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Synthesis and molecular modeling studies of indole-based antitumor agents

Riham F. George,[a] Siva S. Panda,[b] El-Sayed M. Shalaby,[c] Aladdin M. Srour,[d] I. S. Ahmed Farag[c] and Adel S. Girgis*[e]

[a] *Pharmaceutical Chemistry Department, Faculty of Pharmacy, Cairo University, Cairo, Egypt*

[b]*Department of Chemistry & Physics, Augusta University, Augusta, GA 30912, USA*

[c] *X-Ray Crystallography Lab., Physics Division, National Research Centre, Dokki, Giza 12622, Egypt*

[d] *Therapeutical Chemistry Department, National Research Centre, Dokki, Giza 12622, Egypt*

[e] *Pesticide Chemistry Department, National Research Centre, Dokki, Giza 12622, Egypt*

* Corresponding author: E-mail: girgisas10@yahoo.com, Fax: +33370931, Tel: +01220447199

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Figure S116. (A) Constraint distances "H – PosIon-1 = 9.375, H – PosIon-2 = 4.037, H – HBA = 6.763, PosIon-1 – PosIon-2 = 5.848, PosIon-1 – HBA = 3.869, PosIon-2 – HBA = 4.300 Å" and (B) constraint angles "H – PosIon-1 – PosIon-2 = 15.24, H – PosIon-1 – HBA = 47.33, PosIon-2 – H – PosIon-1 = 37.11 °" of the generated 3D-pharmacophore for the synthesized bio-active spiro-compounds **30-63** against HeLa (cervical carcinoma) cell line which contains two positive ionizables (PosIon-1, PosIon-2; red), one hydrophobic (H; light blue) and one hydrogen bonding acceptor (HBA; green).

Figure S117. 3D-pharmacophore mapped on the synthesized bio-active spiro-compounds **30-63** against HeLa (cervical carcinoma) cell line.

Table S1. Experimental and optimized intramolecular geometrical parameters (bond lengths, Å) of compounds **46** and **48**.

Geometric parameters	Compound **46**			Compound **48**		
	Exp. X-ray	AM1	PM3	Exp. X-ray	AM1	PM3
F1—C21	1.366	1.354	1.343	1.388	1.354	1.343
F2—C31	1.376	1.354	1.343	1.374	1.354	1.343
C1—C2	1.519	1.524	1.519	1.517	1.524	1.519
C1—C14	1.554	1.582	1.562	1.559	1.582	1.562
C1—C24	1.585	1.575	1.578	1.575	1.575	1.578
C1—N1	1.472	1.473	1.508	1.445	1.473	1.508
C2—C3	1.356	1.381	1.384	1.384	1.381	1.384
C2—C7	1.391	1.432	1.412	1.389	1.432	1.412
C3—C4	1.398	1.403	1.397	1.411	1.403	1.397
C4—C5	1.362	1.391	1.390	1.326	1.391	1.390
C5—C6	1.369	1.400	1.396	1.400	1.400	1.396
C6—C7	1.381	1.395	1.389	1.355	1.395	1.389
C7—N3	1.402	1.409	1.437	1.386	1.409	1.437
C8—N3	1.492	1.445	1.478	1.528	1.445	1.479
C8—N4	1.455	1.472	1.493	1.454	1.472	1.493
C9—C10	1.500	1.530	1.526	1.511	1.530	1.526
C9—N4	1.413	1.457	1.488	1.472	1.457	1.488

C10—C11	1.512	1.515	1.521	1.459	1.515	1.521
C11—C12	1.504	1.514	1.521	1.476	1.514	1.521
C12—C13	1.489	1.530	1.526	1.492	1.530	1.526
C13—N4	1.450	1.454	1.488	1.423	1.454	1.488
C14—O1	1.213	1.238	1.217	1.223	1.238	1.218
C14—N3	1.372	1.407	1.437	1.377	1.407	1.437
C15—N1	1.454	1.439	1.471	1.474	1.439	1.471
C16—C17	1.532	1.538	1.528	1.517	1.538	1.528
C16—N1	1.462	1.457	1.482	1.416	1.457	1.482
C17—C18	1.508	1.489	1.502	1.497	1.489	1.502
C17—C24	1.575	1.558	1.567	1.565	1.558	1.567
C18—C19	1.380	1.400	1.397	1.389	1.400	1.397
C18—C23	1.388	1.404	1.398	1.374	1.404	1.398
C19—C20	1.390	1.391	1.388	1.385	1.391	1.388
C20—C21	1.368	1.406	1.400	1.347	1.406	1.400
C21—C22	1.340	1.407	1.400	1.343	1.407	1.400
C22—C23	1.406	1.390	1.389	1.360	1.390	1.389
C24—C25	1.537	1.525	1.542	1.528	1.525	1.542
C24—C35	1.530	1.538	1.541	1.546	1.538	1.541
C25—C26	1.492	1.483	1.496	1.482	1.483	1.496

C25—O2	1.207	1.239	1.217	1.213	1.239	1.217
C26—C27	1.332	1.347	1.343	1.324	1.347	1.343
C26—C34	1.512	1.498	1.493	1.489	1.498	1.493
C27—C28	1.477	1.454	1.462	1.461	1.454	1.462
C28—C29	1.383	1.401	1.397	1.385	1.401	1.397
C28—C33	1.406	1.405	1.400	1.419	1.405	1.400
C29—C30	1.399	1.391	1.388	1.367	1.391	1.388
C30—C31	1.350	1.406	1.400	1.377	1.406	1.400
C31—C32	1.345	1.408	1.401	1.343	1.408	1.401
C32—C33	1.384	1.389	1.388	1.391	1.389	1.388
C34—N2	1.467	1.454	1.487	1.462	1.453	1.487
C35—N2	1.465	1.452	1.485	1.466	1.452	1.485
C36—C37	1.504	1.520	1.517	1.524	1.528	1.527
C36—N2	1.469	1.452	1.487	1.476	1.450	1.485
C37—C38	---	---	---	1.460	1.506	1.512
RMSE	---	0.0256	0.0269	---	0.0312	0.0329
Maximum difference	---	0.067	0.075	---	0.083	0.066

Table S2. Experimental and optimized intramolecular geometrical parameters (bond angles, °) of compounds **46** and **48**.

Geometric parameters	Compound **46**			Compound **48**		
	Exp. X-ray	AM1	PM3	Exp. X-ray	AM1	PM3
C2—C1—C14	102.2	100.7	100.9	99.5	100.7	100.9
C2—C1—C24	117.8	113.7	114.4	119.5	113.7	114.4
C14—C1—C24	110.6	112.4	114.7	111.7	112.4	114.7
C2—C1—N1	109.2	110.1	107.5	110.7	110.1	107.5
C14—C1—N1	114.5	112.0	113.1	112.7	112.0	113.1
C24—C1—N1	103.0	107.9	106.2	103.1	107.9	106.2
C1—C2—C3	132.4	129.9	129.1	130	129.9	129.1
C1—C2—C7	108.3	109.6	110.8	110.1	109.6	110.8
C3—C2—C7	118.9	120.4	120.0	119.5	120.4	120.0
C2—C3—C4	120.3	118.9	118.7	118.1	118.9	118.7
C3—C4—C5	119.2	120.7	120.9	121	120.7	120.9
C4—C5—C6	122.1	121.5	121.1	121.3	121.5	121.1
C5—C6—C7	117.7	118.1	117.8	118.4	118.1	117.8
C2—C7—C6	121.7	120.4	121.5	121.6	120.4	121.5
C2—C7—N3	110.4	110.4	110.0	110.6	110.4	110.0
C6—C7—N3	127.7	129.1	128.6	127.7	129.1	128.6
N3—C8—N4	118.7	116.3	108.6	116.6	116.3	108.6

C10—C9—N4	112.3	115.4	113.5	110.8	115.4	113.5
C9—C10—C11	111.5	110.7	110.8	112.8	110.7	110.8
C10—C11—C12	109.6	111.2	110.9	112.9	111.2	110.9
C11—C12—C13	112.2	111.1	111.1	113.8	111.1	111.1
C12—C13—N4	109.5	115.6	113.8	109.8	115.6	113.8
C1—C14—O1	126.4	126.6	129.1	126.9	126.6	129.1
C1—C14—N3	107.5	109.1	109.0	109.7	109.1	109.0
O1—C14—N3	126.1	124.0	121.8	123.4	124.0	121.8
C17—C16—N1	103.9	107.0	104.0	105.8	107.0	104.0
C16—C17—C18	115.4	113.7	113.0	114.4	113.7	113.0
C16—C17—C24	104.8	105.0	104.6	103.2	105.0	104.7
C18—C17—C24	116.3	116.5	116.0	117.3	116.5	116.0
C17—C18—C19	122.5	122.9	121.5	124.6	122.9	121.5
C17—C18—C23	119.2	118.3	119.2	117.5	118.3	119.2
C19—C18—C23	118.3	118.8	119.3	117.9	118.8	119.3
C18—C19—C20	121.1	121.0	121.0	120.8	121.0	121.0
C19—C20—C21	118.6	119.6	118.9	117.8	119.6	118.9
C20—C21—C22	122.4	120.0	121.0	123.1	120.0	121.0
C20—C21—F1	117.6	120.0	119.5	117.1	120.0	119.5
C22—C21—F1	120.0	120.0	119.5	119.5	120.0	119.5

C21—C22—C23	119.1	119.4	119.1	119	119.4	119.1
C22—C23—C18	120.4	121.1	120.7	121.2	121.1	120.7
C17—C24—C1	103.7	103.8	103.3	104.1	103.8	103.3
C17—C24—C25	110.2	110.0	111.5	111.5	110.0	111.5
C1—C24—C25	108.4	111.5	111.8	108.7	111.5	111.8
C17—C24—C35	113.6	110.0	109.2	113.2	110.0	109.2
C1—C24—C35	113.5	113.0	114.3	112.3	113.0	114.3
C25—C24—C35	107.3	108.4	106.7	107	108.4	106.6
C24—C25—C26	117.1	118.1	117.3	118.9	118.1	117.3
C24—C25—O2	122.6	121.4	122.4	120	121.4	122.4
C26—C25—O2	120.3	120.5	120.3	121	120.5	120.2
C25—C26—C27	117.7	118.7	119.2	117.4	118.7	119.2
C25—C26—C34	119.8	118.4	115.9	118.2	118.4	115.9
C27—C26—C34	122.4	122.9	124.9	124.4	122.9	124.9
C26—C27—C28	128.2	127.0	127.6	126.5	127.0	127.6
C27—C28—C29	123.6	122.1	122.2	125.3	122.1	122.2
C27—C28—C33	119.2	118.8	118.2	118.2	118.8	118.2
C29—C28—C33	117.2	119.2	119.5	116.5	119.2	119.5
C28—C29—C30	121.6	120.9	120.8	122.2	120.9	120.8
C29—C30—C31	117.4	119.5	119.0	118.6	119.5	119.0

C30—C31—C32	124.4	120.2	121.1	123.3	120.2	121.1
C30—C31—F2	117.3	119.9	119.5	118.1	119.9	119.5
C32—C31—F2	118.2	119.9	119.4	118.5	119.9	119.4
C31—C32—C33	117.9	119.5	119.0	117.8	119.5	119.0
C28—C33—C32	121.3	120.8	120.6	121.7	120.8	120.6
C26—C34—N2	111.5	113.5	110.7	112.2	113.5	110.6
C24—C35—N2	109.8	112.5	112.2	109	112.5	112.1
C37—C36—N2	113.5	117.8	116.4	110.3	117.7	116.3
C1—N1—C16	106.0	109.3	108.7	106.7	109.3	108.7
C1—N1—C15	114.4	116.7	118.6	115.7	116.7	118.6
C16—N1—C15	113.9	114.4	114.5	114.7	114.4	114.5
C36—N2—C34	111.4	113.9	113.6	113.1	114.1	113.7
C36—N2—C35	113.4	113.8	113.7	111.8	113.9	113.9
C34—N2—C35	107.8	112.1	112.6	108	112.1	112.6
C8—N3—C7	124.1	125.5	122.6	123.3	125.5	122.6
C8—N3—C14	123.3	124.3	124.3	125.4	124.4	124.3
C7—N3—C14	111.5	110.1	108.3	110.1	110.1	108.3
C8—N4—C13	113.7	114.6	114.4	112.7	111.7	114.4
C8—N4—C9	114.3	111.7	113.6	117.3	114.6	113.5
C13—N4—C9	111.7	111.3	111.7	111.8	111.3	111.7

C36—C37—C38	---	---	---	113.3	110.4	110.6
RMSE	---	2.0361	2.3048	---	2.1406	2.2722
Maximum difference	---	6.1	10.1	---	7.4	8.0

Table S3. Molecular descriptor values of the BMLR-QSAR model for the antitumor active indole-based compounds **30**, **31**, **33-40**, **42-49** and **51-63** against HeLa (cervical carcinoma) cell line.

Entry	Compd.	Descriptors[a]				
		D_1	D_2	D_3	D_4	D_5
1	**30**	3	136.7752	0	198.5068	0
2	**31**	3	136.6096	0	198.9305	0
3	**33**	3	136.7861	0	200.3036	0
4	**34**	3	136.3403	0	198.6065	0
5	**35**	3	136.6457	0	198.5477	0
6	**36**	3	136.6001	0	199.3658	0
7	**37**	3	136.8132	0	200.4607	0
8	**38**	3	136.7001	0	200.1806	0
9	**39**	3	136.6039	0	199.6096	0
10	**40**	3	136.7263	0	200.3751	0
11	**42**	3	136.4878	0	199.1451	0
12	**43**	3	136.3863	2	199.4495	0
13	**44**	3	136.3733	2	199.6382	0
14	**45**	3	136.608	2	198.6234	0
15	**46**	3	136.4379	2	199.2208	0
16	**47**	3	136.5666	2	199.5591	0
17	**48**	3	136.7948	2	199.3765	0
18	**49**	3	136.7274	2	200.4381	0
19	**51**	3	136.8106	2	199.4803	0
20	**52**	3	136.4403	0	199.0356	0
21	**53**	3	136.6514	0	200.3557	0
22	**54**	3	136.5028	0	198.4583	0
23	**55**	3	136.8162	0	200.0913	0
24	**56**	3	136.3108	0	199.4149	0
25	**57**	3	136.6281	0	200.6326	0
26	**58**	3	136.3404	0	200.0663	0

27	**59**	3	136.7904	0	199.6677	0
28	**60**	7	136.4145	0	199.7037	0
29	**61**	7	136.0955	0	198.4843	0
30	**62**	9	136.6493	0	199.747	68.44892
31	**63**	9	136.4786	0	198.6001	0

[a] D_1 = Number of double bonds, D_2 = Max. n-n repulsion for bond C-C, D_3 = Number of F atoms, D_4 = Max. e-e repulsion for bond C-O, D_5 = HBSA H-bonding surface area (MOPAC PC).

Table S4. Crystal data and refinement details for compounds **46** and **48**.

Parameter	Compd. **46**	Compd. **48**
Chemical formula	$C_{37}H_{40}F_2N_4O_2$	$C_{38}H_{42}F_2N_4O_2$
M_r	610.73	624.76
Crystal system, space group	Monoclinic, $P2_1/c$	Monoclinic, $P2_1/c$
a, b, c (Å)	12.1284 (4), 15.8117 (6), 17.2351 (7)	12.3371 (4), 16.2079 (7), 17.0271 (9)
β (°)	101.641 (2)	100.522 (2)
V (Å^3)	3237.2 (2)	3347.5 (3)
Z	4	4
μ (mm^{-1})	0.09	0.09
Crystal size (mm)	0.16 × 0.15 × 0.12	0.25 × 0.18 × 0.15
Crystal color	Colorless	Colorless
No. of measured, independent and observed [I> 2.0σ(I)] reflections	10280, 9953, 4135	14424, 8040, 4203
R_{int}	0.056	0.044
R[F^2> 2σ(F^2)], wR(F^2), S	0.052, 0.093, 1.10	0.068, 0.131, 1.01
No. of reflections, parameters	4135, 406	4203, 415
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.24, −0.25	0.24, −0.31
CCDC Number	CCDC 1455157	CCDC 1455158

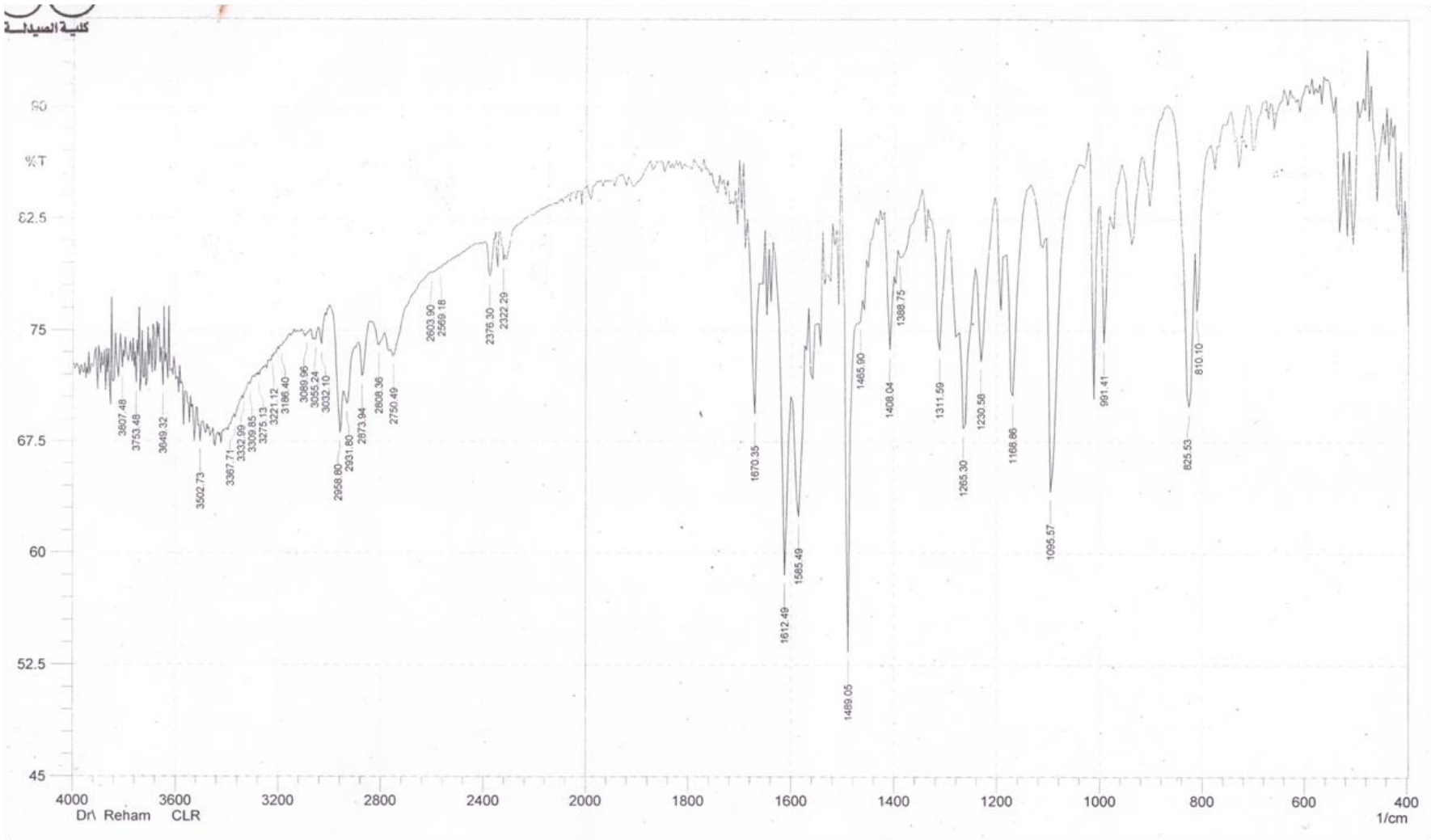


Figure S1. IR spectrum of compound **14** (KBr pellet).

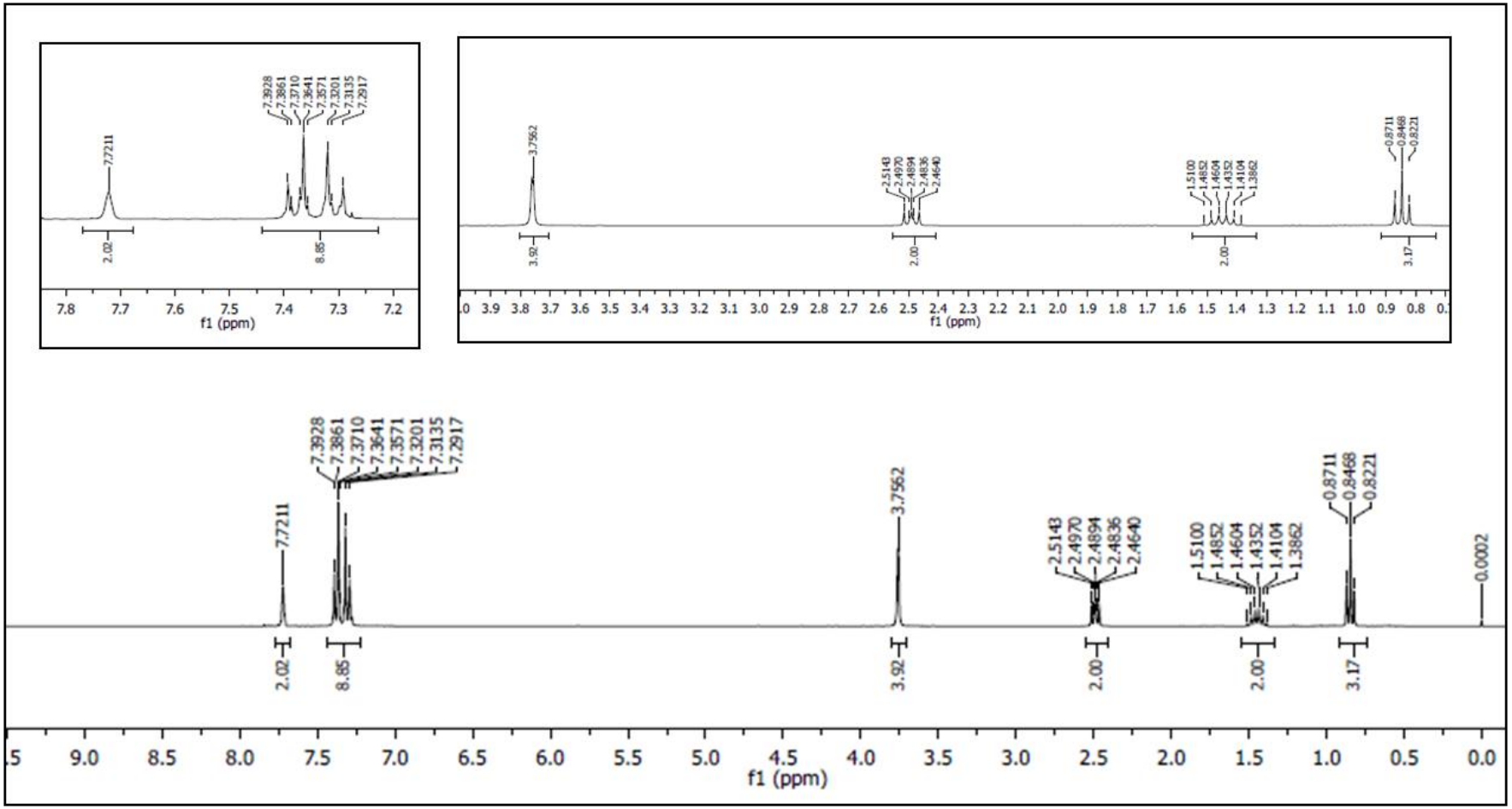


Figure S2. ^{1}H-NMR spectrum of compound **14** in $CDCl_3$.

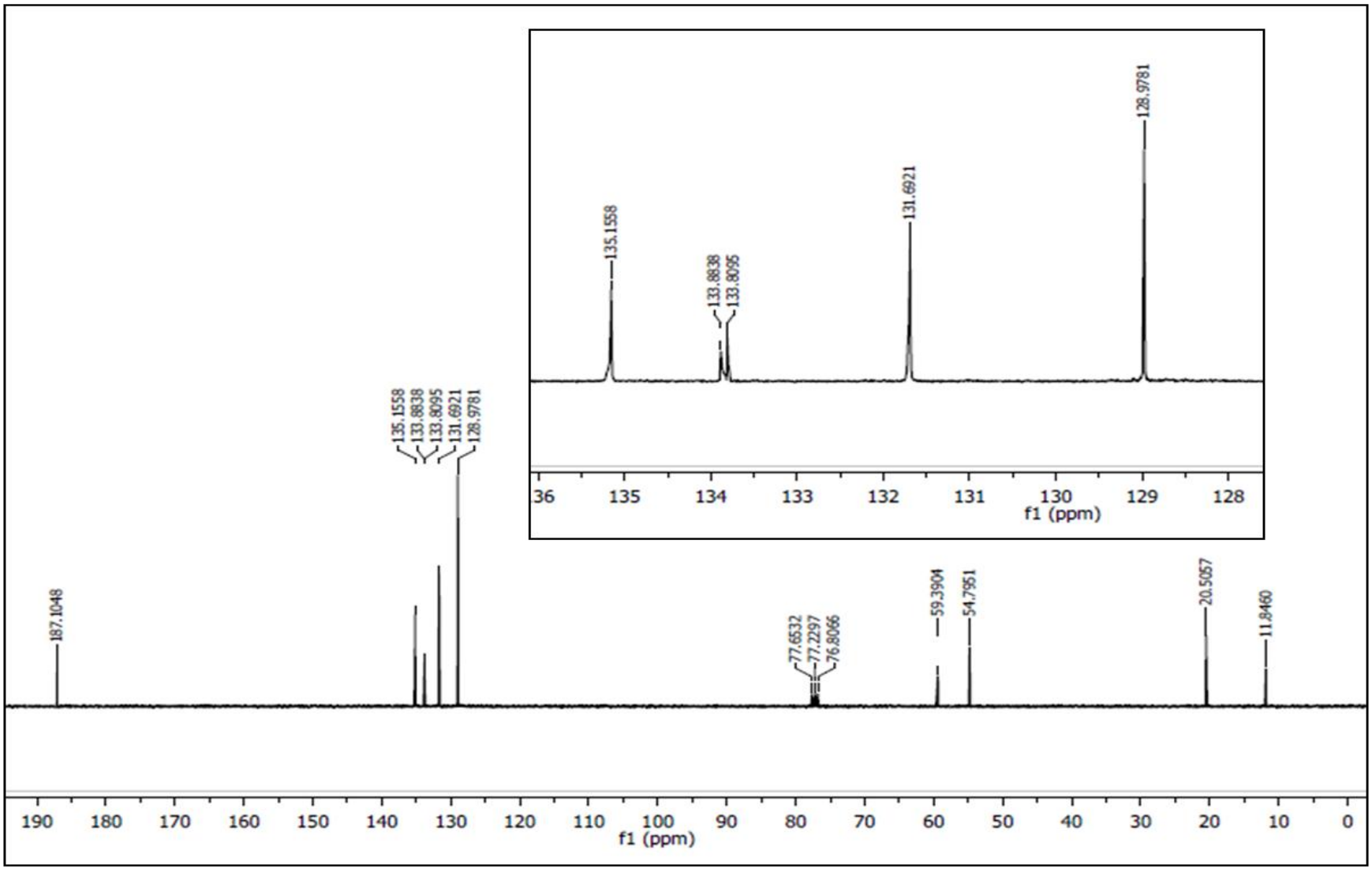


Figure S3. ^{13}C-NMR spectrum of compound **14** in $CDCl_3$.

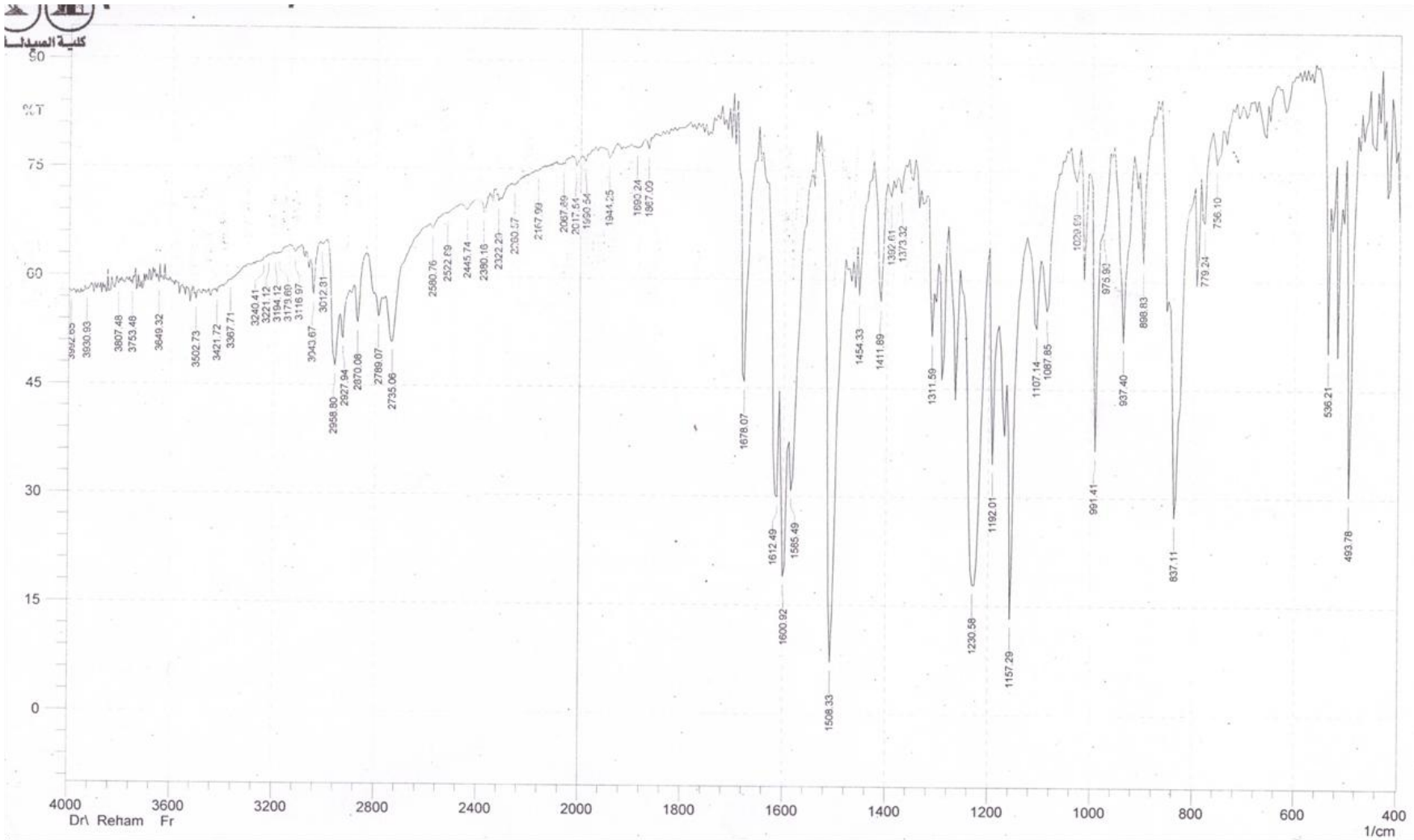


Figure S4. IR spectrum of compound **19** (KBr pellet).

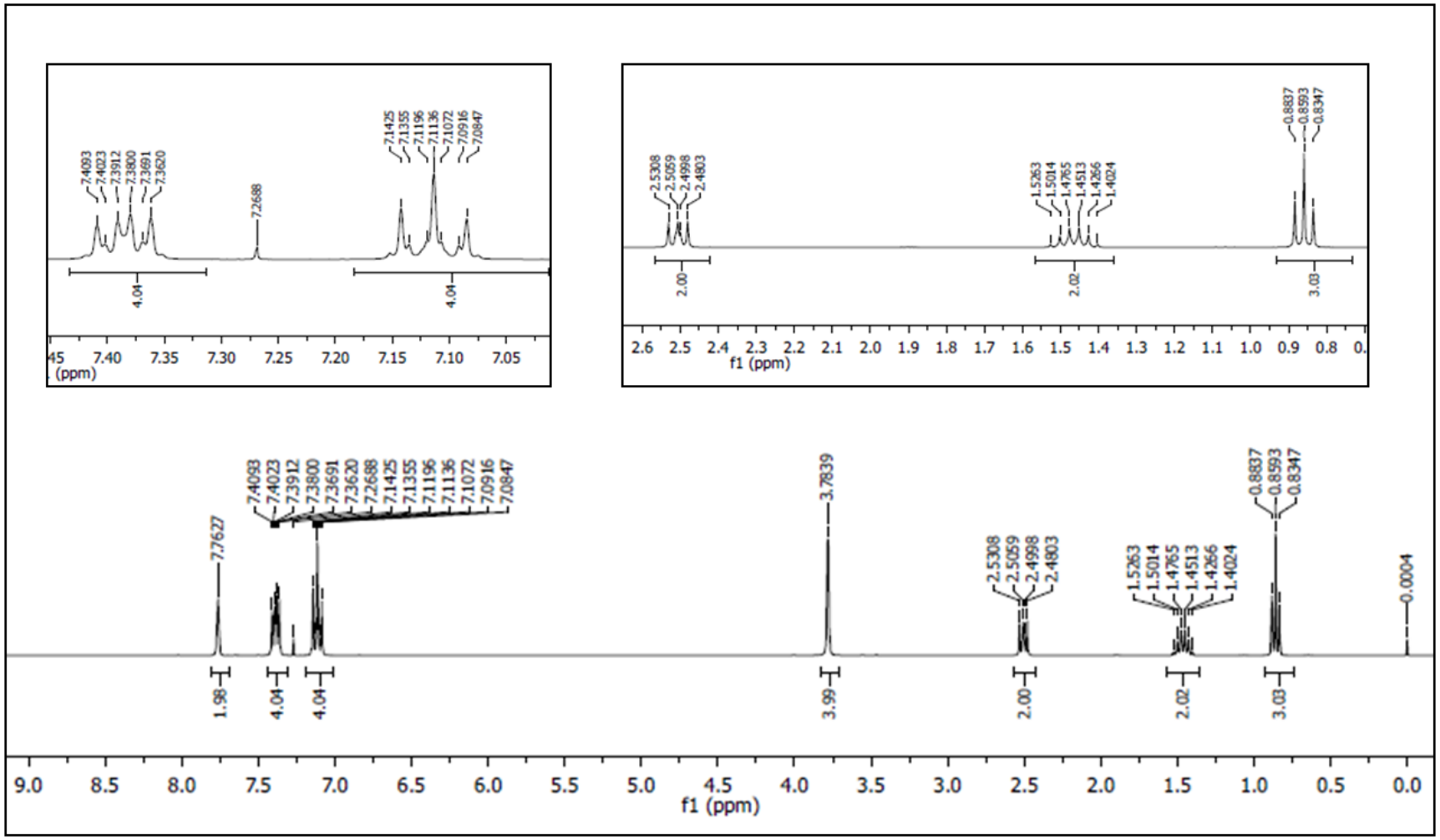


Figure S5. ^{1}H-NMR spectrum of compound **19** in $CDCl_3$.

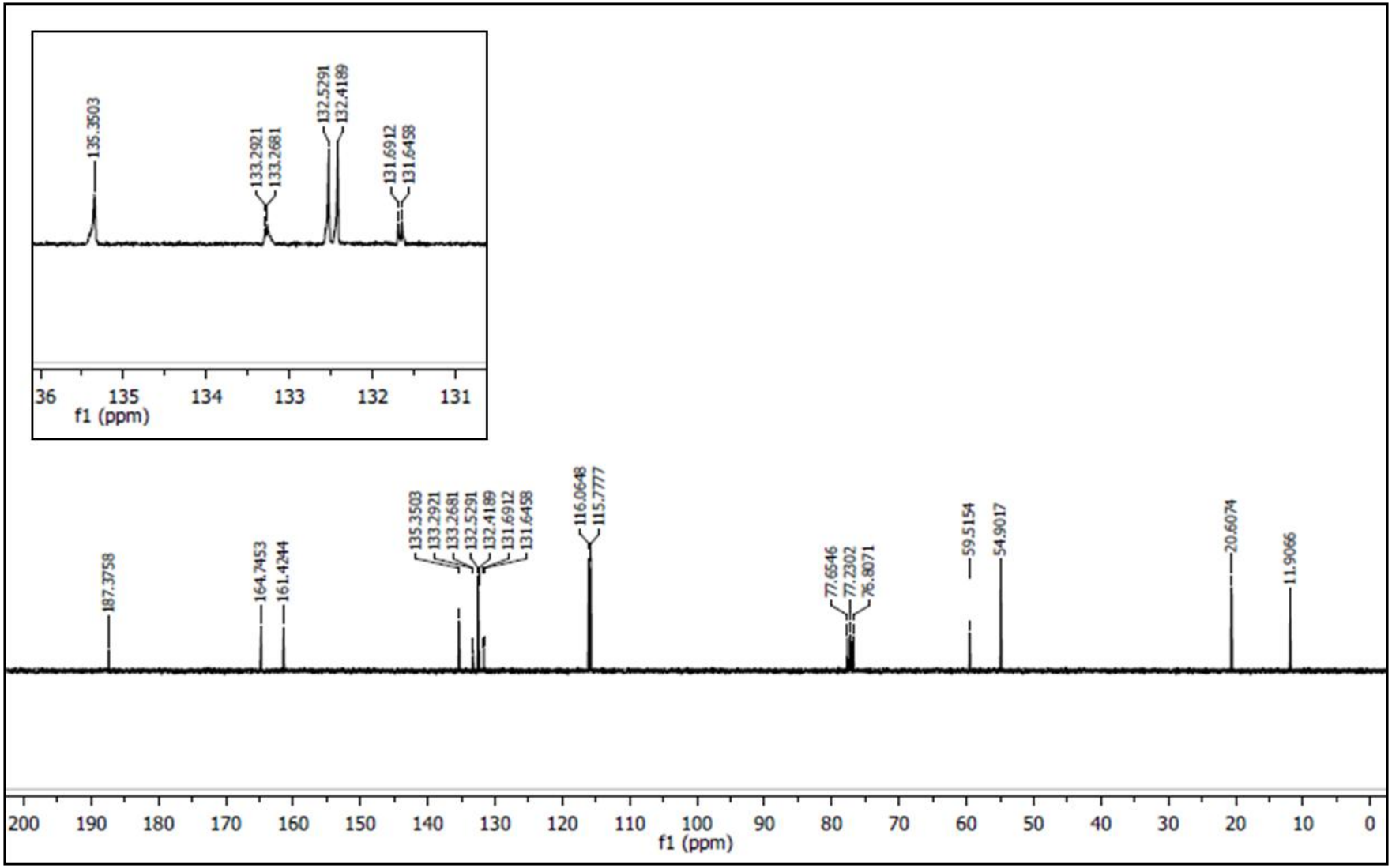


Figure S6. ^{13}C-NMR spectrum of compound **19** in $CDCl_3$.

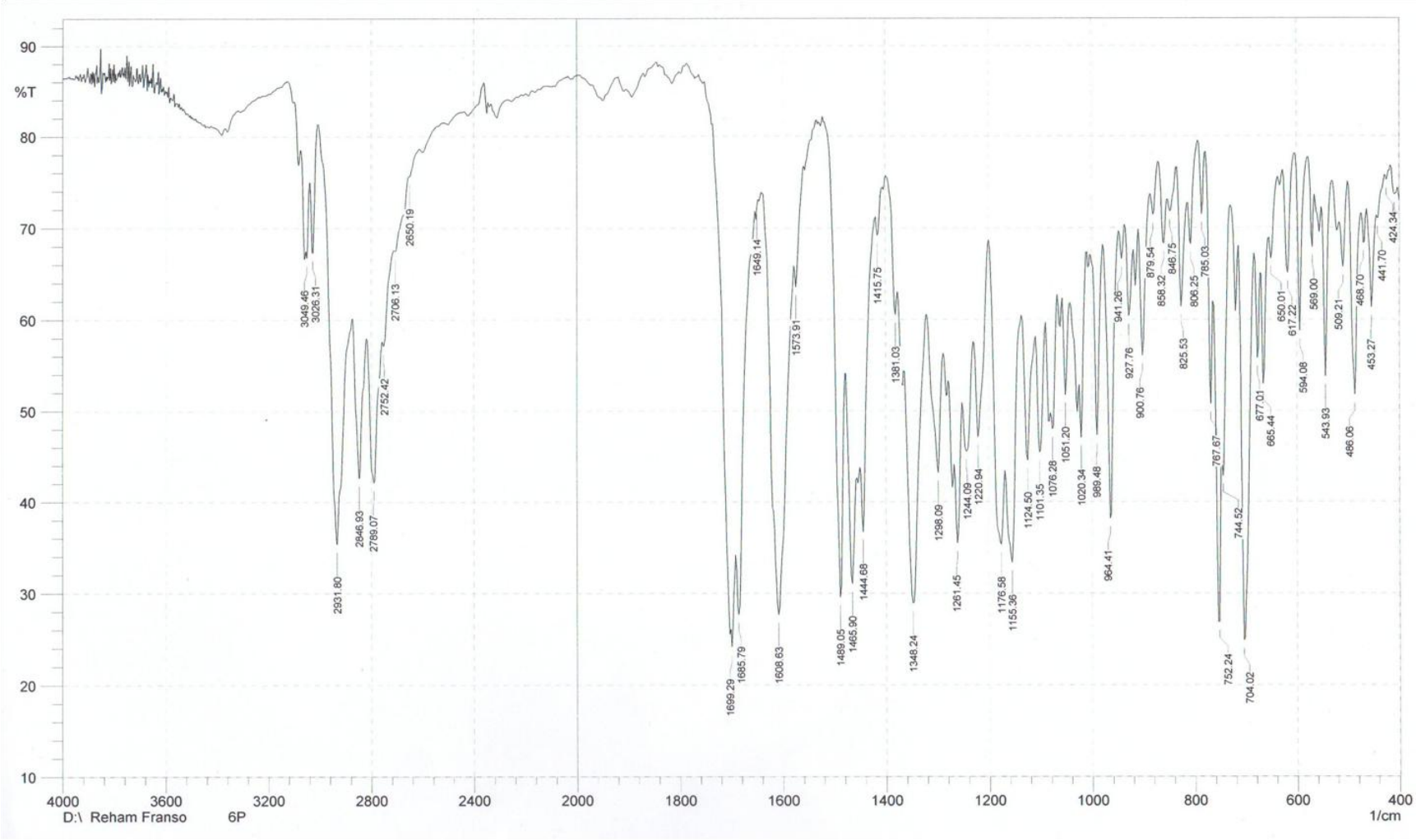


Figure S7. IR spectrum of compound **30** (KBr pellet).

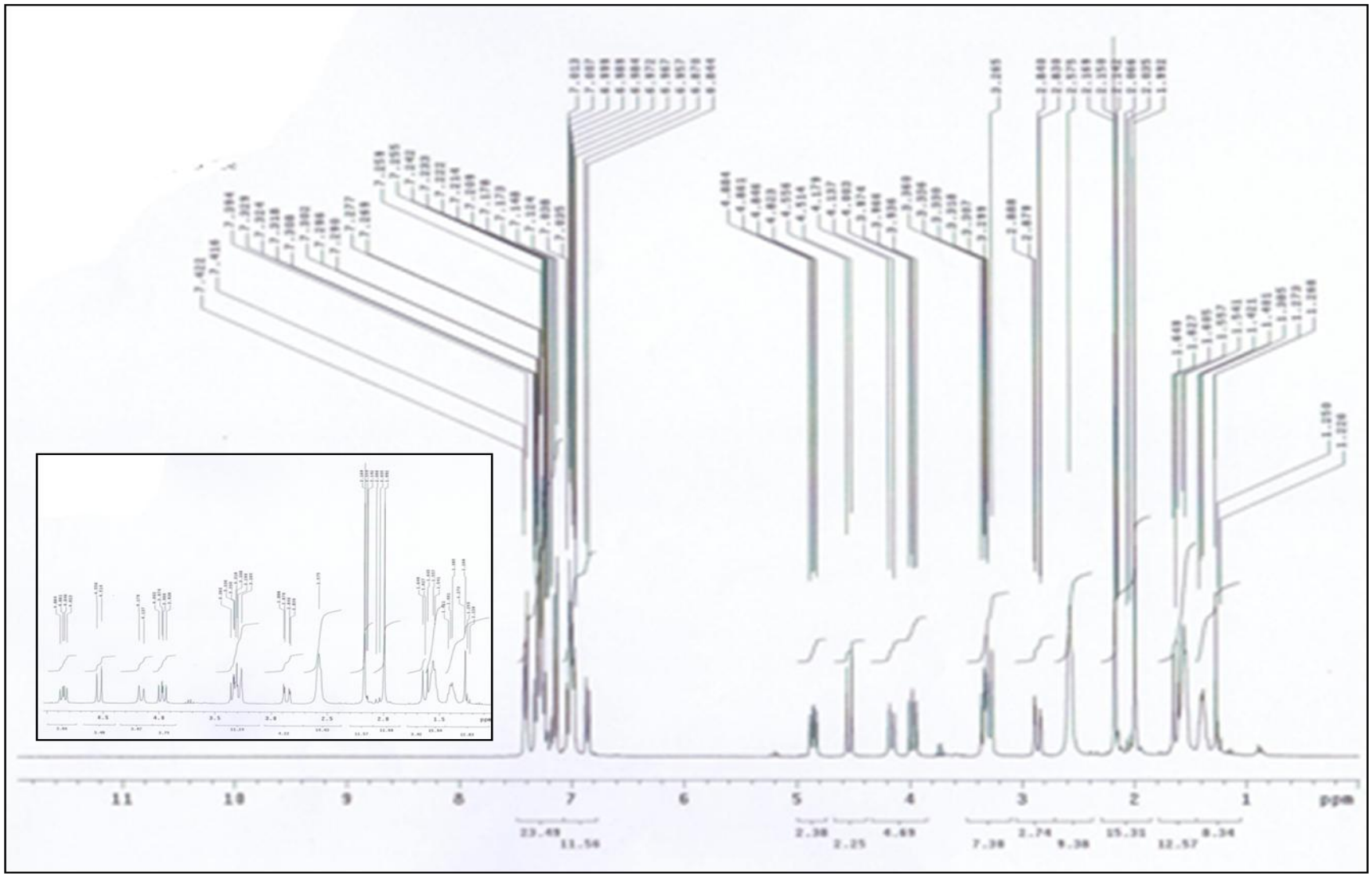


Figure S8. ^{1}H-NMR spectrum of compound **30** in $CDCl_3$.

