gel (3.0 g) were placed in a stainless-steel jar (50 mL) with two stainless-steel balls (d_{MB} = 1.4 cm) milling at 30 Hz for 30 min (two jars), then the reaction mixture was aging in an opened flask (500 mL) for 96 h. After the reaction was completed, the contents were purified directly by column chromatography on silica gel using EtOAc/*n*-hexane (1:2) as eluent to give **3ag**. (c) **4c** (5.0 mmol, 1.0 equiv.), **2b** (11 mmol, 2.2 equiv.), TFA (η = 0.01) and silica gel (3.0 g) were placed in a stainless-steel jar (50 mL) with two stainless-steel balls (d_{MB} = 1.4 cm) milling at 30 Hz for 30 min (two jars), then the reaction mixture was aging in an opened flask (500 mL) for 96 h. After the reaction was completed, the contents were purified directly by column chromatography on silica gel using EtOAc/*n*-hexane (1:3) as eluent to give **5cb**.

4.2 Purity calculation of 3aa produced from Scheme S3a

To measure the purity of **3aa** produced from the gram-scale synthesis (**Scheme S3a**), 50 mg "product" was measured by NMR, and 15 mg mesitylene was added as an internal standard.

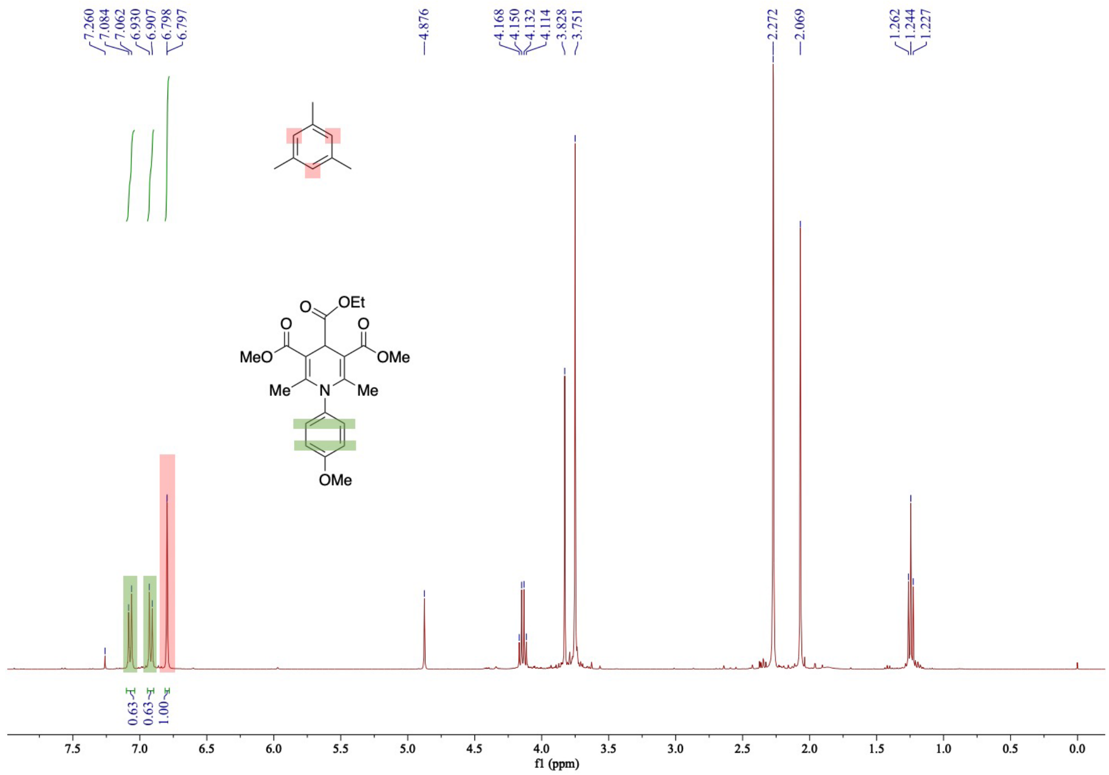
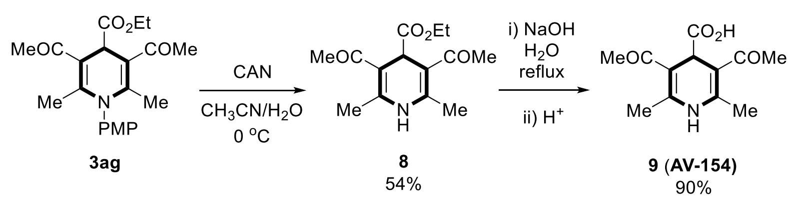


Figure S8 ^{1}H NMR of product **3aa** with internal standard mesitylene

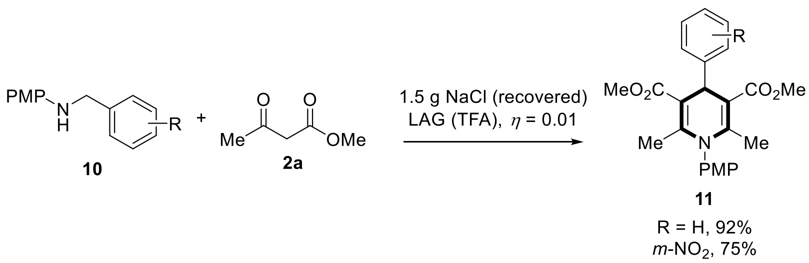
$$\text{Purity} = \frac{0.63}{2}(H\ integral\ of\ \mathbf{3aa}) \div \frac{1}{3}(H\ integral\ of\ mesitylene) \times \frac{15(mass\ of\ mesitylene)}{120(Mw\ of\ mesitylene\ )} \times 403(Mw\ of\ \mathbf{3aa}) \div 50(mass\ of\ crude\ product) = 95.2\%$$

4.3 Further transformations



Scheme S4 Further transformation of **3ag.** Reaction conditions: To a stirred solution of **3ag** (186 mg, 0.5 mmol) in CH_3CN (5 mL) was added slowly ceric ammonium nitrate (CAN, 677 mg, 1.25 mmol, 2.5 equiv.) in distilled water (5.0 mL) at 0 °C under N_2. The combined reaction mixture was further stirred at the same temperature for about 1 h. Progress of this was monitored by TLC and quenched by adding the saturated $NaHCO_3$ solution to bring the pH 10 and extracted with EtOAc (4 × 5 mL). The combined organic layer was washed with brine solution, dried over Na_2SO_4 and evaporated under vacuum. The crude product was separated by column chromatography eluting with Hexane/EA/TEA (70:30:1) respectively, afforded **8** (71.6 mg, 54% yield). To a solution of **8** (0.132 g, 0.5 mmol) in 5 mL of water was added NaOH (1.0 equiv.), reflux for 1 h. After cooling to room temperature, the reaction mixture was acidified by 1 M HCl (pH 10 to 3) to yield 57.6 mg of **9** as a yellow precipitate.

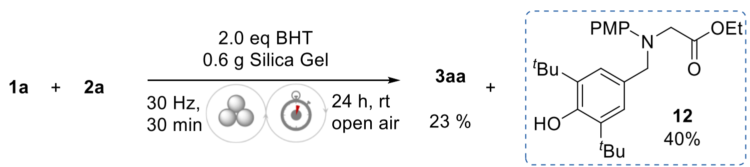
4.4 Synthesis of calcium channel blocker analogs



Scheme S5 Synthesis of calcium channel blocker analogs. Reaction conditions: A mixture of **10** (0.5 mmol, 1.0 equiv.), **2a** (1.1 mmol, 2.2 equiv.), LAG (TFA, $\eta = 0.01$) and NaCl (1.5 g) were placed in a stainless-steel jar (25 mL) with two stainless-steel balls and pre-grinded at 30 Hz for 30 min. After the milling was finished, the contents were scratched off the jars and aging in an opened flask (100 mL) for 48 h at rt. Then, the reaction mixtures were dissolved in EtOAc and filtered to give the recovered NaCl as offwhite solid *which can be directly used for the next reaction after drying under reduced pressure (the recovery yields were ranging from 96.3% to 97.1%, and the average consumption of NaCl for single reaction is 50 mg)*. The filtrate was concentrated and rinsed with EtOAc/cyclohexane (5:1) in a Buchner funnel (with a thin layer of SiO_2), and then concentrated under vacuum to give desired products.

5. Experimental probes on reaction mechanism

5.1 Control experiments



Scheme S6 Radical trapping experiments. Reaction conditions: **1a** (0.5 mmol, 1.0 equiv.), **2a** (1.1 mmol, 2.2 equiv.), silica gel (0.6 g) and BHT (2.0 equiv.) were placed in a stainless-steel jar (25 mL) with two stainless-steel balls (d_{MB} = 1.4 cm) in a mixer mill, milling at 30 Hz for 30 min. Then aging in an opened flask for 24 h at rt.

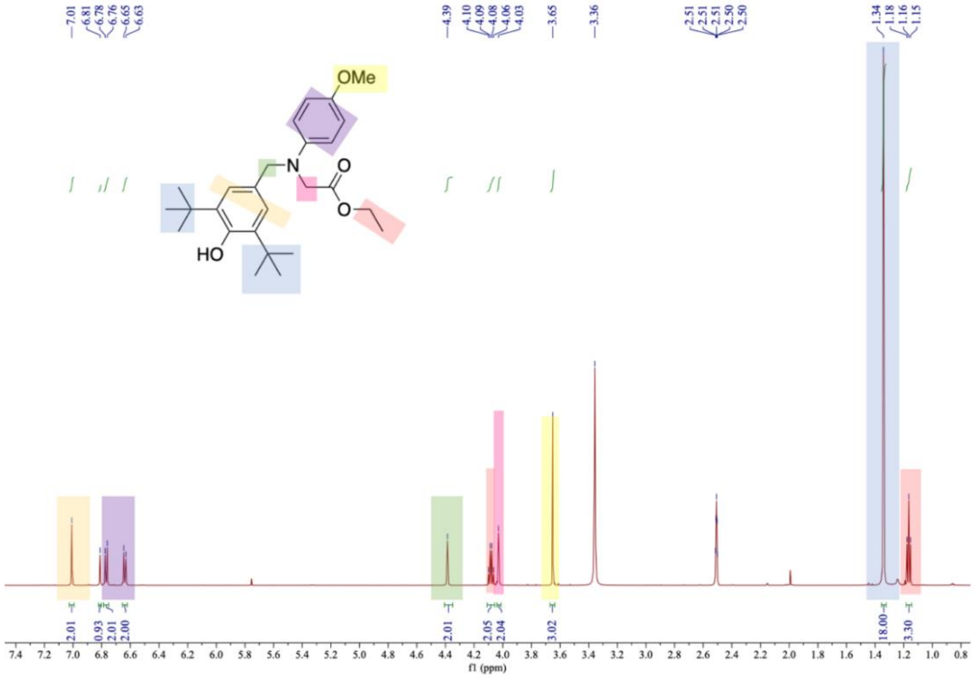


Figure S9 ^{1}H NMR of **1a-BHT** (**12**)

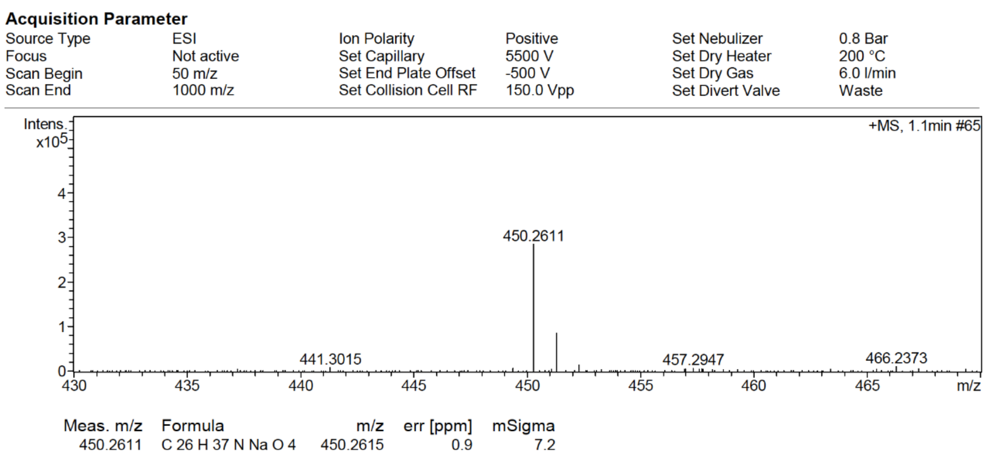
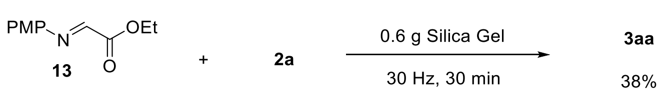
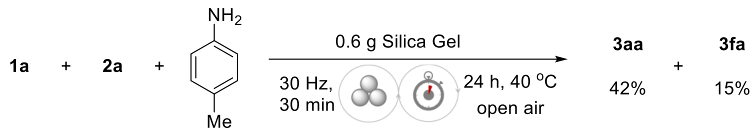


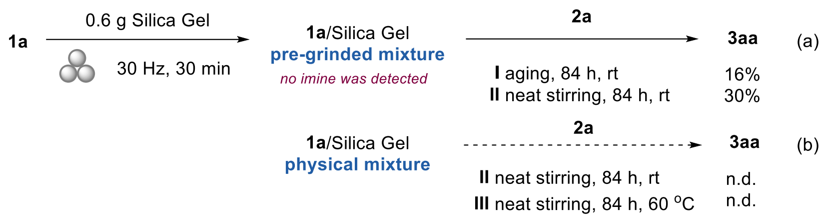
Figure S10 Mass spectrum of **1a-BHT** (**12**)



Scheme S7 Reaction of **13** and **2a** under ball-milling. Reaction conditions: **13** (0.5 mmol, 1.0 equiv.), **2a** (1.1 mmol, 2.2 equiv.) and silica gel (0.6 g) were placed in a stainless-steel jar (25 mL) with two stainless-steel balls (d_{MB} = 1.4 cm) in a mixer mill, milling at 30 Hz for 30 min.



Scheme S8 Three-component reaction of **1a**, **2a** and *p*-toluidine. Reaction conditions: **1a** (0.5 mmol, 1.0 equiv.), **2a** (1.1 mmol, 2.2 equiv.), *p*-toluidine (0.5 mmol, 1.0 equiv.) and silica gel (0.6 g) were placed in a stainless-steel jar (25 mL) with two stainless-steel balls (d_{MB} = 1.4 cm) in a mixer mill, milling at 30 Hz for 30 min. Then aging in an opened flask for 24 h at rt.



Scheme S9 The effects of pre-grinding and neat stirring. Reaction conditions: (a) **1a** (0.5 mmol, 1.0 equiv.) and 0.6 g silica gel were placed in a stainless-steel jar (25 mL) with two stainless-steel balls (d_{MB} = 1.4 cm) in a mixer mill, milling at 30 Hz for 30 min. After the milling was finished, the contents were scratched off the jars and aging in an opened flask for 84 h, (**I**, without agitation; **II**, with neat stirring); (b) **1a** (0.5 mmol, 1.0 equiv.) and 0.6 g silica gel were physically mixed and placed in an opened flask for 84 h (**I**, with neat stirring at rt; **II**, with neat stirring at 60 °C). (rt = room temperature, n.d. = not detected).

5.2 Physical adsorption test

Preparation of *C*-30: 0.6 g silica gel was placed in a stainless-steel jar (25 mL) with two stainless-steel balls (d_{MB} = 1.4 cm) in a mixer mill, milling at 30 Hz for 30 min. After the milling was finished, the mixture was washed with ethyl acetate.

Preparation of *BM*-30: **1a** (0.5 mmol), **2a** (1.1 mmol) and 0.6 g silica gel were placed in a stainless-steel jar (25 mL) with two stainless-steel balls (d_{MB} = 1.4 cm) in a mixer mill, milling at 30 Hz for 30 min. After the milling was finished, the mixture was washed with ethyl acetate.

ASAP 2010 was used to measure the BET surface area at 77.29 K by nitrogen physisorption. Before the test, the samples were evacuated at 393 K for 6 h.

5.3 Particle size distribution of silica gel

The particle size distribution of silica gel was measured by Malvern Mastersizer 2000. After neat grinding of the silica gel, the particle size distribution of silica gel was drastically changed (Figure S11), and large particles were identified due to the aggregation of silica gel particles. In contrast, no obvious aggregation was founded (the average particle size of silica gel was greatly decreased, see Table 5) when the milling process proceeded in the presence of organic reactants (BM-30w), which might be attributed to the protective effect of the substrates.

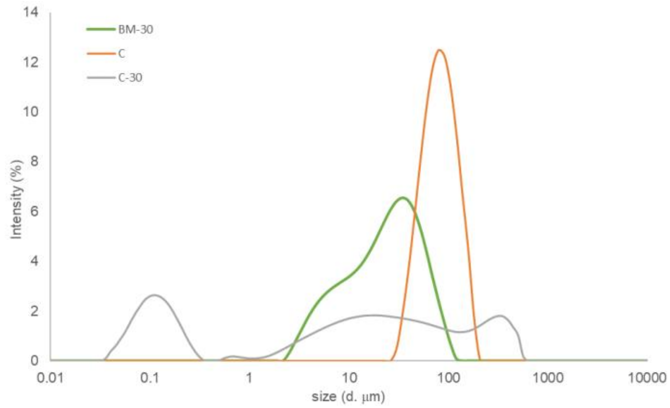


Figure S11 Particle size distribution of silica gel

6. Green chemistry metrics calculations

6.1 Calculation of *E*-factor and reaction mass efficiency (RME)

The *E*-factor is the actual amount of waste produced in the process, defined as everything but the desired product. It takes the chemical yield into account and includes reagents, solvent losses, and all process aids. A higher *E*-factor means more waste and, consequently, greater negative environmental impact. The ideal *E*-factor is zero[5].

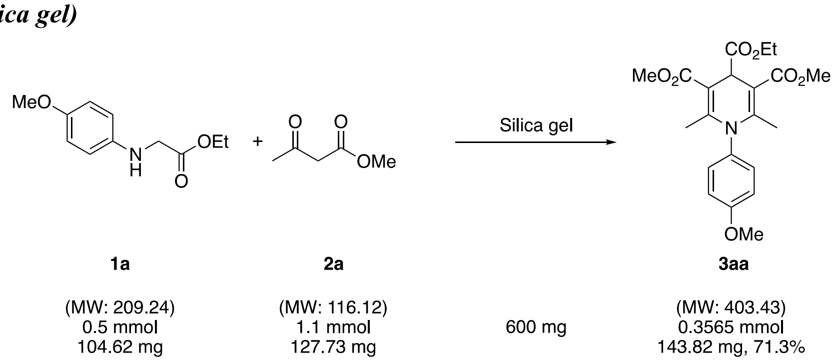
$$\boldsymbol{E}\ \textbf{factor} = \frac{\Sigma \mathrm{m(reactants)} + \Sigma \mathrm{m(reacgents)} + \Sigma \mathrm{m(solvents)} + \Sigma \mathrm{m(additives)} - \Sigma \mathrm{m(desired\ product)}}{\Sigma \mathrm{m(desired\ product)}}$$

The quantitative reaction mass efficiency (RME) and *E*-factor are related by the equation as follows[6],

$$\textbf{RME} = \frac{1}{1+E}$$

Calculation of *E*-factor for the synthesis of 3aa

This work (silica gel)

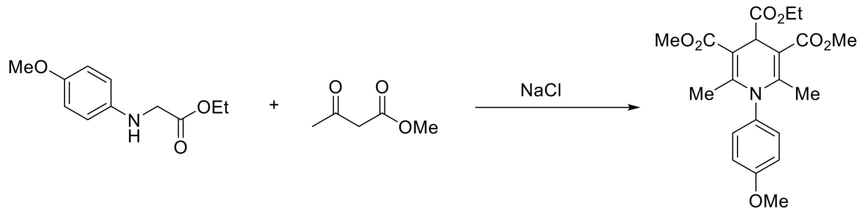


$$\boldsymbol{E}\ \textbf{factor} = \frac{104.62\ (\mathbf{1a}) + 127.73\ (\mathbf{2a}) + 600\ (\mathrm{silica\ gel}) - 143.82\ (\mathbf{3aa})}{143.82\ (\mathbf{3aa})}$$

$$= 4.79\ kg\ waste/1kg\ product$$

$$\boldsymbol{RME} = \frac{1}{1+4.79} = 17.3\%$$

This work (NaCl, recovered and reused for 5 times, see section 3.8)



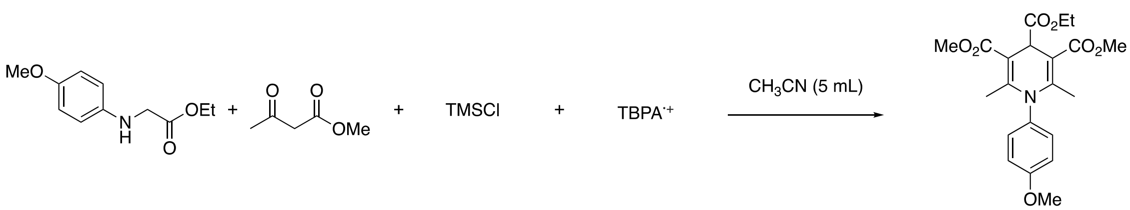
1a	**2a**		**3aa**
(MW: 209.24)	(MW: 116.12)		(MW: 403.43)
0.5 mmol	1.1 mmol	46 mg	0.3565 mmol
104.62 mg	127.73 mg		129.01 mg, 64%

$$\boldsymbol{E}\ \mathbf{factor} = \frac{104.62\ (\mathbf{1a}) + 127.73\ (\mathbf{2a}) + 46\ (\mathrm{NaCl}) - 129.01\ (\mathbf{3aa})}{129.01\ (\mathbf{3aa})}$$

$$= 1.16\ kg\ waste/1kg\ product$$

$$\boldsymbol{RME} = \frac{1}{1 + 1.16} = 46.3\%$$

Jia's 2014 work[7]



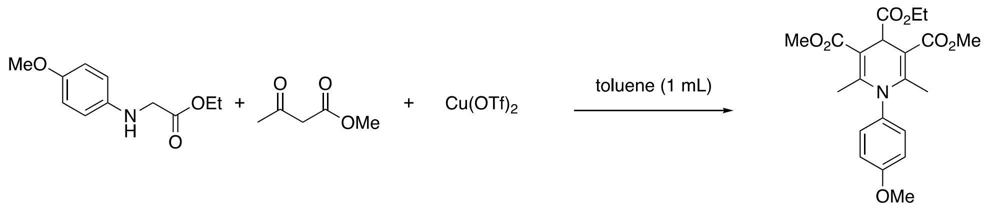
1a	**2a**				**3aa**
(MW: 209.24)	(MW: 116.12)	(MW: 108.64)	(MW: 817.49)	5 mL	(MW: 403.43)
0.5 mmol	1.25 mmol	0.05 mmol	0.05 mmol	3828.5 mg	0.39 mmol
104.62 mg	145.15 mg	5.43 mg	40.88 mg		157.34 mg, 78%

$$\boldsymbol{E}\ \mathbf{factor} = \frac{104.62\ (\mathbf{1a}) + 145.15\ (\mathbf{2a}) + 5.43\ (\mathrm{TMSCl}) + 40.88\ (\mathrm{TBPA}) + 3828.5\ (\mathrm{CH3CN}) - 157.34\ (\mathbf{3aa})}{157.34\ (\mathbf{3aa})}$$

$$= 25.87\ kg\ waste/1kg\ product$$

$$\boldsymbol{RME} = \frac{1}{1 + 25.87} = 3.7\%$$

***Zhu & Le's 2016 work*[8]**



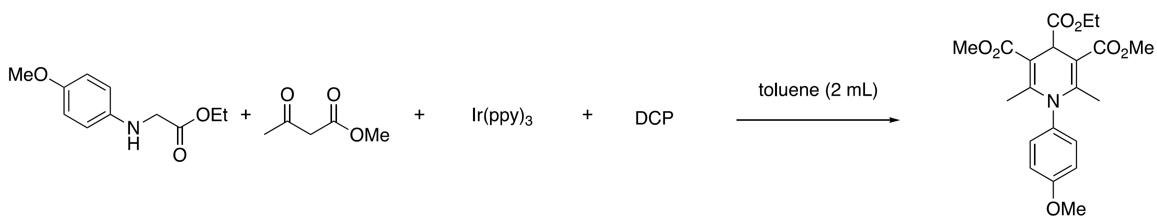
1a	2a			3aa
(MW: 209.24) 0.2 mmol 41.65 mg	(MW: 116.12) 0.44 mmol 51.09 mg	(MW: 361.68) 0.02 mmol 7.23 mg	1 mL 872.0 mg	(MW: 403.43) 0.146 mmol 58.90 mg, 73%

$$\boldsymbol{E}\ \textbf{factor} = \frac{41.56\ (\mathbf{1a}) + 51.09\ (\mathbf{2a}) + 7.23\ (\mathrm{Cu(OTf)2}) + 872.0\ (\mathrm{toluene}) - 58.90\ (\mathbf{3aa})}{58.90\ (\mathbf{3aa})}$$

$$= 15.50\ kg\ waste/1kg\ product$$

$$\boldsymbol{RME} = \frac{1}{1 + 15.50} = 6.1\%$$

***Zhu & Le's 2020 work*[9]**



1a	2a				3aa
(MW: 209.24) 0.2 mmol 41.65 mg	(MW: 116.12) 0.44 mmol 51.09 mg	(MW: 654.79) 0.002 mmol 1.31 mg	(MW: 270.37) 0.4 mmol 108.15 mg	2 mL 1744.0 mg	(MW: 403.43) 0.112 mmol 45.18 mg, 56%

$$\boldsymbol{E}\ \textbf{factor} = \frac{41.56\ (\mathbf{1a}) + 51.09\ (\mathbf{2a}) + 1.31\ (\mathrm{Ir(ppy)3}) + 108.15\ (\mathrm{DCP}) + 1733.0\ (\mathrm{toluene}) - 45.18\ (\mathbf{3aa})}{45.18\ (\mathrm{3aa})}$$

$$= 42.08\ kg\ waste/1kg\ product$$

$$\boldsymbol{RME} = \frac{1}{1 + 42.08} = 2.3\%$$

6.2 Calculation of power demands

The power for each running facilities (MM 400 RetschGmbh, *ball milling*; MS 300 Hot Plate Magnetic Stirrer, *heating and stirring*) were measured by power detector.

The power demand was calculated according to the equation as follows[10],

$$\mathrm{E} = \frac{\mathrm{E_{line\ power}}}{\mathrm{batch\ size} \times \mathrm{yield}}$$

This work

Item	Ball milling (30 Hz)
Power (W)	102
Time (h)	0.5
$E_{line\ power}$ (W·h)	51

$$E = \frac{51}{1\ \text{mmol (batch size, two jars)} \times 0.71\ \text{(yield)}} = 71.3\ \text{W·h·mmol}^{-1}$$

Jia's 2014 work

Item	Heating	Heat preservation	Stirring
Power (W)	240	1	2.5
Time (h)	0.1	4	4
$E_{line\ power}$ (W·h)	24	4	10

$$E = \frac{24 + 4 + 10}{0.5\ \text{mmol} \times 0.78\ \text{(yield)}} = 97.4\ \text{W·h·mmol}^{-1}$$

Zhu & Le's 2016 work

Item	Heating	Heat preservation	Stirring
Power (W)	240	1	2.5
Time (h)	0.1	12	12
$E_{line\ power}$ (W·h)	24	12	30

$$E = \frac{24 + 12 + 30}{0.2\ \text{mmol} \times 0.73\ \text{(yield)}} = 425\ \text{W·h·mmol}^{-1}$$

Zhu & Le's 2020 work

Item	Irradiation	Stirring
Power (W)	18	2.5
Time (h)	12	12
$E_{line\ power}$ (W·h)	216	30

$$E = \frac{216 + 30}{0.2\ \text{mmol} \times 0.56\ \text{(yield)}} = 2196\ \text{W·h·mmol}^{-1}$$

6.3 DOZN^{TM} 2.0 data for this work

The DOZN 2.0 tool is accessible here: https://bioinfo.merckgroup.com/dozn

DOZN Quantitative Scoring Analysis

Welcome, My Account Log out

Contact Us

Home (product-list.xhtml) > / Product Detail

Assess Product Greenness

Download

Product Information

*Product Name

3aa (mechano)

*Mass

0.143

*Unit

g

*Product Number

N/A

*Brand

OTHER

* Other Brand

Other

Coproducts

No Coproducts found

ADD A COPRODUCT

Reaction Conditions

Default Unit (Applies to each individual reaction condition)

*Time Unit

( ) min (•) hr

*Pressure Unit

( ) Torr ( ) mBar (•) atm

*Temperature Unit

(•) °C ( ) °F ( ) K

Reaction Condition #1 Remove

Name of Synthesis Step

Ball milling

Time

0.5

Time Unit

hr

Pressure Input Method

( ) Exact Value (•) General Conditions

Pressure Score

No mention of vacuum or pressure change

Temperature Input Method

( ) Exact Value (•) General Conditions

Temperature Score

Room temperature

Reaction Condition #2 Remove

Name of Synthesis Step

aging

Time

84.0

Time Unit

hr

Pressure Input Method

○ Exact Value ◉ General Conditions

Pressure Score

No mention of vacuum or pressure change

Temperature Input Method

○ Exact Value ◉ General Conditions

Temperature Score

Room temperature

ADD A REACTION CONDITION

Raw Materials

Weight Unit (Applies to each individual raw material)

***Unit**

◉g ○kg

Raw Material #1 Remove

***Product Name**

2a

***Product Number**

537365

***Brand**

SIGMA-ALDRICH

***Mass**

0.127

Is Waste?

Yes No (selected: No)

Is Renewable?

Yes No (selected: No)

Is Solvent?

Yes No (selected: No)

B Score

1

Used As

Reactant

Reaction Conditions

☐ **Ball milling** ☐ **aging**

Raw Material #2 Remove

***Product Name**

1a

***Product Number**

392262

***Brand**

OTHER

*** Other Brand**

Fluorochem

***Mass**

0.1045

Is Waste?

Yes No (selected: No)

Is Renewable?

Yes No (selected: No)

Is Solvent?

Yes No (selected: No)

B Score

1

Used As

Reactant

Reaction Conditions

☐ **Ball milling** ☐ **aging**

Raw Material #3 Remove

***Product Name**

SG

***Product Number**

89943

***Brand**

SIGMA-ALDRICH

***Mass**

0.6

Is Waste?

(•) Yes ( ) No

Waste Severity

Solid waste, non-hazardous(drying agents etc.)

Is Derivative?

( ) Yes (•) No

Is Renewable?

( ) Yes (•) No

Is Solvent?

( ) Yes (•) No

B Score

1

Used As

Auxiliary

Reaction Conditions

[ ] **Ball milling** [ ] **aging**

ADD A RAW MATERIAL

Process Information

***B score of Product**

1

***Mass used for B score of Product**

0.143

***Unit**

g

***Number of Catalytic Steps**

0

***Number of Synthesis Steps**

1

Is Monitored?

Yes No

SAVE SAVE & CALCULATE

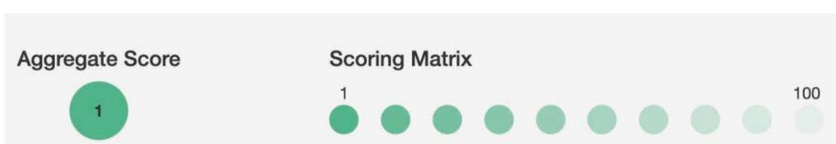
DOZN SCORE RESULT

Download

Aggregate Score

1

Scoring Matrix



Principle	Score
#1 Prevention	8.39
#2 Atom Economy	5.81
#3 Less Hazardous Chemical Synthesis	6.81
#4 Designing Safer Chemicals	2.00
#5 Safer Solvents and Auxiliaries	0.00
#6 Design for Energy Efficiency	0.00
#7 Use of Renewable Feedstocks	5.81
#8 Reduce Derivatives	0.00
#9 Catalysis	1.00
#10 Design for Degradation	2.00
#11 Real-time analysis for Pollution Prevention	1.00
#12 Inherently Safer Chemistry for Accident Prevention	6.81

Note: For more information on above Principles (click here (http://www.sigmaaldrich.com/chemistry/greener-alternatives/green-chemistry.html))

Groups	Principles	Score
#1 Improved Resource Use	1, 2, 7, 8, 9, 11	3.67
#2 Increased Energy Efficiency	6	0.00
#3 Reduced Human and Environmental Hazards	3, 4, 5, 10, 12	3.52

Note: The intent of the DOZN tool is to compare relative “greenness” for similar products or processes, as indicated by a lower DOZN score.

Figure S12 DOZN data of AA strategy for the synthesis **3aa**

6.4 DOZN^{TM} 2.0 groups according to the 12 Principles of Green Chemistry

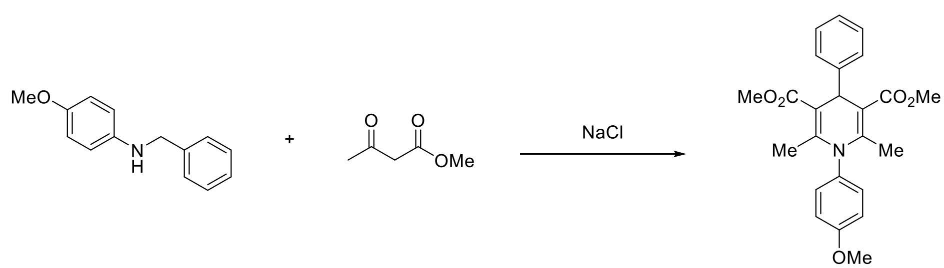
Table S4 The groups of DOZN 2.0

Groups	12 Principles of Green Chemistry
Improved resource use	1: Waste prevention
	2: Atom economy
	7: Use of renewable feedstock
	8: Reduce derivatives
	9: Catalysis
	11: Real-time analysis for pollution prevention
Energy efficiency	6: Design for energy efficiency
Reduced human and environmental hazards	3: Less hazardous chemical synthesis
	4: Designing safer chemicals
	5: Safer solvents and auxiliaries
	10: Design for degradation
	12: Inherently safer chemistry for accident prevention

6.5 Comparison of the greenness between AA facilitated CDC strategy and Hantzsch strategy

The Hantzsch method is a classic strategy for the synthesis of 1,4-DHPs, and some impressive modified approaches with significantly improved greenness have been reported[11]. In spite of the structure of the synthesized 1,4-DHPs were not identical, it is also useful to compare the relative greenness of our method with Hantzsch method that produce similar products.

This work (NaCl, recovered and reused for 5 times, see section 3.8)



11a

(MW: 213.28) 0.5 mmol 106.64 mg

(MW: 116.12) 1.1 mmol 127.73 mg

NaCl recovered 50 mg LAGs 3.6 mg

(MW: 407.47) 0.46 mmol 187.44 mg, 92%

$$\boldsymbol{E}\ \textbf{factor} = \frac{106.64 + 127.73 + 50 + 3.6 - 187.44}{187.44}$$

$$= 0.54\ kg\ waste/1kg\ product$$

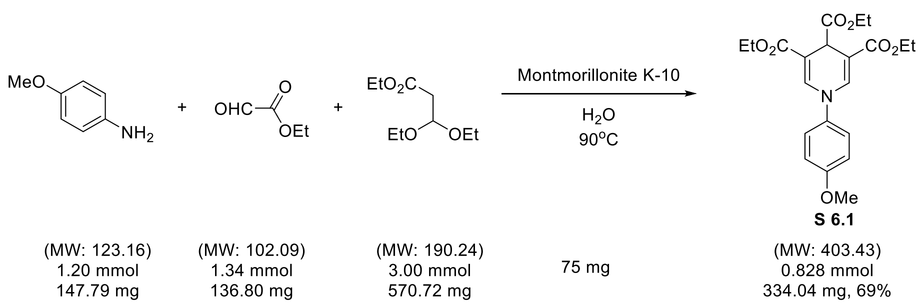
$$\boldsymbol{RME} = \frac{1}{1 + 0.54} = 64.9\%$$

***Power demands* (E)**

Item	Ball milling (30 Hz)
Power (W)	102
Time (h)	0.5
$E_{line\ power}$ (W·h)	51

$$\mathbf{E} = \frac{51}{1\ \text{mmol (batch size, two jars)} \times 0.92\ \text{(yield)}} = 55.4\ \text{W·h·mmol}^{-1}$$

***Pal's work*[11a]**



$$\boldsymbol{E}\ \textbf{factor} = \frac{147.79 + 136.80 + 570.72 + 75.00 - 334.04}{334.04}$$

$$= 1.79\ kg\ waste/1kg\ product$$

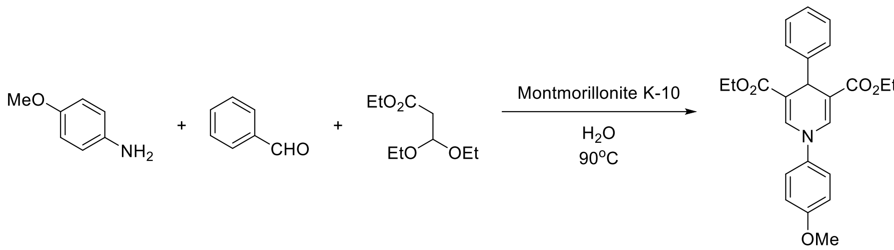
$$\boldsymbol{RME} = \frac{1}{1 + 1.79} = 35.8\%$$

***Power demands* (E)**

Item	Heating	Heat preservation	Stirring
Power (W)	–	1	2.5
Time (h)	–	10	10
$E_{line\ power}$ (W·h)	24*	10	25

*The heating time was estimated according to previous calculation.

$$\mathbf{E} = \frac{24 + 10 + 25}{1.2\ \text{mmol} \times 0.69\ \text{(yield)}} = 71\ \text{W·h·mmol}^{-1}$$



S 6.2

(MW: 123.16) 1.20 mmol 147.79 mg	(MW: 106.12) 1.34 mmol 142.20 mg	(MW: 190.24) 3.00 mmol 570.72 mg	75 mg	(MW: 407.47) 0.852 mmol 347.16 mg, 71%

$$\boldsymbol{E}\ \textbf{factor} = \frac{147.79 + 142.20 + 570.72 + 75 - 346.16}{346.16}$$

$$= 1.70\ kg\ waste/1kg\ product$$

$$\boldsymbol{RME} = \frac{1}{1 + 1.70} = 37.0\%$$

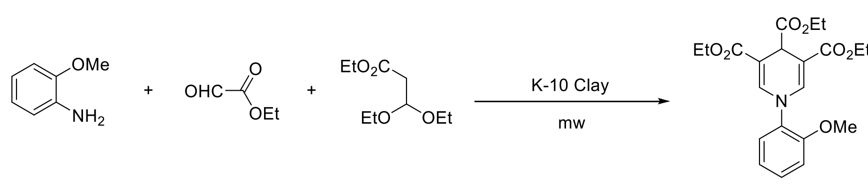
Power demands **(E)**

Item	Heating	Heat preservation	Stirring
Power (W)	–	1	2.5
Time (h)	–	9	9
$E_{line\ power}$ (W·h)	24*	9	22.5

*The heating time was estimated according to previous calculation.

$$\mathbf{E} = \frac{24 + 9 + 22.5}{1.2\ \text{mmol} \times 0.71\ \text{(yield)}} = 65\ \text{W·h·mmol}^{-1}$$

Reddy's work[11b]



S 6.3

(MW: 123.16) 0.98 mmol 120.70 mg	(MW: 102.09) 1.00 mmol 102.09 mg	(MW: 190.24) 2.40 mmol 456.58 mg	K-10 Clay 120.61 mg	(MW: 403.43) 0.608 mmol 245.12 mg, 62%

$$\boldsymbol{E}\ \textbf{factor} = \frac{120.70 + 102.09 + 456.58 + 120.61 - 245.12}{245.12}$$

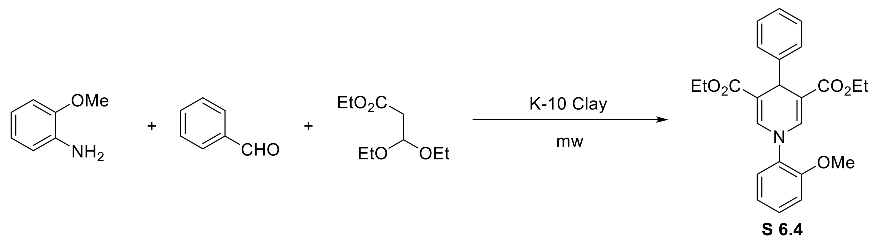
$$= 2.26\ kg\ waste/1kg\ product$$

$$\boldsymbol{RME} = \frac{1}{1 + 2.26} = 30.7\%$$

***Power demands* (E)**

Item	Irradiation	Stirring
Power (W)	250	2.5
Time (h)	1/30	5/12
$E_{line\ power}$ (W·h)	8.33	1.04

$$\mathbf{E} = \frac{8.33 + 1.04}{0.98\ \text{mmol} \times 0.62\ \text{(yield)}} = 15\ \text{W·h·mmol}^{-1}$$



(MW: 123.16) 0.98 mmol 120.70 mg	(MW: 106.12) 1.0 mmol 106.12 mg	(MW: 190.24) 2.40 mmol 456.58 mg	K-10 Clay 120.61 mg	(MW: 407.47) 0.706 mmol 287.67 mg, 72%

$$\boldsymbol{E}\ \textbf{factor} = \frac{120.70 + 106.12 + 456.58 + 120.61 - 287.67}{287.67}$$

$$= 1.79\ kg\ waste/1kg\ product$$

$$\boldsymbol{RME} = \frac{1}{1 + 1.79} = 35.8\%$$

***Power demands* (E)**

Item	Irradiation	Stirring
Power (W)	250	2.5
Time (h)	1/30	1/3
$E_{line\ power}$ (W·h)	8.33	0.83

$$\mathbf{E} = \frac{8.33 + 0.83}{0.98\ \text{mmol} \times 0.72\ \text{(yield)}} = 13\ \text{W·h·mmol}^{-1}$$

Table S5 The green metrics assessment results of different strategies

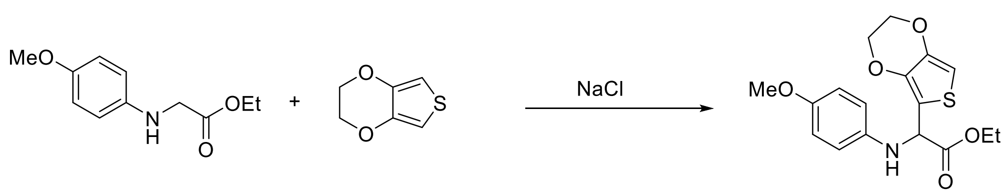
	Compounds	*E*-factor (kg/kg)	RME (%)	E (W·h·mmol^{-1})
This work	**3aa**	1.16	46.3	71
	11a	0.54	64.9	55
Pal's work	**S6.1**	1.79	35.8	71

	S6.2	1.70	37.0	65
Reddy's work	**S6.3**	2.26	30.7	15
	S6.4	1.79	35.8	13

As shown in Table S5. Reddy's work has advantage in terms of power demands due to its short energy input time (2 min). Nevertheless, column chromatography was not required for the purification of **3aa**, that would save considerable time, energy and solvents. It should be noted that Reddy's and Pal's Hantzsch strategies have worse performance on *E*-factor and RME, since the use of ethyl 3,3-diethoxypropanoate instead of ethyl glyoxylate (which is labile and needs to be kept in toluene) as substrate has largely reduced the atom economy. In contrast, our cascade CDC strategy could give products by losing H_2O as only waste. Moreover, the Hantzsch strategies require heating-up process (conventional heating or microwave irradiation), while our protocol can be carried out at room temperature (the stainless-steel vessel internal temperature was mensurated by IR thermometer and showed no higher than 30 °C after pre-grinding at 30 Hz for 30 min).

6.6 Comparison of the greenness for the synthesis of *α*-substituted glycine ester

This work (NaCl, recovered and reused for 5 times, see section 3.8)



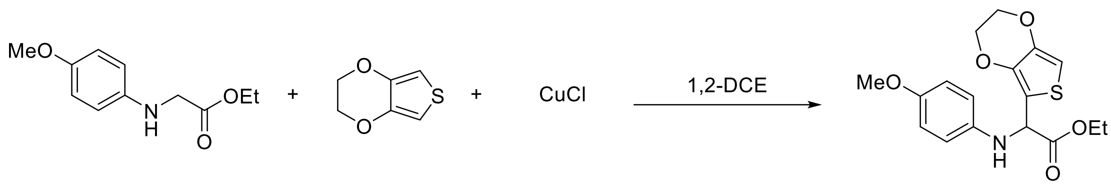
1a	**6h**		**7ah**
(MW: 209.24) 0.5 mmol 104.62 mg	(MW: 142.17) 0.5 mmol 71.09 mg	51 mg	(MW: 349.40) 0.35 mmol 122.29 mg, 70%

$$\boldsymbol{E}\ \textbf{factor} = \frac{104.62 + 71.09 + 51 - 122.29}{122.29}$$

$$= 0.85\ kg\ waste/1kg\ product$$

$$\boldsymbol{RME} = \frac{1}{1 + 0.85} = 53.9\%$$

Chandrasekharam's work[12]



1a	6h			7ah
(MW: 209.24) 0.5 mmol 104.62 mg	(MW: 142.17) 0.5 mmol 71.09 mg	(MW: 99) 0.05 mmol 4.95 mg	2 mL 2514 mg	(MW: 349.40) 0.30 mmol 104.82 mg, 60%

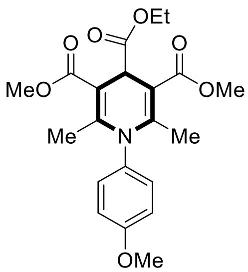
$$\boldsymbol{E}\ \mathbf{factor} = \frac{104.62 + 71.09 + 4.95 + 2514 - 104.82}{104.82}$$

$$= 24.71\ kg\ waste/1kg\ product$$

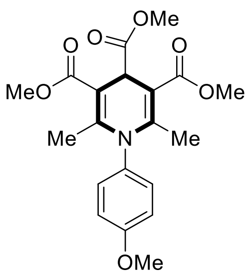
$$\boldsymbol{RME} = \frac{1}{1 + 24.71} = 3.9\%$$

7. Characterization data

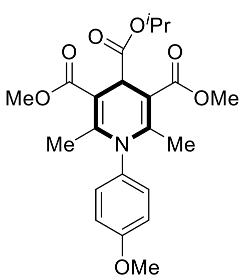
7.1 Characterization data for products 3, 5, 7, 8, 9 and 11



4-Ethyl 3,5-dimethyl 1-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,4,5-tricarboxylate (**3aa**)[8]
Yellow solid (143.8 mg, 71% yield); mp 101−103 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.07 (d, *J* = 8.8 Hz, 1H), 6.92 (d, *J* = 8.8 Hz, 1H), 4.86 (s, 1H), 4.14 (q, *J* = 7.1 Hz, 1H), 3.84 (s, 3H), 3.75 (s, 6H), 2.06 (s, 6H), 1.24 (t, *J* = 7.1 Hz, 1H).

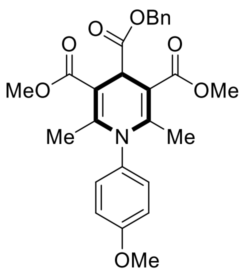


Trimethyl 1-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,4,5-tricarboxylate (**3ba**)
Yellow oil (150.0 mg, 77% yield); **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.03 (d, *J* = 8.9 Hz, 2H), 6.88 (d, *J* = 8.9 Hz, 2H), 4.86 (s, 1H), 3.80 (s, 3H), 3.71 (s, 6H), 3.65 (s, 3H), 2.03 (s, 6H). **^{13}C NMR** (125 MHz, Chloroform-*d*) δ 174.0, 167.6 (2C), 159.4, 149.8 (2C), 132.4, 131.2 (2C), 114.4 (2C), 100.4 (2C), 55.4, 52.0, 51.4 (2C), 39.5, 18.0 (2C). **HRMS (ESI)** *m/z* calcd for $C_{20}H_{24}NO_7$ $[M+H]^+$, 390.1547, found 390.1537.

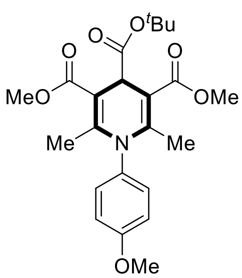


4-Isopropyl 3,5-dimethyl 1-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,4,5-tricarboxylate (**3ca**)
Yellow oil (167.9 mg, 81% yield); **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.06 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 4.90–5.00 (m, 1H), 4.77 (s, 1H), 3.82 (s, 3H), 3.72 (s, 6H), 2.03 (s, 6H), 1.20 (d, *J* = 6.2 Hz, 6H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 173.1, 167.9 (2C), 159.4, 149.5 (2C), 132.6, 131.2 (2C), 114.4

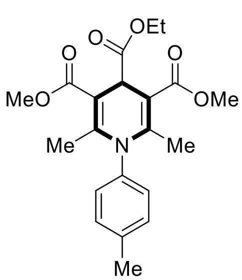
(2C), 100.8 (2C), 67.8, 55.4, 51.3 (2C), 40.1, 21.7 (2C), 18.1 (2C). **HRMS (ESI)** *m/z* calcd for $C_{22}H_{28}NO_7$ $[M+H]^+$, 418.1860, found 418.1851.



4-Benzyl 3,5-dimethyl 1-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,4,5-tricarboxylate (**3da**)
Pale yellow oil (141.6 mg, 61% yield); **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.33–7.28 (m, 5H), 6.91–6.80 (m, 4H), 5.14 (s, 2H), 4.96 (s, 1H), 3.82 (s, 3H), 3.72 (s, 6H), 2.04 (s, 6H). **^{13}C NMR** (125 MHz, Chloroform-*d*) δ 173.2, 167.7 (2C), 159.4, 150.0 (2C), 136.4, 132.4, 131.2 (2C), 128.4 (2C), 127.9, 127.7 (2C), 114.4 (2C), 100.4 (2C), 66.3, 55.5, 51.4 (2C), 39.8, 18.1 (2C). **HRMS (ESI)** *m/z* calcd for $C_{26}H_{28}NO_7$ $[M+H]^+$, 466.1860, found 466.1864.

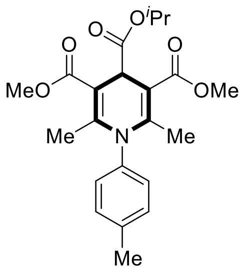


4-(Tert-butyl) 3,5-dimethyl 1-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,4,5-tricarboxylate (**3ea**)
Yellowish solid (118.6 mg, 55% yield); mp 120−123 °C; **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.02 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 9.0 Hz, 2H), 4.73 (s, 1H), 3.80 (s, 3H), 3.72 (s, 6H), 2.03 (s, 6H), 1.39 (s, 9H). **^{13}C NMR** (125 MHz, Chloroform-*d*) δ 172.5, 168.0 (2C), 159.4, 149.0 (2C), 132.7, 131.2 (2C), 114.4 (2C), 101.2 (2C), 80.2, 55.4, 51.2 (2C), 40.7, 27.9 (3C), 18.0 (2C). **HRMS (ESI)** *m/z* calcd for $C_{23}H_{27}NO_7$ $[M+H]^+$, 432.2017, found 432.2014.

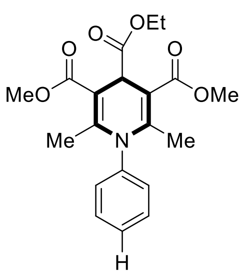


4-Ethyl 3,5-dimethyl 2,6-dimethyl-1-(p-tolyl)-1,4-dihydropyridine-3,4,5-tricarboxylate (**3fa**)[8]

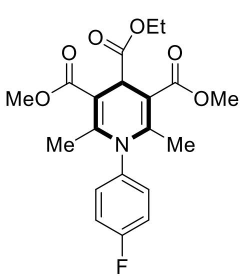
Colorless oil (125.1 mg, 65% yield); **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 7.22 (d, *J* = 8.2 Hz, 2H), 7.03 (d, *J* = 8.2 Hz, 2H), 4.86 (s, 1H), 4.14 (q, *J* = 7.1 Hz, 3H), 3.75 (s, 6H), 2.39 (s, 3H), 2.05 (s, 6H), 1.24 (t, *J* = 7.1 Hz, 3H).



4-Isopropyl 3,5-dimethyl 2,6-dimethyl-1-(p-tolyl)-1,4-dihydropyridine-3,4,5-tricarboxylate (**3ga**)
Yellow oil (142.3 mg, 71% yield); **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.19 (d, *J* = 8.0 Hz, 2H), 7.01 (d, *J* = 8.0 Hz, 2H), 4.99–4.92 (m, 1H), 4.78 (s, 1H), 3.71 (s, 6H), 2.36 (s, 3H), 1.19 (d, *J* = 6.3 Hz, 6H). **^{13}C NMR** (125 MHz, Chloroform-*d*) δ 173.1, 167.9 (2C), 149.2 (2C), 138.6, 137.4, 129.9 (4C), 100.8 (2C), 67.8, 51.2 (2C), 40.2, 21.6 (2C), 21.0, 18.1 (2C). **HRMS (ESI)** *m/z* calcd for $C_{22}H_{27}NNaO_6$ $[M+Na]^+$, 424.1731, found 424.1738.

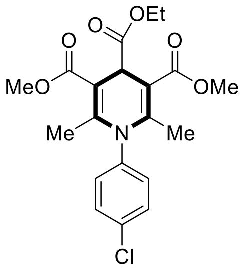


4-Ethyl 3,5-dimethyl 2,6-dimethyl-1-phenyl-1,4-dihydropyridine-3,4,5-tricarboxylate (**3ha**)[13]
Colorless oil (144.2 mg, 78% yield); **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.46–7.40 (m, 3H), 7.19–7.15 (m, 2H), 4.87 (s, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.75 (s, 6H), 2.05 (s, 6H), 1.25 (t, *J* = 7.1 Hz, 3H).

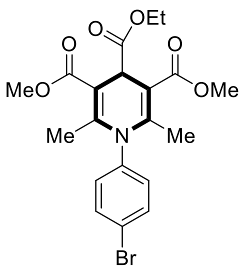


4-Ethyl 3,5-dimethyl 1-(4-fluorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,4,5-tricarboxylate (**3ia**)
Yellow oil (125.7 mg, 64% yield); **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.19–7.08 (m, 4H), 4.84 (s, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.74 (s, 6H), 2.04 (s, 6H), 1.24 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (125 MHz, Chloroform-*d*) δ 173.5, 167.7 (2C), 162.3 (d, J_1 = 248.2 Hz, 2C), 149.0 (2C), 136.0 (d, J_4 = 3.5 Hz, 2C), 132.1 (d, J_3 =

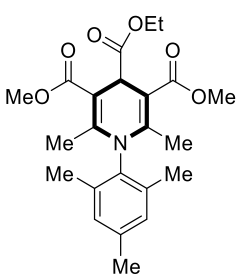
8.6 Hz, 2C), 116.4 (d, J_2 = 22.7 Hz, 2C), 101.3 (2C), 60.8, 51.5 (2C), 39.9, 18.1 (2C), 14.2. **^{19}F NMR** (400 MHz, Chloroform-*d*) δ -111.73. **HRMS (ESI)** *m/z* calcd for $C_{20}H_{22}{}^{19}FNO_6$ $[M+H]^+$, 392.1504, found 392.1496.



4-Ethyl 3,5-dimethyl 1-(4-chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,4,5-tricarboxylate (**3ja**)[13]
Yellow oil (93.8 mg, 46% yield); **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 7.41 (d, *J* = 8.6 Hz, 2H), 7.14 (d, *J* = 8.6 Hz, 2H), 4.85 (s, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.75 (s, 6H), 2.05 (s, 6H), 1.28 (t, *J* = 7.1 Hz, 3H).

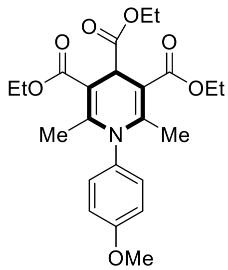


4-Ethyl 3,5-dimethyl 1-(4-bromophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,4,5-tricarboxylate (**3ka**)
Yellow oil (141.6 mg, 63% yield); **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.58–7.55 (m, 2H), 7.10–7.04 (m, 2H), 4.84 (s, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.75 (s, 6H), 2.04 (s, 6H), 1.24 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (125 MHz, Chloroform-*d*) δ 173.5, 167.7 (2C), 148.6 (2C), 139.2, 132.7 (2C), 132.1 (2C), 122.9, 101.4 (2C), 60.8, 51.5 (2C), 40.0, 18.1 (2C), 14.2. **HRMS (ESI)** *m/z* calcd for $C_{20}H_{22}{}^{79}BrNNaO_7$ $[M+Na]^+$, 474.0523, found 474.0531.

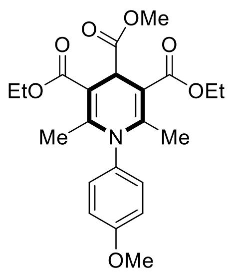


4-ethyl 3,5-dimethyl 1-mesityl-2,6-dimethyl-1,4-dihydropyridine-3,4,5-tricarboxylate (**3na**)
Yellow oil (124.6 mg, 60% yield); **^{1}H NMR** (400 MHz, Chloroform-d) δ 6.92 (s, 2H), 4.90 (s, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.74 (s, 6H), 2.30 (s, 3H), 2.06 (d, *J* = 5.2 Hz, 6H), 1.95 (s, 6H), 1.21 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, Chloroform-d) δ 173.8, 168.3 (2C), 138.6, 136.9 (2C), 136.8 (2C), 135.5, 129.5, 129.2,

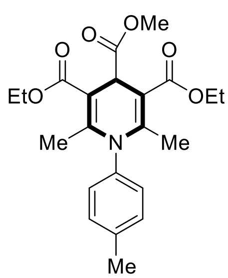
100.0 (2C), 60.6, 51.3 (2C), 40.3, 21.0, 17.80, 17.7, 16.9 (2C), 14.2. **HRMS (ESI)** *m/z* calcd for $C_{23}H_{30}NO_6$ $[M+H]^+$, 416.2078, found 416.2073.



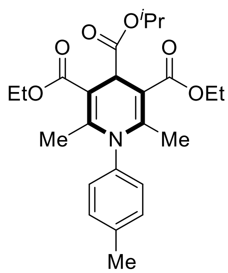
Triethyl 1-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,4,5-tricarboxylate (**3ab**)[8]
Yellowish solid (183.2 mg, 85% yield); mp 104−105 °C (lit. mp 106−107 °C); **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.07 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 4.84 (s, 1H), 4.26–4.10 (m, 6H), 3.82 (s, 3H), 2.04 (s, 6H), 1.28 (t, *J* = 7.1 Hz, 6H), 1.23 (t, *J* = 7.1 Hz, 3H).



3,5-Diethyl 4-methyl 1-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,4,5-tricarboxylate (**3bb**)
Yellow solid (136.3 mg, 65% yield); mp 96−101 °C; **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.06 (d, *J* = 8.9 Hz, 2H), 6.90 (d, *J* = 8.9 Hz, 2H), 4.87 (s, 1H), 4.26–4.13 (m, 4H), 3.82 (s, 3H), 3.67 (s, 3H), 2.04 (s, 6H), 1.27 (t, *J* = 7.1 Hz, 6H). **^{13}C NMR** (125 MHz, Chloroform-*d*) δ 174.4, 167.4 (2C), 159.4, 149.3 (2C), 132.6, 131.3 (2C), 114.4 (2C), 100.9 (2C), 60.1 (2C), 55.4, 51.9, 39.8, 18.1 (2C), 14.2 (2C). **HRMS (ESI)** *m/z* calcd for $C_{22}H_{27}NNaO_7$ $[M+Na]^+$, 440.1680, found 440.1691.

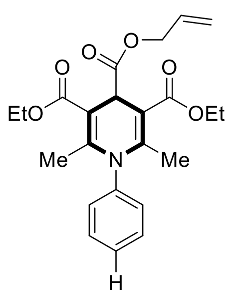


3,5-Diethyl 4-methyl 2,6-dimethyl-1-(p-tolyl)-1,4-dihydropyridine-3,4,5-tricarboxylate (**3lb**)[8]
Yellow oil (157.5 mg, 78% yield); **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.23–7.19 (m, 2H), 7.06–7.01 (m, 2H), 4.89 (s, 1H), 4.27–4.15 (m, 4H), 3.69 (s, 3H), 2.39 (s, 3H), 2.04 (s, 6H), 1.29 (t, *J* = 7.1 Hz, 6H).



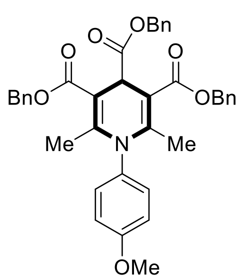
3,5-Diethyl 4-isopropyl 2,6-dimethyl-1-(p-tolyl)-1,4-dihydropyridine-3,4,5-tricarboxylate (**3gb**)[8]

Yellow oil (144.7 mg, 67% yield); **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.22–7.18 (m, 2H), 7.07 – 7.02 (m, 2H), 5.03–4.93 (m, 1H), 4.81 (s, 1H), 4.26–4.14 (m, 4H), 2.38 (s, 3H), 2.03 (s, 6H), 1.30 (t, *J* = 7.1 Hz, 6H), 1.22 (d, *J* = 6.3 Hz, 6H).



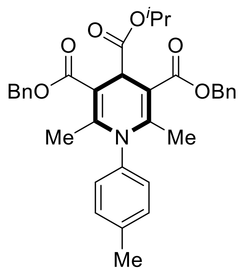
4-Allyl 3,5-diethyl 2,6-dimethyl-1-phenyl-1,4-dihydropyridine-3,4,5-tricarboxylate (**3mb**)

Pale yellow solid (125.6 mg, 63% yield); mp 70−72 °C; **^{1}H NMR** (400 MHz, DMSO-*d*$_6$) δ 7.58–7.43 (m, 3H), 7.26 (d, *J* = 6.3 Hz, 2H), 5.94–5.81 (m, 1H), 5.26–5.14 (m, 2H), 4.84 (s, 1H), 4.56 (d, *J* = 4.5 Hz, 2H), 4.19–4.06 (m, 4H), 1.97 (s, 6H), 1.20 (t, *J* = 6.9 Hz, 6H). **^{13}C NMR** (150 MHz, DMSO-*d*$_6$) δ 172.3, 166.5 (2C), 148.4 (2C), 139.4, 132.7, 130.2, 129.6 (2C), 129.0 (2C), 116.5, 100.2 (2C), 64.4, 59.8 (2C), 17.7 (2C), 14.2 (2C). **HRMS (ESI)** *m/z* calcd for $C_{23}H_{27}NNaO_6$ $[M+Na]^+$, 436.1730, found 436.1736.

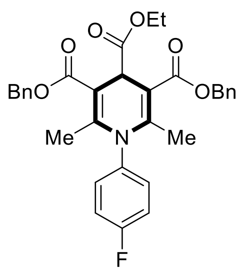


Tribenzyl 1-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,4,5-tricarboxylate (**3dc**)

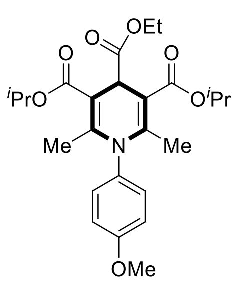
Yellow oil (177.0 mg, 57% yield); **^{1}H NMR** (400 MHz, DMSO-*d*$_6$) δ 7.37–7.08 (m, 17H), 6.93 (d, *J* = 6.4 Hz, 2H), 5.11 (s, 4H), 5.04 (s, 2H), 4.99 (s, 1H), 3.75 (s, 3H), 1.95 (s, 6H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 173.4, 167.1 (2C), 159.5, 150.5 (2C), 136.6 (2C), 136.3, 132.3, 128.5, 128.5 (4C), 128.4 (2C), 128.0 (2C), 127.9 (2C), 127.8 (2C), 127.7 (4C), 114.5 (2C), 100.5 (2C), 66.5, 66.0 (2C), 55.5, 39.8, 18.3 (2C). **HRMS (ESI)** *m/z* calcd for $C_{38}H_{35}NNaO_7$ $[M+Na]^+$, 640.2306, found 640.2325.



3,5-Dibenzyl 4-isopropyl 2,6-dimethyl-1-(p-tolyl)-1,4-dihydropyridine-3,4,5-tricarboxylate (**3gc**)
Yellow oil (187.7 mg, 68% yield); **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.41–7.30 (m, 10H), 7.22 (d, *J* = 8.2 Hz, 2H), 7.06 (d, *J* = 8.2 Hz, 2H), 5.24–5.15 (m, 4H), 5.00 (s, 1H), 4.93 (h, *J* = 6.2 Hz, 1H), 2.39 (s, 3H), 2.08 (s, 6H), 1.09 (d, *J* = 6.2 Hz, 6H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 173.2, 167.1 (2C), 149.8 (2C), 138.7, 137.3, 136.5 (2C), 130.0 (2C), 129.9 (2C), 128.4 (4C), 127.7 (2C), 127.6 (4C), 100.6 (2C), 68.0, 65.8 (2C), 40.0, 21.6 (2C), 21.1, 18.2 (2C). **HRMS (ESI)** *m/z* calcd for $C_{34}H_{35}NNaO_6$ [M+Na]$^+$, 576.2357, found 576.2360.

