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Boric acid as an efficient and green catalyst for the synthesis of 2-amino-4,6-diarylnicotinonitrile under microwave irradiation in solvent-free conditions

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Abstract: Microwave irradiation has been used to improve the one-pot synthesis of substituted 2-amino-4,6-diarylnicotinonitrile in the presence of boric acid as an efficient and green catalyst under solvent-free conditions within 48–60 s. All the analogs that have not been reported previously were characterized by their melting points, IR, ^{1}H NMR, and ^{13}C NMR spectra. One of the structures was verified by the analysis of a single crystal. The reported synthetic procedure provided remarkable advantages such as short reaction times, excellent yield, facile workup, and the use of a green catalyst.

Key words: Boric acid, microwave irradiation, solvent-free, green method, 2-amino-4,6-diarylnicotinonitrile

1. Introduction

Pyridine analogs, as privileged medicinal scaffolds, have exhibited several pharmacological activities such as IKK-β and HIV-1 integrase inhibition, antiinflammatory, antiparkinsonism, antitumor, antihepatitis B, herbicidal, antimicrobial, cardiovascular, and analgesic effects. In addition, these analogs are valuable intermediates in the preparation of diverse heterocyclic compounds.[1–4]

Although boric acid is a weak inorganic acid, it has been utilized extensively as an effective and green catalyst in organic synthesis, and it has attracted much attention because of numerous advantages such as excellent solubility in water, green nature, commercial availability, chemically stable nature, low cost, nontoxic nature, applicability as a recyclable catalyst, and simple handling.[5–8]

The removal of toxic solvents in organic synthesis is introduced as the most significant purpose of green chemistry that includes solvent-free reactions. Solvent-free reactions have attracted noticeable attention because they enhance yield, save energy, reduce pollution, prevent solvent wastes, toxicity, and facilitate the methods. Under solvent-free conditions, the greater concentration of reaction media generally originates in more desirable kinetics than in the solution. For developing solvent-free reactions, microwave-assisted solvent-free reactions have been introduced, which are rapid, green, and efficient.[9–12]

Multicomponent reactions (MCRs) provide fast and facile access to the variety of small molecules, which

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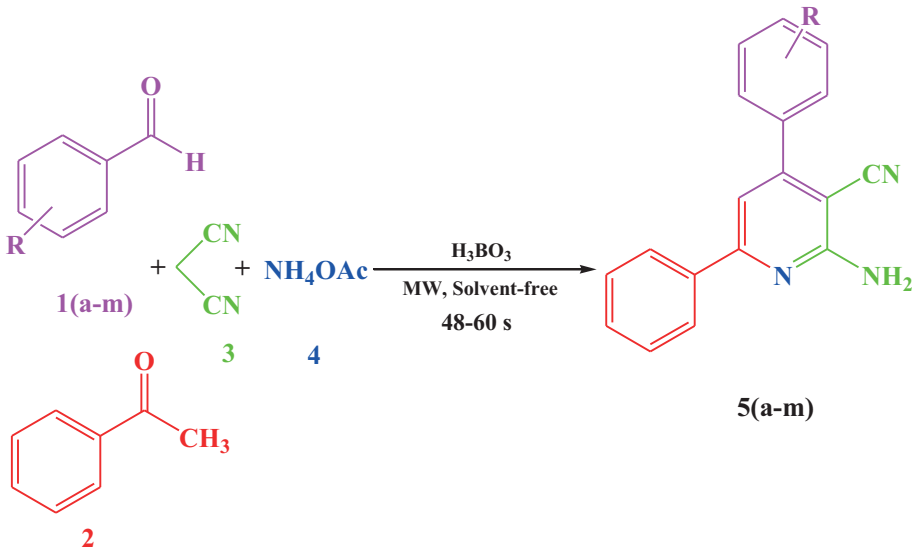
are useful for novel drug discovery in organic and medicinal chemistry. One of the significant characteristics of MCRs is that they suggest simple and rapid paths to functionalized compounds. Therefore, these procedures reduce the cost, time, and byproducts because they do not need the isolation of intermediates.[13,14]

There are several works in the literature concerning the formation of 2-amino-3-cyanopyridines by MCRs but the majority of these approaches need long reaction times, harsh reaction conditions, and toxic solvents that have low yields. However, an effective and facile MCR in mild conditions is still required.

Herein, we present a green and easy method for the preparation of 2-amino-3-cyanopyridine derivatives in the presence of boric acid as an efficient and recoverable additive under microwave irradiation conditions, as demonstrated in Scheme 1. All analogs that have not been reported previously were elucidated by their melting point, IR, ^{1}H NMR, and ^{13}C NMR spectra and a single crystal.



Scheme 1. Synthesis of 2-amino-4,6-diarylnicotinonitrile in the presence of H_3BO_3.

2. Results and discussion

The effect of the catalyst in the synthesis of 2-amino-4,6-diarylnicotinonitrile derivatives under microwave irradiation in solvent-free conditions was evaluated in terms of catalyst amount, microwave power, and reaction times. For this purpose, the reaction of 4-chlorobenzaldehyde **1b** (1 mmol), acetophenone **2** (1 mmol), malononitrile **3** (1.5 mmol), and ammonium acetate **4** (1 mmol) was elected as a model reaction.

At the beginning, the effect of boric acid amount in the formation of compound **5b** was evaluated (Table 1, Entry 2). It was found that the reaction did not proceed in the absence of boric acid catalyst (Table 1, Entry 1). As shown in Table 1, the highest yield of the product was achieved when 1 mmol of boric acid was utilized.

The influence of microwave power was measured within 500 to 650 W. Increasing the microwave power from 500 to 600 W, the reaction yield increased, but at 650 W the yield decreased. In addition, this reaction was studied under thermal conditions without microwave irradiation in the presence of boric acid catalyst and also without any other additives in solvent-free conditions (Table 2). Finally, solvent-free conditions under microwave irradiation were prioritized due to short reaction times and excellent yields.

Table 1. Effect of the catalyst amount on the preparation of 2-amino-4,6-diarylnicotinonitrile derivatives.

Entry	Catalyst (mmol)	Time (min)	Yield[a] (%)
1	None	15	-
2	0.5	1	69
3	1	1	92
4	1.5	1	85

Reaction conditions: 4-chlorobenzaldehyde **1** (1 mmol), acetophenone **2** (1 mmol), malononitrile **3** (1 mmol), ammonium acetate **4** (1 mmol) under microwave irradiation at 600 W in solvent-free conditions. [a]Isolated yield.

Table 2. Effect of microwave power on the synthesis of 2-amino-4,6-diarylnicotinonitrile derivatives.

Entry	Catalyst (mmol)	Microwave power (W)	Time (min)	Temperature	Yield[a] (%)
1	-	-	240	110	-
2	1	-	120	110	57
3	1	500	1	-	68
4	1	550	1	-	80
5	1	600	1	-	92
6	1	650	1	-	86

Reaction conditions: 4-chlorobenzaldehyde **1** (1 mmol), acetophenone **2** (1 mmol), malononitrile **3** (1 mmol), ammonium acetate **4** (1 mmol) with 1 mmol boric acid in solvent-free conditions. [a]Isolated yield.

The results and conditions of the synthesis of differently substituted aryl aldehydes to 2-amino-4,6-diarylnicotinonitrile derivatives **5a**–**5m** are summarized in Table 3.

A reasonable mechanism is suggested in Scheme 2 for the synthesis of 2-amino-4,6-diarylnicotinonitrile analogs. It was proposed that the first step of the reaction included the primary generation of the dicyano olefin I by the Knoevenagel condensation between aryl aldehydes and malononitrile. In the second step, intermediate I reacted with intermediate II, which was generated from the reaction of acetophenone with ammonium acetate leading to intermediate III. Finally, after the cyclization via air oxidation, the target compounds (**5a**–**5m**) were formed. Therefore, the catalyst facilitated the generation of intermediates I–IV.

The structure of compound **5d** was confirmed by single-crystal X-ray analysis (Figure 1a). The crystal is isomorphic with the 4-(3-chlorophenyl) derivative reported previously, and its molecular structure, as well as the crystal packing, revealed many features common to that analog. The phenyl ring in **5d** is coplanar with the pyridyl ring, with the interplanar angle amounting to 2.32(2)°. The chlorophenyl ring is twisted relative to the central pyridyl ring at 64.23(2)°. Similarly as in the crystal of the isomorphic 4-(3-chlorophenyl) compound, the amino and nitrile groups of two adjacent molecules of **5d** interact with each other via two N–H$\cdots$N hydrogen bonds to form centrosymmetric dimers and the $R_2^2(12)$ ring motifs [N–H, H$\cdots$N, N$\cdots$N distances = 0.80(2), 2.25(2), 3.049(2) Å, N–H$\cdots$N angle = 170(2)°; Figure 1b]. The neighboring dimers are further linked by $\pi\cdots\pi$ stacking interactions between the pyridyl rings, with the centroid$\cdots$centroid distance = 3.546(2) Å, perpendicular centroid$\cdots$ring distance of 3.444(1) Å, and offset amounting to 0.85 Å.

Table 3. Three-component condensation of aldehydes, acetophenone, malononitrile, and ammonium acetate for the synthesis of 2-amino-4,6-diarylnicotinonitrile derivatives.

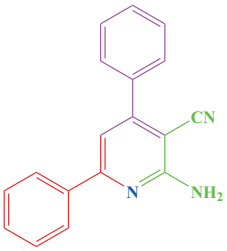
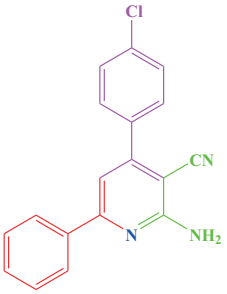
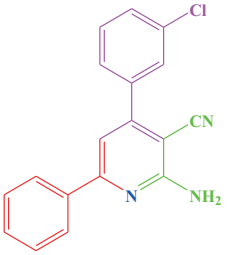
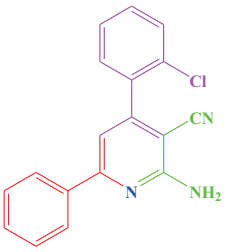
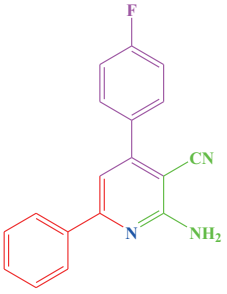
Entry	R	Product	Time (s)	Yield (%) [a]	M.P (° C)	References
1	H	 **5a**	56	88	187-189	186-87 [4]
2	4-Cl	 **5b**	60	92	180-182	221-24 [4]
3	3-Cl	 **5c**	60	89	168-170	-
4	2-Cl	 **5d**	60	90	193-196	[5]
5	4-F	 **5e**	48	94	149-151	[5]

Table 3. Continued.

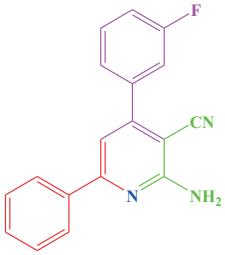
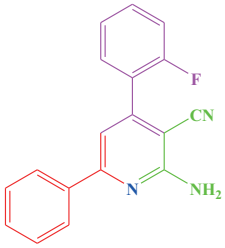
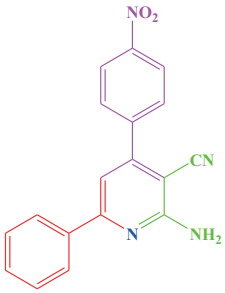
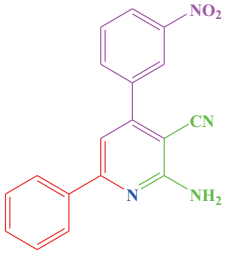
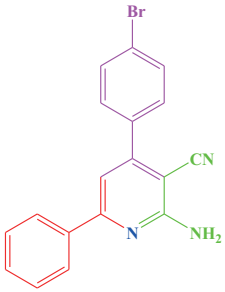
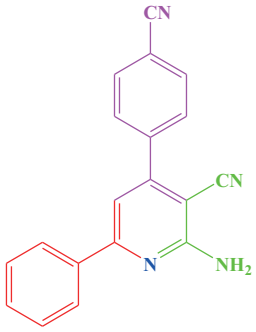
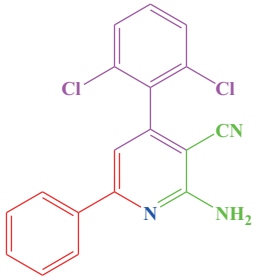
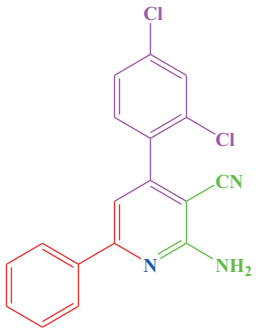
Entry	R	Product	Time (s)	Yield (%) [a]	M.P (º C)	References
6	3-F	 **5f**	49	89	162-165	-
7	2-F	 **5g**	56	90	178-180	-
8	4-NO_2	 **5h**	48	89	218-220	[5]
9	3-NO_2	 **5i**	50	94	201-203	[5]
10	4-Br	 **5j**	49	92	197-199	[5]

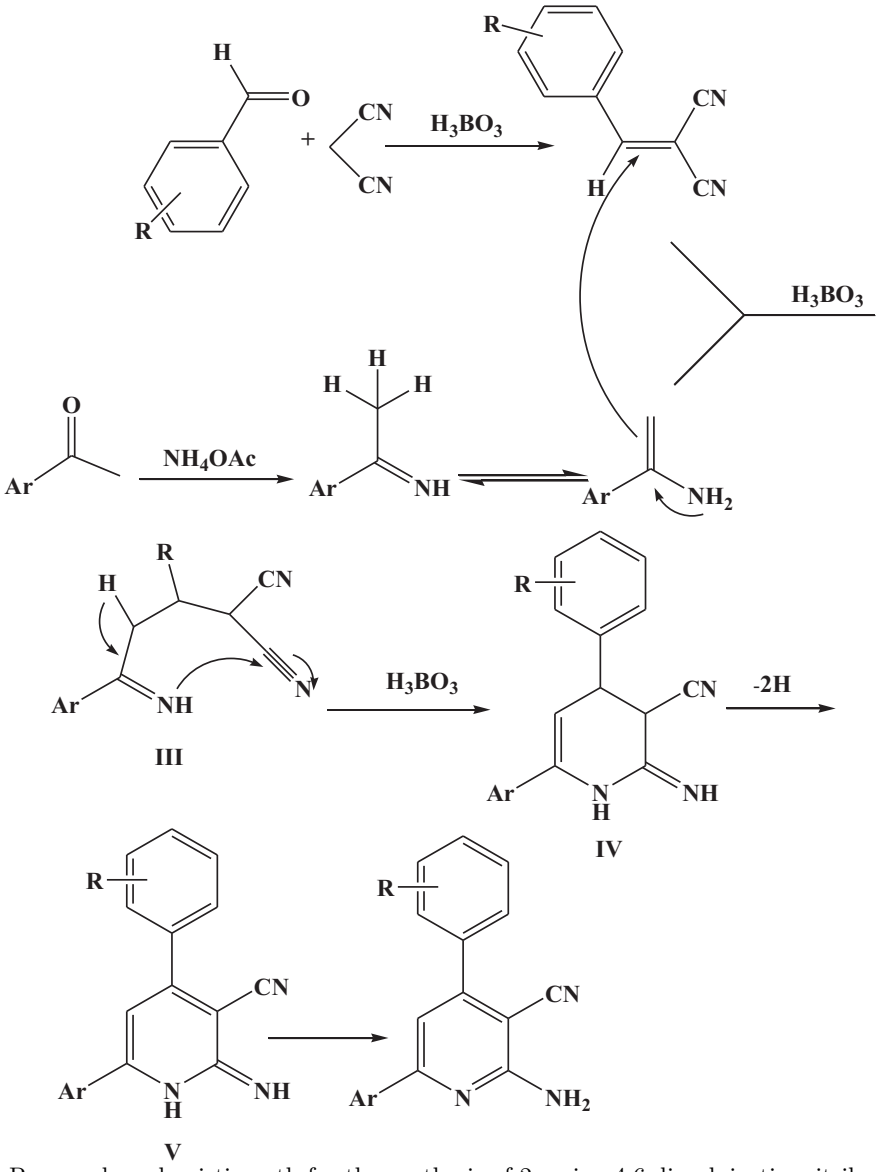
Table 3. Continued.

Entry	R	Product	Time (s)	Yield (%) [a]	M.P (° C)	References
11	4-CN	 **5k**	49	96	185-187	[5]
12	2,6-$(Cl)_2$	 **5l**	56	86	174-176	-
13	2,4-$(Cl)_2$	 **5m**	50	87	179-181	-

Reaction conditions: benzaldehyde **1a**–**1m** (1 mmol), acetophenone **2** (1 mmol), malononitrile **3** (1 mmol), ammonium acetate **4** (1 mmol) with 1 mmol boric acid under microwave irradiation at 600 W in solvent-free condition. [a]Isolated yield.

2.1. Conclusions

We have presented a green and efficient procedure for the synthesis of 2-amino-4,6-diarylnicotinonitriles with boric acid as a green and recoverable catalyst. Short reaction time (48–60 s), ecofriendly style, simple workup, and the use of green catalyst are some of the significant advantages of this procedure. The structures of all the synthesized compounds were elucidated by their melting points, IR, ^{1}H NMR, and ^{13}C NMR spectra. Furthermore, the structure of **5d** was confirmed by single-crystal X-ray analysis.



Scheme 2. Proposed mechanistic path for the synthesis of 2-amino-4,6-diarylnicotinonitrile derivatives.

3. Experimental

3.1. Materials and instruments

Reagents and solvents were prepared from Merck, Fluka, and Aldrich. TLC was utilized to follow the reactions. IR spectra were recorded on a Jasco 6300 FTIR spectrometer. The microwave-assisted approaches were performed in a Milestone microwave oven operating at 1600 W. ^{1}H ($CDCl_3$ and DMSO-d_6) and ^{13}C NMR ($CDCl_3$ and DMSO-d_6) spectra were measured on a Bruker DRX-250 Avance spectrometer at 250.13 and 62.90 MHz, respectively. Melting points were recorded on an Electrothermal 9100 apparatus (LABEQUIP LTD., Markham, Canada).

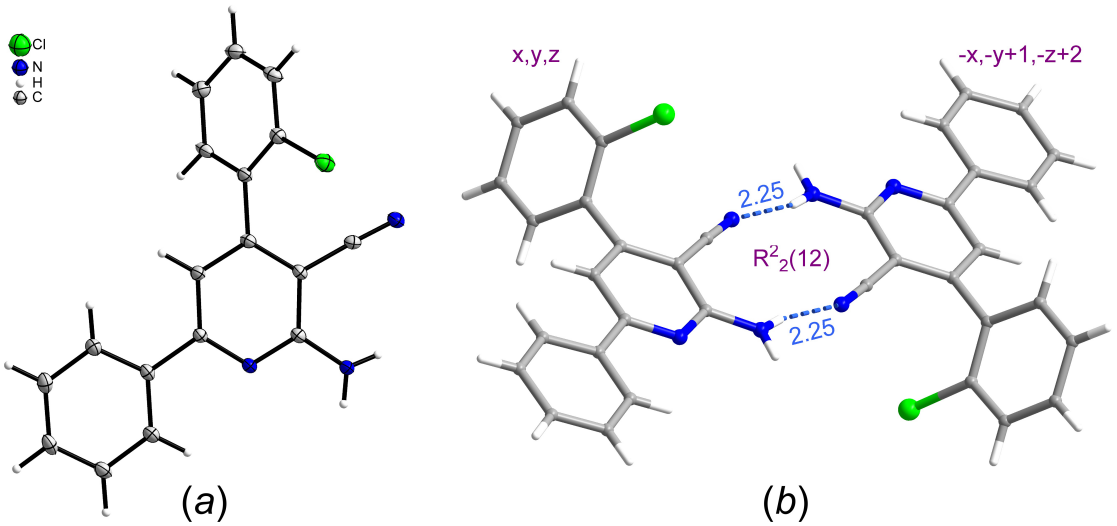


Figure 1. X-ray crystal structure of **5d**: molecule (a) and centrosymmetric molecular dimer (b). Displacement ellipsoids in (a) are drawn at the 50% probability level. Blue dashed lines in (b) represent N–H$\cdots$N hydrogen bonds.

3.2. General procedure for the synthesis of 2-amino-4,6-diarylnicotinonitriles

Derivatives of aldehyde **1a**–**1m** (1 mmol), acetophenone **2** (1 mmol), malononitrile **3** (1 mmol), and ammonium acetate **4** (1.5 mmol) and H_3BO_3 (1 mmol) were taken in a glass vial and irradiated in a microwave oven (600 W). The progress of the reaction was detected by TLC (n-hexane: EtOAc, 10:6). After the fulfillment of the reaction, 3 mL of ethanol was added to the reaction mixture. Then the solid product was collected by filtration and the pure products were achieved through recrystallization from hot ethanol. All analogs that have not been previously represented were identified by the melting point, IR, ^{1}H NMR, and ^{13}C NMR spectra. The structure of **5d** was verified by the analysis of single-crystal X-ray.

3.3. Spectral data of selected products

2-Amino-4,6-diphenylnicotinonitrile (Table 3, entry 1): White solid, yield: 88%, mp: 187–189 °C; IR (KBr): 3463 and 3303 (NH_2), 3178 (ArH), 2205 (CN), 1637 (C=N), 1585 (C=C) 1258 (C-N); ^{1}H NMR (250.13 MHz, DMSO): δ 7.01 (s, 2H, NH_2), 7.25 (s, 1H, aromatic), 7.45–7.53 (m, 6H, aromatic), 7.65 (t, 2H, J = 2.5 Hz), 8.10 (d, 2H, J = 2.5 Hz); ^{13}C NMR (62.90 MHz, $CDCl_3$): δ 111.12 (pyridine C-5), 117.12 (CN), 127.32–137.93 (benzene), 155.12 (pyridine C-4), 159.82 (pyridine C-6), 160.23 (pyridine C-2).

2-Amino-4-(4-chlorophenyl)-6-phenylnicotinonitrile (Table 3, entry 2): Cream solid, yield: 92%, mp: 221–224 °C; IR (KBr, cm^{-1}): 3484 and 3362 (NH_2), 2215 (CN), 1631 (C=N), 1574 (C=C), 1259 (C-N); ^{1}H NMR (250.13 MHz, DMSO): δ 7.05(s, 2H, NH_2), 7.26 (s, 1H, aromatic), 7.46–7.47(m, 3H, aromatic), 7.59–7.71(m, 4H, aromatic), 8.10 (d, 2H, J = 2.75 Hz, aromatic); ^{13}C NMR (62.90 MHz, $CDCl_3$): δ 110.98 (pyridine C-5), 127.31, 128.83, 129.23, 129.51, 130.33, 160.21 (pyridine C-2).

2-Amino-4-(3-chlorophenyl)-6-phenylnicotinonitrile (Table 3, entry 3): Yellow crystal, yield: 89%, mp: 168–170 °C; IR (KBr): 3469 and 3305 (NH_2), 2205 (CN), 1635 (C=N), 1578 (C=C), 1258 (C-N); ^{1}H NMR (250.13 MHz, DMSO): δ 7.06 (s, 2H, NH_2), 7.30 (s, 1H, aromatic), 7.46–7.61 (m, 6H, aromatic), 7.74 (s, 1H, aromatic), 8.12 (d, 2H, aromatic, J = 3.5 Hz); ^{13}C NMR (62.90 MHz, $CDCl_3$): δ 110.99 (pyridine C-5),

116.68 (CN), 126.38, 127.32, 128.22, 128.81, 129.84, 130.20, 130.35, 134.90, 137.66, 138.61 (pyridine C-4), 153.51 (pyridine C-6), 160.17 (pyridine C-2).

2-Amino-4-(2-chlorophenyl)-6-phenylnicotinonitrile (Table 3, entry 4): Yellow crystal, yield: 90%, mp: 199–201 °C; IR (KBr): 3489 and 3341 (NH_2), 2228 (CN), 1623 (C=N), 1571 (C=C), 1253 (C-N); ^{1}H NMR (250.13 MHz, DMSO): δ 6.53 (s, 2H, NH_2), 7.25 (s, 1H, aromatic), 7.36–7.46 (m, 5H, aromatic), 7.55 (m, 2H, aromatic), 8.10 (2, 2H, aromatic, J = 2.5 Hz); ^{13}C NMR (62.90 MHz, $CDCl_3$): δ 112.20 (pyridine C-5), 127.08, 127.36, 128.79, 130.27, 130.64, 152.97 (pyridine C-4), 159.62 (pyridine C-6).

2-Amino-4-(4-fluorophenyl)-6-phenylnicotinonitrile (Table 3, entry 5): White solid, yield: 94%, mp: 164–166 °C; IR (KBr): 3474 and 3393 (NH_2), 2206 (CN), 1644 (C=N), 1574 (C=C) 1233 (C-N); ^{1}H NMR (250.13 MHz, DMSO): δ 7.03 (s, 2H, NH_2), 7.25 (s, 1H, aromatic), 7.34–7.46 (m, 5H, aromatic), 7.73 (t, 2H, aromatic, J = 7.5 Hz), 8.10 (d, 2H, aromatic, J = 7.5 Hz); ^{13}C NMR (62.90 MHz, $CDCl_3$): δ 111.09 (pyridine C-5), 115.90 (d, $^2J_{CF}$ = 22.01 Hz), 117.01 (CN), 127.32, 128.81, 130.08, 130.22 (d, $^3J_{CF}$ = 08.80 Hz), 137.82, 154.01 (pyridine C-4), 159.96 (pyridine C-6), 160.25 (d, $^1J_{CF}$ = 250.34 Hz), 165.67 (pyridine C-2).

