ejpmr, 2017,4(2), 126-151

SJIF Impact Factor 4.161

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

A NOVEL COPPER-CATALYZED C-C BOND CLEAVAGE OF ARYL (HETEROARYL) ALKYL KETONES FOR C-N BOND FORMATION

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Article Received on 02/12/2016 **Article Revised on 22/12/2016** **Article Accepted on 12/01/2017**

ABSTRACT

A direct generation of amide from aryl (heteroaryl) alkyl ketones has been accomplished via copper(II) catalyzed C-C bond cleavage in the presence of diisopropylamine at moderate temperature. The transformation steps for amide formation comprise catalytic generation of α-bromo carbonyl species followed by nucleophilic displacement of bromide with sodium azide in the presence of diisopropylamine. The final step involves the formation of imine by heating in situ followed by hydrolysis to give the related amide.

KEYWORDS: ketones, cleavage reaction, amide, cupper catalist.

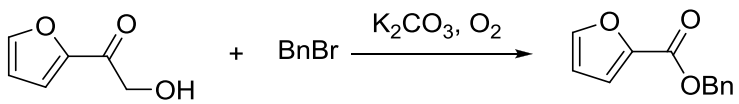
INTRODUCTION

Manipulation of carbon-carbon bonds is an important issue in both organic chemistry and industry.[1] The chemoselective cleavage of C-C bonds has always been long standing interest and a challenge for chemists over the past few decades.[2] The inert nature of the C-C single bond which is thermodynamically stable has driven a lot of attention for its chemoselective cleavage. Since these bonds have been coordinated with metal catalyst weakly, their activity is lesser than most organic compounds.[3] To cleave such bonds, special substrates such as strained like three- and four-membered rings to improve the C-C single bond reactivity, and suitable catalytic systems to decrease their activation energy was used.[2] In addition, oxidative cleavage is one of the favorite methods.[4] However, oxidative cleavage of C-C bonds needs harsh reaction conditions with stoichiometric amounts of oxidants, such as peroxides[5] and toxic metal salts.[6]

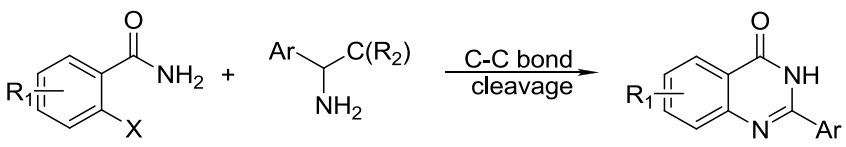
Aryl ketones are among the ubiquitous structural motifs in the synthesis of natural products and pharmaceutical compounds, and the direct transformation of them is more interesting among organic chemists.[7]

Transformation of aryl ketones to amides under mild conditions is a big challenge and a fascinating area for the synthetic community. Recently Jiang and co-workers[8] reported an interesting transition-metal free aerobic oxidative cleavage and esterification of the C-C bond of α-hydroxyketones (Scheme 1a). Also, Wang and co-workers[9] have reported the copper-catalyzed domino reaction for cleavage of C-C bond (Scheme 1b). Herein, we report a novel copper-catalyzed C-C bond cleavage reaction for C-N bond formation which enables the direct transformation of aryl alkyl ketones into benzamides with high efficiency (Scheme 1c).

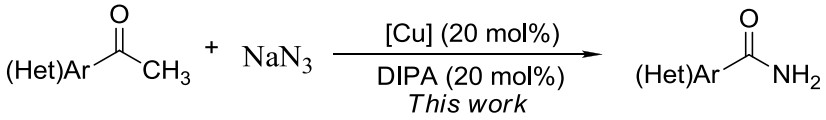
a) C-O bond formation



b) C-N bond formation



c) C-N bond formation



Scheme 1: C-C single-bond cleavage

Experimental

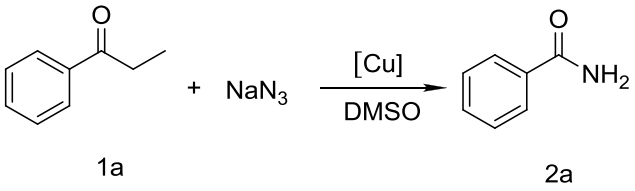
General Methods: All manipulations were identified with ^{1}H-NMR spectra with a Bruker AVIII-500 AND 300 spectrometer.[13] C-NMR spectra were obtained by the same NMR spectrometer. The melting points of products were determined with an Electrothermal Type 9100 melting point apparatus. The mass spectra were scanned on a Varian Mat CH-7 at 70 eV. The mass spectra were scanned on a Varian Mat CH-7 at 70 eV. The IR spectra were obtained on an Avatar 370 FT-IR Thermo-Nicolet spectrometer. Materials obtained from commercial suppliers were used without further purification, the most starting materials was purchased from Merck (Germany) and Fluka (Buchs, Switzerland).

Typical procedure for synthesis of aryl (hetroaryl) amide: A mixture of aryl (heteroaryl) alkyl ketones (0.5 mmol) and $CuBr_2$ (22.3 mg, 0.1 mmol) in dimethyl sulfoxide (DMSO) (2.0 mL) was stirred at room temperature for 10 minutes. Then sodium azide (NaN_3) (94.5 mg, 1.5 mmol) and diisopropylamine (DIPA)[10] (0.014 mL) was added and the reaction mixture was heated to 120 °C and stirred for 2 hours. The progress of the reaction was monitored by TLC using ethyl acetate/ petroleum ether (1:1) as eluent, then the reaction mixture was extracted with ethyl acetate and brine. The extracted was dried over sodium sulfate; the organic solvent was evaporated and the remaining solid was purified by flash column chromatography on silica gel (ethyl acetate/ petroleum ether 1:1) to obtain the products.

The products was monitored by TLC and it is noteworthy that this reaction did not proceed in the absence of catalyst and base (entries 6 and 7).

For evaluation of the proposed amide fragment, coupling began with exposure of propiophenone and to a series of copper catalysts.

Table 1: Screening of the reaction conditions[a]

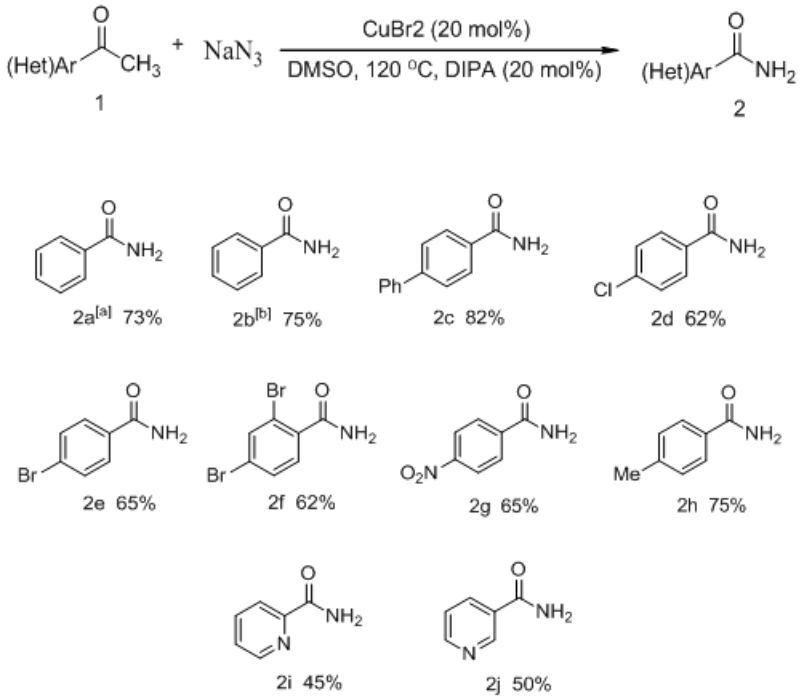


Entry	[Cu] (mol %)	Base	T [˚C]	Yield[b] %
1	CuBr (20)	DIPA	90	0
2	CuI (20)	DIPA	90	0
3	$CuCl_2$ (20)	DIPA	90	Trace
4	$CuBr_2$ (10)	DIPA	90	34
5	$CuBr_2$ (20)	DIPA	90	60
6	-	DIPA	120	0
7	$CuBr_2$ (20)	-	120	0
8	$CuBr_2$ (20)	DIPA	120	73
9	$CuBr_2$ (20)	TEA	120	68
10	$CuBr_2$ (20)	KOH	120	Trace
11	$CuBr_2$ (20)	NaOH	120	Trace
12	$CuBr_2$ (20)	K_2CO_3	120	Trace
13	$Cu(OAc)_2$ (20)	DIPA	120	35
14	$Cu(NO_3)_2$ (20)	DIPA	120	30

[a]Reaction were performed on DMSO (2mL) for 2 hours. [b]Yields of isolated products.

RESULTS AND DISCUSSION

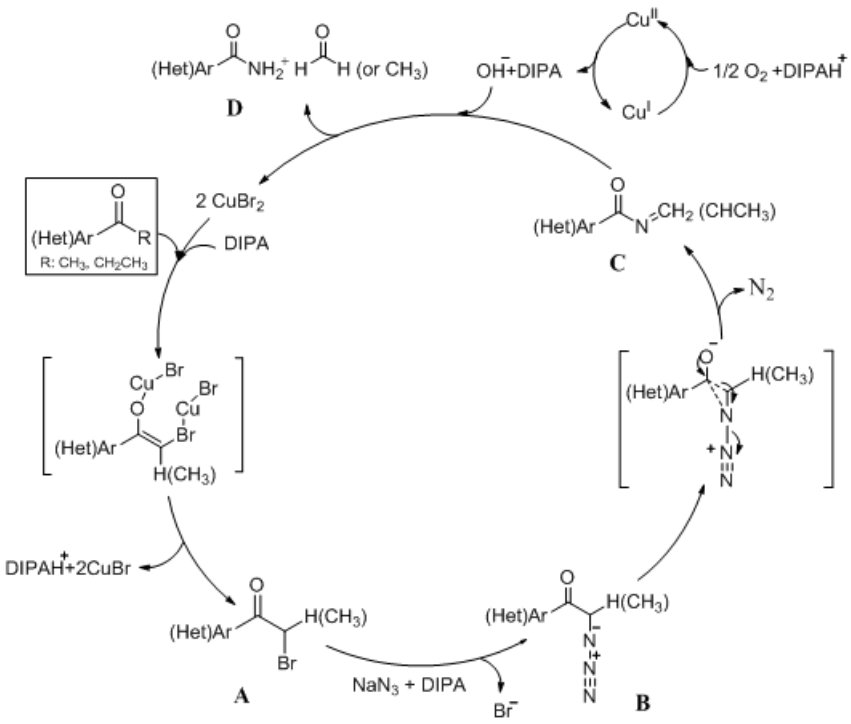
To extend the scope of this transformation several others alkyl aryl or heteroaryl carbonyl compounds were subjected to the same reaction conditions and the results are shown in Scheme 2. It is notable that electron donating substituents on alkyl aryl ketones facilitate the reaction and the corresponding benzamides are obtained in relatively better yields (2c, 2h).



Scheme 2. Transformation of aryl methyl ketones

Also, to distinguish these pathways, a series of Cu(*II*) salts that did not contain halogens such as $Cu(OAc)_2$, $Cu(NO_3)_2$ was used to evaluate the generation of α-halo ketones, and no desired amides were observed in any case (table 1, entries 13 and 14). These control experiments indicate that the ketone substrate possibly first reacts with copper(*II*) bromide and generate the α-bromo species[11] and then react with sodium azide. It seems that, based on MacMillan and co-workers, reports[11], diisopropylamin acts as a weak base, and by forming enolate allows the copper catalyst to coordinate with it, and the reductive elimination of a bromide from the copper-bound enolate was happened to form the desired α-bromocarbonyl and Cu(*0*). Under this reaction conditions, a diverse range of carbonyl substrates can undergo bromination at the α-position easily.[11] The choice of solvent also appeared to be crucial in this transformation. As it shown in table 1, in our case dimethyl sulfoxide was the best solvent, presumably due to solvent stabilization and its metal-coordinating properties.[12]

To elucidate the mechanism of this reaction, it was carried out unambiguously with phenacyl bromide as α-bromo carbonyl species both in the absence and presence of copper(*II*) bromide. The reaction situation was the same with the general experiment, except adding copper(*II*) bromide as catalyst; no desired products were observed in the absence of copper(*II*) bromide. It could show that copper(*II*) bromide not only plays an important role in the preparing of α-bromocarbonyl as an intermediate[11], it is more important for the other step of reaction, as well..

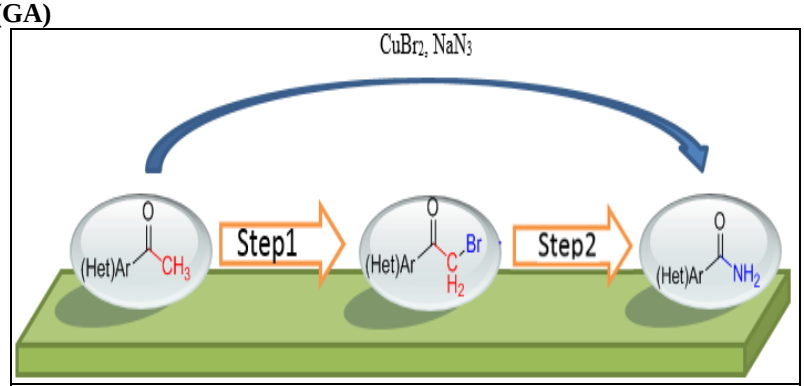


Scheme 3: Mechanistic proposal.

Based on our results, a plausible mechanism for this transformation is depicted in Scheme 3. Copper(*II*) catalyzed α-bromination of the carbonyl compound is the first step in this transformation and plays a significant role to produce the α-bromo species (A) as the proper substrate for the next step nucleophilic displacement of the bromine atom with sodium azide in the presence of diisopropylamine (B). It seems likely the reaction proceed through the transformation of an aziridine intermediate to the N-methyleneacetamide (C)[13] and hydrolysis to furnish the related benzamide (D). (Scheme. 3)

According to the proposed mechanism, acetaldehyde would be generated during the reaction. To ensure the mechanism of reaction and generation of acetaldehyde, this reaction was repeated under optimized condition. By starting the reaction, one condenser was connected to the reaction vessel and conducted the gas which was generated through the reaction to the other vessel in the low temperature. By arrival of these gases to this cold vessel, it was converted to the liquid phase. This liquid compound was examined by 2,4-dinitrophenylhydrazine and Tollens' reagent to predict the generation of aldehyde during the reaction. 2.4-dintrophenylhydrazine in the connection with this liquid, proceeded the orange sediment, an in the connection with Tollens' reagent, the precipitation of elemental silver was perfumed. Based on the above results, we can ensure the integrity of the mechanism.

Graphical Abstract (GA)



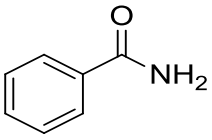
Converting aryl(heteroaryl) ketones to their amide derivatives by using azide, ketines and $CuBr_2$.

Content

General Information

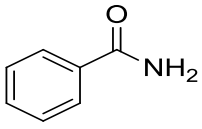
All manipulations were identified with ^{1}H-NMR spectra with a Bruker AVIII-500 AND 300 spectrometer.[13] C-NMR spectra were obtained by the same NMR spectrometer. The melting points of products were determined with an Electrothermal Type 9100 melting point apparatus. The mass spectra were scanned on a Varian Mat CH-7 at 70 eV. The mass spectra were scanned on a Varian Mat CH-7 at 70 eV. The IR spectra were obtained on an Avatar 370 FT-IR Thermo-Nicolet spectrometer. Materials obtained from commercial suppliers were used without further purification, the most starting materials was purchased from Merck (Germany) and Fluka (Buchs, Switzerland).

Benzamide (2a)[1]



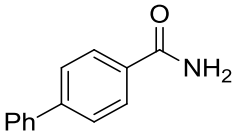
whit solid 0.044 g (73 %); m.p.128-130 °C; IR (KBr) (υmax/cm-1): 3371, 3173 (NH_2), 1659 (C=O); ^{1}H NMR: (500 MHz, DMSO-d6) δ7.95 (brs, 1H), 7.84 (d, *J*= 5.0 Hz, 2 H), 7.50-7.47(t, *J*= 10, 3 H), 7.43-7.32 (t, *J*= 10 , 3H), 7.24 (brs, 1H); ^{13}C NMR: (125 MHz, DMSO-d6) δ167.9, 134.3, 131.2, 128.2, 127.5; MS (EI, 70 eV) *m/z* 121, 105, 76, 51, 28.

Benzamide (2b)[1]



whit solid 0.046 g (75 %) ; m.p.128-130 °C; IR (KBr) (υmax/cm-1): 3371, 3178 (NH2), 1659 (C=O); ^{1}H NMR: (500 MHz, DMSO-d6) δ7.95 (brs, 1H), 7.85 (d, *J*= 5.0 Hz, 2 H), 7.50-7.47(t, *J*= 10, 3 H), 7.43-7.40 (t, *J*= 10 , 3 H), 7.32 (brs, 1H); ^{13}C NMR: (125 MHz, DMSO-d6) δ167.9, 134.3, 131.2, 128.2, 127.5; MS (EI, 70 eV) *m/z* 121, 105, 76, 51, 28.

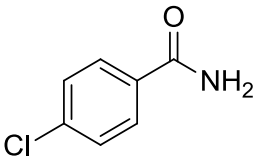
[1,1'-Biphenyl]-4-carboxamide (2c)[2]



white solid 0.82 g (82 %); m.p. 86-88 °C; IR (KBr) (υmax/cm-1): 3406, 3188 (NH_2), 1650 (C=O); 1H NMR: (300 MHz, DMSO-d6) δ8.04 (brs, 1

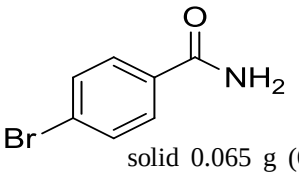
H), 7.98 (d, *J*= 9.0 Hz, 2 H), 7.78-7.73(m, 4 H), 7.51-7.48 (t, *J*= 9, *J*=3 , 2H), 7.44-7.41 (m, 2H); MS (EI, 70 eV) *m/z* 197, 195, 180, 151, 76, 29.

