

Synthesis of 4-Arylpiperidines from 1-Benzyl-4-Piperidone: Application of the Shapiro Reaction and Alkenylsilane Cross-Coupling

Christie Morrill* and Neelakandha S. Mani

*Department of Drug Discovery, Johnson & Johnson Pharmaceutical R&D LLC
3210 Merryfield Row, San Diego, California 92121*

CMorril3@prdus.jnj.com

Supporting Information

S-2: General experimental methods

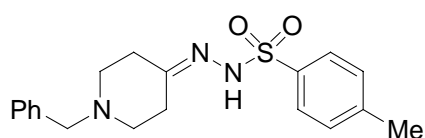
S-2 - S-5: Experimental procedures

S-2 - S-9: Characterization data (^1H NMR, ^{13}C NMR, and HRMS) for compounds **2**, **4**, **6-7**, and all compounds reported in Tables 2 and 3

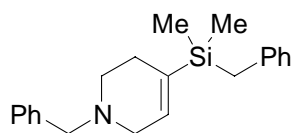
S-10 - S-35: ^1H and ^{13}C NMR spectra for compounds **2**, **4**, **6-7**, and all compounds reported in Tables 2 and 3

General experimental methods:

^1H and ^{13}C NMR spectra were recorded on Bruker 400 or 500 MHz NMR spectrometers. Flash column chromatography was performed on CombiFlash Companion systems (Isco, Inc.) with RediSep pre-packed silica gel cartridges. HRMS (ESI) was performed on a Bruker μTof . Elemental analysis was performed by NuMega Resonance Labs, Inc. (San Diego, CA 92121). All commercially available reagents were purchased and used without further purification.

Experimental procedures:***N*-(1-Benzyl-piperidin-4-ylidene)-*N'*-tosyl-hydrazine (**2**)**

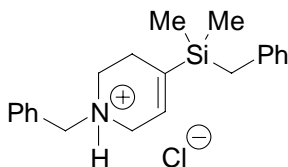
To a 2-L round-bottomed flask, added 86 g (462 mmol) *p*-toluene sulfonhydrazide (**1**) and 1 L ethanol, then placed under a nitrogen atmosphere. [Reaction formed a white suspension.] With mechanical stirring, added 75 mL (420 mmol) 1-benzyl-4-piperidone. [Reaction quickly became almost completely clear, and after about 15 minutes, **2** began to precipitate.] Let stir at room temperature for a total of 3.5 hours, then collected the precipitate via filtration, rinsing the filter cake with cold ethanol. Let the filter cake dry under vacuum (room temperature, ca. 0.2 torr) for a few hours, then ground the solid into a fine powder with mortar and pestle and placed under vacuum overnight (room temperature, ca. 0.2 torr). Obtained 111 g of **2** as a crystalline, white solid (74%, >95% purity by ^1H NMR). This material was used in subsequent reactions without further purification. ^1H NMR (500 MHz, CDCl_3): δ = 7.82 (2H, d, J = 8.3 Hz), 7.27 (7H, m), 3.49 (2H, s), 2.51 (2H, t, J = 5.9 Hz), 2.46 (2H, t, J = 6.0 Hz), 2.42 (3H, s), 2.34 (4H, m). ^{13}C NMR (125 MHz, CDCl_3): δ = 159.6, 143.9, 138.0, 135.4, 129.5, 128.9, 128.3, 128.1, 127.2, 62.3, 53.2, 51.8, 34.5, 26.8, 21.6. HRMS: $\text{M}+\text{H}$ calculated for $\text{C}_{19}\text{H}_{23}\text{N}_3\text{O}_2\text{S}$ = 358.1584; observed m/z = 358.1595 (-3.1 ppm). Melting point = 159-161 $^\circ\text{C}$. [Material decomposed to form an orange solid around 150 $^\circ\text{C}$.]

1-Benzyl-4-(benzyl(dimethyl)silanyl)-1,2,3,6-tetrahydro-pyridine (4**)**

To a 1-L round-bottomed flask, added 18.6 g (52 mmol) **2** and 260 mL hexanes. Placed under a nitrogen atmosphere, added 40 mL (267 mmol) TMEDA, placed in a dry ice/acetone bath, and let stir for about 25 minutes. [Reaction formed a white suspension.] Via addition funnel, added 160 mL (256 mmol) *n*-butyllithium solution (1.6 M in

hexanes) dropwise over about 20 minutes. [Reaction turned into a yellow-orange suspension, and the internal temperature rose by about 10 °C.] Let stir at –78 °C for 15 minutes after all of the *n*-butyllithium solution had been added, then removed flask from the dry ice bath and let stir for an additional 1.5 hours. [The internal temperature reached room temperature (ca. 18 °C) over the course of about 1 hour. Over this time period, bubbling was observed, and the reaction slowly became reddish-orange and then reddish-brown.] Next, placed reaction in an ice bath, let stir for about 10 minutes, then added 14 mL (77 mmol) benzyldimethylsilyl chloride (neat) via syringe over about 1 minute. [Reaction quickly turned more reddish in color, and the internal temperature rose by about 15 °C.] Let reaction stir overnight (ca. 16 hours), without maintaining the ice bath. The following day, placed reaction in an ice bath, let stir for about 15 minutes, and then slowly added 400 mL water, portionwise at first. [Reaction turned from reddish-brown to bright yellow, and the internal temperature rose by about 20 °C.] Transferred to a separatory funnel, separated the aqueous and organic layers, and extracted the aqueous layer two times with 300 mL hexanes. [The aqueous and organic layers did not separate immediately, but clean separation was achieved by letting the mixture sit undisturbed for 10-15 minutes.] Dried the combined organic layers with Na₂SO₄, concentrated *in vacuo*, and purified the crude material by silica gel chromatography (automated column, 330 g SiO₂, 0% to 20% EtOAc in hexanes gradient). Obtained 12.19 g of **4** as an orange oil (73%). ¹H NMR (500 MHz, CDCl₃): δ = 7.32 (5H, m), 7.21 (2H, t, *J* = 7.6 Hz), 7.08 (1H, t, *J* = 7.4 Hz), 7.00 (2H, d, *J* = 7.0 Hz), 5.93 (1H, m), 3.59 (2H, s), 3.03 (2H, m), 2.53 (2H, t, *J* = 5.6 Hz), 2.15 (2H, m), 2.15 (2H, s), 0.036 (6H, s). ¹³C NMR (100 MHz, CDCl₃): δ = 140.1, 138.2, 135.2, 134.8, 129.2, 128.18, 128.17, 128.0, 127.0, 123.9, 63.0, 54.3, 49.7, 28.0, 25.1, –4.5. HRMS: M+H calculated for C₂₁H₂₇NSi = 322.1986; observed *m/z* = 322.2000 (–4.5 ppm).

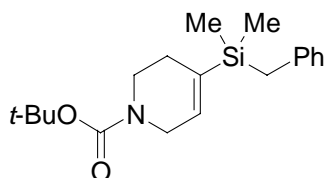
1-Benzyl-4-(benzyldimethylsilanyl)-1,2,3,6-tetrahydro-pyridine hydrochloride (**6**)



To a 250-mL Erlenmeyer flask, open to air, added 10.81 g (33.6 mmol) **4** and 70 mL isopropanol. Let stir at room temperature for about 5 minutes, then added 4.2 mL (50.4 mmol) concentrated HCl. [No immediate precipitation was observed.] Let stir at room temperature overnight. The following day, [A large amount of precipitate was observed at this time.] placed in an ice bath, let stir for approximately 2 hours, then filtered, rinsing the filter cake with approximately 15 mL of cold isopropanol. Obtained 7.85 g of **6** as a white, crystalline solid (65%). [Upon treatment of the mother liquor with 3 M NaOH solution, followed by column chromatography, 2.56 g (7.96 mmol) **4** was recovered.] For **6**: ¹H NMR (500 MHz, CDCl₃): δ = 12.61 (1H, s), 7.63 (2H, m), 7.40 (3H, m), 7.18 (2H, t, *J* = 7.6 Hz), 7.05 (1H, t, *J* = 7.4 Hz), 6.96 (2H, d, *J* = 7.1 Hz), 5.75 (1H, m), 4.18 (1H, dd, *J* = 13.0, 5.4 Hz), 4.08 (1H, dd, *J* = 13.0, 5.8 Hz), 3.74 (1H, d, *J* = 17.0 Hz), 3.32

(2H, m), 2.83 (1H, m), 2.67 (1H, m), 2.14 (2H, s), 2.12 (1H, m), 0.085 (3H, s), 0.080 (3H, s). ^{13}C NMR (125 MHz, CDCl_3): δ = 139.0, 137.4, 131.2, 130.0, 129.2, 128.4, 128.3, 128.0, 126.8, 124.4, 58.2, 49.2, 47.3, 24.8, 23.2, -4.50, -4.54. HRMS: M+H calculated for $\text{C}_{21}\text{H}_{28}\text{NSi}$ = 323.2064; observed m/z = 323.2079 (-4.7 ppm). Elemental analysis: calculated: C: 70.46%, H: 7.88%, N: 3.91%; observed: C: 70.74% (+0.28%), H: 8.24% (+0.36%), N: 4.08% (+0.17%). Melting point = 173-175 °C. [Possible decomposition observed at melting point temperature.]

4-(Benzyltrimethylsilyl)-3,6-dihydro-2H-pyridine-1-*t*-butoxycarbonyl (**7**)



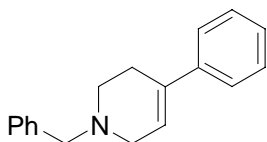
To a 250-mL round-bottomed flask, added 7.2 g (16.8 mmol) **4** and 170 mL CH_2Cl_2 . Placed, under a nitrogen atmosphere, in an ice bath. When the internal temperature fell below 4 °C, added 2.8 mL (25.7 mmol) 1-chloroethylchloroformate. Let temperature rise gradually to 18 °C over about 2 hours, then heated to reflux via heating mantle. Let stir at reflux for 2 hours. Next, let cool to room temperature, removed solvent *in vacuo*, added 170 mL MeOH, and then let stir at reflux for 1 hour. After letting cool to room temperature, added 85 mL 1,4-dioxane, 85 mL 1 N aqueous KOH solution, and 5.5 g (25.2 mmol) di-*t*-butyl dicarbonate. Let stir at room temperature overnight. The following day, extracted 3 times with 250 mL methyl *t*-butyl ether, dried with Na_2SO_4 , and purified by silica gel chromatography (automated column, 120 g SiO_2 , 0% to 10% EtOAc in hexanes gradient). Partitioned column fractions into 2 parts: first part contained 3.0 g of a yellow oil, which was shown to be **7** (ca. 90% purity by ^1H NMR); second part contained 1.8 g of a yellow oil that became a solid upon refrigeration, which was shown to be **7** (>95% purity by ^1H NMR). Overall yield was approximately 80%. ^1H NMR (600 MHz, $\text{DMSO}-d_6$, 80 °C): δ = 7.18 (2H, t, J = 7.5 Hz), 7.04 (1H, t, J = 7.3 Hz), 6.99 (2H, d, J = 7.6 Hz), 5.92 (1H, s), 3.83 (2H, m), 3.34 (2H, t, J = 5.6 Hz), 2.15 (2H, s), 2.05 (2H, br), 1.43 (9H, s), 0.030 (6H, s). ^{13}C NMR (150 MHz, $\text{DMSO}-d_6$, 80 °C): δ = 153.5, 139.1, 134.9, 133.2, 127.4, 127.3, 123.3, 78.1, 43.9, 39.5, 27.6, 26.0, 23.8, -5.0. HRMS: M+H calculated for $\text{C}_{19}\text{H}_{29}\text{NO}_2\text{Si}$ = 332.2040; observed m/z = 332.2036 (-1.3 ppm). Note: Applied the more pure portion of **7** to the cross-coupling reaction, generating known compound **8**.^{14b}

Representative procedure for the cross-coupling of aryl iodides. To a 4-mL vial, added 100 mg (0.28 mmol) **6** and 6 mg (0.0058 mmol) tris(dibenzylideneacetone)-dipalladium(0)-chloroform adduct ($\text{Pd}_2\text{dba}_3\text{-CHCl}_3$). Next added 0.3 mL THF, 48 μL (0.43 mmol) iodobenzene, and finally 1.1 mL (1.1 mmol) TBAF solution (1 M in THF). [Reaction quickly became clear upon TBAF addition.] Let stir at room temperature for 18 hours. At the end of the reaction, added 200 μL triethylamine [in order to neutralize any residual acid], let stir briefly, concentrated *in vacuo*, and purified the crude material

directly by silica gel chromatography (automated column, 12 g SiO₂, 0% to 20% EtOAc in hexanes gradient). Obtained 63 mg (90%) of 1-benzyl-4-phenyl-1,2,3,6-tetrahydro-pyridine as a yellow oil.

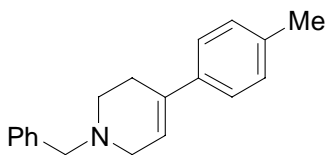
Representative procedure for the cross-coupling of aryl bromides. To a 4-mL vial, added 100 mg (0.28 mmol) **6**, 4 mg (0.015 mmol) palladium(II) bromide (PdBr₂), and 8 mg (0.027 mmol) 2-(di-*t*-butylphosphino)biphenyl (2-(*t*-Bu₂P)bp). Next added 0.3 mL THF, 44 μ L (0.42 mmol) bromobenzene, and finally 1.1 mL (1.1 mmol) TBAF solution (1 M in THF). [Reaction quickly became clear upon TBAF addition.] Let stir at 50 °C for 20 hours. At the end of the reaction, added 200 μ L triethylamine [in order to neutralize any residual acid], let stir briefly, concentrated *in vacuo*, and purified the crude material directly by silica gel chromatography (automated column, 12 g SiO₂, 0% to 20% EtOAc in hexanes gradient). Obtained 52 mg (74%) of 1-benzyl-4-phenyl-1,2,3,6-tetrahydro-pyridine as a yellow oil.

1-Benzyl-4-phenyl-1,2,3,6-tetrahydro-pyridine

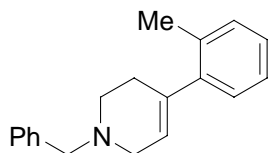


¹H NMR (400 MHz, CDCl₃): δ = 7.30 (10H, m), 6.05 (1H, m), 3.63 (2H, s), 3.17 (2H, m), 2.71 (2H, t, *J* = 5.7 Hz), 2.56 (2H, m). ¹³C NMR (125 MHz, CDCl₃): δ = 140.9, 138.2, 134.9, 129.2, 128.23, 128.21, 127.1, 126.9, 124.9, 121.9, 62.7, 53.3, 49.9, 28.0. HRMS: M+H calculated for C₁₈H₁₉N = 250.1590; observed *m/z* = 250.1602 (-4.7 ppm).

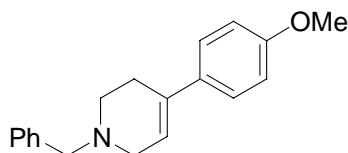
1-Benzyl-4-*p*-tolyl-1,2,3,6-tetrahydro-pyridine



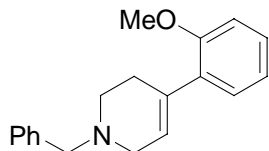
¹H NMR (500 MHz, CDCl₃): δ = 7.33 (7H, m), 7.11 (2H, d, *J* = 7.9 Hz), 6.02 (1H, m), 3.63 (2H, s), 3.16 (2H, m), 2.70 (2H, t, *J* = 5.7 Hz), 2.54 (2H, m), 2.32 (3H, s). ¹³C NMR (125 MHz, CDCl₃): δ = 138.3, 138.0, 136.5, 134.7, 129.2, 128.9, 128.2, 127.0, 124.7, 121.0, 62.7, 53.3, 50.0, 28.0, 21.0. HRMS: M+H calculated for C₁₉H₂₁N = 264.1747; observed *m/z* = 264.1741 (2.2 ppm).

1-Benzyl-4-*o*-tolyl-1,2,3,6-tetrahydro-pyridine

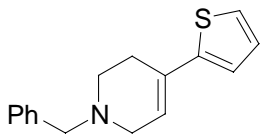
^1H NMR (500 MHz, CDCl_3): δ = 7.37 (2H, d, J = 8.3 Hz), 7.32 (2H, t, J = 7.4 Hz), 7.25 (1H, t, J = 7.2 Hz), 7.11 (4H, m), 5.51 (1H, m), 3.64 (2H, s), 3.13 (2H, m), 2.67 (2H, t, J = 5.6 Hz), 2.35 (2H, m), 2.28 (3H, s). ^{13}C NMR (125 MHz, CDCl_3): δ = 142.9, 138.2, 137.0, 135.0, 130.0, 129.2, 128.2, 127.0, 126.7, 125.5, 123.6, 62.7, 52.9, 49.8, 30.7, 19.9. HRMS: $\text{M}+\text{H}$ calculated for $\text{C}_{19}\text{H}_{21}\text{N}$ = 264.1747; observed m/z = 264.1746 (0.3 ppm).

