CHAPTER 3

Microwave-Assisted Chemoselective Transamidation of Secondary Amides by Selective N-C(O) Bond Cleavage Under Catalyst, Additive and Solvent-Free Conditions

Chapter 3

Microwave-Assisted Chemoselective Transamidation of Secondary Amides by Selective N-C(O) Bond Cleavage under Catalyst, Additive and Solvent-Free Conditions

3.1 Introduction

The amides constitute a crucial functional group in pharmaceutical chemistry, polymer science, and synthetic chemistry [1–4]. Various health disorders can be prevented as well as treated with the carboxamide functional group containing moieties [5–7] (**Figure 3.1)**. Due to the significance of amides, a great deal of work has been put into creating synthetic processes for producing a variety of amides. The most promising method for creating amide bonds among the several methods is the transamidation of amide with amine [8, 9] which offers a straightforward, rapid approach with good atom economy. Although transamidation of secondary amides is challenging but due to the importance of secondary amides in natural products and pharmacologically active molecules [10, 11], the recent focus was given to this group of substrates.

Garg and co-workers have developed two-step strategies for the transamidation of secondary amides, in the first step amides were activated through steric and electronic distortion of the N−C(O) amide bond to give non-planar *N*-Boc amides. In the second step, transamidation with various nucleophilic amines in the presence of Ni catalyst was achieved [12–14].

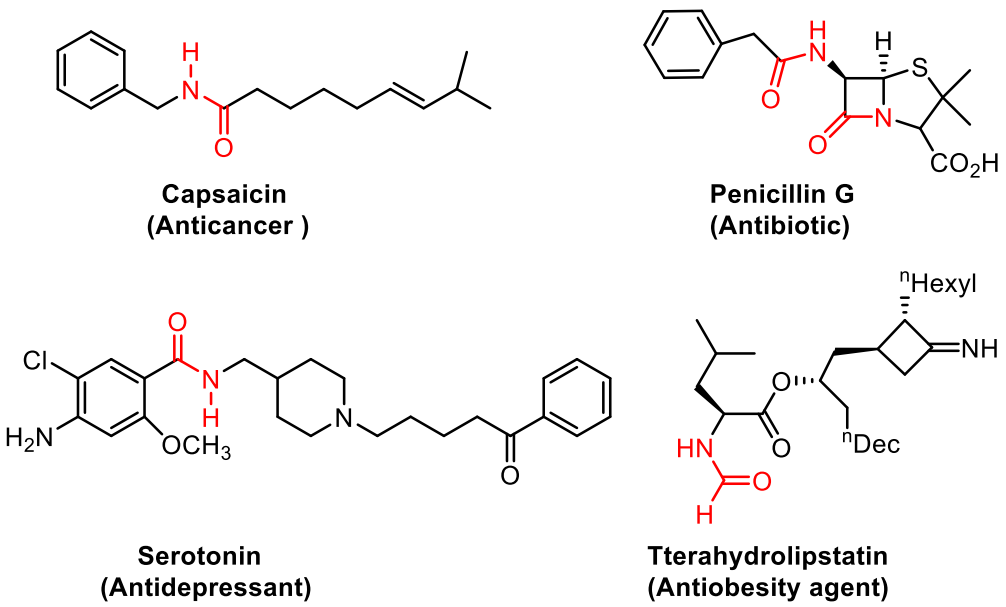
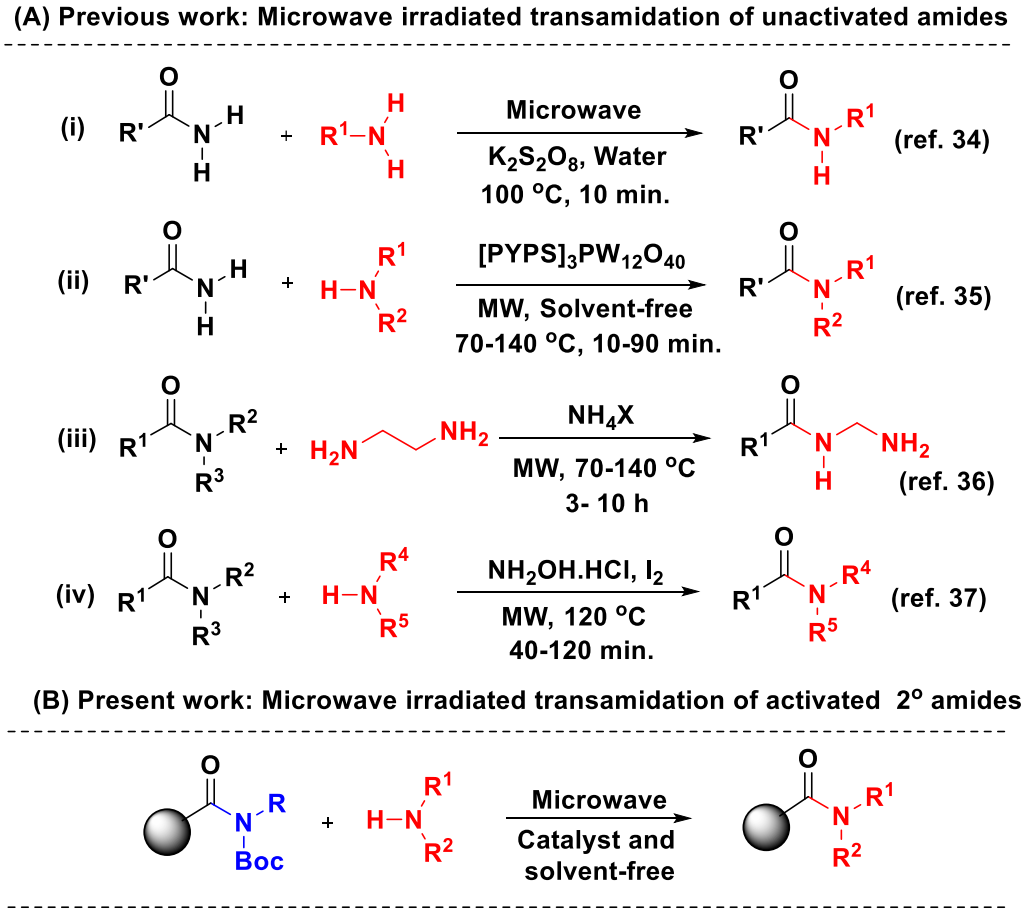


Figure 3.1 Some examples of bioactive substituted amides.

On the other hand, Szostak and co-workers have demonstrated transamidation of *N*-*tert*-butoxycarbonyl (*N*-Boc) [15, 16], *N*-toluenesulphonate (*N*-Ts) activated secondary amides with palladium [17–20], base catalysts [21], and recently in the absence of any additives under mild conditions [22]. Recently transamidation of *N*-Boc, *N*-nitroso, *N*-tosyl and *N*-pivaloyl activated primary and secondary amides have been reported without any catalyst under mild conditions [23–28], and Xile Hu et. al reported nickel-catalyzed reductive transamidation of secondary amides with nitroarenes as the nitrogen source [29].

Microwave irradiations (MWI) are a non-conventional and environmentally friendly energy source and have been successfully employed recently to promote organic transformations [30–33]. A handful number of microwave-irradiated transamidation has

been reported including transamidation of unactivated primary amides with $K_2S_2O_8$ [34], heteropoly anion-based ionic liquids as catalysts [35], and transamidation of tertiary amides with ammonium-salt as catalyst [36], unactivated primary, secondary, and tertiary amides using iodine and hydroxylamine hydrochloride as a catalyst [37].



Scheme 3.1 (A) Previous work: microwave irradiated transamidation of unactivated amides (i-iv). **(B)** Present work: catalyst and solvent-free, chemoselective transamidation of *N*-Boc secondary amides.

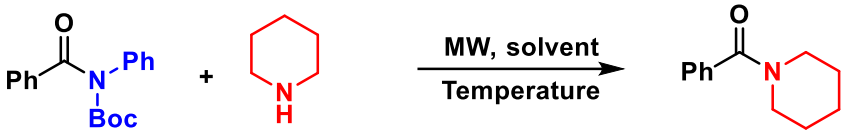
However, despite their several merits, the transamidation reactions of unactivated secondary amides took a longer time and involved a catalyst. The transamidation reactions

can be easily carried out for primary or tertiary amides without the prerequisite of amide activation, while transamidation of secondary amides involves the use of activated amides. Therefore, the development of a simple, catalyst-free, metal-free, additive-free, and environmentally acceptable approach for transamidation of activated secondary amides via unconventional methods is still in demand.

Using non-toxic solvents and planning for energy efficiency are the two most important green chemistry concepts in organic synthesis [38–40]. This demanded to switch from conventional thermal procedures to non-conventional methods while synthesising organic compounds. In 2018, we reported cerium-catalyzed transamidation of *N*-($COCF_3$) activated secondary amides through a non-conventional heating system under ultrasonic irradiation [41]. This encouraged the use of non-conventional heating system for transamidation reactions. Herein, we utilized a microwave-irradiated green method for a metal and additive-free transamidation of *N*-Boc activated secondary amides under solvent free-conditions. Microwave technology has received a lot of attention in the field of organic synthesis, because microwaves can speed up the rate of reaction and frequently noticeably shorten the reaction time, provide better yields and higher purity, uniform, and selective heating with lower energy usage, achieve greater reproducibility of reactions, and aid in developing convenient and cleaner synthetic routes [31, 42–44]. The primary goal of employing microwave technology was to make this transition as "green" as possible by increasing reaction efficiency and reducing the time and energy required for the reaction.

As far as our knowledge this is the first report on transamidation of *N*-Boc activated secondary amides under microwave irradiation (**Scheme 3.1**).

Table 3.1 Optimization of reaction conditions for transamidation of *N*-Boc, *N*-phenylbenzamide under microwave irradiation[a]



1a 2a 3a

Entry	Solvent	microwave power (W)	Temp. (°C)	Time (min.)	Yields (%)[b]
1	Water	150	60	60	30
2	Ethanol	150	60	60	35
3	Methanol	150	60	60	38
4	1,4 Dioxane	150	60	60	32
5	DMF	150	60	60	55
6	DMSO	150	60	60	45
7	Acetonitrile	150	60	60	40
8	-	150	60	15	62
9	-	200	60	12	75
10	-	300	60	10	80
11	-	350	60	10	80
12	-	300	70	10	85
13	-	**300**	**80**	**8**	**93**
14	-	300	100	8	93
15[c]	-	-	80	4 h	20

[a]**Reaction conditions:** *tert*-butylbenzoyl(phenyl)carbamate **1a** (1. 0 mmol), piperidine **2a** (1.5 mmol), in solvent (1ml) under Microwave-irradiation. [b]Isolated yield. [c]Conventional heating at 80 °C for 4 h.

3.2 Result and discussion

3.2.1 Optimization of reaction conditions

Initially, the unactivated amide, such as *N*-phenyl benzamide, was subjected to the transamidation reaction with piperidine **2a** to obtain the product **3a**. The reaction was conducted under microwave irradiation without catalysts, additives, and promoters at 150 W. However, the desired product **3a** was not obtained under the above-said conditions. Then we performed the reaction with *N*-activated secondary amide, *i.e.*, *N*-Boc, *N*-phenylbenzamide **1a** with piperidine **2a** under the same reaction conditions. To our delight, this reaction gave the product **3a** a good yield. Encouraged by this result, *N*-Boc, *N*-phenylbenzamide **1a**, and piperidine **2a** were chosen as model substrates, and different reaction conditions were examined.

