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Rapid and simple synthesis of secondary aromatic amines under solvent-free phase transfer catalytic conditions

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ABSTRACT

In this study, we report an efficient synthesis method of various secondary aromatic amine derivatives. Secondary anilines containing aromatic structure, which are valuable intermediates broadly used in the manufacturing of pharmaceuticals, dyestuffs, synthetic rubbers, herbicides, etc. A reaction of *meta*-substituted primary anilines with *non* and *para*-methyl substituted benzyl chlorides, catalyzed by tetrabutylammonium bromide as a phase transfer catalyst in solvent-free condition under microwave irradiation, has been developed. A frequently used processing technique employed in microwave-assisted organic synthesis involves solvent-less procedure was established with many advantages, including mild reaction conditions, short reaction times, simple work-up procedures, moderate to good yields and eco-friendly approach.The target compounds (1-18), were obtained in moderate to good yields (26-65 %). The obtained ^{1}H NMR, ^{13}C NMR and mass spectroscopic data are in accordance with the predicted structures. It is likely that the developed procedure can give an easy accession to synthesize various intermediate secondary amine products in future studies.

Keywords:*Microwave irradiation, solvent-free, phase transfer catalysis, eco-friendly.*

1. INTRODUCTION

Amination of aryl halides has been an considerable and frequently traditional reaction for the synthesis of the exciting compounds containing *N*-aryl structure, which are valuable intermediates broadly used in the manufacturing of pharmaceuticals, dyestuffs, synthetic rubbers, herbicides, insecticides and agrochemicals [1-3]. N-Arylated compounds can be prepared by the nucleophilic displacement between anilines and aryl halides in the presence of a base such as carbonates or hydroxides instoichiometric amounts [4-6]. The nucleophilic substitution of aryl halides with amines normally requires excessive amounts of reagents, high polarity solvents such as acetonitrile, dimethylformamide and dimethylsulphoxide at high temperature and under high pressure [7]. Furthermore, this traditional procedures are limited by its non-selectivity due to the formation of *N*,*N*-diarylated products and quaternary ammonium salts [8].

Since the mid-1980s, the use of microwave-heated chemical reactions has shown indisputable benefits in organic synthesis. Remarkable augmentations, improved yields, and green environmental reaction processes have been presented for different reaction types in literature [9]. And the absence of solvent in reaction medium reduces the risk of explosions. Furthermore, solvents are frequently expensive and sometimes difficult to remove from the reaction mediums. The combination of solvent-free conditions and microwave irradiation significantly reduces reaction times, enhances conversions as well as selectivity and has eco-friendly advantages, known as green chemistry [10-12]. This method was successfully applied to the synthesis of *N*-aryl amines in dry media as described by Yadav and co-workers [13].

In the present paper, we report an efficient and fast procedure for synthesis of 3-substituted *N*-benzylaniline derivatives under solvent-free microwave irradiation condition, in the presence of K_2CO_3 and a catalytic amount of tetrabutylammonium bromide (TBAB) as phase transfer catalyst (Figure 1).

2. EXPERIMENTAL SECTION

2.1. Materials and Methods

The ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectras were recorded with tetramethylsilane (TMS) as the internal standard on a Bruker FT-400 MHz spectrometer by using $CDCl_3$ as the solvent. Benzaniline compounds were synthesized with CEM microwave laboratory oven. Reaction progress and product mixtures were routinely checked by thin-layer chromatography (TLC) on Merck SilicaGel F254 aluminum plates. Column chromatography was performed with silicagel (70–230 Mesh). m-Anisidine, m-toluidine, 3-chloroaniline, m-phenetidine, 3-ethylaniline, 3-fluoroaniline, benzylchloride, 4-methylbenzylchloride, tetra-butylammonium bromide (TBAB)andK_2CO_3 were purchased from Sigma-Aldrich. 3-Bromoaniline, 3-iodoaniline were obtained from Merck Chemical.

2.2. General synthesis procedure under solvent-free phase transfer catalysis conditions

A mixture of substituted aniline (10 mmol), benzyl chloride or p-methylbenzyl chloride (5 mmol) was adsorbed either on a mixture of potassium carbonate (6.25 mmol) and TBAB (1 mmol) and then the resulting fine powder was irradiated with CEM microwave (150 W, 120 ^{o}C) for 5 minutes. Completion of the reaction was checked by TLC and all of the compounds were purified by

column chromotography on silica gel with hexane:ethyl acetate (9:1) mobil phase. Synthesis pathway is shown on Figure 1.

Physical data (% yield, molecular weight, chemical formula etc…) of the all synthesized compounds are tabulated in **Table 1**.

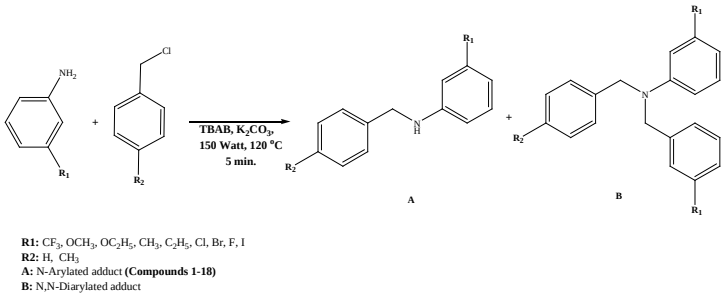

Figure 1. Synthesis of the compounds.

2.3. Spectral data of the new synthesized compounds (2,4-6,8-10,12,14,16,18)

(4-Methyl-benzyl)-m-tolyl-amine(2): Brown liquid, yield: 45%, ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 2.25 (s, 3H), 2.30 (s, 3H), 4.53 (s, 2H, CH_2-N), 6.72- 6.70 (d, 1H, Hf, J= 7.6 Hz), 6.85 (s, 1H, Hc), 7.01 (bs, 4H, Ha, Hb), 7.12- 7.11 (d, 1H, Hd, J= 8.1 Hz), 7.20-7.15 (m, 1H, He). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) 141.50, 138.21, 136.70, 130.28, 129.01, 127.56, 126.01, 115.33, 57.14, 22.56, 20.4. LC-MS calcd [M+1] 212.4.

(4-Methyl-benzyl)-(3-trifluoromethyl-phenyl)-amine(4): Yellow liquid, yield: 58%, ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 2.18 (s, 3H, Ph-CH_3), 4.31 (s, 2H, CH_2-N), 6.44-6.41 (d, 1H, J= 8.2 Hz, Hf), 6.55-6.52 (d, 2H, J=7.6 Hz, Ha), 6.85-6.82 (d, 4H, J= 7.6 Hz, Hb), 7.01-7.09 (m, 1H, He),7.12-7.10 (d, 1H, J=7.4 Hz, Hd), 7.22 (s, 1H, Hc).^{13}C NMR (400 MHz, $CDCl_3$, ppm) 144.80, 139.21, 134.70, 128.28, 127.01, 126.56, 119.41, 119.33, 56.14, 19.5. LC-MS calcd [M+1] 266.1.

