

New Journal of Chemistry

Electronic Supporting Information

Synthesis and Biological Evaluation of Benzimidazoles/1,3,5-Triazine-2,4-diamine Hybrid Compounds: A New Class of Multifunction Alzheimer Targeting Agents

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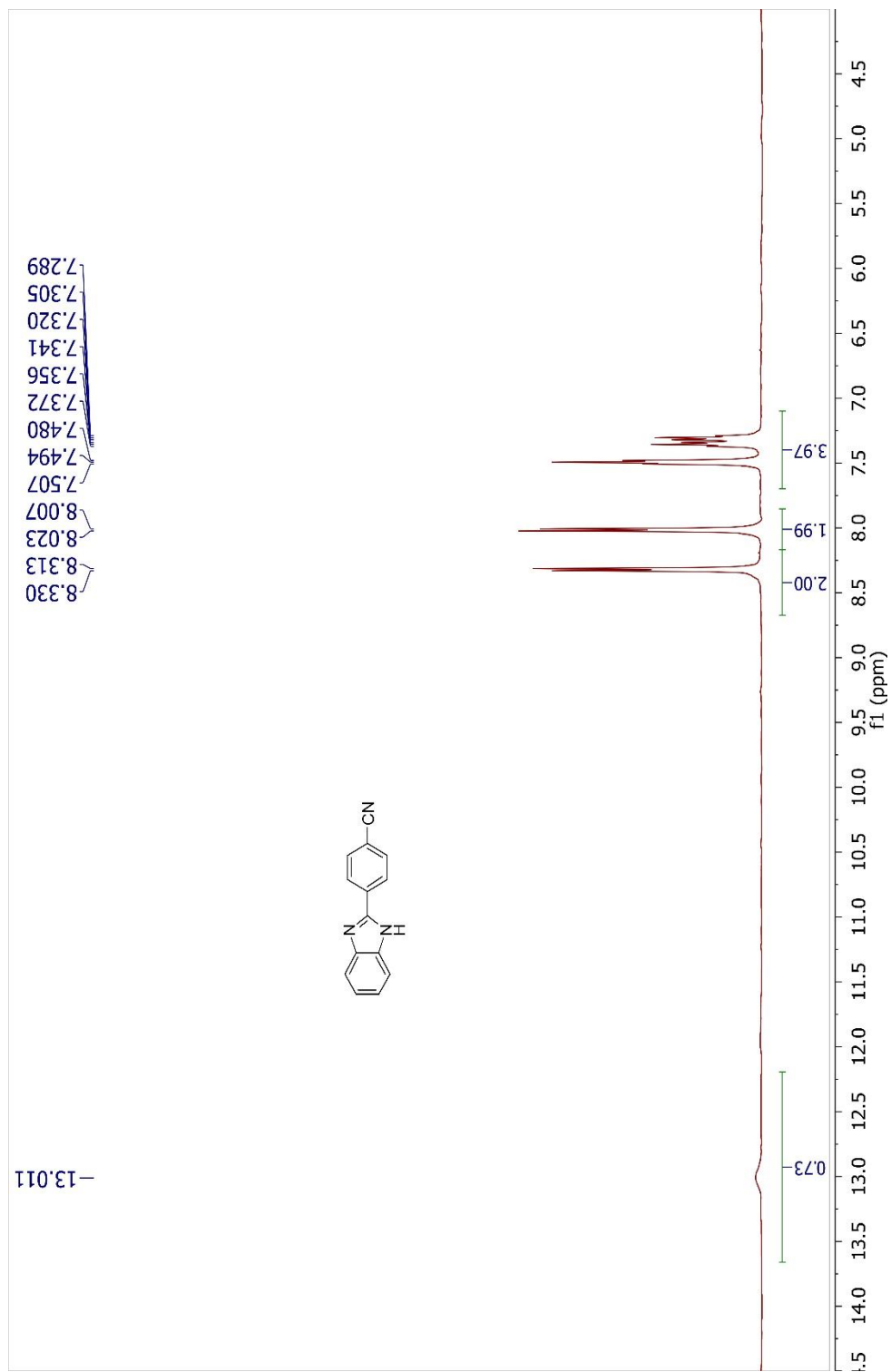


Figure 1. ¹H-NMR spectrum of compound (3)

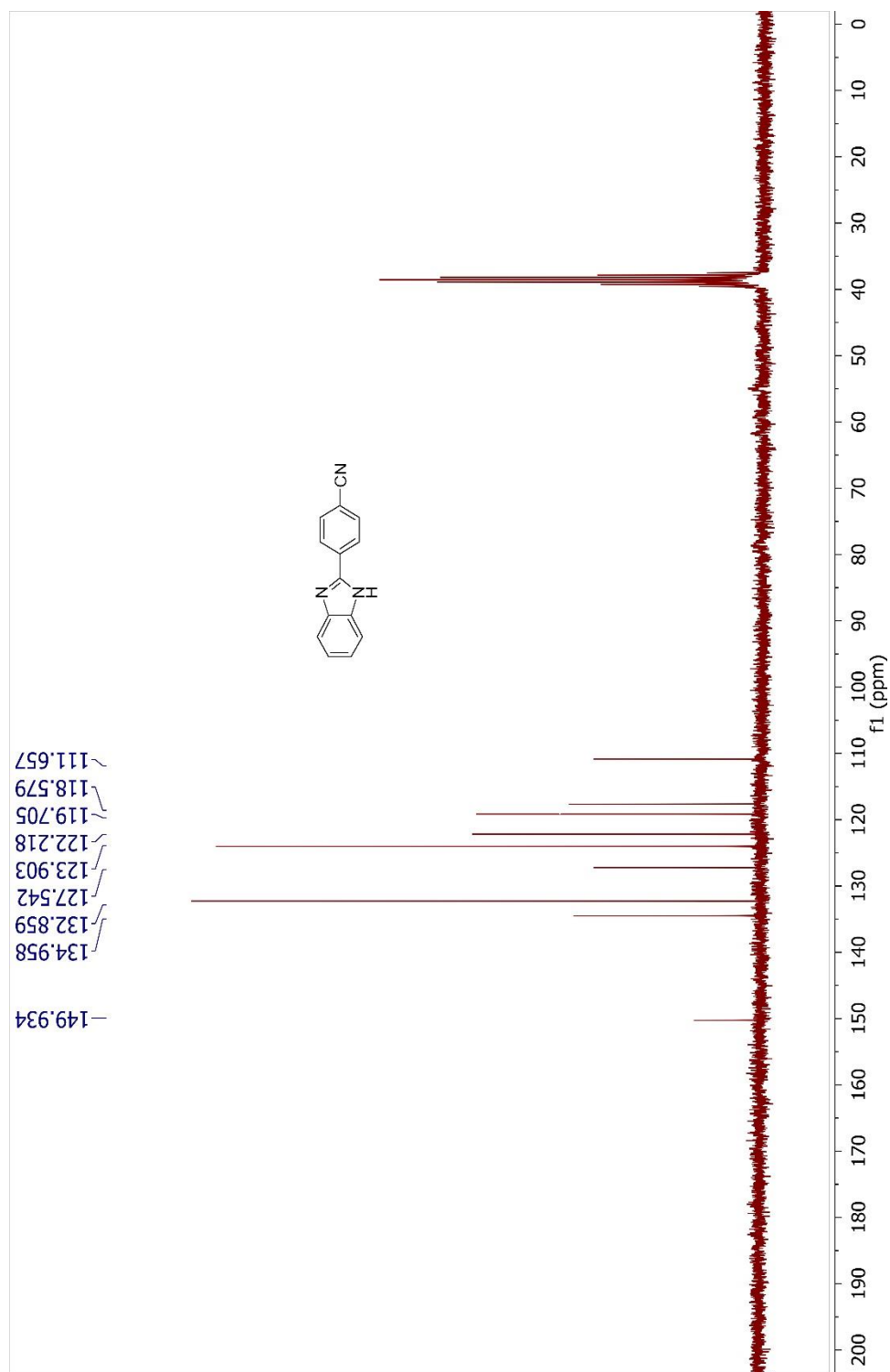


Figure 2. ^{13}C -NMR spectrum of compound (3)

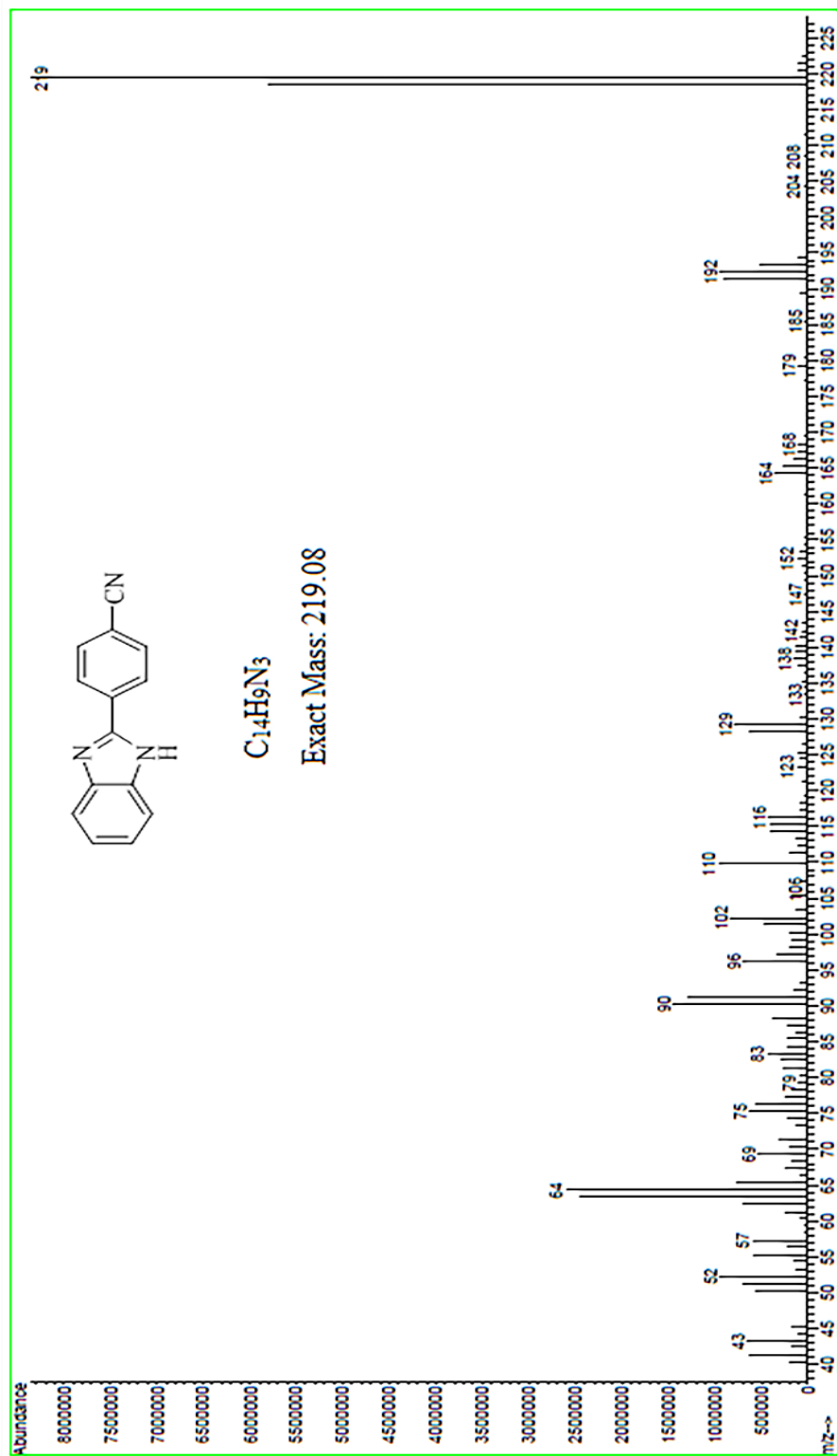


Figure 3. MASS spectrum of compound (3)

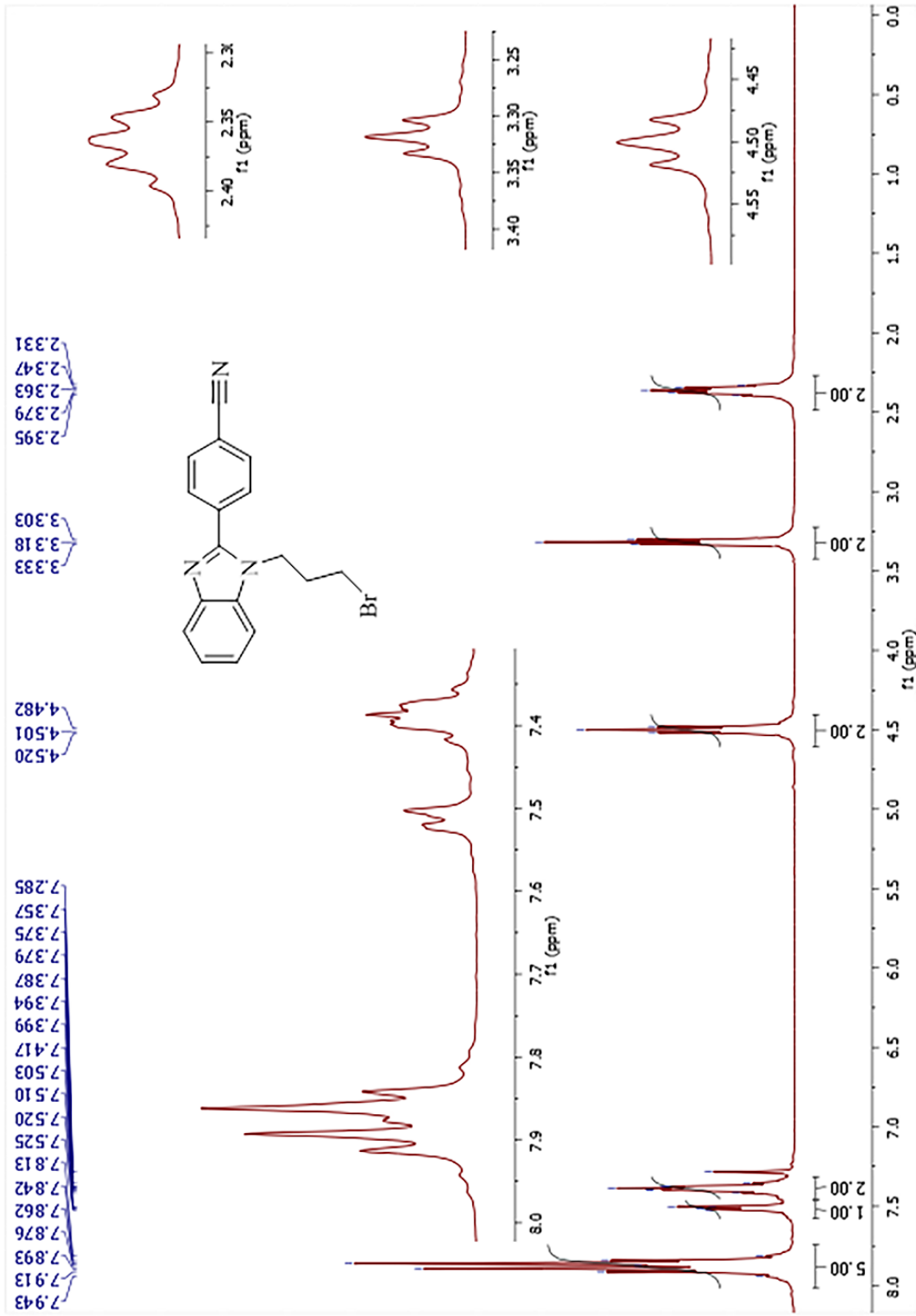


Figure 4. ¹H-NMR spectrum of compound (5a)

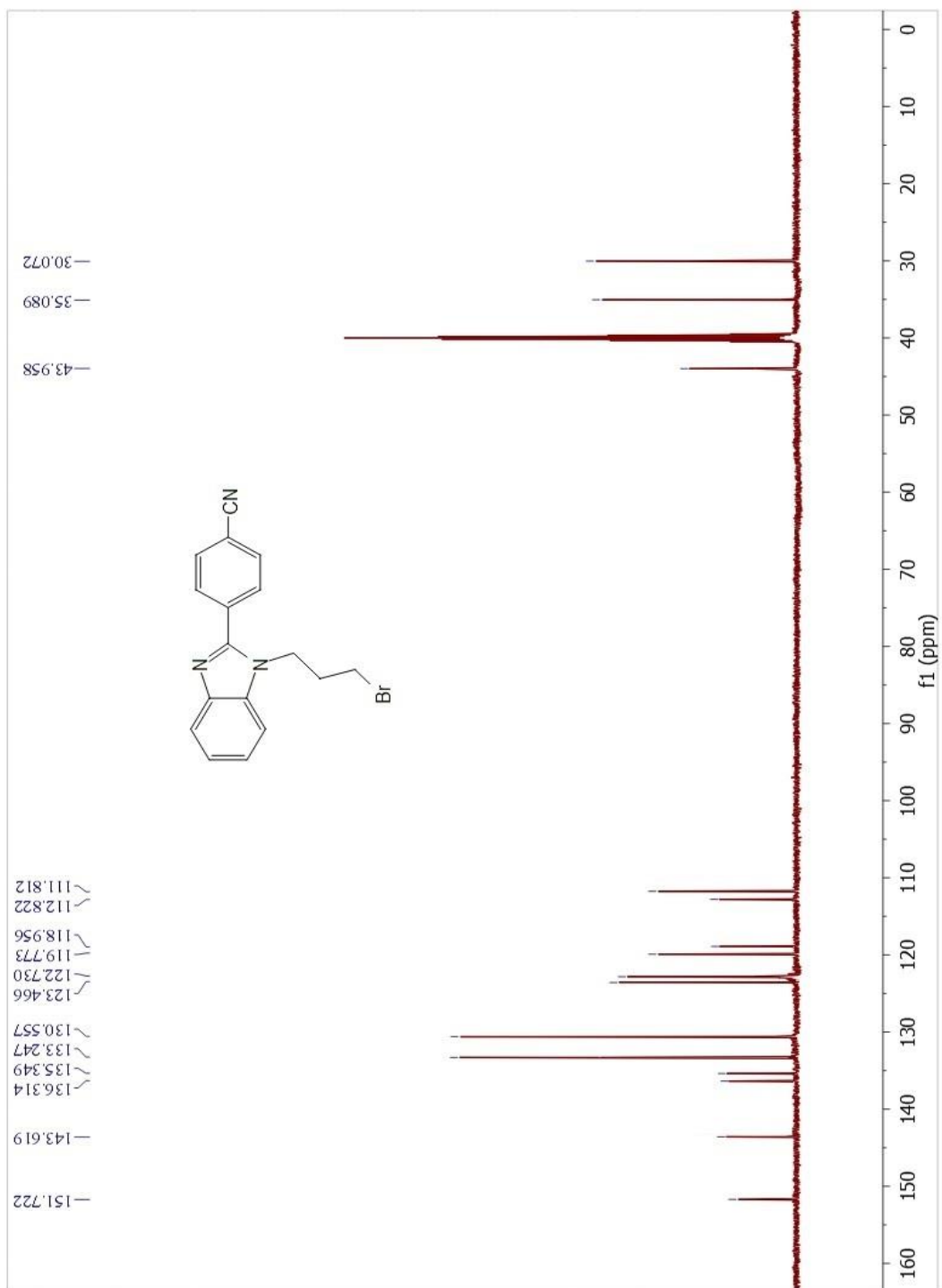


Figure 5. ^{13}C -NMR spectrum of compound (5a)

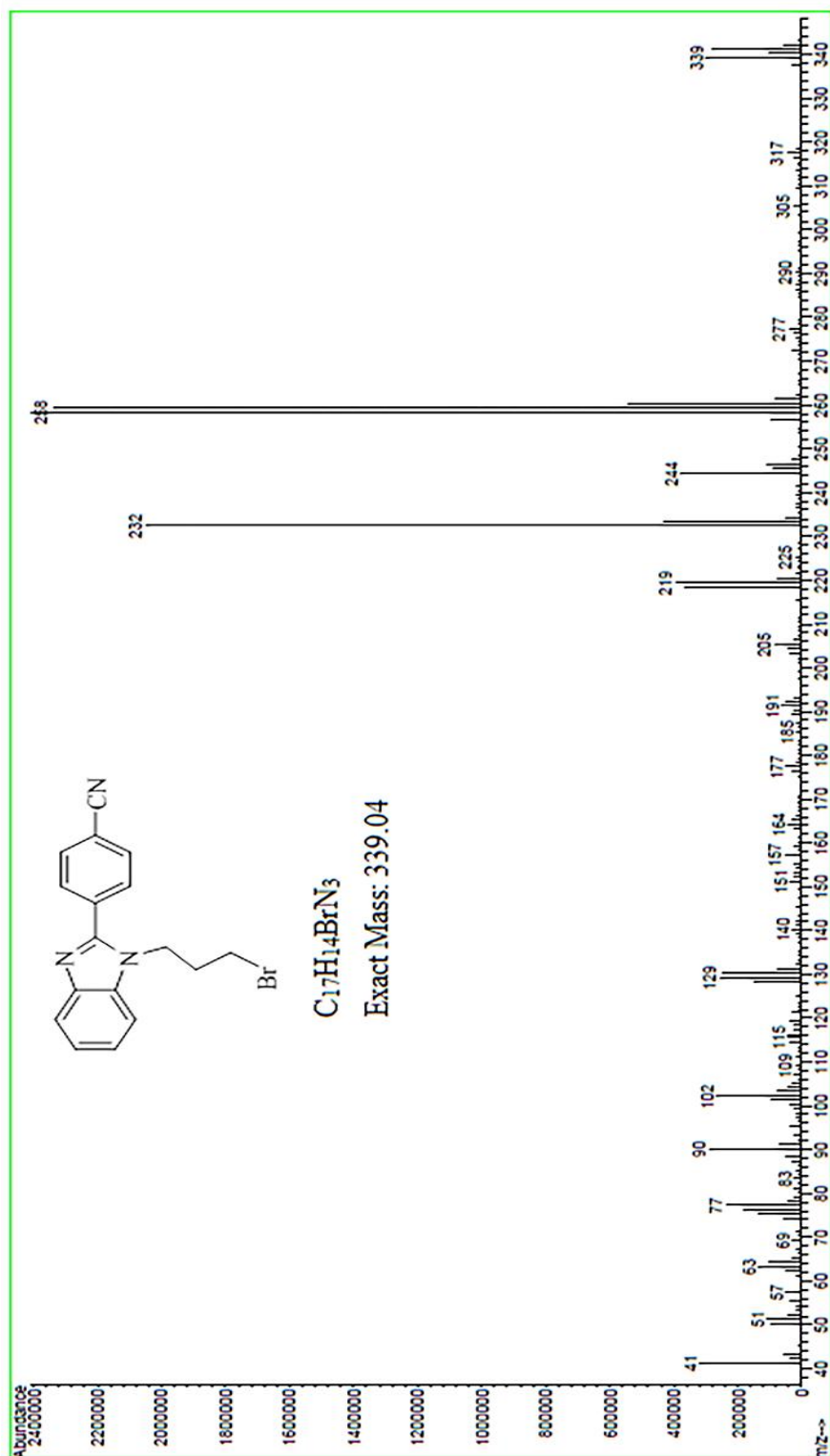


Figure 6. MASS spectrum of compound (5a)

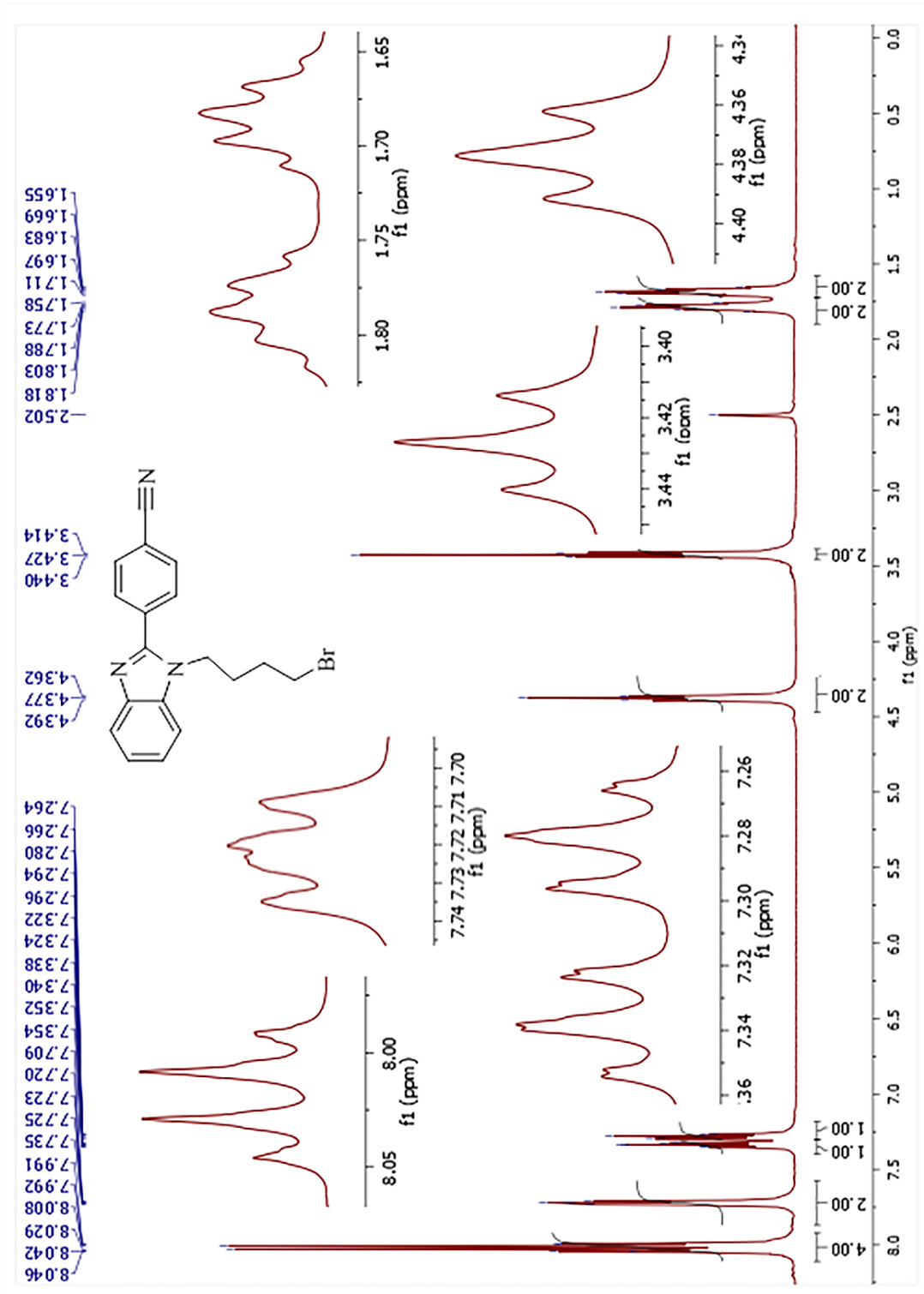


Figure 7. ¹H-NMR spectrum of compound (5b)

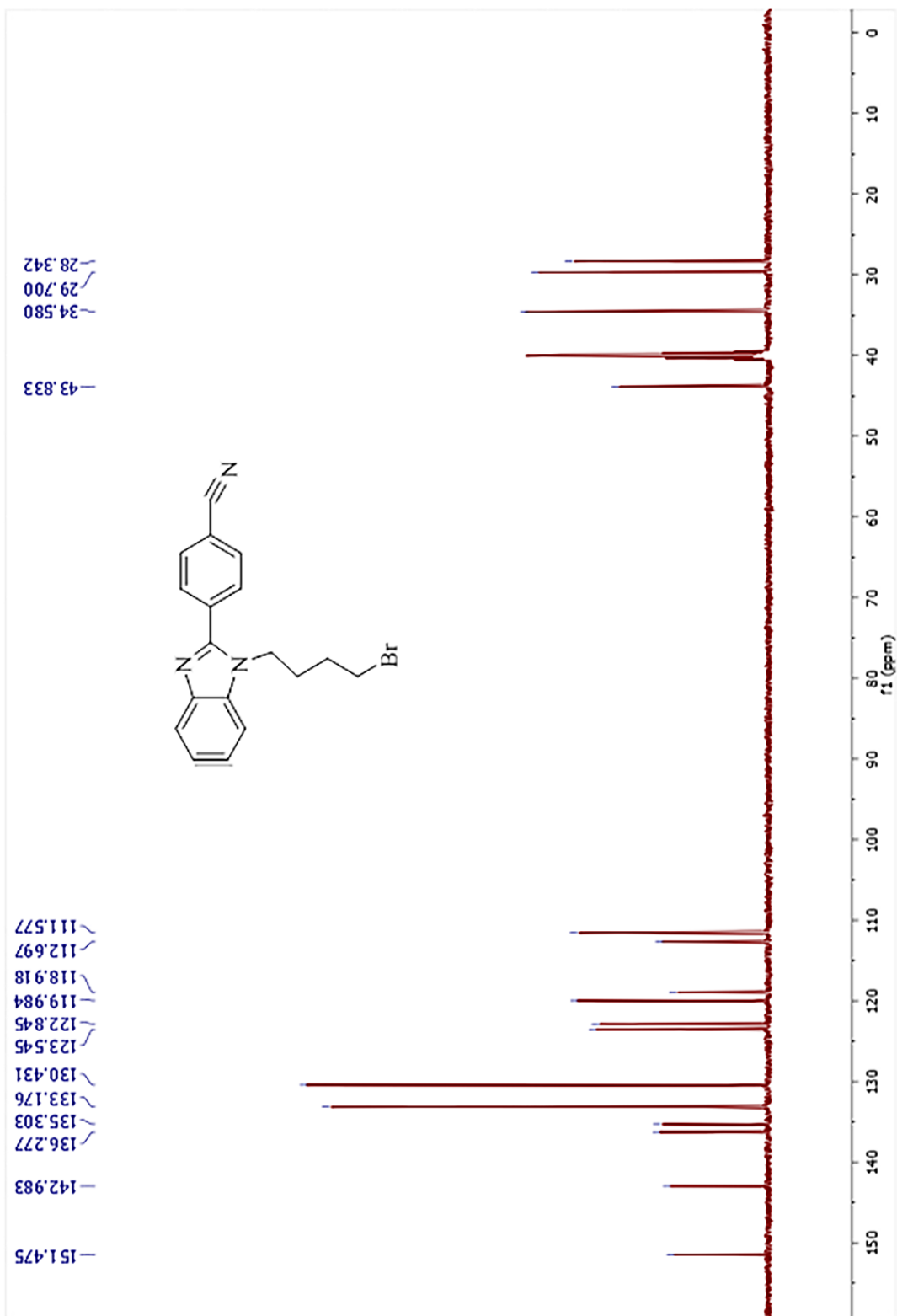


Figure 8. ^{13}C -NMR spectrum of compound (5b)

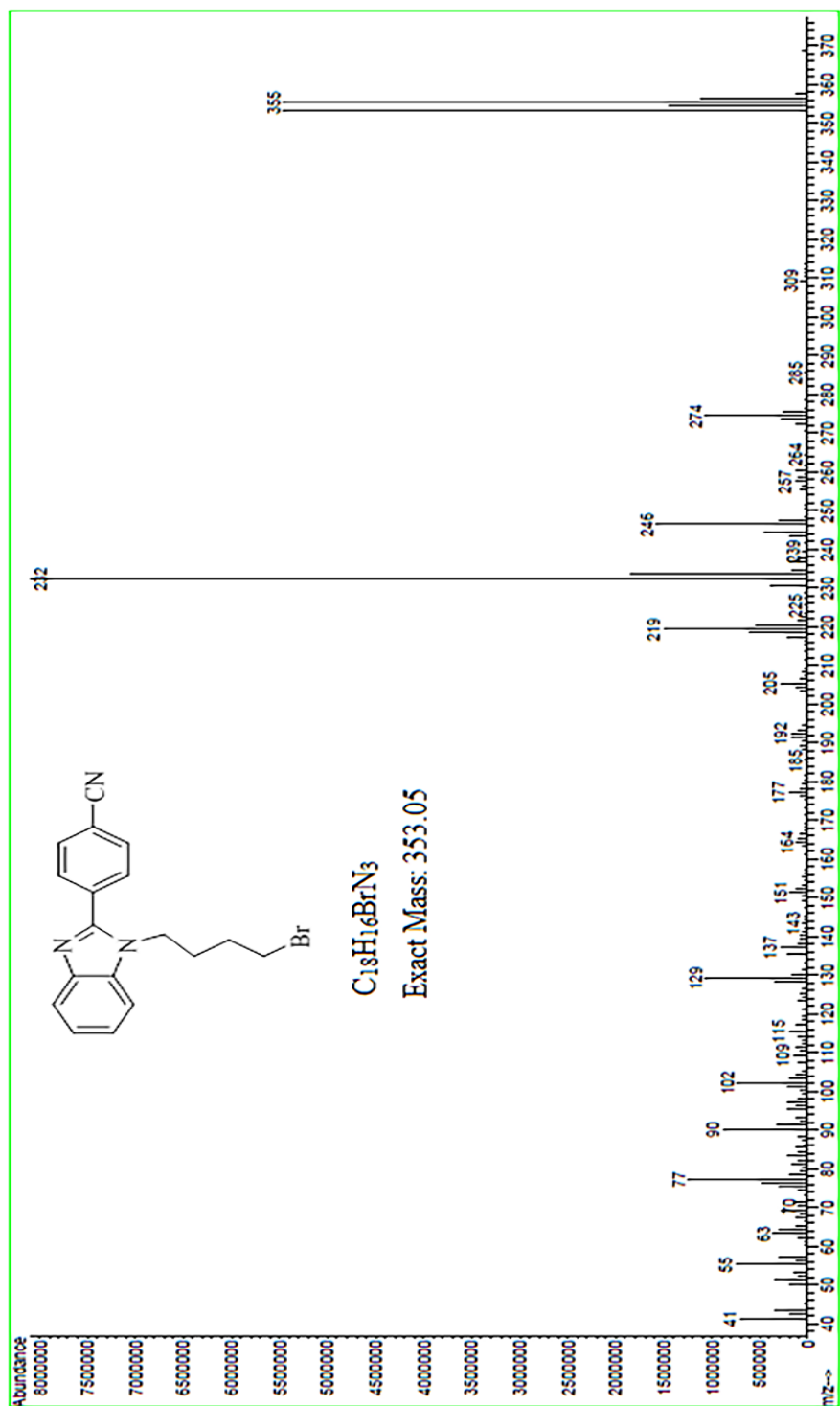


Figure 9. MASS spectrum of compound (5b)

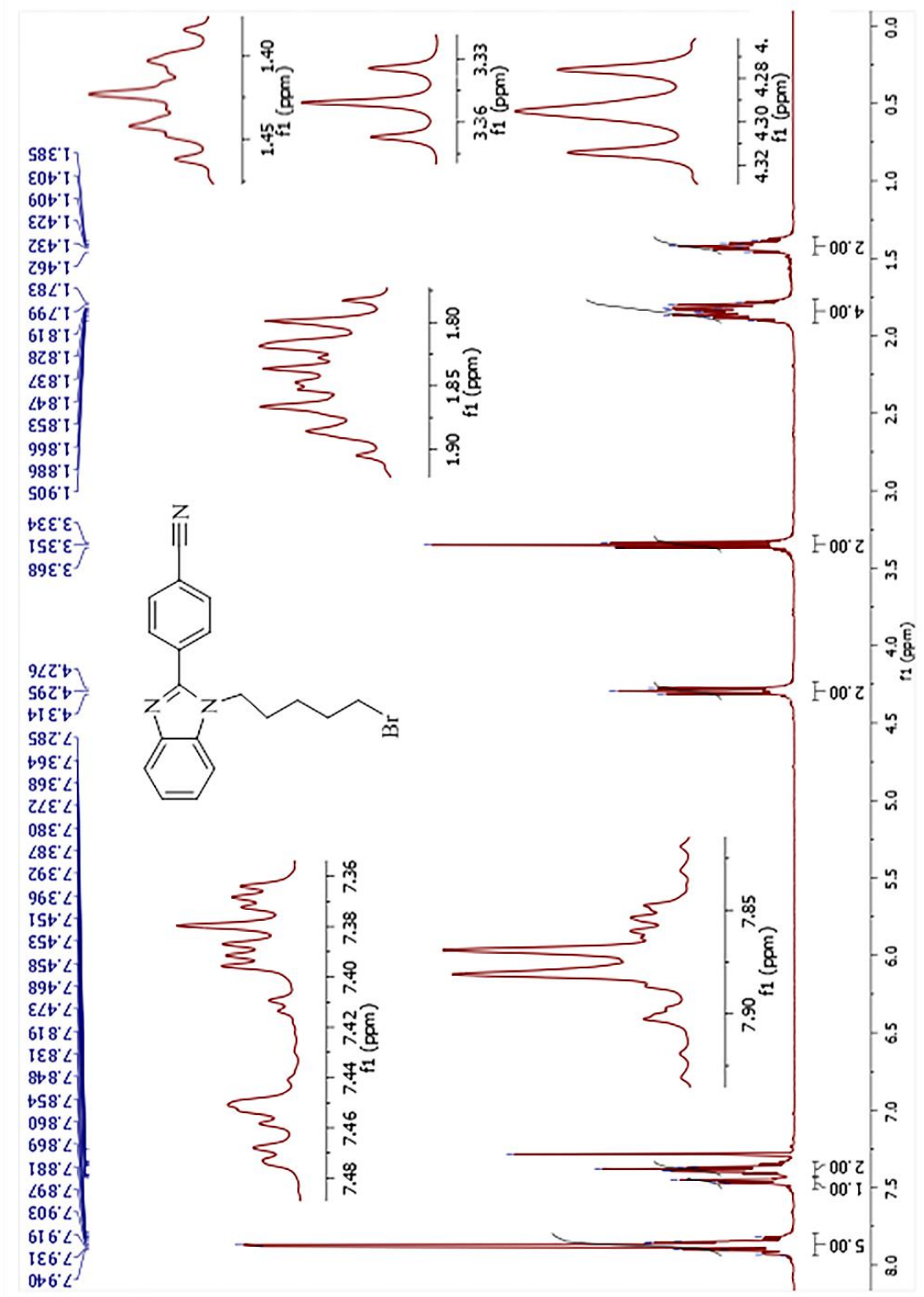


Figure 10. ¹H-NMR spectrum of compound (5c)

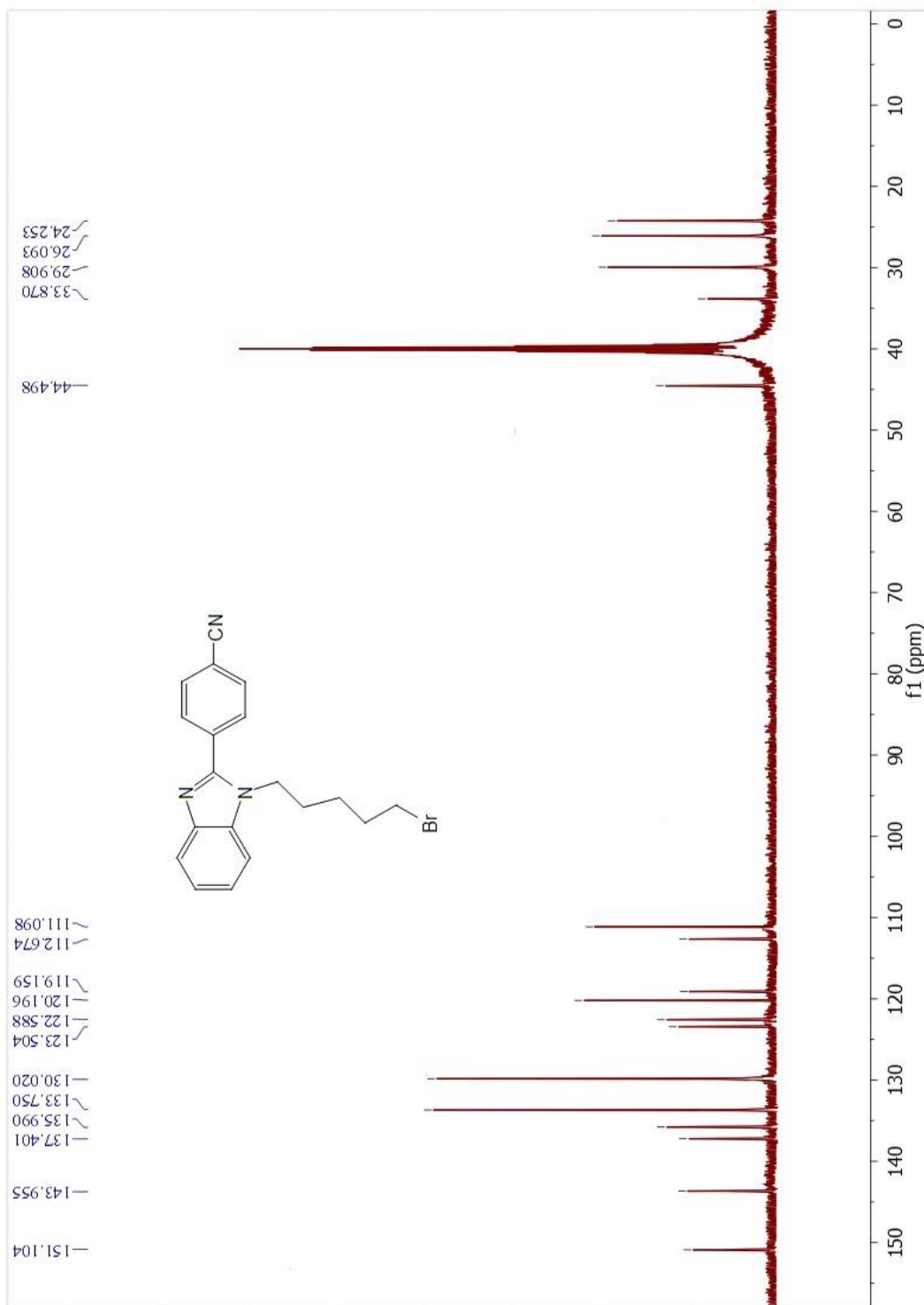


Figure 11. ^{13}C -NMR spectrum of compound (5c)

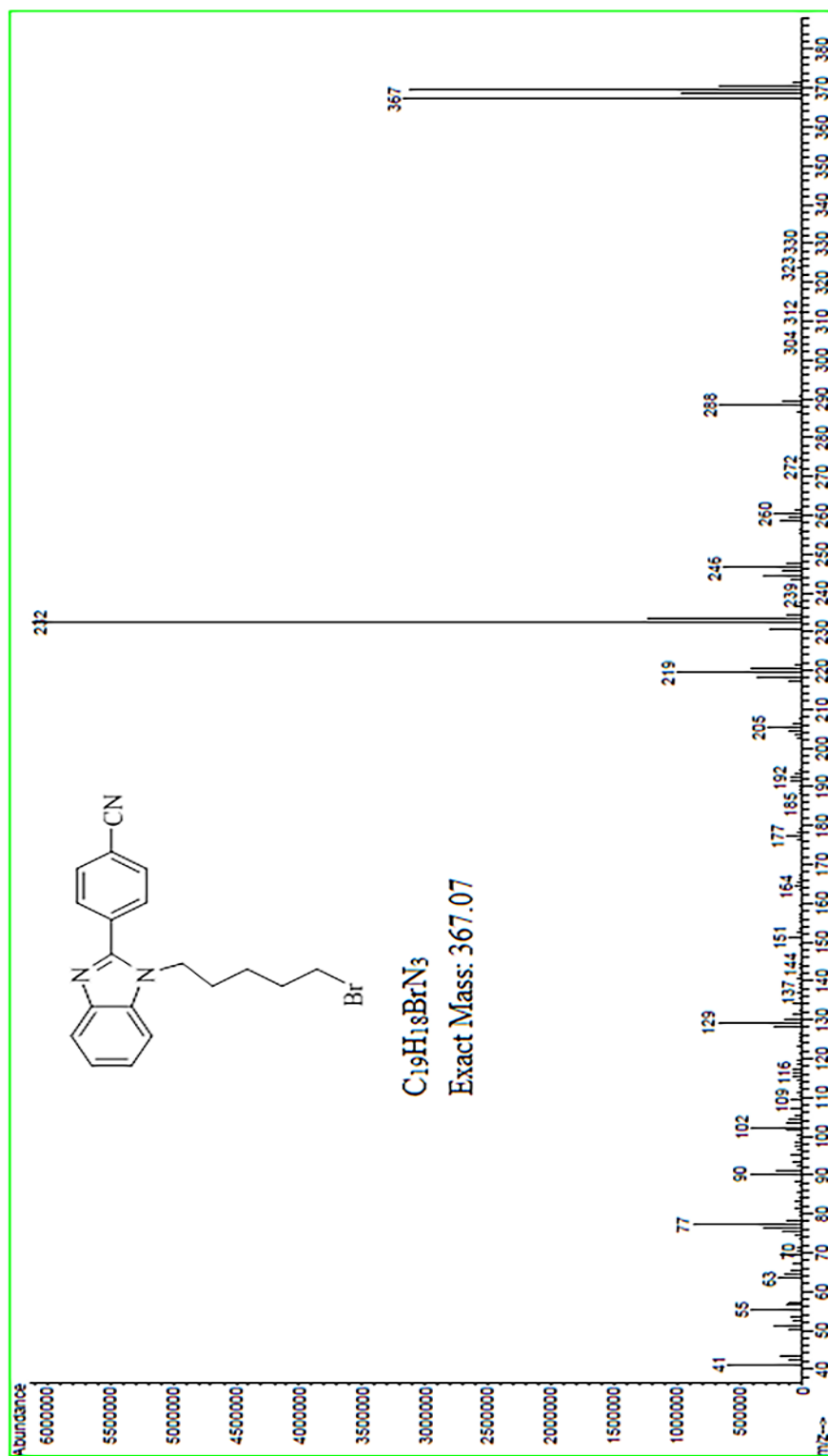


Figure 12.
MASS spectrum of compound (5c)