1-Benzyl-4-(4-methoxy-phenyl)-1,2,3,6-tetrahydro-pyridine

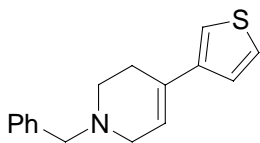
^1H NMR (500 MHz, CDCl_3): δ = 7.30 (7H, m), 6.83 (2H, d, J = 8.9 Hz), 5.96 (1H, m), 3.78 (3H, s), 3.62 (2H, s), 3.15 (2H, m), 2.69 (2H, t, J = 5.7 Hz), 2.52 (2H, m). ^{13}C NMR (125 MHz, CDCl_3): δ = 158.6, 138.3, 134.2, 133.5, 129.2, 128.2, 127.0, 125.9, 120.2, 113.6, 62.7, 55.2, 53.3, 50.0, 28.1. HRMS: $\text{M}+\text{H}$ calculated for $\text{C}_{19}\text{H}_{21}\text{NO}$ = 280.1696; observed m/z = 280.1702 (-2.2 ppm).

1-Benzyl-4-(2-methoxy-phenyl)-1,2,3,6-tetrahydro-pyridine

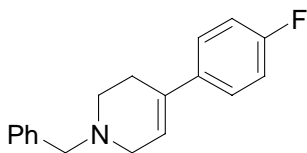
^1H NMR (500 MHz, CDCl_3): δ = 7.40 (2H, d, J = 7.1 Hz), 7.34 (2H, t, J = 7.5 Hz), 7.22 (3H, m), 6.91 (1H, td, J = 7.4, 0.77 Hz), 6.86 (1H, d, J = 8.2 Hz), 5.79 (1H, m), 3.80 (3H, s), 3.66 (2H, s), 3.18 (2H, m), 2.69 (2H, t, J = 5.7 Hz), 2.56 (2H, m). ^{13}C NMR (125 MHz, CDCl_3): δ = 156.8, 138.2, 135.5, 131.9, 129.4, 129.2, 128.2, 128.0, 127.0, 123.9, 120.5, 110.7, 62.8, 55.3, 53.2, 49.9, 29.5. HRMS: $\text{M}+\text{H}$ calculated for $\text{C}_{19}\text{H}_{21}\text{NO}$ = 280.1696; observed m/z = 280.1697 (-0.4 ppm).

1-Benzyl-4-thiophen-2-yl-1,2,3,6-tetrahydro-pyridine

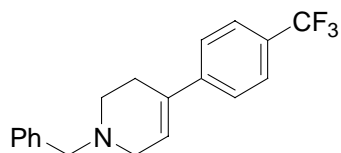
^1H NMR (400 MHz, CDCl_3): δ = 7.32 (5H, m), 7.10 (1H, dd, J = 4.6, 1.6 Hz), 6.94 (2H, m), 6.07 (1H, m), 3.62 (2H, s), 3.14 (2H, m), 2.69 (2H, t, J = 5.7 Hz), 2.56 (2H, m). ^{13}C NMR (125 MHz, CDCl_3): δ = 145.4, 138.2, 129.6, 129.1, 128.2, 127.12, 127.08, 123.1, 121.7, 121.0, 62.5, 52.9, 49.6, 28.3. HRMS: $\text{M}+\text{H}$ calculated for $\text{C}_{16}\text{H}_{17}\text{NS}$ = 256.1154; observed m/z = 256.1160 (-2.2 ppm).

1-Benzyl-4-thiophen-3-yl-1,2,3,6-tetrahydro-pyridine

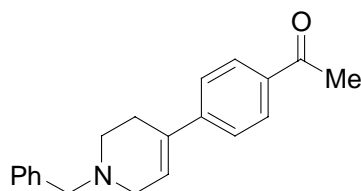
^1H NMR (500 MHz, CDCl_3): δ = 7.28 (7H, m), 7.06 (1H, m), 6.04 (1H, m), 3.61 (2H, s), 3.13 (2H, m), 2.68 (2H, t, J = 5.7 Hz), 2.52 (2H, m). ^{13}C NMR (125 MHz, CDCl_3): δ = 142.6, 138.3, 130.4, 129.1, 128.2, 127.0, 125.3, 124.6, 121.0, 118.6, 62.6, 53.0, 49.7, 28.0. HRMS: $\text{M}+\text{H}$ calculated for $\text{C}_{16}\text{H}_{17}\text{NS}$ = 256.1154; observed m/z = 256.1163 (-3.3 ppm).

1-Benzyl-4-(4-fluoro-phenyl)-1,2,3,6-tetrahydro-pyridine

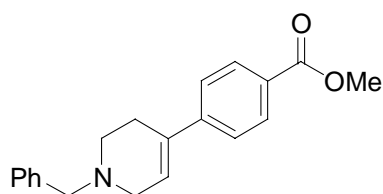
^1H NMR (400 MHz, CDCl_3): δ = 7.32 (7H, m), 6.98 (2H, t, J = 8.8 Hz), 5.99 (1H, m), 3.63 (2H, s), 3.15 (2H, m), 2.70 (2H, t, J = 5.7 Hz), 2.52 (2H, m). ^{13}C NMR (125 MHz, CDCl_3): δ = 162.0 (d, J = 246 Hz), 138.2, 137.0 (d, J = 3.2 Hz), 134.0, 129.2, 128.3, 127.1, 126.4 (d, J = 7.8 Hz), 121.8, 115.0 (J = 21 Hz), 62.7, 53.2, 49.9, 28.2. HRMS: $\text{M}+\text{H}$ calculated for $\text{C}_{18}\text{H}_{18}\text{NF}$ = 268.1496; observed m/z = 268.1506 (-3.7 ppm).

1-Benzyl-4-(4-trifluoromethyl-phenyl)-1,2,3,6-tetrahydro-pyridine

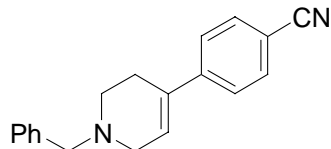
^1H NMR (400 MHz, CDCl_3): δ = 7.50 (2H, d, J = 8.3 Hz), 7.40 (2H, d, J = 8.2 Hz), 7.29 (5H, m), 6.09 (1H, m), 3.59 (2H, s), 3.13 (2H, m), 2.66 (2H, t, J = 5.7 Hz), 2.49 (2H, m). ^{13}C NMR (100 MHz, CDCl_3): δ = 144.2, 138.0, 133.8, 129.1, 128.7 (q, J = 32 Hz), 128.2, 127.1, 125.1 (q, J = 3.8 Hz), 124.9, 124.3 (q, J = 272 Hz), 124.1, 62.6, 53.1, 49.6, 27.8. HRMS: $\text{M}+\text{H}$ calculated for $\text{C}_{19}\text{H}_{18}\text{NF}_3$ = 318.1464; observed m/z = 318.1468 (-1.2 ppm).

1-[4-(1-Benzyl-1,2,3,6-tetrahydro-pyridin-4-yl)-phenyl]-ethanone

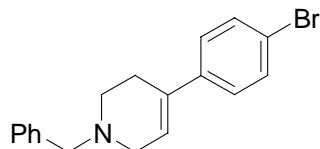
^1H NMR (400 MHz, CDCl_3): δ = 7.88 (2H, d, J = 8.6 Hz), 7.44 (2H, d, J = 8.5 Hz), 7.30 (5H, m), 6.19 (1H, m), 3.62 (2H, s), 3.17 (2H, m), 2.71 (2H, t, J = 5.7 Hz), 2.56 (2H, m), 2.55 (3H, s). ^{13}C NMR (125 MHz, CDCl_3): δ = 197.5, 145.3, 138.0, 135.5, 134.1, 129.1, 128.4, 128.2, 127.1, 124.8, 124.5, 62.6, 53.2, 49.7, 27.8, 26.4. HRMS: $\text{M}+\text{H}$ calculated for $\text{C}_{20}\text{H}_{21}\text{NO}$ = 292.1696; observed m/z = 292.1707 (-3.8 ppm).

4-(1-Benzyl-1,2,3,6-tetrahydro-pyridin-4-yl)-benzoic acid methyl ester

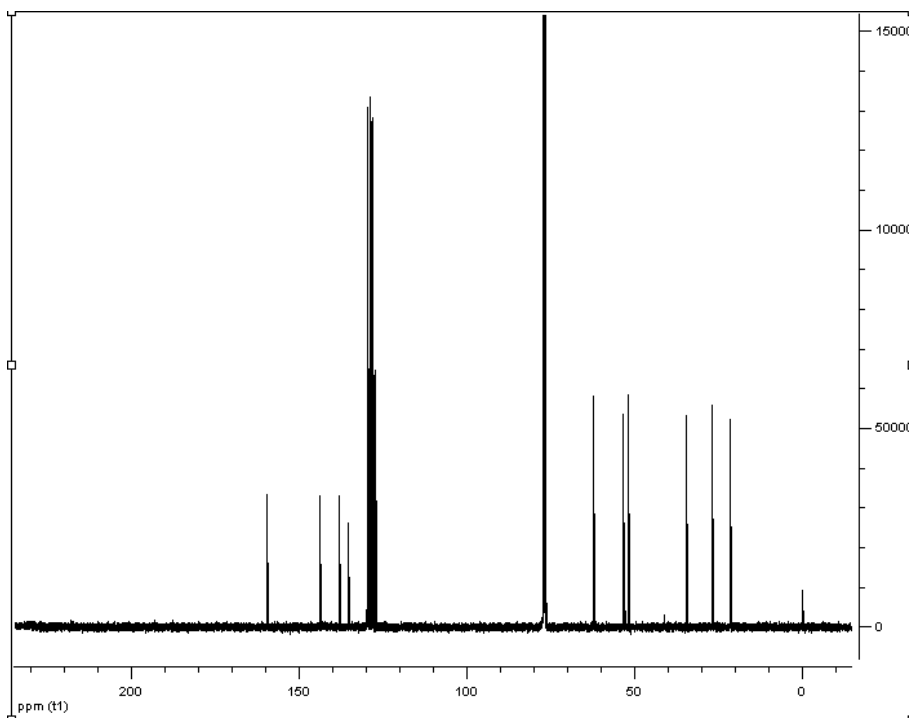
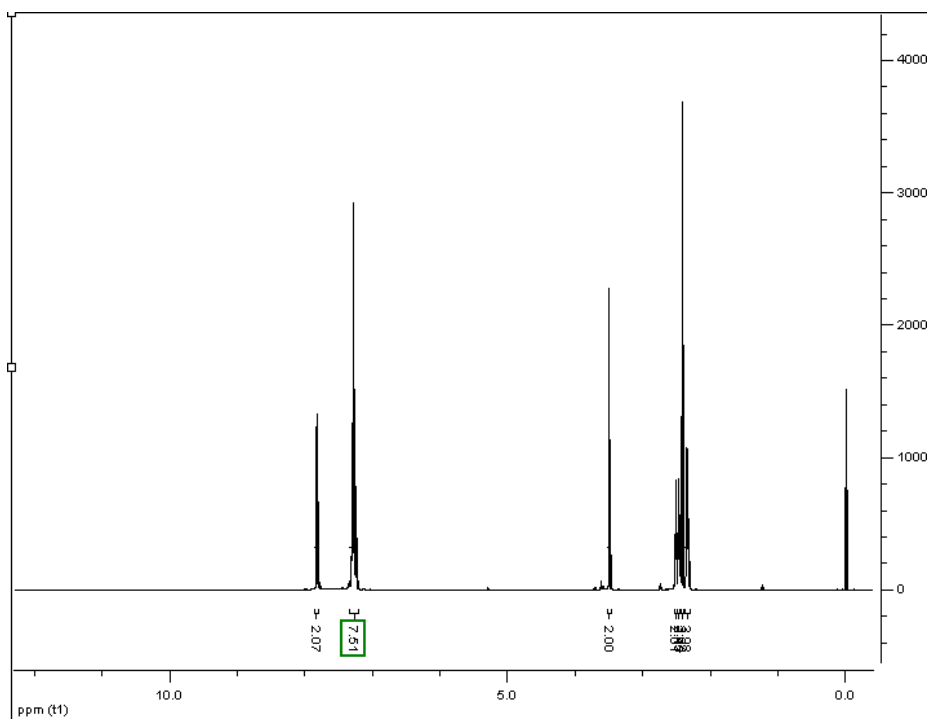
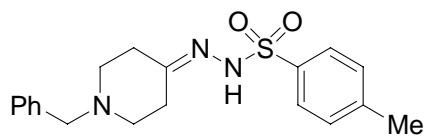
^1H NMR (500 MHz, CDCl_3): δ = 7.97 (2H, d, J = 8.5 Hz), 7.43 (2H, d, J = 8.5 Hz), 7.34 (5H, m), 6.19 (1H, m), 3.89 (3H, s), 3.63 (2H, s), 3.18 (2H, m), 2.71 (2H, t, J = 5.7 Hz), 2.56 (2H, m). ^{13}C NMR (125 MHz, CDCl_3): δ = 166.9, 145.1, 138.1, 134.2, 129.6, 129.1, 128.4, 128.2, 127.1, 124.6, 124.2, 62.6, 53.3, 51.9, 49.7, 27.8. HRMS: $\text{M}+\text{H}$ calculated for $\text{C}_{20}\text{H}_{21}\text{NO}_2$ = 308.1645; observed m/z = 308.1647 (-0.6 ppm).

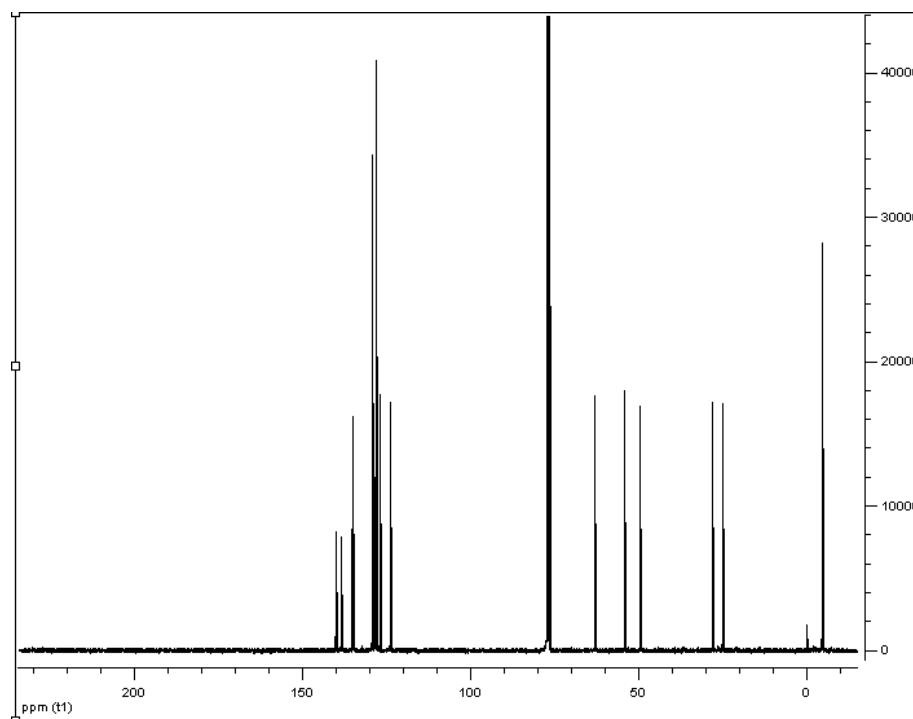
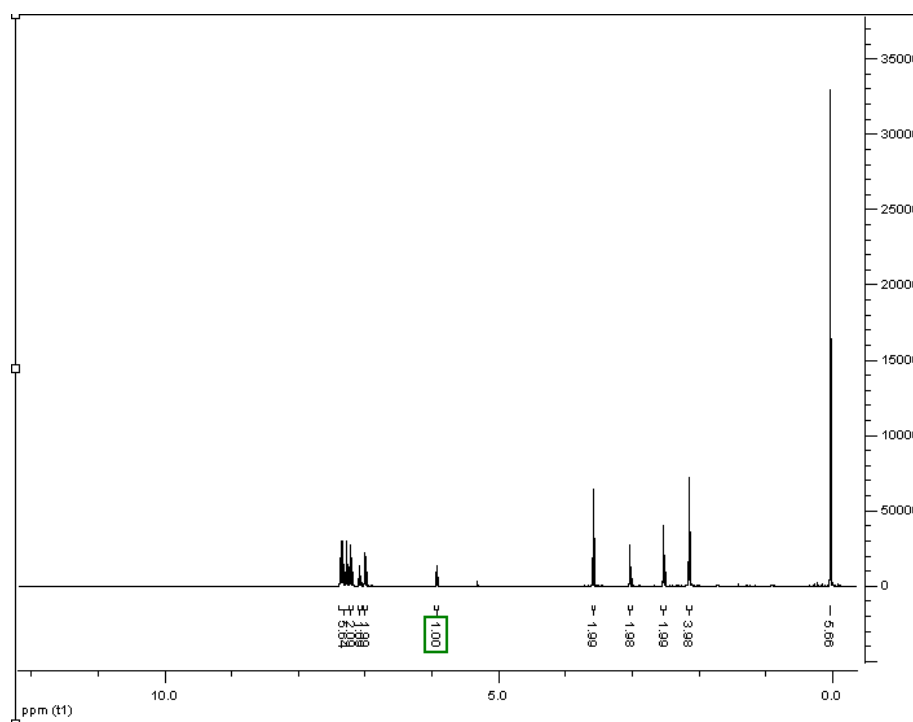
4-(1-Benzyl-1,2,3,6-tetrahydro-pyridin-4-yl)-benzonitrile