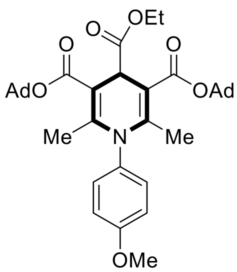


3,5-Dibenzyl 4-ethyl 1-(4-fluorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,4,5-tricarboxylate (**3ic**)
Yellow oil (212.3 mg, 78% yield); **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.40–7.35 (m, 4H), 7.35–7.29 (m, 6H), 7.22–7.16 (m, 2H), 7.15–7.09 (m, 2H), 5.26–5.14 (m, 4H), 5.01 (s, 1H), 4.05 (q, *J* = 7.1 Hz, 2H), 2.07 (s, 6H), 1.11 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 173.6, 166.8 (2C), 162.2 (d, J_1 = 248.3 Hz, 2C), 149.4 (2C), 136.4 (2C), 135.8 (d, J_4 = 3.6 Hz, 2C), 132.0 (d, J_3 = 8.6 Hz, 2C), 128.3 (4C), 127.7 (2C), 127.6 (4C), 116.43 (d, J_2 = 22.6 Hz, 2C), 101.2 (2C), 65.9 (2C), 60.7, 39.8, 18.1 (2C), 14.0. **^{19}F NMR** (400 MHz, Chloroform-*d*) δ -111.66. **HRMS (ESI)** *m/z* calcd for $C_{32}H_{30}{}^{19}FNNaO_6$ [M+Na]$^+$, 566.1949, found 566.1976.



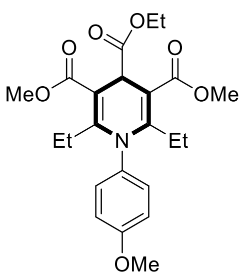
4-Ethyl 3,5-diisopropyl 1-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,4,5-tricarboxylate (**3ad**)[8]

Yellow oil (168.1 mg, 73% yield); **^{1}H NMR** (600 MHz, Chloroform-d) δ 7.08–7.05 (m, 2H), 6.91–6.88 (m, 2H), 5.09–5.02 (m, 2H), 4.83 (s, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.81 (s, 3H), 2.02 (s, 6H), 1.27–1.22 (m, 15H).



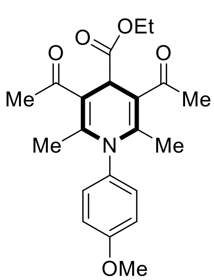
3,5-Di(adamantan-1-yl) 4-ethyl 1-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,4,5-tricarboxylate (**3ae**)

Yellow solid (198.6 mg, 62% yield); mp 201−207 °C; **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.04 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 4.75 (s, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.78 (s, 3H), 2.13 (s, 18H), 1.96 (s, 6H), 1.67–1.59 (m, 12H), 1.24 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (125 MHz, Chloroform-*d*) δ 174.0, 166.5 (2C), 159.2, 148.1 (2C), 132.9, 131.3 (2C), 114.1 (2C), 102.4 (2C), 79.9 (2C), 60.3, 55.3, 41.4 (6C), 40.7, 36.2 (6C), 30.7 (6C), 17.9 (2C), 14.3. **HRMS (ESI)** *m/z* calcd for $C_{39}H_{50}NO_7$ $[M+H]^+$, 644.3582, found 644.3587.



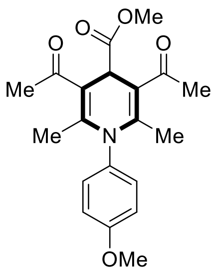
4-Ethyl 3,5-dimethyl 2,6-diethyl-1-(4-methoxyphenyl)-1,4-dihydropyridine-3,4,5-tricarboxylate (**3af**)

Yellow oil (148.2 mg, 69% yield); **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.20 (d, *J* = 8.1 Hz, 2H), 6.92–6.89 (m, 2H), 4.84 (s, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.83 (s, 3H), 3.74 (s, 6H), 2.73–2.66 (m, 2H), 2.43–2.35 (m, 2H), 1.22 (t, *J* = 7.1 Hz, 3H), 0.91 (t, *J* = 7.3 Hz, 6H). **^{13}C NMR** (125 MHz, Chloroform-*d*) δ 173.9, 167.1 (2C), 159.5, 156.4 (2C), 132.0 (2C), 131.3, 114.2 (2C), 100.9 (2C), 60.6, 55.4, 51.3 (2C), 39.4, 23.3 (2C), 14.2, 13.4 (2C). **HRMS (ESI)** *m/z* calcd for $C_{23}H_{29}NNaO_7$ $[M+Na]^+$, 454.1836, found 454.1852.

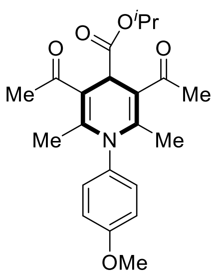


Ethyl 3,5-diacetyl-1-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-4-carboxylate (**3ag**)[8]

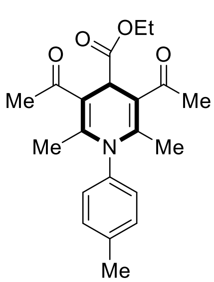
Yellow oil (116.2 mg, 63% yield); **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.06 (d, *J* = 8.7 Hz, 2H), 6.92 (d, *J* = 8.7 Hz, 2H), 4.72 (s, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.84 (s, 3H), 2.41 (s, 6H), 2.01 (s, 6H), 1.25 (t, *J* = 7.1 Hz, 3H).



Methyl 3,5-diacetyl-1-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-4-carboxylate (**3bg**)
Yellow oil (107.7 mg, 60% yield); **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.06 (d, *J* = 8.6 Hz, 2H), 6.93 (d, *J* = 9.0 Hz, 2H), 4.77 (s, 1H), 3.84 (s, 3H), 3.70 (s, 3H), 2.41 (s, 6H), 2.02 (s, 6H). **^{13}C NMR** (125 MHz, Chloroform-*d*) δ 197.9 (2C), 173.5, 159.6, 148.6 (2C), 132.3, 131.1 (2C), 114.6 (2C), 110.2 (2C), 55.5, 52.2, 40.8, 30.2 (2C), 18.9 (2C). **HRMS (ESI)** *m/z* calcd for $C_{20}H_{23}NNaO_5$ $[M+Na]^+$, 380.1468, found 380.1471.

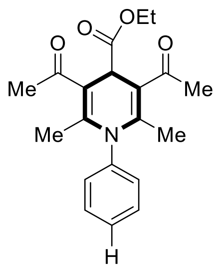


Isopropyl 3,5-diacetyl-1-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-4-carboxylate (**3cg**)
Yellow oil (132.7 mg, 69% yield); **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.07 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 5.01–4.95 (m, 1H), 4.66 (s, 1H), 3.84 (s, 3H), 2.41 (s, 6H), 2.01 (s, 6H), 1.23 (d, *J* = 6.3 Hz, 6H). **^{13}C NMR** (125 MHz, Chloroform-*d*) δ 198.0 (2C), 172.5, 159.6, 148.4 (2C), 132.4, 131.2 (2C), 114.6 (2C), 110.3 (2C), 68.6, 55.5, 41.3, 30.1 (2C), 21.7 (2C), 18.8 (2C). **HRMS (ESI)** *m/z* calcd for $C_{22}H_{28}NO_5$ $[M+H]^+$, 386.1962, found 386.1957.

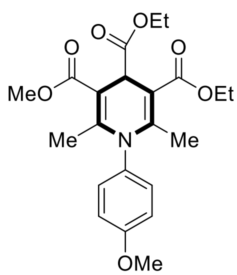


Ethyl 3,5-diacetyl-2,6-dimethyl-1-(p-tolyl)-1,4-dihydropyridine-4-carboxylate (**3fg**)[14]

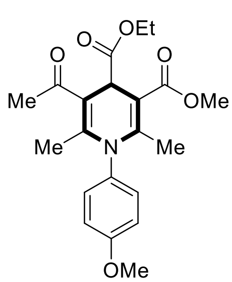
Yellow oil (101.3 mg, 57% yield); **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.22 (d, *J* = 8.0 Hz, 2H), 7.02 (d, *J* = 8.0 Hz, 2H), 4.73 (s, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 2.41 (s, 6H), 2.39 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H).



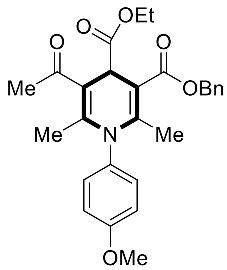
Ethyl 3,5-diacetyl-2,6-dimethyl-1-phenyl-1,4-dihydropyridine-4-carboxylate (**3hg**)[14]
Yellowish solid (52.4 mg, 31% yield); mp 76−80 °C (lit. mp 77−80 °C); **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.49–7.40 (m, 3H), 7.21–7.15 (m, 2H), 4.74 (s, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 2.42 (s, 6H), 2.01 (s, 6H), 1.27 (t, *J* = 7.1 Hz, 3H).



3,4-Diethyl 5-methyl 1-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,4,5-tricarboxylate (**3aab**)
Yellow oil (70.1 mg, 34% yield); **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.11–7.03 (m, 2H), 6.96–6.88 (m, 2H), 4.85 (s, 1H), 4.28–4.11 (m, 4H), 3.84 (s, 3H), 3.75 (s, 3H), 2.06 (s, 3H), 2.05 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.24 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (125 MHz, Chloroform-*d*) δ 173.7, 168.0, 167.4, 159.4, 149.7, 149.2, 132.7, 131.3 (2C), 114.4 (2C), 101.2, 100.6, 60.6, 60.1, 55.4, 51.4, 40.0, 18.2, 18.1, 14.3, 14.2. **HRMS (ESI)** *m/z* calcd for $C_{22}H_{27}NNaO_7$ $[M+Na]^+$, 440.1680, found 440.1689.

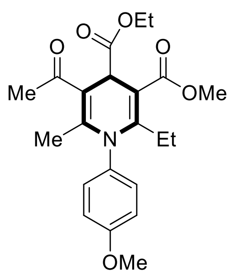


4-Ethyl 3-methyl 5-acetyl-1-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,4-dicarboxylate (**3aag**)[8]
Yellow oil (91.7 mg, 48% yield); **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.11–7.01 (m, 2H), 6.94–6.90 (m, 2H), 4.77 (s, 1H), 4.19–4.10 (m, 2H), 3.84 (s, 3H), 3.75 (s, 3H), 2.42 (s, 3H), 2.09 (s, 3H), 1.98 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H).



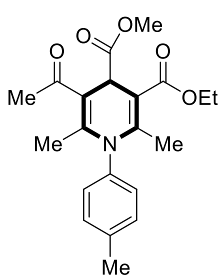
3-Benzyl 4-ethyl 5-acetyl-1-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,4-dicarboxylate (**3acg**)

Yellow oil (65.4 mg, 28% yield); **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.38–7.32 (m, 4H), 7.31–7.27 (m, 1H), 7.06 (d, *J* = 8.9 Hz, 2H), 6.91 (d, *J* = 8.9 Hz, 2H), 5.25 (d, *J* = 12.7 Hz, 1H), 5.18 (d, *J* = 12.7 Hz, 1H), 4.84 (s, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.82 (s, 3H), 2.40 (s, 3H), 2.10 (s, 3H), 1.98 (s, 3H), 1.19 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (125 MHz, Chloroform-*d*) δ 198.8, 173.2, 166.9, 159.5, 150.5, 147.9, 136.5, 132.4, 131.1 (2C), 128.4 (2C), 127.8, 127.7 (2C), 114.5 (2C), 109.6, 100.5, 65.9, 60.9, 55.4, 40.8, 29.7, 18.6, 18.2, 14.1. **HRMS (ESI)** *m/z* calcd for $C_{27}H_{29}NNaO_6$ $[M+Na]^+$, 486.1887, found 486.1892.



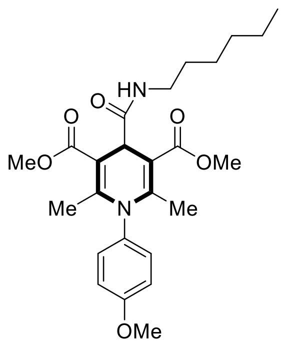
4-Ethyl 3-methyl 5-acetyl-2-ethyl-1-(4-methoxyphenyl)-6-methyl-1,4-dihydropyridine-3,4-dicarboxylate (**3afg**)

Yellow oil (63.4 mg, 32% yield); **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.13 (d, *J* = 8.4 Hz, 2H), 6.94–6.90 (m, 2H), 4.77 (s, 1H), 4.19–4.11 (m, 2H), 3.84 (s, 3H), 3.76 (s, 3H), 2.43 (s, 3H), 2.00 (s, 3H), 1.25 (s, 3H), 0.93 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 198.9, 173.4, 167.0, 159.5, 156.2, 148.7, 132.0, 131.3 (2C), 114.3 (2C), 109.7, 100.2, 60.9, 55.5, 51.5, 40.5, 29.9, 23.3, 18.6, 14.2, 13.4. **HRMS (ESI)** *m/z* calcd for $C_{22}H_{27}NNaO_7$ $[M+Na]^+$, 424.1736, found 424.1731.



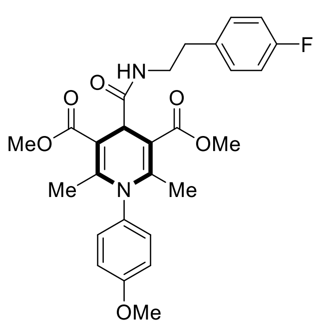
3-Ethyl 4-methyl 5-acetyl-2,6-dimethyl-1-(p-tolyl)-1,4-dihydropyridine-3,4-dicarboxylate (**3lbg**)

Yellow oil (85.5 mg, 46% yield); **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.22 (d, *J* = 8.0 Hz, 2H), 7.02 (d, *J* = 8.0 Hz, 2H), 4.82 (s, 1H), 4.25–4.18 (m, 2H), 3.70 (s, 3H), 2.41 (s, 3H), 2.39 (s, 3H), 2.08 (s, 3H), 1.98 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (125 MHz, Chloroform-*d*) δ 198.7, 173.8, 167.2, 149.5, 147.9, 138.8, 137.2, 130.0 (2C), 130.0 (2C), 109.3, 100.9, 60.3, 52.1, 40.7, 29.8, 21.1, 18.7, 18.2, 14.3. **HRMS (ESI)** *m/z* calcd for $C_{21}H_{25}NO_5$ [M+H]$^+$, 372.1806, found 372.1794.



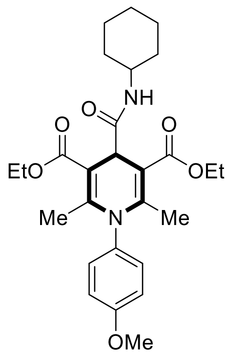
Dimethyl 4-(hexylcarbamoyl)-1-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**5aa**)

Yellow oil (137.4 mg, 60% yield); **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.15 (d, J = 8.4 Hz, 2H), 6.92–6.87 (m, 2H), 6.29 (t, J = 5.4 Hz, 1H), 4.43 (s, 1H), 3.81 (s, 3H), 3.71 (s, 6H), 3.23–3.18 (m, 2H), 2.03 (s, 6H), 1.50–1.44 (m, 2H), 1.29–1.24 (m, 6H), 0.86–0.83 (m, 3H). **^{13}C NMR** (125 MHz, Chloroform-*d*) δ 173.0, 168.2 (2C), 159.4, 150.4 (2C), 132.8, 131.3 (2C), 114.3 (2C), 101.2 (2C), 55.4, 51.4 (2C), 40.8, 39.4, 31.4, 29.6, 26.4, 22.5, 18.4 (2C), 13.9. **HRMS (ESI)** *m/z* calcd for $C_{25}H_{35}N_2O_6$ [M+H]$^+$, 459.2489, found 459.2476.



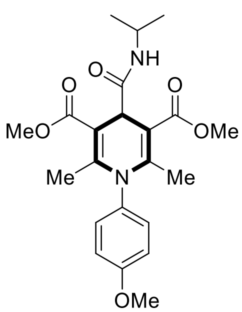
Dimethyl 4-((4-fluorophenethyl)carbamoyl)-1-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**5ba**)

Yellow oil (126.6 mg, 51% yield); **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.16–7.08 (m, 4H), 6.97–6.89 (m, 4H), 6.40 (t, J = 5.7 Hz, 1H), 4.42 (s, 1H), 3.83 (s, 3H), 3.67 (s, 6H), 3.48 (q, J = 6.7 Hz, 2H), 2.78 (t, J = 6.7 Hz, 2H), 2.03 (s, 6H). **^{13}C NMR** (125 MHz, Chloroform-*d*) δ 173.0, 168.1 (2C), 161.4 (d, J_1 = 242.4 Hz), 159.4, 150.4 (2C), 134.8 (d, J_4 = 2.3 Hz), 132.7, 131.2 (2C), 130.1 (d, J_3 = 7.6 Hz, 2C), 115.1 (d, J_2 = 21.1 Hz, 2C), 114.4 (2C), 101.0 (2C), 55.4, 51.4 (2C), 40.5, 40.5, 34.8, 18.4 (2C). **^{19}F NMR** (600 MHz, Chloroform-*d*) δ -117.09. **HRMS (ESI)** *m/z* calcd for $C_{27}H_{30}FN_2O_6$ [M+H]$^+$, 497.2082, found 497.2068.



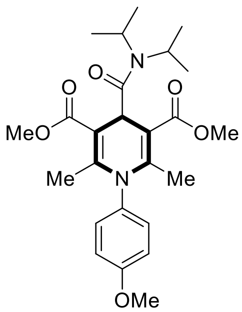
Diethyl 4-(cyclohexylcarbamoyl)-1-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**5cb**)

Yellow oil (146.2 mg, 60% yield); **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 7.17 (brs, 2H), 6.92–6.87 (m, 2H), 6.18 (d, *J* = 8.2 Hz, 1H), 4.38 (s, 1H), 4.21–4.14 (m, 4H), 3.81 (s, 3H), 3.73–3.68 (m, 1H), 2.03 (s, 6H), 1.89–1.85 (m, 2H), 1.71–1.63 (m, 3H), 1.59–1.55 (m, 1H), 1.41 (s, 1H), 1.28 (t, *J* = 7.1 Hz, 6H), 1.19 –1.12 (m, 3H). **^{13}C NMR** (150 MHz, Chloroform-*d*) δ 172.3, 167.8 (2C), 159.3, 150.1 (2C), 133.0, 131.3 (2C), 114.3 (2C), 101.4 (2C), 60.2 (2C), 55.4, 47.9, 41.3, 33.0 (2C), 25.6 (2C), 24.7, 18.4 (2C), 14.4 (2C). **HRMS (ESI)** *m/z* calcd for $C_{27}H_{36}N_2NaO_6$ $[M+Na]^+$, 507.2471, found 507.2465.



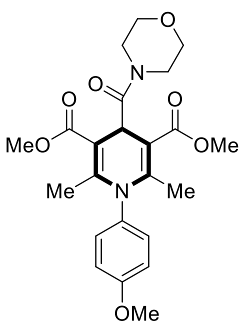
Dimethyl 4-(isopropylcarbamoyl)-1-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**5da**)

Yellow oil (118.7 mg, 57% yield); **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.17 (brd, 2H), 6.90 (d, *J* = 9.0 Hz, 2H), 6.08 (d, *J* = 7.7 Hz, 1H), 4.38 (s, 1H), 4.03–3.96 (m, 1H), 3.82 (s, 3H), 3.73 (s, 6H), 2.04 (s, 6H), 1.13 (d, *J* = 6.5 Hz, 6H). **^{13}C NMR** (125 MHz, Chloroform-*d*) δ 172.2, 168.1 (2C), 159.4, 150.4 (2C), 132.87, 131.3 (2C), 116.4 (2C), 101.3 (2C), 55.7, 55.4 (2C), 51.4, 41.1, 22.7 (2C), 18.4 (2C). **HRMS (ESI)** *m/z* calcd for $C_{22}H_{29}N_2O_6$ $[M+H]^+$, 417.2020, found 417.1993.



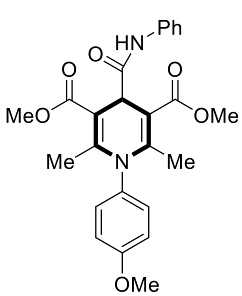
Dimethyl 4-(diisopropylcarbamoyl)-1-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**5ea**)

Yellow oil (185.7 mg, 81% yield); **^{1}H NMR** (500 MHz, DMSO-d_6) δ 7.36 (d, J = 9.0 Hz, 2H), 7.05 (d, J = 9.0 Hz, 2H), 4.95 (s, 1H), 4.60–4.52 (m, 1H), 3.80 (s, 3H), 3.64 (s, 6H), 3.44–3.36 (m, 1H), 1.94 (s, 6H), 1.26 (d, J = 6.7 Hz, 6H), 1.14 (d, J = 6.5 Hz, 6H). **^{13}C NMR** (125 MHz, Chloroform-d) δ 172.3, 168.1 (2C), 159.2, 150.2 (2C), 133.3, 131.5 (2C), 114.2 (2C), 101.6 (2C), 55.4, 51.2 (2C), 45.7, 37.4, 21.2, 20.7, 18.5 (2C). **HRMS (ESI)** *m/z* calcd for $C_{25}H_{34}N_2NaO_6$ $[M+Na]^+$, 481.2309, found 481.2331.



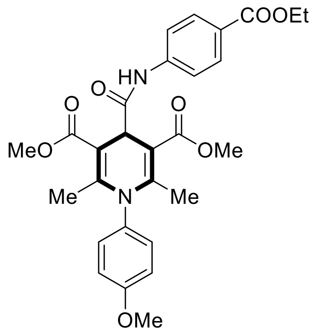
Dimethyl 1-(4-methoxyphenyl)-2,6-dimethyl-4-(morpholine-4-carbonyl)-1,4-dihydropyridine-3,5-dicarboxylate (**5fa**)

Yellow oil (155.6 mg, 70% yield); **^{1}H NMR** (500 MHz, DMSO-d_6) δ 7.38 (d, J = 9.0 Hz, 2H), 7.05 (d, J = 9.0 Hz, 2H), 4.90 (s, 1H), 3.80 (s, 3H), 3.75 (brs, 2H), 3.65 (s, 6H), 3.62 (brs, 2H), 3.56–3.44 (m, 4H), 1.94 (s, 6H). **^{13}C NMR** (150 MHz, Chloroform-d) δ 173.8, 167.8 (2C), 159.4, 151.4 (2C), 133.1, 131.2 (2C), 114.4 (2C), 101.5 (2C), 67.2, 67.0, 55.4, 51.3 (2C), 47.3, 42.7, 35.5, 18.6 (2C). **HRMS (ESI)** *m/z* calcd for $C_{23}H_{39}N_2O_7$ $[M+H]^+$, 445.1969, found 445.1942.



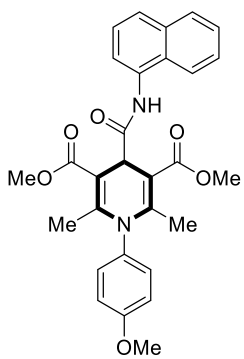
Dimethyl 1-(4-methoxyphenyl)-2,6-dimethyl-4-(phenylcarbamoyl)-1,4-dihydropyridine-3,5-dicarboxylate (**5ga**)

Yellow oil (137.4 mg, 61% yield); **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 8.73 (s, 1H), 7.60–7.57 (m, 2H), 7.32–7.28 (m, 2H), 7.13 (d, *J* = 9.0 Hz, 2H), 7.05 (t, *J* = 7.4 Hz, 1H), 6.91 (d, *J* = 9.0 Hz, 2H), 5.28 (s, 1H), 4.64 (s, 1H), 3.82 (s, 3H), 3.77 (s, 6H), 2.06 (s, 6H). **^{13}C NMR** (125 MHz, Chloroform-*d*) δ 171.0, 168.5 (2C), 159.5, 150.7 (2C), 138.9, 132.5, 131.2 (2C), 128.8 (2C), 123.4, 119.3 (2C), 100.6 (2C), 55.4, 51.7 (2C), 41.7, 18.6 (2C). **HRMS (ESI)** *m/z* calcd for $C_{25}H_{27}N_2O_6$ $[M+H]^+$, 451.1864, found 451.1836.



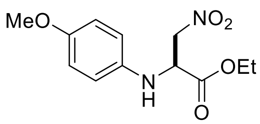
Dimethyl 4-((4-(ethoxycarbonyl)phenyl)carbamoyl)-1-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**5ha**)

Grey solid (216.5 mg, 83% yield); mp 114−117 °C; **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 9.08 (s, 1H), 8.00–7.96 (m, 2H), 7.66–7.62 (m, 2H), 7.13–7.09 (m, 2H), 6.93–6.88 (m, 2H), 4.64 (s, 1H), 4.33 (q, *J* = 7.1 Hz, 2H), 3.82 (s, 3H), 3.77 (s, 6H), 2.05 (s, 6H), 1.37 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (125 MHz, Chloroform-*d*) δ 171.3, 168.6 (2C), 166.2, 159.5, 150.8 (2C), 143.0, 132.4, 131.1 (2C),130.6 (2C), 125.06, 118.5 (2C), 114,5(2C), 100.3 (2C), 60.7, 55.4, 51.8 (2C), 41.8, 18.6 (2C), 14.3. **HRMS (ESI)** *m/z* calcd for $C_{28}H_{31}N_2O_8$ $[M+H]^+$, 523.2075, found 523.2064.



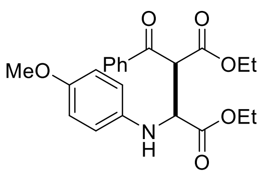
Dimethyl 1-(4-methoxyphenyl)-2,6-dimethyl-4-(naphthalen-1-ylcarbamoyl)-1,4-dihydropyridine-3,5-dicarboxylate (**5ia**)

Maroon oil (100.2 mg, 40% yield); **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 9.14 (s, 1H), 8.24–8.21 (m, 1H), 8.07–8.04 (m, 1H), 7.87–7.84 (m, 1H), 7.63 (d, *J* = 8.1 Hz, 1H), 7.57–7.53 (m, 1H), 7.51–7.45 (m, 2H), 7.18–7.12 (m, 2H), 6.93–6.88 (m, 2H), 4.86 (s, 1H), 3.84–3.82 (m, 9H), 2.09 (s, 6H). **^{13}C NMR** (125 MHz, Chloroform-*d*) δ 171.6, 168.6 (2C), 159.5, 150.8 (2C), 134.1, 133.6, 132.6, 131.3 (2C), 128.7, 126.3, 126.0, 125.9, 125.72, 124.38, 120.78, 118.62, 114.5 (2C), 100.9 (2C), 55.5, 51.8 (2C), 41.8, 18.6 (2C). **HRMS (ESI)** *m/z* calcd for $C_{29}H_{29}N_2O_6$ [M+H]$^+$, 502.2054, found 502.2037.



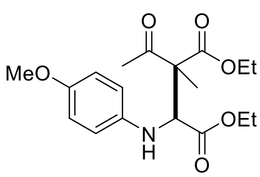
ethyl 2-((4-methoxyphenyl)amino)-3-nitropropanoate (**7aa**)[15]

Yellow oil (87.1 mg, 65% yield); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 6.76 – 6.71 (m, 2H), 6.69 – 6.63 (m, 2H), 5.69 (d, *J* = 8.5 Hz, 1H), 4.97 (dd, *J* = 13.8, 5.2 Hz, 1H), 4.85 (dd, *J* = 13.8, 6.9 Hz, 1H), 4.75 (d, *J* = 6.5 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.64 (s, 3H), 1.16 (t, *J* = 7.1 Hz, 3H).



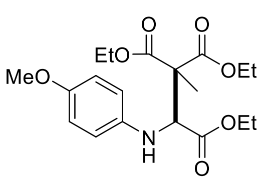
diethyl 2-benzoyl-3-((4-methoxyphenyl)amino)succinate (**7ab**)[16]

Pale yellow oil (123.7 mg, 62% yield); **^{1}H NMR** (600 MHz, Chloroform-d) δ 7.98 – 7.90 (m, 2H), 7.59 – 7.54 (m, 1H), 7.48 – 7.42 (m, 2H), 6.84 – 6.53 (m, 4H), 5.07 – 4.93 (m, 1H), 4.87 – 4.76 (m, 1H), 4.17 – 4.07 (m, 4H), 3.70 (s, 3H), 1.21 – 1.05 (m, 6H).



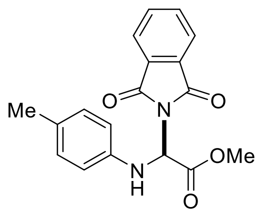
diethyl 2-acetyl-3-((4-methoxyphenyl)amino)-2-methylsuccinate (**7ac**)[16]

Yellow oil (158.1 mg, 90% yield); **^{1}H NMR** (400 MHz, Chloroform-d) δ 6.83 – 6.67 (m, 4H), 4.48 (s, 1H), 4.29 – 4.19 (m, 2H), 4.15 – 4.07 (m, 2H), 3.74 (s, 3H), 2.30 (s, 3H), 1.57 (s, 3H), 1.33 – 1.26 (m, 3H), 1.22 – 1.14 (m, 3H).



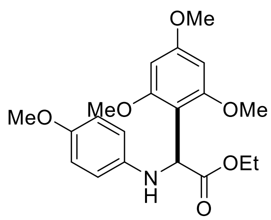
triethyl 1-((4-methoxyphenyl)amino)propane-1,2,2-tricarboxylate (**7ad**)[17]

Yellow oil (152.5 mg, 80% yield); **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 6.83 – 6.67 (m, 4H), 4.48 (s, 1H), 4.27 – 4.09 (m, 6H), 3.73 (s, 3H), 1.63 (s, 3H), 1.31 – 1.17 (m, 9H); **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 171.3, 170.4, 170.2, 153.3, 141.3, 116.5 (2C), 114.6 (2C), 63.3, 61.8 (2C), 61.4, 58.1, 55.6, 19.0, 14.0 (2C), 13.9.



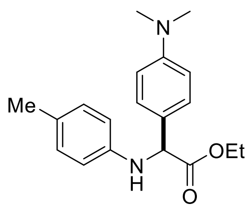
methyl 2-(1,3-dioxoisoindolin-2-yl)-2-(p-tolylamino)acetate (**7le**)[18]

Yellow solid (142.6 mg, 88% yield), mp 138−140 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.87 – 7.81 (m, 2H), 7.75 – 7.70 (m, 2H), 6.99 (d, *J* = 8.3 Hz, 2H), 6.74 (d, *J* = 8.4 Hz, 2H), 6.22 (s, 1H), 3.83 (s, 3H), 2.20 (s, 3H).



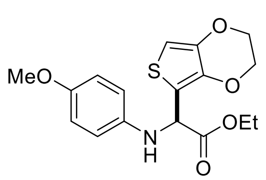
ethyl 2-((4-methoxyphenyl)amino)-2-(2,4,6-trimethoxyphenyl)acetate (**7af**)[19]

White solid, mp 75−77 °C (135.0 mg, 72% yield); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 6.67 (d, *J* = 9.0 Hz, 2H), 6.61 (d, *J* = 9.0 Hz, 2H), 6.23 (s, 2H), 5.37 (d, *J* = 7.4 Hz, 1H), 5.05 (d, *J* = 9.2 Hz, 1H), 4.10 – 3.99 (m, 2H), 3.76 (s, 9H), 3.62 (s, 3H), 1.07 (t, *J* = 7.1 Hz, 3H).



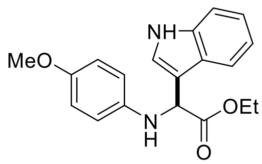
ethyl 2-(4-(dimethylamino)phenyl)-2-(p-tolylamino)acetate (**7fg**)[20]

Brown oil (96.8 mg, 62% yield); **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.34 (d, *J* = 8.5 Hz, 2H), 6.94 (d, *J* = 8.5 Hz, 2H), 6.71 (d, *J* = 8.4 Hz, 2H), 6.50 (d, *J* = 8.4 Hz, 2H), 4.95 (s, 1H), 4.67 (s, 1H), 4.28 – 4.19 (m, 1H), 4.16 – 4.07 (m, 1H), 2.94 (s, 6H), 2.20 (s, 3H), 1.22 (t, *J* = 7.1 Hz, 3H).



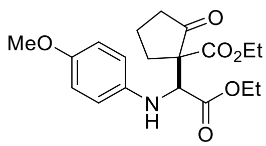
ethyl 2-(2,3-dihydrothieno[3,4-b][1,4]dioxin-5-yl)-2-((4-methoxyphenyl)amino)acetate (**7ah**)[12]

Brown oil (123.9 mg, 71% yield); **^{1}H NMR** (400 MHz, Chloroform-d) δ 6.78 – 6.72 (m, 2H), 6.68 – 6.62 (m, 2H), 6.25 (s, 1H), 5.26 (s, 1H), 4.28 – 4.17 (m, 6H), 3.72 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H).



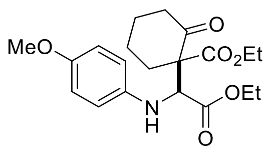
ethyl 2-(1H-indol-3-yl)-2-((4-methoxyphenyl)amino)acetate (**7ai**)[21]

Brown oil (134.5 mg, 83% yield); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 11.11 (s, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.42 (d, J = 2.5 Hz, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.13 – 7.07 (m, 1H), 7.04 – 6.99 (m, 1H), 6.74 – 6.64 (m, 4H), 5.74 (d, J = 7.9 Hz, 1H), 5.30 (d, J = 5.2 Hz, 1H), 4.15 – 4.08 (m, 1H), 4.07 – 4.00 (m, 1H), 3.63 (s, 3H), 1.11 (t, J = 7.1 Hz, 3H).



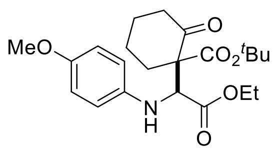
ethyl 1-(2-ethoxy-1-((4-methoxyphenyl)amino)-2-oxoethyl)-2-oxocyclopentane-1-carboxylate (**7aj**)[16]

Yellow oil (163.5 mg, 90% yield); **^{1}H NMR** (600 MHz, Chloroform-d) δ 8.56 (s, 1H), 6.92 (d, J = 8.9 Hz, 2H), 6.80 (d, J = 8.9 Hz, 2H), 5.58 (t, J = 2.7 Hz, 1H), 4.24 (q, J = 7.1 Hz, 2H), 4.09 (q, J = 7.1 Hz, 2H), 3.79 (s, 3H), 3.08 – 3.05 (m, 2H), 2.70 – 2.67 (m, 2H), 2.05 – 2.00 (m, 2H), 1.32 (t, J = 7.1 Hz, 3H), 1.21 (t, J = 7.1 Hz, 3H).



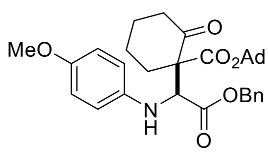
ethyl 1-(2-ethoxy-1-((4-methoxyphenyl)amino)-2-oxoethyl)-2-oxocyclohexane-1-carboxylate (**7ak**)[16]

Yellow oil (158.4 mg, 84% yield); **^{1}H NMR** (600 MHz, Chloroform-d) δ 6.77 – 6.74 (m, 2H), 6.72 – 6.69 (m, 2H), 5.99 (s, 1H), 4.18 (q, J = 7.1 Hz, 2H), 4.06 (q, J = 7.1 Hz, 2H), 3.75 (s, 3H), 3.05 – 3.01 (m, 2H), 2.51 (t, J = 6.3 Hz, 2H), 1.81 – 1.77 (m, 2H), 1.55 (brs, 1.5H), 1.31 – 1.28 (m, 3.5H), 1.20 (t, J = 7.1 Hz, 3H).



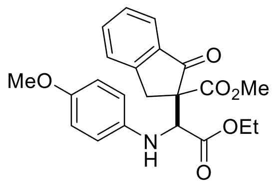
tert-butyl 1-(2-ethoxy-1-((4-methoxyphenyl)amino)-2-oxoethyl)-2-oxocyclohexane-1-carboxylate (**7al**)[22]

Yellow oil (162.1 mg, 80% yield); **^{1}H NMR** (400 MHz, Chloroform-d) δ 6.80 – 6.63 (m, 4H), 4.26 – 4.06 (m, 3H), 3.74 (s, 3H), 2.90 – 2.23 (m, 4H), 2.07 – 1.60 (m, 4H), 1.47 (s, 9H), 1.23 – 1.15 (m, 3H).



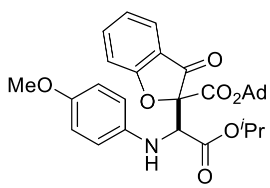
adamantan-1-yl 1-(2-(benzyloxy)-1-((4-methoxyphenyl)amino)-2-oxoethyl)-2-oxocyclohexane-1-carboxylate (**7dm**)

Yellow oil (212.6 mg, 78% yield); **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.31 – 7.14 (m, 5H), 6.84 – 6.57 (m, 4H), 5.18 – 5.03 (m, 2H), 4.33 (s, 1H), 3.75 (s, 3H), 2.91 – 2.69 (m, 1H), 2.52 – 2.23 (m, 3H), 2.20 – 2.03 (m, 9H), 2.01 – 1.66 (m, 4H), 1.65 – 1.58 (m, 6H); **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 207.8, 171.9, 153.0, 142.2, 135.5, 128.3, 128.3, 128.2, 128.0, 128.0, 116.4, 115.6, 114.8, 114.6, 82.9, 67.1, 66.6, 62.0, 55.7, 41.0, 40.9, 40.8, 36.0 (3C), 35.3, 30.8 (3C), 30.8, 26.7, 22.3, 21.4. **HRMS (ESI)** *m/z* calcd for $C_{33}H_{40}NO_6$ $[M+H]^+$, 546.2856, found 546.2850.



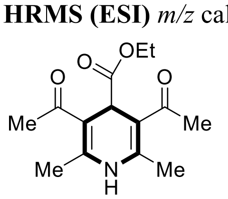
methyl 2-(2-ethoxy-1-((4-methoxyphenyl)amino)-2-oxoethyl)-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (**7an**)

Yellow oil (172.8 mg, 87% yield); **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.79 – 7.73 (m, 1H), 7.63 – 7.59 (m, 1H), 7.51 – 7.46 (m, 1H), 7.41 – 7.35 (m, 1H), 6.85 – 6.70 (m, 4H), 5.02 (s, 1H), 4.14 – 4.02 (m, 2H), 3.84 – 3.77 (m, 1H), 3.76 – 3.70 (m, 6H), 3.35 – 3.29 (m, 1H), 1.01 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (125 MHz, Chloroform-*d*) δ 199.4, 171.7, 169.3, 153.7, 152.7, 141.0, 140.6, 135.4, 127.8, 126.2, 124.9, 117.2, 116.9, 114.7, 114.6, 62.9, 62.8, 61.6, 55.6, 53.1, 33.4, 14.0; **HRMS (ESI)** *m/z* calcd for $C_{22}H_{24}NO_6$ $[M+H]^+$, 398.1604, found 398.1601.



adamantan-1-yl 2-(2-isopropoxy-1-((4-methoxyphenyl)amino)-2-oxoethyl)-3-oxo-2,3-dihydrobenzofuran-2-carboxylate (**7co**)

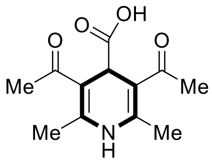
Yellow solid (226.6 mg, 85% yield); mp 148−150 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.69 (d, *J* = 7.7 Hz, 1H), 7.63 (t, *J* = 8.0 Hz, 1H), 7.23 (d, *J* = 8.9 Hz, 1H), 7.14 (t, *J* = 7.4 Hz, 1H), 6.89 – 6.76 (m, 4H), 5.03 (s, 1H), 4.73 – 4.67 (m, 1H), 3.76 (s, 3H), 2.13 – 2.00 (m, 9H), 1.58 (s, 6H), 0.97 (d, *J* = 6.3 Hz, 3H), 0.55 (d, *J* = 6.2 Hz, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 192.2, 171.7, 168.1, 153.6, 140.8, 138.1, 124.8, 122.9, 116.8 (2C), 114.6 (2C), 113.4, 93.2, 84.7, 70.1, 62.3, 55.7, 40.8 (3C), 35.9 (3C), 30.9 (3C), 21.4, 20.6. **HRMS (ESI)** *m/z* calcd for $C_{31}H_{36}NO_7$ $[M+H]^+$, 534.2492, found 534.2491.



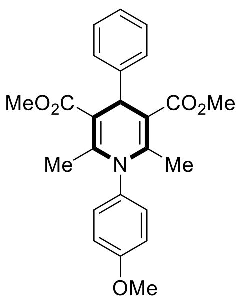
Ethyl 3,5-diacetyl-2,6-dimethyl-1,4-dihydropyridine-4-carboxylate (**8**)

Yellow oil (71.6 mg, 54% yield); **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 6.15 (s, 1H), 4.81 (s, 1H), 4.08 (q, *J* = 7.1 Hz, 2H), 2.38 (s, 6H), 2.31 (s, 6H), 1.21 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (150 MHz, Chloroform-*d*) δ

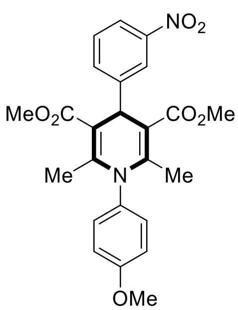
197.4 (2C), 173.0, 144.3 (2C), 108.3 (2C), 61.2, 41.6, 29.7 (2C), 20.1 (2C), 14.1. **HRMS (ESI)** *m/z* calcd for $C_{14}H_{20}NO_4$ $[M+H]^+$, 288.1206, found 288.1196.



3,5-Diacetyl-2,6-dimethyl-1,4-dihydropyridine-4-carboxylic acid (**9**)[23]
Yellow solid (57.6 mg, 90% yield); mp 170−172 °C (lit. mp 173−174 °C); **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.92 (s, 1H), 4.61 (s, 1H), 2.27 (s, 6H), 2.23 (s, 6H).

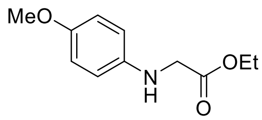


dimethyl 1-(4-methoxyphenyl)-2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (**11a**)[24]
Brown solid (187.3 mg, 92% yield); mp 147−149 °C (lit. mp 148−149 °C); **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.35 (d, *J* = 7.4 Hz, 2H), 7.31 – 7.26 (m, 2H), 7.21 – 7.16 (m, 1H), 7.00 (d, *J* = 7.7 Hz, 2H), 6.92 (d, *J* = 8.2 Hz, 2H), 5.14 (s, 1H), 3.84 (s, 3H), 3.69 (s, 6H), 2.07 (s, 6H).



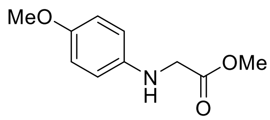
dimethyl 1-(4-methoxyphenyl)-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**11b**)
Yellow solid; mp 154−155 °C (169.7 mg, 75% yield); **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 8.27 (t, *J* = 2.0 Hz, 1H), 8.07 – 8.04 (m, 1H), 7.74 – 7.72 (m, 1H), 7.44 (t, *J* = 7.9 Hz, 1H), 7.13 – 7.10 (m, 2H), 6.99 – 6.97 (m, 2H), 5.19 (s, 1H), 3.86 (s, 3H), 3.70 (s, 6H), 2.10 (s, 6H). **^{13}C NMR** (150 MHz, Chloroform-*d*) δ 168.0 (2C), 159.6, 149.2, 149.1, 148.6, 133.8 (2C), 132.4, 128.8 (2C), 122.3, 121.4, 114.8 (2C), 104.7 (2C), 55.6, 51.4 (2C), 38.7, 18.7 (2C). **HRMS (ESI)** *m/z* calcd for $C_{24}H_{25}N_2O_7$ $[M+H]^+$, 453.1673, found 453.1671.

7.2 Characterization data for reactants 1, 4 and 10



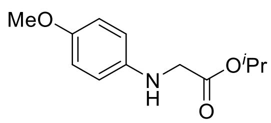
ethyl (4-methoxyphenyl)glycinate (**1a**)[25]

Colorless solid (401.4 mg, 96% yield); mp 59−60 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 6.71 (d, *J* = 8.4 Hz, 2H), 6.50 (d, *J* = 8.4 Hz, 2H), 5.56 (s, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.81 (s, 2H), 3.63 (s, 3H), 1.18 (t, *J* = 7.1 Hz, 3H).



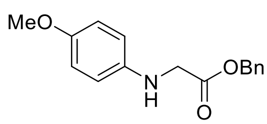
methyl (4-methoxyphenyl)glycinate (**1b**)[26]

Pale brown solid (370.7 mg, 95% yield); mp 79−80 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 6.74 – 6.68 (m, 2H), 6.53 – 6.48 (m, 2H), 3.84 (s, 2H), 3.63 (s, 6H).



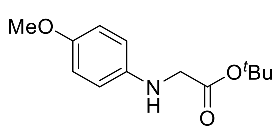
isopropyl (4-methoxyphenyl)glycinate (**1c**)

Yellow solid (419.4 mg, 94% yield); **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 6.80 – 6.78 (m, 2H), 6.60 – 6.58 (m, 2H), 5.12 – 5.08 (m, 1H), 3.83 (s, 2H), 3.74 (s, 3H), 1.26 (d, *J* = 6.3 Hz, 6H). **^{13}C NMR** (150 MHz, Chloroform-*d*) δ 170.9, 152.6, 141.3, 114.9 (2C), 114.4 (2C), 68.9, 55.7, 47.1, 21.8 (2C). **HRMS (ESI)** *m/z* calcd for $C_{12}H_{18}NO_3$ $[M+H]^+$, 224.1487, found 224.1483.



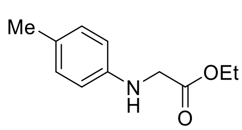
benzyl (4-methoxyphenyl)glycinate (**1d**)[26]

White solid (498.9 mg, 92% yield); mp 73−74 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.43 – 7.29 (m, 5H), 6.81 – 6.77 (m, 2H), 6.62 – 6.58 (m, 2H), 5.21 (s, 2H), 3.93 (s, 2H), 3.75 (s, 3H).



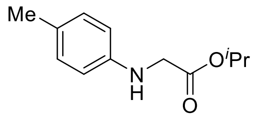
tert-butyl (4-methoxyphenyl)glycinate (**1e**)[26]

Yellow oil (422.1 mg, 89% yield); **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 6.79 (d, *J* = 8.9 Hz, 2H), 6.58 (d, *J* = 8.9 Hz, 2H), 3.76 (s, 2H), 3.74 (s, 3H), 1.48 (s, 9H).



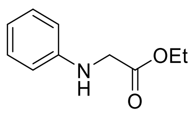
ethyl p-tolylglycinate (**1f**)[25]

White solid (359.2 mg, 93% yield); mp 48−50 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 6.88 (d, J = 8.4 Hz, 2H), 6.45 (d, J = 8.4 Hz, 2H), 4.10 (q, J = 7.1 Hz, 2H), 3.83 (s, 2H), 2.14 (s, 3H), 1.18 (t, J = 7.1 Hz, 3H).



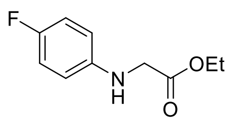
isopropyl p-tolylglycinate (**1g**)

White solid (385.2 mg, 93% yield); mp 39−40 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.03 (d, J = 8.1 Hz, 2H), 6.56 (d, J = 8.3 Hz, 2H), 5.13 (hept, J = 6.3 Hz, 1H), 3.86 (s, 2H), 2.27 (s, 3H), 1.30 (d, J = 6.3 Hz, 6H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 170.9, 144.9, 129.8 (2C), 127.4, 113.2 (2C), 68.9, 46.5, 21.9, 20.5. **HRMS (ESI)** *m/z* calcd for $C_{12}H_{18}NO_2$ $[M+H]^+$, 208.1338, found 208.1341.



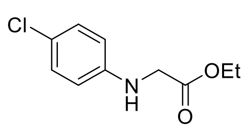
ethyl phenylglycinate (**1h**)[25]

White solid (307.9 mg, 86% yield); mp 56−57 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.07 (t, J = 7.7 Hz, 2H), 6.62 – 6.48 (m, 3H), 4.11 (q, J = 7.1 Hz, 2H), 3.87 (s, 2H), 1.19 (t, J = 7.1 Hz, 3H).



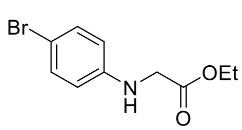
ethyl (4-fluorophenyl)glycinate (**1i**)[25]

Colourless solid (315.3 mg, 80% yield); mp 73−74 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 6.93 – 6.84 (m, 2H), 6.53 – 6.47 (m, 2H), 4.08 (q, J = 7.1 Hz, 2H), 3.83 (s, 2H), 1.16 (t, J = 7.1 Hz, 3H).



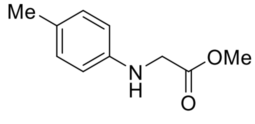
ethyl (4-chlorophenyl)glycinate (**1j**)[25]

Colourless solid (345.1 mg, 81% yield); mp 95−97 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.09 (d, J = 8.2 Hz, 2H), 6.55 (d, J = 8.4 Hz, 2H), 4.11 (q, J = 7.1 Hz, 2H), 3.88 (s, 2H), 1.19 (t, J = 7.1 Hz, 3H).



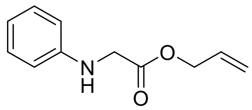
ethyl (4-bromophenyl)glycinate (**1k**)[25]

Colourless solid (416.3 mg, 81% yield); mp 96−97 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.21 – 7.14 (m, 2H), 6.52 – 6.45 (m, 2H), 4.12 – 4.04 (m, 2H), 3.88 – 3.82 (m, 2H), 1.33 – 1.19 (m, 3H).



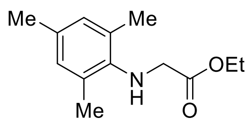
methyl p-tolylglycinate (**1l**)[27]

White solid (322.4 mg, 90% yield); mp 87−88 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 6.88 (d, J = 8.3 Hz, 2H), 6.45 (d, J = 8.3 Hz, 2H), 3.85 (s, 2H), 3.63 (s, 3H), 2.14 (s, 3H).



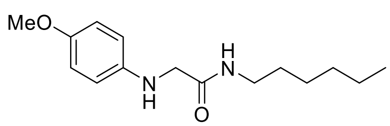
allyl phenylglycinate (**1m**)

Brown oil (290.5 mg, 76% yield); **^{1}H NMR** (400 MHz, Chloroform-d) δ 7.24 – 7.17 (m, 2H), 6.81 – 6.73 (m, 1H), 6.65 – 6.61 (m, 2H), 6.00 – 5.88 (m, 1H), 4.71 – 4.68 (m, 2H), 3.95 (s, 2H). **^{13}C NMR** (100 MHz, Chloroform-d) δ 171.0, 147.0, 131.7, 129.5 (2C), 119.0, 118.5, 113.2 (2C), 66.0, 46.0. **HRMS (ESI)** *m/z* calcd for $C_{11}H_{14}NO_2$ $[M+H]^+$, 192.1025, found 192.1031.



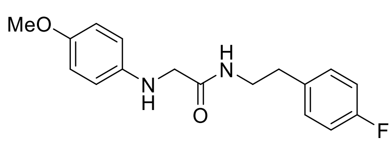
ethyl mesitylglycinate (**1n**)[28]

Colorless oil (367.1 mg, 83% yield); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 6.72 (s, 2H), 4.07 (q, J = 7.1 Hz, 2H), 3.82 – 3.68 (m, 2H), 2.16 (d, J = 24.4 Hz, 9H), 1.16 (t, J = 7.1 Hz, 3H).



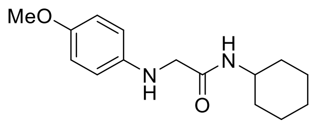
N-hexyl-2-((4-methoxyphenyl)amino)acetamide (**4a**)

Brown oil (427.9 mg, 81% yield); **^{1}H NMR** (400 MHz, Chloroform-d) δ 6.84 (s, 1H), 6.78 (d, J = 8.4 Hz, 2H), 6.56 (d, J = 8.4 Hz, 2H), 3.76 – 3.69 (m, 5H), 3.28 – 3.22 (m, 2H), 1.48 – 1.40 (m, 2H), 1.23 (brs, 6H), 0.84 (t, J = 6.4 Hz, 3H). **^{13}C NMR** (100 MHz, Chloroform-d) δ 170.6, 153.1, 141.2, 114.9 (2C), 114.4 (2C), 55. 7, 49.7, 39.1, 31.4, 29.5, 26.4, 22.5, 13.9. **HRMS (ESI)** *m/z* calcd for $C_{15}H_{25}N_2O_2$ $[M+H]^+$, 265.1916, found 265.1910.



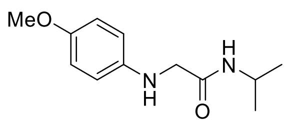
N-(4-fluorophenethyl)-2-((4-methoxyphenyl)amino)acetamide (**4b**)

Yellow solid (501.6 mg, 83% yield); mp 102−104 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.85 (t, J = 5.9 Hz, 1H), 7.19 – 7.14 (m, 2H), 7.09 – 7.00 (m, 2H), 6.72 (d, J = 8.8 Hz, 2H), 6.45 (d, J = 8.7 Hz, 2H), 5.57 (s, 1H), 3.64 (s, 3H), 3.52 (s, 2H), 3.30 (q, J = 6.8 Hz, 2H), 2.68 (t, J = 7.1 Hz, 2H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 170.5, 159.8 (d, J_1 = 239.8 Hz), 151.3, 142.5, 135.5 (d, J_4 = 3.1 Hz), 130.4 (d, J_3 = 7.8 Hz, 2C), 114.9 (d, J_2 = 20.8 Hz, 2C), 114.6 (2C), 113.4 (2C), 55.3, 48.0, 34.3. **HRMS (ESI)** *m/z* calcd for $C_{17}H_{20}FN_2O_2$ $[M+H]^+$, 303.1509, found 303.1517.



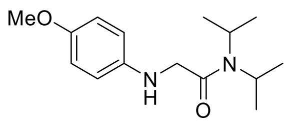
N-cyclohexyl-2-((4-methoxyphenyl)amino)acetamide (**4c**)

White solid (450.6 mg, 86% yield); mp 94.0−94.8 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 6.79 (d, *J* = 7.6 Hz, 2H), 6.71 (d, *J* = 5.6 Hz, 1H), 6.58 (d, *J* = 7.6 Hz, 2H), 3.82 (dd, *J* = 8.9, 4.1 Hz, 1H), 3.75 (s, 3H), 3.71 (s, 2H), 1.85 (d, *J* = 12.0 Hz, 2H), 1.69 – 1.55 (m, 3H), 1.40 – 1.29 (m, 2H), 1.16 – 1.03 (m, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 169.6, 153.2, 141.2, 114.9, 114.6, 55.7, 50.0, 47.8, 33.0, 25.4, 24.8. **HRMS (ESI)** *m/z* calcd for $C_{15}H_{23}N_2O_2$ $[M+H]^+$, 263.1760, found 263.1750.



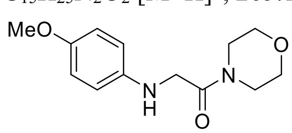
N-isopropyl-2-((4-methoxyphenyl)amino)acetamide (**4d**)

Pale brown solid (390.9 mg, 88% yield); mp 60−61 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 6.84 – 6.73 (m, 2H), 6.64 (s, 1H), 6.59 – 6.51 (m, 2H), 4.16 – 4.07 (m, 1H), 3.76 – 3.71 (m, 3H), 3.69 (t, *J* = 2.4 Hz, 2H), 1.15 – 1.08 (m, 6H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 169.8, 153.1, 141.3, 114.9 (2C), 114.5 (2C), 55.7, 49.9, 41.0, 22.6 (2C). **HRMS (ESI)** *m/z* calcd for $C_{12}H_{19}N_2O_2$ $[M+H]^+$, 223.1447, found 223.1439.



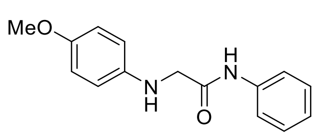
N,N-diisopropyl-2-((4-methoxyphenyl)amino)acetamide (**4e**)

White solid (433.2 mg, 82% yield); mp 99−100 °C; **^{1}H NMR** (400 MHz, DMSO-*d*$_6$) δ 6.71 (d, *J* = 8.1 Hz, 2H), 6.61 (d, *J* = 8.3 Hz, 2H), 5.13 (s, 1H), 4.11 – 3.97 (m, 1H), 3.75 (s, 2H), 3.64 (s, 3H), 3.52 – 3.42 (m, 1H), 1.32 (d, *J* = 5.7 Hz, 6H), 1.15 (d, *J* = 5.7 Hz, 6H). **^{13}C NMR** (100 MHz, DMSO-*d*$_6$) δ 167.6, 150.9, 142.4, 114.5 (2C), 113.5 (2C), 55.3, 46.9, 46.6, 44.9 (2C), 20.4 (2C), 20.4 (2C). **HRMS (ESI)** *m/z* calcd for $C_{15}H_{25}N_2O_2$ $[M+H]^+$, 265.1916, found 265.1908.



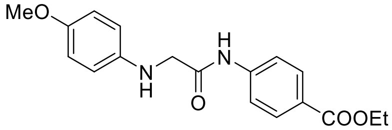
2-((4-methoxyphenyl)amino)-1-morpholinoethan-1-one (**4f**)

White solid (395.2 mg, 79% yield); mp 110−111 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 6.80 (d, *J* = 8.1 Hz, 2H), 6.61 (d, *J* = 8.4 Hz, 2H), 3.85 (s, 2H), 3.76 – 3.64 (m, 9H), 3.46 (s, 2H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 168.0, 152.4, 141.5, 114.9 (2C), 114.4 (2C), 66.8, 66.4, 55.8, 46.3, 44.7, 42.3. **HRMS (ESI)** *m/z* calcd for $C_{13}H_{19}N_2O_3$ $[M+H]^+$, 251.1396, found 251.1387.



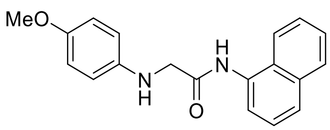
2-((4-methoxyphenyl)amino)-N-phenylacetamide (**4g**)[29]

Light yellow solid (445.6 mg, 87% yield); mp 101−103 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.71 (s, 1H), 7.57 – 7.49 (m, 2H), 7.31 (dd, *J* = 8.5, 7.4 Hz, 2H), 7.11 (t, *J* = 7.5 Hz, 1H), 6.85 – 6.78 (m, 2H), 6.68 – 6.63 (m, 2H), 3.86 (s, 2H), 3.75 (s, 3H).



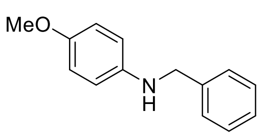
ethyl 4-(2-((4-methoxyphenyl)amino)acetamido)benzoate (**4h**)

White solid (525.0 mg, 80% yield); mp 140−141 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.90 (s, 1H), 8.00 (d, *J* = 8.0 Hz, 2H), 7.62 (d, *J* = 8.0 Hz, 2H), 6.82 (d, *J* = 7.9 Hz, 2H), 6.65 (d, *J* = 7.9 Hz, 2H), 4.35 (q, *J* = 6.9 Hz, 2H), 3.88 (s, 2H), 3.75 (s, 3H), 1.38 (t, *J* = 6.9 Hz, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 169.4, 166.1, 153.8, 141.3, 140.7, 130.7 (2C), 126.2, 118.8 (2C), 115.1 (2C), 114.9 (2C), 60.9, 55.7, 50.8, 14.3. **HRMS (ESI)** *m/z* calcd for $C_{18}H_{21}N_2O_4$ $[M+H]^+$, 329.1501, found 329.1493.



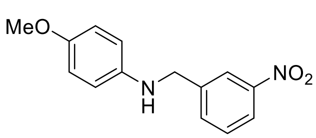
2-((4-methoxyphenyl)amino)-N-(naphthalen-1-yl)acetamide (**4i**)

Pale maroon solid (379.6 mg, 62% yield); mp 162-163 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.90 (s, 1H), 8.00 (d, *J* = 8.0 Hz, 2H), 7.62 (d, *J* = 7.9 Hz, 2H), 6.82 (d, *J* = 7.9 Hz, 2H), 6.65 (d, *J* = 7.8 Hz, 2H), 4.35 (q, *J* = 6.8 Hz, 2H), 3.88 (s, 2H), 3.75 (s, 3H), 1.38 (t, *J* = 6.9 Hz, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 169.4, 166.1, 153.8, 141.3, 140.7, 130.7 (2C), 126.2 (2C), 118.8 (2C), 115.1 (2C), 114.9 (2C), 60.9, 55.7, 50.8, 14.3. **HRMS (ESI)** *m/z* calcd for $C_{19}H_{19}N_2O_2$ $[M+H]^+$, 307.1447, found 307.1441.



N-benzyl-4-methoxyaniline (**10a**)[30]

Pale yellow solid (189.7 mg, 89% yield); mp 48−50 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.44 – 7.34 (m, 4H), 7.34 – 7.27 (m, 1H), 6.85 – 6.79 (m, 2H), 6.66 – 6.62 (m, 2H), 4.31 (s, 2H), 3.77 (s, 3H).



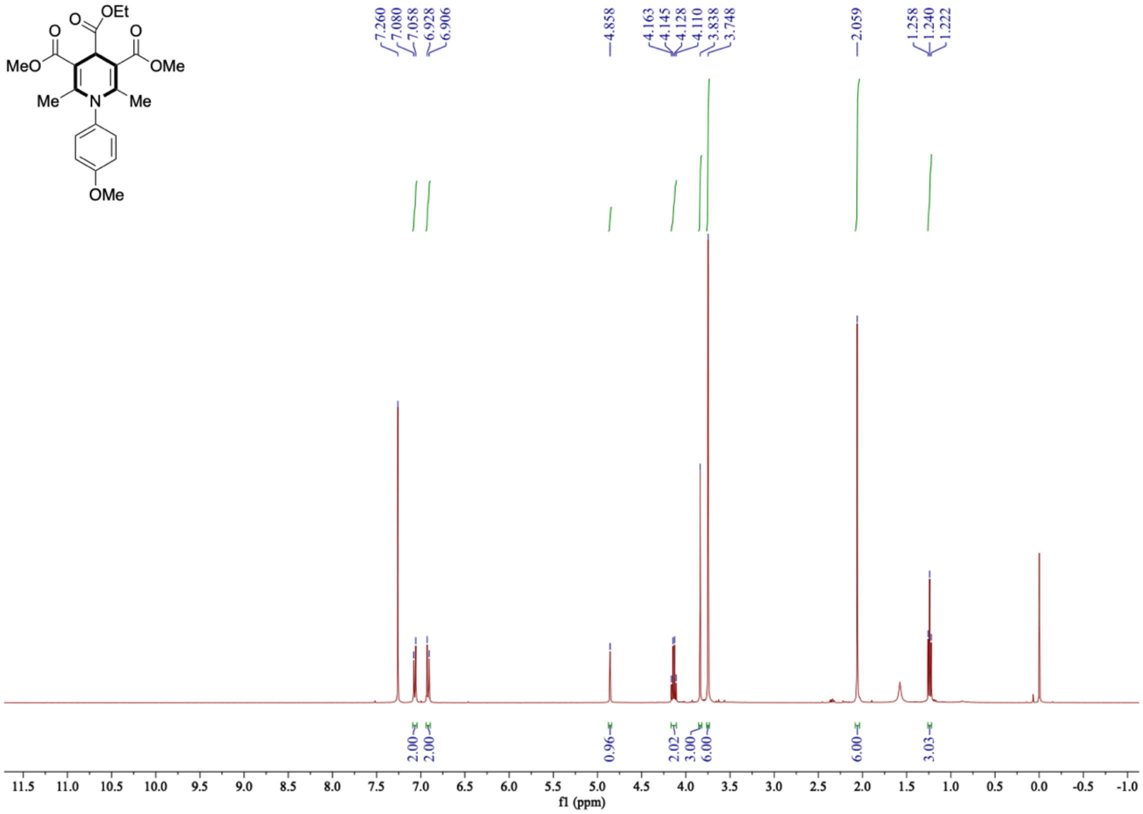
4-methoxy-N-(2-nitrobenzyl)aniline (**10b**)[31]

Red oil (211.6 mg, 82% yield); **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.24 (t, *J* = 2.0 Hz, 1H), 8.14 – 8.07 (m, 1H), 7.76 – 7.67 (m, 1H), 7.50 (t, *J* = 7.9 Hz, 1H), 6.81 – 6.73 (m, 2H), 6.61 – 6.54 (m, 2H), 4.41 (s, 2H), 3.73 (s, 3H).