2-Amino-4-(3-fluoroophenyl)-6-phenylnicotinonitrile (Table 3, entry 6): Cream solid, yield: 89%, mp: 162–165 °C; IR (KBr): 3473 and 3311 (NH_2), 2206 (CN), 1645 (C=N), 1575 (C=C), 1234 (C-N); ^{1}H NMR (250.13 MHz, DMSO): δ_H 7.03 (s, 2H, NH_2), 7.25 (s, 1H, aromatic), 7.34–7.47 (m, 5H, aromatic), 7.72 (t, 2H, aromatic, J = 5.5 Hz), 8.10 (d, 2H, aromatic, J = 5 Hz); ^{13}C NMR (62.90 MHz, $CDCl_3$): δ_C 111.08 (pyridine C-5), 115.89 (d, $^2J_{CF}$ = 22.01 Hz), 116.24 (CN), 116.99, 127.32, 128.80, 130.08 (d, $^3J_{CF}$ = 08.80 Hz), 133.00, 137.82, 154.00 (pyridine C-4), 160.25 (d, $^1J_{CF}$ = 250.97 Hz), 161.69 (pyridine C-6), 165.68 (pyridine C-2).

2-Amino-4-(2-fluorophenyl)-6-phenylnicotinonitrile (Table 3, entry 7): Cream solid, yield: 90%, mp: 178–180 °C; IR (KBr): 3465 and 3305 (NH_2), 2206 (CN), 1637 (C=N), 1587 (C=C), 1256 (C-N); ^{1}H NMR (250.13 MHz, DMSO): δ 7.08 (s, 2H, NH_2), 7.25 (s, 1H, aromatic), 7.36–7.39 (m, 2H, aromatic), 7.46–7.56 (m, 5H, aromatic), 8.09 (d, 2H, aromatic, J = 2.5 Hz); ^{13}C NMR (62.90 MHz, $CDCl_3$): δ 112.22 (pyridine C-5), 116.26 (d, $^2J_{CF}$ = 21.38 Hz), 116.47 (CN), 124.59, 127.36, 128.79, 130.25, 130.55, 131.54 (d, $^3J_{CF}$ = 08.17 Hz), 137.79, 149.59 (pyridine C-4), 159.86 (pyridine C-6), 161.22 (pyridine C-2).

2-Amino-4-(4-nitrophenyl)-6-phenylnicotinonitrile (Table 3, entry 8): Dark brown solid, yield: 89%, mp: 216–218 °C; IR (KBr): 3489 and 3375 (NH_2), 2210 (CN), 1636 (C=N), 1571 (C=C), 1261 (C-N); ^{1}H NMR (250.13 MHz, DMSO): δ 7.11 (s, 2H, NH_2), 7.30 (s, 1H, aromatic), 7.46–7.59 (m, 4H, aromatic), 7.91 (d, 2H, aromatic, J = 7.5 Hz), 8.10 (s, 1H, aromatic), 8.34 (d, 2H, aromatic, J = 7.5 Hz); ^{13}C NMR (62.90 MHz, DMSO): δ 109.59 (pyridine C-5), 118.90 (CN), 124.16, 127.37, 129.12, 130.01, 130.43, 130.64, 137.65, 154.47 (pyridine C-6), 161.19 (pyridine C-2).

2-Amino-4-(3-nitrophenyl) -6-phenylnicotinonitrile (Table 3, entry 9): Yellow powder, yield: 94%, mp: 208–210 °C; IR (KBr): 3478 and 3362 (NH_2), 2218 (CN), 1622 (C=N), 1577 (C=C), 1259 (C-N); ^{1}H NMR (250.13 MHz, DMSO): δ 7.14 (s, 2H, NH_2), 7.40–7.48 (m, 4H, aromatic), 7.85 (t, 2H, aromatic, J = 7.5 Hz), 8.13 (s, 1H, pyridine ring), 8.37 (d, 2H, aromatic, J = 7.5 Hz), 8.49 (s, 1H, aromatic); ^{13}C NMR (62.90 MHz, $CDCl_3$): δ 110.88 (pyridine C-5), 123.28, 124.46, 127.37, 128.88, 130.09, 130.59, 134.11, 138.50, 160.20 (pyridine C-2).

2-Amino-4-(4-bromophenyl)-6-phenylnicotinonitrile (Table 3, entry 10): Cream solid, yield: 92%, mp: 186–188 °C; IR (KBr): 3472 and 3305 (NH_2), 2206 (CN), 1642 (C=N), 1574 (C=C), 1258 (C-N); ^{1}H NMR (250.13 MHz, $CDCl_3$): δ 7.05 (s, 2H, NH_2), 7.26 (s, 1H, aromatic), 7.46–7.47 (m, 3H, aromatic), 7.59–7.71 (m, 4H, aromatic), 8.10 (d, 2H, aromatic, J = 5 Hz); ^{13}C NMR (62.90 MHz, $CDCl_3$): δ 110.90 (pyridine C-5), 116.88 (CN), 124.40, 127.32, 128.83, 129.74, 130.34, 132.20, 135.77, 137.73, 153.84 (pyridine C-4), 160.07 (pyridine C-6), 160.22 (pyridine C-2).

2-Amino-4-(4-cyanophenyl)-6-phenylnicotinonitrile (Table 3, entry 11): Yellow solid, yield: 96%, mp: 185–187 °C; IR (KBr): 3475 and 3363 (NH_2), 2204 (CN), 1618 (C=N), 1574 (C=C), 1261 (C-N); ^{1}H NMR (250.13 MHz, DMSO): δ 7.12 (s, 2H, NH_2), 7.30 (s, 1H, aromatic), 7.46–7.536 (m, 4H, aromatic), 7.85 (d, 2H, aromatic, J = 7.5 Hz); ^{13}C NMR (62.90 MHz, $CDCl_3$): δ 110.77 (pyridine C-5), 113.63 (CN), 115.37, 116.45, 118.12, 119.67, 127.34, 128.33, 128.87, 128.99, 129.21, 129.99, 130.55, 132.69, 137.45, 141.29, 152.92 (pyridine C-4), 160.23 (pyridine C-6), 160.41(pyridine C-2).

2-Amino-4-(2,6-dichlorophenyl)-6-phenylnicotinonitrile (Table 3, entry 12): Yellow crystal, yield: 86%, mp: 174–176 °C; IR (KBr): 3489 and 3373 (NH_2), 2214 (CN), 1666 (C=N), 1577(C=C), 1215 (C-N); ^{1}H NMR (250.13 MHz, DMSO): δ 7.18 (s, 2H, NH_2), 7.26 (s, 1H, aromatic), 7.46–7.57 (m, 4H, aromatic), 7.65–7.68 (m, 2H, aromatic), 8.09 (d, 2H, aromatic, J = 2.5 Hz); ^{13}C NMR (62.90 MHz, $CDCl_3$): δ 111.80 (pyridine C-5), 115.56 (CN), 127.39, 128.39, 128.79, 130.35, 130.84, 134.05, 137.63, 150.77 (pyridine C-4), 159.61 (pyridine C-6), 160.22 (pyridine C-2).

2-Amino-4-(2,4-dichlorophenyl)-6-phenylnicotinonitrile (Table 3, entry 13): Dark yellow crystal, yield: 87%, mp: 179–181 °C; IR (KBr): 3480 and 3377 (NH_2), 2212 (CN), 1682 (C=N), 1615 (C=C), 1266 (C-N); ^{1}H NMR (250.13 MHz, DMSO): δ 7.13 (s, 2H, NH_2), 7.21 (s, 1H, aromatic), 7.45–7.47 (m, 3H, aromatic), 7.55–7.58 (m, 3H, aromatic), 8.09 (d, 2H, aromatic, J = 5 Hz); ^{13}C NMR (62.90 MHz, $CDCl_3$): δ 111.98 (pyridine C-5), 116.05 (CN), 127.38, 127.55, 128.84, 130.16, 131.14, 133.23, 134.36, 136.11, 137.59, 151.87 (pyridine C-6), 159.87 (pyridine C-2).

3.4. Single-crystal X-ray crystallography

A crystal of compound **5d** was prepared via slow evaporation method. The crystallographic measurement of **5d** was carried out on a Kuma KM4-CCD κ-geometry automated four-circle diffractometer equipped with a CCD camera Sapphire2 and graphite-monochromatized Mo Kα radiation (λ = 0.71073 Å). Data were collected at 100(2) K by utilizing the Oxford-Cryosystems cooler and corrected for the Lorentz and polarization effects. Data collection, cell refinement, data reduction, and analysis were performed with KM4-CCD software, CrysAlisPro[15] Analytical absorption correction was applied. Due to isomorphism of **5d** with the 4-(3-chlorophenyl) derivative reported by us previously,[16] the cell setting of **5d** was related to that of the 4-(3-chlorophenyl) compound, which resulted in nonstandard axial order. Transformation matrix $\boldsymbol{P}$ from used (**a**,**b**,**c**) to standard (**a′**,**b′**,**c′**) setting is 0 0 1 –1 0 0 0 –1 –1, where (**a**,**b**,**c**) $\cdot$ $\boldsymbol{P}$ = (**a′**,**b′**,**c′**). The refinement of the structure of **5d** (full-matrix least squares technique with the anisotropic thermal parameters for non-H atoms performed with the use of SHELXL-2014)[17] was started by using the coordinates of C and N atoms taken from the 4-(3-chlorophenyl) derivative. H atoms were found in difference Fourier maps and refined isotropically. In the final refinement cycles, C-bound H atoms were repositioned in their calculated positions and refined using a riding model, with C-H = 0.95 Å and U_{iso}(H) = 1.2U_{eq}(C). Amine H atoms were refined freely. Figures were generated

using the DIAMOND program.[18].. The crystallographic information file was deposited with the Cambridge Crystallographic Data Centre (http://www.ccdc.cam.ac.uk/; deposition number CCDC 1832185, and prepared as Supplementary information).

Crystal data for **5d**: $C_{18}H_{12}ClN_3$, Mr = 305.76, yellowish block, crystal size 0.50 ×0.34 ×0.30 mm, triclinic, space group $P\bar{1}$, a = 10.055(3), b = 9.398(2), c = 9.599(2) Å, α = 66.21(2)°, β = 58.81(3)°, γ = 81.78(2)°, V = 707.5(4) Å^3, T = 100(2) K, Z = 2, μ = 0.27 mm^{-1} (for Mo Kα, λ = 0.71073 Å), analytical absorption correction, T_{min} = 0.876, T_{max} = 0.944, 8269 reflections measured, 3754 unique (R_{int} = 0.036), 3507 observed ($I>2\sigma(I)$), (sin θ/λ)max = 0.703 Å^{-1}, 207 parameters, 0 restraints, $R1$ = 0.052, w$R2$ = 0.143 (observed refl.), GOOF = S = 1.04, ($\Delta\rho_{max}$) = 0.79, and ($\Delta\rho_{min}$) = –0.39 e Å^{-3}.

Acknowledgment

This work was supported by the Iran National Science Foundation.

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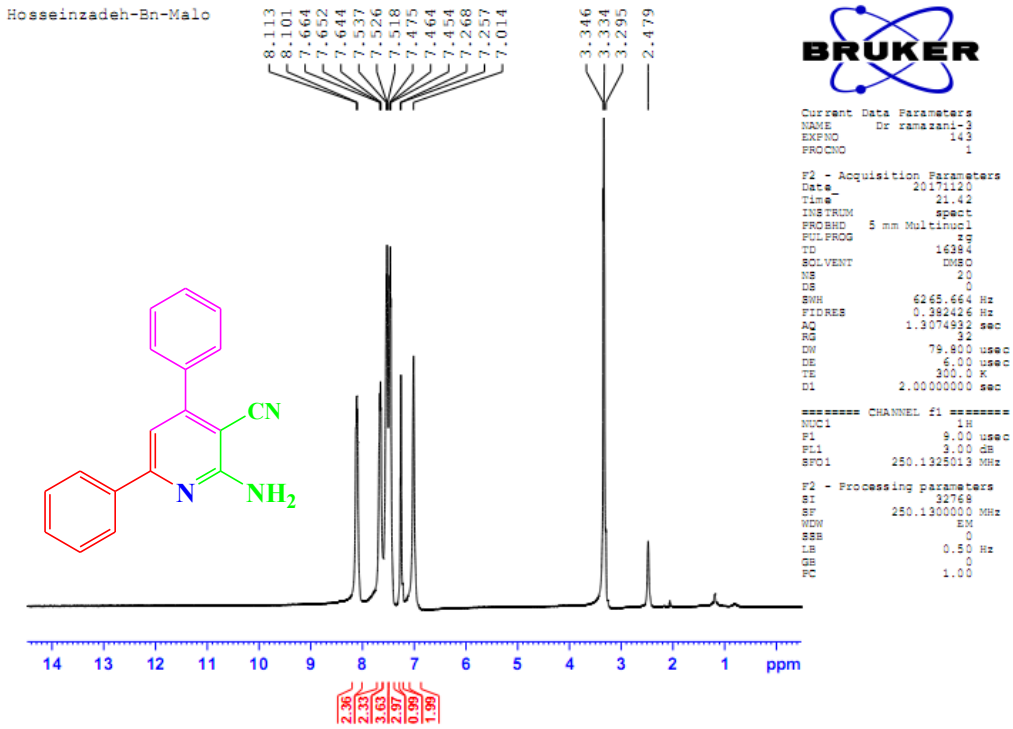
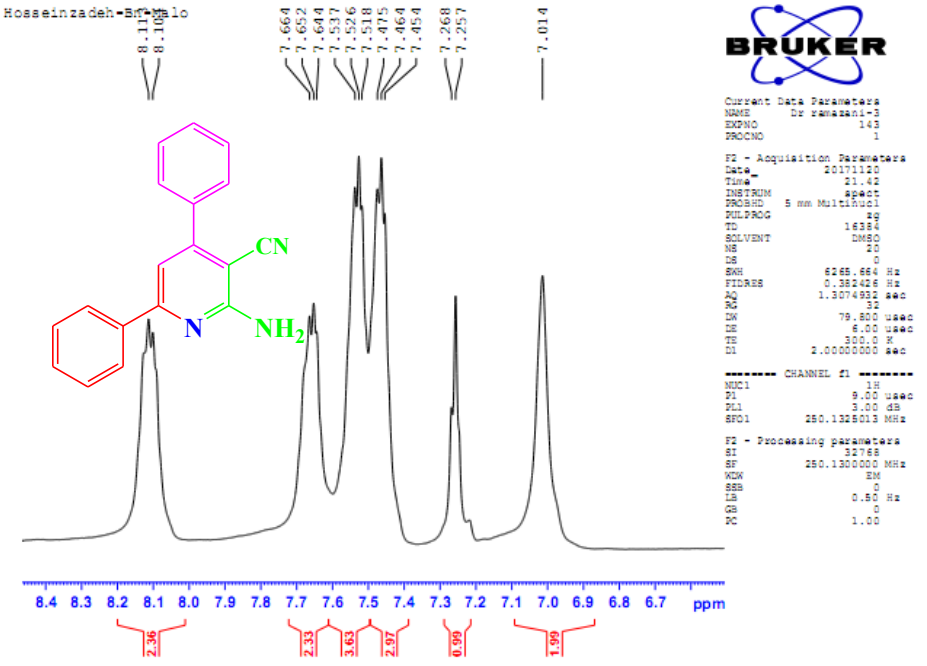
Supplementary information: Spectral data of products

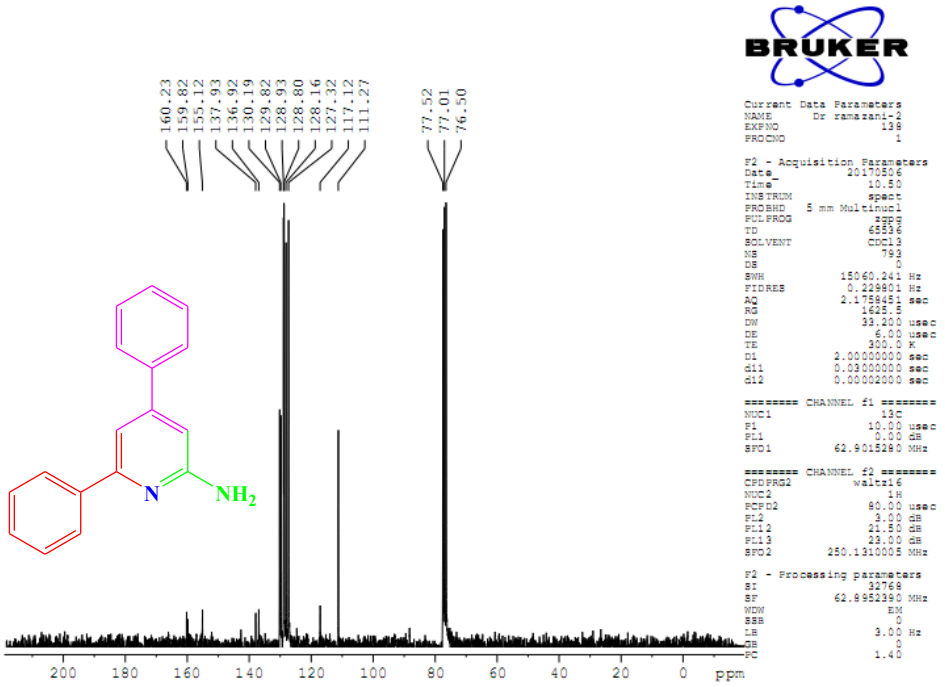
2-Amino-4,6-diphenylnicotinonitrile (Table 3, entry 1):

^{1}H NMR (250 MHz, DMSO)

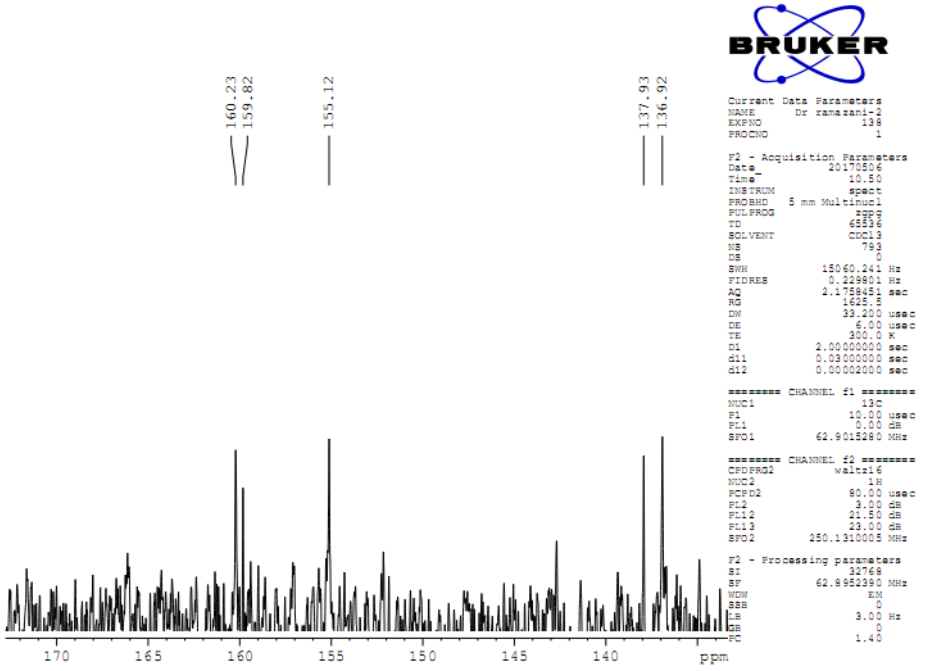




^{13}C NMR (62.9 MHz, $CDCl_3$-d_6)



Expanded ^{13}C NMR (62.9 MHz, $CDCl_3$-d_6)



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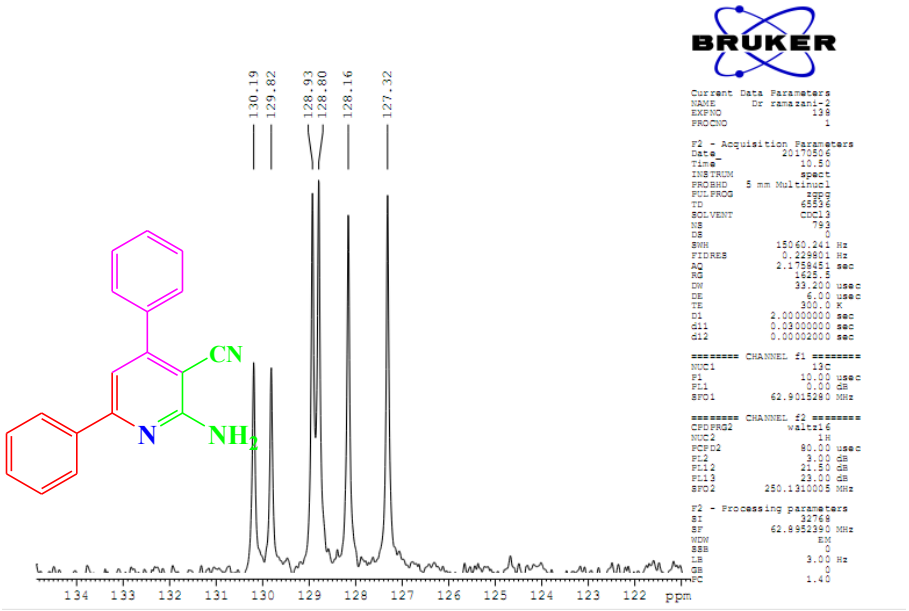

2-Amino-4-(4-chlorophenyl)-6-phenylnicotinonitrile (Table 3, entry 2):