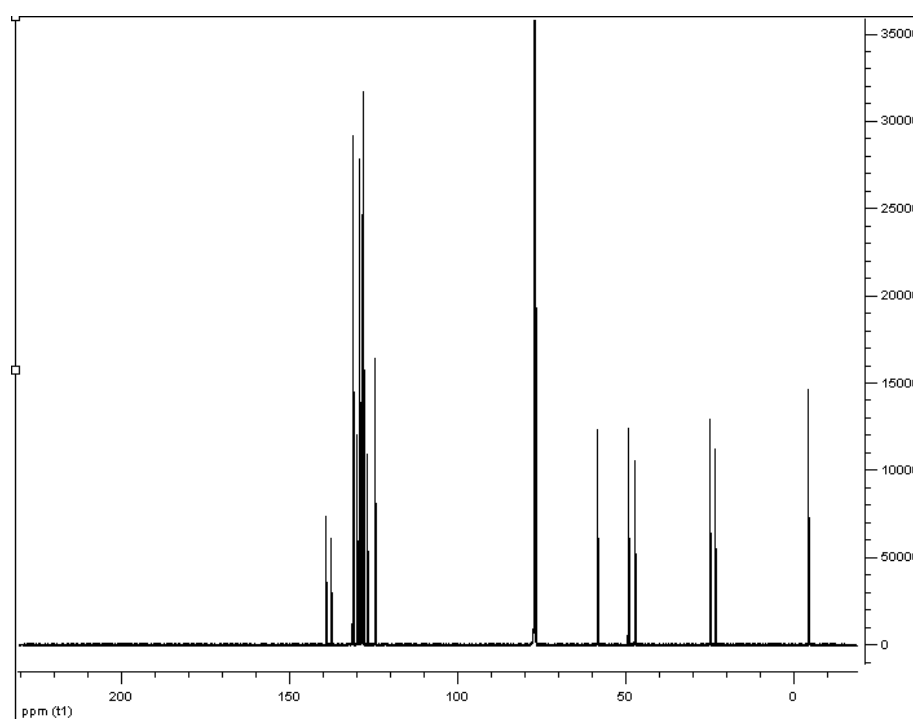
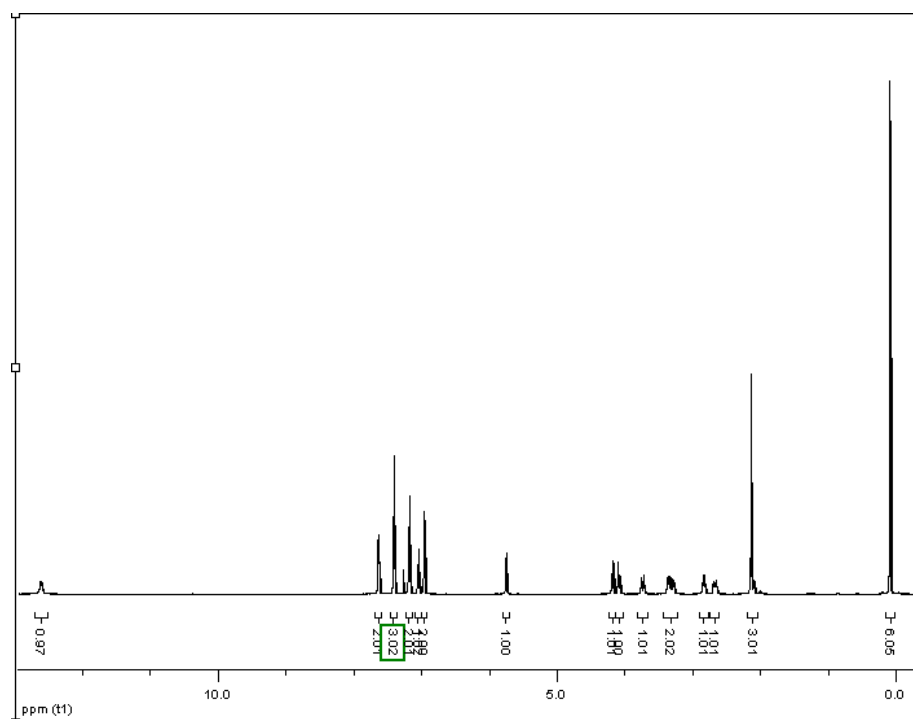
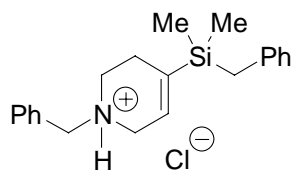
^1H NMR (500 MHz, CDCl_3): δ = 7.58 (2H, d, J = 8.6 Hz), 7.45 (2H, d, J = 8.5 Hz), 7.32 (5H, m), 6.20 (1H, m), 3.64 (2H, s), 3.19 (2H, m), 2.72 (2H, t, J = 5.7 Hz), 2.53 (2H, m). ^{13}C NMR (125 MHz, CDCl_3): δ = 145.1, 137.9, 133.6, 132.1, 129.1, 128.2, 127.1, 125.4, 125.3, 119.0, 110.2, 62.5, 53.2, 49.6, 27.7. HRMS: $M+H$ calculated for $\text{C}_{19}\text{H}_{18}\text{N}_2$ = 275.1543; observed m/z = 275.1554 (-4.1 ppm).

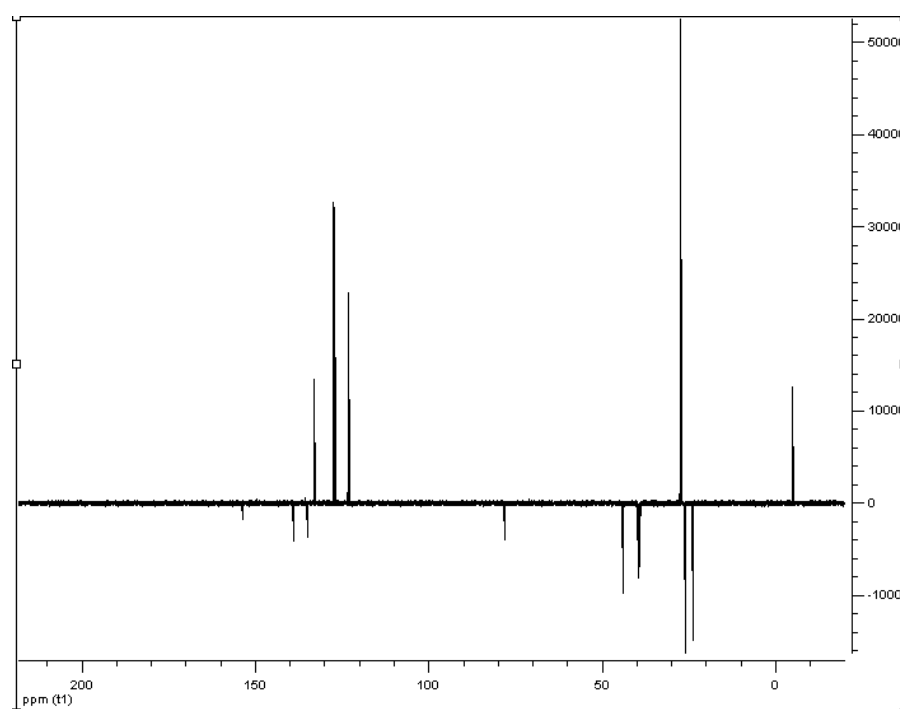
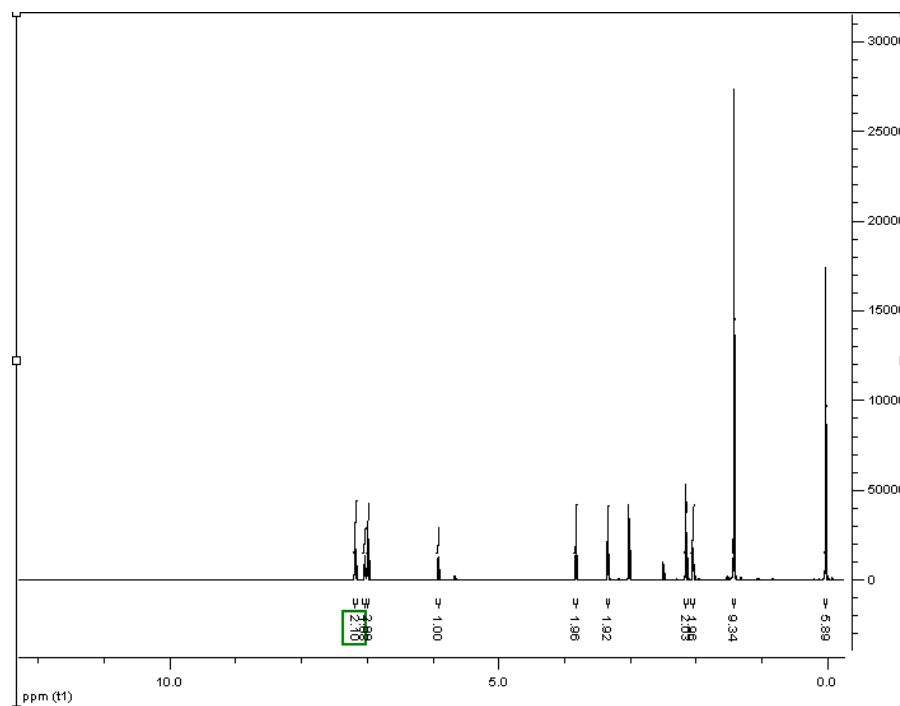
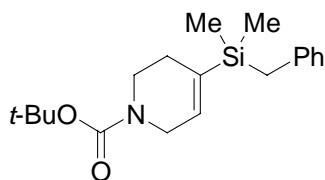
1-Benzyl-4-(4-bromo-phenyl)-1,2,3,6-tetrahydro-pyridine

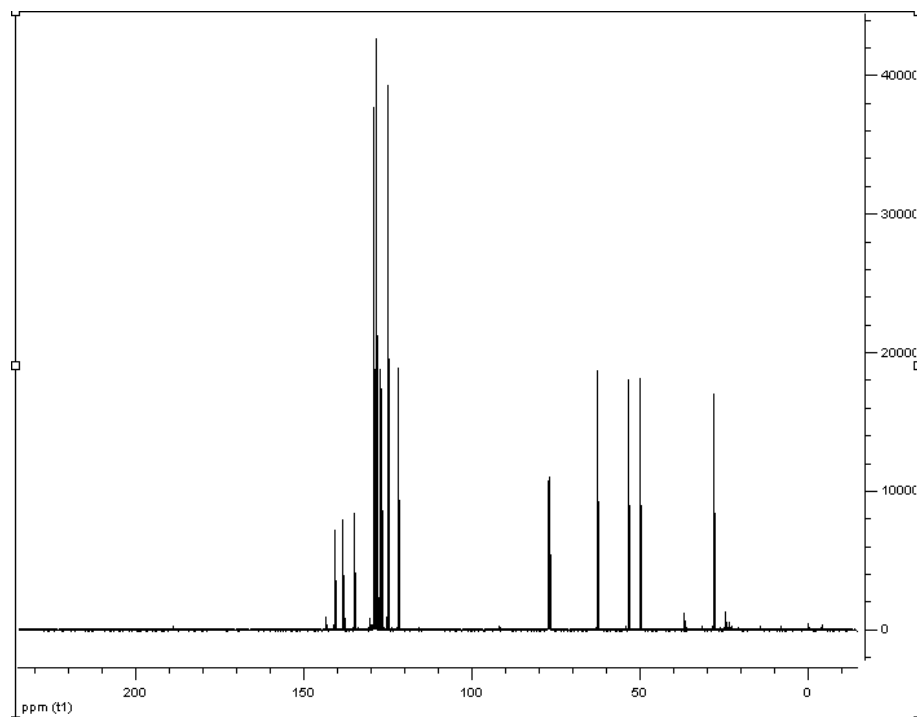
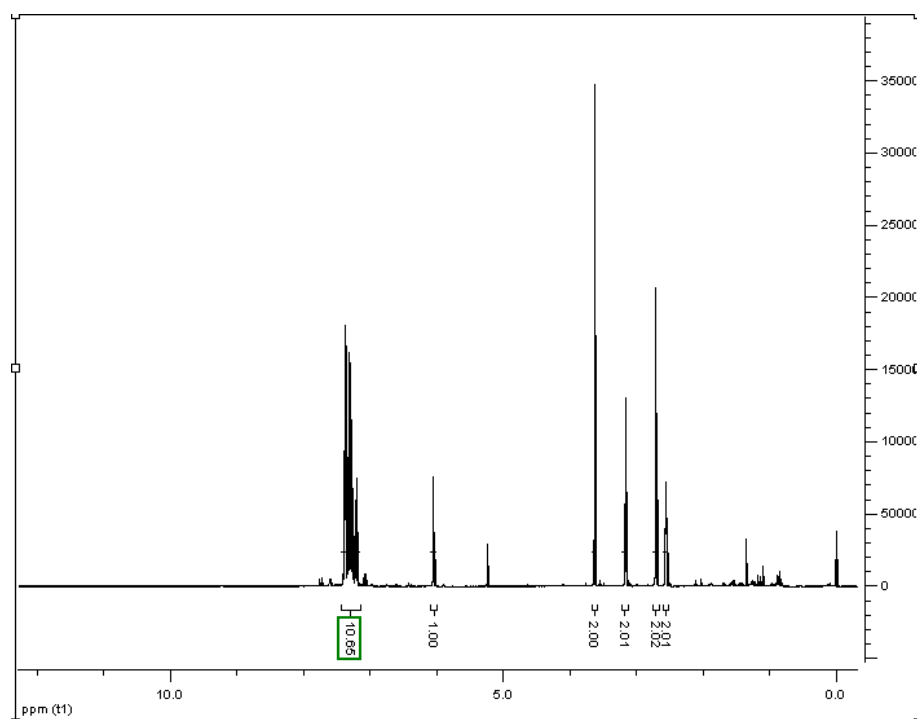
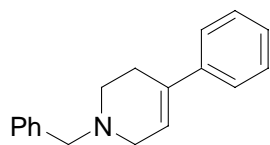
^1H NMR (400 MHz, CDCl_3): δ = 7.32 (9H, m), 6.05 (1H, m), 3.63 (2H, s), 3.14 (2H, m), 2.70 (2H, t, J = 5.7 Hz), 2.50 (2H, m). ^{13}C NMR (125 MHz, CDCl_3): δ = 139.7, 138.1, 134.0, 131.3, 129.2, 128.3, 127.1, 126.5, 122.6, 120.7, 62.7, 53.2, 49.8, 27.9. HRMS: $M+H$ calculated for $\text{C}_{18}\text{H}_{18}\text{NBr}$ = 328.0695; observed m/z = 328.0702 (-2.0 ppm).

