Supporting Information

Regioselective Metal-free Decarboxylative Multicomponent Coupling of α-Amino acids, Aldehydes and Isonitriles leading to *N*-substituted azacyclic-2-carboxamides with Antithrombotic activity

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Experiment to ascertain that the water liberated during imine formation is utilized for the hydrolysis step.

To a flame-dried screw-capped vial equipped with a magnetic stir bar and and dry toluene (5 mL) containing 4Å molecular sieves was added 4-cyanobenzaldehyde **2b** (0.2 g, 1.52 mmol), L-proline (0.21 g, 1.83 mmol,) and cyclohexyl isonitrile **3A** (0.23 ml, 1.83 mmol) under nitrogen atmosphere. The reaction mixture was allowed to stir for 20 min. To this reaction mixture was added D_2O (1.52 mmol. 26µL) and the solution was stirred at 110 ^oC for 5 h. On completion the reaction mixture was directly subjected to purification via silica gel column chromatography to afford the product **4bA** (0.293 g, 63 %) as colorless oil.

^{1}H-NMR spectrum of **4bA** obtained from the above procedure showed only 46% deuterium incorporation at the amide functionality reflecting that the water eliminated at the time of imine formation takes part in hydrolysis (Compare Figure S-2 and Figure S-3).

Isotope Labeling Experiments. Similar conditions as described above were used for isotope labeling studies with the exception of using $H_2{}^{18}O$ (97 %) instead of D_2O and molecular sieves. The incorporation of ^{18}O in the reaction products was determined by subjecting reaction mixture for Mass Spectocopy (HRMS) analysis which exhibited the presence of a mixture of ^{16}O (311 amu) and ^{18}O (313 amu) prolinamide **4bA** (Figure S-1).

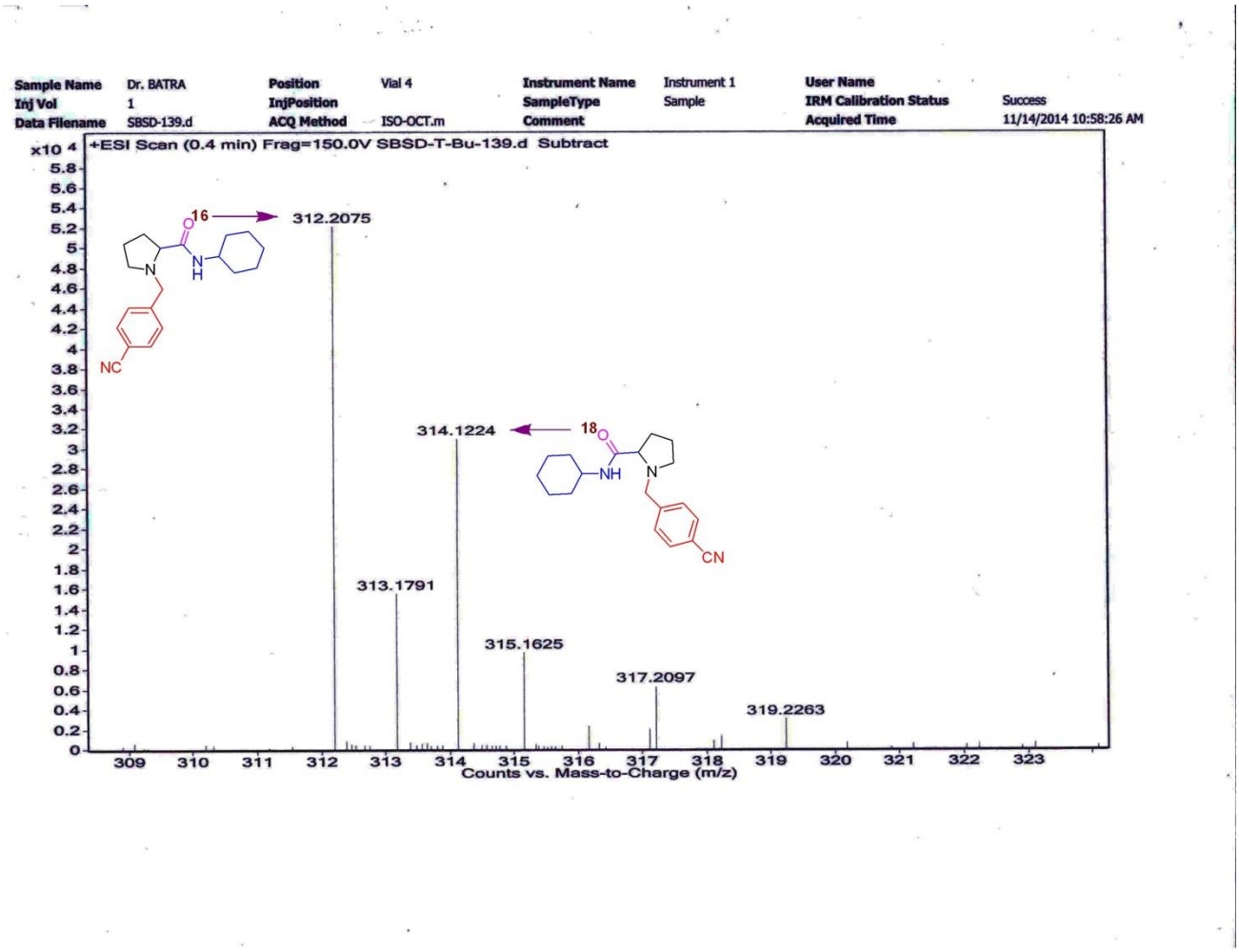


Figure S-1. HRMS spectrum of **4bA-^{16}O/^{18}O** mixture.

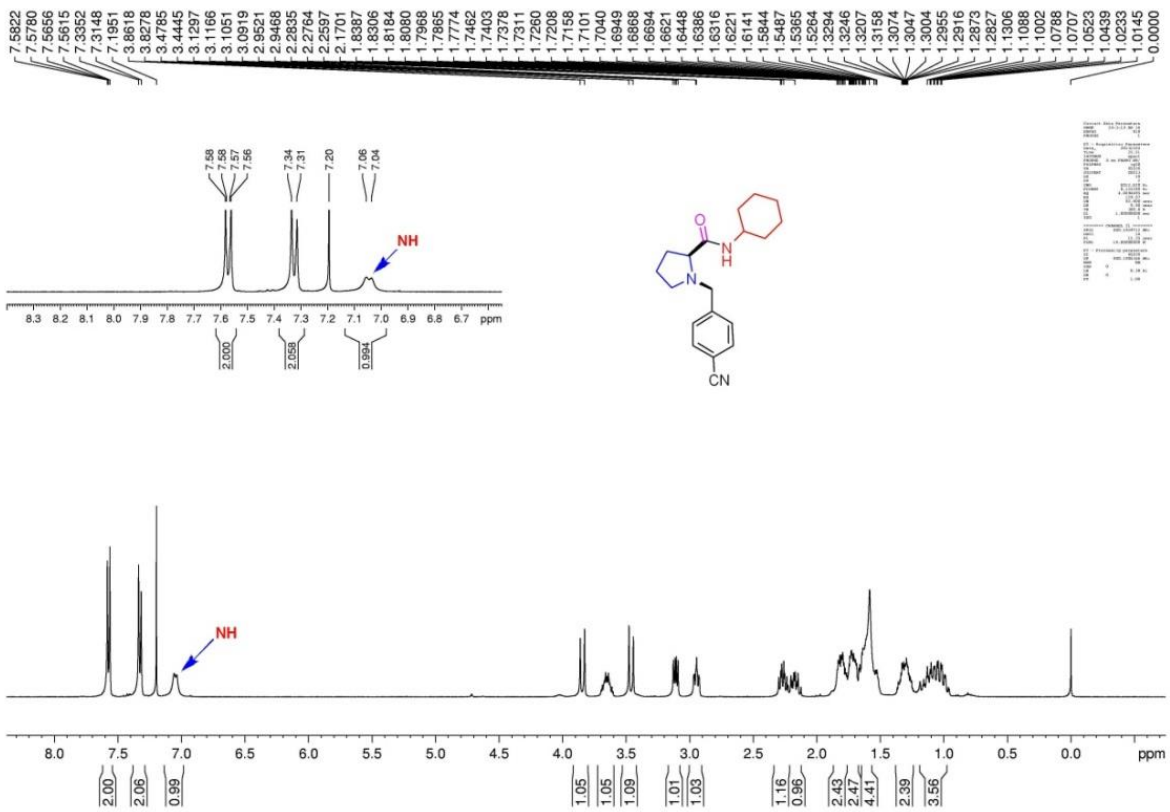


Figure S-2. ^{1}H-NMR spectrum of **4bA**

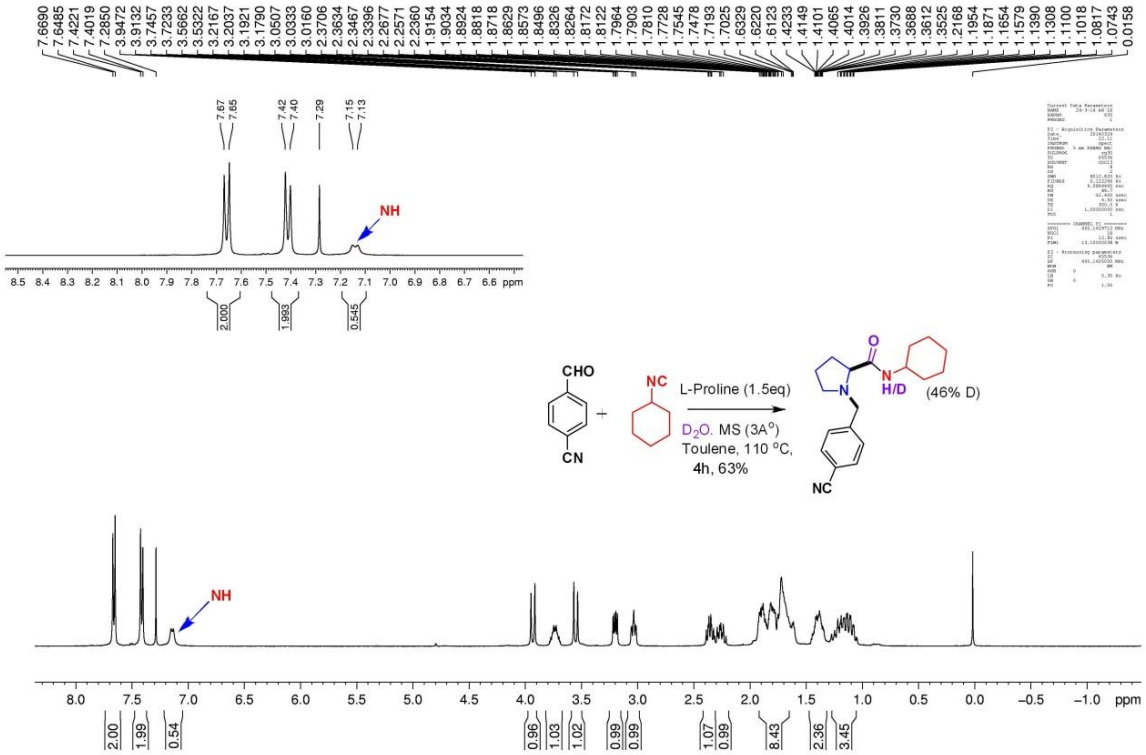


Figure S-3. ^{1}H-NMR spectrum of **4bA** obtained from the reaction performed in D_2O

MATERIALS AND METHODS

1) Blood Collection: Human blood was collected in 3.8% tri-sodium citrateas anticoagulant in the ratio of 9:1.

2) Isolation of human plasma

Human blood was collected in 3.8% tri-sodium citrate in the ratio of 9:1 (v/v).Plasma was isolated from whole blood by centrifuging it at 2000 g for 15 min. After centrifugation, the upper layer of plasma was collected in another tube and all three coagulation parameters [Thrombin time (TT), Prothrombin time (PT) and activated partial thromboplastin time (aPTT)] were assessed in plasma.

3) Isolation of human platelets

Human platelets were isolated from whole blood as described previously.[1] Briefly, to obtain platelet rich plasma (PRP), blood was centrifuged at room temperature at 150g for 10 min, the upper turbid layer of PRP was collected and platelet count was adjusted to $2x10^8$ cells/mL with 0.9% normal saline.

4) Coagulation Parameters (*in vitro*).

All assays were performed using commercial kits as per manufacturer's instructions (Diagnostica Stago, France). Briefly, human blood was collected by venipuncture from healthy donors in 3.8% tri-sodium-citrate and centrifuged at 2500g for 15 min to obtain platelet poor plasma. All three coagulation parameters i.e. TT, PT and aPTT were evaluated in platelet poor plasma (PPP) according to manufacturer's instruction and measured by a coagulometer (Start4 Semi automated, Stago, France) within 2 h of sample collection.

5) Platelet Aggregation assay: Aggregation in Human platelet rich plasma (*in vitro*)

Turbidimetric method was used to measure platelet aggregation, using a four channel Whole Blood Aggregometer, Chrono-log Corp, USA. All the twenty-one test compounds were tested initially at 30 µM concentration. Platelet rich plasma (2×10^8 platelets/ml, 0.49 ml) was pre-warmed to 37°C for 3 minutes, then incubated with test samples (30 µM) or an isovolumetric solvent control (0.5% DMSO) for 5 minutes before addition of the agonists such as collagen (2 µg/ml), TRAP (12.5 µM), ADP (5 µM), Arachidonic acid (0.5mM). The reactions were allowed to proceed for at least 5 minutes, and the extent of aggregation was expressed in light-transmission percentage. The percentage of aggregation was calculated by using Aggrolink Software.

6) Collagen and epinephrine induced thromboembolism in Mice (*in vivo*)

The compound to be tested, standard drug or the vehicle was administered by oral route one hour prior to the thrombotic challenge.[2] Ten mice per group were used for evaluating the effect of test compound, aspirin and vehicle. A mixture of collagen and epinephrine was injected into the tail vein to induce hind limb paralysis or death. Results have been reported as percentage protection, which represents protection against collagen and epinephrine induced thrombosis and expressed as;

Percent Protection = $[1-(P_{test} / P_{control})] \times 100$

P_{test} - number of animals paralyzed/dead in test sample/standard drug treated group

$P_{control}$ - number of animals paralyzed/dead in vehicle treated group.

7) Tail bleeding time

Bleeding time in mice was evaluated by the method of Dejana et.al.[3] Tip of mice tail (approximately 2 mm) was cut with a sharp razor blade. The time elapsed from the tip incision to the stoppage of bleeding was determined as the bleeding time. The change in bleeding time was compared with vehicle treated mice and results have been depicted as fold increase.

8) Ferric chloride ($FeCl_3$) induced thrombosis in mice

Mice were anesthetized by urethane (1.25 g/kg, *i.p*) and kept on heat controlled operating table (Harvard Apparatus, USA). The carotid artery was carefully dissected by cervical incision and a pulsed Doppler flow probe (LDF-100C Laser Doppler Flowmetry, BIOPAC Systems, USA) was placed around it to record the blood flow velocity and patency of blood vessel using Biopac Data Acquisition System software (Acq*Knowledge*, MP150 Data Acquisition System, BIOPAC Systems, USA). After stabilization period of 20 min, intravascular thrombosis was induced by the topical application of 10% $FeCl_3$ soaked Whatmann filter paper. Intravascular thrombosis was monitored as the time taken for cessation of carotid artery blood flow i.e. time to occlusion (TTO).

9) Statistical Analysis

Data are represented as Mean±SEM, of at least 5 to 6 independent experiments and were analysed by one way ANOVA test followed by Tukey's multiple comparison test. Data were considered significant at $p < 0.0001$.

REFERENCES:

1. Prakash, P.; Misra, A.; Surin, W.R.; Jain, M.; Bhatta, R. S.; Pal, R.; Raj, K.; Barthwal, M. K.; Dikshit, M. *Thromb. Res*. **2011**, *127*, 111-118.
2. Kumar, A. K. S.; Misra, A.; Siddiqi, T. I.; Srivastava, S.; Jain, M.; Bhatta, R. S.; Barthwal , M.; Dikshit, M.; Dikshit. D. K. *Eur. J. Med. Chem.* **2014**, *81*, 456-472.
3. Dejana, E.; Callioni, A.; Quintana, A. *Thromb Res.* **1979**, *15*, 191-197.

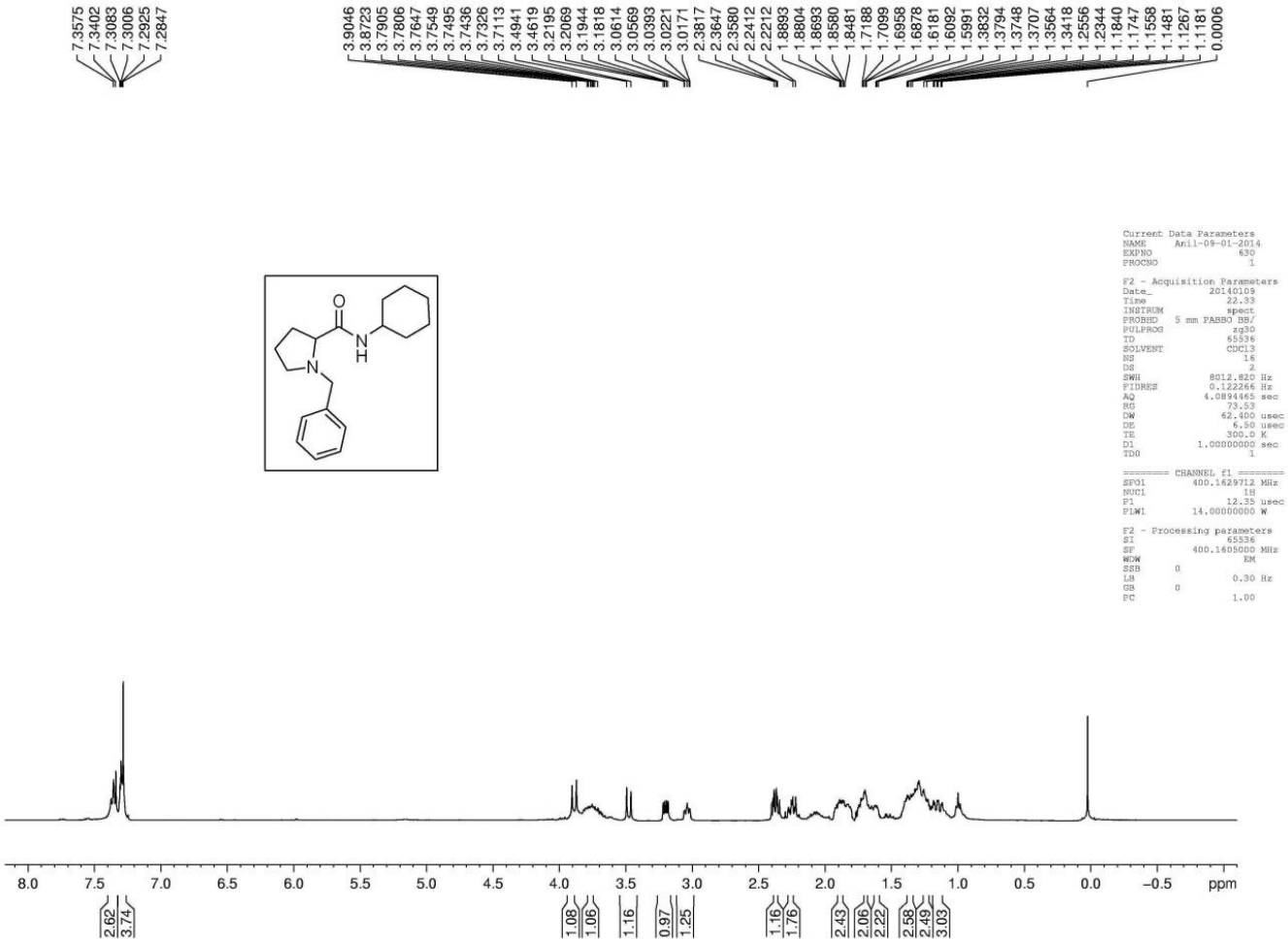


Figure S-4 ^{1}H-NMR spectrum of 1-Benzyl-*N*-cyclohexylpyrrolidine-2-carboxamide **(4aA)**.

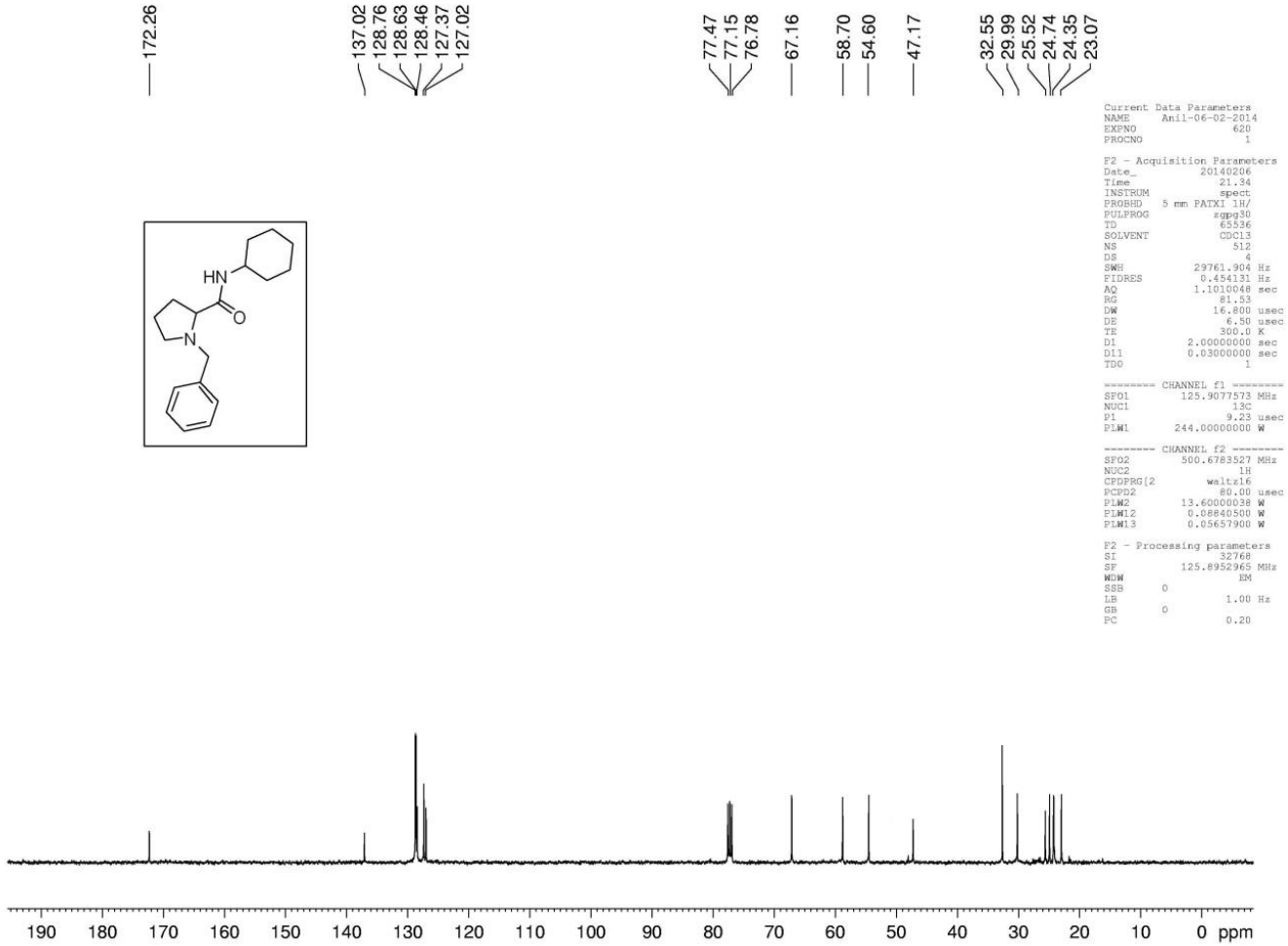


Figure S-5. ^{13}C-NMR spectrum of 1-Benzyl-*N*-cyclohexylpyrrolidine-2-carboxamide **(4aA)**.

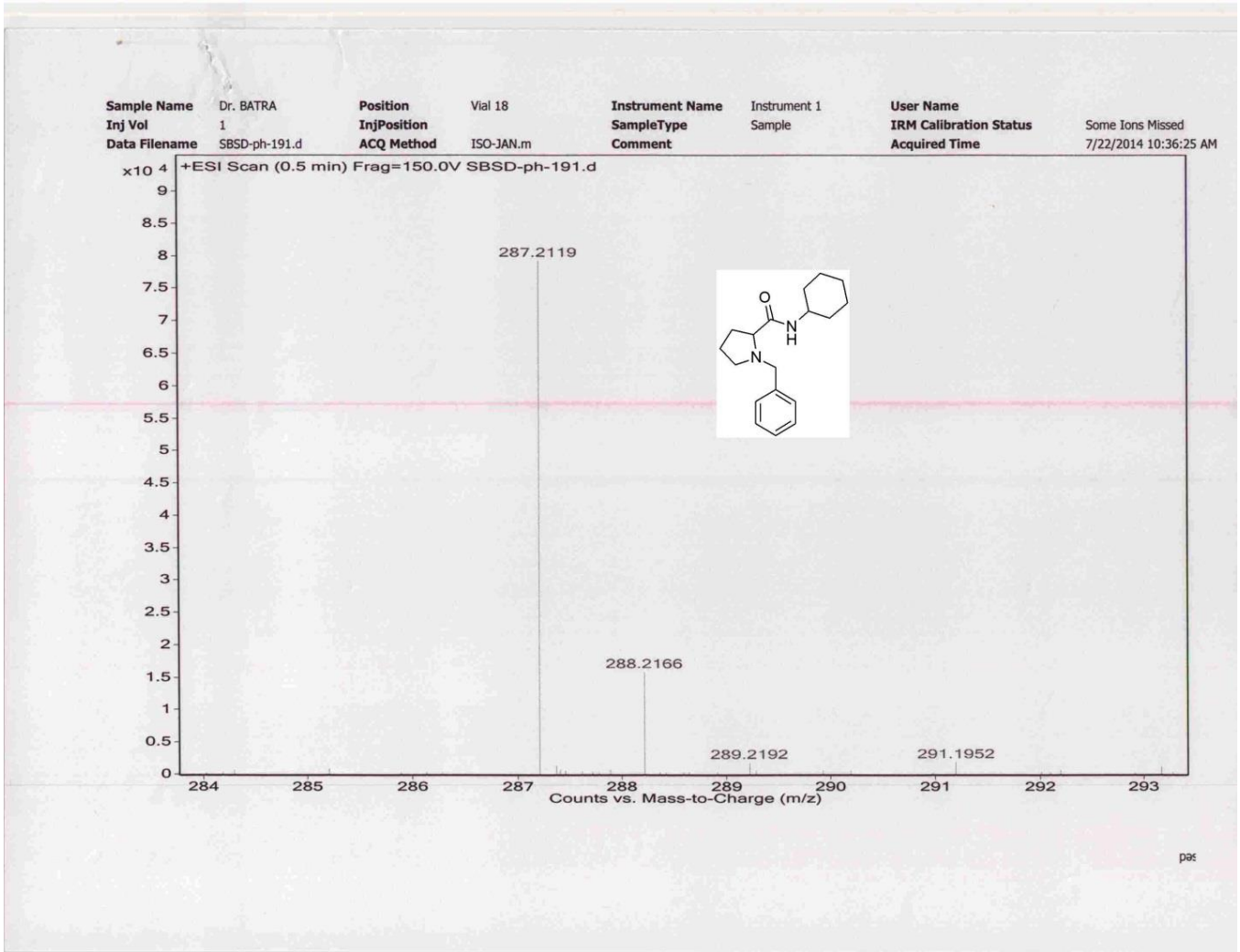


Figure S-6. HRMS spectrum of 1-Benzyl-*N*-cyclohexylpyrrolidine-2-carboxamide **(4aA)**.

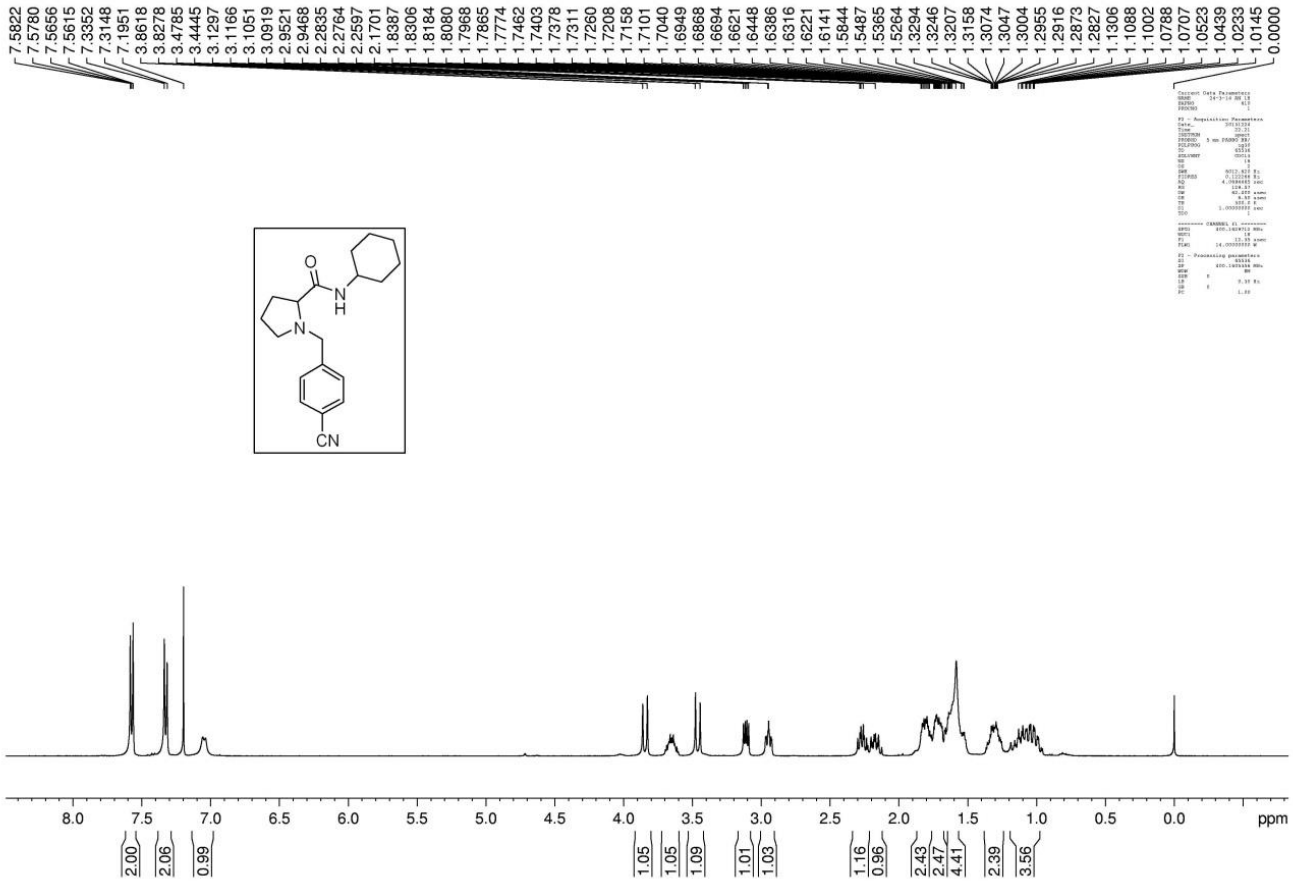


Figure S-7. ^{1}H-NMR spectrum of 1-(4-Cyanobenzyl)-*N*-cyclohexylpyrrolidine-2-carboxamide **(4bA)**.

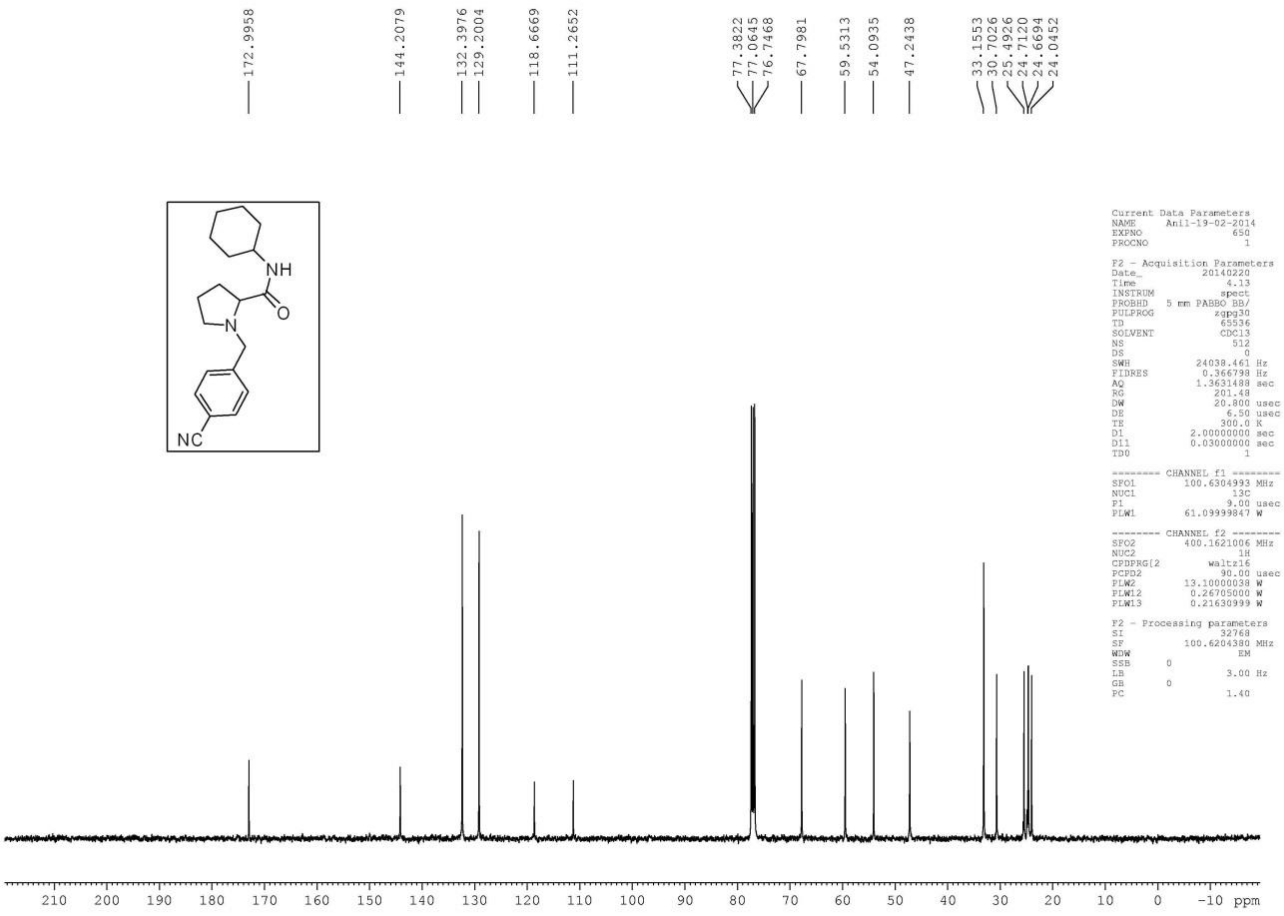


Figure S-8. ^{13}C-NMR spectrum of 1-(4-Cyanobenzyl)-*N*-cyclohexylpyrrolidine-2-carboxamide **(4bA)**.

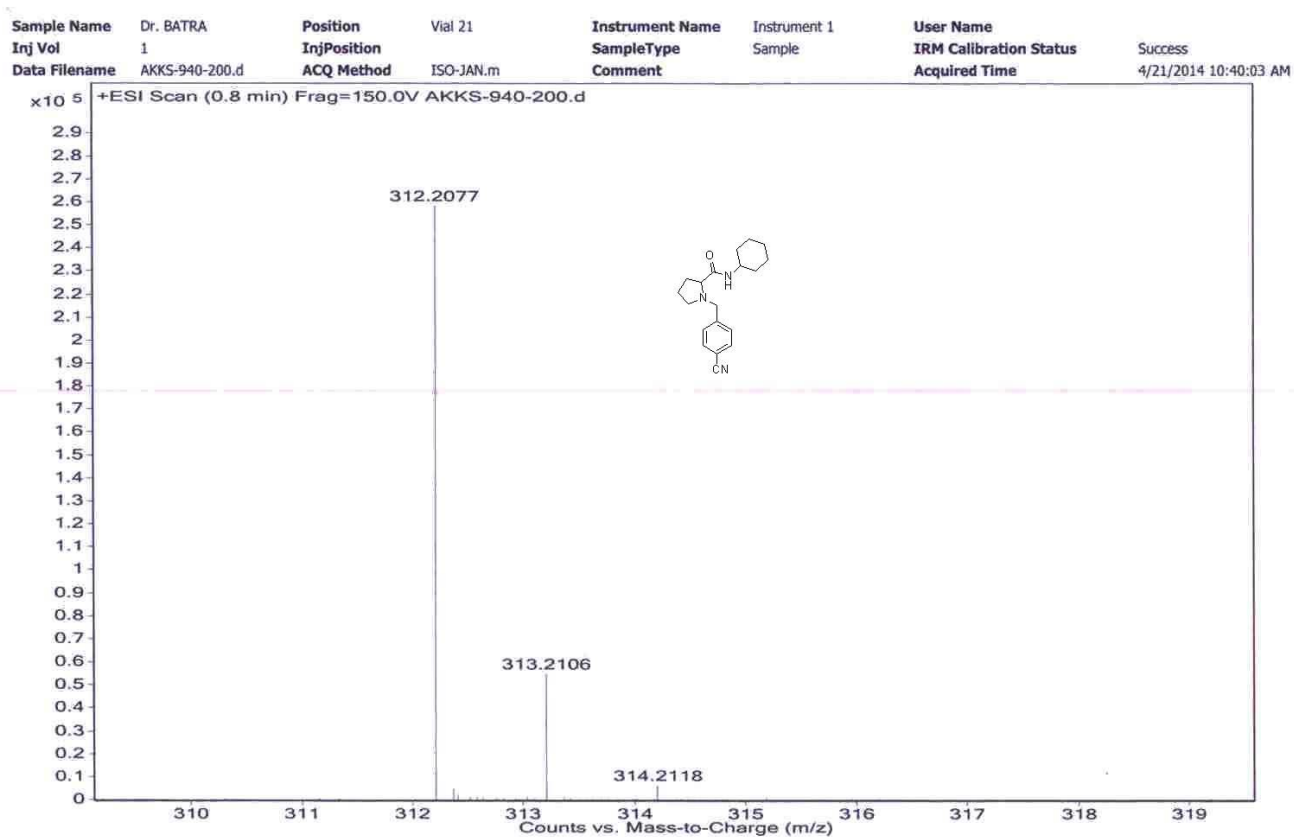


Figure S-9. HRMS spectrum of 1-(4-Cyanobenzyl)-*N*-cyclohexylpyrrolidine-2-carboxamide **(4bA**).

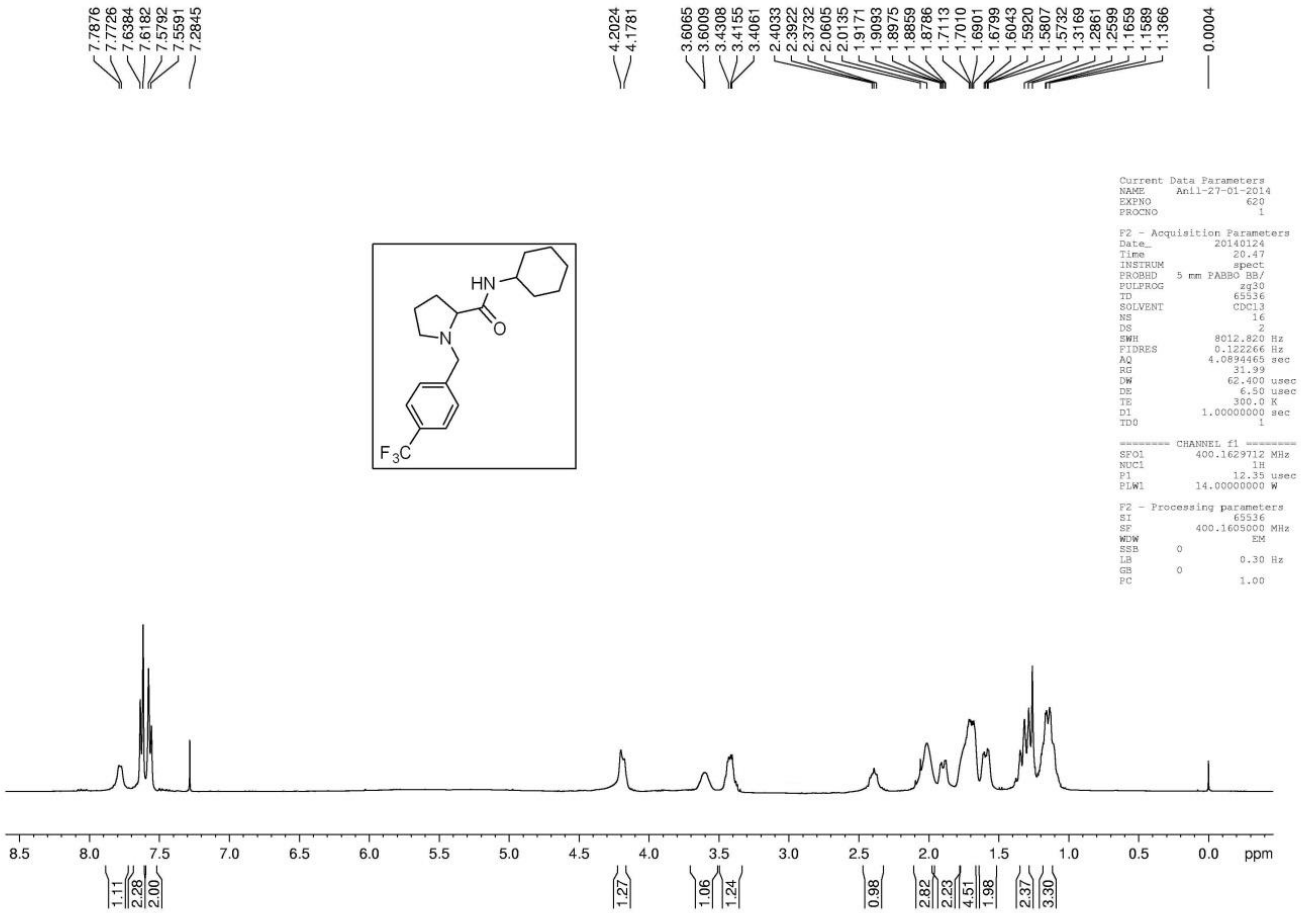


Figure S-10. ^{1}H-NMR spectrum of *N*-cyclohexyl-1-(4-(trifluoromethyl)benzyl)pyrrolidine-2-carboxamide (**4cA**).

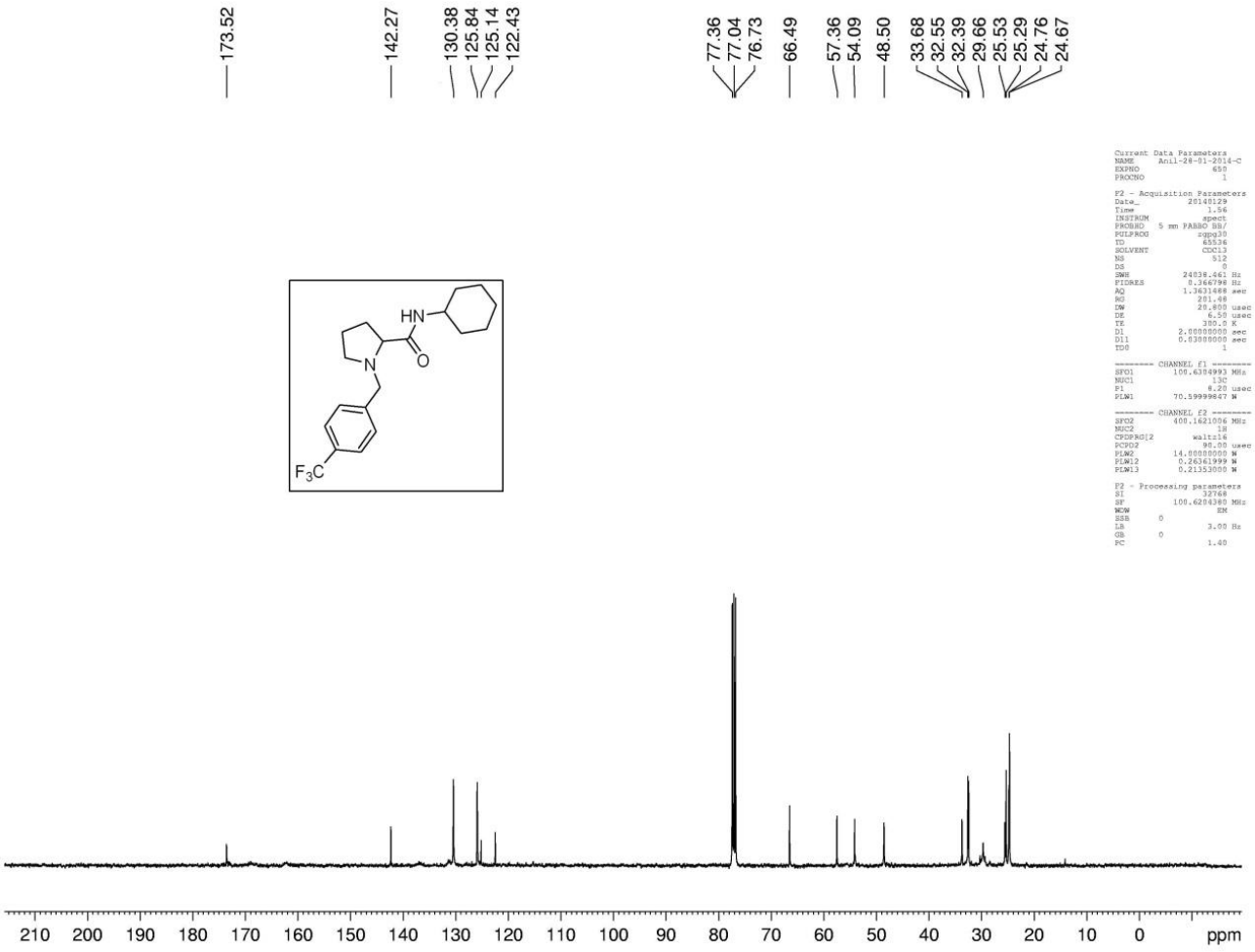


Figure S-11. ^{13}C-NMR spectrum of *N*-cyclohexyl-1-(4-(trifluoromethyl)benzyl)pyrrolidine-2-carboxamide (**4cA**).

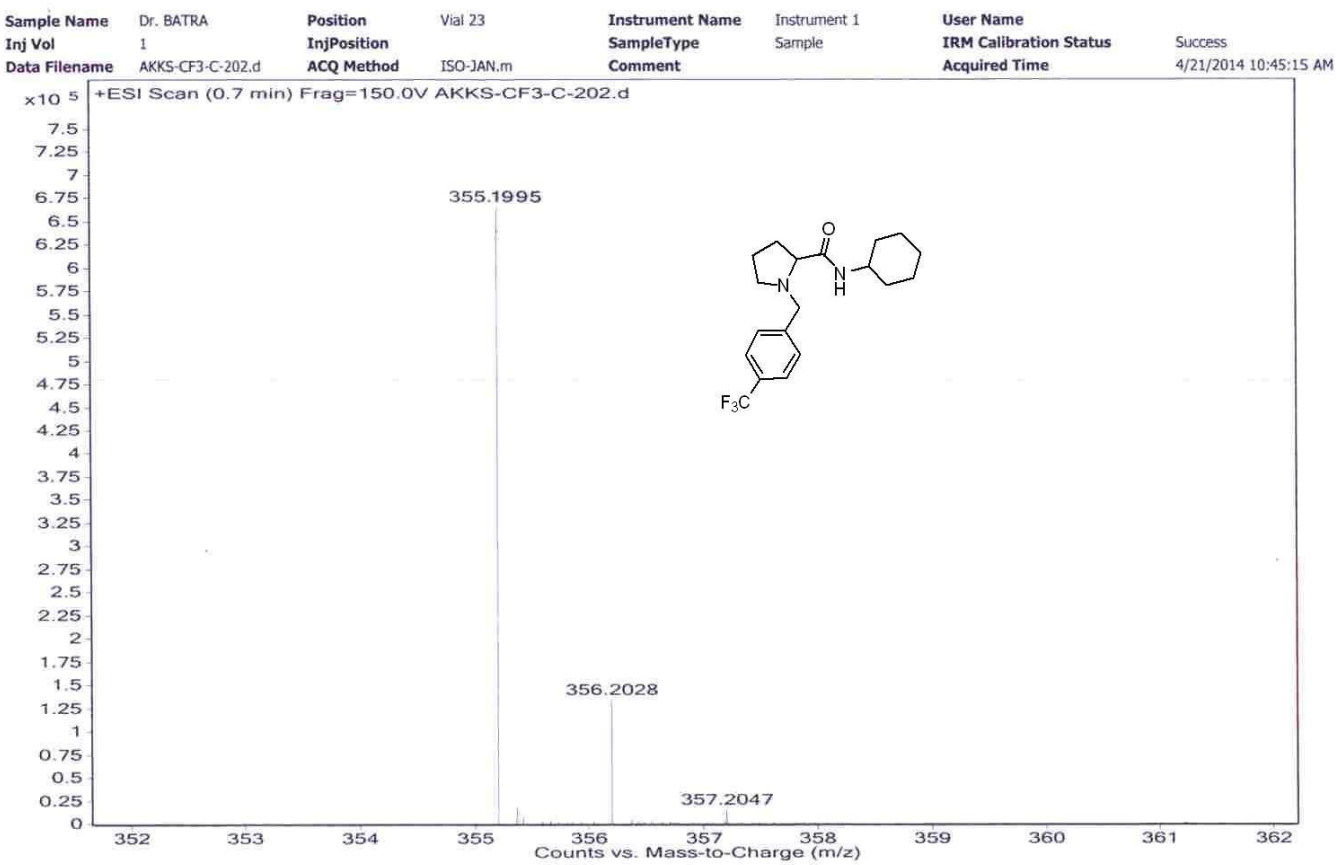
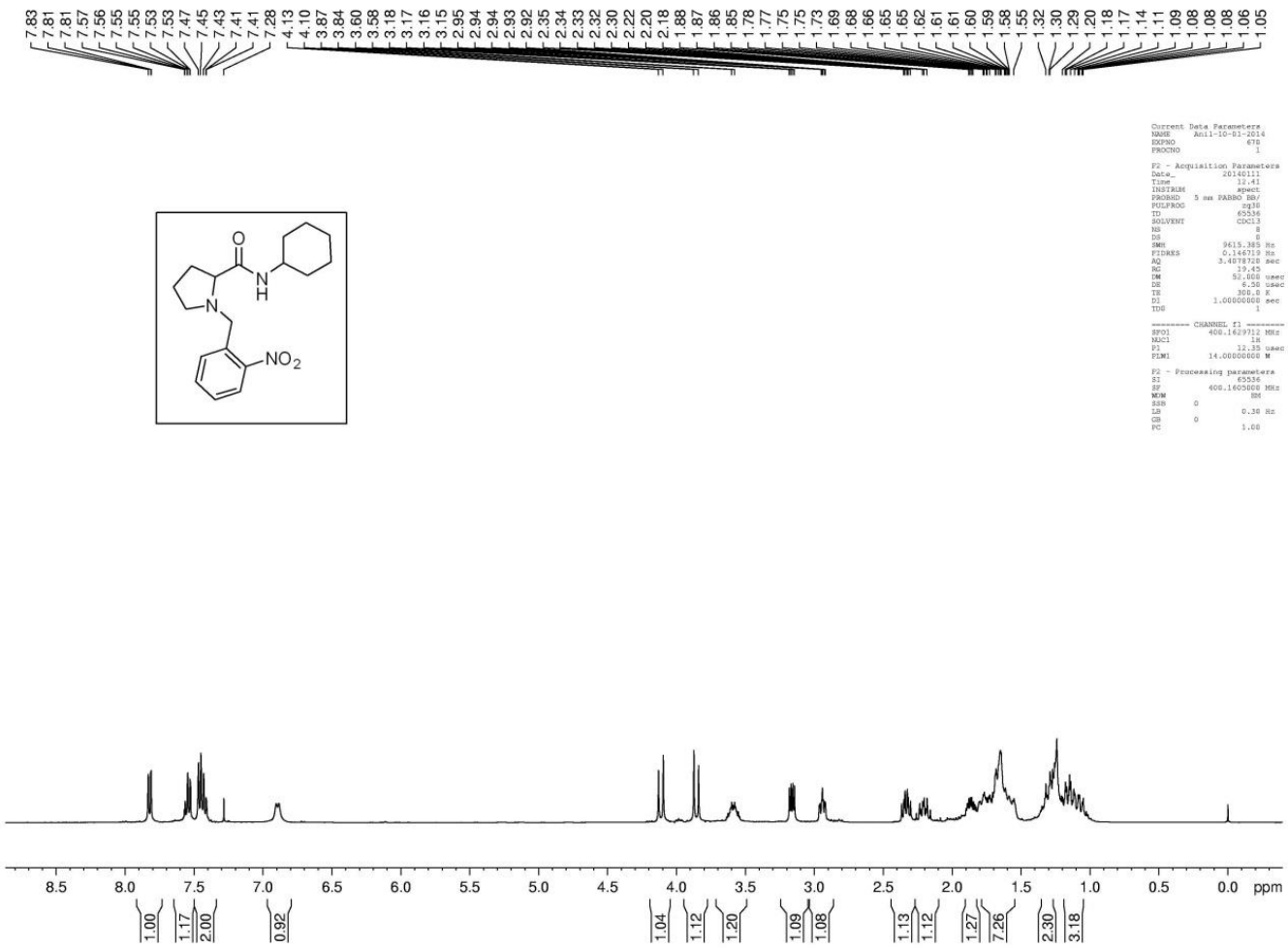


Figure S-12. HRMS spectrum of *N*-cyclohexyl-1-(4-(trifluoromethyl)benzyl)pyrrolidine-2 carboxamide (**4cA**).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1.00 1.17 2.00 0.92 1.04 1.12 1.20 1.09 1.08 1.13 1.12 1.27 7.26 2.30 3.18

Figure S-13. ^{1}H-NMR spectrum of *N*-cyclohexyl-1-(2-nitrobenzyl)pyrrolidine-2-carboxamide (**4dA**).