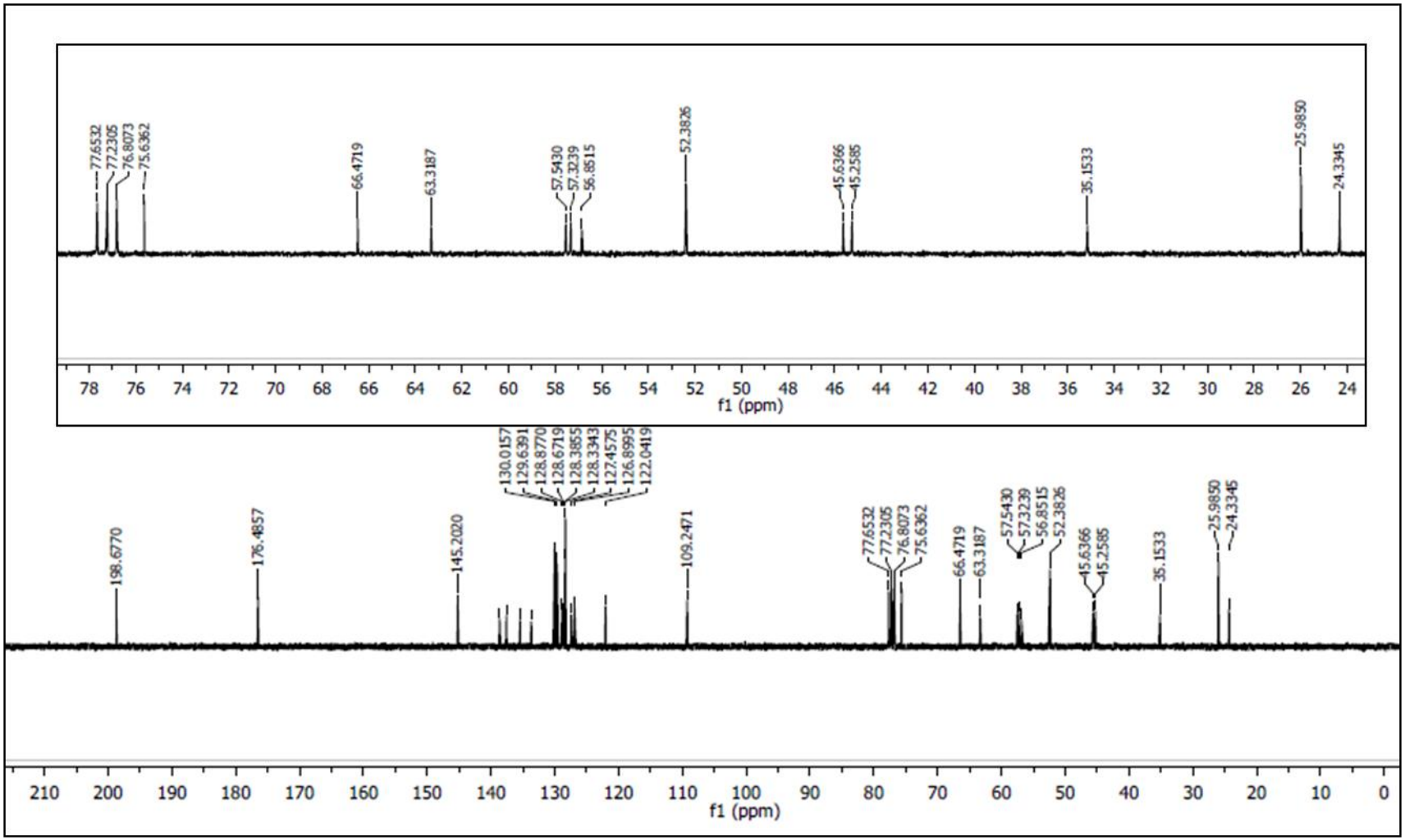


Figure S9. ^{13}C-NMR spectrum of compound **30** in $CDCl_3$.

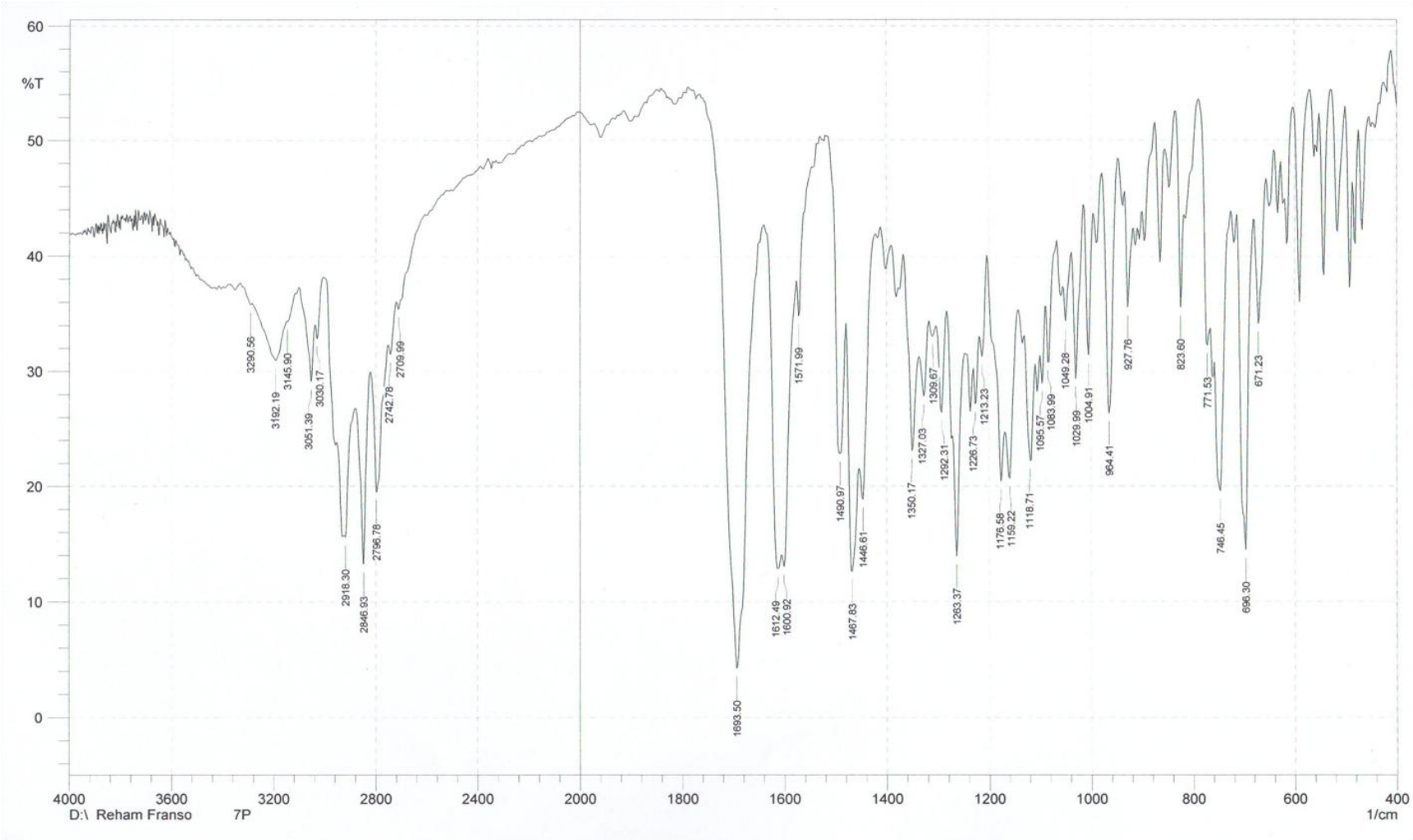


Figure S10. IR spectrum of compound **31** (KBr pellet).

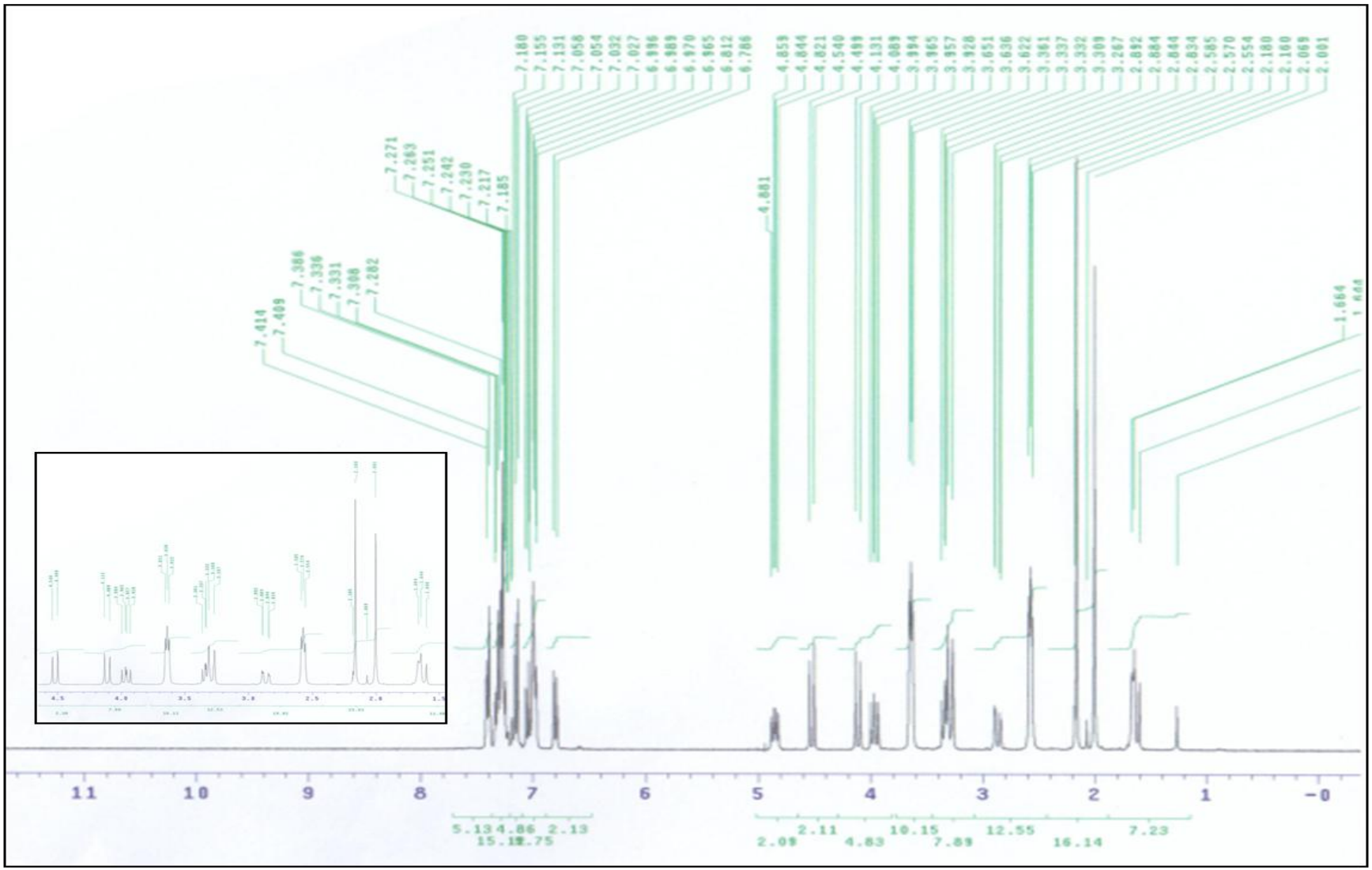


Figure S11. ^{1}H-NMR spectrum of compound **31** in $CDCl_3$.

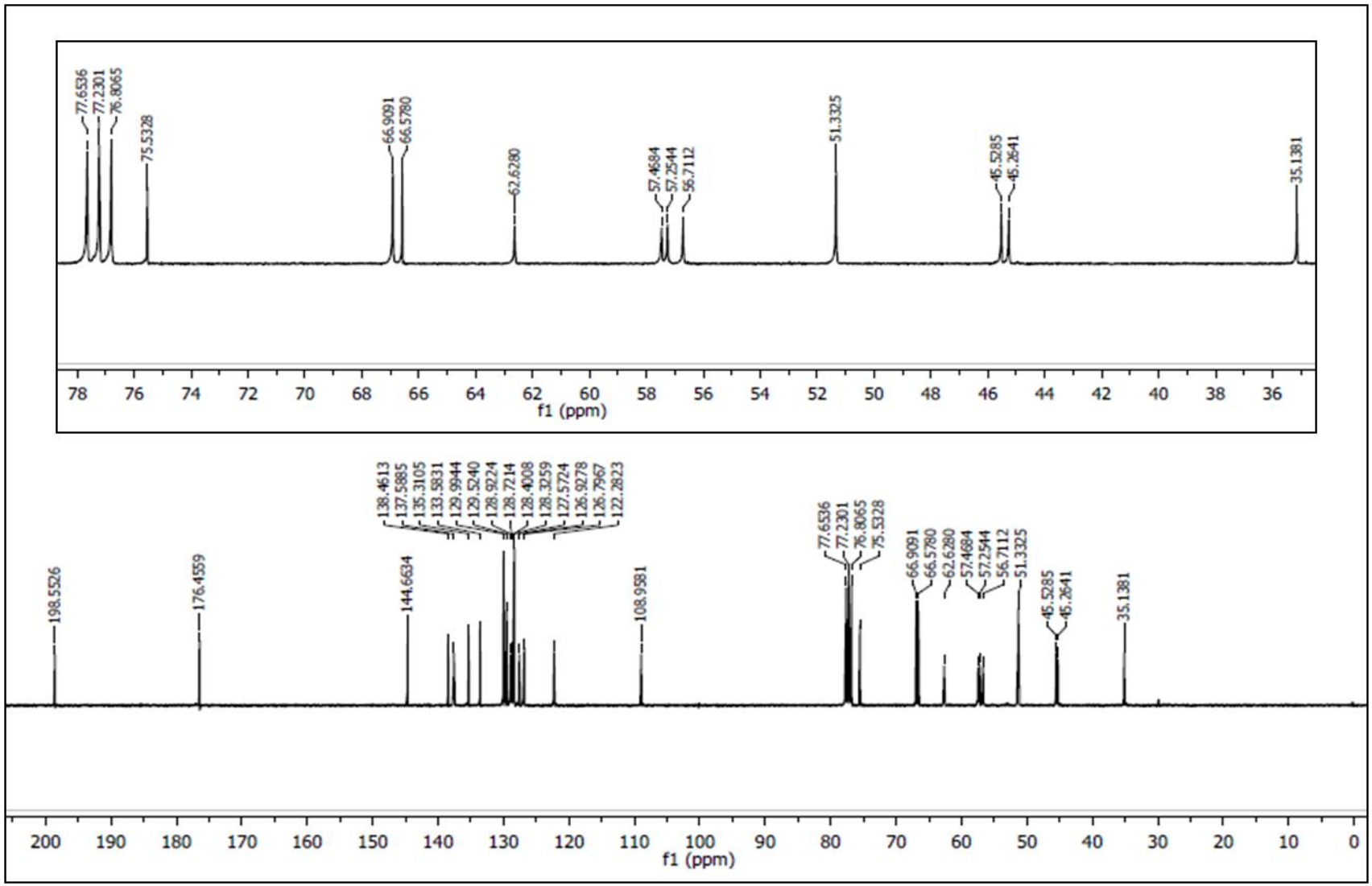


Figure S12. ^{13}C-NMR spectrum of compound **31** in $CDCl_3$.

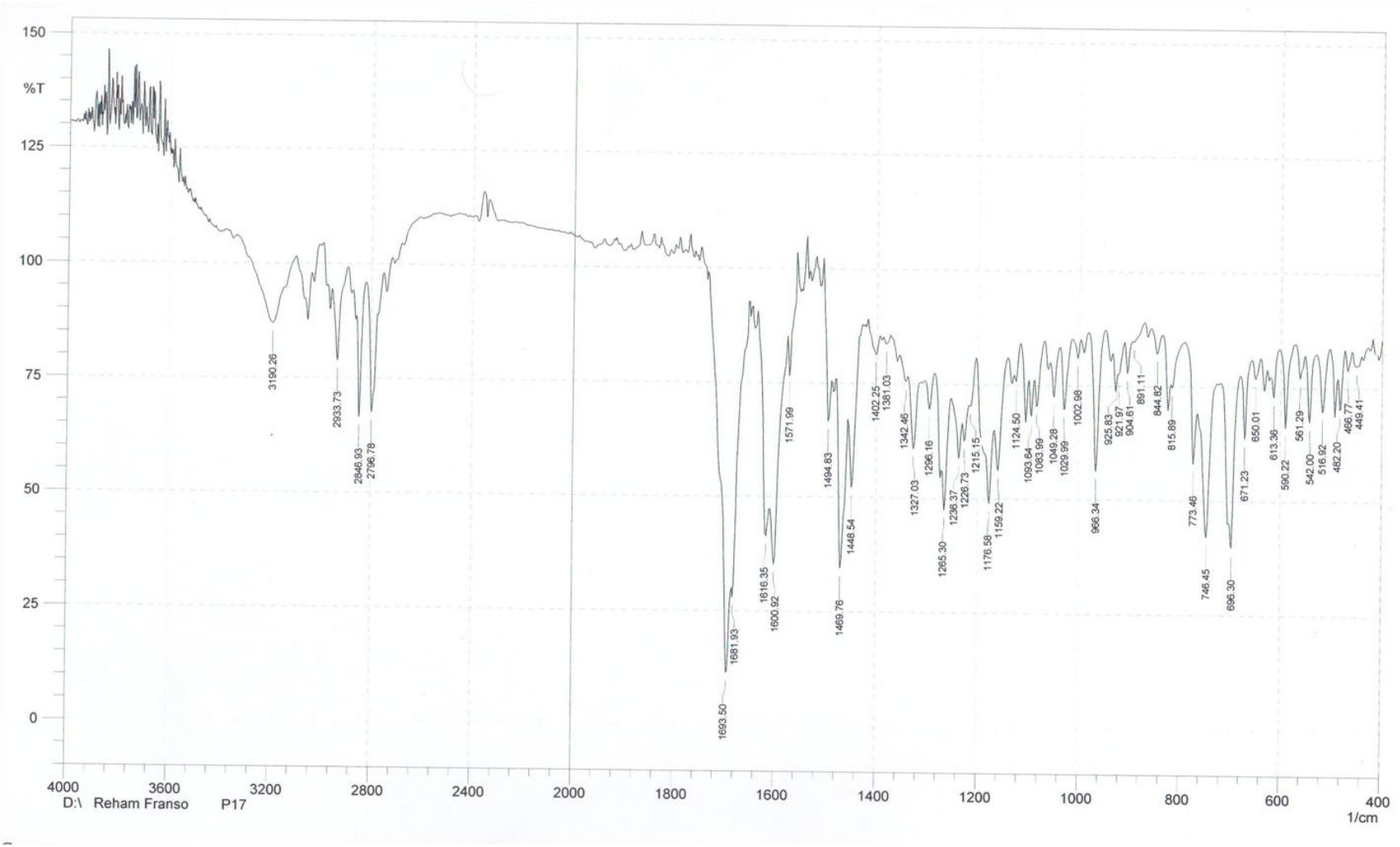


Figure S13. IR spectrum of compound **32** (KBr pellet).

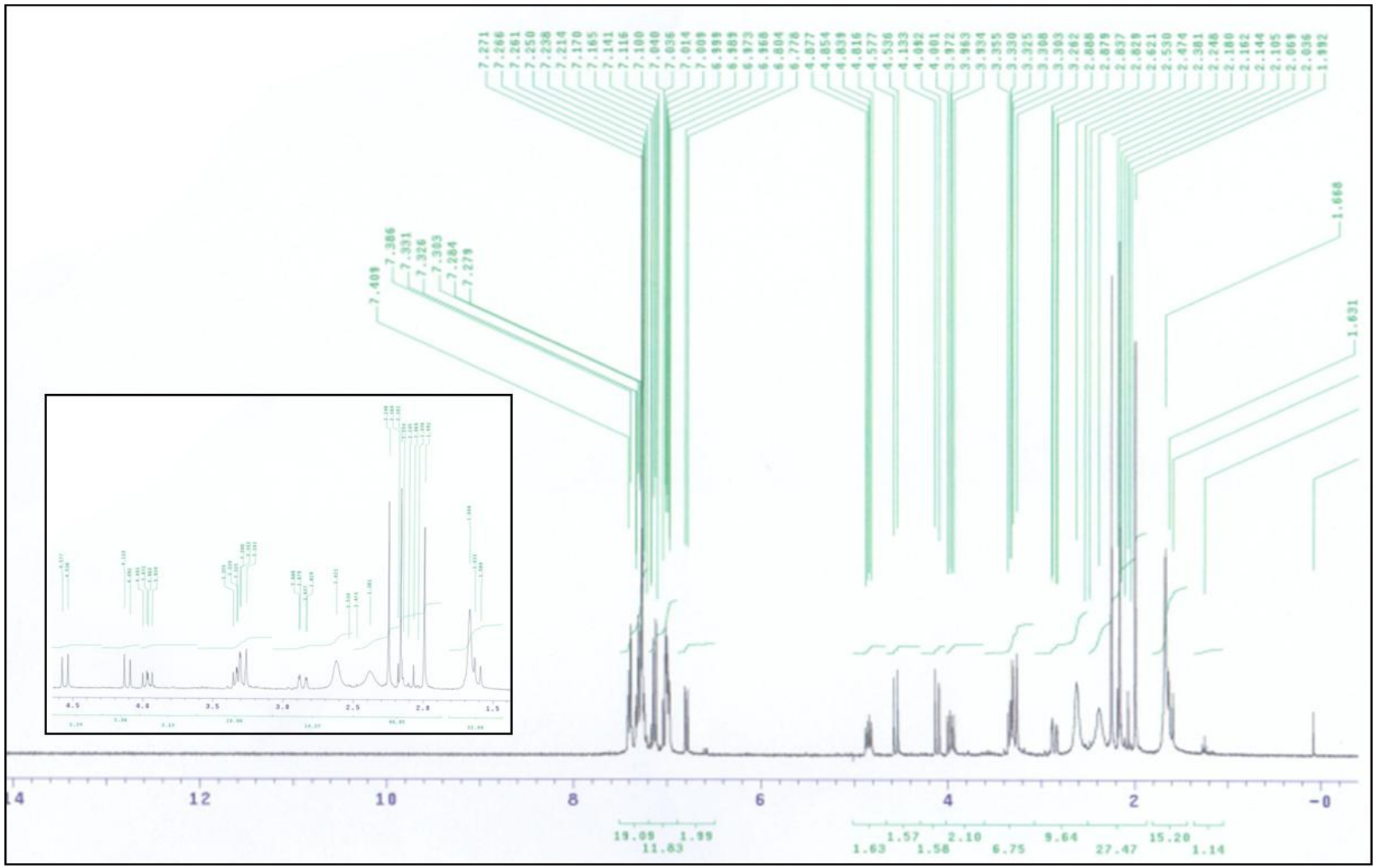


Figure S14. ^{1}H-NMR spectrum of compound **32** in $CDCl_3$.

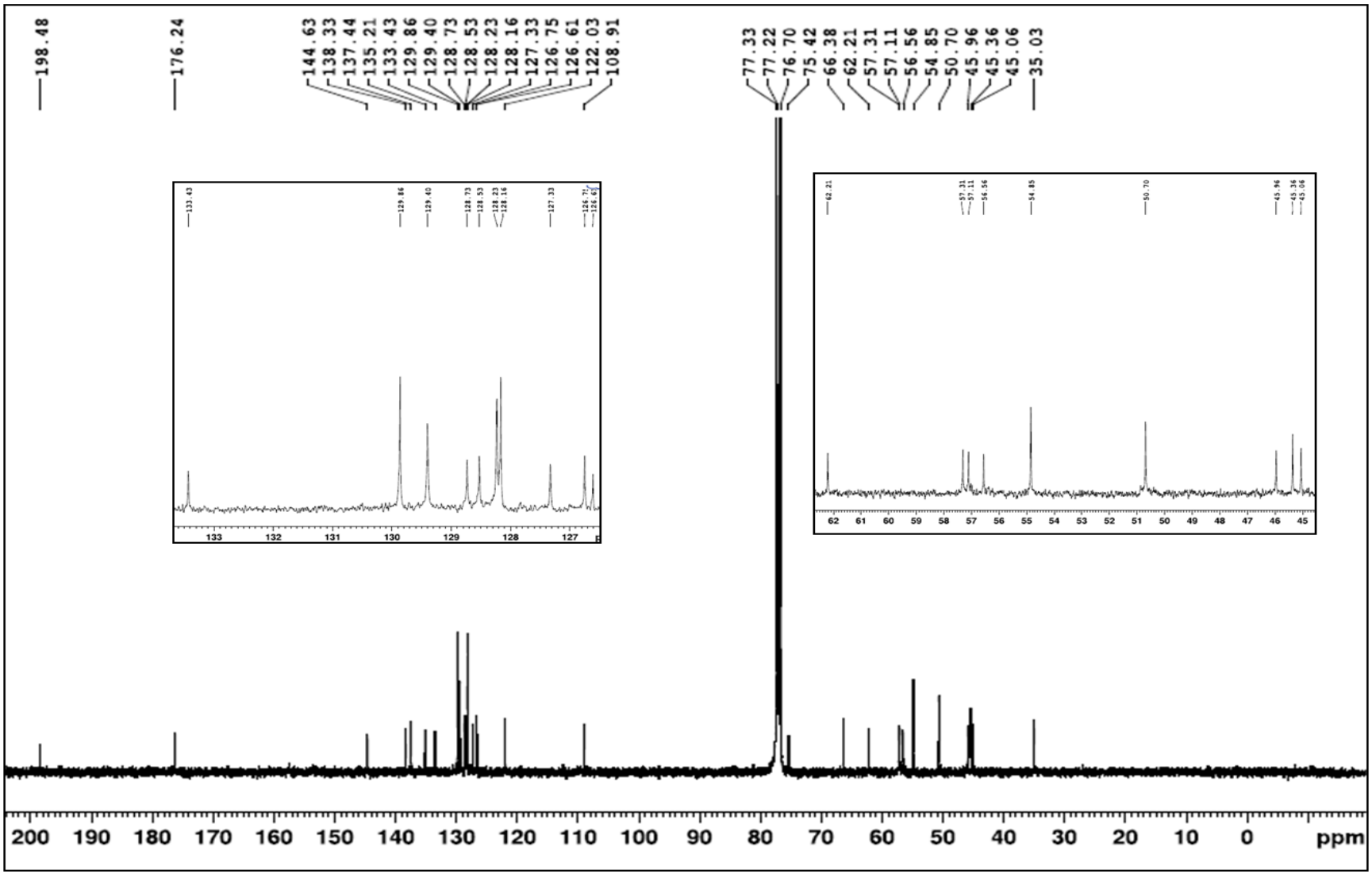


Figure S15. ^{13}C-NMR spectrum of compound **32** in $CDCl_3$.

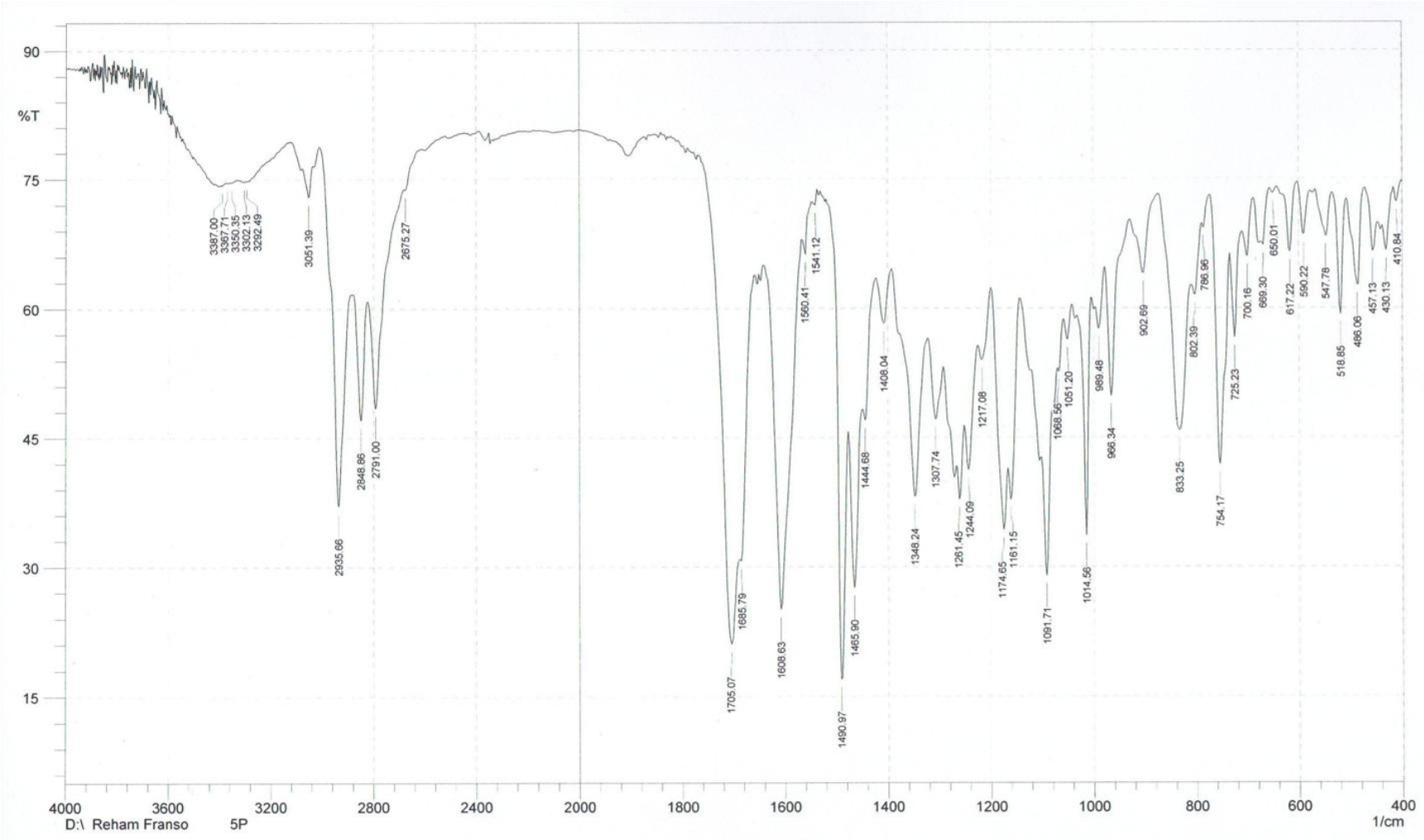


Figure S16. IR spectrum of compound **33** (KBr pellet).

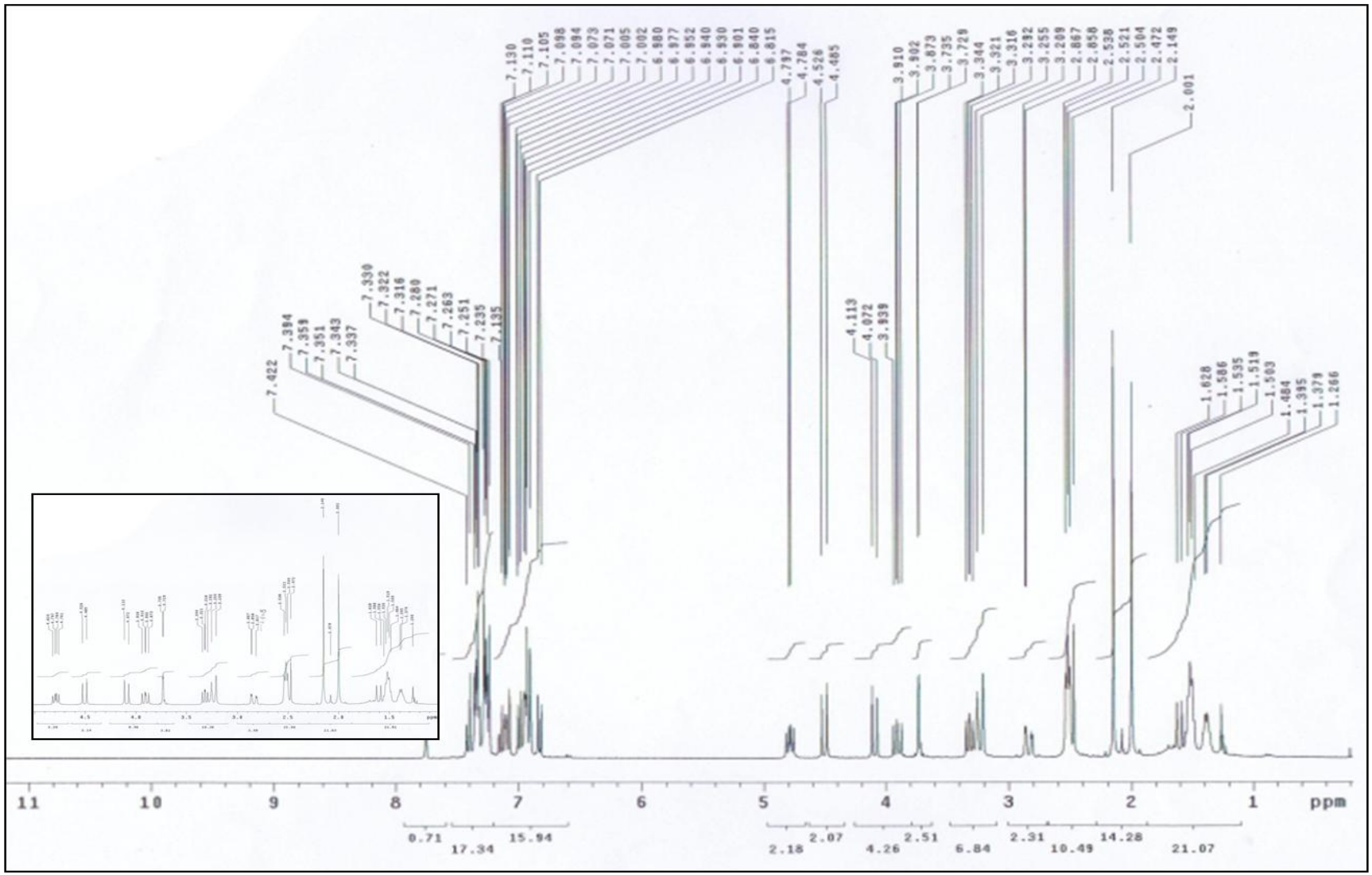


Figure S17. ^{1}H-NMR spectrum of compound **33** in $CDCl_3$.

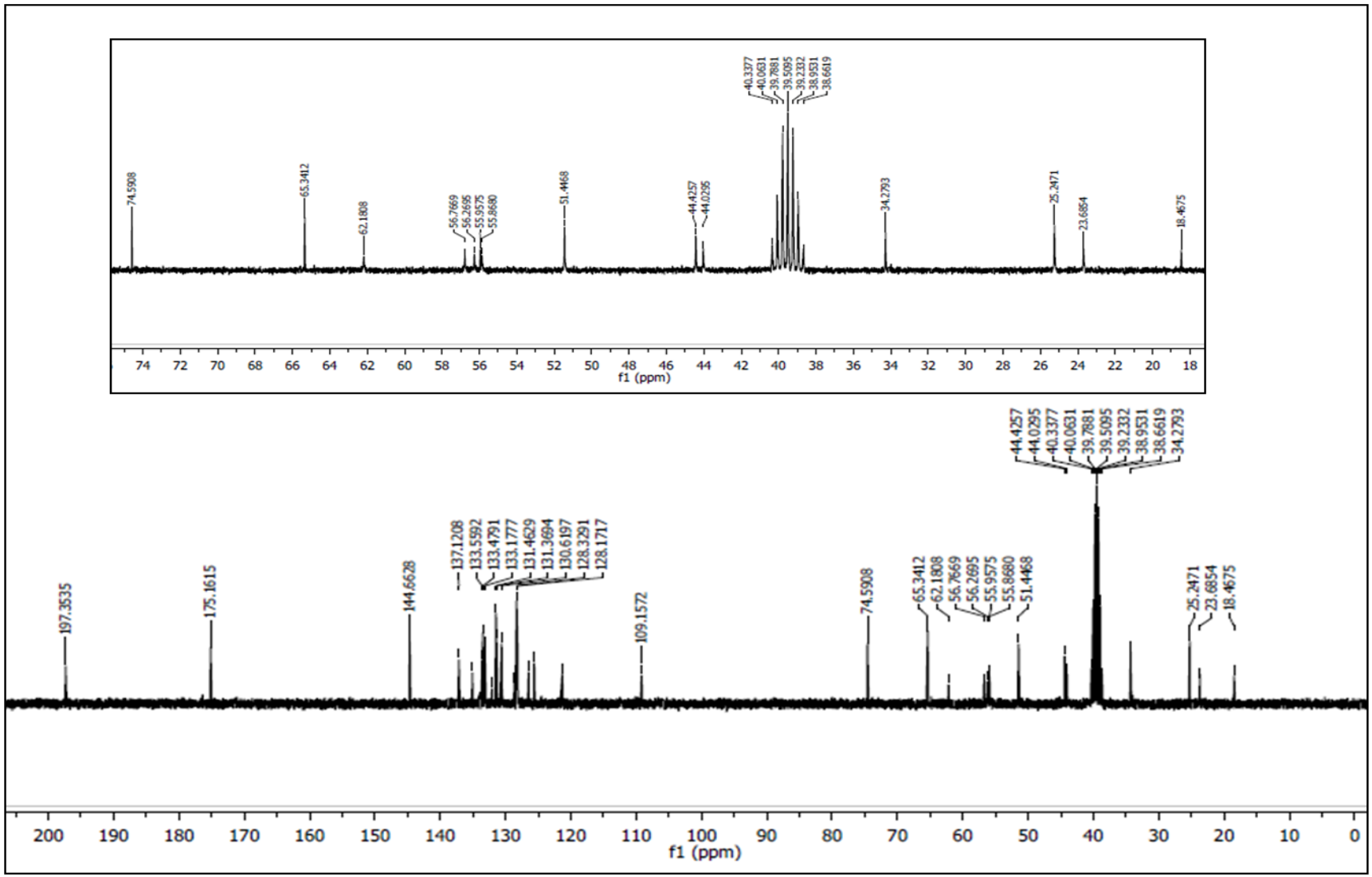


Figure S18. ^{13}C-NMR spectrum of compound **33** in DMSO-d_6.

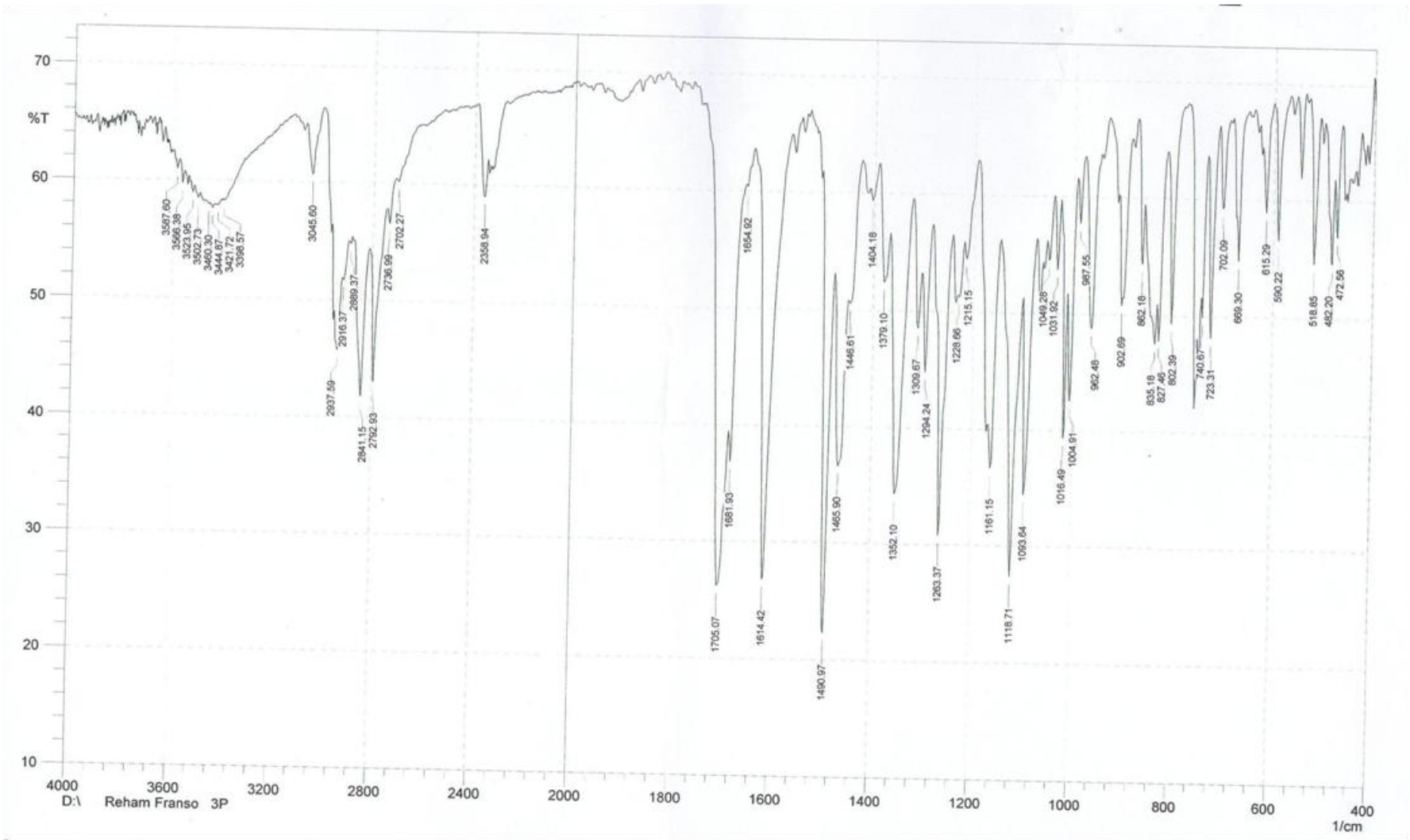


Figure S19. IR spectrum of compound **34** (KBr pellet).

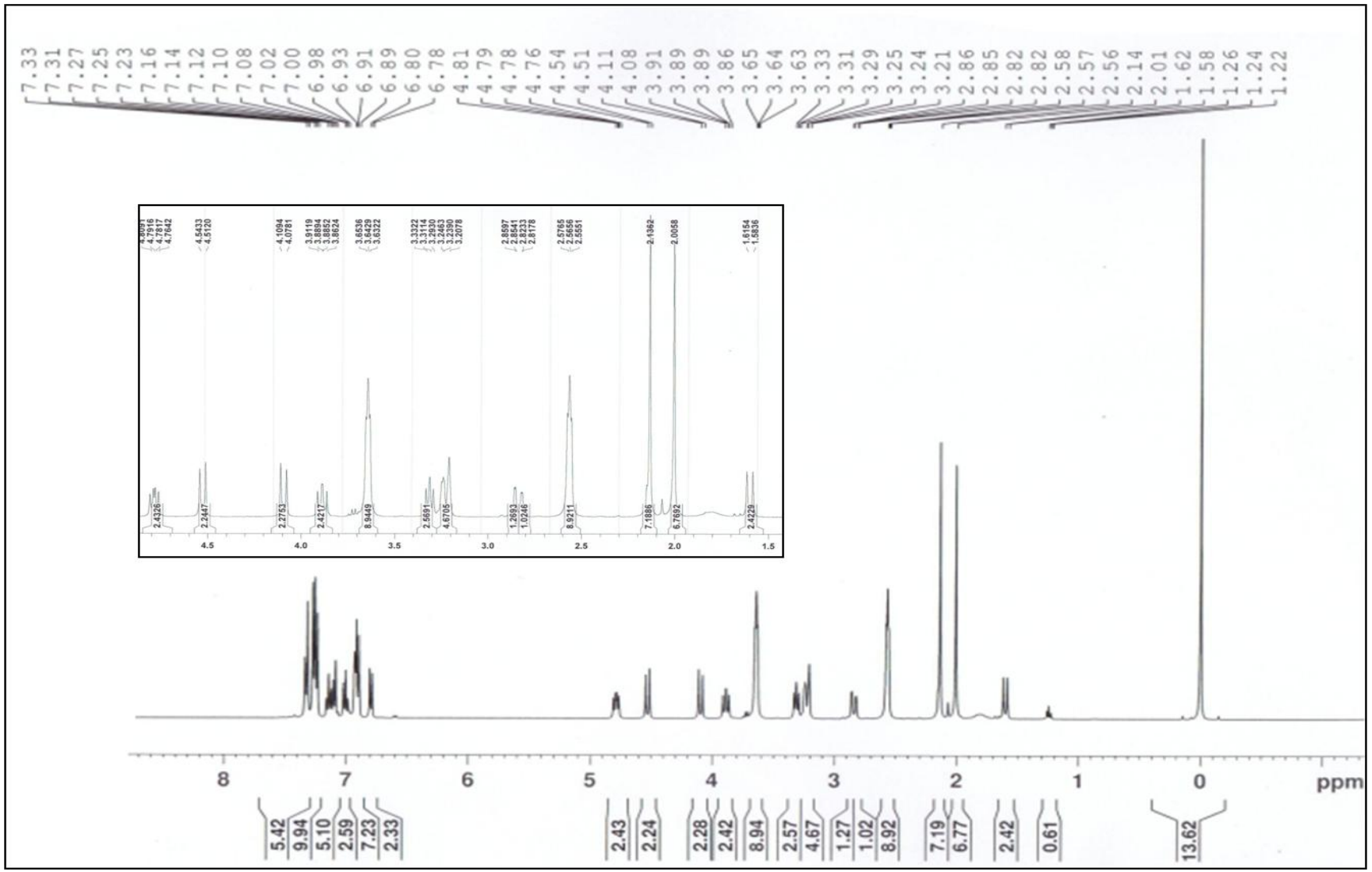


Figure S20. ^{1}H-NMR spectrum of compound **34** in $CDCl_3$.

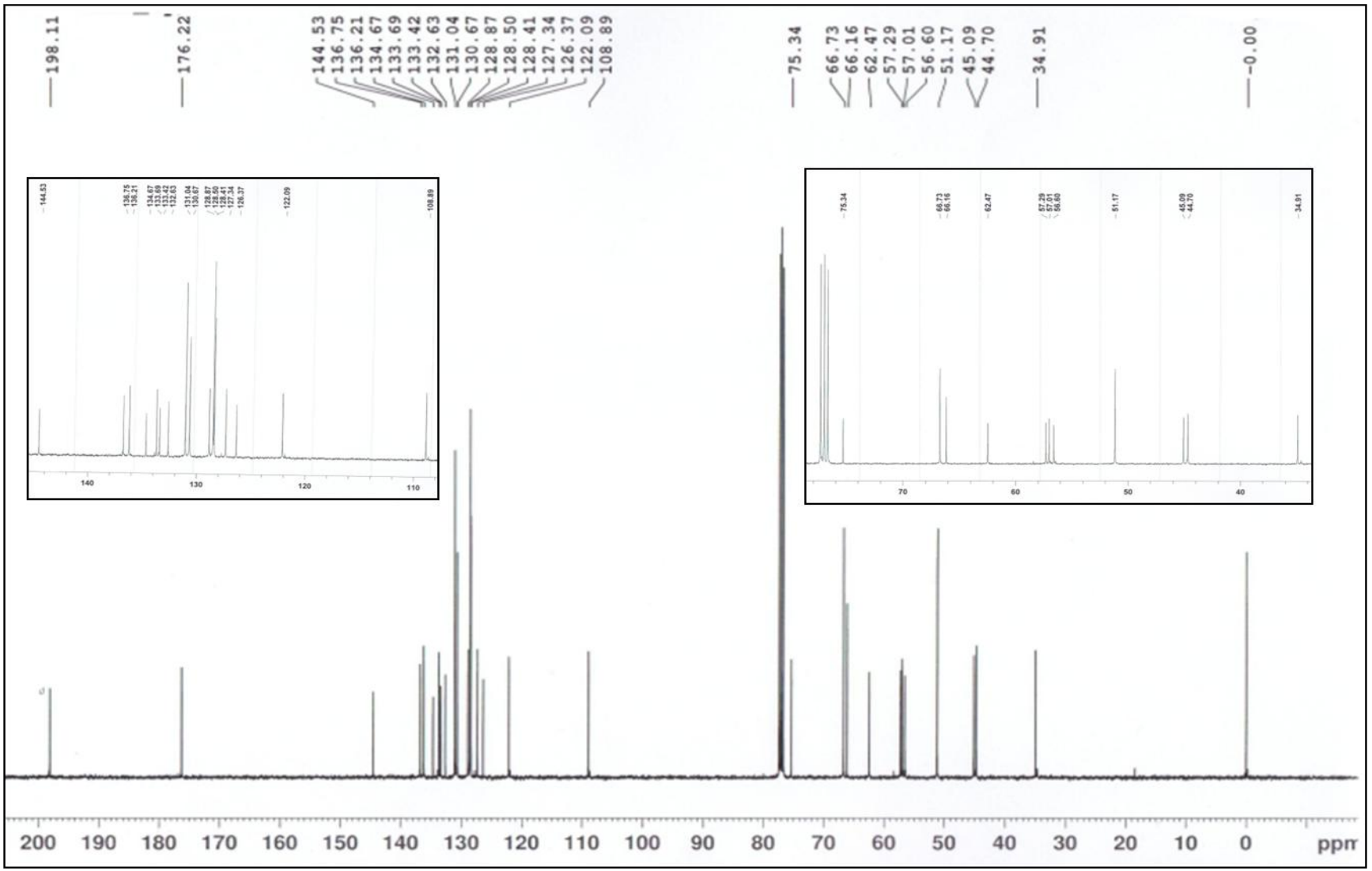


Figure S21. ^{13}C-NMR spectrum of compound **34** in $CDCl_3$.