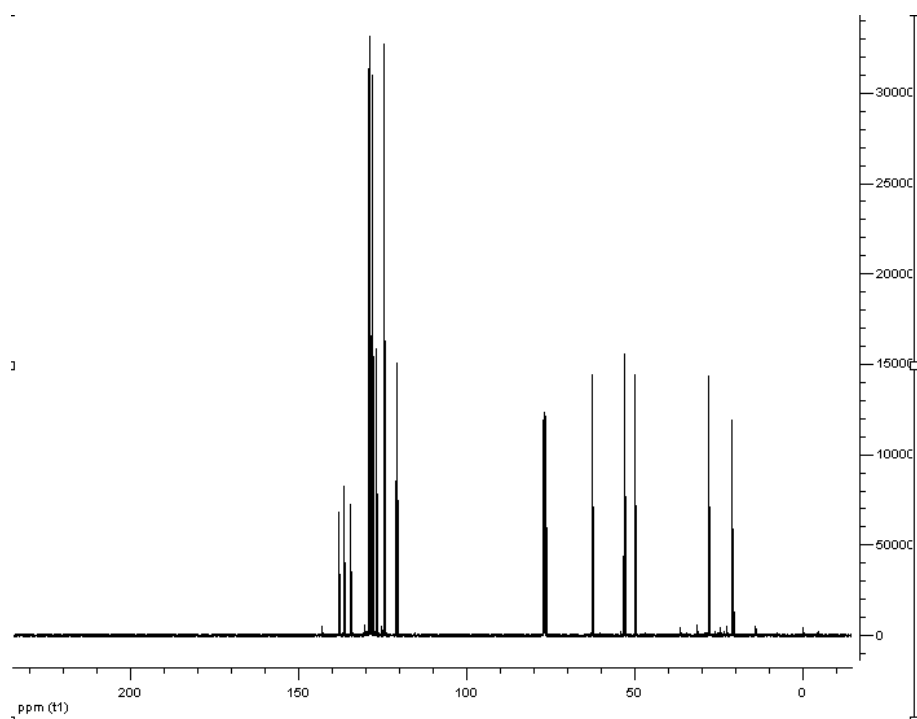
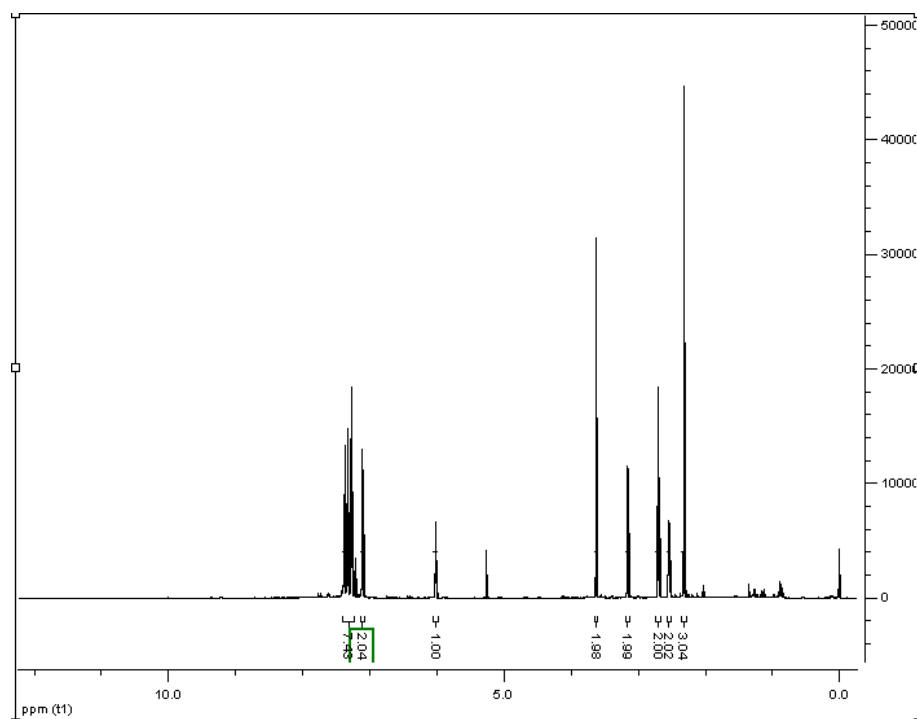
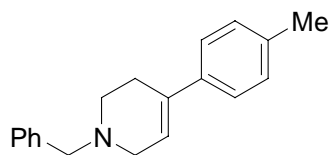
***N*-(1-Benzyl-piperidin-4-ylidene)-*N'*-tosyl-hydrazine (2)**

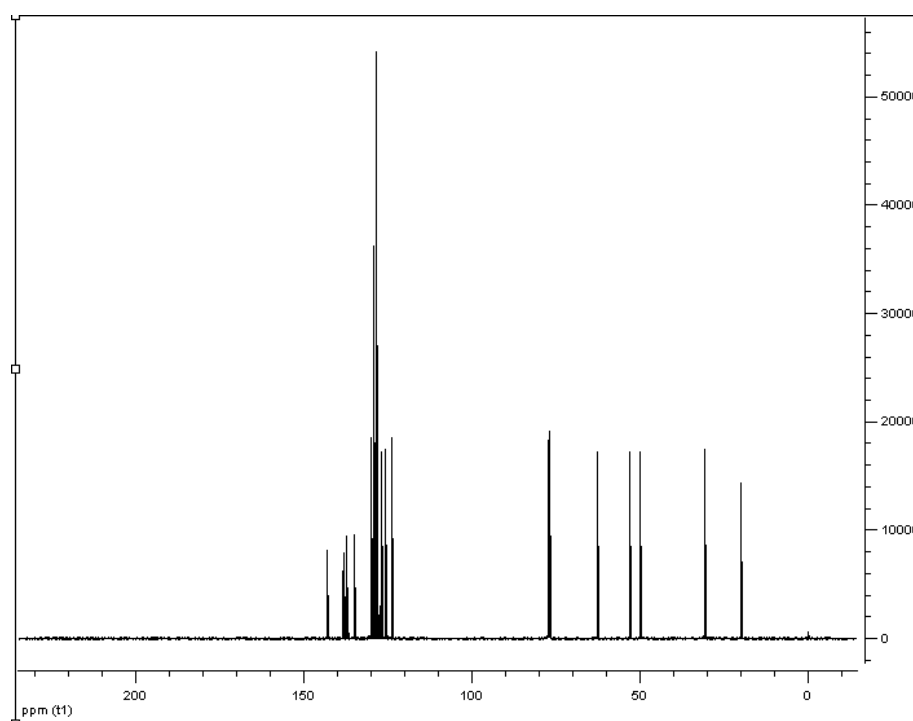
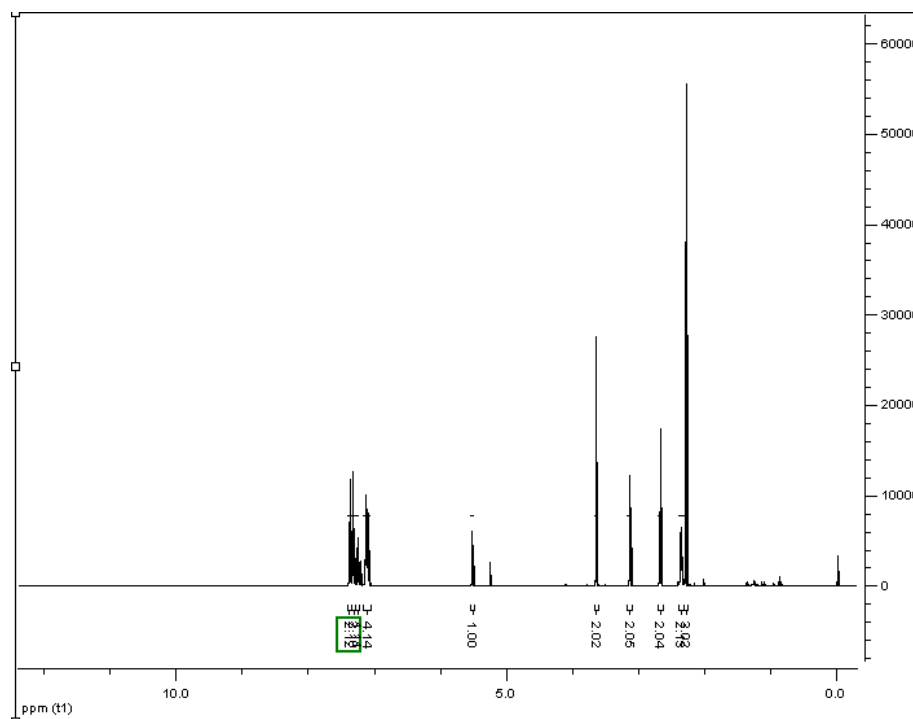
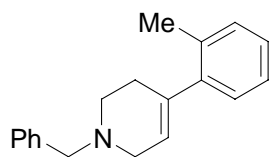
CC(C)(Cc1ccccc1)c2ccn(Cc3ccccc3)cc2

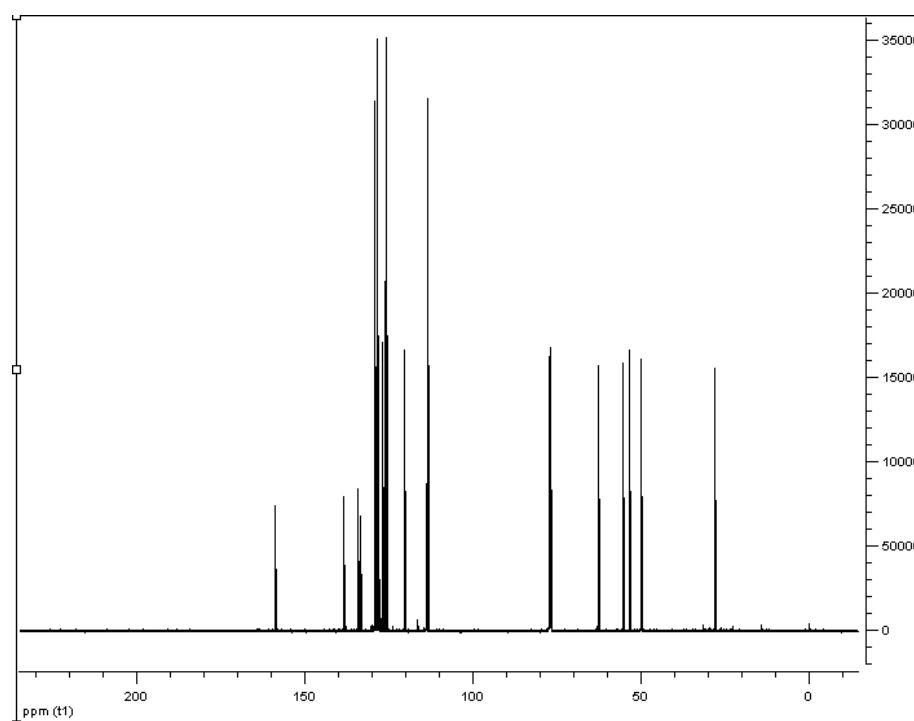
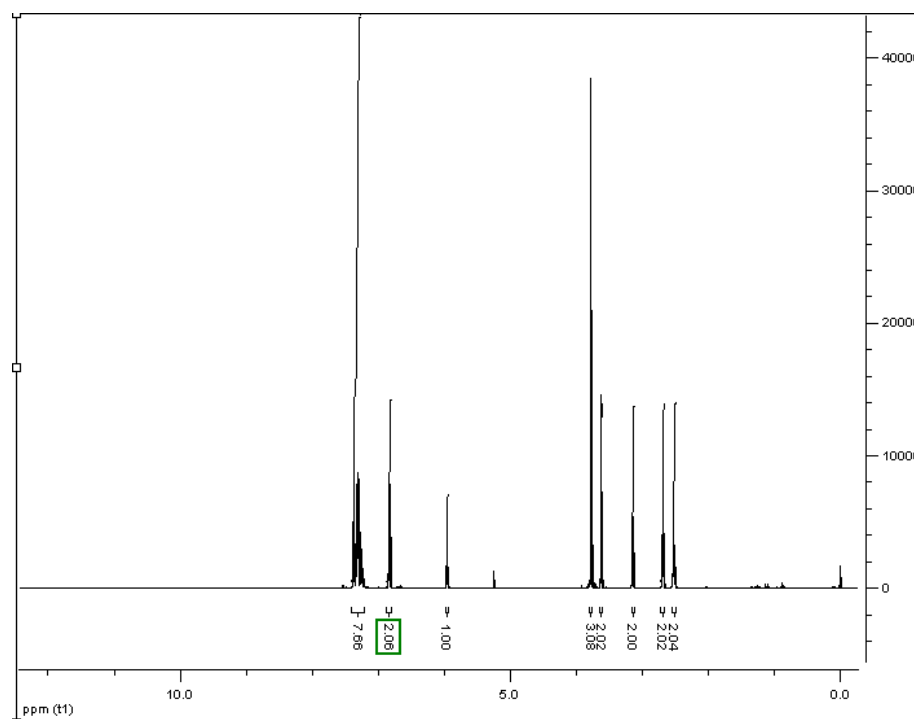
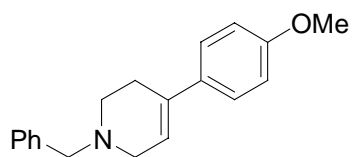
1-Benzyl-4-(benzyl(dimethyl)silanyl)-1,2,3,6-tetrahydro-pyridine hydrochloride (6)

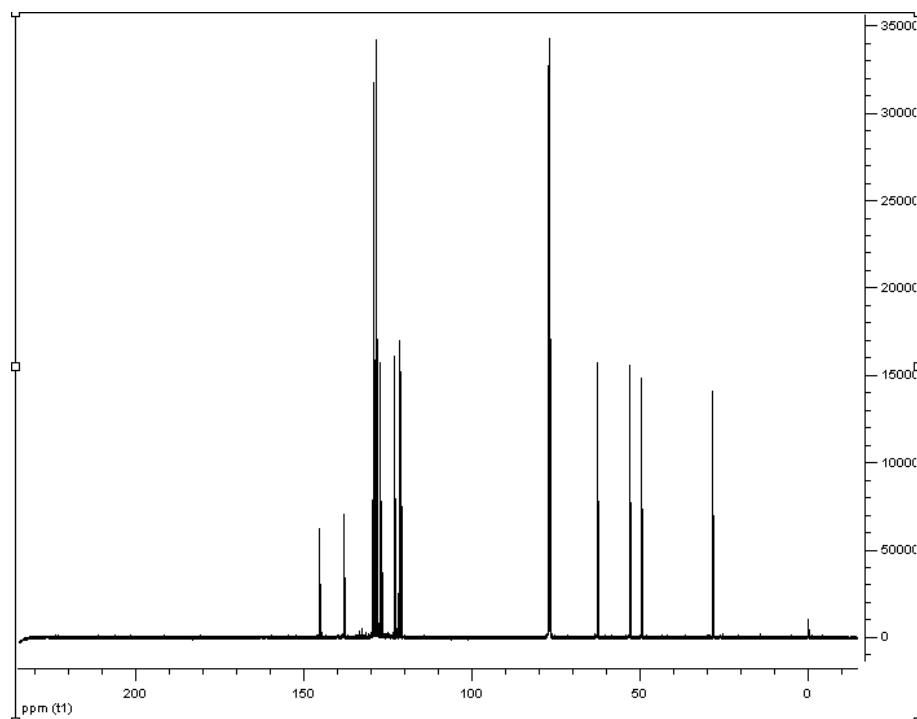
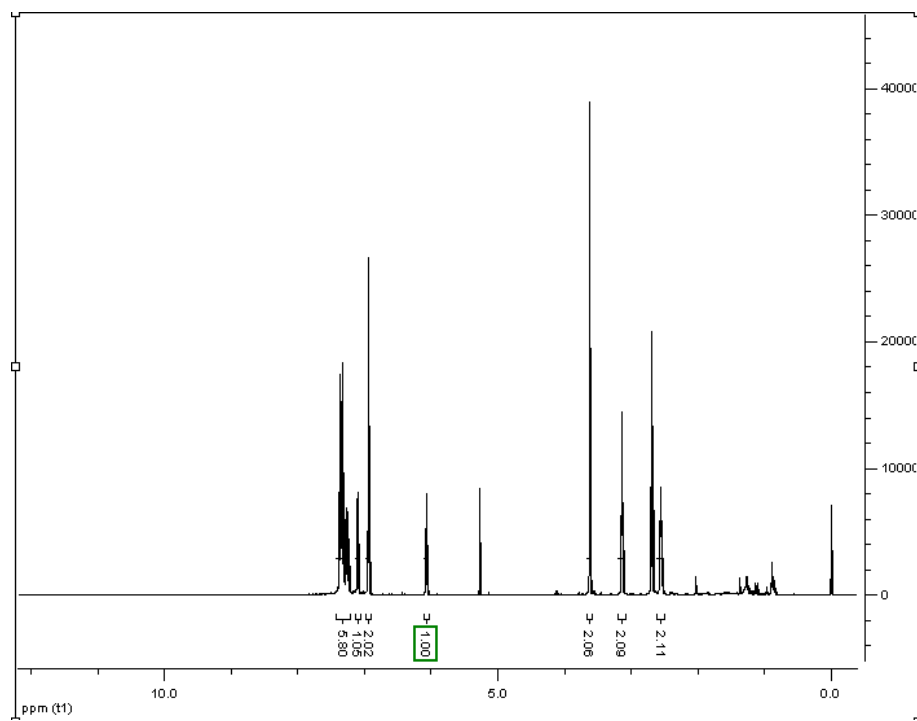
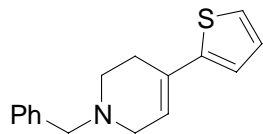
4-(Benzyldimethylsilanyl)-3,6-dihydro-2H-pyridine-1-*t*-butoxycarbonyl (7)