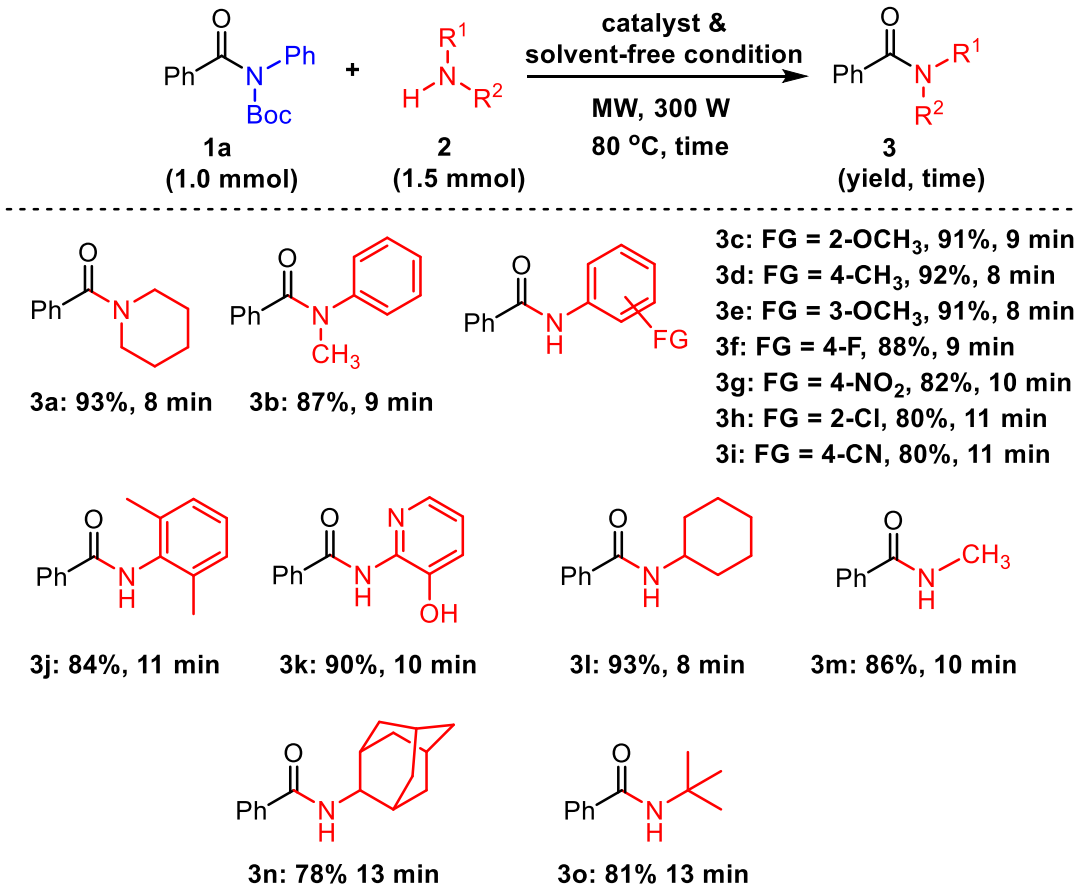
The reaction was carried out in different polar solvents like water, ethanol, methanol, DMF, 1,4- dioxane, dichloromethane, and acetonitrile under controlled microwave irradiation at 150 W in catalyst-free condition for 1 h at 60 ^{o}C, which offered only 30 to 55% of the desired product **3a** (**Table 3.1, entry 1-7**). Hence, the reaction was carried out in solvent-free conditions at 150 W at 60 ^{o}C. Surprisingly the reaction gave the product **3a** in 62% yield within 15 min (**Table 3.1, entry 8**). Next, we investigated the effect of microwave power on the yield of the product formation by varying microwave power from 150 W to 350 W in solvent-free conditions at 60 ^{o}C. A better yield of 80% was obtained at 300 W in 10 min (**Table 3.1, entry 10**). To find the optimal temperature, we conducted the

experiments at progressively higher temperatures, 70 ^{o}C, 80 ^{o}C and 100 ^{o}C. Interestingly the reaction at 80 ^{o}C under solvent-free conditions was driven to completion with the desired product **3a** to a maximum yield of 93% in 8 min (**Table 3.1, entry 13**). Further, an increase in temperature above 80 °C did not show any improvement in yield (**Table 3.1, entries 14**). To understand the assistance effect of microwave the model reaction was conducted under the same reaction conditions in the conventional heating method (without microwave) it gave only 20 % yield of the product **3a** even after 4 h (**Table 3.1, entries 15**). This suggests that *N*-Boc, *N*-phenylbenzamide **1a**, (1.0 mmol), piperidine **2a**, (1.5 mmol) at 80 °C in MW, 300 W under catalyst and solvent-free is the optimal condition for this transamidation reaction and the structure was identified by ^{1}H, ^{13}C and HRMS spectra.

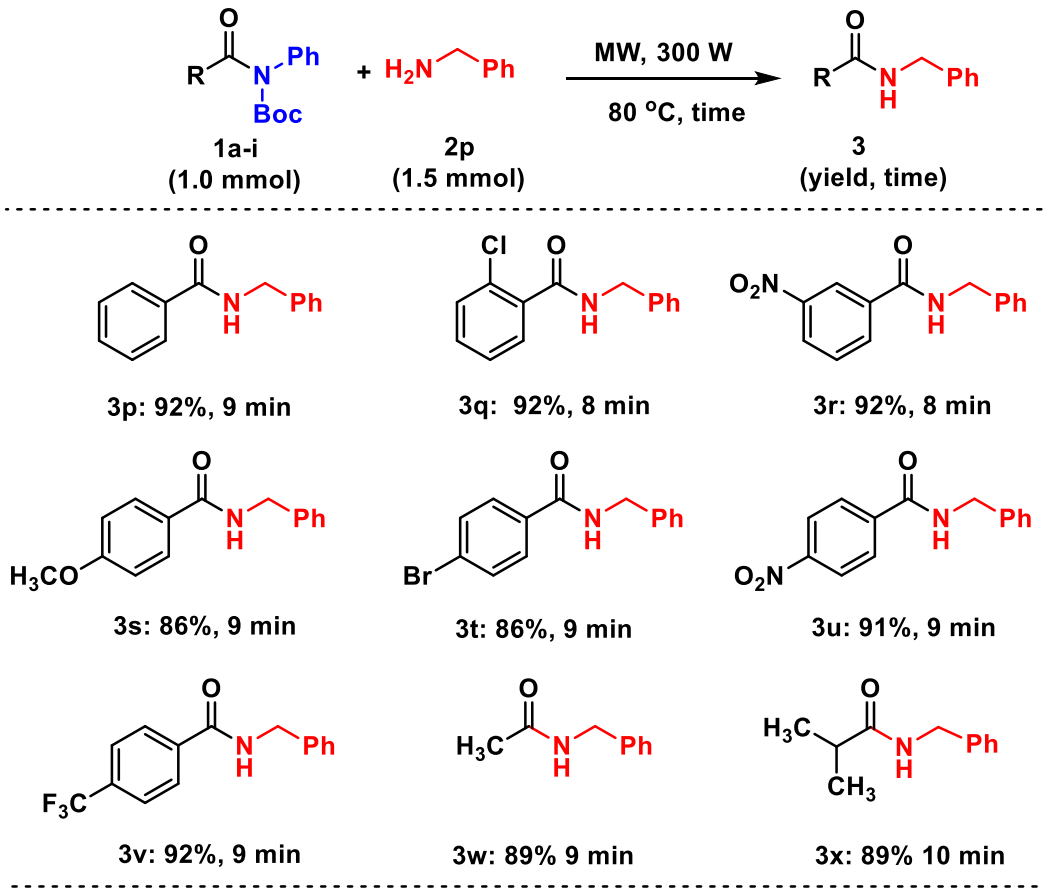
3.2.2 Substrate Scope

Once the optimal conditions are in our hands (**Table 3.1, entry 13**), we next explore the scope and limitations of this developed transamidation methodology. We examined the variety of *N*-Boc activated aliphatic and aromatic amides with a series of electron-donating, electron-withdrawing, primary, secondary aromatic, aliphatic and sterically hindered amines and found that they reacted smoothly under optimized reaction conditions (**Scheme 3.2-3.5**). After completion of the reaction, the reaction mixture was cooled to room temperature diluted with ethyl acetate, and washed water. The organic layer was dried over Na_2SO_4 and concentrated under vacuum and the crude product was purified by column

chromatography on silica gel using *n*-hexane-ethyl acetate as eluent to give the desired products (**3a-3ah**).



Scheme 3.2 Microwave-irradiated catalyst and solvent-free transamidation of *N*-Boc aromatic amides with amines.

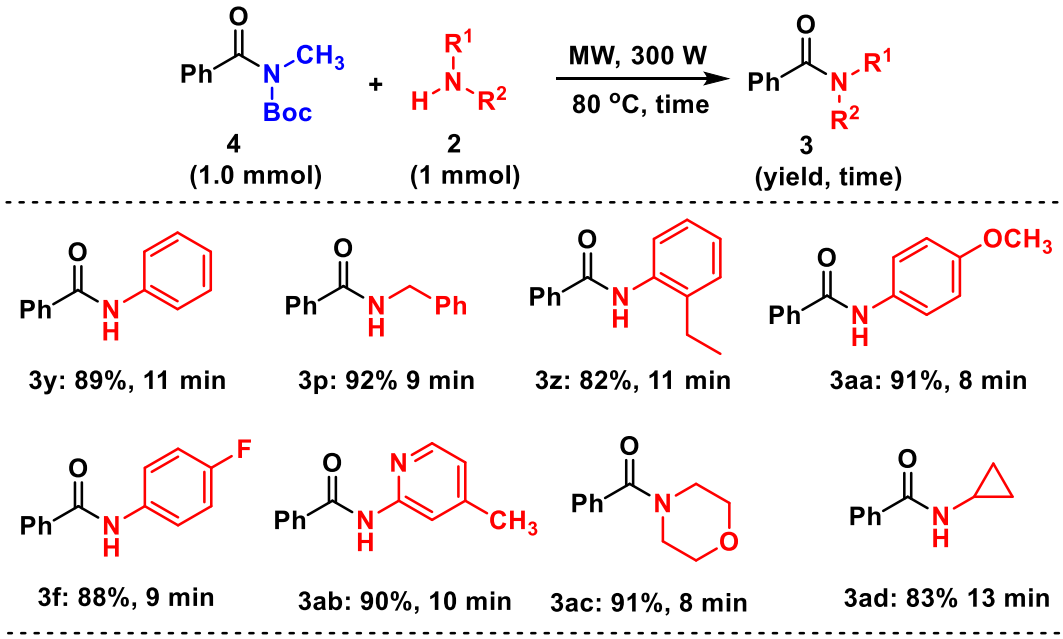


Scheme 3.3 Microwave-irradiated catalyst and solvent-free transamidation of *N*-Boc amides with benzyl amine.

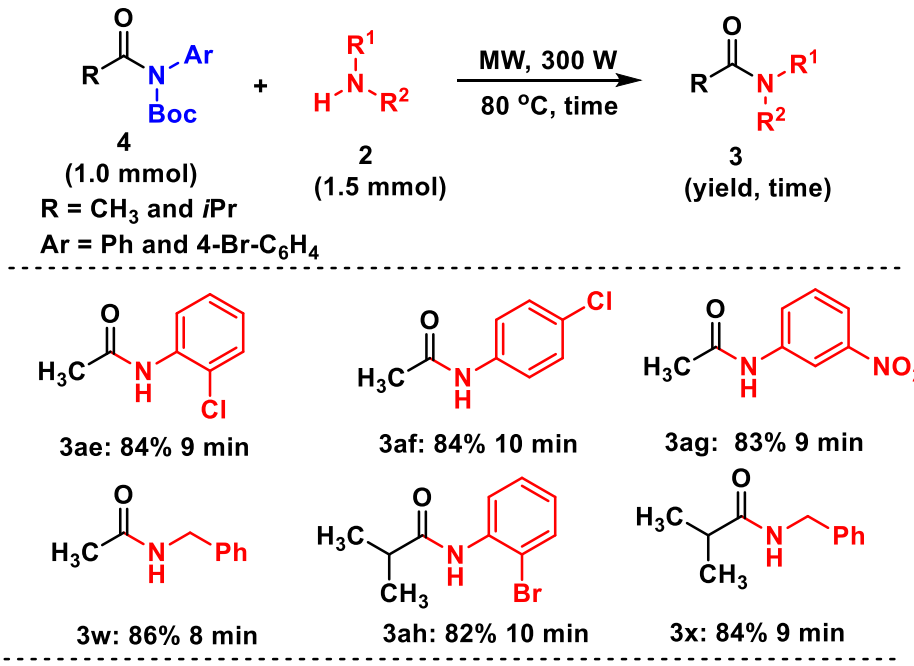
It was observed that the yields of reaction are related to both the structure and electronic properties of amines; in fact weakly nucleophilic aromatic amines and nucleophilic aliphatic amines both reacted smoothly (**Scheme 3.2**, **3a-3o**). Electron donating groups on ortho, meta (methoxy) and para (methyl) positions of aryl amines were well tolerated and showed good to excellent yields under optimized conditions (**Scheme 3.2, 3c-3e**). Whereas electron-withdrawing groups at ortho position (-Cl) and para position (-F, -CN, -NO_2), due to its decreased nucleophilicity gave moderate to good yields [45–49] (**3f-3i**). However,

the low reaction rate for **3j** (84 %), **3n** (78%) and **3o** (81%), is due to the sterically hindered amines [15, 50].

