

Supplementary Material (ESI) for **RSC Advances**
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Supporting Information

L-Proline-catalyzed three-component domino reactions in the synthesis of novel densely functionalized pyrazolo[3,4-*b*]pyridines

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Supporting Information

- (i) NMR discussion
- (ii) Copies of NMR spectra and ESI-MS for compounds **4a-4w**.
- (iii) Copies of ¹⁹FNMR spectra for eight representative compounds.
- (iv) Mechanism study - NMR spectra.

NMR discussion

1. Structure determination of **4a**.

The structure of 3-methyl-1-aryl-1*H*-pyrazolo[3,4-*b*]pyridine derivatives **4** is in accord with elemental analysis and spectroscopic (^1H , ^{13}C and 2D NMR) data as illustrated for a representative example **4a**.

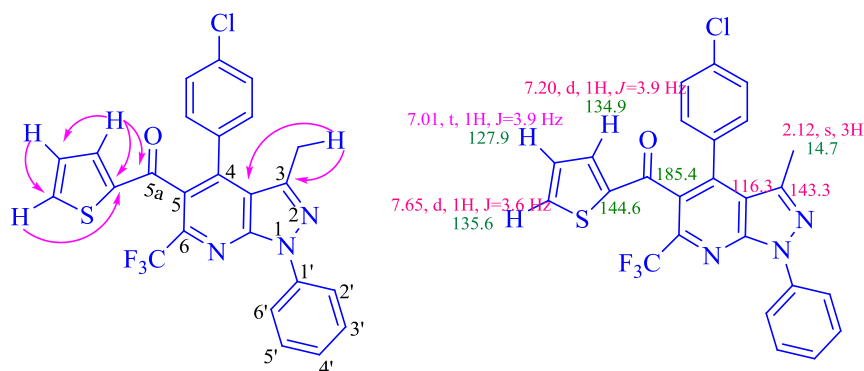


Figure 1. Selected ^1H and ^{13}C chemical shifts of **4a**

In the ^1H NMR spectrum of **4c**, the H-3'' gives a doublet at 7.20 ppm ($J = 3.9$ Hz), which shows (i) a C,H-COSY correlation with carbon signal at 134.9 ppm, assigning it to C-3'' and (ii) HMBCs (Figure 2) with C-5a, C-2'', C-4'' at 185.4, 144.6 and 127.9 ppm respectively. Similarly, the H-4'' gives a triplet at 7.01 ppm ($J = 3.9$ Hz), which shows (i) a C,H-COSY correlation with carbon signal at 127.9 ppm assigning it to C-4'' and (ii) HMBCs with C-2'' and C-5'' at 144.6 and 135.6 ppm respectively. The H-5'' gives a doublet at 7.65 ppm ($J = 3.6$ Hz) and C,H-COSY correlation with carbon signal at 135.6 ppm, besides showing HMBCs with C-2'' and C-4'' at 144.6 and 127.9 ppm respectively. The methyl hydrogens of the pyrazole sub-structure appear as a singlet at 2.12 ppm and show HMBCs with the signals at 143.4 and 116.3 ppm assignable to C-3 and C-3b respectively. The mass spectrum of **4c** has a M^+ peak at 498.1 in accord with the proposed structure. A single crystal X-ray crystallographic study of **4o** confirmed the structure deduced from NMR spectroscopic data (Figure 1).

2. Structural determination of **5r**

Methoxy protons of **5r** appear as a singlet at 3.83 ppm in ^1H -NMR and the corresponding carbon appears at 55.4 ppm. This carbon signal shows a HMBC with C-4''. The pyrazole methyl hydrogens appear as a singlet at 1.99 ppm and show HMBCs with the signals at 146.1 and 105.6 ppm assignable to C-3 and C-3b respectively. H-4 appears as a triplet at 4.19 ppm, this multiplicity arises from coupling with the two diastereotopic 5-CH₂ hydrogens which occur as a multiplet. By a C,H-COSY correlation with the signal at 4.19 ppm, the C-4 is assigned to signal at 34.6 ppm. H-4 gives the HMBCs with C-3, C-3b and C-6 at 146.1, 105.6 and 165.1 respectively. Other HMBC correlations shown in Figure 2 support the structure **5r**.

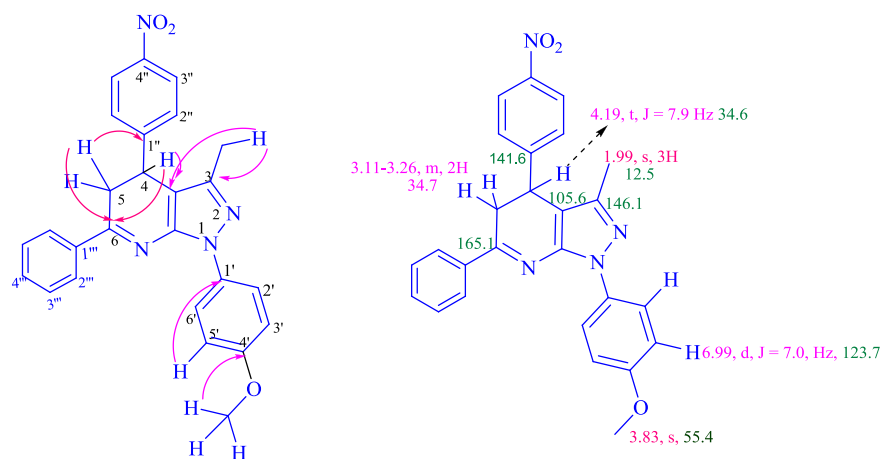


Figure 2. Selected ^1H and ^{13}C chemical shifts of **5r**

3. Structural determination of **4x**.

The pyrazole methyl hydrogens appear as a singlet at 2.13 ppm, which shows HMBCs with the signals at 143.4 and **116.3** ppm assignable to C-3 and C-3b respectively. Methoxy protons of anisole appear as a singlet at 3.77 ppm and the corresponding carbon occurs at 55.1 ppm, assigned by C,H-COSY spectrum. The signals assigned and the HMBC correlations support the structure and stereochemistry of **4x**.

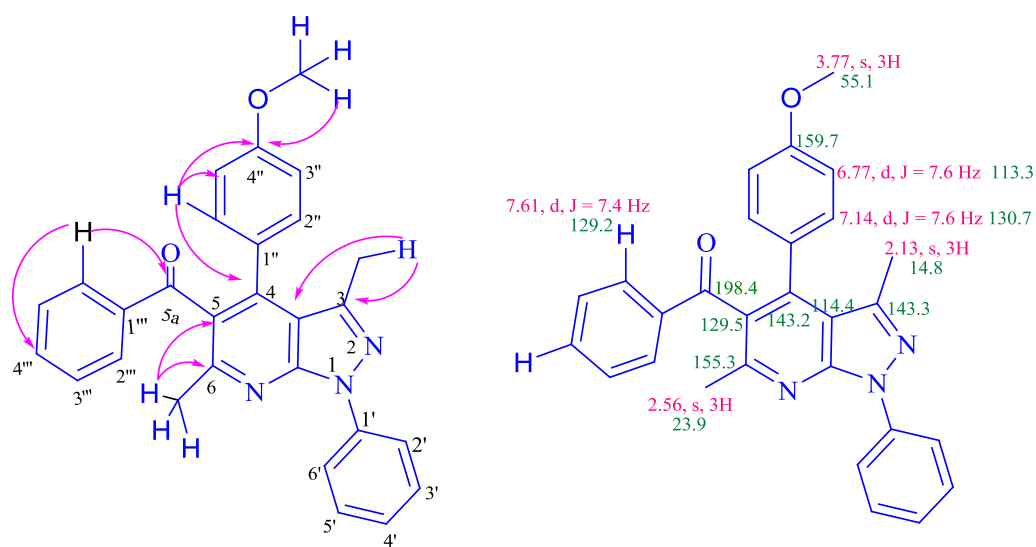


Figure 3. Selected ¹H and ¹³C chemical shifts of **4x**

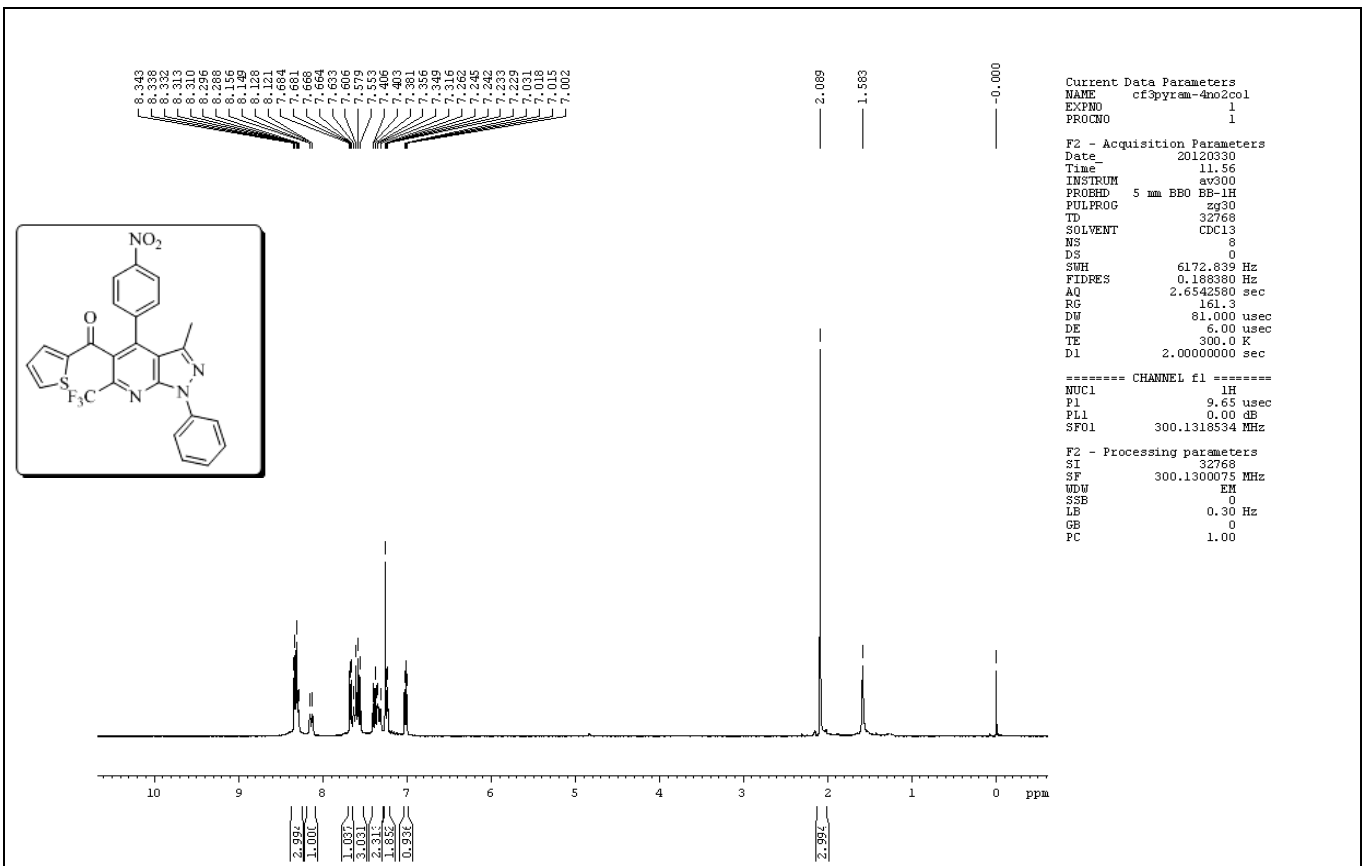


Figure 1. ¹H NMR spectrum of 4b

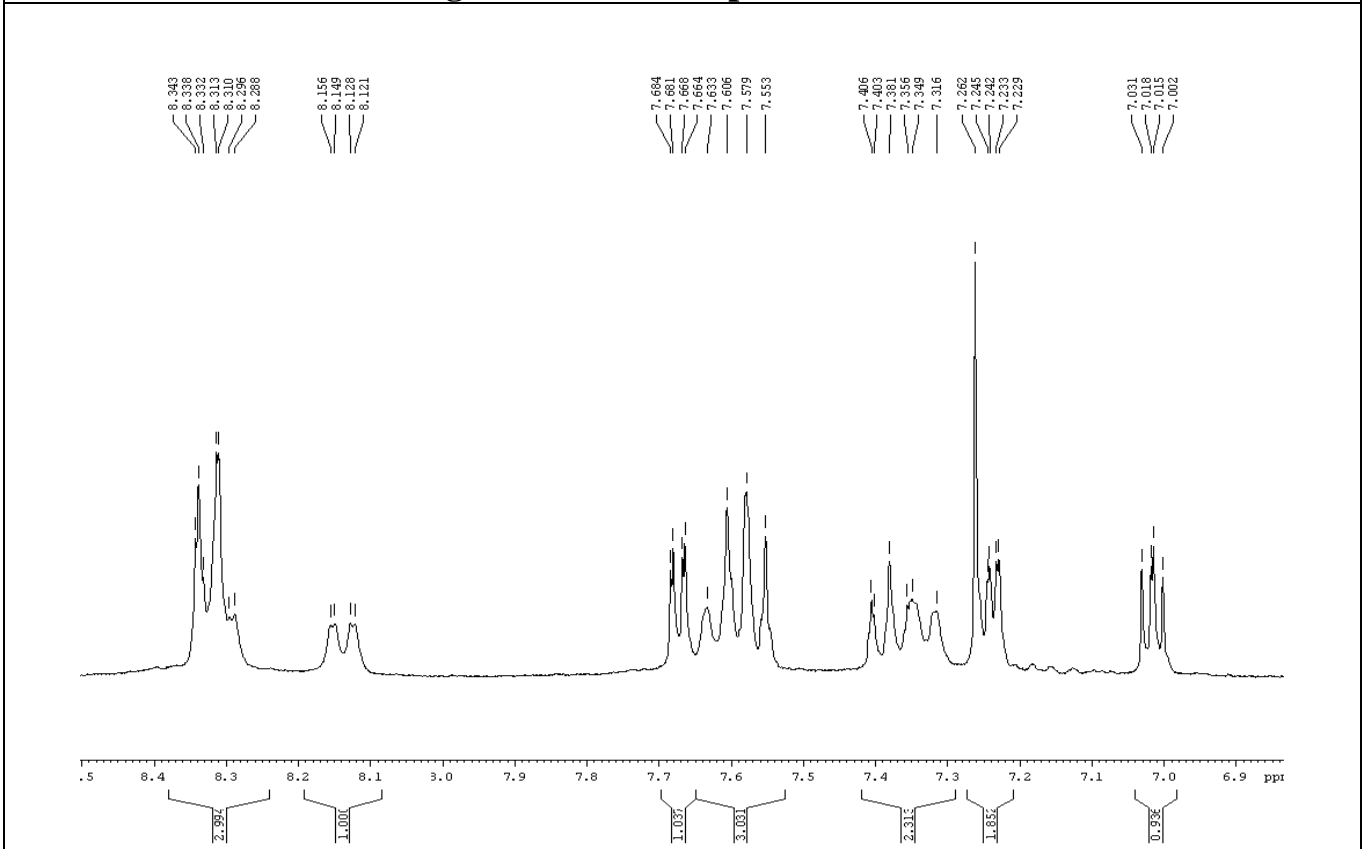


Figure 2. ¹H NMR spectrum of 4b-expansion

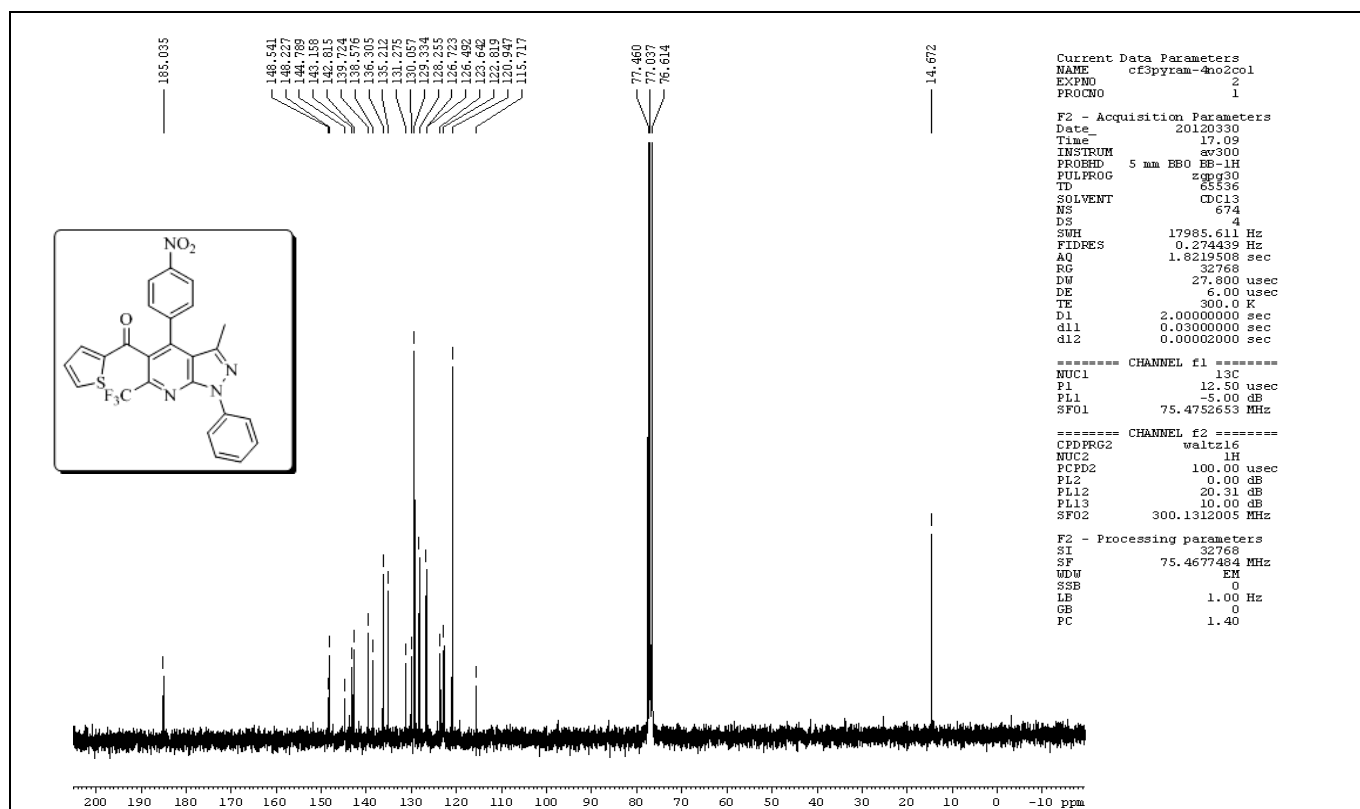


Figure 3. ^{13}C NMR spectrum of 4b

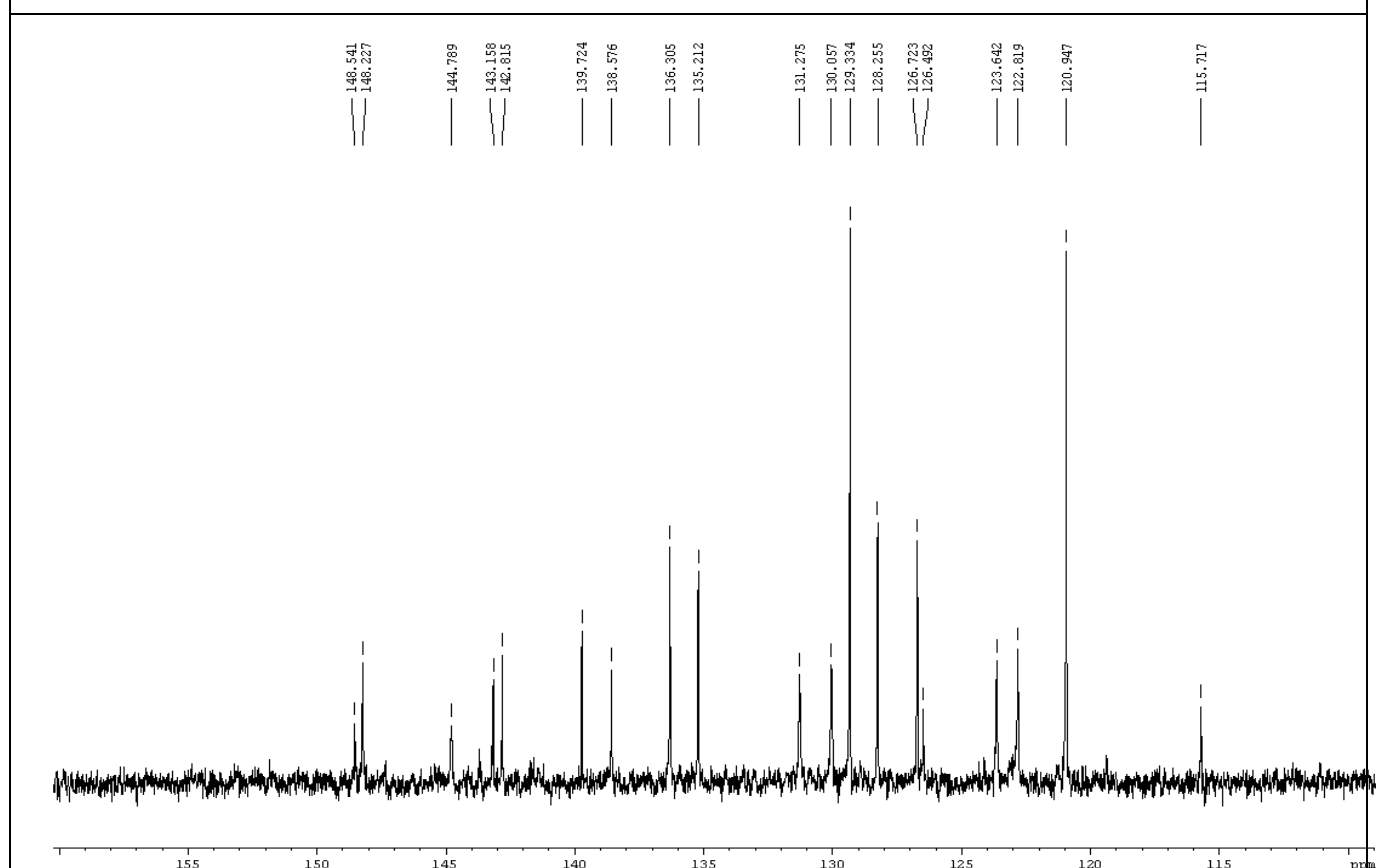


Figure 4. ^{13}C NMR spectrum of 4b-expansion

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T: ITMS + c ESI Full ms [100.00-1000.00]

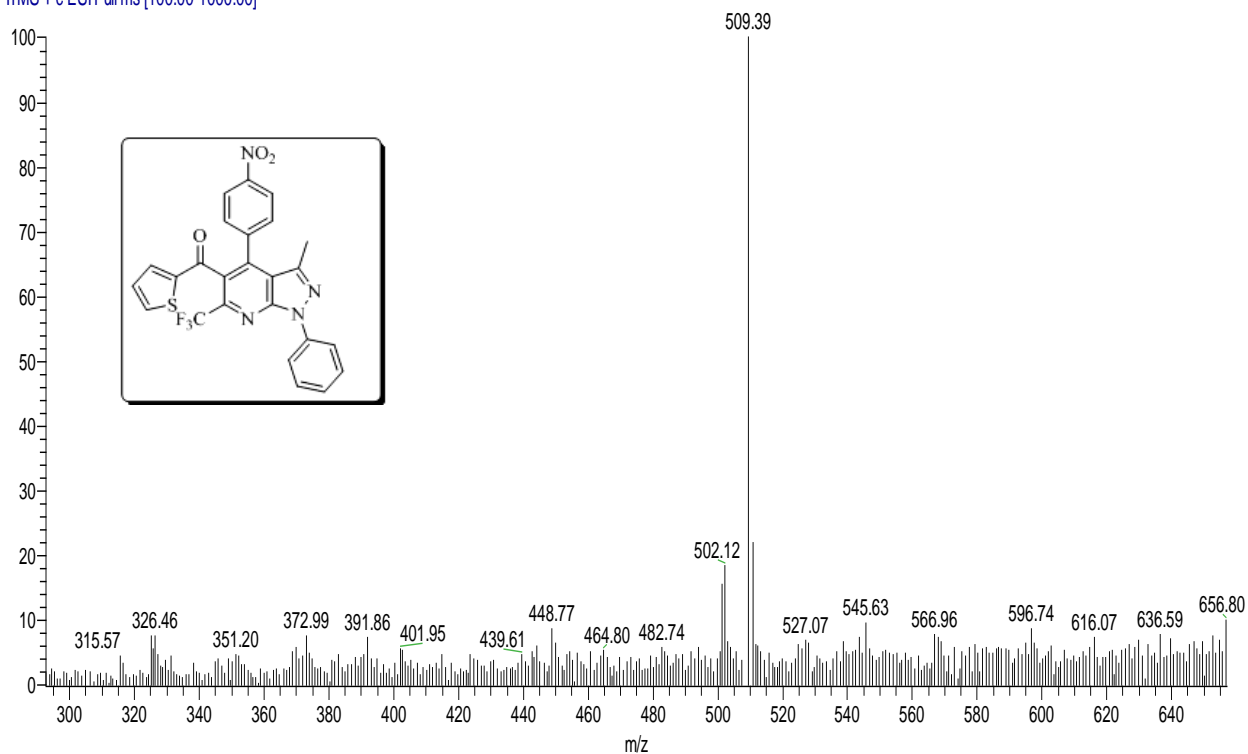


Figure 5. Mass spectrum of 4b

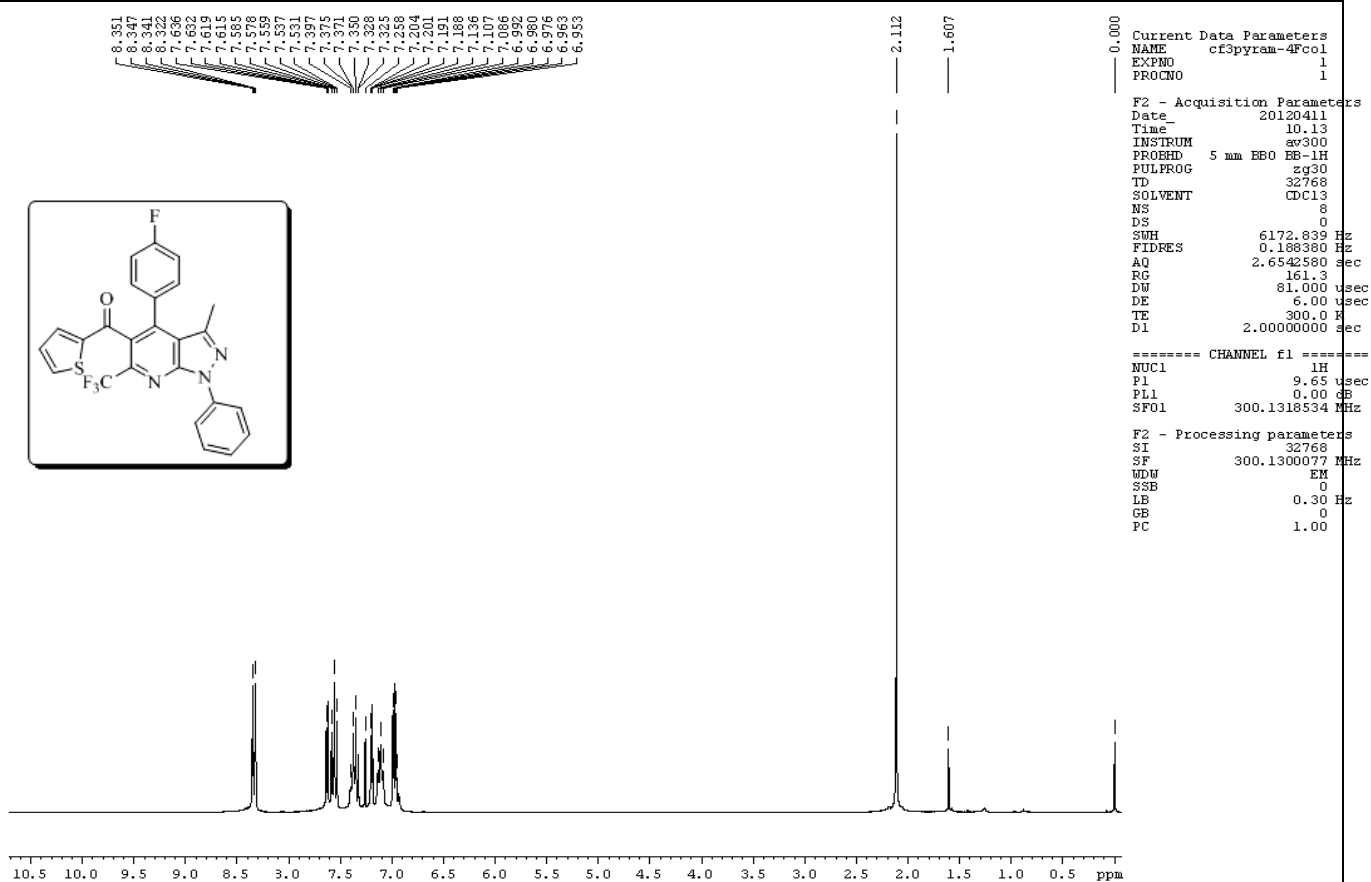


Figure 6. ¹H NMR spectrum of 4c

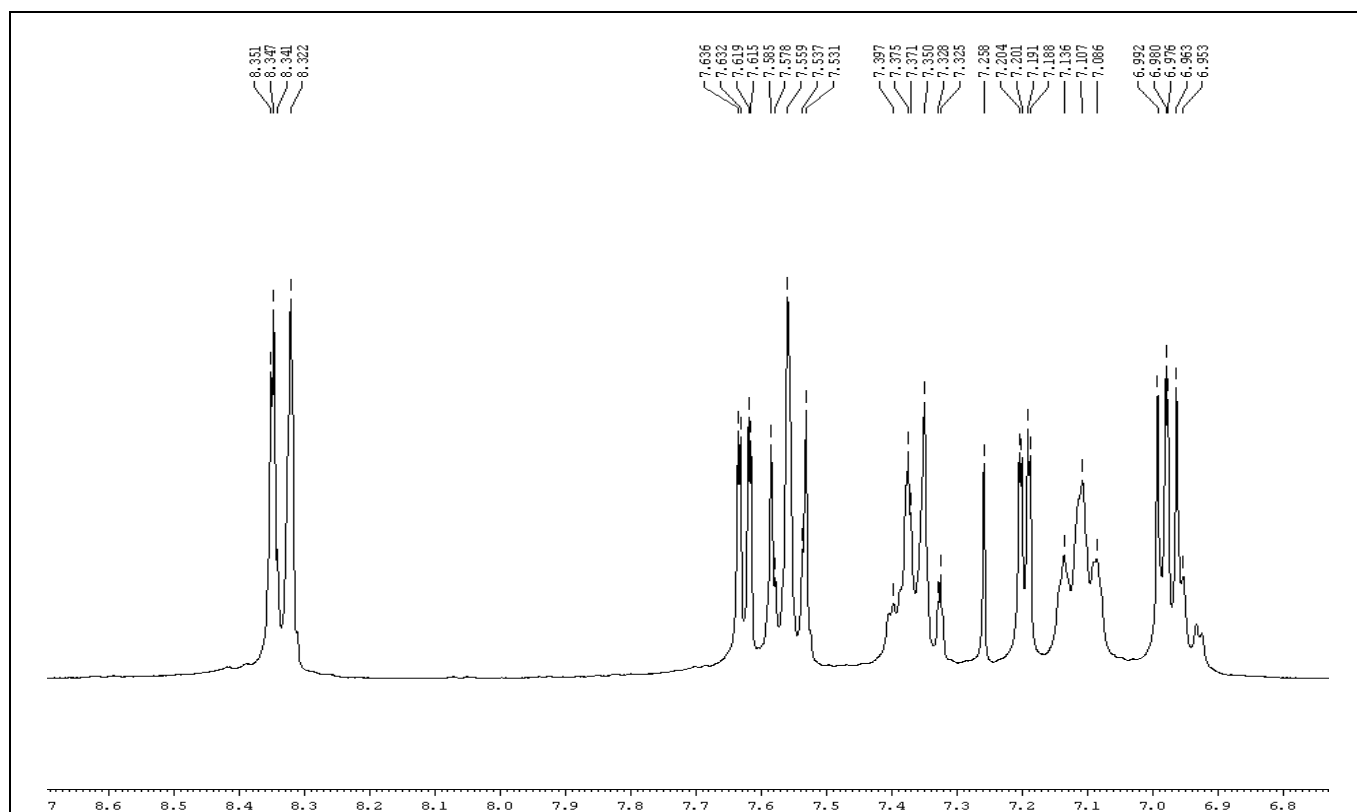


Figure 7. ^1H NMR spectrum of 4c-expansion

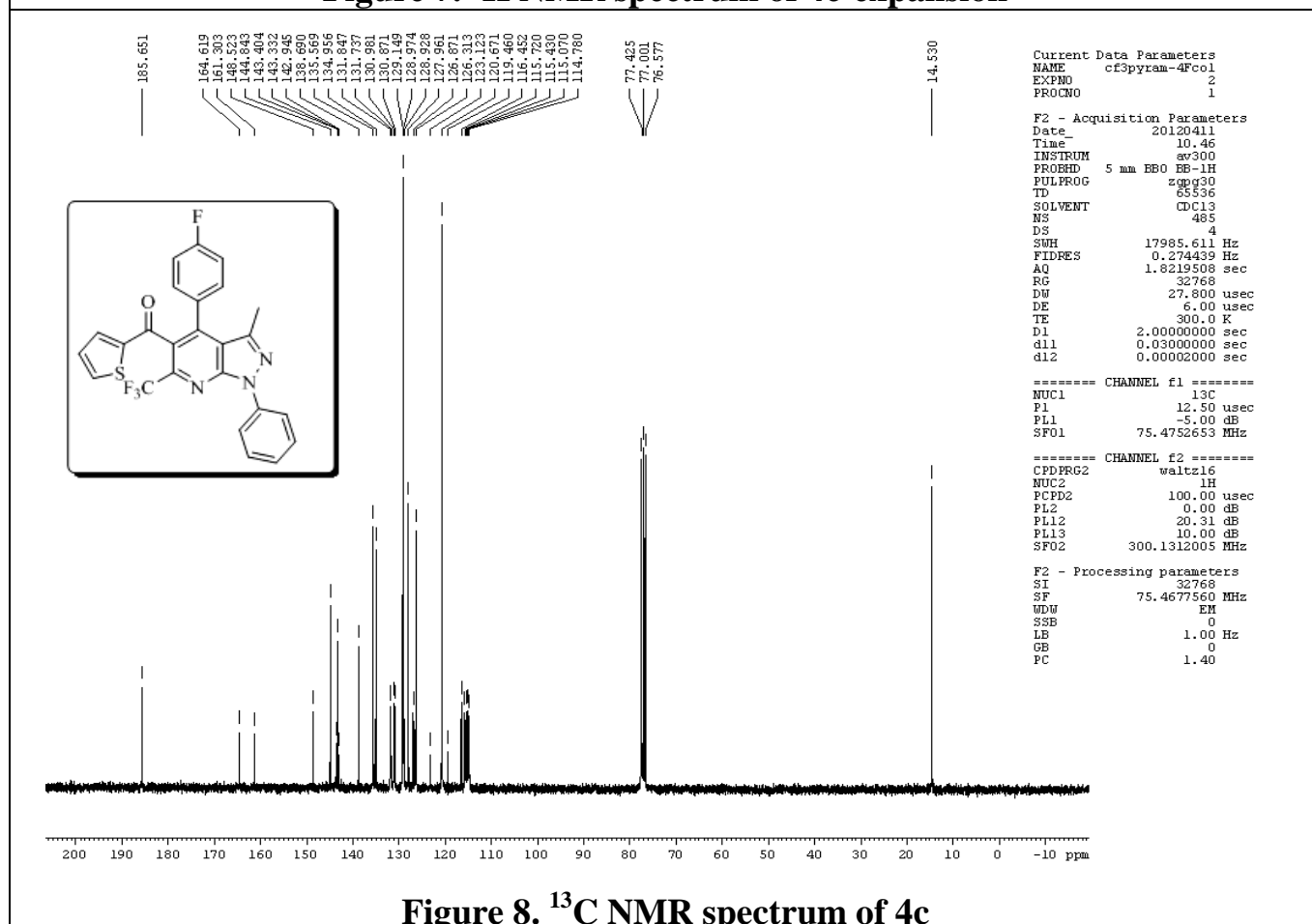


Figure 8. ^{13}C NMR spectrum of 4c

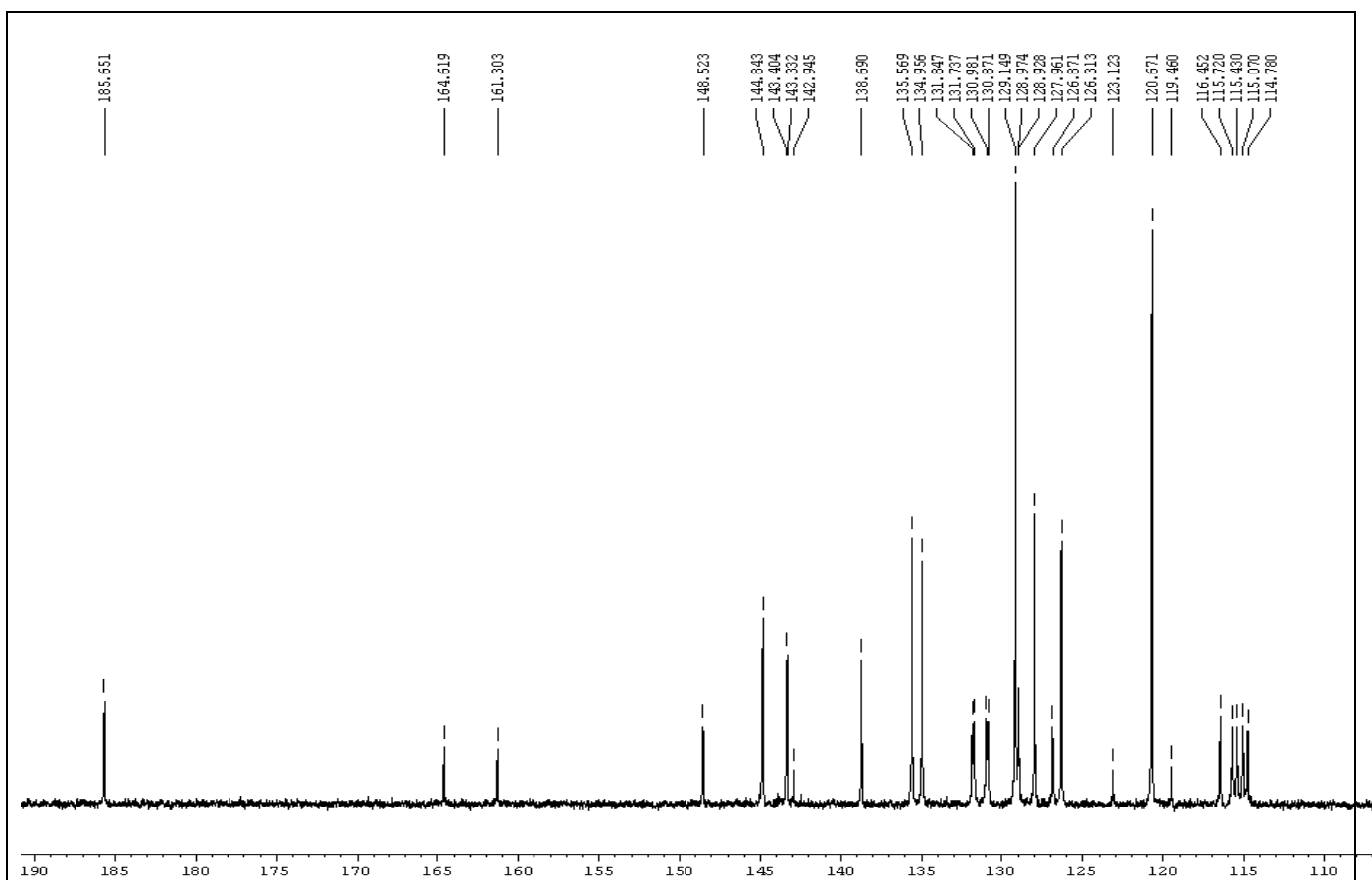


Figure 9. ^{13}C NMR spectrum of 4c-expansion

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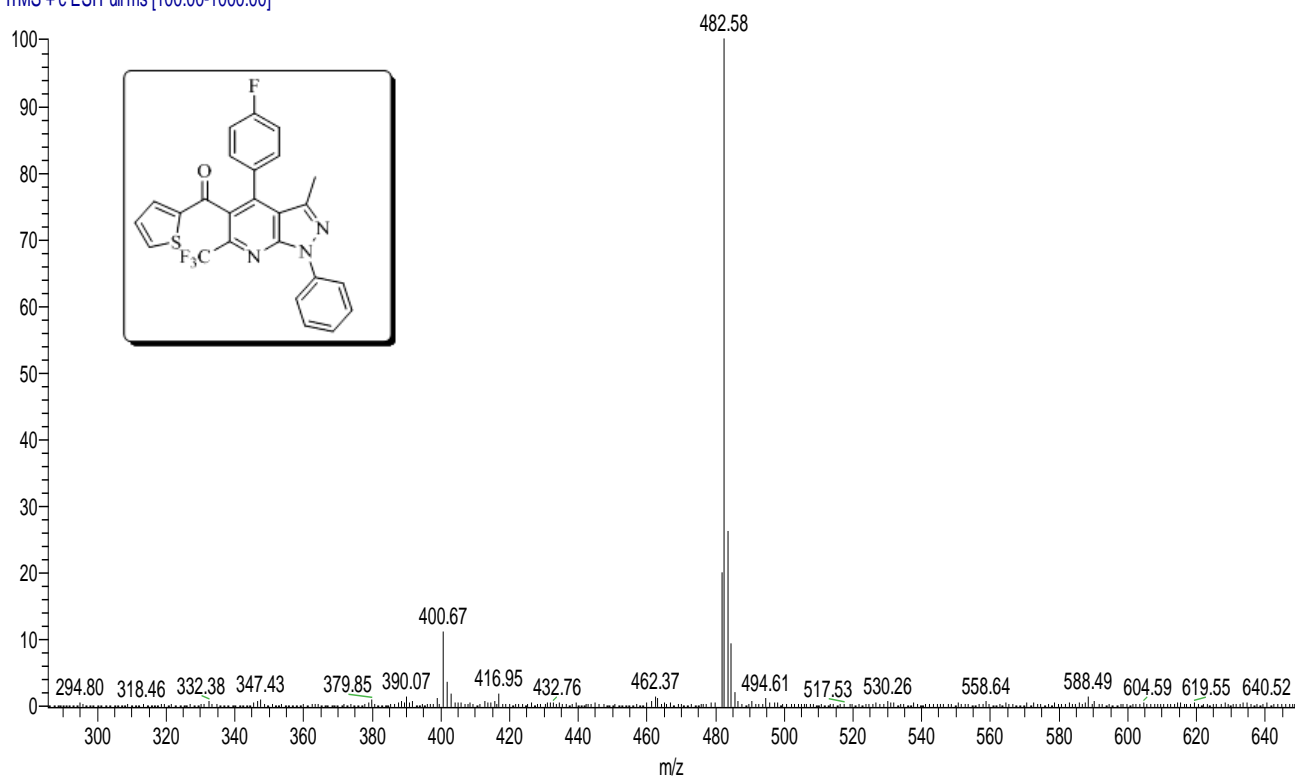


