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Graphical Abstract

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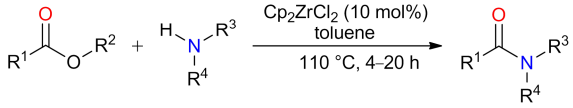

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Zirconium-catalyzed direct amide bond formation between carboxylic esters and amines

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ABSTRACT

Development of catalytic amide bond formation reactions from readily available starting materials remains a challenging task for modern organic chemistry. Herein, we report that unactivated carboxylic esters and amines react in the presence of 10 mol% of zirconocene dichloride (Cp_2ZrCl_2) in toluene at 110 °C to afford amides in very good to excellent conversions. The Zr-catalyzed reaction is amenable for the amidation of aliphatic and aromatic carboxylic esters with primary and secondary amines. The reaction proceeds with almost complete retention of configuration for chiral esters and chiral amines.

1. Introduction

The amide bond is one of the central bonds in nature. It provides a covalent linkage between adjacent amino acids for the formation of diverse classes of biologically functional proteins. Amide bonds are also present in other naturally occuring molecules, including nucleobases of DNA, and cofactors, such as coenzyme A, NADH, tetrahydrofolic acid, flavin mononucleotide, and glutathione.[1]

A recent study by the consortium of leading pharma companies has ranked the development of novel catalytic amide bond formation reactions as number one among the contemporary synthetic challenges for the medicinal chemistry research.[2] Current synthetic methods for the formation of amide bonds are limited to the use of stoichiometric amounts of activating agents, which makes the existing methods nonoptimal from the perspective of atom economy and green chemistry.[3] Due to its relevance in chemical sciences, development of catalytic amide bond formation has become one of the emerging areas of modern organic chemistry.[4] Several catalytic methods for the formation of amide bonds using readily accessible carboxylic acids and amines have been reported.[5] In addition, catalytic transamidation reactions have also been developed in the past decade.[6]

In comparison with carboxylic acids and amides, there has been limited success in developing catalytic variations of direct amidation of carboxylic esters. The common occurrence of carboxylic esters as intermediates in the multistep syntheses of organic molecules raises the necessity of developed catalytic methods for their conversion into other important functionalities such as the amides. Despite the fact that the catalytic conversion of carboxylic acids into amides has an advantage in atom economy (releases only one water molecule), acids have a potential to undergo decarboxylation at elevated temperature, are difficult to purify by chromatography, and undergo deprotonation reactions with various reagents. On the other hand, due to enhanced thermodynamic stability of amides, catalytic transamidation of primary carboxamides is typically carried out at harsh experimental conditions (110–140 °C). In this context, using carboxylic esters as starting material may circumvent some of these drawbacks of related carboxylic acids and amides. Recent studies have demonstrated that carboxylic esters react with stoichiometric amounts of aminoalcohols in the presence of various organocatalysts *via* a mechanism in which the nucleophilic attack of alcohol gives the ester intermediate which subsequently undergoes the O-N acyl transfer reaction to afford the final amide bond.[7] A metal-catalyzed direct amidation of carboxylic esters has been achieved in the presence of Ru-pincer complexes,[8] lanthanum(III) triflate,[9] zirconium(IV) alkoxide in the presence of 1-hydroxy-7-azabenzotriazole additive,[10] and iridium(III) complexes under solvent-free conditions.[11] Amides can also be prepared from carboxylic esters and amines in the presence of stoichiometric amounts of $CaCl_2$ or $Mg(OCH_3)_2$.[12] Recently, an elegant conversion of carboxylic esters into the corresponding amides in the presence of catalytic amounts of simple sodium methoxide in toluene has also been reported.[13]

Similarly, a two-fold excess of potassium *tert*-butoxide mediates a direct amidation of carboxylic esters under mild reaction conditions.[14]

We have envisaged that the widely used carboxylic esters could undergo direct amide bond formation with amines in the presence of transition metal ions as catalysts. We hypothesized that, if successful, the proposed catalytic reaction would be based on the activation of esters by the complexation of their C=O oxygen by the transition metal that acts as a Lewis acid and is not directly consumed in the reaction. Herein, we report that Cp_2ZrCl_2 catalyzes direct amide bond formation between structurally diverse carboxylic esters and amines in very good to excellent yields.

2. Results and Discussion

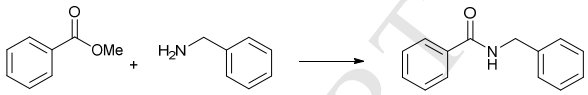
Initially, we have screened a series of common transition metals and simple organocatalysts as potential catalysts for the reaction between methyl benzoate (1.0 equiv.) and benzylamine (1.3 equiv.) in anhydrous toluene at 110 °C for 20 hours (Table 1). Tested catalysts in the series also included those that have been previously proven to catalyze direct amide bond formation between amines and carboxylic acids or amides.[5-6] Pleasingly, we have found that direct amide bond formation proceeds in 85% conversion in the presence of 10 mol% of Cp_2ZrCl_2 (Table 1, entry 1). Other reagents from group IV, including Cp_2TiCl_2, and $TiCl_4$, were found to possess poor catalytic properties for the conversion of methyl benzoate into *N*-benzylbenzamide (Table 1, entries 2–3). Cp_2HfCl_2 was found to be almost as effective (78% conversion) as Cp_2ZrCl_2, but its increased cost relative to the zirconium-based catalyst makes it less attractive for further use as a catalyst for direct amidation of esters (Table 1, entry 4).

The first row transition metal salts were observed to catalyze the amide bond formation in poor conversions (2–57%) (Table 1, entries 5–12). $CoCl_2$ and MnI_2 were the only two transition metal salts evaluated that gave reasonable amounts of the amide product, whereas most of copper-, zinc-, nickel-, and iron-based salts afforded <30% of *N*-benzylbenzamide. $AlCl_3$ and $InBr_3$, both possessing Lewis acid properties, were found to have little catalytic activity for the formation of the amide bond (Table 2, entries 13–14).

We next evaluated potential small molecule organocatalysts that have the ability to activate other carbonyl-containing compounds towards the nucleophilic attack. In the presence of 10 mol% of hydroxylamine hydrochloride, L-proline, urea, thiourea, and imidazole, respectively, less than 25% of amide was formed for our standard reaction, demonstrating that these compounds do not exhibit catalytic properties for the conversion of the ester into the amide (Table 1, entries 15–19). The model reaction was only poorly catalyzed by HCl yielding 30% amide; this result implies that high catalytic activity of Cp_2ZrCl_2 does not derive from its potential decomposition into HCl (Table 1, entry 20). The control reaction in the absence of any catalyst showed that methyl benzoate and benzylamine produced only very small amounts (9%) of corresponding *N*-benzylbenzamide under standard conditions (Table 1, entry 21).

In order to gain some deeper insight into why Cp_2ZrCl_2 exhibits superior catalytic activity for amidation of methyl benzoate relative to other Lewis acids, we evaluated its simple analogues as catalysts for the model reaction (Fig. 1). Substitutions on Cp_2ZrCl_2 were introduced with the aim of probing the chemical character of ligands that chelate the Zr(IV) cation. Decreasing the number of Cp ligands had a substantial effect on the catalytic properties of the catalyst; in the presence of 10 mol% of $CpZrCl_3$ and $ZrCl_4$, 71% and 24% of *N*-benzylbenzamide was formed. The presence of two sterically larger and more electron-rich pentamethylcyclopentadienyl substitutents (as in Cp^*ZrCl_2) resulted in significantly lower conversion (44%), highlighting the importance of the size and electronics of the Cp-like substitutent. Similarly, replacement of two Cp ligands by bulkier indenyl counterparts led to 60% conversion, again demonstrating that the size of Cp-type ligand affects the catalytic properties for direct amidation. Interestingly, catalytic amidation of methyl benzoate in the presence of 10 mol% of $Cp_2Zr(OTf)_2$ only afforded *N*-benzylbenzoate in 55% conversion.

Table 1. Screening of catalysts for amide bond formation between carboxylic esters and amines[a]



Entry	Catalyst	Conversion (%)[b]
1	Cp_2ZrCl_2	85
2	Cp_2TiCl_2	45
3	$TiCl_4$	34
4	Cp_2HfCl_2	78
5	$Cu(OTf)_2$	33
6	CuCl	4
7	$ZnCl_2$	20
8	$FeCl_3$	11
9	$Fe(OTf)_2$	31
10	MnI_2	57
11	$CoCl_2$	56
12	$NiCl_2$	2
13	$AlCl_3$	7
14	$InBr_3$	42
15	$HONH_2 \cdot HCl$	19
16	L-proline	21
17	Urea	9
18	Thiourea	23
19	Imidazole	16
20	HCl	30
21	-	9

[a] Methyl benzoate (5 mmol), benzylamine (6.5 mmol), catalyst (10 mol%), anhydrous toluene (1.2 mL), 110 °C, 20 h. [b] Conversion determined by GC.

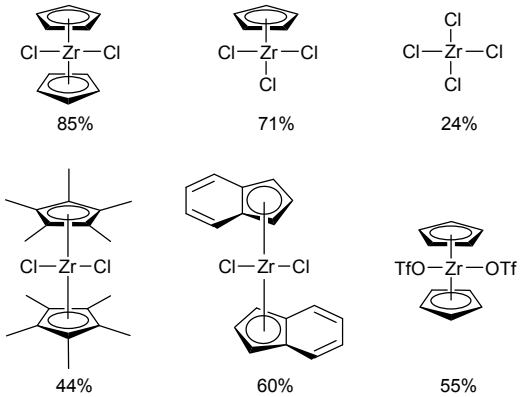
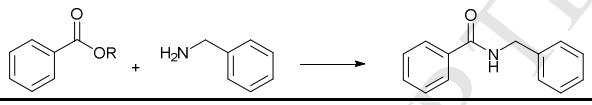


Fig. 1. Cp_2ZrCl_2 and its analogues as catalysts for direct amidation of methyl benzoate with benzylamine.

Examinations of the effect of the solvent, temperature, catalyst loading, molarity of the solution, and time for the reaction between methyl benzoate and benzylamine in the presence of Cp_2ZrCl_2 provided us with the most optimal reaction conditions for the catalytic amide bond formation (see Supporting Information). Overall, these results demonstrate that the conversion of methyl benzoate into *N*-benzylbenzamide occurs efficiently when heated at 110 °C for 20 hours in toluene (2 M) in the presence of 10 mol% Cp_2ZrCl_2. The reaction between *N*-benzylbenzamide and 1.3 equiv. of methanol in the presence of 10 mol% Cp_2ZrCl_2 under standard conditions did not afford any observable amounts of methyl benzoate, indicating that the our catalytic amide bond formation is not reversible.

The effect of the side chain of benzoate esters on the Cp_2ZrCl_2-catalyzed direct amide bond formation with benzylamine under standard reaction conditions was then investigated (Table 2). Reactions with longer linear alkylated benzoates proceeded with only 37–58% conversions (30–52% yields). *Iso*-propyl benzoate and *sec*-butyl benzoate reacted with benzylamine under catalytic conditions to afford the corresponding amides in 22% and 26% conversions, respectively. Notably, sterically hindered *tert*-butyl benzoate only reacted poorly under standard catalytic conditions affording 9% of *N*-benzylbenzamide. Reactions with benzyl benzoate and allyl benzoate proceeded efficiently with 65–70% conversions (58–59% isolated yields). Direct amidations of vinyl benzoate and phenyl benzoate were observed to give quantitative conversions, but these have also been found with the control reactions in the absence of Cp_2ZrCl_2 catalyst (Table 2, entries 10–11). All background reactions using alkylated benzoate esters in the absence of catalyst afforded only traces (<9%) of *N*-benzylbenzamide product (Table 2, entries 1–9). These results indicate that the Zr-promoted amide bond formation takes place with several aromatic esters, but most efficiently with sterically accessible esters.

Table 2. The effect of the side-chain of the ester on zirconium-catalyzed[a] and uncatalyzed[b] amidation of carboxylic esters and amines



Entry	R	Catalytic Conversion (%)	Uncatalytic Conversion (%)
1	Me	85[c] (78)[d]	9
2	Et	58 (52)	2
3	Pr	40 (32)	3
4	*iso*-Pr	22 (15)	6
5	Bu	37 (30)	1
6	*sec*-Bu	26 (23)	2
7	*tert*-Bu	9 (4)	1
8	Bn	70 (59)	4
9	Allyl	65 (58)	7
10	Vinyl	100	96
11	Ph	100	100

[a] Alkyl benzoate (5 mmol), benzylamine (6.5 mmol), Cp_2ZrCl_2 (10 mol%), anhydrous toluene (1.2 mL), 110 °C, 20 h. [b] Conditions as in catalysis, but in the absence of Cp_2ZrCl_2. [c] Conversion determined by GC. [d] Isolated yield.

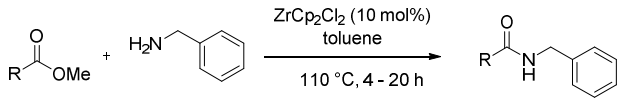
Having shown that Cp_2ZrCl_2 catalyzes the amide bond formation between methyl benzoate and benzylamine, we then investigated the scope of the reaction by examining various esters and amines under standard reactions conditions (Tables 3 and 4). Methyl benzoates bearing electron-withdrawing substituents at the *para* position of the aromatic ring reacted with benzylamine to afford corresponding amides in 70–91% conversions (Table 3). In contrast, the electron-donating *para*-OMe analogue yielded only 52% of amide, demonstrating that the perturbation of the electrophilic character of the C=O group of the ester has a substantial effect on the overall progress of the catalytic reaction. In this regard, it is not surprising that the same trend has been observed for the background reactions; *para*-NO_2 gave the highest conversion (26%), whereas *para*-OMe the lowest conversion (1%) (see Supporting Information).

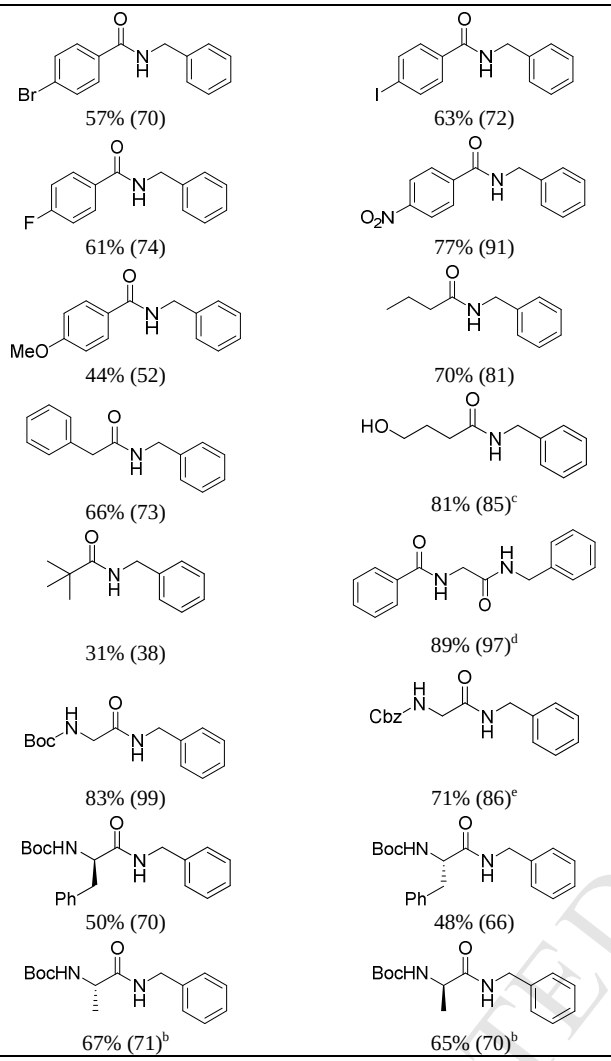
The more-favorable electronics and sterics of aliphatic esters caused a significant decrease in the reaction time for direct amidation of aliphatic esters when compared to amidation of aromatic esters. The reactions between methyl butyrate and methyl phenylacetate with benzylamine proceeded at 110 °C for 4 hours to give 81% and 73% conversions, respectively. Cyclic γ-butyrolactone underwent uncatalyzed ring opening in the presence of benzylamine to yield the corresponding amide quantitatively under standard reaction conditions (the reaction also proceeded in excellent yield (98%) at 50 °C for 20 hours). The background reaction, however, only led to 21% amide when carried out at 50 °C for 1 hour, whereas the Cp_2ZrCl_2-catalyzed reaction gave 85% of the amide under the same conditions. In addition, amidation of sterically hindered *tert*-$BuCOOCH_3$ only afforded 38% of the corresponding amide; this result is in agreement with low transamidation conversion of *tert*-$BuCONH_2$ with benzylamine in the presence of 10 mol% of Cp_2ZrCl_2.[6d]

Methyl and ethyl esters of protected amino acids underwent Cp_2ZrCl_2-catalyzed amidations with benzylamine in only 4 hours at 110 °C. We were pleased that acid-sensitive *N*-protecting groups of amino acids remained unaffected by the employed reaction conditions. Ethyl hippurate gave excellent conversions (97%) for the catalytic reaction, and only 4% amide for the uncatalyzed reaction. Similarly, Boc-protected methyl glycinate was also converted into the corresponding amide in 99% conversion, whereas the background reaction in the absence of the catalyst only afforded the amide in 15% conversion. Cbz-protected methyl glycinate underwent Cp_2ZrCl_2-catalyzed amidation in 1 hour at 110 °C affording 86% of the corresponding amide. The reaction under our conditions (and also at 50 °C) was not applicable for amidation of base-sensitive esters, such as Fmoc-protected methyl glycinate, due to deprotection of the Fmoc group in the presence of equimolar amounts of amine.

Notably, reactions of enantiopure Boc-protected methyl esters of alanines proceeded with virtually complete (>99%) retention of the chiral configuration under our catalytic conditions (see Supporting Information). Similarly, sterically hindered Boc-L-Phe-OMe and Boc-D-Phe-OMe underwent Cp_2ZrCl_2-catalyzed reaction with benzylamine with almost complete retention (>98.5%) of configuration.

Table 3. Amidation of various esters with benzylamine[a]



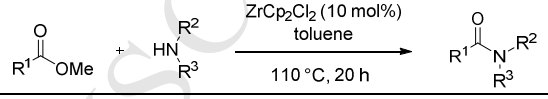


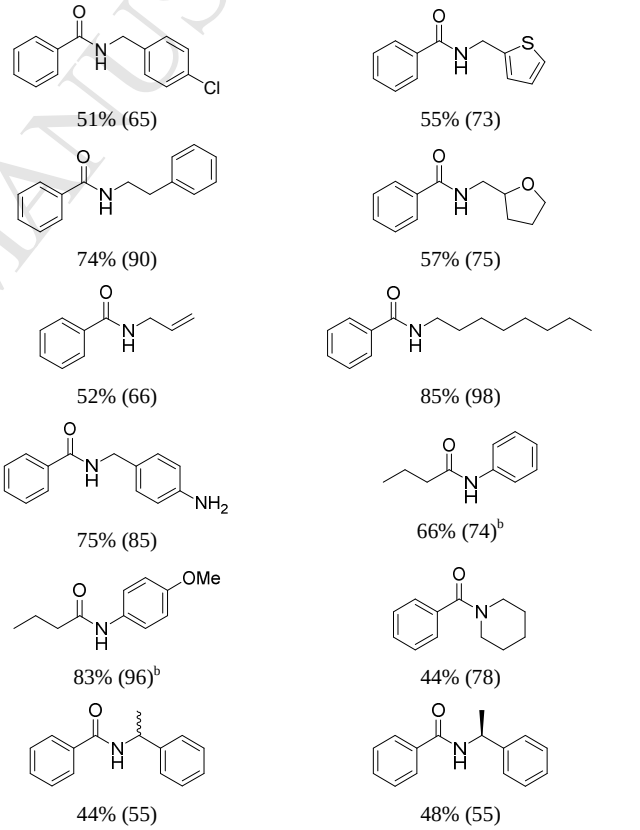
[a] Reaction conditions: ester (5.0 mmol), benzyl amine (6.5 mmol), Cp_2ZrCl_2 (10 mol%). 4 h for aliphatic esters, 20 h for aromatic esters. Isolated yield (Conversion). [b] Reaction time 8 h. [c] 1 h at 50 °C. [d] Ethyl ester of hippuric acid was used. [e] 1 h at 110 °C.

A diverse set of amines was then evaluated for the catalytic and uncatalytic direct amidation of methyl benzoate under standard conditions (Table 4). Primary amines, including *para*-chlorobenzylamine, 2-(aminomethyl)thiophene, and phenethylamine all reacted very well affording corresponding amides in 65%, 73%, and 90% conversions, respectively. Tetrahydrofurfurylamine, allylamine, and octylamine also efficiently reacted with methyl benzoate to produce amides in 75%, 66%, and 98% conversions under catalytic conditions. Notably, 4-aminobenzylamine that contains two different types of primary amines (i.e. a less nucleophilic aromatic NH_2 and a more nucleophilic aliphatic NH_2) exclusively reacted through its aliphatic amine to afford the amide in excellent 85% conversion. In this regard, it is not surprising that aniline did not react with methyl benzoate at 110 °C for 20 hours (we observed only 1% conversion). At harsher conditions at 140 °C, however, aniline reacted with methyl benzoate in the presence of 10 mol% of Cp_2ZrCl_2 to yield 74% of amide, whereas background reaction only produced traces (1%) of the amide. The amidation of more nucleophilic 4-methoxyaniline proceeded to 96% conversion at 140 °C under catalytic conditions, whereas background reaction only afforded 3% of the amide. The utility of our catalytic method was further demonstrated by the amidation of methyl benzoate with a representative secondary amine piperidine that also proceeded well with 78% conversion. Background reactions for all amines afforded <20% amides, indicating that catalytic amounts of Cp_2ZrCl_2 are required for the efficient direct amidation reaction (see Supporting Information).

Zirconium-catalyzed reaction between methyl benzoate and racemic and enantiomerically pure (*S*)-1-phenylethylamine yielded the corresponding amides in 55% conversion (Table 4). We attribute the decreased conversion to increased sterics of this amine relative to primary benzylamine. It is noteworthy that Cp_2ZrCl_2-catalyzed amidation reaction occurs with the complete retention of configuration, without noticeable recamization (see Supporting Information).

Table 4. Expanded substrate scope for amidation reaction[a]





[a] Reaction conditions: ester (5.0 mmol), amine (6.5 mmol), Cp_2ZrCl_2 (10 mol%). Isolated yield (Conversion). [b] Reaction was performed in *o*-xylene at 140 °C for 20 h.

3. Conclusions

In conclusion, we have developed the Cp_2ZrCl_2-catalyzed direct amidation of structurally diverse carboxylic esters. This redox-free condensation reaction is applicable for amidation of unactivated aliphatic and aromatic esters with primary and secondary amines, and proceeds with almost complete retention of configuration. Development of related catalytic amide bond formations is currently ongoing in our laboratory.

4. Experimental Section

General procedure:
Carboxylic ester (5.0 mmol), amine (6.5 mmol), and Cp_2ZrCl_2 (146.7 mg, 0.5 mmol) were suspended in 1.2 mL of anhydrous toluene. The reaction was stirred at 110 °C for 4–20 hours. The solvent was then removed under reduced pressure. The crude product was purified on a Biotage Isolera™ One using a Biotage SNAP Ultra cartridge (12 g or 25 g, 10–60% EtOAc in *n*-heptane) to isolate the desired amide.

N-Benzylbenzamide
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82 (d, *J* = 9 Hz, 2H), 7.52–7.29 (m, 8H), 6.60 (bs, 1H), 4.65 (d, *J* = 6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.7, 138.6, 134.7, 131.9, 129.1, 128.9, 128.3, 127.9, 127.3, 44.5; MS (ESI): *m/z* 212.1 (M + H$^+$); HRMS (ESI): (M + H$^+$), found 212.1091. $[C_{14}H_{14}NO]^+$ requires 212.1075.

N-Benzyl-4-nitrobenzamide
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.26 (d, *J* = 9 Hz, 2H), 7.96 (d, *J* = 9 Hz, 2H), 6.75 (bs, 1H), 7.41–7.30 (m, 5H), 4.65 (d, *J* = 3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.7, 150.0, 140.3, 137.8, 129.3, 128.6, 128.3, 124.2, 44.8; MS (ESI): *m/z* 257.1 (M + H$^+$); MS (ESI): *m/z* 257.0941 (M + H$^+$); HRMS (ESI): (M + H$^+$), found 257.0941. $[C_{14}H_{14}NO]^+$ requires 212.0926.

N-(Thiophen-2-ylmethyl)benzamide
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.80 (d, *J* = 6 Hz, 2H), 7.54–7.40 (m, 3H), 7.25 (d, *J* = 5.1 Hz, 1H), 7.05 (d, *J* = 3.6 Hz, 1H), 6.98 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.67 (bs, 1H), 4.81 (d, *J* = 3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 167.5, 141.2, 134.5, 132.0, 128.9, 127.4, 127.3, 126.6, 125.7, 39.2; MS (ESI): *m/z* 217.9 (M + H$^+$); HRMS (ESI): (M + Na$^+$), found 240.0481. $[C_{12}H_{11}NOSNa]^+$ requires 240.0459.

N-Benzyl-4-fluorobenzamide
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.81 (dd, *J* = 6 Hz, *J* = 9 Hz, 2H), 7.38–7.29 (m, 5H), 7.11 (t, *J* = 9 Hz, 2H), 6.50 (bs, 1H), 4.64 (d, *J* = 6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.7, 163.4, 138.4, 129.7, 129.2, 128.3, 128.1, 116.1, 115.8, 44.6; MS (ESI): *m/z* 230.0 (M + H$^+$); HRMS (ESI): (M + H$^+$), found 230.1000. $[C_{14}H_{13}NOF]^+$ requires 230.0981.

N-Benzyl-4-bromobenzamide
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68 (d, *J* = 9 Hz, 2H), 7.57 (d, *J* = 9 Hz, 2H), 7.41–7.29 (m, 5H), 6.54 (bs, 1H), 4.63 (d, *J* = 6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.8, 138.3, 133.6, 132.2, 139.2, 129.0, 128.3, 128.1, 126.6, 44.6; MS (ESI): *m/z* 290.0 (M + H$^+$); HRMS (ESI): (M + H$^+$), found 290.0203. $[C_{14}H_{13}NOBr]^+$ requires 290.0181.

N-Benzyl-4-iodobenzamide
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.79 (d, *J* = 9 Hz, 2H), 7.53 (d, *J* = 9 Hz, 2H), 7.41–7.29 (m, 5H), 6.51 (bs, 1H), 4.63 (d, *J* = 6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.9, 138.4, 138.2, 134.1, 129.2, 129.0, 128.3, 128.1, 98.9, 44.6; MS (ESI): *m/z* 338.1 (M + H$^+$); HRMS (ESI): (M + H$^+$), found 338.0057. $[C_{14}H_{13}NOI]^+$ requires 338.0042.

N-(4-Chlorobenzyl)benzamide
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.80 (d, *J* = 6 Hz, 2H), 7.55–7.50 (m, 1 H), 7.46–7.40 (m, 2H), 7.34–7.28 (m, 4H), 6.67 (bs, 1H), δ 4.60 (d, *J* = 6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.8, 137.2, 134.5, 133.7, 132.0, 129.5, 129.2, 130.0, 127.3, 43.7; MS (ESI): *m/z* 246.1 (M + H; HRMS (ESI): (M + H$^+$), found 246.0711. $[C_{14}H_{13}NOCl]^+$ requires 246.0686.

N-Benzyl-4-methoxybenzamide
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.79 (d, *J* = 9 Hz, 2H), 7.38–7.29 (m, 5H), 6.92 (d, *J* = 9 Hz, 2H), 6.50 (bs, 1H), 4.63 (d, *J* = 3 Hz, 2H), δ 3.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.2, 162.6, 138.8, 129.2, 129.1, 128.2, 127.9, 127.0, 114.1, 55.8, 44.4; MS (ESI): *m/z* 242.1 (M + H$^+$); HRMS (ESI): (M + H$^+$), found 242.1190. $[C_{15}H_{16}NO_2]^+$ requires 242.1181.

4-Benzoylpiperidine
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39 (s, 5H), 3.68 (bs, 2H), 3.34 (bs, 2H), 1.68 (bs, 4H), 1.52 (bs, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.6, 136.9, 128.7, 127.1, 49.1, 43.5, 26.9, 26.0, 24.9; MS (ESI): *m/z* 190.2 (M + H$^+$); HRMS (ESI): (M + H$^+$), found 190.1231. $[C_{12}H_{16}NO]^+$ requires 190.1232.

N-Allylbenzamide
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82 (dd, *J* = 8.4 Hz, 2.4 Hz, 2H), 7.53–7.36 (m, 3H), 6.50 (bs, 1H), 6.00–5.87 (m, 1H), 5.23 (dd, *J* = 10.2 Hz, 1.5 Hz, 2H), 4.08 (t, *J* = 10.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.8, 134.9, 131.8, 130.3, 128.9, 127.3, 116.9, 42.8; MS (ESI): *m/z* 162.1 (M + H$^+$); HRMS (ESI): (M + H$^+$), found 162.0928. $[C_{10}H_{12}NO]^+$ requires 162.0919.

N-Benzyl-4-hydroxybutanamide
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.21 (m, 4H), 6.51 (s, 1H), 4.37 (d, *J* = 5.7 Hz, 2H), 3.62 (t, *J* = 5.8 Hz, 2H), 3.53 (s, 1H), 2.37–2.30 (m, 2H), 1.89–1.79 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.5, 138.1, 128.6, 127.7, 127.4, 77.4, 77.0, 76.7, 62.0, 43.6, 33.7, 28.1; MS (ESI): *m/z* 194.1 (M + H$^+$); HRMS (ESI): (M + H$^+$), found 194.1178. $[C_{11}H_{16}NO_2]^+$ requires 194.1181.

N-Benzylpivalamide
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47–6.91 (m, 5H), 5.96 (s, 1 H), 4.43 (d, *J* = 5.6 Hz, 2H), 1.23 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 178.3, 138.6, 128.7, 127.6, 127.4, 77.3, 77.0, 76.7, 43.5, 38.7, 27.6; MS (ESI): *m/z* 192.1 (M + H$^+$); HRMS (ESI): (M + H$^+$), found 192.1397. $[C_{12}H_{18}NO]^+$ requires 192.1388.