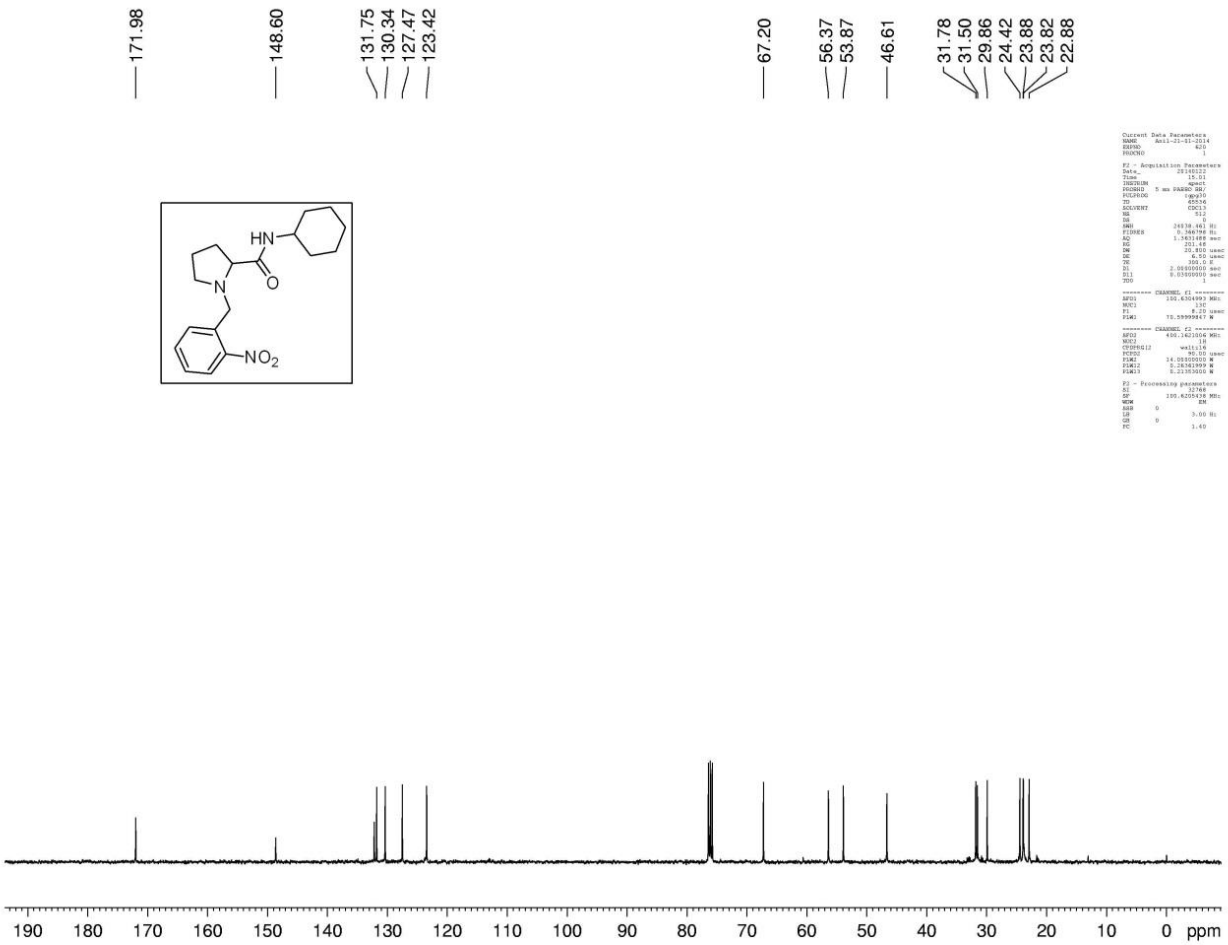

Figure S-14 . ^{13}C-NMR spectrum of *N*-cyclohexyl-1-(2-nitrobenzyl)pyrrolidine-2-carboxamide (**4dA**).

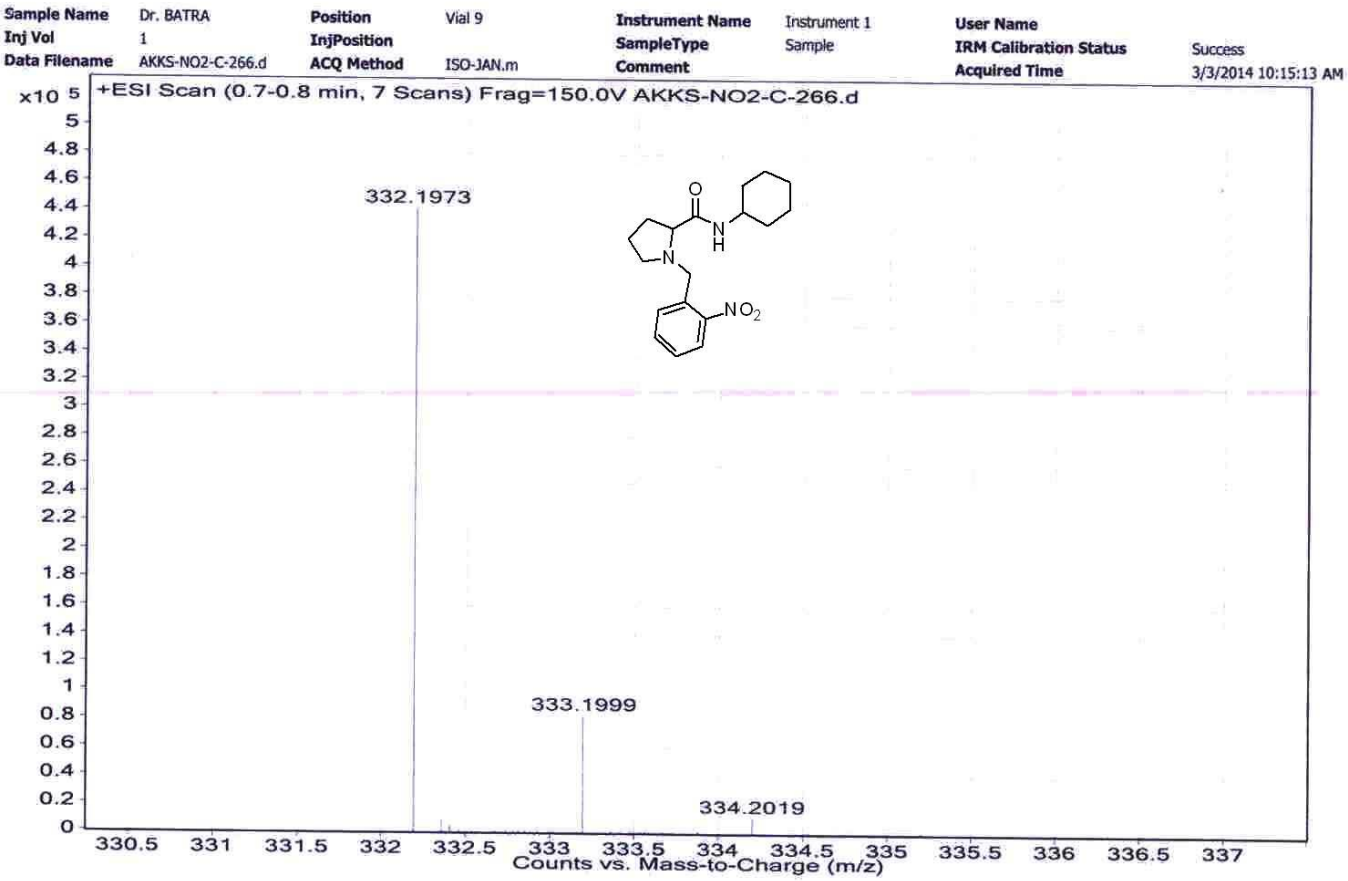

Figure S-15. HRMS spectrum of *N*-cyclohexyl-1-(2-nitrobenzyl)pyrrolidine-2-carboxamide (**4dA**).

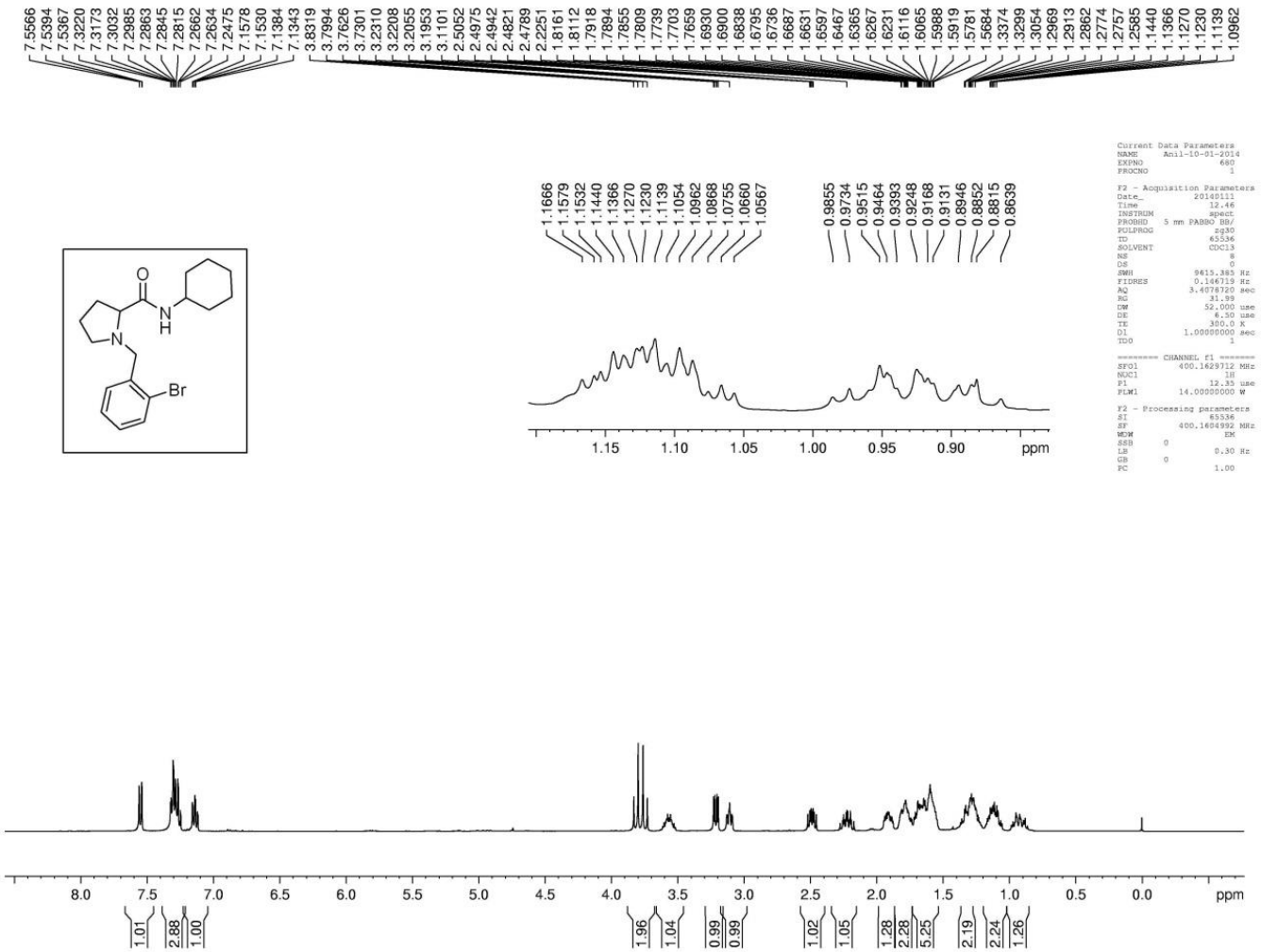

Figure S-16. ^{1}H-NMR spectrum of 1-(2-Bromobenzyl)-*N*-cyclohexylpyrrolidine-2-carboxamide (**4eA**).

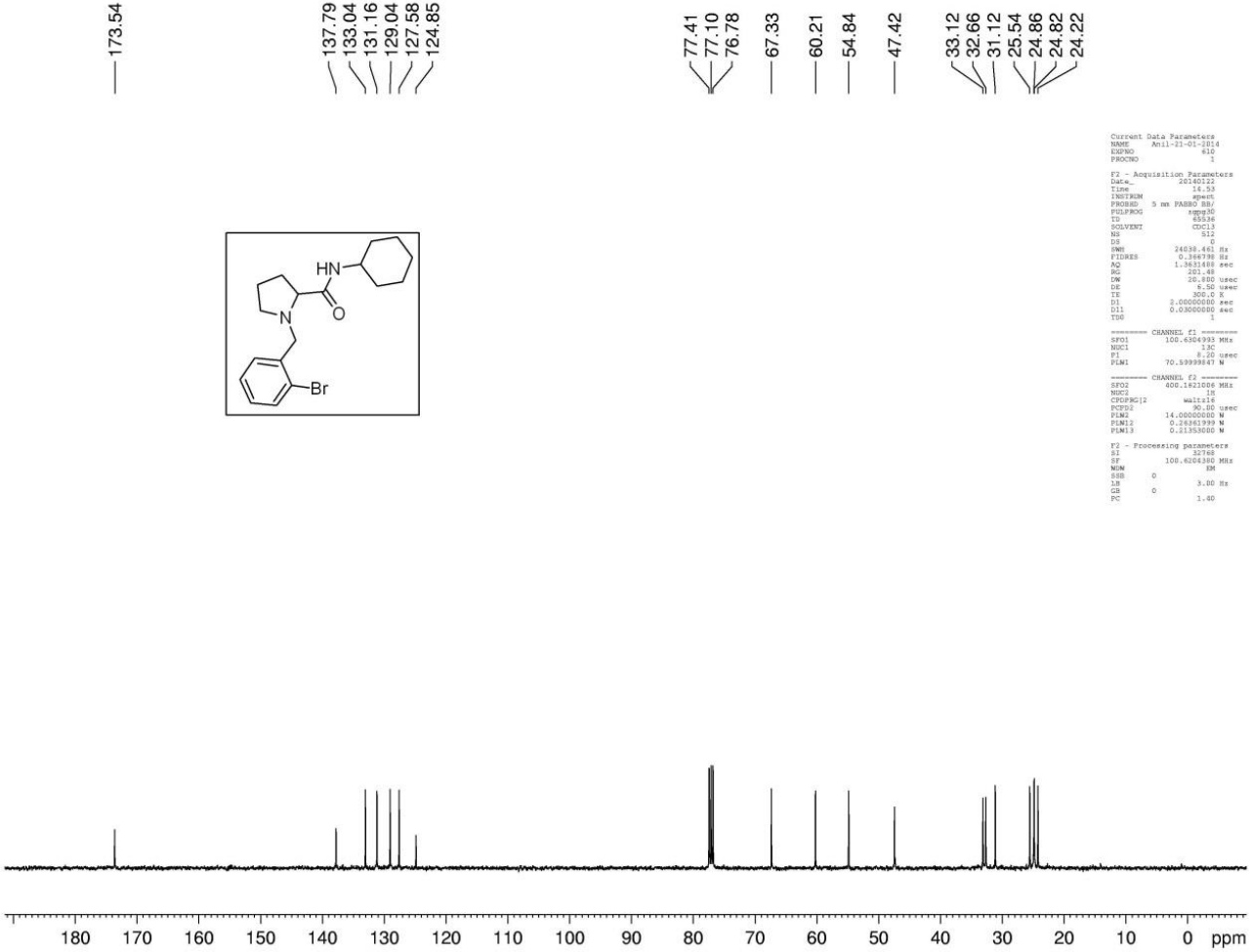

Figure S-17. ^{13}C-NMR spectrum of 1-(2-Bromobenzyl)-*N*-cyclohexylpyrrolidine-2-carboxamide (**4eA**).

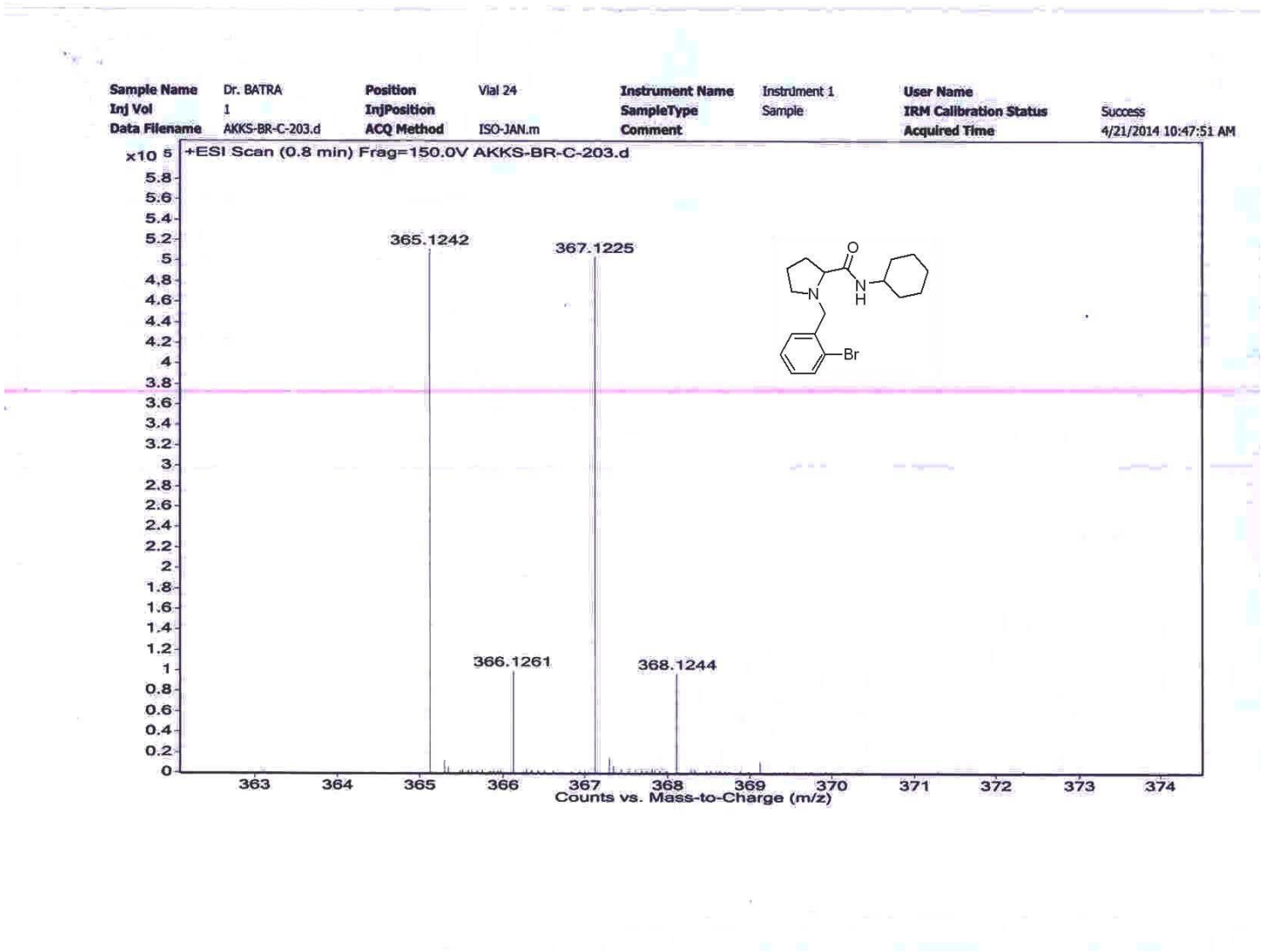

Figure S-18. HRMS spectrum of 1-(2-Bromobenzyl)-*N*-cyclohexylpyrrolidine-2-carboxamide (**4eA**).

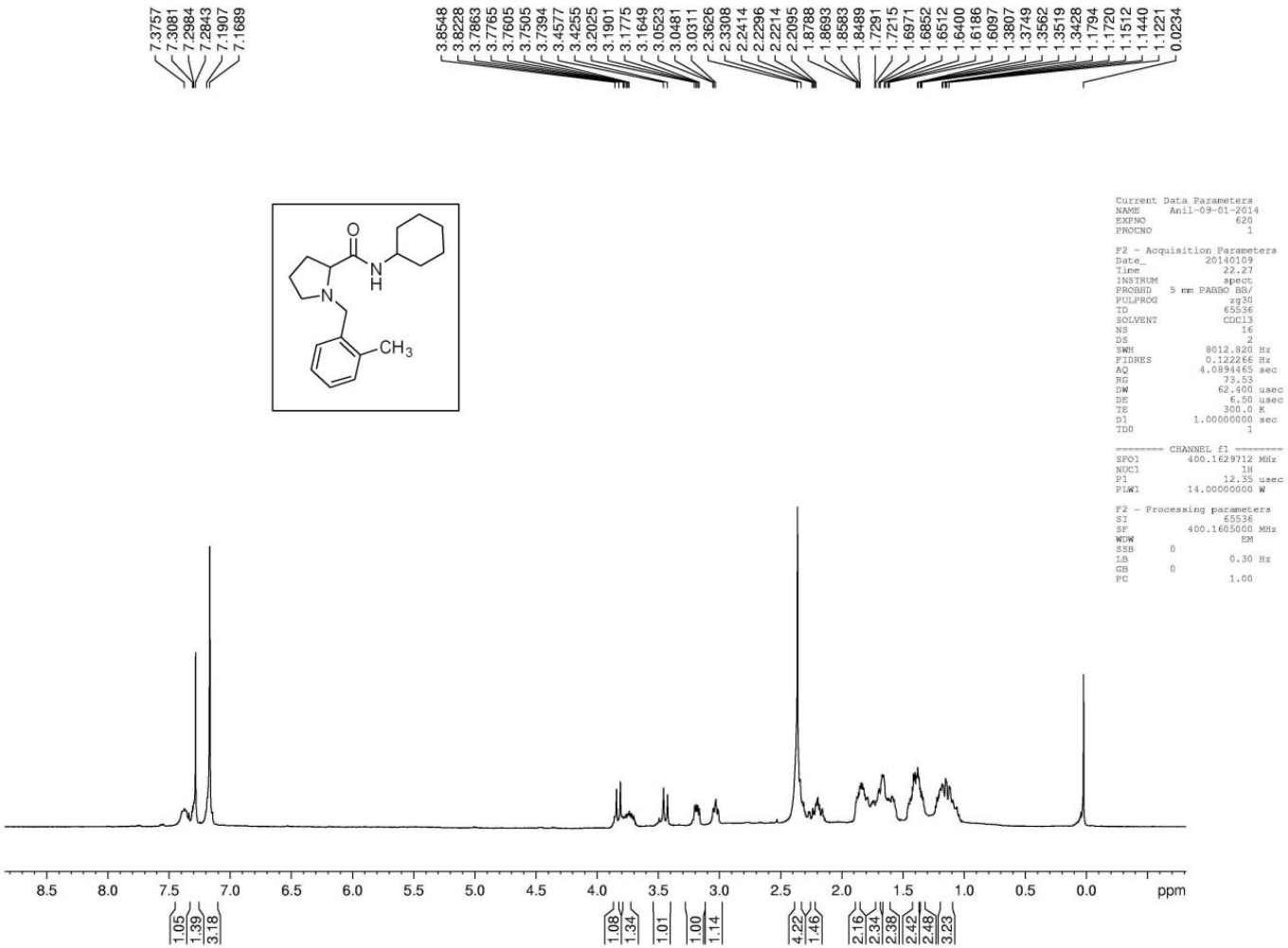

Figure S-19. ^{1}H-NMR spectrum of *N*-cyclohexyl-1-(2-methylbenzyl)pyrrolidine-2-carboxamide (**4fA**).

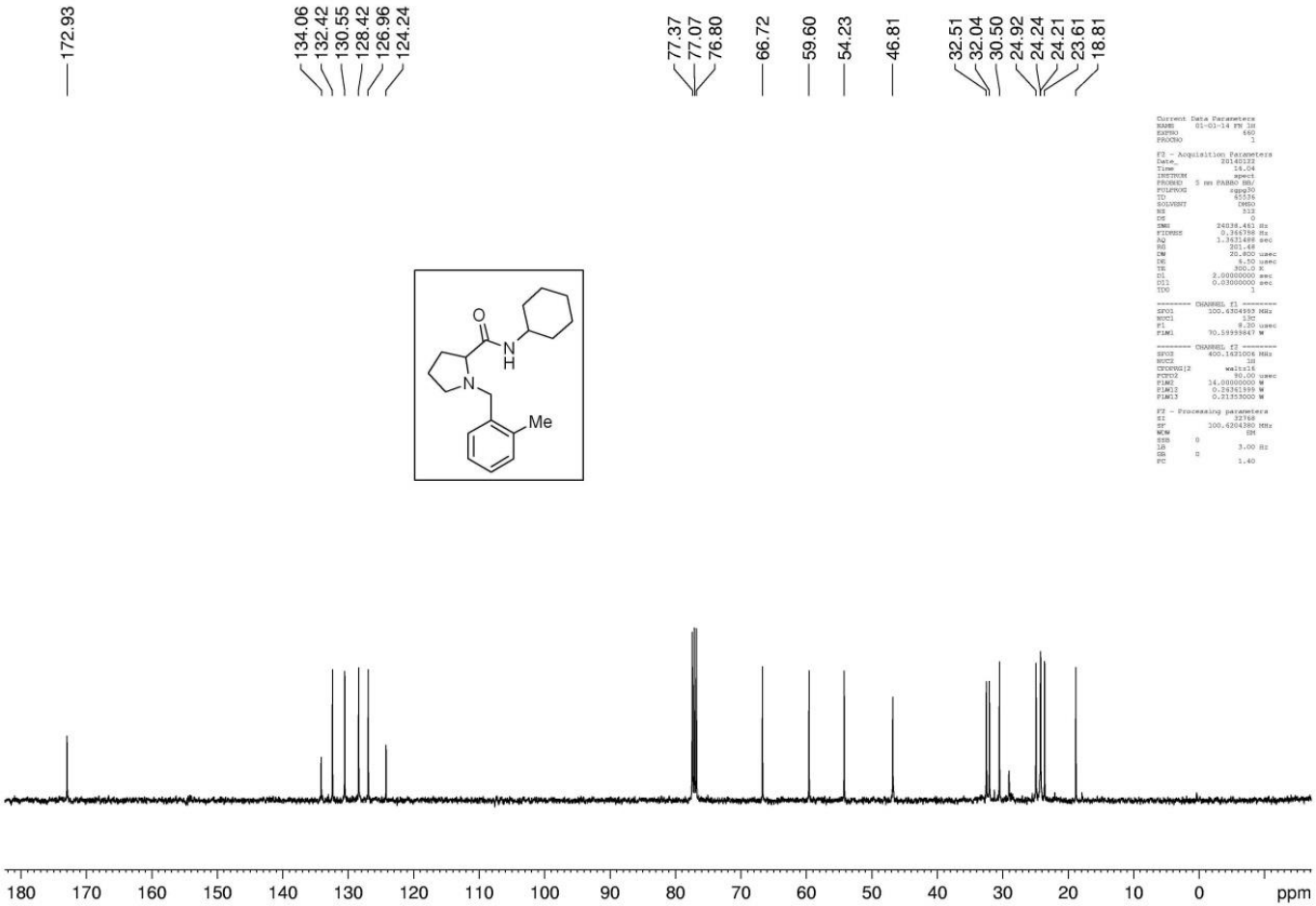

Figure S-20. ^{13}C-NMR spectrum of *N*-cyclohexyl-1-(2-methylbenzyl)pyrrolidine-2-carboxamide (**4fA**)

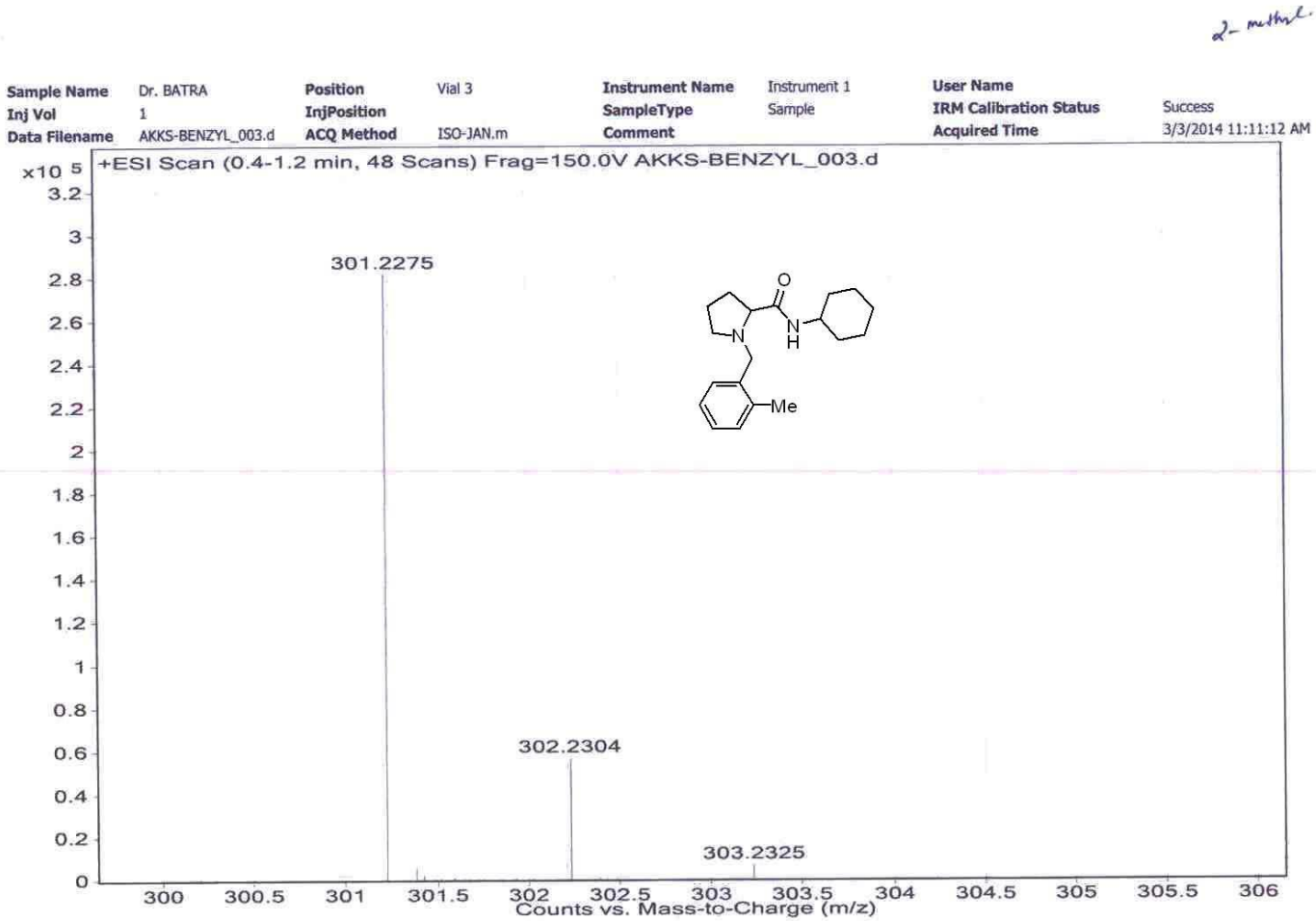

Figure S-210. HRMS spectrum of *N*-cyclohexyl-1-(2-methylbenzyl)pyrrolidine-2-carboxamide (**4fA**)

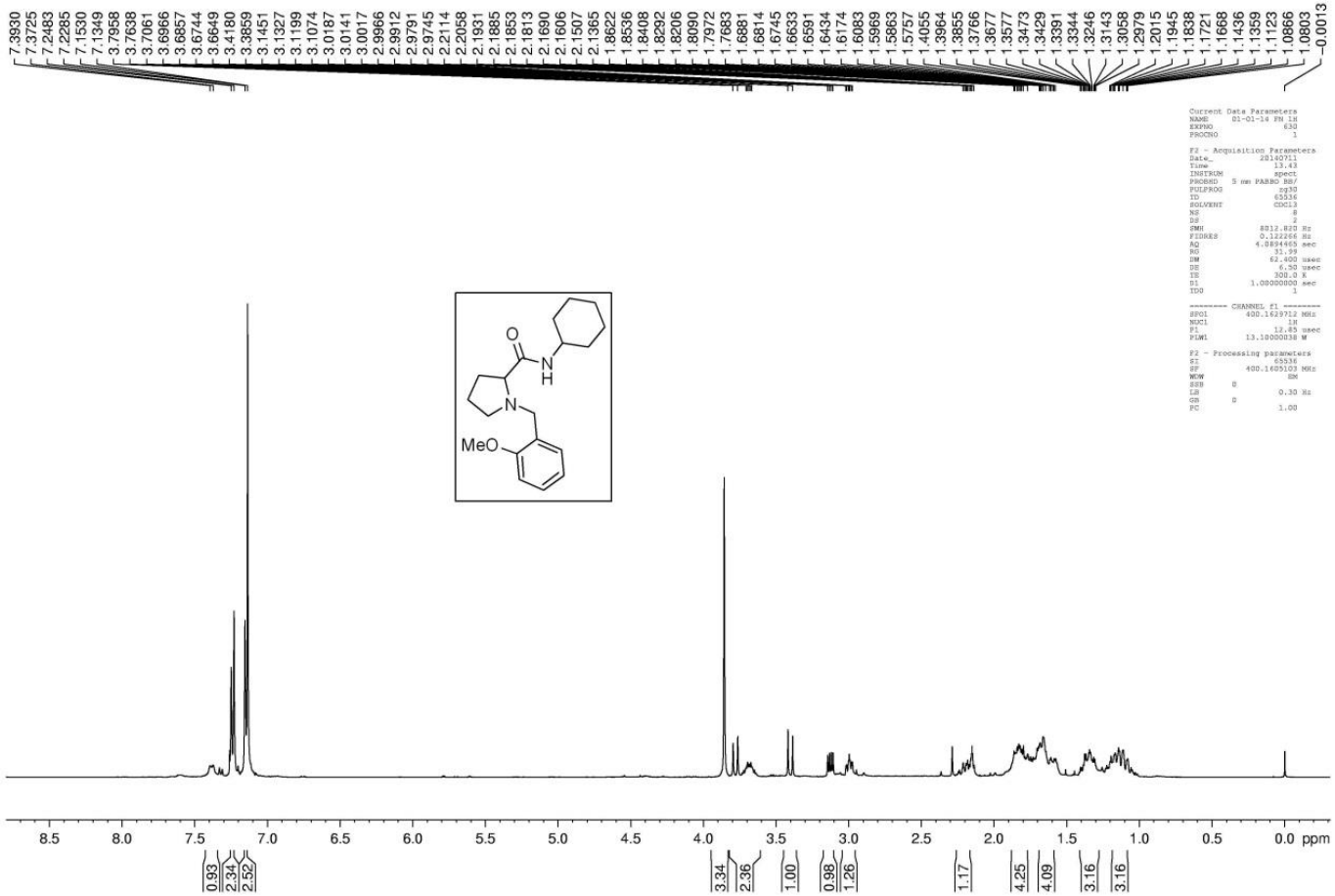

Figure S-22. ^{1}H-NMR spectrum of *N*-cyclohexyl-1-(2-methoxybenzyl)pyrrolidine-2-carboxamide **(4gA).**

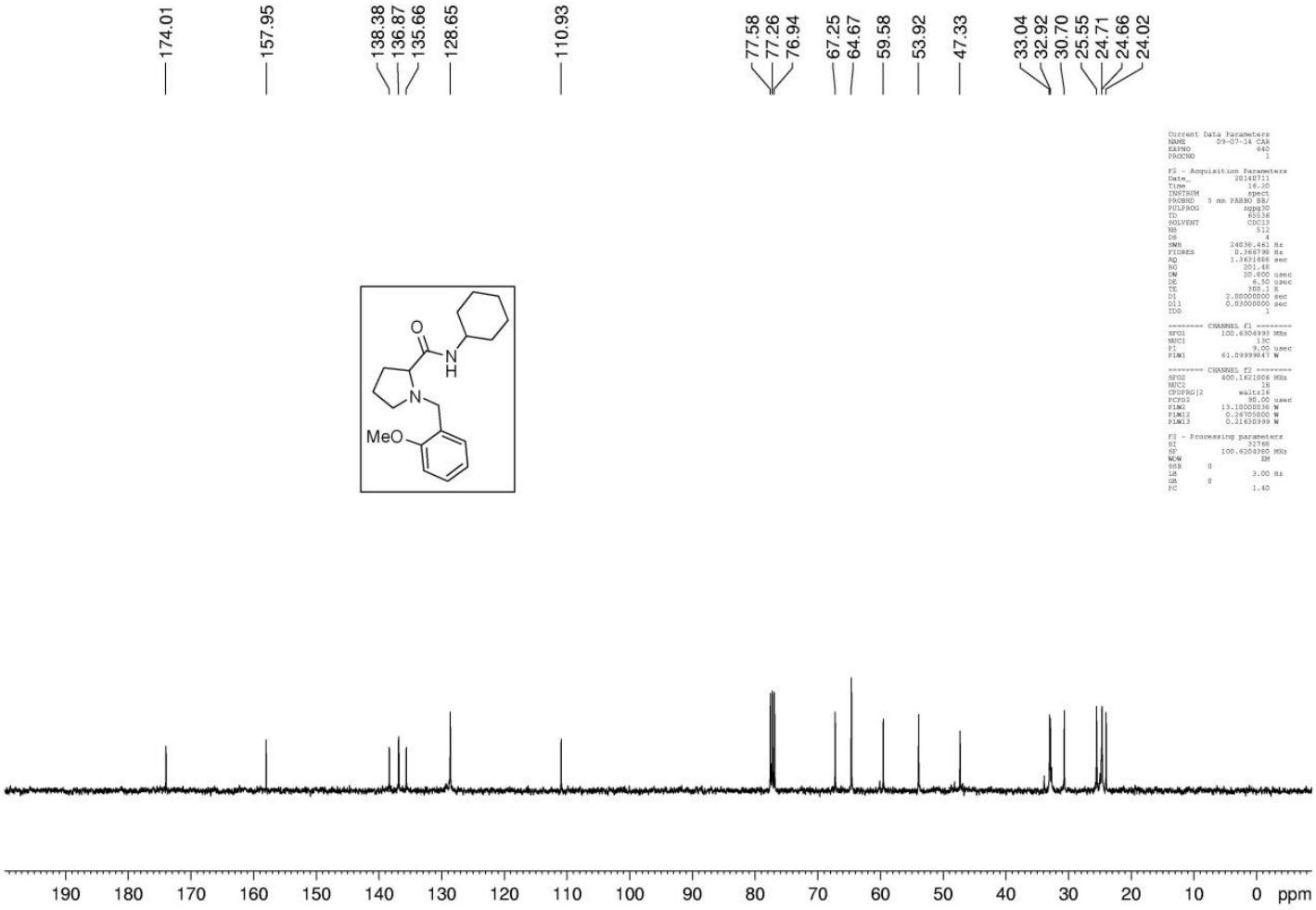

Figure S-23. ^{13}C-NMR spectrum of *N*-cyclohexyl-1-(2-methoxybenzyl)pyrrolidine-2-carboxamide **(4gA).**

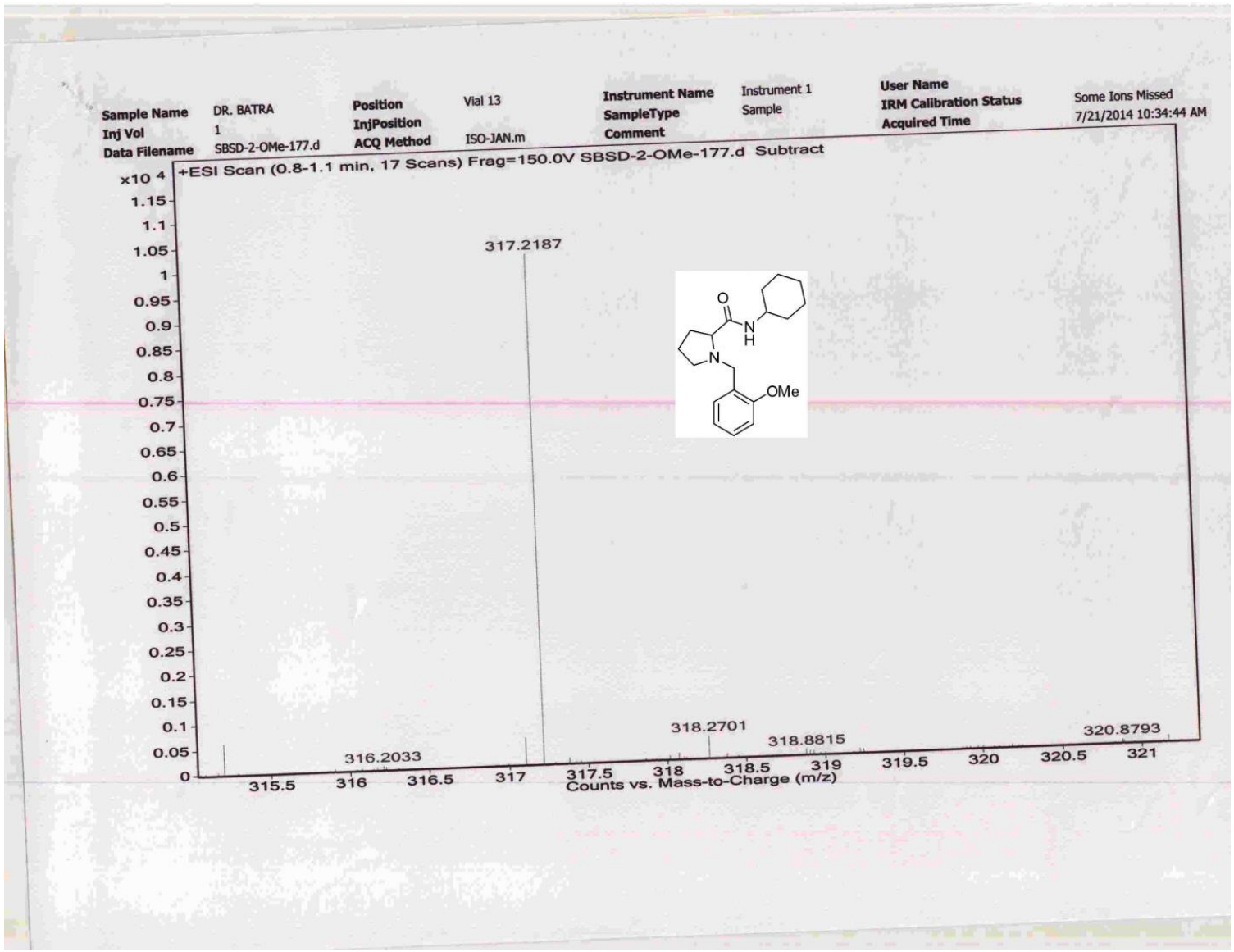

Figure S-24. HRMS spectrum of *N*-cyclohexyl-1-(2-methoxybenzyl)pyrrolidine-2-carboxamide **(4gA).**

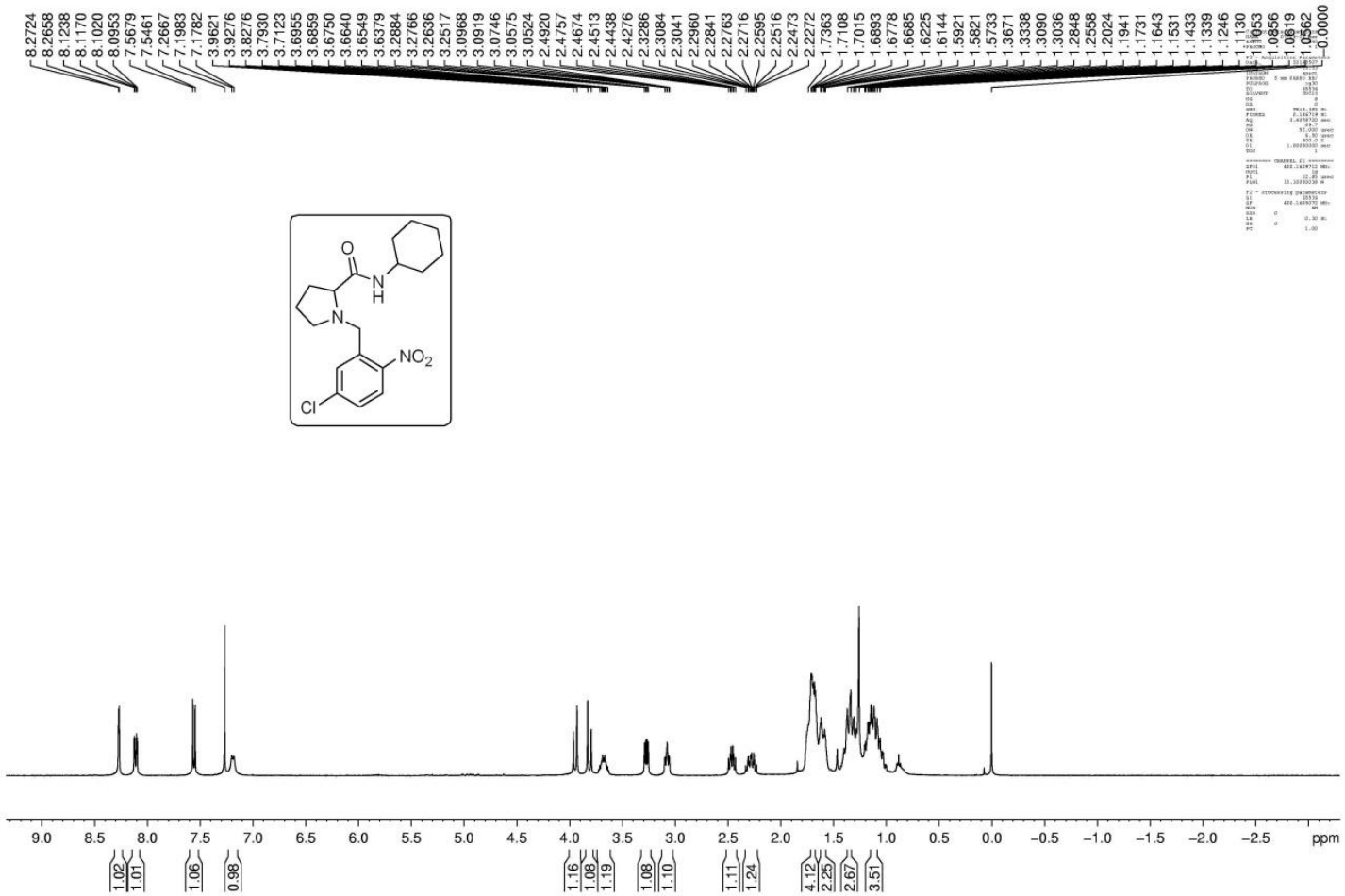

Figure S-25. ^{1}H-NMR spectrum of 1-(5-Chloro-2-nitrobenzyl)-*N*-cyclohexylpyrrolidine-2-carboxamide(**4hA**).