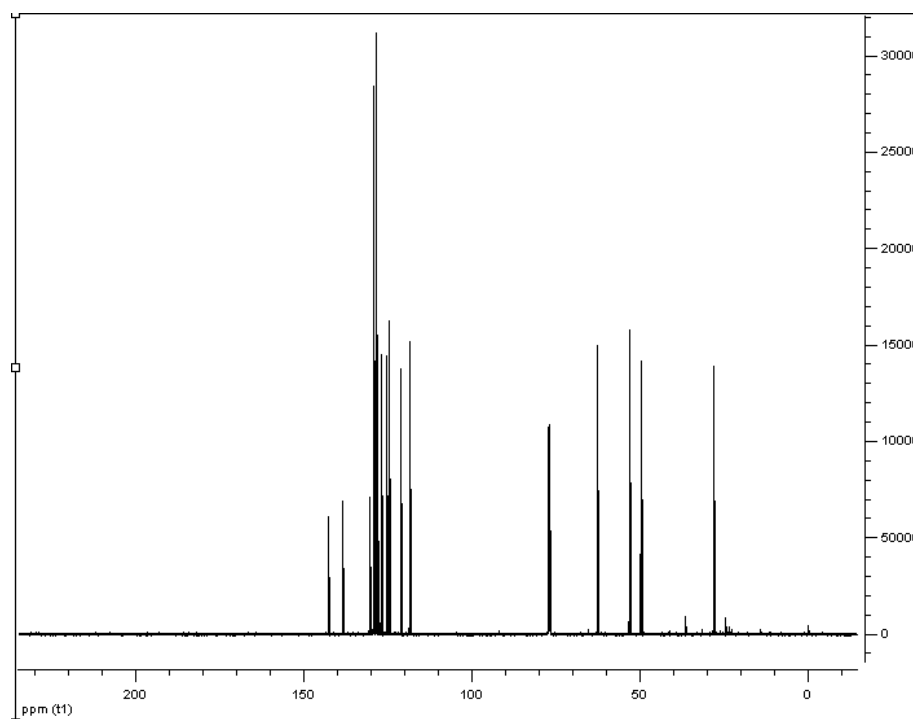
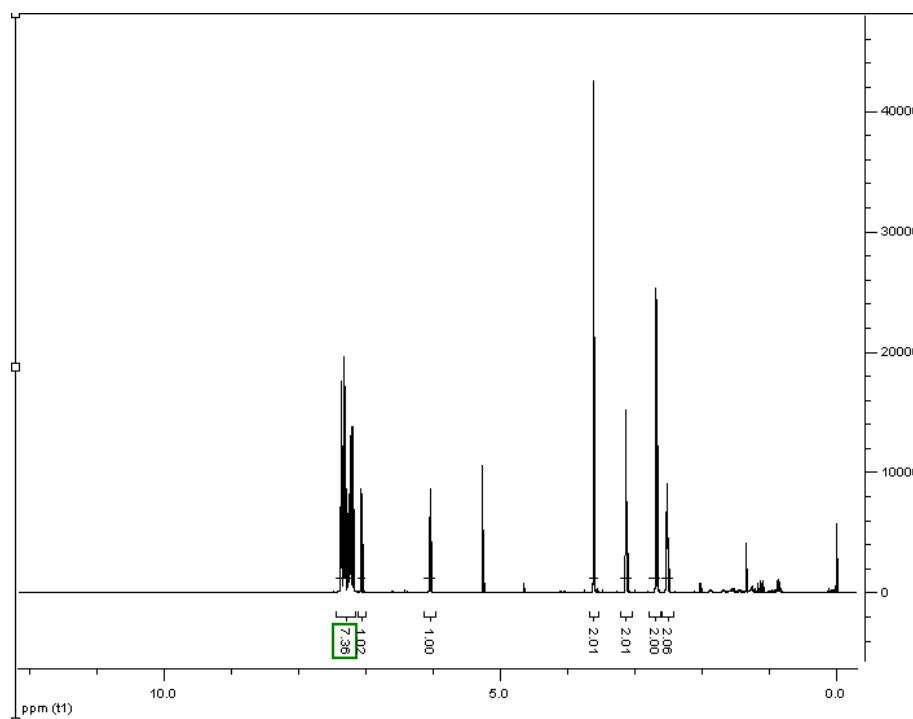
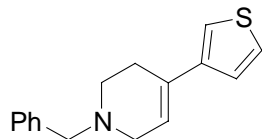
1-Benzyl-4-phenyl-1,2,3,6-tetrahydro-pyridine (Table 2, entry 1)

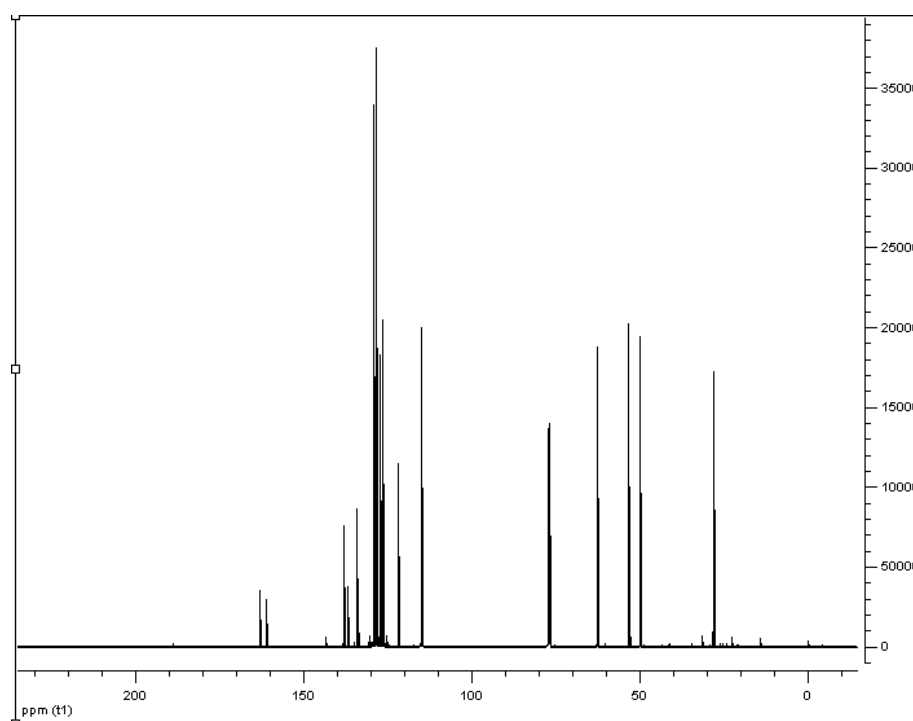
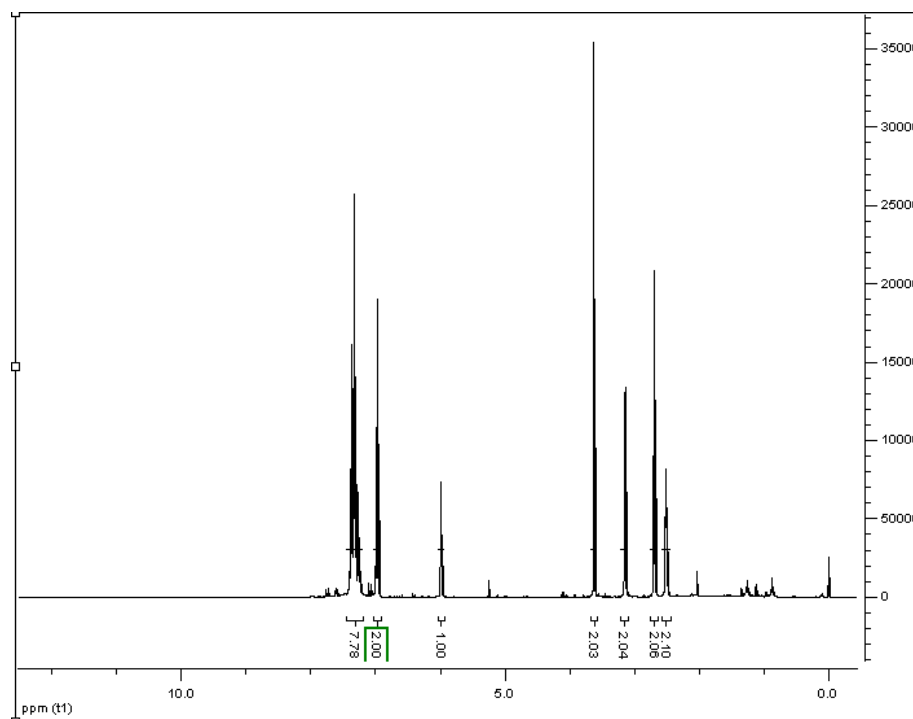
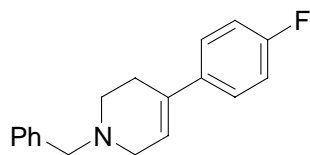
1-Benzyl-4-*p*-tolyl-1,2,3,6-tetrahydro-pyridine (Table 2, entry 2)

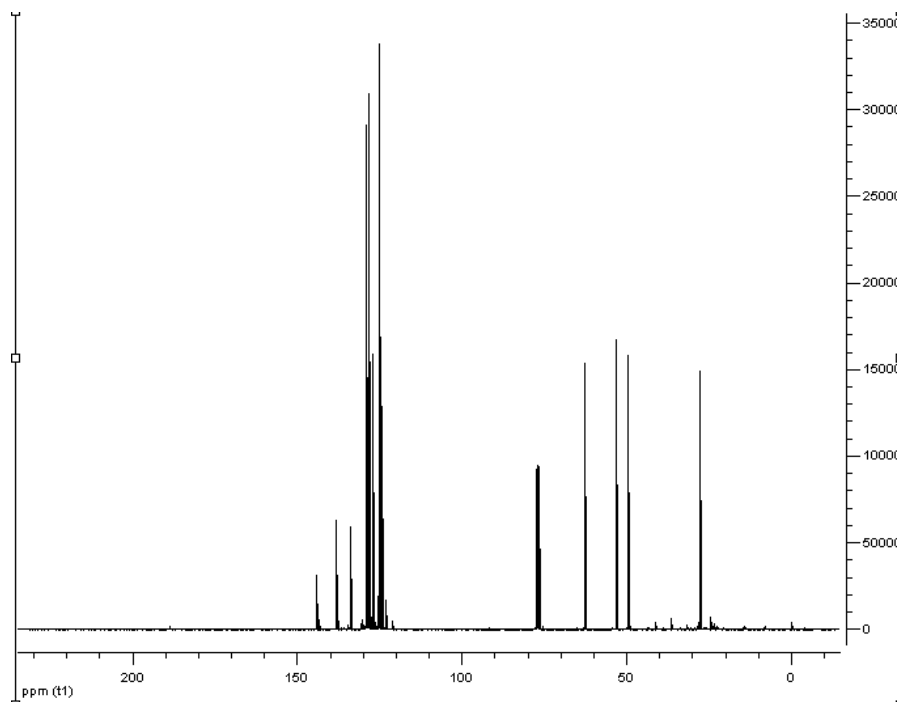
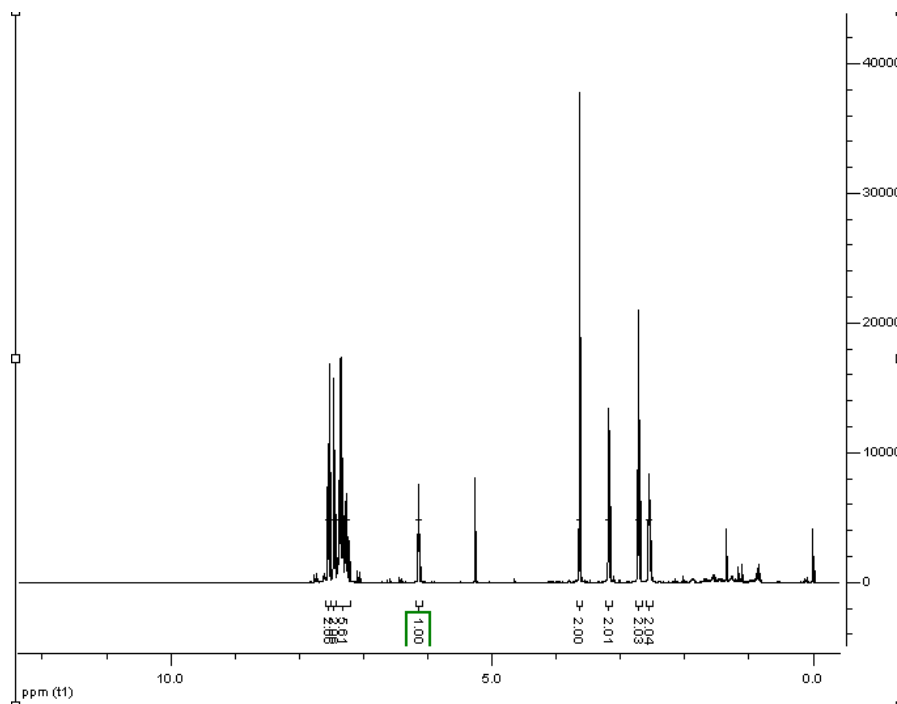
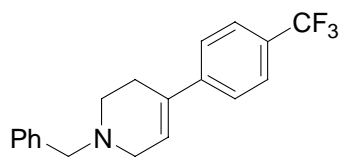
1-Benzyl-4-*o*-tolyl-1,2,3,6-tetrahydro-pyridine (Table 2, entry 4)

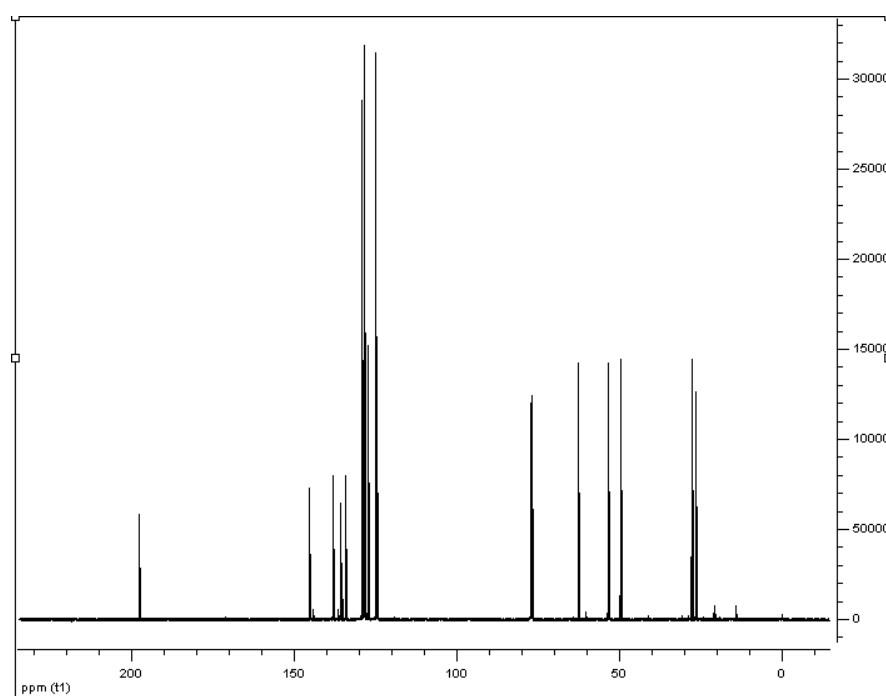
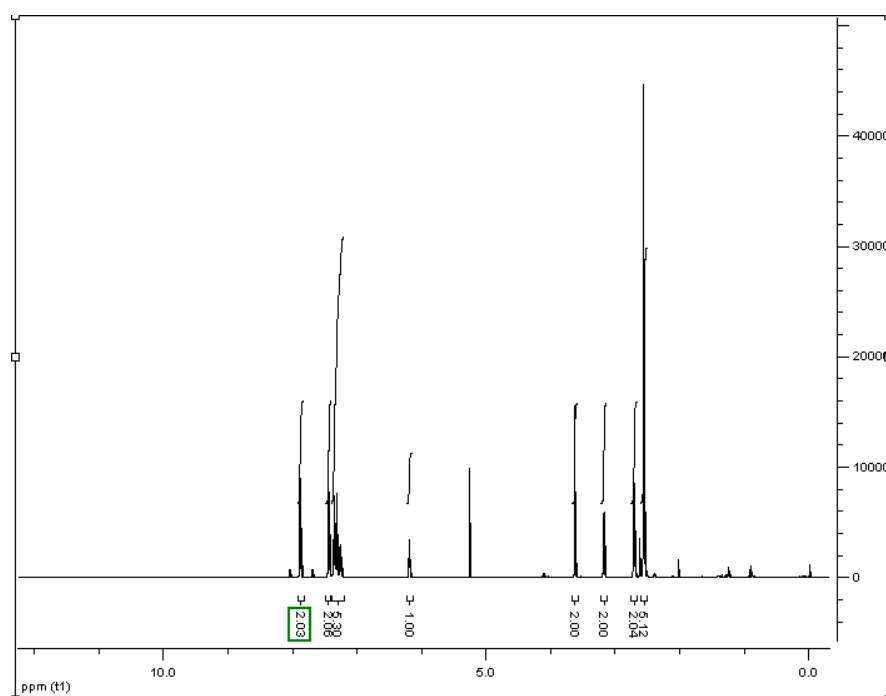
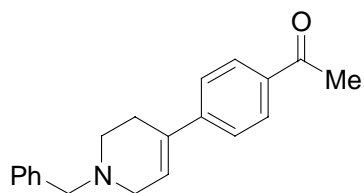
1-Benzyl-4-(4-methoxy-phenyl)-1,2,3,6-tetrahydro-pyridine (Table 2, entry 5)