Benzyl (2-(benzylamino)-2-oxoethyl)carbamate
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44–7.08 (m, 10H), 6.35 (s, 1H), 5.43 (s, 1H), 5.09 (s, 2H), 4.44 (d, *J* = 5.7 Hz, 2H), 3.89 (d, *J* = 5.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.3, 156.1, 137.2, 135.5, 128.3, 127.8, 127.6, 127.3, 127.2, 105.7, 77.0, 76.5, 76.1, 66.8, 44.2, 43.7; MS (ESI): *m/z* 298.9 (M + H$^+$); HRMS (ESI): (M + Na$^+$), found 321.1227. $[C_{17}H_{18}N_2O_3Na]^+$ requires 321.1215.

(R,S)-N-(1-Phenylethyl)benzamide
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.80 (d, *J* = 9 Hz, 2H), 7.53–7.29 (m, 8H), 6.41 (bs, 1H), 5.37 (quin., J = 6 Hz, 1H), 1.63 (d, *J* = 6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.9, 143.5, 135.0, 131.8, 129.1, 128.9, 127.8, 127.3, 126.6, 49.6, 22.1; MS (ESI): *m/z* 226.0 (M + H$^+$); ; HRMS (ESI): (M + H$^+$), found 226.1249. $[C_{15}H_{16}NO]^+$ requires 226.1232; $[\alpha]^{21}_D$ 0.0 (c 0.73, MeOH).

(S)-N-(1-Phenylethyl)benzamide
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.78 (d, *J* = 9 Hz, 2H), 7.53–7.30 (m, 8H), 6.46 (bs, 1H), 5.36 (quin., *J* = 6 Hz, 1H), 1.62 (d, *J* = 6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.9, 143.5, 135.0, 131.8, 129.1, 128.9, 127.8, 127.3, 126.6, 49.6, 22.1; MS (ESI): *m/z* 226.0 (M + H$^+$); HRMS (ESI): (M + H$^+$), found 226.1244. $[C_{15}H_{16}NO]^+$ requires 226.1232. $[\alpha]^{21}_D$ 4.9 (c 1.00, MeOH).

tert-Butyl (2-(benzylamino)-2-oxophenyl)carbamate
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 (bs, 1H), 7.23–7.11 (m, 5H), 5.87 (bs, 1H), 4.26 (d, *J* = 6 Hz, 2H), 3.86 (d, *J* = 6 Hz, 2H), 1.32

(s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.8, 156.5, 138.3, 129.1, 128.0, 127.9, 80.7, 44.9, 43.8, 28.6; MS (ESI): *m/z* 287.0 (M + Na^+); HRMS (ESI): (M + Na^+), found 287.1374. $[C_{14}H_{20}N_2O_3Na]^+$ requires 287.1372.

(S)-tert-Butyl (1-(benzylamino)-1-oxopropan-2-yl)carbamate
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36–7.24 (m, 5H), 6.59 (bs, 1H), 5.03 (bs, 1H), 4.46 (d, *J* = 3 Hz, 2H), 4.20 (bs, 1H), 1.43 (s, 9H), 1.39 (d, *J* = 9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.9, 155.9, 138.4, 129.1, 128.0, 127.8, 50.6, 43.8, 28.7, 18.7; MS (ESI): *m/z* 278.8 (M + H^+); HRMS (ESI): (M + Na^+), found 301.1534. $[C_{15}H_{22}N_2O_3Na]^+$ requires 301.1528; $[\alpha]^{21}_D$ –24.7 (c 0.82, MeOH).

(R)-tert-Butyl (1-(benzylamino)-1-oxopropan-2-yl)carbamate
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36–7.25 (m, 5H), 6.60 (bs, 1H), 5.03 (bs, 1H), 4.46 (d, *J* = 3 Hz, 2H), 4.20 (bs, 1H), 1.43 (s, 9H), 1.38 (d, *J* = 9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.9, 155.9, 138.4, 129.0, 128.0, 127.8, 50.6, 43.8, 28.7, 18.7; MS (ESI): *m/z* 278.9 (M + H^+); HRMS (ESI): (M + Na^+), found 301.1531. $[C_{15}H_{22}N_2O_3Na]^+$ requires 301.1528; $[\alpha]^{21}_D$ 21.8 (c 0.84, MeOH).

(S)-tert-Butyl (1-(benzylamino)-1-oxo-3-phenylpropan-2-yl)carbamate
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32–7.09 (m, 10H), 6.17 (bs, 1H), 5.10 (bs, 1H), 4.41–4.36 (m, 3H), 3.12–3.08 (m, 2H), 1.41 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.4, 155.7, 138.1, 137.4, 129.7, 129.0, 128.0, 127.8, 127.3, 118.5, 80.6, 56.4, 43.8, 40.0, 28.6; MS (ESI): *m/z* 354.9 (M + H^+); HRMS (ESI): (M + Na^+), found 377.1846. $[C_{21}H_{26}N_2O_3Na]^+$ requires 377.1841; $[\alpha]^{21}_D$ –2.3 (c 0.22, MeOH).

(R)-tert-Butyl (1-(benzylamino)-1-oxo-3-phenylpropan-2-yl)carbamate
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29–7.09 (m, 10H), 6.16 (s, 1H), 5.09 (s, 1H), 4.35 (d, *J* = 5.6 Hz, 3H), 3.08 (m, 2H), 1.38 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.0, 168.0, 137.6, 136.6, 129.3, 128.7, 128.6, 127.6, 127.4, 126.9, 77.3, 77.0, 76.7, 68.3, 56.0, 43.4, 38.6, 28.2; MS (ESI): *m/z* 354.9 (M + H^+); HRMS (ESI): (M + Na^+), found 377.1843. $[C_{21}H_{26}N_2O_3Na]^+$ requires 377.1841; $[\alpha]^{21}_D$ 2.3 (c 0.44, MeOH).

N-Benzylbutyramide
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38–7.26 (m, 5H), 5.94 (bs, 1H), 5.44 (d, *J* = 6 Hz, 2H), 2.20 (t, *J* = 9 Hz, 2H), 1.70 (sext., *J* = 9 Hz, 2H), 0.97 (t, *J* = 9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.2, 138.8, 129.0, 128.1, 127.8, 43.9, 39.0, 19.5, 14.1; MS (ESI): *m/z* 178.1 (M + H^+); HRMS (ESI): (M + Na^+), found 200.1055. $[C_{11}H_{15}NONa]^+$ requires 200.1051.

N-((Tetrahydrofuran-2-yl)methyl)benzamide
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.79 (d, *J* = 6 Hz, 2H), 7.53–7.40 (m, 3H), 6.60 (bs, 1H), 4.12–4.04 (m, 1H), (dd, *J* = 9 Hz, 6 Hz, 1H) , 7.38–7.74 (m, 2H), 3.40–3.31 (m, 1H), 2.09–1.88 (m, 3H), 1.68–1.57 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.9, 134.9, 131.8, 128.9, 127.3, 78.2, 68.5, 44.0, 29.0, 26.3; MS (ESI): *m/z* 206.1 (M + H^+); HRMS (ESI): (M + H^+), found 206.1189. $[C_{12}H_{16}NO_2]^+$ requires 206.1181.

N-Benzyl-2-phenylacetamide
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41–7.17 (m, 10H), 5.83 (bs, 1H), 4.41 (d, *J* = 6 Hz, 2H), 3.64 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.2, 138.5, 135.2, 129.8, 129.4, 129.0, 127.8, 127.8, 127.7, 44.2, 43.9; MS (ESI): *m/z* 226.1 (M + H^+); HRMS (ESI): (M + H^+), found 226.1247 $[C_{15}H_{16}NO]^+$ requires 226.1232.

N-(4-Aminobenzyl)benzamide
^{1}H NMR (300 MHz, $(CD_3)_2SO$)): δ 8.84 (t, *J* = 6 Hz, 1H), 7.88 (d, *J* = 6 Hz, 2H), 7.55–7.42 (m, 3H), 6.99 (d, *J* = 9 Hz, 2H), 6.52 (d, *J* = 9 Hz, 2H), 4.94 (s, 2H), 4.31 (d, *J* = 6 Hz, 2H); ^{13}C NMR (75 MHz, $(CD_3)_2SO$): δ 165.9, 147.5, 134.6, 131.0, 128.2, 127.2, 126.6, 113.7, 112.1, 42.3; MS (ESI): *m/z* 226.9 (M + H^+); HRMS (ESI): (M + Na^+), found 249.1014. $[C_{14}H_{14}N_2ONa]^+$ requires 249.1004.

N-(2-Benzylamino)-2-oxoethyl)benzamide
^{1}H NMR (300 MHz, $(CD_3)_2SO$): δ 8.79 (t, *J* = 6 Hz, 1H), 8.44 (t, *J* = 6 Hz, 1H), 7.91 (d, *J* = 9 Hz, 2H), 7.59–7.44 (m, 3H), 7.36–7.20 (m, 5H), 4.31 (d, *J* = 6Hz, 2H), 3.94 (d, *J* = 6 Hz, 2H); ^{13}C NMR (75 MHz, $(CD_3)_2SO$)): δ 169.0, 166.5, 139.4, 134.0, 131.3, 128.2, 127.4, 127.1, 126.7, 42.7, 42.0; MS (ESI): *m/z* 291.1 (M + Na^+); HRMS (ESI): (M + Na^+), found 291.1113. $[C_{16}H_{16}N_2O_2Na]^+$ requires 291.1110.

N-Phenethylbenzamide
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72 (d, *J* = 6 Hz, 2H), 7.52–7.27 (m, 8H), 6.27 (bs, 1H), 3.72 (q, *J* = 12 Hz, 6 Hz, 2H), 2.96 (t, *J* = 6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.8, 139.3, 135.0, 131.7, 129.2, 129.1, 128.9, 127.2, 127.0, 41.5, 36.1; MS (ESI): *m/z* 226.1 (M + H^+); HRMS (ESI): (M + H^+), found 226.1245. $[C_{15}H_{16}NO]^+$ requires 226.1232.

N-Phenylbutyramide
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54 (d, *J* = 6 hz, 2H), 7.46 (bs, 1H), 7.32 (t, *J* = 6 Hz, 2H), 7.11 (t, *J* = 6 Hz, 1H), 2.35 (t, *J* = 6 Hz, 2H), 1.77 (m, 2H), 1.01 (t, *J* = 6 Hz)); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.8, 138.4, 129.3, 124.5, 120.2, 40.0, 19.4, 14.1; MS (ESI): *m/z* 164.1 (M + H^+); HRMS (ESI): (M + H^+), found 164.1075. $[C_{10}H_{14}NO]^+$ requires 164.1075.

N-(p-Methoxy)phenylbutyramide
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (bs, 1H), 7.40 (d, *J* = 6 Hz, 2H), 6.82 (d, *J* = 6 Hz, 2H), 3.77 (s, 3H), 2.30 (t, *J* = 6 Hz, 2H), 1.73 (m, 2H), 0.98 (t, *J* = 6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.3, 156.3, 131.1, 121.8, 114.0, 55.4, 39.4, 19.1, 13.7; MS (ESI): *m/z* 194.1 (M + H^+); HRMS (ESI): (M + H^+), found 194.1184. $[C_{11}H_{16}NO_2]^+$ requires 194.1181.

N-Octylbenzamide
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 – 7.75 (m, 2H), 7.50 – 7.39 (m, 3H), 6.23 (bs, 1H), 3.47–3.42 (m, 2H),1.64–1.57 (m, 2H), 1.41–1.21 (m, 10H), 0.88 (t, *J* = 6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 167.9, 135.2, 131.6, 128.9, 127.2, 40.5, 32.2, 30.0, 29.7, 29.6, 27.4, 23.0, 15.4; MS (ESI): *m/z* 234.3 (M + H^+); HRMS (ESI): (M + H^+), found 234.1868. $[C_{15}H_{24}NO]^+$ requires 234.1858.

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Supporting Information

Zirconium-catalyzed direct amide bond formation between carboxylic esters and amines

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Contents

1. Materials and methods

Solvents were dried by purging over activated alumina columns in a MBraun MB SPS800 and stored under nitrogen. Chemicals were purchased from commercial sources and were used without further purification. Reactions were carried out under an inert atmosphere of dry nitrogen or argon. Standard syringe techniques were applied for the transfer of dry solvents and air- or moisture-sensitive reagents.

NMR spectra were recorded on a Bruker DMX 300 (300 MHz), and a Varian 400 (400 MHz) spectrometer in $CDCl_3$ solutions. ^1H NMR chemical shifts are given in ppm with respect to tetramethylsilane (TMS, δ 0.00 ppm) as internal standard, ^{13}C NMR shift are given in ppm with respect to $CHCl_3$ (δ 77.4 ppm) or $(CD_3)_2SO$ (δ 39.5 ppm). Coupling constants are reported as *J*-values in Hz.

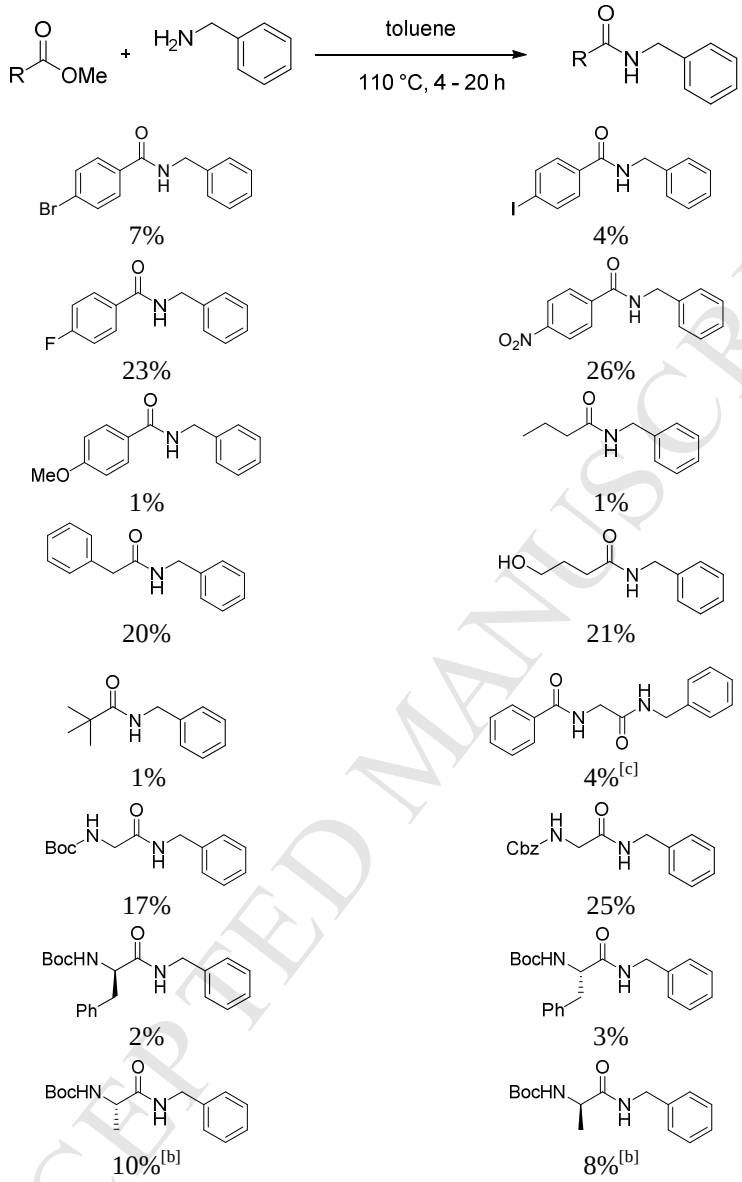
Gas chromatography (GC) was performed on a Shimadzu GC2010+, containing an Agilent DB-1 column (30 m, 0.32 mm ID, 0.25 Am DF) using FID detection. The chiral HPLC measurements were performed on a Shimadzu LC2010C Analytical HPLC system equipped with a 250 x 4.6 ID mm Diacel Chiralpak AD-H column with Heptane/Isopropanol (90:10 v/v). Mass spectra were recorded on a Thermo Finnigan LCQ Advantage Max electrospray-ion trap mass spectrometer.

2. General procedures

Amine (6.5 mmol) and ester (5.0 mmol) were suspended in 1.2 mL of anhydrous toluene. While stirring, zirconocene dichloride (146.7 mg, 0,5 mmol), was added. The reaction was stirred at 110 °C for 4 - 20 hours. The solvent was then removed under reduced pressure. The crude product was purified on a Biotage Isolera™ One using a Biotage SNAP Ultra cartridge (12g or 25g, 10-60% EtOAc in n-heptane) to isolate the desired amide.

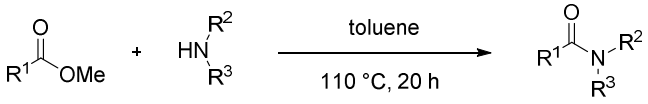
3. Uncatalyzed reaction conversions

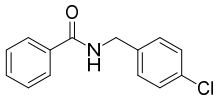
Scheme S1. Uncatalyzed conversions[a]



[a] Reaction conditions: ester (5.0 mmol), benzyl amine (6.5 mmol). 4 h for aliphatic esters, 20 h for aromatic esters. [b] Reaction time 8 h. [c] Ethyl ester of hippuric acid was used.

Scheme S2. Uncatalyzed conversions[a]

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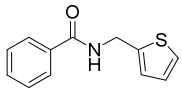
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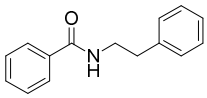
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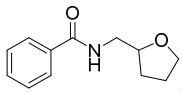
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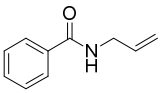
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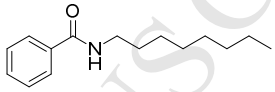
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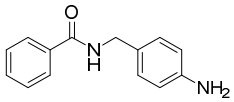
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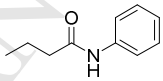
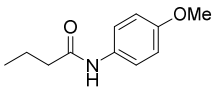
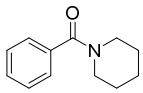

1%[b]


3%[b]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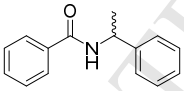
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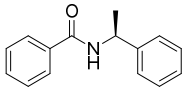

1%

[a] Reaction conditions: ester (5.0 mmol), benzyl amine (6.5 mmol). 4 h for aliphatic esters, 20 h for aromatic esters. [b] Reaction was performed in *o*-xylene at 140 °C for 20 hours.

4. Solvent effect

Table S1. Effect of solvent

Entry	Solvent	Temperature (°C)	Conversion (%)
1	toluene	110	85
2	dioxane	100	63
3	n-heptane	100	78
4	cyclohexane	81	41
5	THF	66	49

5. Molarity effect

Table S2. Effect of molarity

Entry	Molarity (M)	Cat. conversion (%)	Uncat.conversion (%)
1	0.5	25	1
2	1	57	2
3	2	85	9
4	neat	93	31

6. Catalyst load

Table S3. Catalyst load

Entry	Catalyst load (%)	Conversion (%)
1	1	26
2	2	38
3	5	54
4	10	85

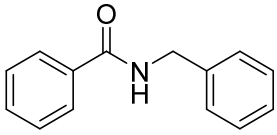
7. Time course

Table S4. Effect of time

Entry	Time (hours)	Conversion (%)
1	0	0
2	0.5	40
3	1	45
4	2	48
5	4	54
6	6	59
7	8	67
8	20	85

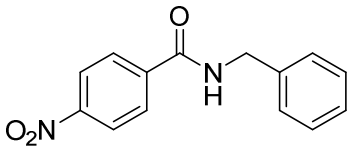
8. Characterization of products

_N_-benzylbenzamide[1]



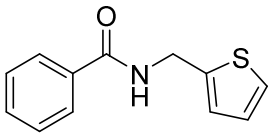
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82 (d, J = 9 Hz, 2H), 7.52–7.29 (m, 8H), 6.60 (bs, 1H), 4.65 (d, J = 6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.7, 138.6, 134.7, 131.9, 129.1, 128.9, 128.3, 127.9, 127.3, 44.5; MS (EI): *m/z* 212.1 ($M + H^+$).

_N_-benzyl-4-nitrobenzamide[2]



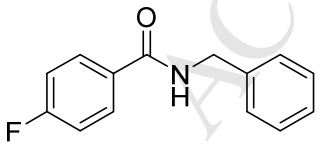
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.26 (d, J = 9 Hz, 2H), 7.96 (d, J = 9 Hz, 2H), 6.75 (bs, 1H), 7.41-7.30 (m, 5H), 4.65 (d, J = 3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.7, 150.0, 140.3, 137.8, 129.3, 128.6, 128.3, 124.2, 44.8; MS (EI): *m/z* 257.1 ($M + H^+$).

_N_-(thiophen-2-ylmethyl)benzamide[3]



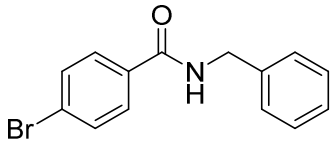
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.80 (d, J = 6 Hz, 2H), 7.54-7.40 (m, 3H), 7.25 (d, J = 5.1 Hz, 1H), 7.05 (d, J = 3.6 Hz, 1H), 6.98 (dd, J = 5.1, 3.6 Hz, 1H), 6.67 (bs, 1H), 4.81 (d, J = 3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 167.5, 141.2, 134.5, 132.0, 128.9, 127.4, 127.3, 126.6, 125.7, 39.2; MS (EI): *m/z* 217.9 ($M + H^+$).

_N_-benzyl-4-fluorobenzamide[4]



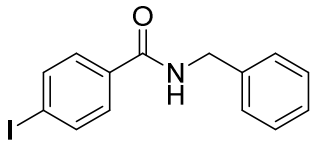
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.81 (dd, J = 6 Hz, J = 9 Hz, 2H), 7.38-7.29 (m, 5H), 7.11 (t, J = 9 Hz, 2H), 6.50 (bs, 1H), 4.64 (d, J = 6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.7, 163.4, 138.4, 129.7, 129.2, 128.3, 128.1, 116.1, 115.8, 44.6; MS (EI): *m/z* 230.0 ($M + H^+$).

***N*-benzyl-4-bromobenzamide**[5]



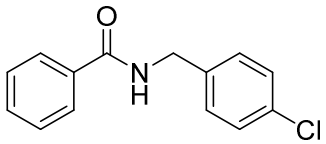
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68 (d, J = 9 Hz, 2H), 7.57 (d, J = 9 Hz, 2H), 7.41-7.29 (m, 5H), 6.54 (bs, 1H), 4.63 (d, J = 6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.8, 138.3, 133.6, 132.2, 139.2, 129.0, 128.3, 128.1, 126.6, 44.6; MS (EI): *m/z* 292.0 ($M + H^+$).

***N*-benzyl-4-iodobenzamide**[6]



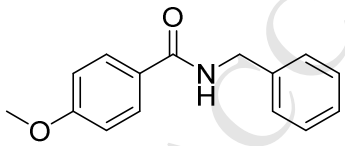
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.79 (d, J = 9 Hz, 2H), 7.53 (d, J = 9 Hz, 2H), 7.41-7.29 (m, 5H), 6.51 (bs, 1H), 4.63 (d, J = 6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.9, 138.4, 138.2, 134.1, 129.2, 129.0, 128.3, 128.1, 98.9, 44.6; MS (EI): *m/z* 338.1 ($M + H^+$).

***N*-(4-chlorobenzyl)benzamide**[7]



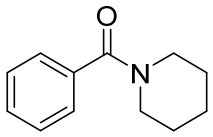
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.80 (d, J = 6 Hz, 2H), 7.55-7.50 (m, 1 H), 7.46-7.40 (m, 2H), 7.34-7.28 (m, 4H), 6.67 (bs, 1H), δ 4.60 (d, J = 6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.8, 137.2, 134.5, 133.7, 132.0, 129.5, 129.2, 130.0, 127.3, 43.7; MS (EI): *m/z* 246.1 ($M + H^+$).

***N*-benzyl-4-methoxybenzamide**[2]



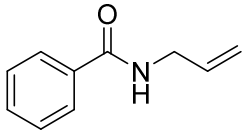
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.79 (d, J = 9 Hz, 2H), 7.38-7.29 (m, 5H), 6.92 (d, J = 9 Hz, 2H), 6.50 (bs, 1H), 4.63 (d, J = 3 Hz, 2H), δ 3.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.2, 162.6, 138.8, 129.2, 129.1, 128.2, 127.9, 127.0, 114.1, 55.8, 44.4; MS (EI): *m/z* 242.1 ($M + H^+$).

4-benzoylpiperidine[8]



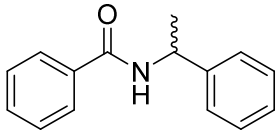
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39 (s, 5H), 3.68 (bs, 2H), 3.34 (bs, 2H), 1.68 (bs, 4H), 1.52 (bs, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.6, 136.9, 128.7, 127.1, 49.1, 43.5, 26.9, 26.0, 24.9; MS (EI): *m/z* 190.2 ($M + H^+$).

***N*-allylbenzamide**[9]



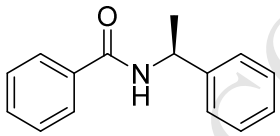
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82 (dd, J = 8.4 Hz, 2.4 Hz, 2H), 7.53-7.36 (m, 3H), 6.50 (bs, 1H), 6.00-5.87 (m, 1H), 5.23 (dd, J = 10.2 Hz, 1.5 Hz, 2H), 4.08 (t, J = 10.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.8, 134.9, 131.8, 130.3, 128.9, 127.3, 116.9, 42.8; MS (EI): *m/z* 162.1 ($M + H^+$).

(*R,S*)-*N*-(1-phenylethyl)benzamide[2]



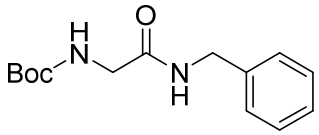
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.80 (d, J = 9 Hz, 2H), 7.53-7.29 (m, 8H), 6.41 (bs, 1H), 5.37 (quin., J = 6 Hz, 1H), 1.63 (d, J = 6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.9, 143.5, 135.0, 131.8, 129.1, 128.9, 127.8, 127.3, 126.6, 49.6, 22.1; MS (EI): *m/z* 226.0 ($M + H^+$); $[\alpha]^{21}_{D}$ 0.0 (*c* 0.73, MeOH).

(*S*)-*N*-(1-phenylethyl)benzamide[2]



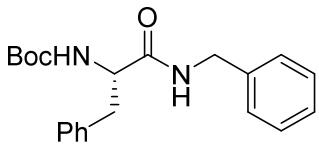
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.78 (d, J = 9 Hz, 2H), 7.53-7.30 (m, 8H), 6.46 (bs, 1H), 5.36 (quin., J = 6 Hz, 1H), 1.62 (d, J = 6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.9, 143.5, 135.0, 131.8, 129.1, 128.9, 127.8, 127.3, 126.6, 49.6, 22.1; MS (EI): *m/z* 226.0 ($M + H^+$); $[\alpha]^{21}_{D}$ 4.9 (*c* 1.00, MeOH).

tert-butyl (2-(benzylamino)-2-oxoethyl)carbamate[10]



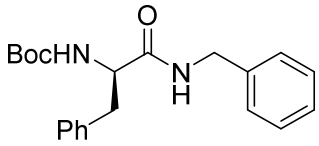
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 (bs, 1H), 7.23-7.11 (m, 5H), 5.87 (bs, 1H), 4.26 (d, J = 6 Hz, 2H), 3.86 (d, J = 6 Hz, 2H), 1.32 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.8, 156.5, 138.3, 129.1, 128.0, 127.9, 80.7, 44.9, 43.8, 28.6; MS (EI): *m/z* 287.0 (M + Na^+).

(S)-tert-Butyl (1-(benzylamino)-1-oxo-3-phenylpropan-2-yl)carbamate[11]



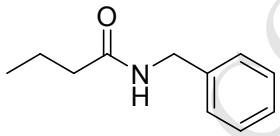
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32-7.09 (m, 10H), 6.17 (bs, 1H), 5.10 (bs, 1H), 4.41-4.36 (m, 3H), 3.12-3.08 (m, 2H), 1.41 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.4, 155.7, 138.1, 137.4, 129.7, 129.0, 128.0, 127.8, 127.3, 118.5, 80.6, 56.4, 43.8, 40.0, 28.6; MS (EI): *m/z* 354.9 (M + H^+); $[\alpha]^{21}_D$ -2.3 (*c* 0.22, MeOH).

(R)-tert-Butyl (1-(benzylamino)-1-oxo-3-phenylpropan-2-yl)carbamate[11]



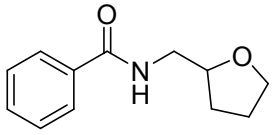
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 - 7.09 (m, 10H), 6.16 (s, 1H), 5.09 (s, 1H), 4.35 (d, J = 5.6 Hz, 3H), 3.08 (m, 2H), 1.38 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.0, 168.0, 137.6, 136.6, 129.3, 128.7, 128.6, 127.6, 127.4, 126.9, 77.3, 77.0, 76.7, 68.3, 56.0, 43.4, 38.6, 28.2; MS (EI): *m/z* 354.9 (M + H^+); $[\alpha]^{21}_D$ 2.3 (*c* 0.44, MeOH).

***N*-benzylbutyramide**[12]



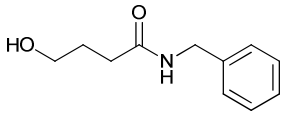
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38-7.26 (m, 5H), 5.94 (bs, 1H), 5.44 (d, J = 6 Hz, 2H), 2.20 (t, J = 9 Hz, 2H), 1.70 (sext., J = 9 Hz, 2H), 0.97 (t, J = 9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.2, 138.8, 129.0, 128.1, 127.8, 43.9, 39.0, 19.5, 14.1; MS (EI): *m/z* 178.1 (M + H^+).

***N*-((tetrahydrofuran-2-yl)methyl)benzamide**[13]



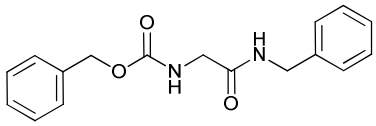
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.79 (d, J = 6 Hz, 2H), 7.53-7.40 (m, 3H), 6.60 (bs, 1H), 4.12-4.04 (m, 1H), (dd, J = 9 Hz, 6 Hz, 1H) , 7.38-7.74 (m, 2H), 3.40-3.31 (m, 1H), 2.09-1.88 (m, 3H), 1.68-1.57 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.9, 134.9, 131.8, 128.9, 127.3, 78.2, 68.5, 44.0, 29.0, 26.3; MS (EI): *m/z* 206.1 ($M + H^+$).