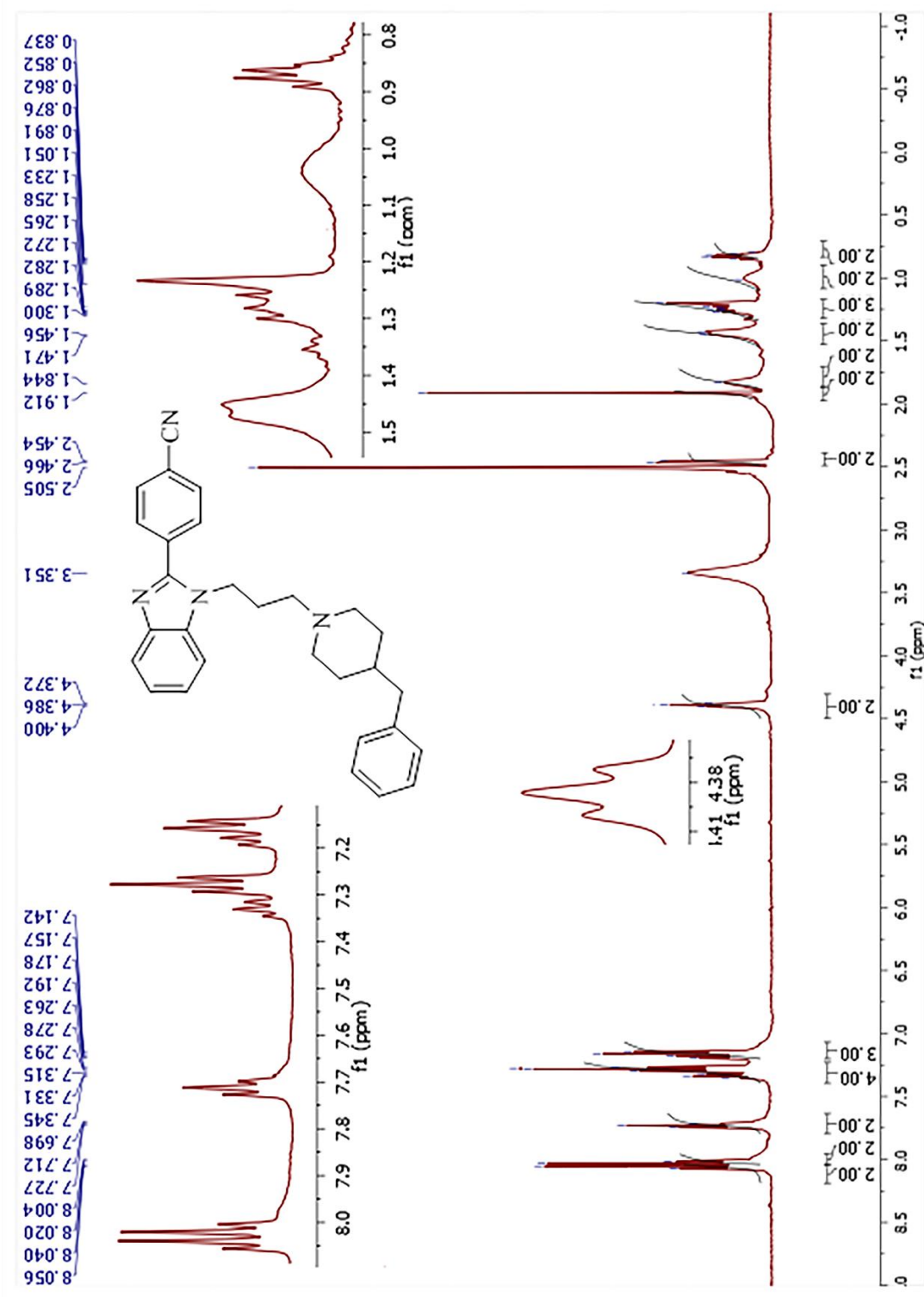


Figure 13. $^1\text{H-NMR}$ spectrum of compound (7a)

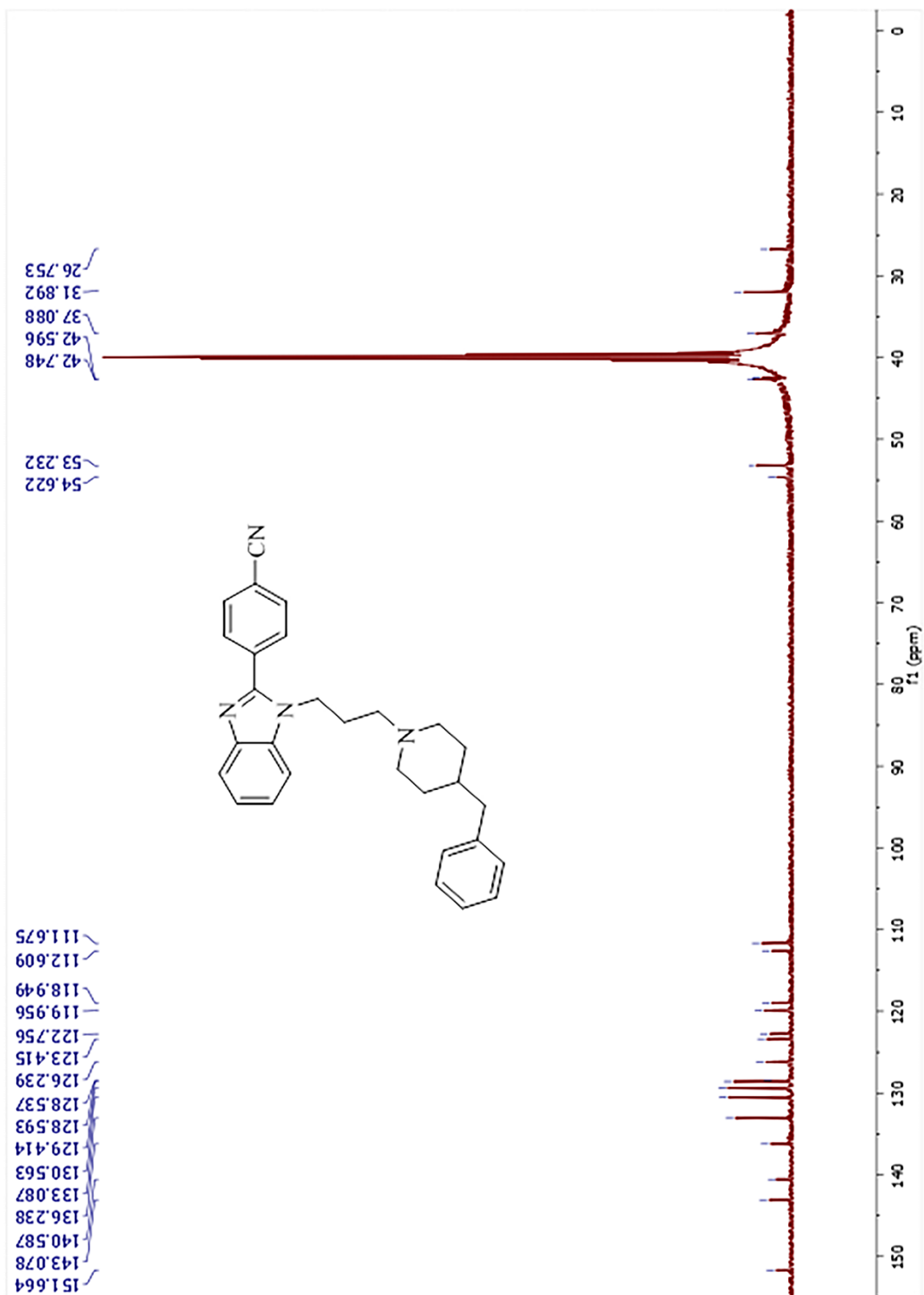


Figure 14. ^{13}C -NMR spectrum of compound (7a)

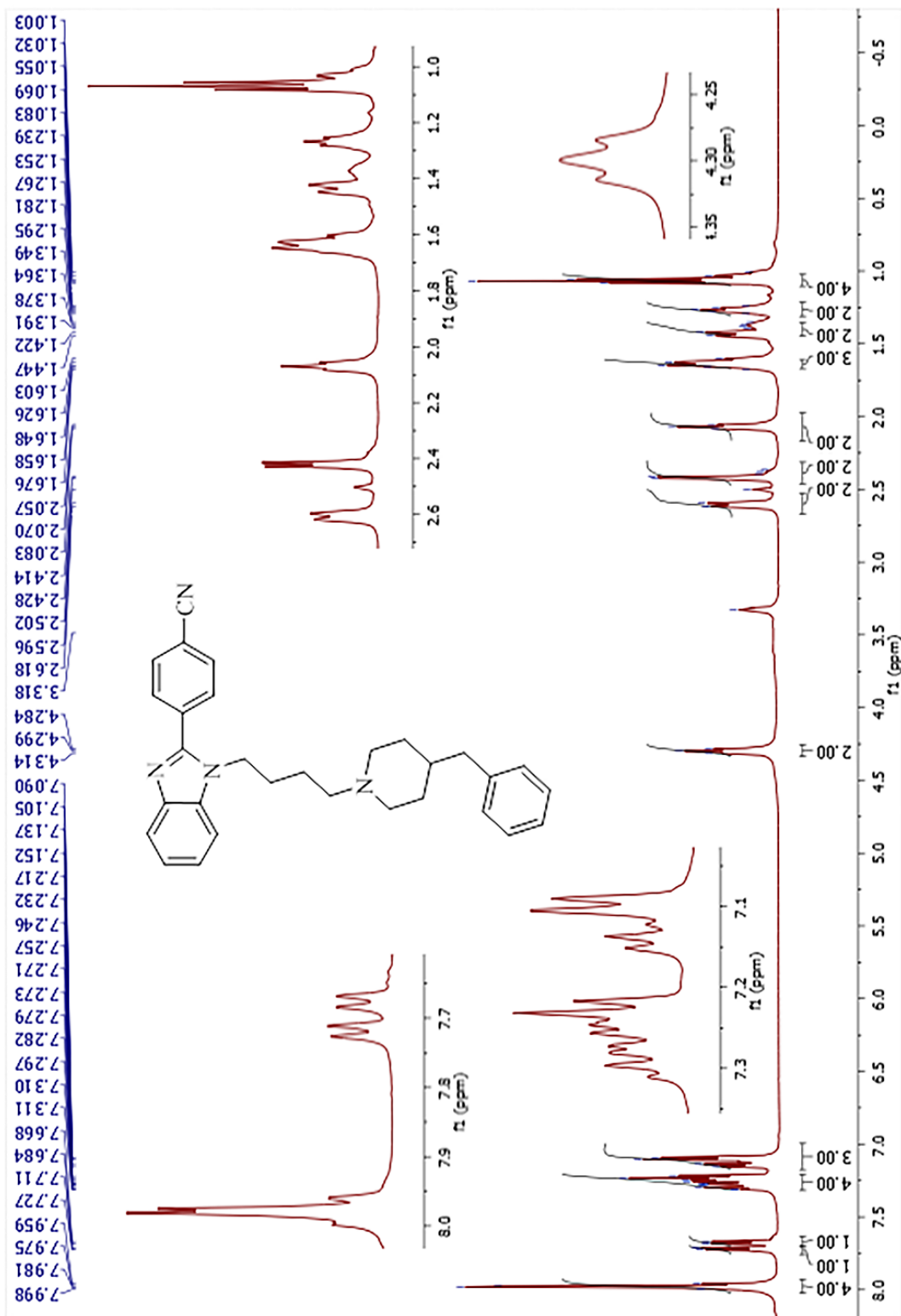


Figure 15. ¹H-NMR spectrum of compound (7b)

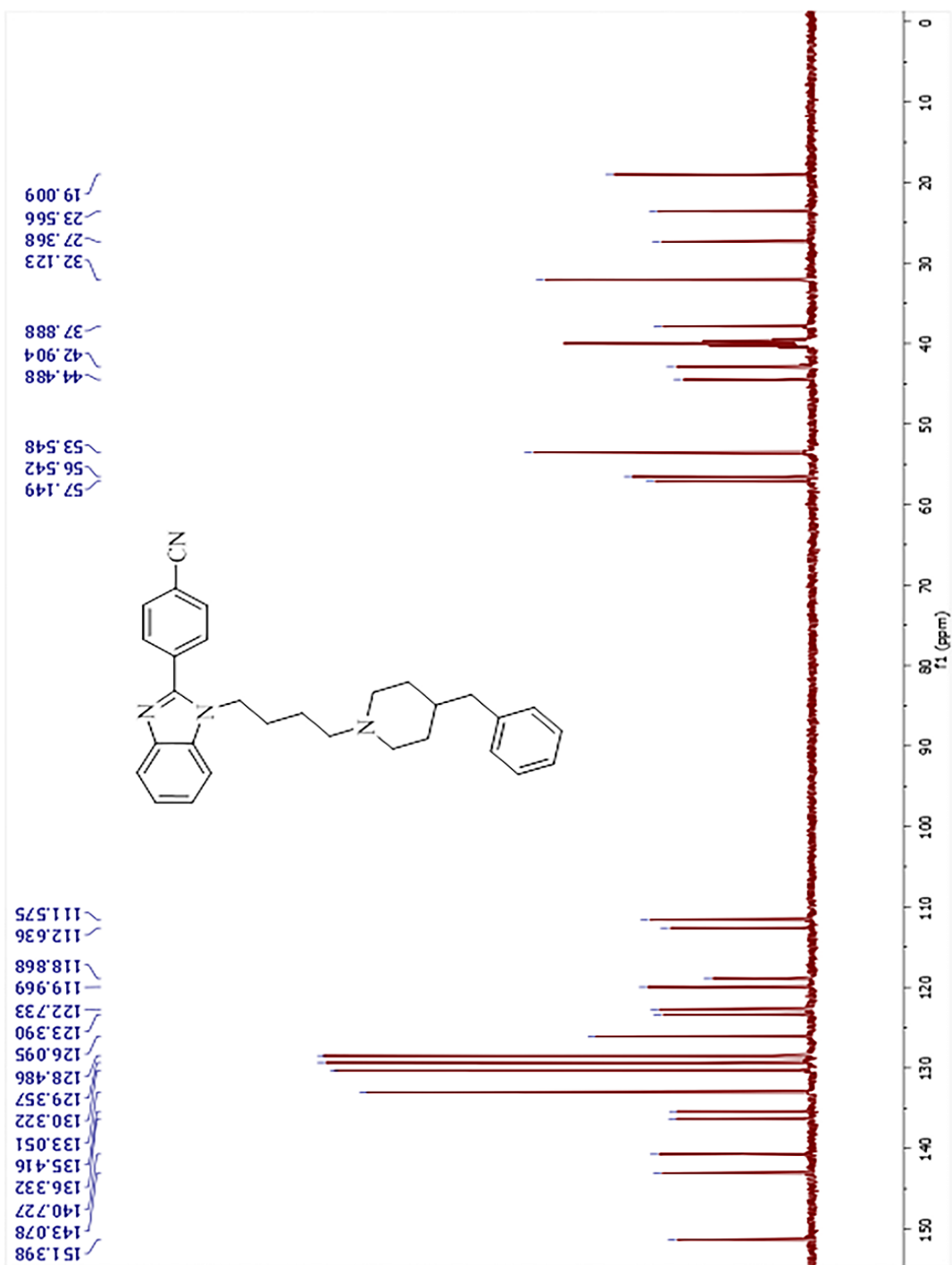


Figure 16. ^{13}C -NMR spectrum of compound (7b)

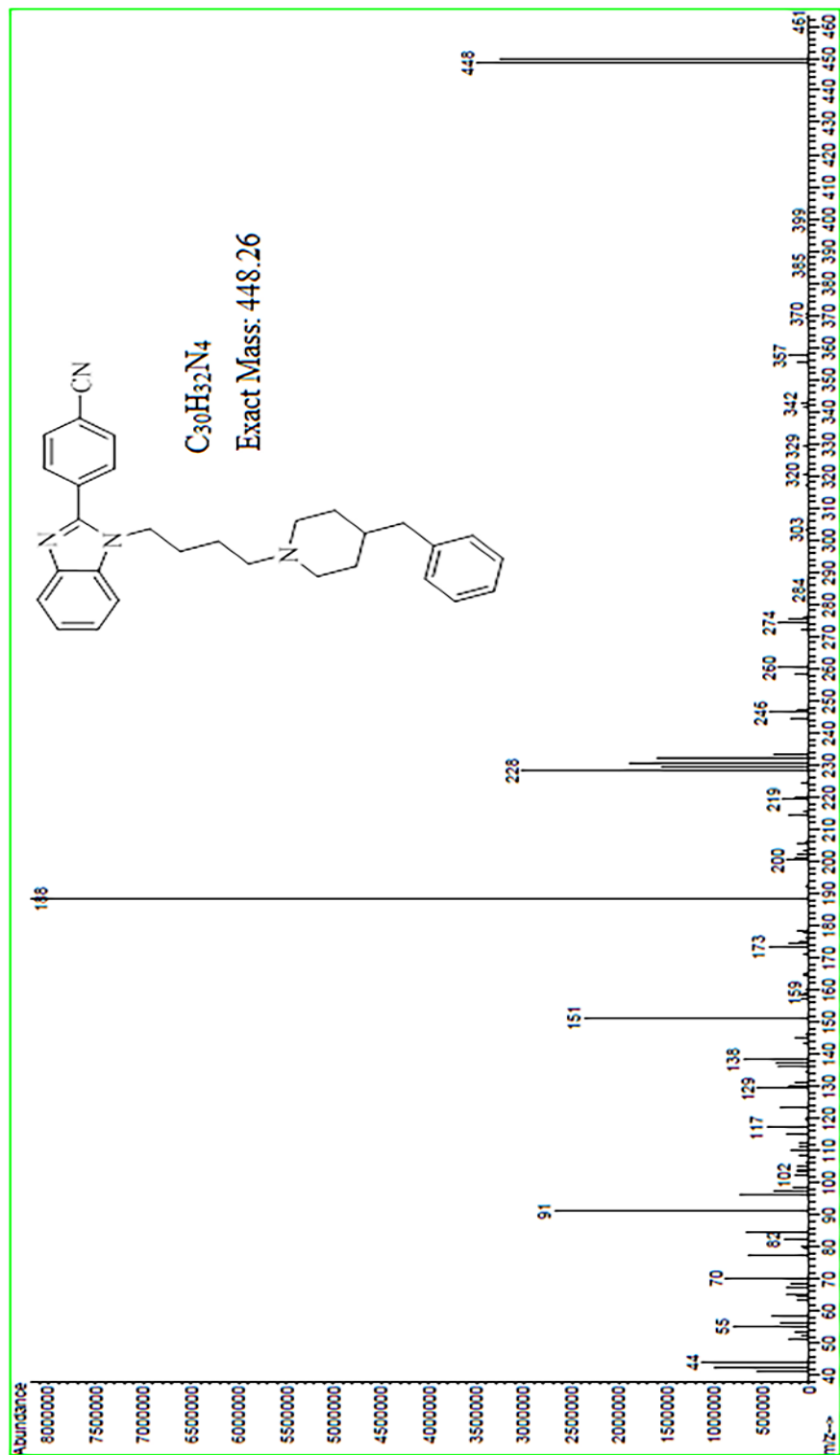


Figure 17. MASS spectrum of compound (7b)

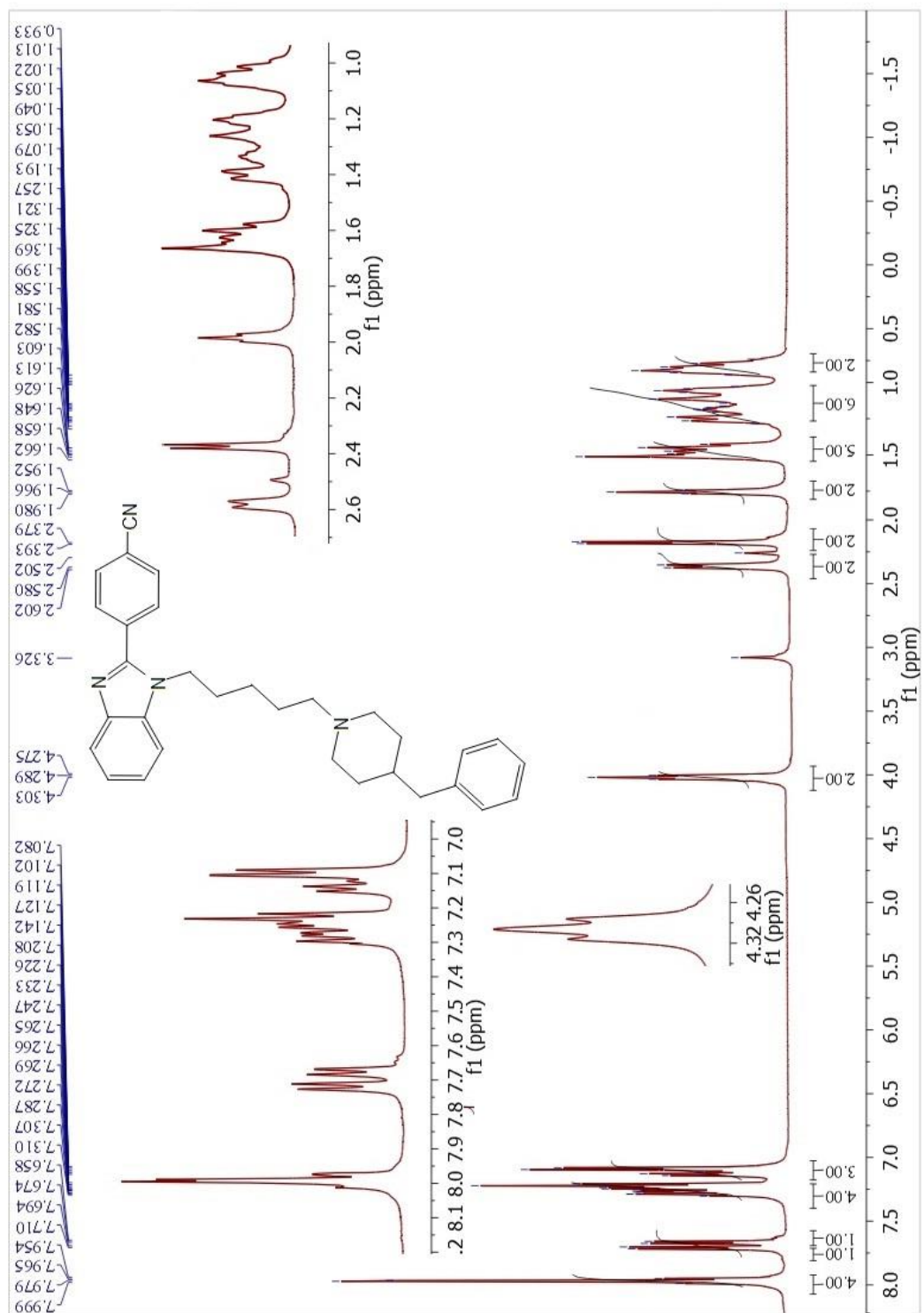


Figure 18. $^1\text{H-NMR}$ spectrum of compound (7c)

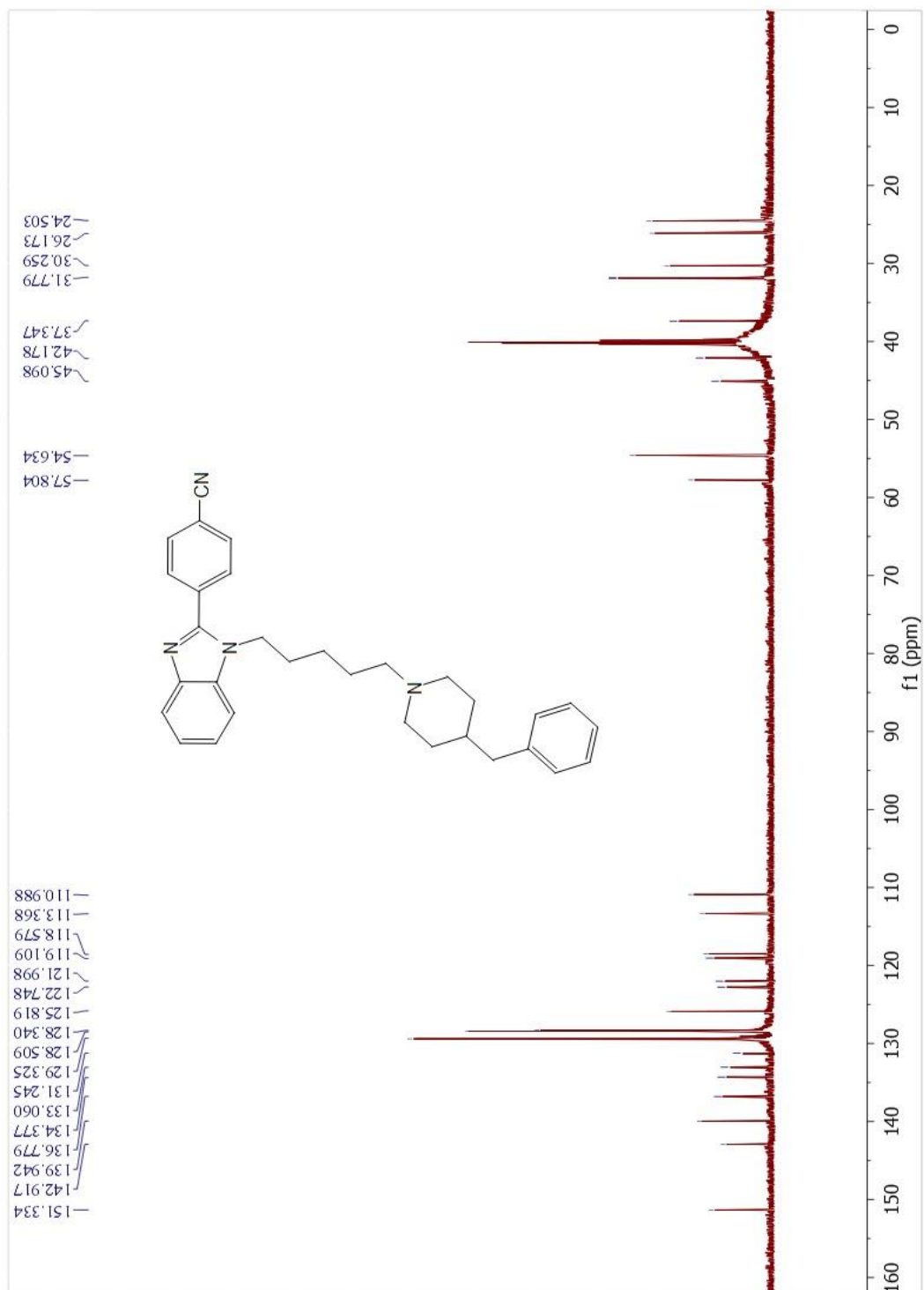


Figure 19. ¹³C-NMR spectrum of compound (7c)

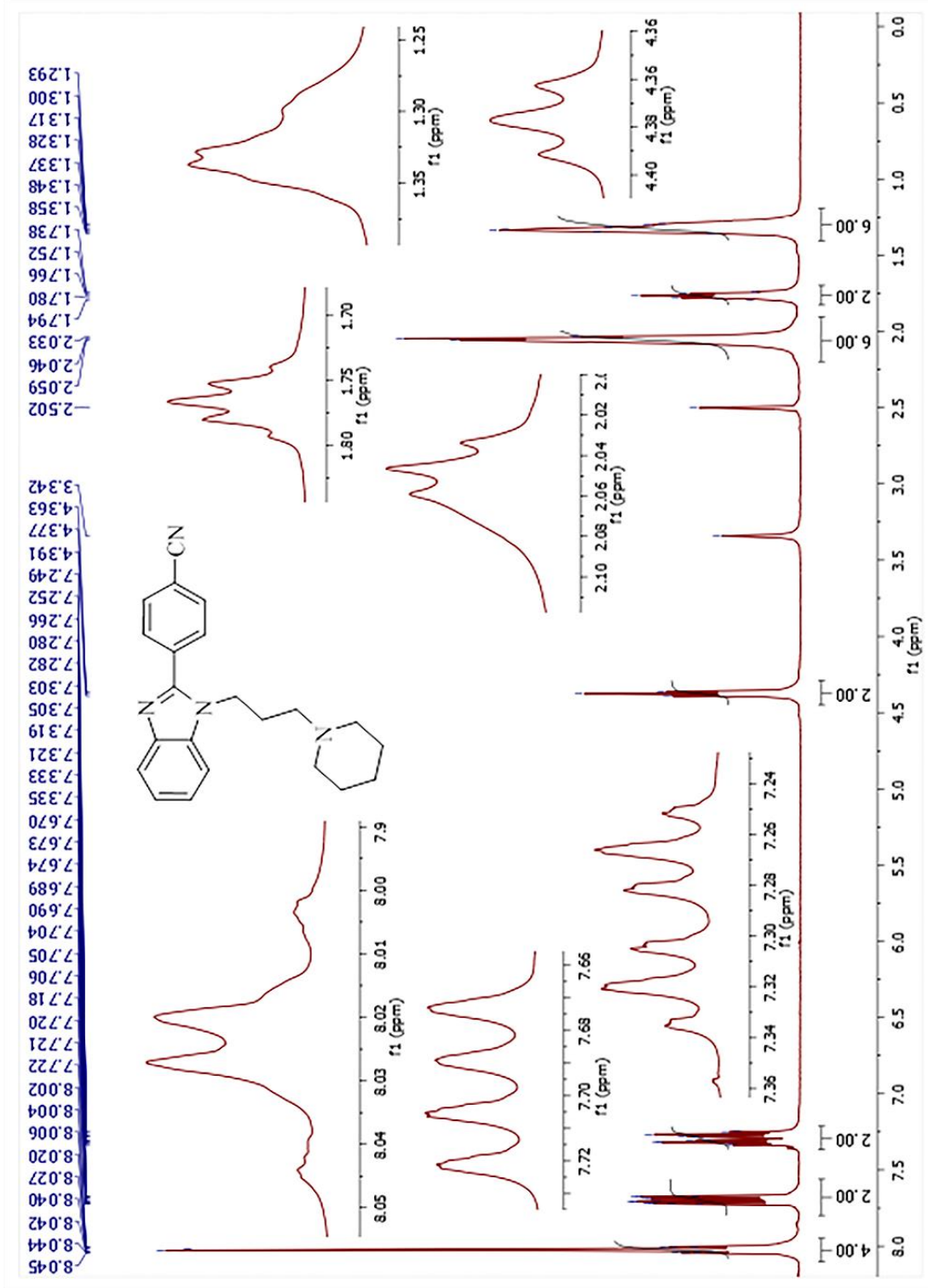


Figure 20. ¹H-NMR spectrum of compound (7d)

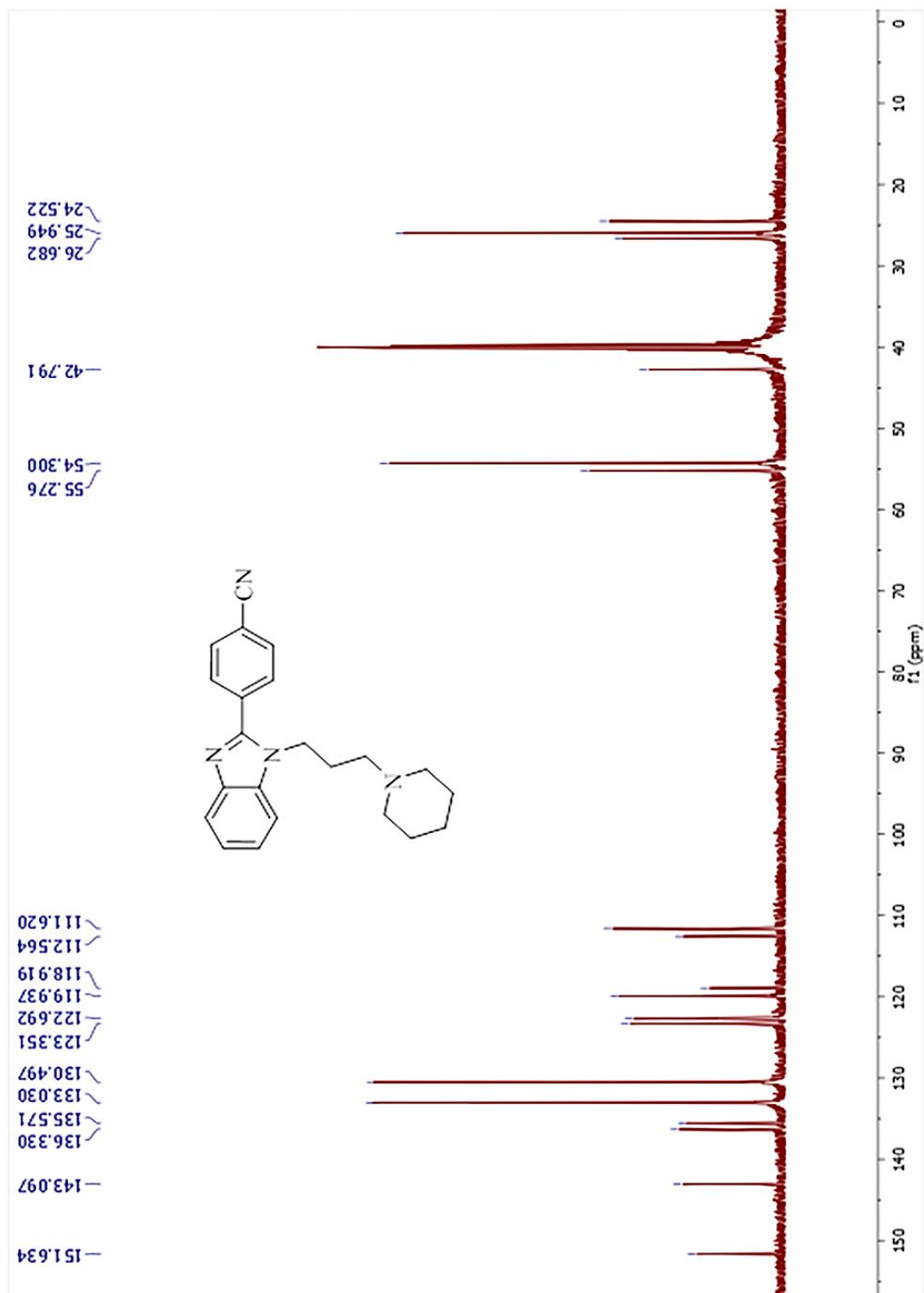


Figure 21. ^{13}C -NMR spectrum of compound (7d)

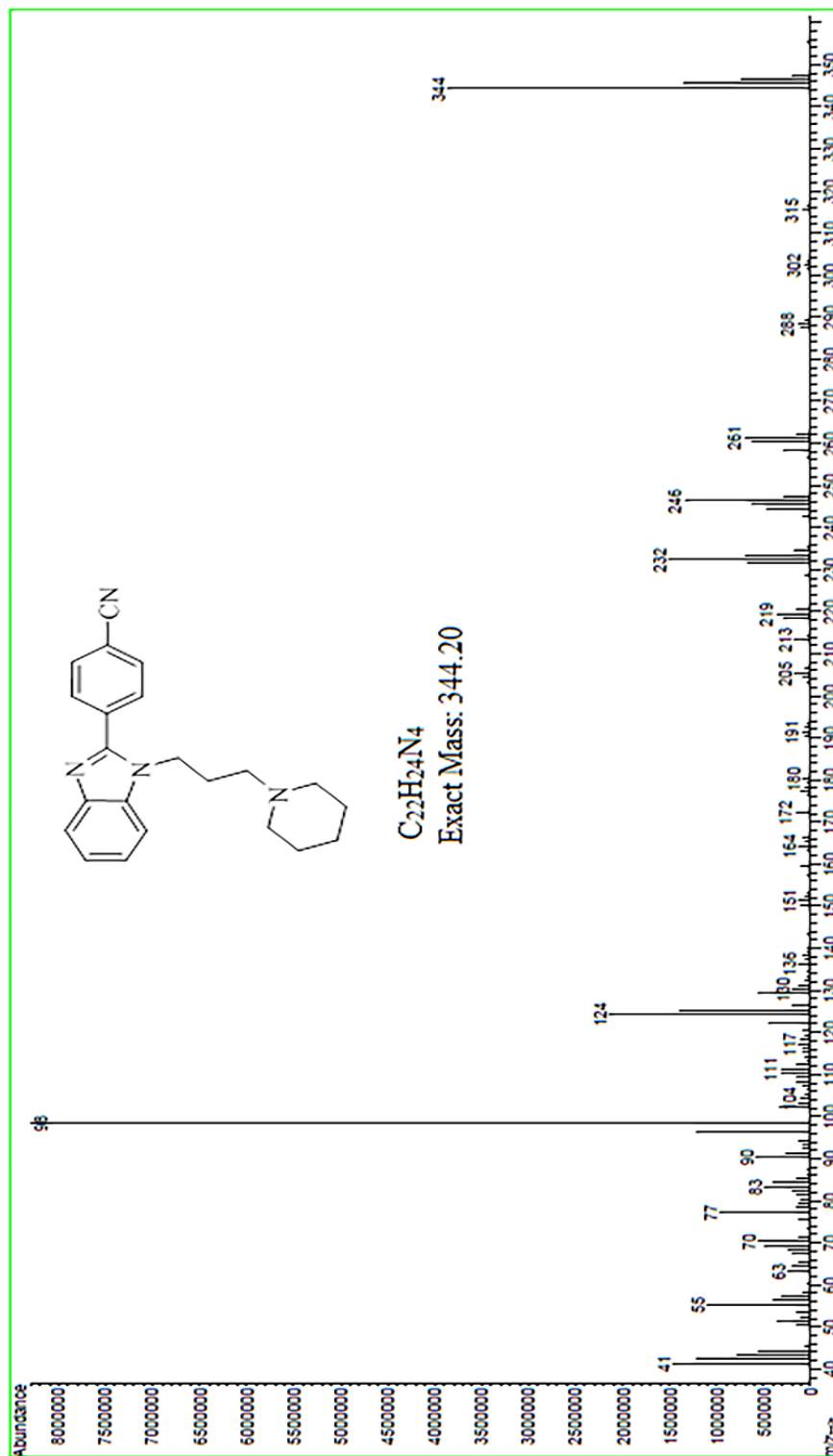


Figure 22. MASS spectrum of compound (7d)

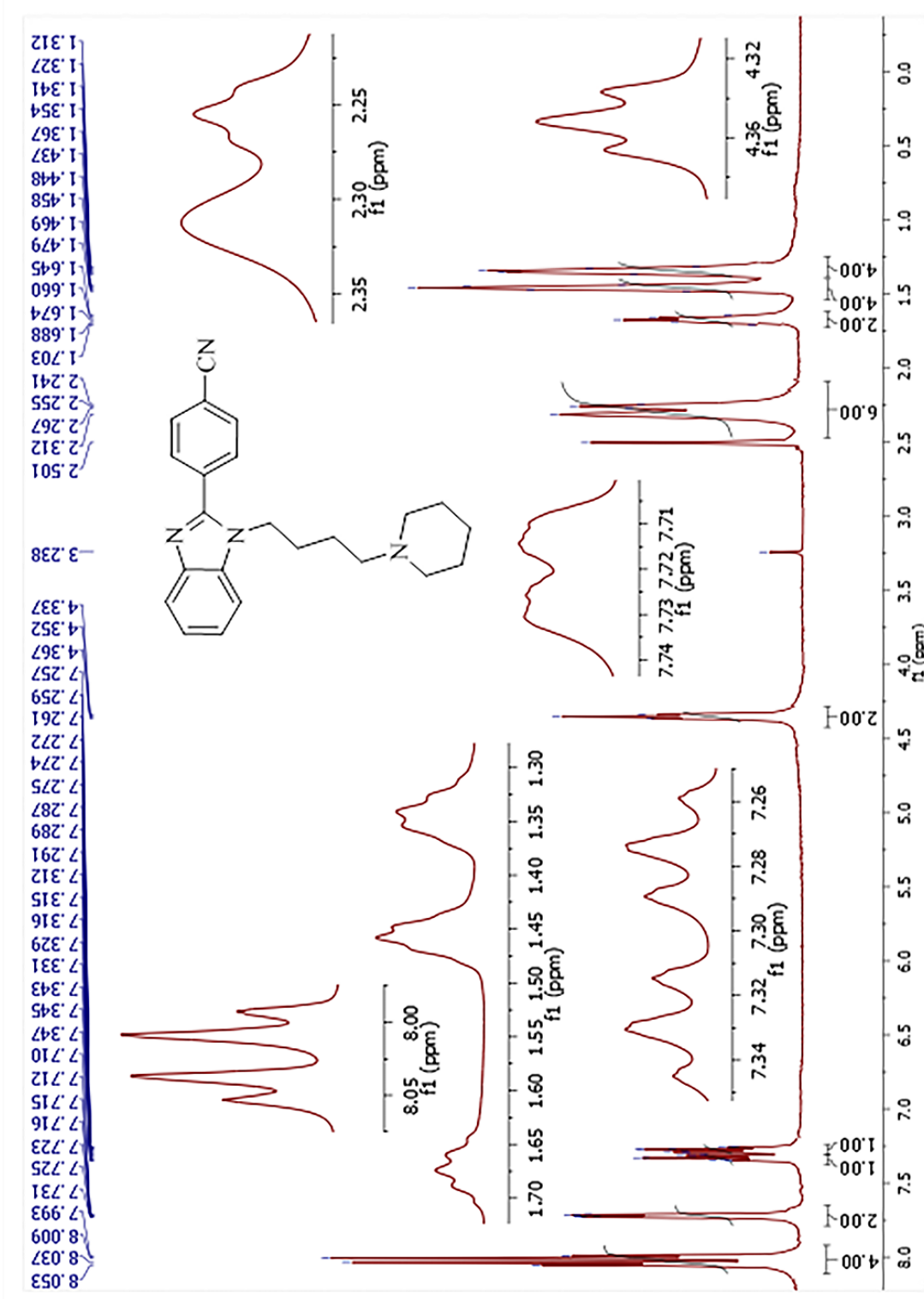


Figure 23. $^1\text{H-NMR}$ spectrum of compound (7e)