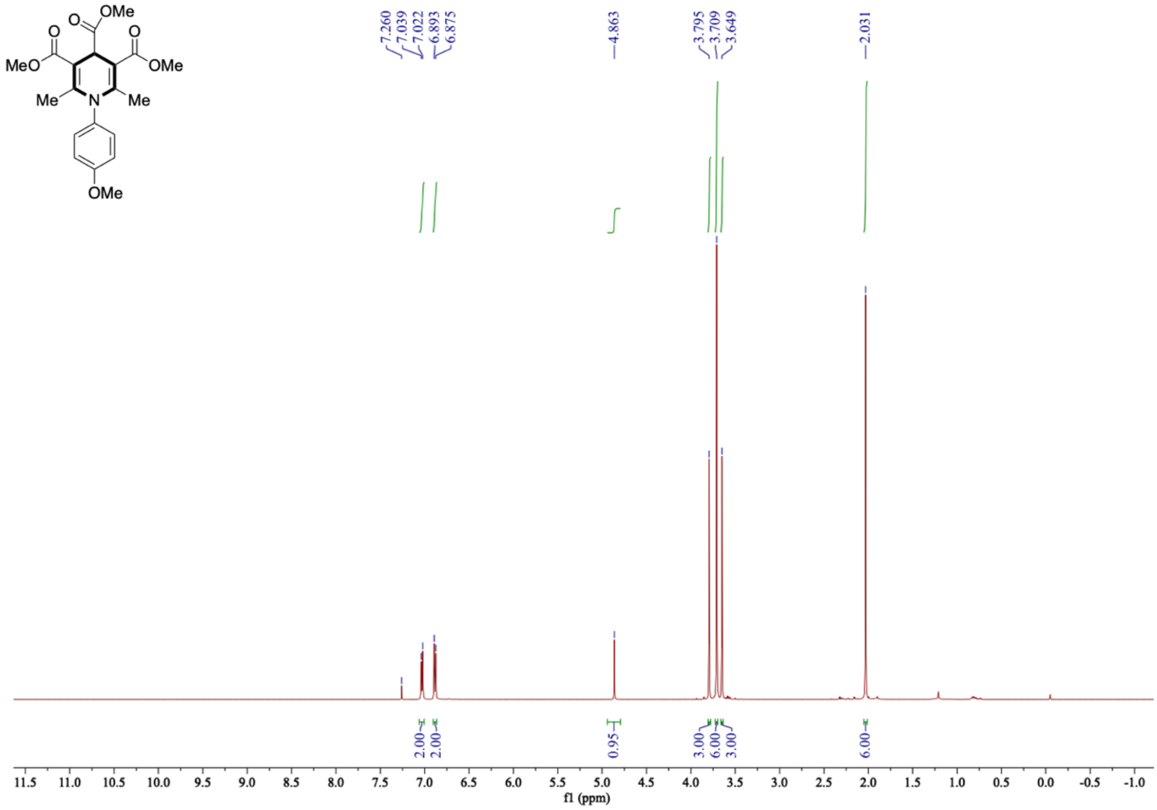
8. NMR spectra

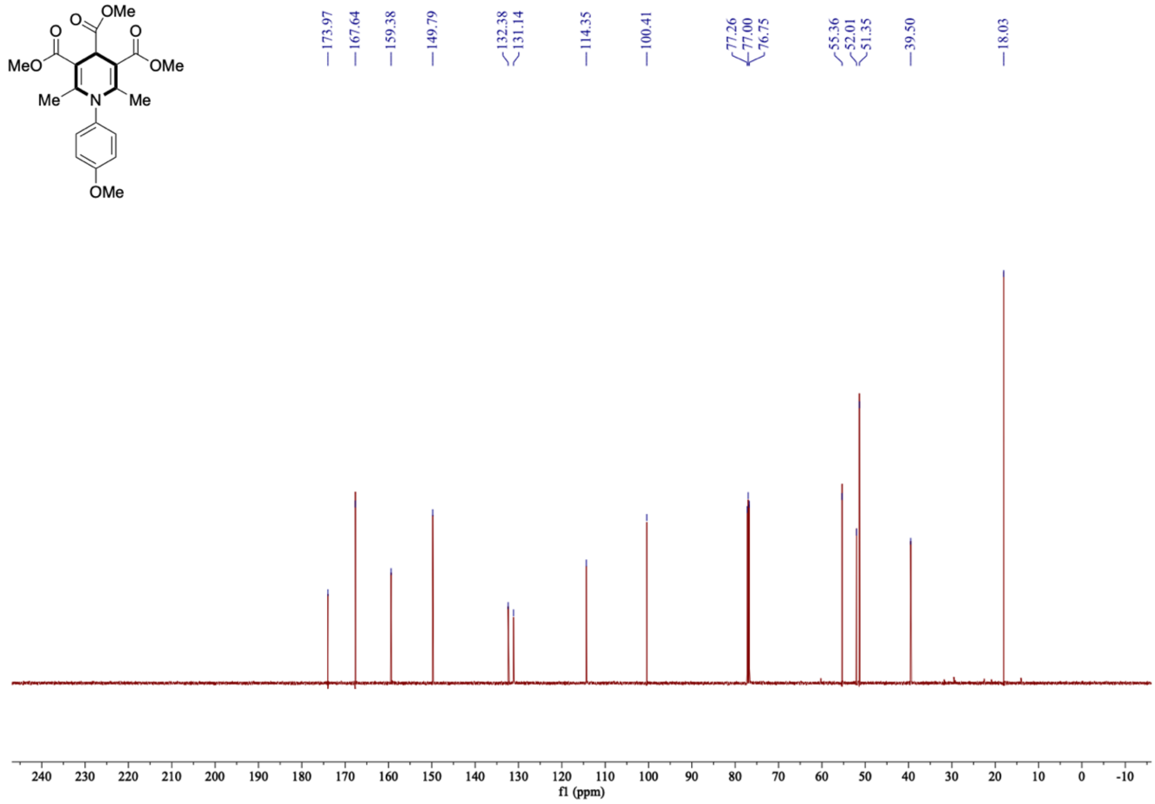
For products 3, 5, 7, 8, 9 and 11

4-Ethyl 3,5-dimethyl 1-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,4,5-tricarboxylate (**3aa**)

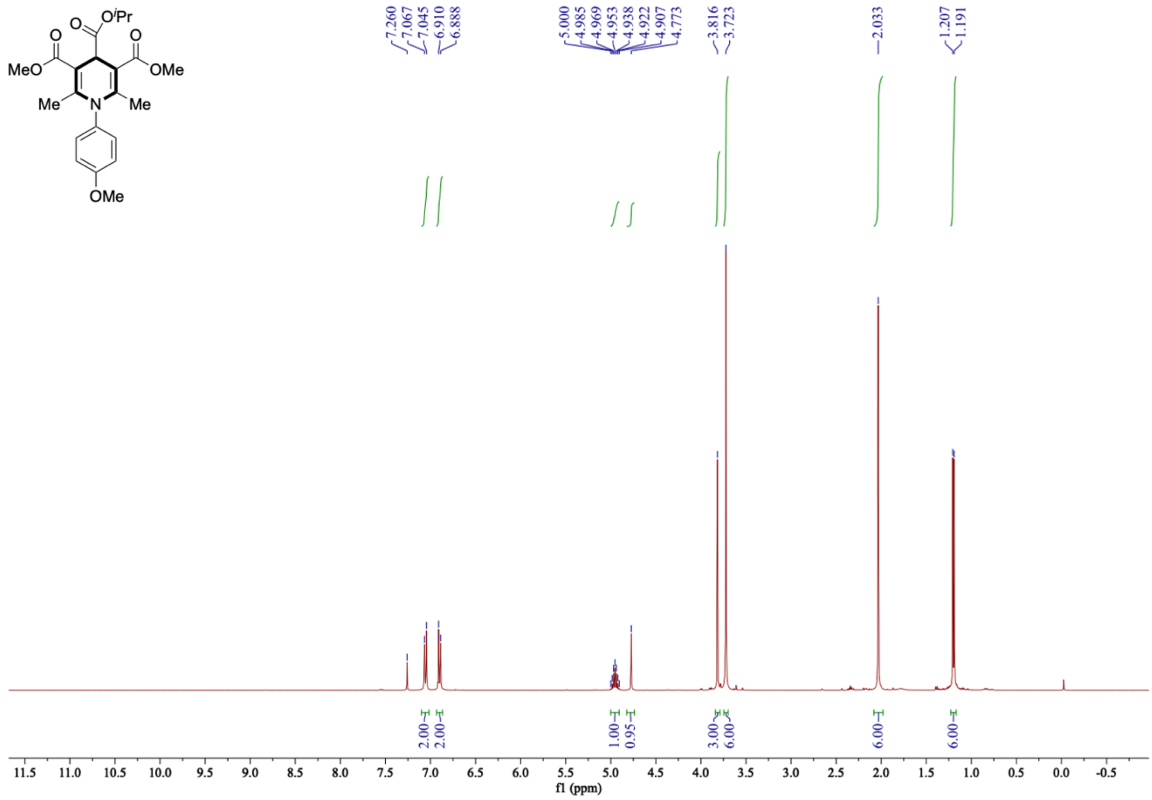


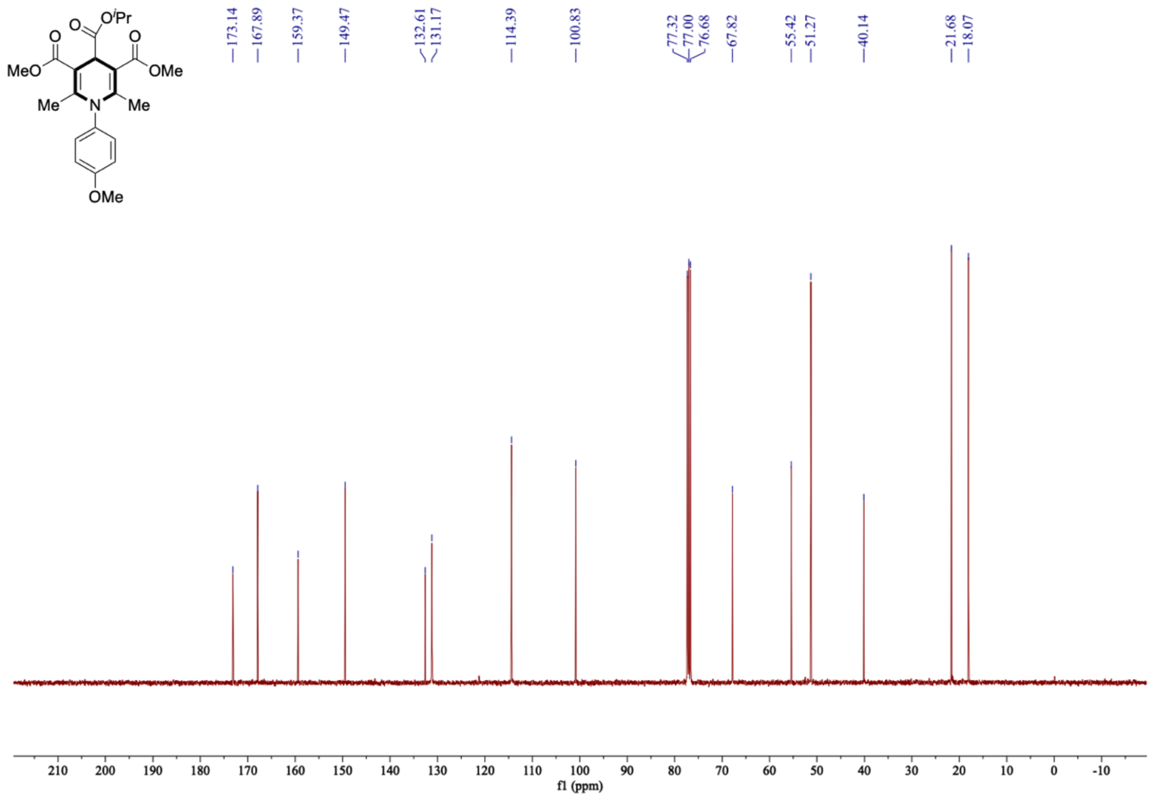
Trimethyl 1-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,4,5-tricarboxylate (**3ba**)



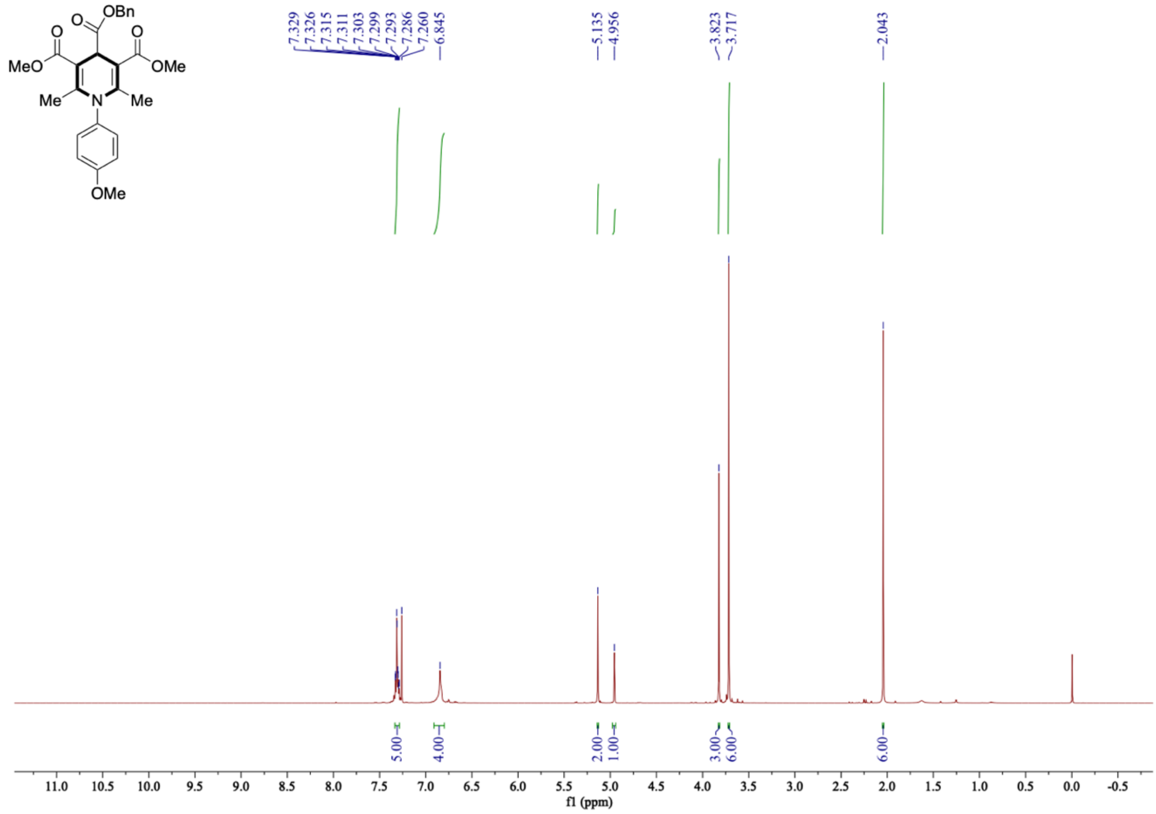


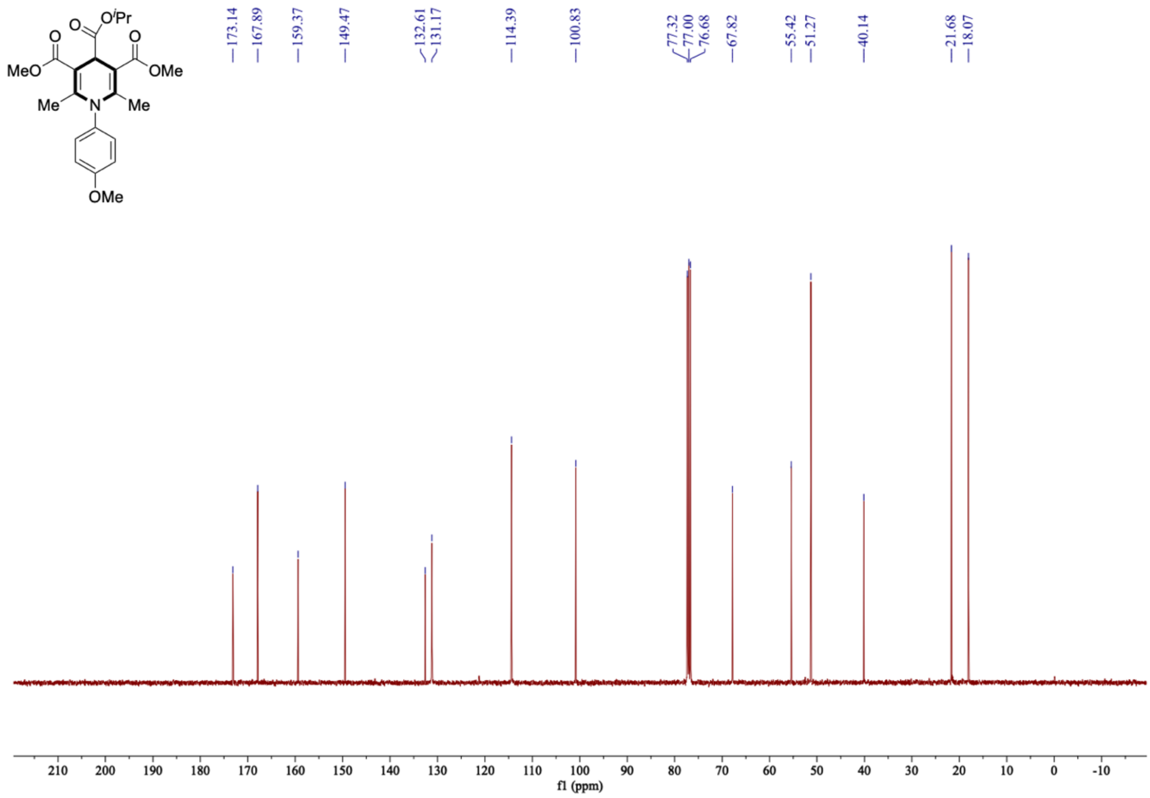
4-Isopropyl 3,5-dimethyl 1-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,4,5-tricarboxylate (**3ca**)



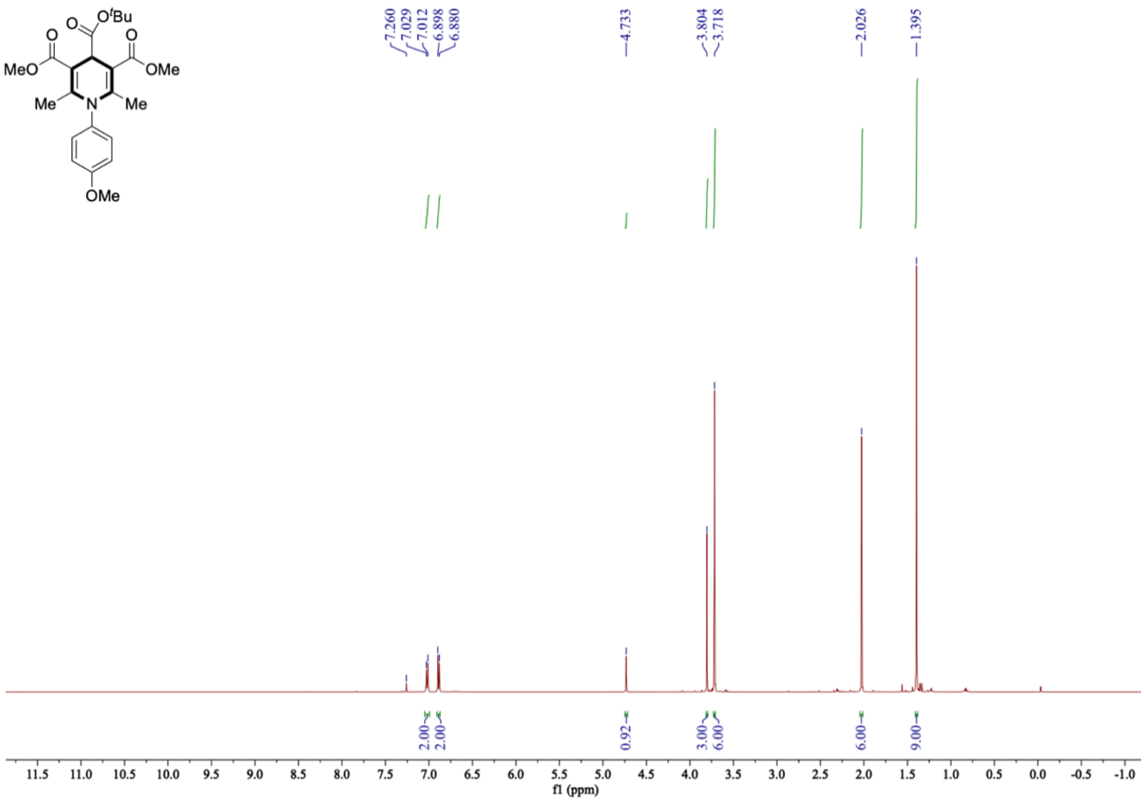


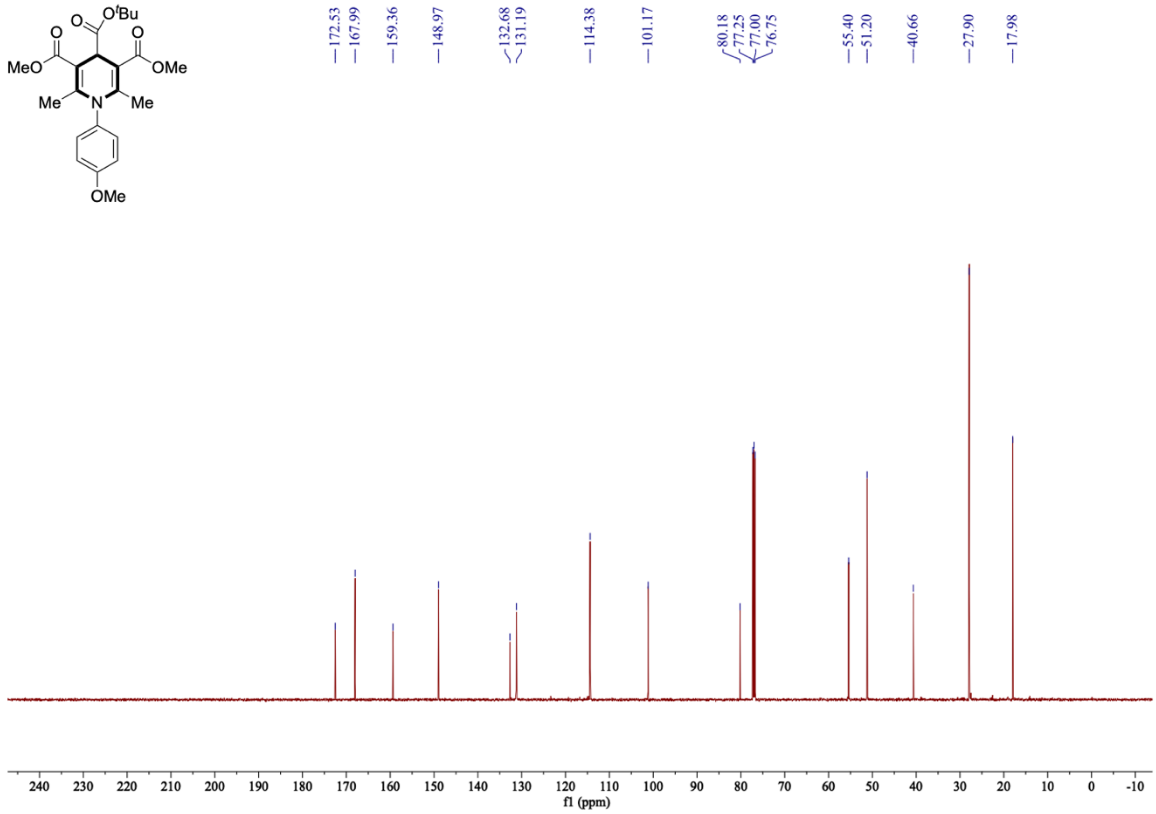
4-Benzyl 3,5-dimethyl 1-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,4,5-tricarboxylate (**3da**)



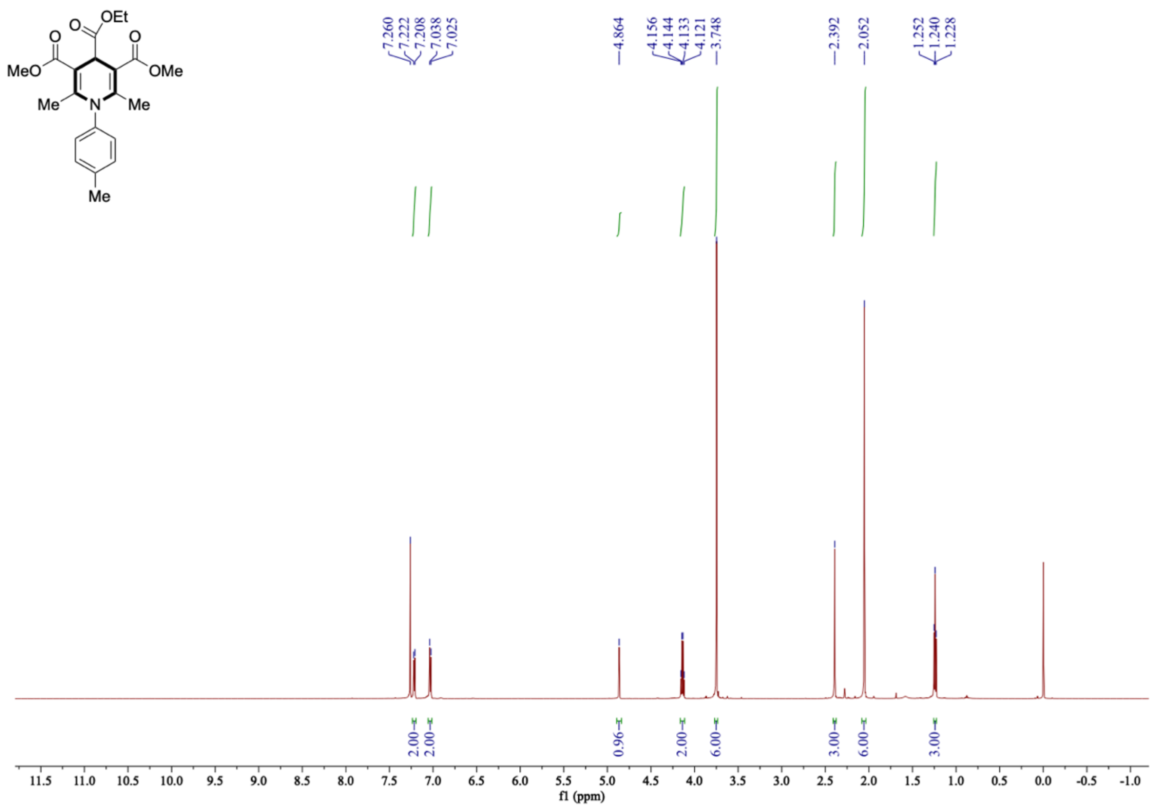


4-(tert-butyl) 3,5-Dimethyl 1-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,4,5-tricarboxylate (**3ea**)

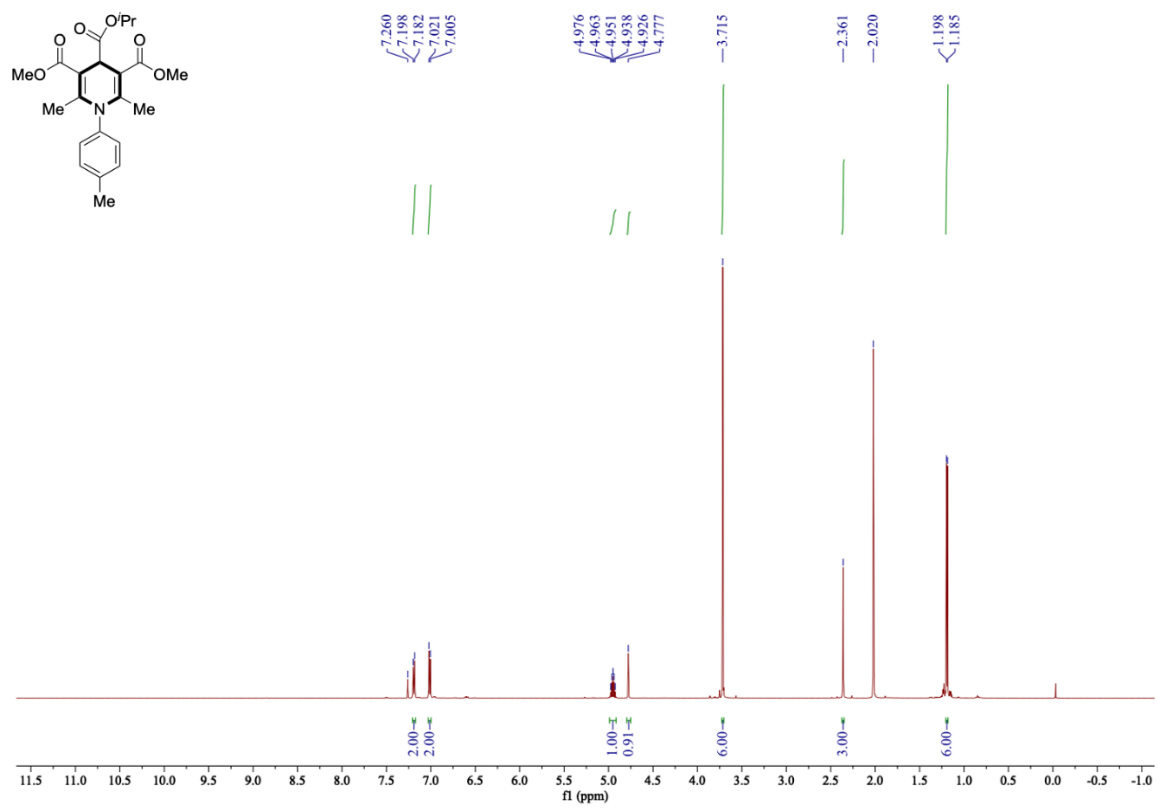


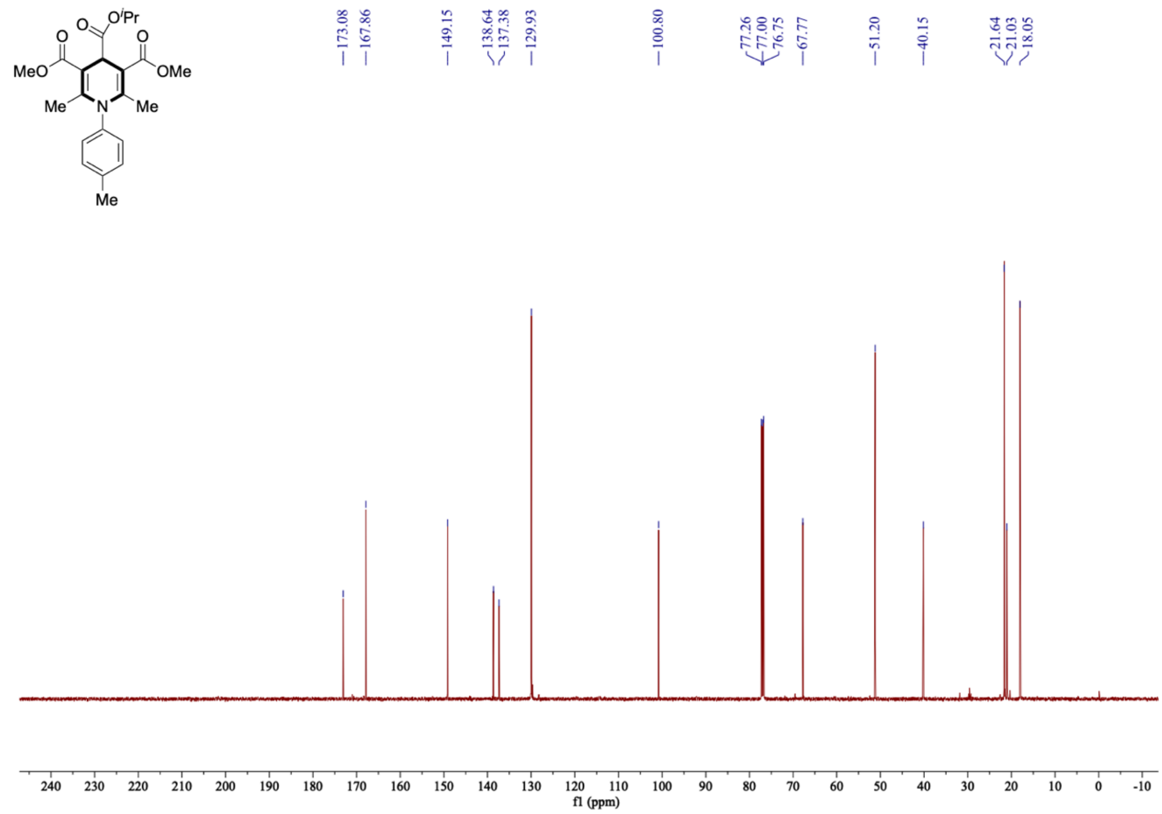


4-Ethyl 3,5-dimethyl 2,6-dimethyl-1-(p-tolyl)-1,4-dihydropyridine-3,4,5-tricarboxylate (**3fa**)

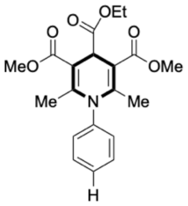


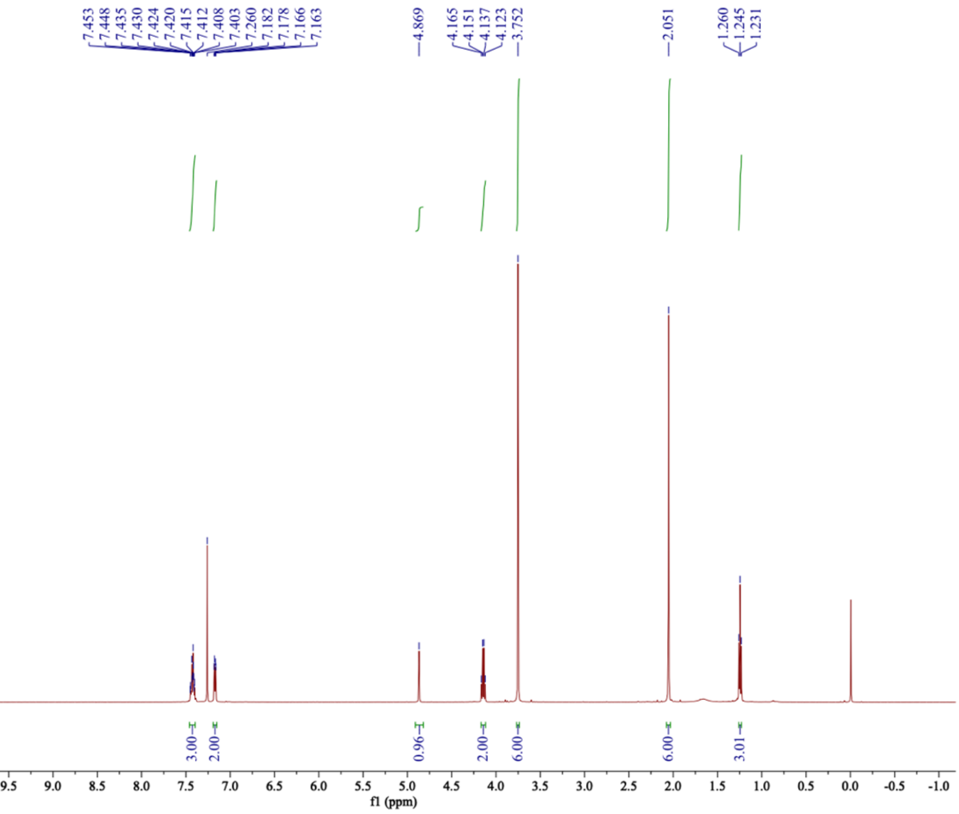
4-Isopropyl 3,5-dimethyl 2,6-dimethyl-1-(p-tolyl)-1,4-dihydropyridine-3,4,5-tricarboxylate (**3ga**)



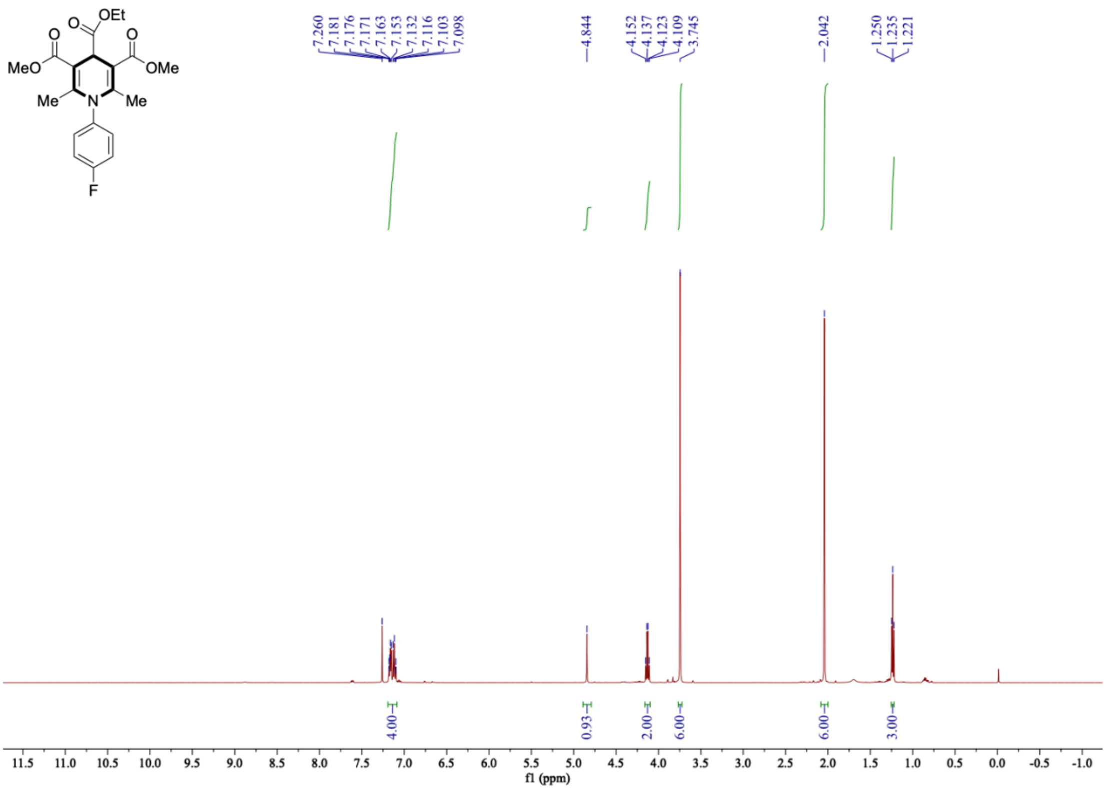


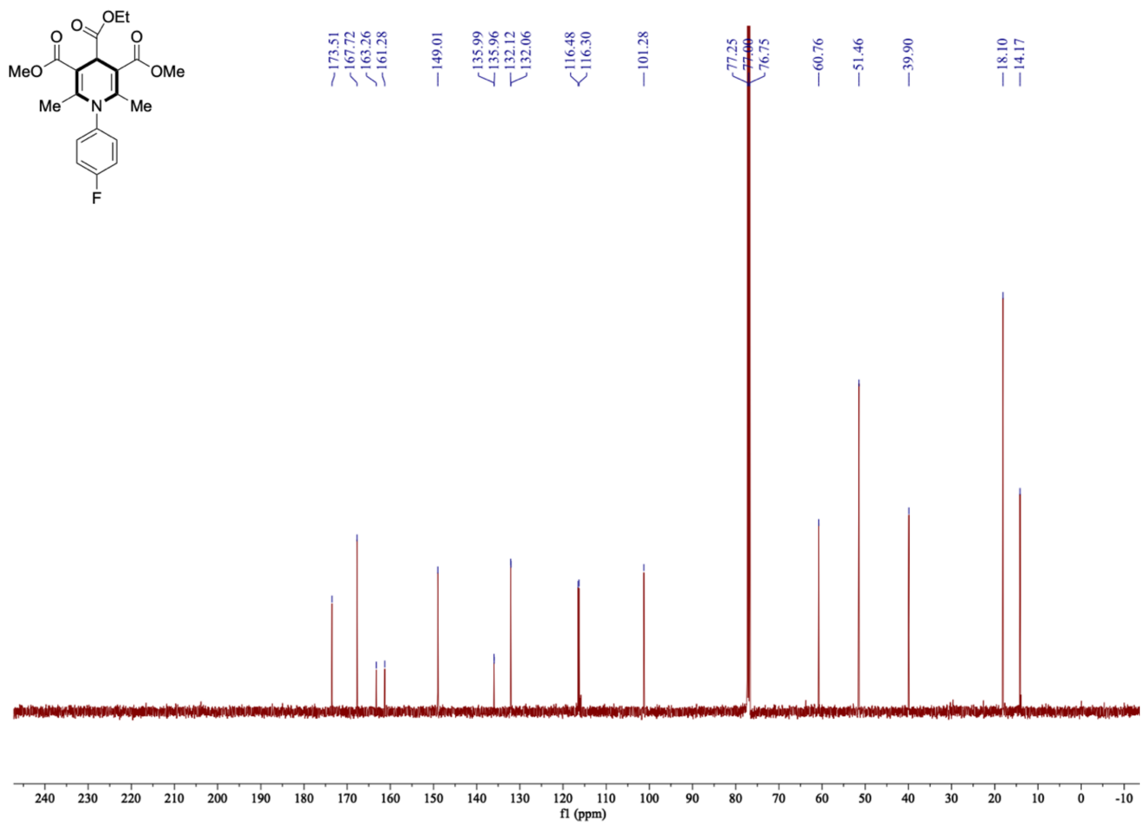
4-Ethyl 3,5-dimethyl 2,6-dimethyl-1-phenyl-1,4-dihydropyridine-3,4,5-tricarboxylate (**3ha**)

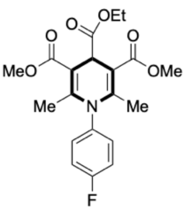


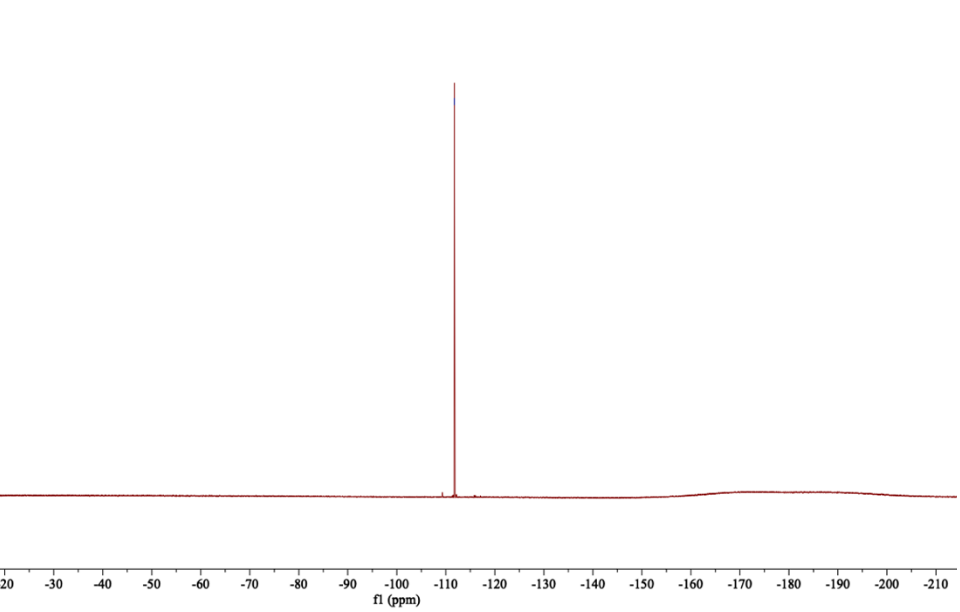


4-Ethyl 3,5-dimethyl 1-(4-fluorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,4,5-tricarboxylate (**3ia**)

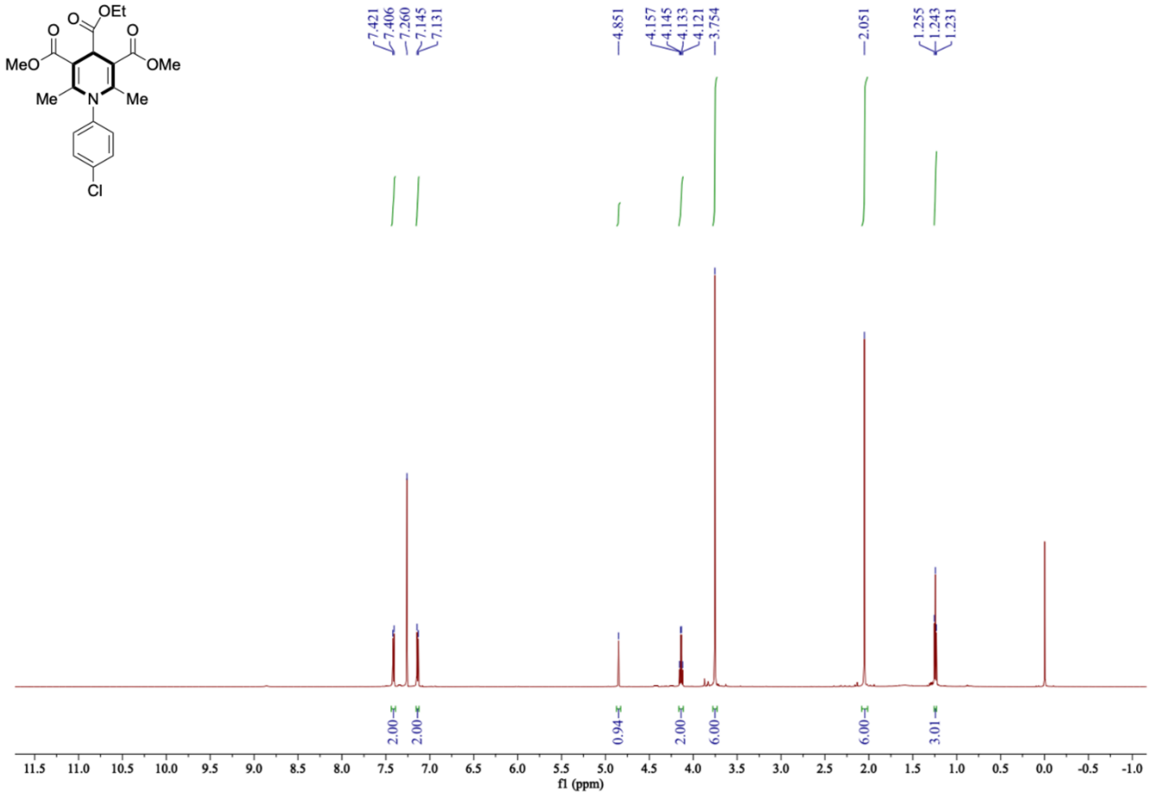




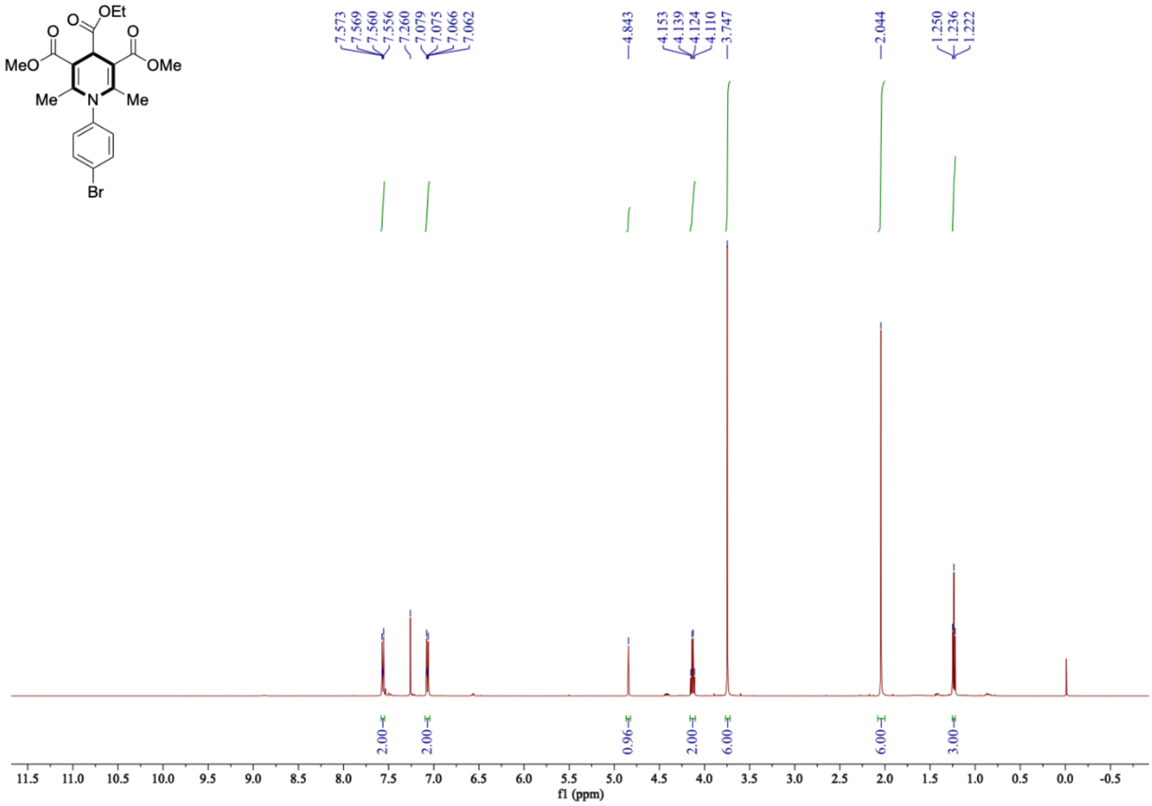

OEt
O
O
O
MeO
OMe
Me
N
Me
F

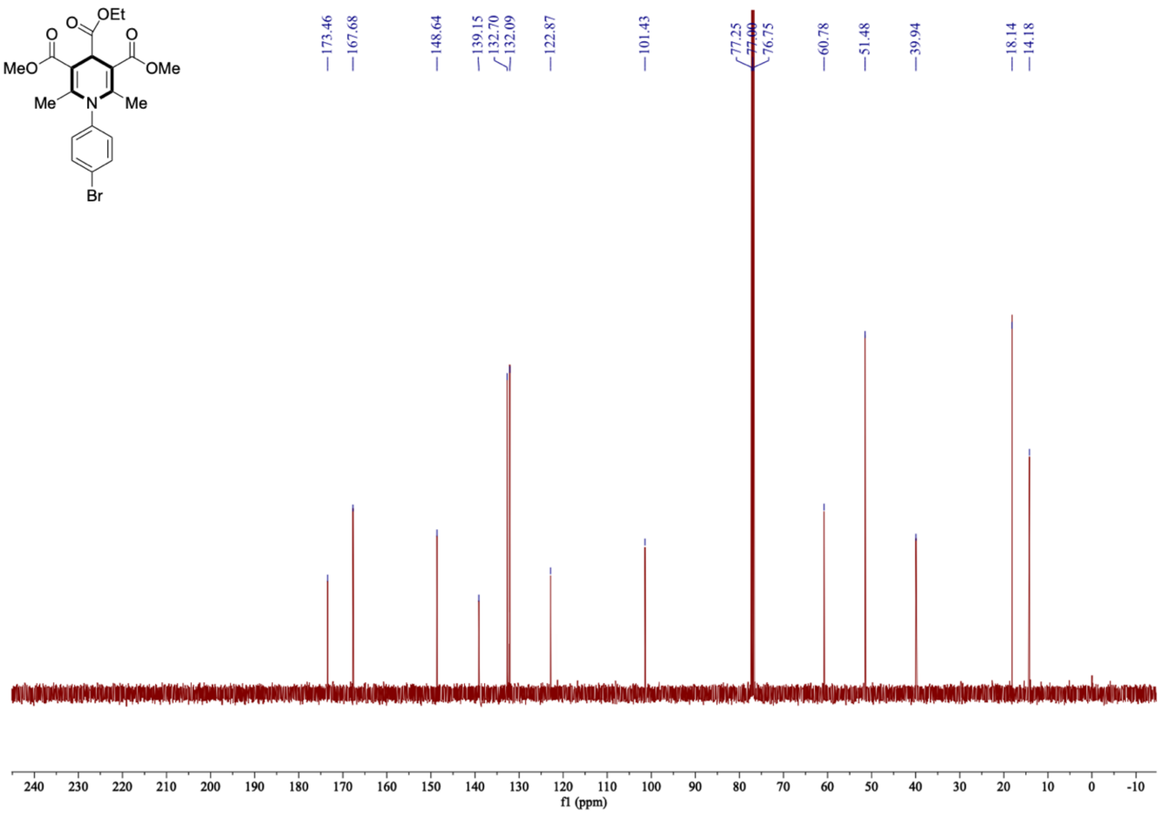

-111.73
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

4-Ethyl 3,5-dimethyl 1-(4-chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,4,5-tricarboxylate (**3ja**)

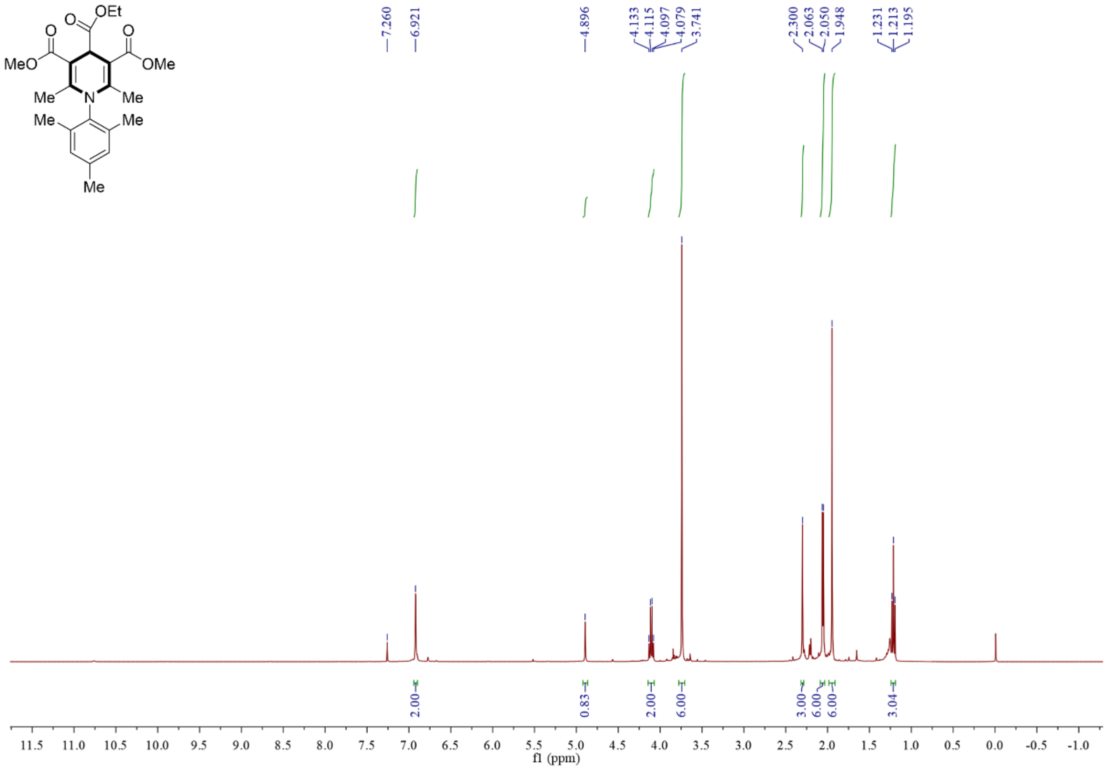


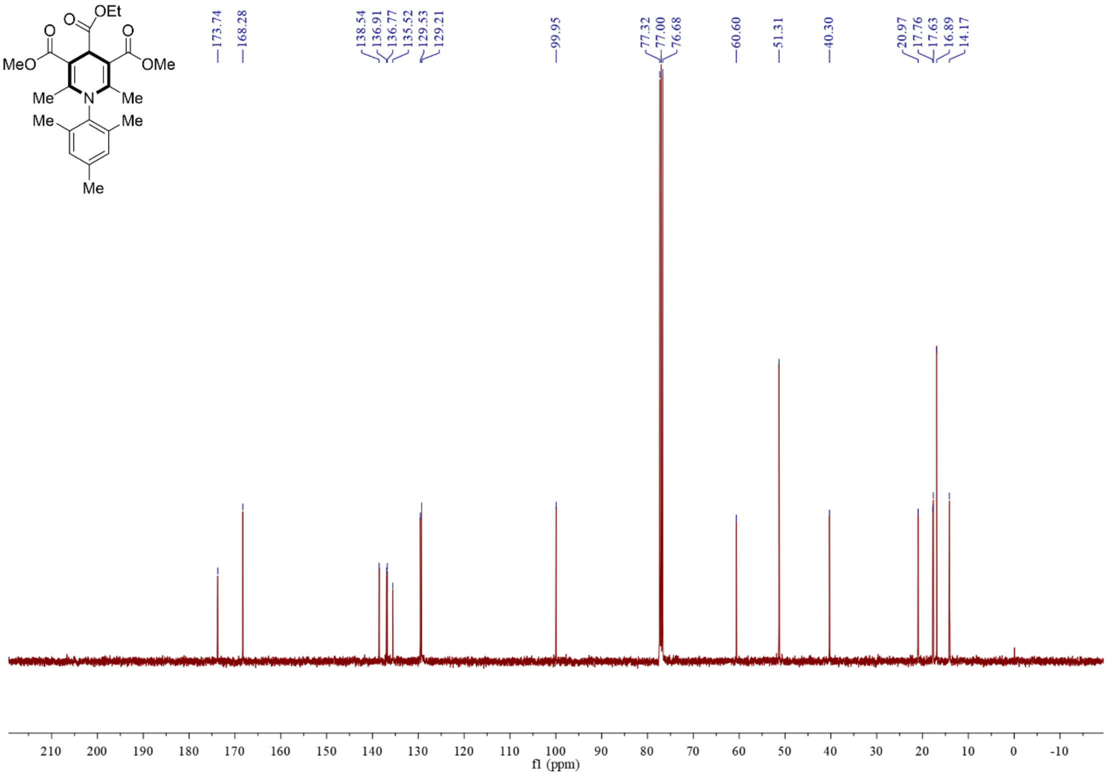
4-Ethyl 3,5-dimethyl 1-(4-bromophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,4,5-tricarboxylate (**3ka**)



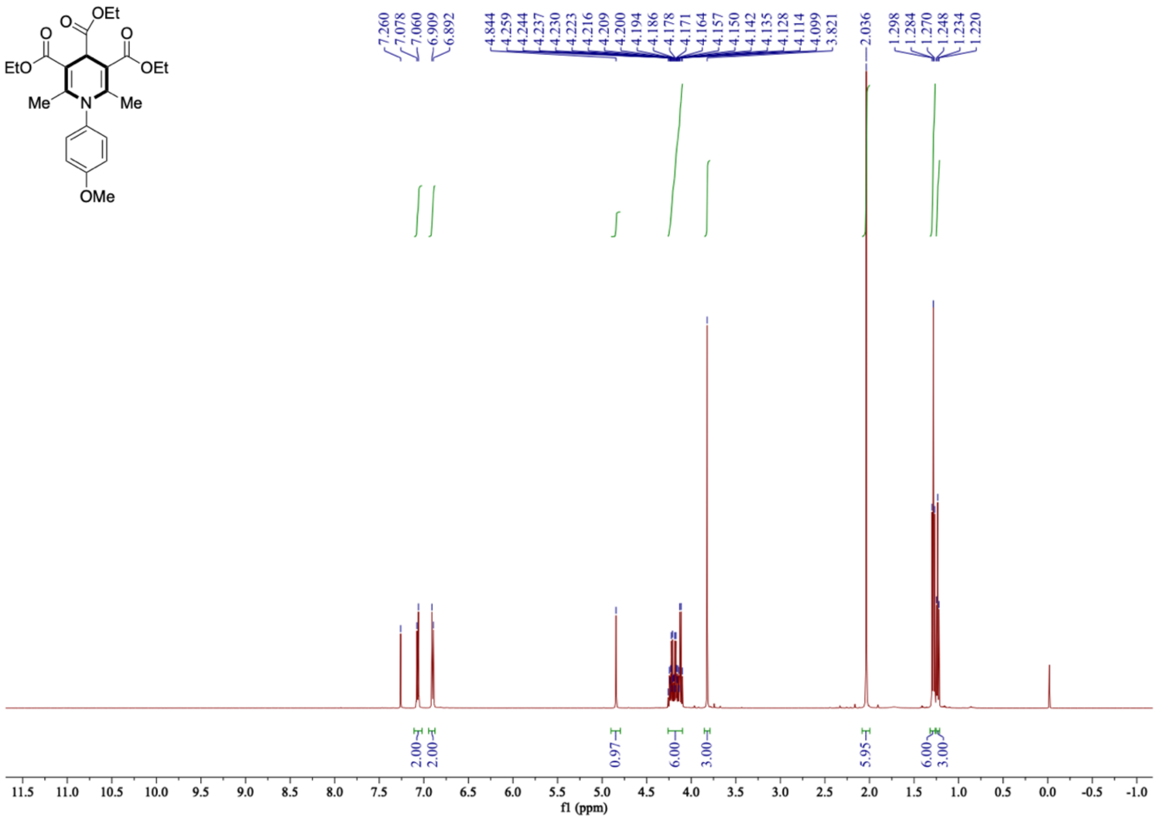


4-ethyl 3,5-dimethyl 1-mesityl-2,6-dimethyl-1,4-dihydropyridine-3,4,5-tricarboxylate (**3na**)