N-benzyl-4-hydroxybutanamide[14]



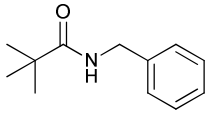
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 - 7.21 (m, 4H), 6.51 (s, 1H), 4.37 (d, J = 5.7 Hz, 2H), 3.62 (t, J = 5.8 Hz, 2H), 3.53 (s, 1H), 2.37 - 2.30 (m, 2H), 1.89 - 1.79 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.52, 138.10, 128.64, 127.68, 127.44, 77.35, 77.04, 76.72, 62.02, 43.60, 33.67, 28.14; MS (EI): *m/z* 194.1 ($M + H^+$).

benzyl (2-(benzylamino)-2-oxoethyl)carbamate[15]



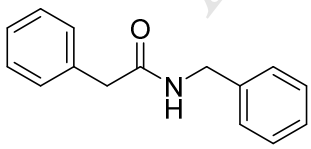
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 - 7.08 (m, 10H), 6.35 (s, 1H), 5.43 (s, 1H), 5.09 (s, 2H), 4.44 (d, J = 5.7 Hz, 2H), 3.89 (d, J = 5.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.26, 156.13, 137.22, 135.53, 128.27, 127.81, 127.62, 127.26, 127.15, 105.66, 76.95, 76.53, 76.11, 66.78, 44.20, 43.66; MS (EI): *m/z* 298.9 ($M + H^+$)

***N*-benzylpivalamide[16]**



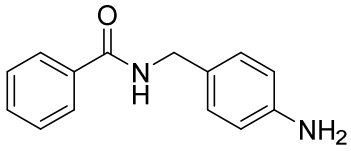
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 - 6.91 (m, 5H), 5.96 (s, 1 H), 4.43 (d, J = 5.6 Hz, 2H), 1.23 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 178.25, 138.61, 128.67, 127.60, 127.38, 77.34, 77.02, 76.70, 43.54, 38.69, 27.59; MS (EI): *m/z* 191.1 ($M + H^+$).

***N*-benzyl-2-phenylacetamide[17]**



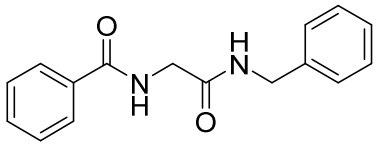
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41-7.17 (m, 10H), 5.83 (bs, 1H), 4.41 (d, J = 6 Hz, 2H), 3.64 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.2, 138.5, 135.2, 129.8, 129.4, 129.0, 127.8, 127.8, 127.7, 44.2, 43.9; MS (EI): *m/z* 226.1 ($M + H^+$).

***N*-(4-aminobenzyl)benzamide**[18]



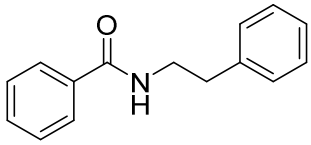
^{1}H NMR (300 MHz, $(CD_3)_2SO$)): δ 8.84 (t, J = 6 Hz, 1H), 7.88 (d, J = 6 Hz, 2H), 7.55-7.42 (m, 3H), 6.99 (d, J = 9 Hz, 2H), 6.52 (d, J = 9 Hz, 2H), 4.94 (s, 2H), 4.31 (d, J = 6 Hz, 2H); ^{13}C NMR (75 MHz, $(CD_3)_2SO$): δ 165.9, 147.5, 134.6, 131.0, 128.2, 127.2, 126.6, 113.7, 112.1, 42.3; MS (EI): *m/z* 226.9 ($M + H^+$).

***N*-(2-benzylamino)-2-oxoethyl)benzamide**[19]



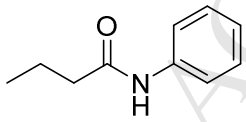
^{1}H NMR (300 MHz, $(CD_3)_2SO$): δ 8.79 (t, J = 6 Hz, 1H), 8.44 (t, J = 6 Hz, 1H), 7.91 (d, J = 9 Hz, 2H), 7.59-7.44 (m, 3H), 7.36-7.20 (m, 5H), 4.31 (d, J = 6Hz, 2H), 3.94 (d, J = 6 Hz, 2H); ^{13}C NMR (75 MHz, $(CD_3)_2SO$)): δ 169.0, 166.5, 139.4, 134.0, 131.3, 128.2, 127.4, 127.1, 126.7, 42.7, 42.0; MS (EI): *m/z* 291.1 ($M + Na^+$).

***N*-phenethylbenzamide**[2]



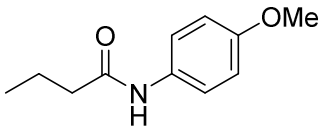
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72 (d, J = 6 Hz, 2H), 7.52-7.27 (m, 8H), 6.27 (bs, 1H), 3.72 (q, J = 12 Hz, 6 Hz, 2H), 2.96 (t, J = 6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.8, 139.3, 135.0, 131.7, 129.2, 129.1, 128.9, 127.2, 127.0, 41.5, 36.1; MS (EI): *m/z* 226.1 ($M + H^+$).

***N*-phenylbutyramide**[20]



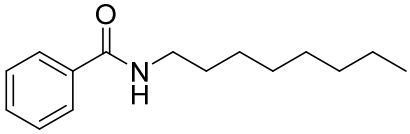
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54 (d, J = 6 hz, 2H), 7.46 (bs, 1H), 7.32 (t, J = 6 Hz, 2H), 7.11 (t, J = 6 Hz, 1H), 2.35 (t, J = 6 Hz, 2H), 1.77 (m, 2H), 1.01 (t, J = 6 Hz)); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.8, 138.4, 129.3, 124.5, 120.2, 40.0, 19.4, 14.1; MS (EI): *m/z* 164.1 ($M + H^+$).

_N_-(p-methoxy)phenylbutyramide[21]



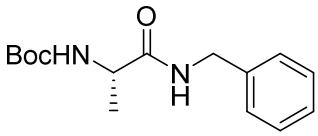
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (bs, 1H), 7.40 (d, J = 6 Hz, 2H), 6.82 (d, J = 6 Hz, 2H), 3.77 (s, 3H), 2.30 (t, J = 6 Hz, 2H), 1.73 (m, 2H), 0.98 (t, J = 6 Hz, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.3, 156.3, 131.1, 121.8, 114.0, 55.4, 39.4, 19.1, 13.7; MS (EI): *m/z* 194.1 ($M + H^+$).

_N_-octylbenzamide[22]



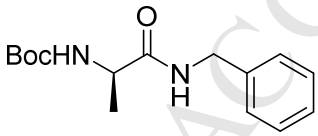
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 – 7.75 (m, 2H), 7.50 – 7.39 (m, 3H), 6.23 (bs, 1H), 3.47 – 3.42 (m, 2H),1.64 – 1.57 (m, 2H), 1.41 – 1.21 (m, 10H), 0.88 (t, J = 6 Hz, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.9, 135.2, 131.6, 128.9, 127.2, 40.5, 32.2, 30.0, 29.7, 29.6, 27.4, 23.0, 15.4; MS (EI): *m/z* 243.3 ($M + H^+$).

(S)-tert-Butyl (1-(benzylamino)-1-oxopropan-2-yl)carbamate[23]



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36 – 7.24 (m, 5H), 6.59 (bs, 1H), 5.03 (bs, 1H), 4.46 (d, J = 3 Hz, 2H), 4.20 (bs, 1H), 1.43 (s, 9H), 1.39 (d, J = 9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.9, 155.9, 138.4, 129.1, 128.0, 127.8, 50.6, 43.8, 28.7, 18.7; MS (EI): *m/z* 278.8 ($M + H^+$); $[\alpha]^{21}_D$ -24.7 (*c* 0.82, MeOH).

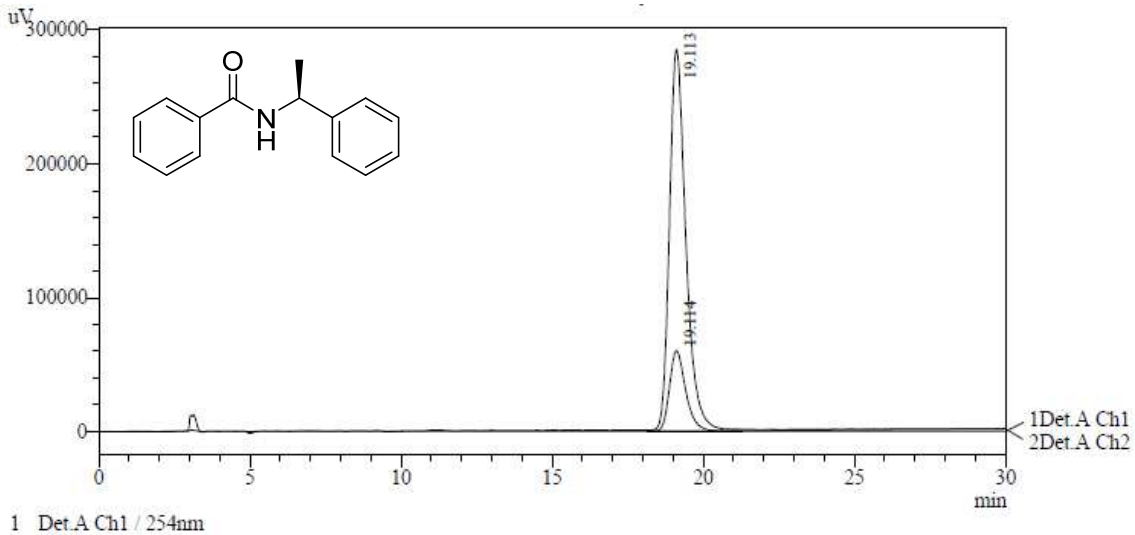
(R)-tert-Butyl (1-(benzylamino)-1-oxopropan-2-yl)carbamate[23]



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36 – 7.25 (m, 5H), 6.60 (bs, 1H), 5.03 (bs, 1H), 4.46 (d, J = 3 Hz, 2H), 4.20 (bs, 1H), 1.43 (s, 9H), 1.38 (d, J = 9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.9, 155.9, 138.4, 129.0, 128.0, 127.8, 50.6, 43.8, 28.7, 18.7; MS (EI): *m/z* 278.9 ($M + H^+$); ; $[\alpha]^{21}_D$ 21.8 (*c* 0.84, MeOH).

9. Chiral HPLC data

(*S*)-*N*-(1-phenylethyl)benzamide



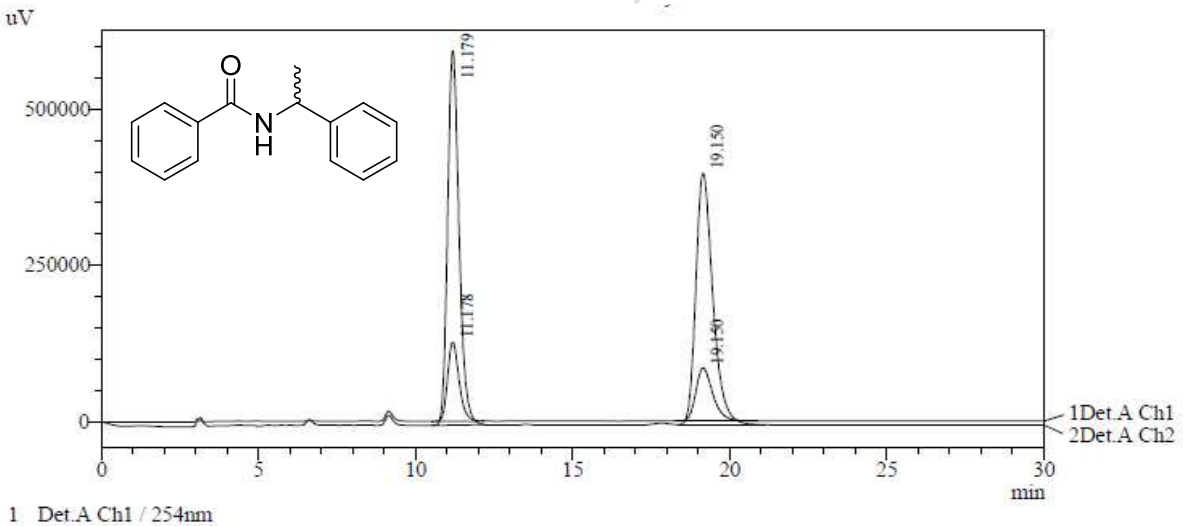
1 Det.A Ch1 / 254nm
2 Det.A Ch2 / 215nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	19.114	2262892	60185	100.000	100.000
Total		2262892	60185	100.000	100.000

(*R,S*)-*N*-(1-phenylethyl)benzamide



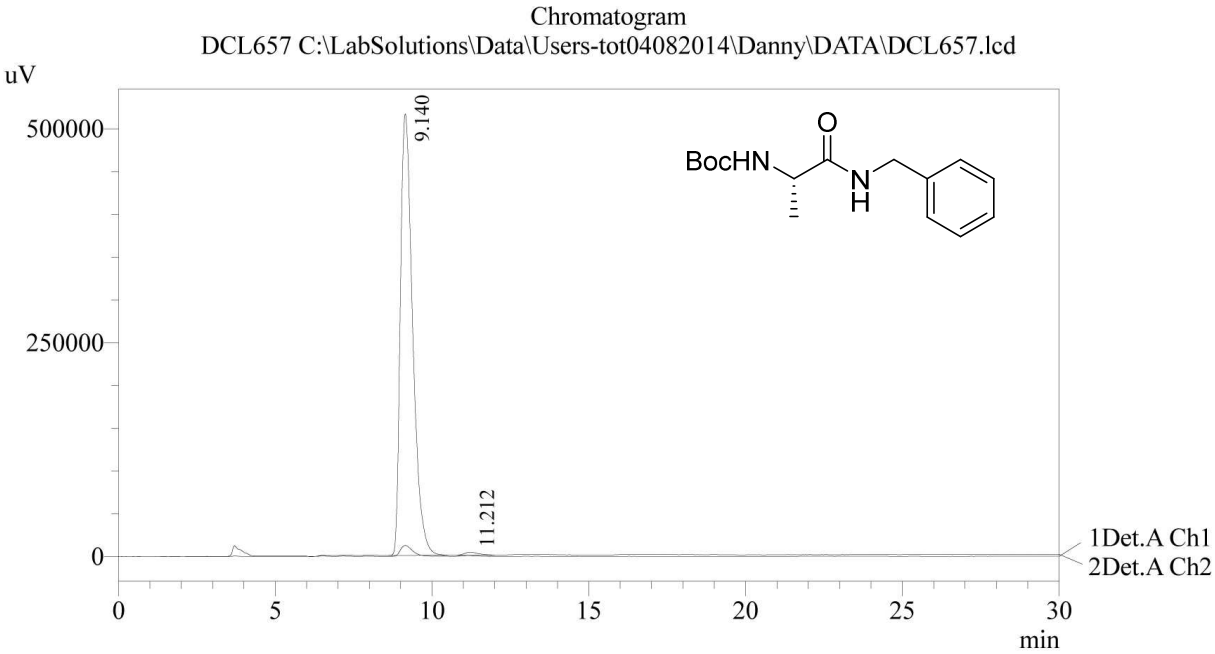
1 Det.A Ch1 / 254nm
2 Det.A Ch2 / 215nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	11.178	3214917	126226	50.060	59.787
2	19.150	3207150	84902	49.940	40.213
Total		6422067	211127	100.000	100.000

(S)-tert-Butyl (1-(benzylamino)-1-oxopropan-2-yl)carbamate



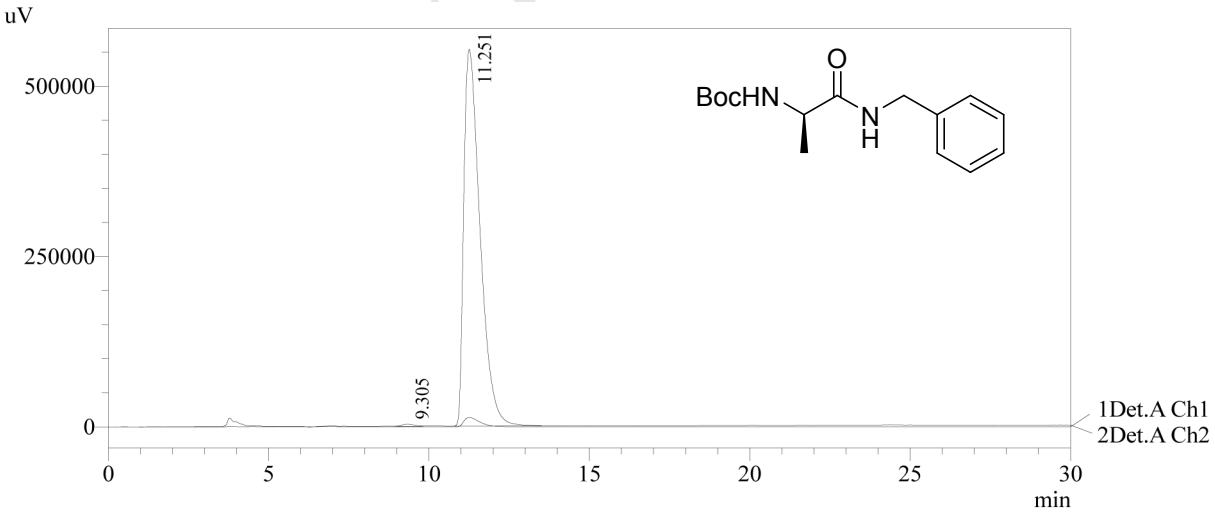
1 Det.A Ch1 / 254nm
2 Det.A Ch2 / 215nm

PeakTable

Detector A Ch2 215nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	9.140	14036704	515959	99.177	99.298
2	11.212	116551	3647	0.823	0.702
Total		14153256	519606	100.000	100.000

(R)-tert-Butyl (1-(benzylamino)-1-oxopropan-2-yl)carbamate



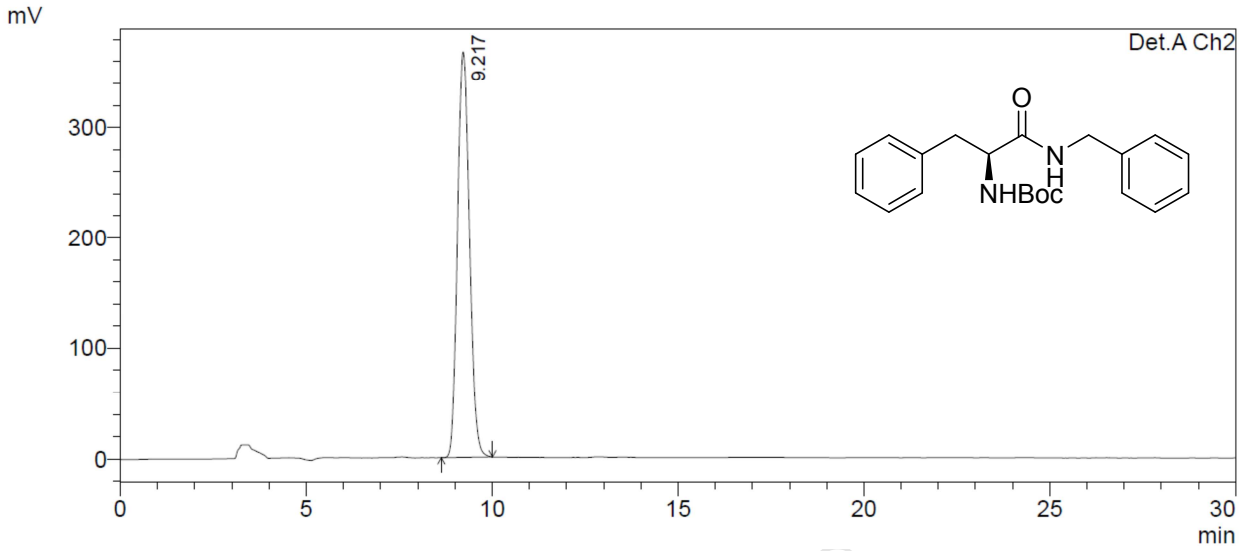
1 Det.A Ch1 / 254nm
2 Det.A Ch2 / 215nm

PeakTable

Detector A Ch2 215nm

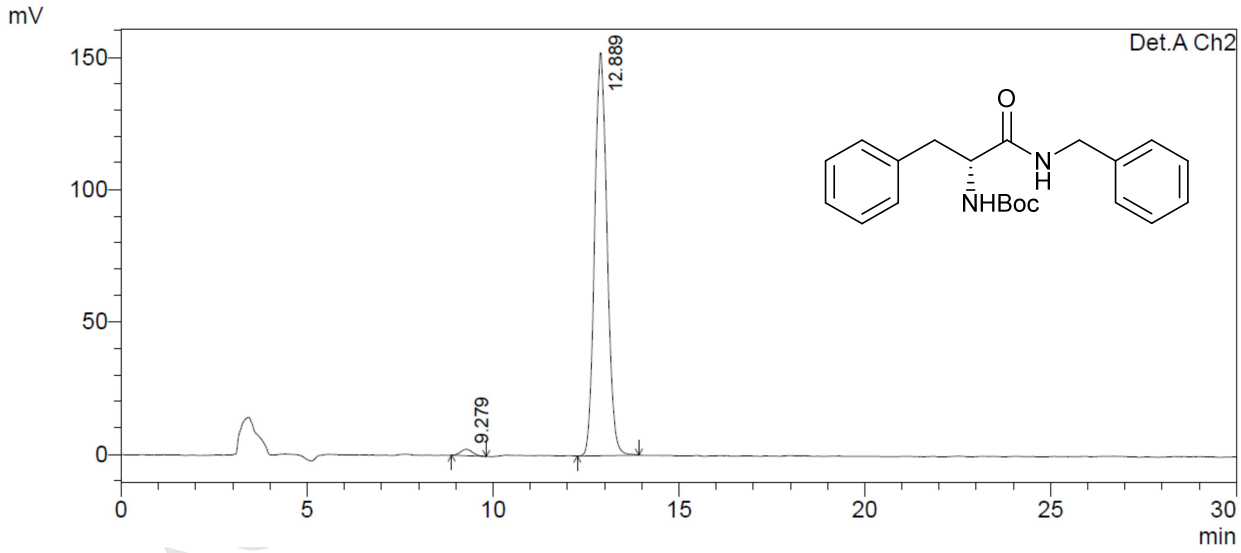
Peak#	Ret. Time	Area	Height	Area %	Height %
1	9.305	82239	3160	0.420	0.568
2	11.251	19511242	552907	99.580	99.432
Total		19593480	556067	100.000	100.000

(S)-tert-Butyl (1-(benzylamino)-1-oxo-3-phenylpropan-2-yl)carbamate



Peak#	Ret. Time	Area	Height	Area %	Height %
1	9.217	8212798	366800	100.000	100.000
Total		8212798	366800	100.000	100.000

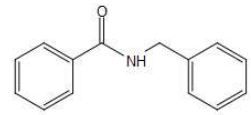
(R)-tert-Butyl (1-(benzylamino)-1-oxo-3-phenylpropan-2-yl)carbamate

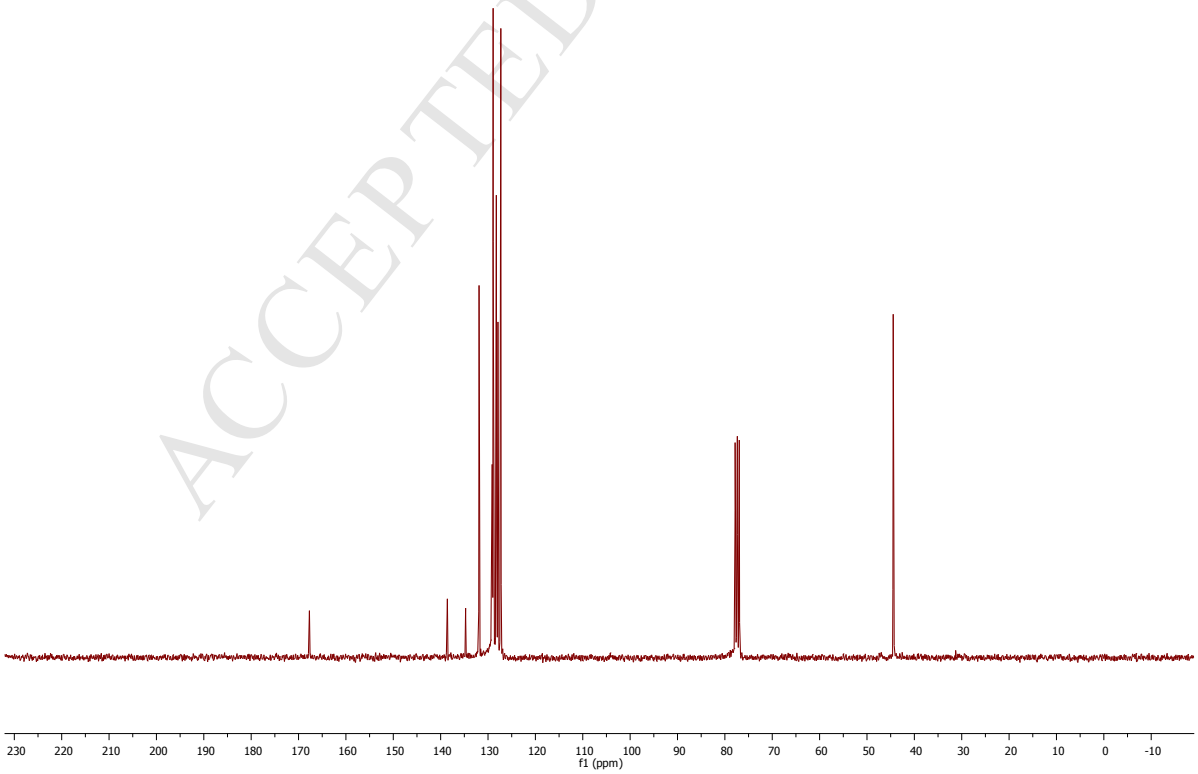


Peak#	Ret. Time	Area	Height	Area %	Height %
1	9.279	54972	2472	1.529	1.597
2	12.889	3540681	152299	98.471	98.403
Total		3595653	154770	100.000	100.000

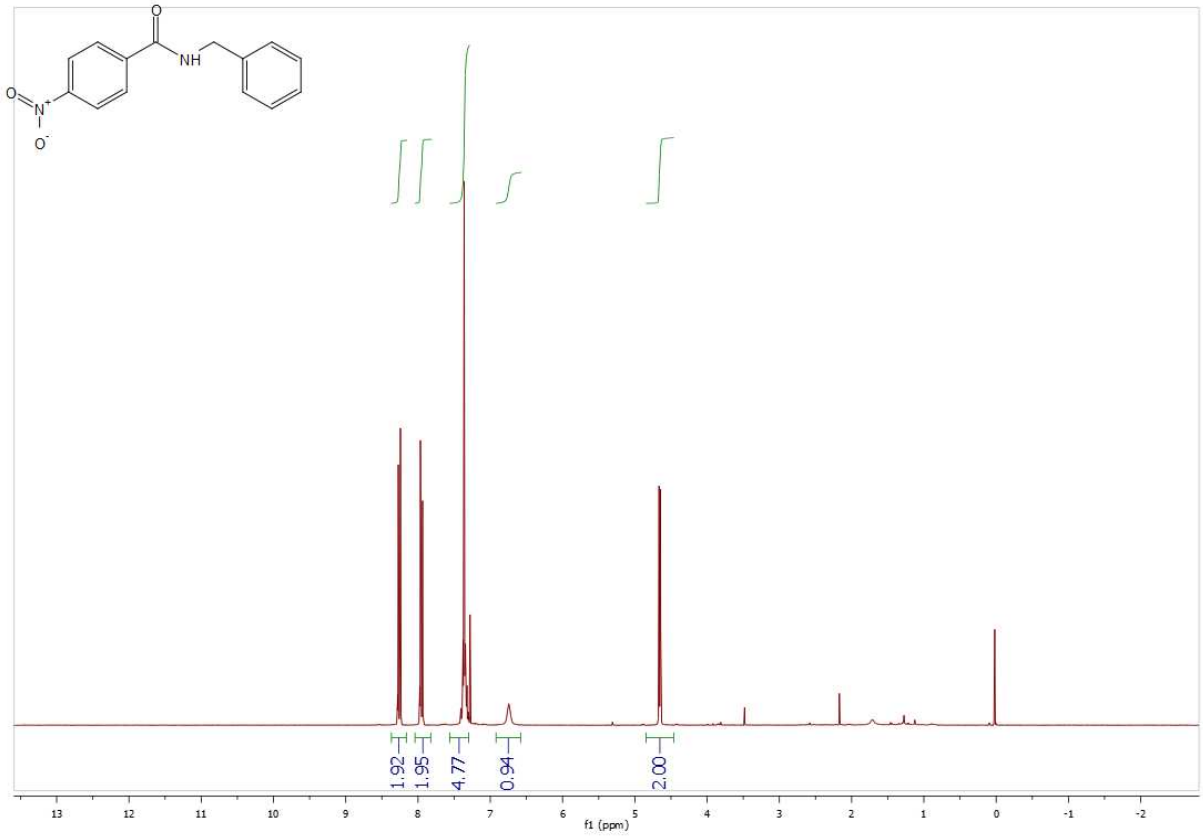
10. ^{1}H and ^{13}C NMR spectra of products