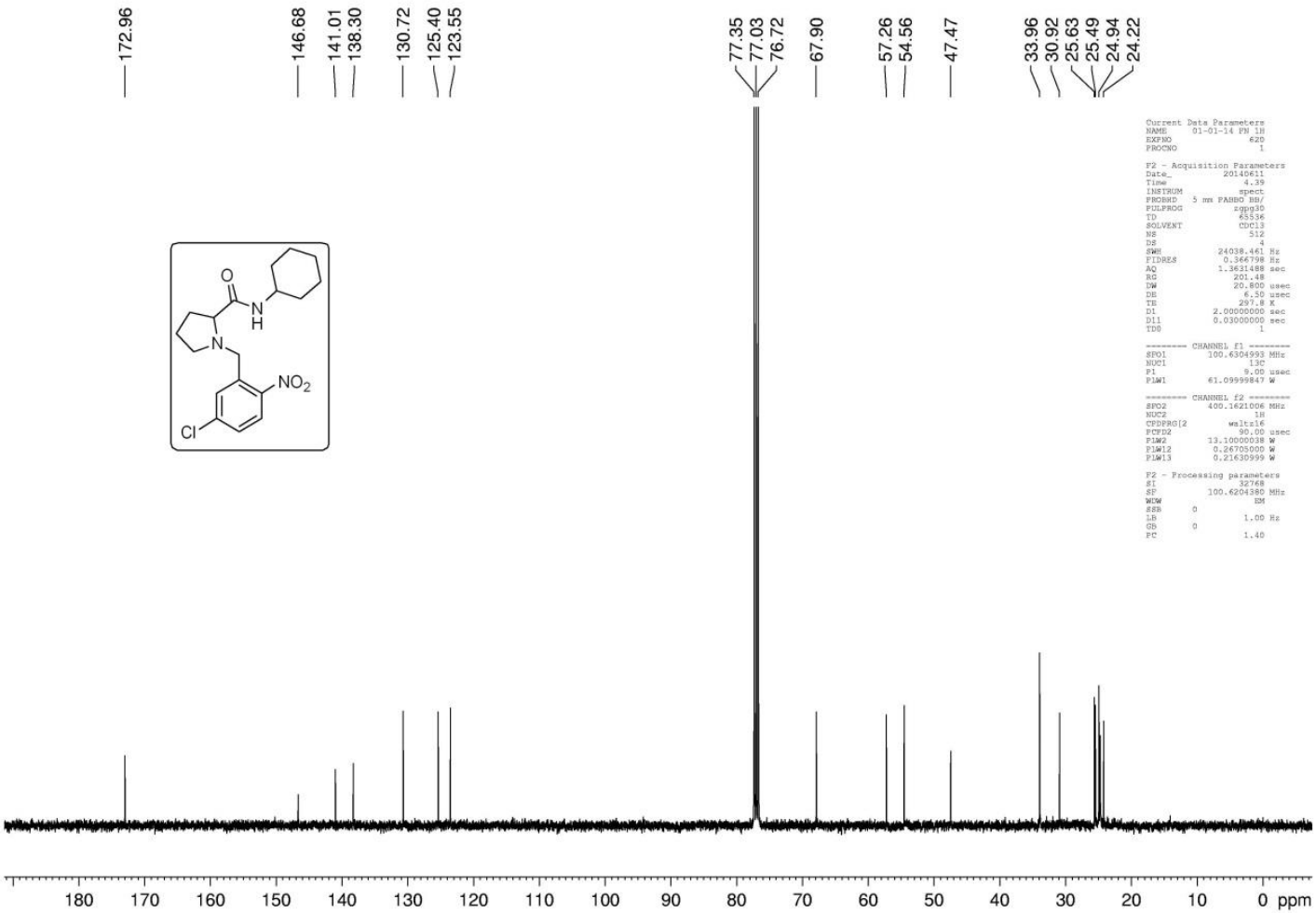

Figure S-26. ^{13}C-NMR spectrum of 1-(5-Chloro-2-nitrobenzyl)-*N*-cyclohexylpyrrolidine-2-carboxamide(**4hA**).

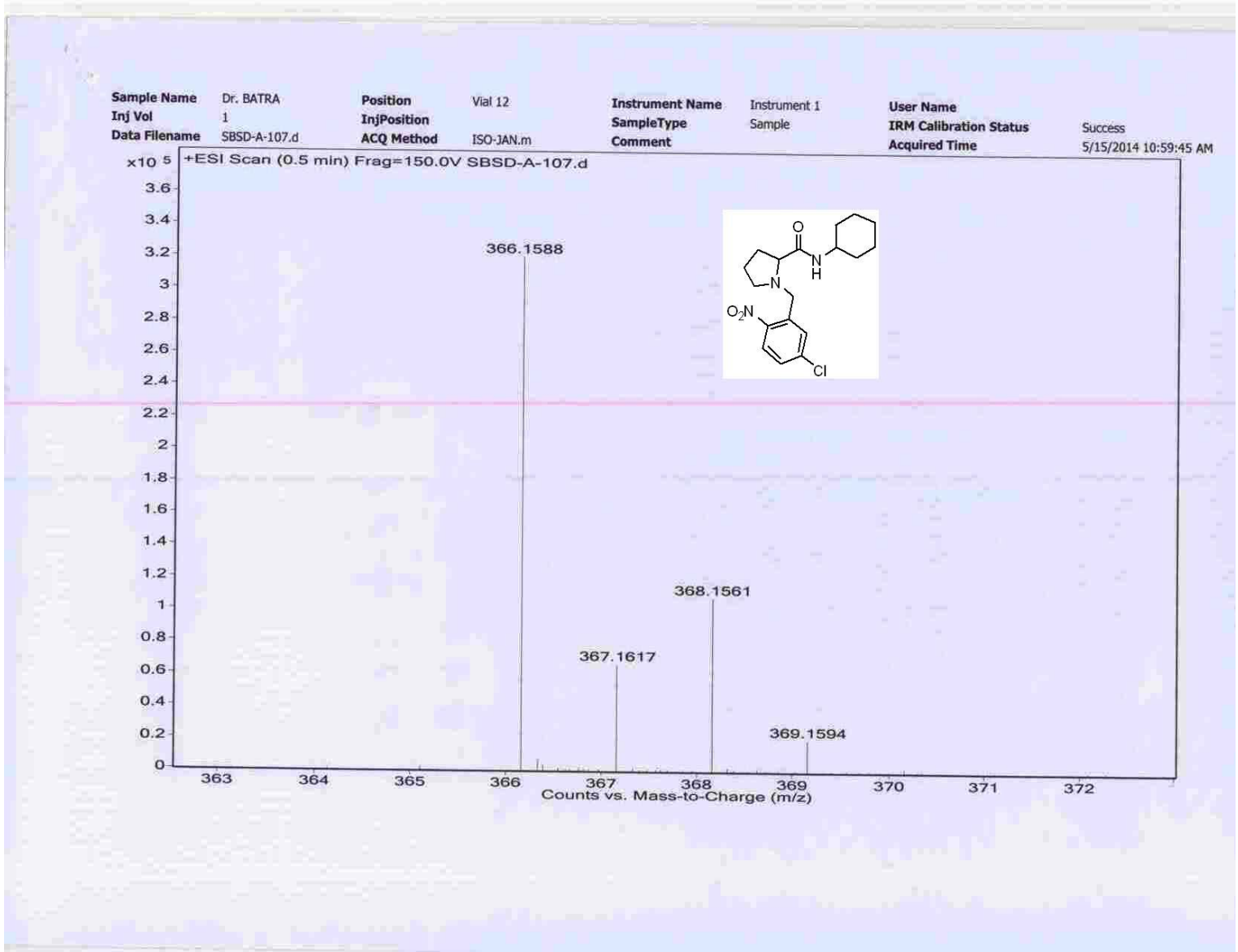

Figure S-27. HRMS spectrum of 1-(5-Chloro-2-nitrobenzyl)-*N*-cyclohexylpyrrolidine-2-carboxamide (**4hA**).

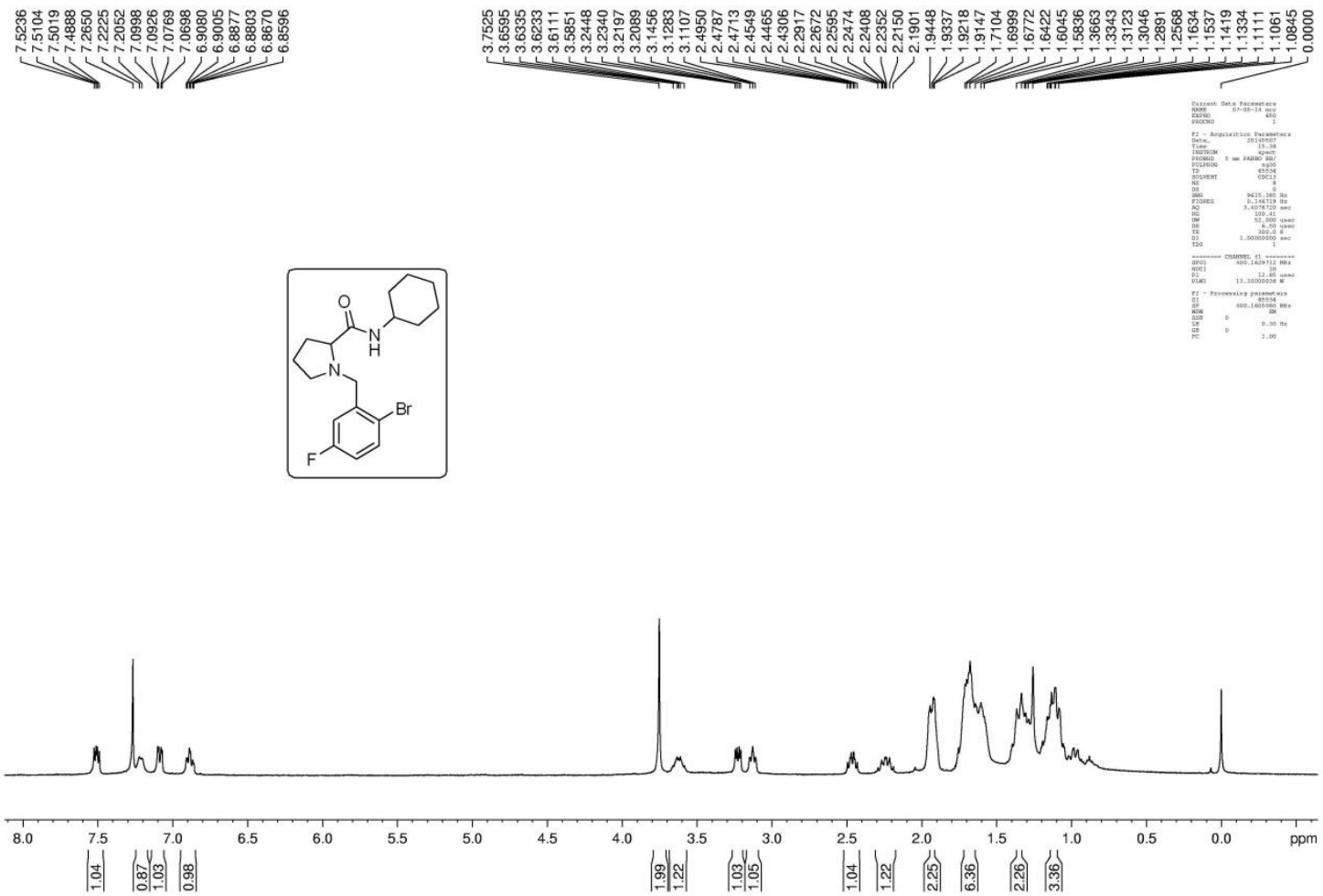

Figure S-28. ^{1}H-NMR spectrum of 1-(2-Bromo-5-fluorobenzyl)-*N*-cyclohexylpyrrolidine-2-carboxamide (**4iA**).

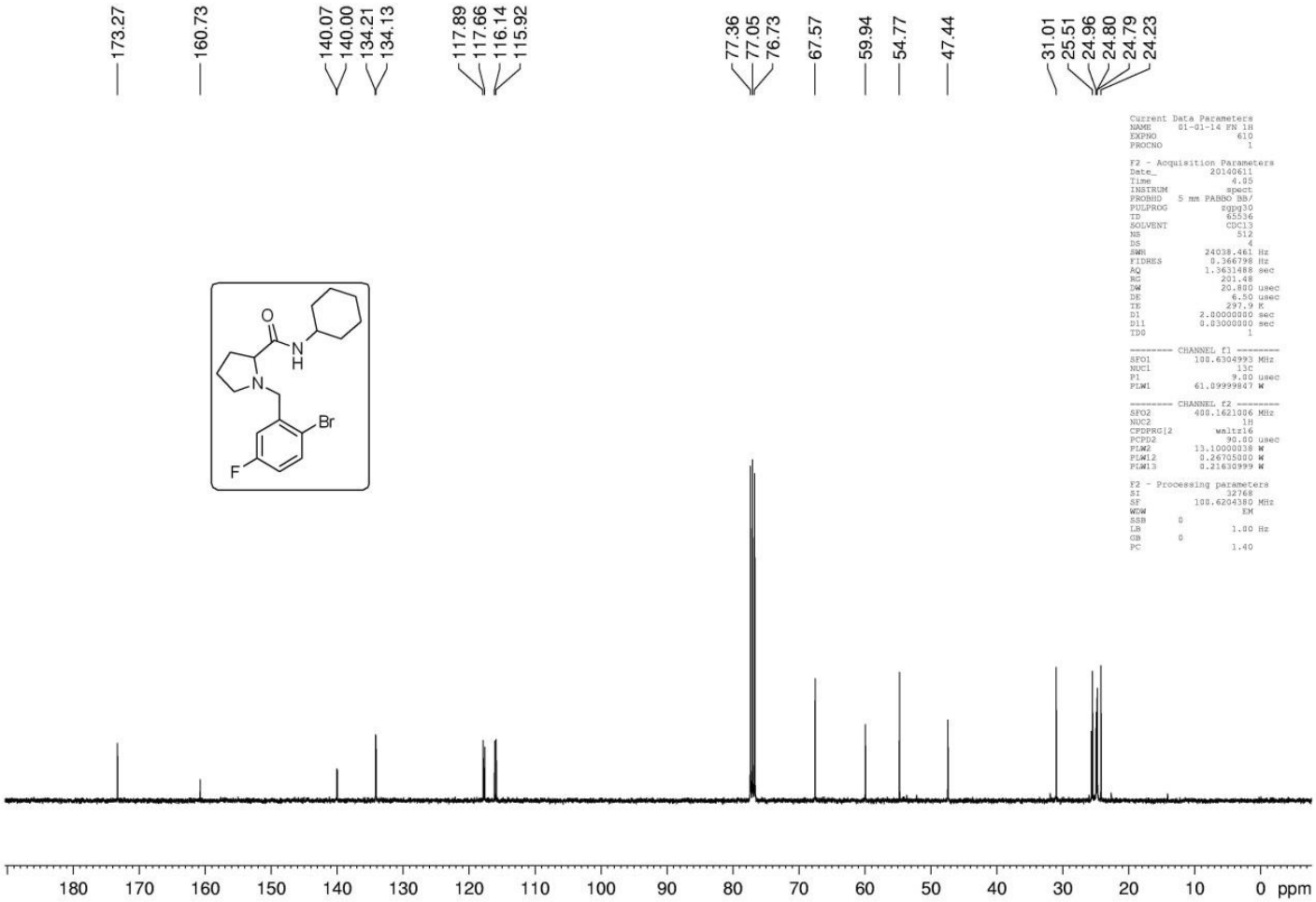

Figure S-29. ^{13}C-NMR spectrum of 1-(2-Bromo-5-fluorobenzyl)-*N*-cyclohexylpyrrolidine-2-carboxamide (**4iA**).

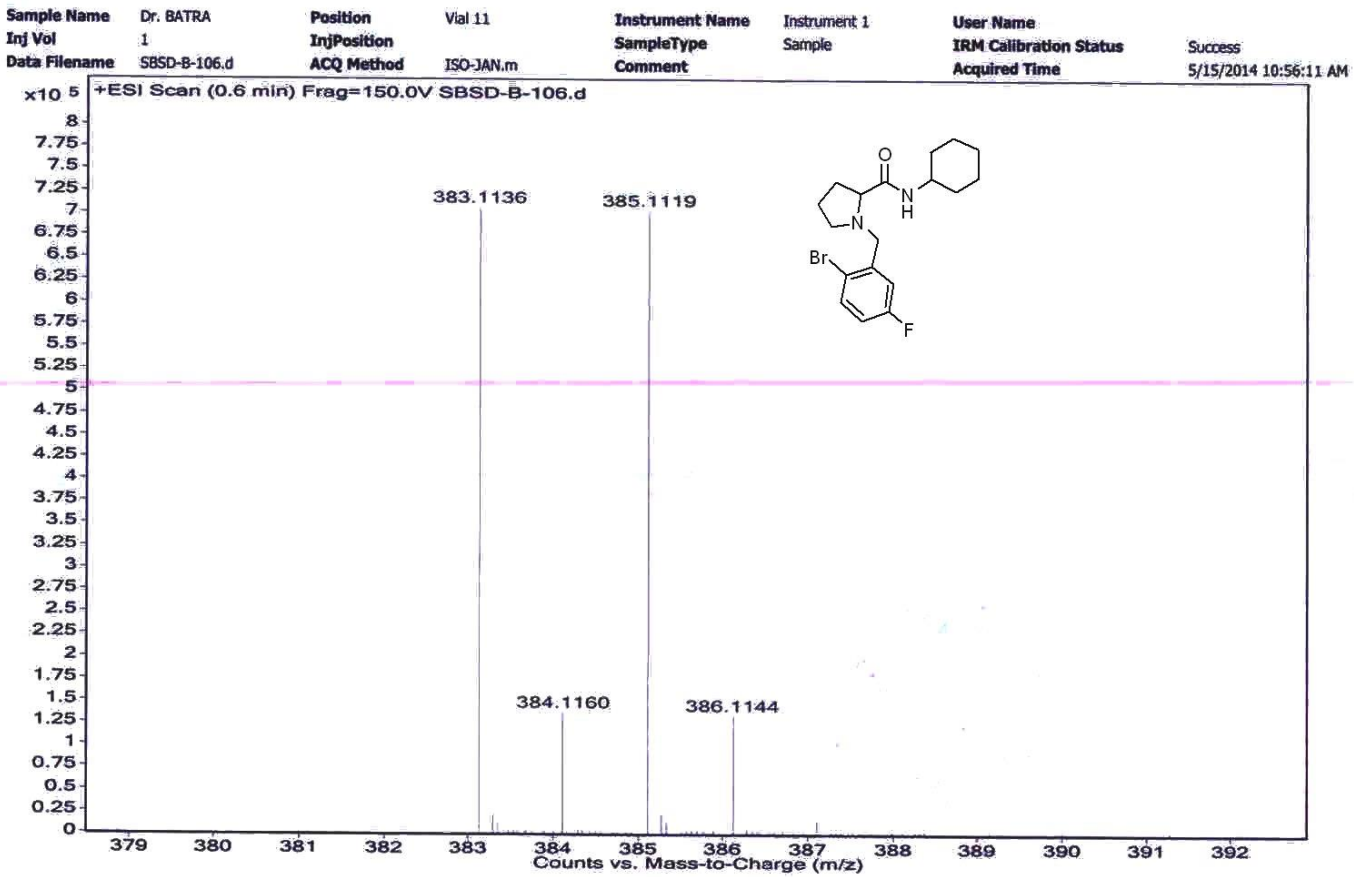

Figure S-30. HRMS spectrum of 1-(2-Bromo-5-fluorobenzyl)-*N*-cyclohexylpyrrolidine-2-carboxamide (**4iA**).

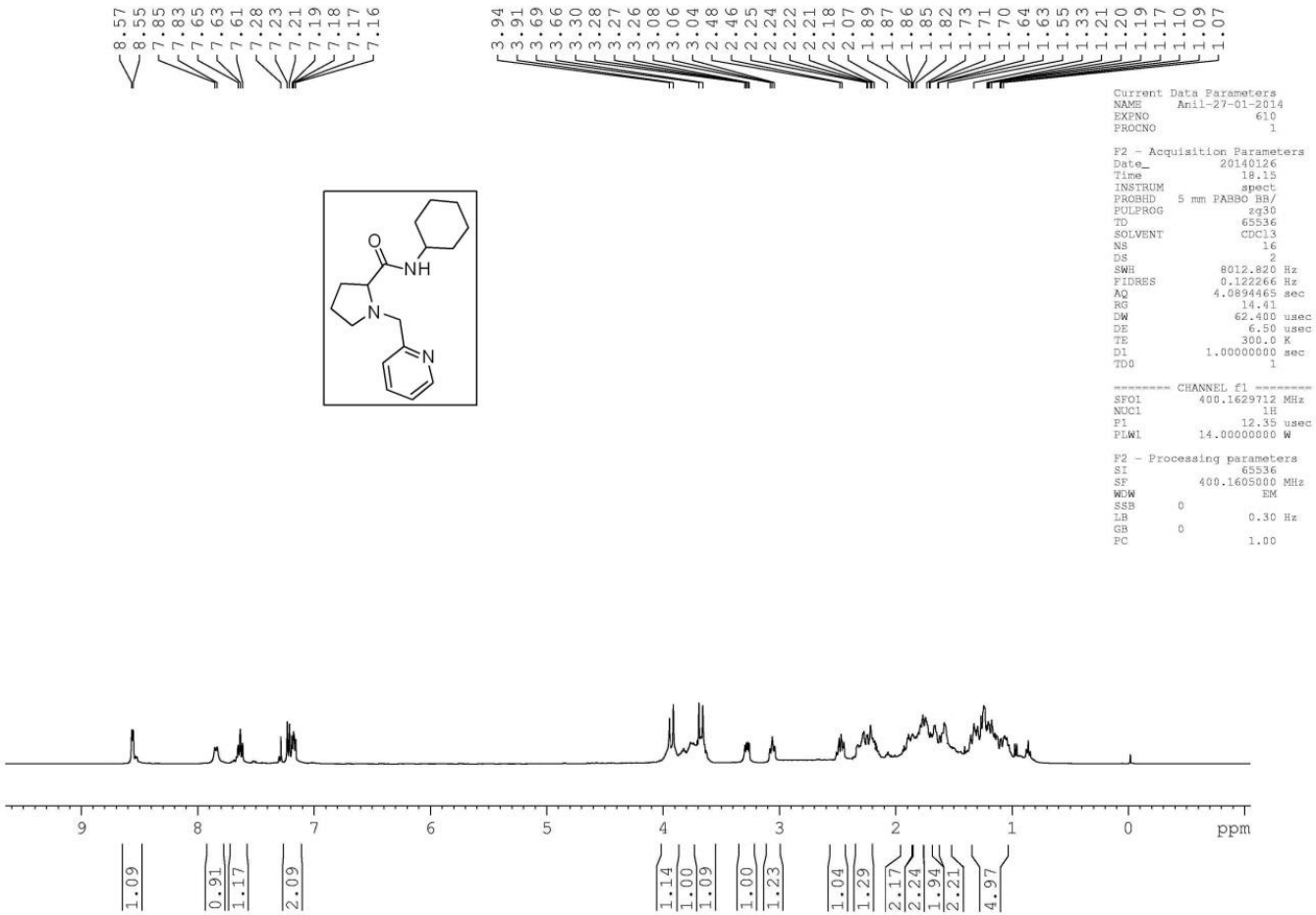

Figure S-31. ^{1}H-NMR spectrum of *N*-cyclohexyl-1-(pyridin-2-ylmethyl)pyrrolidine-2-carboxamide **(4jA)**.

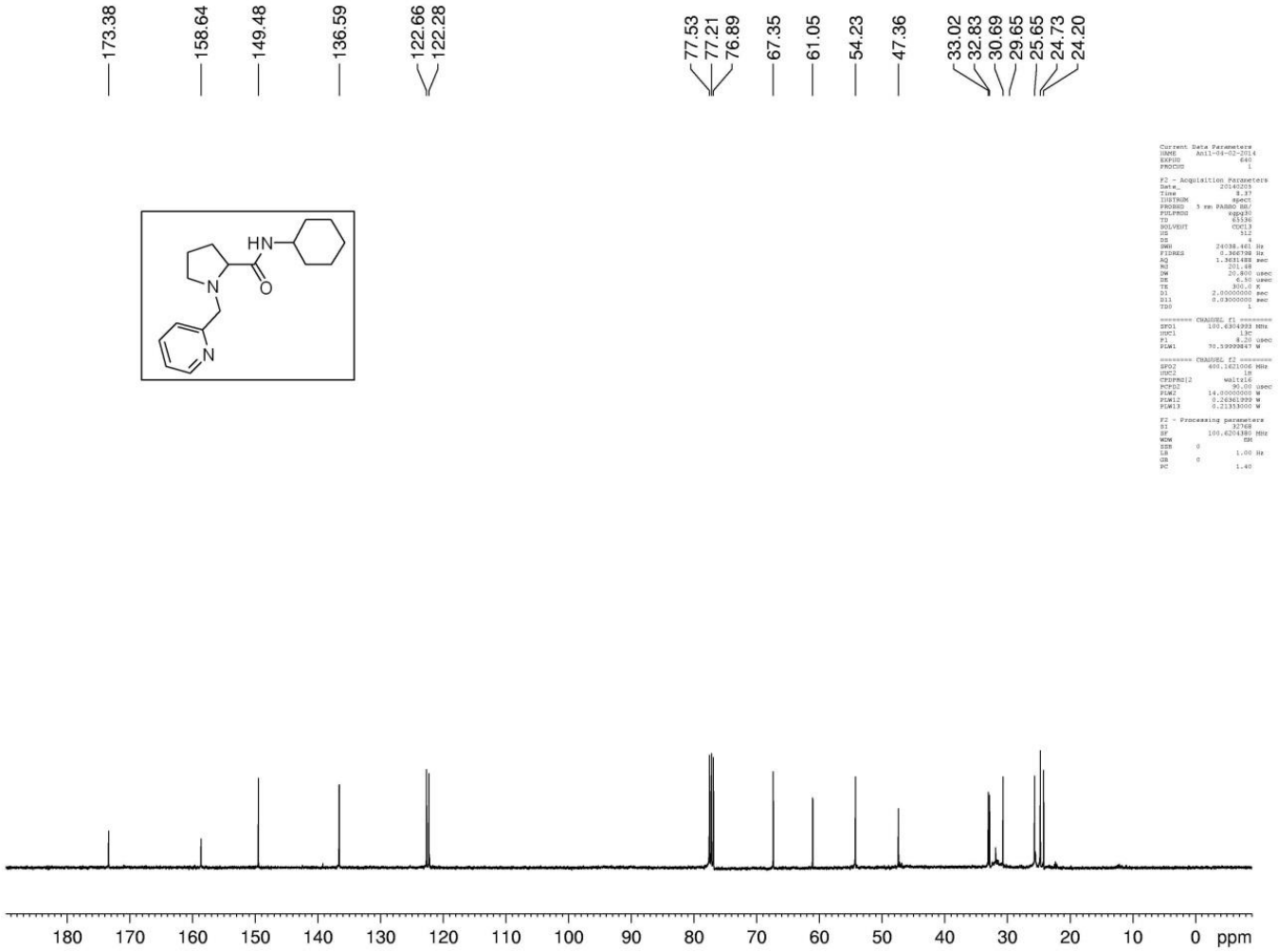

Figure S-32. ^{13}C-NMR spectrum of *N*-cyclohexyl-1-(pyridin-2-ylmethyl)pyrrolidine-2-carboxamide **(4jA)**.

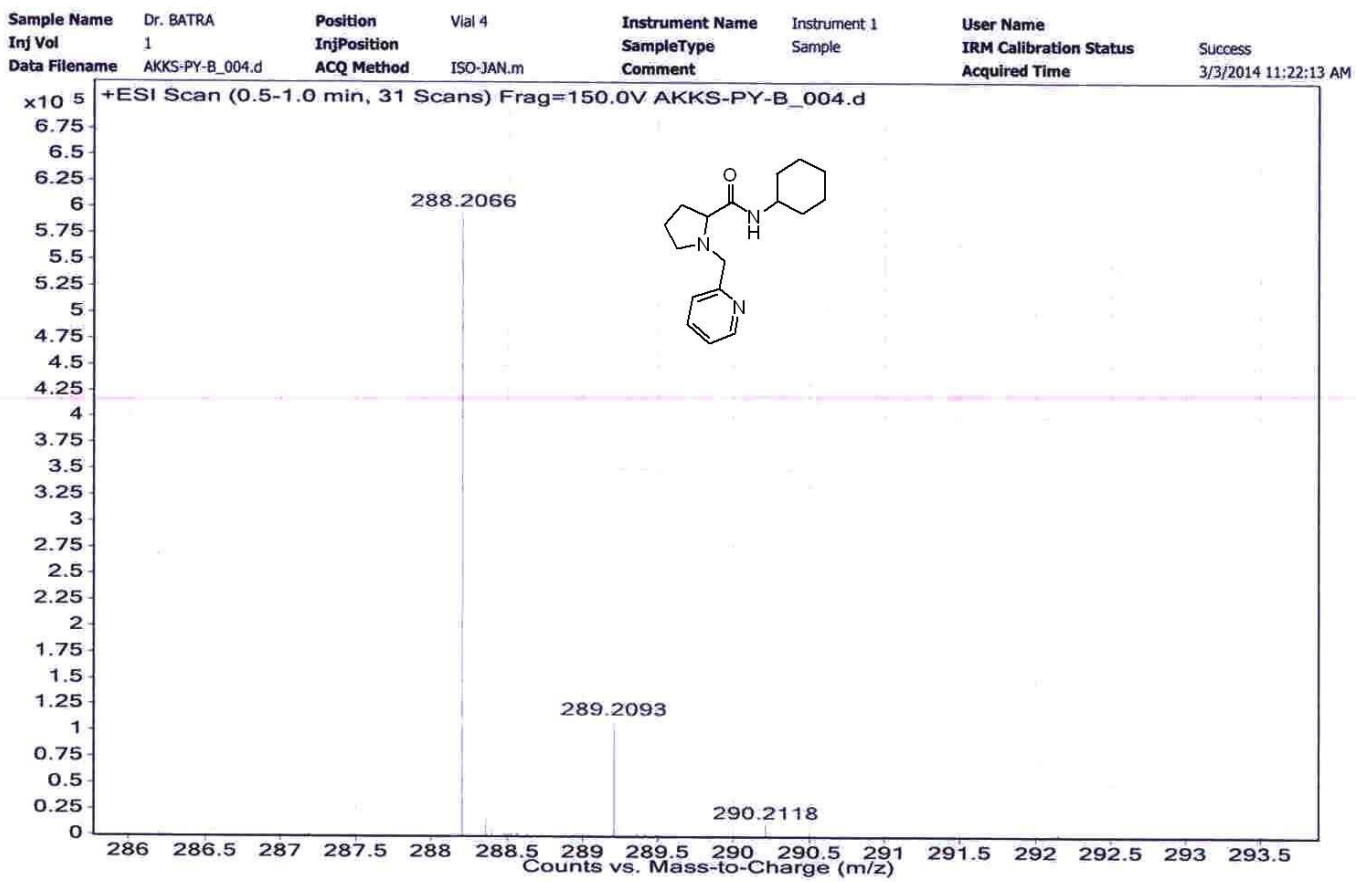

Figure S-33. HRMS spectrum of *N*-cyclohexyl-1-(pyridin-2-ylmethyl)pyrrolidine-2-carboxamide **(4jA)**.

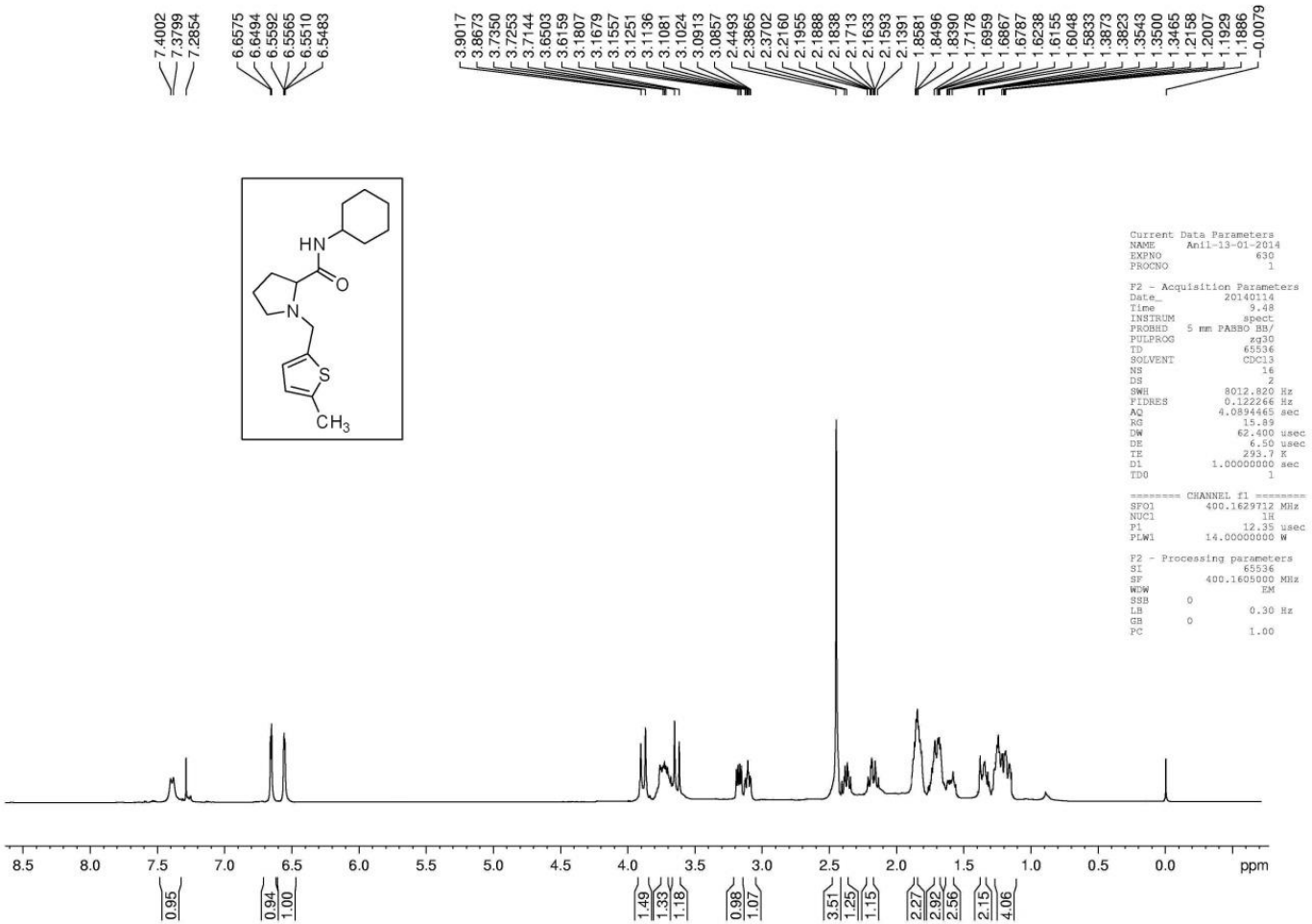

Figure S-34. ^{1}H-NMR spectrum of *N*-cyclohexyl-1-((5-methylthiophen-2-yl)methyl)pyrrolidine-2-carboxamidecarboxamide **(4kA).**

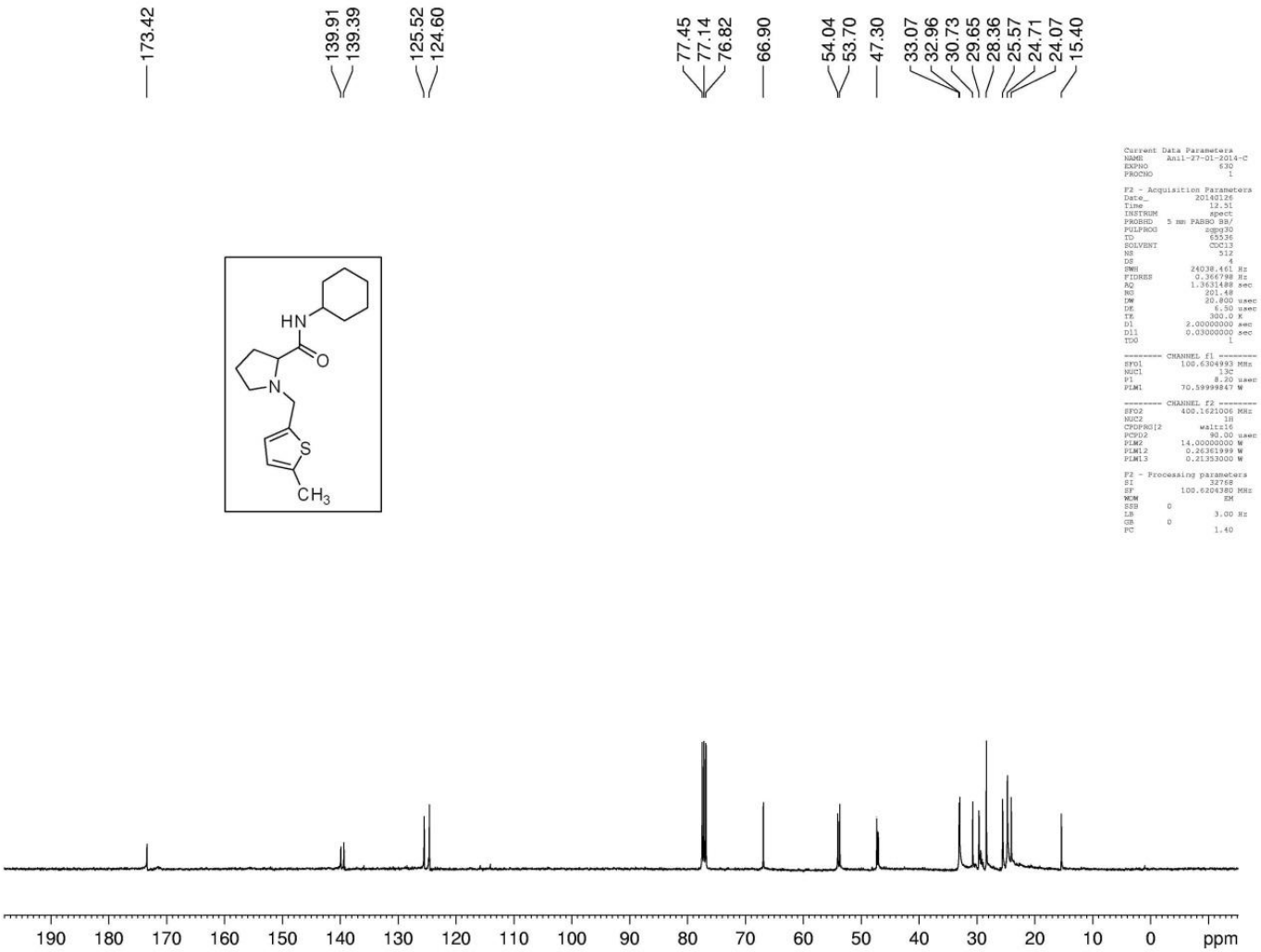

Figure S-35. ^{13}C-NMR spectrum of *N*-cyclohexyl-1-((5-methylthiophen-2-yl)methyl)pyrrolidine-2-carboxamide **(4kA).**

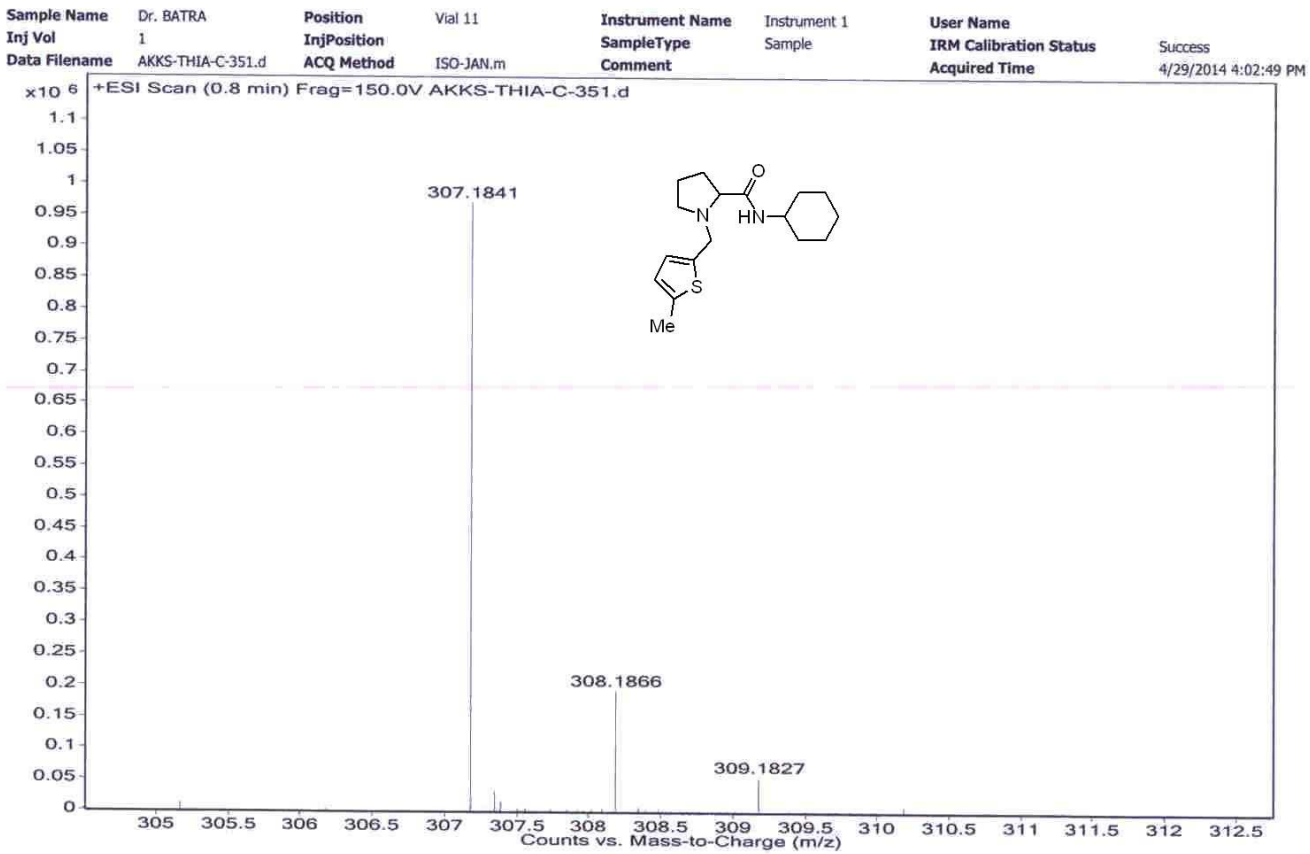

Figure S-36. HRMS spectrum of *N*-cyclohexyl-1-((5-methylthiophen-2-yl)methyl)pyrrolidine-2-carboxamide **(4kA).**

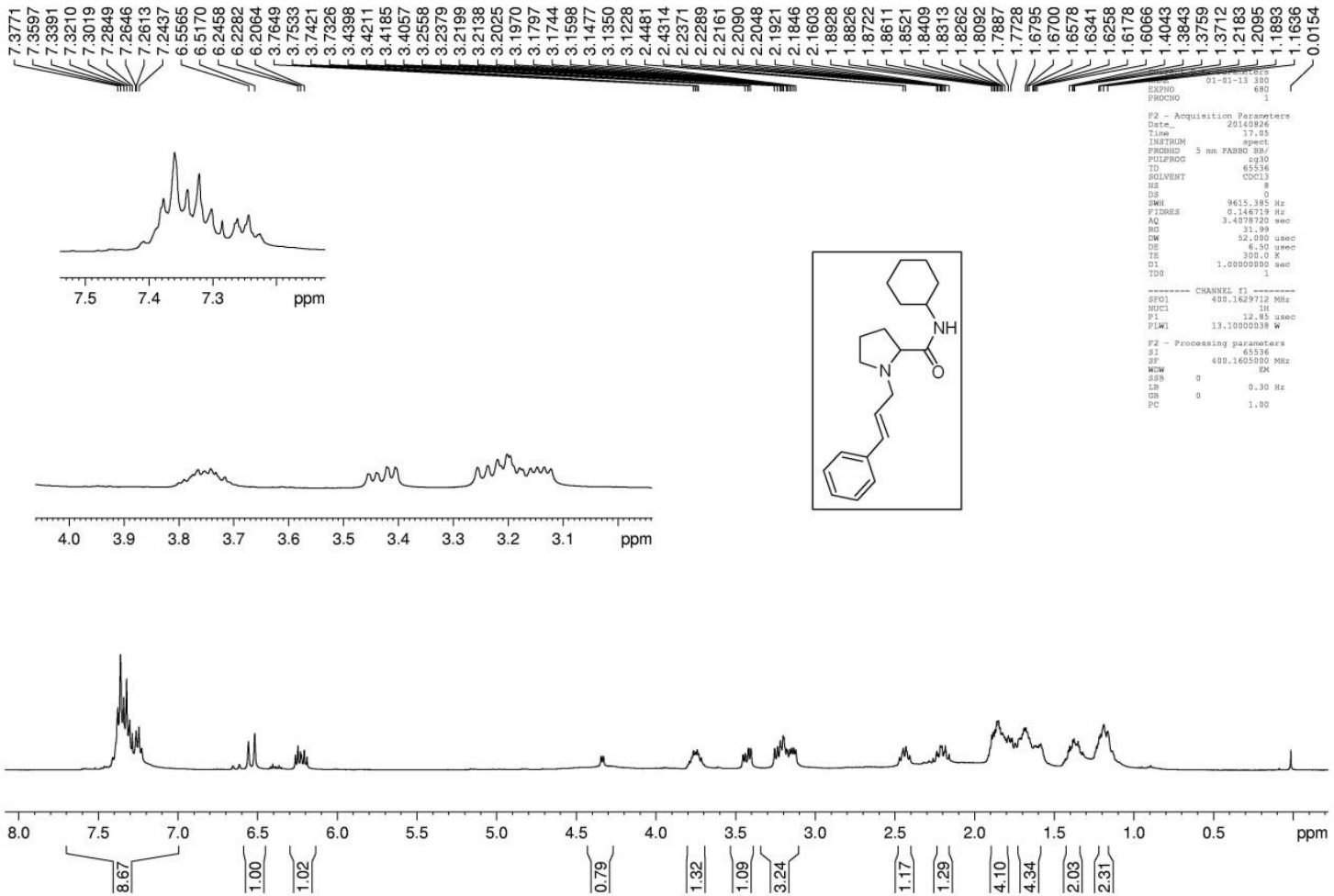

Figure S-37. ^{1}H-NMR spectrum of 1-Cinnamyl-*N*-cyclohexylpyrrolidine-2-carboxamide (**4lA**).

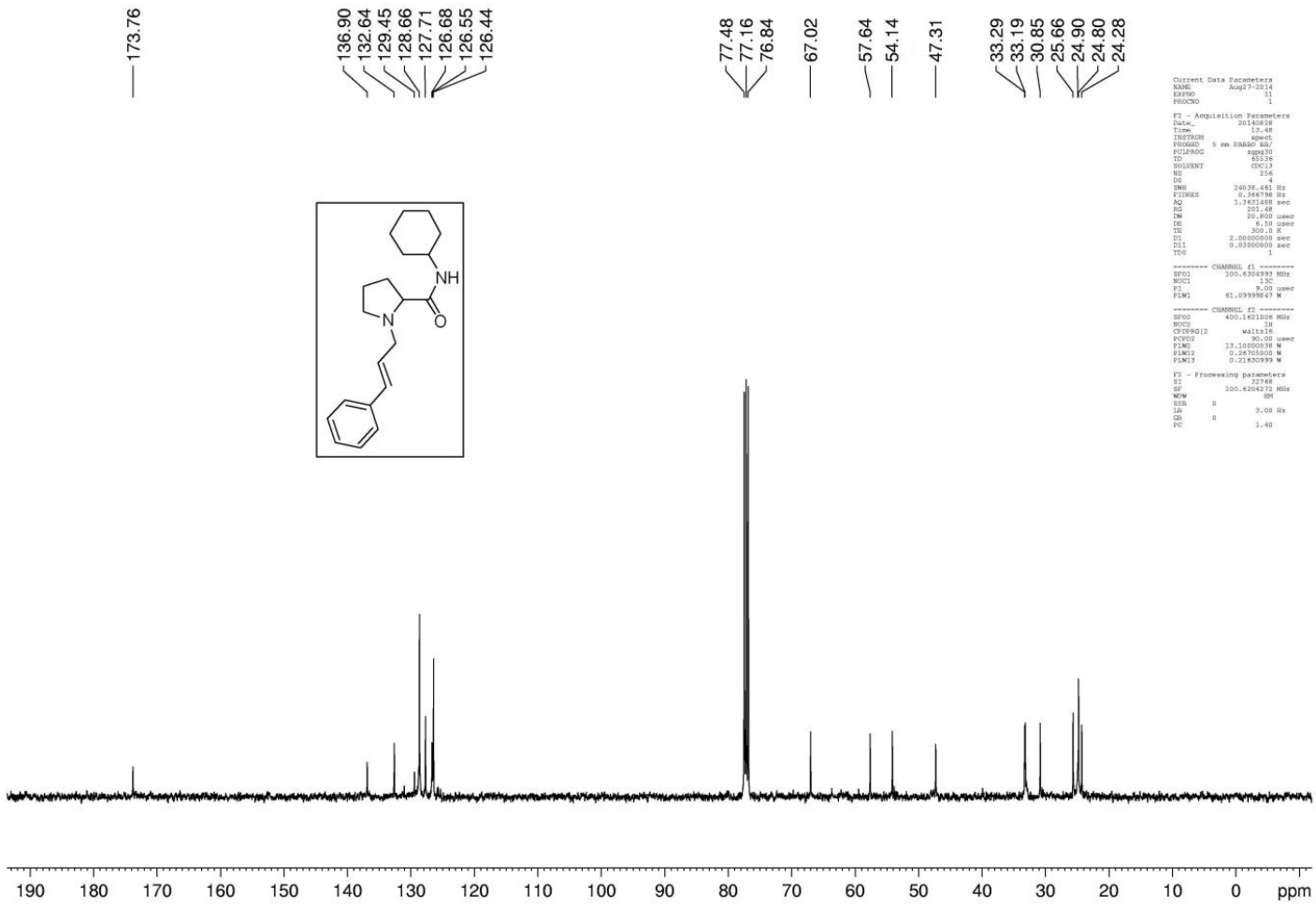

Figure S-38. ^{13}C-NMR spectrum of 1-Cinnamyl-*N*-cyclohexylpyrrolidine-2-carboxamide (**4lA**).