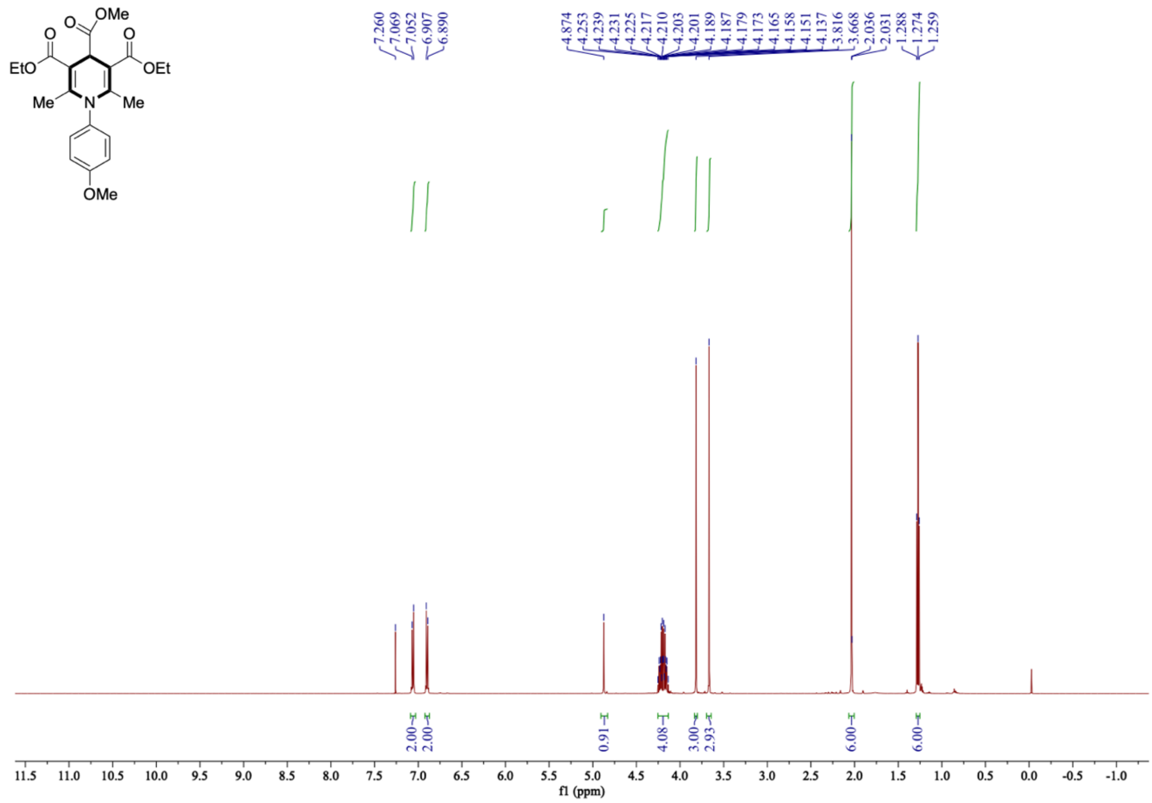


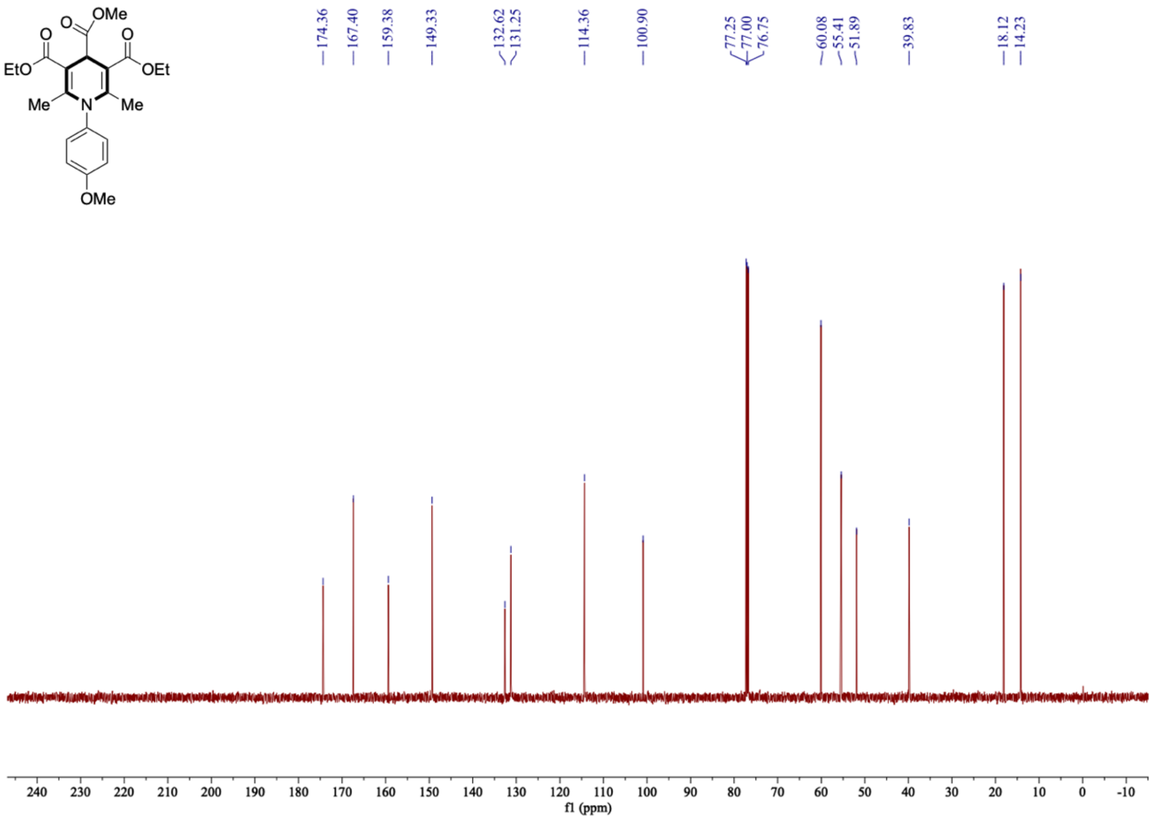


Triethyl 1-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,4,5-tricarboxylate (**3ab**)

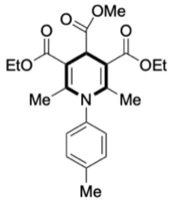


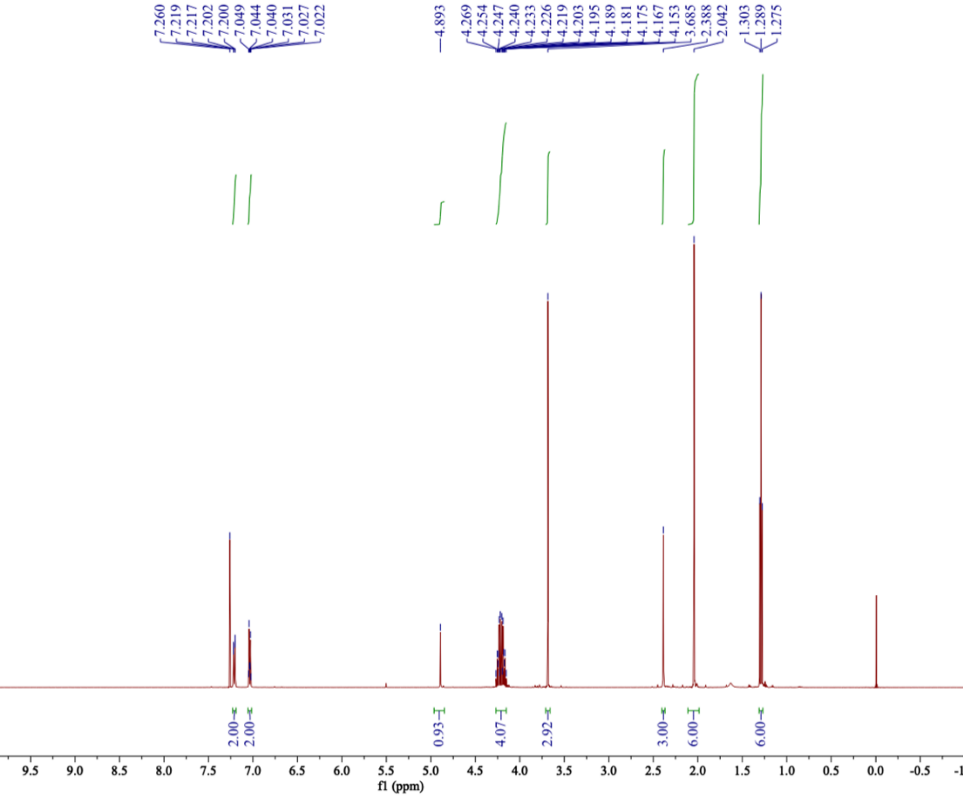
3,5-Diethyl 4-methyl 1-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,4,5-tricarboxylate (**3bb**)



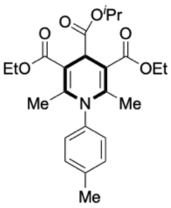


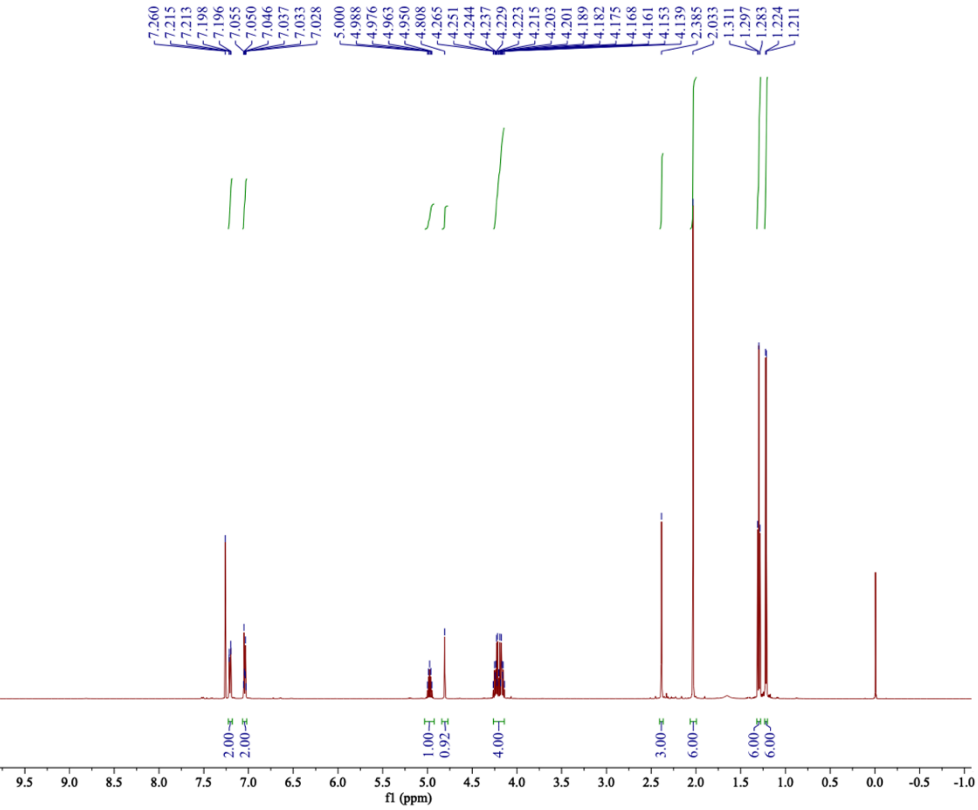
3,5-Diethyl 4-methyl 2,6-dimethyl-1-(p-tolyl)-1,4-dihydropyridine-3,4,5-tricarboxylate (**3lb**)



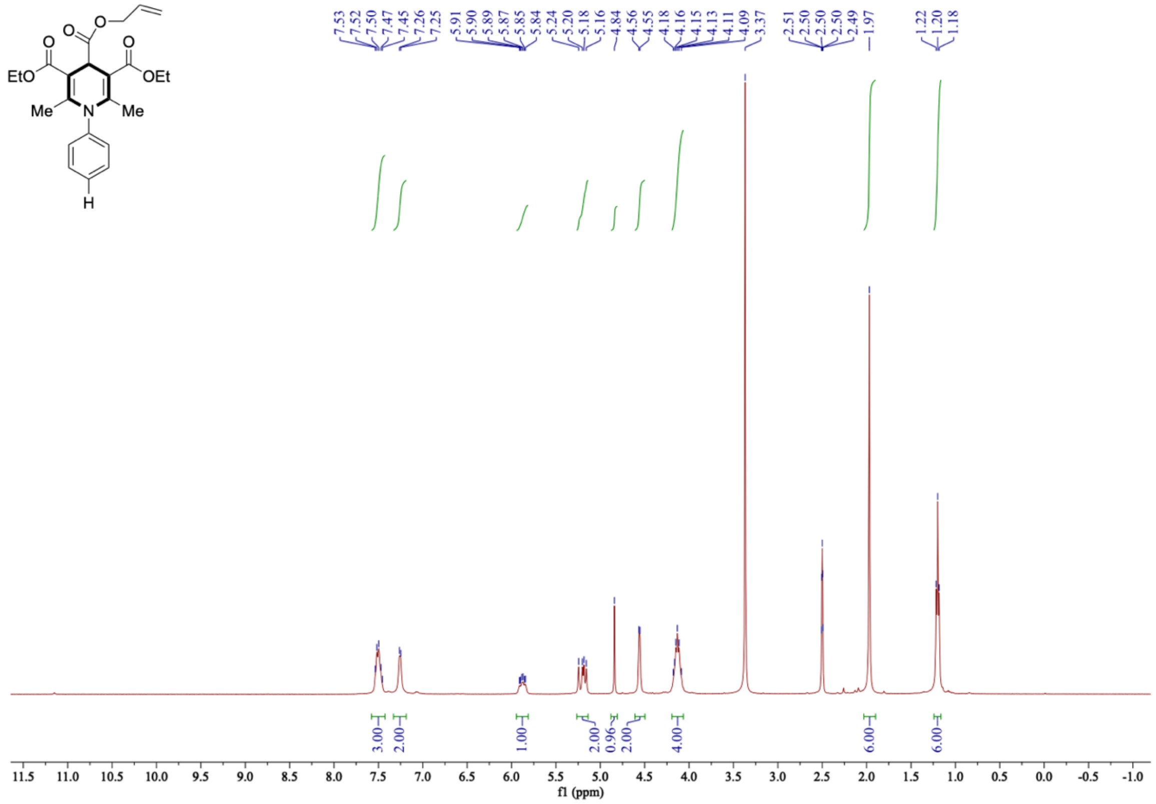


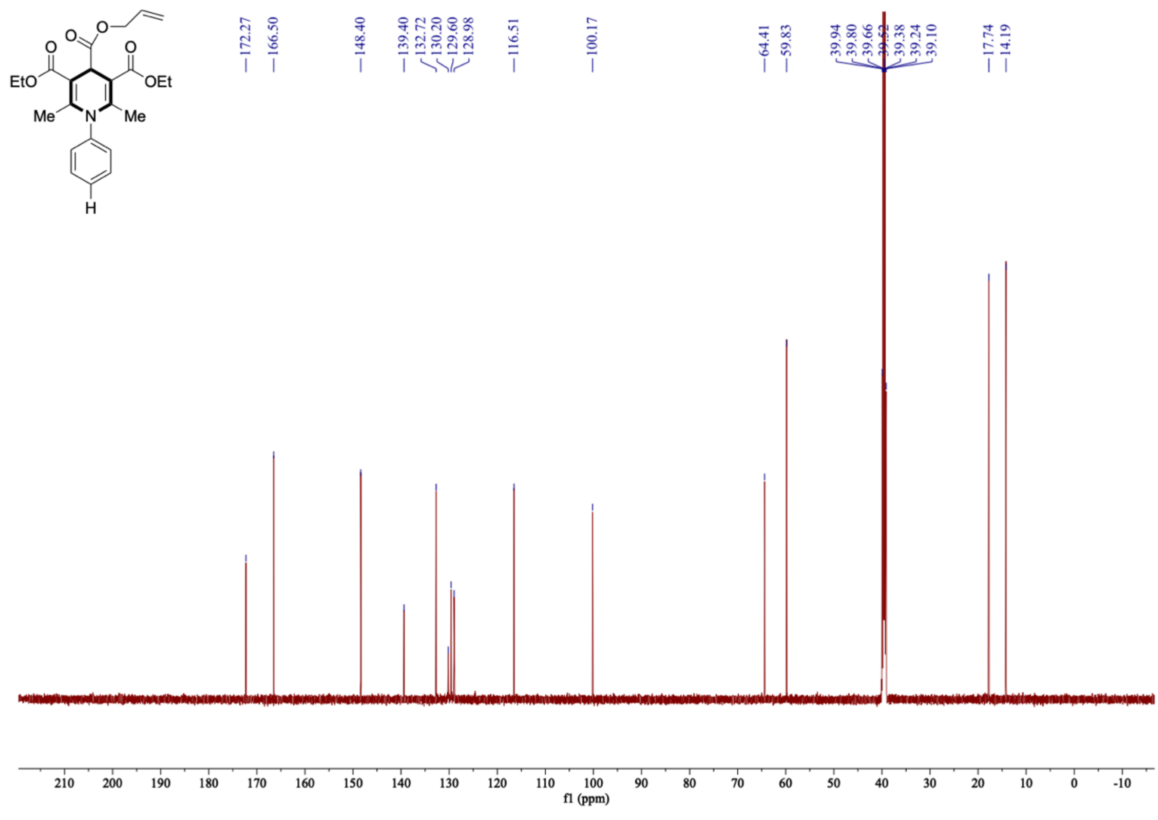
3,5-diethyl 4-isopropyl 2,6-dimethyl-1-(p-tolyl)-1,4-dihydropyridine-3,4,5-tricarboxylate (**3gb**)



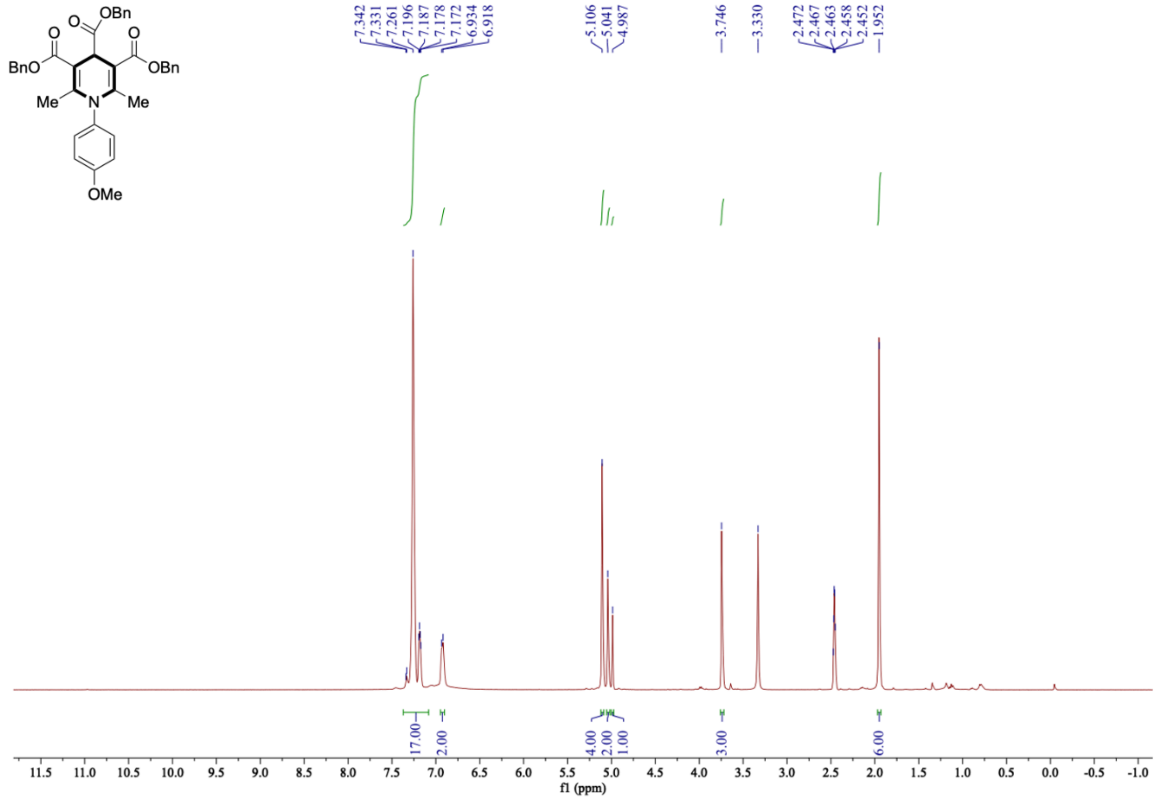


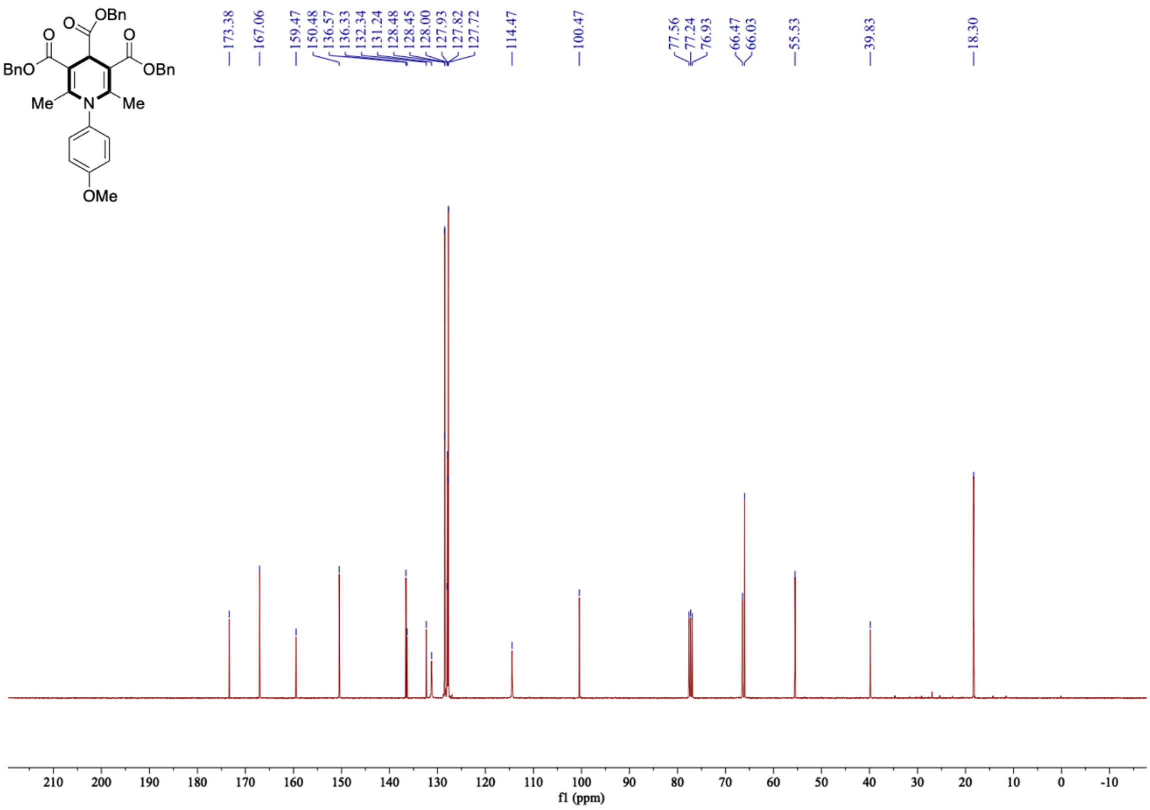
4-Allyl 3,5-diethyl 2,6-dimethyl-1-phenyl-1,4-dihydropyridine-3,4,5-tricarboxylate (**3mb**)



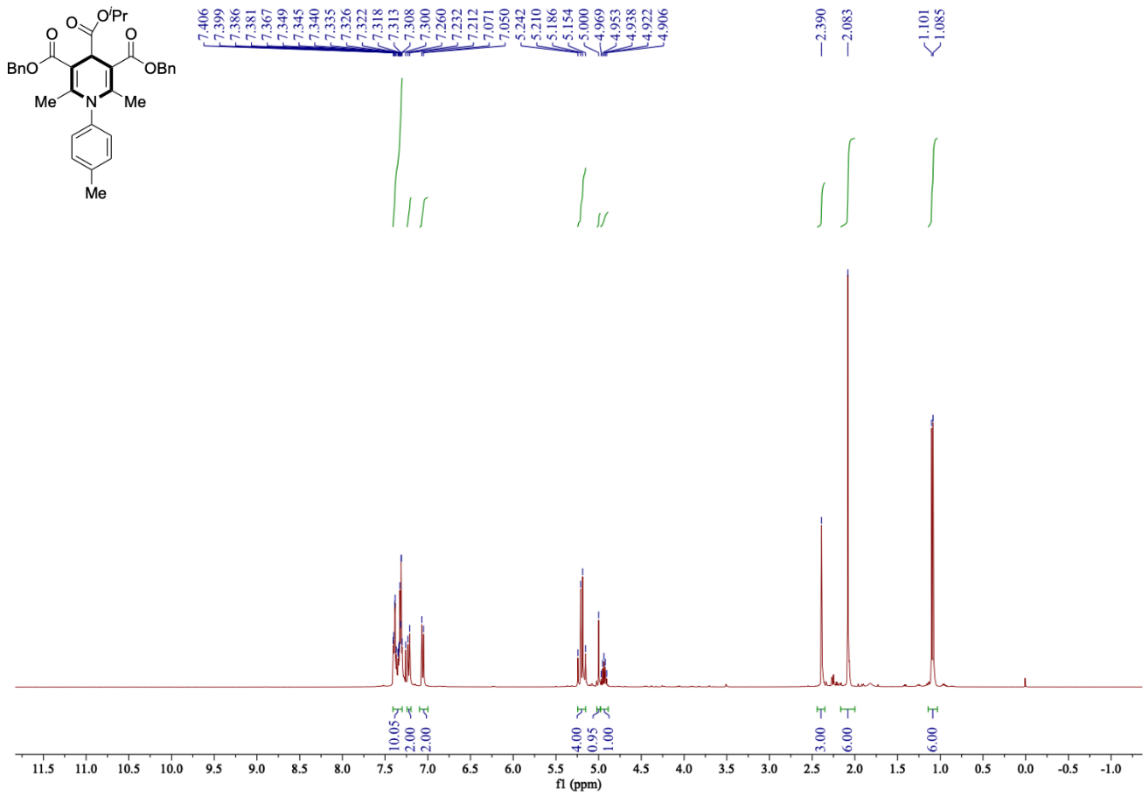


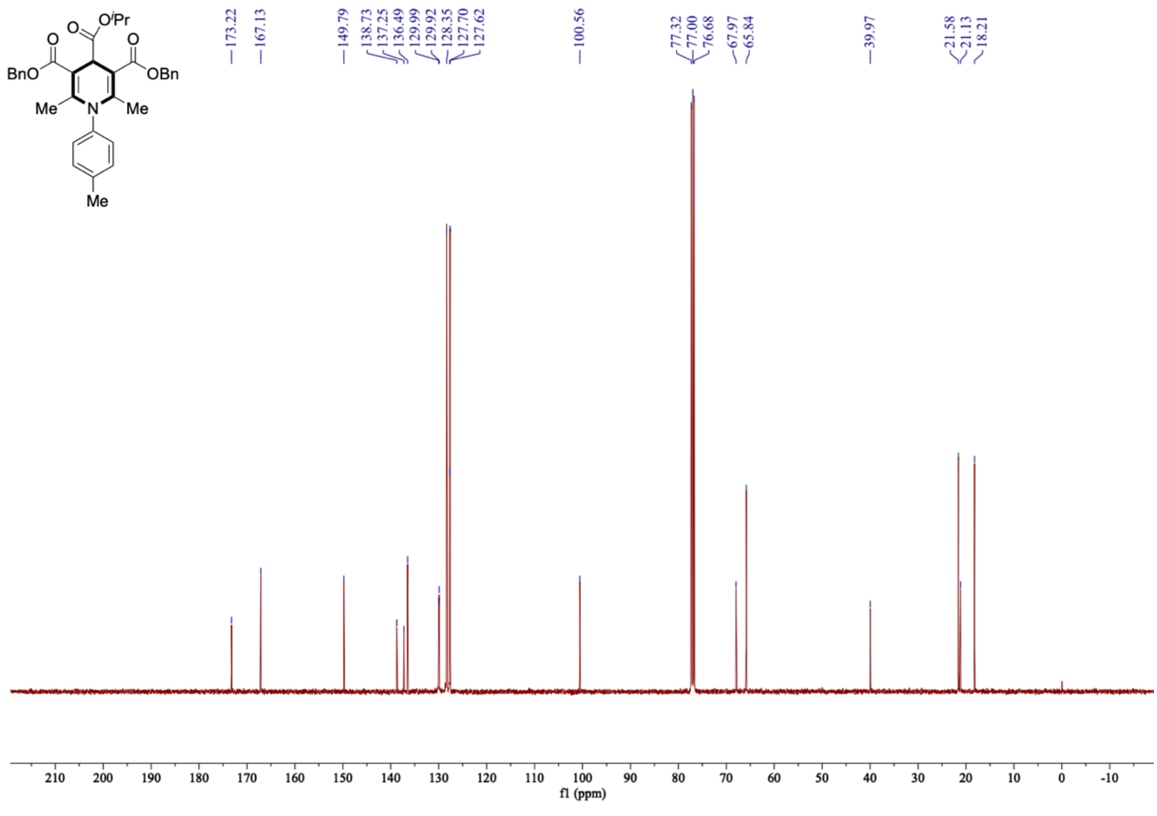
Tribenzyl 1-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,4,5-tricarboxylate (**3dc**)



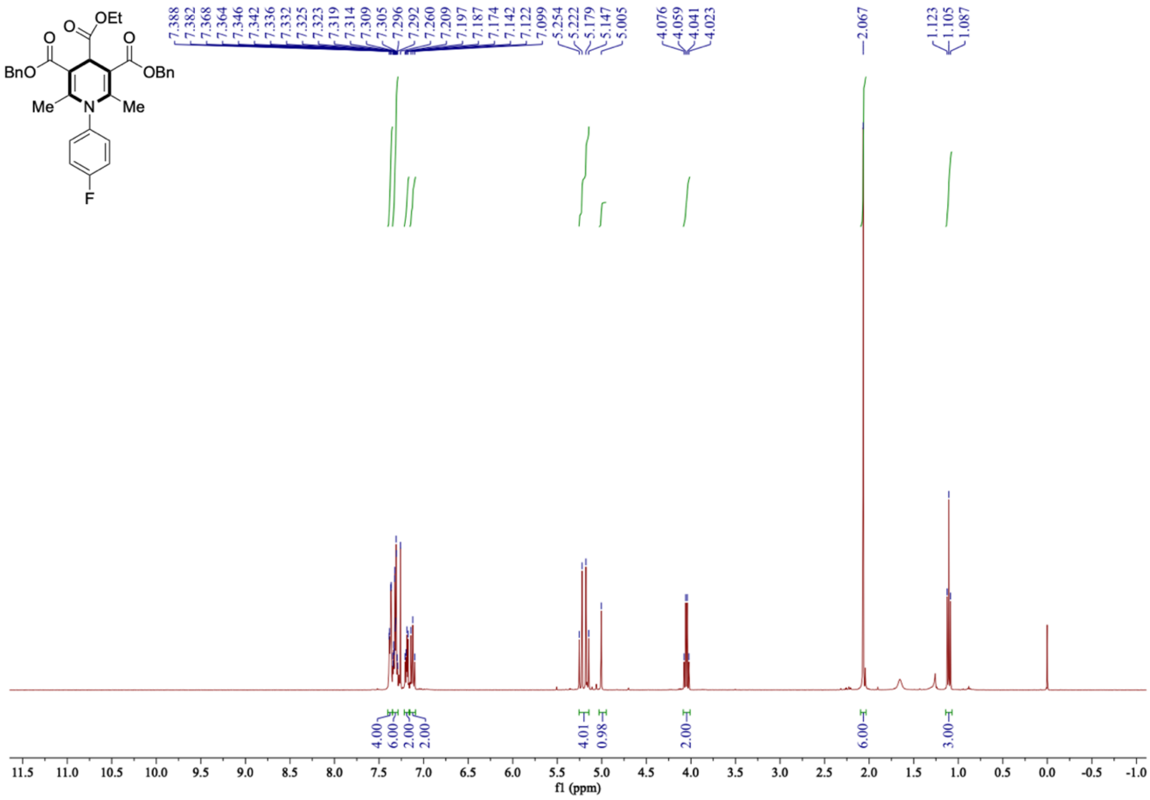


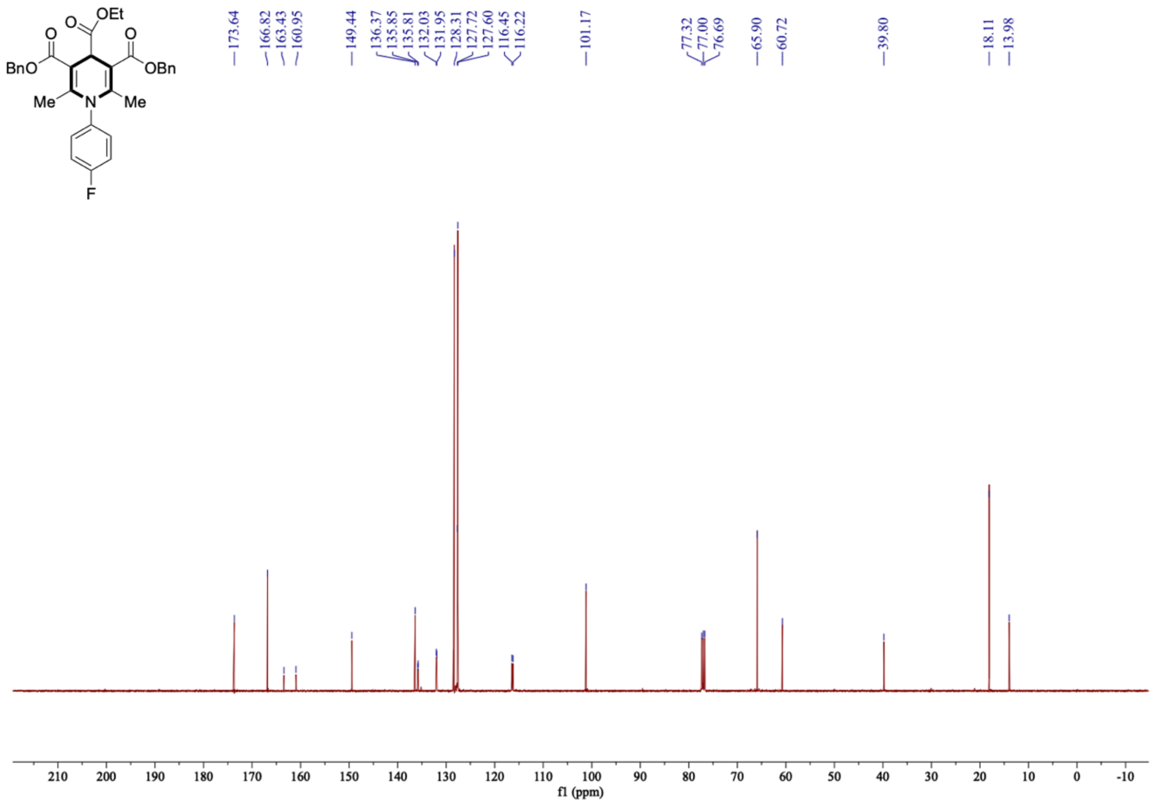
3,5-Dibenzyl 4-isopropyl 2,6-dimethyl-1-(p-tolyl)-1,4-dihydropyridine-3,4,5-tricarboxylate (**3gc**)

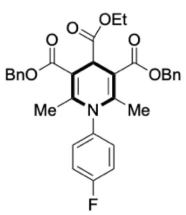


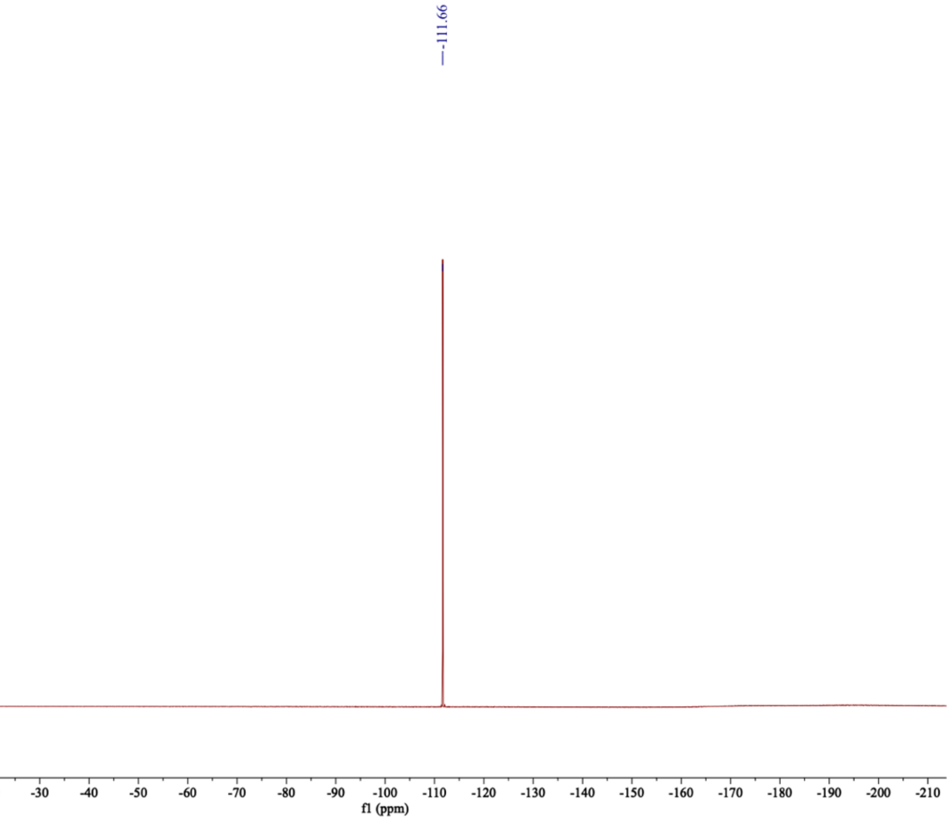


3,5-Dibenzyl 4-ethyl 1-(4-fluorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,4,5-tricarboxylate (**3ic**)

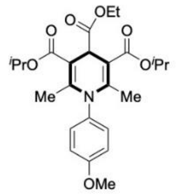


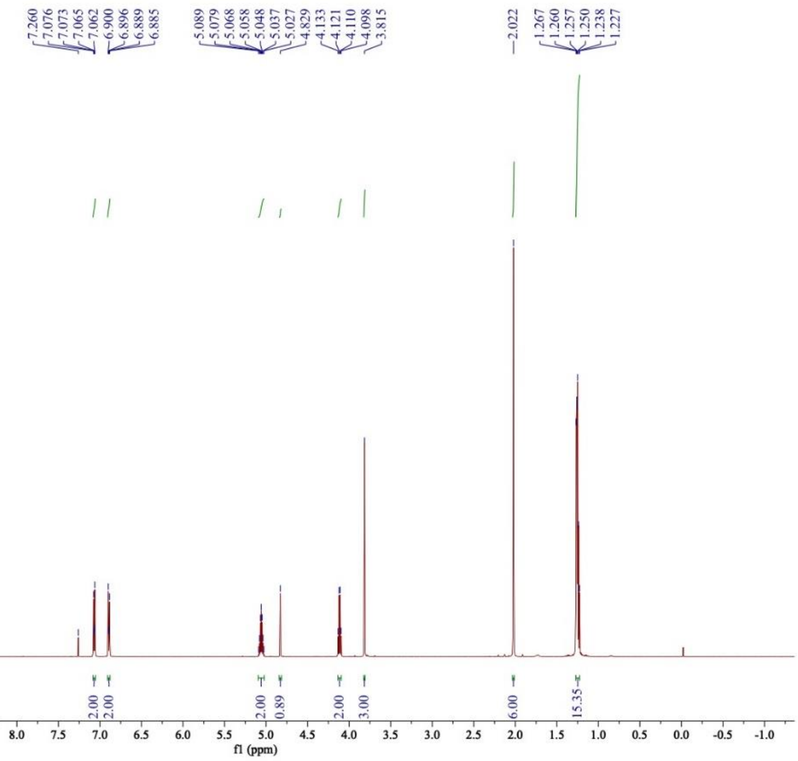



OEt
O
O
O
BnO
OBn
Me
N
Me
F

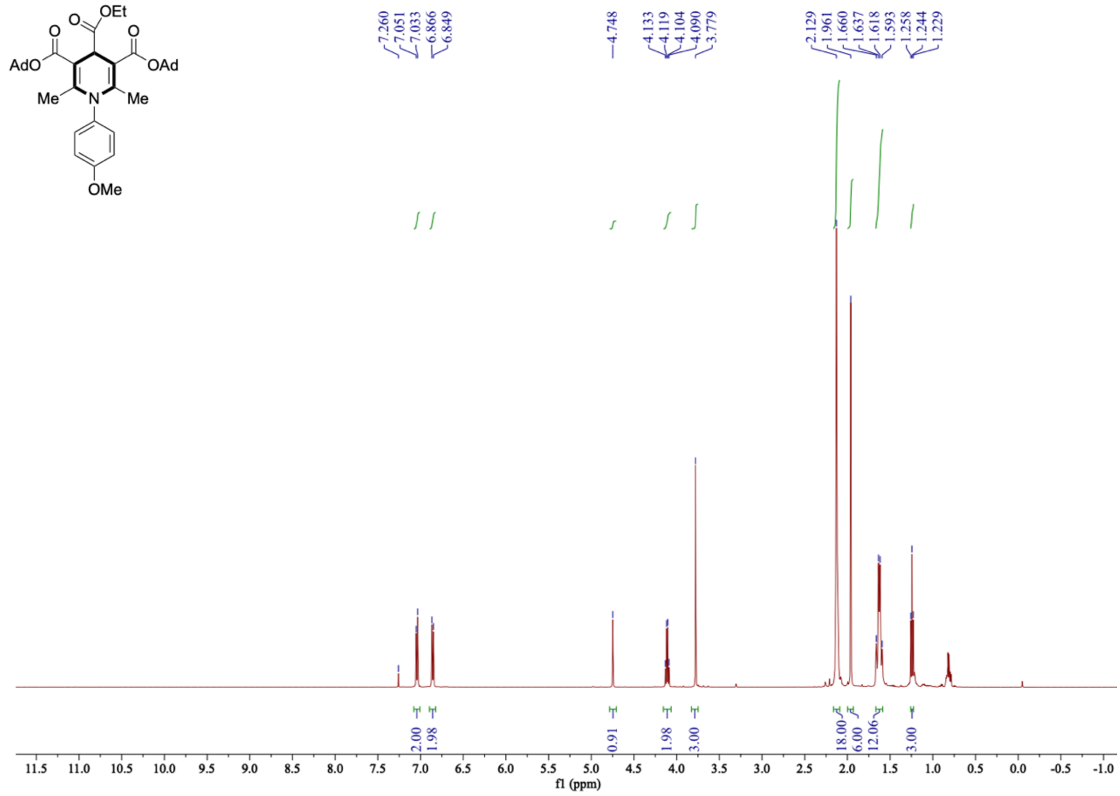

-111.66
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

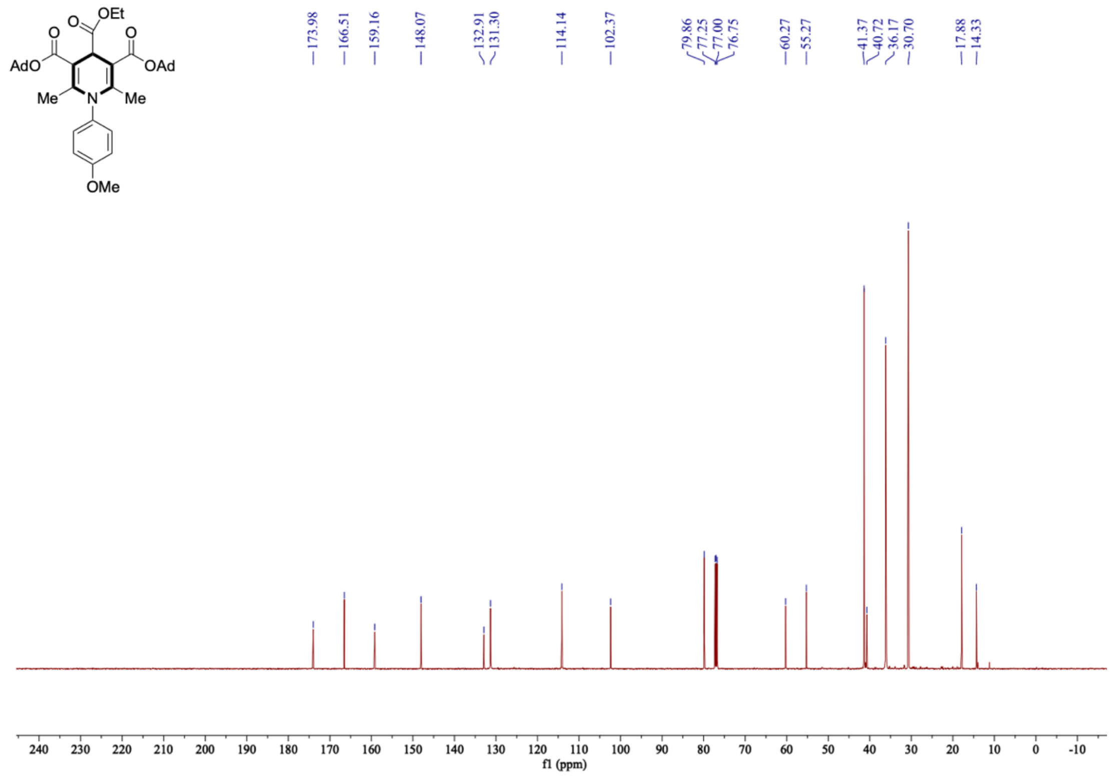
4-Ethyl 3,5-diisopropyl 1-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,4,5-tricarboxylate (**3ad**)



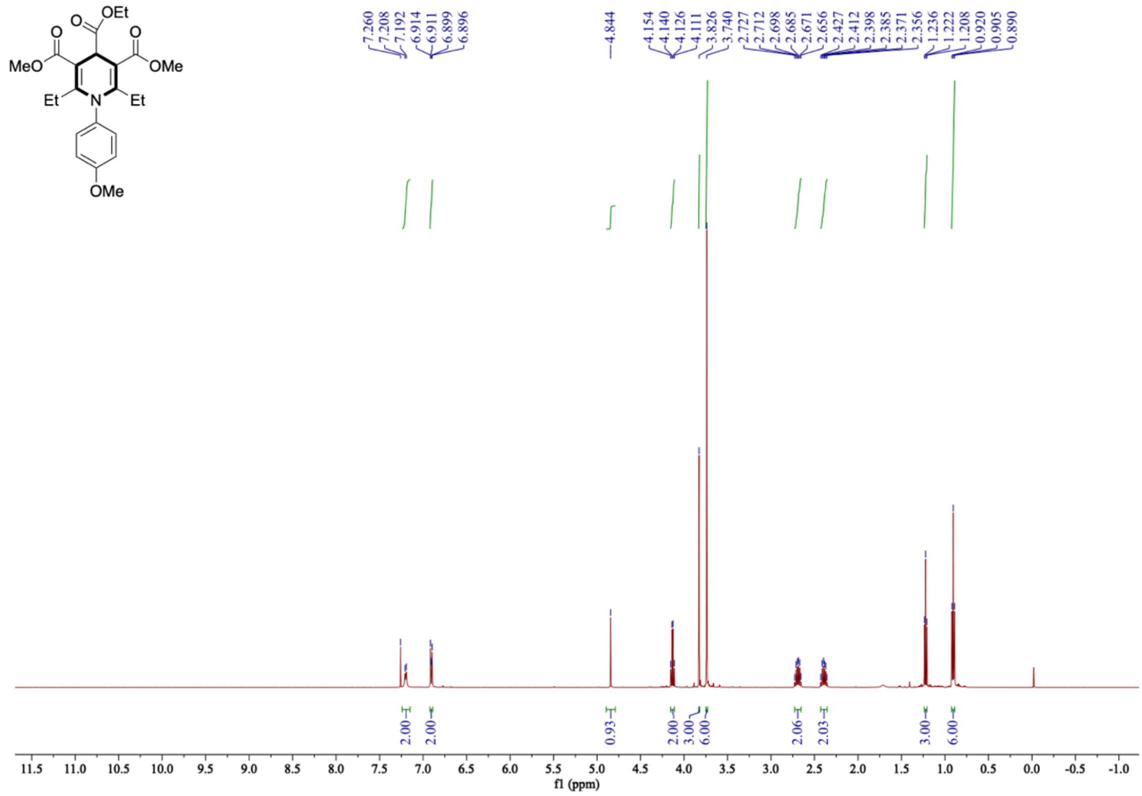


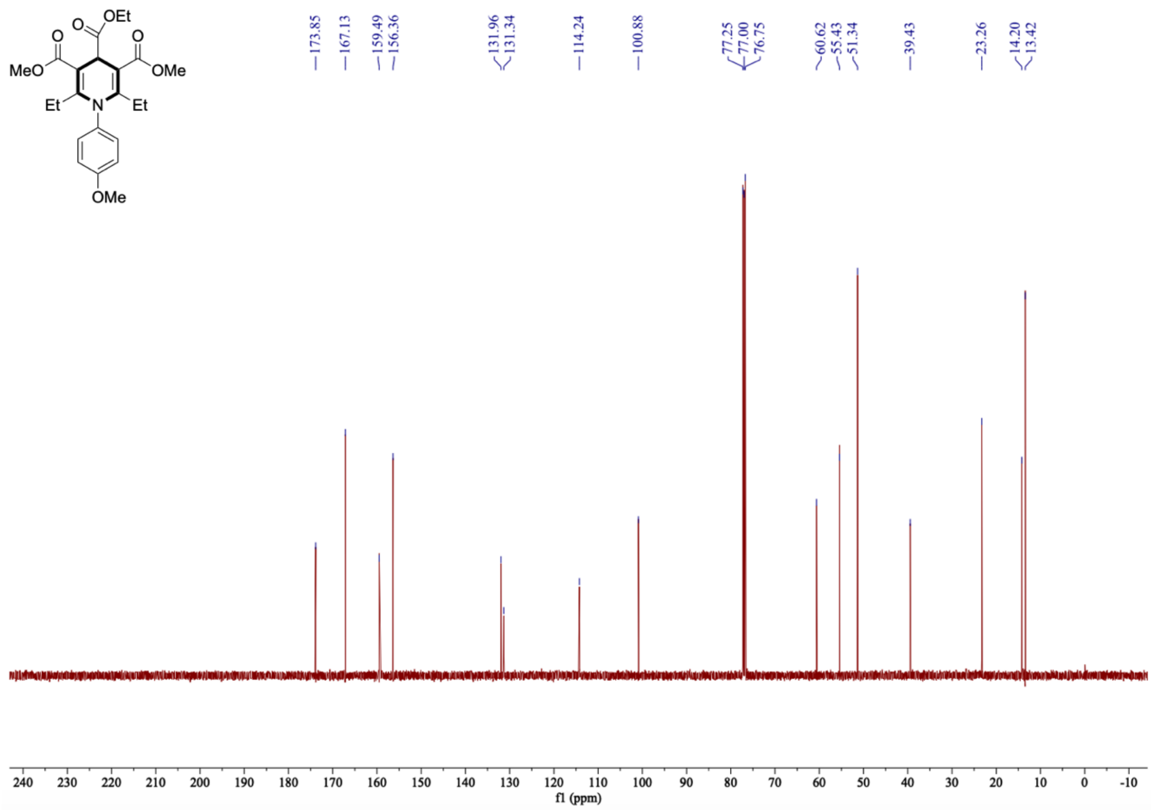
3,5-Di(adamantan-1-yl) 4-ethyl 1-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,4,5-tricarboxylate (**3ae**)



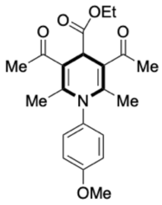


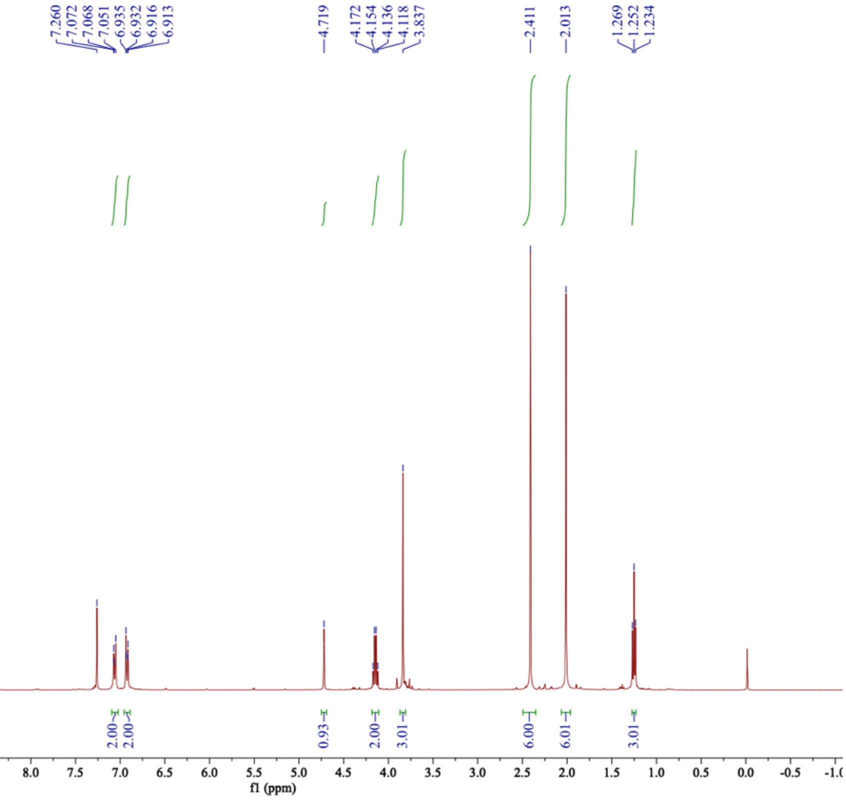
4-Ethyl 3,5-dimethyl 2,6-diethyl-1-(4-methoxyphenyl)-1,4-dihydropyridine-3,4,5-tricarboxylate (**3af**)



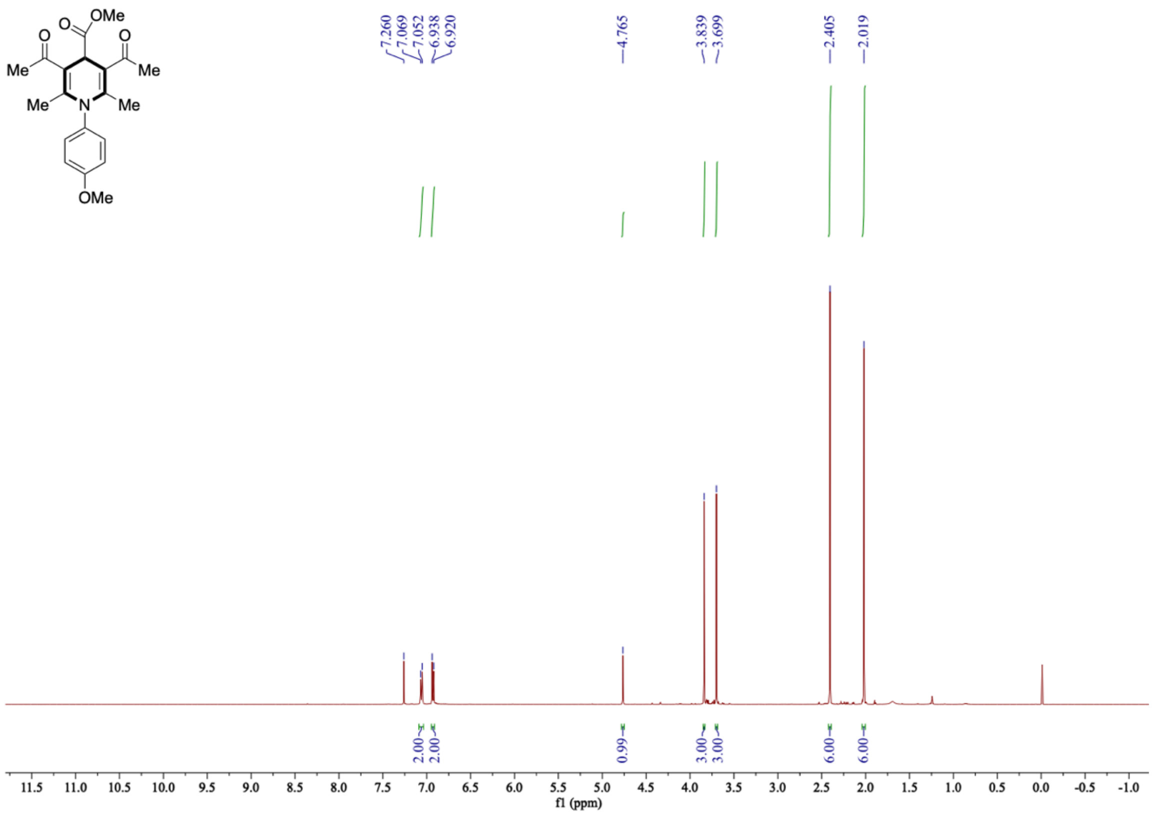


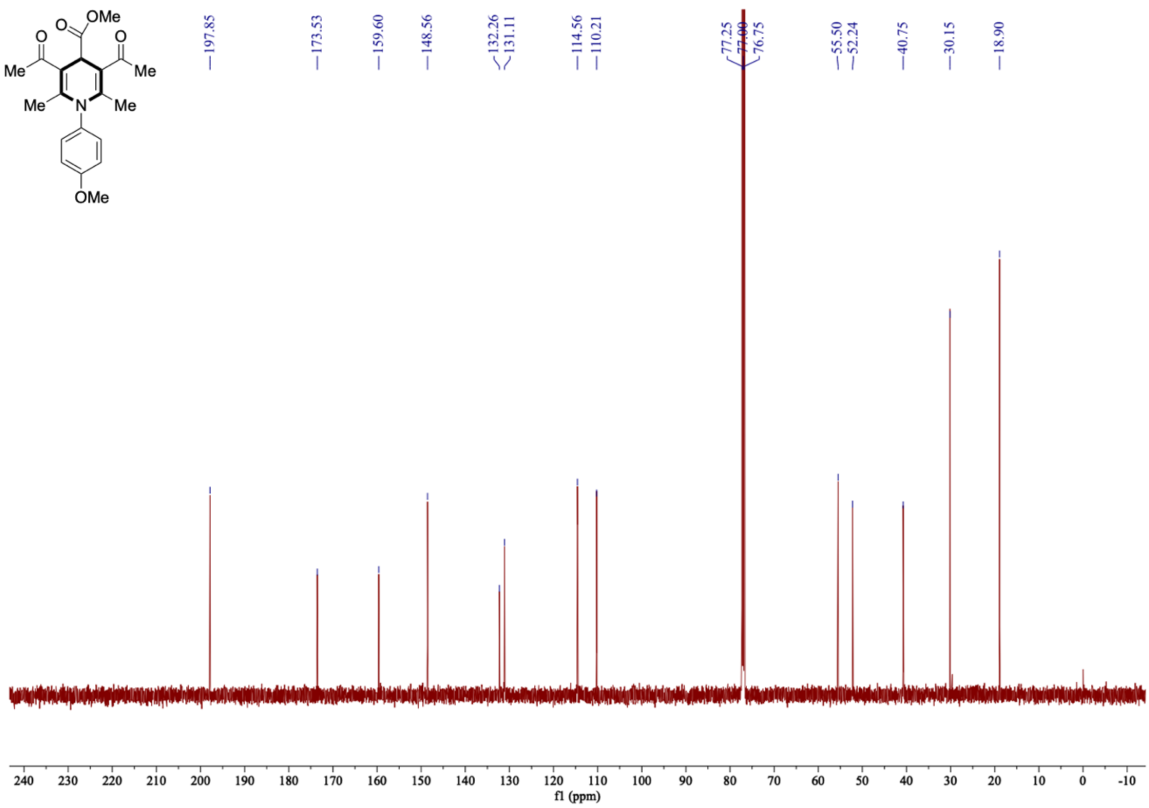
Ethyl 3,5-diacetyl-1-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-4-carboxylate (**3ag**)



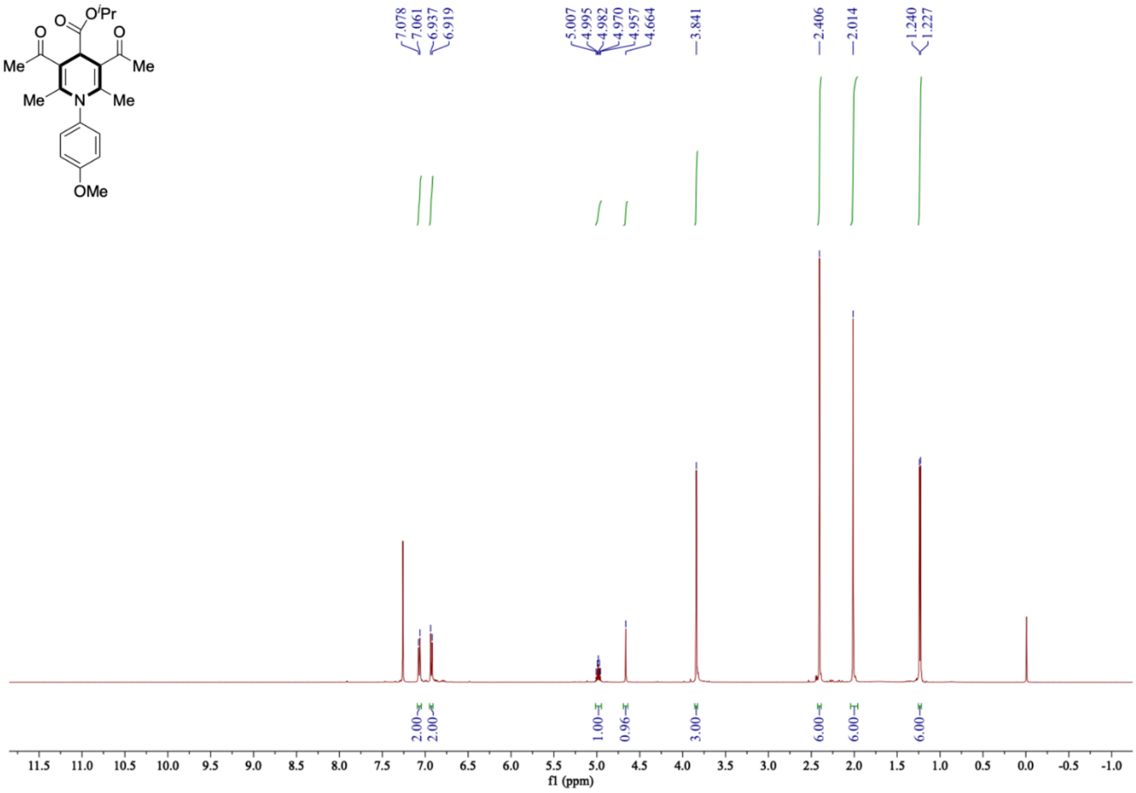


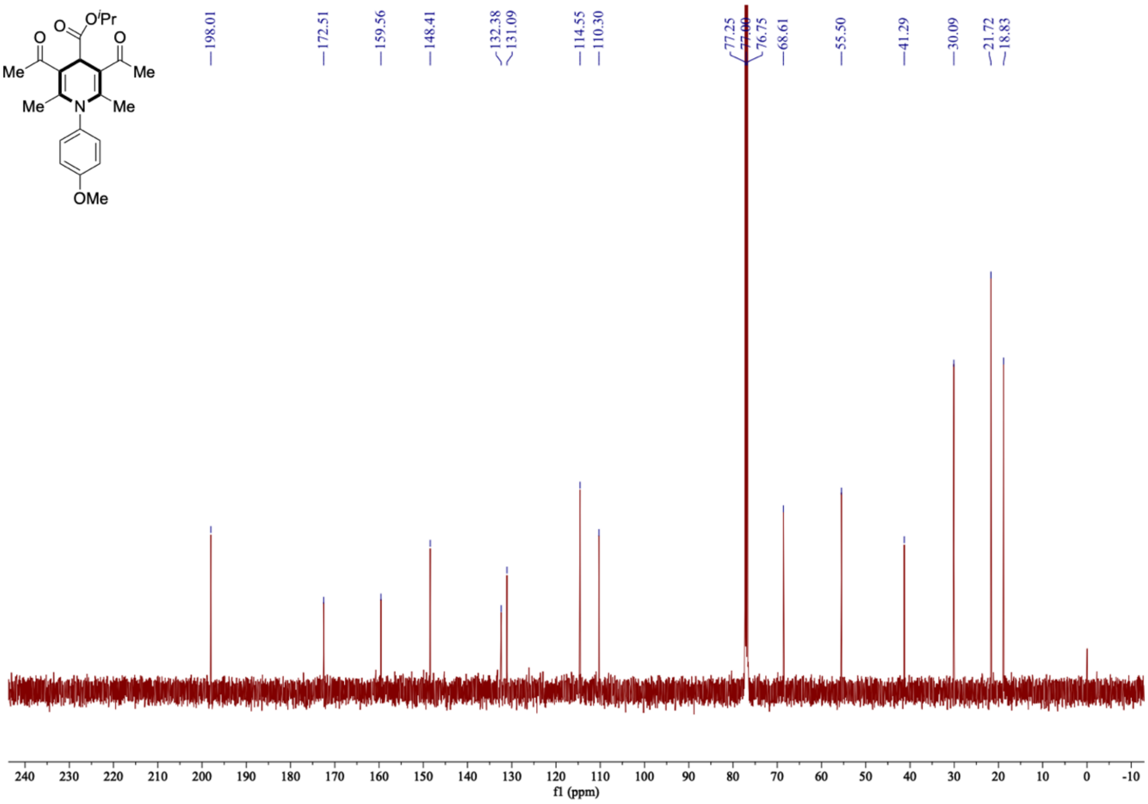
Methyl 3,5-diacetyl-1-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-4-carboxylate (**3bg**)