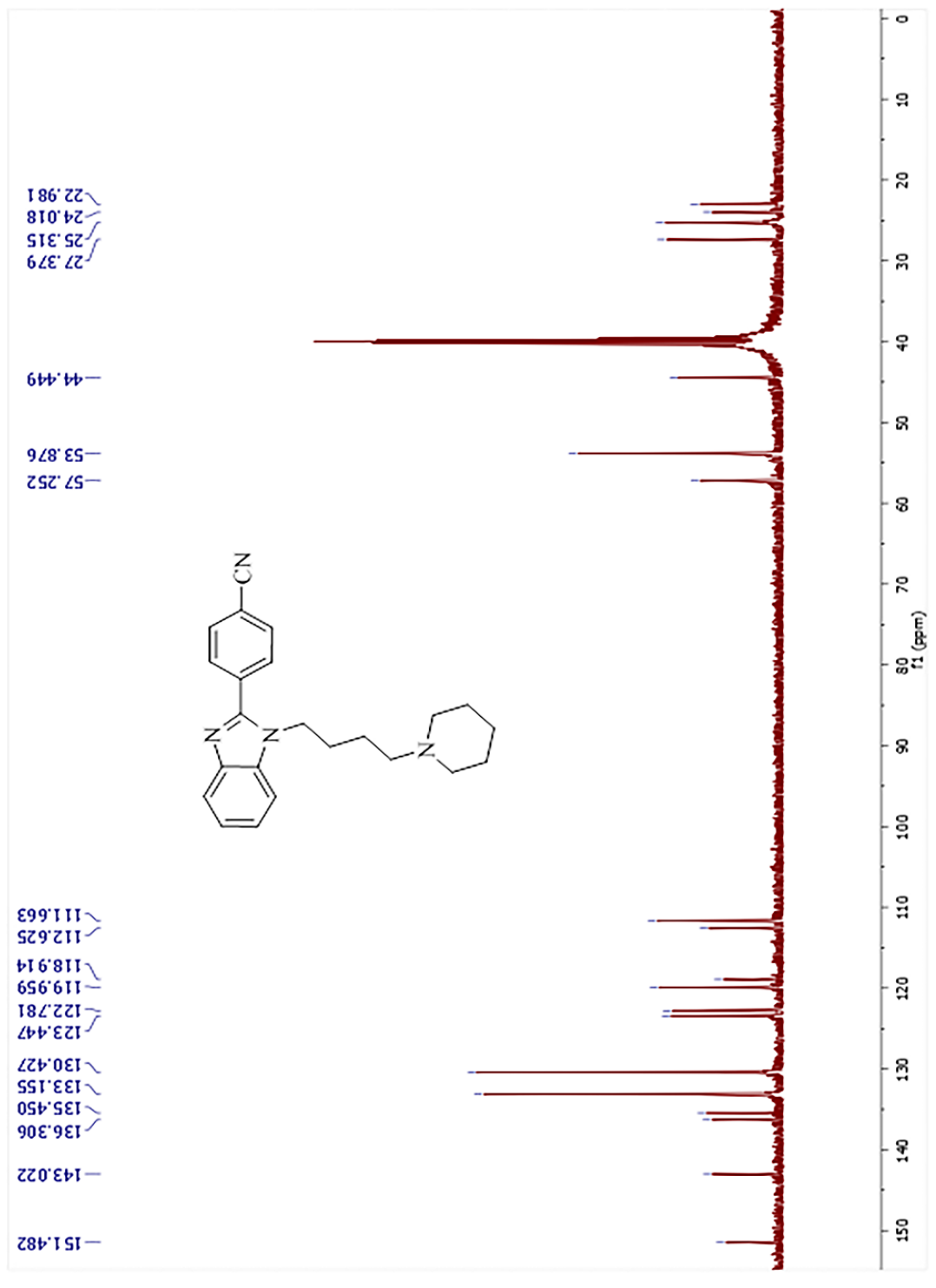


Figure 24. ^{13}C -NMR spectrum of compound (7e)

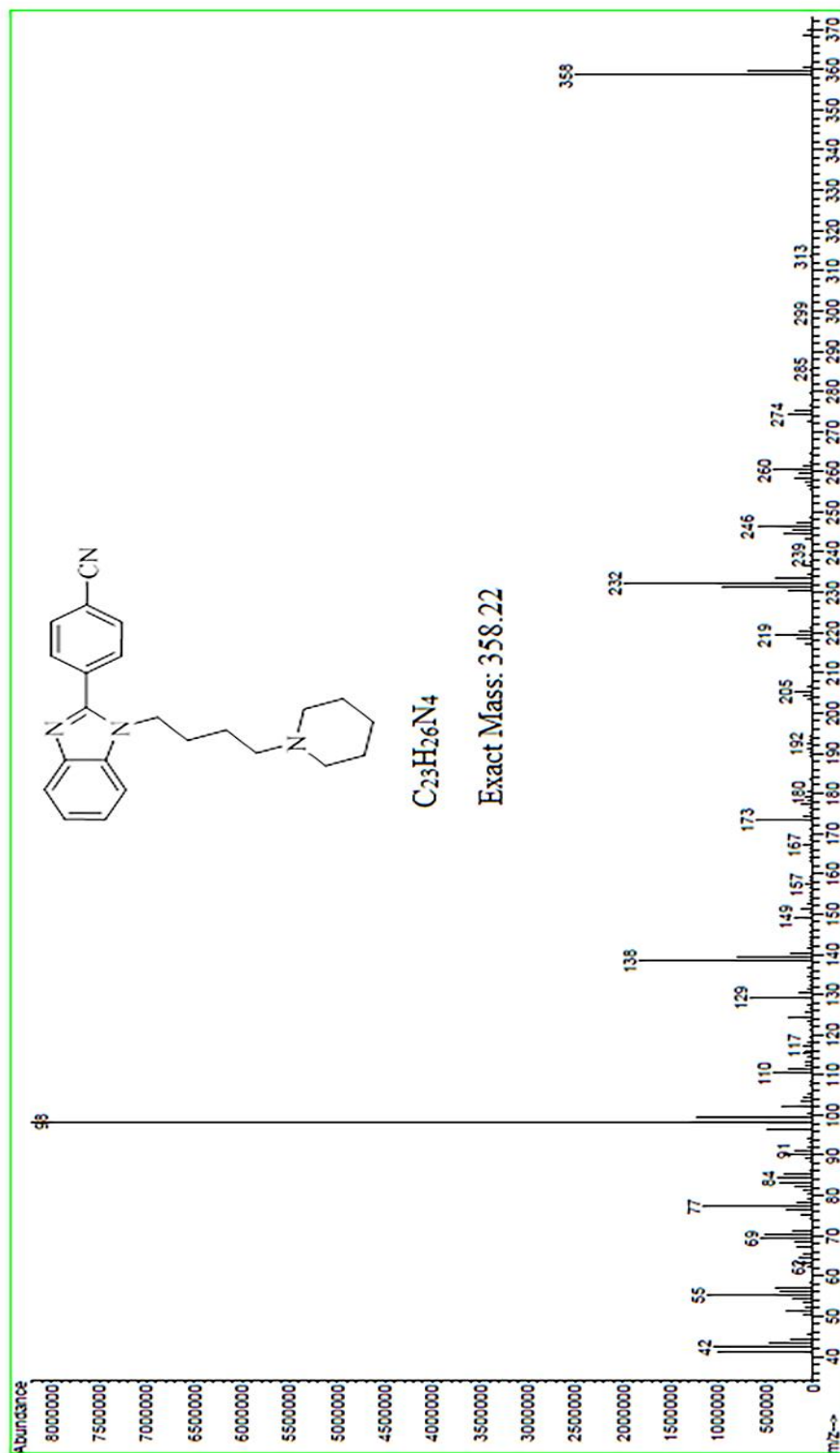


Figure 25. MASS spectrum of compound (7e)

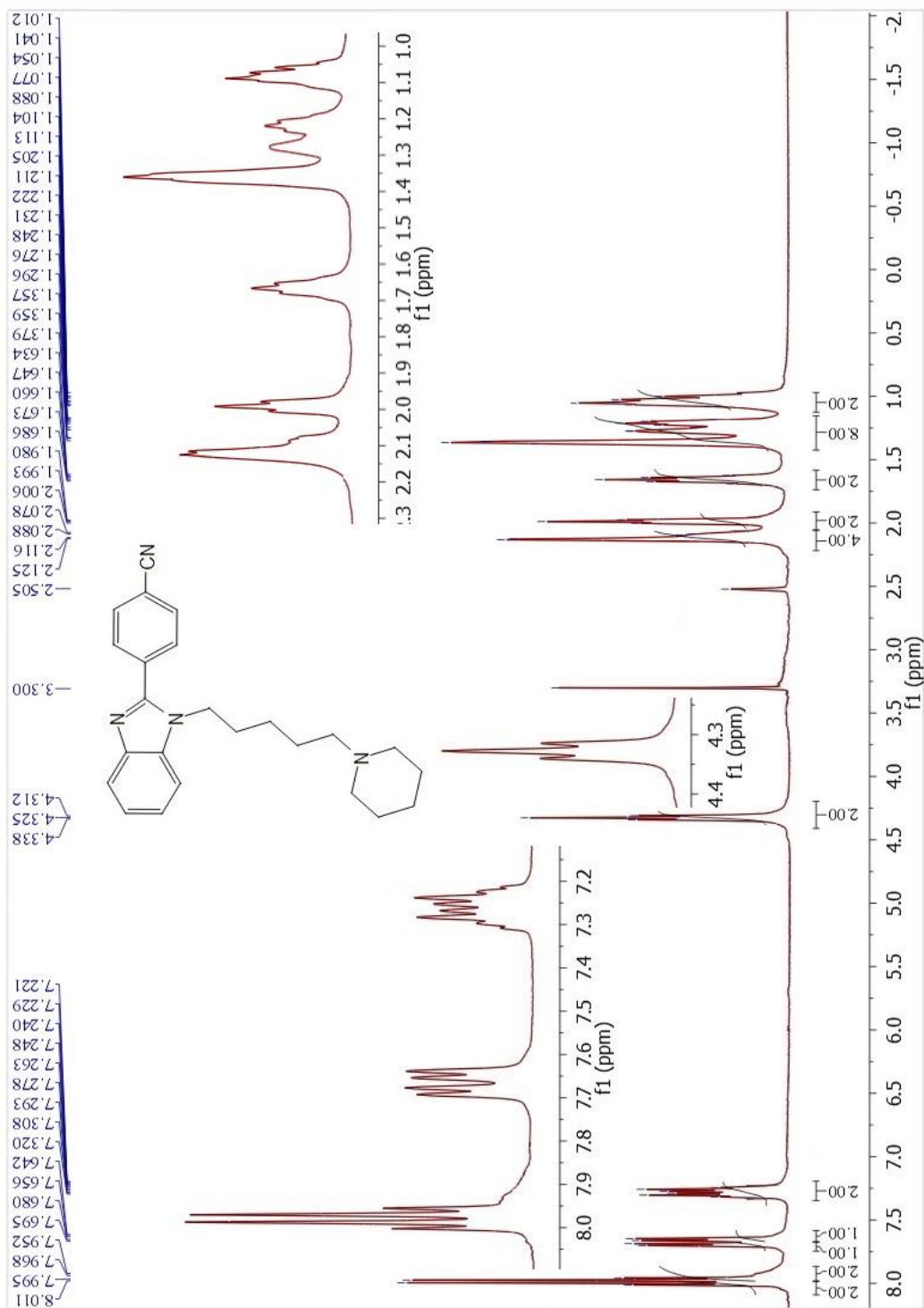


Figure 26. $^1\text{H-NMR}$ spectrum of compound (7f)

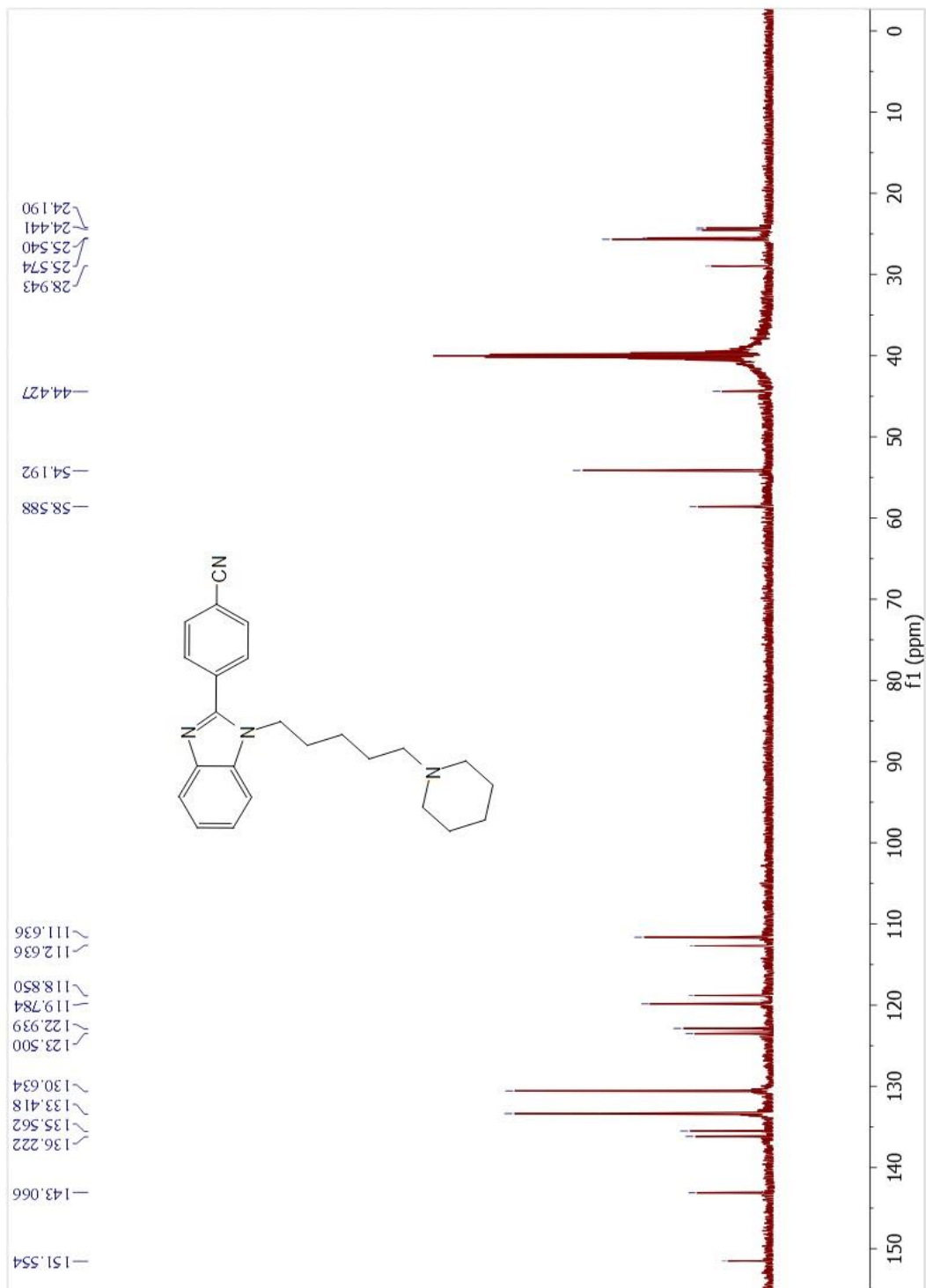


Figure 27. ^{13}C -NMR spectrum of compound (7f)

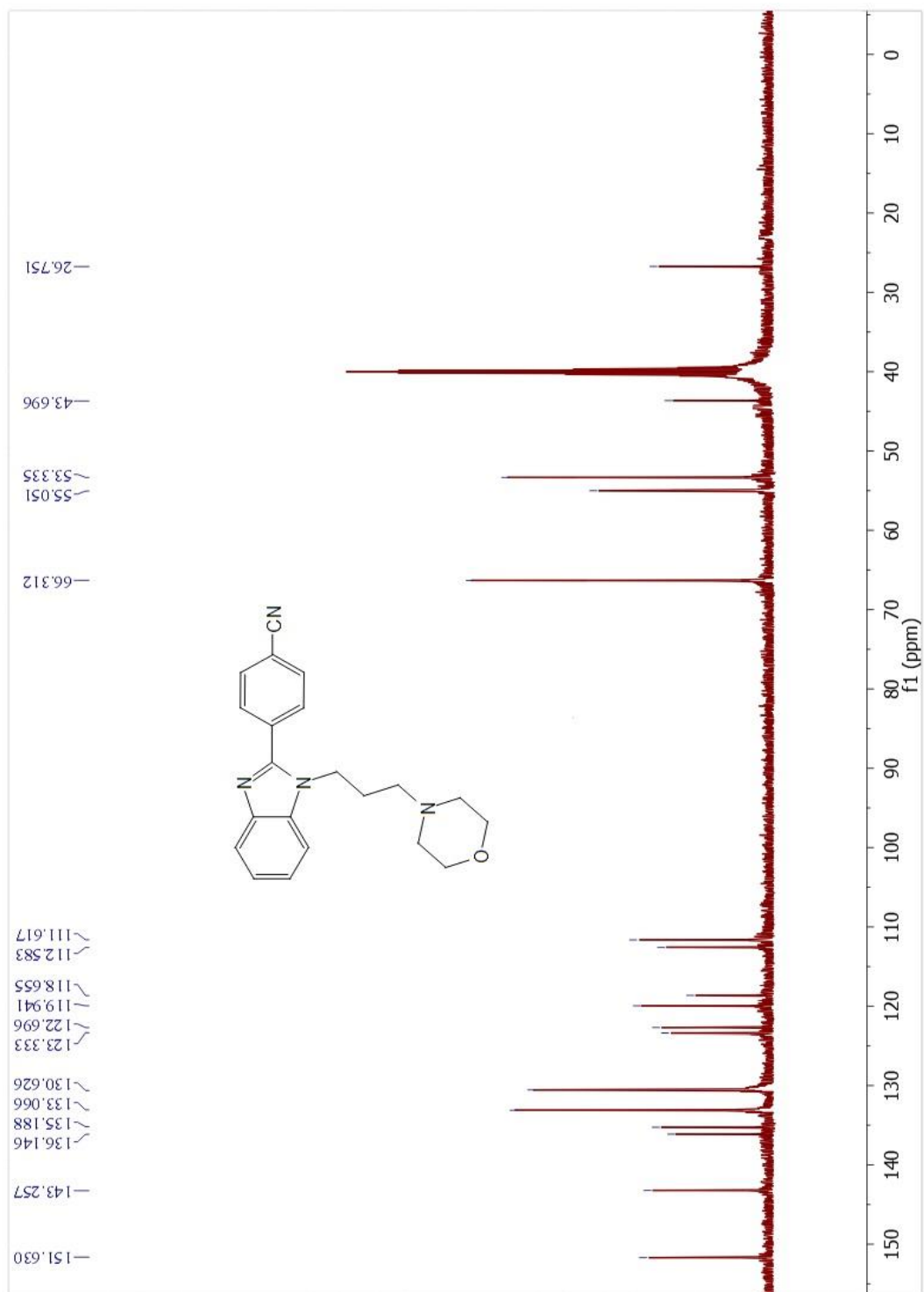


Figure 29. ^{13}C -NMR spectrum of compound (7g)

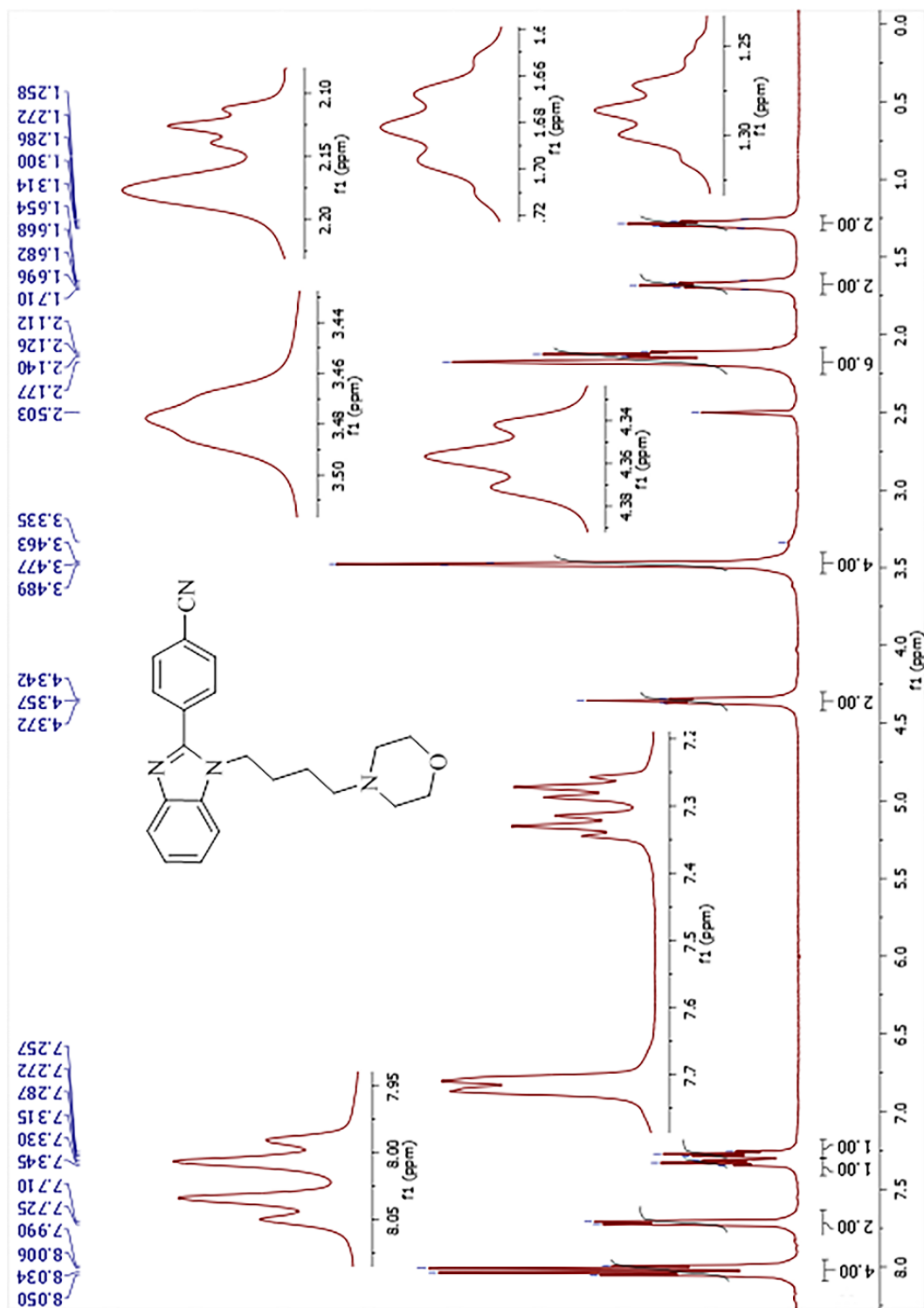


Figure 30. ¹H-NMR spectrum of compound (7h)

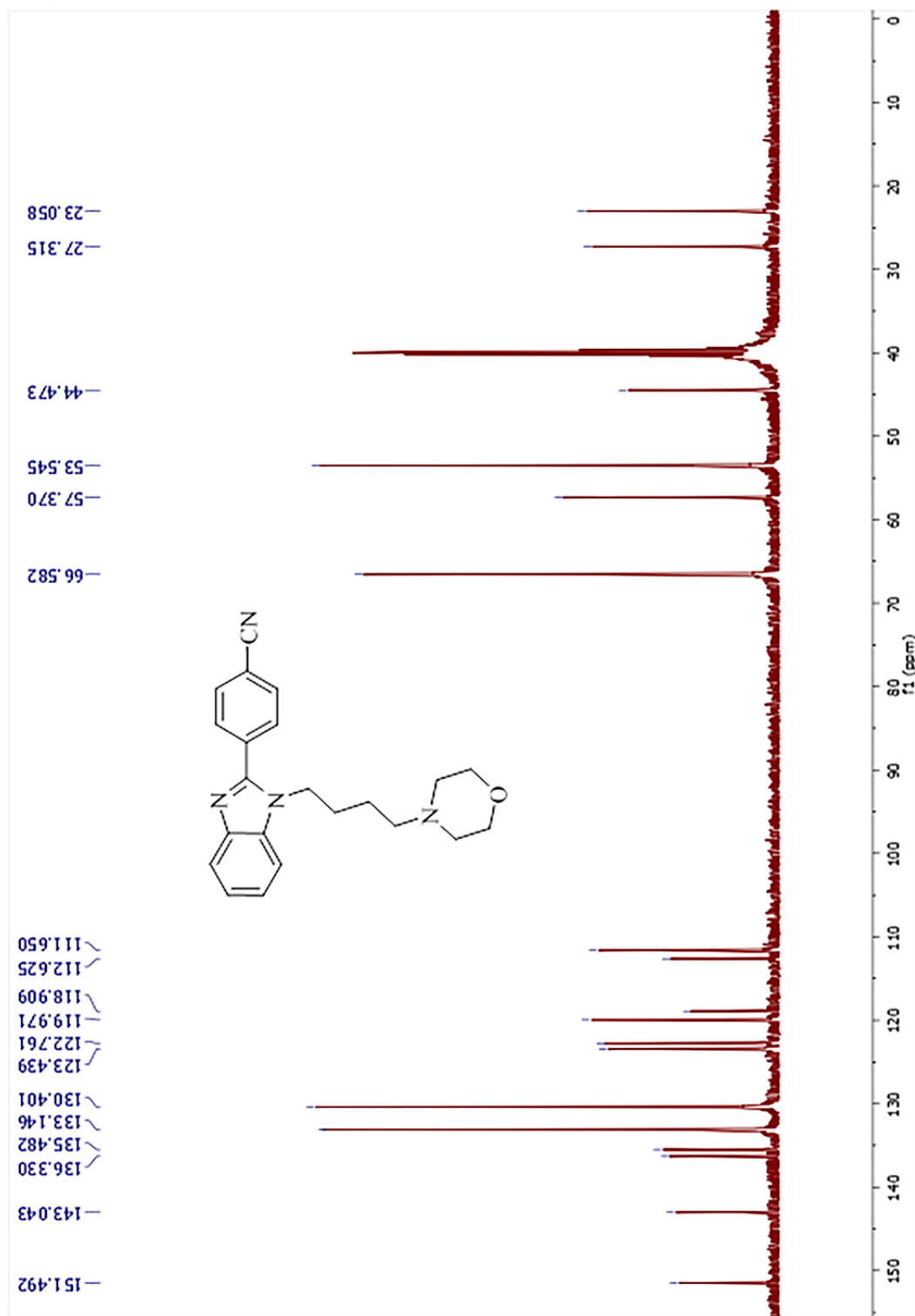


Figure 31. ¹³C-NMR spectrum of compound (7h)

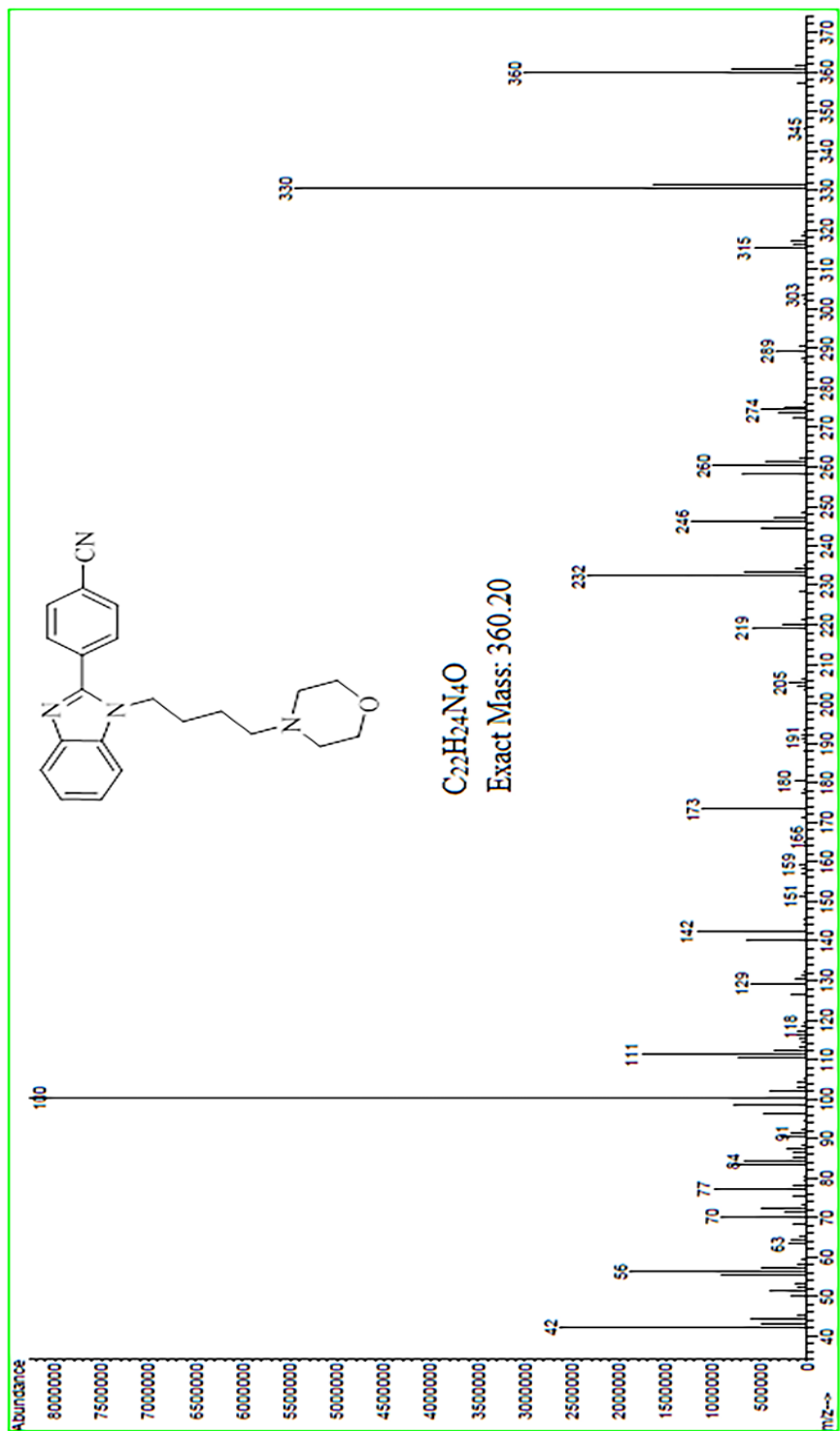


Figure 32. MASS spectrum of compound (7h)

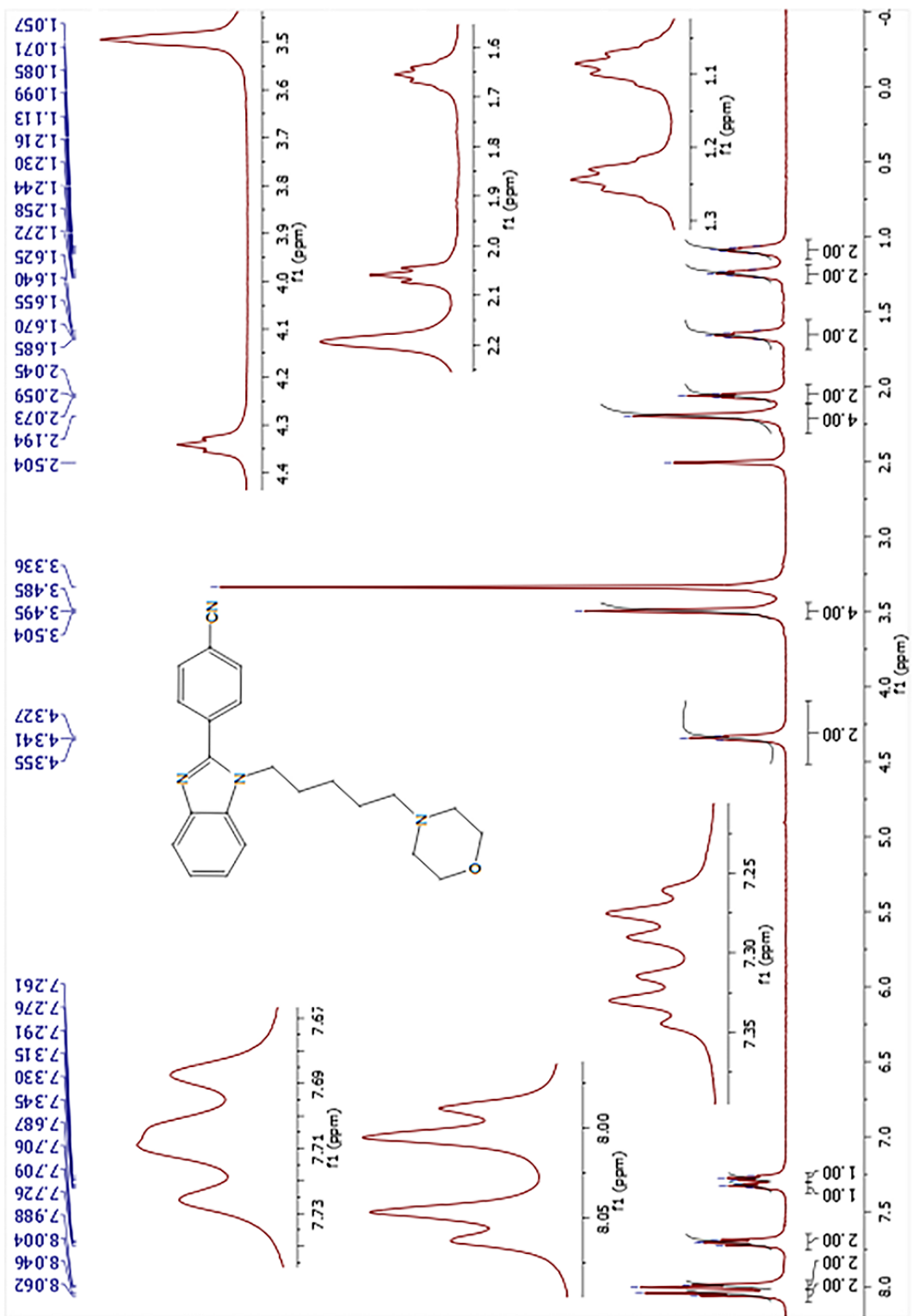


Figure 33. ¹H-NMR spectrum of compound (7i)

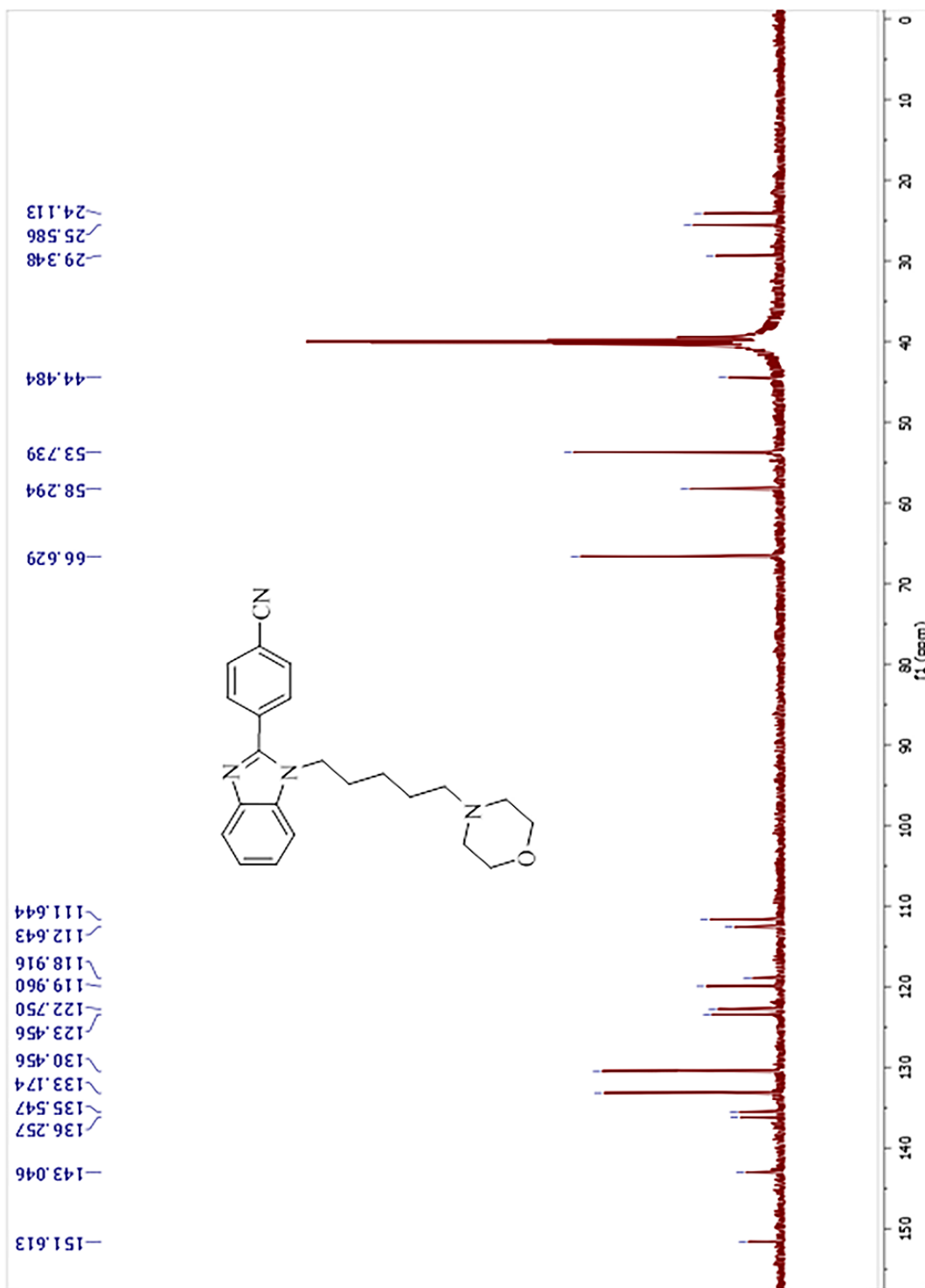


Figure 34. ^{13}C -NMR spectrum of compound (7i)

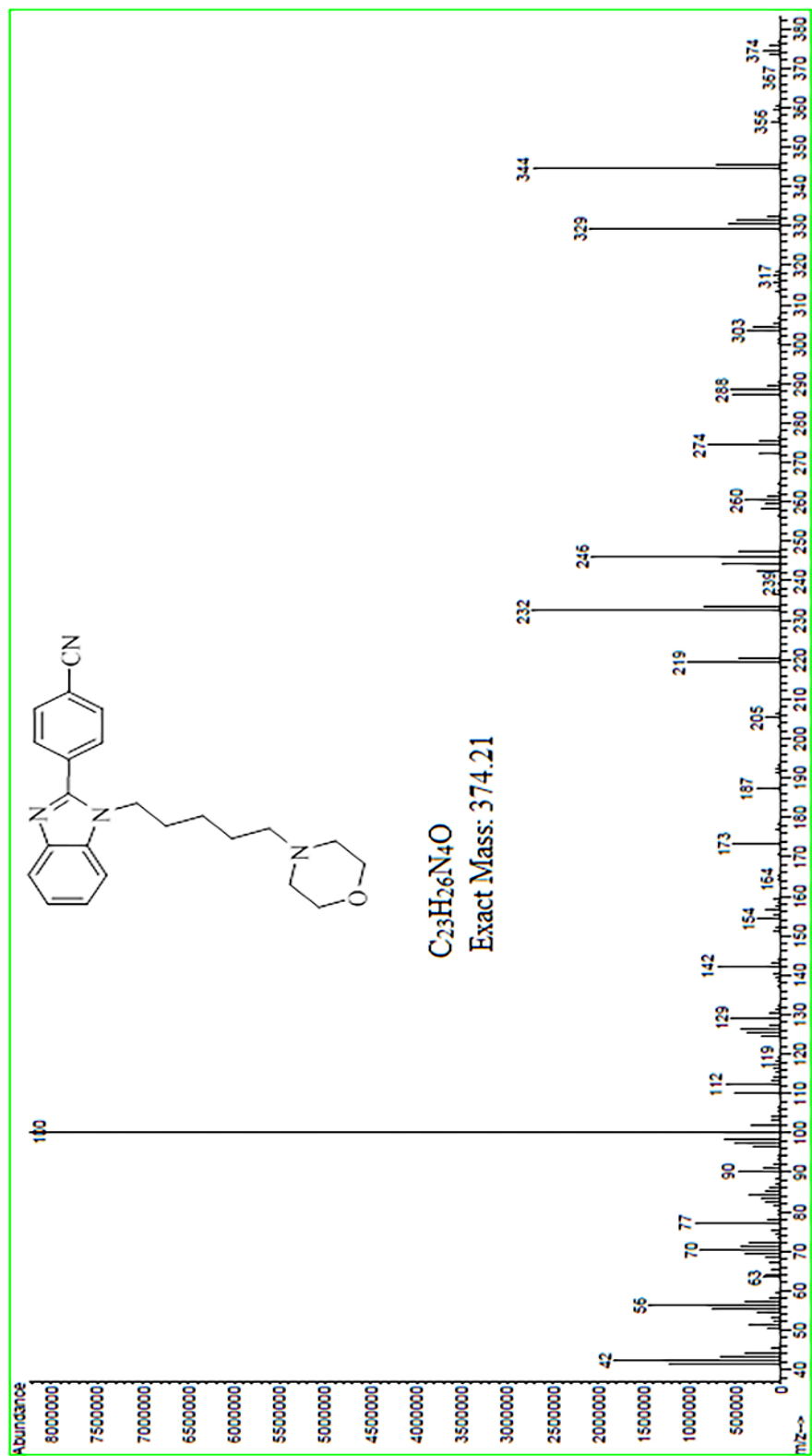


Figure 35. MASS spectrum of compound (7i)

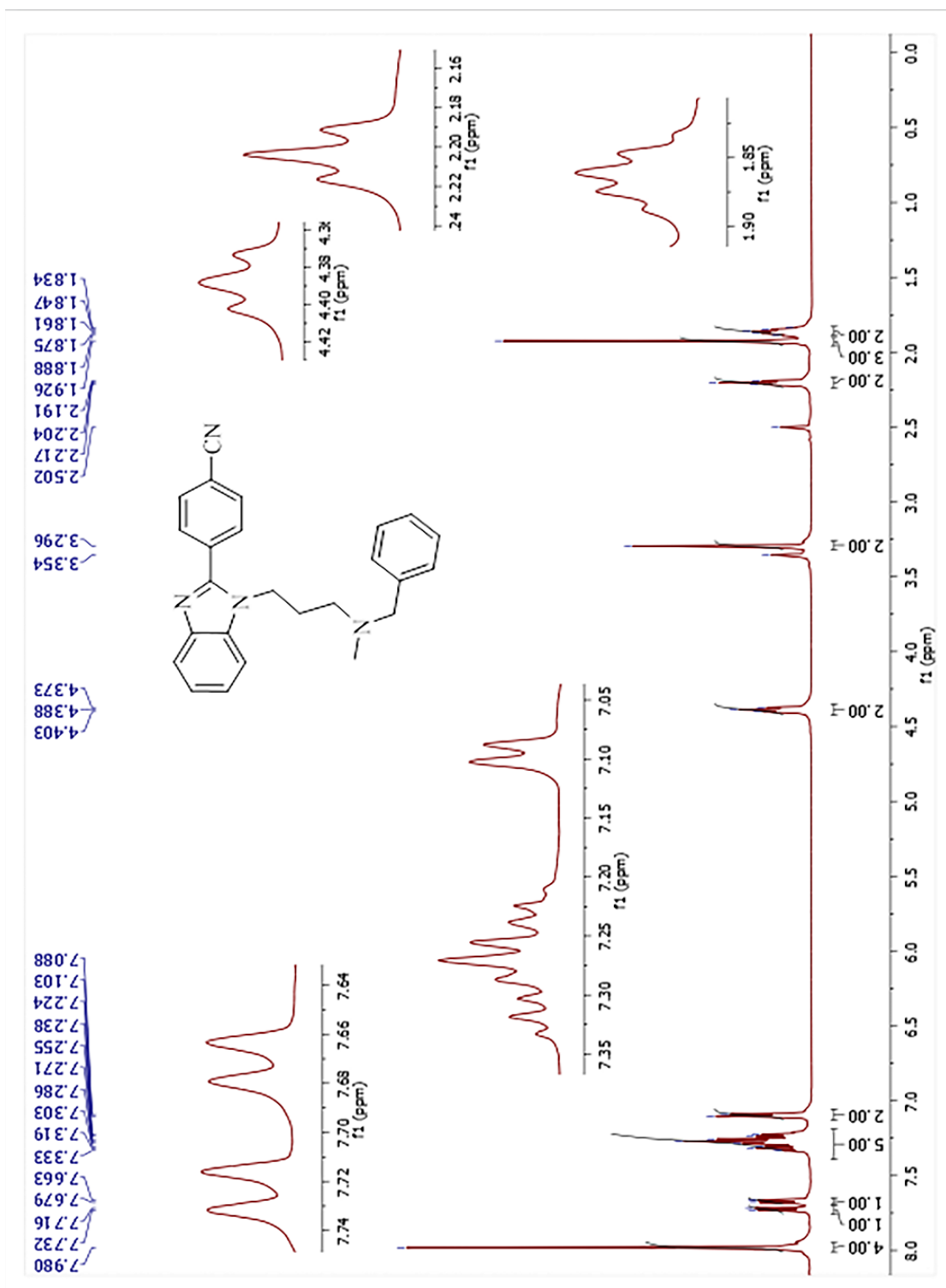


Figure 36. ¹H-NMR spectrum of compound (7j)