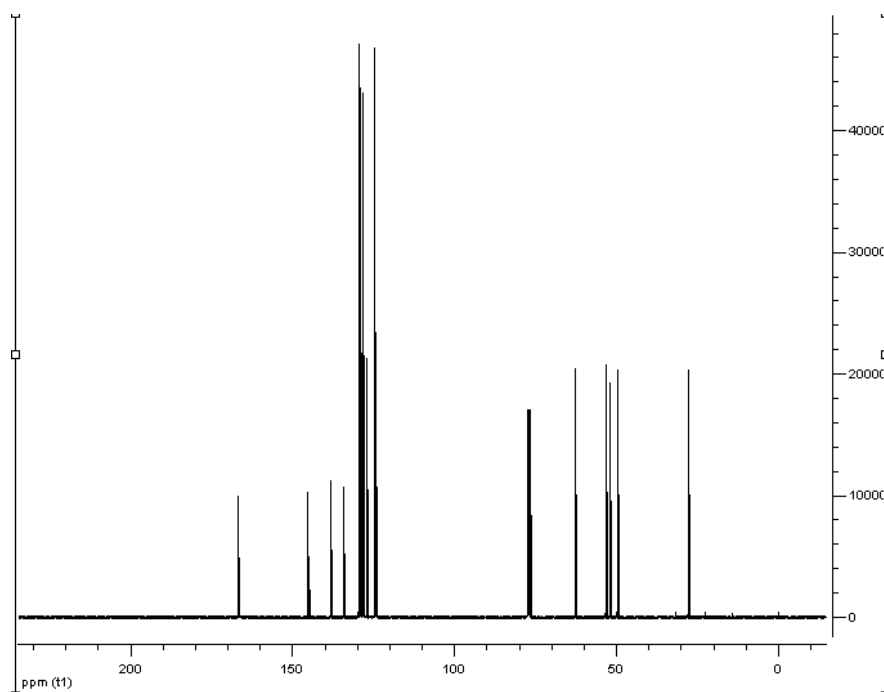
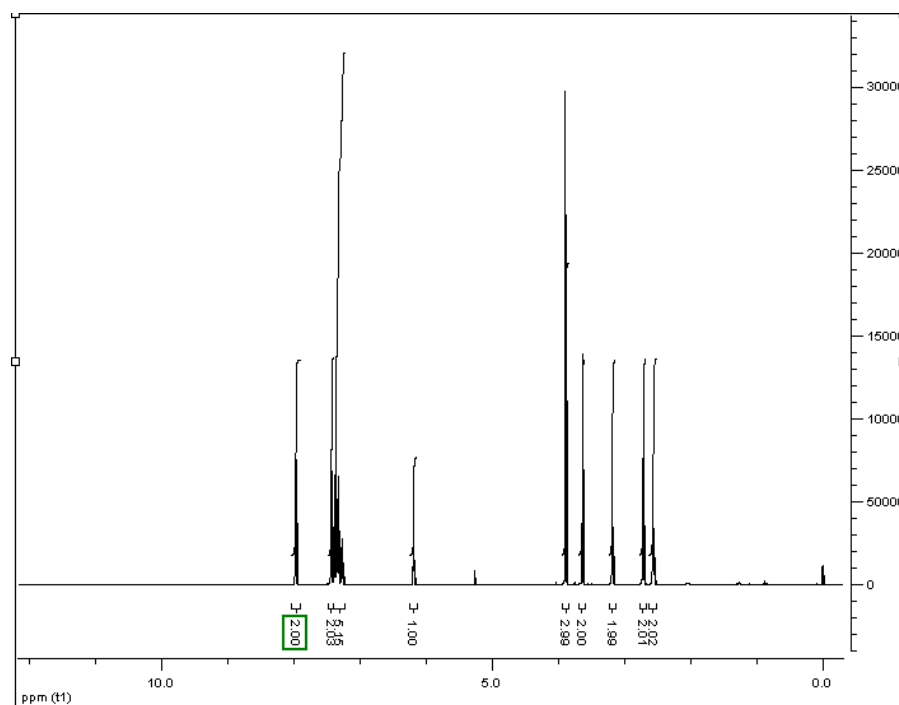
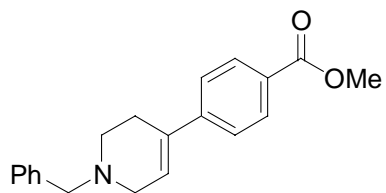
1-Benzyl-4-thiophen-2-yl-1,2,3,6-tetrahydro-pyridine (Table 2, entry 9)

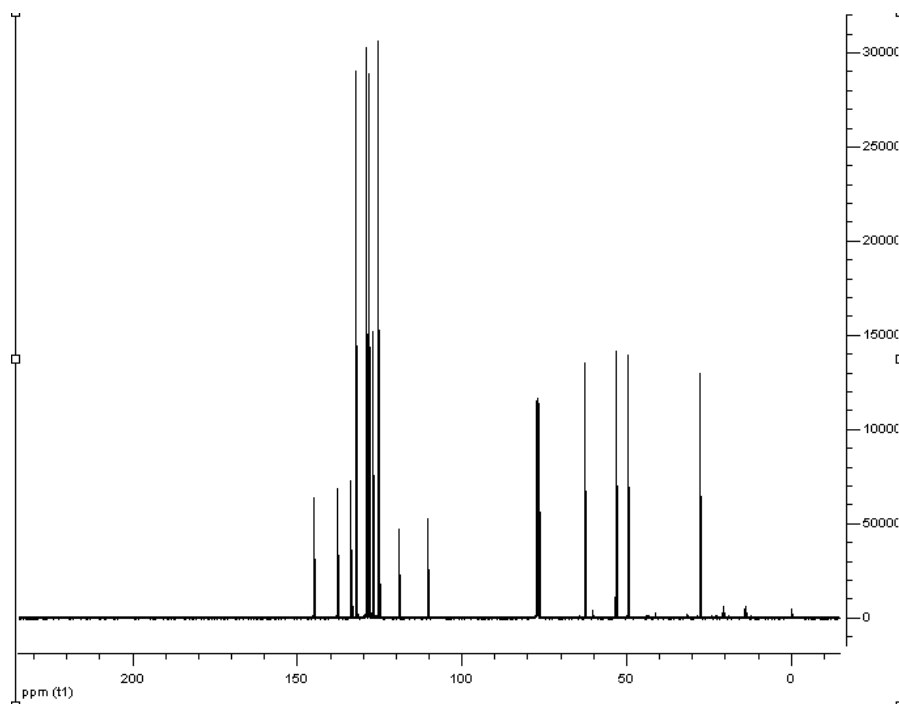
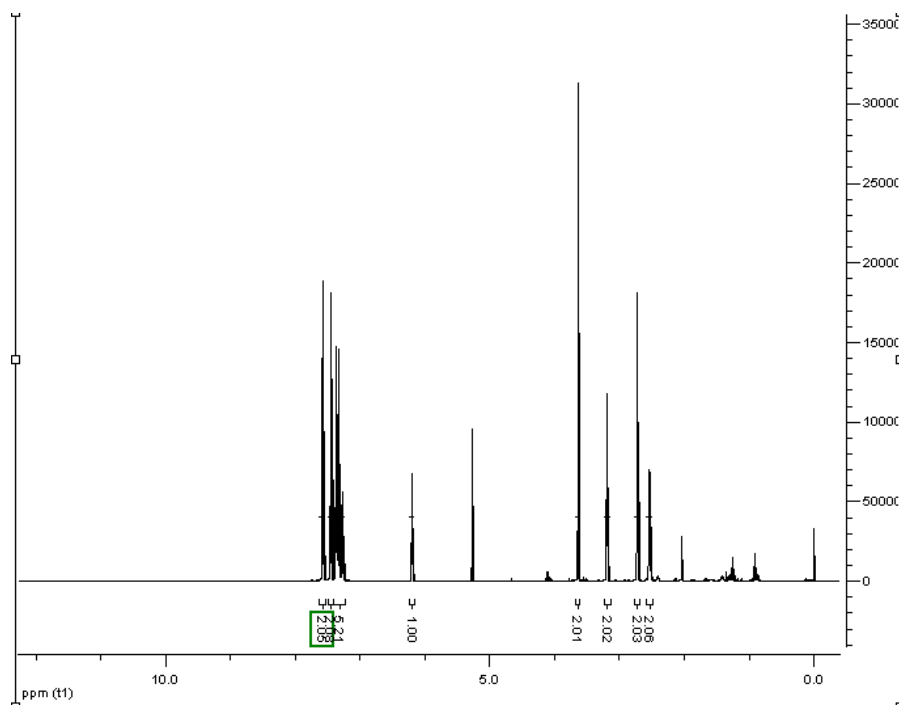
1-Benzyl-4-thiophen-3-yl-1,2,3,6-tetrahydro-pyridine (Table 2, entry 10)

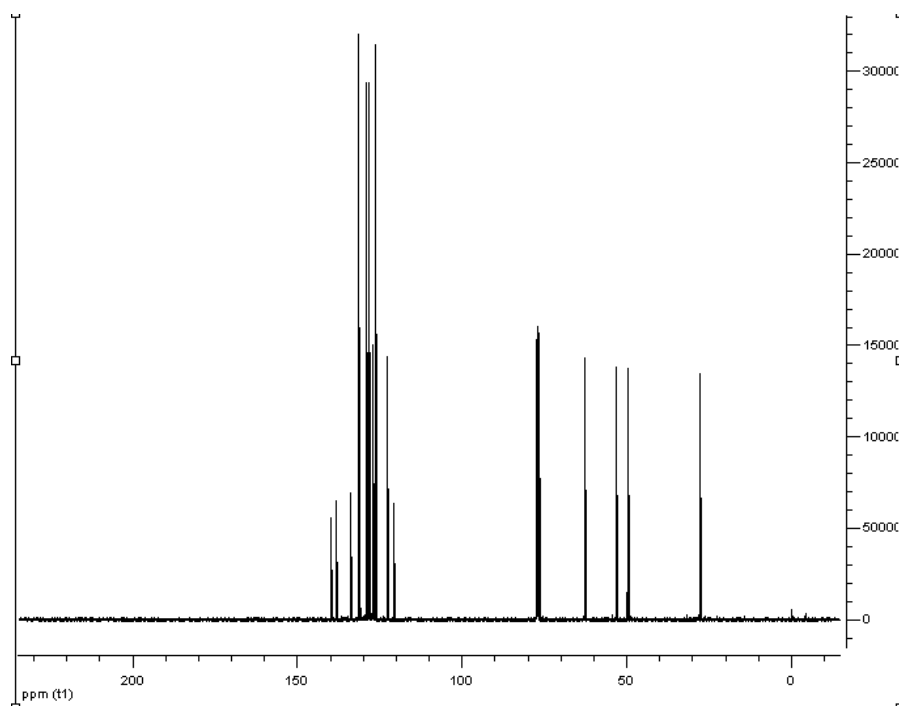
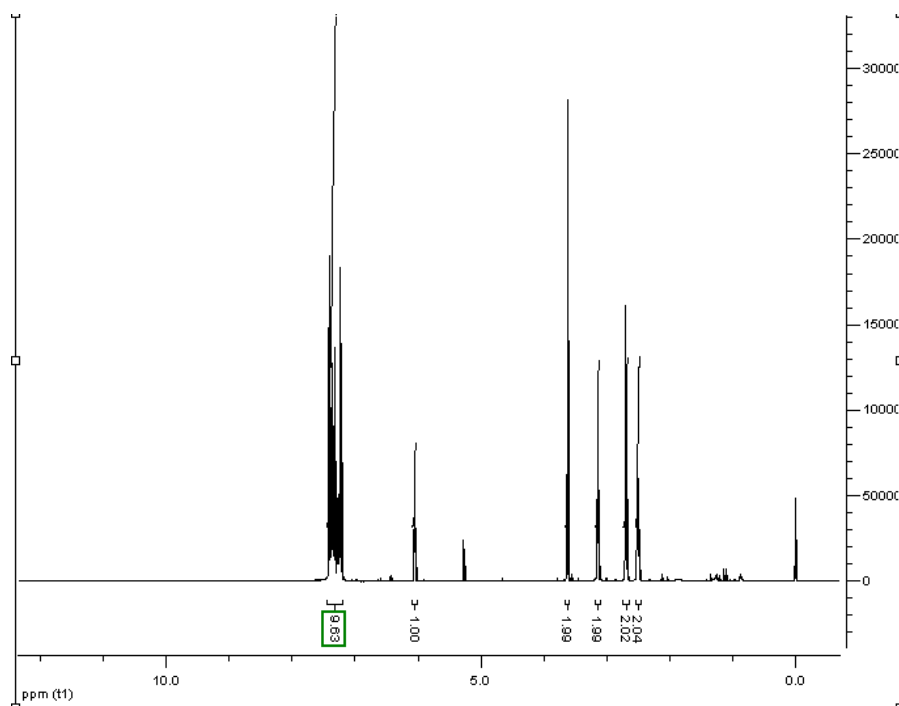
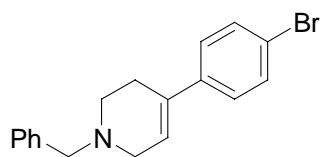
1-Benzyl-4-(4-fluoro-phenyl)-1,2,3,6-tetrahydro-pyridine (Table 2, entry 11)

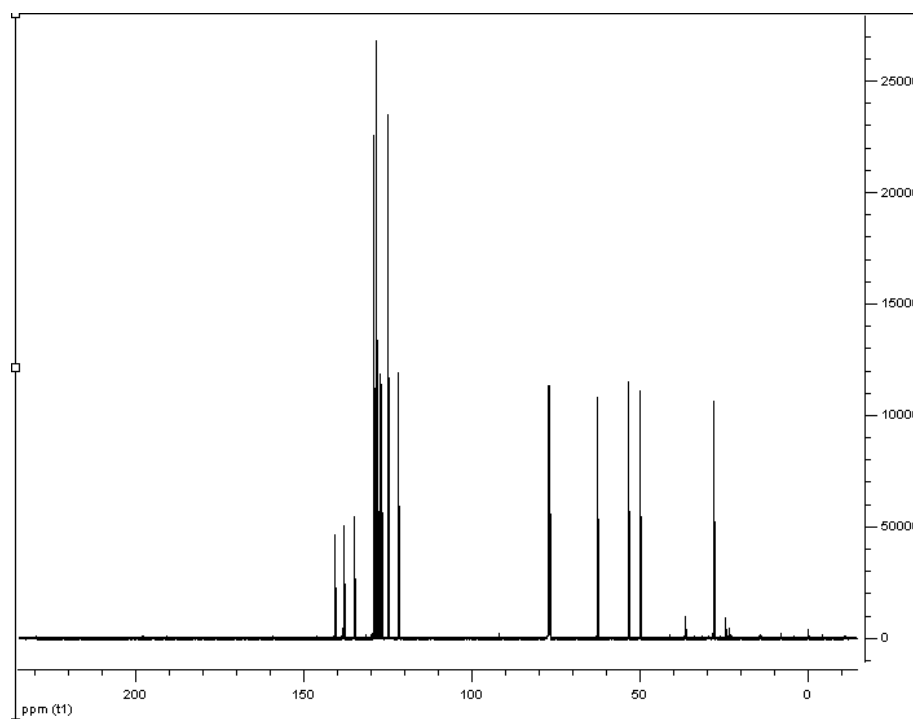
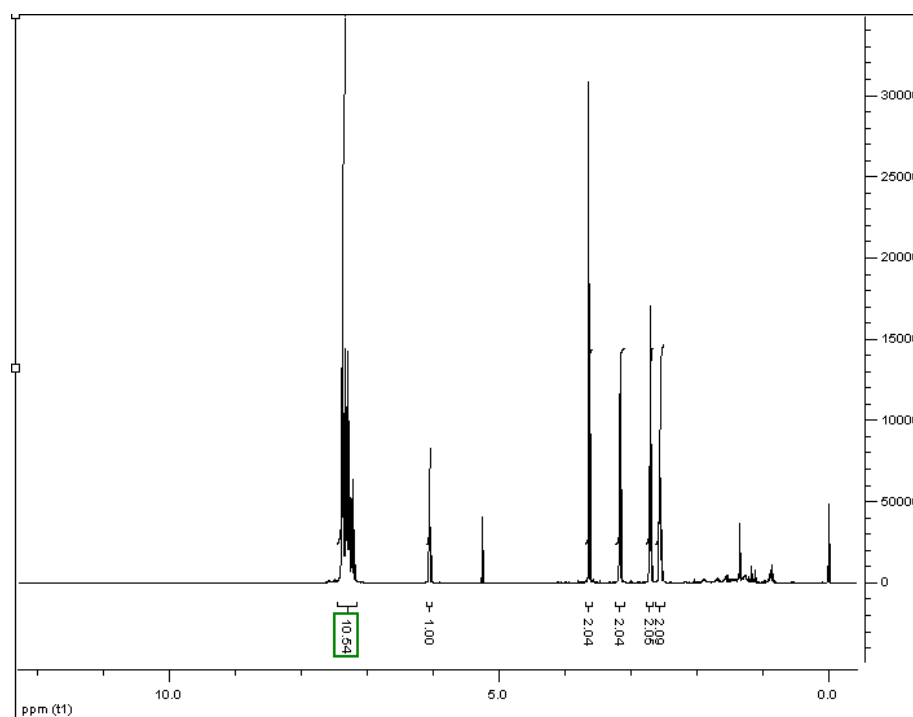
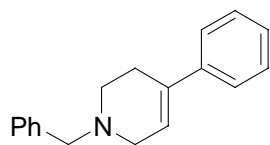
1-Benzyl-4-(4-trifluoromethyl-phenyl)-1,2,3,6-tetrahydro-pyridine (Table 2, entry 12)