4-chlorobenzamide (2d)[1]



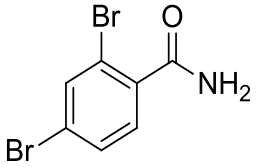
white solid 0.048 g (62 %); m.p. 172-176 °C; IR (KBr) (υmax/cm-1): 3369, 3179 (NH_2), 1658 (C=O); ^{1}H NMR: (500 MHz, DMSO-d6) δ8.03 (brs, 1 H), 7.86 (d, *J*= 7.5 Hz, 2 H), 7. 48(d, *J*= 7.5, 2 H), 7.42 (brs, 1H); ^{13}C NMR: (125 MHz, DMSO-d6) δ166.8, 136.1, 133.1, 129.4, 128.3; MS (EI, 70 eV) *m/z* 156, 154, 138, 111, 75, 28.

4-bromobenzamide (2e)[1]



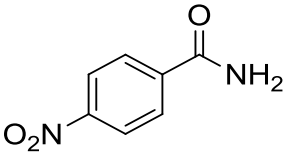
white solid 0.065 g (65 %); m.p. 190-193 °C; IR (KBr) (υmax/cm-1): 3363, 3180 (NH_2), 1659 (C=O); ^{1}H NMR: (500 MHz, DMSO-d6) δ7.89 (brs, 1 H), 7.57-7.55 (d, *J*= 10.0 Hz, 2 H),7.16-7.14 (d, *J*= 10.0, 2 H), 6.92 (brs, 1H; MS (EI, 70 eV) *m/z* 199, 184, 154, 76, 29.

2,4- dibromobenzamide (2f)[3, 4]



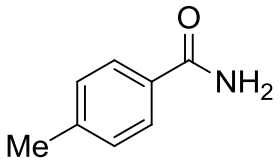
white solid 0.086 g (62 %); m.p. 180-183 °C; IR (KBr) (υmax/cm-1): 3363, 3177 (NH_2), 1659 (C=O); ^{1}H NMR: (500 MHz, DMSO-d6) δ8.04 (brs, 1 H), 7.77 (m, 2 H), 7.62 (d, 1 H), 7.41 (s, 1H), MS (EI, 70 eV) *m/z* 277, 197, 184, 148, 28.

4-nitrobenzamide (2g)[1]



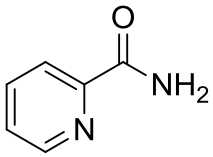
white solid 0.054 g (65 %); m.p. 198-200 °C; IR (KBr) (υmax/cm-1): 3417, 3309 (NH_2), 1666 (C=O); ^{1}H NMR: (500 MHz, DMSO-d6) δ 8.27(m, 3 H), 8.06 (d, *J*= 5.0 Hz, 2 H), 7.70 (brs, 1H); MS (EI, 70 eV) *m/z* 166, 150, 104, 76, 28.

4-methylbenzamide (2h)[1]



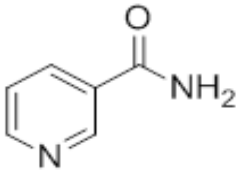
white solid 0.051 g (75 %); m.p.159-162°C; IR (KBr) (υmax/cm-1): 3347, 3165 (NH_2), 1671 (C=O); ^{1}H NMR: (500 MHz, DMSO-d6) δ7.86 (brs, 1 H), 7.75-7.74 (d, *J*= 5.0 Hz, 2 H), 7.21- 7.20 (m, 3 H); ^{13}C NMR: (125 MHz, DMSO-d6) δ167.8, 141.1, 131.5, 128.7, 127.5; MS (EI, 70 eV) *m/z* 135, 91, 77, 65, 29.

Picolinamide (2i)[5]



white solid 0.028 g (45 %); m.p. 104-106 °C; IR (KBr) (υmax/cm-1): 3419, 3175 (NH2), 1663 (C=O); ^{1}H NMR: (300 MHz, DMSO-d6) δ8.64 (d, j=3 Hz, 2 H), 8.13-7.97(m, 3 H), 7.66-7-59 (m, 2 H); MS (EI, 70 eV) *m/z* 122, 105, 78, 28.

Nicotinamide (2i)[5]



white solid 0.031 g (50 %); m.p. 128-130 °C; IR (KBr) (υmax/cm-1): 3371, 3165 (NH2), 1680 (C=O); ^{1}H NMR: (300 MHz, DMSO-d6) δ9.04 (brs, 1 H), 8.72-8.70 (dd, *J*= 3.0 Hz, 1 H), 8.24-8.18 (m, 2 H), 7.62 (brs, 1H), 7.53-7.49 (m, 1H); MS (EI, 70 eV) *m/z* 122, 105, 76, 28.

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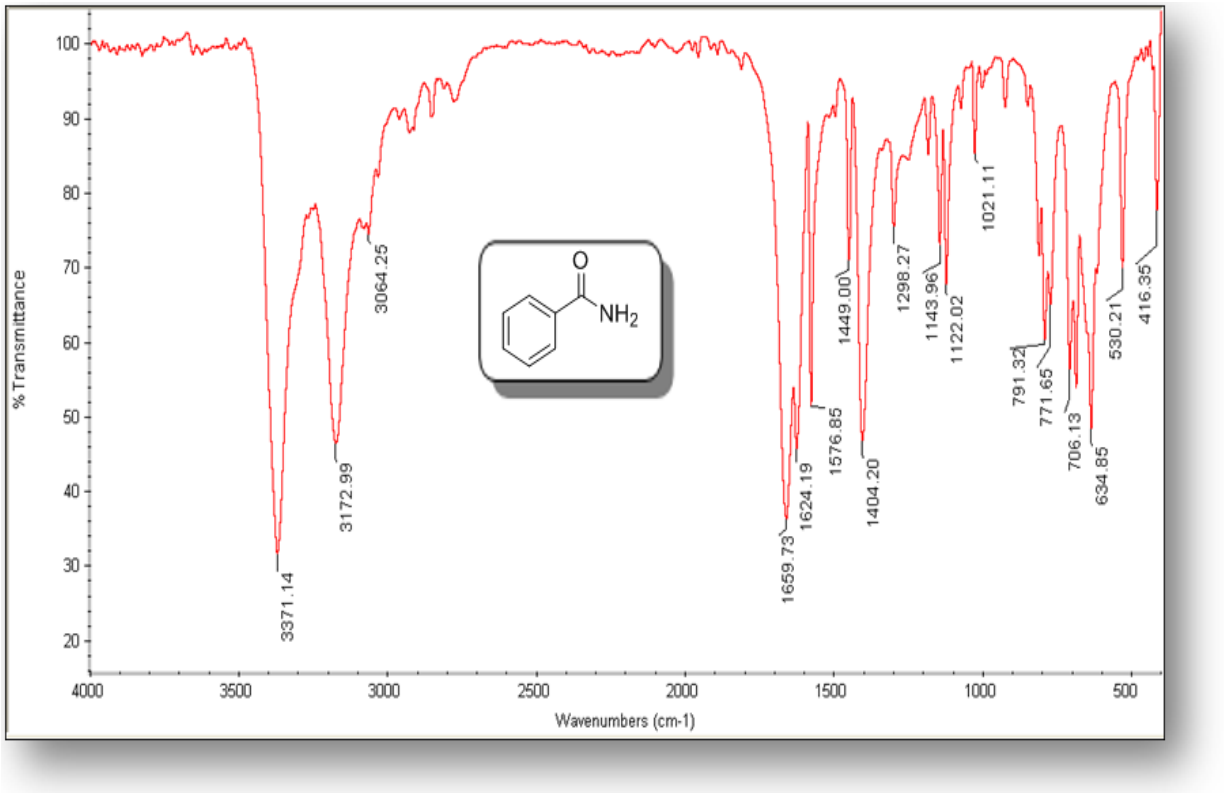

Figure 1a. FT-IR (neat) of benzamide (scheme 2, 2a)

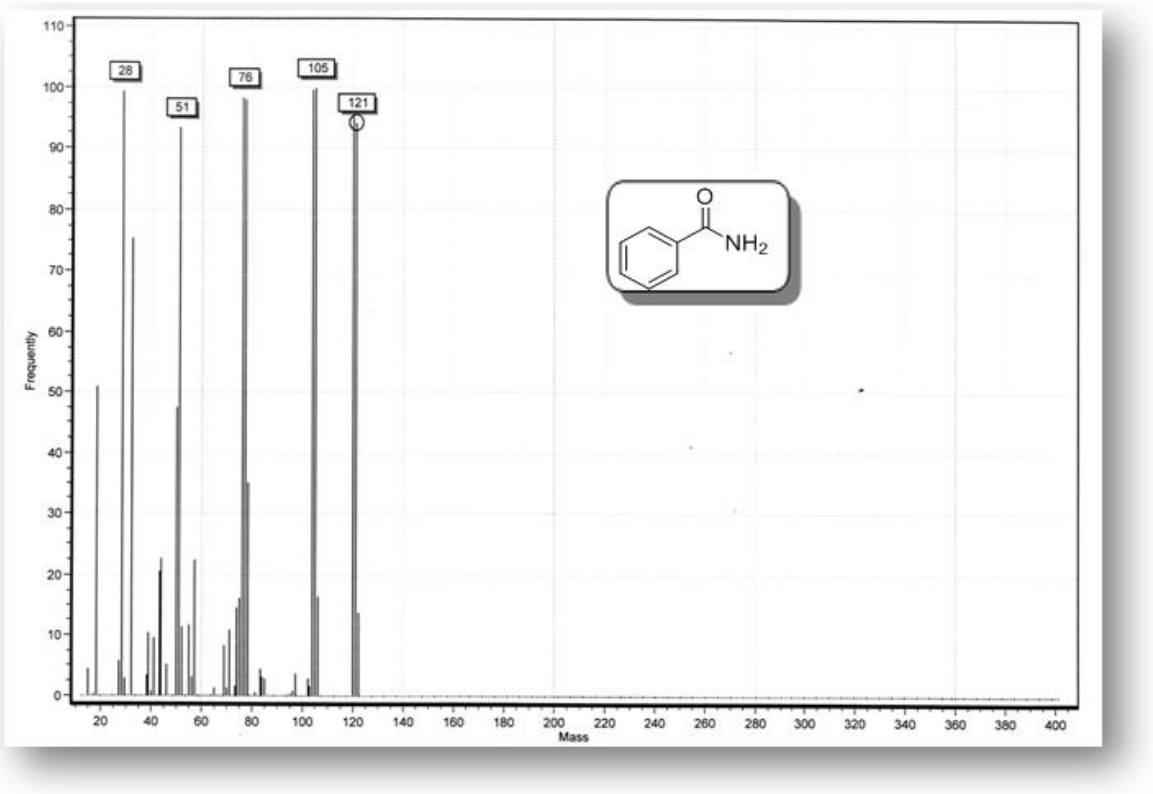

Figure 1b. Mass spectrum of benzamide (Scheme 2, 2a)

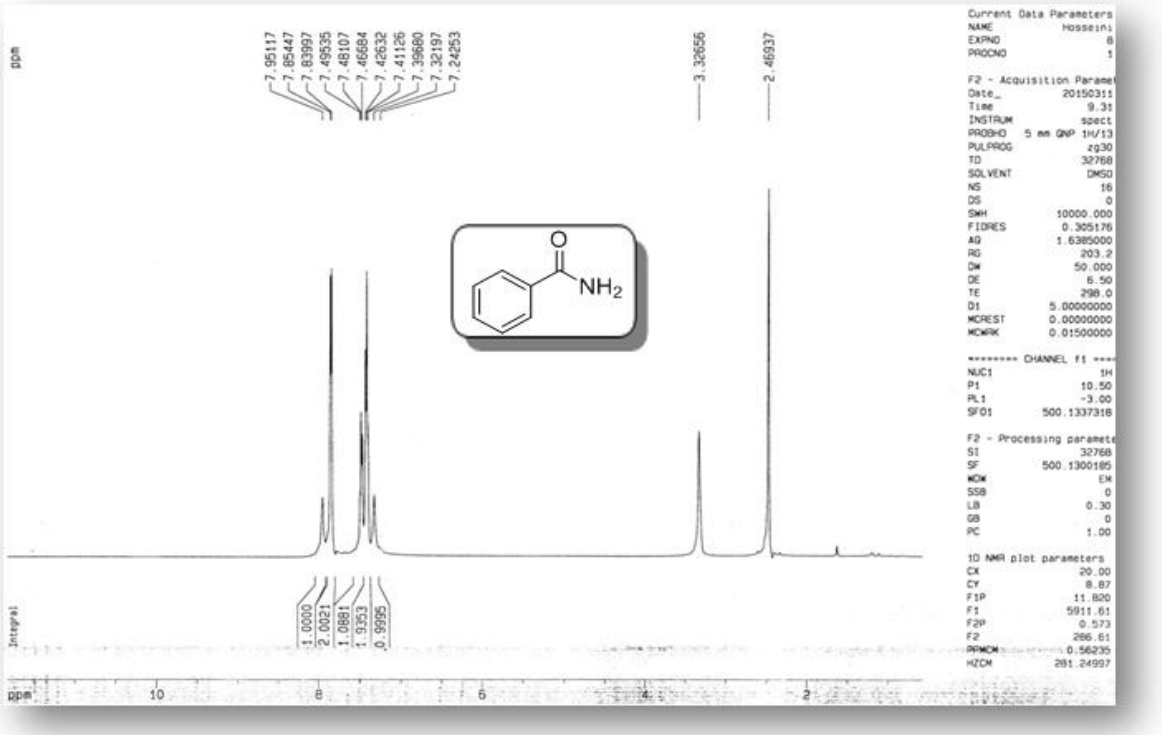

Figure 1c. ^{1}H NMR (500 MHz, DMSO-*d6*) of benzamide (Scheme2, 2a)

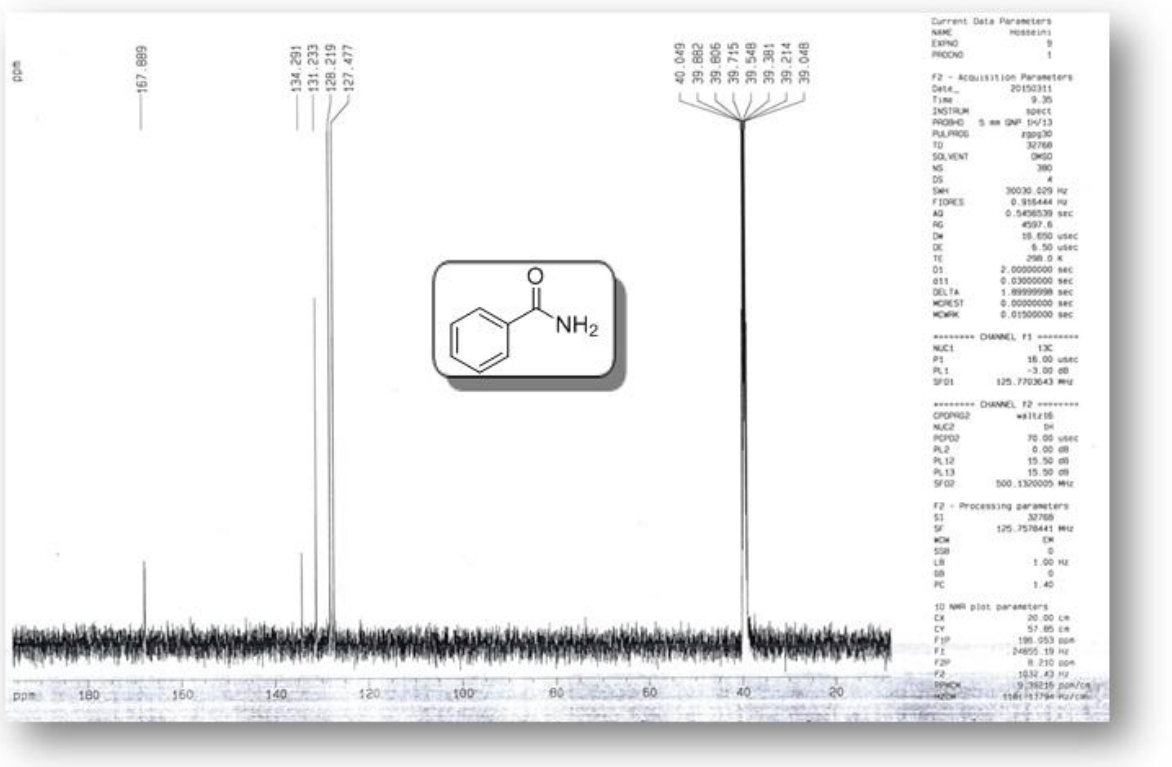

Figure 1d.[13] CNMR (125 MHz, DMSO-*d6*) of benzamide (Scheme 2, 2a)