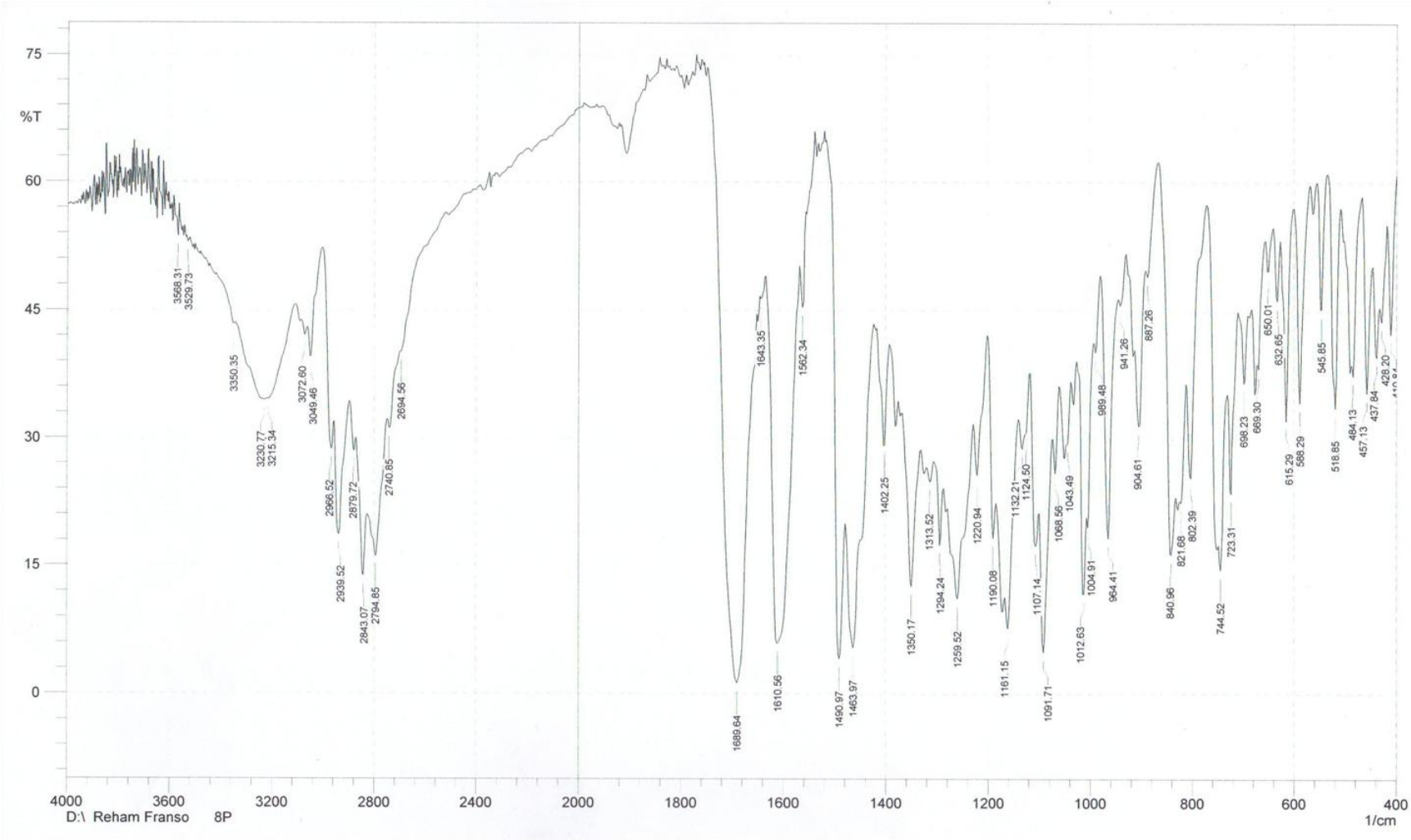


Figure S22. IR spectrum of compound **35** (KBr pellet).

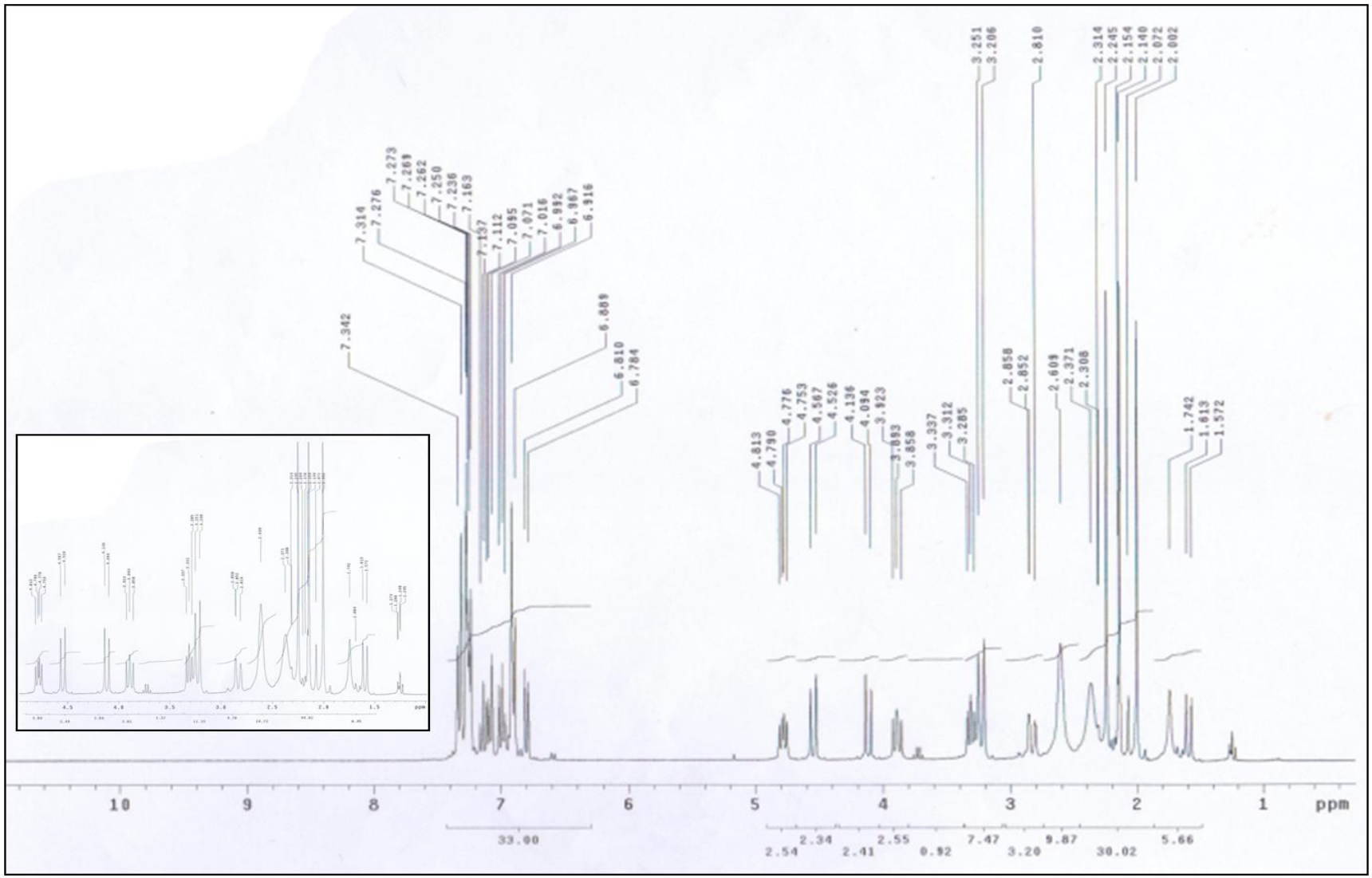


Figure S23. ^{1}H-NMR spectrum of compound **35** in $CDCl_3$.

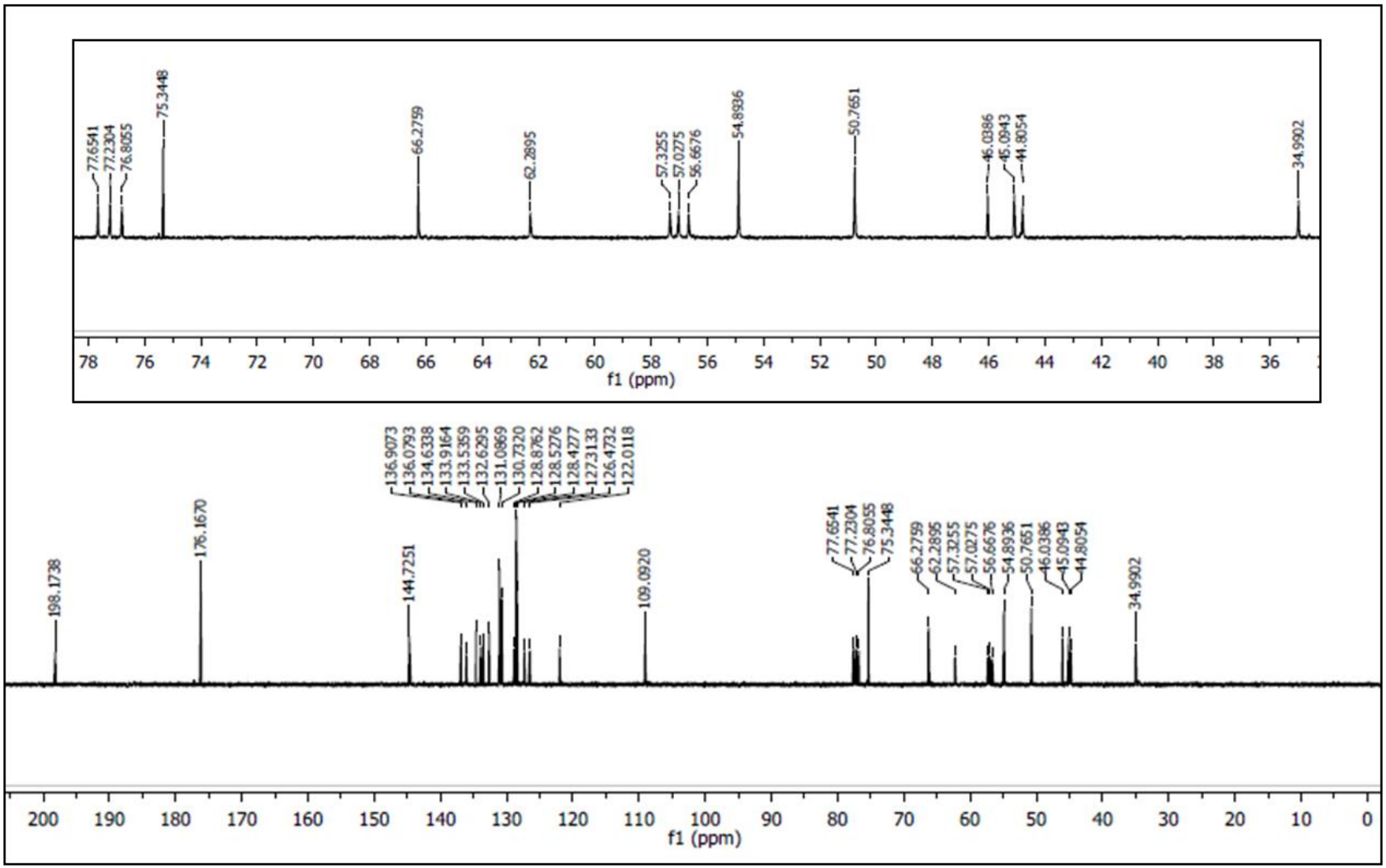


Figure S24. ^{13}C-NMR spectrum of compound **35** in $CDCl_3$.

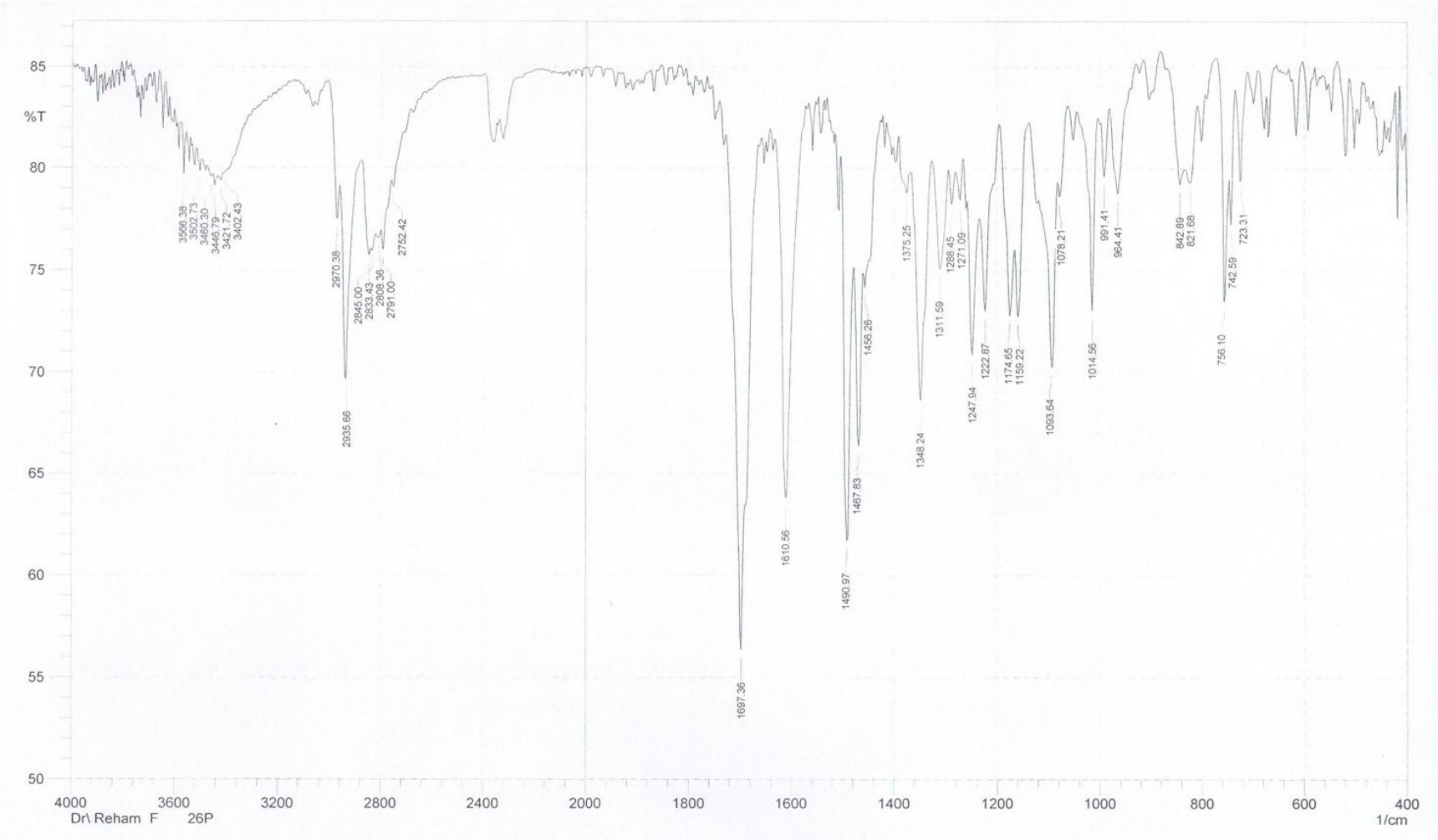


Figure S25. IR spectrum of compound **36** (KBr pellet).

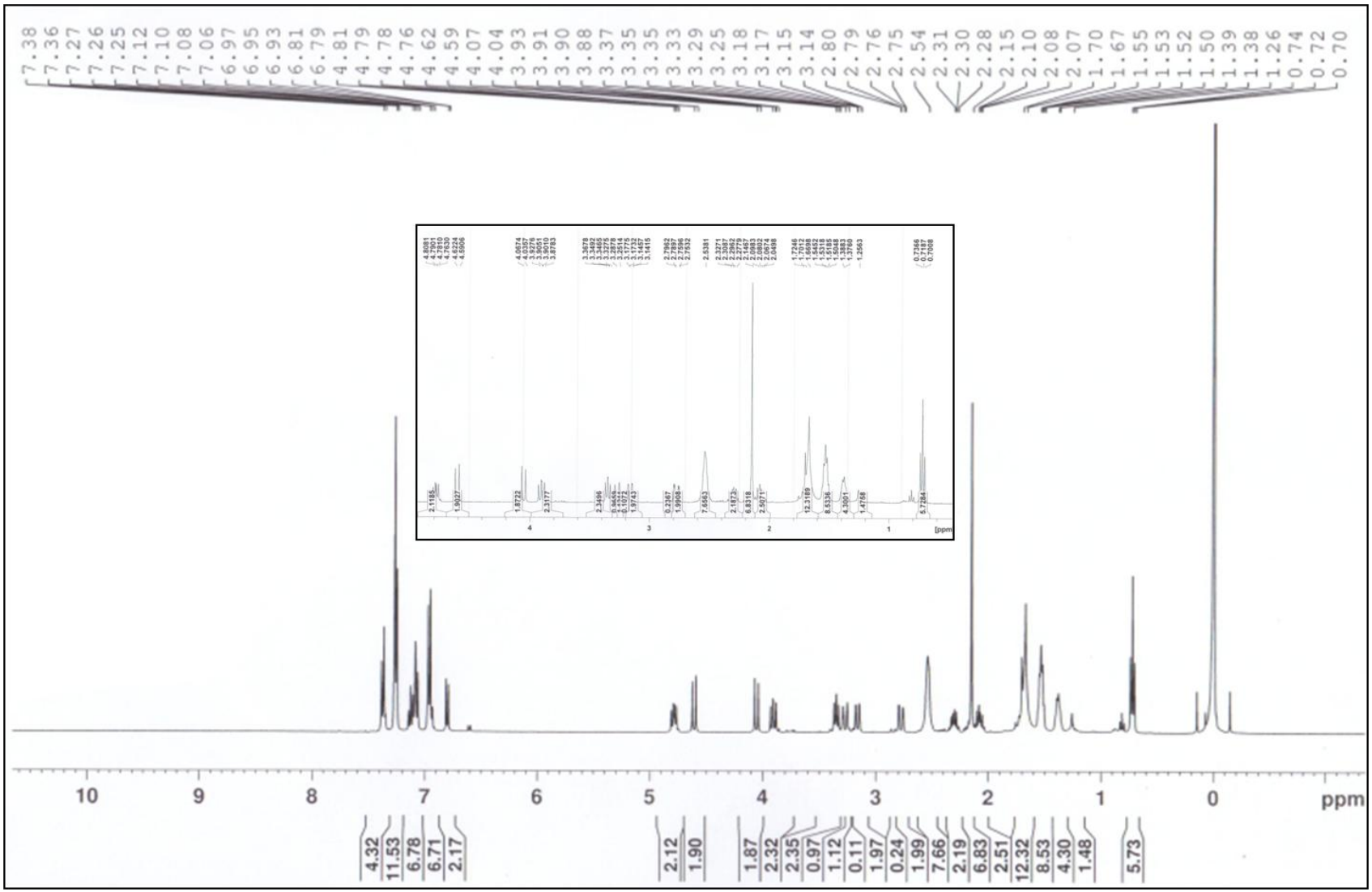


Figure S26. ^{1}H-NMR spectrum of compound **36** in $CDCl_3$.

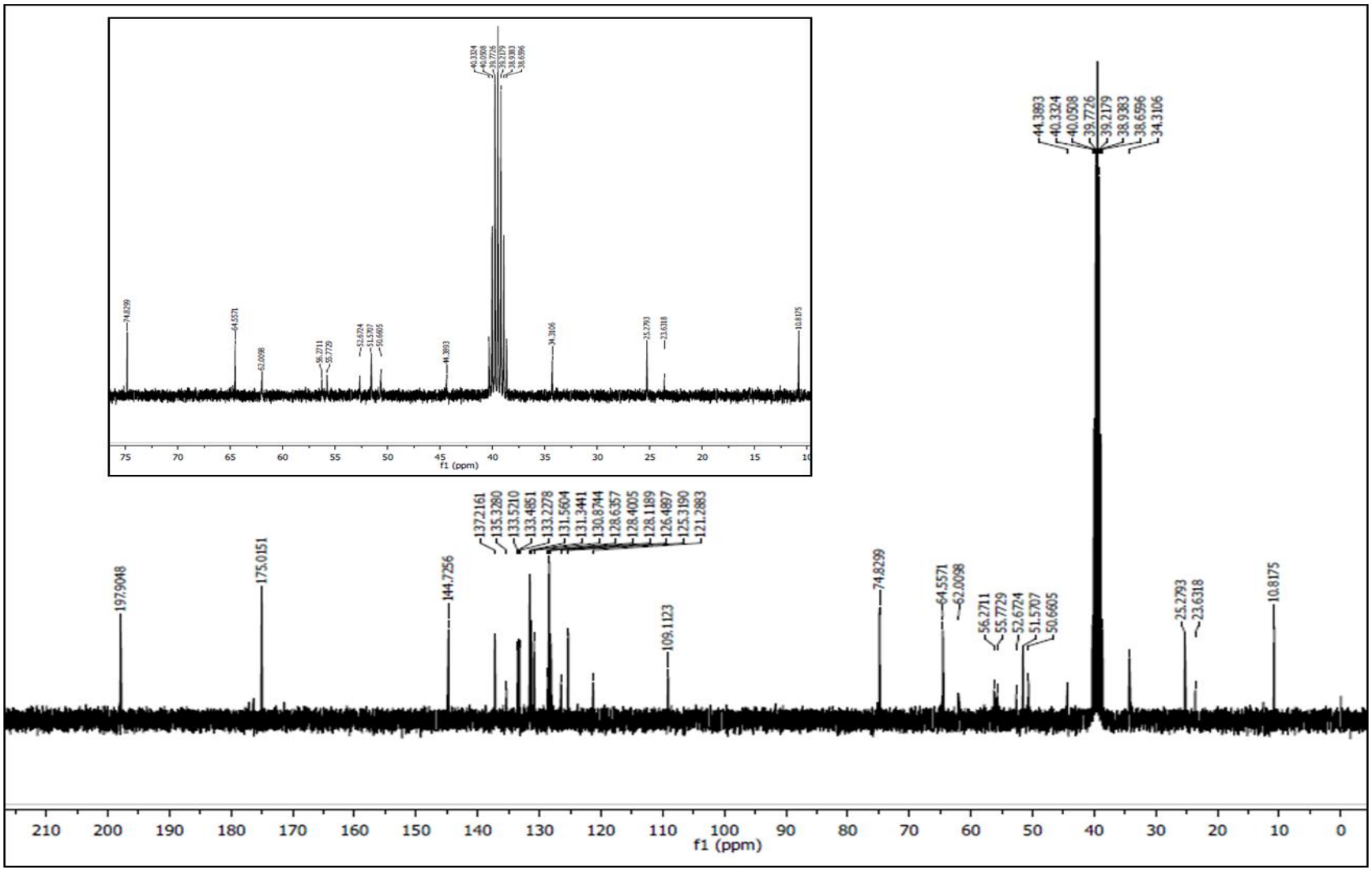


Figure S27. ^{13}C-NMR spectrum of compound **36** in DMSO-d_6.

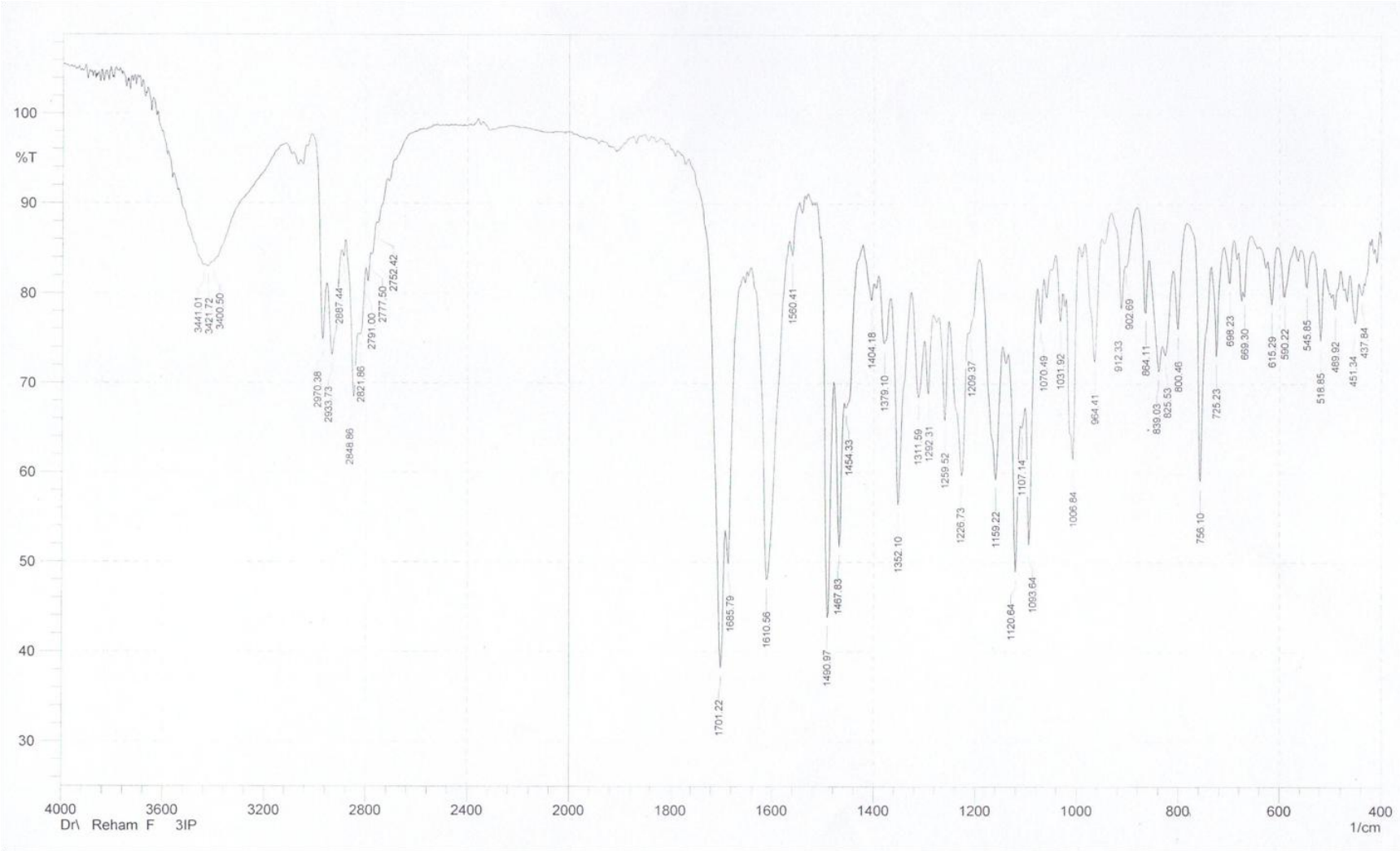


Figure S28. IR spectrum of compound **37** (KBr pellet).

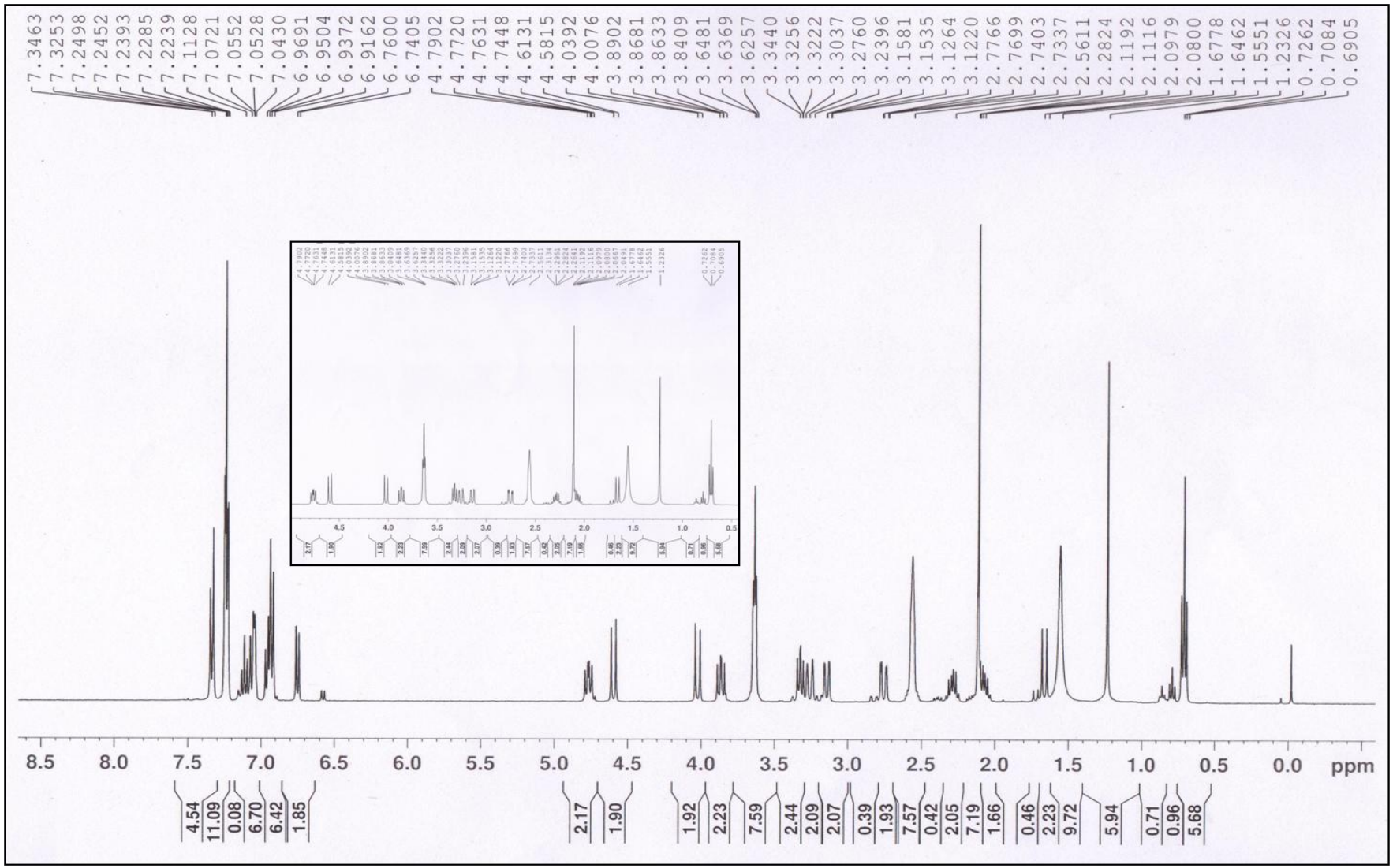


Figure S29. ^{1}H-NMR spectrum of compound **37** in $CDCl_3$.

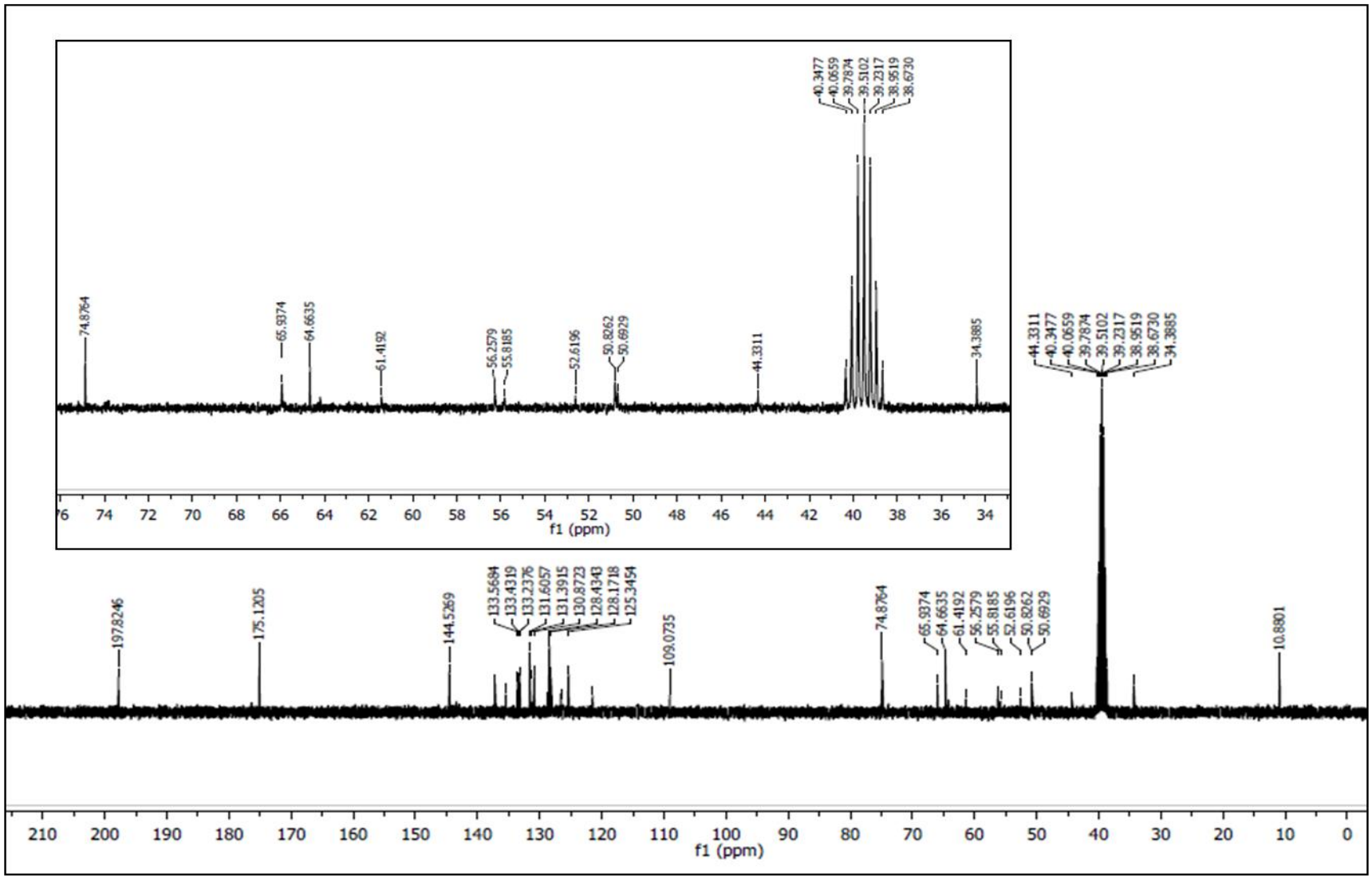


Figure S30. ^{13}C-NMR spectrum of compound **37** in DMSO-d_6.

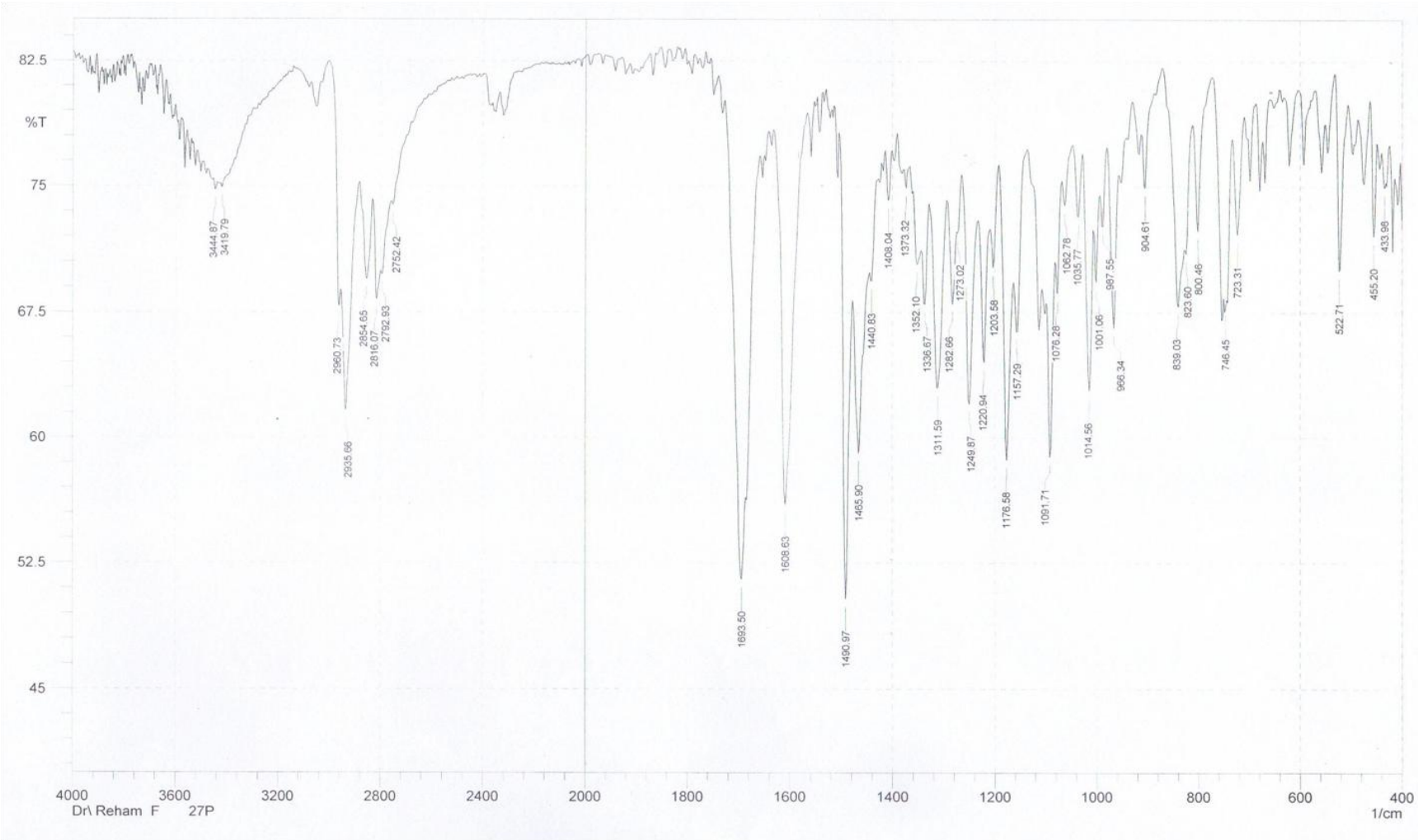


Figure S31. IR spectrum of compound **38** (KBr pellet).

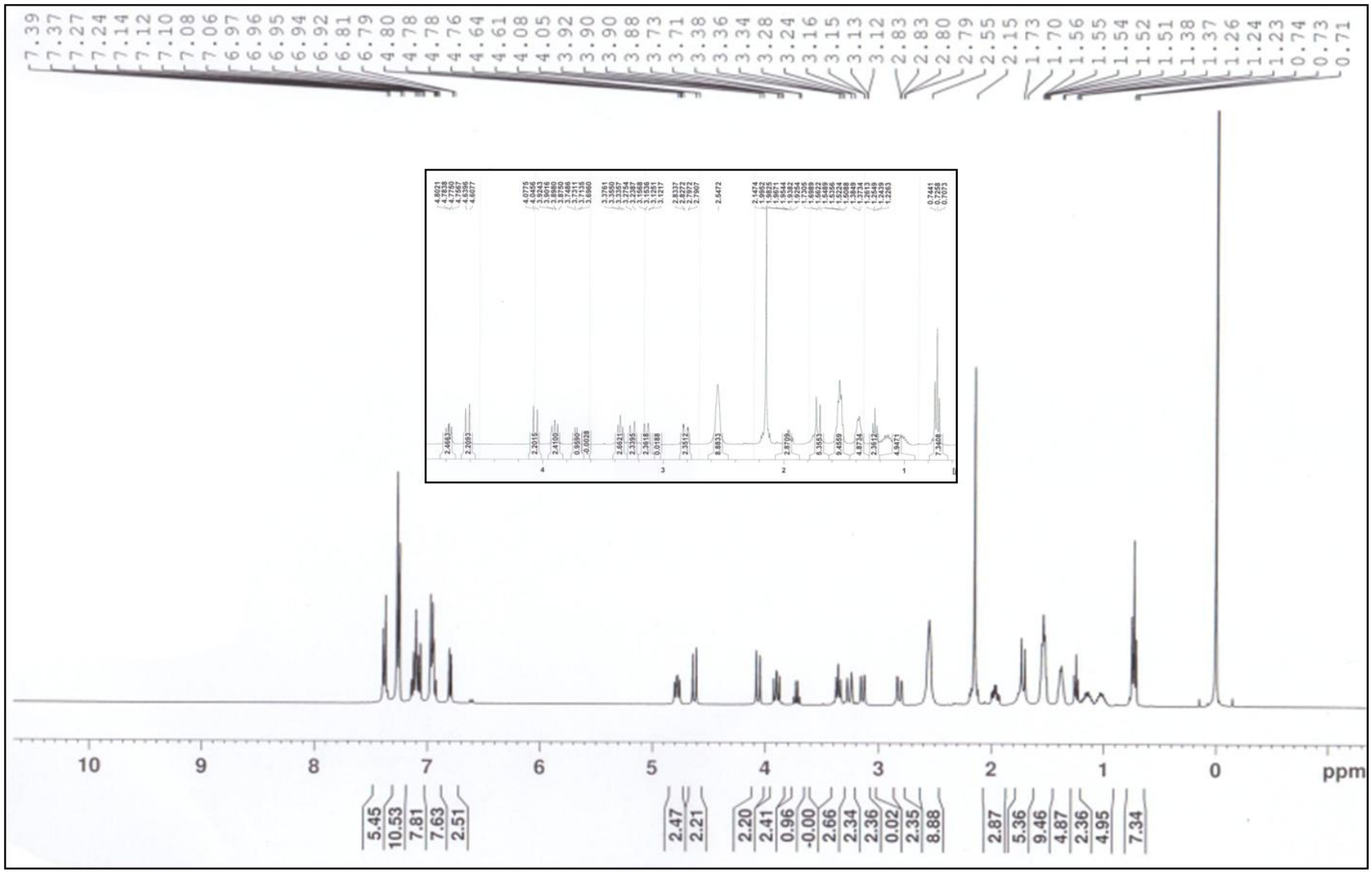


Figure S32. ^{1}H-NMR spectrum of compound **38** in $CDCl_3$.

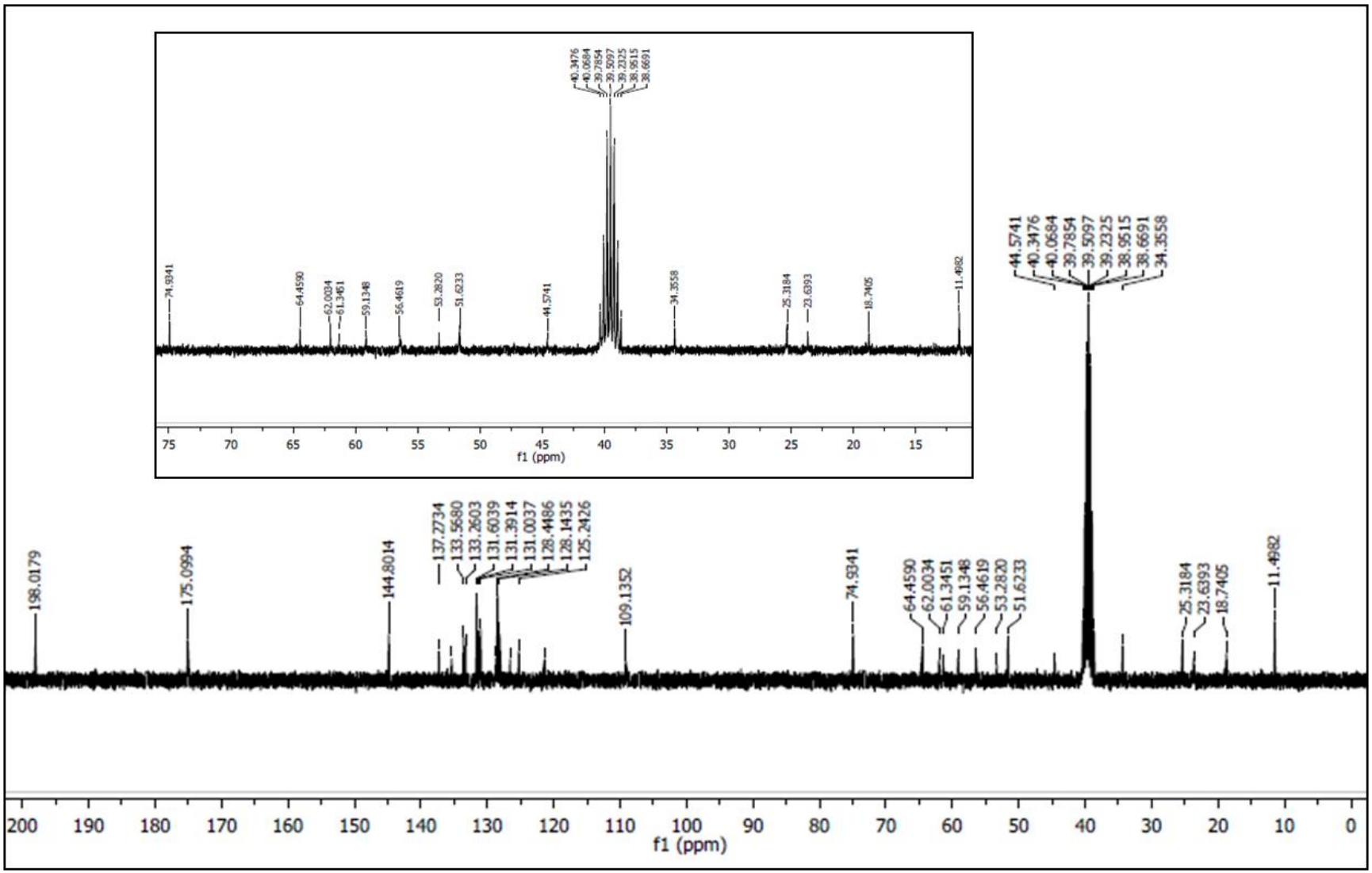


Figure S33. ^{13}C-NMR spectrum of compound **38** in DMSO-d_6.