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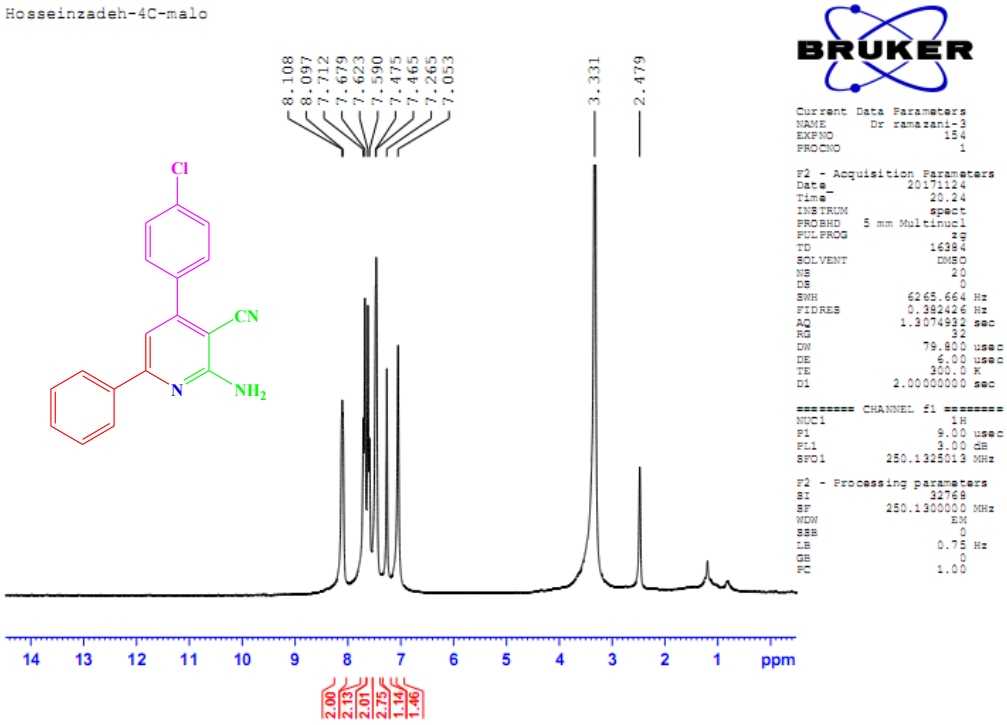
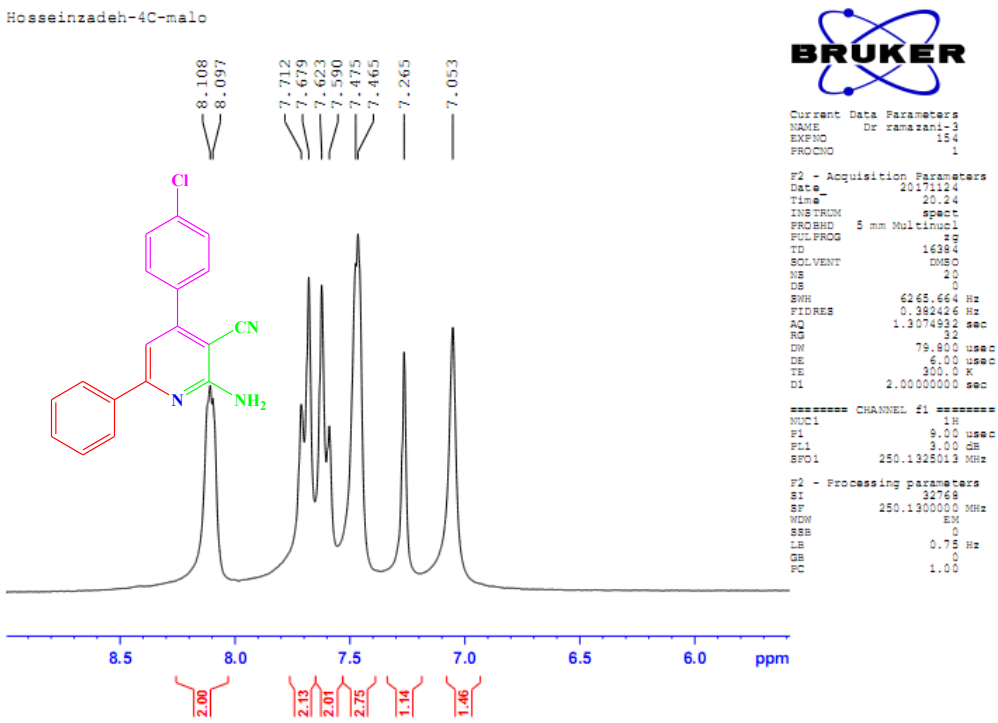
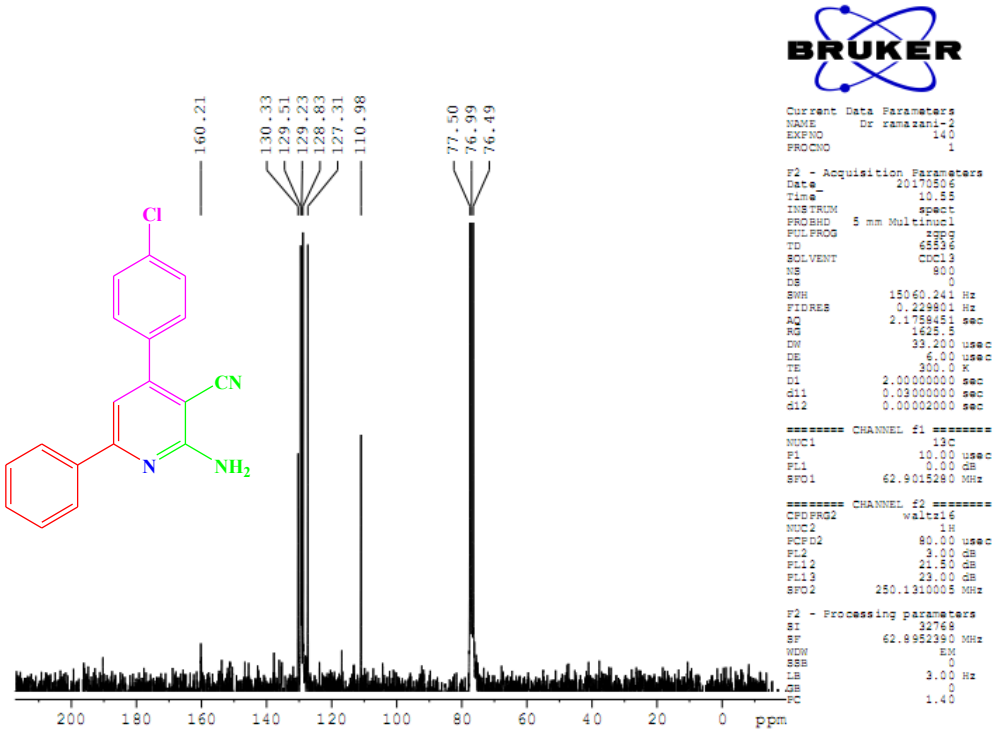
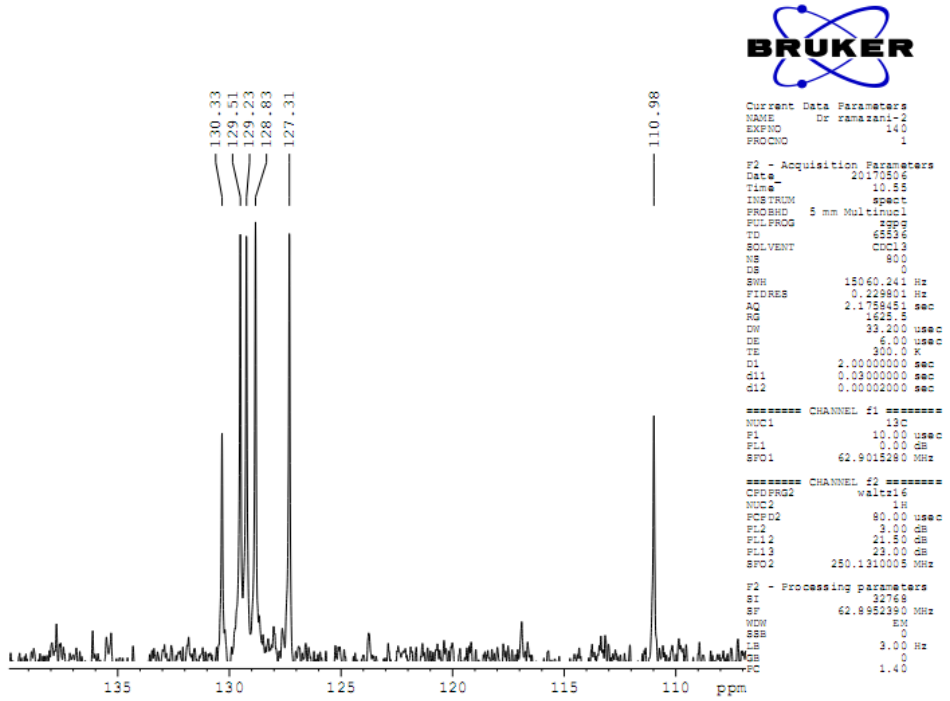




^{13}C NMR (62.9 MHz, $CDCl_3$)



Expanded ^{13}C NMR (62.9 MHz, $CDCl_3$)



2-Amino-4-(3-chlorophenyl)-6-phenylnicotinonitrile (Table 3, entry 3):

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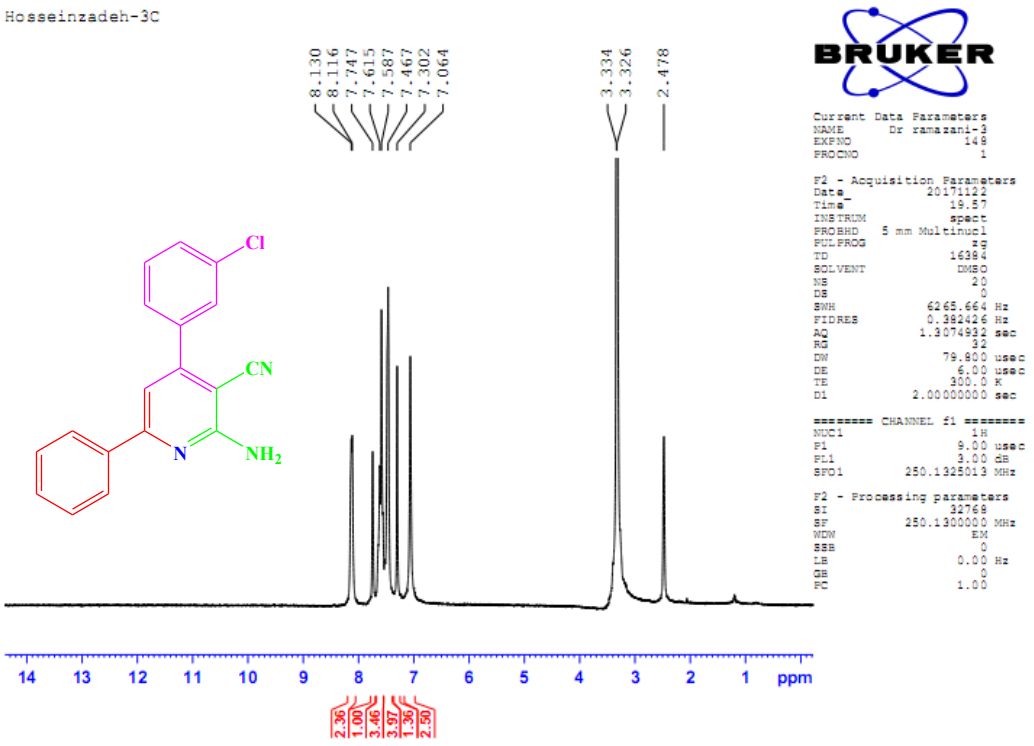
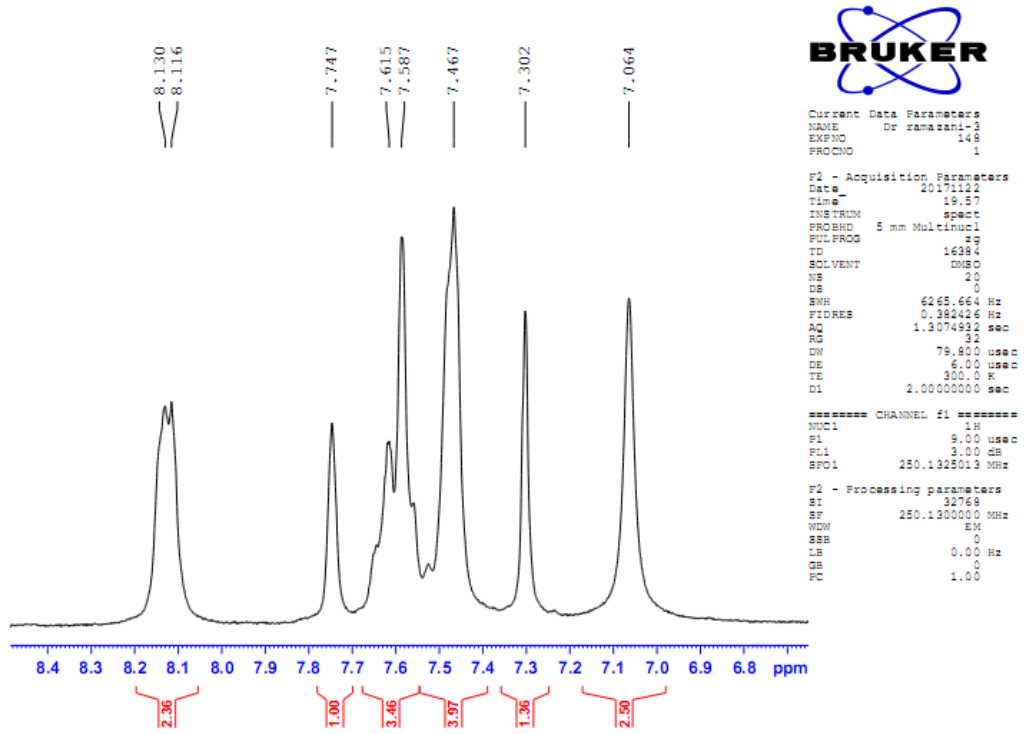
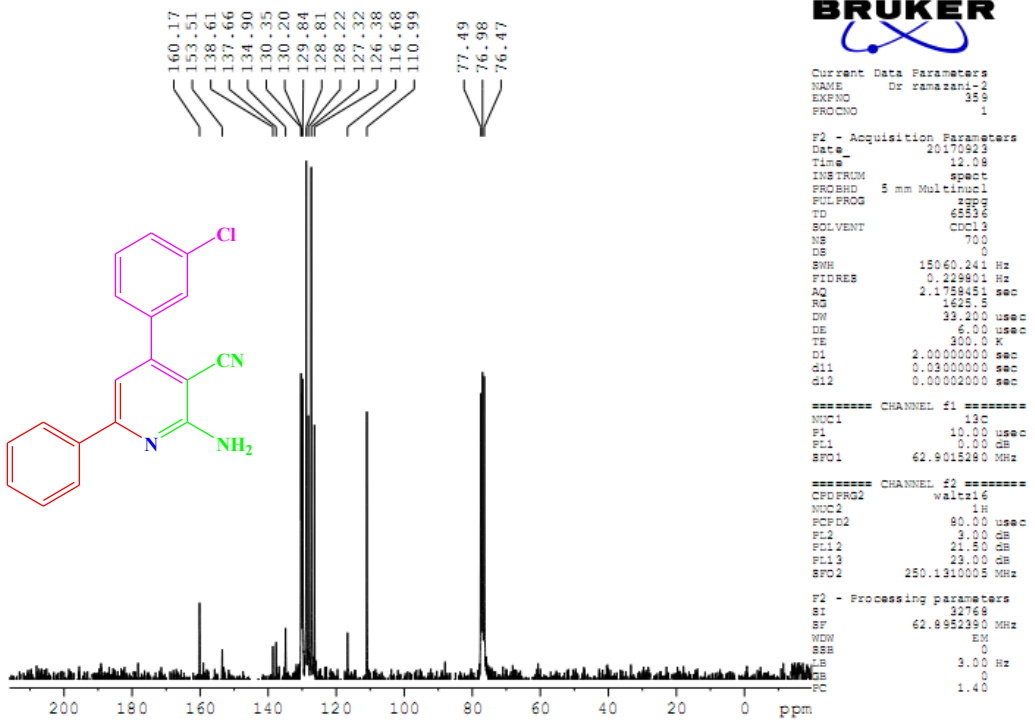
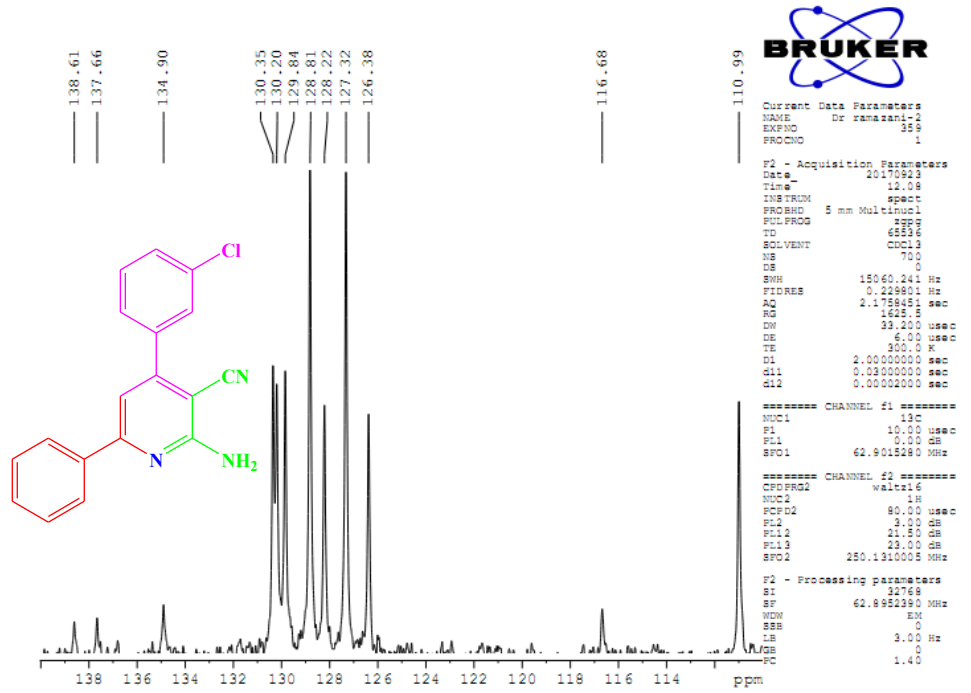




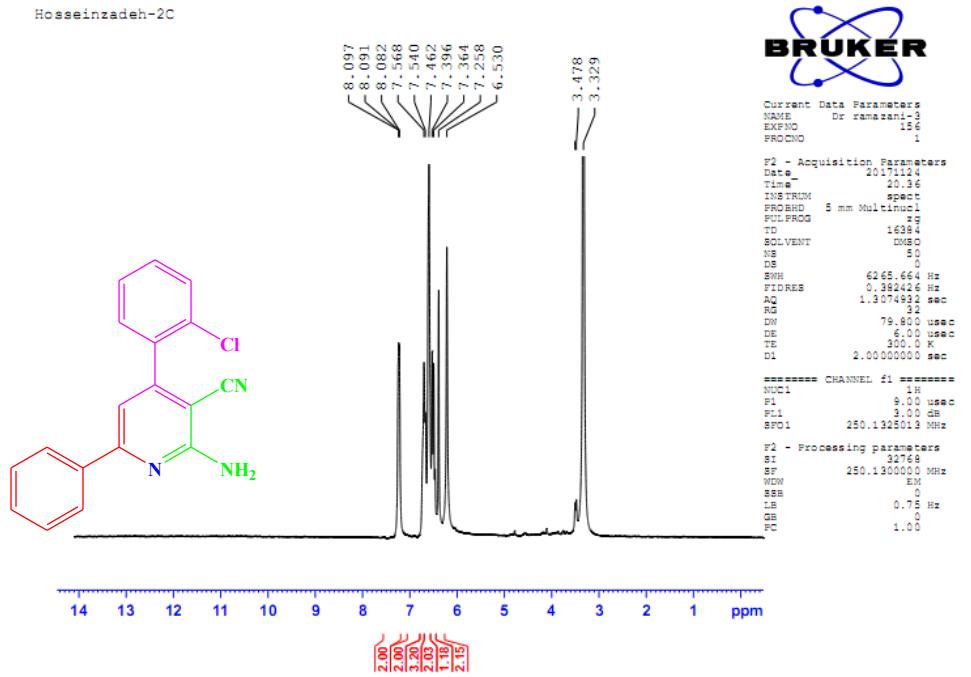
^{13}C NMR (62.9 MHz, $CDCl_3$)

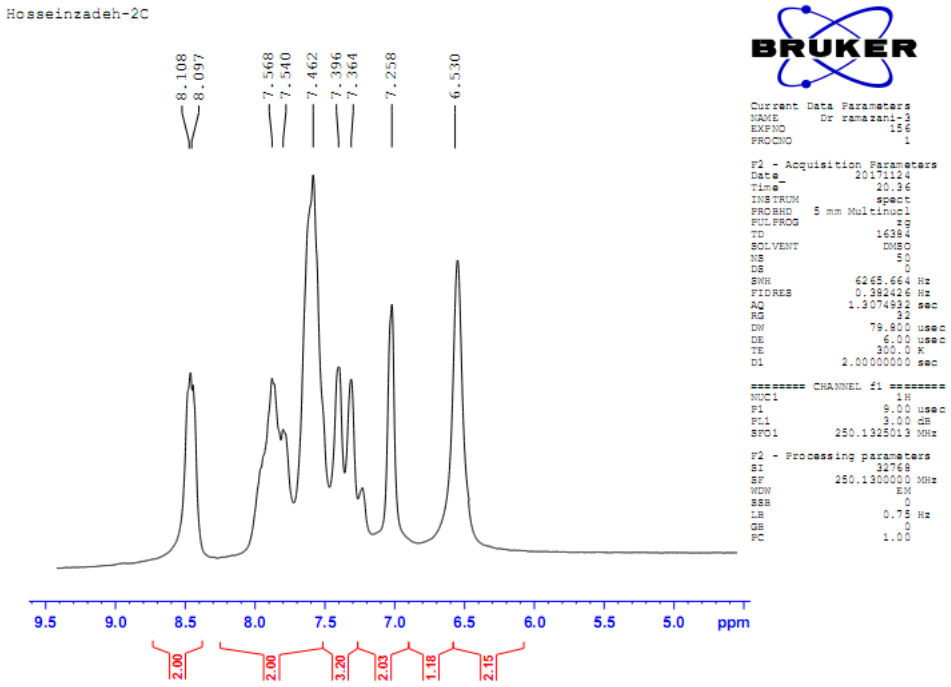




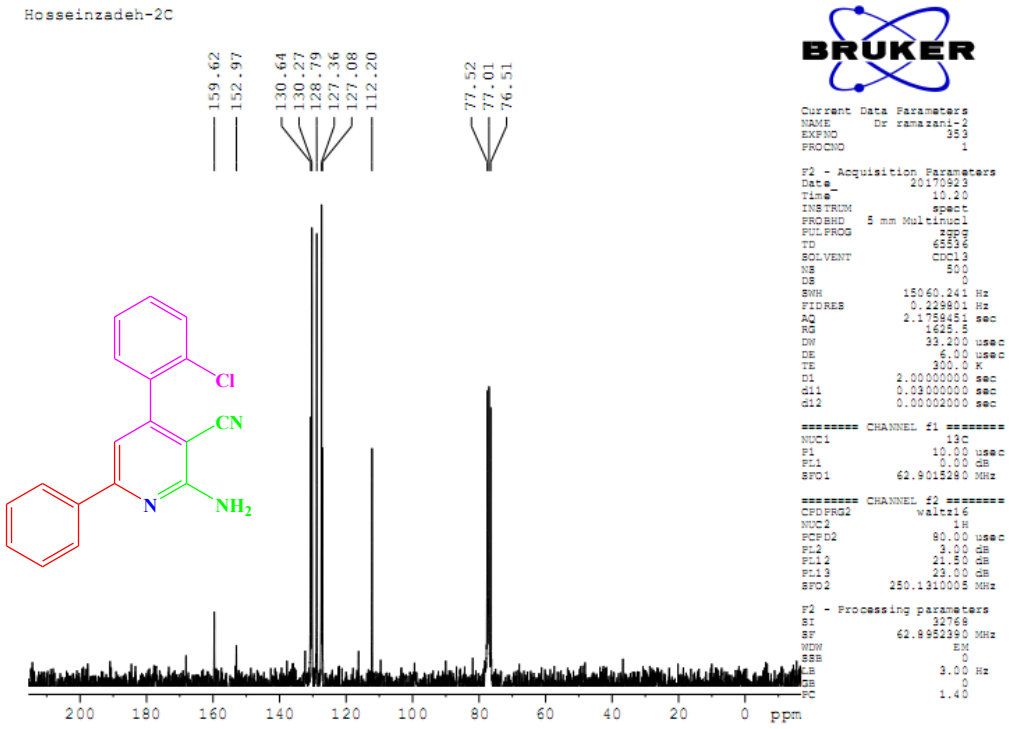
2-Amino-4-(2-chlorophenyl)-6-phenylnicotinonitrile (Table 3, entry 4):

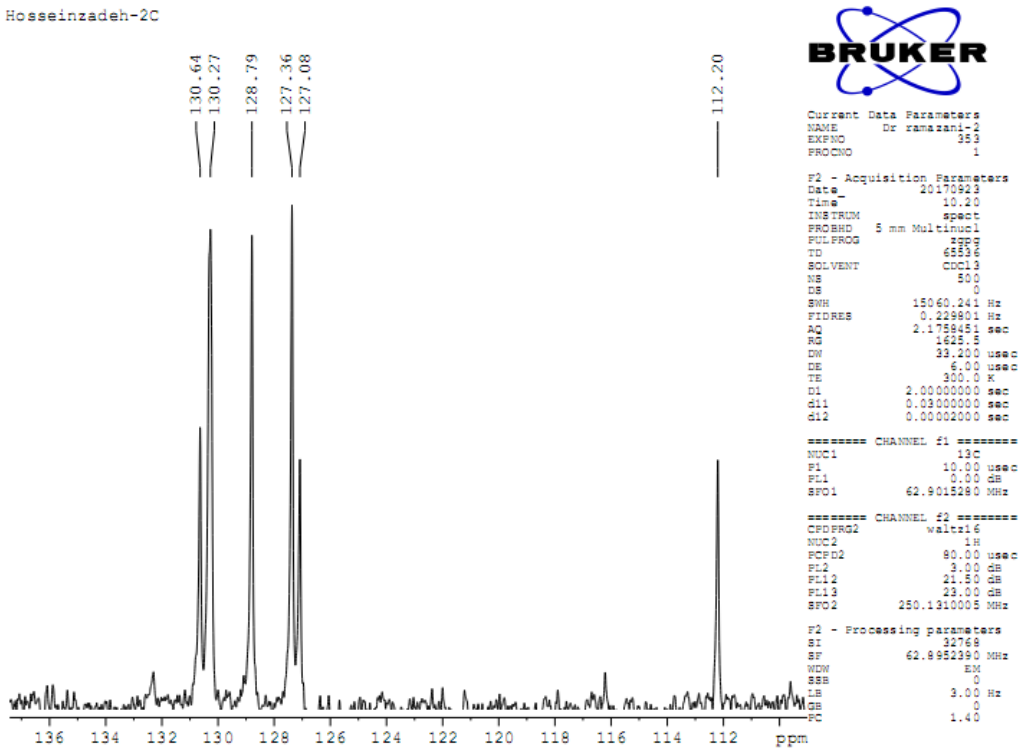
^{1}H NMR (250 MHz, DMSO)





^{13}C NMR (62.9 MHz, $CDCl_3$)





2-Amino-4-(4-fluorophenyl)-6-phenylnicotinonitrile (Table 3, entry 5):

