Synthesis, Identification and Molecular Docking Studies of *N*-Functionalized Piperidine Derivatives Linked to 1,2,4-Triazole Ring

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Supporting Information

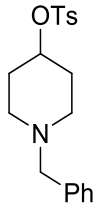
Contents of supporting information

1. General Experimental procedures: All reagents were purchased from commercial sources and used without additional purification unless stated otherwise. THF was freshly distilled over sodium and benzophenone under nitrogen gas. Anhydrous CH_3OH, DMF, DCE and acetone were purchased. All reactions were conducted in flame-dried glassware under an inert atmosphere of nitrogen or argon. Brine is a saturated aqueous solution of sodium chloride. Petroleum ether refers to light petroleum ether (b.p. 40-60 °C), and water refers to deionised water. Solvents evaporation was performed using a rotary evaporator under reduced pressure. TLC was performed on Merck silica gel 60 F_{254} and visualised by UV lamp and aqueous alkaline potassium permanganate.

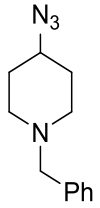
Flash column chromatography was performed over silica gel Fluka 60. ^{1}H and ^{13}C NMR spectral data were recorded using a Bruker AV400 or Bruker AV(III)400HD spectrometer. Chemical shifts of ^{1}H NMR spectra are expressed in ppm from internal tetramethylsilane (TMS) = 0 on the δ scale and are referenced to residual peak in the NMR solvent in $CDCl_3$ (7.26 ppm). Chemical shifts of ^{13}C NMR spectra are expressed in ppm relative to the solvent signal in $CDCl_3$ (77.16 ppm). Infrared spectral data were recorded using a Perkin-Elmer 1600 FTIR spectrometer. Mass spectrometry data were recorded using a Bruker MicroTOF spectrometer in ESI mode. Compound names are assigned according to standard IUPAC nomenclature.

2. Preparation of 1-benzylpiperidin-4-yl-4-methylbenzenesulfonate 3: To a solution of 1-benzylpiperidin-4-one **1** (10 g, 52.8 mmol, 1.0 equiv.) in anhydrous MeOH (100 mL) at room temperature, $NaBH_4$ (2.4 g, 63.4 mmol, 1.2 equiv.) was then added slowly. After completion of the addition, the mixture was stirred at room temperature. The reaction was monitored by TLC (petroleum ether/ethyl acetate) and LCMS until no ketone **1** remained. Saturated aqueous solution of NH_4Cl (50 mL) was then added to the reaction mixture, and stirred for 15 minutes, ethyl acetate (50 mL) was added before the layers were separated, and the aqueous layer was washed with ethyl acetate (2 × 25 mL). The combined organic layers were dried over anhydrous $MgSO_4$ before filtration and concentrating *in vacuo* to give the crude alcohol **2**. The crude **2** (9 g, 47.1 mmol, 1.0 equiv.) was then dissolved in DCM (75 mL) before adding DMAP (574 mg, 4.7 mmol, 0.1 equiv.). The mixture was cooled to 0 °C then Et_3N (7.9 mL, 56.5 mmol, 1.2 equiv.) was added dropwise to the reaction mixture followed by the dropwise addition a solution of *p*-TsCl (10.8 g, 56.5 mmol, 1.2 equiv.) in DCM (25 mL) at 0 °C. The reaction mixture was allowed to room temperature overnight (14 hours). The suspension was filtered through a short pad of silica gel and washed the silica bed with sufficient amount of DCM. Then the solvent was removed under reduced pressure to give the crude product and it was absorbed on silica straightaway to load the column. The product **3** was purified by flash column chromatography over silica gel (eluting with 5:1 petroleum ether/ethyl acetate) to

give the desired tosylated alcohol **3** (11.7 g, 33.9 mmol, 72%) as a white solid, m.p. = 66-68 °C; IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ = 3084, 3055, 3021 (C-H_{aro}), 2981, 2955, 2862 (C-H_{ali}), 1341, 1102 (S=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.82-7.79 (2H, m), 7.38-7.34 (2H, m), 7.25-7.16 (5H, m), 4.58-4.53 (1H, m), 3.46 (2H, s), 2.66-2.57 (2H, m), 2.42 (3H, s), 2.32-2.24 (2H, m), 1.89-1.73 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 144.7, 138.2, 134.9, 130.1, 129.3, 128.4, 127.8, 127.3, 79.3, 63.2, 50.4, 31.8, 21.8; HRMS (ESI) m/z, calculated for [$C_{19}H_{23}NNaO_3S^+$] [M+Na^+]$^+$ 368.1291, found 368.1293. Data consistent with literature (Denmark and Cresswell, 2013).

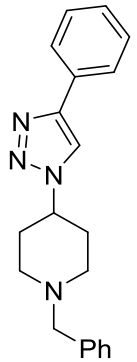


3. Preparation of 4-azido-1-benzylpiperidine 4: This compound was synthesised according to the modified procedure in the literature (Ritschel, Sasse and Maier, 2007). To a solution of **3** (11 gm, 31.8 mmol, 1.0 equiv.) in DMF (40 mL), NaN_3 (3.1 gm, 47.7 mmol, 1.5 equiv.) was then added before heating to 90 °C for 15 hours. The reaction mixture was cooled to room temperature and H_2O (50 mL) was added before extracting the organic layer with ethyl acetate (2 × 25 mL), washed with saturated brine (2 × 25 mL), and dried over anhydrous $MgSO_4$. Flash column chromatography over silica gel (eluting with 2:1 petroleum ether/ethyl acetate) provided **4** (4.5 g, 21 mmol, 66%) as a colourless oil; IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ = 3082, 3064, 3027 (C-H_{aro}), 2979, 2959, 2861 (C-H_{ali}), 2129 (N_3); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.38-7.23 (5H, m), 3.47 (2H, s), 3.41-3.27 (1H, m), 2.68-2.61 (2H, m), 2.39-2.34 (2H, m), 1.85-1.73 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 138.2, 129.1, 128.3, 127.2, 62.8, 57.5, 50.1, 30.8; HRMS (ESI) m/z, calculated for [$C_{12}H_{16}N_4Na^+$] [M+Na^+]$^+$ 239.1267, found 239.1266.

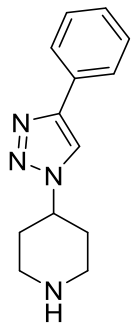


4. Preparation of 1-benzyl-4-(4-phenyl-1H-1,2,3-triazol-1-yl)piperidine 5: The title compound **5** has been synthesised according to the modified procedure of literature (Dawood and Hamed, 2019; Slimi *et al.*, 2015). To a solution of **4** (4.3 g, 19.9 mmol, 1.0 equiv.) and phenylacetylene (2.6 mL, 23.9 mmol, 1.2 equiv.) in THF:acetone (5:1) (60 mL). The reaction mixture was then stirred at ambient temperature for 15 minutes before slowly adding of a solution of CuI (379 mg, 1.99 mmol, 10.0 mol%) in THF (10 mL). After completion of the addition, the reaction mixture was heated at reflux for 24 hours, after

which TLC indicated the consumption of the starting material **4**. The solvents were then evaporated, and the organic phase was extracted with ethyl acetate (2 × 25 mL), washed with H_2O (25 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Flash column chromatography over silica gel (eluting with 6:1 petroleum ether/ethyl acetate) afforded the desired triazole product **5** (4.5 g, 14.1 mmol, 71%) as a white solid, m.p. = 205-207 °C; IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ = 3122 (C-H_{alkene}), 3078, 3065, 3016 (C-H_{aro}), 2971, 2933, 2847 (C-H_{ali}), 1643 (C=C); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.69-7.59 (3H, m), 7.54-7.46 (2H, m), 7.37-7.24 (5H, m), 6.07 (1H, s), 3.48 (2H, s), 3.42-3.28 (1H, m), 2.69-2.62 (2H, m), 2.38-2.33 (2H, m), 1.89-1.79 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 148.3, 144.7, 138.2, 134.4, 133.2, 129.1, 128.3, 127.1, 126.6, 117.2, 62.6, 57.1, 51.5, 30.4; HRMS (ESI) m/z, calculated for $[C_{20}H_{22}N_4Na^+]$ $[M+Na]^+$ 341.1737, found 341.1735.

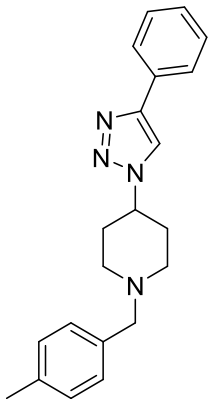


5. Preparation of 4-(4-phenyl-1H-1,2,3-triazol-1-yl)piperidine 6: To a suspension of **5** (4.2 g, 13.2 mmol, 1.0 eq.) in ethyl acetate (25 mL), wad added 10% Pd/C (10% w/w) under H_2 gas balloon. The reaction mixture was then stirred at room temperature for a reaction time of 16 hours and purified on short pad of Celite®. The organic layer was concentrated under reduced pressure. Flash column chromatography over silica gel (eluting with 1:1 petroleum ether/ethyl acetate) gave the desired amine **6** (2.7 g, 12 mmol, 91%) as a colourless oil; IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ = 3275 (N-H), 3122 (C-H_{alkene}), 3078, 3065, 3016 (C-H_{aro}), 2971, 2933, 2847 (C-H_{ali}), 1644 (C=C); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.66-7.57 (3H, m), 7.48-7.41 (2H, m), 6.08 (1H, s), 3.44-3.35 (1H, m), 2.67-2.59 (2H, m), 2.41-2.33 (2H, m), 2.26-2.15 (1H, m), 1.87-1.73 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 148.5, 144.4, 134.6, 133.3, 126.8, 117.4, 57.4, 51.3, 30.6; HRMS (ESI) m/z, calculated for $[C_{13}H_{16}N_4Na^+]$ $[M+Na]^+$ 251.1267, found 251.1267.

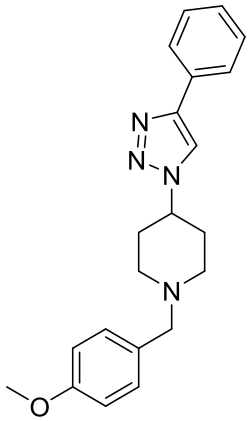


6. General procedure for reductive amination to synthesise 1-benzyl-4-(4-phenyl-1H-1,2,3-triazol-1-yl)piperidine derivatives 8a-f: The crude material of amine **6** (350 mg, 1.5 mmol, 1.0 eq.) was dissolved in DCE (20 mL) in a 100 mL round bottom flask. Aromatic aldehydes **7a**-**f** (2.25 mmol, 1.5 eq.) and acetic acid (215 μL, 3.75 mmol, 2.5 eq.) were then added and the resulting mixture stirred at room temperature for 2 hours. A solution of sodium triacetoxyborohydride (381 mg, 1.8 mmol, 1.2 eq.) in DCE (10 mL) was added dropwise. The reaction mixture was stirred overnight (14 hours) at room temperature then washed with 1.0 M HCl (2 × 15 mL). The aqueous phase was basified using saturated aqueous $NaHCO_3$ (15 mL) solution then extracted with ethyl acetate (2 × 15 mL), washed with water (2 × 15 mL), and the combined extracts, dried over anhydrous $MgSO_4$, filtered and solvent removed *in vacuo*. Flash column chromatography (petroleum ether/ethyl acetate) provided the desired products **8a**-**f**.