Benzyl-(3-ethyl-phenyl)-amine(5): Brown liquid, yield: 42%, ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 1.05-1.01 (t, 3H, $CH_2\mathbf{CH_3}$), 2.54-2.48 (q, 2H, $\mathbf{CH_2}CH_3$), 4.68 (s, 2H, CH_2-N), 6.74-6.71 (d, 2H, J= 7.6 Hz, Hf), 7.01-7.06 (m, 6H, Ha, He), 7.12-7.08 (m, 6H, Hb, Hd), 7.18 (s, 2H, Hc). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) 142.80, 140.21, 128.70, 128.48, 128.01, 127.56, 113.21, 57.84, 25.65, 16.5.LC-MS calcd [M+1] 212.3.

(3-Ethyl-phenyl)-(4-methyl-benzyl)-amine(6): Brown liquid, yield: 42%, ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 1.18-1.14 (t, 3H, $CH_2\mathbf{CH_3}$), 2.14 (s, 3H, Ph-CH_3), 2.34-2.22 (q, 2H, $\mathbf{CH_2}CH_3$), 4.74 (s, 2H, CH_2-N), 6.74-6.70 (bs, 2H, Hc,Hf), 7.68 (bs, 4H, Ha, Hb), 7.08-7.04 (d, 1H, J= 7.09 Hz, Hd), 7.14-7.13 (m, He, 1H). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) 140.80, 139.21, 135.61, 129.18, 128.71, 128.66, 127.21, 112.68, 57.84, 28.65, 21.33, 16.5.LC-MS calcd. [M+1] 226.5.

(3-Methoxy-phenyl)-(4-methyl-benzyl)-amine(8): Brown liquid, yield: 56%, ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 2.20 (s, 3H, Ph-CH_3), 3.64 (s, 3H, OCH_3), 4.55 (s, 2H, CH_2-N), 6.80- 6.78 (d, 1H, J= 7.8 Hz, Hf), 6.85 (s, 1H, Hc), 7.01 (bs, 4H, Ha, Hb), 7.18-7.15 (d, 1H, J= 7.7 Hz, Hd), 7.21-7.19 (m, 1H, He). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) 152.80, 139.21, 135.70, 135.48, 129.36, 127.16, 116.21, 115.28, 57.14, 55.65, 20.90. LC-MS calcd [M+1] 228.1.

Benzyl-(3-ethoxy-phenyl)-amine(9): Yellow liquid, yield: 26%, ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 1.32-1.28 (t, 3H, $CH_2\mathbf{CH_3}$), 3.73-3.71 (q, 2H, $CH_2\mathbf{CH_3}$), 4.58 (s, 2H, CH_2-N), 6.50-6.48 (d, 1H, J= 7.8 Hz, Hf), 6.89 (s, 1H, Hc), 7.07-7.10 (d, 2H, J= 7.60 Hz, Ha), 7.15-7.12 (m, 1H, Hi), 7.19-7.17 (m, 3H, Hb,He), 7.24-7.22 (d, 1H, J=7.4 Hz, Hd). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) 147.80, 142.21, 135.70, 128.48, 127.01, 126.56, 115.21, 112.93, 67.84, 55.65, 14.3.LC-MS calcd [M+1] 228.7.

(3-Ethoxy-phenyl)-(4-methyl-benzyl)-amine(10): Brown liquid, yield: 35%, ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 1.38-1.35 (t, 3H, $OCH_2\mathbf{CH_3}$), 2.20 (s, 3H, CH_3), 3.82-3.79 (q,2H, $O\mathbf{CH_2}CH_3$), 4.68 (s, 2H, CH_2-N), 6.34 (s, 1H, Hc), 6.48-6.44 (d, 1H, J= 7.85 Hz, Hf), 6.80-6.76 (d, 1H, J= 8.01 Hz, Hd), 7.04-7.03 (bs, 4H, Ha, Hb), 7.13-7.08 (m, 1H, He). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) 147.11, 135.21, 134.70, 133.25, 129.48, 128.61, 116.91, 112.23, 66.84, 59.65, 25.23, 14.3.LC-MS calcd [M+1] 242.5.

(3-Fluoro-phenyl)-(4-methyl-benzyl)-amine(12): Orange oil, yield: 54%, ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 2.21 (s, 3H, CH_3), 4.78 (s, 2H, CH_2-N), 6.74-6.69 (m, 2H, Hc,Hf),6.91-6.83 (d, 2H, J=8.0 Hz, Ha), 7.00-6.97 (d, 2H, J= 8.0 Hz, Hb),7.23-7.21(d, 1H, J=8.0 Hz, Hd), 7.30-7.28 (m, 1H, He). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) 151.11, 139.41, 139.10, 135.25, 129.08, 127.21, 116.33, 113.93, 55.65, 22.23.LC-MS calcd [M+1] 216.

Table 1. Physical data of synthesized compounds (**1-18**).

Compound	Aniline (R_1)	Benzyl chloride (R_2)	Chemical Formula	Mol. Weight	Yield (%)
1	CH_3	H	$C_{14}H_{15}N$	197.12	60
2	CH_3	CH_3	$C_{15}H_{17}N$	211.14	45
3	CF_3	H	$C_{14}H_{12}F_3N$	251.09	38
4	CF_3	CH_3	$C_{15}H_{14}F_3N$	265.11	58
5	C_2H_5	H	$C_{15}H_{17}N$	211.14	42
6	C_2H_5	CH_3	$C_{16}H_{19}N$	225.15	42
7	OCH_3	H	$C_{14}H_{15}NO$	213.12	65
8	OCH_3	CH_3	$C_{15}H_{17}NO$	227.13	56
9	OC_2H_5	H	$C_{15}H_{17}NO$	227.13	26
10	OC_2H_5	CH_3	$C_{16}H_{19}NO$	241.15	35
11	F	H	$C_{13}H_{12}FN$	201.10	65
12	F	CH_3	$C_{14}H_{14}FN$	215.11	54
13	Cl	H	$C_{13}H_{12}ClN$	217.07	58
14	Cl	CH_3	$C_{14}H_{14}ClN$	231.08	42
15	Br	H	$C_{13}H_{12}BrN$	261.02	50
16	Br	CH_3	$C_{14}H_{14}BrN$	275.03	36
17	I	H	$C_{13}H_{12}IN$	309.00	40
18	I	CH_3	$C_{14}H_{14}IN$	323.02	39

(3-Chloro-phenyl)-(4-methyl-benzyl)-amine (14): Brown liquid, yield: 42%, ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 2.19 (s, 3H, CH_3), 4.80 (s, 2H, CH_2-N), 6.79 (s, 1H, Hc), 7.00 (bs, 4H, Ha, Hb), 7.04- 7.02 (d, 1H, J= 7.6 Hz, Hf), 7.28- 7.24 (m, 1H, He), 7.30-7.29 (d, 1H, J= 7.8 Hz, Hd). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) 141.65, 139.91, 135.47, 130.05, 129.10, 127.15, 122.28, 113.71, 57.65, 20.93.LC-MS calcd [M+1] 232.8.