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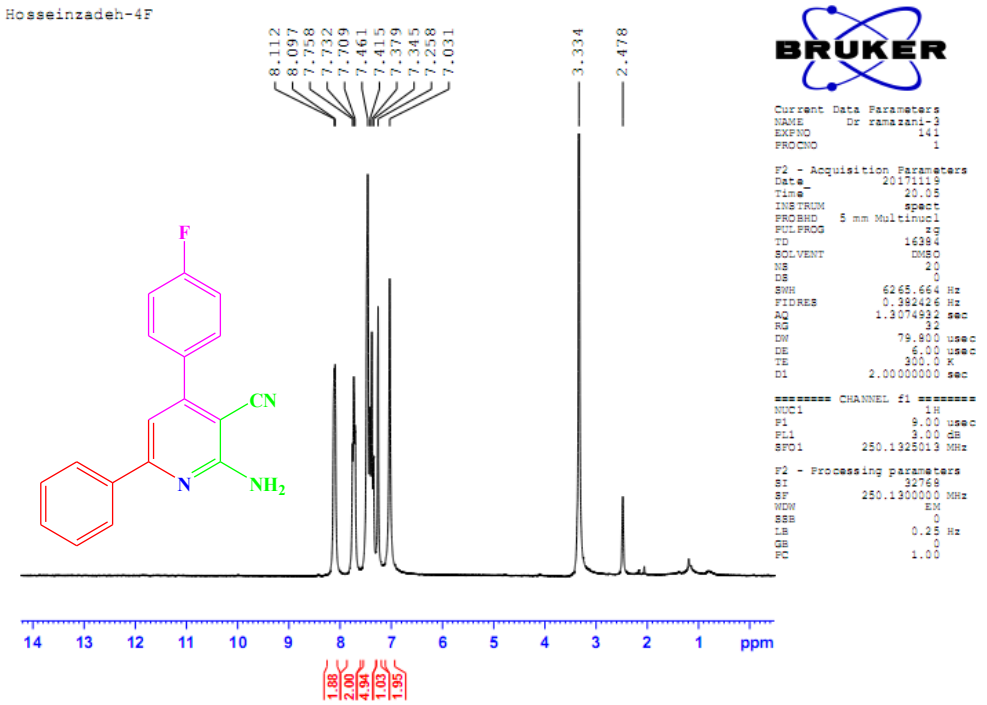
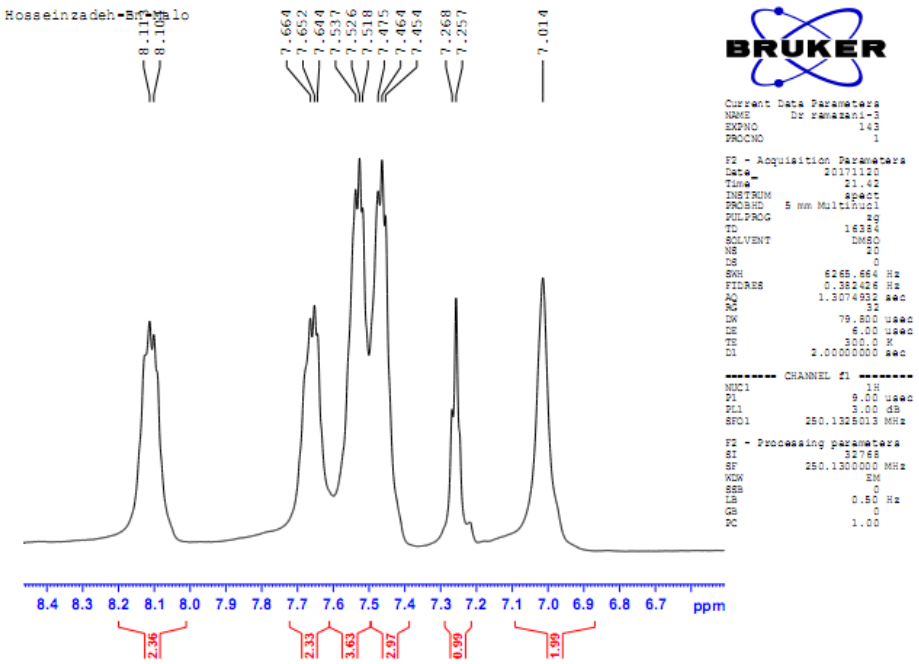
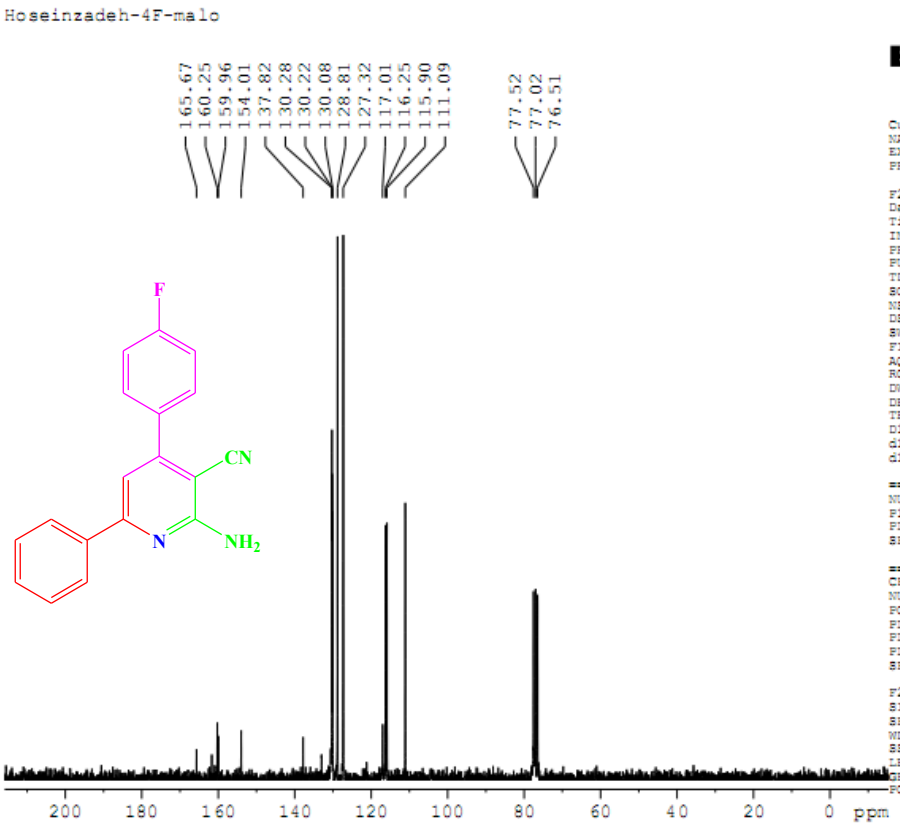
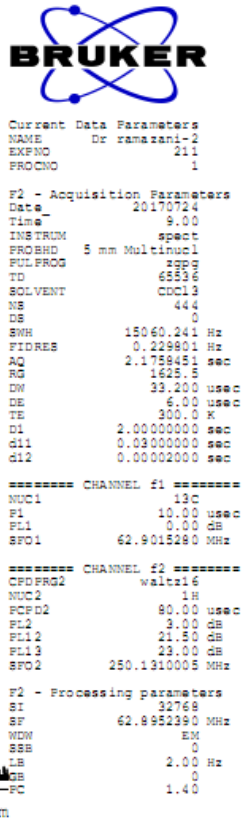


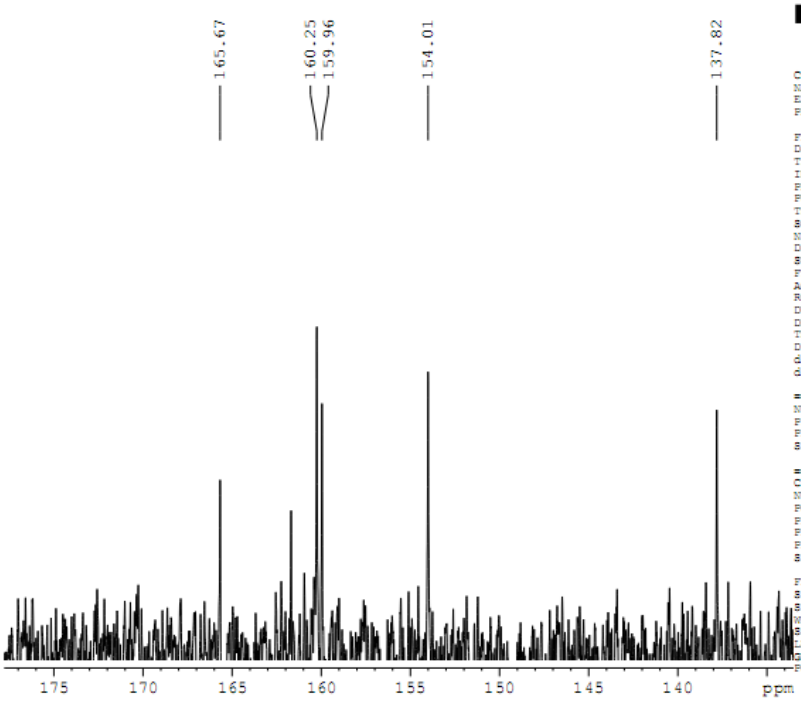


^{13}C NMR (62.9 MHz, $CDCl_3$)





Hoseinzadeh-4F-malo

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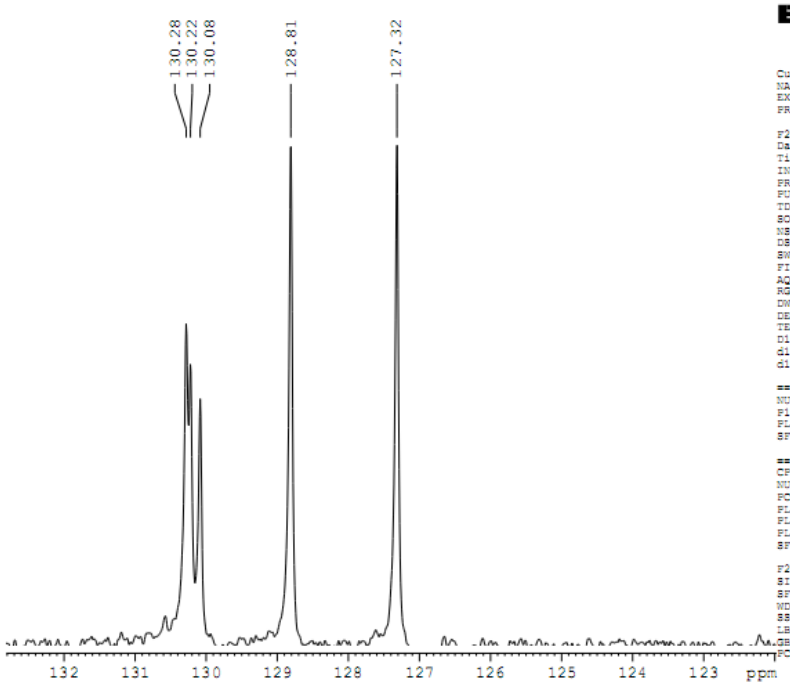
Hoseinzadeh-4F-malo

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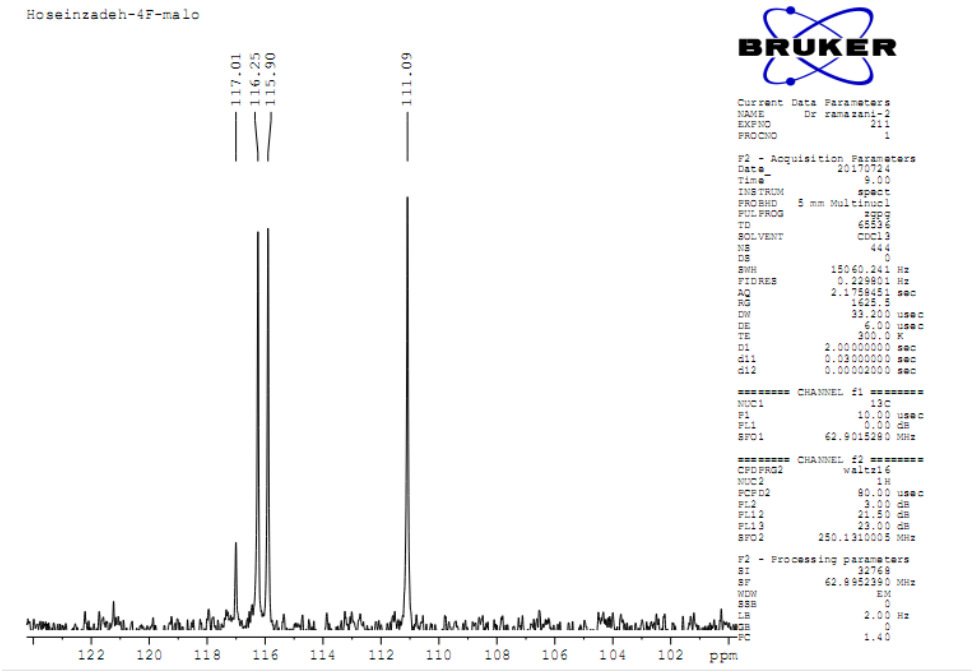

2-Amino-4-(3-fluorophenyl)-6-phenylnicotinonitrile (Table 3, entry 6):

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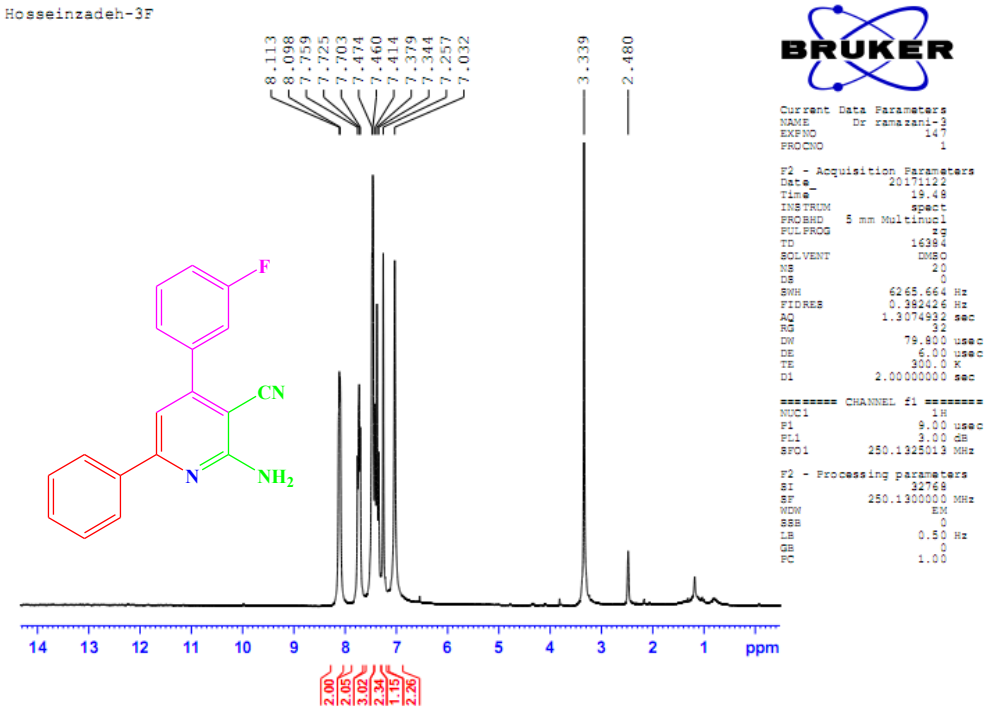
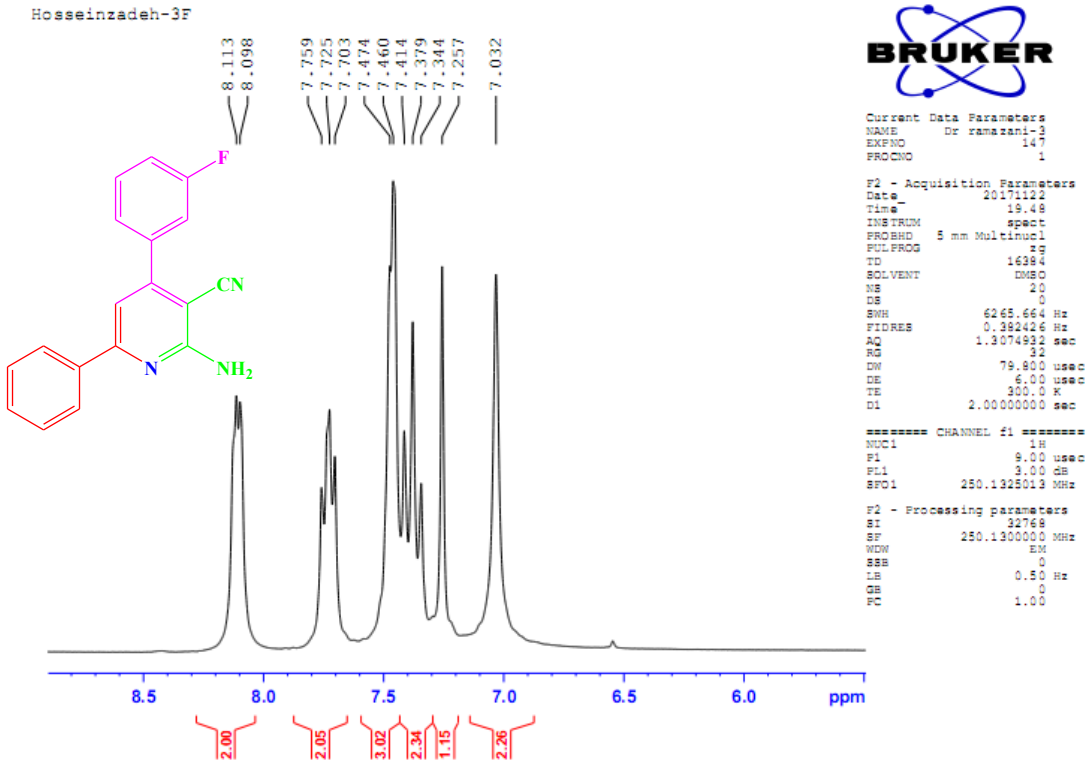
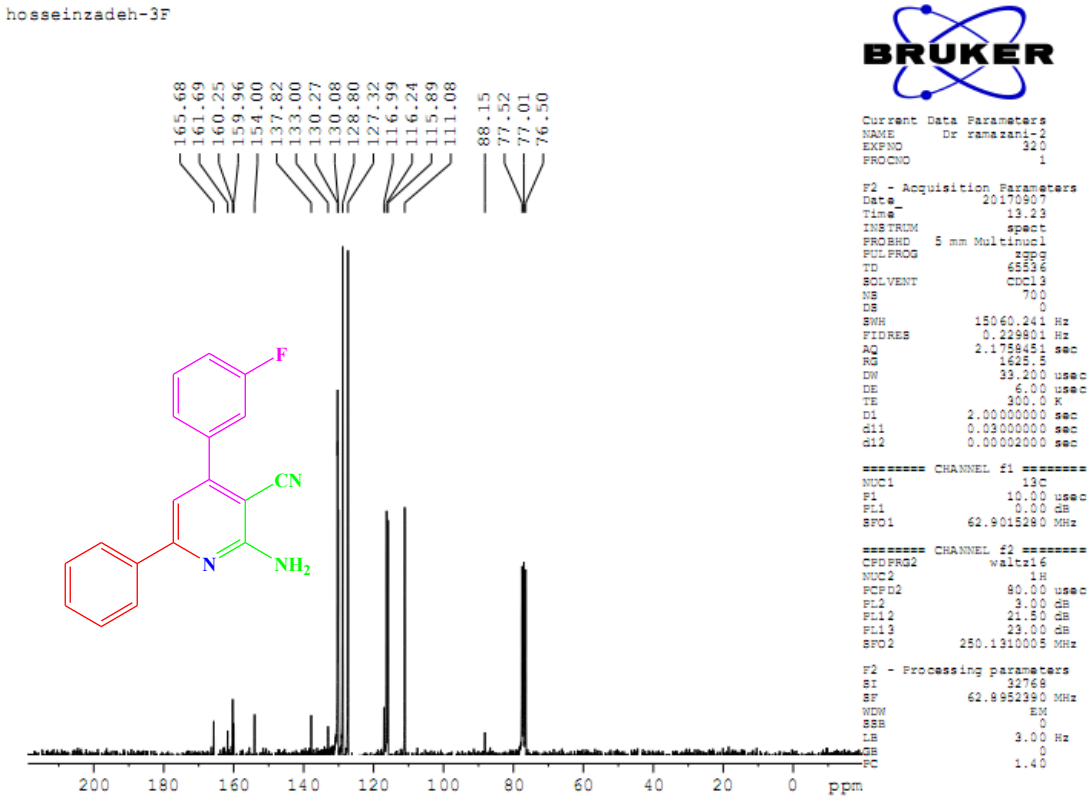
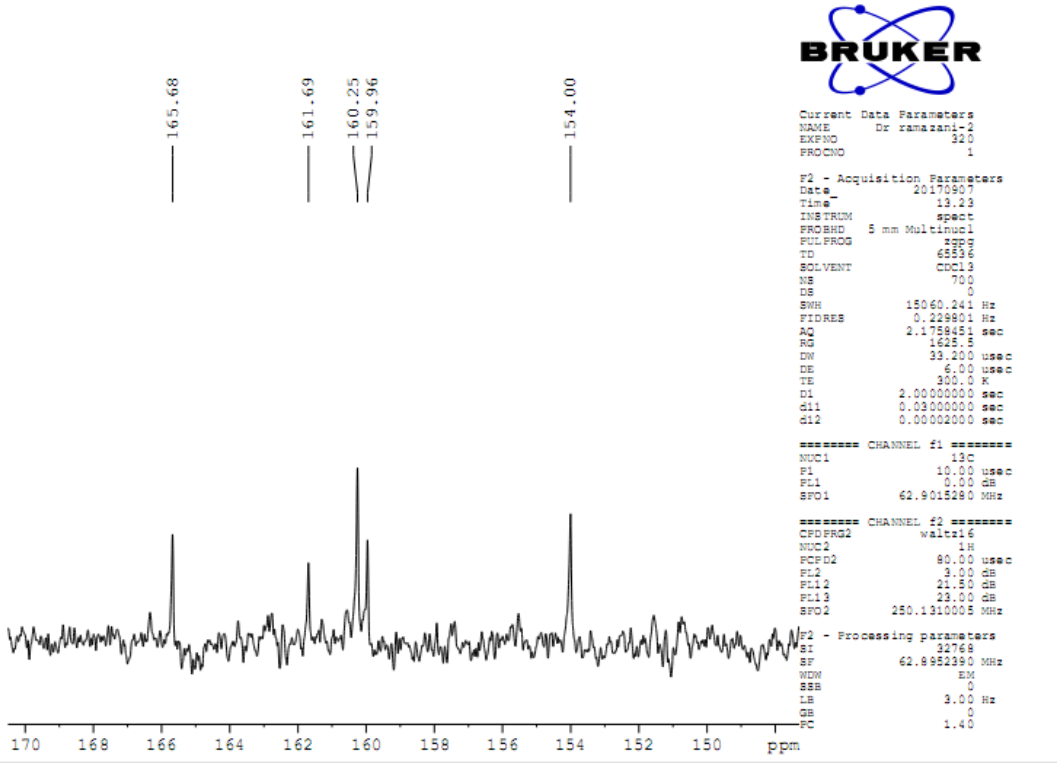




^{13}C NMR (62.9 MHz, $CDCl_3$)

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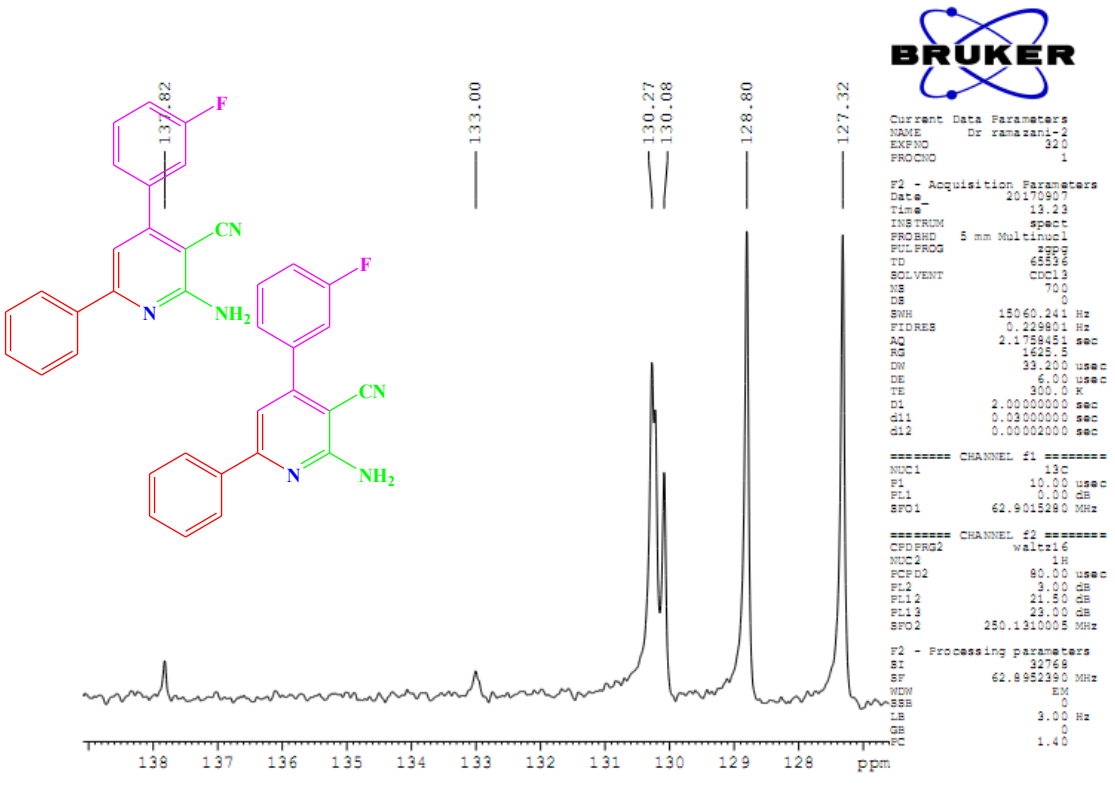
PL1 0.00 dB
SFO1 62.9015280 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 3.00 dB
PL12 21.50 dB
PL13 23.00 dB
SFO2 250.1310005 MHz
F2 - Processing parameters
SI 32768
SF 62.8952390 MHz
WDW EM
SSB 0
LB 3.00 Hz
GB 0
PC 1.40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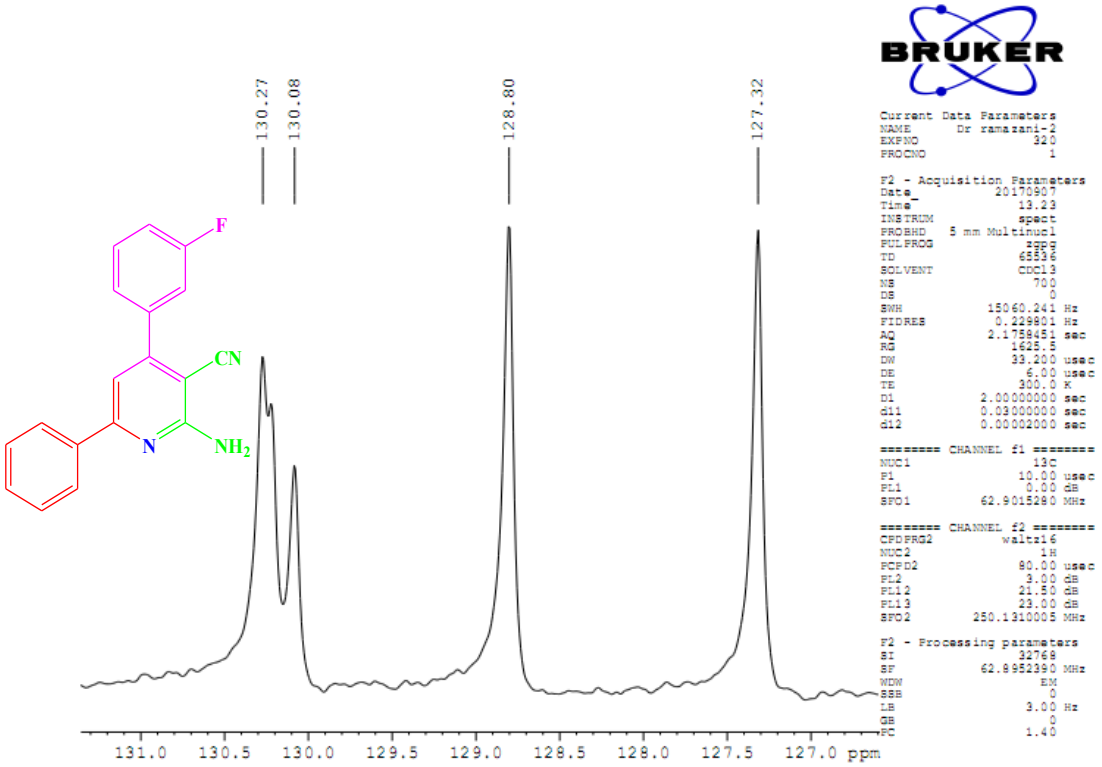
133.00
130.27
130.08
128.80
127.32
F
CN
N
NH2
F
CN
N
NH2
138
137
136
135
134
133
132
131
130
129
128
ppm
BRUKER
Current Data Parameters
NAME Dr ramazani-2
EXPNO 320
PROCNO 1
F2 - Acquisition Parameters
Date_ 20170907
Time 13.23
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zgpg
TD 65536
SOLVENT CDCl3
NS 700
DS 0
SWH 15060.241 Hz
FIDRES 0.229801 Hz
AQ 2.17584451 sec
RG 1625.5
DW 33.200 usec
DE 6.00 usec
TE 300.0 K
D1 2.00000000 sec
d11 0.03000000 sec
d12 0.00002000 sec
======== CHANNEL f1 ========
NUC1 13C
P1 10.00 usec
PL1 0.00 dB
SFO1 62.9015280 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 3.00 dB
PL12 21.50 dB
PL13 23.00 dB
SFO2 250.1310005 MHz
F2 - Processing parameters
SI 32768
SF 62.8952390 MHz
WDW EM
SSB 0
LB 3.00 Hz
GB 0
PC 1.40