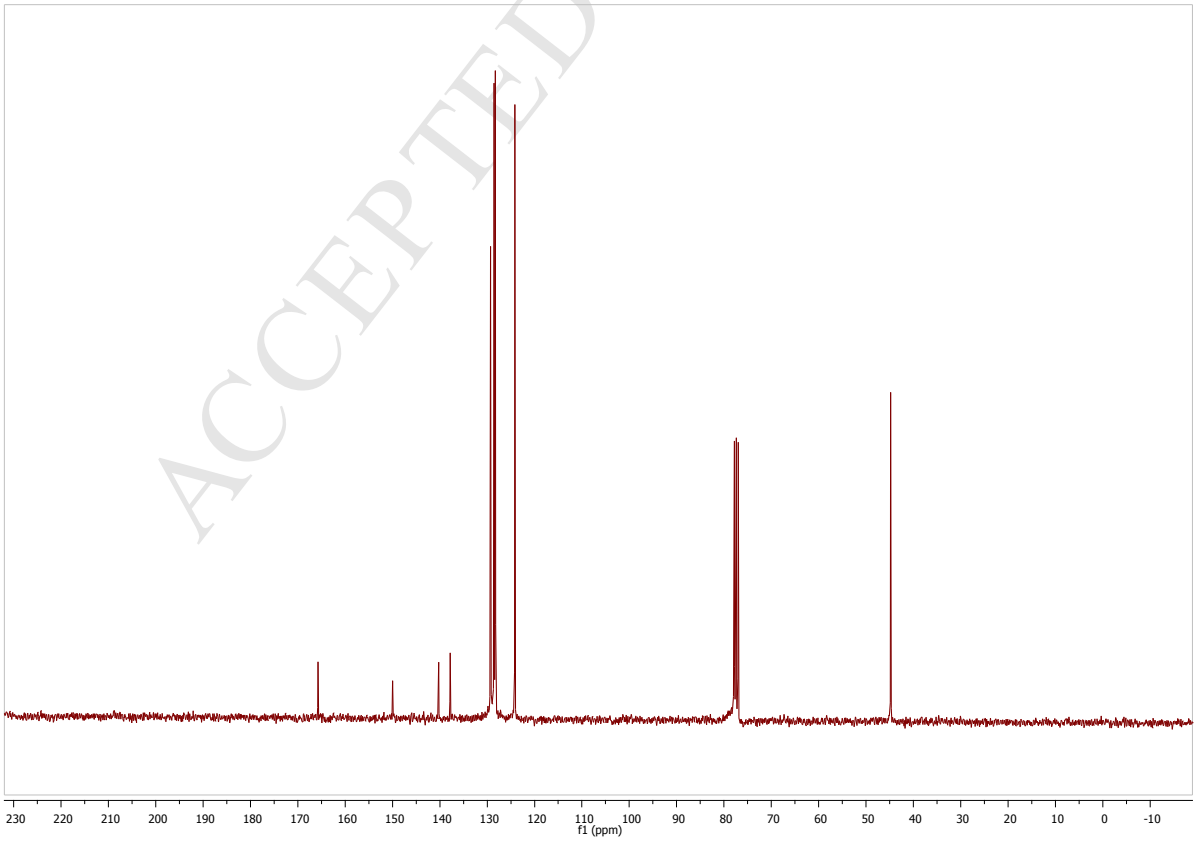
***N*-benzylbenzamide**



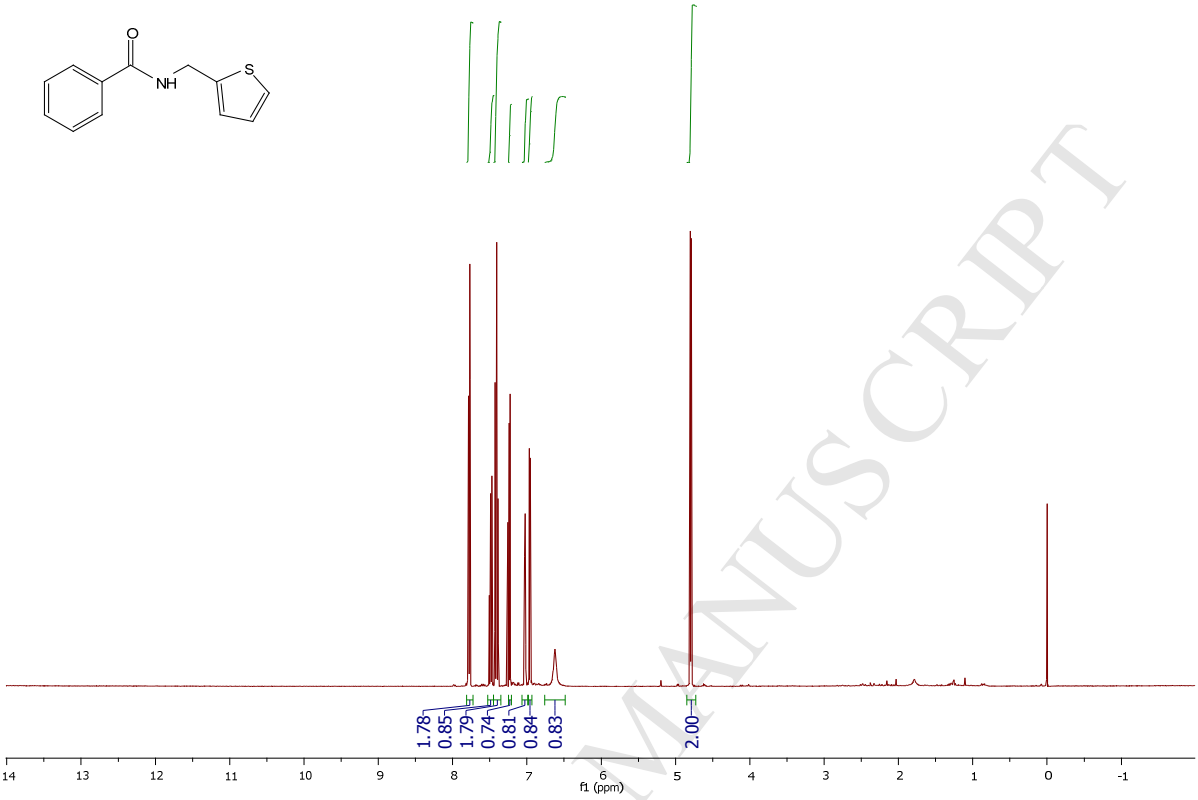


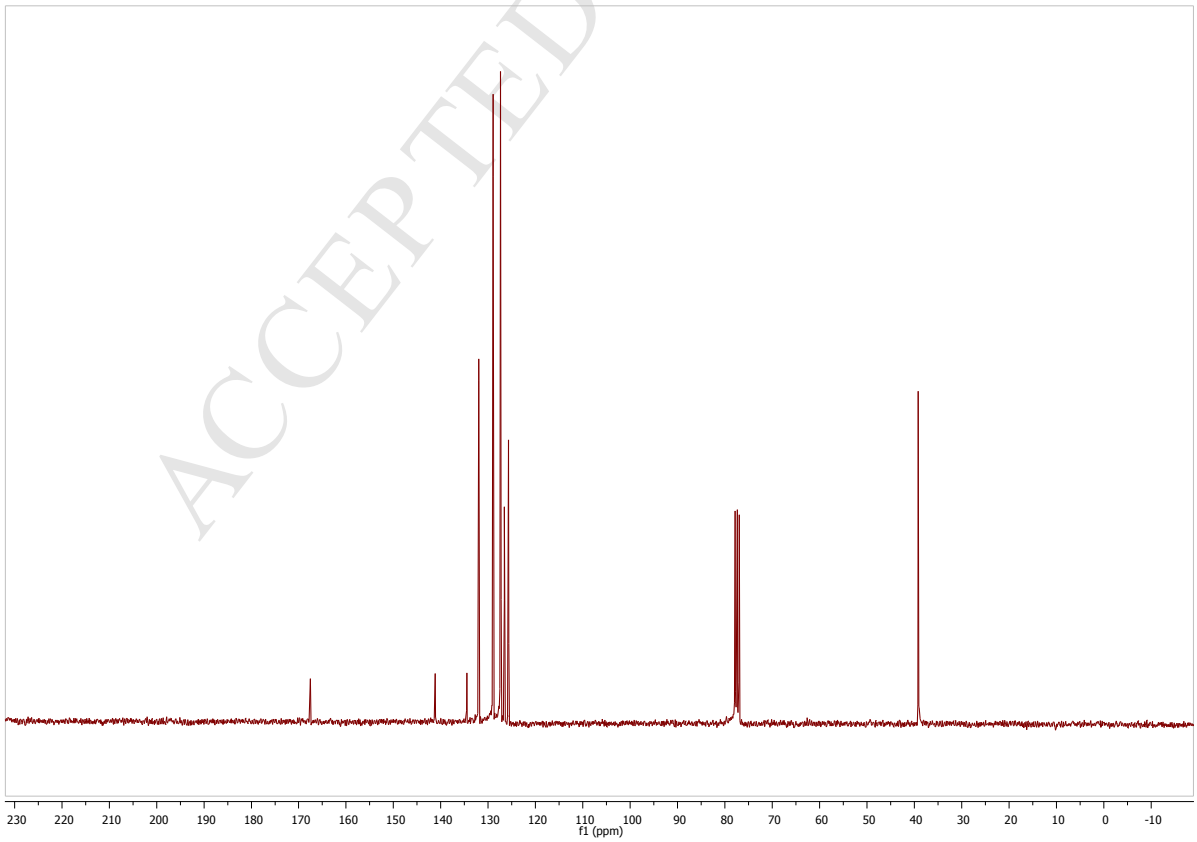
_N_-benzyl-4-nitrobenzamide



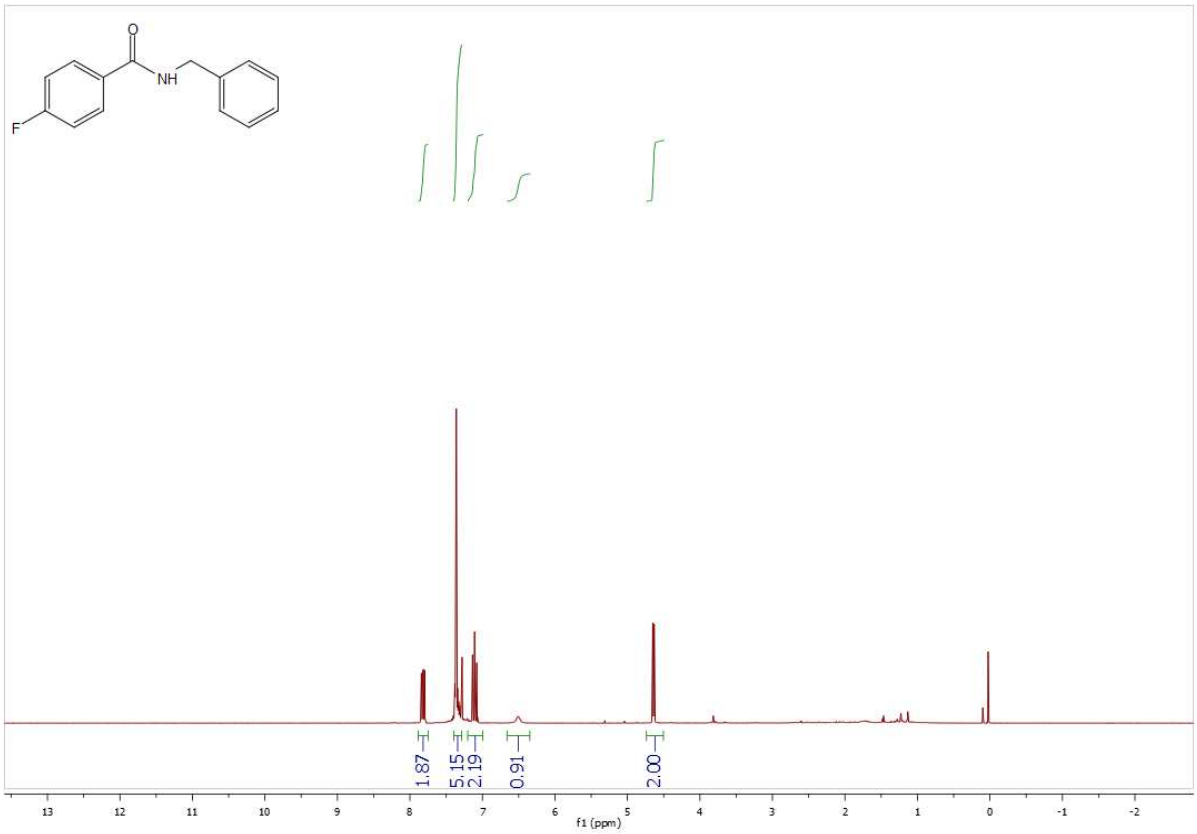


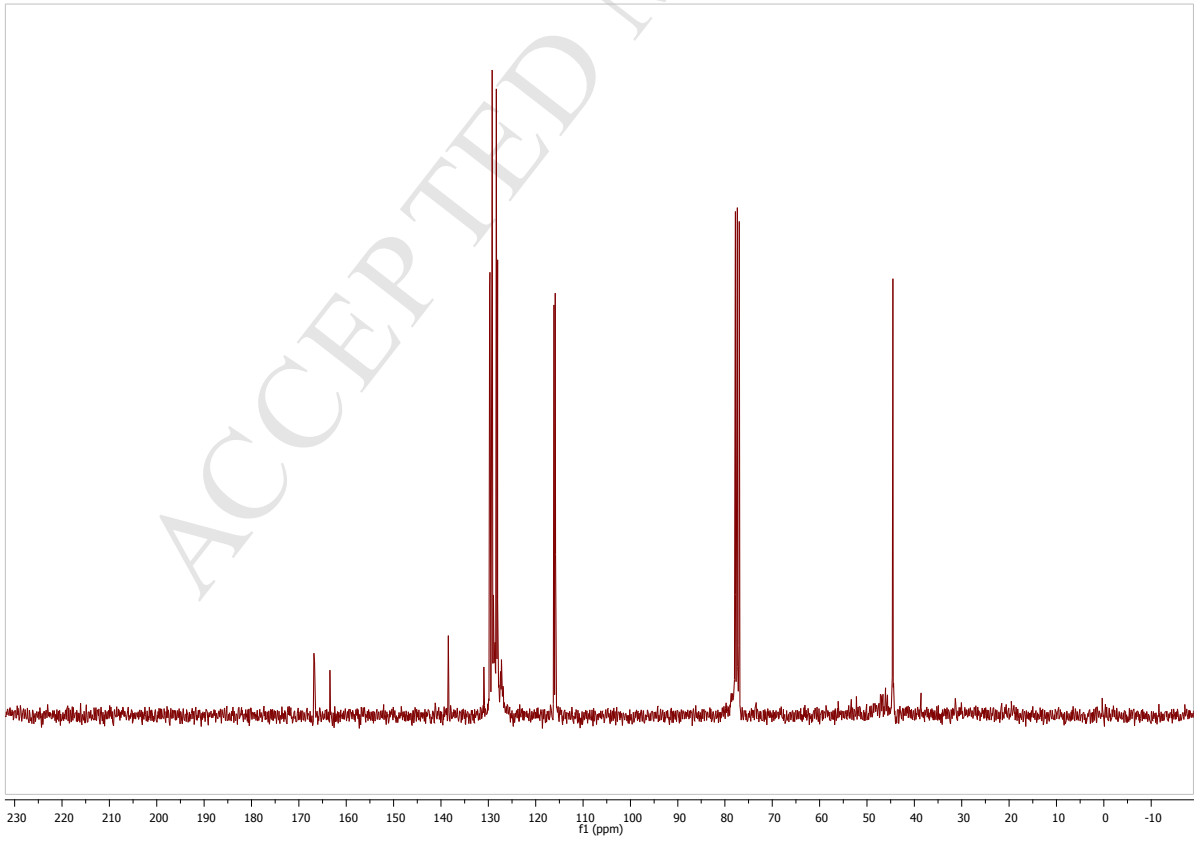
_N_-(thiophen-2-ylmethyl)benzamide



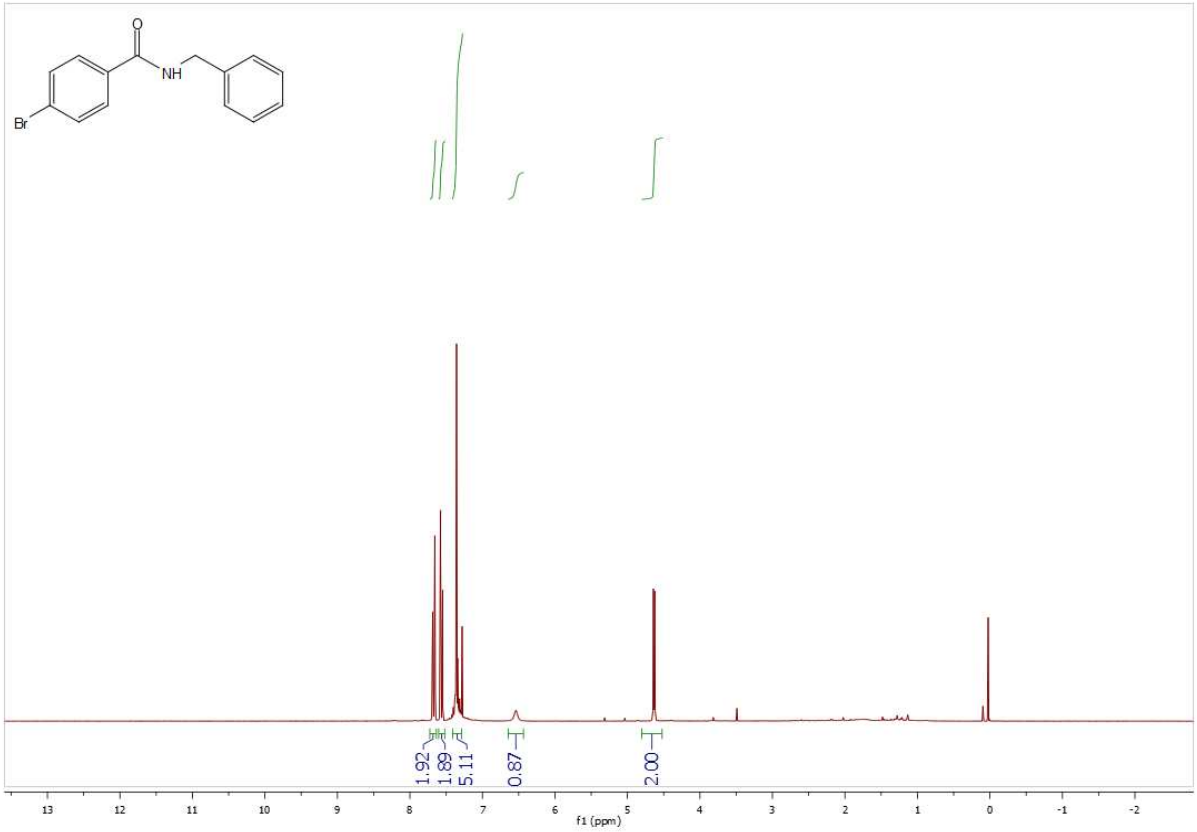


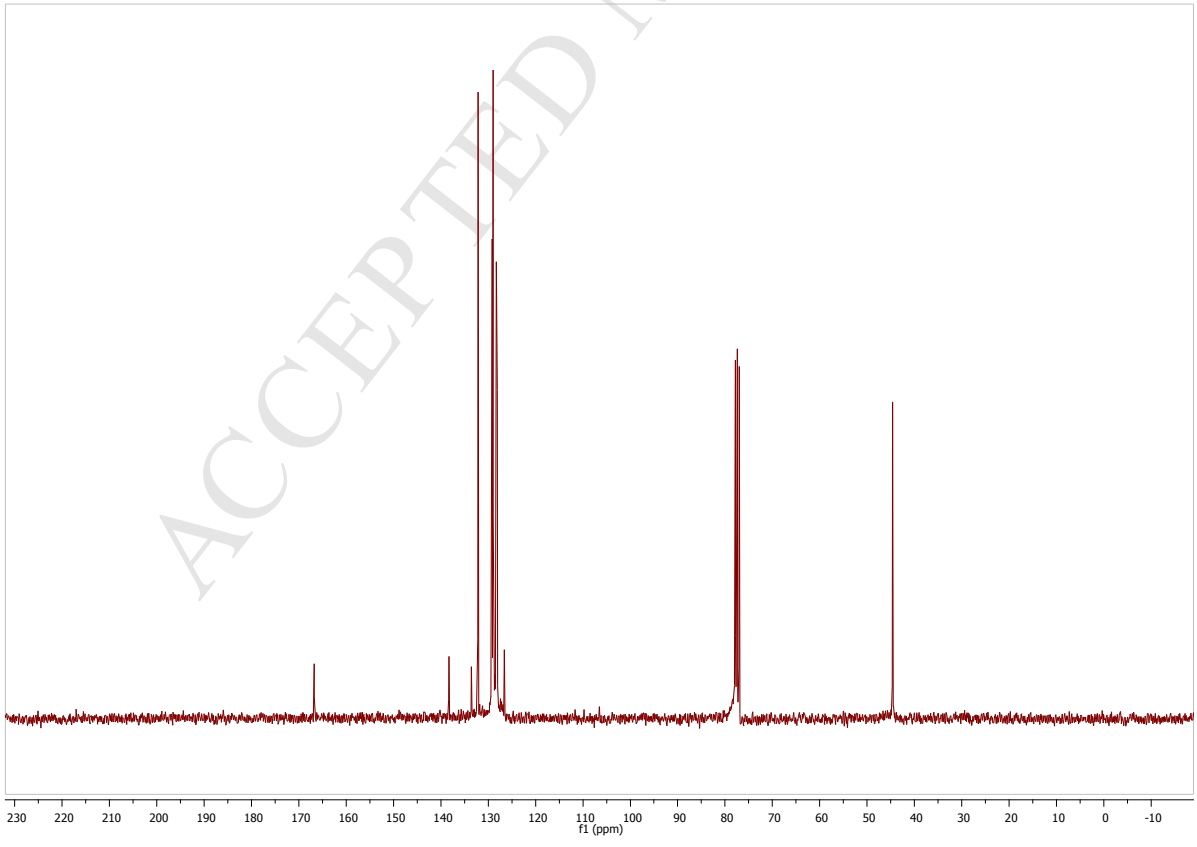
***N*-benzyl-4-fluorobenzamide**



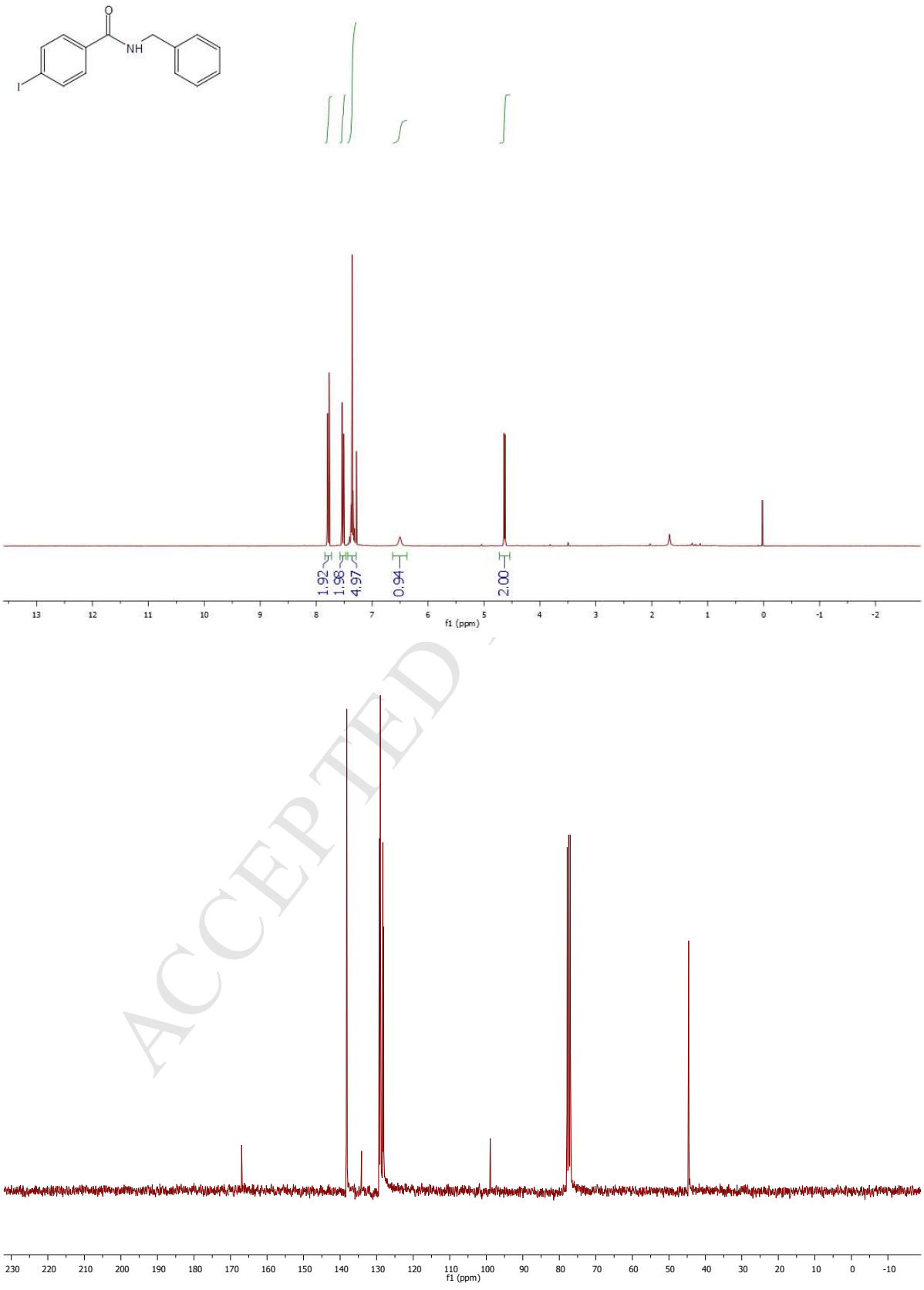


***N*-benzyl-4-bromobenzamide**

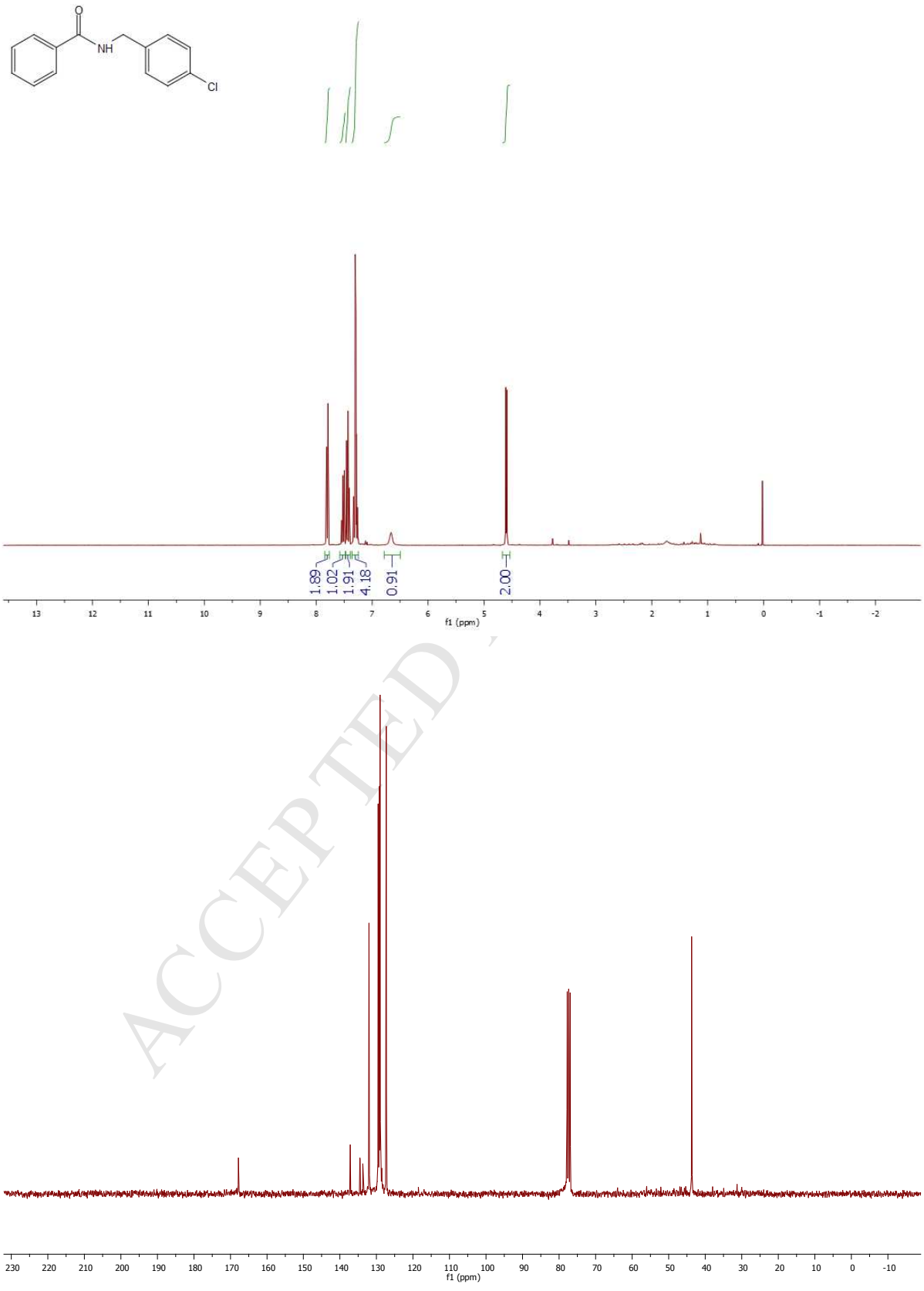




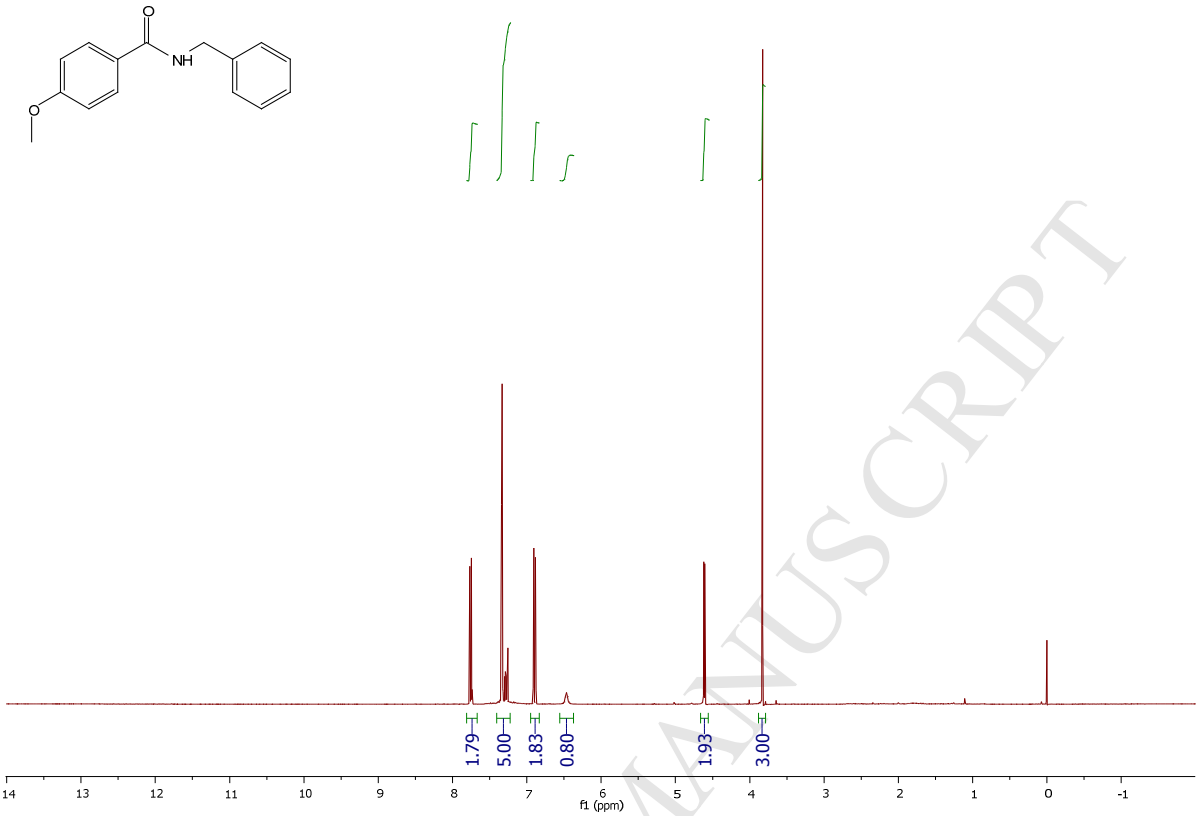