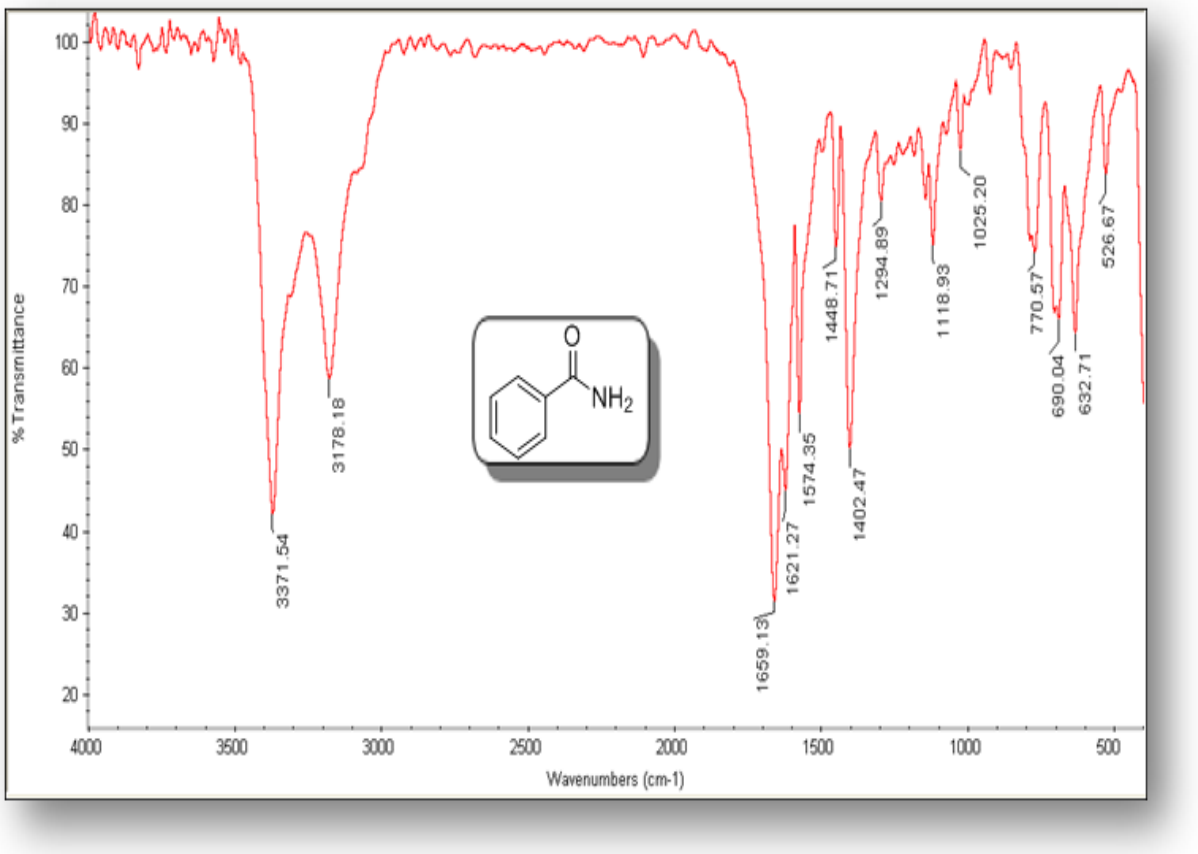

Figure 2a. FT-IR (neat) of benzamide (scheme 2, 2b)

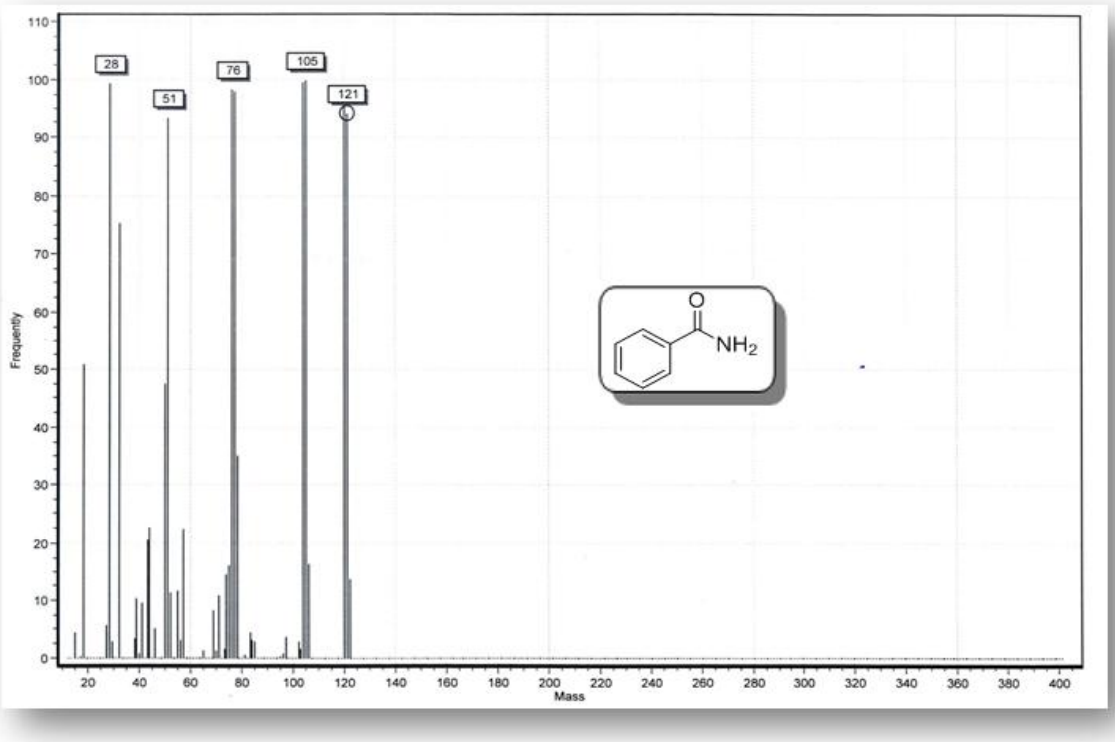

Figure 2b. Mass spectrum of benzamide (Scheme 2, 2b)

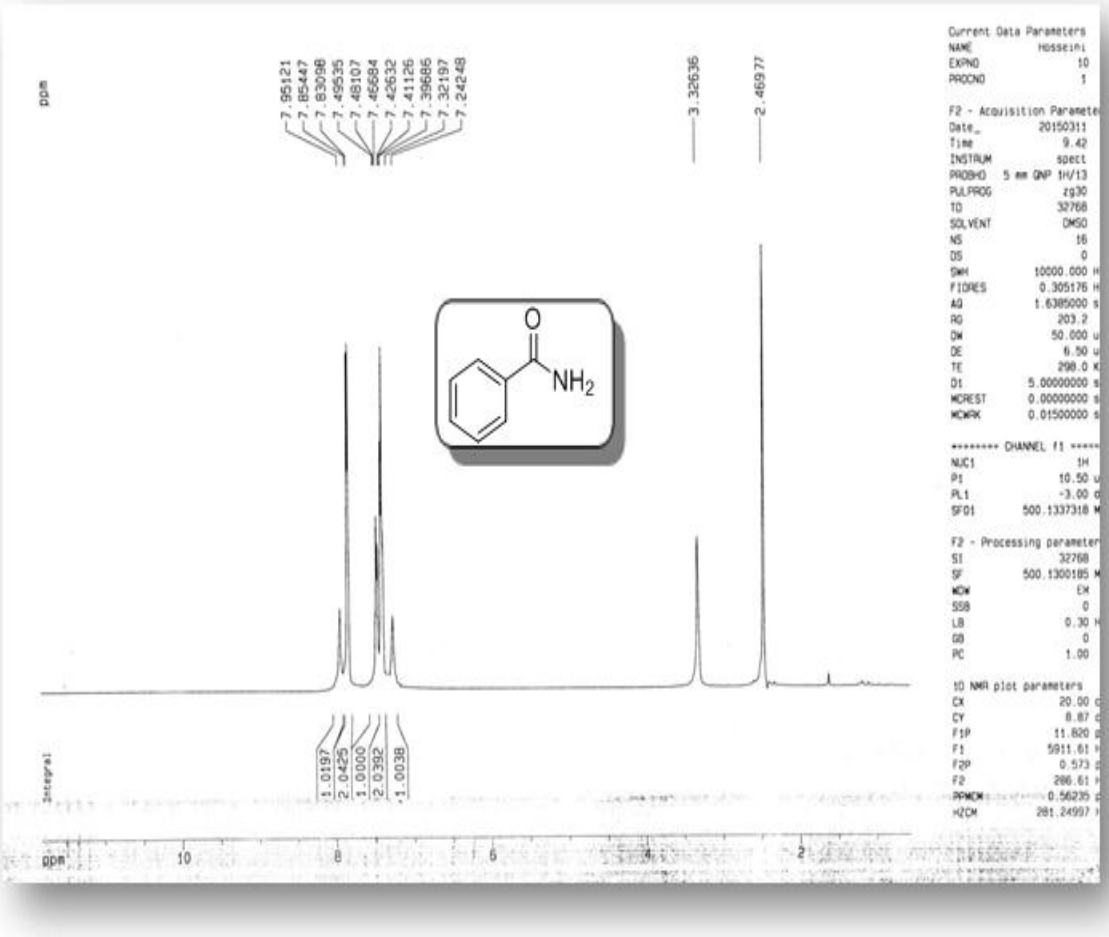

Figure 2c: ^{1}H NMR (500 MHz, DMSO-*d6*) of benzamide (Scheme 2, 2b)

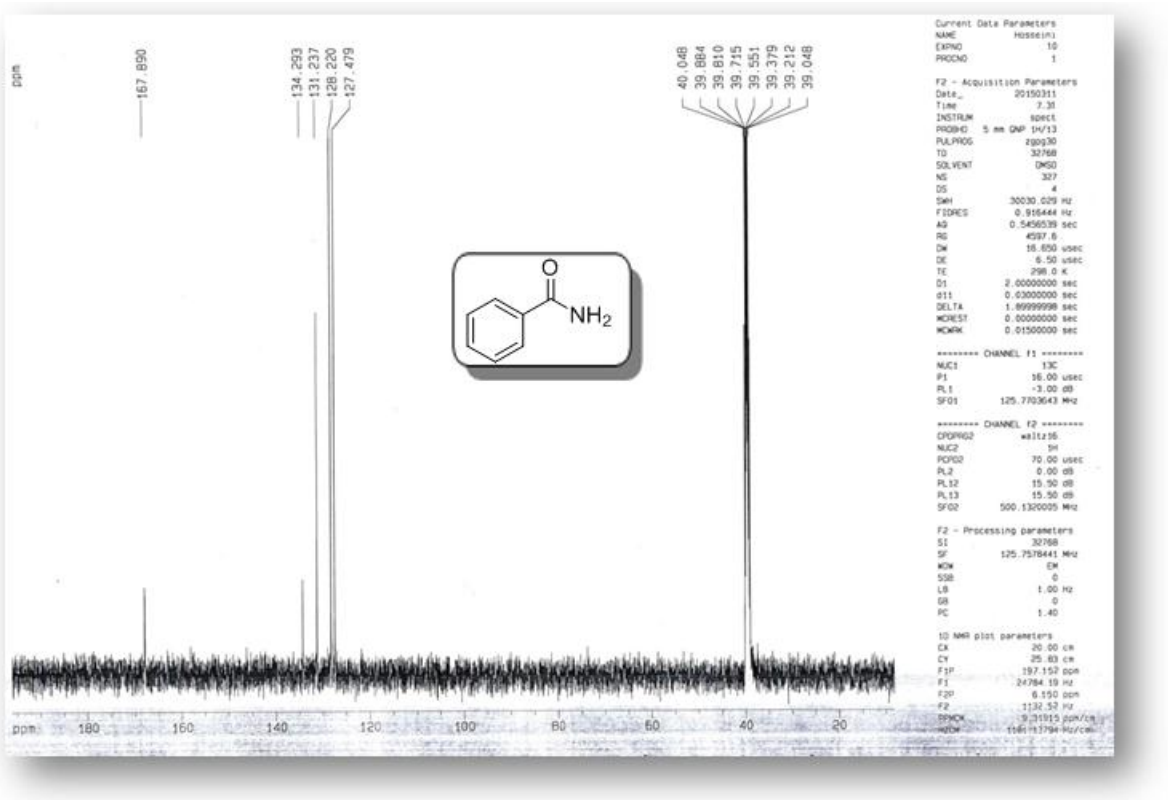

Figure 2d.[13] CNMR (125 MHz, DMSO-*d6*) of benzamide (Scheme 2, 2b)

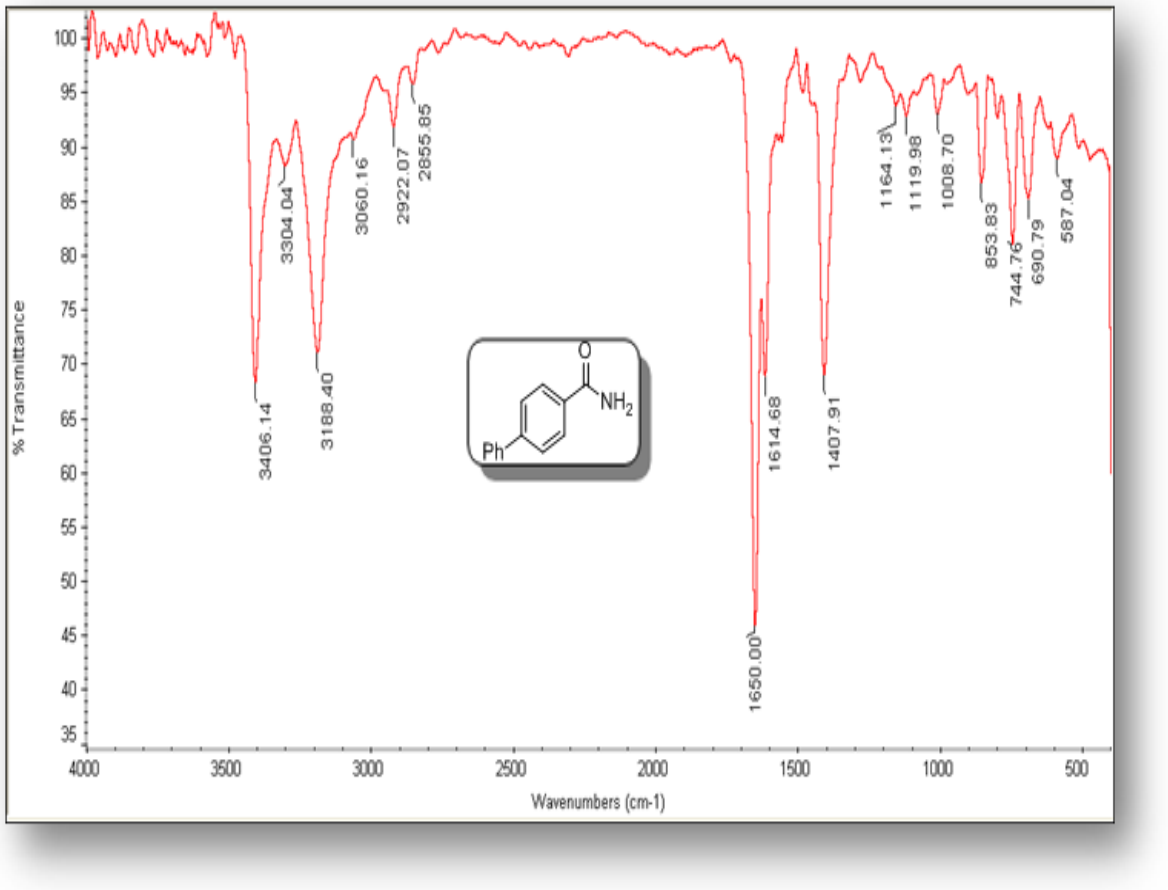

Figure 3a. FT-IR (neat) of 4-phenylbenzamide (Scheme 2, 2c)

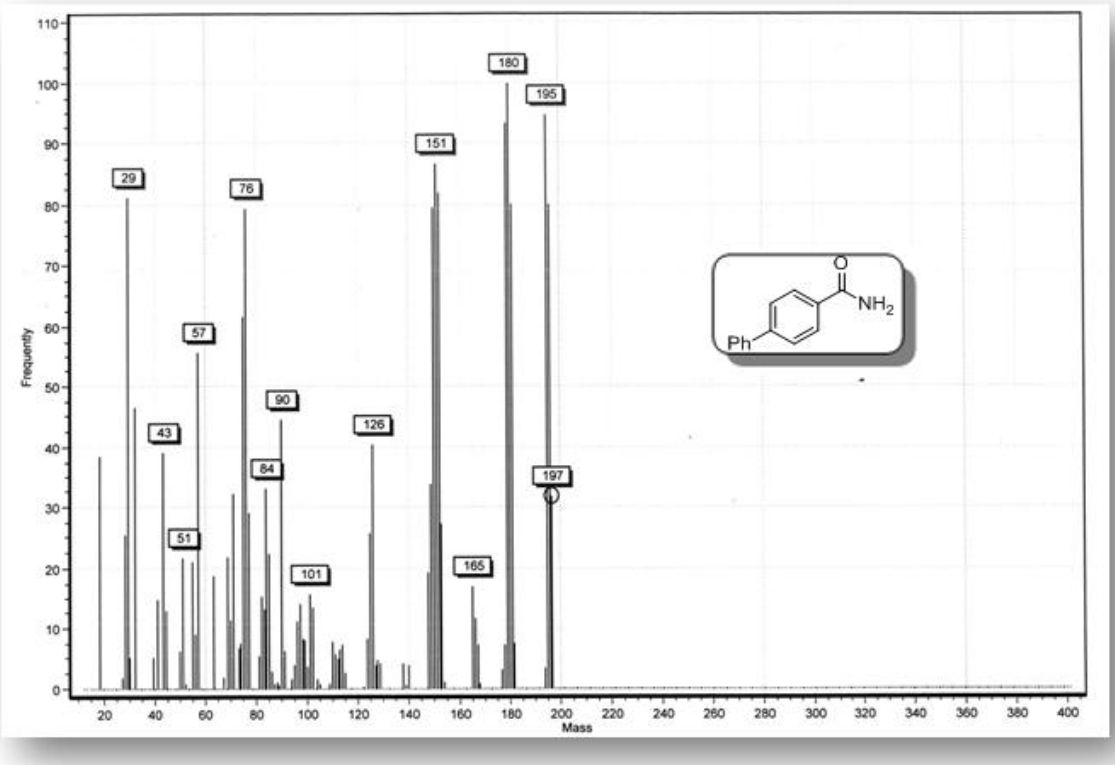

Figure 3b. Mass spectrum of 4-phenylbenzamide (Scheme 2, 2c)