BRUKER

Current Data Parameters
NAME Dr ramazani-2
EXPNO 320
PROCNO 1

F2 - Acquisition Parameters
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Time 13.23
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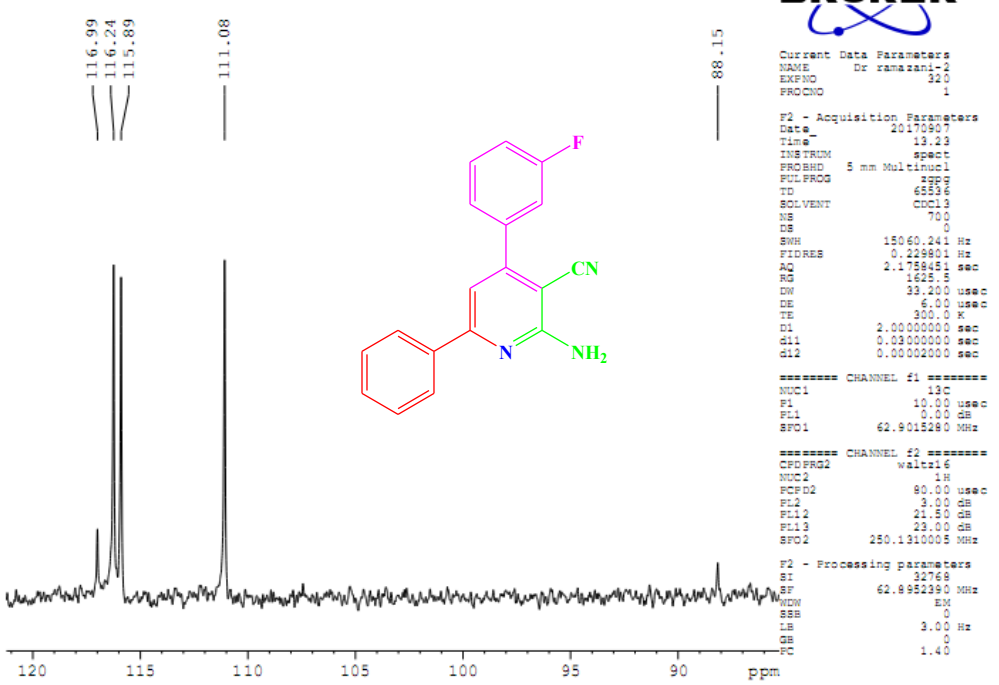
PULPROG zgpg
TD 65536
SOLVENT CDCl3
NS 700
DS 0
SWH 15060.241 Hz
FIDRES 0.229801 Hz
AQ 2.1758451 sec
RG 1625.5
DW 33.200 usec
DE 6.00 usec
TE 300.0 K
D1 2.00000000 sec
d11 0.03000000 sec
d12 0.00002000 sec

======== CHANNEL f1 ========
NUC1 13C
P1 10.00 usec
PL1 0.00 dB
SFO1 62.9015280 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 3.00 dB
PL12 21.50 dB
PL13 23.00 dB
SFO2 250.1310005 MHz

F2 - Processing parameters
SI 32768
SF 62.8952390 MHz
WDW EM
SSB 0
LB 3.00 Hz
GB 0
PC 1.40



BRUKER

Current Data Parameters
NAME Dr ramazani-2
EXPNO 320
PROCNO 1

F2 - Acquisition Parameters
Date_ 20170907
Time 13.23
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zgpg
TD 65536
SOLVENT CDCl3
NS 700
DS 0
SWH 15060.241 Hz
FIDRES 0.229801 Hz
AQ 2.1758451 sec
RG 1625.5
DW 33.200 usec
DE 6.00 usec
TE 300.0 K
D1 2.00000000 sec
d11 0.03000000 sec
d12 0.00002000 sec

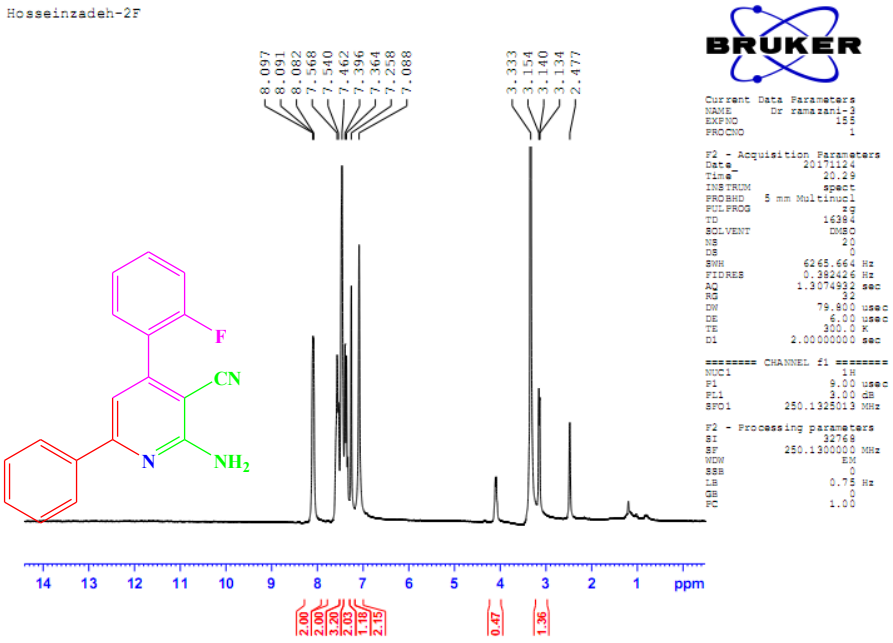
======== CHANNEL f1 ========
NUC1 13C
P1 10.00 usec
PL1 0.00 dB
SFO1 62.9015280 MHz

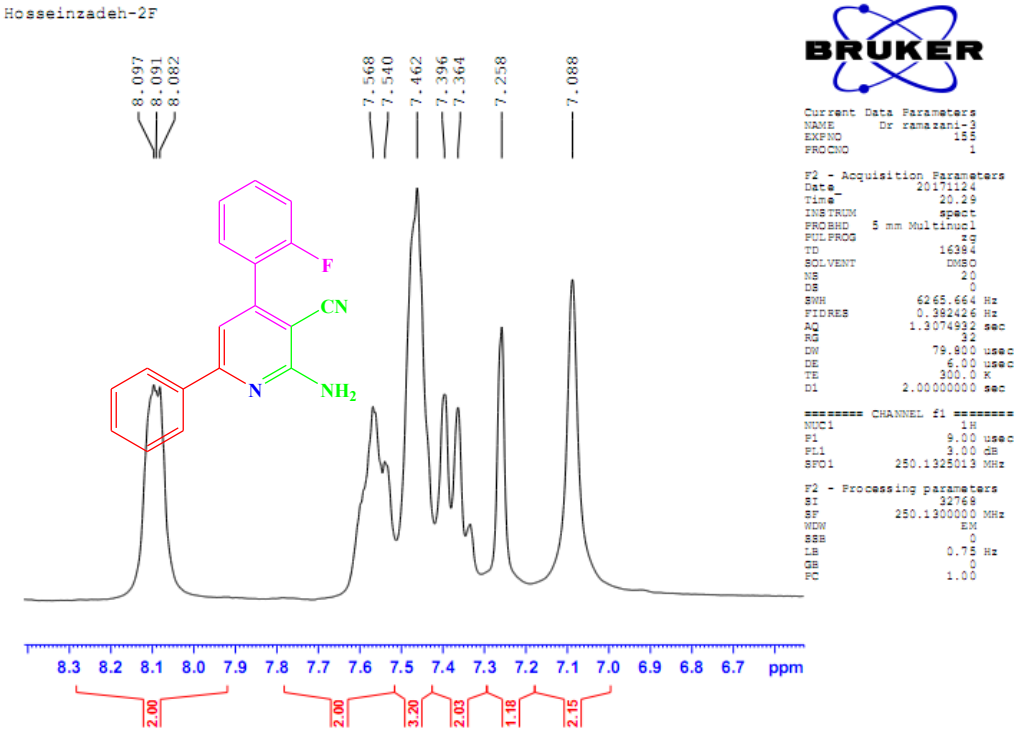
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 3.00 dB
PL12 21.50 dB
PL13 23.00 dB
SFO2 250.1310005 MHz

F2 - Processing parameters
SI 32768
SF 62.8952390 MHz
WDW EM
SSB 0
LB 3.00 Hz
GB 0
PC 1.40

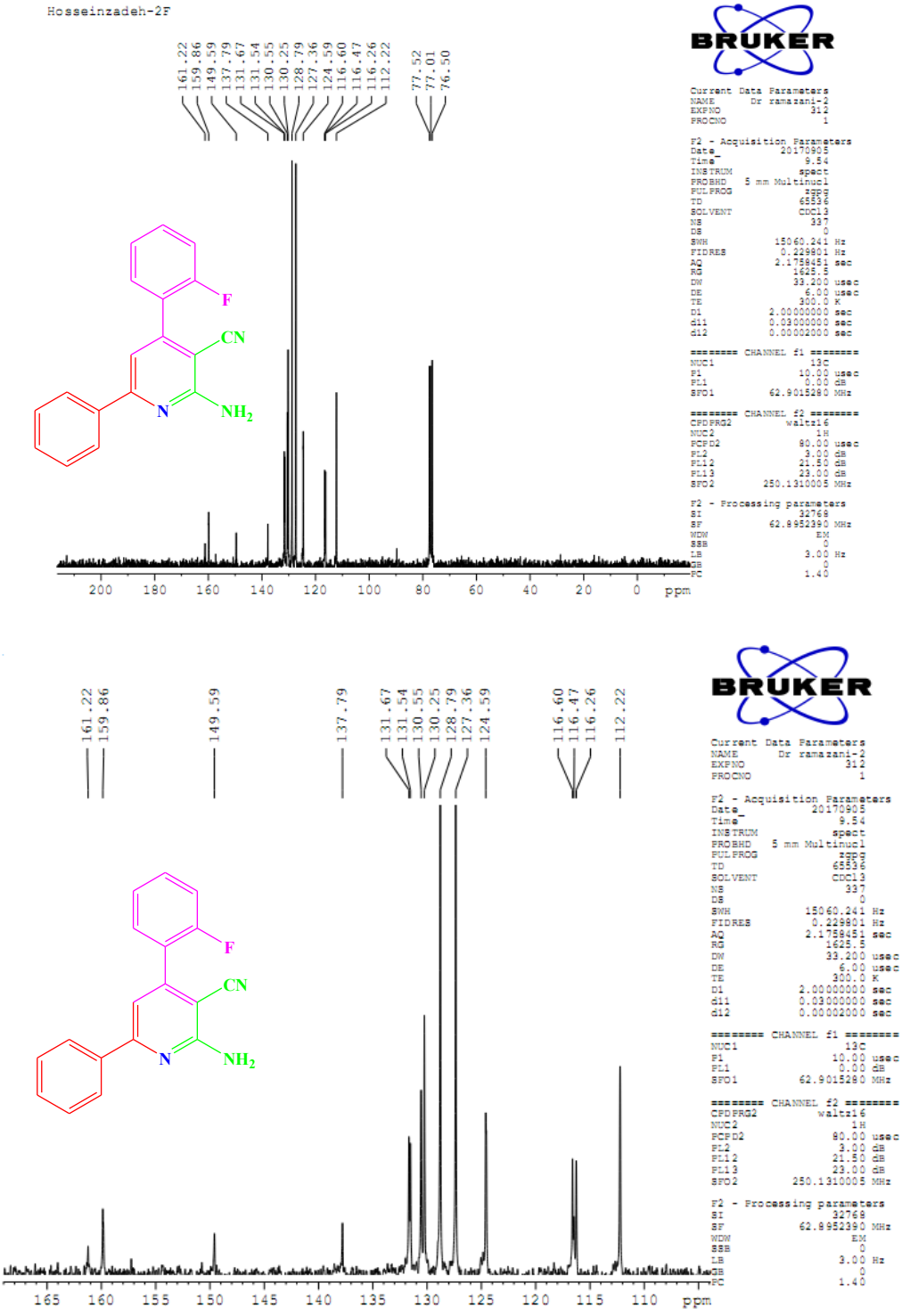
2-Amino-4-(2-fluorophenyl)-6-phenylnicotinonitrile (Table 3, entry 7):

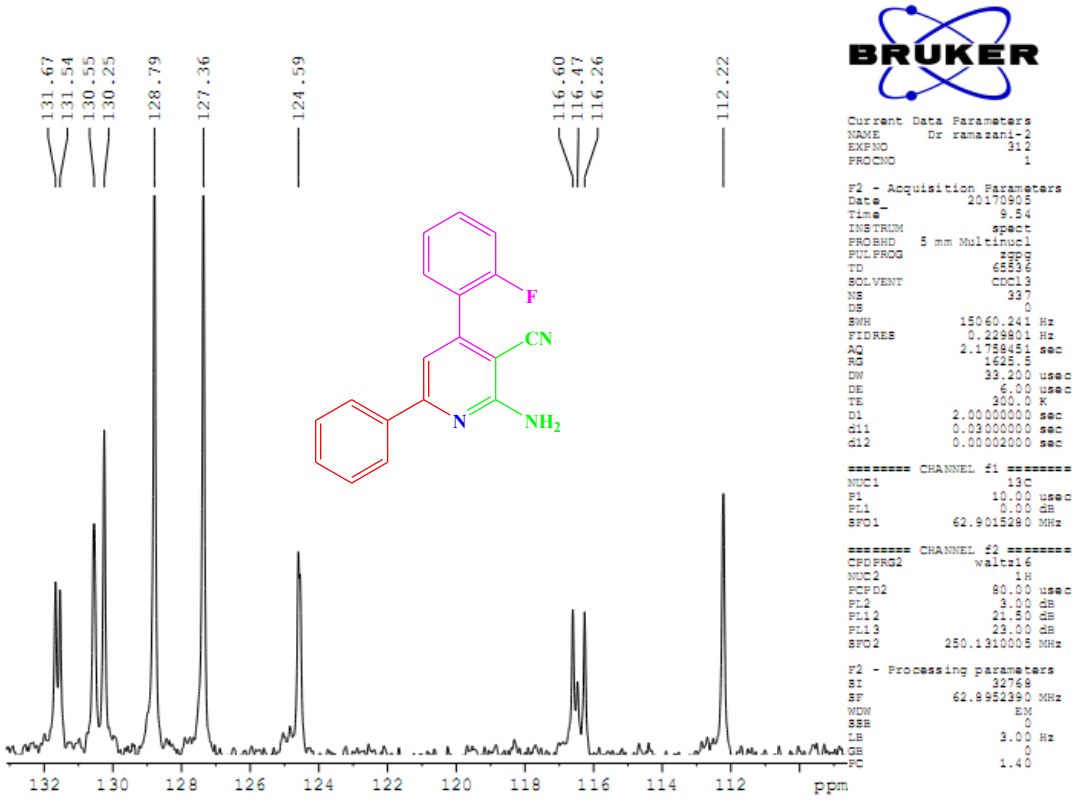
^{1}H NMR (250 MHz, DMSO)





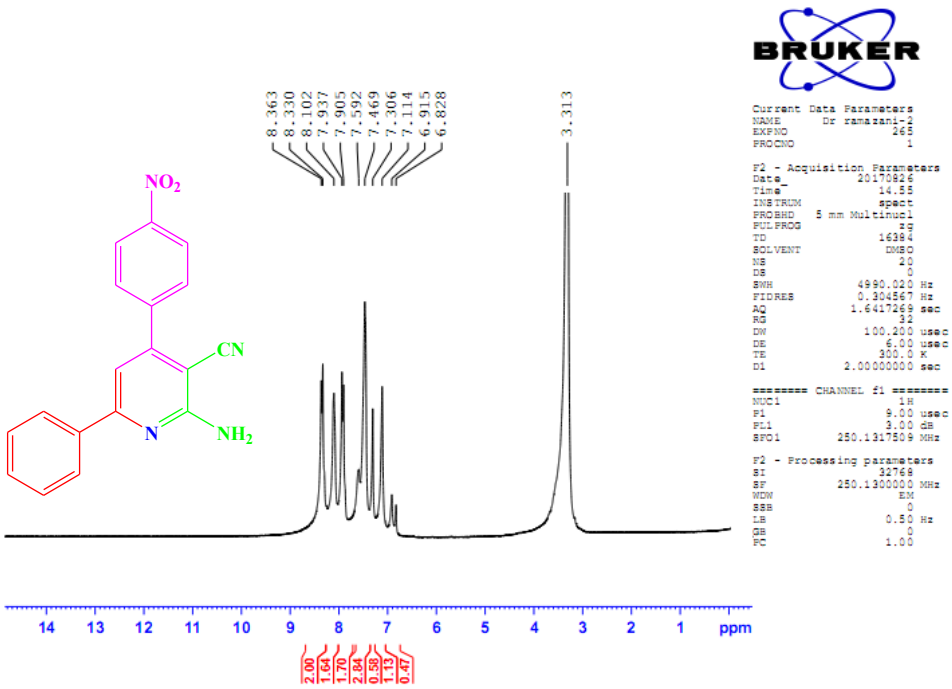
^{13}C NMR (62.9 MHz, $CDCl_3$)

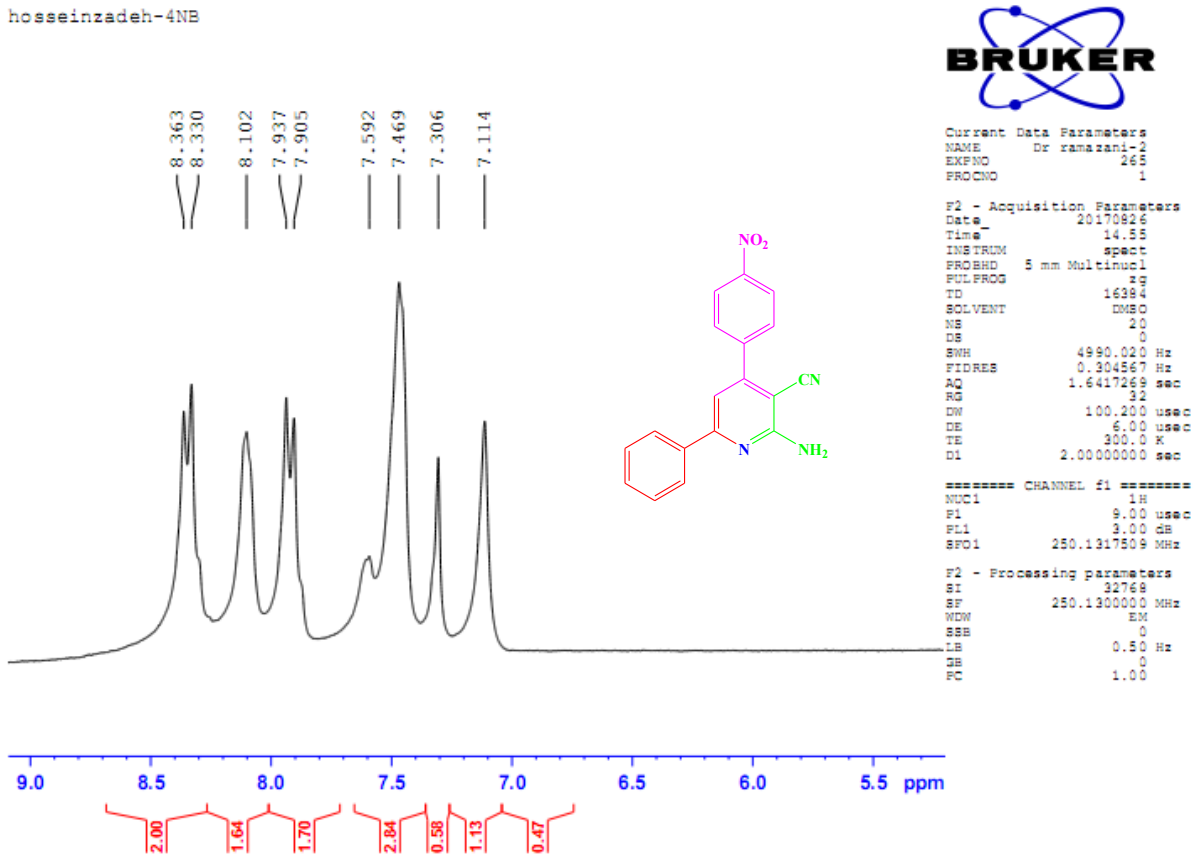




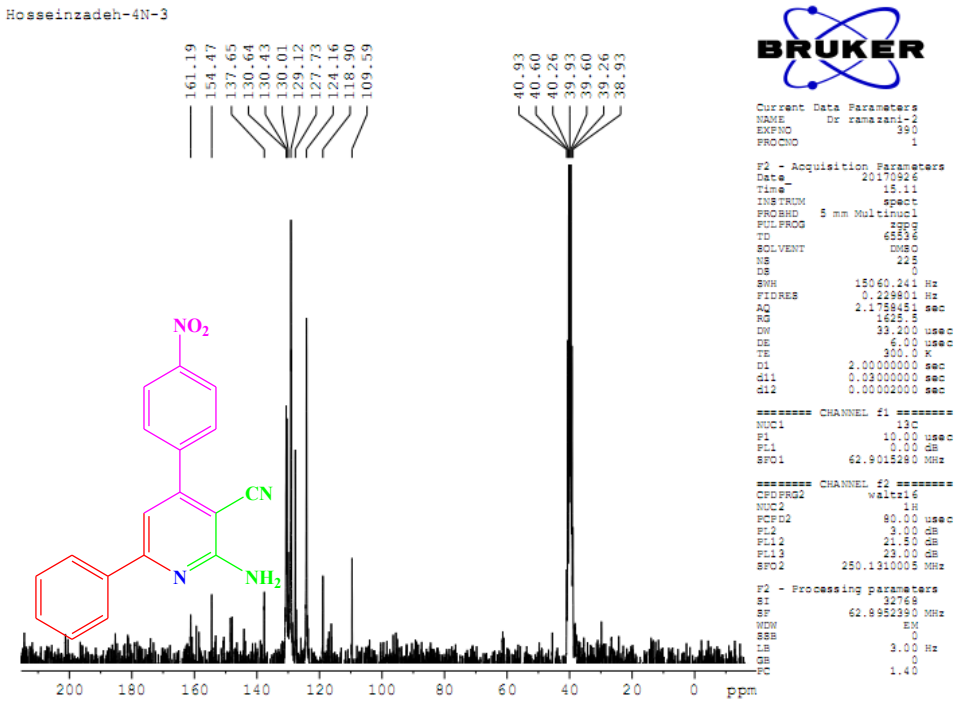
2-Amino-4-(4-nitrophenyl)-6-phenylnicotinonitrile (Table 3, entry 8):