(3-Bromo-phenyl)-(4-methyl-benzyl)-amine (16): Brown liquid, yield: 36%, ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 2.13 (s, 3H, CH_3), 4.63 (s, 2H, CH_2-N), 6.84-6.80 (d, 1H, Hf, J= 7.6 Hz), 7.01-6.85 (d, 2H, J= 7.8 Hz, Ha), 7.03-7.02 (d, 2H, J= 7.8 Hz, Hb), 7.15 (s, 1H, Hc), 7.21-7.19 (d, 1H, J=7.6 Hz, Hd), 7.30-7.24 (m, 1H, He). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) 142.65, 139.41, 135.77, 132.05, 129.00, 127.05, 114.28, 111.71, 56.65, 21.93.LC-MS calcd [M+1] 276.3.

(3-Iodo-phenyl)-(4-methyl-benzyl)-amine (18): Brown liquid, yield: 39%, ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 2.25 (s, 3H), 4.87 (s, 2H, CH_2-N), 6.70 (d, 1H, J= 7.64 Hz, Hf), 7.14-7.12 (m, 1H, He), 7.26 (bs, Ha, Hb, 4H), 7.40 (s, 1H, Hc), 7.66 (d, 1H, J= 7.89 Hz, Hd). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) 142.40, 139.61, 138.87, 135.05, 129.10, 127.55, 113.28, 100.71, 57.00, 20.03.LC-MS calcd [M+1] 324.2(see Supplementary data).

4. RESULTS SECTION

We have developed a rapid and easy alternative method for the synthesis of *N*-arylamines by aromatic nucleophilic substitution of benzyl chloride or p-methylbenzyl chloride with various primary aromatic amines with under the association of solvent-free phase transfer catalysis and microwave heating. This method which was frequently used in microwave chemistry have different advantages as "*GreenChemistry*" since they provide absence of harmful organic solvents which account for a great proportion of the waste material generated in organic synthesis thereby preventing environmental pollution and health risks.The other benefits of this protocol include the easily accessible and inexpensive starting materials, the versatility of the substrate, the experimentally straightforward procedure and the reasonable product yields (26-65 %) under the mild reaction conditions. All synthesized compounds were identified by ^{1}H NMR, ^{13}C NMR and mass spectra. To the best of our knowledge, eight compounds (2, 4-6, 10, 12, 16 and 18) were synthesized and reported for the first time in this work. And the other compounds 1, 3, 7-9, 11, 14, 15 and 17 were firstly synthesized by using microwave irradiation. All of the compounds synthesized very short reaction times (5 min.) as they were compared with traditional methods (10 min - 48 hour).

5.CONCLUSION

In conclusion, this efficient and fast technique will provide the momentum for many chemists to switch from conventional heating to solvent-free microwave chemistry and we believe that this work will contribute to the synthesis of various secondary aniline derivatives by using this method.

5. REFERENCES

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6. ACKNOWLEDGEMENTS

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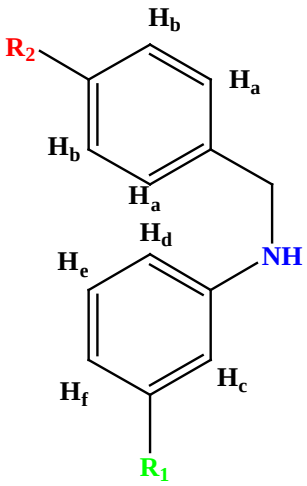
7. SUPPLEMENTARY FILES

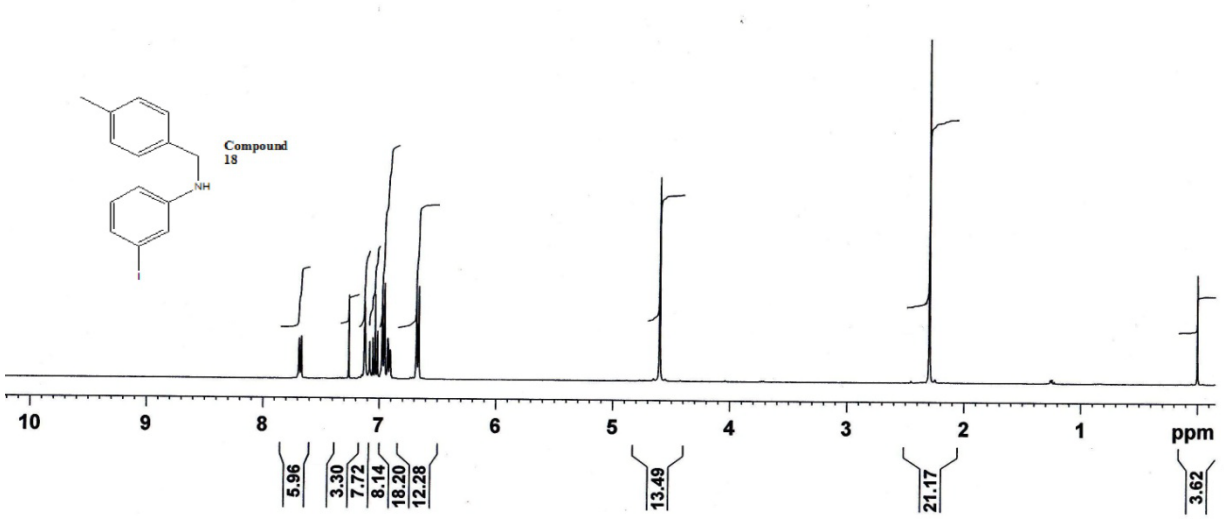
^{1}H and ^{13}C NMR Spectrums of the new synthesized compounds