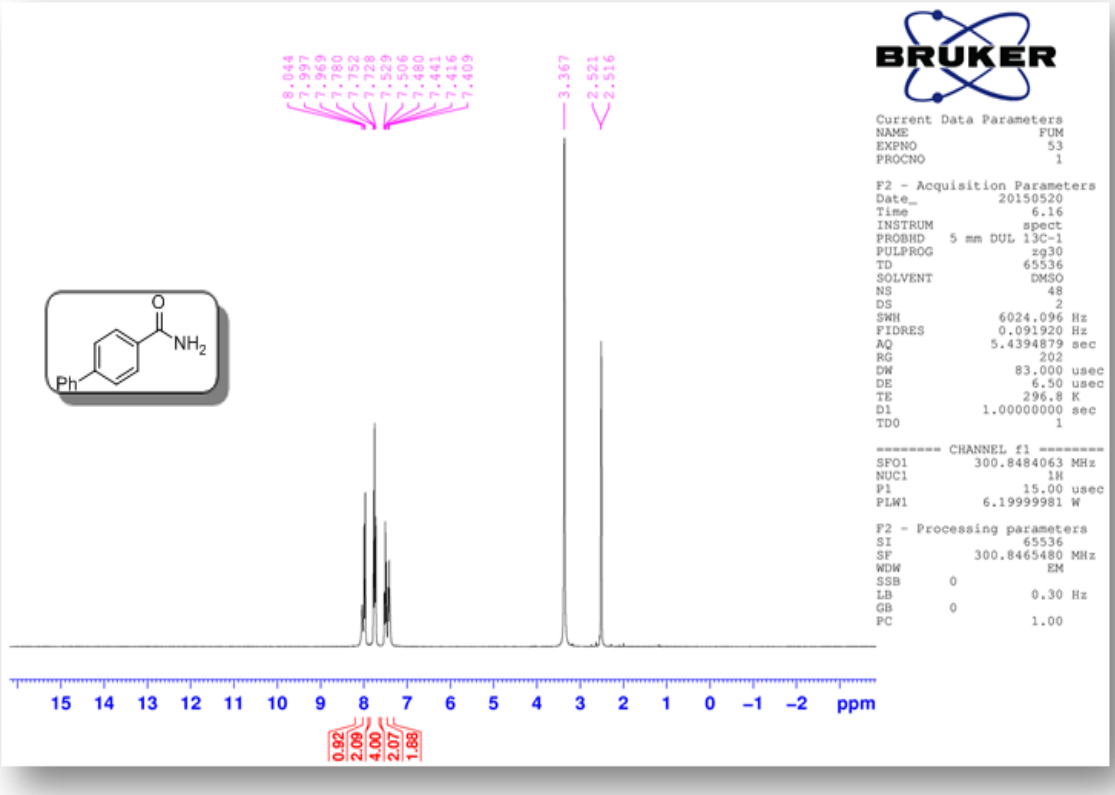

Figure 3c. ^{1}H NMR (300 MHz, DMSO-*d6*) of 4-phenylbenzamide (Scheme 2, 2c)

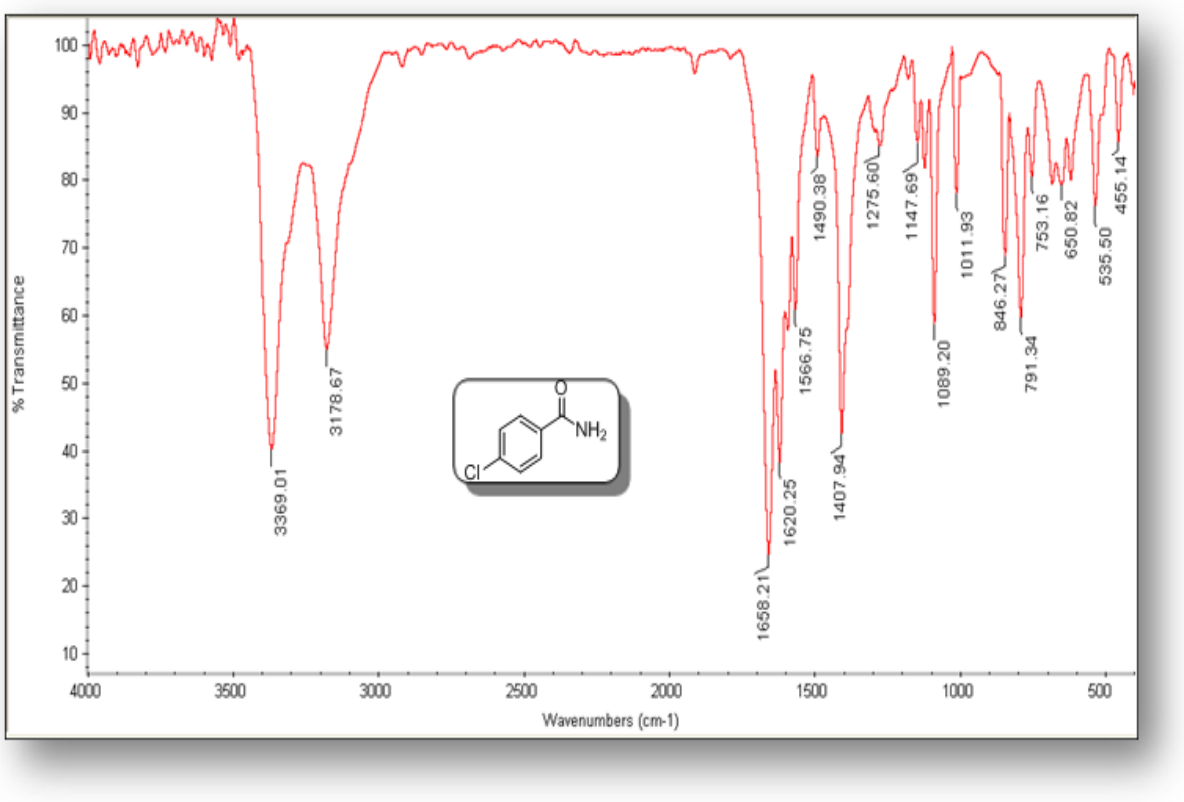

Figure 4a. FT-IR (neat) of 4-chlorobenzamide (scheme 2, 2d)

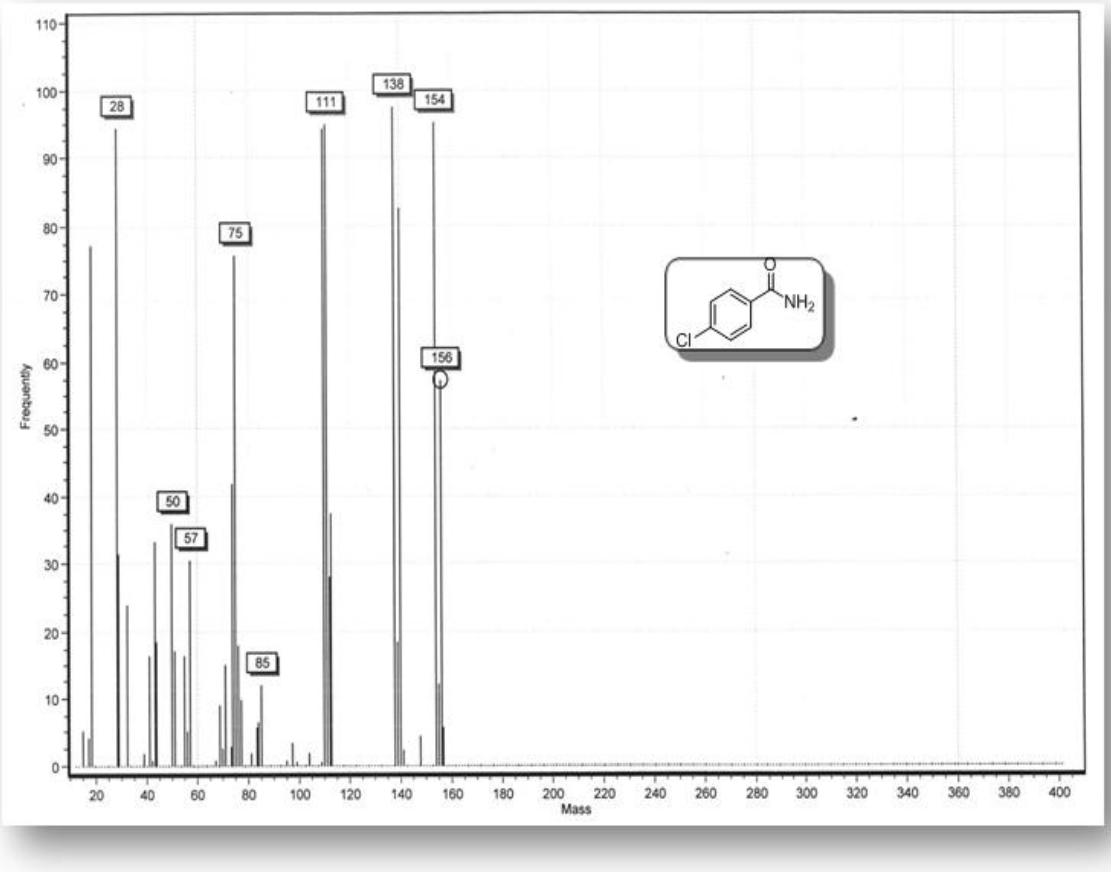

Figure 4b. Mass spectrum of 4-chlorobenzamide (Scheme 2, 2d)

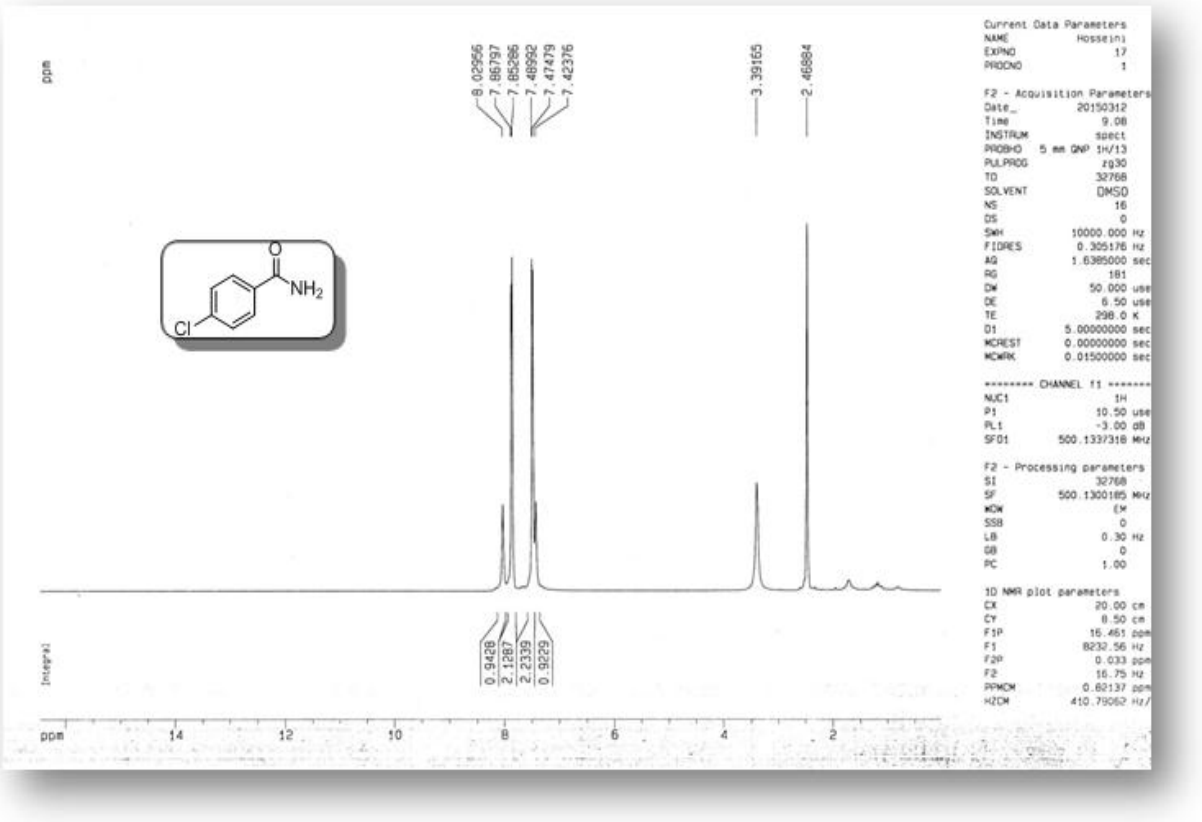

Figure 4c. ^{1}H NMR (500 MHz, DMSO-*d6*) of 4-chlorobenzamide (Scheme 2, 2d)

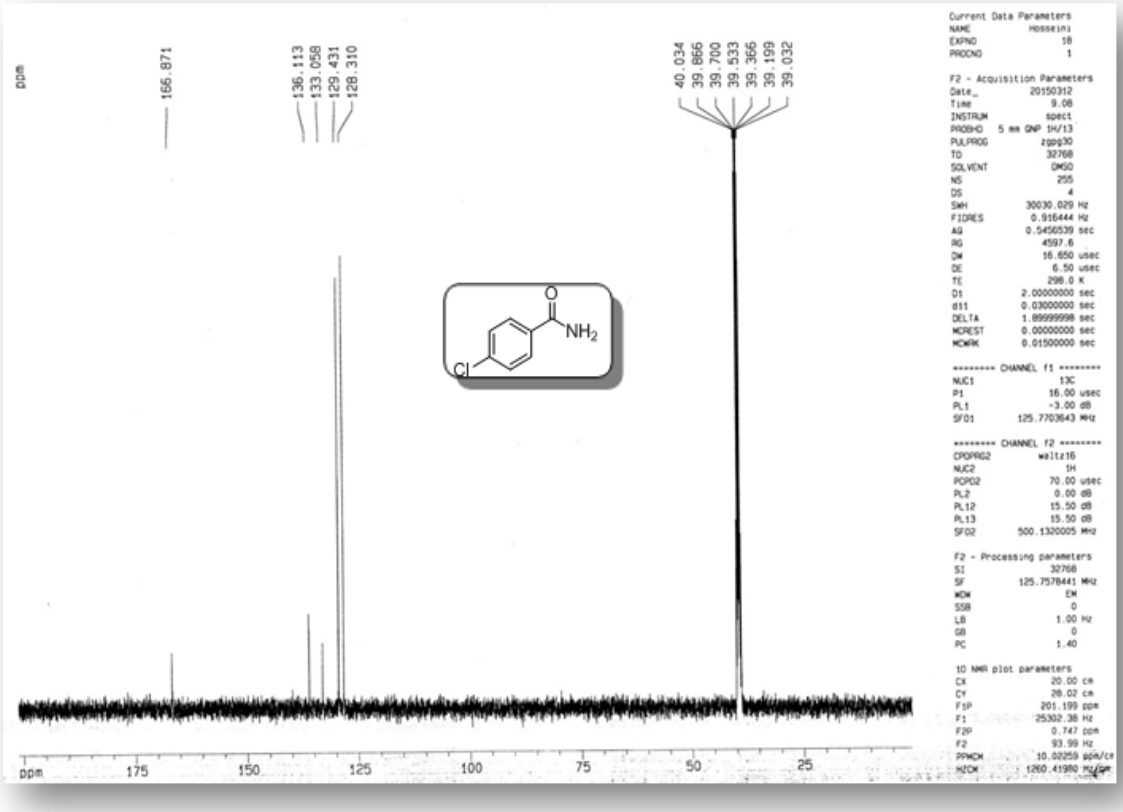

Figure 4d.[13] CNMR (125 MHz, DMSO-*d6*) of 4-chlorobenzamide (Scheme 2, 2d)

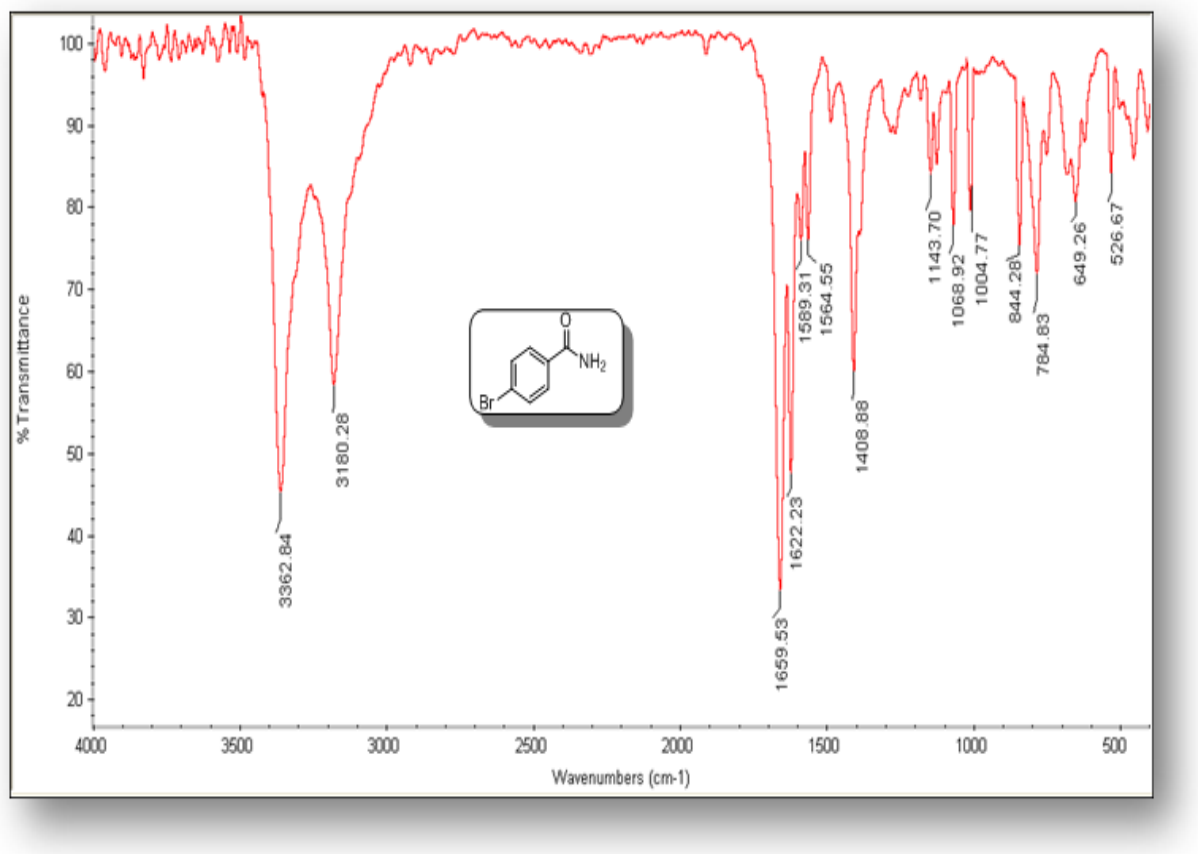

Figure 5a. FT-IR (neat) of 4-bromobenzamide (Scheme 2, 2e)