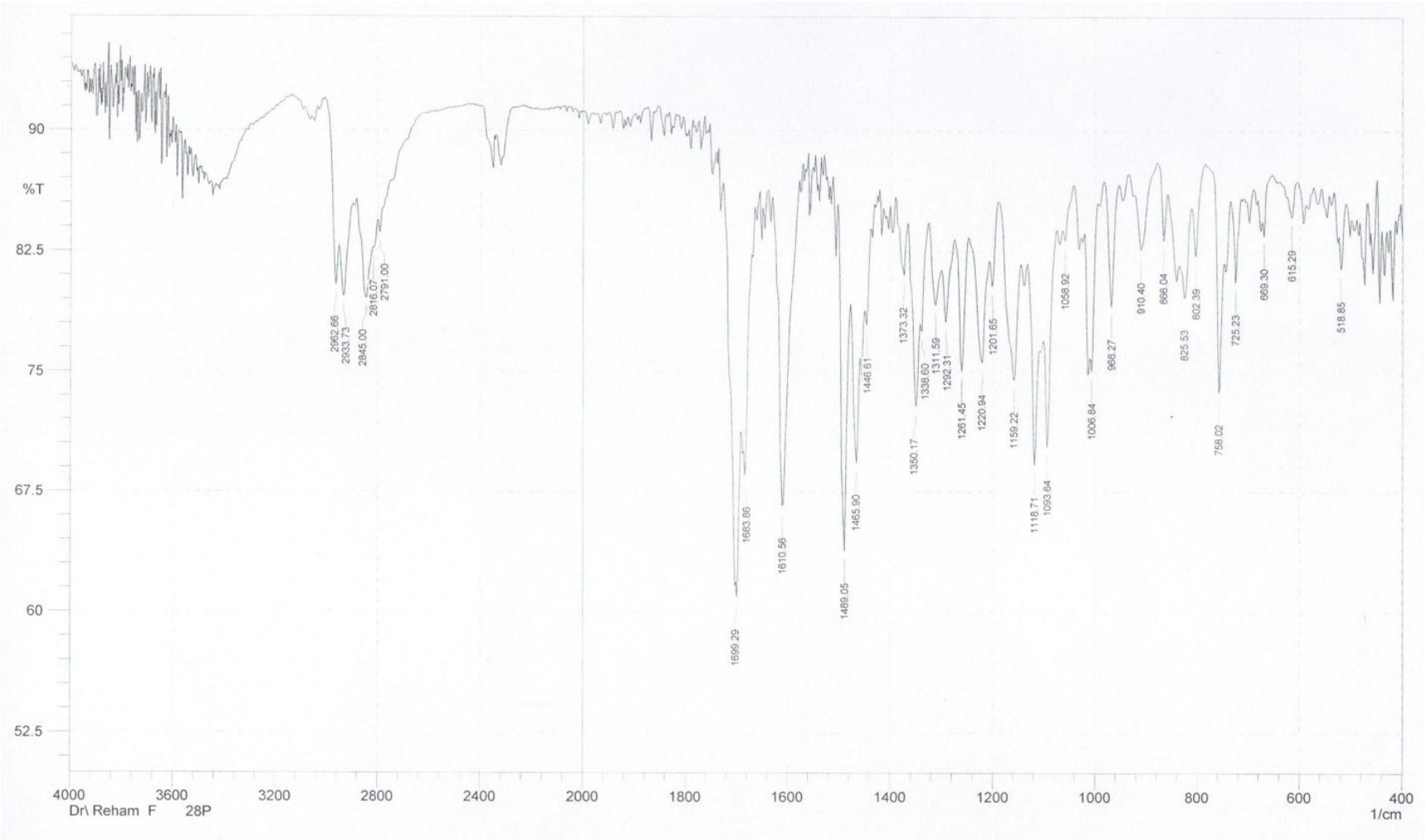


Figure S34. IR spectrum of compound **39** (KBr pellet).

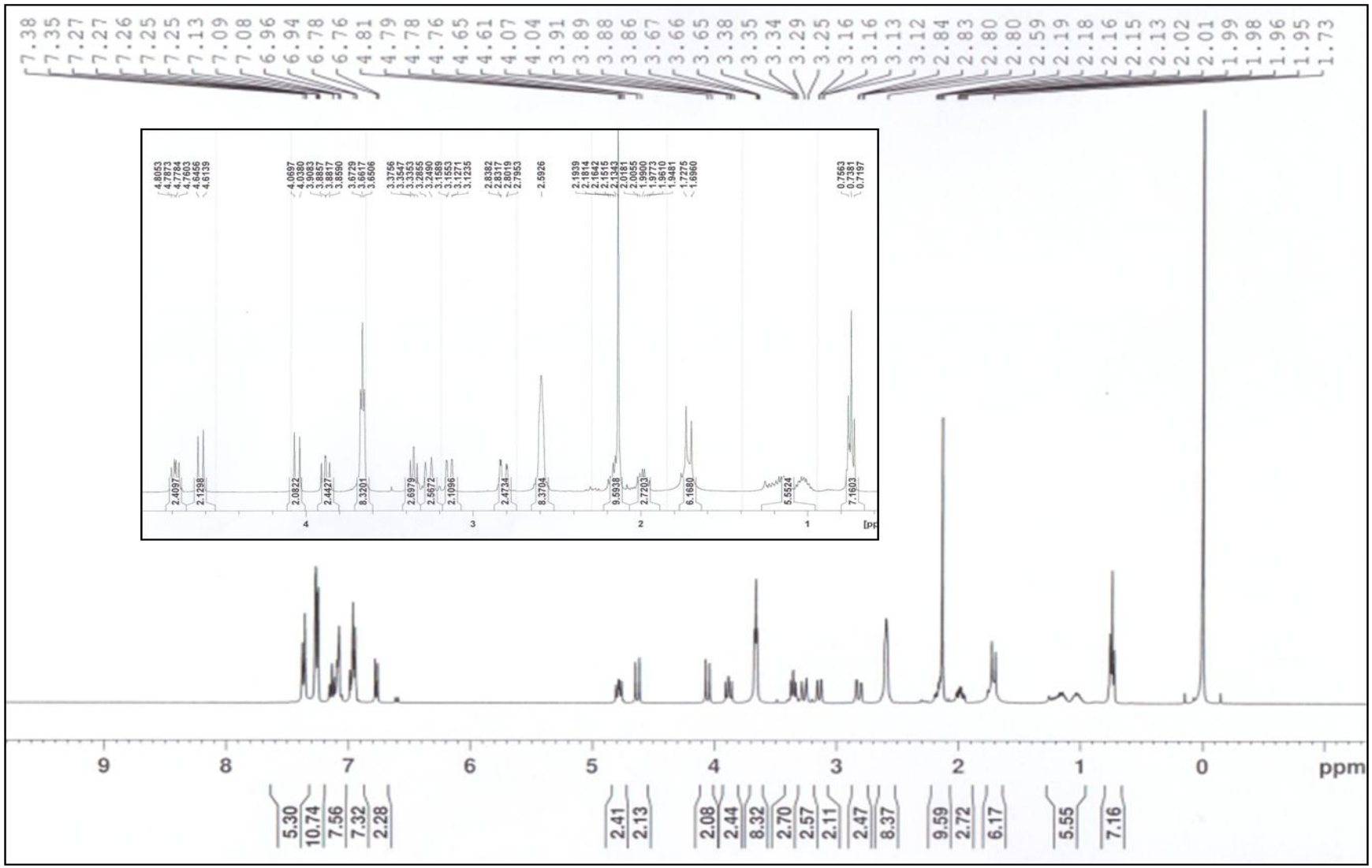


Figure S35. ^{1}H-NMR spectrum of compound **39** in $CDCl_3$.

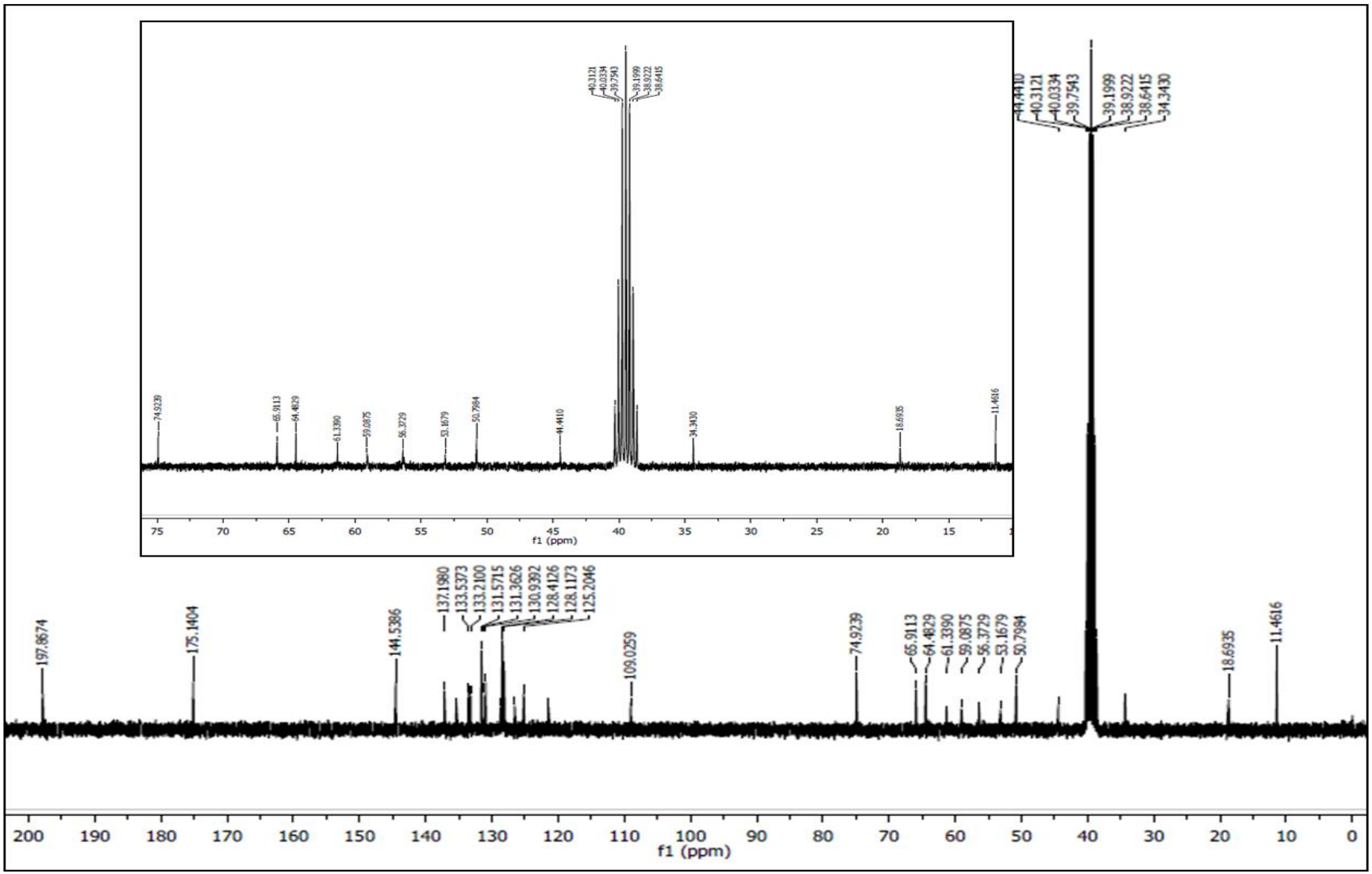


Figure S36. ^{13}C-NMR spectrum of compound **39** in DMSO-d_6.

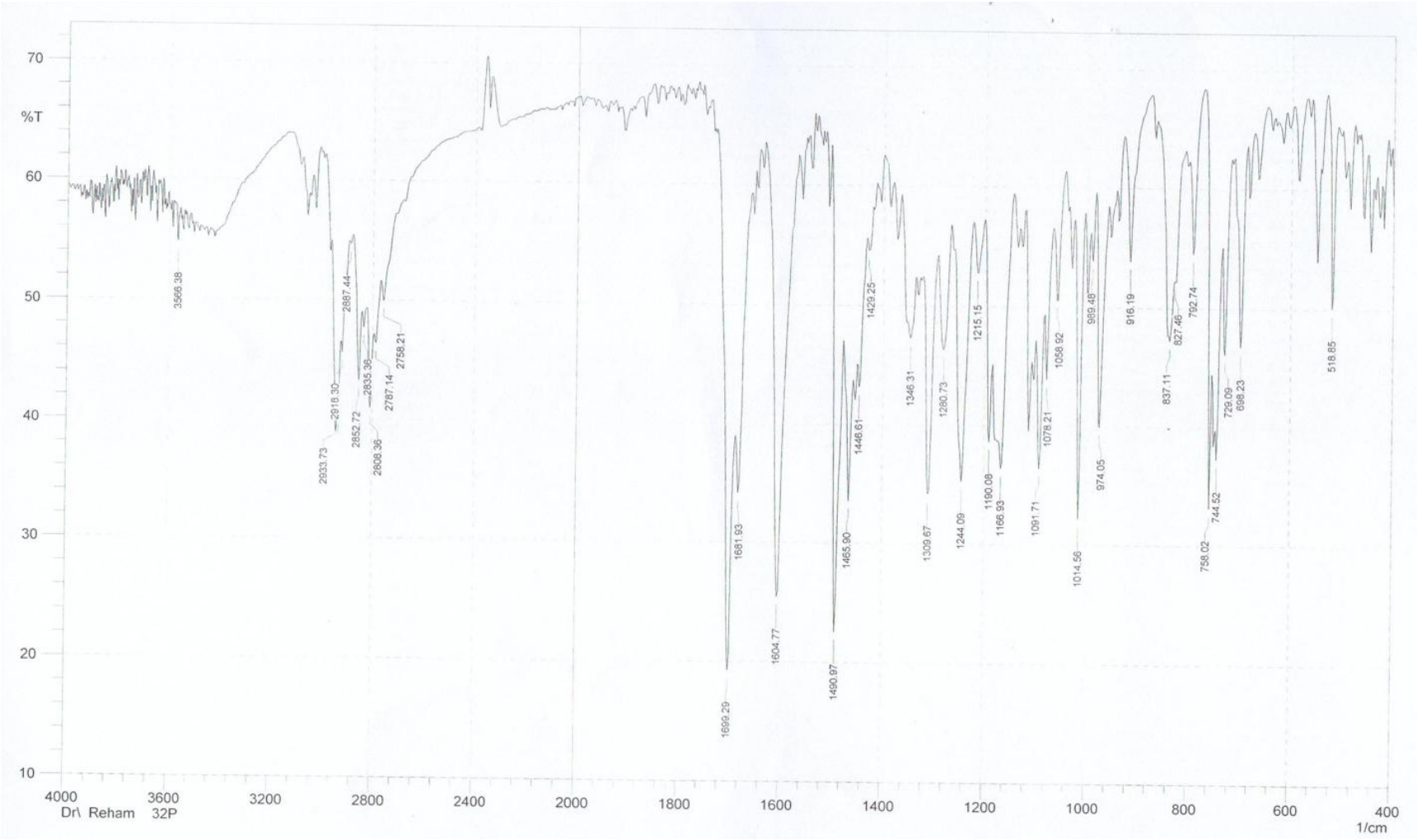


Figure S37. IR spectrum of compound **40** (KBr pellet).

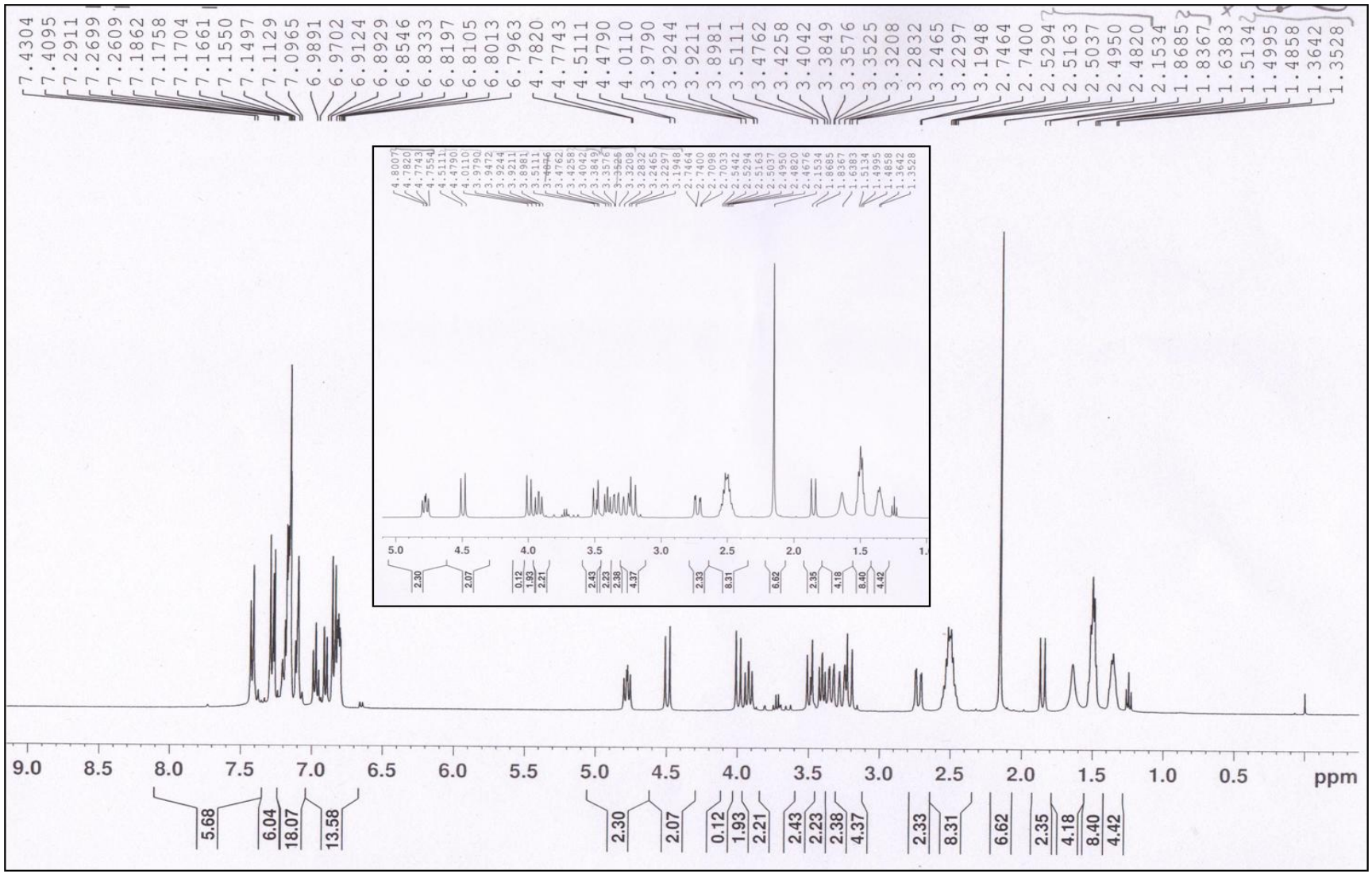


Figure S38. ^{1}H-NMR spectrum of compound **40** in $CDCl_3$.

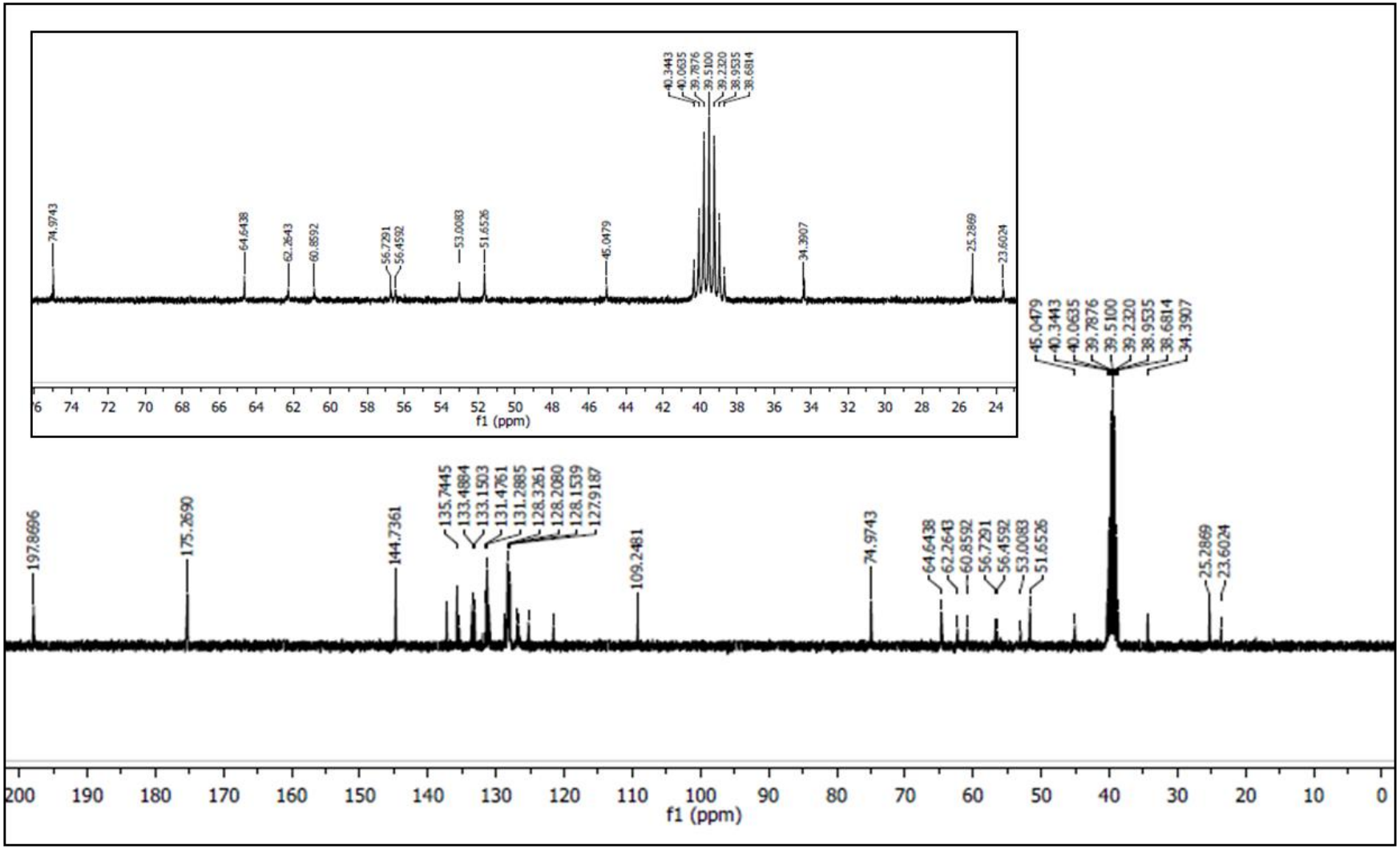


Figure S39. ^{13}C-NMR spectrum of compound **40** in DMSO-d_6.

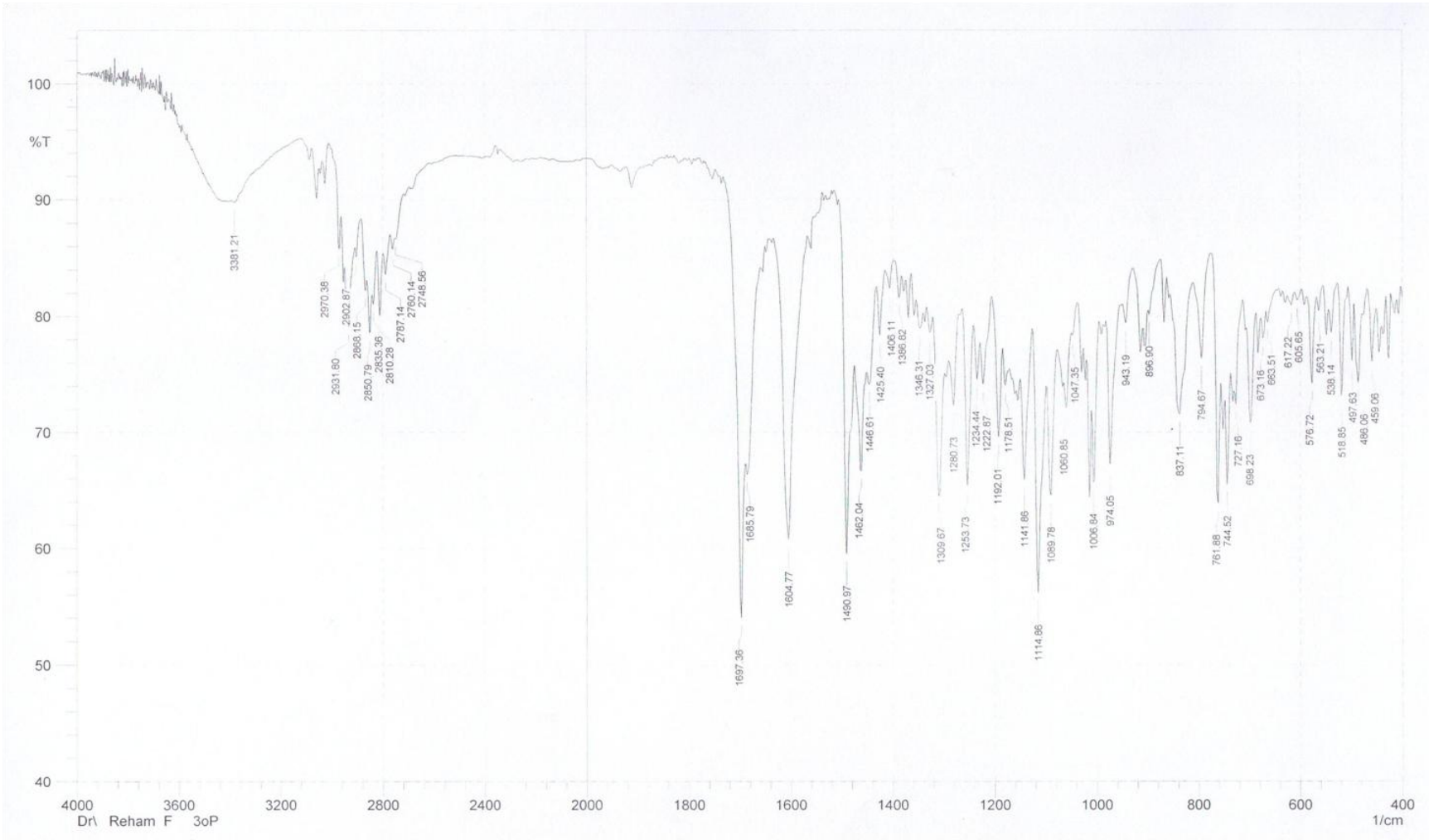


Figure S40. IR spectrum of compound **41** (KBr pellet).

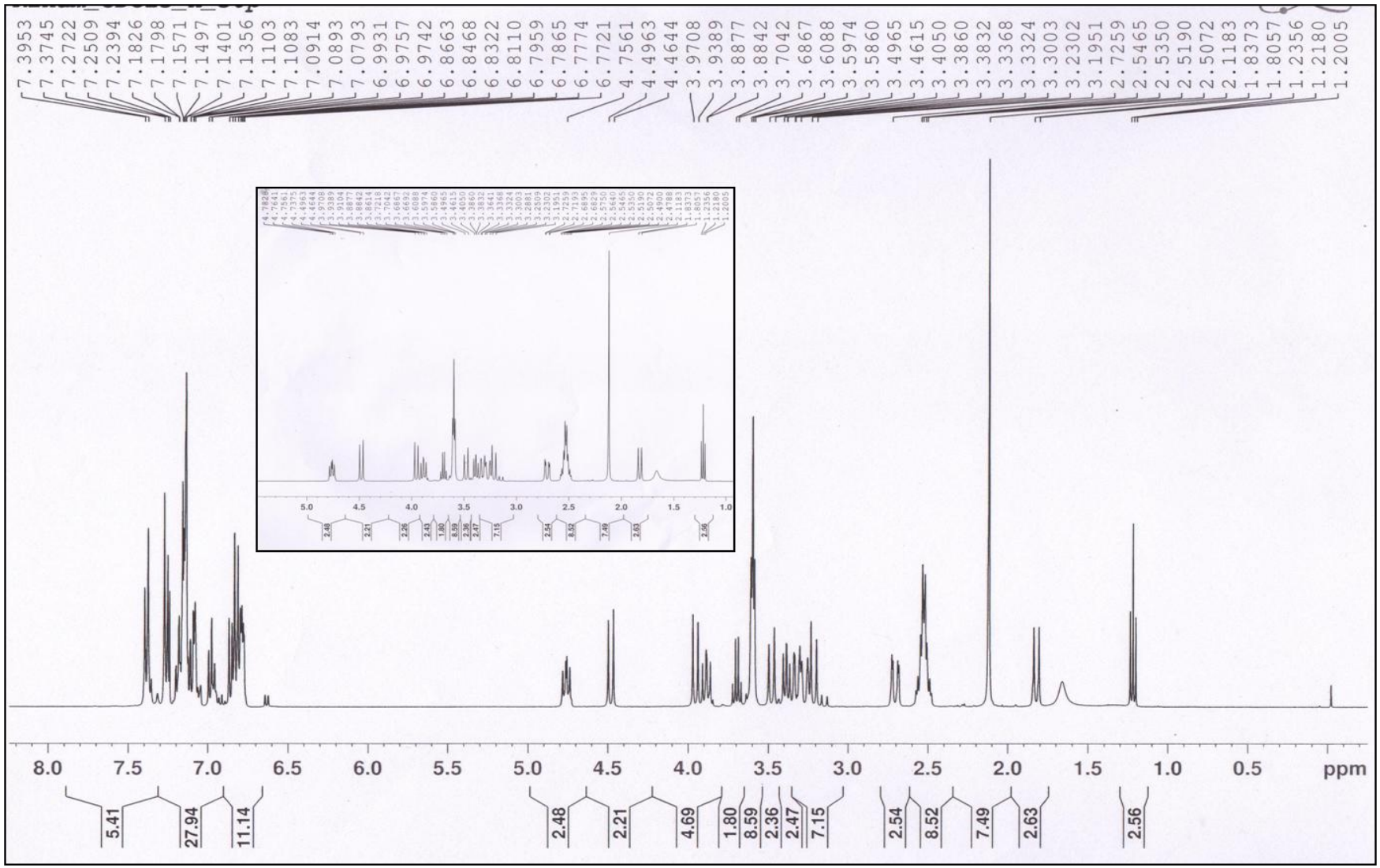


Figure S41. ^{1}H-NMR spectrum of compound **41** in $CDCl_3$.

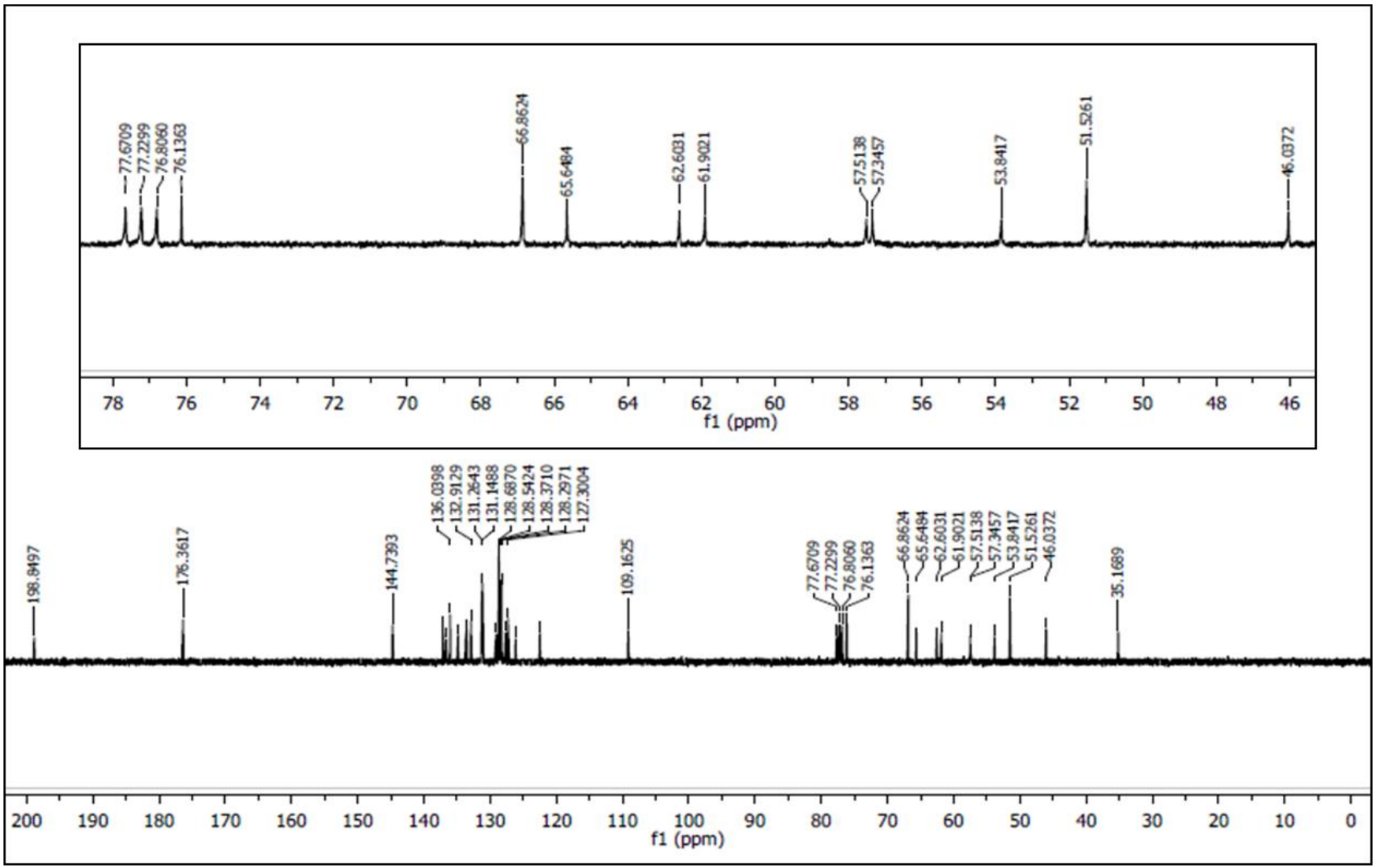


Figure S42. ^{13}C-NMR spectrum of compound **41** in $CDCl_3$.

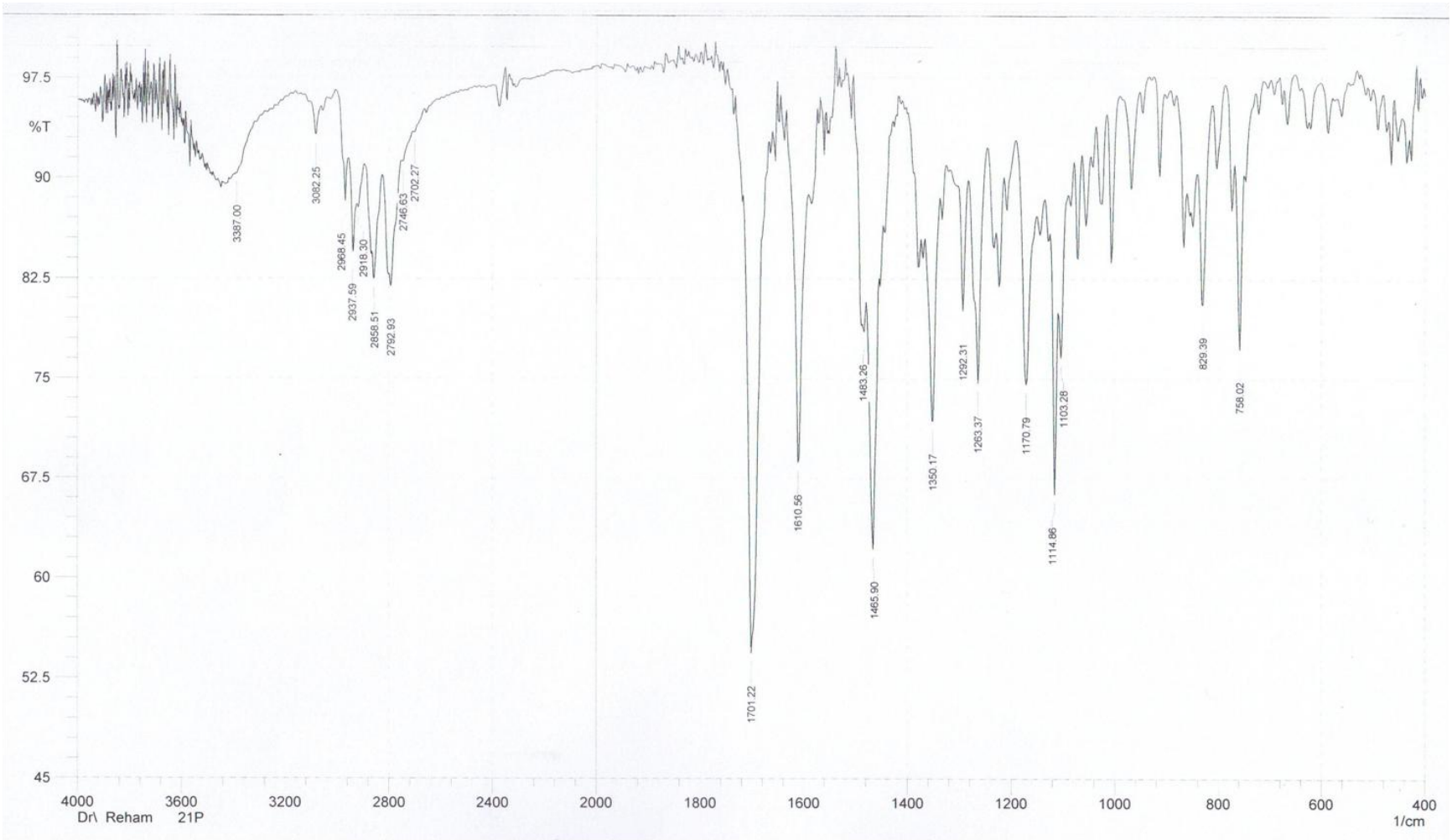


Figure S43. IR spectrum of compound **42** (KBr pellet).

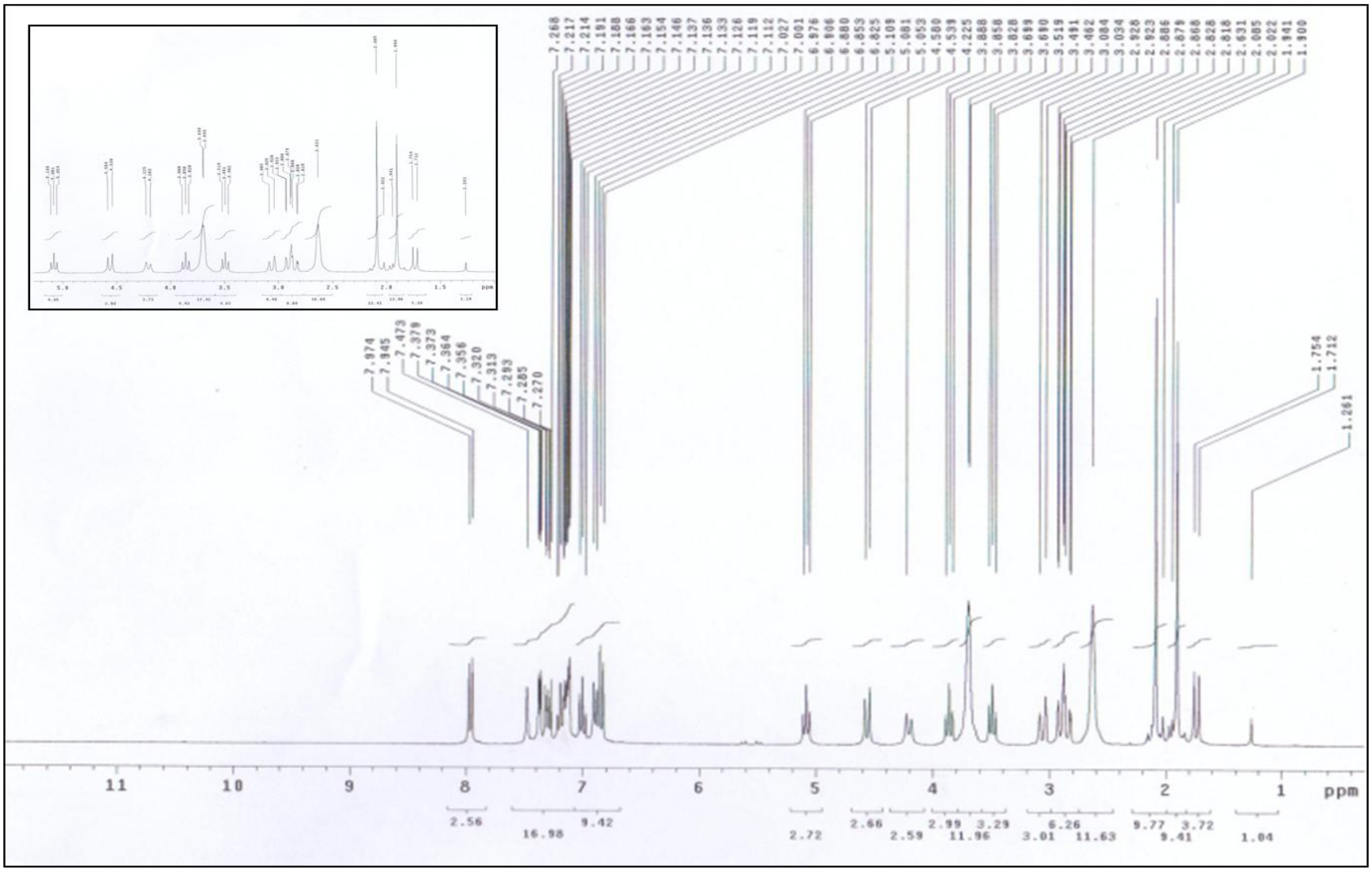


Figure S44. ^{1}H-NMR spectrum of compound **42** in $CDCl_3$.

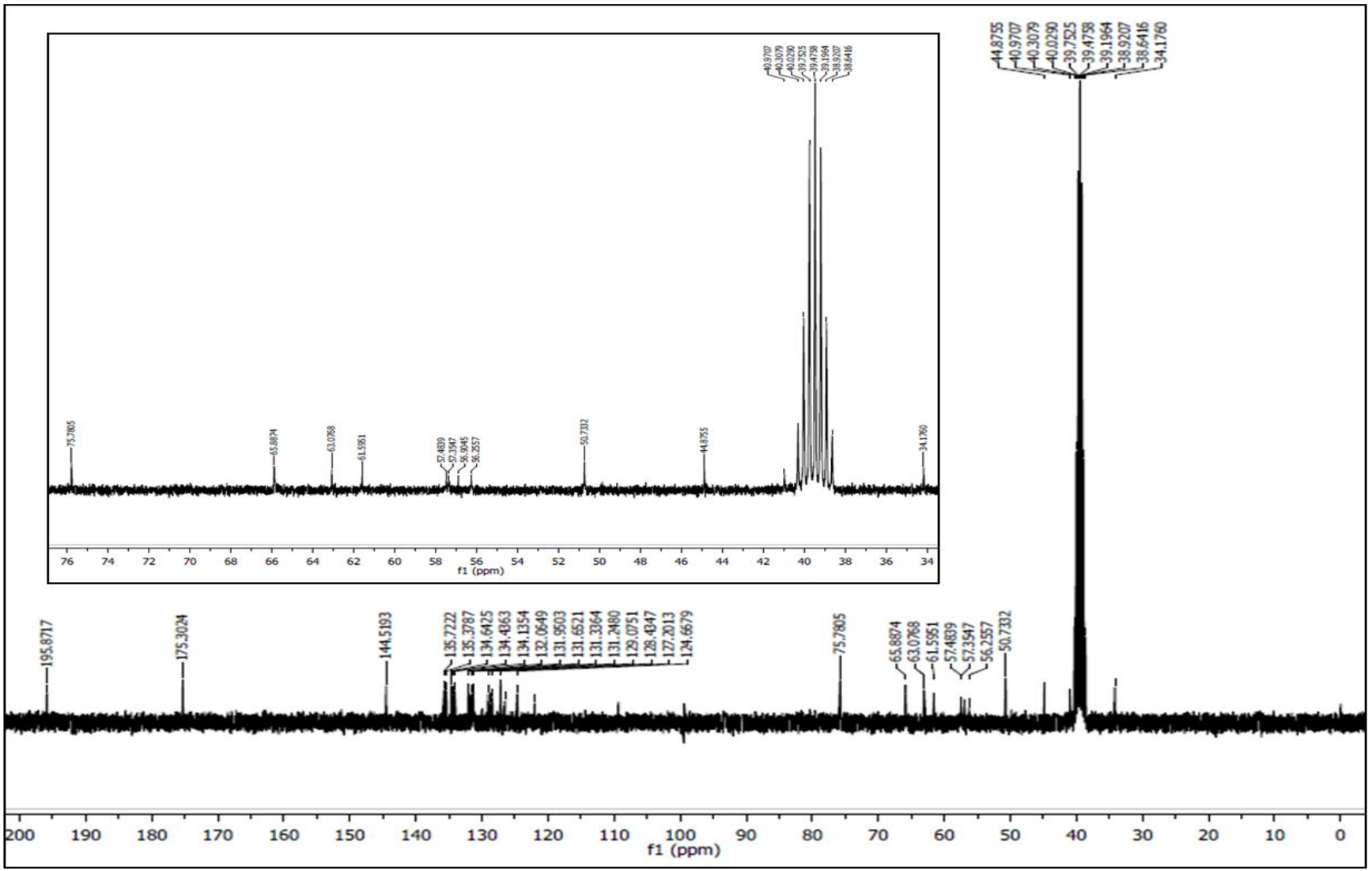


Figure S45. ^{13}C-NMR spectrum of compound **42** in DMSO-d_6.