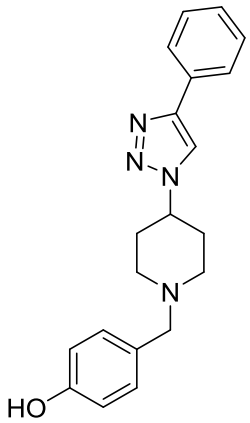
1-(4-methylbenzyl)-4-(4-phenyl-1H-1,2,3-triazol-1-yl)piperidine (8a): General procedure of reductive amination was followed to provide **8a** as a yellow oil (344 mg, 1 mmol, 69%); IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ = 3115 (C-H_{alkene}), 3071, 3056, 3022 (C-H_{aro}), 2971, 2952, 2849 (C-H_{ali}), 1648 (C=C); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.67-7.61 (2H, m), 7.51-7.44 (2H, m), 7.34-7.27 (5H, m), 6.06 (1H, s), 3.47 (2H, s), 3.41-3.37 (1H, m), 2.69-2.64 (2H, m), 2.39 (3H, s), 2.32-2.27 (2H, m), 1.85-1.75 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 148.1, 144.6, 138.3, 134.4, 133.0, 129.2, 128.3, 127.2, 126.2, 117.1, 62.4, 57.2, 51.2, 30.2, 21.0; HRMS (ESI) m/z, calculated for [$C_{21}H_{25}N_4^+$] $[M+H]^+$ 333.2074, found 333.2076.



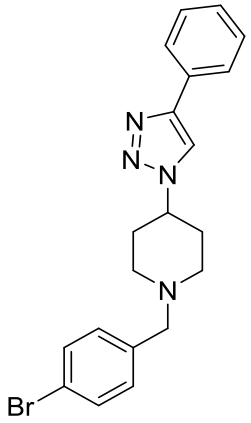
1-(4-methoxybenzyl)-4-(4-phenyl-1H-1,2,3-triazol-1-yl)piperidine (8b): General procedure of reductive amination was followed to give **8b** as a pale yellow oil (400 mg, 975 μmol, 65%); IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ = 3116 (C-H_{alkene}), 3073, 3062, 3019 (C-H_{aro}), 2967, 2942, 2854 (C-H_{ali}), 1655 (C=C), 1236, 1038 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.68-7.62 (2H, m), 7.55-7.48 (2H, m), 7.35-7.26 (5H, m), 6.06 (1H, s), 3.84 (3H, s), 3.47 (2H, s), 3.39-3.35 (1H, m), 2.68-2.63 (2H, m), 2.35-2.28 (2H, m), 1.88-1.77 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 148.3, 144.4, 138.1, 134.4, 132.2, 129.2, 128.1, 127.3, 126.5, 117.1, 62.5, 57.0, 55.5, 51.3, 30.2; HRMS (ESI) m/z, calculated for [$C_{21}H_{25}N_4O^+$] $[M+H]^+$ 349.2023, found 349.2024.



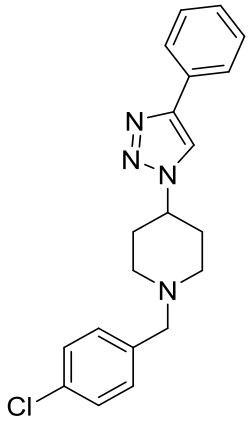
4-((4-(4-phenyl-1H-1,2,3-triazol-1-yl)piperidin-1-yl)methyl)phenol (8c): General procedure of reductive amination was followed to afford **8c** as a yellow oil (296 mg, 885 μmol, 59%); IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ = 3365 (O-H), 3112 (C-H_{alkene}), 3070, 3055, 3024 (C-H_{aro}), 2973, 2966, 2850 (C-H_{ali}), 1648 (C=C); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.65-7.59 (2H, m), 7.49-7.44 (2H, m), 7.31-7.23 (5H, m), 6.05 (1H, s), 3.46 (2H, s), 3.33-3.28 (1H, m), 2.67-2.60 (2H, m), 2.35-2.28 (2H, m), 1.88-1.73 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 148.2, 144.5, 141.1, 134.1, 132.8, 128.7, 128.1, 126.7, 126.1, 116.7, 62.1, 56.6, 50.5, 30.4; HRMS (ESI) m/z, calculated for [$C_{20}H_{23}N_4O^+$] $[M+H]^+$ 335.1866, found 335.1865.



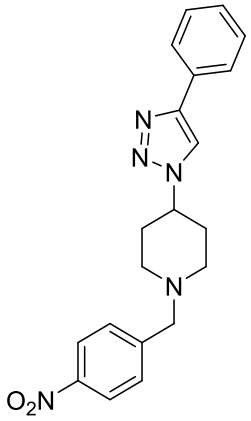
1-(4-bromobenzyl)-4-(4-phenyl-1H-1,2,3-triazol-1-yl)piperidine (8d): General procedure of reductive amination was followed to provide **8d** as a colourless oil (437 mg, 1.1 mmol, 75%); IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ = 3120 (C-H_{alkene}), 3072, 3050, 3023 (C-H_{aro}), 2967, 2953, 2857 (C-H_{ali}), 1659 (C=C), 1090 (C-Br); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.69-7.57 (2H, m), 7.50-7.43 (2H, m), 7.29-7.18 (5H, m), 6.08 (1H, s), 3.48 (2H, s), 3.39-3.34 (1H, m), 2.69-2.59 (2H, m), 2.32-2.27 (2H, m), 1.83-1.76 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 148.2, 144.2, 139.5, 134.4, 133.4, 129.2, 128.2, 127.4, 126.7, 117.4, 62.7, 57.2, 51.2, 30.3; HRMS (ESI) m/z, calculated for [$C_{20}H_{21}BrN_4Na^+$] $[M+Na]^+$ 419.0842, found 419.0844.



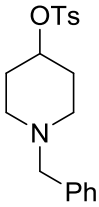
1-(4-chlorobenzyl)-4-(4-phenyl-1H-1,2,3-triazol-1-yl)piperidine (8e): General procedure of reductive amination was followed to give **8e** as a yellow oil (423 mg, 1.2 mmol, 79%); IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ = 3113 (C-H_{alkene}), 3029 (C-H_{aro}), 2968, 2944, 2859 (C-H_{ali}), 1649 (C=C), 1088 (C-Cl); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.77-7.71 (2H, m), 7.53-7.47 (2H, m), 7.30-7.16 (5H, m), 6.08 (1H, s), 3.49 (2H, s), 3.33-3.20 (1H, m), 2.67-2.60 (2H, m), 2.36-2.29 (2H, m), 1.89-1.79 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 148.3, 144.3, 139.6, 134.6, 133.1, 129.4, 128.4, 127.5, 126.2, 117.6, 62.3, 57.3, 51.2, 30.5; HRMS (ESI) m/z, calculated for [$C_{20}H_{22}ClN_4^+$] $[M+H]^+$ 353.1528, found 353.1529.



1-(4-nitrobenzyl)-4-(4-phenyl-1H-1,2,3-triazol-1-yl)piperidine (8f): General procedure of reductive amination was followed to afford **8f** as a colourless oil (472 mg, 1.3 mmol, 82%); IR $\upsilon_{max}(CHCl_3)/cm^{-1}$ = 3119 (C-H_{alkene}), 3080, 3045, 3025 (C-H_{aro}), 2985, 2956, 2859 (C-H_{ali}), 1637 (C=C), 1482, 1341 (NO_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.72-7.62 (2H, m), 7.59-7.49 (2H, m), 7.34-7.25 (5H, m), 6.08 (1H, s), 3.49 (2H, s), 3.39-3.31 (1H, m), 2.70-2.61 (2H, m), 2.48-2.36 (2H, m), 1.90-1.81 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 148.6, 144.4, 140.2, 134.3, 133.3, 129.2, 128.4, 127.3, 126.7, 117.4, 62.5, 57.1, 51.2, 30.7; HRMS (ESI) m/z, calculated for [$C_{20}H_{22}N_5O_2^+$] $[M+H]^+$ 364.1768, found 364.1767.