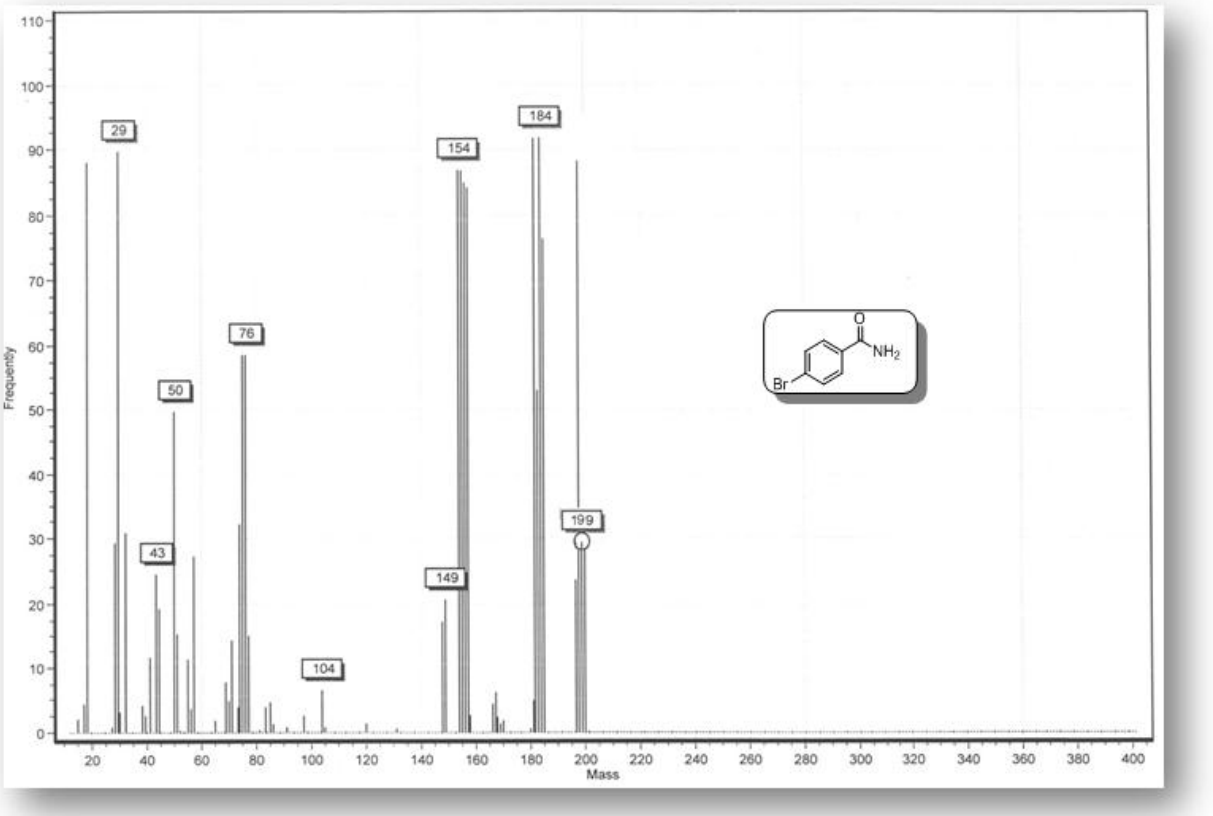

Figure 5b. Mass spectrum of 4-bromobenzamide (Scheme 2, 2e)

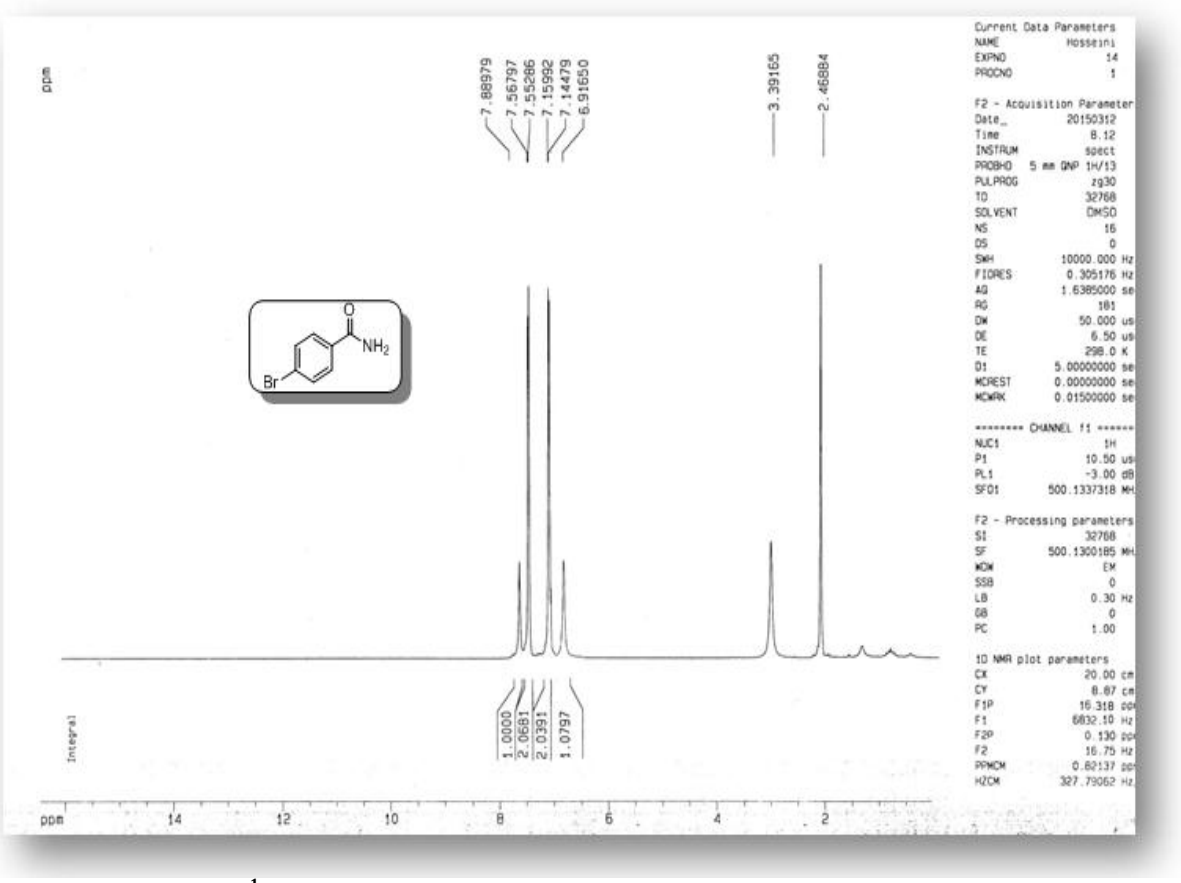

Figure 5c. ^{1}H NMR (500 MHz, DMSO-*d6*) of 4-bromobenzamide (Scheme 2, 2e).

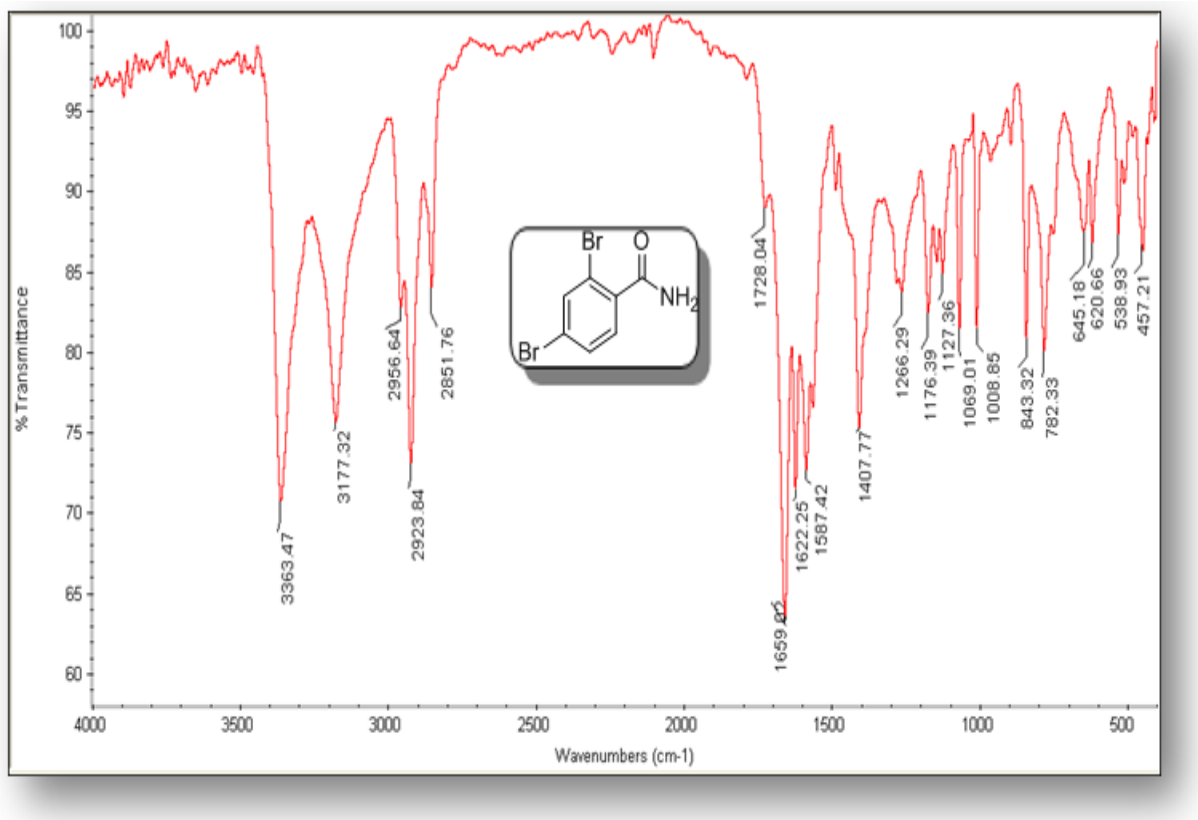

Figure 6a. FT-IR (neat) of 2,4-dibromobenzamide (Scheme 2, 2f)

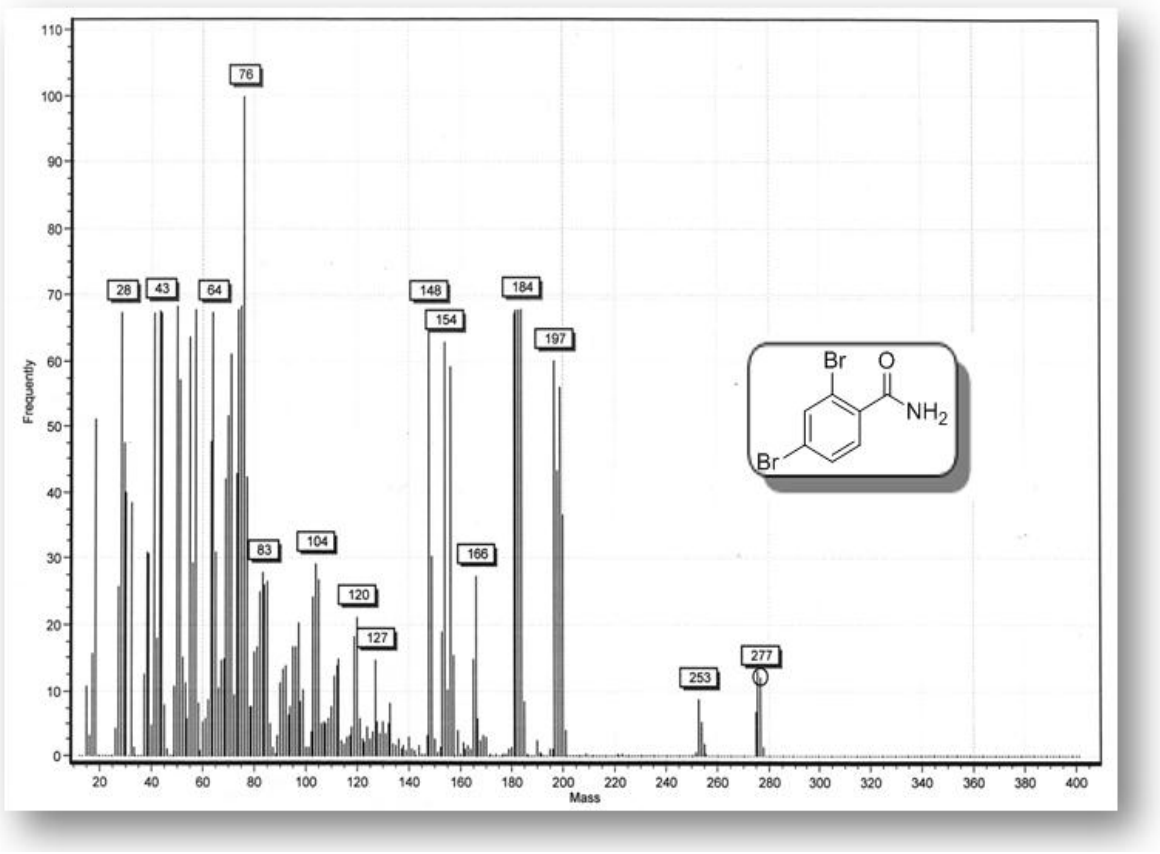

Figure 6b. Mass spectrum of 2,4-dibromobenzamide (Scheme 2, 2f)

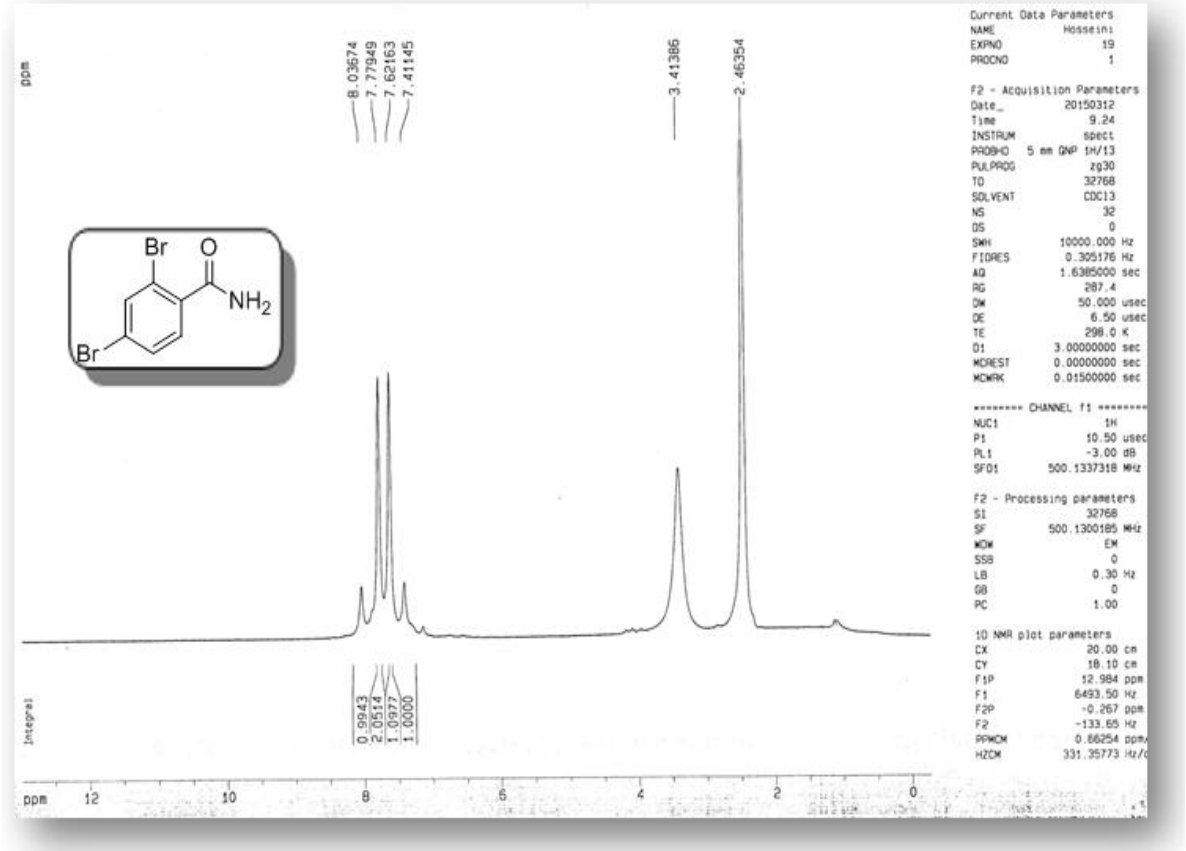

Figure 6c: ^{1}H NMR (500 MHz, DMSO-*d6*) of 2,4-dibromobenzamide (Scheme 2, 2f).