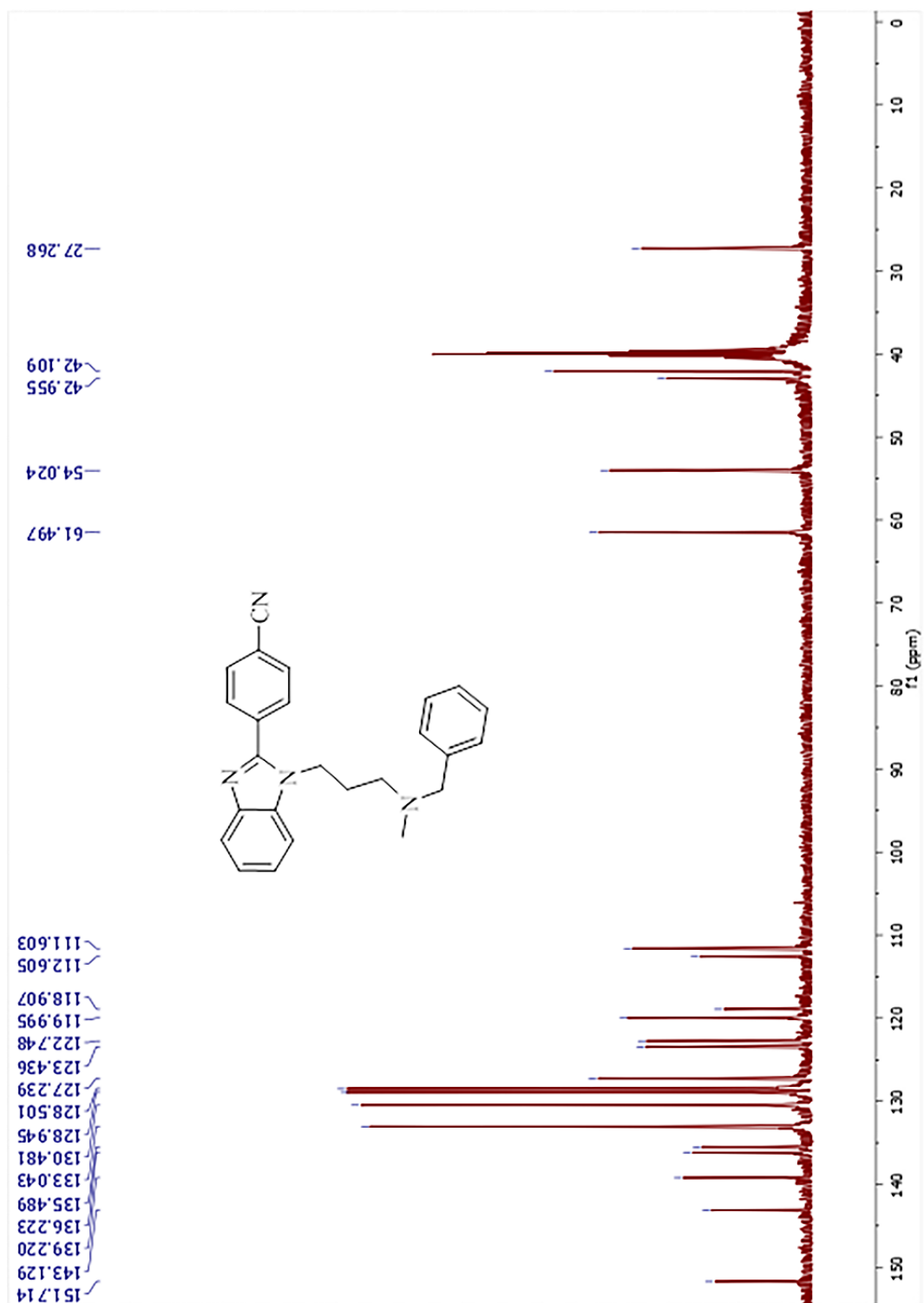


Figure 37. ^{13}C -NMR spectrum of compound (7j)

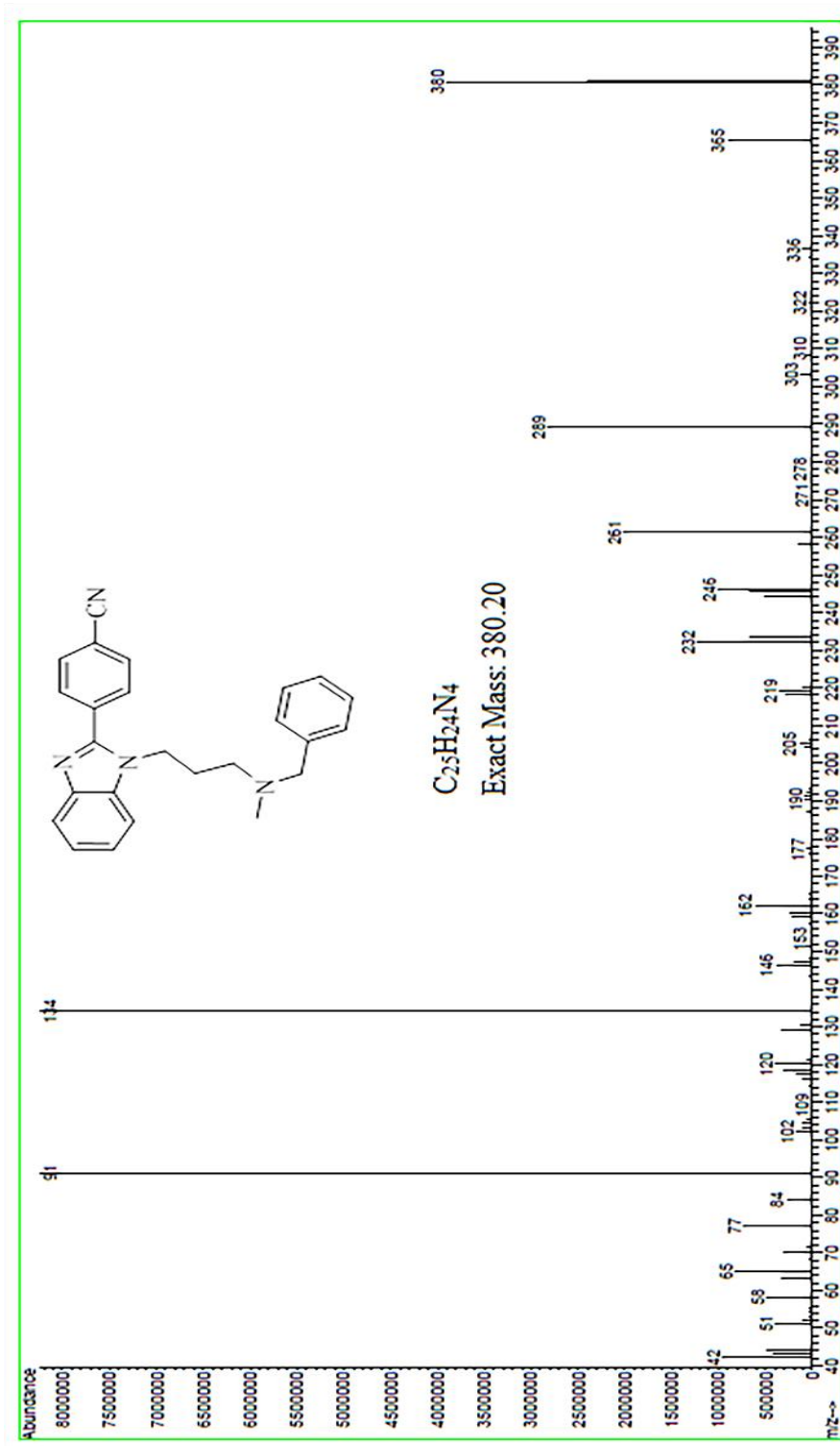


Figure 38. MASS spectrum of compound (7j)

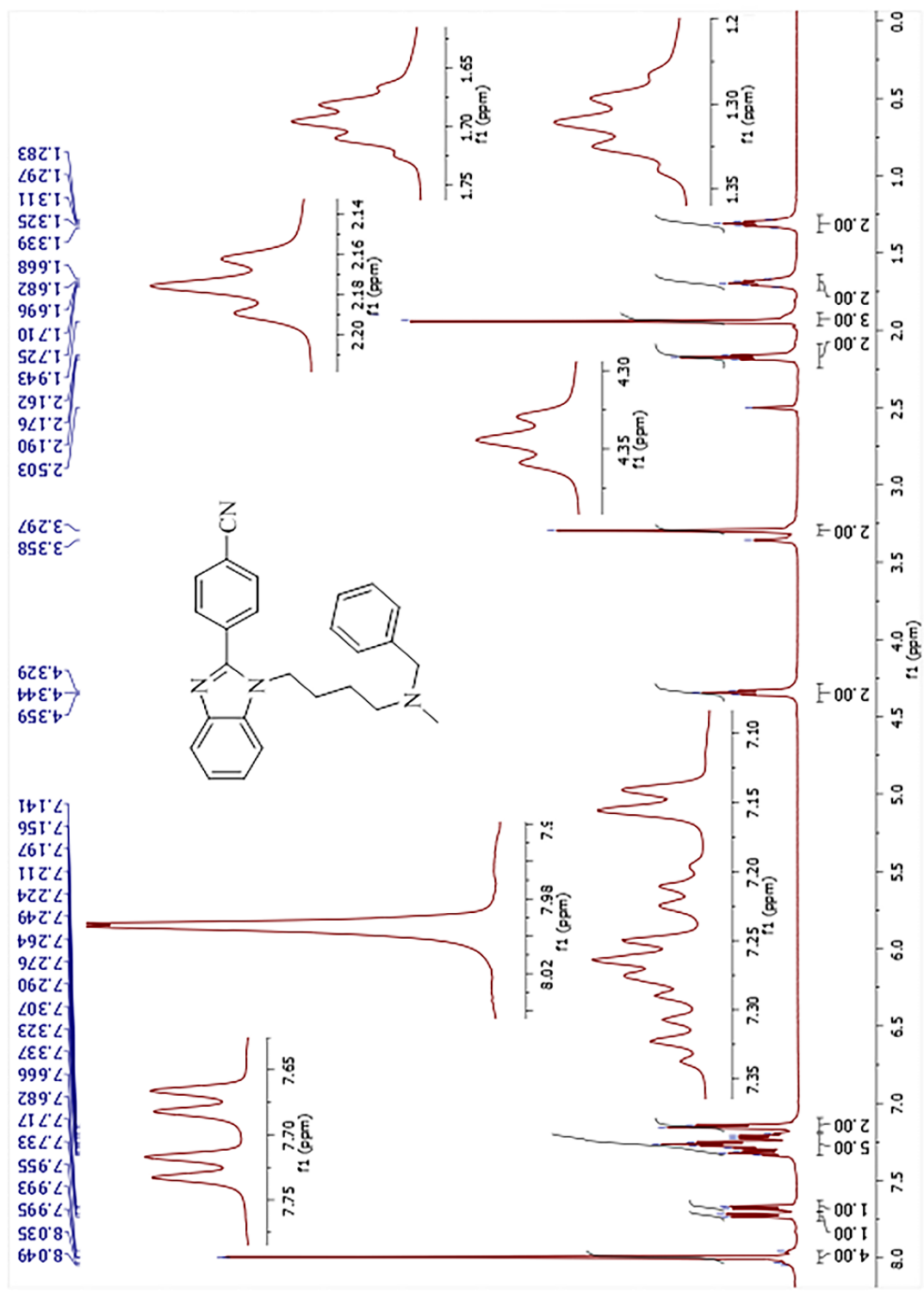


Figure 39. ¹H-NMR spectrum of compound (7k)

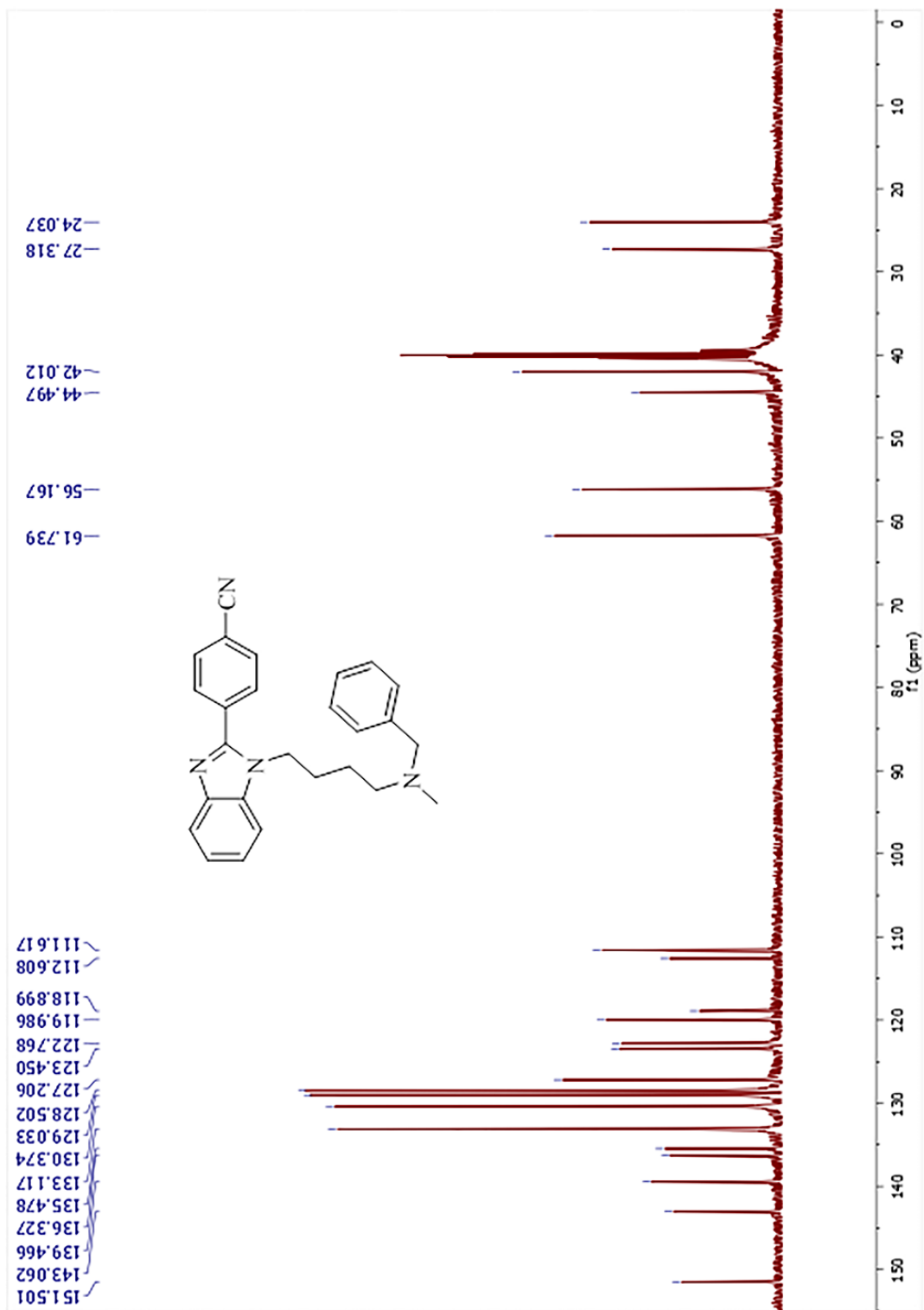


Figure 40. ¹³C-NMR spectrum of compound (7k)

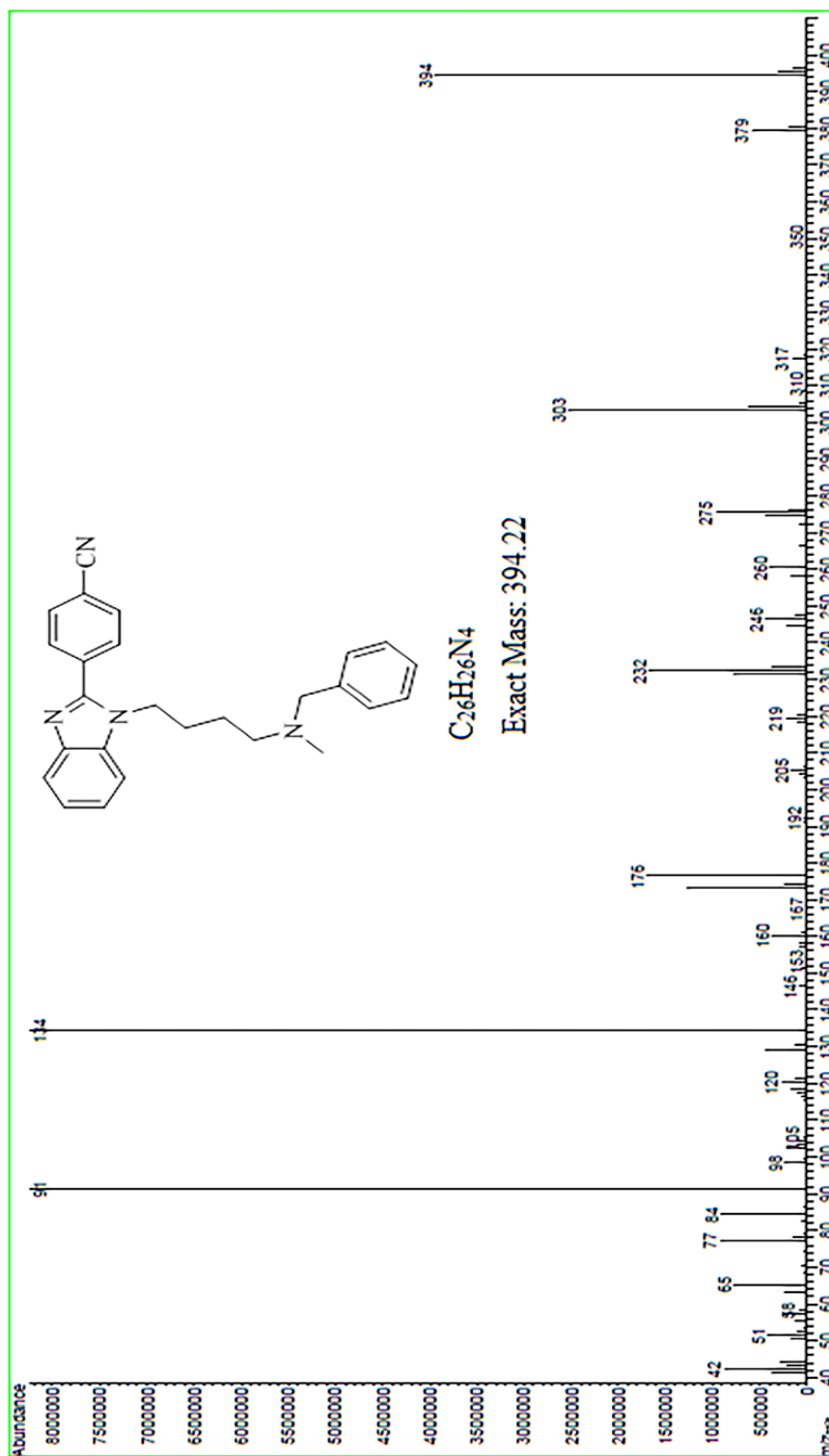


Figure 41. MASS spectrum of compound (7k)

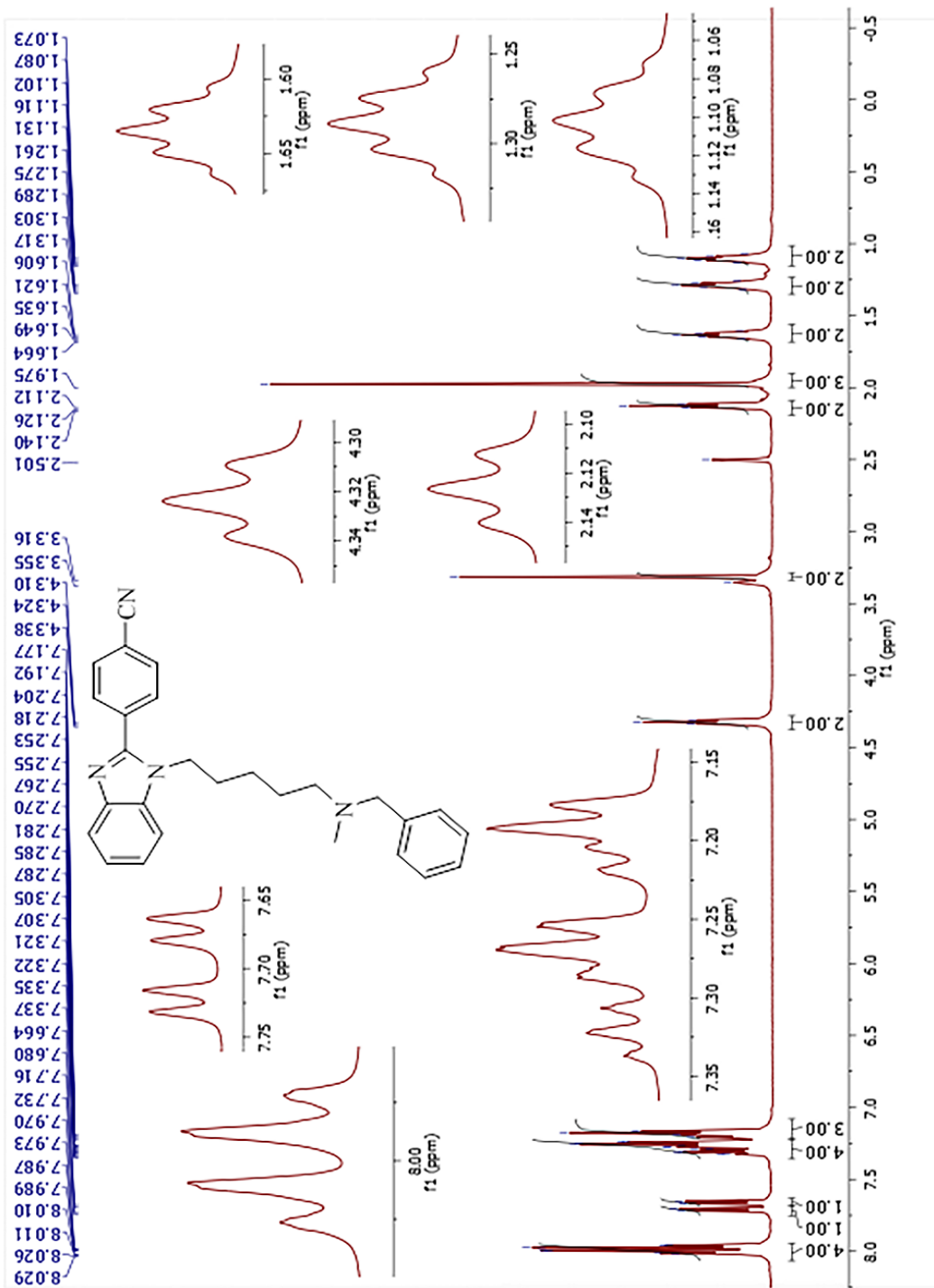


Figure 42. ¹H-NMR spectrum of compound (7I)

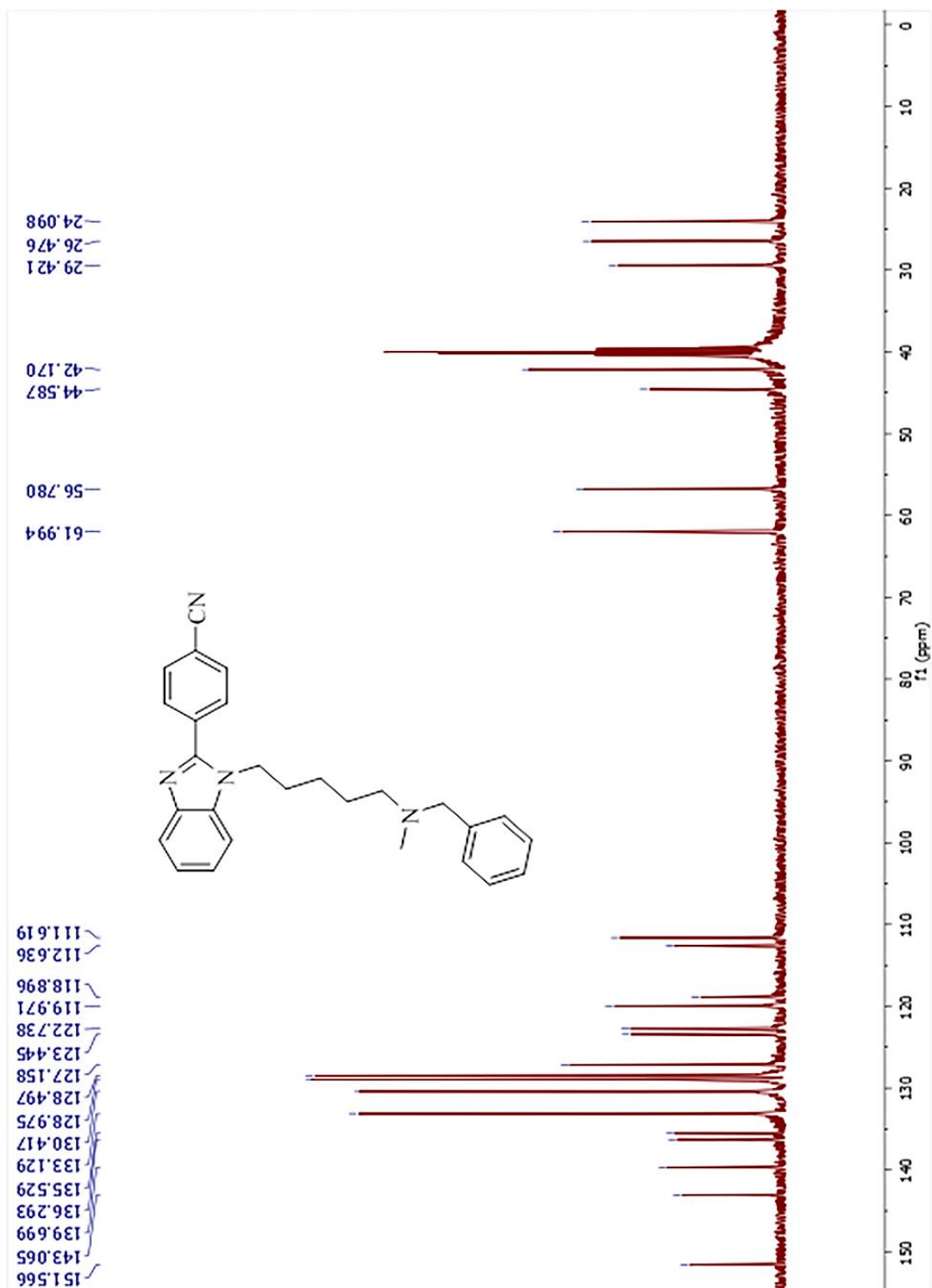


Figure 43. ^{13}C -NMR spectrum of compound (71)

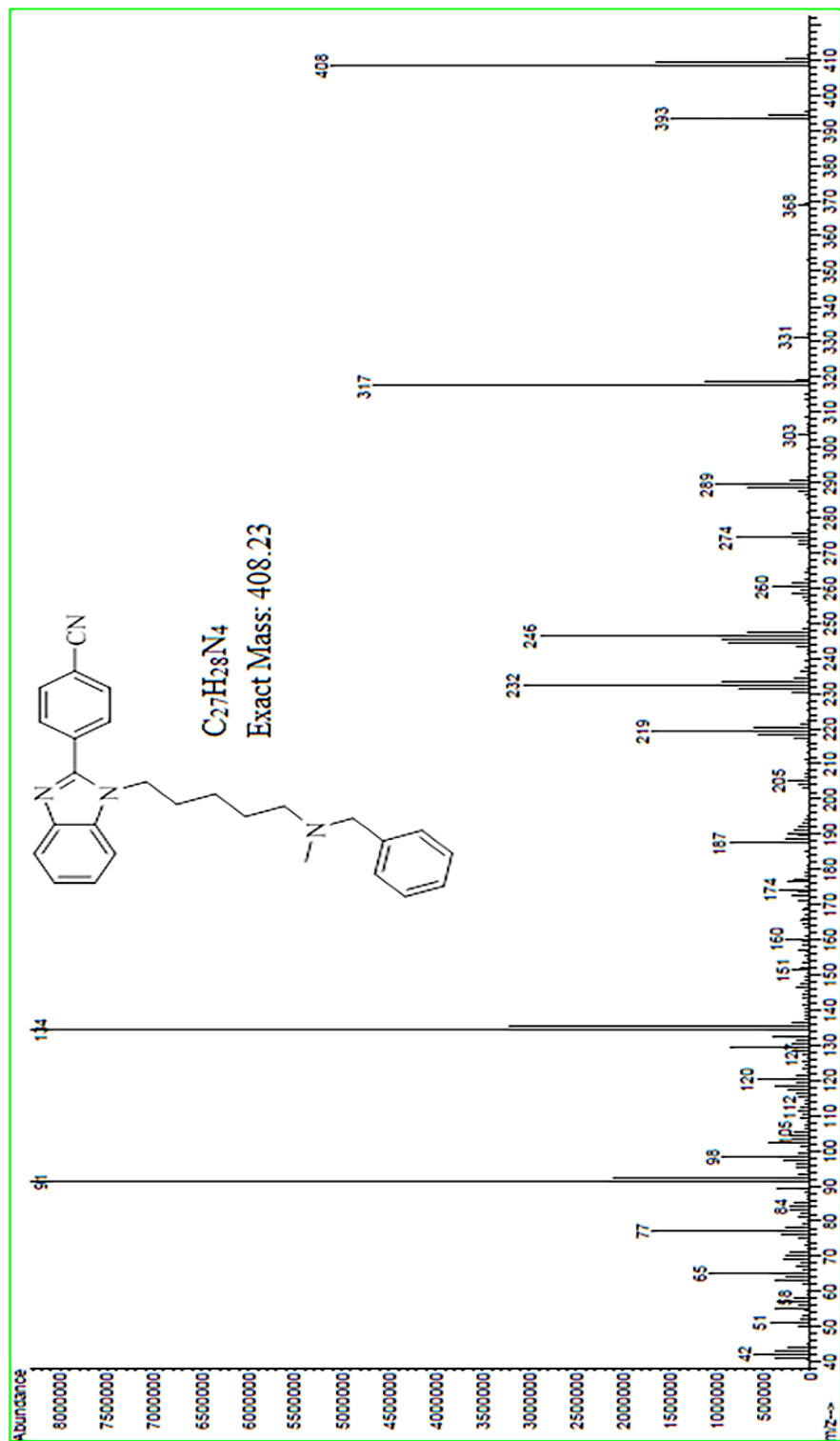


Figure 44. MASS spectrum of compound (71)

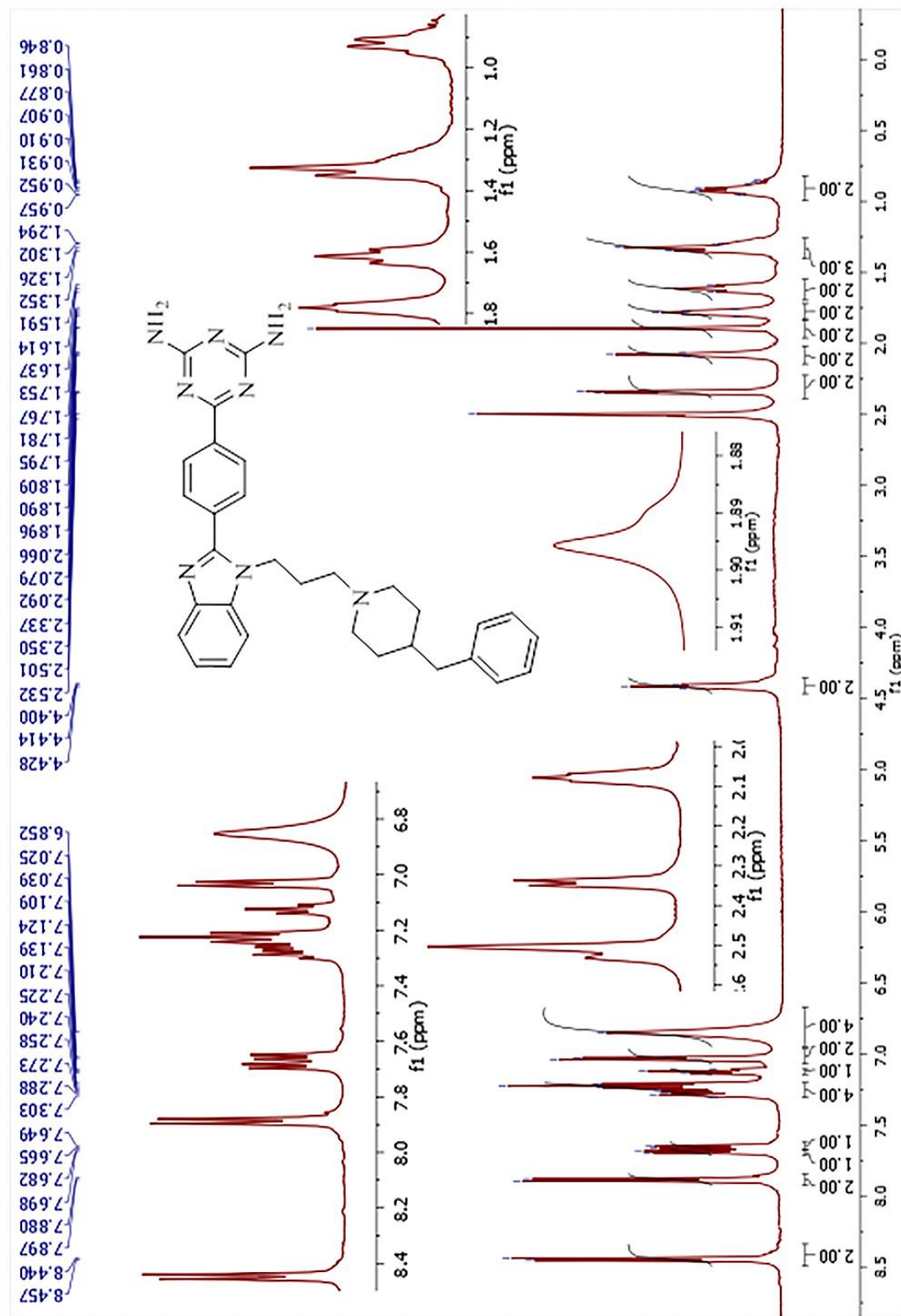


Figure 45. ¹H-NMR spectrum of compound (9a)

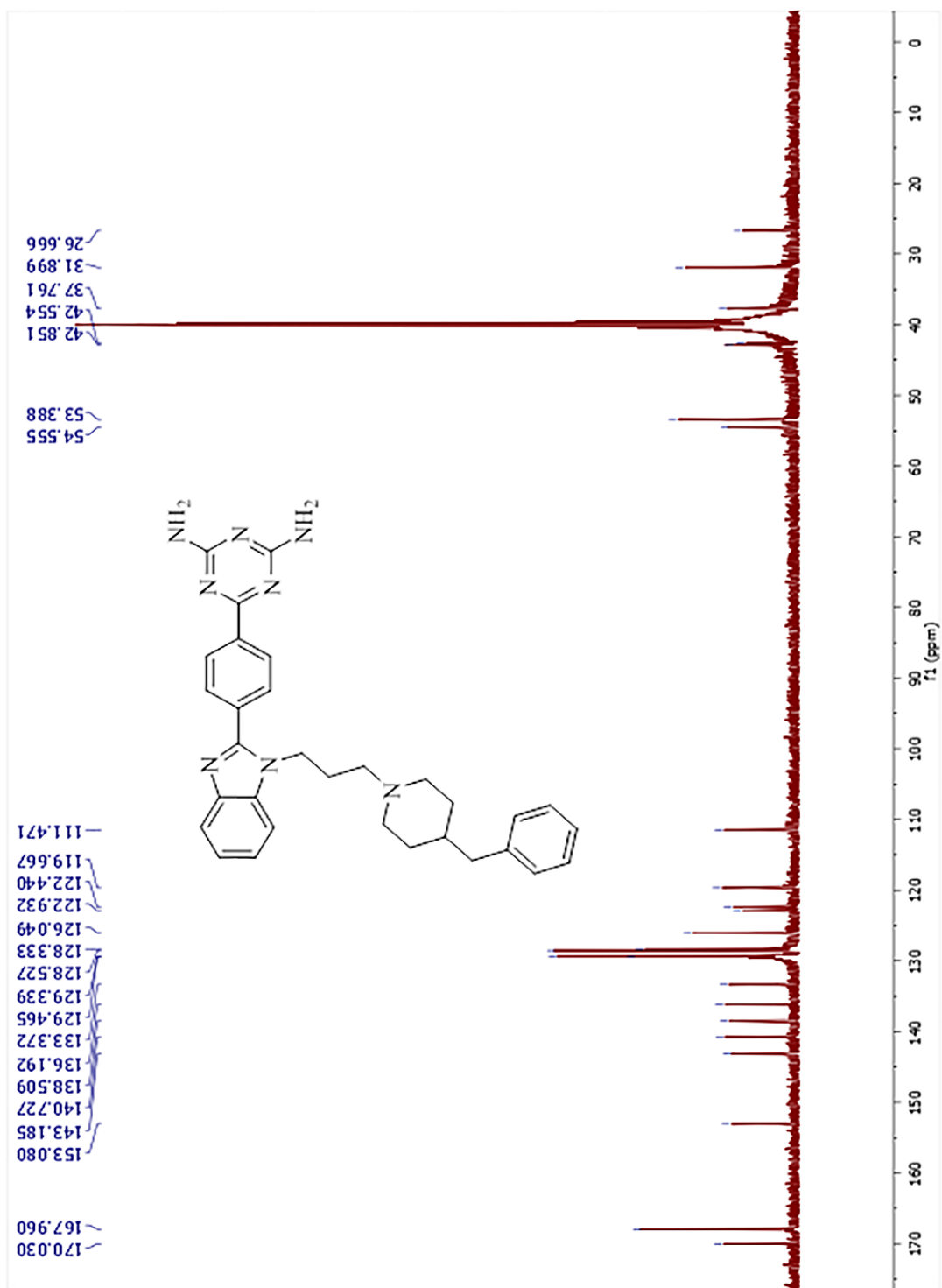


Figure 46. ^{13}C -NMR spectrum of compound (9a)

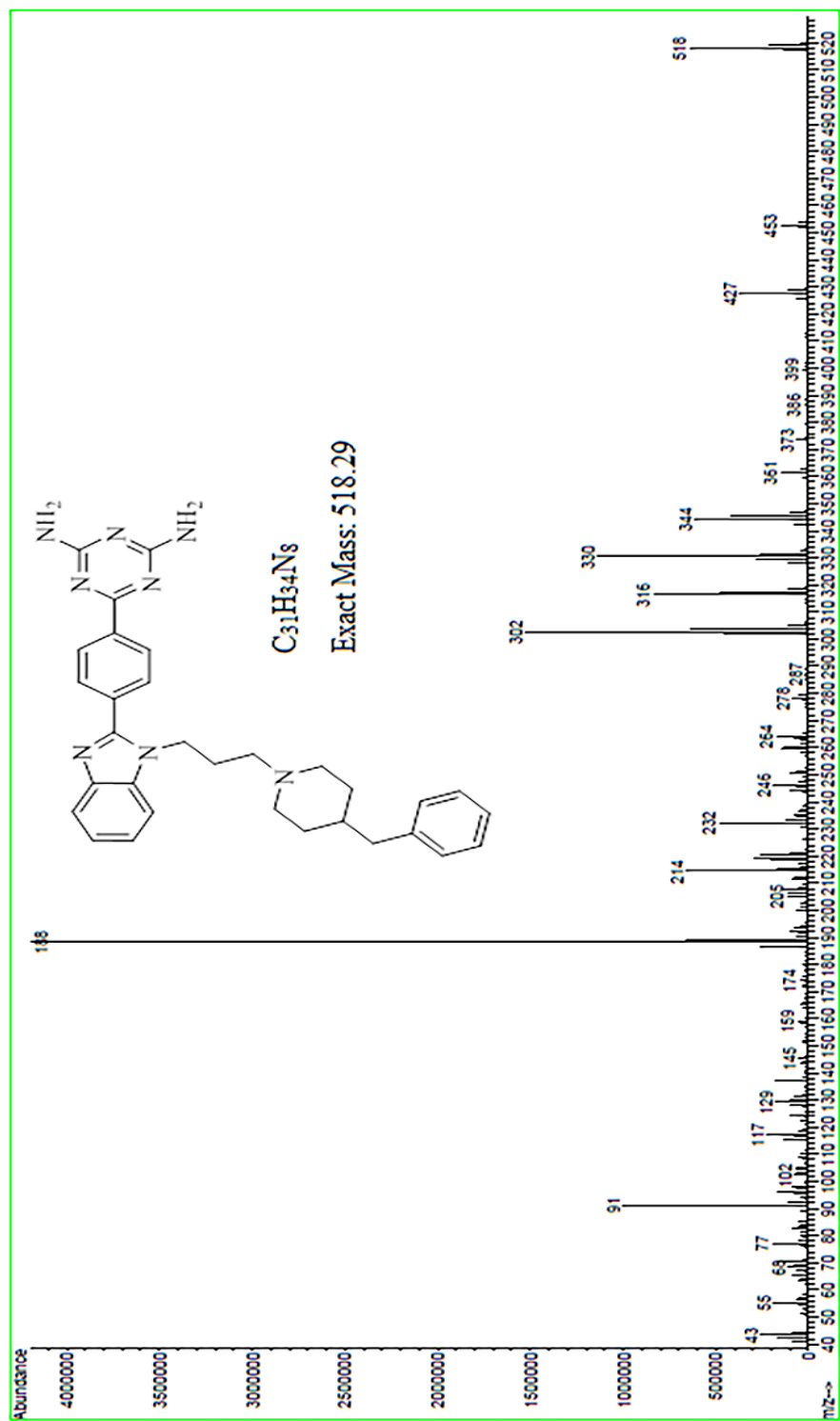


Figure 47. MASS spectrum of compound (9a)