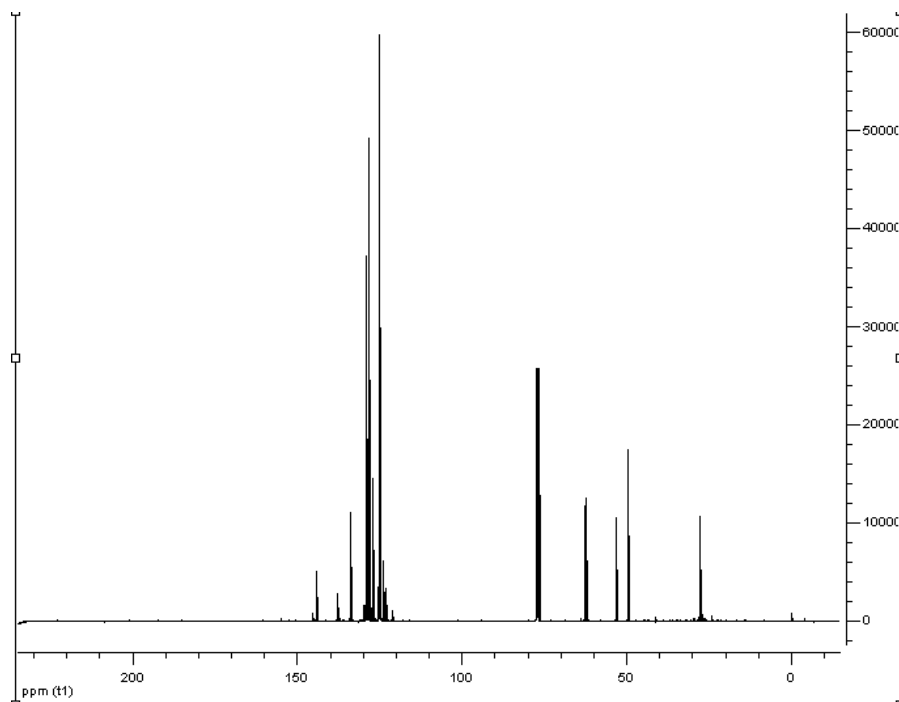
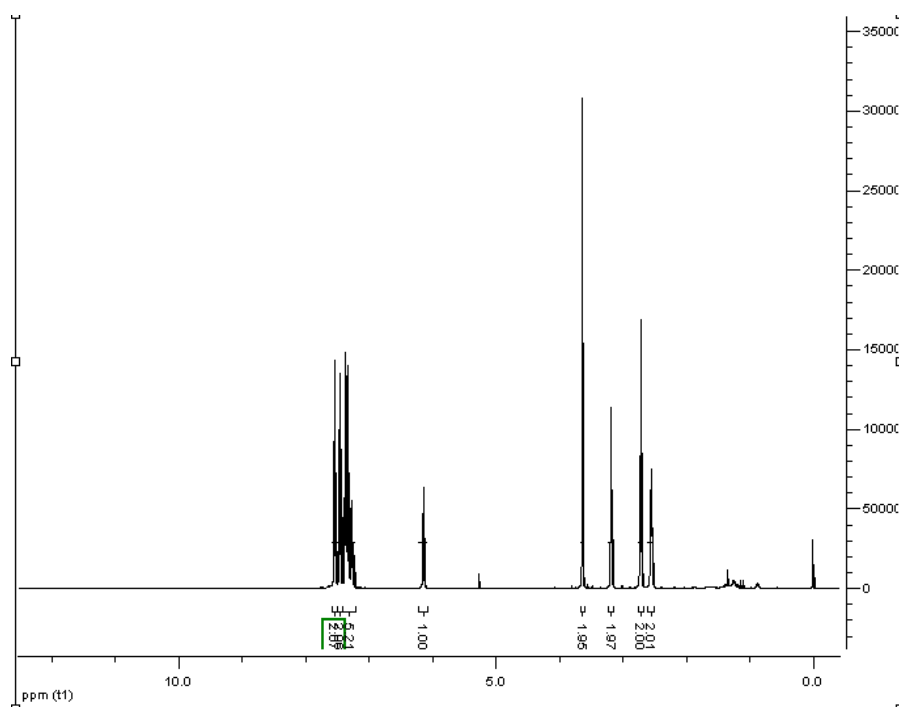
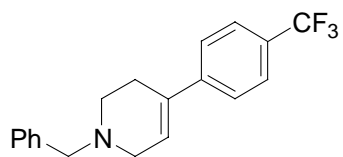
1-[4-(1-Benzyl-1,2,3,6-tetrahydro-pyridin-4-yl)-phenyl]-ethanone (Table 2, entry 13)

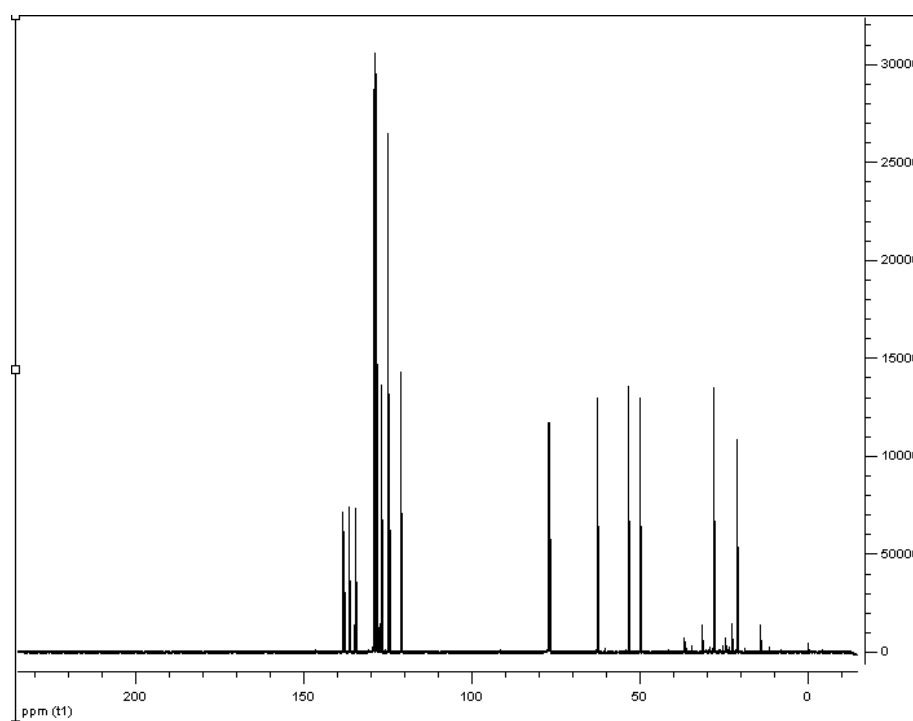
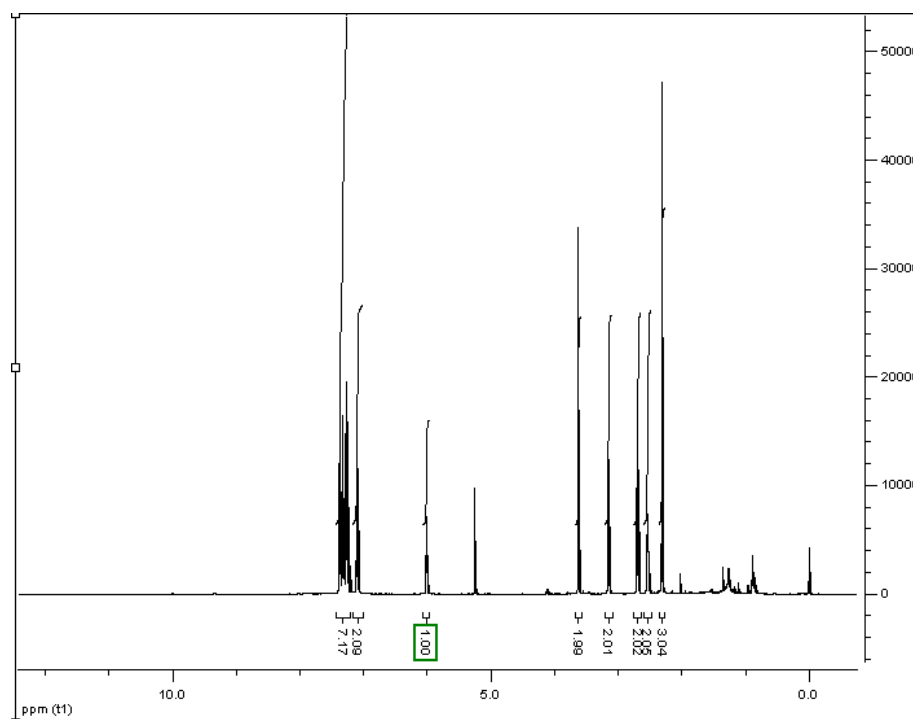
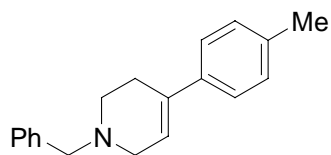
4-(1-Benzyl-1,2,3,6-tetrahydro-pyridin-4-yl)-benzoic acid methyl ester (Table 2, entry 14)

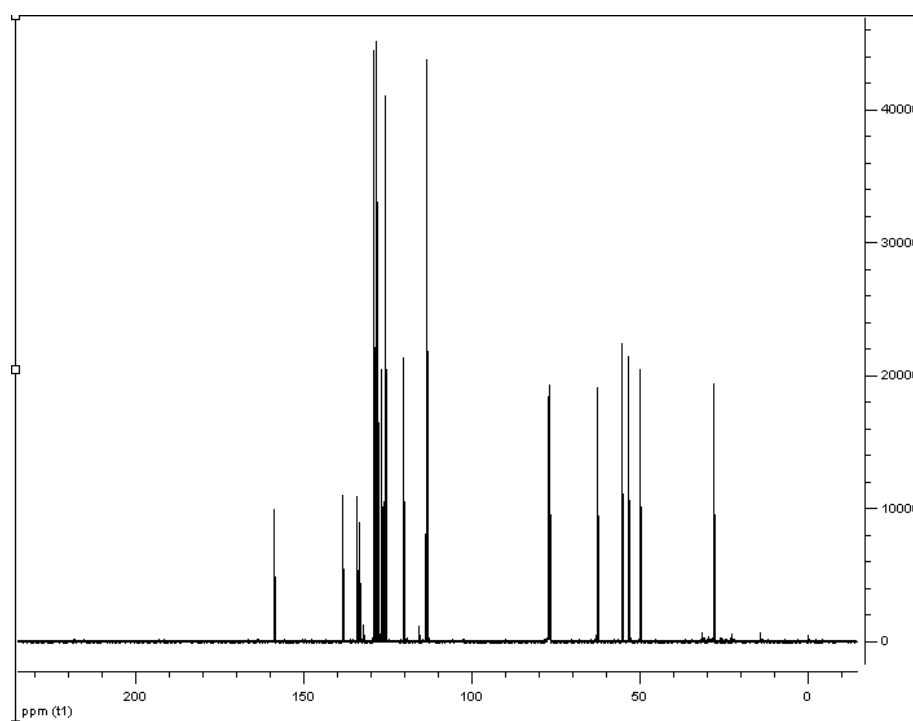
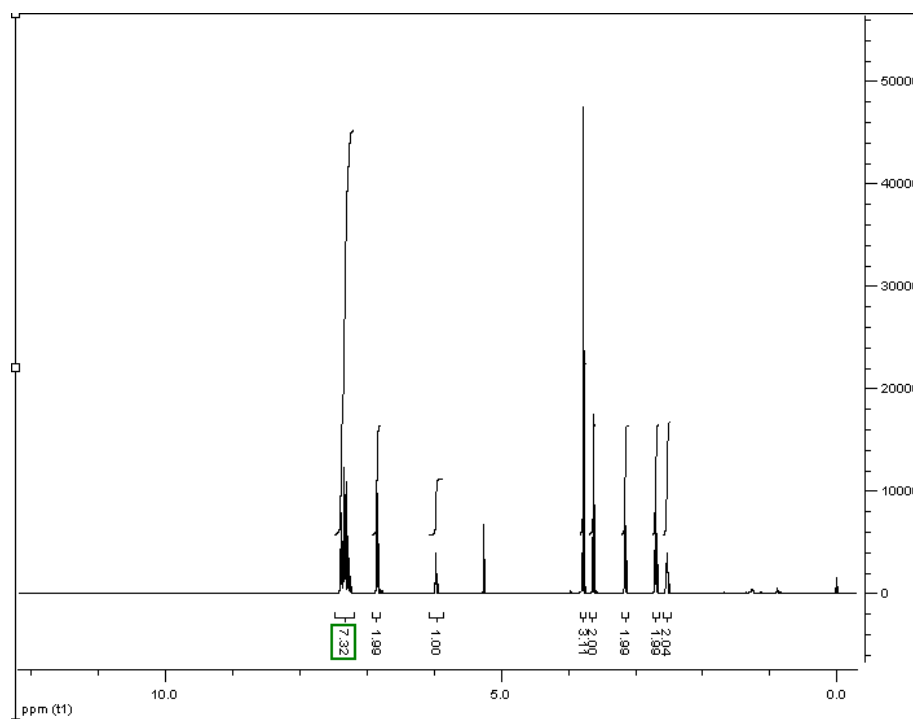
N#Cc1ccc(cc1)C2=CN(Cc3ccccc3)CC=C2