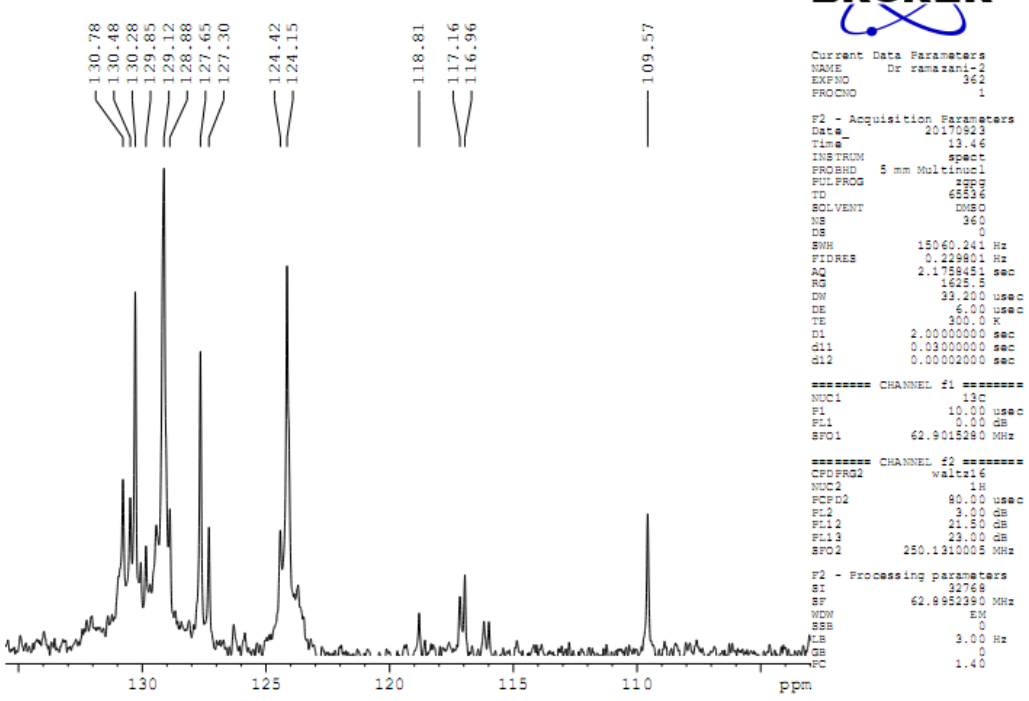
^{1}H NMR (250 MHz, DMSO-d$_6$)





^{13}C NMR (62.9 MHz, DMSO-d_6)





BRUKER

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EXPNO                 362
PROCNO                  1

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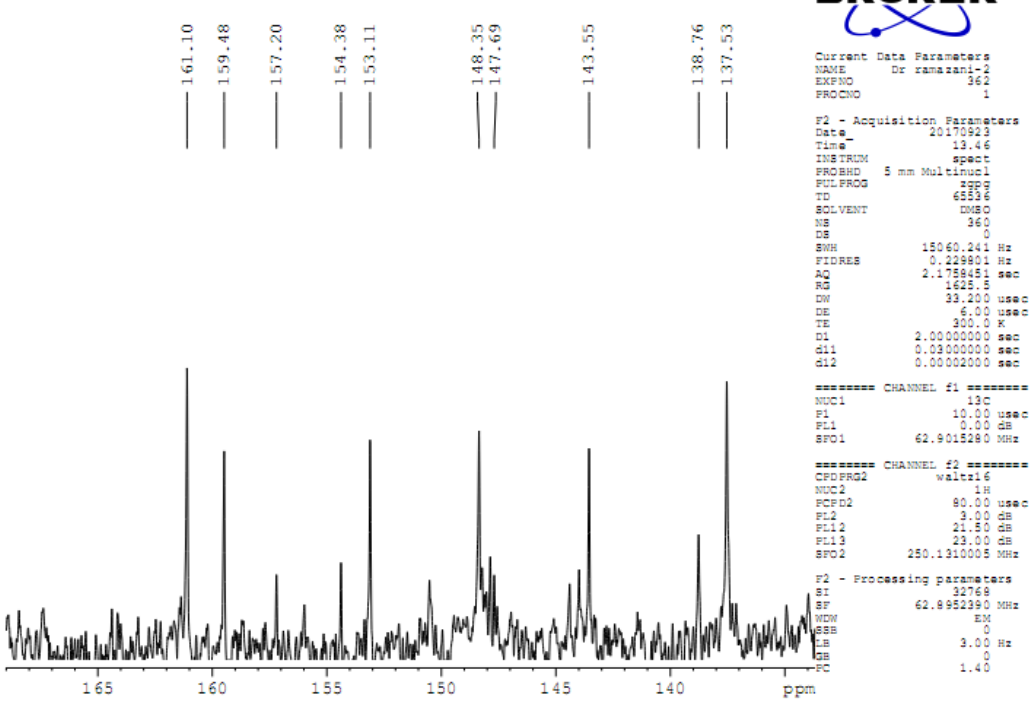
Time              13.46
INSTRUM            spect
PROBHD   5 mm Multinucl
PULPROG            zgpg
TD                65536
SOLVENT            DMSO
NS                   360
DS                     0
SWH           15060.241 Hz
FIDRES        0.229801 Hz
AQ            2.1758451 sec
RG                1625.5
DW               33.200 usec
DE                6.00 usec
TE                300.0 K
D1           2.00000000 sec
d11          0.03000000 sec
d12          0.00002000 sec

======== CHANNEL f1 ========
NUC1                13C
P1                10.00 usec
PL1                0.00 dB
SFO1         62.9015280 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                1H
PCPD2             80.00 usec
PL2               3.00 dB
PL12             21.50 dB
PL13             23.00 dB
SFO2        250.1310005 MHz

F2 - Processing parameters
SI                 32768
SF           62.8952390 MHz
WDW                   EM
SSB                    0
LB                3.00 Hz
GB                     0
PC                1.40
```



BRUKER

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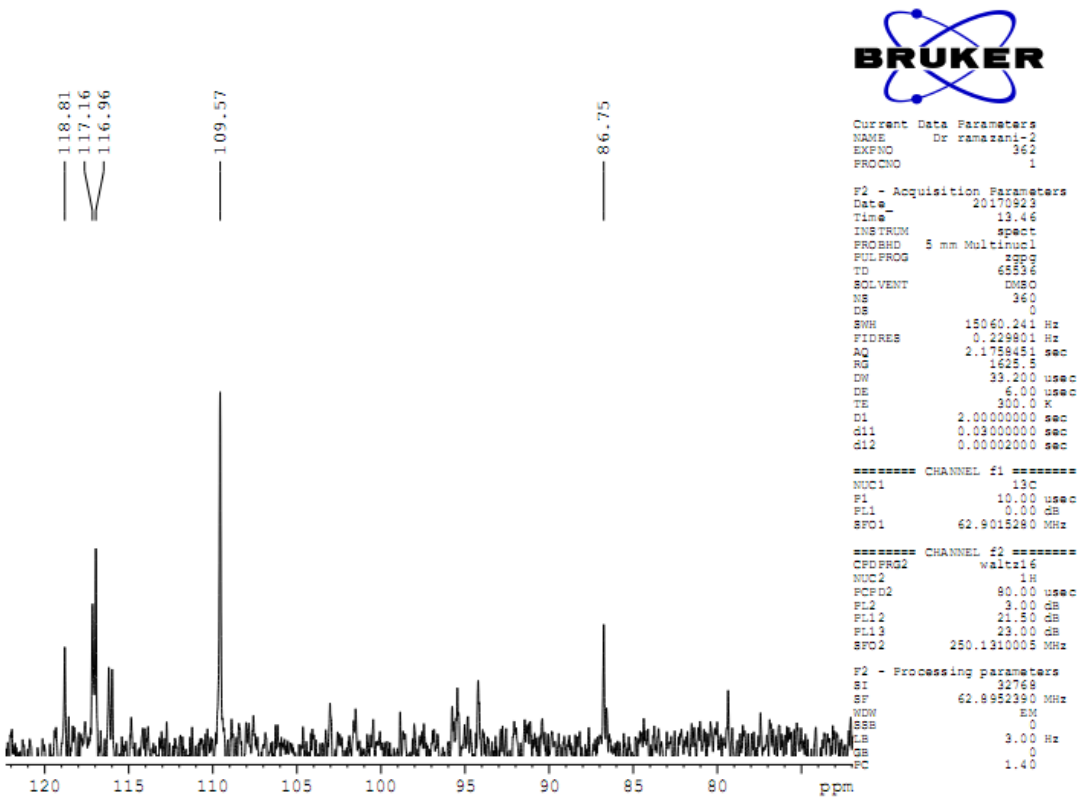
Current Data Parameters
NAME        Dr ramazani-2
EXPNO                 362
PROCNO                  1

F2 - Acquisition Parameters
Date_           20170923
Time              13.46
INSTRUM            spect
PROBHD   5 mm Multinucl
PULPROG            zgpg
TD                65536
SOLVENT            DMSO
NS                   360
DS                     0
SWH           15060.241 Hz
FIDRES        0.229801 Hz
AQ            2.1758451 sec
RG                1625.5
DW               33.200 usec
DE                6.00 usec
TE                300.0 K
D1           2.00000000 sec
d11          0.03000000 sec
d12          0.00002000 sec

======== CHANNEL f1 ========
NUC1                13C
P1                10.00 usec
PL1                0.00 dB
SFO1         62.9015280 MHz

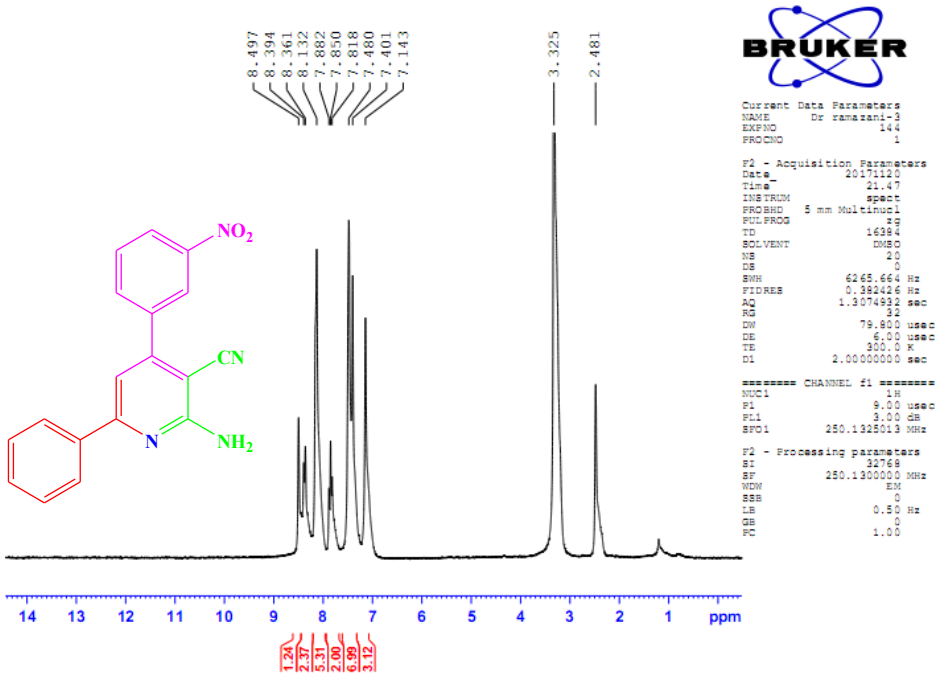
======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                1H
PCPD2             80.00 usec
PL2               3.00 dB
PL12             21.50 dB
PL13             23.00 dB
SFO2        250.1310005 MHz

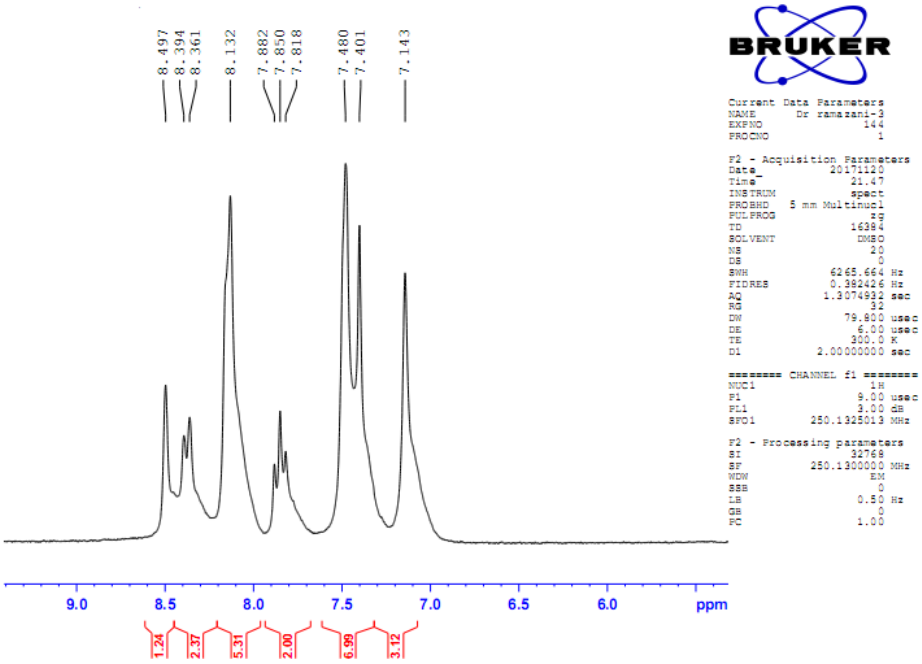
F2 - Processing parameters
SI                 32768
SF           62.8952390 MHz
WDW                   EM
SSB                    0
LB                3.00 Hz
GB                     0
PC                1.40
```



2-Amino-4-(3-nitrophenyl) -6-phenylnicotinonitrile (Table 3, entry 9):

^{1}H NMR (250 MHz, DMSO)





BRUKER

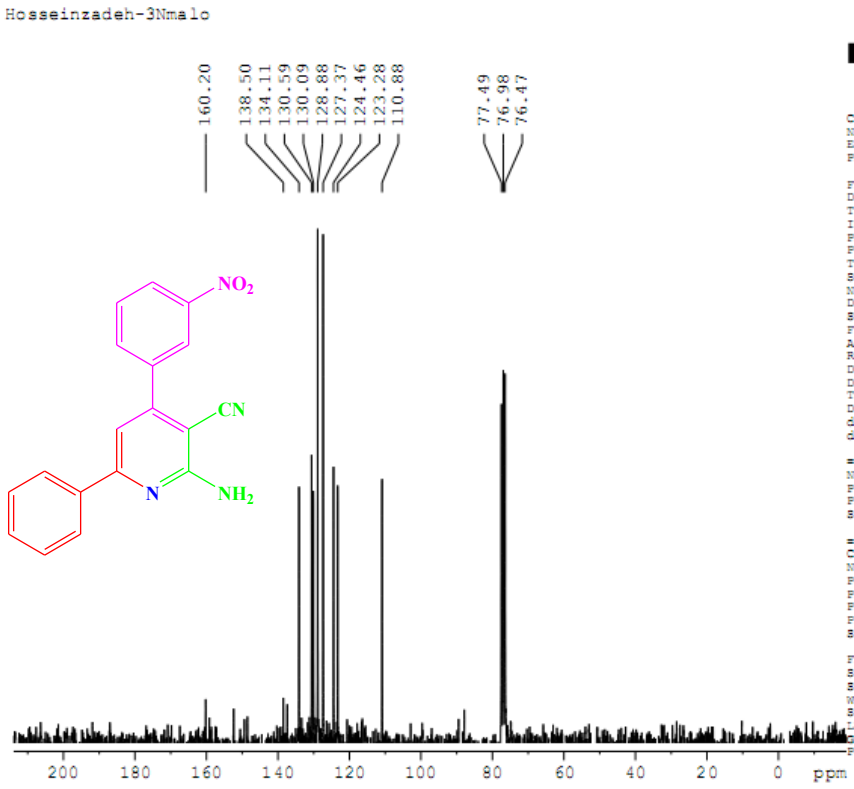
```
Current Data Parameters
NAME        Dr ramazani-3
EXPNO               144
PROCNO                1

F2 - Acquisition Parameters
Date_          20171120
Time               21.47
INSTRUM             spect
PROBHD   5 mm Multinucl
PULPROG             zg
TD                 16384
SOLVENT             DMSO
NS                    20
DS                     0
SWH             6265.664 Hz
FIDRES          0.382426 Hz
AQ              1.3074932 sec
RG                    32
DW                79.800 usec
DE                 6.00 usec
TE                300.0 K
D1             2.00000000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                 9.00 usec
PL1                3.00 dB
SFO1         250.1325013 MHz

F2 - Processing parameters
SI                 32768
SF          250.1300000 MHz
WDW                   EM
SSB                    0
LB                  0.50 Hz
GB                     0
PC                  1.00
```

^{13}C NMR (62.9 MHz, $CDCl_3$)



BRUKER

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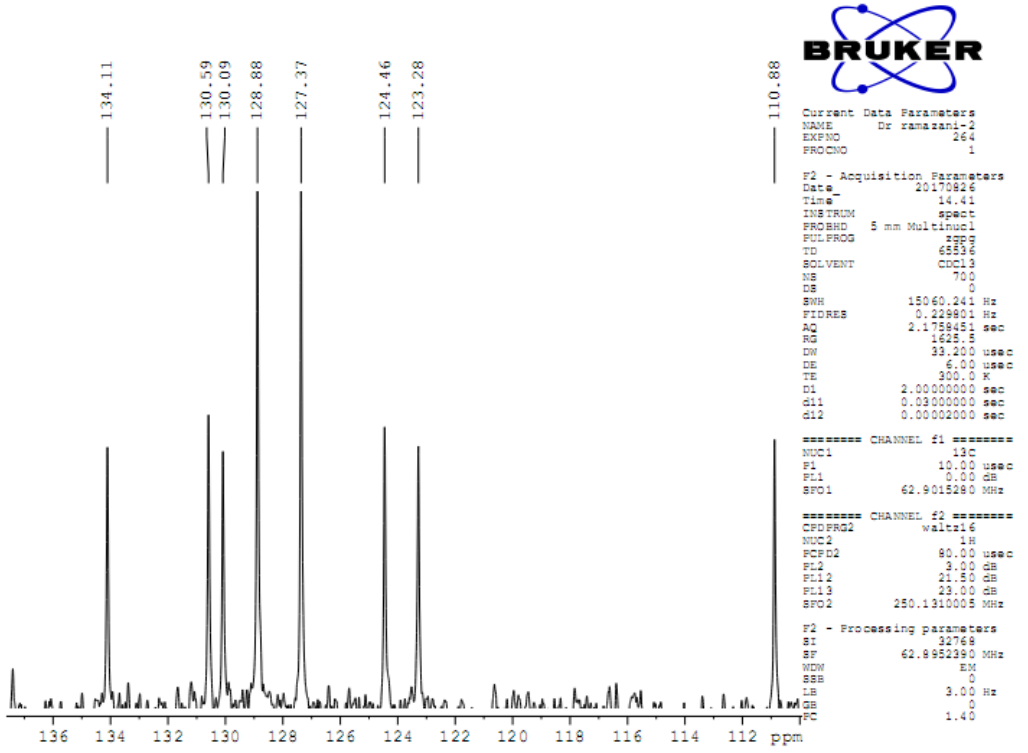
Current Data Parameters
NAME        Dr ramazani-2
EXPNO               264
PROCNO                1

F2 - Acquisition Parameters
Date_          20170826
Time               14.41
INSTRUM             spect
PROBHD   5 mm Multinucl
PULPROG          zgpg30
TD                 65536
SOLVENT            CDCl3
NS                   700
DS                     0
SWH            15060.241 Hz
FIDRES          0.229801 Hz
AQ              2.1758451 sec
RG                 1625.5
DW                33.200 usec
DE                 6.00 usec
TE                300.0 K
D1             2.00000000 sec
d11            0.03000000 sec
d12            0.00002000 sec

======== CHANNEL f1 ========
NUC1                 13C
P1                10.00 usec
PL1                0.00 dB
SFO1          62.9015280 MHz

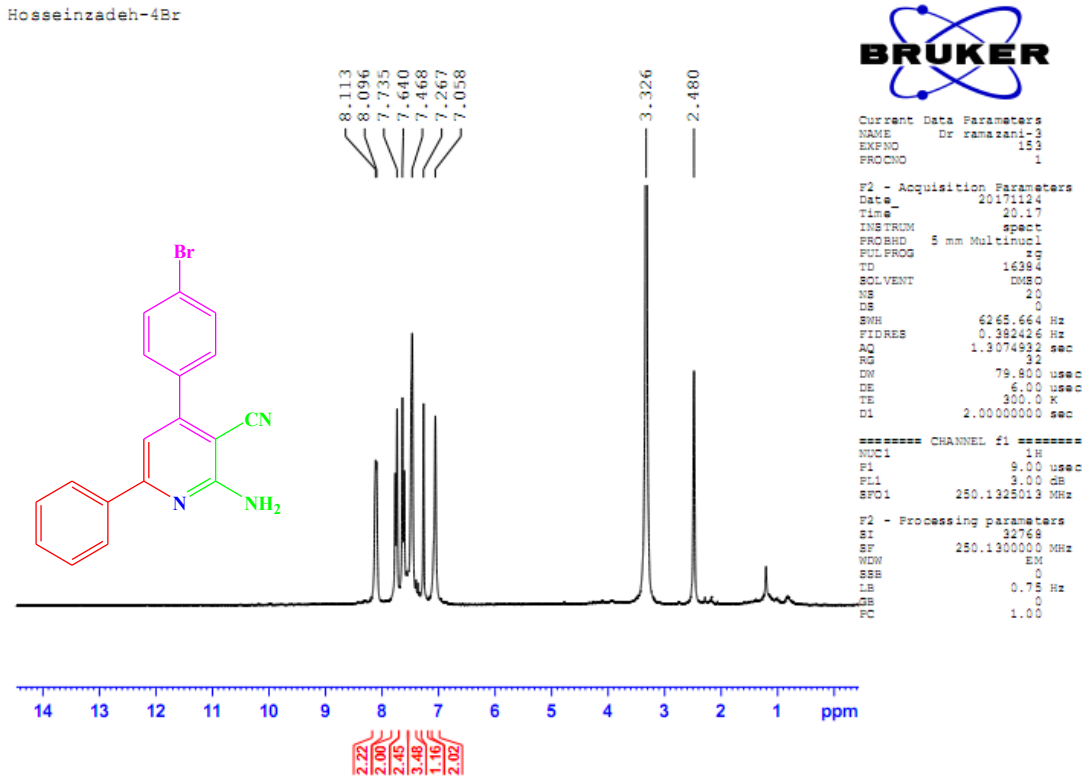
======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2             80.00 usec
PL2                3.00 dB
PL12              21.50 dB
PL13              23.00 dB
SFO2         250.1310005 MHz

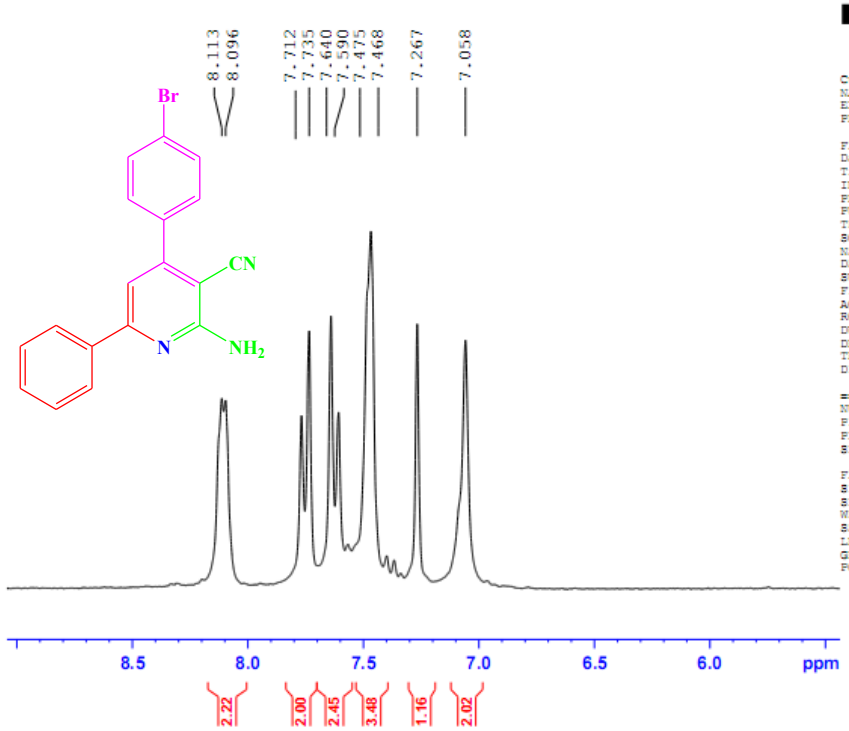
F2 - Processing parameters
SI                 32768
SF          62.8952390 MHz
WDW                   EM
SSB                    0
LB                  3.00 Hz
GB                     0
PC                  1.40
```



2-Amino-4-(4-bromophenyl)-6-phenylnicotinonitrile (Table 3, entry 10):

^{1}H NMR (250 MHz, DMSO)





BRUKER

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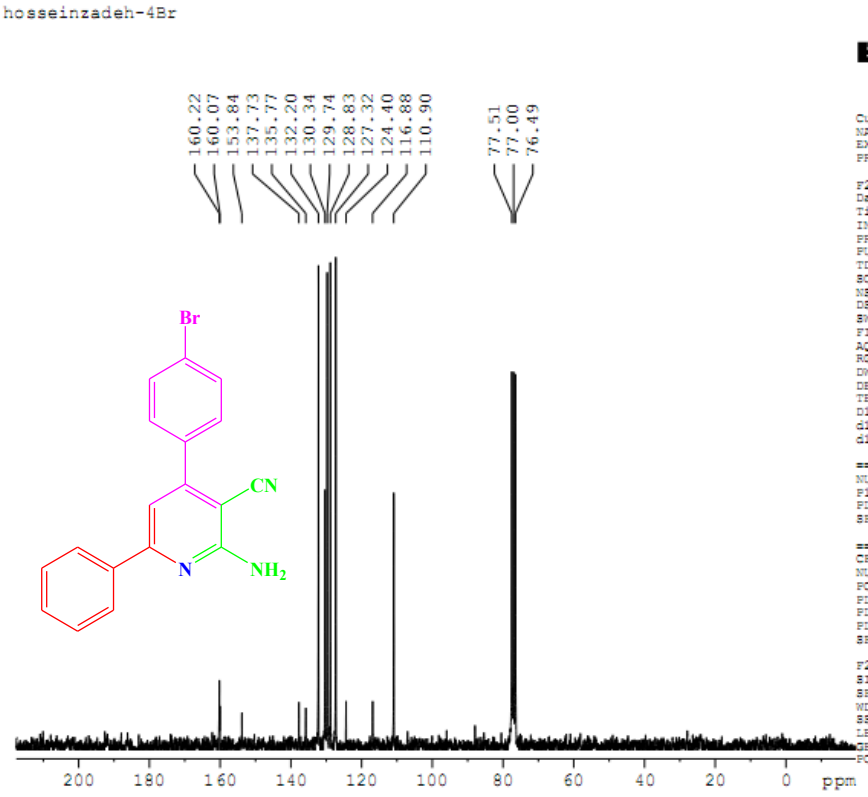
Current Data Parameters
NAME          Dr ramazani-3
EXPNO                   153
PROCNO                    1

F2 - Acquisition Parameters
Date_              20171124
Time                  20.17
INSTRUM                spect
PROBHD    5 mm Multinucl
PULPROG                zg
TD                    16384
SOLVENT                DMSO
NS                       20
DS                        0
SWH                6265.664 Hz
FIDRES            0.382426 Hz
AQ                1.3074992 sec
RG                       32
DW                  79.800 usec
DE                   6.00 usec
TE                  300.0 K
D1                2.00000000 sec

======== CHANNEL f1 ========
NUC1                      1H
P1                     9.00 usec
PL1                    3.00 dB
SFO1           250.1325013 MHz

F2 - Processing parameters
SI                       32768
SF             250.1300000 MHz
WDW                       EM
SSB                        0
LB                      0.75 Hz
GB                         0
PC                      1.00
```