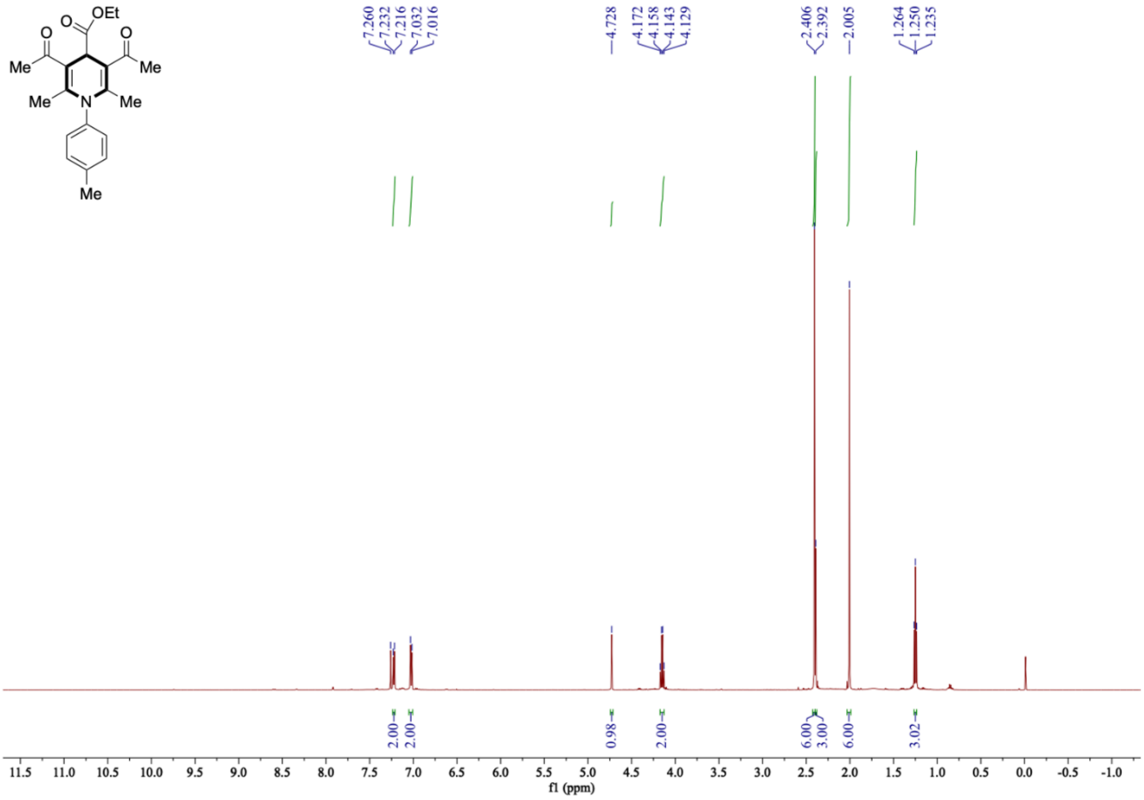


Isopropyl 3,5-diacetyl-1-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-4-carboxylate (**3cg**)

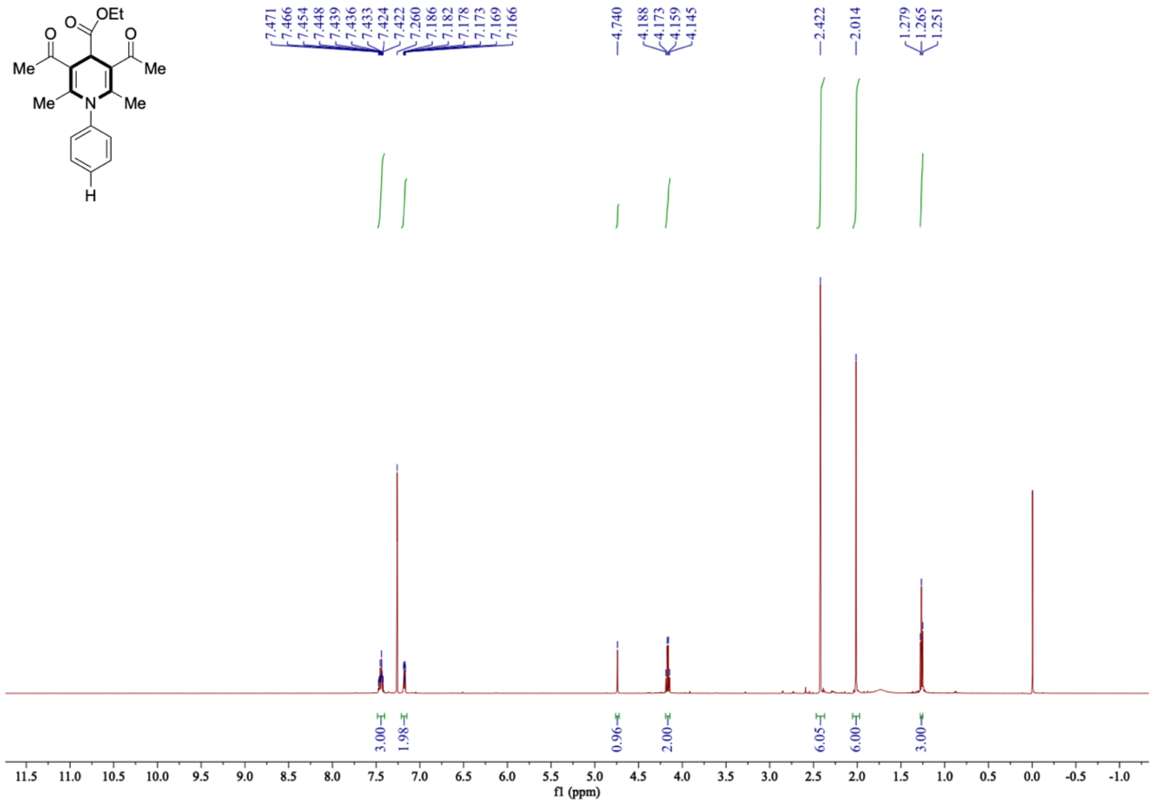




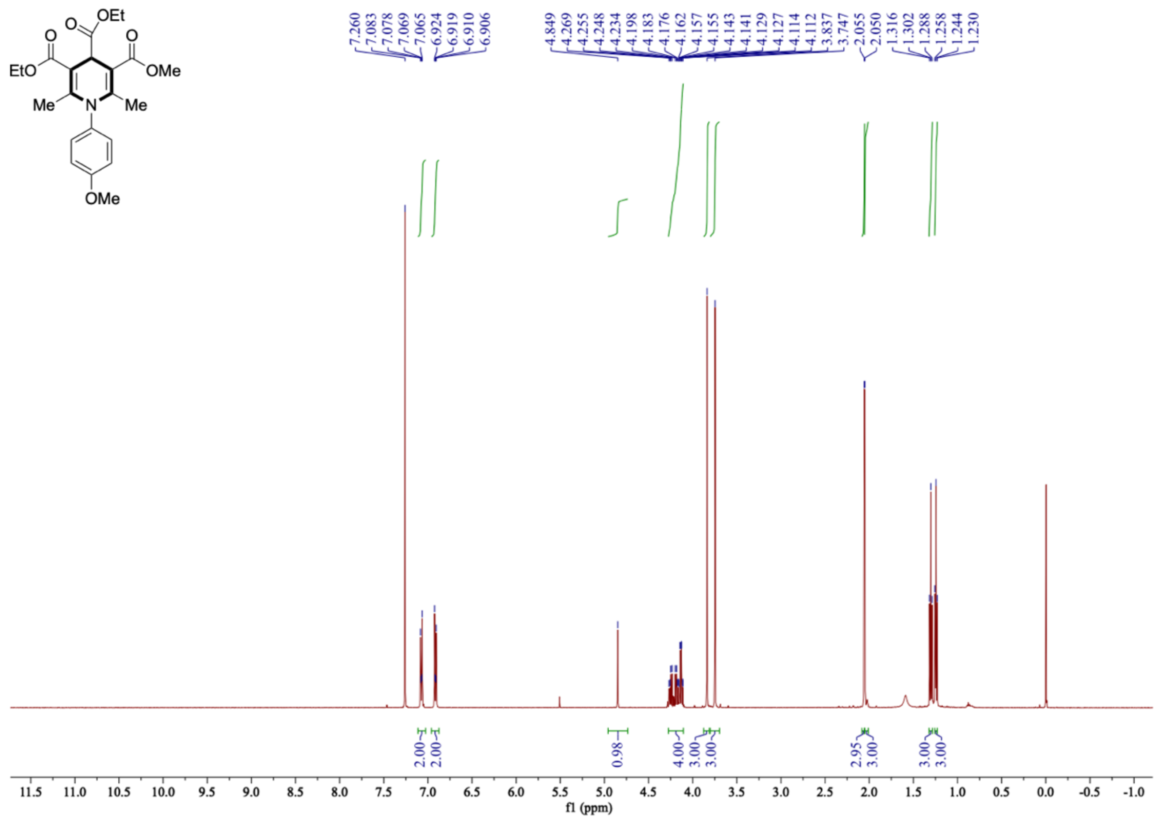
Ethyl 3,5-diacetyl-2,6-dimethyl-1-(p-tolyl)-1,4-dihydropyridine-4-carboxylate (**3fg**)

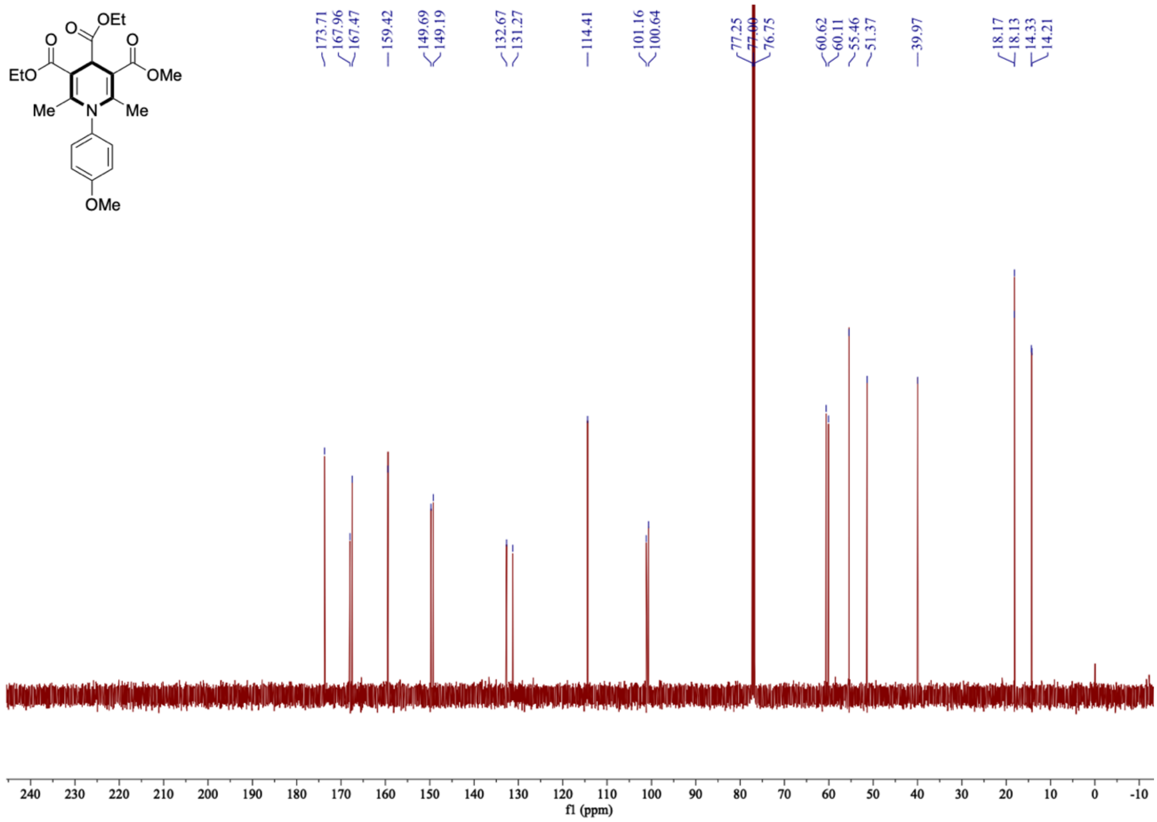


Ethyl 3,5-diacetyl-2,6-dimethyl-1-phenyl-1,4-dihydropyridine-4-carboxylate (**3hg**)

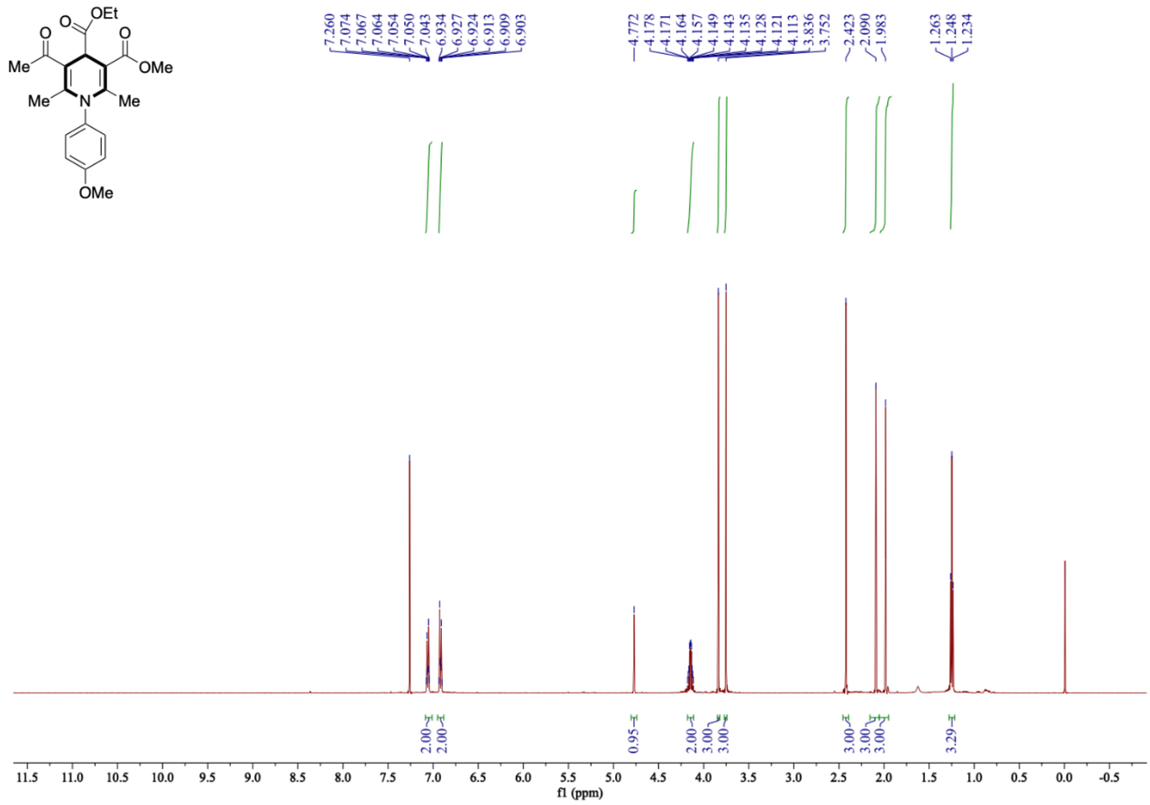


3,4-Diethyl 5-methyl 1-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,4,5-tricarboxylate (**3aab**)

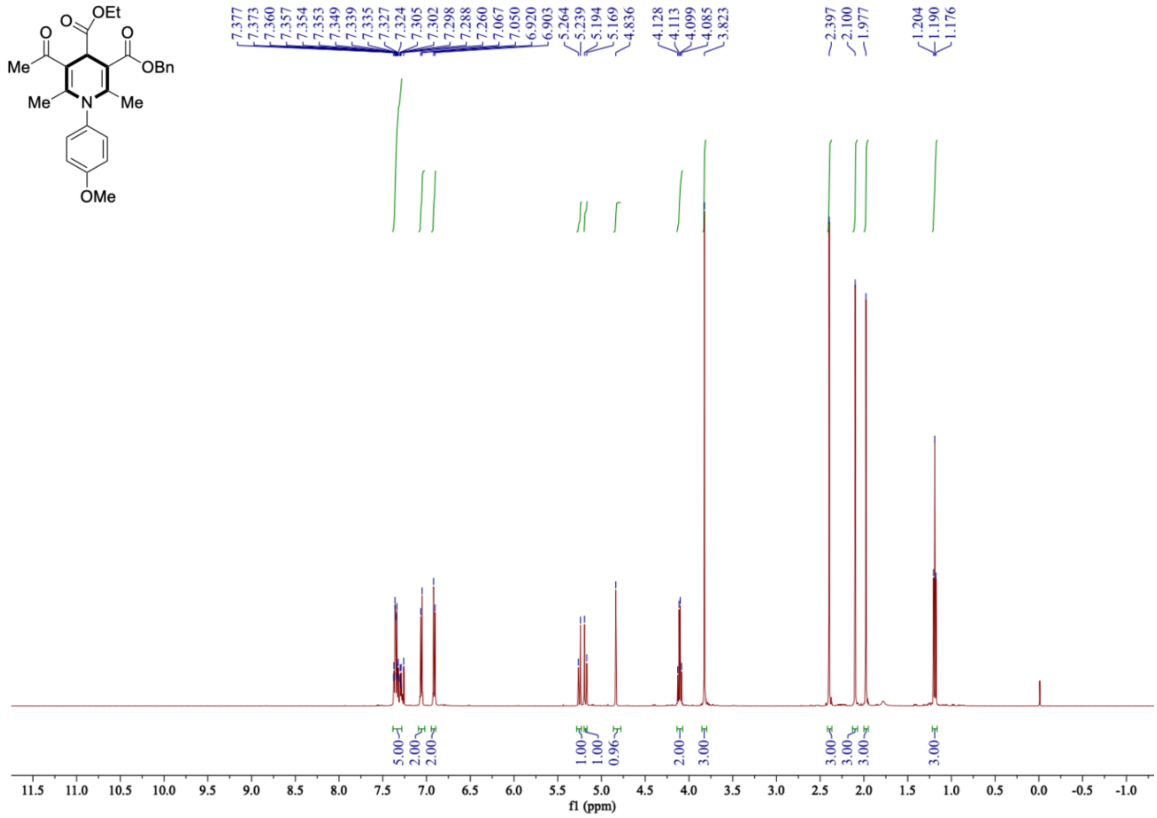


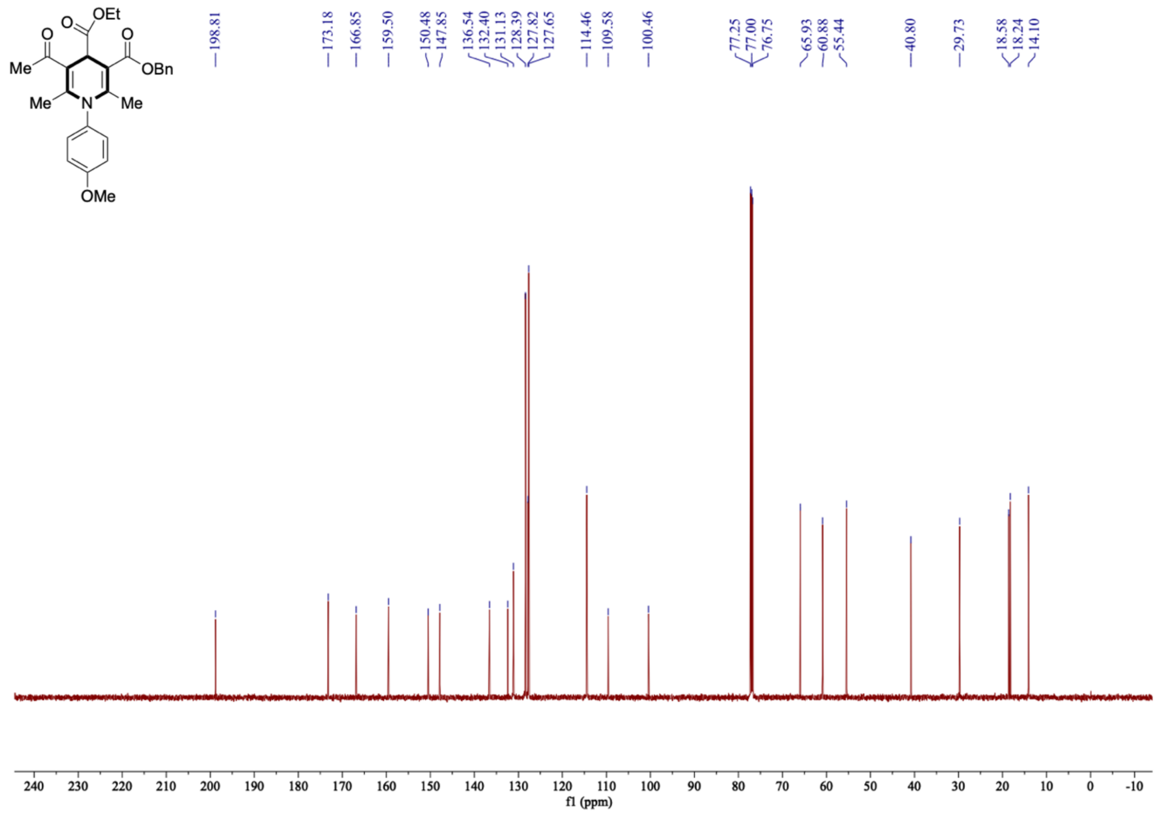


4-Ethyl 3-methyl 5-acetyl-1-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,4-dicarboxylate (**3aag**)

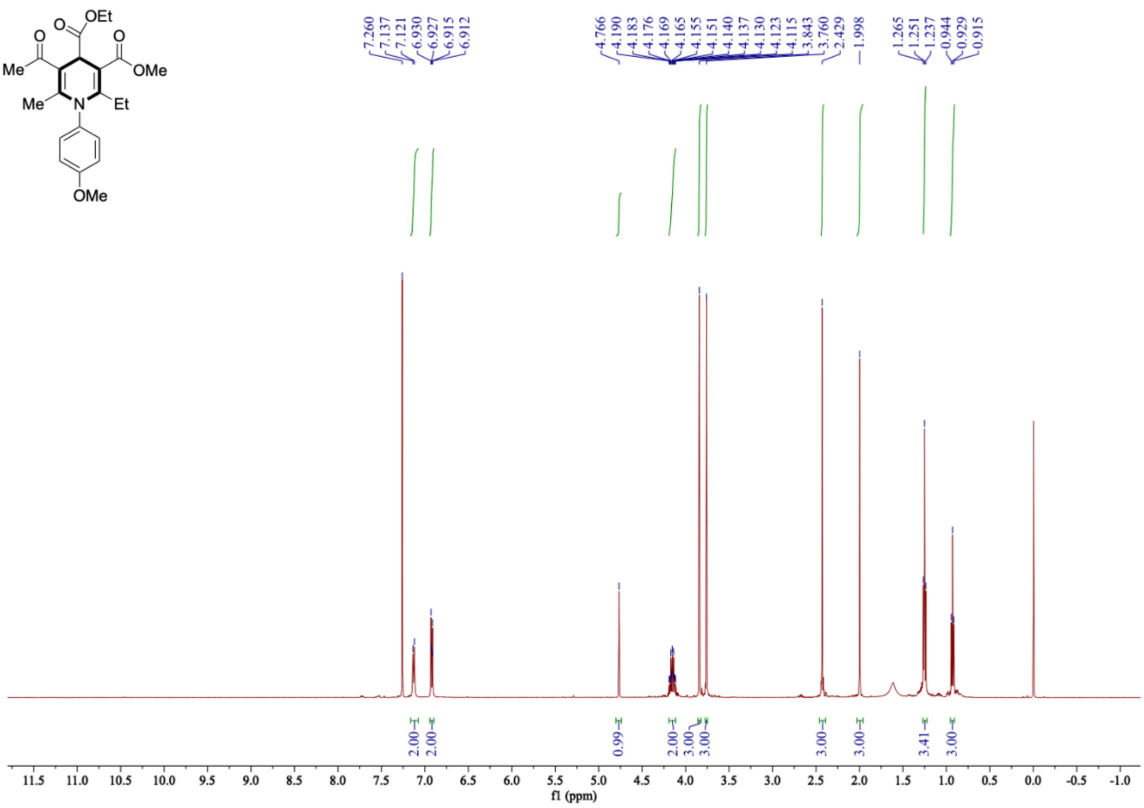


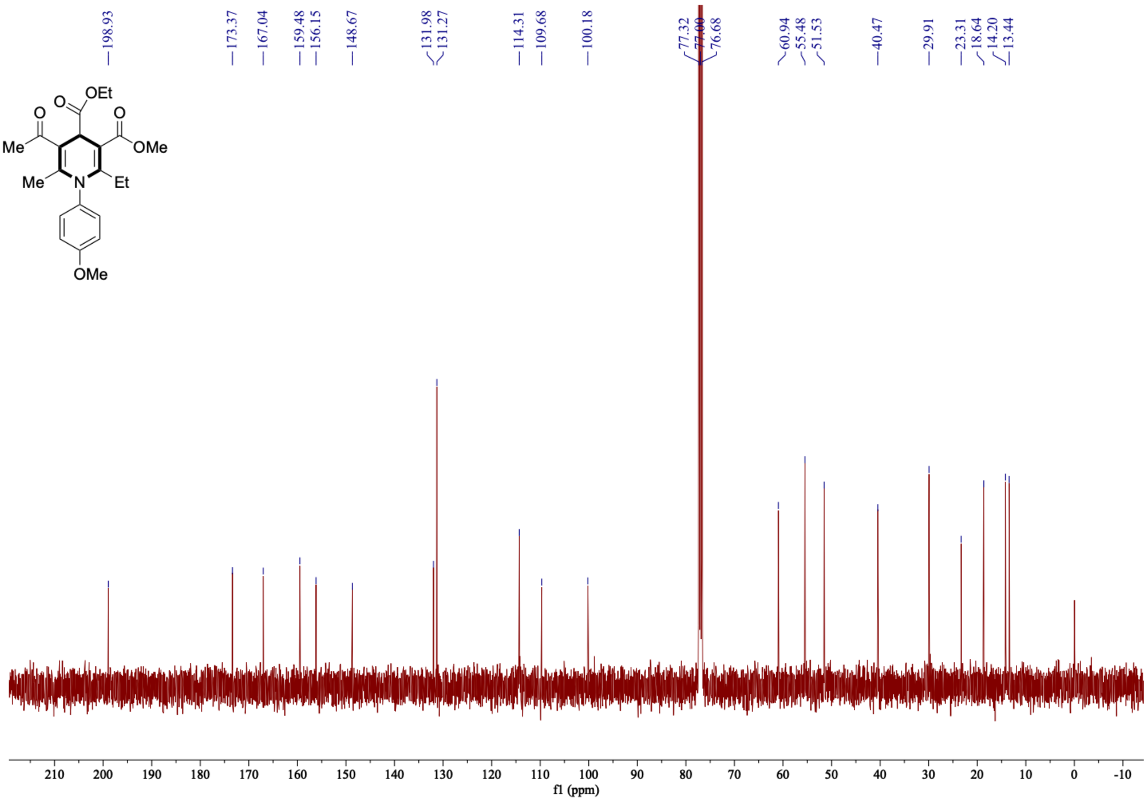
3-Benzyl 4-ethyl 5-acetyl-1-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,4-dicarboxylate (**3acg**)



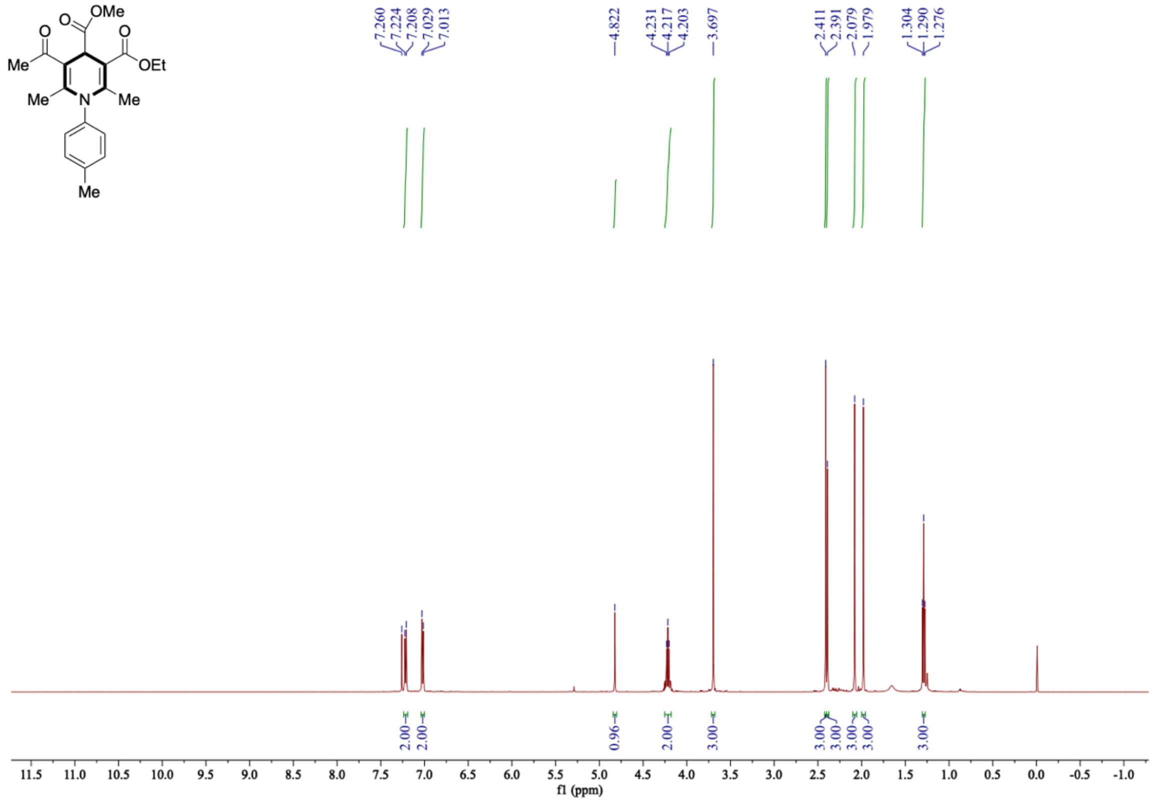


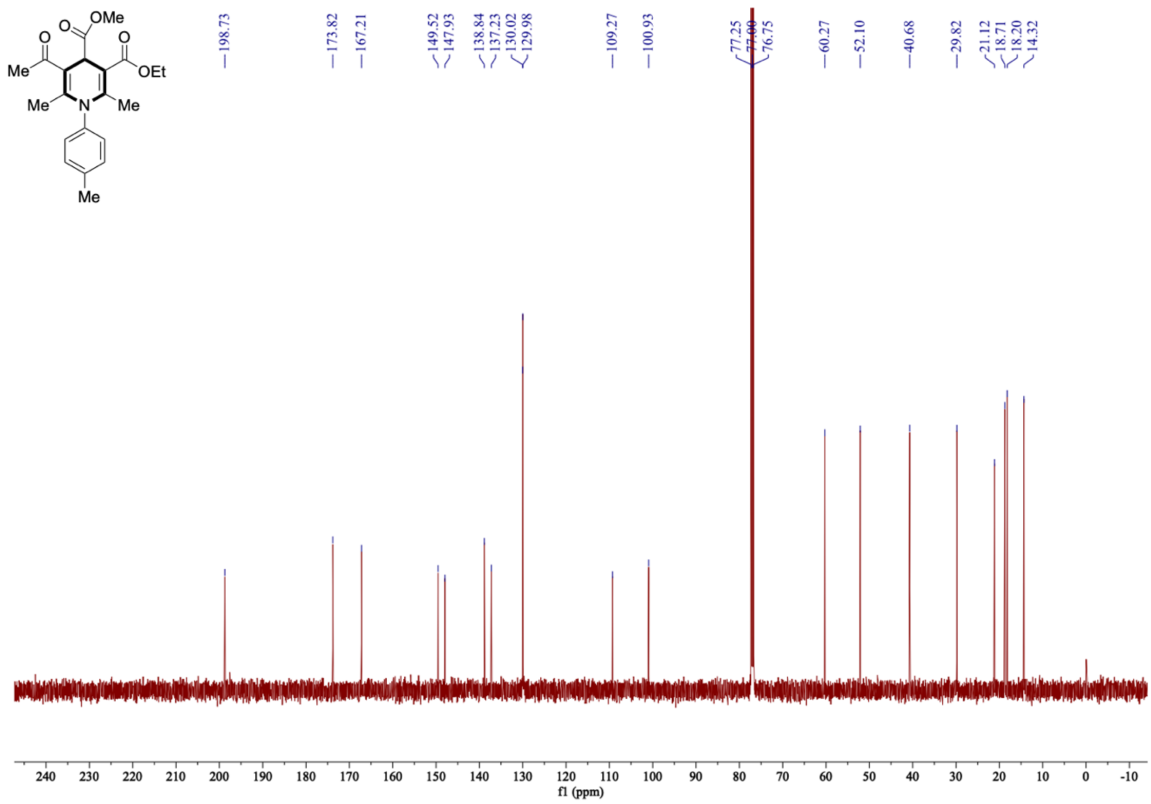
4-Ethyl 3-methyl 5-acetyl-2-ethyl-1-(4-methoxyphenyl)-6-methyl-1,4-dihydropyridine-3,4-dicarboxylate (**3aeg**)



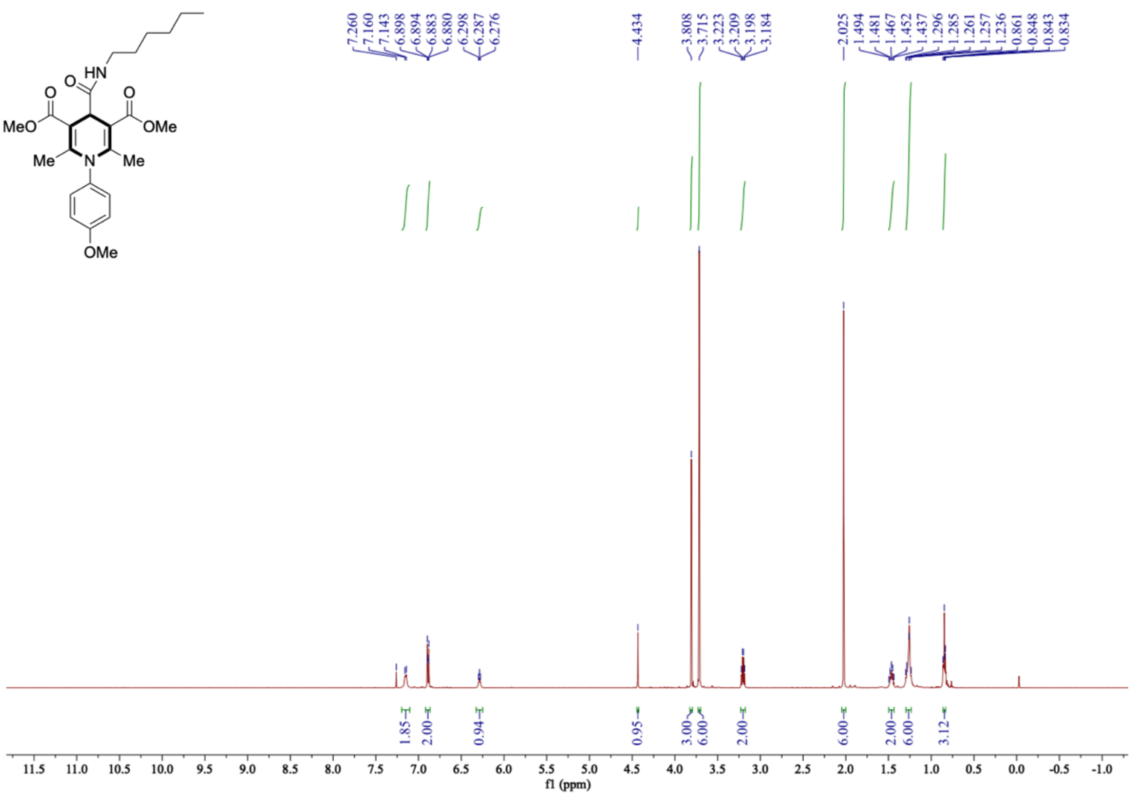


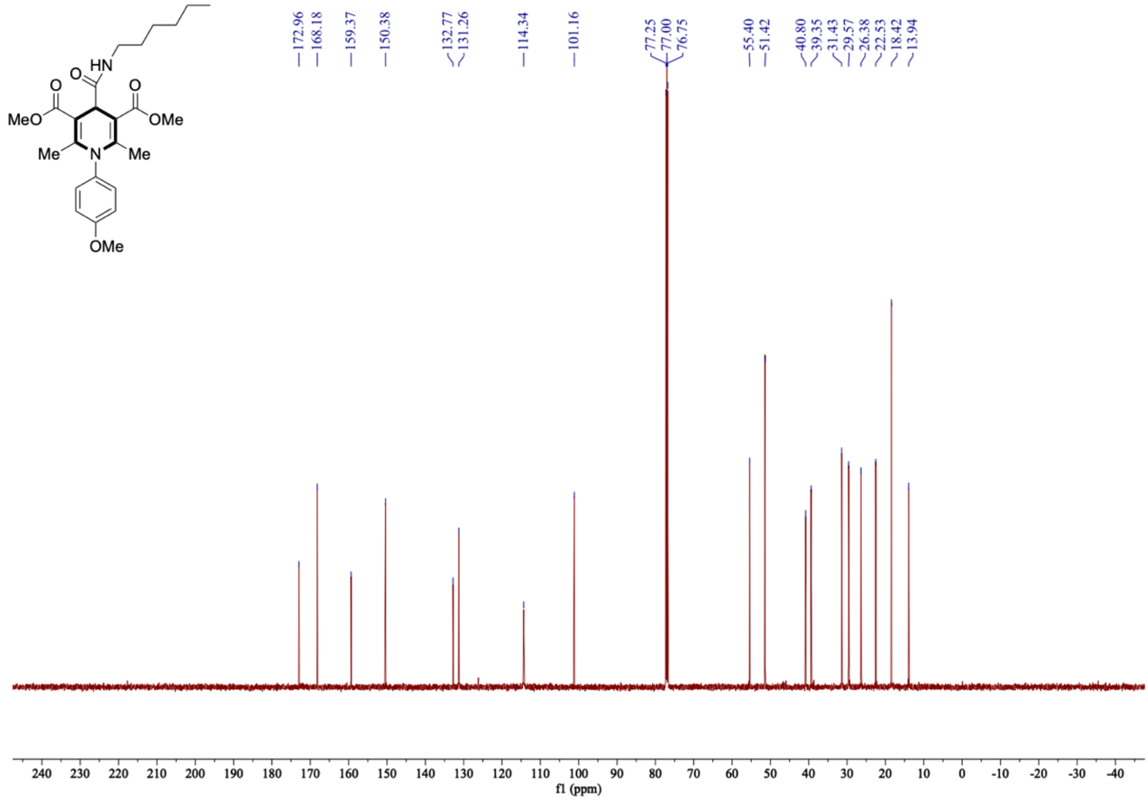
3-Ethyl 4-methyl 5-acetyl-2,6-dimethyl-1-(p-tolyl)-1,4-dihydropyridine-3,4-dicarboxylate (**3lbg**)



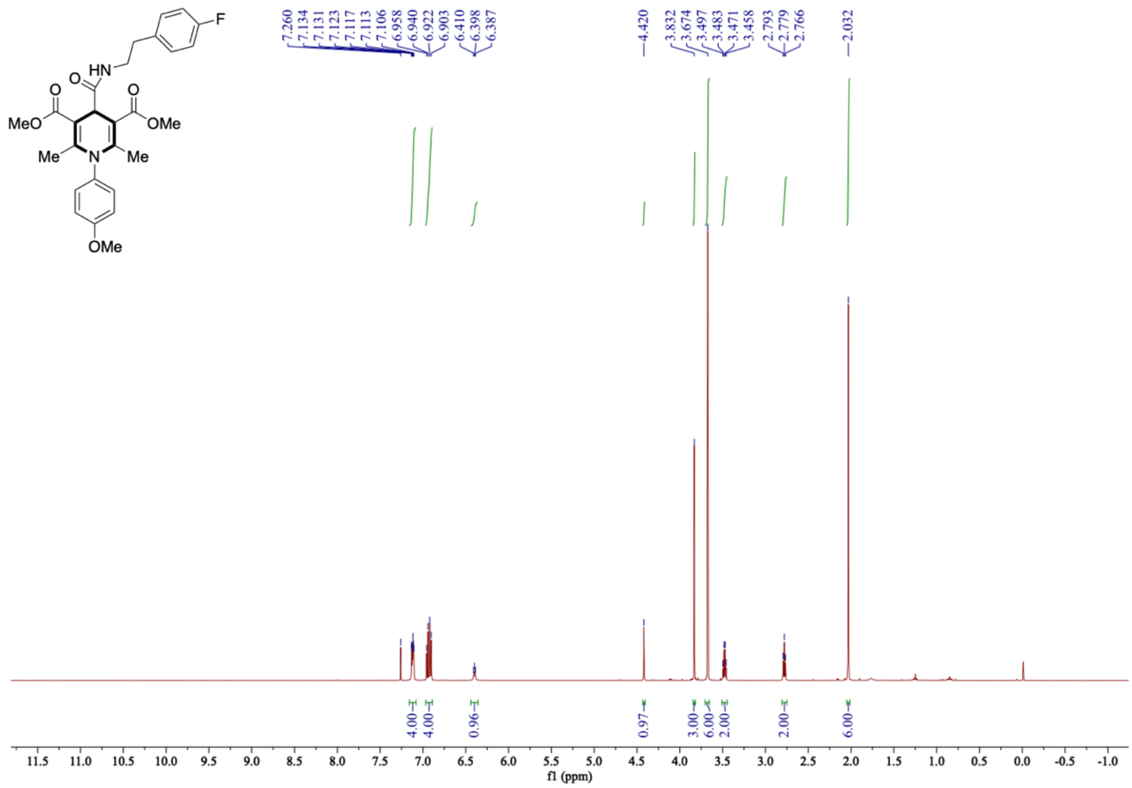


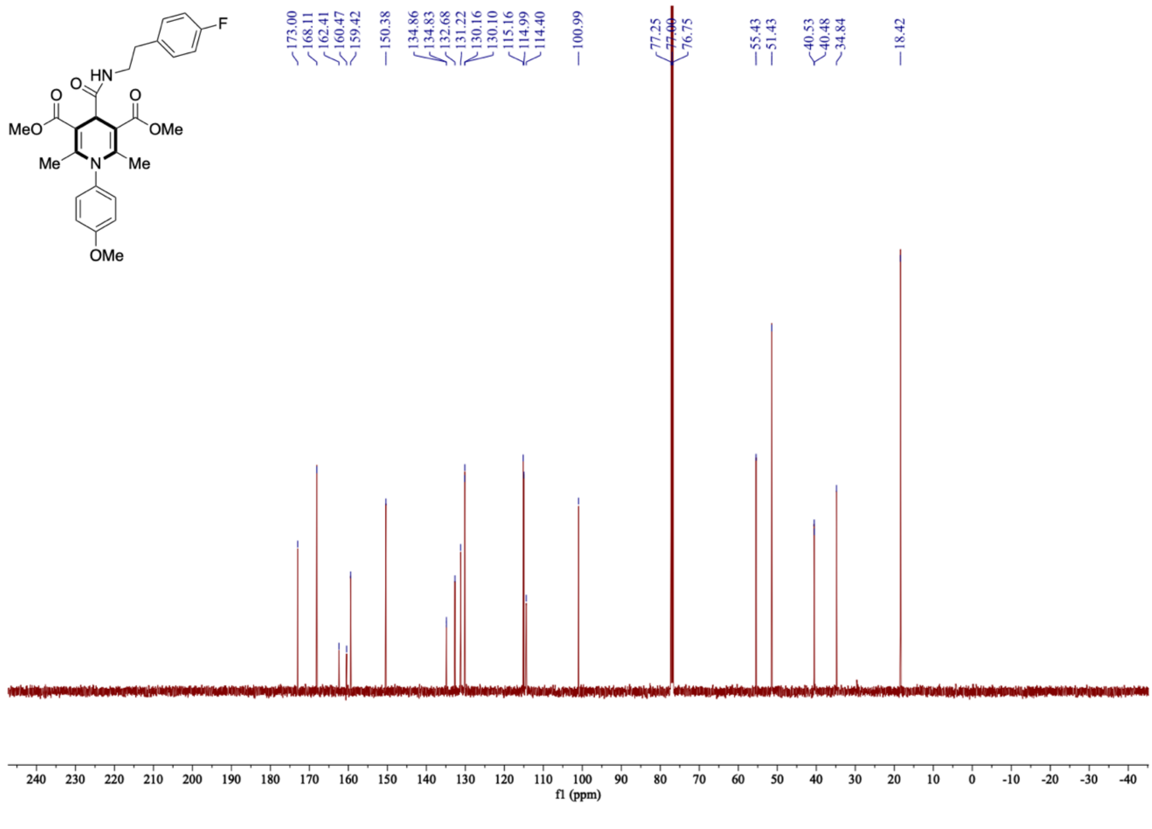
Dimethyl 4-(hexylcarbamoyl)-1-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**5aa**)

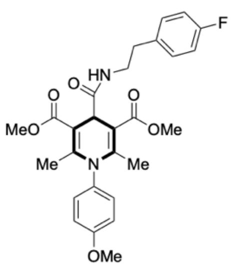


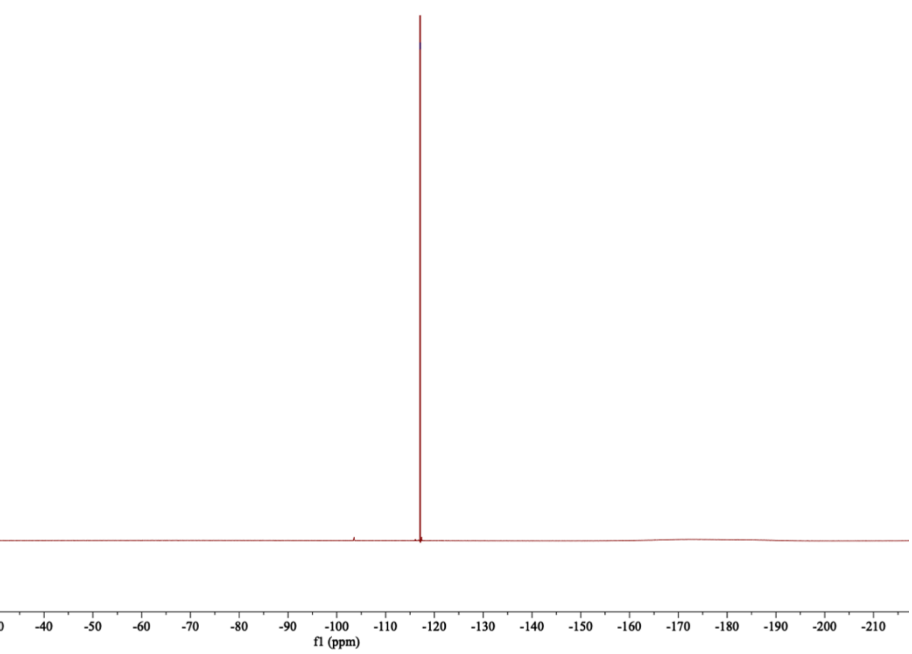


Dimethyl 4-((4-fluorophenethyl)carbamoyl)-1-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**5ba**)

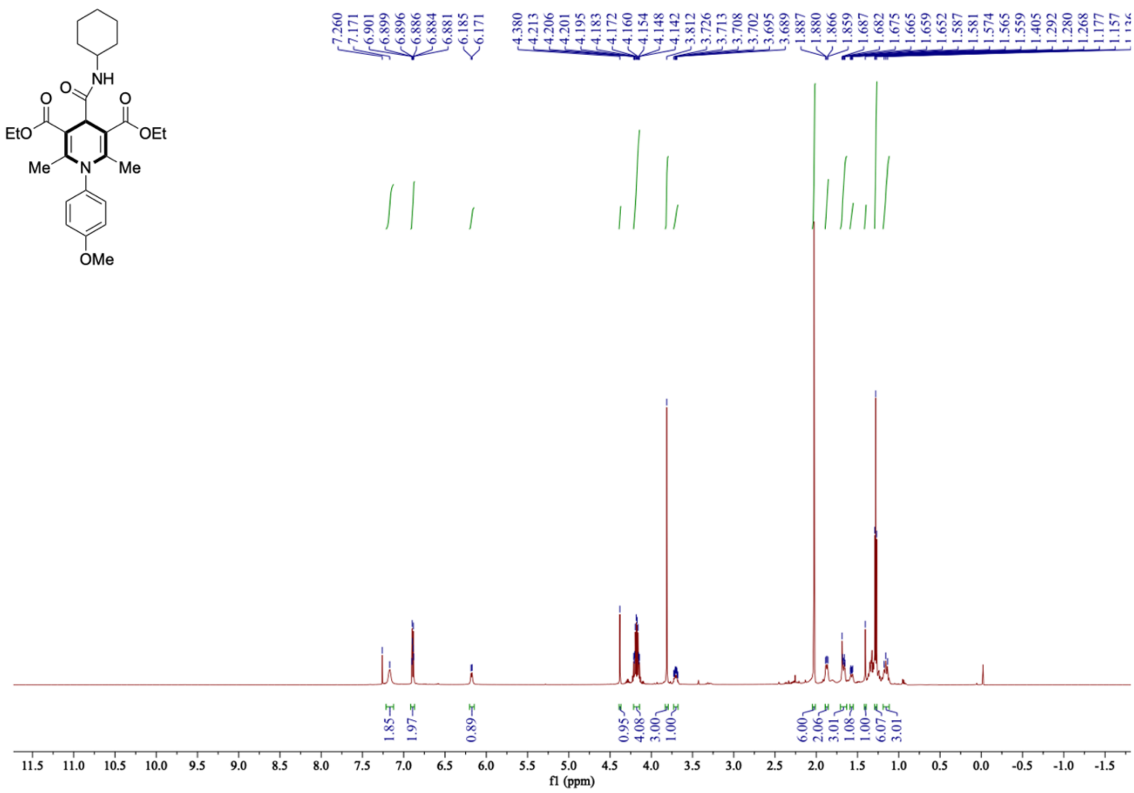


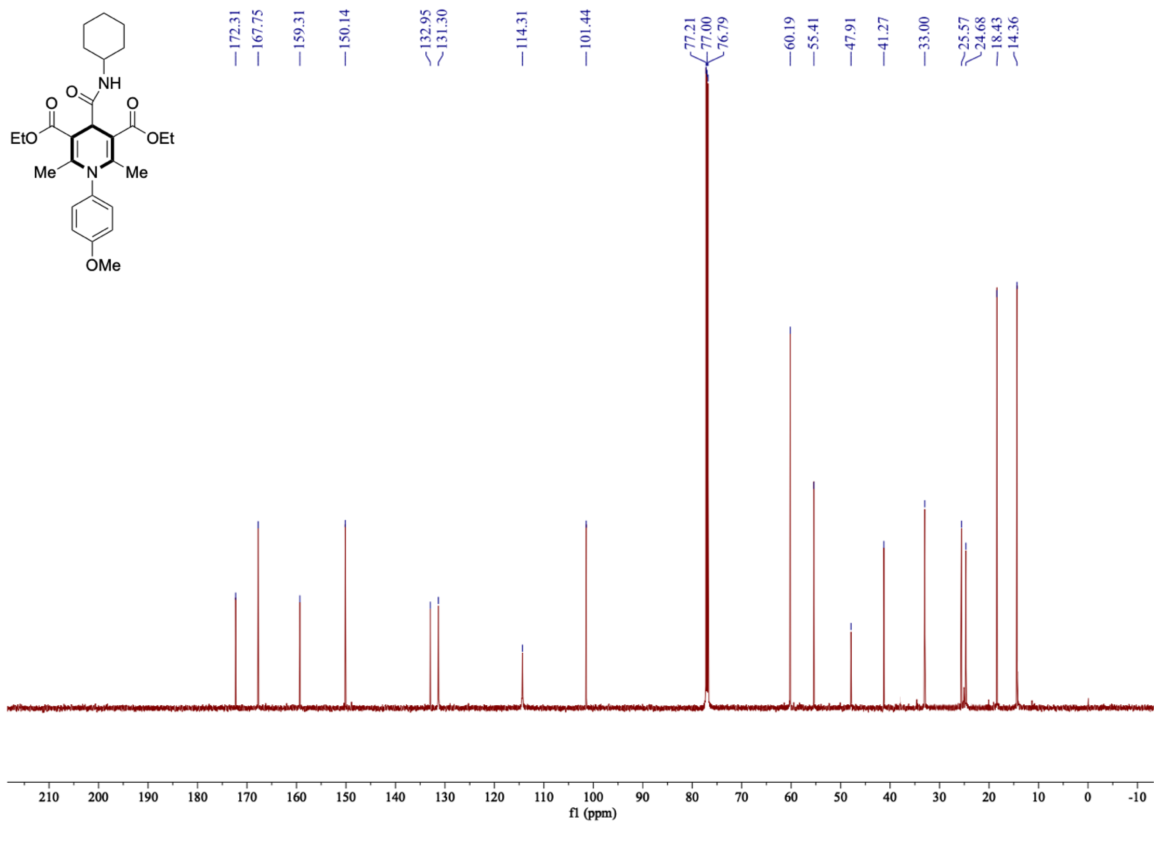



F
HN
O
O
O
MeO
OMe
Me
N
Me
OMe

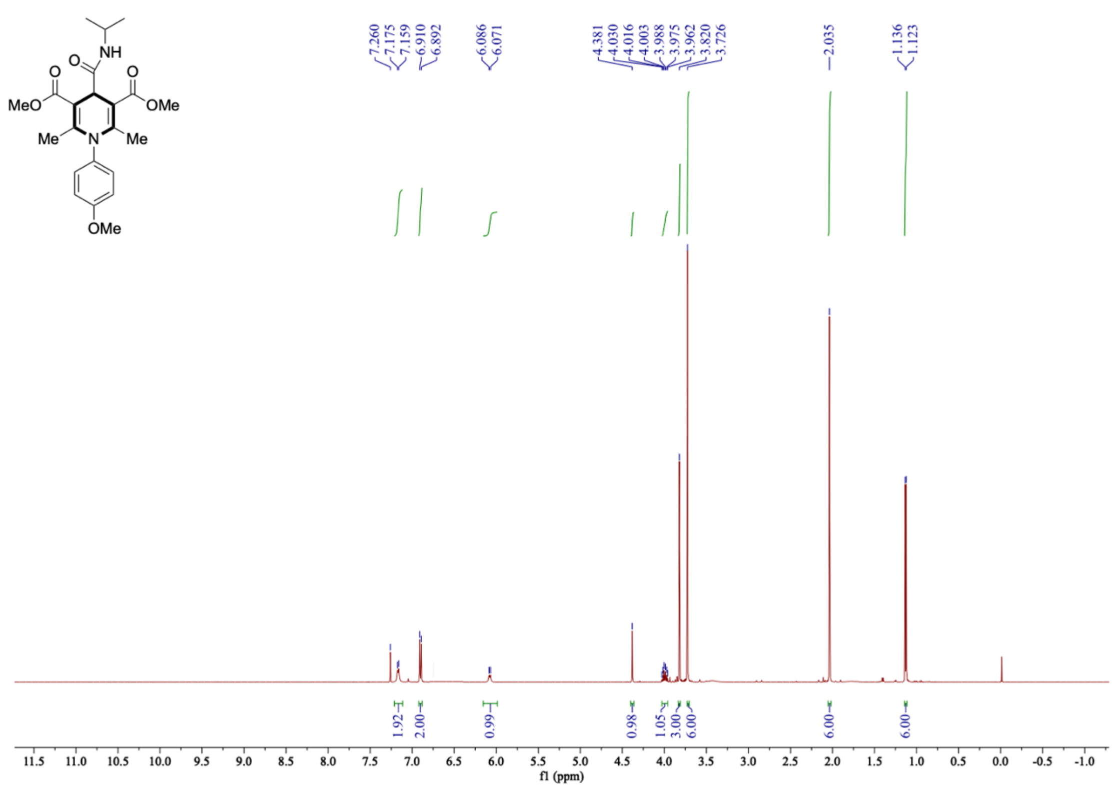

-117.087
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

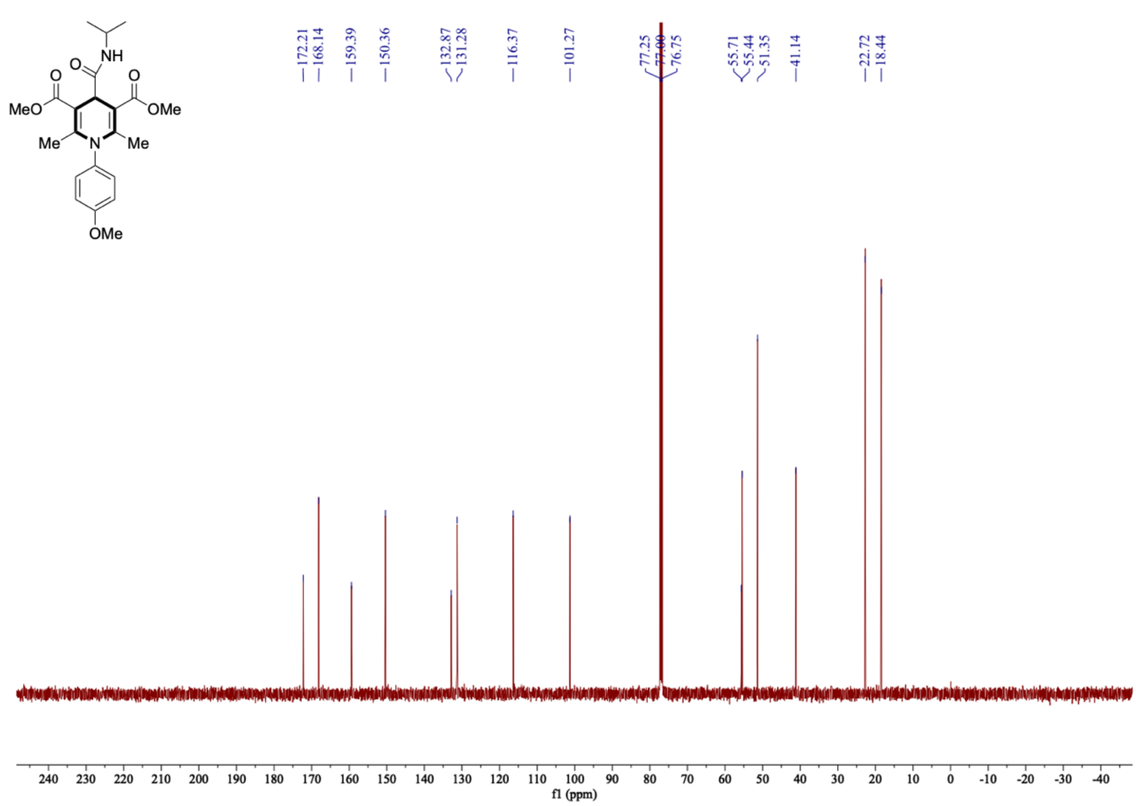
Diethyl 4-(cyclohexylcarbamoyl)-1-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**5cb**)



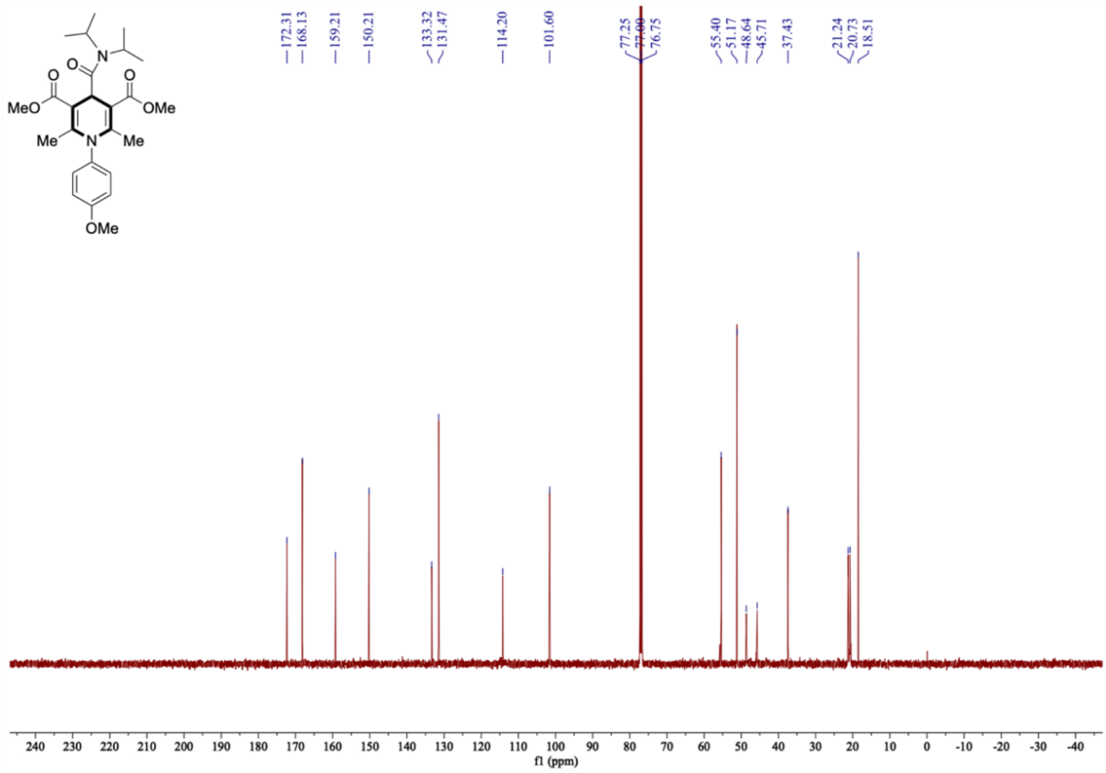


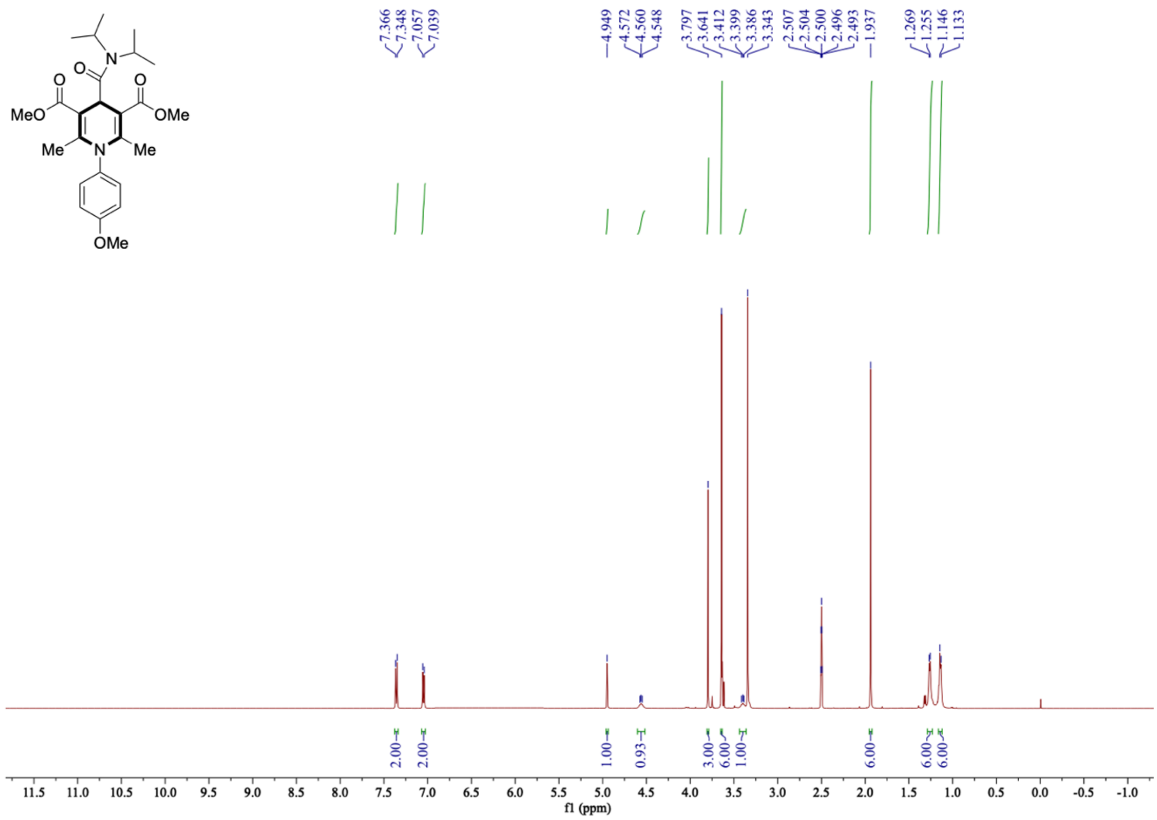
Dimethyl 4-(isopropylcarbamoyl)-1-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**5da**)