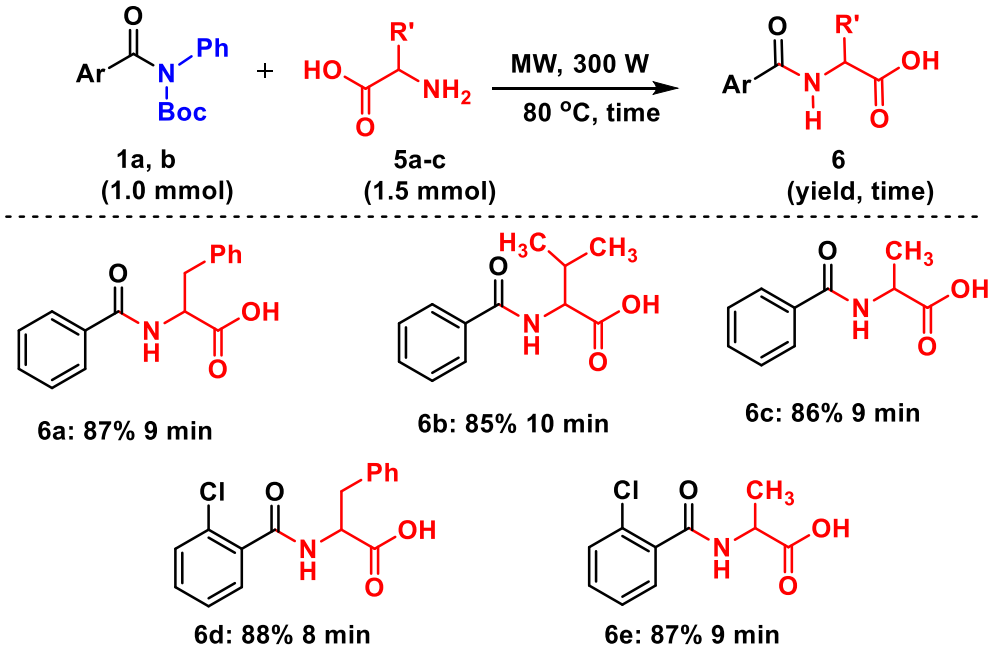
Further examined the scope of the developed methodology with Boc-activated secondary amides such as *tert*-butyl benzoyl(phenyl)carbamate (**1a**), *tert*-butyl (2-chlorobenzoyl)(phenyl)carbamate (**1b**), with various amino-acid-derived nucleophiles (**Scheme 3.6**) such as Phenylalanine (**5a**), valine (**5b**), and alanine (**5c**) delivered the secondary amides *viz* benzoylphenylalanine (**6a**), Benzoylvaline (**6b**), Benzoylalanine (**6c**), 2-chlorobenzoyl)phenylalanine (**6d**), (2-chlorobenzoyl)alanine (**6e**) in good to excellent yields (**6a-e**).



Scheme 3.4 Microwave-irradiated catalyst and solvent-free transamidation of *tert*-butyl benzoyl(methyl)carbamate with aliphatic and aromatic amines.



Scheme 3.5 Microwave-irradiated catalyst and solvent-free transamidation of *N*-Boc activated aliphatic amides with amines.

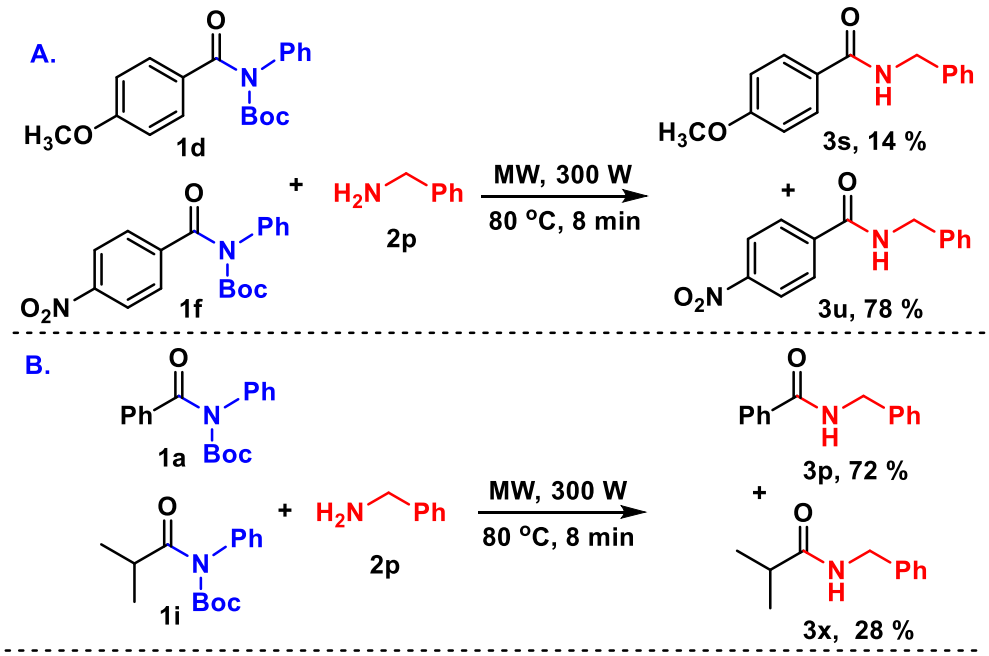


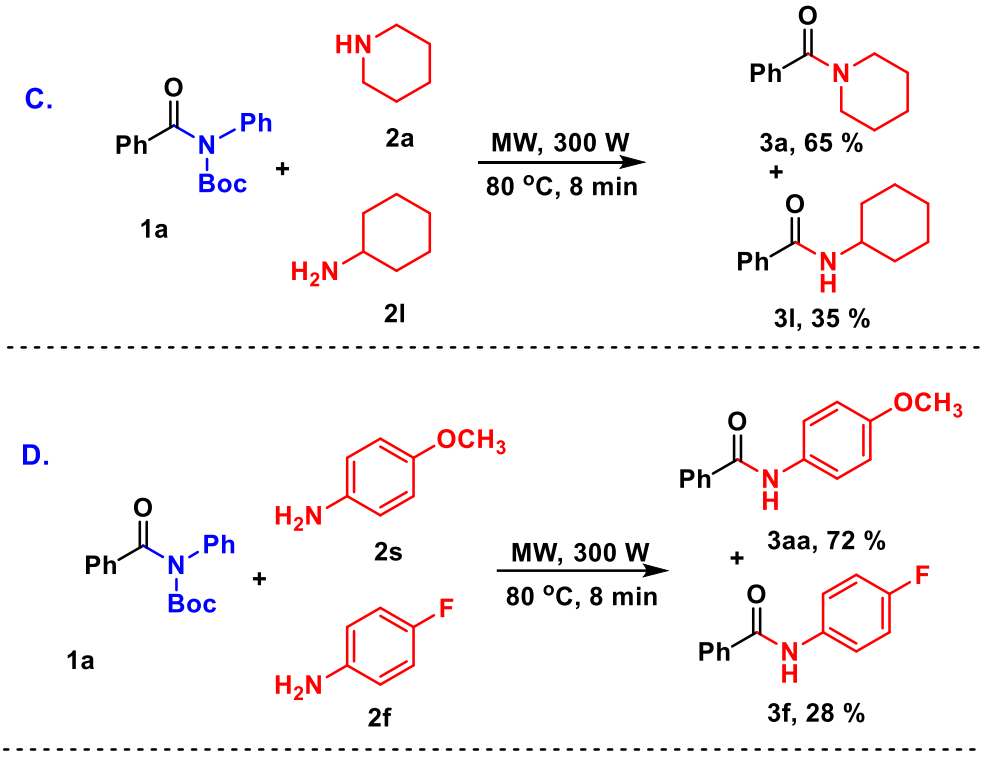
Scheme 3.6 Microwave-irradiated catalyst and solvent-free transamidation of *N*-Boc activated amides with amino acids.

3.3 Mechanistic studies

3.3.1 Competition reactions

To understand the reaction mechanism of secondary amide transamidation under microwave irradiation, the following factors might be helpful: reaction rate, selectivity pattern, and steric, electronic influences of amides and amines. Experiments involving intermolecular competition between various amides and amines were conducted in this context. Competition reaction between electron donating and electron withdrawing amides with benzylamine gave **3u** as a major product, indicating electron withdrawing amides to be more reactive than electron donating amides (**Scheme 3.7 A**).



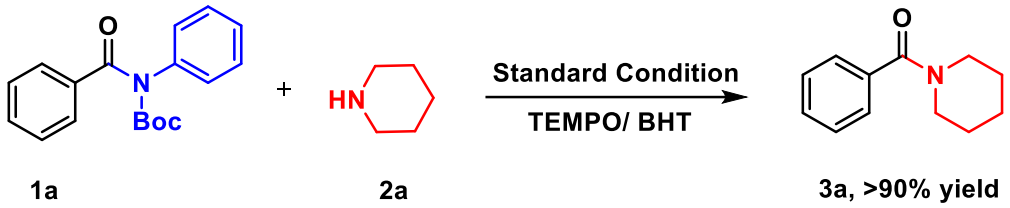


Scheme 3.7 Selectivity of amides and amines in transamidation reaction (Competition reactions).

The following experiment was conducted between aromatic and alkyl amides, and observed to be aromatic amides are more reactive (**Scheme 3.7 B**). Furthermore, intermolecular competition reactions between amides and different amines revealed nucleophilicity of amines is dominating factor (**Scheme 3.7 C**, **D**).

3.3.2 Control experiments

To support the microwave-mediated transamidation's mechanistic pathway, further control experiments were carried out on model reaction (**Scheme 3.8**) with 4.0 equiv. of radical scavenger TEMPO (2,2,6,6-tetramethylpiperidin-1-yl) oxidant) and BHT (butylated hydroxytoluene) separately under optimized reaction conditions. Both TEMPO/BHT did not quench the reaction, this shows that the reaction does not proceed via radical intermediate but through a nucleophilic pathway. Overall, these results provide a strong support for the acyl substitution mechanism of the amide bonds [23].



Scheme 3.8 Control experiments with radical scavengers.

3.3.3 Plausible reaction Mechanism

A plausible reaction pathway for the conversion of carbonyl derivatives into the corresponding amides is outlined in (**Figure 3.2**).

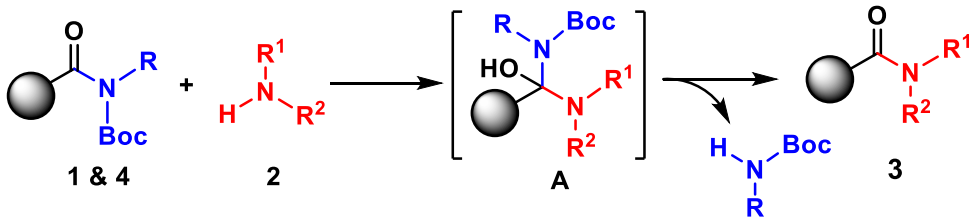
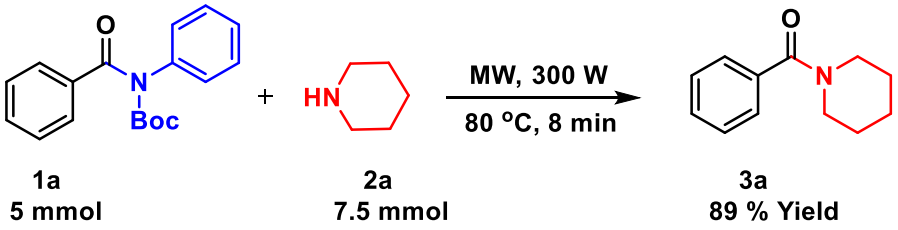


Figure 3.2 Proposed mechanism for microwave-irradiated transamidation of secondary amides.

Based on the literature [21, 22], and our finding a plausible mechanism for the transamidation reaction is shown in (**Figure 3.2**). The reaction of activated amide with amine generates thetetrahedral intermediate (**A**). This unstable intermediate undergoes C-N bond cleavage to provide the desired transamidation product (**3**).

3.4 Gram-scale synthesis of 3a

After that we tested the practical applicability of this protocol in multigram scale synthesis (**Scheme 3.9**). The reaction of *N*-Boc, *N*-phenylbenzamide **1a** (1.56 g, 5.0 mmol), and piperidine **2a** (0.64 ml, 7.5 mmol) gave the desired transamidated product **3a** in (1.95g) 89% yield under the optimized reaction conditions.

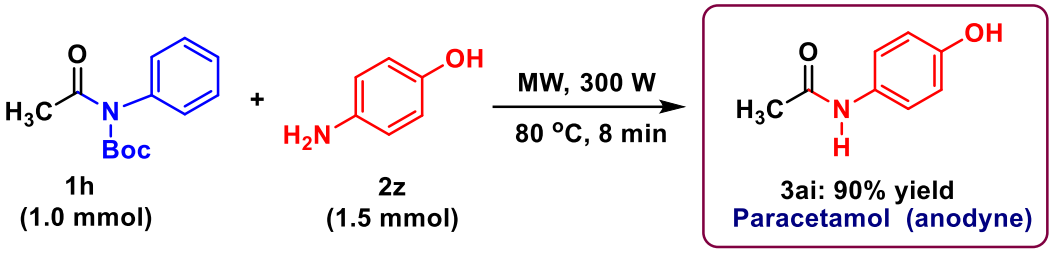


Scheme 3.9 Gram-scale procedure for transamidation of *N*-Boc amide with amine.