***N*-benzyl-4-iodobenzamide**

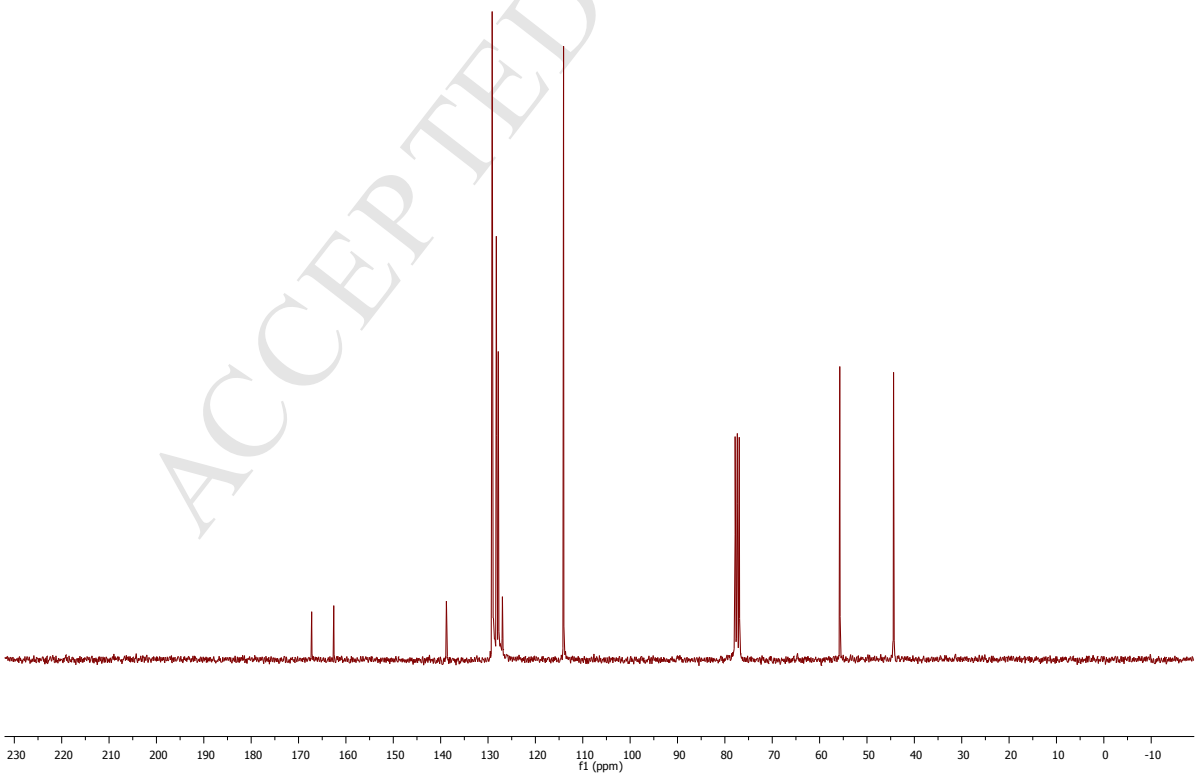


***N*-(4-chlorobenzyl)benzamide**

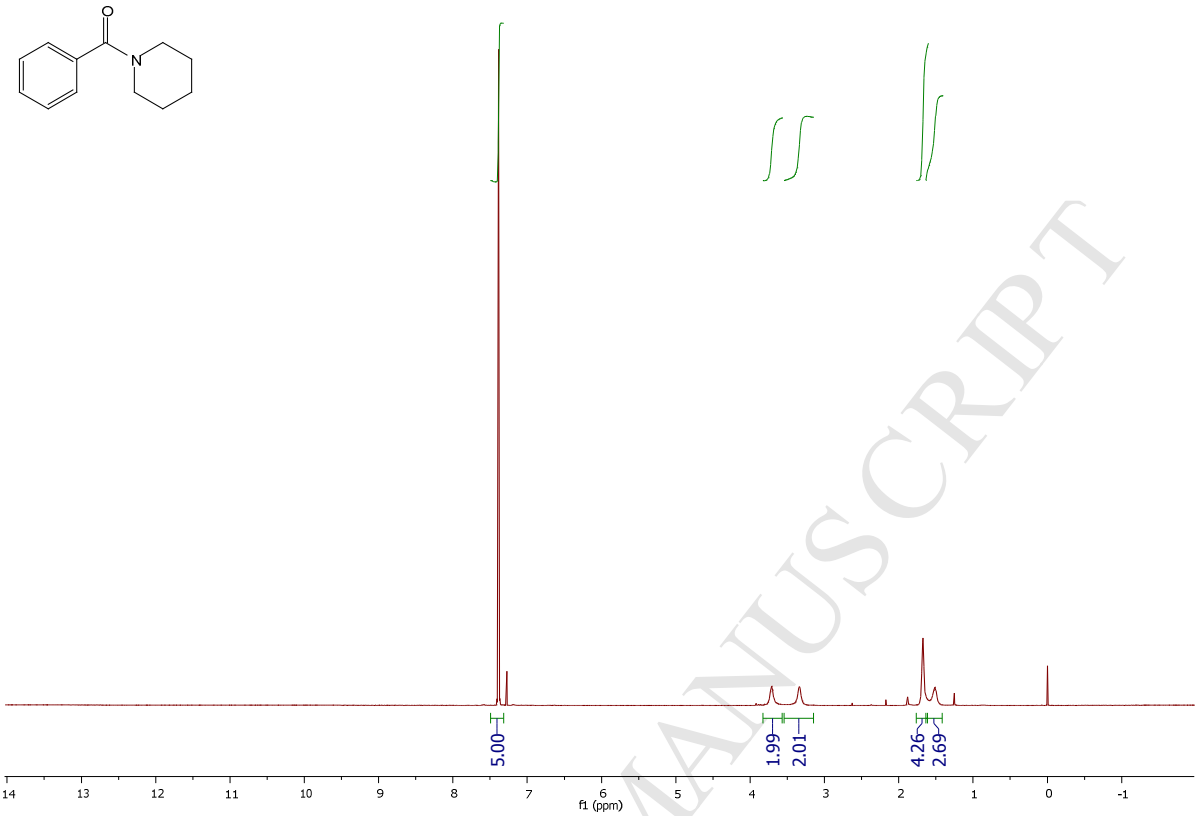


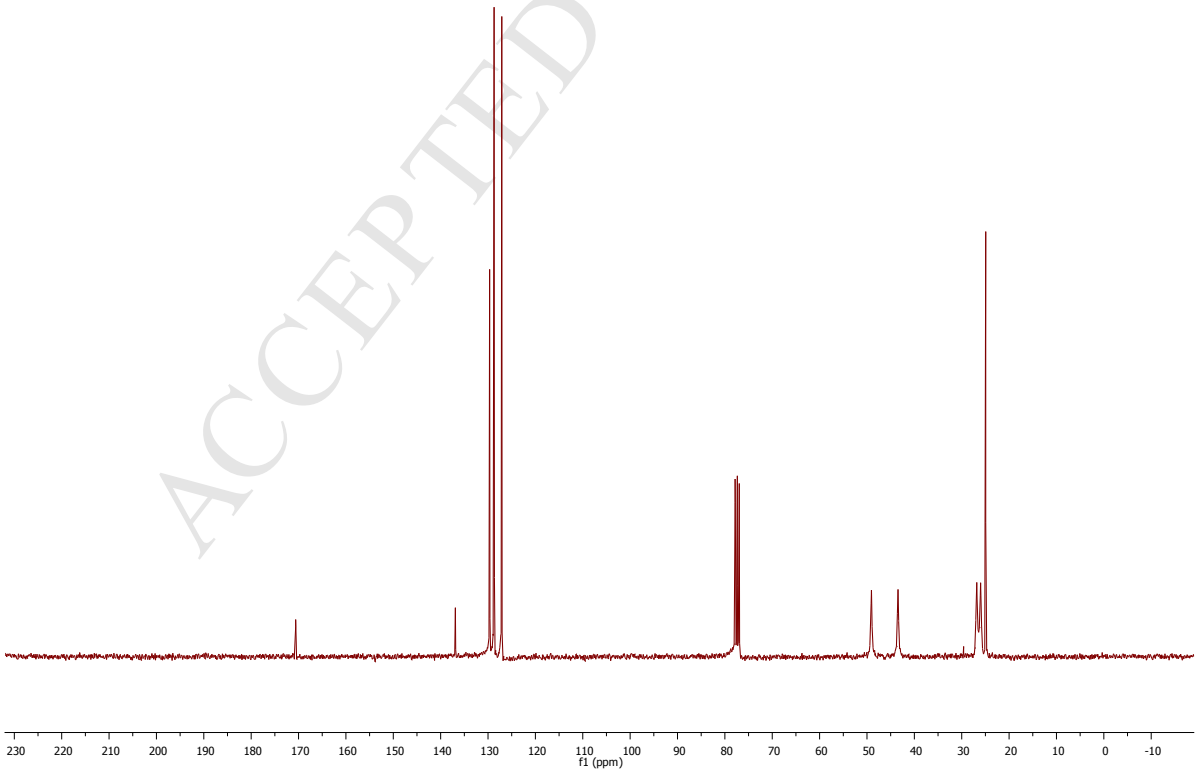
***N*-benzyl-4-methoxybenzamide**



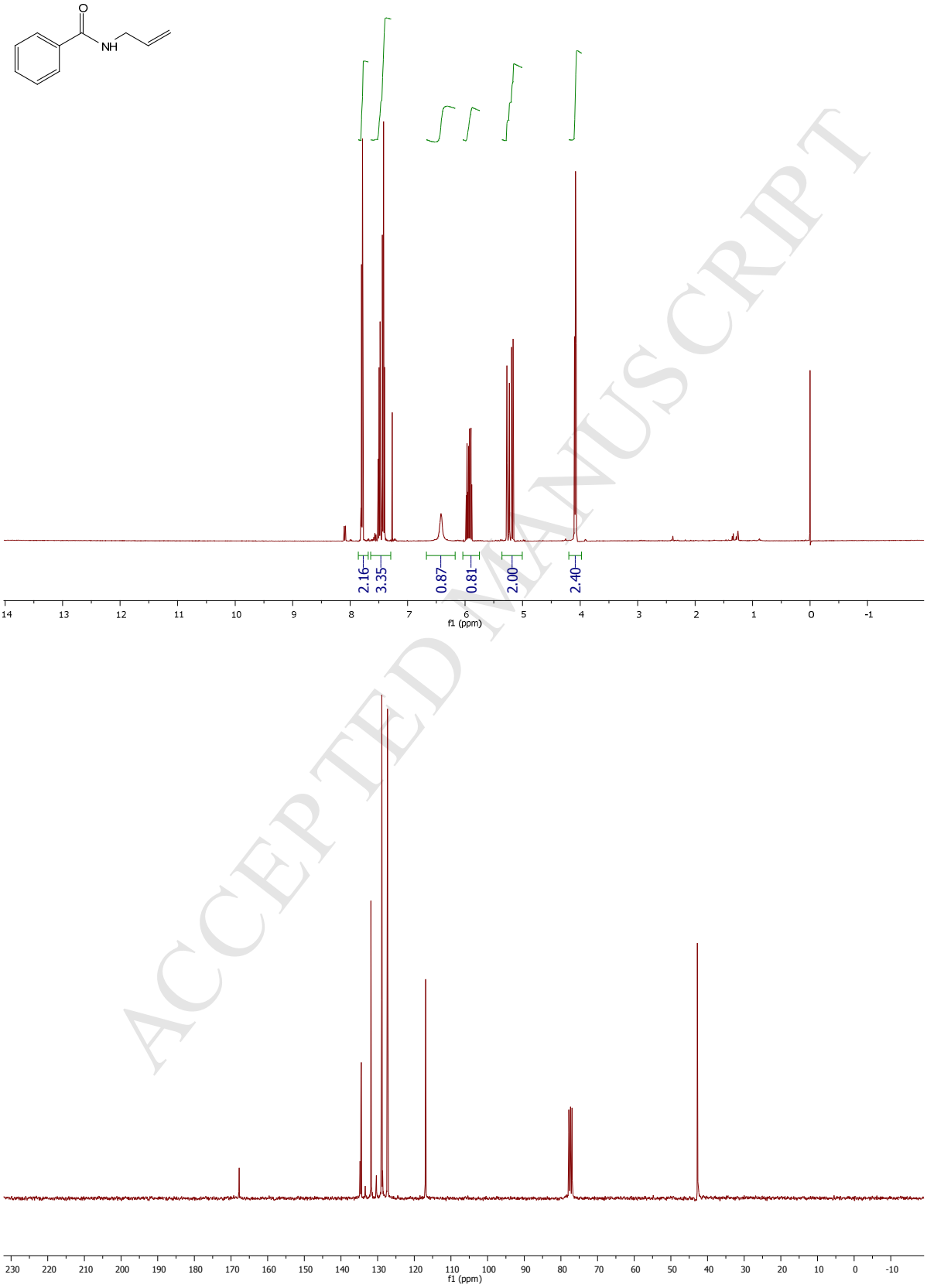


4-benzoylpiperidine

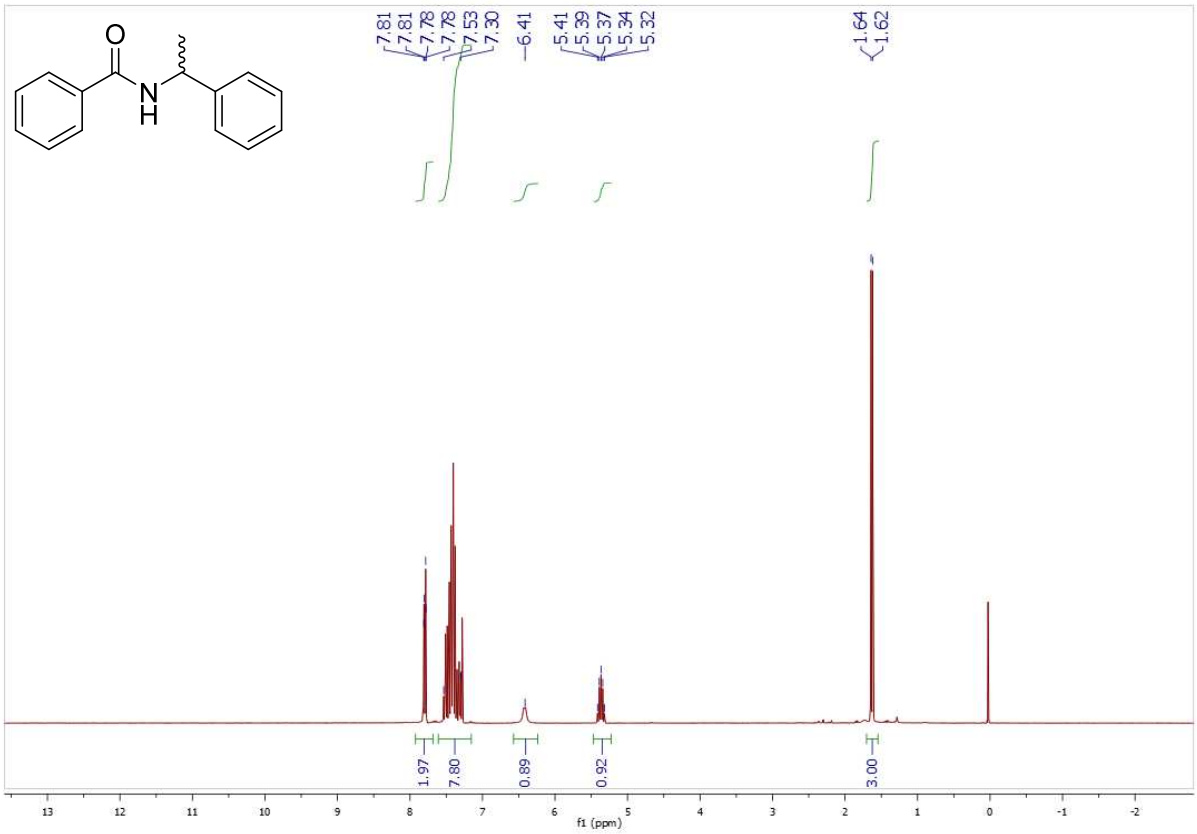


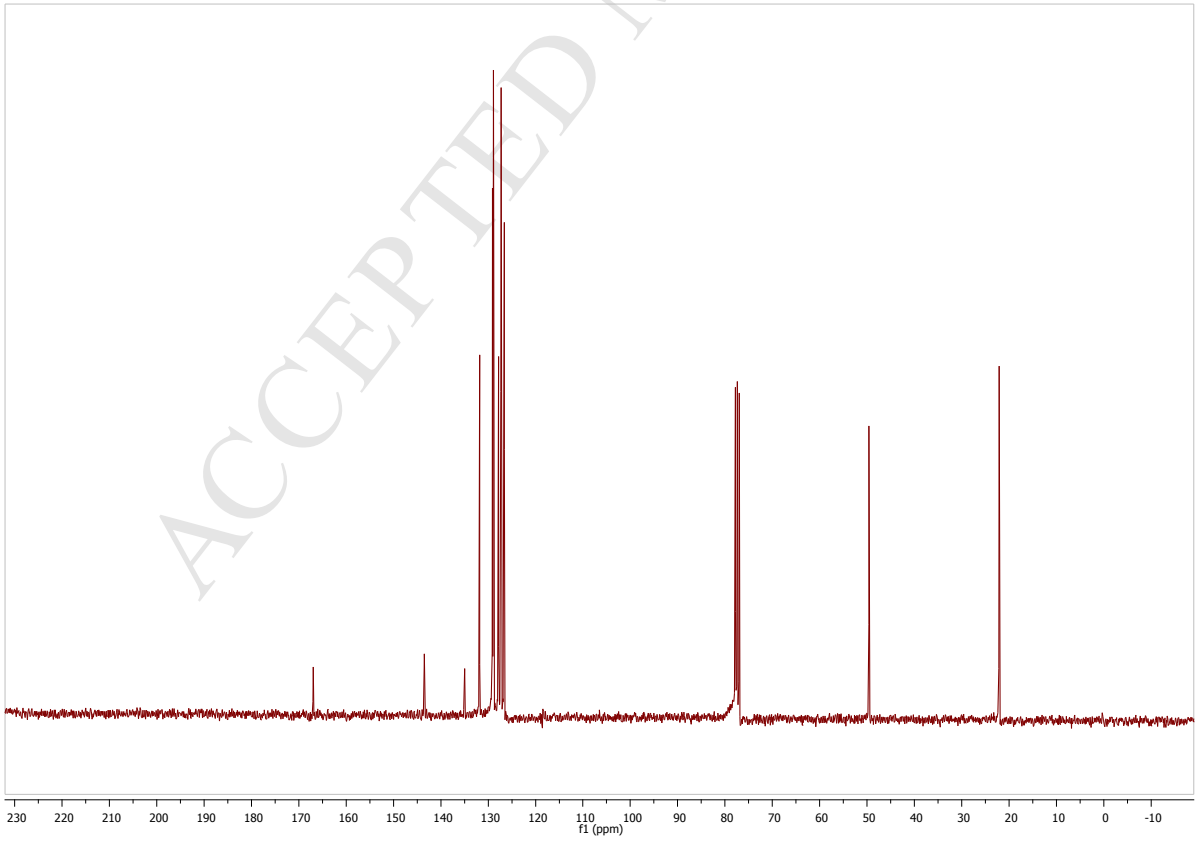


_N_-allylbenzamide

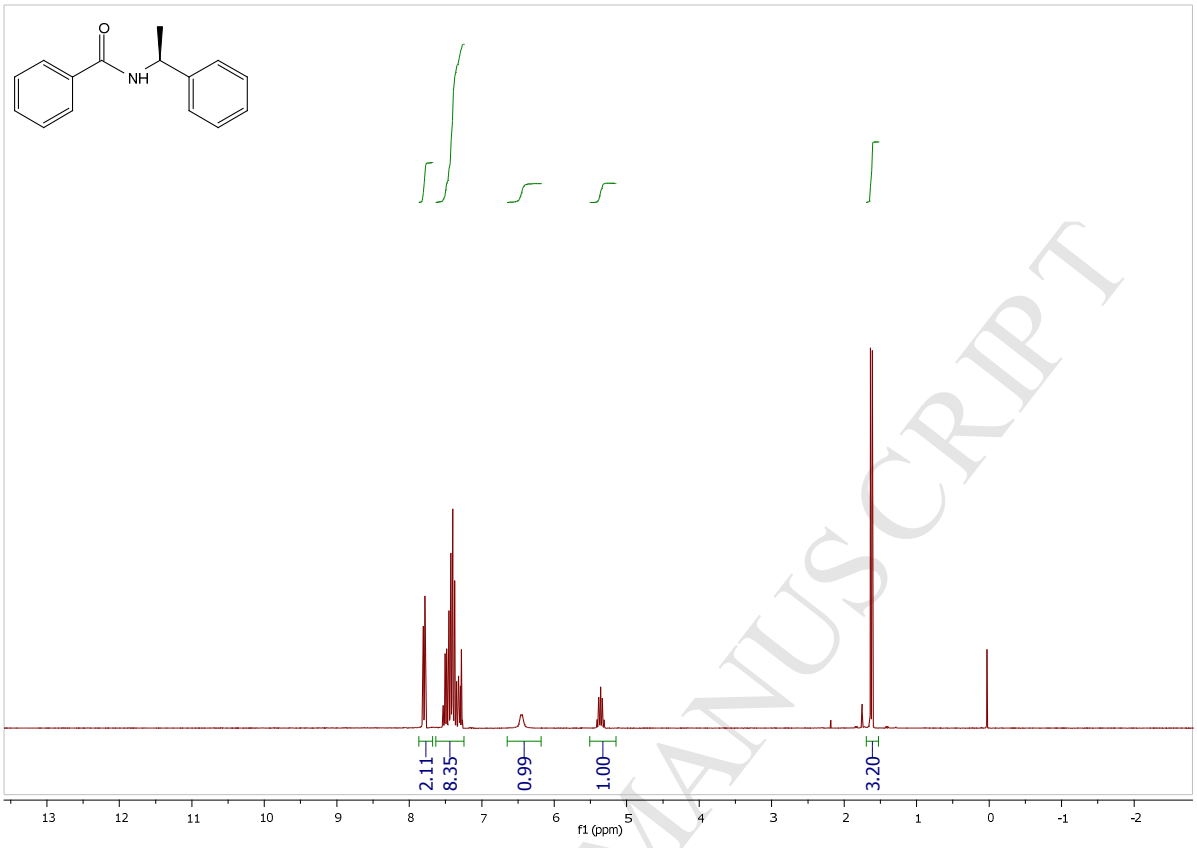


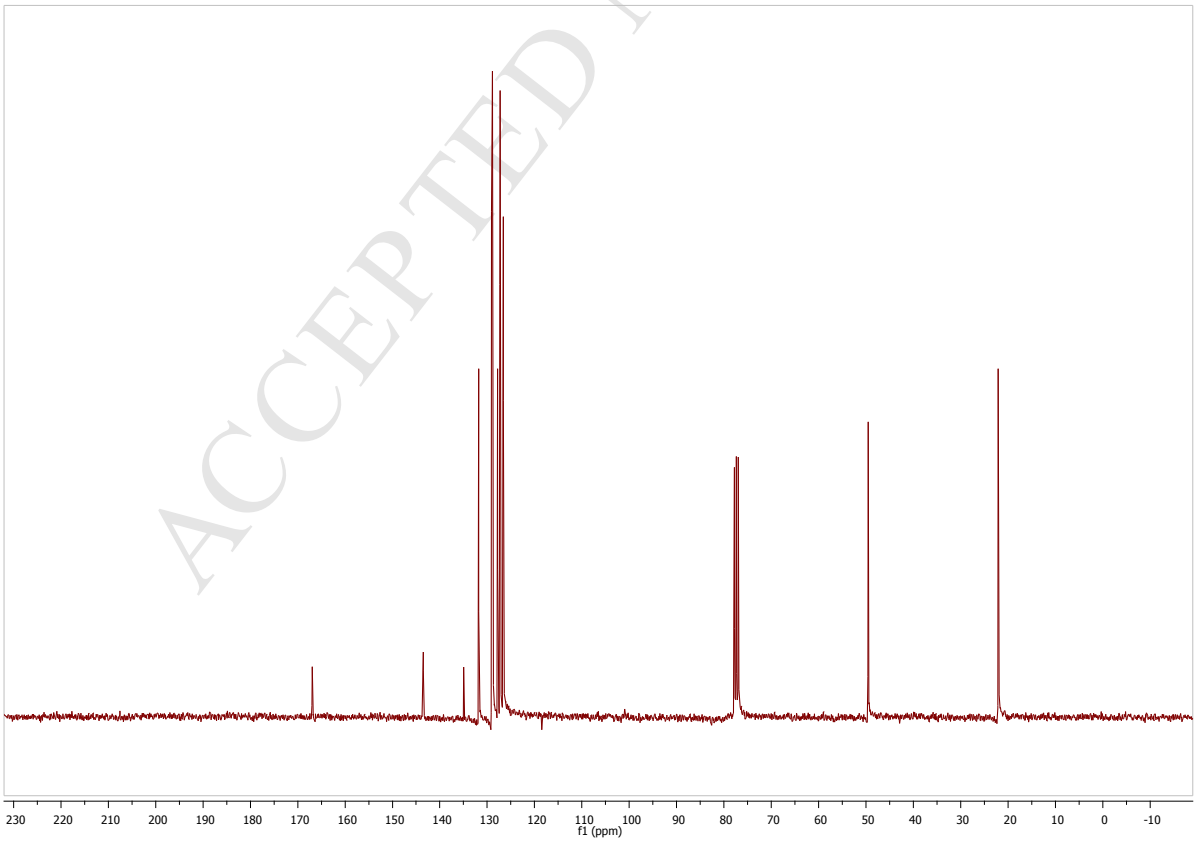
(*R,S*)-*N*-(1-phenylethyl)benzamide



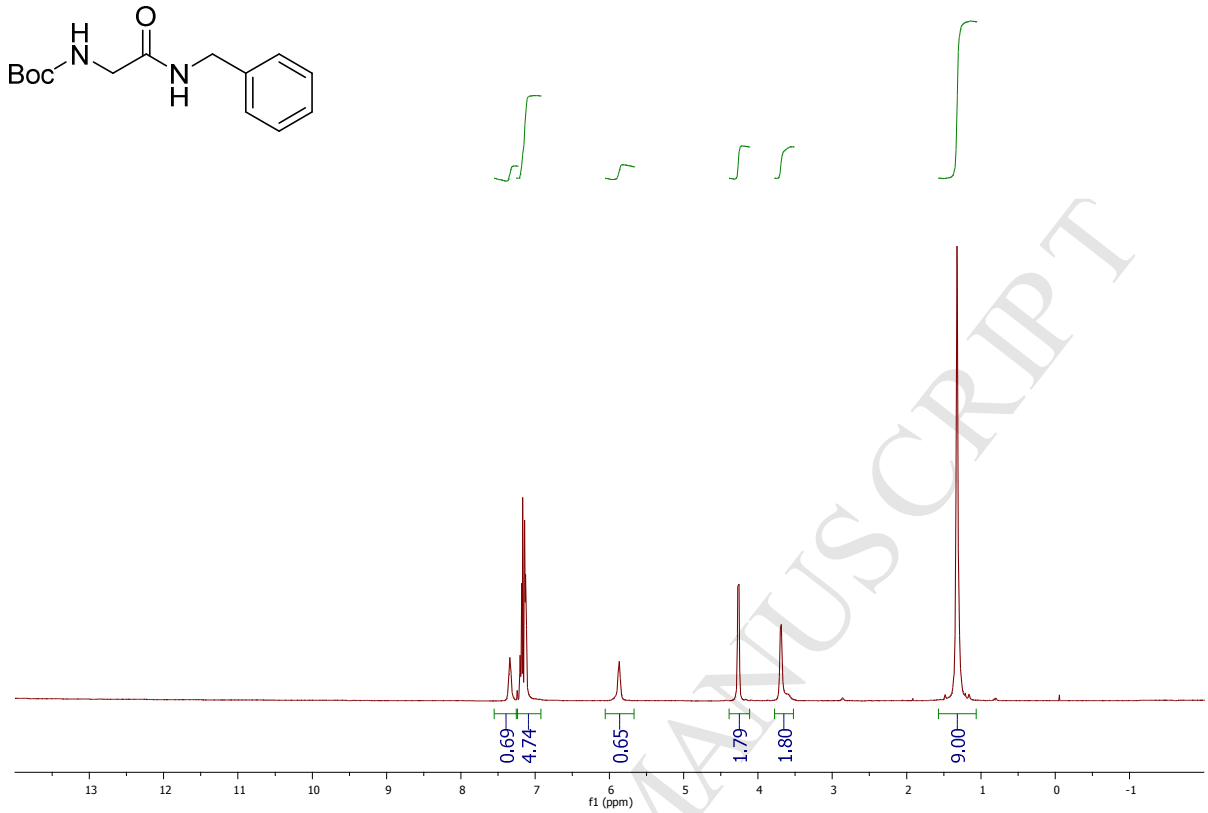


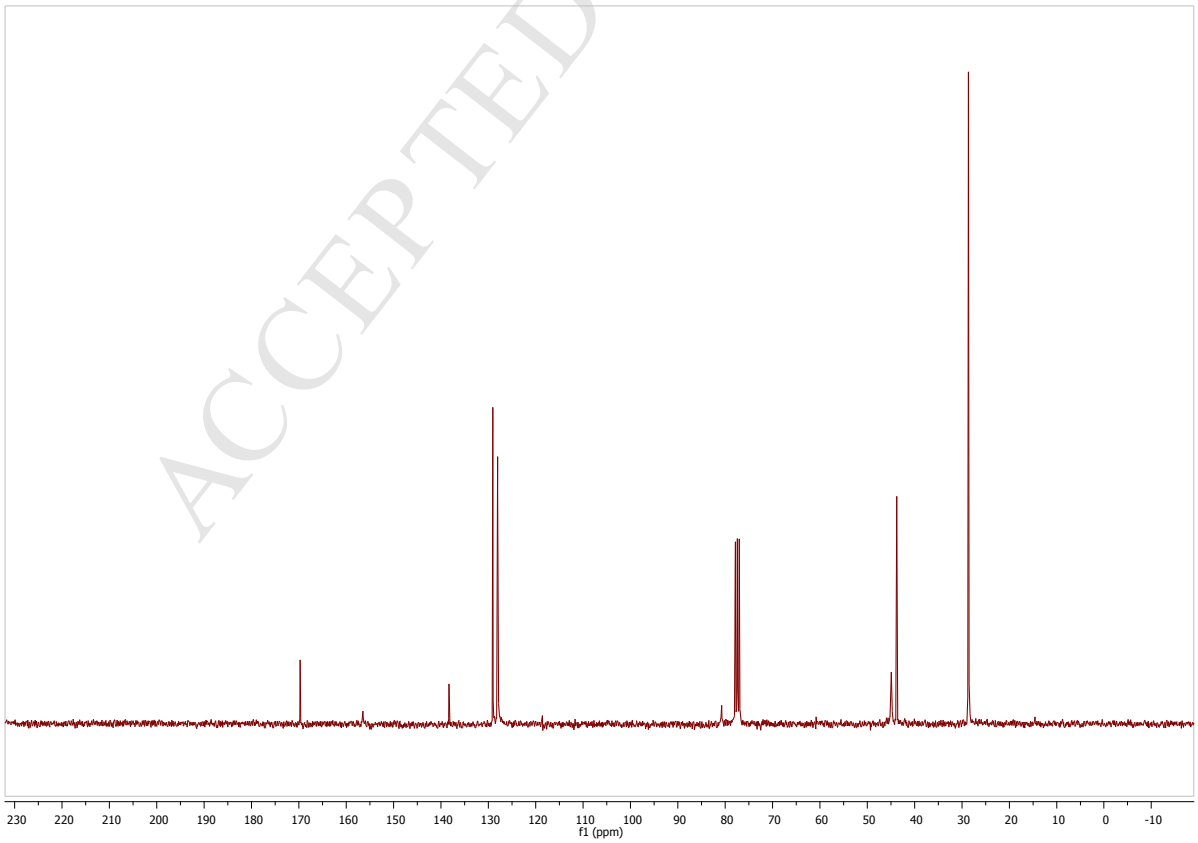
(*S*)-*N*-(1-phenylethyl)benzamide