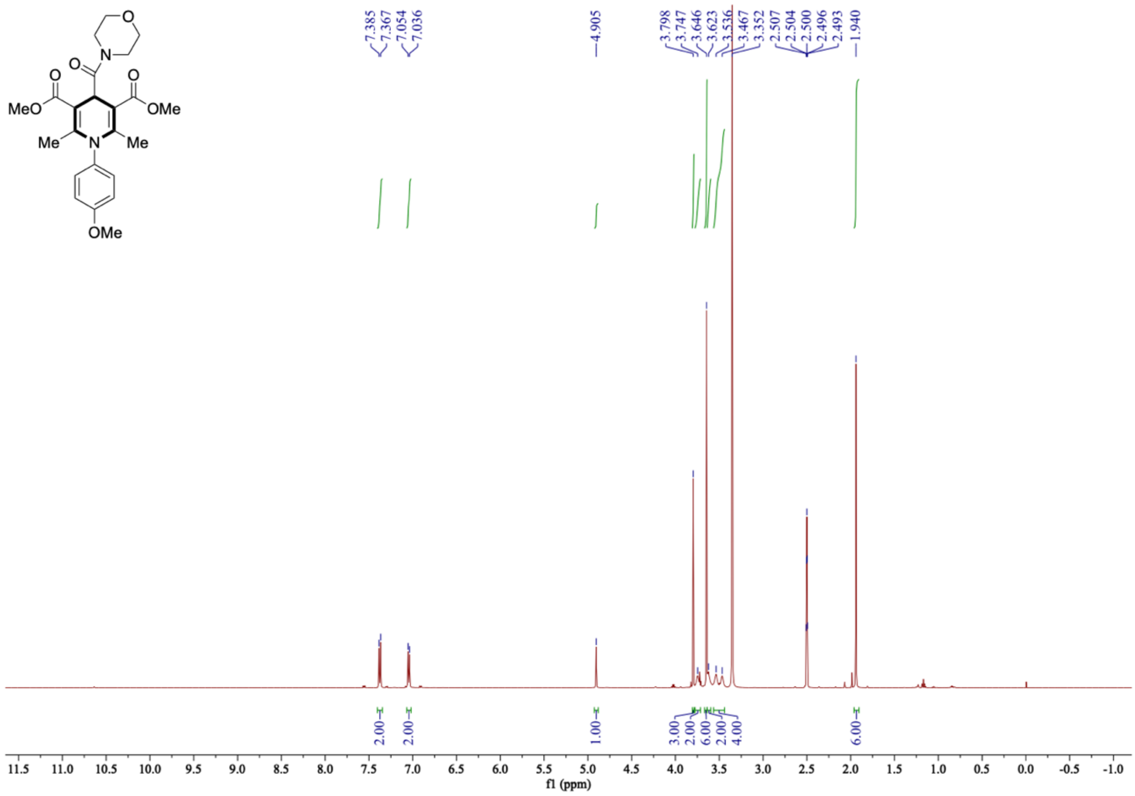


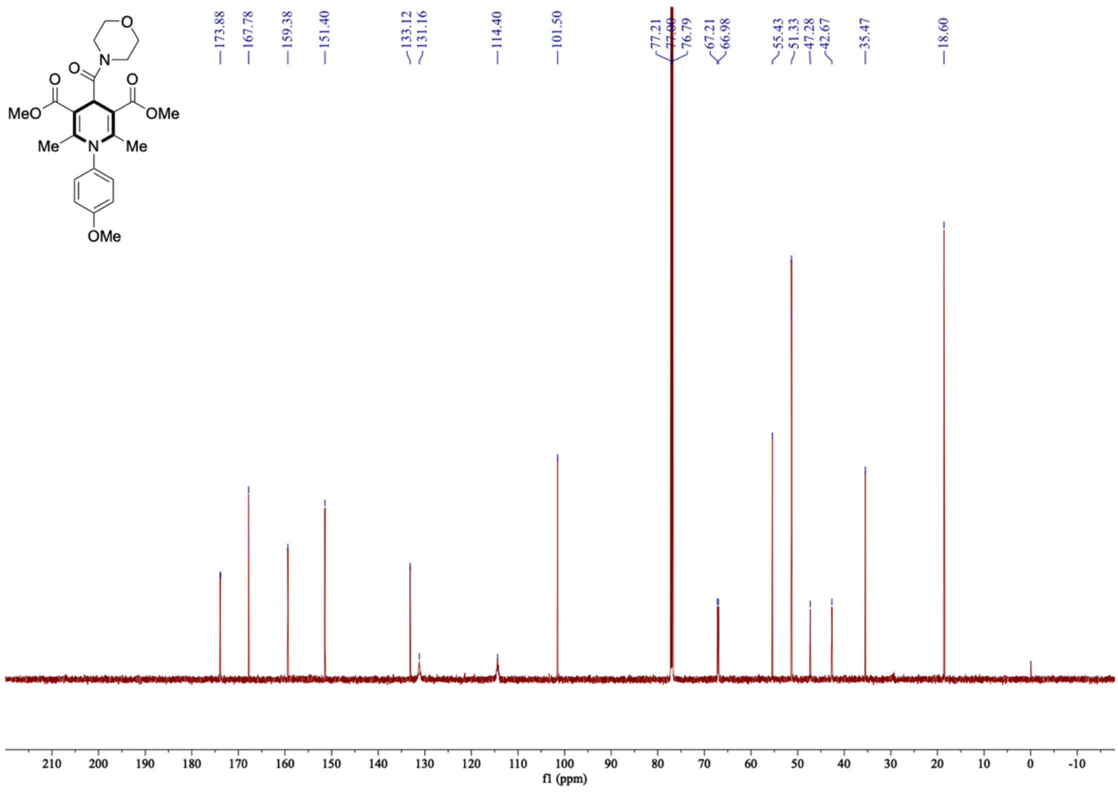
Dimethyl 4-(diisopropylcarbamoyl)-1-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**5ea**)



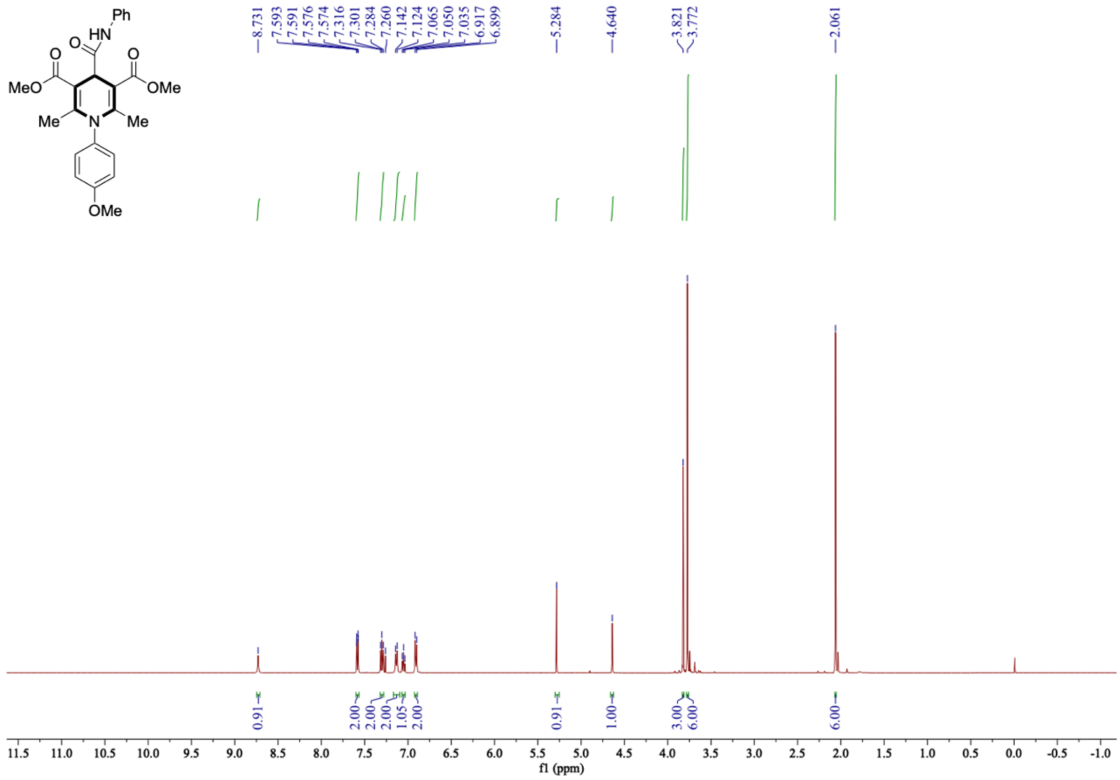


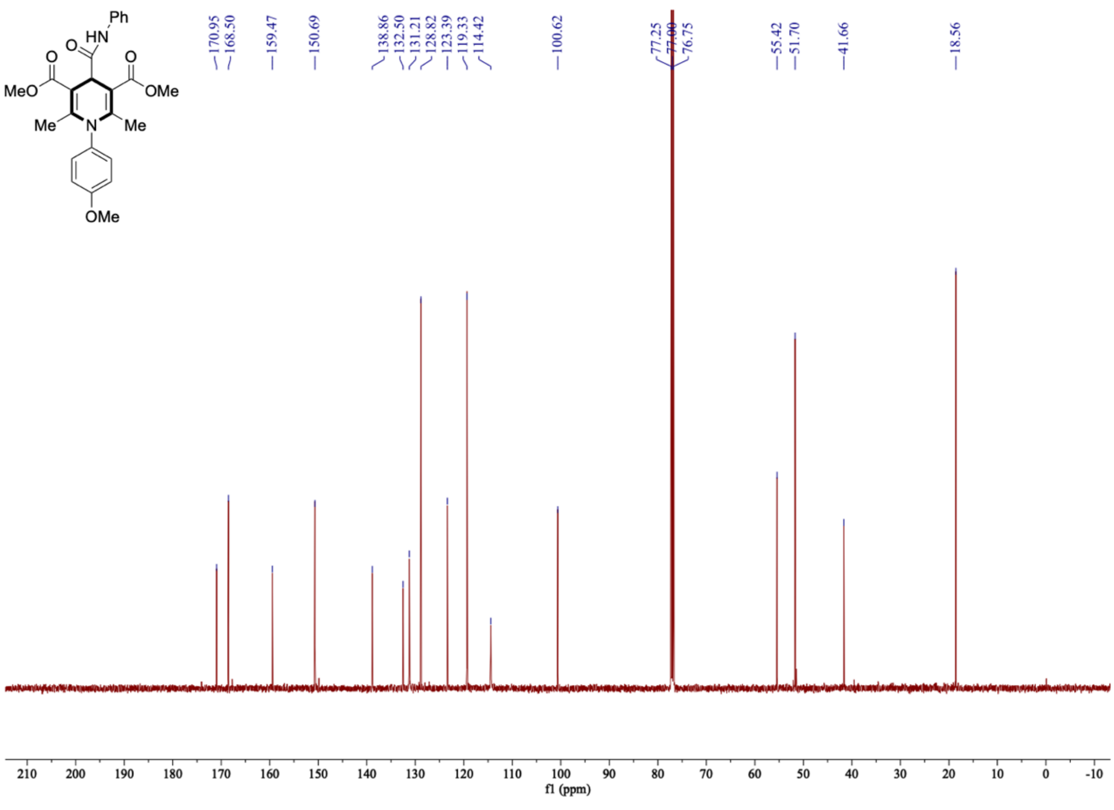
Dimethyl 1-(4-methoxyphenyl)-2,6-dimethyl-4-(morpholine-4-carbonyl)-1,4-dihydropyridine-3,5-dicarboxylate (**5fa**)



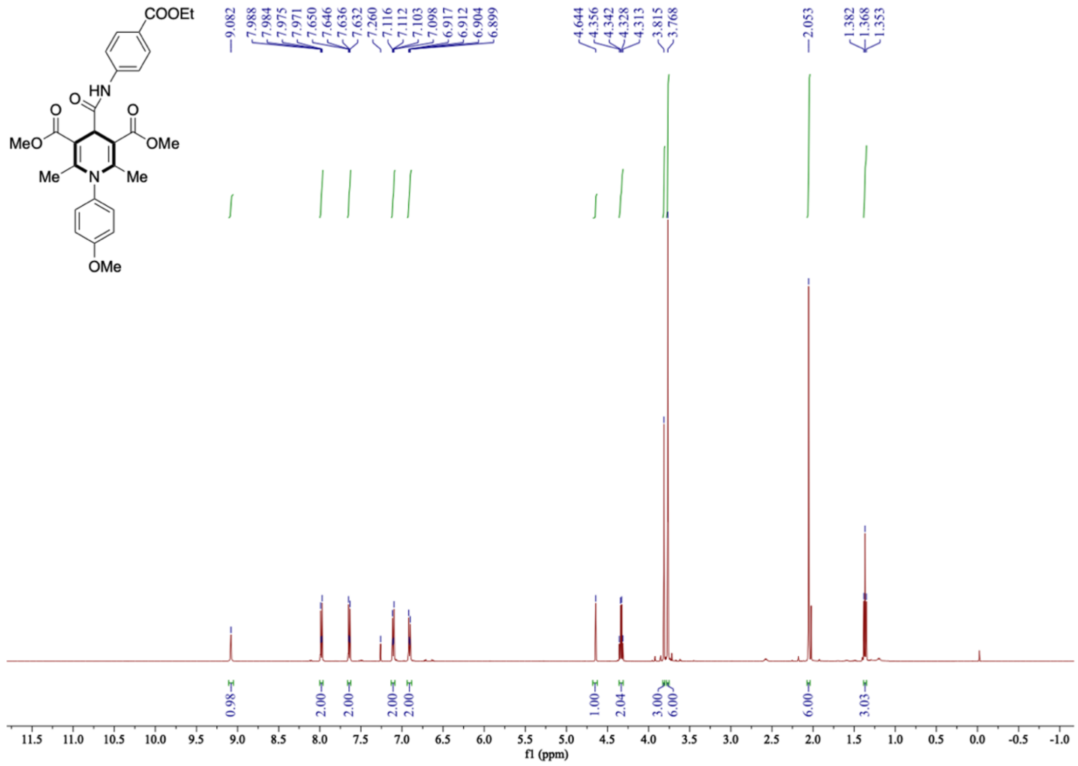


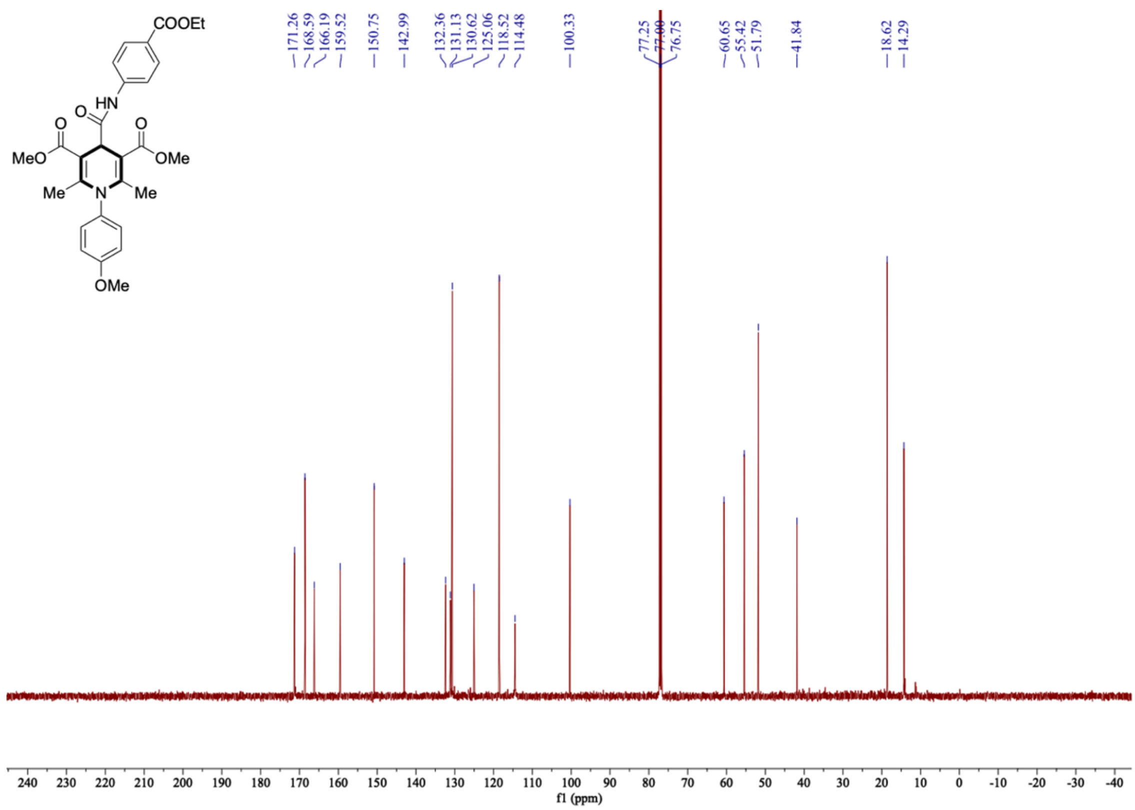
Dimethyl 1-(4-methoxyphenyl)-2,6-dimethyl-4-(phenylcarbamoyl)-1,4-dihydropyridine-3,5-dicarboxylate (**5ga**)



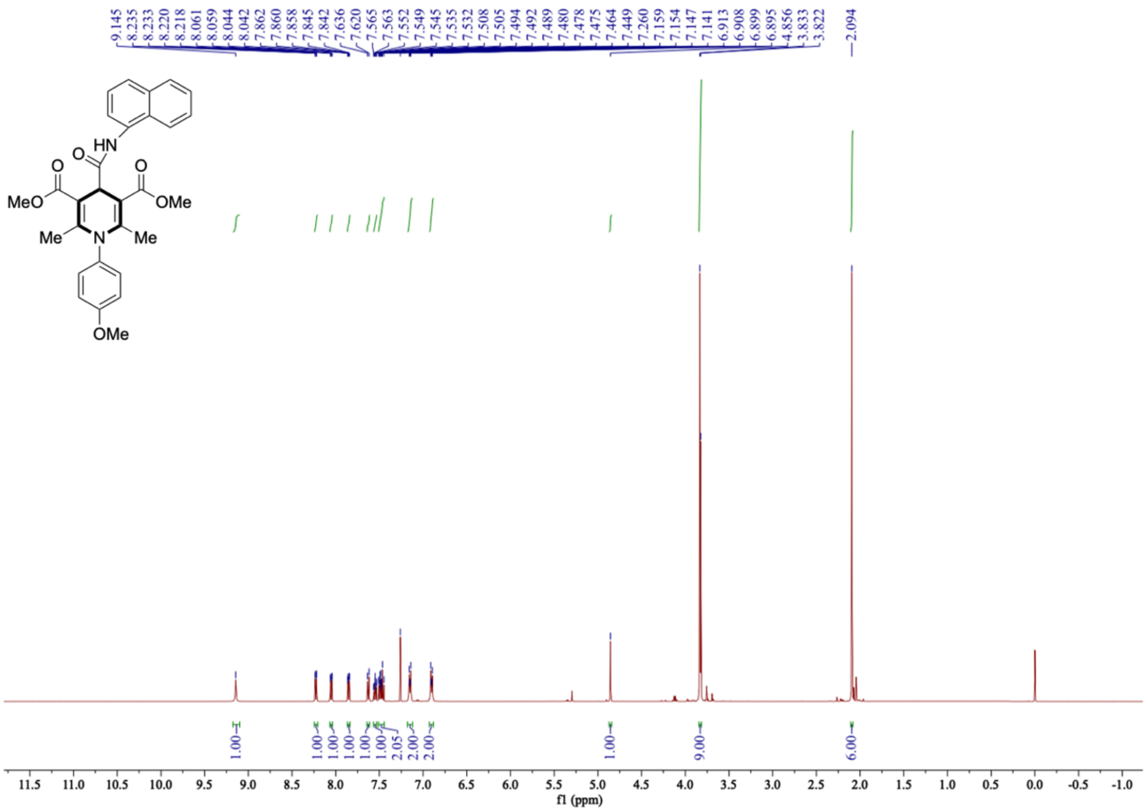


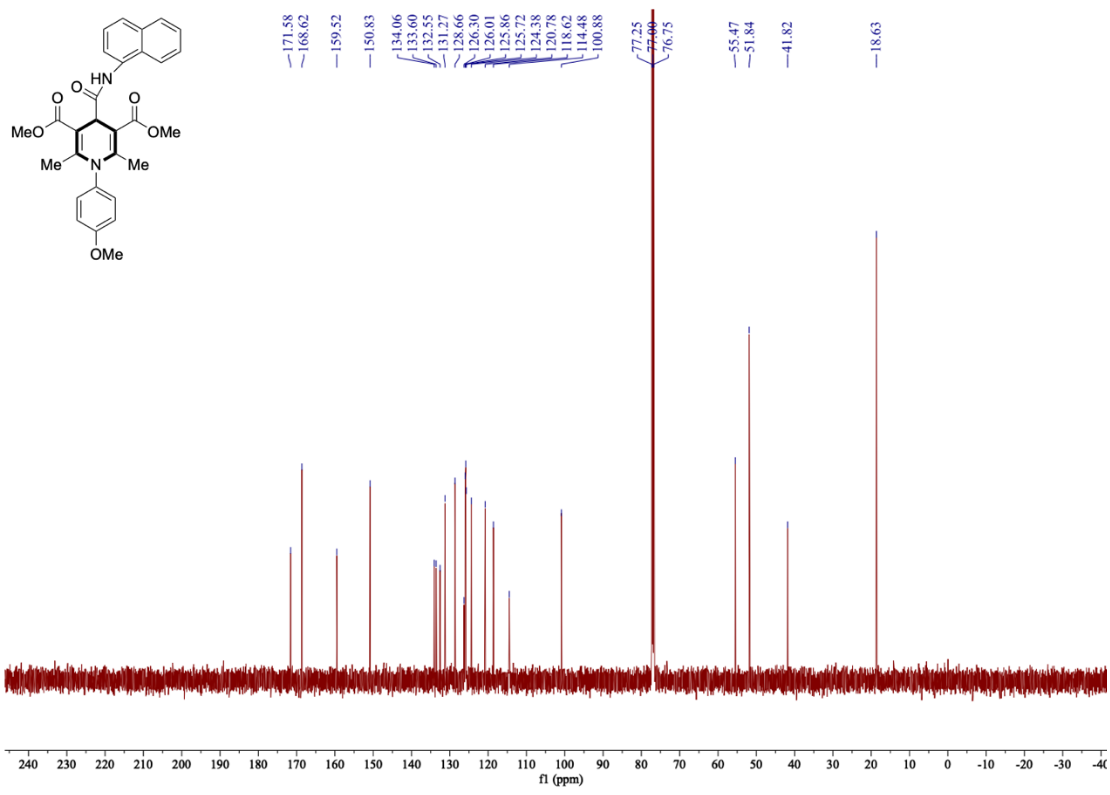
Dimethyl 4-((4-(ethoxycarbonyl)phenyl)carbamoyl)-1-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**5ha**)



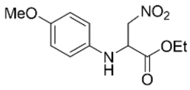


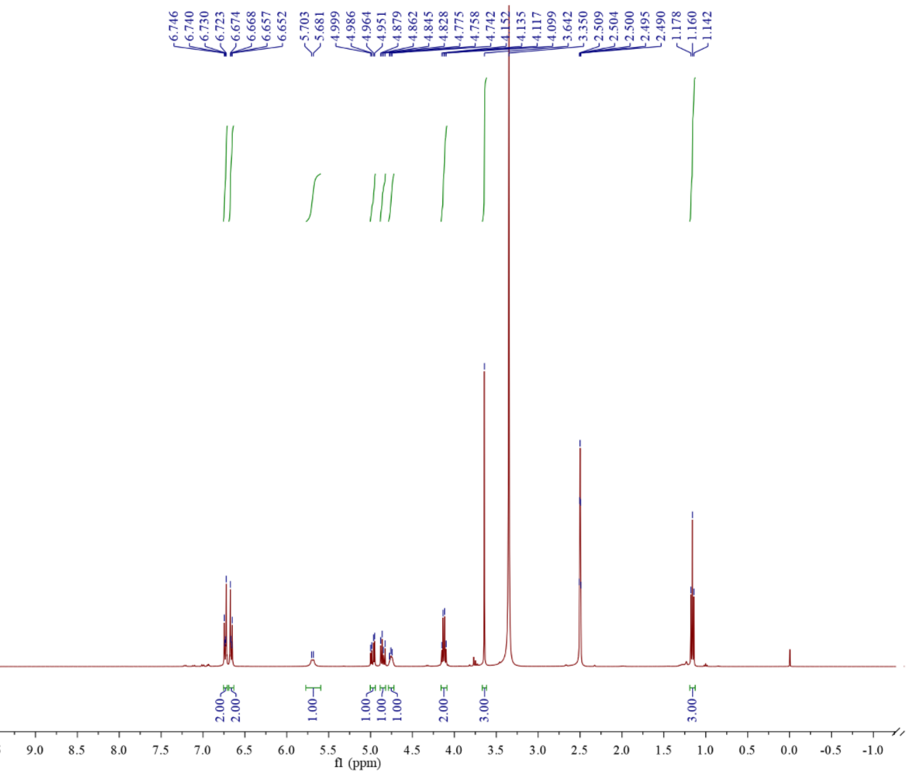
Dimethyl 1-(4-methoxyphenyl)-2,6-dimethyl-4-(naphthalen-1-ylcarbamoyl)-1,4-dihydropyridine-3,5-dicarboxylate (**5ia**)



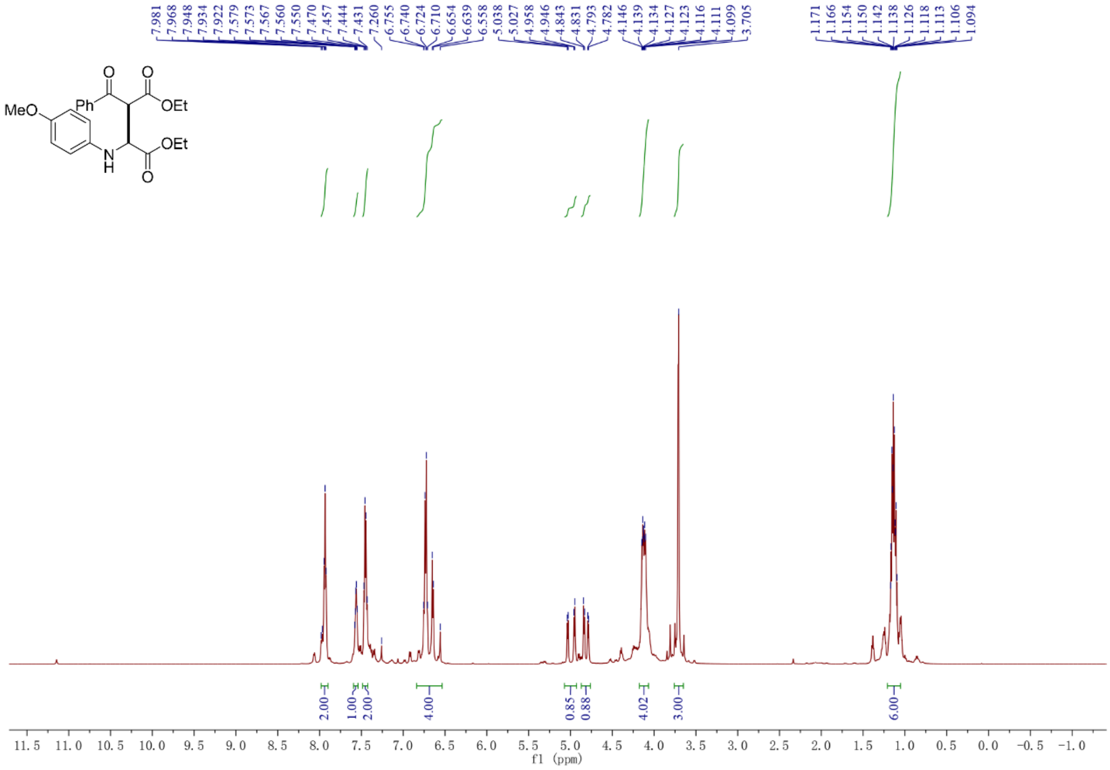


ethyl 2-((4-methoxyphenyl)amino)-3-nitropropanoate (**7aa**)

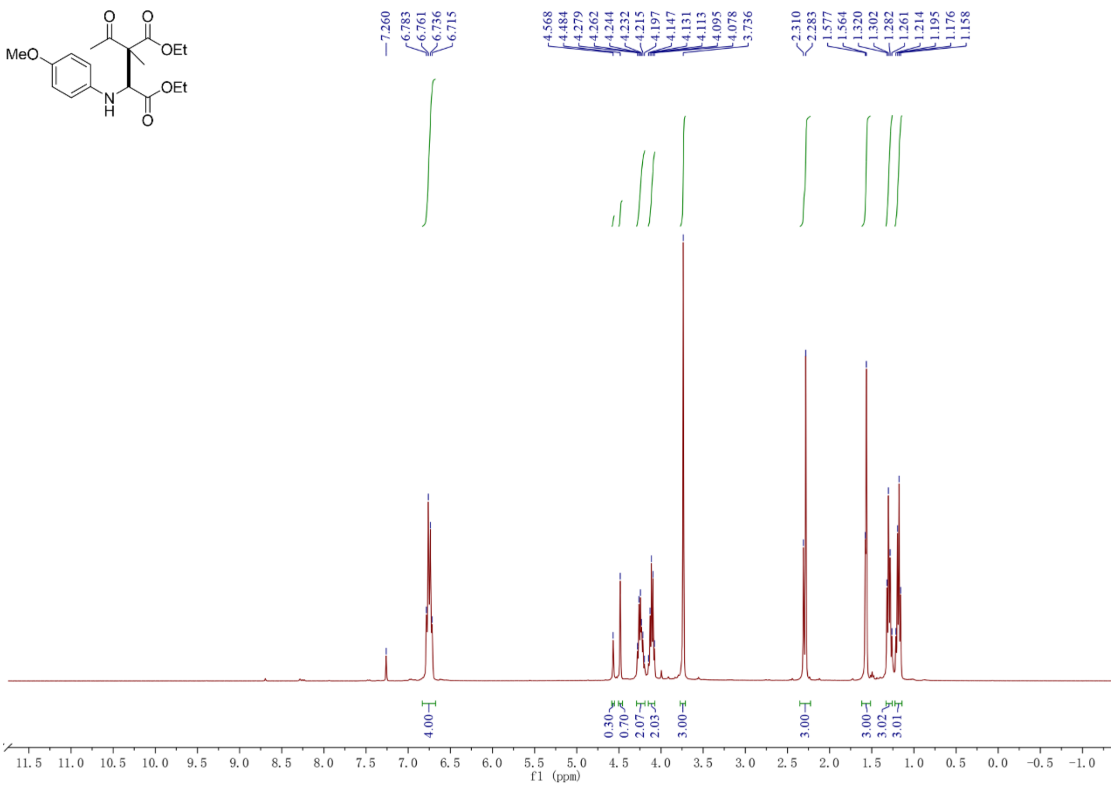




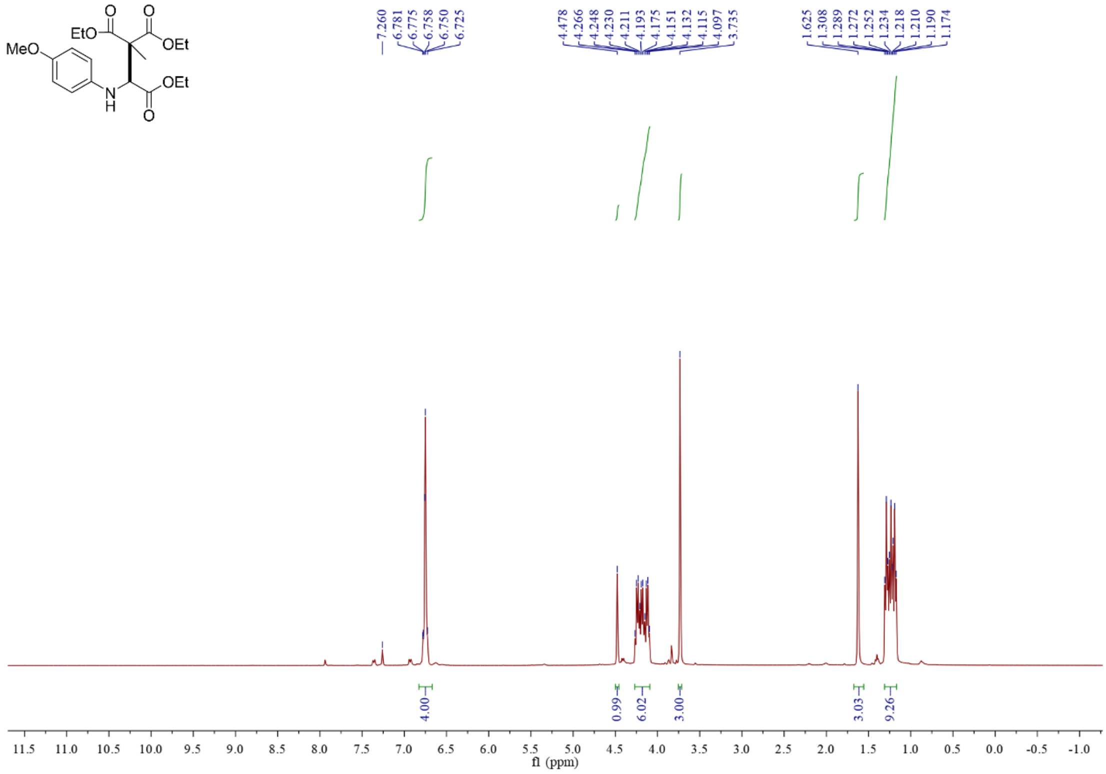
diethyl 2-benzoyl-3-((4-methoxyphenyl)amino)succinate (**7ab**)

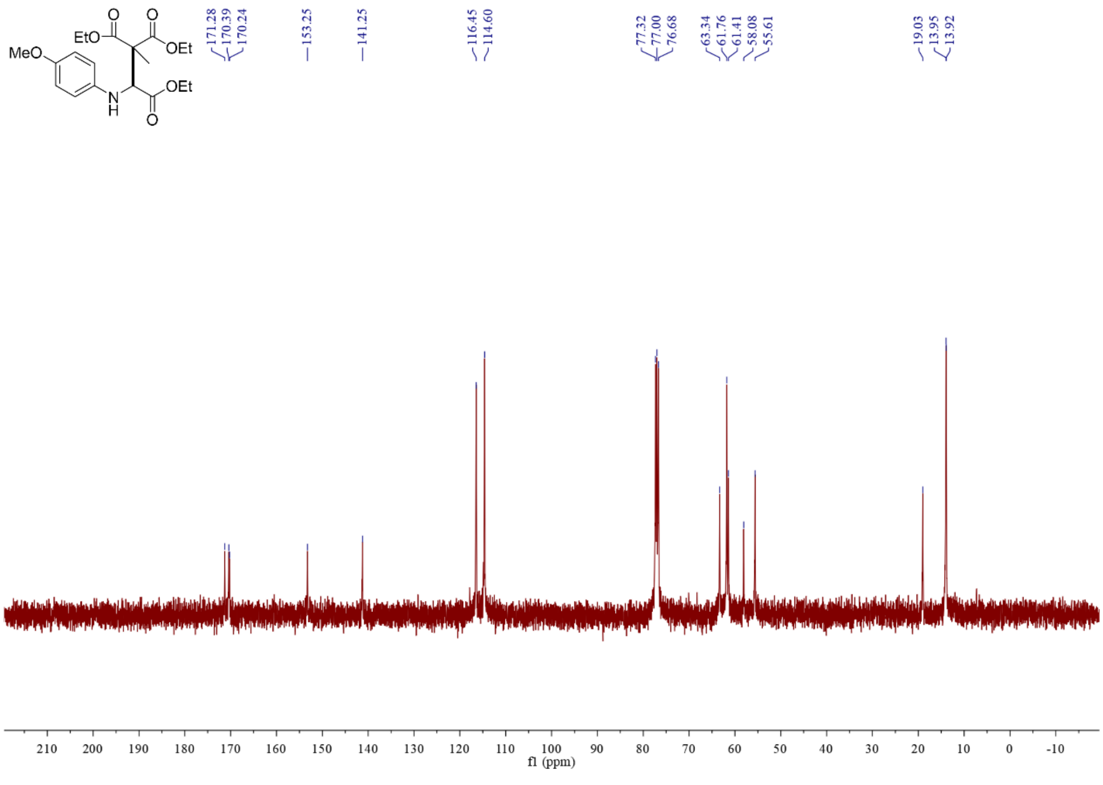


diethyl 2-acetyl-3-((4-methoxyphenyl)amino)-2-methylsuccinate (**7ac**)

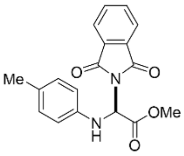


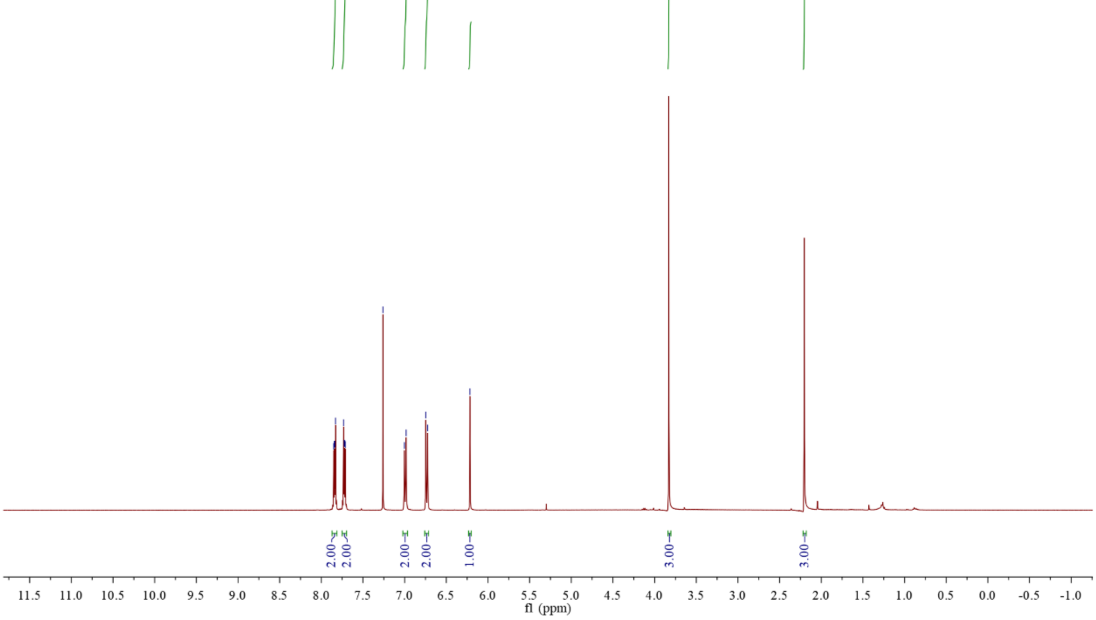
triethyl 1-((4-methoxyphenyl)amino)propane-1,2,2-tricarboxylate (**7ad**)



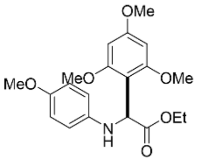


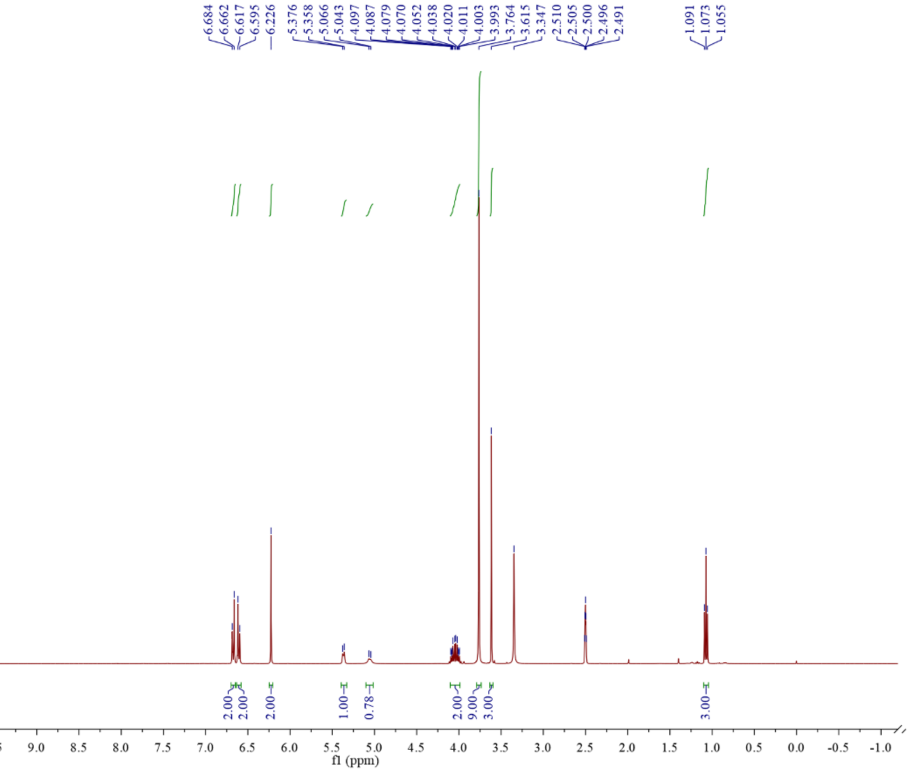
methyl 2-(1,3-dioxoisoindolin-2-yl)-2-(p-tolylamino)acetate (**7le**)



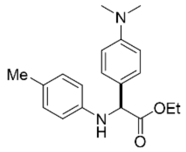


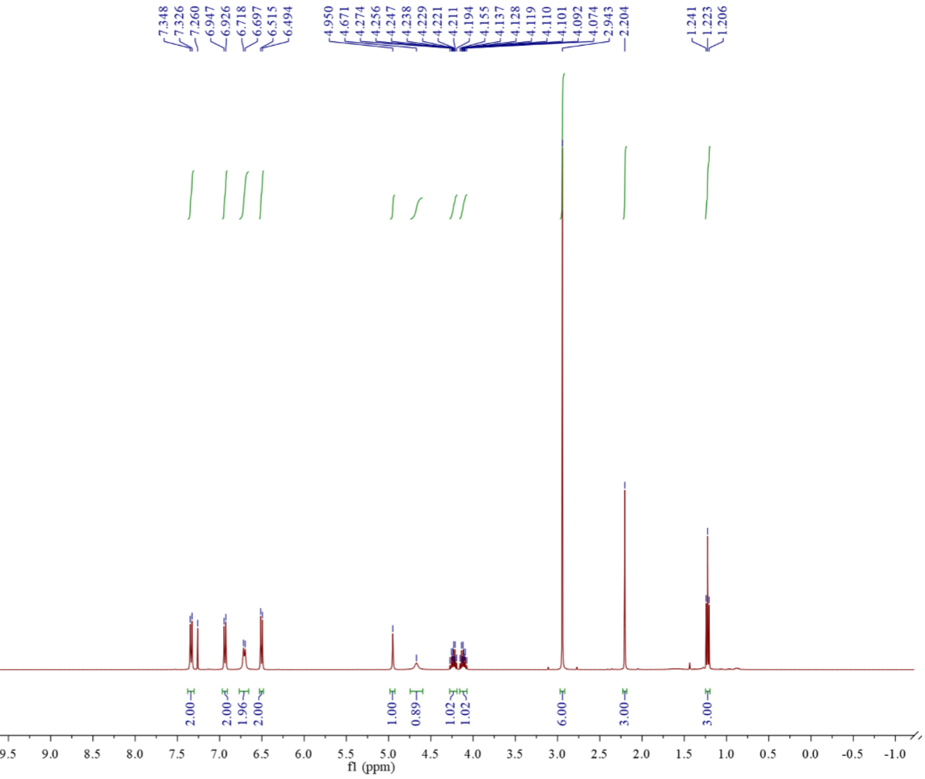
ethyl 2-((4-methoxyphenyl)amino)-2-(2,4,6-trimethoxyphenyl)acetate (**7af**)



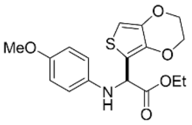


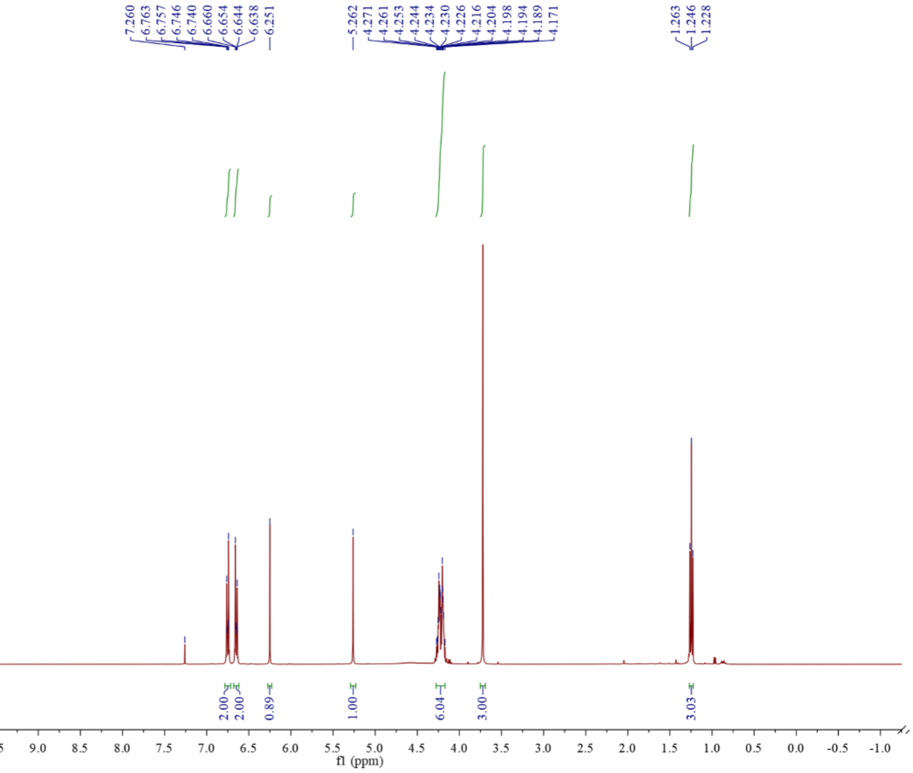
ethyl 2-(4-(dimethylamino)phenyl)-2-(p-tolylamino)acetate (**7fg**)



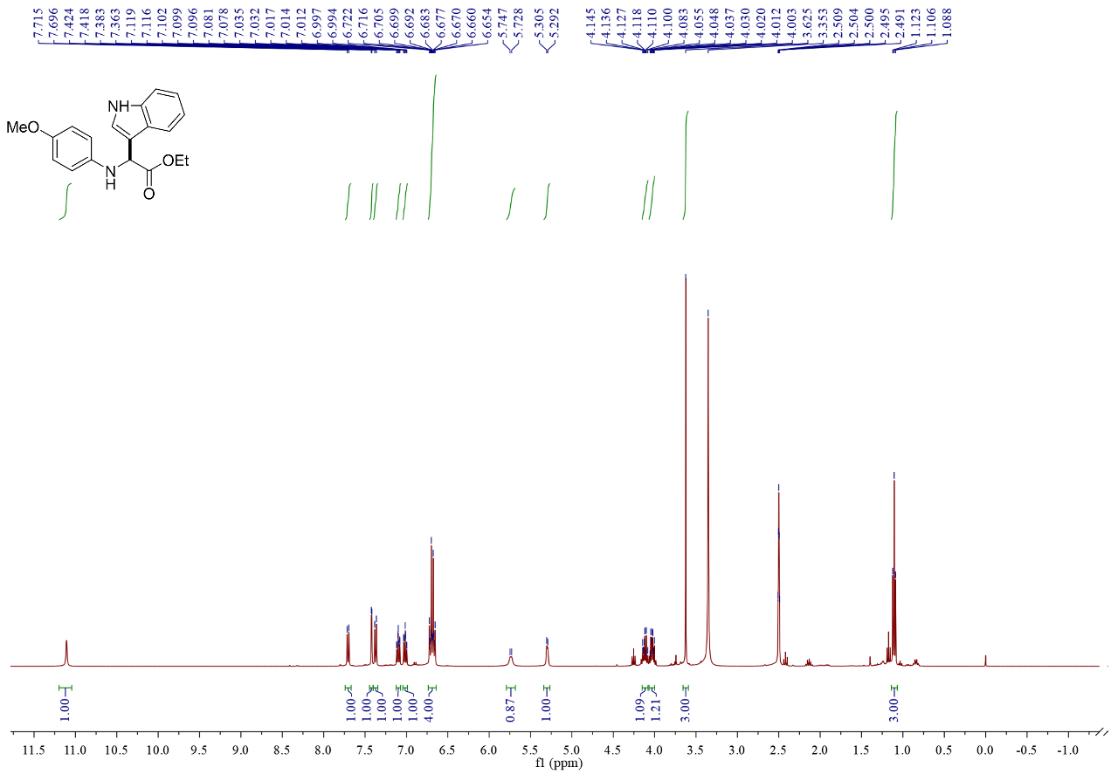


ethyl 2-(2,3-dihydrothieno[3,4-b][1,4]dioxin-5-yl)-2-((4-methoxyphenyl)amino)acetate (**7ah**)

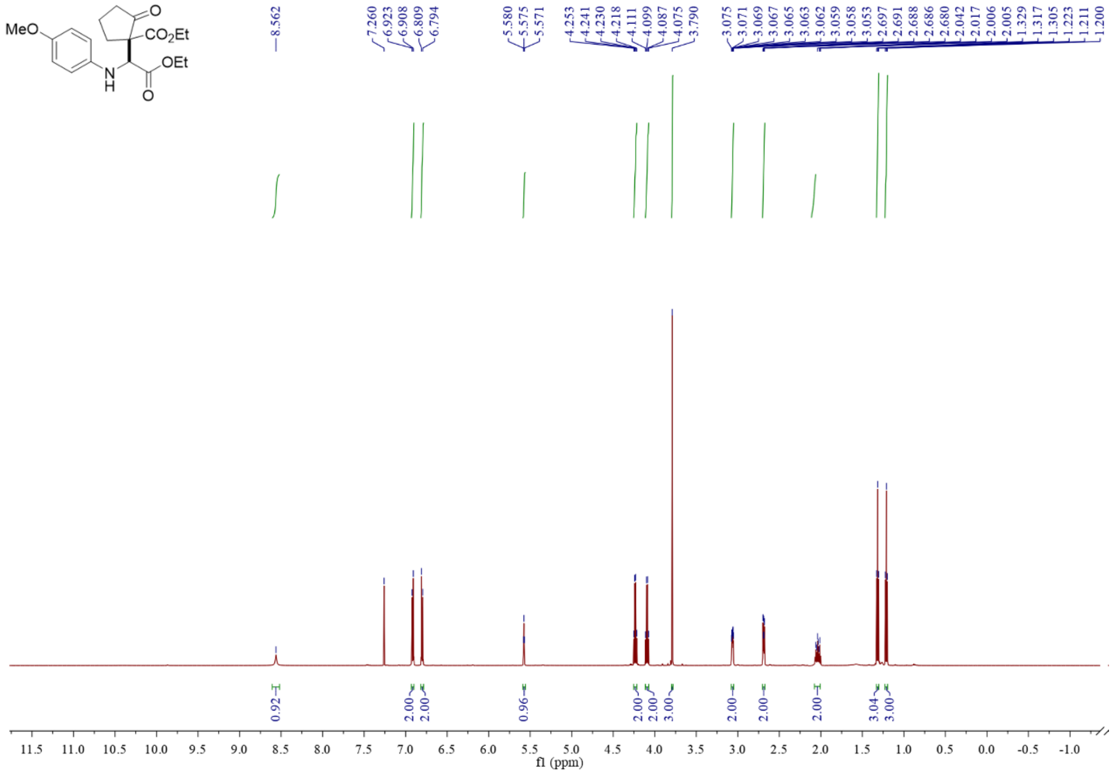




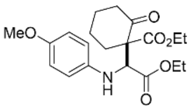
ethyl 2-(1H-indol-3-yl)-2-((4-methoxyphenyl)amino)acetate (**7ai**)

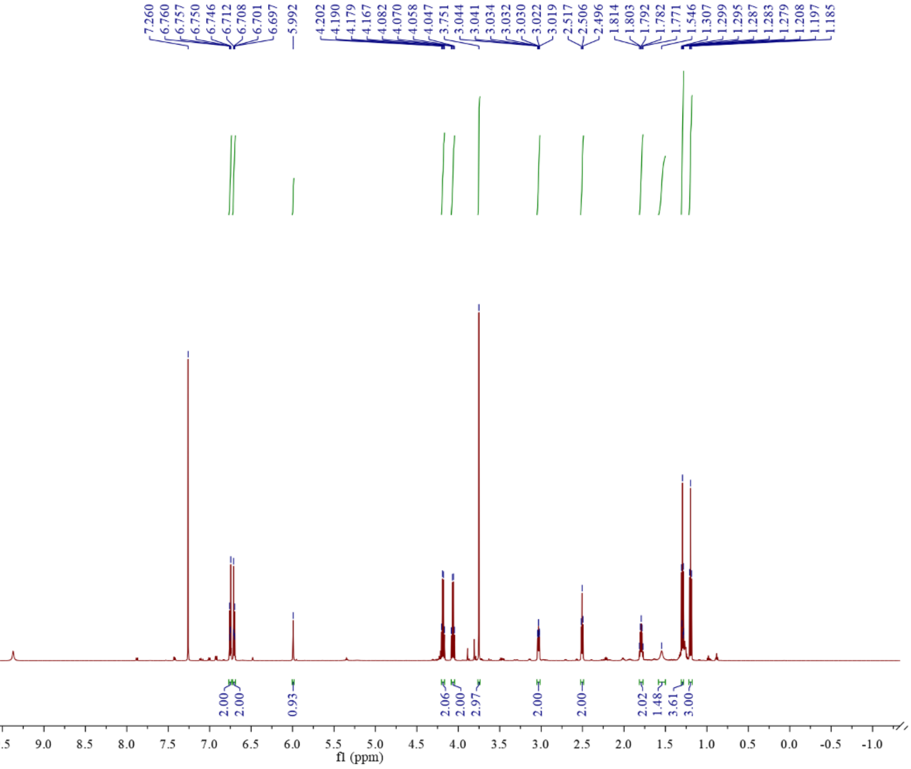


ethyl 1-(2-ethoxy-1-((4-methoxyphenyl)amino)-2-oxoethyl)-2-oxocyclopentane-1-carboxylate (**7aj**)

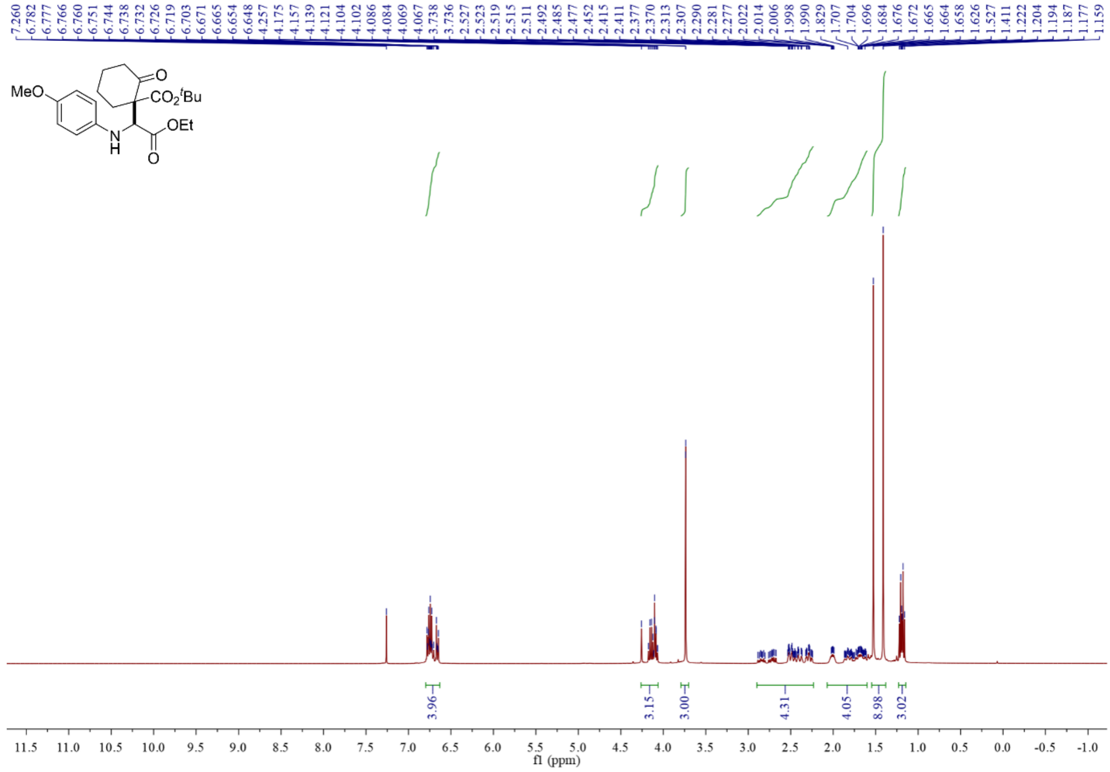


ethyl 1-(2-ethoxy-1-((4-methoxyphenyl)amino)-2-oxoethyl)-2-oxocyclohexane-1-carboxylate (**7ak**)

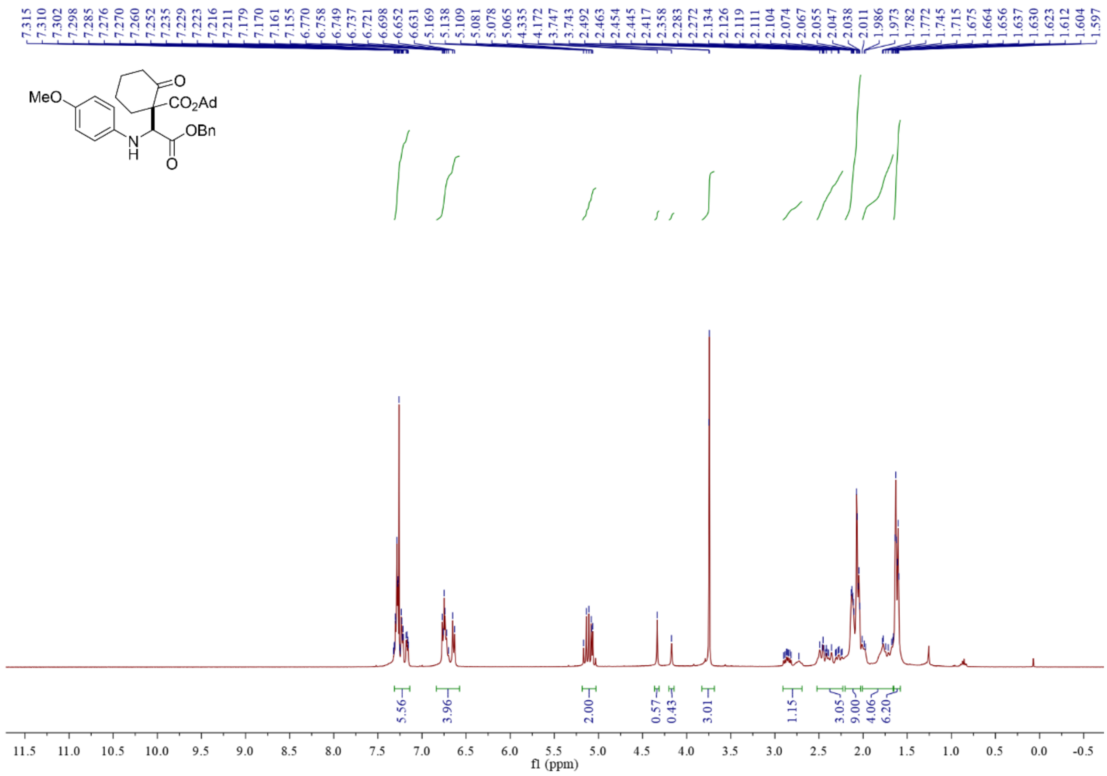


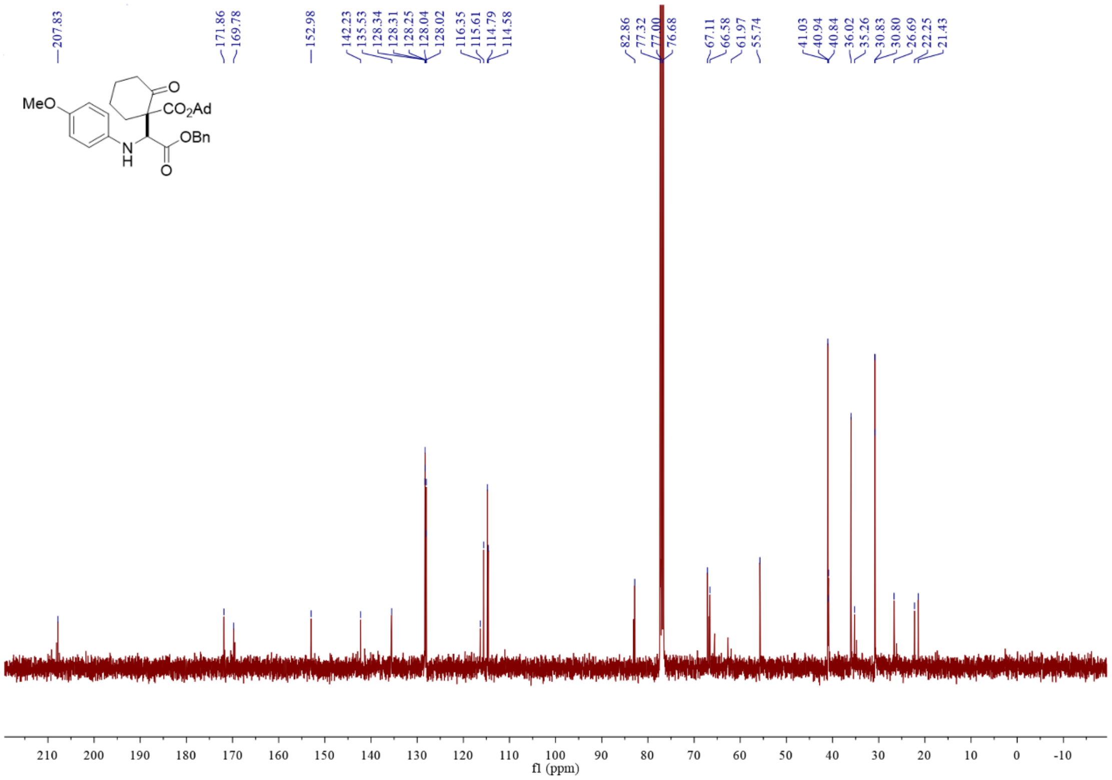


tert-butyl 1-(2-ethoxy-1-((4-methoxyphenyl)amino)-2-oxoethyl)-2-oxocyclohexane-1-carboxylate (**7al**)