3.5 Appilcation of this methodology (synthesis of Paracetamol)

After exploring the scope of various amides, we attempted to synthesize Paracetamol, an analgesic and antipyretic drug commonly used as a pain reliever and fever reducer, using this developed transamidation method. The reaction of *N*-Boc acetanilide **1h** (1.0 equiv) with *p*-hydroxy aniline **2z** (1.5 equiv) gave the desired product *N*-(4-hydroxyphenyl)

acetamide **3ai** in 90% yield **(Scheme 3.10)**. These examples illustrate the potential synthetic utility of this method.



Scheme 3.10 Synthesis of Paracetamol by transamidation of *N*-Boc, acetanilide.

3.6 Experimental section

3.6.1 General procedure for the synthesis of amides

All amides used in the study were synthesized by previously reported methods [51].

3.6.2 General procedure for synthesis of *N*-Boc activated secondary amides

N-Boc-activated amides were synthesized according to the reported method [21]. To an oven-dried round bottom flask, amide (1.0 equiv.), DMAP (0.1 equiv.) and dichloromethane were added, the reaction temperature was maintained at 0 °C to this Boc anhydride (1.5 equiv.) was added dropwise. After the addition of Boc anhydride, the reaction mixture was stirred for 14-24 h at room temperature. The progress of the reaction was monitored with TLC, after the completion of the reaction, mixture was concentrated under reduced pressure and purified by column chromatography and the product was obtained in excellent yield.

3.6.3 General procedure for metal-free transamidation of *N*-Boc activated secondary amides with amines

A mixture of appropriate *N*-Boc activated amide (1.0 mmol) and amine (1.5 mmol) was placed in a 10-mL pressurised vials with ‘‘snap-on’’ cap and irradiated in the microwave using 300 W power at 80 °C for 8-10 min. The completion of the reaction was monitored with TLC, after completion the reaction mixture was cooled to room temperature and diluted with ethyl acetate, and washed water. The organic layer was dried over Na_2SO_4 and concentrated under vacuum and the crude product was purified by column chromatography on silica gel using *n*-hexane-ethyl acetate as eluent to give the desired products.

3.7 Analytical data

3.7.1 Analytical data of starting materials

***tert*-Butyl benzoyl(phenyl)carbamate (1a)** Yield 95%; white solid; m.p. 97 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.76 (d, 2H), 7.54 – 7.53 (m, 1H), 7.47 – 7.43 (m, 4H), 7.37 – 7.36 (m, 1H), 7.30 (d, 2H), 1.25 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 172.9, 153.5, 139.3, 137.1, 131.9, 129.4, 128.4, 128.3, 128.1, 127.9, 83.6, 27.6; HRMS (ESI) for $C_{18}H_{19}NO_3$ (m/z) $[M + H]^+$ calcd: 298.1365, found: 298.1382.

***tert*-Butyl (2-chlorobenzoyl)(phenyl)carbamate (1b)** Yield 94%; white solid; m.p. 235–238 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52 – 7.40 (m, 3H), 7.39 –7.28 (m, 6H), 1.22 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 170.1, 152.6, 138.8, 138.2, 131.2, 130.6, 129.9, 129.7,

129.2, 128.8, 128.8, 127.5, 84.4, 27.9; HRMS (ESI) for $C_{18}H_{18}ClNO_3$ (m/z) $[M + H]^+$ calcd: 332.0975, found: 332.0963.

***tert*-Butyl (3-nitrobenzoyl)(phenyl)carbamate (1c)** Yield 95%; white solid; m.p. 223–225 ^oC; ^1H NMR (500 MHz, $CDCl_3$): δ 8.45 (s, 1H), 8.30 (d, 1H), 7.96 – 7.94 (d, 1H), 7.58 – 7.55 (t, 1H), 7.40 – 7.36 (t, 2H), 7.32 – 7.29 (t, 1H), 7.29 –7.18 (m, 2H), 1.20 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 170.3, 152.9, 148.0, 138.5, 133.8, 129.6, 129.5, 128.4, 128.1, 126.0, 123.0, 84.5, 28.5, 27.7; HRMS (ESI) for $C_{18}H_{18}N_2O_5$ (m/z) $[M + H]^+$ calcd: 343.1216, found: 343.1243.

***tert*-Butyl (4-methoxybenzoyl)(phenyl)carbamate (1d)** Yield 88%; white solid; m.p. 143–145^oC; ^1H NMR (500 MHz, $CDCl_3$): δ 7.45 (d, 2H), 7.33 (t, 2H), 7.23 (d, 2H), 7.16 (t, 1H), 6.79 (d, 2H), 3.71 (s, 3H), 1.08 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.7, 162.3, 153.8, 138.2, 130.0, 129.6, 128.5, 128.1, 127.4, 113.4, 82.8, 55.4, 27.5; HRMS (ESI) for $C_{19}H_{21}NO_4$ (m/z) [M + H]+ calcd: 328.1471, found: 328.1467.

***tert*-Butyl (4-bromobenzoyl)(phenyl)carbamate (1e)** Yield 88%; white solid; m.p. 83–85^oC; ^1H NMR (500 MHz, $CDCl_3$): δ 7.71 (d, 2H), 7.62 (d, 2H), 7.39 – 7.27 (m, 4H), 7.13 (t, 1H), 1.21 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.8, 162.4, 153.4, 138.2, 130.2, 129.8, 128.6, 128.2, 127.5, 113.5, 79.3, 27.7; HRMS (ESI) for $C_{18}H_{18}BrNO_3$ (m/z) [M + H]+ calcd: 376.0470, found: 376.0483.

***tert*-Butyl (4-nitrobenzoyl)(phenyl)carbamate (1f)** Yield 88%; white solid; (m.p. 103 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.33 (d, 2H), 7.92 (d, 2H), 7.39 – 7.30 (m, 4H), 7.29 – 7.11 (m, 1H), 1.21 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.4, 162.0, 153.5, 137.9, 129.8, 129.3, 128.2, 127.8, 127.0, 113.0, 28.6, 27.2; HRMS (ESI) for $C_{18}H_{18}N_2O_5$ (m/z [M + H]+ calcd: 343.1216, found: 343.1204.

***tert*-Butyl b(4-trifluoromethyl)(benzoyl)(phenyl)carbamate (1g)** Yield 88%; white solid; m.p. 125–127^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.61 (d, 2H), 7.55 (d, 2H), 7.38 – 7.36 (t, 2H), 7.31 (d, 2H), 7.24 (t, 1H), 1.09 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.2, 153.4, 141.6, 137.9, 132.7 (q, *J* = 32.8 Hz, 1C), 129.0, 128.6, 128.0, 127.8, 125.6 (q, *J* = 3.8 Hz, 1C), 125.2 (q, *J* = 272.1 Hz, 1C), 84.3, 27.8; ^{19}F NMR (471 MHz, $CDCl_3$): δ -63.2; HRMS (ESI) for $C_{19}H_{18}F_3NO_3$ (m/z) [M + H]+ calcd: 366.1239, found: 366.1254.

***tert*-Butyl benzoyl(methyl)carbamate (1h)** Yield 87%; yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52 (m, 2H), 7.47 – 7.45 (m, 1H), 7.41 – 7.38 (m, 2H), 3.32 (s, 3H), 1.16 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 173.7, 153.6, 137.9, 130.9, 128.1, 127.5, 83.0, 71.8, 32.6, 27.4; HRMS (ESI) for $C_{13}H_{17}NO_3$ (m/z) $[M + H]^+$ calcd: 236.1208, found: 236.1219.

***tert*-Butyl acetyl(phenyl)carbamate (1i)** Yield 84%; white solid; (m.p. 58 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43 – 7.36 (m, 2H), 7.35 – 7.28 (m, 1H), 7.11 – 7.10 (m, 2H), 2.59 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 172.9, 152.8, 138.9, 128.9, 128.2, 127.8, 83.2, 27.8, 26.3; HRMS (ESI) for $C_{13}H_{17}NO_3$ (m/z) $[M + H]^+$ calcd: 236.1208, found: 236.1251.

***tert*-Butyl acetyl(4-bromophenyl)carbamate (1j)** Yield 84%; white solid; (m.p. 122 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54 (d, 2H), 6.99 (d, 2H), 2.61 (s, 3H), 1.41 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 172.8, 152.4, 137.9, 132.2, 129.9, 121.7, 83.6, 27.9, 26.5; HRMS (ESI) for $C_{13}H_{16}BrNO_3$ (m/z) $[M + H]^+$ calcd: 314.0314, found: 314.0308.

***tert*-Butyl isobutyryl(phenyl)carbamate (1k)** Yield 82%; yellow oil; (^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 –7.27 (t, 2H), 7.23 – 7.21 (d, 1H) 6.99 – 6.97 (m, 2H), 3.57 –3.53 (m, 1H), 1.30 (s, 9H), 1.15 (d, 6H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 180.5, 152.8, 139.5, 128.9, 128.2, 128.2, 127.5, 82.9, 34.8, 34.7, 27.9, 19.6; HRMS (ESI) for $C_{15}H_{21}NO_3$ (m/z) $[M + H]^+$ calcd: 264.1521, found: 264.1543.

3.7.2 Analytical data of transamidation products

Phenyl(piperidin-1-yl)methanone (3a) Yield 93%; white solid; m.p. 48 °C; ^{1}H NMR (500 MHz, $CDCl_3$): *δ* 7.43 – 7.29 (m, 5H), 3.74 (s, 2H), 3.36 (s, 2H), 1.77 (s, 2H), 1.70 (s, 2H), 1.54 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 170.5, 135.3, 129.8, 128.6, 127.0, 48.7, 43.0, 24.5; HRMS (ESI) for $C_{12}H_{15}NO$ (m/z) $[M + H]^+$ calcd: 190.1189, found: 190.1223.

***N*-Methyl-*N*-phenylbenzamide (3b)** Yield 87%; yellow oil; (^{1}H NMR (500 MHz, $CDCl_3$): *δ* 7.25 (d, 2H), 7.18 – 7.11 (m, 3H), 7.09 – 7.05 (m, 3H), 6.98 – 6.97 (d, 2H), 3.44 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): *δ* 170.8, 145.0, 126.0, 129.7, 129.3, 128.8, 127.8, 127.0, 123.6, 38.5; HRMS(ESI) for $C_{14}H_{13}NO$ (m/z) $[M + H]^+$ calcd: 212.0997, found: 212.1023.

***N*-(2-Methoxyphenyl)benzamide (3c)** Yield 91%; white solid; m.p. 60 ^{o}C; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.54 (d, 2H), 7.90 (m, 2H), 7.55 – 7.51 (m, 3H), 7.50 (m, 2H), 6.93 (s, 1H), 3.92 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 165.5, 148.4, 135.6, 131.9, 129.0, 128.1, 127.3, 124.1, 121.5, 121.5, 120.1, 110.2, 56.1; HRMS (ESI) for $C_{14}H_{13}NO_2$ (m/z) $[M + H]^+$ calcd: 228.0946, found: 228.0932.

***N*-(4-Methylphenyl)benzamide (3d)** Yield 92%; white solid; m.p. 158 ^{o}C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.17 (s, 1H), 7.96 (d, 2H), 7.67 (d, 2H), 7.60 – 7.57 (m, 1H), 7.54 (d, 2H), 7.17 (d, 2H), 2.29 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 165.8, 137.1, 135.5, 133.0, 131.9, 129.5, 128.8, 128.1, 120.9, 21.0; HRMS (ESI) for $C_{14}H_{13}NO$ (m/z) $[M + H]^+$ calcd: 212.0997, found: 212.0930.

***N*-(3-Methoxylphenyl)benzamide (3e)** Yield 91%; white solid; m.p. 108 ^{o}C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.68 (d, 2H), 7.39 (s, 1H), 7.67 (d, 2H), 7.36 – 7.31 (m, 3H), 7.23 – 7.16 (m, 1H), 7.15 (m, 1H), 6.93 (d, 1H), 6.74 – 6.72 (m, 1H), 3.81 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 165.8, 156.7, 138.9, 135.2, 131.3, 129.3, 128.9, 127.1, 112.2, 110.2, 105.3, 55.6; HRMS (ESI) for $C_{14}H_{13}NO_2$ (m/z) $[M + H]^+$ calcd: 228.0946, found: 228.0957.

***N*-(4-Fluorophenyl)benzamide (3f)** Yield 88%; white solid m.p. 185–187^{o}C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.36 (s, 1H), 8.00 – 7.85 (d, 2H), 7.83 (d, 2H), 7.65 (m, 1H), 7.60 (d, 2H), 7.59 – 7.23 (m, 2H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 165.8, 159.6 (d, J = 240.6 Hz, 1C), 135.7, 135.0 (d, J = 6.3 Hz, 1C), 131.9, 128.7, 127.9, 122.5 (d, J = 7.6 Hz,

1C), 115.5 (d, *J* = 22.7 Hz, 1C); ^{19}F NMR (471 MHz, $CDCl_3$): δ - 117.8; HRMS (ESI) for $C_{13}H_{10}FNO$ (m/z) $[M + H]^+$ calcd: 216.0746, found: 216.0732.