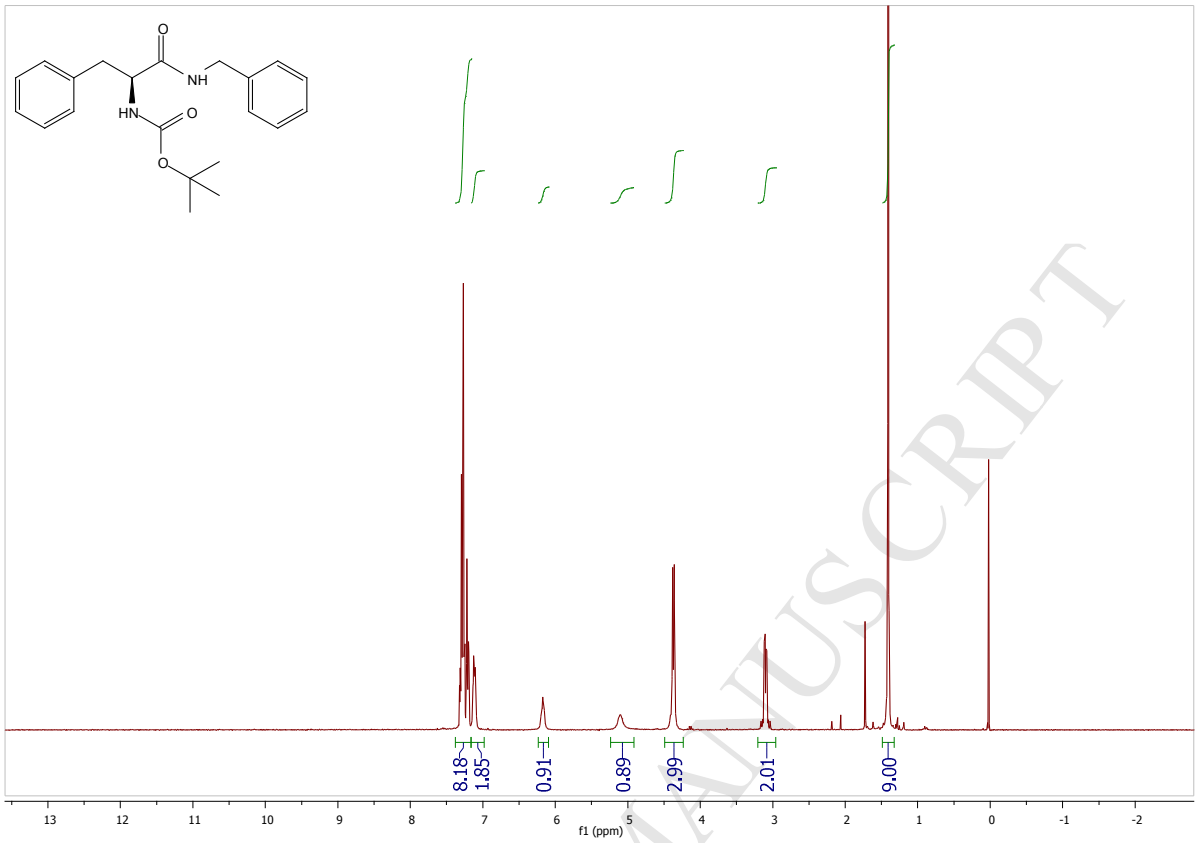


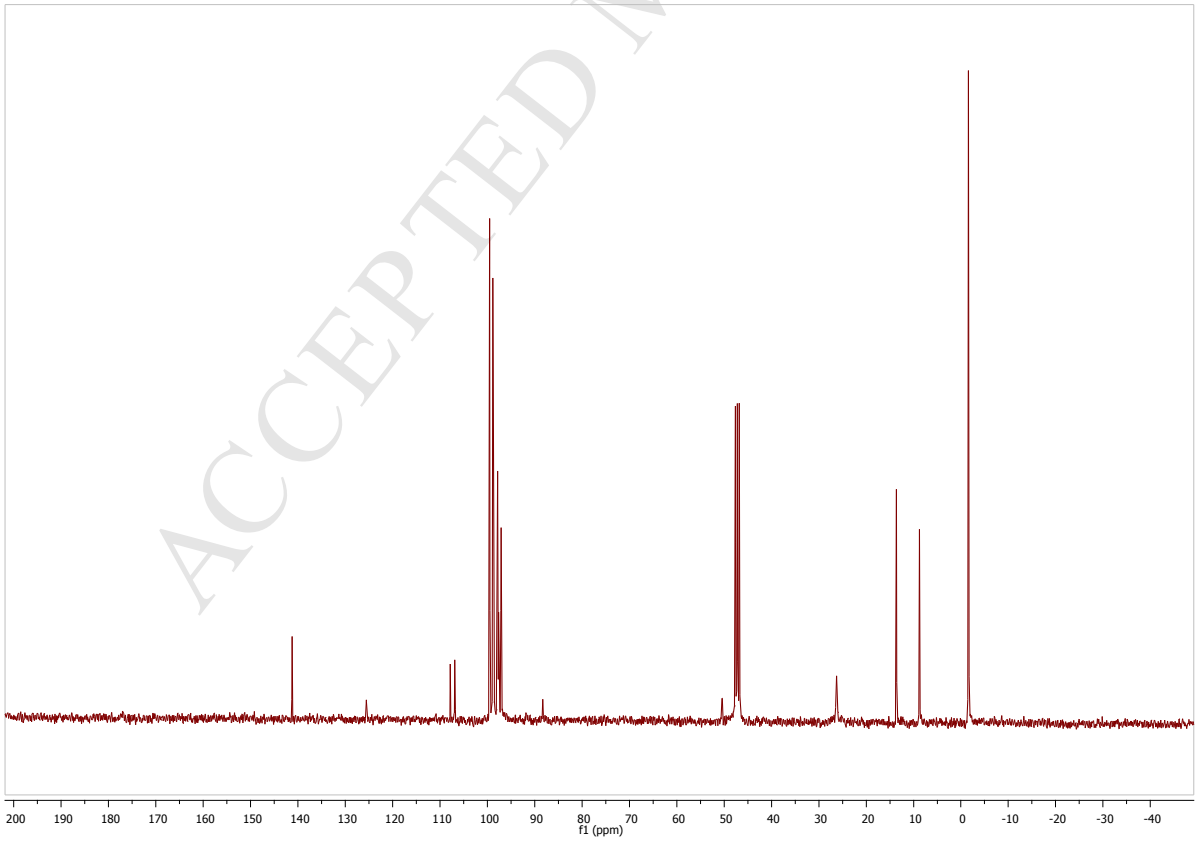
tert-butyl (2-(benzylamino)-2-oxoethyl)carbamate





(S)-tert-Butyl (1-(benzylamino)-1-oxo-3-phenylpropan-2-yl)carbamate





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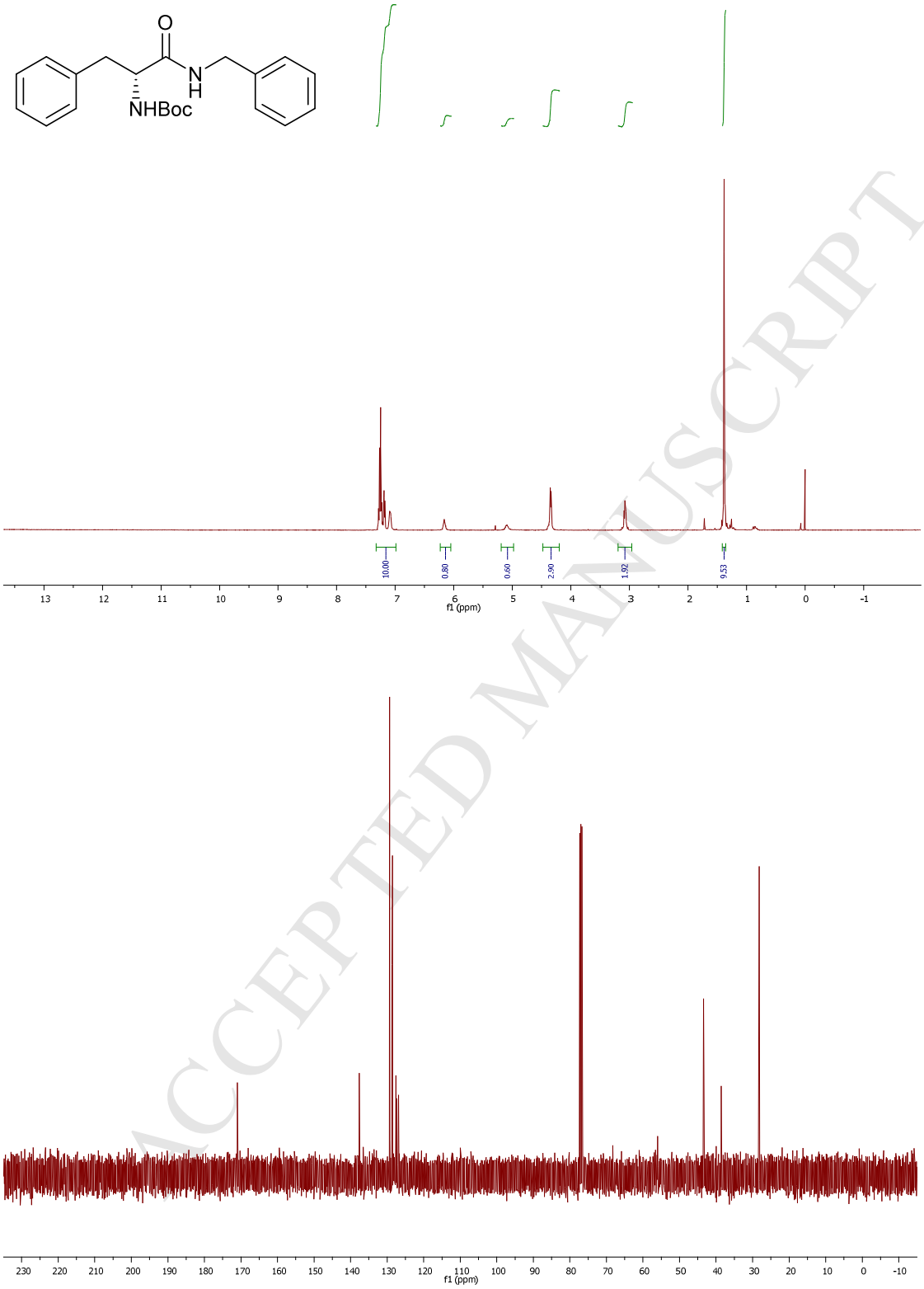
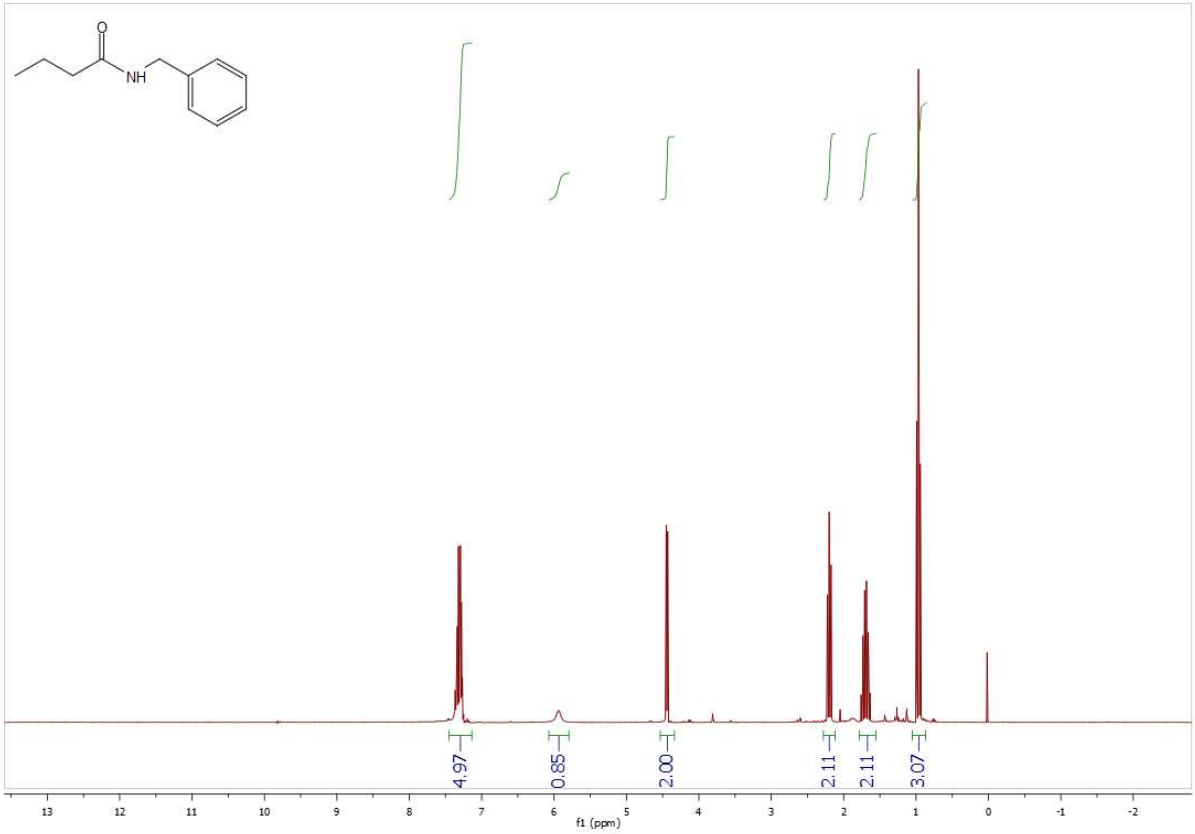
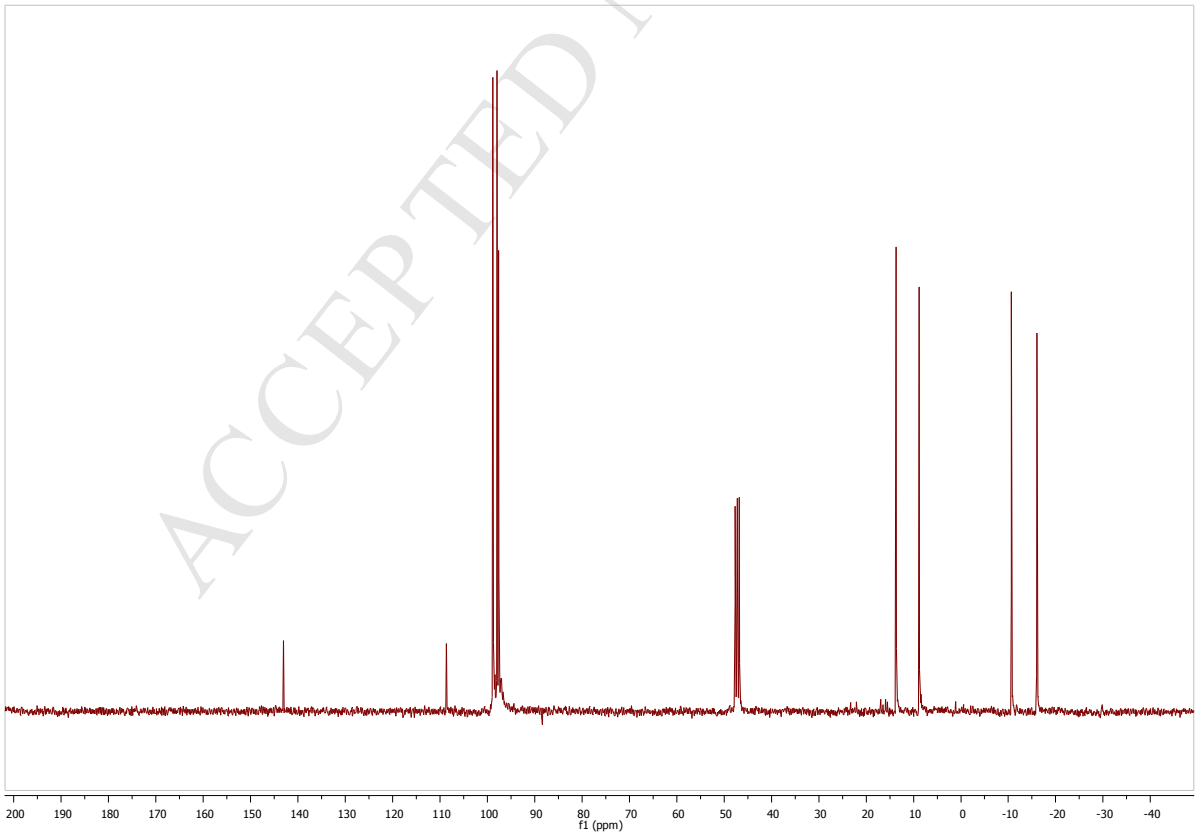


***N*-benzylbutyramide**





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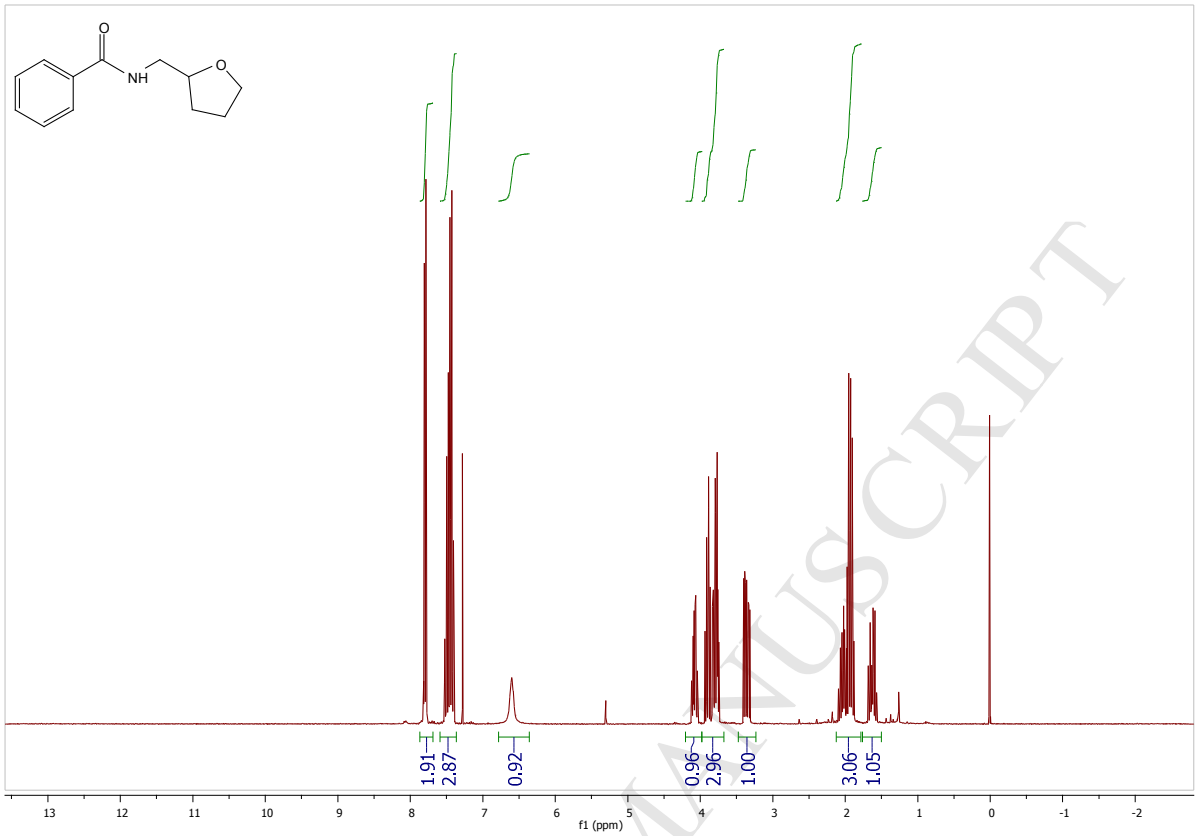
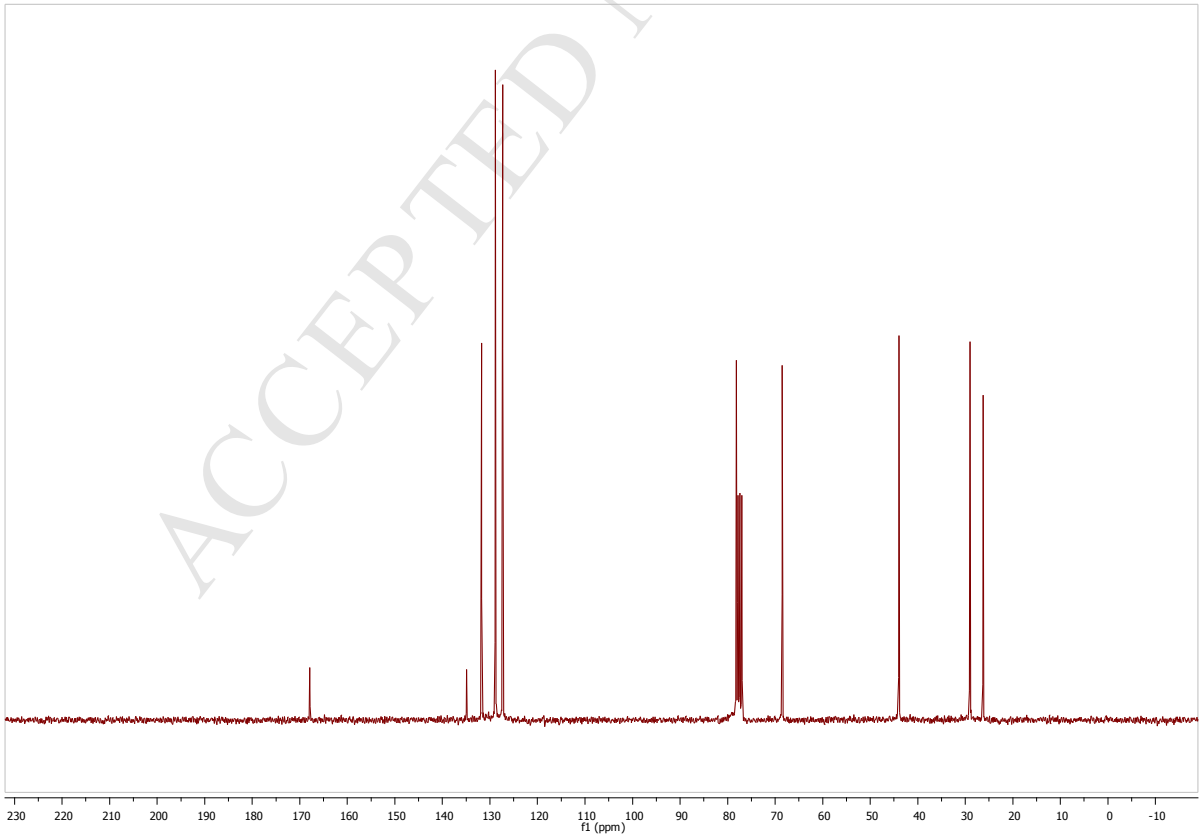
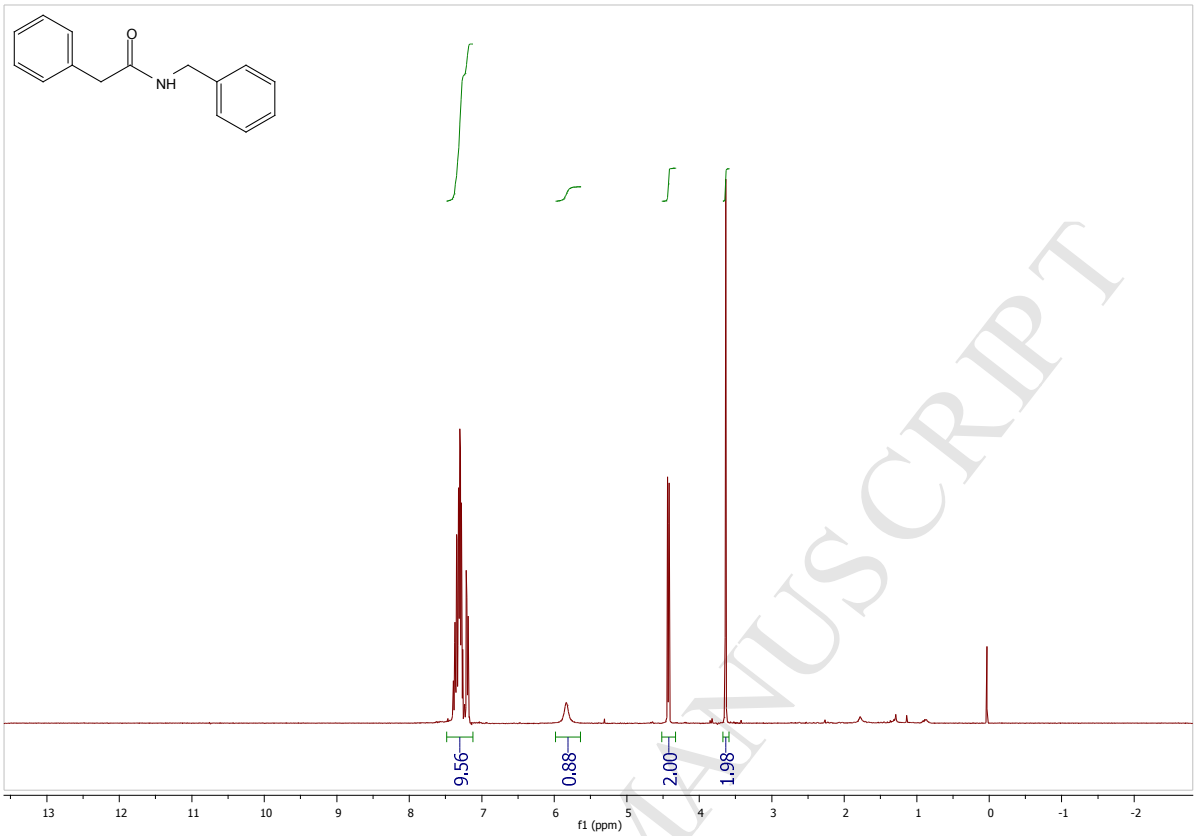
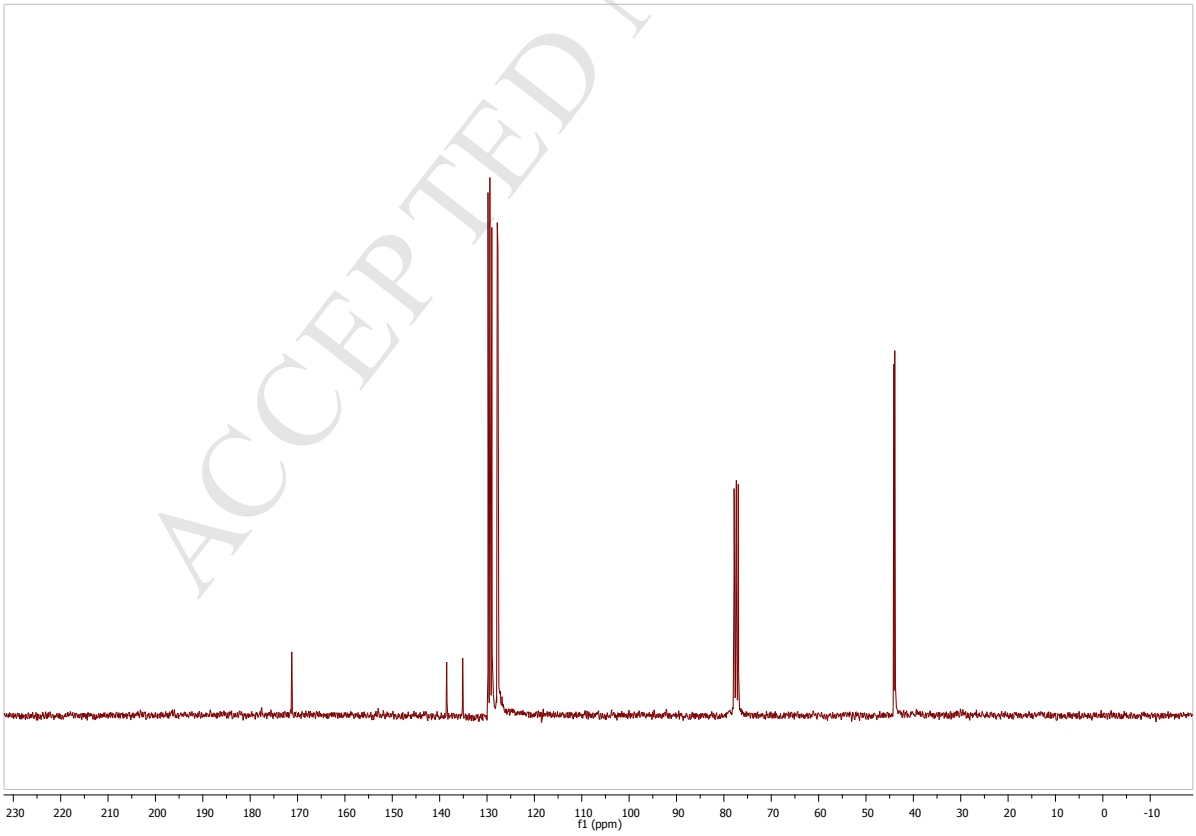