^{13}C NMR (62.9 MHz, $CDCl_3$)



BRUKER

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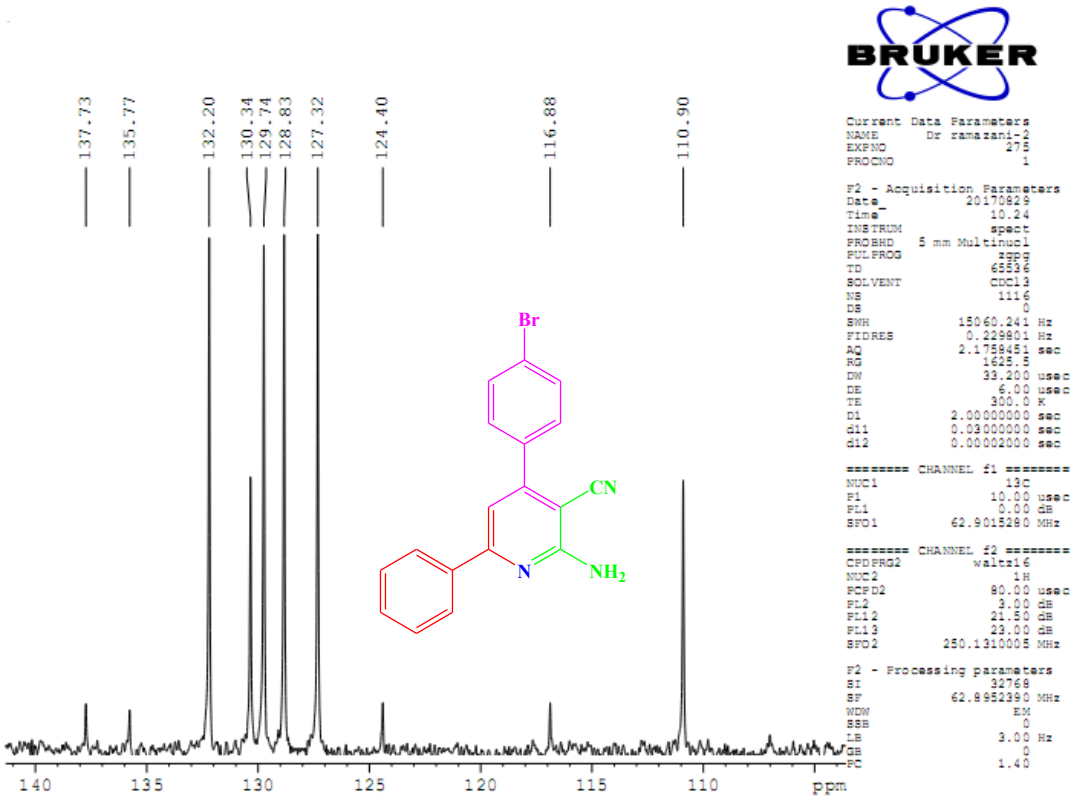
Current Data Parameters
NAME          Dr ramazani-2
EXPNO                   275
PROCNO                    1

F2 - Acquisition Parameters
Date_              20170829
Time                  10.24
INSTRUM                spect
PROBHD    5 mm Multinucl
PULPROG             zgpg
TD                    65536
SOLVENT               CDCl3
NS                     1116
DS                        0
SWH               15060.241 Hz
FIDRES            0.229801 Hz
AQ                2.1758451 sec
RG                     1625.5
DW                  33.200 usec
DE                   6.00 usec
TE                  300.0 K
D1                2.00000000 sec
d11               0.03000000 sec
d12               0.00002000 sec

======== CHANNEL f1 ========
NUC1                      13C
P1                    10.00 usec
PL1                    0.00 dB
SFO1           62.9015280 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                      1H
PCPD2                 80.00 usec
PL2                    3.00 dB
PL12                  21.50 dB
PL13                  23.00 dB
SFO2           250.1310005 MHz