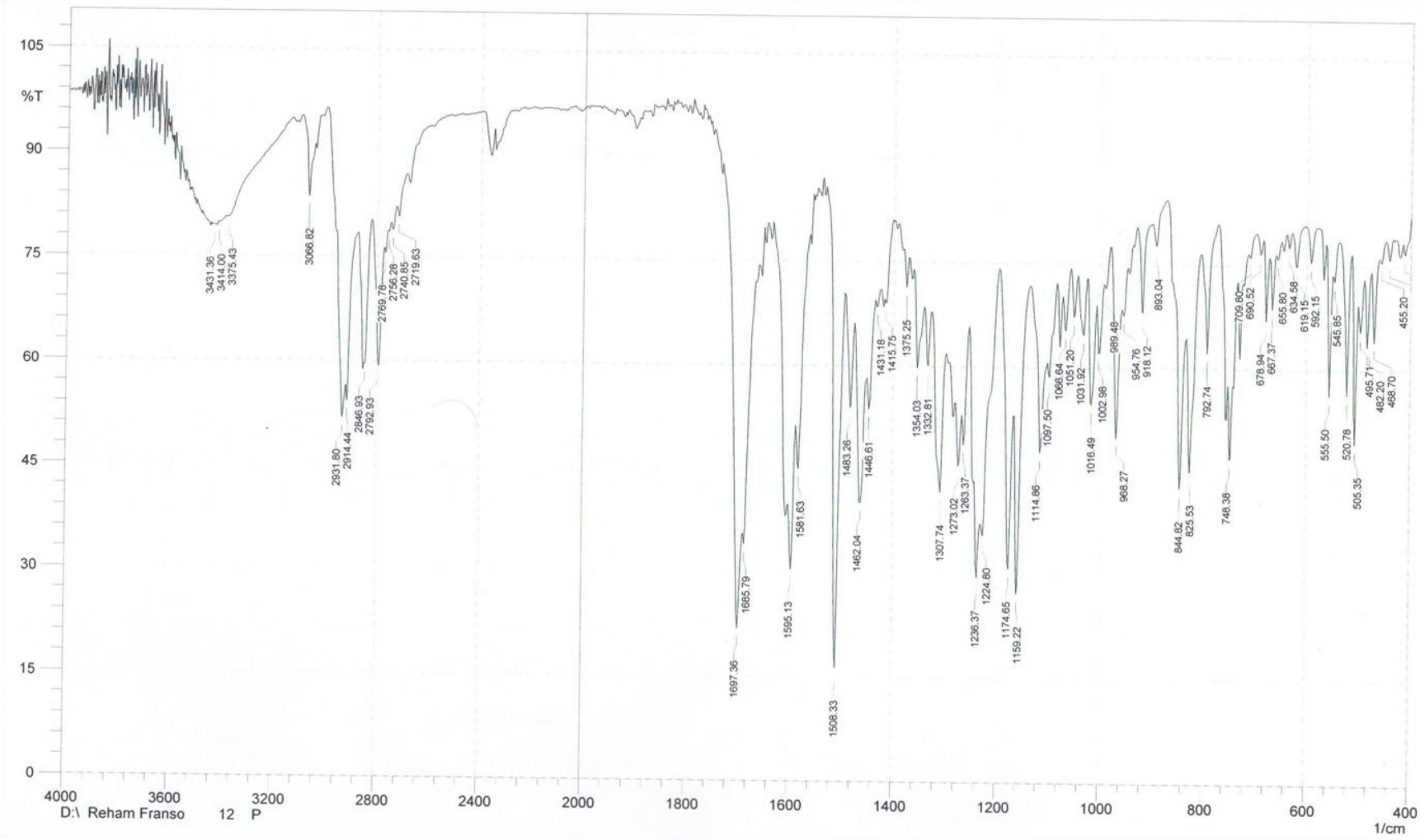


Figure S46. IR spectrum of compound **43** (KBr pellet).

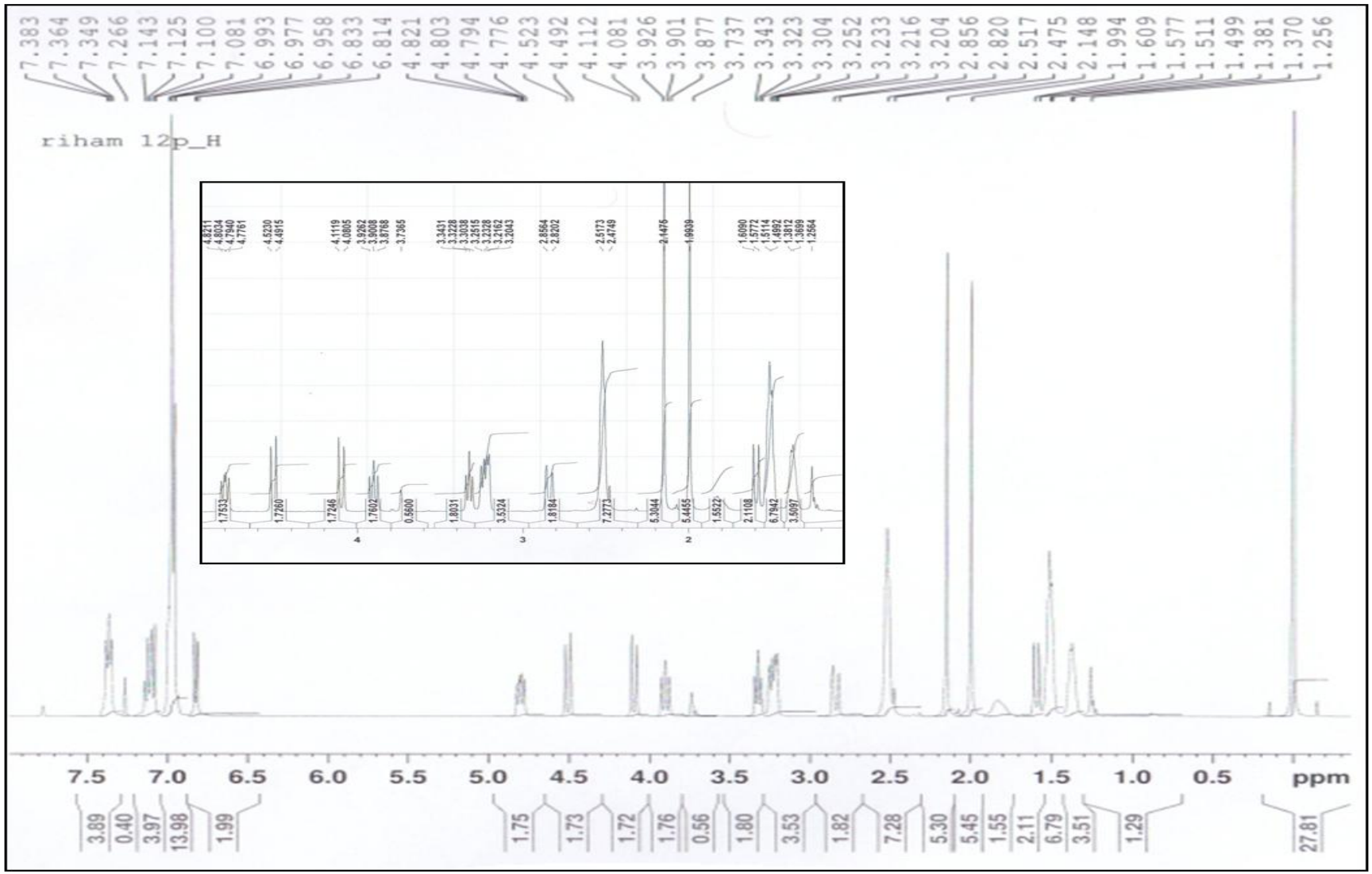


Figure S47. ^{1}H-NMR spectrum of compound **43** in $CDCl_3$.

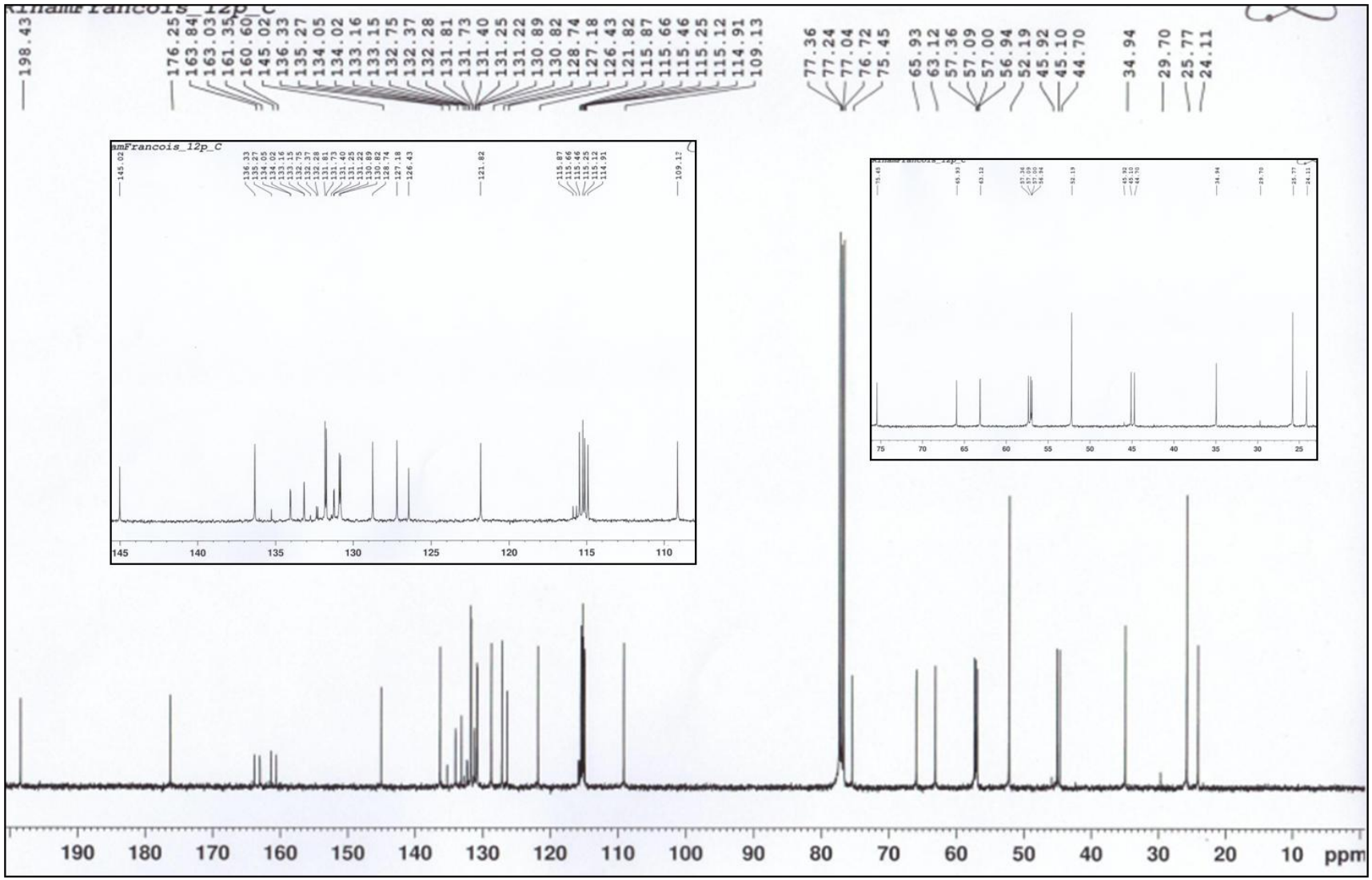


Figure S48. ^{13}C-NMR spectrum of compound **43** in $CDCl_3$.

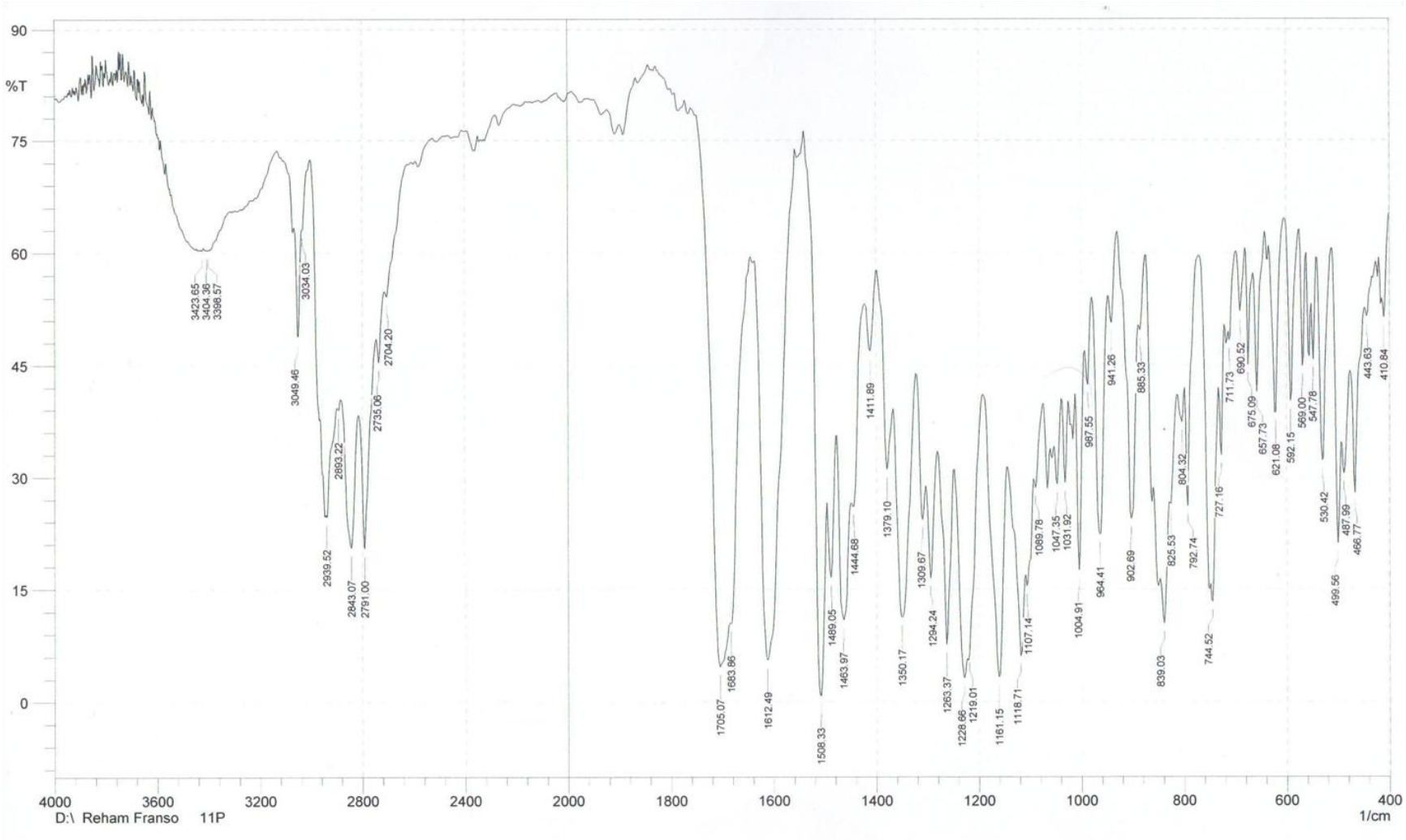


Figure S49. IR spectrum of compound **44** (KBr pellet).

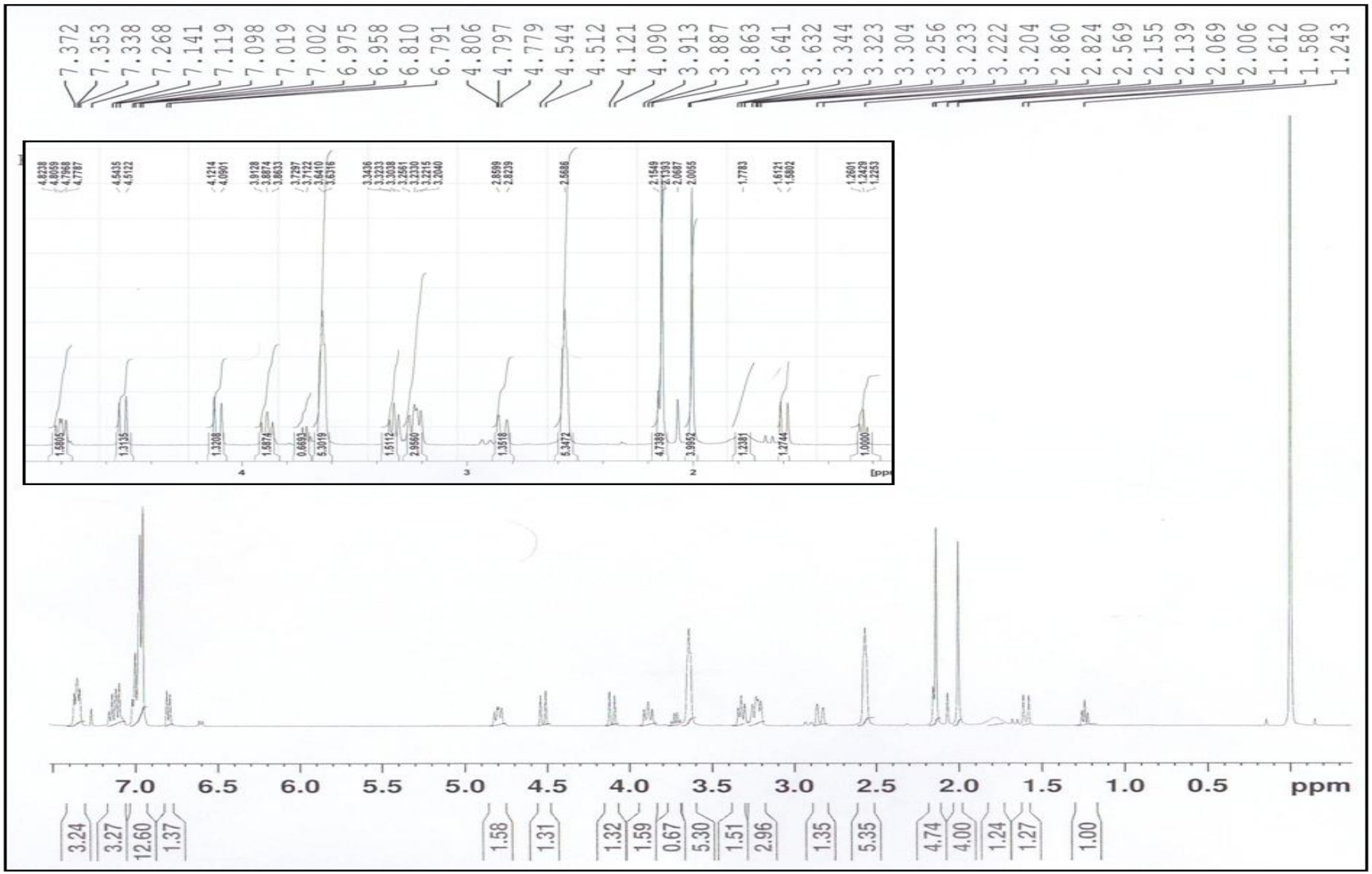


Figure S50. ^{1}H-NMR spectrum of compound **44** in $CDCl_3$.

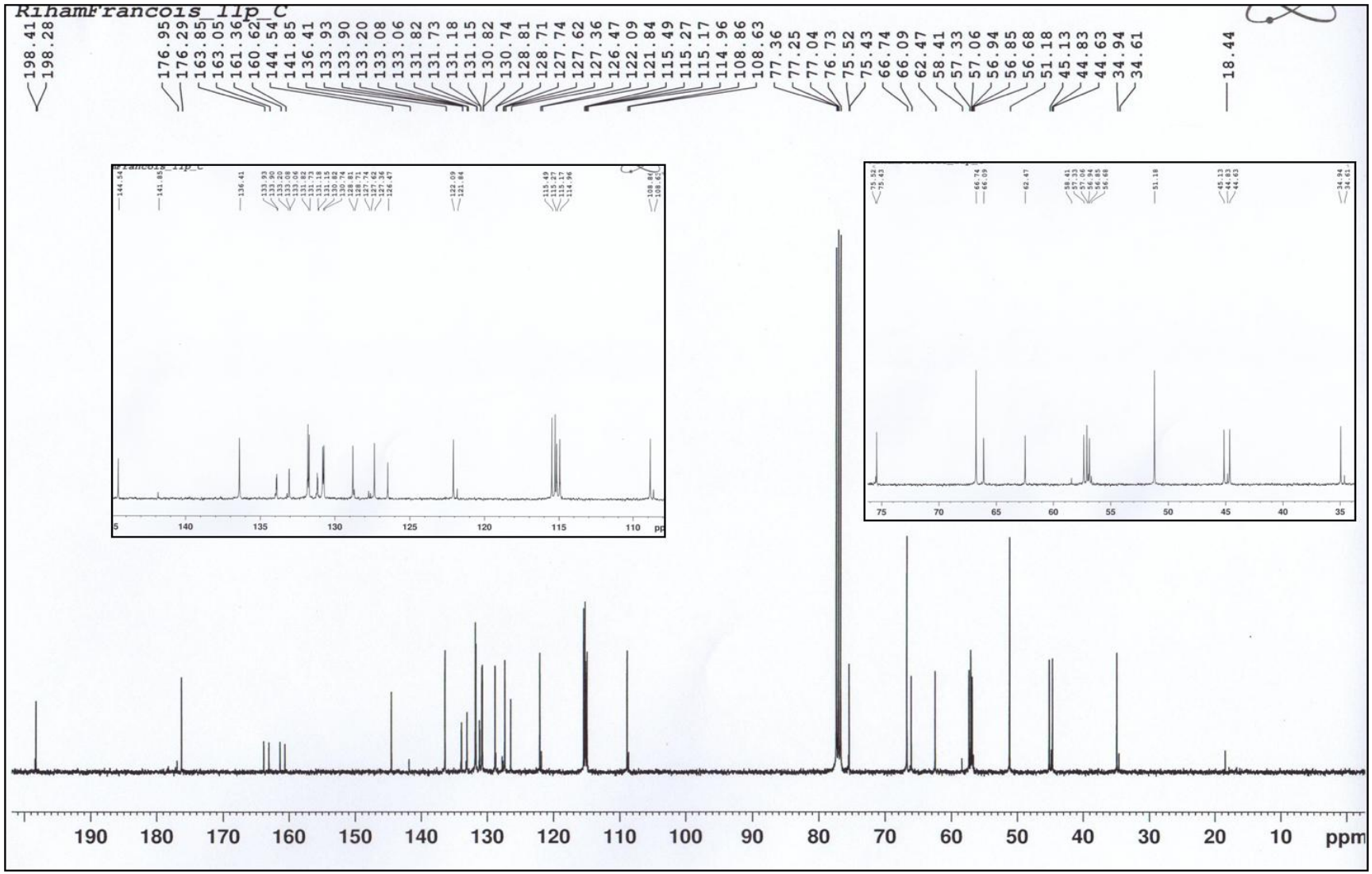


Figure S51. ^{13}C-NMR spectrum of compound **44** in $CDCl_3$.

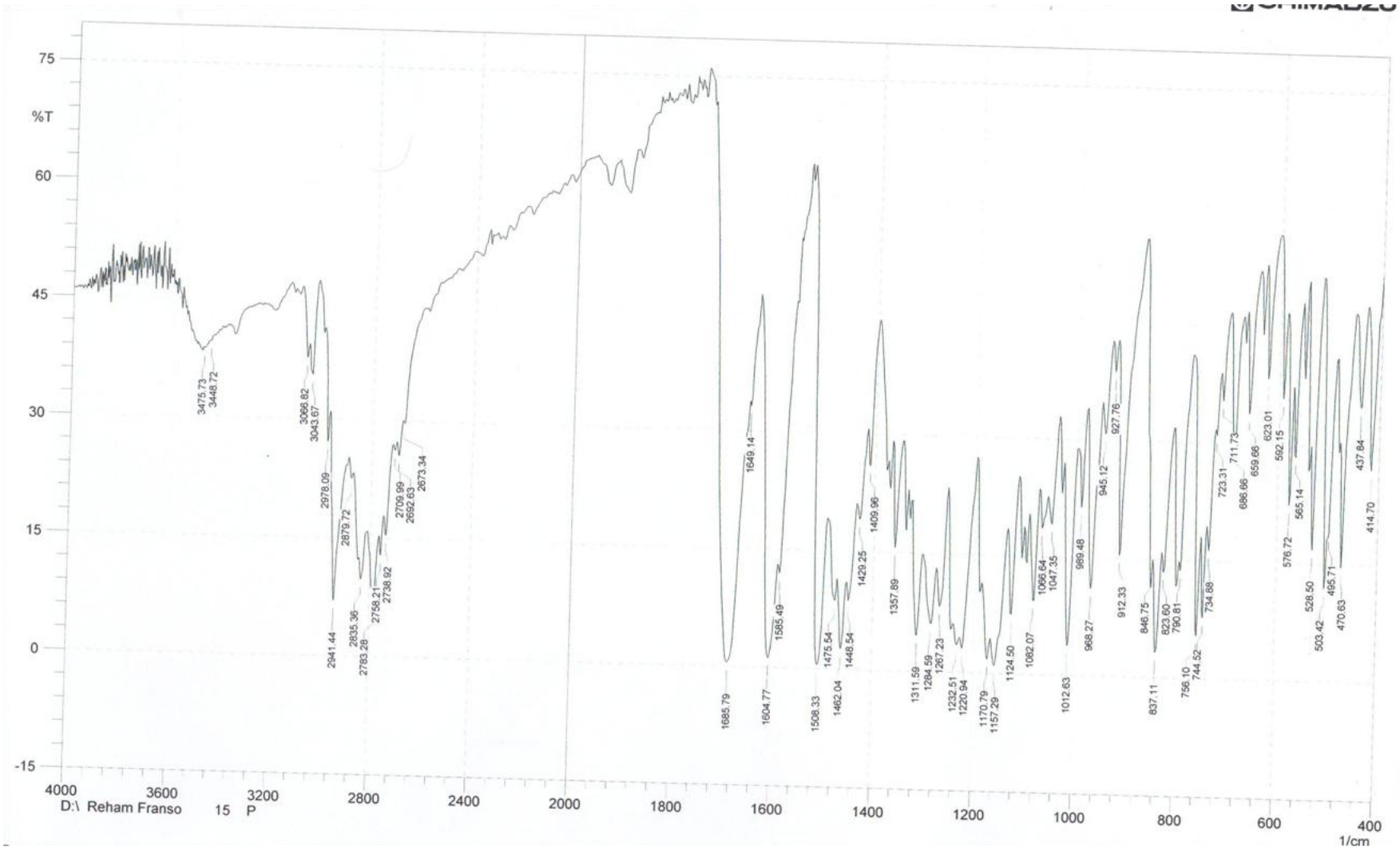


Figure S52. IR spectrum of compound **45** (KBr pellet).

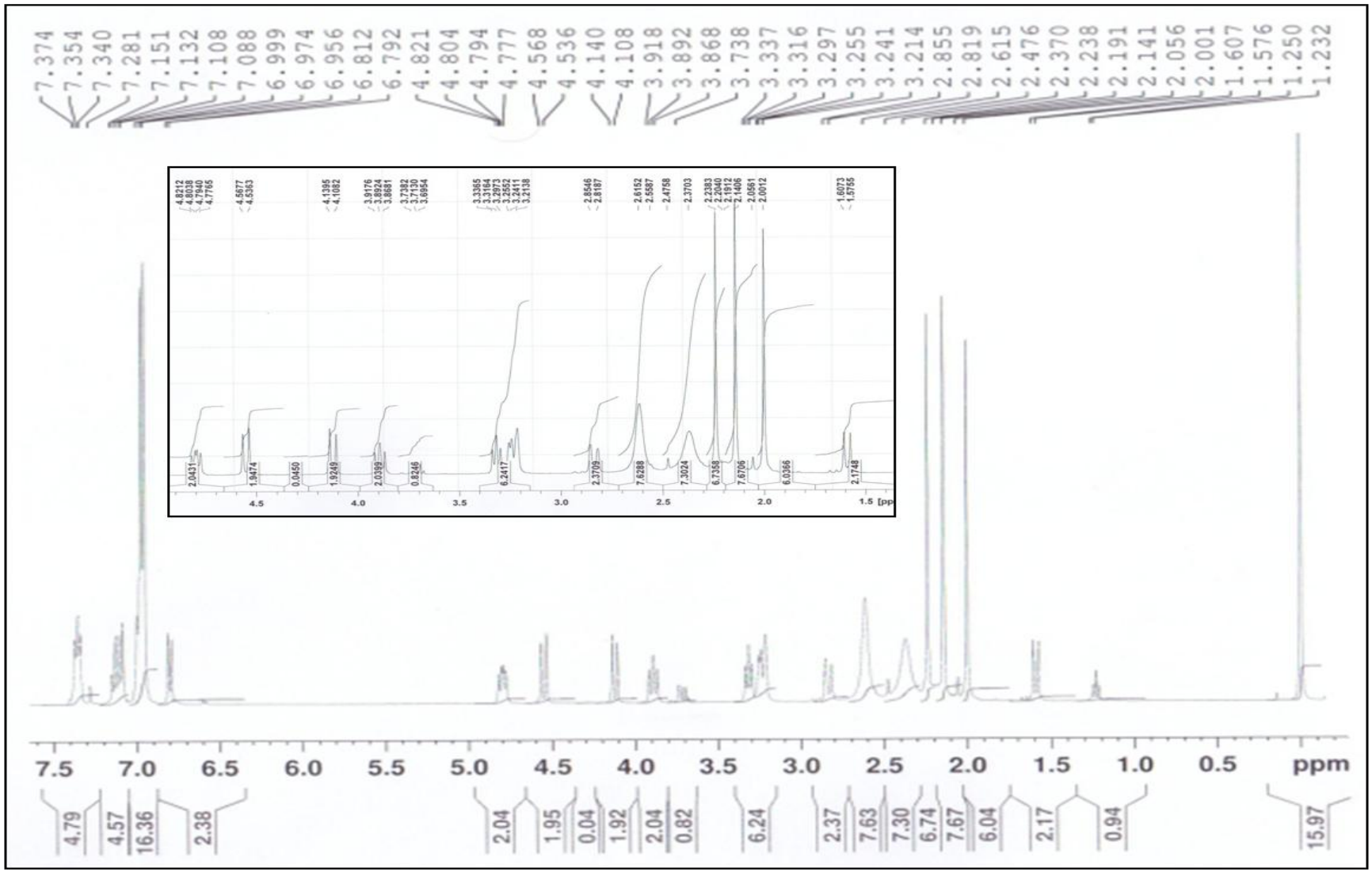


Figure S53. ^{1}H-NMR spectrum of compound **45** in $CDCl_3$.

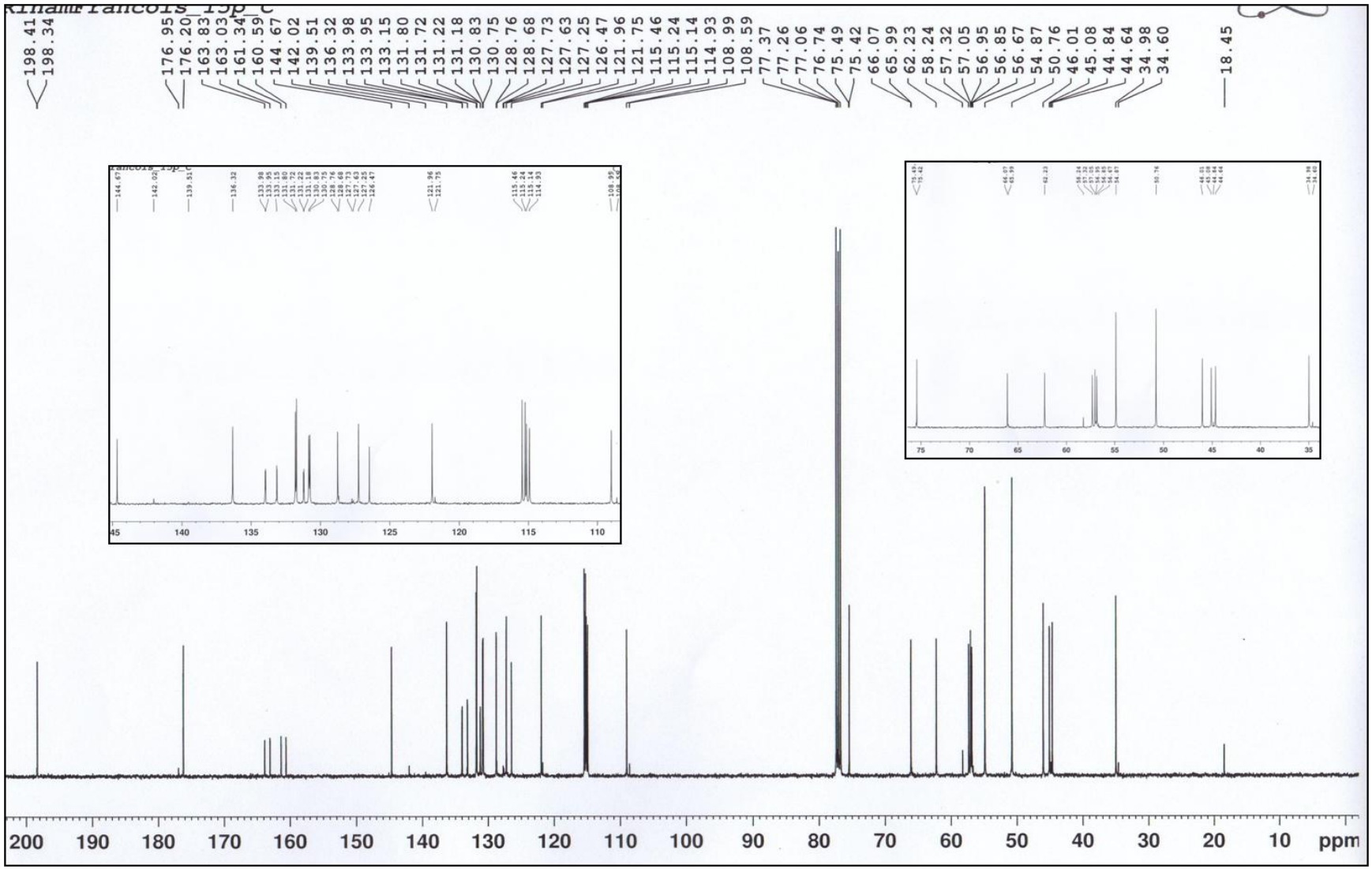


Figure S54. ^{13}C-NMR spectrum of compound **45** in $CDCl_3$.

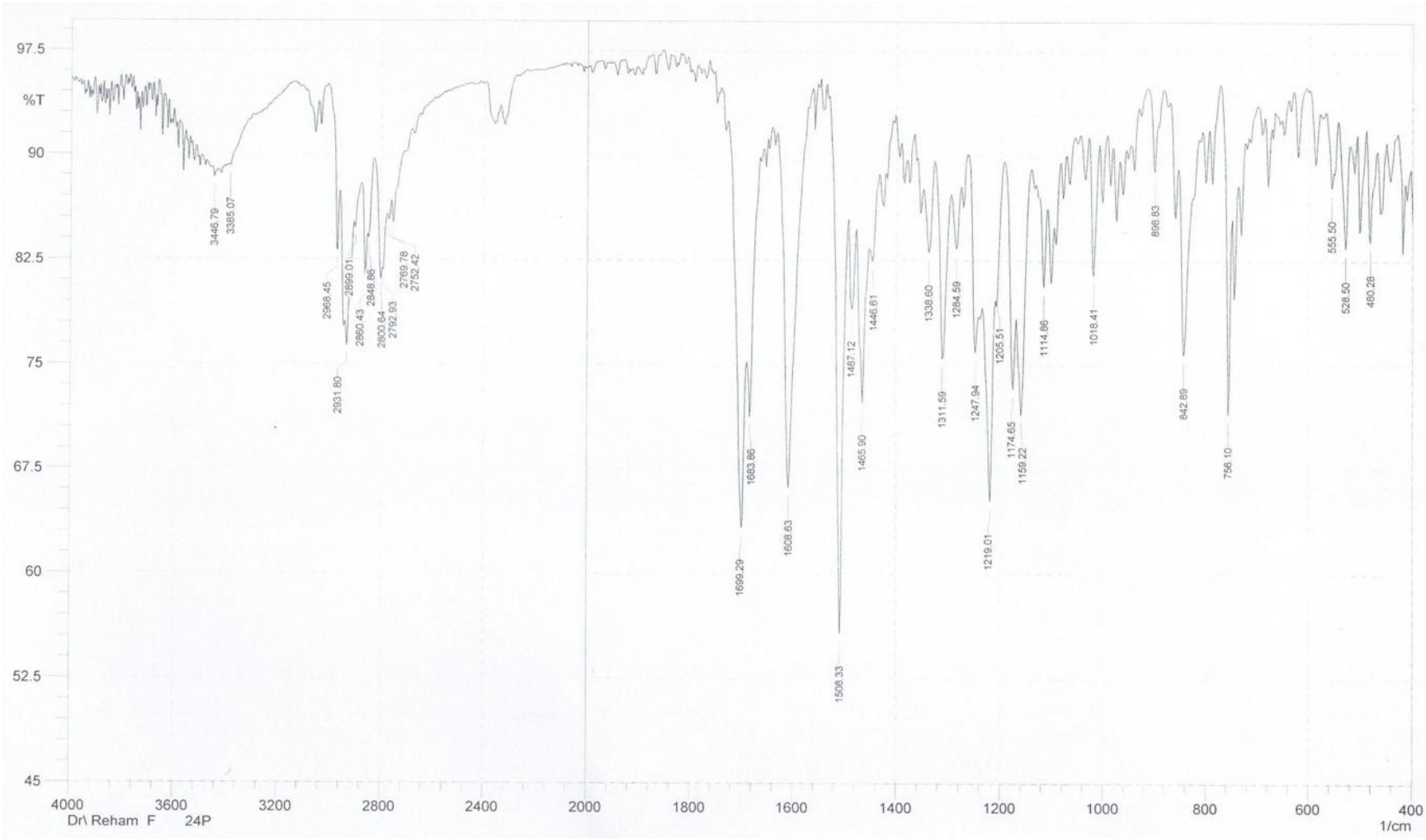


Figure S55. IR spectrum of compound **46** (KBr pellet).

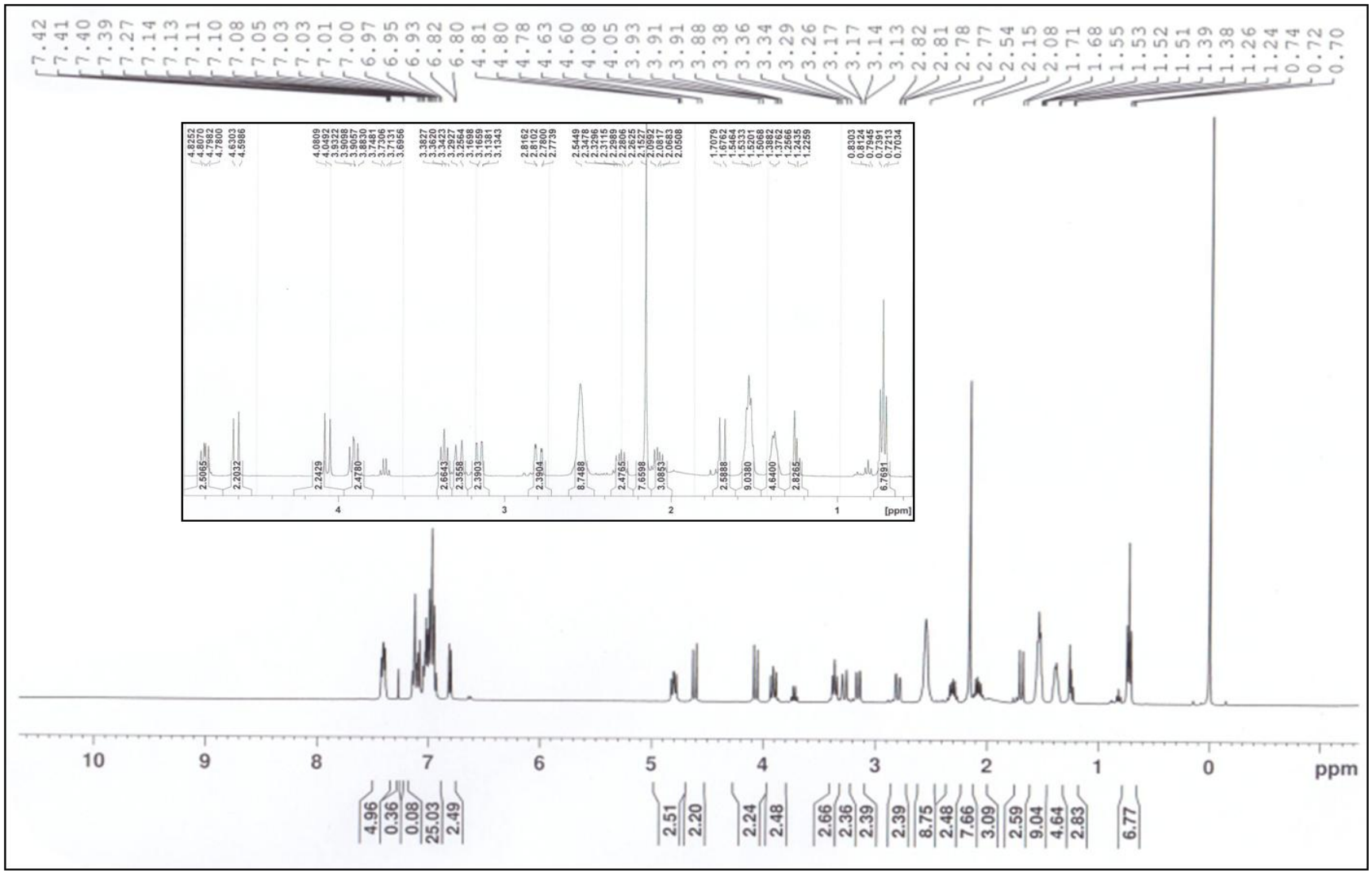


Figure S56. ^{1}H-NMR spectrum of compound **46** in $CDCl_3$.

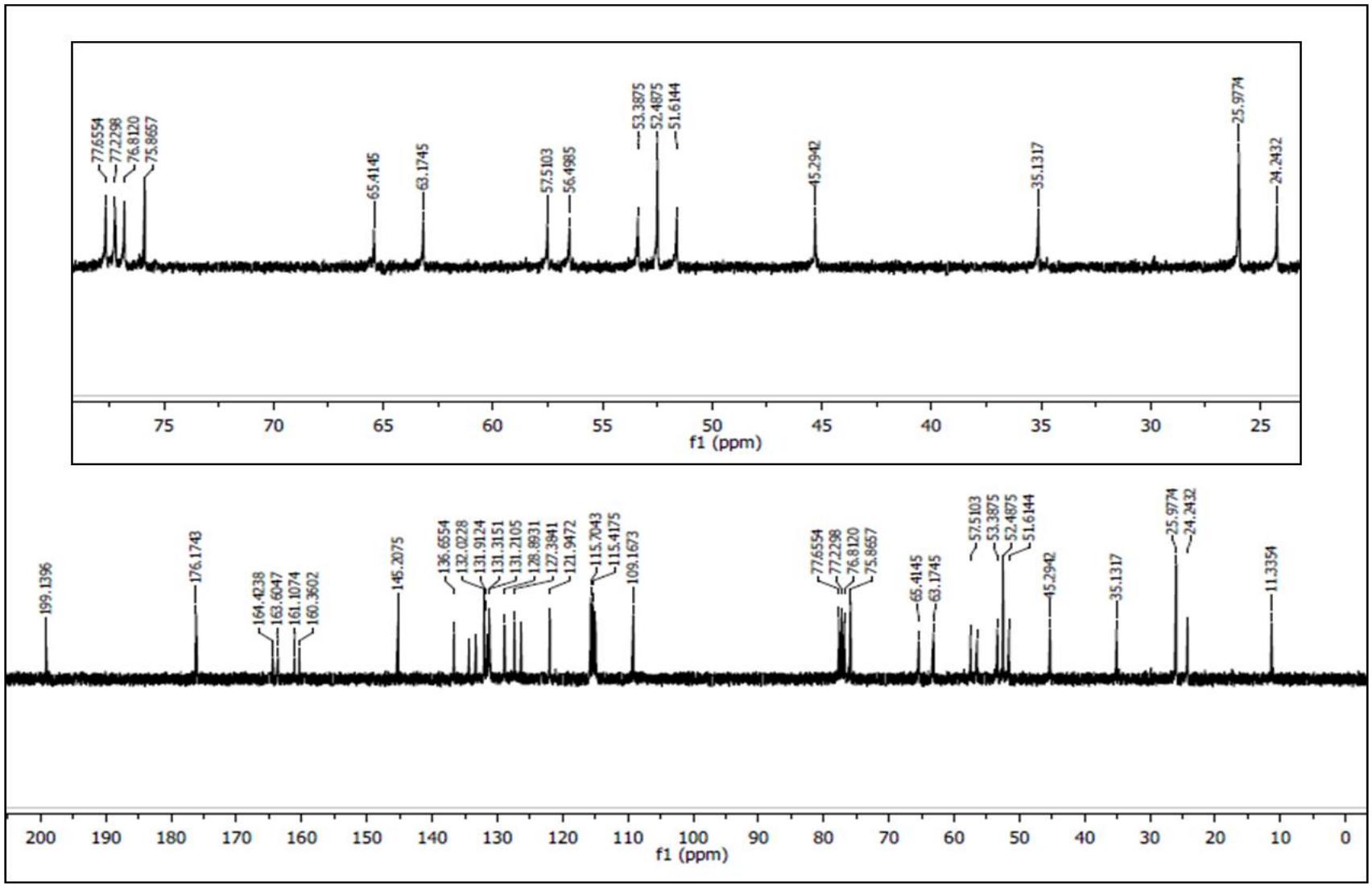


Figure S57. ^{13}C-NMR spectrum of compound **46** in $CDCl_3$.

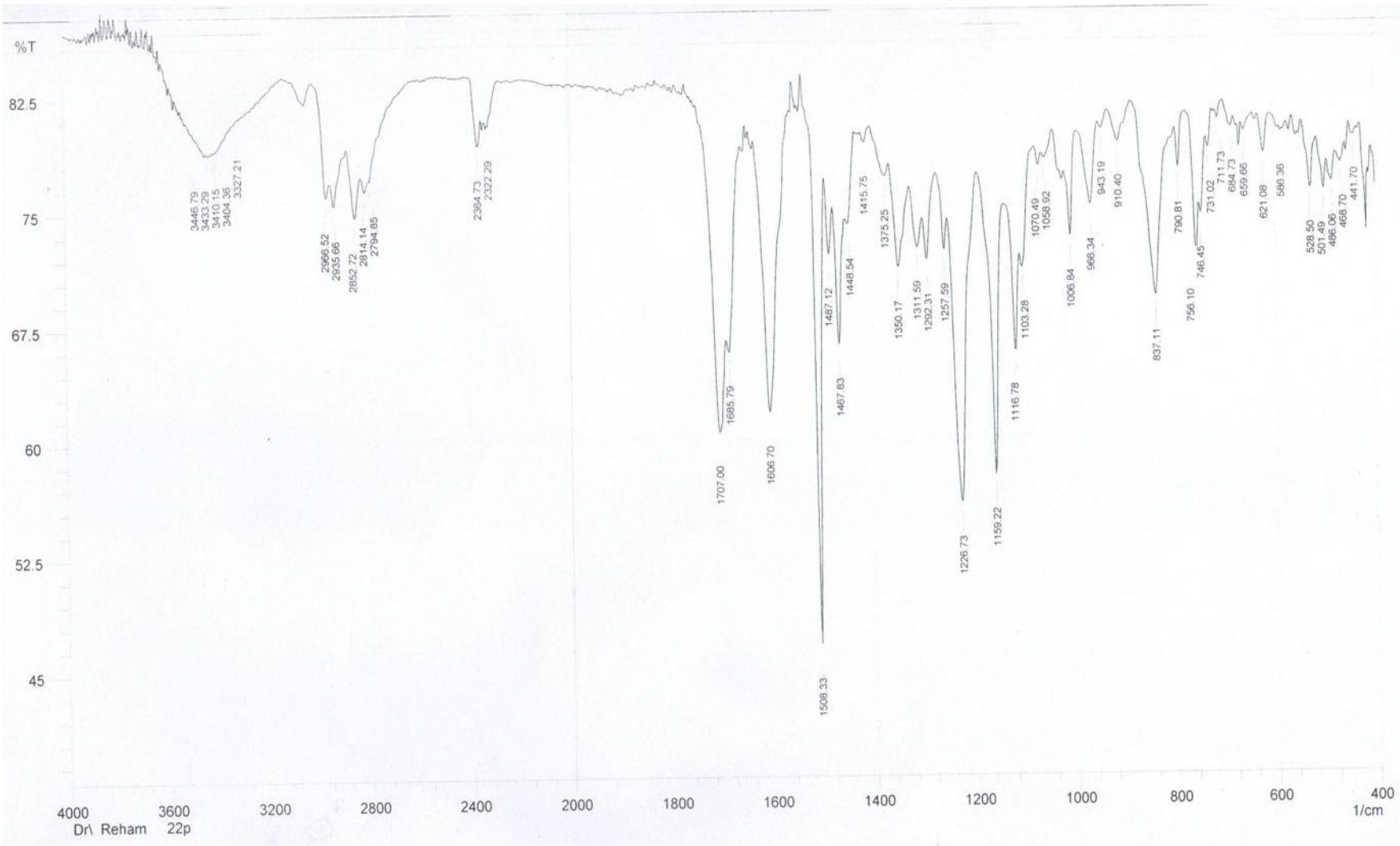


Figure S58. IR spectrum of compound **47** (KBr pellet).