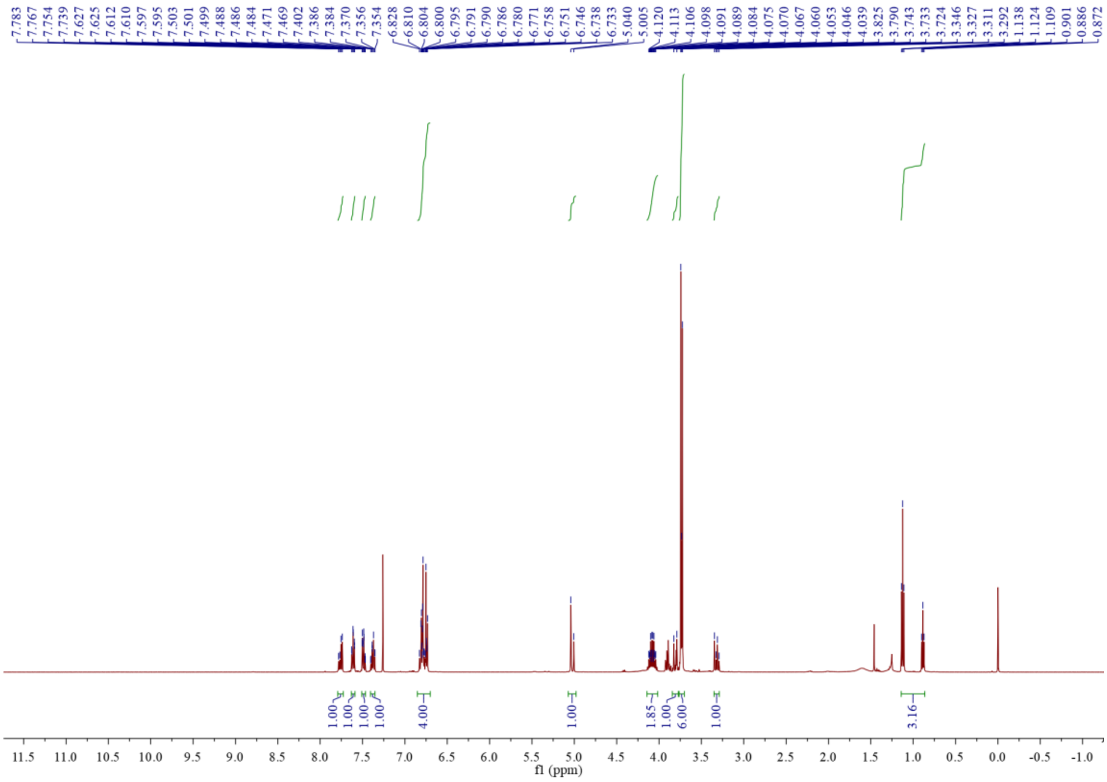


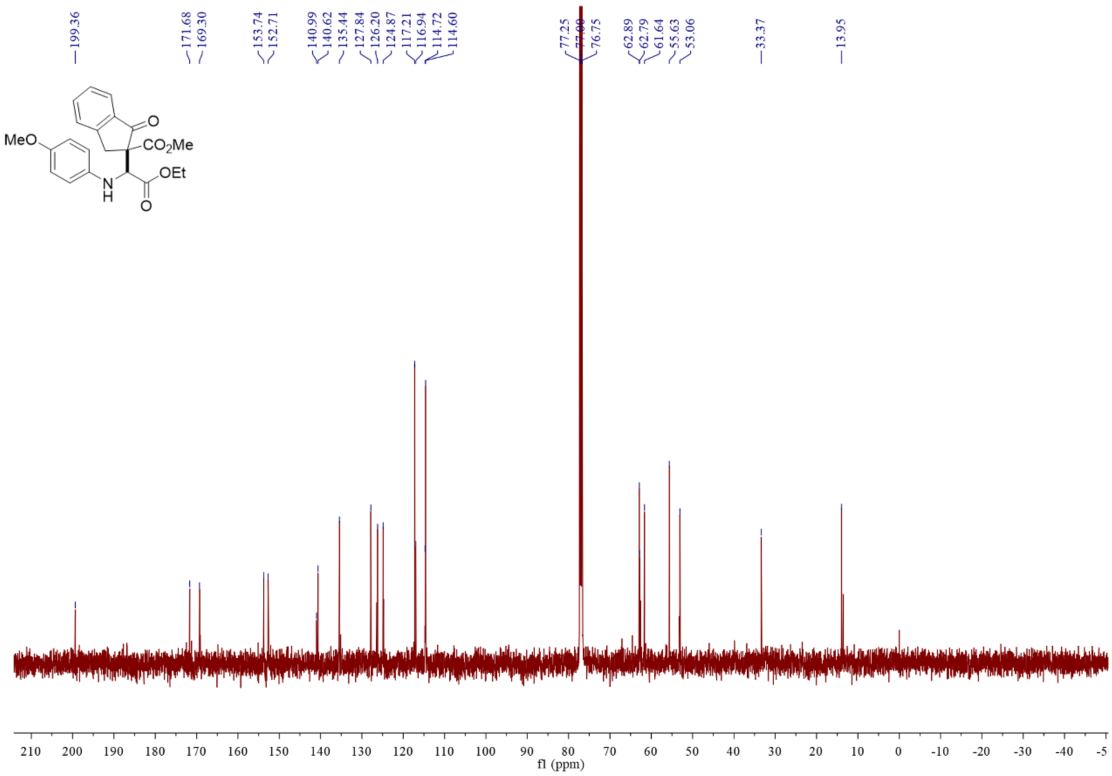
adamantan-1-yl 1-(2-(benzyloxy)-1-((4-methoxyphenyl)amino)-2-oxoethyl)-2-oxocyclohexane-1-carboxylate (**7dm**)



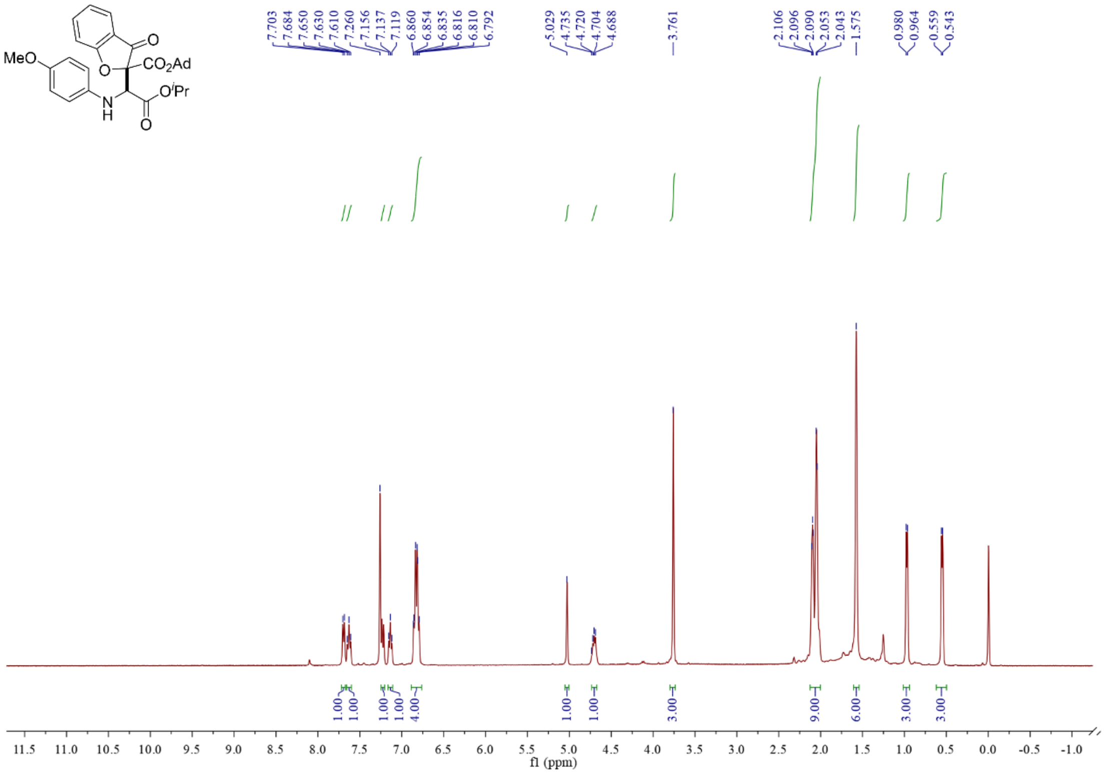


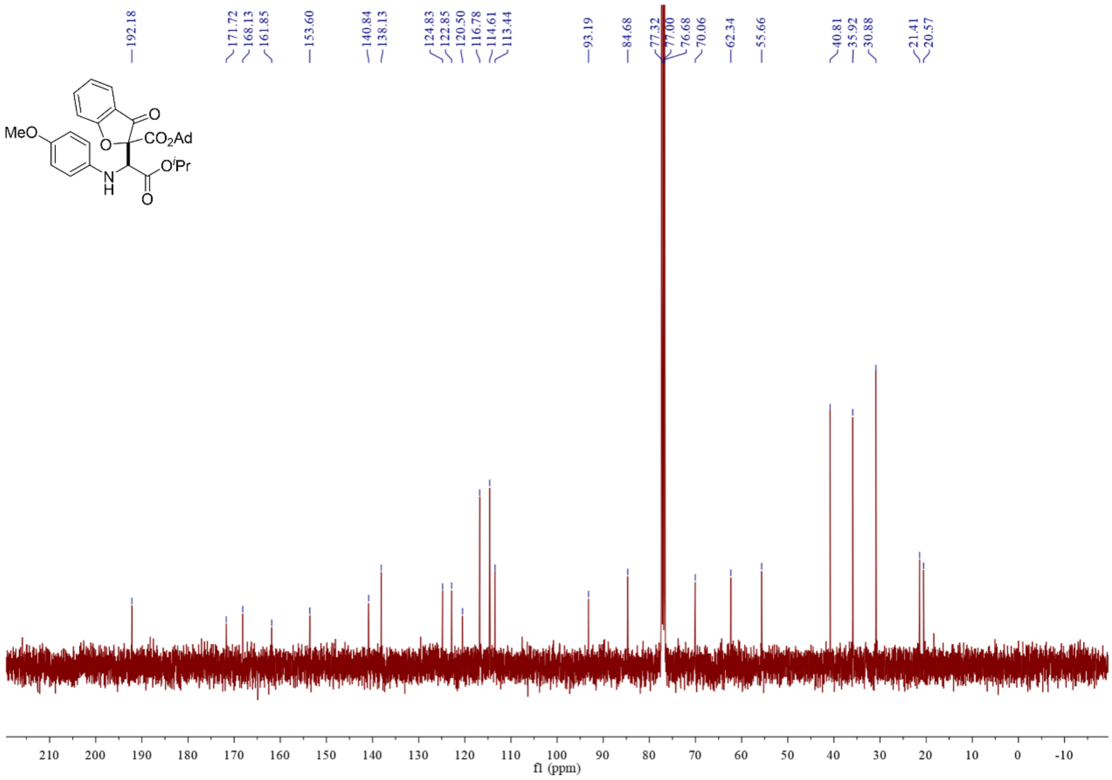
methyl 2-(2-ethoxy-1-((4-methoxyphenyl)amino)-2-oxoethyl)-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (**7an**)



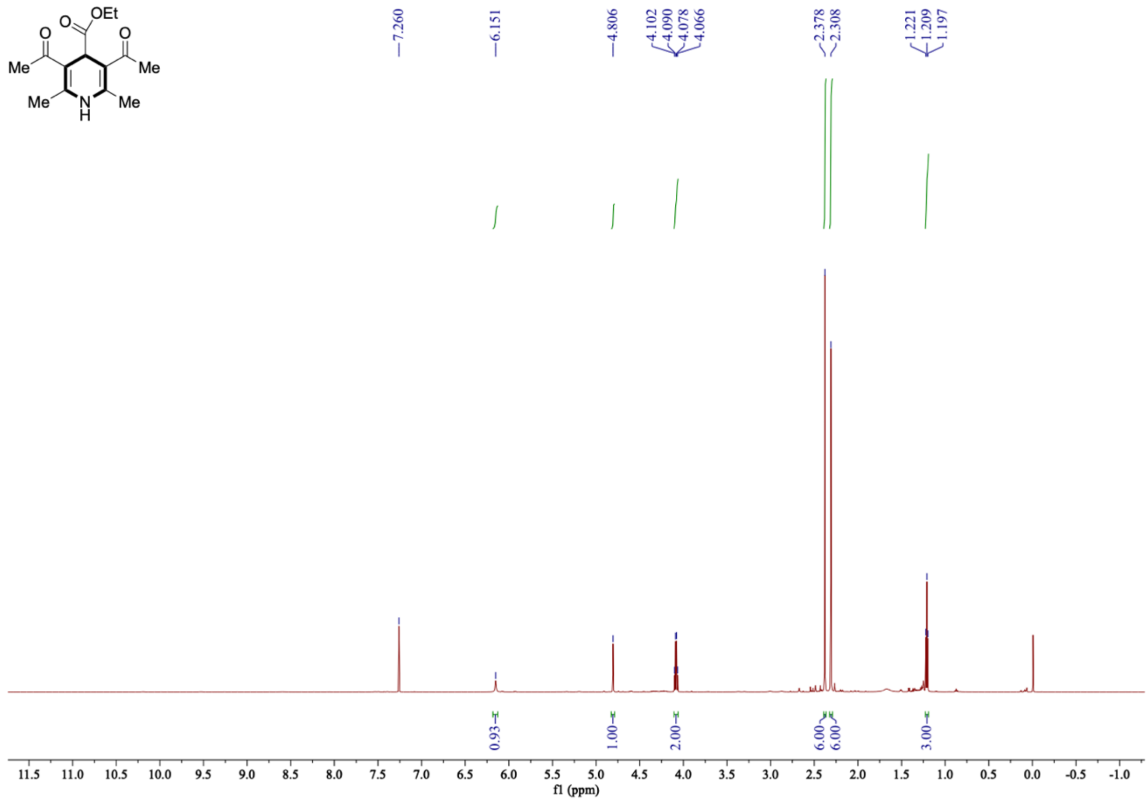


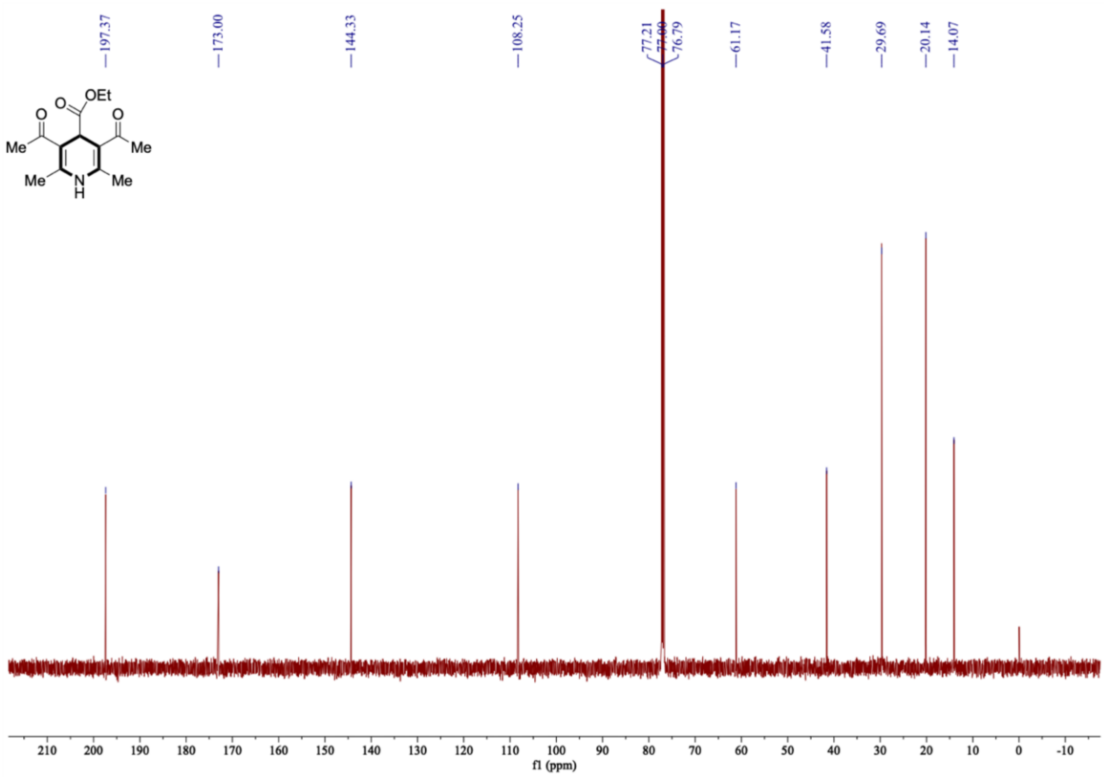
adamantan-1-yl 2-(2-isopropoxy-1-((4-methoxyphenyl)amino)-2-oxoethyl)-3-oxo-2,3-dihydrobenzofuran-2-carboxylate (**7co**)



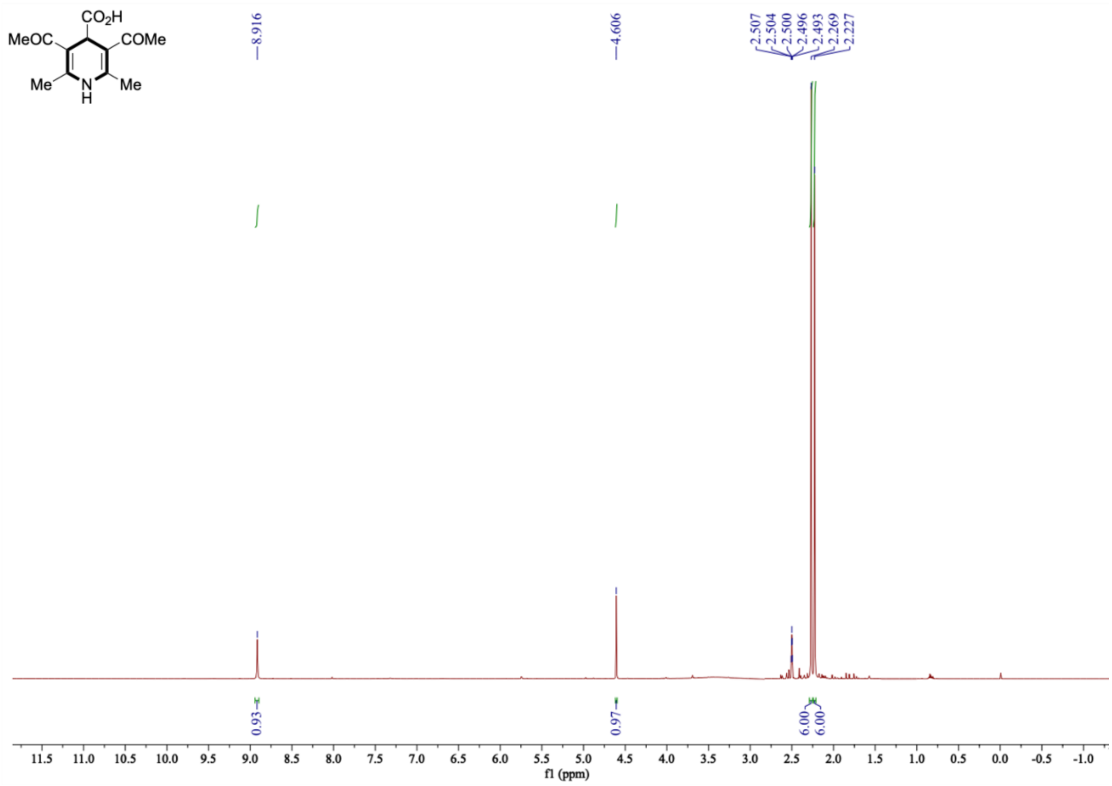


Ethyl 3,5-diacetyl-2,6-dimethyl-1,4-dihydropyridine-4-carboxylate (**8**)

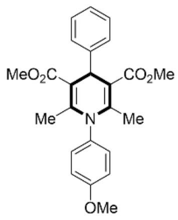


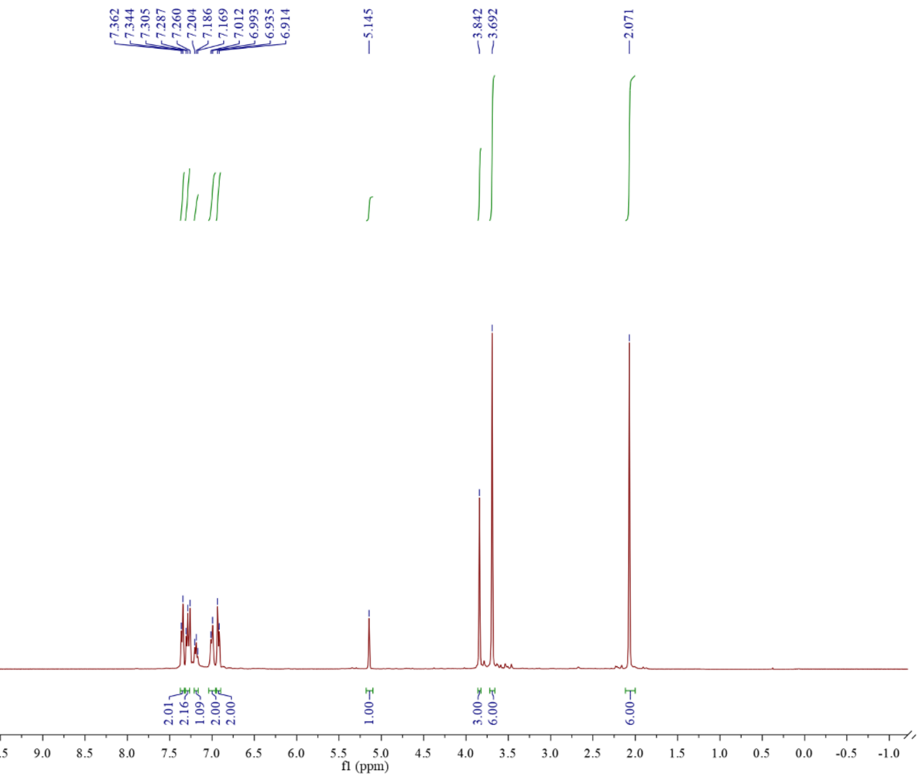


3,5-Diacetyl-2,6-dimethyl-1,4-dihydropyridine-4-carboxylic acid (**9**)

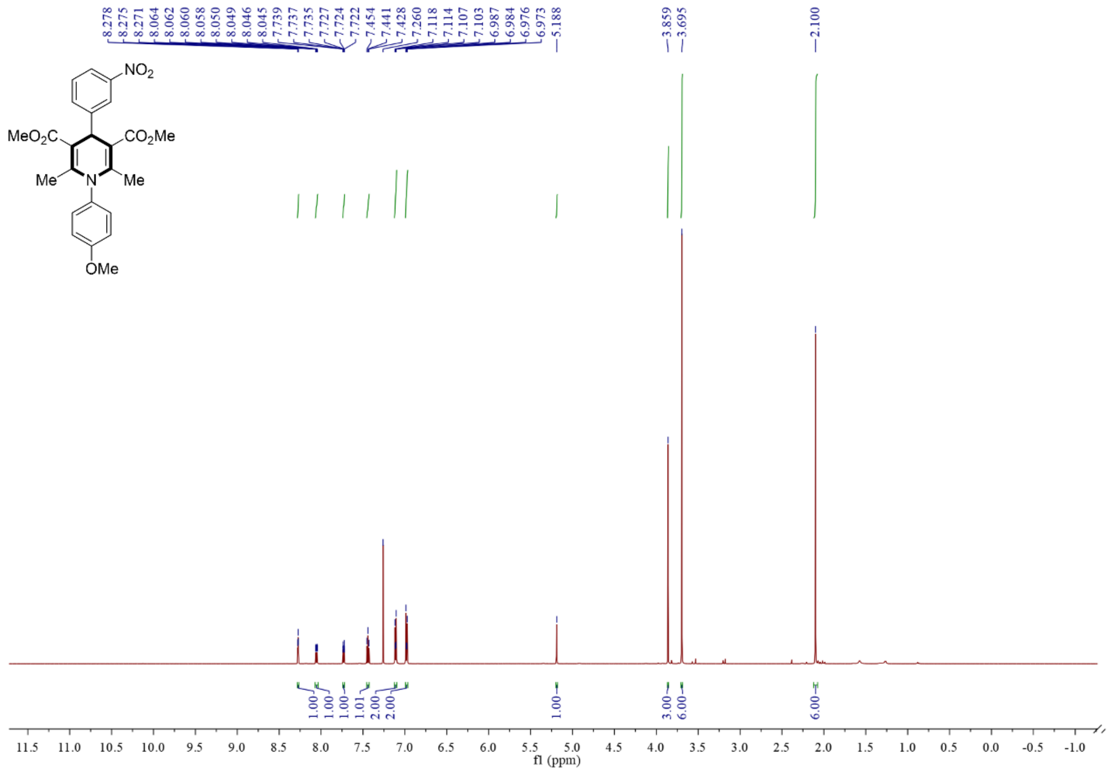


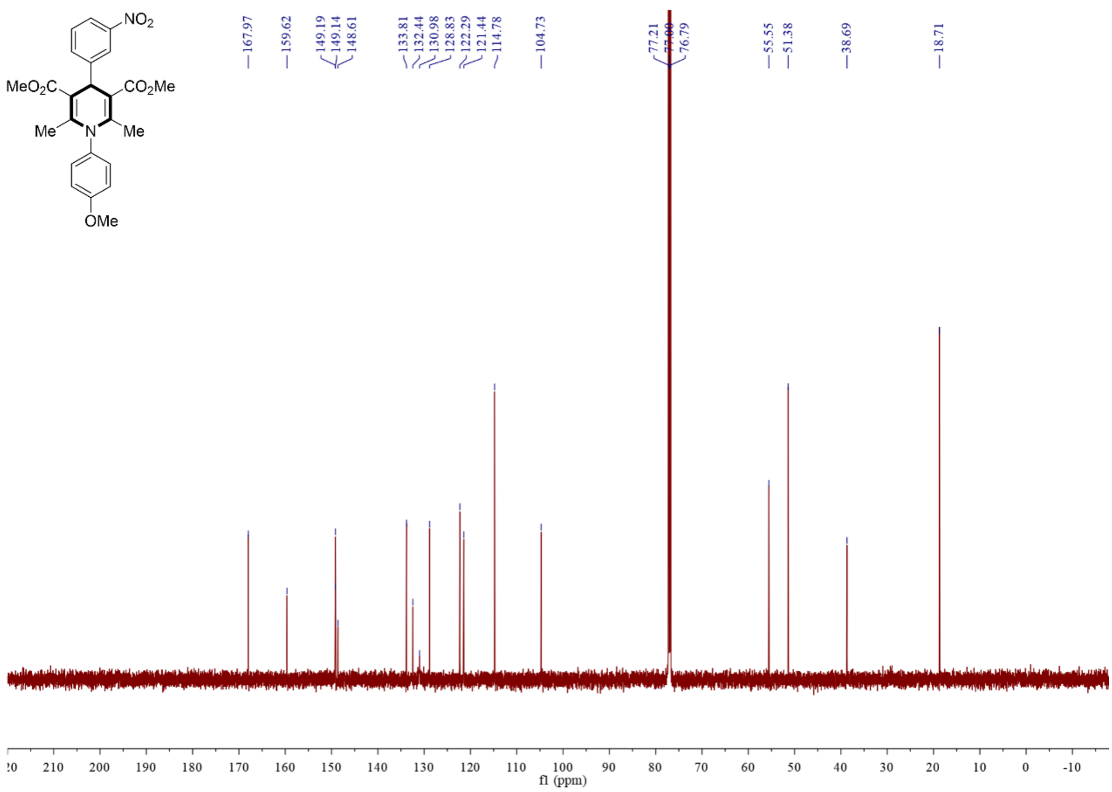
dimethyl 1-(4-methoxyphenyl)-2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (**11a**)





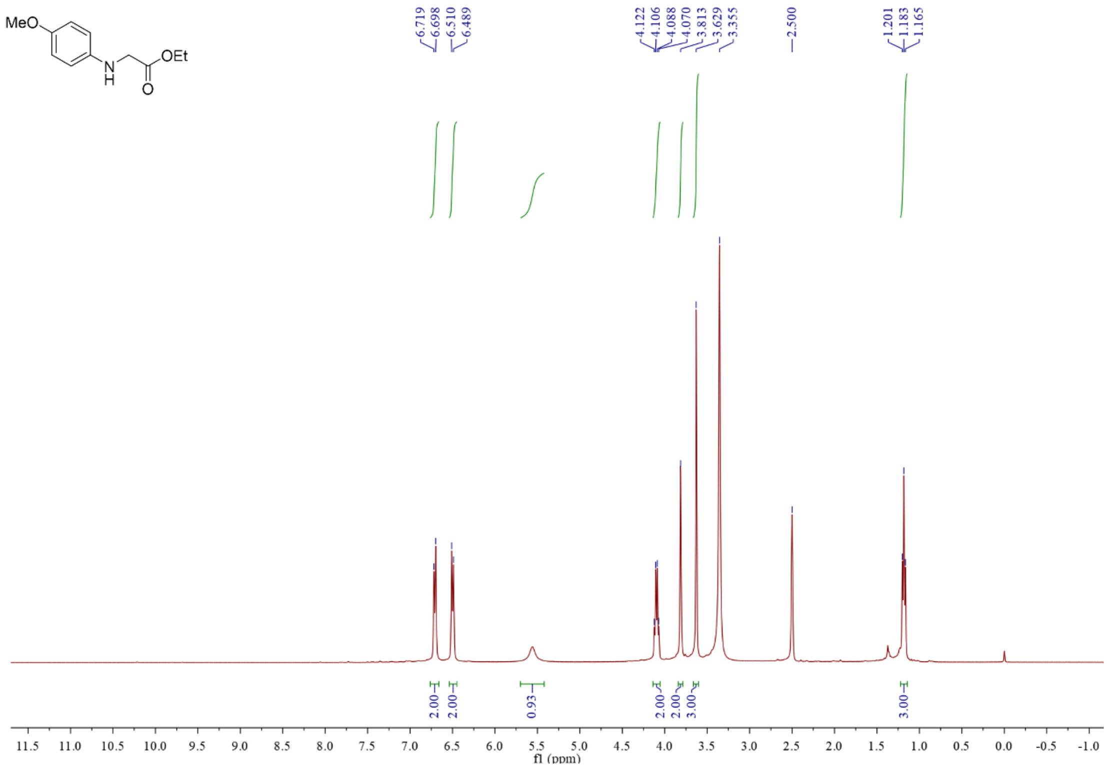
dimethyl 1-(4-methoxyphenyl)-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**11b**)



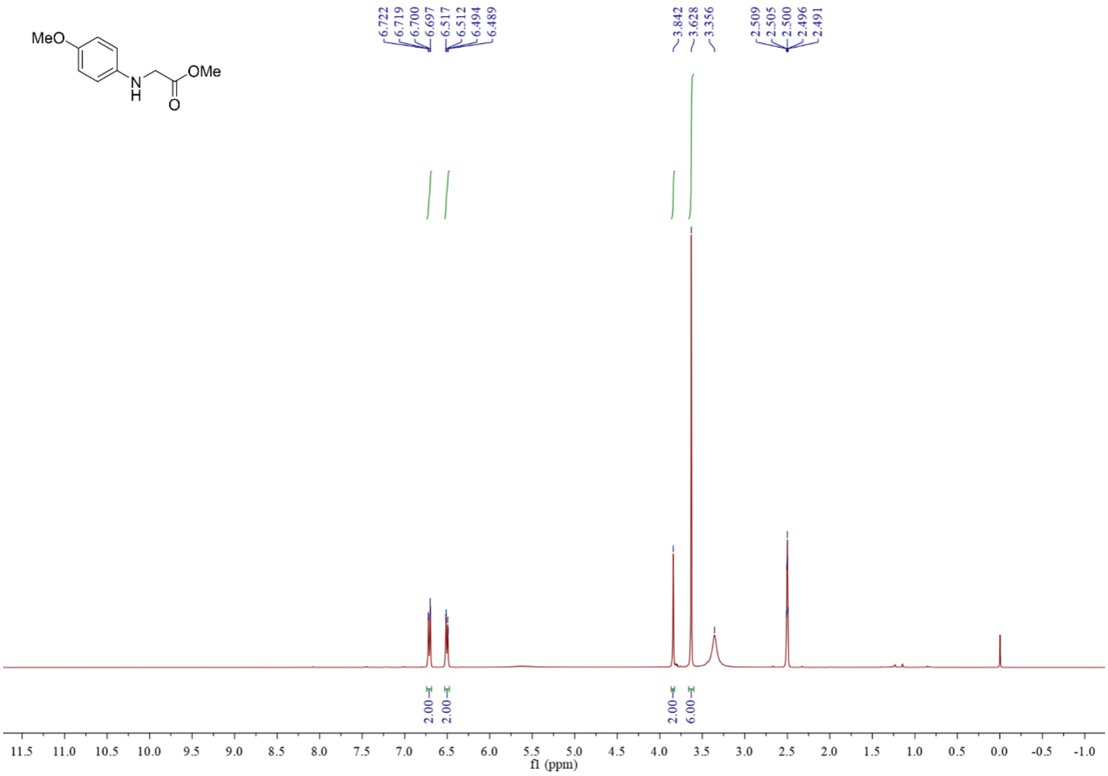


For reactants 1, 4 and 10

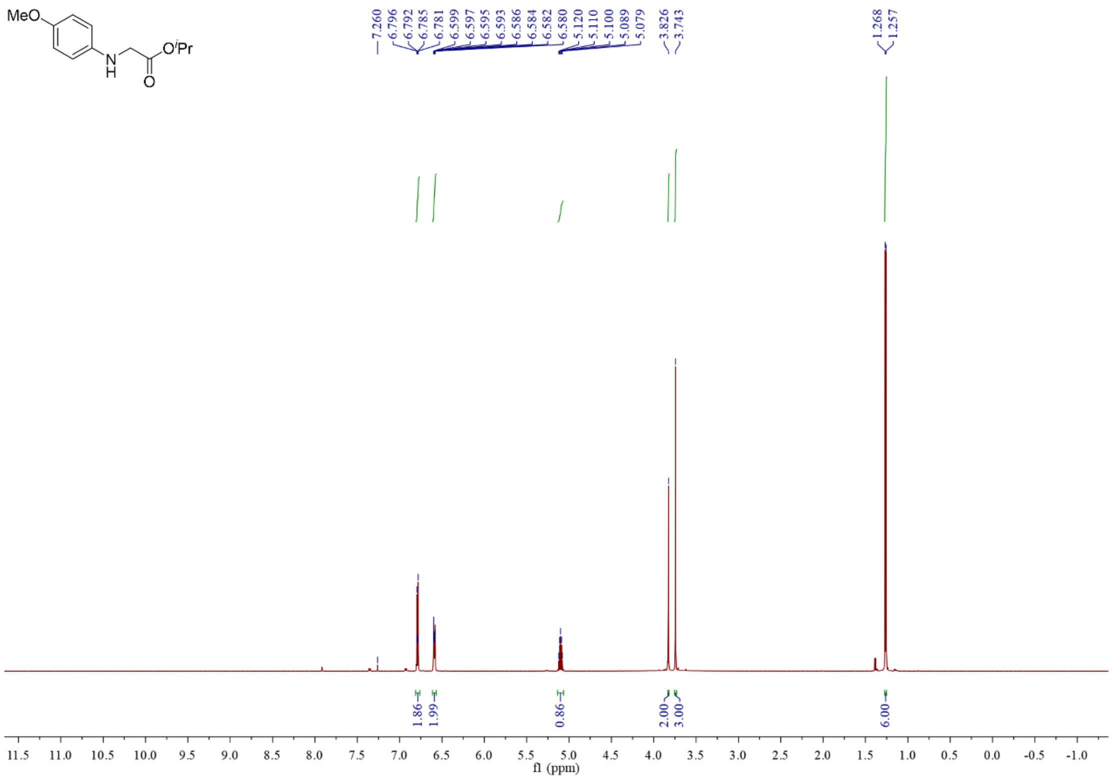
ethyl (4-methoxyphenyl)glycinate (**1a**)

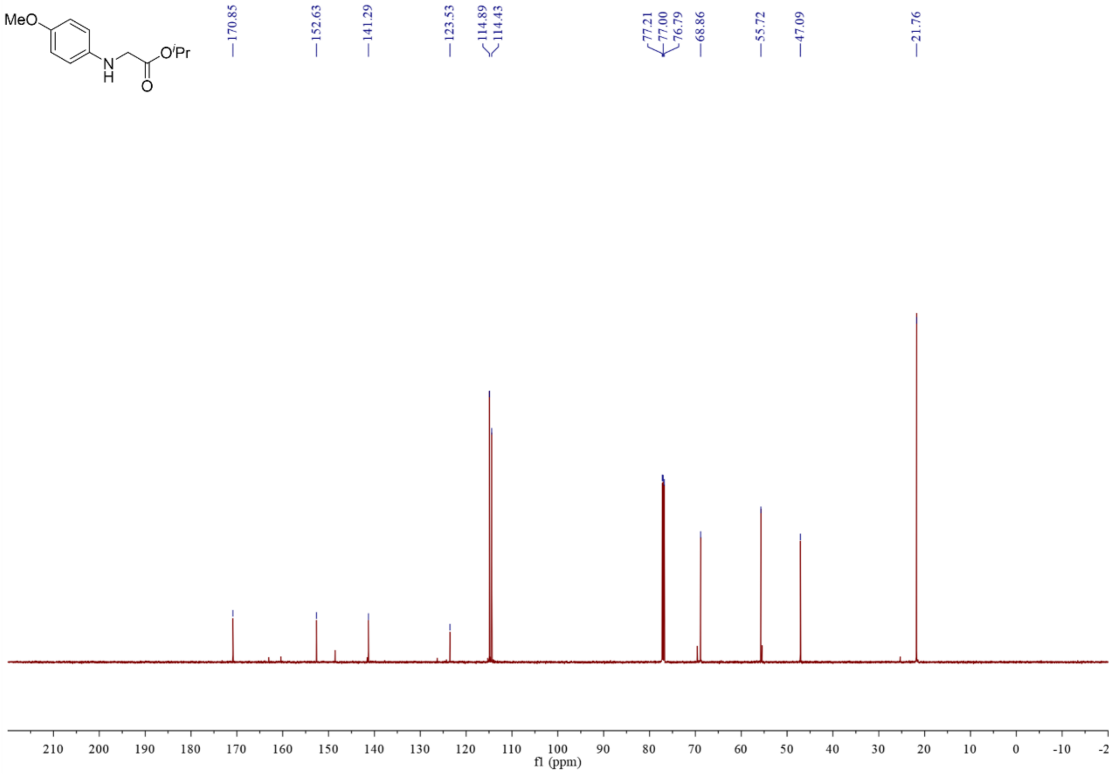


methyl (4-methoxyphenyl)glycinate (**1b**)

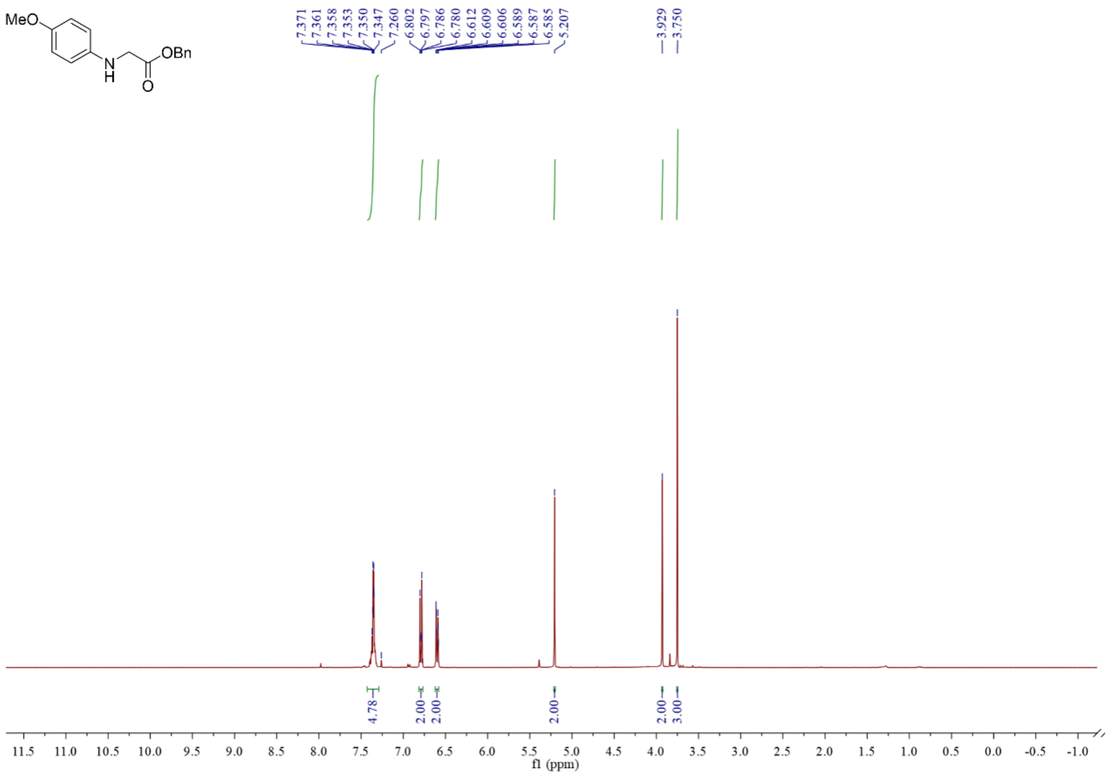


isopropyl (4-methoxyphenyl)glycinate (**1c**)

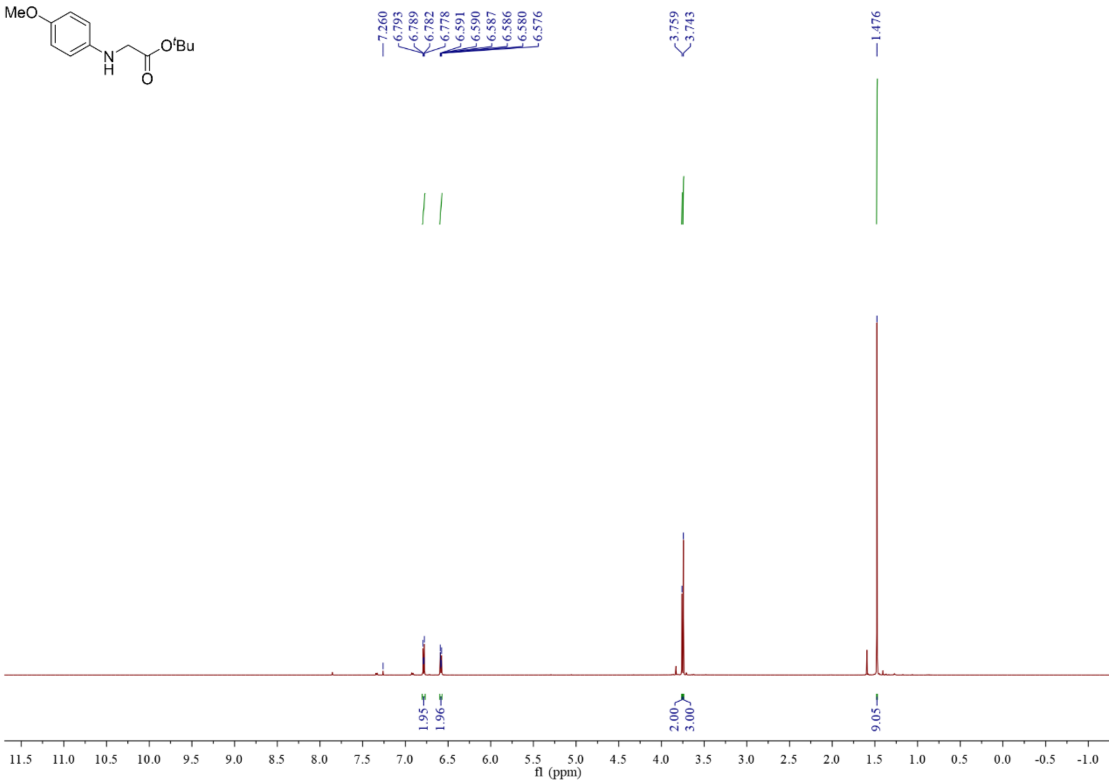




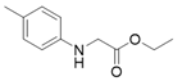
benzyl (4-methoxyphenyl)glycinate (**1d**)

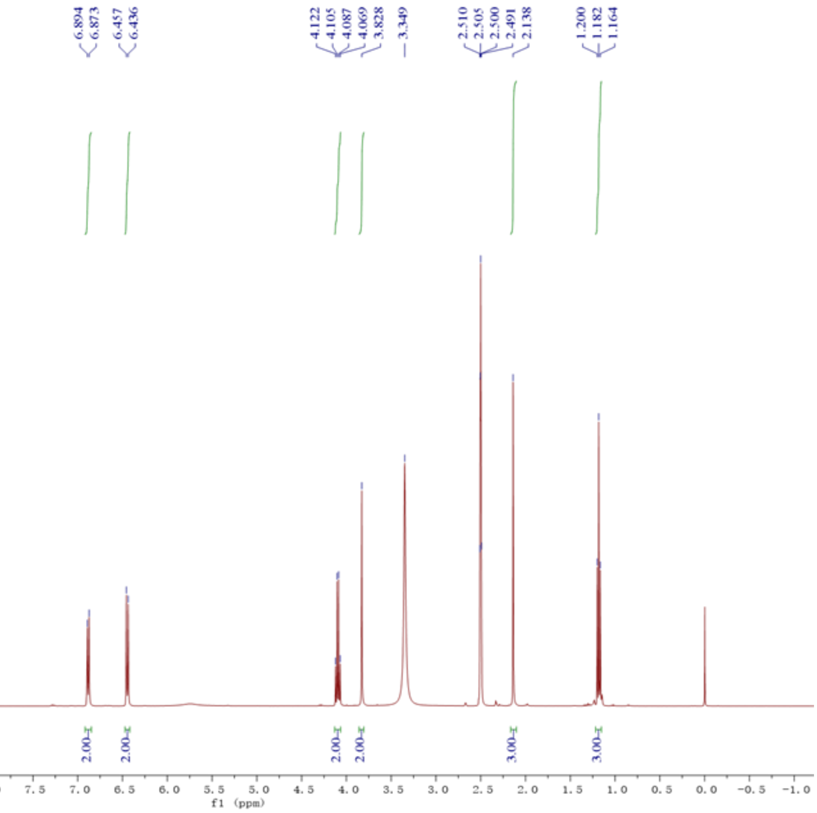


tert-butyl (4-methoxyphenyl)glycinate (**1e**)

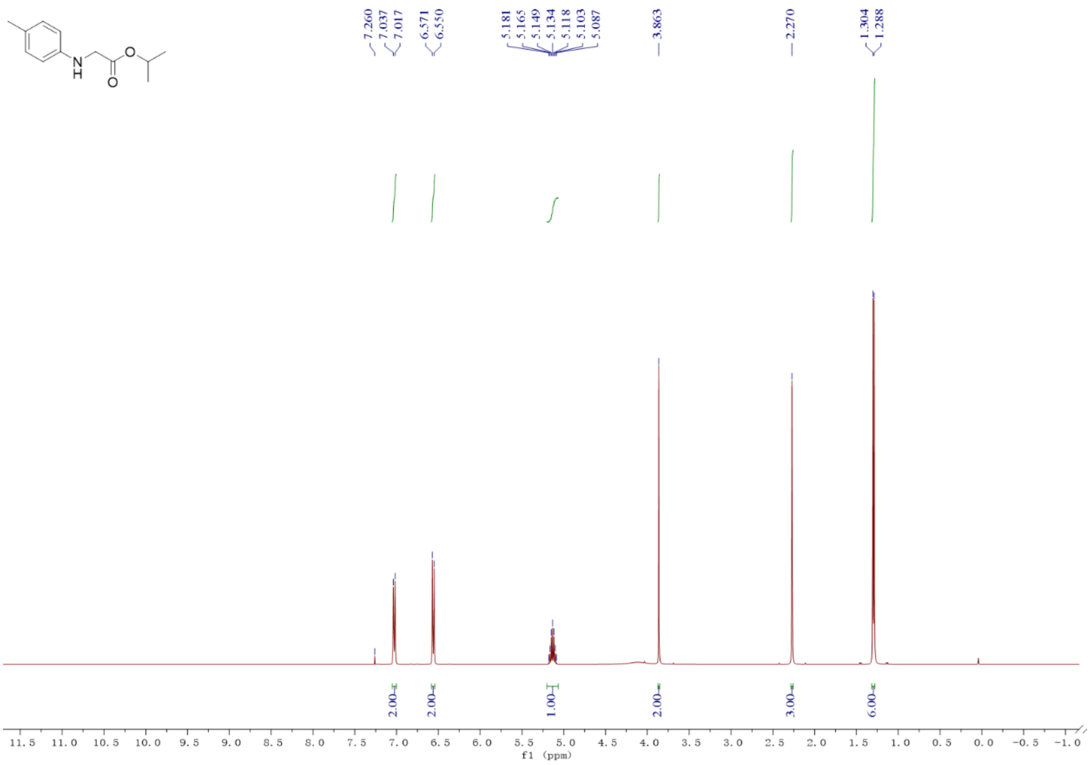


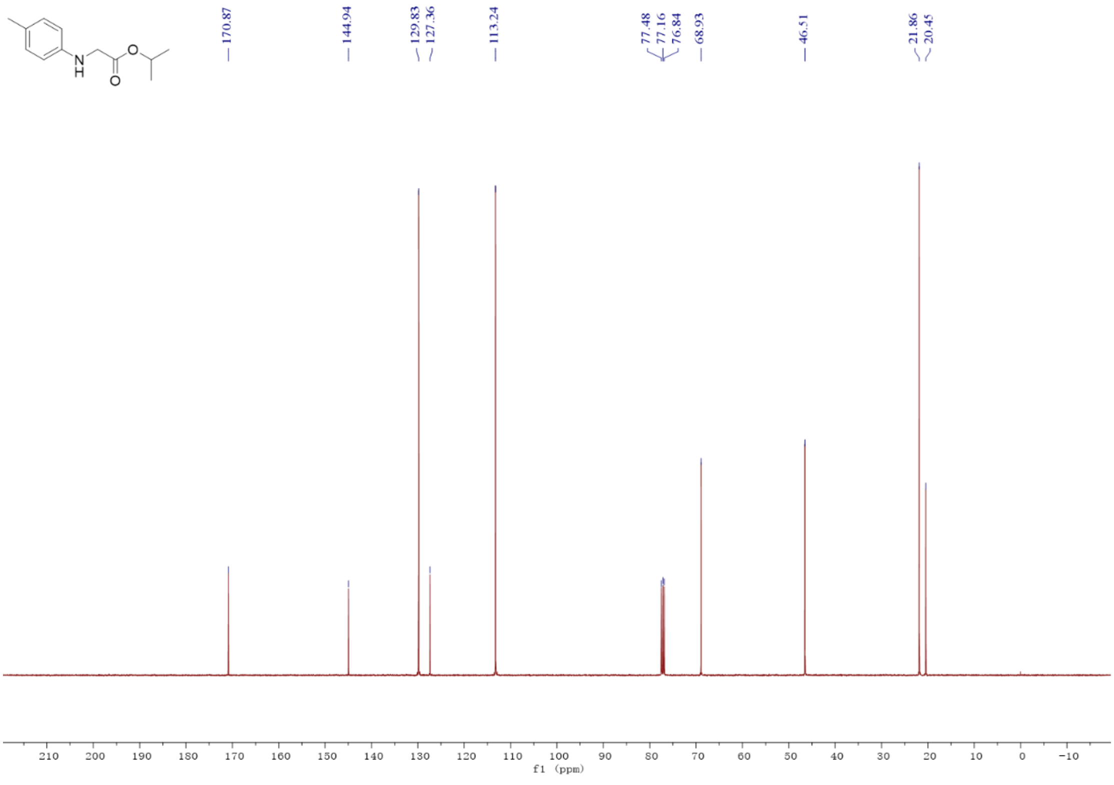
ethyl p-tolylglycinate (**1f**)



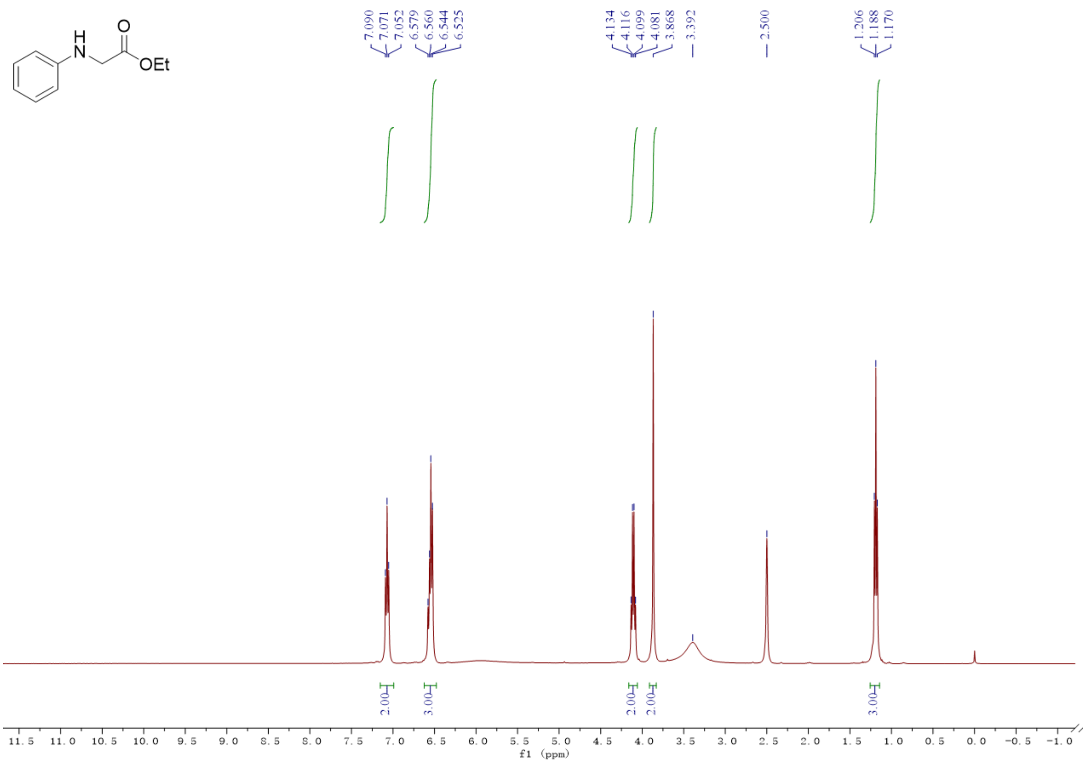


isopropyl p-tolylglycinate (**1g**)

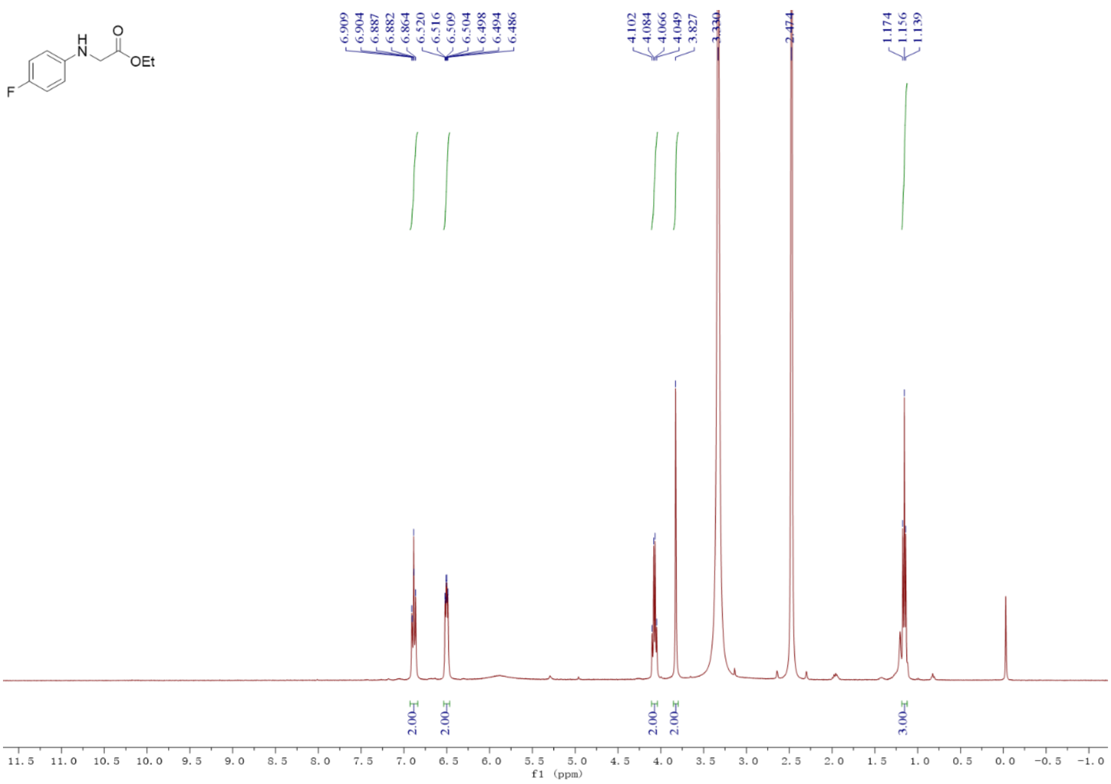




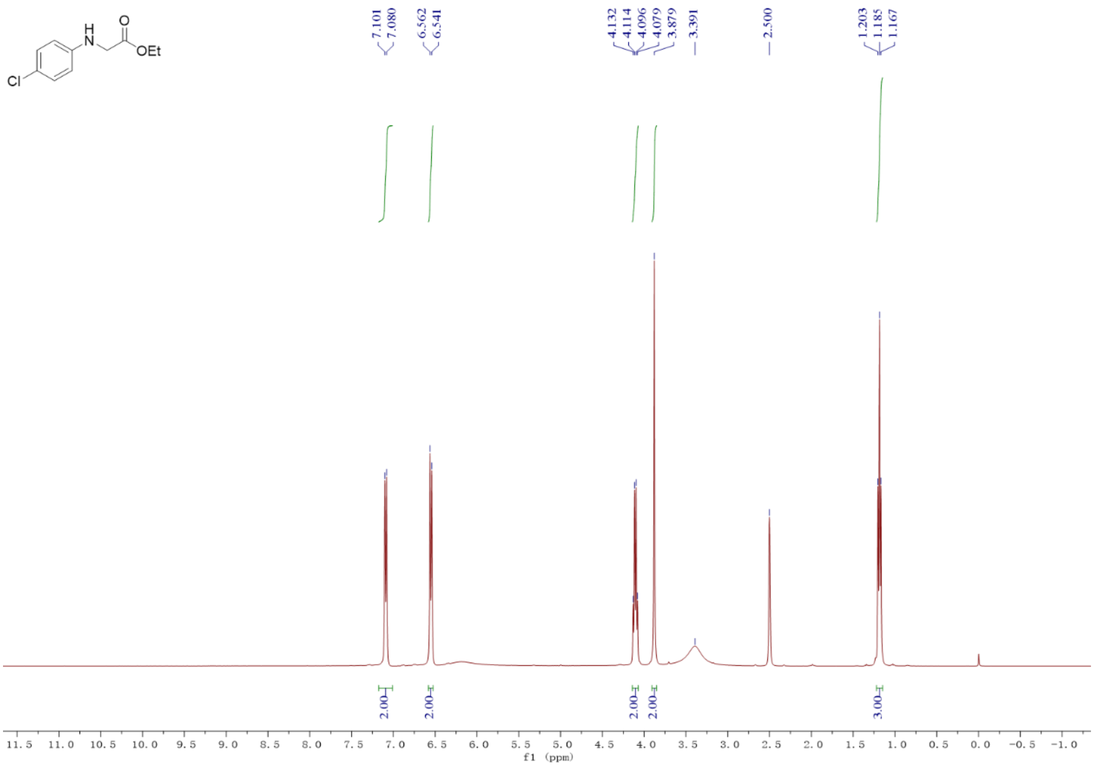
ethyl phenylglycinate (**1h**)



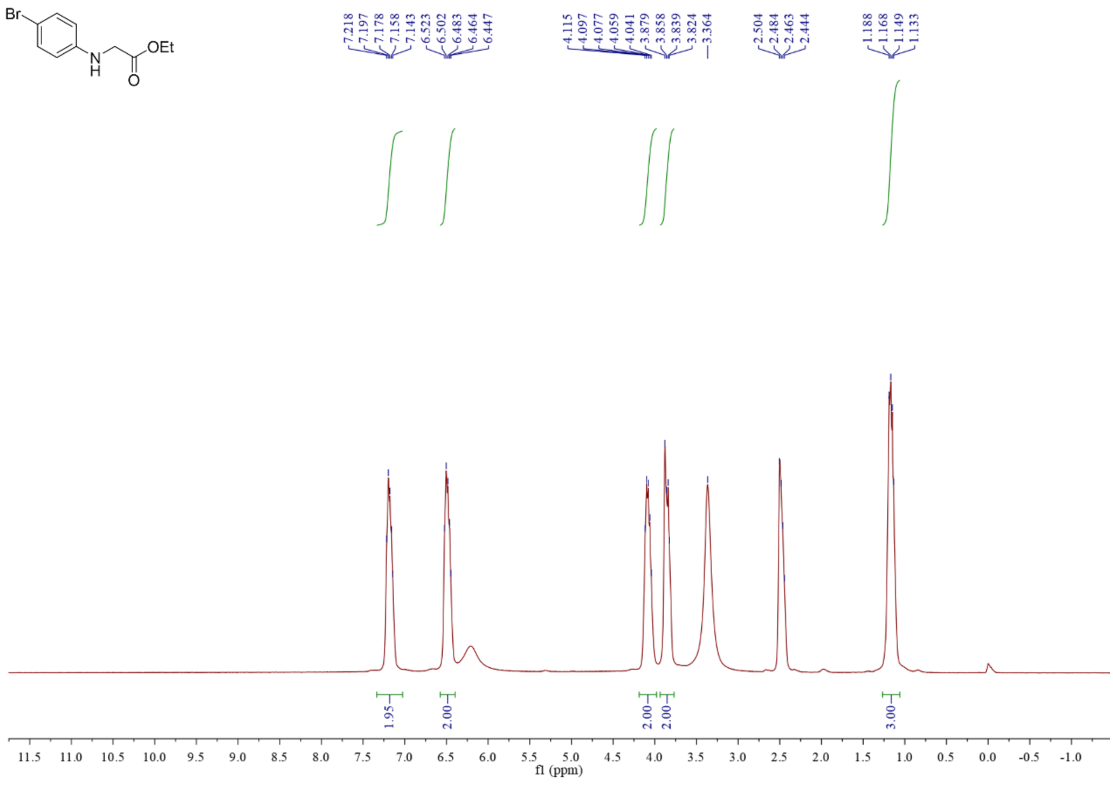
ethyl (4-fluorophenyl)glycinate (**1i**)



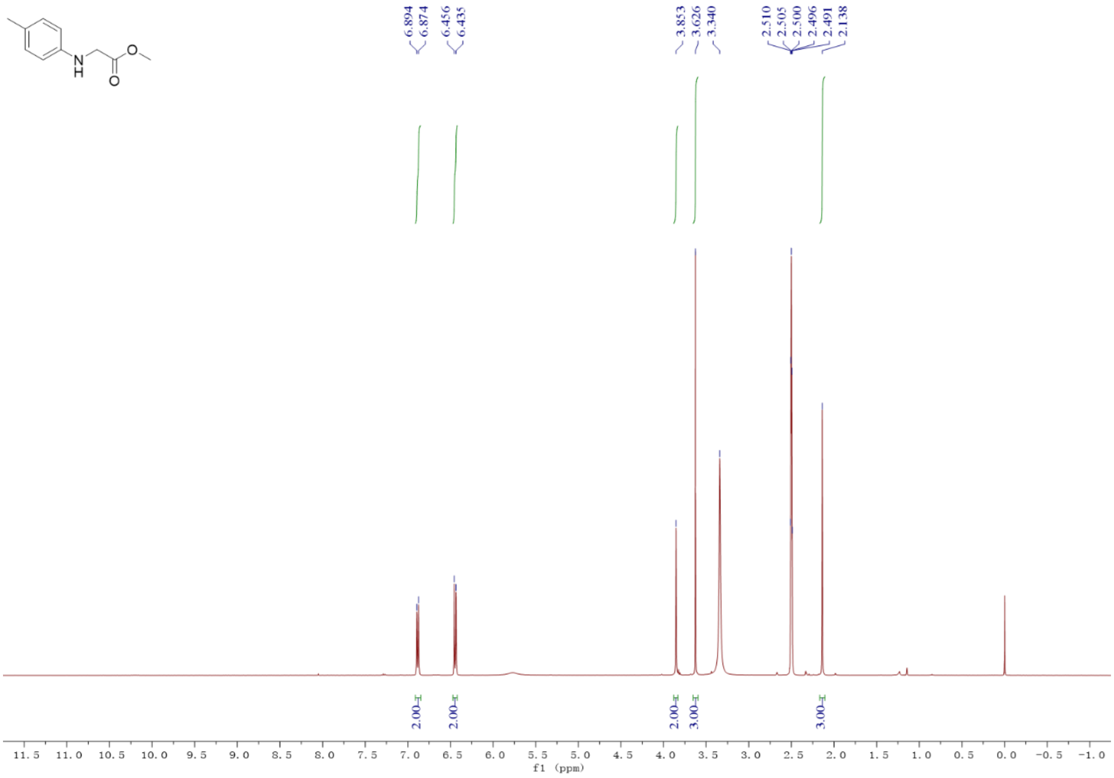
ethyl (4-chlorophenyl)glycinate (**1j**)



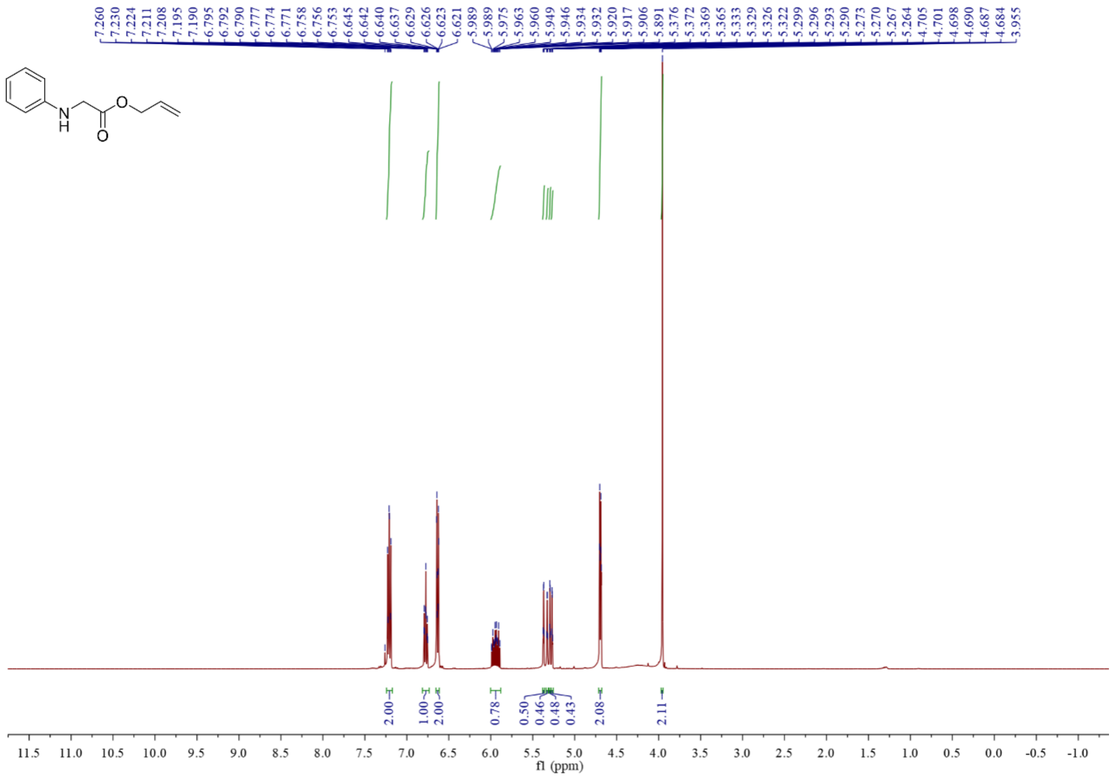
ethyl (4-bromophenyl)glycinate (**1k**)