7. ^{1}H and ^{13}C NMR spectra



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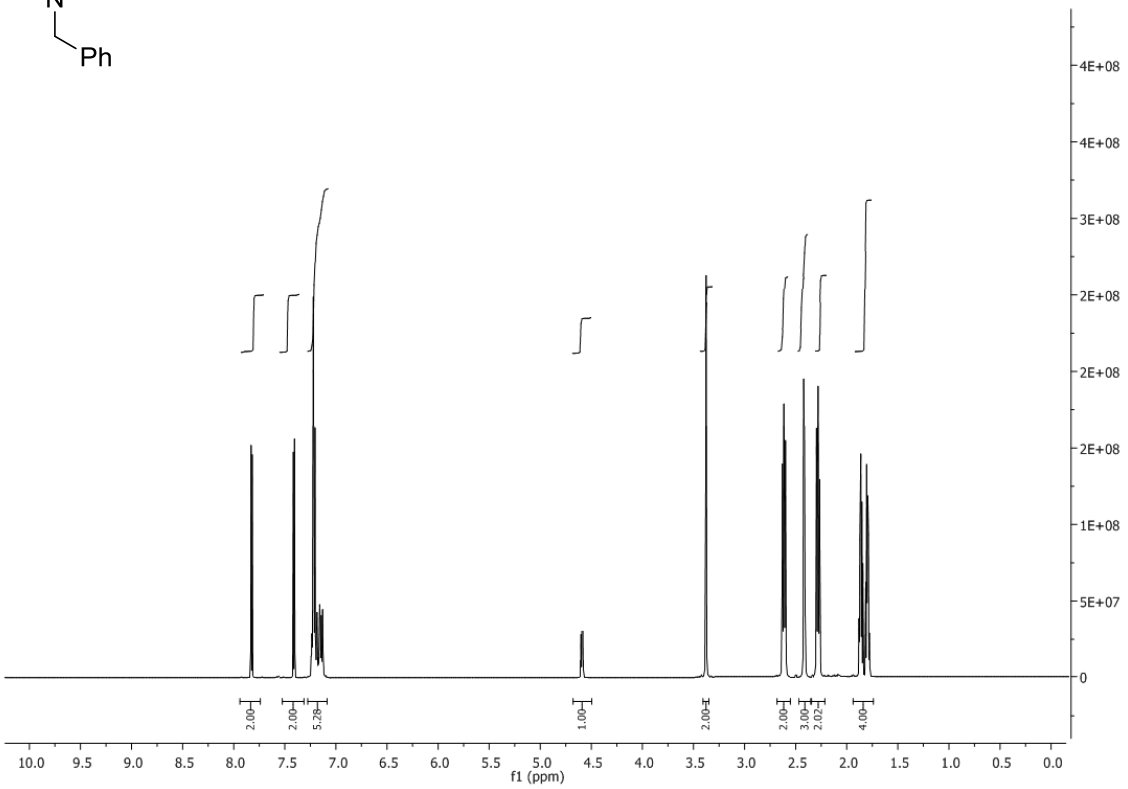
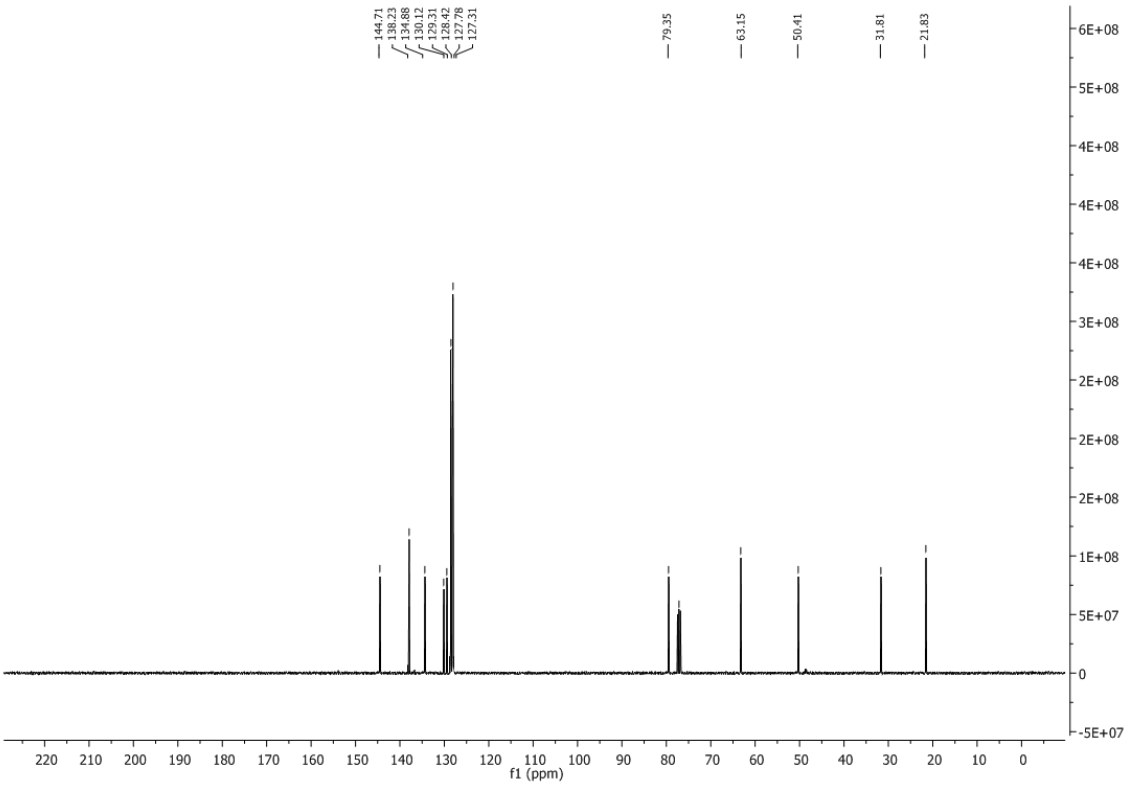
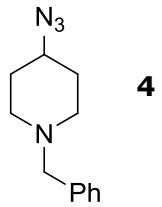
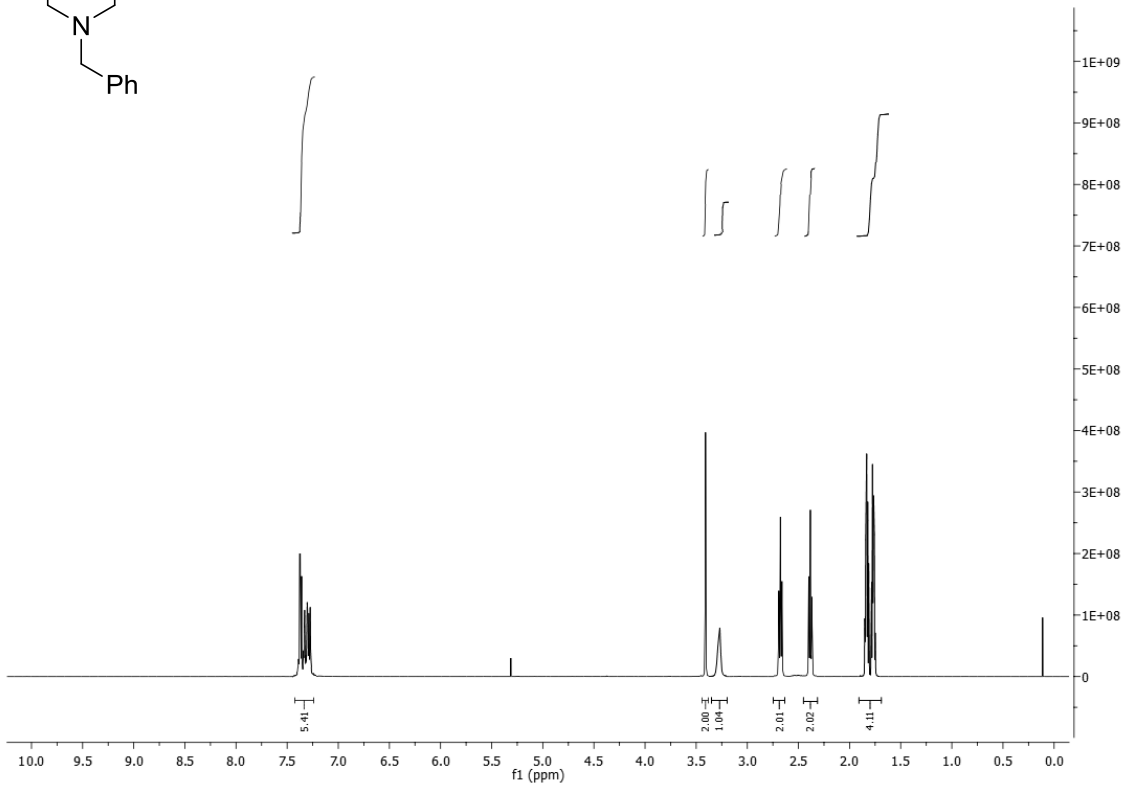





N3
N
Ph

4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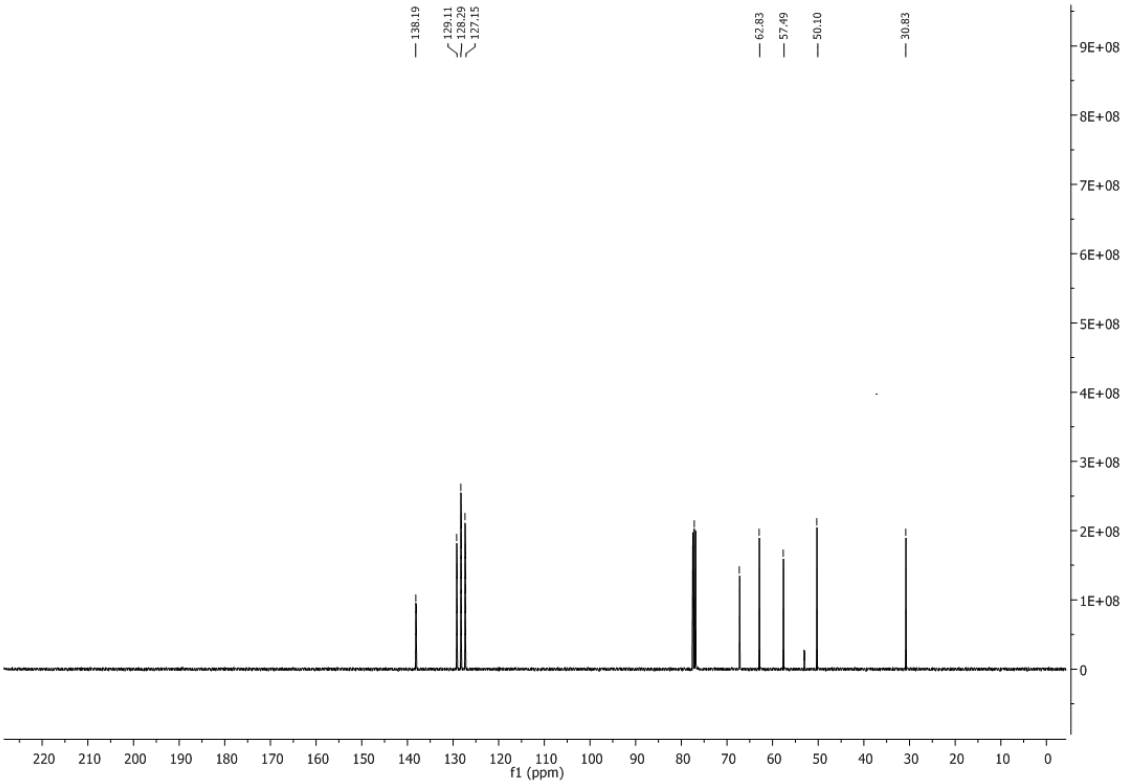
1.04
2.01
2.02
4.11
f1 (ppm)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127.15
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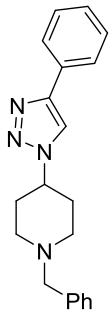
30.83
f1 (ppm)