***N*-(4-Nitrophenyl)benzamide (3g)** Yield 82%; white solid; m.p. 196 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.84 (s, 1H), 8.29 (d, 2H), 8.08 (d, 2H), 7.67 – 7.64 (m, 1H), 8.00 (d, 2H), 7.59 – 7.57(m, 2H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 166.5, 145.6, 142.7, 134.4, 132.5, 128.8, 128.1, 125.0, 120.1; HRMS (ESI) for $C_{13}H_{10}N_2O_3$ (m/z) $[M + H]^+$ calcd: 243.0691, found: 243.0684.

***N*-(2-Chlorophenyl)benzamide (3h)** Yield 80%; white solid; m.p. 97 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.58 (d, 1H), 8.45 (s, 1H), 7.93 (d, 2H), 7.60 – 7.58 (t, 1H), 7.57 – 7.50 (t, 2H), 7.42 (dd, 1H), 7.34 – 7.26 (m, 1H), 7.08 – 7.07 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 165.6, 135.0, 134.9, 132.5, 129.3, 129.2, 128.2, 127.4, 125.0, 123.3, 121.8; HRMS (ESI) for $C_{13}H_{10}ClNO$ (m/z) $[M + H]^+$ calcd: 231.0451, found: 231.0434.

***N*-(4-Cynophenyl)benzamide (3i)** Yield 80%; yellow solid; m.p. 168–170 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.03 (s, 1H), 7.88 (d, 1H), 7.79 (d, 1H), 7.67 – 7.64 (m, 3H), 7.61 – 7.50 (m, 2H), 7.48 – 7.34 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 173.2, 142.1, 133.6, 133.5, 129.5, 129.2, 128.9, 127.3, 120.0; HRMS (ESI) for $C_{14}H_{10}N_2O$ (m/z) $[M + H]^+$ calcd: 223.0793, found: 223.0798.

***N*-(2,6-Dimethylphenyl)benzamide (3j)** Yield 84%; white solid; m.p. 167-169 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95 (d, 2H), 7.61 – 751 (t, 1H), 7.43 (t, 2H), 7.28 (s, 1H), 7.19

– 7.14 (m, 3H), 2.31 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 166.3, 135.9, 134.9, 134.2, 132.2, 129.1, 128.6, 127.9, 127.6, 18.8; HRMS (ESI) for $C_{15}H_{15}NO$ (m/z) $[M + H]^+$ calcd: 226.1154, found: 226.1173.

***N*-(3-Hydroxypyridin-2-yl)benzamide (3k)** Yield 90%; White solid; m.p. 95–97 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.97 (d, 1H), 7.71 (d, 2H), 7.40 − 7.35 (m, 1H), 7.29 (m, 2H,), 7.27 (s, 1H), 7.24 (d, 1H), 7.23 (m, 1H,) 4.54 (s, 1H,); ^{13}C NMR (126 MHz, DMSO-d_6): δ 168.9, 146.7, 143.3, 138.9, 134.5, 131.4, 129.9, 129.9, 124.1, 120.4; HRMS (ESI) for $C_{12}H_{10}N_2O_2$ (m/z) $[M + H]^+$ calcd: 215.0742, found: 215.0778.

***N*-Cyclohexylbenzamide (3l)** Yield 93%; white solid; m.p. 154–156 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$):δ 7.75 – 7.74 (m, 2H), 7.49 – 7.42 (m, 1H), 7.40 – 7.26 (d, 2H), 5.99 (s, 1H), 4.00 – 3.95 (d, 1H), 2.04 – 2.02 (m, 2H), 1.76 –1.74 (m, 2H), 1.69 – 1.64 (m, 1H), 1.46 – 1.41 (m, 2H), 1.39 – 1.20 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 166.9, 135.4, 131.6, 128.8, 127.2, 49.0, 33.6, 25.9, 25.2; HRMS (ESI) for $C_{13}H_{17}NO$ (m/z) $[M + H]^+$ calcd: 204.1310, found: 204.1329.

***N*-Methylbenzamide (3m)** Yield 86%; yellow solid; m.p. 82–83 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$):δ 7.76 – 7.74 (m, 2H), 7.48 – 7.39 (m, 1H), 7.38 – 7.26 (m, 2H), 6.42 (s, 1H), 2.99 – 2.98 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 168.6, 134.8, 131.5, 128.7, 127.0, 27.0; HRMS (ESI) for C_8H_9NO (m/z) $[M + H]^+$ calcd: 136.0684, found: 136.0670.

***N*-(3s,5s,7s)-Adamantan-1-yl)benzamide (3n)** Yield 78%; white solid; (m.p. 143–145 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 – 7.72 (m, 2H), 7.50 – 7.46 (m, 1H), 7.44 – 7.28 (t, 2H), 5.82 (s, 1H), 2.15 (s, 9H), 1.77 (d, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.9, 162.6, 136.3, 134.8, 131.3, 130.8, 129.1, 129.1, 128.7, 126.9, 52.5, 41.9, 36.6, 29.7; HRMS (ESI) for $C_{17}H_{21}NO$ (m/z) $[M + H]^+$ calcd: 256.1623, found: 256.1641.

***N*-(tert-Butyl)benzamide (3o)** Yield 81%; white solid; m.p. 136 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73 – 7.71 (m, 2H), 7.47 – 7.43 (m, 1H), 7.40 – 7.26 (m, 2H), 1.48 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.0, 136.0, 131.23, 128.6, 126.8, 51.7, 29.0; HRMS (ESI) for $C_{11}H_{15}NO$ (m/z) $[M + H]^+$ calcd: 178.1154, found: 178.1169.

***N*-Benzylbenzamide (3p)** Yield 92%; white solid; m.p. 103–105 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.83 (d, 2H,), 7.55 (t, 1H), 7.48 – 7.39 (m, 2H), 7.35 – 7.29 (m, 4H), 6.43 (m, 1H), 4.69 (d, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 167.5, 138.4, 134.6, 131.8, 129.0, 128.8, 128.1, 127.8, 127.1, 44.4; HRMS (ESI) for $C_{14}H_{13}NO$ (m/z) $[M + H]^+$ calcd: 212.0997, found: 212.0981.

***N*-Benzyl-4-fluorobenzamide** Yield 92%; white solid; m.p. 104–106 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 – 7.37 (m, 1H), 7.35 – 7.26 (m, 7H), 6.54 (d, 1H), 4.66 (d, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 165.7, 152.4, 149.2, 144.6, 131.8, 129.0, 120.7, 99.3, 59.8, 53.9, 18.3, 14.5; HRMS (ESI) for $C_{14}H_{12}ClNO$ (m/z) $[M + H]^+$ calcd: 246.0607, found: 246.0618.

***N*-Benzyl-3-nitrobenzamide (3r)** Yield 92%; white solid; m.p. 94–96 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.62 (s, 1H), 8.35 (d, 1H), 8.19 (d, 1H), 7.64 (m, 1H), 7.36 – 7.35 (m, 5H),

6.90 (t, 1H), 4.67 (d, 2H); ^{13}C NMR (126 MHz, $CDCl_3$):δ 165.0, 148.1, 137.5, 135.9, 133.3, 129.9, 128.9, 127.9, 127.9, 126.1, 121.8, 44.4; HRMS (ESI) for $C_{14}H_{12}N_2O_3$ (m/z) $[M + H]^+$ calcd: 257.0848, found: 257.0832.

***N*-Benzyl-4-methoxybenzamide (3s)** Yield 86%; white solid; m.p. 125 ^oC; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.00 (d, 1H), 7.67 (d, 2H), 7.25 – 7.16 (m, 4H), 6.89 (d, 2H), 6.80 (s, 1H), 4.54 (d, 2H), 3.80 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 167.1, 167.1, 164.8, 162.5, 162.5, 138.6, 133.0, 129.08, 129.0, 128.1, 127.8, 126.9, 121.5, 114.3, 114.0, 55.6, 44.3; HRMS (ESI) for $C_{15}H_{15}NO_2$ (m/z) $[M + H]^+$ calcd: 242.1103, found: 242.1137.

***N*-Benzyl-4-bromobenzamide (3t)** Yield 86%; white solid; m.p. 161–162 ^oC; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.41 (s, 1H), 7.47 (d, 2H), 7.35 (d, 2H), 6.69 – 6.60 (m, 5H), 4.49 (d, 2H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 165.6, 140.0, 138.0, 131.3, 130.4, 130.3, 128.7, 127.7, 127.2, 121.0, 120.9, 53.9; HRMS (ESI) for $C_{14}H_{12}BrNO$ (m/z) $[M + H]^+$ calcd: 290.0102, found: 290.0126.

***N*-Benzyl-4-nitrobenzamide (3u)** Yield 92%; white solid; m.p. 146–167 ^oC; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79 – 7.66 (m, 3H), 7.65 – 7.61 (m, 3H), 7.49 (t, 2H), 7.26 – 7.18 (m, 1H), 4.98 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 166.1, 137.7, 137.6, 133.4 (q, J = 32.7 Hz, 1C), 128.9, 127.9, 127.8, 127.5, 125.7 (q, J = 3.8 Hz, 1C), 124.7 (q, J = 273.4 Hz, 1C), 44.2; ^{19}F NMR (471 MHz, $CDCl_3$): δ - 62.9; HRMS (ESI) for $C_{15}H_{12}F_3NO$ (m/z) $[M + H]^+$ calcd: 280.0871, found: 280.0855.

***N*-Benzylacetamide (3w)** Yield 89%; white solid; m.p. 60 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27 – 7.15 (m, 5H), 6.23 (s, 1H), 4.27 (d, 2H), 1.87 (s, 3H);^{13}C NMR (126 MHz, $CDCl_3$): δ 170.2, 138.4, 128.7, 127.9, 127.5, 59.7, 43.7, 23.2; HRMS (ESI) for $C_9H_{11}NO$ (m/z) $[M + H]^+$ calcd: 150.0841, found: 150.0868.

***N*-Benzylisobutyramide (3x)**

Yield 89%; white solid; m.p. 91 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33 (d, 2H), 7.32 – 7.26 (m, 3H), 5.82 (s, 1H), 4.43 (d, 2H), 2.41 – 2.36 (m, 1H), 1.19 (d, 6H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 176.9, 138.7, 128.9, 127.9, 127.6, 43.6, 35.8, 19.8; HRMS (ESI) for $C_{11}H_{15}NO$ (m/z) $[M + H]^+$ calcd: 178.1154, found: 178.1163.

***N*-Phenylbenzamide (3y)** Yield 89%; white solid; m.p. 164 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.90-7.88 (d, 3H), 7.68 – 7.57 (d, 2H), 7.56 – 7.48 (t, 1H), 7.40-7.37 (t, 2H), 7.19 (t, 2H), 7.16 (t, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 165.8, 137.9, 135.0, 131.8, 129.1, 128.8, 127.0, 124.6, 120.3; HRMS (ESI) for $C_{13}H_{11}NO$ (m/z) $[M + H]^+$ calcd: 198.0841, found: 198.0853.

***N*-(2-Ethylphenyl)benzamide (3z)** Yield 82%; white solid; m.p. 159 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.97 (d, 1H), 7.90 (d, 2H), 7.60 (s, 1H), 7.58 (t, 1H), 7.52 (t, 2H), 7.29 (t, 2H), 7.19 (t, 1H), 2.73 (q, 2H), 1.32 (t, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 166.0, 135.6, 135.3, 135.2, 132.0, 129.0, 128.8, 127.2, 127.0, 125.9, 124.1, 24.6, 14.2; HRMS (ESI) for $C_{15}H_{15}NO$ (m/z) $[M + H]^+$ calcd: 226.1154, found: 226.1132.

***N*-(4-Methoxyphenyl)benzamide (3aa)** Yield 91%; green solid; m.p. 154–156 ^{o}C;^{1}H NMR (500 MHz, $CDCl_3$): δ 7.89 (m, 3H), 7.55 (m, 3H), 7.50 – 7.47 (m, 2H), 6.29 (d, 2H), 3.83 (s,3H);^{13}C NMR (126 MHz, $CDCl_3$): δ 165.7, 135.0, 131.7, 131.0, 128.7, 127.0, 122.2, 114.3, 99.3, 55.2; HRMS (ESI) for $C_{14}H_{13}NO_2$ (m/z) $[M + H]^+$ calcd: 228.0946, found: 228.0977.

