Electronic Supplementary Material (ESI) for Chemical Communications

Supporting Information

Copper Catalyzed Oxidative Coupling of Amines with Formamides: A New Approach for the Synthesis of Unsymmetrical Urea Derivatives

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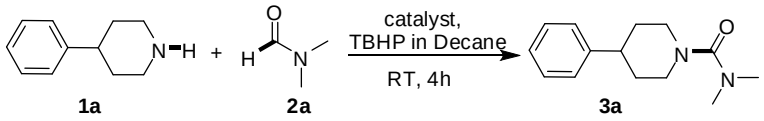
1. General Information :

All chemicals were purchased from Sigma-Aldrich and S.D Fine Chemicals, AVRA chemicals Pvt. Ltd. India and used as received. ACME silica gel (100–200 mesh) was used for column chromatography and Thin layer chromatography (TLC) was carried out on TLC Silica gel 60 F_{254} and compounds were visualized by UV light, I_2 vapors, phosphomolybdic acid stain, ninhydrin stain. All the other chemicals and solvents were obtained from commercial sources and purified using standard methods.. The IR values are reported in reciprocal centimeters (cm^{-1}). All ^{1}H, ^{13}C $\{^{1}H\}$ NMR spectra were recorded on a Avance-300, Inova-400, Inova-500 MHz Spectrometer. Chemical shifts (δ) are reported in ppm, using TMS (δ =0) as an internal standard in $CDCl_3$. The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quintet; dd, doublet of doublet; dt, doublet of triplet. The coupling constants (*J*), are reported in Hertz (Hz). Mass spectral data were compiled using MS (ESI), HRMS mass spectrometers. HPLC data recorded on SHIMAZDU HPLC Instrument equipped with DIODE ARRAY detector; Mobile phase: methanol :water = 90% +10% (1.5% acetic acid in HPLC water); Flow rate: 0.5 ml/min.; Column: LUX5M AMYLOSE-2 (phenomenox).; UV-range : 190 nm.

2.Optimization of raction conditions : [a]



1a **2a** **3a**

entry	catalyst	Oxidant	Reaction time	yield[b] (%)
1	CuI	TBHP in Decane	4 h	48
2	CuBr	TBHP in Decane	4 h	47
3	CuCl	TBHP in Decane	4 h	43
4	$CuBr_2$	TBHP in Decane	4 h	64
5	$CuCl_2$	TBHP in Decane	4 h	45
6	$Cu(CH_3COO)_2$	TBHP in Decane	4 h	24
7	$CuBr_2$	TBHP in Water	4 h	55
8	$CuBr_2$	H_2O_2	4 h	N.R
9	$CuBr_2$	TBPB	4 h	N.R
10	$CuBr_2$	TBP	4 h	N.R
11	$CuBr_2$	TAP	4 h	N.R
12	$CuBr_2$	-	4 h	N.R
13	-	TBHP in Decane	4 h	N.R
14	$CuBr_2$	TBHP in Decane	24 h	55
15	**$CuBr_2$**	**TBHP in Decane**	**1 h**	**65**
16[c]	$CuBr_2$	TBHP in Decane	1 h	52
17[d]	$CuBr_2$	TBHP in Decane	1 h	59

[a] Reaction conditions: **1a** (1 equiv), catalyst (5 mol%), DMF **2a** (2 mL, 27 equiv.), Oxidant (1.5 equiv.), r.t., 4 h. [b] Isolated yields. [c] 20 equivalents of DMF has taken in 2 mL of CH_3CN solvent and reaction time 1 h. [d] 0.2 mL of pyridine was added as an additive.

2. Experimental section:

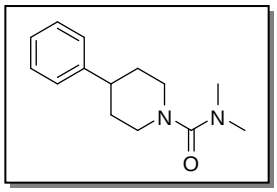
General procedure for the synthesis of aliphatic urea derivatives (Scheme 2, 3a-3v).

A solution of Amine (**1a-l**) (1.0 mmol), $CuBr_2$ (11 mg, 5 mol%) in 2 mL of the respective formamide (**2a-d)** was stirred at room temperature. To the same solution, a 5-6 M TBHP solution in decane (1.5 mmol) was added drop wise and stirred for 1hr. After completion of reaction time, formamide was either evaporated was removed under reduced pressure or directly proceeded for the conventional work up with ethyl acetate water mixture. The organic layer was separated and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure afforded the crude product, which was purified by column chromatography on silica gel (hexane/ethyl acetate 4:6).

General procedure for the synthesis of aromatic or hetero aromatic ureas (Scheme 3, 5a-5f).

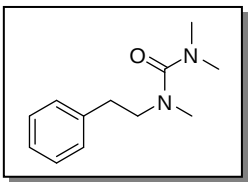
A solution of 2-carbonyl-substituted anilines (4**a-f**) (1.0 mmol), $Cu(OTf)_2$ (18 mg, 5 mol%) in 2 mL of dimethyl formamide **2a** was stirred at room temperature. To the same solution, 5-6 M TBHP solution in decane (1.5 mmol) was added drop wise, temperature raised to 80^o C, and stirred for 3 h. After cooling to room temperature, the reaction mixture was extracted with ethyl acetate and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure afforded the crude product, which was purified by column chromatography on silica gel (hexane/ethyl acetate 8:2).

4. Spectroscopic data for the products:



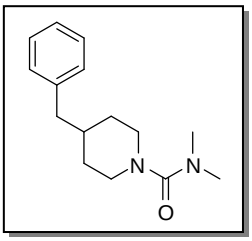
_N, N_-dimethyl-4-phenylpiperidine-1-carboxamide : (scheme 2, entry1, 3a)

Isolated yield = 65%; IR cm^{-1}: 2931, 1643, 1491, 1451, 1392, 1193, 1064, 904, 757, 700. ^{1}H NMR δ(300 MHz, $CDCl_3$) 7.18 – 7.33 (m, 5H), 3.75 – 3.84 (m, 2H), 2.81 – 2.9 (m, 8H), 2.66 (tt, *J* = 3.7, 11.8 Hz, 1H), 1.82 – 1.91 (m, 2H), 1.63 – 1.76 (m, 2H). ^{13}C NMR δ (75 MHz, CDCl3): 165, 145.7, 128.3, 126.6, 126.2, 47.4, 42.8, 38.4, 33.1. MS (ESI): m/z = 233 $(M+H)^+$. HRMS ESI $(M+H)^+$ m/z calcd for $C_{14}H_{21}N_2O$ $(M+H)^+$ = 233.16484, found = 233.16449.



1, 1, 3-trimethyl-3-phenethylurea : (scheme 2, entry 2, 3b)

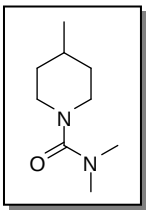
Isolated yield = 52% ; IR cm^{-1}: 2926, 1641, 1496, 1454, 1383, 1167, 1122, 747, 700. ^{1}H NMR δ(300 MHz, $CDCl_3$) 7.28-7.3 (m, Ar, 2H), 7.18-7.24 (m, Ar, 3H), 3.4 (t, *J* = 7.5 Hz, 2H), 2.85 (t, *J* = 7.5 Hz, 2H), 2.81 (s, 3H), 2.74 (s, 6H). ^{13}C NMR δ(75 MHz, CDCl3): 165.1, 139.2, 128.5, 128.2, 126, 51.7, 38.4, 36.8, 33.9. MS (ESI): m/z = 207 $(M+H)^+$. HRMS ESI $(M+H)^+$ m/z calcd for $C_{12}H_{19}N_2O$ $(M+H)^+$ = 207.14919, found = 207.14900.



4-benzyl-_N, N_-dimethylpiperidine-1-carboxamide : (scheme 2, entry 3, 3c)

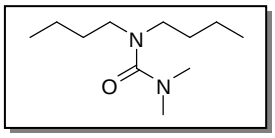
Isolated yield = 49% ; IR cm^{-1}: 2922, 2848, 1643, 1493, 1449, 1393, 1059, 746, 701. ^{1}H NMR δ(300 MHz, $CDCl_3$) 7.28-7.34 (m, Ar, 2H), 7.12-7.21 (m, Ar, 3H), 3.61-3.66 (m, 2H), 2.8 (s, 6H), 2.62-2.72 (m, 2H), 2.54 (d, *J* = 6.7 Hz, 2H), 1.59-1.71 (m, 3H), 1.15-1.28 (m, 2H). ^{13}C NMR δ (75 MHz,

CDCl3): 165, 140.1, 128.9, 128, 125.7, 46.9, 43, 38.4, 38.2, 31.8. MS (ESI): m/z = 247 $(M+H)^+$.HRMS ESI $(M+H)^+$ m/z calcd for $C_{15}H_{23}N_2O$ $(M+H)^+$ = 247.18049, found = 247.17982.



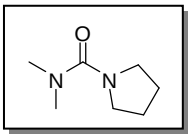
***N, N*, 4-trimethylpiperidine-1-carboxamide : (scheme 2, entry 4, 3d)**

Isolated yield = 36% ; IR cm^{-1}: 2923, 1644, 1493, 1450, 1393, 1135, 1060, 970. ^1H NMR δ(300 MHz, $CDCl_3$) 3.6-3.65 (m, 2H), 2.8 (s, 6H), 2.71 (td, *J* = 2.4, 13 Hz, 2H), 1.6-1.65 (m, 2H), 1.44-1.54 (m, 1H), 1.14 (qd, *J* = 3.9, 12.8 Hz, 2H), 0.94 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR δ(75 MHz CDCl3): 165.1, 47, 38.4, 33.9, 31.1, 21.7. MS (ESI): m/z = 171 $(M+H)^+$. HRMS ESI $(M+H)^+$ m/z calcd for $C_9H_{19}N_2O$ $(M+H)^+$ = 171.14919, found = 171.14894.



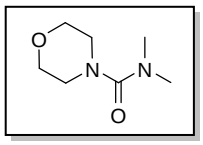
1, 1-dibutyl-3,3-dimethylurea : (scheme 2, entry 5, 3e)

Isolated yield = 29% ; IR cm^{-1}: 2957, 2929, 1648, 1490, 1398, 1200, 1138. ^1H NMR δ(300 MHz, $CDCl_3$) 3.09 (t, *J* = 6.9 Hz, 4H), 2.76 (s, 6H), 1.46 (p, *J* = 6.9 Hz, 4H), 1.22-1.3 (m, 4H), 0.89 (t, *J* = 6.9 Hz, 6H). ^{13}C NMR δ (75 MHz, CDCl3): 165.5, 47.7, 38.6, 30, 20, 13.7. MS (ESI): m/z = 201 $(M+H)^+$. HRMS ESI $(M+H)^+$ m/z calcd for $C_{11}H_{25}N_2O$ $(M+H)^+$ = 201.19614, found = 201.19582.



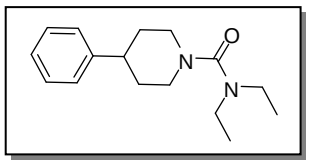
***N,N*-dimethylpyrrolidine-1-carboxamide : (scheme 2, entry 6, 3f)**

Isolated yield = 21% ; IR cm^{-1}: 2930, 2873, 1632, 1453, 1387, 1347, 1064, 777. ^1H NMR δ(300 MHz, $CDCl_3$) 3.3-3.37 (m, 4H), 2.83 (s, 6H), 1.79-1.84 (m, 4H). ^{13}C NMR δ (75 MHz, CDCl3): 163.5, 48.3, 38.1, 25.4. MS (ESI): m/z = 143 $(M+H)^+$. HRMS ESI $(M+H)^+$ m/z calcd for $C_7H_{15}N_2O$ $(M+H)^+$ = 143.11789, found = 143.11758.



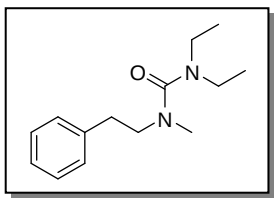
***N, N*-dimethylmorpholine-4-carboxamide : (scheme 2, entry 7, 3g)**

Isolated yield = 34%; IR cm^{-1}: 2854, 1643, 1494, 1392, 1203, 1115, 895. ^{1}H NMR δ(300 MHz, $CDCl_3$) 4.26 (m, 1H), 3.69 (t, *J* = 4.9 Hz, 4 H), 3.23 (t, *J* = 4.9 Hz, 4 H), 2.84 (s, 6H). ^{13}C NMR δ (75 MHz, CDCl3): 164.5, 66.4, 47, 38.1. MS (ESI): m/z = 159 $(M+H)^+$. HRMS ESI $(M+H)^+$ m/z calcd for $C_7H_{15}N_2O_2$ $(M+H)^+$ = 159.11280, found = 159.11266.



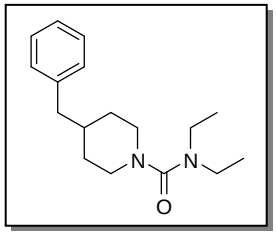
***N, N*-dimethyl-4-phenylpiperidine-1-carboxamide : (scheme 2, entry 8, 3h)**

Isolated yield = 63%; IR cm^{-1}: 2971, 2931, 1641, 1418, 1374, 1274, 1243, 755, 700. ^{1}H NMR δ(300 MHz, $CDCl_3$) 7.3 (t, *J* = 6.9 Hz, 2H), 7.18-7.22 (m, Ar, 3H), 3.74-3.76 (m, 2H), 3.22 (q, *J* = 6.9 Hz, 4H), 2.85 (td, *J* = 2, 12.9 Hz, 2H), 2.65 (tt, *J* = 3.9, 11.9 Hz, 1H), 1.81-1.87 (m, 2H), 1.7 (qd, *J* = 3.9, 11.9 Hz, 2H), 1.13 (t, *J* = 6.9 Hz, 6H). ^{13}C NMR δ(75 MHz, CDCl3): 164.8, 145.8, 128.4, 126.7, 126.2, 47.8, 42.9, 41.7, 33.1, 13.2. MS (ESI): m/z = 261 $(M+H)^+$. HRMS ESI $(M+H)^+$ m/z calcd for $C_{16}H_{25}N_2O$ $(M+H)^+$ = 261.19614, found = 261.19571.



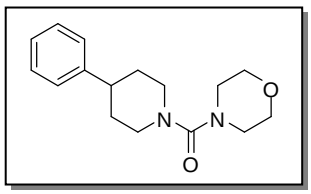
1,1-diethyl-3-methyl-3-phenethylurea : (scheme 2, entry 9, 3i)

Isolated yield = 58%; IR cm^{-1}: 2971, 2931, 1641, 1486, 1398, 1121, 983, 748, 700. ^{1}H NMR δ(300 MHz, $CDCl_3$) 7.17-7.3 (m, Ar, 5H), 3.39 (t, *J* = 7.5 Hz, 2H), 3.1 (q, *J* = 6.9 Hz, 4H), 2.85 (t, *J* = 7.9 Hz, 2H), 2.81 (s, 3H), 1.06 (t, *J* = 6.9 Hz, 6H). ^{13}C NMR δ(75 MHz, CDCl3): 164.9, 139.4, 128.6, 128.3, 126.1, 52, 41.9, 37, 34, 13.1. MS (ESI): m/z = 235 $(M+H)^+$. HRMS ESI $(M+H)^+$ m/z calcd for $C_{14}H_{23}N_2O$ $(M+H)^+$ = 235.18049, found = 235.18019.



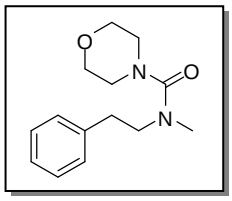
4-benzyl-*N, N*-diethylpiperidine-1-carboxamide : (scheme 2, entry 10, 3j)

Isolated yield = 53%; IR cm^{-1}: 2926, 1642, 1416, 1373, 1250, 964, 745, 700. ^{1}H NMR δ(300 MHz, $CDCl_3$) 7.25-7.3 (m, Ar, 2H), 7.18-7.21 (m, Ar, 1H), 7.12-7.15 (m, Ar, 2H), 3.57-3.62 (m, 2H), 3.17 (q, *J* = 6.7 Hz, 4H), 2.66 (td, *J* = 2.2, 12.8 Hz, 2H), 2.54 (d, *J* = 6.7 Hz, 2H), 1.59-1.7 (m, 3H), 1.18-1.28 (m, 2H), 1.1 (t, *J* = 6.7 Hz, 6H). ^{13}C NMR δ(75 MHz ,CDCl3): 164.7, 140.1, 128.9, 128.1, 125.7, 47.3, 43.1, 41.7, 38.3, 31.9, 13.1. MS (ESI): m/z = 275 $(M+H)^+$. HRMS ESI $(M+H)^+$ m/z calcd for $C_{17}H_{27}N_2O$ $(M+H)^+$ = 275.21179, found = 275.21118.



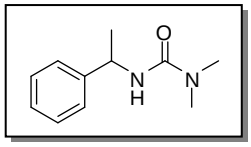
Morpholino(4-phenylpiperidin-1-yl)methanone : (scheme 2, entry 11, 3k)

Isolated yield = 41%; IR cm^{-1}: 2919, 2851, 1643, 1417, 1271, 1223, 1114, 1012, 757, 700. ^{1}H NMR δ(300 MHz, $CDCl_3$) 7.28-7.33 (m, Ar, 2H), 7.18-7.23 (m, Ar, 3H), 3.81-3.87 (m, 2H), 3.7 (t, *J* = 4.5 Hz, 4H), 3.28 (t, *J* = 4.5 Hz, 4H), 2.89 (td, *J* = 2.4, 13 Hz, 2H), 2.67 (tt, *J* = 3.5, 11.8 Hz, 1H), 1.84-1.88 (m, 2H), 1.65-1.75 (m, 2H). ^{13}C NMR δ(75 MHz CDCl3): 163.9, 145.4, 128.3, 126.6, 126.2, 66.5, 47.3, 42.7, 33. MS (ESI): m/z = 275 $(M+H)^+$. HRMS ESI $(M+H)^+$ m/z calcd for $C_{16}H_{23}N_2O_2$ $(M+H)^+$ = 275.17540, found = 275.17499.



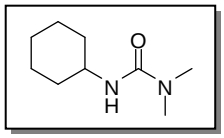
***N*-methyl-*N*-phenethylmorpholine-4-carboxamide : (scheme 2, entry 12, 3l)**

Isolated yield = 40%; IR cm^{-1}: 2923, 1643, 1489, 1453, 1395, 1115, 1068, 749, 701. ^{1}H NMR δ(300 MHz, $CDCl_3$) 7.27-7.31 (m, Ar, 2H), 7.18-7.23 (m, Ar, 3H), 3.6 (t, *J* = 4.9 Hz, 4H), 3.45 (t, *J* = 7.9 Hz, 2H), 3.11 (t, *J* = 4.9 Hz, 4H), 2.84-2.87 (m, 5H). ^{13}C NMR δ(75 MHz ,CDCl3): 164.2, 139, 128.6, 128.3, 126.1, 66.4, 51.3, 47.1, 36.6, 33.7. MS (ESI): m/z = 249 $(M+H)^+$. HRMS ESI $(M+H)^+$ m/z calcd for $C_{14}H_{21}N_2O_2$ $(M+H)^+$ = 249.15975, found = 249.15926.



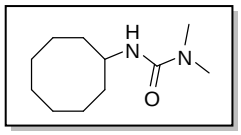
1,1-dimethyl-3-(1-phenylethyl)urea : (scheme 2, entry 13, 3m)

Isolated yield = 49% ; IR cm^{-1}: 2929, 1630, 1528, 1377, 1226, 761, 700. ^{1}H NMR δ(300 MHz, $CDCl_3$) 7.29-7.34 (m, Ar, 4H), 7.21-7.25 (m, 1H), 5.01 (p, *J* = 6.9 Hz, 1H), 4.6 (bs, 1H), 2.89 (s, 6H), 1.48 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR δ (75 MHz, CDCl3): 157.5, 144.4, 128.4, 126.9, 125.9, 49.9, 36, 22.5. MS (ESI): m/z = 193 $(M+H)^+$. HRMS ESI $(M+H)^+$ m/z calcd for $C_{11}H_{17}N_2O$ $(M+H)^+$ = 193.13354, found = 193.13336.



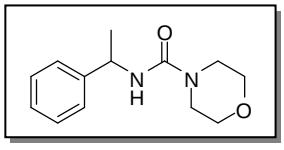
3-cyclohexyl-1, 1-dimethylurea : (scheme 2, entry 14, 3n)

Isolated yield = 56%; IR cm^{-1}: 2930, 1625, 1534, 1388, 1359, 1217, 1030. ^{1}H NMR δ(300 MHz, $CDCl_3$) 4.18 (bs, 1H), 3.56-3.69 (m, 1H), 2.88 (s, 6H), 1.92-1.97 (m, 2H), 1.62-1.73 (m, 4H), 1.29-1.44 (m, 2H), 1.02-1.2 (m, 2H). ^{13}C NMR δ (75 MHz, CDCl3): 157.7, 49.3, 36, 34, 25.6, 25. MS (ESI): m/z = 171 $(M+H)^+$. HRMS ESI $(M+H)^+$ m/z calcd for $C_9H_{19}N_2O$ $(M+H)^+$ = 171.14919, found = 171.14879.



3-cyclooctyl-1, 1-dimethylurea : (scheme 2, entry 15, 3o)

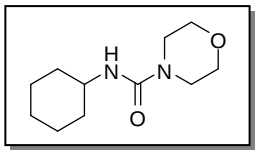
Isolated yield = 43%; IR cm^{-1}: 2921, 1634, 1522, 1340, 1327, 1201, 1021.^{1}H NMR δ(300 MHz, $CDCl_3$) 4.26 (m, 1H), 3.83-3.92 (m, 1H), 2.88 (s, 6H), 1.51-1.88 (m, 14H). ^{13}C NMR δ (75 MHz, CDCl3): 157.5, 50.3, 35.9, 32.9, 27, 25.3, 23.6. MS (ESI): m/z = 199 $(M+H)^+$. HRMS ESI $(M+H)^+$ m/z calcd for $C_{11}H_{23}N_2O$ $(M+H)^+$ = 199.18049, found = 199.18019.



***N*-(1-phenylethyl)morpholine-4-carboxamide : (scheme 2, entry 16, 3p)**

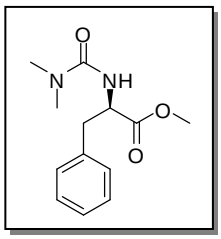
Isolated yield = 33%; IR cm^{-1}: 2970, 2926, 1624, 1530, 1255, 1116, 995, 866, 762, 700, 564. ^{1}H NMR δ(300 MHz, $CDCl_3$) 7.32-7.37 (m, 4H), 7.22-7.29 (m, 1H), 5.02 (p, *J* = 6.7 Hz, 1H), 4.66 (bs, 1H), 3.67 (t, *J* = 4.7 Hz, 4H), 3.32-3.35 (m, 4H), 1.49 (d, *J* = 6,7 Hz, 3H). ^{13}C NMR δ (75 MHz,CDCl3): 156.9,

144.1, 128.4, 127, 125.9, 66.3, 49.9, 43.9, 22.4. MS (ESI): m/z = 235 $(M+H)^+$. HRMS ESI $(M+H)^+$ m/z calcd for $C_{13}H_{19}N_2O_2$ $(M+H)^+$ = 235.14410, found = 235.14359.



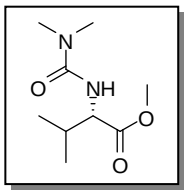
***N*-cyclohexylmorpholine-4-carboxamide : (scheme 2, entry 17, 3q)**

Isolated yield = 29%; IR cm^{-1}: 2929, 1614, 1538, 1454, 1414, 1274, 1252, 1109, 1074, 1027, 999, 855. ^1H NMR δ(300 MHz, $CDCl_3$) 4.26 (bs, 1H), 3.62-3.69 (m, 5H), 3.31 (t, *J* = 4.9 Hz, 4H), 1.95 (dd, *J* = 3.9, 12.9 Hz, 2H), 1.68-1.77 (m, 2H), 1.59-1.63 (m, 1H), 1.32-1.41 (m, 2H), 1.05-1.19 (m, 3H). ^{13}C NMR δ (75 MHz ,CDCl3): 157, 66.4, 49.3, 43.8, 33.8, 25.5, 24.9. MS (ESI): m/z = 213 $(M+H)^+$. HRMS ESI $(M+H)^+$ m/z calcd for $C_{11}H_{21}N_2O_2$ $(M+H)^+$ = 213.15975, found = 213.15929.



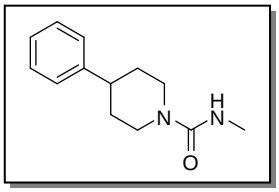
Methyl 2-(3, 3-dimethylureido)-3-phenylpropanoate : (scheme 2, entry 18, 3r)

Isolated yield = 39%; IR cm^{-1}: 2930, 1740, 1639, 1527, 1453, 1382, 1202, 746, 701. ^1H NMR δ(300 MHz, $CDCl_3$) 7.21 – 7.32 (m, 3H), 7.07 – 7.16 (m, 2H), 4.74 – 4.83 (m, 2H), 3.71 (s, 3H), 3.08 – 3.15 (m, 2H), 2.87 (bs, 6H). ^{13}C NMR δ(75 MHz, CDCl3): 173.1, 157.3, 136.2, 129.1, 128.3, 126.8, 54.3, 52, 38.3, 35.9. MS (ESI): m/z = 251 $(M+H)^+$. HRMS ESI $(M+H)^+$ m/z calcd for $C_{13}H_{19}N_2O_3$ $(M+H)^+$ = 251.13902, found = 251.13876.



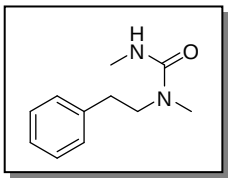
Methyl2-(3, 3-dimethylureido)-3-methylbutanoate : (scheme 2, entry 19, 3s)

Isolated yield = 41%; IR cm^{-1}: 2937, 1744, 1632, 1502, 1435, 1352, 1242, 1085.^1H NMR δ(300 MHz, $CDCl_3$) 4.85 (bs, 1H), 4.42 – 4.46 (m, 1H), 3.73 (s, 3H), 2.94 (bs, 6H), 2.07 – 2.19 (m, 1H), 0.93 (q, *J* = 6.7 Hz, 6H). ^{13}C NMR δ(75 MHz ,CDCl3): 173.8, 157.8, 58.3, 51.8, 36, 31.1, 18.8, 17.7. MS (ESI): m/z = 203 $(M+H)^+$. HRMS ESI $(M+H)^+$ m/z calcd for $C_9H_{19}N_2O_3$ $(M+H)^+$ = 203.13902, found = 203.13894.



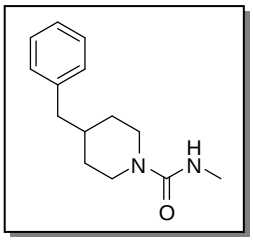
_N_-methyl-4-phenylpiperidine-1-carboxamide : (scheme 2, entry 20, 3t)

Isolated yield = 48%; IR cm^{-1}: 2933, 1626, 1547, 1417, 1395, 1242, 1009, 756, 700. ^{1}H NMR δ(300 MHz, $CDCl_3$) 7.28-7.33 (m, Ar, 2H), 7.18-7.23 (m, Ar, 3H), 4.6 (bs, 1H), 4.06-4.1 (m, 2H), 2.82-2.92 (m, 5H), 2.66 (tt, *J* = 3.5, 12 Hz, 1H), 1.82-1.87 (m, 2H), 1.65 (qd, *J* = 3.9, 12.4 Hz, 2H). ^{13}C NMR δ (75 MHz, CDCl3): 158.3, 145.4, 128.4, 126.6, 126.2, 44.5, 42.5, 32.9, 27.5. MS (ESI): m/z = 219 $(M+H)^+$. HRMS ESI $(M+H)^+$ m/z calcd for $C_{13}H_{19}N_2O$ $(M+H)^+$ = 219.14919, found = 219.14874.



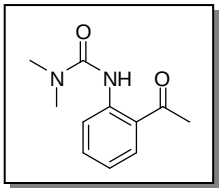
1,3-dimethly-1-phenethylurea : (scheme 2, entry 21, 3u)

Isolated yield = 47%; IR cm^{-1}: 2929, 1630, 1536, 1379, 1305, 1235, 1146, 1078, 1030, 979, 748, 700. ^{1}H NMR δ(300 MHz, $CDCl_3$) 7.18-7.31 (m, Ar, 5H), 4.43 (bs, 1H), 3.47 (t, *J* = 7.1 Hz, 2H), 2.79-2.84 (m, 5H), 2.72 (d, *J* = 4.5 Hz). ^{13}C NMR δ (75 MHz, CDCl3): 158.7, 139.1, 128.6, 128.3, 126.1, 50.8, 34.5, 34.4, 27.4. MS (ESI): m/z = 193 $(M+H)^+$. HRMS ESI $(M+H)^+$ m/z calcd for $C_{11}H_{17}N_2O$ $(M+H)^+$ = 193.13354, found = 193.13330.



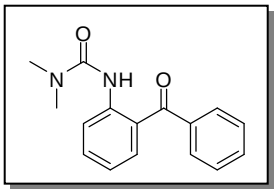
4-benzyl-*N*-methylpiperidine-1-carboxamide : (scheme 2, entry 22, 3v)

Isolated yield = 52% ; IR cm^{-1}: 2918, 1624, 1546, 1417, 1396, 1253, 1149, 1032, 961, 746, 700. ^{1}H NMR δ(300 MHz, $CDCl_3$) 7.25-7.30 (m, Ar, 2H), 7.16-7.21 (m, Ar, 1H), 7.11-7.14 (m, Ar, 2H), 4.54 (bs, 1H), 3.87-3.92 (m, 2H), 2.78 (d, *J* = 3.7 Hz, 3H), 2.69 (td, *J* = 2.2, 12.8 Hz, 2H), 2.53 (d, *J* = 6.7 Hz, 2H), 1.61-1.72 (m, 3H), 1.1-1.23 (m, 2H). ^{13}C NMR δ(75 MHz ,CDCl3): 158.4, 139.9, 128.9, 128, 125.8, 44, 42.9, 37.9, 31.6, 27.4. MS (ESI): m/z = 233 $(M+H)^+$. HRMS ESI $(M+H)^+$ m/z calcd for $C_{14}H_{21}N_2O$ $(M+H)^+$ = 233.16484, found = 233.16444.



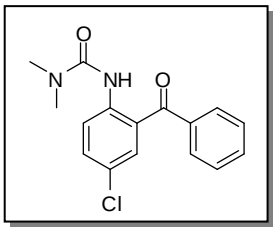
3-(2-acetylphenyl)-1, 1-dimethylurea : (scheme 3, entry 1, 5a)

Isolated yield = 31% ; IR cm^{-1}: 2927, 1677, 1644, 1586, 1530, 1451, 1362, 1313, 1242, 1180, 1163, 959, 758, 695. ^{1}H NMR δ(300 MHz, $CDCl_3$) 11.42 (bs, 1H), 8.65 (dd, *J* = 0.7, 8.4Hz, 1H), 7.86 (dd, *J* = 1.5, 8.1 Hz, 1H), 7.51 (td, *J* = 1.3, 8.4 Hz, 1H), 6.99 (td, *J* = 1.1, 8.1 Hz), 3.09 (bs, 6H), 2.66 (s, 3H). ^{13}C NMR δ(75 MHz CDCl3): 202.8, 155.6, 143.2, 135, 131.5, 120.1, 119.5, 36.2, 29.5. MS (ESI): m/z = 229 $(M+Na)^+$. HRMS ESI $(M+Na)^+$ m/z calcd for $C_{11}H_{14}N_2O_2Na$ $(M+Na)^+$ = 229.09475, found = 229.09441.



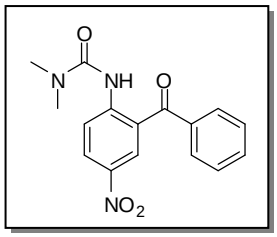
3-(2-benzoylphenyl)-1, 1-dimethylurea : (scheme 3, entry 2, 5b)

Isolated yield = 38% ; IR cm^{-1}: 2928, 1678, 1629, 1582, 1523, 1447, 1361, 1255, 1176, 938, 752, 700, 644. ^{1}H NMR δ(300 MHz, $CDCl_3$) 10.77 (bs, 1H), 8.56 (dd, *J* = 1.1, 8.6 Hz, 1H), 7.65 – 7.67 (m, 2H), 7.45 – 7.61 (m, 5H), 6.95 (td, *J* = 1.1, 8.1 Hz, 1H), 3.11 (bs, 6H). ^{13}C NMR δ (75 MHz, CDCl3): 200.3, 155.5, 143.1, 139, 134.5, 133.9, 131.9, 129.5, 128.1, 121.6, 120.3, 119.9, 36.2. MS (ESI): m/z = 269 $(M+H)^+$. HRMS ESI $(M+H)^+$ m/z calcd for $C_{16}H_{17}N_2O_2$ $(M+H)^+$ = 269.12845, found = 269.12799.