Figure 10. Mass spectrum of 4c

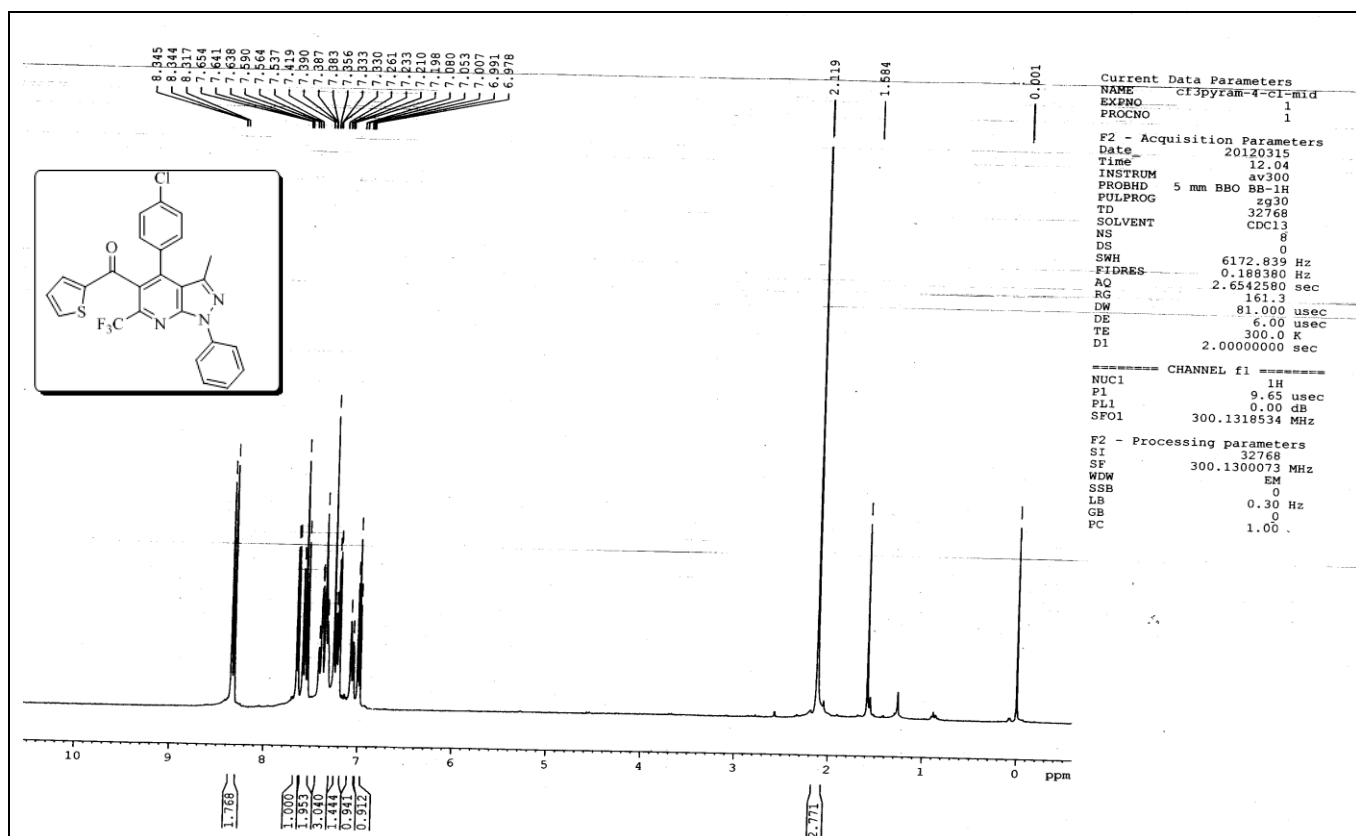


Figure 11. ^1H NMR spectrum of 4a

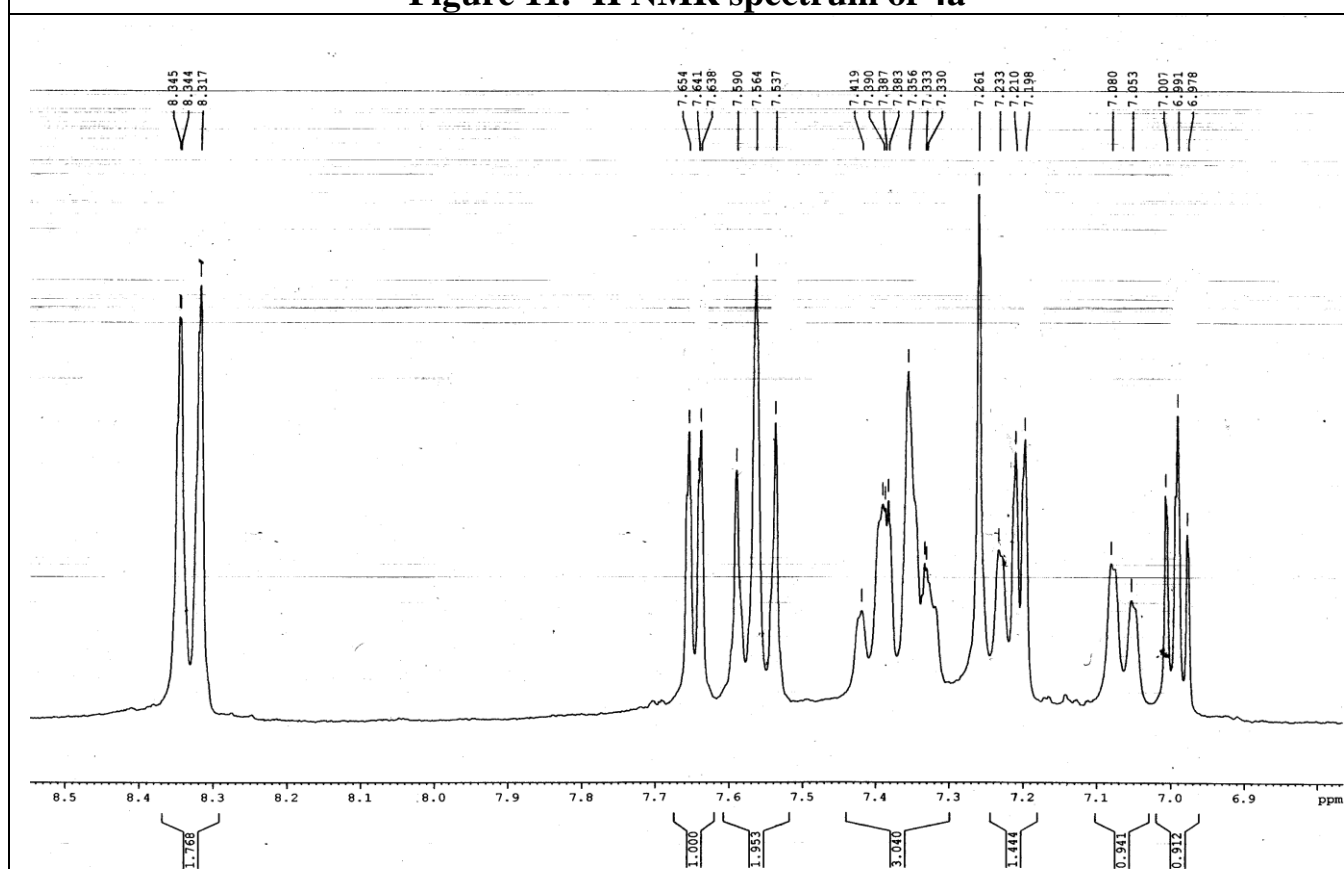


Figure 12. ^1H NMR spectrum of 4a-expansion

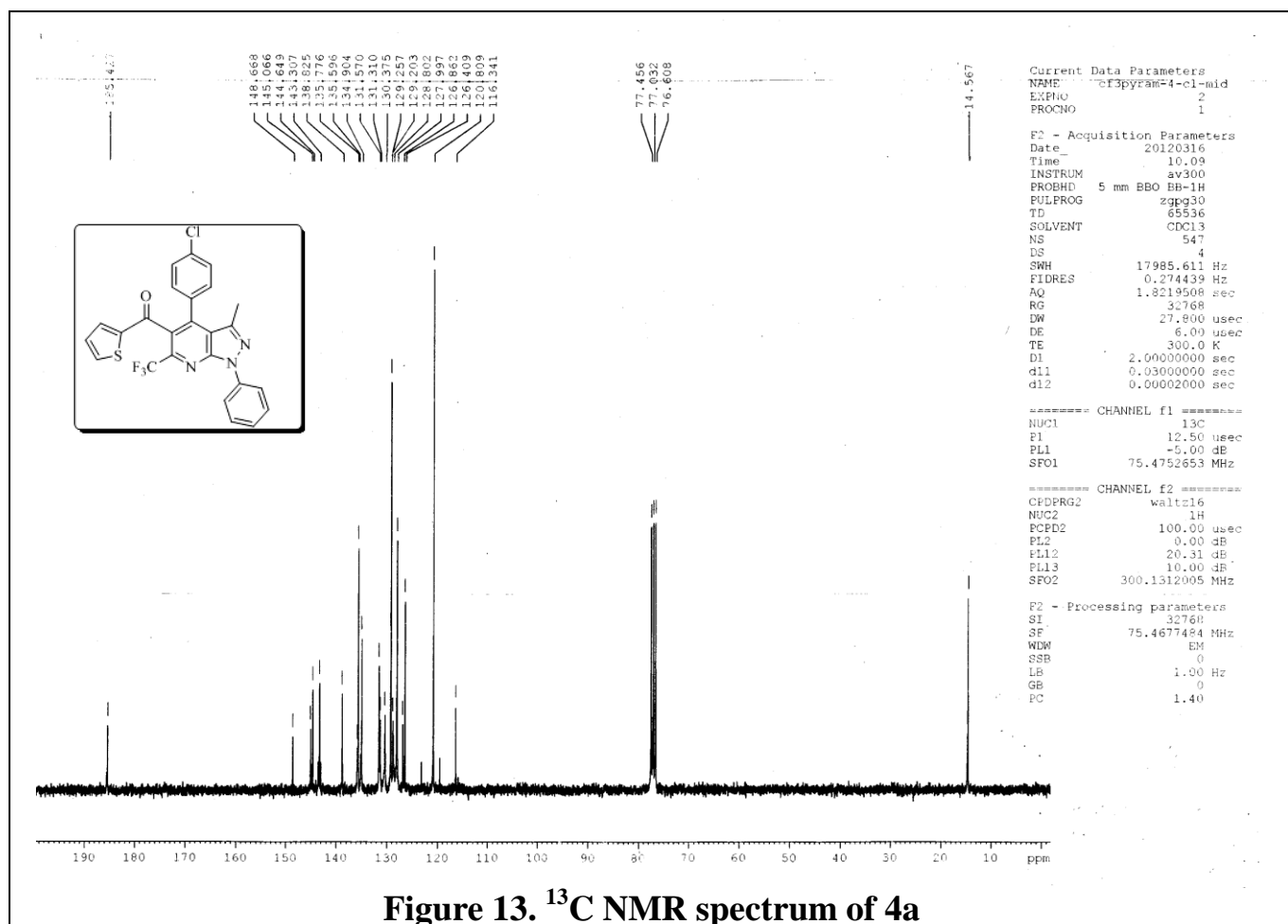


Figure 13. ^{13}C NMR spectrum of 4a

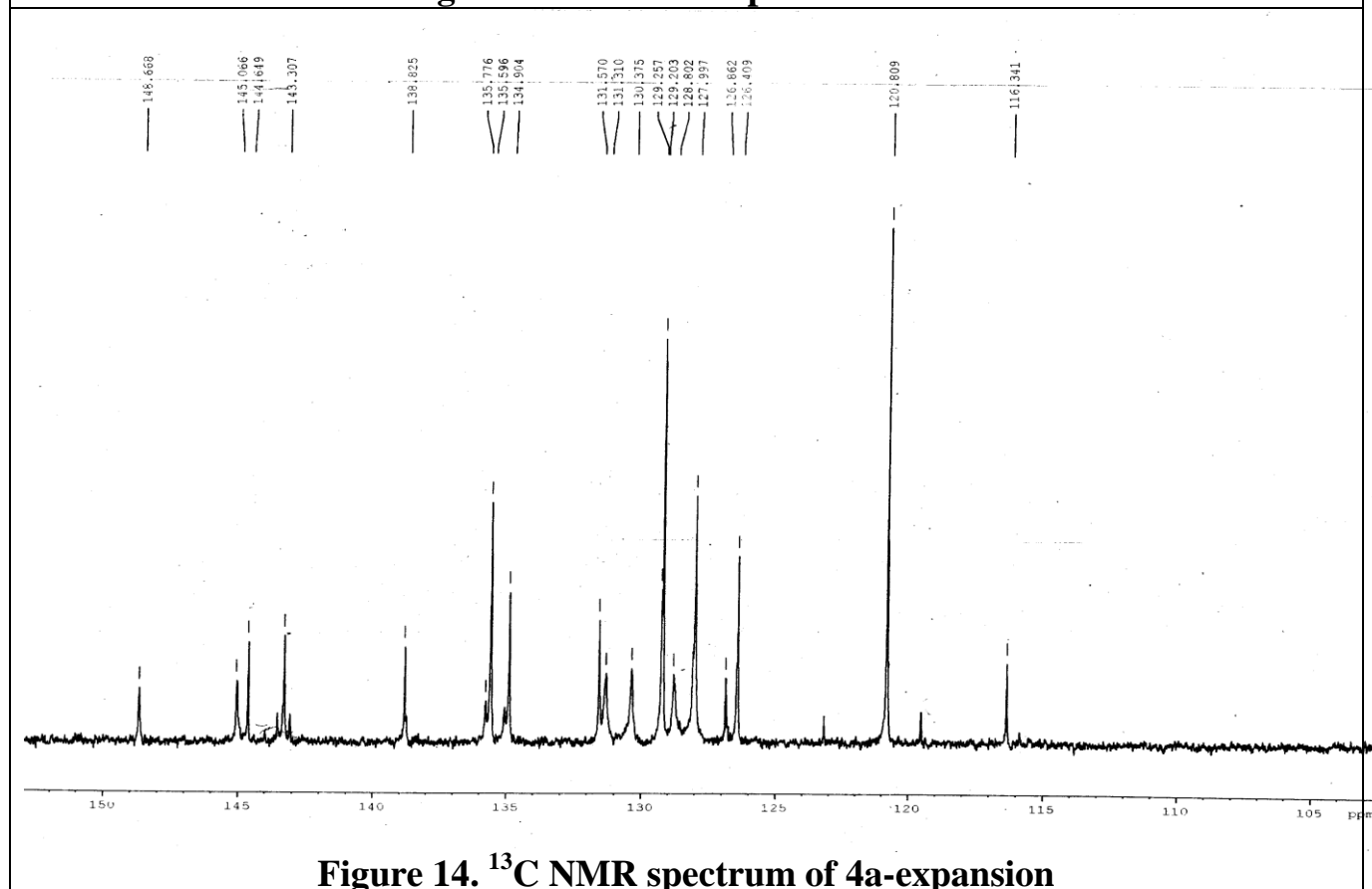


Figure 14. ^{13}C NMR spectrum of 4a-expansion

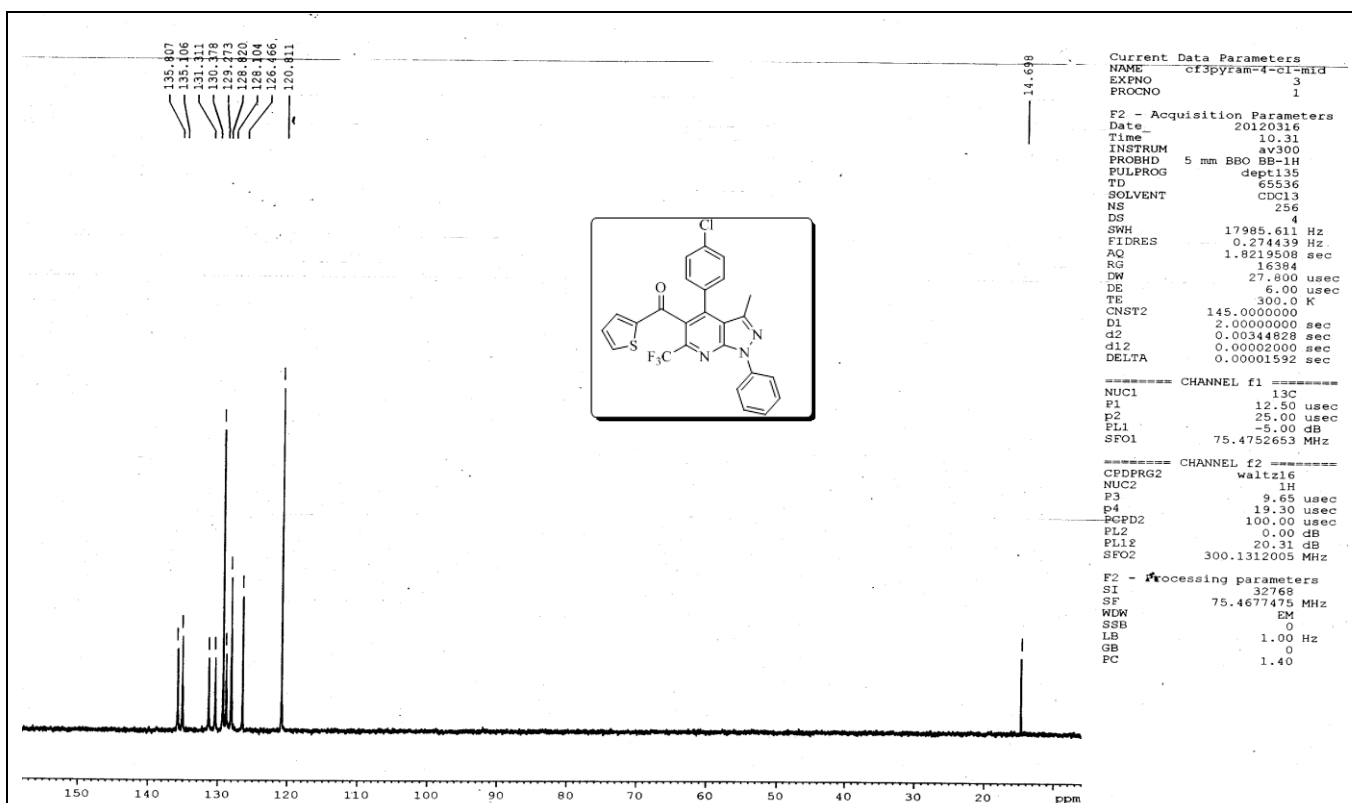


Figure 15. Dept-135 spectrum of 4a

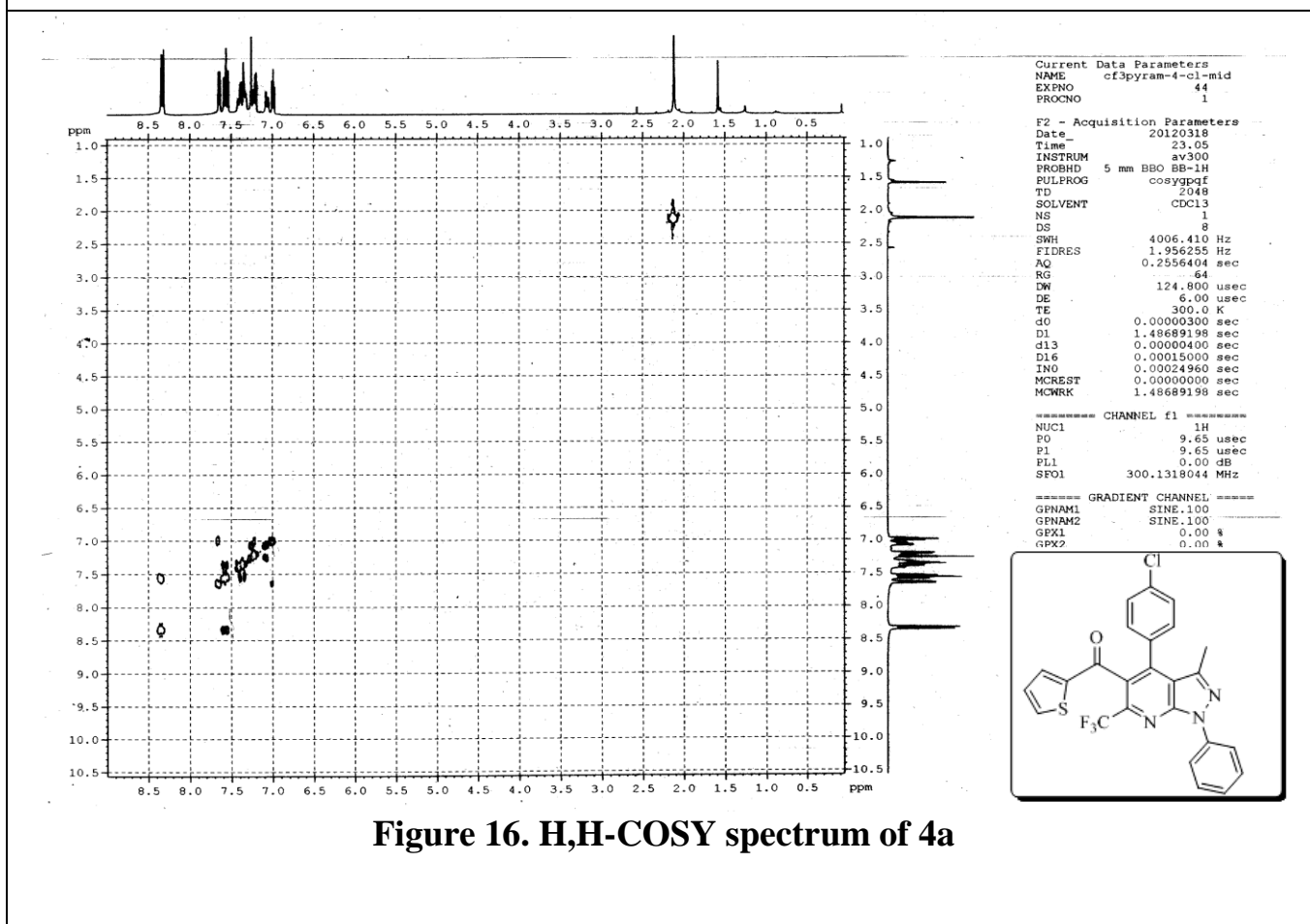


Figure 16. H,H-COSY spectrum of 4a

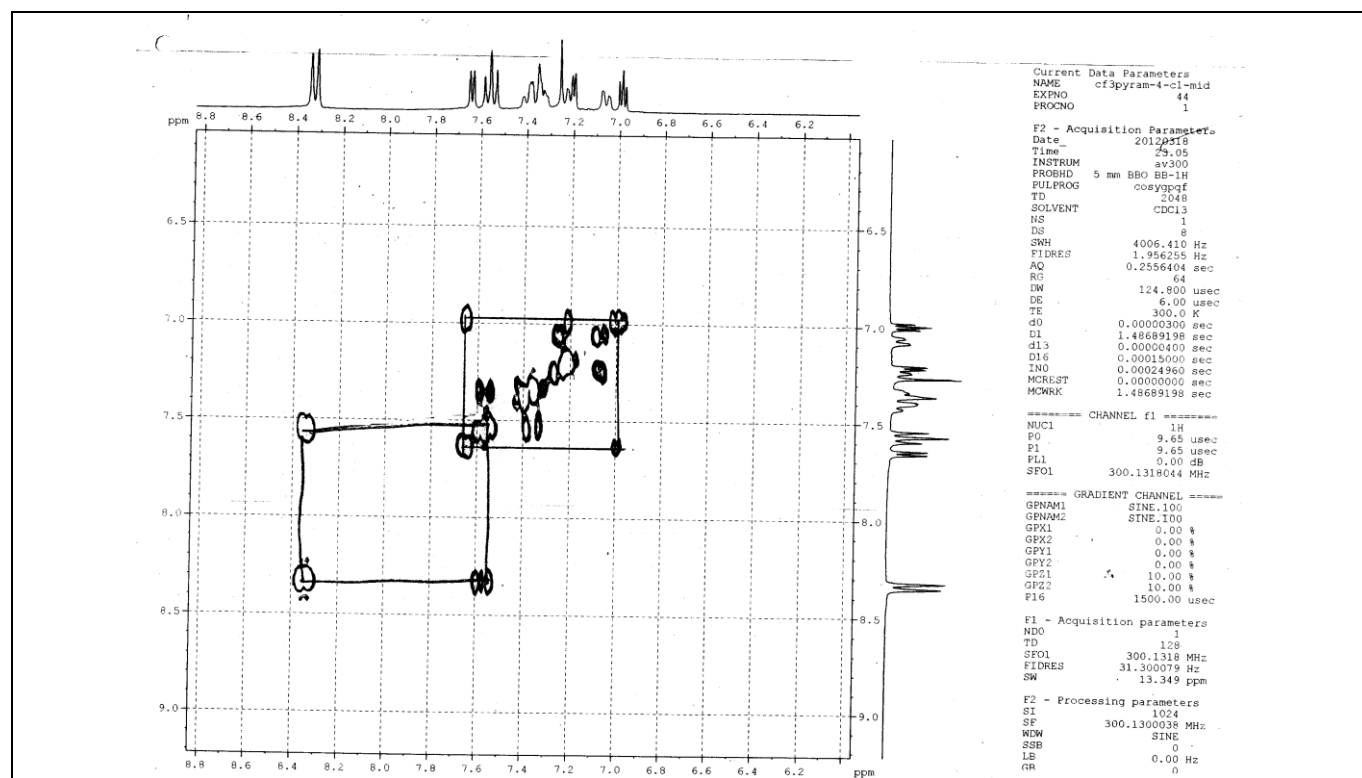


Figure 17. H,H-COSY spectrum of 4a-expansion

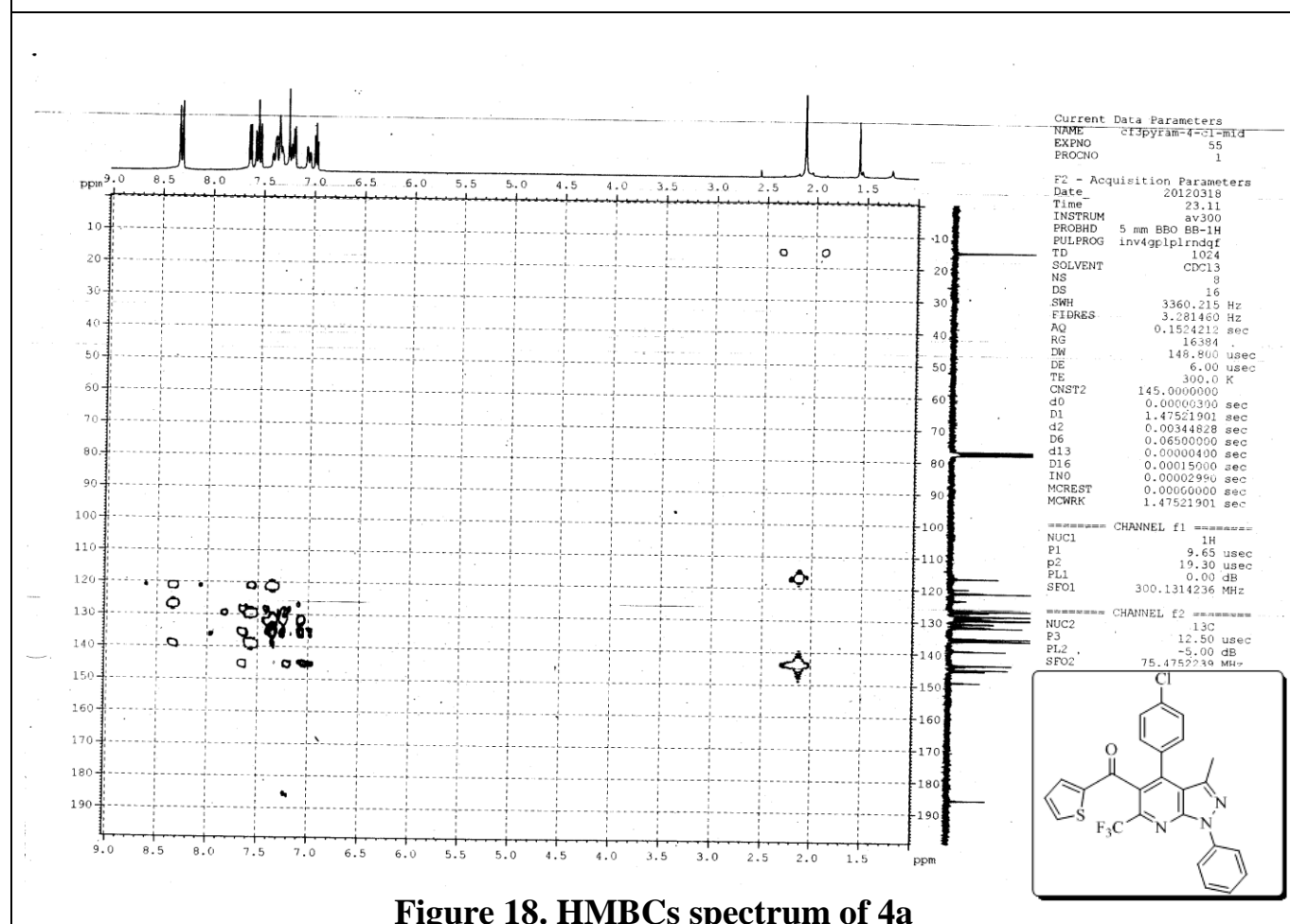


Figure 18. HMBCs spectrum of 4a

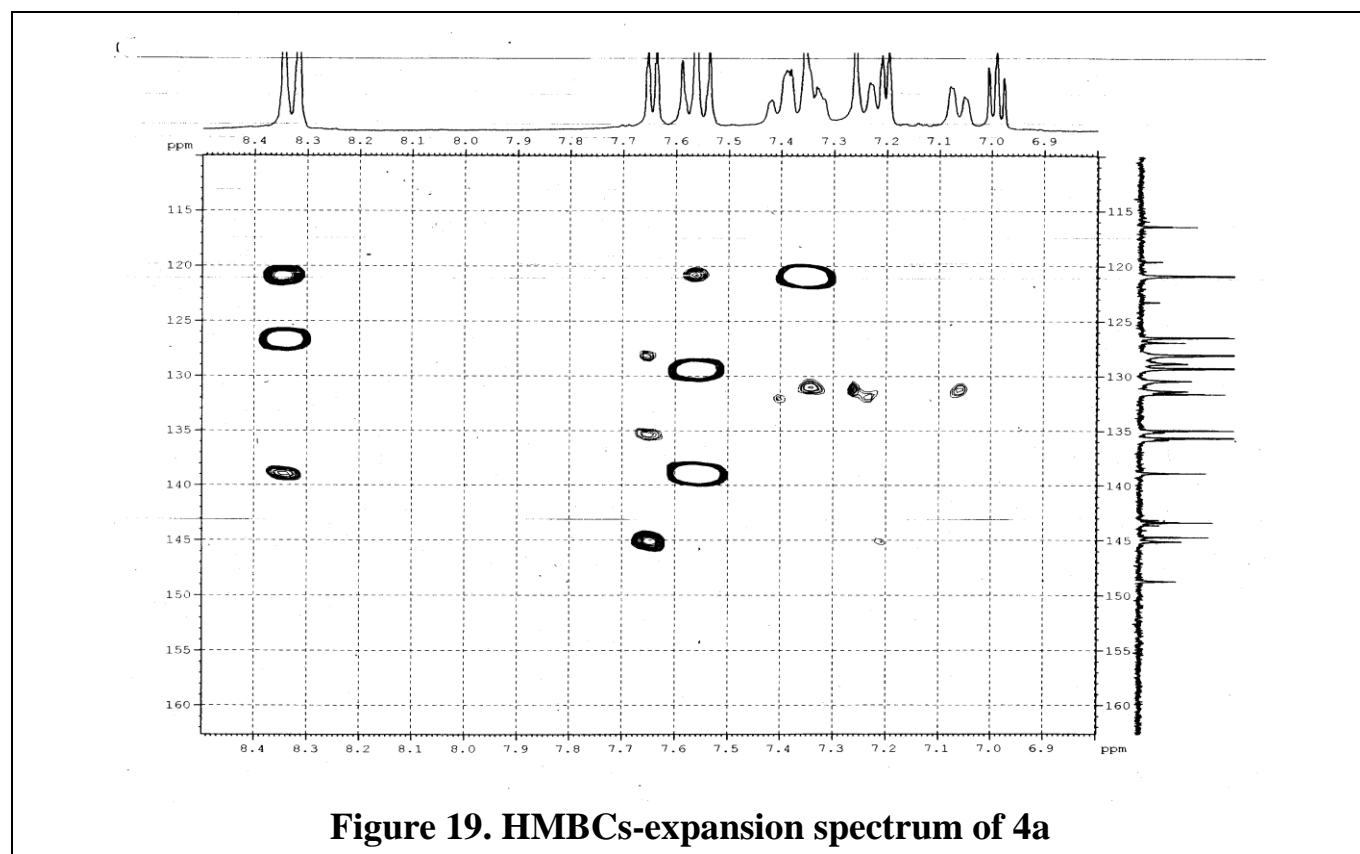


Figure 19. HMBCs-expansion spectrum of 4a

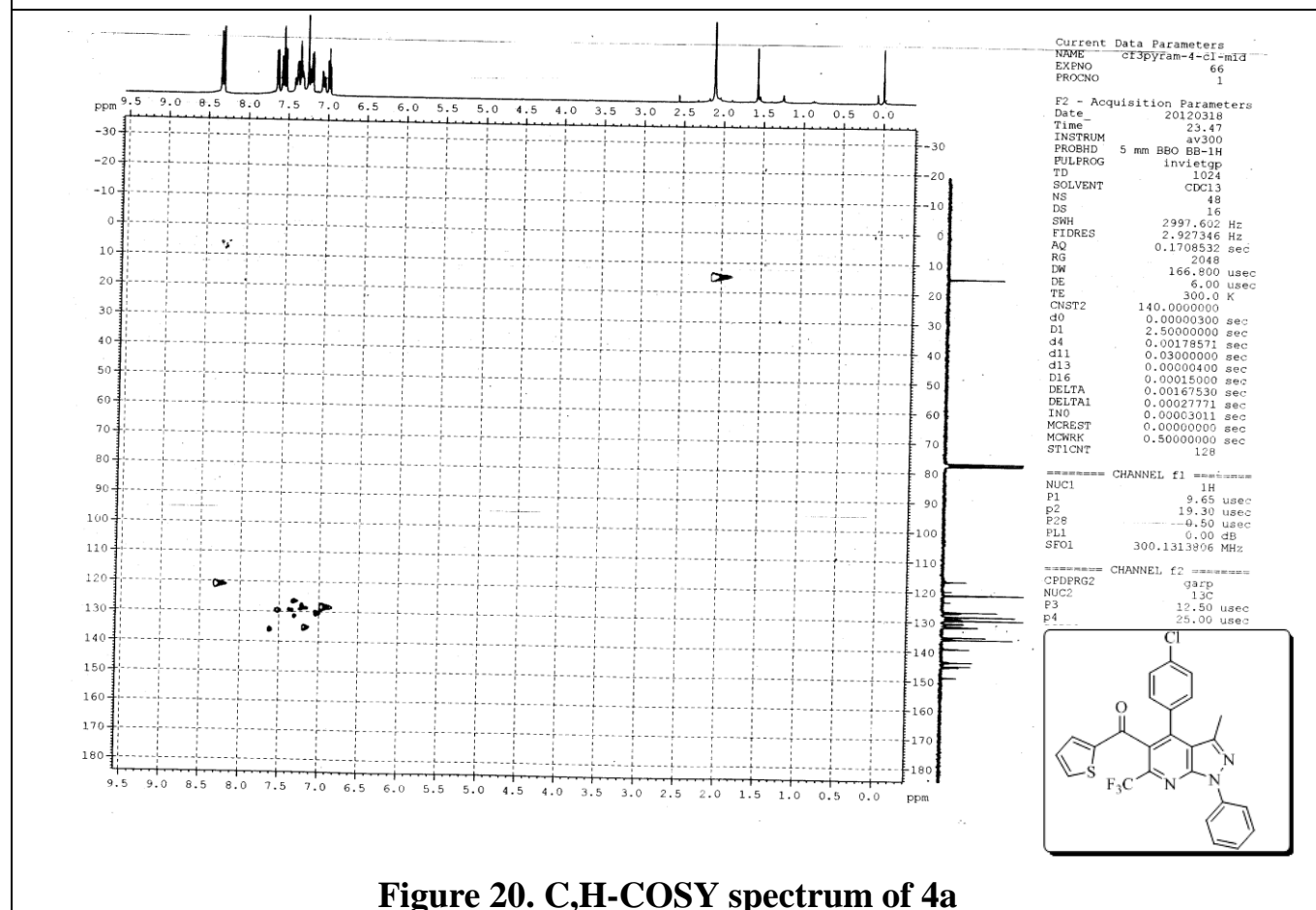


Figure 20. C,H-COSY spectrum of 4a

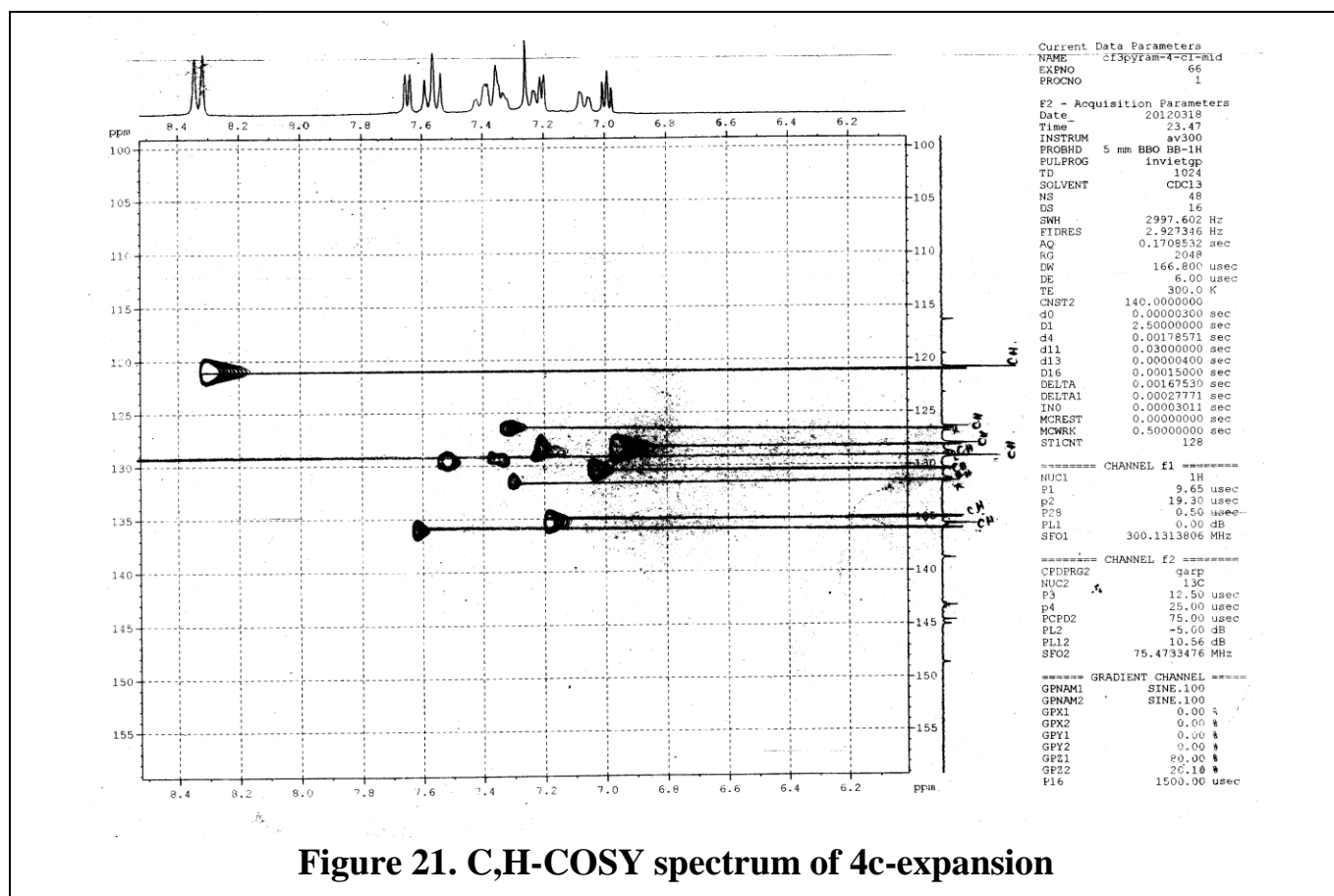


Figure 21. C,H-COSY spectrum of 4c-expansion

CF3-4CT-MID_120403123010 #78 RT: 0.18 AV: 1 NL: 3.06E4
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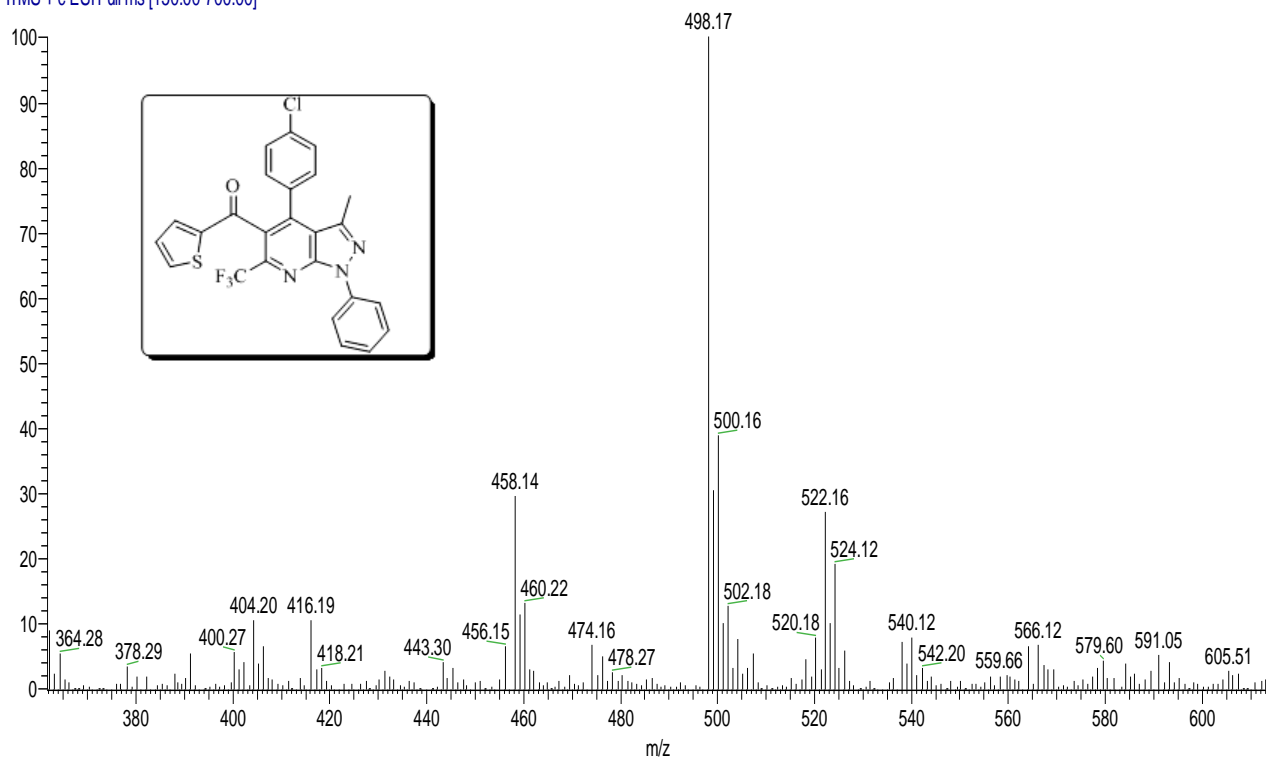


Figure 22. Mass spectrum of 4c

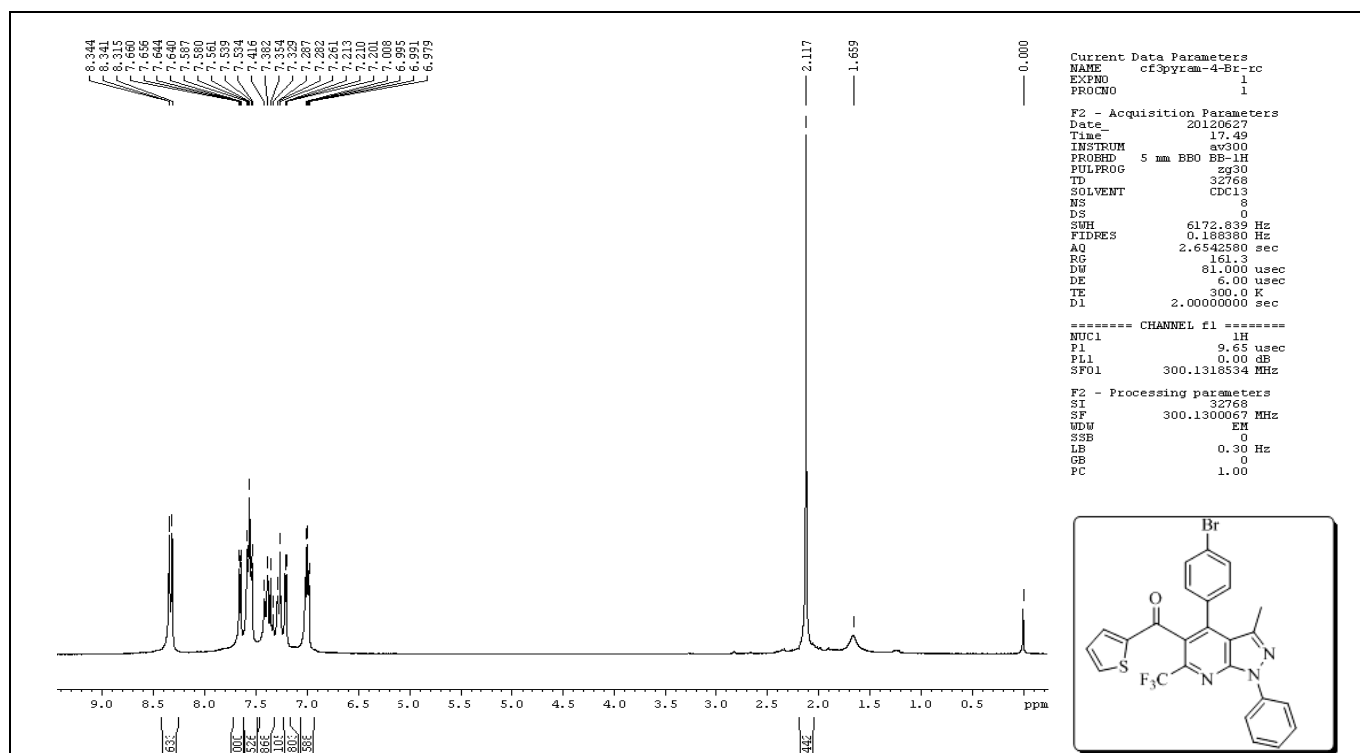


Figure 23. ¹H NMR spectrum of 4d

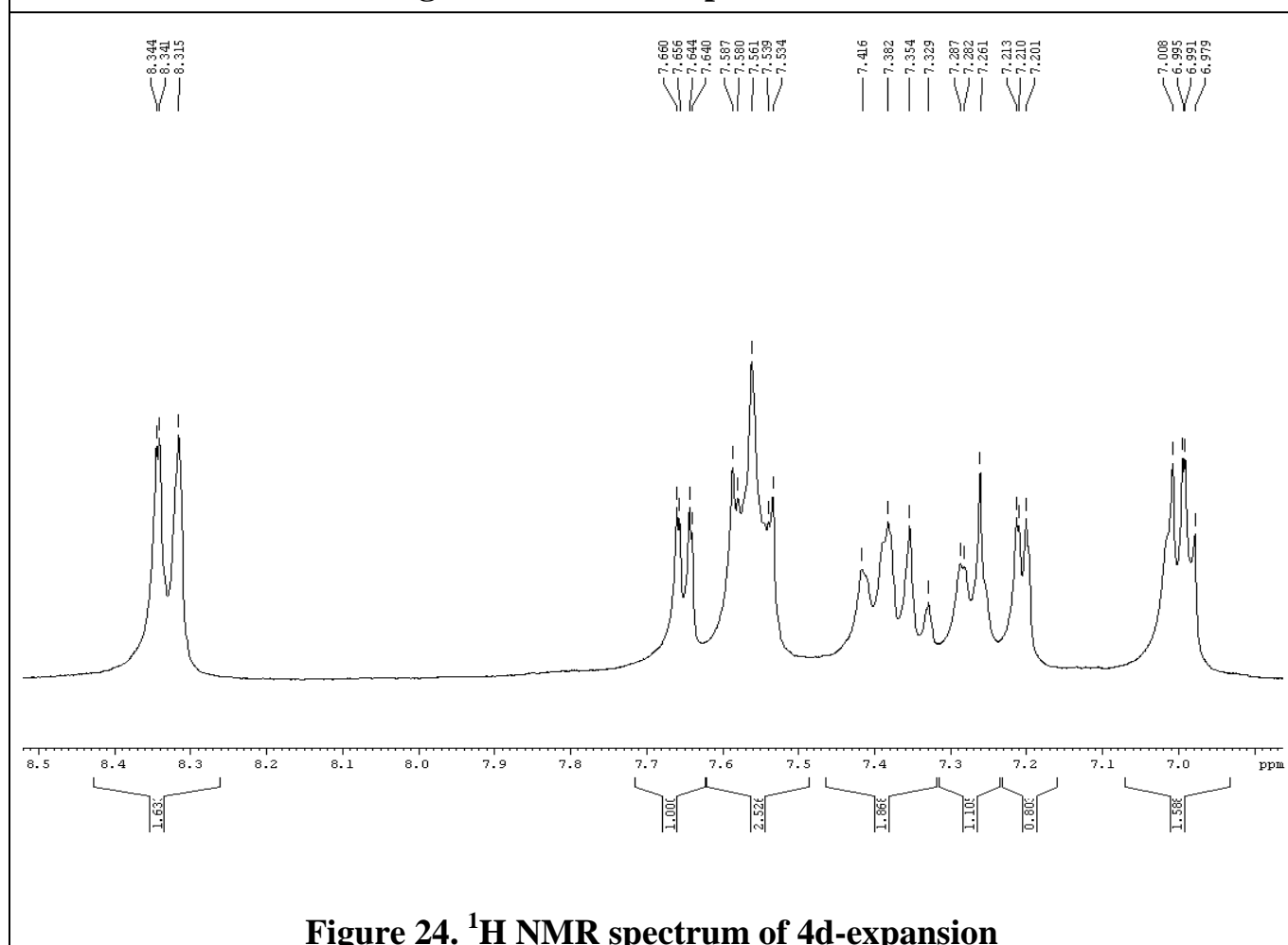


Figure 24. ¹H NMR spectrum of 4d-expansion

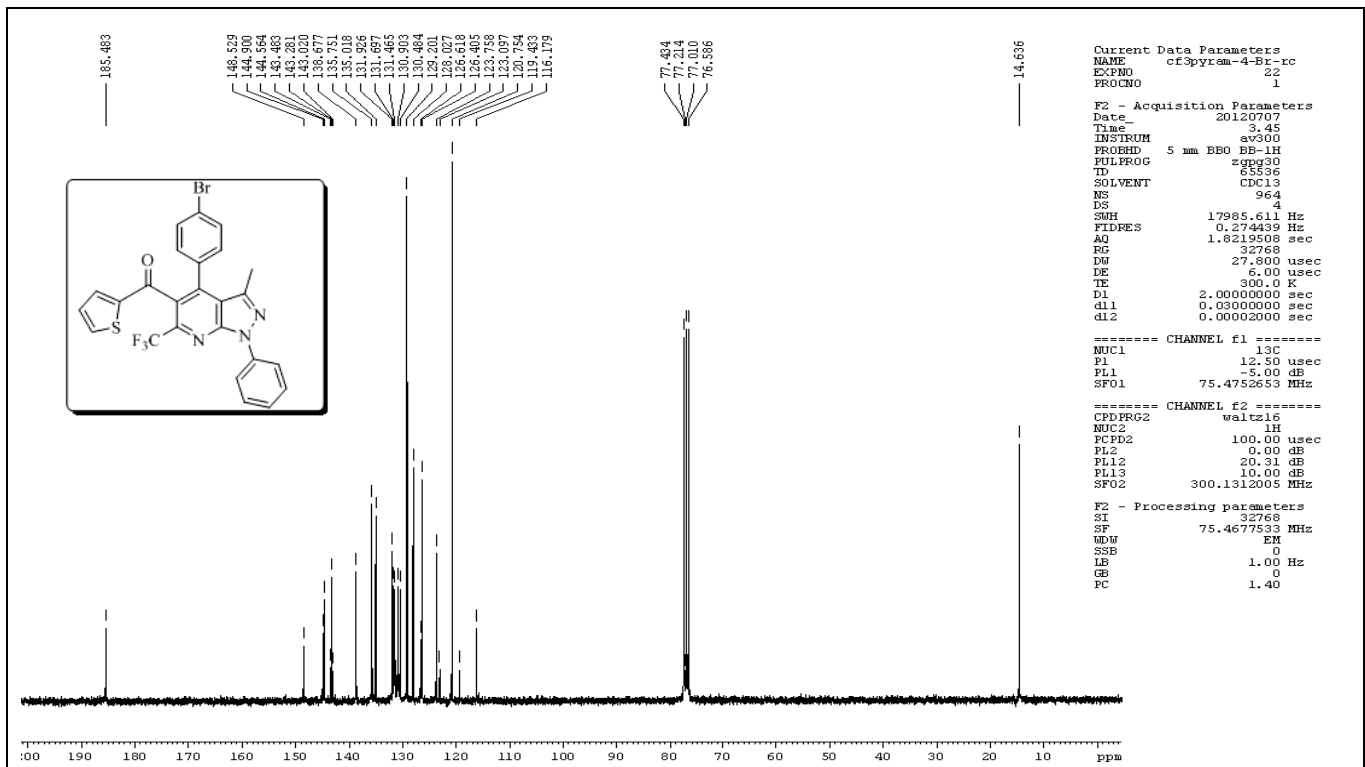


Figure 25. ^{13}C NMR spectrum of 4d

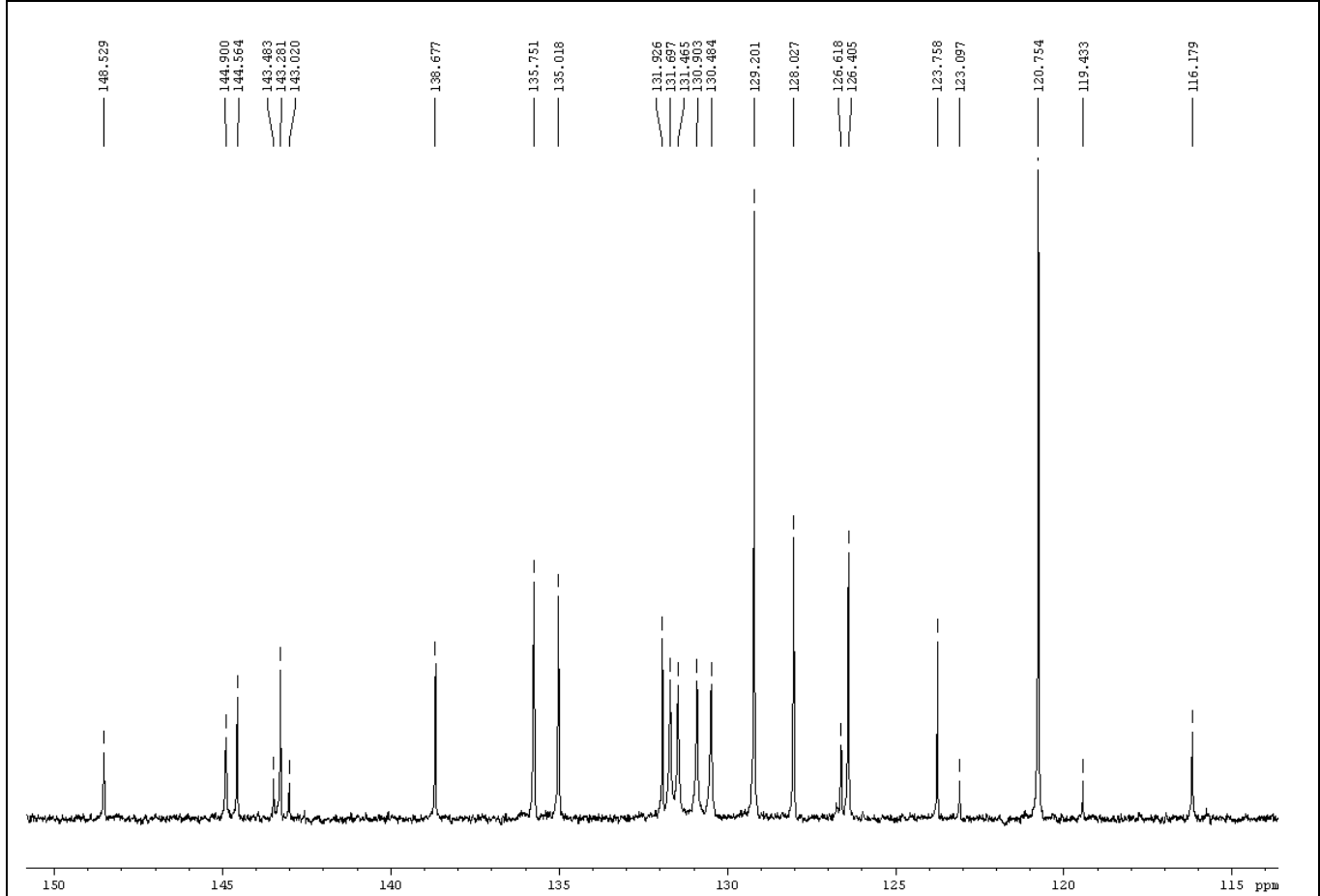


Figure 26. ^{13}C NMR spectrum of 4d-expansion

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T: ITMS + c ESI Full ms [100.00-1000.00]