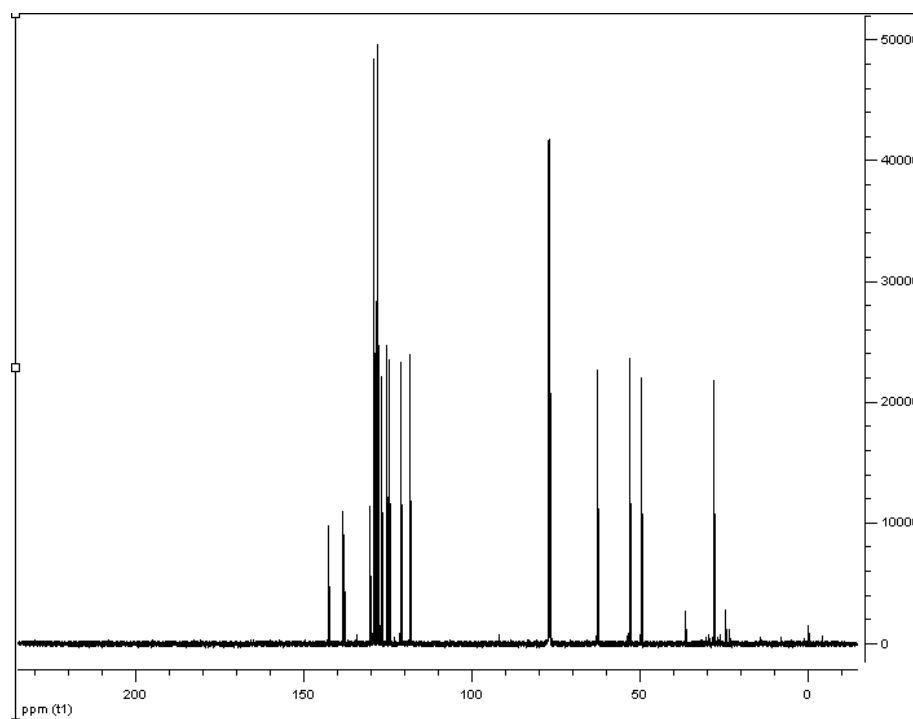
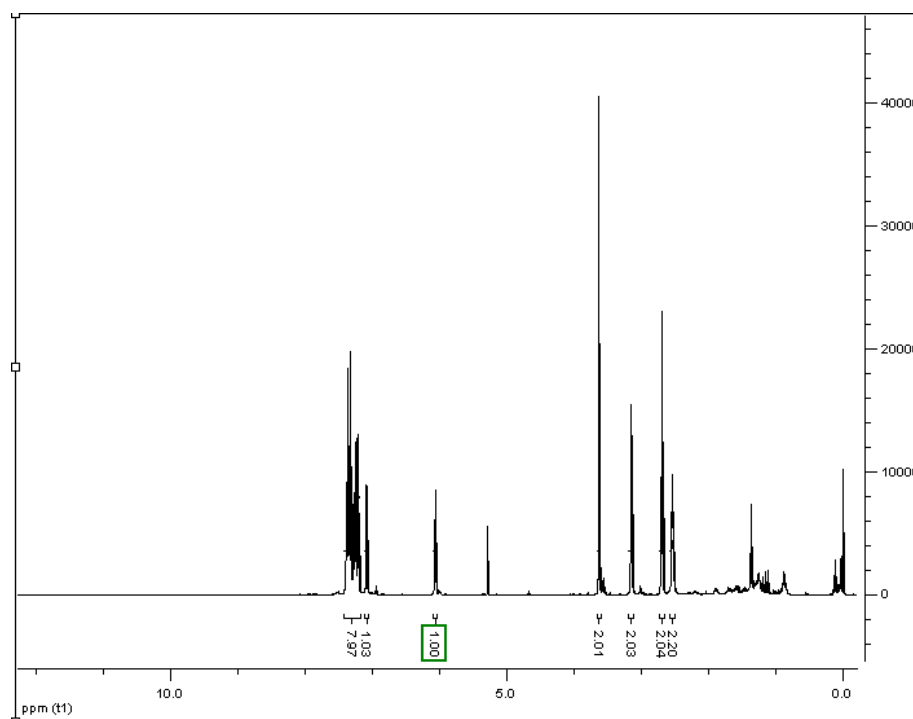
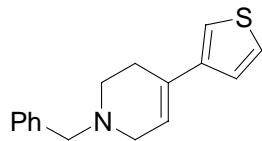
1-Benzyl-4-(4-bromo-phenyl)-1,2,3,6-tetrahydro-pyridine (Table 2, entry 16)

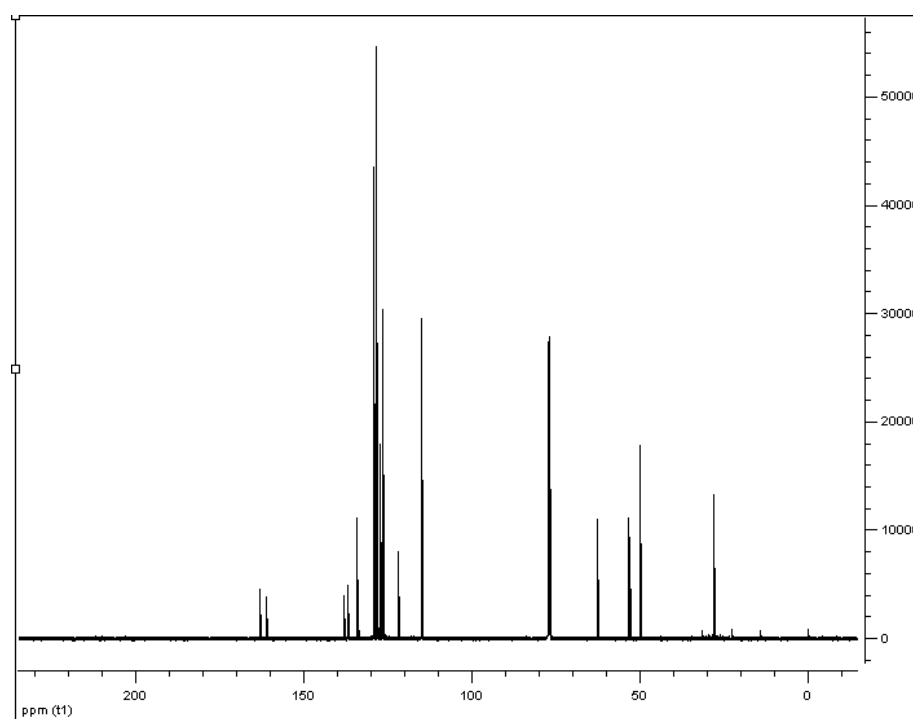
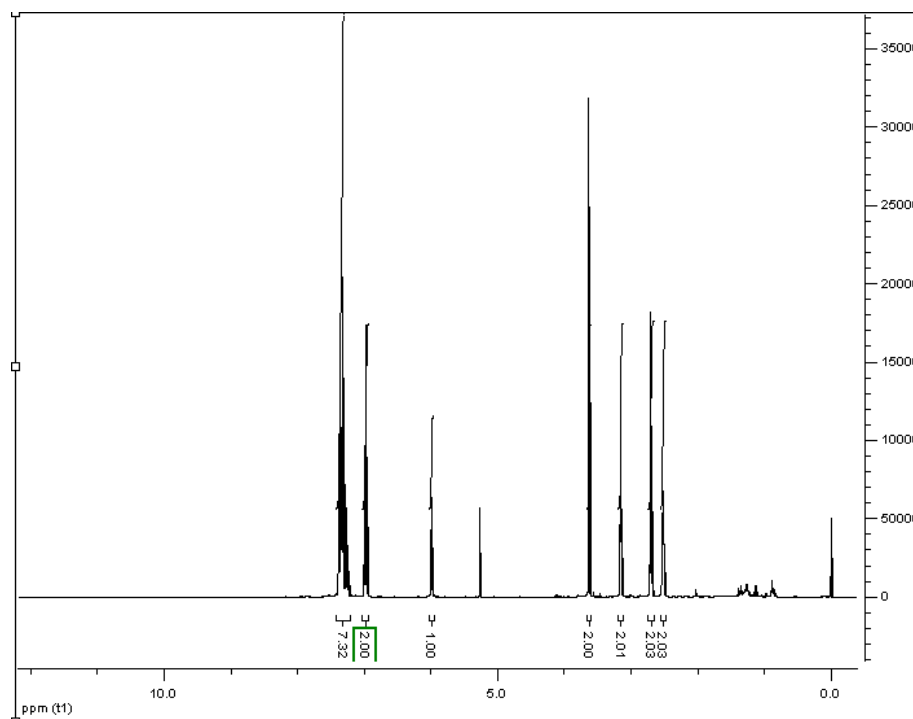
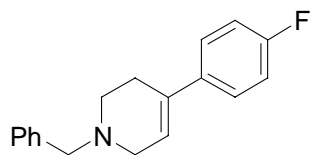
1-Benzyl-4-phenyl-1,2,3,6-tetrahydro-pyridine (Table 3, entry 4)

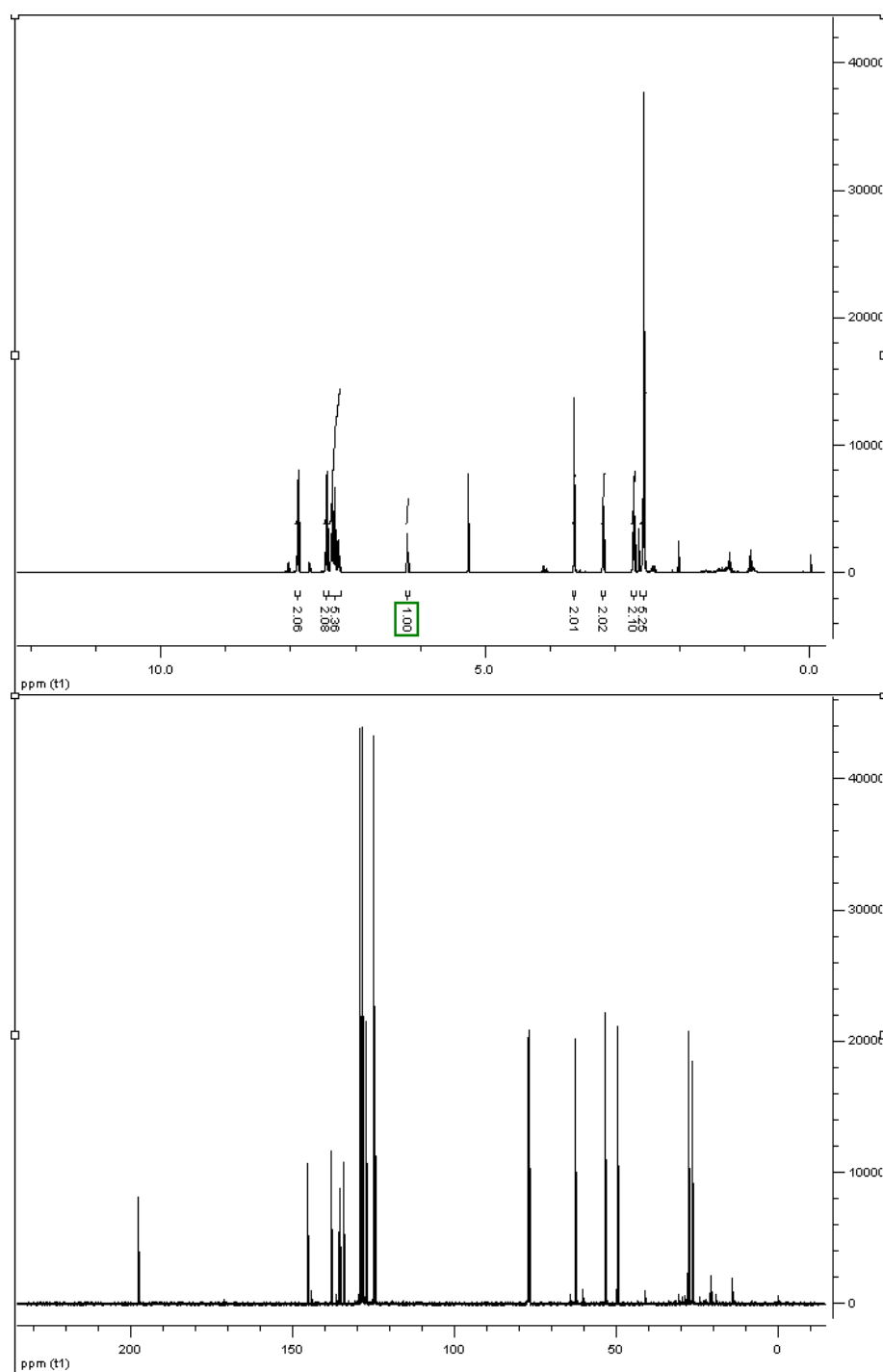
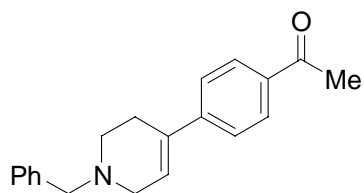
1-Benzyl-4-(4-trifluoromethyl-phenyl)-1,2,3,6-tetrahydro-pyridine (Table 3, entry 8)

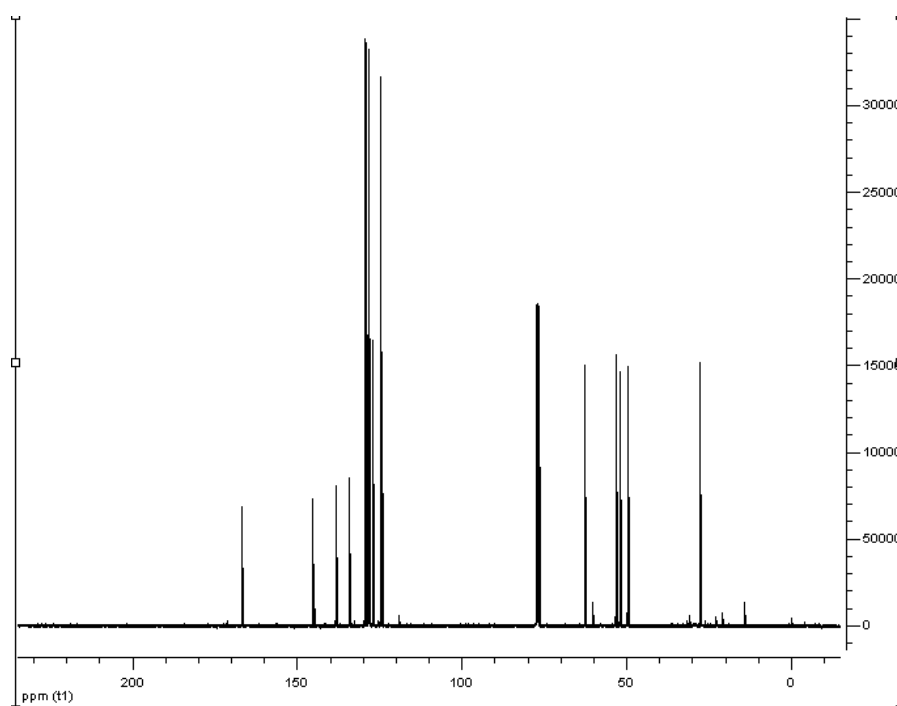
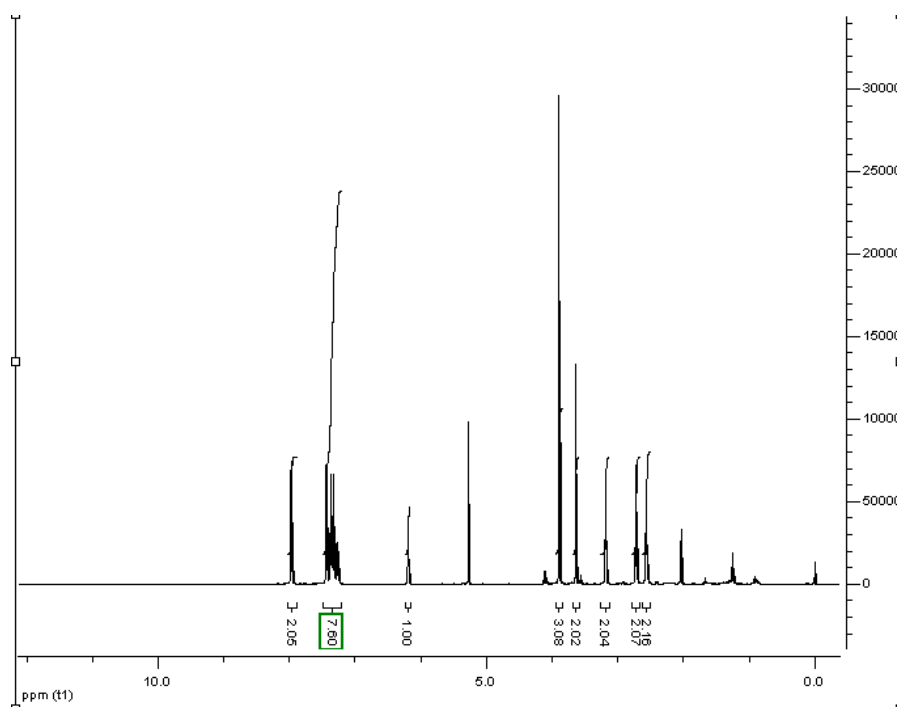
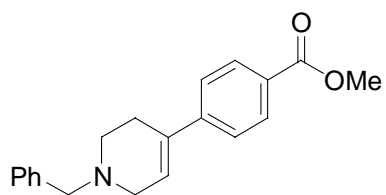
1-Benzyl-4-*p*-tolyl-1,2,3,6-tetrahydro-pyridine (Table 3, entry 9)

COc1ccc(cc1)C2=CN(Cc3ccccc3)CC2

1-Benzyl-4-thiophen-3-yl-1,2,3,6-tetrahydro-pyridine (Table 3, entry 11)

1-Benzyl-4-(4-fluoro-phenyl)-1,2,3,6-tetrahydro-pyridine (Table 3, entry 12)

1-[4-(1-Benzyl-1,2,3,6-tetrahydro-pyridin-4-yl)-phenyl]-ethanone (Table 3, entry 13)

4-(1-Benzyl-1,2,3,6-tetrahydro-pyridin-4-yl)-benzoic acid methyl ester (Table 3, entry 14)

N#Cc1ccc(cc1)C2=CN(Cc3ccccc3)CC=C2