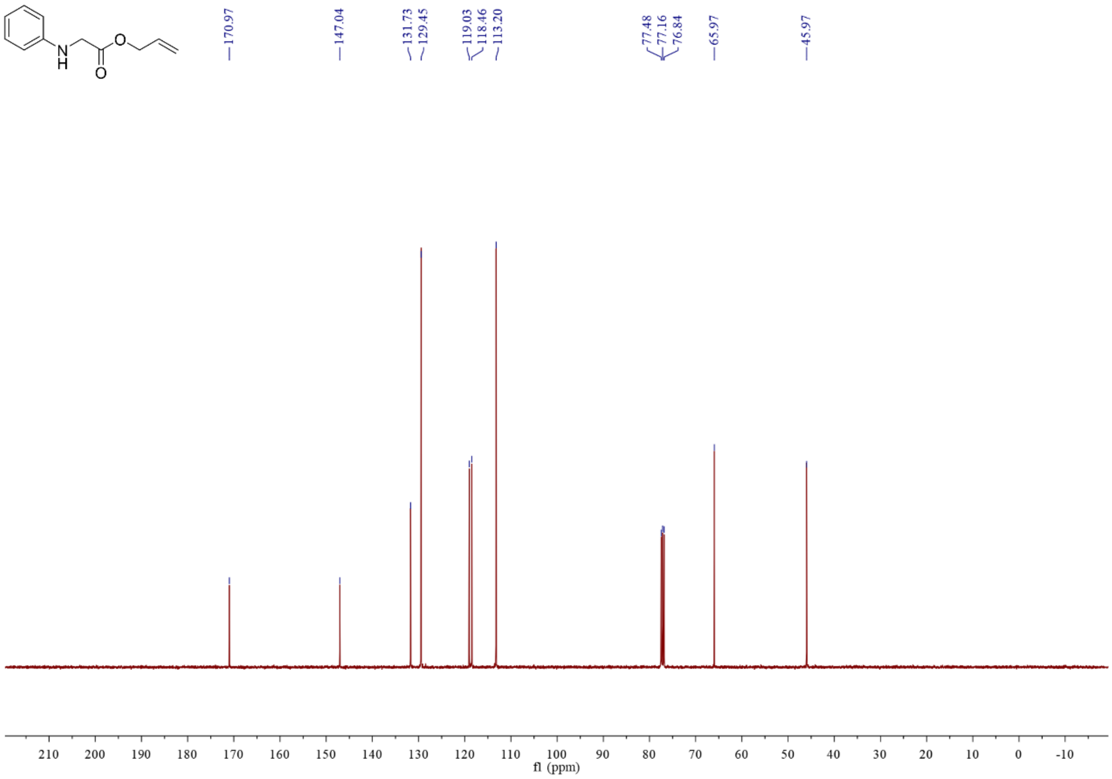


methyl p-tolylglycinate (**1l**)

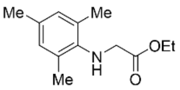


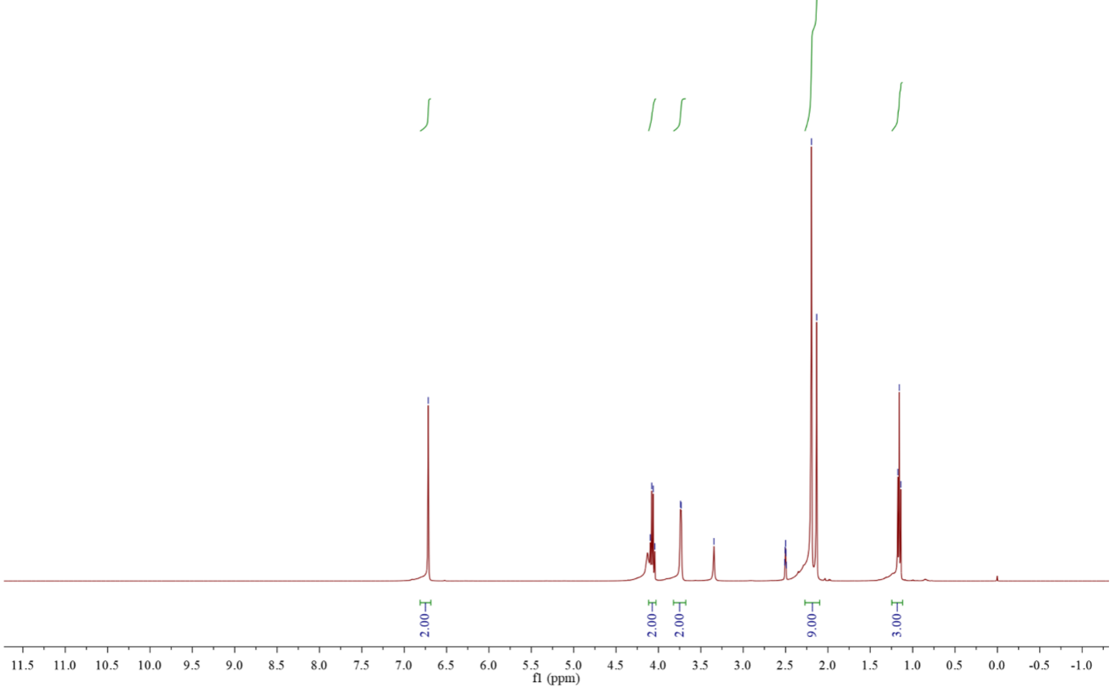
allyl phenylglycinate (**1m**)



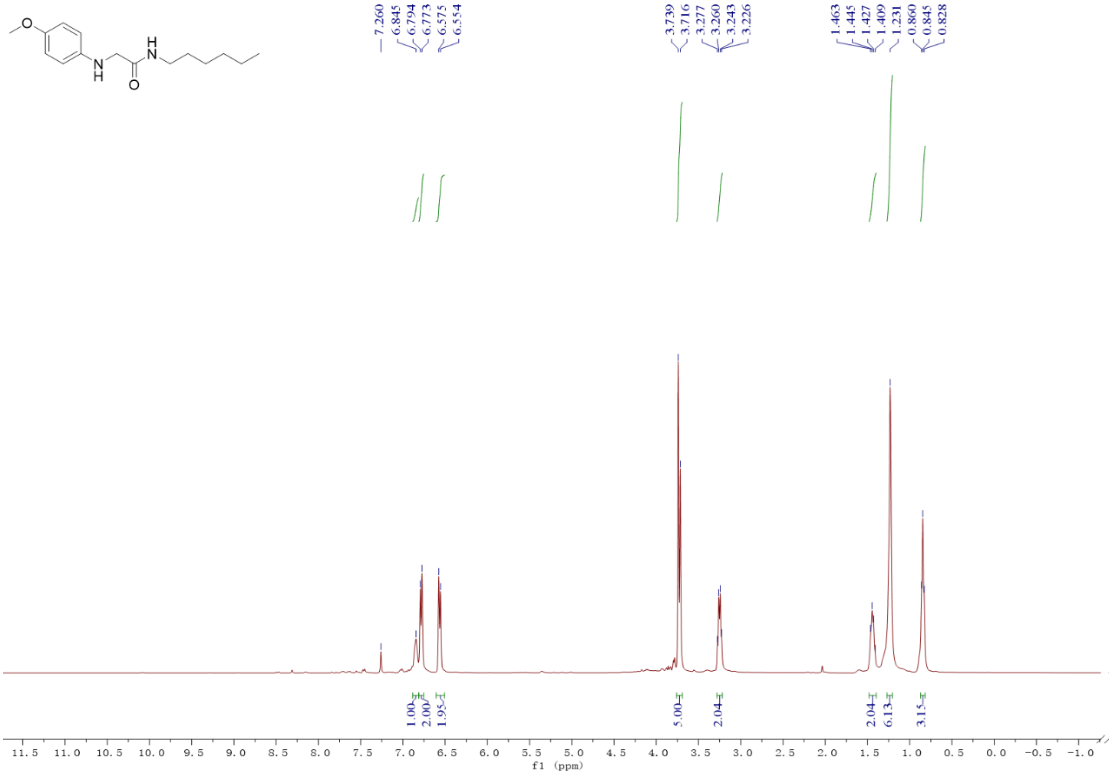


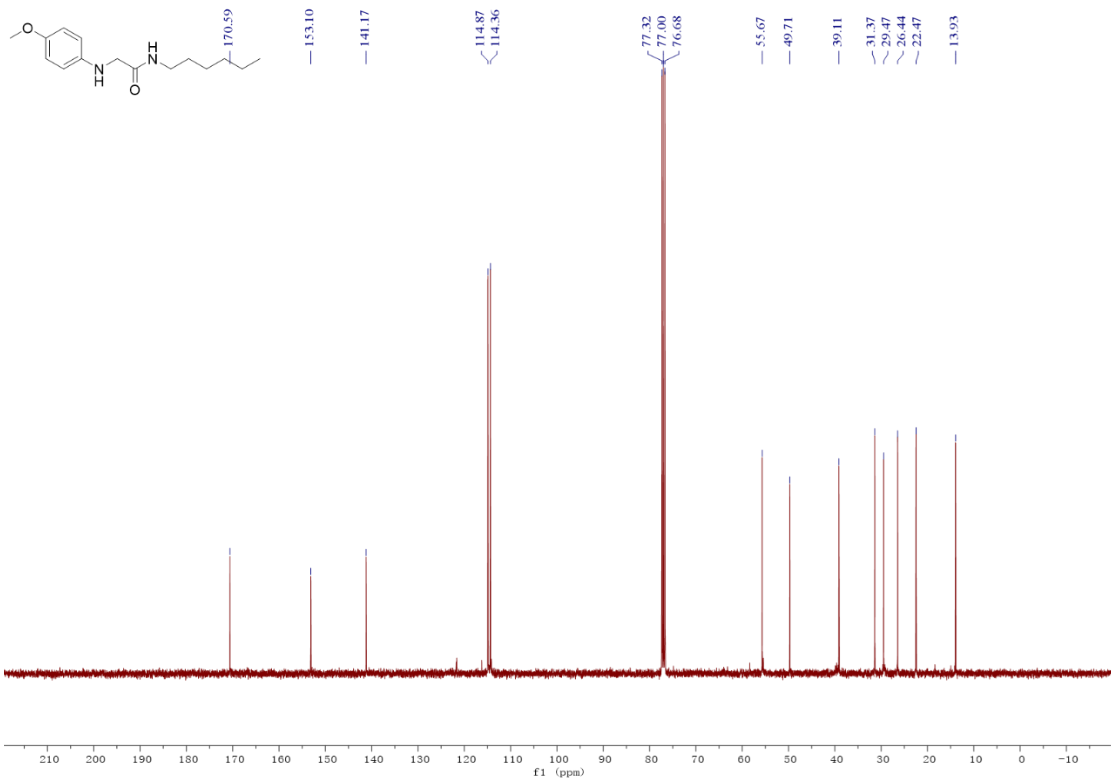
ethyl mesitylglycinate (**1n**)



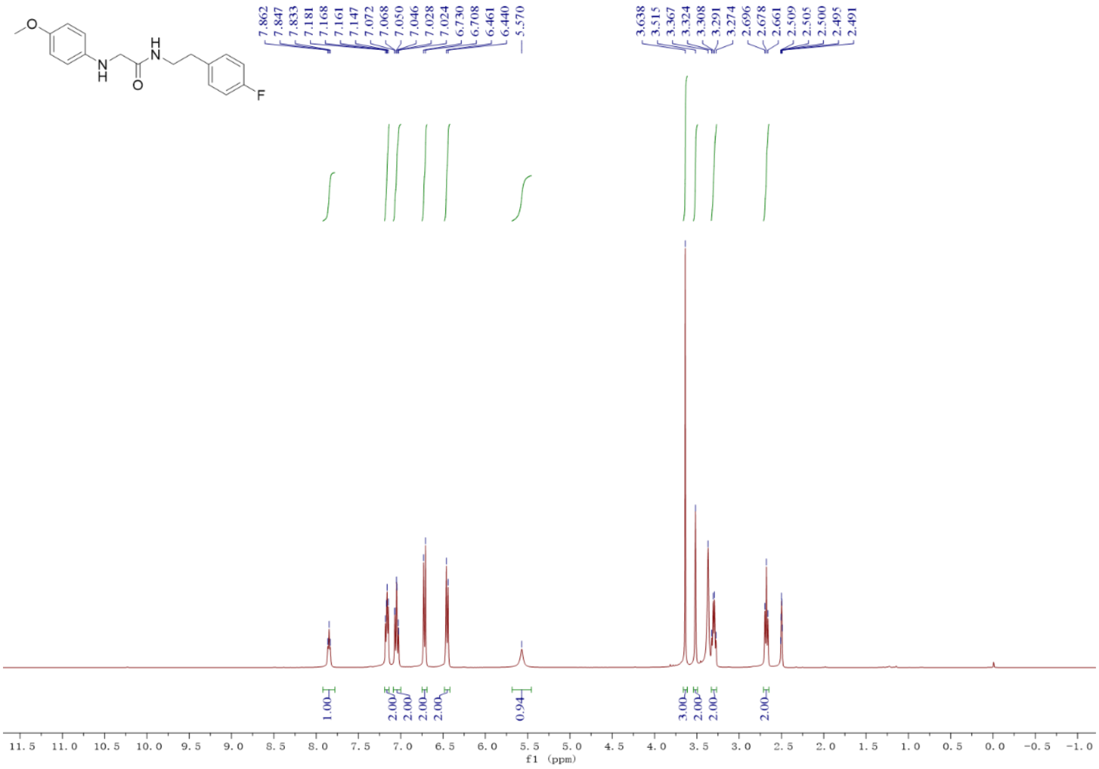


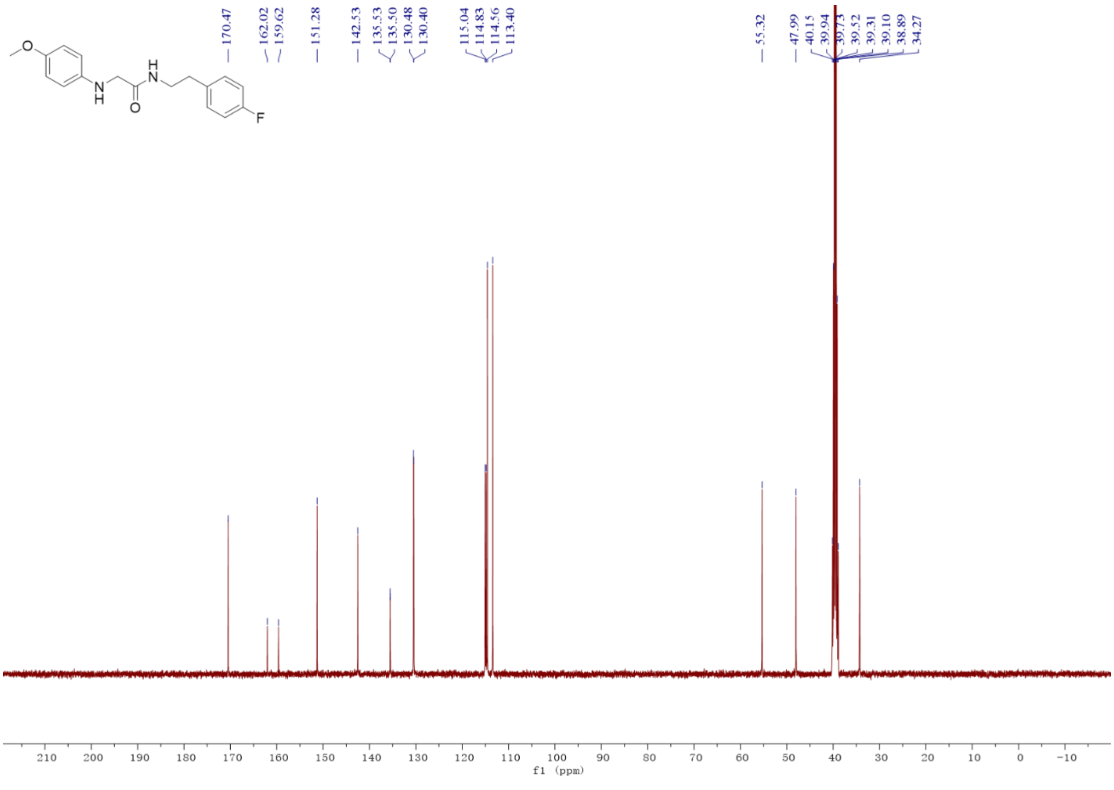
N-hexyl-2-((4-methoxyphenyl)amino)acetamide (**4a**)



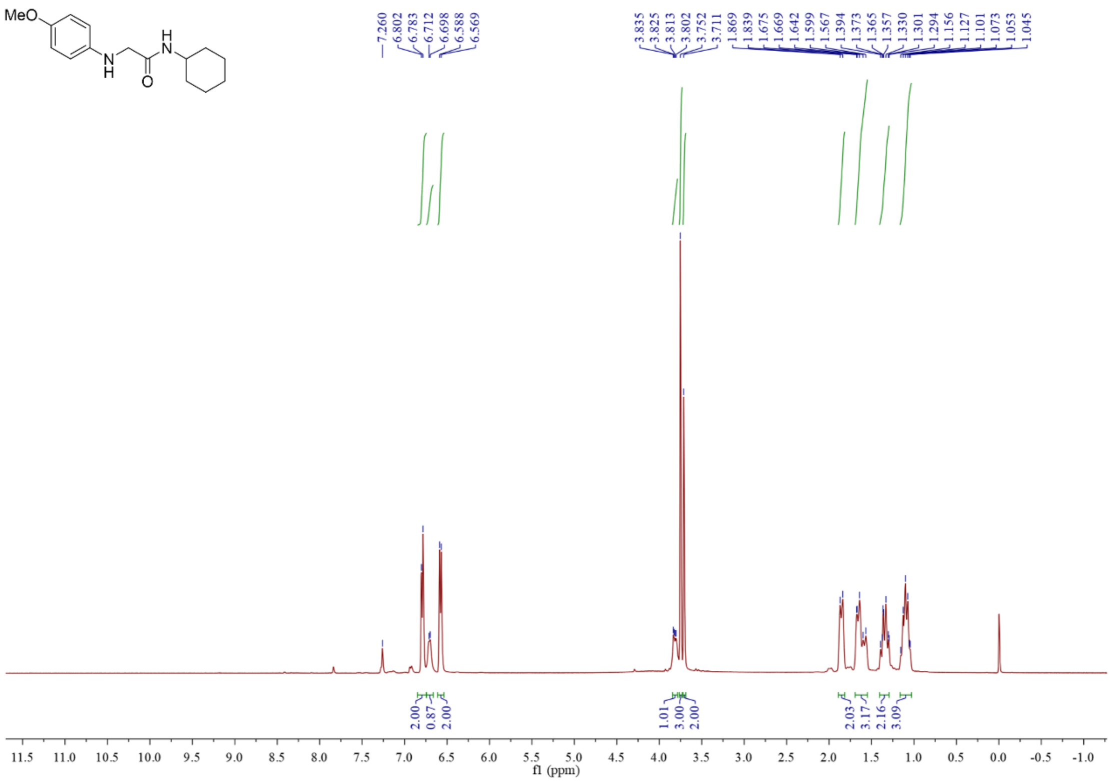


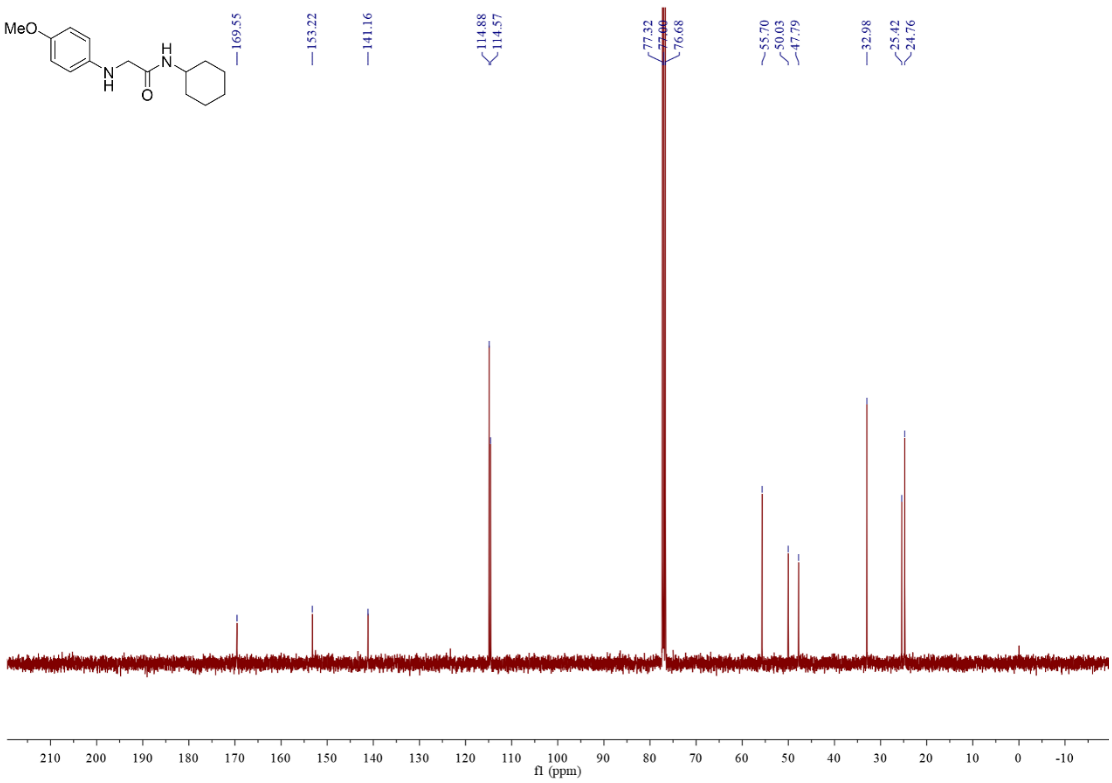
N-(4-fluorophenethyl)-2-((4-methoxyphenyl)amino)acetamide (**4b**)



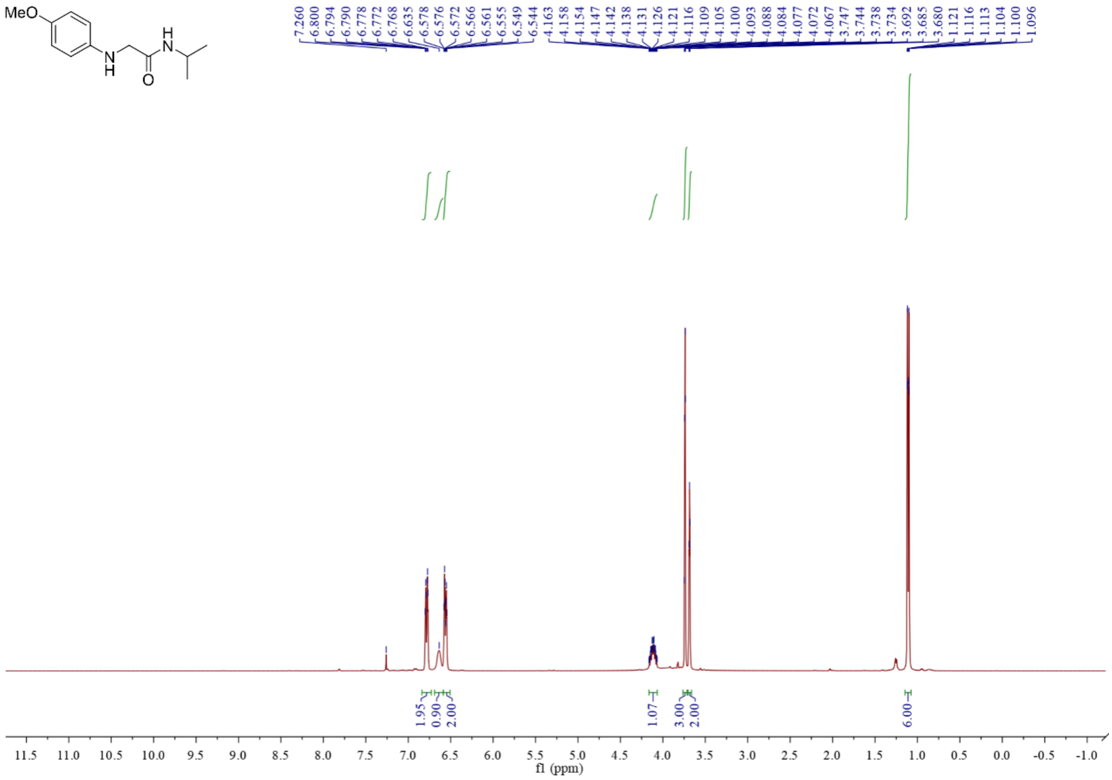


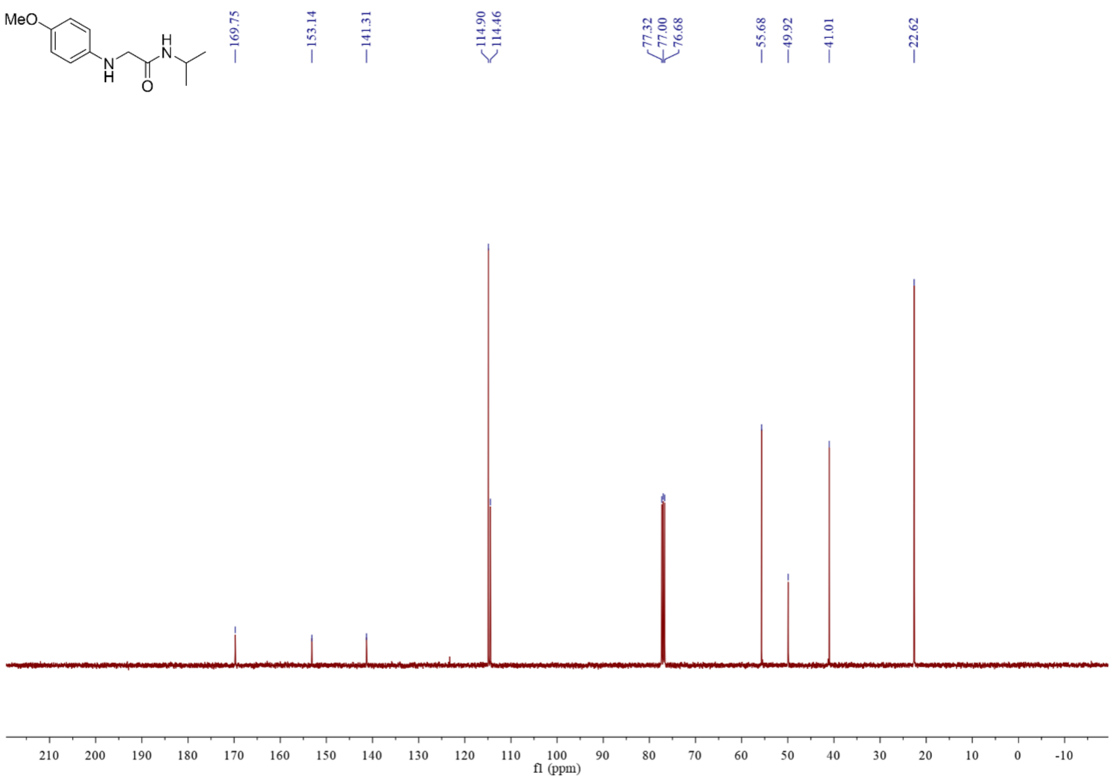
N-cyclohexyl-2-((4-methoxyphenyl)amino)acetamide (**4c**)



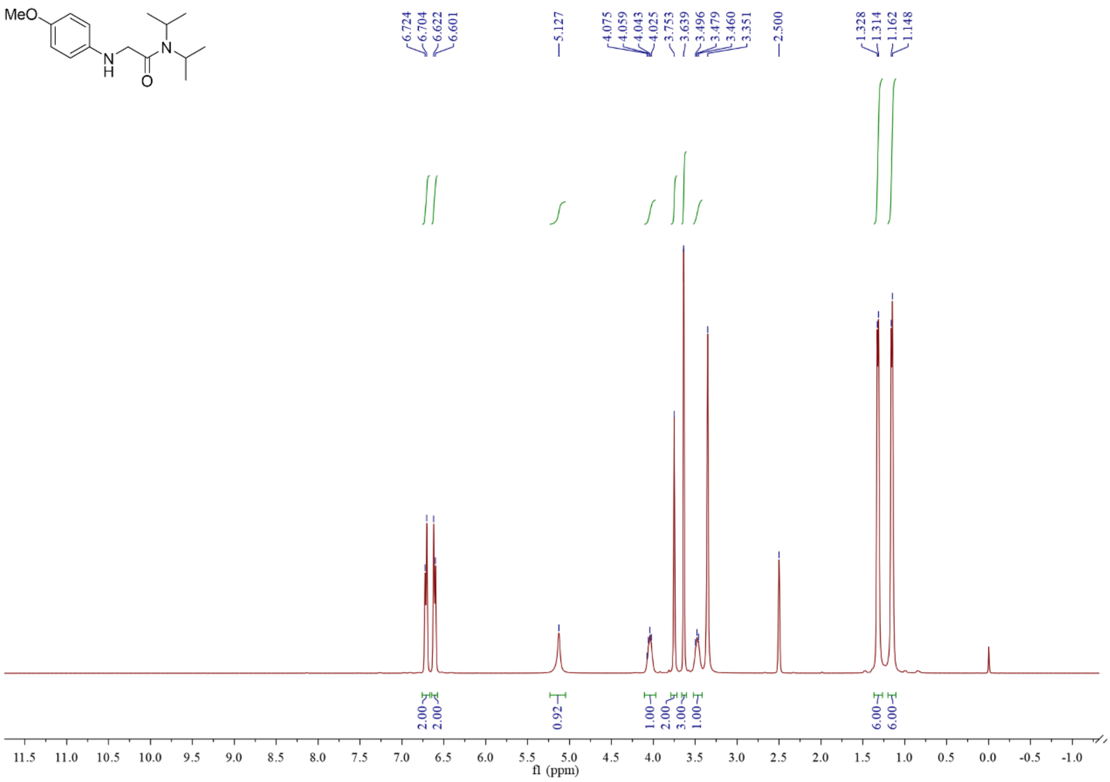


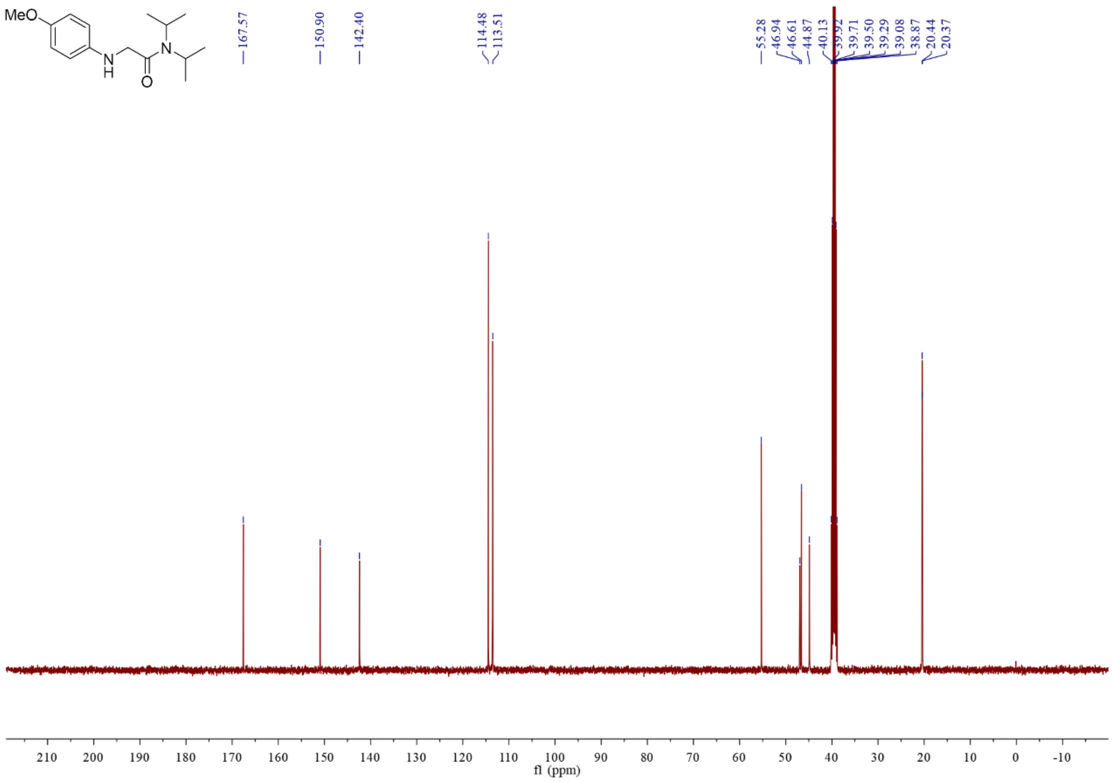
N-isopropyl-2-((4-methoxyphenyl)amino)acetamide (**4d**)



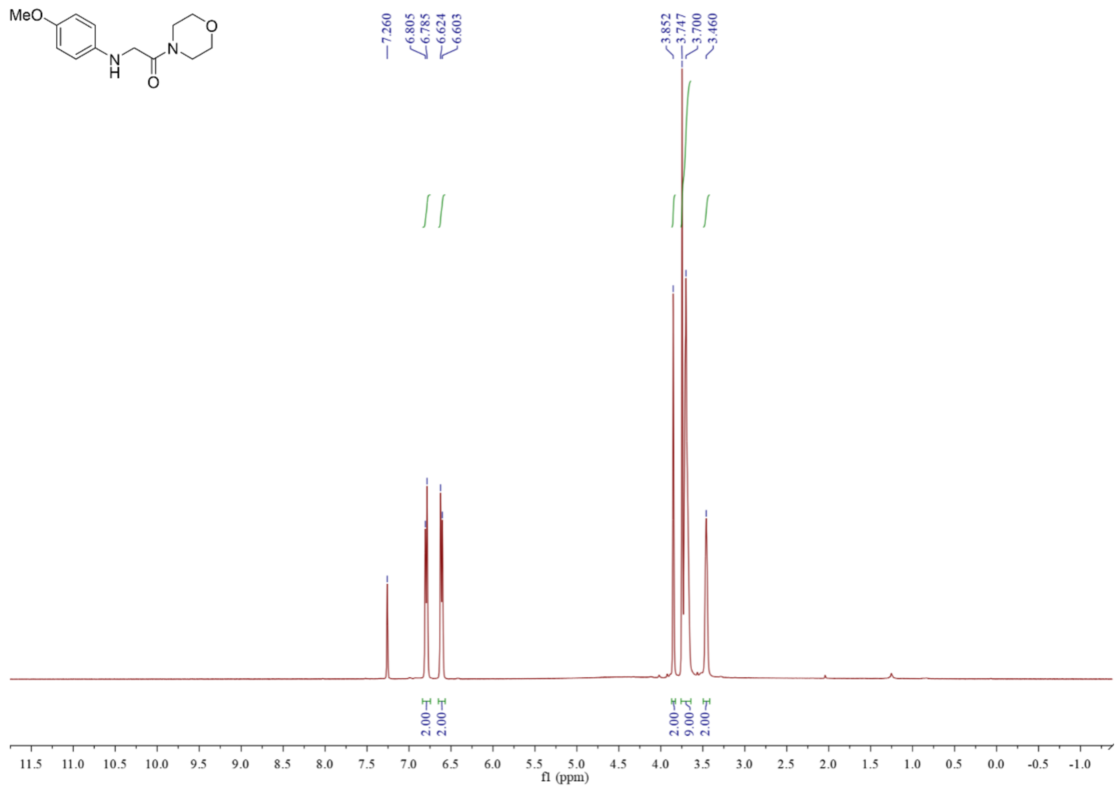


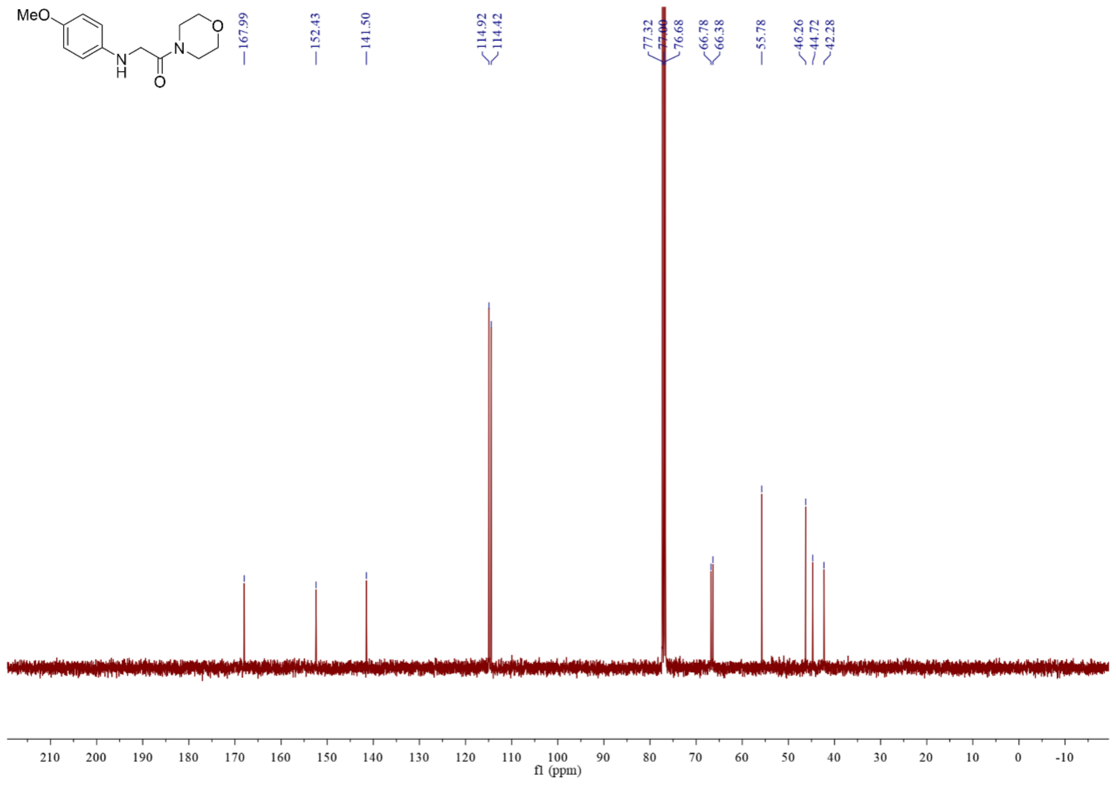
N,N-diisopropyl-2-((4-methoxyphenyl)amino)acetamide (**4e**)



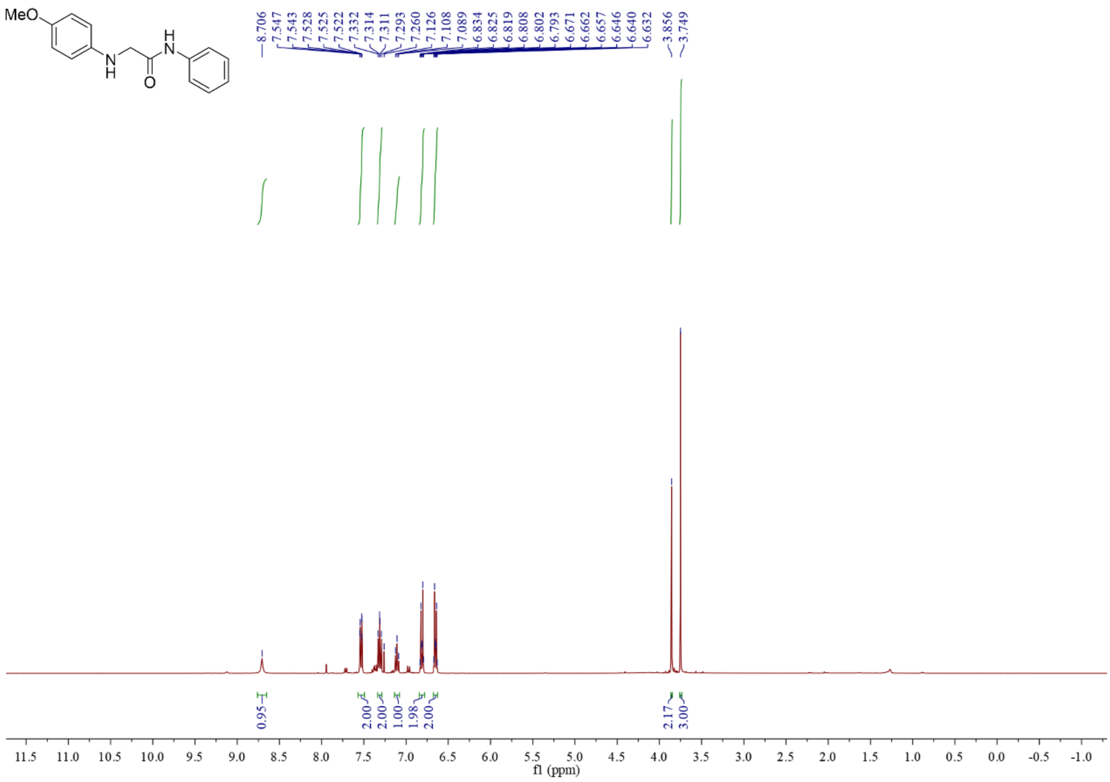


2-((4-methoxyphenyl)amino)-1-morpholinoethan-1-one (**4f**)

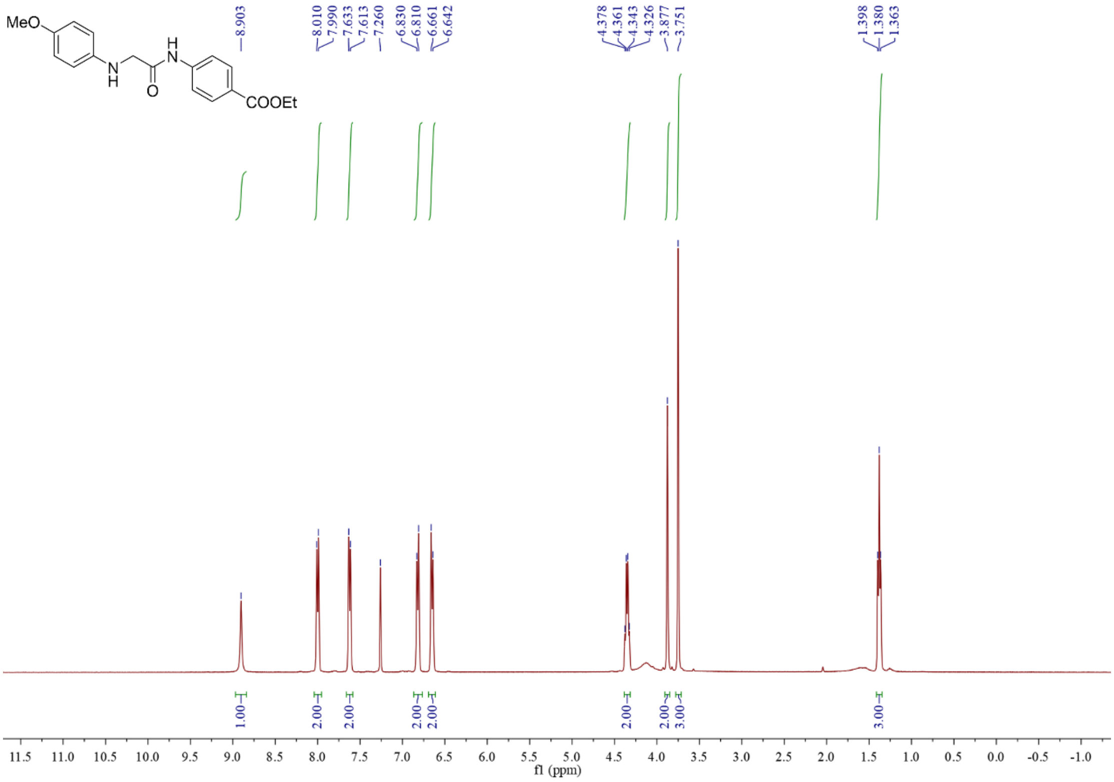


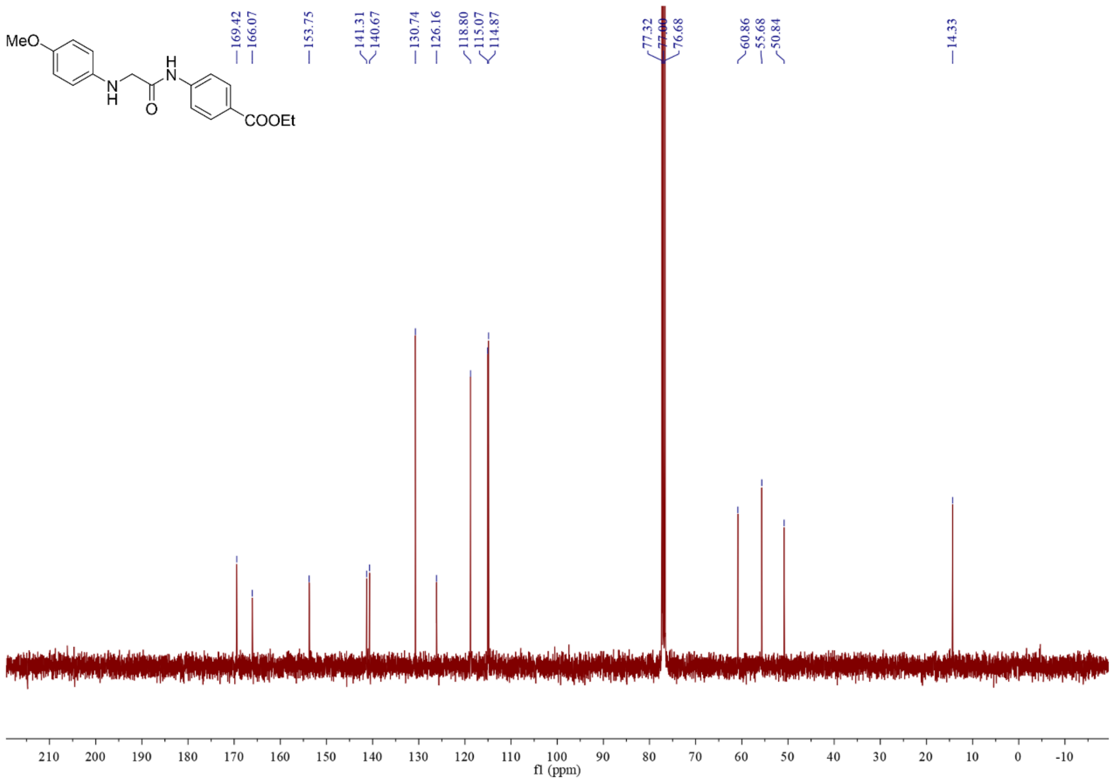


2-((4-methoxyphenyl)amino)-N-phenylacetamide (**4g**)

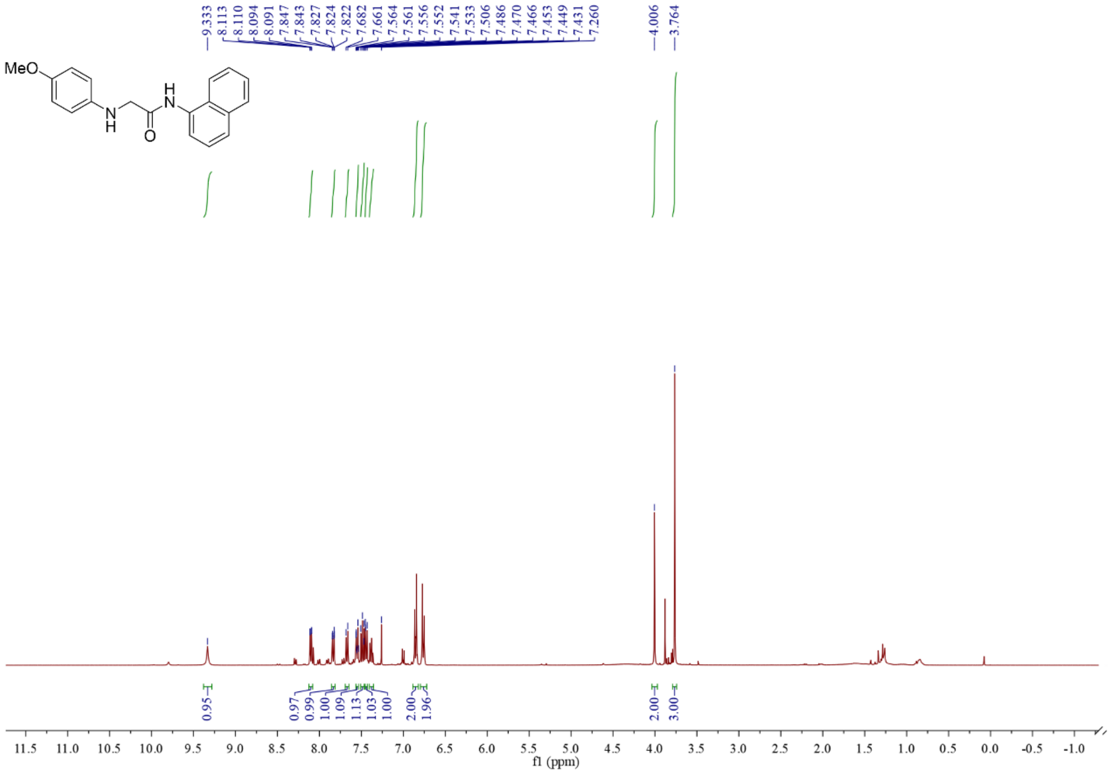


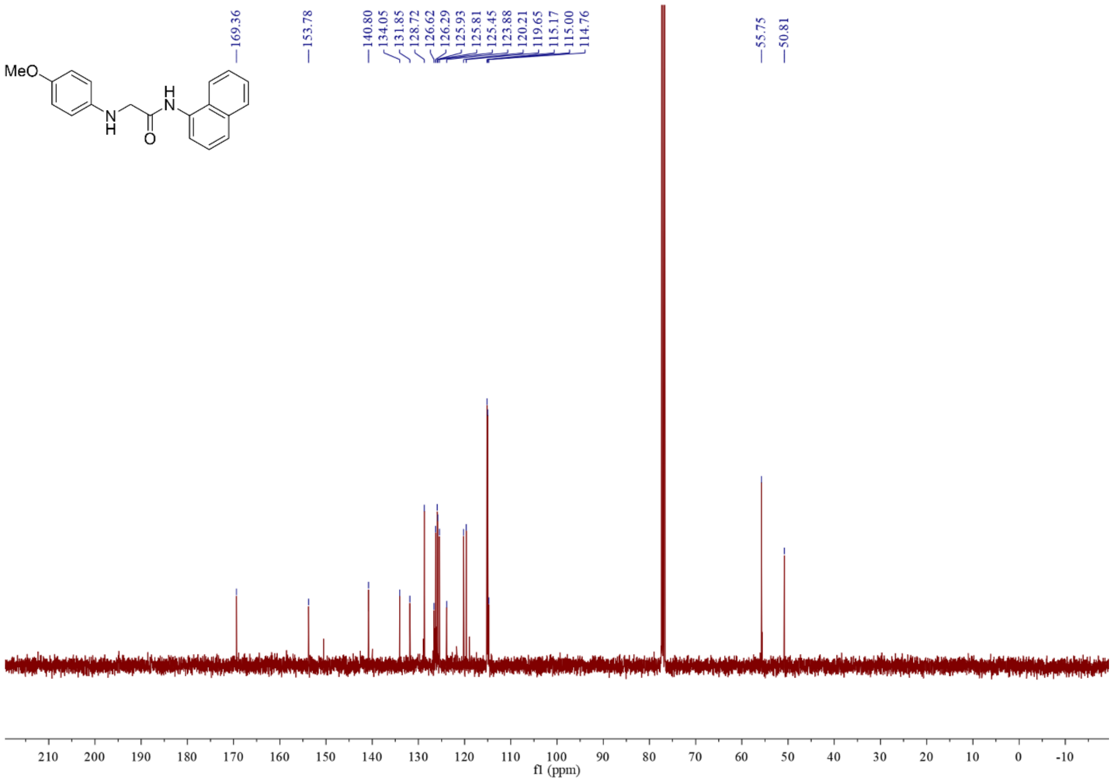
ethyl 4-(2-((4-methoxyphenyl)amino)acetamido)benzoate (**4h**)



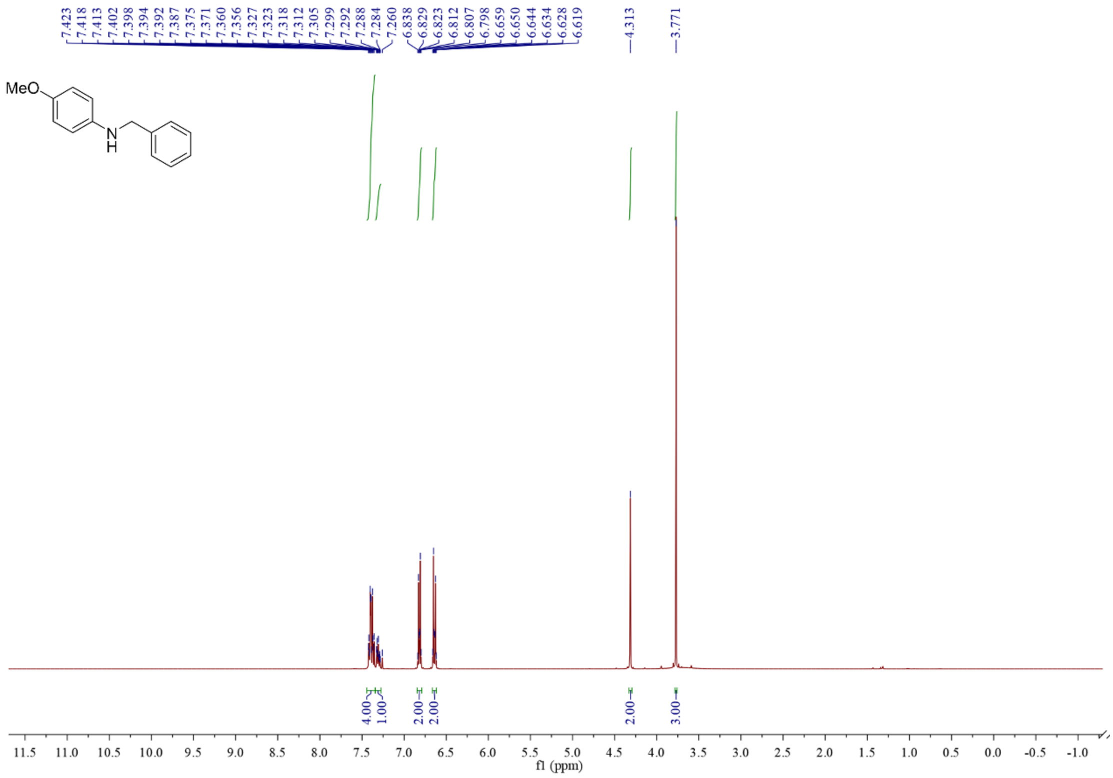


2-((4-methoxyphenyl)amino)-N-(naphthalen-1-yl)acetamide (**4i**)

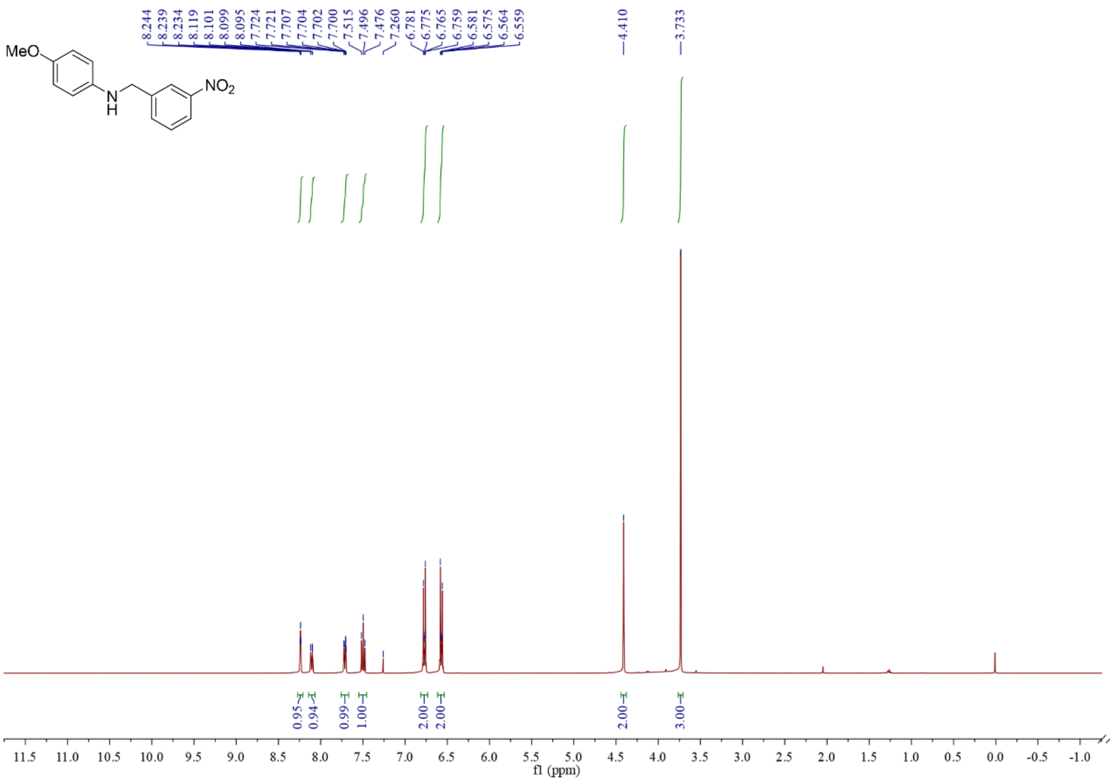




N-benzyl-4-methoxyaniline (**10a**)



4-methoxy-N-(2-nitrobenzyl)aniline (**10b**)



9. References

[1] N. Sharma, H. Sharma, M. Kumar, M. Grishina, U. Pandit, Poonam and B. Rathi, *Org. Biomol. Chem.*, 2022, 20, 6673–6679.

[2] C. Huo, Y. Yuan, M. Wu, X. Jia, X. Wang, F. Chen, J. Tang, *Angew. Chem. Int. Ed*., **2014**, *53*, 1–5.

[3] a) R. Schmidt, C. Burmeister, M. Baláž, A. Kwade, A. Stolle, *Org. Process Res. Dev*., **2015**, *19*, 427–436. b) J. Andersen, J. Mack, *Chem. Sci*., **2017**, *8*, 5447–5453.

[4] a) G. Jadhav, I. Kaur, M. Maryati, B. Airhihen, P. Fischer and G. Winkler, Bioorg. *Med. Chem. Lett.*, **2015**, *25*, 4219–4224; b) I. Stoikov, A. Yantemirova, R. Nosov, I. Rizvanov, A. Julmetov, V. Klochkov, I. Antipin, A. Konovalova and I. Zharov, *Org. Biomol. Chem*., **2011**, *9*, 3225–3234; c) R. Rohlmann, T. Stopka, H. Richter and O. Mancheño, *J. Org. Chem*., **2013**, *78*, 6050–6064.

[5] R. Sheldon, *Green Chem*., **2007**, *9*, 1273-1283.

[6] J. Andraos and M. Sayed, *J. Chem. Educ*., **2007**, *84*, 1004–1010.

[7] X. Jia, Y. Wang, F. Peng, C. Huo, L. Yu, J. Liu and X. Wang, *Adv. Synth. Catal*., **2014**, *356*, 1210–1216.

[8] Z. Zhu, Z. Xie and Z. Le, *J. Org. Chem.*, **2016**, 81, 9449–9454.

[9] X. Zhu, Z. Zhu, D. Guo, S. Liu, J. Ji, J. Tang, E. Yuan, Z. Xie and Z. Le, *Tetrahedron*, **2020**, *76*, 131353.

[10] (a) F. Schneider, T. Szuppa, A. Stolle, B. Ondruschka and H. Hopf, *Green Chem*., **2009**, *11*, 1894–1899; (b) Q. Xu, X. Sheng, N. Li, J. Zhang, H. Shi, M. Niu, Q. Ping and Ning Li, *ACS Sustainable Chem. Eng.*, **2021**, *9*, 8232–8237.

[11] (a) T. Reddy, G. Reddy, L. Reddy,C. Meda, K. Parsa, K. Kumar,Y. Lingappa and M. Pal, *Eur. J. Med. Chem*., **2013**, *62*, 395−404; (b) G. Reddy, V. Reddy and T. Reddy, *Der Pharma Chem.*, **2016**, *8*, 289−300.

[12] D. Ramana, L. Chowhan and M. Chandrasekharam, *ChemistrySelect*, **2017**, *2*, 2241–2244.

[13] X. Chen, X. Huang, Y. Chen, F. He and X. Li, *Lett. Org. Chem.*, **2009**, *6*, 213–218.

[14] Y. Liu, J. Liu, X. Wang, T. Cheng and R. Li, *Tetrahedron*, **2013**, *69*, 5242–5247.

[15] Z. Zhu, Z. Le and Z. Xie, *Synlett*, **2016**, *28*, 485–488.

[16] G. Zhang, Y. Zhang and R. Wang, *Angew. Chem. Int. Ed*., **2011**, *50*, 10429–10432.

[17] S. Kobayashi, M. Salter, Y. Yamazaki and Y. Yamashita, *Chem. Asian J*., **2010**, *5*, 493–495.

[18] L. Xiao, Z. Zhu, D. Guo, Z. Xie, Y. Lu and Z. Le, *Synlett*, **2018**, *29*, 1659–1663.

[19] S. Li, X. Yang, Y. Wang, H. Zhou, B. Zhang, G. Huang, Y. Zhang and Y. Li, *Adv. Synth. Catal*., **2018**, *360*, 4452–4456.

[20] Y. Wei, J. Wang, Y. Wang, X. Yao, C. Yang and C. Huo, *Org. Biomol. Chem.*, **2018**, *16*, 4985–4989.

[21] C. Huo, Y. Yuan, M. Wu, X. Jia, X. Wang, F. Chen and J. Tang, *Angew. Chem. Int. Ed*., **2014**, *53*, 13544–13547.

[22] Y. Hamashima, N. Sasamoto, D. Hotta, H. Somei, N. Umebayashi, and Mikiko Sodeok, *Angew. Chem. Int. Ed*., **2005**, *44*, 1525–1529.

[23] I. Goba, B. Turovska, S. Belyakov and E. Liepinsh, *J. Mol. Struct*., **2014**, *1074*, 549–558.

[24] A. Manvar, R. Pissurlenkar, V. Virsodia, K. Upadhyay, D. Manvar, A. Mishra, H. Acharya, A. Parecha, C. Dholakia, A. Shah and E. Coutinho, *Mol. Divers*., **2010**, *14*, 285–305.

[25] W. Huang and W. Sha, *J. Chem. Res*., **2013**, *37*, 460−463.

[26] T. Inokuma, T. Jichu, K. Nishida, A. Shigenaga and A. Otaka, *Chem. Pharm. Bull*., **2017**, *65*, 573−581.

[27] J. Zhang, J. Jiang, Y. Li, Y. Zhao and X. Wan, *Org. Lett*., **2013**, *15*, 3222–3225.

[28] Y. Song, H. Zhang, J. Guo, Y. Shao, Y. Ding, L. Zhu and X. Yao, *Eur. J. Org. Chem*., **2021**, 5914–5921.

[29] M. Zhang, S. Imm, S. Bahn, H. Neumann and M. Beller, *Angew. Chem. Int. Ed*., **2011**, *50*, 11197–11201.

[30] D. Bagal, R. Watile, M. Khedkar, K. Dhake and B. Bhanage, *Catal. Sci. Technol*., **2012**, *2*, 354–358.

[31] U. Sharma, N. Kumar, P. Verma, V. Kumara and B. Singh, *Green Chem*., **2012**, *14*, 2289–2293.