***N*-(4-Methylpyridin-2-yl)benzamide (3ab)** Yield 90%; White solid; m.p. 115–116 ^{o}C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.12 (d, 1H), 7.76 (d, 2H), 7.63 (s, 1H), 7.63 – 7.51 (m, 1H), 7.33 – 7.28 (m, 2H), 7.23 (s, 1H), 7.06 (s, 1H), 2.31 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 165.8, 152.8, 152.3, 148.2, 133.0, 131.9, 129.5, 128.8, 127.7, 120.8, 19.2; HRMS (ESI) for $C_{13}H_{12}N_2O$ (m/z) $[M + H]^+$ calcd: 213.0950, found: 213.0978.

Morpholino(phenyl)methanone (3ac) Yield 91%; yellow solid; m.p.73–75 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42 – 7.40 (m, 5H), 3.77 – 3.45 (m, 8H), ^{13}C NMR (126 MHz, $CDCl_3$): δ 170.5, 135.3, 129.9, 128.6, 127.0, 66.9, 48.2, 42.6; HRMS (ESI) for $C_{11}H_{13}NO_2$ (m/z) $[M + H]^+$ calcd: 192.0946, found: 192.0955.

***N*-Cyclopropylbenzamide (3ad)** Yield 83%; white solid; m.p. 55–57 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65 (d, 2H), 7.38 – 7.17 (m, 3H), 6.36 (d, 1H), 2.80 – 2.77 (m, 1H), 0.75 (s, 2H), 0.52 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 169.1, 134.6, 131.6, 128.7, 127.0, 23.3, 6.9; HRMS (ESI) for $C_{10}H_{11}NO$ (m/z) $[M + H]^+$ calcd: 162.0841, found: 162.0867.

***N*-(2-Chlorophenyl)acetamide (3ae)**

Yield 84%; white solid; m.p. 84–86 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.28 (d, 1H), 7.55 (s, 1H, NH), 7.29 (d, 1H), 7.20 (m, 1H), 7.19 – 6.19 (m, 1H), 2.16 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 168.4, 134.7, 129.1, 127.8, 124.7, 122.7, 121.8, 25.0; HRMS (ESI) for C_8H_8ClNO (m/z) $[M + H]^+$ calcd: 170.0294, found: 170.0263.

***N*-(4-Chlorophenyl)acetamide (3af)** Yield 87%; white solid; m.p. 178 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75 (s, 1H), 7.42 (m, 4H), 2.17 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 168.4, 136.9, 131.9, 121.5, 116.9, 24.6; HRMS (ESI) for C_8H_8ClNO (m/z) $[M + H]^+$ calcd: 170.0294, found: 170.0298.

***N*-(2-Nitrophenyl)acetamide (3ag)** Yield 83%; white solid; m.p. 93 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.57 (s, 1H), 8.08 (s, 1H), 7.73 (d, 1H), 7.54 (d, 1H), 7.33 – 7.28 (m, 1H), 2.17 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 168.8, 150.7, 138.0, 127.3, 124.3, 122.4, 120.1, 24.5; HRMS (ESI) for $C_8H_8N_2O_3$ (m/z) $[M + H]^+$ calcd: 181.0535, found: 181.0553.

***N*-(2-Bromophenyl)isobutyramide (3ah)** Yield 82%; white solid; m.p. 95 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.42 (d, 1H), 7.73 (s, 1H), 7.39 (d, 1H), 7.30 (m, 2H), 7.29 – 7.03 (m, 1H), 4.01 (d, 2H), 2.65 – 2.59 (m, 1H), 1.10 (d, 6H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 175.29, 134.80, 129.04, 127.88, 124.57, 122.57, 129.02, 121.67, 37.12, 19.70; HRMS(ESI) for $C_{10}H_{12}BrNO$ (m/z) $[M + H]^+$ calcd: 242.0102, found: 242.0132.

***N*-(4-Hydroxyphenyl)acetamide (3ai)** Yield 84%; white solid; m.p. 168 ^{o}C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.64 (s, 1H), 9.13 (s, 1H), 7.34 – 7.32 (m, 2H), 6.68 – 6.66 (m, 2H), 1.98 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 167.5, 153.1, 131.0, 120.8, 114.9, 23.7; HRMS (ESI) for $C_8H_9NO_2$ (m/z) $[M + H]^+$ calcd: 152.0633, found: 152.0701.

***N*-Benzoyl phenylalanine (6a)** Yield 87%; white solid; m.p. 181–183 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.61 (d, 2H), 7.43 (t, 1H), 7.33 (t, 2H), 7.23 –7.16 (m, 3H), 7.13 (d, 2H), 6.59 (d, 1H), 5.01 (t, 1H), 3.30 – 3.16 (dd, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 174.6, 167.8, 135.7, 133.4, 132.0, 129.4, 128.7, 127.3, 127.1, 53.7, 37.3; HRMS (ESI) for $C_{16}H_{15}NO_3$ (m/z) $[M + H]^+$ calcd: 270.1052, found: 270.1073.

***N*-Benzoylvaline (6b)** Yield 85%; white solid; m.p. 130 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81 (d, 2H), 7.50 (t, 1H), 7.45 (t, 2H), 6.80 (d, 1H), 4.80 – (m, 1H), 2.36 (t, 1H), 1.05 (d, 6H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 175.8, 168.1, 168.0, 133.8, 131.9, 128.7, 127.1, 57.6, 31.3, 19.0, 17.8; HRMS (ESI) for $C_{12}H_{15}NO_3$ (m/z) $[M + H]^+$ calcd: 222.1051, found: 222.1040.

***N*-Benzoylalanine (6c)** Yield 86%; white solid; m.p. 163 – 165 ^{o}C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.67 (d, 1H), 7.90 (d, 2H), 7.56 (t, 1H), 7.48 (t, 2H), 5.14 (s, 1H), 4.45 – 4.42 (m, 1H), 1.41 (d, 3H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 174.7, 166.7, 134.4, 131.8, 128.1, 127.9, 18.6, 17.3; HRMS (ESI) for $C_{10}H_{11}NO_3$ (m/z) $[M + H]^+$ calcd: 194.0739, found: 194.0714.

***N*-(2-Chlorobenzoyl)phenylalanine (6d)** Yield 88%; white solid; m.p. 190 – 192 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75 (d, 1H), 7.40 (d, 1H), 7.35 (t, 1H), 7.29 (t, 1H), 7.24 (dd,

2H), 7.18 (dd, 2H), 7.15 (t, 1H), 6.61 (d, 1H), 5.01 (t, 1H), 3.30 (dd, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 174.6, 167.8, 135.7, 134.0, 133.4, 132.0, 129.4, 128.7, 127.3, 59.8, 127.1, 53.7, 38.0; HRMS (ESI) for $C_{16}H_{14}ClNO_3$ (m/z) $[M + H]^+$ calcd: 304.0662, found: 304.0683.

***N*- (2-Chlorobenzoyl)alanine (6e)** Yield 87%; white solid; m.p. 171–173ºC; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.69 (d, 1H), 8.33 (d, 1H), 8.32 (t, 1H), 7.64 (t, 1H), 7.57 (d, 1H), 4.45 (m, 1H), 1.43 (d, 3H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 174.8, 166.7, 134.4, 131.9, 129.4, 128.7, 127.9, 49.6, 19.7; HRMS (ESI) for $C_{10}H_{10}ClNO_3$ (m/z) $[M + H]^+$ calcd: 228.0349, found: 228.0356.

3.8 Spectral data of few products

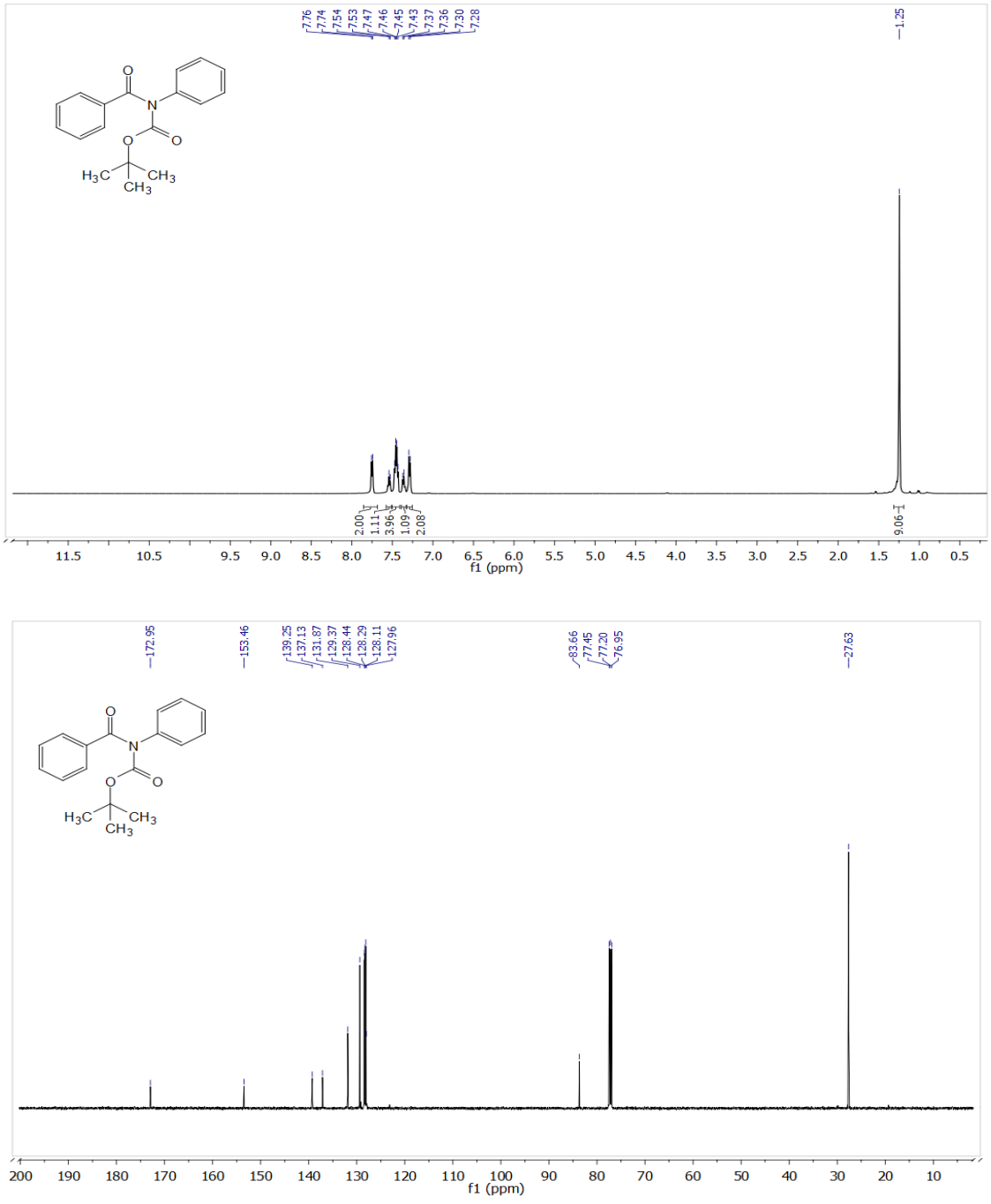


Figure 3.3 ^{1}H and ^{13}C NMR of *tert*-butyl benzoyl(phenyl)carbamate (**1a**).