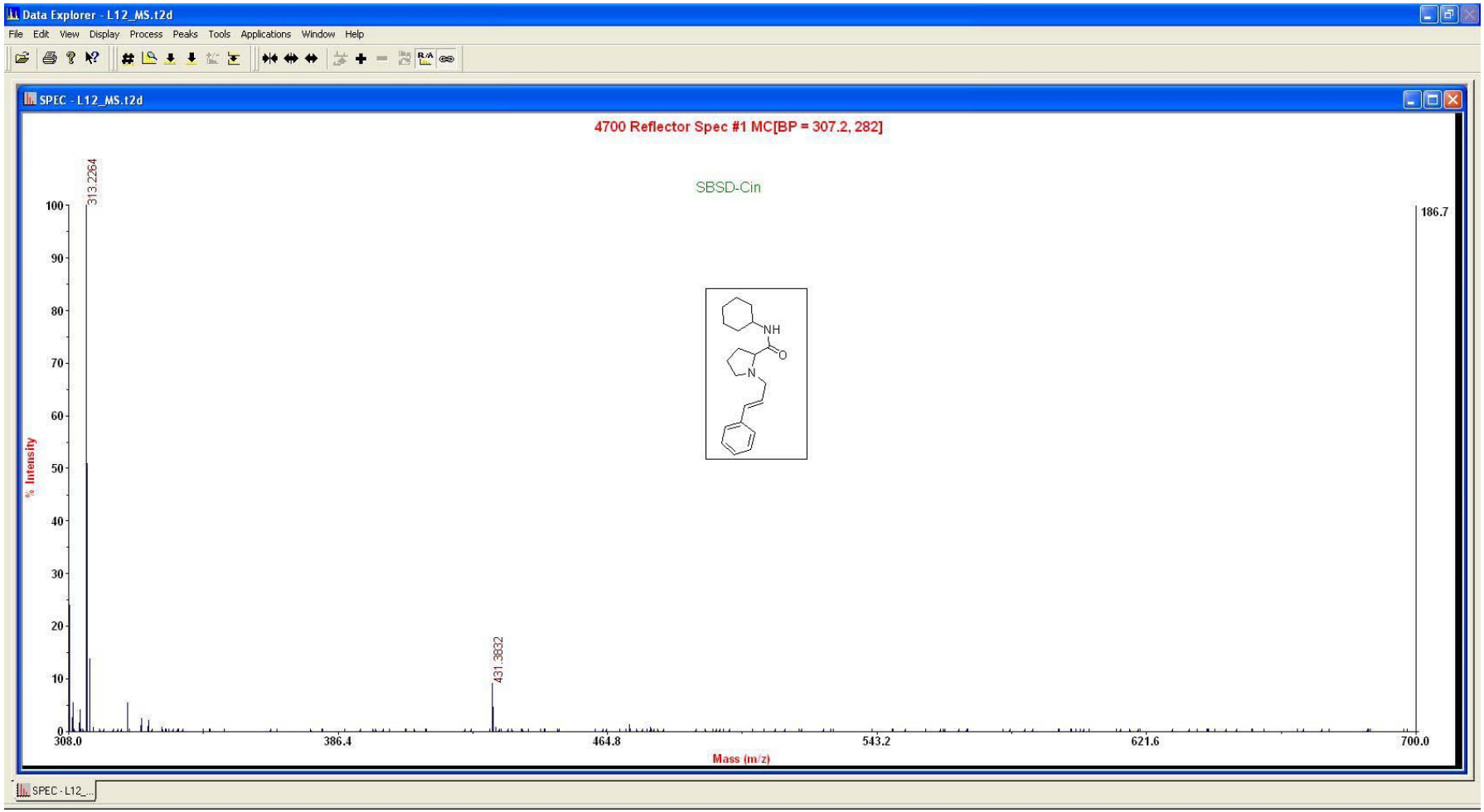

Figure S-39. HRMS spectrum of1-Cinnamyl-*N*-cyclohexylpyrrolidine-2-carboxamide (**4lA**).

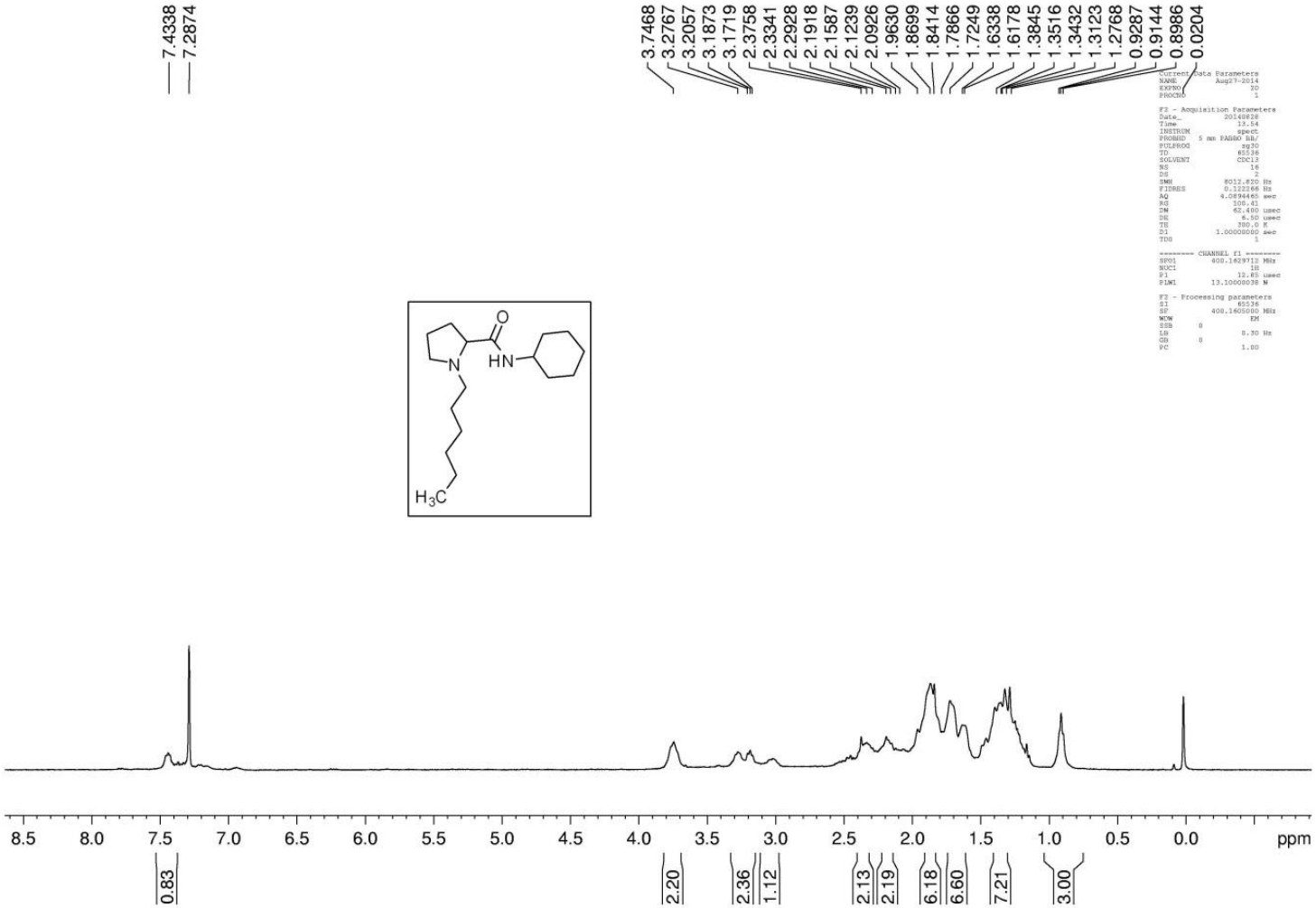

Figure S-40. ^{1}H-NMR spectrum of *N*-cyclohexyl-1-hexylpyrrolidine-2-carboxamide (**4mA**).

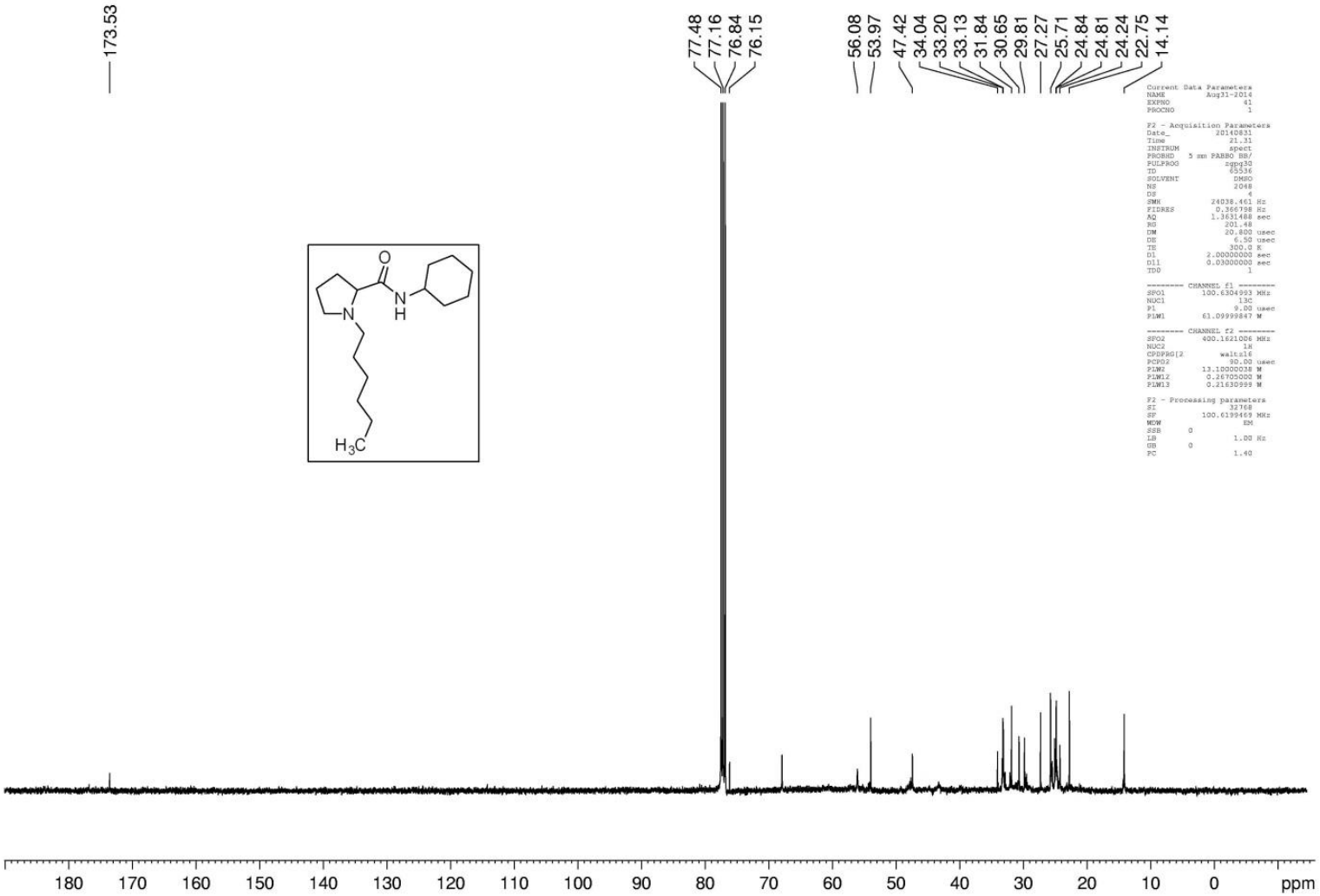

Figure S-41. ^{13}C-NMR spectrum of *N*-cyclohexyl-1-hexylpyrrolidine-2-carboxamide (**4mA**).

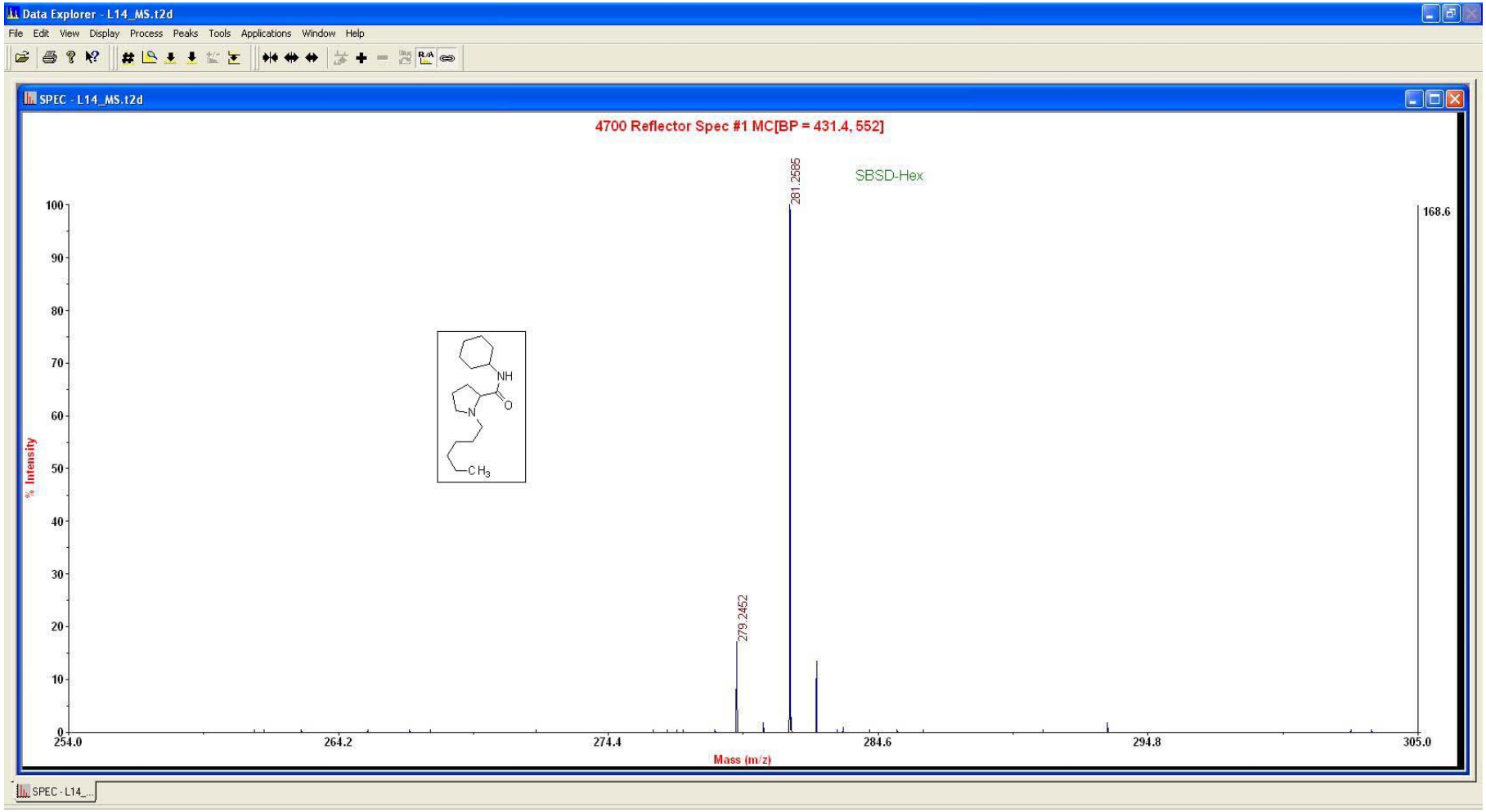

Figure S-42. HRMS spectrum of *N*-cyclohexyl-1-hexylpyrrolidine-2-carboxamide (**4mA**).

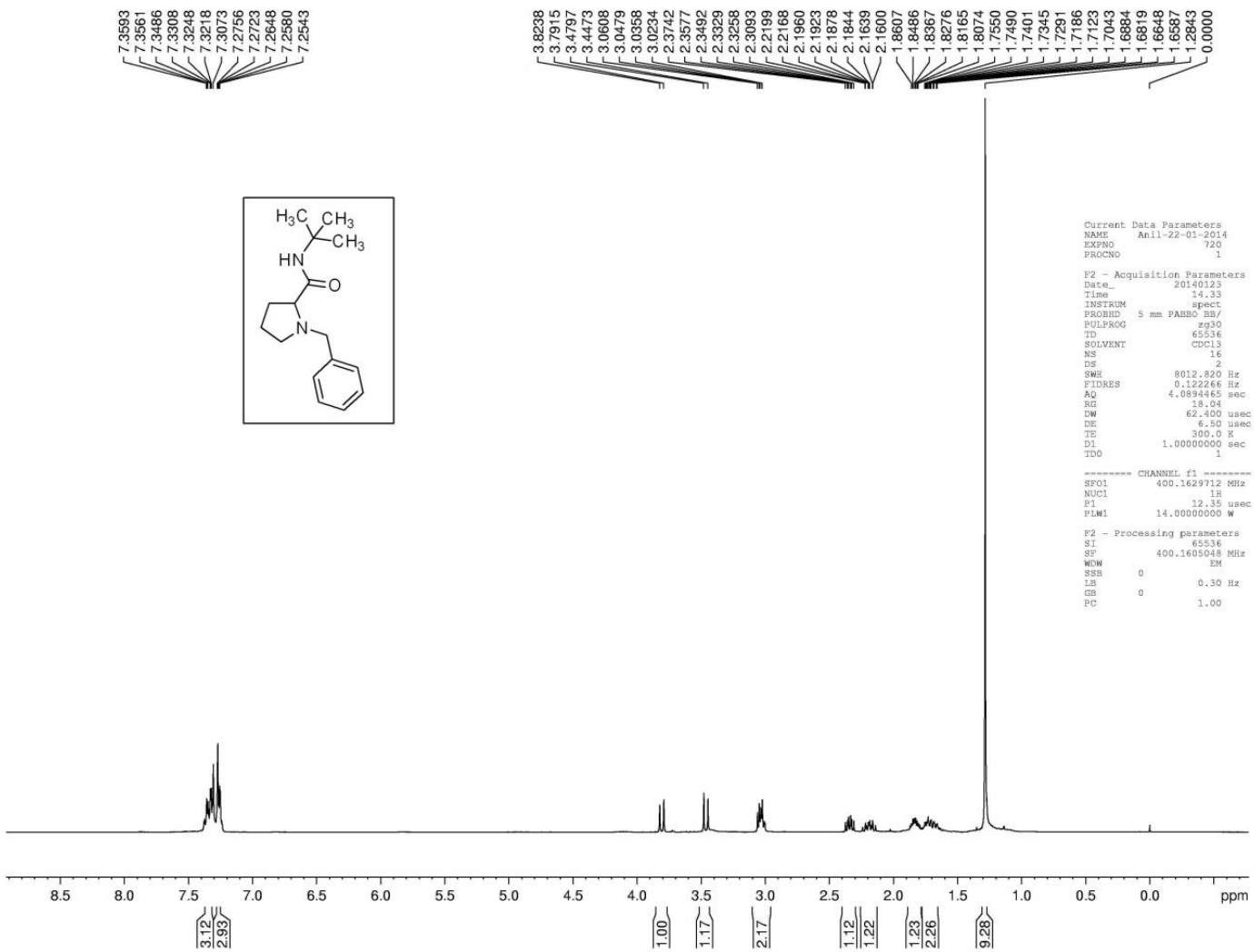

Figure S-43. ^{1}H-NMR spectrum of 1-Benzyl-*N*-*tert*-butylpyrrolidine-2-carboxamide **(4aB)**.

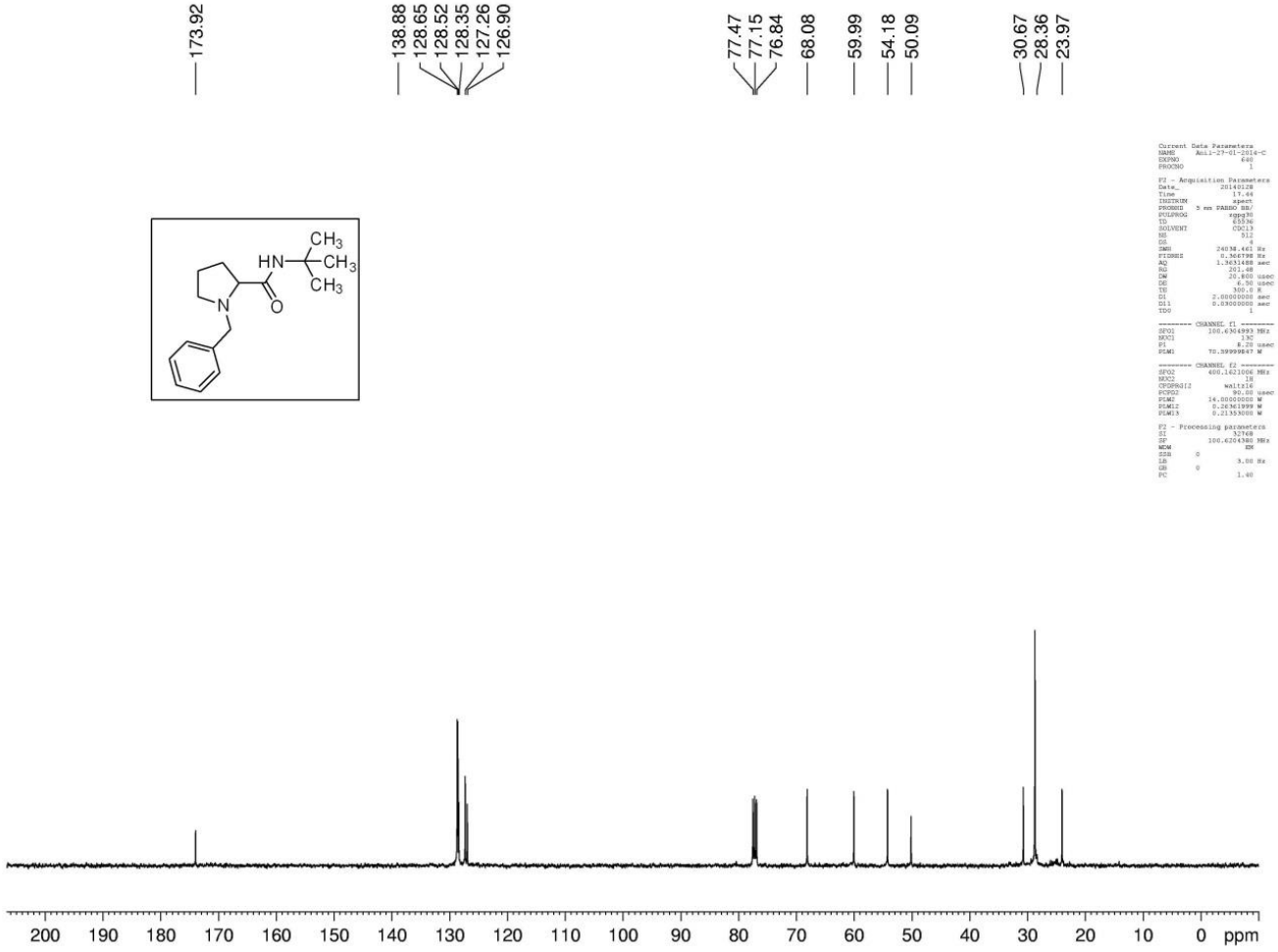

Figure S-44. ^{13}C-NMR spectrum of 1-Benzyl-*N*-*tert*-butylpyrrolidine-2-carboxamide **(4aB)**.

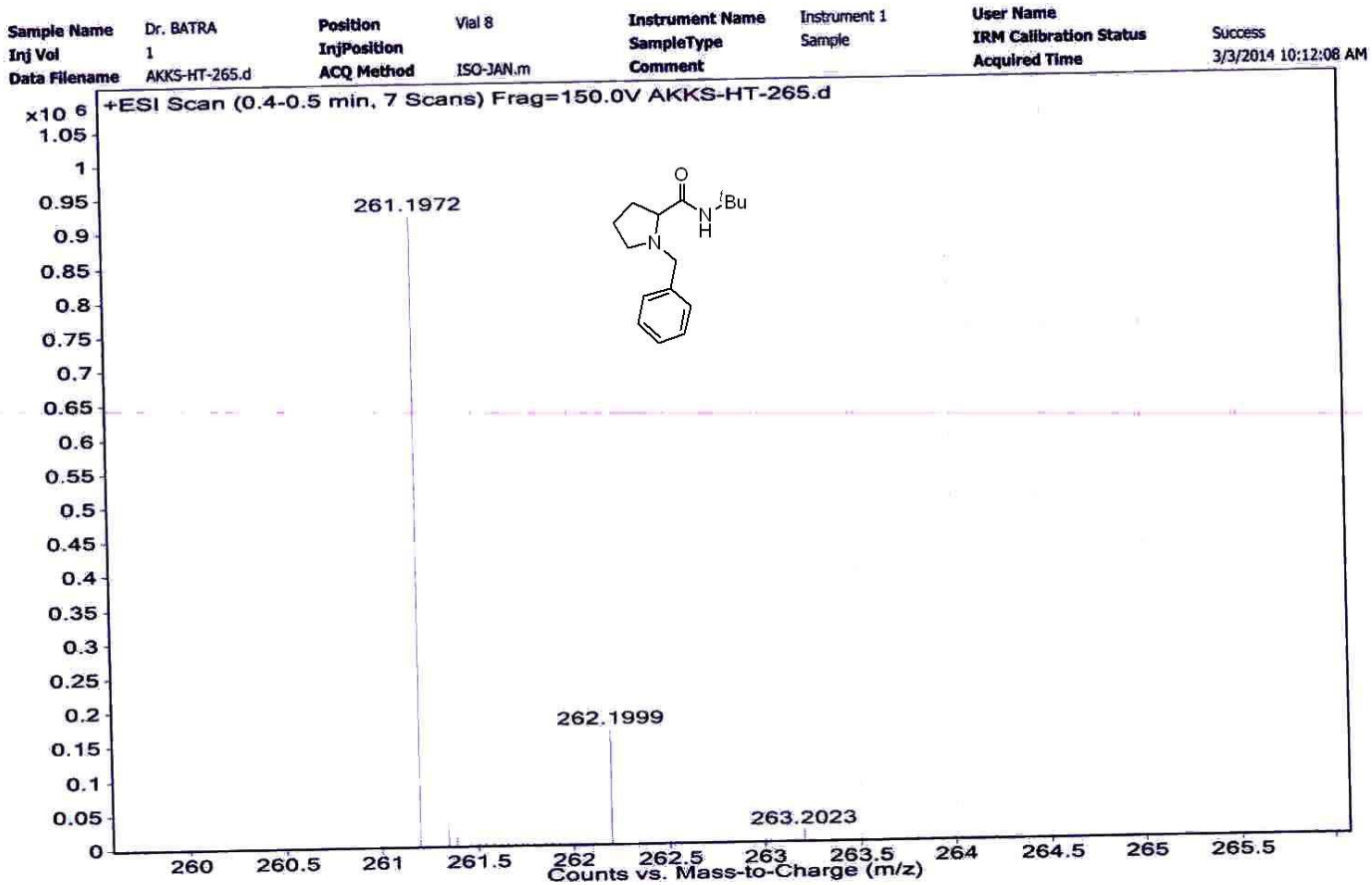

Figure S-45. HRMS spectrum of 1-Benzyl-*N*-*tert*-butylpyrrolidine-2-carboxamide **(4aB)**.

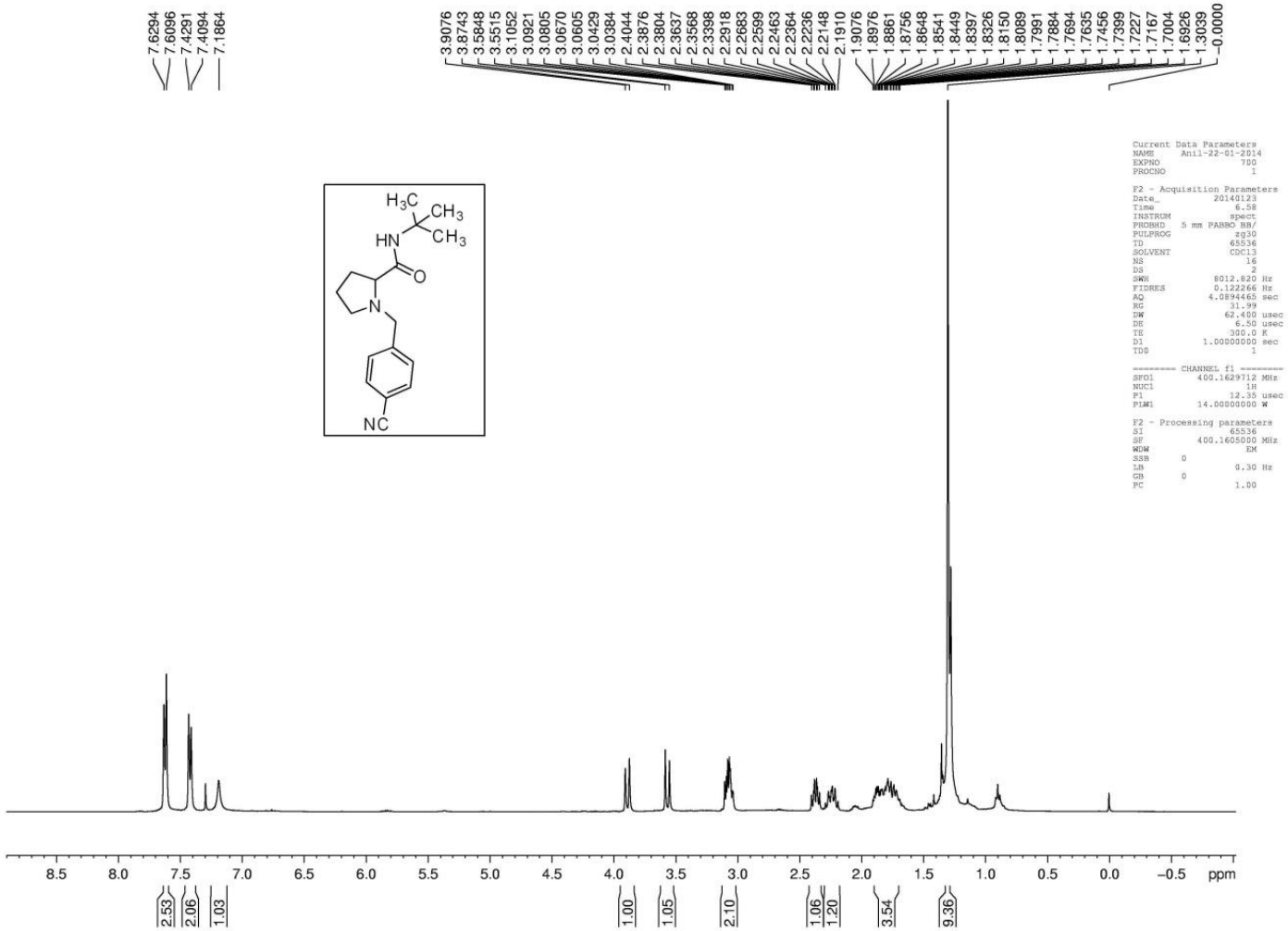

Figure S-46. ^{1}H-NMR spectrum of *N-tert*-butyl-1-(4-cyanobenzyl)pyrrolidine-2-carboxamide **(4bB).**

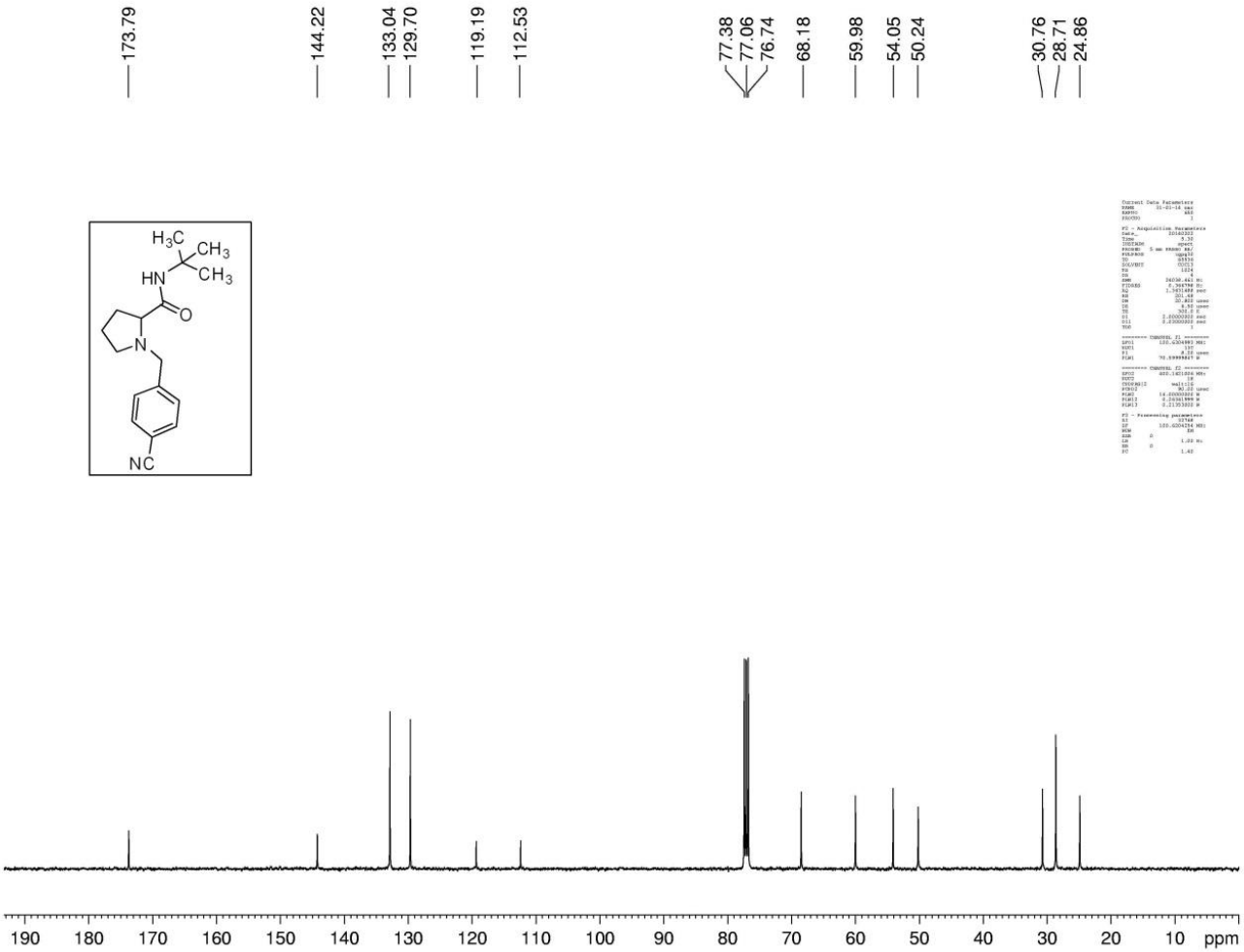

Figure S-47. ^{13}C-NMR spectrum of *N-tert*-butyl-1-(4-cyanobenzyl)pyrrolidine-2-carboxamide **(4bB).**

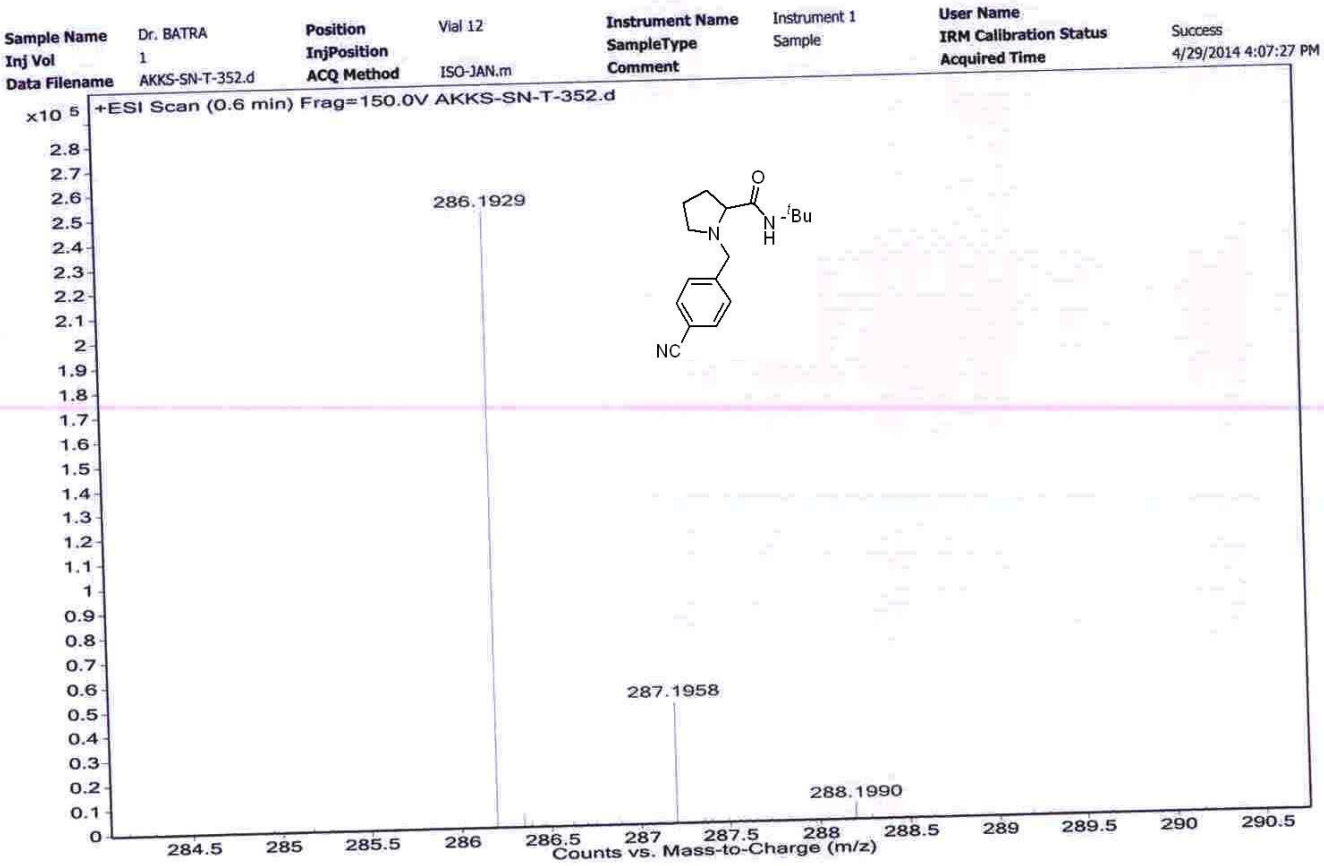

Figure S-48. HRMS spectrum of *N-tert*-butyl-1-(4-cyanobenzyl)pyrrolidine-2-carboxamide**(4bB).**

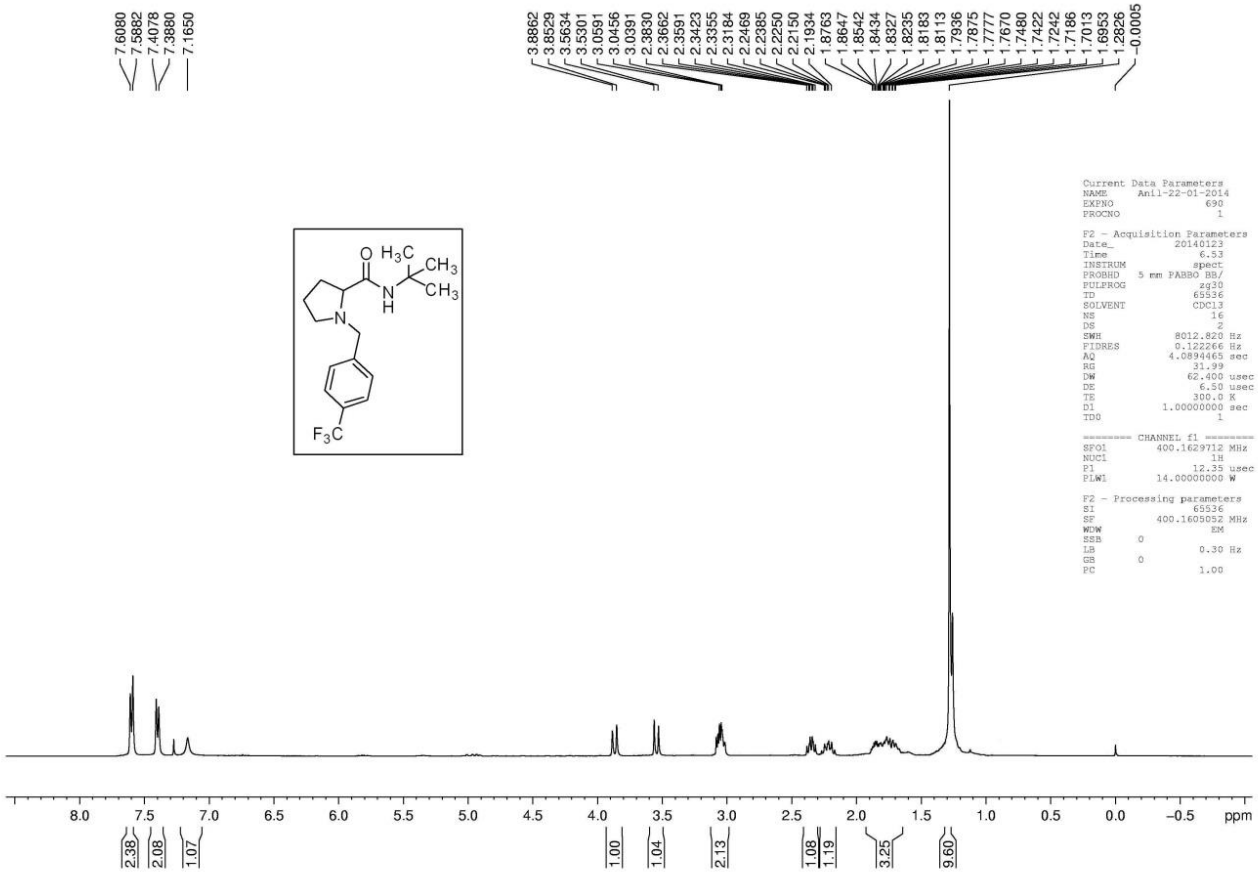

Figure S-49. ^{1}H-NMR spectrum of *N-tert*-butyl-1-(4-(trifluoromethyl)benzyl)pyrrolidine-2-carboxamide **(4cB)**.

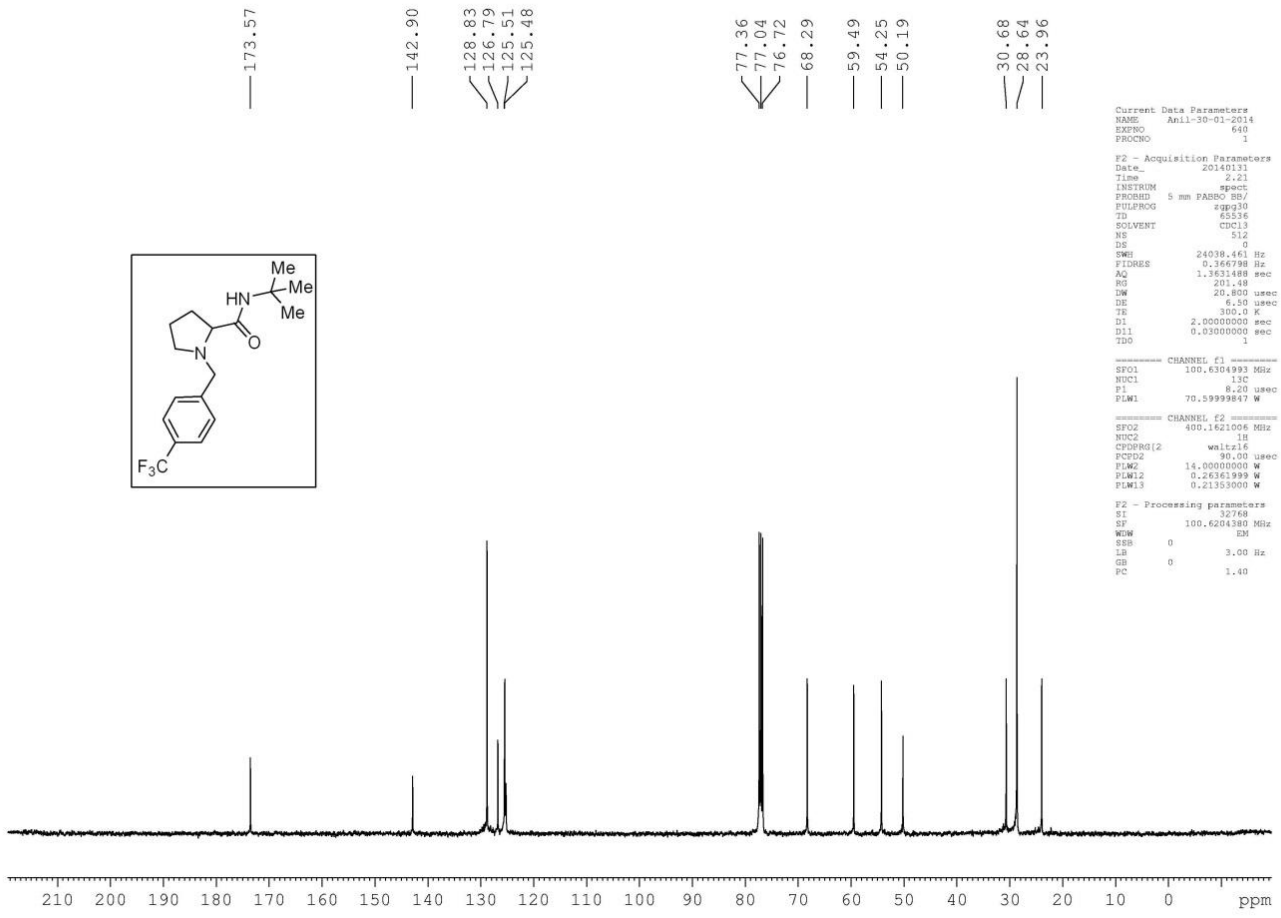

Figure S-50. ^{13}C-NMR spectrum of *N-tert*-butyl-1-(4-(trifluoromethyl)benzyl)pyrrolidine-2-carboxamide **(4cB)**.

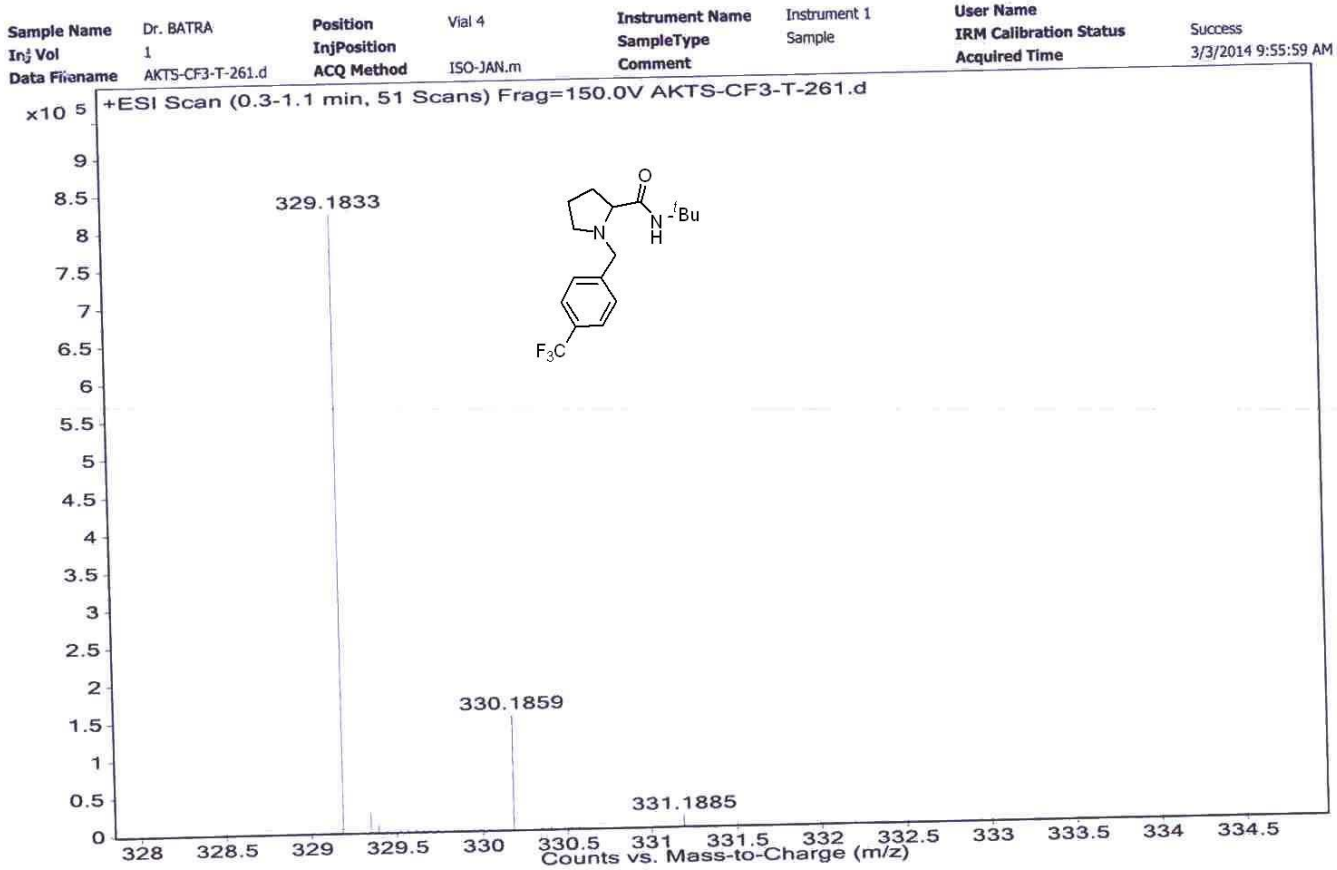

Figure S-51. HRMS spectrum of *N-tert*-butyl-1-(4-(trifluoromethyl)benzyl)pyrrolidine-2-carboxamide **(4cB)**.