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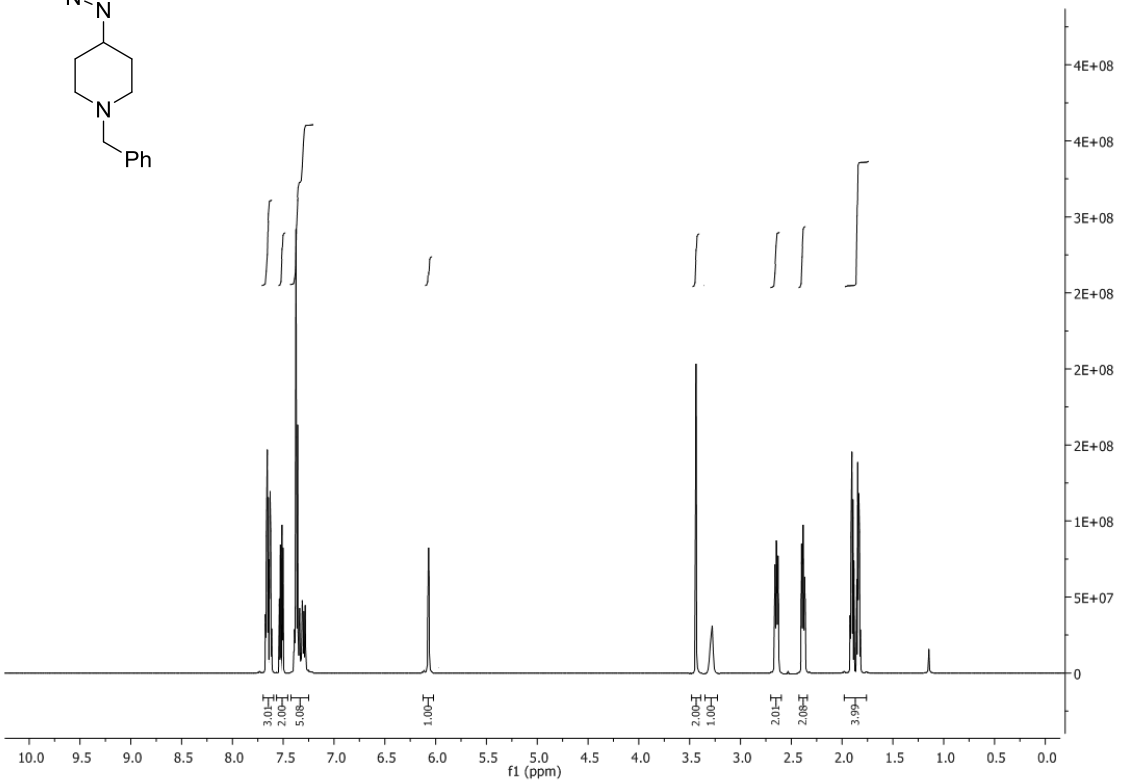
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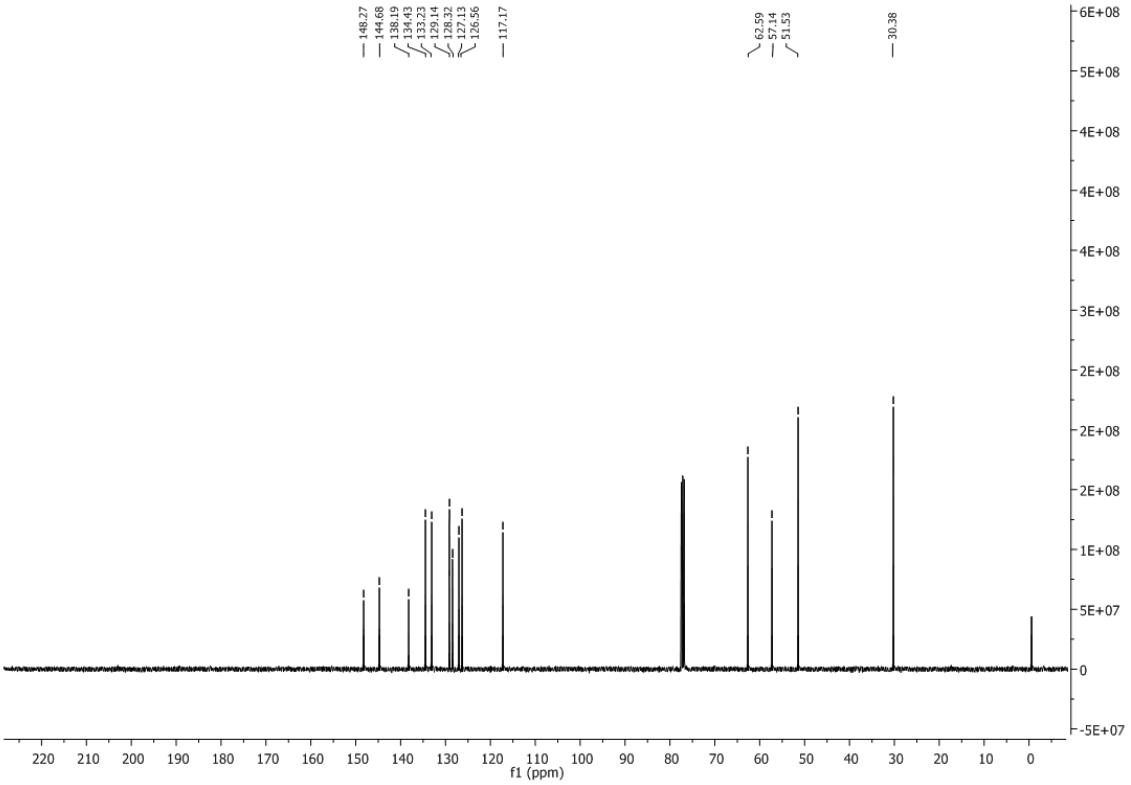
1.00
2.00
1.00
2.01
2.08
3.99
f1 (ppm)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117.17
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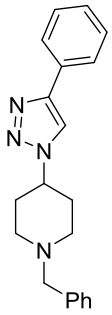
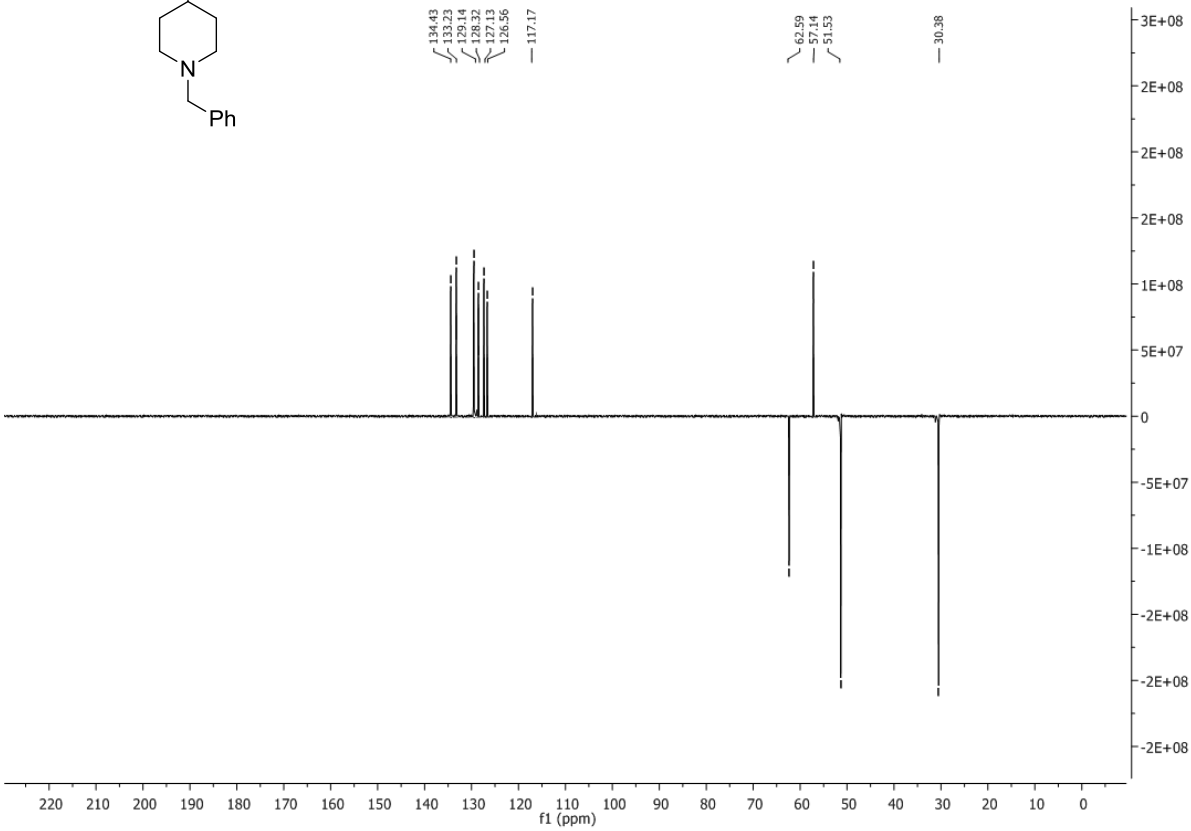
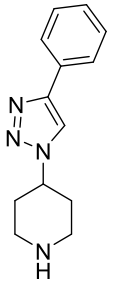
51.53
30.38
f1 (ppm)