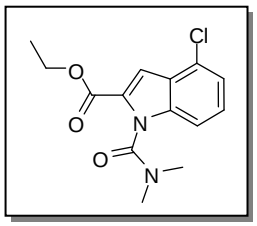
3-(2-benzoyl-4-chlorophenyl)-1, 1-dimethylurea : (scheme 3, entry 3, 5c)

Isolated yield = 39% ; IR cm^{-1}: 2929, 1677, 1634, 1578, 1512, 1397, 1362, 1240, 1175, 950, 832, 747, 701. ^{1}H NMR δ(300 MHz, $CDCl_3$) 10.6 (bs, 1H), 8.54 - 8.57 (m, 1H), 7.59 – 7.68 (m, 3H), 7.47 – 7.53 (m, 4H), 3.09 (bs, 6H). ^{13}C NMR δ (75 MHz, CDCl3): 199, 155.2, 141.6, 138.3, 134.2, 132.7, 129.5, 128.4, 124.9, 122.7, 122, 36.2. MS (ESI): m/z = 303 $(M+H)^+$. HRMS ESI $(M+H)^+$ m/z calcd for $C_{16}H_{16}ClN_2O_2$ $(M+H)^+$ = 303.08948, found = 303.08905.



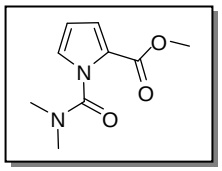
3-(2-benzoyl-4-nitrophenyl)-1, 1-dimethylurea : (scheme 3, entry 4, 5d)

Isolated yield = 35% ; IR cm^{-1}: 2925, 2854, 1694, 1623, 1508, 1332, 1252, 959, 750, 697, 553. ^{1}H NMR δ(300 MHz, $CDCl_3$) 11.21 (bs, 1H), 8.83 (d, *J* = 9 Hz, 1H), 8.51 (d, *J* = 3 Hz, 1H), 8.38 (dd, *J* = 3, 9.8 Hz, 1H), 7.64 – 7.69 (m, 3H), 7.55 (t, *J* = 6.7 Hz, 2H), 3.15 (bs, 6H). ^{13}C NMR δ (75 MHz, CDCl3): 199, 154.4, 148.6, 139.7, 137.8, 133, 129.6, 129.1, 128.7, 120.2, 120.1, 36.4. MS (ESI): m/z = 314 $(M+H)^+$. HRMS ESI $(M+H)^+$ m/z calcd for $C_{16}H_{16}N_3O_4$ $(M+H)^+$ = 314.11353, found = 314.11322.



Methyl 4-chloro-1-(dimethylcarbamoyl)-*1H*-indole-2-carboxylate : (scheme 3, entry 5, 5e)

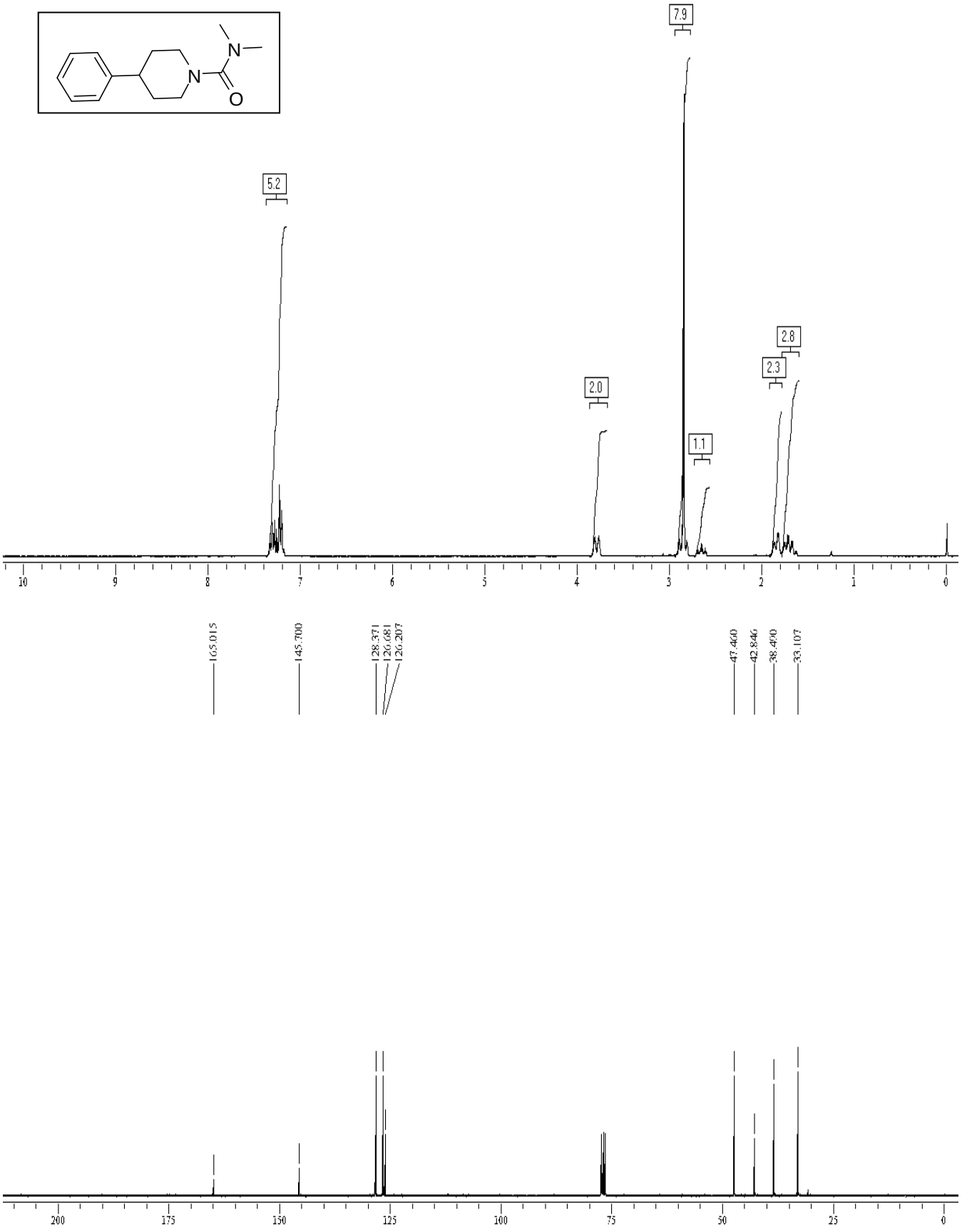
Isolated yield = 37%; IR cm^{-1}: 2929, 1708, 1530, 1441, 1390, 1245, 1199, 1060, 763, 729. ^{1}H NMR δ(300 MHz, $CDCl_3$) 7.66 (bs, 1H), 7.32 – 7.34 (m, 1H), 7.24 – 7.27 (m, 2H), 4.38 (q, *J* = 6.9 Hz, 2H), 3.25 (bs, 3H), 2.79 (bs, 3H), 1.39 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR δ (75 MHz, CDCl3): 160.4, 152.7, 135.3, 129.1, 127.4, 126.5, 121.8, 112.2, 110.9, 61.2, 37.7, 36.8, 14.1. MS (ESI): m/z = 295 $(M+H)^+$. HRMS ESI $(M+H)^+$ m/z calcd for $C_{14}H_{16}ClN_2O_3$ $(M+H)^+$ = 295.08440, found = 295.08401.

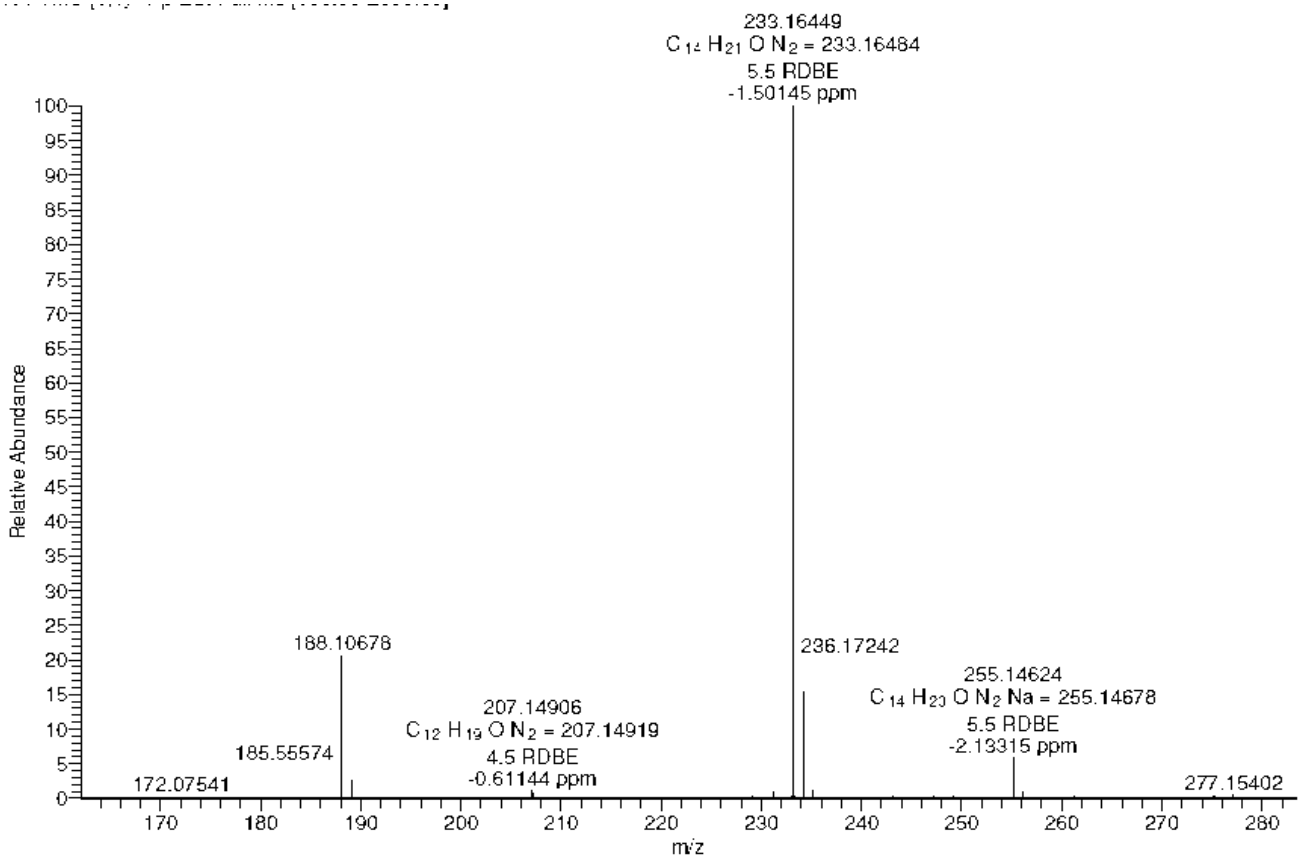


Methyl 1-(dimethylcarbamoyl)-*1H*-pyrrole-2-carboxylate : (scheme 3, entry 6, 5f)

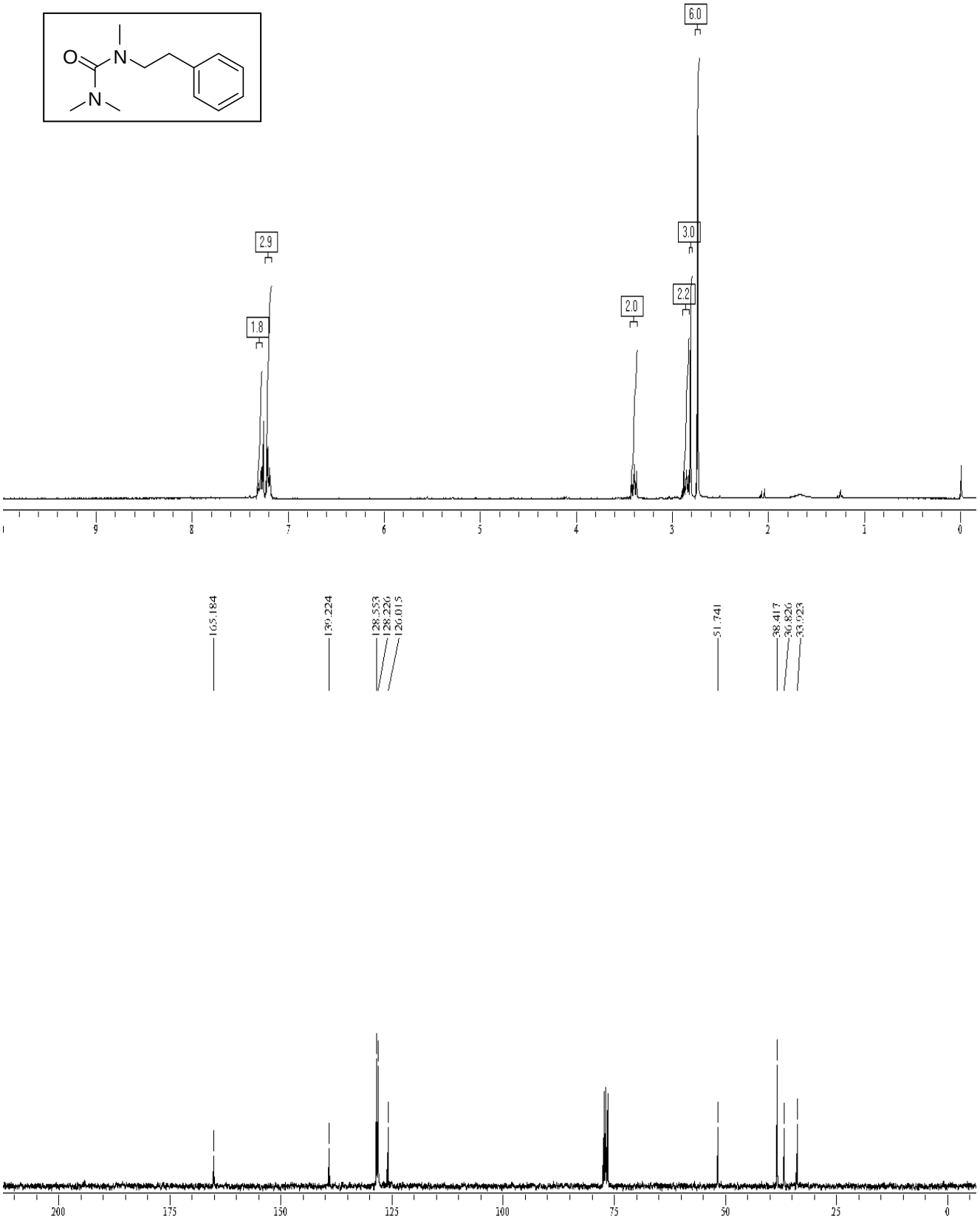
Isolated yield = 40%; IR cm^{-1}: 2925, 1704, 1442, 1393, 1292, 1236, 1141, 1093, 1060, 755. ^{1}H NMR δ(300 MHz, $CDCl_3$) 6.95 – 6.98 (m, 2H), 6.26 – 6.29 (m, 1H), 3.83 (s, 3H), 3.17 (bs, 3H), 2.71 (bs, 3H). ^{13}C NMR δ(75 MHz, CDCl3): 160.4, 153.4, 125, 122.5, 117.5, 110.2, 51.5, 37.7, 36.6. MS (ESI): m/z = 197 $(M+H)^+$. HRMS ESI $(M+H)^+$ m/z calcd for $C_9H_{13}N_2O_3$ $(M+H)^+$ = 197.09207, found = 197.09167.

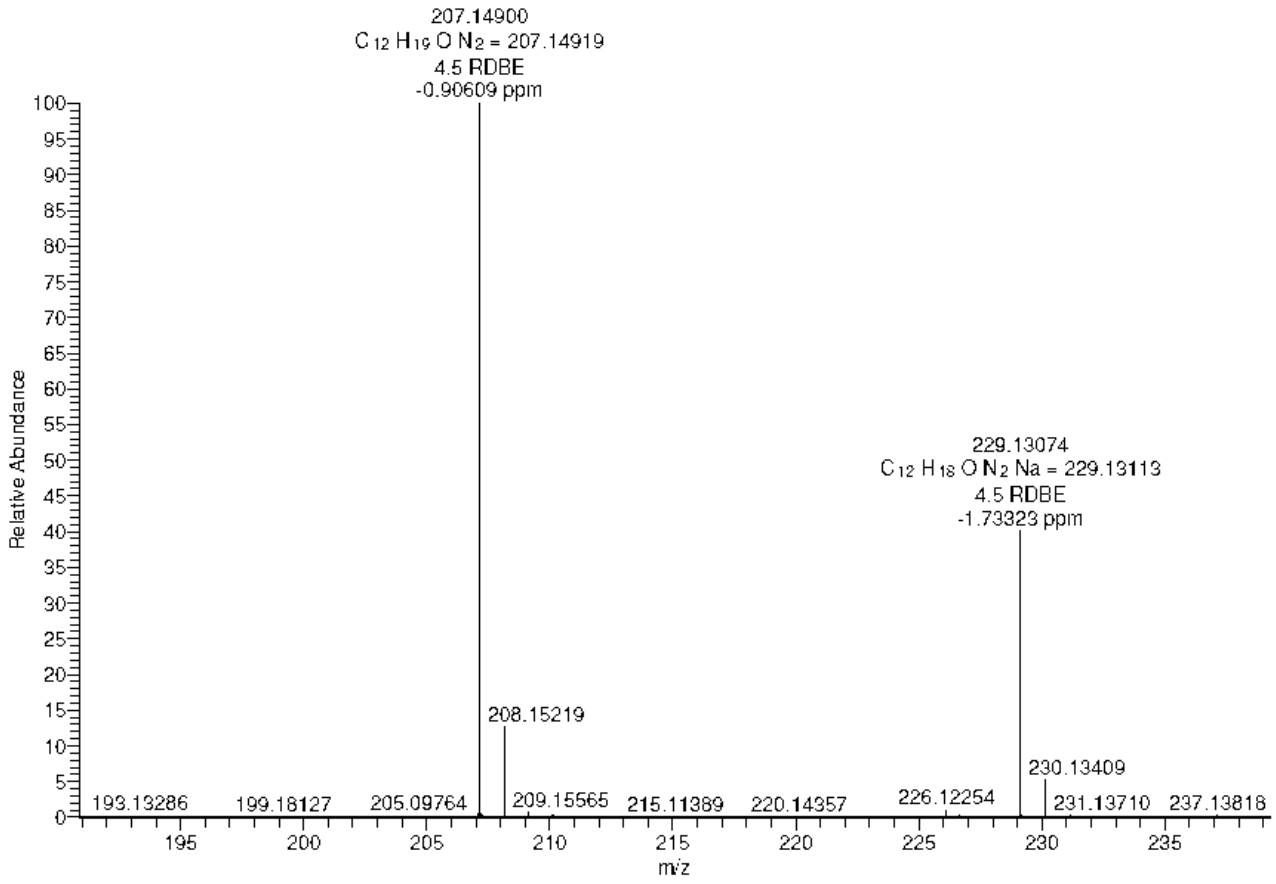
5. Copies of ^{1}H NMR and ^{13}C NMR spectra : compound 3a



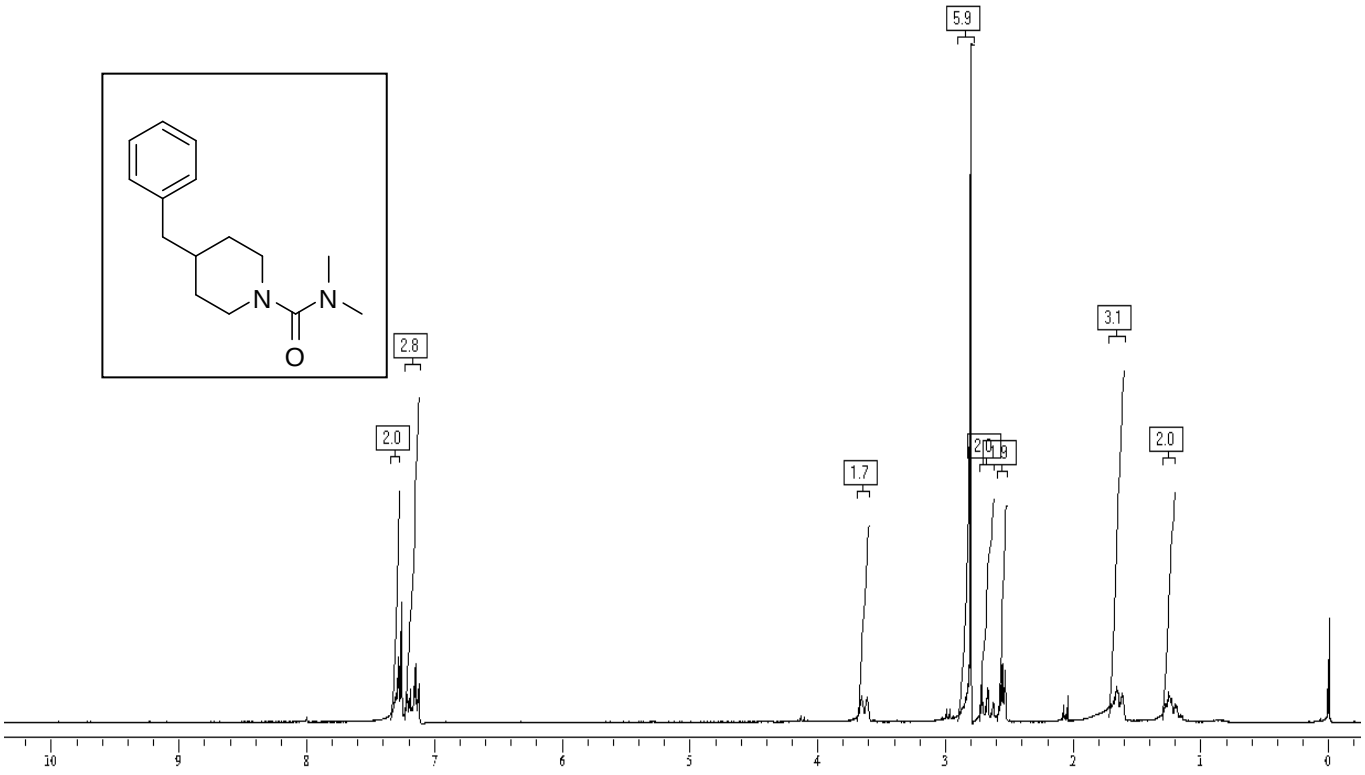


Compound 3b

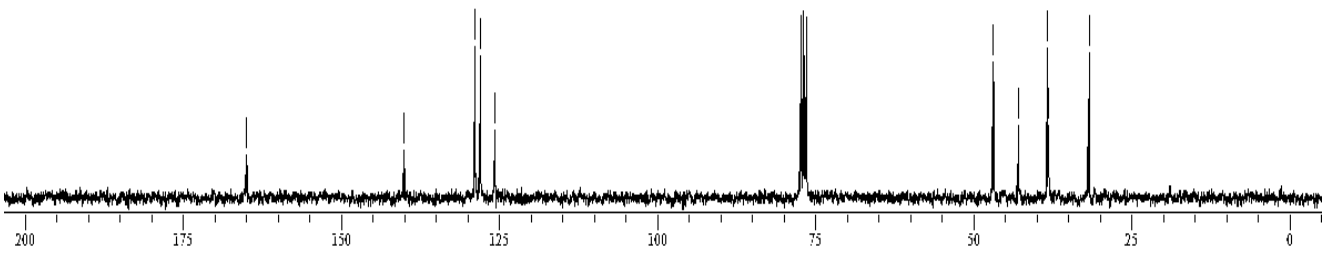


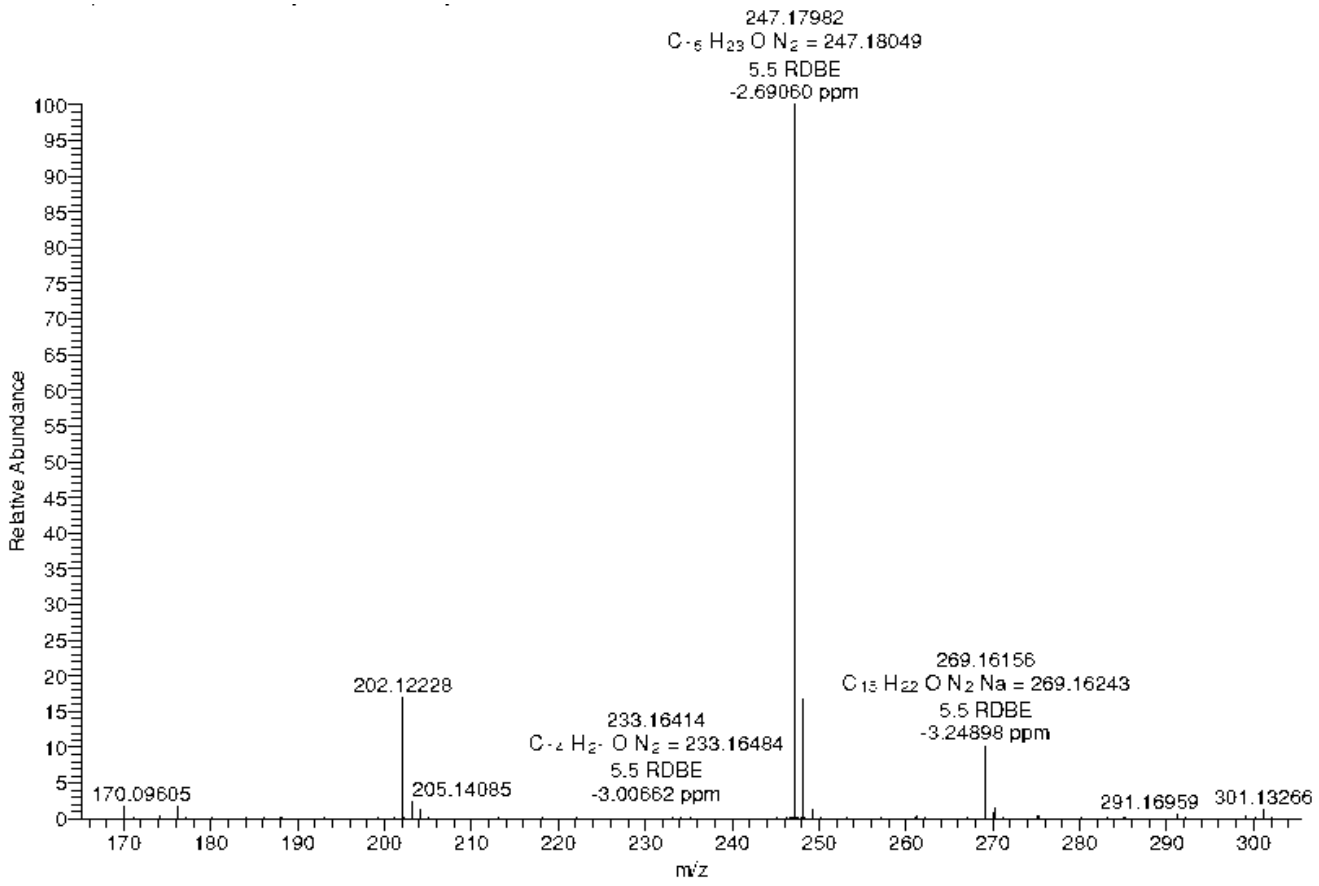

207.14900
C 12 H 19 O N 2 = 207.14919
4.5 RDBE
-0.90609 ppm
229.13074
C 12 H 18 O N 2 Na = 229.13113
4.5 RDBE
-1.73323 ppm
Relative Abundance
m/z
193.13286
199.18127
205.09764
208.15219
209.15565
215.11389
220.14357
226.12254
230.13409
231.13710
237.13818