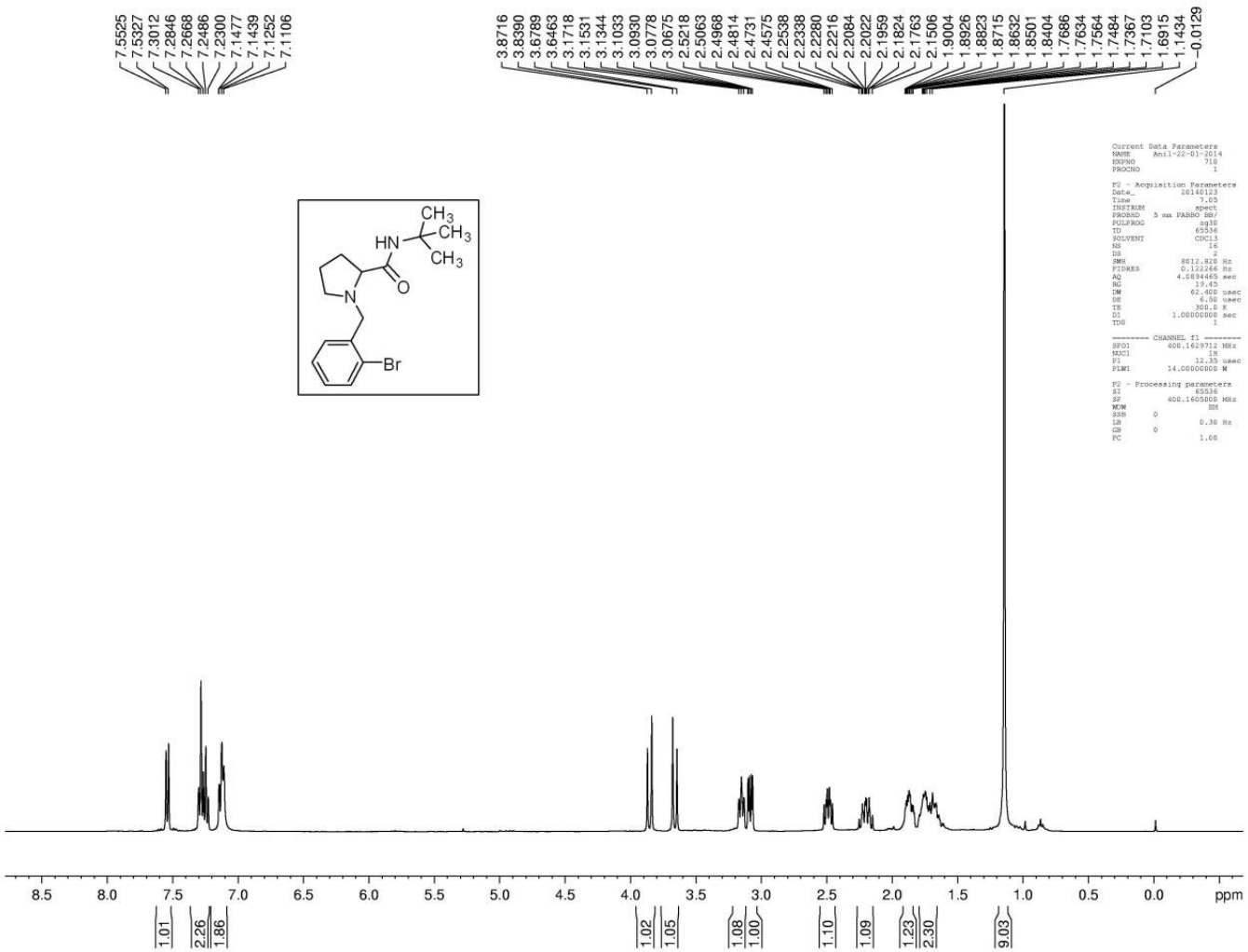

Figure S-52. ^{1}H-NMR spectrum of 1-(2-Bromobenzyl)-*N*-*tert*-butylpyrrolidine-2-carboxamide **(4eB)**.

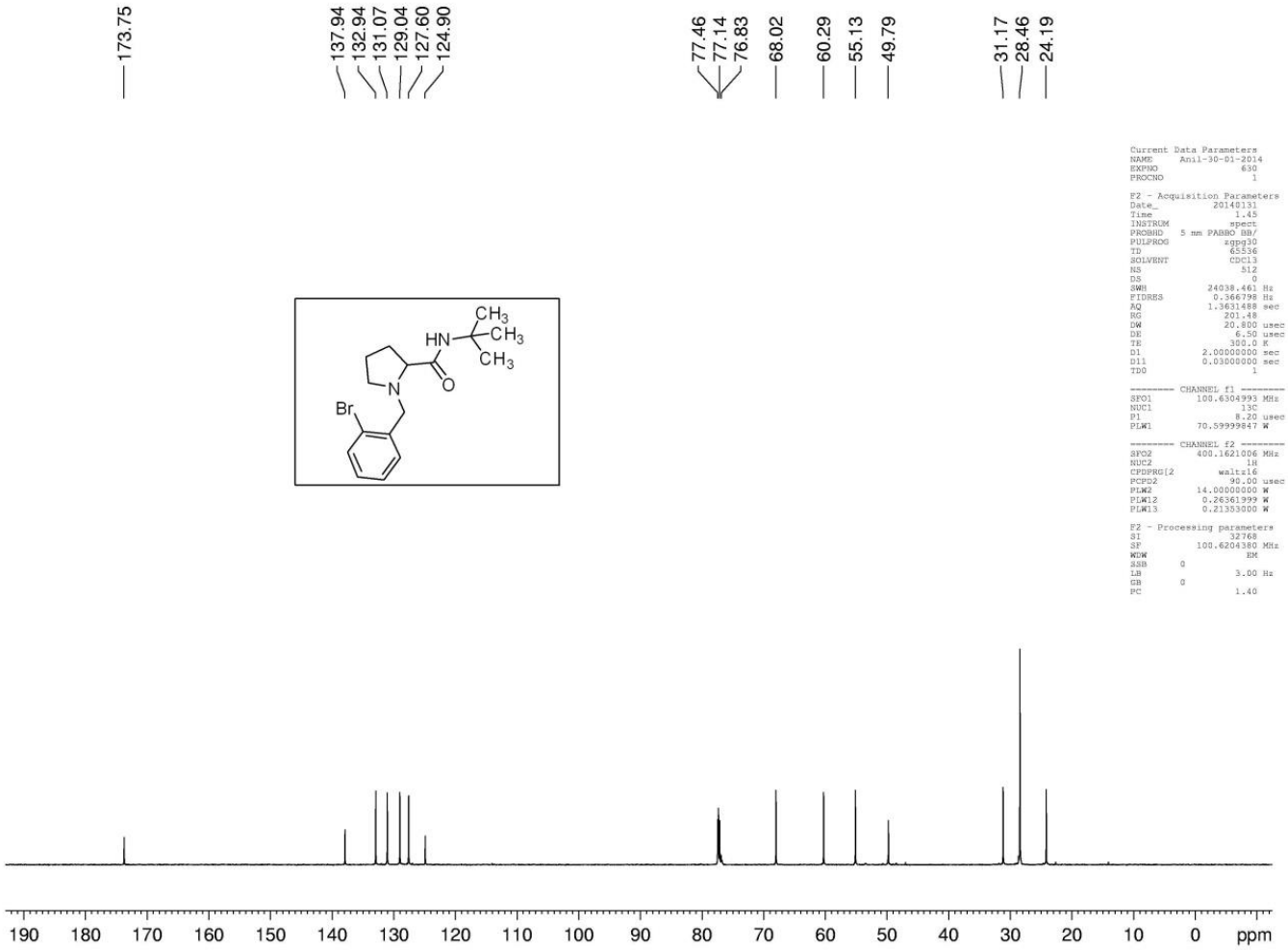

Figure S-53. ^{13}C-NMR spectrum of 1-(2-Bromobenzyl)-*N*-*tert*-butylpyrrolidine-2-carboxamide **(4eB)**.

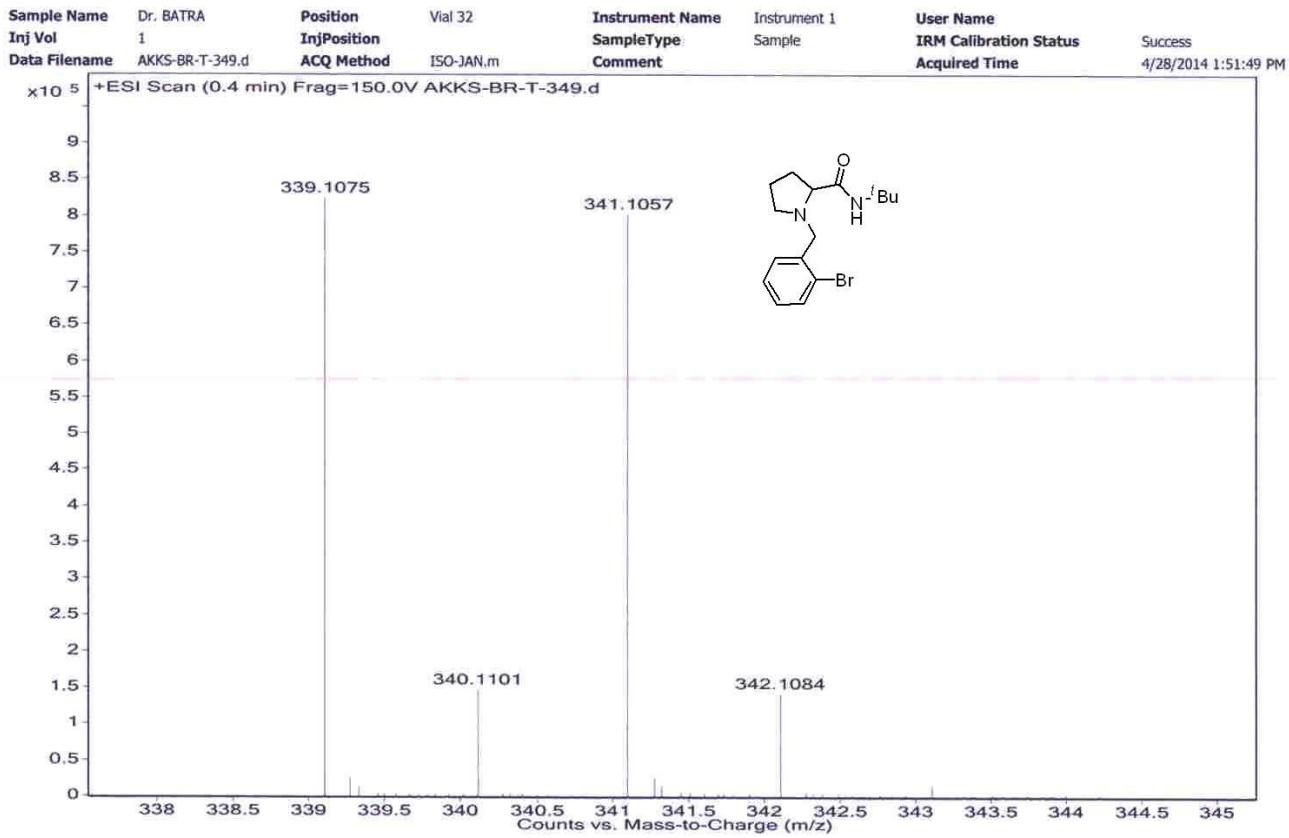

Figure S-54. HRMS spectrum of 1-(2-Bromobenzyl)-*N*-*tert*-butylpyrrolidine-2-carboxamide **(4eB)**.

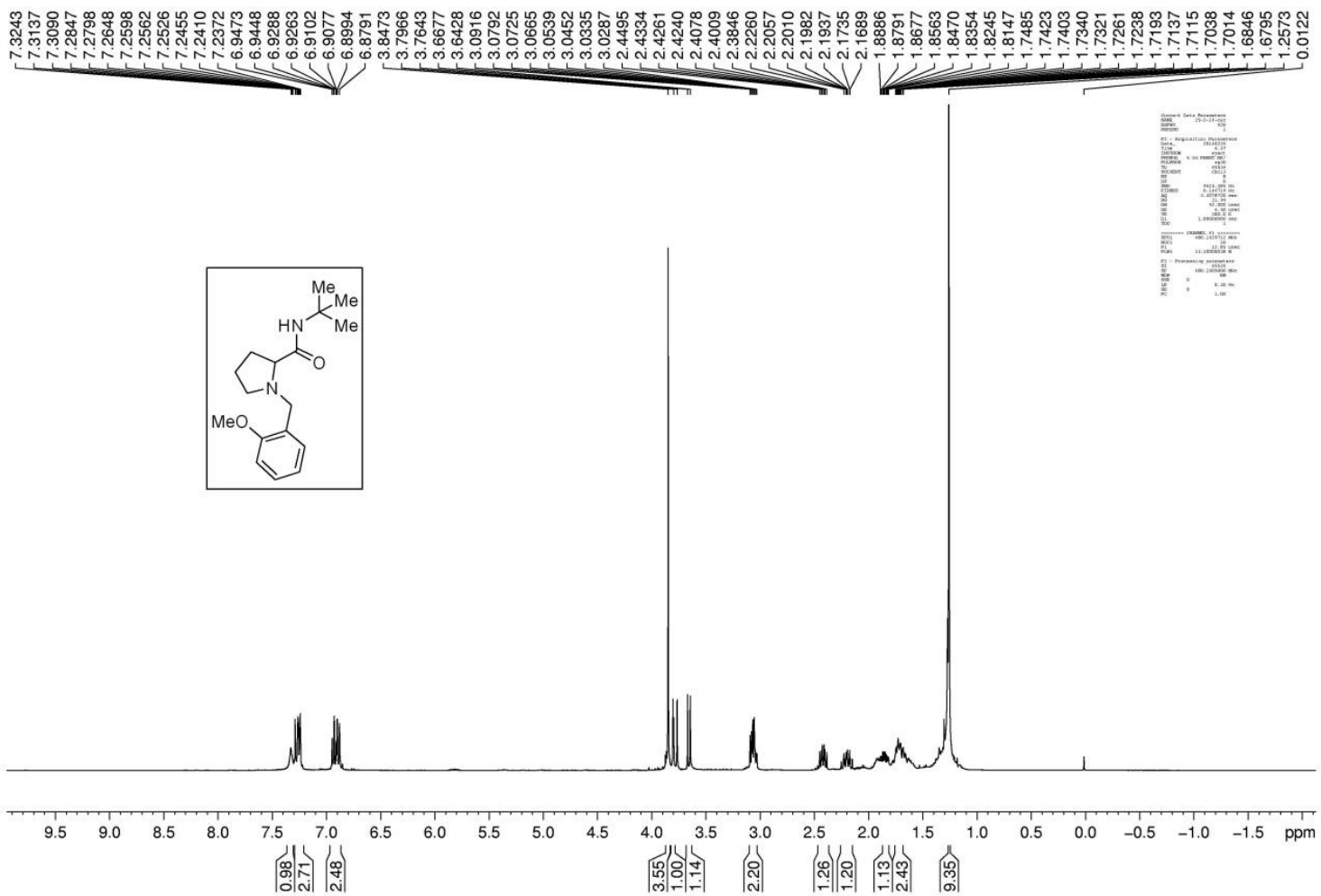

Figure S-55. ^{1}H-NMR spectrum of *N-tert*-butyl-1-(2-methoxybenzyl)pyrrolidine-2-carboxamide **(4gB)**.

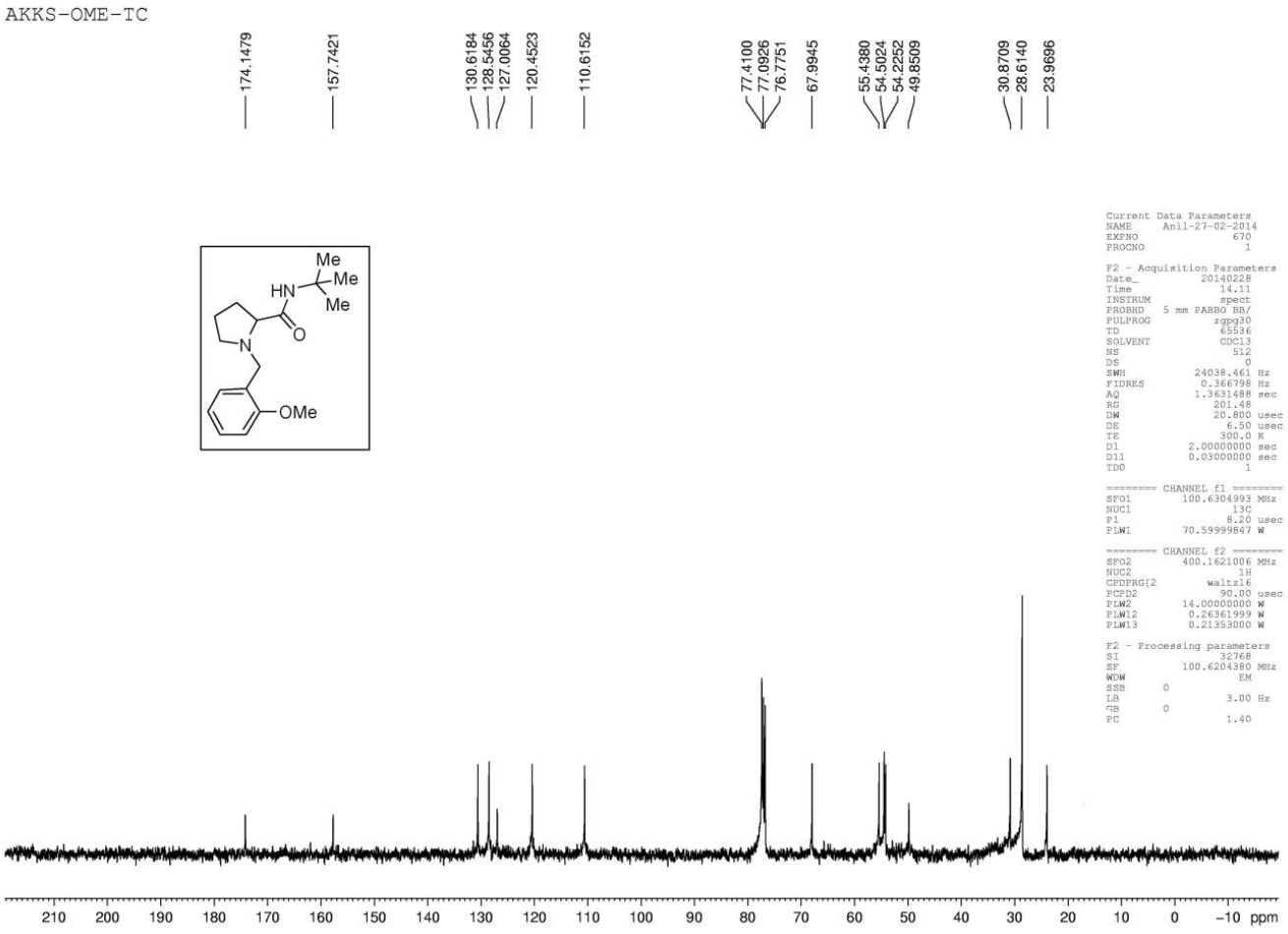

Figure S-56. ^{13}C-NMR spectrum of *N-tert*-butyl-1-(2-methoxybenzyl)pyrrolidine-2-carboxamide **(4gB)**.

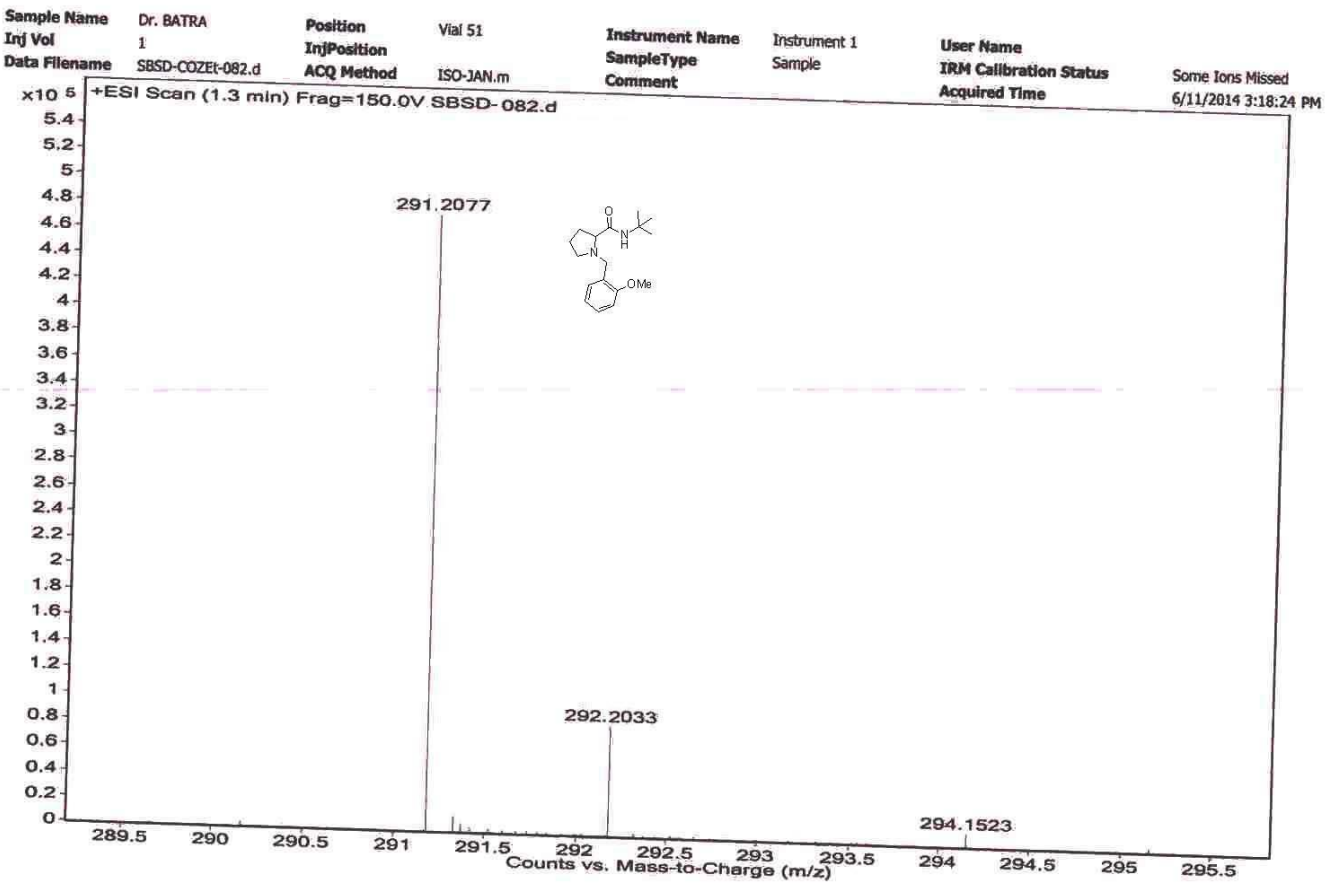

Figure S-57. HRMS spectrum of *N-tert*-butyl-1-(2-methoxybenzyl)pyrrolidine-2-carboxamide **(4gB)**.

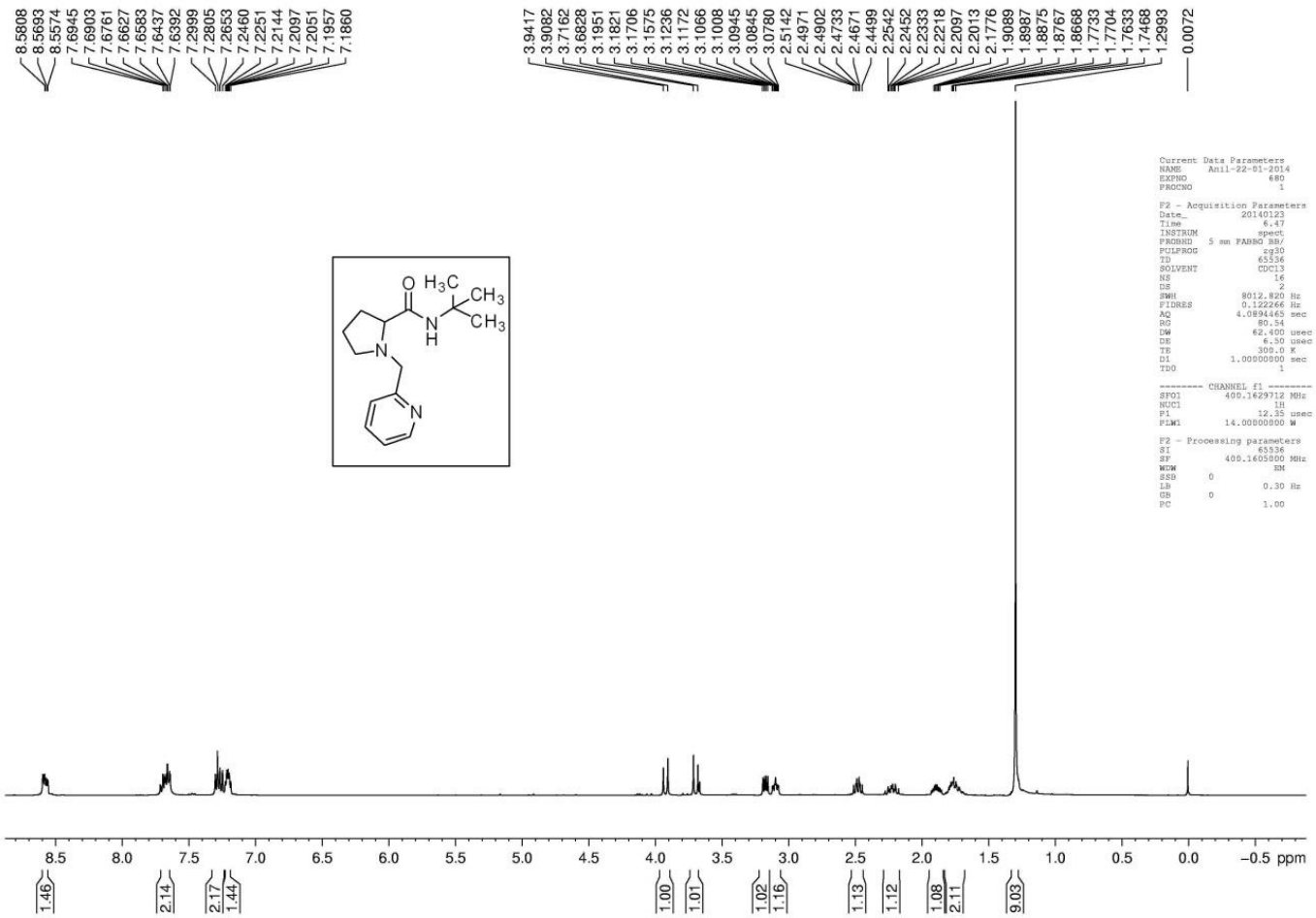

Figure S-58. ^{1}H-NMR spectrum of *N-tert*-butyl-1-(pyridin-2-ylmethyl)pyrrolidine-2-carboxamide **(4jB)**.

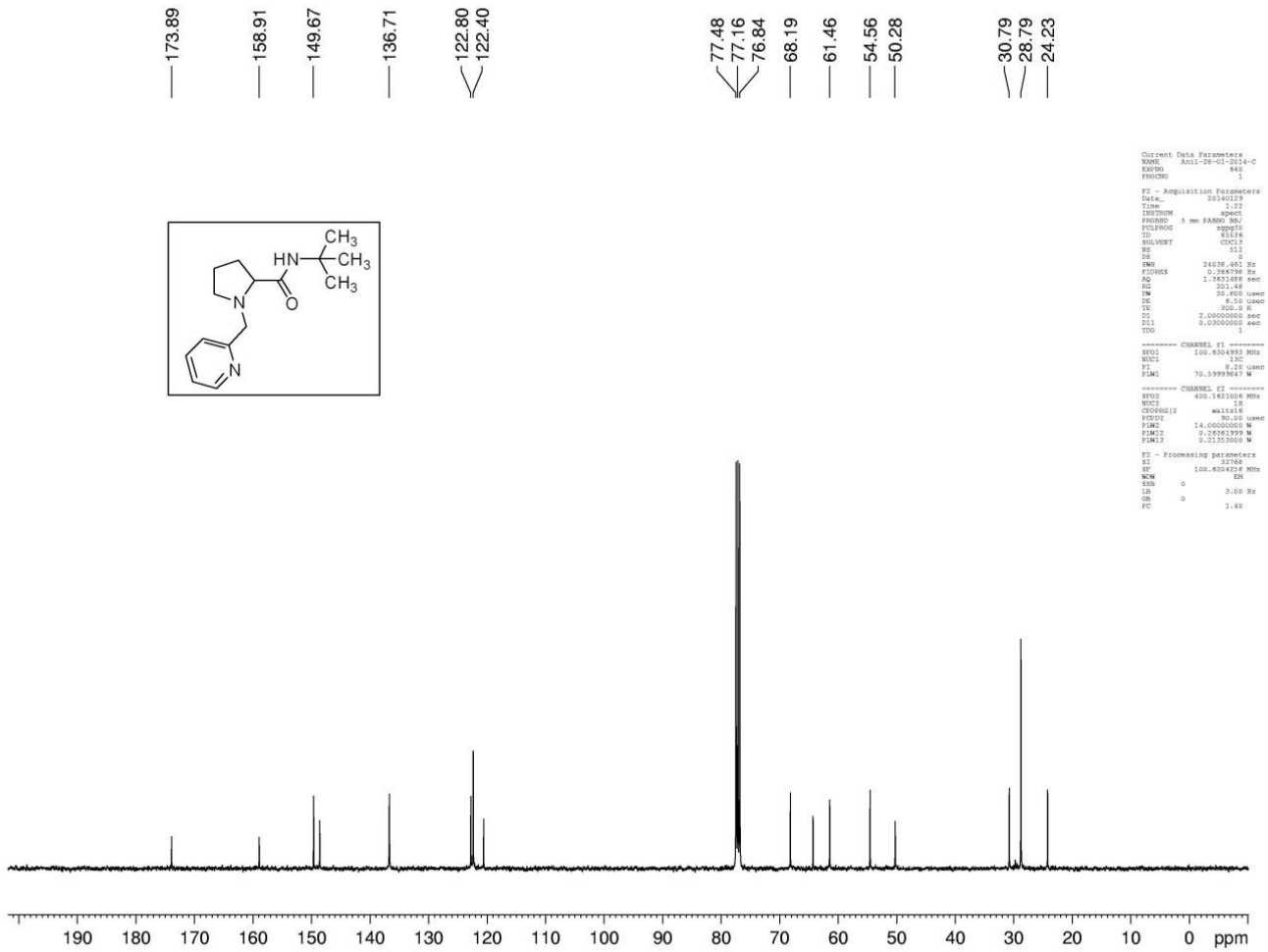

Figure S-59. ^{13}C-NMR spectrum of *N-tert*-butyl-1-(pyridin-2-ylmethyl)pyrrolidine-2-carboxamide **(4jB)**.

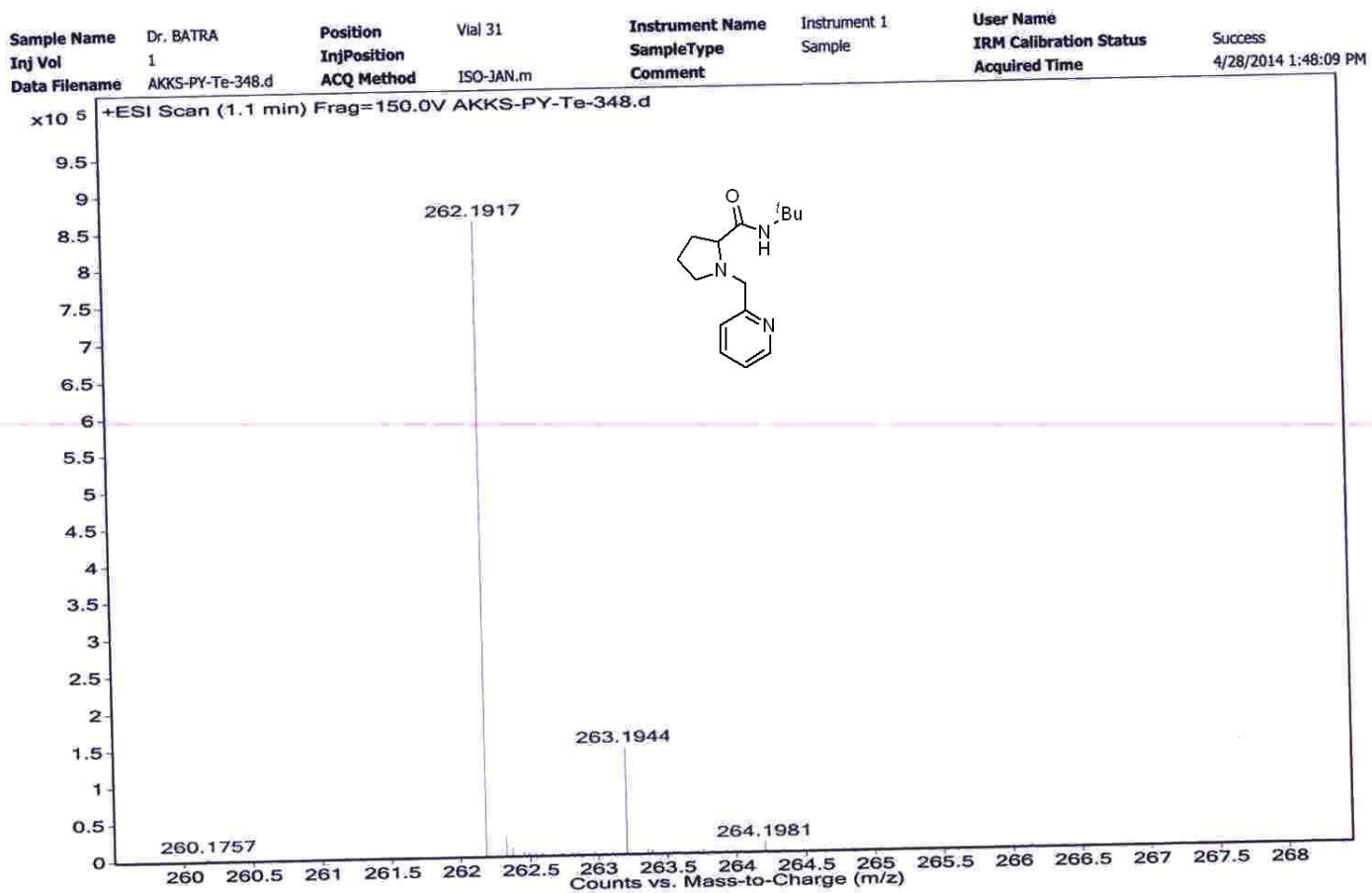

Figure S-60. HRMS spectrum of *N-tert*-butyl-1-(pyridin-2-ylmethyl)pyrrolidine-2-carboxamide **(4jB)**.

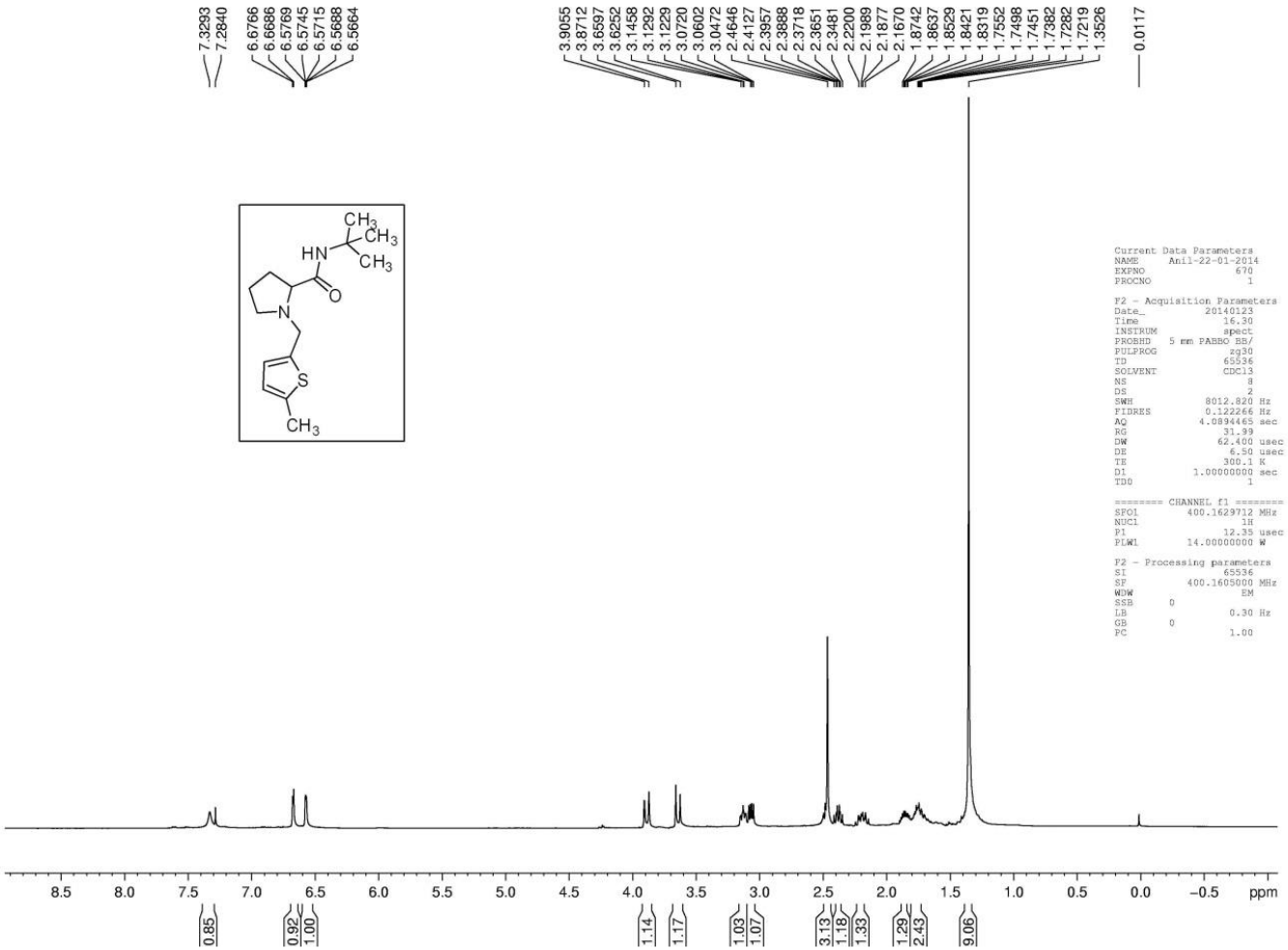

Figure S-61. ^{1}H-NMR spectrum of *N-tert*-butyl-1-((5-methylthiophen-2-yl)methyl)pyrrolidine-2-carboxamide **(4kB)**.

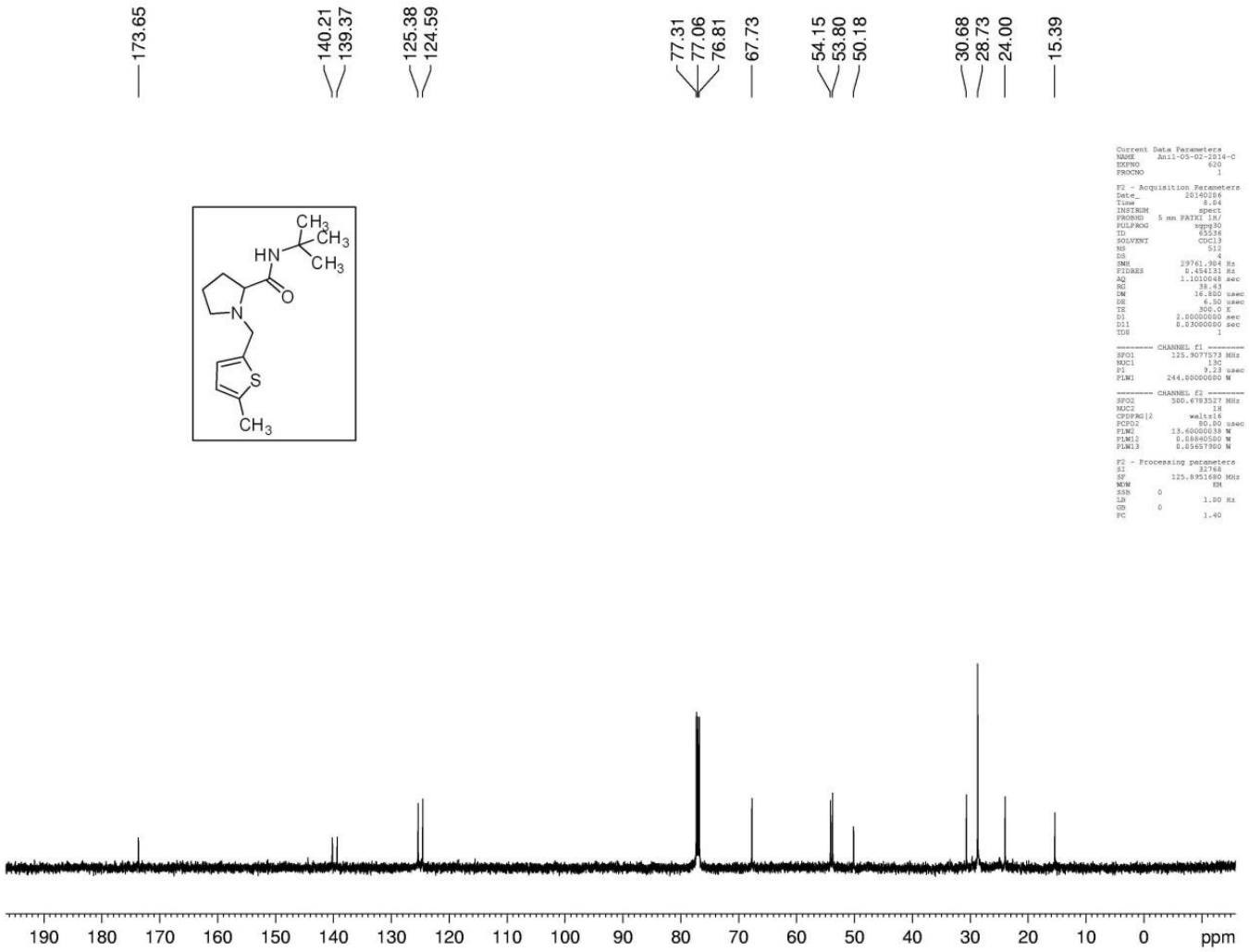

Figure S-62. ^{13}C-NMR spectrum of *N-tert*-butyl-1-((5-methylthiophen-2-yl)methyl)pyrrolidine-2-carboxamide **(4kB)**.

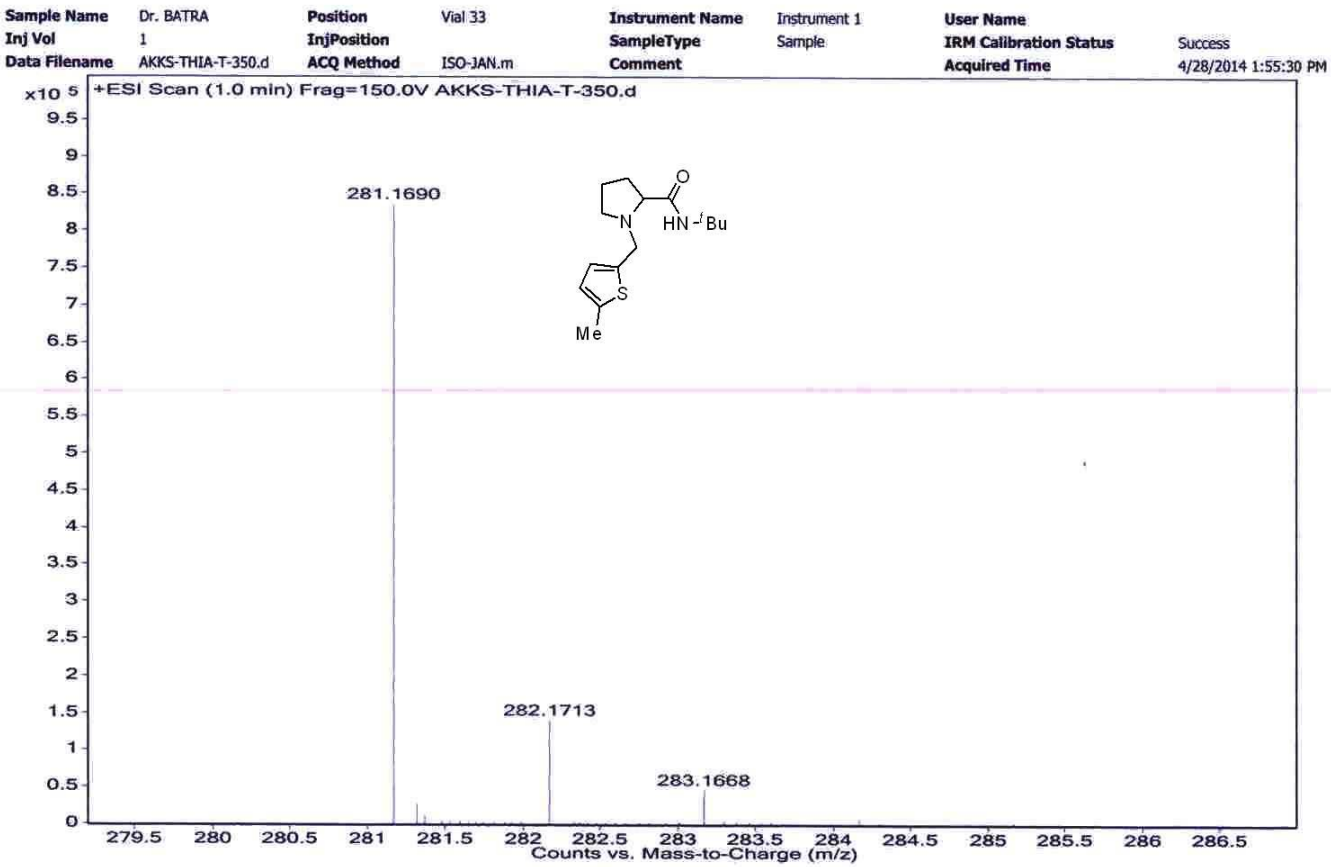

Figure S-63. HRMS spectrum of *N*-*tert*-butyl-1-((5-methylthiophen-2-yl)methyl)pyrrolidine-2-carboxamide **(4kB)**.

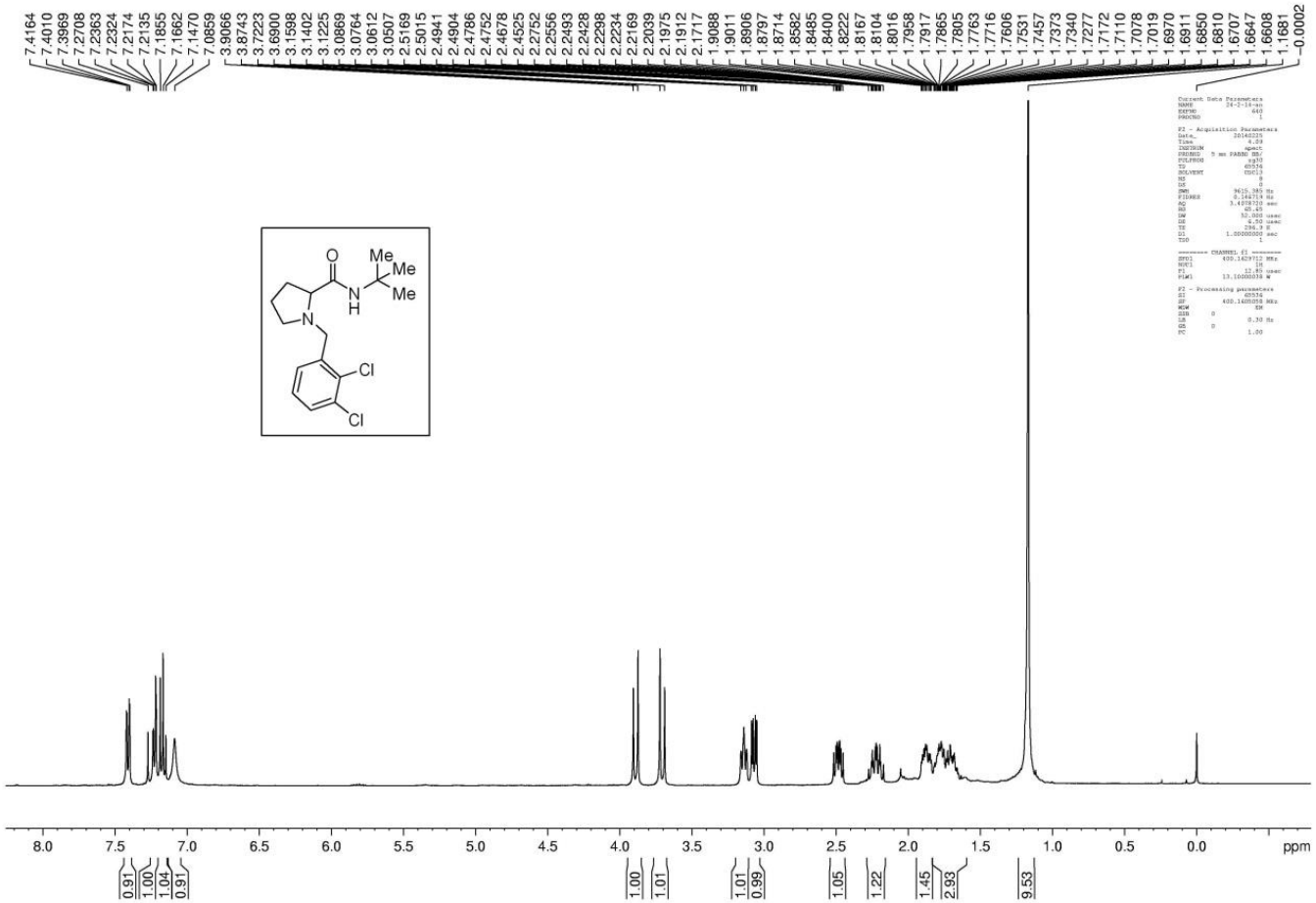

Figure S-64. ^{1}H-NMR spectrum of *N-tert*-butyl-1-(2,3-dichlorobenzyl)pyrrolidine-2-carboxamide **(4lB)**.