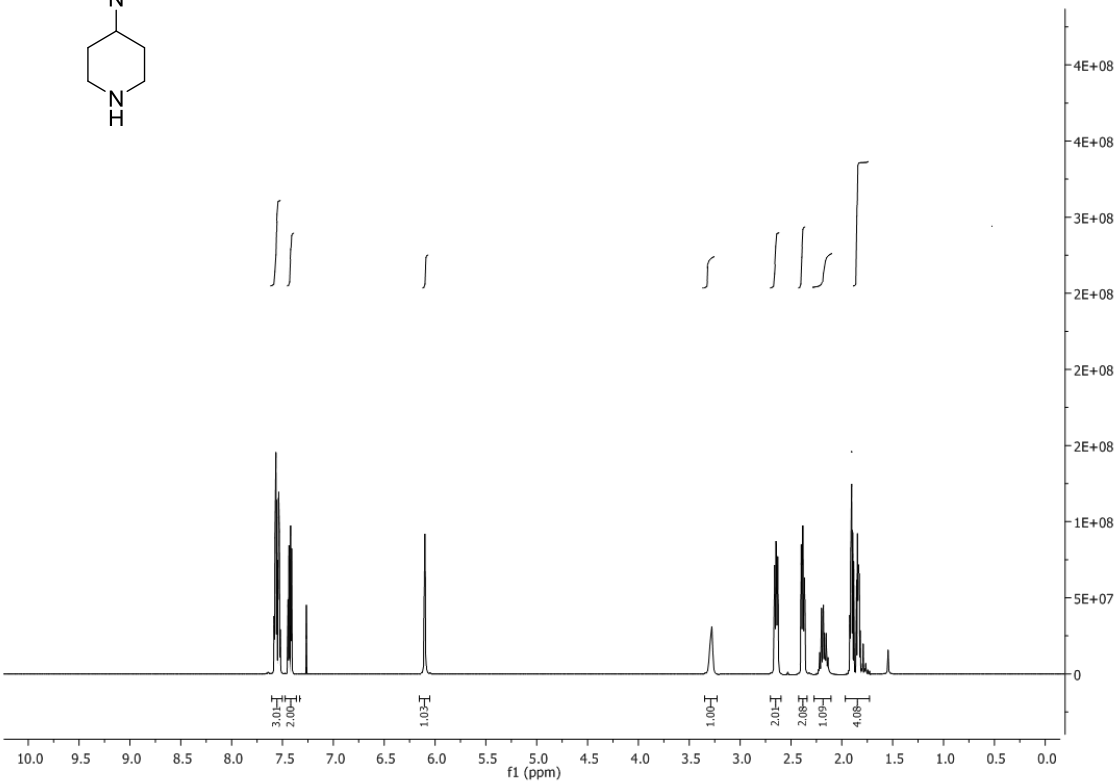

N
N
N
N
Ph

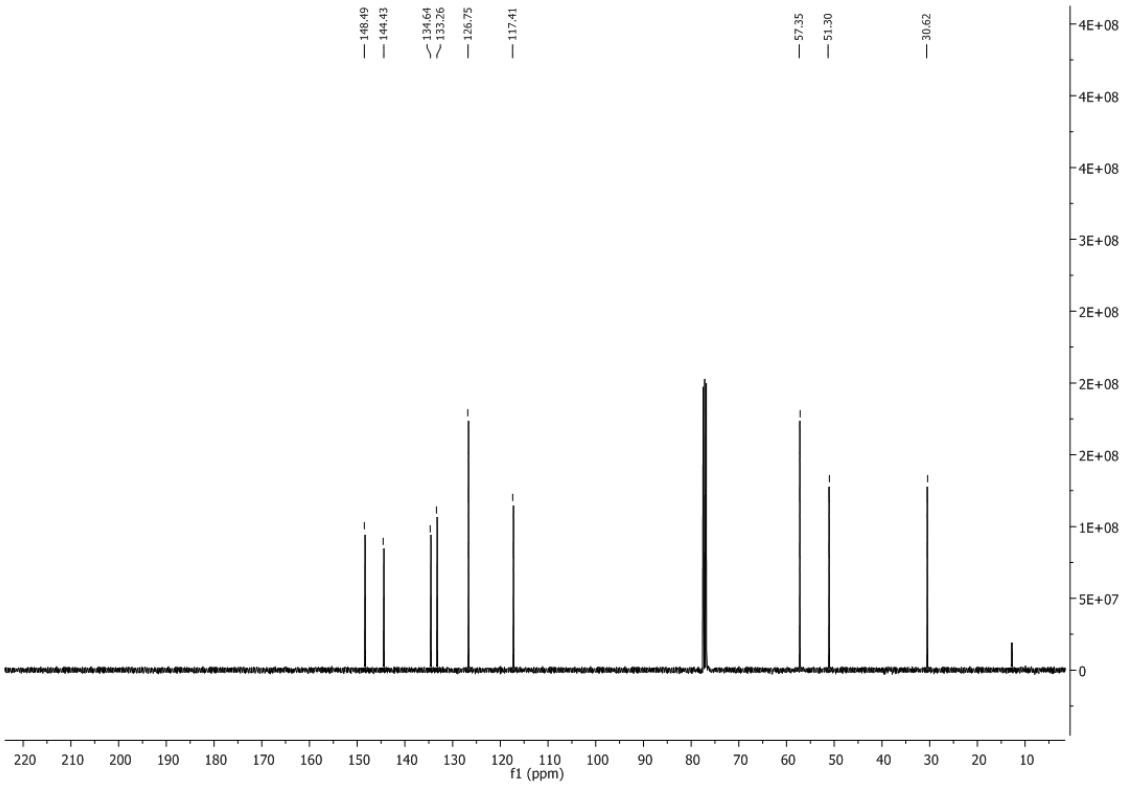
5

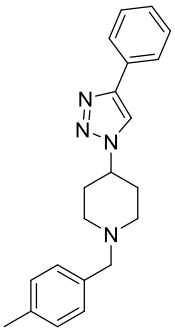

134.43
133.23
129.14
128.32
127.13
126.56
117.17
62.59
57.14
51.53
30.38
3E+08
2E+08
2E+08
2E+08
1E+08
5E+07
0
-5E+07
-1E+08
-2E+08
-2E+08
-2E+08
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



6


3.01
2.00
1.03
1.00
2.01
2.08
1.09
4.08
f1 (ppm)


148.49
144.43
134.64
133.26
126.75
117.41
57.35
51.30
30.62
f1 (ppm)



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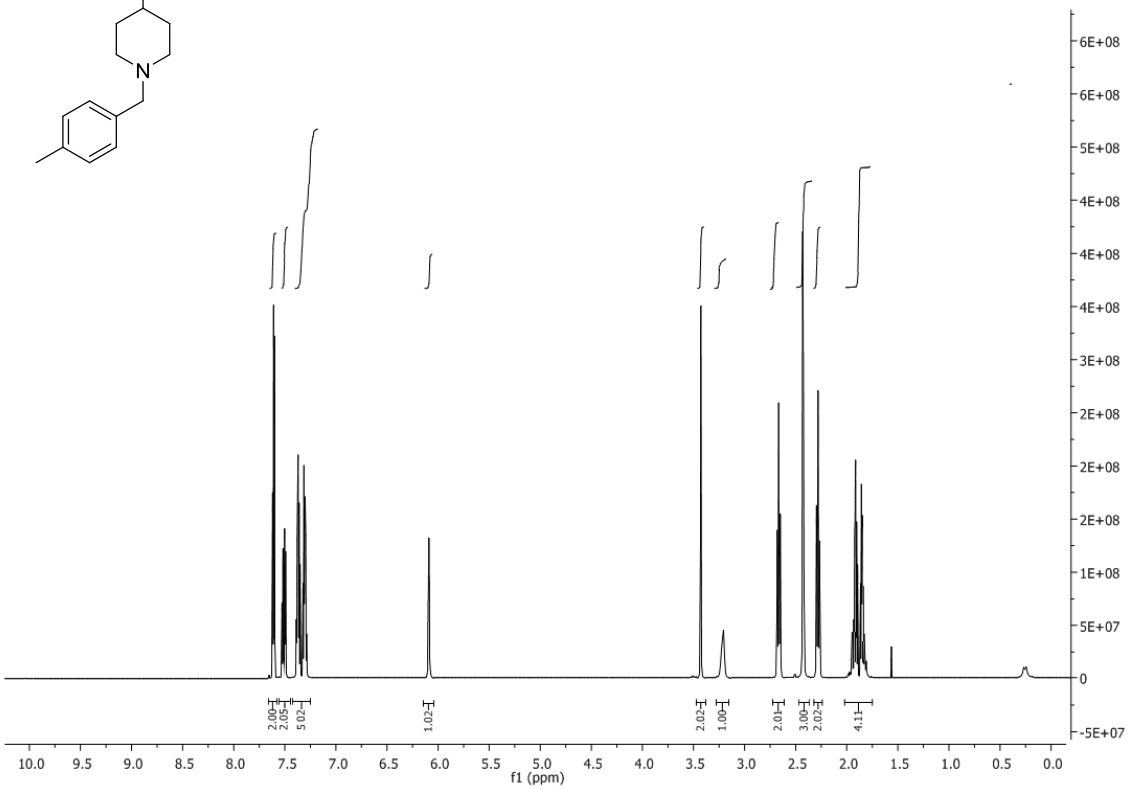
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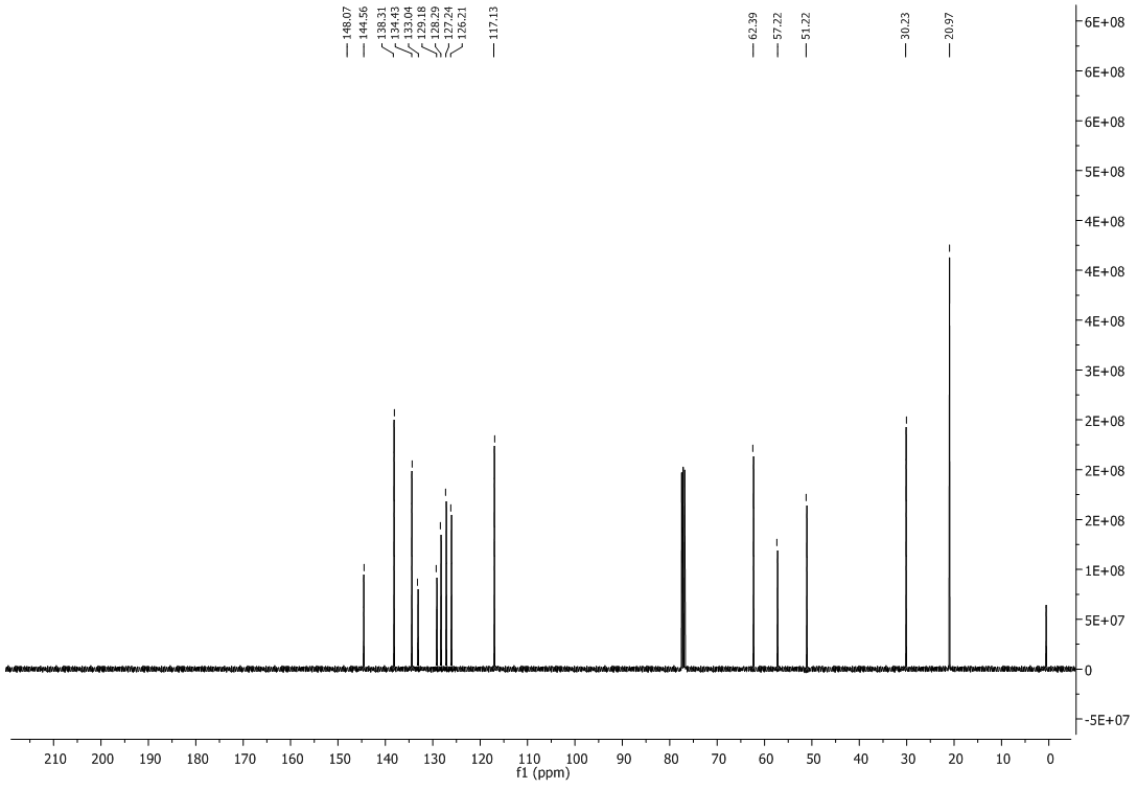
2.05
5.02
1.02
2.02
1.00
2.01
3.00
2.02
4.11
f1 (ppm)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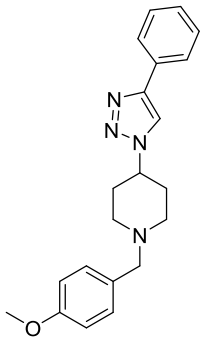
144.56
138.31
134.43
133.04
129.18
128.29
127.24
126.21
117.13
62.39
57.22
51.22
30.23
20.97
f1 (ppm)