Compound 3c

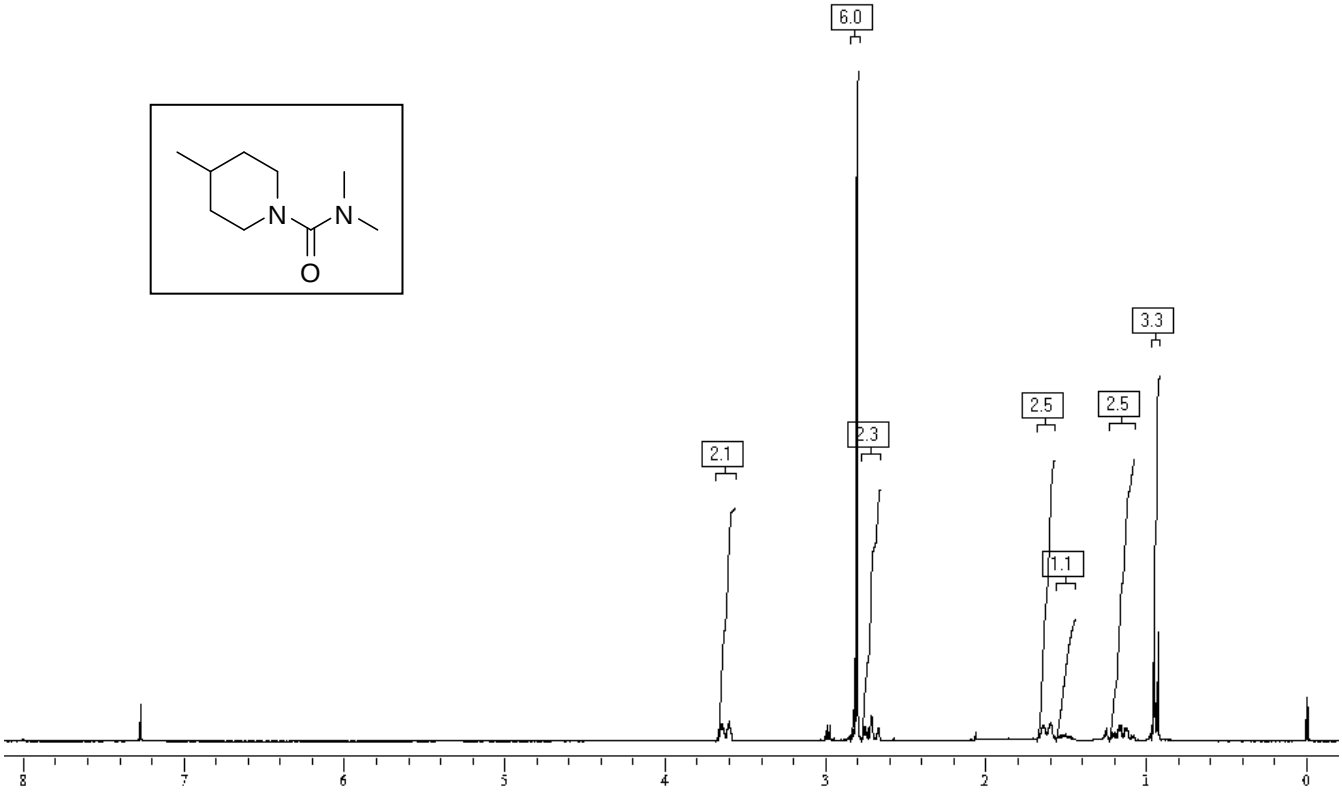

5.9
2.8
2.0
1.7
3.1
2.0
10
9
8
7
6
5
4
3
2
1
0

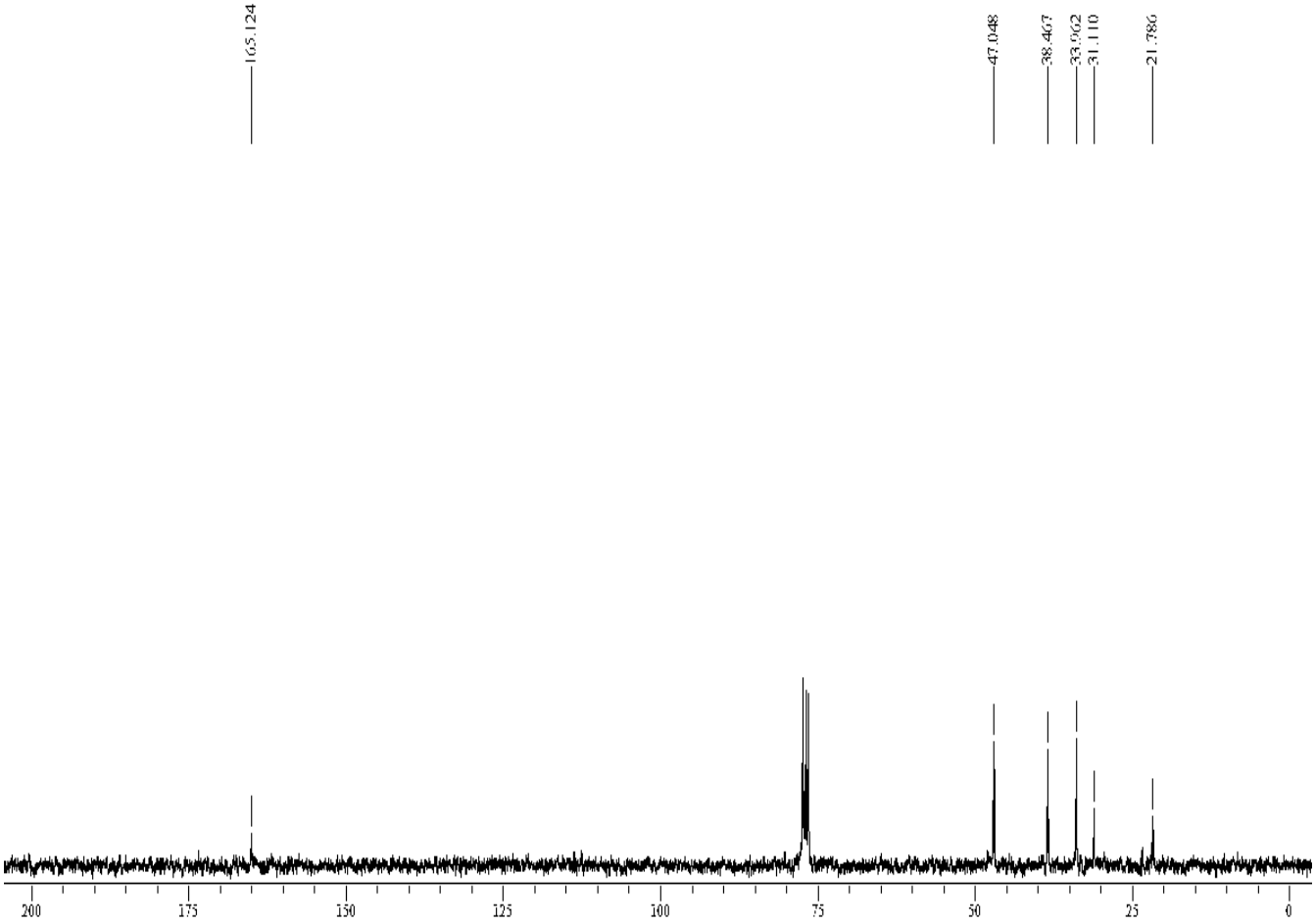

165.025
140.128
128.954
128.086
125.775
46.694
43.073
38.423
38.262
31.883

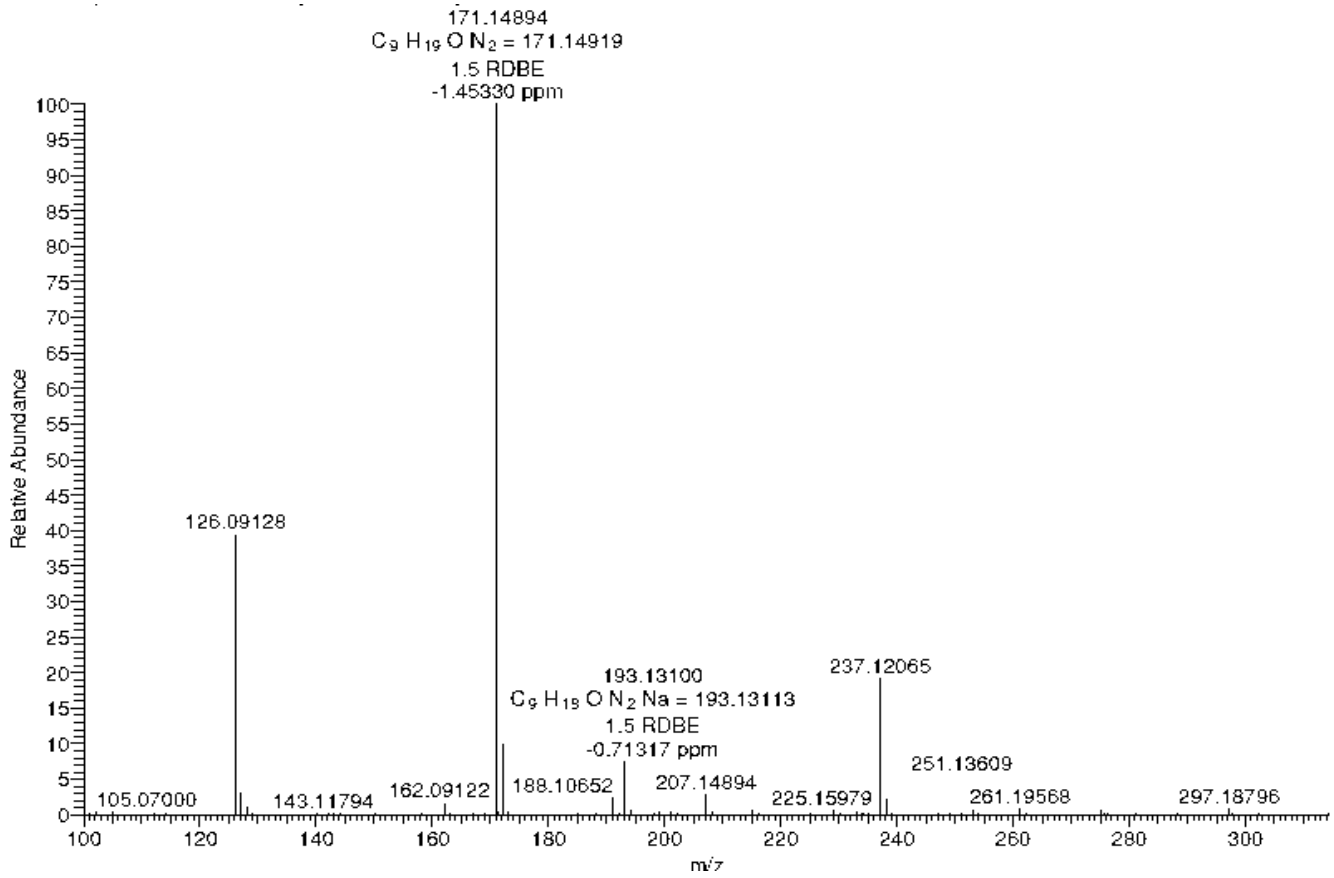

200
175
150
125
100
75
50
25
0



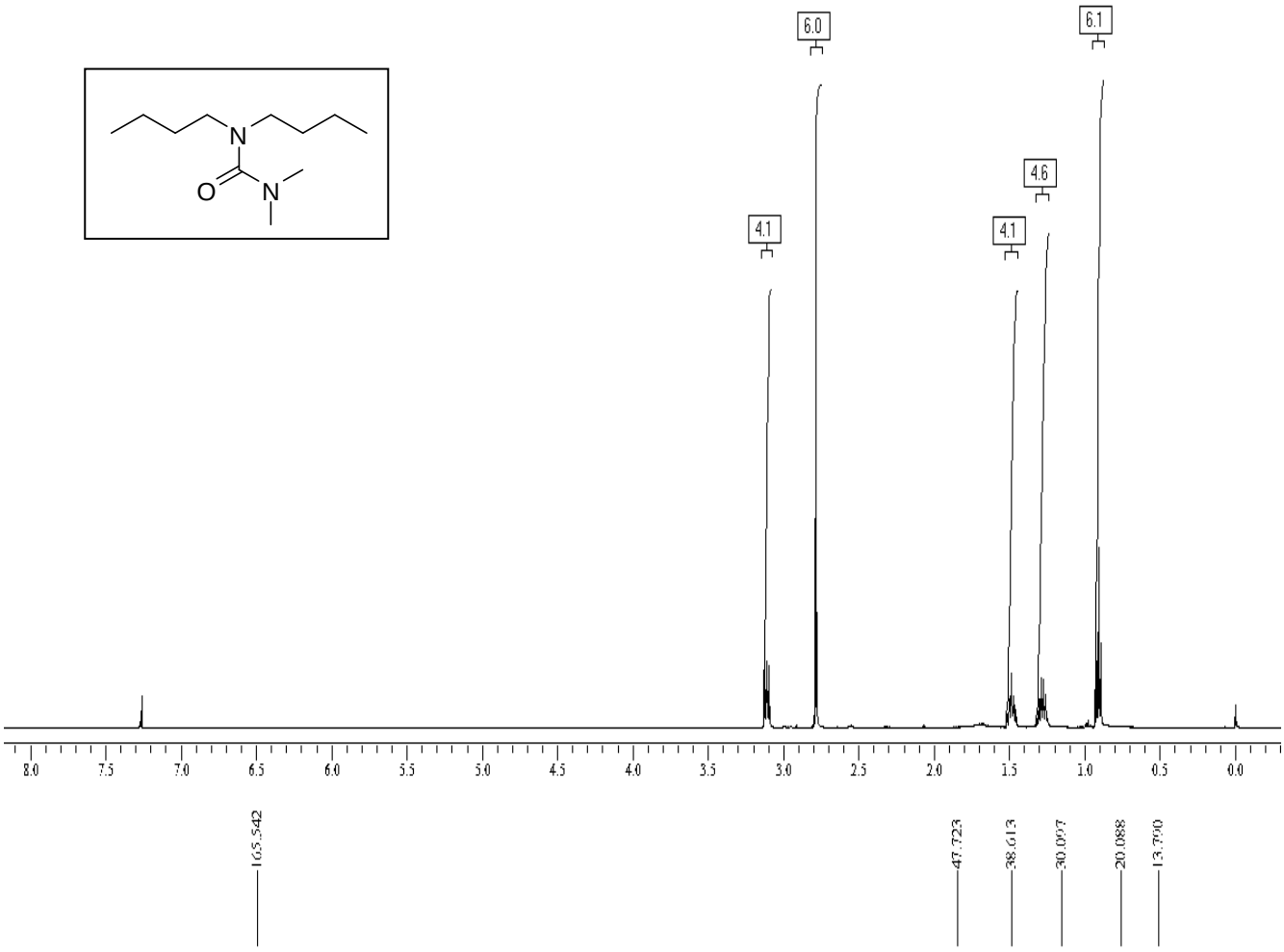
Compound 3d

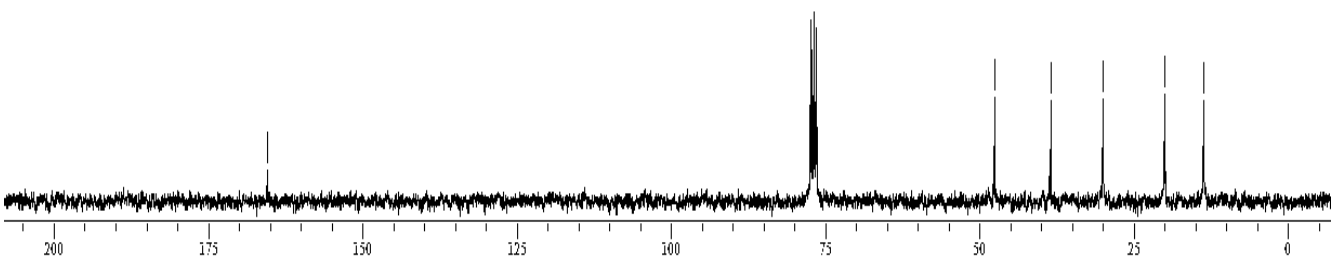


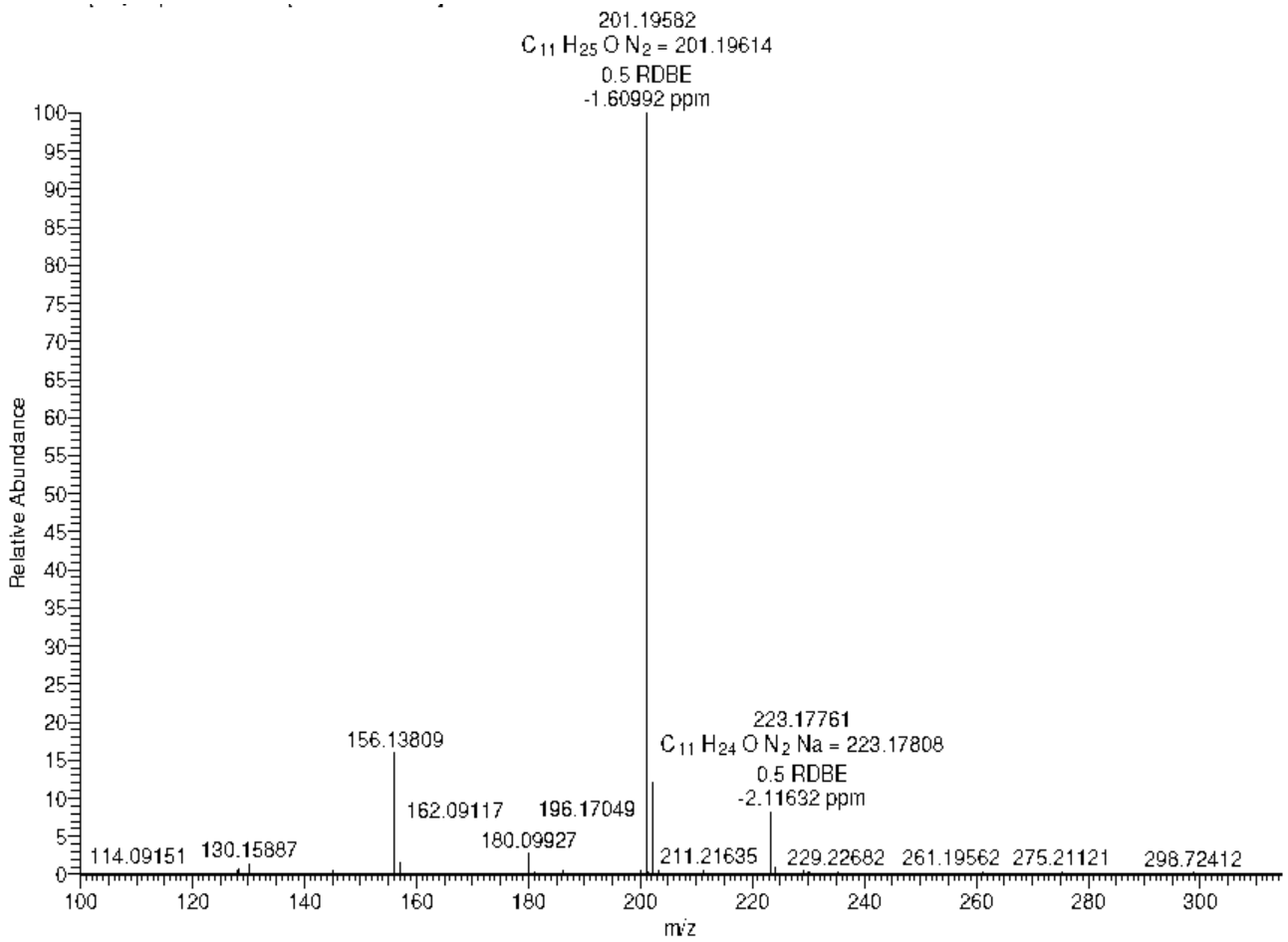




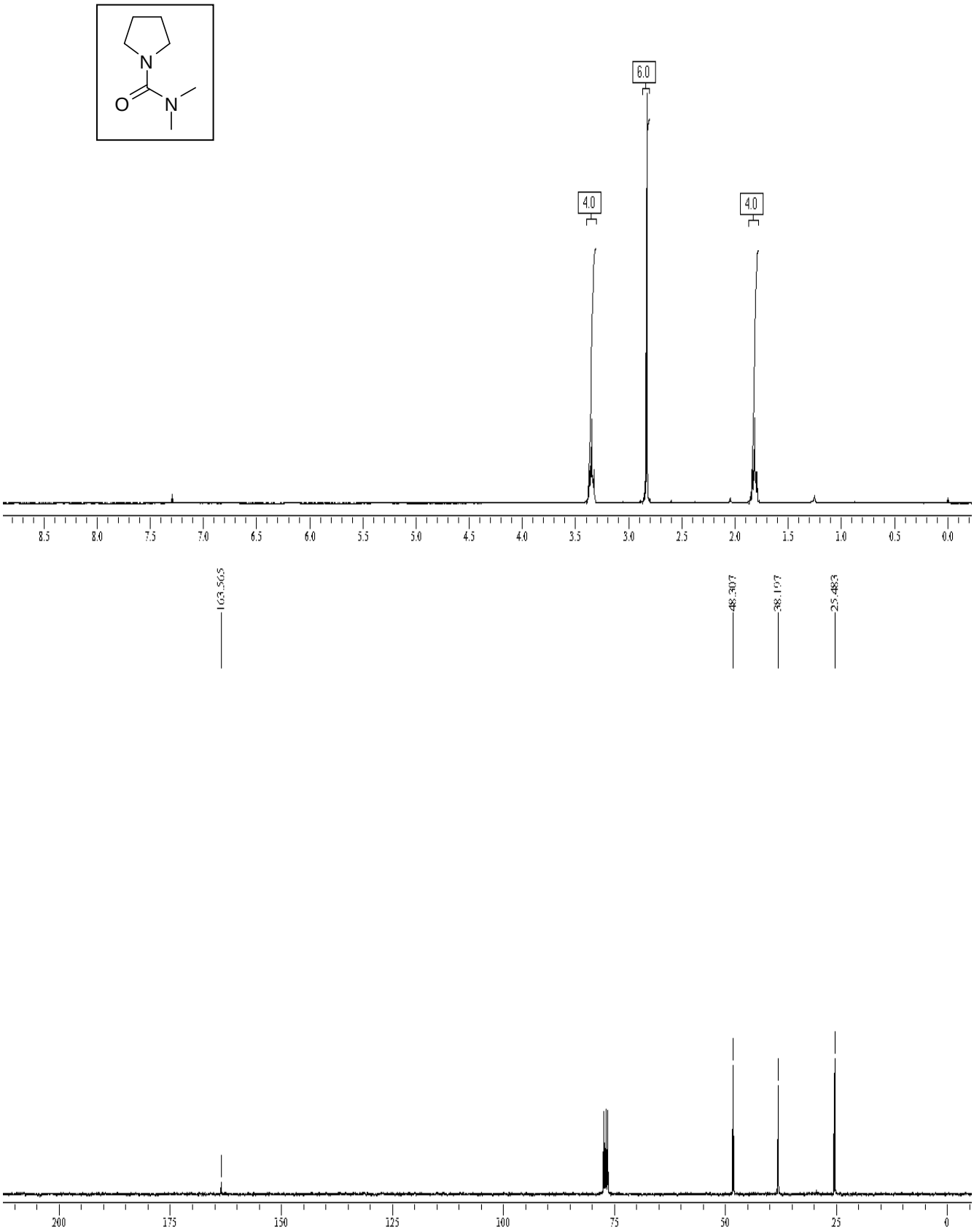
Compound 3e

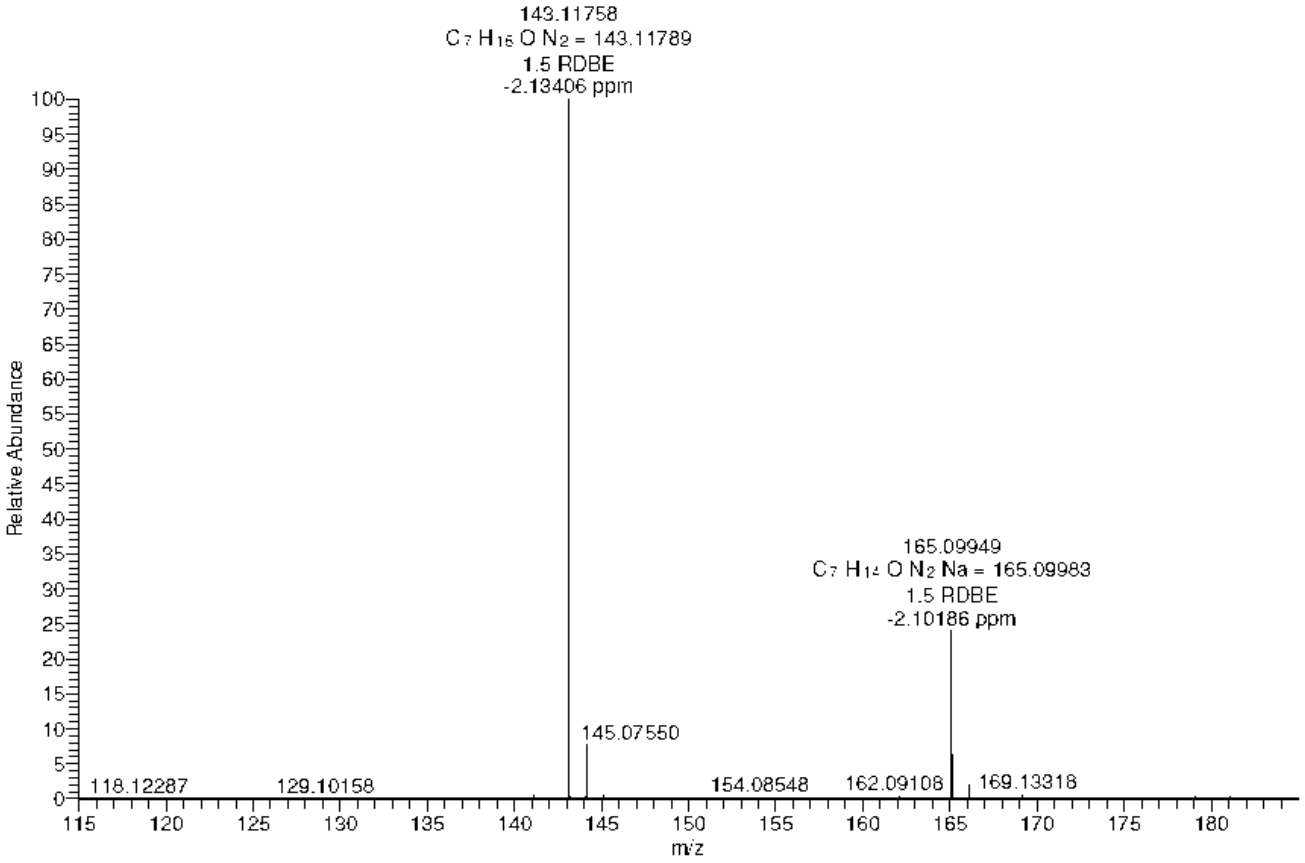




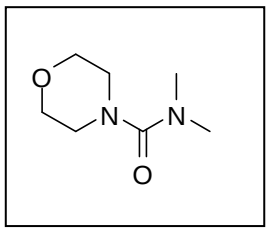


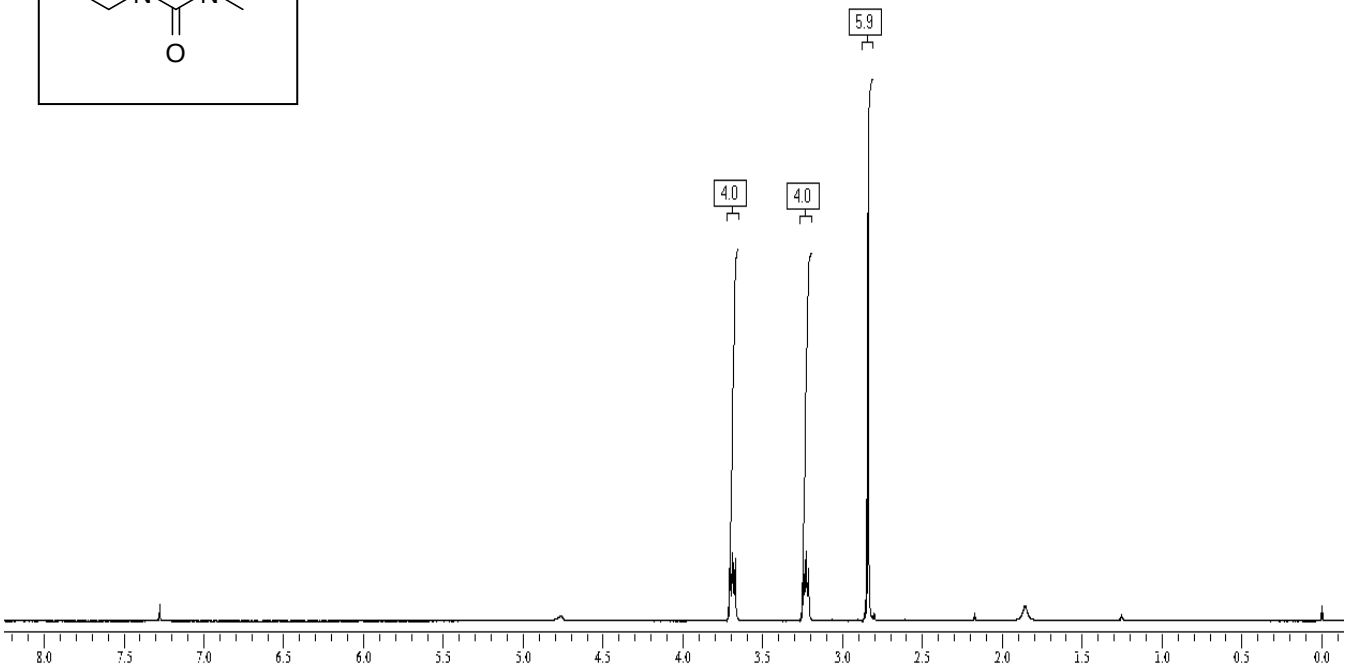
Compound 3f

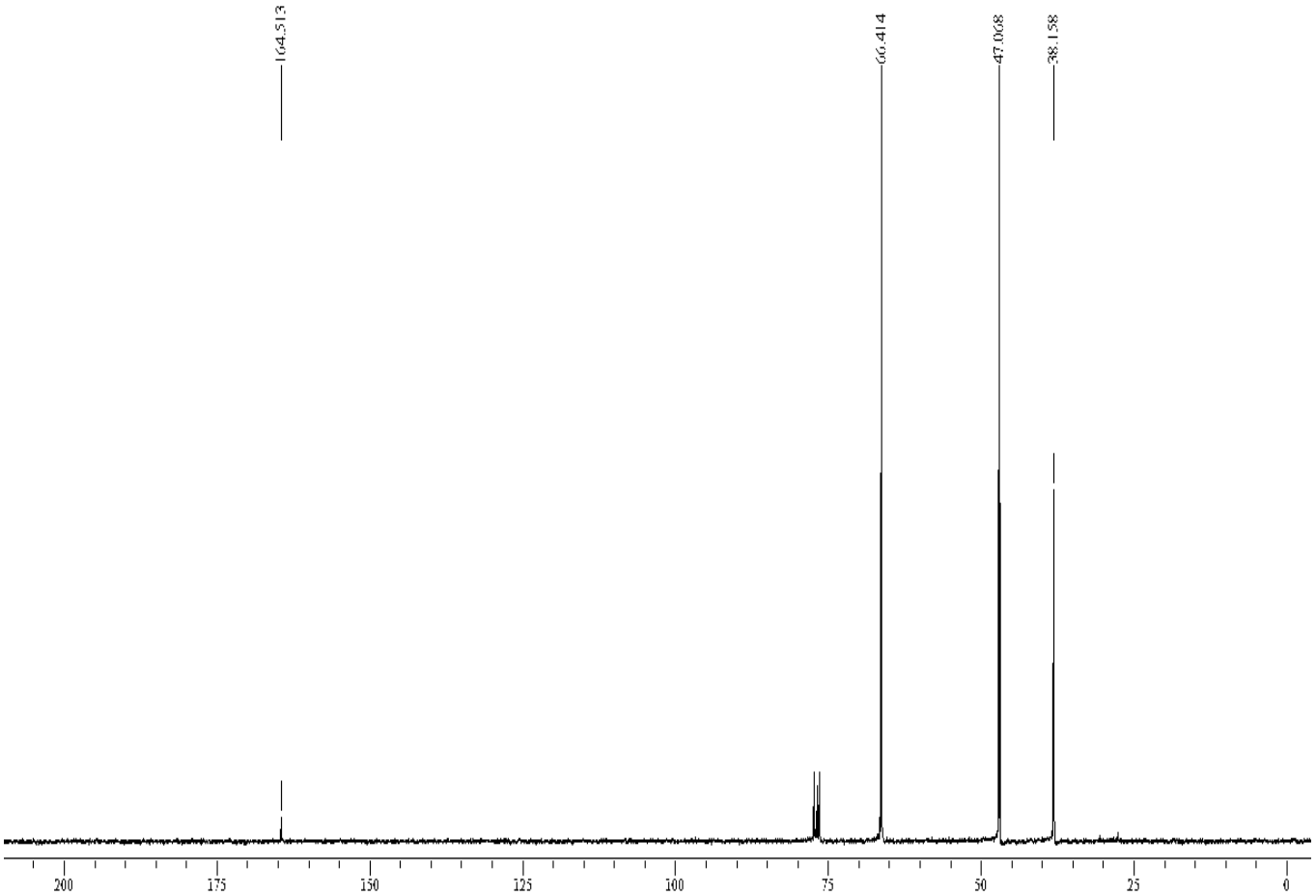


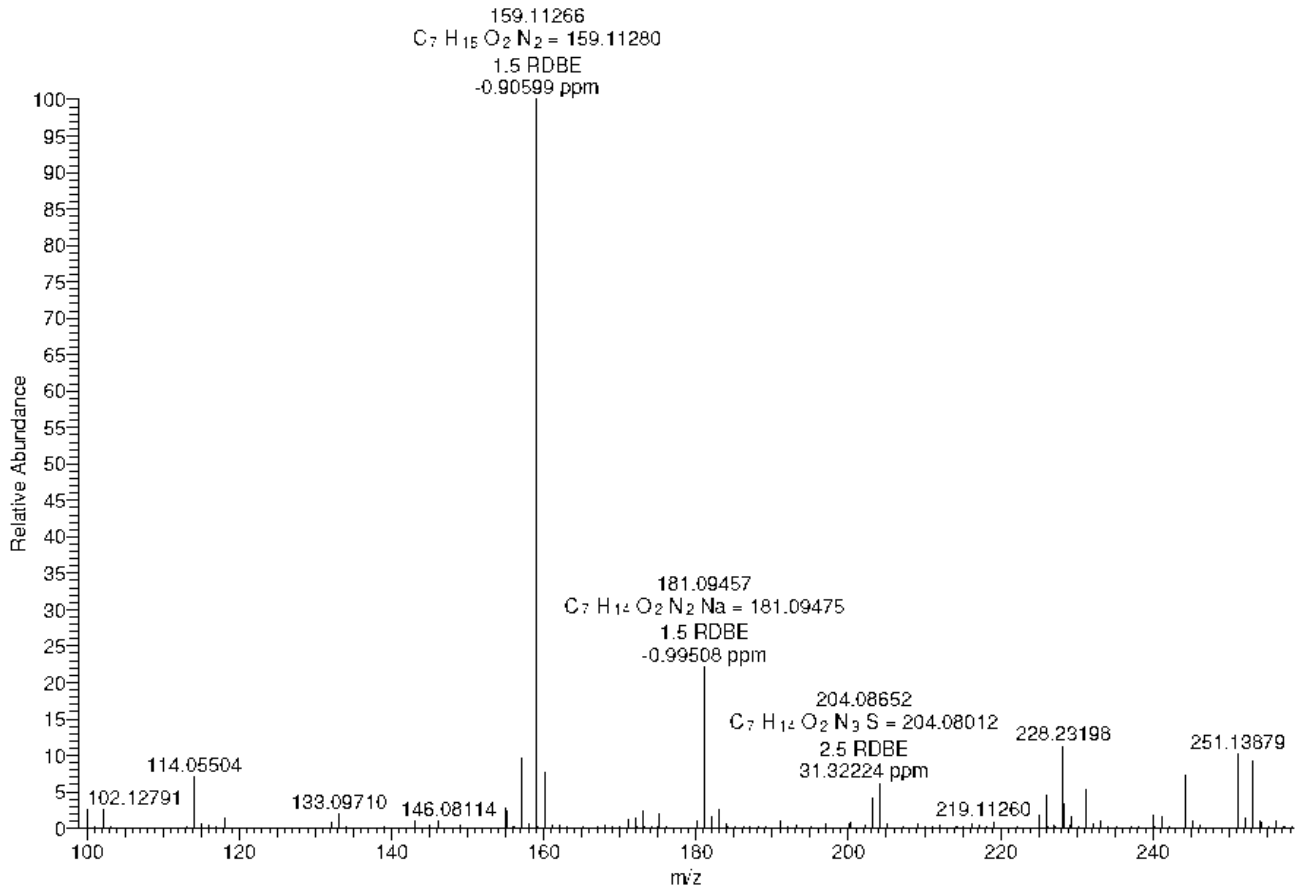


Compound 3g

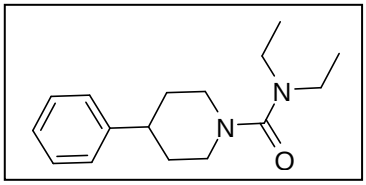


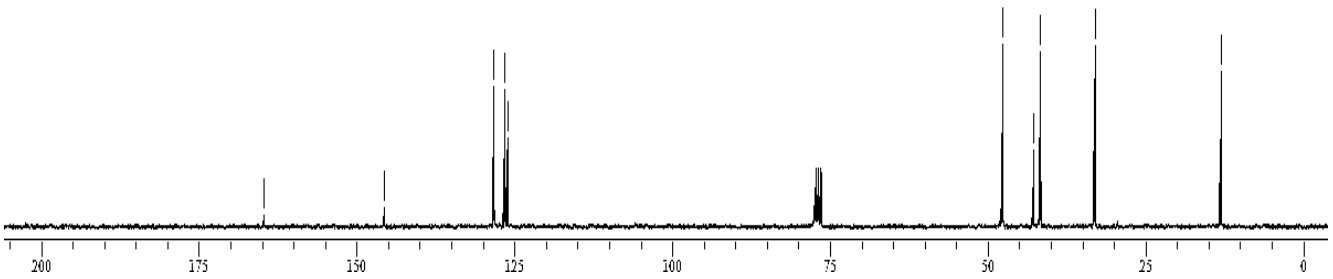


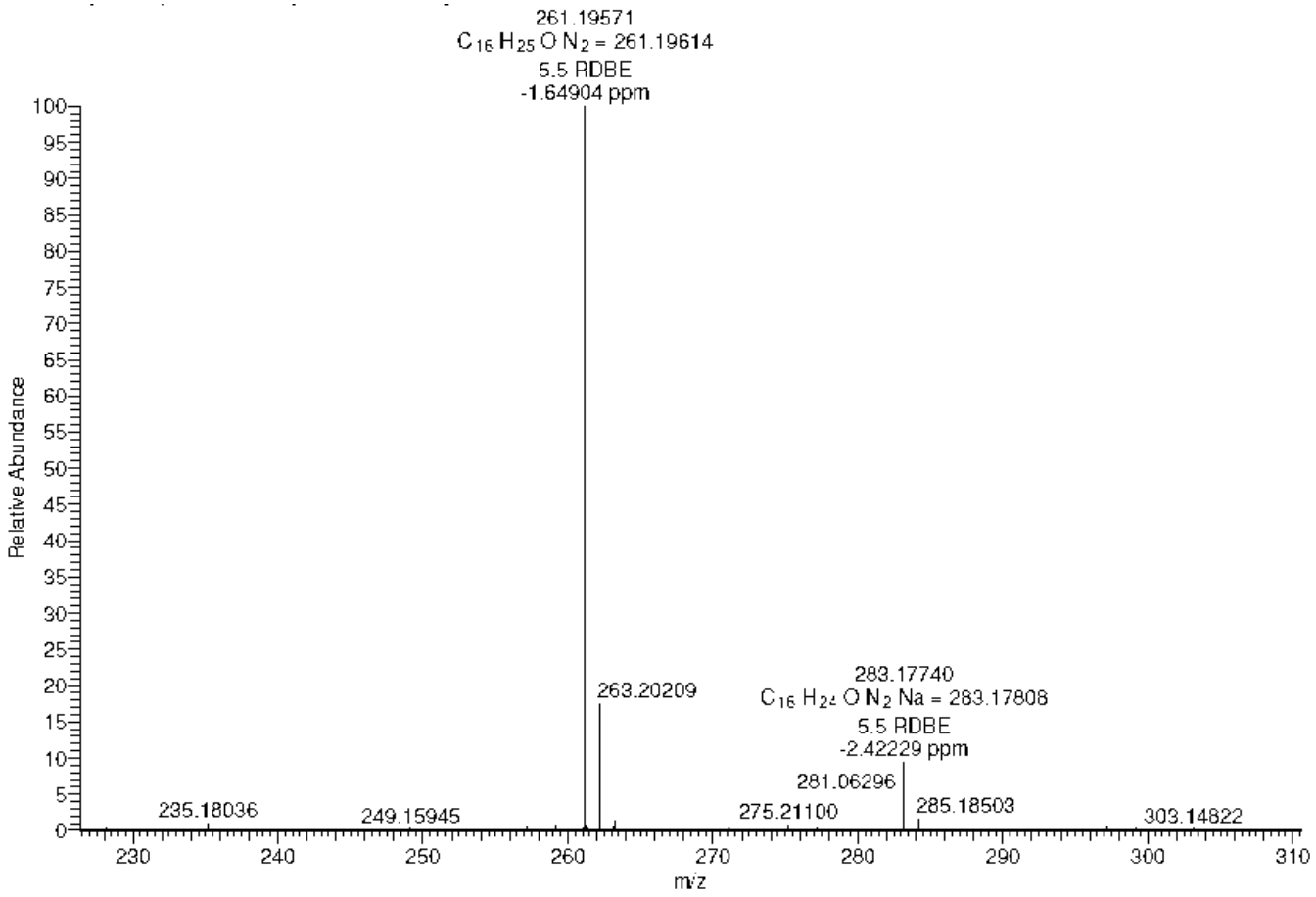



159.11266
C7 H15 O2 N2 = 159.11280
1.5 RDBE
-0.90599 ppm
181.09457
C7 H14 O2 N2 Na = 181.09475
1.5 RDBE
-0.99508 ppm
204.08652
C7 H14 O2 N3 S = 204.08012
2.5 RDBE
31.32224 ppm
114.05504
102.12791
133.09710
146.08114
219.11260
228.23198
251.13879
Relative Abundance
m/z