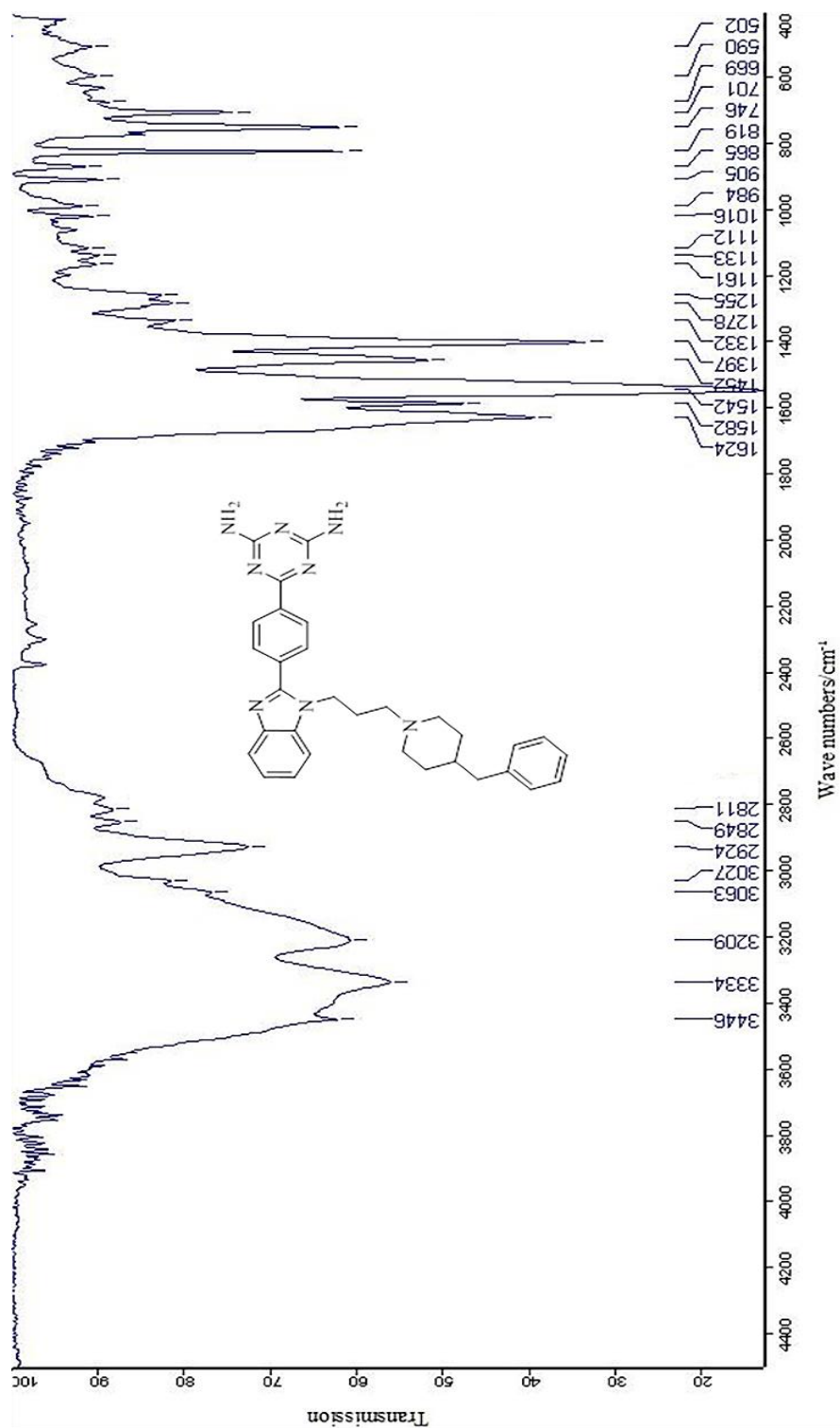


Figure 48. IR spectrum of compound (9a)

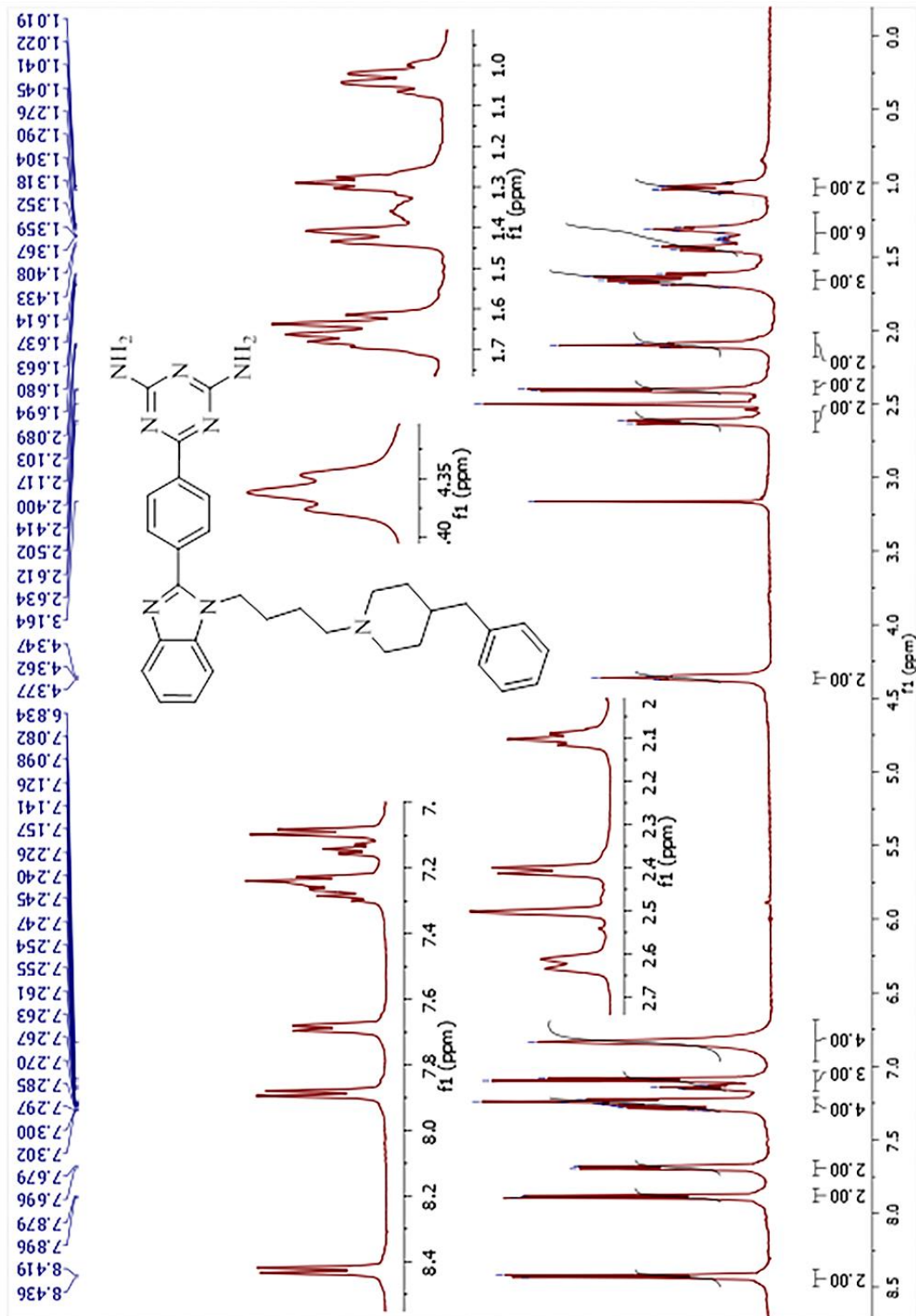


Figure 49. ¹H-NMR spectrum of compound (9b)

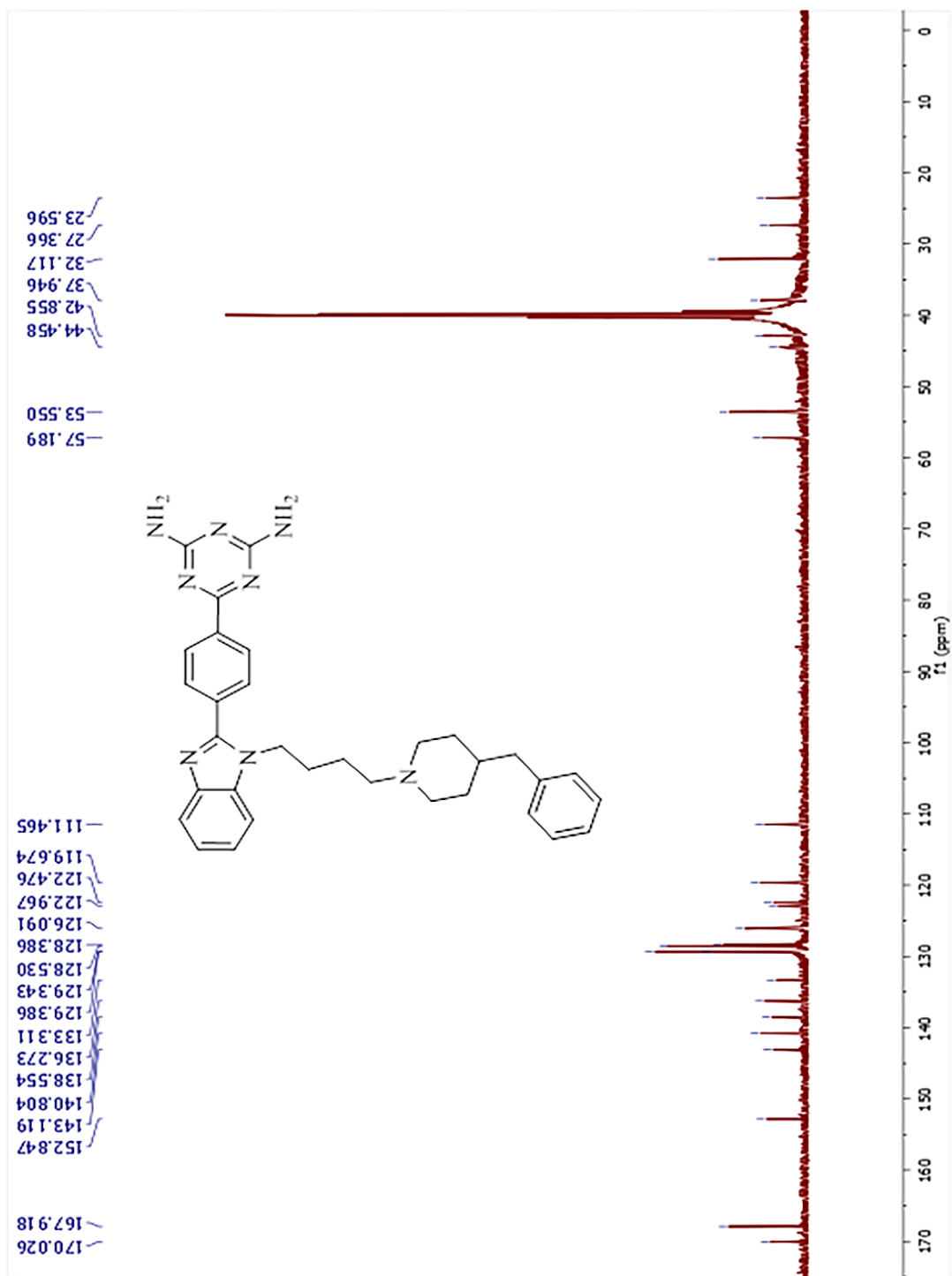


Figure 50. ^{13}C -NMR spectrum of compound (9b)

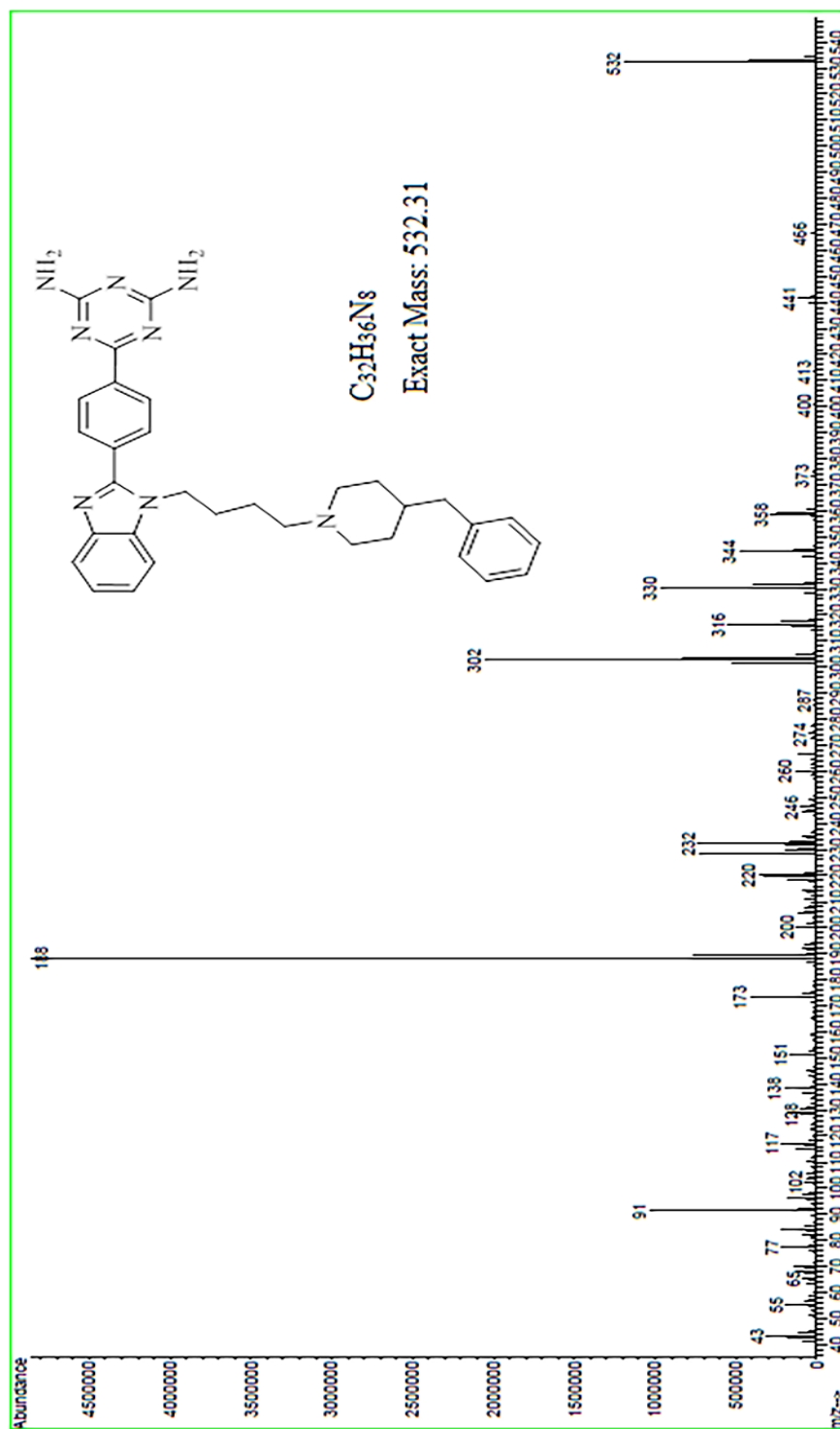


Figure 51. MASS spectrum of compound (9b)

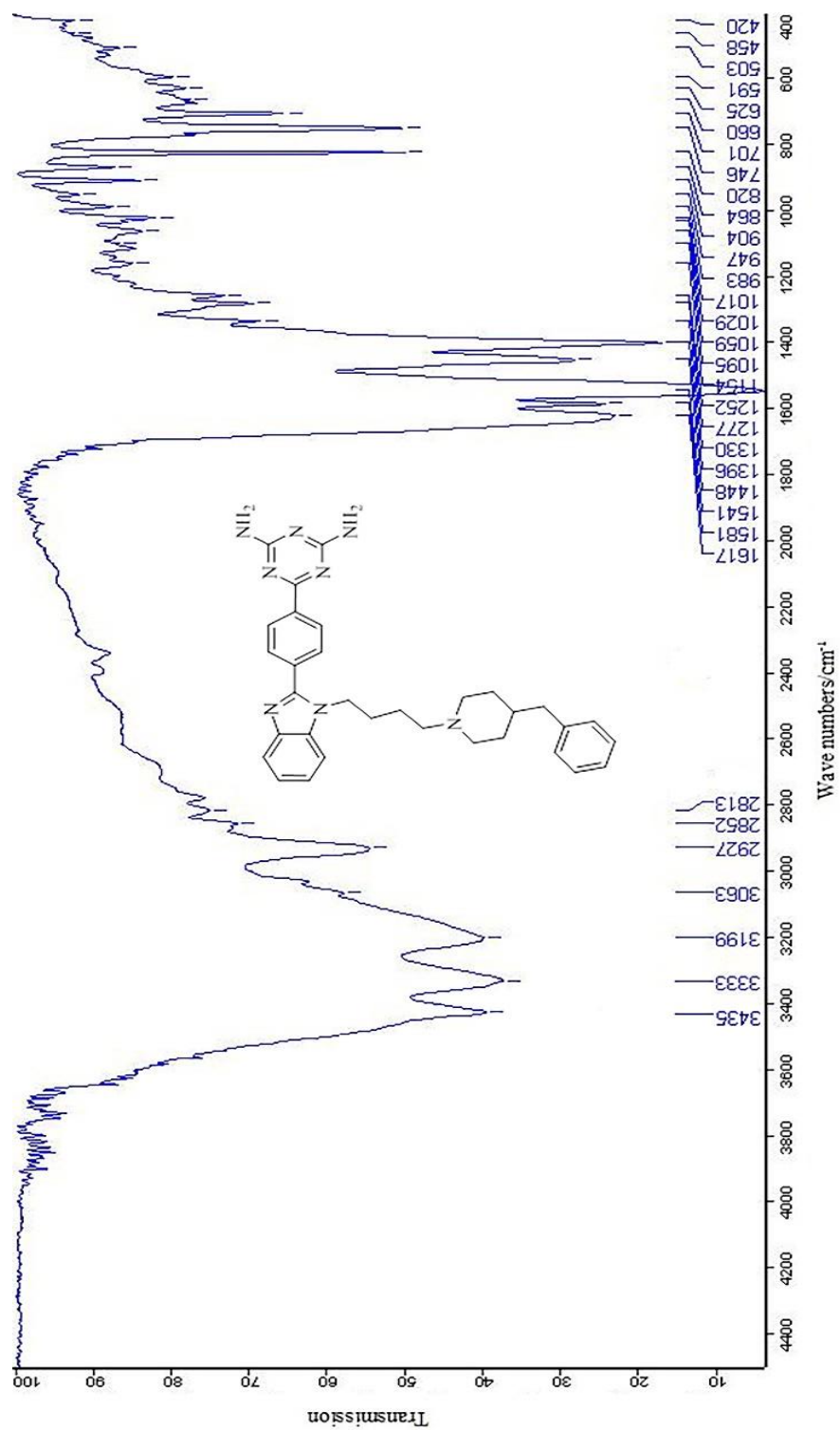


Figure 52. IR spectrum of compound (9b)

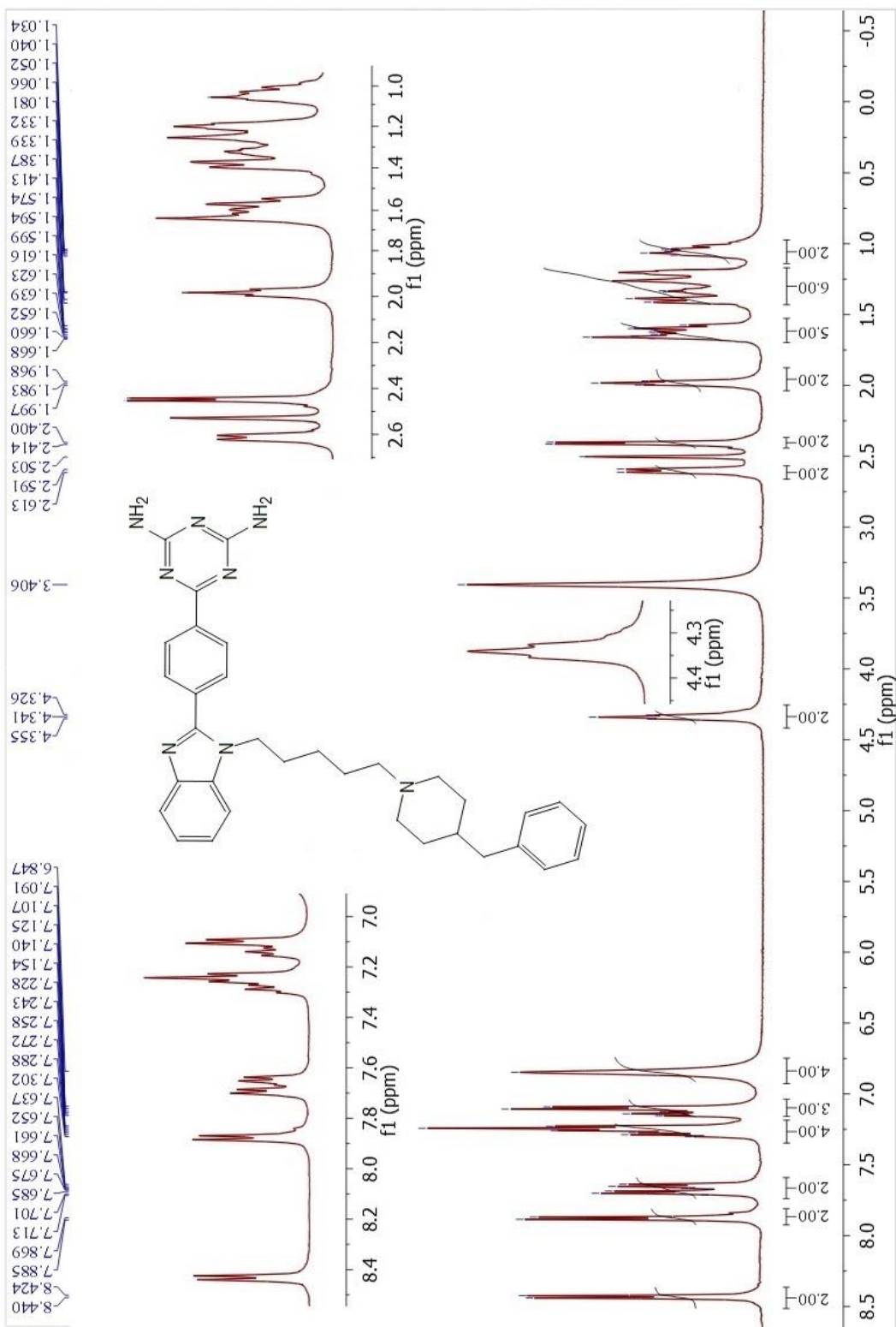


Figure 53. $^1\text{H-NMR}$ spectrum of compound (9c)

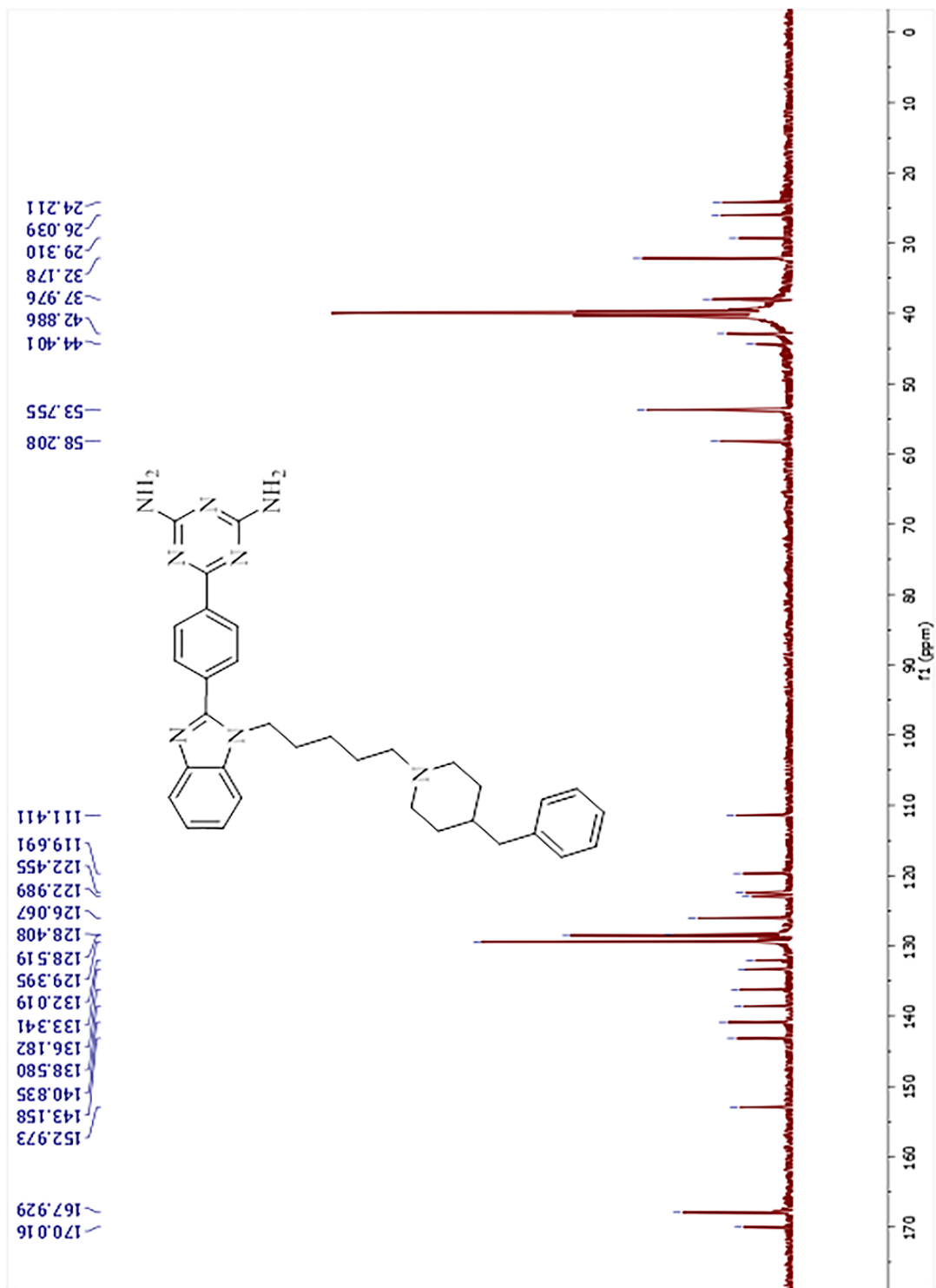


Figure 54. ^{13}C -NMR spectrum of compound (9c)

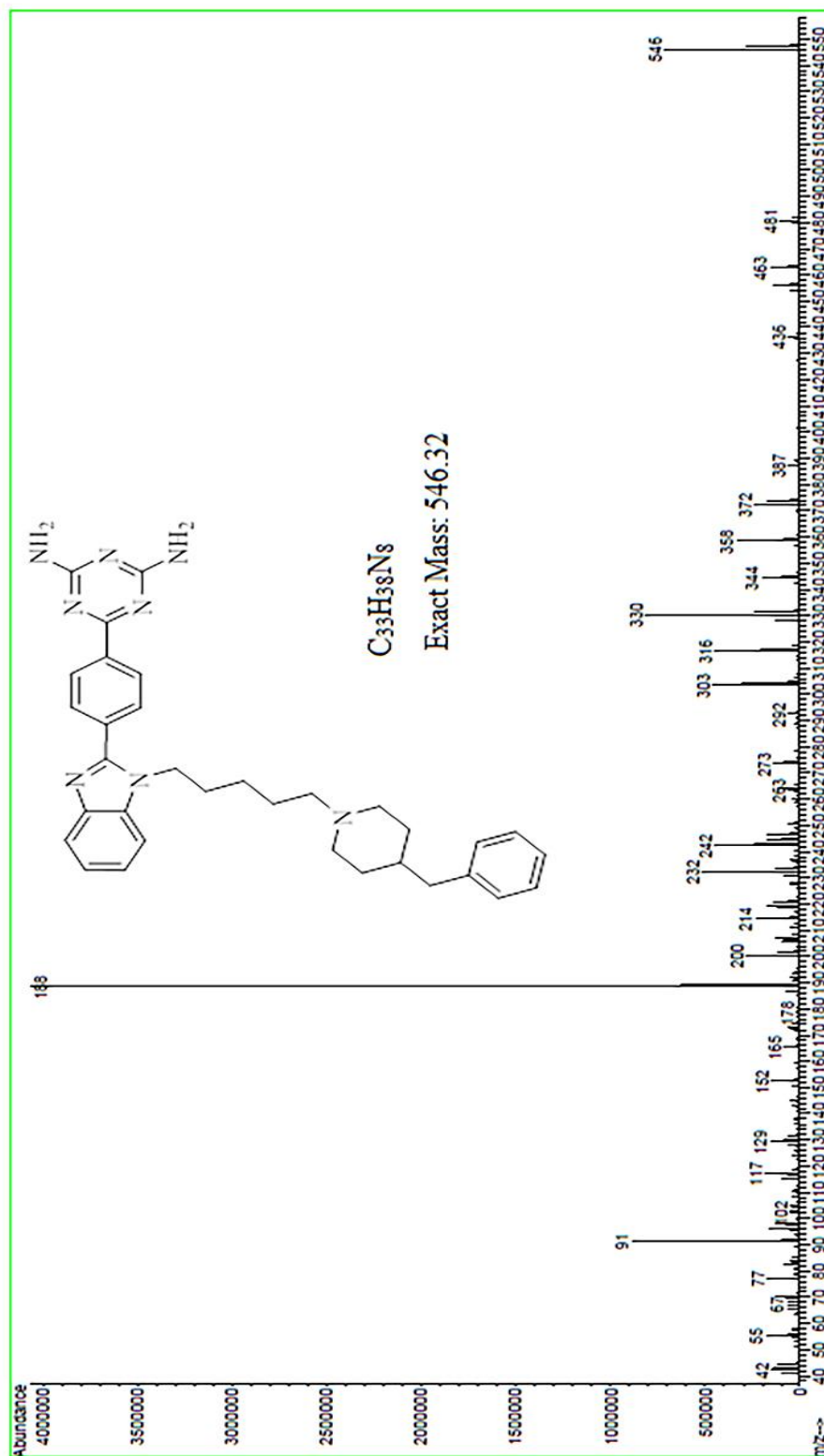


Figure 55. MASS spectrum of compound (9c)

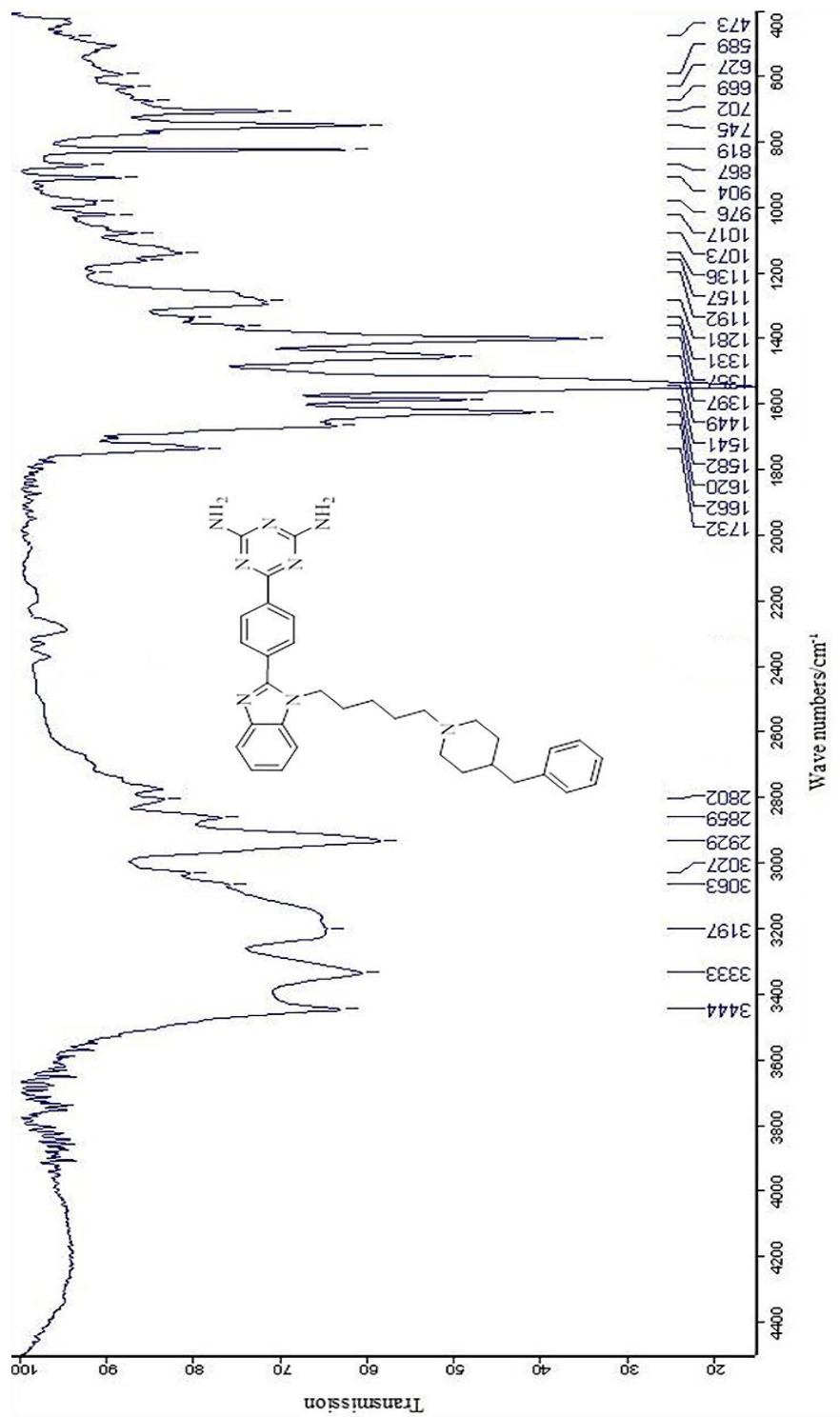


Figure 56. IR spectrum of compound (9c)

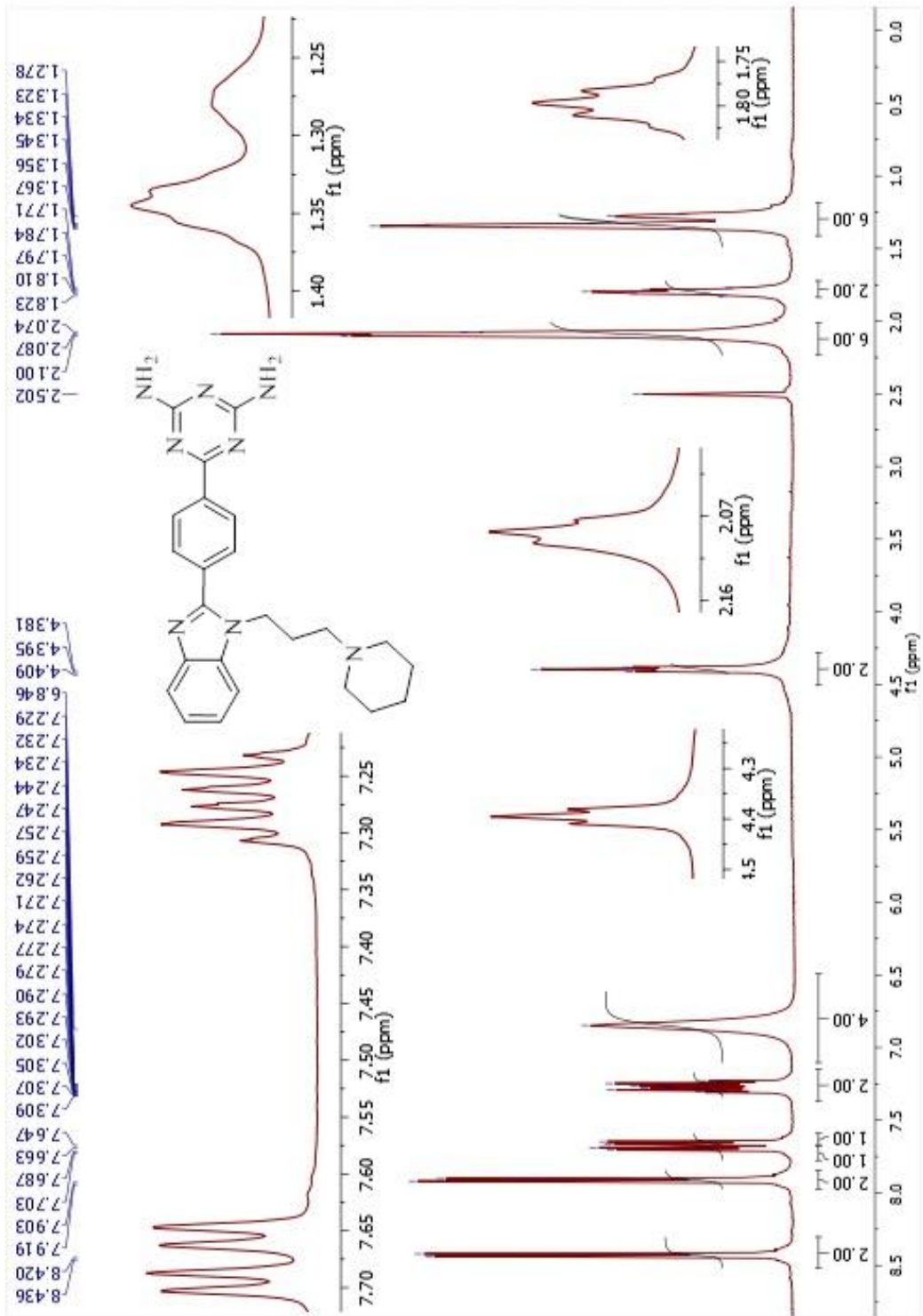


Figure 57. ¹H-NMR spectrum of compound (9d)

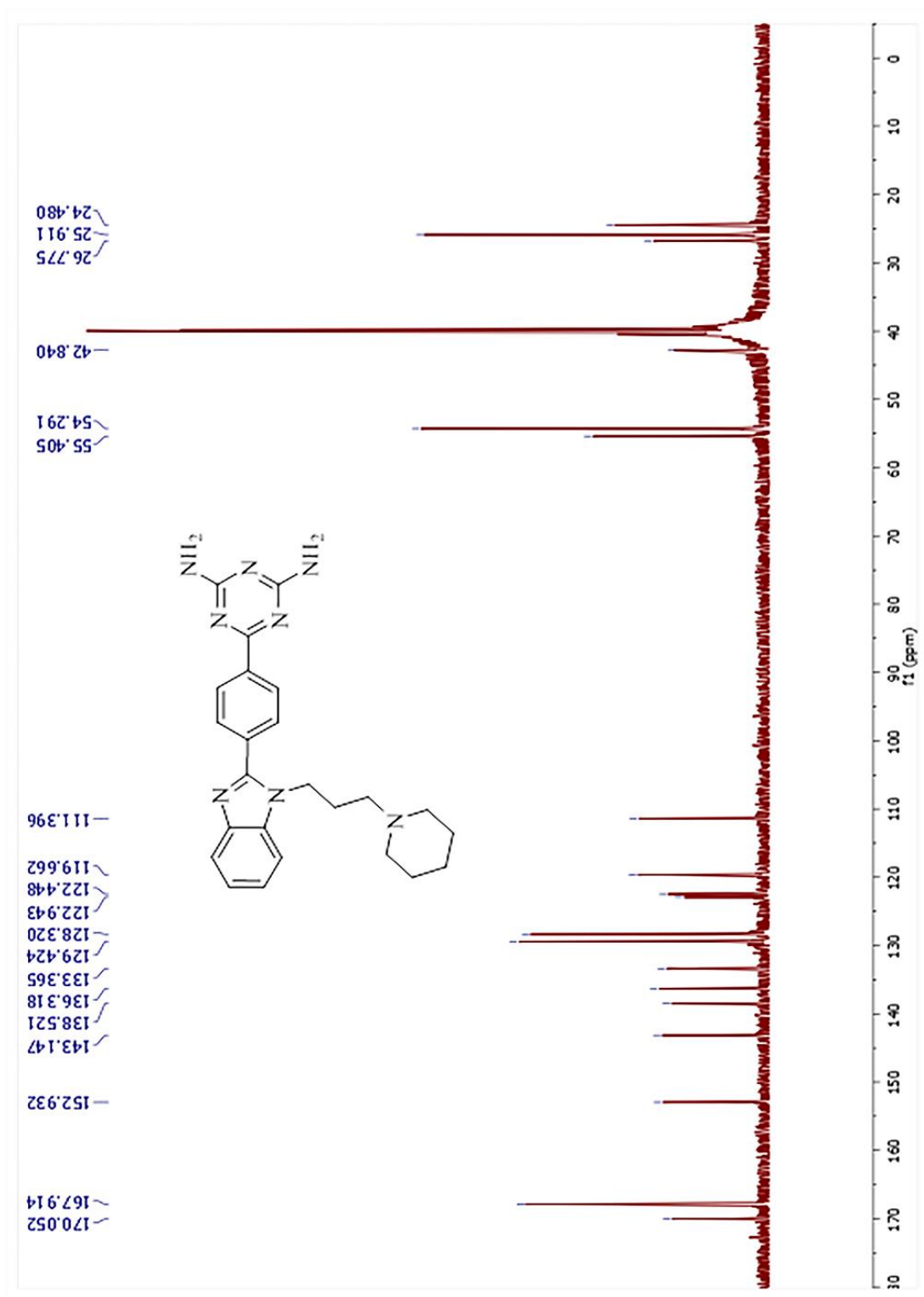


Figure 58. ^{13}C -NMR spectrum of compound (9d)

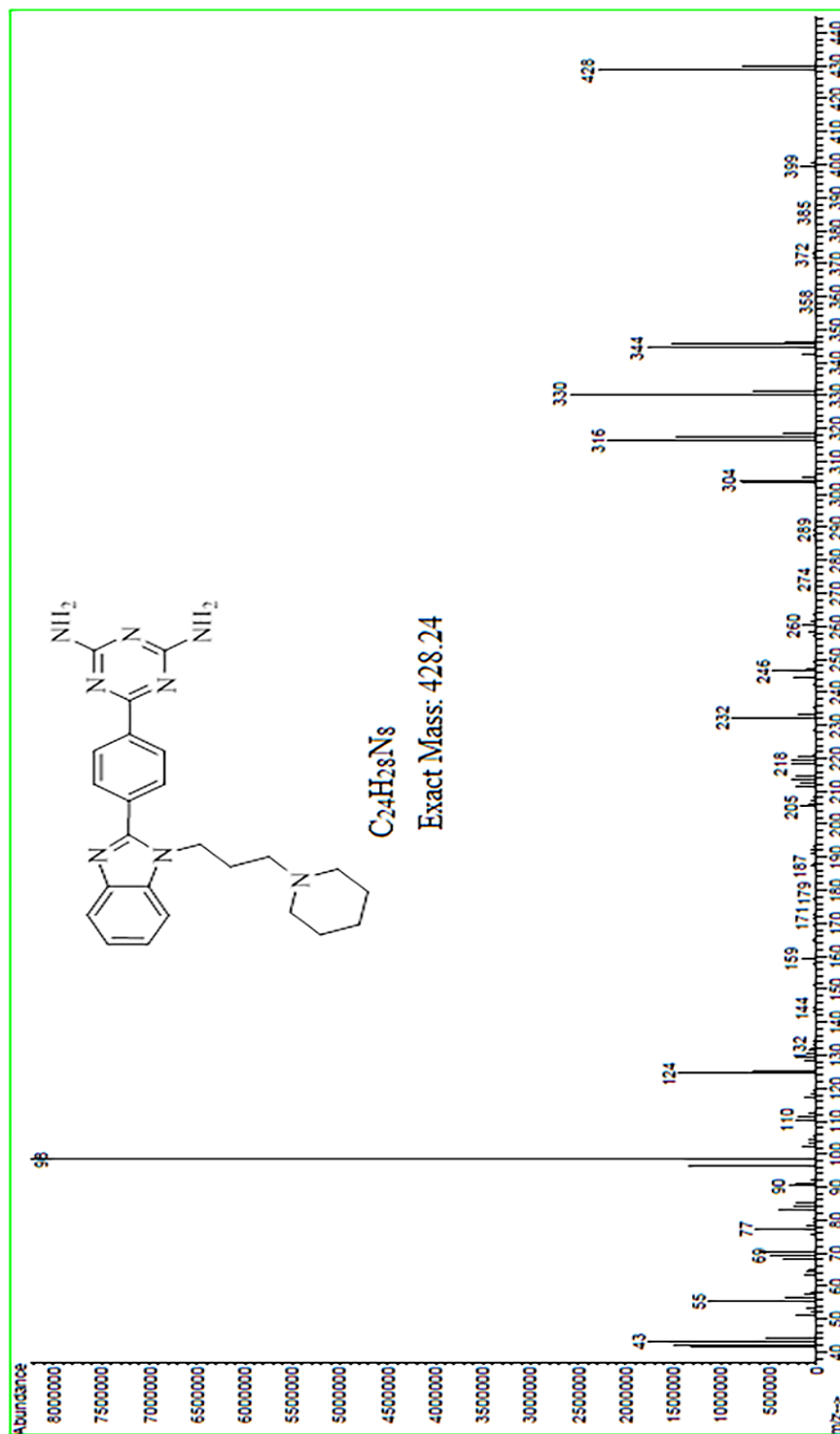


Figure 59. MASS spectrum of compound (9d)