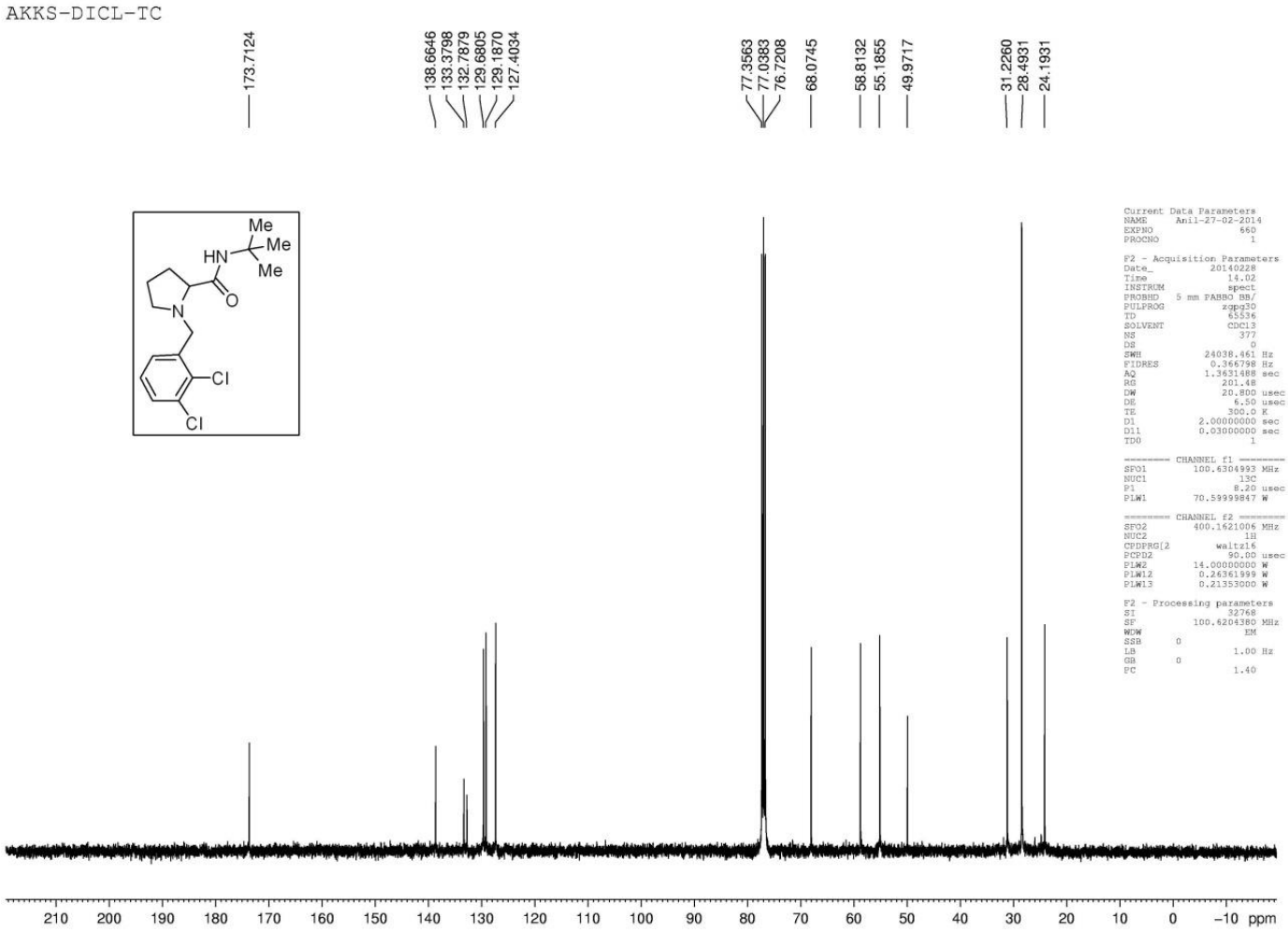

Figure S-65. ^{13}C-NMR spectrum of *N-tert*-butyl-1-(2,3-dichlorobenzyl)pyrrolidine-2-carboxamide **(4lB)**

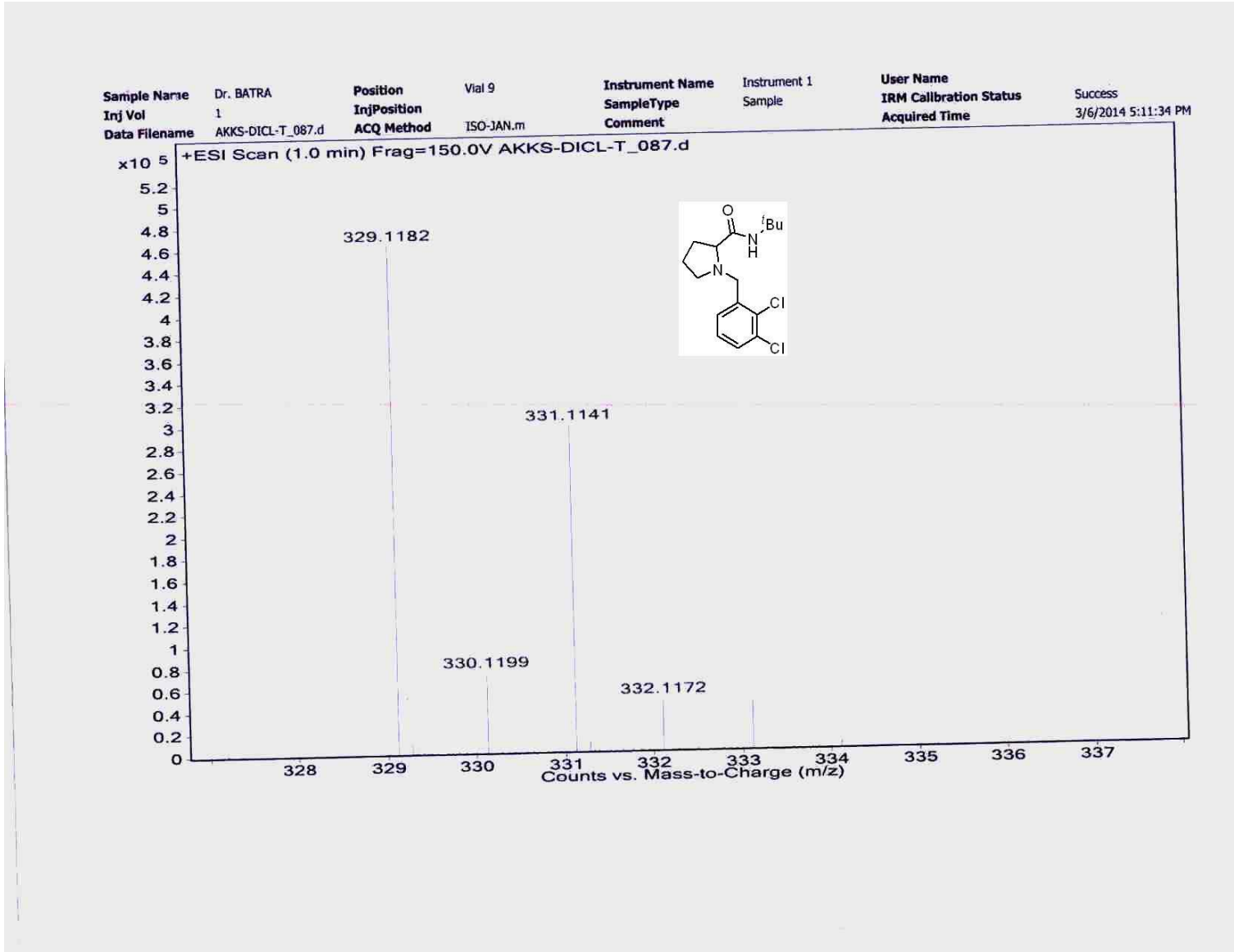

Figure S-66. HRMS spectrum of *N-tert*-butyl-1-(2,3-dichlorobenzyl)pyrrolidine-2-carboxamide **(4lB)**.

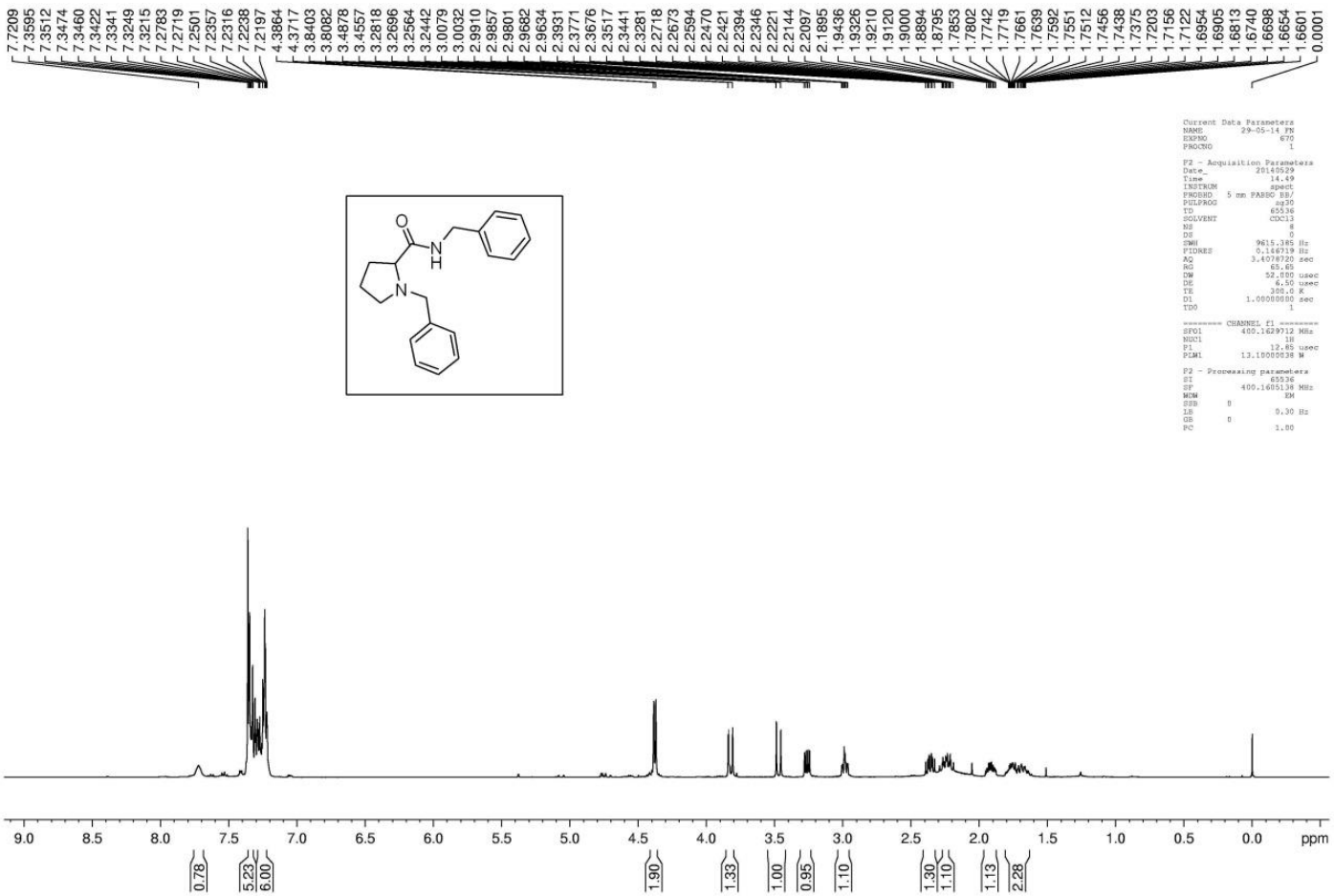

Figure S-67. ^{1}H-NMR spectrum of *N*,1-dibenzylpyrrolidine-2-carboxamide **(4aC)**.

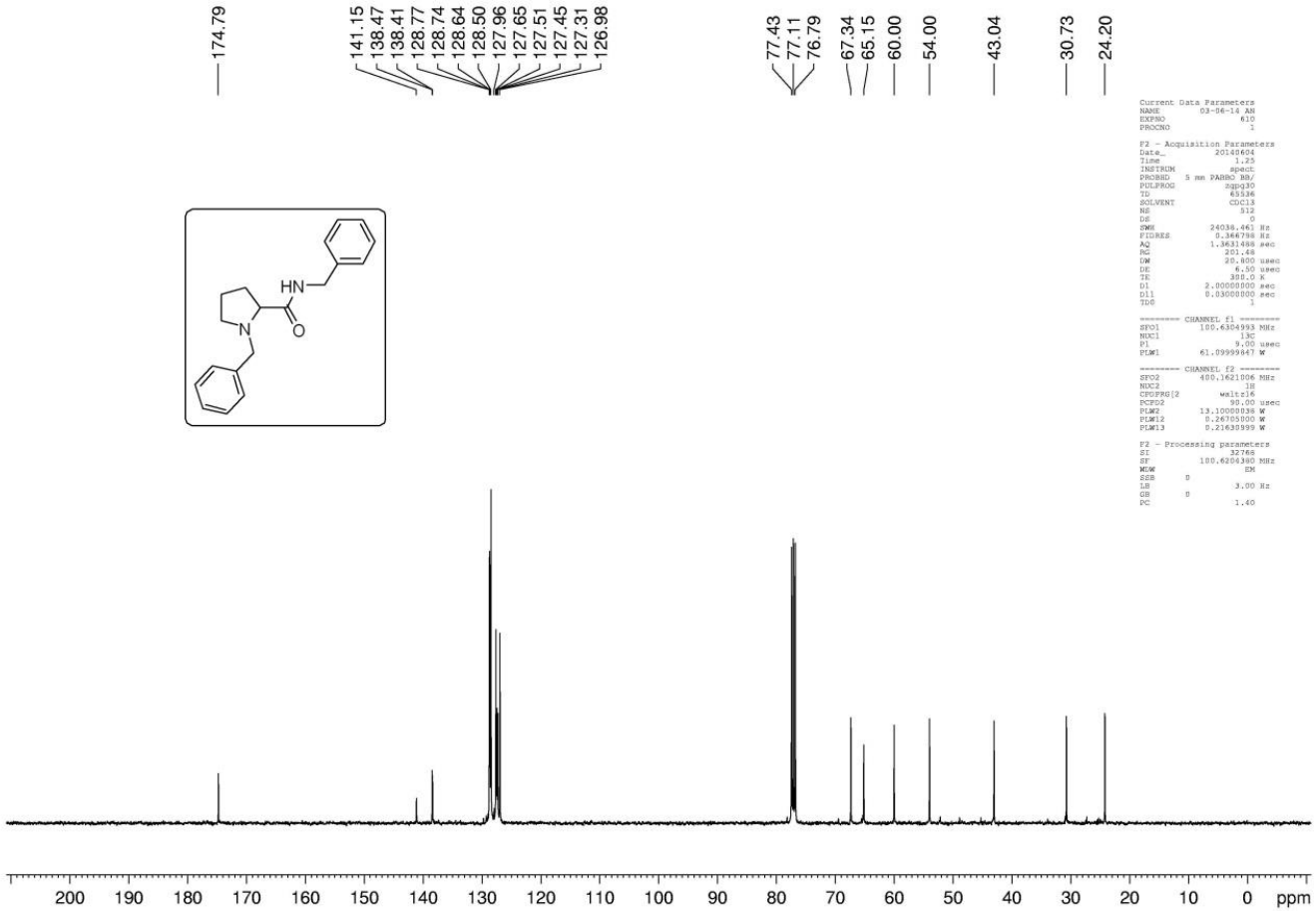

Figure S-68. ^{13}C-NMR spectrum of *N*,1-dibenzylpyrrolidine-2-carboxamide **(4aC)**.

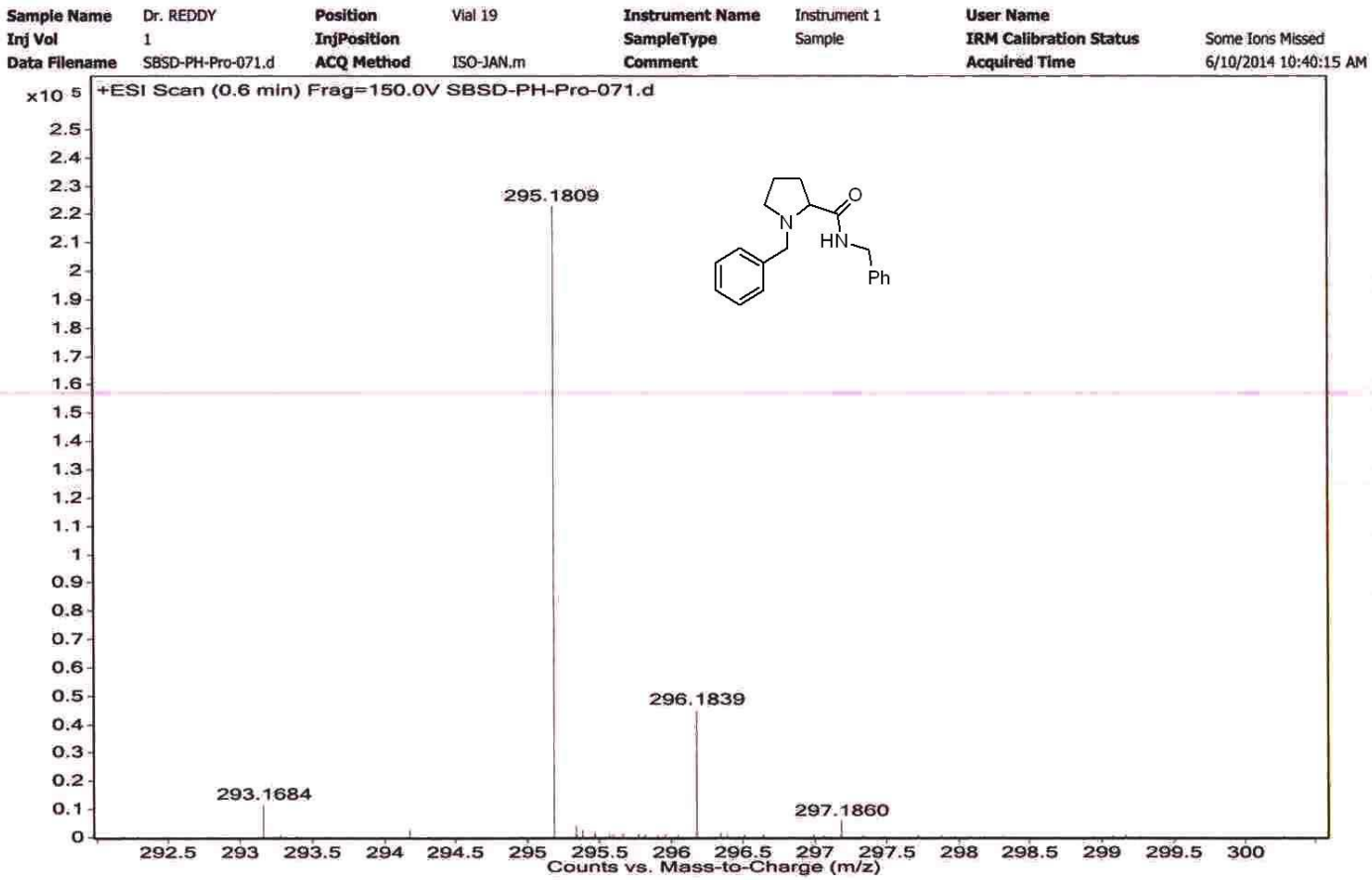

Figure S-69. HRMS spectrum of *N*,1-dibenzylpyrrolidine-2-carboxamide **(4aC)**.

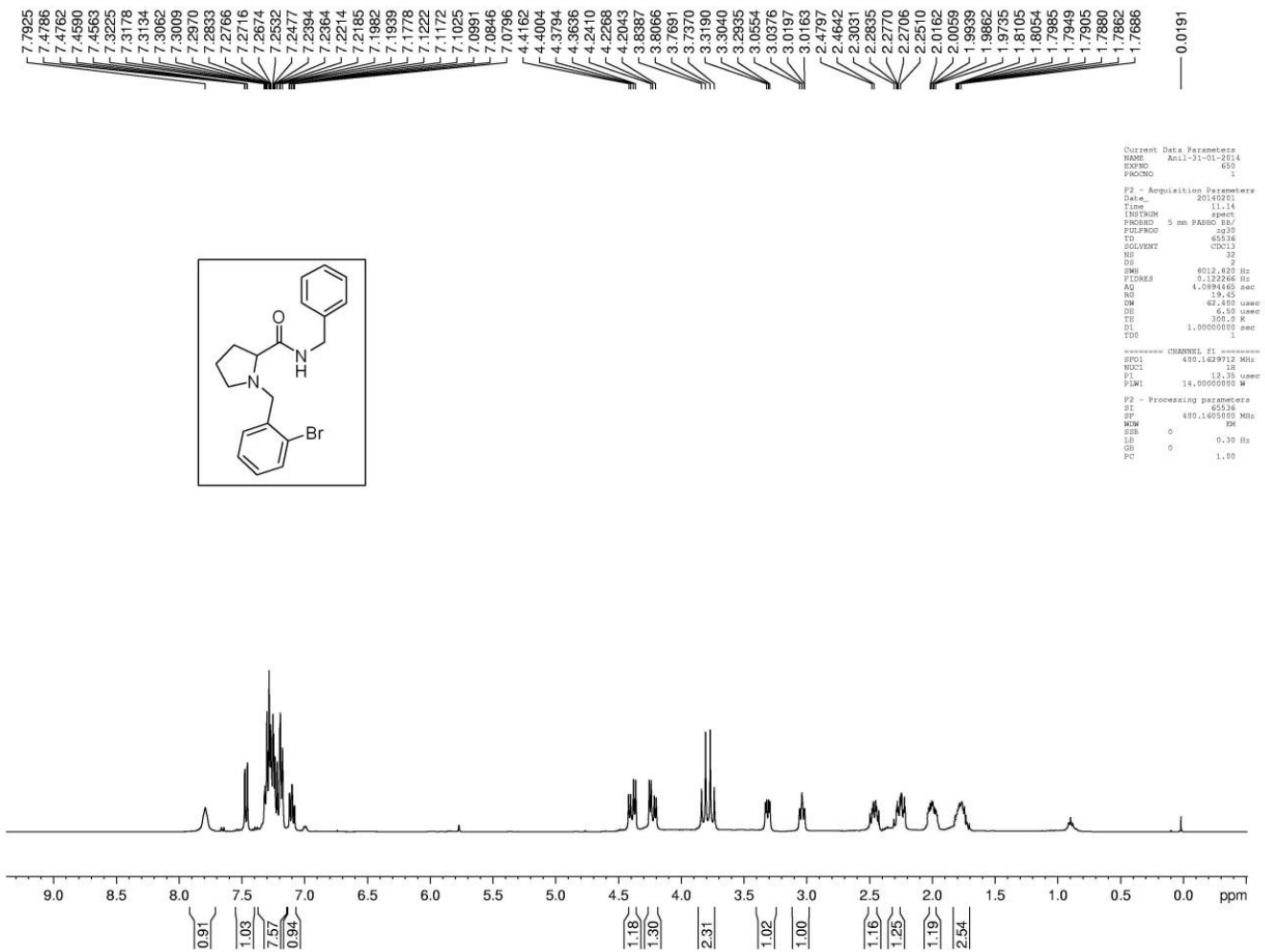

Figure S-70. ^{1}H-NMR spectrum of *N*-benzyl-1-(2-bromobenzyl)pyrrolidine-2-carboxamide **(4eC)**.

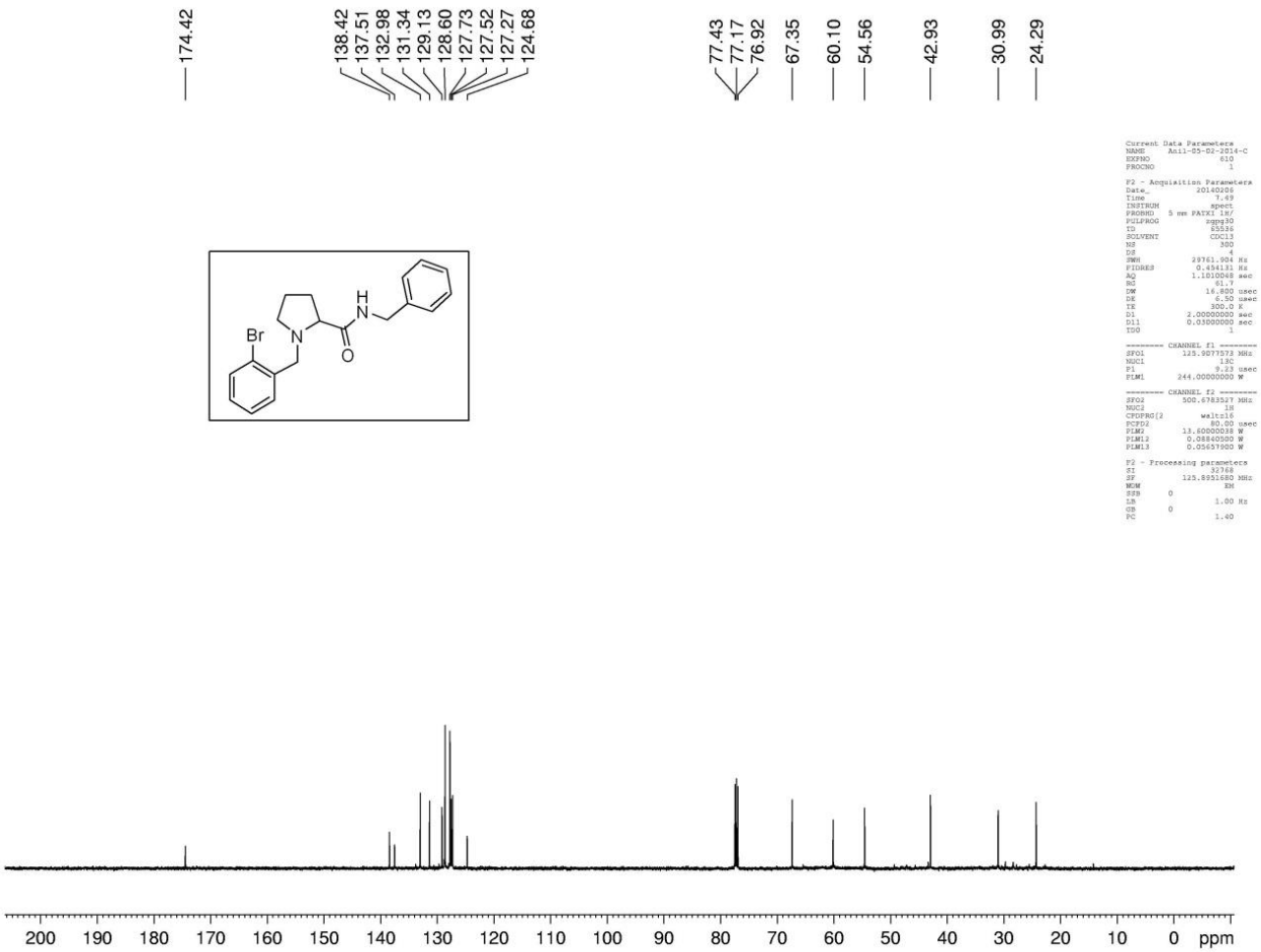

Figure S-71. ^{13}C-NMR spectrum of *N*-benzyl-1-(2-bromobenzyl)pyrrolidine-2-carboxamide **(4eC)**.

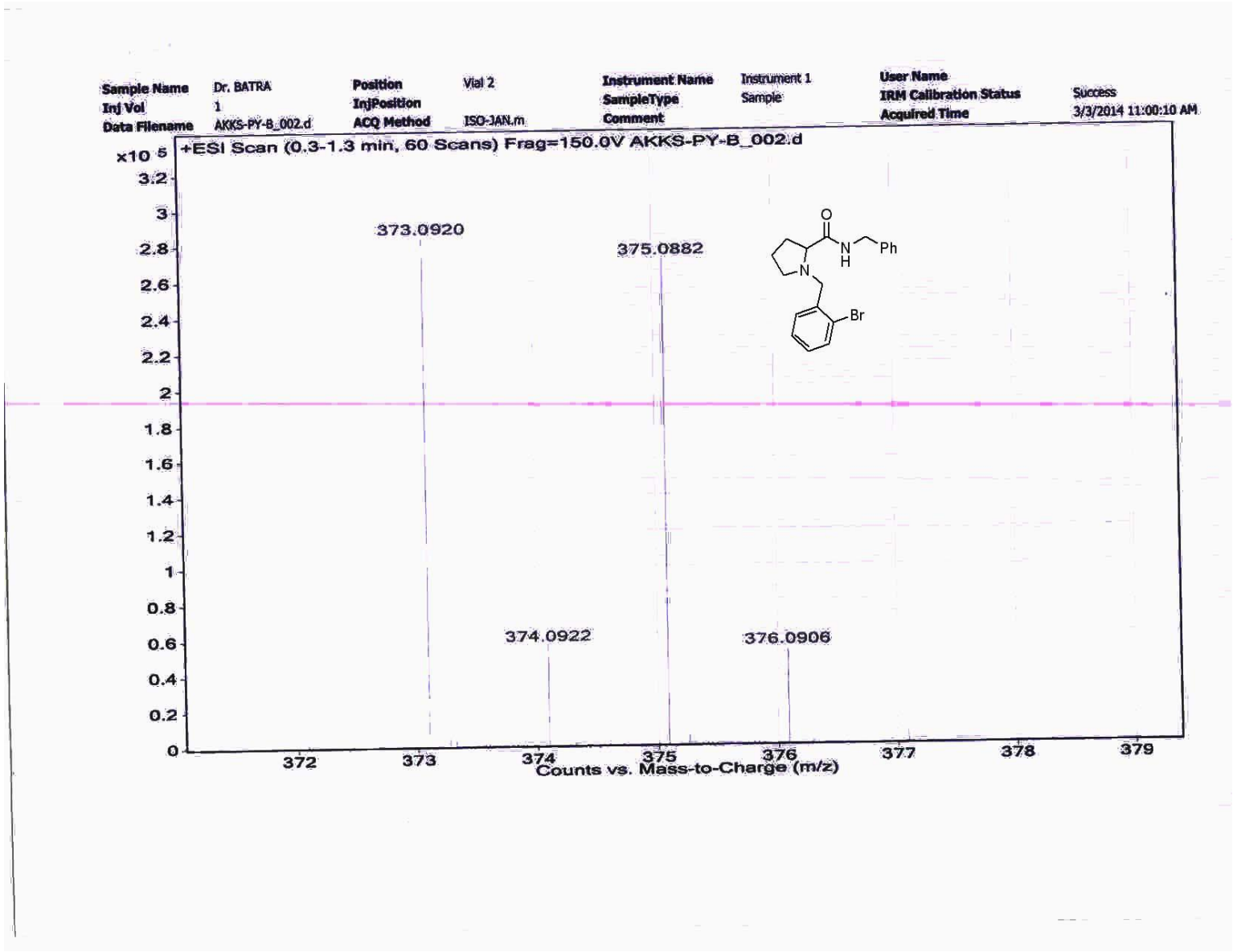

Figure S-72. HRMS spectrum of *N*-benzyl-1-(2-bromobenzyl)pyrrolidine-2-carboxamide **(4eC)**.

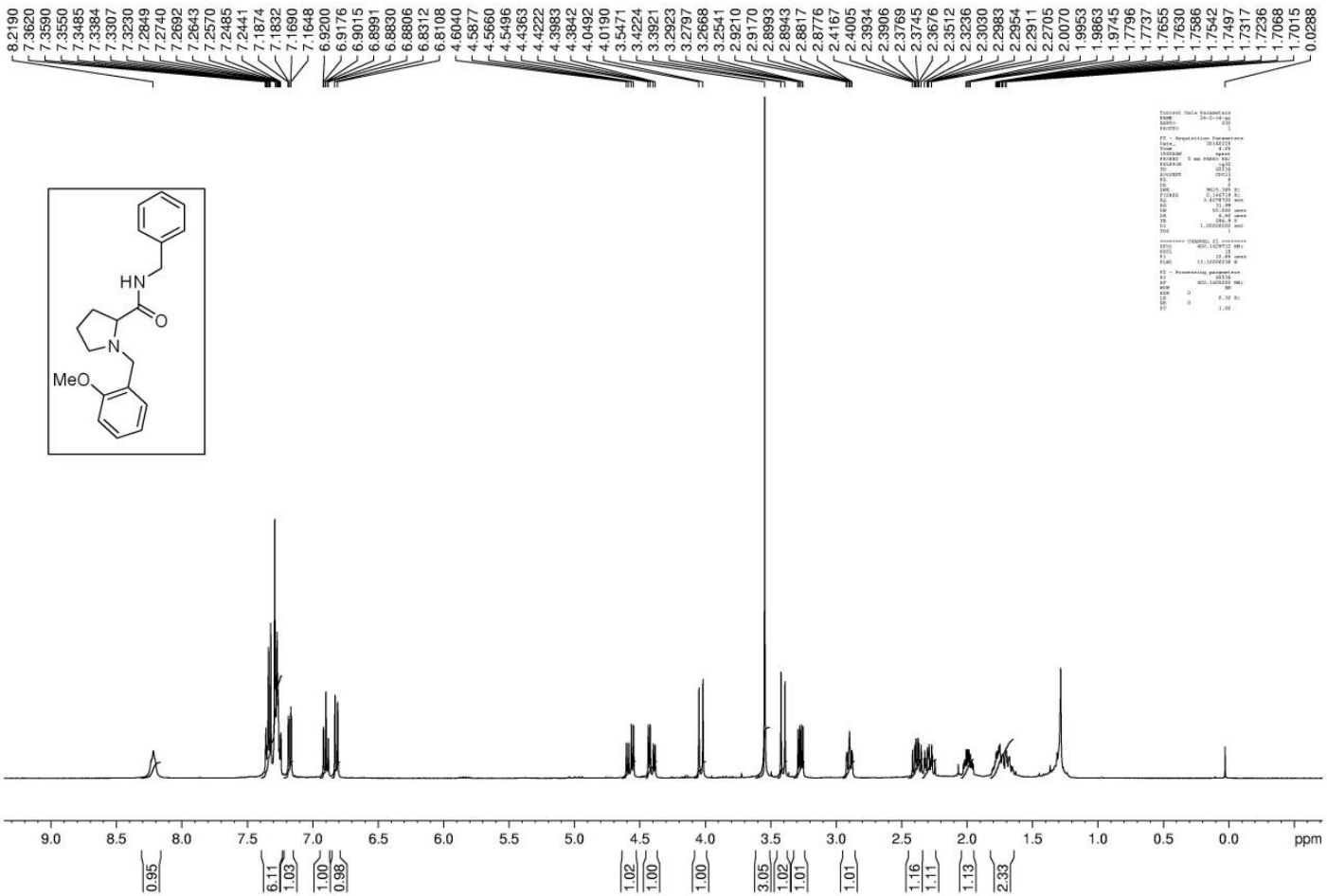

Figure S-73. ^{1}H-NMR spectrum of *N*-benzyl-1-(2-methoxybenzyl)pyrrolidine-2-carboxamide **(4gC).**

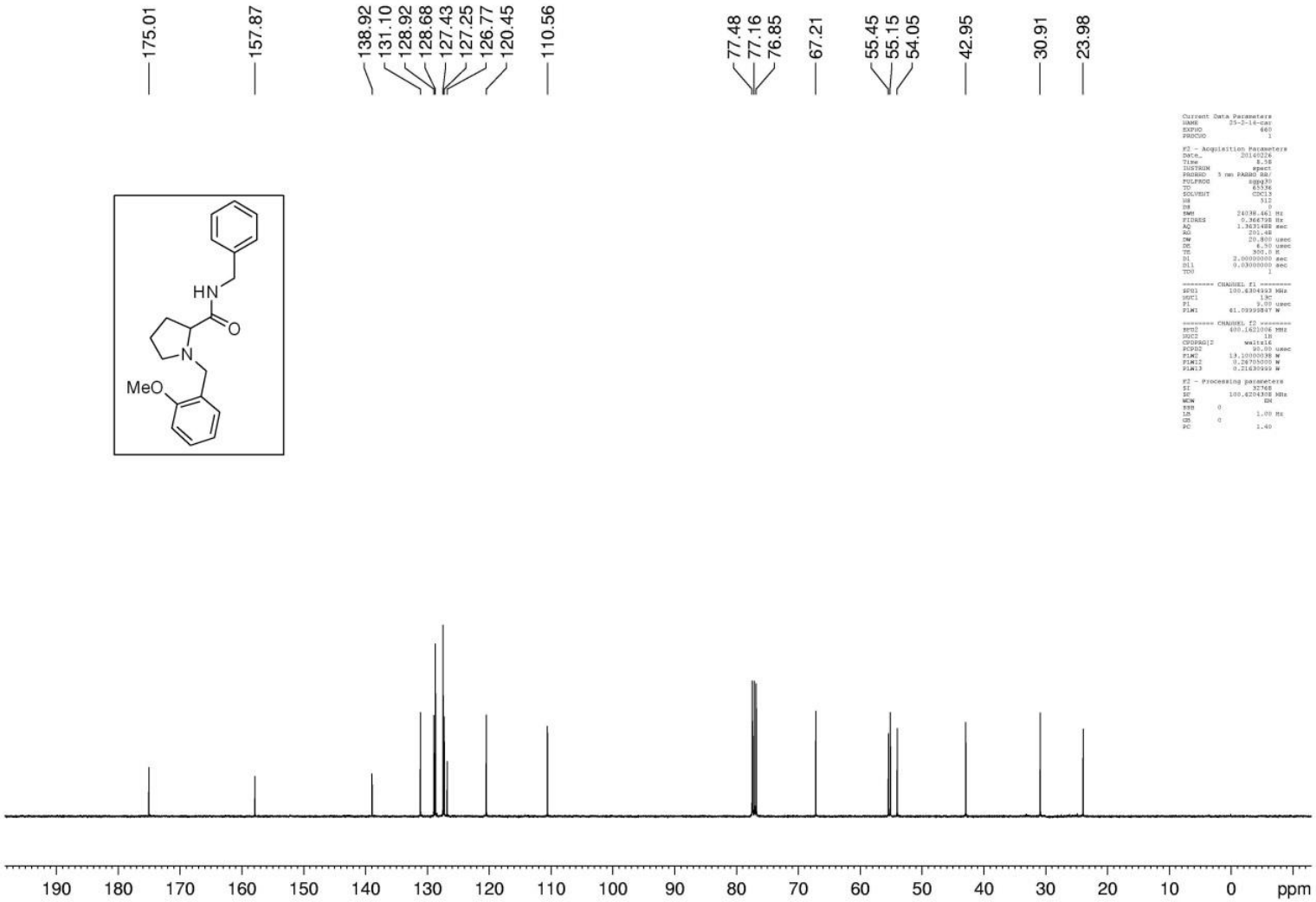

Figure S-74. ^{13}C-NMR spectrum of *N*-benzyl-1-(2-methoxybenzyl)pyrrolidine-2-carboxamide **(4gC).**

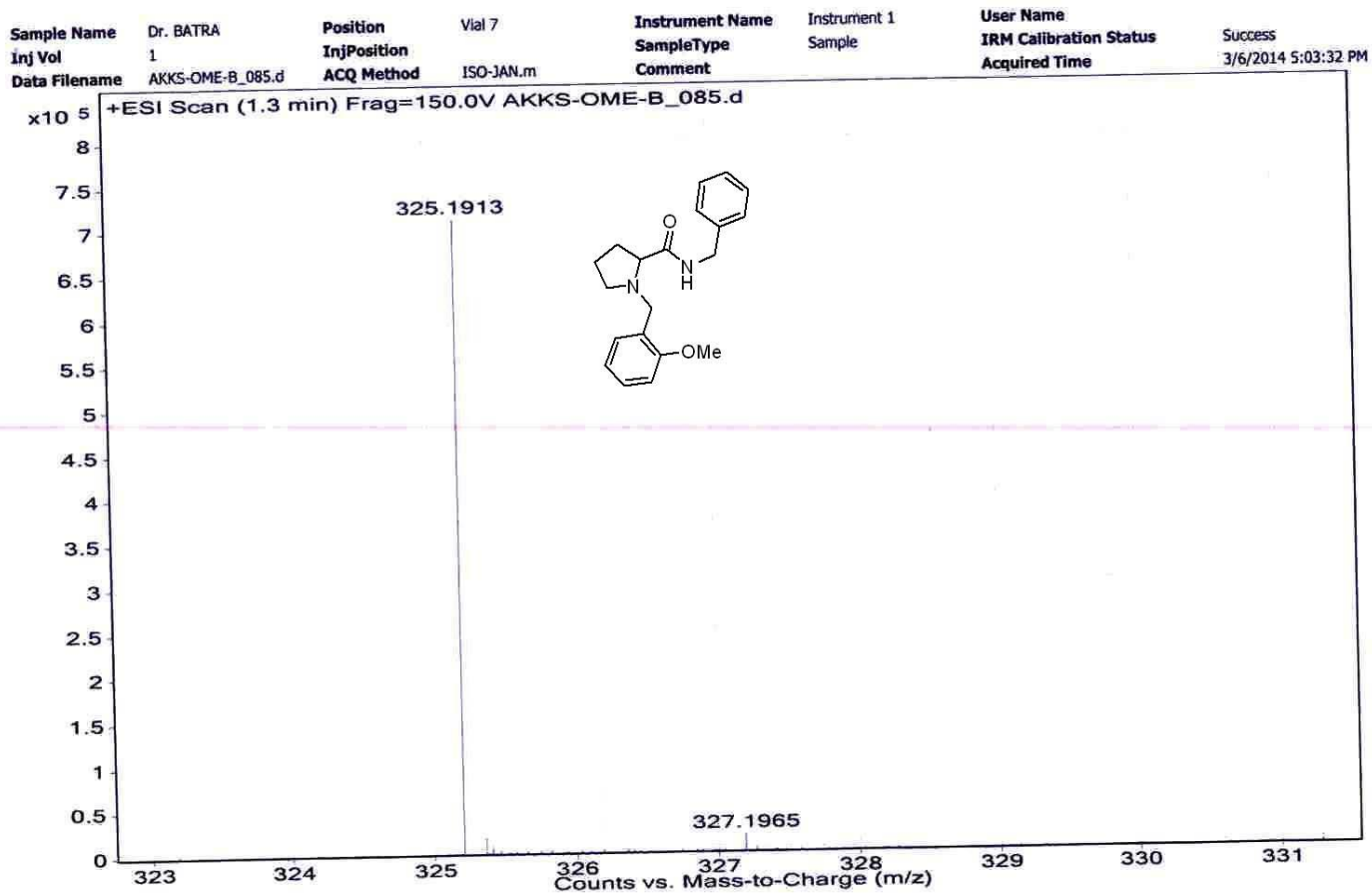

Figure S-75. HRMS spectrum of *N*-benzyl-1-(2-methoxybenzyl)pyrrolidine-2-carboxamide **(4gC).**

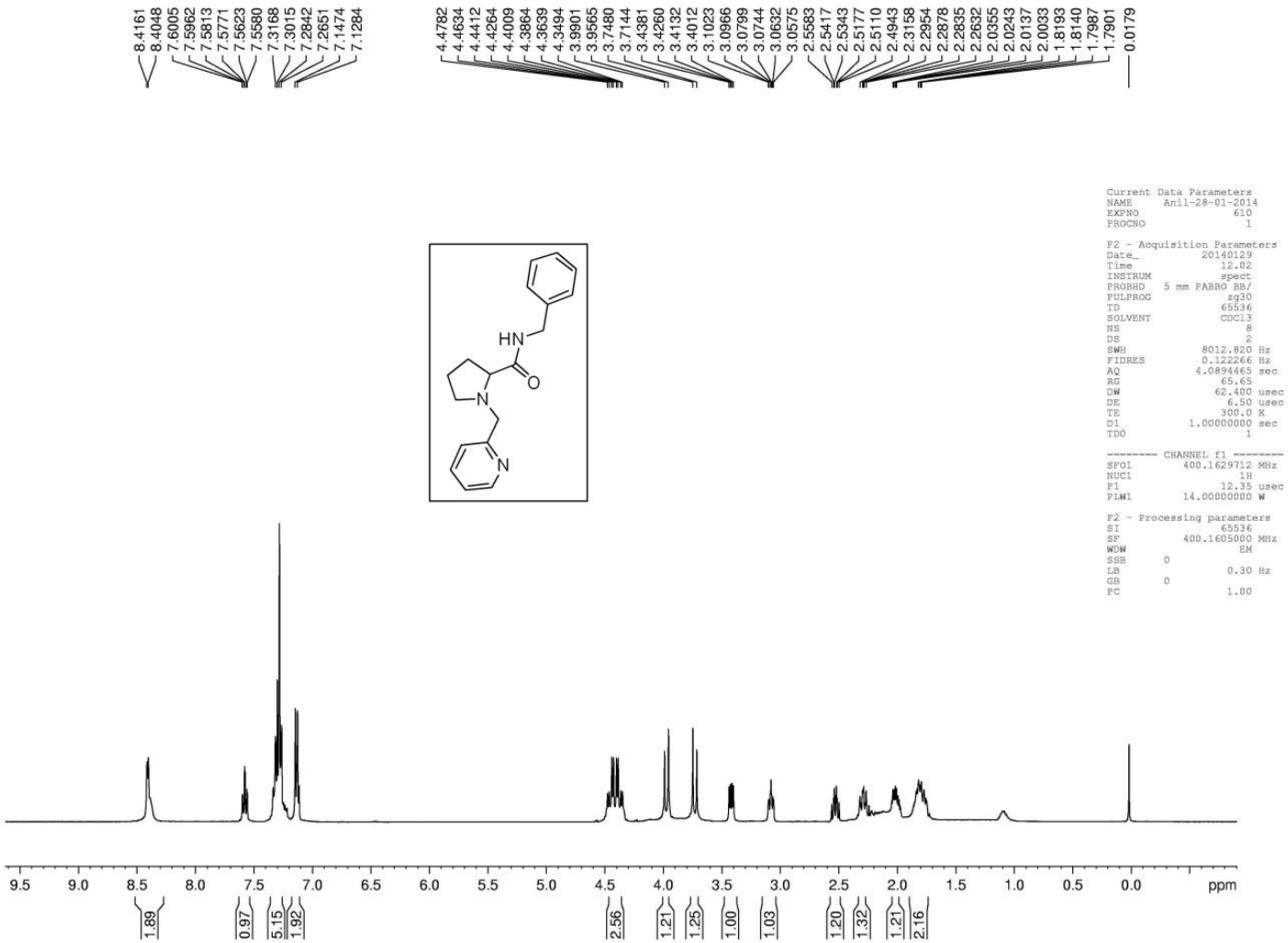

Figure S-76. ^{1}H-NMR spectrum of *N*-benzyl-1-(pyridin-2-ylmethyl)pyrrolidine-2-carboxamide **(4jC)**.

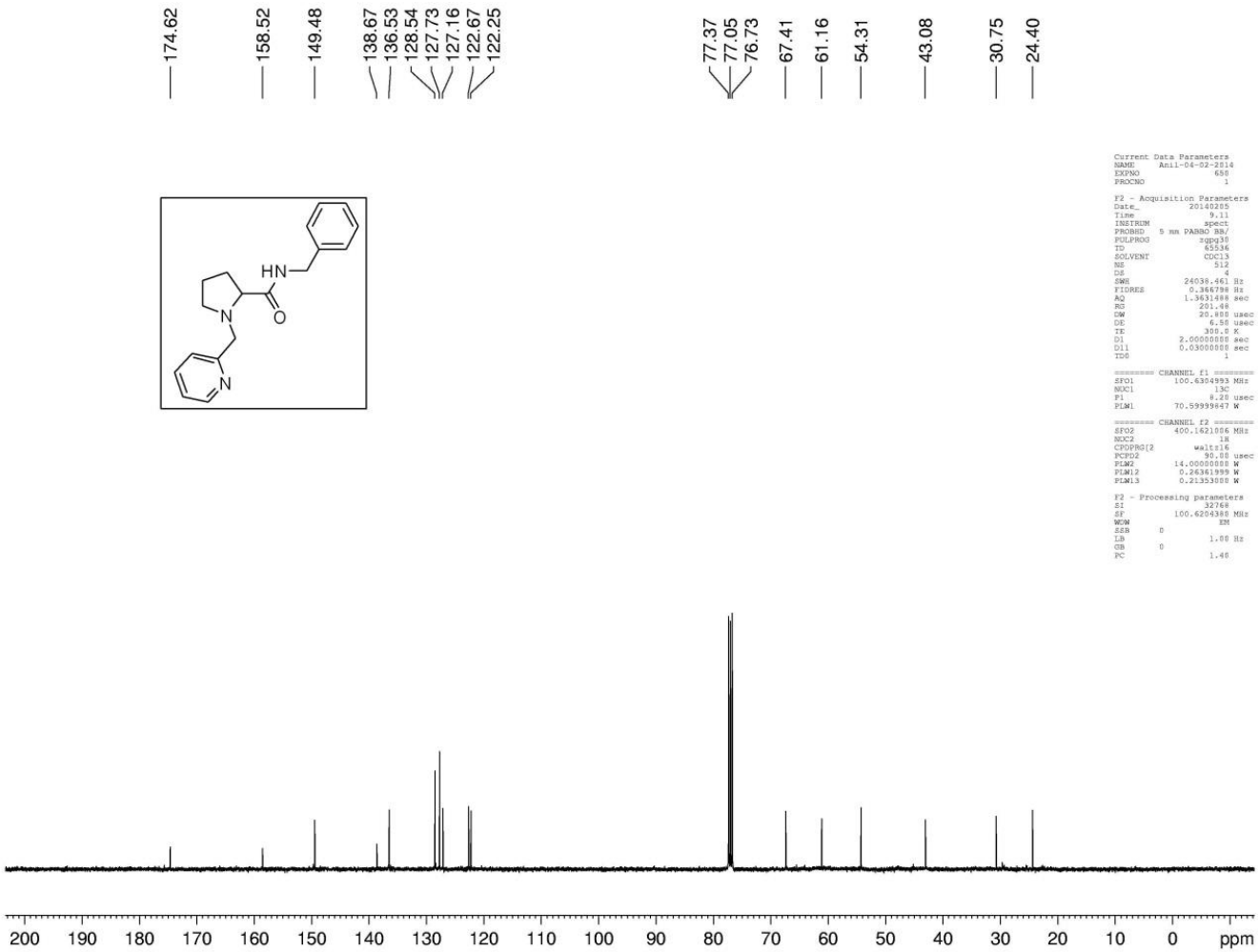

Figure S-77. ^{13}C-NMR spectrum of *N*-benzyl-1-(pyridin-2-ylmethyl)pyrrolidine-2-carboxamide **(4jC)**.

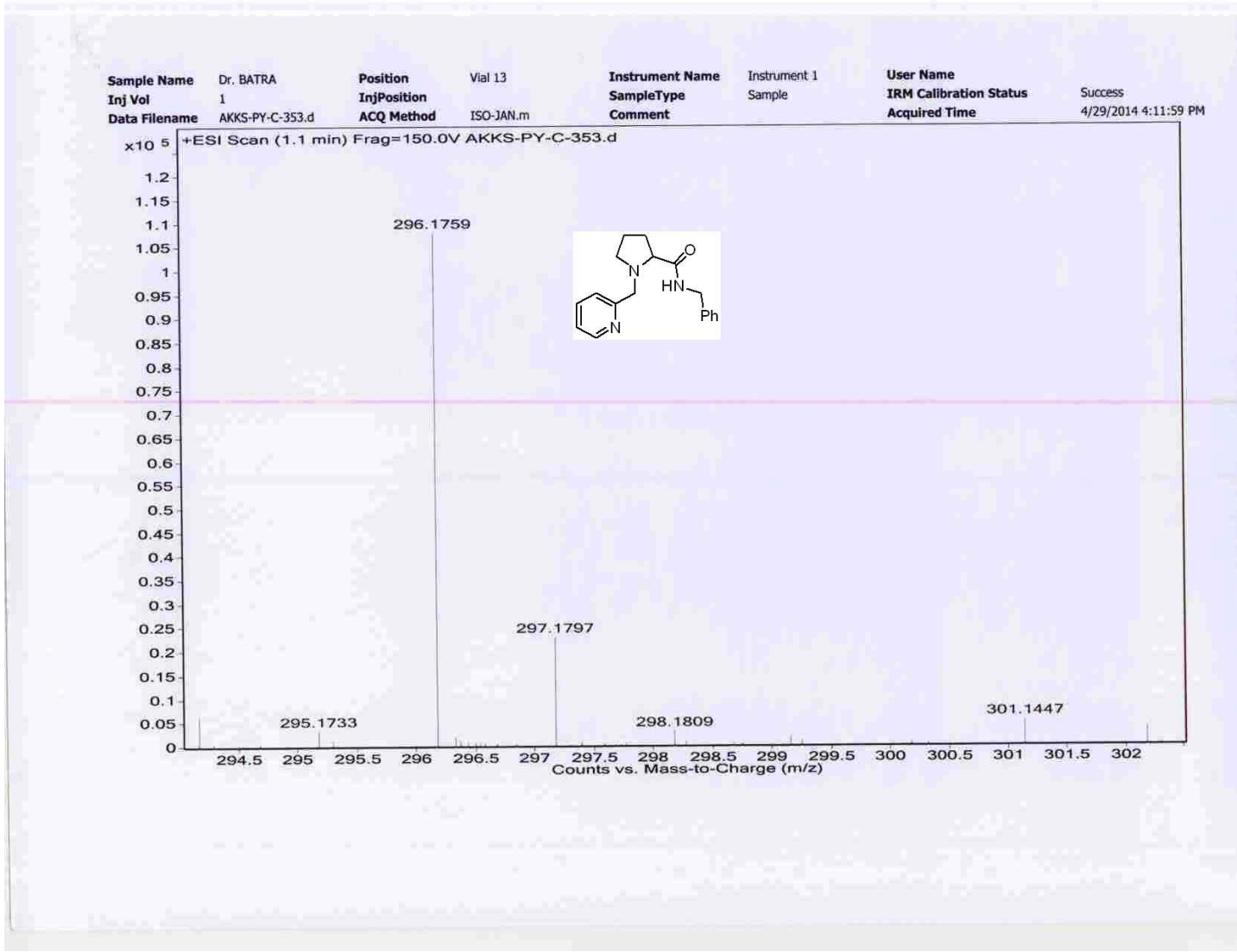

Figure S-78. HRMS spectrum of *N*-benzyl-1-(pyridin-2-ylmethyl)pyrrolidine-2-carboxamide **(4jC)**.