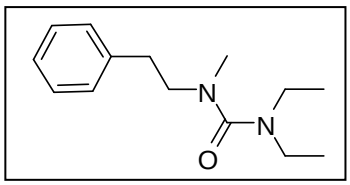
Compound 3h

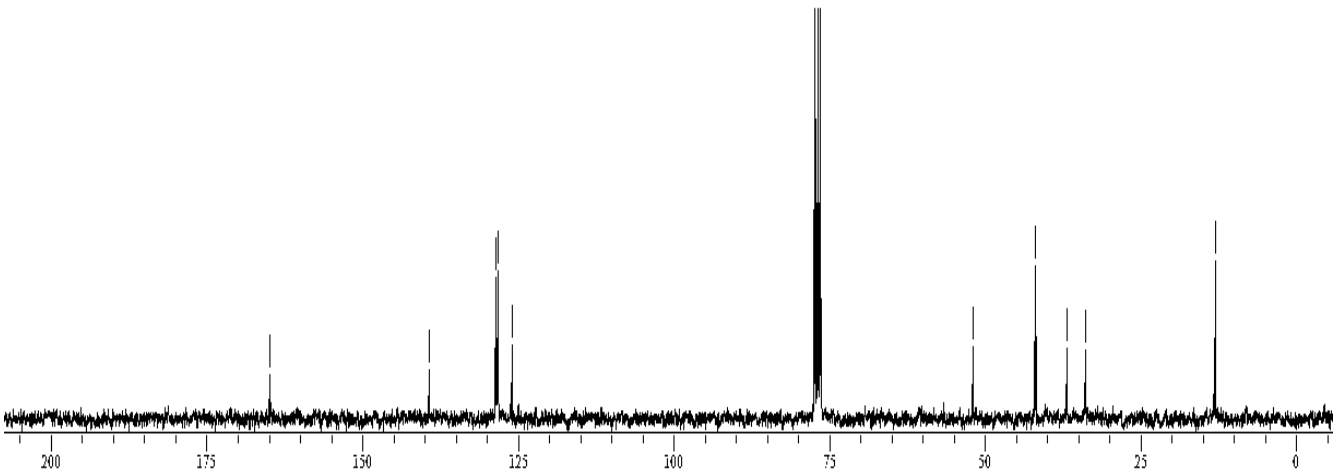


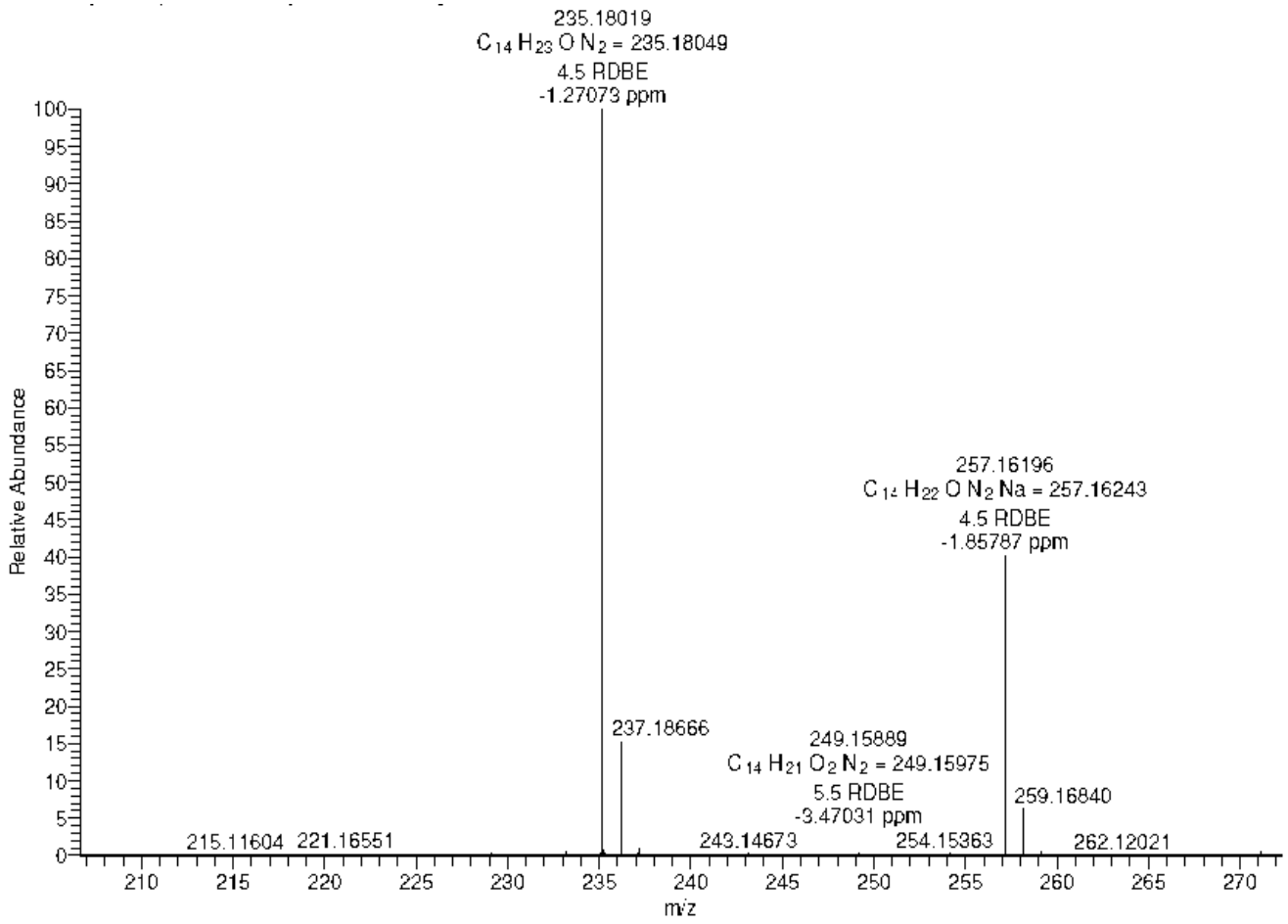




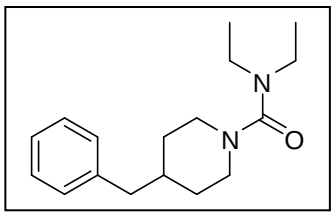
Compound 3i

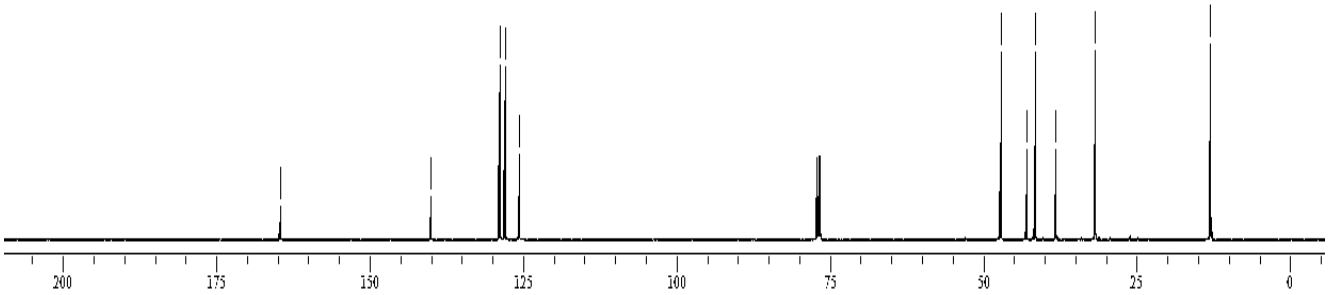


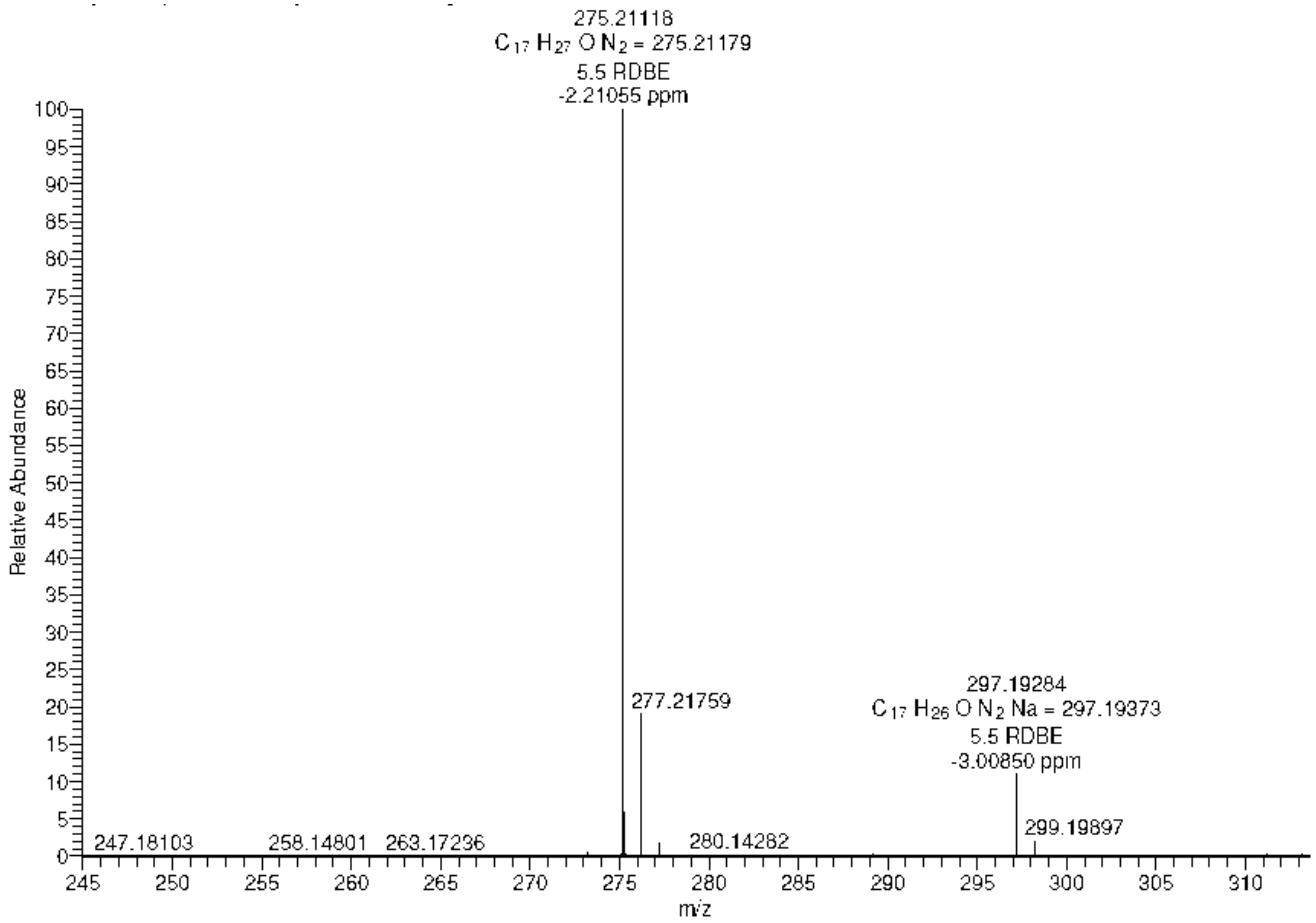



235.18019
C14 H23 O N2 = 235.18049
4.5 RDBE
-1.27073 ppm
257.16196
C14 H22 O N2 Na = 257.16243
4.5 RDBE
-1.85787 ppm
237.18666
249.15889
C14 H21 O2 N2 = 249.15975
5.5 RDBE
-3.47031 ppm
259.16840
215.11604
221.16551
243.14673
254.15363
262.12021
Relative Abundance
m/z

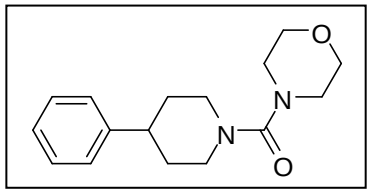
Compound 3j

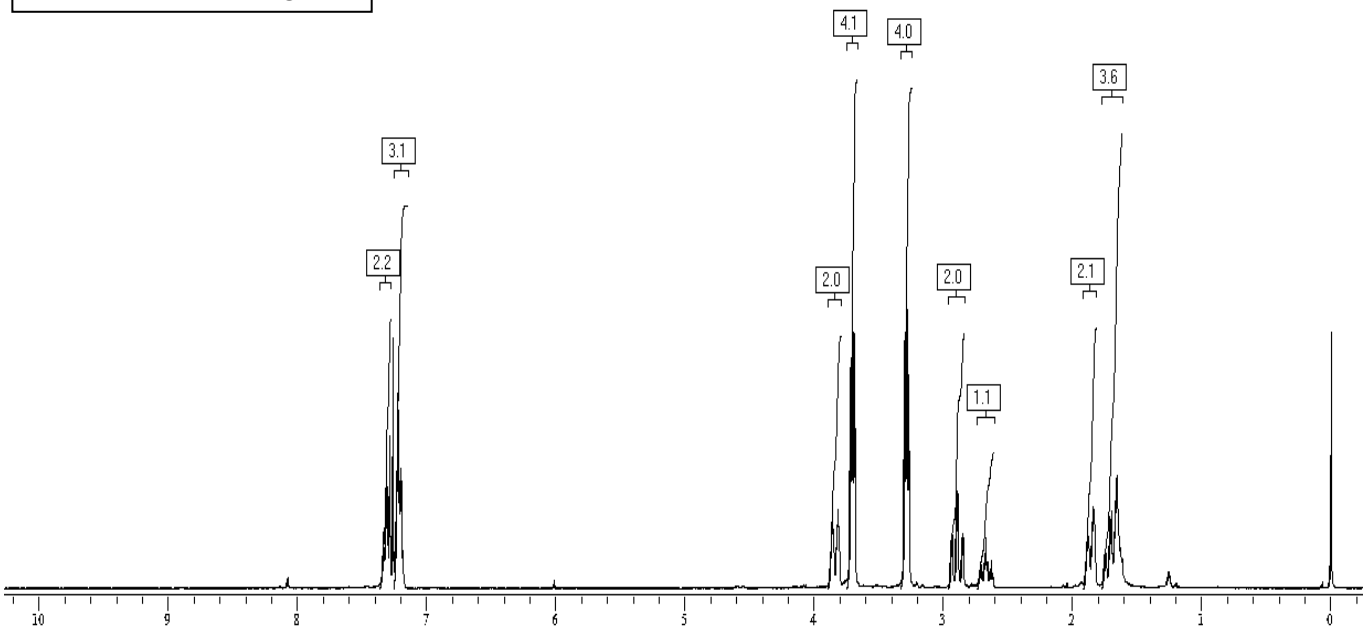


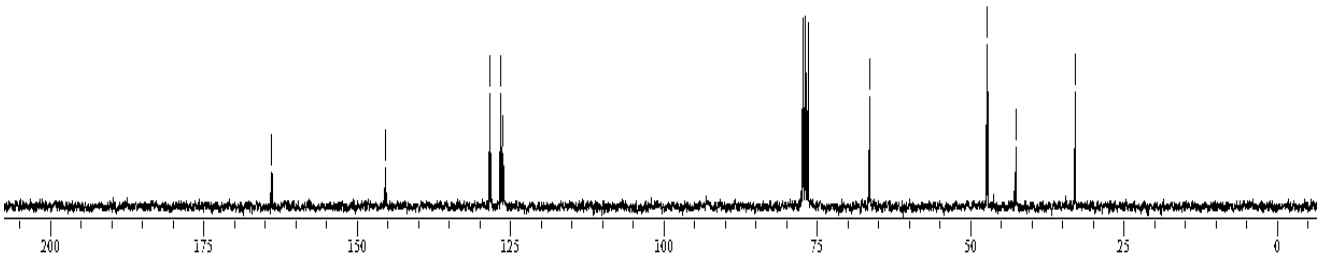


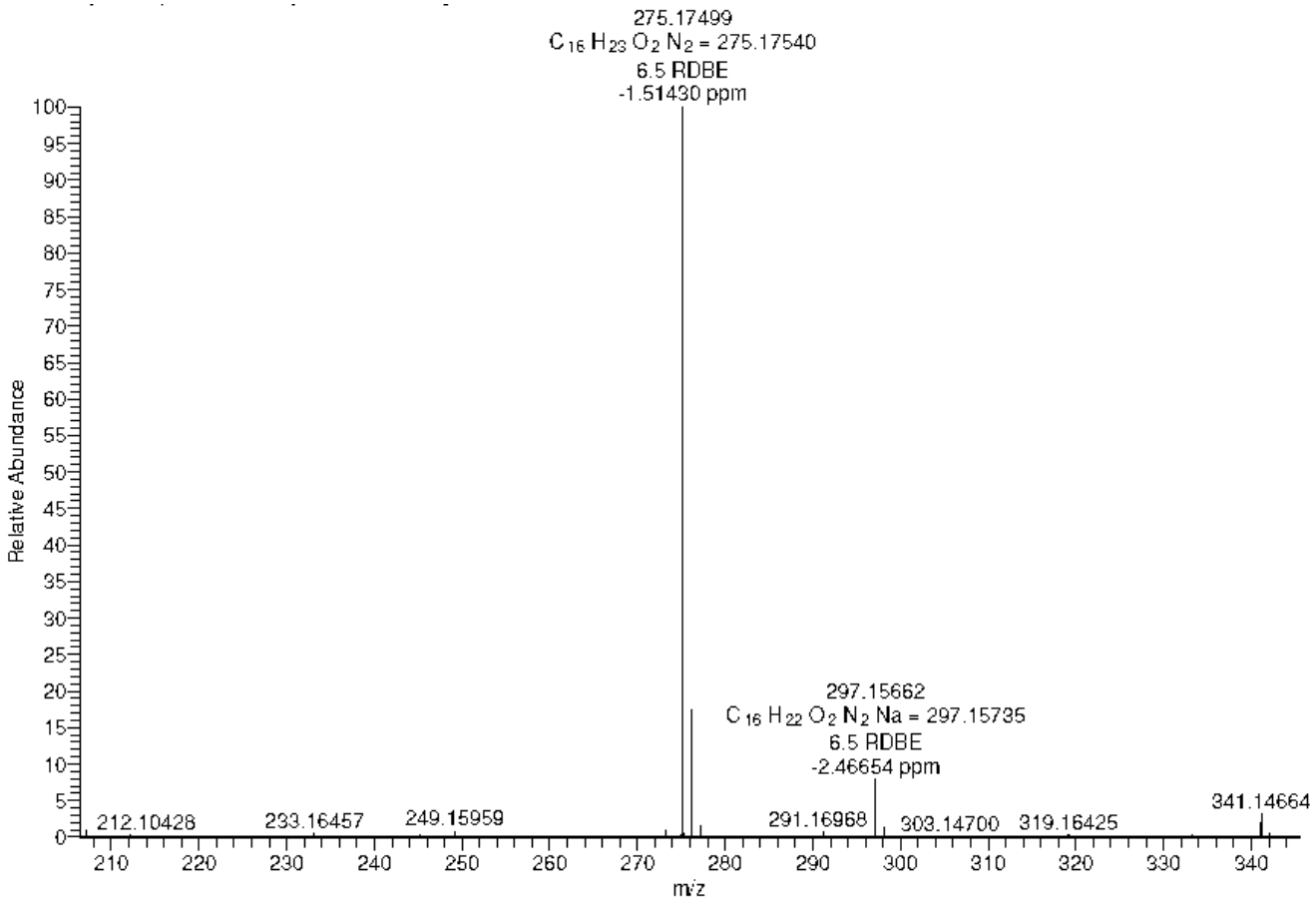


Compound 3k

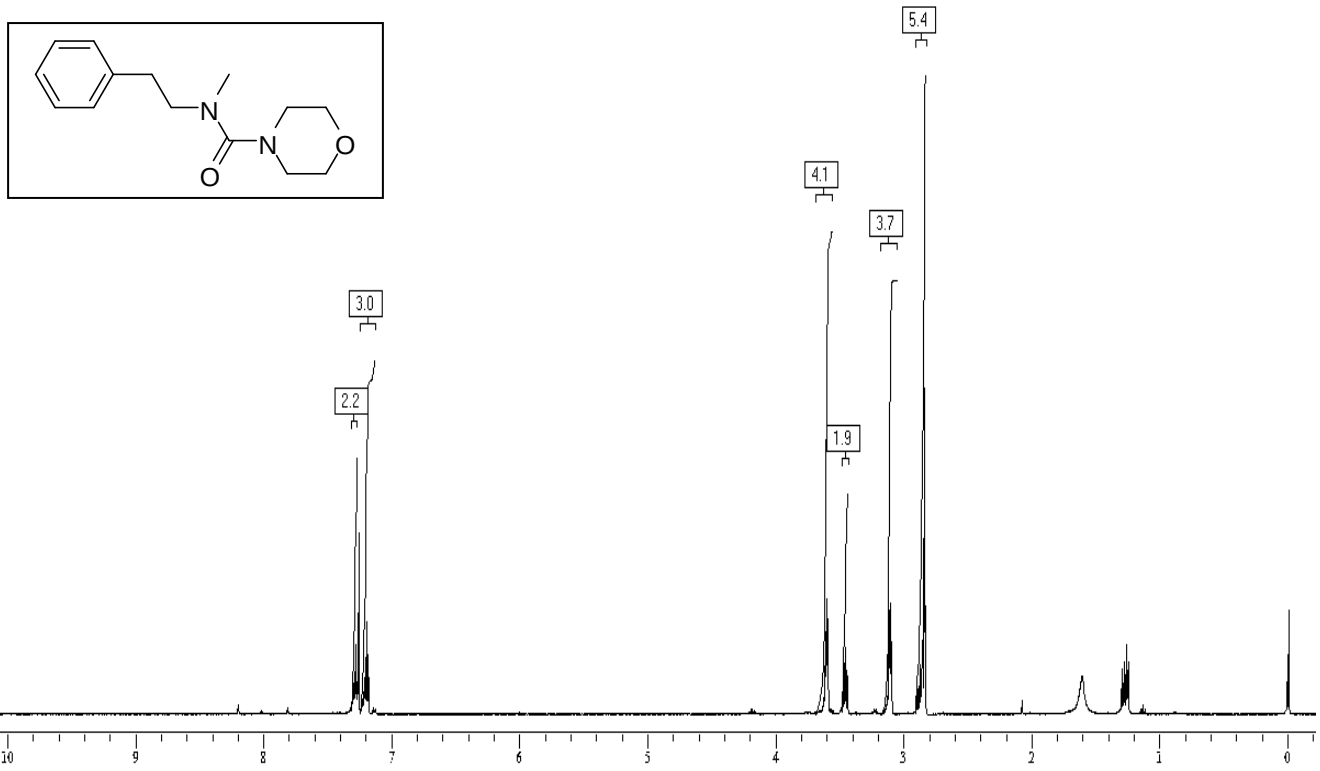


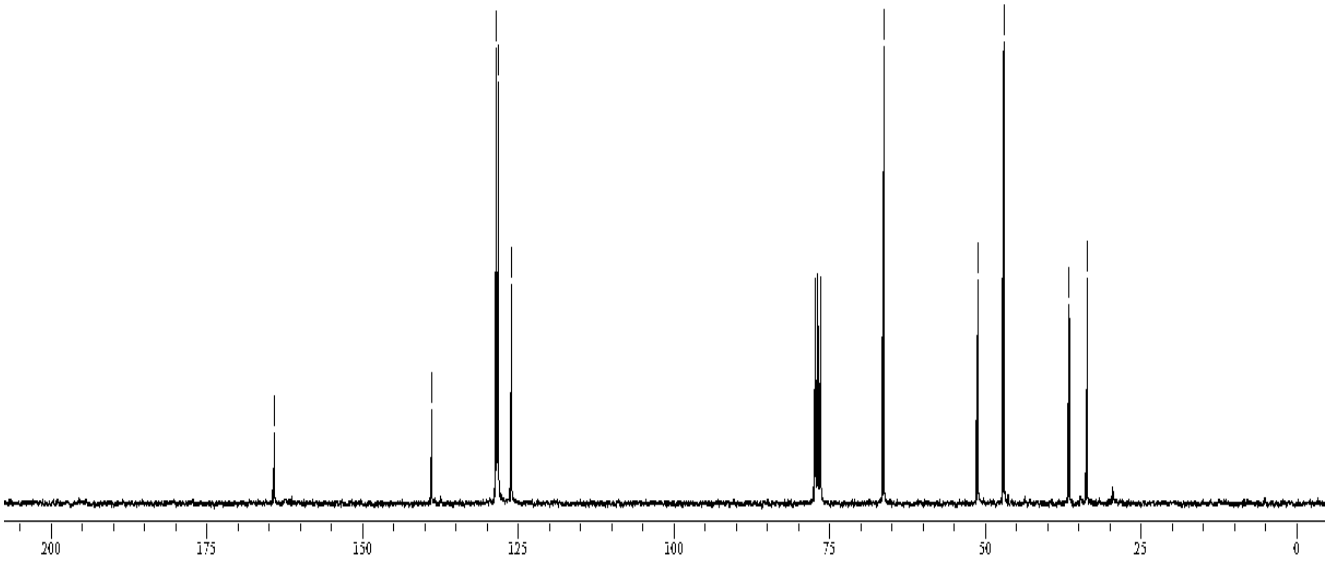


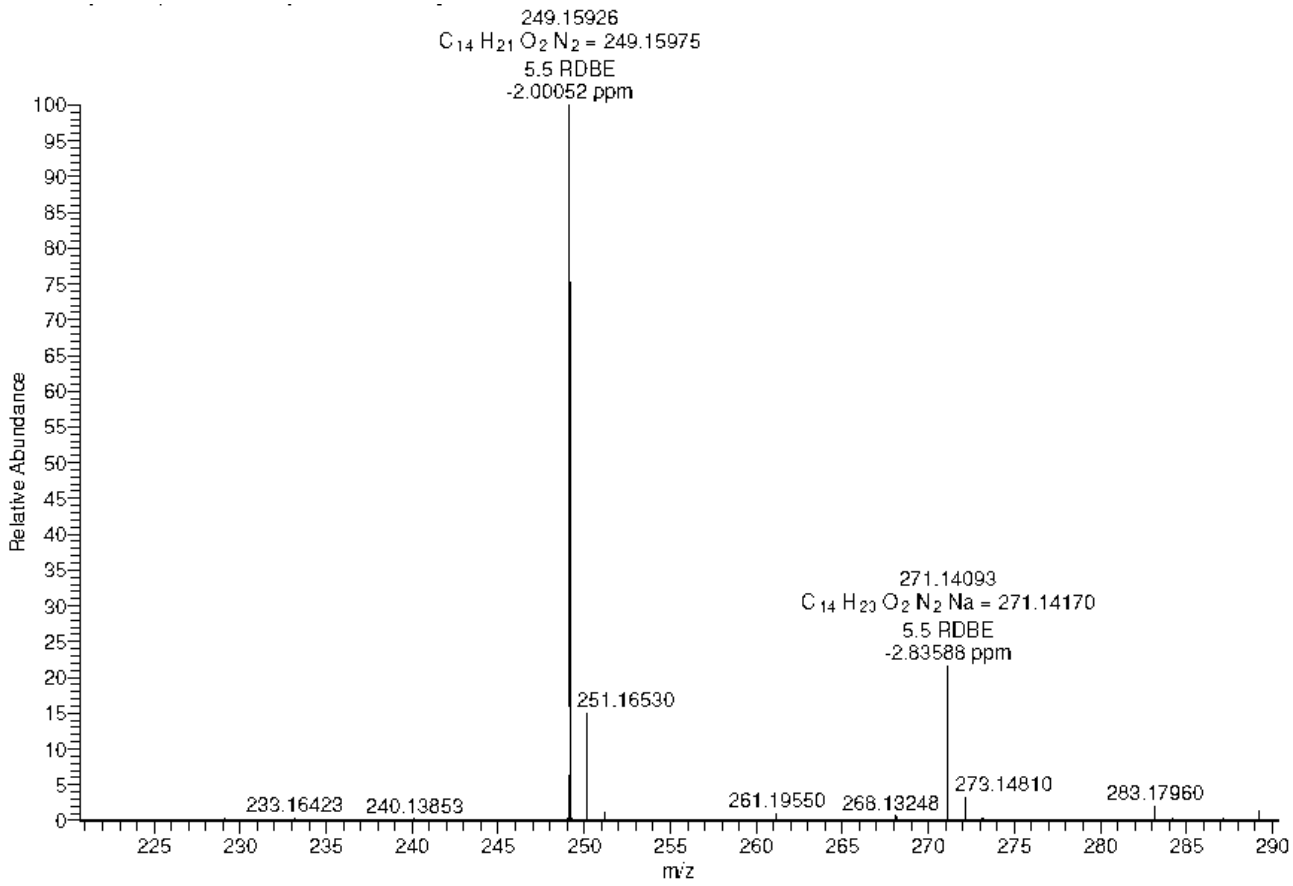



275.17499
C16 H23 O2 N2 = 275.17540
6.5 RDBE
-1.51430 ppm
297.15662
C16 H22 O2 N2 Na = 297.15735
6.5 RDBE
-2.46654 ppm
212.10428
233.16457
249.15959
291.16968
303.14700
319.16425
341.14664
Relative Abundance
m/z