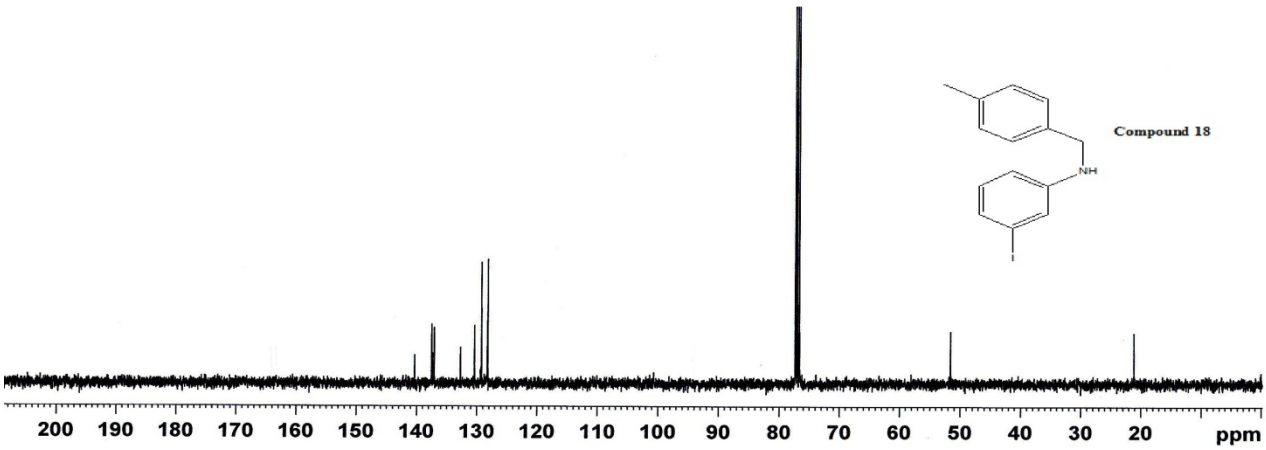
Compounds

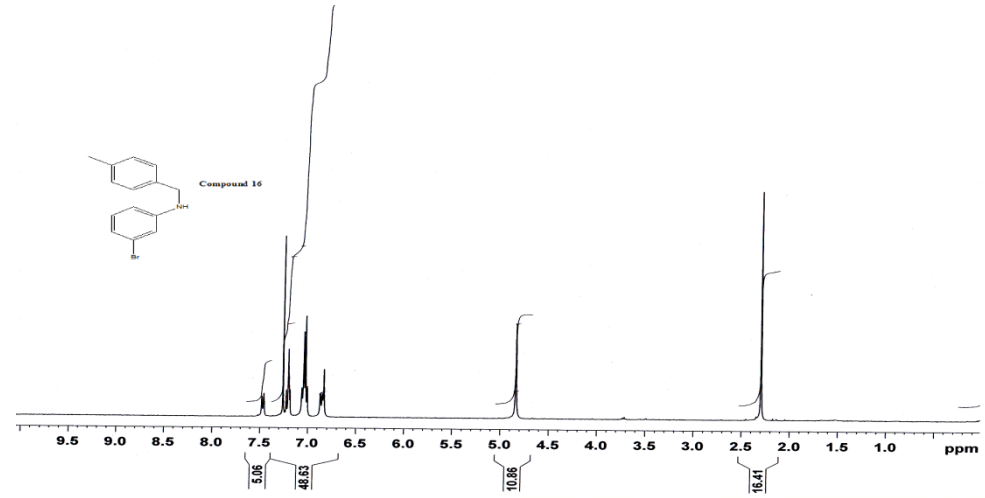


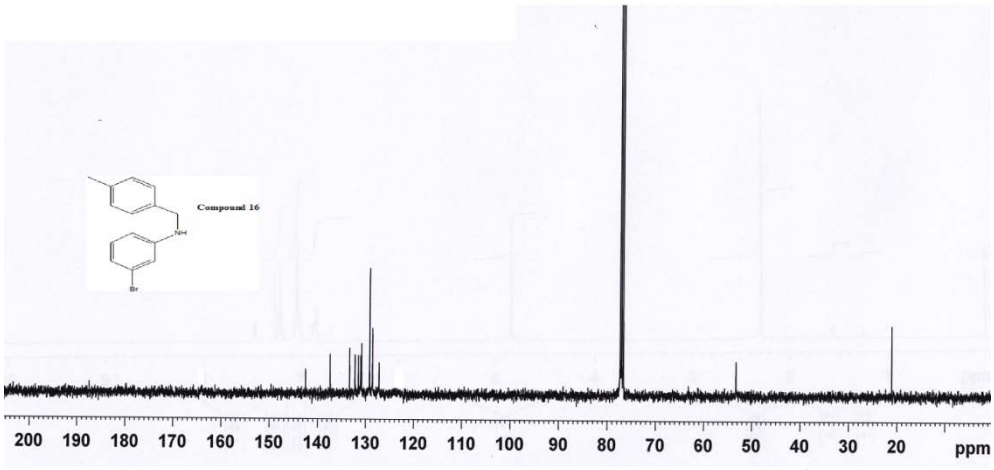
Common splitting patterns and their abbreviations list:

Singlet: (s)
Dublet: (d)
Triplet: (t)
Quartet: (q)
Multiplet : (m)