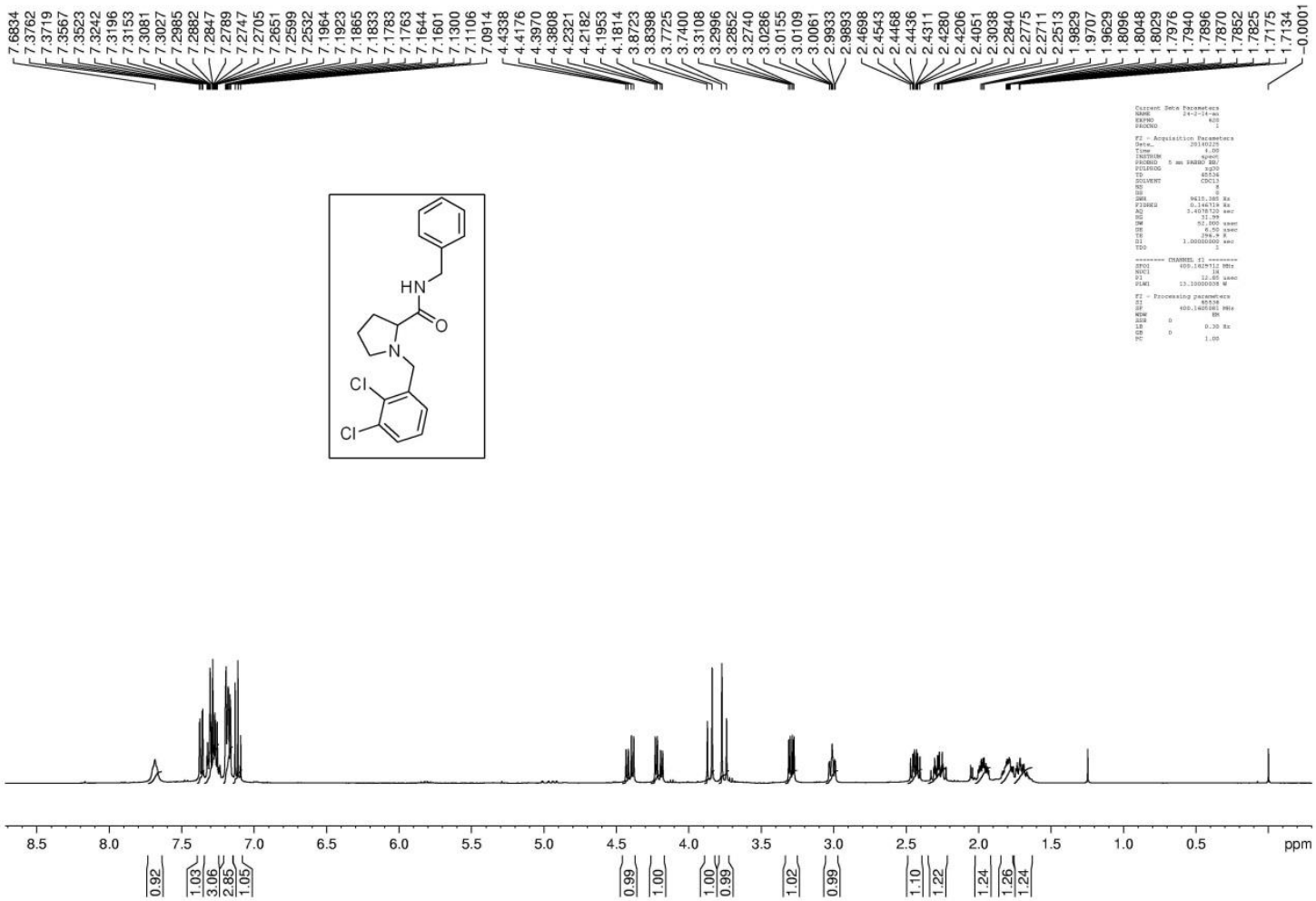

Figure S-79. ^{1}H-NMR spectrum of *N*-benzyl-1-(2,3-dichlorobenzyl)pyrrolidine-2-carboxamide **(4lC).**

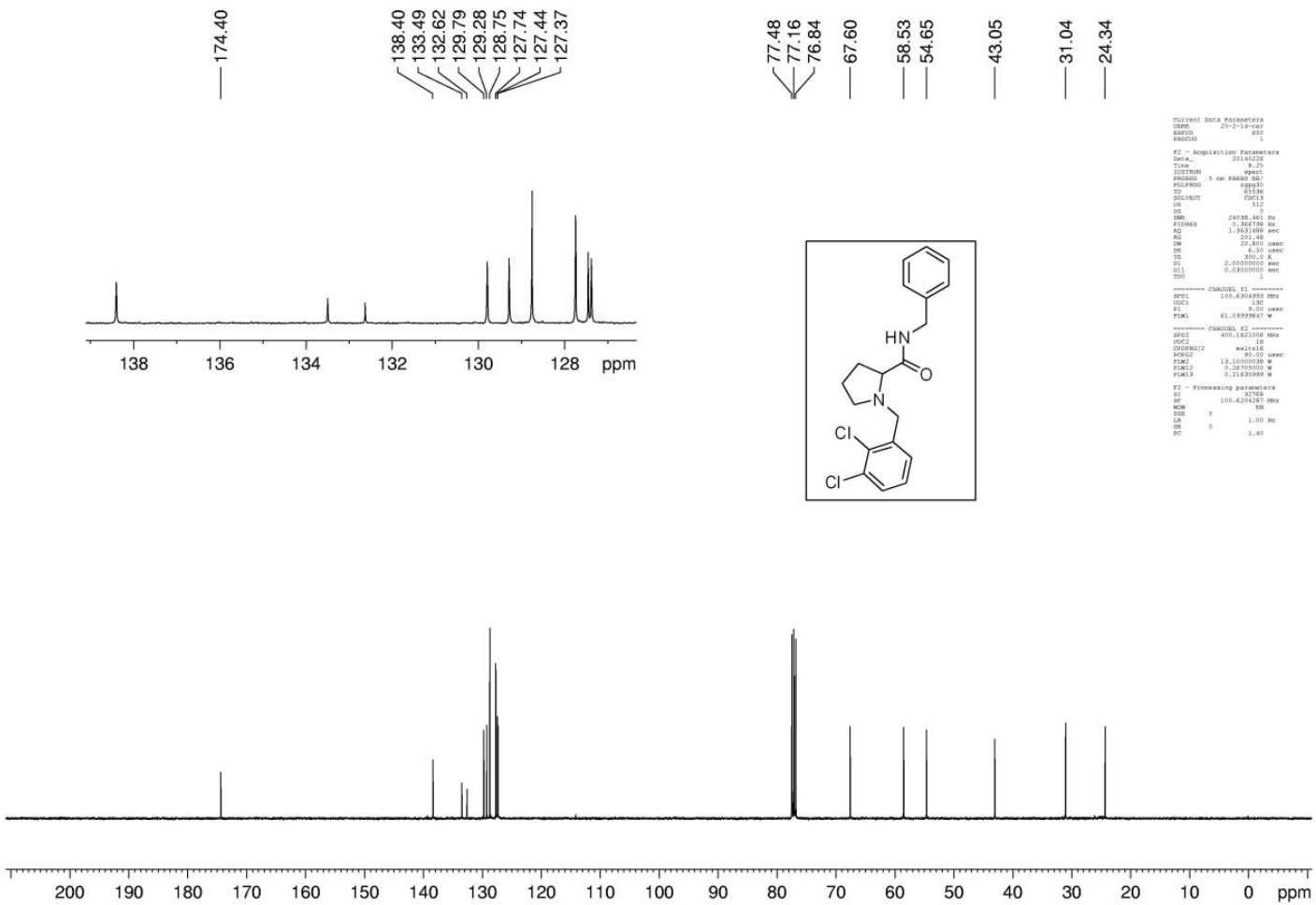

Figure S-80. ^{13}C-NMR spectrum of *N*-benzyl-1-(2,3-dichlorobenzyl)pyrrolidine-2-carboxamide **(4lC).**

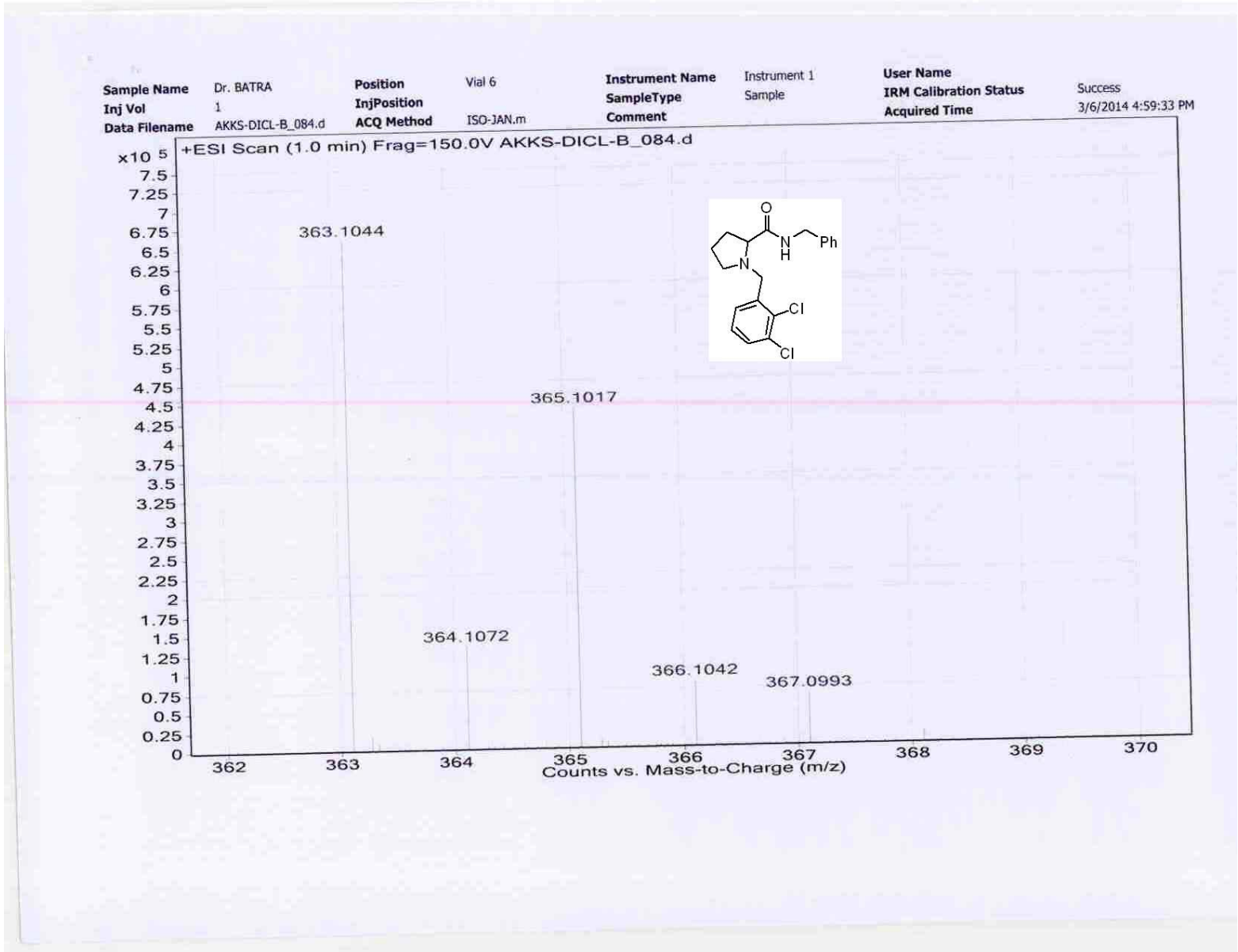

Figure S-81. HRMS spectrum of *N*-benzyl-1-(2,3-dichlorobenzyl)pyrrolidine-2-carboxamide **(4lC).**

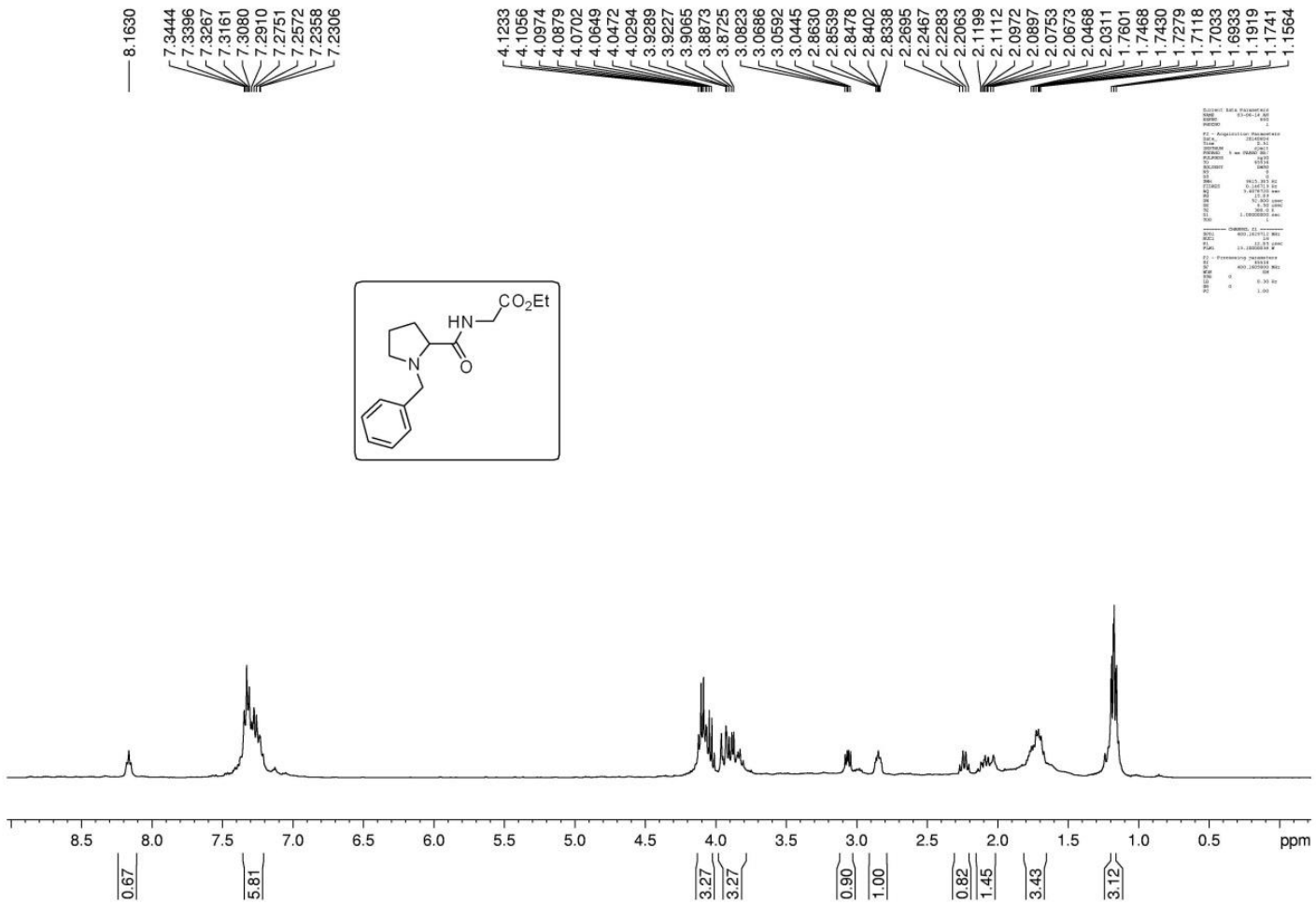

Figure S-82. ^{1}H-NMR spectrum of Ethyl 2-(1-benzylpyrrolidine-2-carboxamido)acetate **(4aD).**

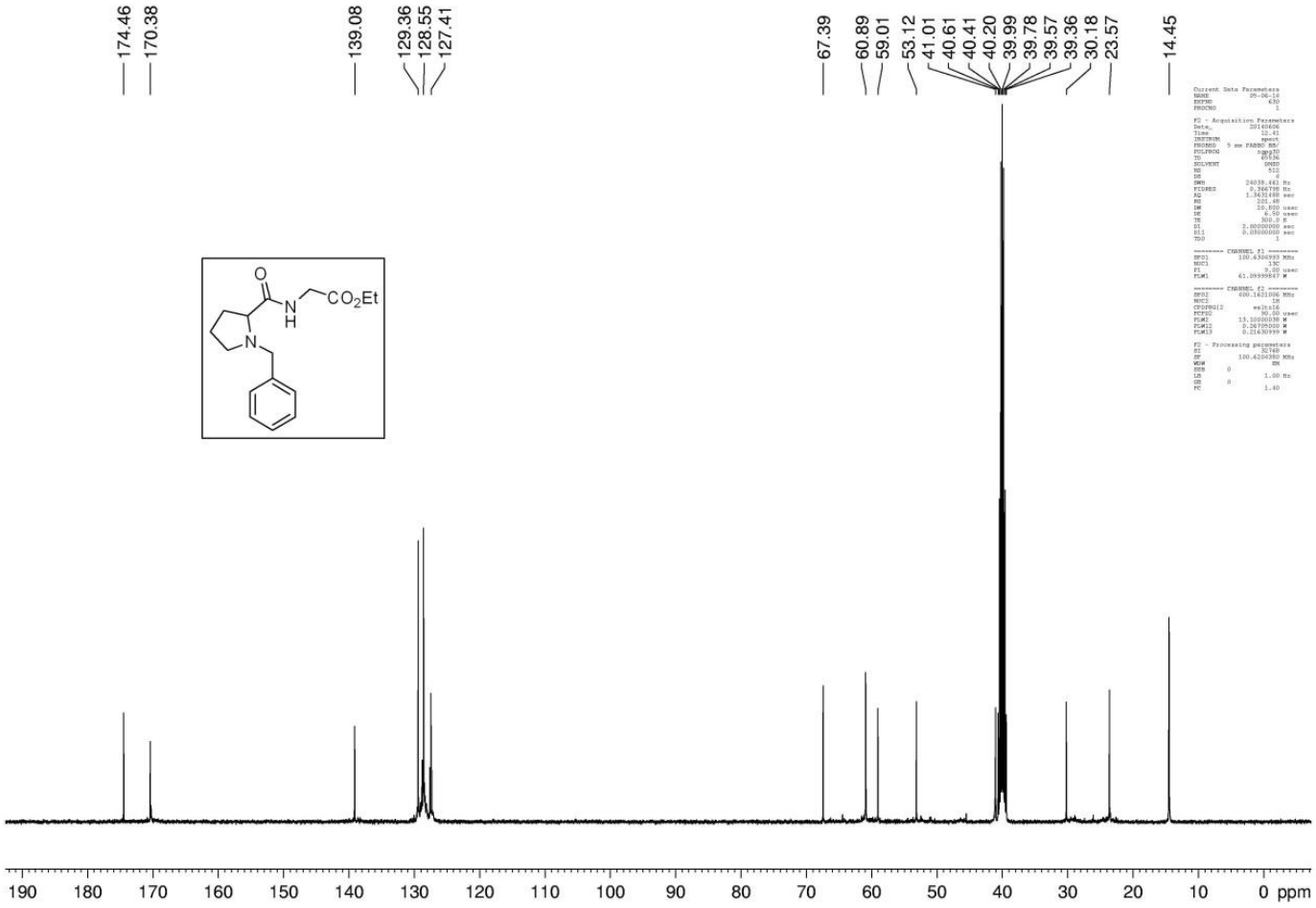

Figure S-83. ^{13}C-NMR spectrum ofEthyl 2-(1-benzylpyrrolidine-2-carboxamido)acetate **(4aD)**

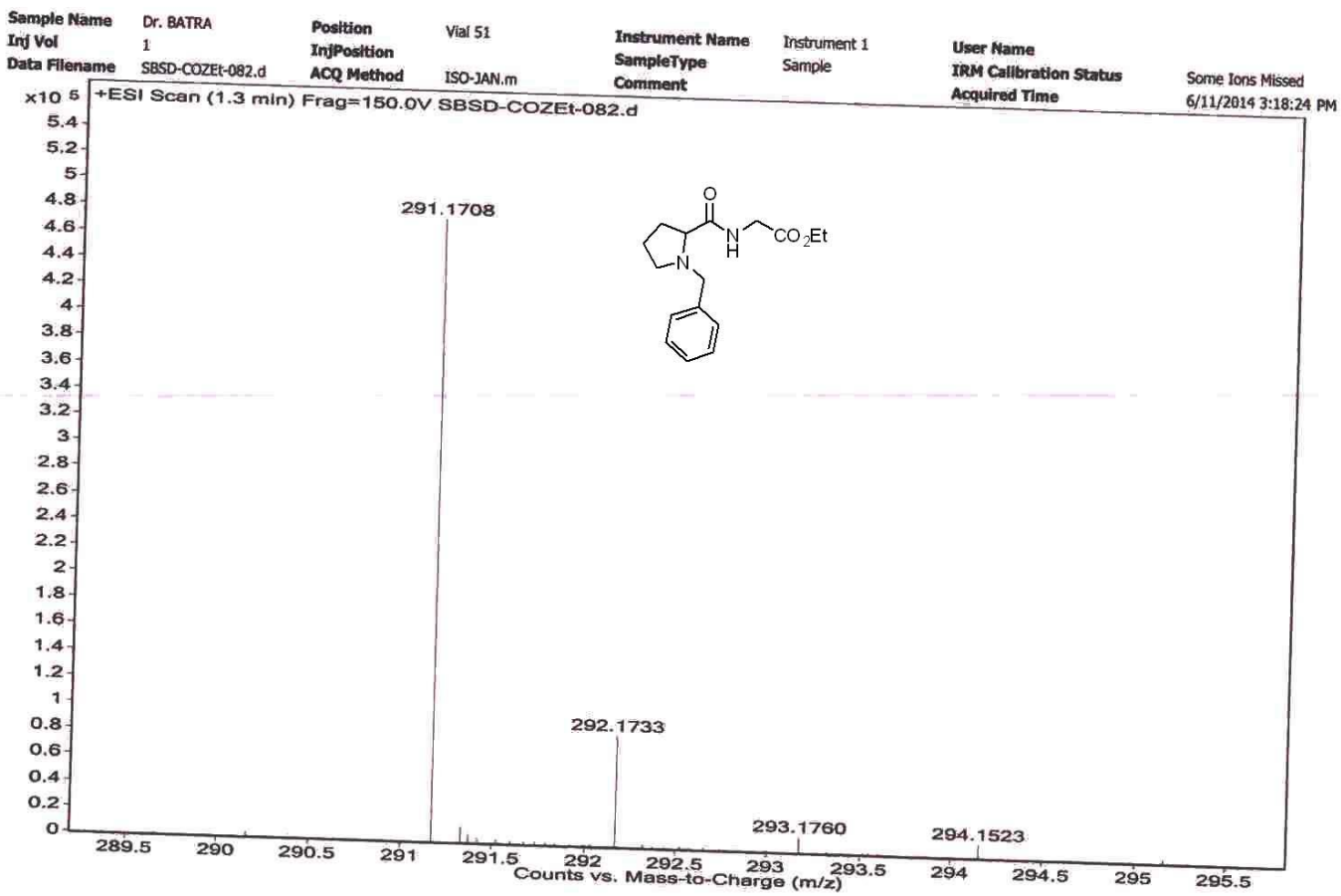

Figure S-84. HRMS spectrum of Ethyl 2-(1-benzylpyrrolidine-2-carboxamido)acetate **(4aD)**

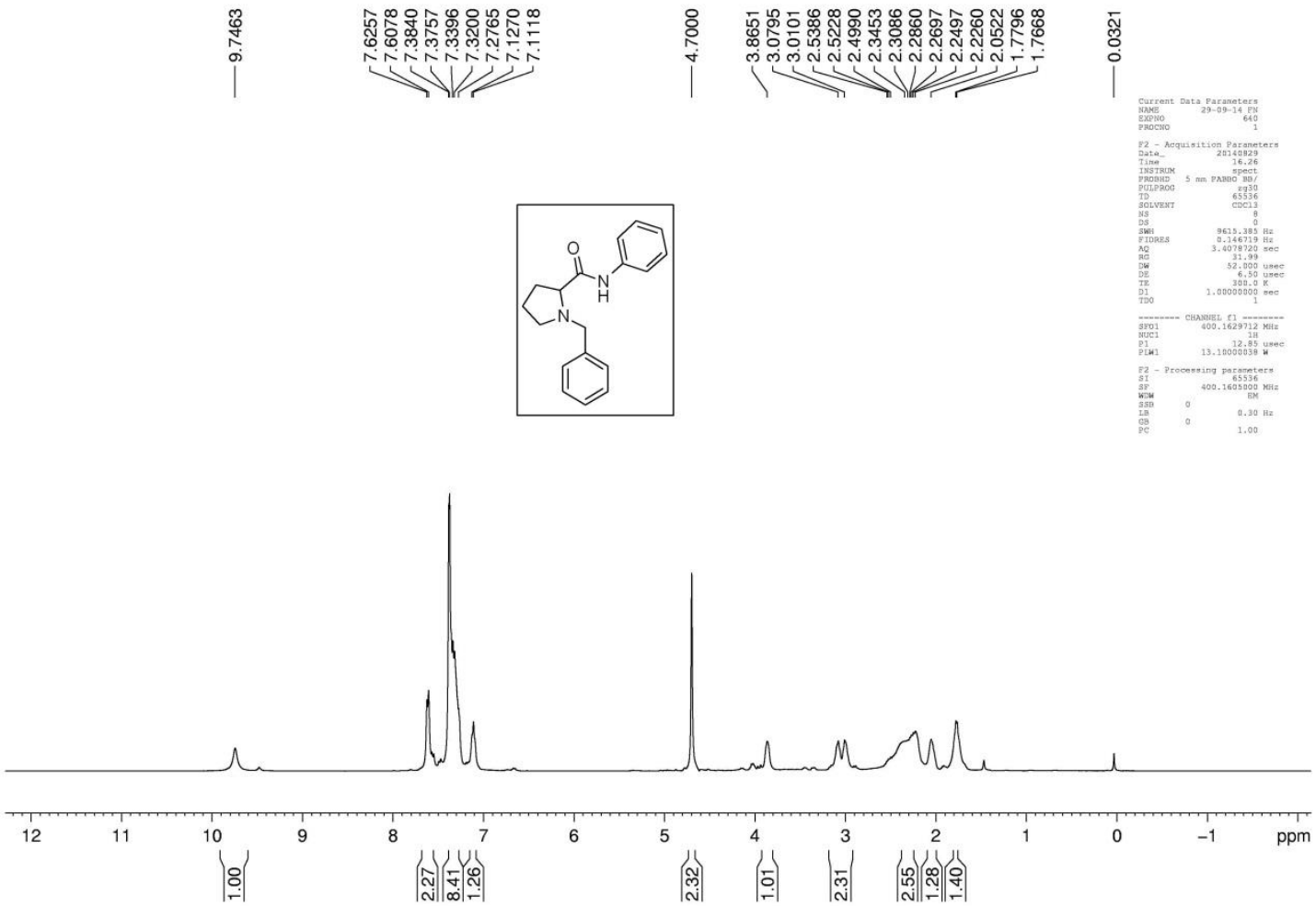

Figure S-85. ^{1}H-NMR spectrum of 1-Benzyl-*N*-phenylpyrrolidine-2-carboxamide (**4aE**).

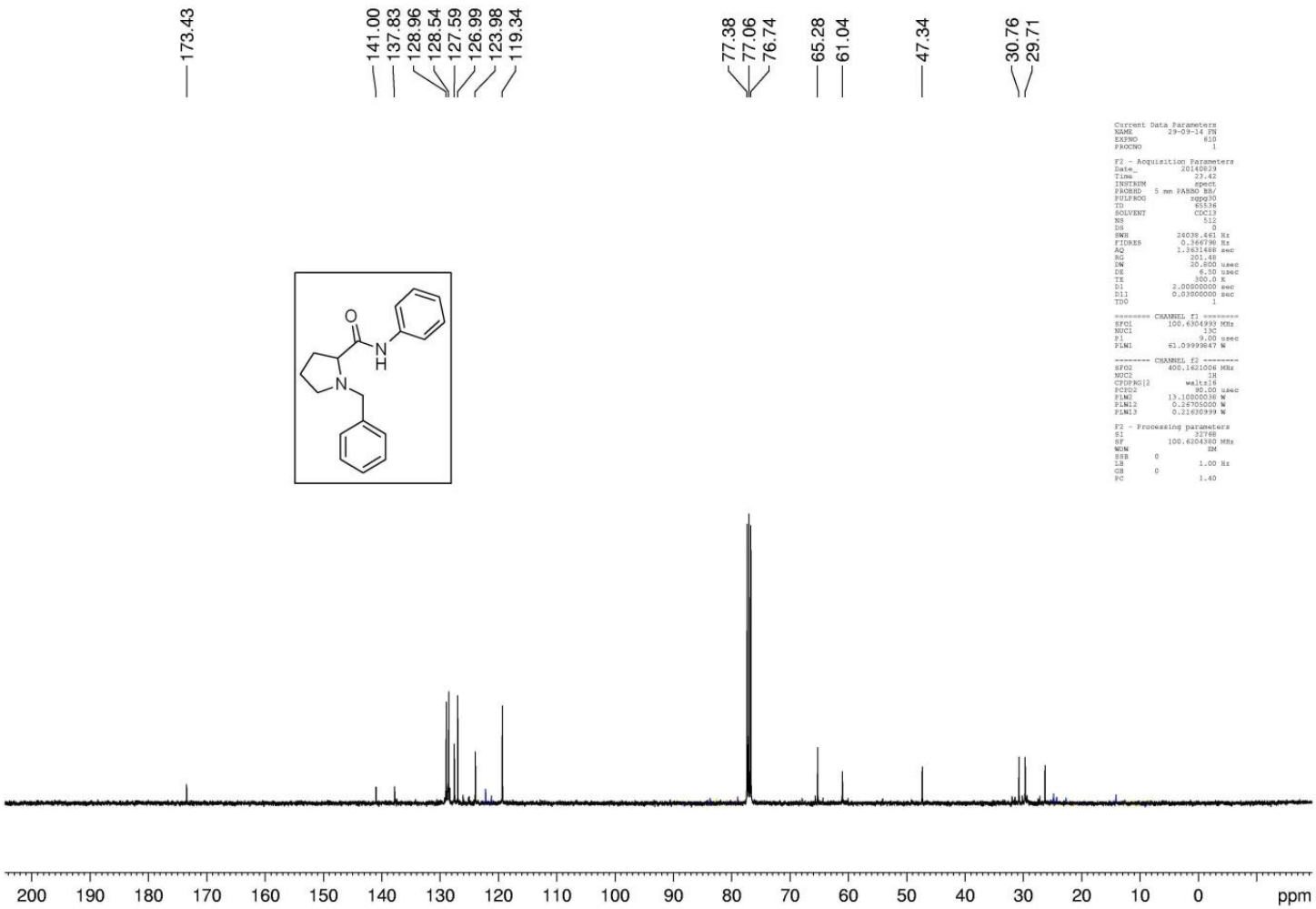

Figure S-86. ^{13}C-NMR spectrum of 1-Benzyl-*N*-phenylpyrrolidine-2-carboxamide (**4aE**).

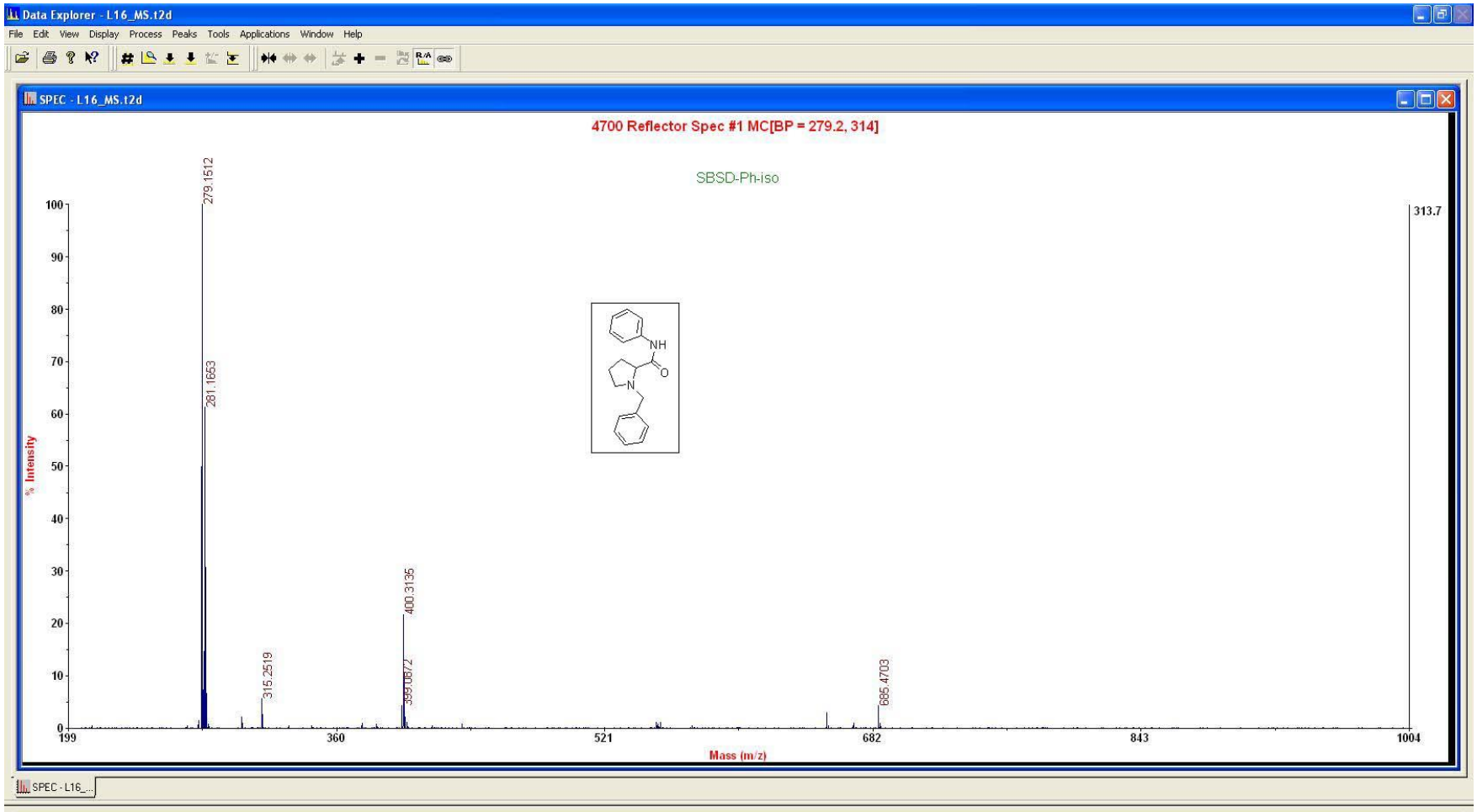

Figure S-87. HRMS spectrum of 1-Benzyl-*N*-phenylpyrrolidine-2-carboxamide (**4aE**).

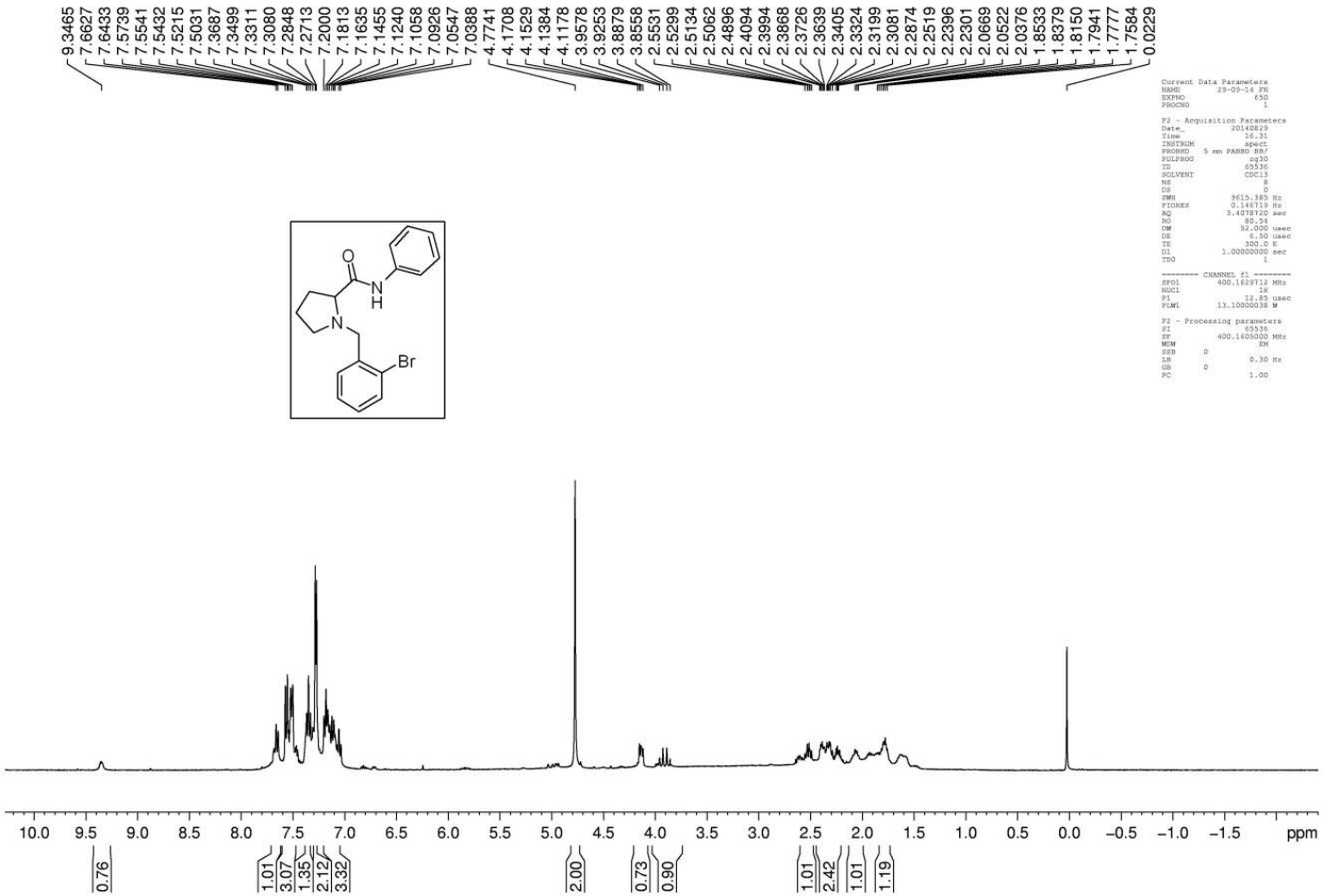

Figure S-88. ^{1}H-NMR spectrum of 1-(2-Bromobenzyl)-*N*-phenylpyrrolidine-2-carboxamide (**4eE**).

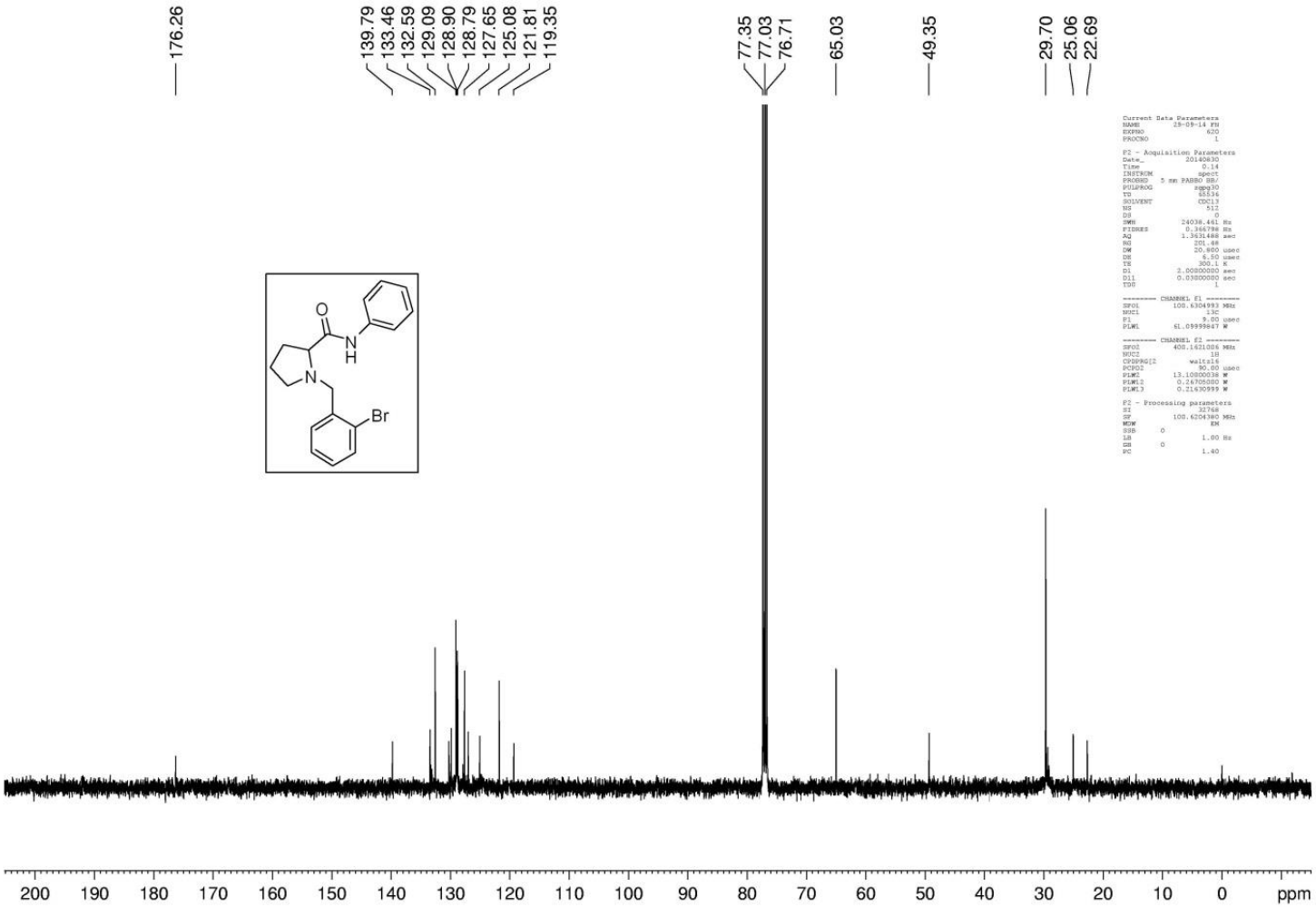

Figure S-89. ^{13}C-NMR spectrum of -(2-Bromobenzyl)-*N*-phenylpyrrolidine-2-carboxamide (**4eE)**

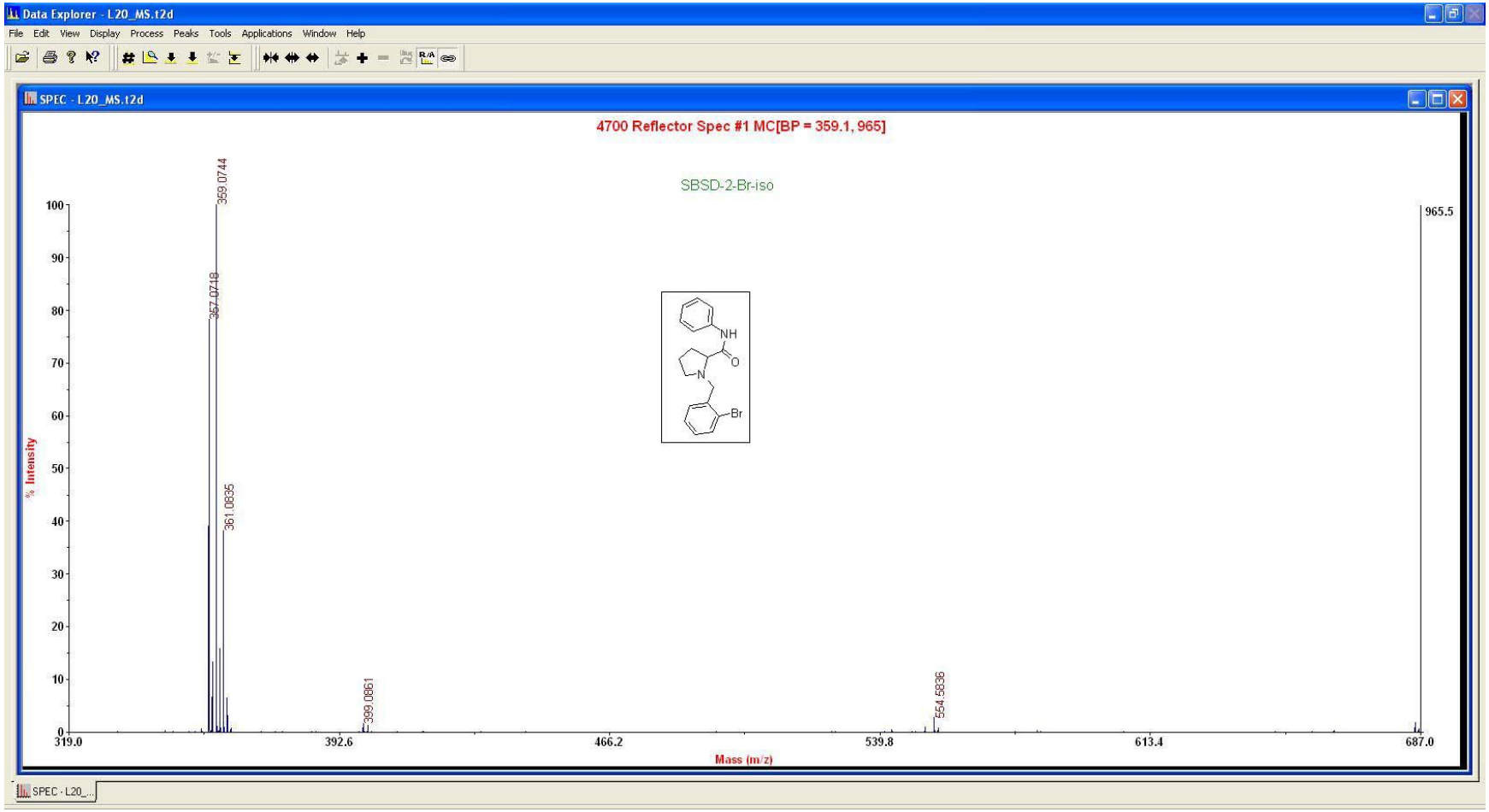

Figure S-90. HRMS spectrum of 1-(2-Bromobenzyl)-*N*-phenylpyrrolidine-2-carboxamide (**4eE)**

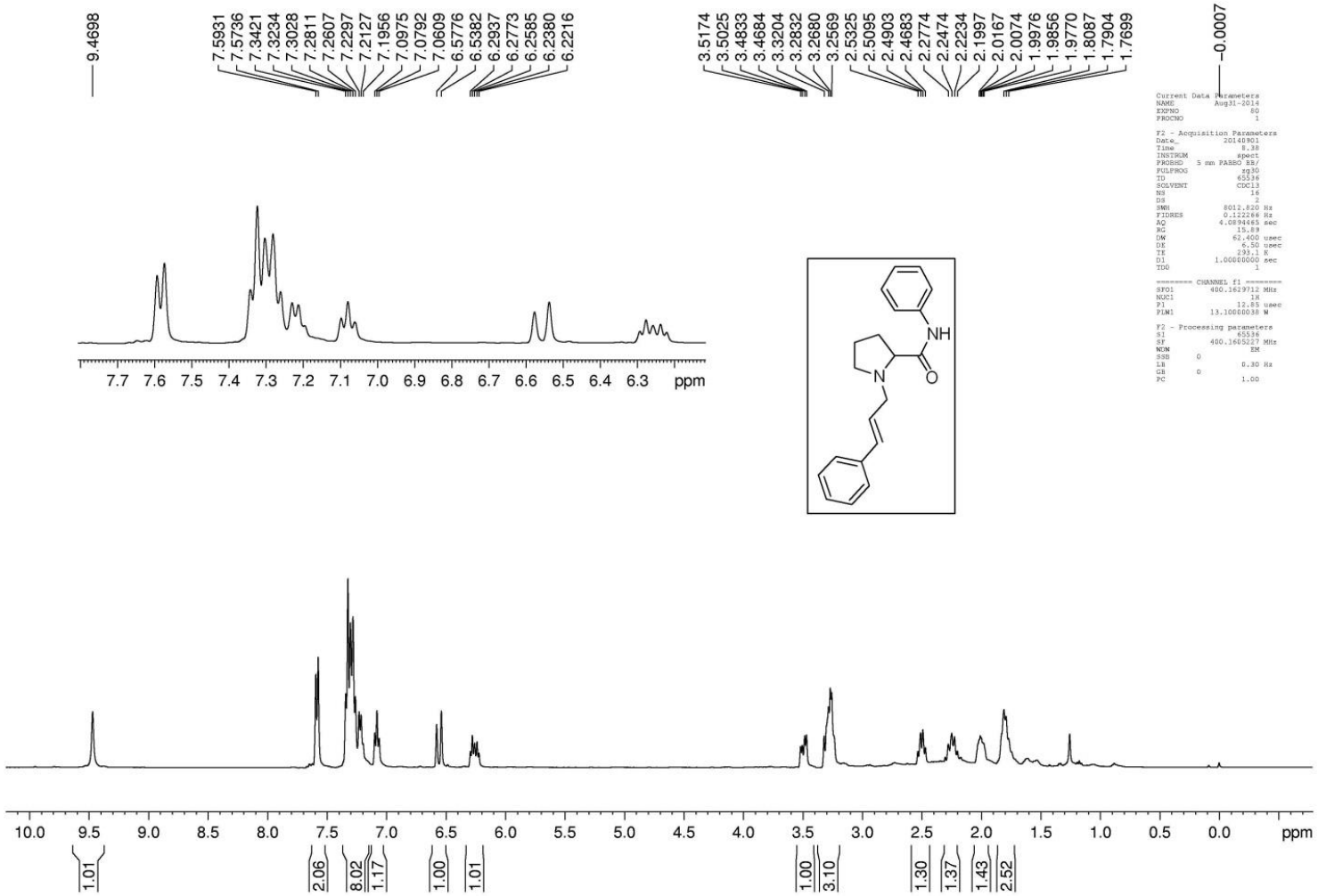

Figure S-91. ^{1}H-NMR spectrum of 1-Cinnamyl-*N*-phenylpyrrolidine-2-carboxamide (**4lE**).