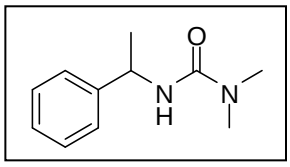
Compound 3l

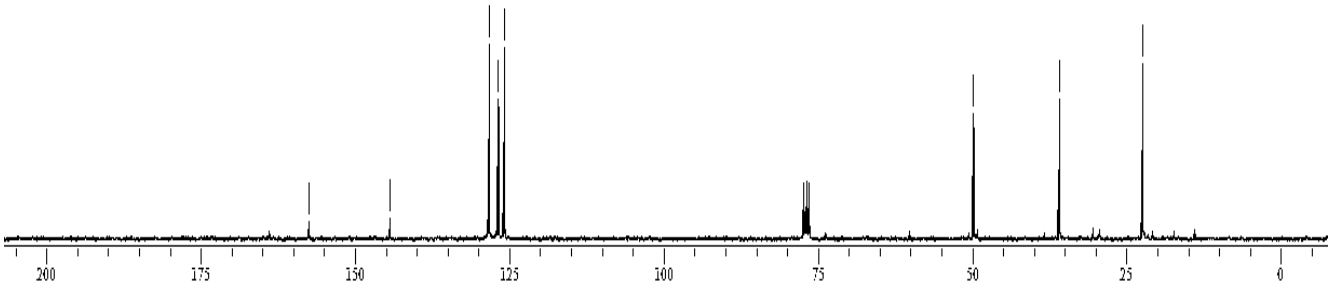


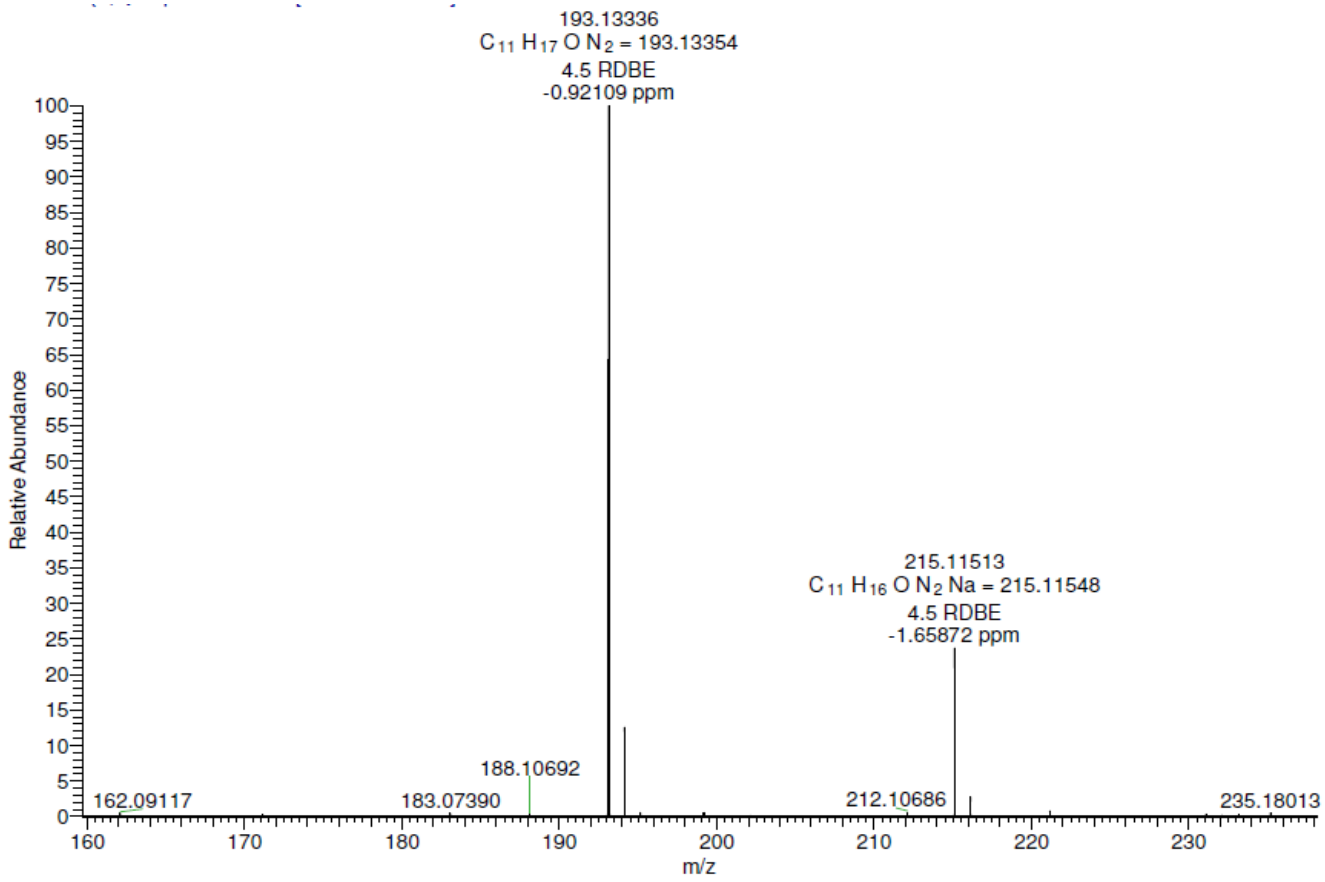




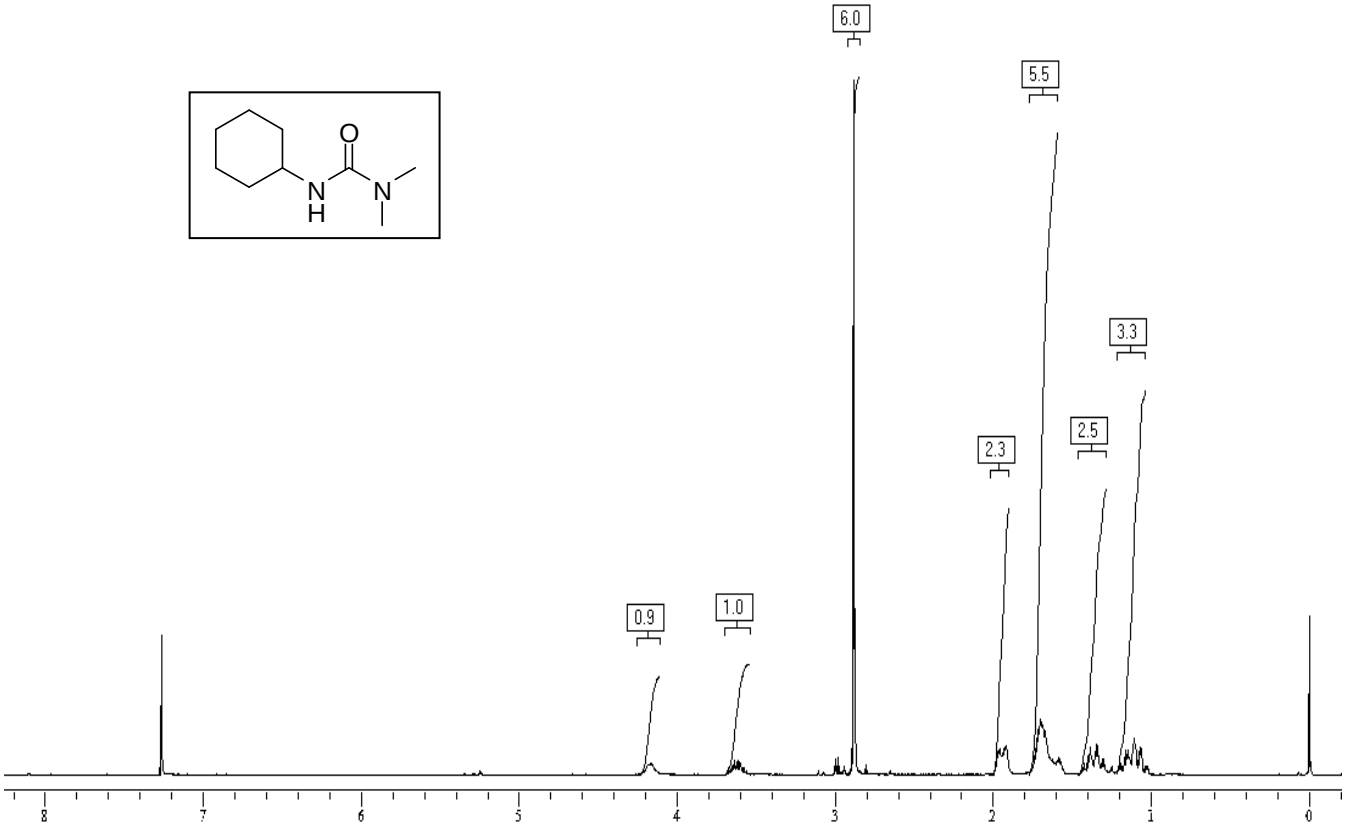
Compound 3m

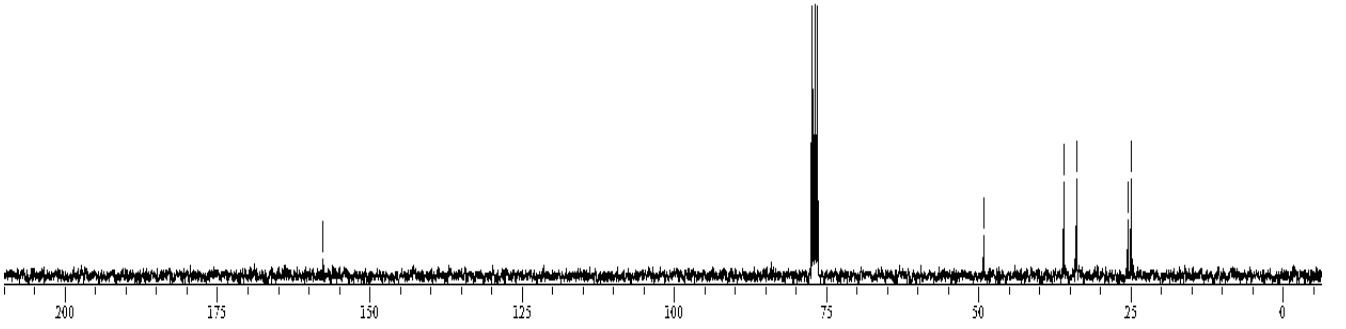


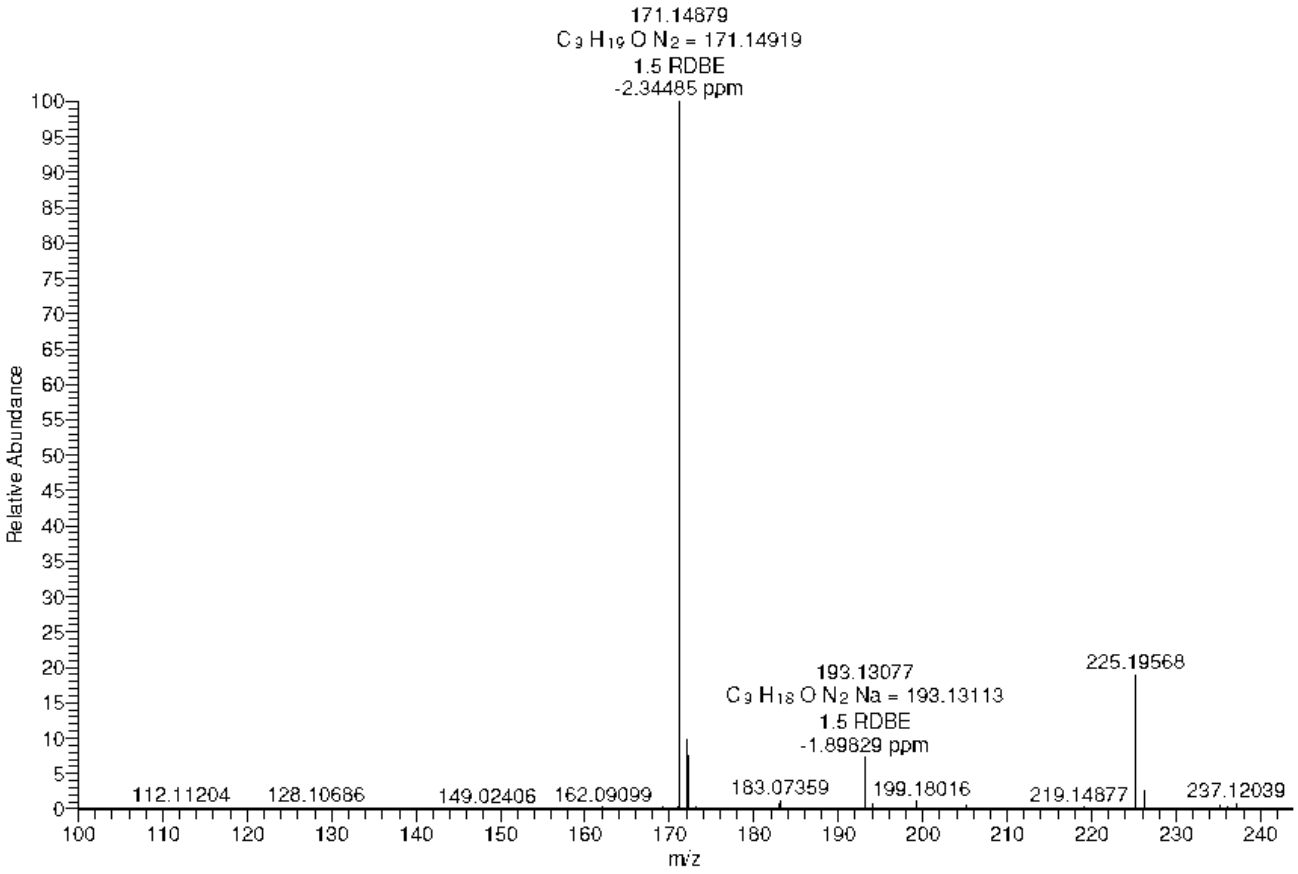




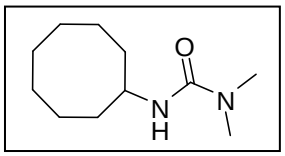
Compound 3n

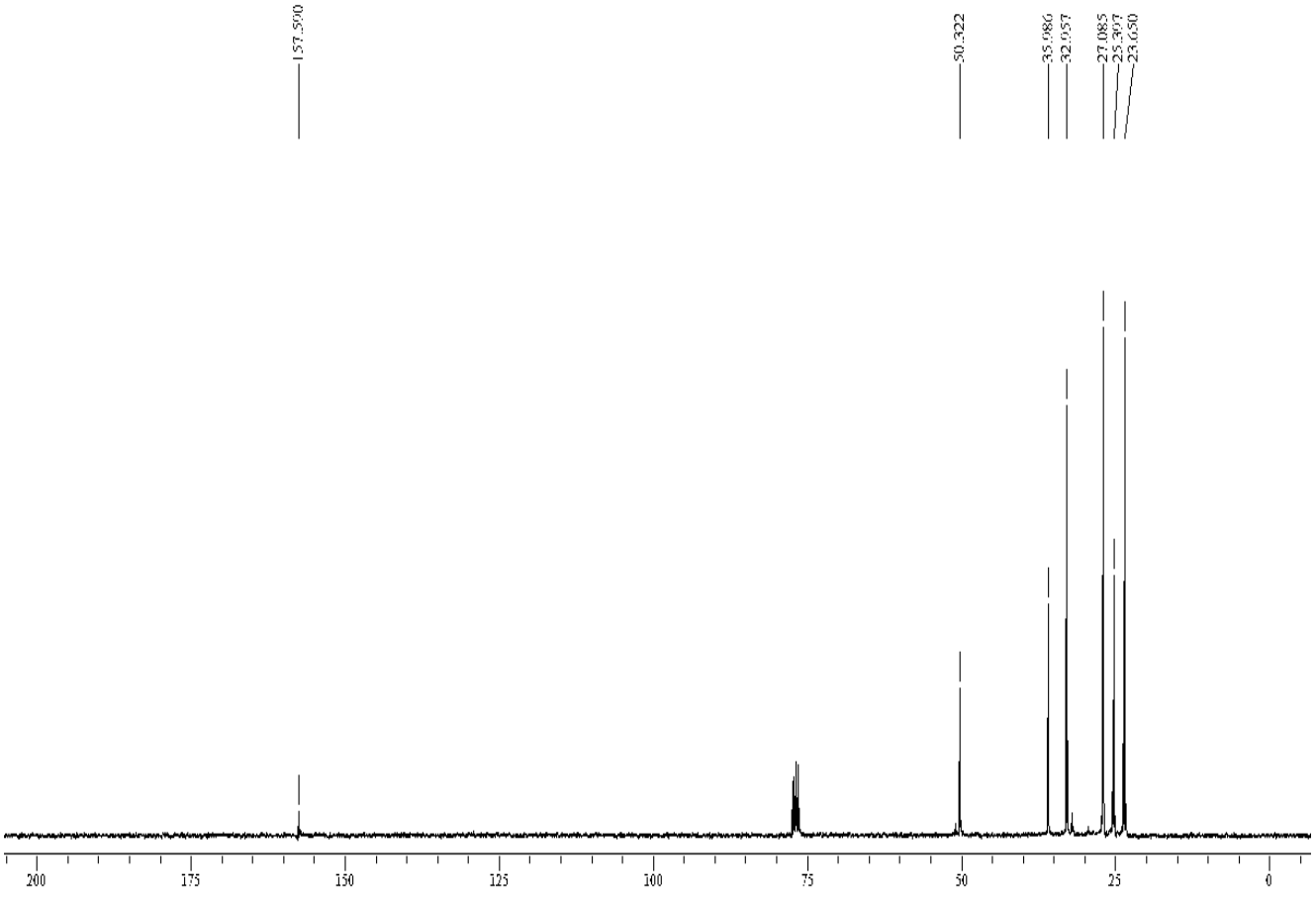


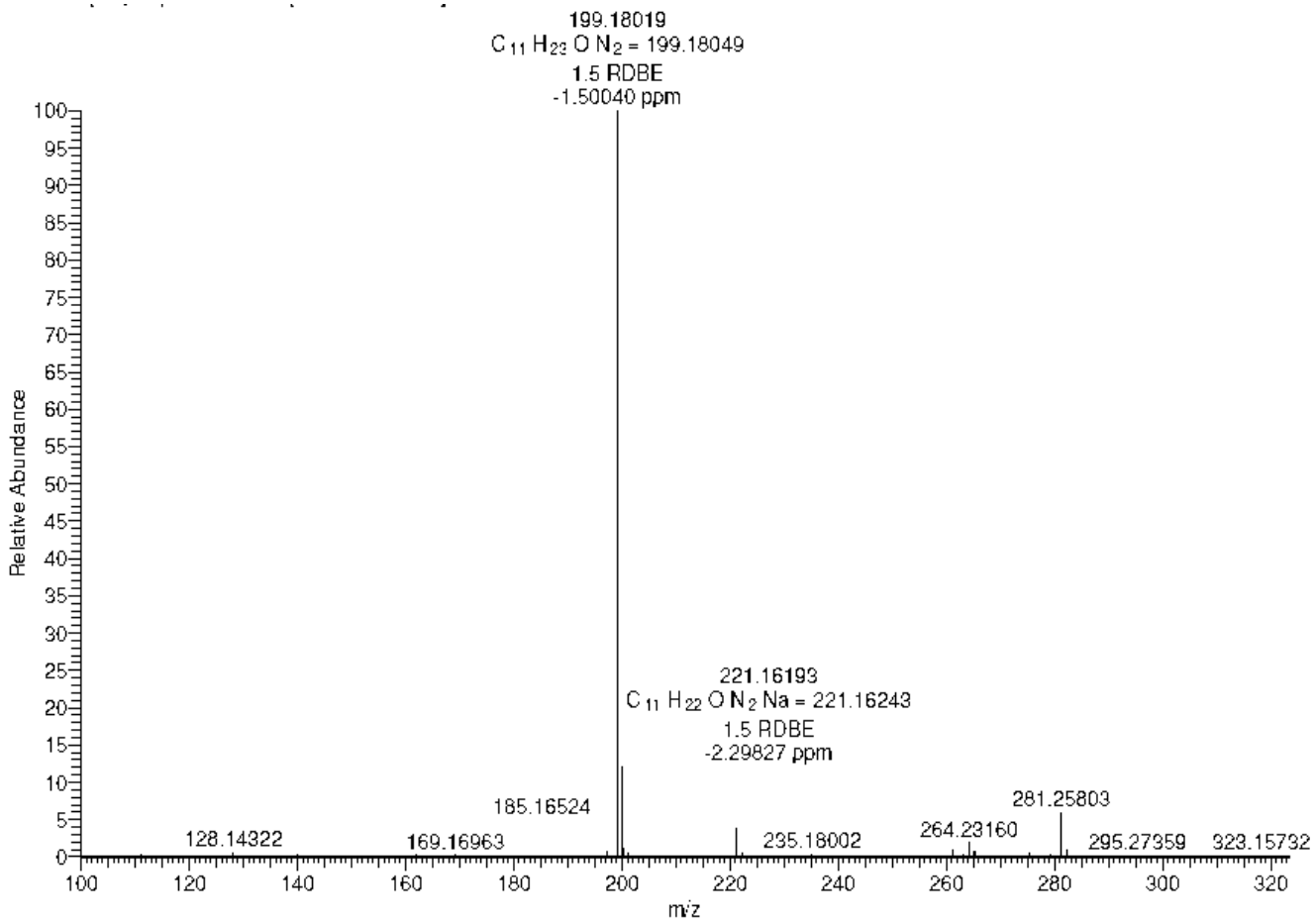




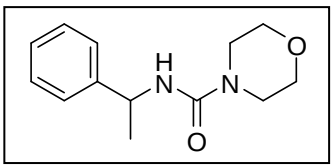
Compound 3o

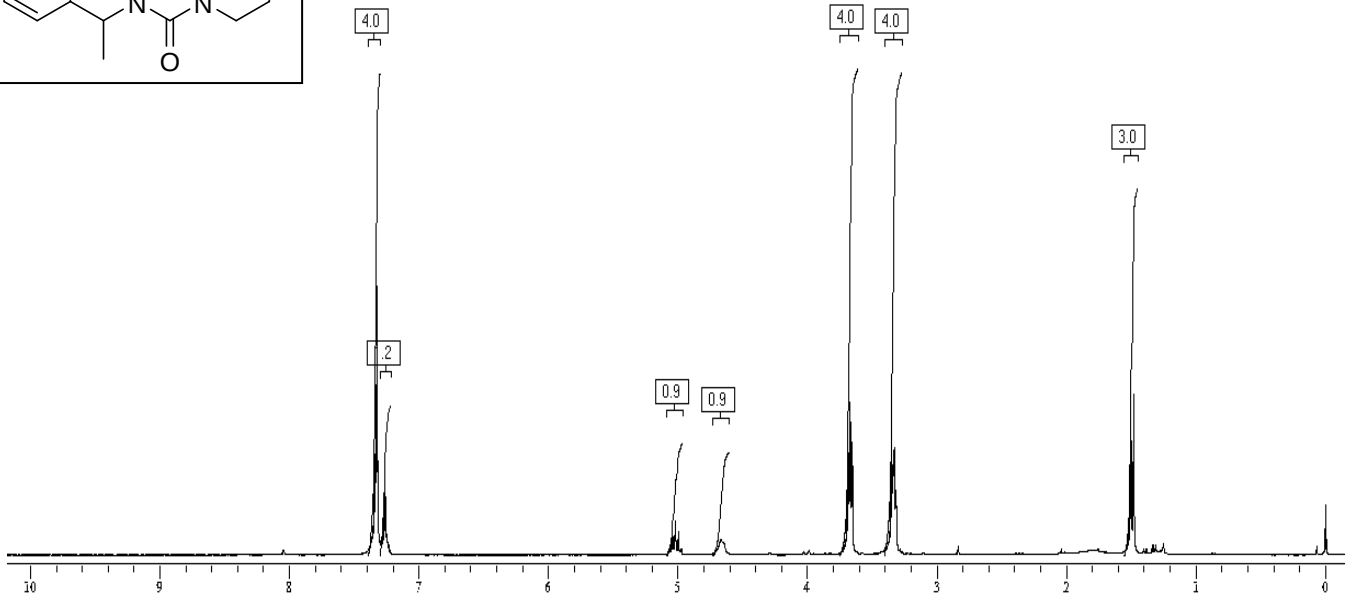


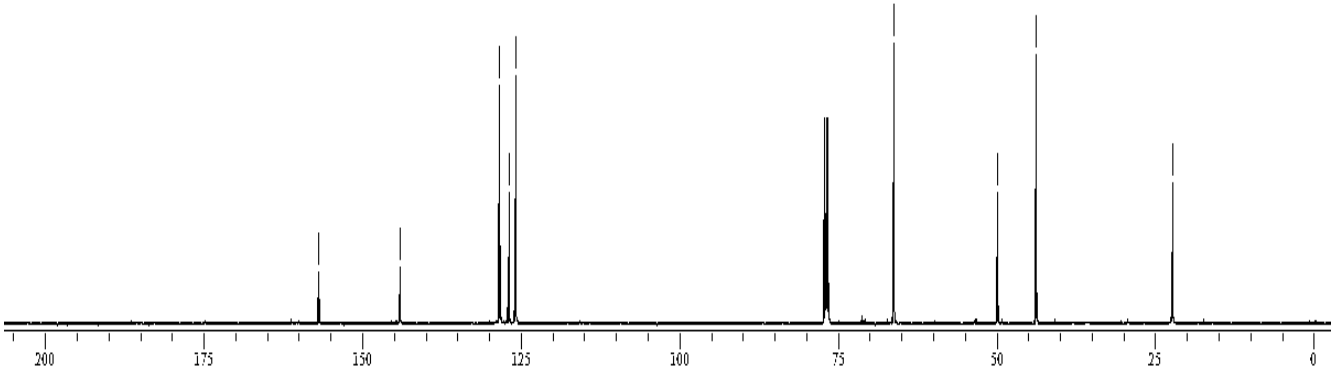


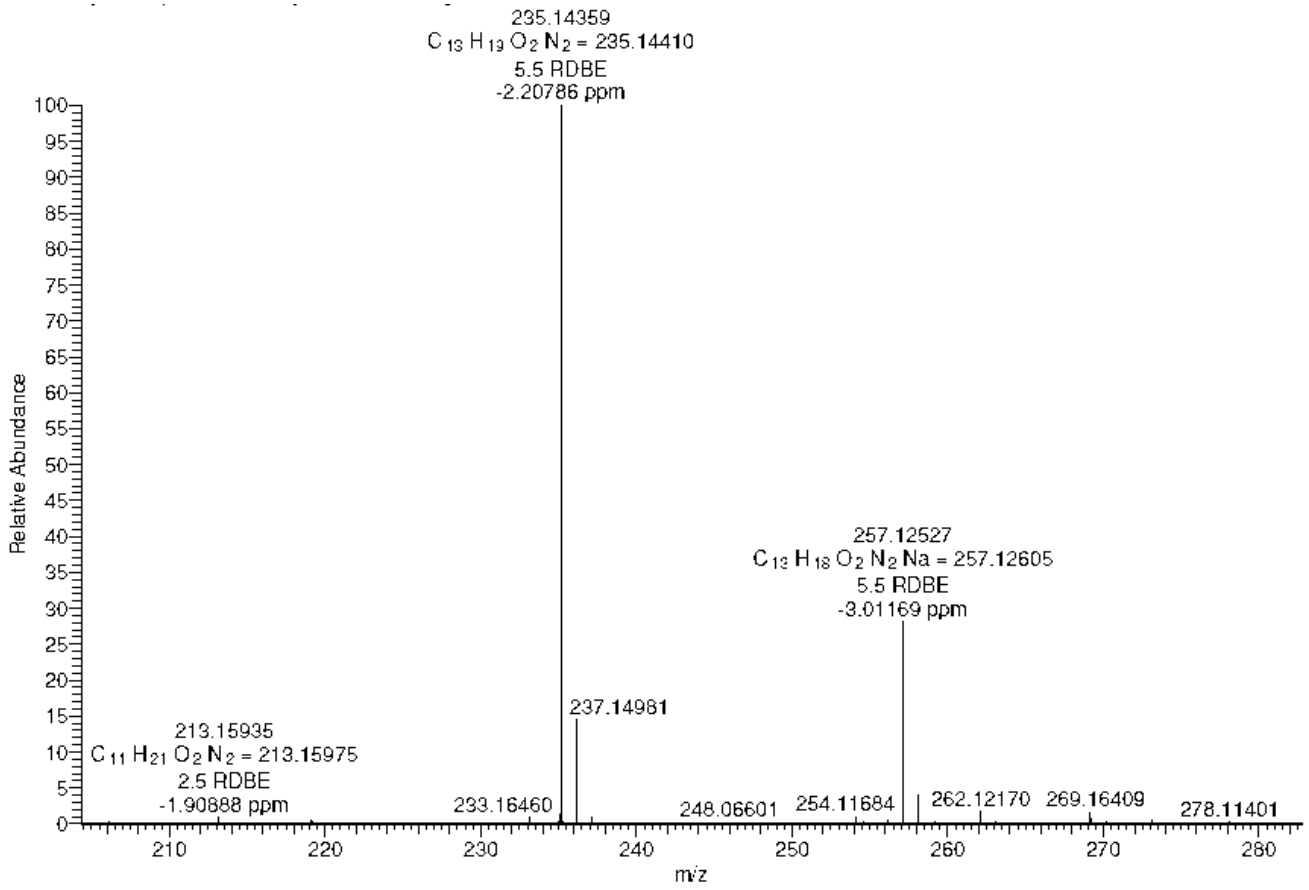


Compound 3p

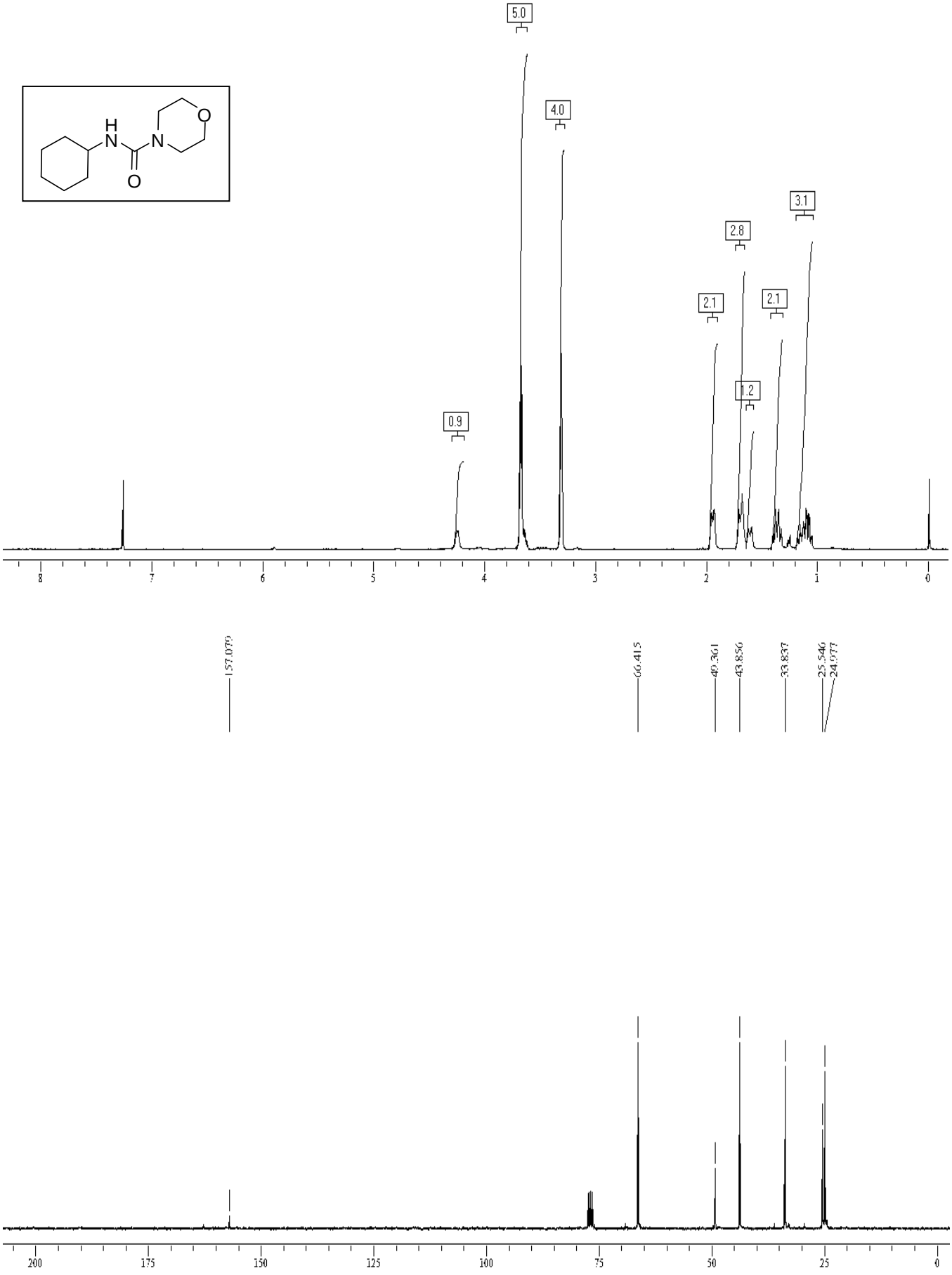


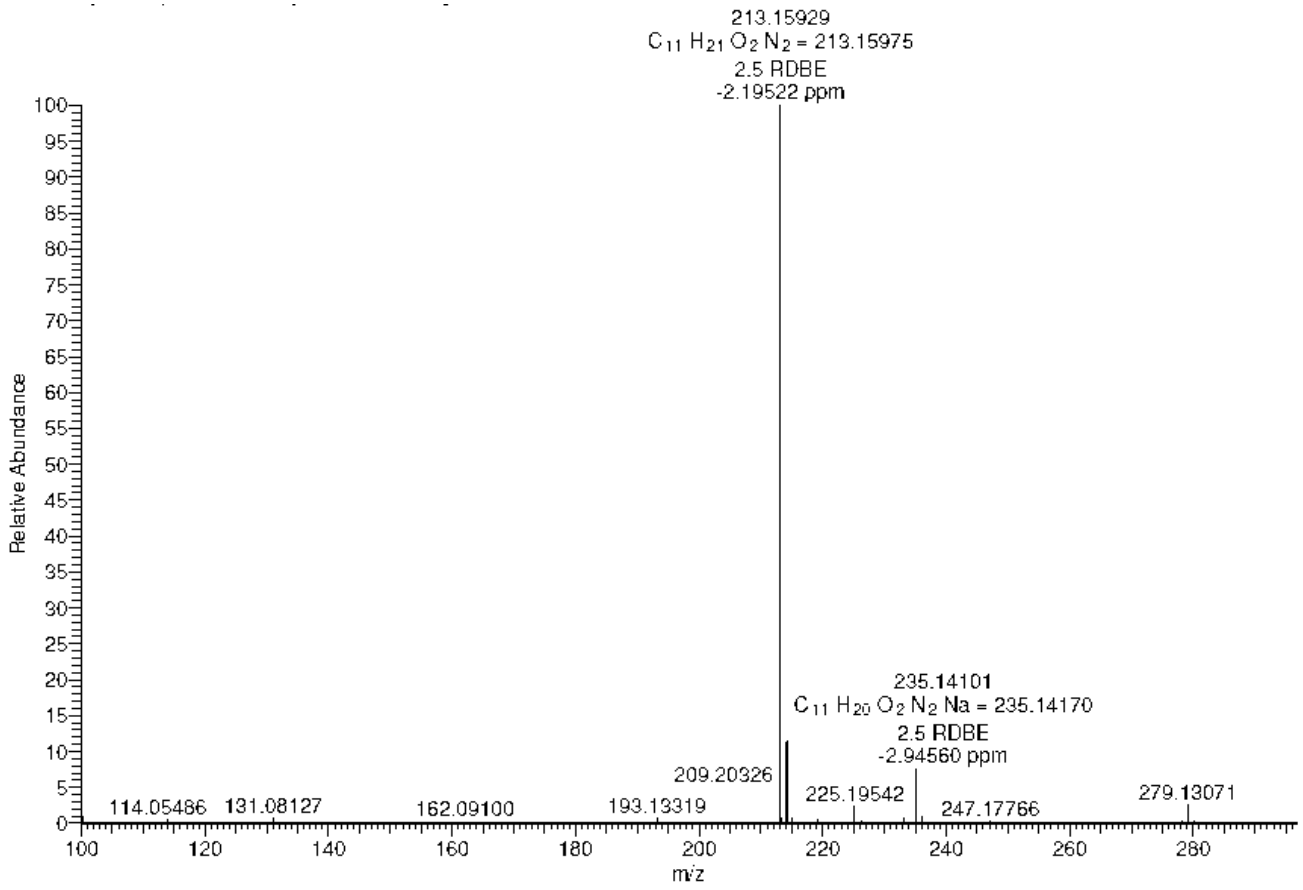




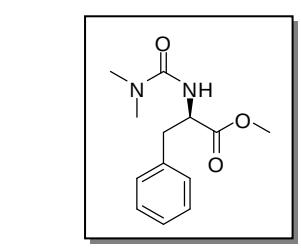


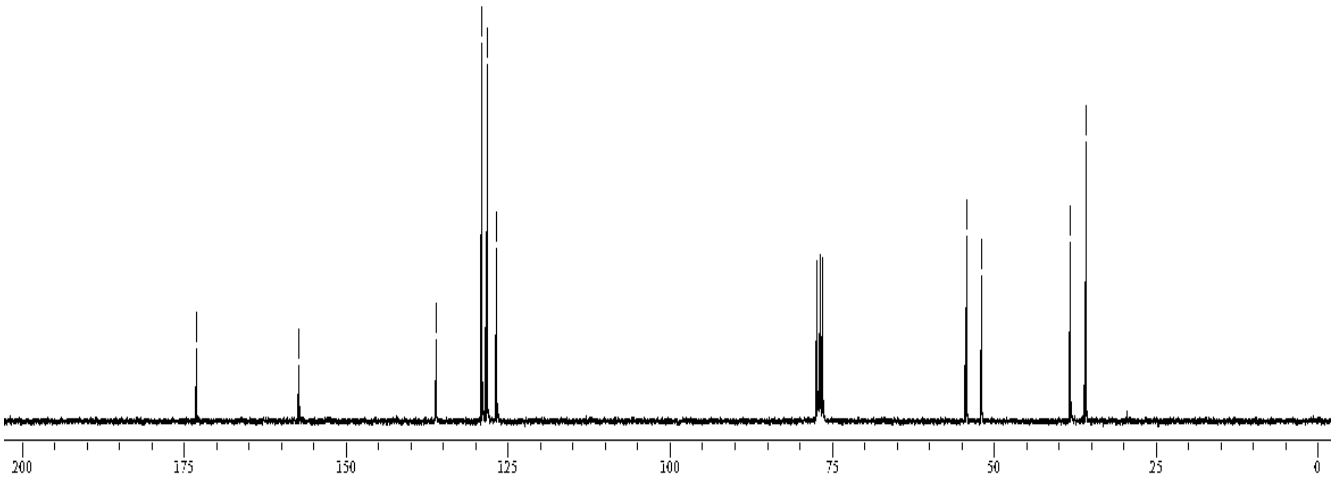
Compound 3q

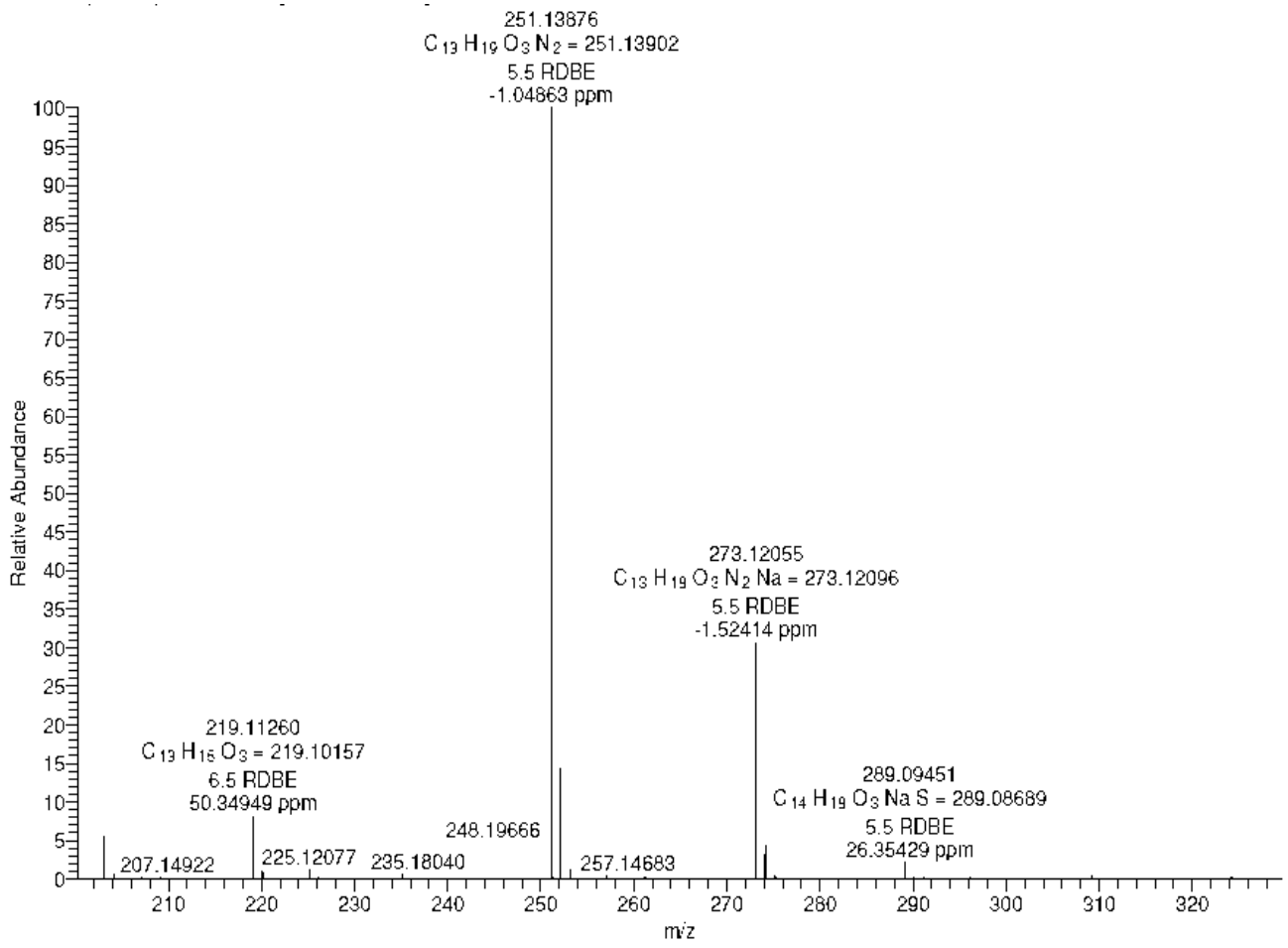



213.15929
C11 H21 O2 N2 = 213.15975
2.5 RDBE
-2.19522 ppm
235.14101
C11 H20 O2 N2 Na = 235.14170
2.5 RDBE
-2.94560 ppm
209.20326
225.19542
247.17766
279.13071
114.05486
131.08127
162.09100
193.13319
Relative Abundance
m/z