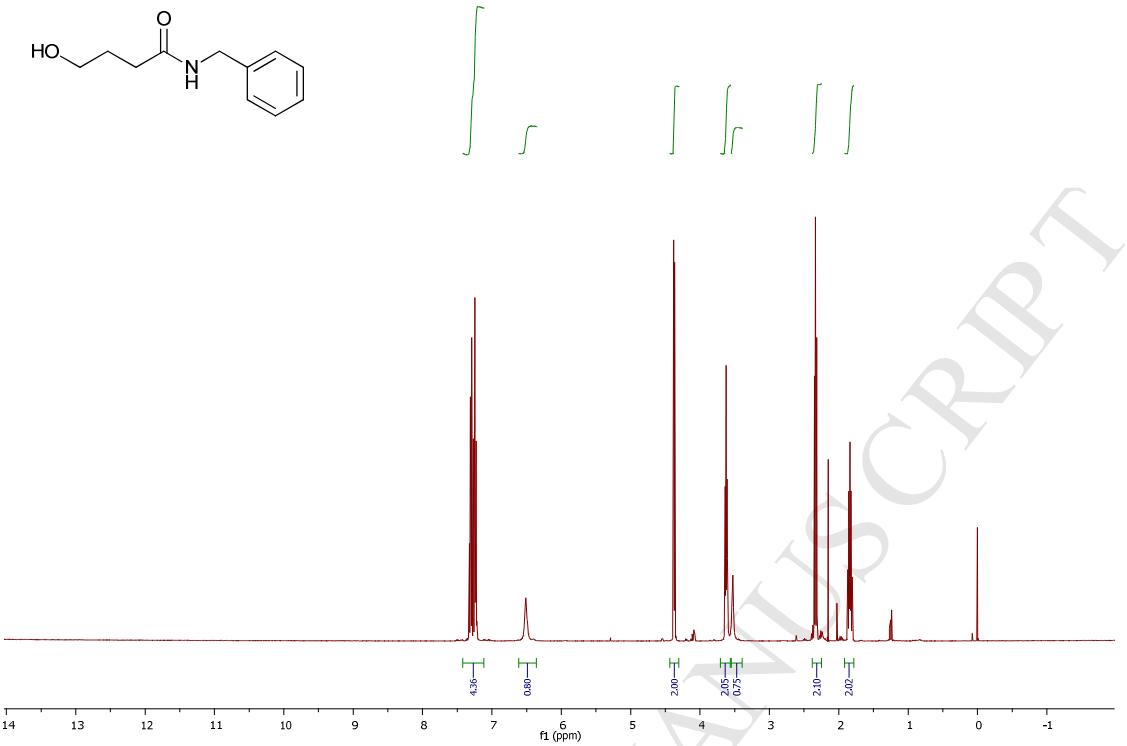


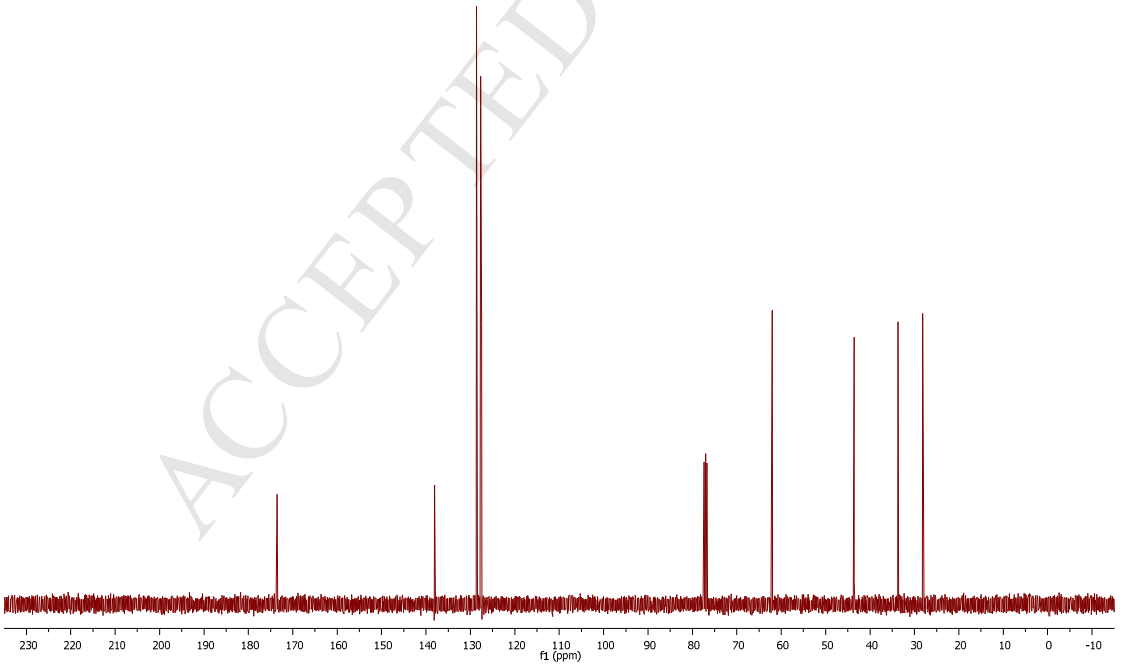
_N_-benzyl-2-phenylacetamide



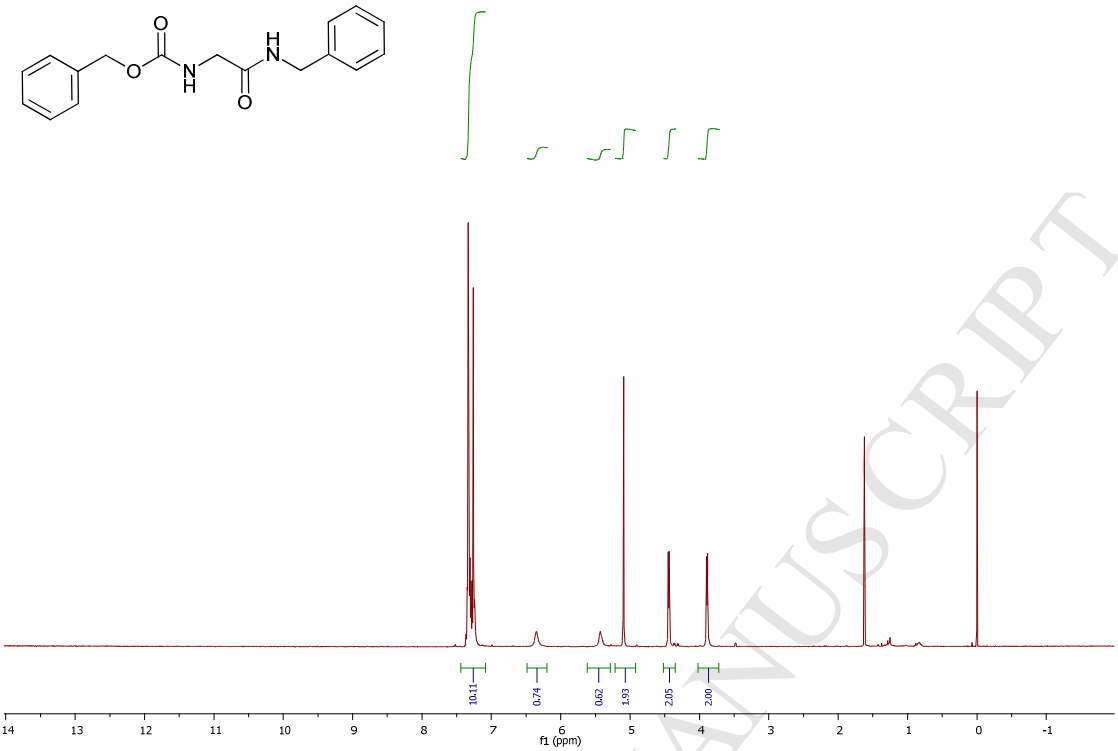


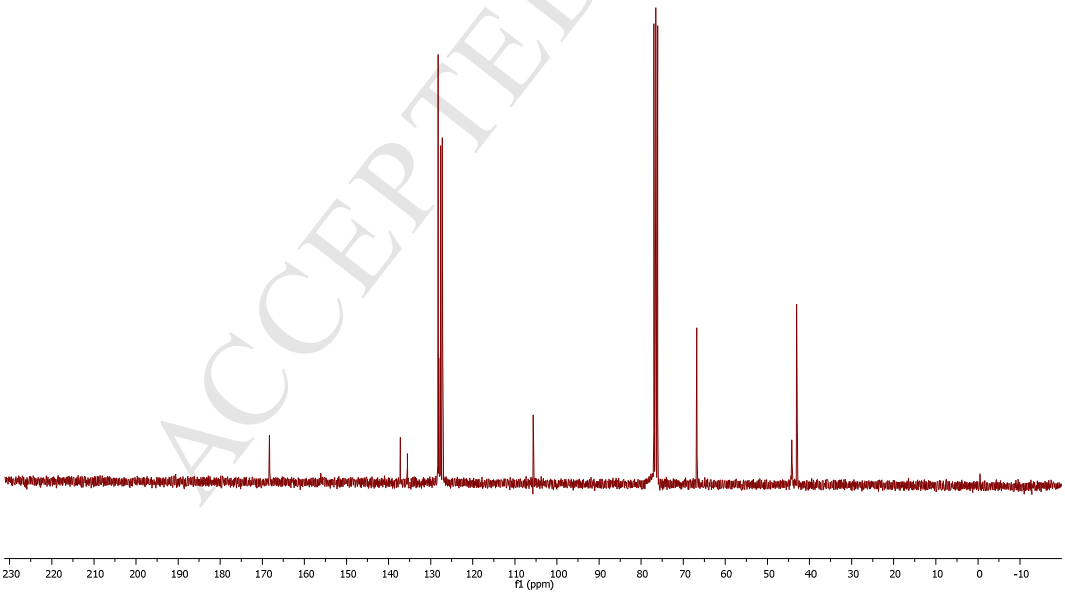
_N_-benzyl-4-hydroxybutanamide



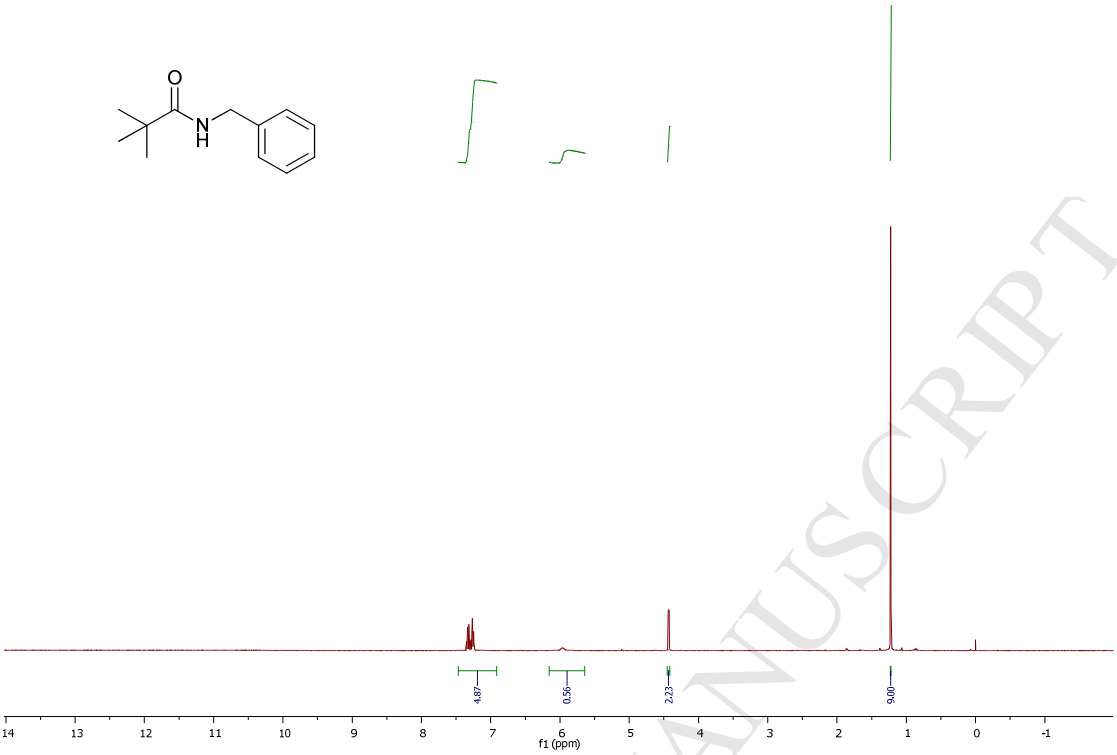


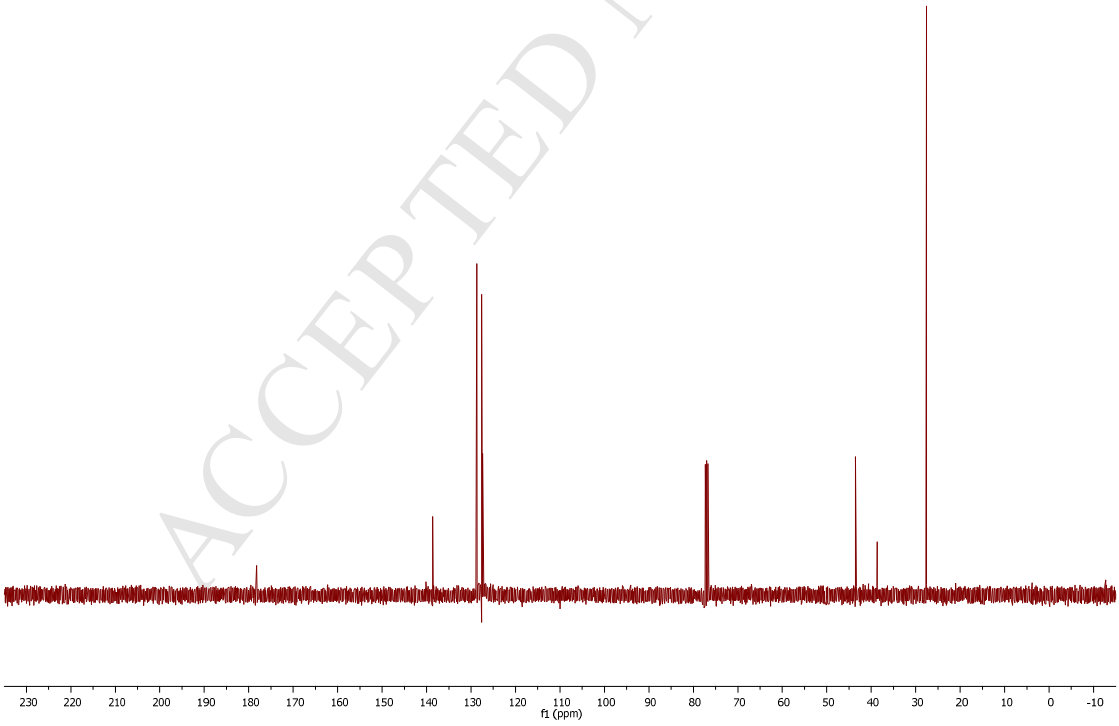
Benzyl (2-(benzylamino)-2-oxoethyl)carbamate