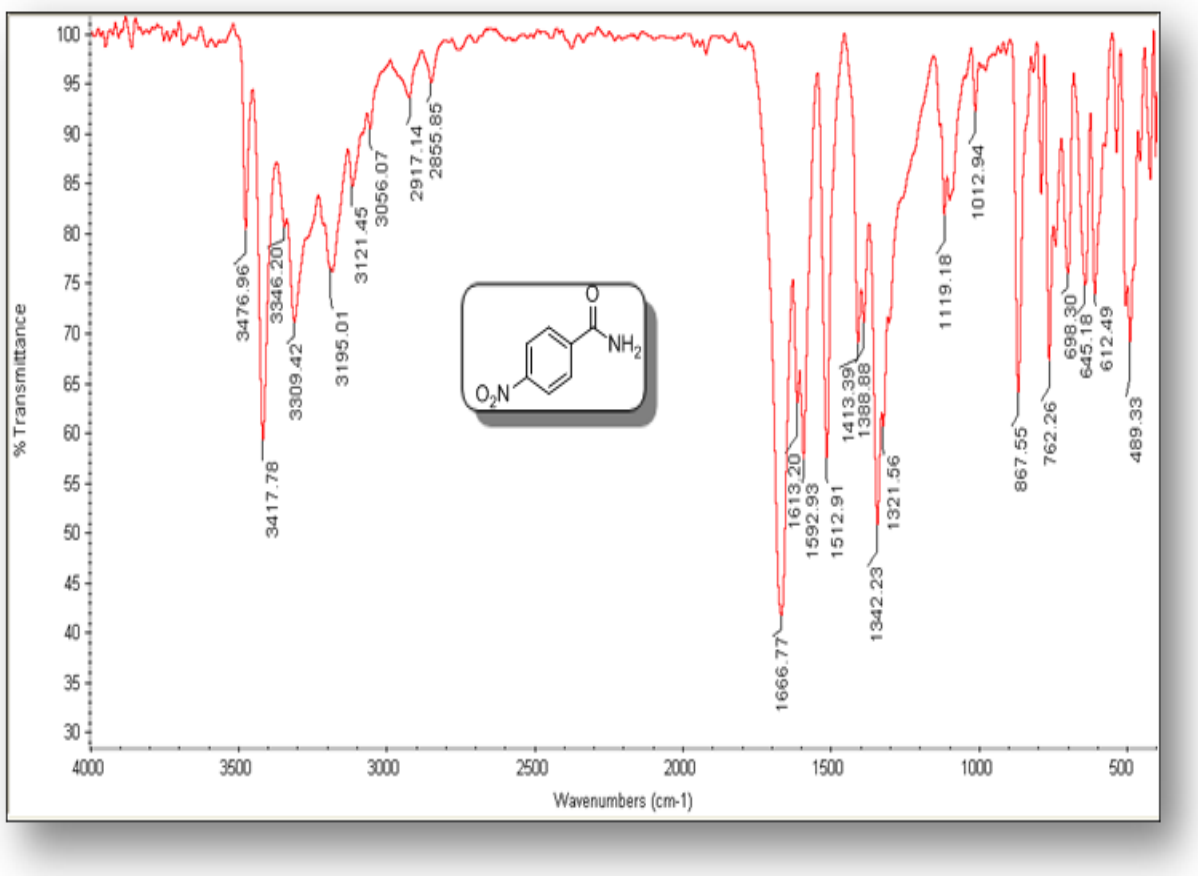

Figure 7a. FT-IR (neat) of 4-nitrobenzamide (Scheme 2, 2g)

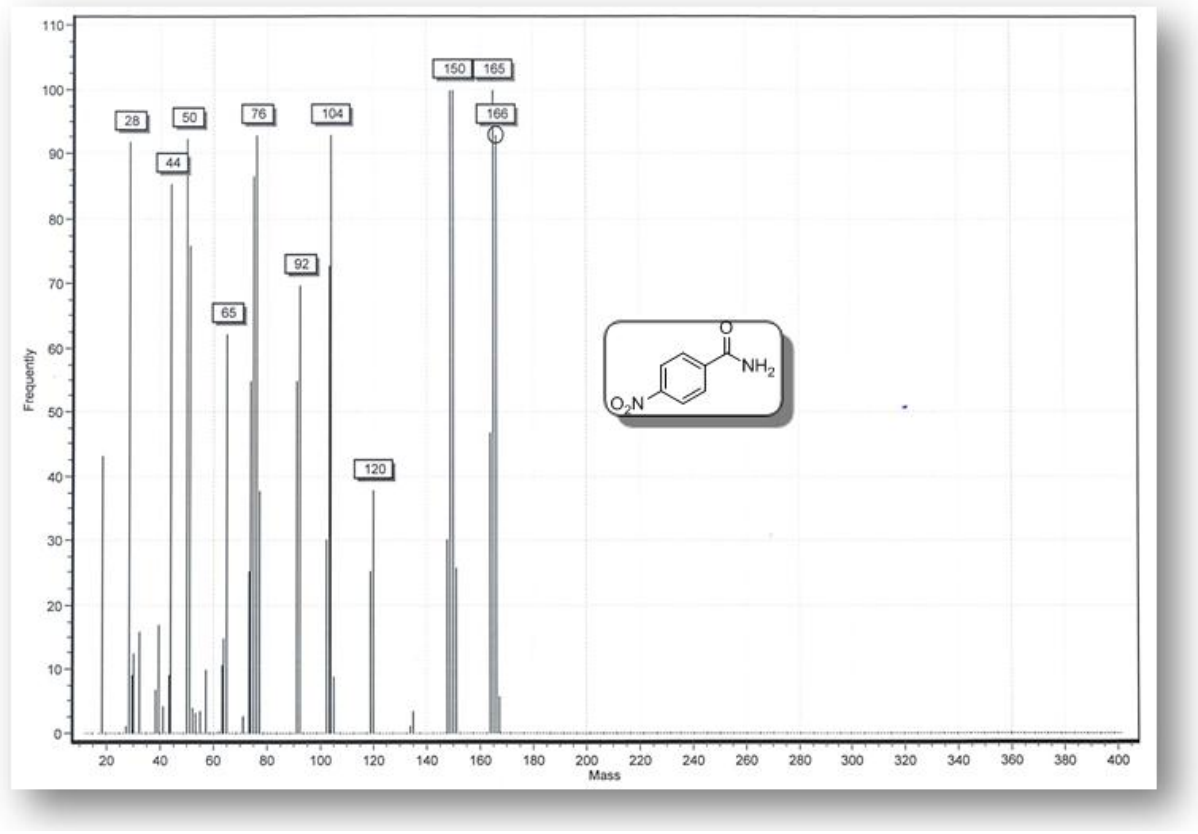

Figure 7b. Mass spectrum of 4-nitrobenzamide (Scheme 2, 2g)

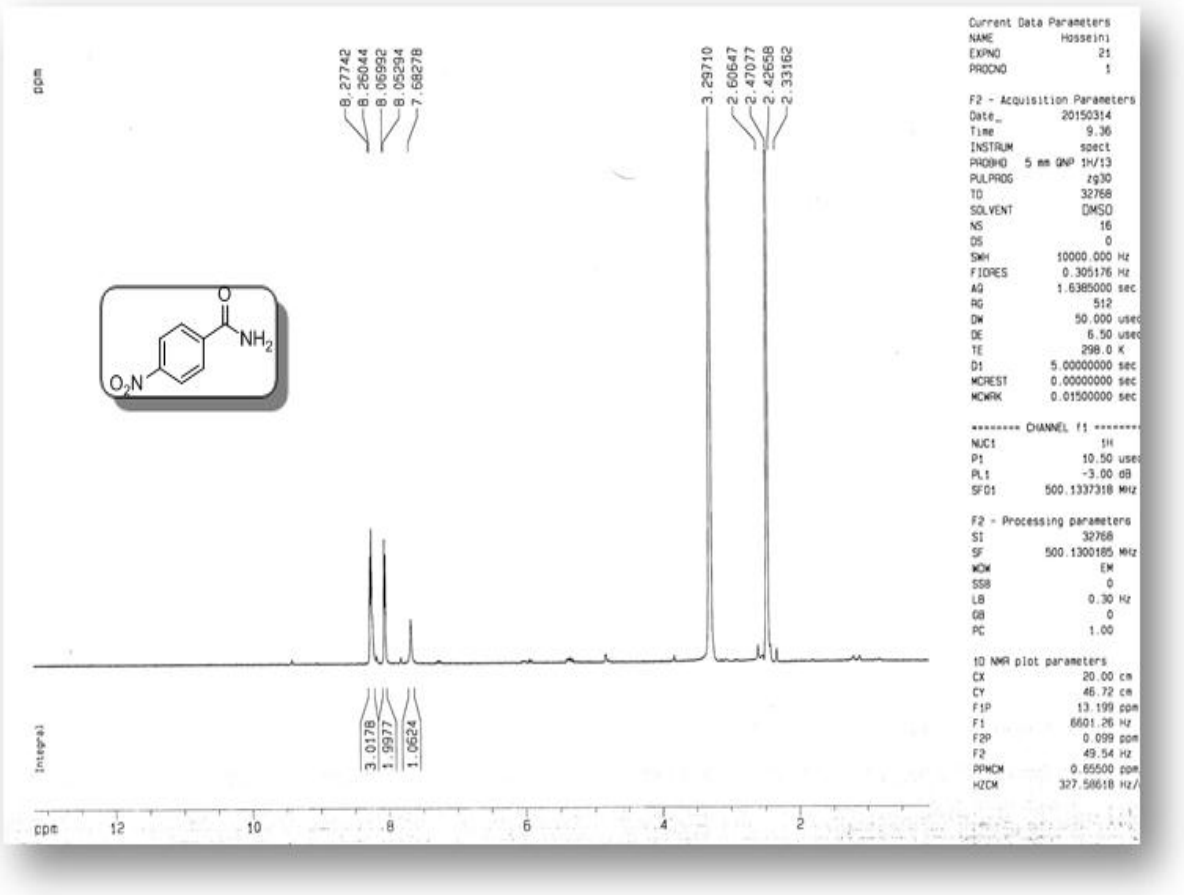

Figure 7c: ^{1}H NMR (500 MHz, DMSO-*d6*) of 4-nitrobenzamide (Scheme 2, 2g).

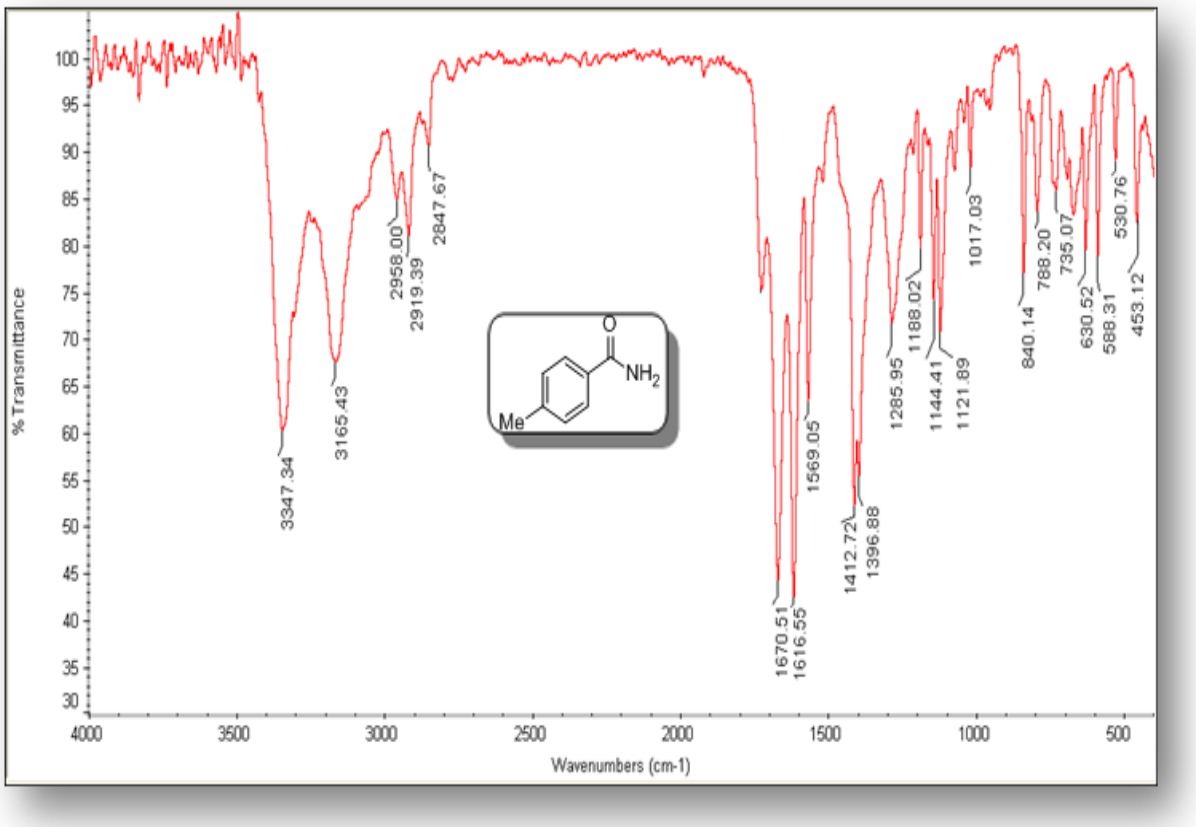

Figure 8a. FT-IR (neat) of 4-methylbenzamide (Scheme 2, 2h)

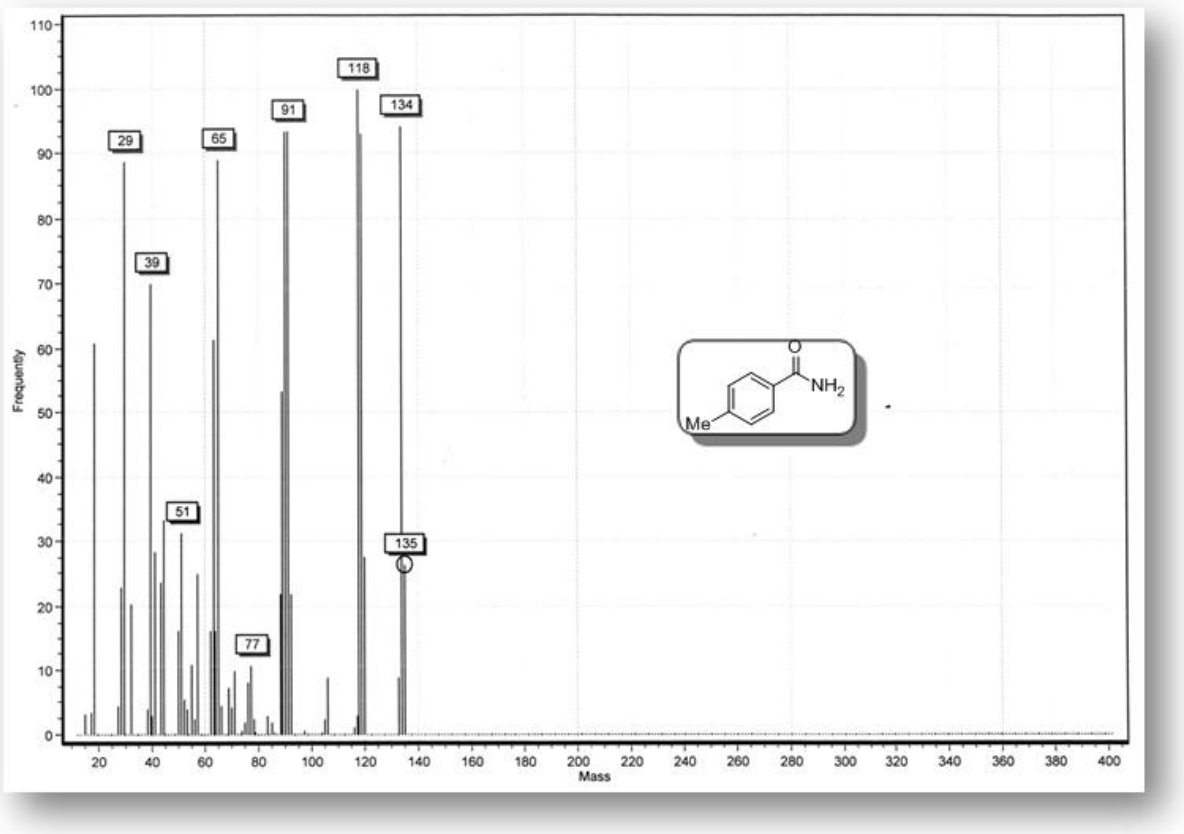

Figure 8b: Mass spectrum of 4-methylbenzamide (Scheme 2, 2h).

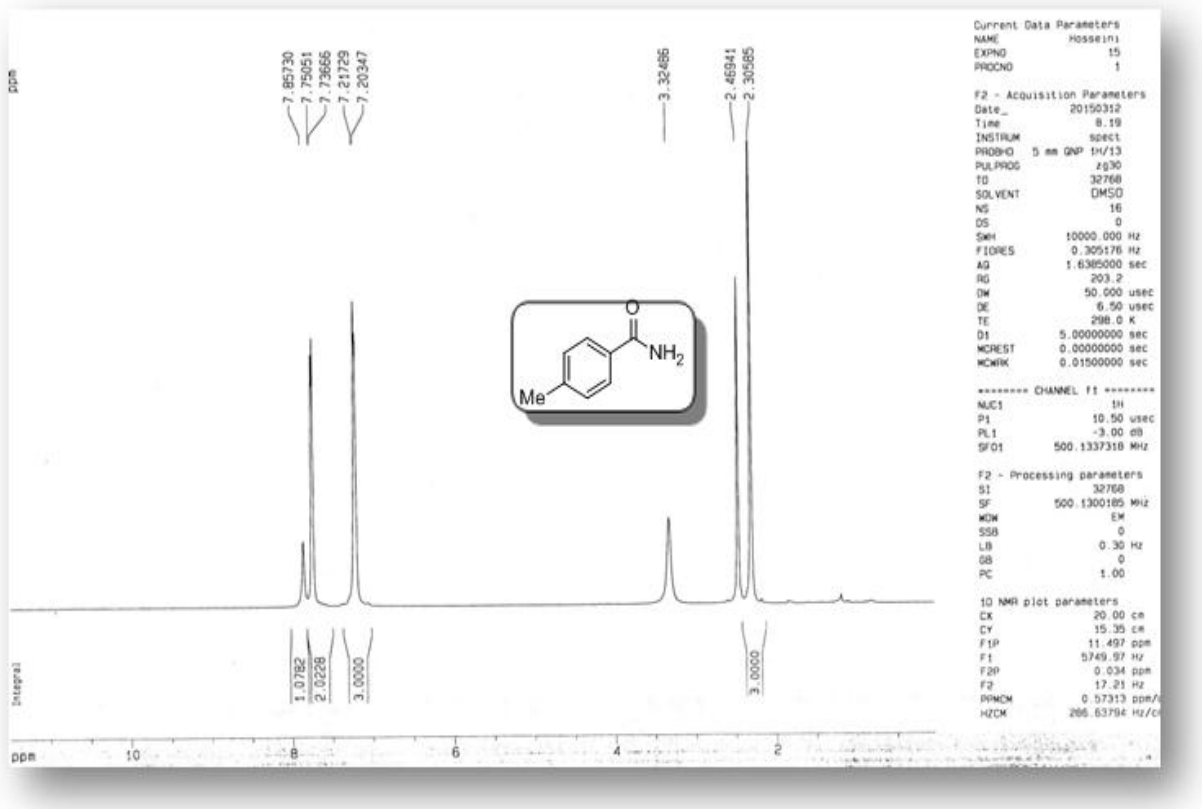

Figure 8c. ^{1}H NMR (500 MHz, DMSO-*d6*) of 4-methylbenzamide (Scheme 2, 2h)