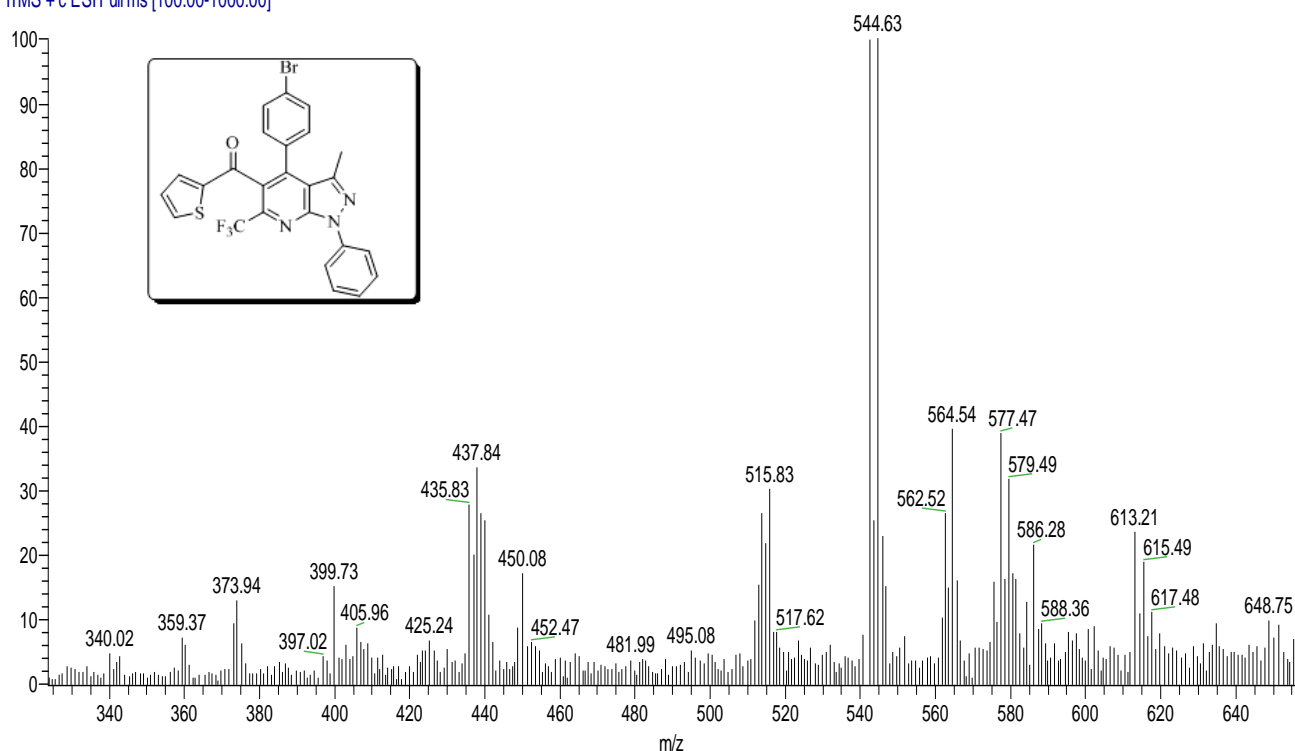


Figure 27. Mass spectrum of 4d

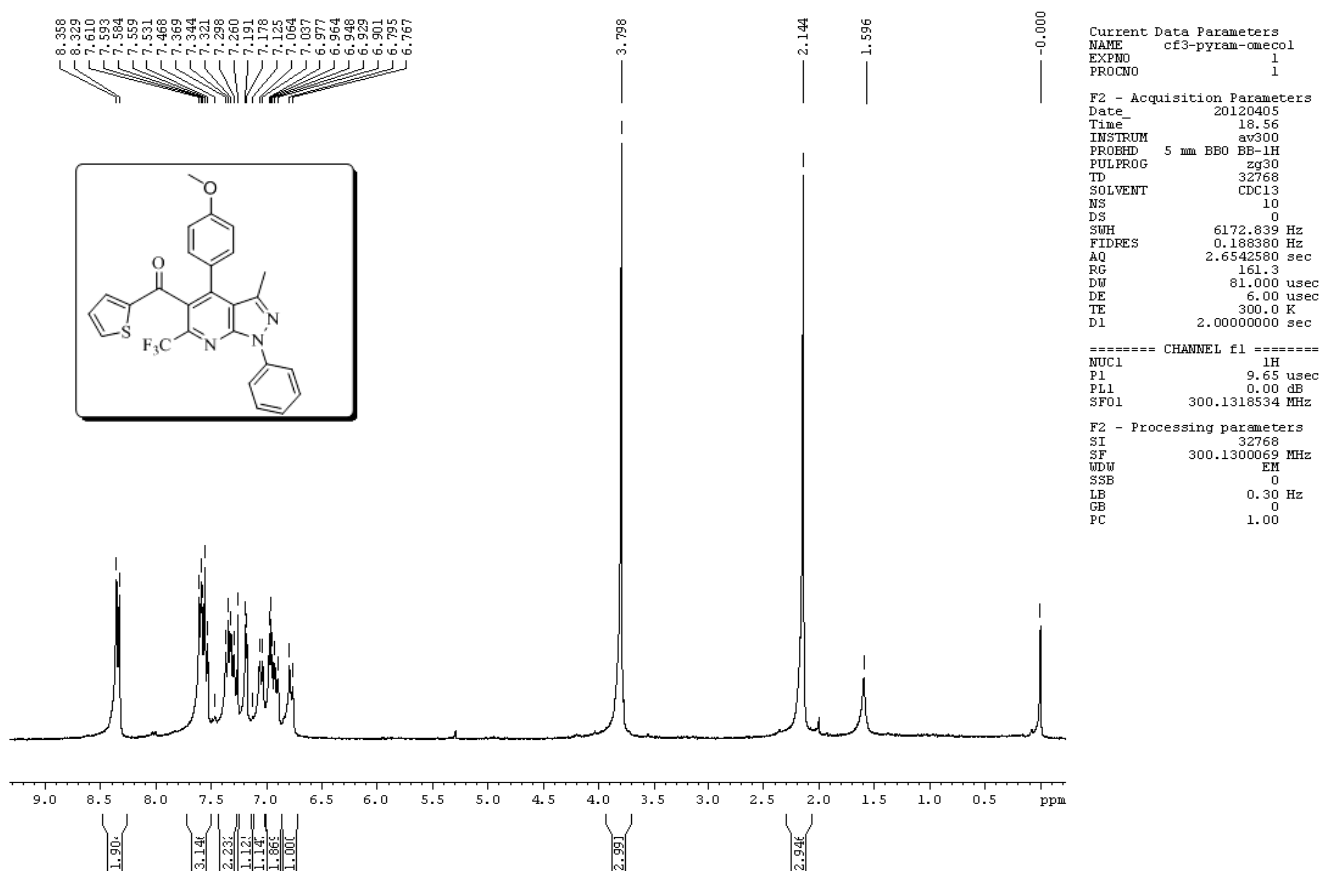


Figure 28. ¹H NMR spectrum of 4e-expansion

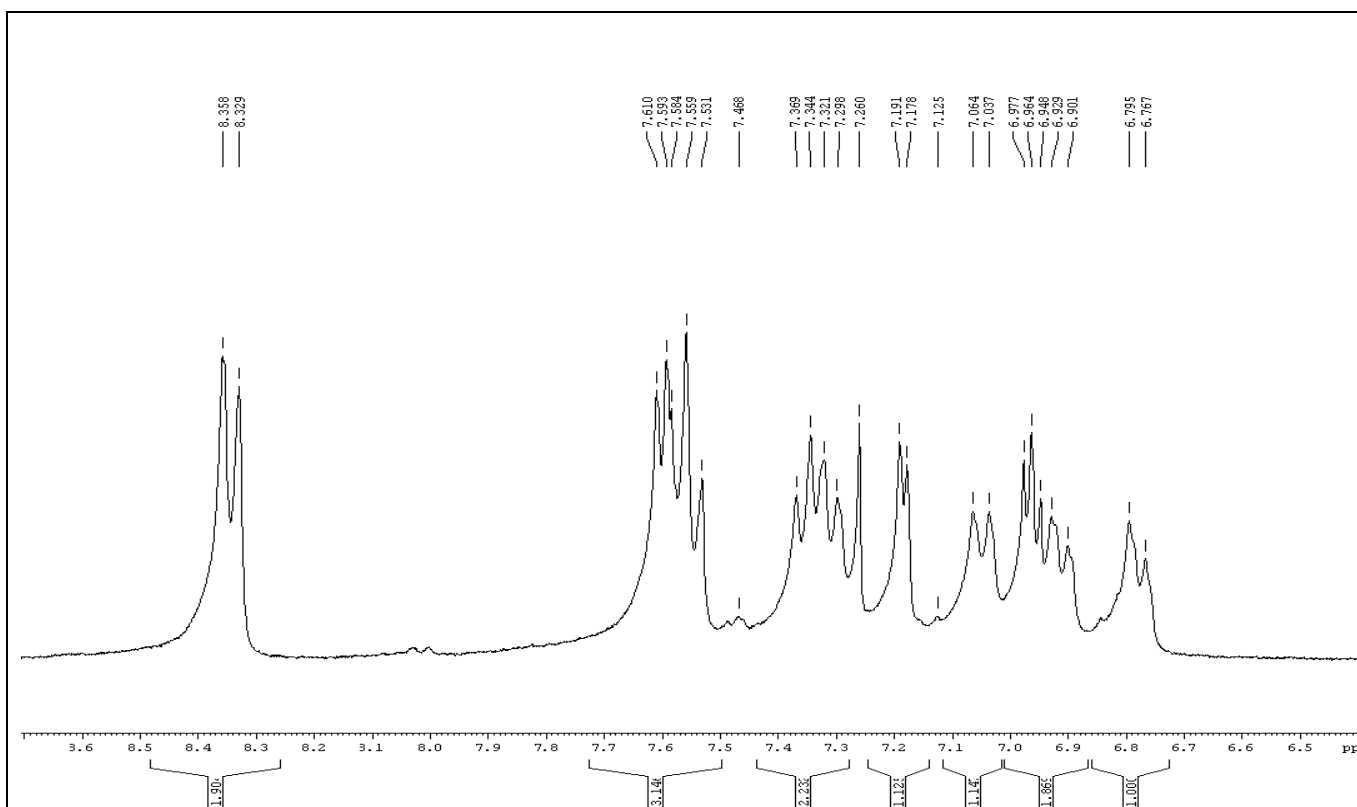


Figure 29. ^1H NMR spectrum of 4e-expansion

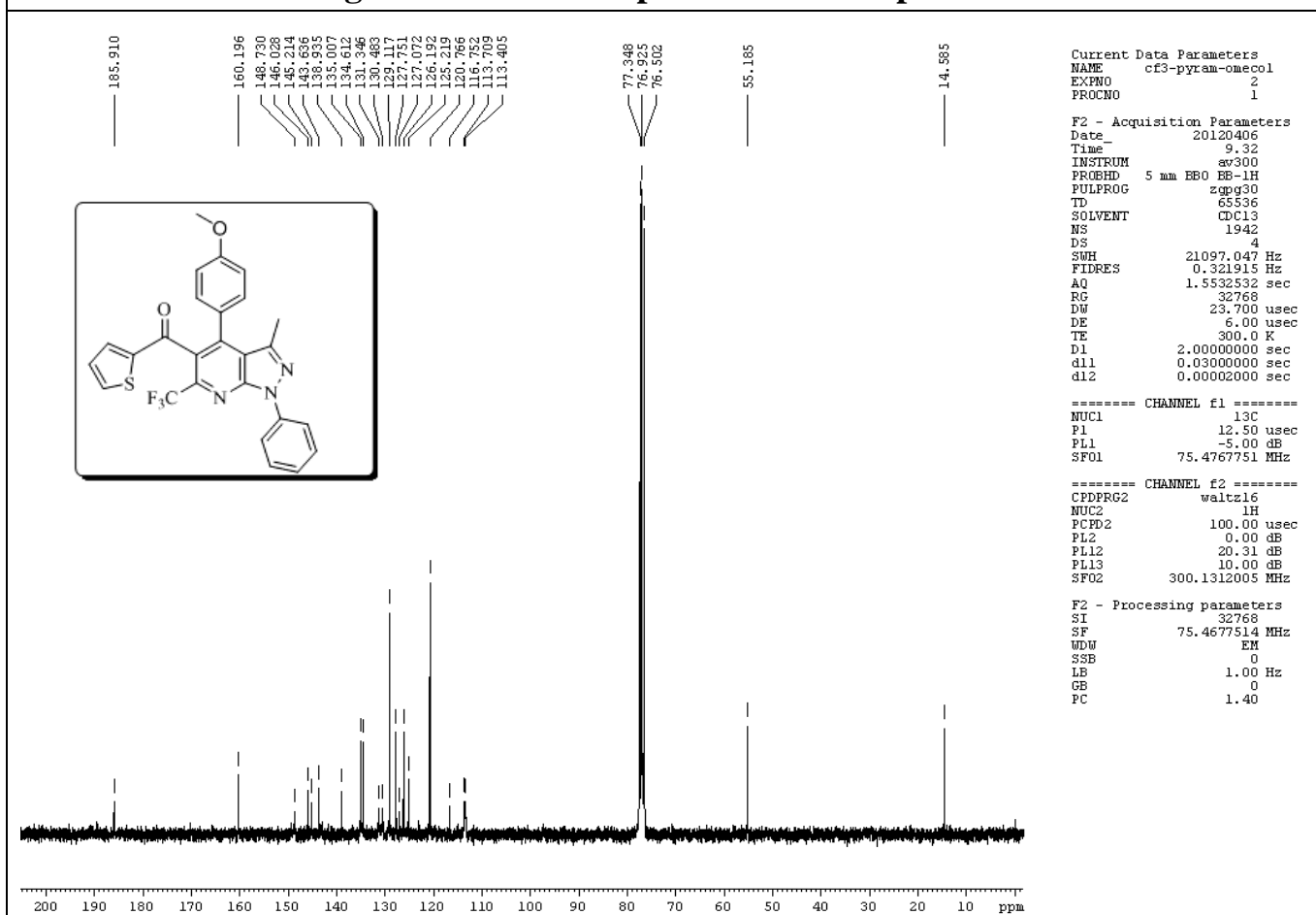


Figure 30. ^{13}C NMR spectrum of 4e

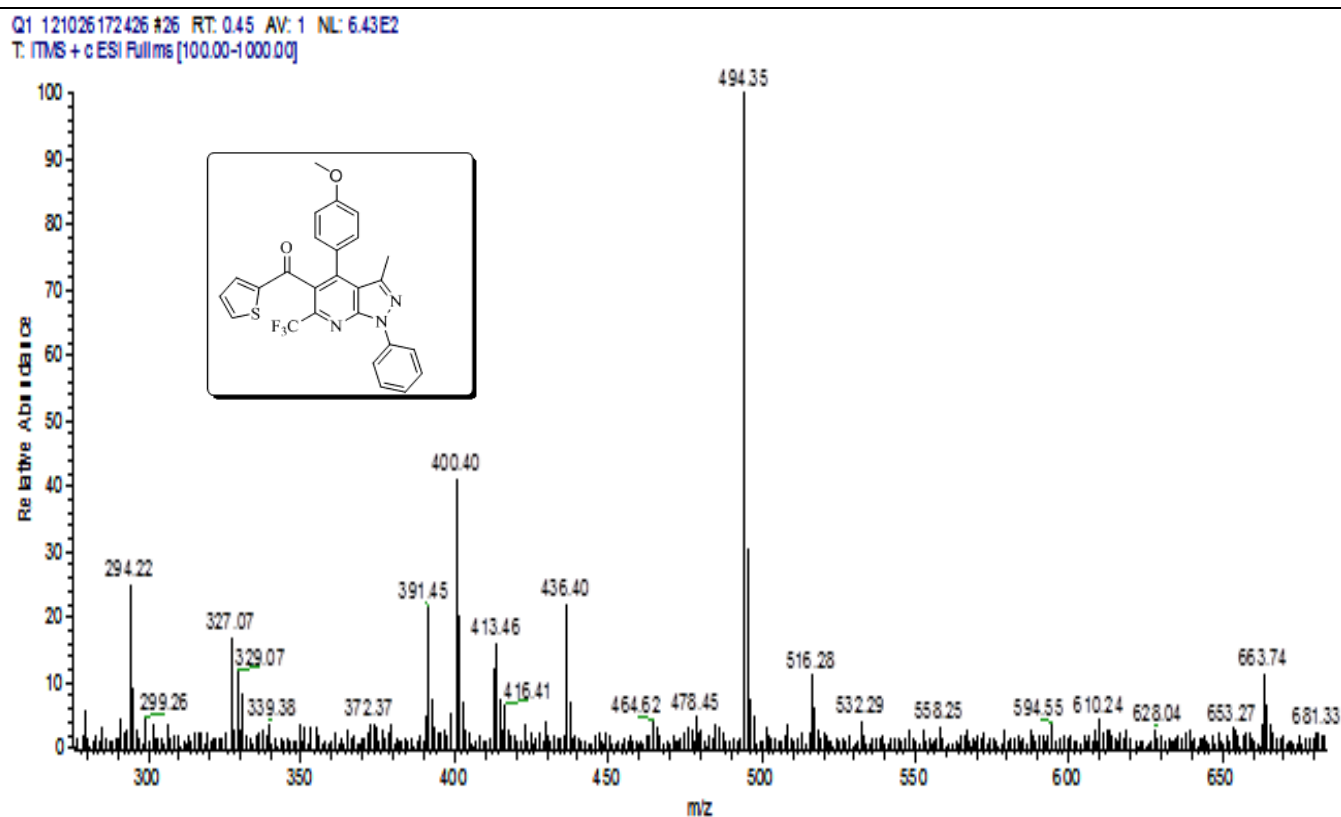


Figure 31. Mass spectrum of 4e

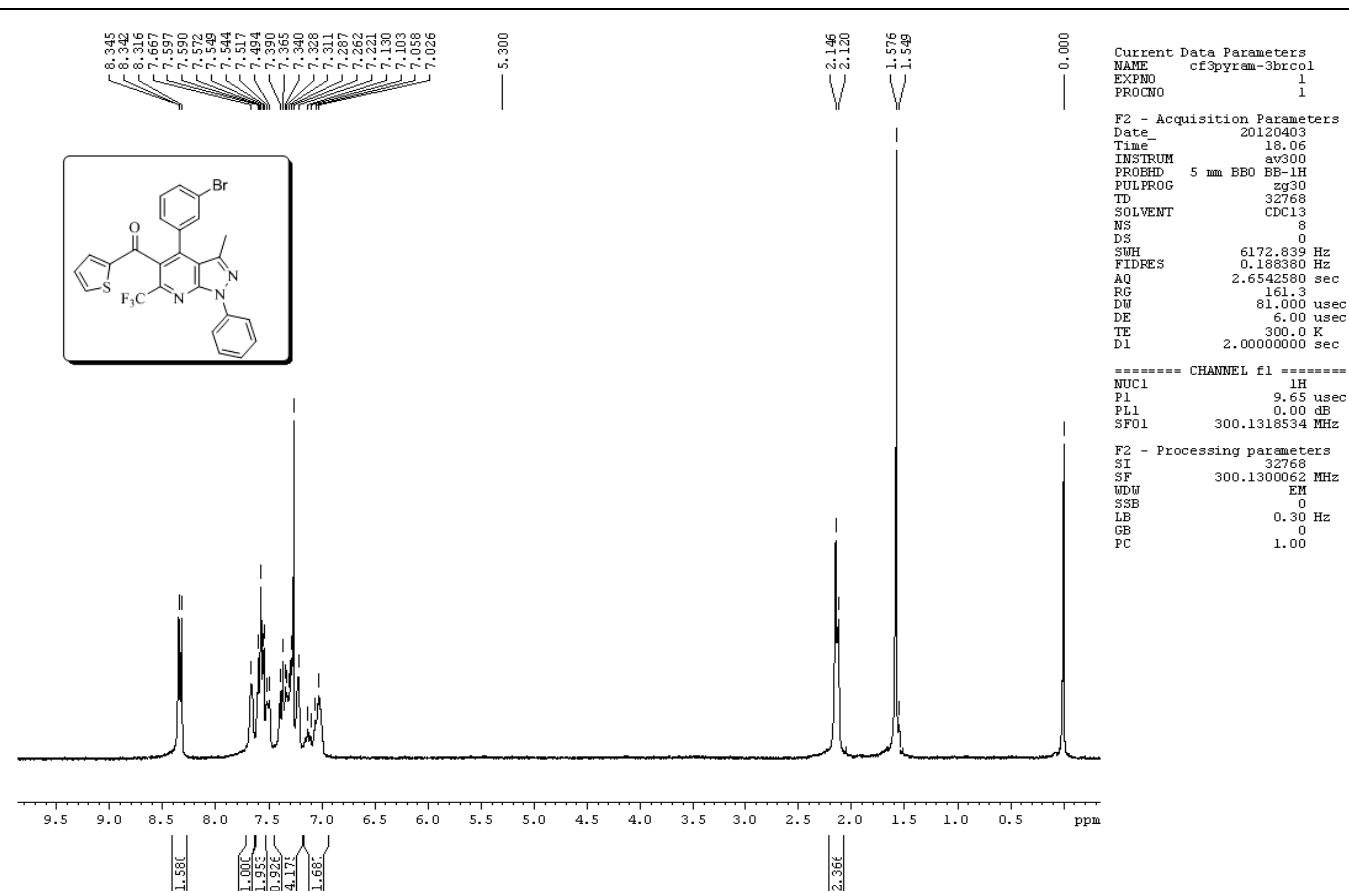
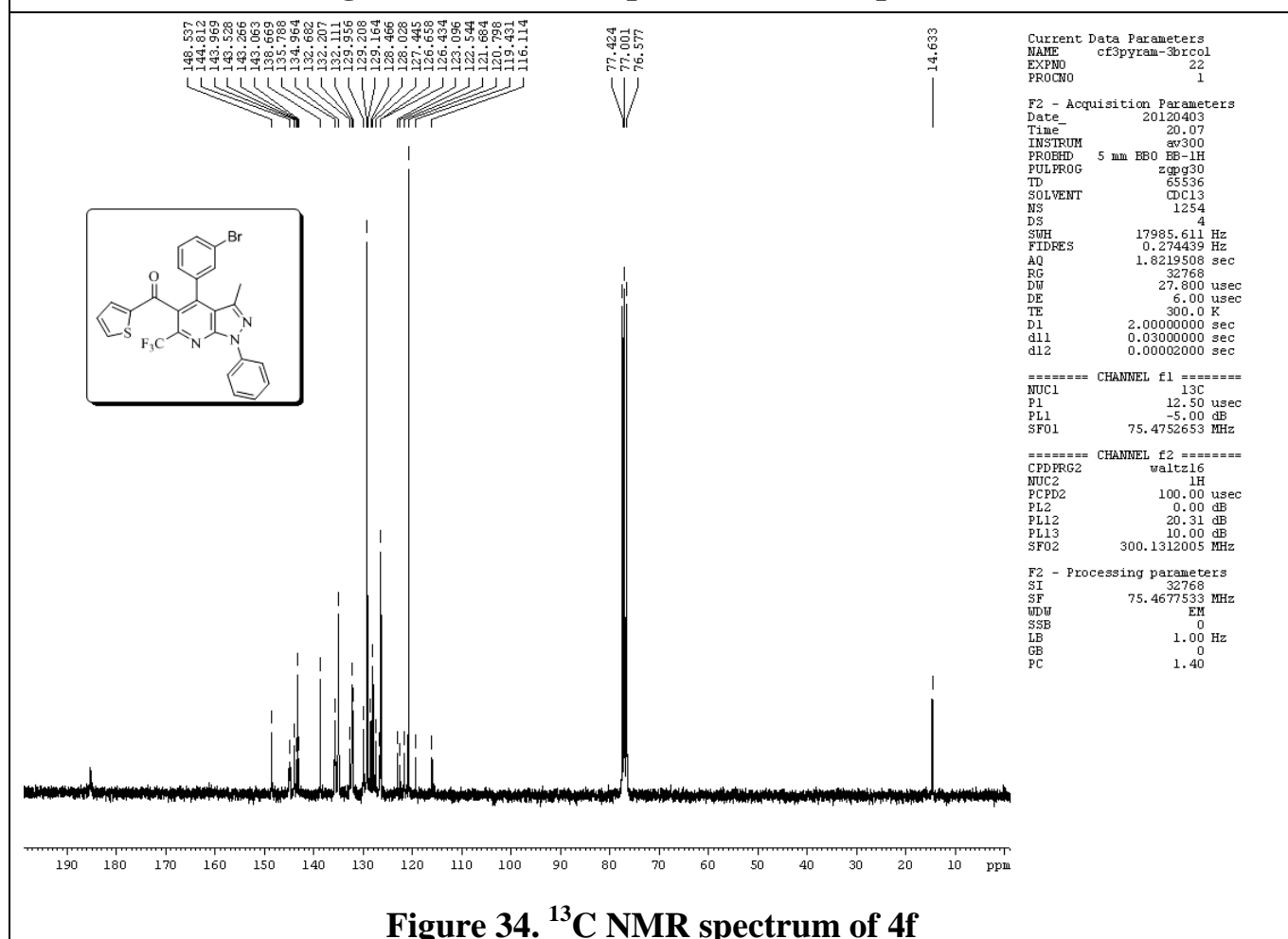
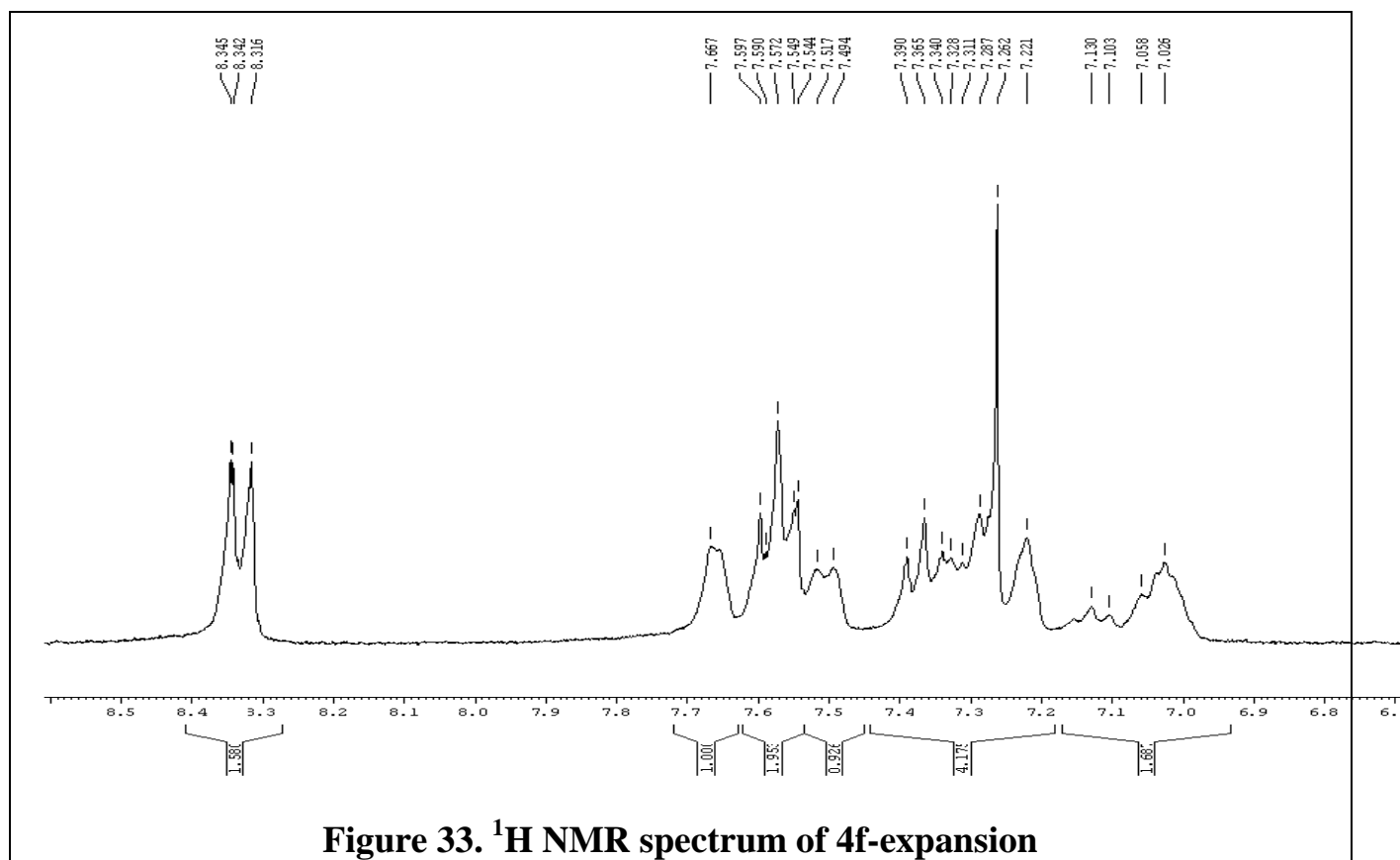


Figure 32. ¹H NMR spectrum of 4f



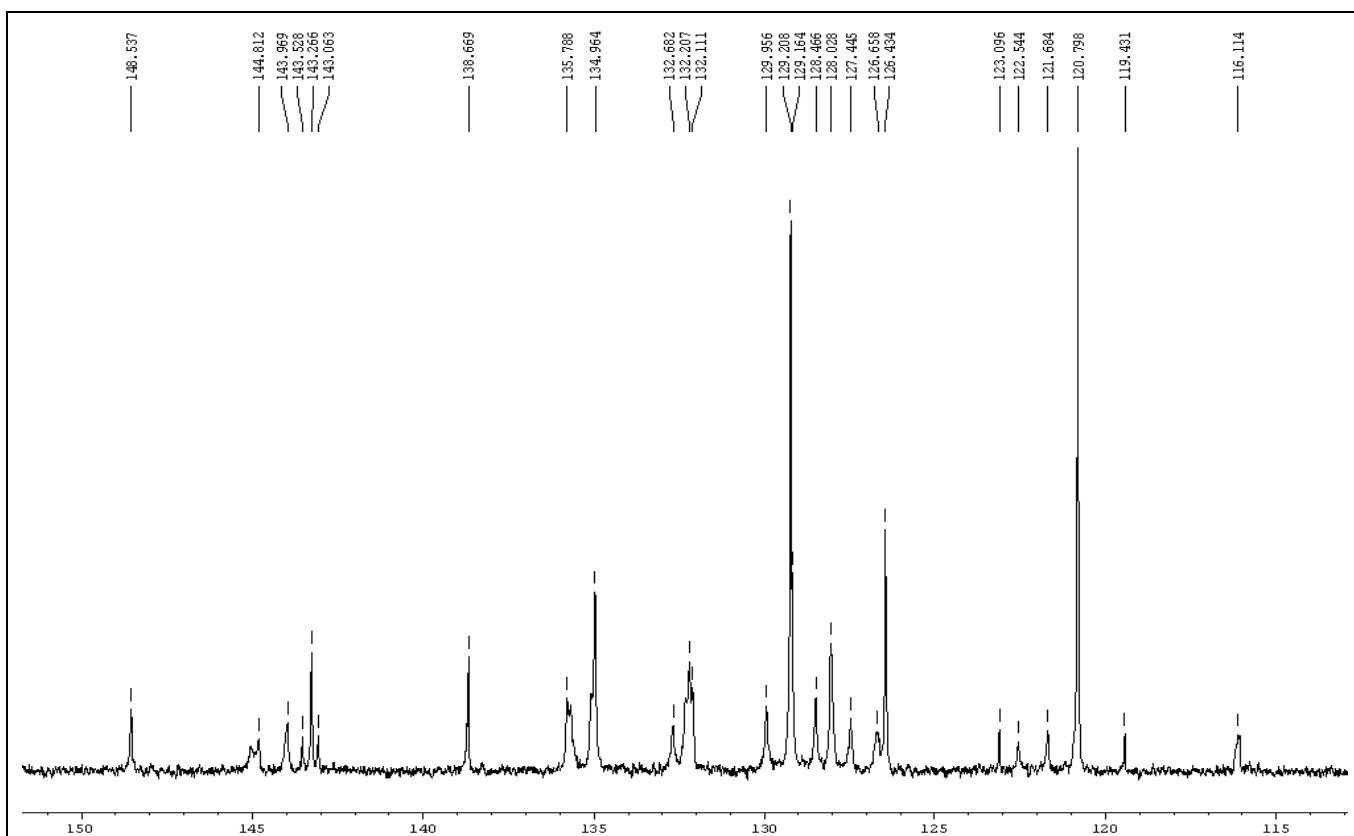


Figure 35. ^{13}C NMR spectrum of 4f-expansion

Q6_121026172426 #34 RT: 0.58 AV: 1 NL: 1.11E3
T: ITMS + c ESI Full ms [100.00-1000.00]

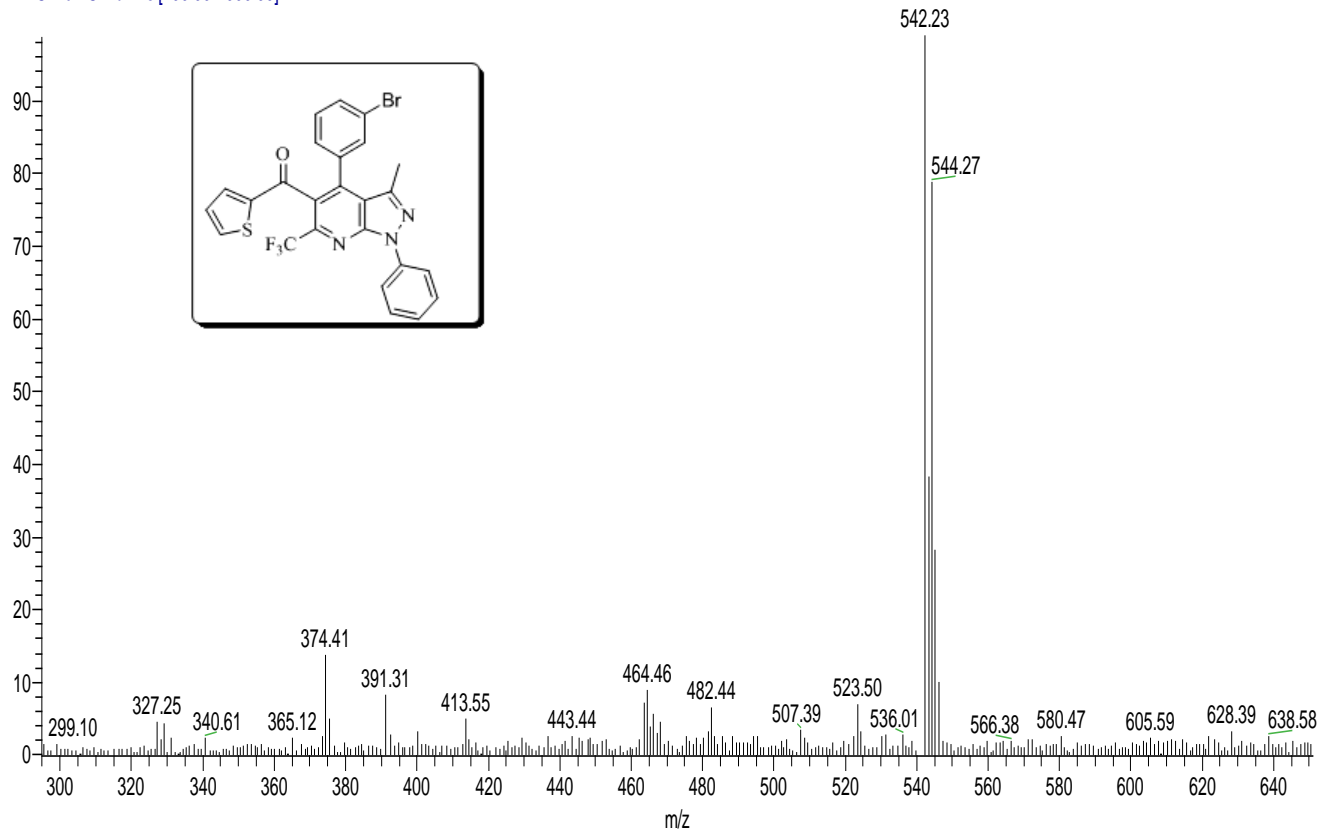
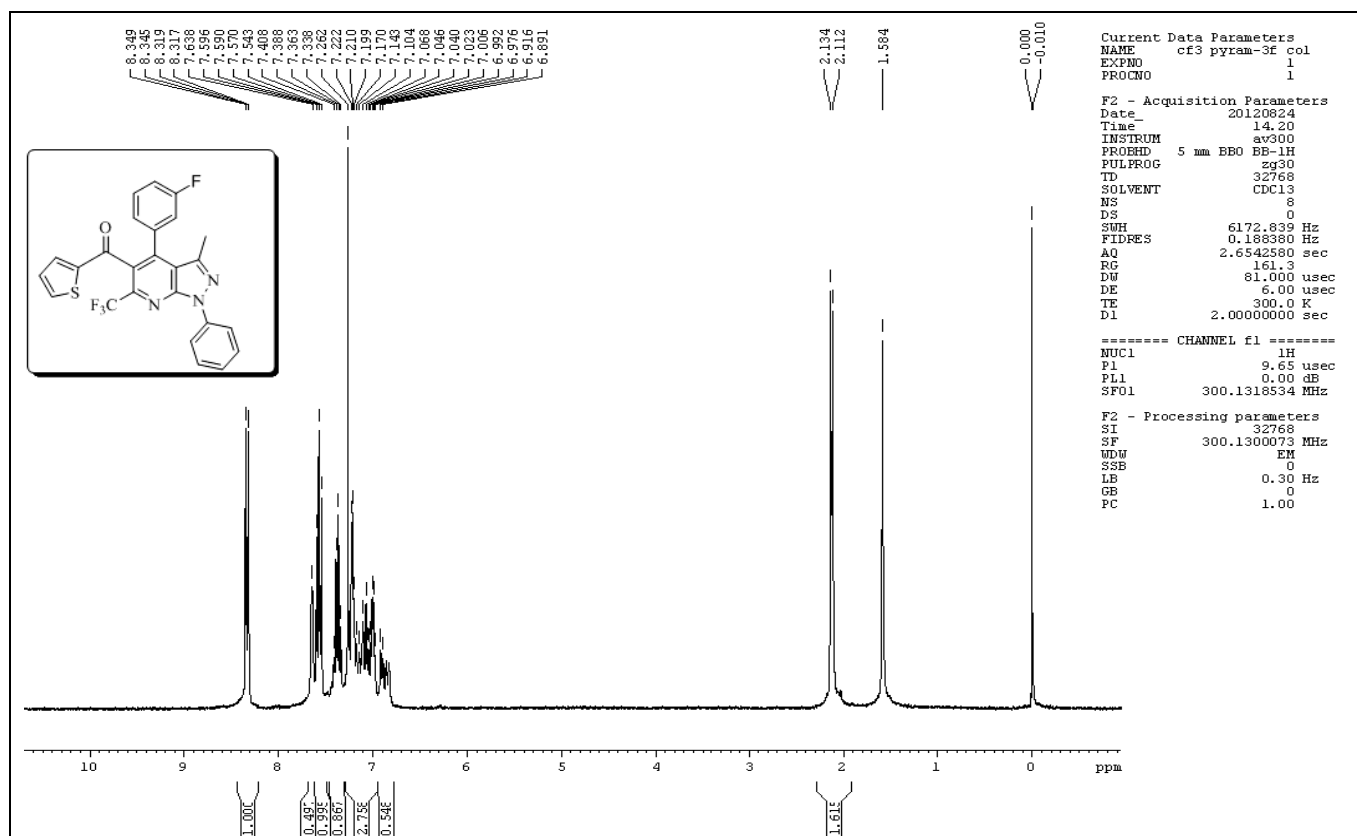


Figure 36. Mass spectrum of 4f



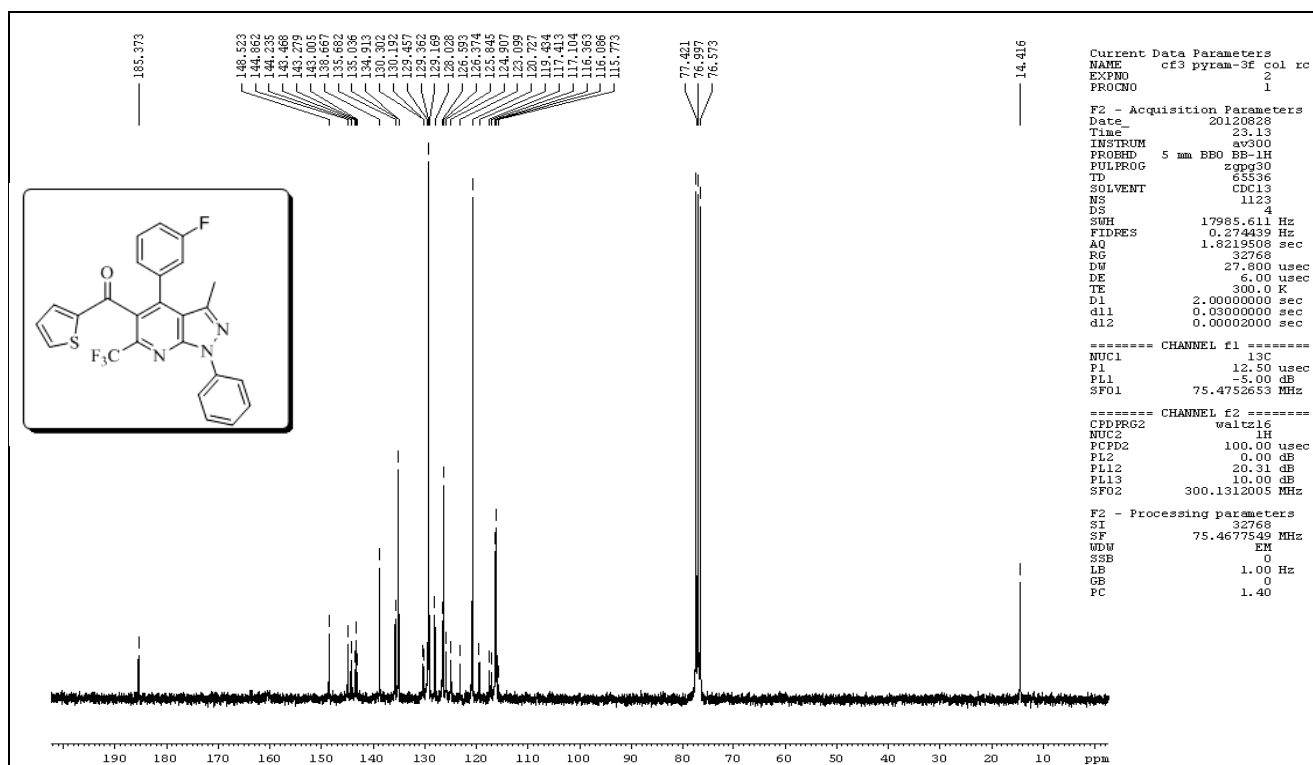


Figure 39. ^{13}C NMR spectrum of 4g

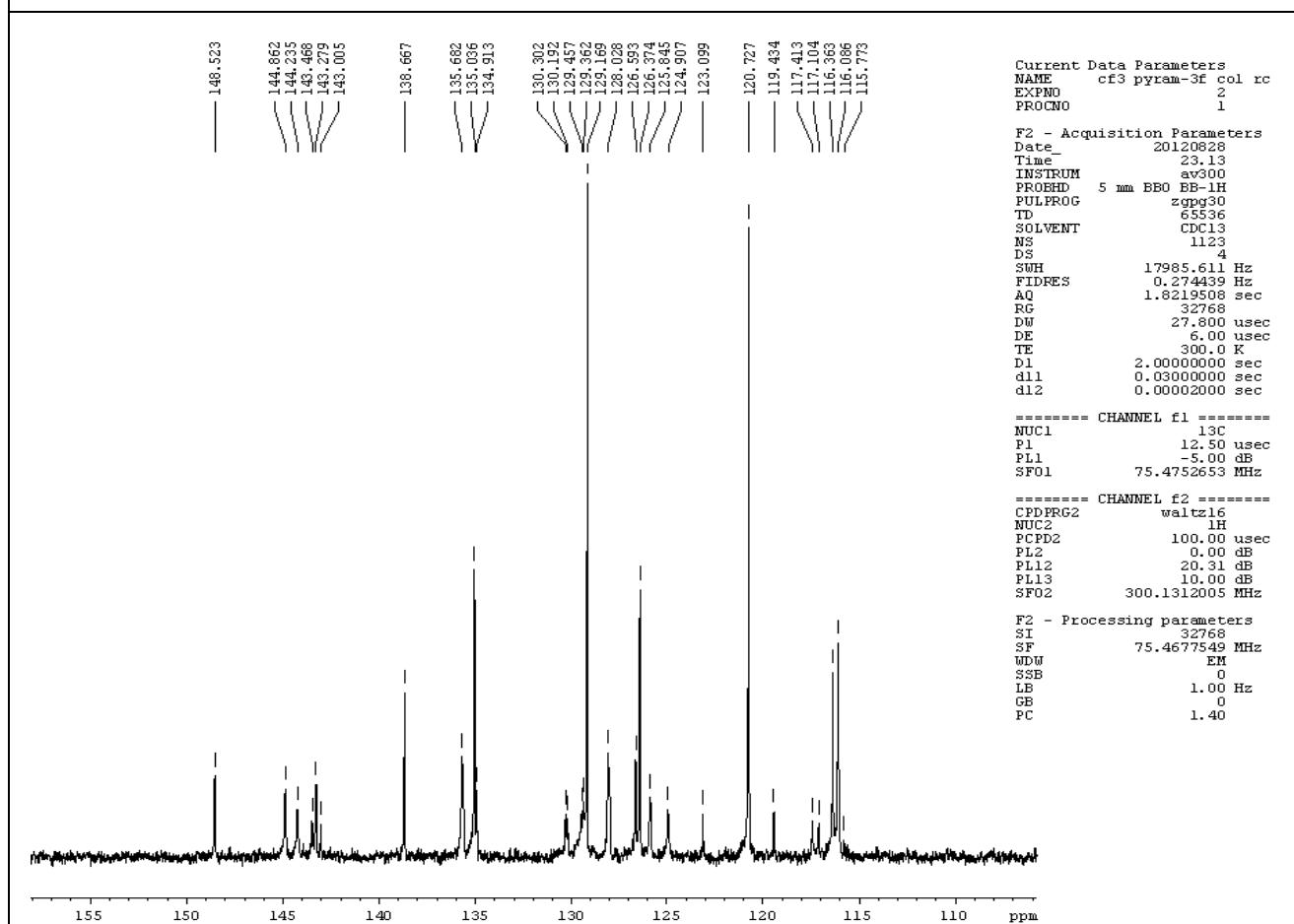


Figure 40. ^{13}C NMR spectrum of 4g-expansion

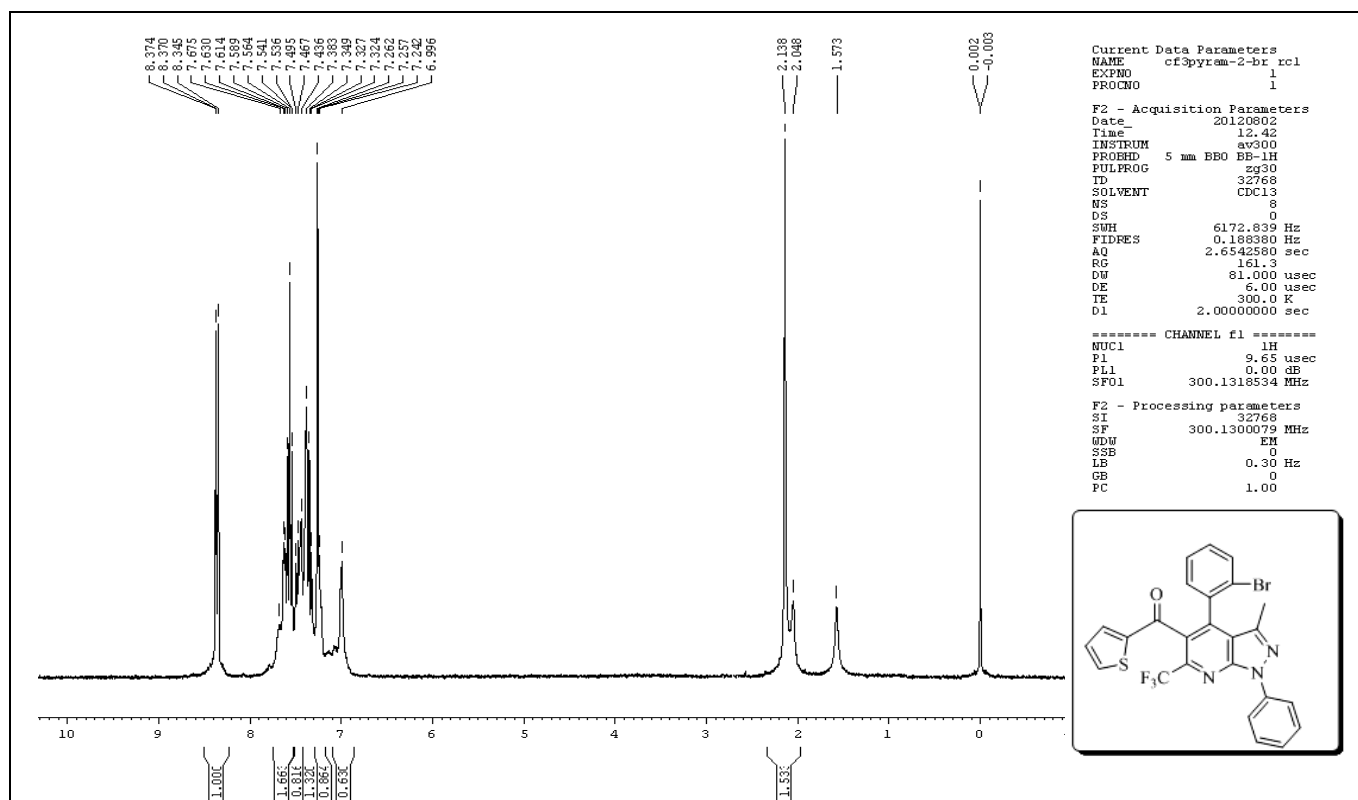


Figure 41. ^1H NMR spectrum of 4h

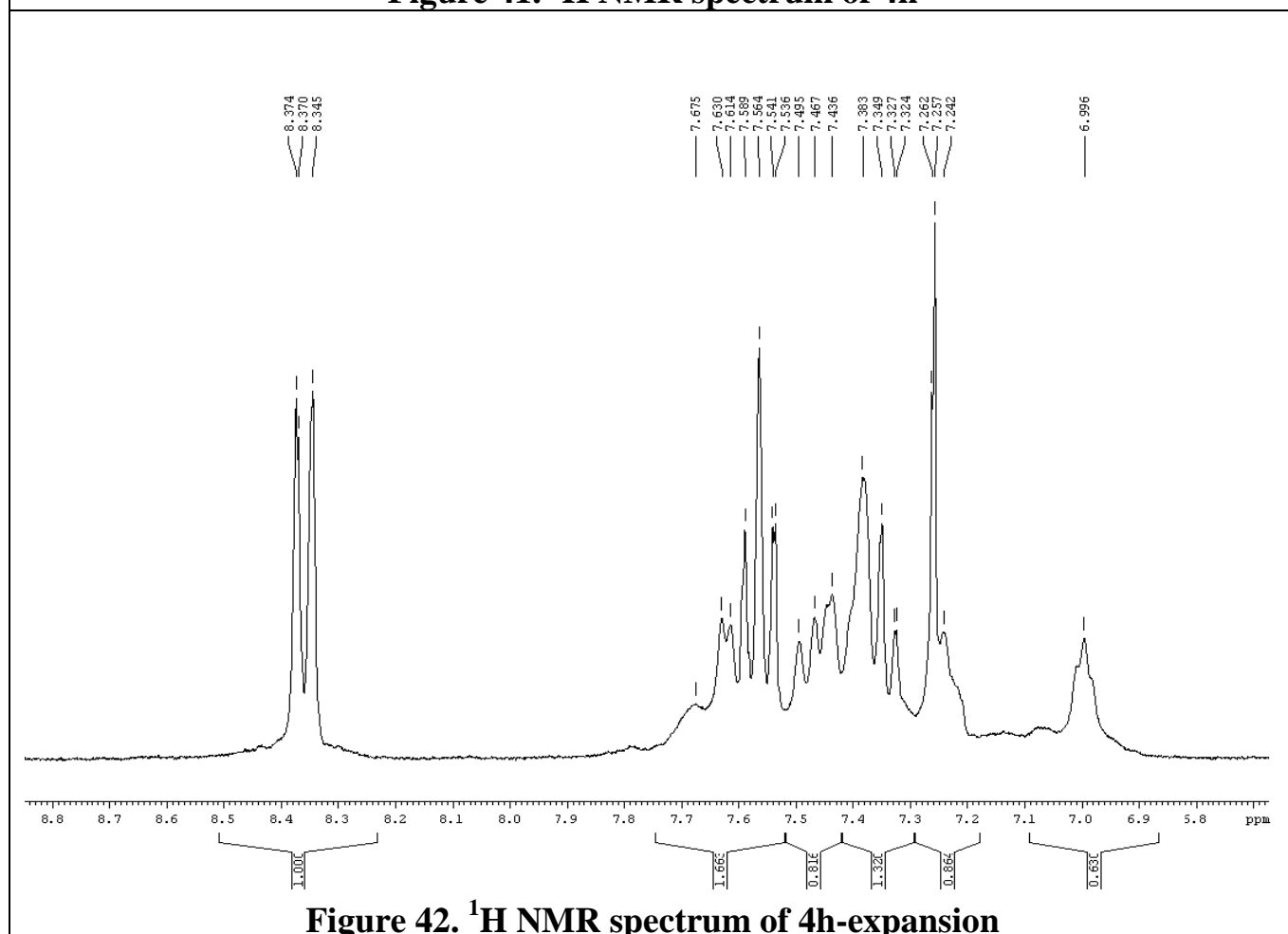


Figure 42. ^1H NMR spectrum of 4h-expansion

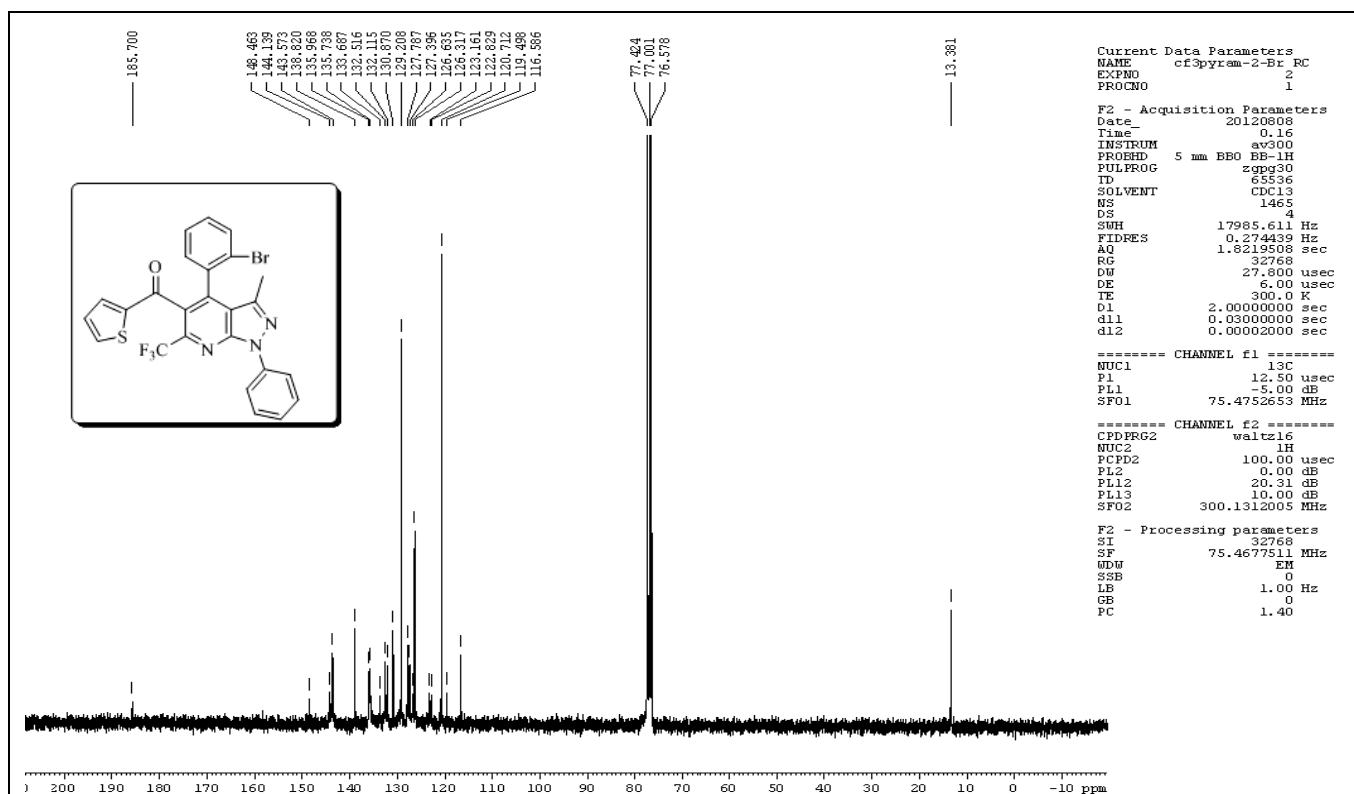


Figure 43. ^{13}C NMR spectrum of 4h

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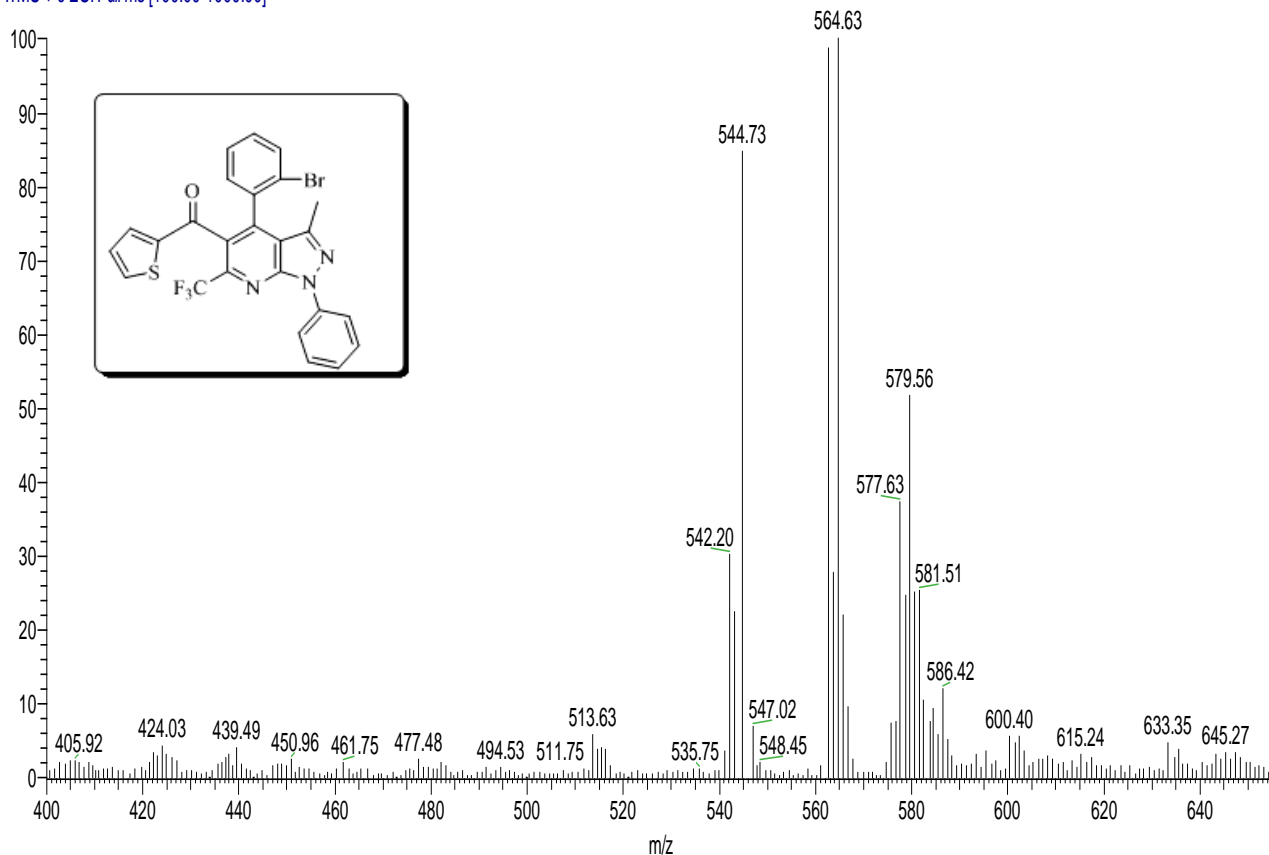


Figure 44. Mass spectrum of 4h

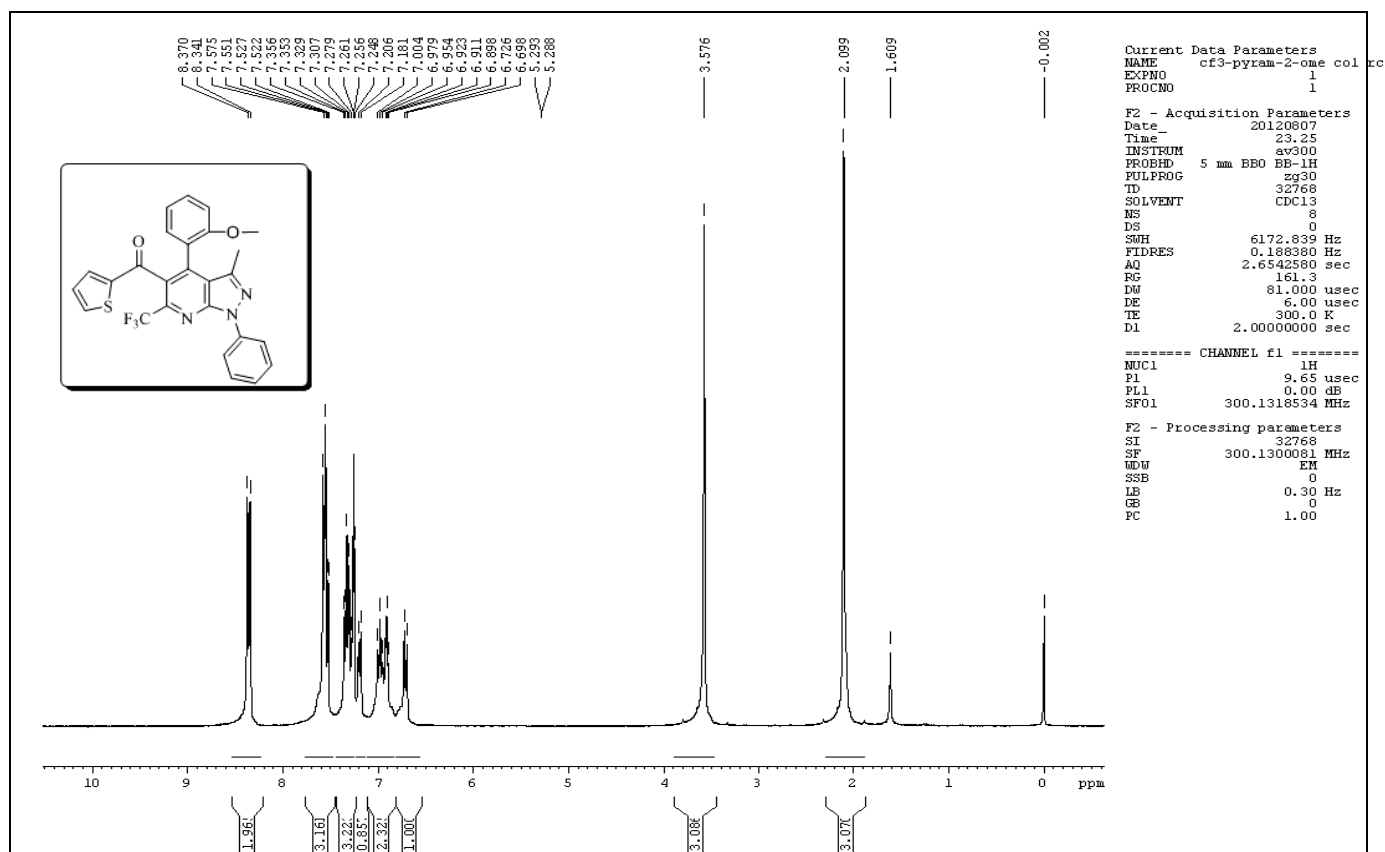


Figure 45. ¹H NMR spectrum of 4i

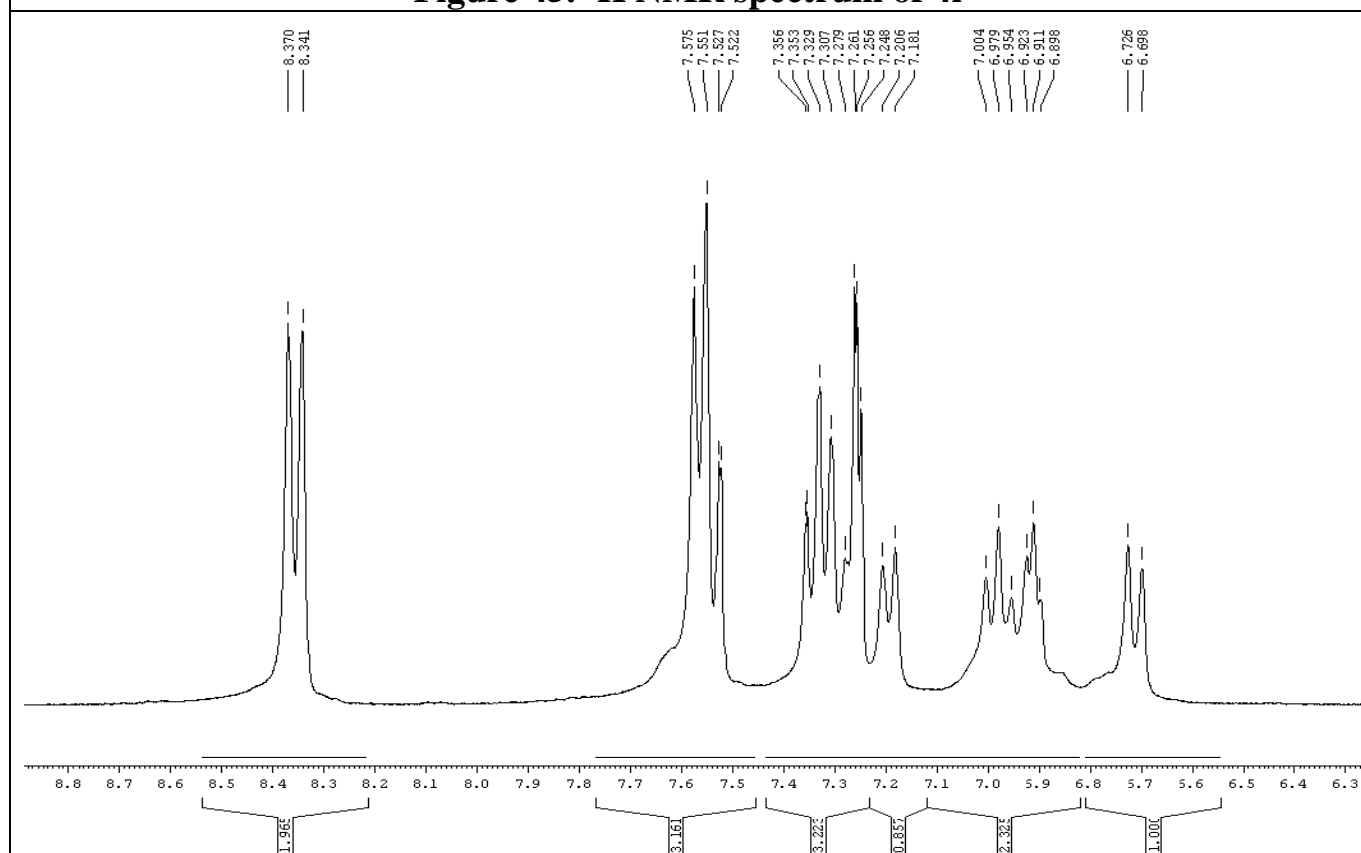


Figure 46. ¹H NMR spectrum of 4i-expansion

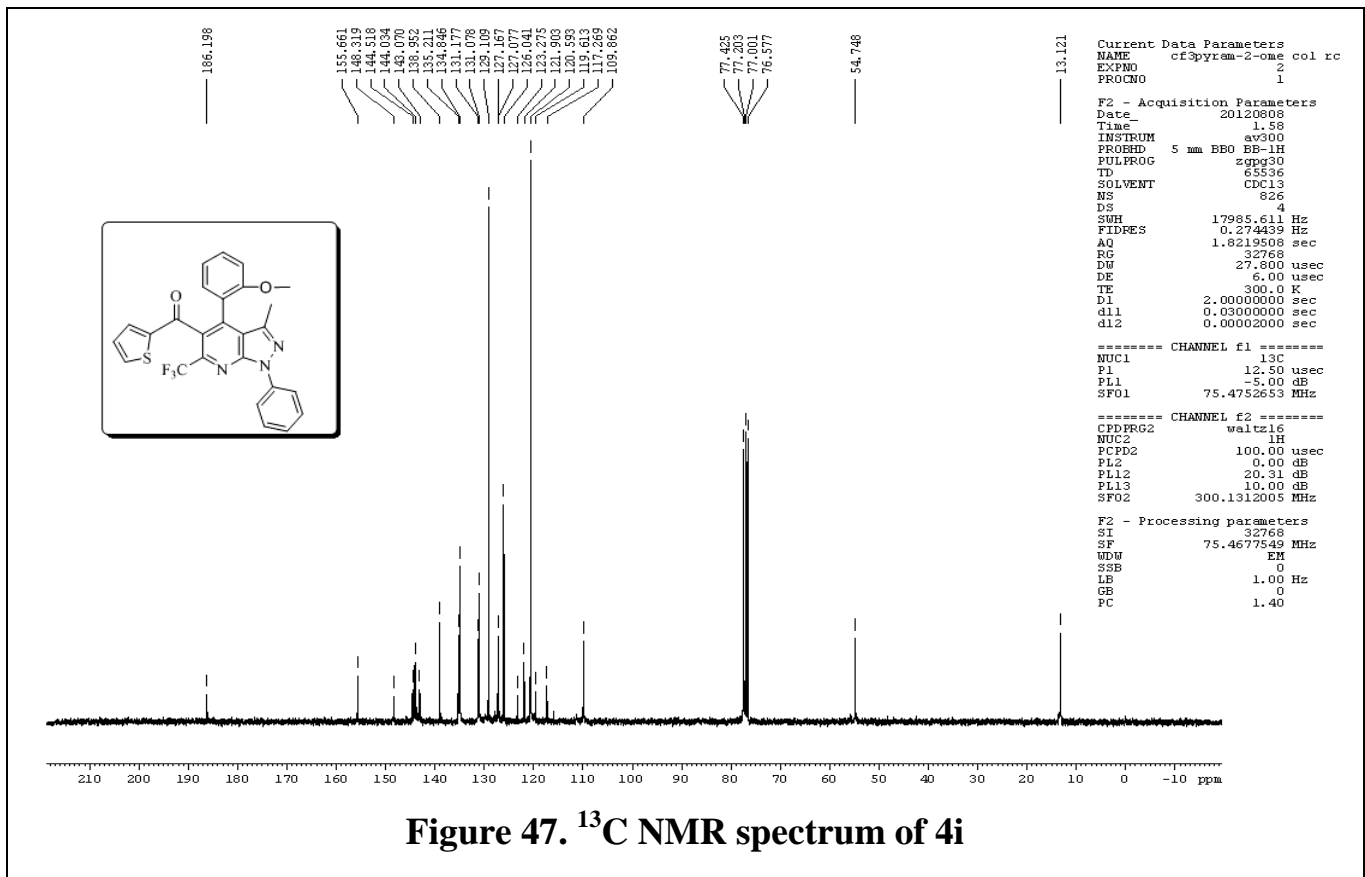


Figure 47. ¹³C NMR spectrum of 4i

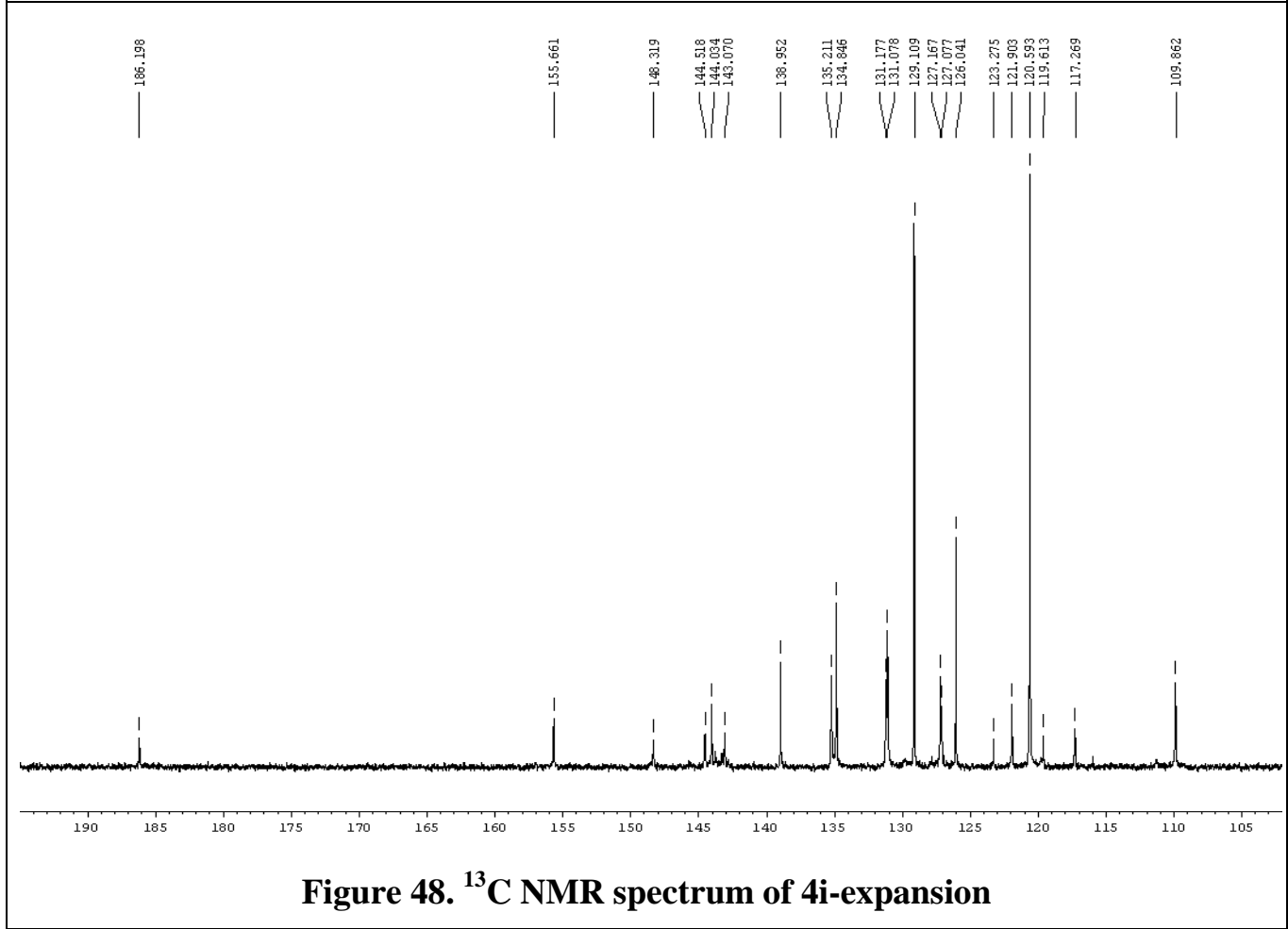


Figure 48. ¹³C NMR spectrum of 4i-expansion

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T: ITMS + c ESI Full ms [100.00-1000.00]