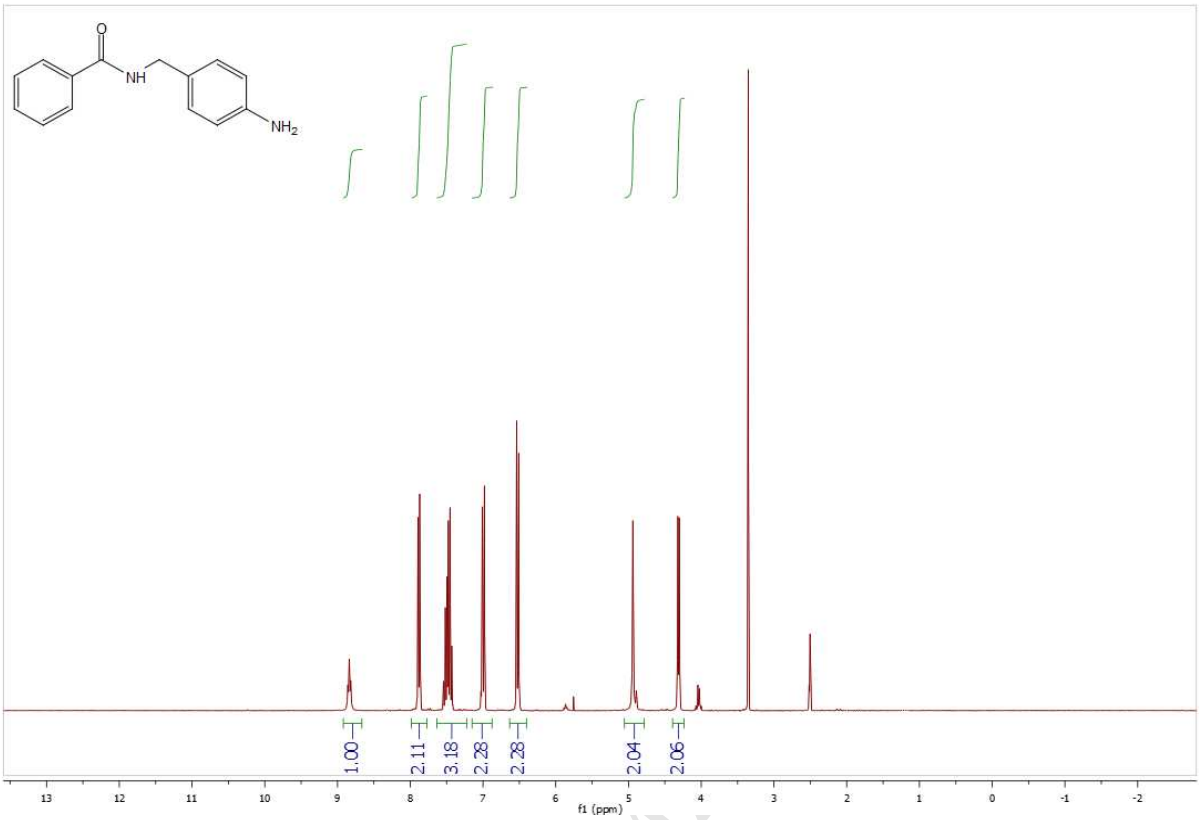


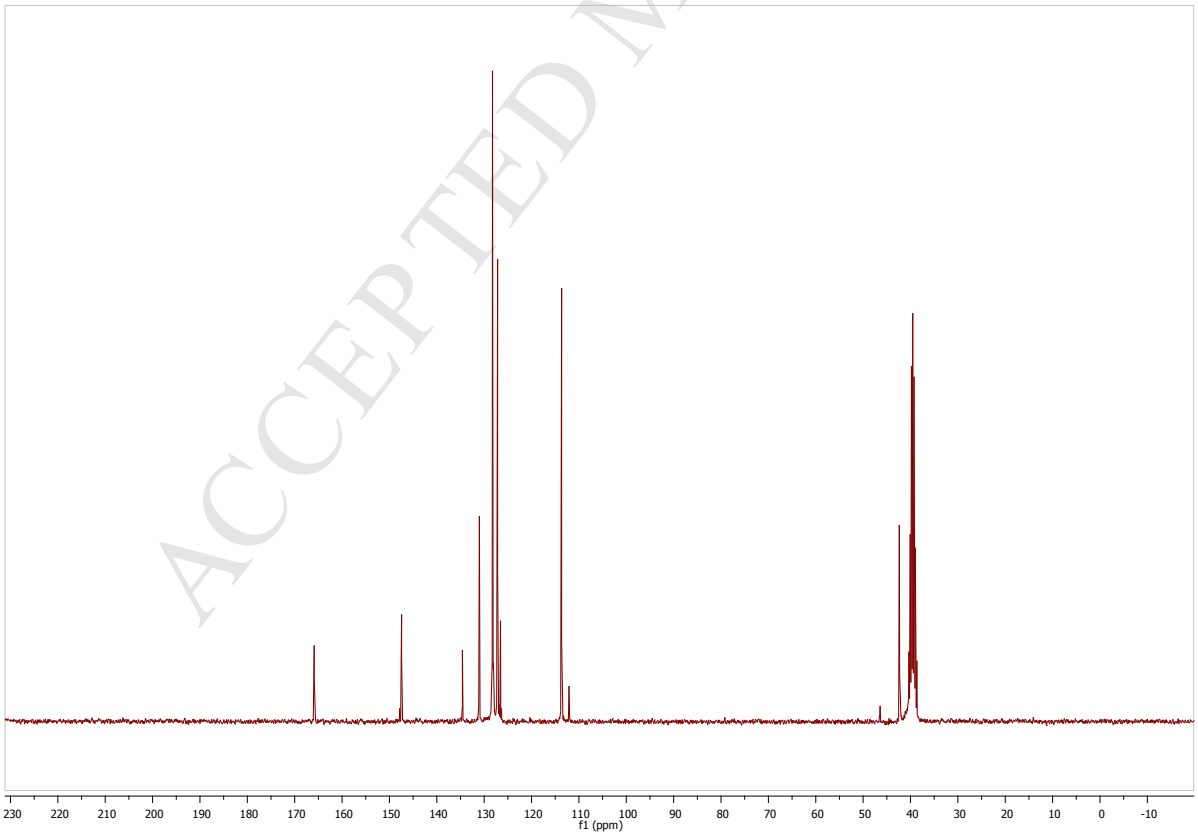
_N_-benzylpivalamide



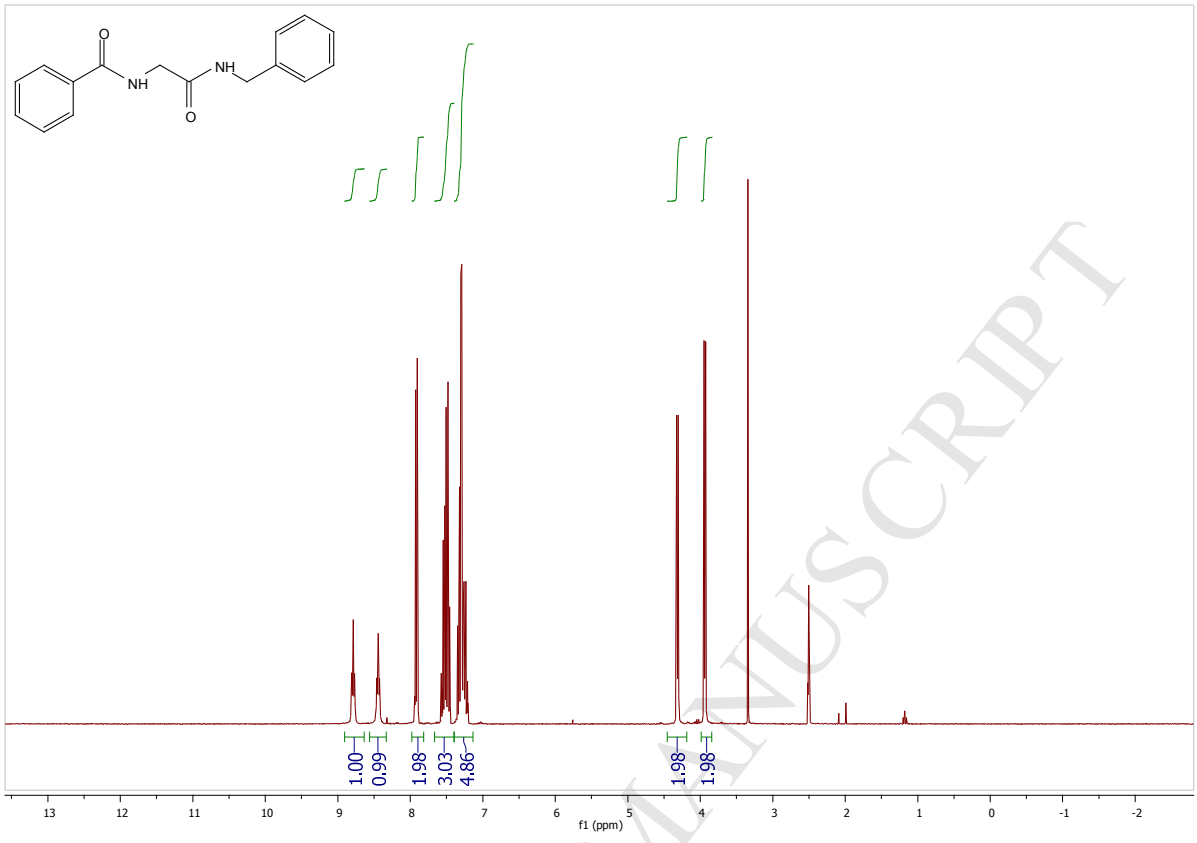


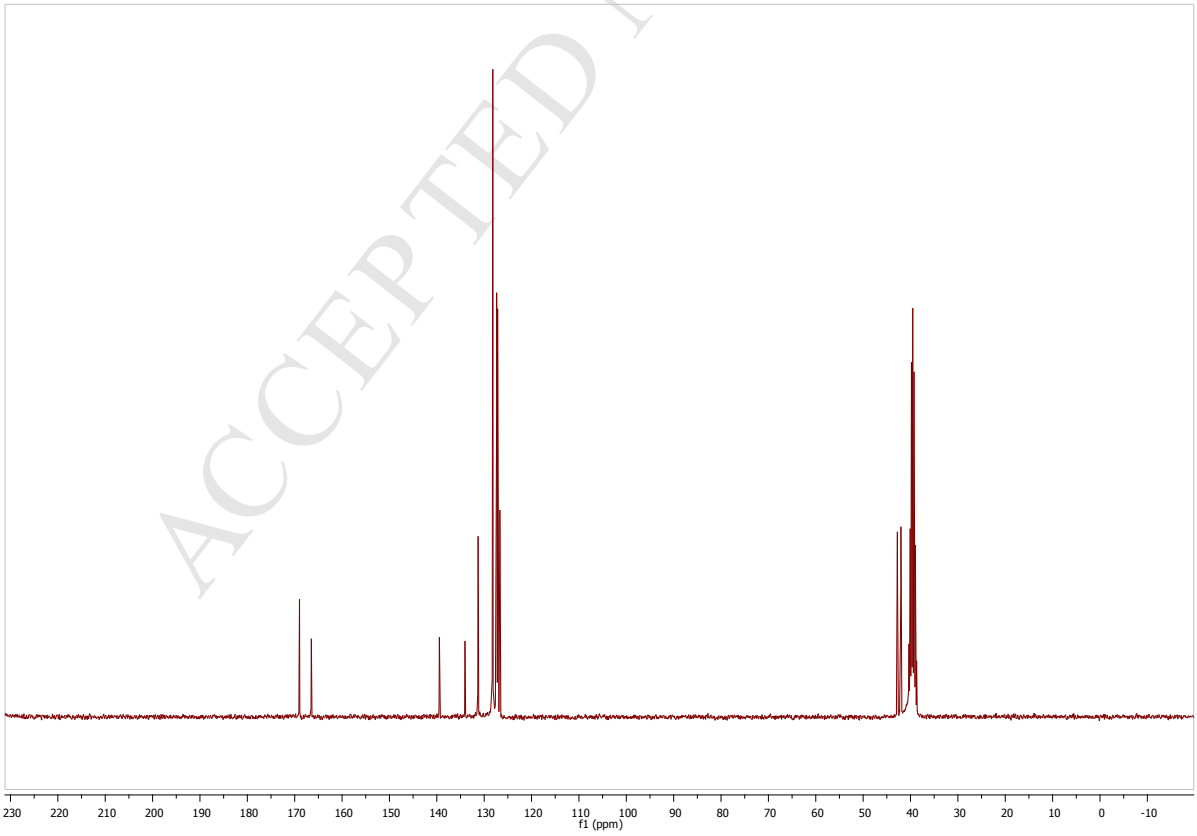
***N*-(4-aminobenzyl)benzamide**



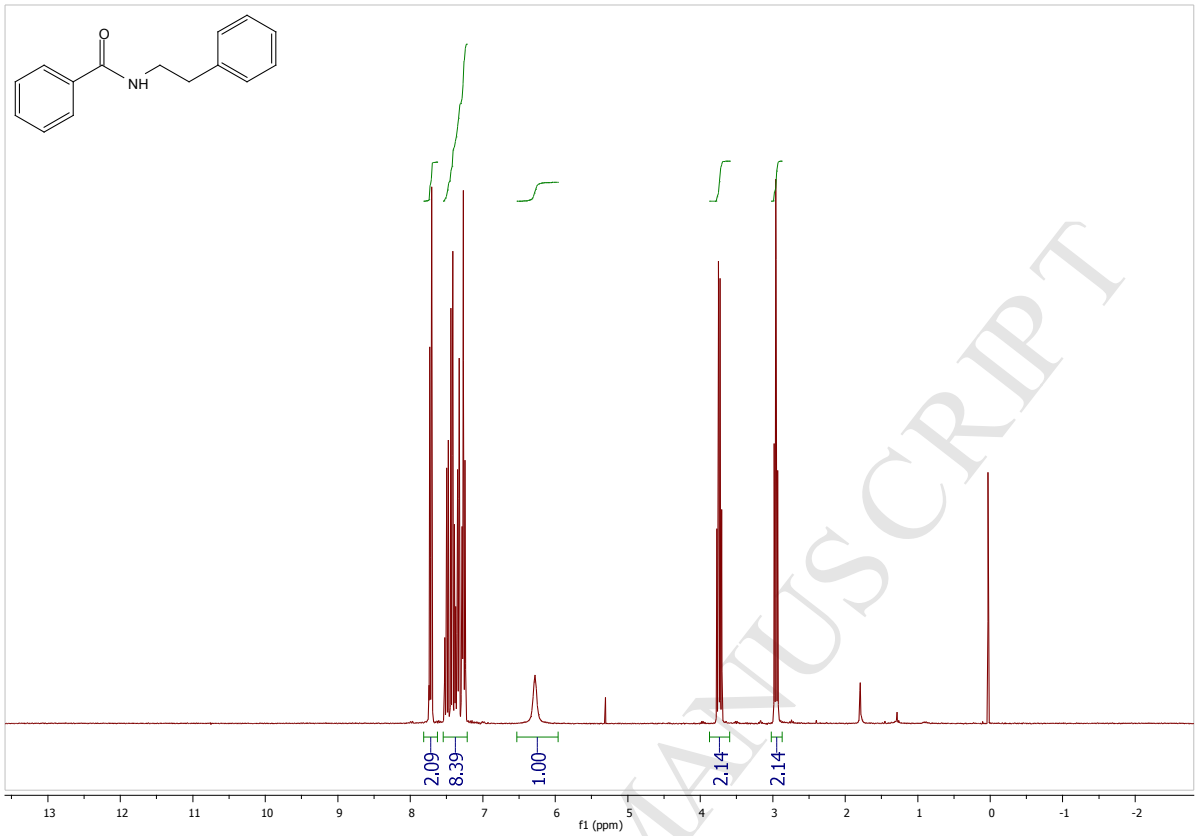


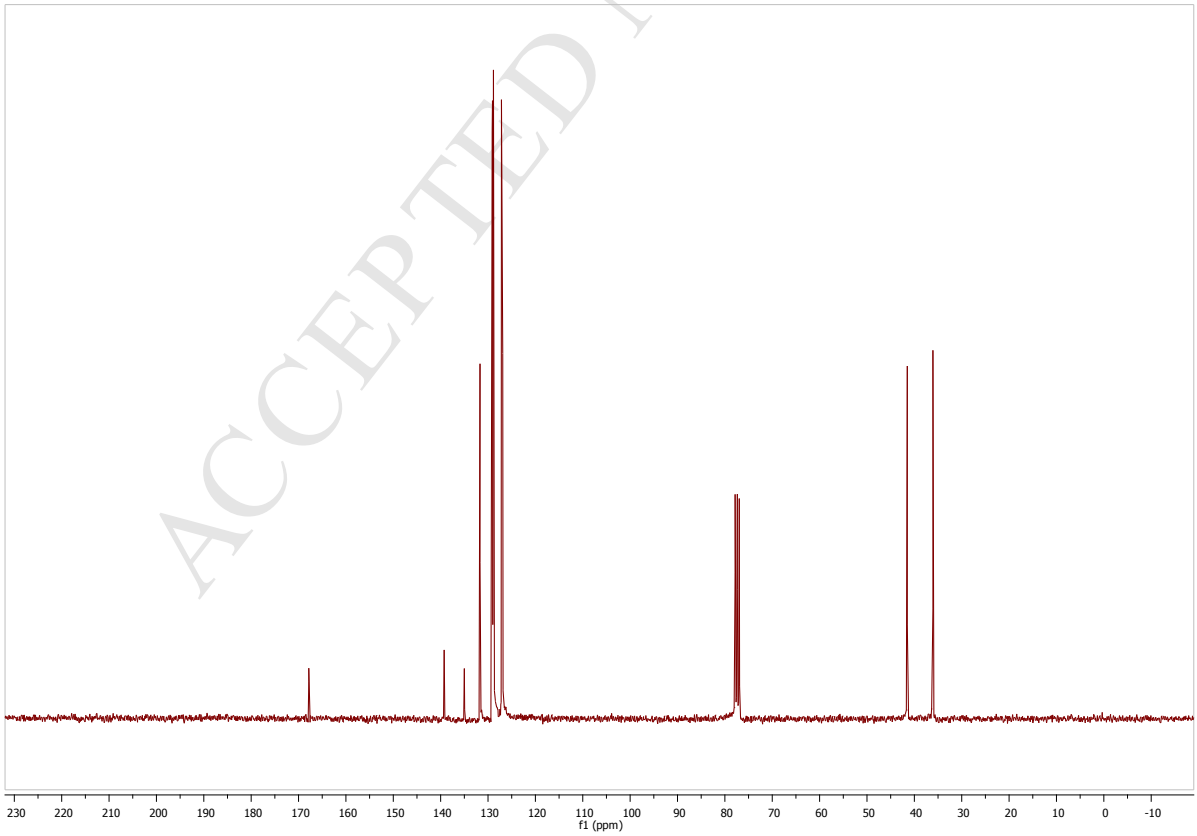
***N*-(2-benzylamino)-2-oxoethyl)benzamide**



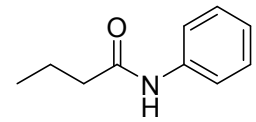


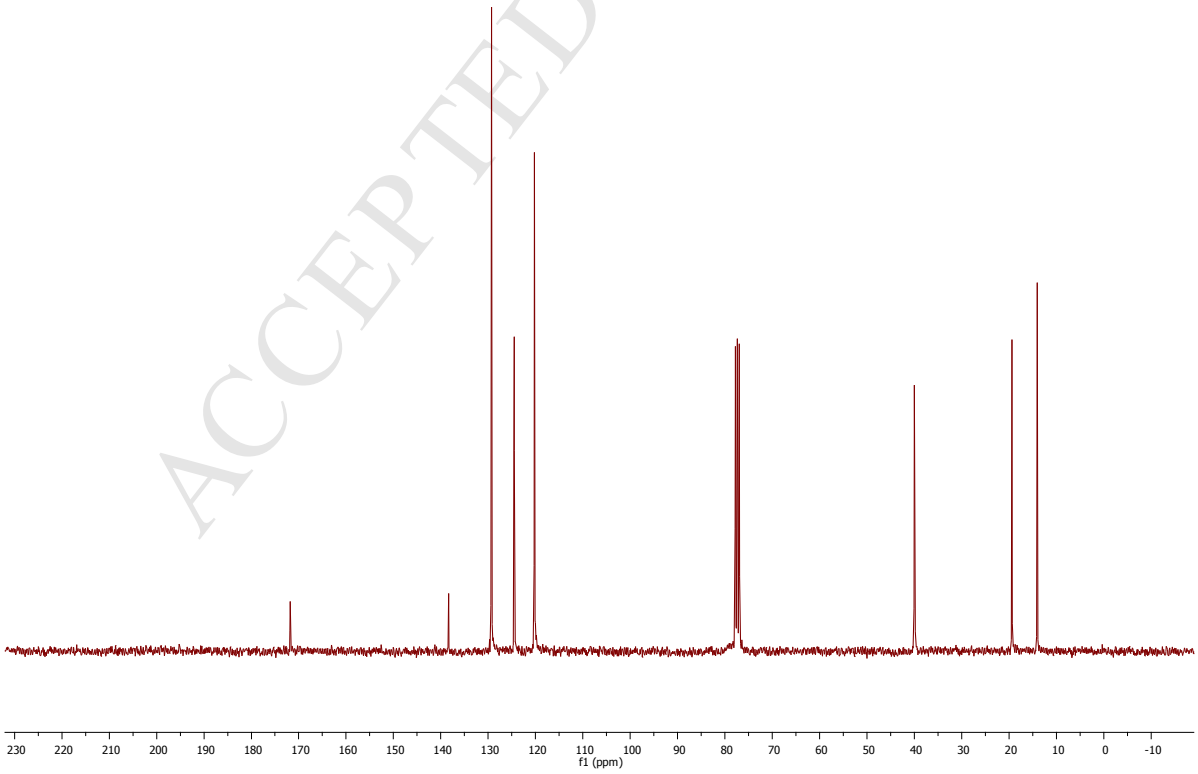
***N*-phenethylbenzamide**



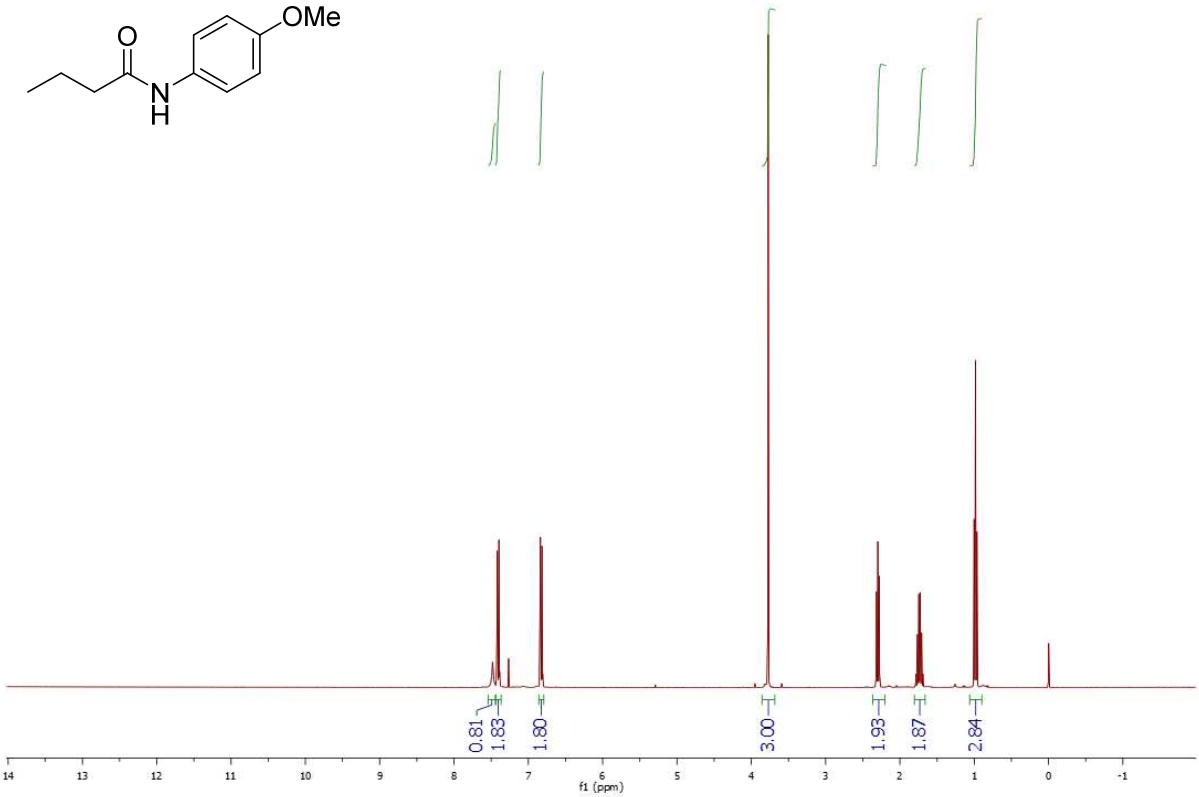


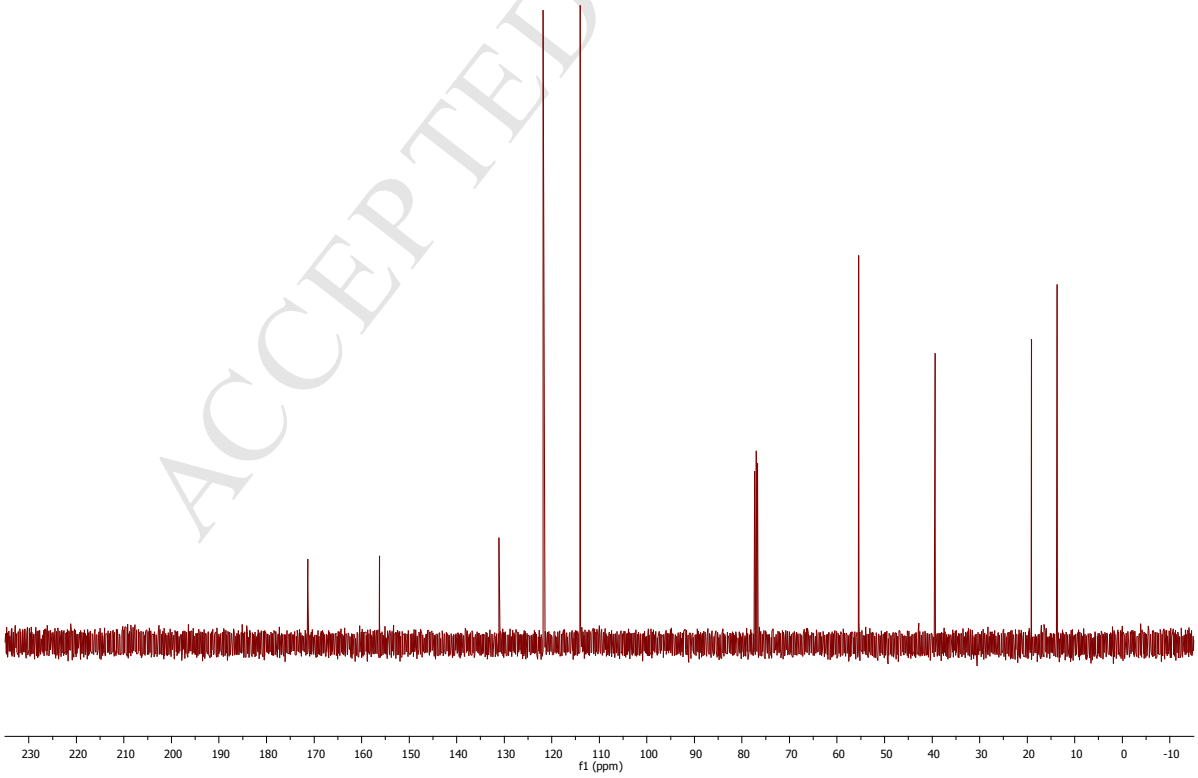
***N*-phenylbutyramide**



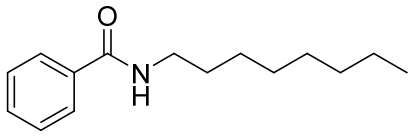


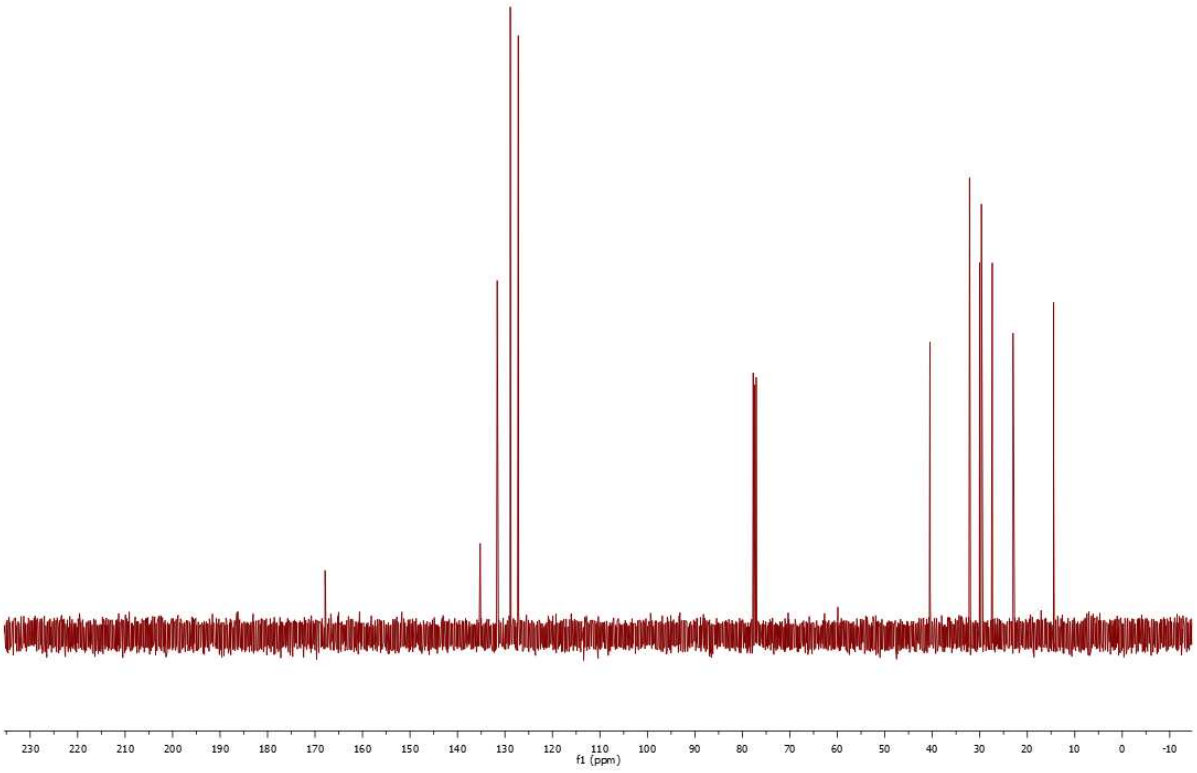
***N*-(p-methoxy)phenylbutyramide**



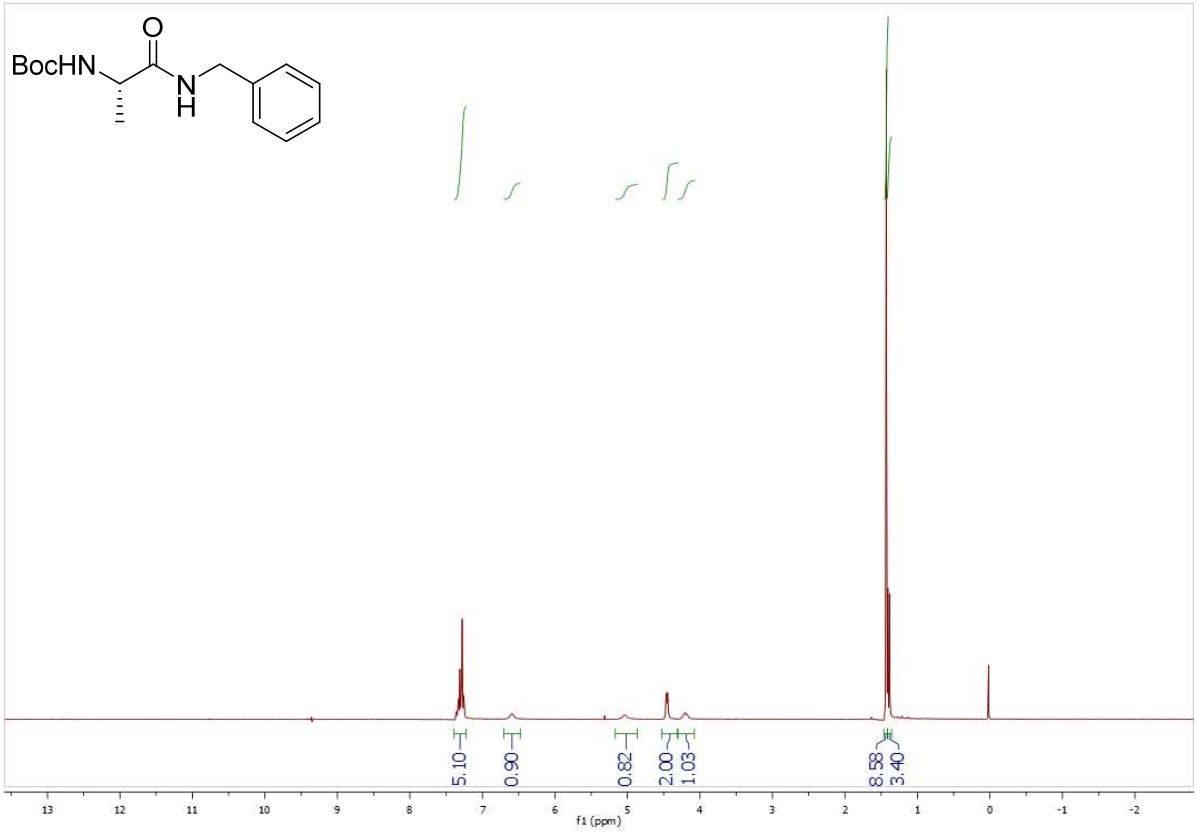


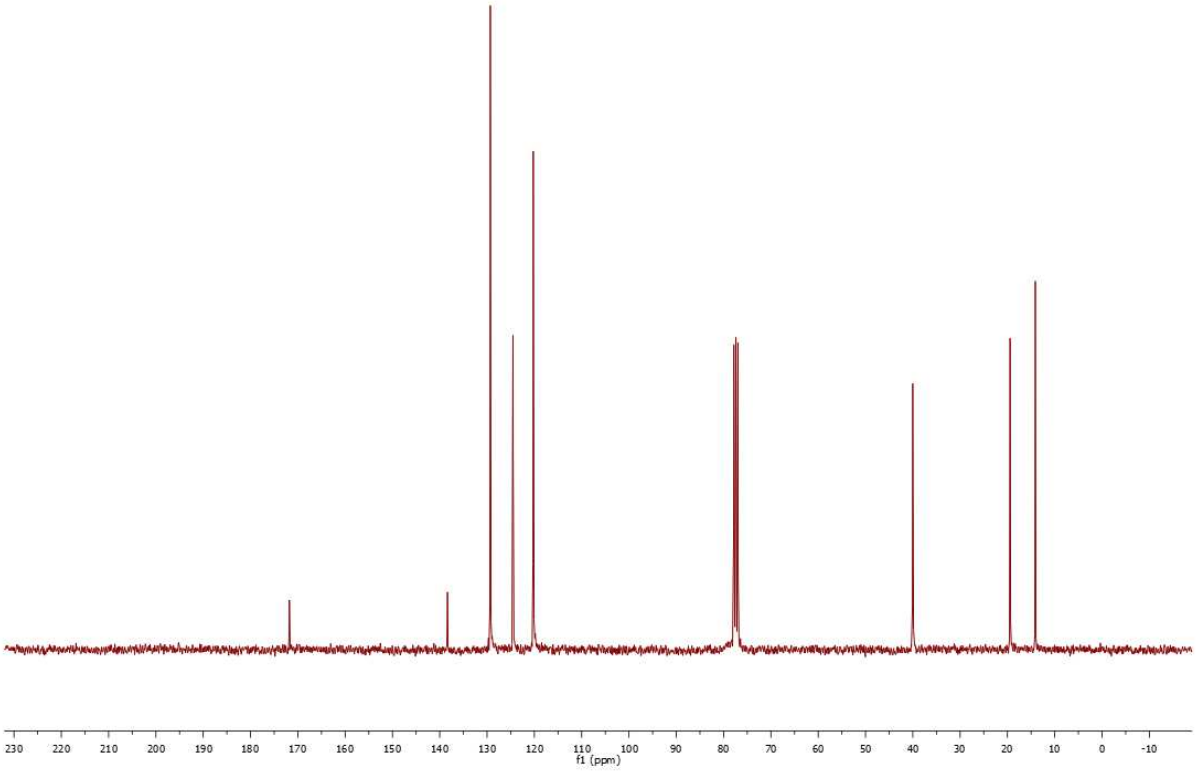
***N*-octylbenzamide**



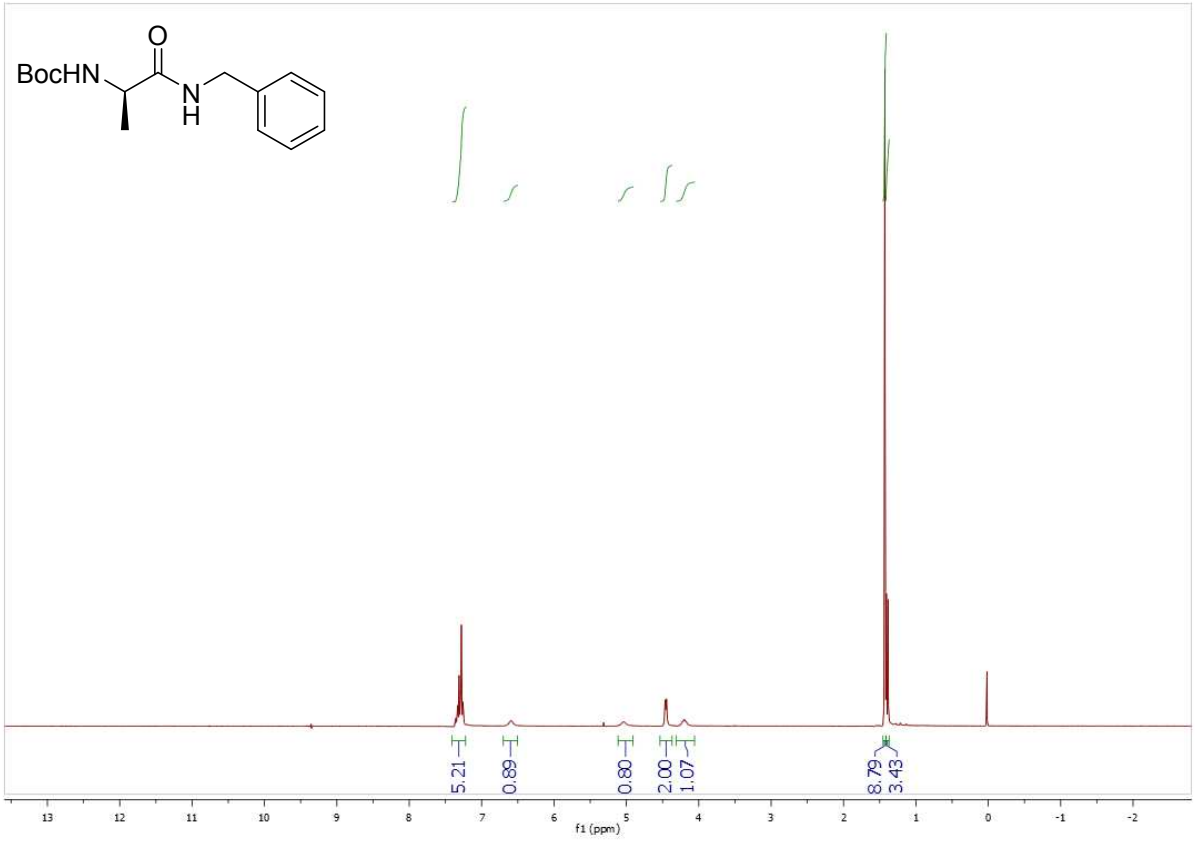


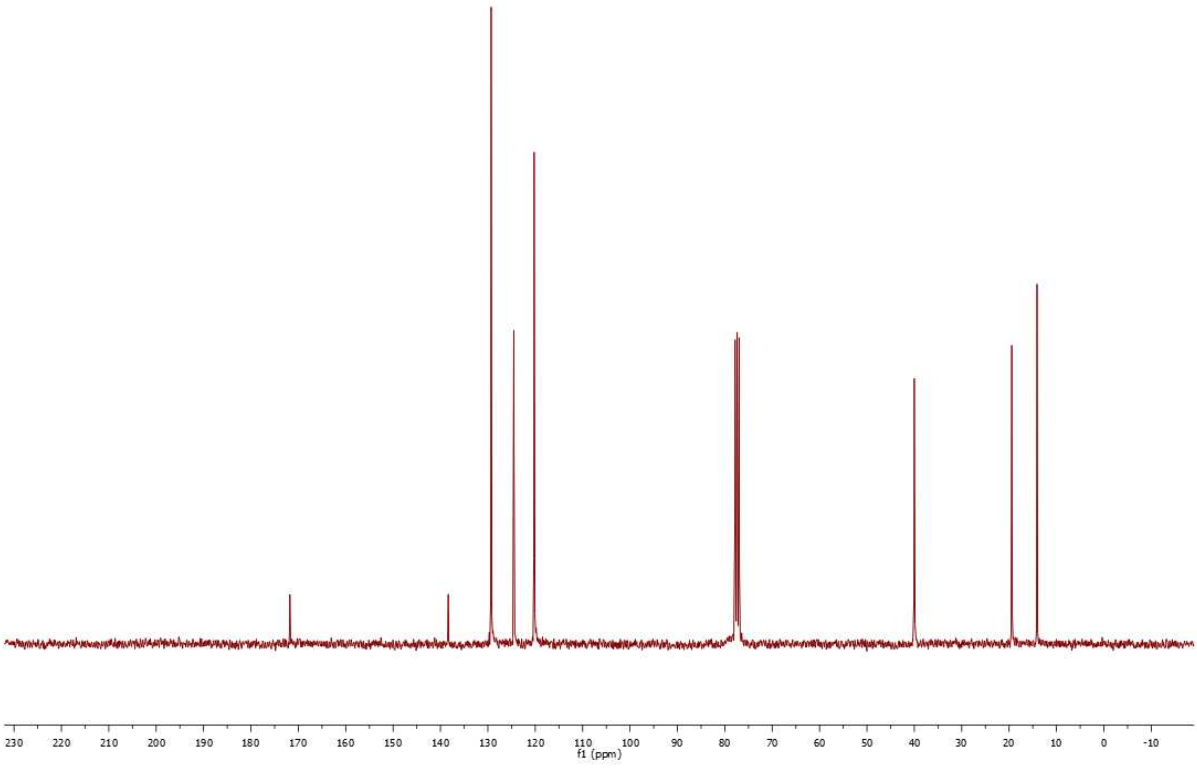
(S)-tert-Butyl (1-(benzylamino)-1-oxopropan-2-yl)carbamate





(R)-tert-Butyl (1-(benzylamino)-1-oxopropan-2-yl)carbamate





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