Compound 16
NH
Br
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
5.06
48.63
10.86
16.41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NH
Br
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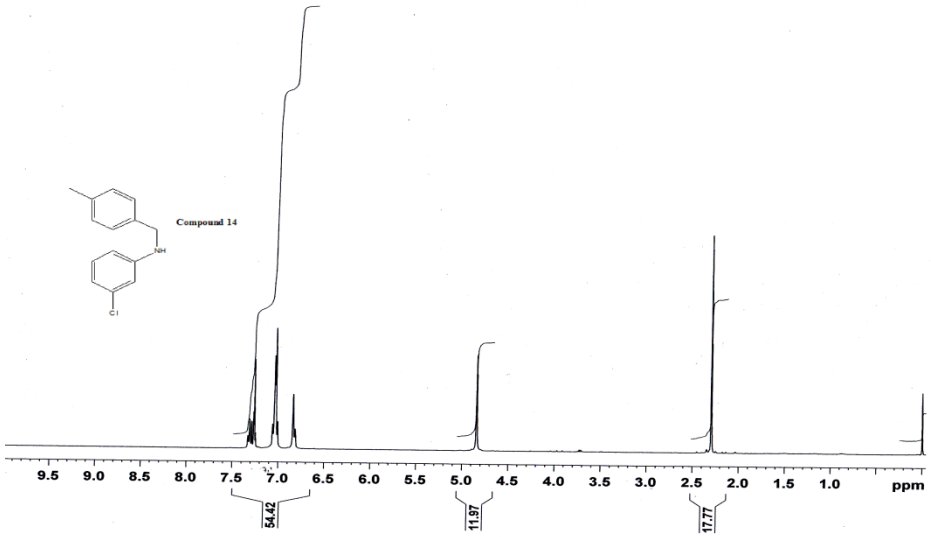
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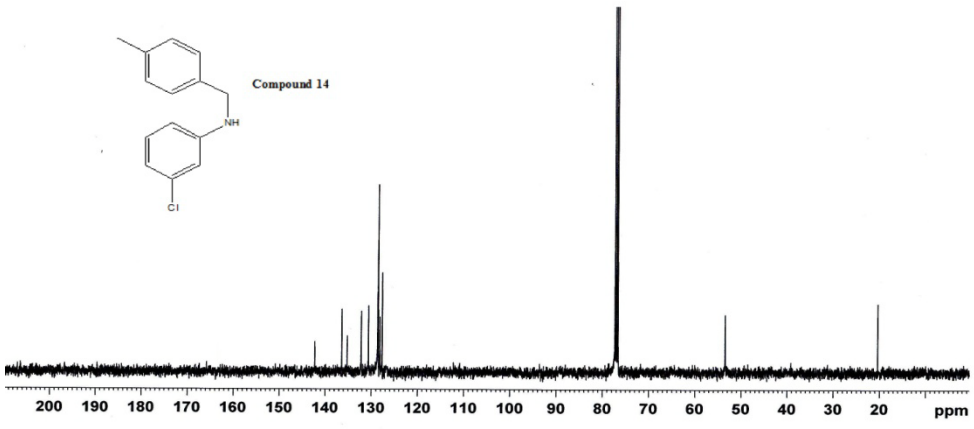
Cl
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
54.42
11.97
17.77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Cl