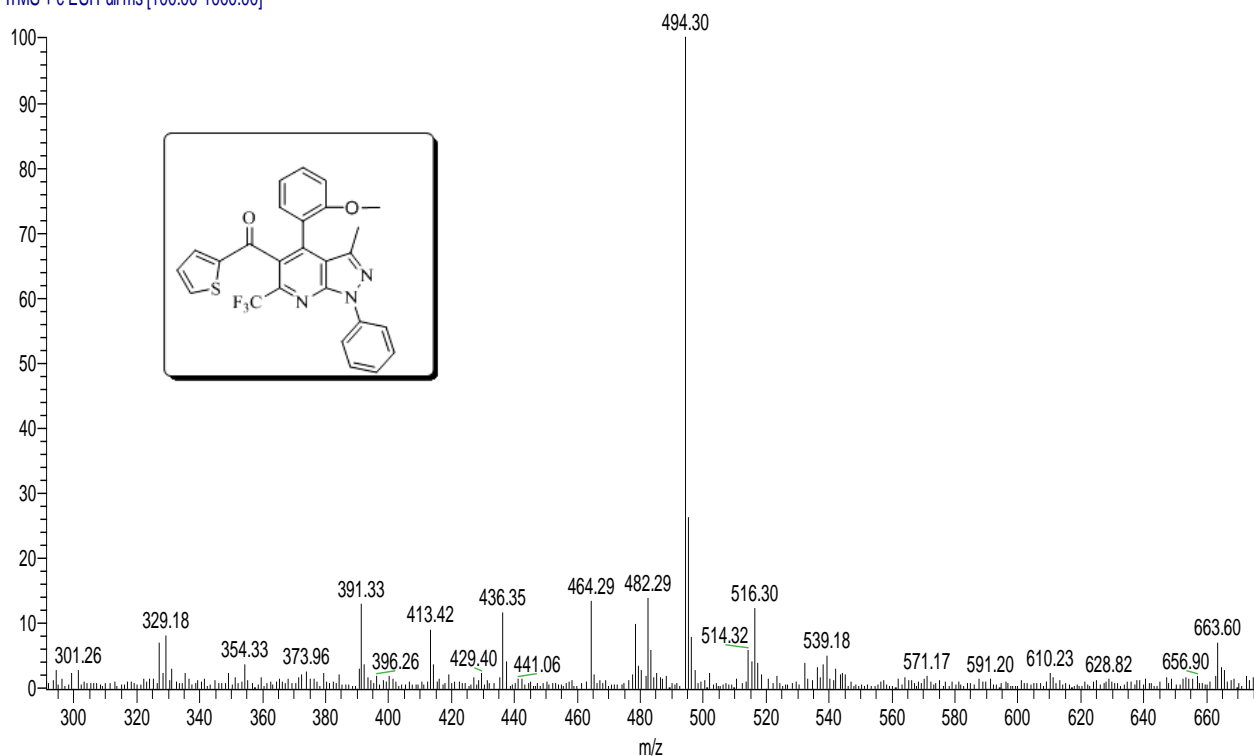


Figure 49. Mass spectrum of 4i

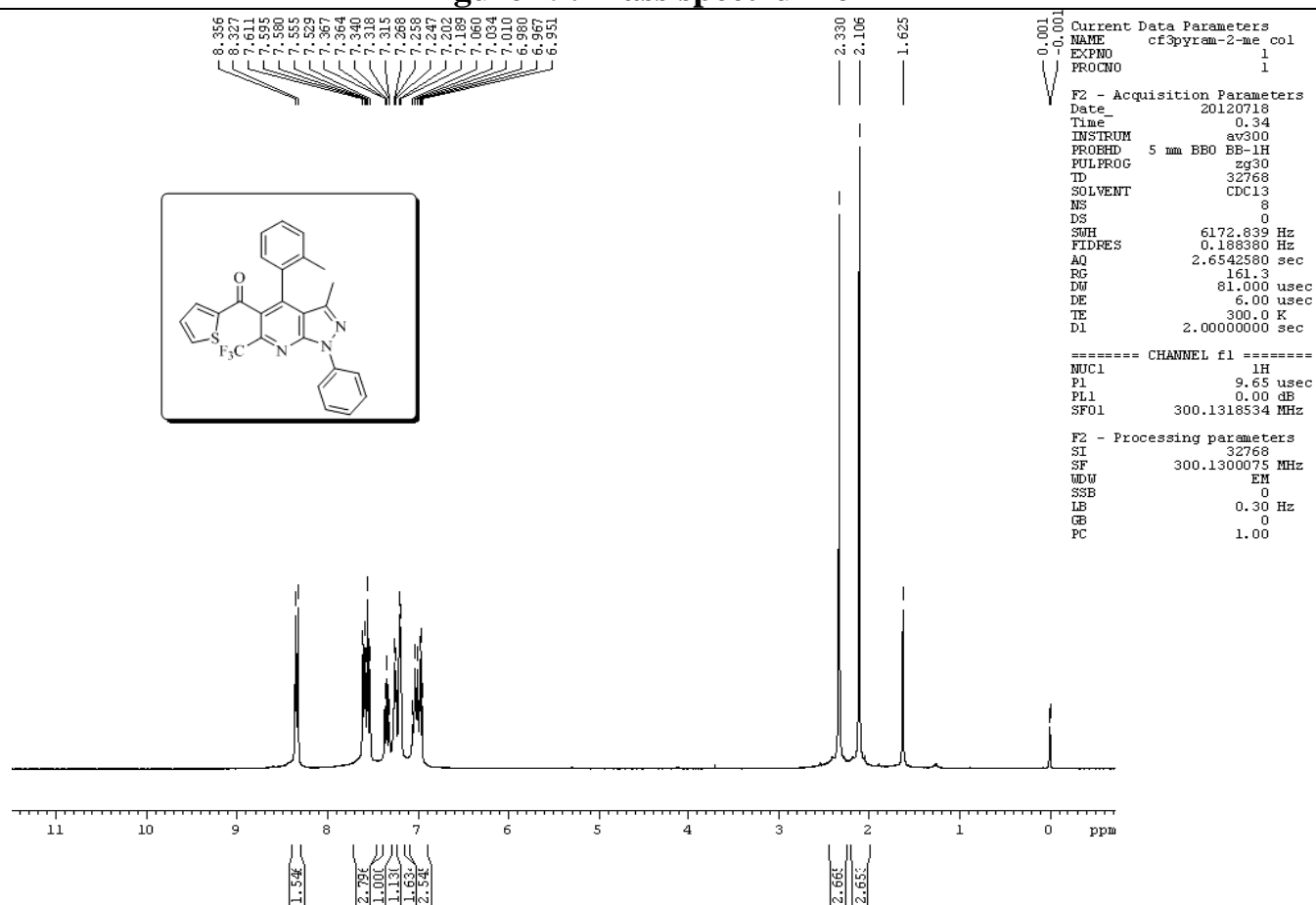
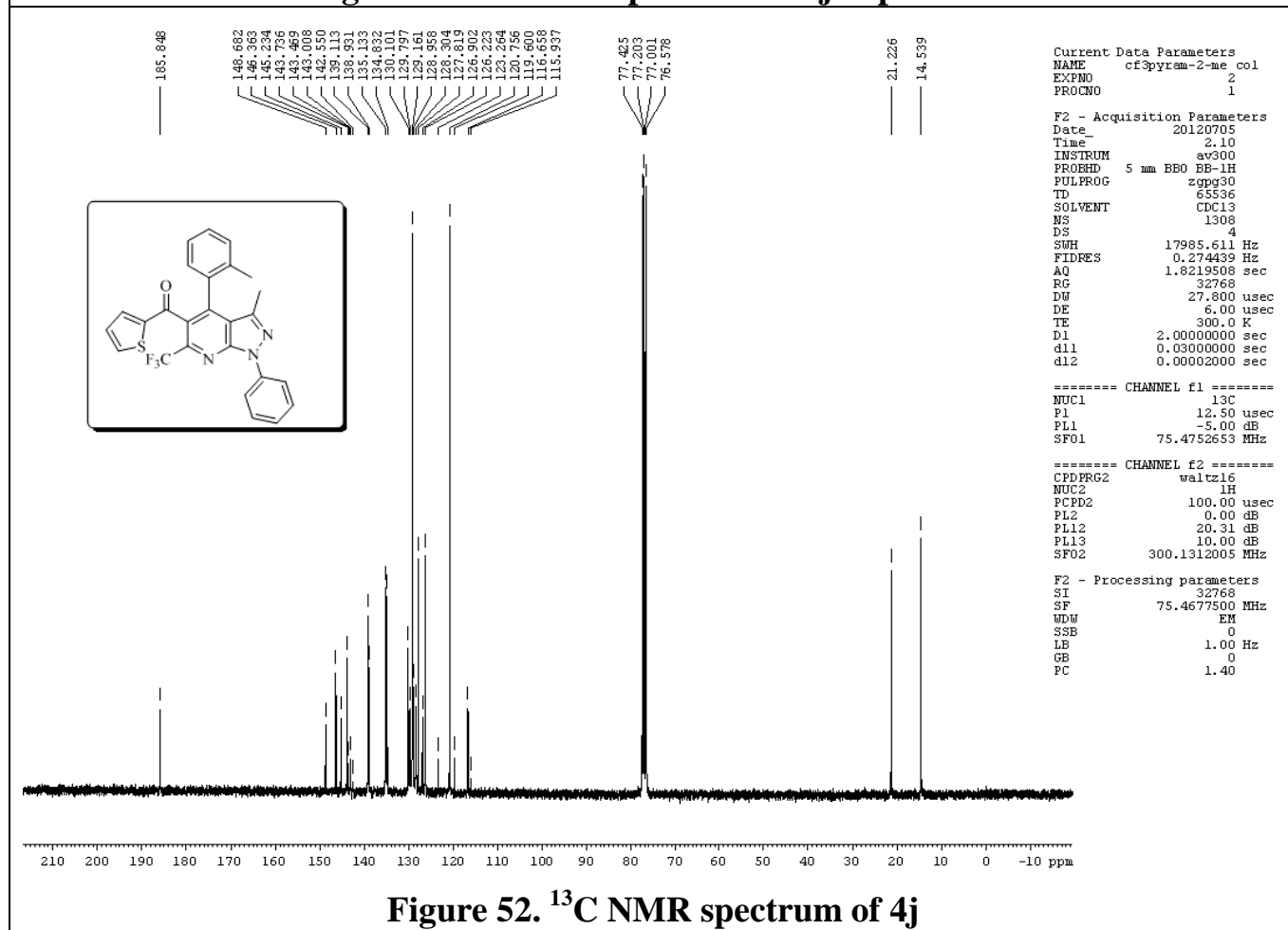
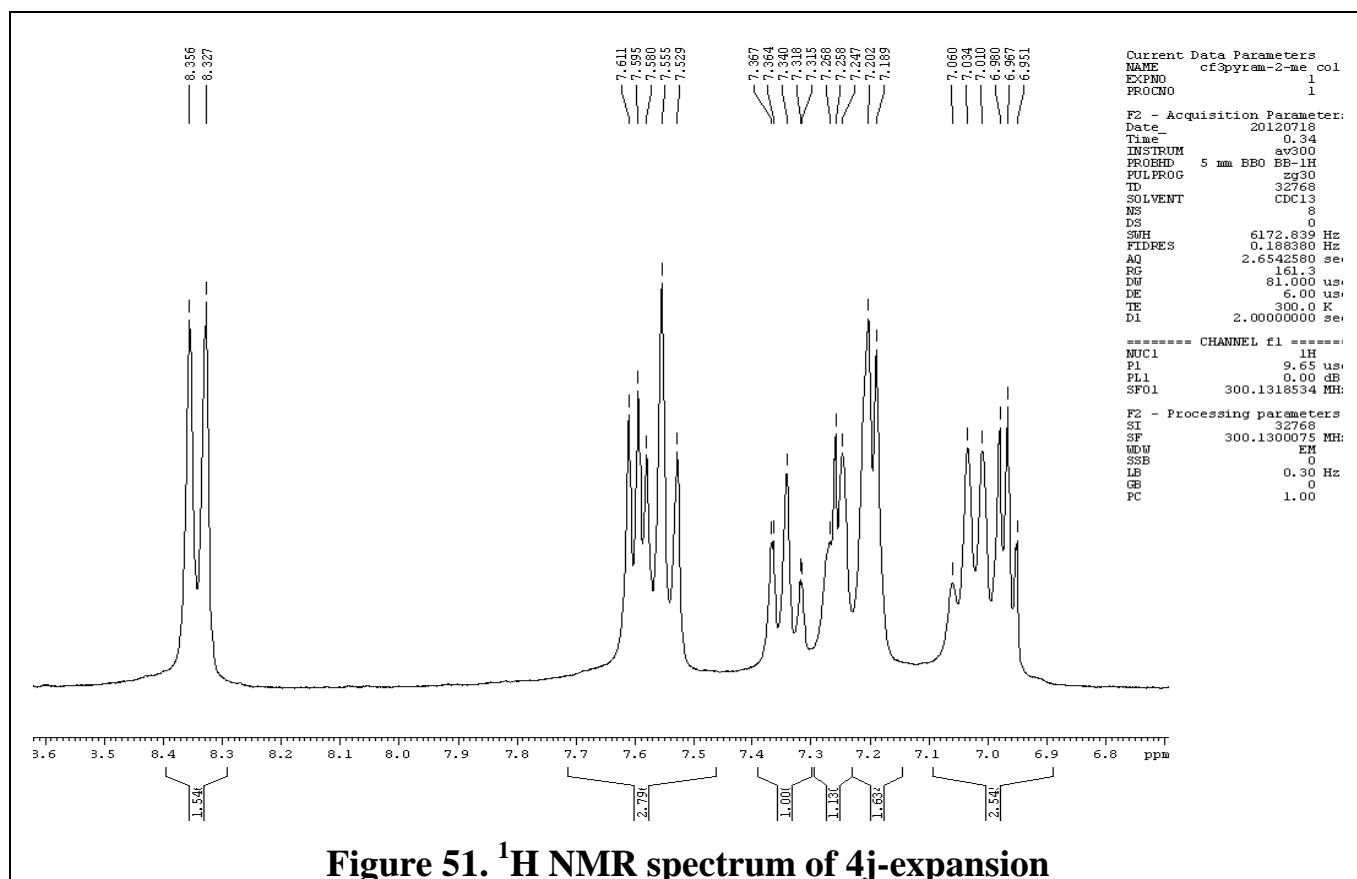
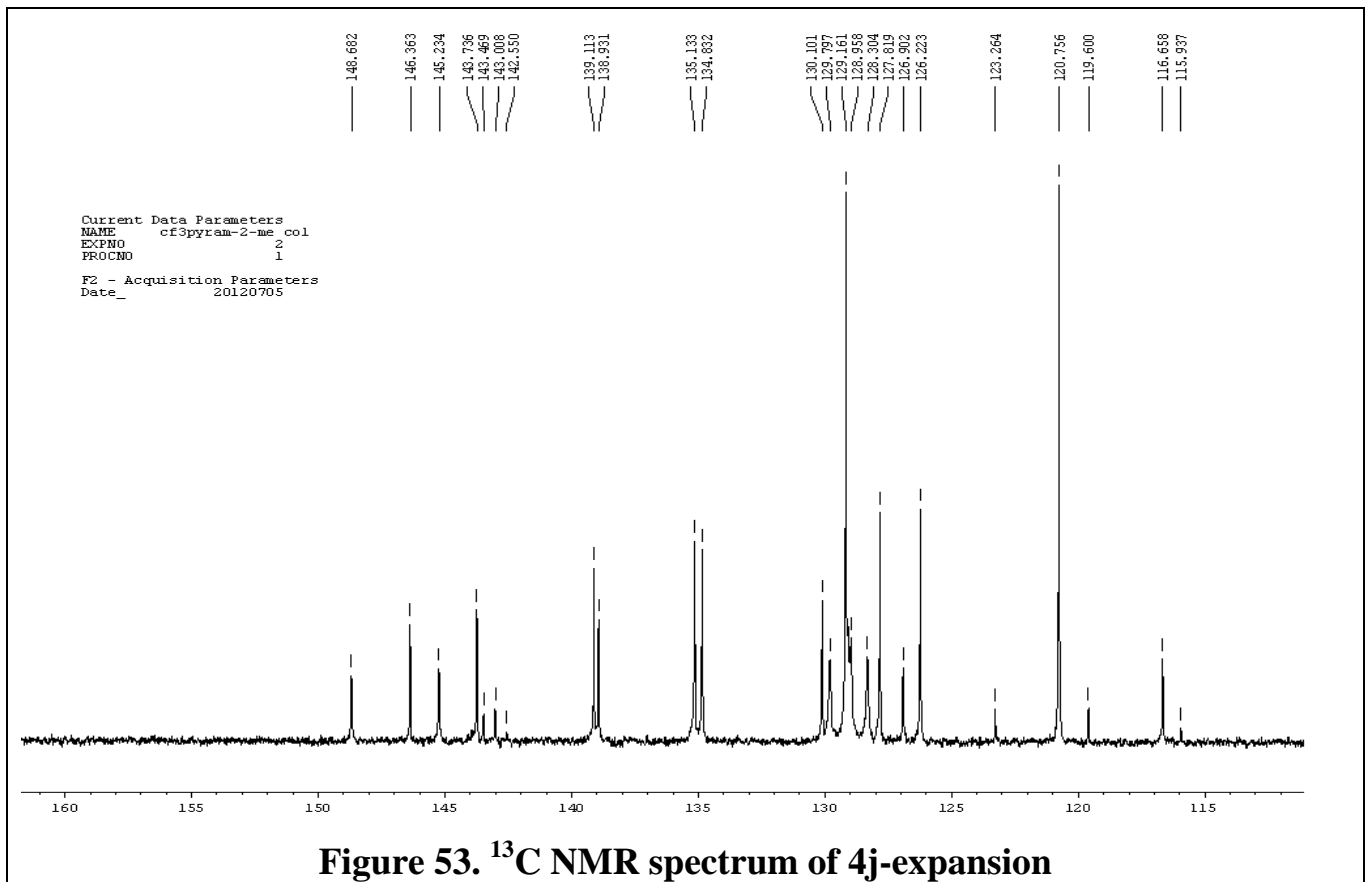
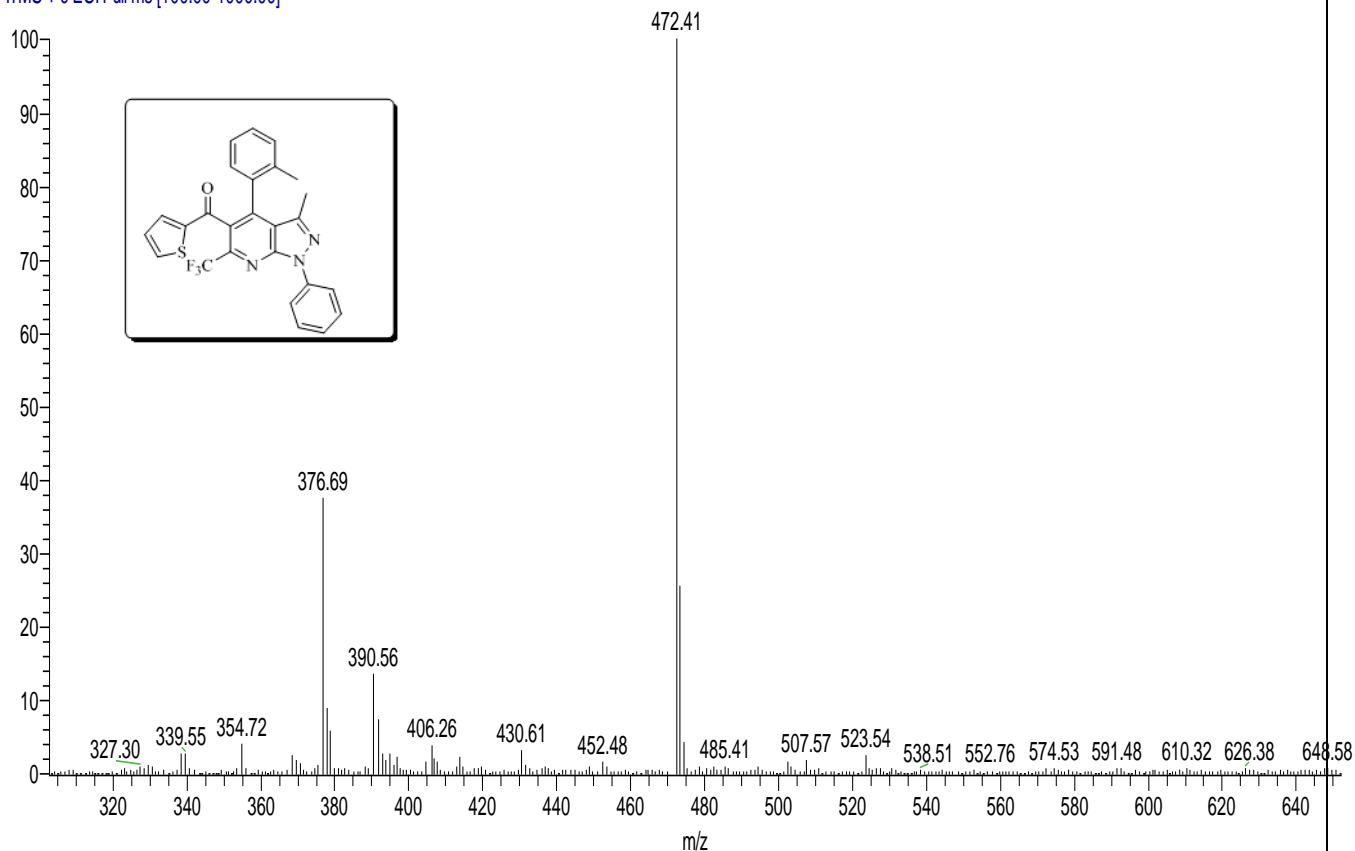


Figure 50. ¹H NMR spectrum of 4j





Q15_121026172426 #34 RT: 0.57 AV: 1 NL: 5.14E3
T: ITMS + c ESI Full ms [100.00-1000.00]



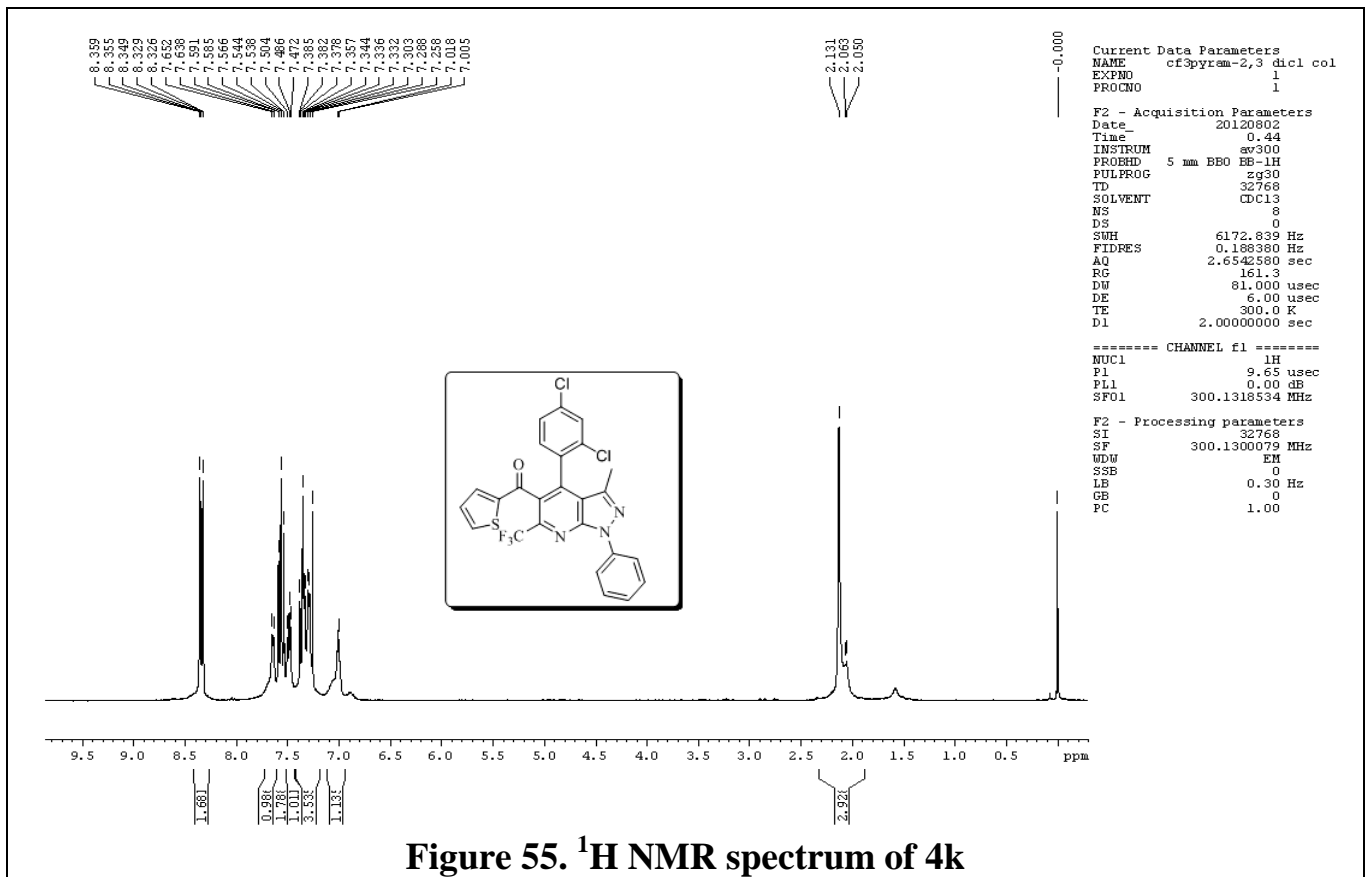


Figure 55. ¹H NMR spectrum of 4k

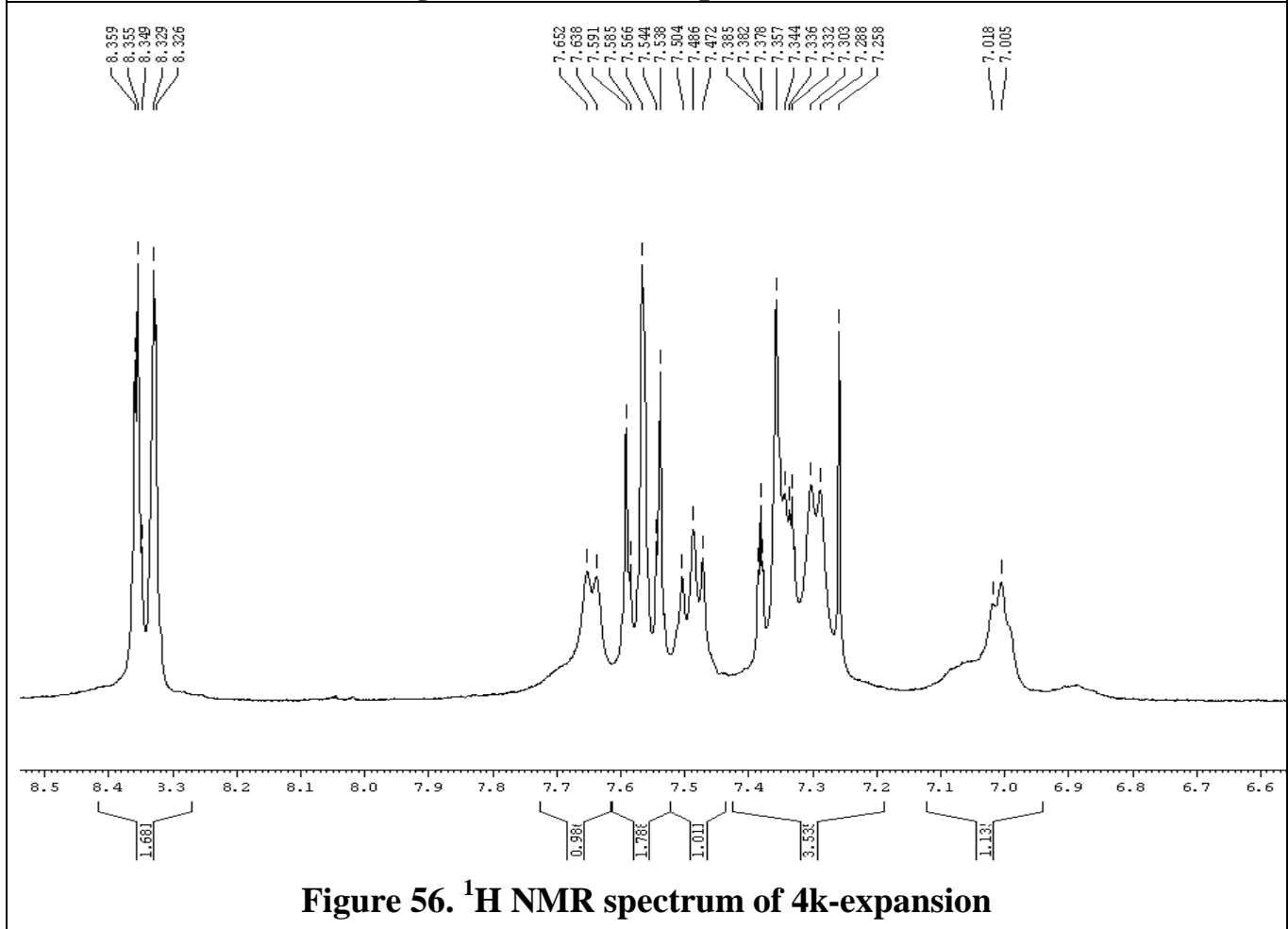


Figure 56. ¹H NMR spectrum of 4k-expansion

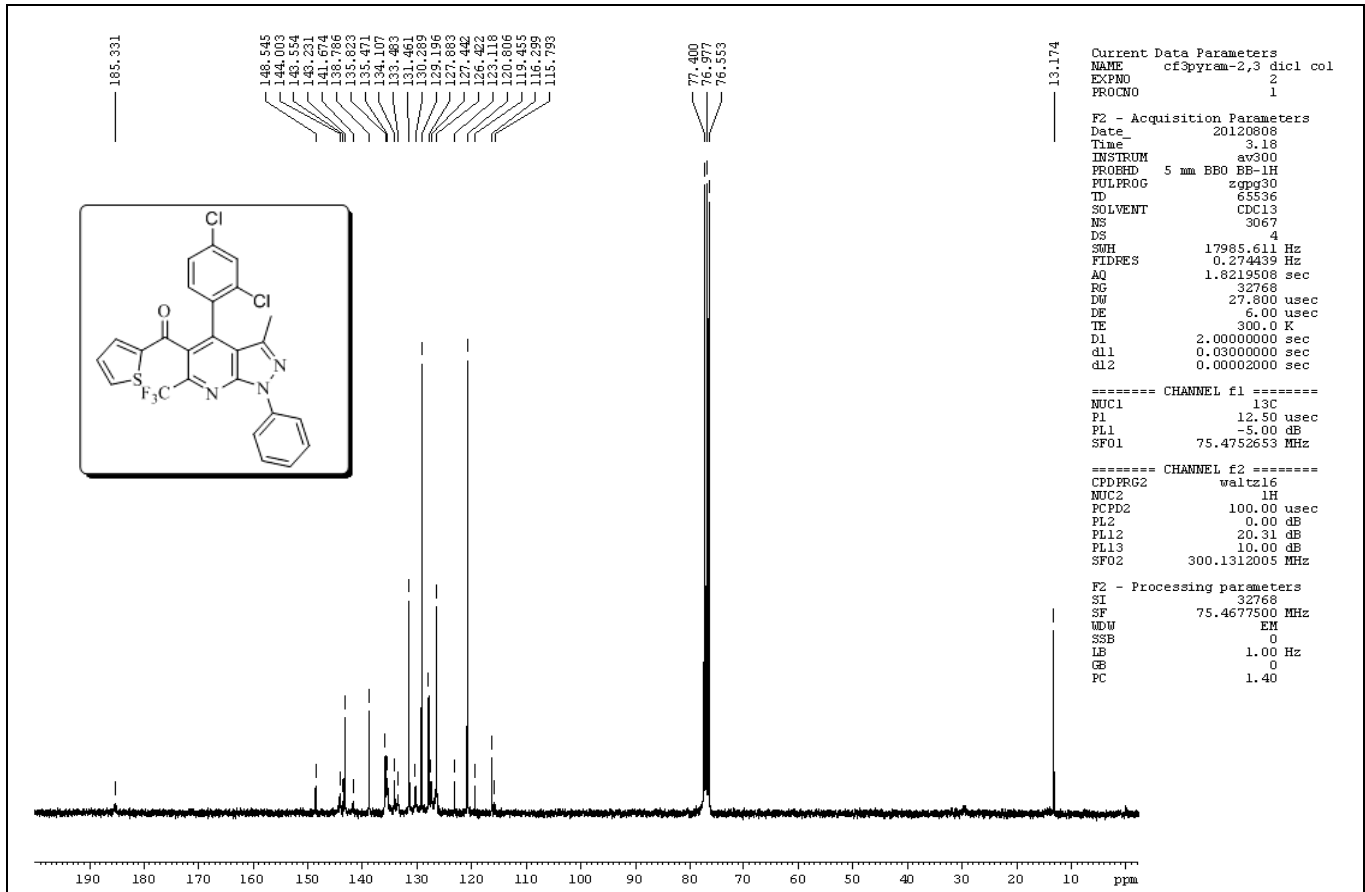


Figure 57. ¹³C NMR spectrum of 4k

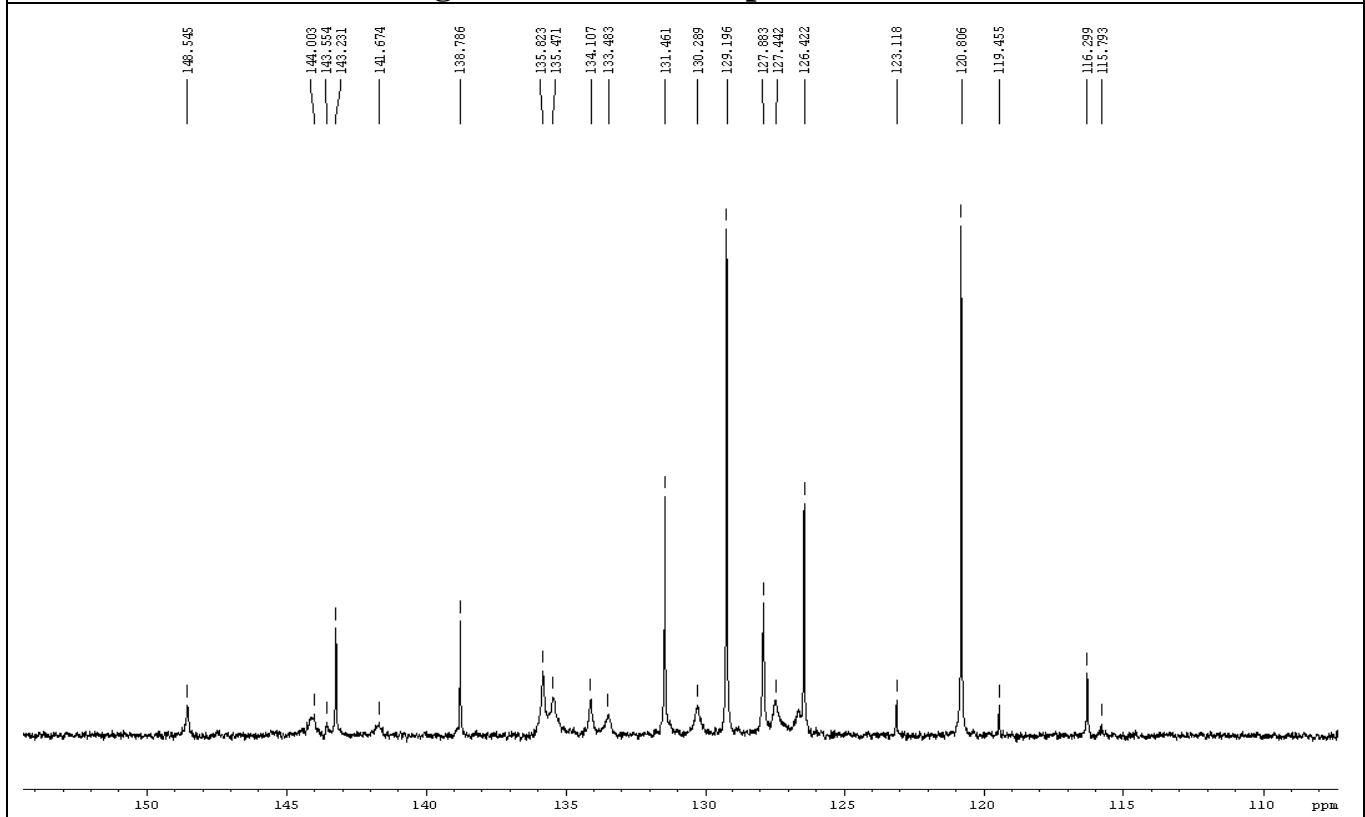


Figure 58. ¹³C NMR spectrum of 4k-expansion

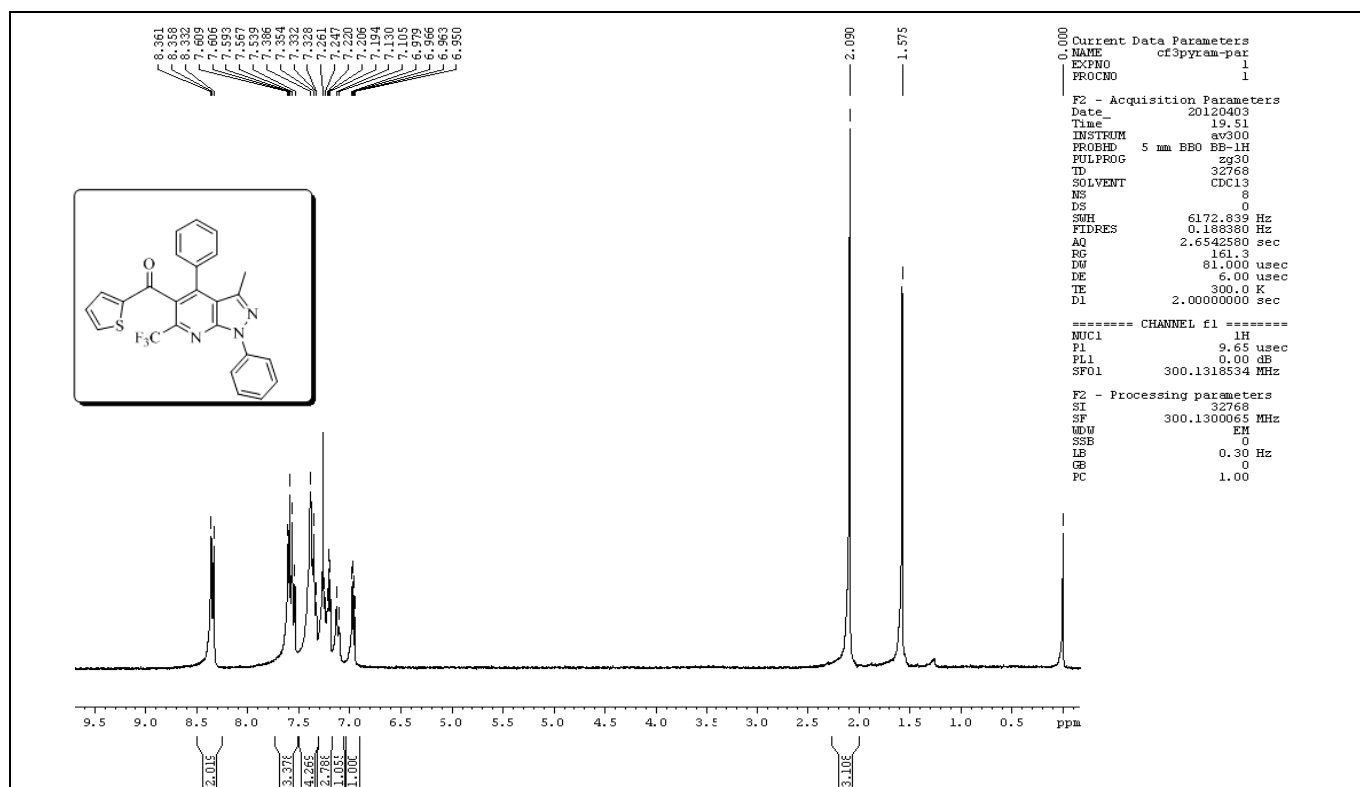


Figure 59. ^1H NMR spectrum of 4l

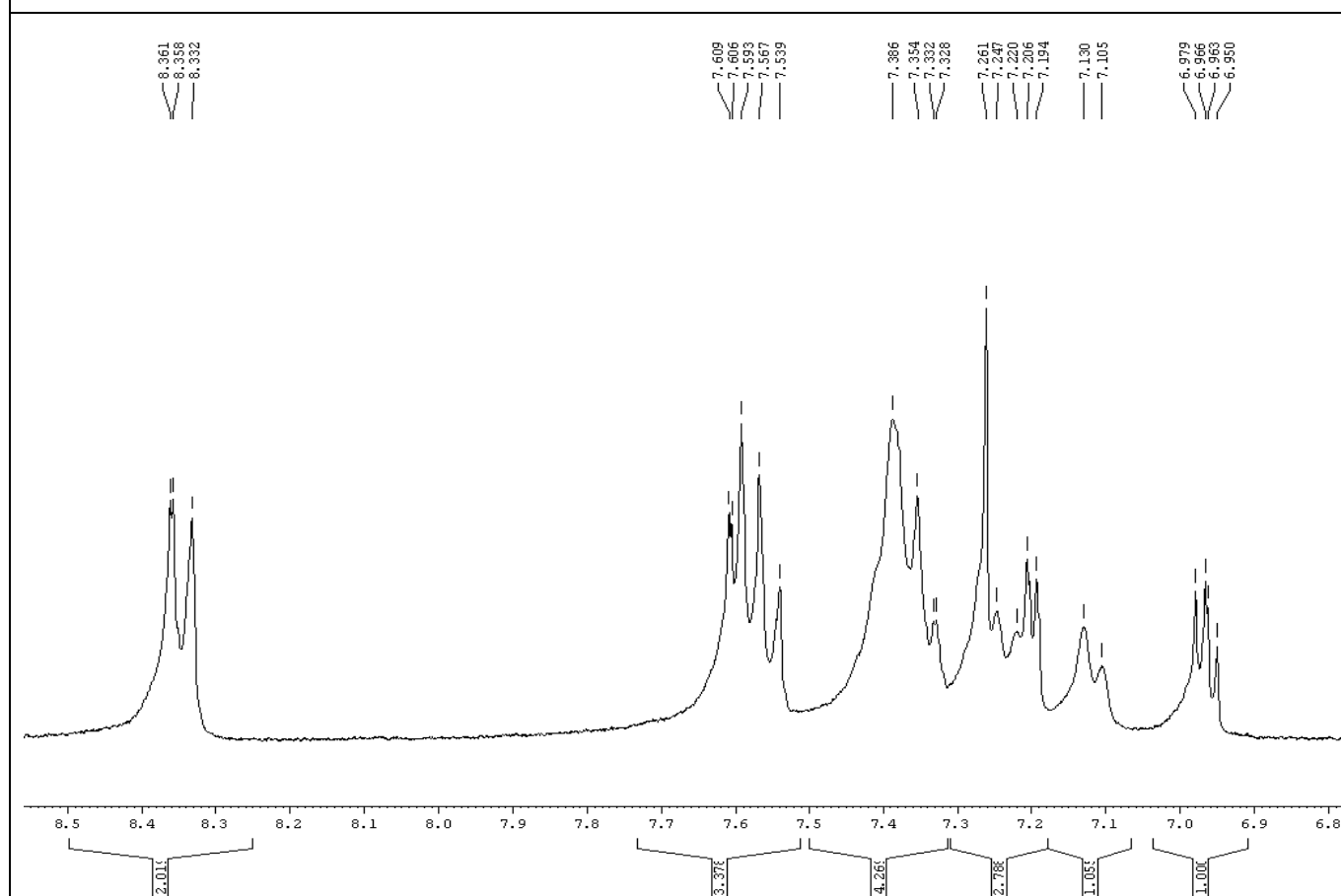


Figure 60. ^1H NMR spectrum of 4l-expansion

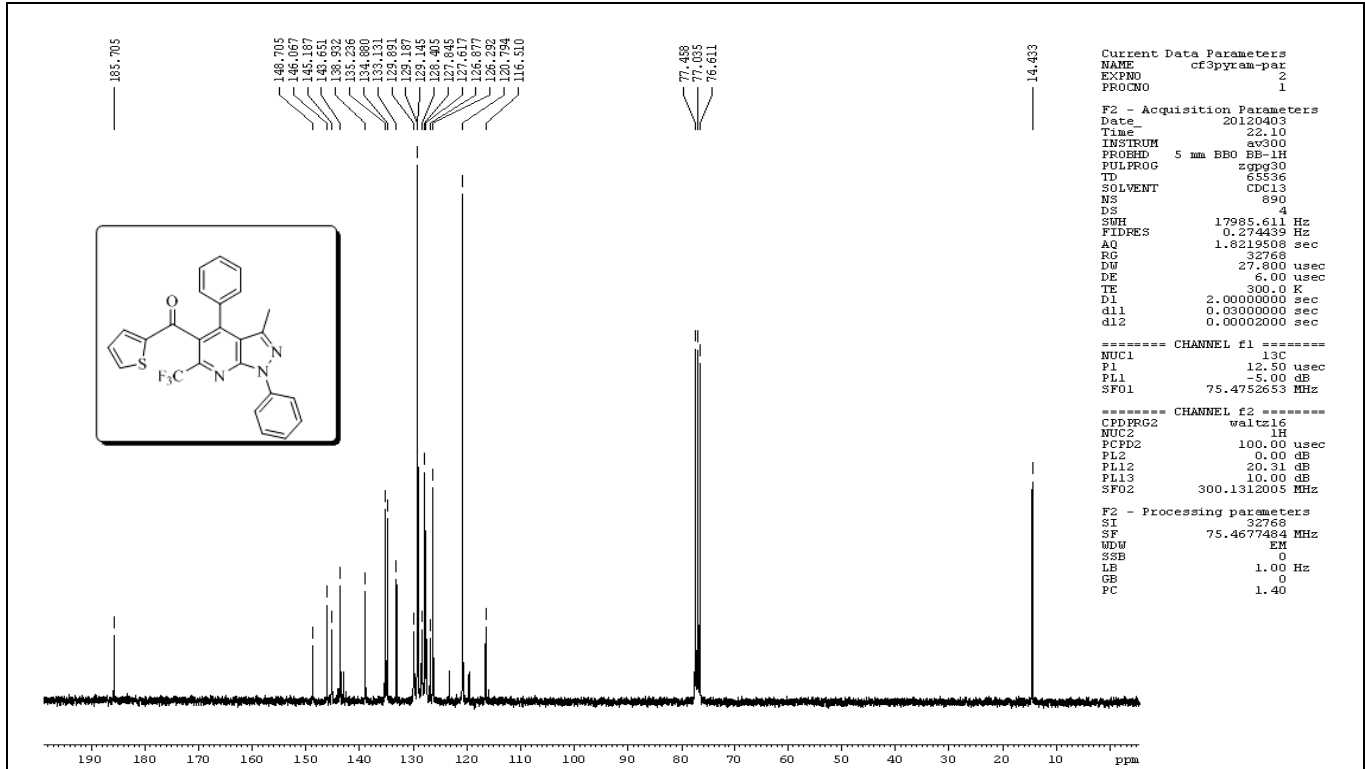


Figure 61. ¹³C NMR spectrum of 4l

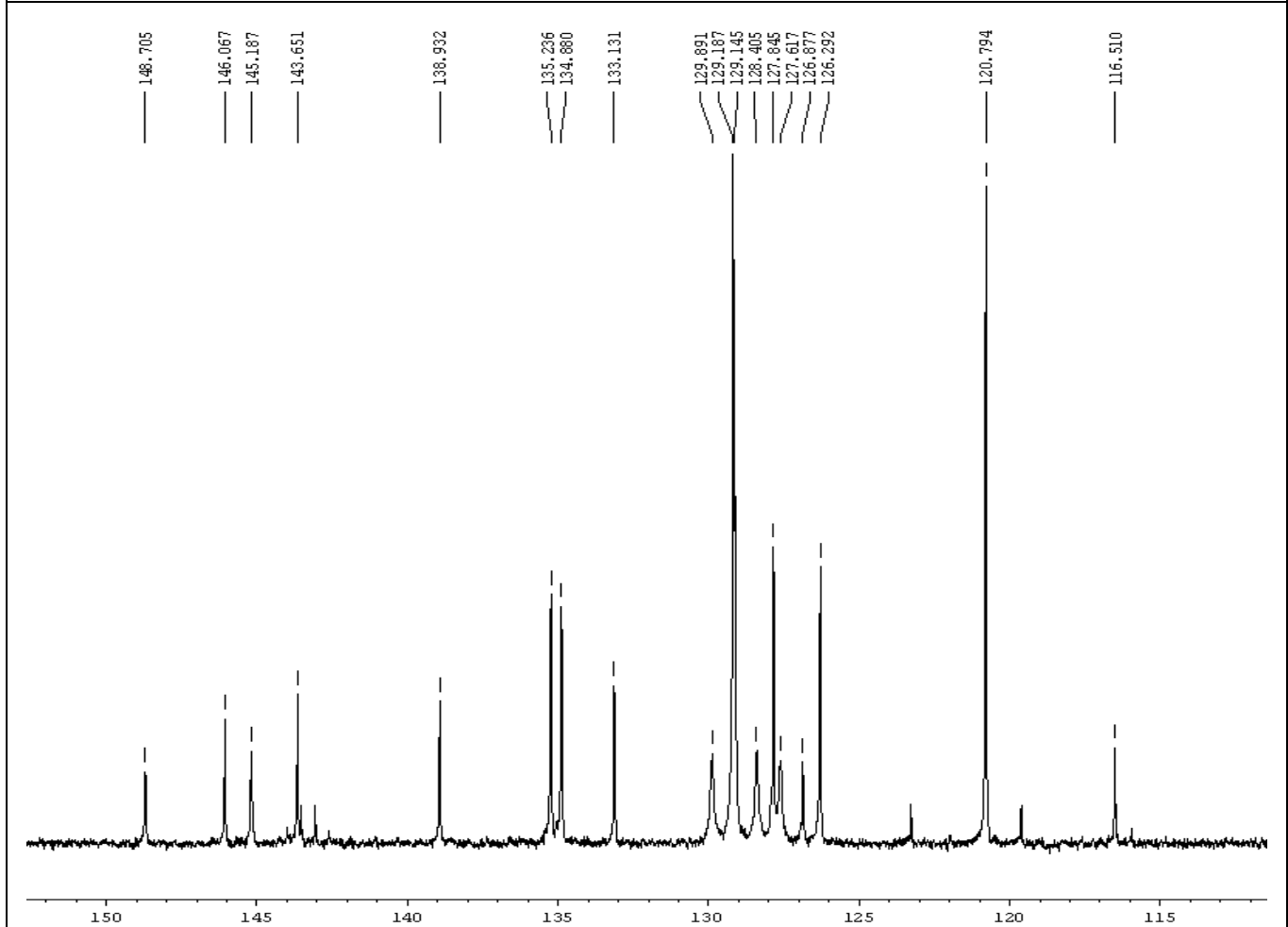


Figure 62. ¹³C NMR spectrum of 4l-expansion

Q4_121026172426 #45 RT: 0.77 AV: 1 NL: 9.17E3
T: ITMS + c ESI Full ms [100.00-1000.00]