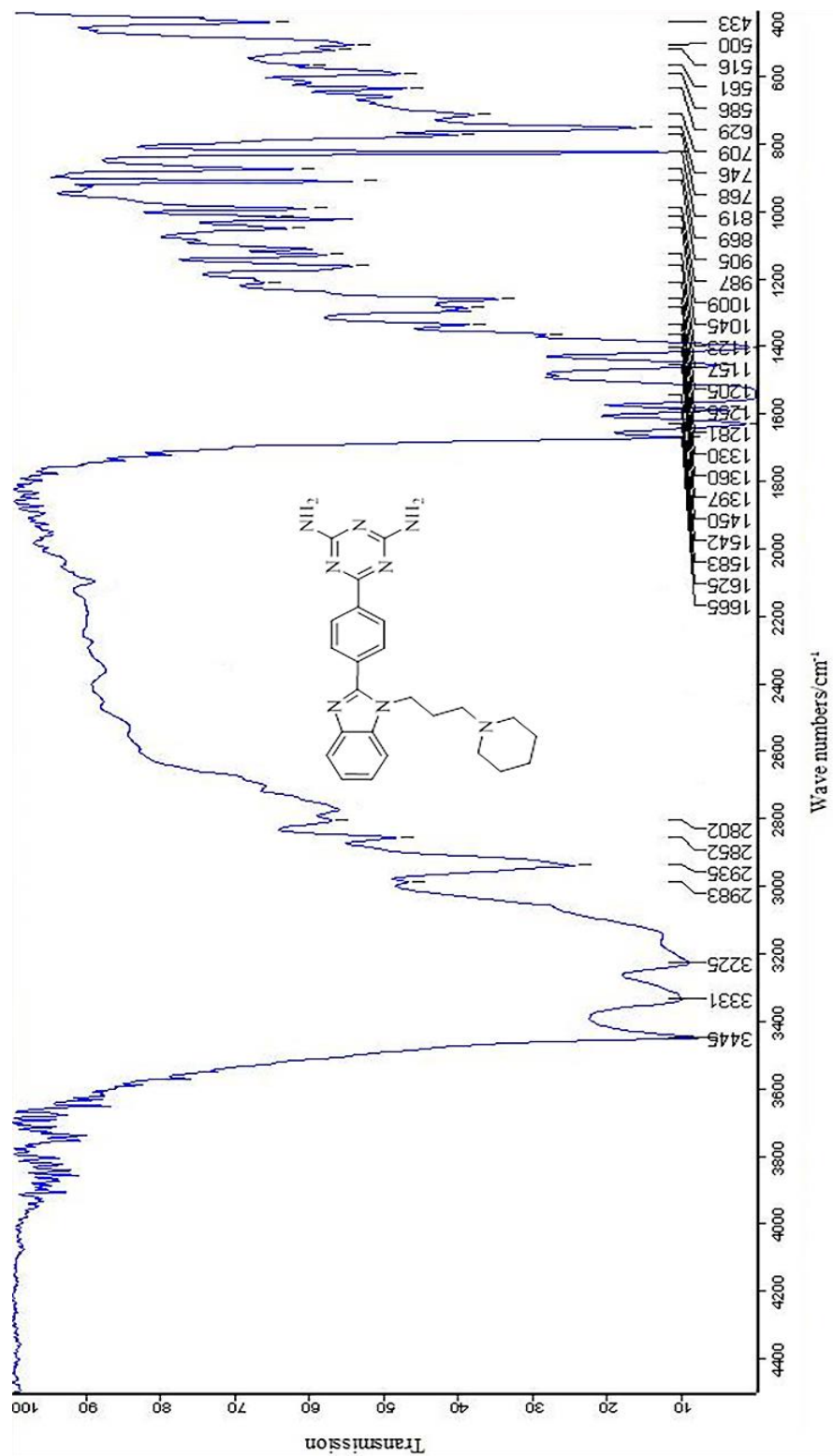


Figure 60. IR spectrum of compound (9d)

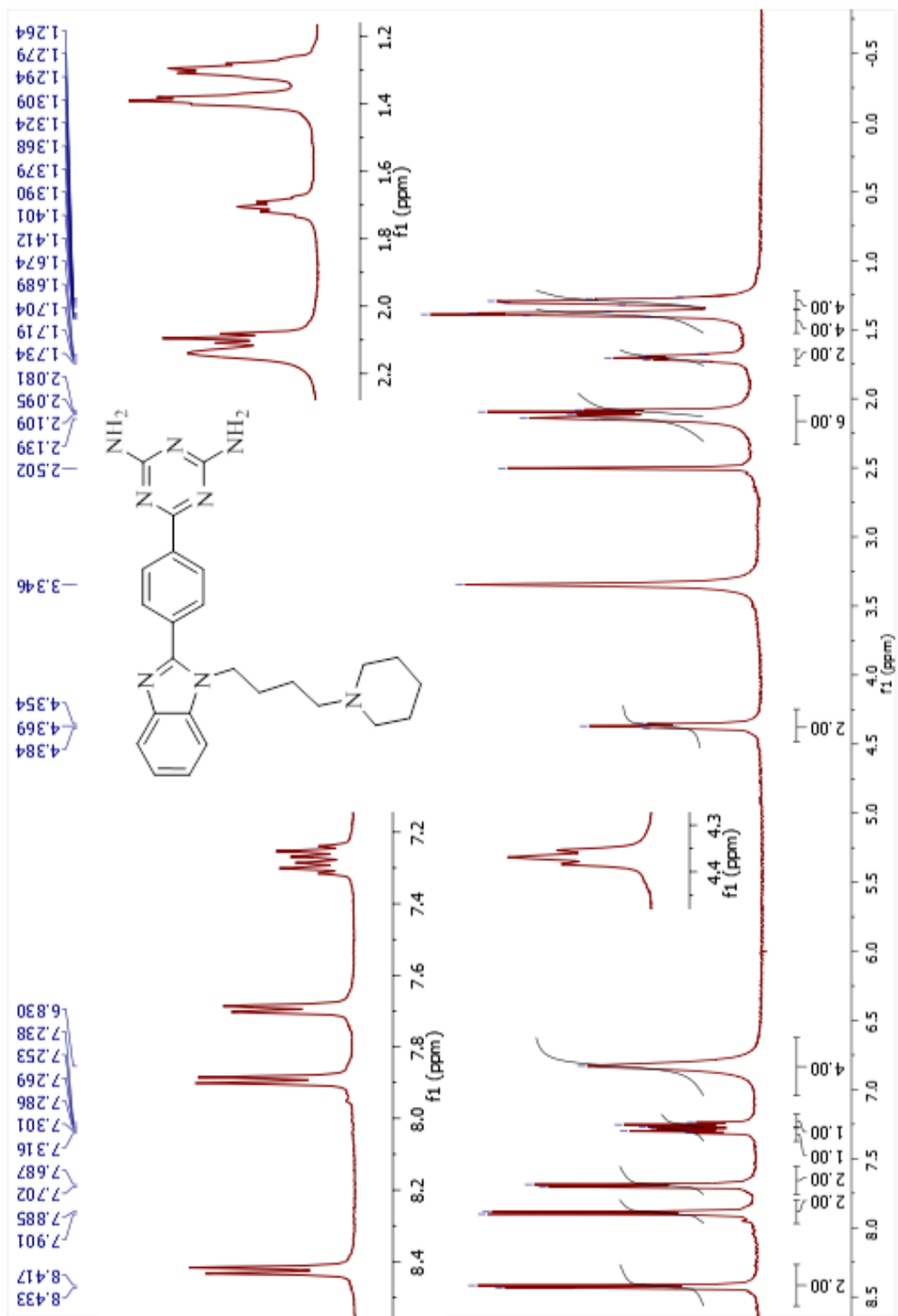


Figure 61. ¹H-NMR spectrum of compound (9e)

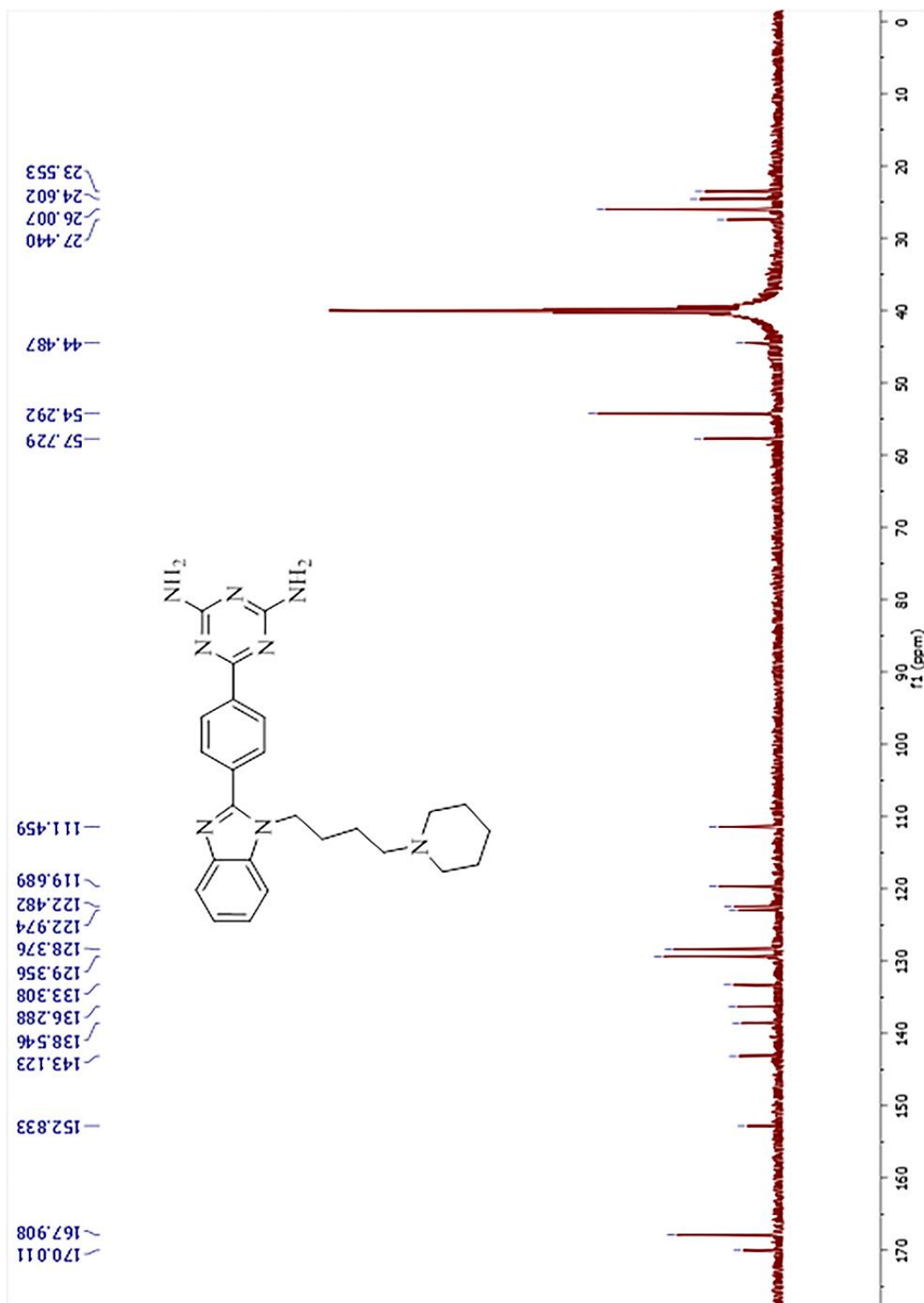


Figure 62. ^{13}C -NMR spectrum of compound (9e)

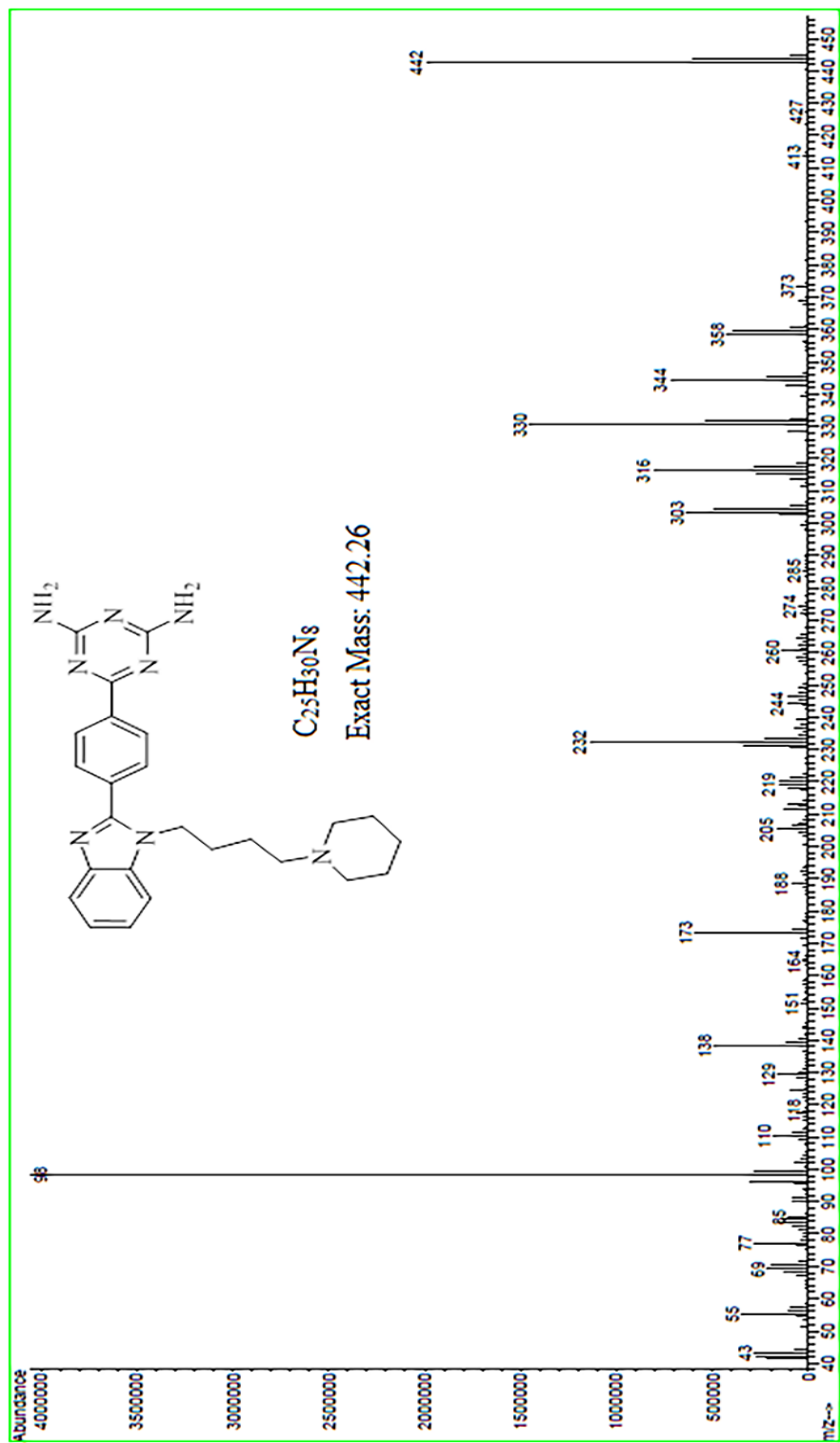


Figure 63. MASS spectrum of compound (9e)

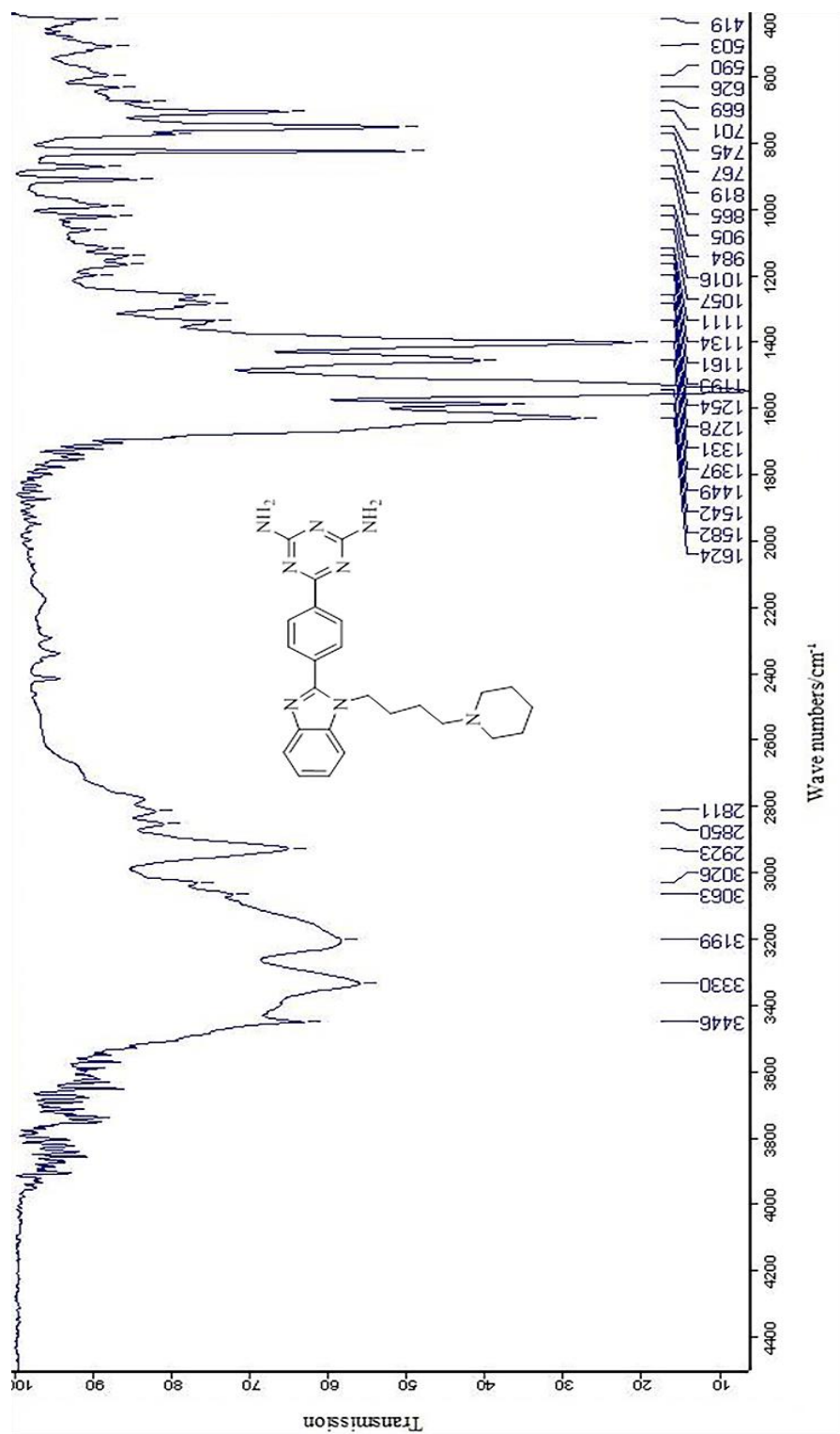


Figure 64. IR spectrum of compound (9e)

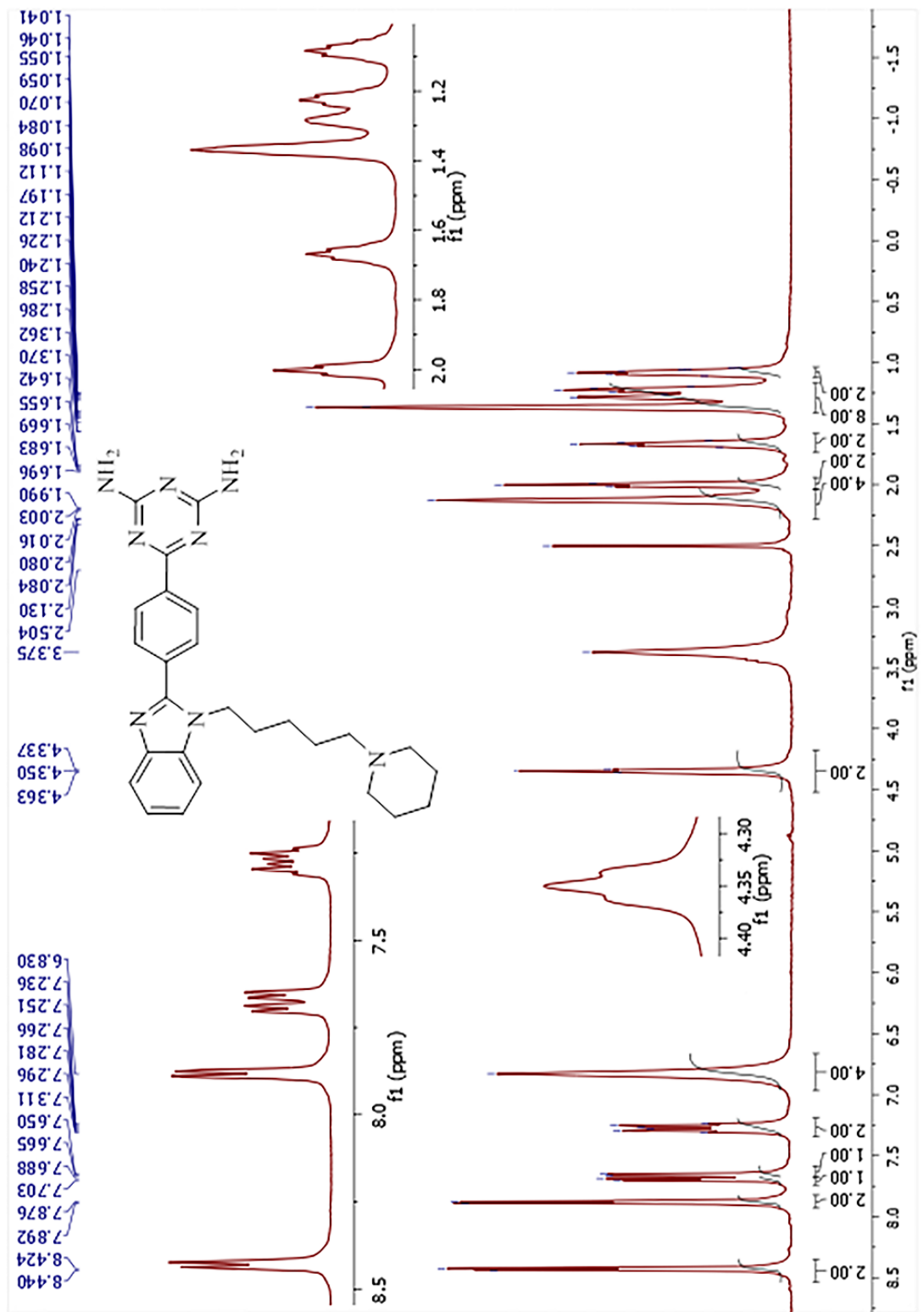


Figure 65. ¹H-NMR spectrum of compound (9f)

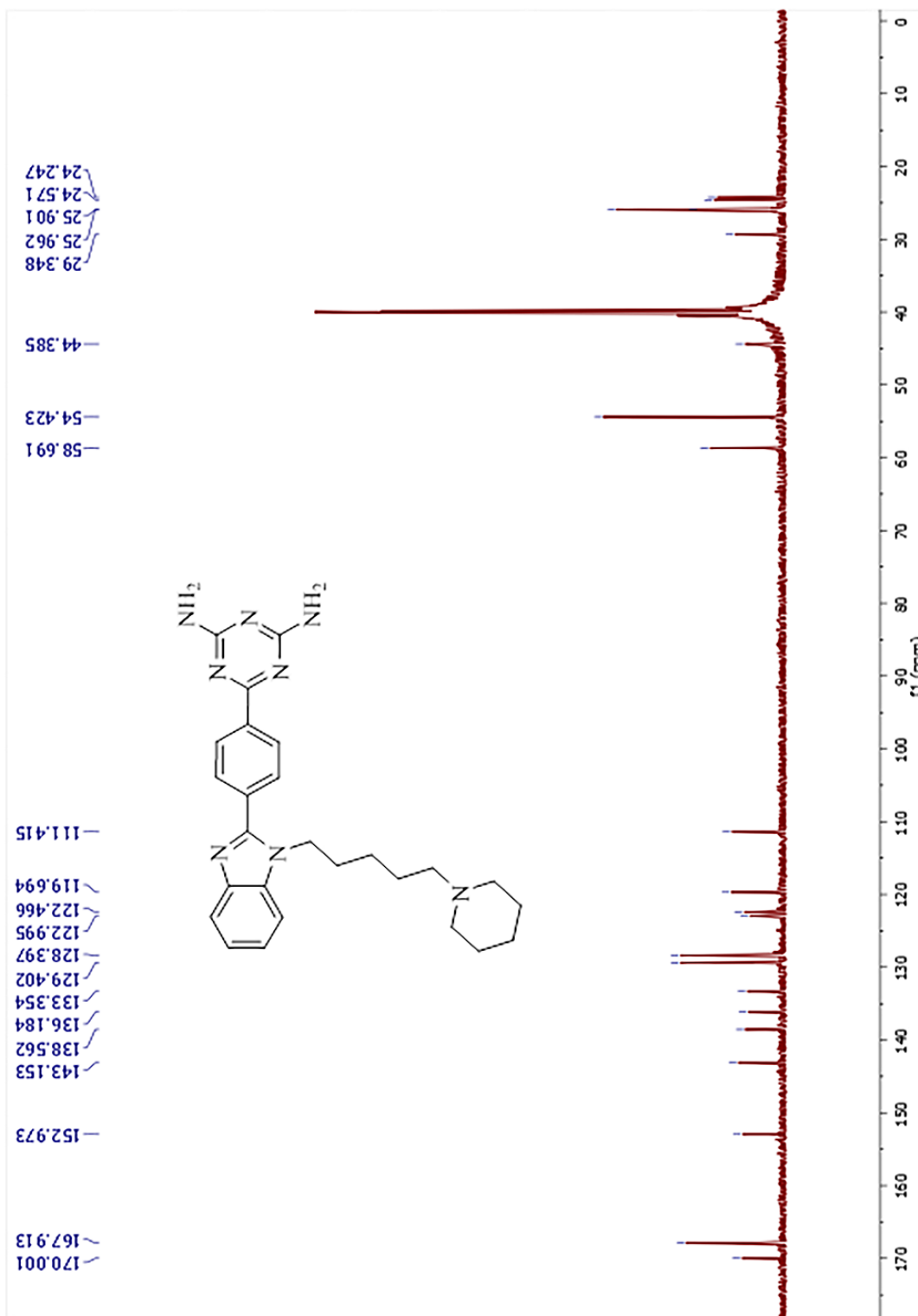


Figure 66. ^{13}C -NMR spectrum of compound (9f)

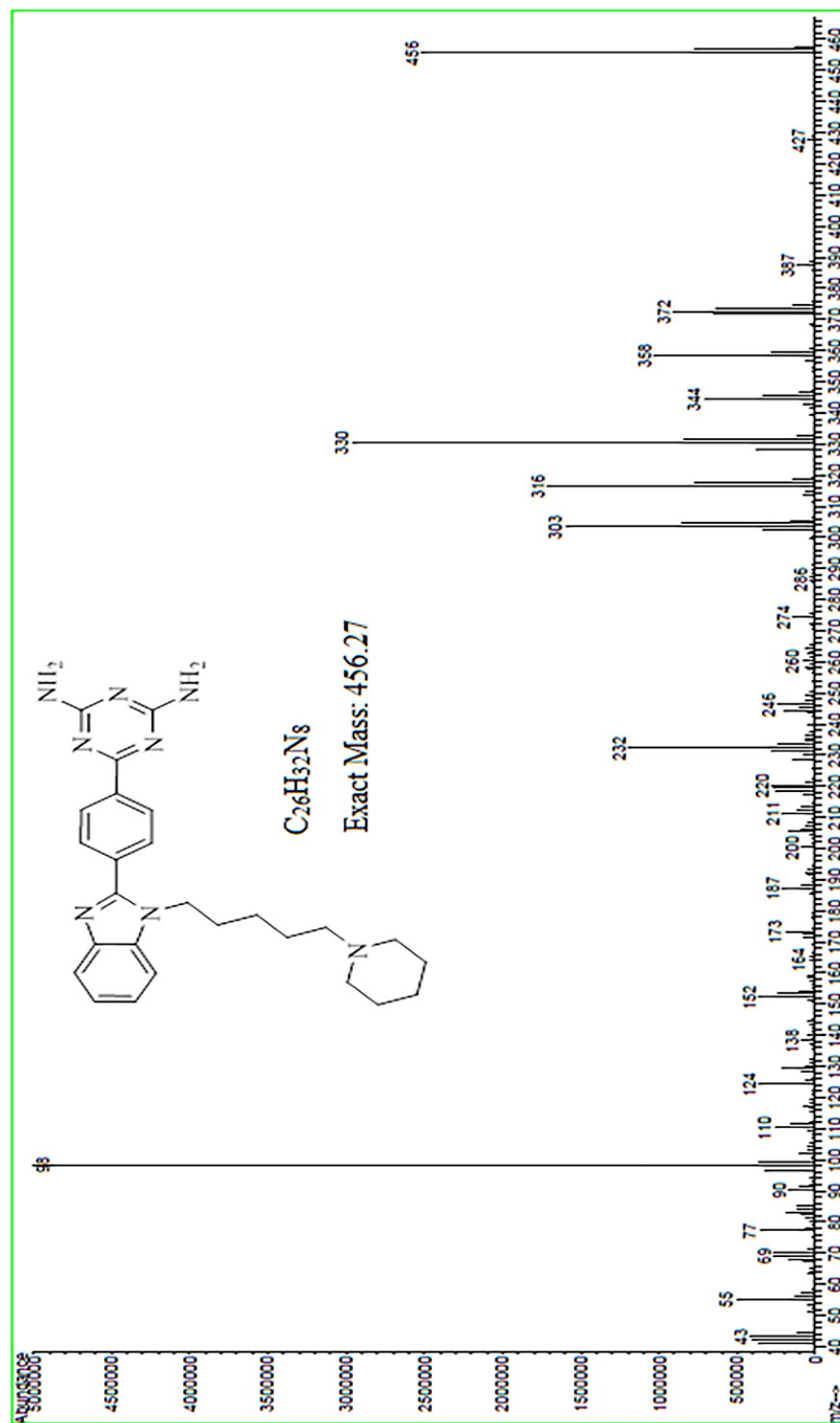


Figure 67. MASS spectrum of compound (9f)

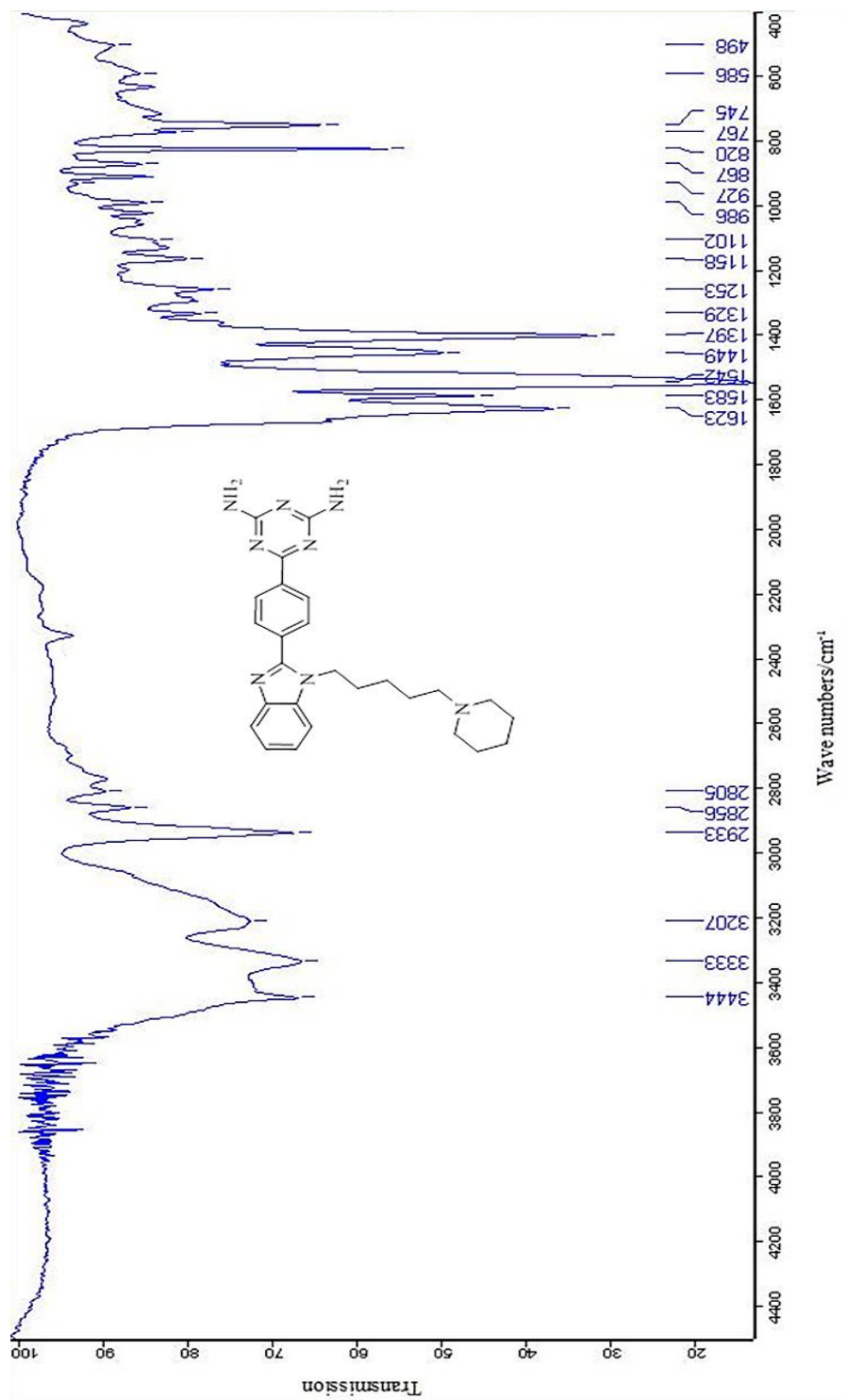


Figure 68. IR spectrum of compound (9f)

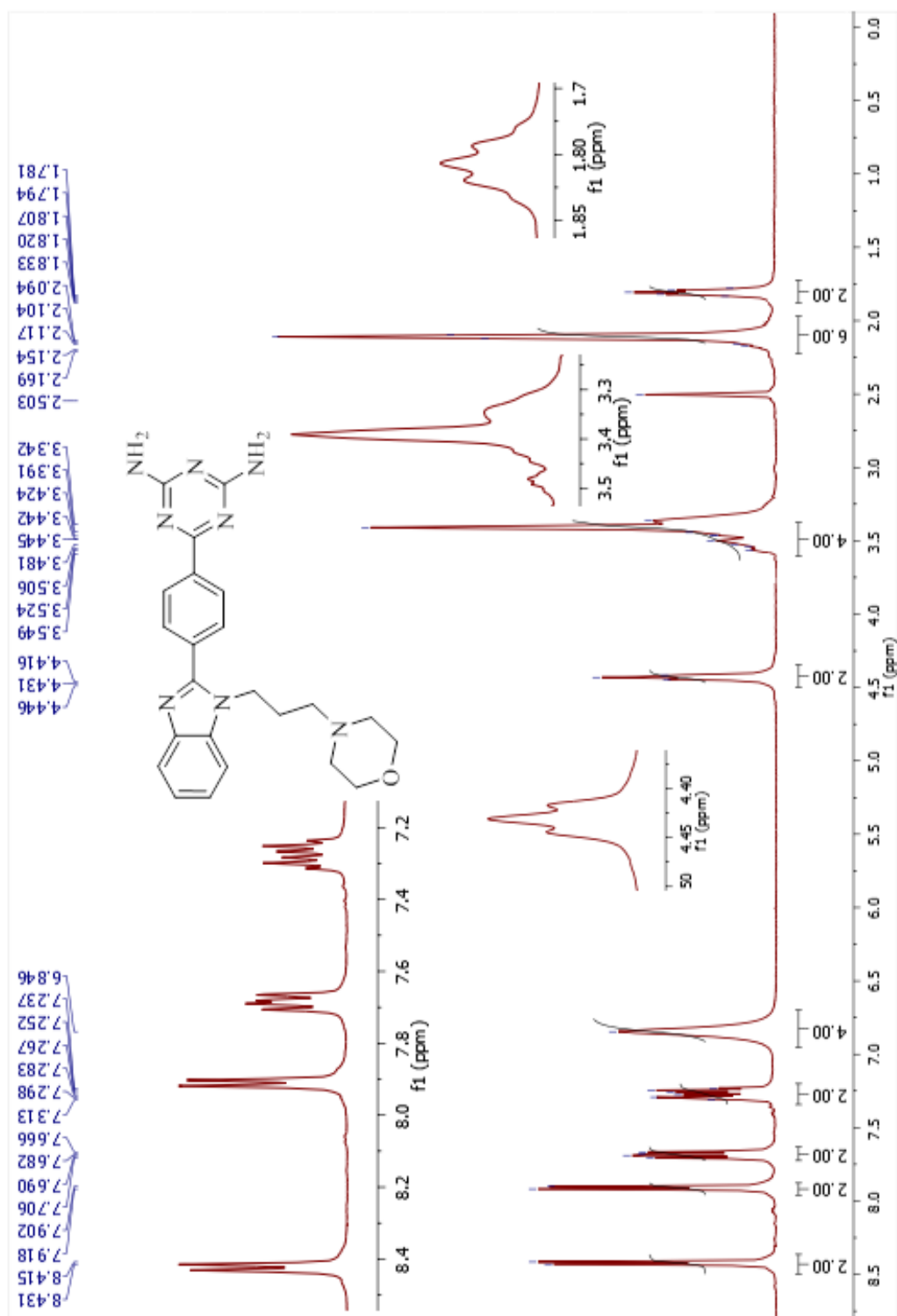


Figure 69. ¹H-NMR spectrum of compound (9g)

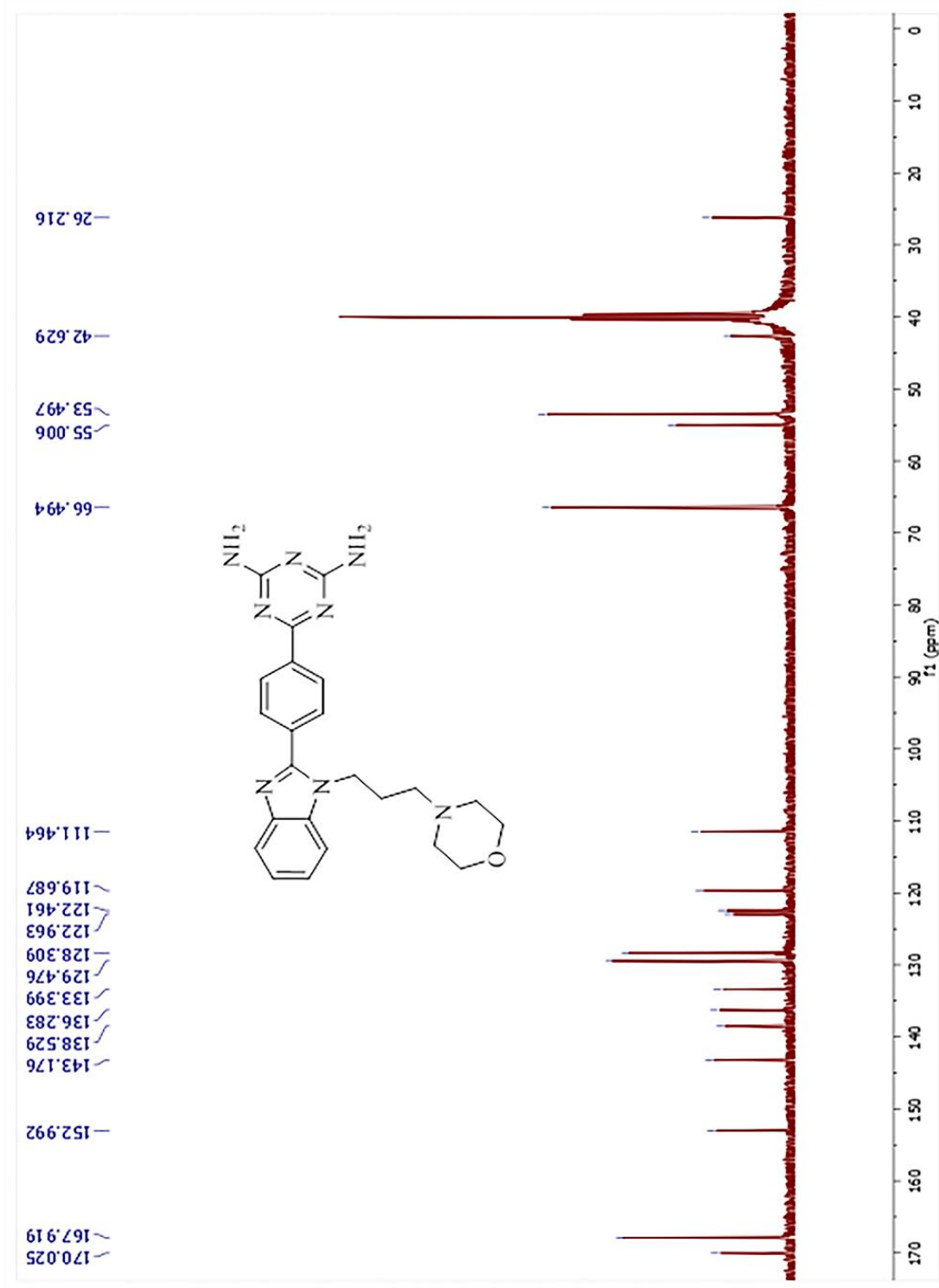


Figure 70. ¹³C-NMR spectrum of compound (9g)

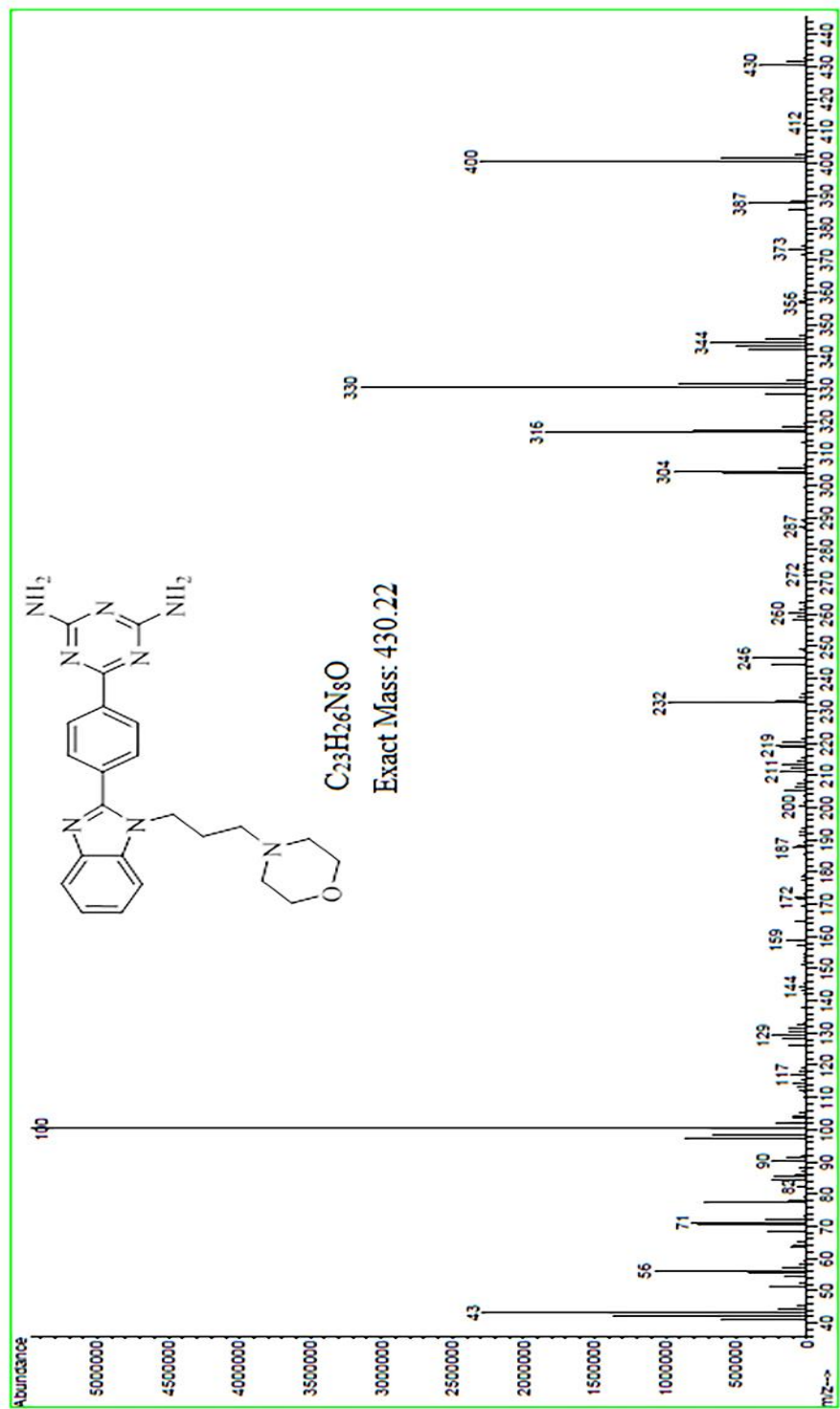


Figure 71. MASS spectrum of compound (9g)