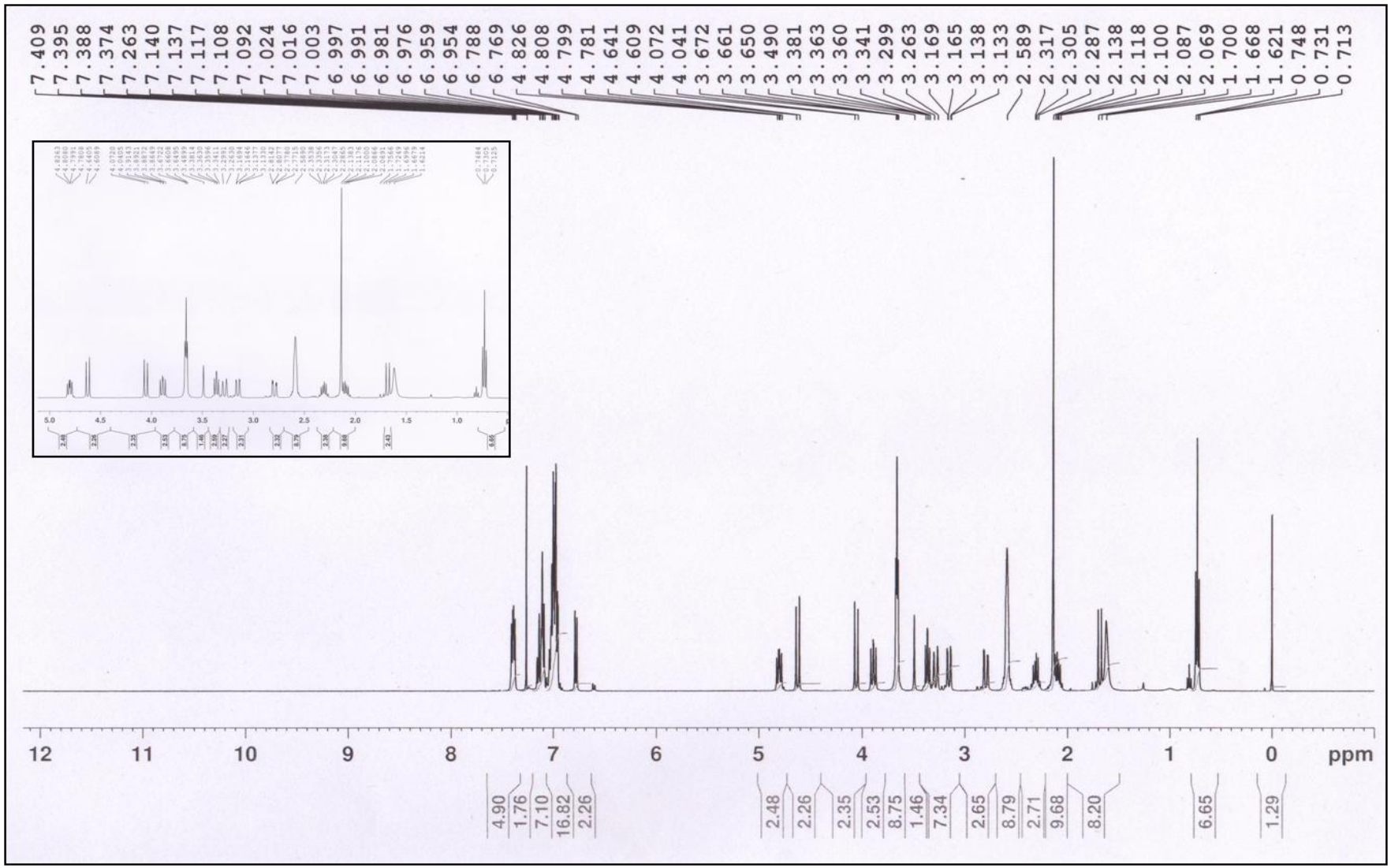


Figure S59. ^{1}H-NMR spectrum of compound **47** in $CDCl_3$.

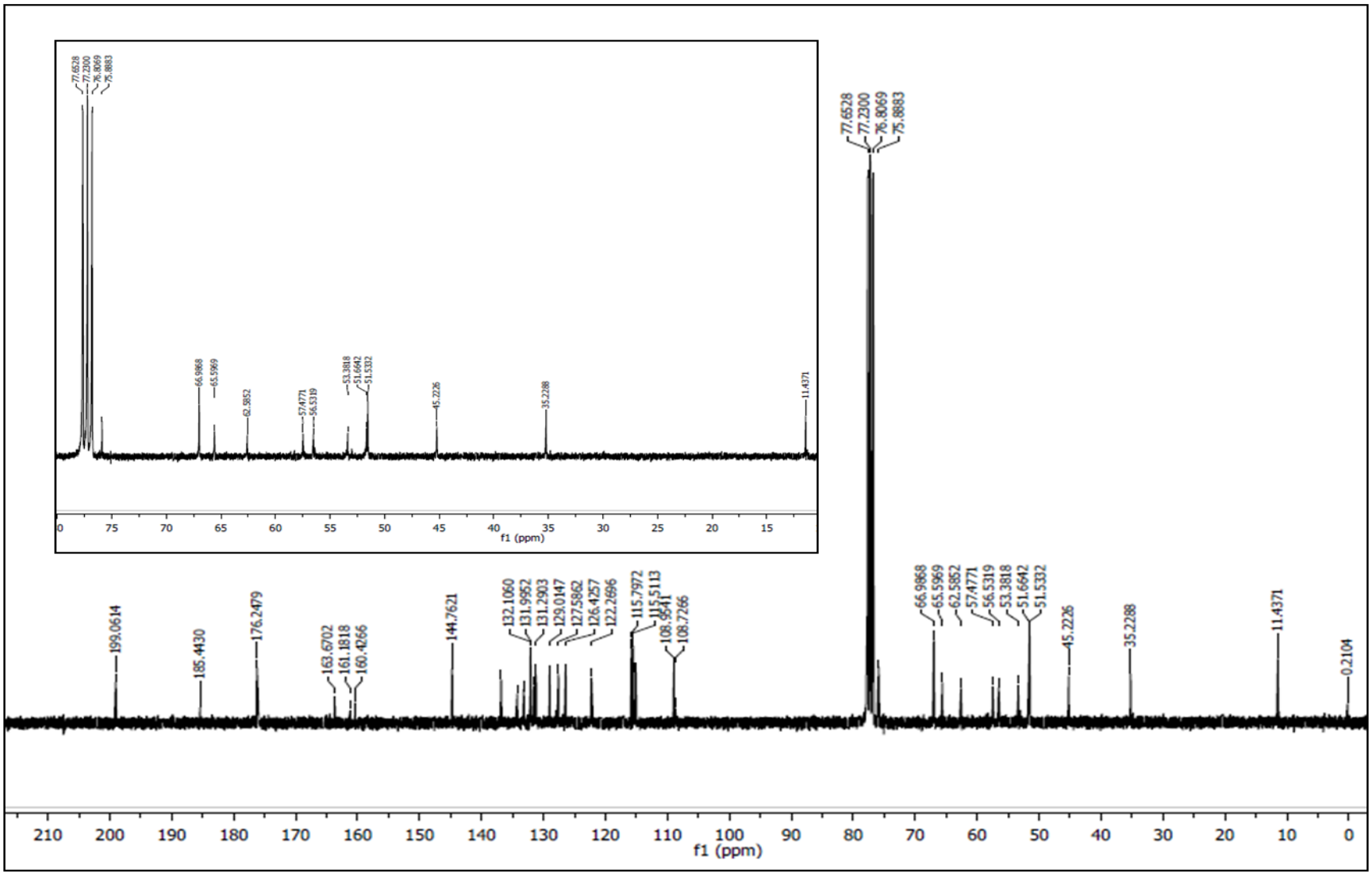


Figure S60. ^{13}C-NMR spectrum of compound **47** in $CDCl_3$.

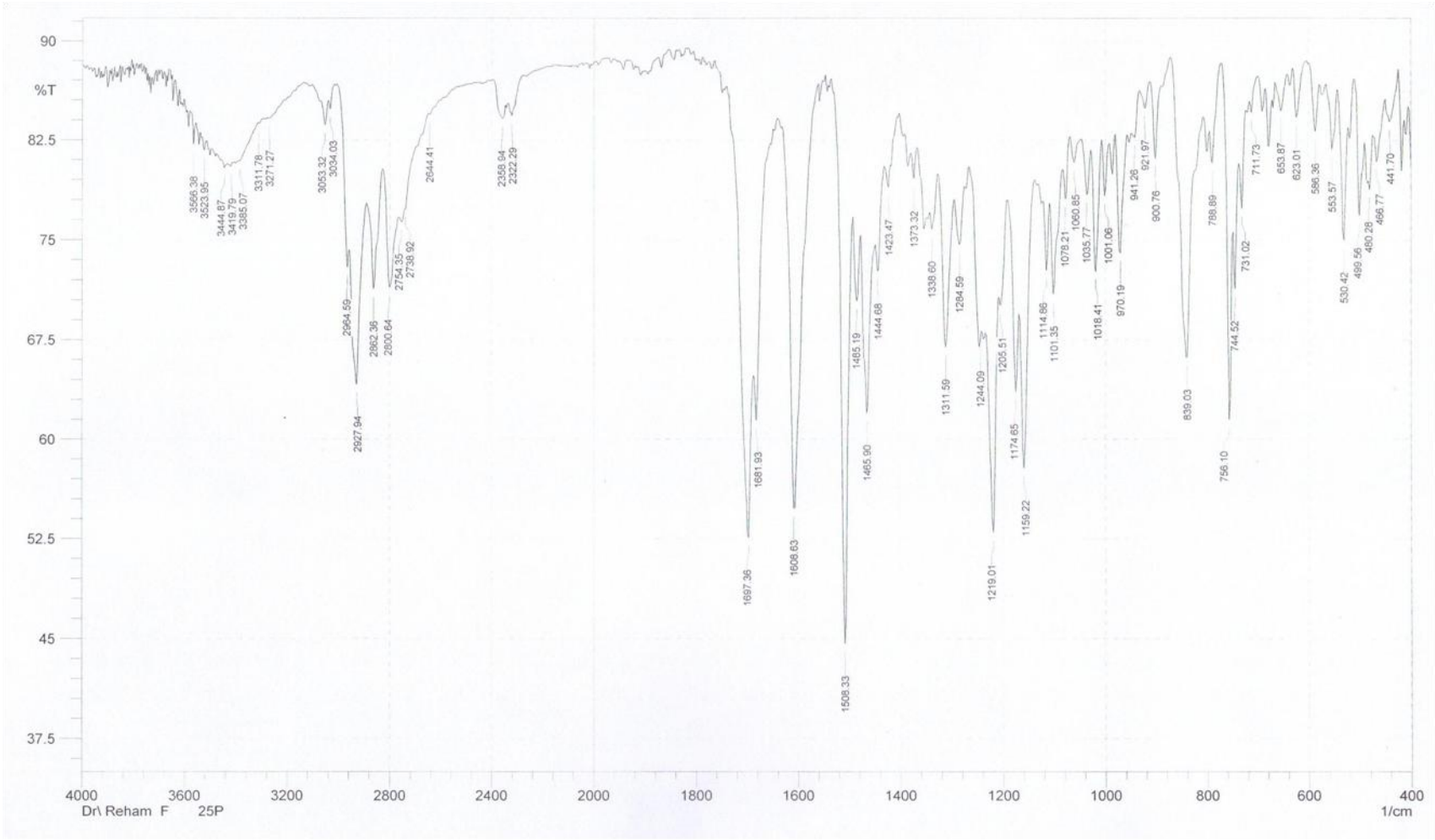


Figure S61. IR spectrum of compound **48** (KBr pellet).

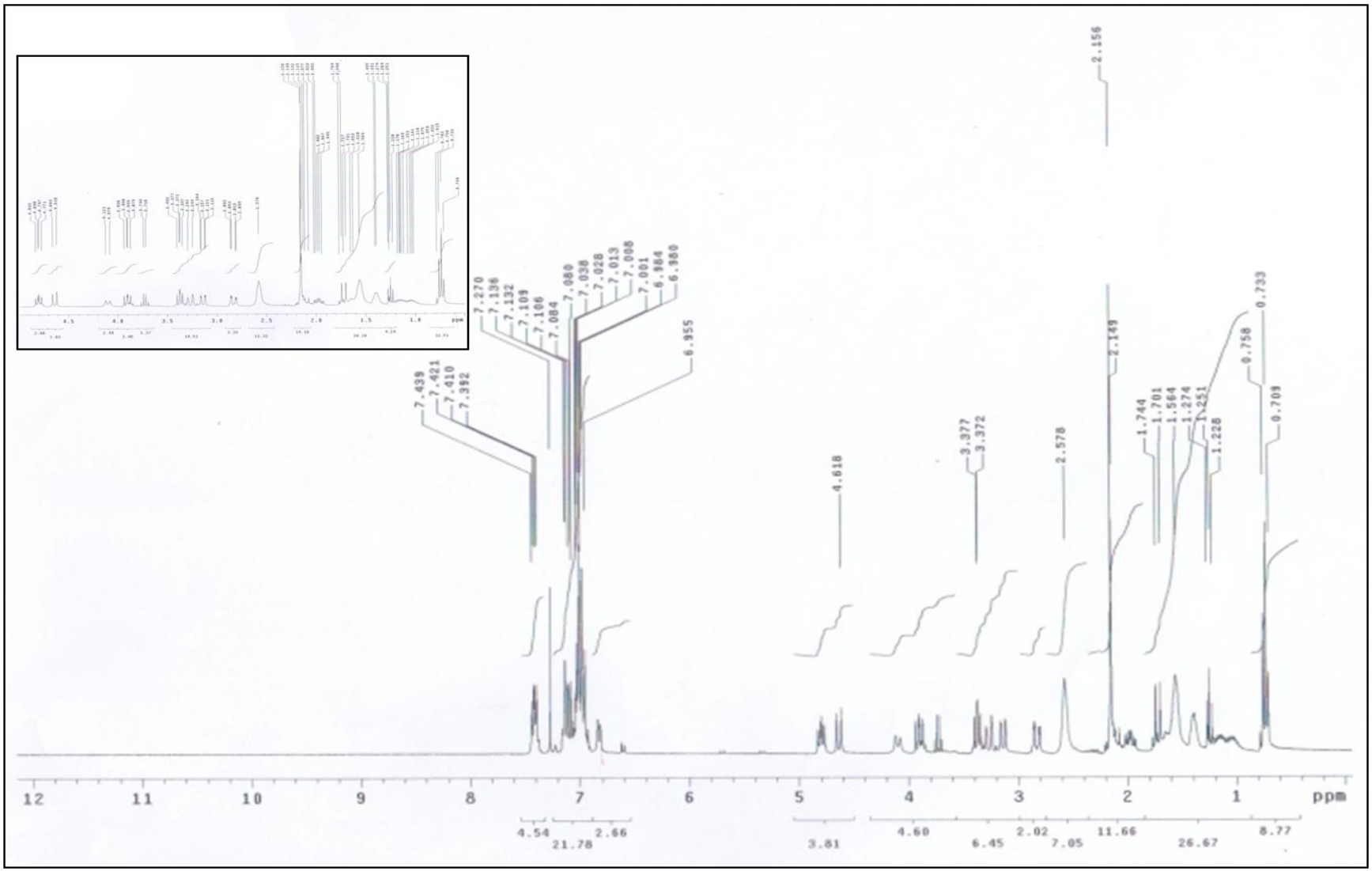


Figure S62. ^{1}H-NMR spectrum of compound **48** in $CDCl_3$.

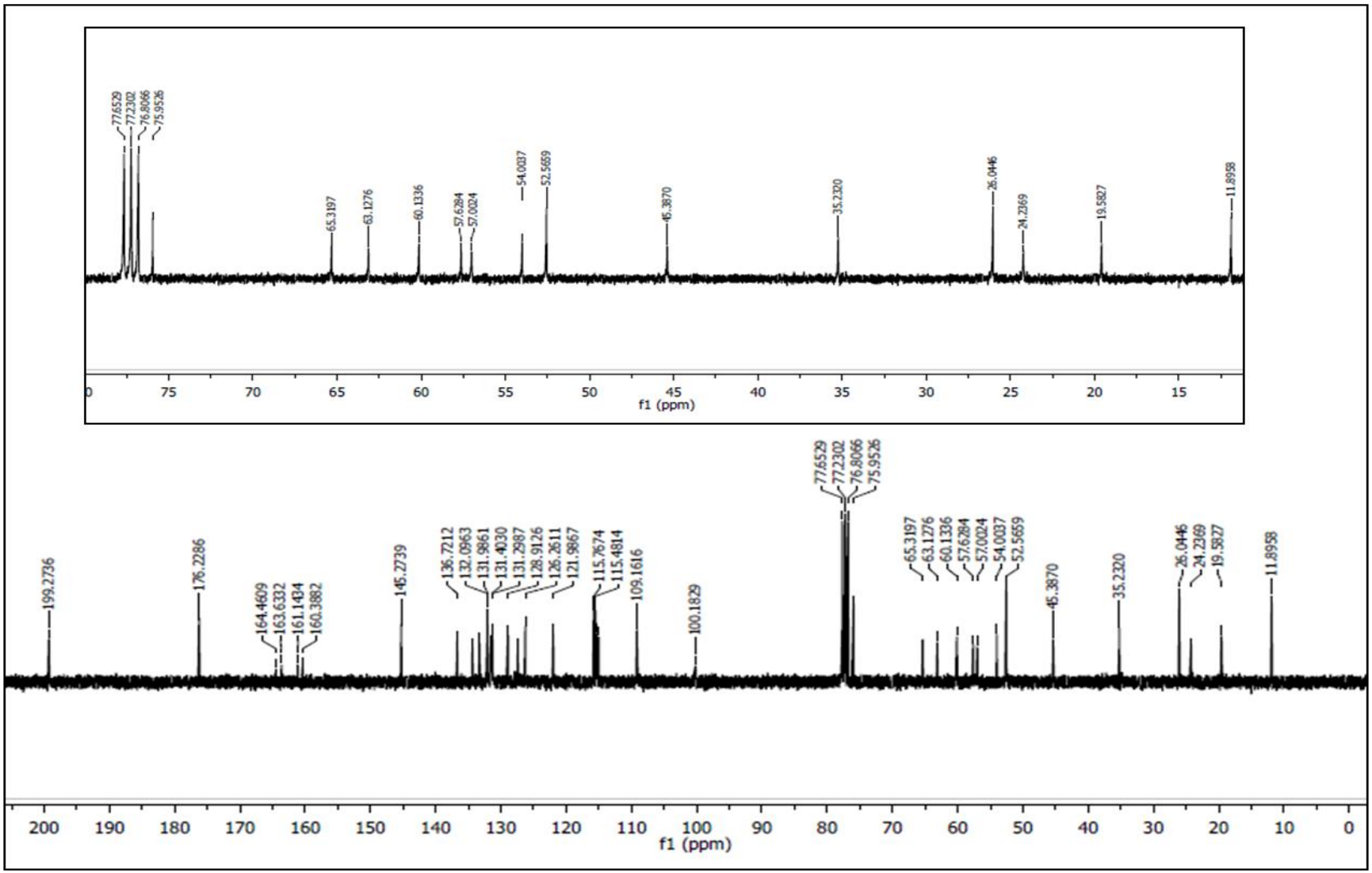


Figure S63. ^{13}C-NMR spectrum of compound **48** in $CDCl_3$.

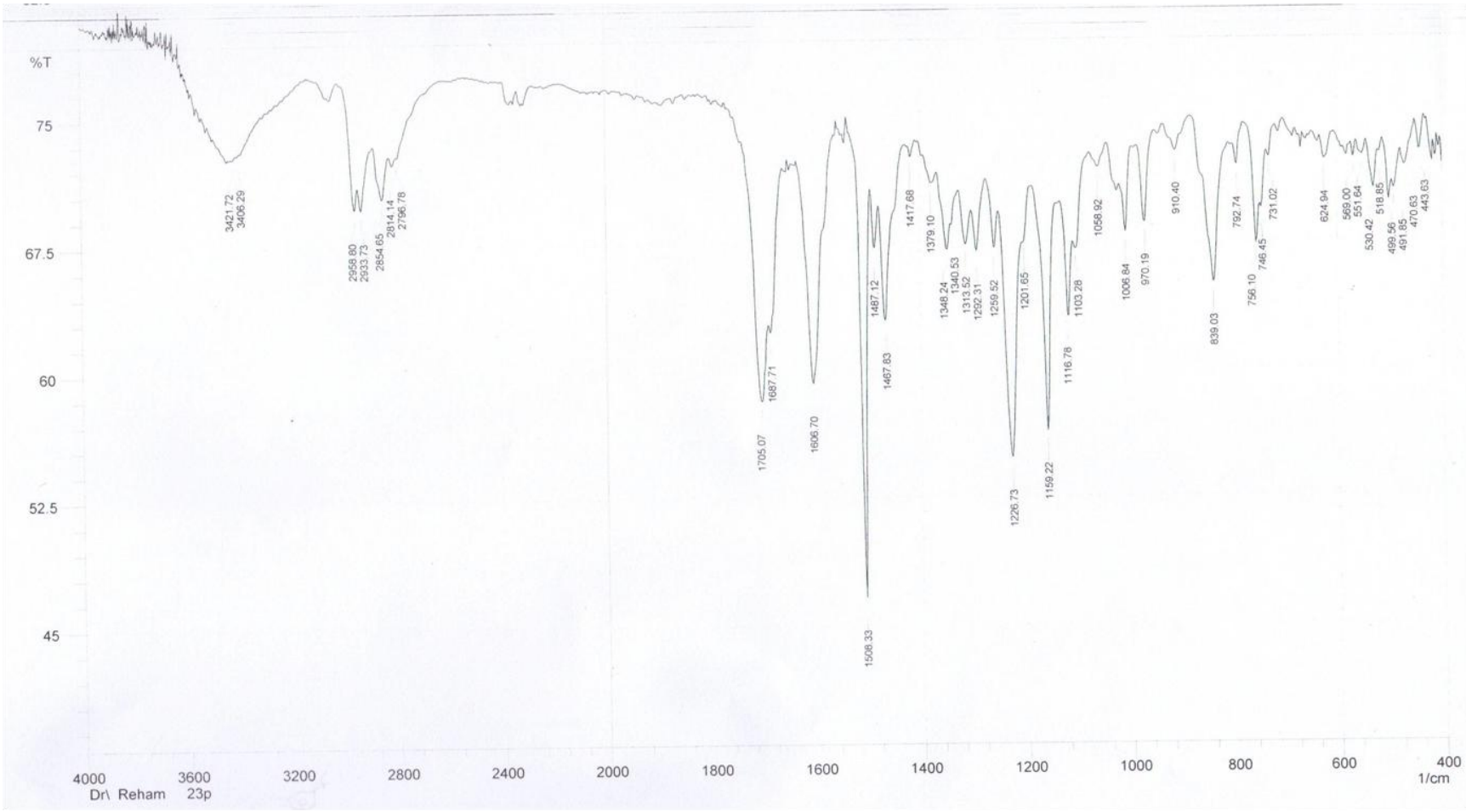


Figure S64. IR spectrum of compound **49** (KBr pellet).

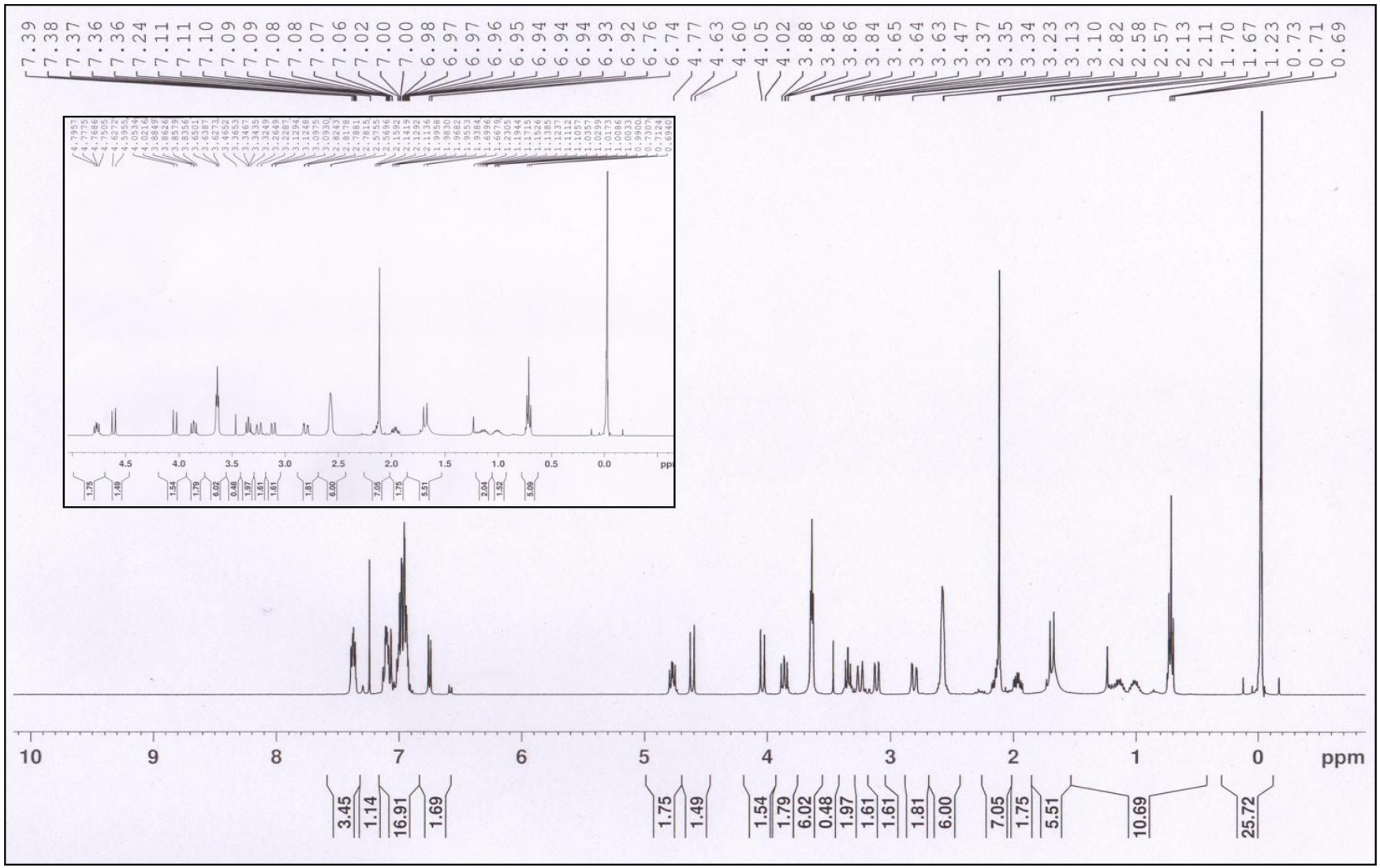


Figure S65. ^{1}H-NMR spectrum of compound **49** in $CDCl_3$.

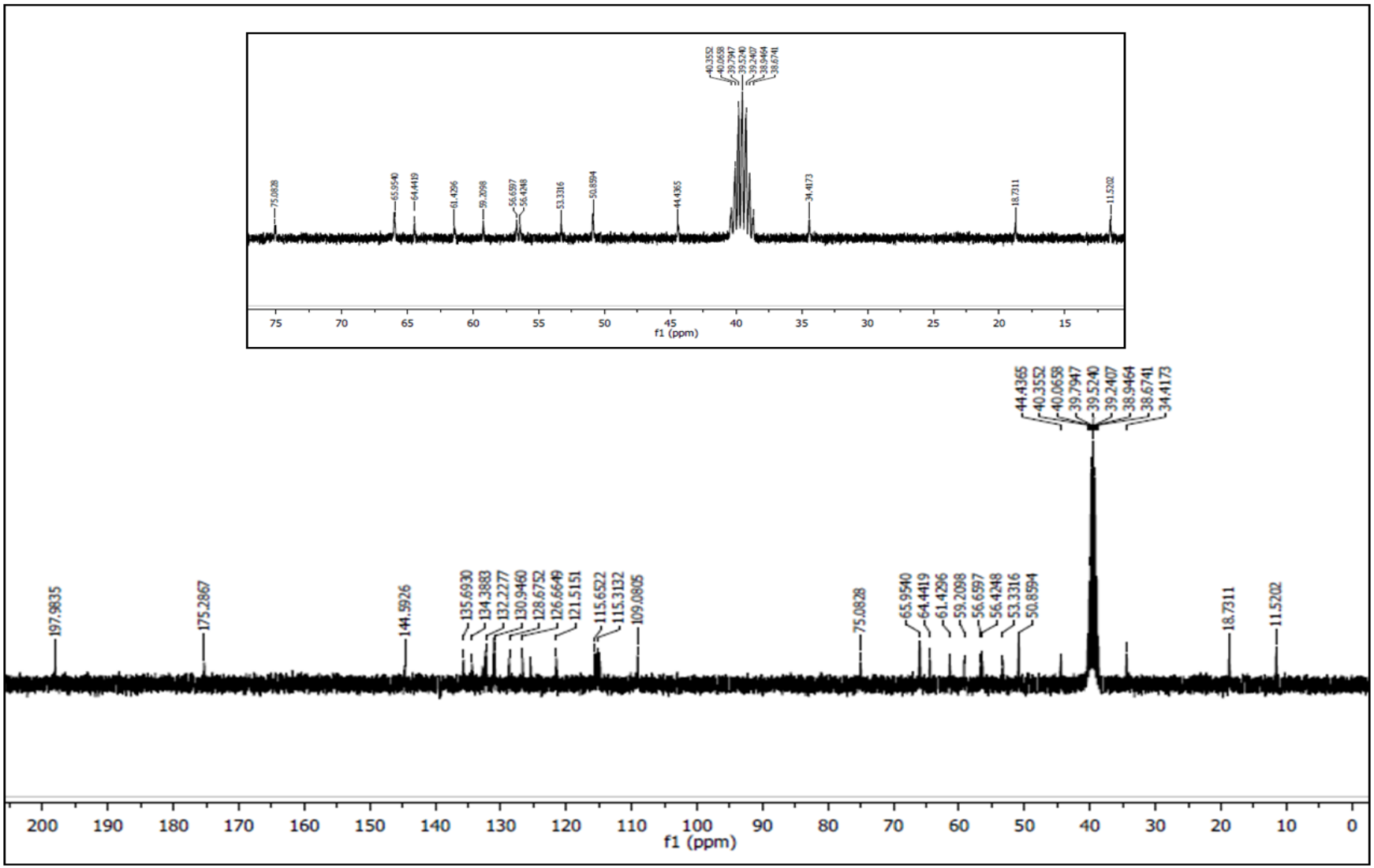


Figure S66. ^{13}C-NMR spectrum of compound **49** in DMSO-d_6.

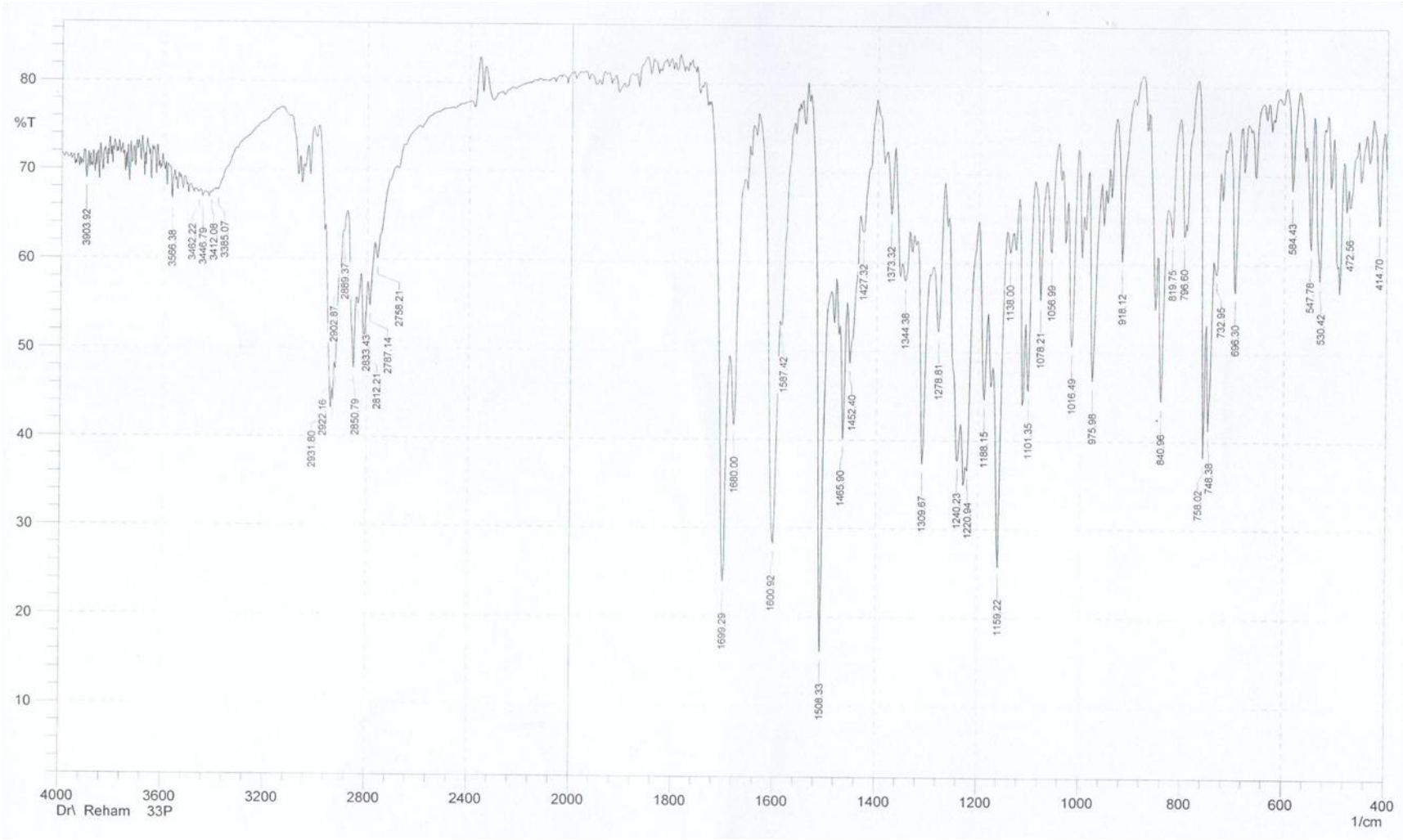


Figure S67. IR spectrum of compound **50** (KBr pellet).

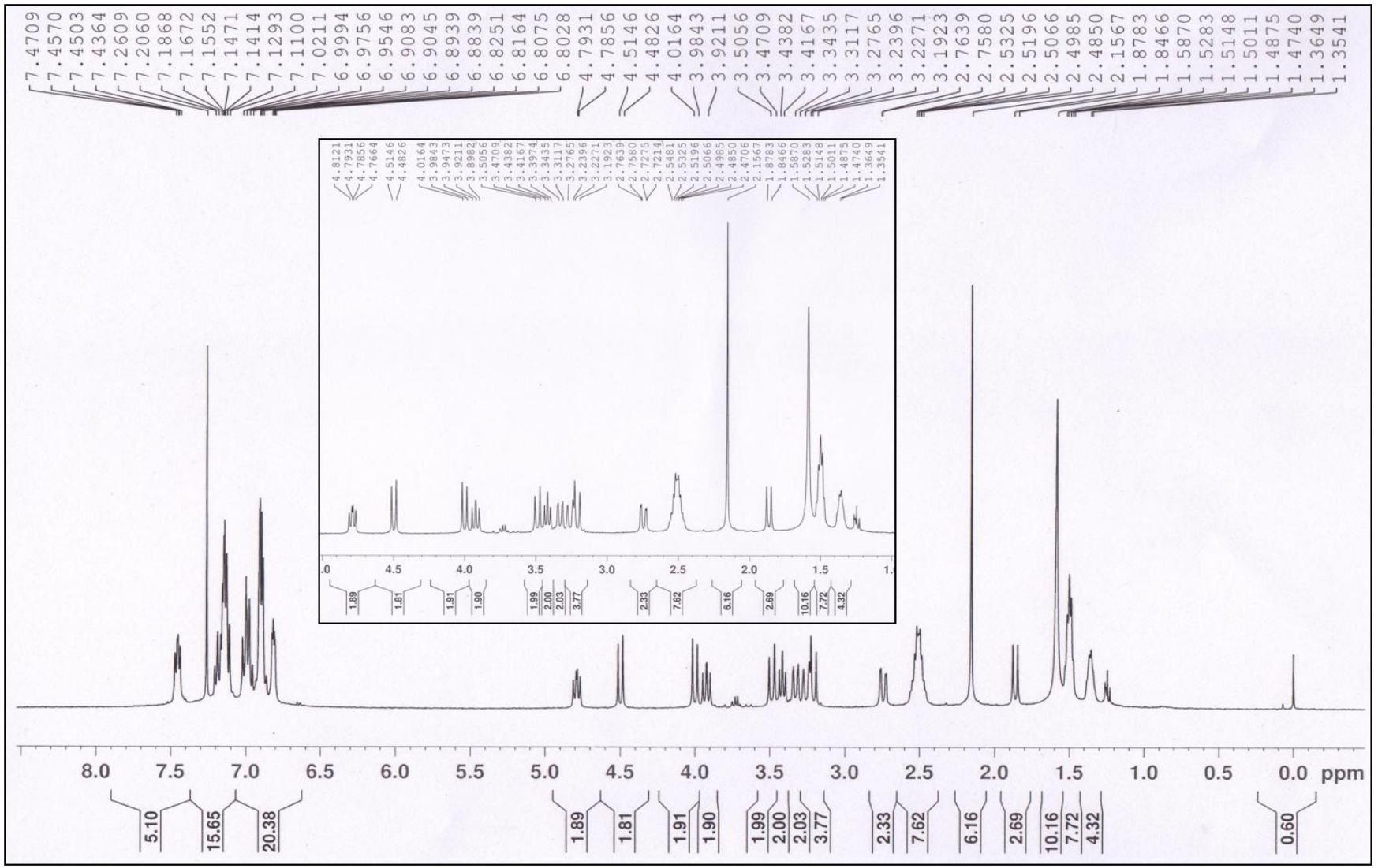


Figure S68. ^{1}H-NMR spectrum of compound **50** in $CDCl_3$.

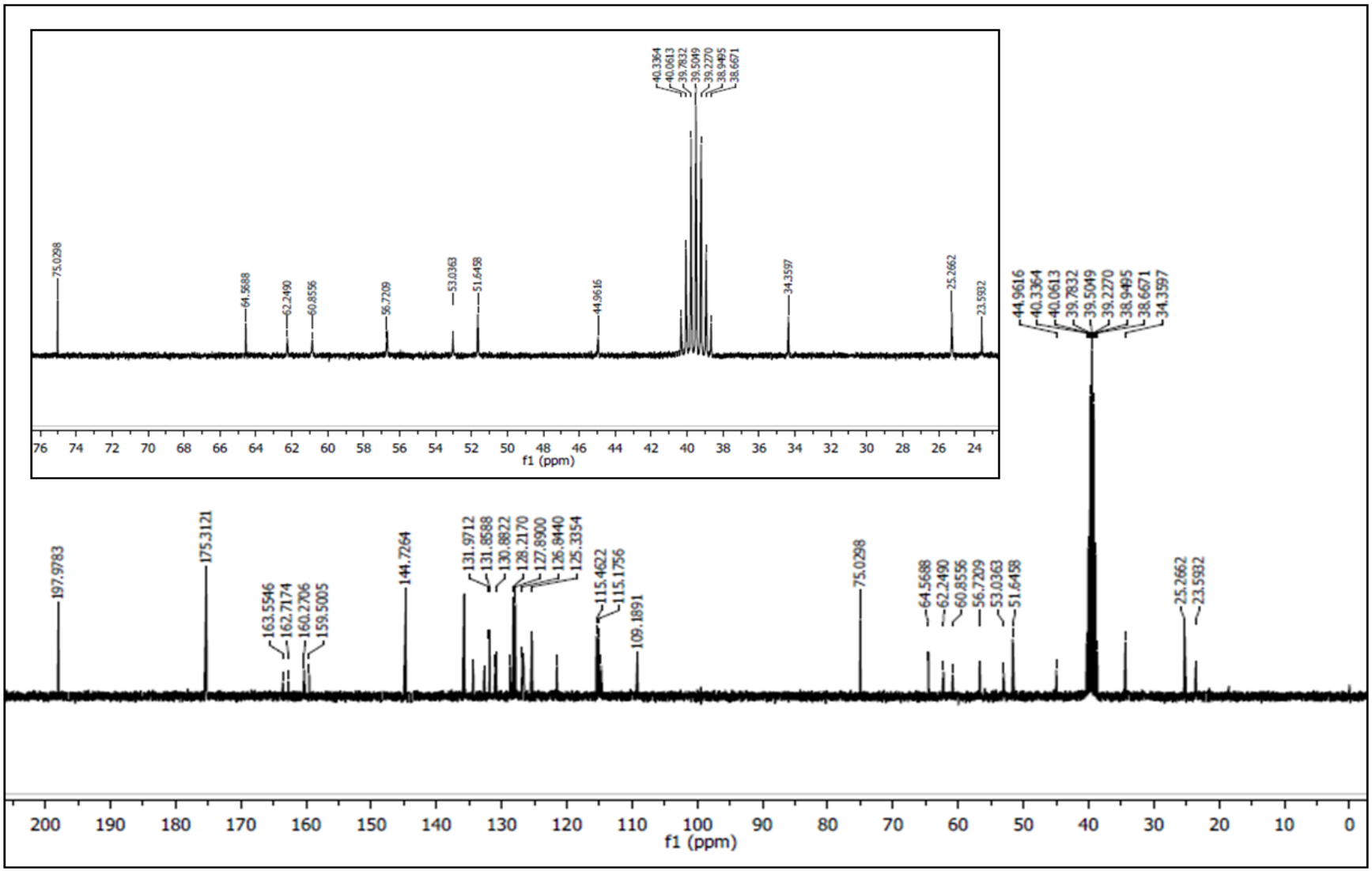


Figure S69. ^{13}C-NMR spectrum of compound **50** in DMSO-d_6.

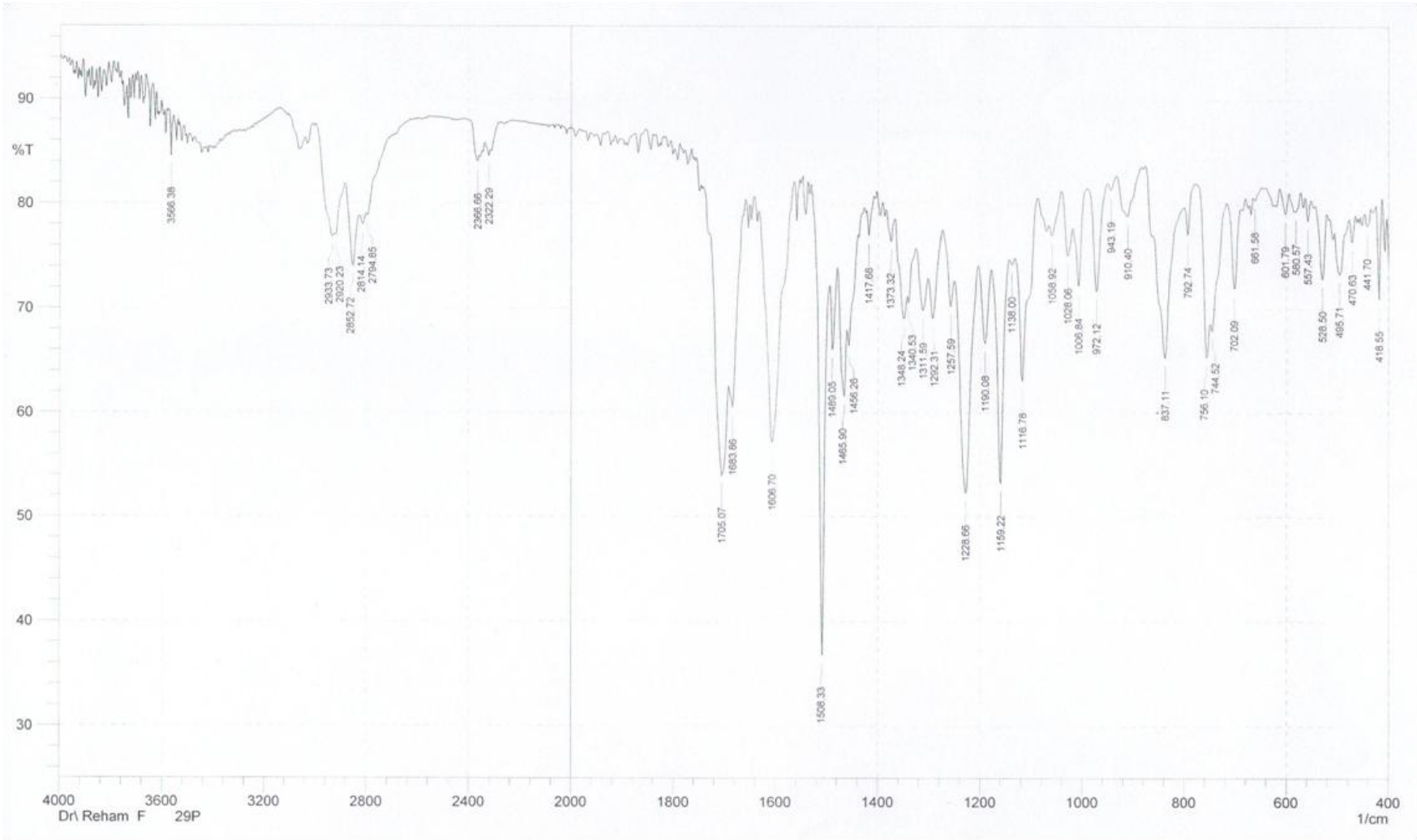


Figure S70. IR spectrum of compound **51** (KBr pellet).