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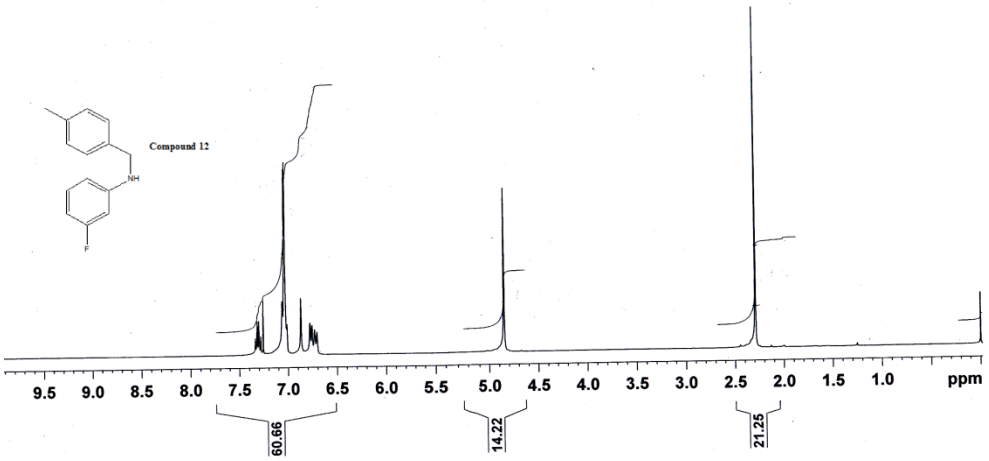
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F
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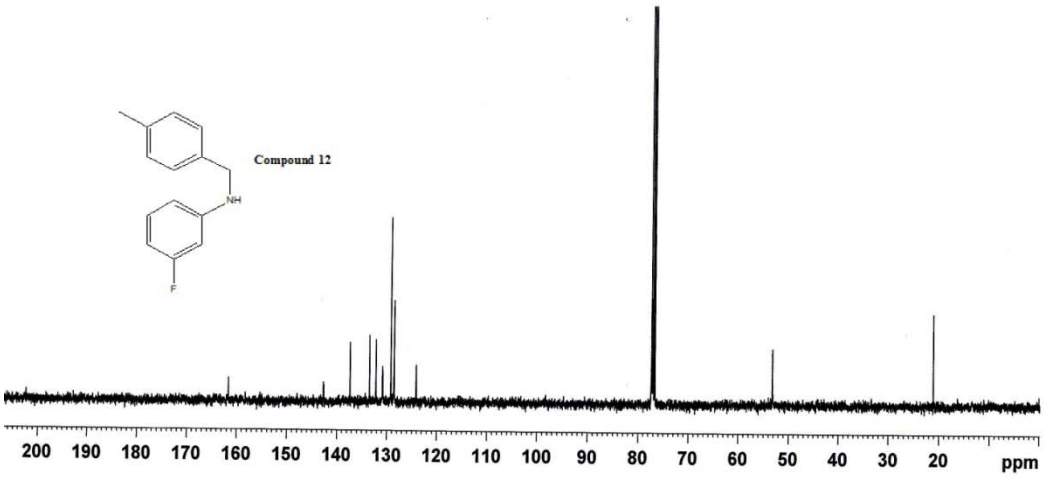
60.66
14.22
21.25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F
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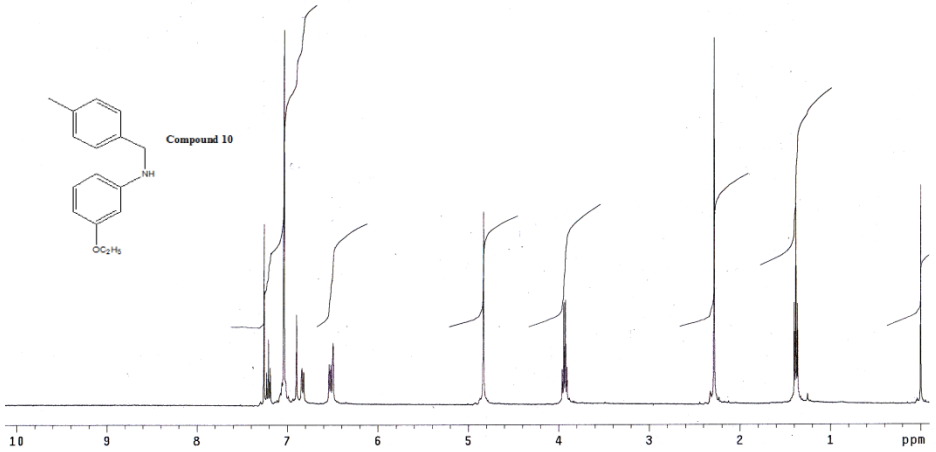
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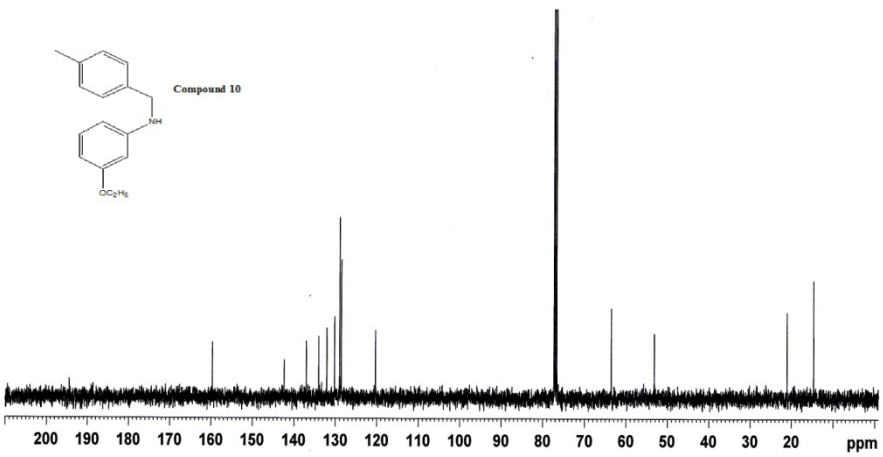