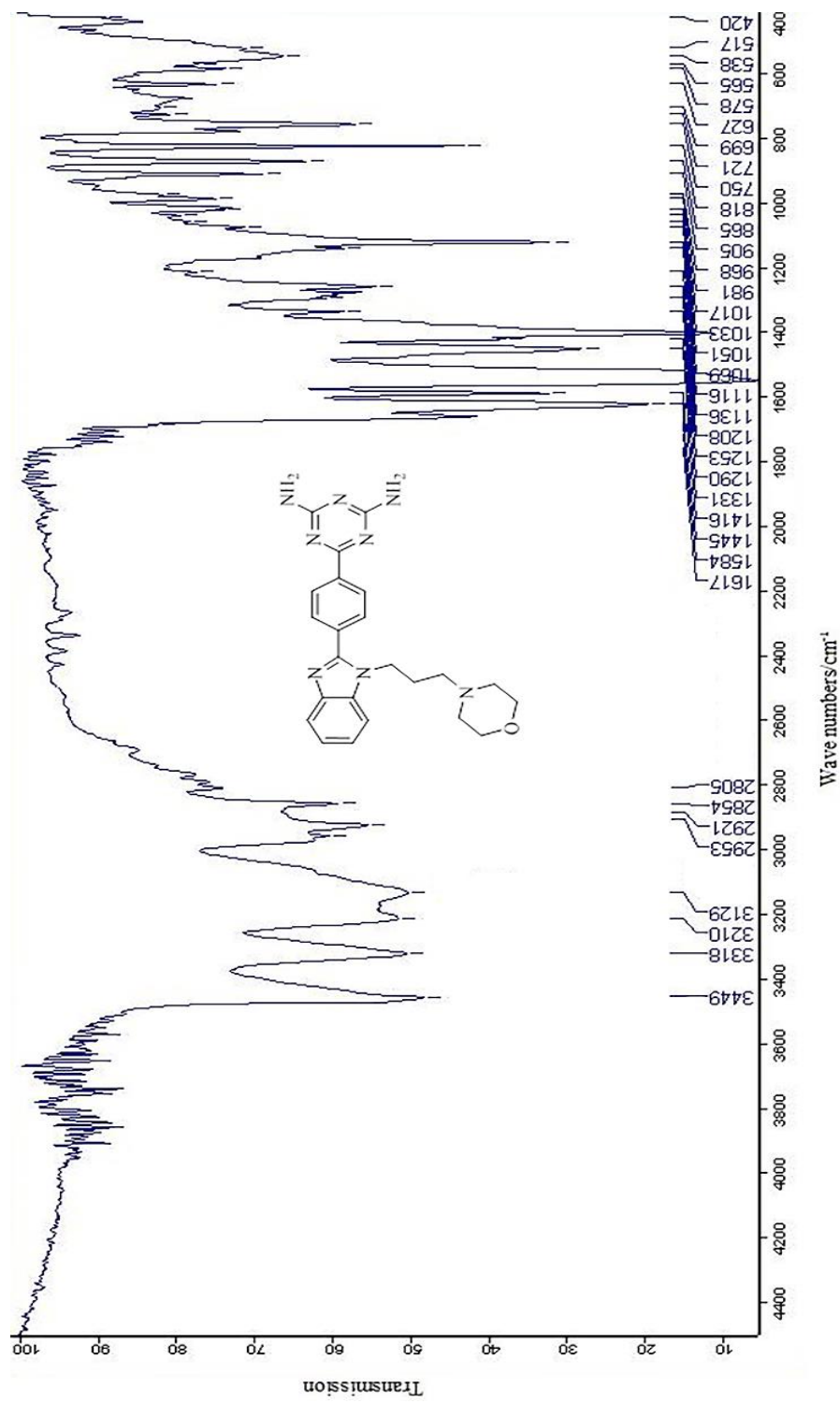


Figure 72. IR spectrum of compound (9g)

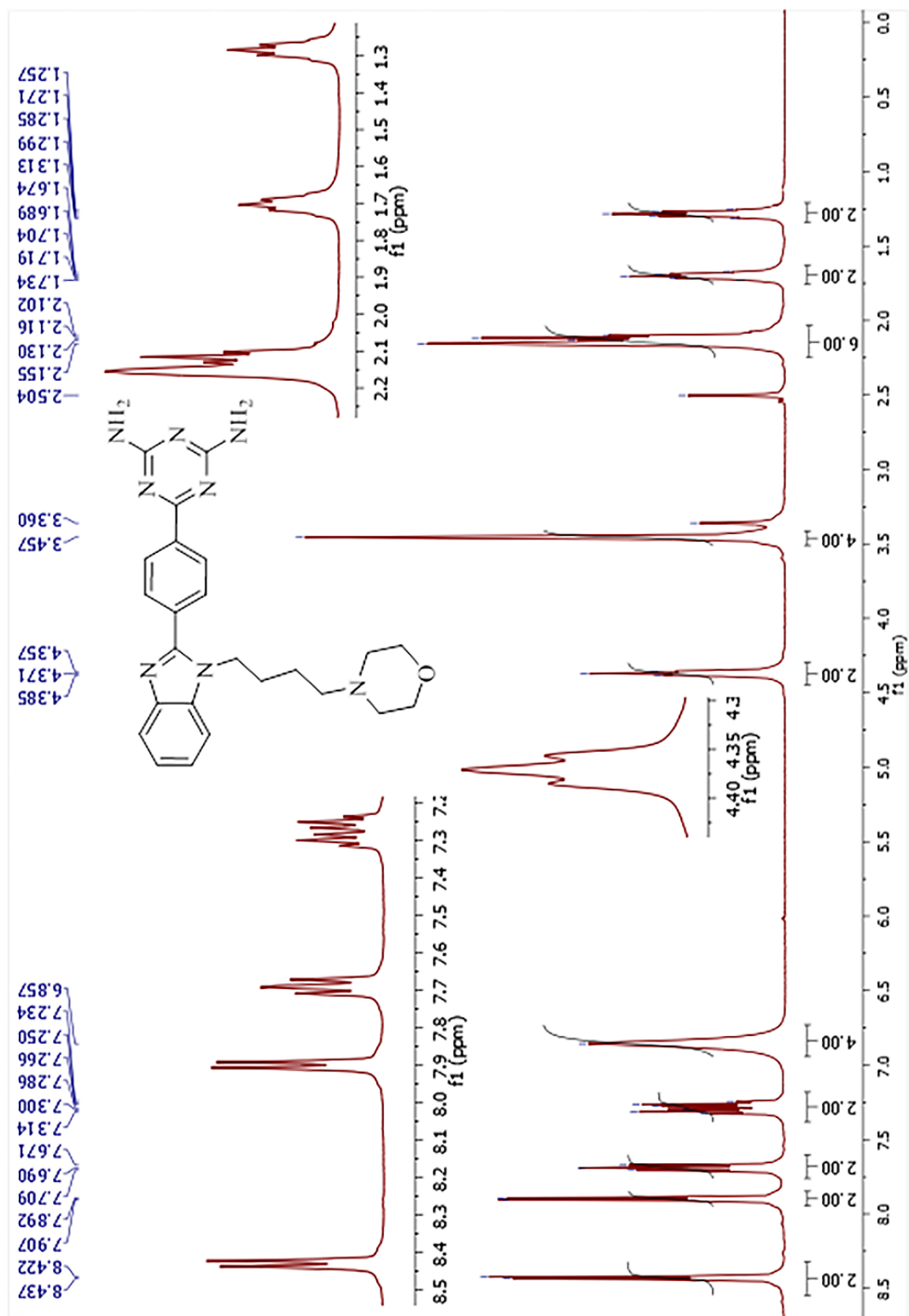


Figure 73. ¹H-NMR spectrum of compound (9h)

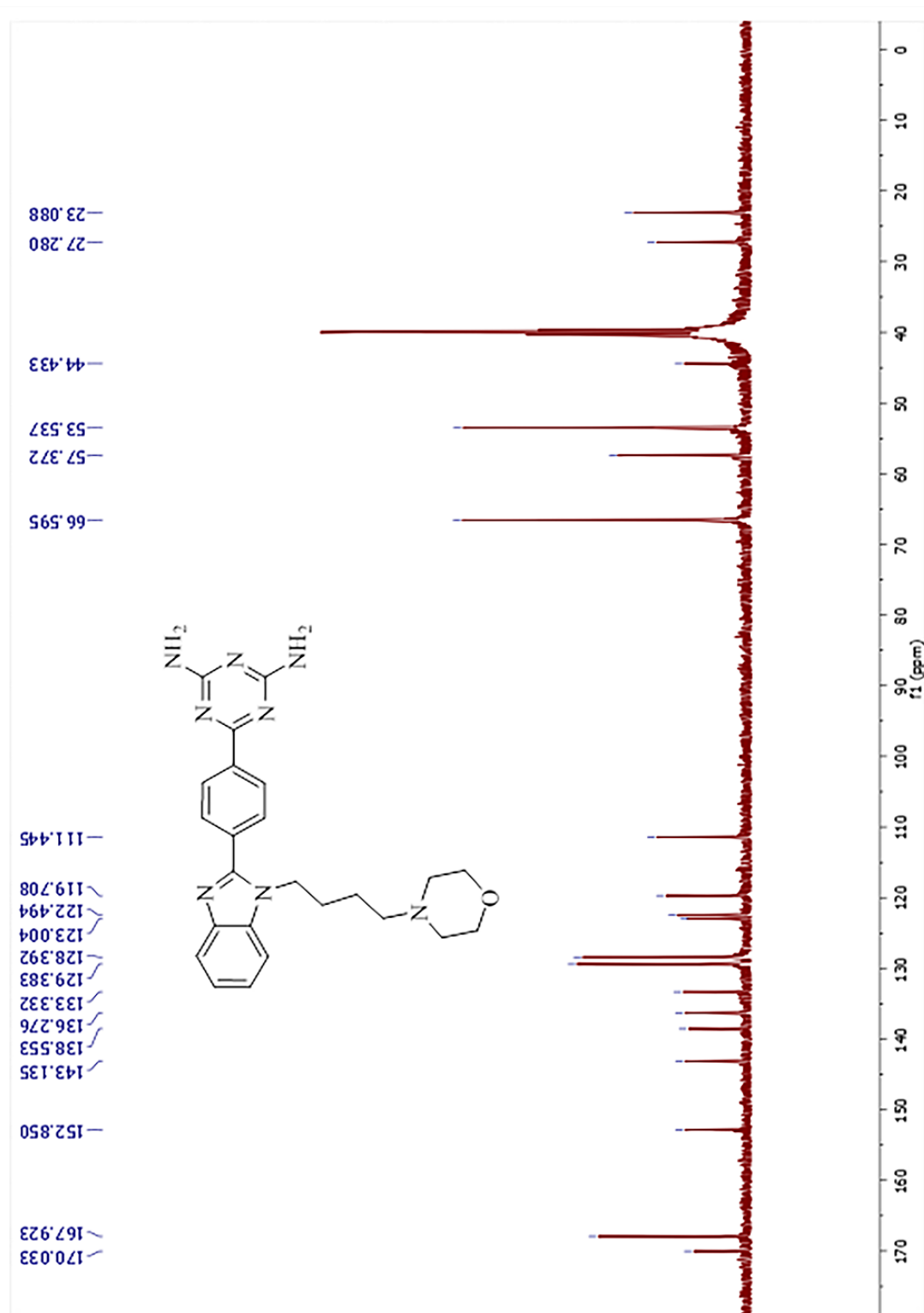


Figure 74. ^{13}C -NMR spectrum of compound (9h)

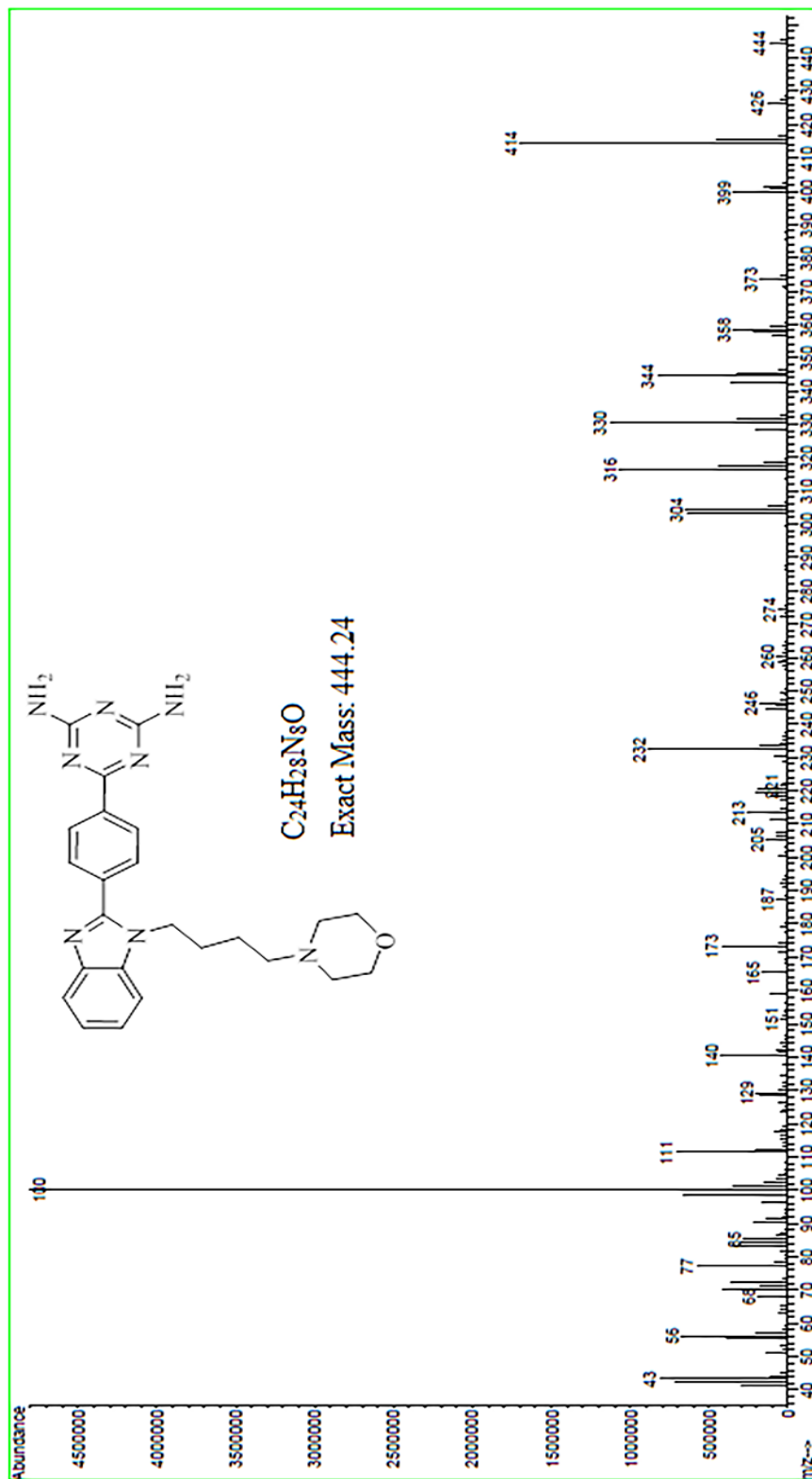


Figure 75. MASS spectrum of compound (9h)

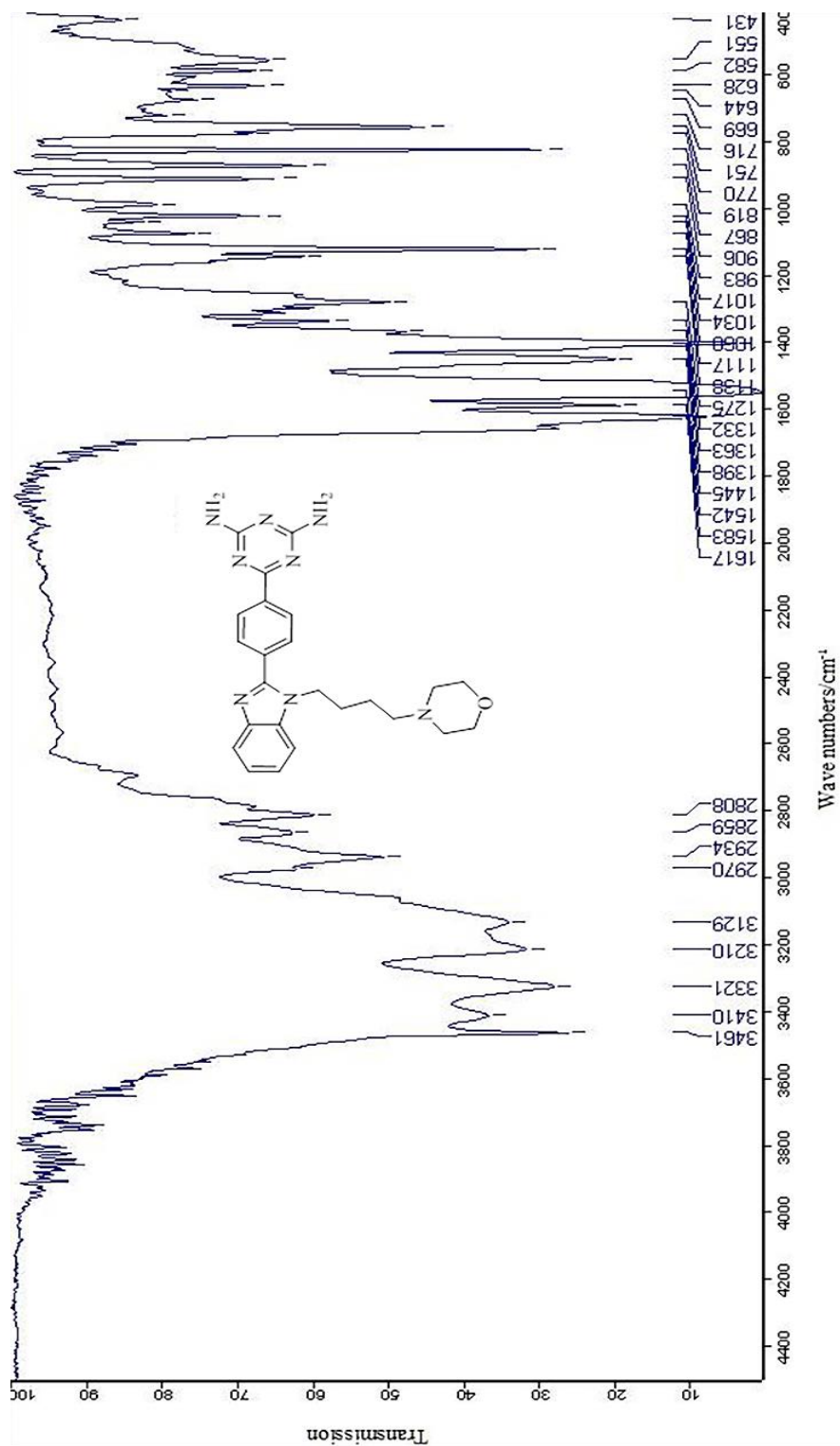


Figure 76. IR spectrum of compound (9h)

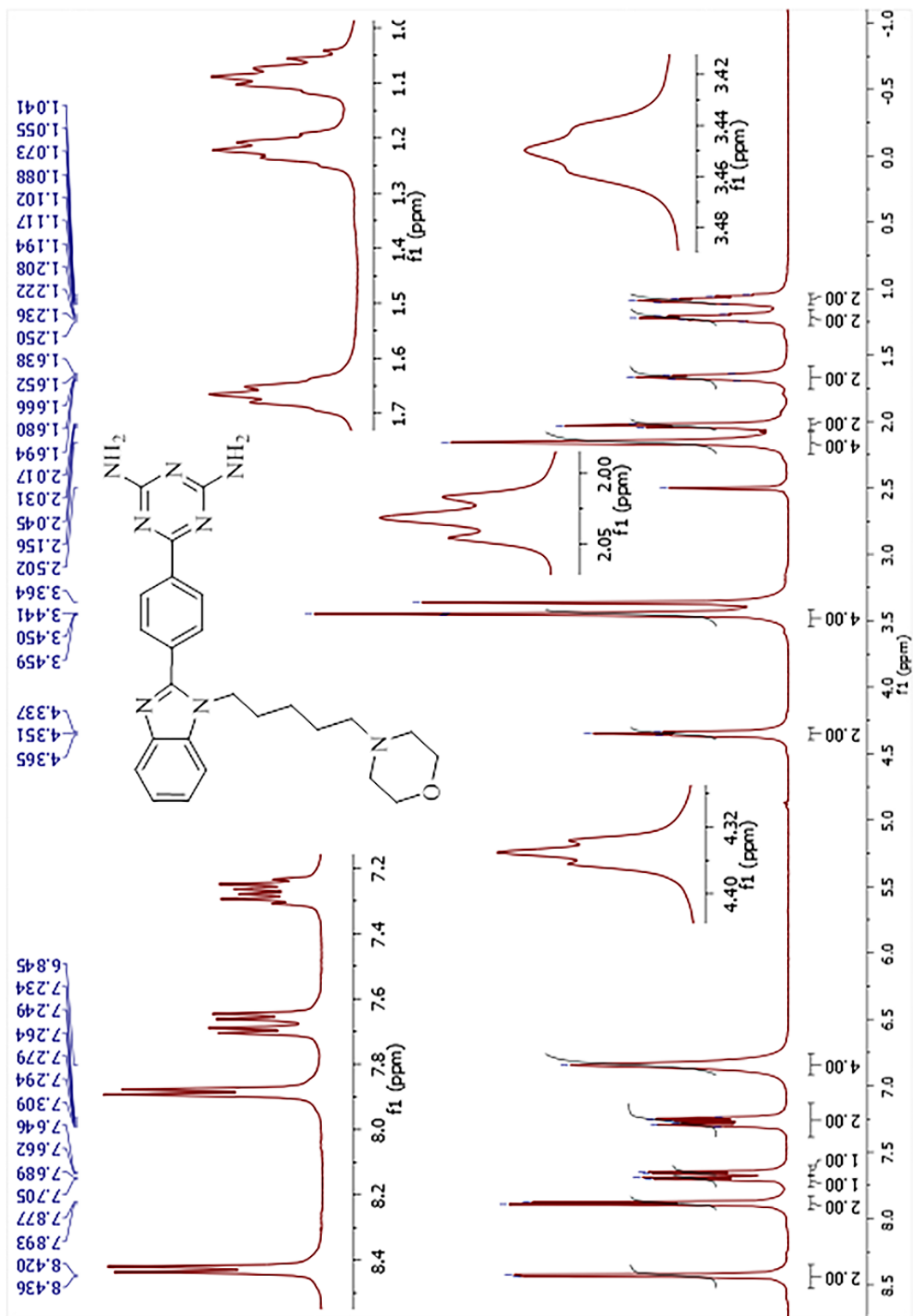


Figure 77. ¹H-NMR spectrum of compound (9i)

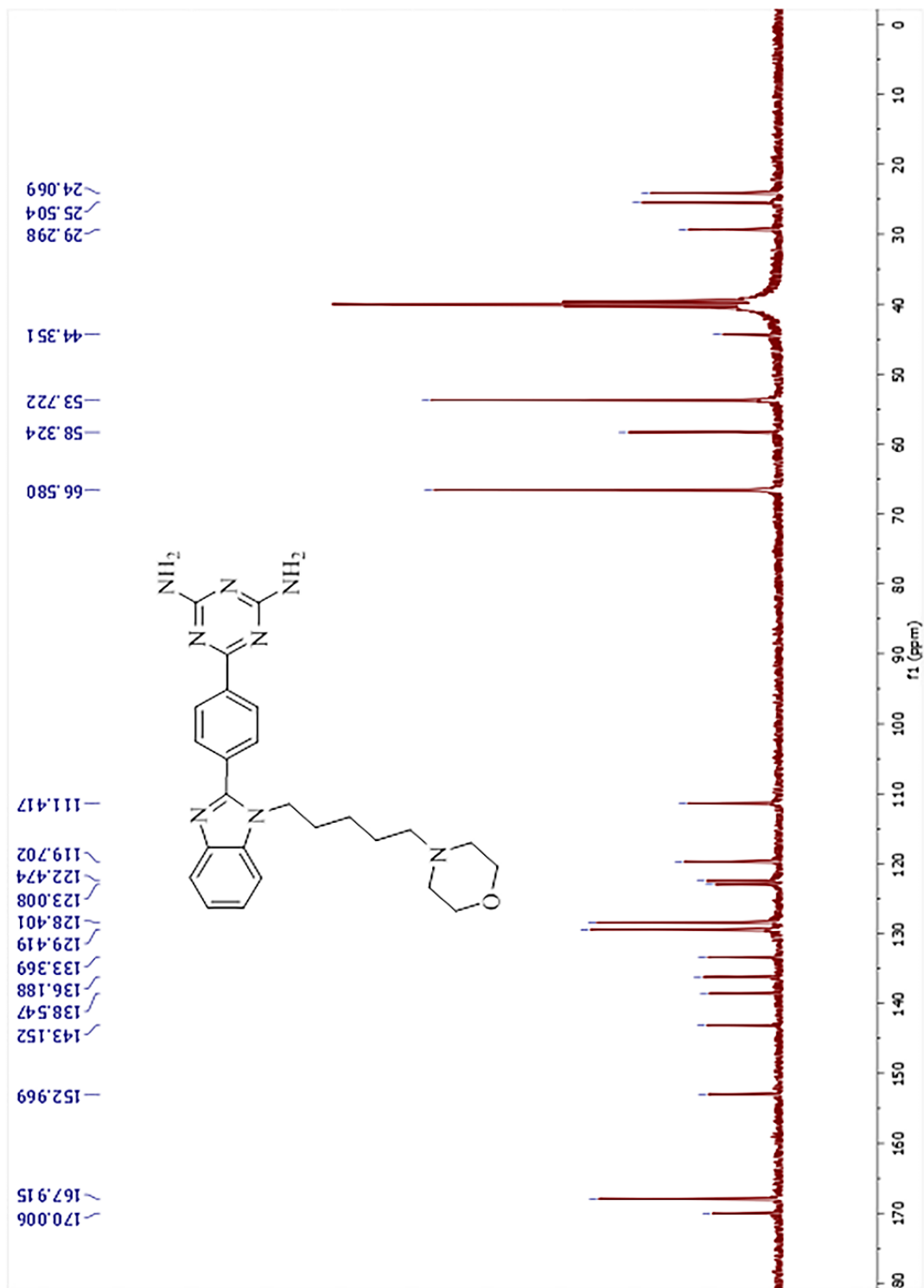


Figure 78. ^{13}C -NMR spectrum of compound (9i)

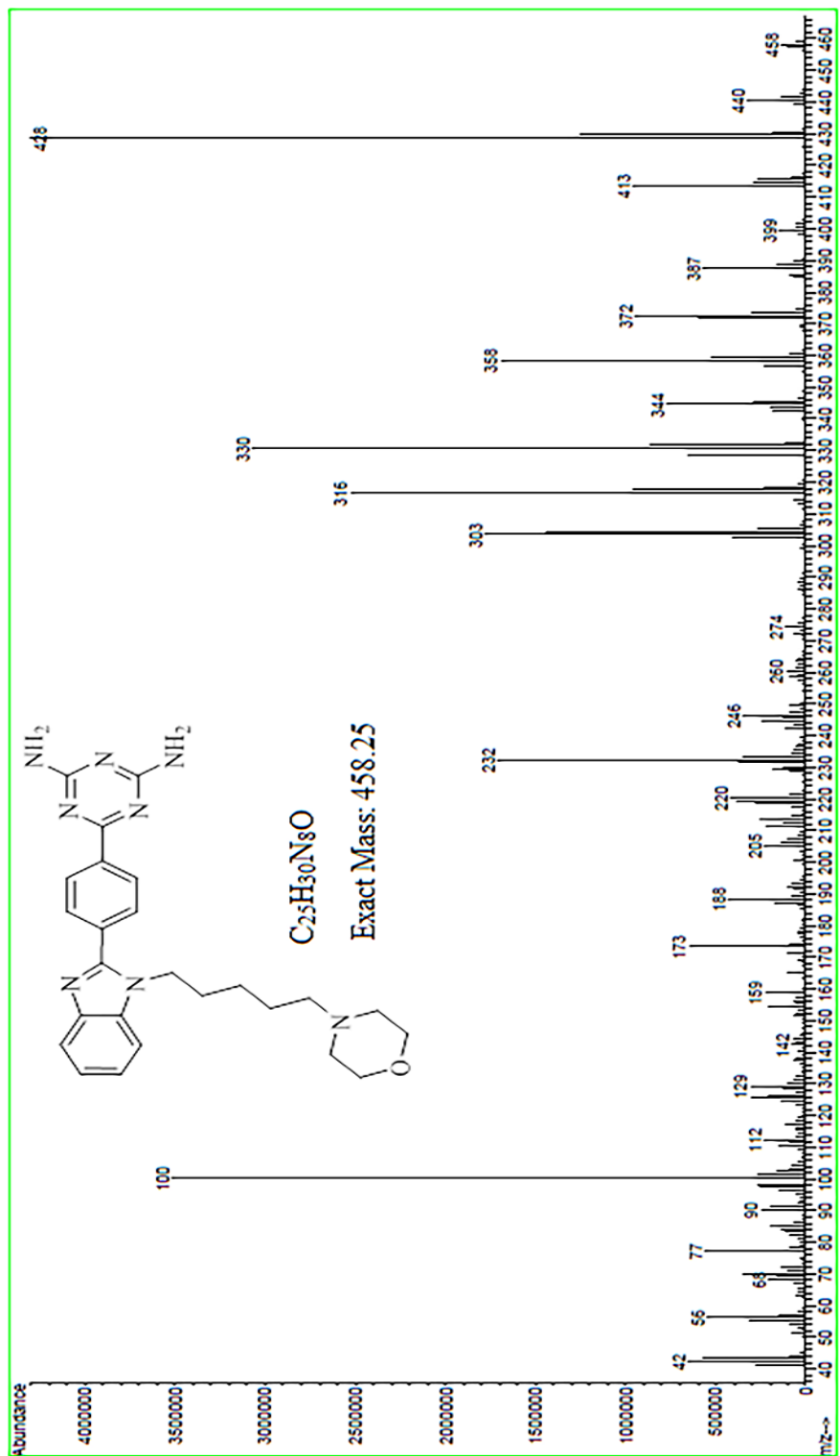


Figure 79. MASS spectrum of compound (9i)

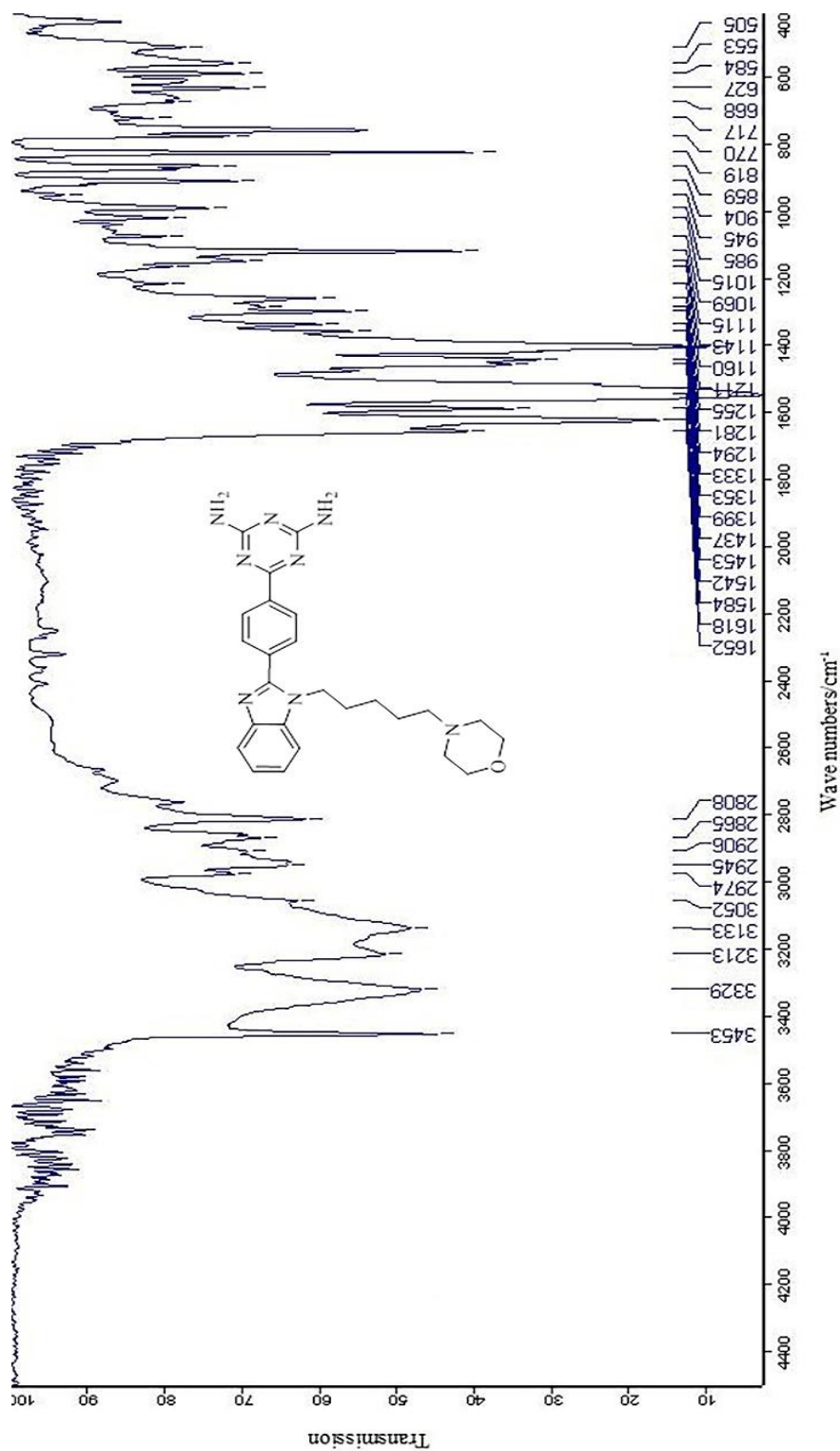


Figure 80. IR spectrum of compound (9i)

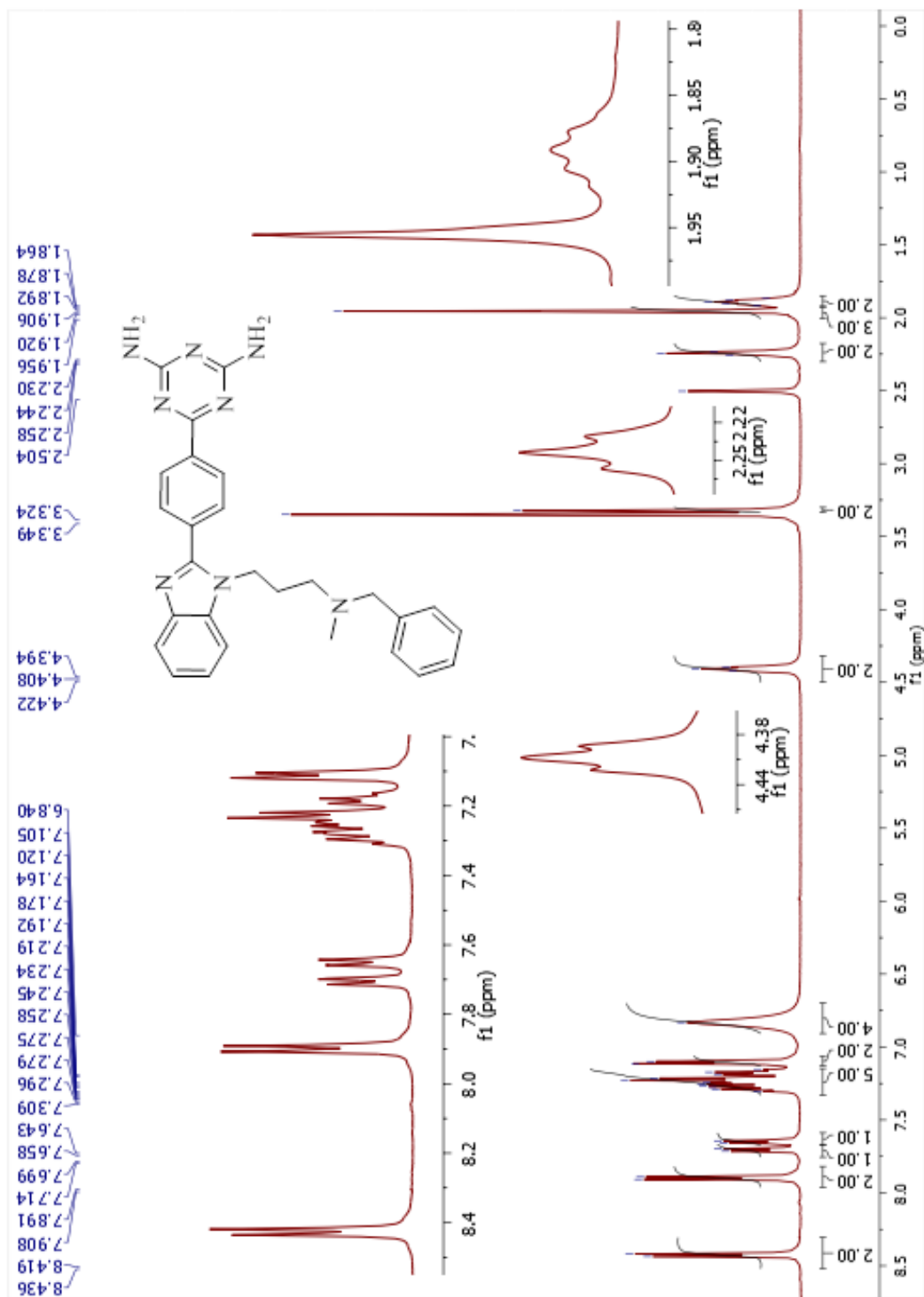


Figure 81. ¹H-NMR spectrum of compound (9j)

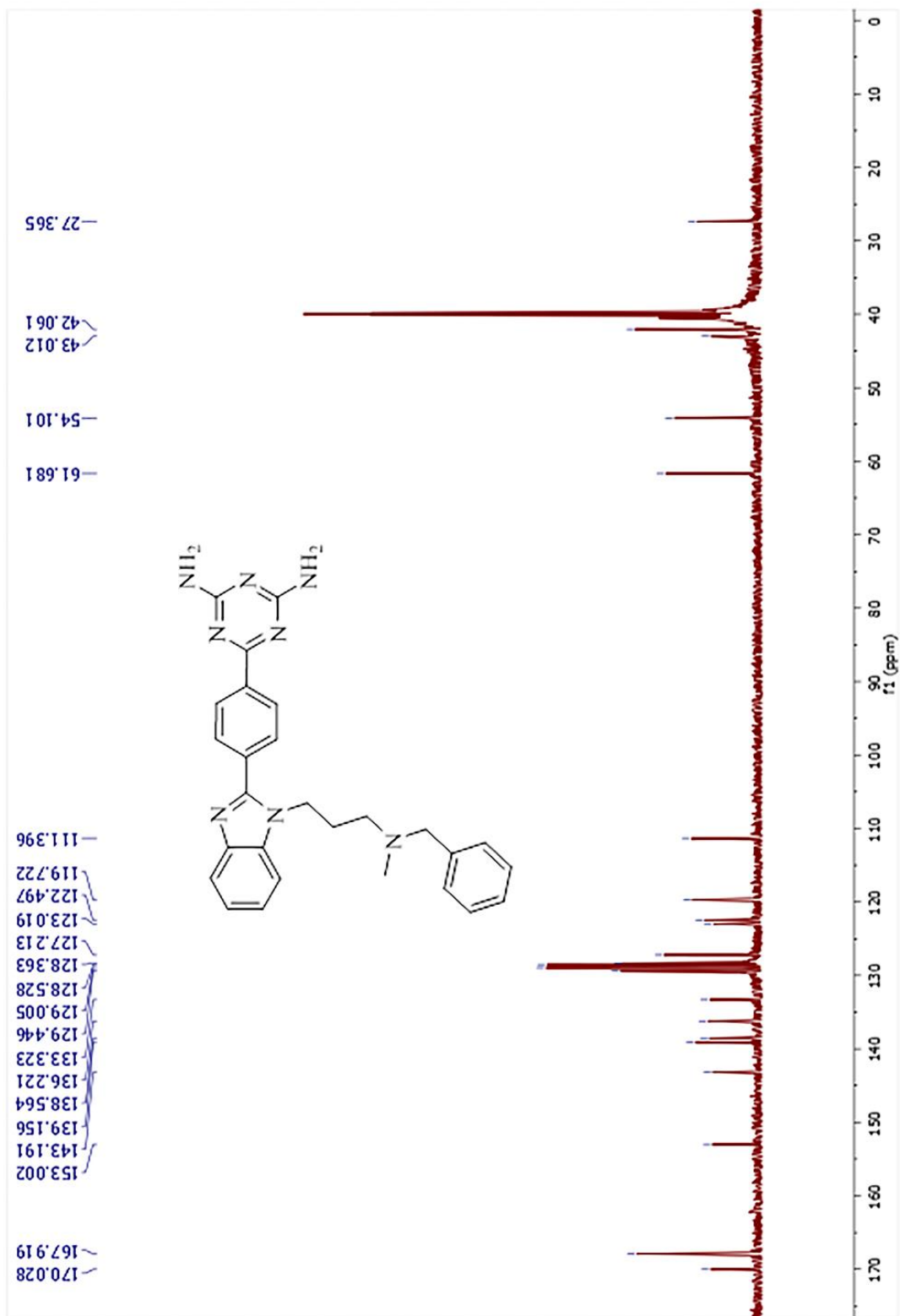


Figure 82. ¹³C-NMR spectrum of compound (9j)