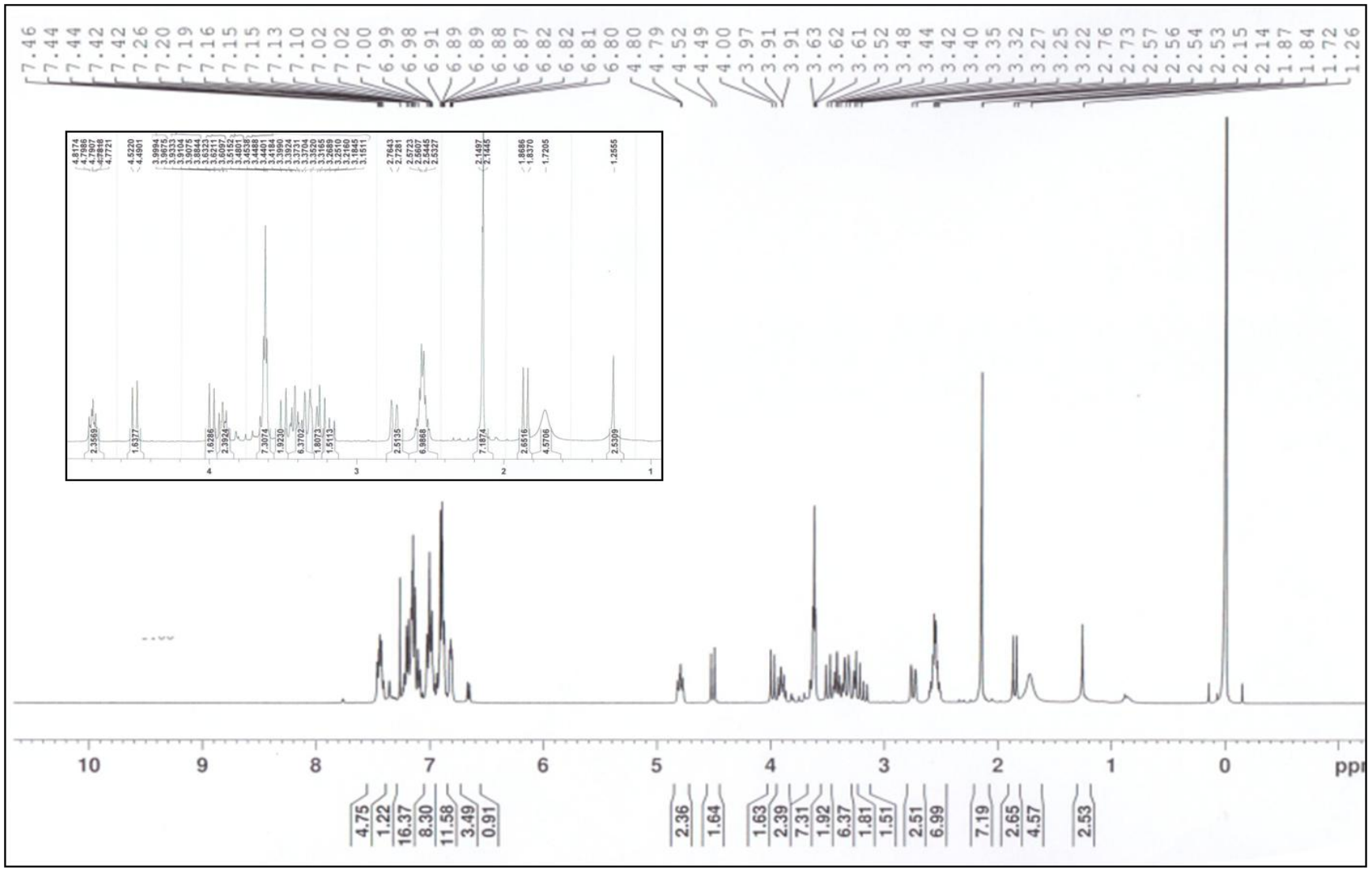


Figure S71. ^{1}H-NMR spectrum of compound **51** in $CDCl_3$.

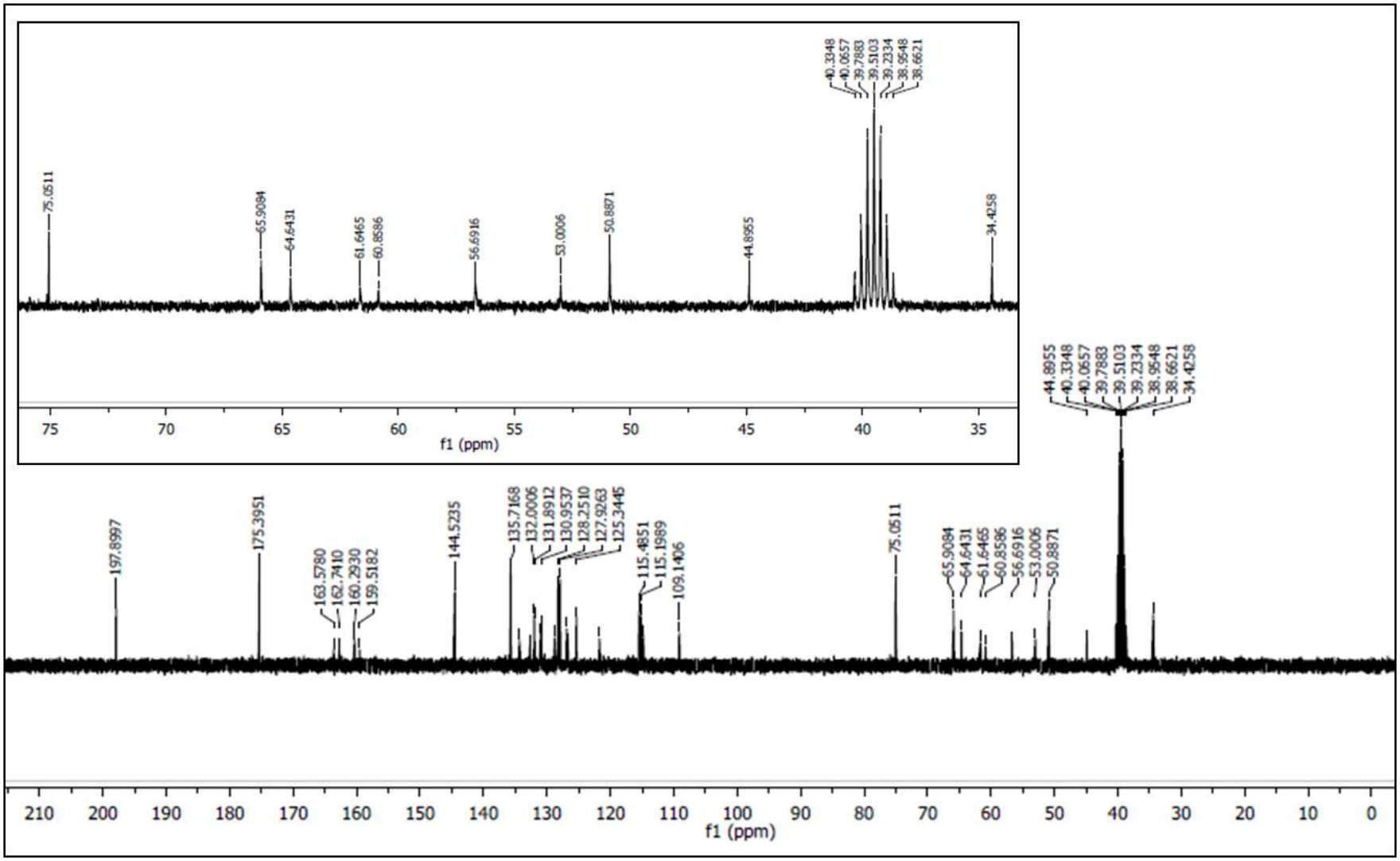


Figure S72. ^{13}C-NMR spectrum of compound **51** in DMSO-d_6.

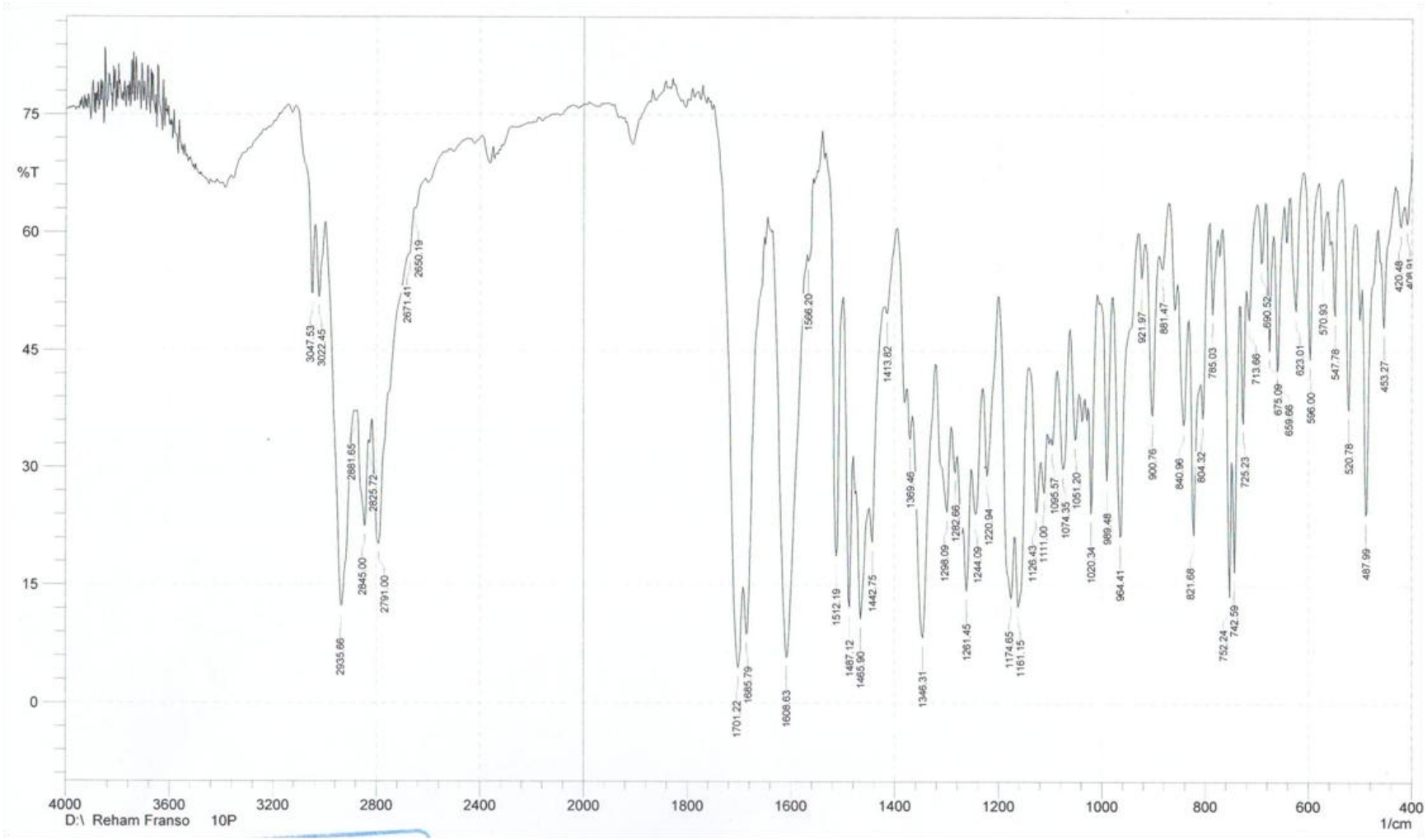


Figure S73. IR spectrum of compound **52** (KBr pellet).

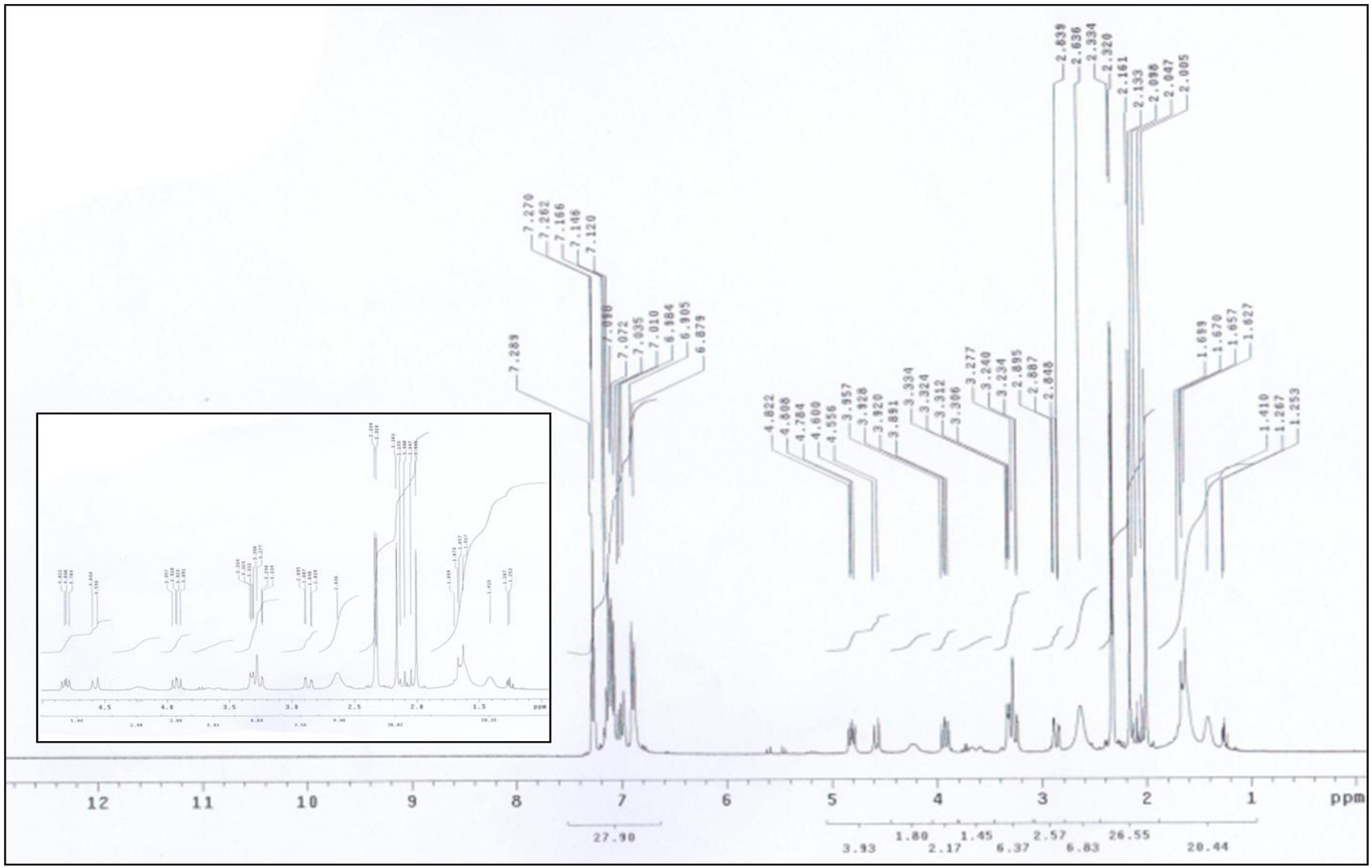


Figure S74. ^{1}H-NMR spectrum of compound **52** in $CDCl_3$.

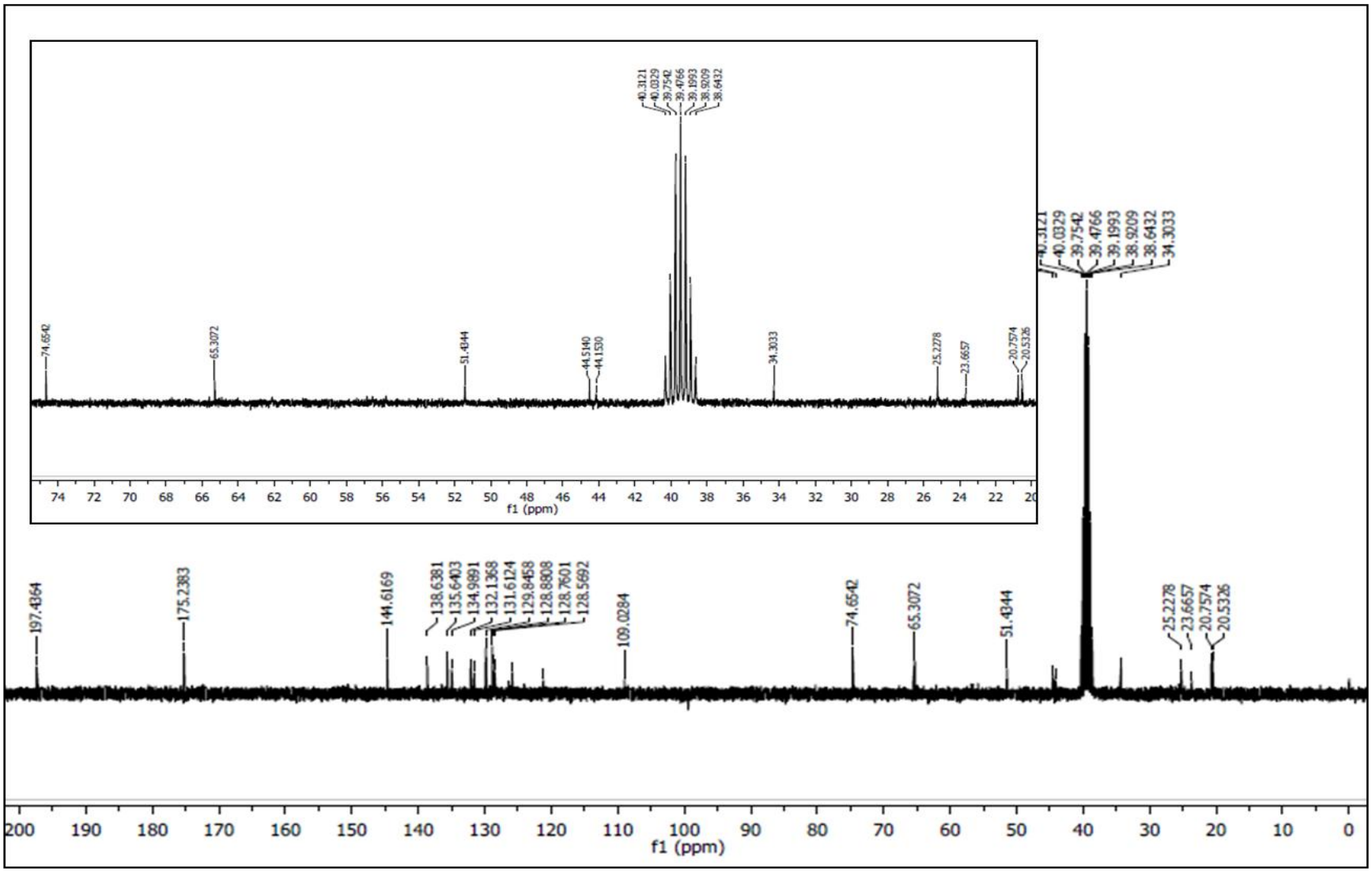


Figure S75. ^{13}C-NMR spectrum of compound **52** in DMSO-d_6.

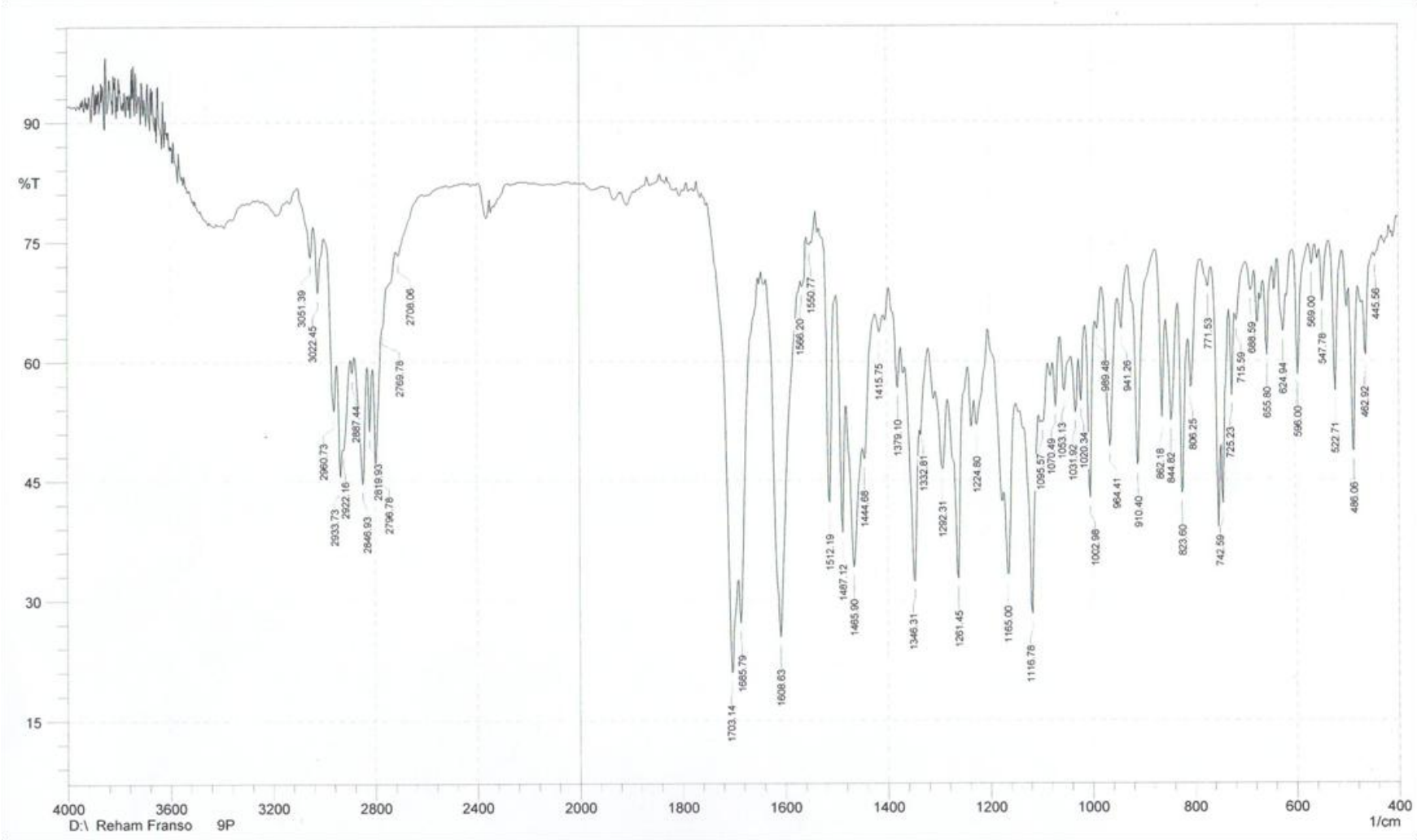


Figure S76. IR spectrum of compound **53** (KBr pellet).

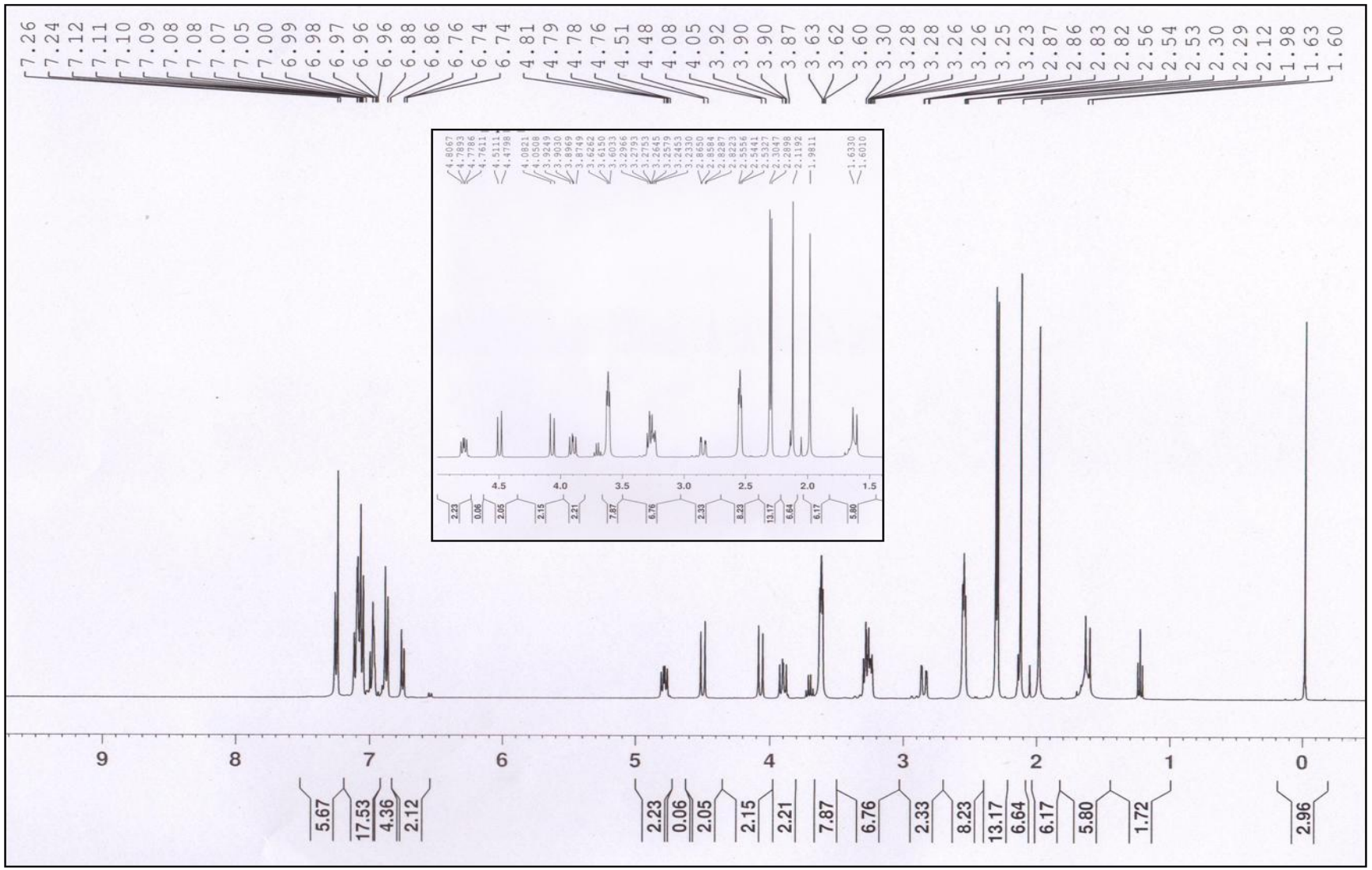


Figure S77. ^{1}H-NMR spectrum of compound **53** in $CDCl_3$.

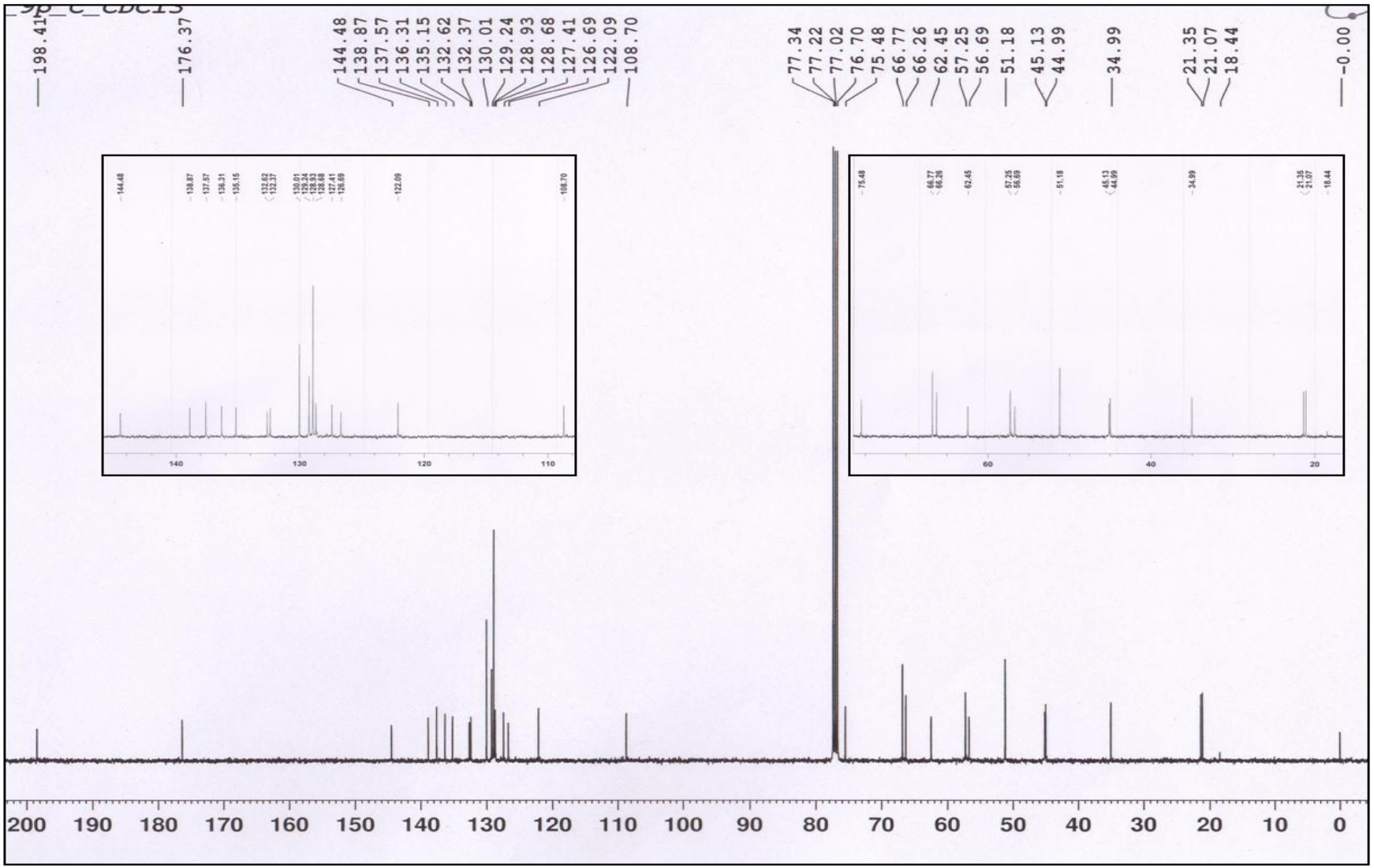


Figure S78. ^{13}C-NMR spectrum of compound **53** in $CDCl_3$.

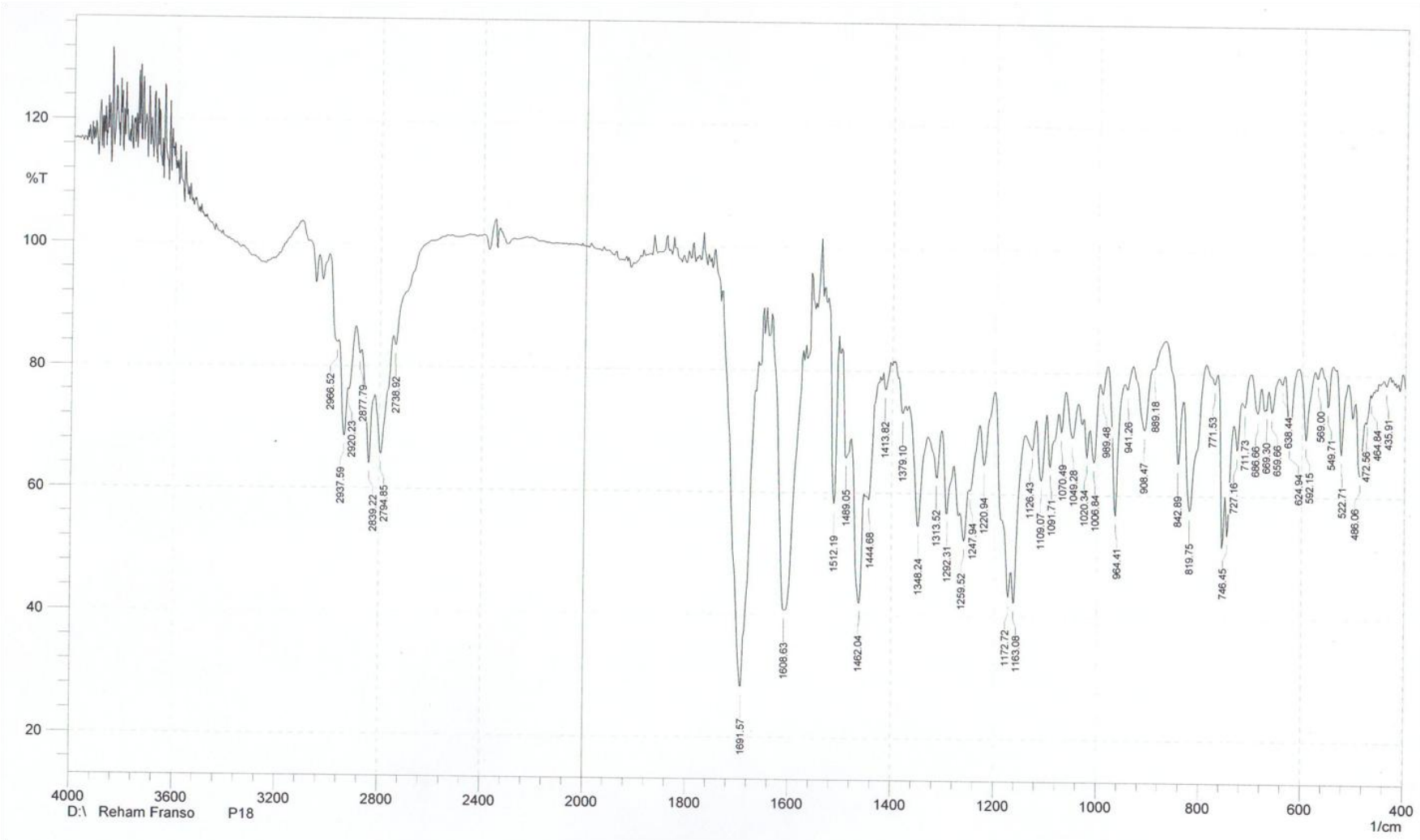


Figure S79. IR spectrum of compound **54** (KBr pellet).

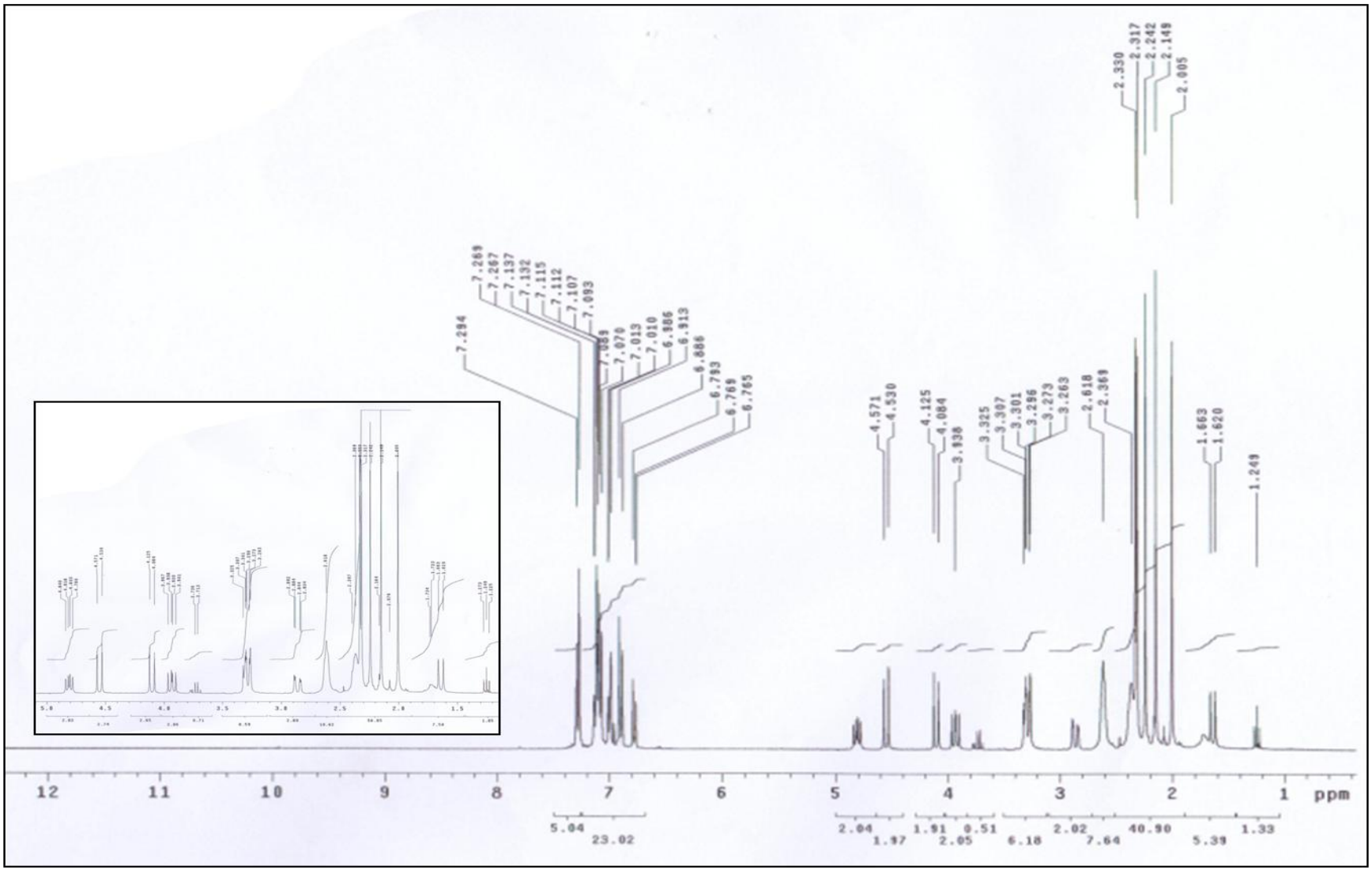


Figure S80. ^{1}H-NMR spectrum of compound **54** in $CDCl_3$.

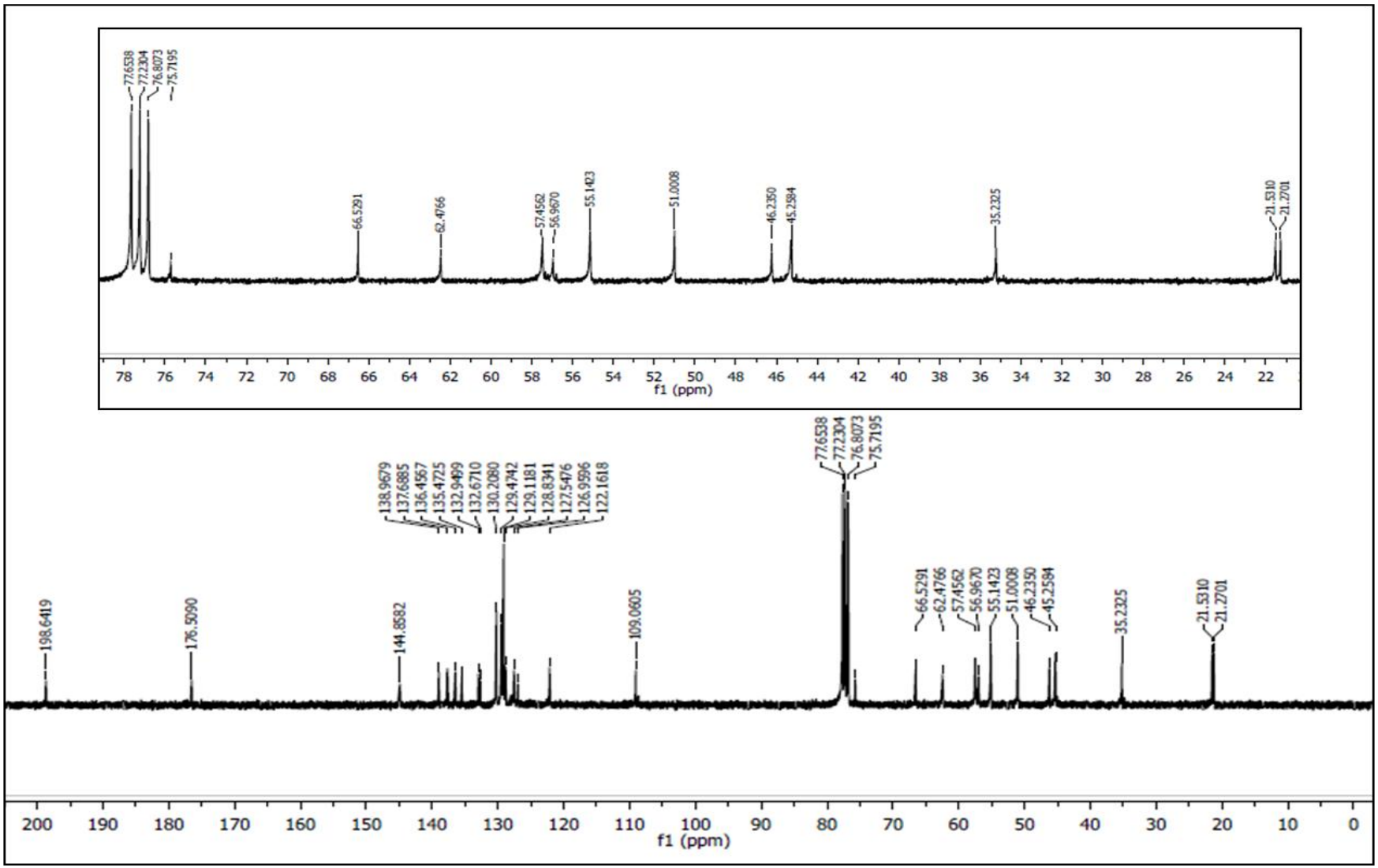


Figure S81. ^{13}C-NMR spectrum of compound **54** in $CDCl_3$.

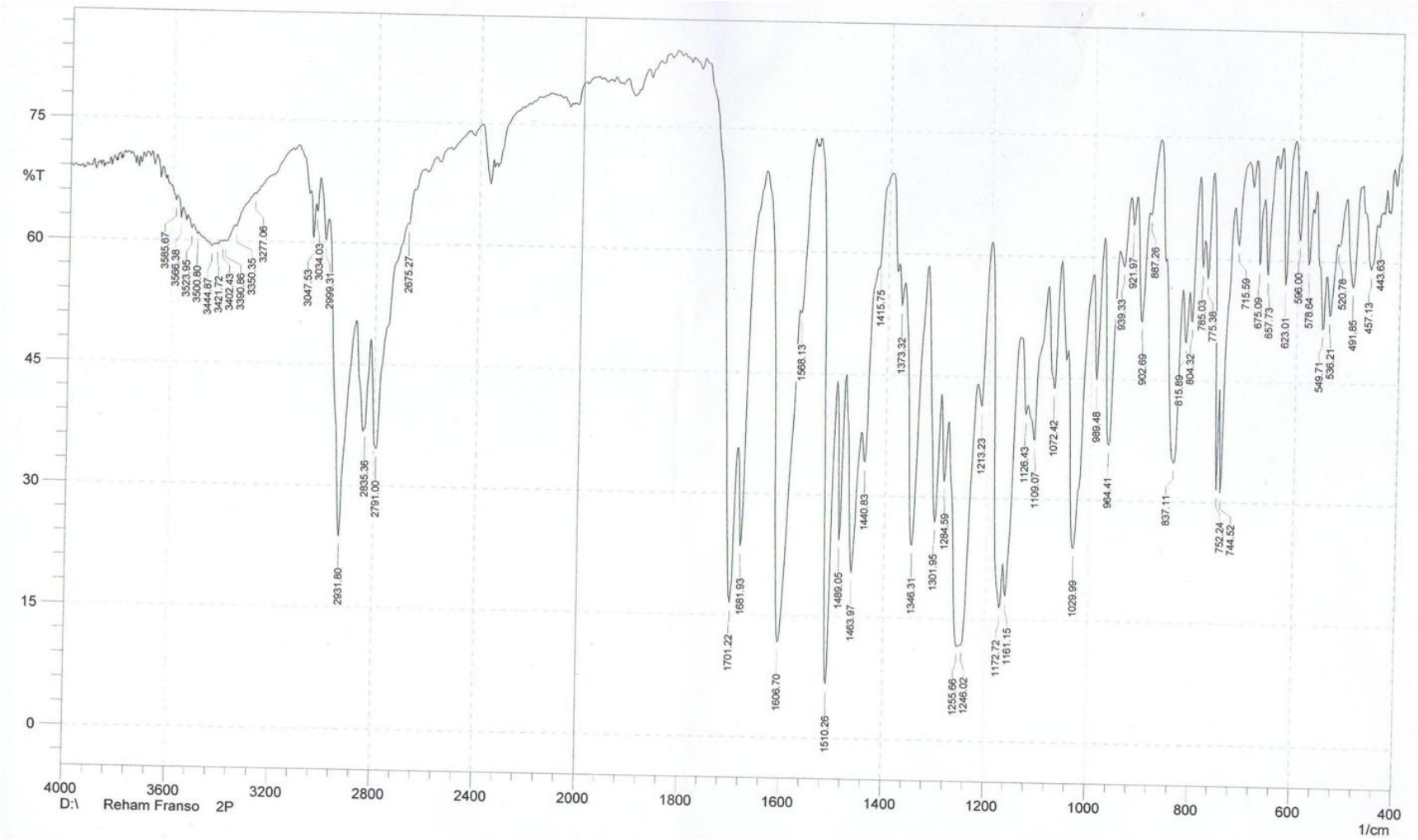


Figure S82. IR spectrum of compound **55** (KBr pellet).

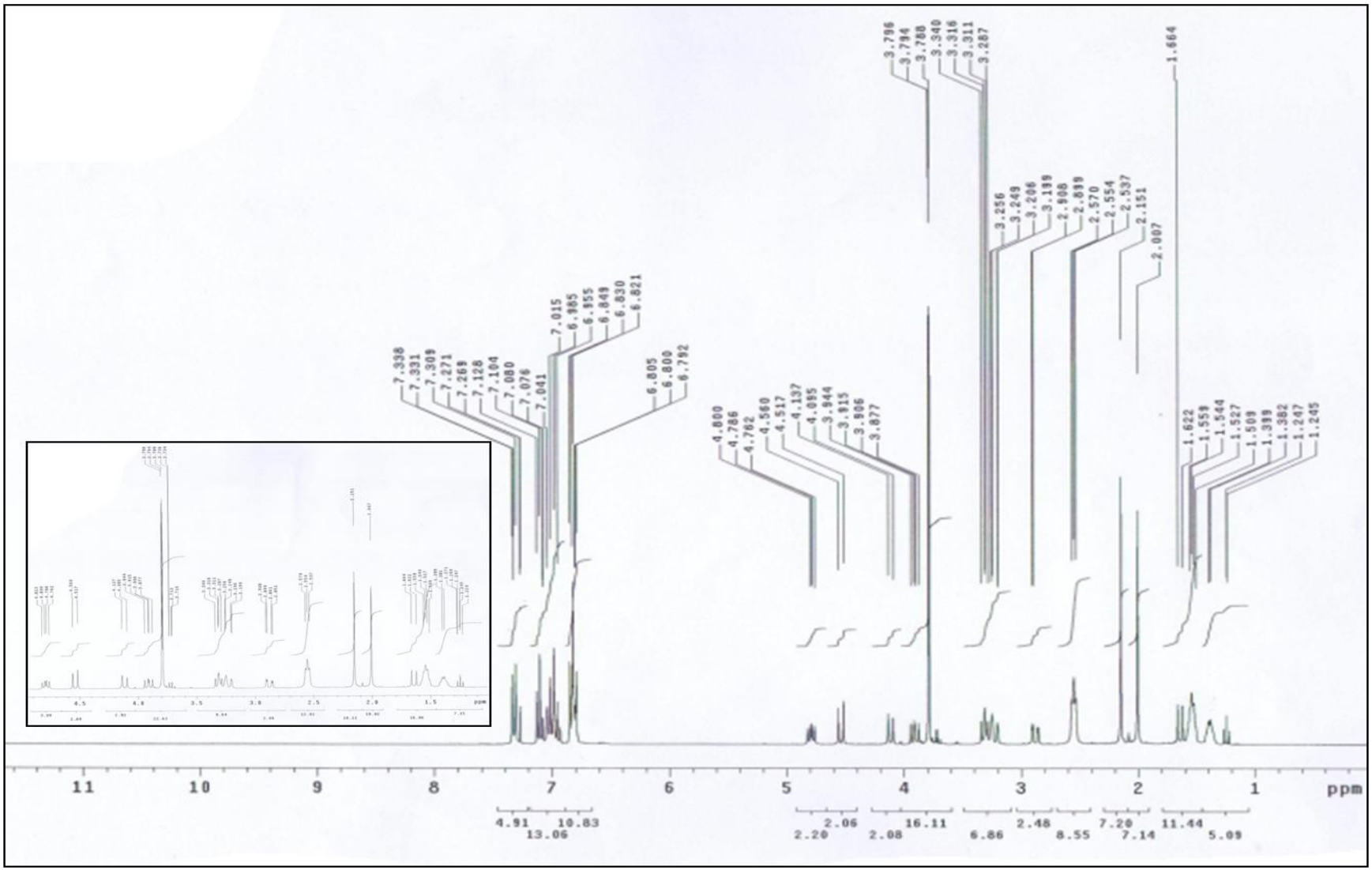


Figure S83. ^{1}H-NMR spectrum of compound **55** in $CDCl_3$.