10 9 8 7 6 5 4 3 2 1 ppm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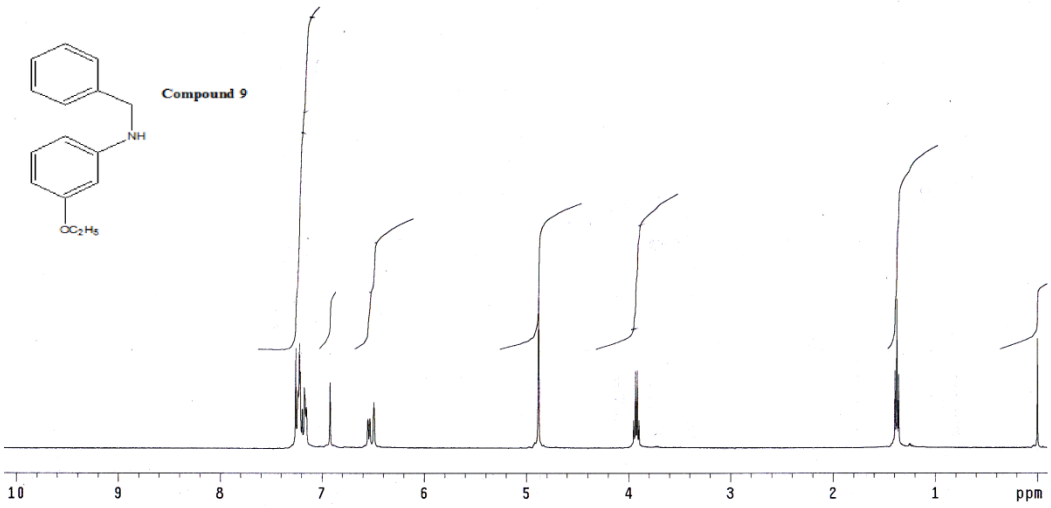
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm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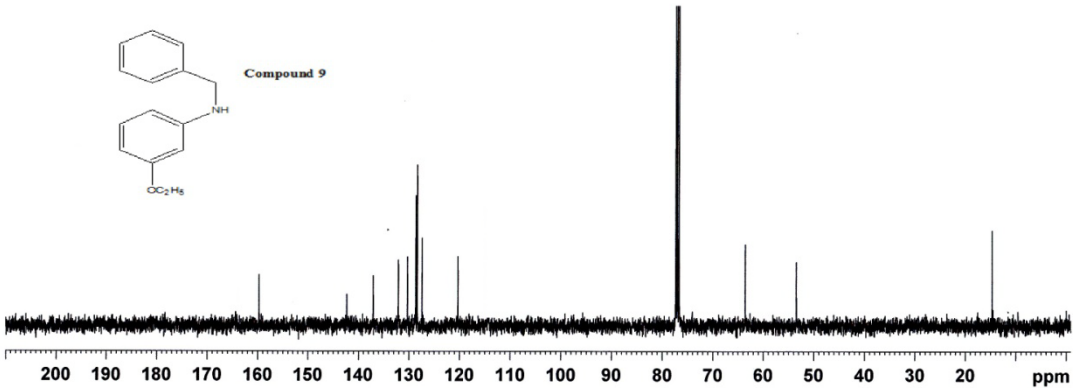
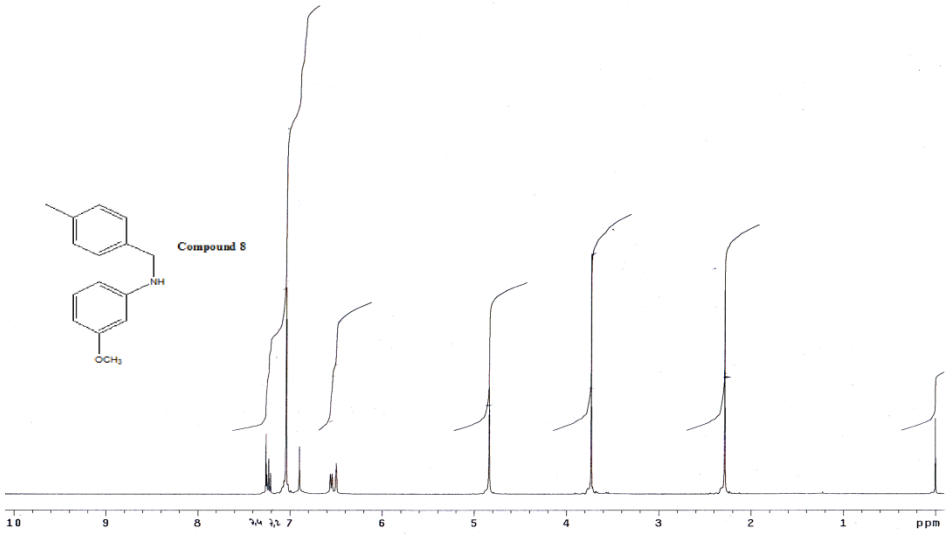
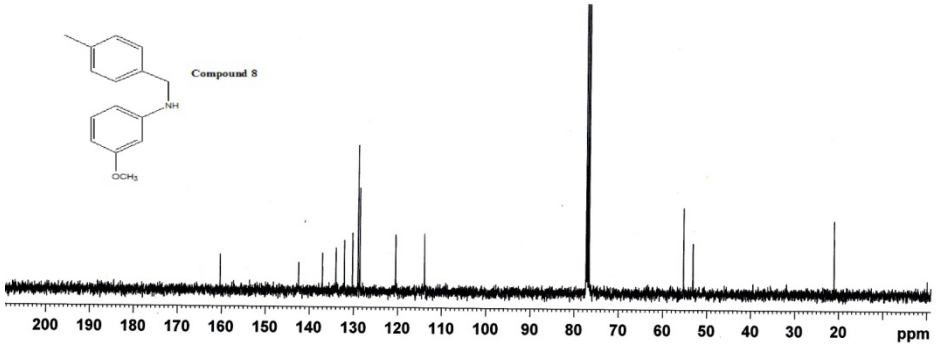
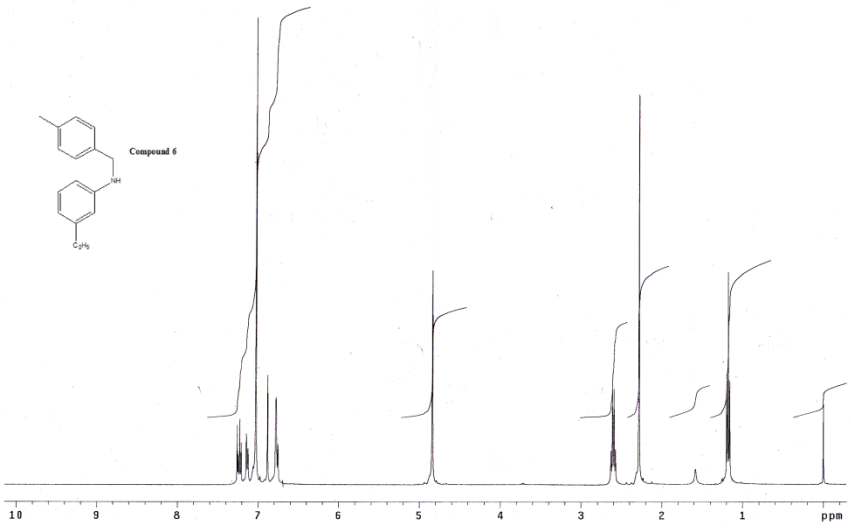
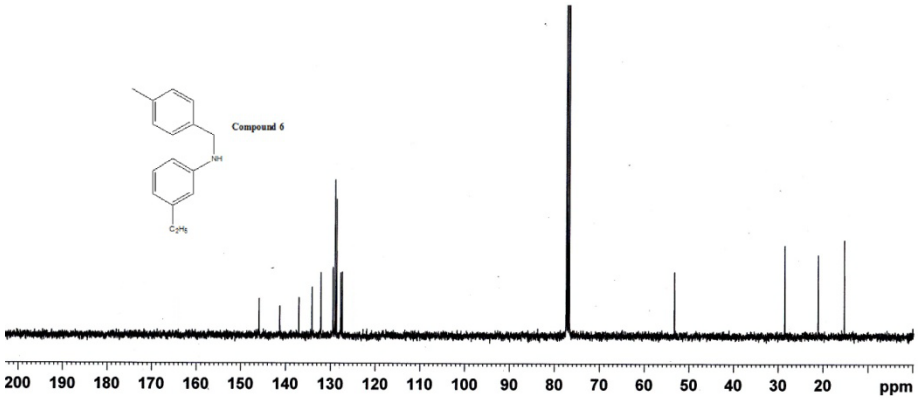
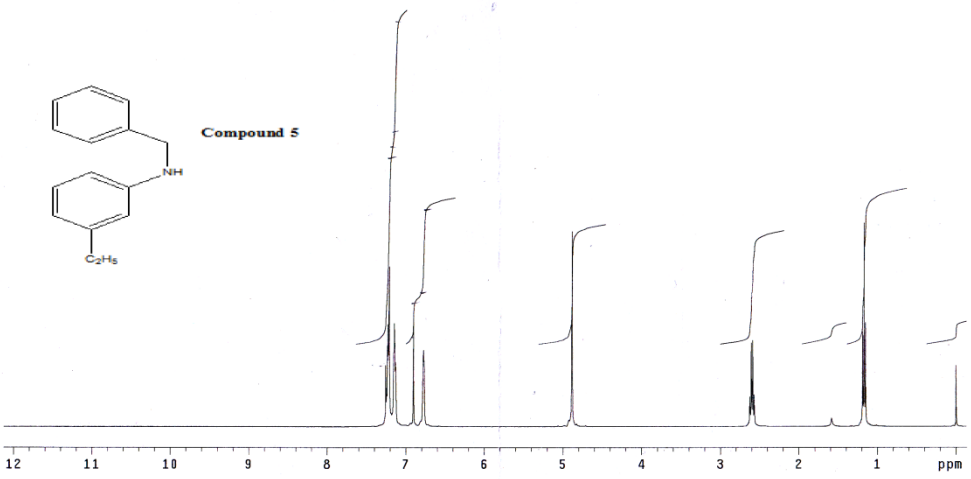