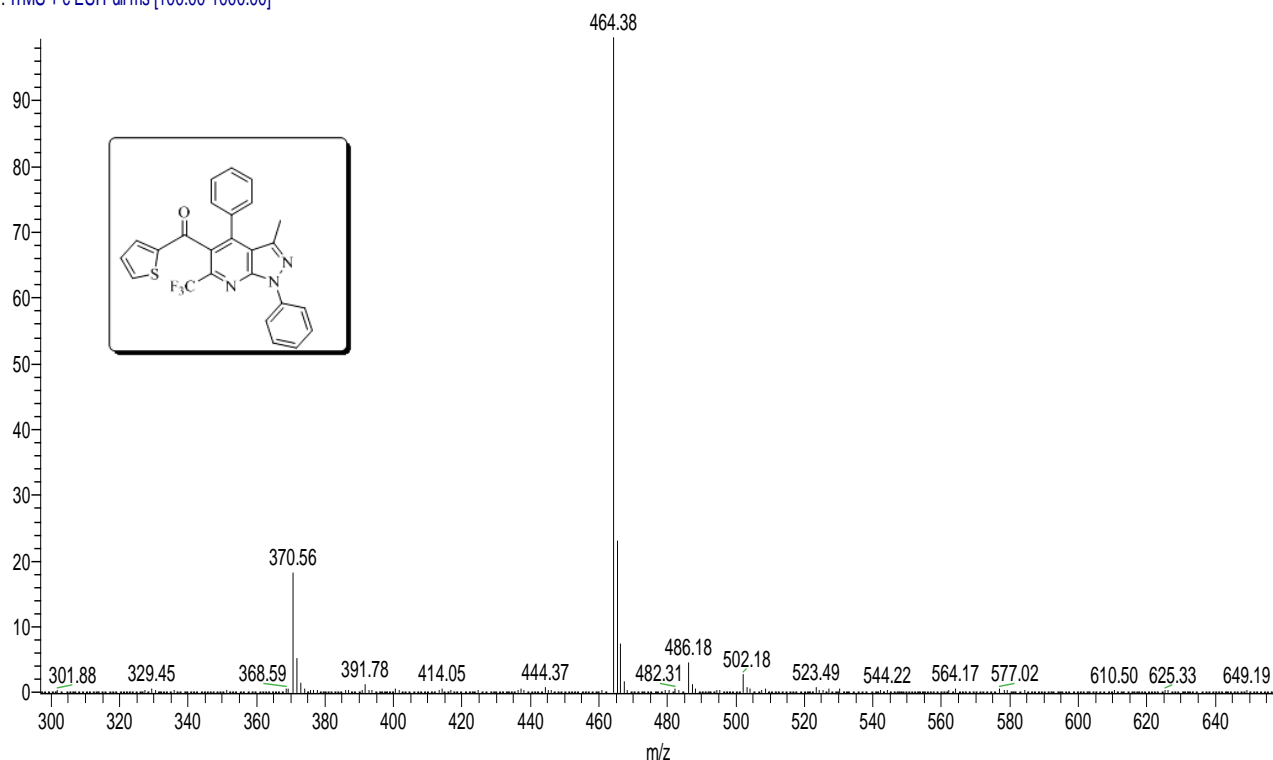


Figure 63. Mass spectrum of 4l

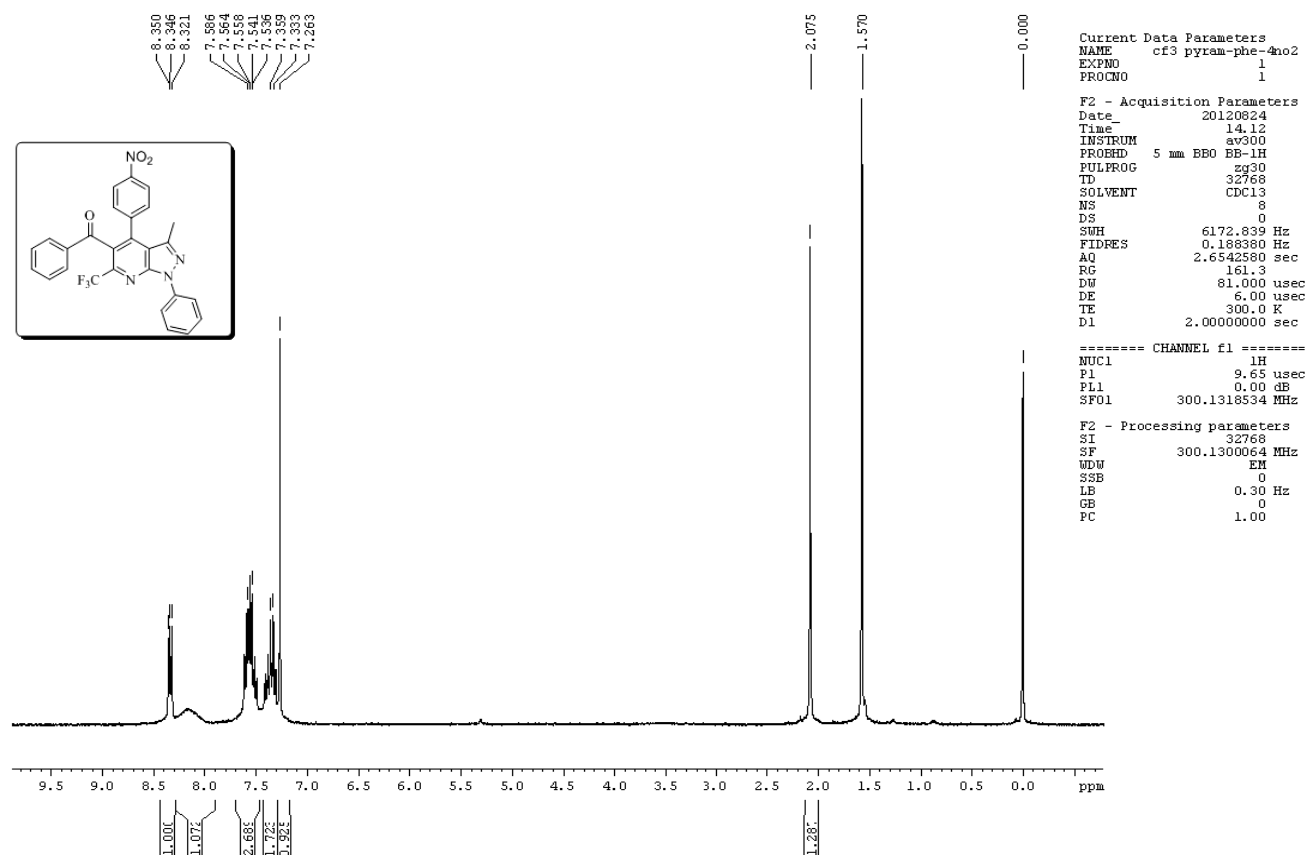


Figure 64. ¹H NMR spectrum of 4m

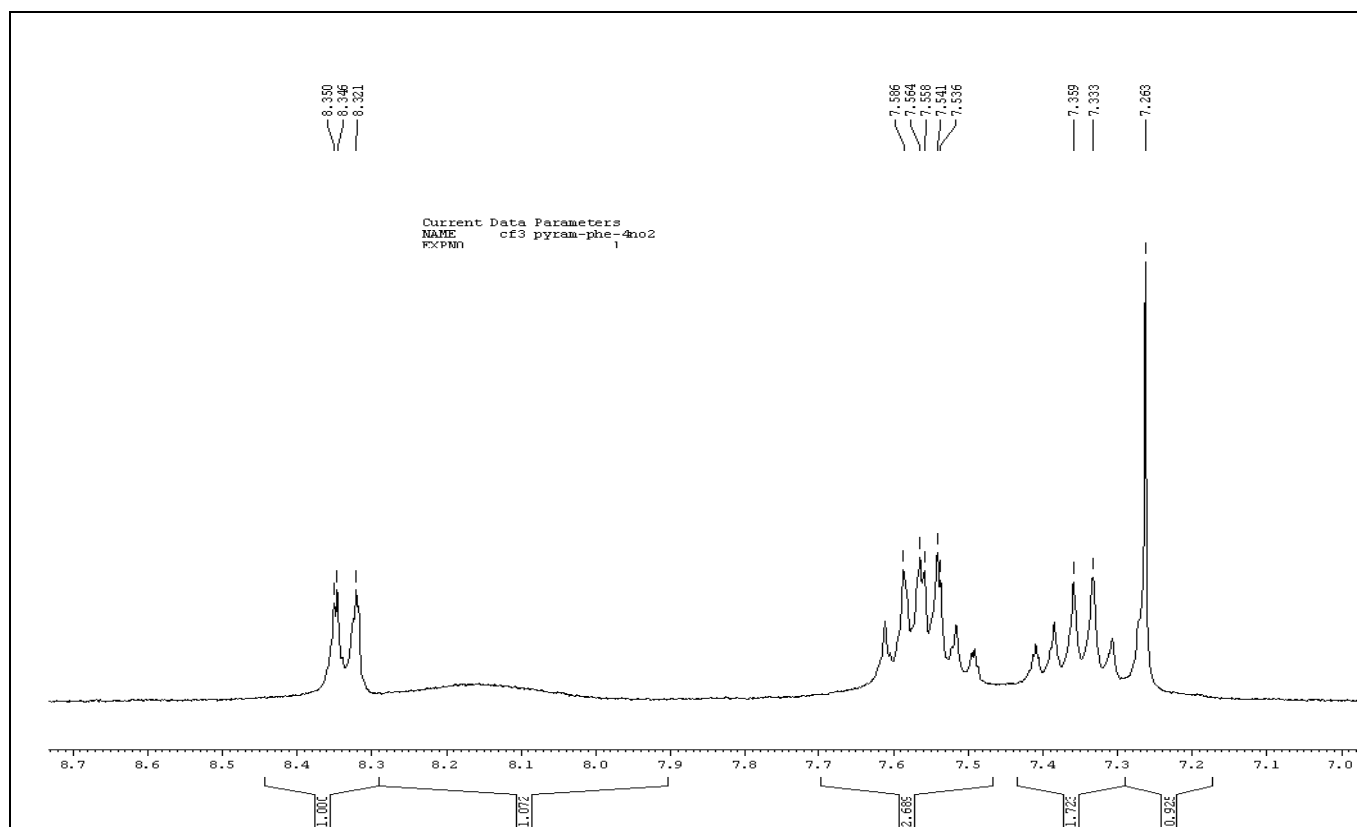


Figure 65. ^1H NMR spectrum of 4m-expansion

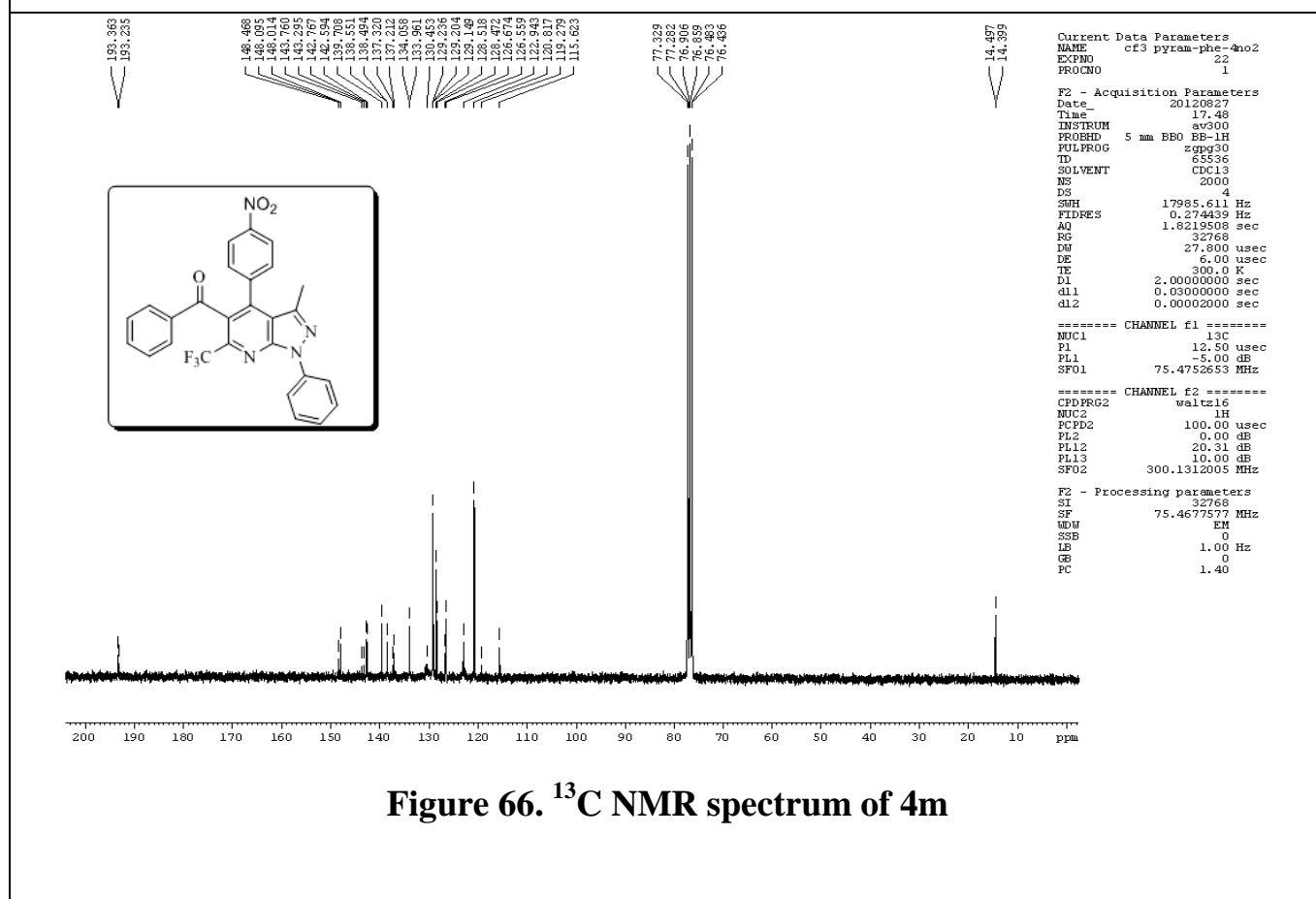
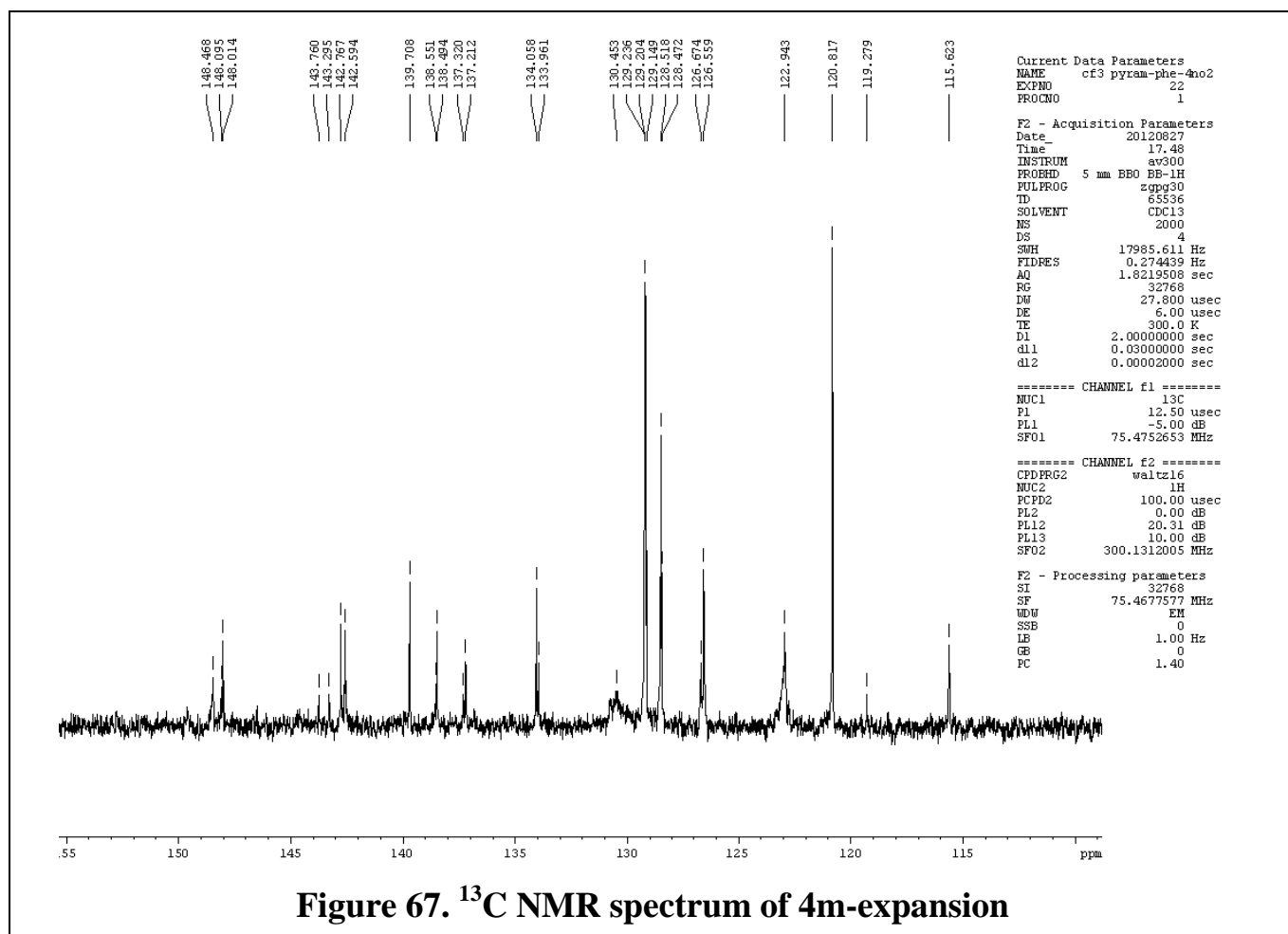
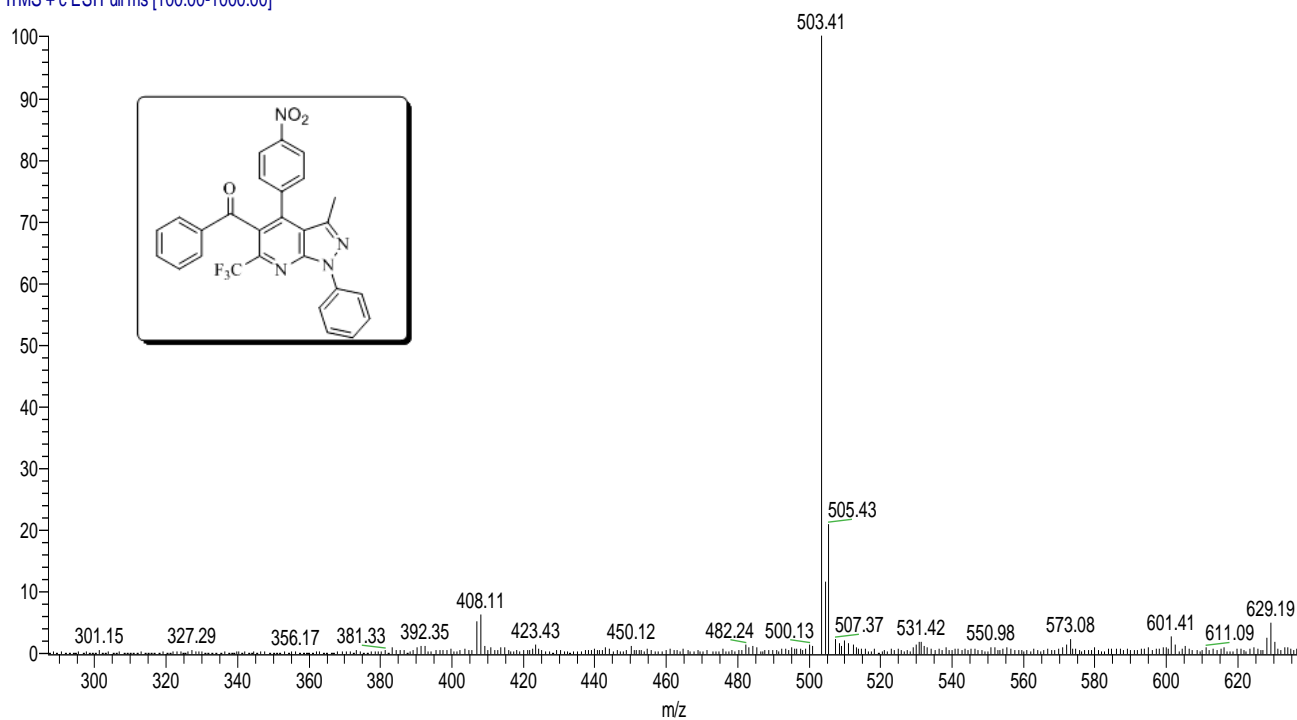


Figure 66. ^{13}C NMR spectrum of 4m



Q13_121026172426 #36 RT: 0.62 AV: 1 NL: 5.04E3
T: ITMS + c ESI Full ms [100.00-1000.00]



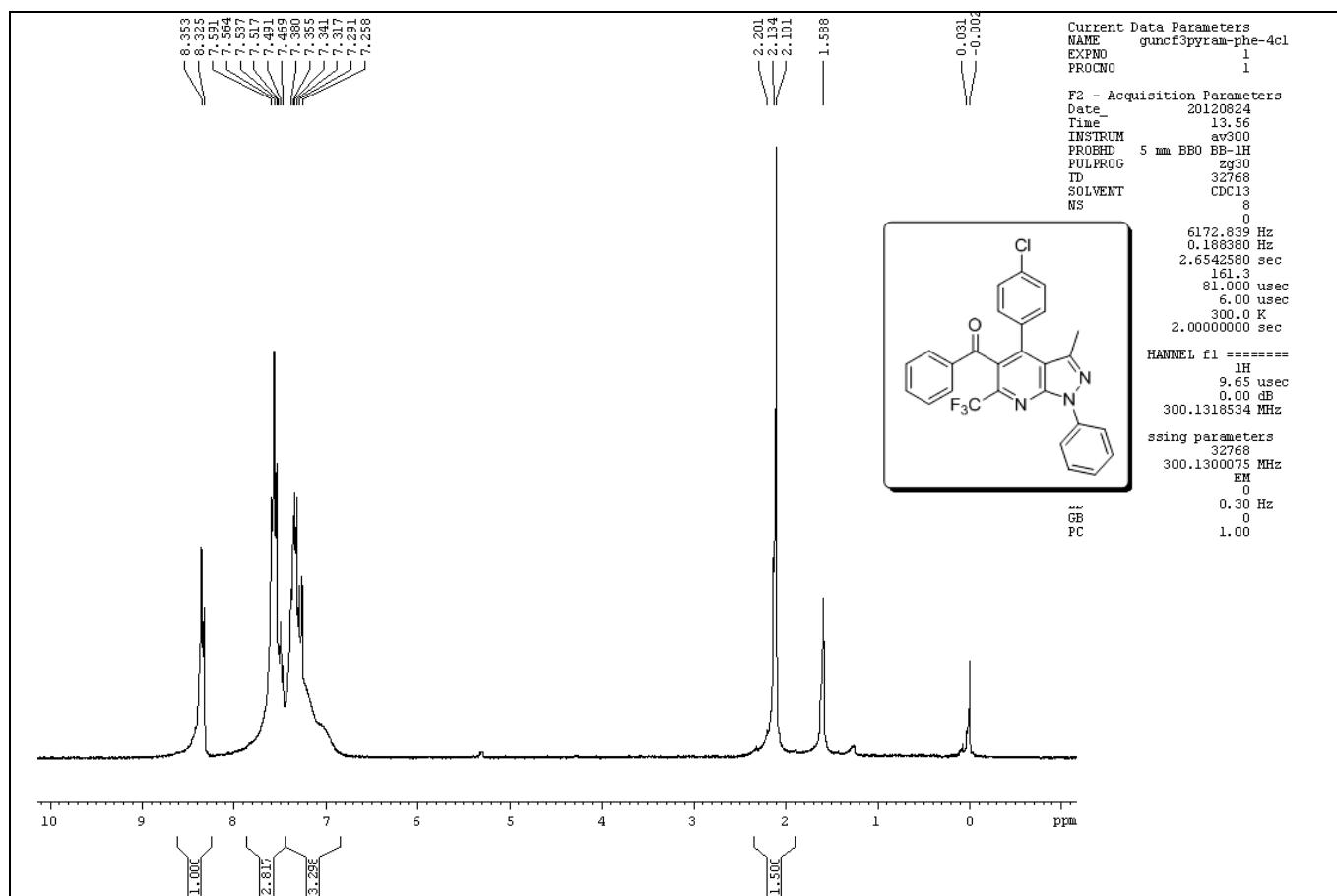


Figure 69. ¹H NMR spectrum of 4n

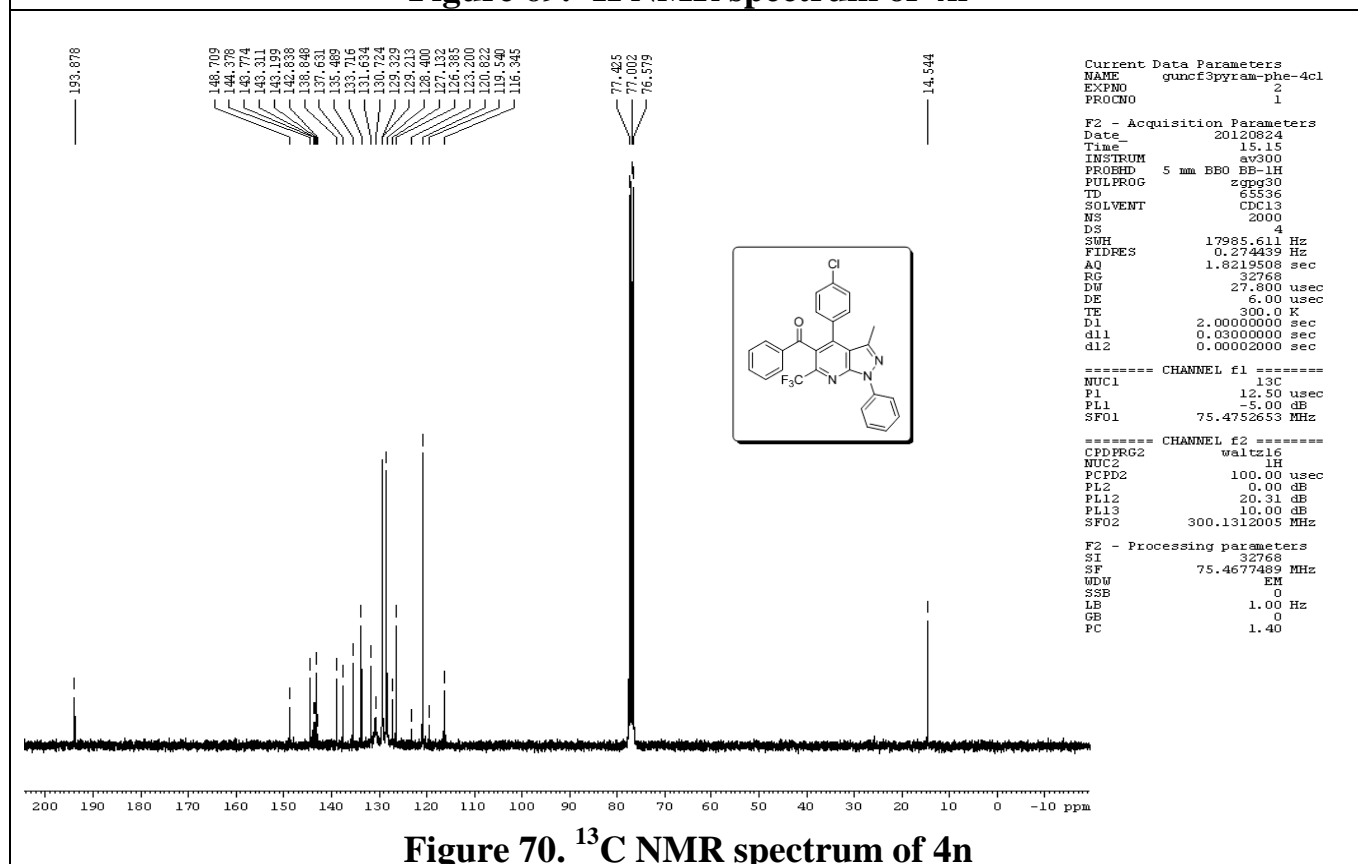


Figure 70. ¹³C NMR spectrum of 4n

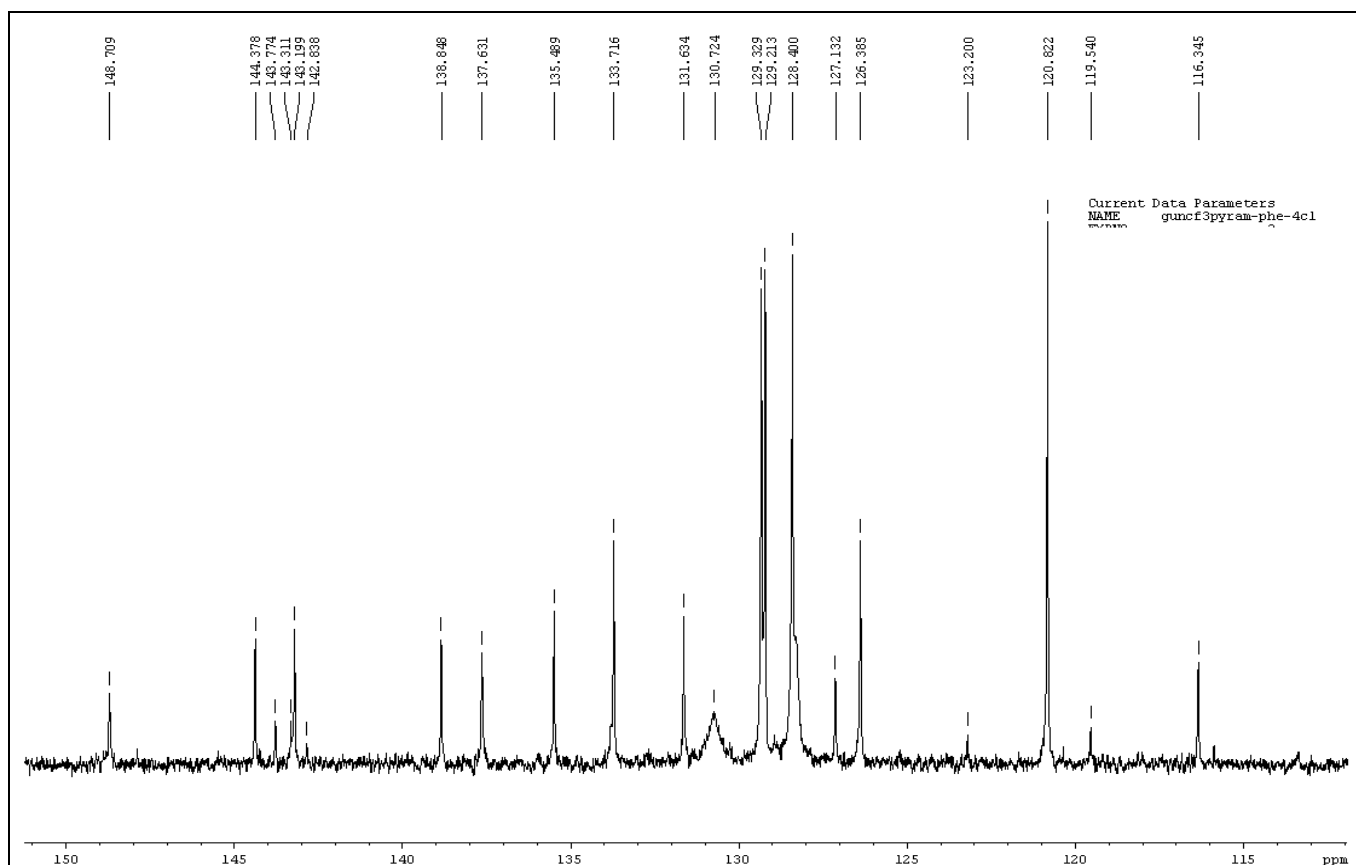


Figure 71. ^{13}C NMR spectrum of 4n-expansion

Q7_121026172426 #53 RT: 0.92 AV: 1 NL: 8.53E2
T: ITMS + c ESI Full ms [100.00-1000.00]

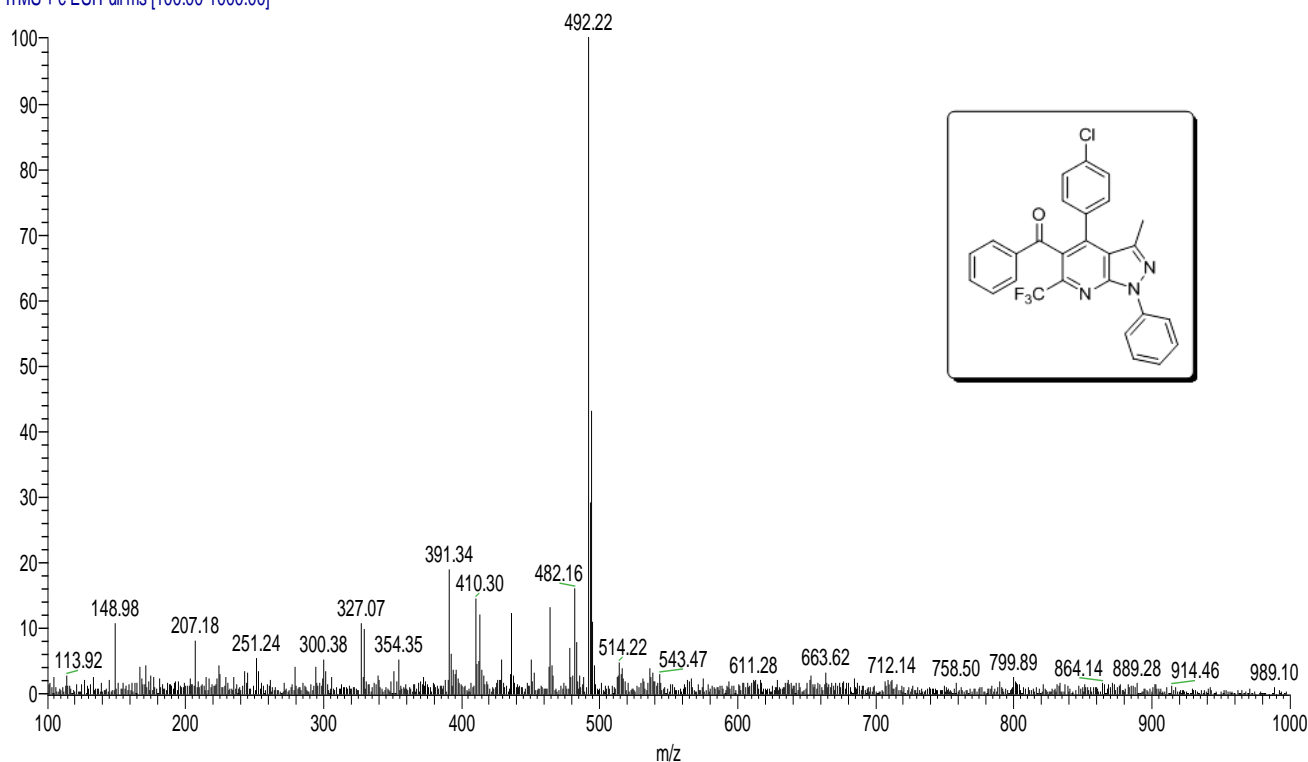


Figure 72. Mass spectrum of 4n

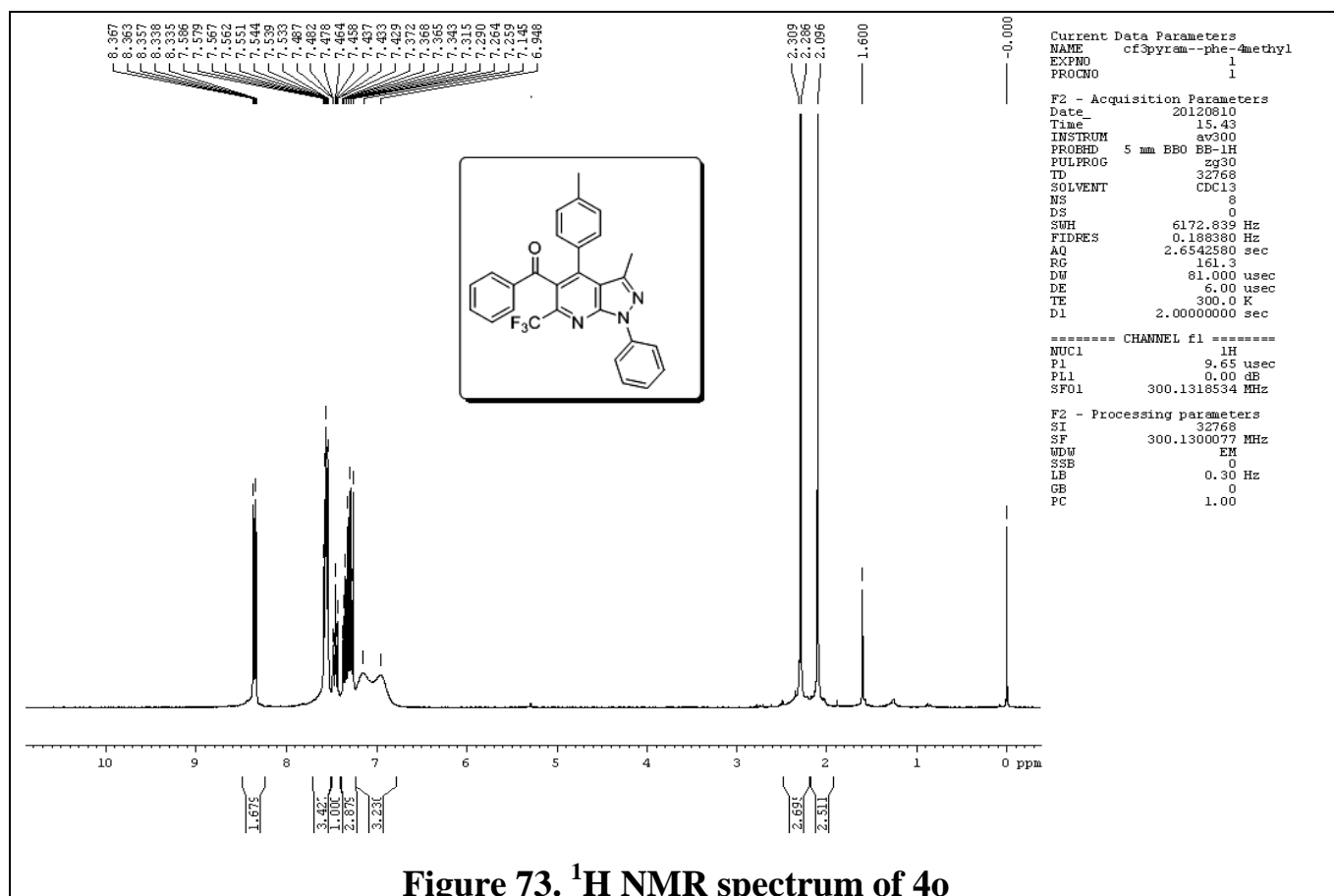


Figure 73. ¹H NMR spectrum of 40

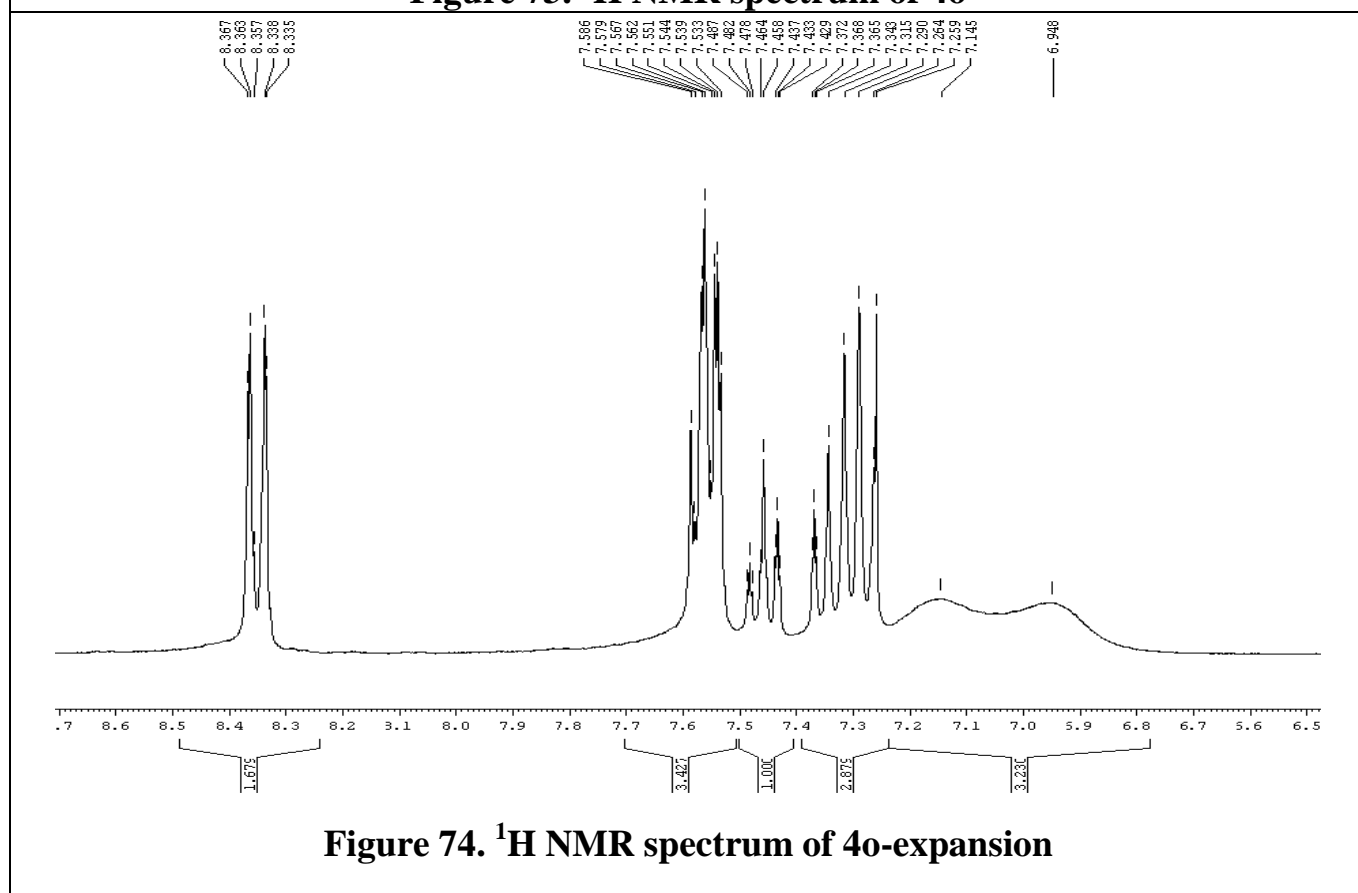


Figure 74. ¹H NMR spectrum of 40-expansion

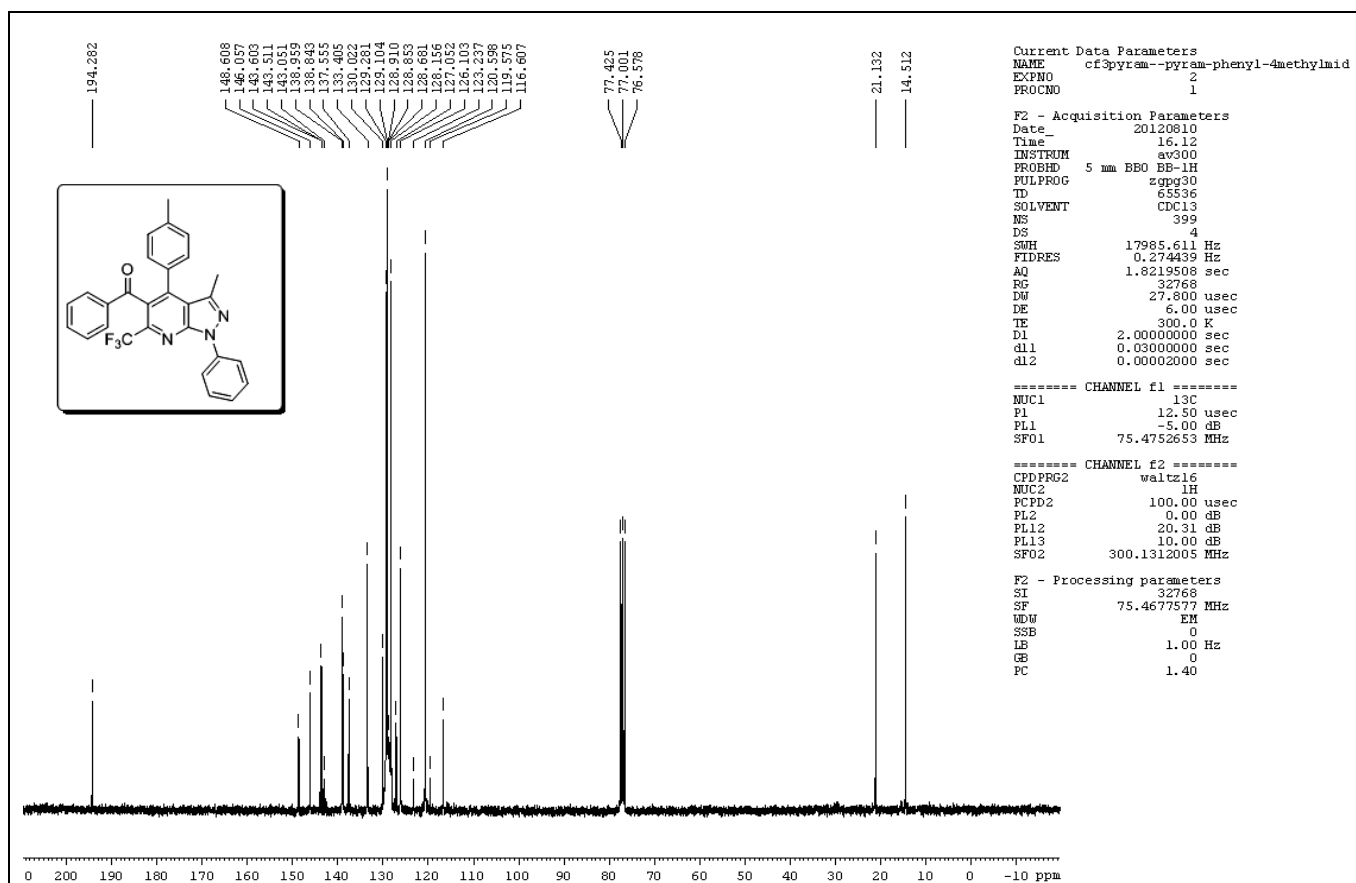


Figure 75. ¹³C NMR spectrum of 4o

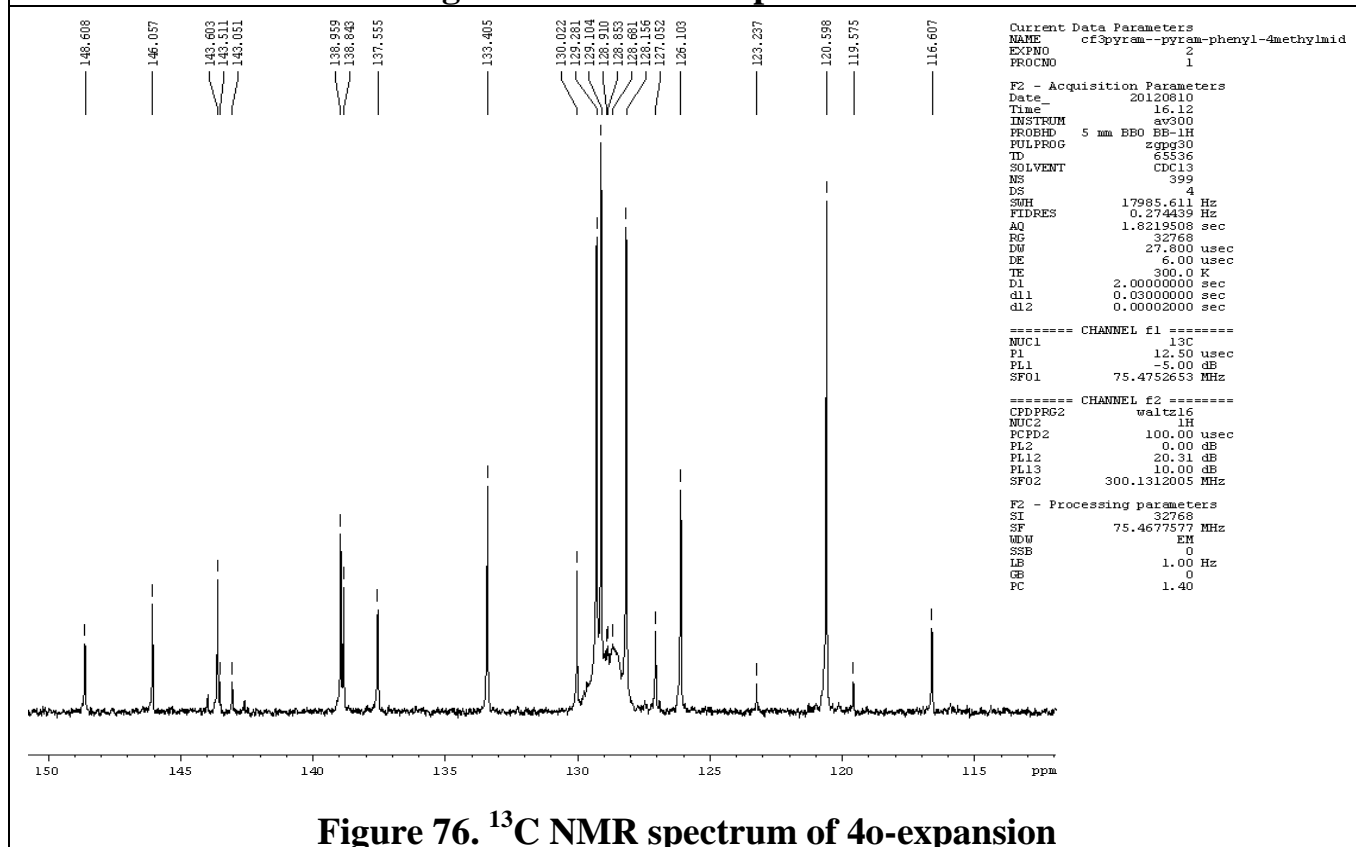


Figure 76. ¹³C NMR spectrum of 4o-expansion

Q8_121026172426 #31 RT: 0.52 AV: 1 NL: 3.49E3
T: ITMS + c ESI Full ms [100.00-1000.00]

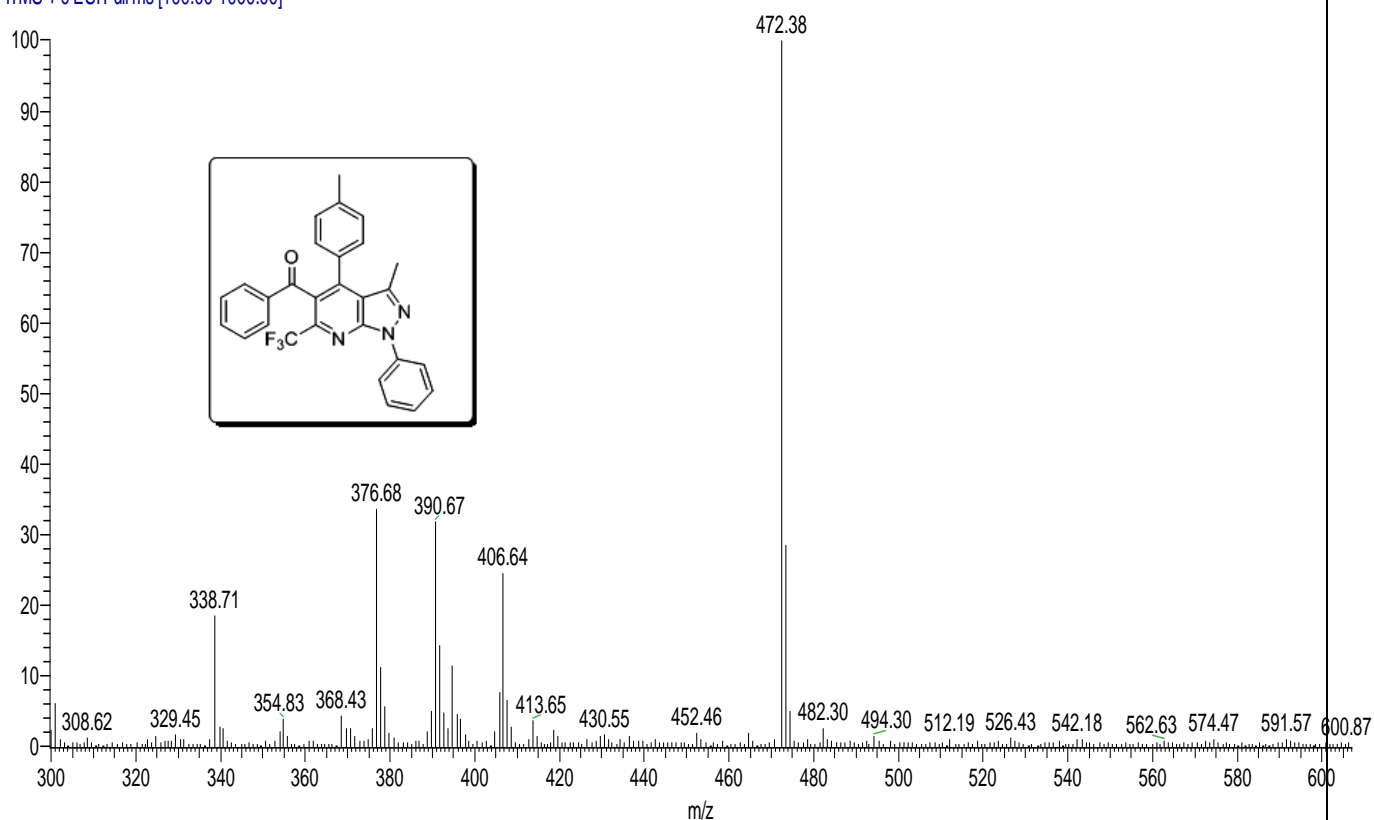


Figure 77. Mass spectrum of 4o

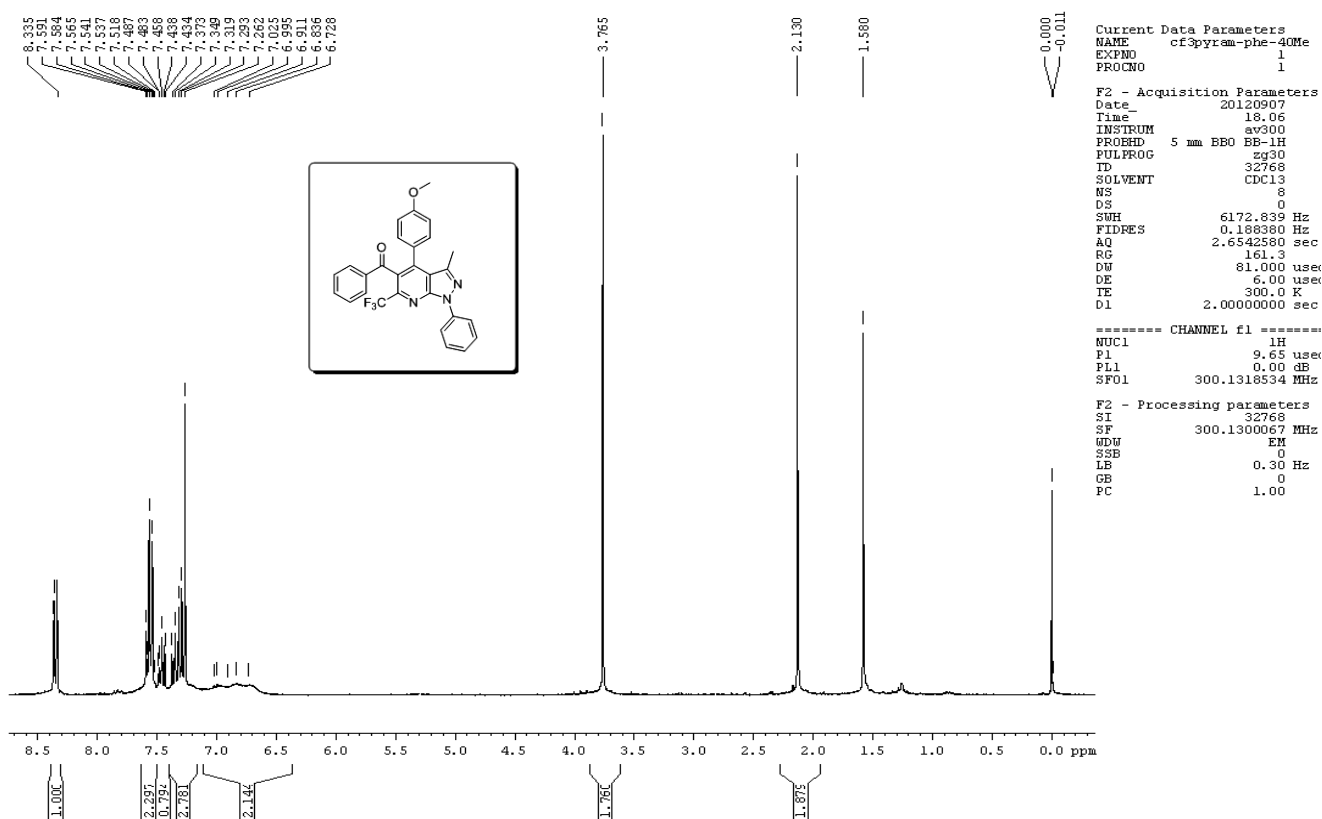


Figure 78. ¹H NMR spectrum of 4p

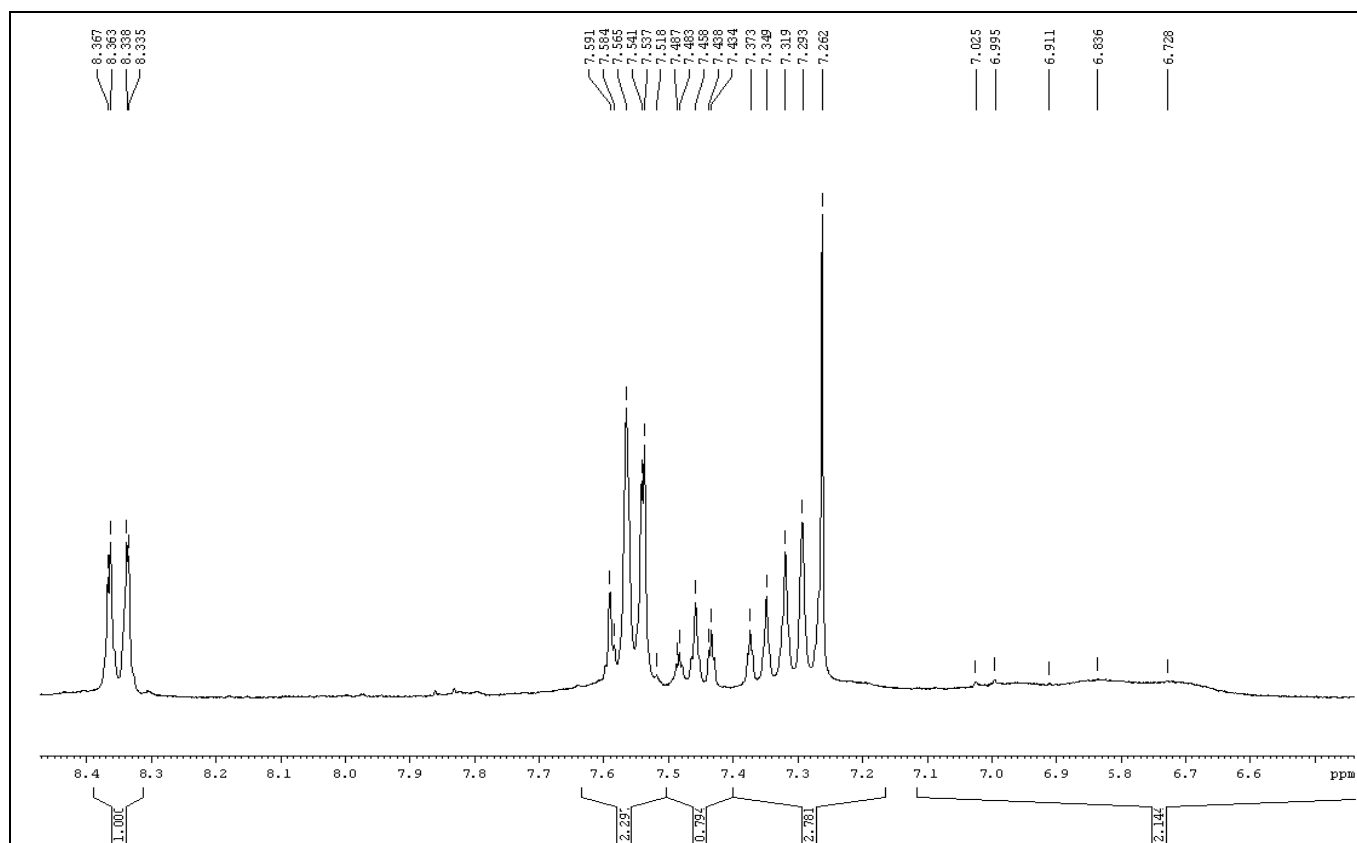


Figure 79. ^1H NMR spectrum of 4p-expansion

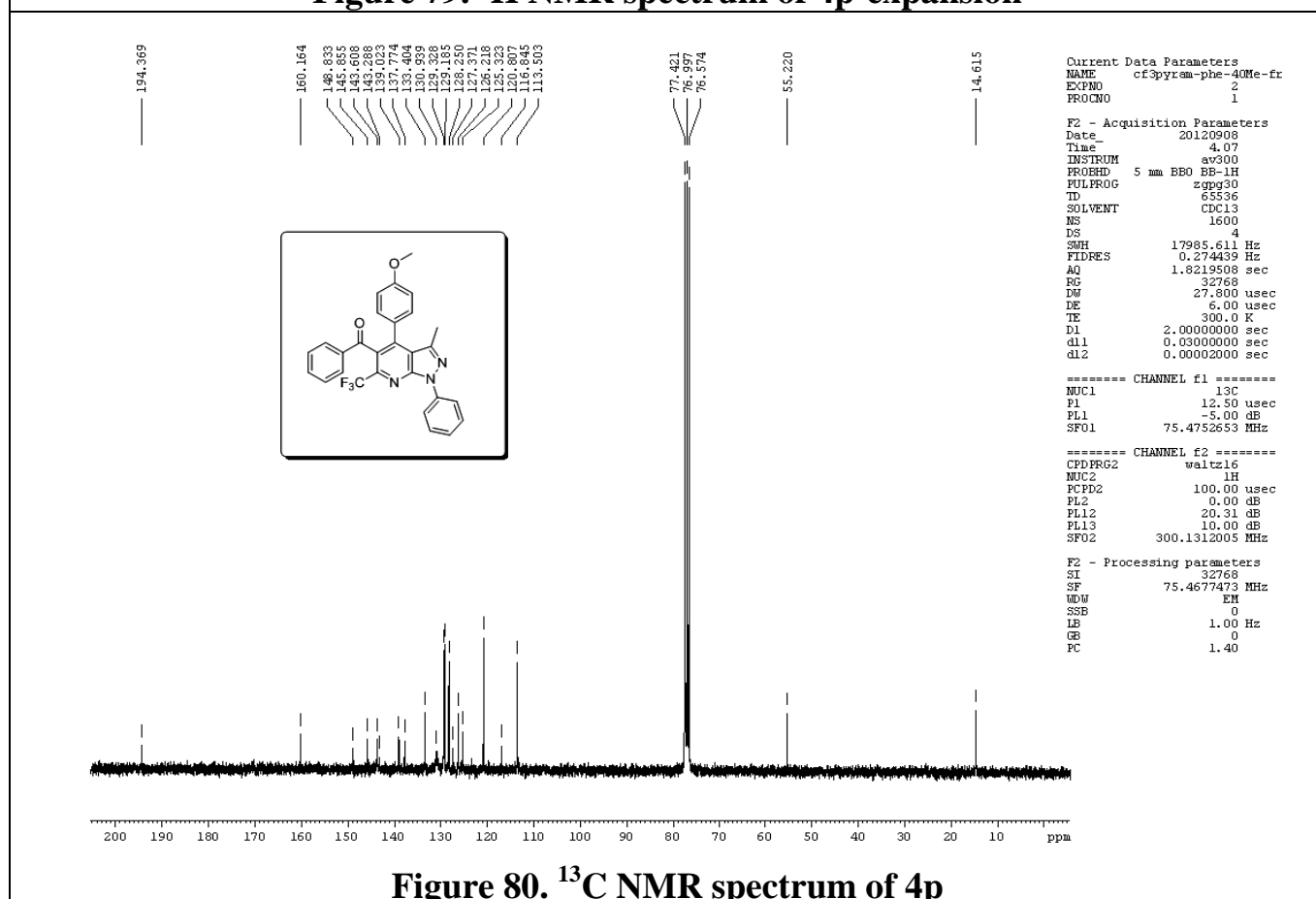


Figure 80. ^{13}C NMR spectrum of 4p

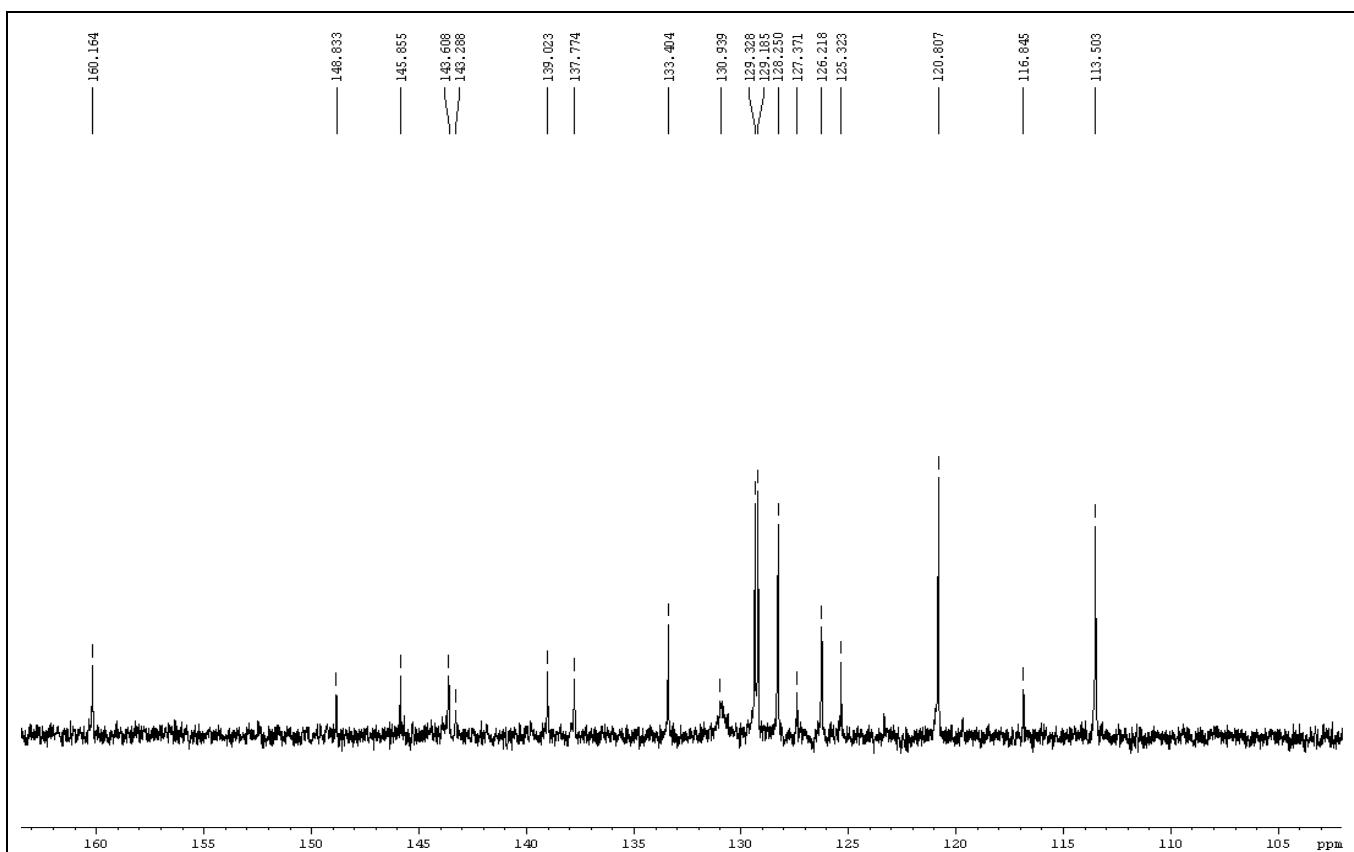


Figure 81. ^{13}C NMR spectrum of 4p-expansion

Q16_121026172426 #38 RT: 0.65 AV: 1 NL: 4.22E3
T: ITMS + c ESI Full ms [100.00-1000.00]