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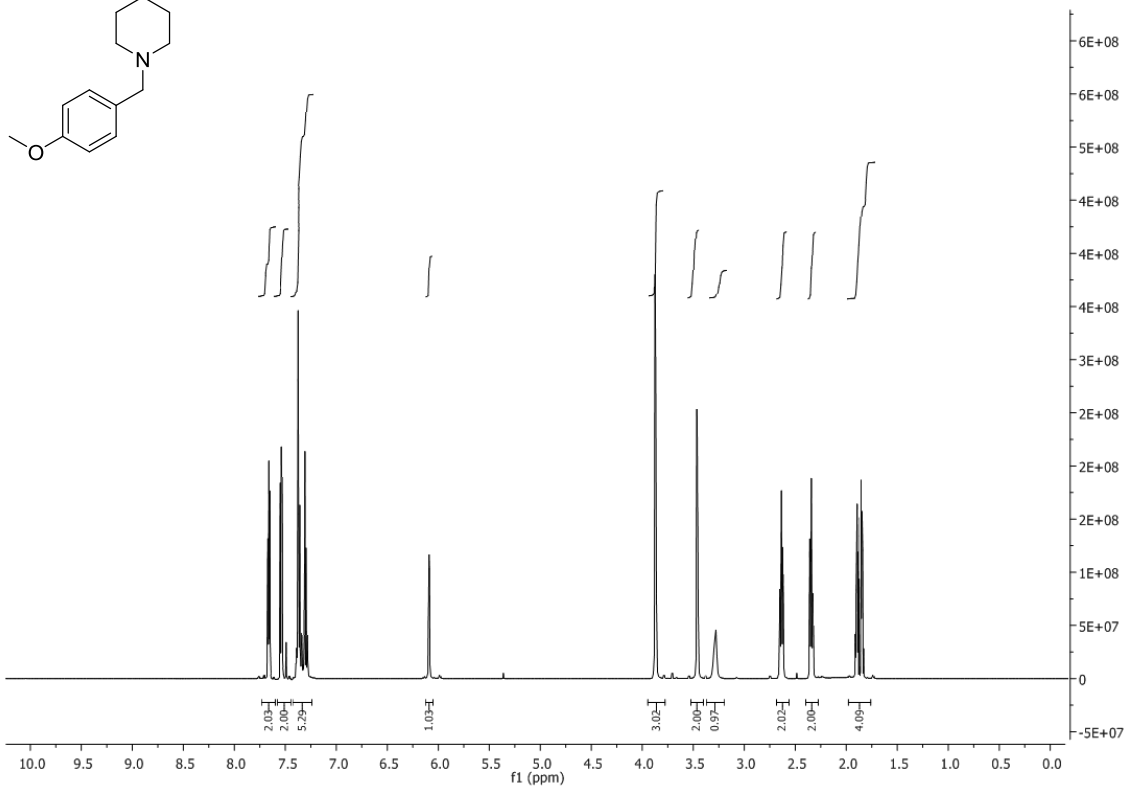
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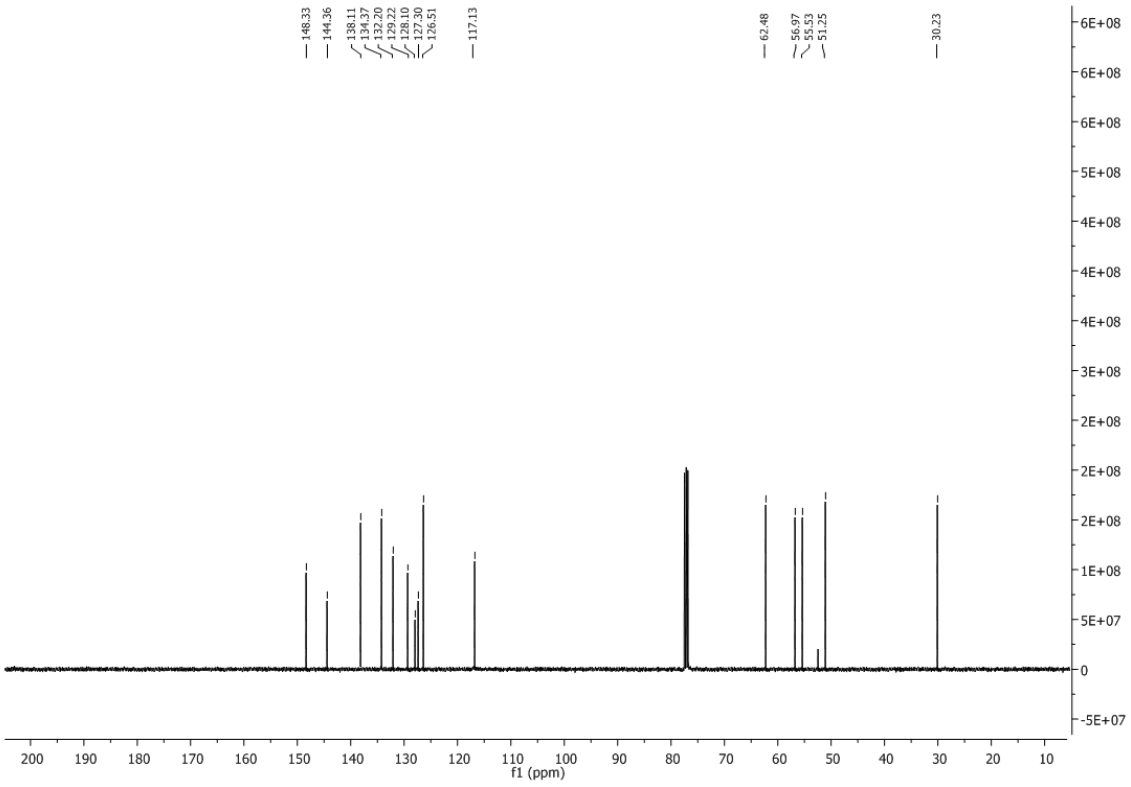
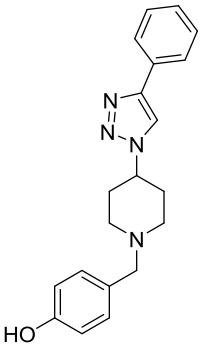
2.00
5.29
1.03
3.02
2.00
0.97
2.02
2.00
4.09
f1 (ppm)


148.33
144.36
138.11
134.37
132.20
129.22
128.10
127.30
126.51
117.13
62.48
56.97
55.53
51.25
30.23
f1 (ppm)