F2 - Processing parameters
SI                       32768
SF             62.8952390 MHz
WDW                       EM
SSB                        0
LB                      3.00 Hz
GB                         0
PC                      1.40
```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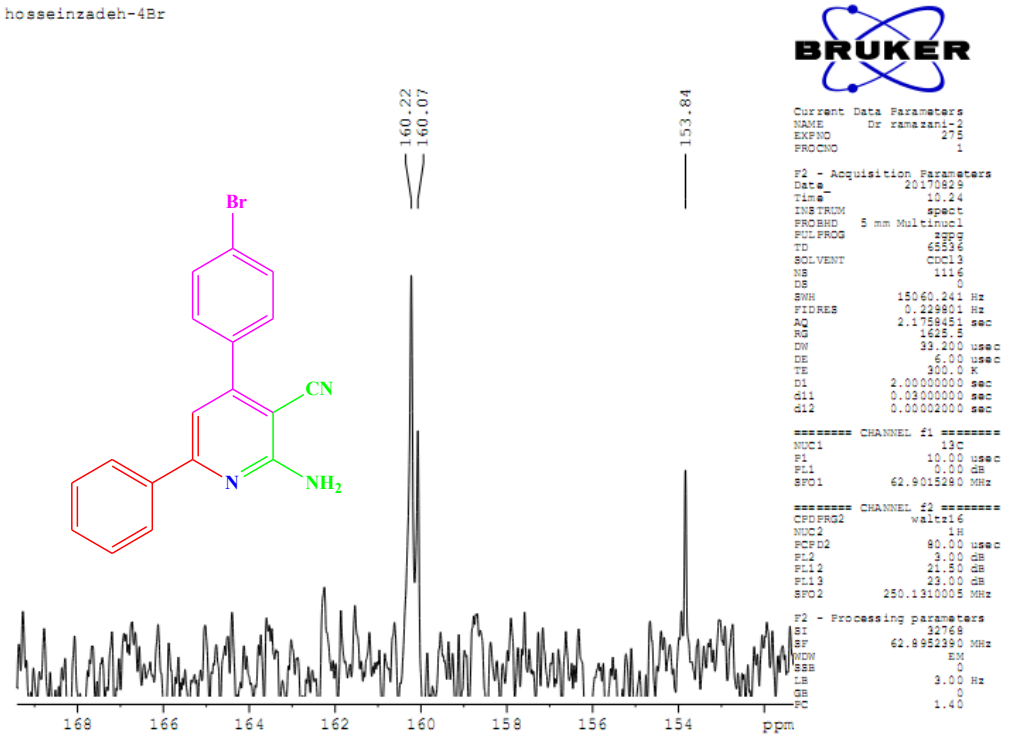
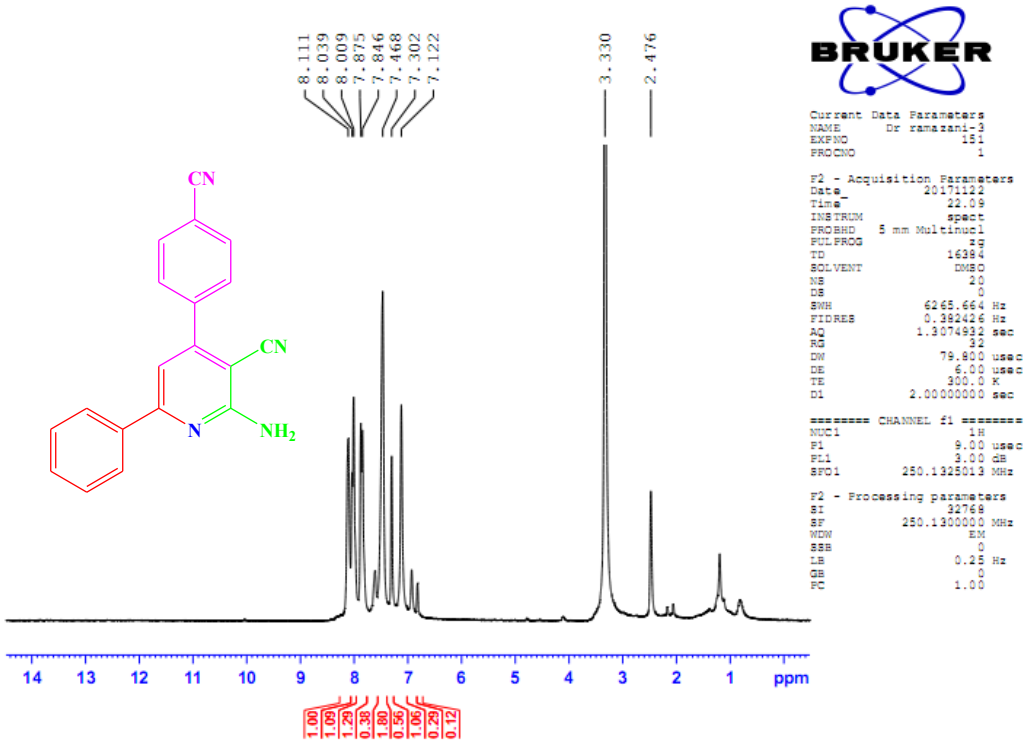
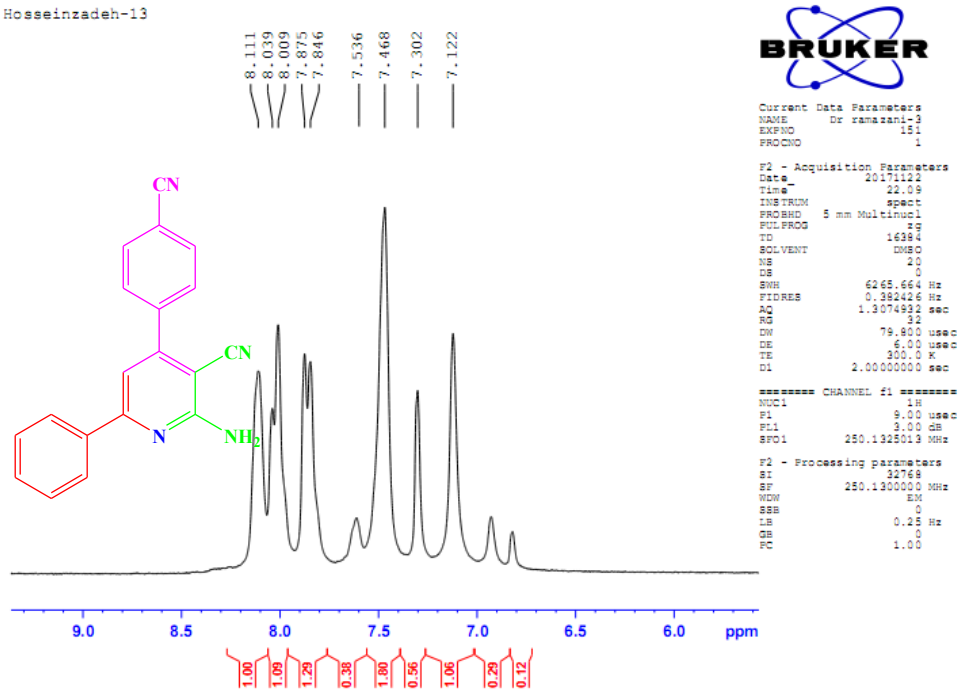
NH2
140
135
130
125
120
115
110
ppm
BRUKER
Current Data Parameters
NAME Dr ramazani-2
EXPNO 275
PROCNO 1
F2 - Acquisition Parameters
Date_ 20170829
Time 10.24
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zgpg
TD 65536
SOLVENT CDCl3
NS 1116
DS 0
SWH 15060.241 Hz
FIDRES 0.229801 Hz
AQ 2.1758451 sec
RG 1625.5
DW 33.200 usec
DE 6.00 usec
TE 300.0 K
D1 2.00000000 sec
d11 0.03000000 sec
d12 0.00002000 sec
======== CHANNEL f1 ========
NUC1 13C
P1 10.00 usec
PL1 0.00 dB
SFO1 62.9015280 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 3.00 dB
PL12 21.50 dB
PL13 23.00 dB
SFO2 250.1310005 MHz
F2 - Processing parameters
SI 32768
SF 62.8952390 MHz
WDW EM
SSB 0
LB 3.00 Hz
GB 0
PC 1.40


hosseinzadeh-4Br
160.22
160.07
153.84
Br
CN
N
NH2
168
166
164
162
160
158
156
154
ppm
BRUKER
Current Data Parameters
NAME Dr ramazani-2
EXPNO 275
PROCNO 1
F2 - Acquisition Parameters
Date_ 20170829
Time 10.24
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zgpg
TD 65536
SOLVENT CDCl3
NS 1116
DS 0
SWH 15060.241 Hz
FIDRES 0.229801 Hz
AQ 2.1758451 sec
RG 1625.5
DW 33.200 usec
DE 6.00 usec
TE 300.0 K
D1 2.00000000 sec
d11 0.03000000 sec
d12 0.00002000 sec
======== CHANNEL f1 ========
NUC1 13C
P1 10.00 usec
PL1 0.00 dB
SFO1 62.9015280 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 3.00 dB
PL12 21.50 dB
PL13 23.00 dB
SFO2 250.1310005 MHz
F2 - Processing parameters
SI 32768
SF 62.8952390 MHz
WDW EM
SSB 0
LB 3.00 Hz
GB 0
PC 1.40

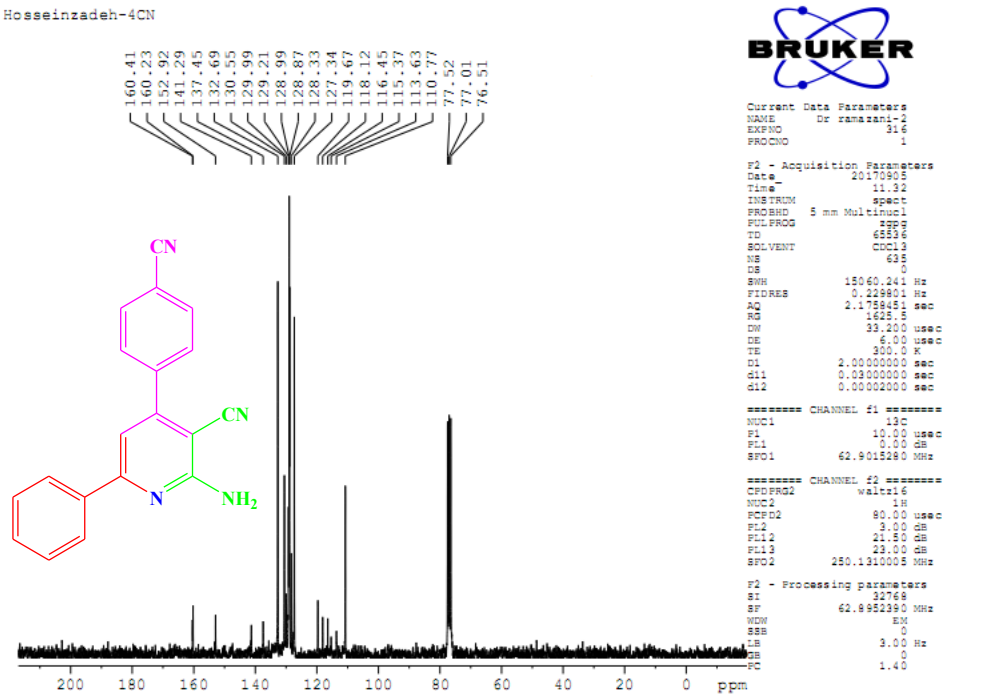
2-Amino-4-(4-cyanophenyl)-6-phenylnicotinonitrile (Table 3, entry 11):

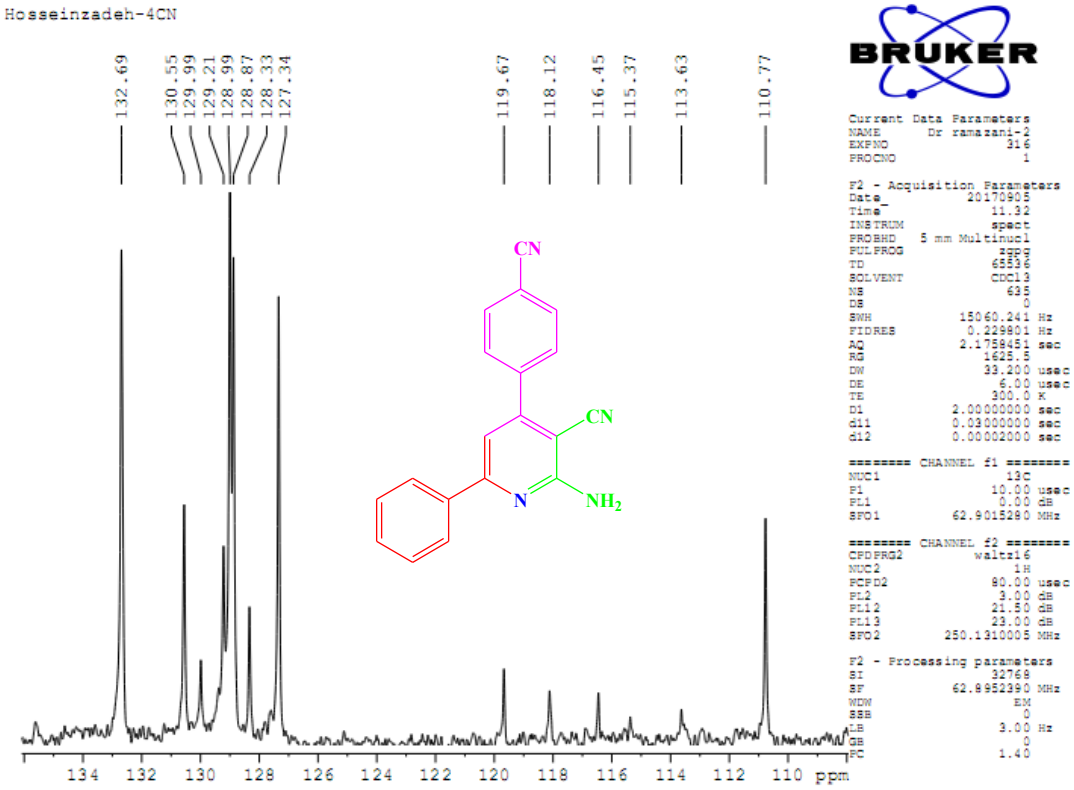
^{1}H NMR (250 MHz, DMSO)

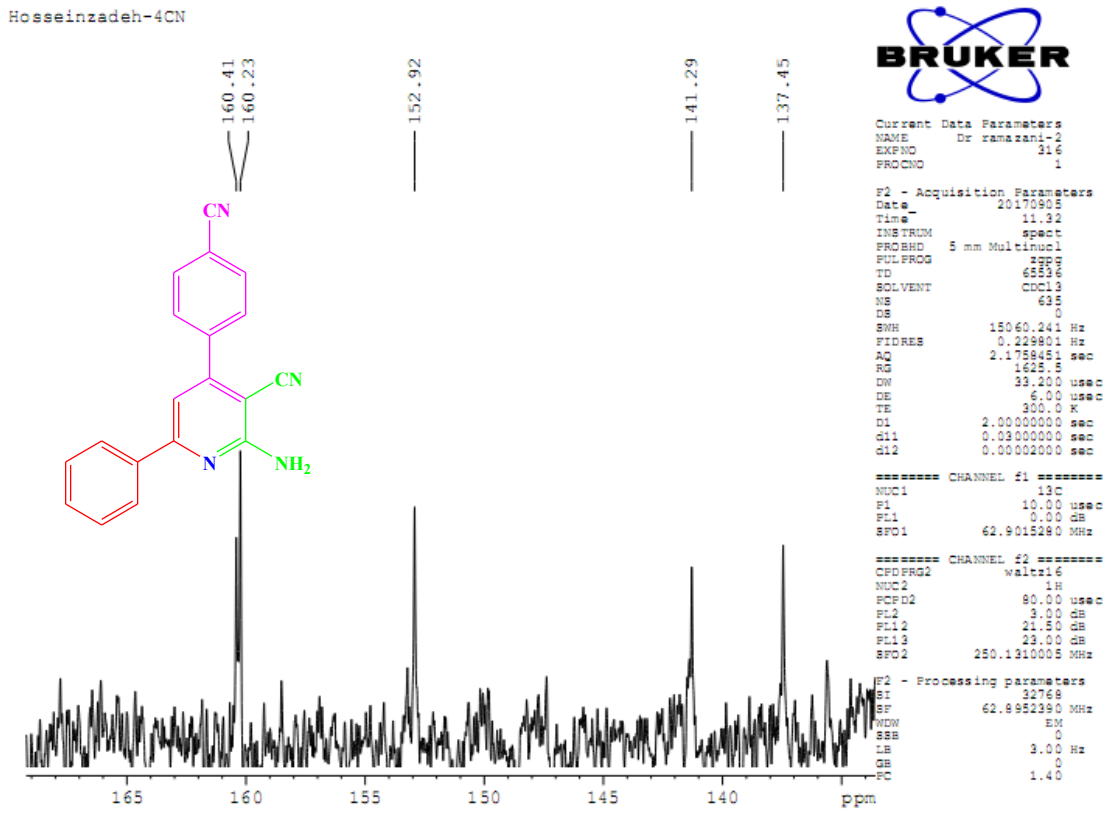




^{13}C NMR (62.9 MHz, $CDCl_3$)

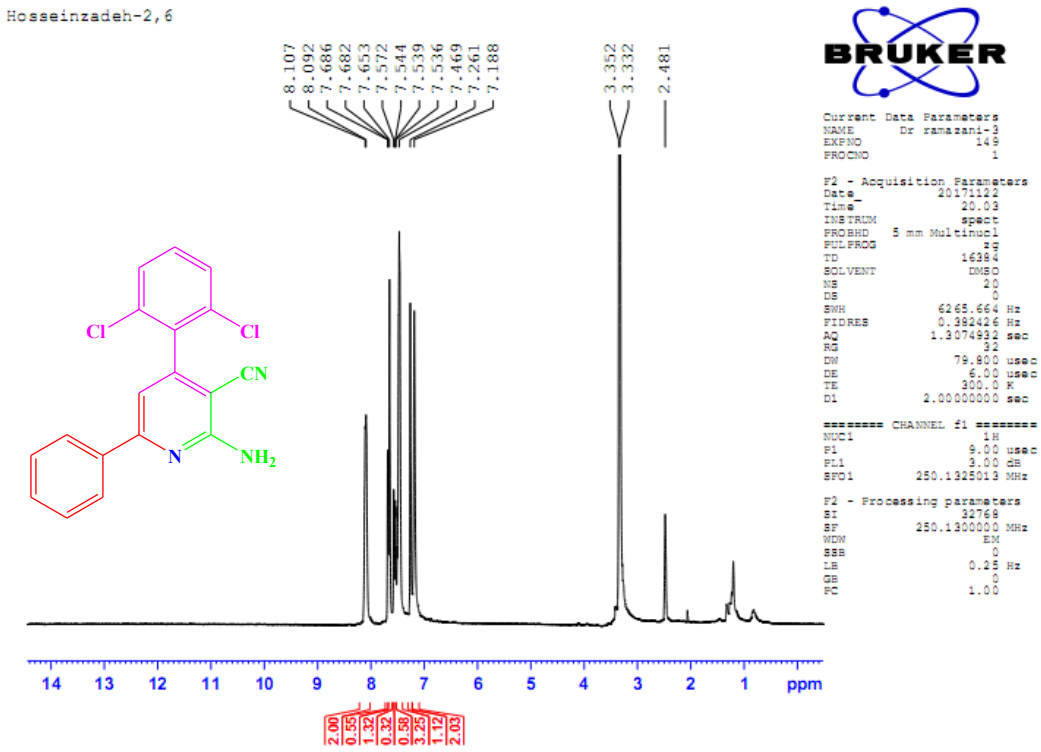


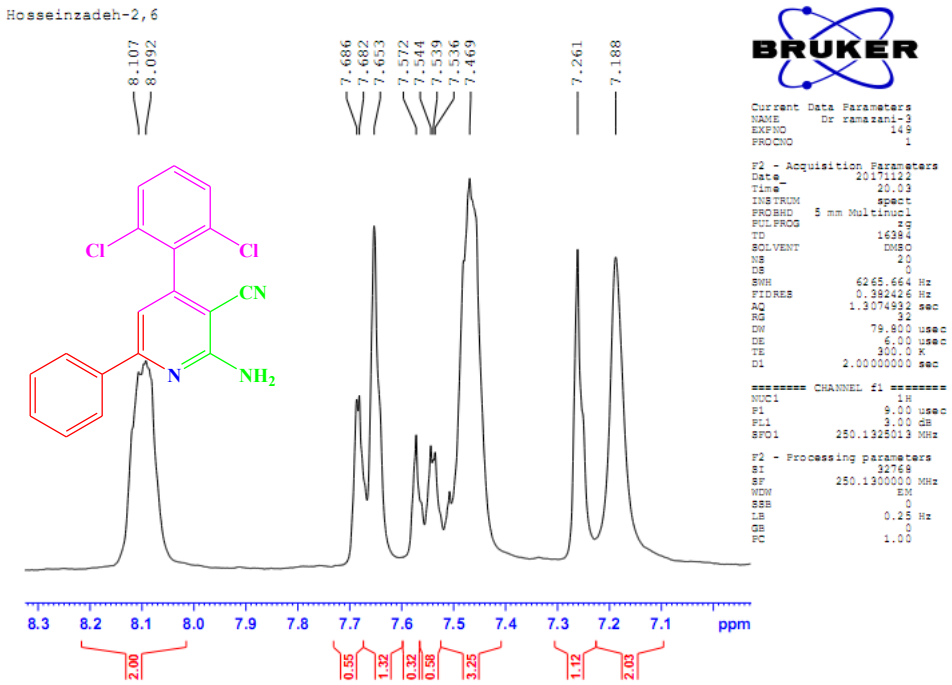




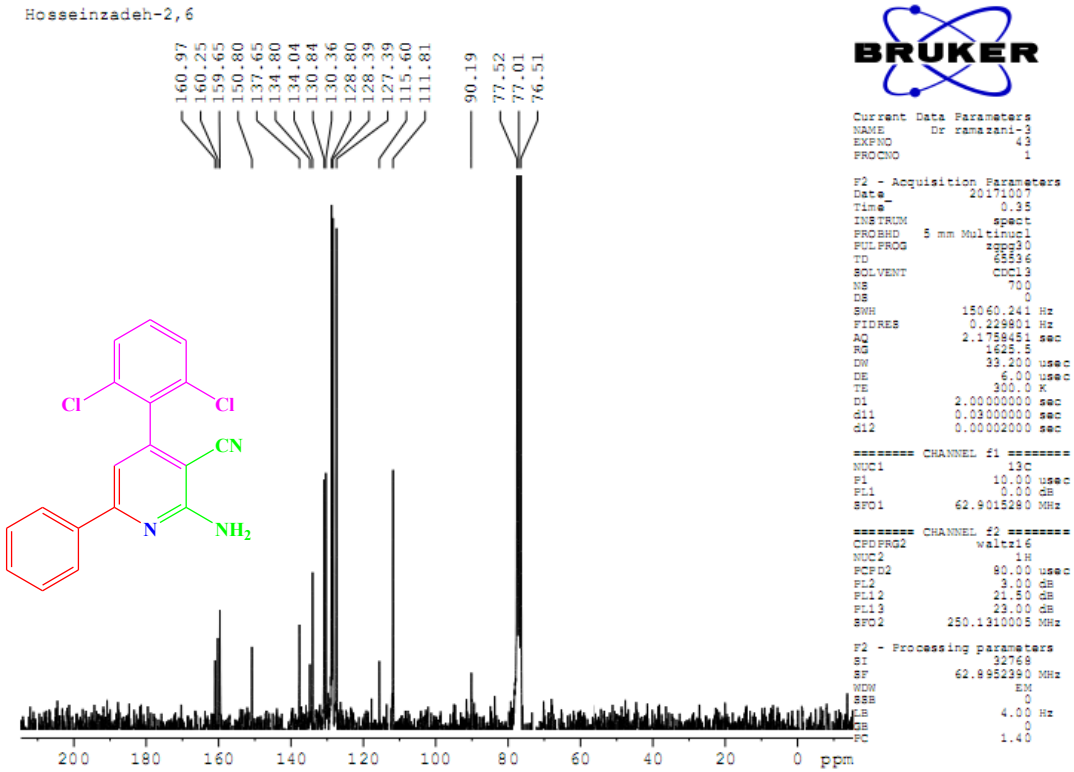
2-Amino-4-(2,6-dichlorophenyl)-6-phenylnicotinonitrile (Table 3, entry 12):

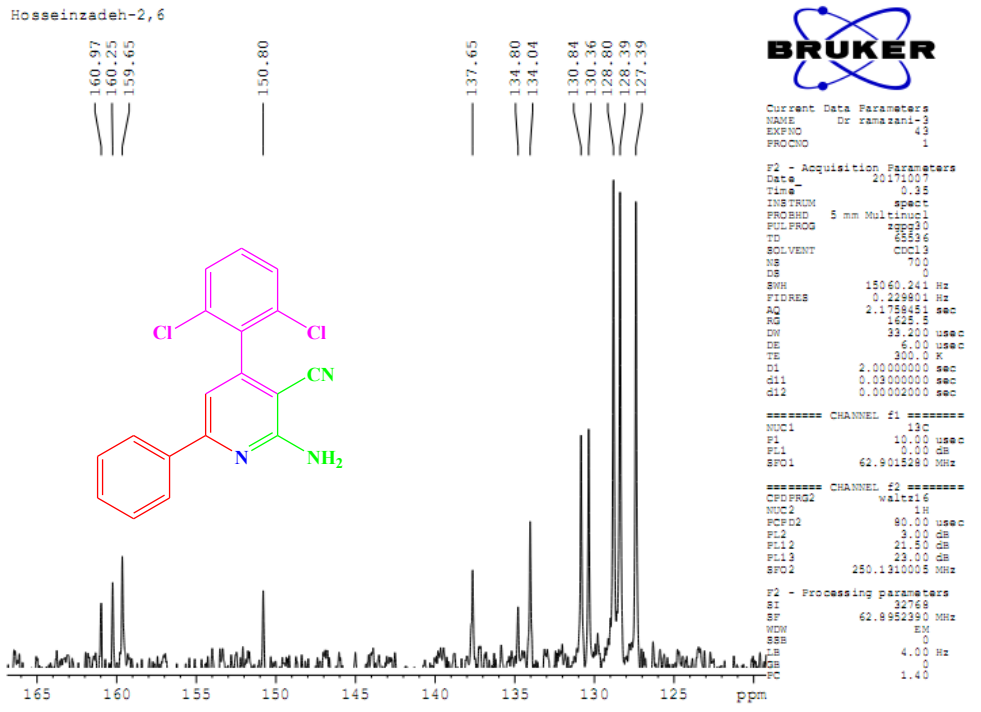
^{1}H NMR (250 MHz, DMSO)





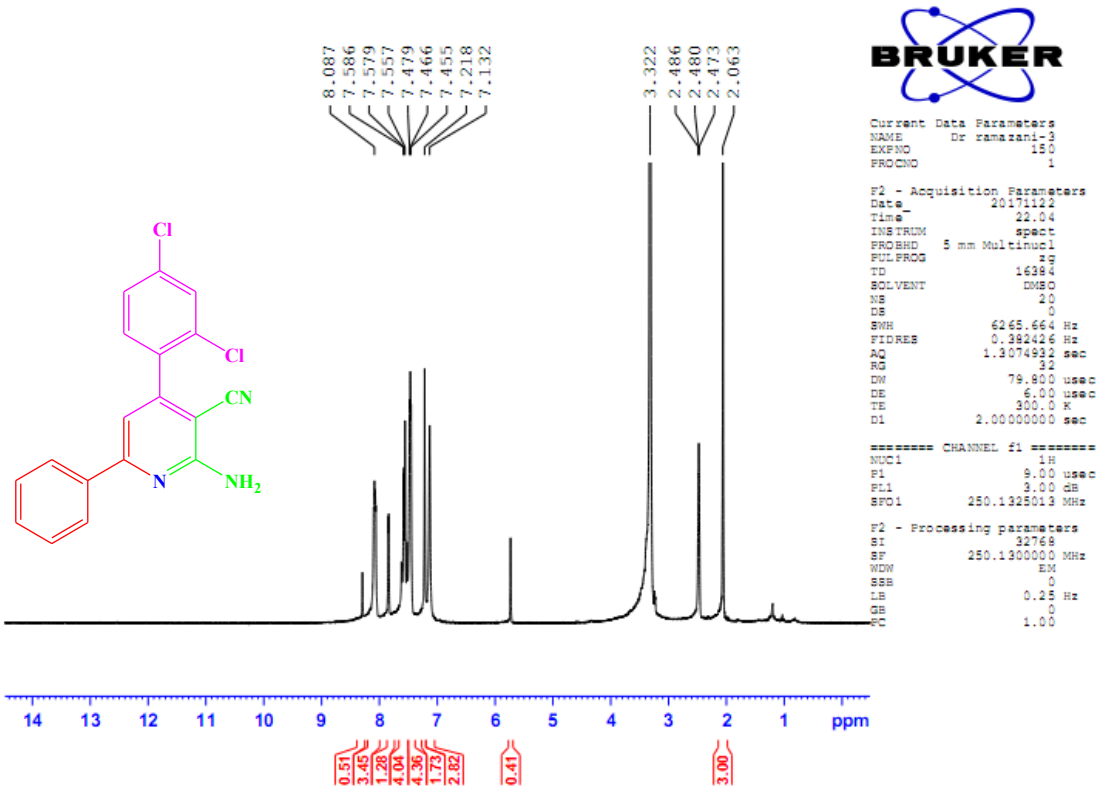
^{13}C NMR (62.9 MHz, $CDCl_3$)

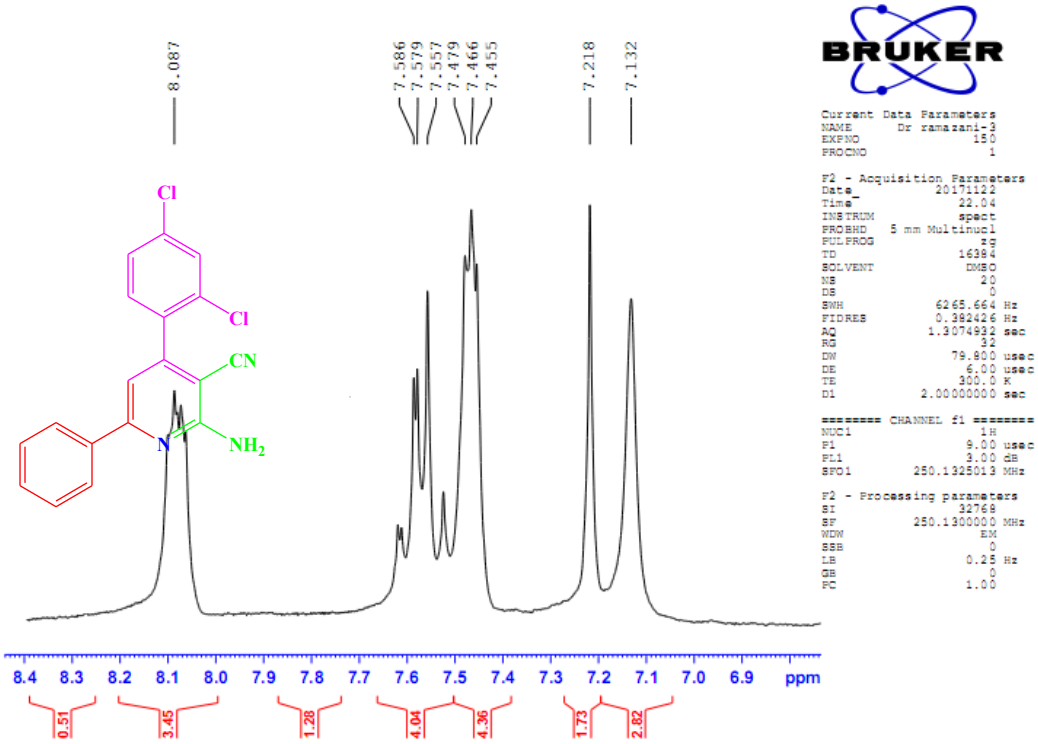




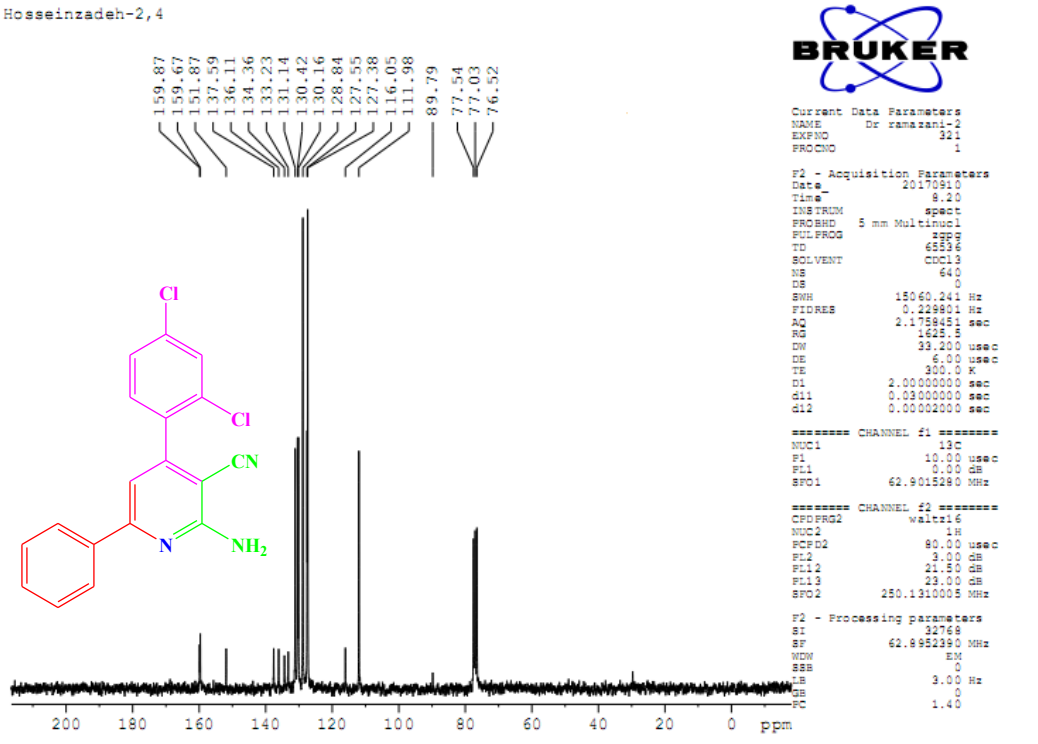
2-Amino-4-(2,4-dichlorophenyl)-6-phenylnicotinonitrile (Table 3, entry 13):

^{1}H NMR (250 MHz, DMSO)

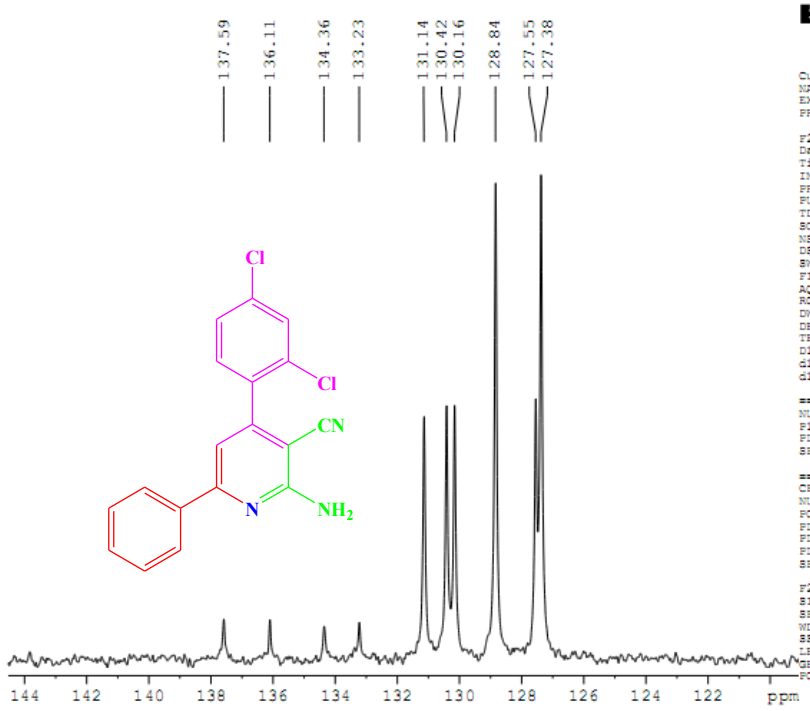




^{13}C NMR (62.9 MHz, $CDCl_3$)



Hosseinzadeh-2,4



BRUKER

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Current Data Parameters
NAME        Dr ramazani-2
EXPNO             321
PROCNO              1

F2 - Acquisition Parameters
Date_          20170910
Time               9.20
INSTRUM           spect
PROBHD   5 mm Multinucl
PULPROG          zgpg
TD              65536
SOLVENT          CDCl3
NS                640
DS                  0
SWH          15060.241 Hz
FIDRES        0.229801 Hz
AQ            2.1758451 sec
RG             1625.5
DW            33.200 usec
DE             6.00 usec
TE              300.0 K
D1          2.00000000 sec
d11         0.03000000 sec
d12         0.00002000 sec

======== CHANNEL f1 ========
NUC1              13C
P1              10.00 usec
PL1              0.00 dB
SFO1        62.9015280 MHz

======== CHANNEL f2 ========
CPDPRG2        waltz16
NUC2              1H
PCPD2           80.00 usec
PL2             3.00 dB
PL12           21.50 dB
PL13           23.00 dB
SFO2        250.1310005 MHz

F2 - Processing parameters
SI              32768
SF          62.8952390 MHz
WDW               EM
SSB                0
LB              3.00 Hz
GB                 0
PC              1.40
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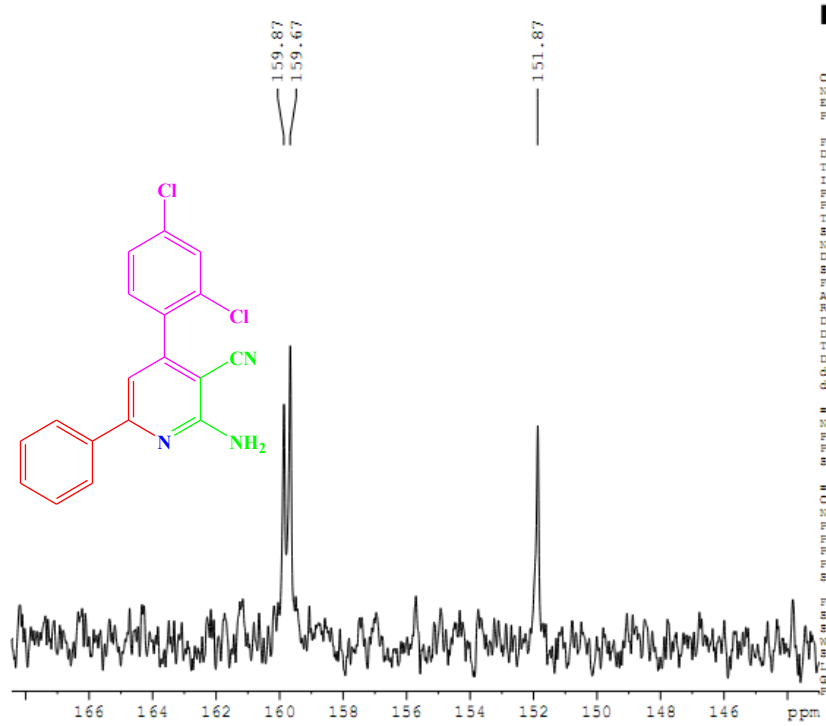
Hosseinzadeh-2,4



BRUKER

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Current Data Parameters
NAME        Dr ramazani-2
EXPNO             321
PROCNO              1

F2 - Acquisition Parameters
Date_          20170910
Time               9.20
INSTRUM           spect
PROBHD   5 mm Multinucl
PULPROG          zgpg
TD              65536
SOLVENT          CDCl3
NS                640
DS                  0
SWH          15060.241 Hz
FIDRES        0.229801 Hz
AQ            2.1758451 sec
RG             1625.5
DW            33.200 usec
DE             6.00 usec
TE              300.0 K
D1          2.00000000 sec
d11         0.03000000 sec
d12         0.00002000 sec

======== CHANNEL f1 ========
NUC1              13C
P1              10.00 usec
PL1              0.00 dB
SFO1        62.9015280 MHz

======== CHANNEL f2 ========
CPDPRG2        waltz16
NUC2              1H
PCPD2           80.00 usec
PL2             3.00 dB
PL12           21.50 dB
PL13           23.00 dB
SFO2        250.1310005 MHz

F2 - Processing parameters
SI              32768
SF          62.8952390 MHz
WDW               EM
SSB                0
LB              3.00 Hz
GB                 0
PC              1.40
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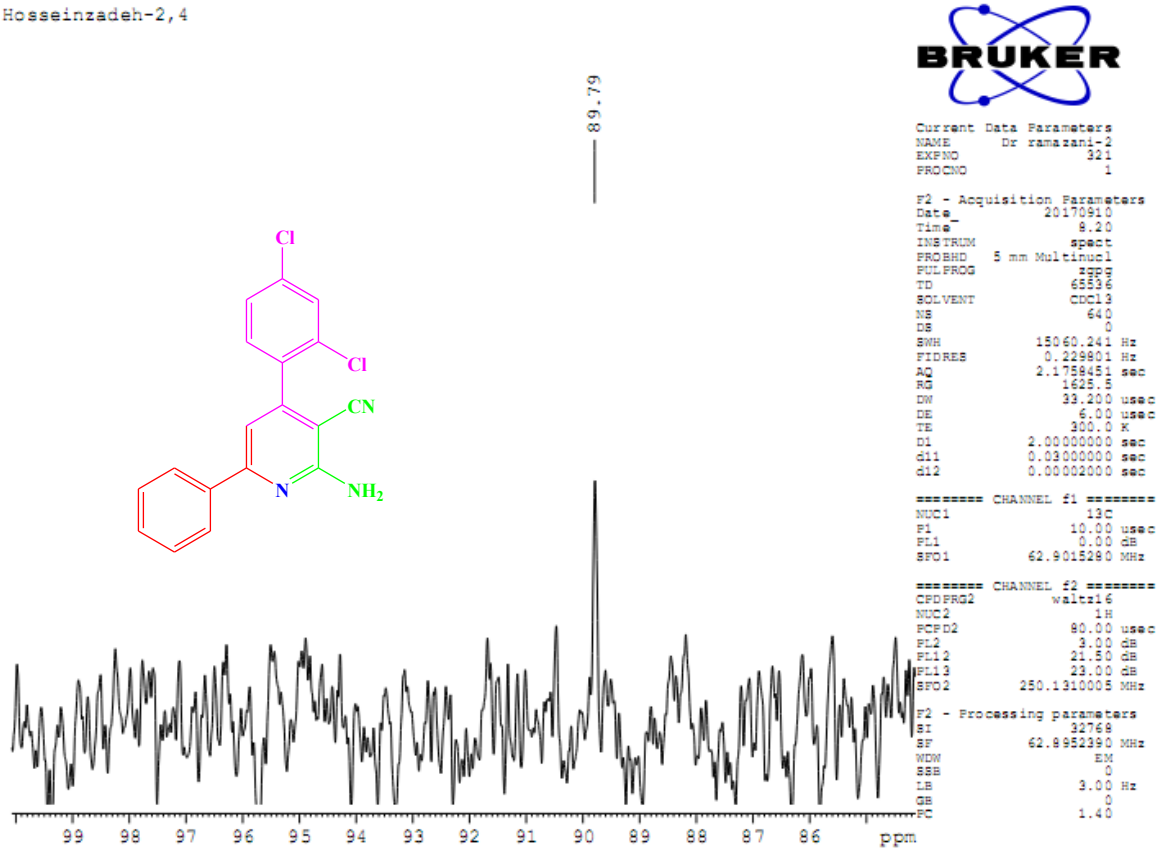
Hosseinzadeh-2,4



BRUKER

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Current Data Parameters
NAME        Dr ramazani-2
EXPNO              321
PROCNO               1

F2 - Acquisition Parameters
Date_          20170910
Time               8.20
INSTRUM           spect
PROBHD   5 mm Multinucl
PULPROG          zgpg
TD               65536
SOLVENT          CDCl3
NS                 640
DS                   0
SWH            15060.241 Hz
FIDRES         0.229801 Hz
AQ             2.1759451 sec
RG               1625.5
DW                33.200 usec
DE                 6.00 usec
TE                300.0 K
D1             2.00000000 sec
d11            0.03000000 sec
d12            0.00002000 sec

======== CHANNEL f1 ========
NUC1              13C
P1                10.00 usec
PL1                0.00 dB
SFO1          62.9015280 MHz

======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2               1H
PCPD2             80.00 usec
PL2                3.00 dB
PL12              21.50 dB
PL13              23.00 dB
SFO2         250.1310005 MHz

F2 - Processing parameters
SI                32768
SF            62.8952390 MHz
WDW                EM
SSB                 0
LB                3.00 Hz
GB                  0
PC                1.40
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