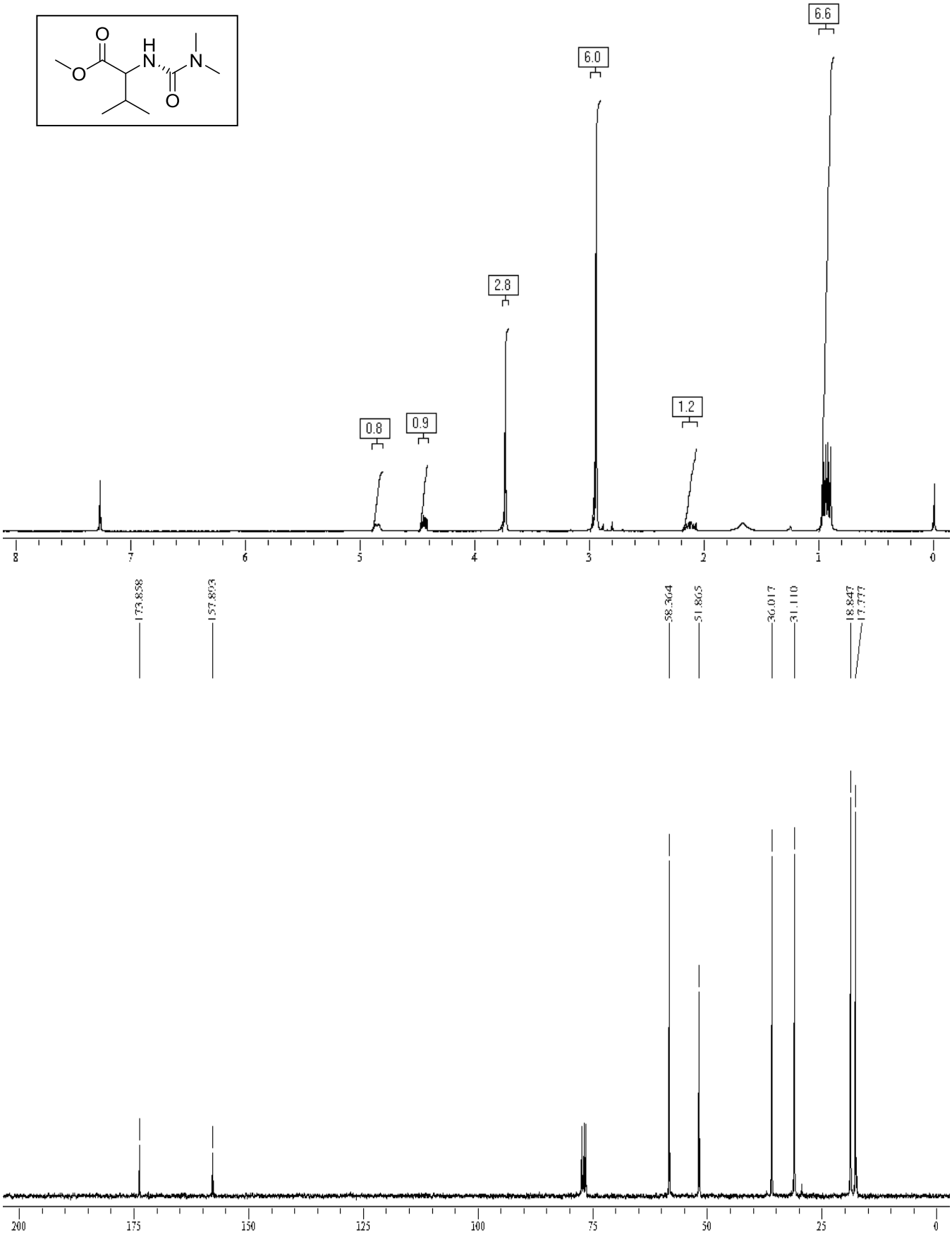
Compound 3r

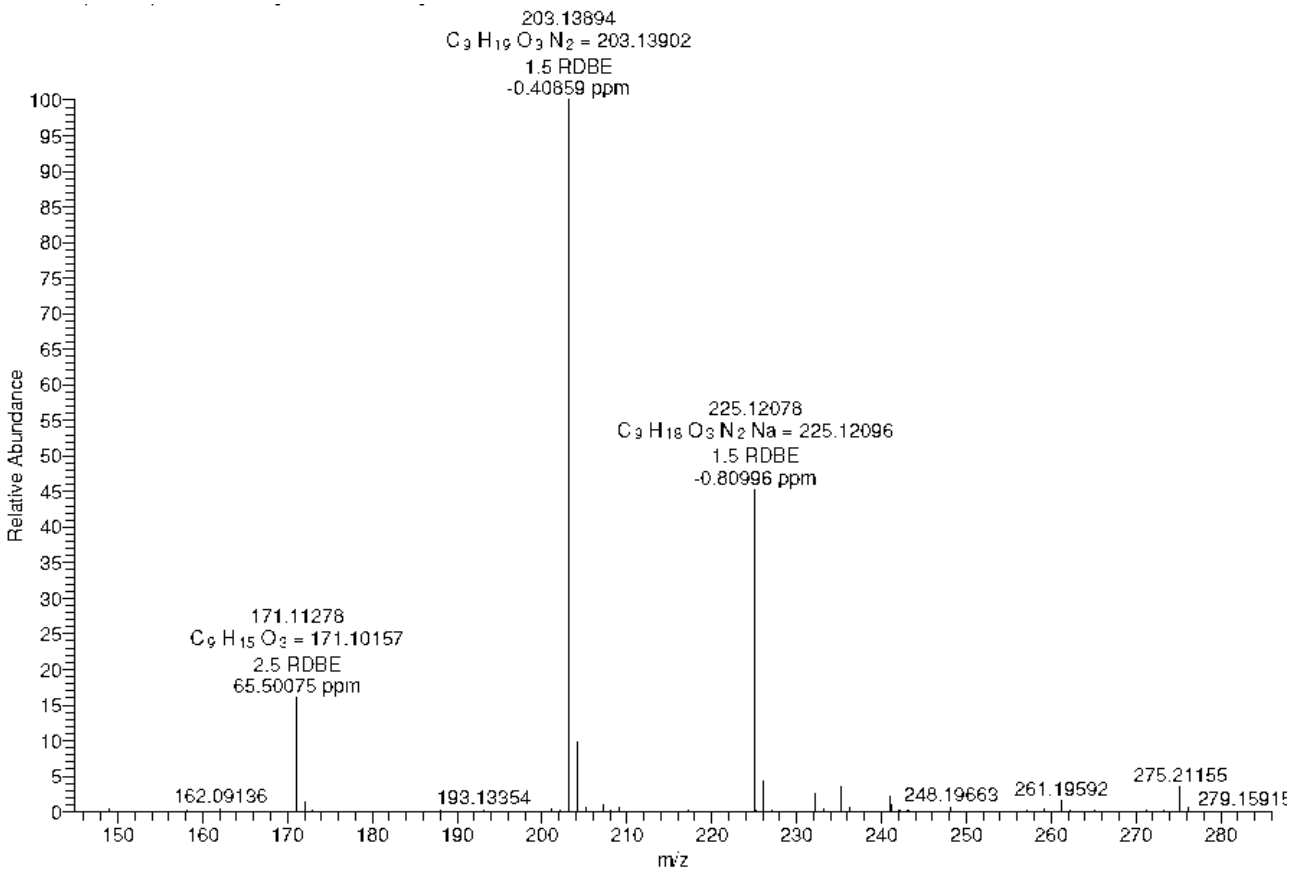




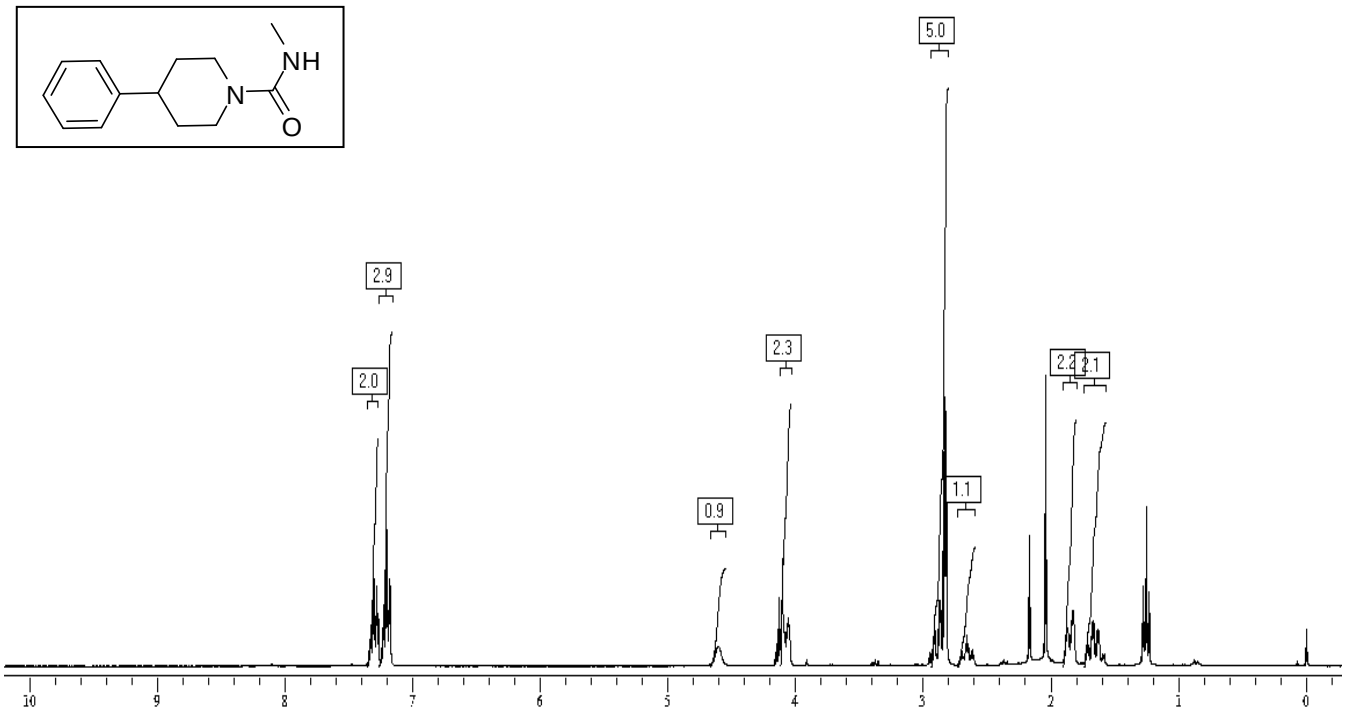


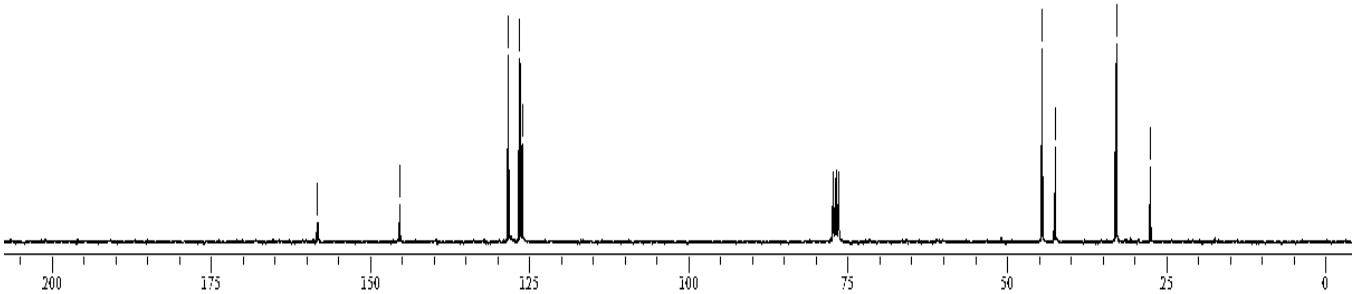
Compound 3s

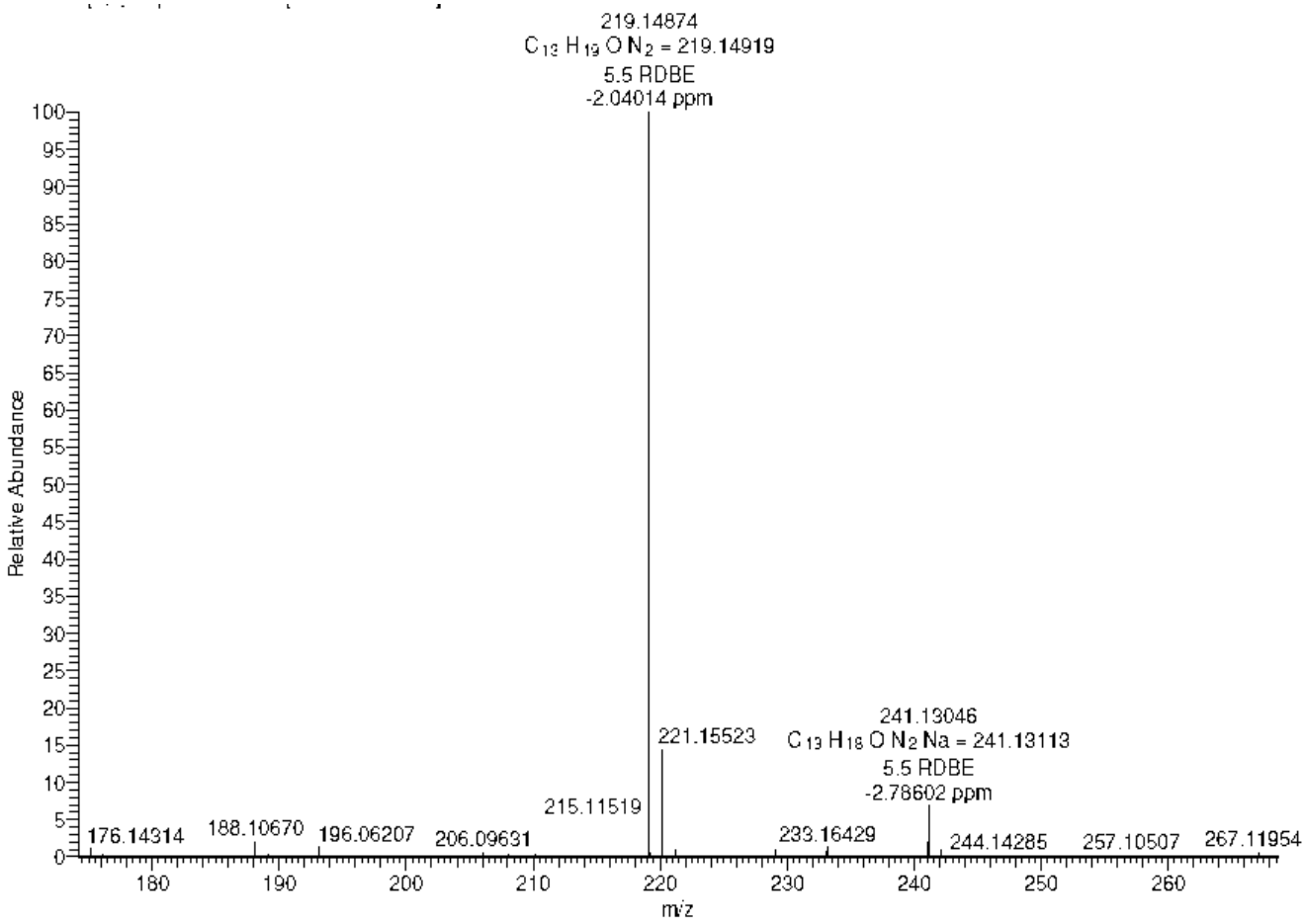




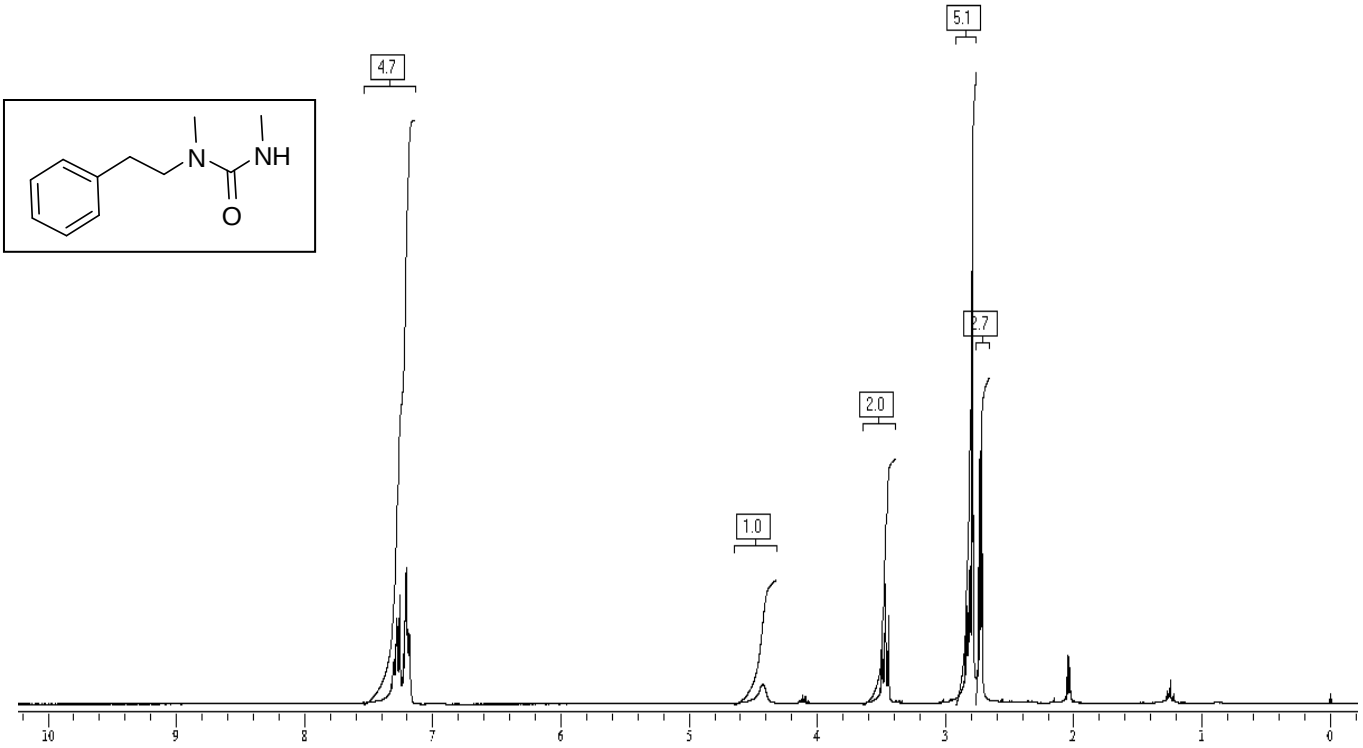
Compound 3t

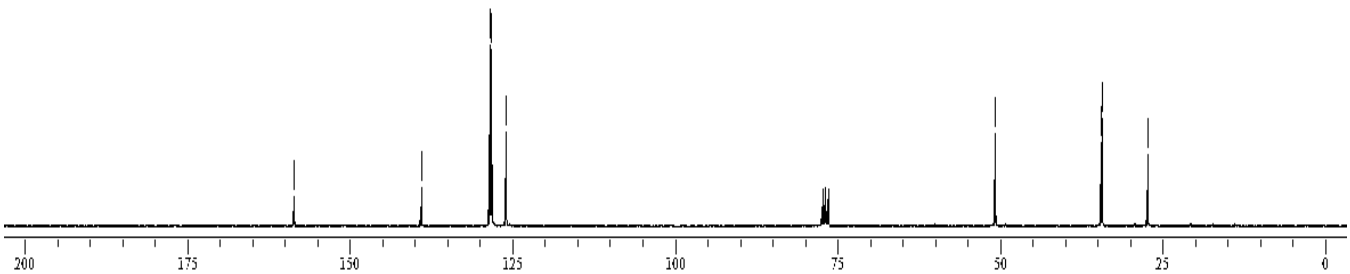


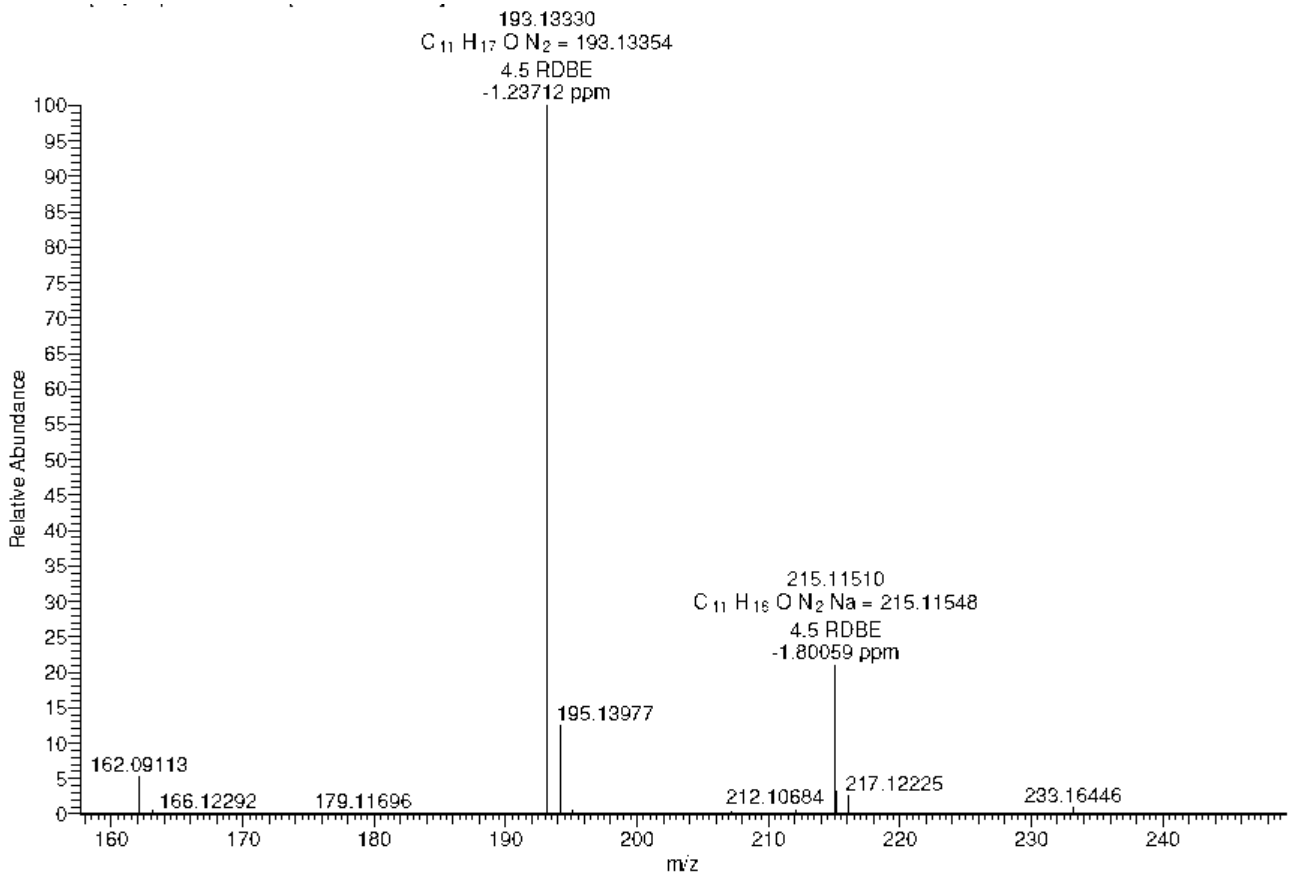




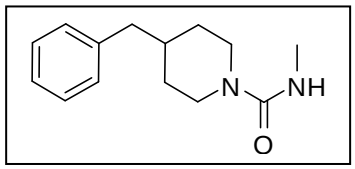
Compound 3u



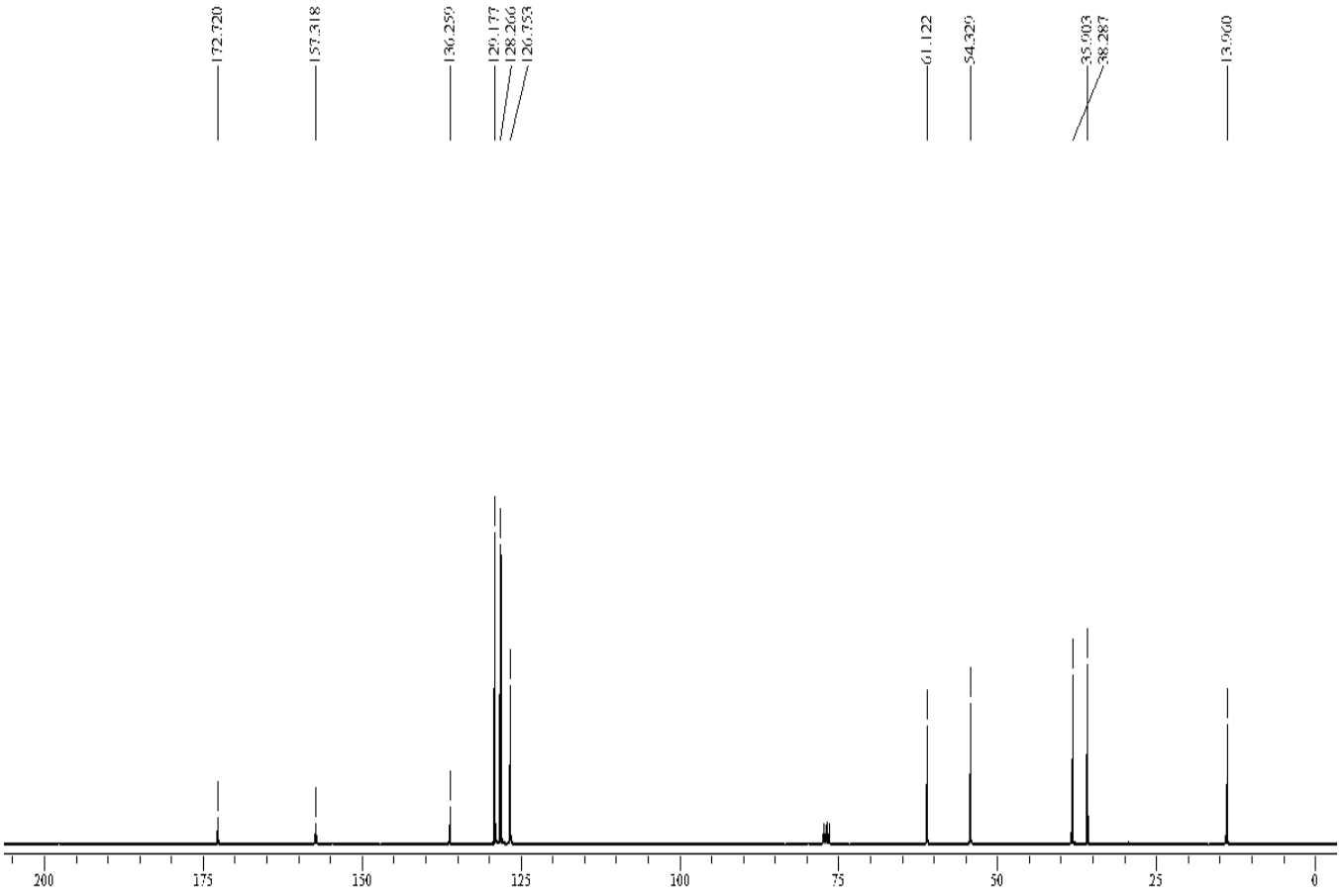


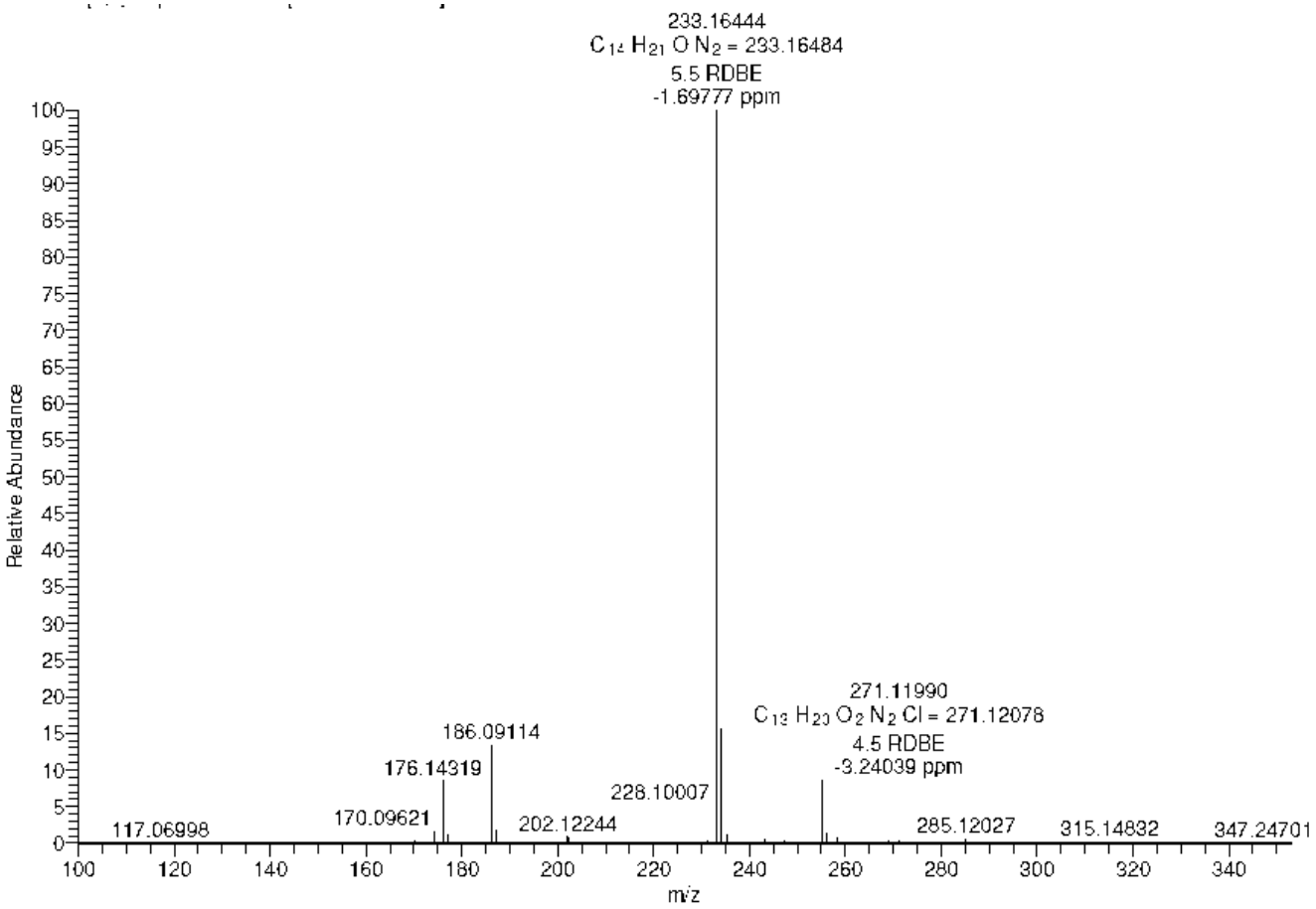


Compound 3v

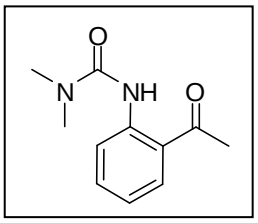

N
NH
O

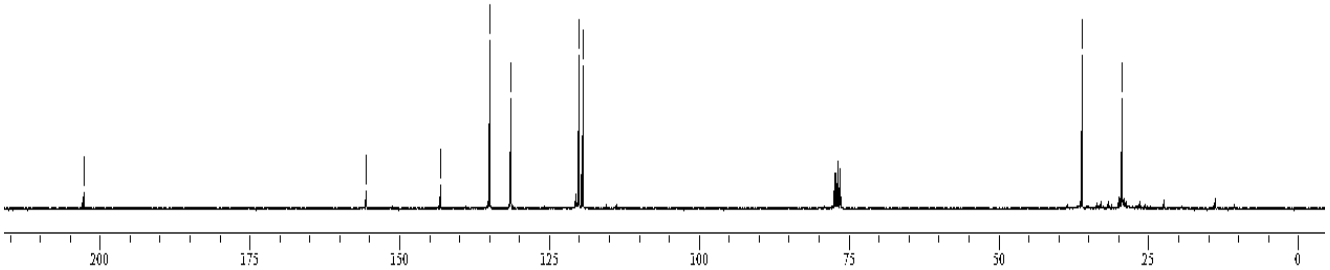
2.9
2.9
2.0
1.9
2.0
2.0
1.9
1.0
0.8
10
9
8
7
6
5
4
3
2
1
0

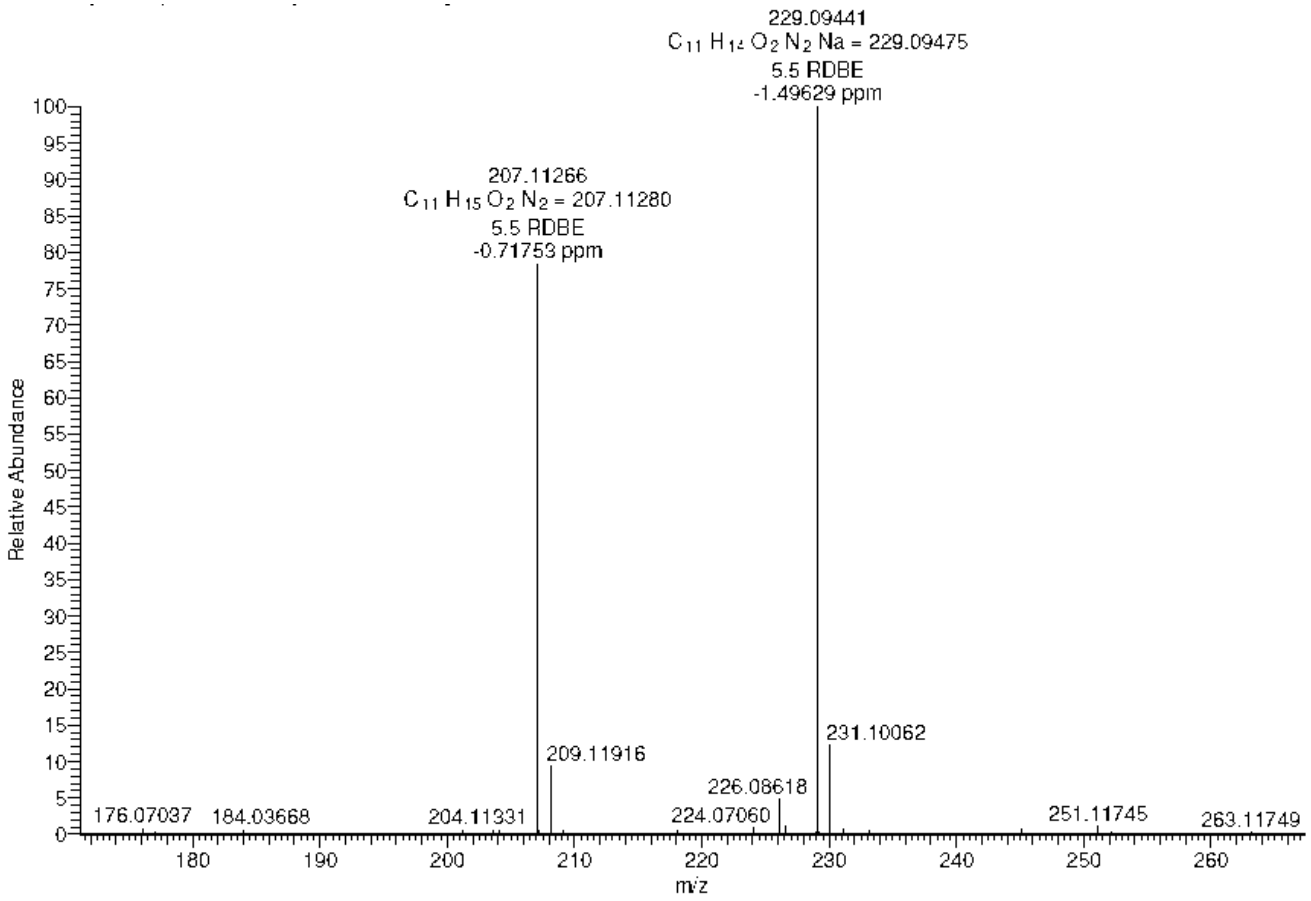

172.720
157.318
136.259
129.177
128.266
126.753
61.122
54.329
35.903
38.287
13.960
200
175
150
125
100
75
50
25
0