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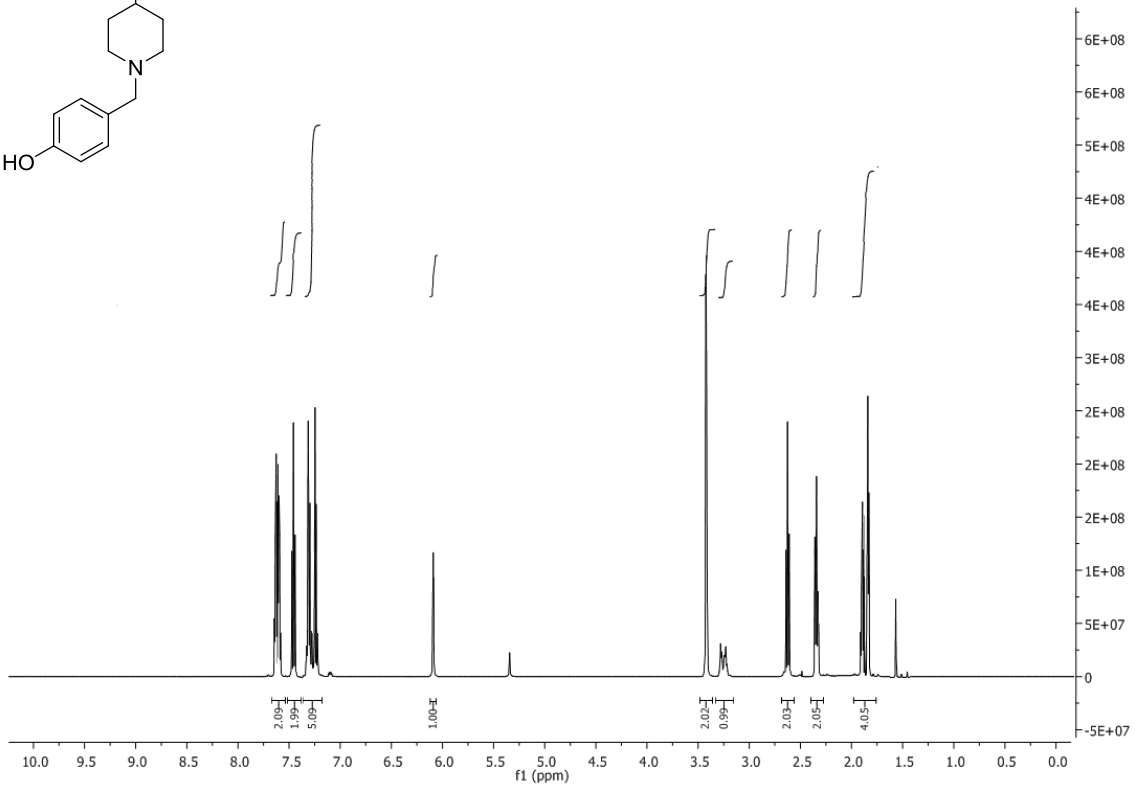
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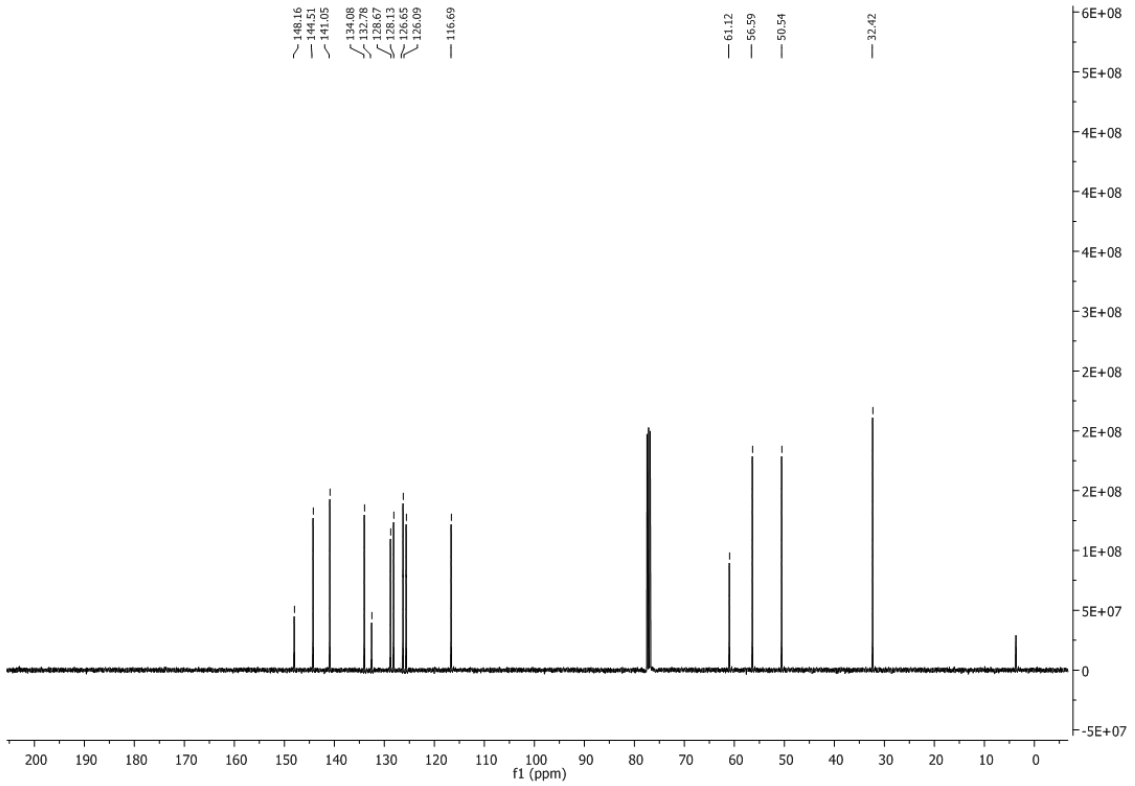
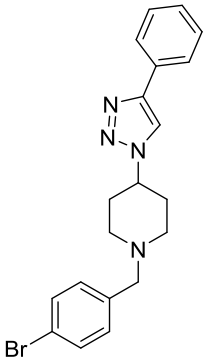
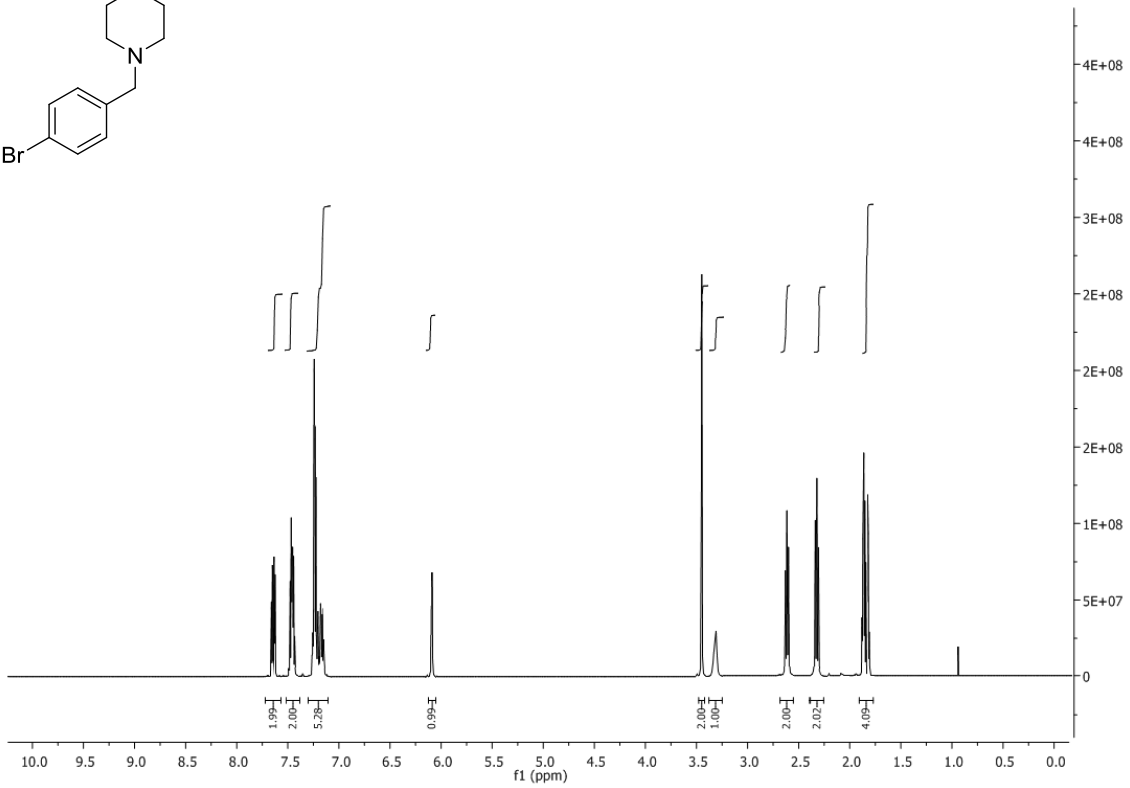
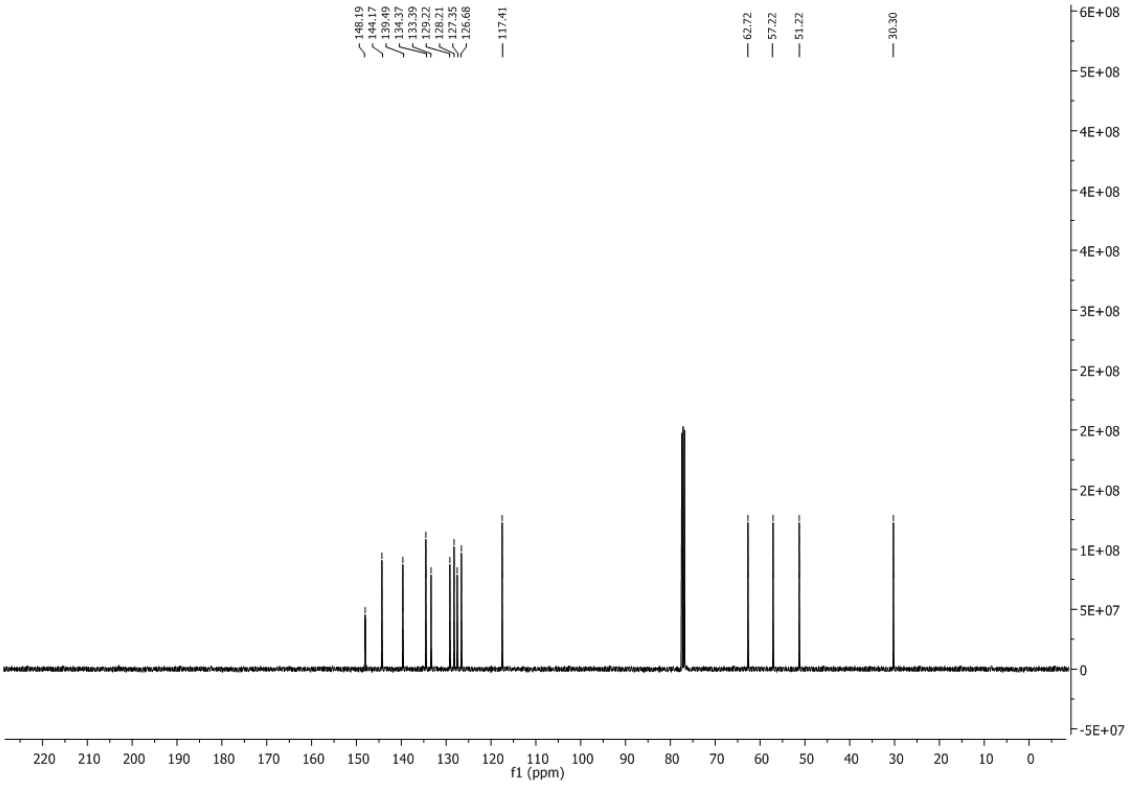
1.99
5.09
1.00
2.02
0.99
2.03
2.05
4.05
f1 (ppm)

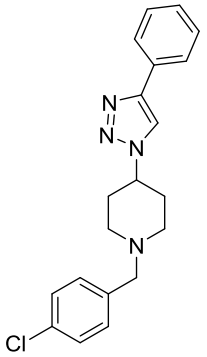

148.16
144.51
141.05
134.08
132.78
128.67
128.13
126.65
126.09
116.69
61.12
56.59
50.54
32.42
f1 (ppm)



8d


1.99
2.00
5.28
0.99
2.00
1.00
2.00
2.02
4.09
f1 (ppm)


148.19
144.17
139.49
134.37
133.39
129.22
128.21
127.35
126.68
117.41
62.72
57.22
51.22
30.30
f1 (ppm)