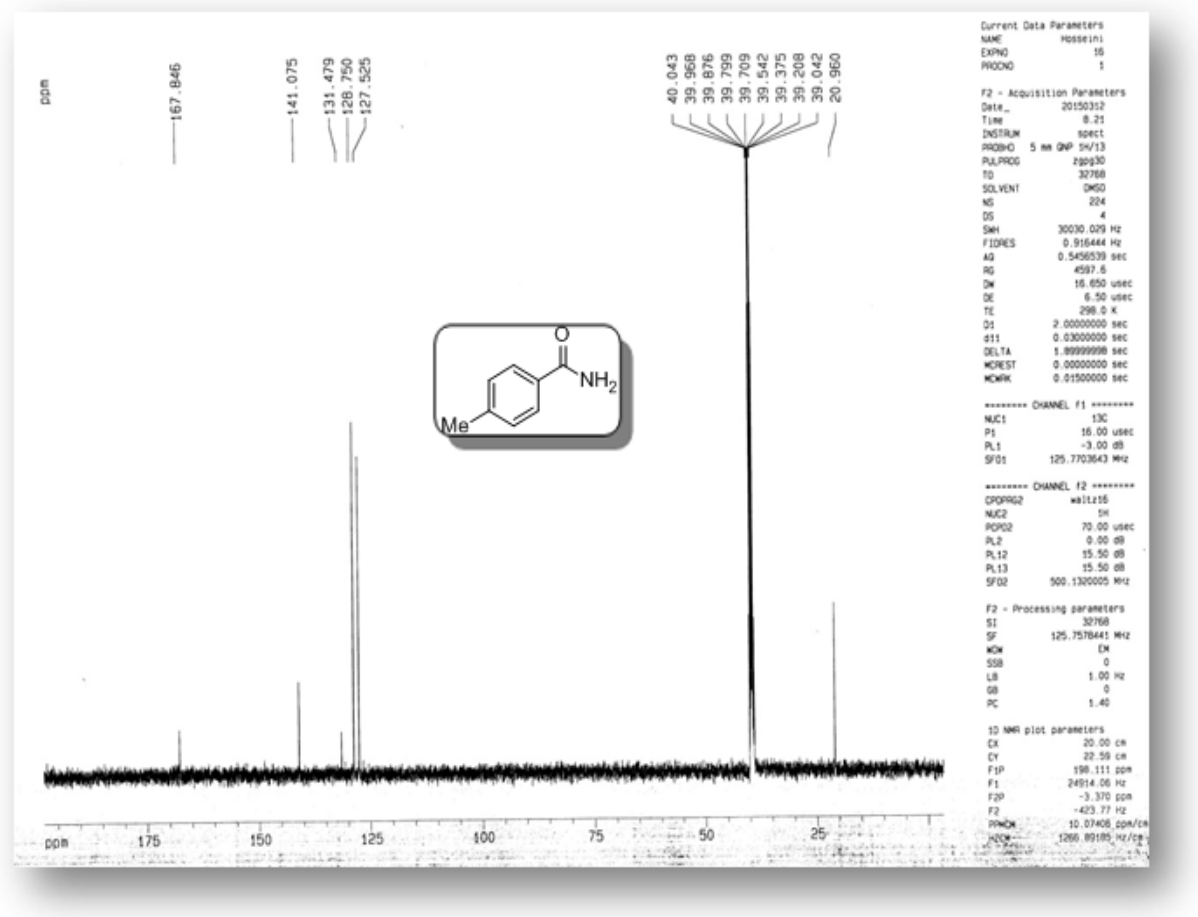

Figure 8d. ^{13}CNMR (125 MHz, DMSO-*d6*) of 4-methylbenzamide (Scheme 2, 2h)

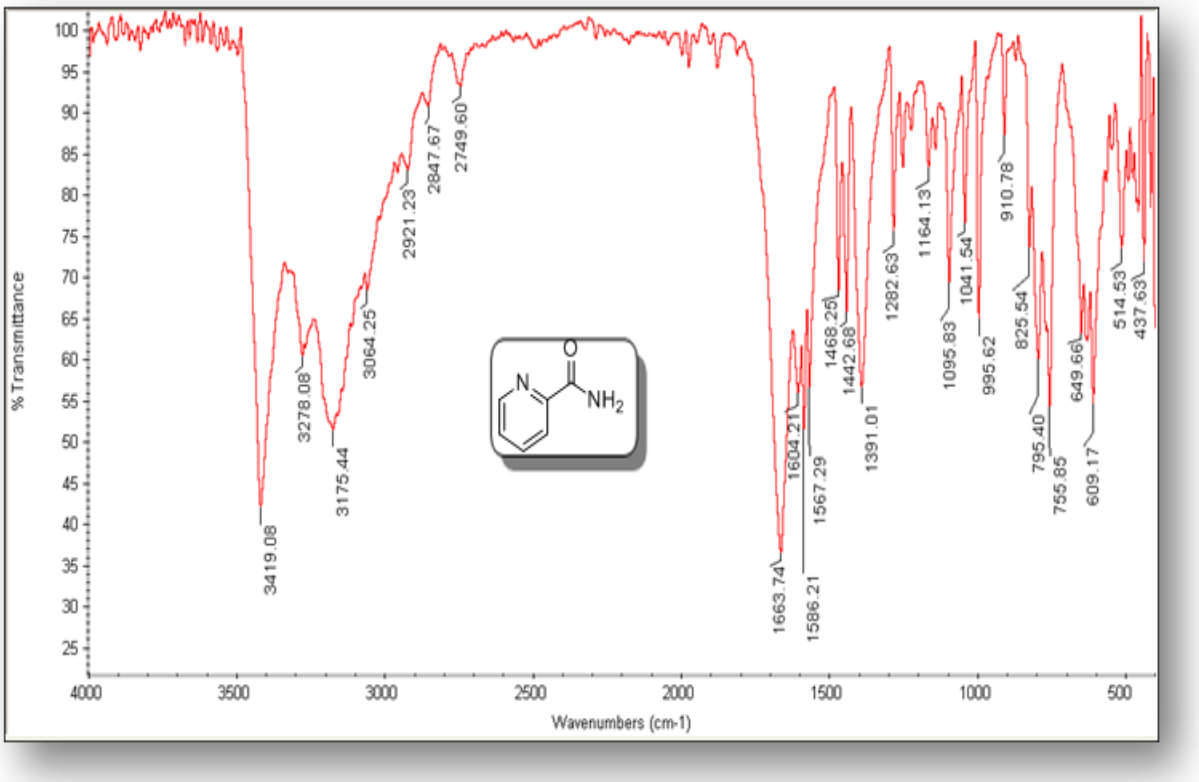

Figure 9a. FT-IR (neat) of picolinamide (Scheme 2, 2i)

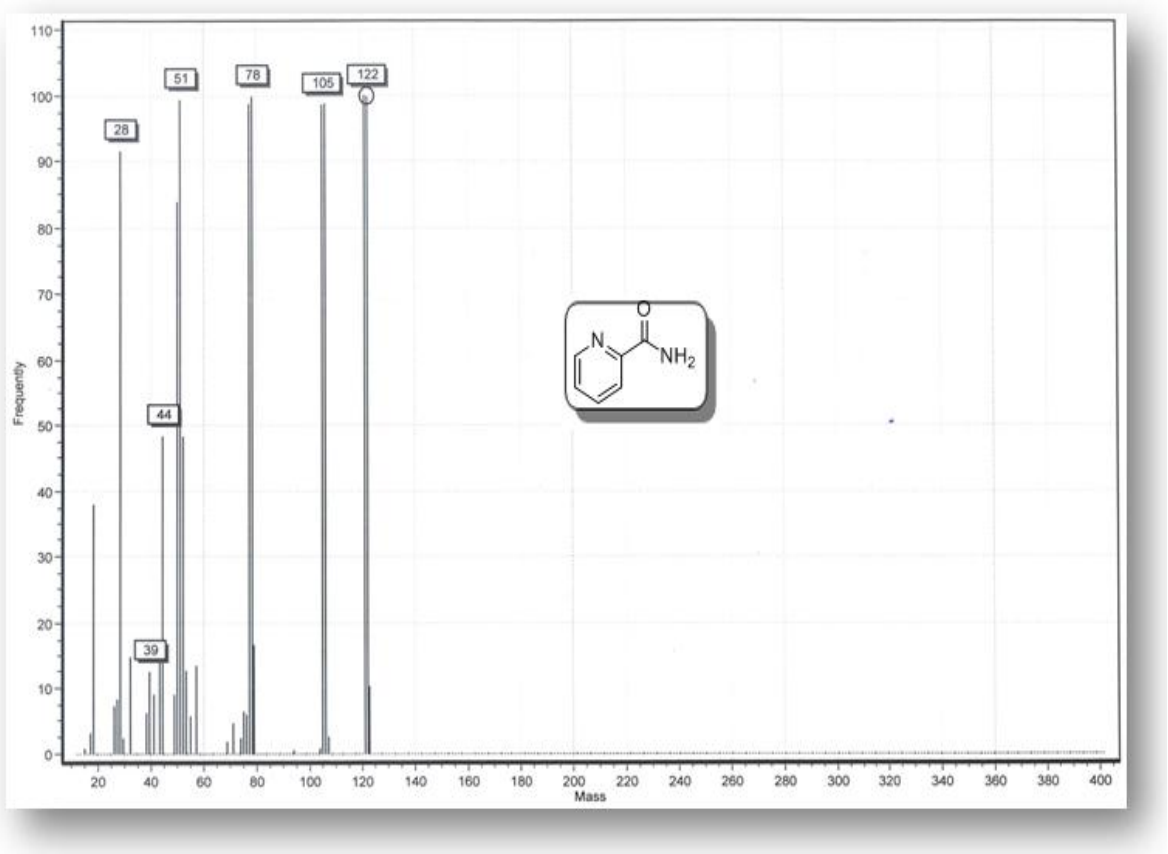

Figure 9b. Mass spectrum of picolinamide (Scheme 2, 2i)

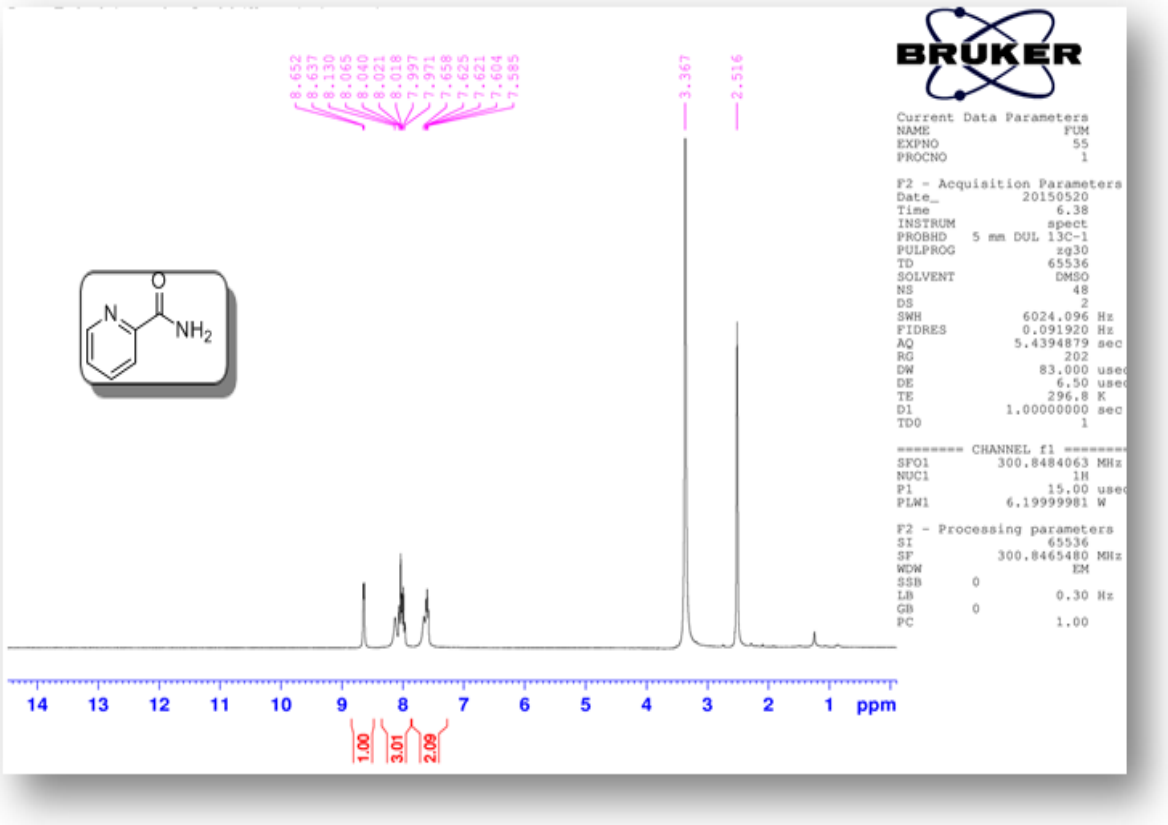

Figure 9c. ^{1}H NMR (300 MHz, DMSO-*d6*) of picolinamide (Scheme 2, 2i)

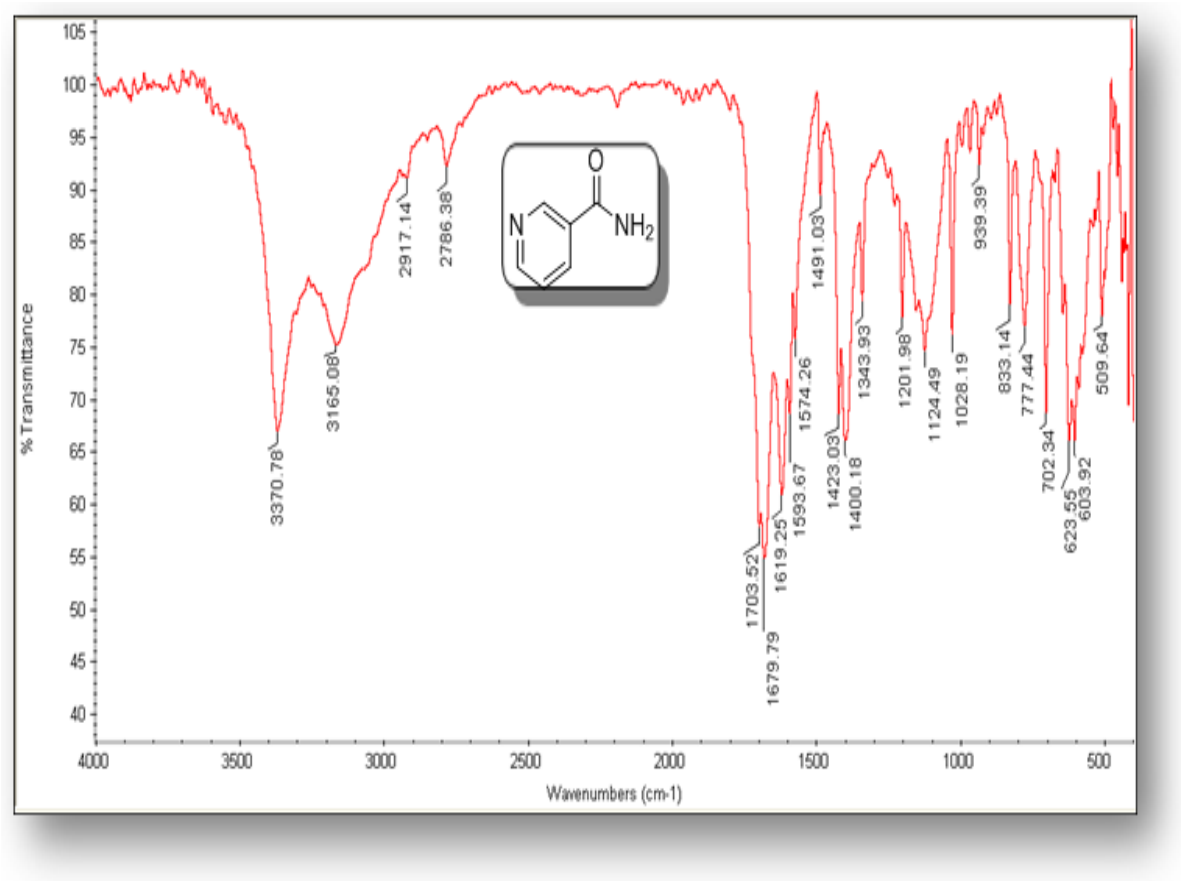

Figure 10a. FT-IR (neat) of nicotinamide (Scheme 2, 2j)

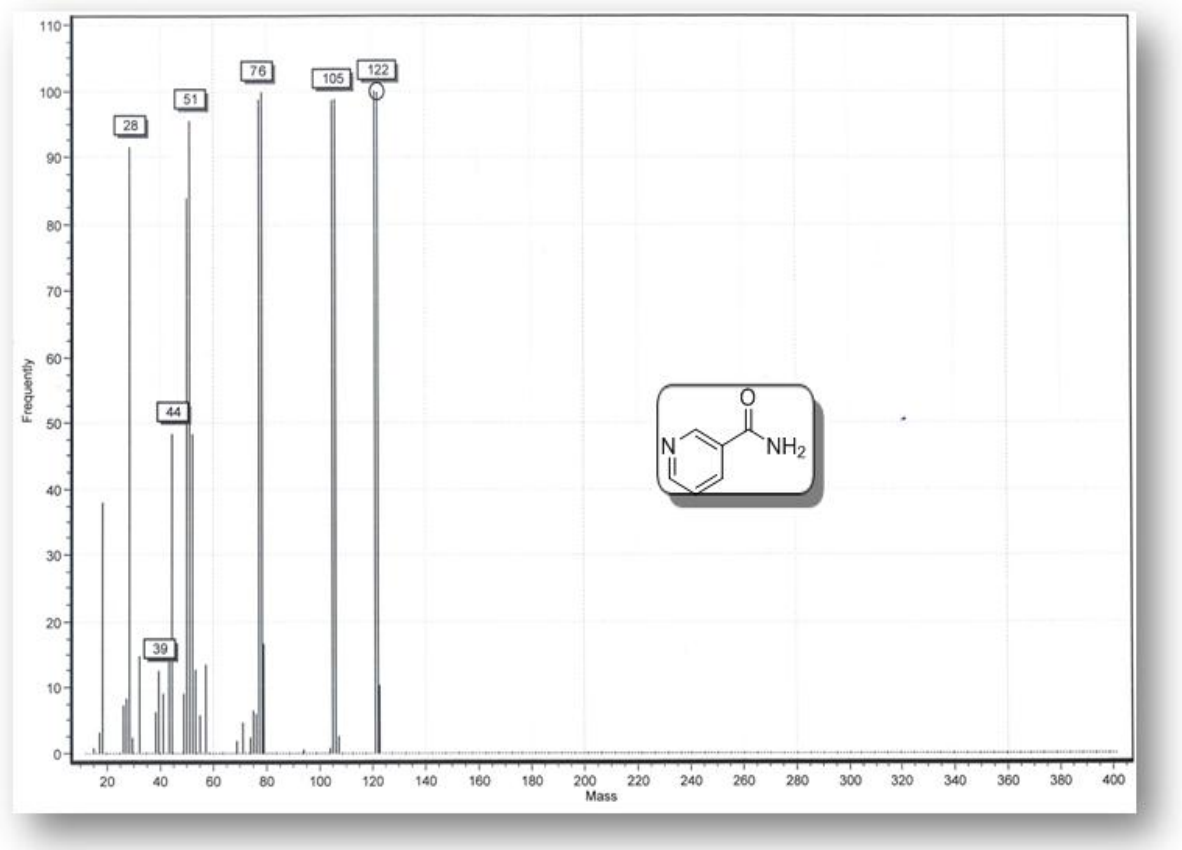

Figure 10b. Mass spectrum of nicotinami (Scheme 2, 2j)