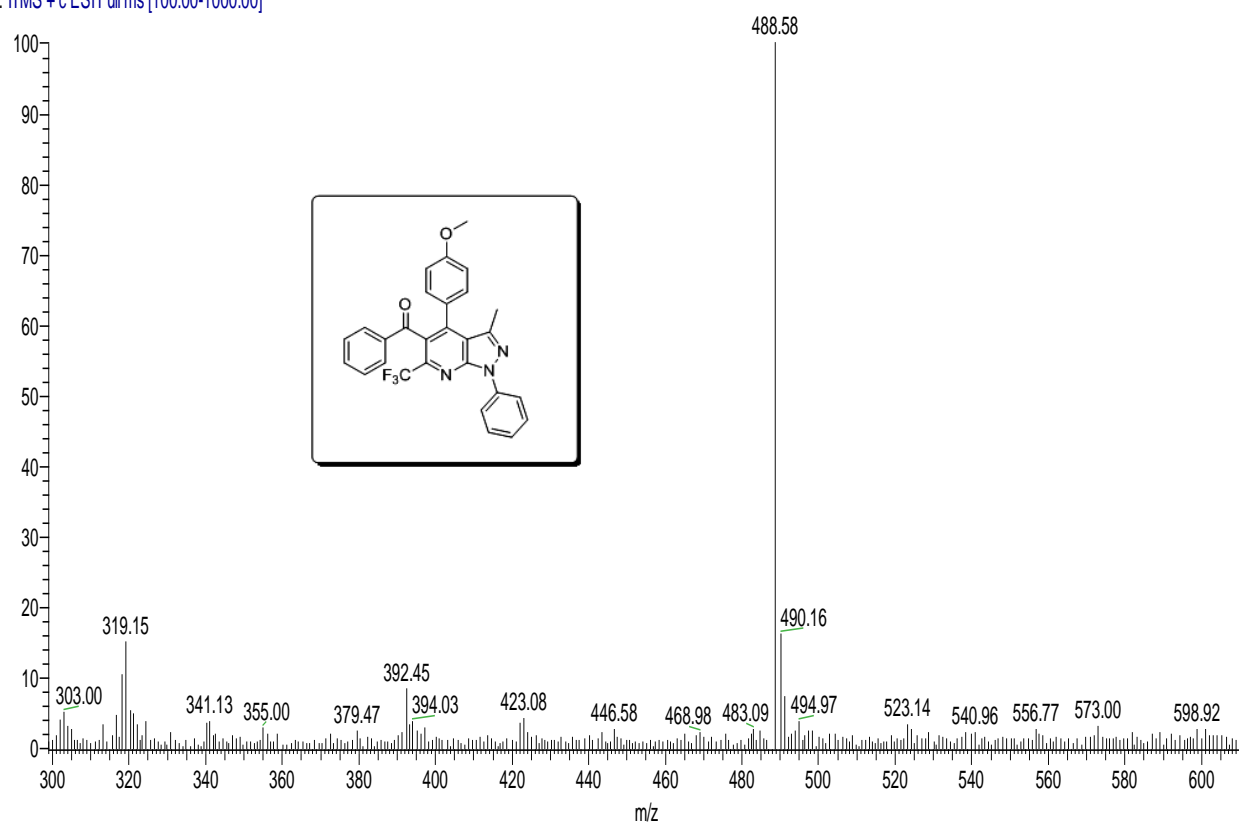


Figure 82. Mass spectrum of 4p

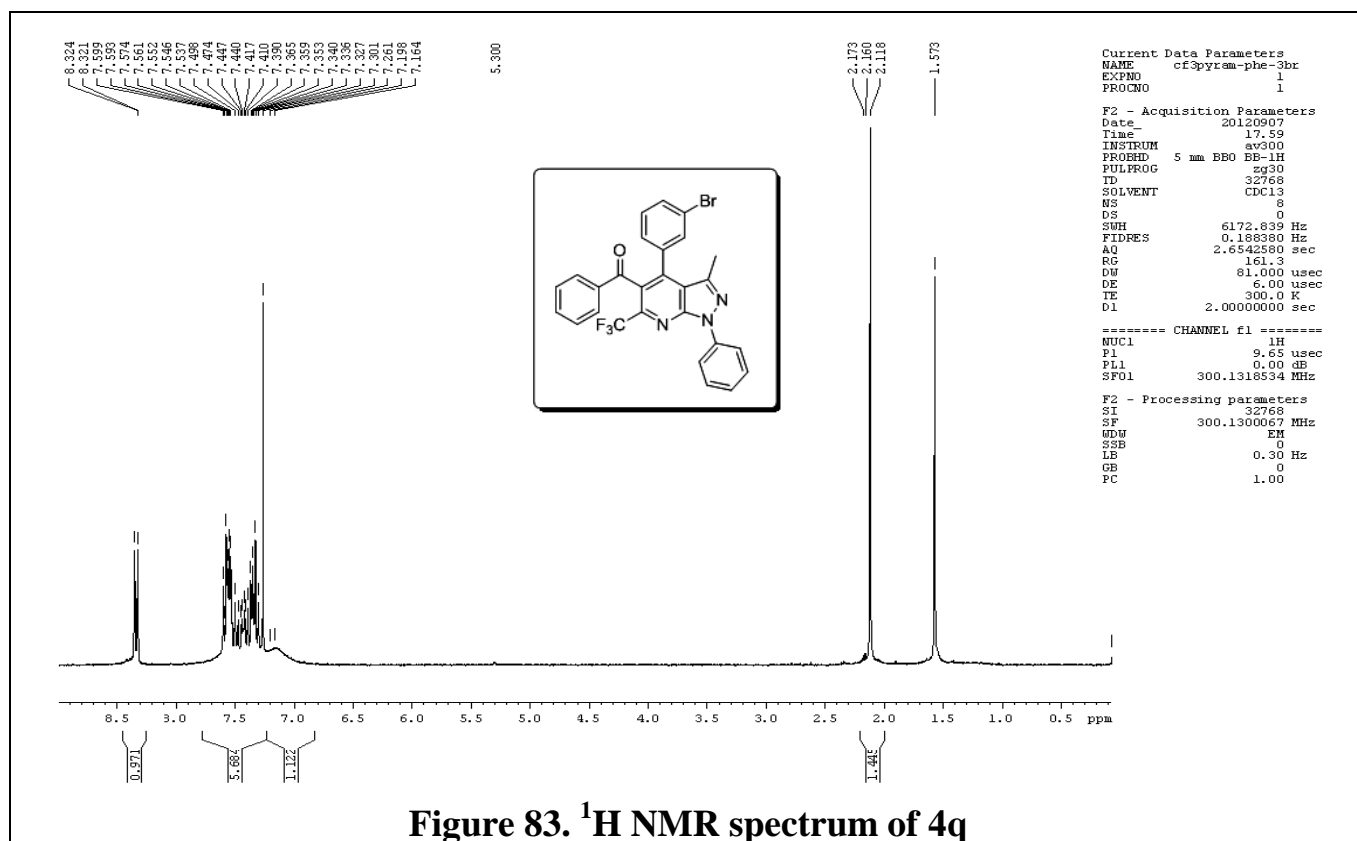


Figure 83. ¹H NMR spectrum of 4q

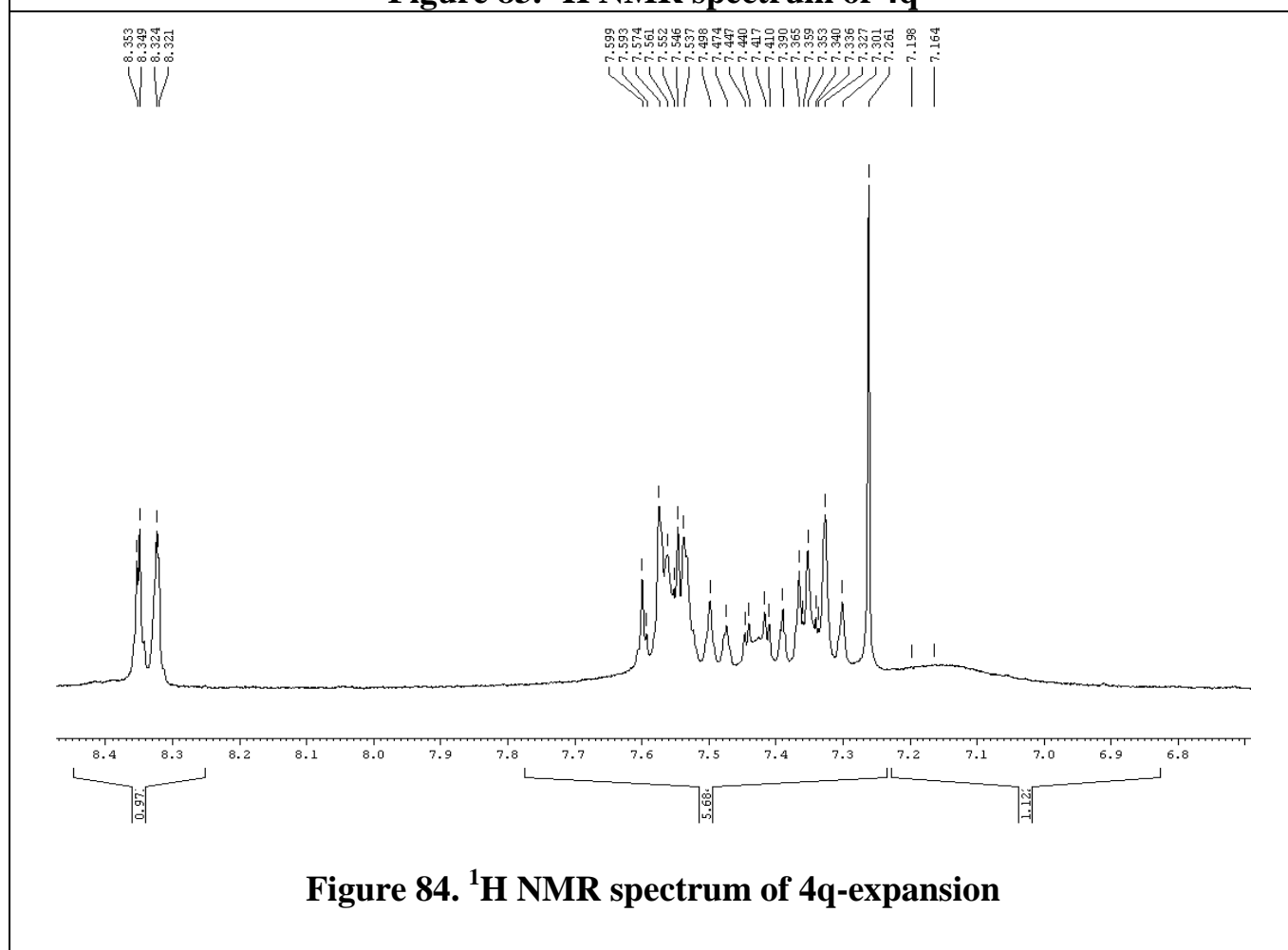


Figure 84. ¹H NMR spectrum of 4q-expansion

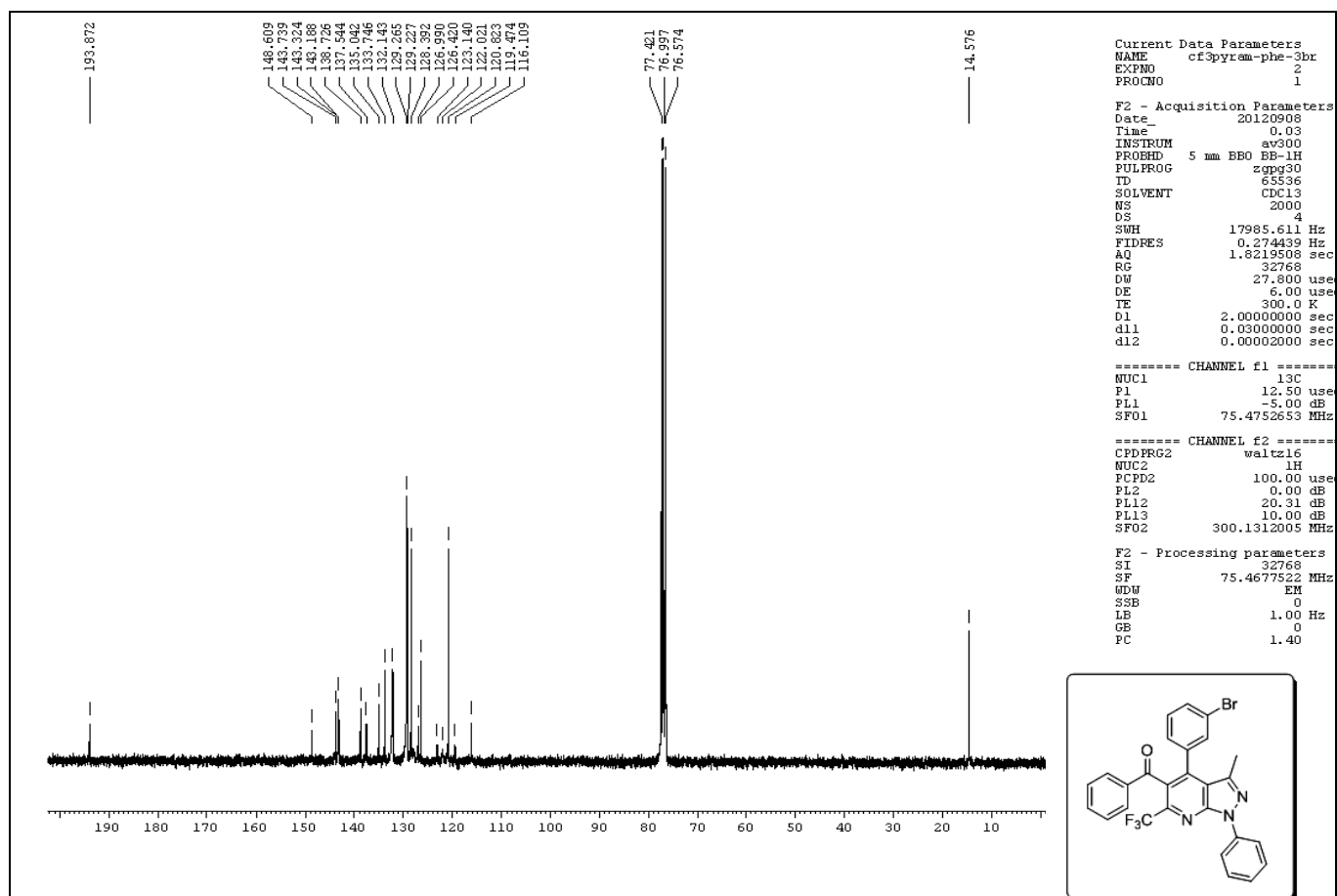


Figure 85. ^{13}C NMR spectrum of 4q

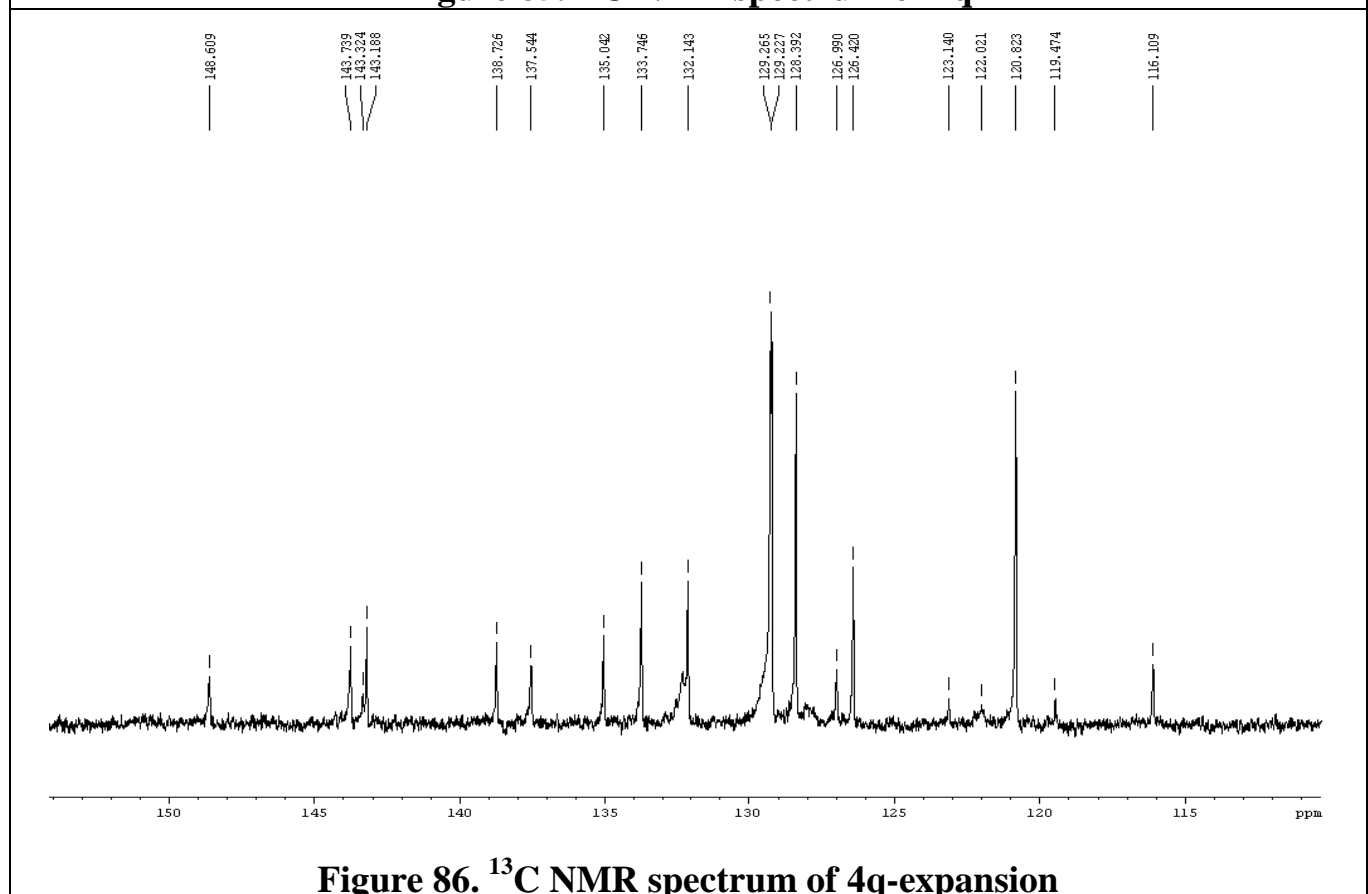


Figure 86. ^{13}C NMR spectrum of 4q-expansion

Q17_121026172426 #49 RT: 0.84 AV: 1 NL: 1.15E3
T: ITMS + c ESI Full ms [100.00-1000.00]

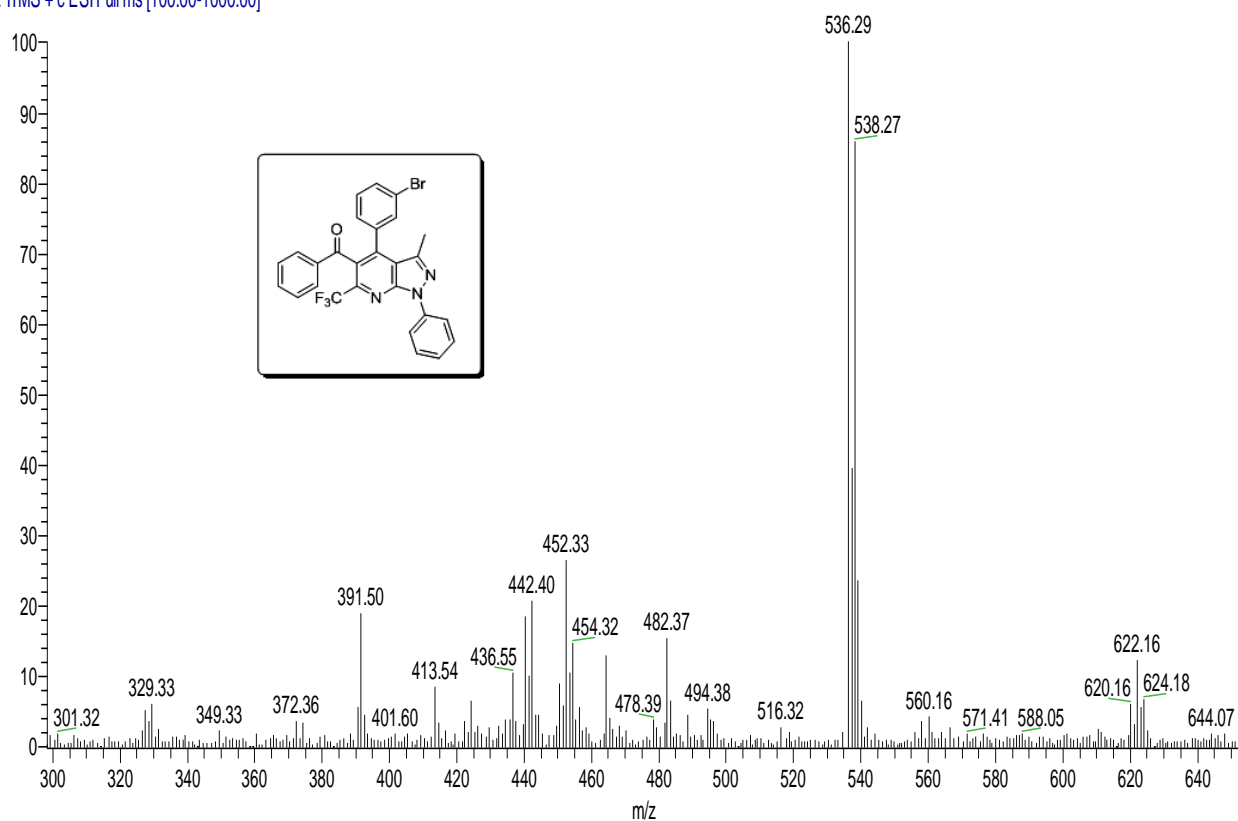


Figure 87. Mass spectrum of 4q

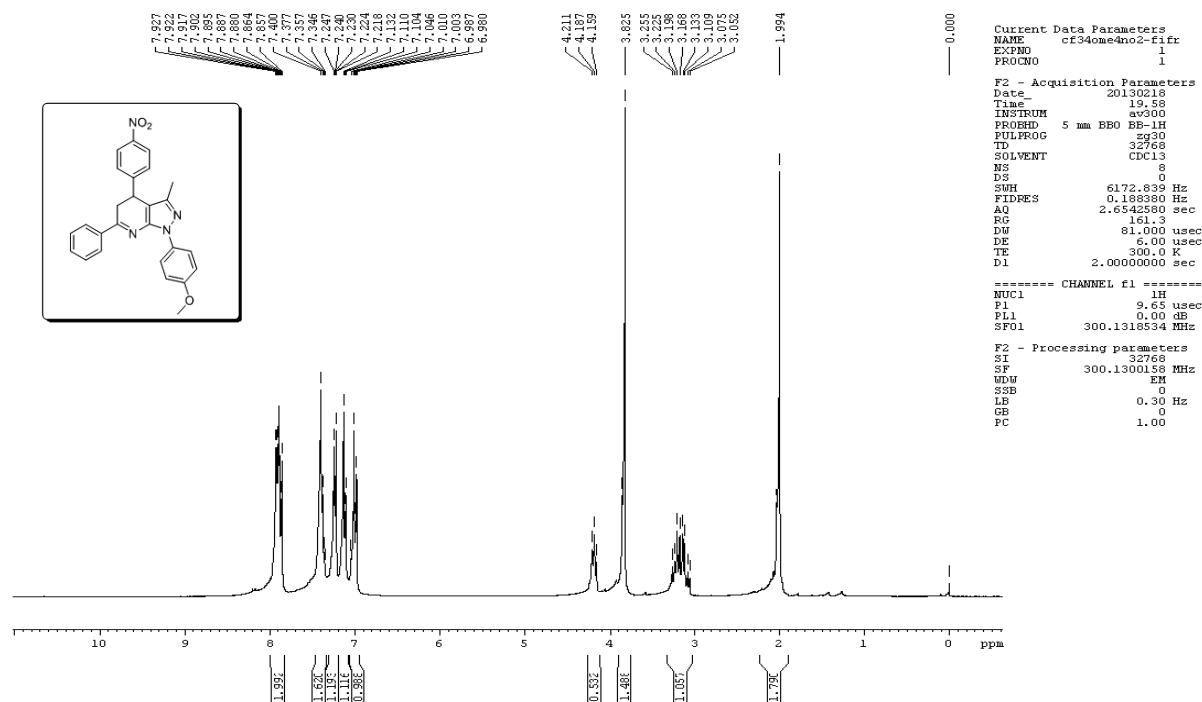
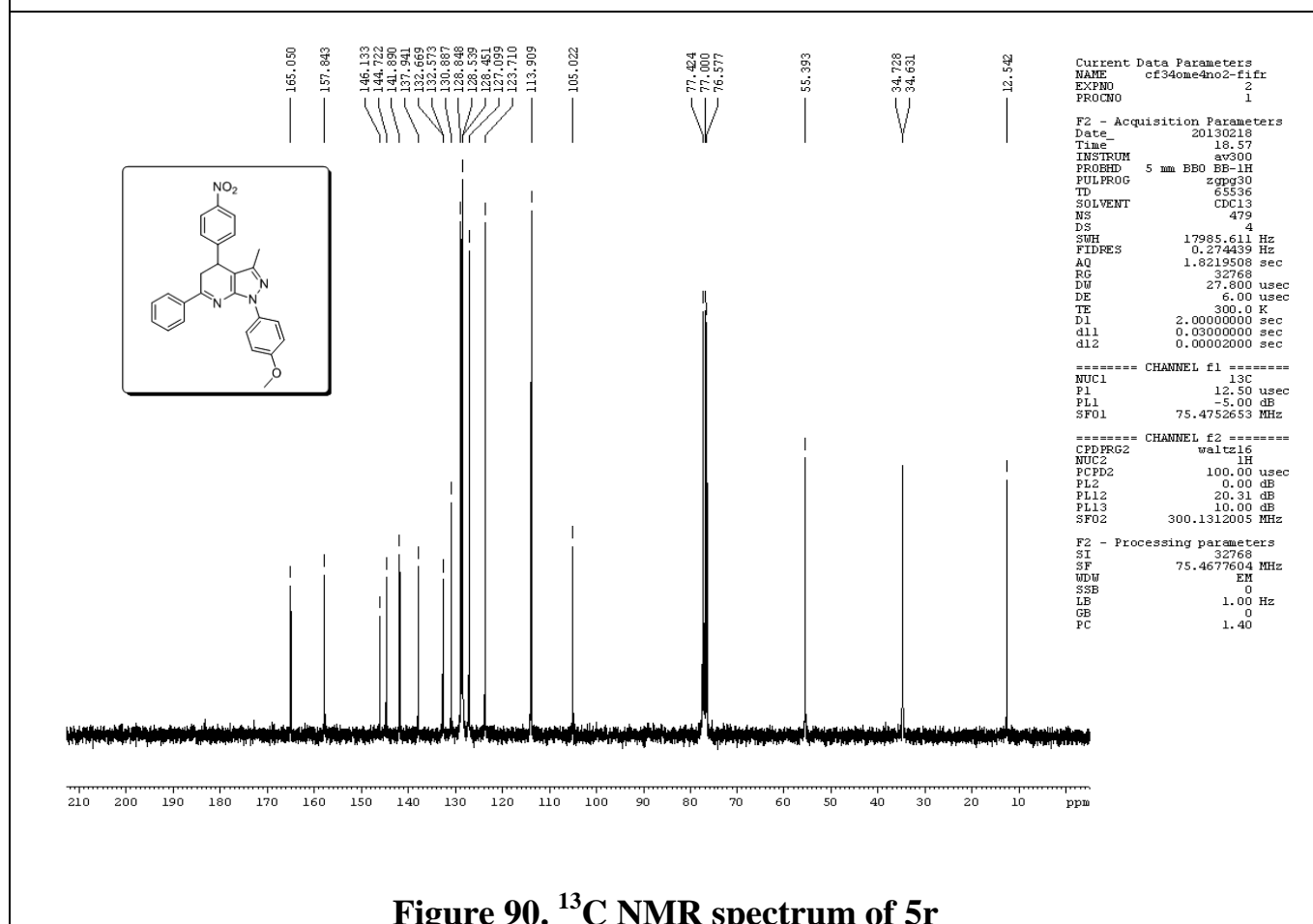
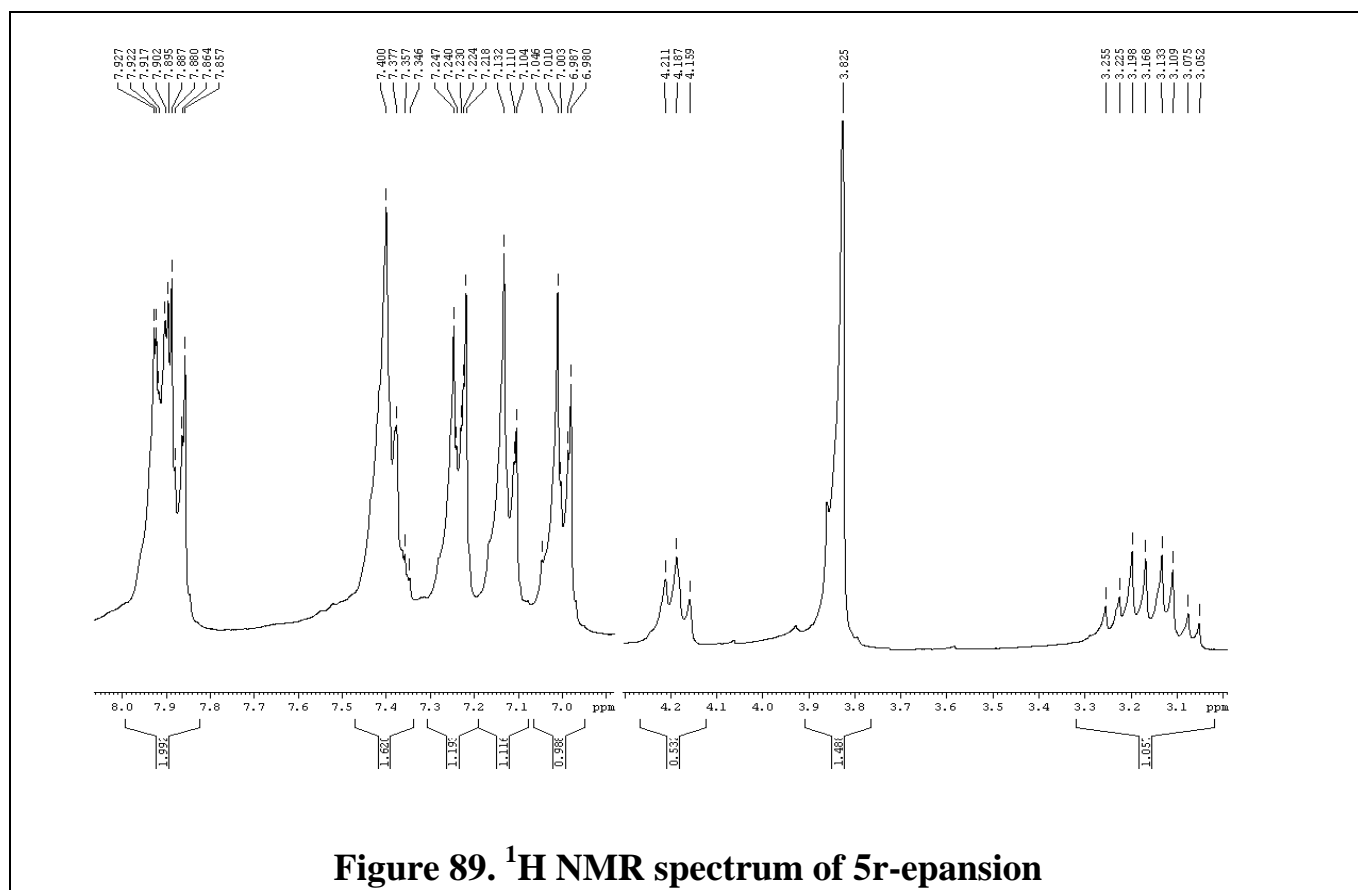


Figure 88. ¹H NMR spectrum of 5r



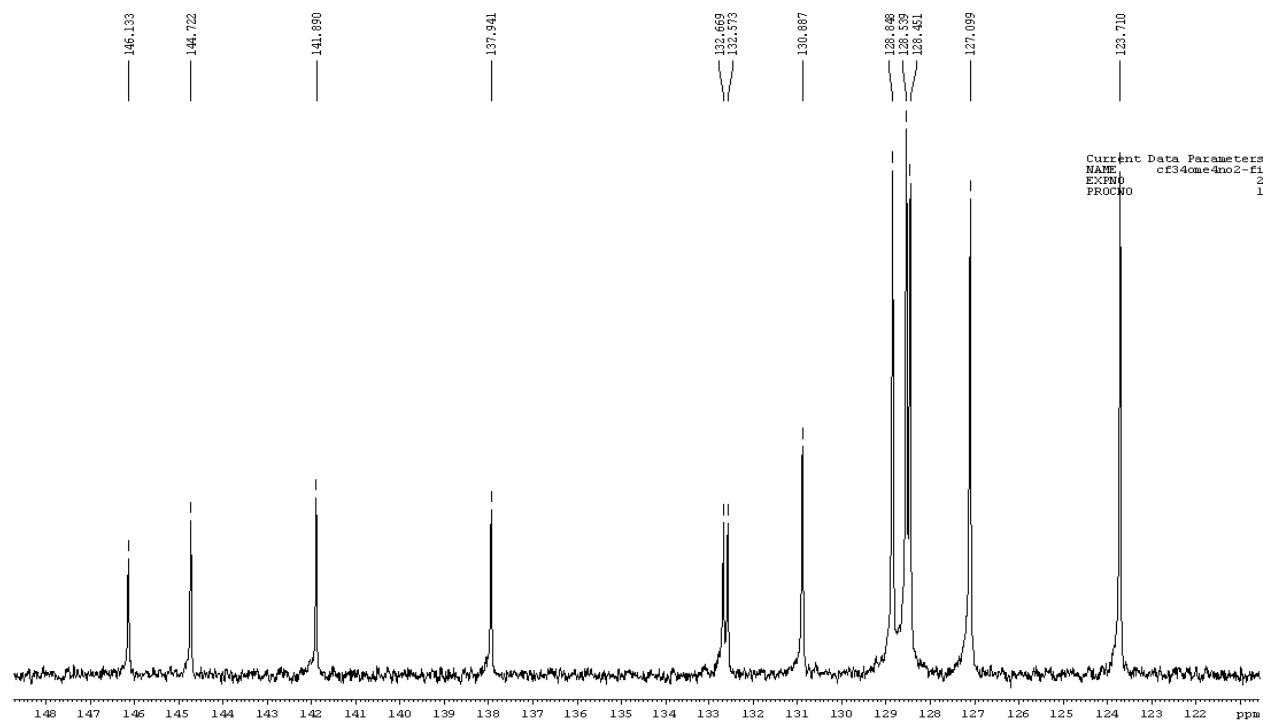


Figure 90. ^{13}C NMR spectrum of 5r-expansion

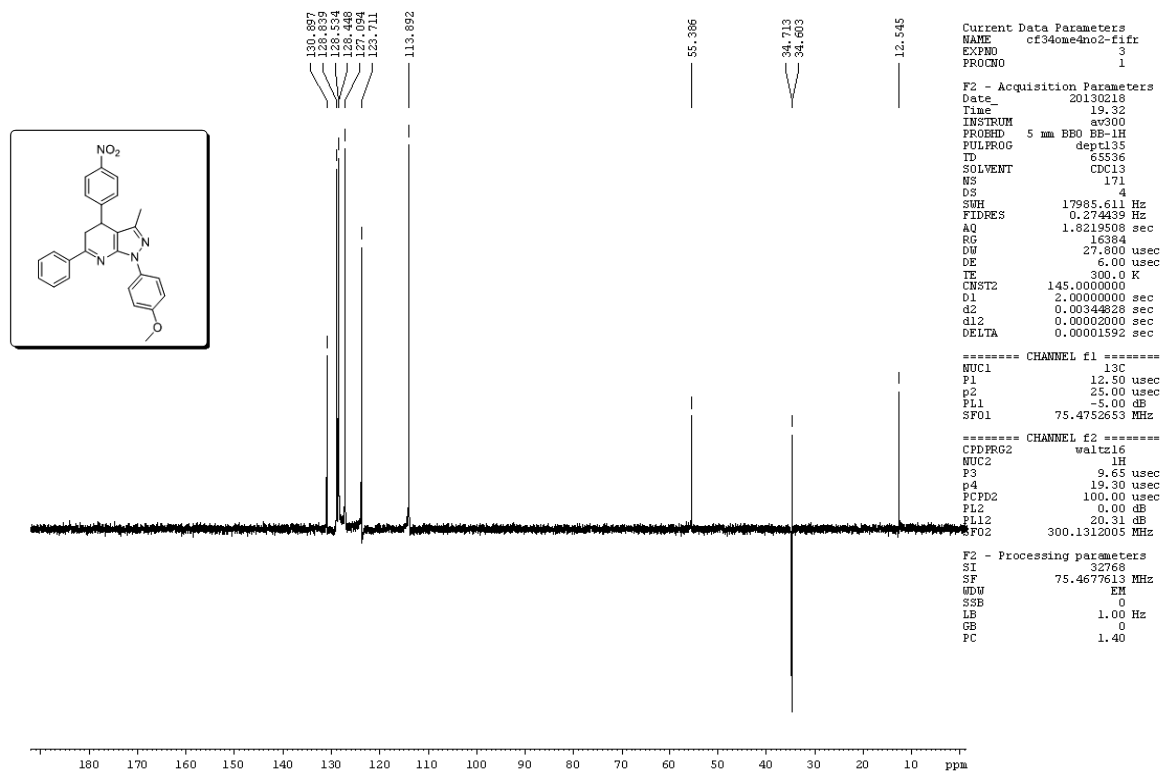


Figure 91. Dept-135 NMR spectrum of 5r

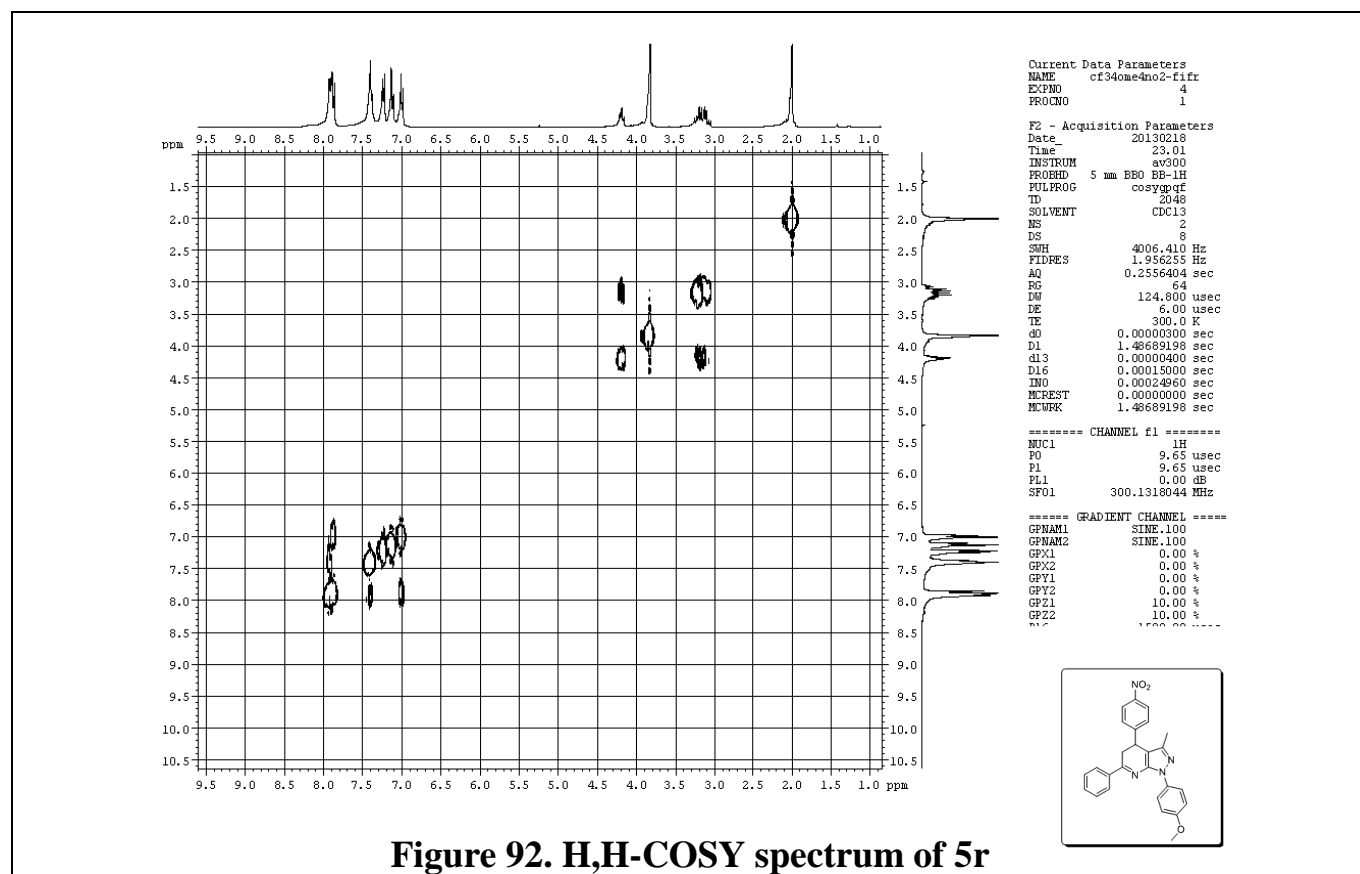


Figure 92. H,H-COSY spectrum of 5r

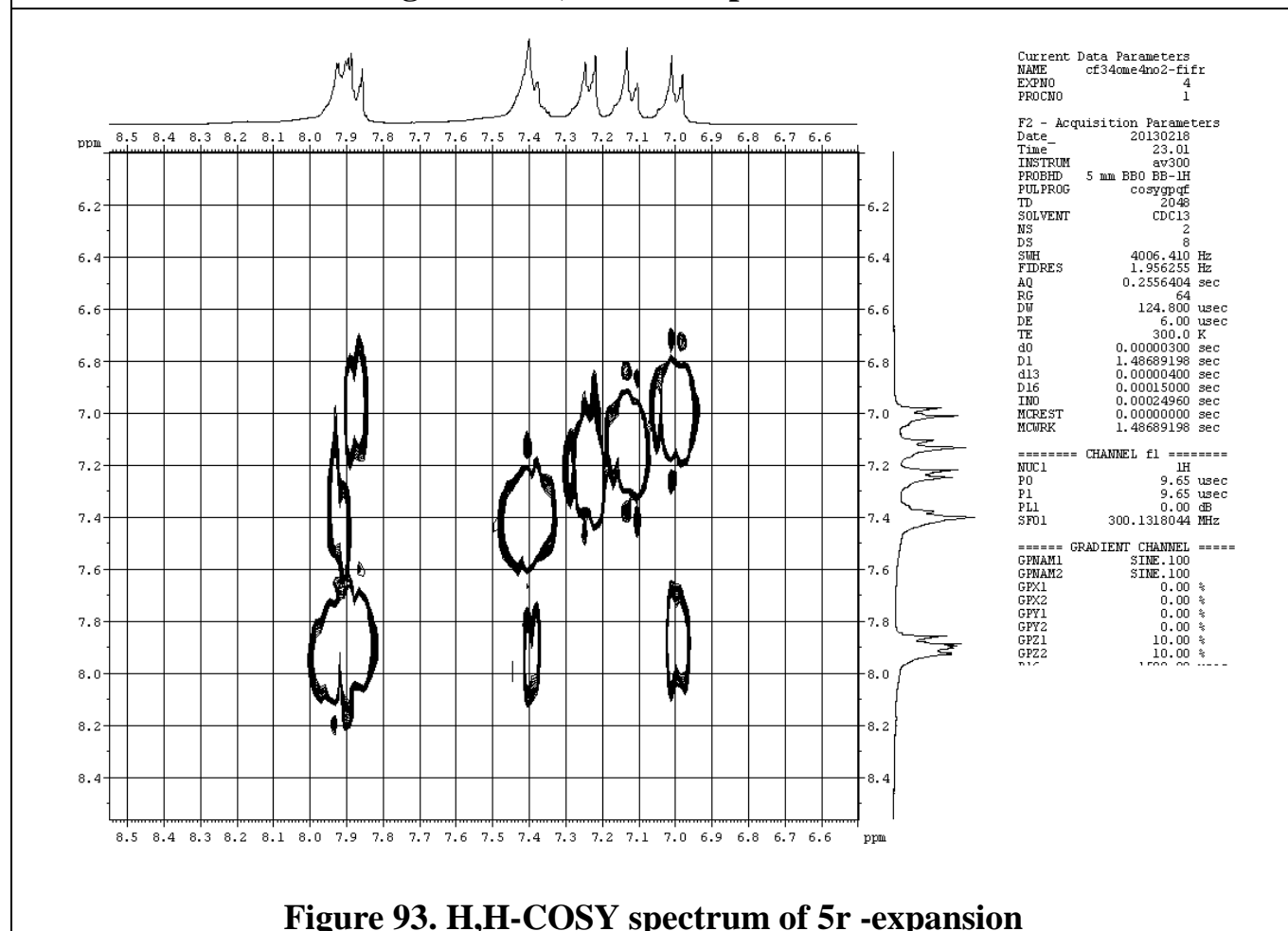


Figure 93. H,H-COSY spectrum of 5r -expansion

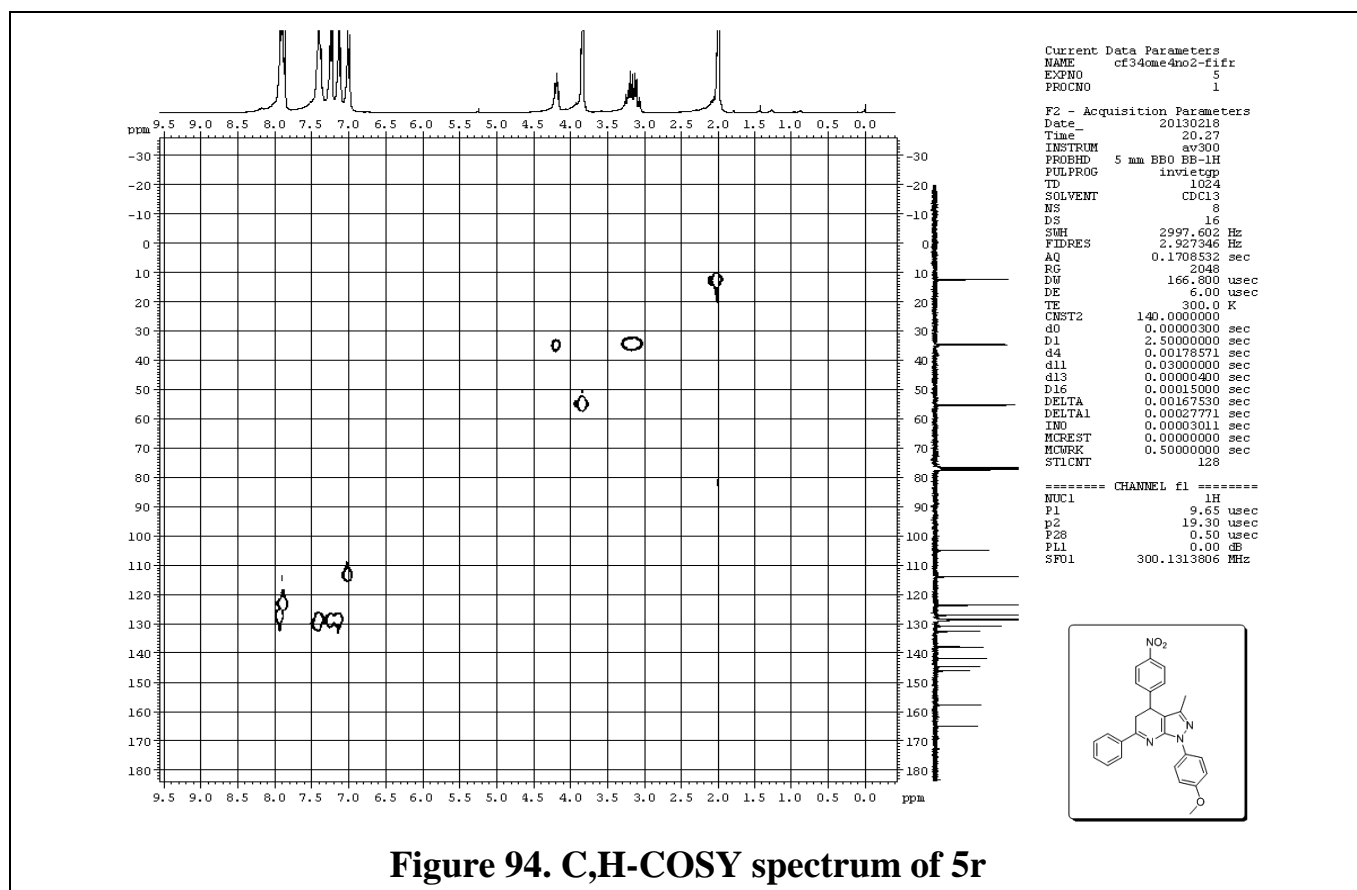


Figure 94. C,H-COSY spectrum of 5r

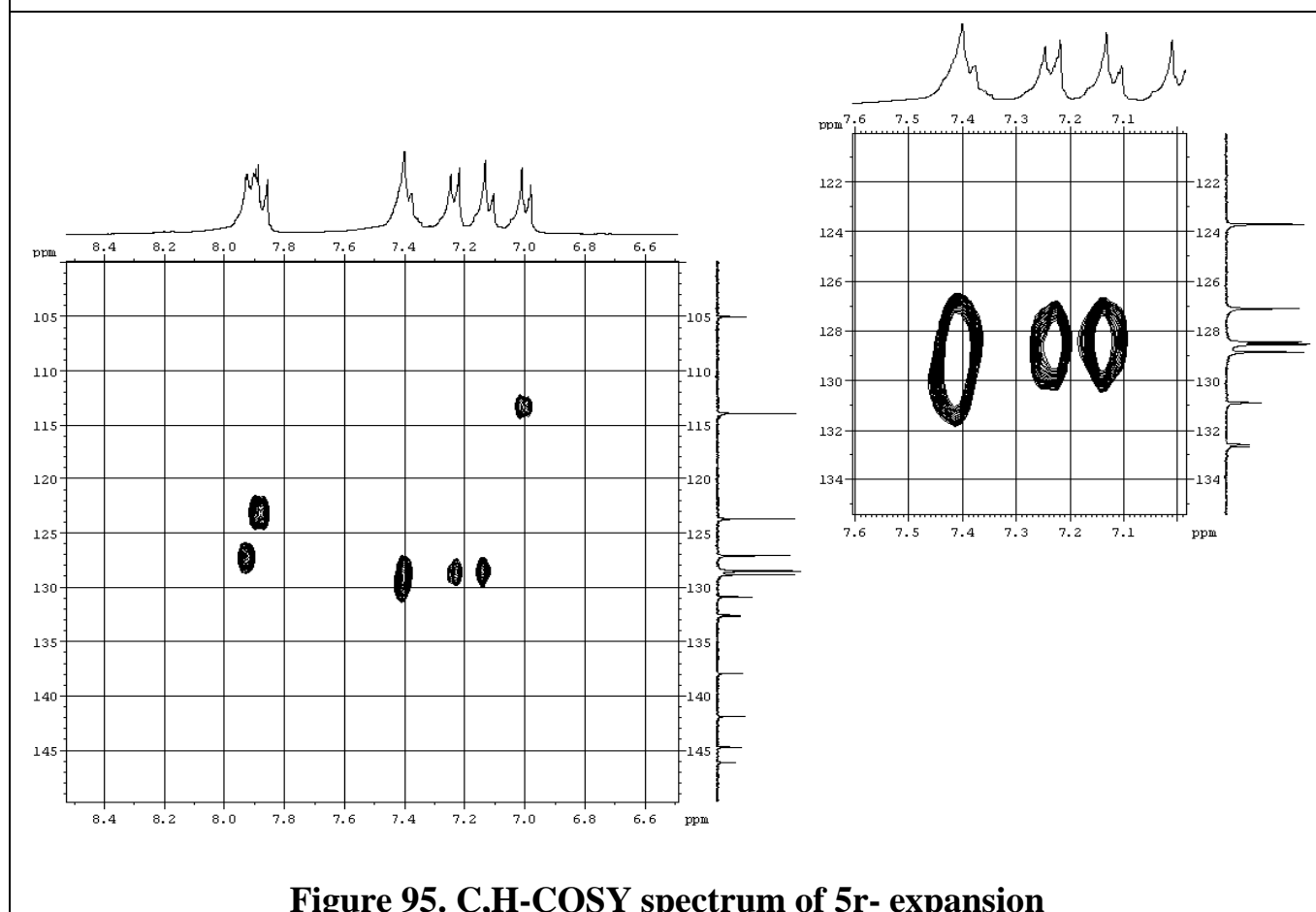


Figure 95. C,H-COSY spectrum of 5r- expansion

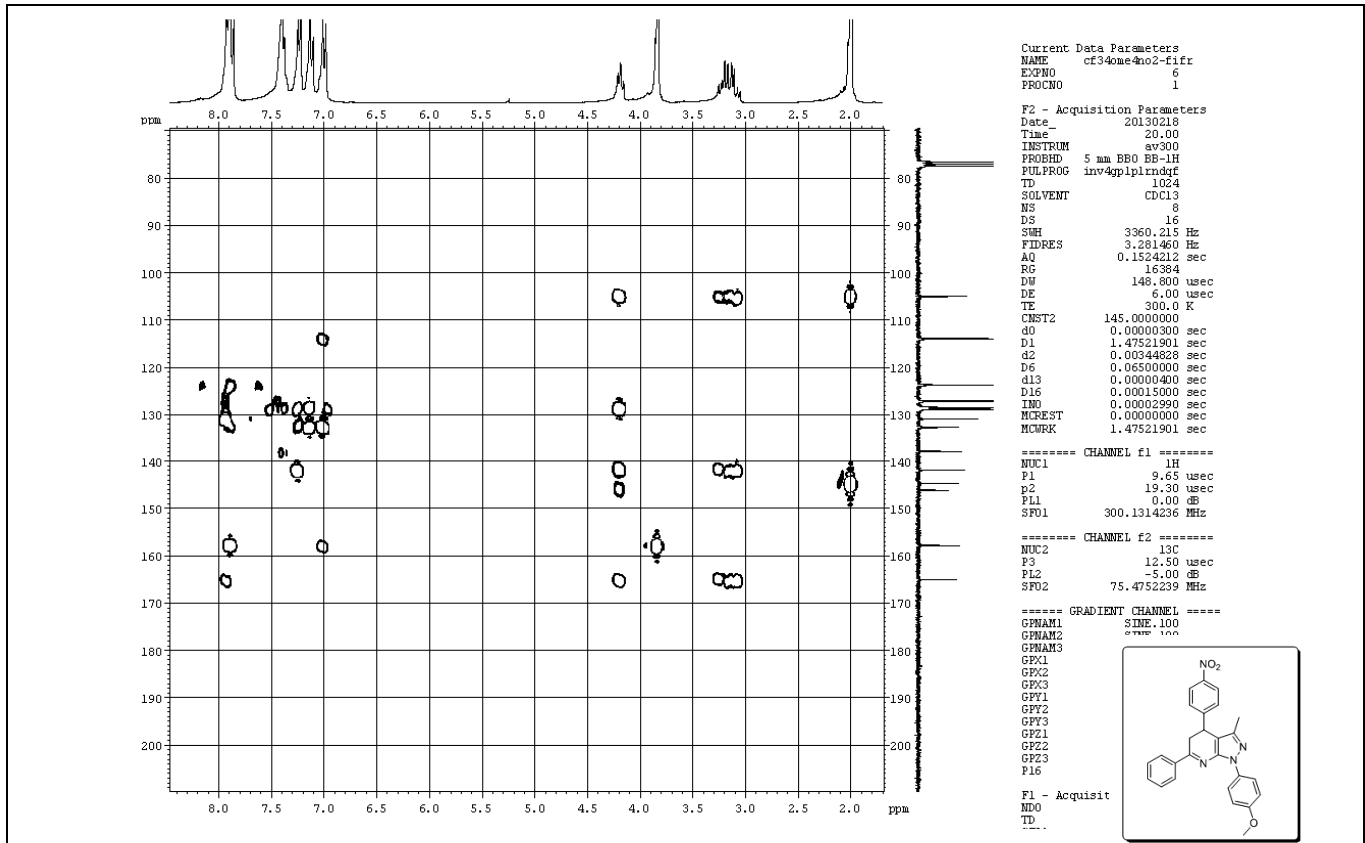


Figure 96. HMBC spectrum of 5r

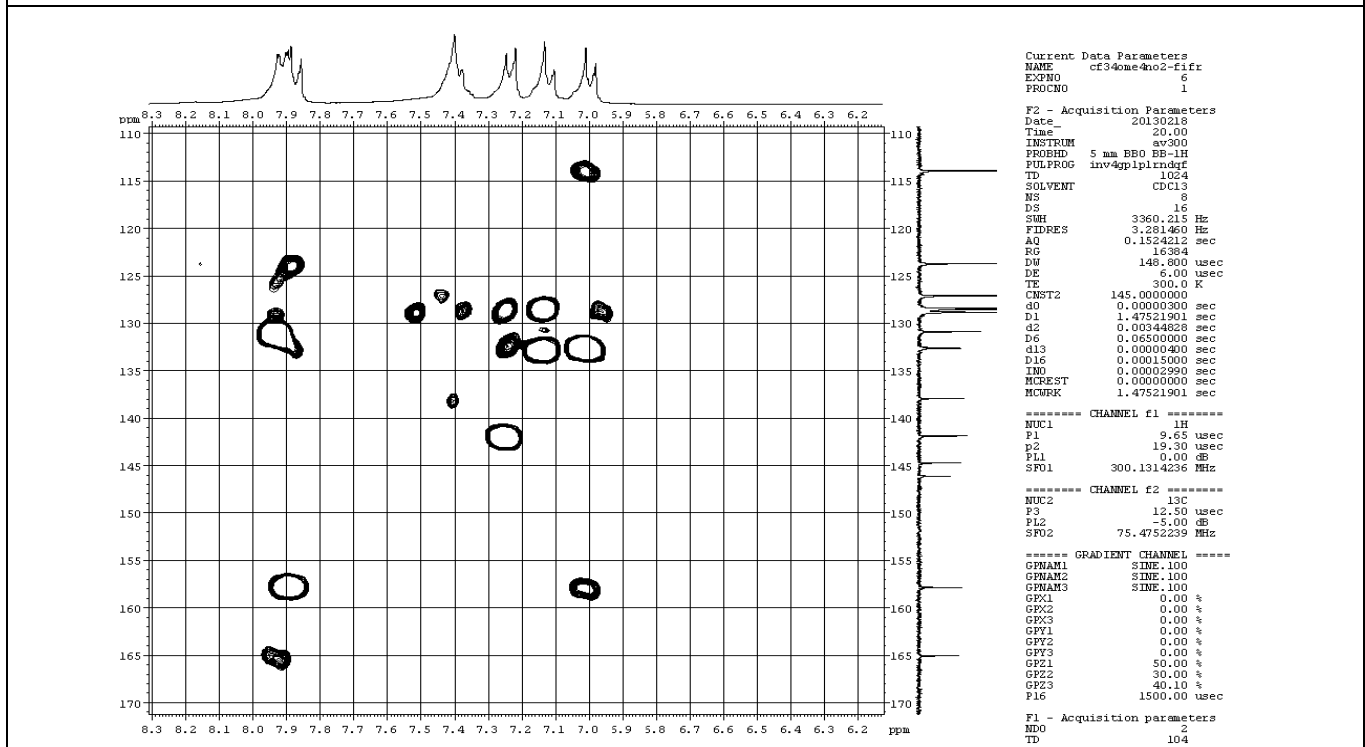
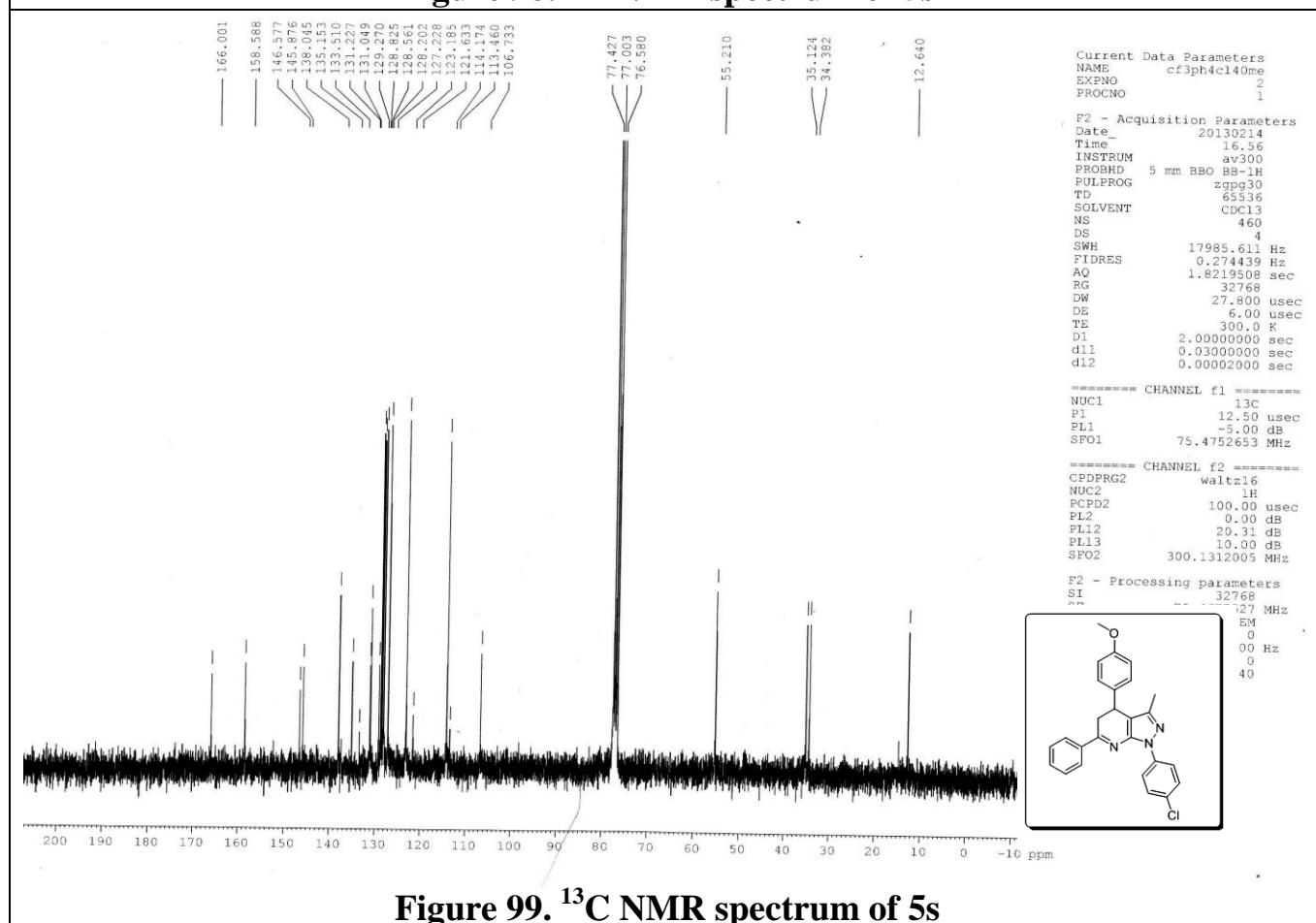
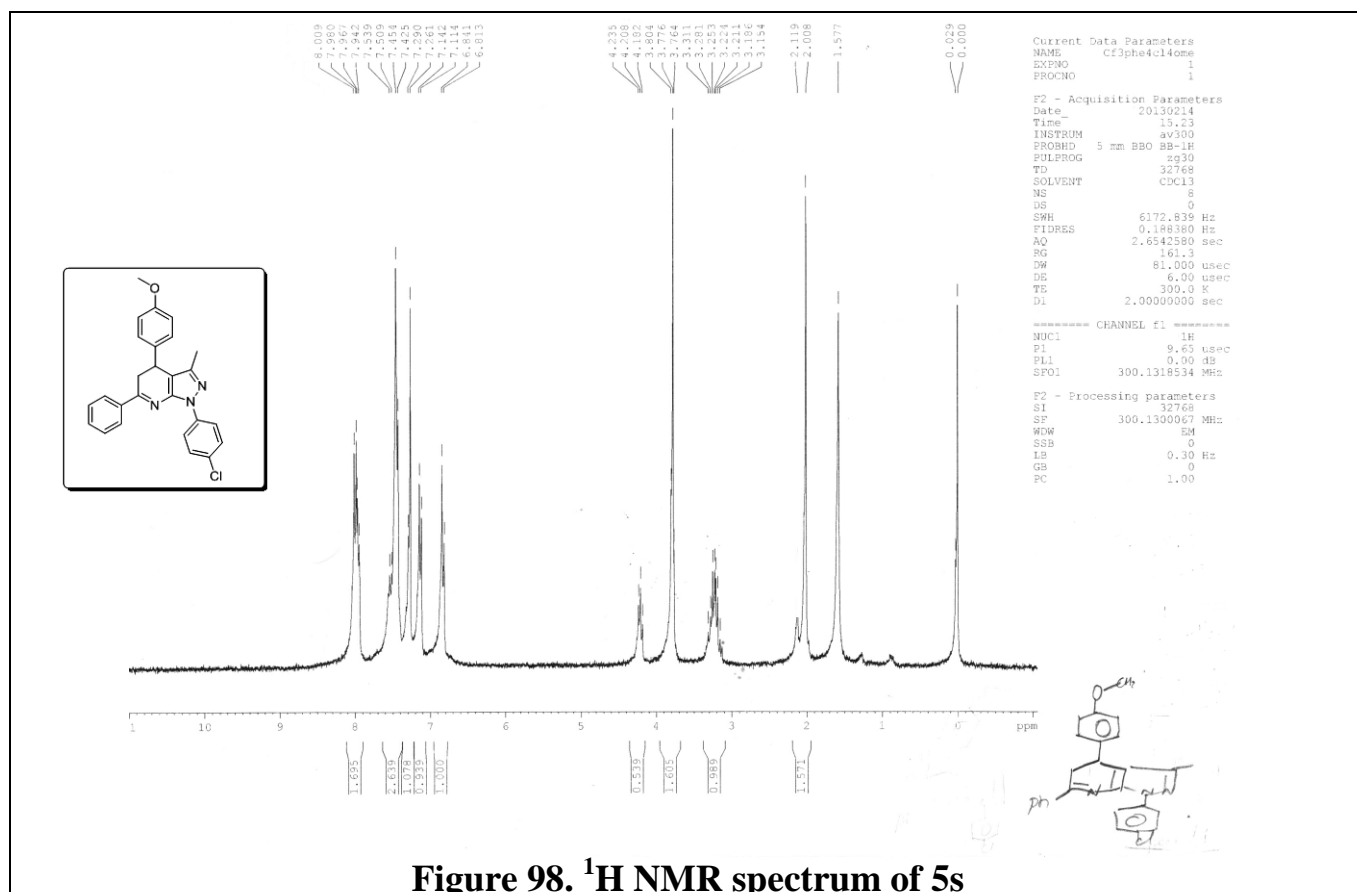
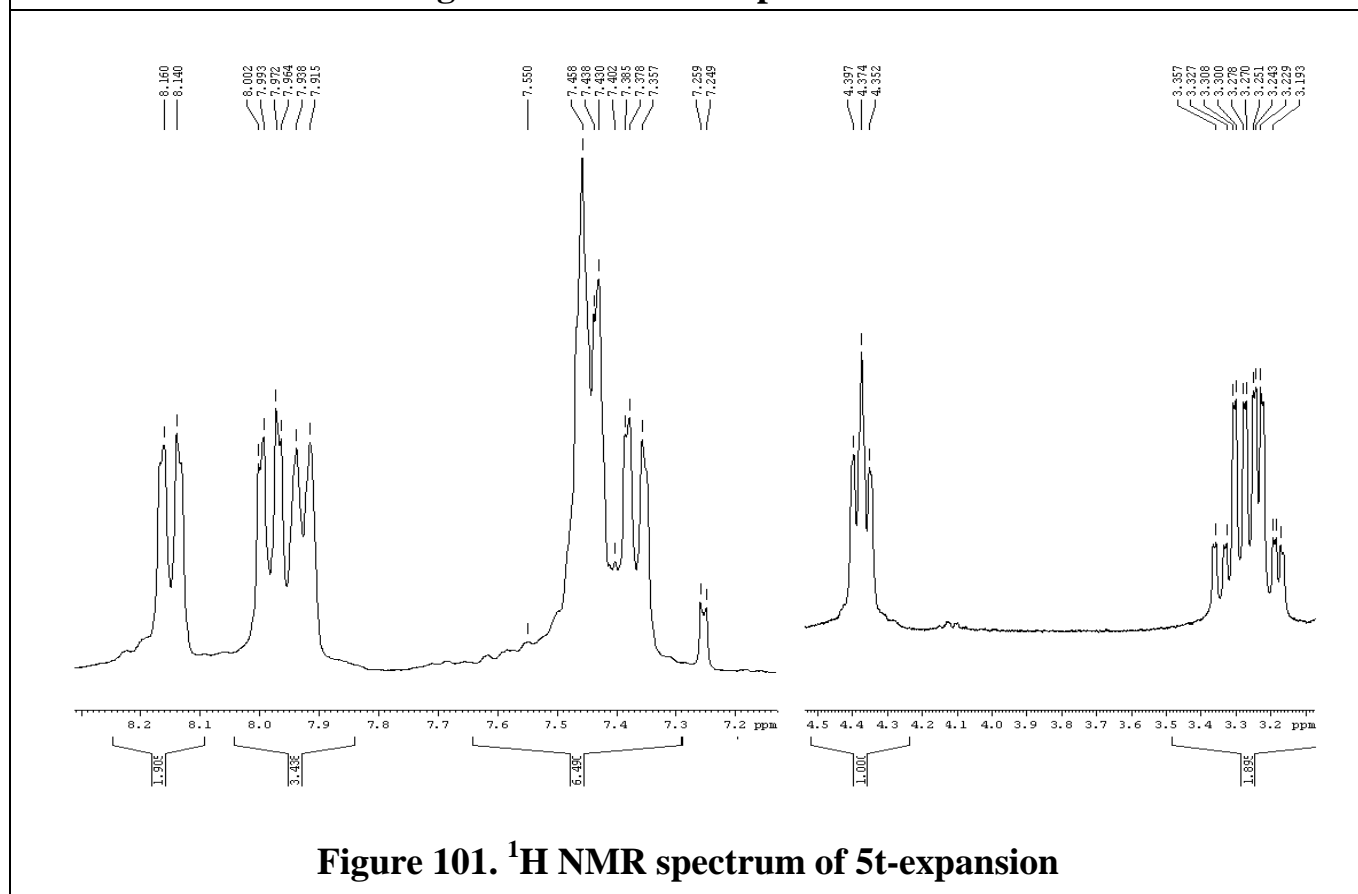
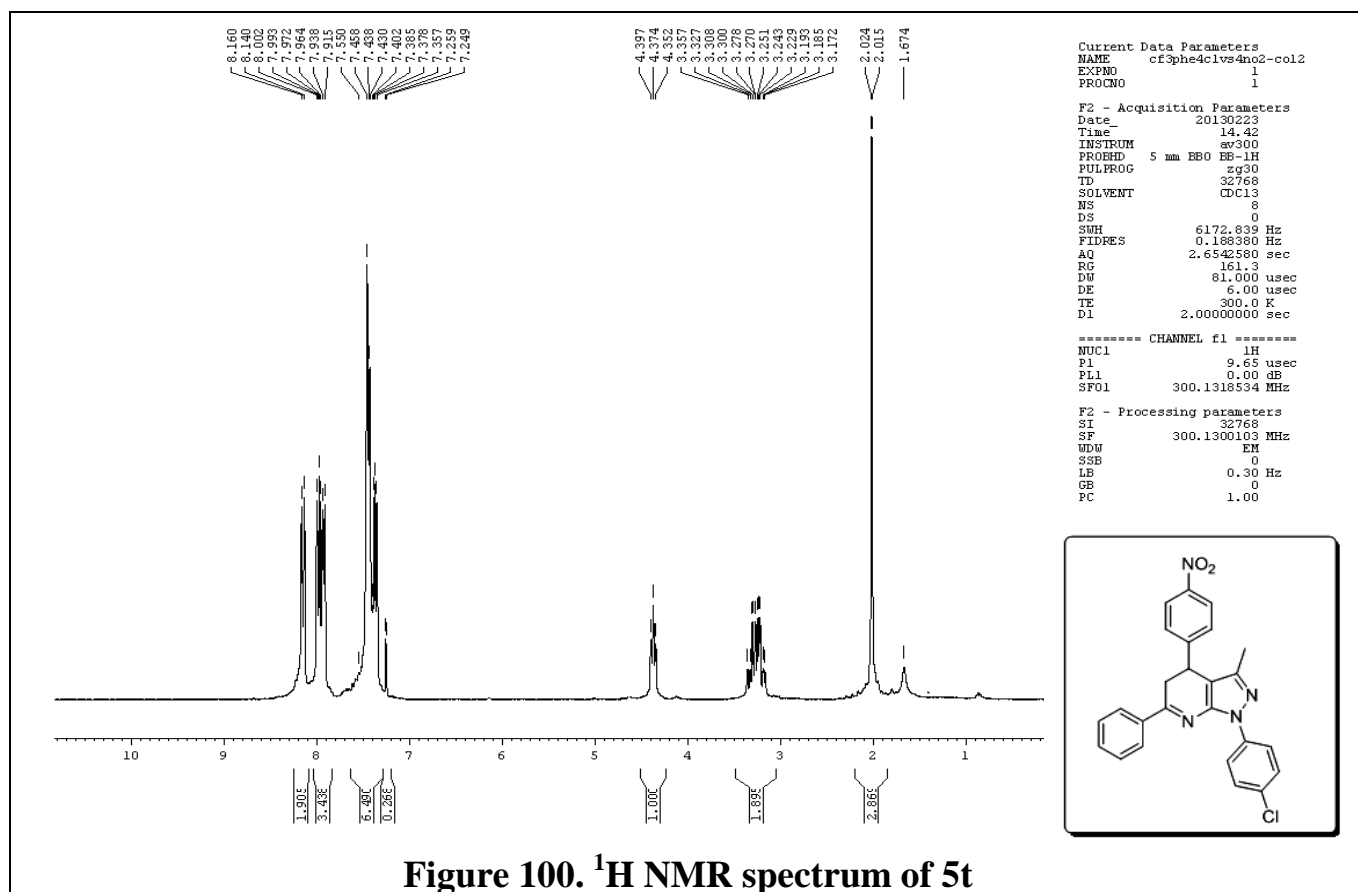


Figure 97. HMBC spectrum of 5r - expansion





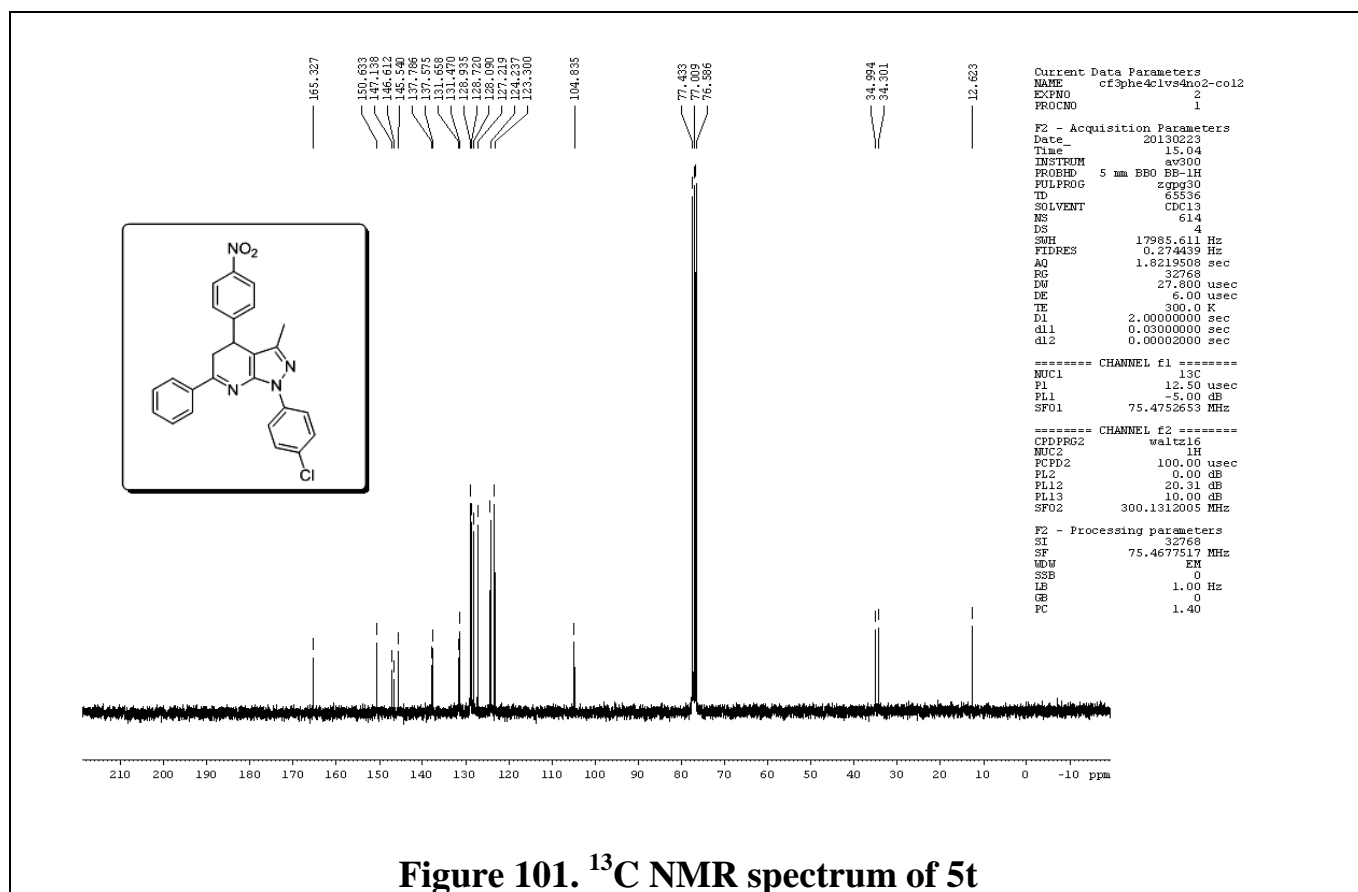


Figure 101. ¹³C NMR spectrum of 5t

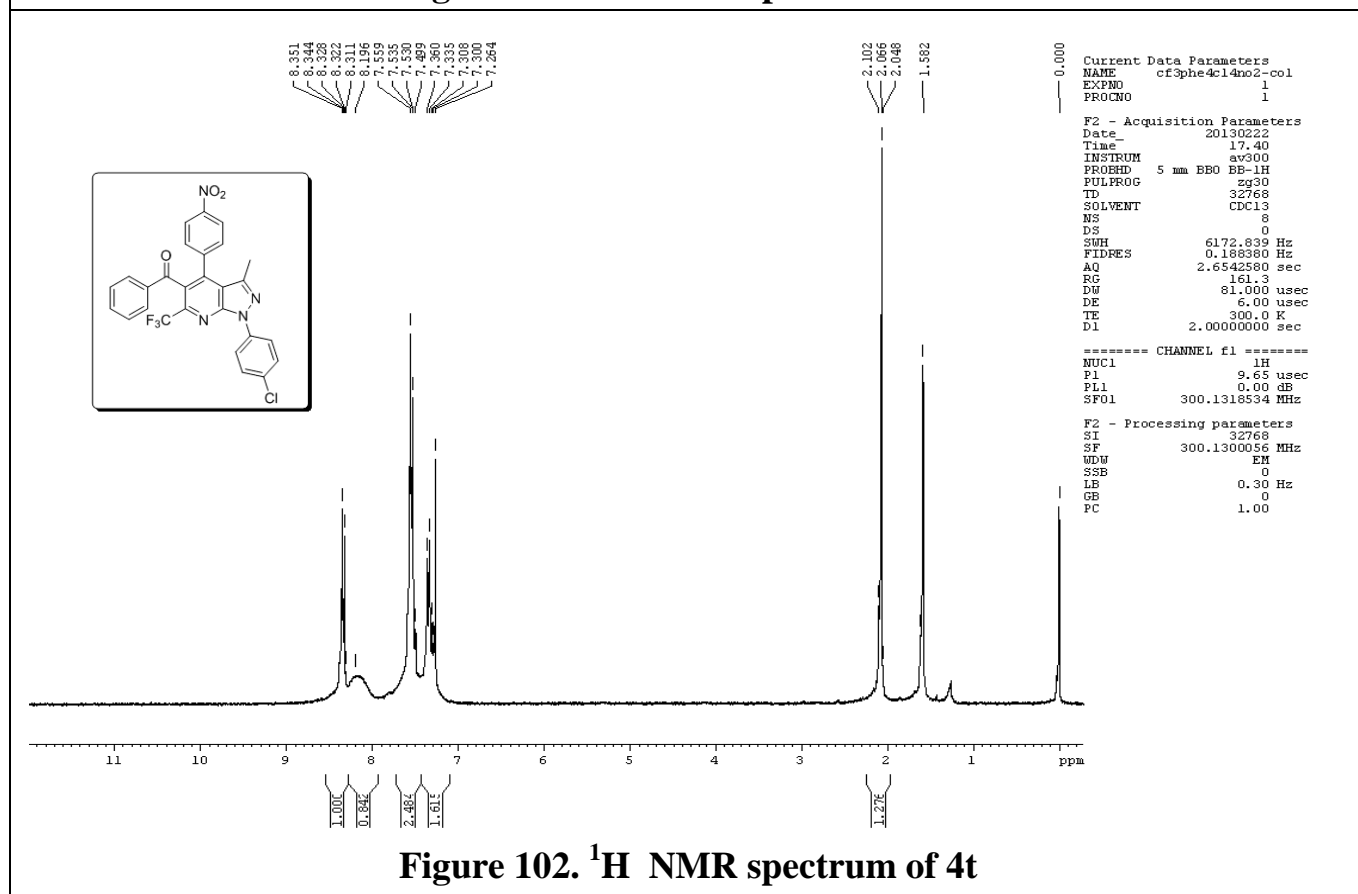
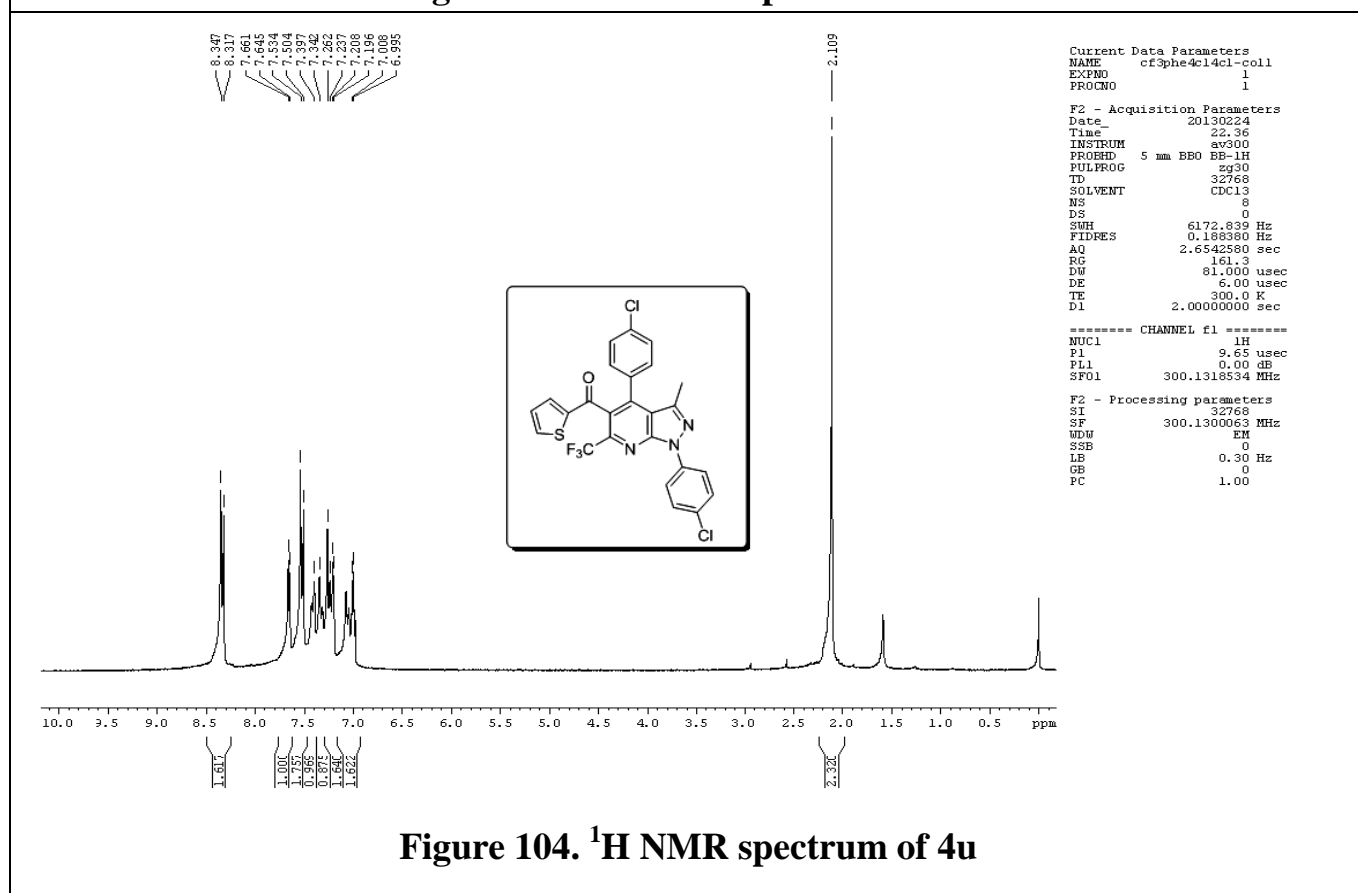
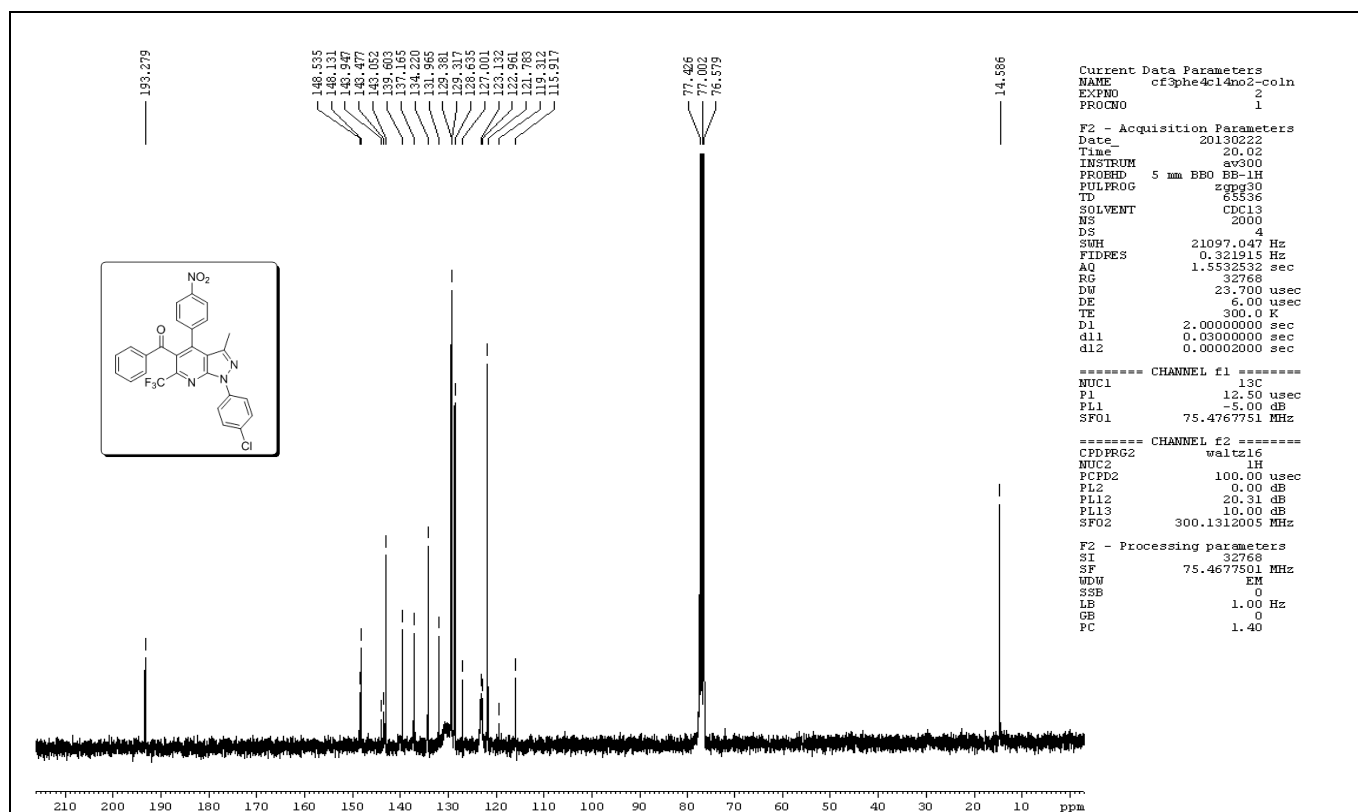