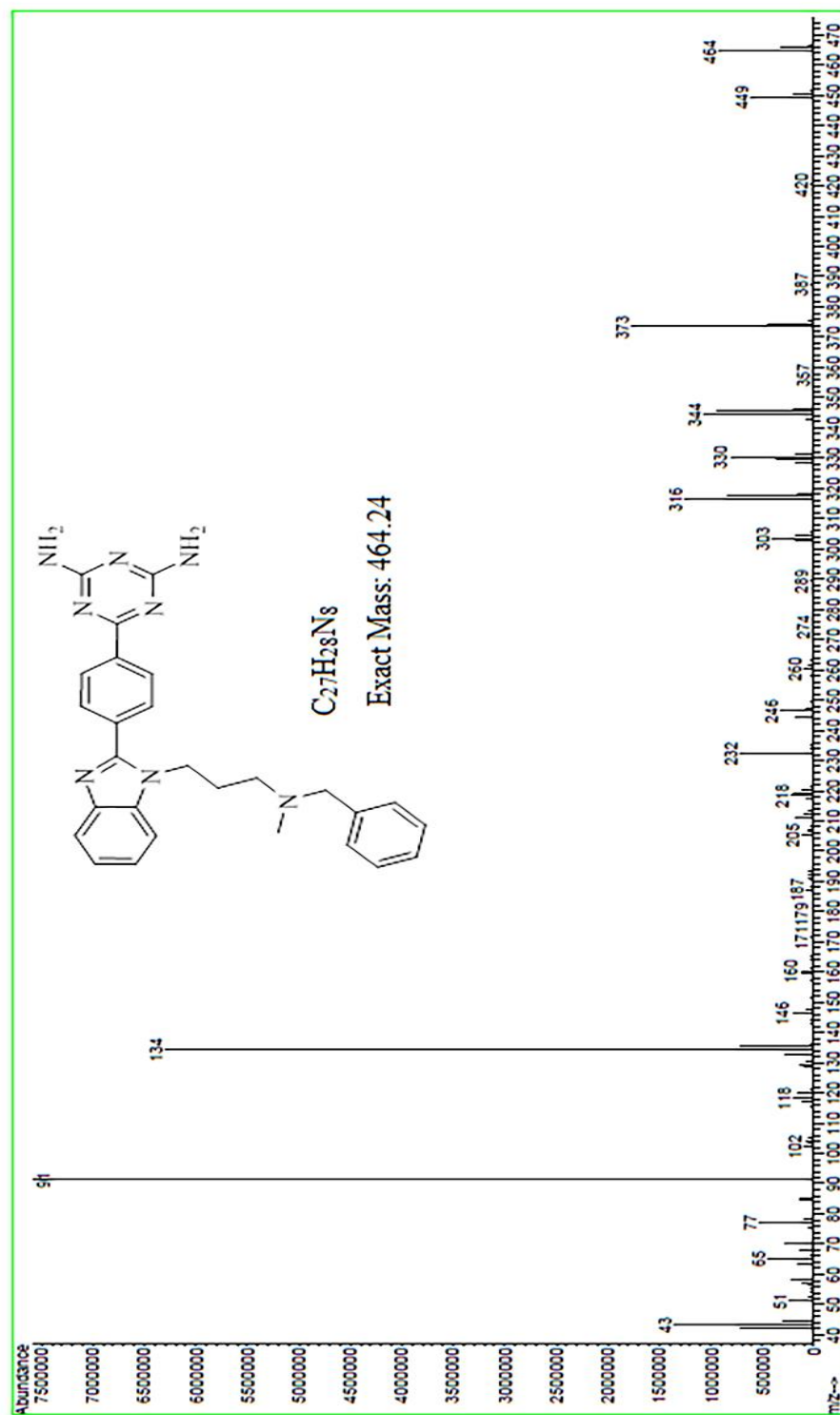


Figure 83. MASS spectrum of compound (9j)

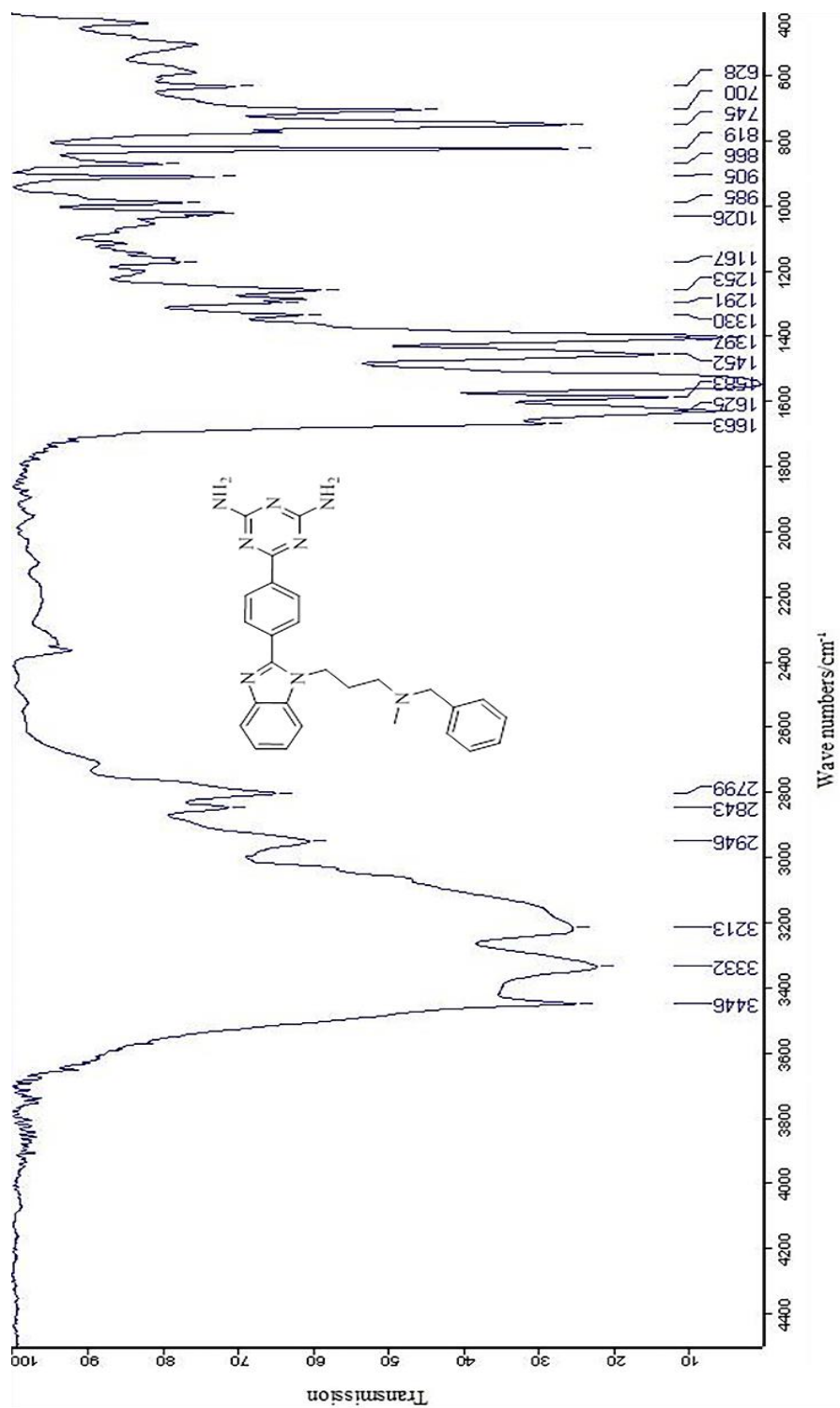


Figure 84. IR spectrum of compound (9j)

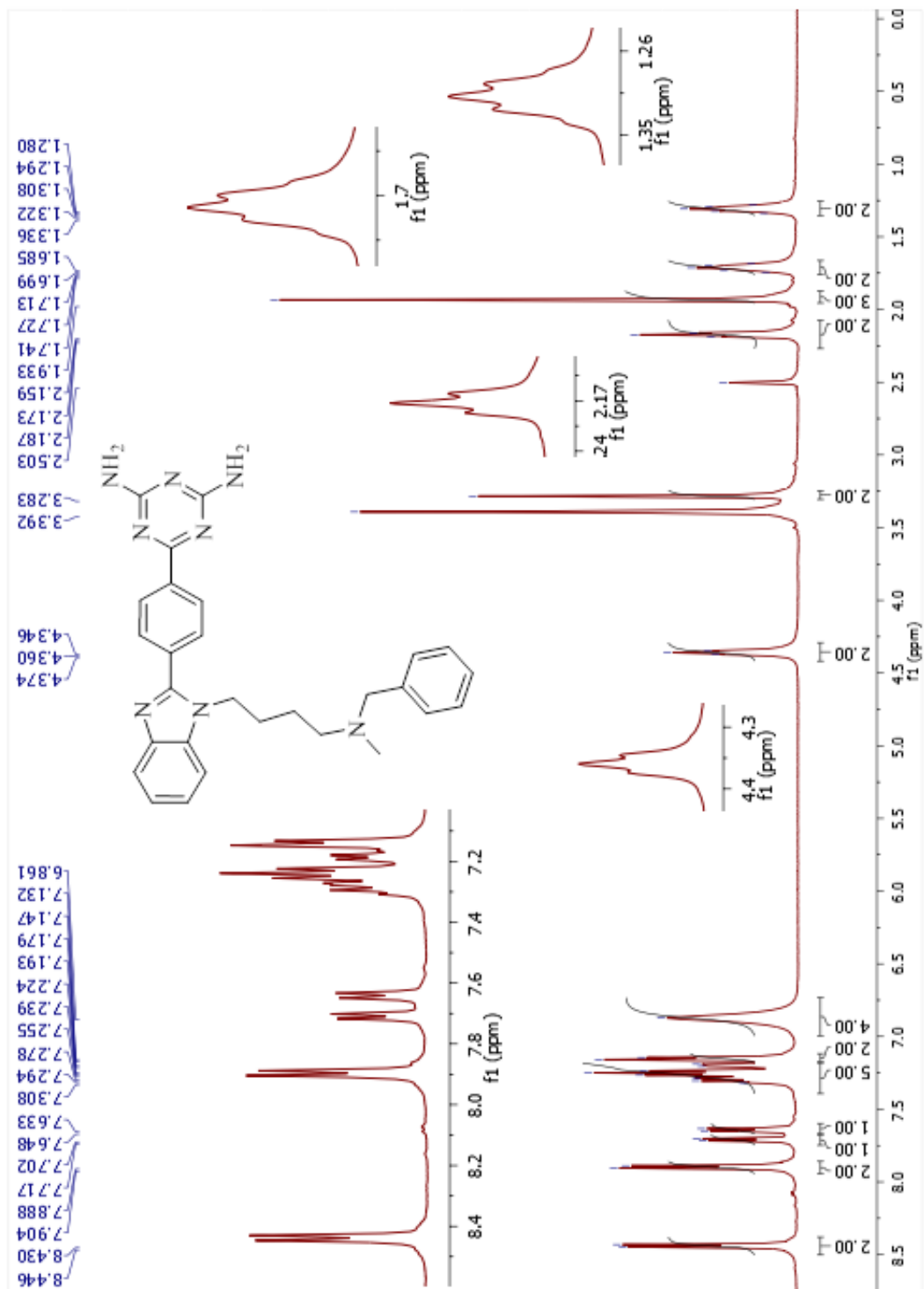


Figure 85. ¹H-NMR spectrum of compound (9k)

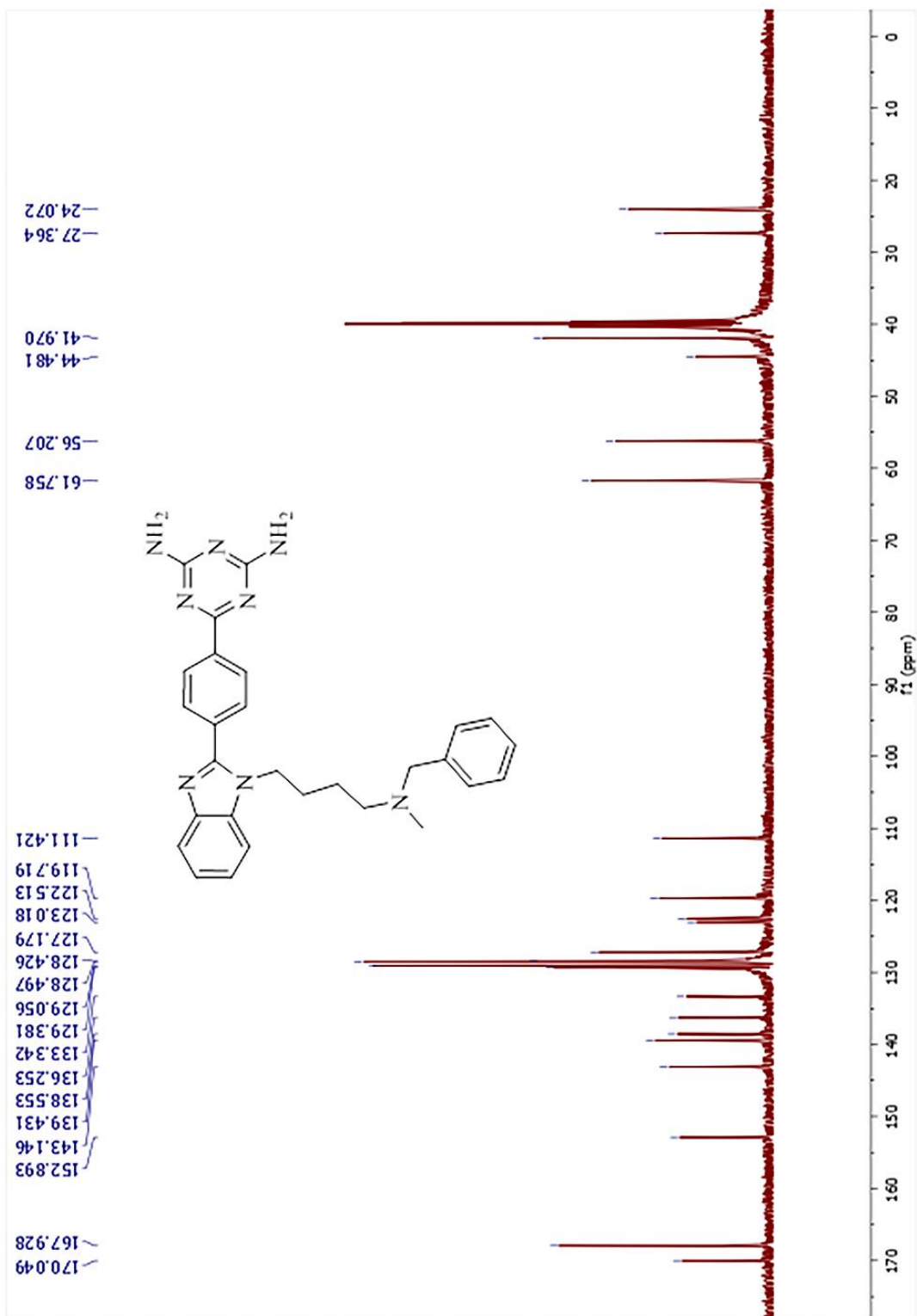


Figure 86. ¹³C-NMR spectrum of compound (9k)

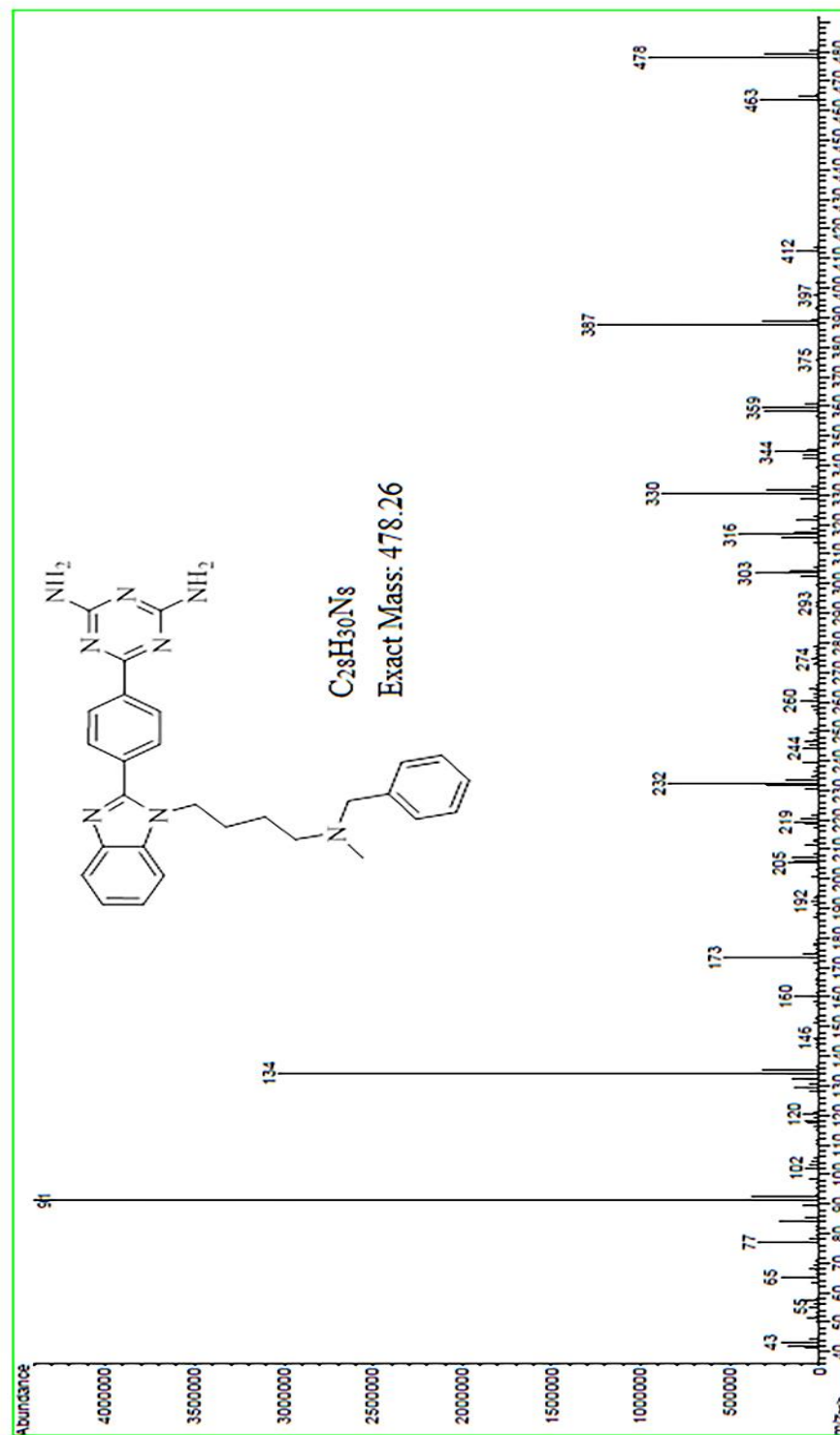


Figure 87. MASS spectrum of compound (9k)

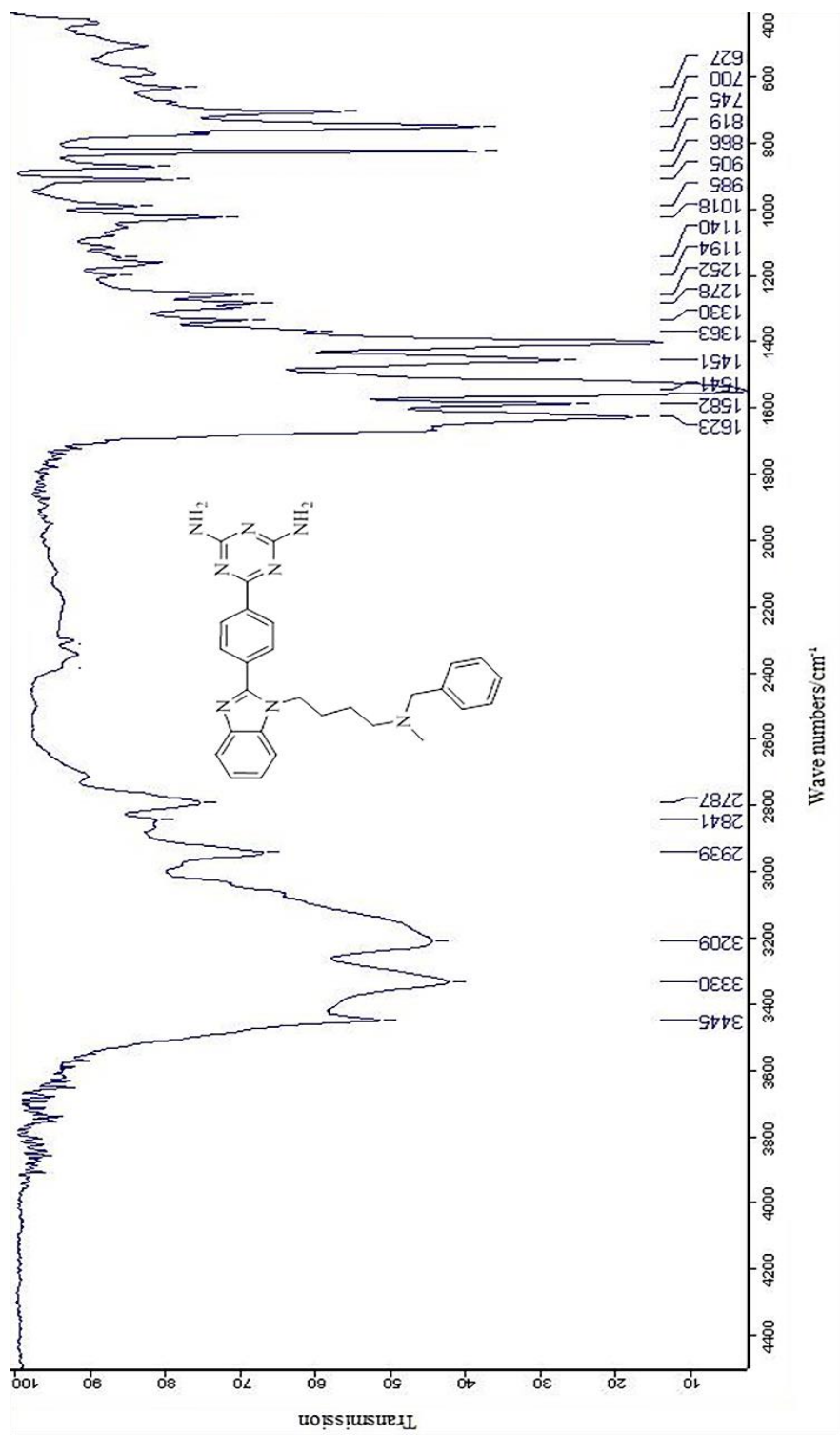


Figure 88. IR spectrum of compound (9k)

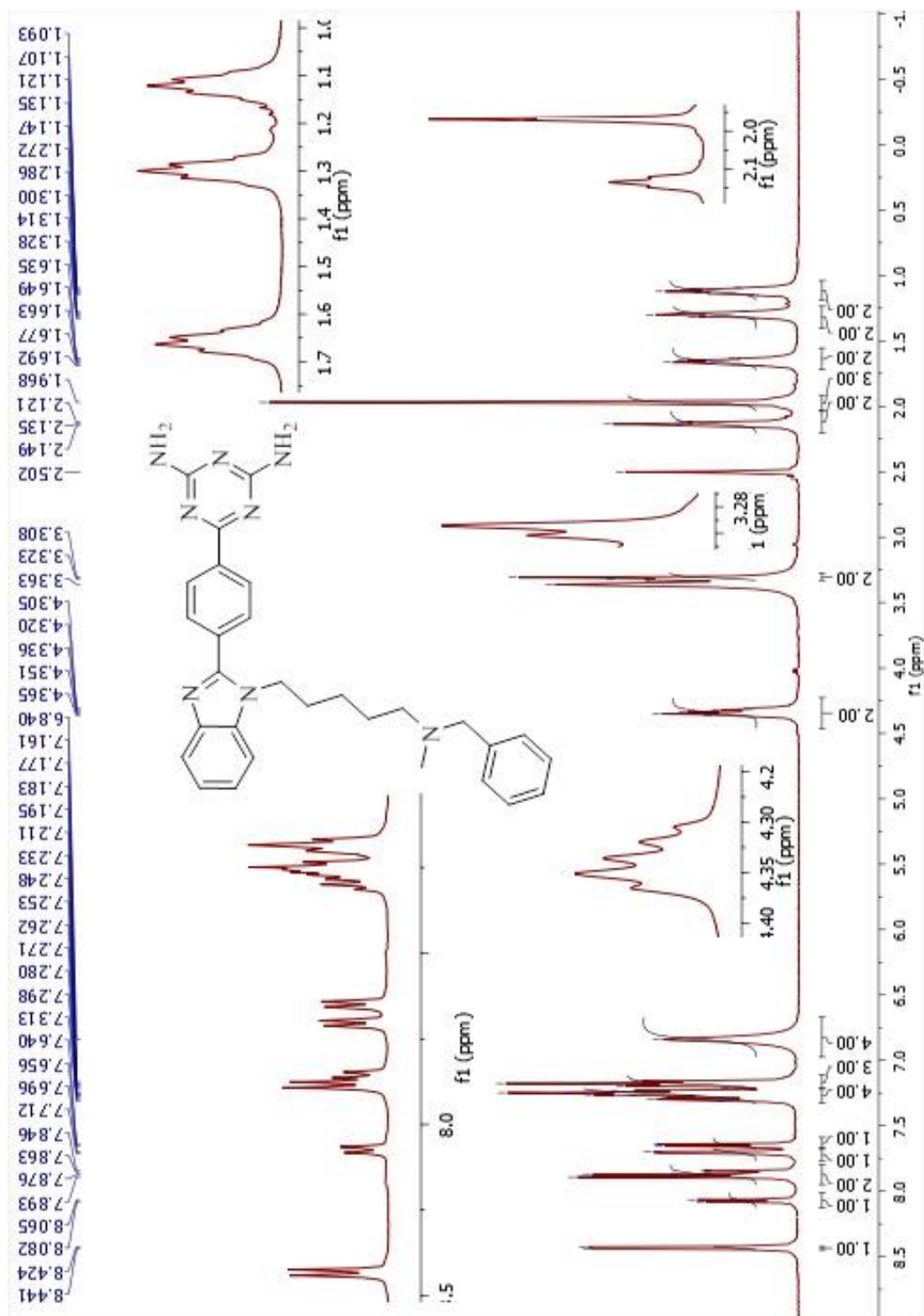


Figure 89. ¹H-NMR spectrum of compound (9l)

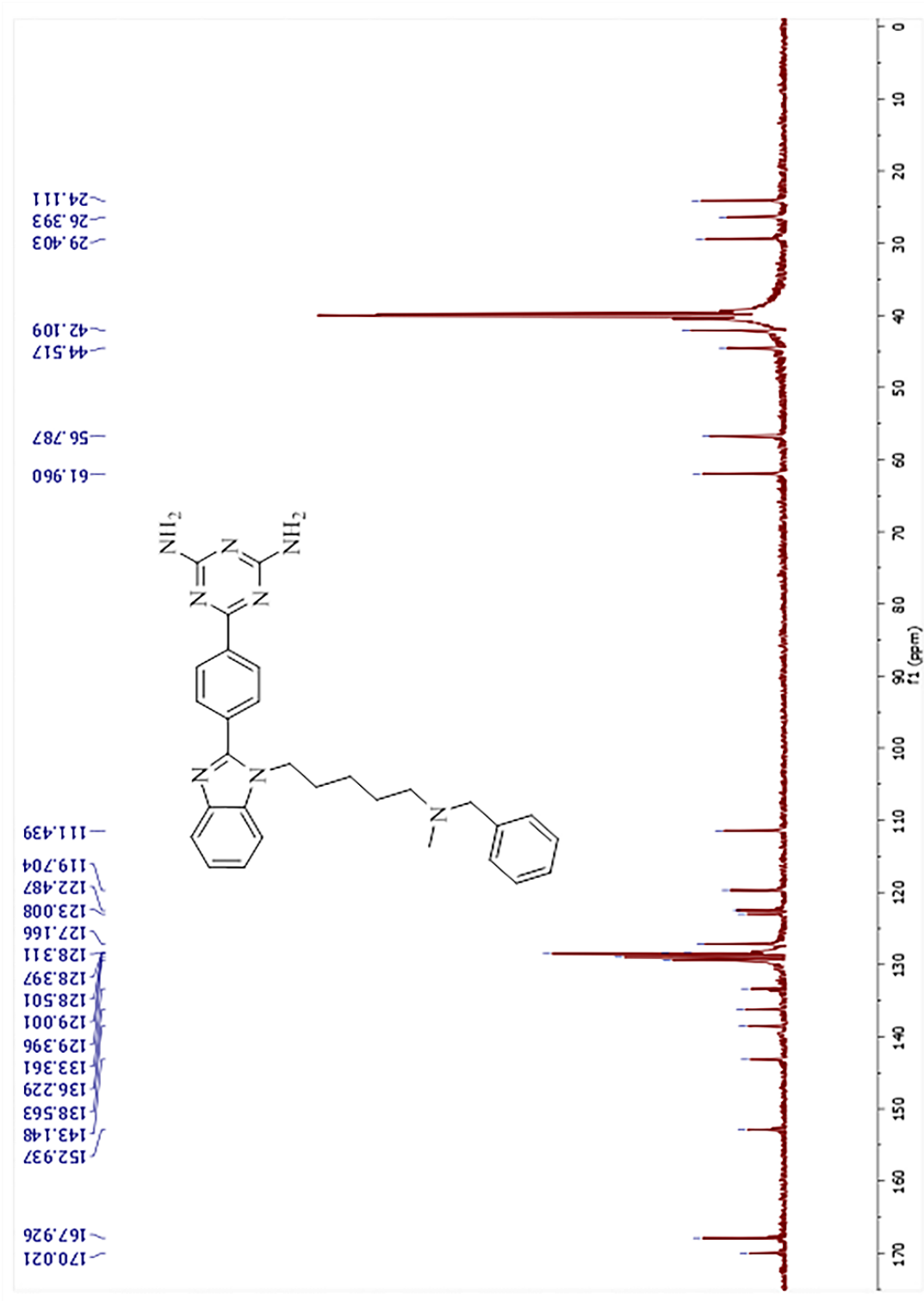


Figure 90. ¹³C-NMR spectrum of compound (91)

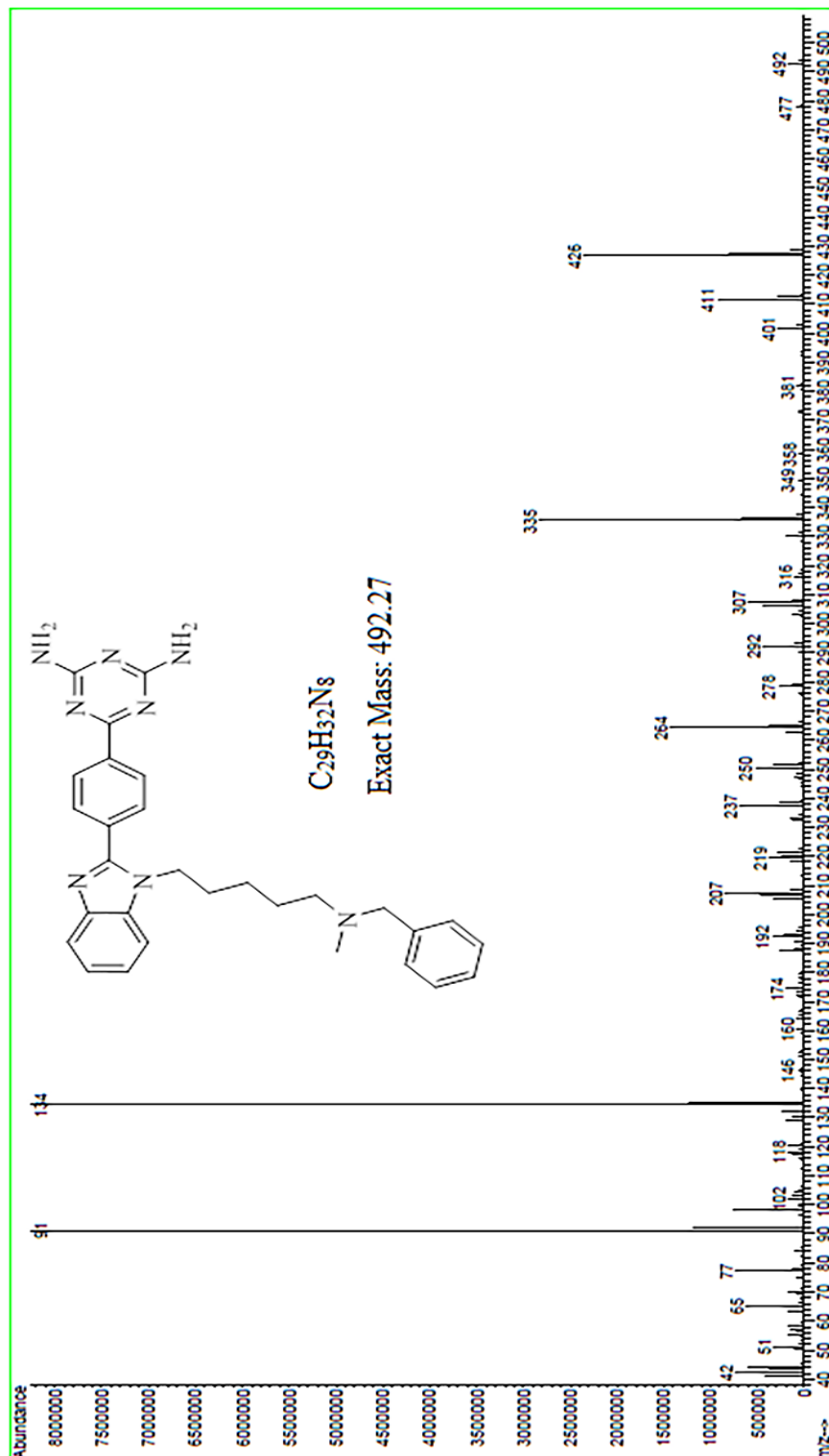


Figure 91. MASS spectrum of compound (91)

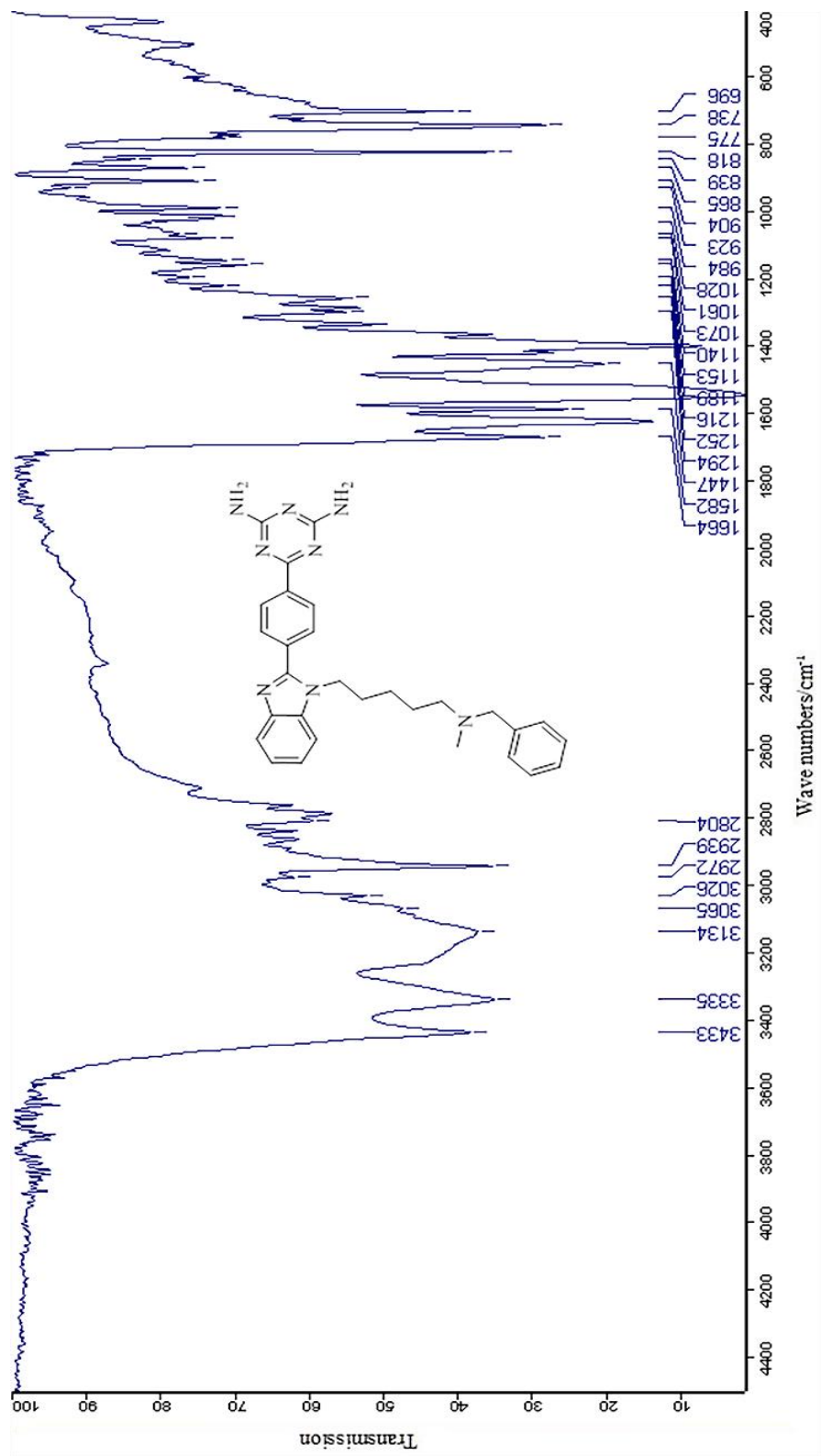


Figure 92. IR spectrum of compound (91)

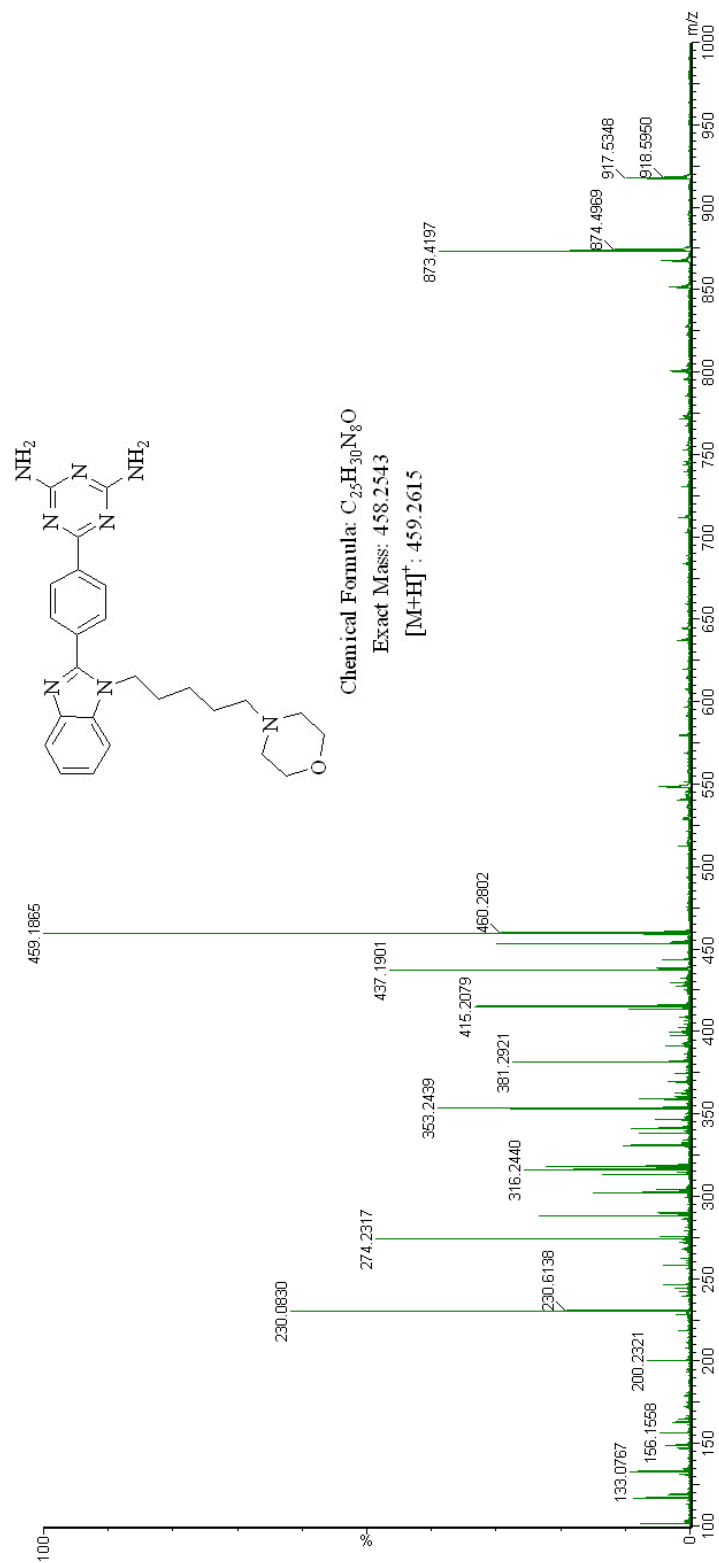


Figure 93. HRMS spectrum of compound (9i)

Table 1S. The predicted binding affinity of the selected ligands with the desired enzyme.

Enzyme	PDB	Compound	ΔG_b (kcal. mol ⁻¹)	Interactions	Residues	Distance Å
AChE	6O4W	9c	-9.33	Hydrogen Bond	SER293	2.48
				Hydrogen Bond	ASP74	2.65
				Hydrophobic (Pi-Pi Stacked)	TRP286	4.99
				Hydrophobic (Amide-Pi Stacked)	GLY120:GLY121	3.48
				Hydrophobic (Pi-Alkyl)	TRP86	4.91
				Hydrophobic (Pi-Alkyl)	TYR341	5.08
				Hydrophobic (Pi-Alkyl)	PHE338	4.10
BuChE	4TPK	9l	-10.05	Hydrogen Bond	HIS438	2.23
				Hydrogen Bond	GLU197	2.51
				Electrostatic (Pi-Anion)	ASP70	4.61
				Hydrophobic (Pi-Pi Stacked)	TRP82	5.30
				Hydrophobic (Pi-Pi Stacked)	TRP82	3.85
				Hydrophobic (Pi-Pi Stacked)	TRP82	3.53
				Hydrophobic (Pi-Pi T-shaped)	TRP231	4.91
				Hydrophobic (Pi-Pi T-shaped)	TRP231	4.80
				Hydrophobic (Pi-Pi T-shaped)	PHE329	5.22
				Hydrophobic (Amide-Pi Stacked)	ILE69:ASP70	4.08
				Hydrophobic (Amide-Pi Stacked)	ILE69:ASP70	4.70
BACE1	1W51	9a	-9.60	Hydrogen Bond	ASP228	2.11
				Hydrogen Bond	ASP32	2.59
				Hydrogen Bond	THR72	2.74
				Hydrogen Bond	GLY11	2.69
				Hydrophobic (Pi-Sigma)	GLN73	2.65
				Electrostatic (Attractive Charge)	ASP32	4.79
				Electrostatic (Attractive Charge)	ASP228	4.64
				Hydrophobic (Pi-Alkyl)	LEU30	4.39
				Hydrophobic (Pi-Alkyl)	ILE110	4.84
				Hydrophobic (Pi-Alkyl)	ILE118	5.426

Table 2S. Physicochemical properties and in silico ADME of the synthesized compounds.

Entry	M _w ^a (g/mol)	log P ^b	HBD ^c	HBA ^d	TPSA (Å ²) ^e	n-RB ^f	Absorption			Distribution
							% HIA ^g	In vitro caco-2 cell permeability (nm s ⁻¹)	In vitro skin permeability (log Kp, cm h ⁻¹)	% <i>In vitro</i> plasma Protein bonding
9a	518.6	3.81	2	5	111.77	8	96.37	21.36	-2.18	85.61
9b	532.64	4.00	2	5	111.77	9	96.44	21.22	-2.06	86.44
9c	546.7	4.19	2	5	111.77	10	96.53	22.5	-1.98	86.16
9d	428.5	2.63	2	5	111.77	6	96.51	20.13	-3.17	77.48
9e	442.5	2.84	2	5	111.77	7	96.43	19.29	-2.97	81.54
9f	456.6	3.04	2	5	111.77	8	96.35	20.64	-2.81	85.20
9g	430.5	1.64	2	6	121.00	6	97.03	18.67	-3.76	50.81
9h	444.5	1.65	2	6	121.00	7	97.04	20.88	-3.56	65.06
9i	458.5	2.06	2	6	121.00	8	97.01	19.79	-3.4	75.35
9j	464.5	3.04	2	5	111.77	8	96.16	20.49	-2.30	86.98
9k	478.6	3.23	2	5	111.77	9	96.18	19.64	-2.16	87.15
9l	492.6	3.43	2	5	111.77	10	96.21	21.31	-2.06	86.67
Rule of Lipinski	≤ 500	≤ 5	≤ 5	≤ 10	≤ 140	≤ 10	-	-	-	-

^a Molecular weight (MW). ^b Logarithm of the partition coefficient between n-octanol and water (log P). ^c Number of hydrogen bond donors (HBD). ^d Number of hydrogen bond acceptors (HBA). ^e Topological polar surface area (TPSA). ^f Number of rotatable bonds (n-RB). ^g Human intestinal absorption