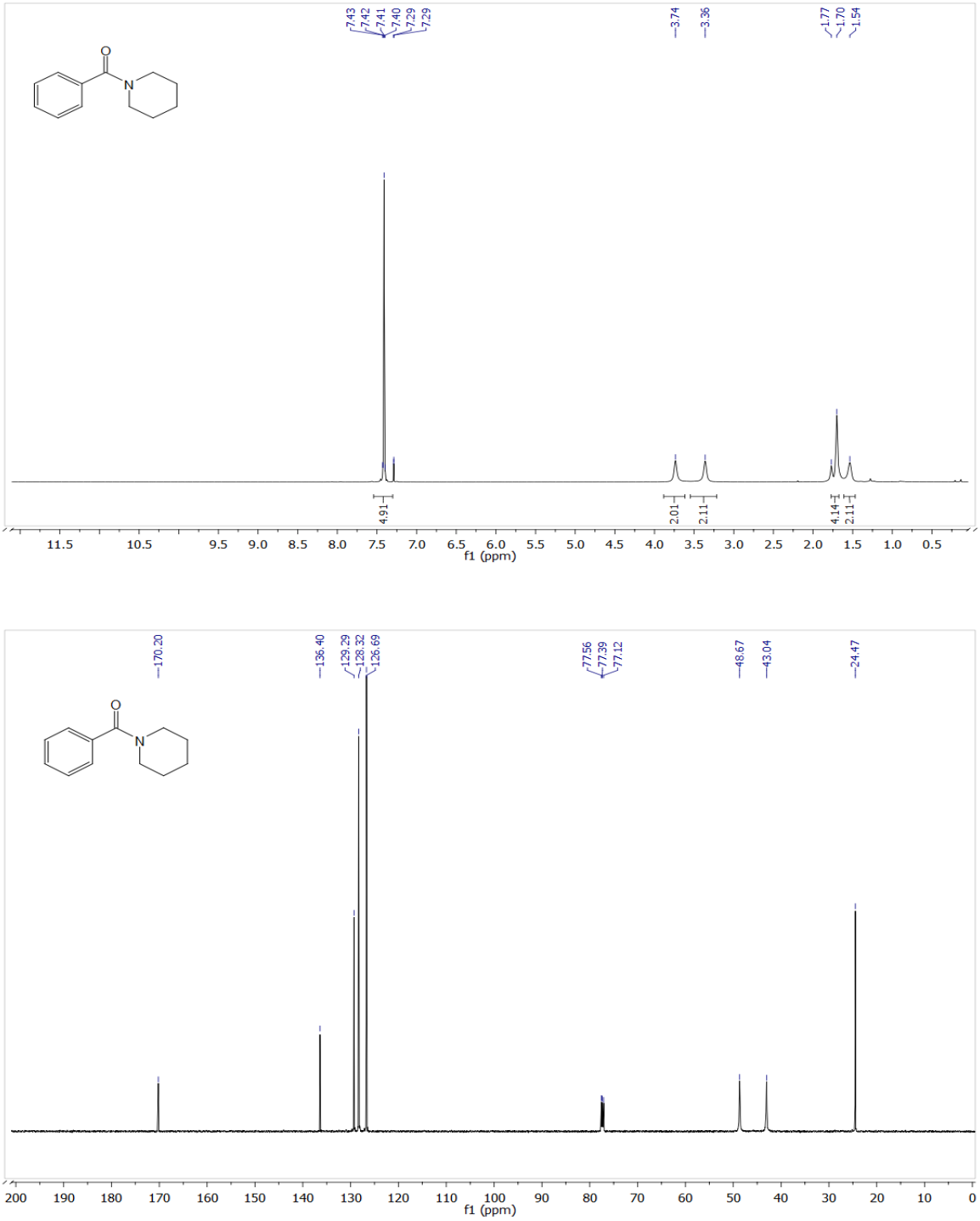


Figure 3.4 ^{1}H and ^{13}C NMR of phenyl(piperidin-1-yl)methanone (**3a**).

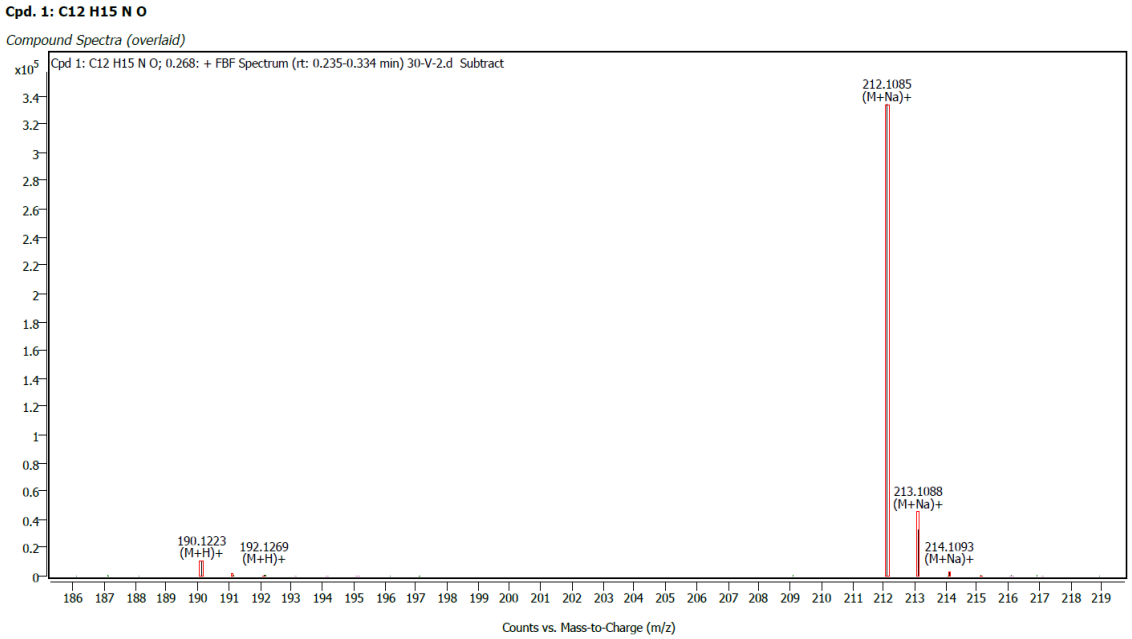


Figure 3.5 Mass Spectra of phenyl(piperidin-1-yl)methanone (**3a**).

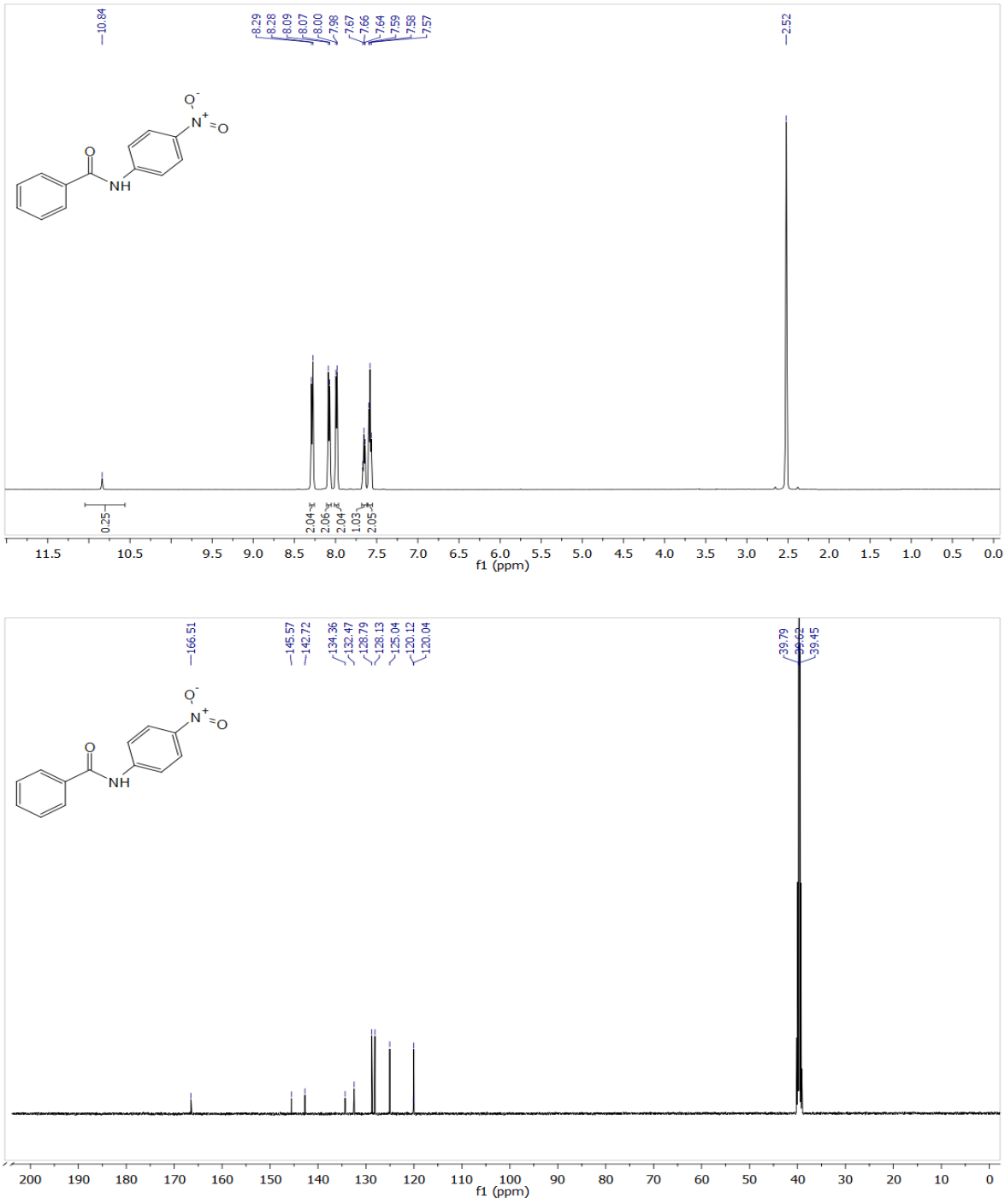


Figure 3.6 ^{1}H and ^{13}C NMR Spectra of *N*-(4-nitrophenyl)benzamide (**3g**)

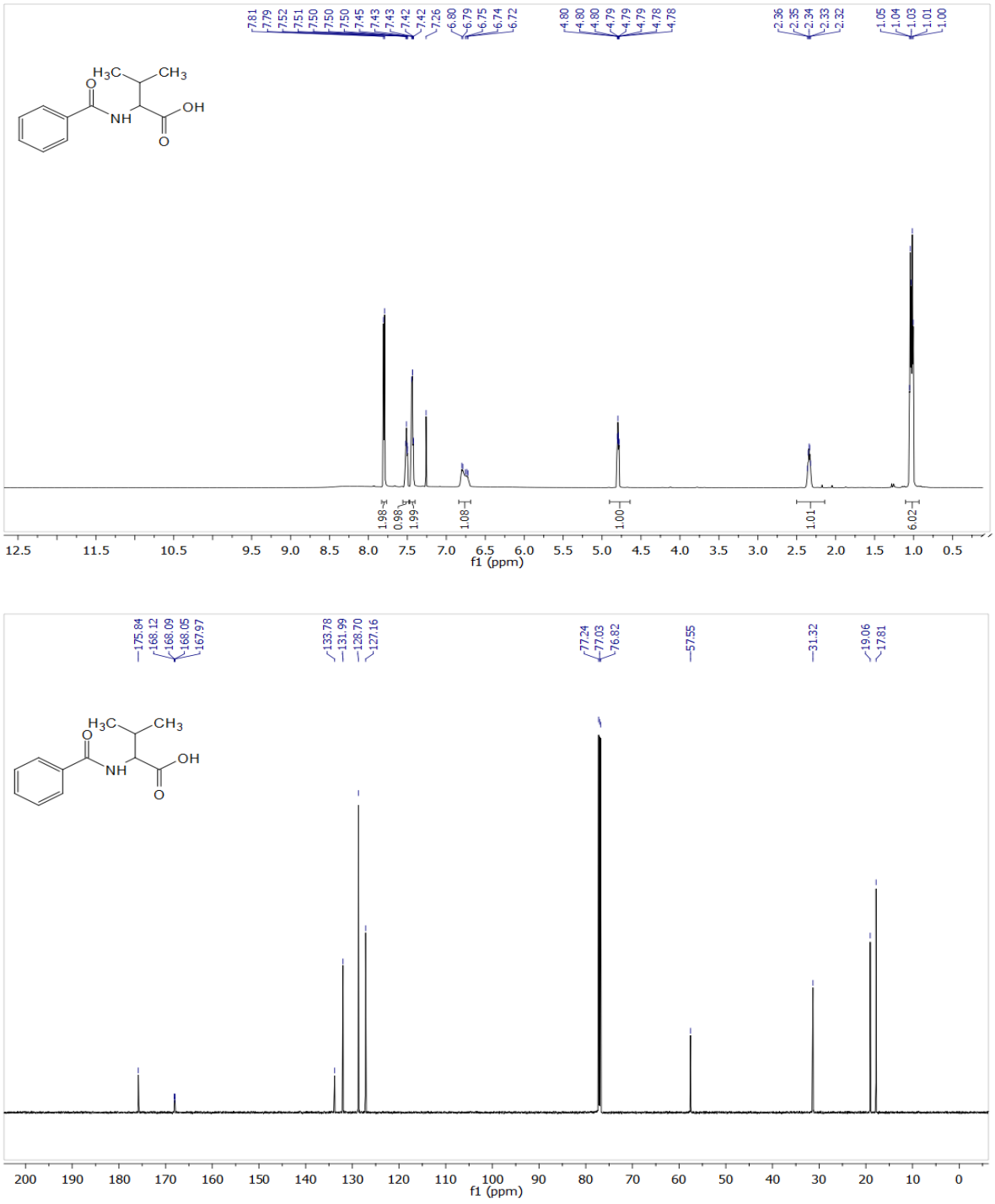


Figure 3.7 ^{1}H and ^{13}C NMR Spectra of *N*-benzoylvaline (**6b**)

3.8 References

[1] C. Lv, R. Zhao, X. Wang, D. Liu, T. Muschin, Z. Sun, C. Bai, A. Bao, Y.S. Bao, "Copper-Catalyzed Transamidation of Unactivated Secondary Amides via C–H and C–N Bond Simultaneous Activations," *The Journal of Organic Chemistry*, **88** (2023) 2140–2157.