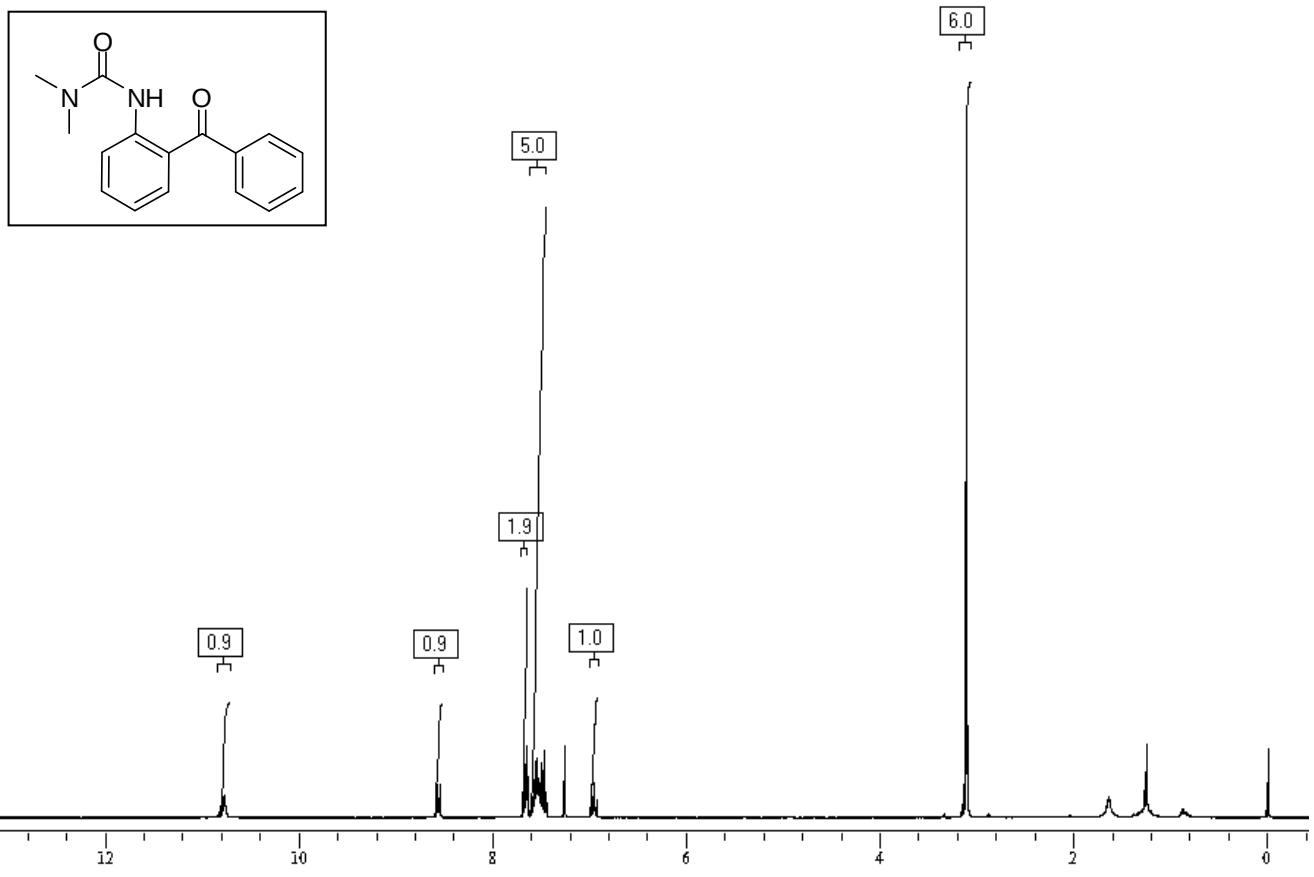
Compound 5a

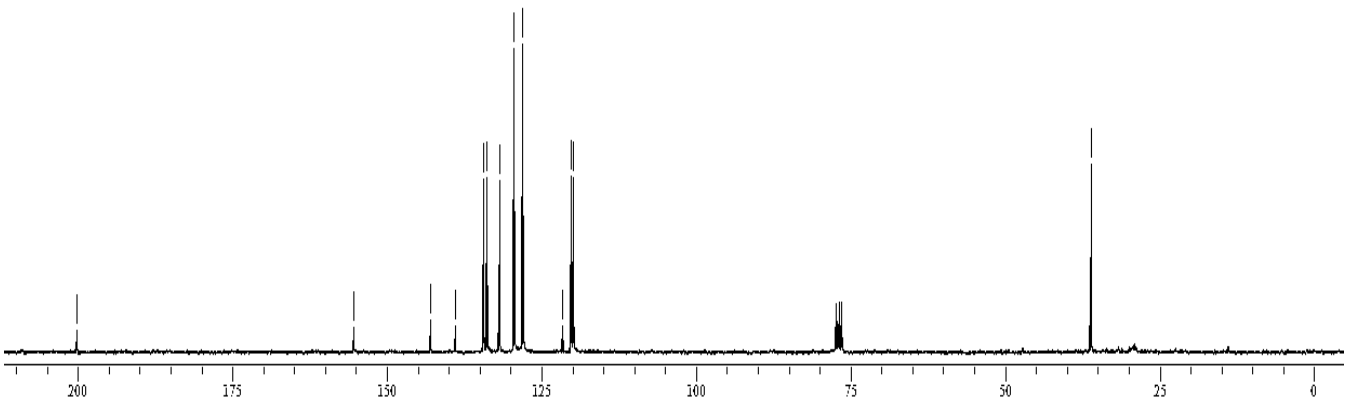


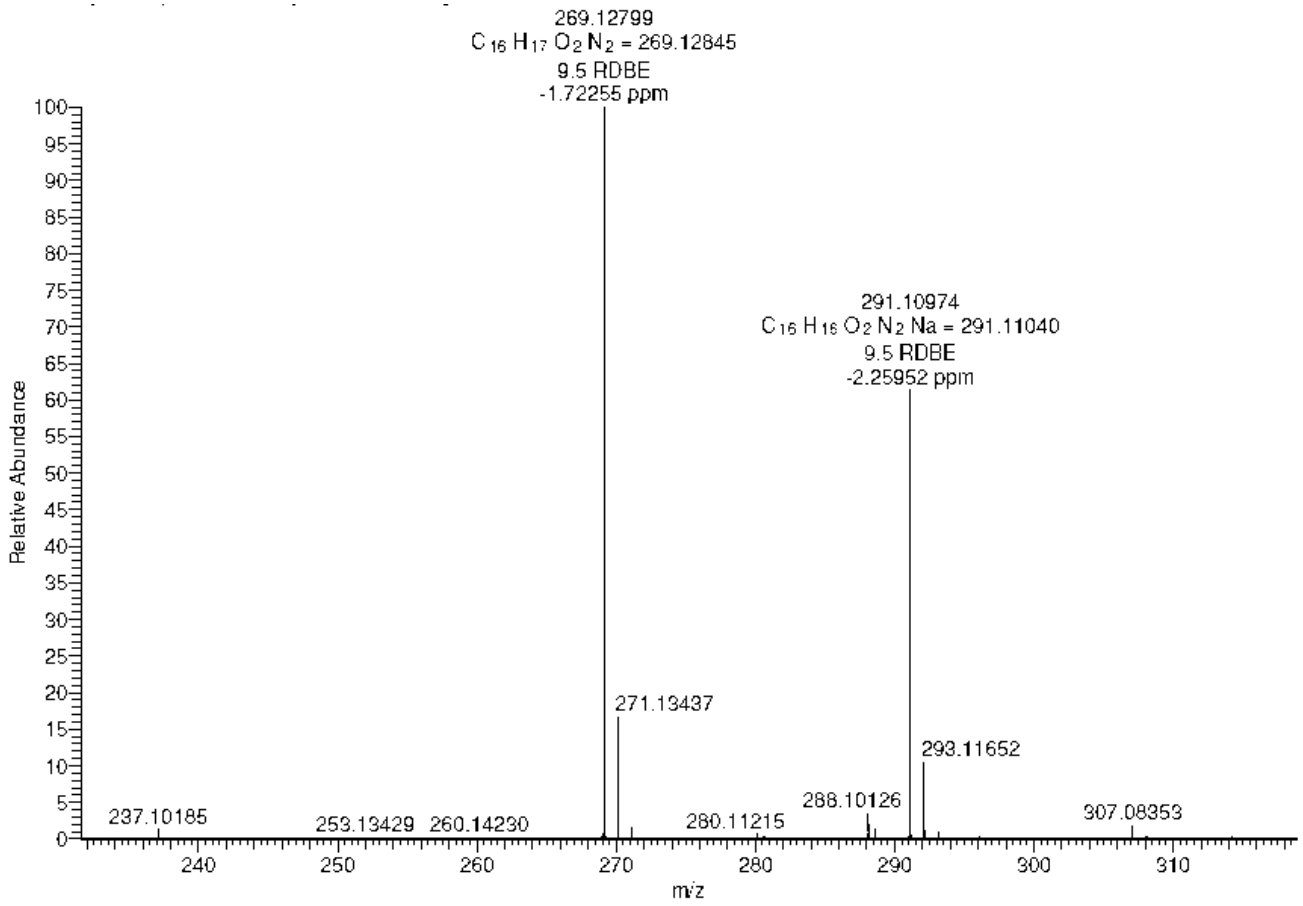




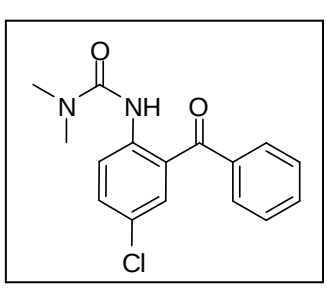
Compound 5b

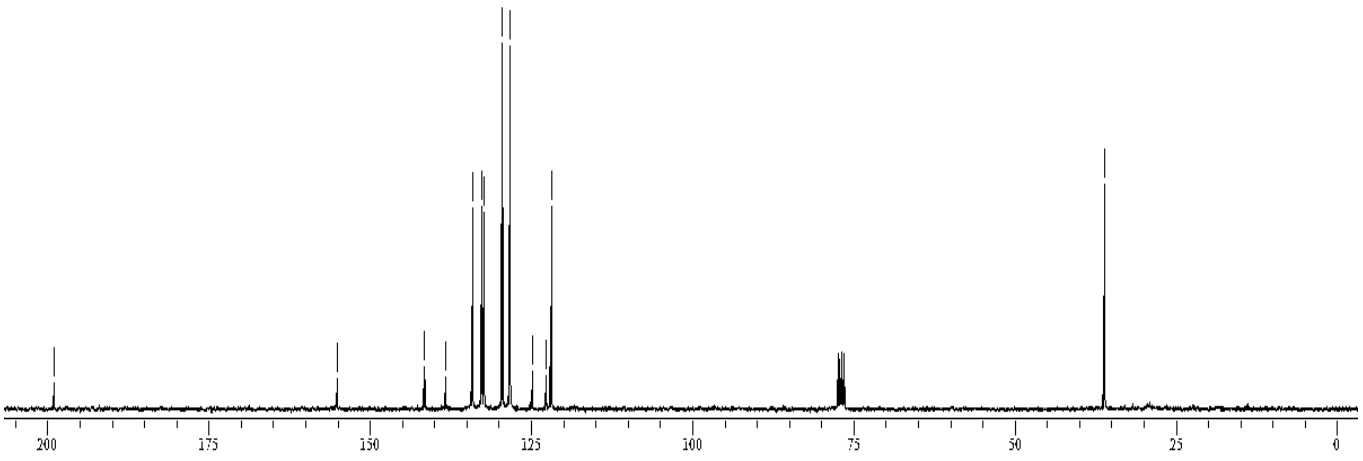


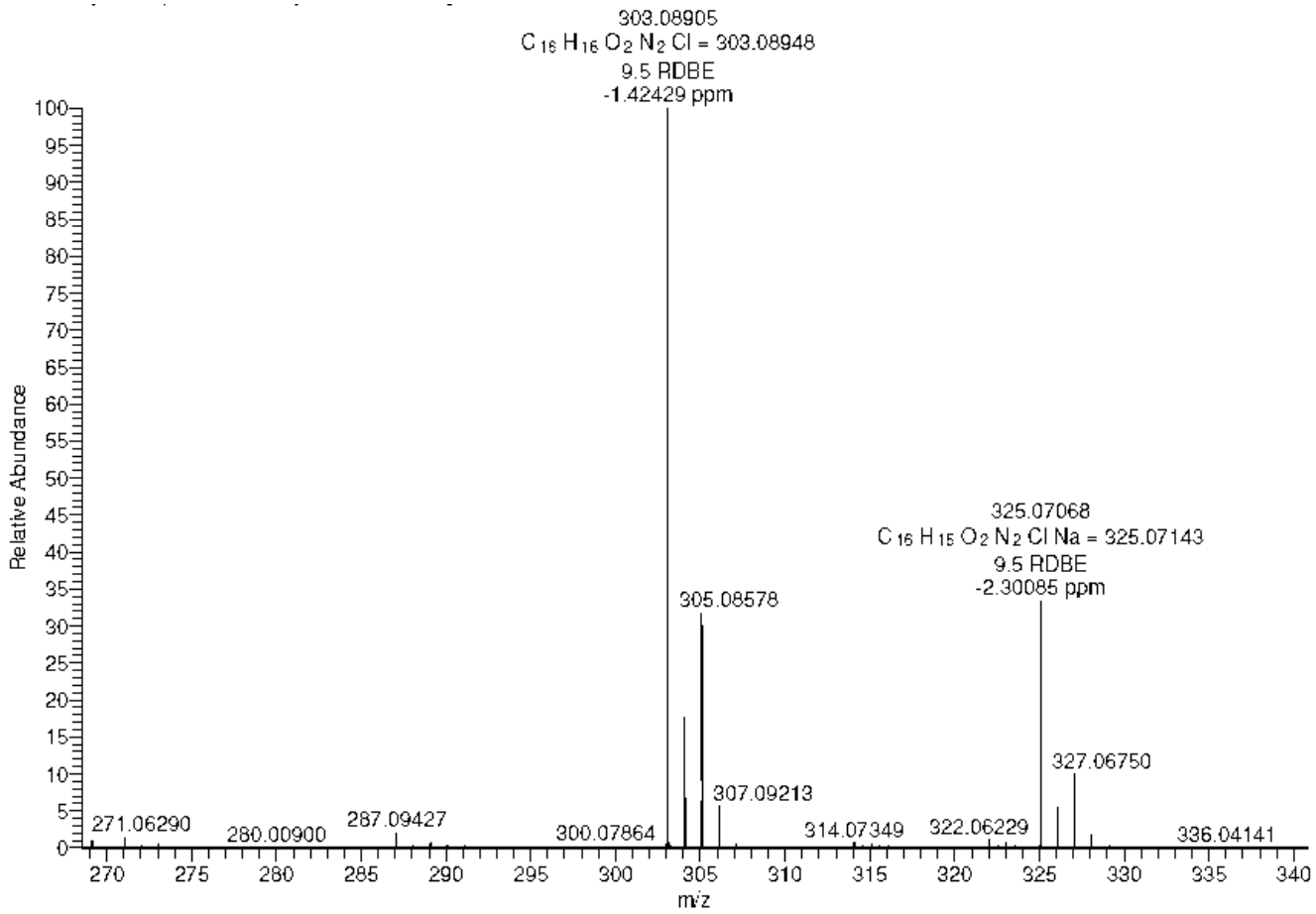




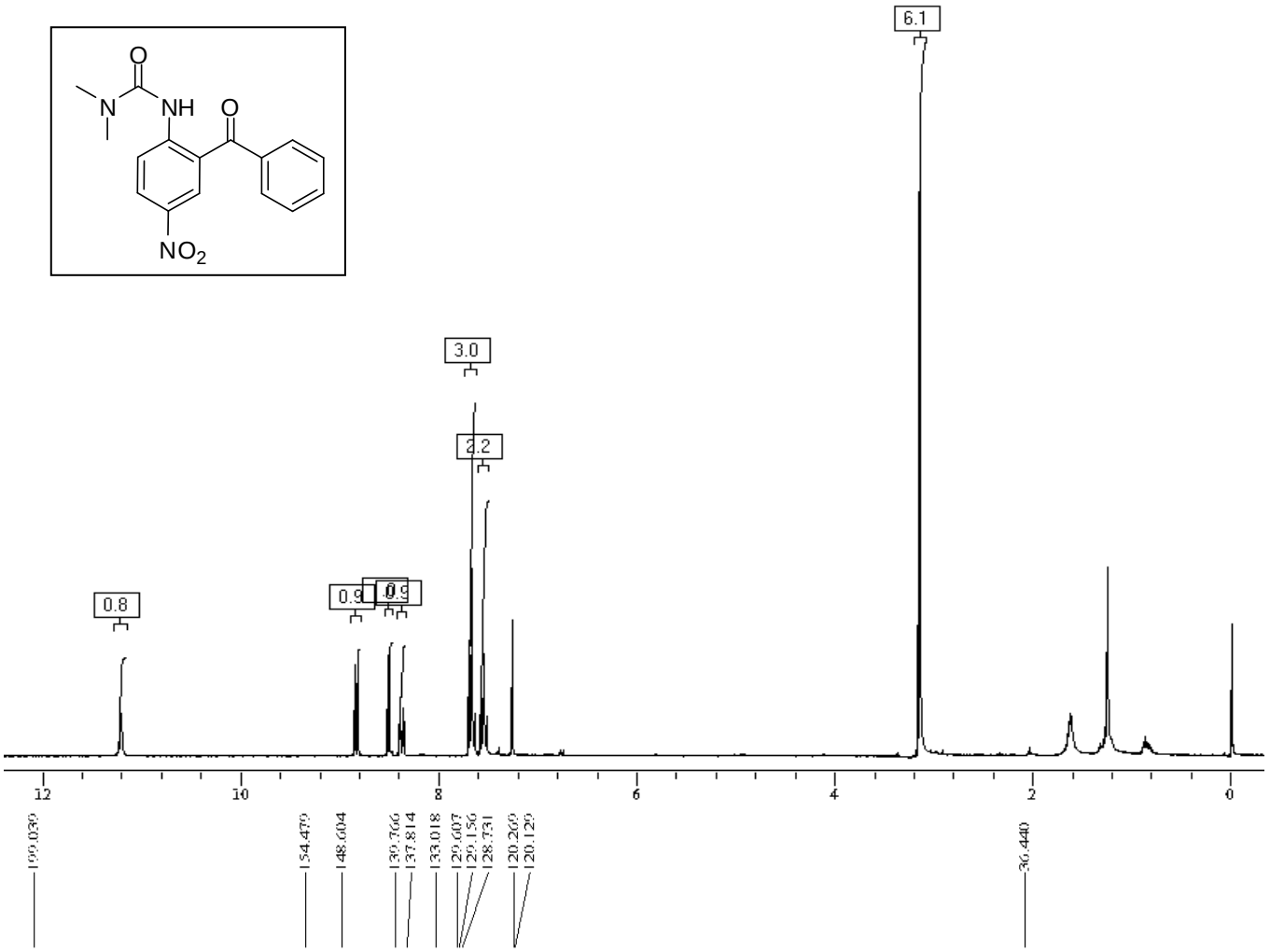
Compound 5c

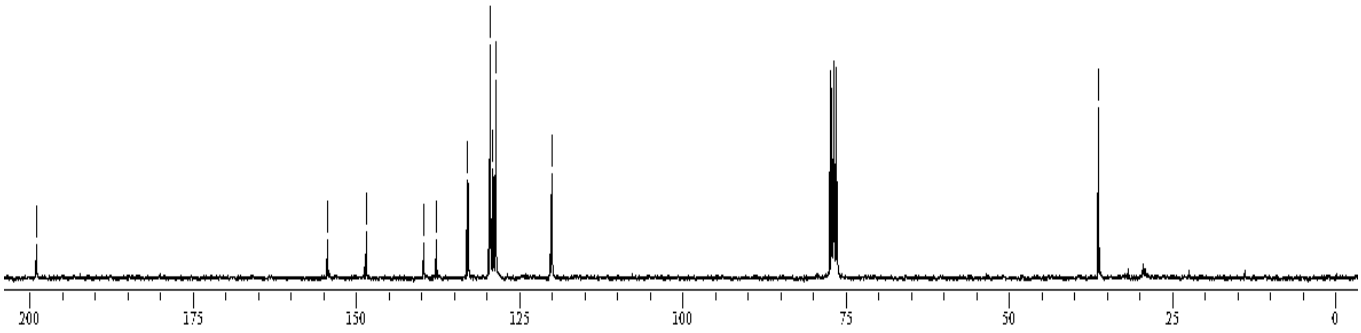


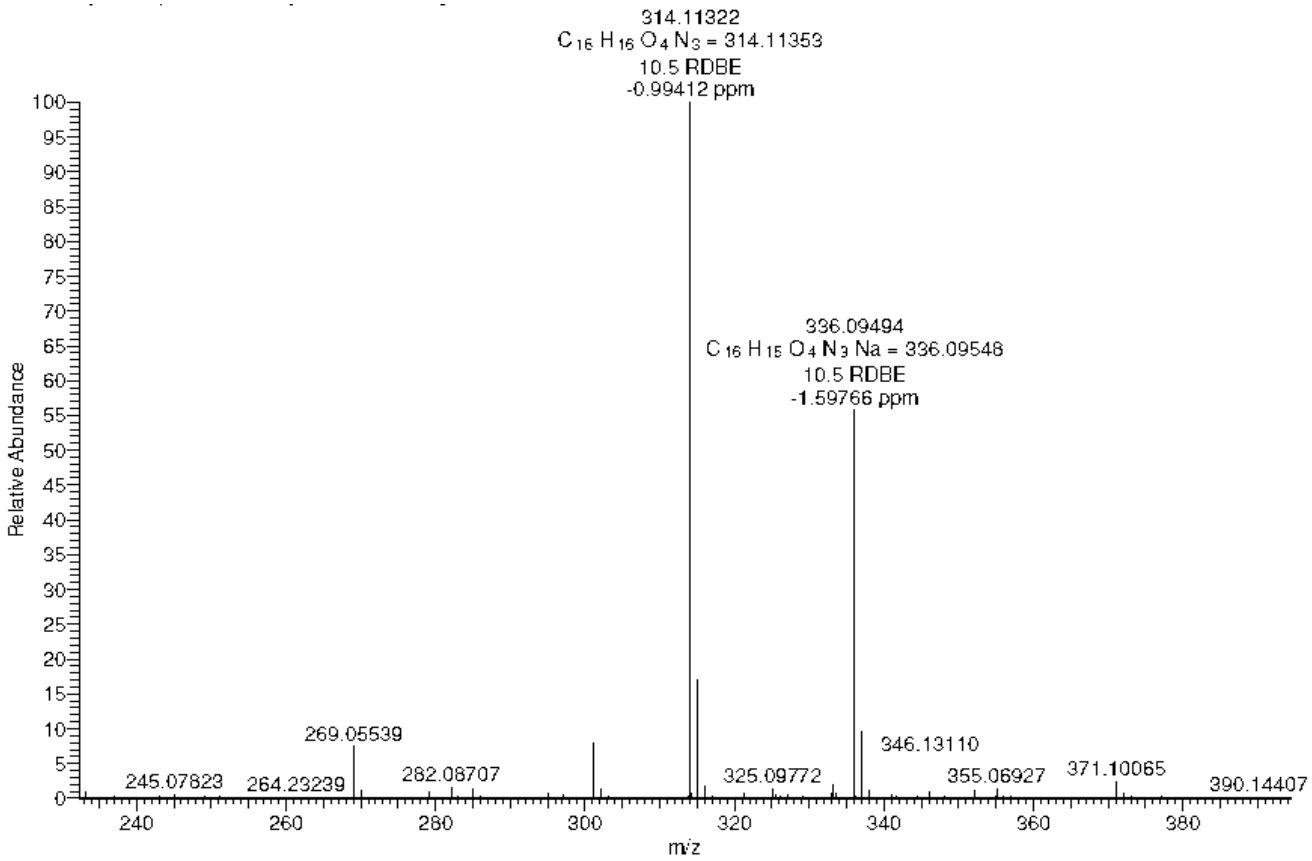




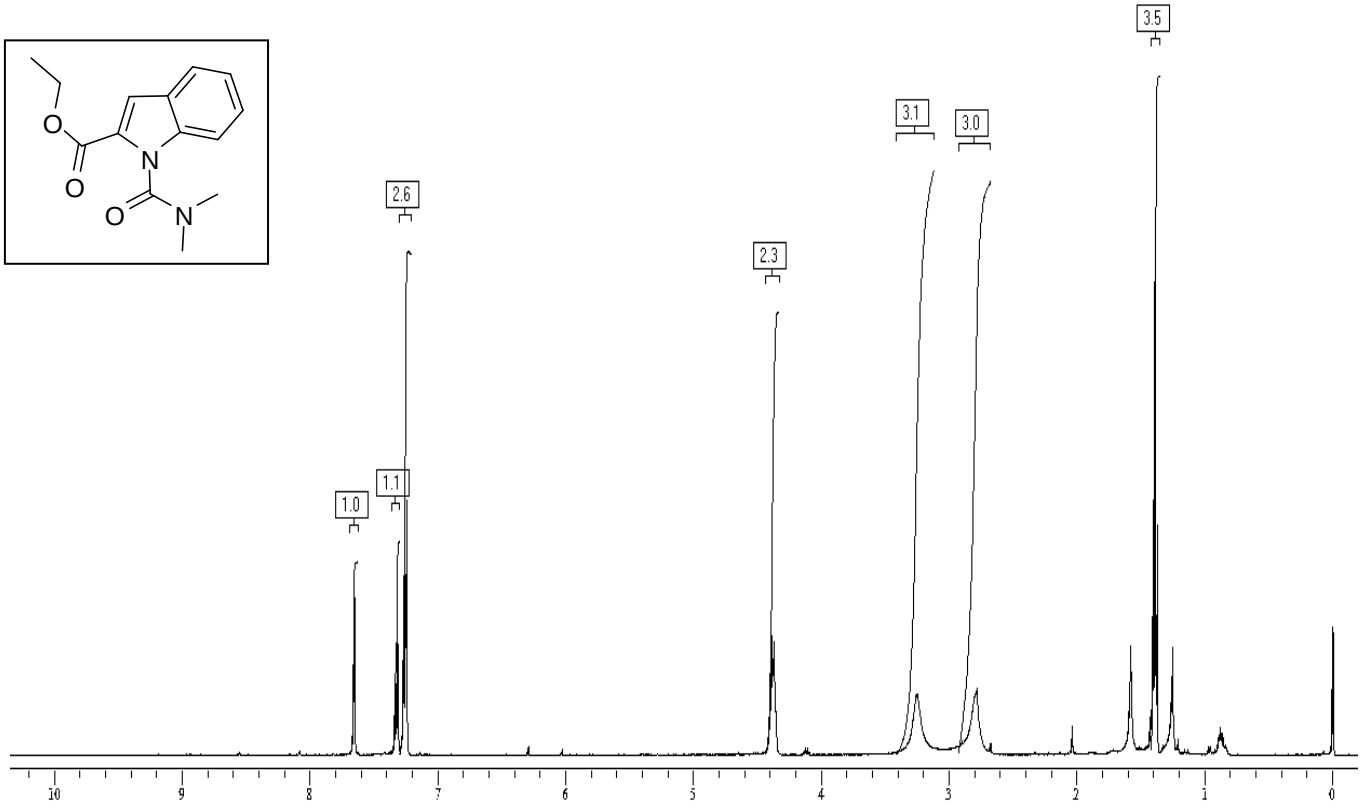
Compound 5d

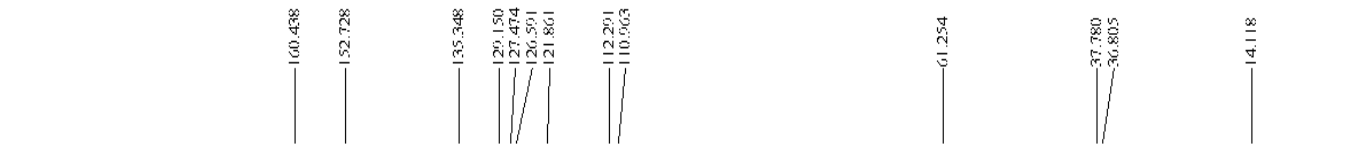


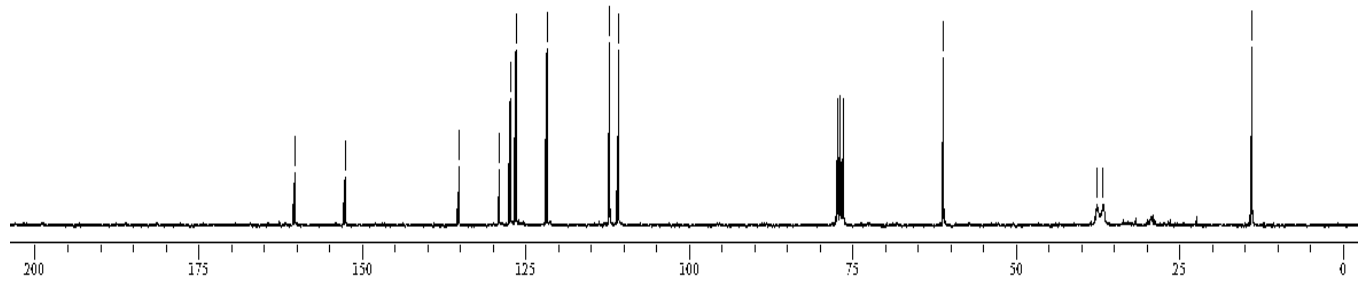


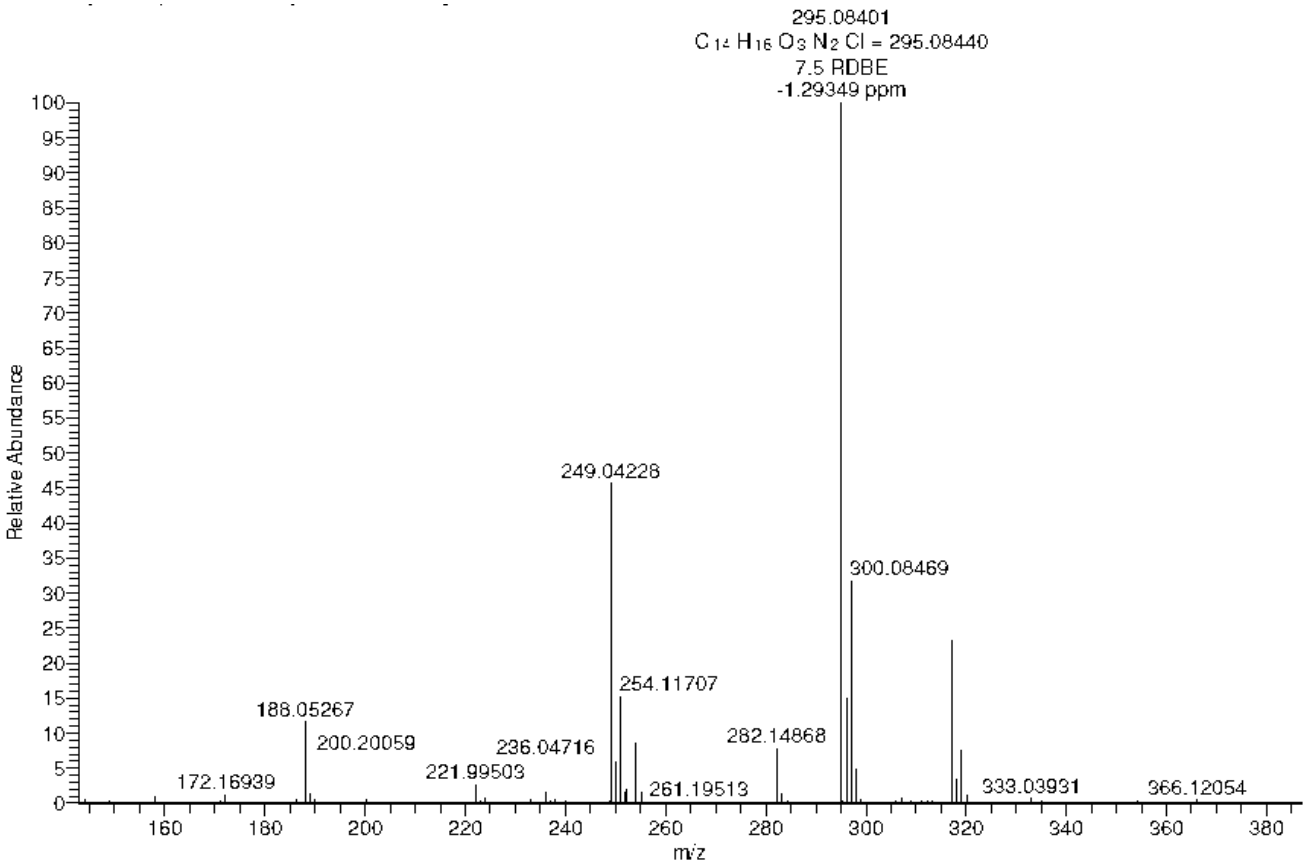

314.11322
C16 H16 O4 N3 = 314.11353
10.5 RDBE
-0.99412 ppm
336.09494
C16 H15 O4 N3 Na = 336.09548
10.5 RDBE
-1.59766 ppm
269.05539
346.13110
245.07823
264.23239
282.08707
325.09772
355.06927
371.10065
390.14407
Relative Abundance
m/z

Compound 5e

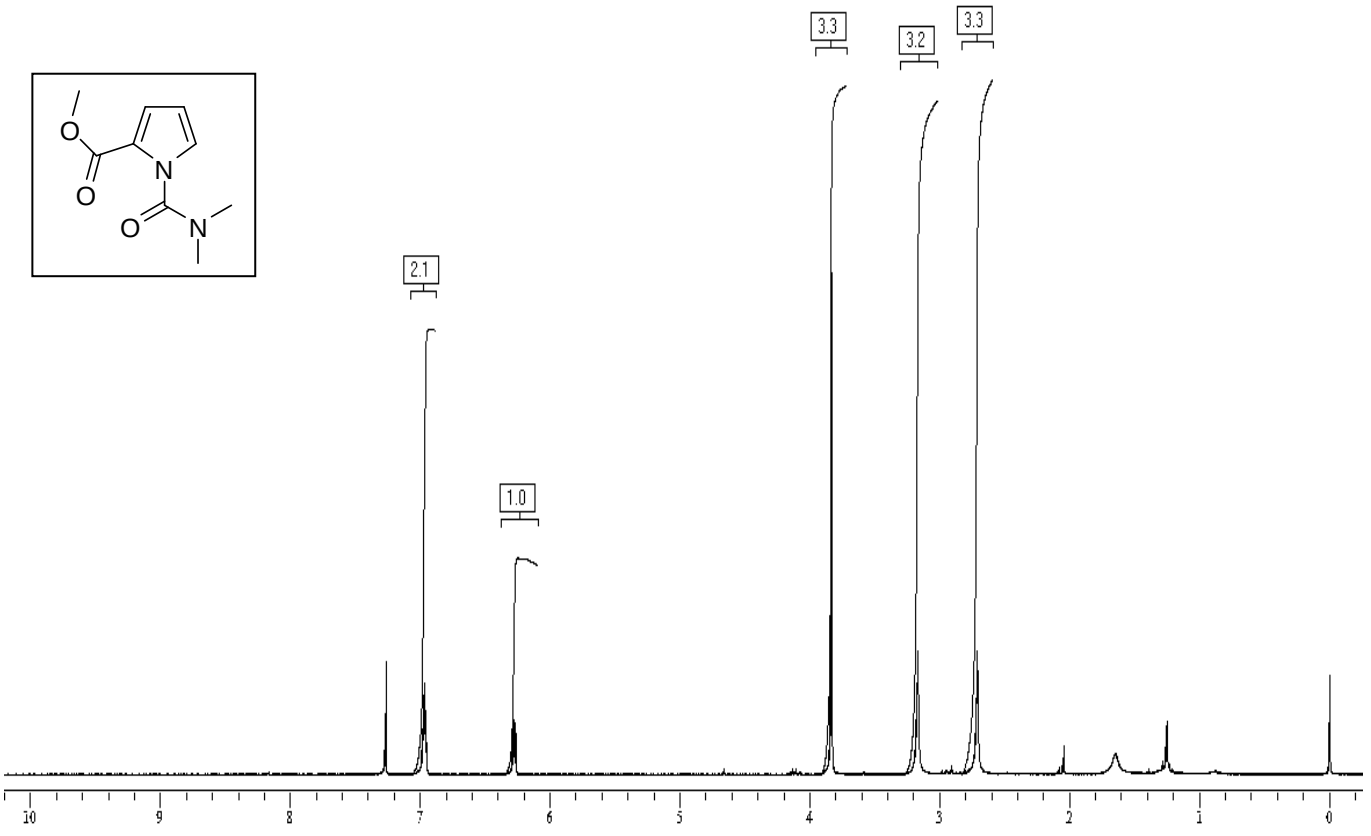


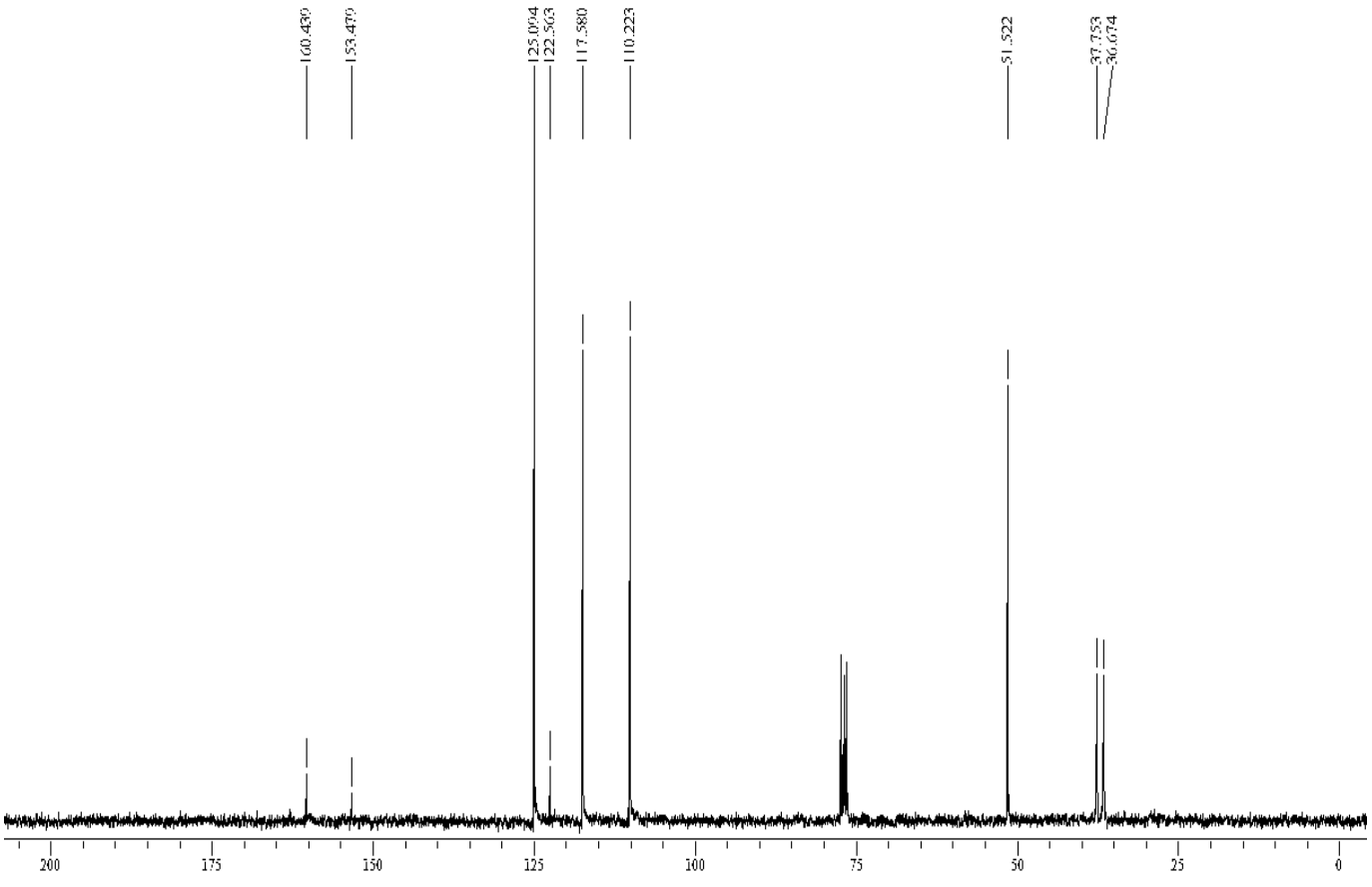


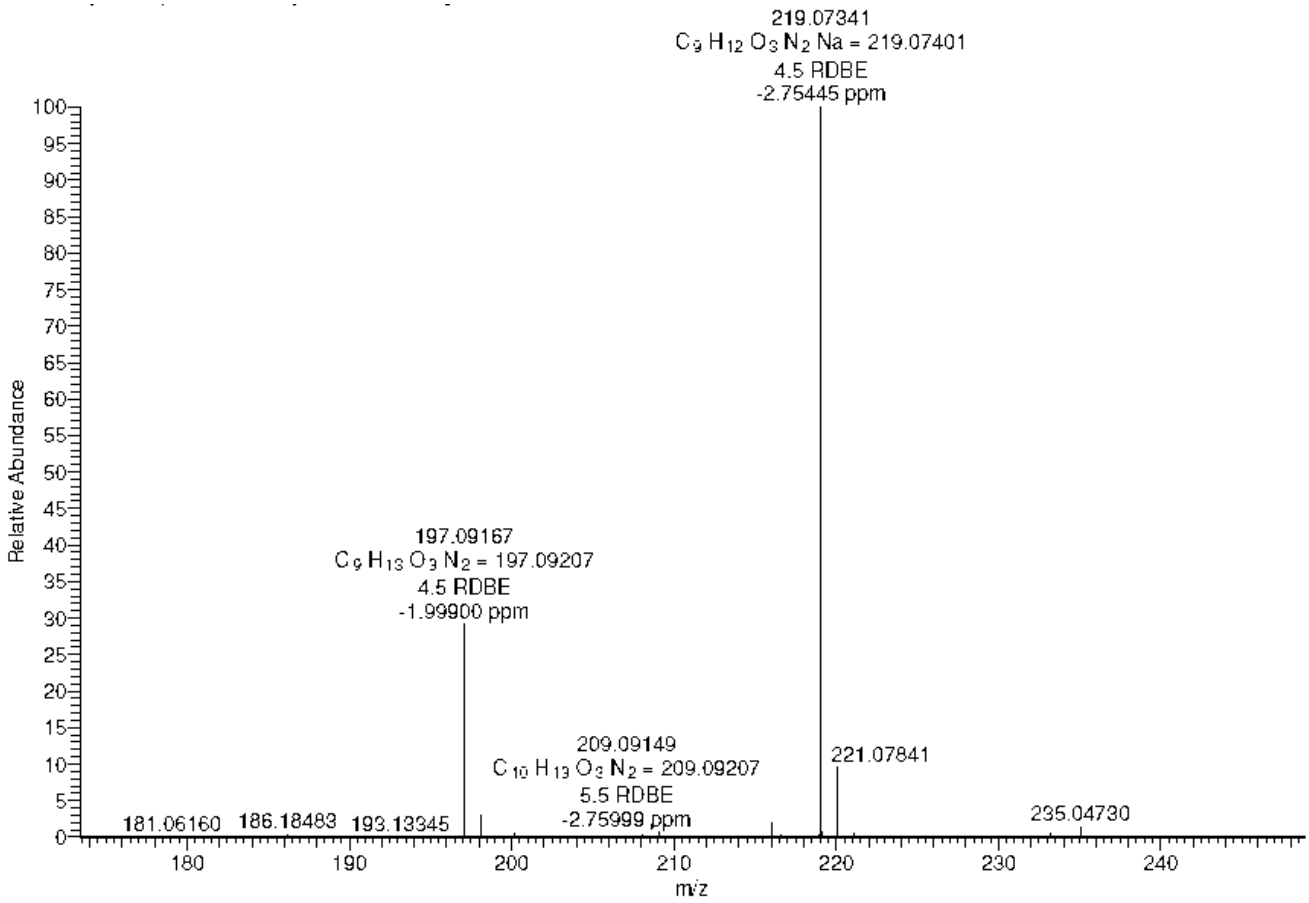




Compound 5f

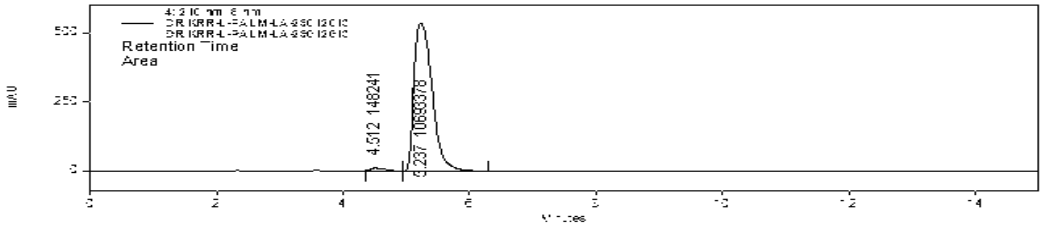






HPLC data of compound 3r :

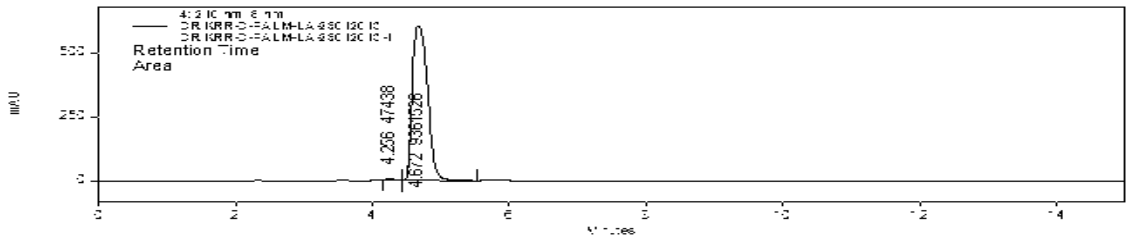
A : reaction between L –Phenyl Alanine Methyl Ester and DMF



4: 210 nm, 8 nm

Name	Retention Time	Area	Area Percent	Lambda Max
	4.512	148241	1.37	202