Compound 9
NH
OC2H5
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

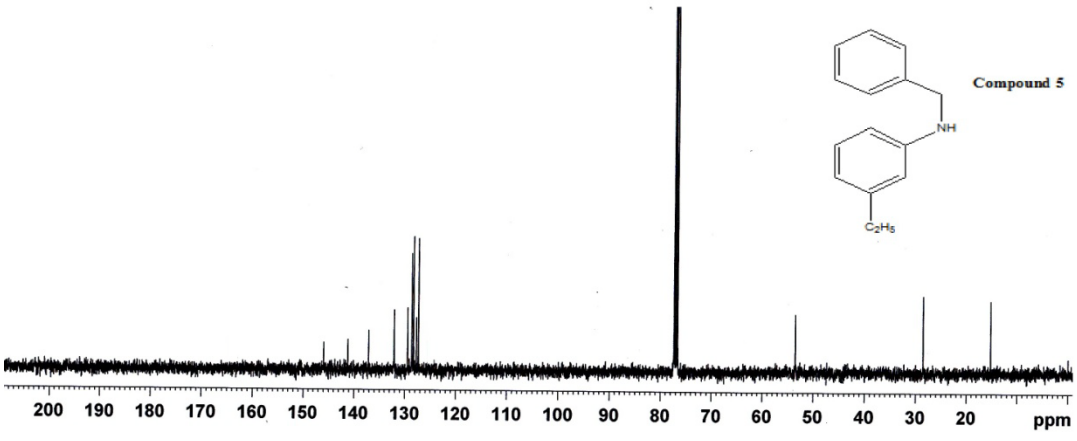

Compound 8
NH
OCH3
10 9 8 7 6 5 4 3 2 1 ppm

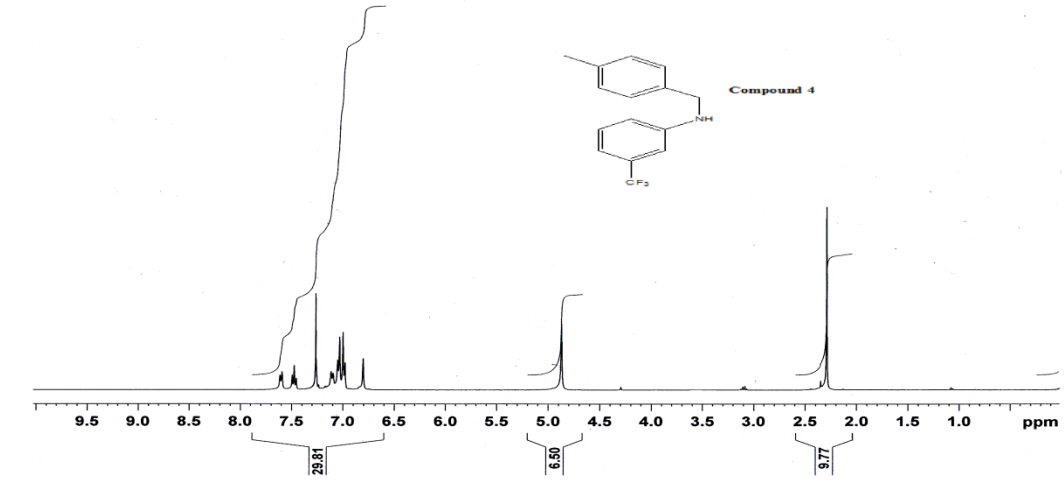

Compound 8
NH
OCH3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

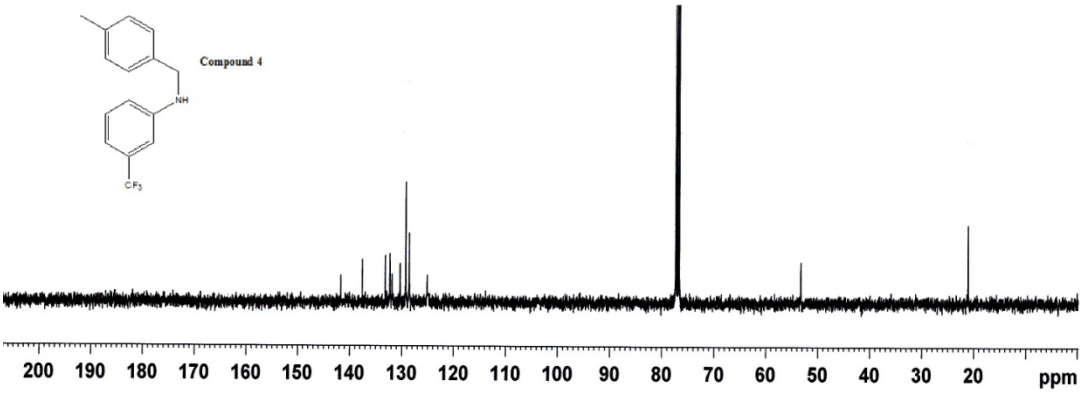

Compound 6
NH
C2H5
10 9 8 7 6 5 4 3 2 1 ppm

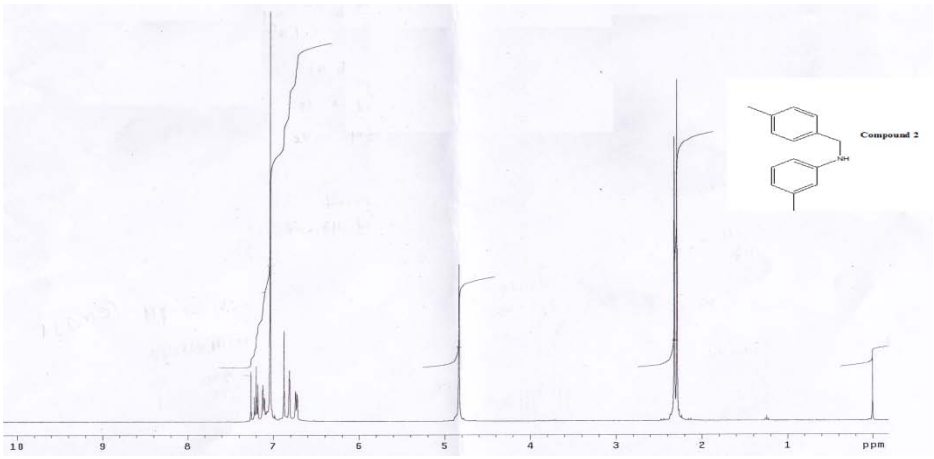

Compound 6
NH
C2H5
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

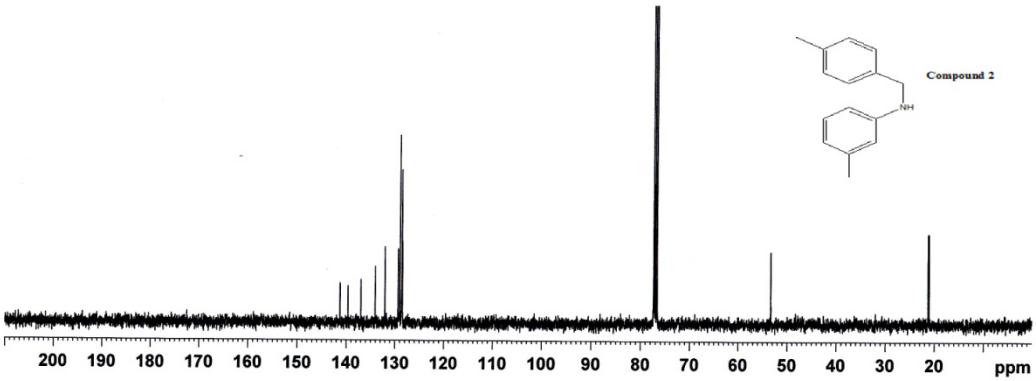

Compound 5
NH
C2H5
12 11 10 9 8 7 6 5 4 3 2 1 ppm


Compound 5
NH
C2H5
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm


Compound 4
NH
CF3
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
29.81
6.50
9.77


Compound 4
NH
CF3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm


Compound 2
NH
10 9 8 7 6 5 4 3 2 1 ppm


Compound 2
NH
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm