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Synthetic methods for biologically relevant organofluorine compounds

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Department: Chemistry

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1.4.3 NMR spectra of the products

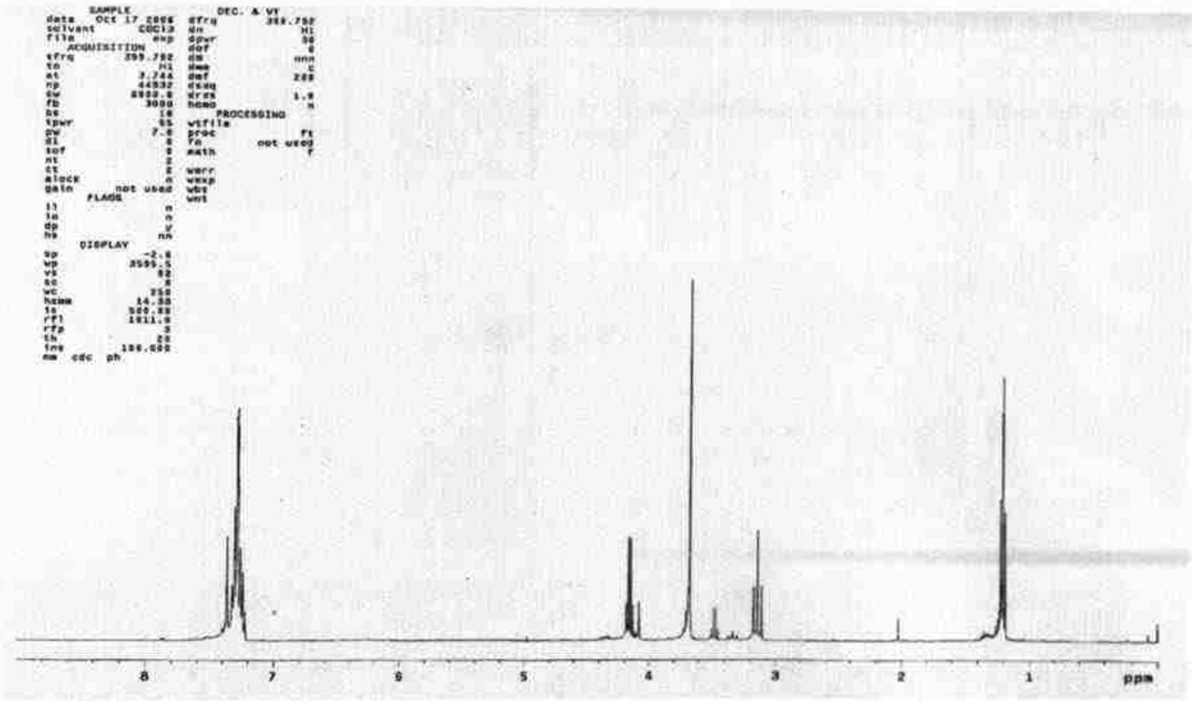

Figure 1.33: ^{1}H NMR spectra of compound **1.80**

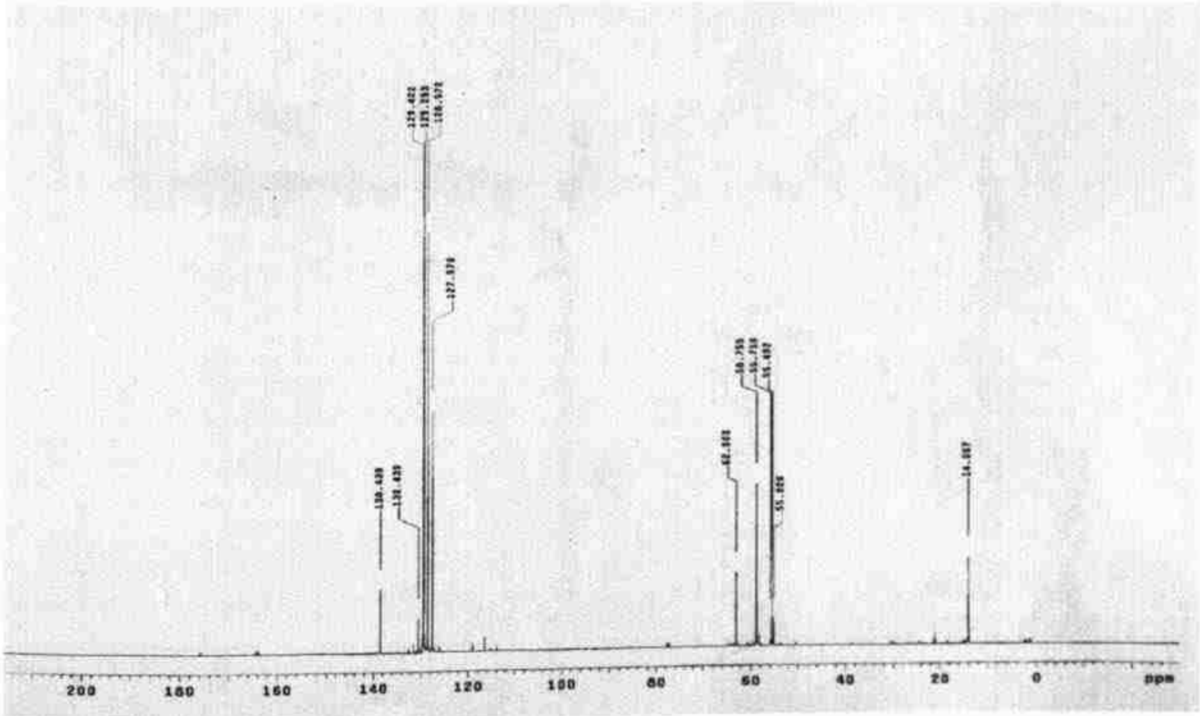

Figure 1.34: ^{13}C NMR spectra of compound **1.80**

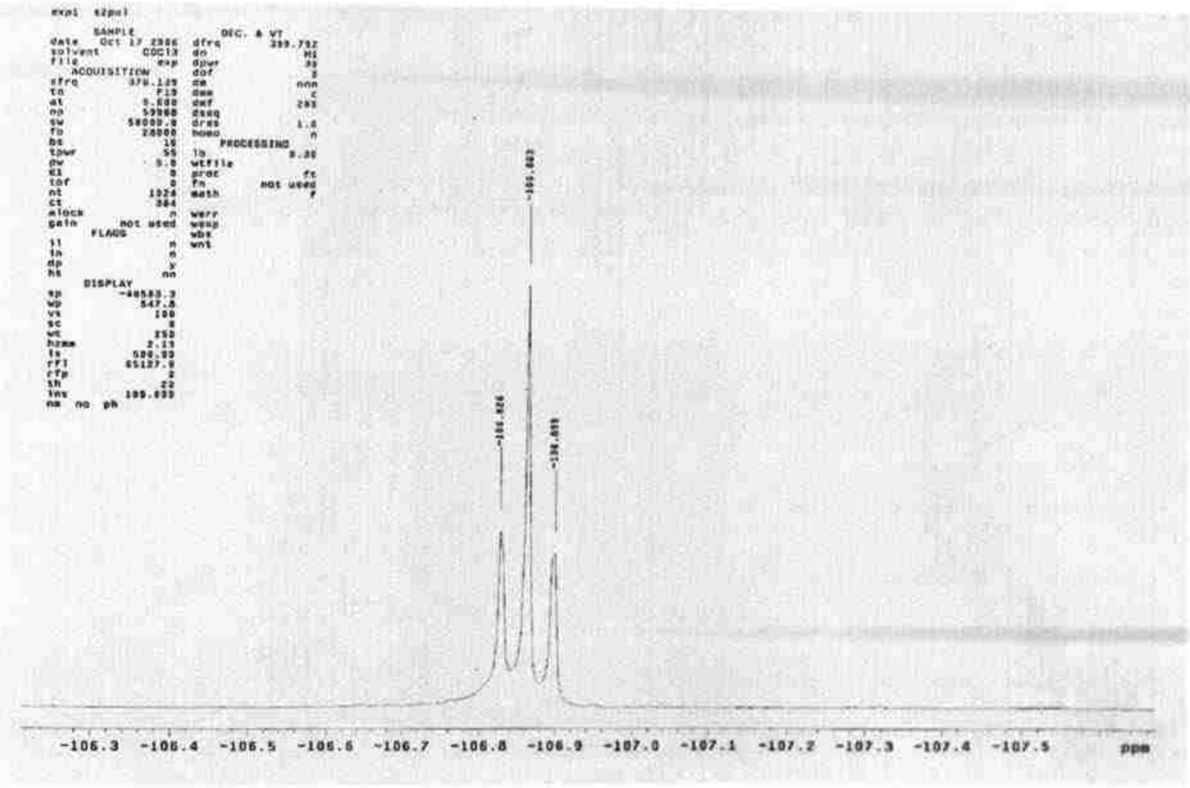

Figure 1.35: ^{19}F NMR spectra of compound **1.80**

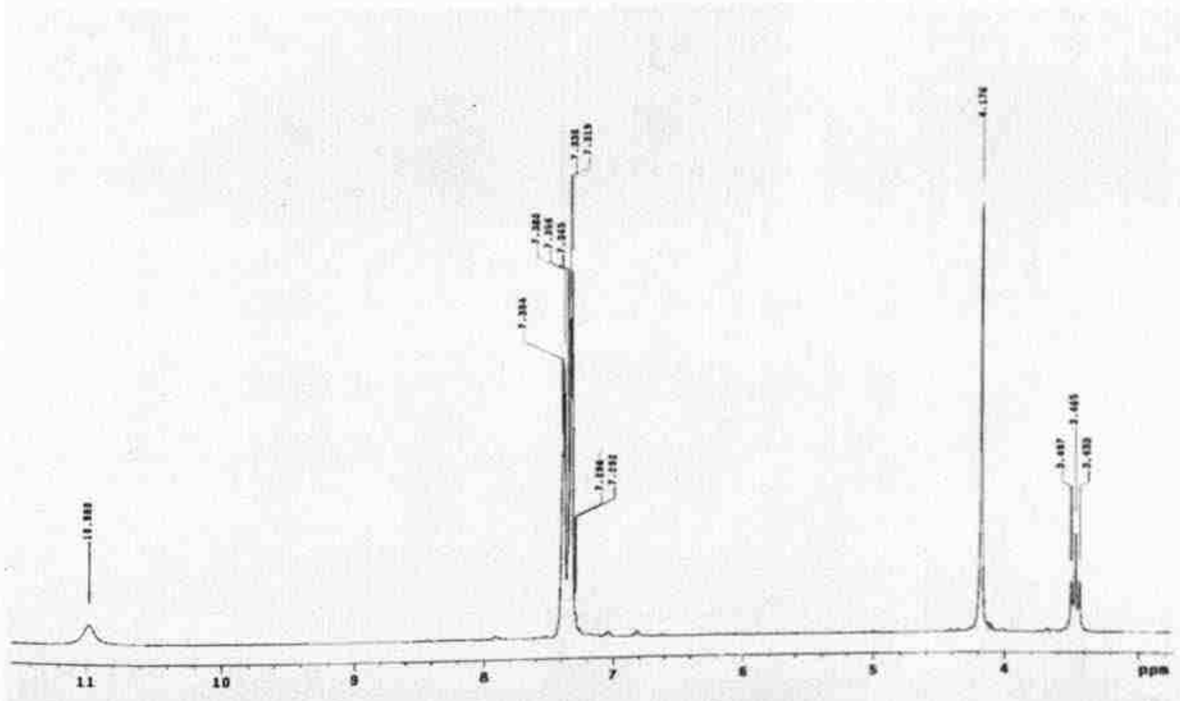

Figure 1.36: ^{1}H NMR spectra of compound **1.81**

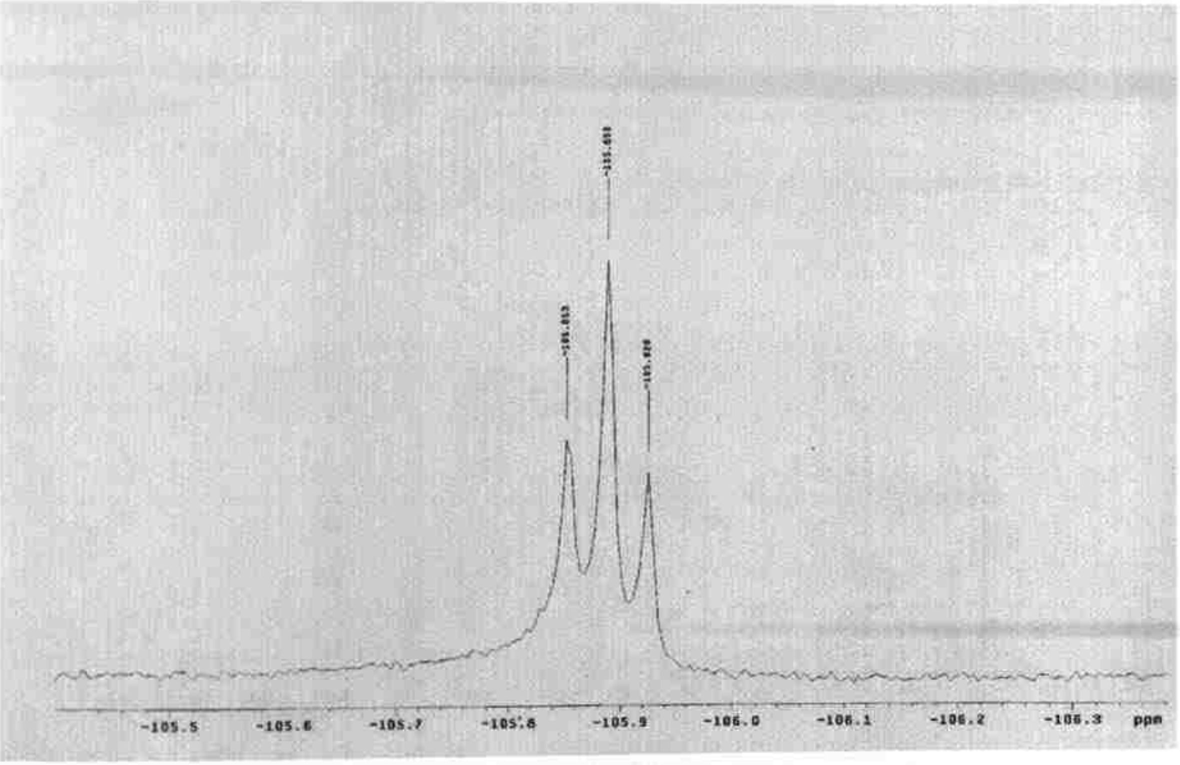

Figure 1.37: ^{19}F NMR spectra of compound **1.81**

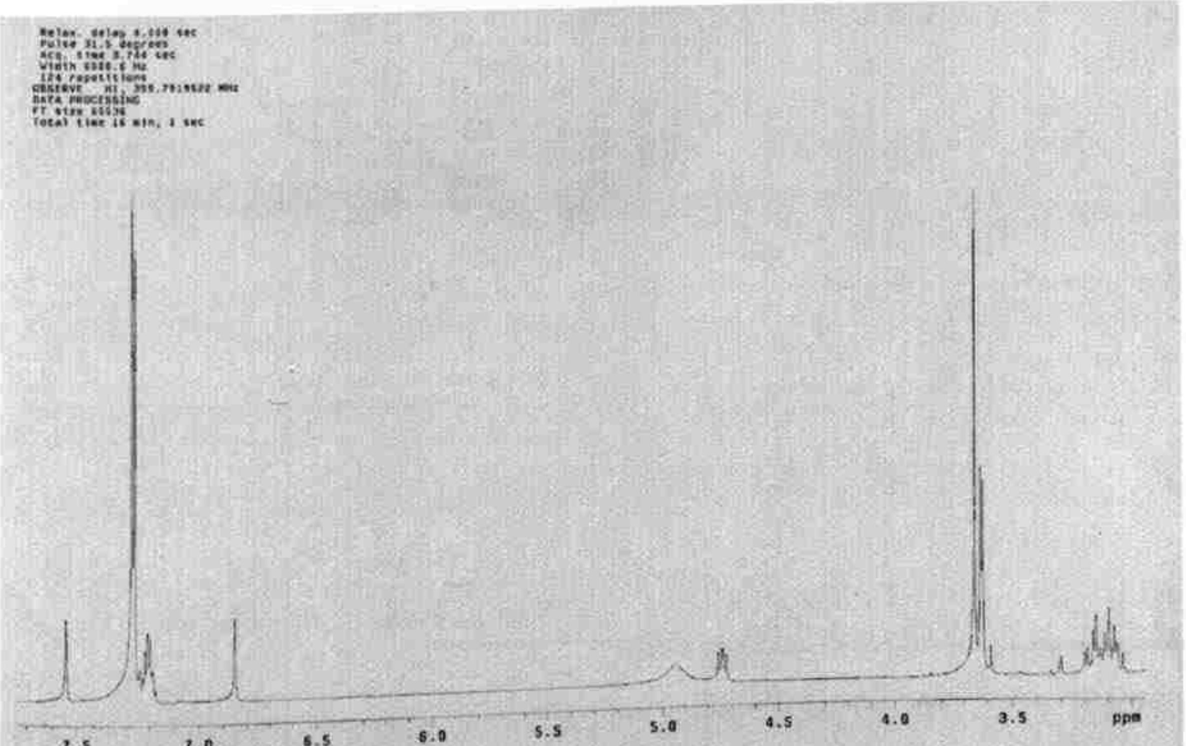

Figure 1.38: ^{1}H NMR spectra of compound **1.83**

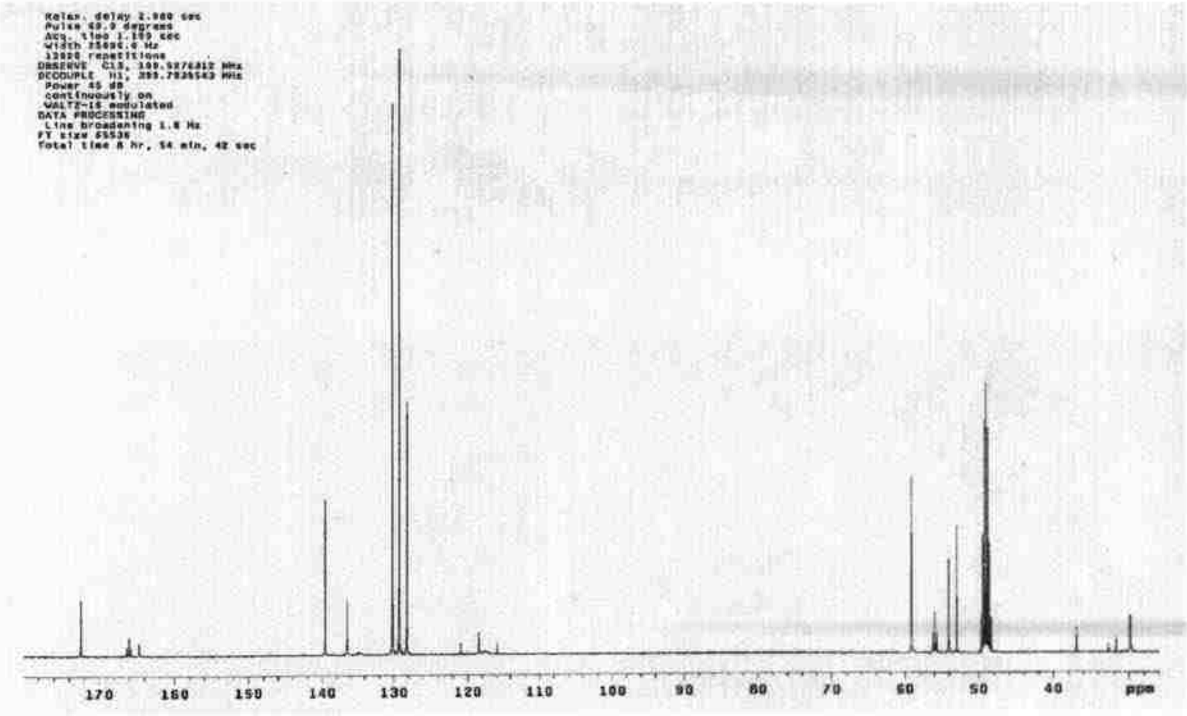

Figure 1.39: ^{13}C NMR spectra of compound **1.83**

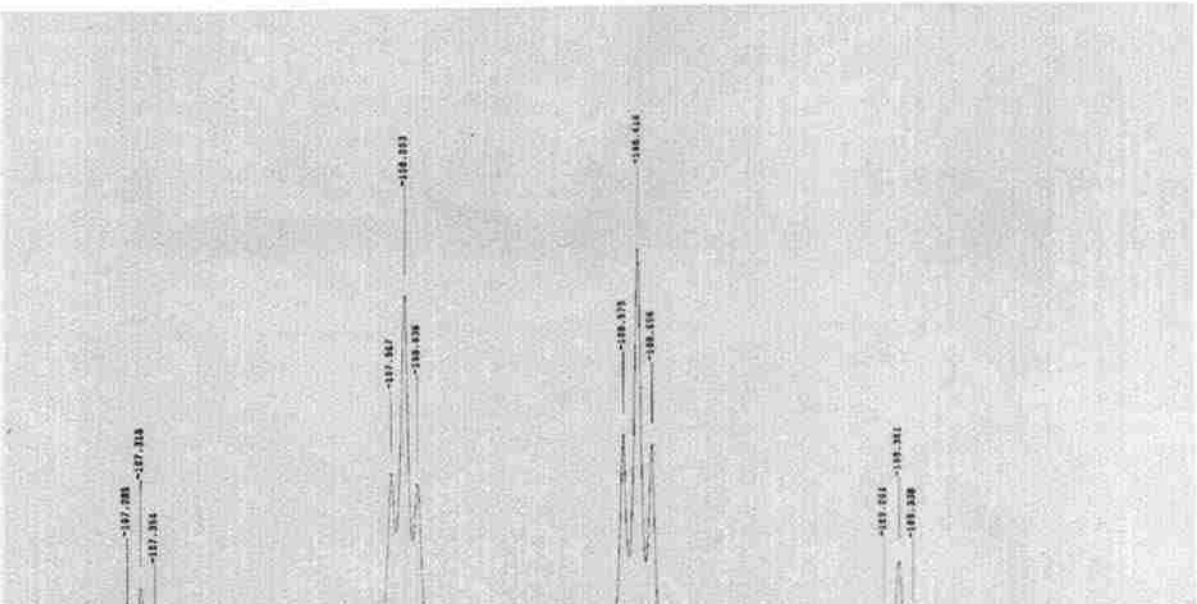

Figure 1.40: ^{19}F NMR spectra of compound **1.83**

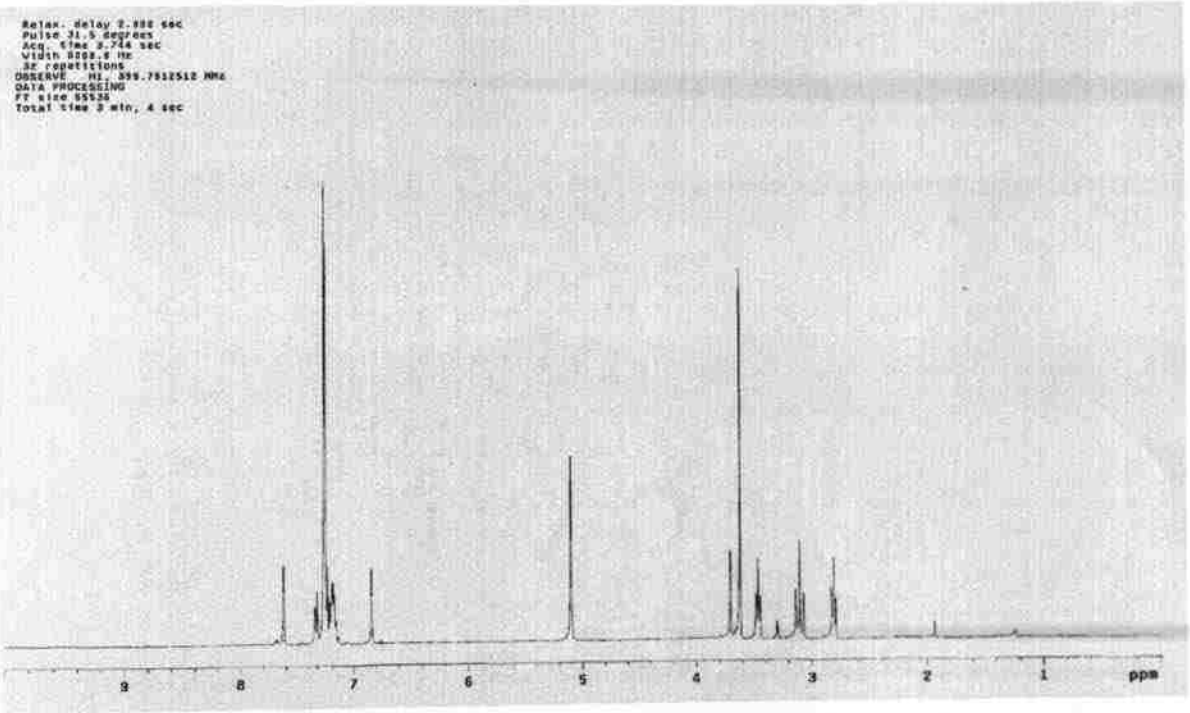

Figure 1.41: ^{1}H NMR spectra of compound **1.85**

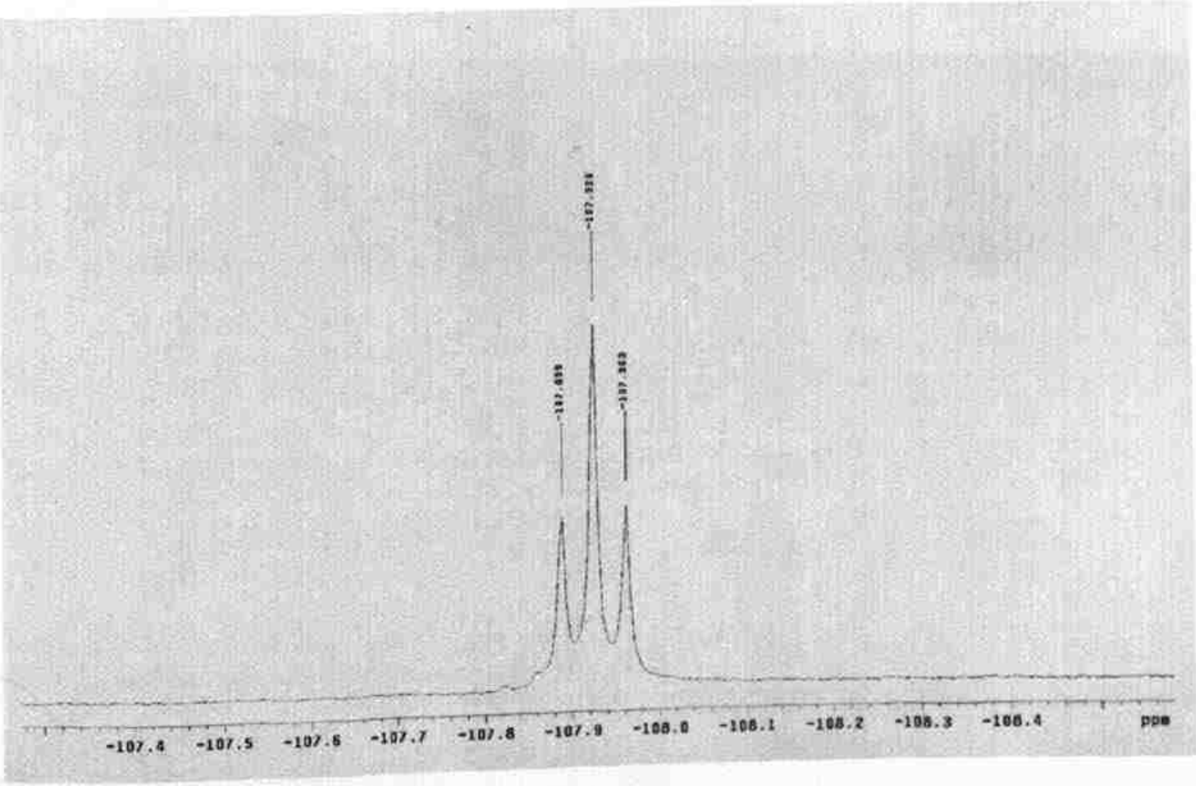

Figure 1.42: ^{19}F NMR spectra of compound **1.85**

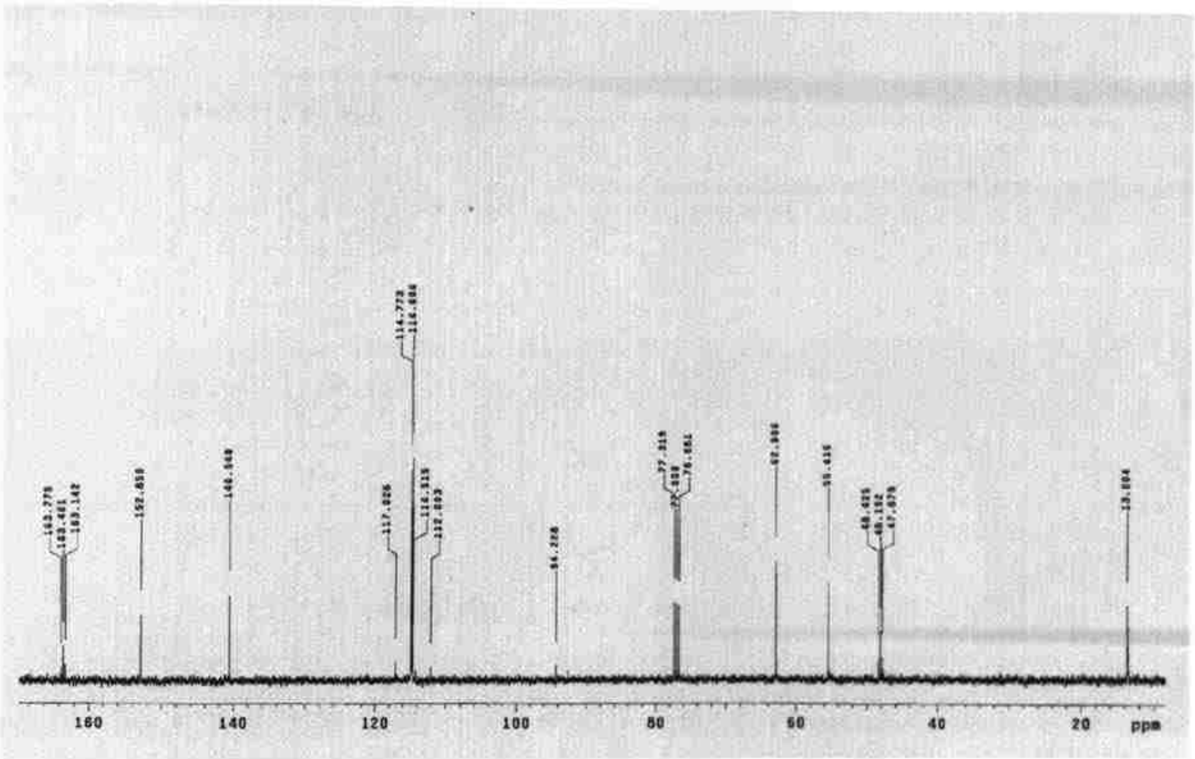

Figure 1.43: ^{13}C NMR spectra of compound **1.87**

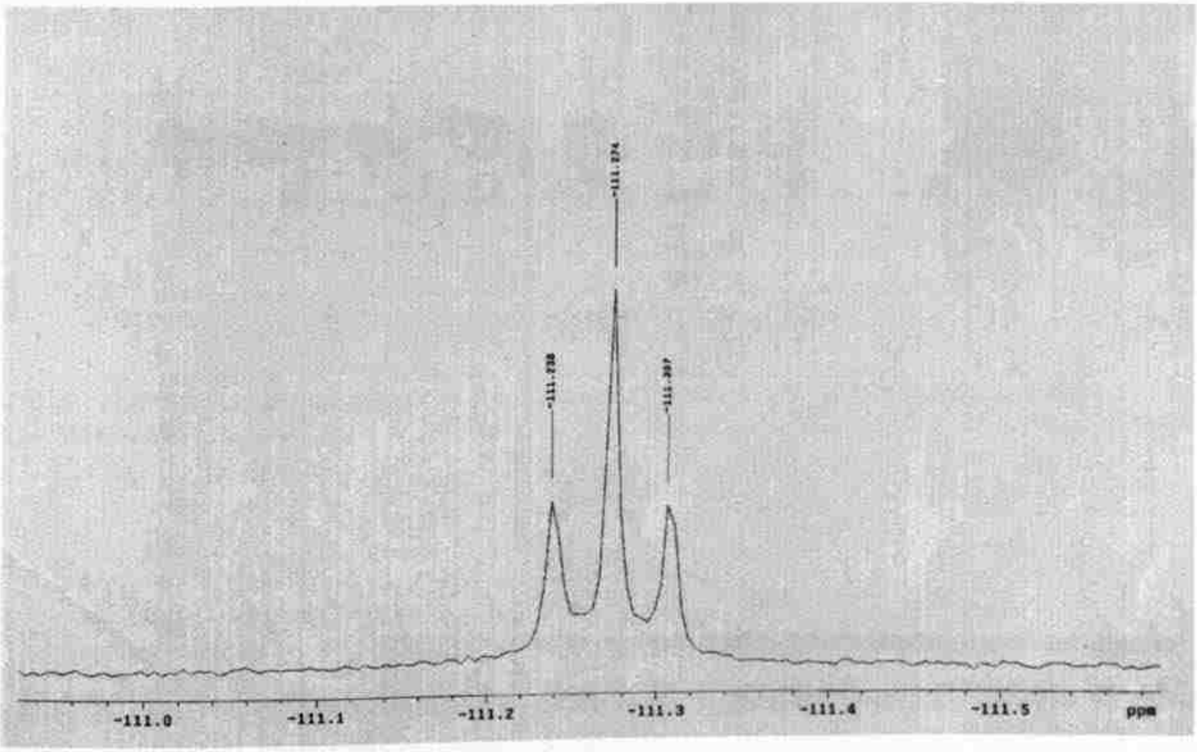

Figure 1.44: ^{19}F NMR spectra of compound **1.87**

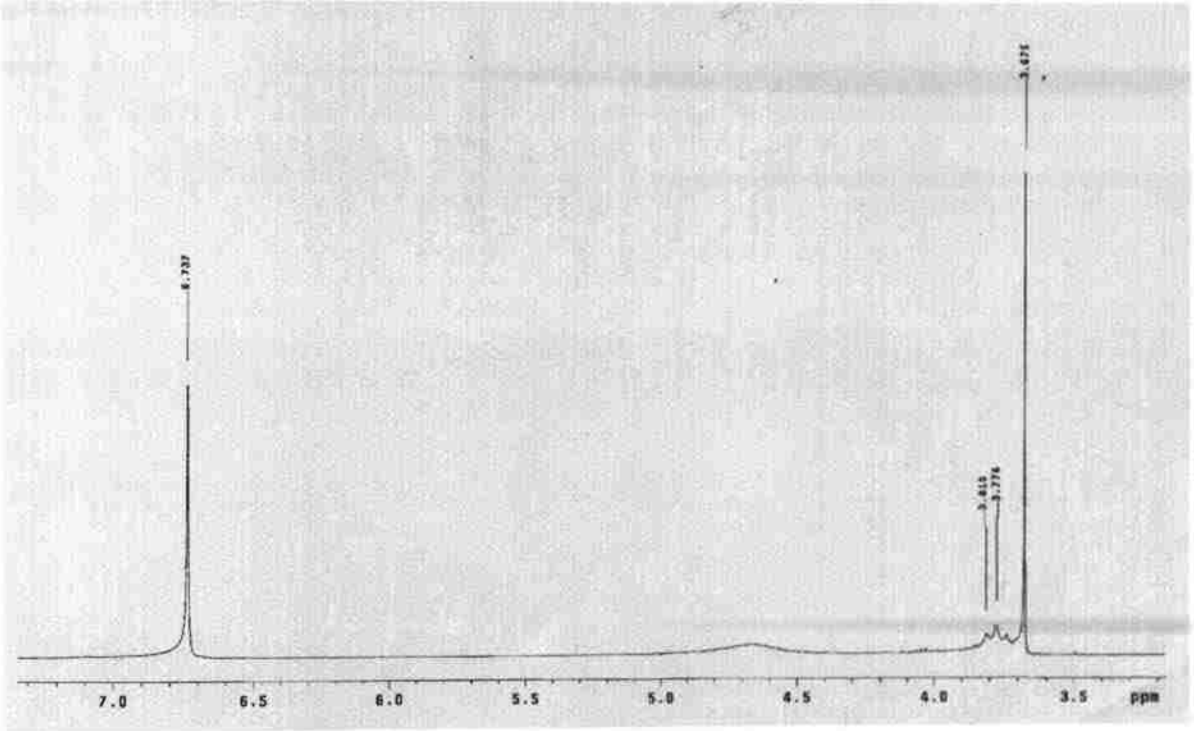

Figure 1.45: ^{1}H NMR spectra of compound **1.88**

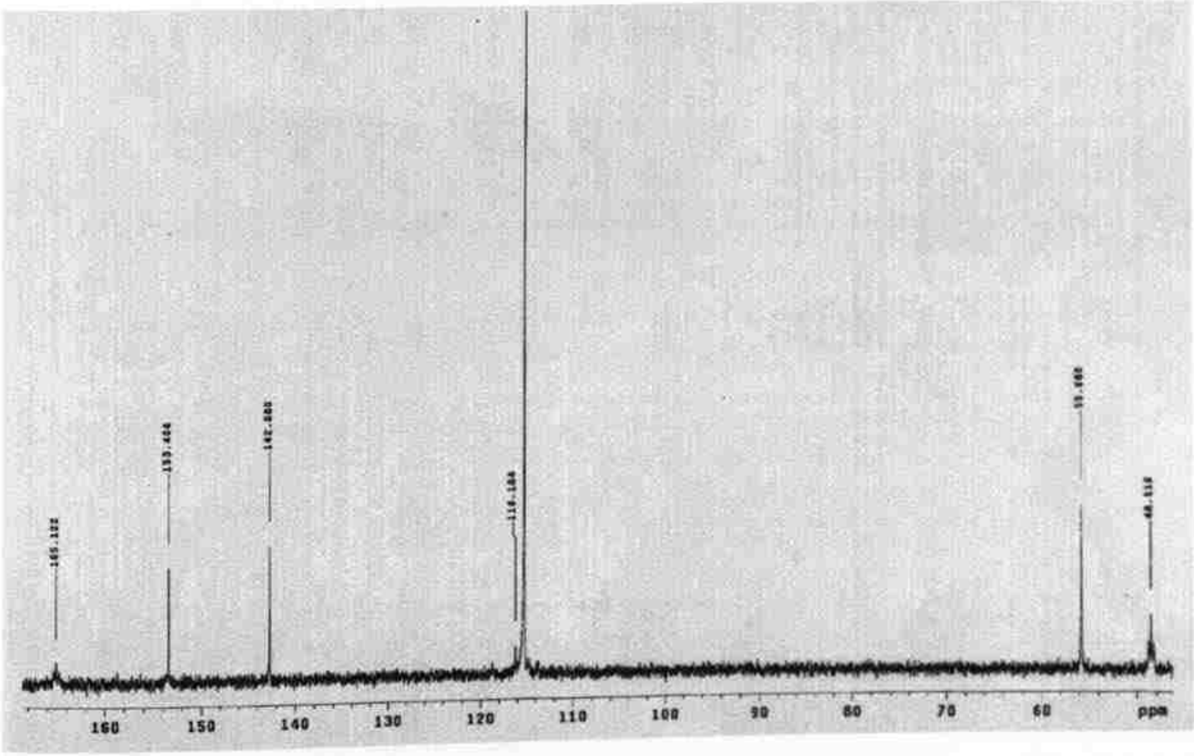

Figure 1.46: ^{13}C NMR spectra of compound **1.88**

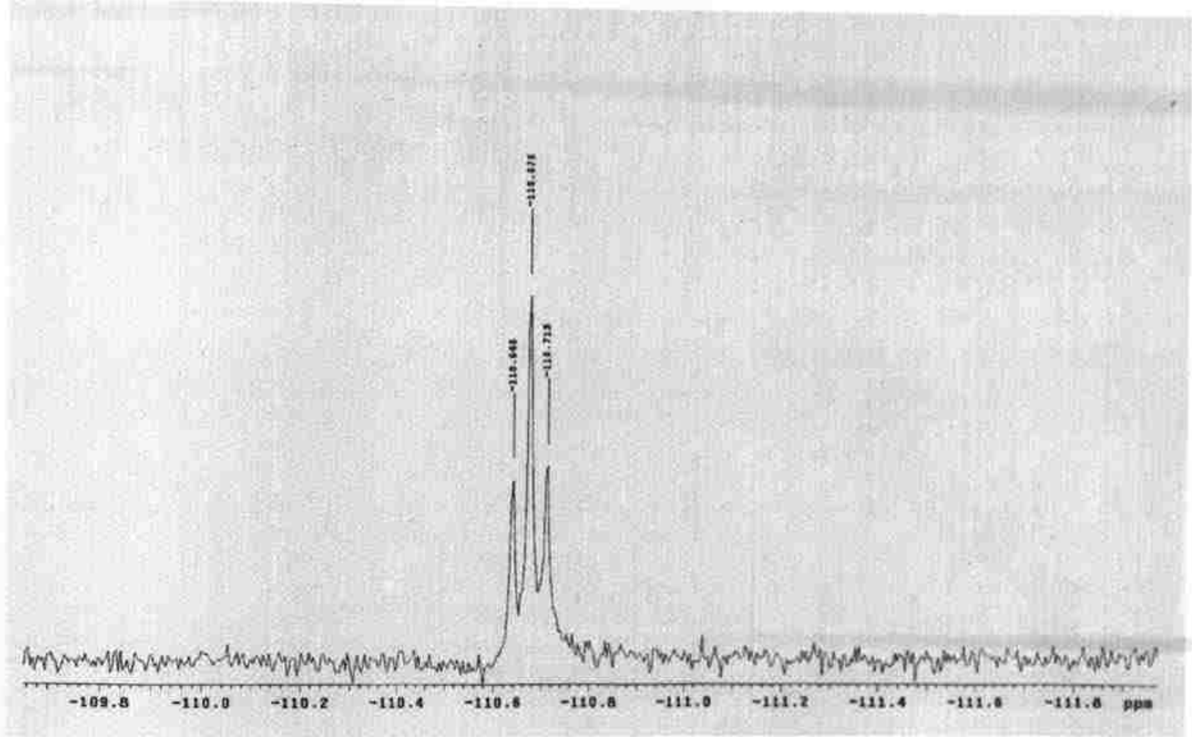

Figure 1.47: ^{19}F NMR spectra of compound **1.88**

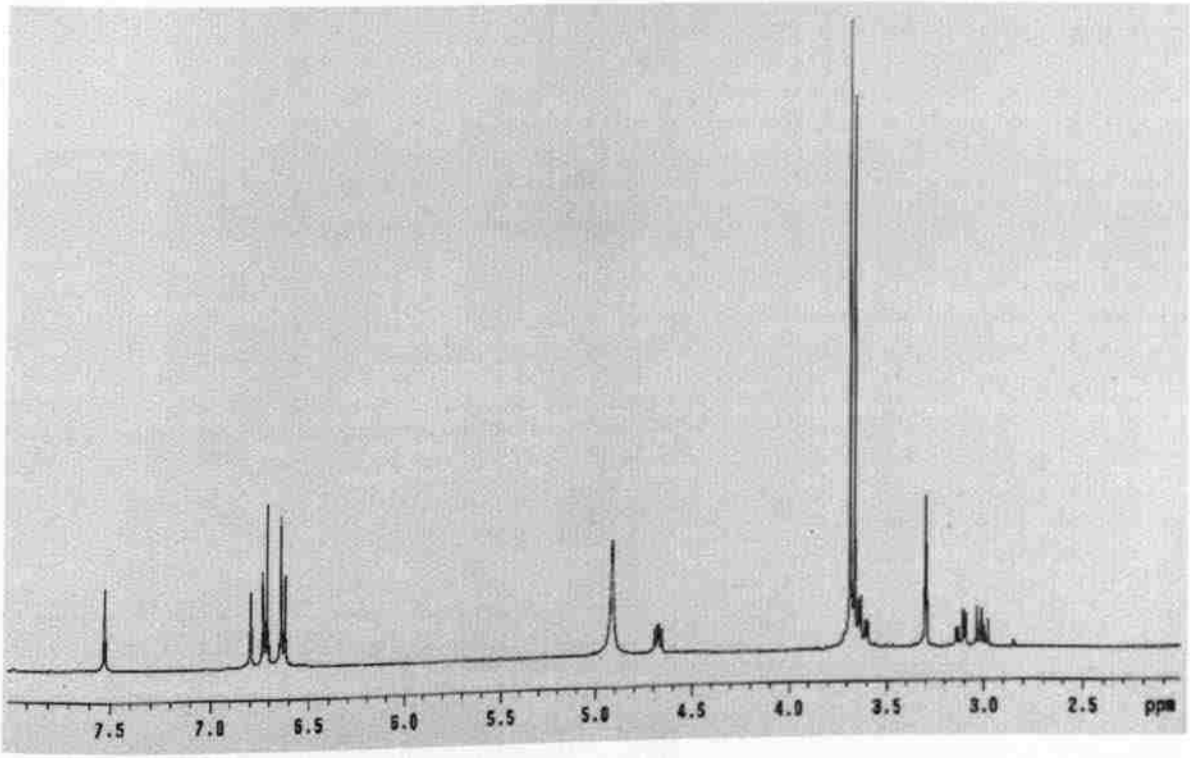

Figure 1.48: ^{1}H NMR spectra of compound **1.89**

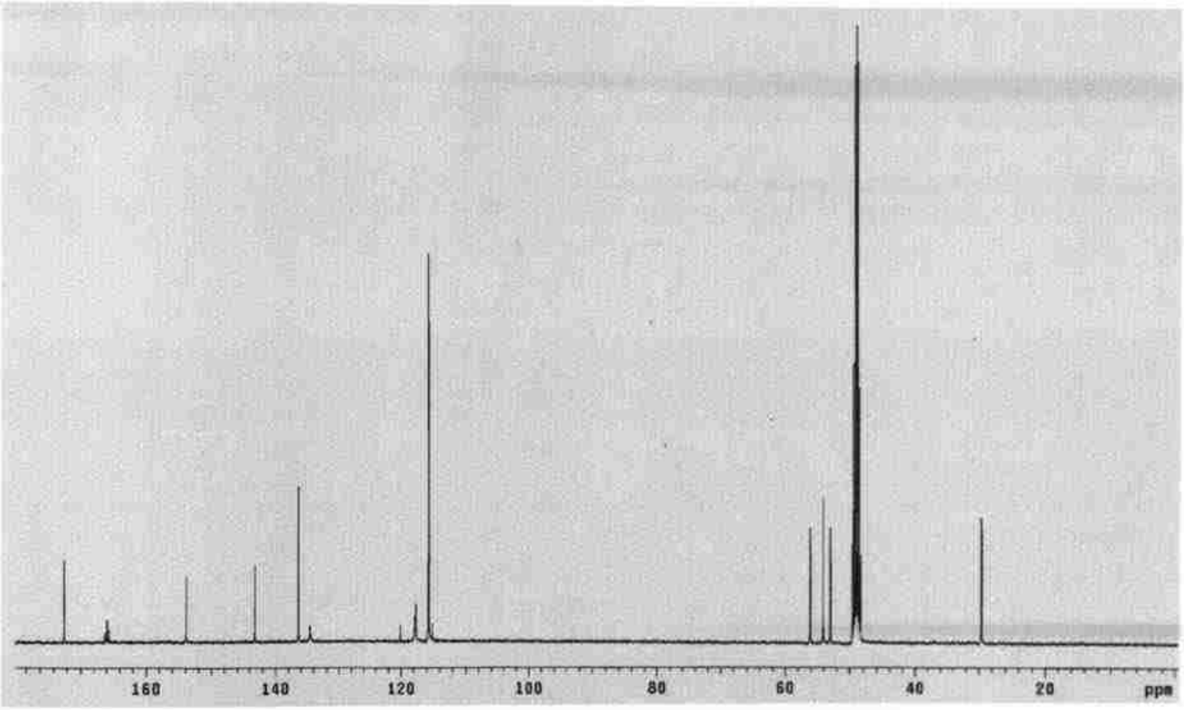

Figure 1.49: ^{1}H spectra of compound **1.89**

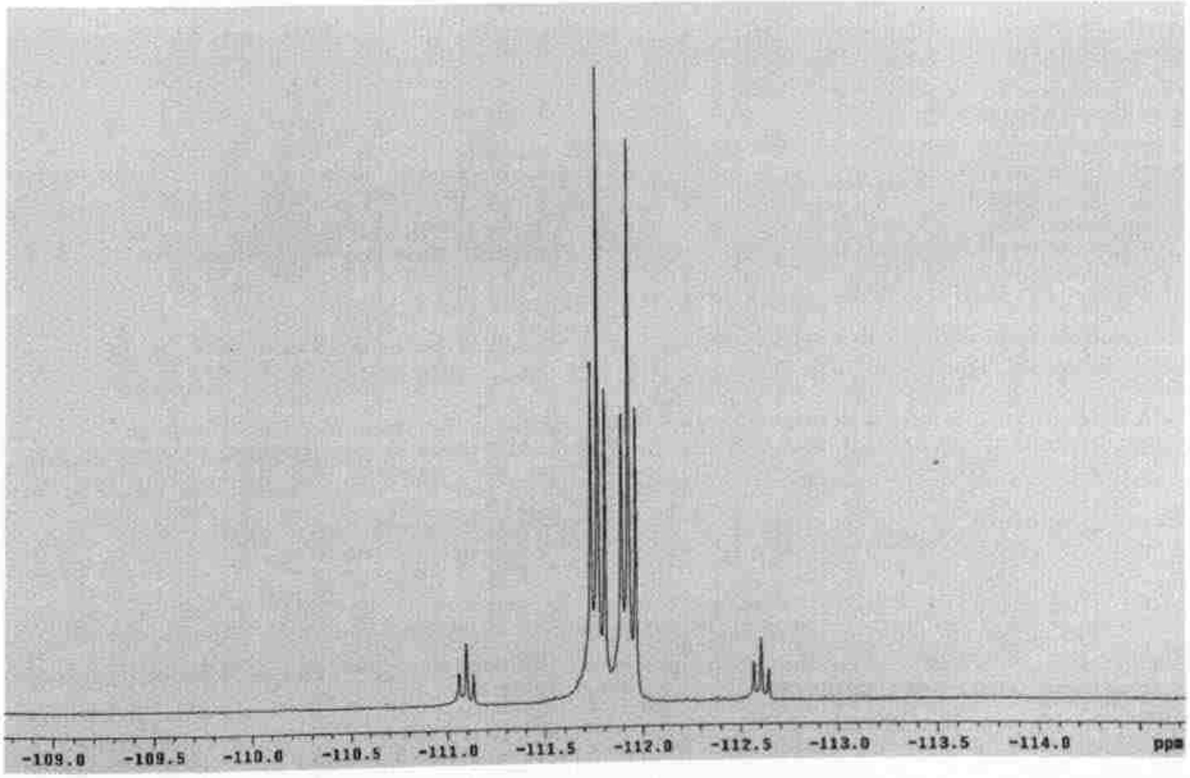

Figure 1.50: ^{19}F NMR spectra of compound **1.89**

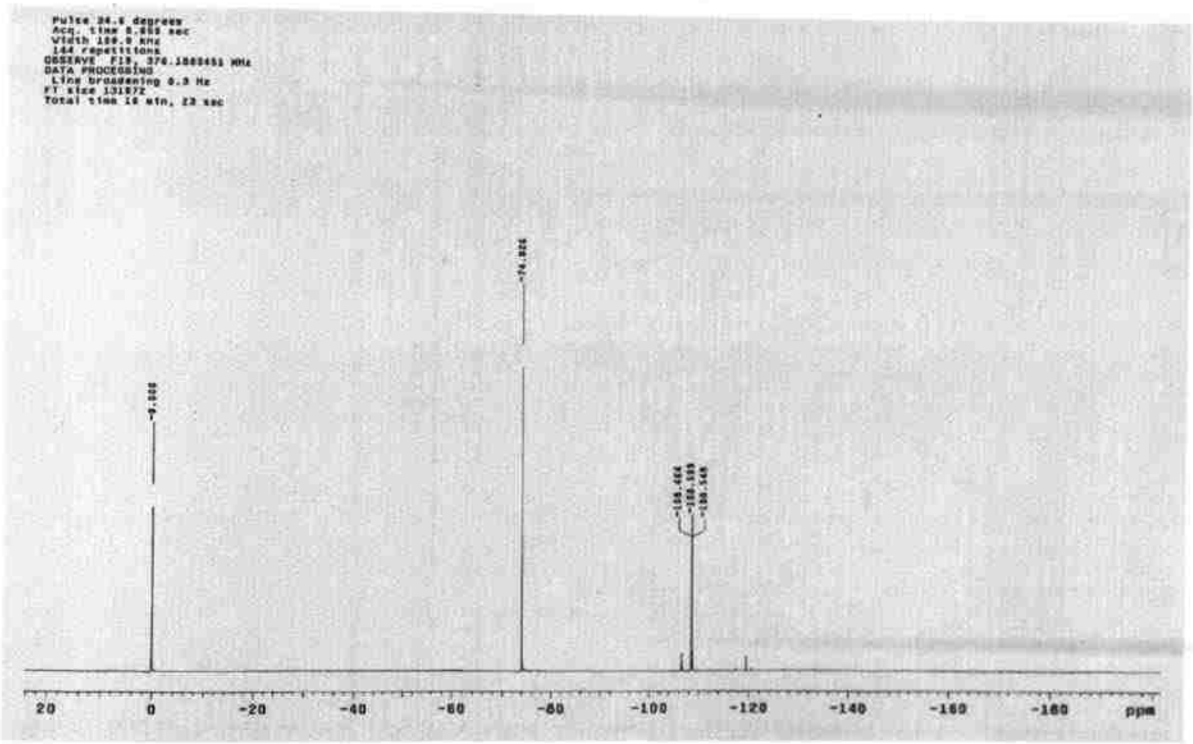

Figure 1.51: ^{1}H NMR spectra of compound **1.93**

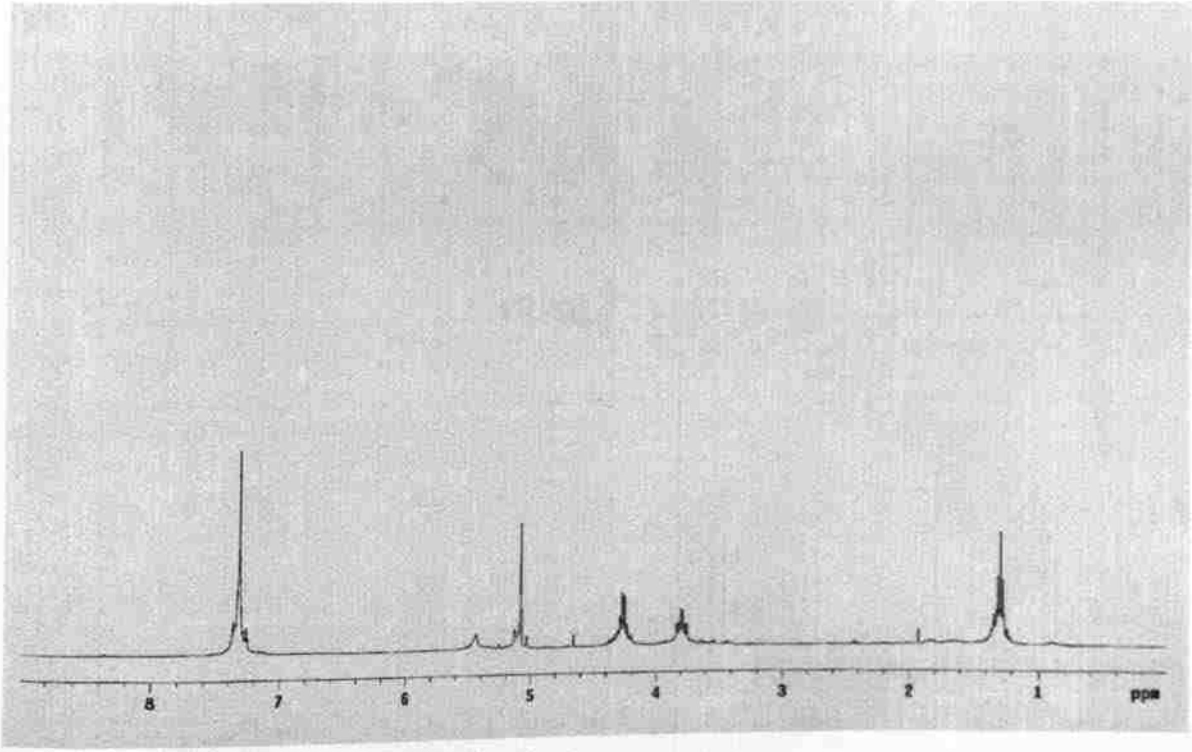

Figure 1.52: ^{1}H NMR spectra of compound **1.92**

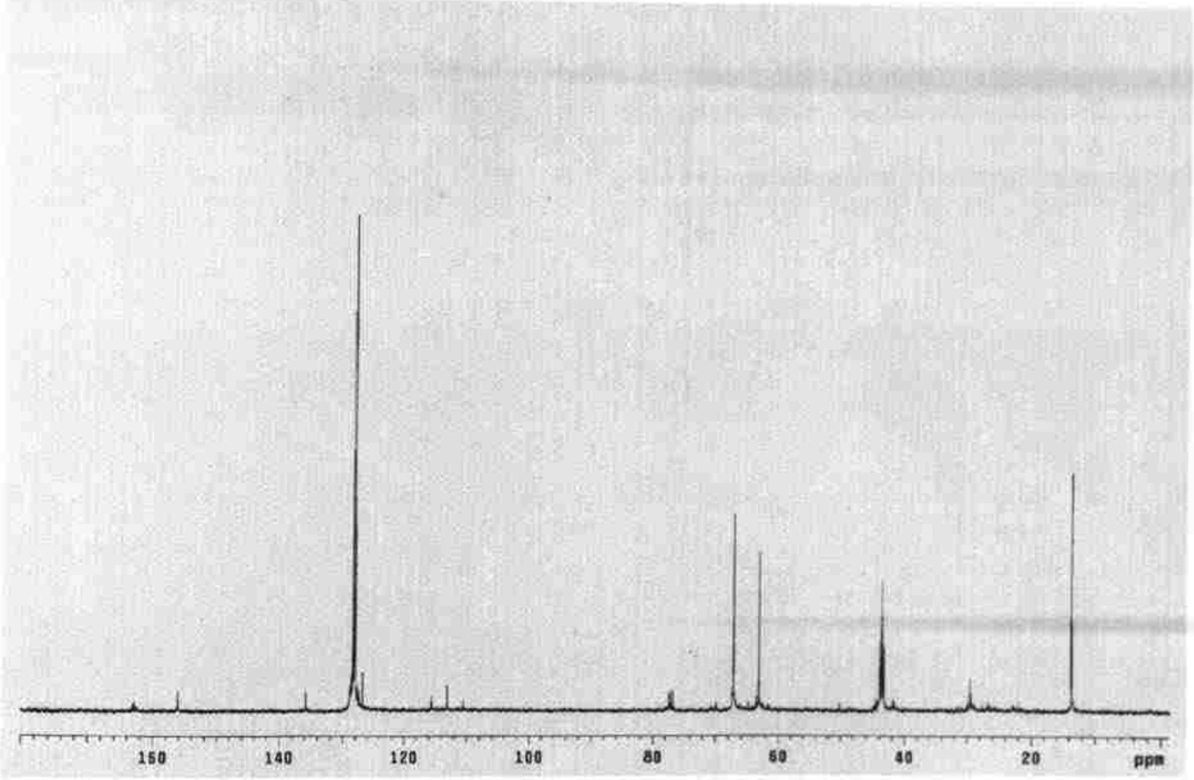

Figure 1.53: ^{13}C NMR spectra of compound **1.92**

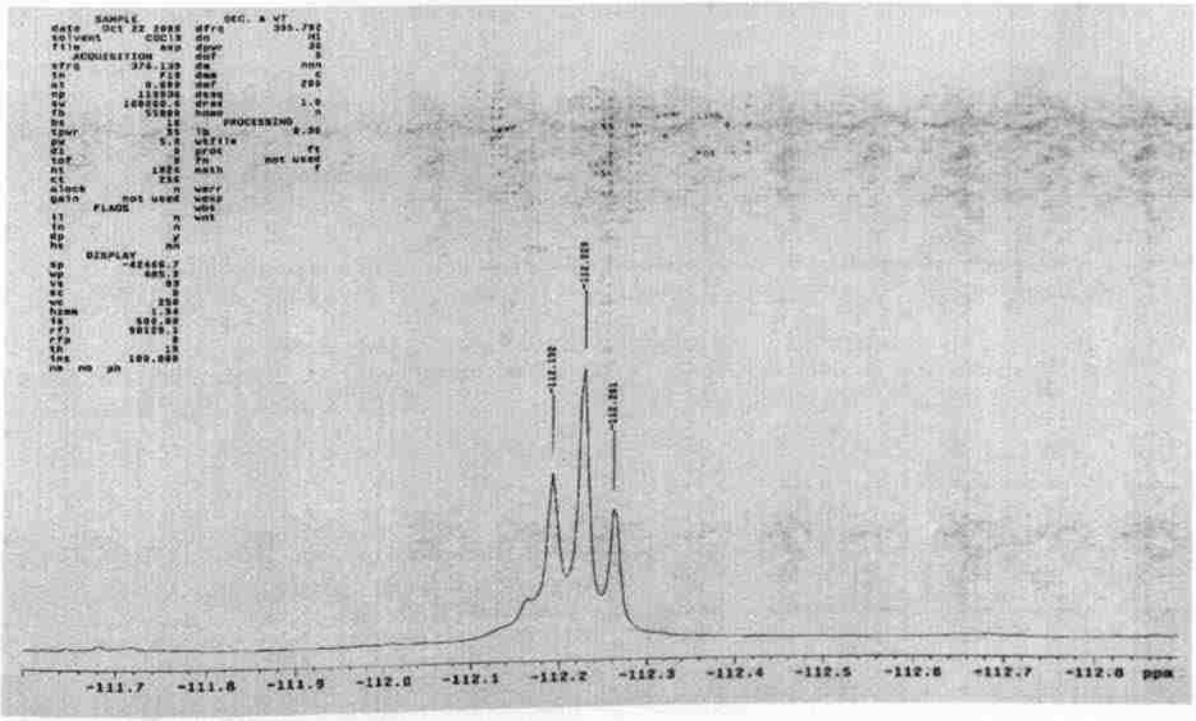

Figure 1.54: ^{19}F NMR spectra of compound **1.92**

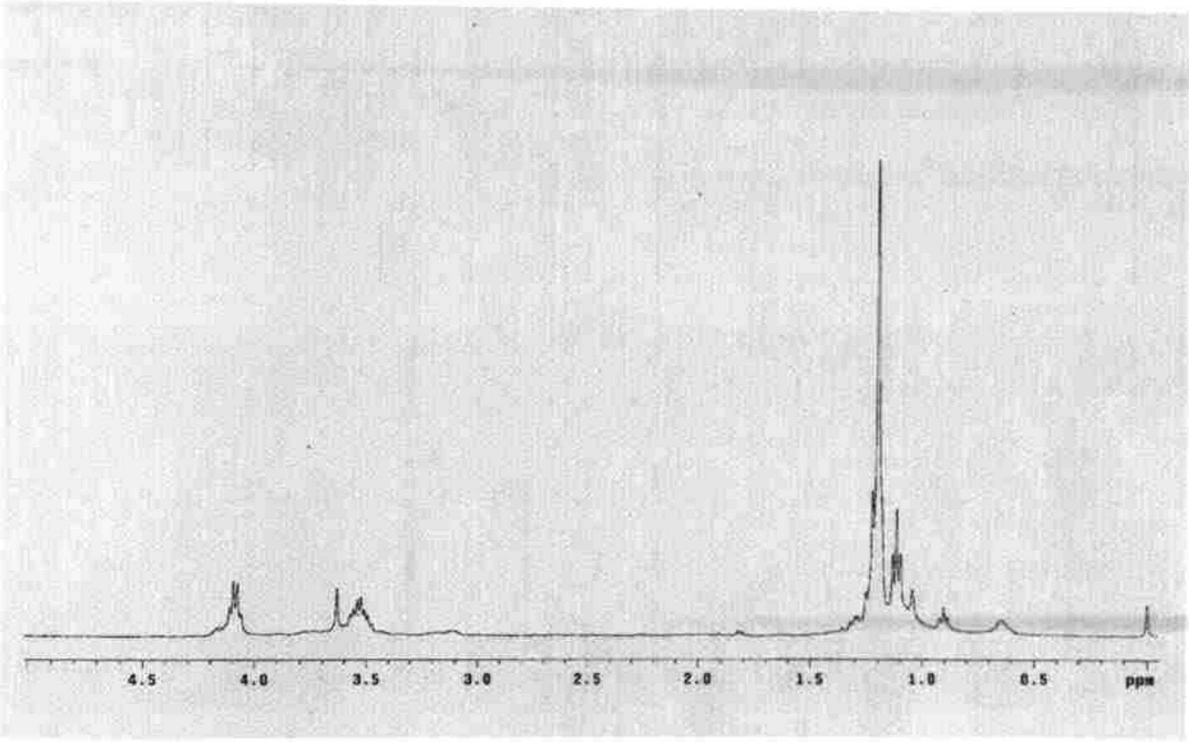

Figure 1.55: ^{1}H NMR spectra of compound **1.94**

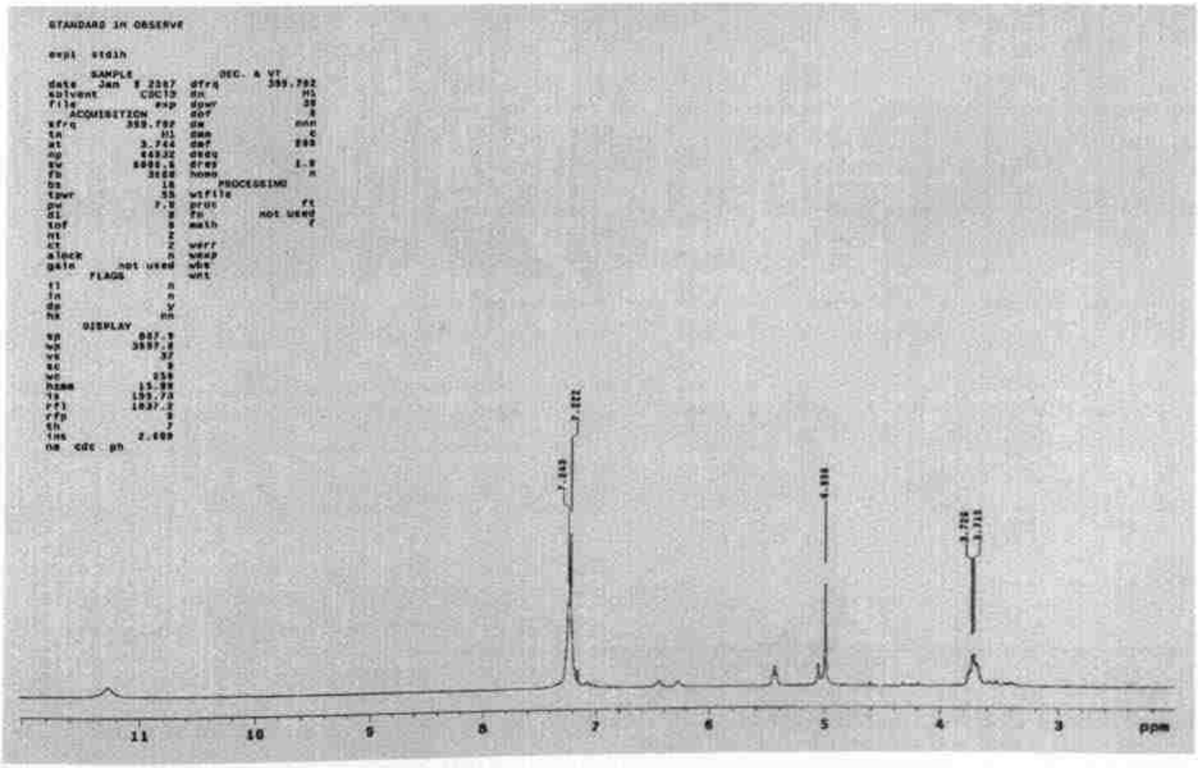

Figure 1.56: ^{1}H NMR spectra of compound **1.95**

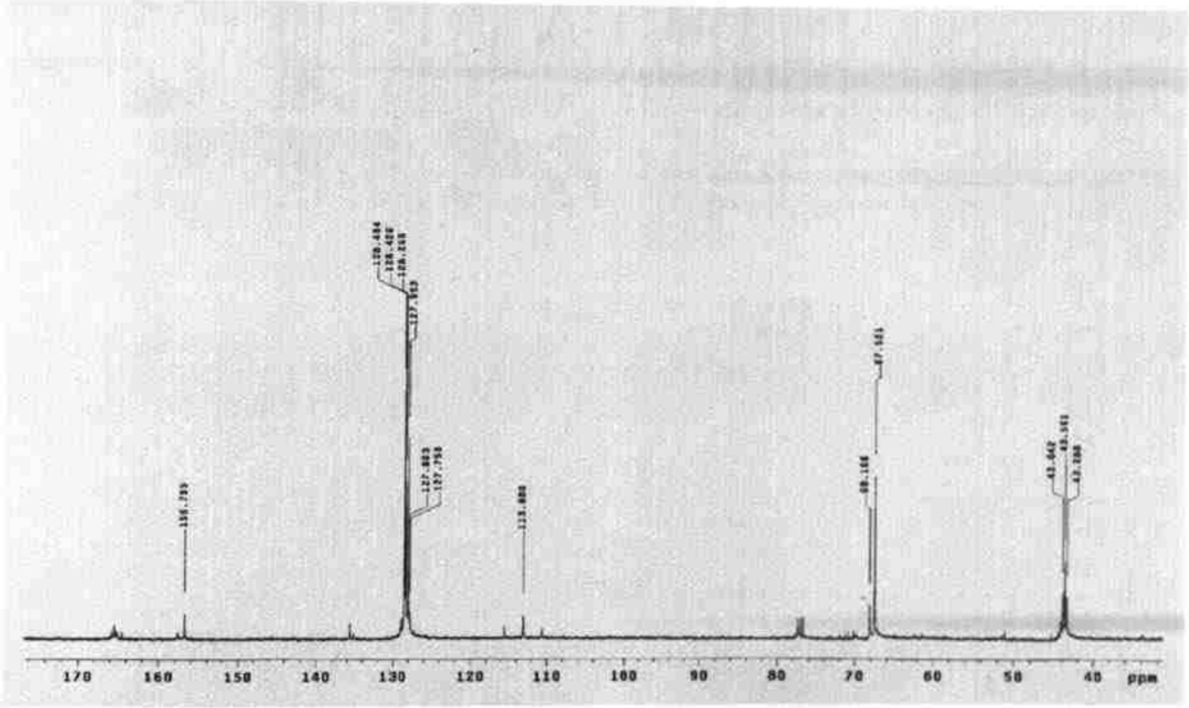

Figure 1.57: ^{13}C NMR spectra of compound **1.95**

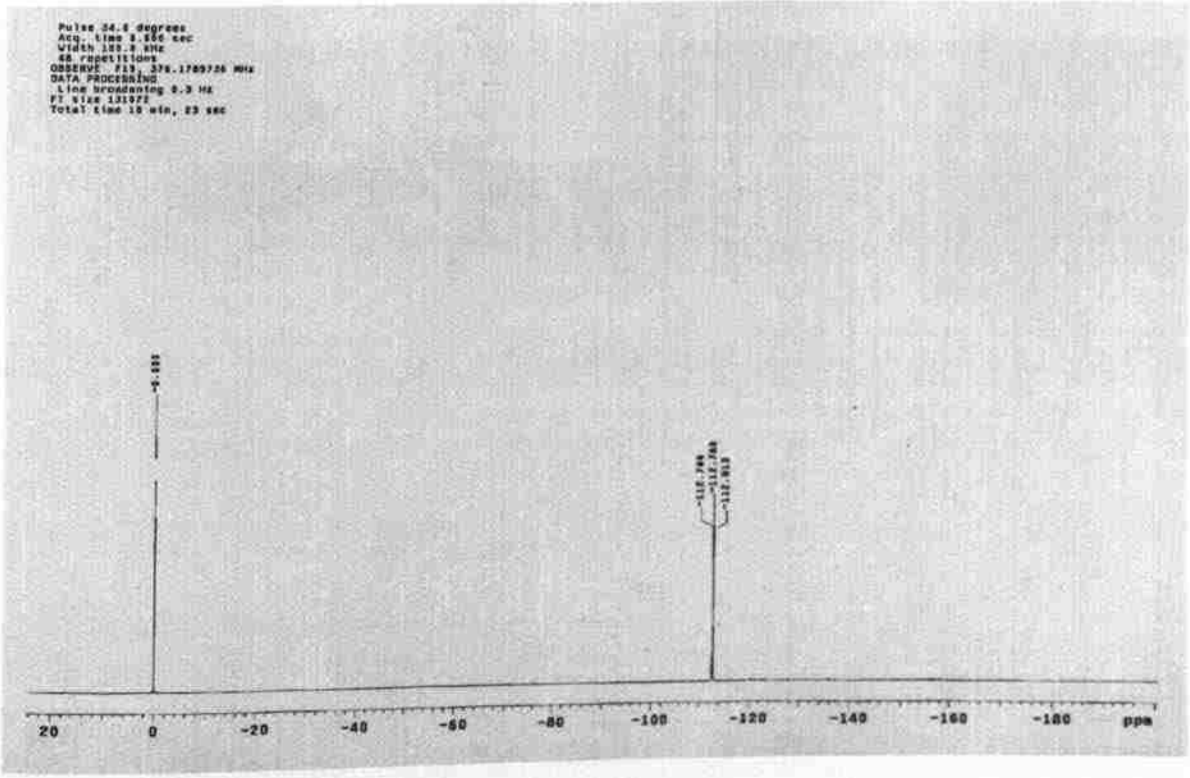

Figure 1.58: ^{19}F NMR spectra of compound **1.95**

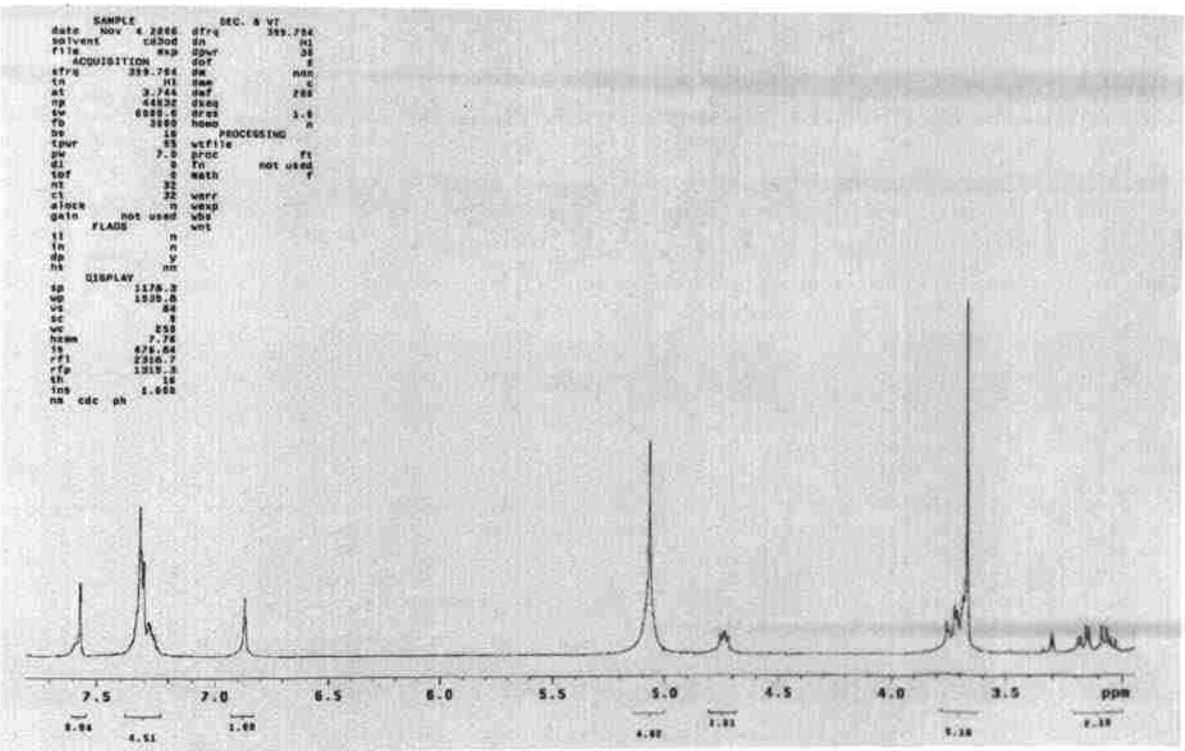

Figure 1.59: ^{1}H NMR spectra of compound **1.96**

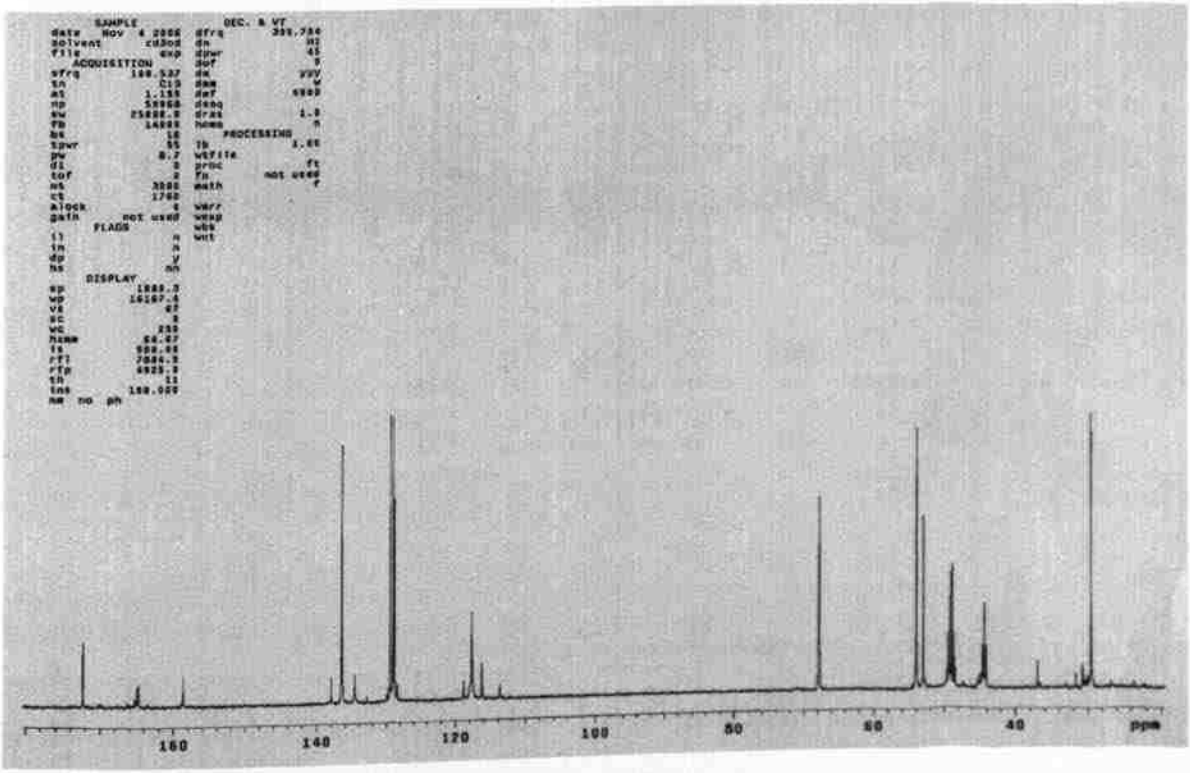

Figure 1.60: ^{13}C NMR spectra of compound **1.96**

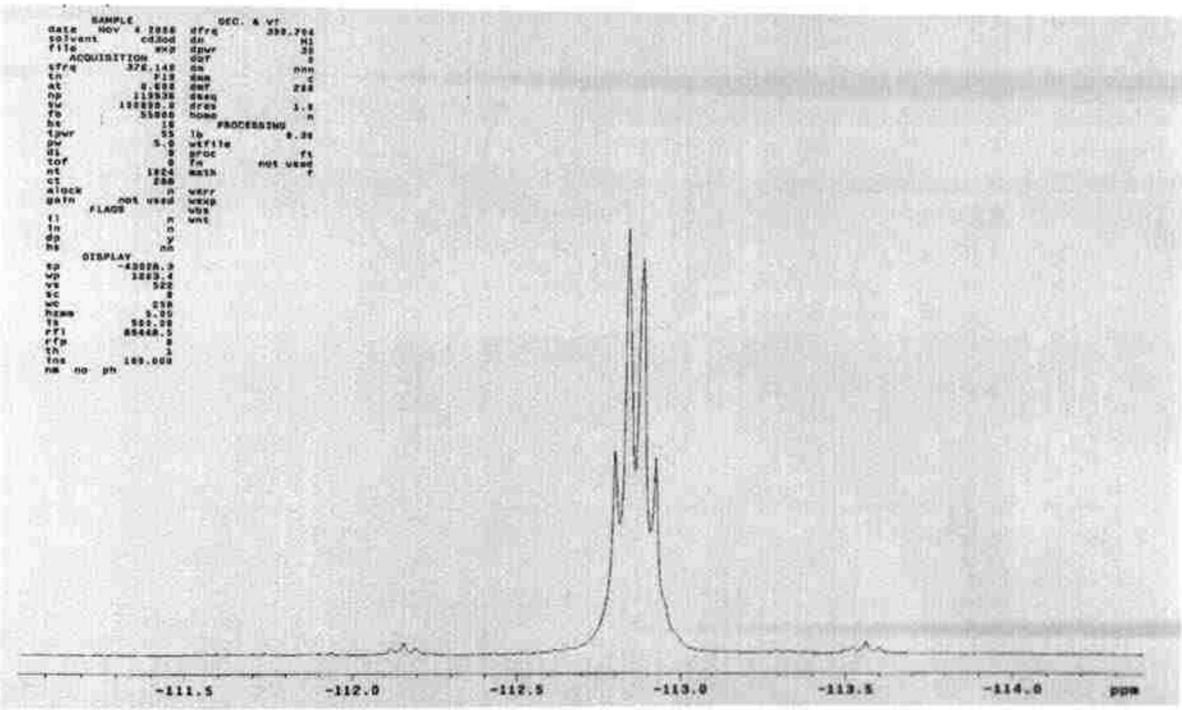

Figure 1.61: ^{19}F NMR spectra of compound **1.96**

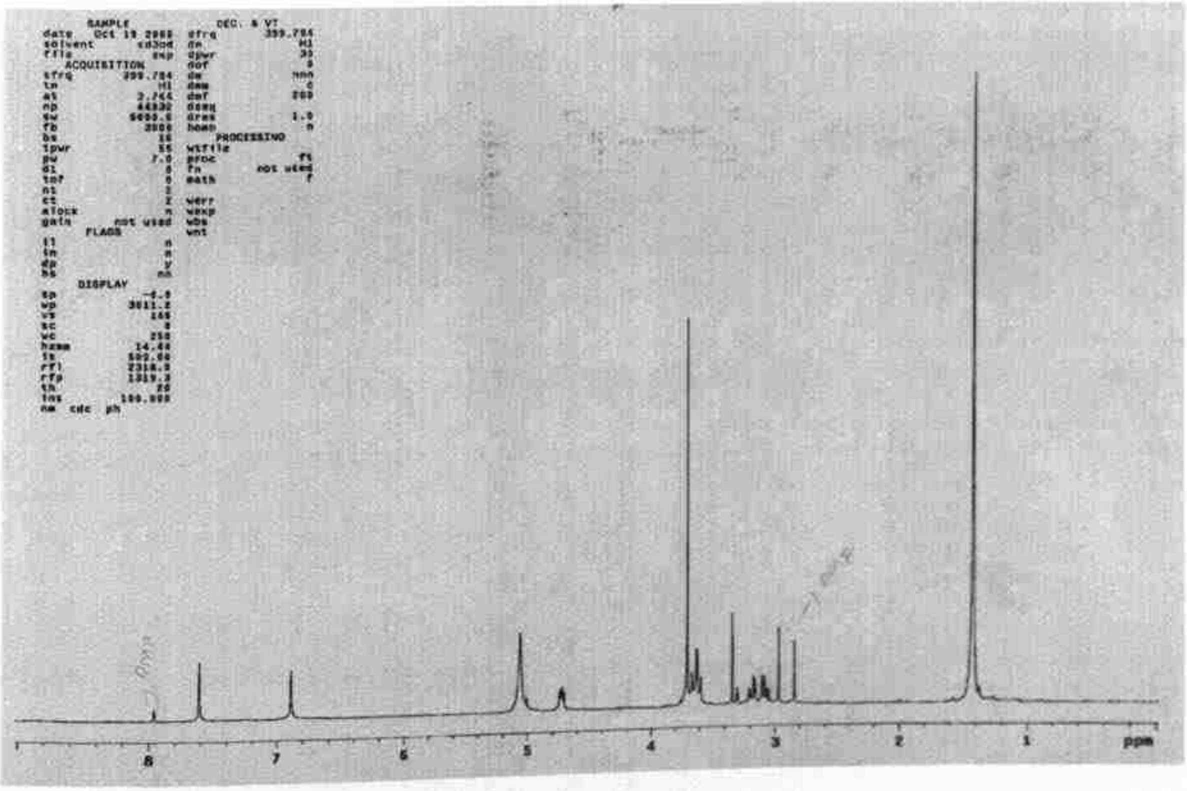

Figure 1.62: ^{1}H NMR spectra of compound **1.98**

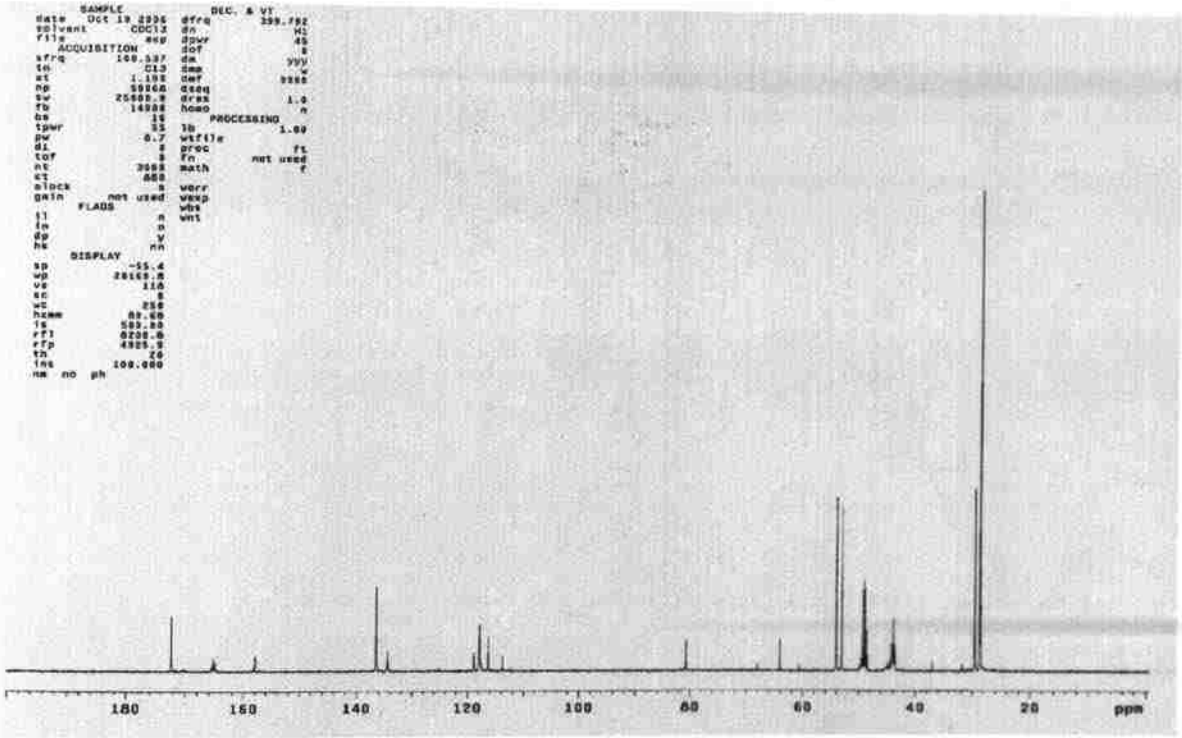

Figure 1.63: ^{13}C NMR spectra of compound **1.98**

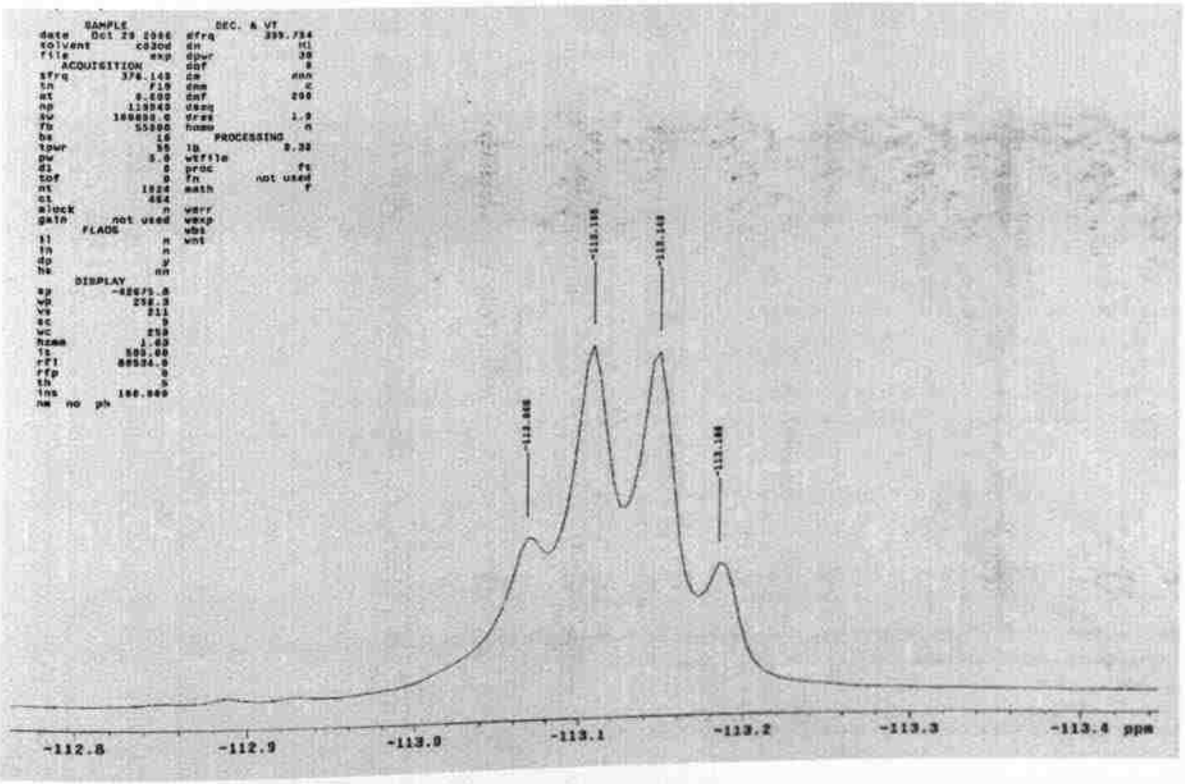

Figure 1.64: ^{19}F NMR spectra of compound **1.98**

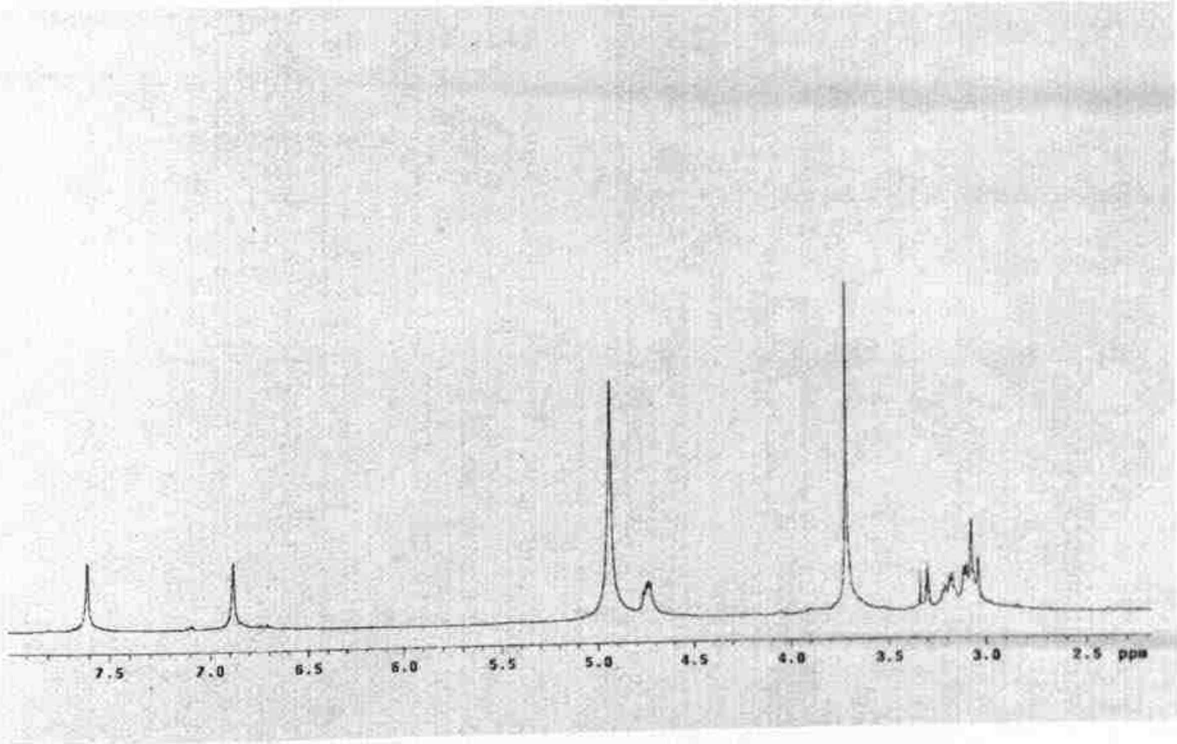

Figure 1.65: ^{1}H NMR spectra of compound **1.90**

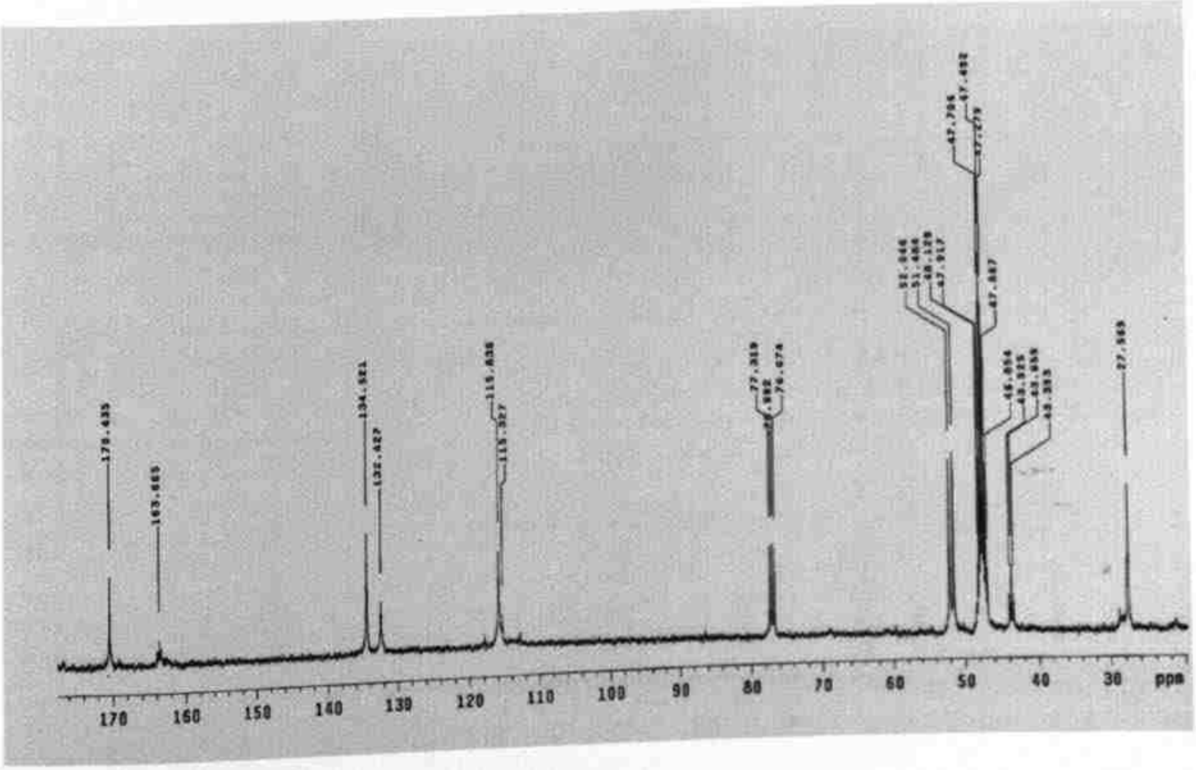

Figure 1.66: ^{13}C NMR spectra of compound **1.90**

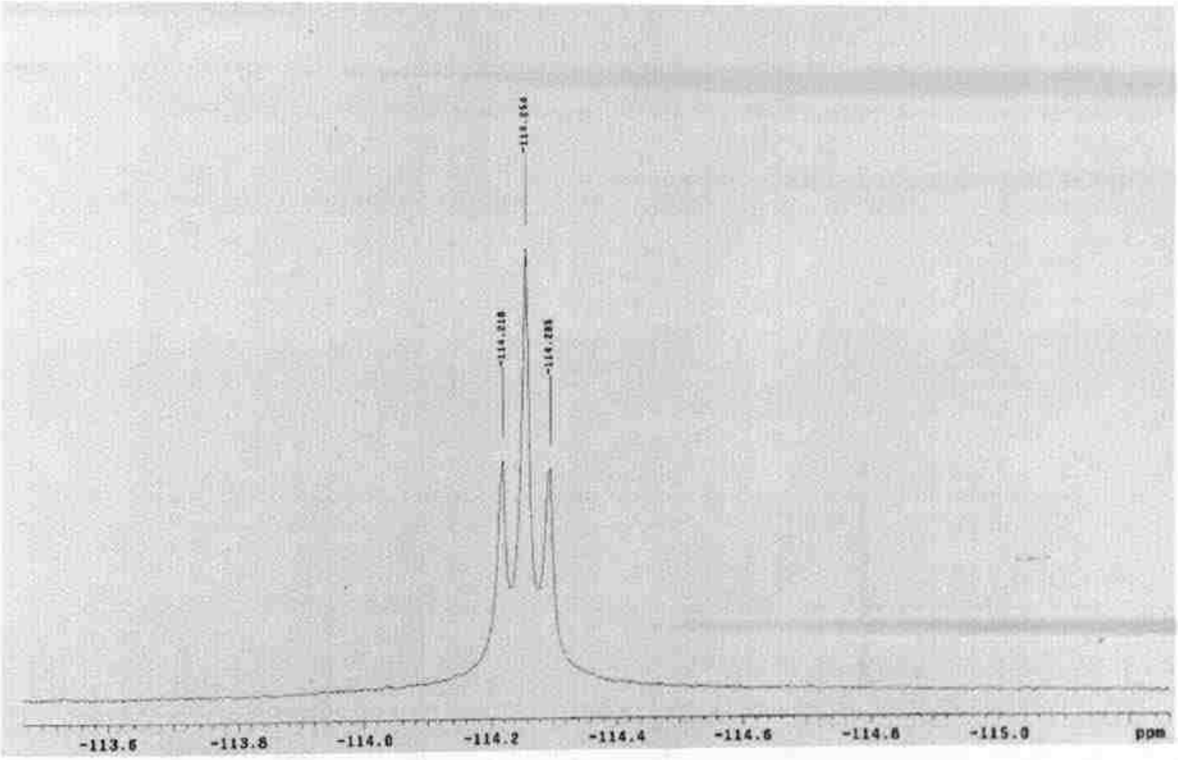

Figure 1.67: ^{19}F NMR spectra of compound **1.90**

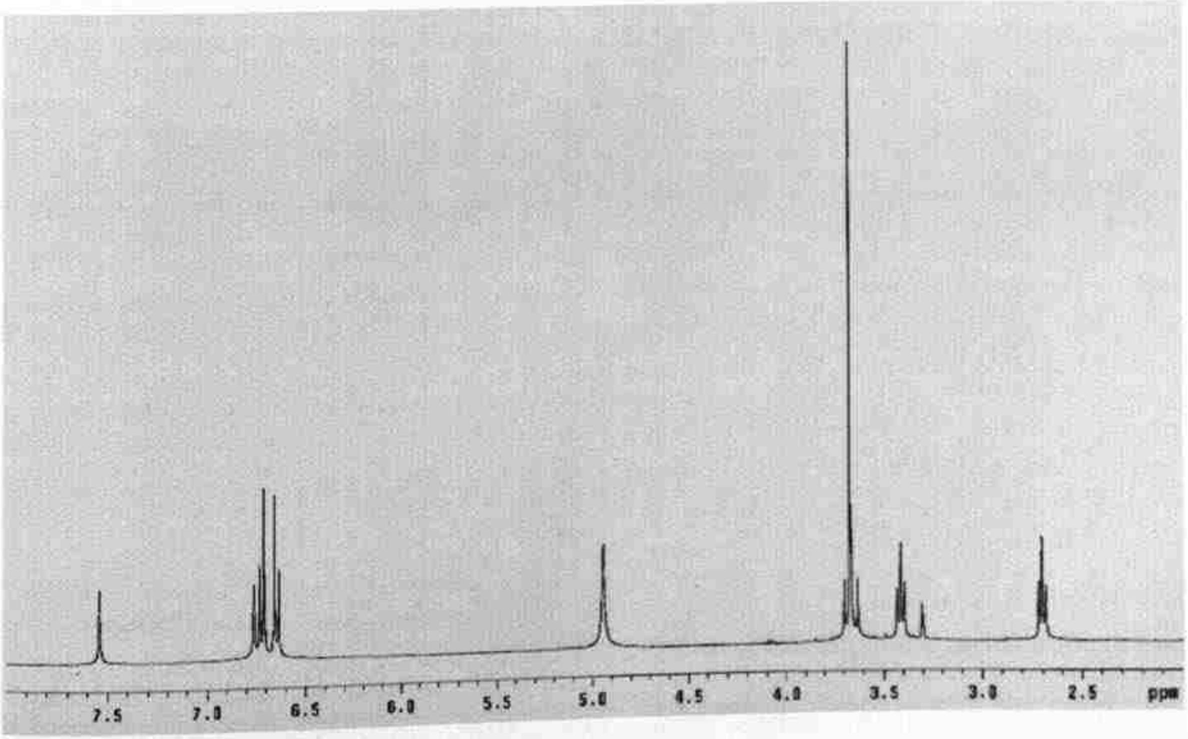

Figure 1.68: ^{1}H NMR spectra of compound **1.99**

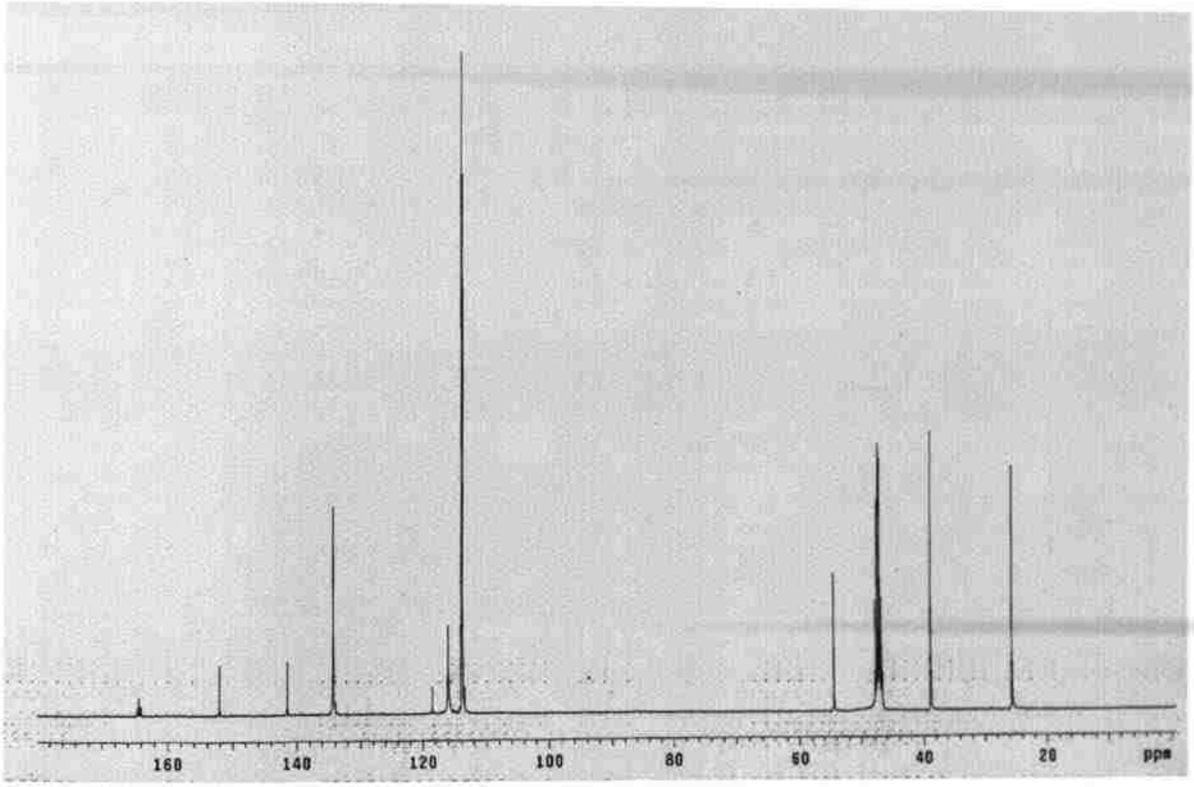

Figure 1.69: ^{13}C NMR spectra of compound **1.99**

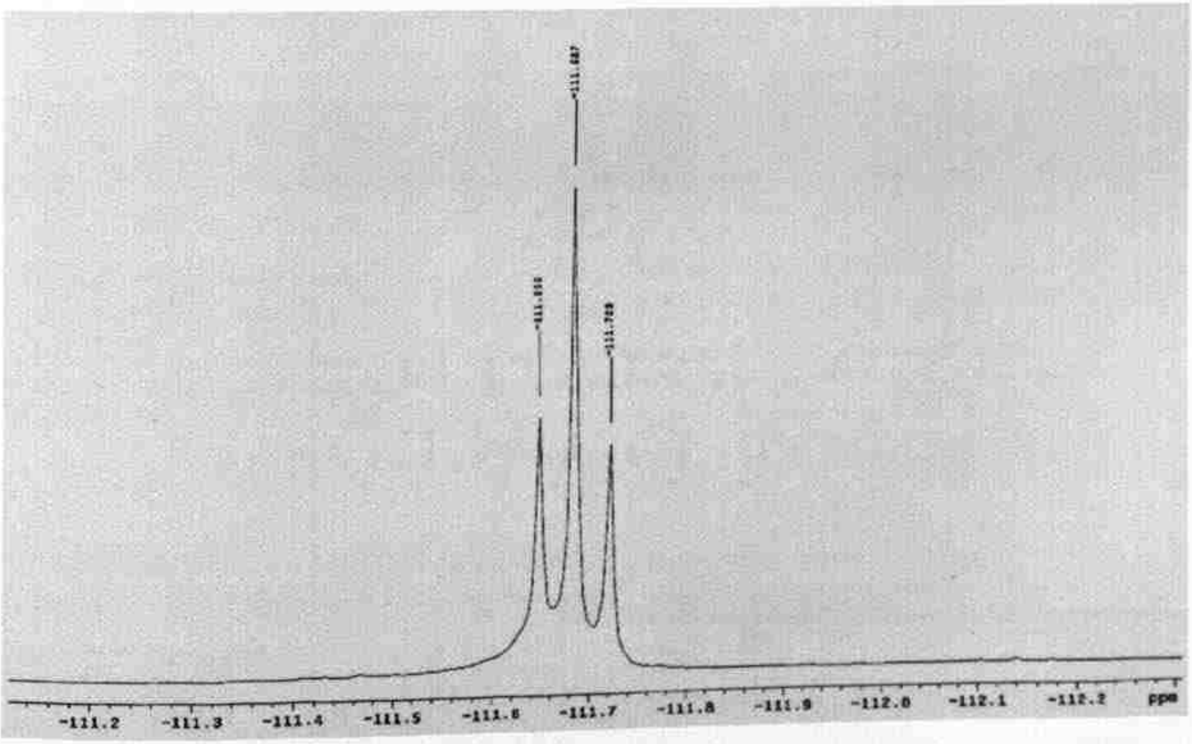

Figure 1.70: ^{19}F NMR spectra of compound **1.99**

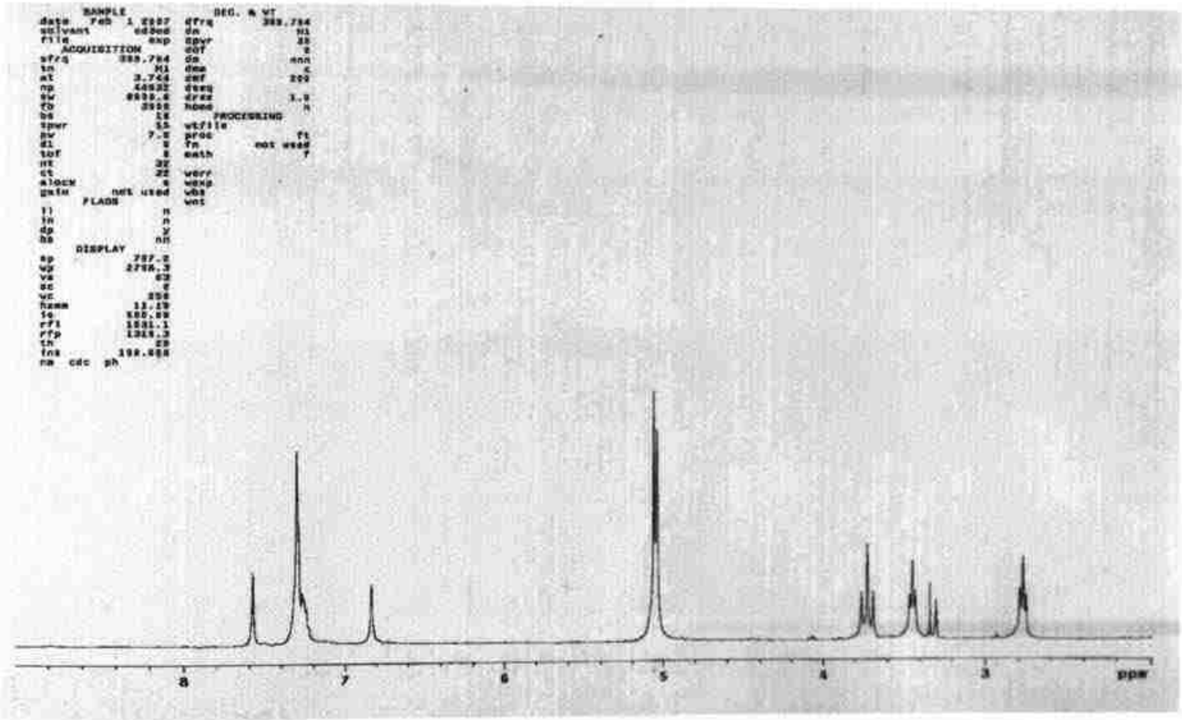

Figure 1.71: ^{1}H NMR spectra of compound **1.101**

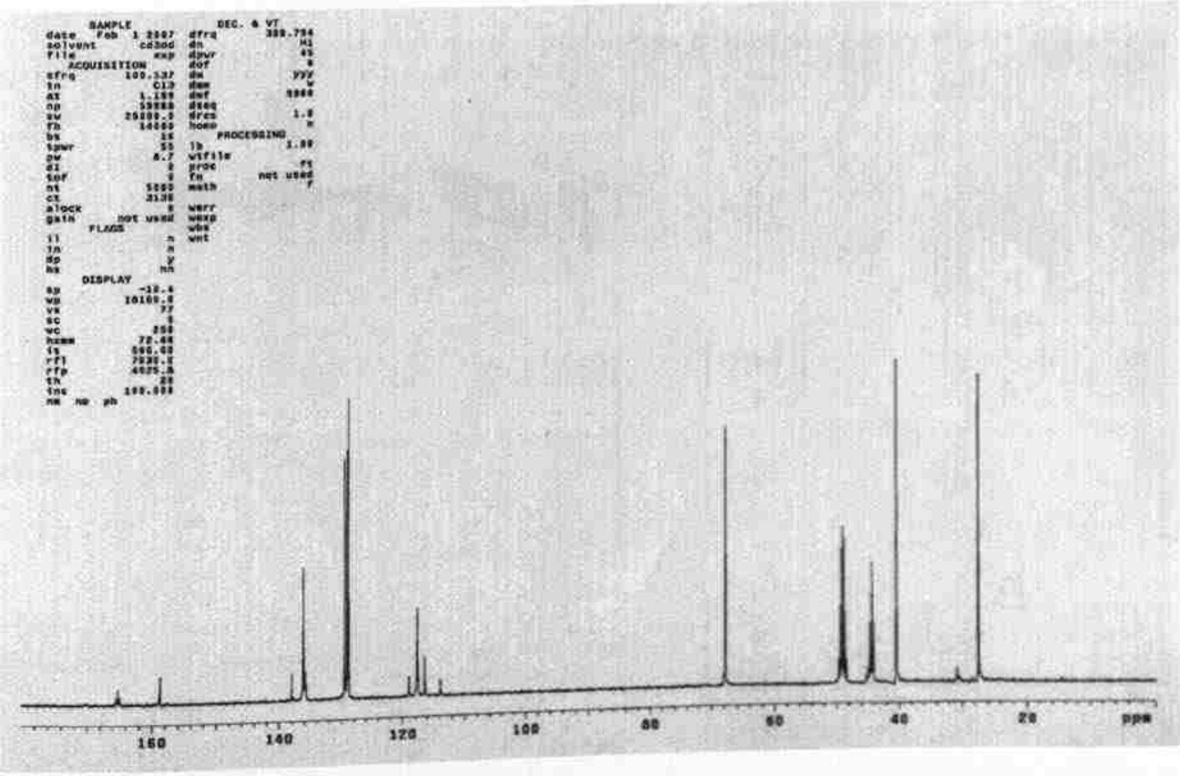

Figure 1.72: ^{13}C NMR spectra of compound **1.101**

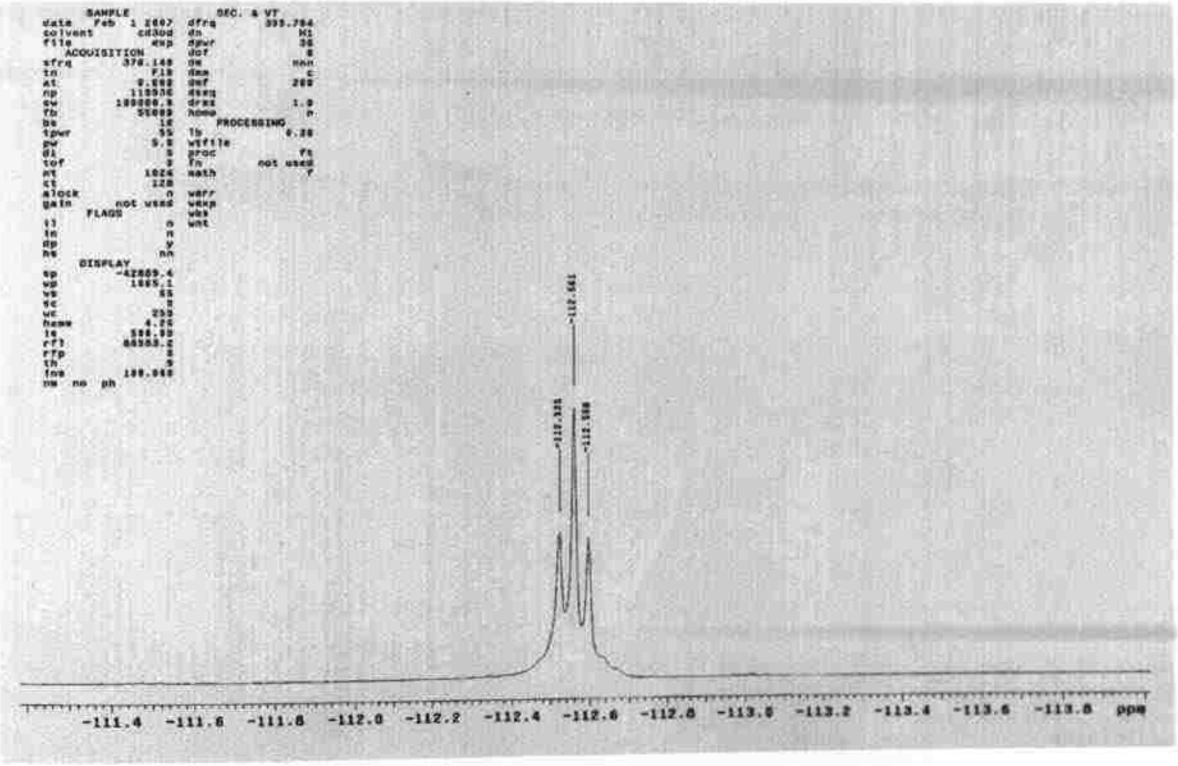

Figure 1.73: ^{19}F NMR spectra of compound **1.101**

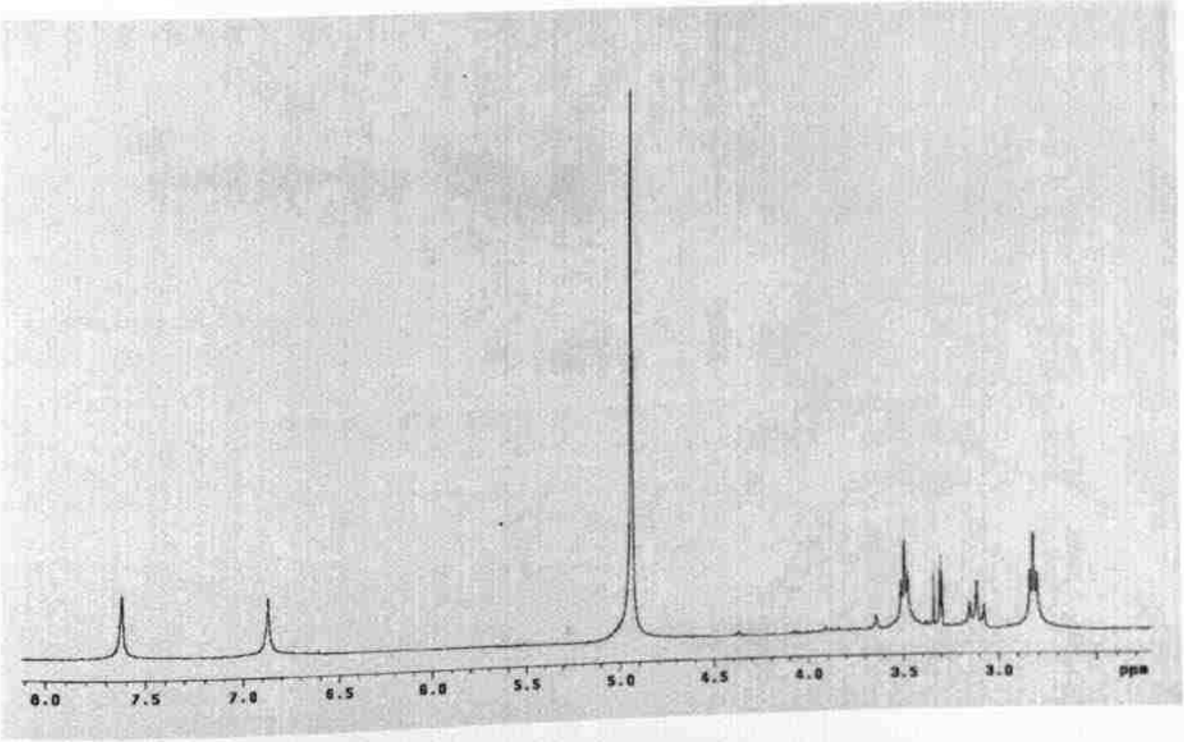

Figure 1.74: ^{1}H NMR spectra of compound **1.100**

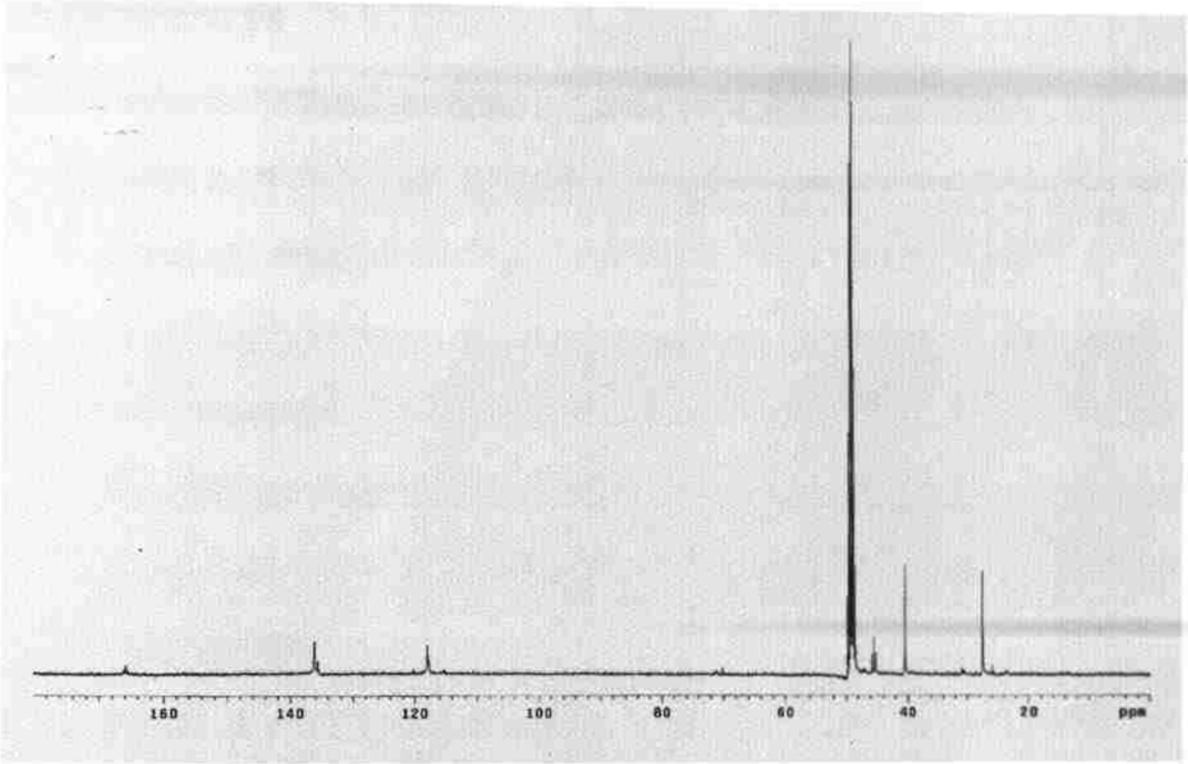

Figure 1.75: ^{13}C NMR spectra of compound **1.100**

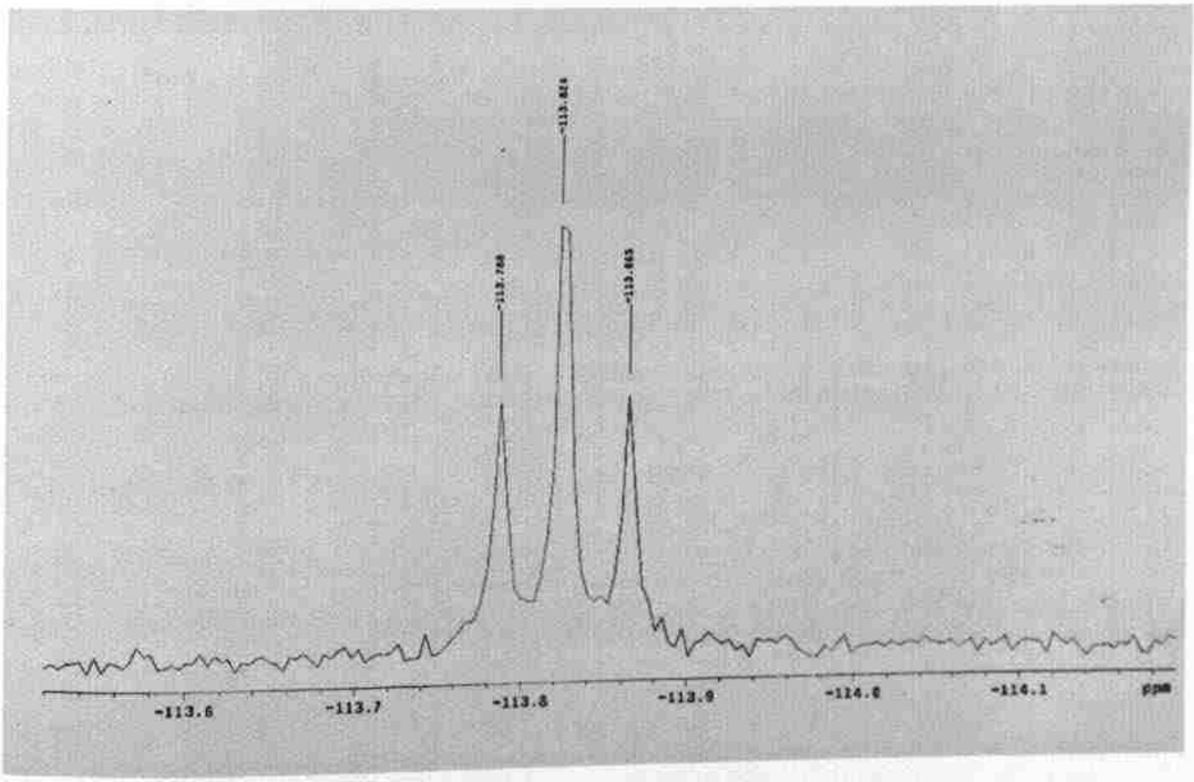

Figure 1.76: ^{19}F NMR spectra of compound **1.100**

1.5 REFERENCES

1. Saitto, S.; Khilber, J.; Luthman, K. *Tetrahedron* **2004**, 60, 6113-6120.
2. Ripka, A.; Rich, D. *Curr. Opin. Chem. Biol.* **1998**, 2, 441.
3. Leung, D.; Abbenante, G.; Fairlie, D. *J. Med. Chem.* **2000**, 43, 305-341.
4. Hudlicky, M., Pavlath, A. E., Eds. *Chemistry of Organic Fluorine Compounds II*; ACS Monograph 187; American Chemical Society: Washington, DC, 1995. See the following chapters: Filler, R.; Kirk, K. Biological Properties of Fluorinated Compounds; Elliott, A. J. Fluorinated Pharmaceuticals; Lang, R. W. Fluorinated Agrochemicals.
5. Smart, B. E. In *Organofluorine Chemistry: Principles and Commercial Applications*; Banks, R. E., Smart, B. E., Tatlow, J. C., Eds.; Plenum Publishing Corporation: New York, 1994; pp 57-88.
6. Welch, J. T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*; John Wiley and Sons: New York, 1991.
7. Rich, D. H. In *Comprehensive Medicinal Chemistry*; Sammes, P. G., Ed.; Pergamon Press: Oxford, U.K. 1990; pp 391-441.
8. Sham, H. L. In *Biomedical Frontiers of Fluorine Chemistry*; Ojima, I., McCarthy, J. R., Welch, J. T., Eds.; American Chemical Society: Washington D.C., 1996; pp 184-195.
9. Oyiliagu, C. E.; Novalen, M.; Kotra, L. P. *Fluorine containing molecules for peptidomimicry : a chemical act to modulate enzymatic activity. Mini-Reviews in organic chemistry* **2006**, 3(2), 99-115.
10. Gelb, M. H.; Svaren, J. P.; Abeles, R. H. *Biochemistry* **1985**, *24*, 1813-1817.

11. Imperiali, B.; Abeles, R. H. *Biochemistry* **1986**, *25*, 3760-3767.

12. Liang, T.-Y.; Abeles, R. H. *Biochemistry* **1987**, *26*, 7603-7608.

13. Brady, K.; Wei, A.; Ringe, D.; Abeles, R. H. *Biochemistry* **1990**, *29*, 7600-7607.

14. Brodbeck, U.; Schweikert, K.; Gentinetta, R.; Rottenberg, M. *Biochim. Biophys. Acta* **1979**, *567*, 357-369.

15. Thaisrivongs, S.; Pals, D. T.; Kati, W. M.; Turner, S. R.; Thomasco, L. M. *J. Med. Chem.* **1985**, *28*, 1553-1555.

16. Thaisrivongs, S.; Pals, D. T.; Kati, W. M.; Turner, S. R.; Thomasco, L. M.; Watt, W. *J. Med. Chem.* **1986**, *29*, 2080-2087.

17. Fearon, K.; Spaltenstein, A.; Hopkins, P. B.; Gelb, M. H. *J. Med. Chem.* **1987**, *30*, 1617-1622.

18. Thaisrivongs, S.; Schostarez, H. J.; Pals, D. T.; Turner, S. R. *J. Med. Chem.* **1987**, *30*, 1837-1842.

19. Peach, M. J. *Physiol. Rev.* **1977**, 57, 313.

20. Ondetti, M. A.; Cushman, D. W. *Annu. Rev. Biochem.* **1982**, 51, 283.

21. Davis, J. O. *Circ. Res.* **1977**, 40, 439.

22. Swales, J. D. *Pharmacol. Ther.* **1979**, 7, 172.

23. Damon, D. B.; Hoover, D. J. *J. Am. Chem. Soc.* **1990**, 112, 6439-6442.

24. Garrett, G. S..; Emge, T. J.; Lee, S. C.; Fisher, E. M.; Dyehouse, K.; McIver, J. M. *J. Org. Chem.* **1991**, 56, 4823-4826.

25. Hoffman, R. V.; Saenz, J. E. *Tetrahedron Lett.* **1997**, 38, 8469-8472.

26. Hoffman, R. V.; Tao, J. *Tetrahedron Lett.* **1998**, 39, 4195-4198.

27. Hoffman, R. V.; Tao, J. *J. Org. Chem.* **1999**, 64, 126-132.

28. Vacca, J. P.; Dorsey, B. D.; Schleif, W. A.; Levin, R. B.; McDaniel, S. L.; Darke, P. L.; Zugay, J.; Quintero, J. C.; Blahy, O. M.; Roth, E.; Sardana, V. V.; Schlabach, A. J.; Graham, P. I.; Condra, J. H.; Gotlib, L.; Holloway, M. K.; Lin, J.; Chen, I.-W.; Vastag, K.; Ostovic, D.; Anderson, P. S.; Emini, E. A.; Huff, J. R. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 4096-4100.

29. Dorsey, B. D.; Levin, R. B.; McDaniel, S. L.; Vacca, J. P.; Guare, J. P.; Darke, P. L.; Zugay, J. A.; Emini, E. A.; Schleif, W. A.; Quintero, J. C.; Lin, J. H.; Chen, I.-W.; Holloway, M. K.; Fitzgerald, P. M. D.; Axel, M. G.; Ostovic, D.; Anderson, P. S.; Huff, J. R. *J. Med. Chem.* **1994**, *37*, 3443-3451.

30. Myers, A. G.; Barbary, J. K.; Zhong. B. *J. Am. Chem. Soc.* **2001**, 123, 7207-7219.

31. Allmendinger, T.; Furet, P.; Hungerbuhler, E. *Tetrahedron Lett.* **1990**, 31, 7297-7300.

32. Abraham, R. J.; Ellison, S. L. R.; Schonholzer, P.; Thomas, W. A. *Tetrahedron* **1986**, 42, 2101-2110.

33. Boros, L. G.; De Corte, B.; Gimi, R. H.; Welch, J. T.; Wu, Y.; Handschumaker, R. E. *Tetrahedron Lett.* **1994**, 35, 6033-6036.

34. Welch, J. T.; Lin, J. *Tetrahedron* **1996**, *52*, 291-304.

35. Van der Veken, P.; Kertèsz, I.; Senten, K.; Haemers, A.; Augustyns, K. *Tetrahedron Lett.* **2003**, *44*, 6231-6234.

36. Veenstra, S. J.; Hauser, K.; Felber, P. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 351-354.

37. Hollenstein, M.; Leumann, C. J. *J. Org. Chem.* **2005**, *70*, 3205-3217.

38. Nakamura, Y.; Okada, M.; Sato, A.; Horikawa, H.; Koura, M.; Saito, A.; Taguchi, T. *Tetrahedron* **2005**, *61*, 5741-5753.

39. Otaka, A.; Watanabe, H.; Mitsuyama, E.; Yukimasa, A.; Tamamura, H.; Fujii, N. *Tetrahedron Lett.* **2002**, *43*, 5845-5847.

40. Otaka, A.; Watanabe, H.; Yukimasa, A.; Sasaki, Y.; Watanabe, H.; Kinoshita, T.; Oishi, S.; Tamamura, H.; Fujii, N. *J. Org. Chem.* **2004**, *69*, 1634-1645.

41. Bartlett, P. A.; Otake, A. *J. Org. Chem.* **1995**, *60*, 3107-3111.

42. Wipf, P.; Henninger, T. C.; Geib, S. J. *J. Org. Chem.* **1998**, 63, 6088-6089.

43. kuznetsova, L.; Ungureanu, I.; Pepe, A.; Zanardi, I.; Wu, X.; Ojima, I. *J. Flour. Chem.* **2004**, 125, 487-500.

44. Ismail, F. *J. Flour. Chem.* **2002**, 118, 27-33.

45. Zanda, M. *New. J. Chem.* **2004**, 28, 1401.

46. Mikami, K.; Itoth, Y.; Yamanaka, M. *Chem. Rev.* **2004**, 104, 1.

47. Jacobson, I.; Reddy, G. *Tetrahedron Lett.* **1996**, *37*, 8263.

48. Jacobson, I.; Reddy, P.; Wasserman, Z.; hardman, K.; Covingyon, M.; Arner, E.; Copeland, R.; Decicco, C.; Magolda, R. *Bioorg. Med. Chem. Lett.* **1998**, 8, 837.

49. Sani, M.; Belotti, D.; Giavazzi, R.; Panzeri, W.; Volonterio, A.; Zanda, M. *Tetrahedron Lett.* **2004**, 47, 1869.

50. Chiba, H.; Agematu, H.; Kaneto, R.; Terasawa, T.; Sakai, K.; Dobashi, K.; Yoshioka, T. *J. Antibiot.* **1999**, *52*, 695.

51. Chiba, H.; Agematu, H.; Dobashi, K.; Yoshioka, T. *J. Antibiot.* **1999**, *52*, 700.

52. Chiba, H.; Agematu, H.; Sakai, K.; Dobashi, K.; Yoshioka, T. *J. Antibiot.* **1999**, *52*, 710.

53. Kawato, H.; Nakayama, K.; Inagaki, H.; Nakajima, R.; Kitamura, A.; Someya, K.; Ohta, T. *Org. Lett.* **2000**, *2*, 973-976.

54. Uoto, K.; Ohsuki, S.; Takenoshita H.; Ishiyama T.; Iimura S.; Hirota Y.; Mitsui I.; Terasawa H.; Soga T. *Chem. Pharm. Bull.* **1997**, *45*, 1793-1804.

55. Nakayama, K.; Kawato, H.; Inagaki, H.; Nakajima, R.; Kitamura, A.; Someya, K.; Ohta, T. *Org. Lett.* **2000**, *2*, 977-980.

56. Reddy, V. P.; Garrett Matthew, R.; Perry, G.; Smith Mark, A. *Sci. Aging Knowl. Environ. (Science's SAGE KE)* **2005**, 18, pe 12

57. Hipkins, A. R. *Int. J. Biochem. Cell. Biol.* **1998**, 30, 863-868.

58. Tabakman, R.; Lazarovici, P.; Kohen,R. *J. Neurosci. Res.* **2002**, 68, 463-469.

59. Hobart, L. J.; Seibel, I.; Yeargans, G. S.; Seidler, N. W. *Life. Sci.* **2004**, 75, 1379-1389.

60. Brownson, C.; Hipkiss, A. R. *Free. Radic. Biol. Med.* **2000**, 28, 1564-1570.

61. Aldini, G.; Carini, M.; Beretta, G.; Bradamante, S.; Facino, R. M. *Biochem. Biophys. Res. Commun.* **2002**, 298, 699-706.

62. Babizhayev, M. A.; Yermakov, V. N.; Semiletov, Y. A.; Deyev, A. I. *Biochemistry (Moscow)* **2000**, 65, 588-598.

63. Chen, Z.; Sakurai, E.; Hu, W.; Jin, C.; Kiso, Y.; Kato, M.; Watanabe, T.; Wei, E.; Yanai, K. *Br. J. Pharmacol.* **2004**, 143, 573-580.

64. Szwergold, B.S. *Biochem. Biophys. Res. Commun.* **2005**, 336, 36-41.

65. Horinishi, H.; Grillo, M.; Margolis, F. L. *J. Neurochem.* **1978**, 31, 909-919.

66. Bonfanti, L.; Peretto, P.; De Marchis, S.; Fasolo, A. *Progress in Nerobiol.* **1999**, 59, 333-353.

67. Quinn, P. J.; Boldyrev, A. A.; Formazuyk, V. E. *Mol. Aspects Med.* **1992**, 13, 379-444.

68. Fujii, T.; Takaoka, M.; Tsuruoka, N.; Kiso, Y.; Tanaka, T.; Matsumura, Y.; *Biol. Pharm. Bull.* **2005**, 28, 361-363.

69. Calcagni, A.; Ciattini, P. G.; Di Stefano, A.; Dupre, S.; Luisi, G.; Pinnen, F.; Rossi, D.; Spirito, A. *Il Farmaco* **1999**, 54, 673-677.

70. Cacciatore, I.; Cocco, A.; Costa, M.; Fontana, M.; Lucente, G.; Pecci, L.; Pinnen, F. *Amino Acids* **2005**, 28, 77-83.

71. Guiotto, A.; Calderan, A.; Ruzza, P.; Osler, A.; Rubini, C.; Jo, D.-G.; Mattson, M. P.; Borini, G. *J. Med. Chem.* **2005**, 48, 6156-6161.

72. Yamamoto, H.; Editor, *Organofluorine compounds: Chemistry and Applications.* 2000.

73. Tozer, M. J.; Herpin, T. F. *Tetrahedron* **1996**, 52, 8619-8683.

74. Kukhar, V. P.; Soloshonok, V. A. *Fluorine-containing Amino Acids. Synthesis and Properties*; Wiley: Chichester, 1995.

75. Marcotte, S.; Pannecoucke, X.; Feason, C.; Quirion, J.-C. *J. Org. Chem.* **1999**, 64, 8461-8464.

76. Vidal, A.; Nefzi, A.; Houghten, R. A. *J. Org. Chem.* **2001**, 66, 8268-8272.

77. Fokina, N. A.; Kornilov, A. M.; Kukhar, V. P. *J. Fluorine Chem.* **2001**, 111, 69-76.

78. Soloshonok, V. A.; Ohkura, H.; Sorochinsky, A.; Voloshin, N.; Markovsky, A.; Belik, M.; Yamazaki, T. *Tetrahedron Lett.* **2002**, 43, 5445-5448.

79. Katritzky, A. R.; Nicholos, D. A.; Qi, M. *Tetrahderon Lett.* **1998**, 39, 7063-7066.

80. Cheguillaume, A.; Lacroix, S.; Marchand-Brynaert, J. *Tetrahedron Lett.* **2003**, 43, 2375-2377.

81. Katrizky, A. R.; Yannakopulou, R.; Lue, P.; Rasala, D.; Urogdi, L. *J. Chem. Soc., Perkin Trans. 1* **1989**, 225-233.

82. Katrizky, A. R.; Yannakopulou, K.; Kuzmierkiewicz, W.; Aurreccoechea, J. M.; Palenik, G. J.; Koziol, A. E.; Szczesniak, M. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2673-2679.

83. Kukla, M. J.; Breslin, H. J.; Bowde, C. R. *J. Med. Chem.* **1985**, 28, 1745-1747.

84. Nicolaou, K.C.; Chen, D. –K.; Huang, X.; Ling, T.; Bella, M.; Snyder, S. A. *J. Am. Chem. Soc.* **2004**, 40, 12888-12896.

85. Cosgun, S.; Mehmet, O.; Hamdoune, F.; Gerardin, C.; Thiebaut, S.; Henry, B.; Amos, J.; Rodehuser, L.; Selve, C.; *J. Fluorine Chem.* **2003**, 107, 375-386.

86. Enders, D.; Grondal, C.; Vrettou, M.; Raabe, G. *Angew. Chem., Int. Ed. Engl.* **2005**, 44, 4079-4083.

87. Lacroix, S.; Cheguillaume, A.; Gerard, S.; Marchand-brynaert, J. *Synthesis* **2003**, 16, 2483-2486.

88. Fustero, S.; Pina, B.; Salavert, E.; Navarro, A.; Ramirez de Arellano, M. C.; Simon Fuentes, A. J. Org. Chem. 2002, 67, 4667-4679.

89. Katrizky, A. R.; Kirichenko, K.; Elsayed, A. M.; Ji, Y.; Fang, Y.; Steel, P. J. *J. Org. Chem.* **2002**, 67, 4957-4959.

90. Cheguillaume, A.; Gillart, J.;Labar, D.; Gregoire, V.; Marchand-Brynaert, J. *Bioorg. Med. Chem.* **2005**, 13, 1357-1367.

91. Guerin, D. J.; Horstmann, T. E.; Miller, Scott. J. *Org. Lett.* **1999**, 1, 1107-1109.

2.1.3 Dithioacetals and dithioketals to *gem*-difluoromethylene compounds:

Dithioacetals and dithioketals derived from aldehydes and ketones were converted to the corresponding *gem*-difluoro-compounds by using 1,3-dibromo-5,5-dimethylhydantoin (DBH) or NBS with the presence of nucleophilic fluorine source PPHF in good yields.[37] But here in these procedures, electrophilic ring bromination has occurred in case of electron rich aromatic systems and gave side products.

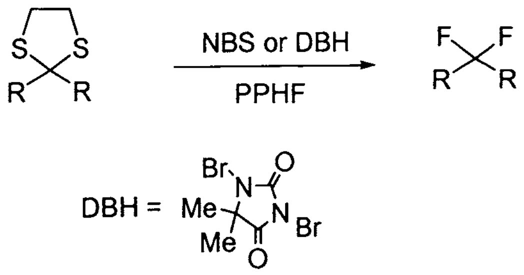

Figure 2.7: Conversion of dithiolanes to *gem*-difluoromethylene compounds using NBS/PPHF and DBH/PPHF

SO_2Cl_2 and SO_2ClF have been used as an alternative to the NBS as a source of electrophilic species in this transformation to facilitate the work up of the reaction, as the only byproducts of the reaction are the volatile SO_2 and HCl.[38] Nitrosonium tetrafluoroborate in the combination with PPHF has also been used for this transformation.[39] The desulfurative fluorination of dithiolanes was also done by using 1-diethylamino-1,1,2,2,3,3-hexafluoropropane in the presence of DBH as a source of electrophilic "Br^+".[40] 1-Diethylamino-1,1,2,2,3,3-hexafluoropropane releases HF on reaction with water and thus acts as nucleophilic fluoride ion source in this reaction. BrF_3 is also an effective reagent to bring about the transformation of dithiolanes to *gem*-difluoro compounds.[41-43]

2.4.4 NMR spectra of products:

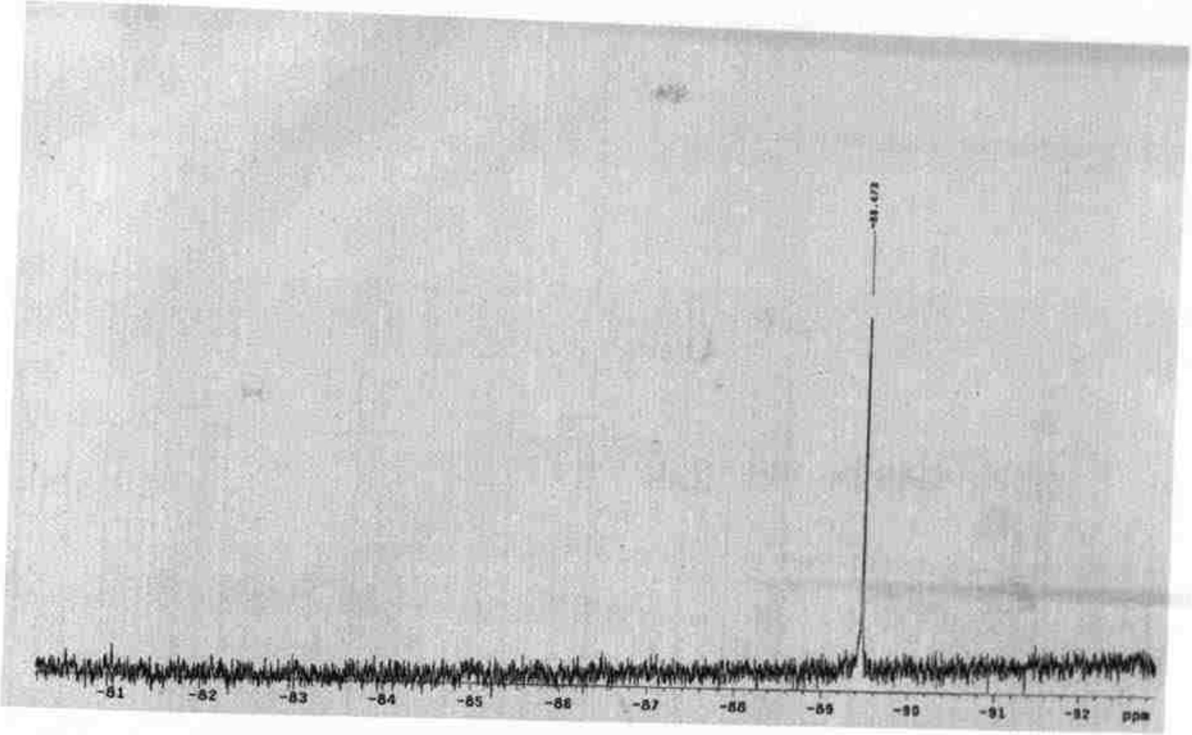

Figure 2.27: ^{19}F NMR spectra of compound **2.10**

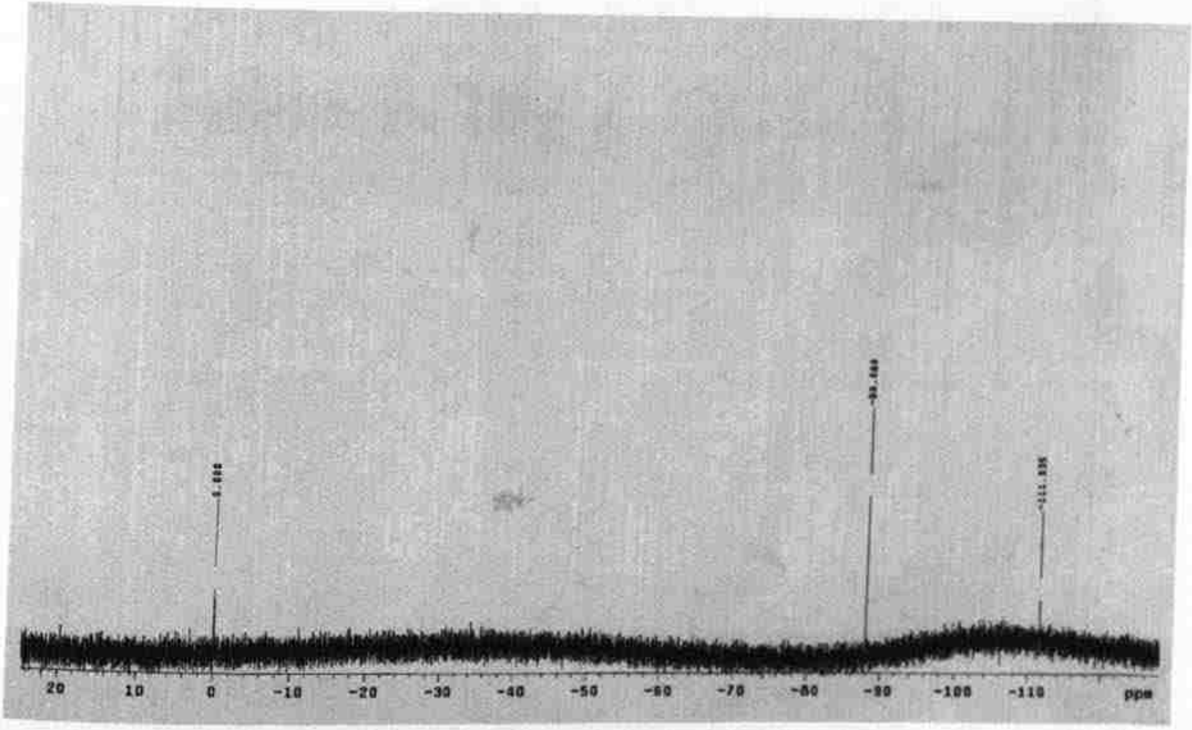

Figure 2.28: ^{19}F NMR spectra of compound **2.11**

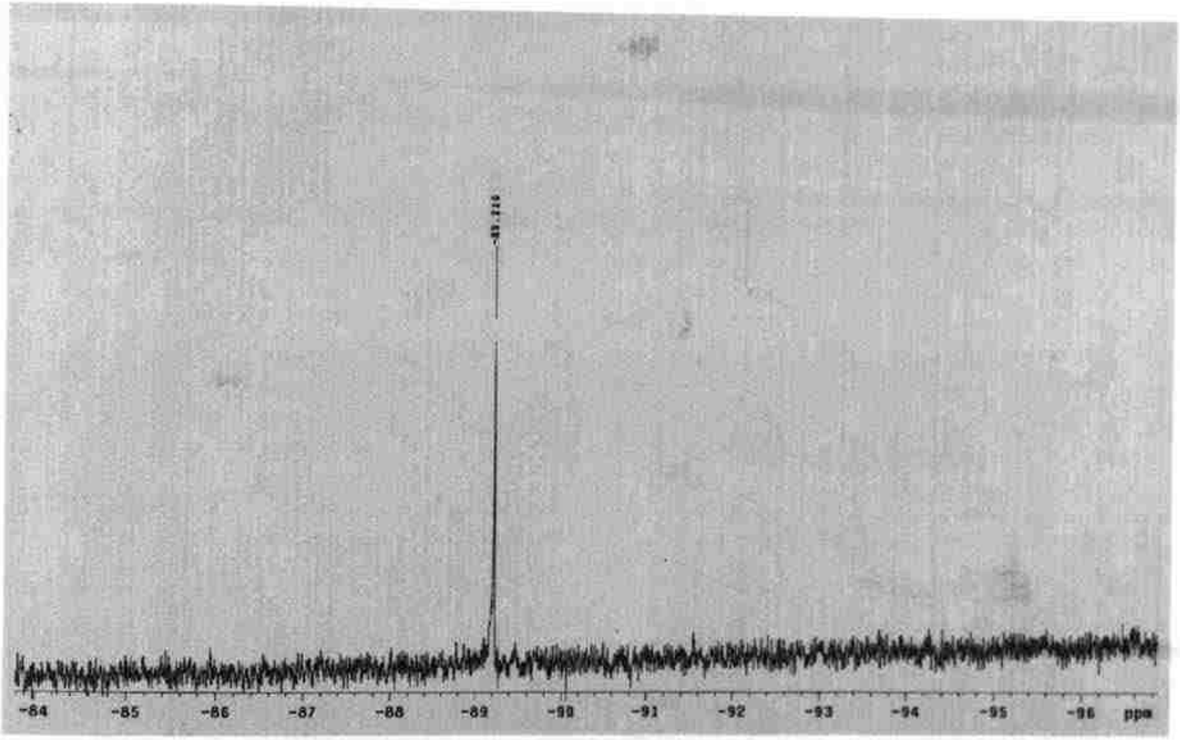

Figure 2.29: ^{19}F NMR spectra of compound **2.12**

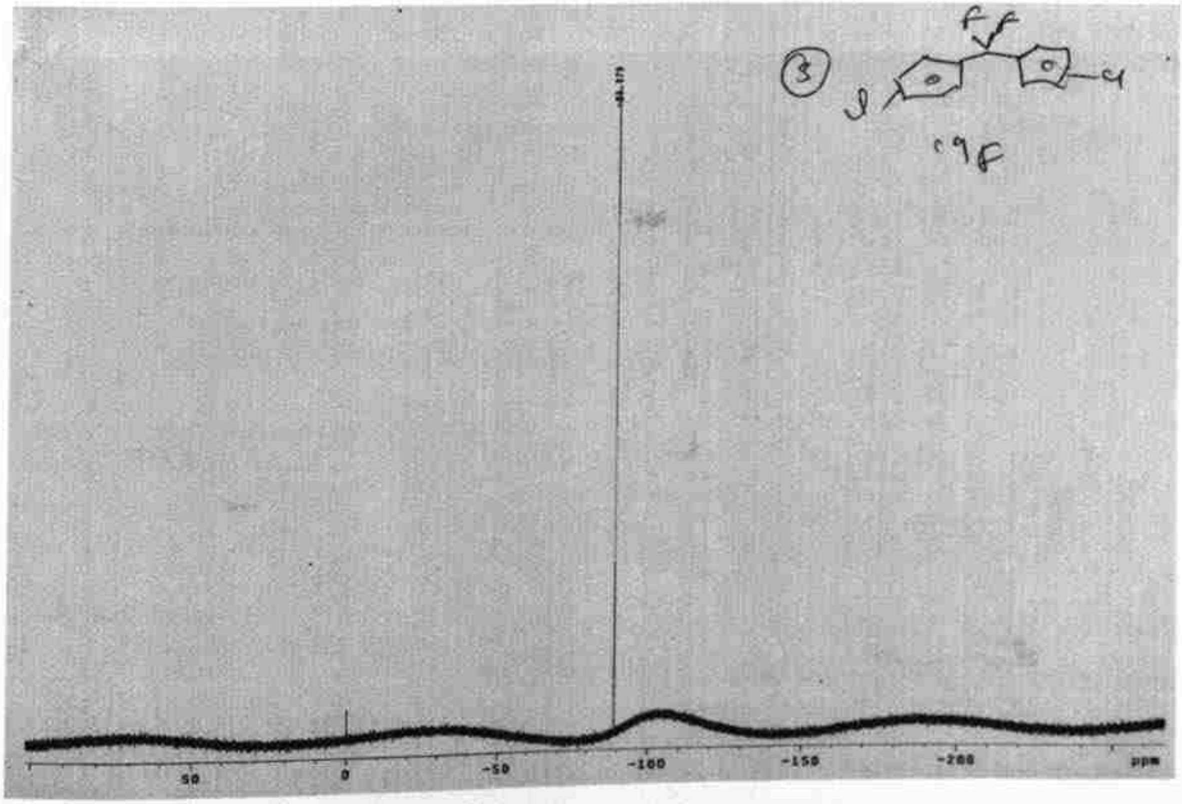

Figure 2.30: ^{19}F NMR spectra of compound **2.13**

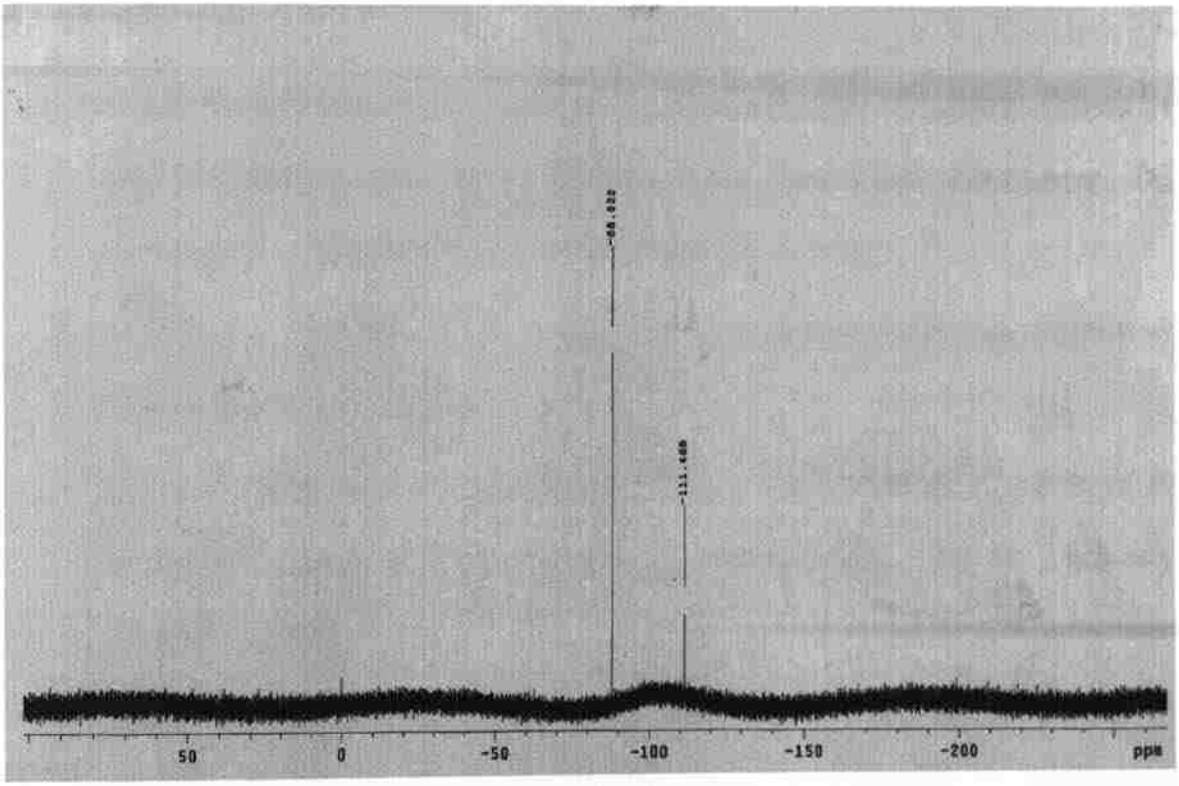

Figure 2.31: ^{19}F NMR spectra of compound **2.14**

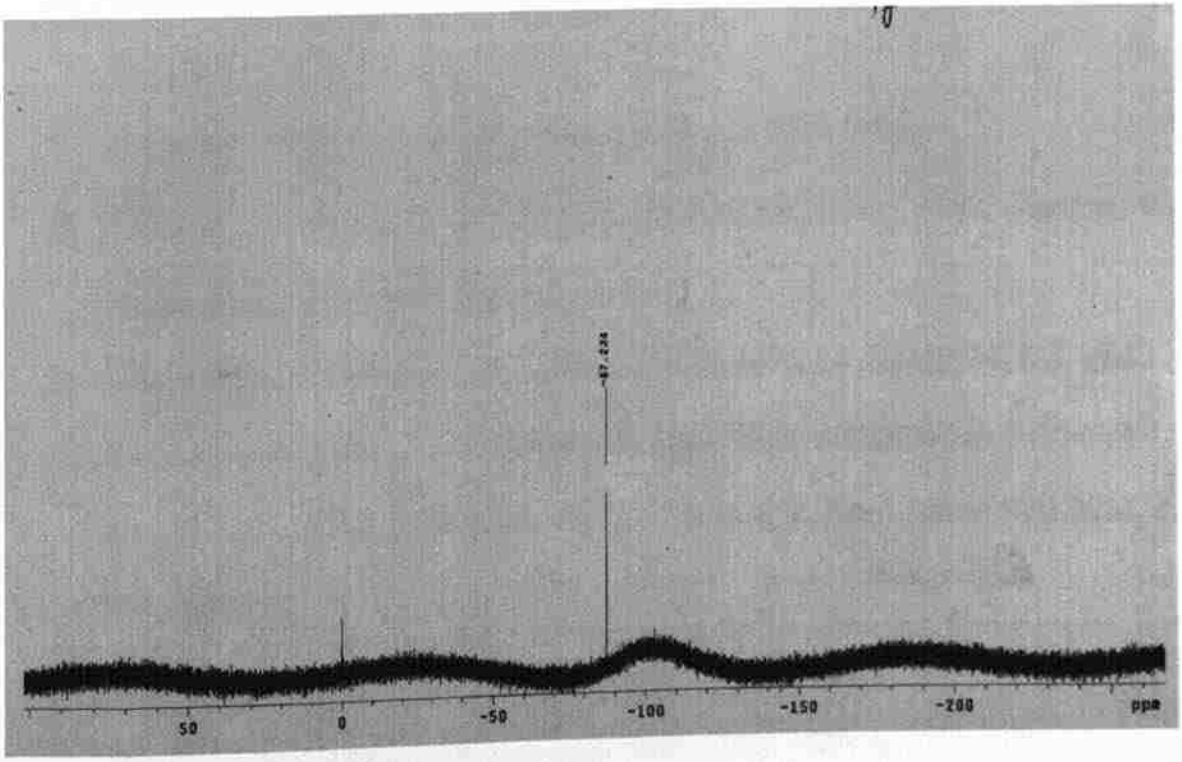

Figure 2.32: ^{19}F NMR spectra of compound **2.15**

3.4.6 NMR spectra of products:

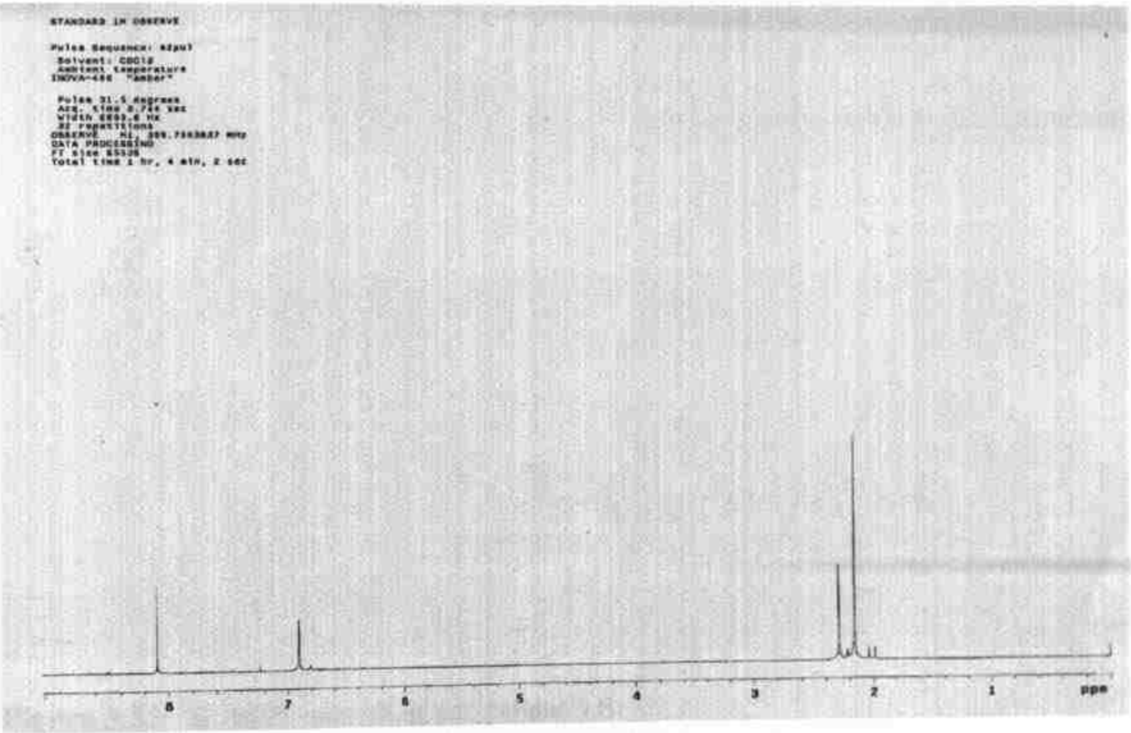

Figure 3.21: ^{1}H NMR spectra of compound **3.6**

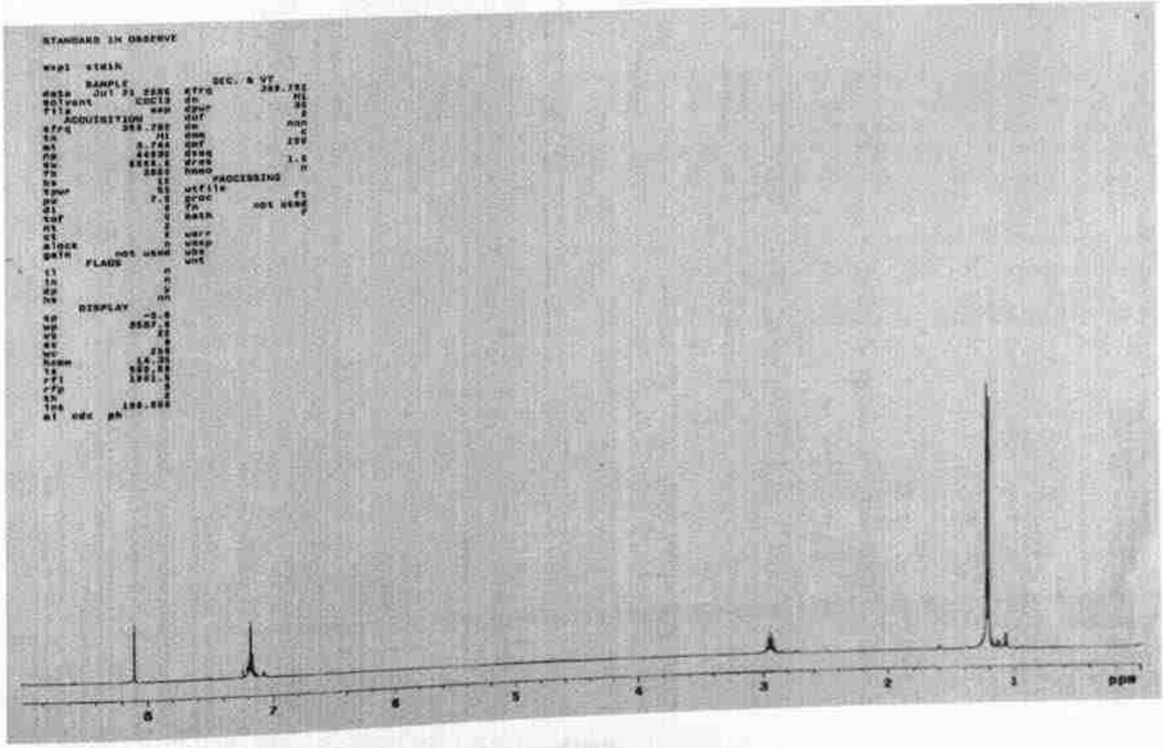

Figure 3.22: ^{1}H NMR spectra of compound **3.7**

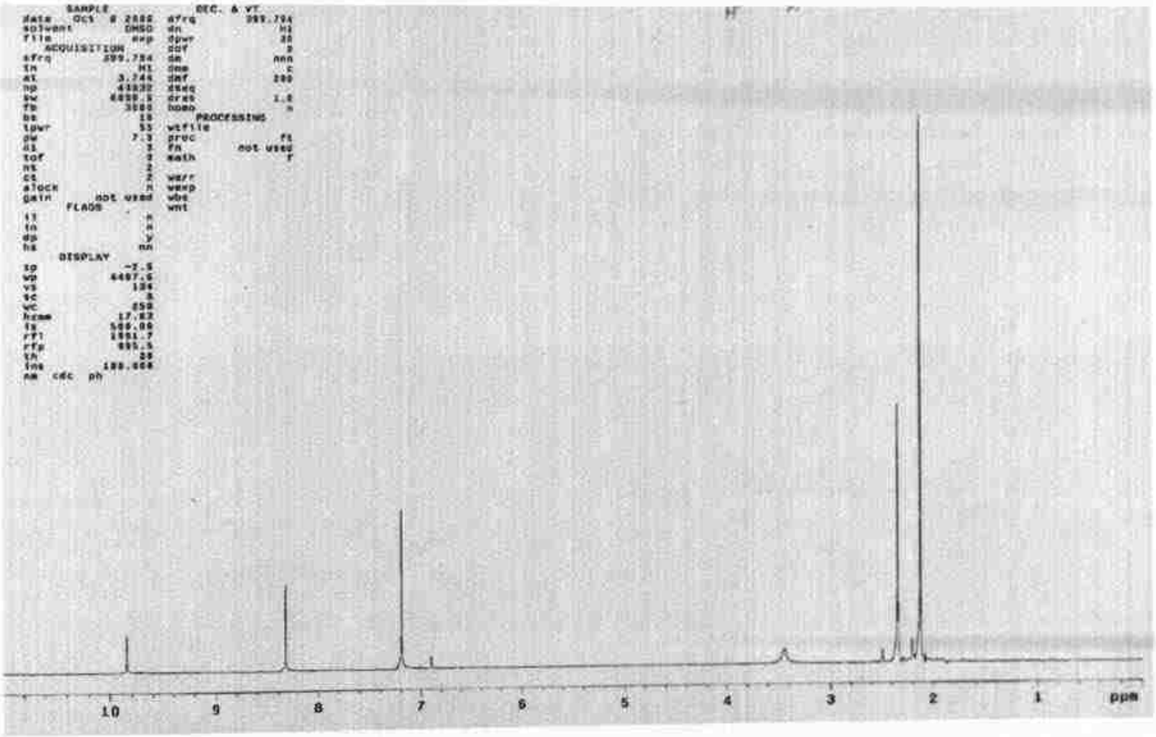

Figure 3.23: ^{1}H NMR spectra of compound **3.8**

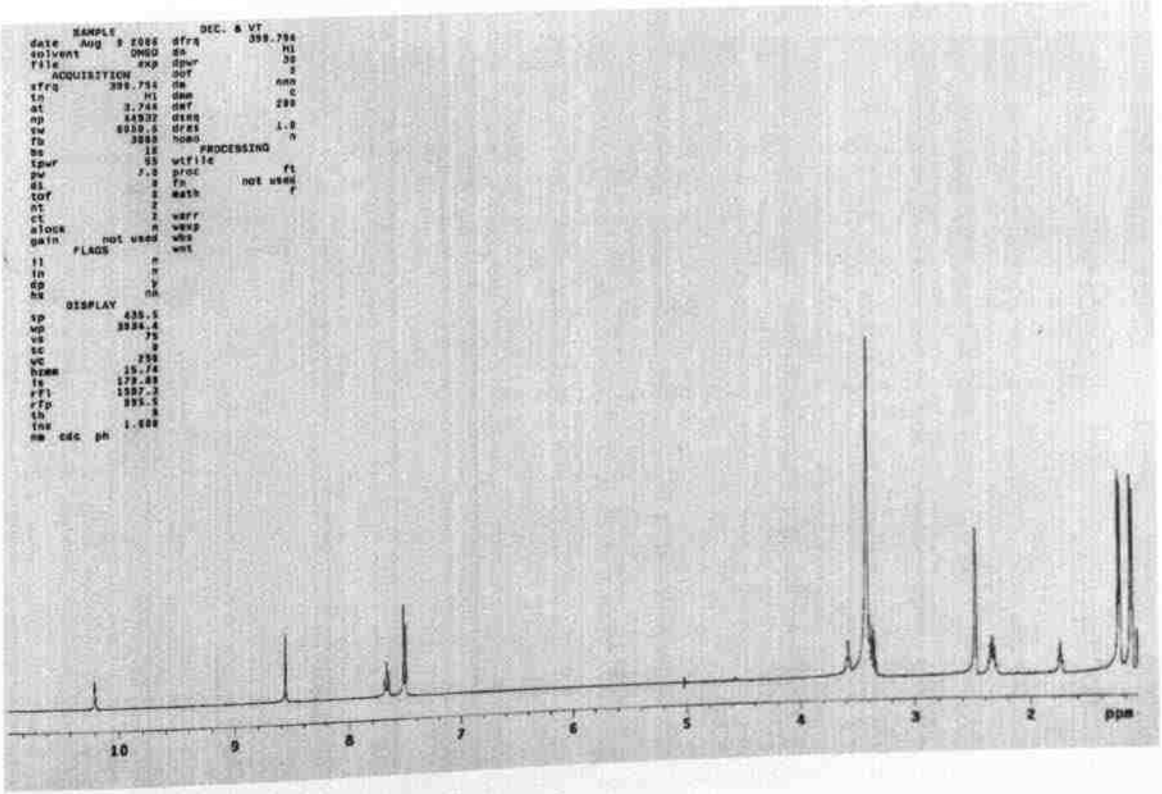

Figure 3.24: ^{1}H NMR spectra of compound **3.9**

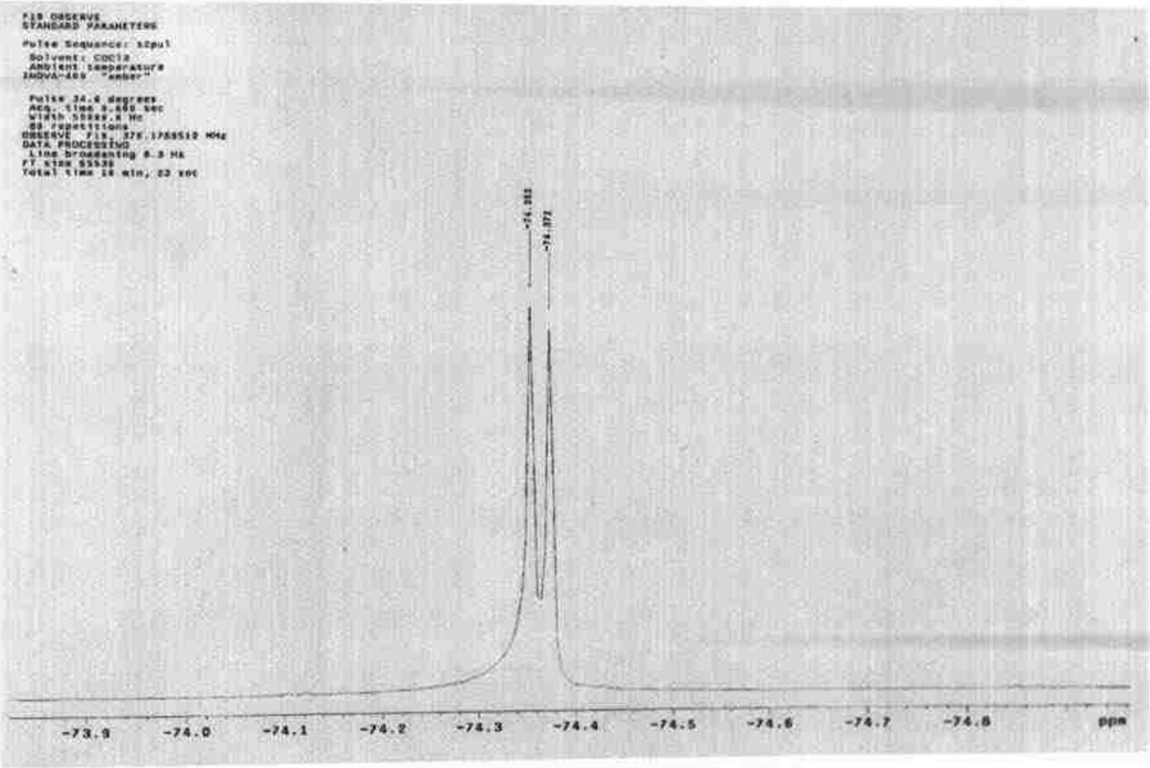

Figure 3.25: ^{19}F NMR spectra of compound **3.11**

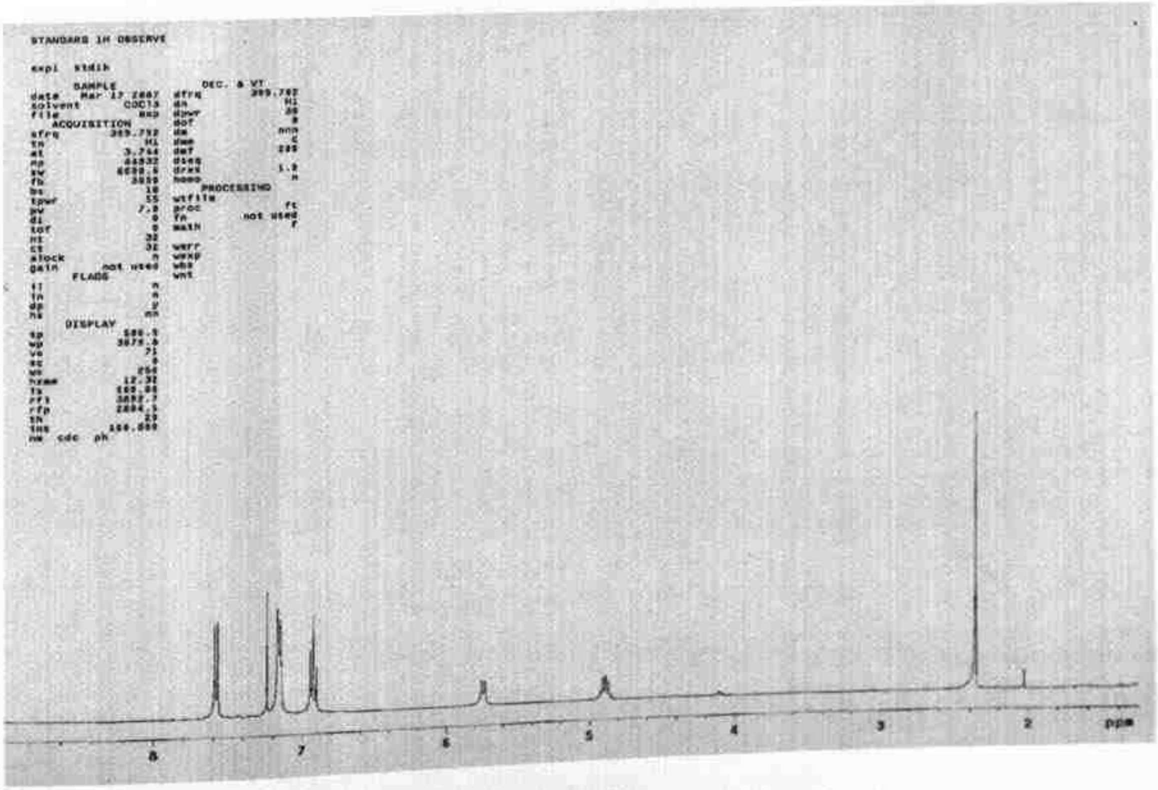

Figure 3.26: ^{1}H NMR spectra of compound **3.16**

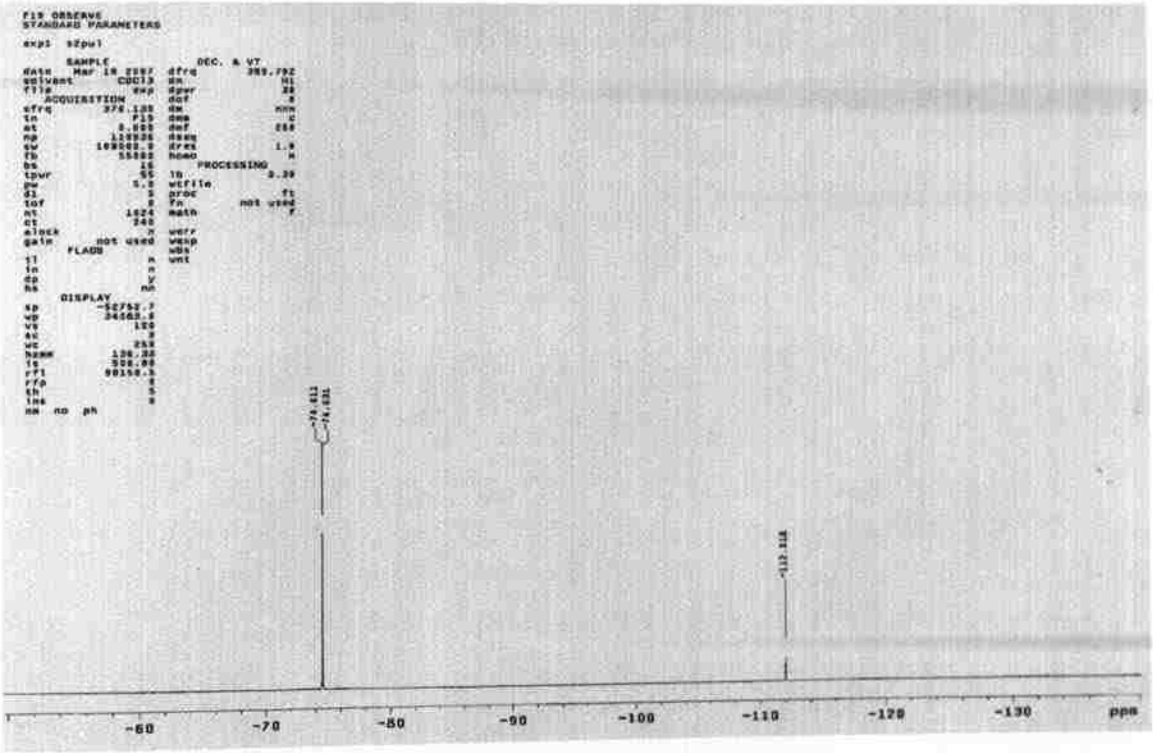

Figure 3.27: ^{19}F NMR spectra of compound **3.16**

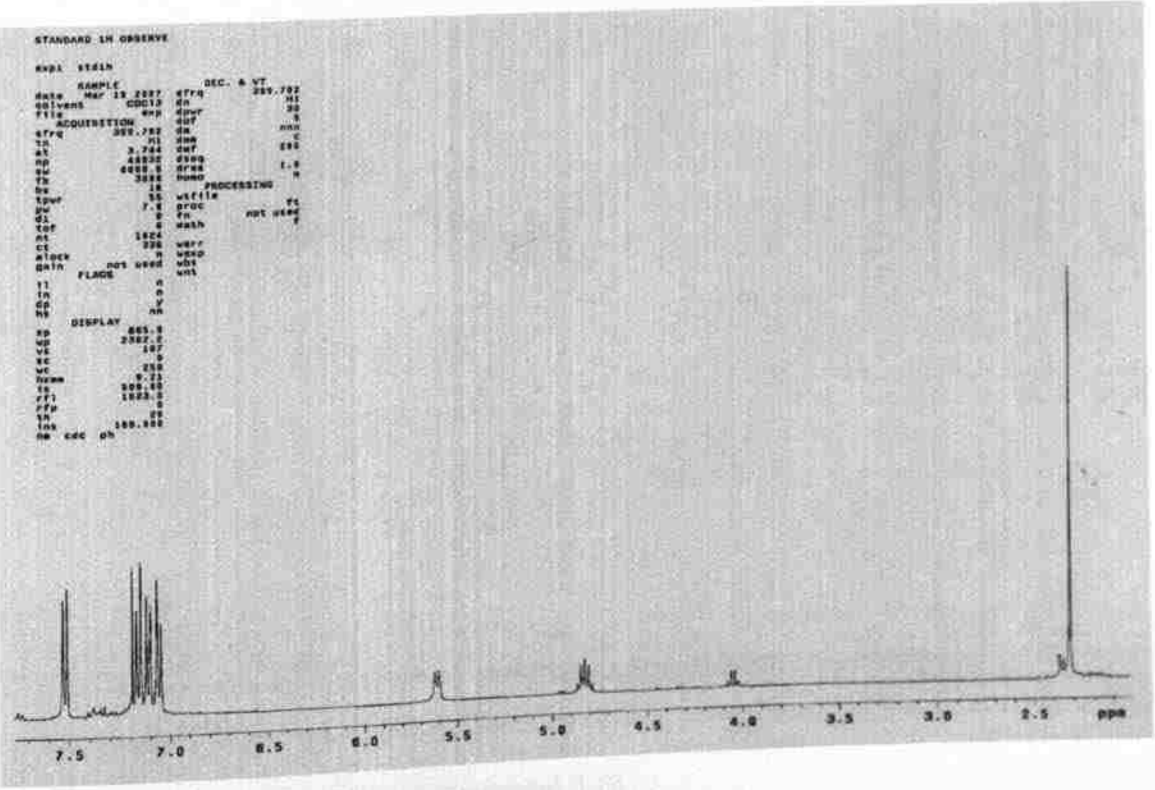

Figure 3.28: ^{1}H NMR spectra of compound **3.17**

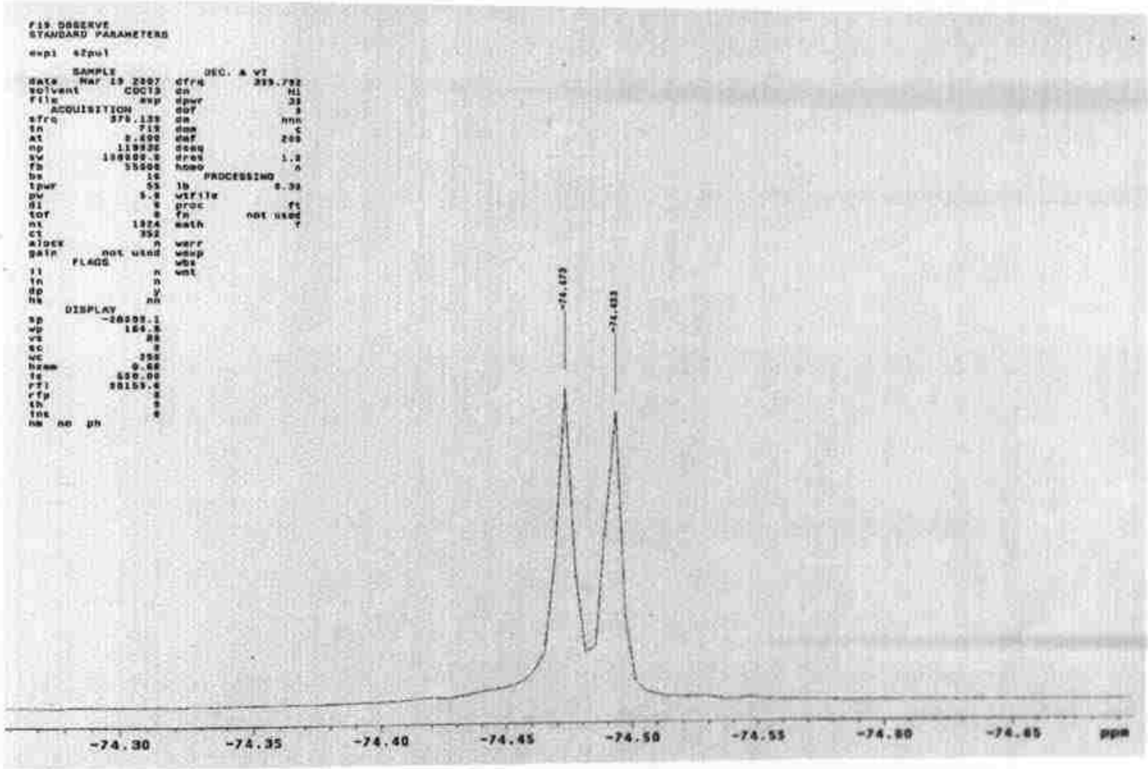

Figure 3.29: ^{19}F NMR spectra of compound **3.17**

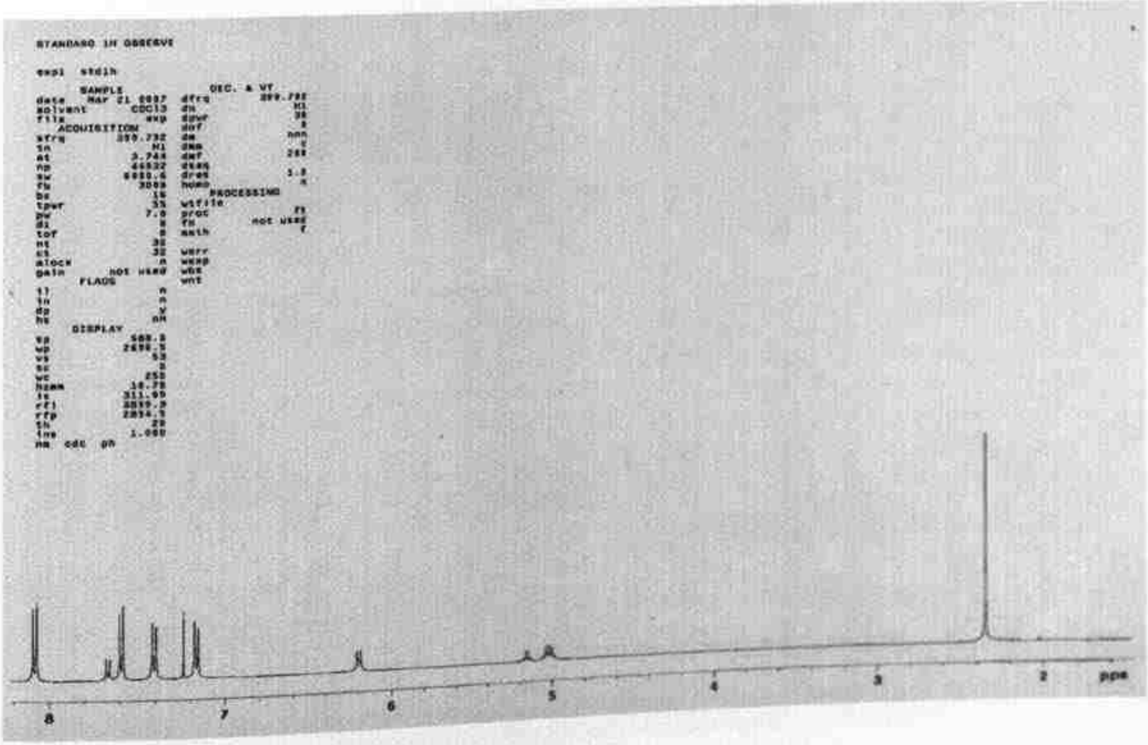

Figure 3.30: ^{1}H NMR spectra of compound **3.18**

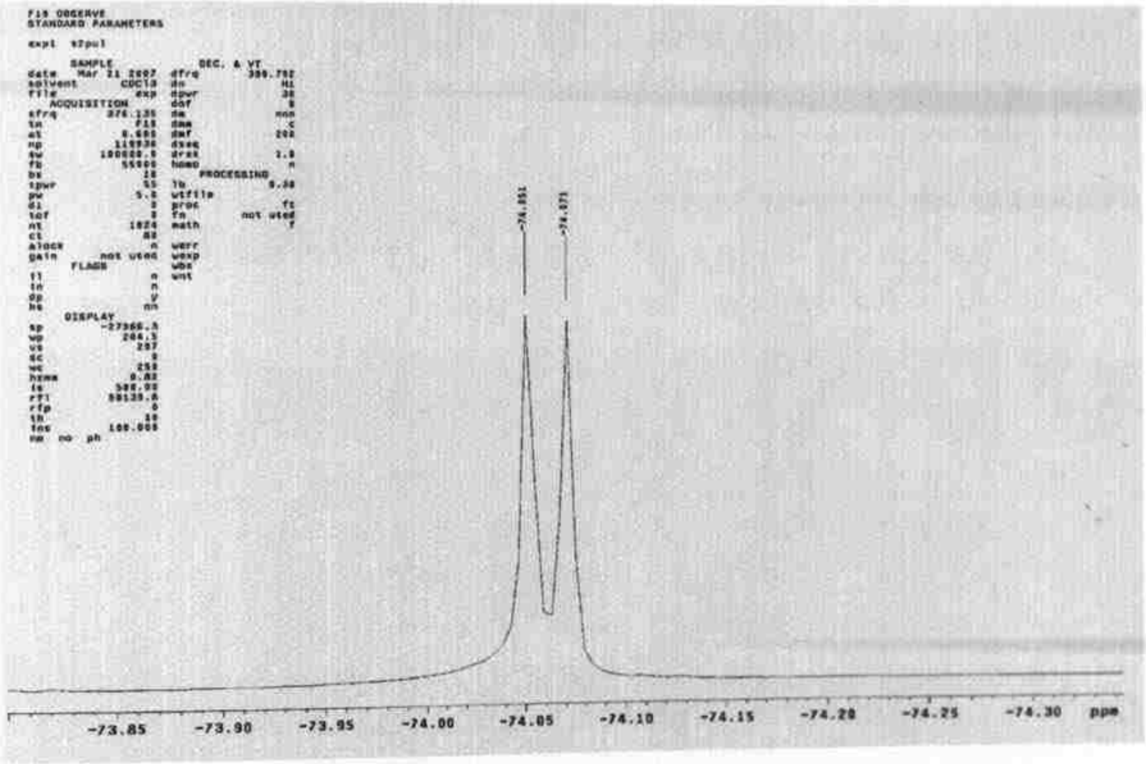

Figure 3.31: ^{19}F NMR spectra of compound **3.18**

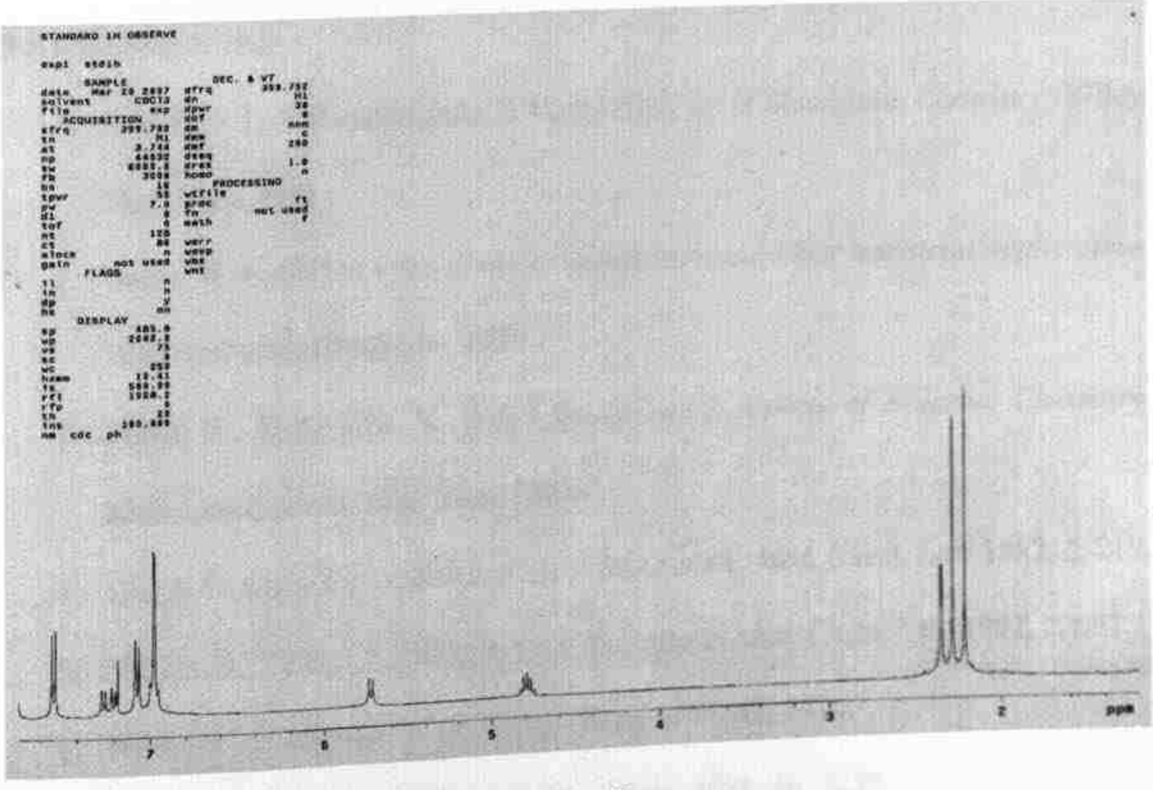

Figure 3.32: ^{1}H NMR spectra of compound **3.19**

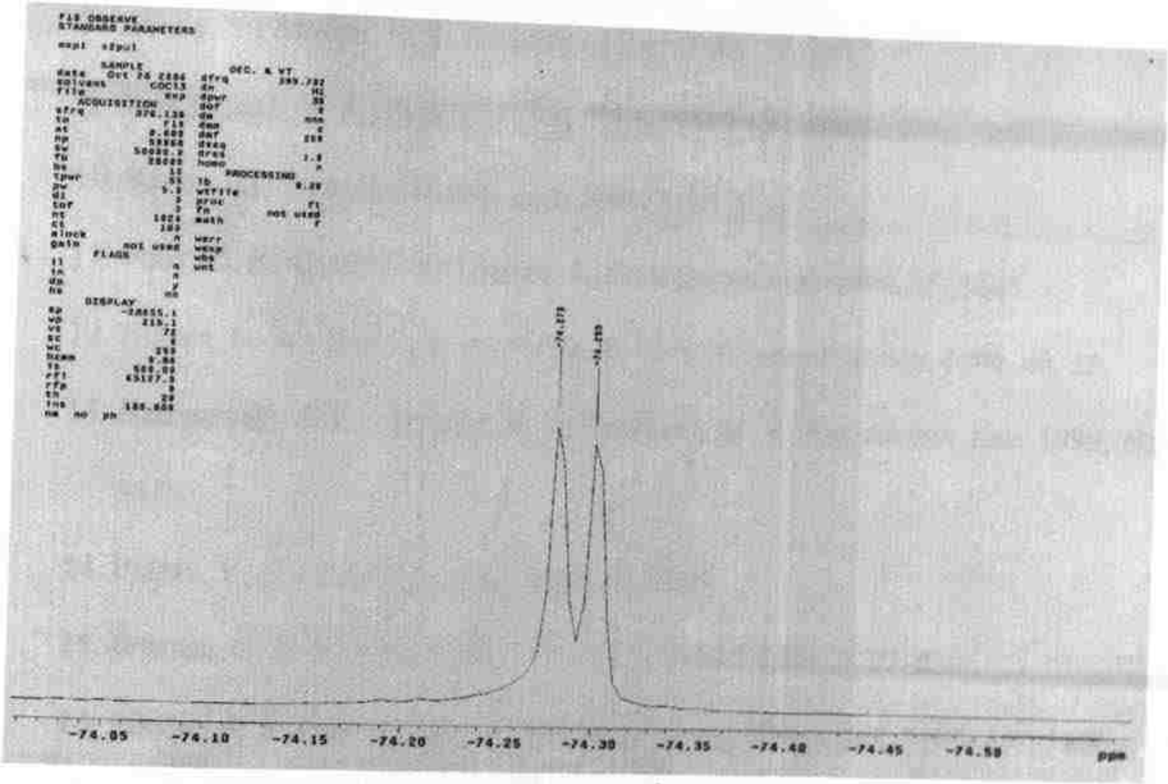

Figure 3.33: ^{19}F NMR spectra of compound **3.19**

3.5 REFERENCES

1. Welch, J. T.; Eshwarakrishna, S. (Eds.) *Fluorine in Bioorganic Chemistry;* Wiley: New York, **1991**.
2. Banks, R. E. (ED.) *Organofluorine Compounds and Their Industrial Applications*, Ellis Horwood: Chichester, **1979**.
3. Filler, R.; Kobayashi, Y. (Eds.) *Biomedicinal Aspects of Fluorine Chemistry*, Kodansha Elsevier: New York, **1982**.
4. Ojima, I.; Kato, K.; Jameison, F. A. *J. Bioorganic. Med. Chem. Lett.* **1992**, 2, 219.
5. Shirlin, D.; Tarnus, C.; Baltzer, S. *J. Bioorganic. Med. Chem. Lett.* **1992**, 2, 651.
6. Pirkle, W. H.; Hanske, J. H. *J. Org. Chem.* **1977**, 42, 2436.
7. Pirkle, W. H.; Simmons, K. A. *J. Org. Chem.* **1981**, 46, 3239.