	5.237	10693378	98.63	204
Totals		10841619	100.00	

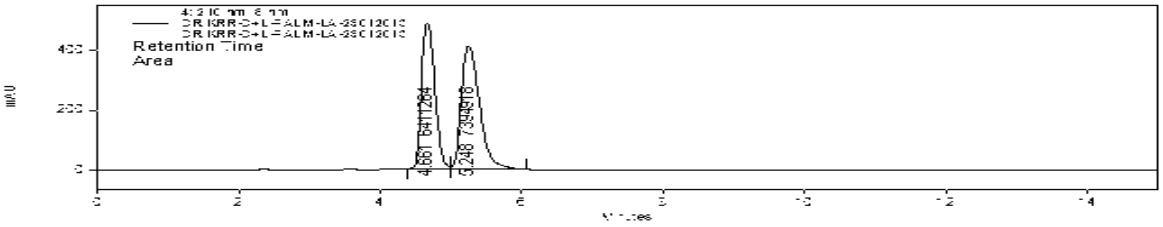
B : Reaction between D – Phenyl Alanine Methyl Ester and DMF



4: 210 nm, 8 nm

Name	Retention Time	Area	Area Percent	Lambda Max
	4.256	47438	0.50	202
	4.672	9361526	99.50	204
Totals		9408964	100.00	

C : Mixture of L + D

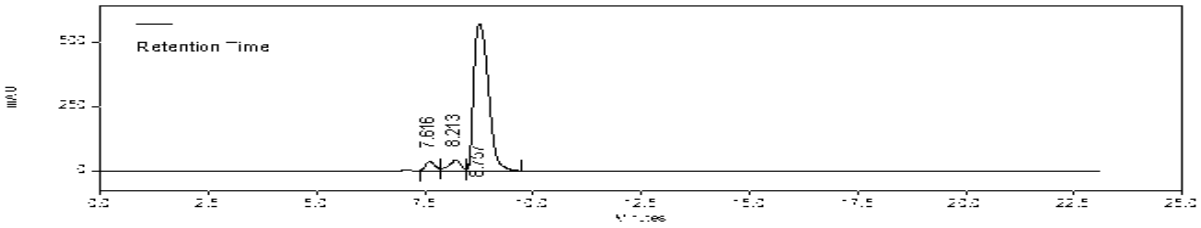


4: 210 nm, 8 nm

Name	Retention Time	Area	Area Percent	Lambda Max
	4.661	6411264	46.44	203
	5.248	7394918	53.56	203
Totals		13806182	100.00	

HPLC data of compound 3s :

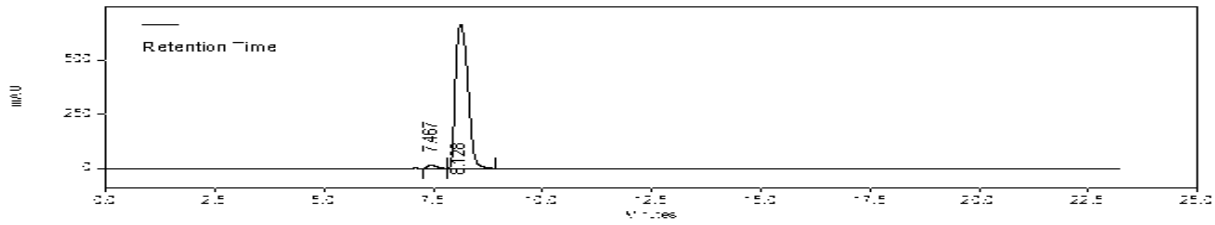
A: (reaction between L-Valine Methyl Ester and DMF)



4: 210 nm, 8 nm

Pk #	Name	Retention Time	Area	Area Percent	Lambda Max
1		7.616	520308	3.56	202
2		8.213	767063	5.25	202
3		8.757	13335947	91.20	204
Totals			14623318	100.00	

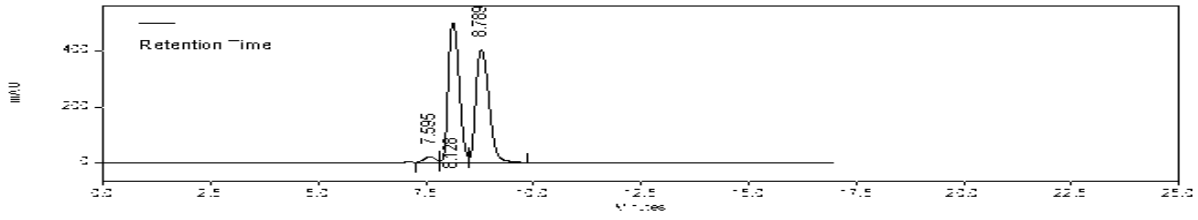
B : (reaction between D – Valine Methyl Ester and DMF)



4: 210 nm, 8 nm

Pk #	Name	Retention Time	Area	Area Percent	Lambda Max
1		7.467	205204	1.56	203
2		8.128	12979150	98.44	203
Totals			13184354	100.00	

C : (mixture of L + D)



4: 210 nm, 8 nm

Pk #	Name	Retention Time	Area	Area Percent	Lambda Max
1		7.595	359566	2.02	202
2		8.128	8781389	49.32	204
3		8.789	8662332	48.66	204
Totals			17803287	100.00	