Figure 102. ¹H NMR spectrum of 4t



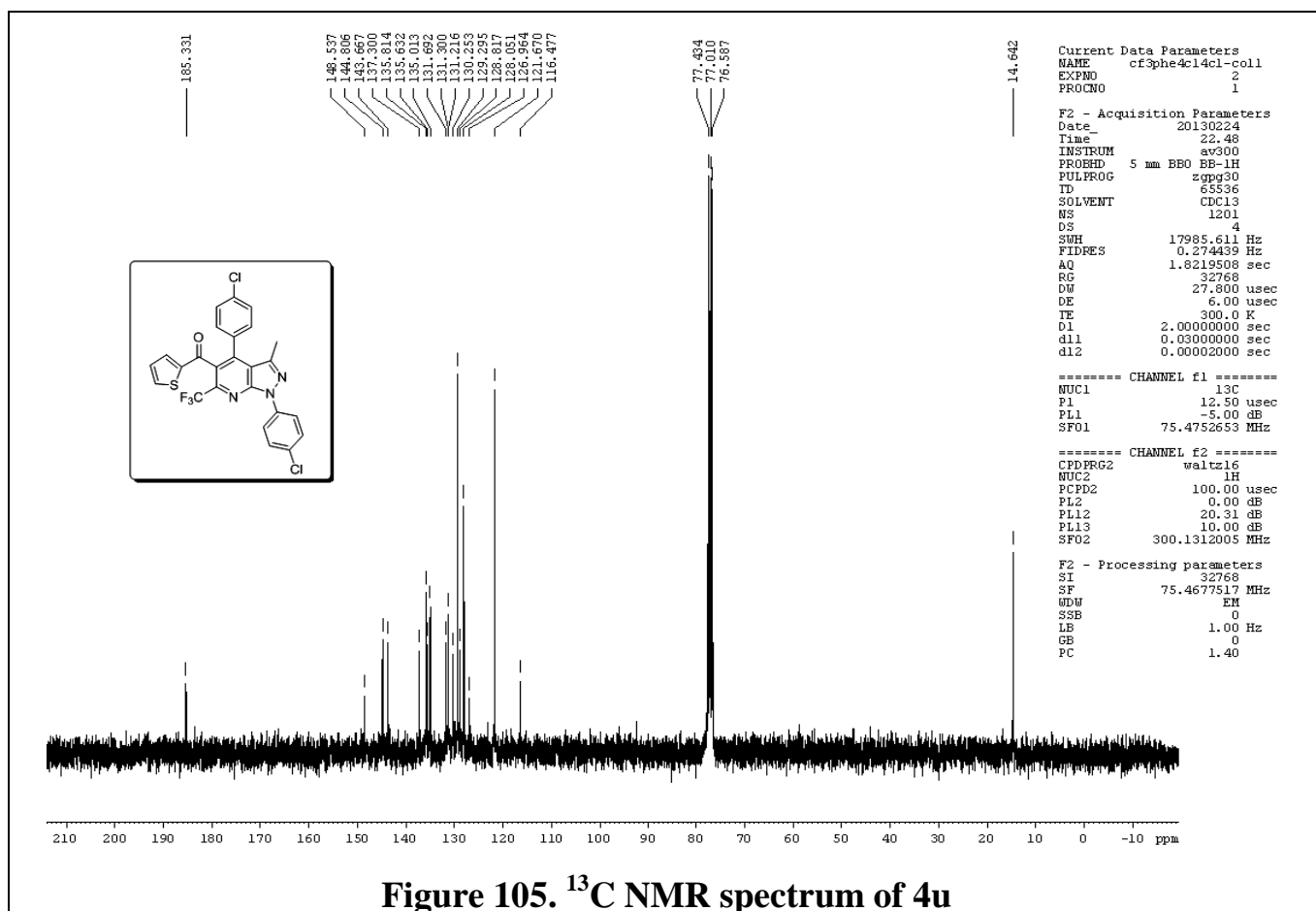


Figure 105. ¹³C NMR spectrum of 4u

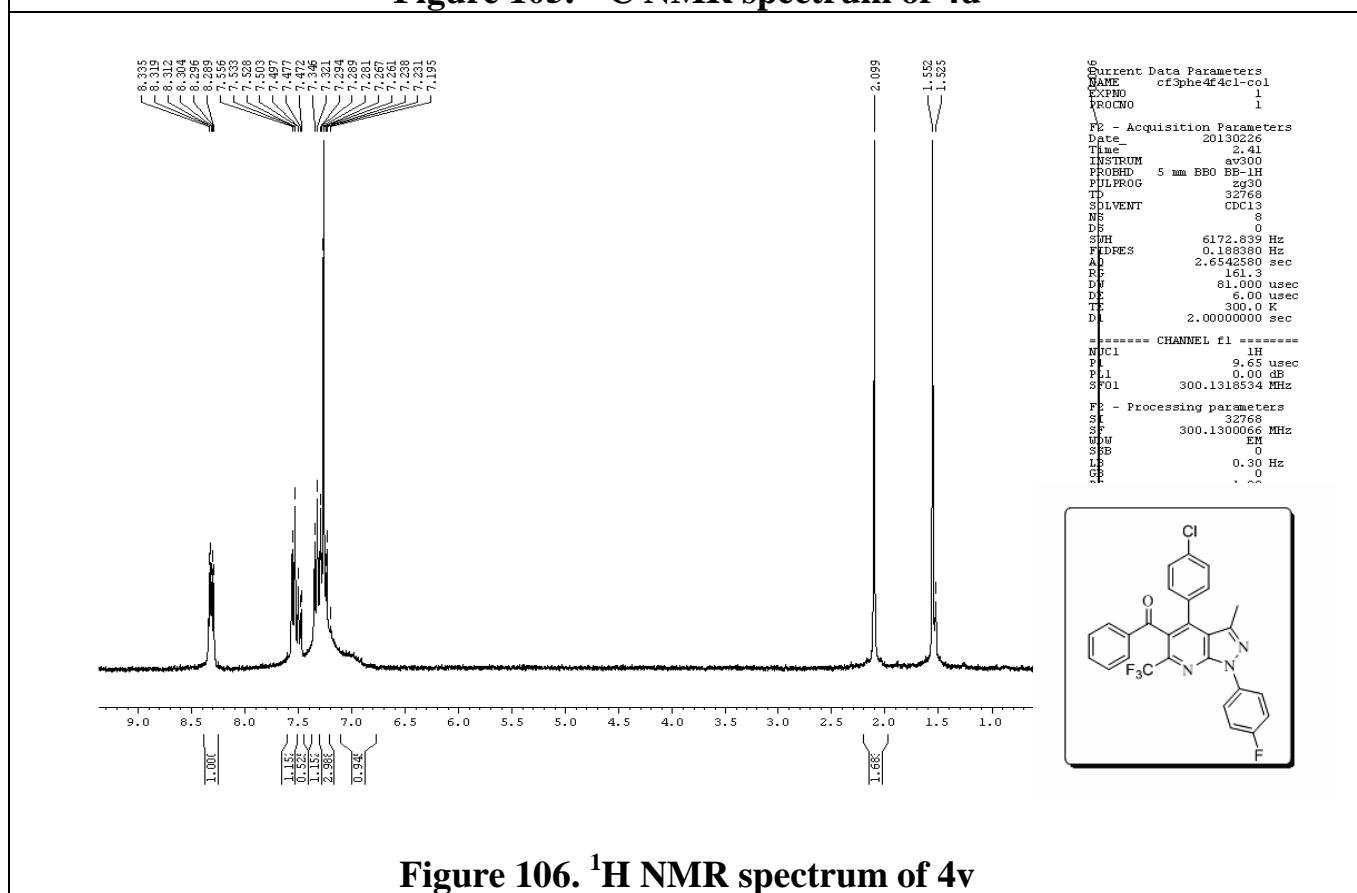


Figure 106. ¹H NMR spectrum of 4v

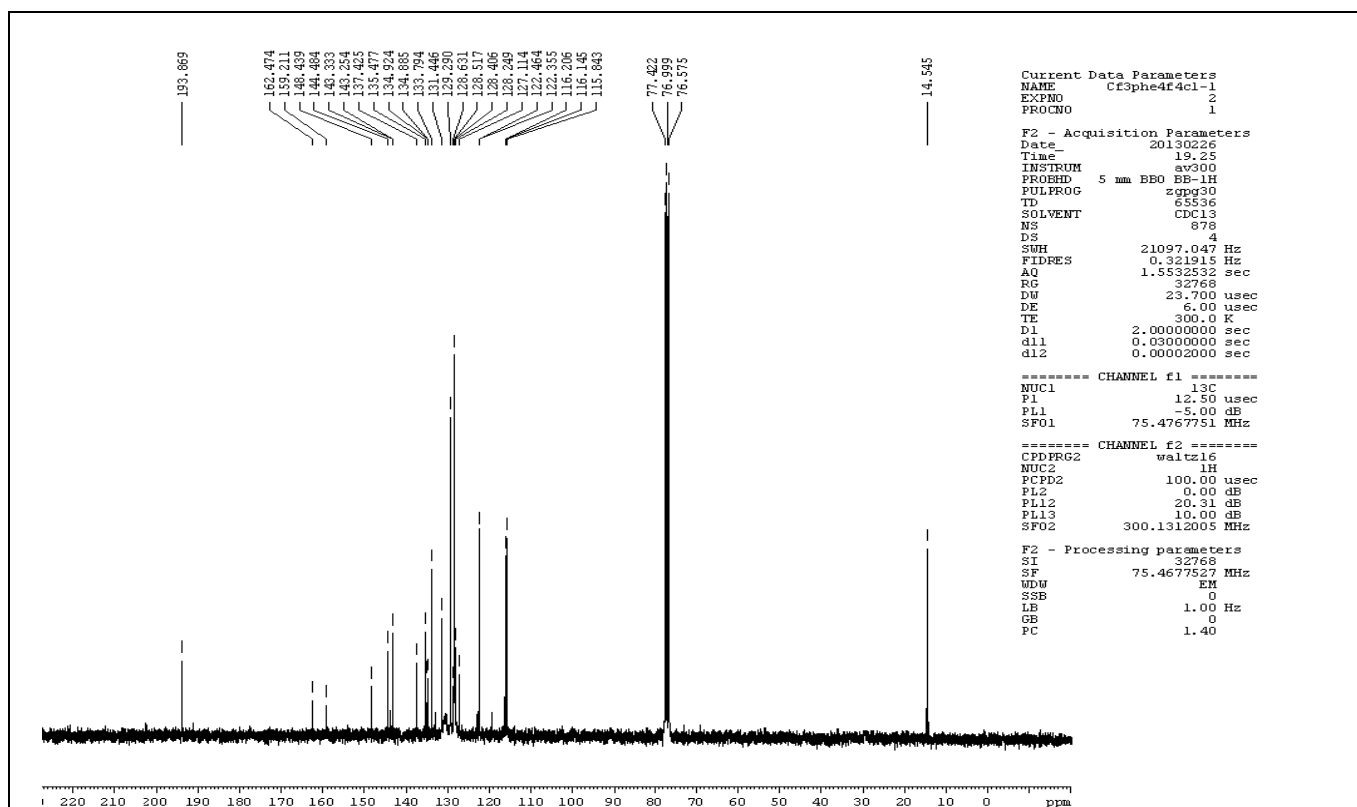


Figure 107. ^{13}C NMR spectrum of 4v

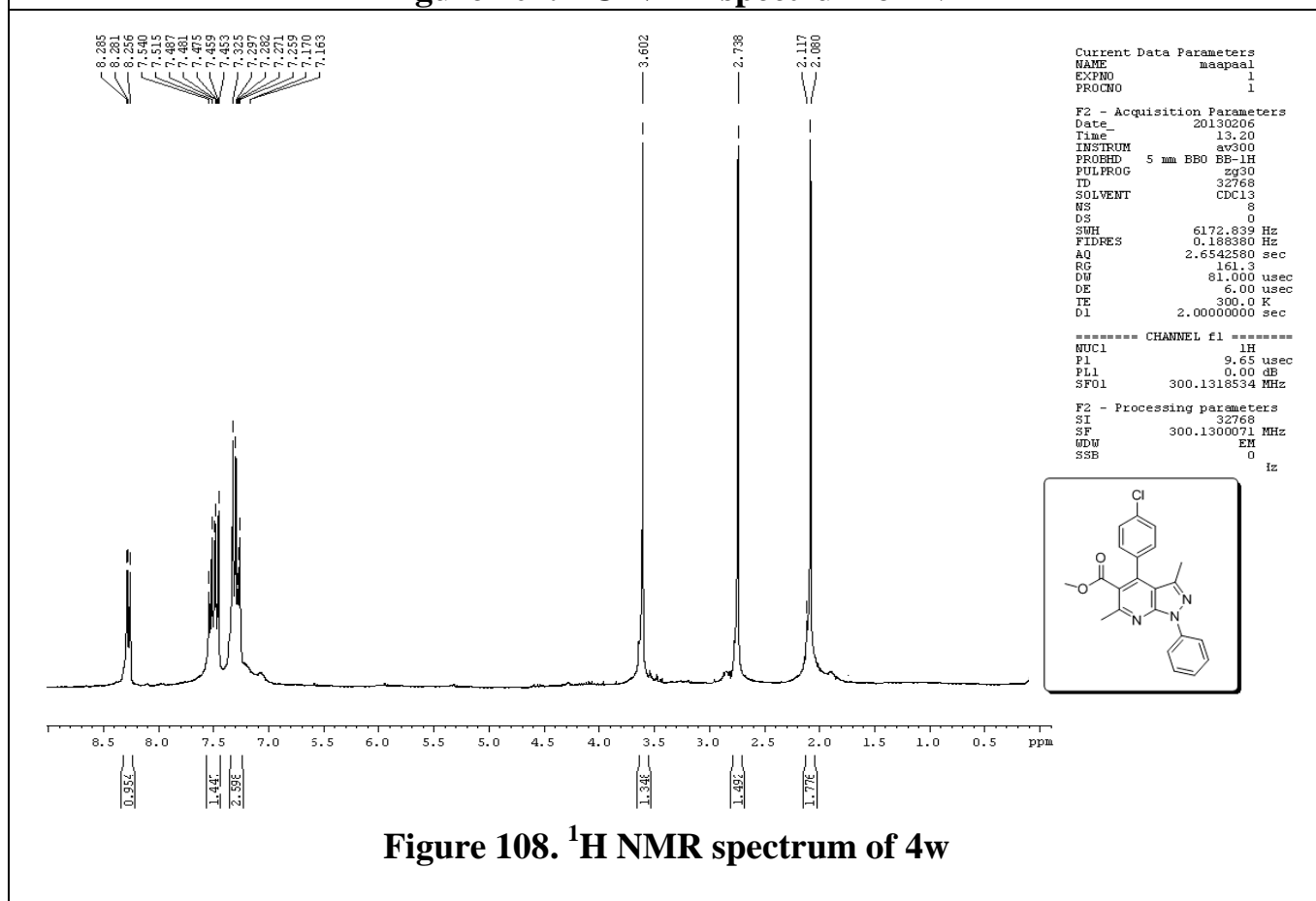


Figure 108. ^1H NMR spectrum of 4w

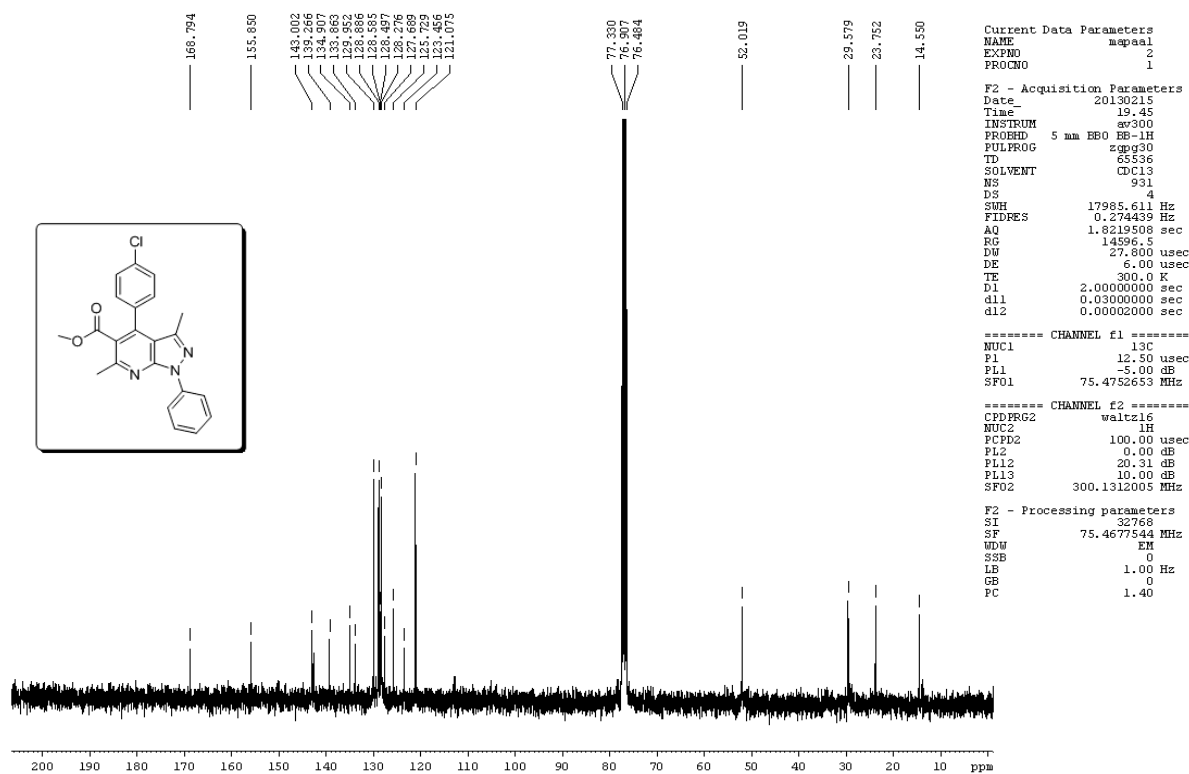


Figure 109. ^{13}C NMR spectrum of 4w

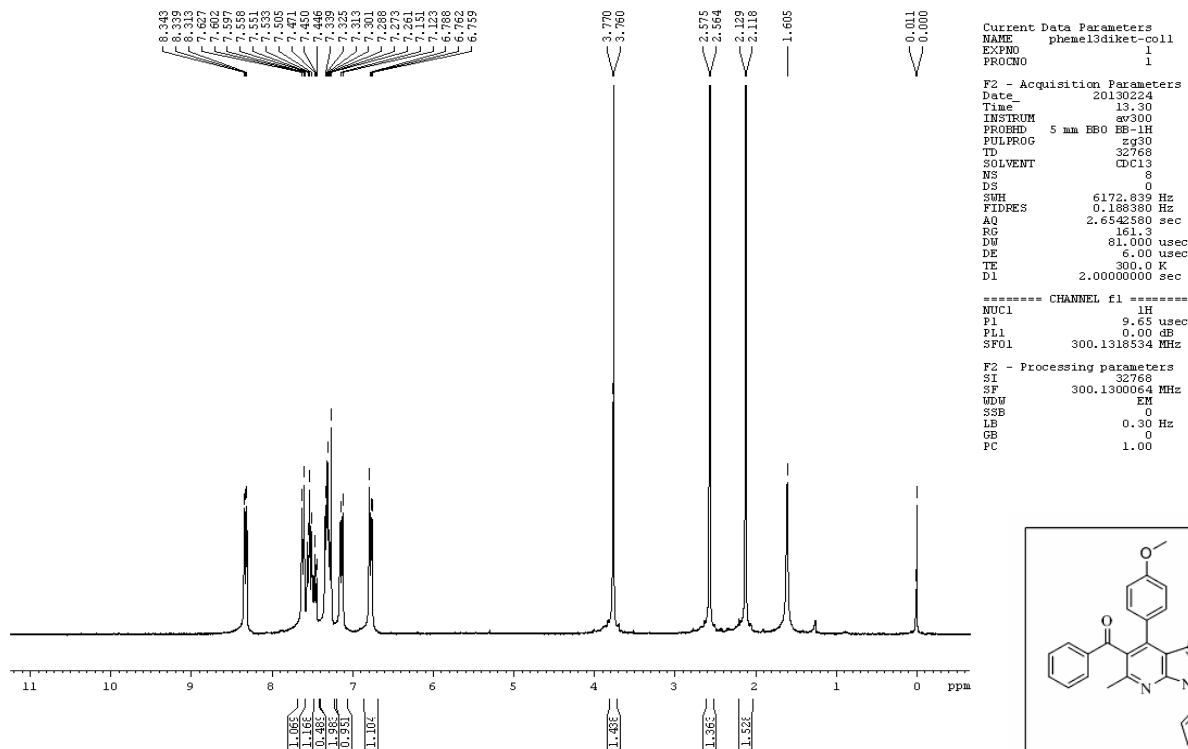


Figure 110. ^1H NMR spectrum of 4x

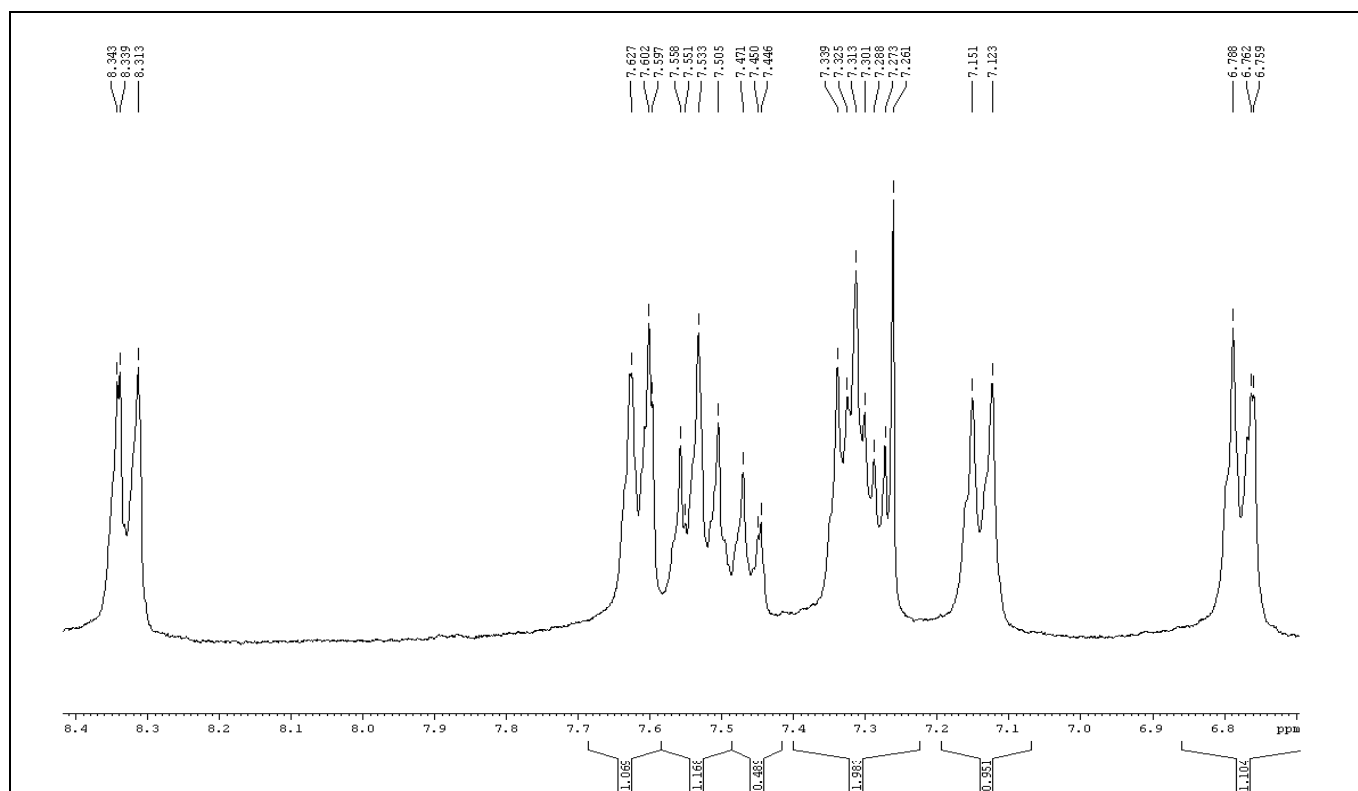


Figure 111. ^1H NMR spectrum of 4x-expansion

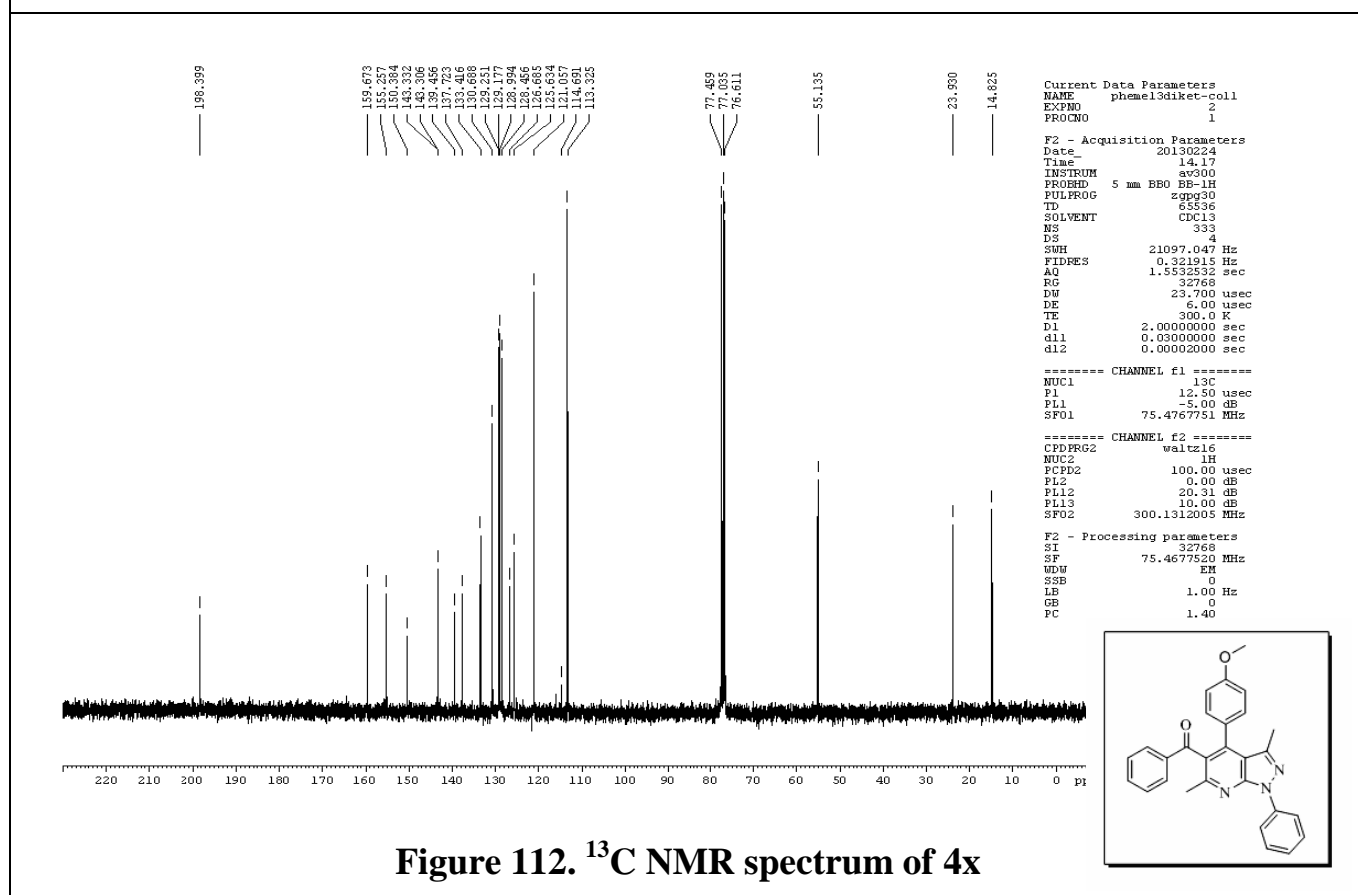


Figure 112. ^{13}C NMR spectrum of 4x

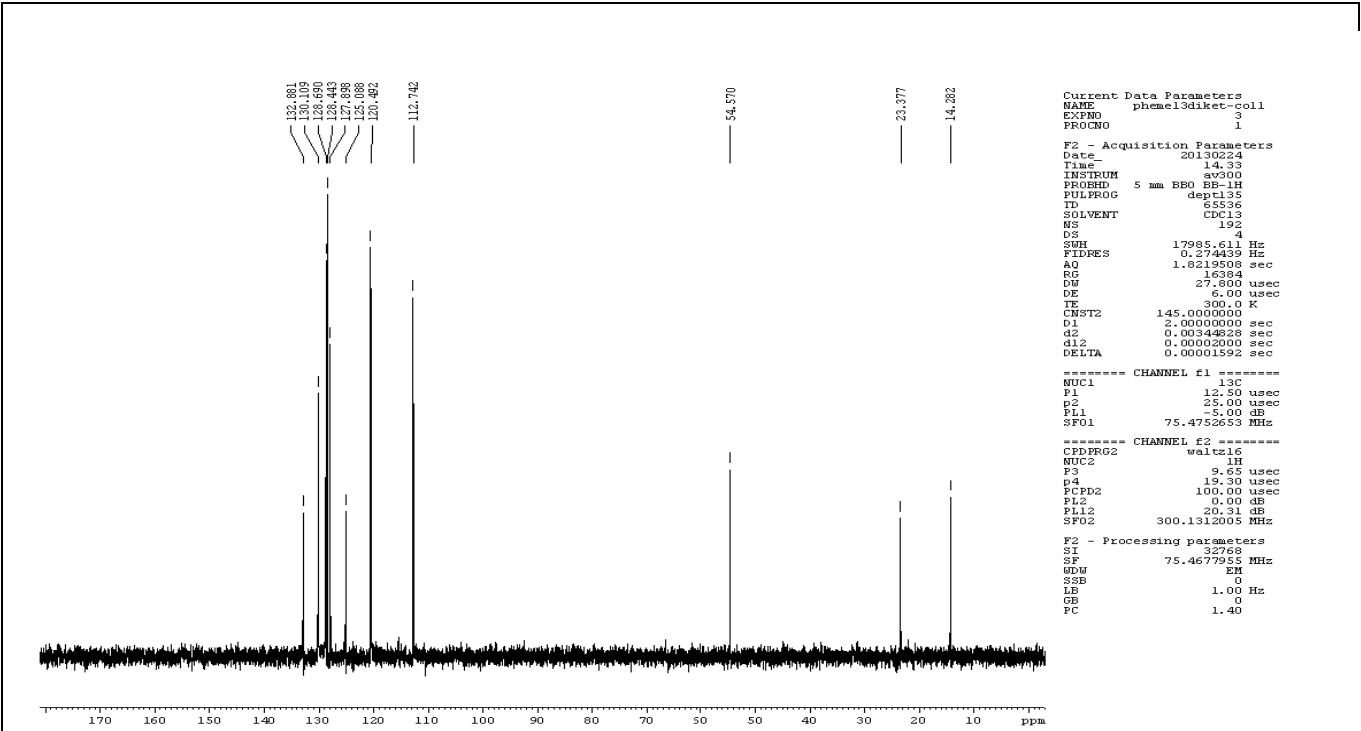


Figure 113.DEPT-135 spectrum of 4x

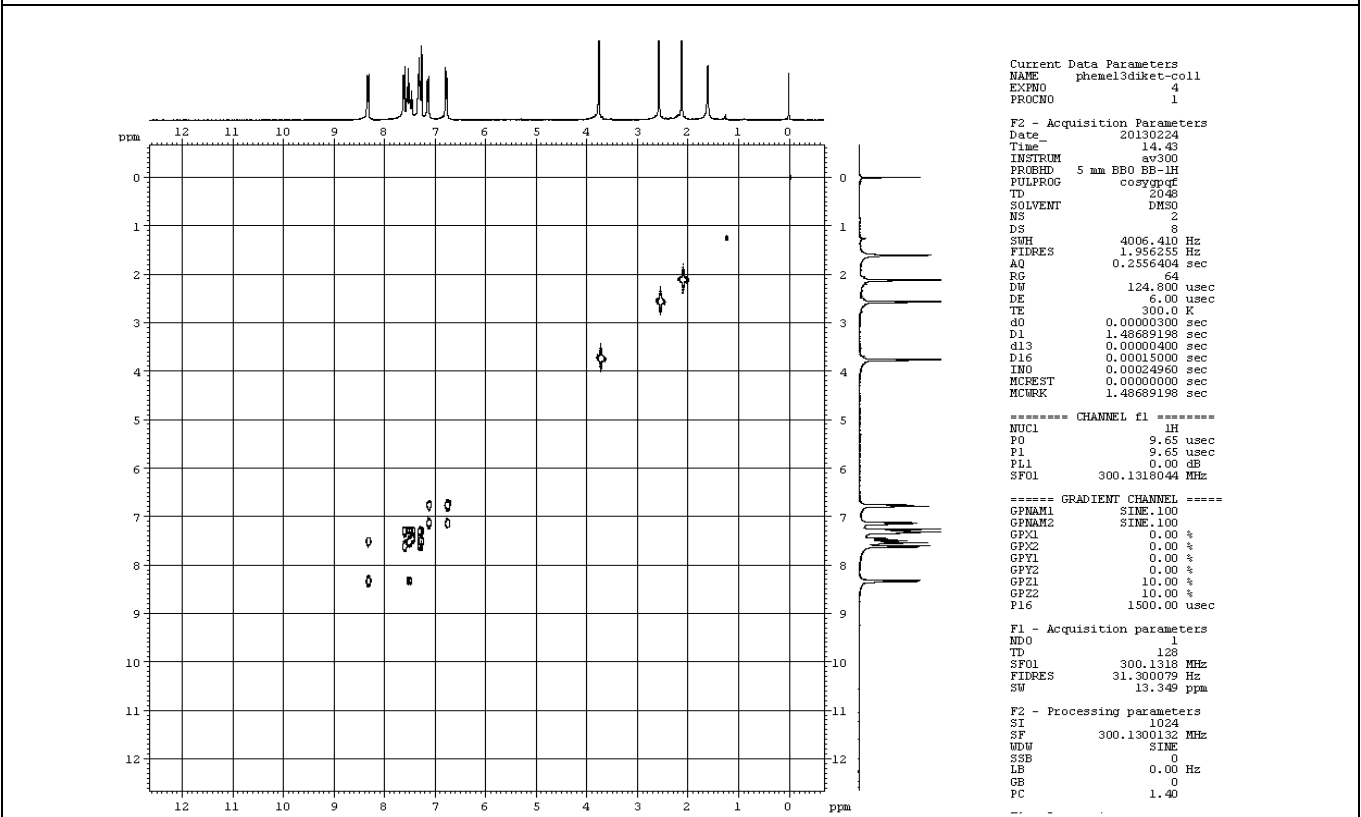


Figure 114. H,H-COSY spectrum of 4x

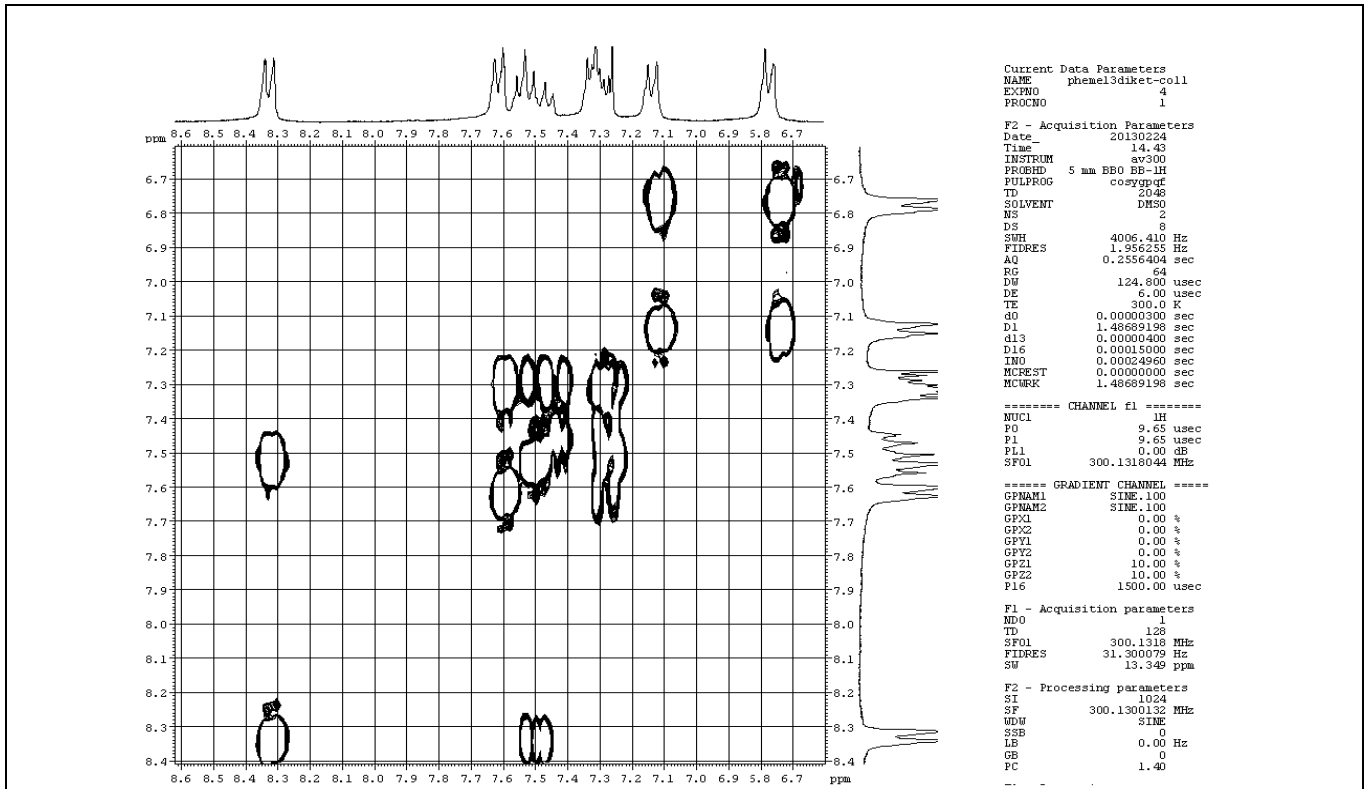


Figure 115. ¹H,¹H-COSY spectrum of 4x-expansion

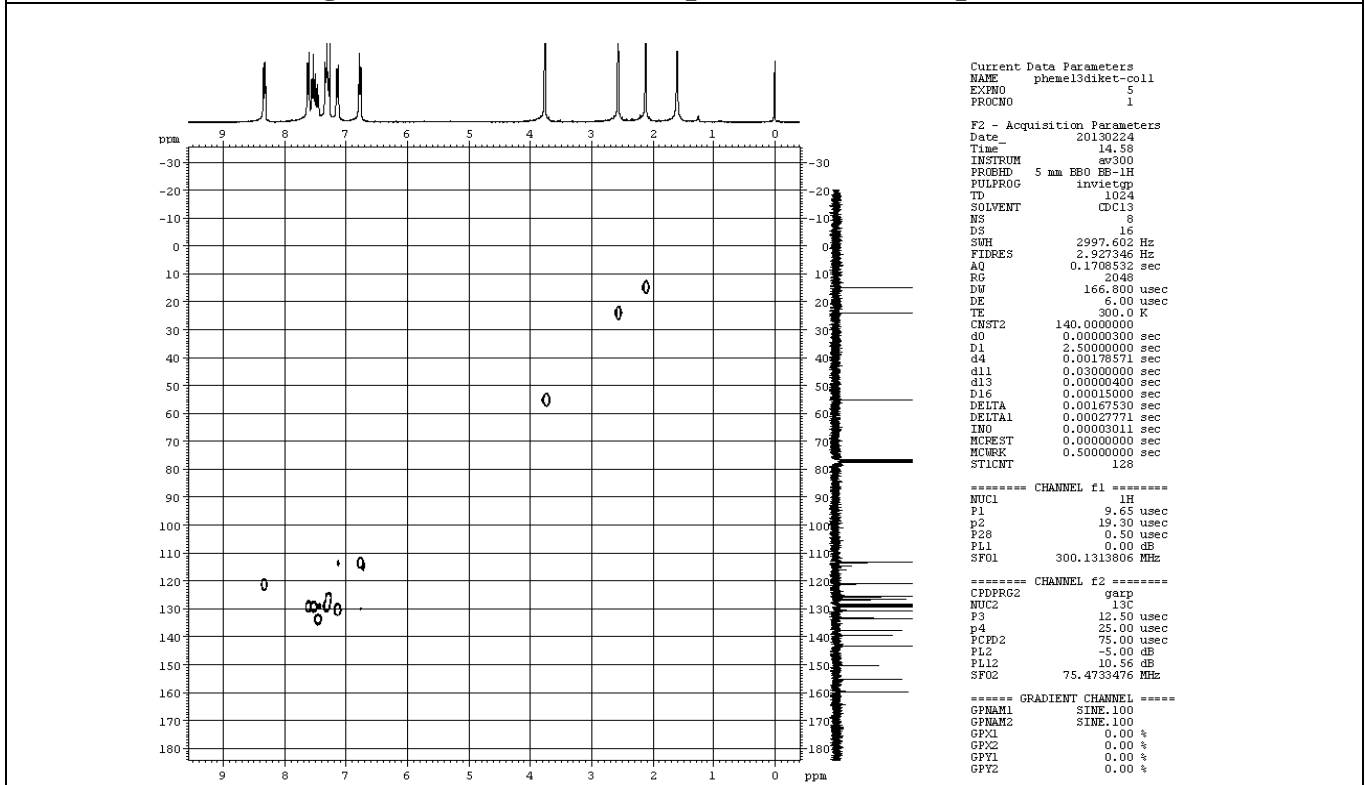


Figure 116. ¹³C,¹H-COSY spectrum of 4x

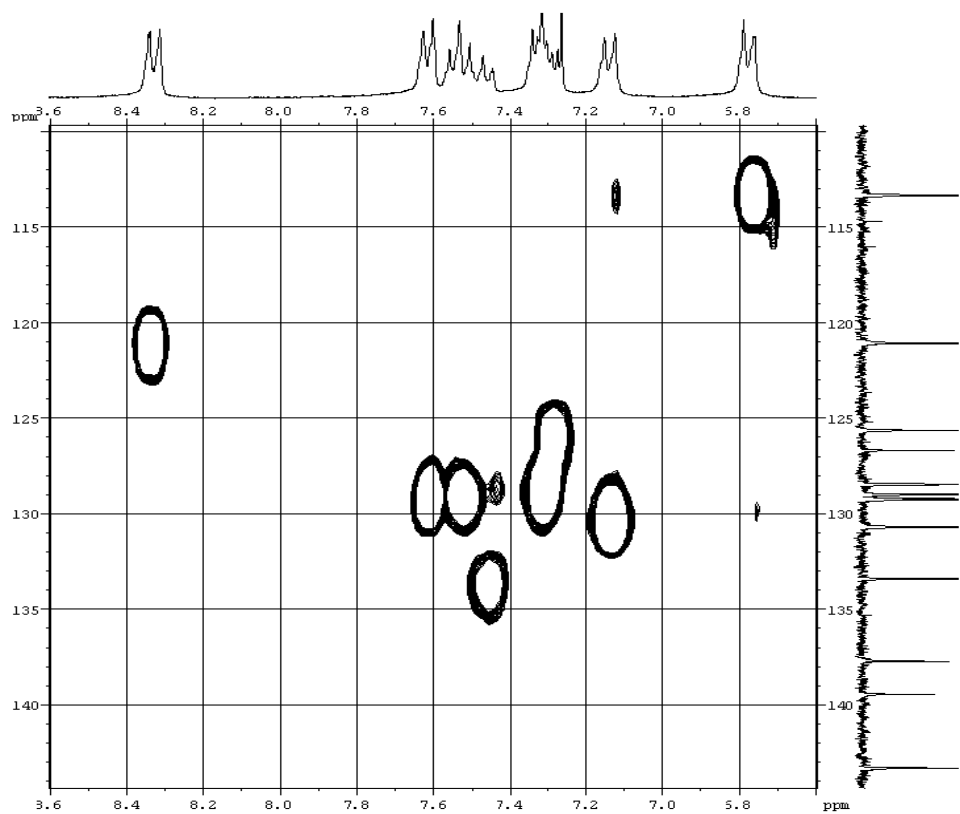


Figure 117. C,H-COSY spectrum of 4x-expansion

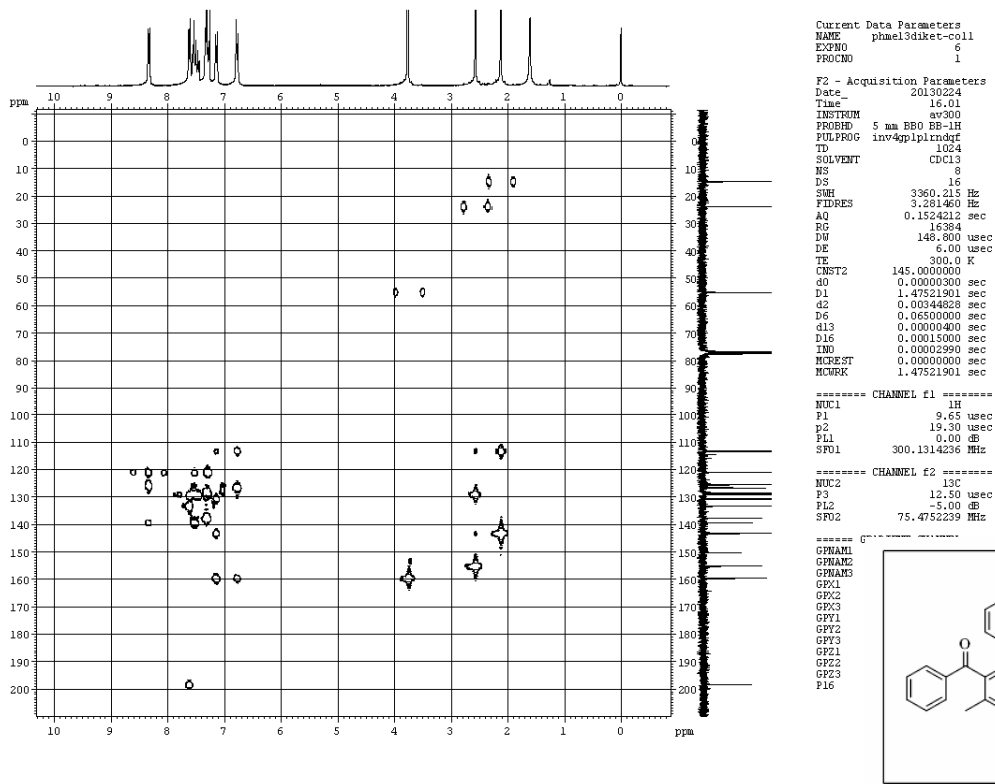


Figure 119. HMBC spectrum of 4x

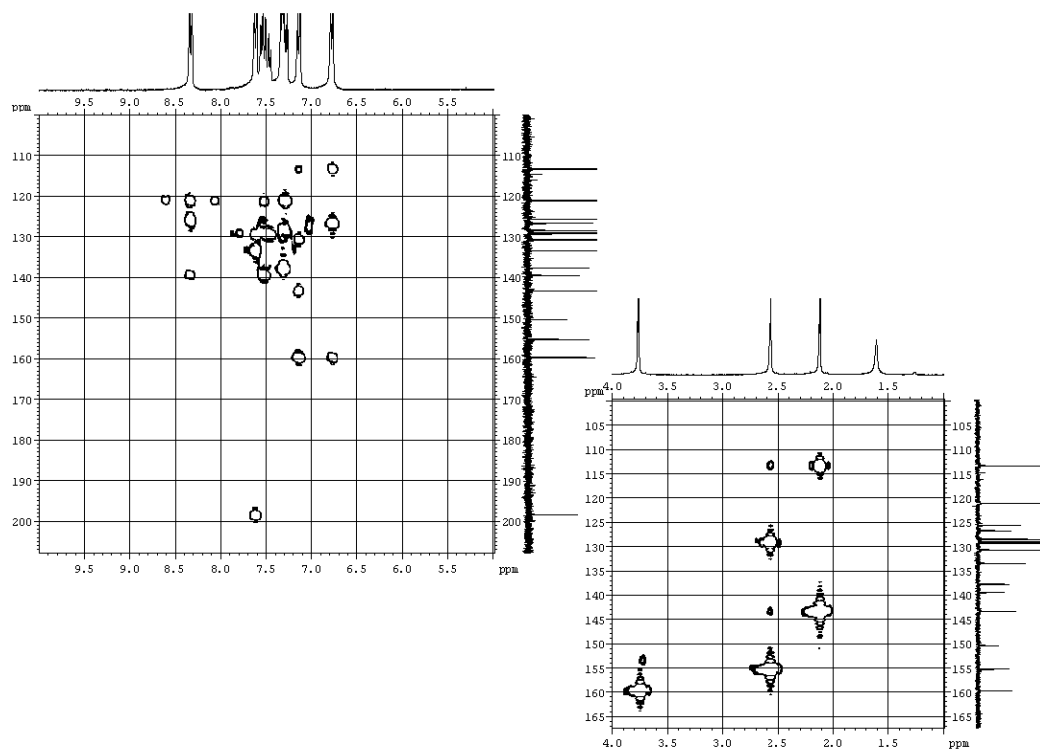


Figure 120. HMBC spectrum of 4x-expansion1

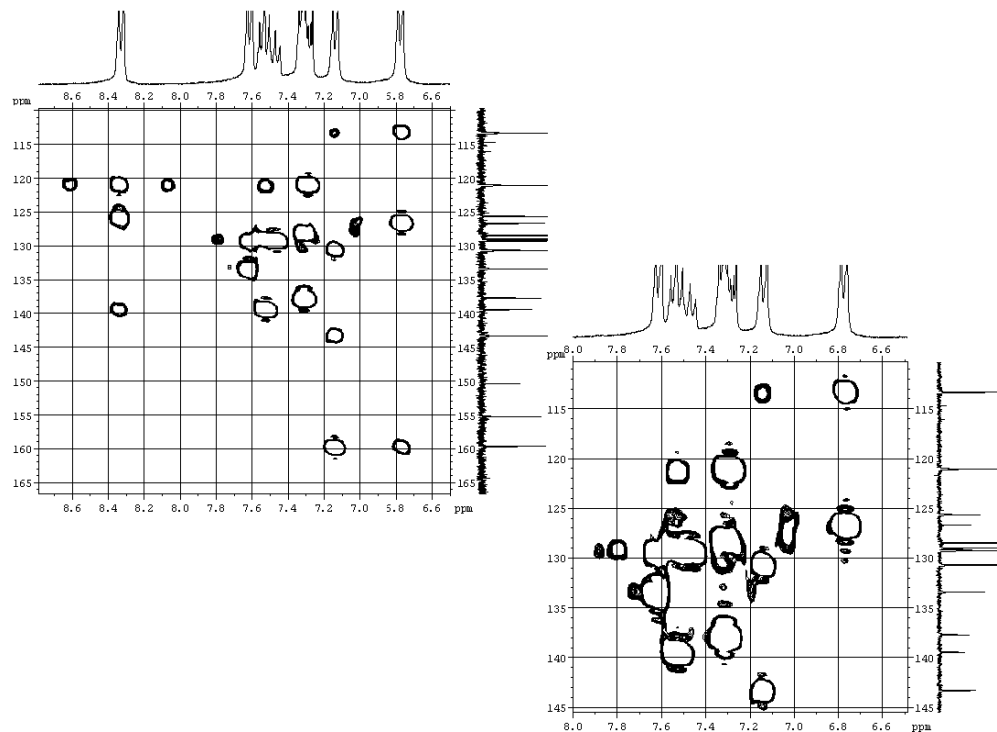


Figure 121. HMBC spectrum of 4x-expansion2

¹⁹F-NMR Spectrums

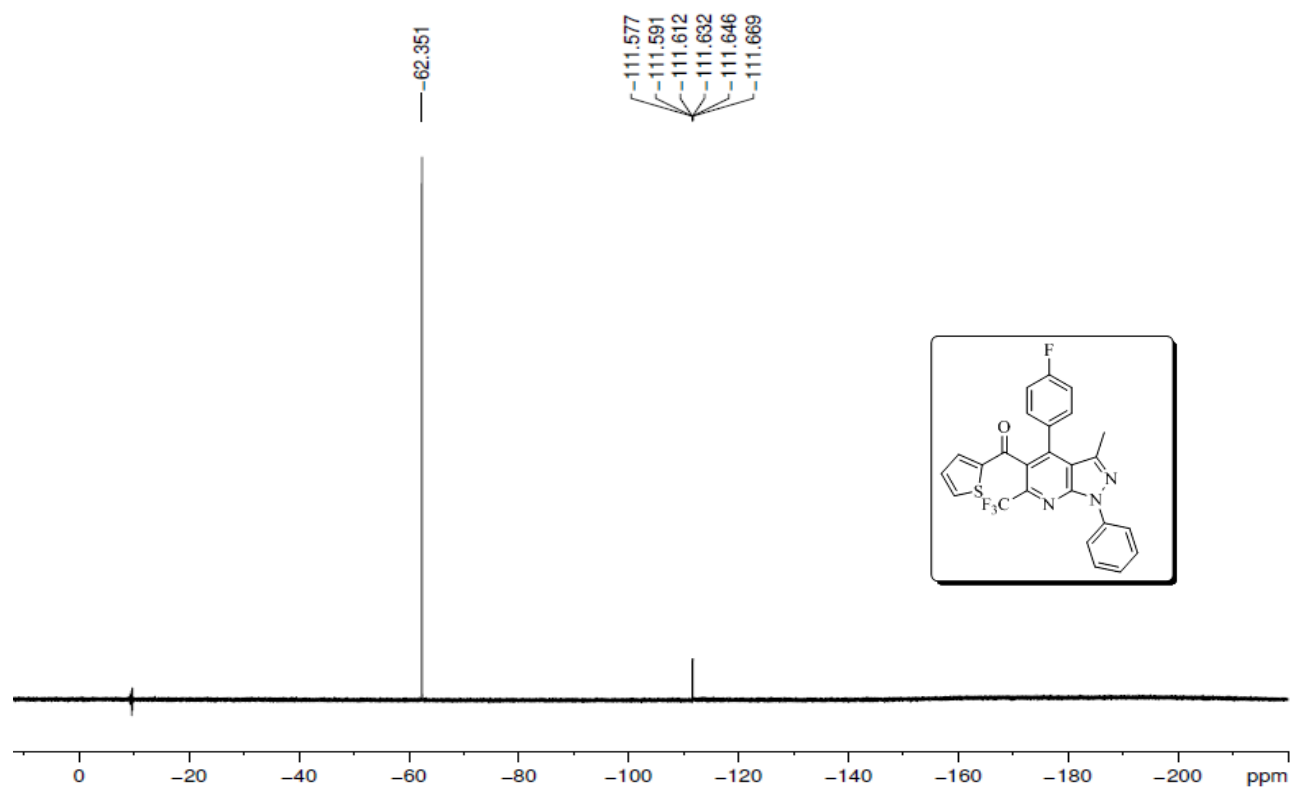


Figure 118. ¹⁹F-NMR Spectrum of 4c

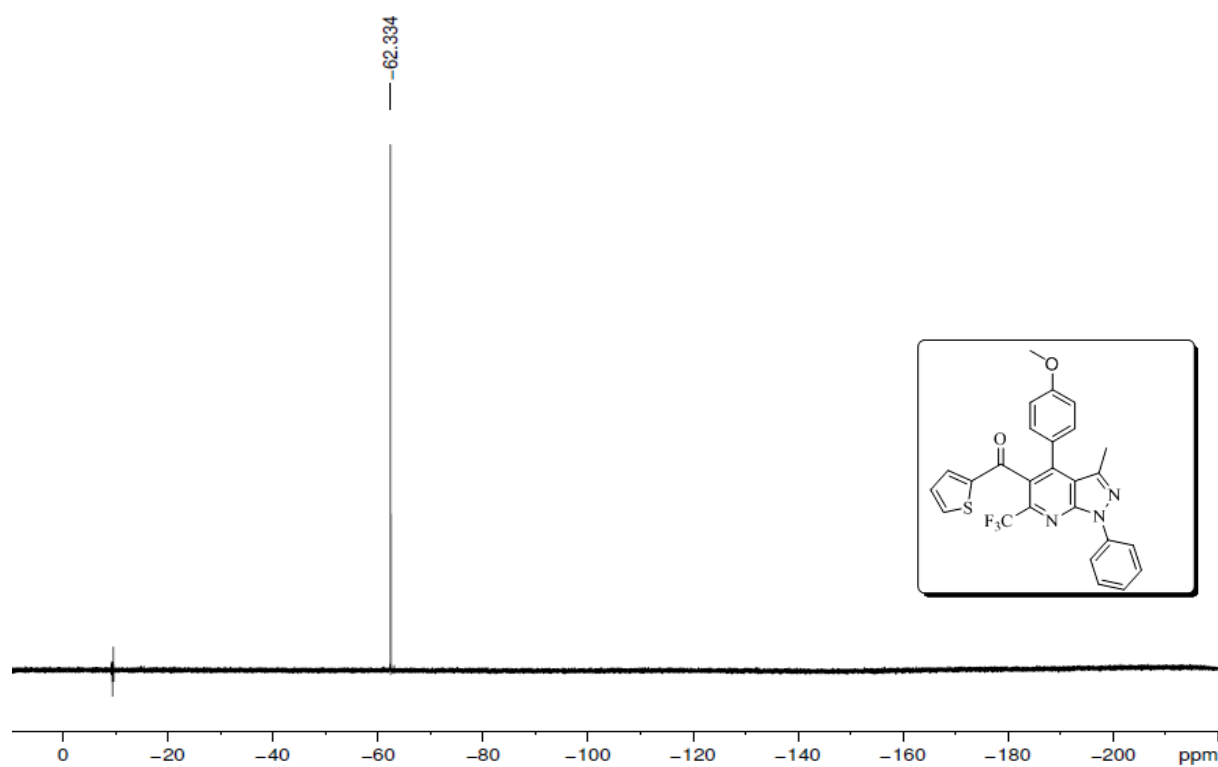


Figure 119. ¹⁹F-NMR Spectrum of 4e

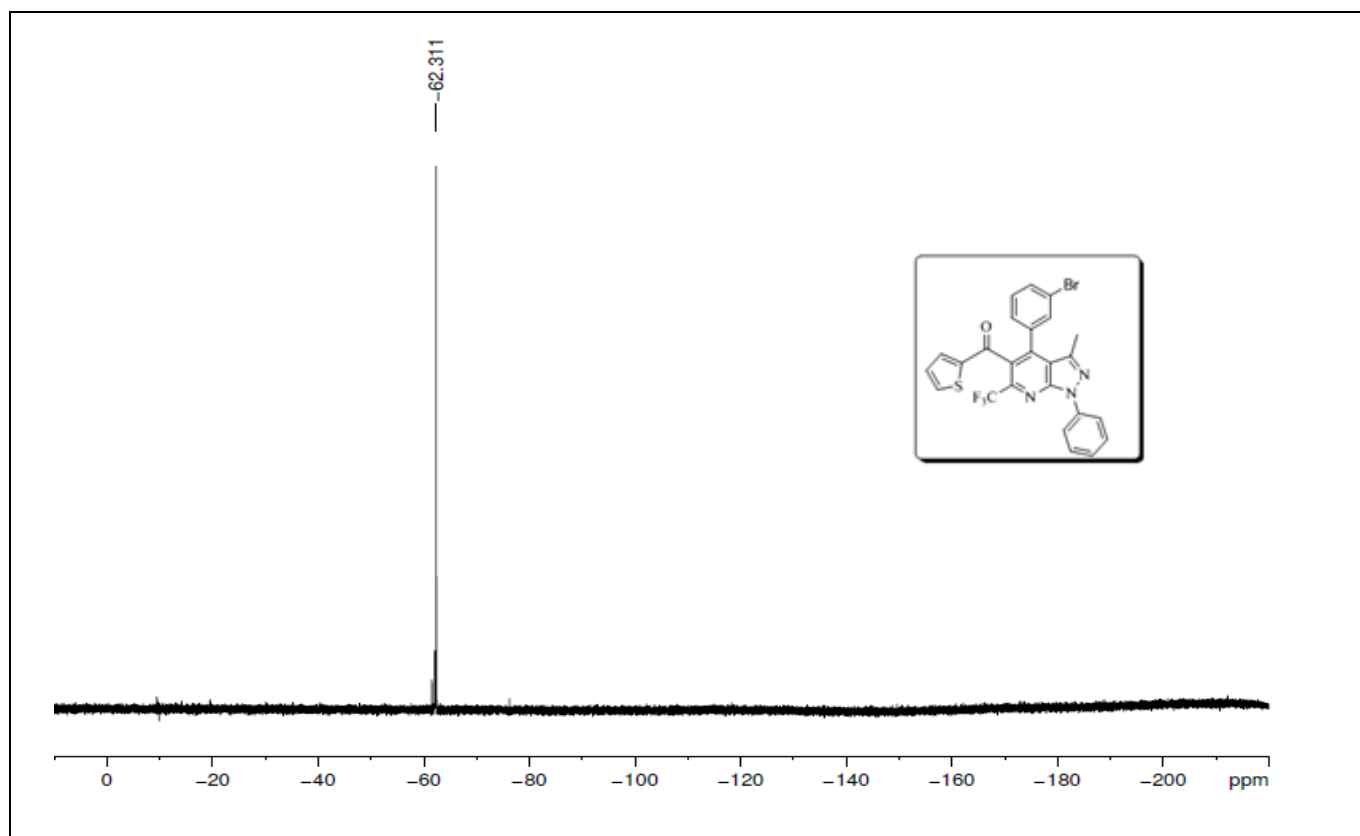


Figure 120. ^{19}F -NMR Spectrum of 4h

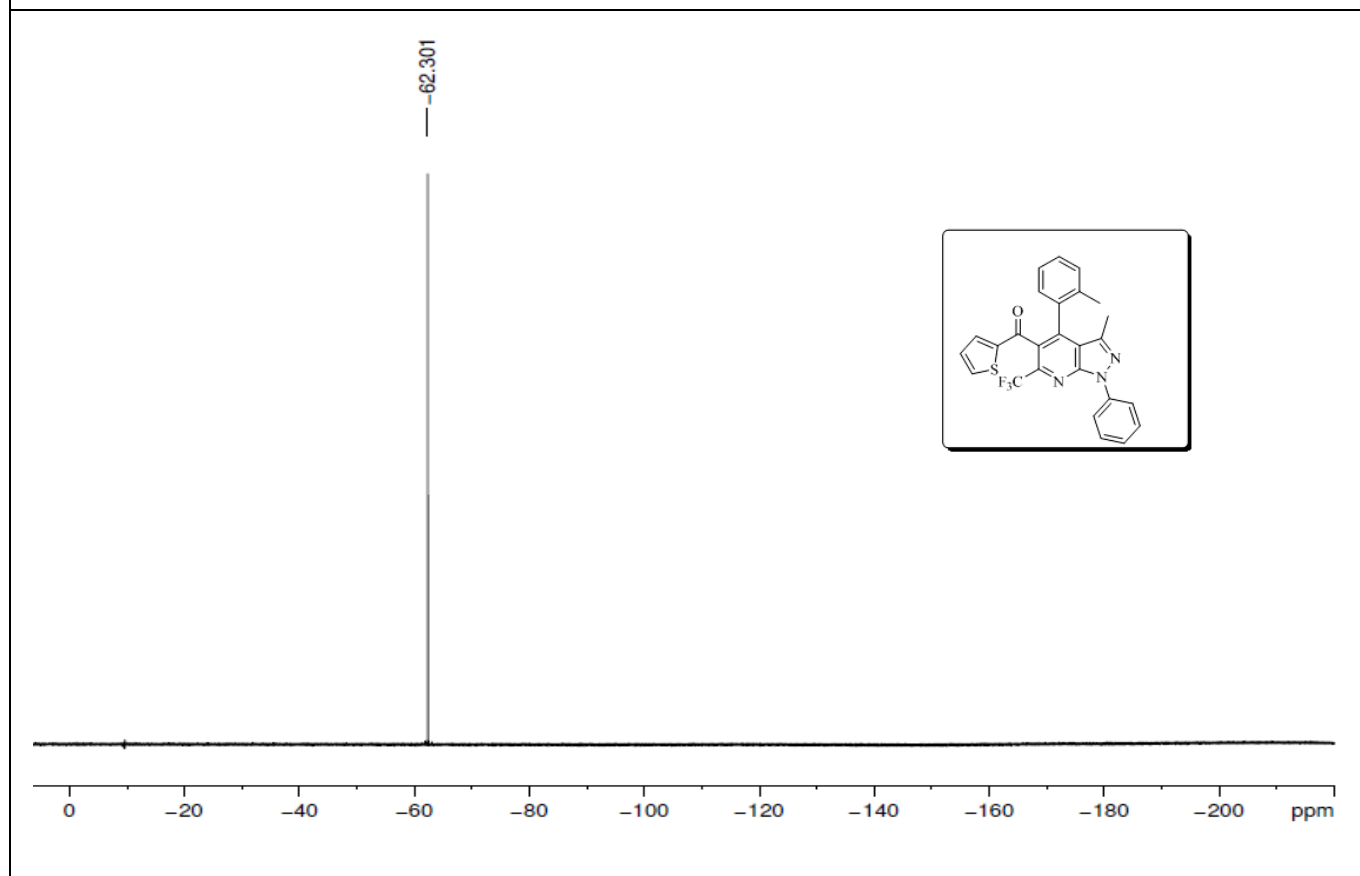


Figure 121. ^{19}F -NMR Spectrum of 4j

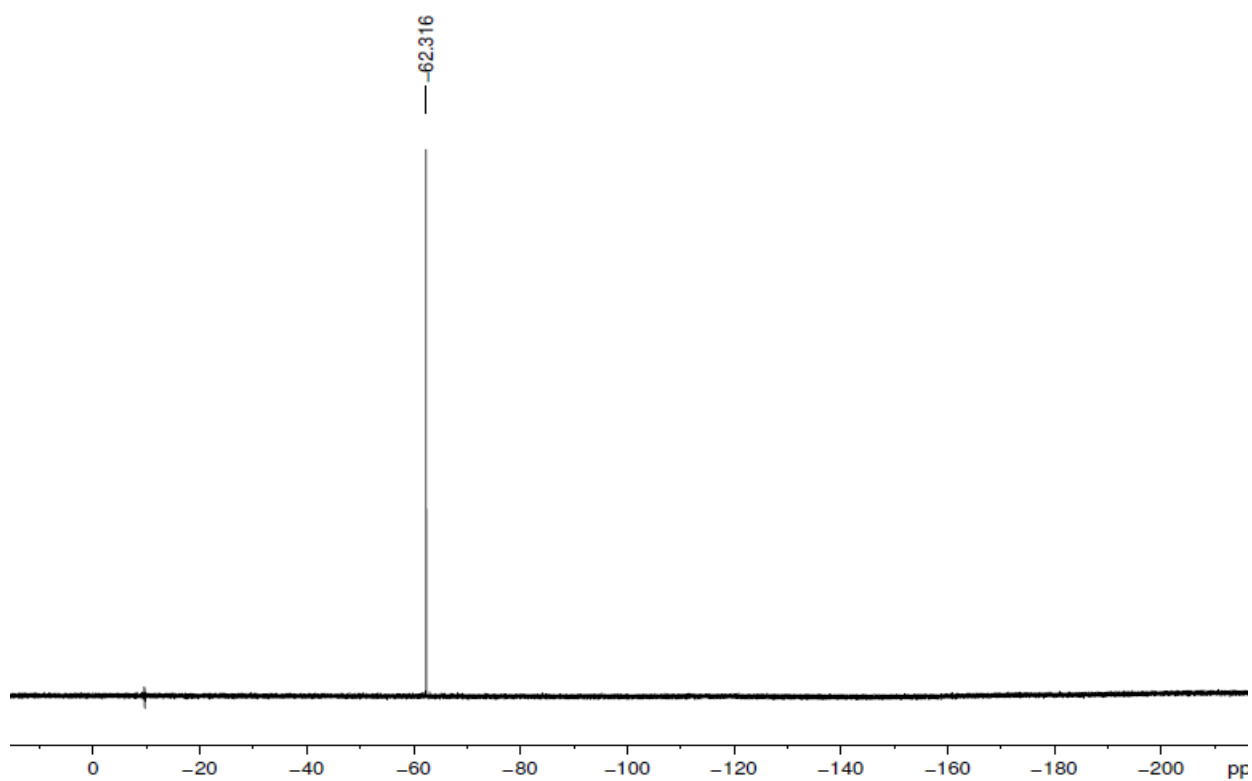


Figure 122. ^{19}F -NMR Spectrum of 4l

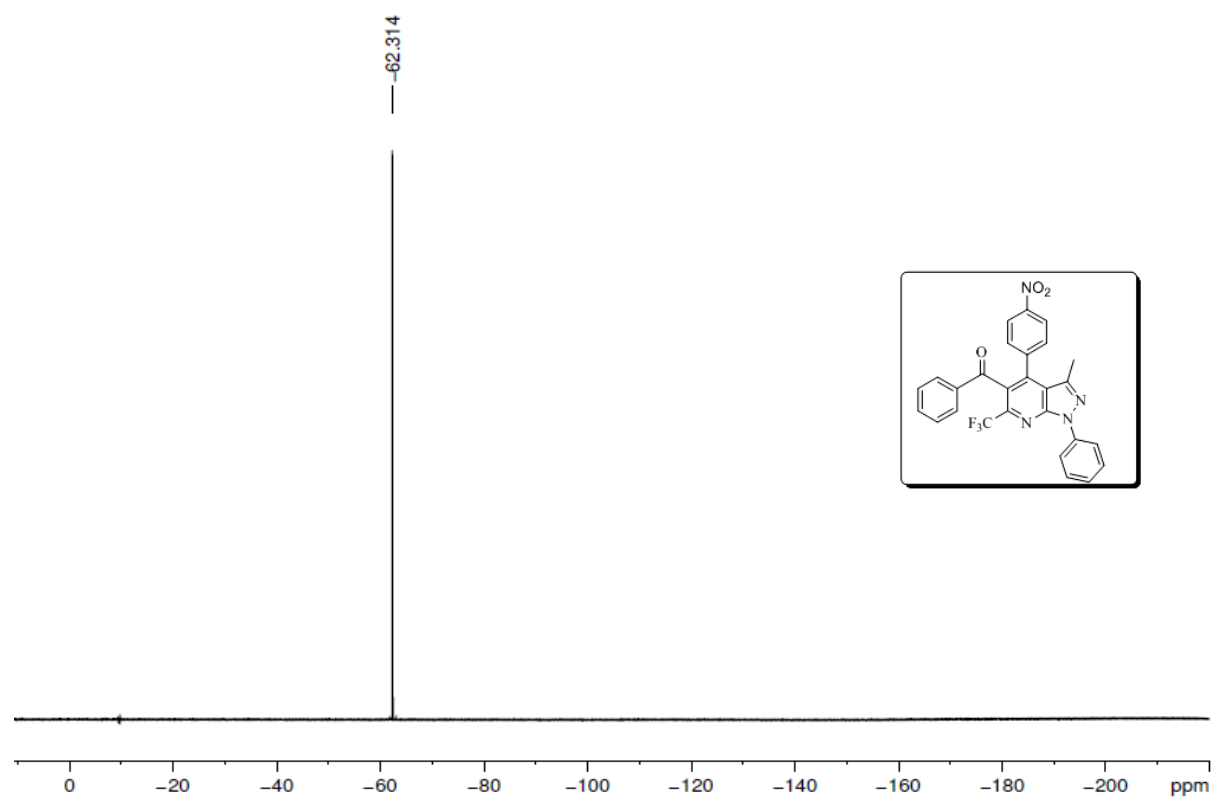


Figure 123. ^{19}F -NMR Spectrum of 4m

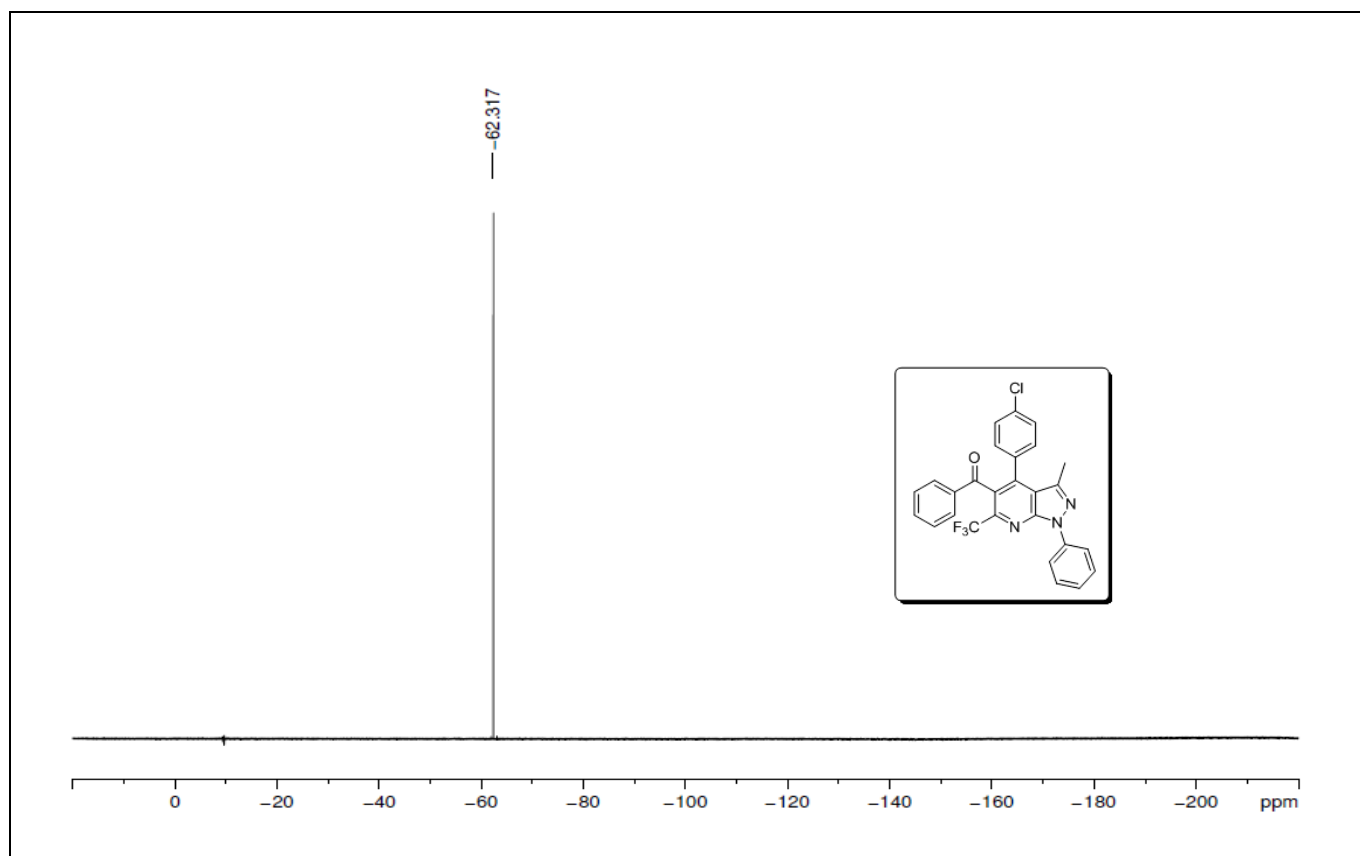


Figure 124. ^{19}F -NMR Spectrum of 4n

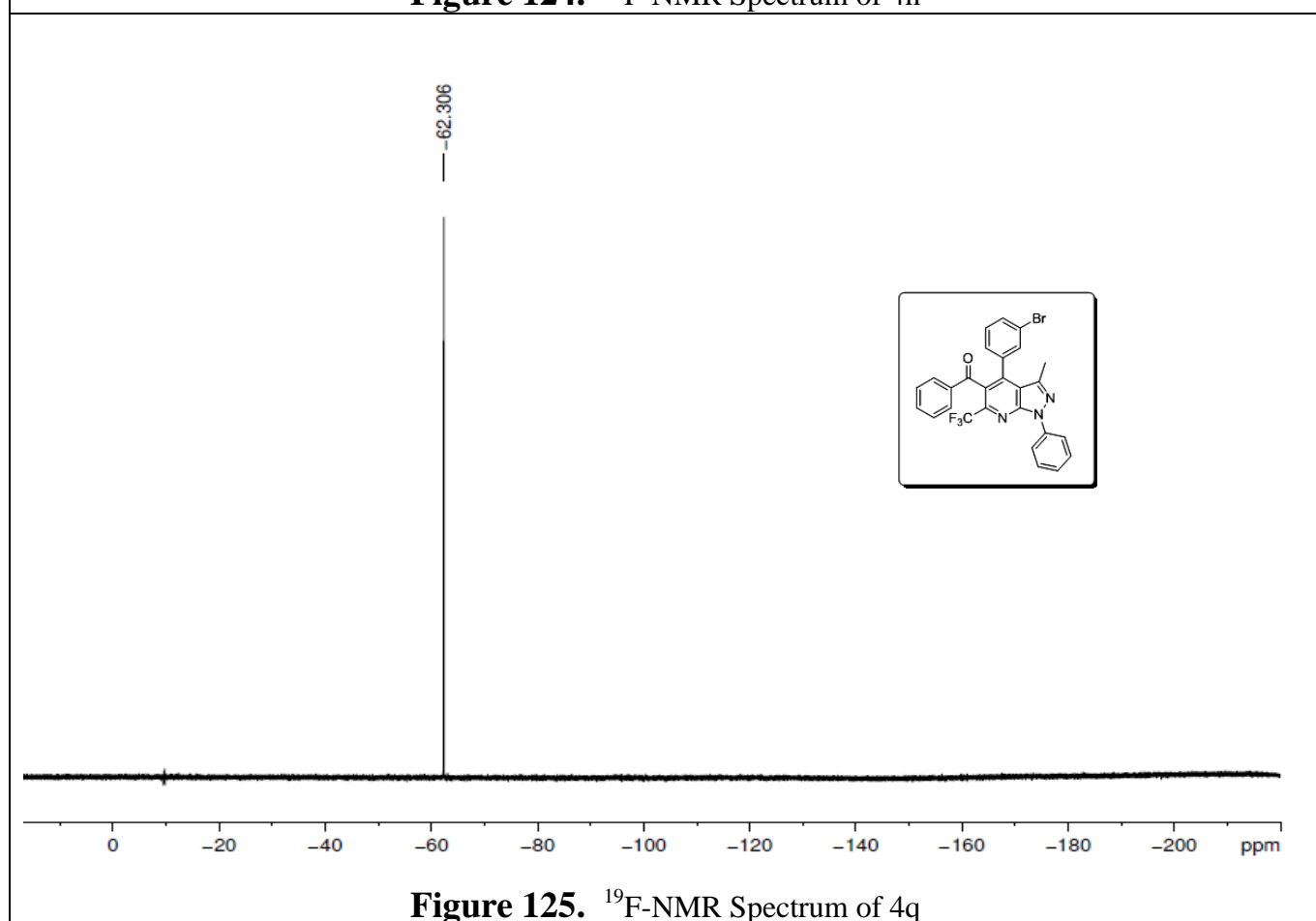


Figure 125. ^{19}F -NMR Spectrum of 4q

Mechanism study NMR spectra -intermediate identification from the reaction

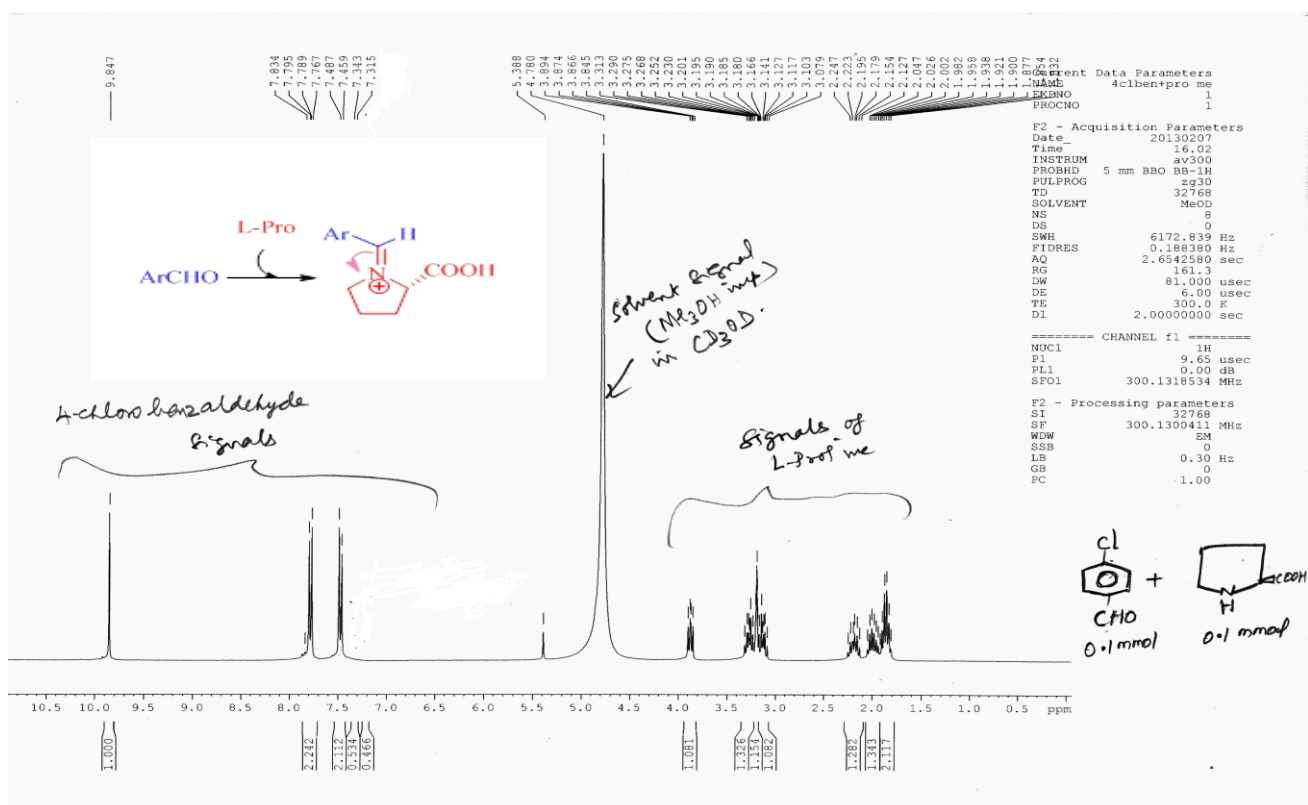


Figure 126. reaction mixture-1

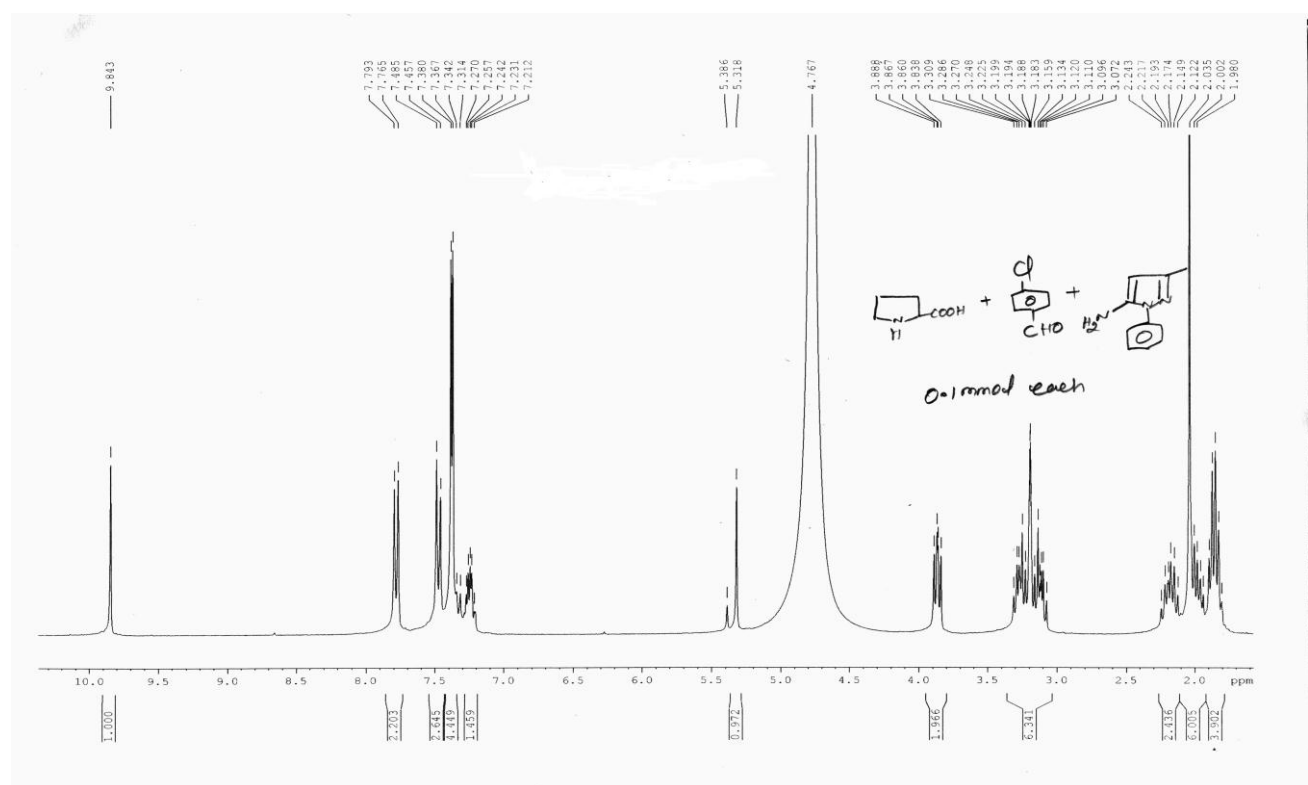


Figure 127. reaction mixture-2