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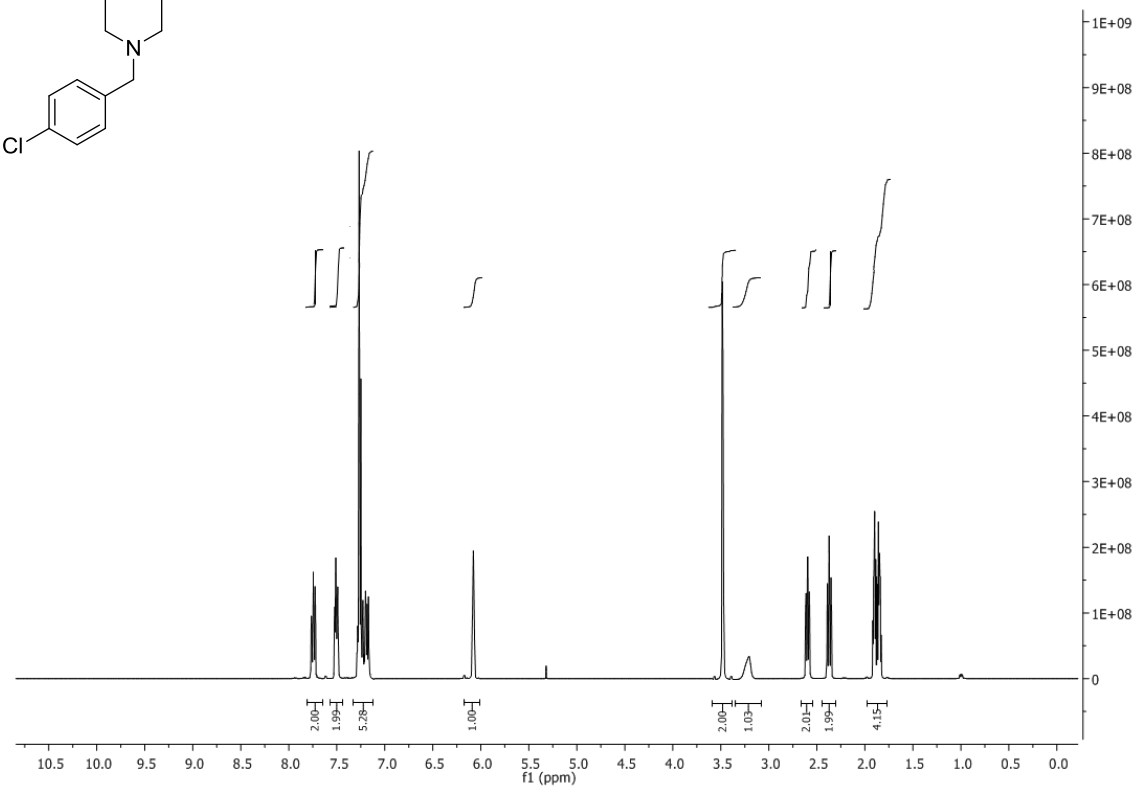
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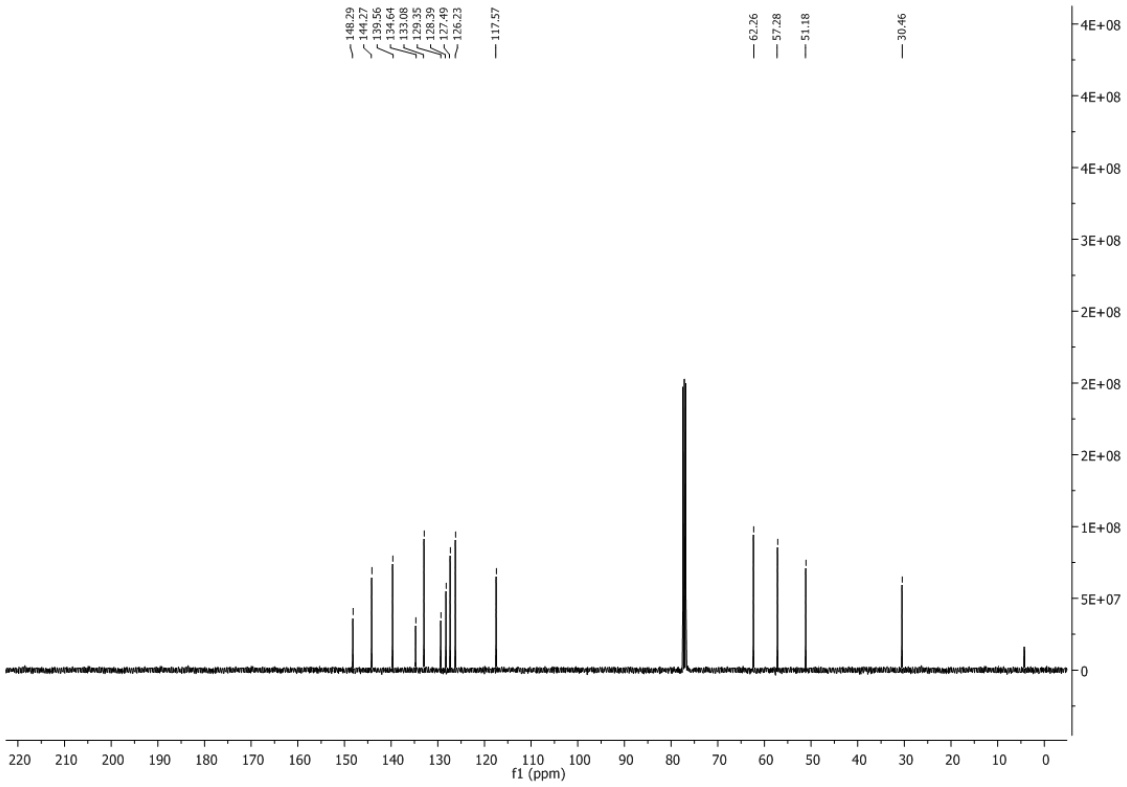
5.28
1.00
2.00
1.03
2.01
1.99
4.15
f1 (ppm)


148.29
144.27
139.56
134.64
133.08
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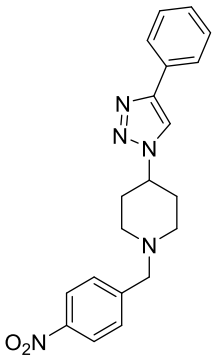
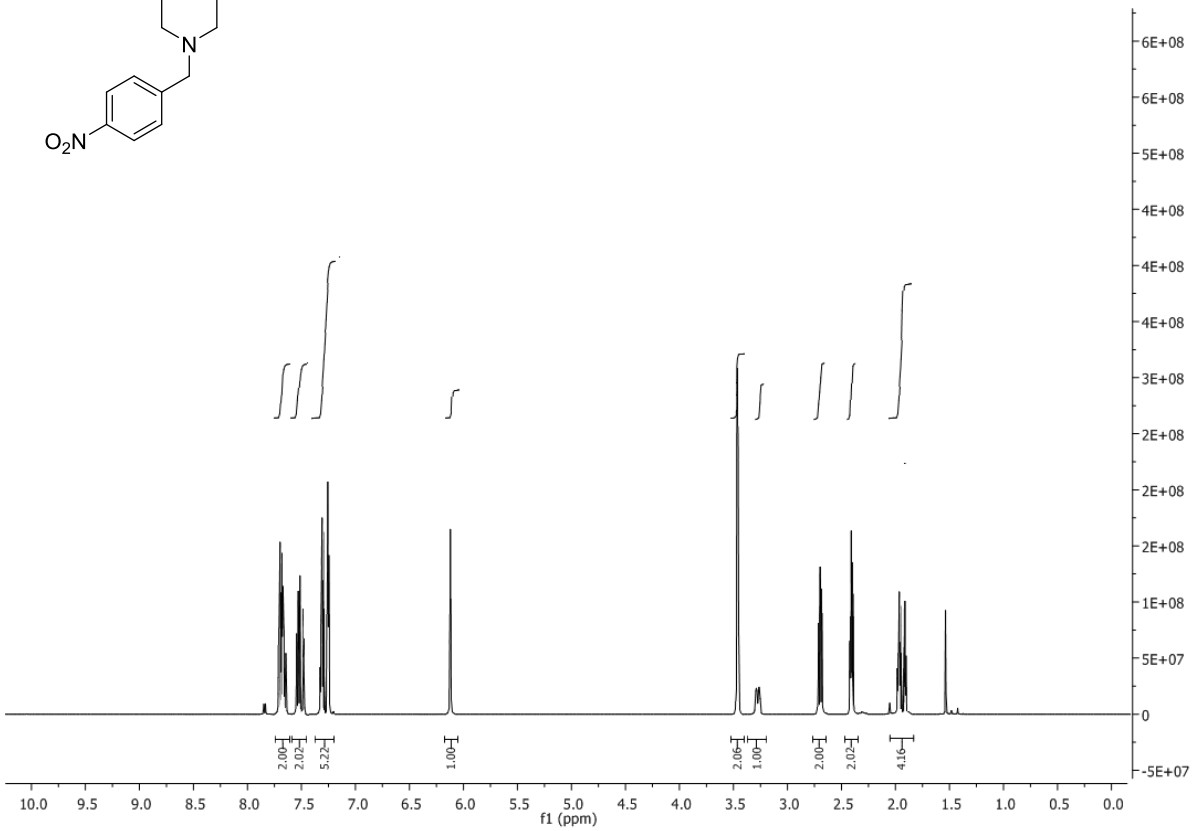
128.39
127.49
126.23
117.57
62.26
57.28
51.18
30.46
f1 (ppm)



8f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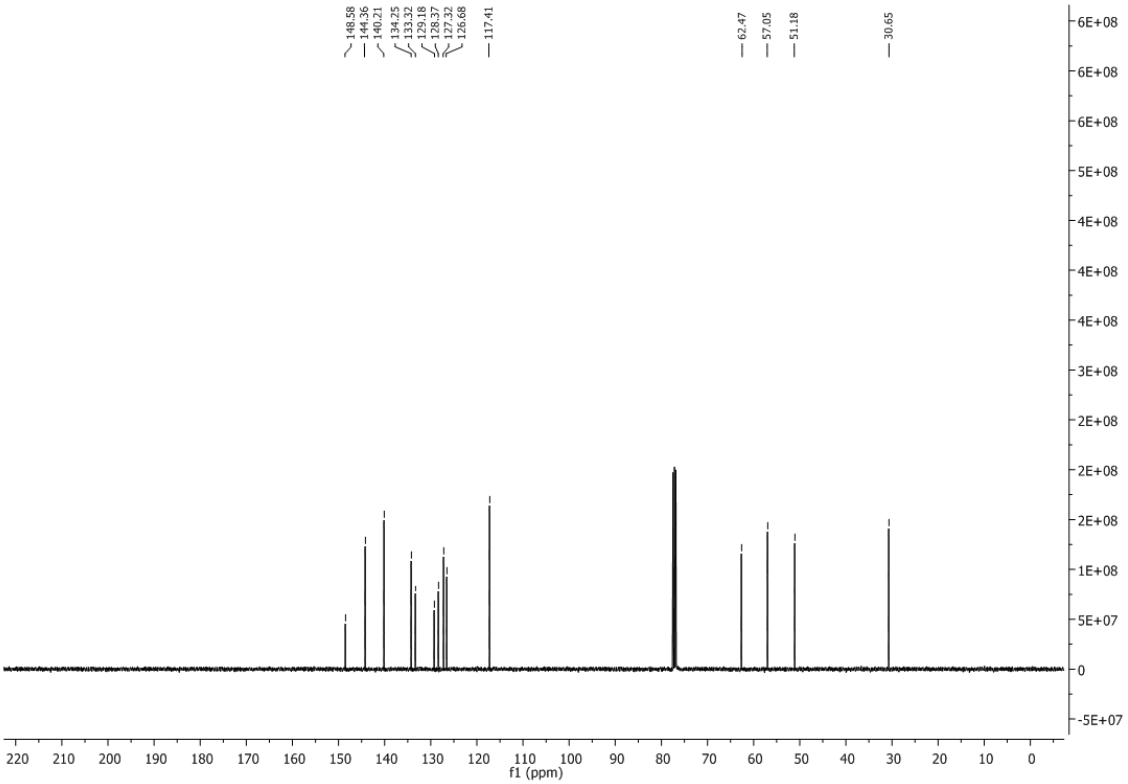
5.22
1.00
2.06
1.00
2.00
2.02
4.16
f1 (ppm)


148.58
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140.21
134.25
133.32
129.18
128.37
127.32
126.68
117.41
62.47
57.05
51.18
30.65
f1 (ppm)

8. Molecular docking study

ChemDraw was used to draw, set charges and run energy minimisation of the compounds **8a**-**f** and the output files were saved mol2 format. Crystal structure of DRD2 bound to Risperidone (PDB ID: 6CM4; resolution: 2.8 Å) was retrieved from protein data bank (Berman *et al.*, 2000). Ligand docking of compounds **8a**-**f** into the crystal structure of DRD2 was carried out using AutoDock 4.2.6 (Morris *et al.*, 2009). Each of these compounds in the PDBQT format was docked separately into the active site of DRD2. All calculations for protein-ligand docking were carried out using default settings. A grid box with the dimensions of X: -16.098, Y: 9.428 and Z: –15.288 Å with a default grid spacing was used. The best conformation was selected with the lowest docked energy from the largest cluster. The interactions between docked compounds and DRD2 receptor were analysed.

9. References

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