[2] J. Buchspies, M. M. Rahman, M. Szostak, "Transamidation of Amides and Amidation of Esters by Selective N–C (O)/O–C (O) Cleavage Mediated by Air-and Moisture-Stable Half-Sandwich Nickel (II)–NHC Complexes," *Molecules*, **26** (2021) 188.

[3] A. Greenberg, CM. Breneman, JF. Liebman, " The amide linkage: Structural significance in chemistry, biochemistry, and materials science," *John Wiley & Sons*, (2000).

[4] D. G. Brown, J. Bostrom, " Analysis of past and present synthetic methodologies on medicinal chemistry: where have all the new reactions gone" *Journal of medicinal chemistry*, **59** (2016) 4443–4458.

[5] A. Mishra, S. Chauhan, P. Verma, S. Singh, V. Srivastava, " TBHP-Initiated Transamidation of Secondary Amides via C−N Bond Activation: A Metal-Free Approach," *Asian Journal of Organic Chemistry*, **8** (2019) 853–857.

[6] J. Chen, Y. Xia, S. Lee, " Transamidation for the Synthesis of Primary Amides at Room Temperature," *Organic Letters*, **22** (2020) 3504–3508.

[7] K. K. Chouhan, D. Chowdhury, A. Mukherjee, " Transamidation of aromatic amines with formamides using cyclic dihydrogen tetrametaphosphate," *Organic & Biomolecular Chemistry*, **20** (2022) 7929–7935.

[8] G. Li, M. Szostak, " Highly selective transition-metal-free transamidation of amides and amidation of esters at room temperature," *Nature Communications*, **9** (2018) 4165.

[9] S. Singh, J. Kandasamy, " Synthesis of 1,3-Dicarbonyl Compounds using N-Cbz Amides as an Acyl Source under Transition-metal-free Conditions at Room Temperature," *Asian Journal of Organic Chemistry*, **11** (2022) e202200416.

[10] D. Eisenberg, " The discovery of the α-helix and β-sheet, the principal structural features of proteins," *Proceedings of the National Academy of Sciences*, **100** (2003) 11207–11210.

[11] P. L. Villabrille, V. Palermo, A. G. Sathicq, P. G. Vazquez, G. P. Romanelli, " Transition metal-doped heteropolyacid catalysts for the suitable multicomponent synthesis of monastrol and bioactive related compounds," *Current Organic Chemistry*, **22** (2018) 94–100.

[12] E. L. Baker, M. M. Yamano, Y. Zhou, S. M. Anthony, N. K. Garg, " A two-step approach to achieve secondary amide transamidation enabled by nickel catalysis," *Nature Communications*, **7** (2016) 11554.

[13] J. E. Dander, E. L. Baker, N. K. Garg, "Nickel-catalyzed transamidation of aliphatic amide derivatives," *Chemical Science*, **8** (2017) 6433–6438.

[14] M. M. Mehta, T. B. Boit, J. E. Dander, N. K. Garg, " Ni-catalyzed Suzuki–Miyaura cross-coupling of aliphatic amides on the benchtop," *Organic Letters*, **22** (2019) 1–5.

[15] Y. Guo, R. Y. Wang, J. X. Kang, Y. N. Ma, C. Q. Xu, J. Li, X. Chen, " Efficient synthesis of primary and secondary amides via reacting esters with alkali metal amidoboranes," *Nature Communications*, **12** (2021) 5964.

[16] Z. Song, T. Xu, J. Wang, Y. Hou, C. Liu, S. Liu, S. Wu, "Secondary metabolites of the genus Amycolatopsis: Structures, bioactivities and biosynthesis," *Molecules*, **26** (2021) 1884.

[17] S. Shi, M. Szostak, "Pd–PEPPSI: A general Pd–NHC precatalyst for Buchwald–Hartwig cross-coupling of esters and amides (transamidation) under the same reaction conditions," *Chemical Communications*, **53** (2017) 10584–10587.

[18] S. Shi, S. P. Nolan, M. Szostak, "Well-defined palladium (II)–NHC precatalysts for cross-coupling reactions of amides and esters by selective N–C/O–C cleavage," *Accounts of Chemical Research*, **51** (2018) 2589–2599.

[19] T. Zhou, G. Li, S. P. Nolan, M. Szostak, "[Pd (NHC)(acac) Cl]: well-defined, air-stable, and readily available precatalysts for Suzuki and Buchwald–Hartwig cross-coupling (TRansamidation) of amides and esters by N–C/O–C activation," *Organic Letters*, **21** (2019) 3304–3309.

[20] P. Lei, Y. Wang, Y. Mu, Y. Wang, Z. Ma, J. Feng, X. Liu, M. Szostak, "Green-Solvent Selection for Acyl Buchwald–Hartwig Cross-Coupling of Amides

(Transamidation)," *ACS Sustainable Chemistry & Engineering*, **9** (2021) 14937–14945.

[21] Y. Liu, S. Shi, M. Achtenhagen, R. Liu, M. Szostak, "Metal-free transamidation of secondary amides via selective N–C cleavage under mild conditions," *Organic Letters*, **19** (2017) 1614–1617.

[22] M. M. Rahman, G. Li, M. Szostak, "Metal-Free Transamidation of Secondary Amides by N–C Cleavage," *The Journal of Organic Chemistry*, **84** (2019) 12091–12100.

[23] S. Singh, S. Popuri, Q. M. Junaid, S. Sabiah, J. Kandasamy, "Diversification of α-ketoamides via transamidation reactions with alkyl and benzyl amines at room temperature," *Organic & Biomolecular Chemistry*, **19** (2021) 7134–7140.

[24] P. Sureshbabu, S. Azeez, P. Chaudhary, J. Kandasamy, "tert-Butyl nitrite promoted transamidation of secondary amides under metal and catalyst free conditions," *Organic & Biomolecular Chemistry*, **17** (2019) 845–850.

[25] V. K. Kanaujiya, V. Tiwari, K. Pattanaik, S. Sabiah, J. Kandasamy, "Synthesis of Glycouronamides by Transamidation Approach at Room Temperature," *Asian Journal of Organic Chemistry*, **11** (2022) e202200315.

[26] S. Singh, P. Sureshbabu, S. Sabiah, J. Kandasamy, "Synthesis of N-Aryl α-Ketoamides, α-Ketoesters, α-Ketothioesters and Their Applications in Quinoxalinone Preparation," *Asian Journal of Organic Chemistry*, **11** (2022) e202200122.

[27] S. Singh, J. Kandasamy, "Synthesis of Acyl Hydrazides from Carboxamides and Hydrazine Hydrate Under Metal-Free Conditions at Room Temperature," *Asian Journal of Organic Chemistry*, **12** (2023) e202300115.

[28] I. A. P. S. Rajan, S. Rajendran, "Amidic resonance not a barrier for transamidation of N -pivaloyl activated amides: catalyst, base and additive free conditions," *Organic & Biomolecular Chemistry*, **21** (2023) 4760–4765.

[29] C. W. Cheung, M. L. Ploeger, X. Hu, "Nickel-Catalyzed Reductive Transamidation of Secondary Amides with Nitroarenes," *ACS Catalysis*, **7** (2017) 7092–7096.

[30] E. Javanmardi, S. Liu, N. Xie, "Exploring Grey Systems Theory-Based Methods and Applications in Sustainability Studies: A Systematic Review Approach," *Sustainability*, **12** (2020) 4437.

[31] K. Martina, G. Cravotto, R. S. Varma, "Impact of Microwaves on Organic Synthesis and Strategies toward Flow Processes and Scaling Up," *The Journal Organic Chemistry*, **86** (2021) 13857–13872.

[32] R. M. Borade, S. B. Somvanshi, S. B. Kale, R. P. Pawar, K. M. Jadhav, "Spinel zinc ferrite nanoparticles: an active nanocatalyst for microwave irradiated solvent free synthesis of chalcones," *Materials Research Express*, **7** (2020) 016116.

[33] N. C. Desai, K. Bhatt, D. J. Jadeja, H. K. Mehta, V. M. Khedkar, D. Sarkar, "Conventional and microwave-assisted organic synthesis of novel antimycobacterial agents bearing furan and pyridine hybrids," *Drug Development Research*, **83** (2022) 416–431.

[34] M. Srinivas, A. D. Hudwekar, V. Venkateswarlu, G. L. Reddy, K. A. A. Kumar, R. A. Vishwakarma, S. D. Sawant, "A metal-free approach for transamidation of amides with amines in aqueous media," *Tetrahedron Letters*, **56** (2015) 4775–4779.

[35] R. Fu, Y. Yang, Z. Chen, W. Lai, Y. Ma, Q. Wang, R. Yuan, "Microwave-assisted heteropolyanion-based ionic liquids catalyzed transamidation of non-activated carboxamides with amines under solvent-free conditions," *Tetrahedron*, **70** (2014) 9492–9499.

[36] Y. Shimizu, H. Morimoto, M. Zhang, T. Ohshima, "Microwave-Assisted Deacylation of Unactivated Amides Using Ammonium-Salt-Accelerated Transamidation," *Angewandte Chemie*, **124** (2012) 8692–8695.

[37] P. S. Girase, V. Kumar, S. Dhawan, R. Karpoormath, "Facile Synthesis of Amides through Transamidation with Iodine under Neat Conditions," *ChemistrySelect*, **7** (2022) e202103237.

[38] A. Ivanković, A. Dronjić, A. M. Bevanda, S. Talić, "Review of 12 Principles of Green Chemistry in Practice," *International Journal of Sustainable and Green Energy*, **6** (2017) 39–48.

[39] T. L. Chen, H. Kim, S. Y. Pan, P. C. Tseng, Y. P. Lin, P. C. Chiang, "Implementation of green chemistry principles in circular economy system towards sustainable development goals: Challenges and perspectives," *Science of The Total Environnment*, **716** (2020) 136998.

[40] R. Ratti, "Industrial applications of green chemistry: Status, Challenges and Prospects," *SN Applied Sciences*, **2** (2020) 263.

[41] A. Mishra, S. Singh, V. Srivastava, "Cerium Catalyzed Transamidation of Secondary Amides under Ultrasound Irradiation: A Breakthrough in Organic Synthesis," *Asian Journal of Organic Chemistry*, **7** (2018) 1600-1604.

[42] A. S. Grewal, K. Kumar, S. Redhu, S. Bhardwaj, "Microwave assisted synthesis: a green chemistry approach," *International Research Journal of Pharmaceutical and Applied Sciences*, **3** (2013) 278–285

[43] S. Nain, R. Singh, S. Ravichandran, "Importance of Microwave Heating In Organic Synthesis," *Advanced Journal of Chemistry*, **2** (2019) 94–104.

[44] M. Henary, C. Kananda, L. Rotolo, B. Savino, E. A. Owens, G. Cravotto, "Benefits and applications of microwave-assisted synthesis of nitrogen containing heterocycles in medicinal chemistry," *RSC Advances*, **10** (2020) 14170–14197.

[45] D. Yang, T. Shin, H. Kim, S. Lee, "Nickel/briphos-catalyzed transamidation of unactivated tertiary amides," *Organic & Biomolecular Chemistry*, **18** (2020) 6053–6057.

[46] I. A. P. S. Rajan, S. Rajendran, "One pot transamidation of N-pivaloyl activated amides with anilines in the absence of catalyst, base and additive," *New Journal of Chemistry*, **47** (2023) 10480–10483.

[47] J. Yin, J. Zhang, C. Cai, G.-J. Deng, H. Gong, "Catalyst-Free Transamidation of Aromatic Amines with Formamide Derivatives and Tertiary Amides with Aliphatic Amines," *Organic Letters*, **21** (2019) 387–392.

[48] S. Vijayapritha, P. Viswanathamurthi, "New half-sandwich (η6-p-cymene) ruthenium (II) complexes with benzothiazole hydrazone Schiff base ligand: synthesis, structural characterization and catalysis in transamidation of carboxamide with primary amines," *Journal of Organometallic Chemistry*, **929** (2020) 121555

[49] G. Li, C. L. Ji, X. Hong, M. Szostak, "Highly Chemoselective, Transition-Metal-Free Transamidation of Unactivated Amides and Direct Amidation of Alkyl Esters by N–C/O–C Cleavage," *Journal of the American Chemical Society*, **141** (2019) 11161–11172.

[50] G. Li, M. Szostak, "Non-Classical Amide Bond Formation: Transamidation and Amidation of Activated Amides and Esters by Selective N–C/O–C Cleavage," *Synthesis*, **52** (2020) 2579–2599.

[51] R. M. D. Figueiredo, J.-S. Suppo, J.-M. Campagne, "Nonclassical Routes for Amide Bond Formation," *Chemical Reviews*, **116** (2016) 12029-12122.