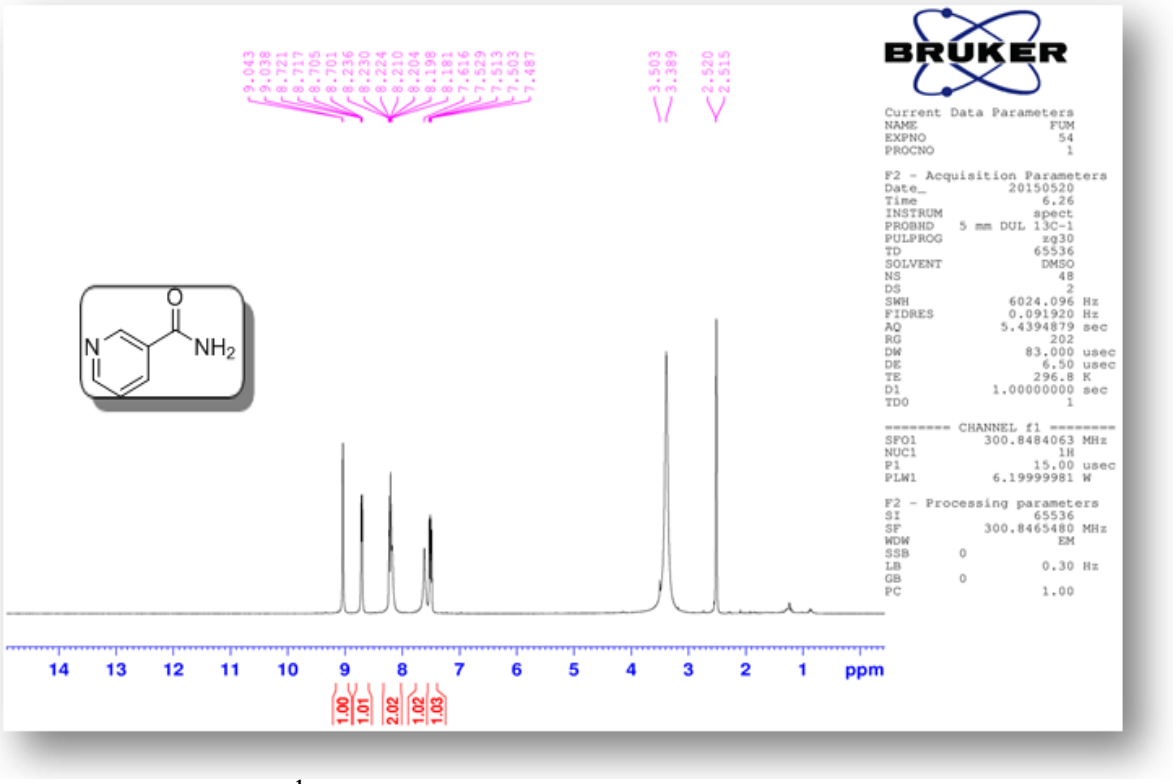

Figure 10c. ^{1}H NMR (300 MHz, DMSO-*d6*) of nicotinamide (scheme 2, 2j)

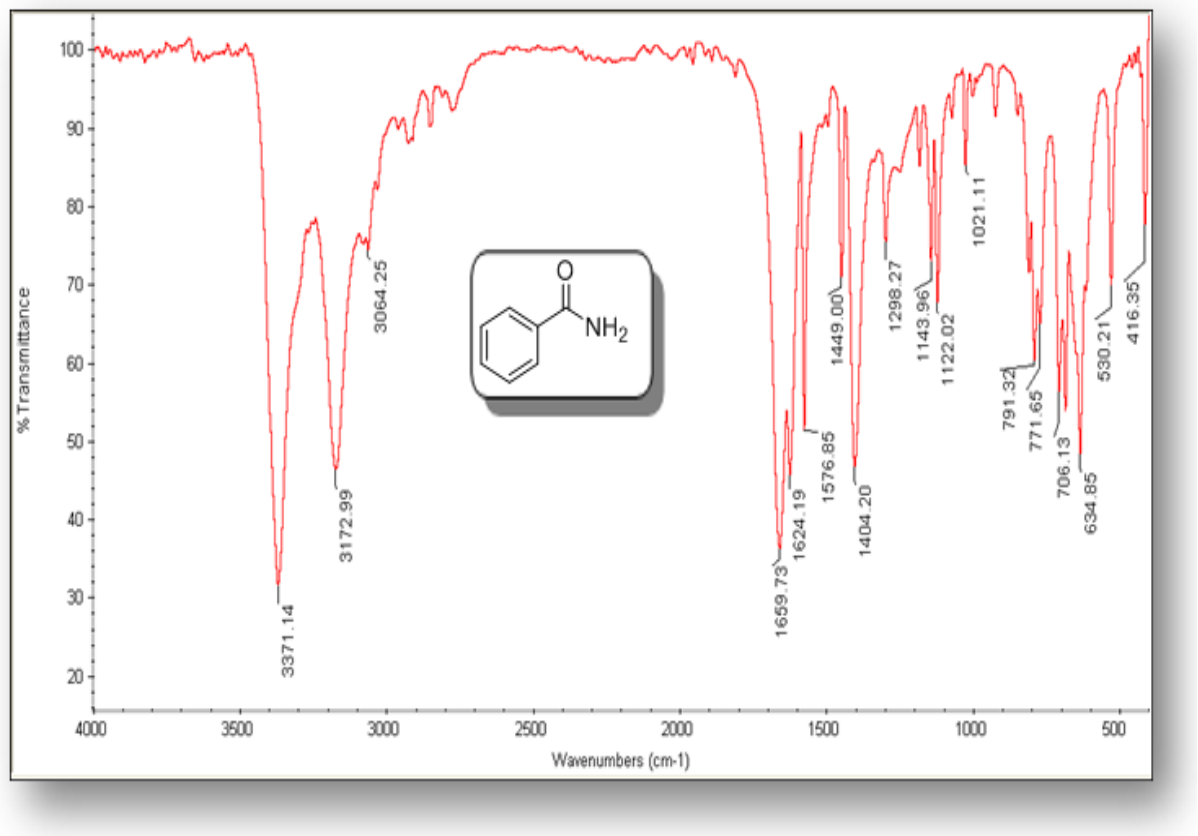

Figure 11a. FT-IR (neat) of benzamide from phenacyl bromide

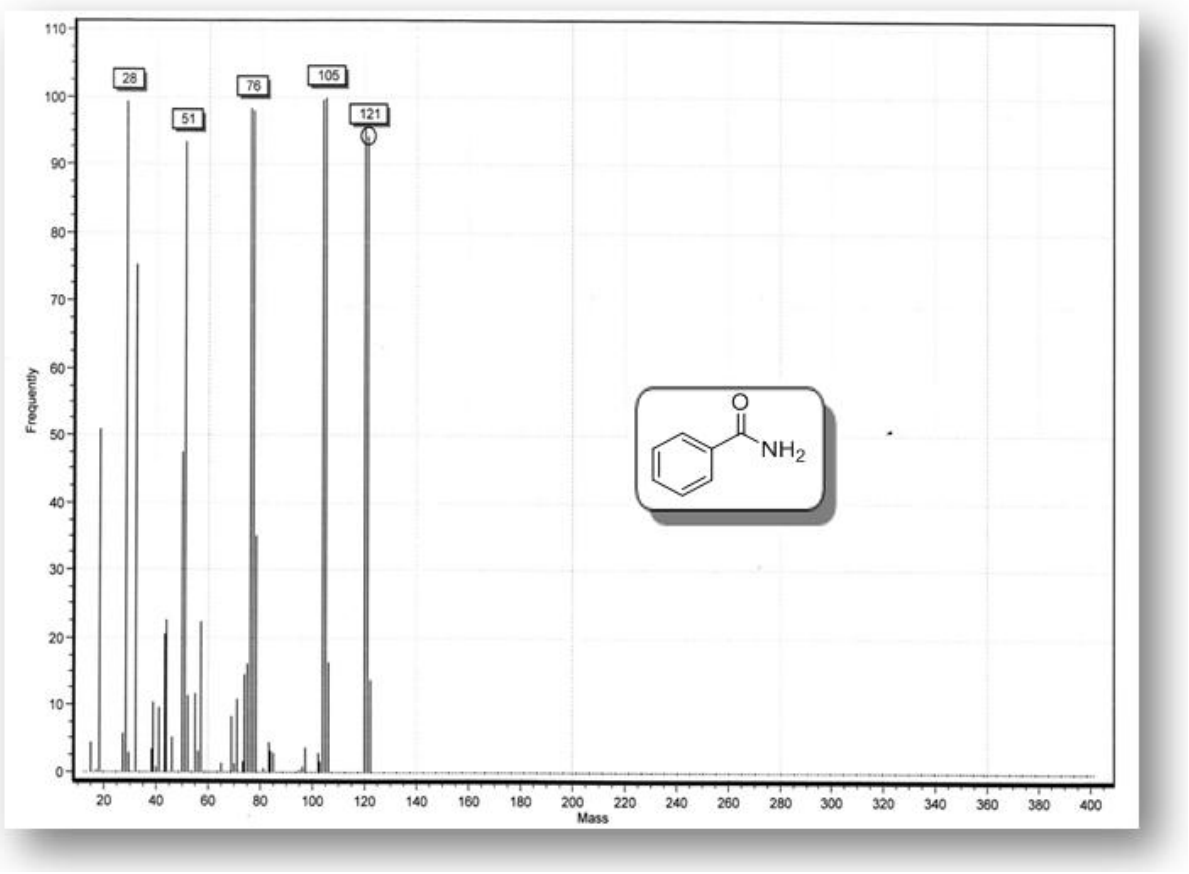

Figure 11b. Mass spectrum of benzamide from phenacyl bromide.

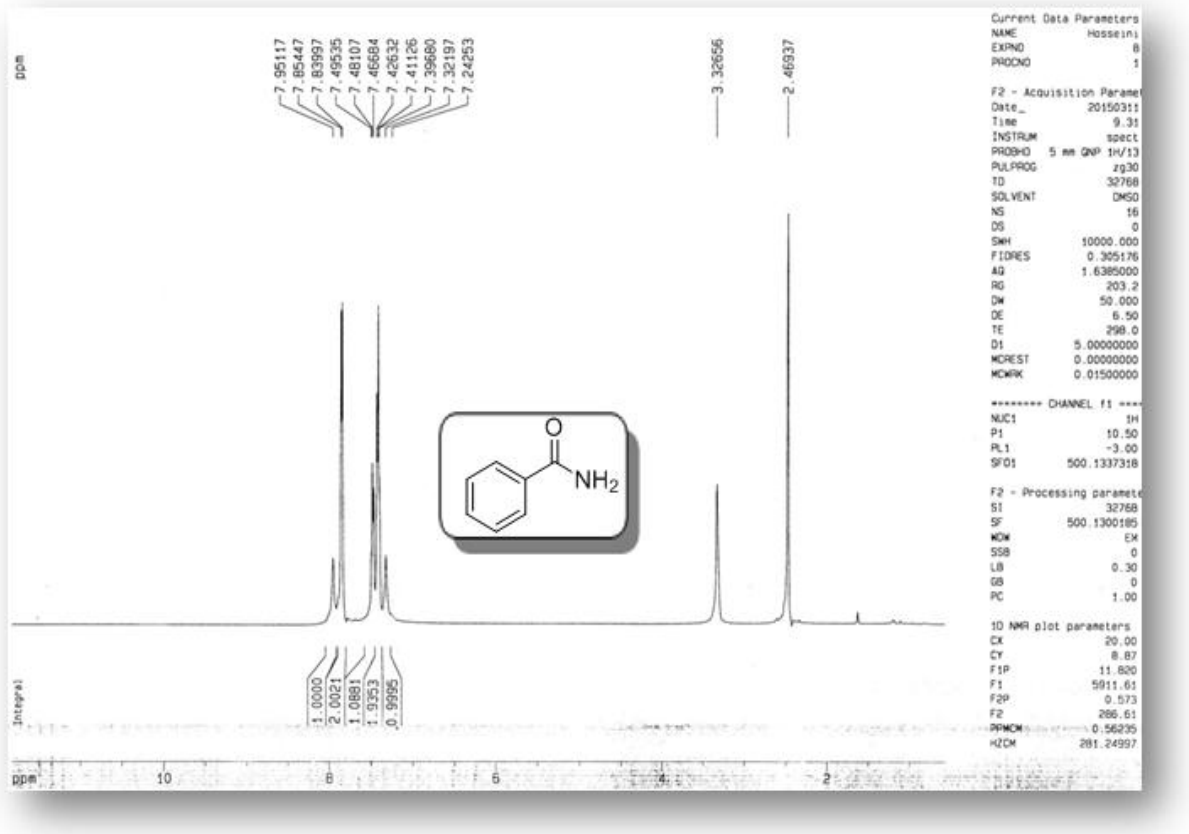

Figure 11c. ^{1}H NMR (500 MHz, DMSO-*d6*) of benzamide from phenacyl bromide.

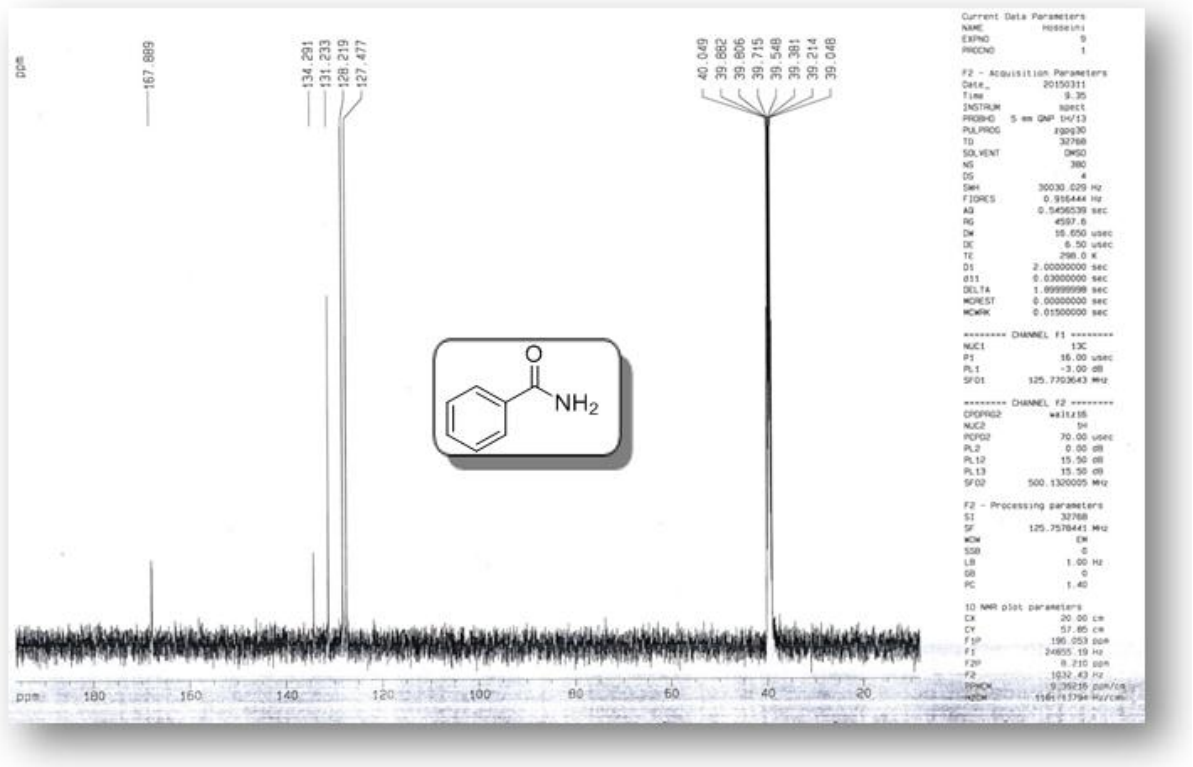

Figure 11d.[13] CNMR (125 MHz, DMSO-*d6*) of benzamide from phenacyl bromide.

CONCLUSIONS

In this article, we have developed a generic approach to the synthesis of aryl or heteroaryl amides via the direct copper catalyzed transformation of various aryl or heteroaryl alkyl ketones in the presence of sodium azide and diisopropylamine in DMSO at 120°C. The novel copper (*II*) catalyzed strategy for chemoselective cleavage of C(CO)-C(alkyl) bond adopted in the reaction is reported for the first time. The inexpensive copper catalyst and base are important features of this strategy. In this way, various aryl or heteroaryl alkyl ketones were converted to the corresponding amides which are frequently used in producing a wide range of important drugs.[14]

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