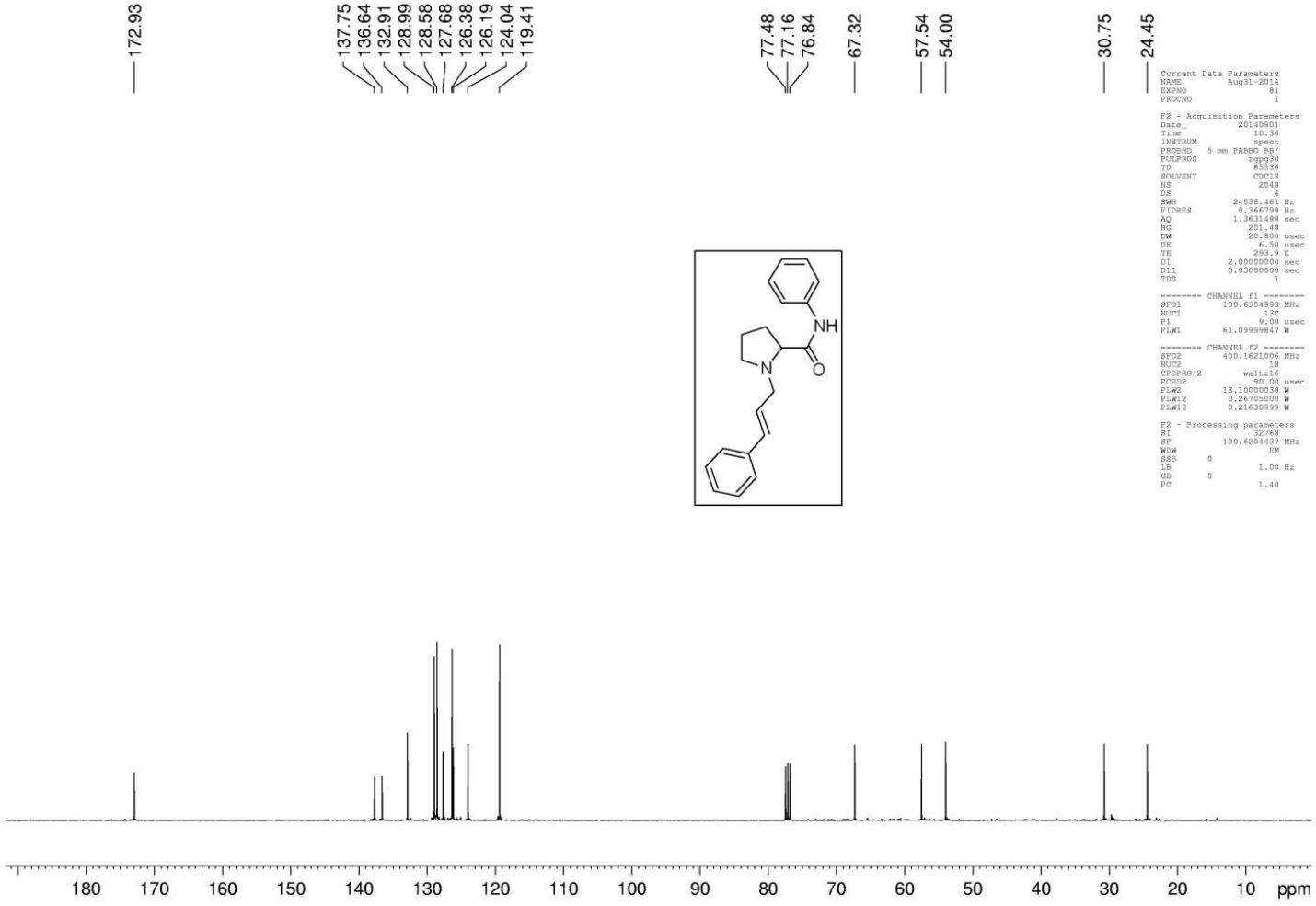

Figure S-92. ^{13}C-NMR spectrum of 1-Cinnamyl-*N*-phenylpyrrolidine-2-carboxamide (**4lE**).

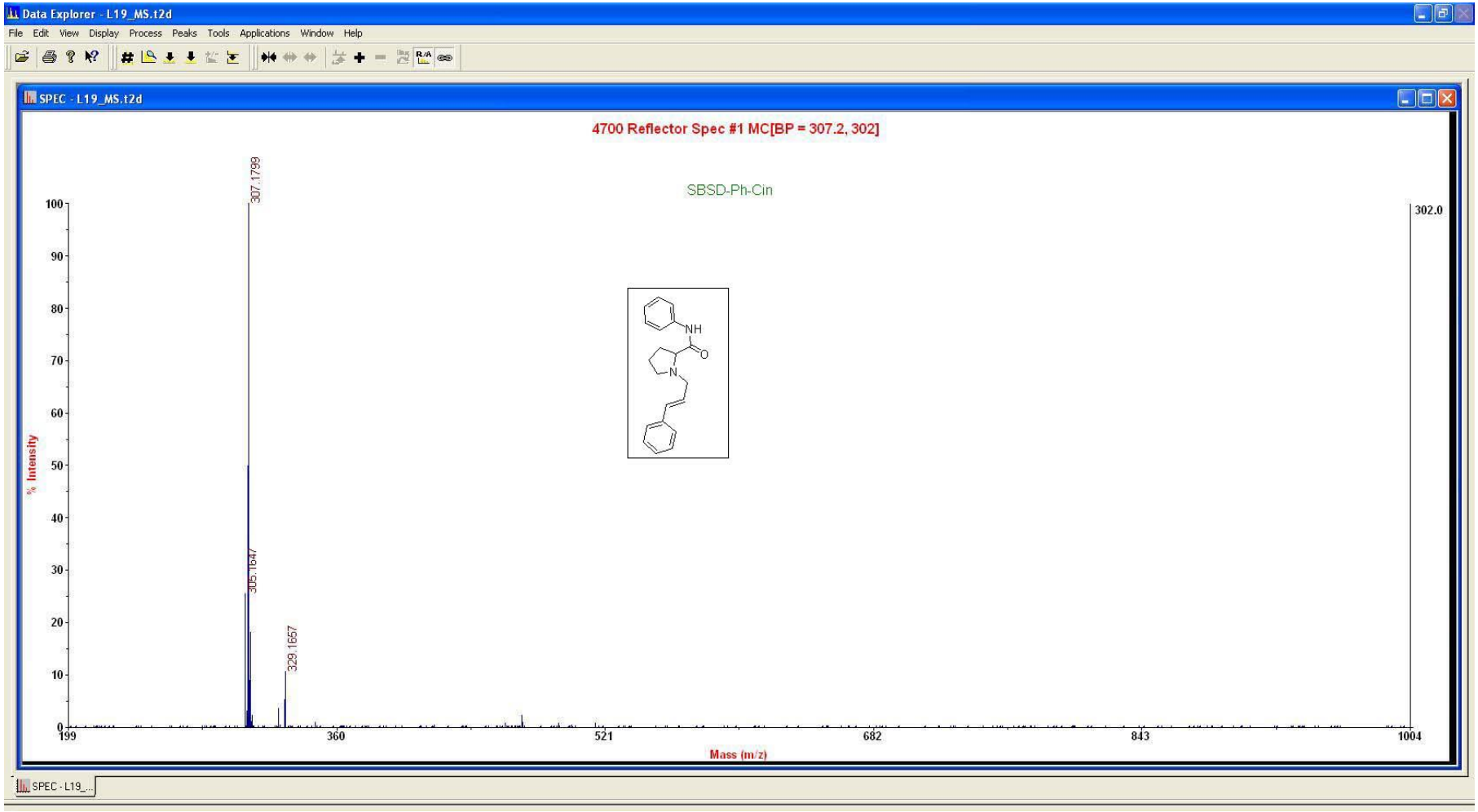

Figure S-93. HRMS spectrum of 1-Cinnamyl-*N*-phenylpyrrolidine-2-carboxamide (**4lE**).

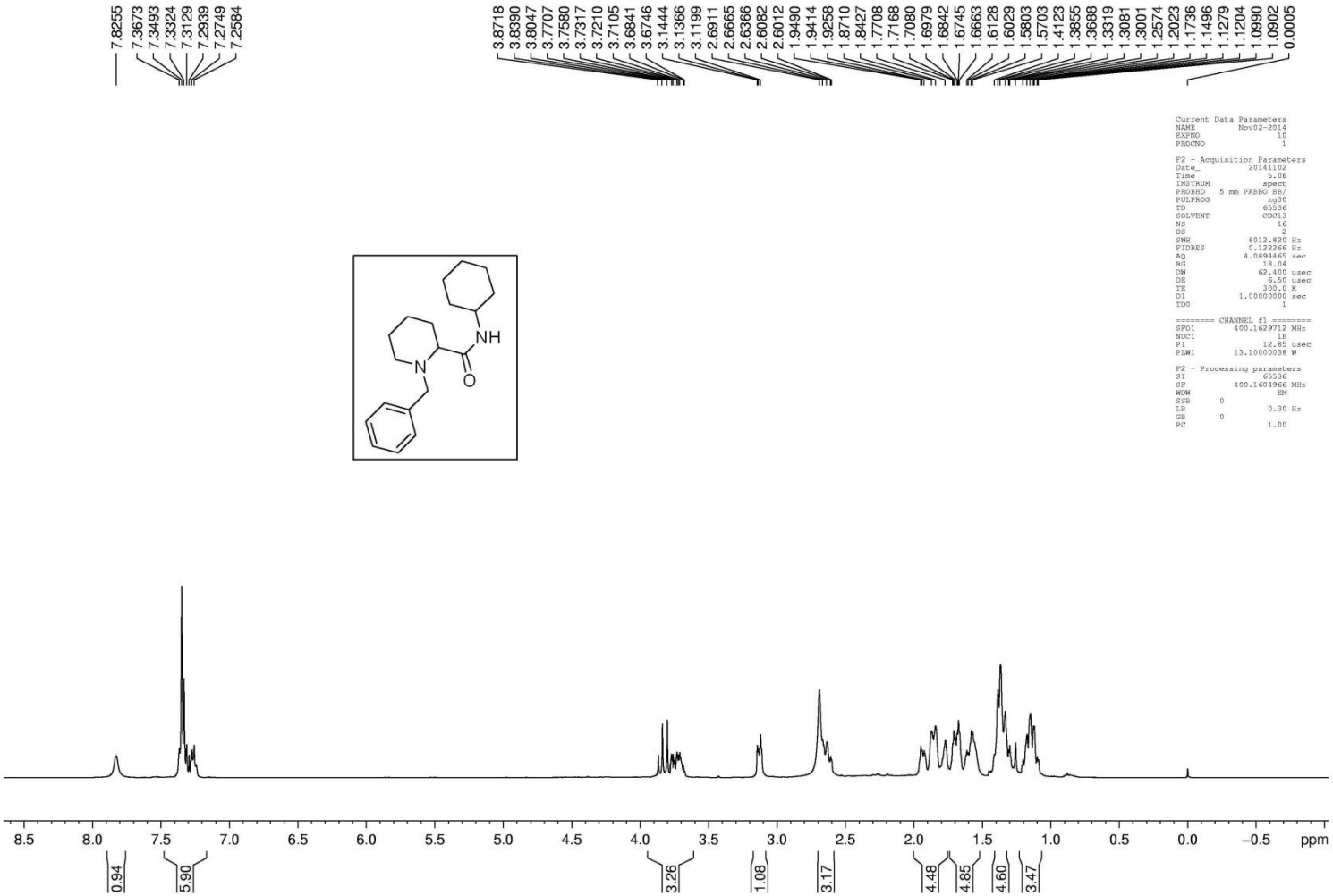

Figure S-94. ^{1}H-NMR spectrum of 1-Benzyl-*N*-cyclohexylpiperidine-2-carboxamide (**5aA**).

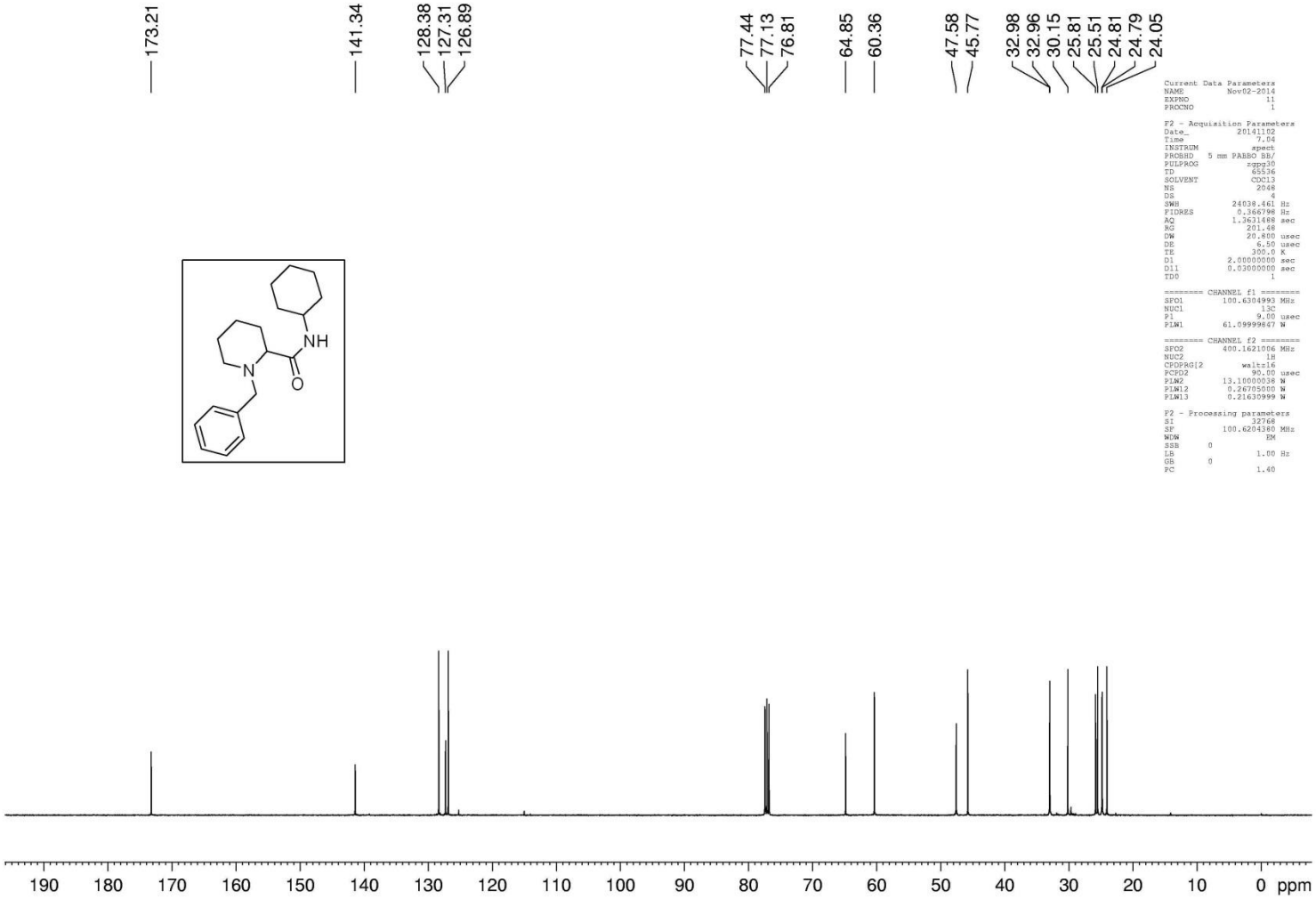

Figure S-95. ^{13}C-NMR spectrum of 1-Benzyl-*N*-cyclohexylpiperidine-2-carboxamide (**5aA**).

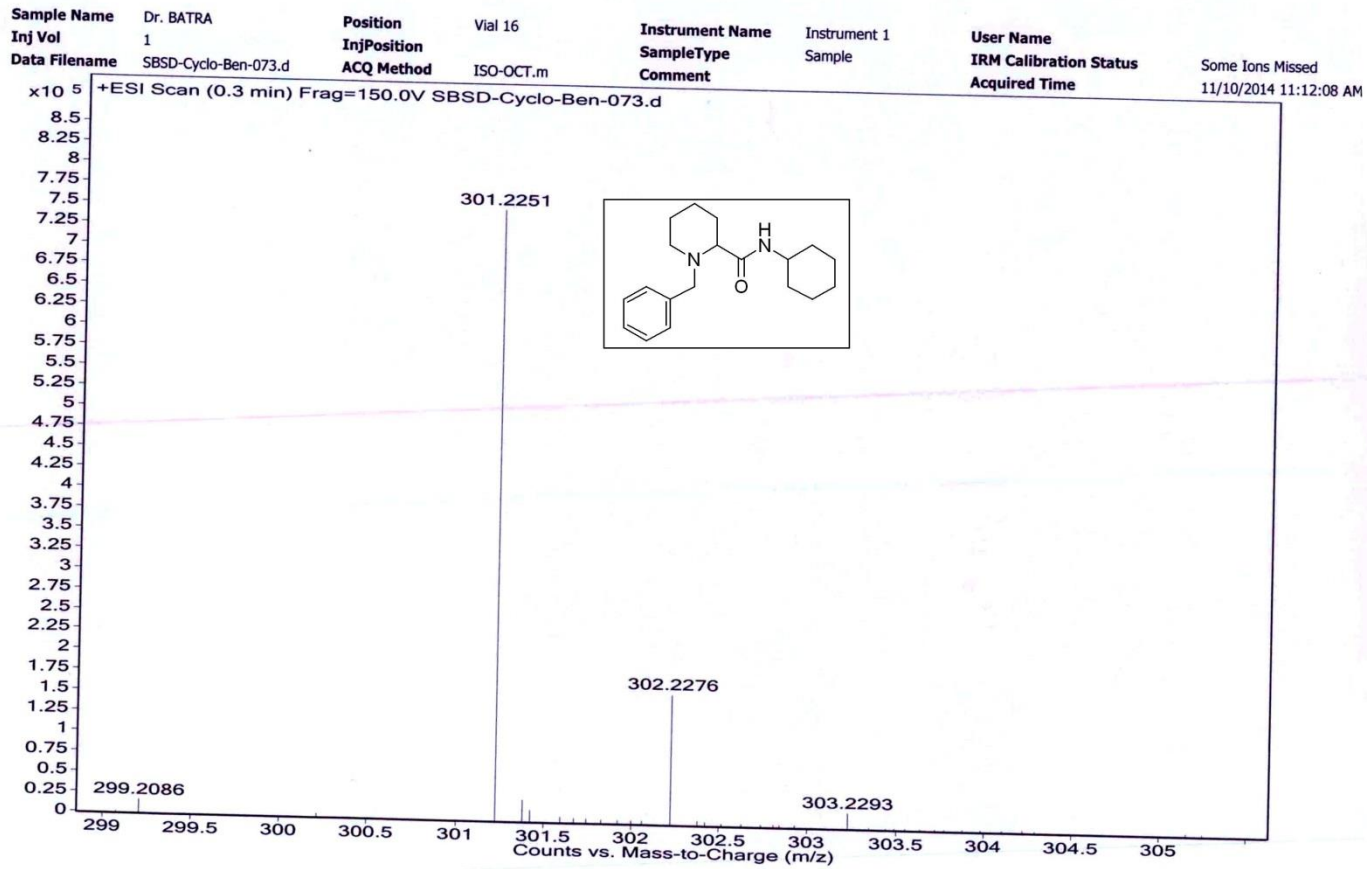

Figure S-96. HRMS spectrum of 1-Benzyl-*N*-cyclohexylpiperidine-2-carboxamide (**5aA**)

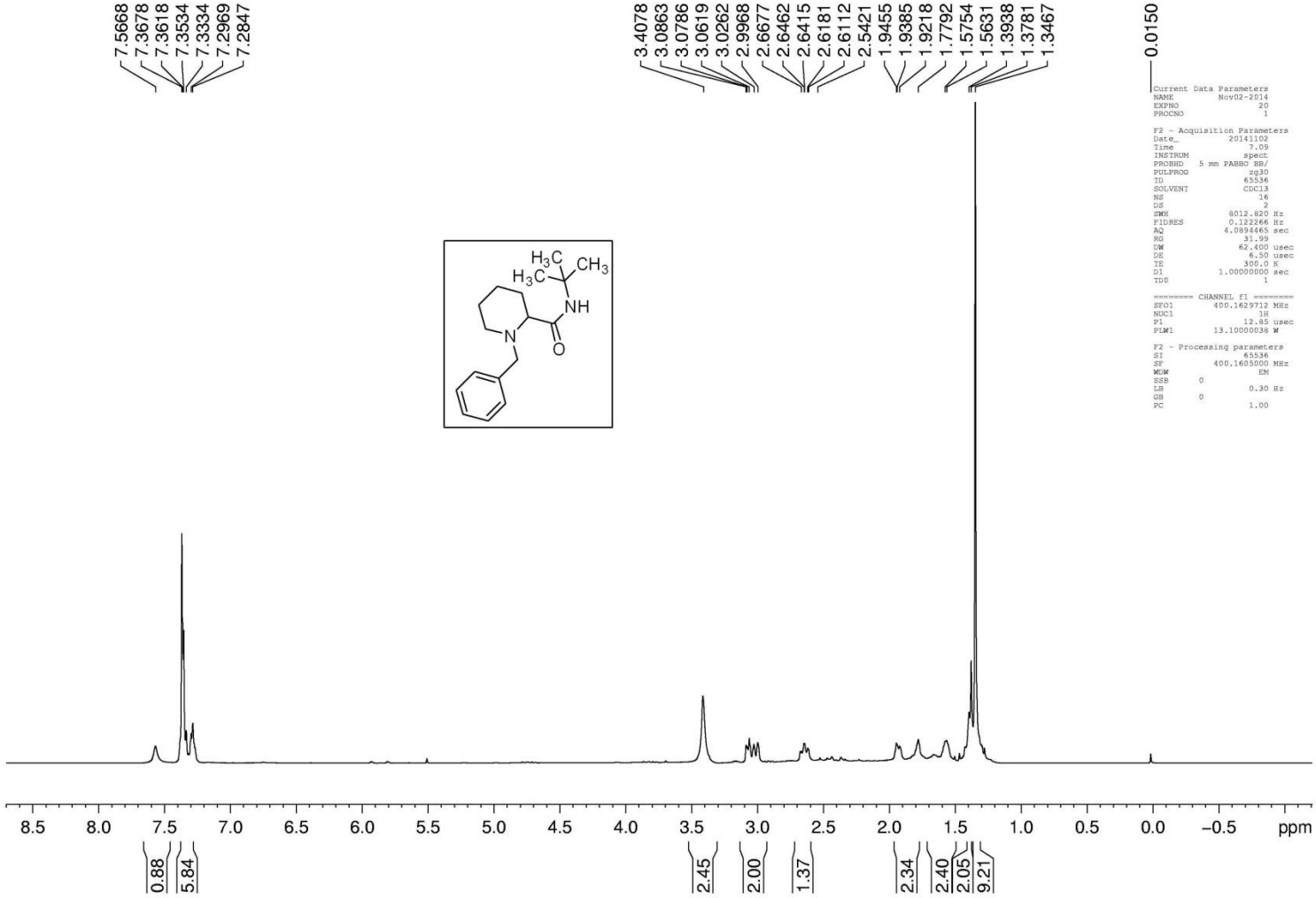

Figure S-97. ^{1}H-NMR spectrum of 1-Benzyl-*N*-*tert*-butylpiperidine-2-carboxamide **(5aB).**

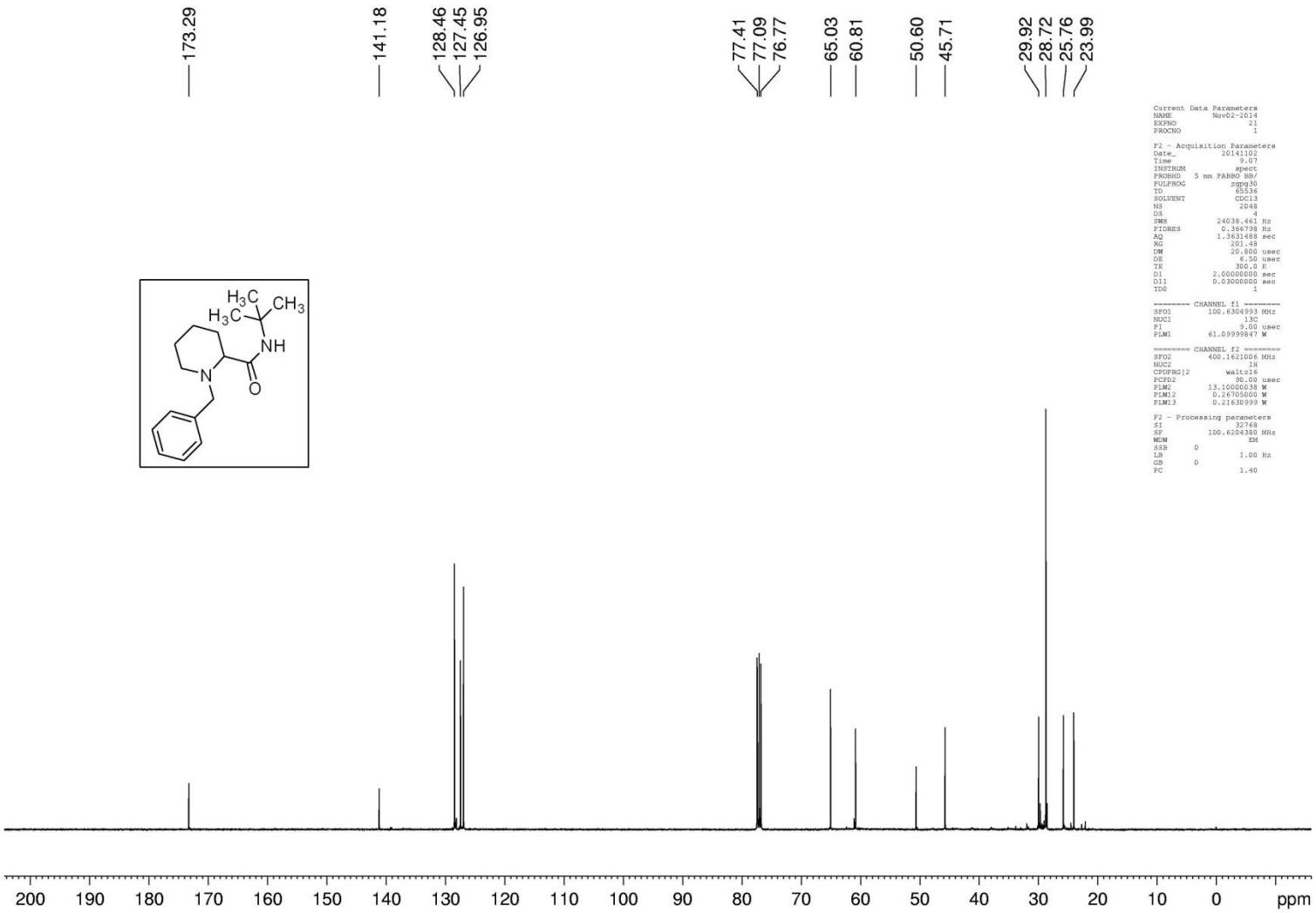

Figure S-98. ^{13}C-NMR spectrum of 1-Benzyl-*N*-*tert*-butylpiperidine-2-carboxamide **(5aB)**.

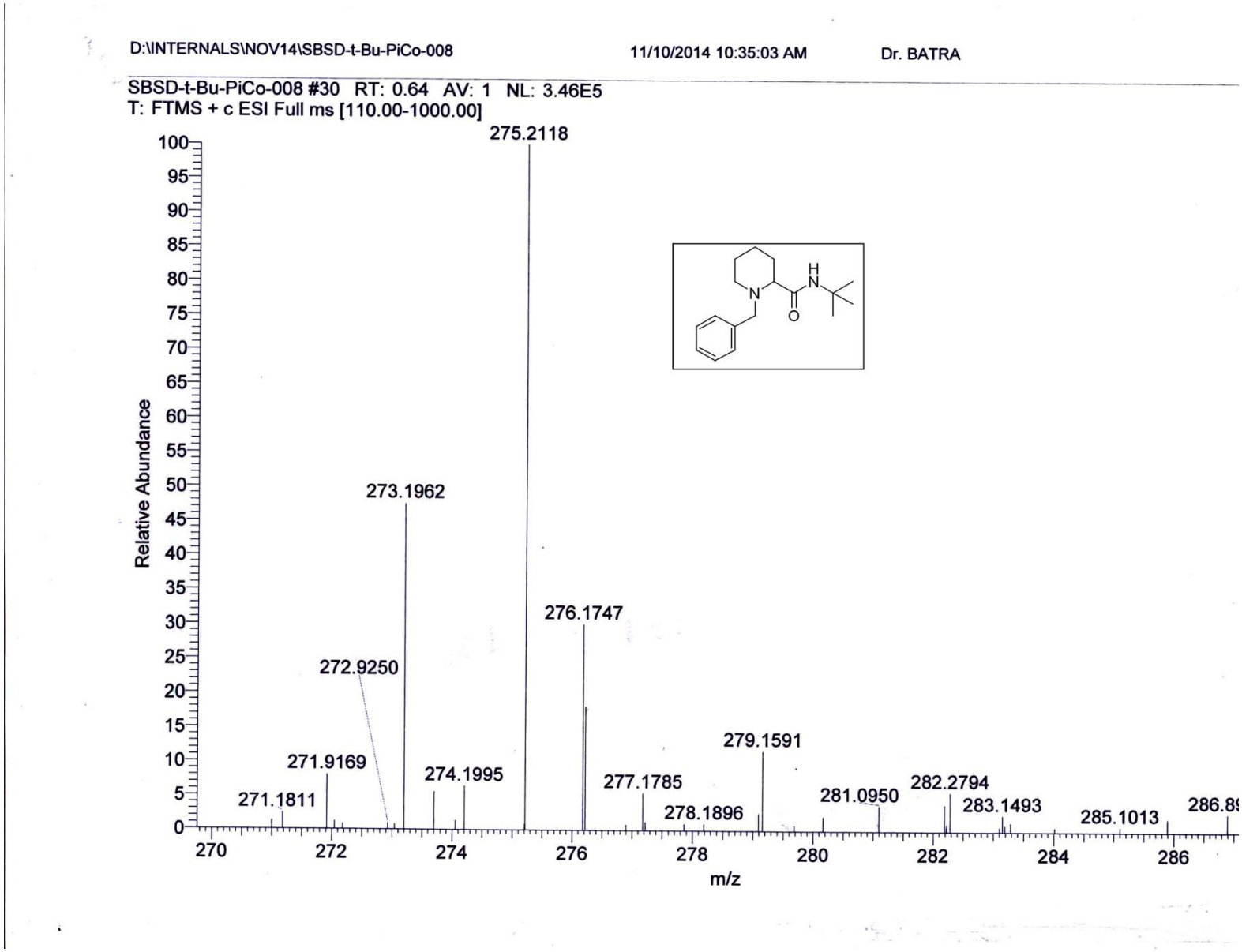

Figure S-99. HRMS spectrum of 1-Benzyl-*N*-*tert*-butylpiperidine-2-carboxamide **(5aB).**

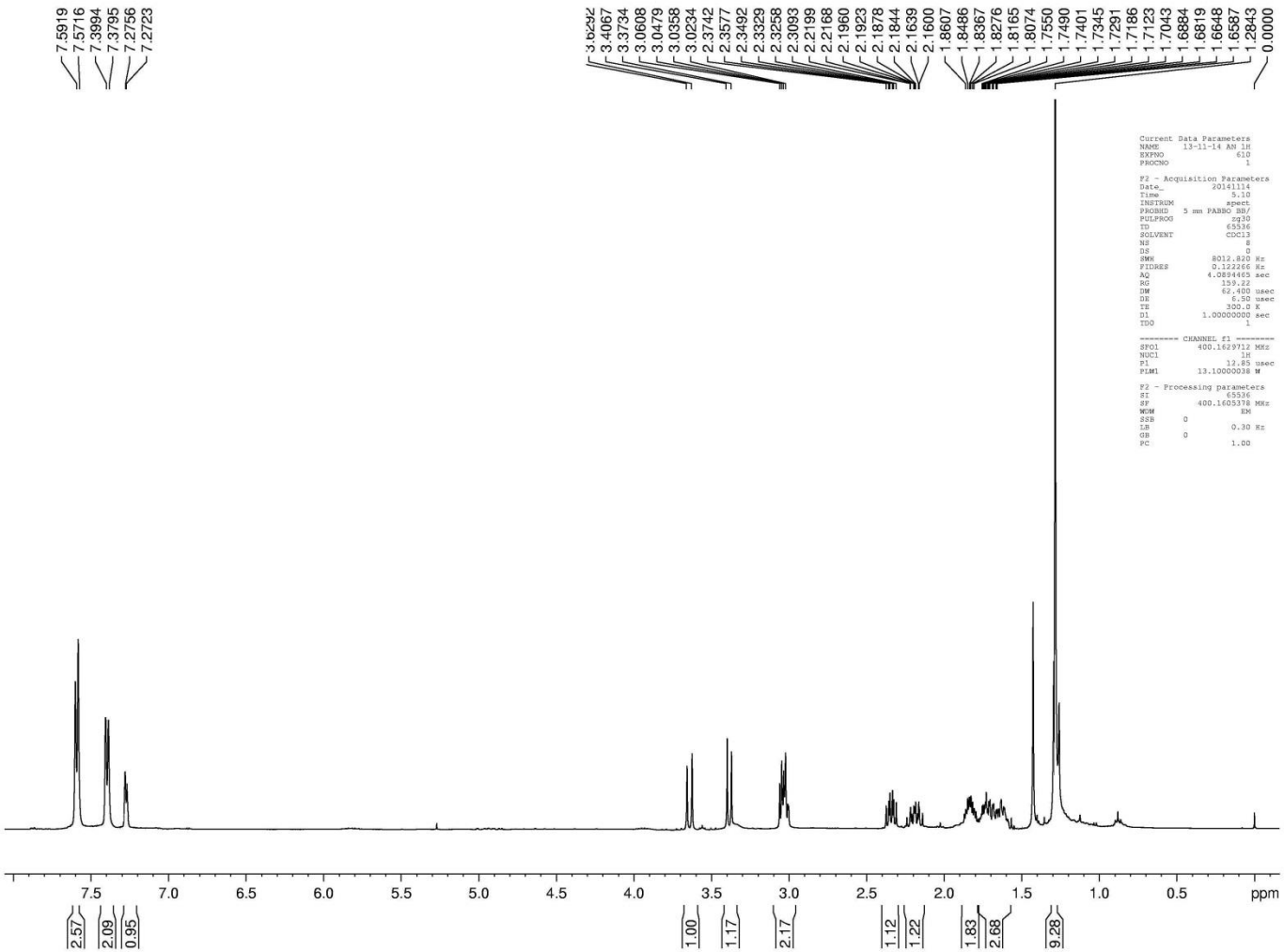

Figure S-100. ^{1}H-NMR spectrum of *N-tert*-butyl-1-(4-cyanobenzyl)piperidine-2-carboxamide (**5bB**).

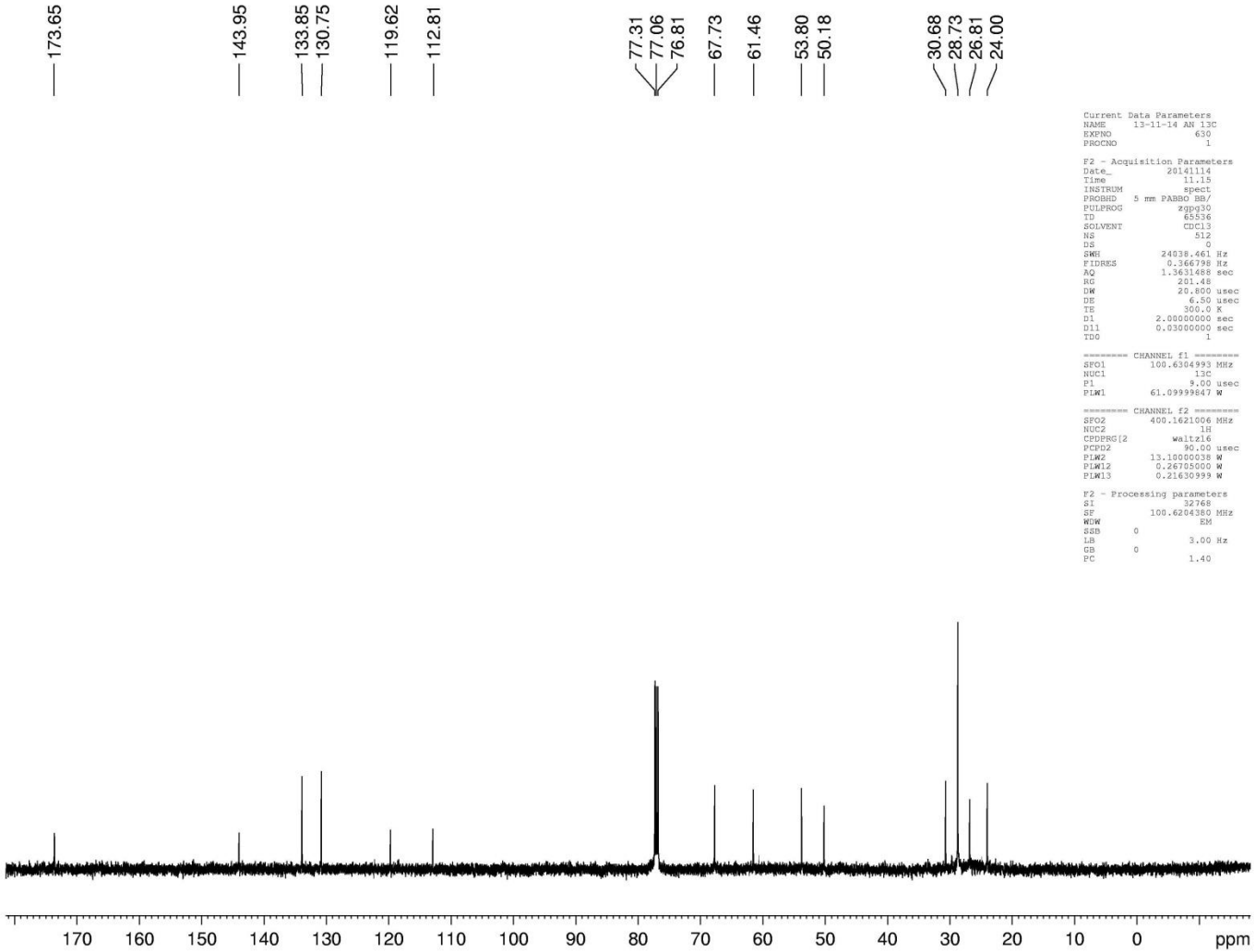

Figure S-101. ^{13}C-NMR spectrum of *N-tert*-butyl-1-(4-cyanobenzyl)piperidine-2-carboxamide (**5bB**).

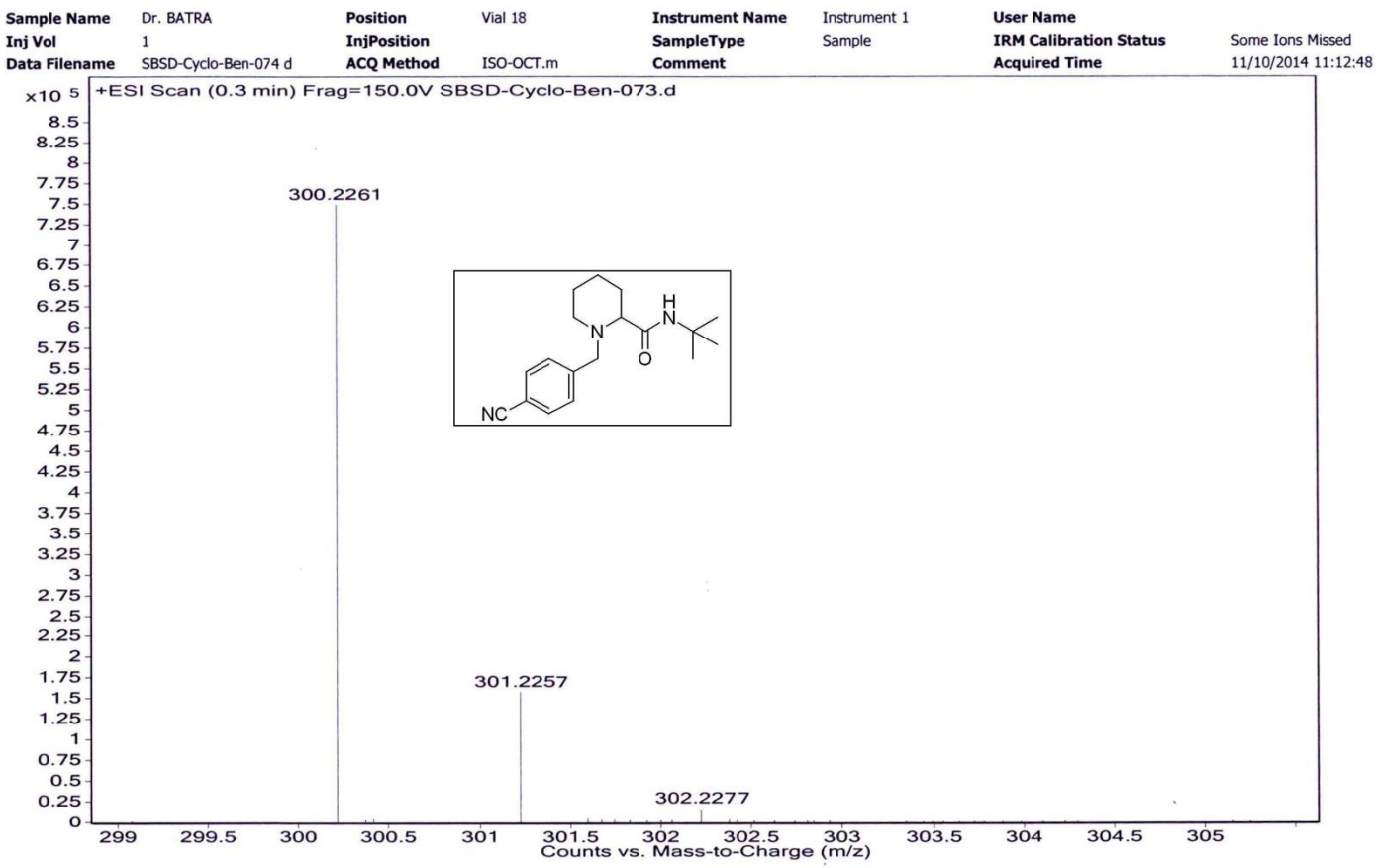

Figure S-102. HRMS spectrum of *N-tert*-butyl-1-(4-cyanobenzyl)piperidine-2-carboxamide (**5bB**).

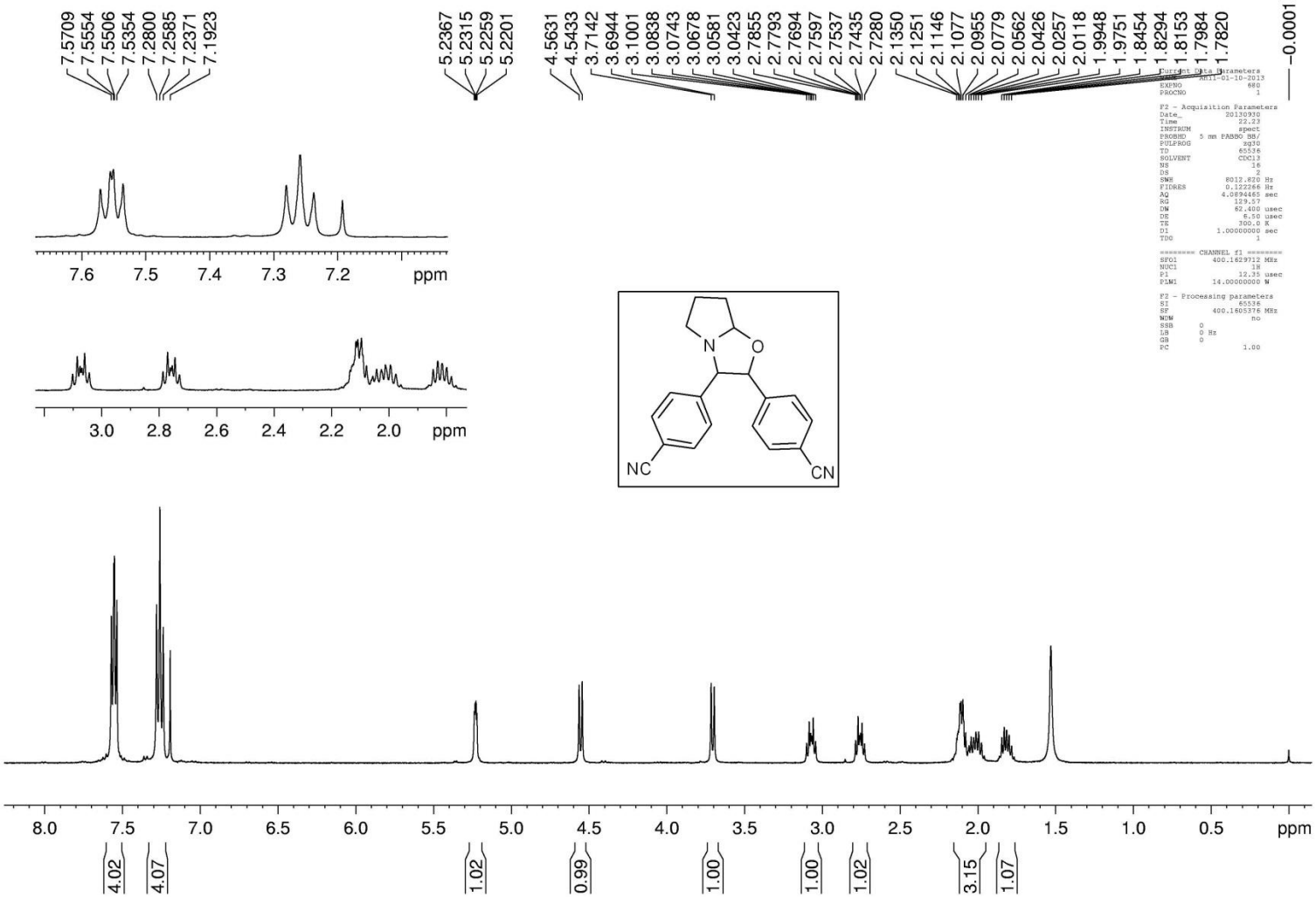

Figure S-103. ^{1}H-NMR spectrum of 4,4'-(Hexahydropyrrolo[2,1-*b*]oxazole-2,3-diyl)dibenzonitrile **(6)**

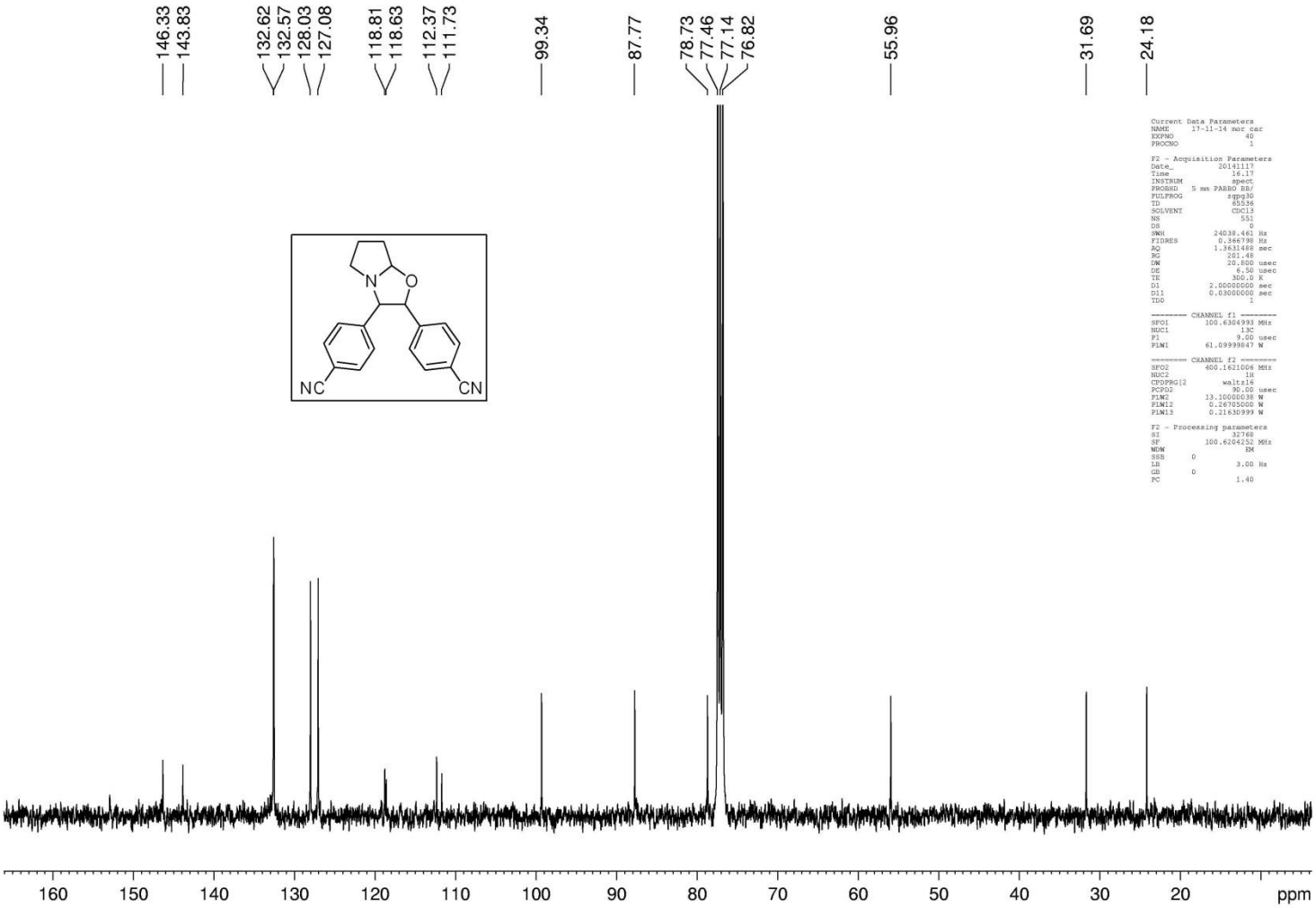

Figure S-104. ^{13}C-NMR spectrum of 4,4'-(Hexahydropyrrolo[2,1-*b*]oxazole-2,3-diyl)dibenzonitrile (**6**).