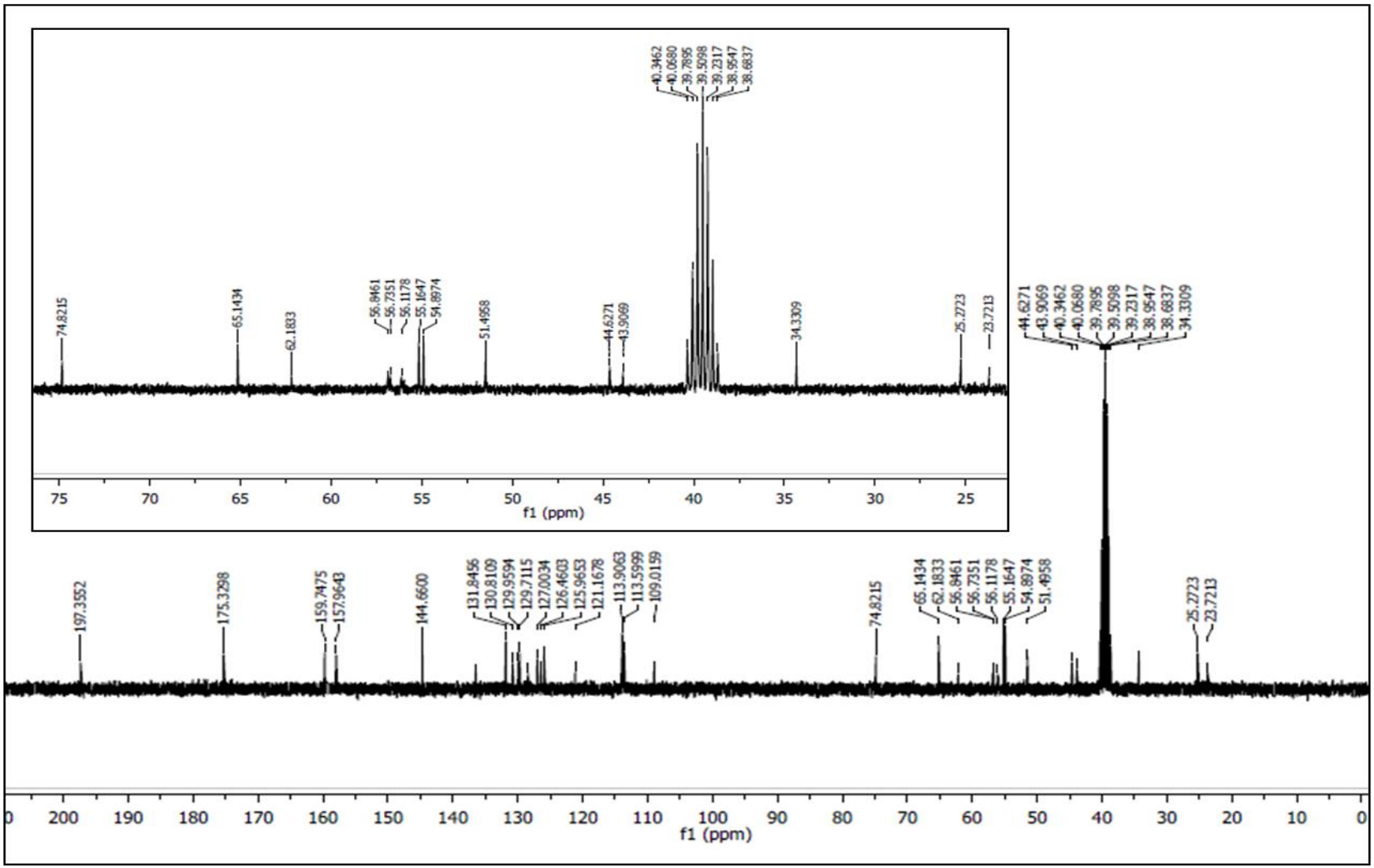


Figure S84. ^{13}C-NMR spectrum of compound **55** in DMSO-d_6.

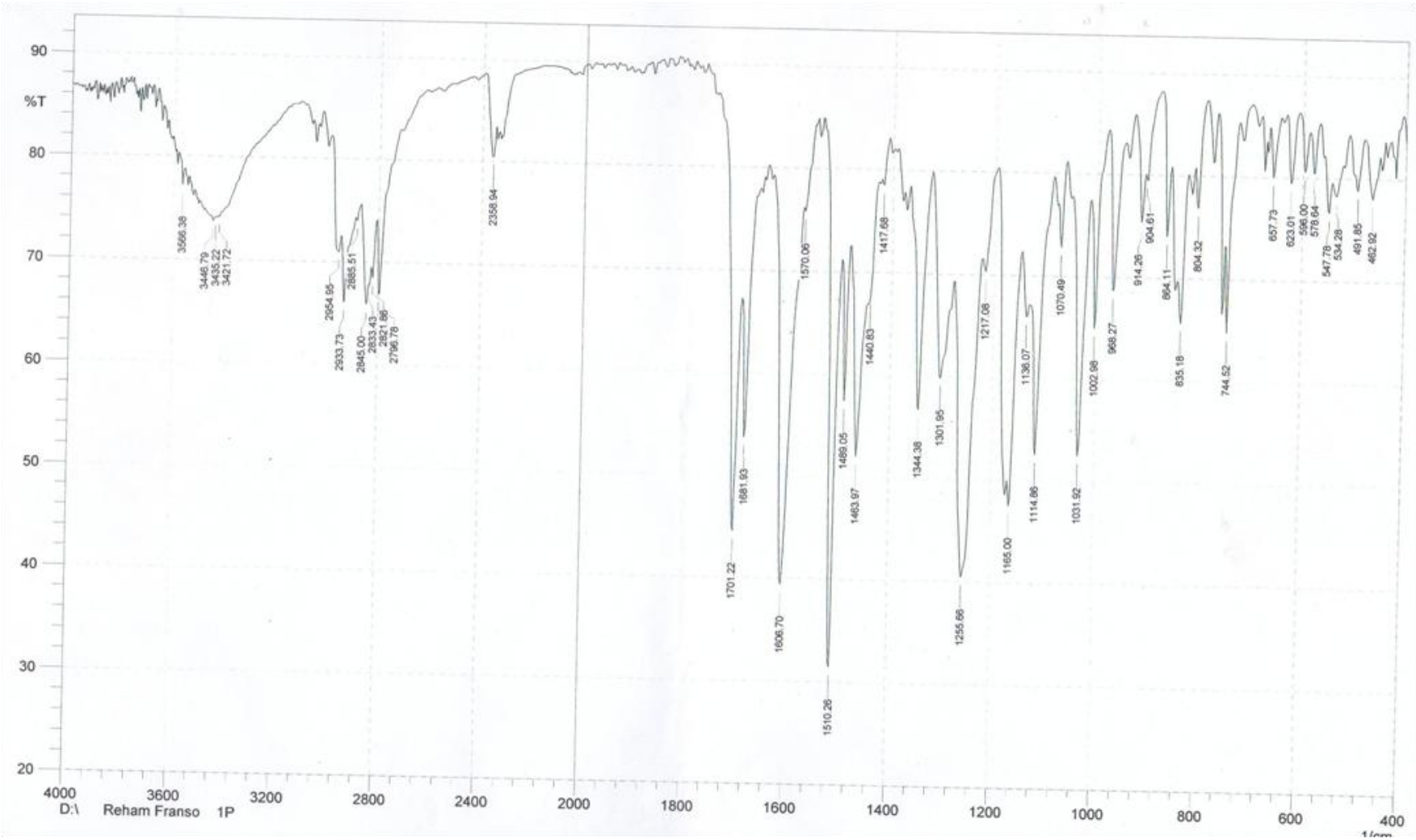


Figure S85. IR spectrum of compound **56** (KBr pellet).

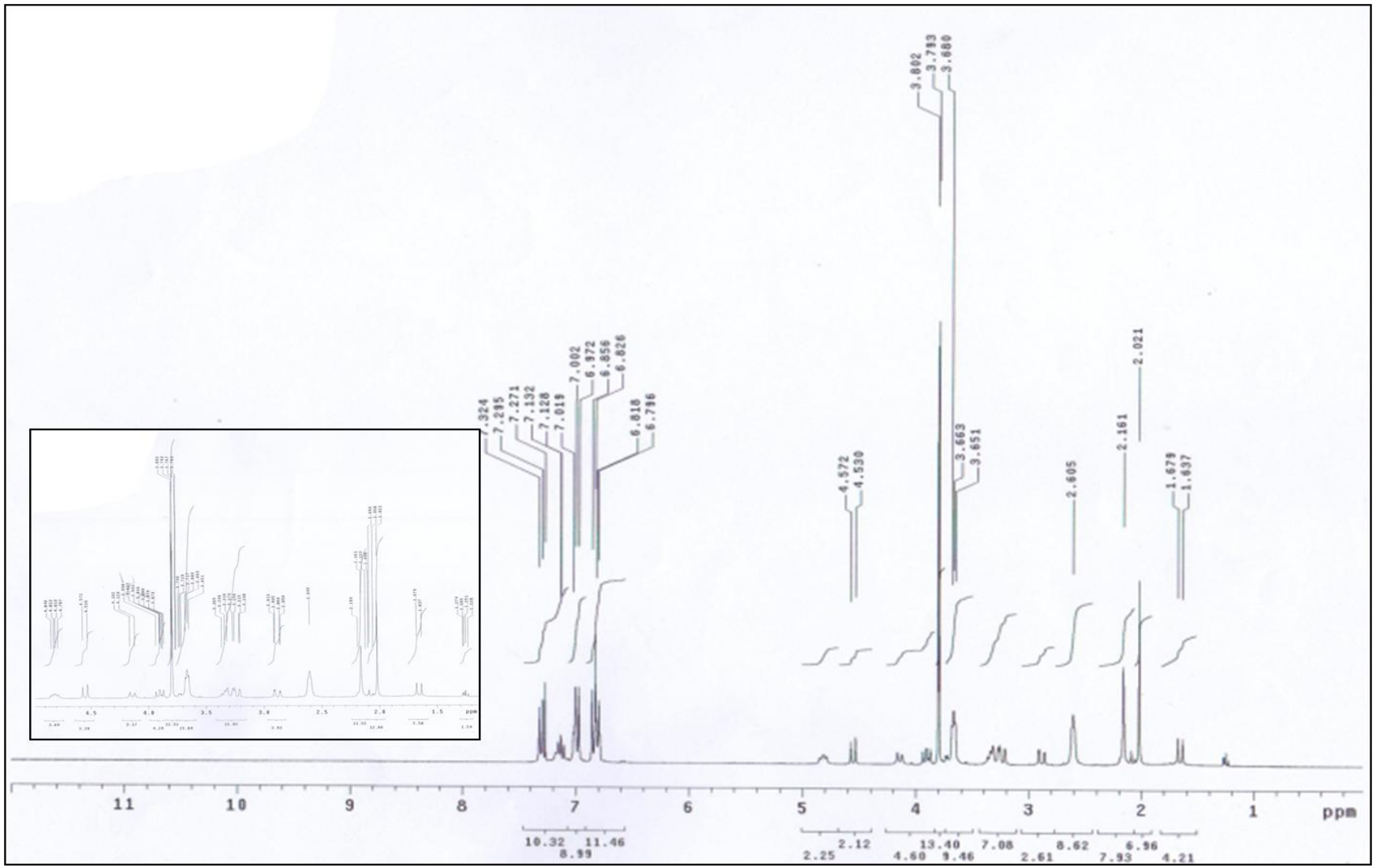


Figure S86. ^{1}H-NMR spectrum of compound **56** in $CDCl_3$.

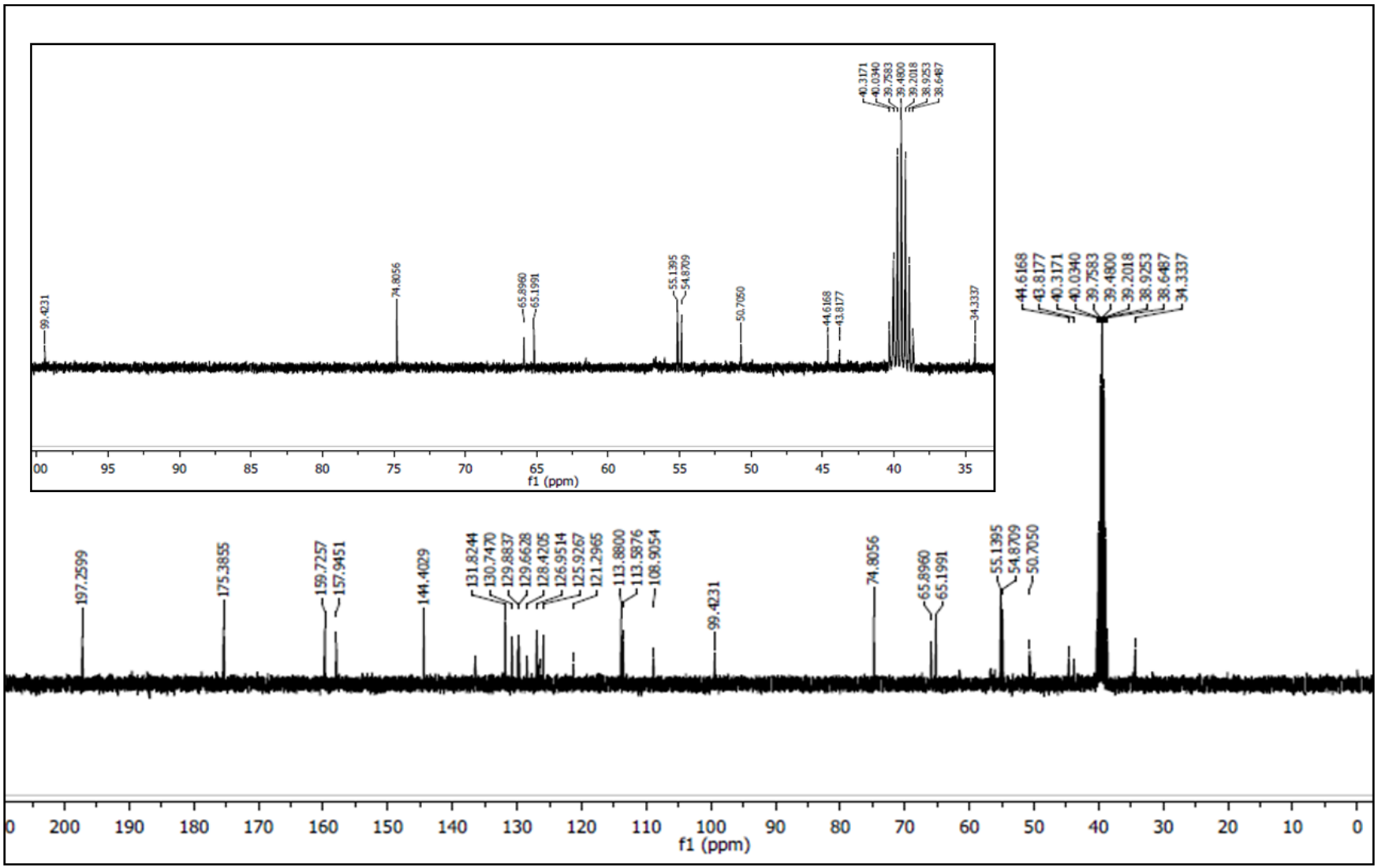


Figure S87. ^{13}C-NMR spectrum of compound **56** in DMSO-d_6.

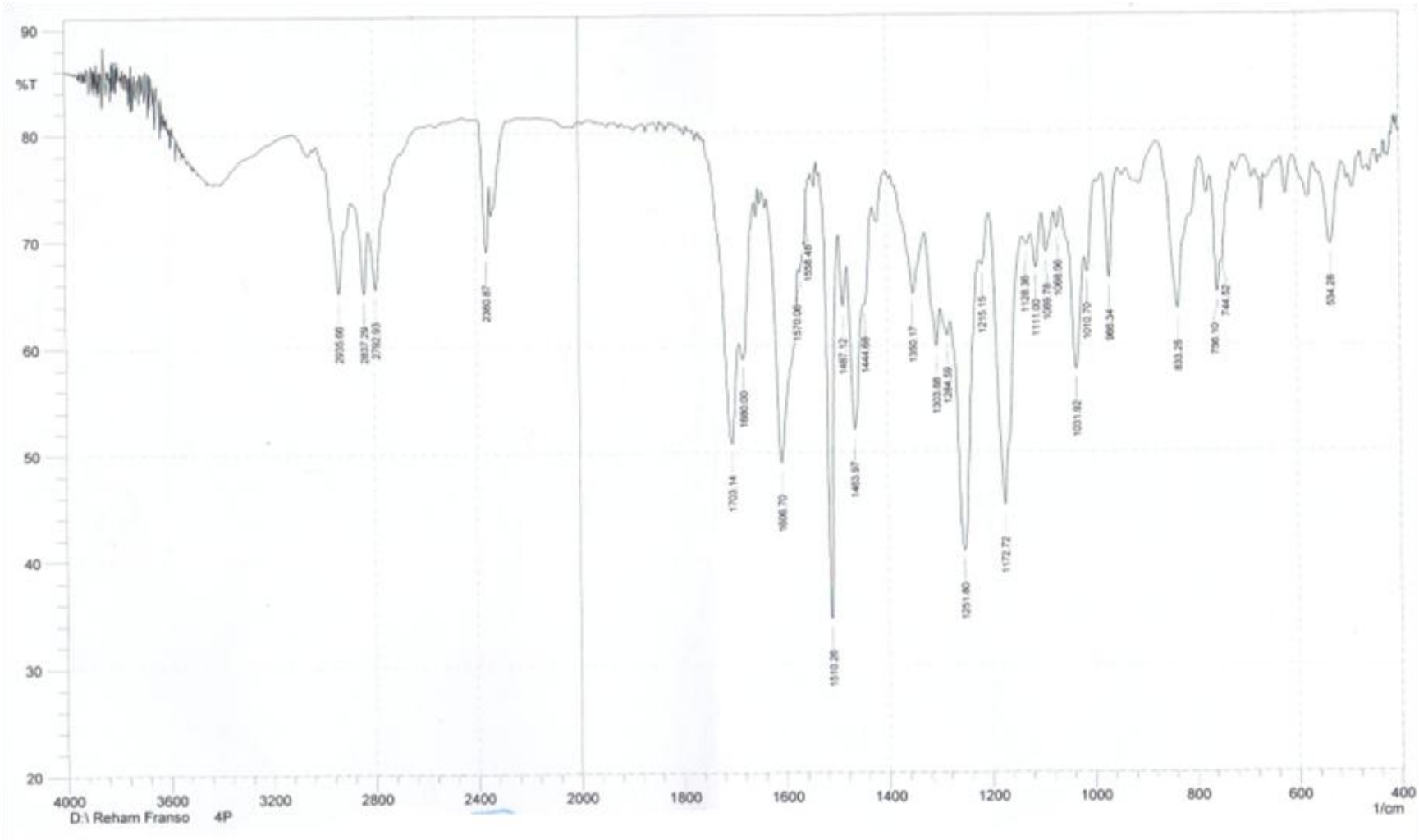


Figure S88. IR spectrum of compound **57** (KBr pellet).

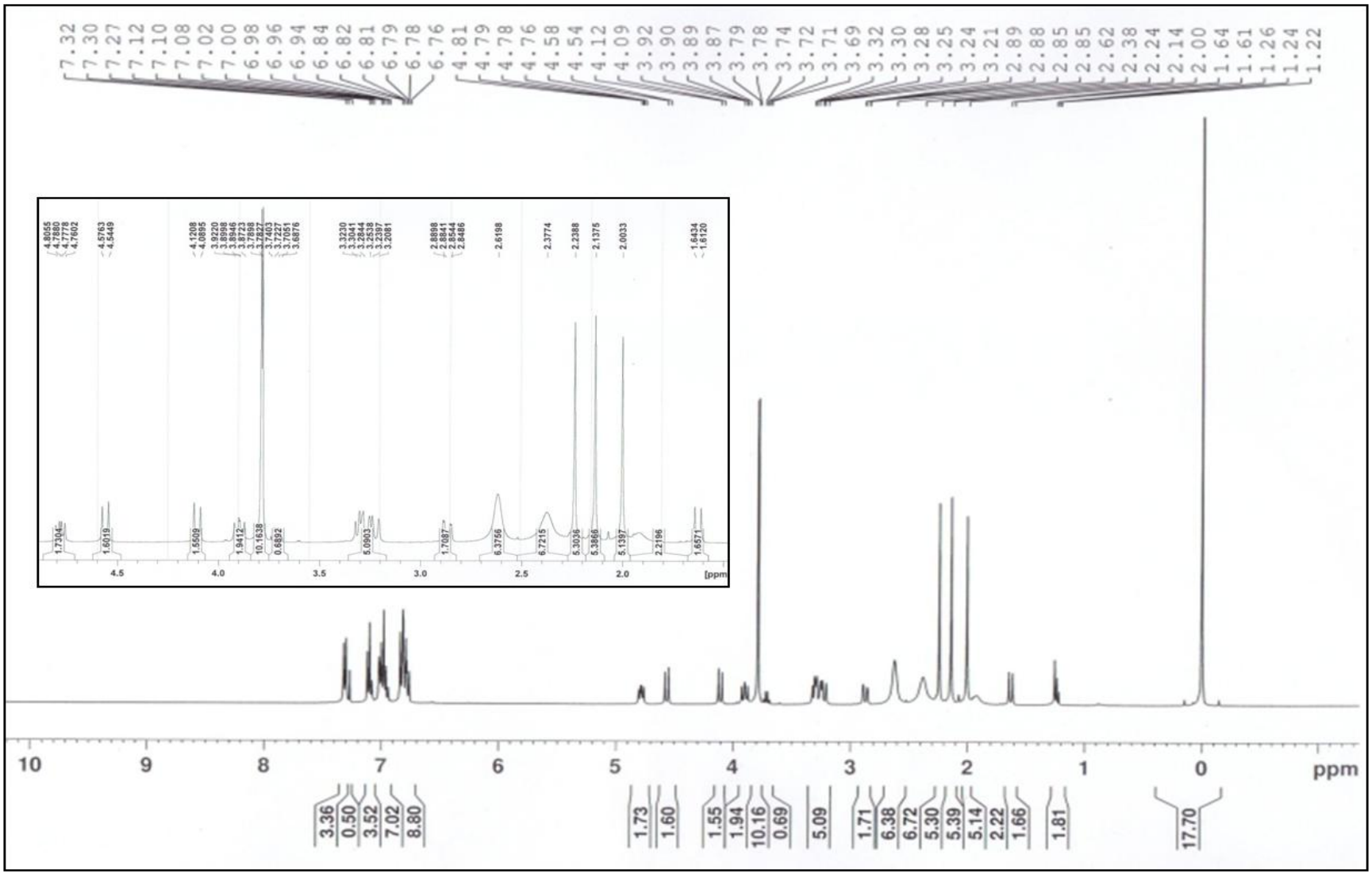


Figure S89. ^{1}H-NMR spectrum of compound **57** in $CDCl_3$.

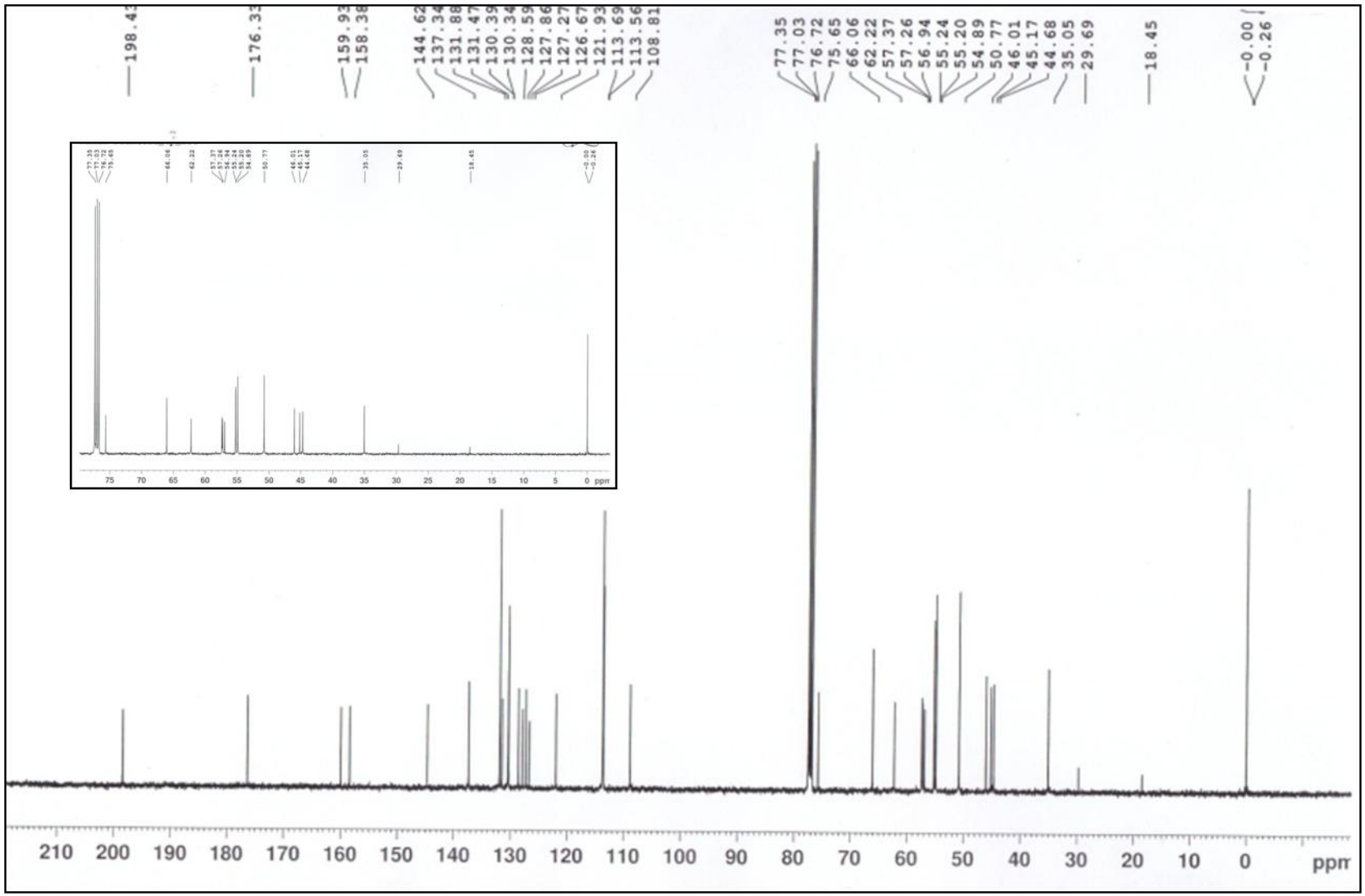


Figure S90. ^{13}C-NMR spectrum of compound **57** in $CDCl_3$.

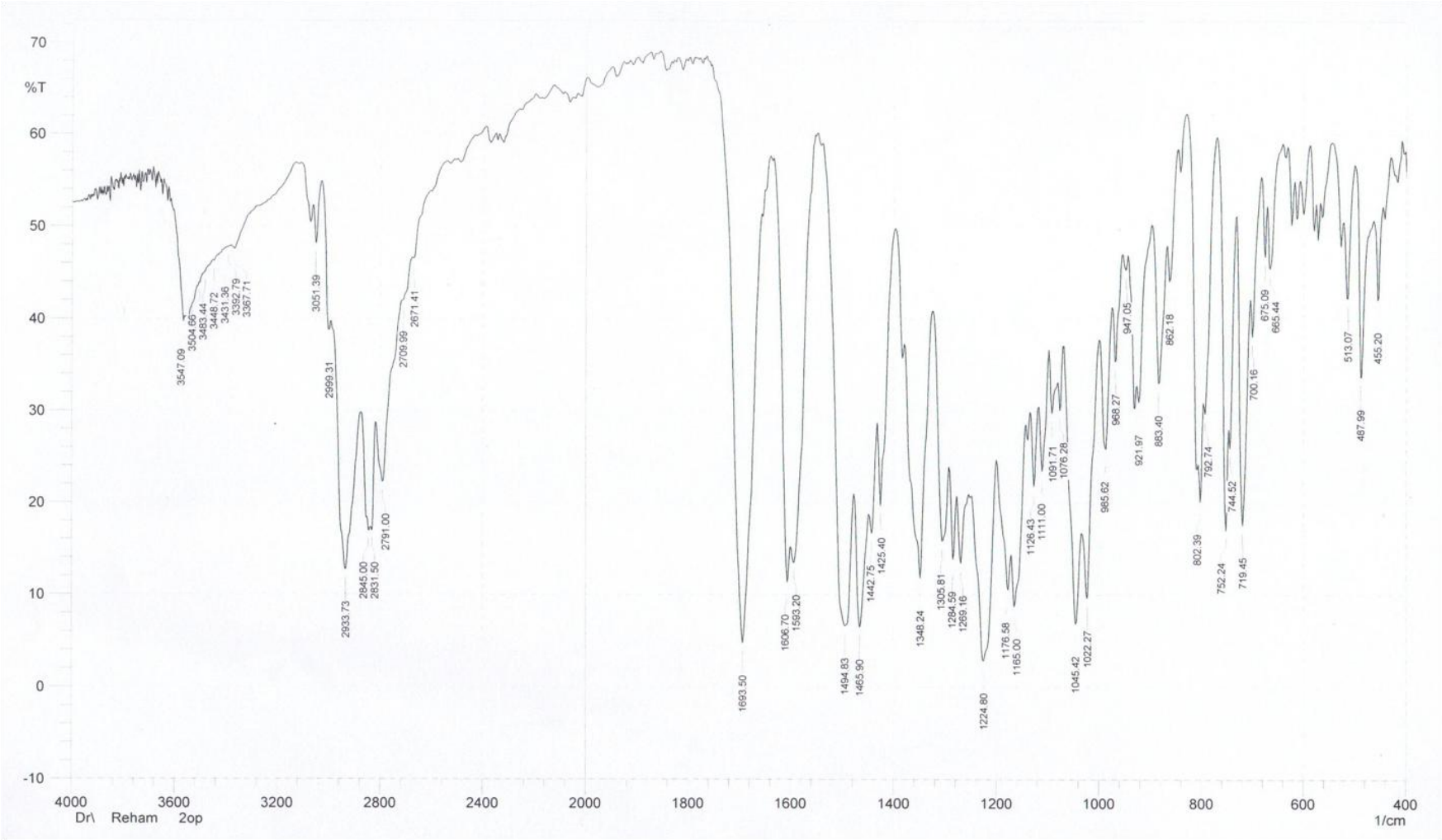


Figure S91. IR spectrum of compound **58** (KBr pellet).

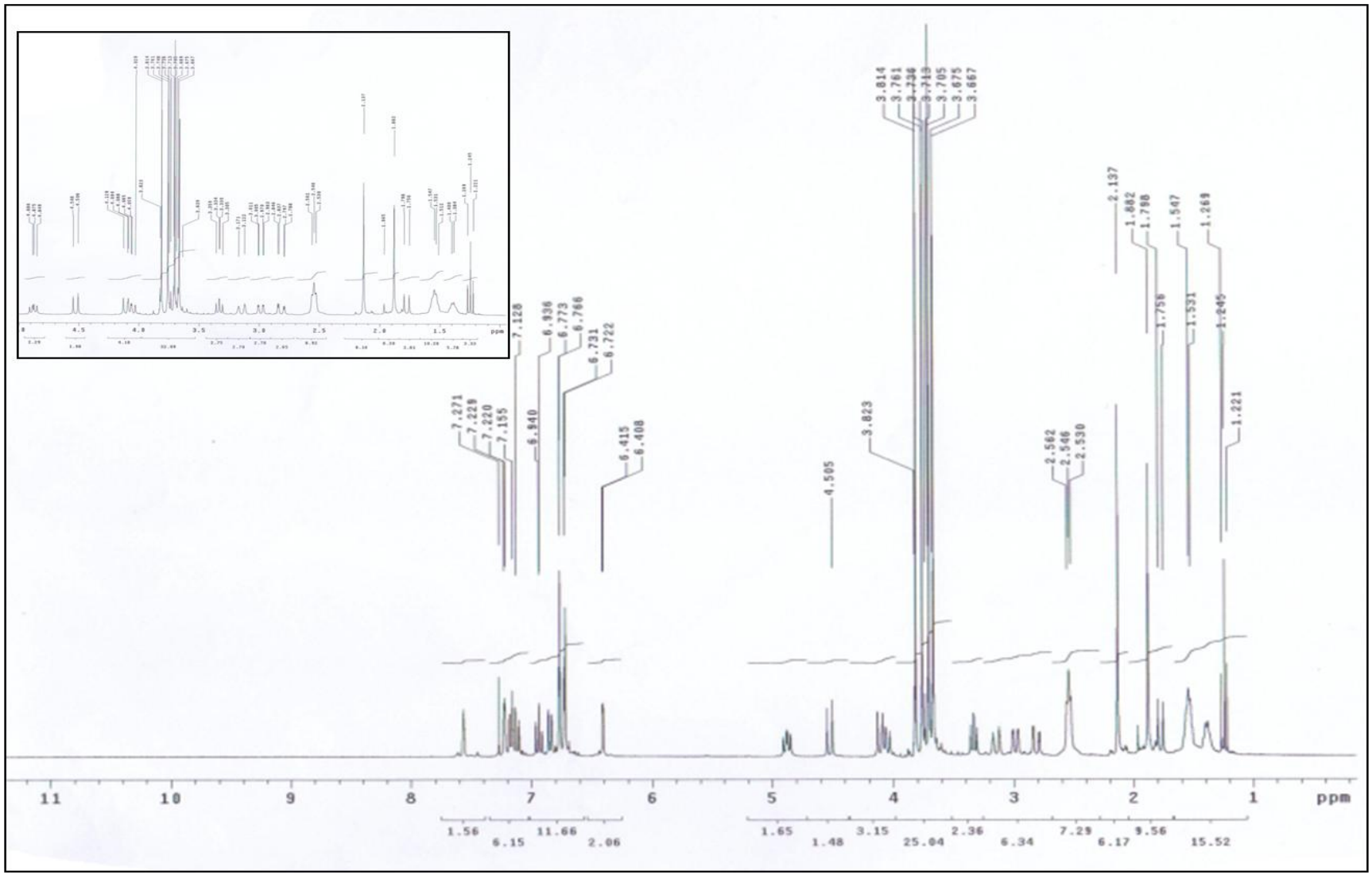


Figure S92. ^{1}H-NMR spectrum of compound **58** in $CDCl_3$.

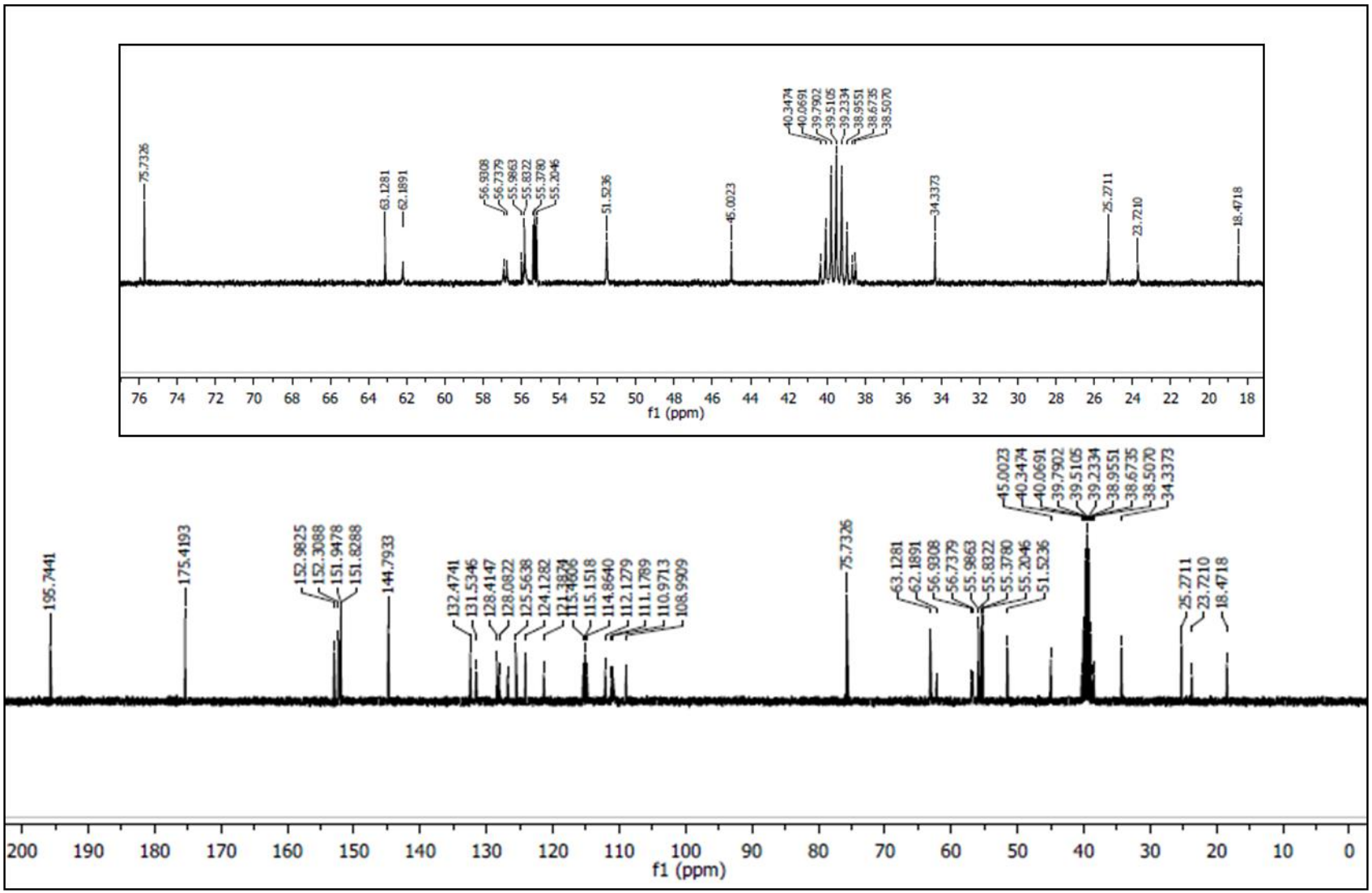


Figure S93. ^{13}C-NMR spectrum of compound **58** in DMSO-d_6.

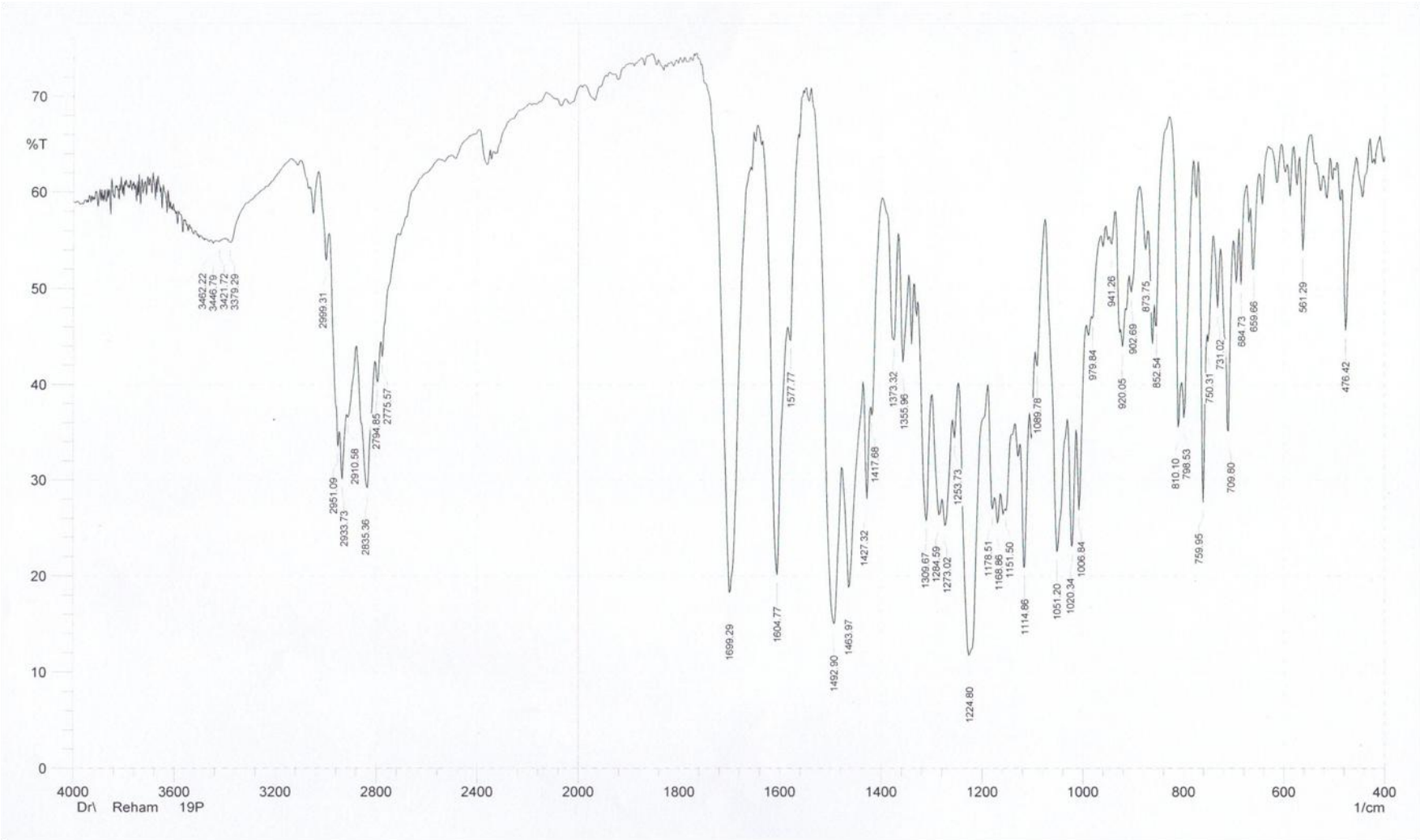


Figure S94. IR spectrum of compound **59** (KBr pellet).

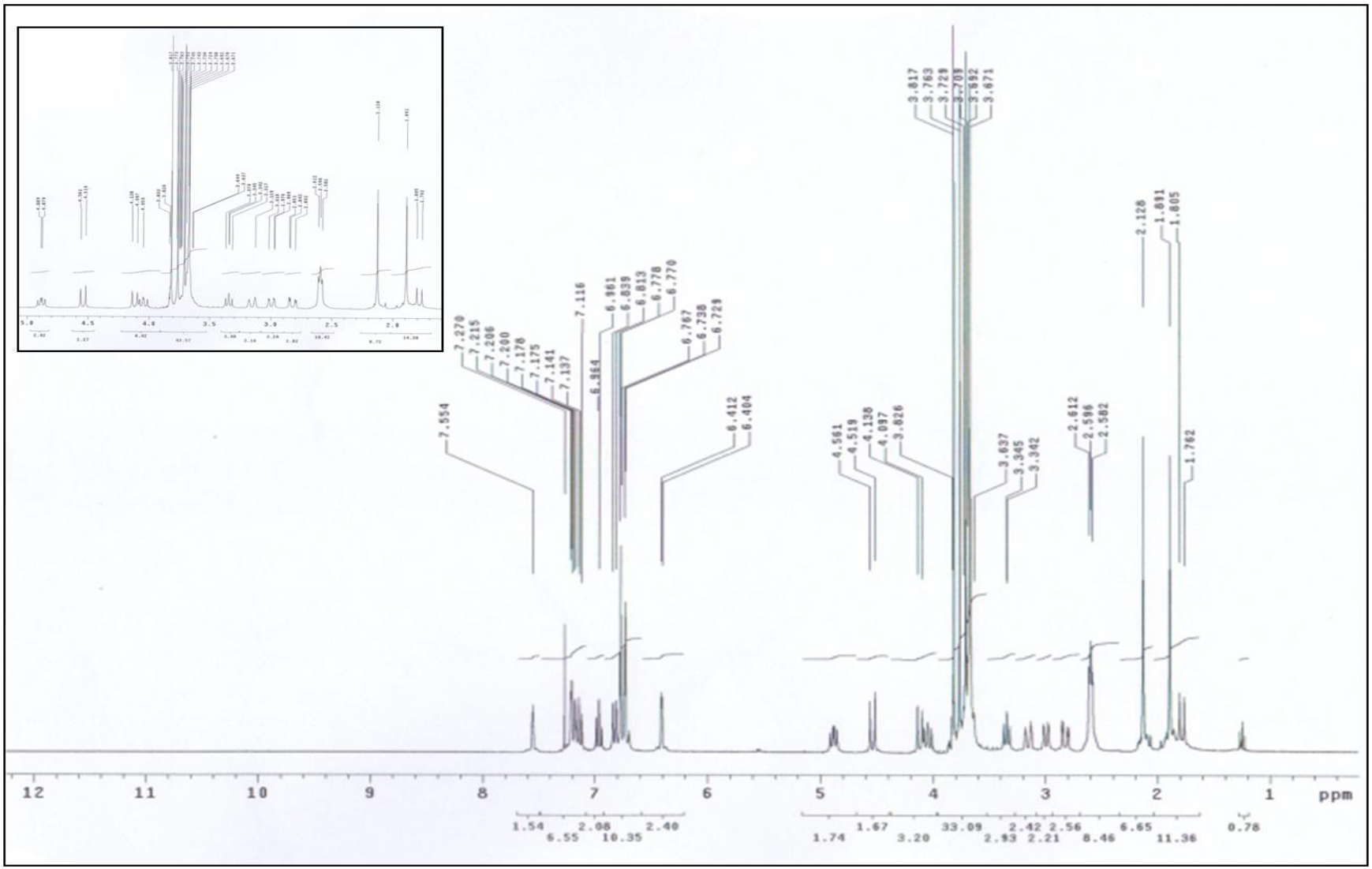


Figure S95. ^{1}H-NMR spectrum of compound **59** in $CDCl_3$.

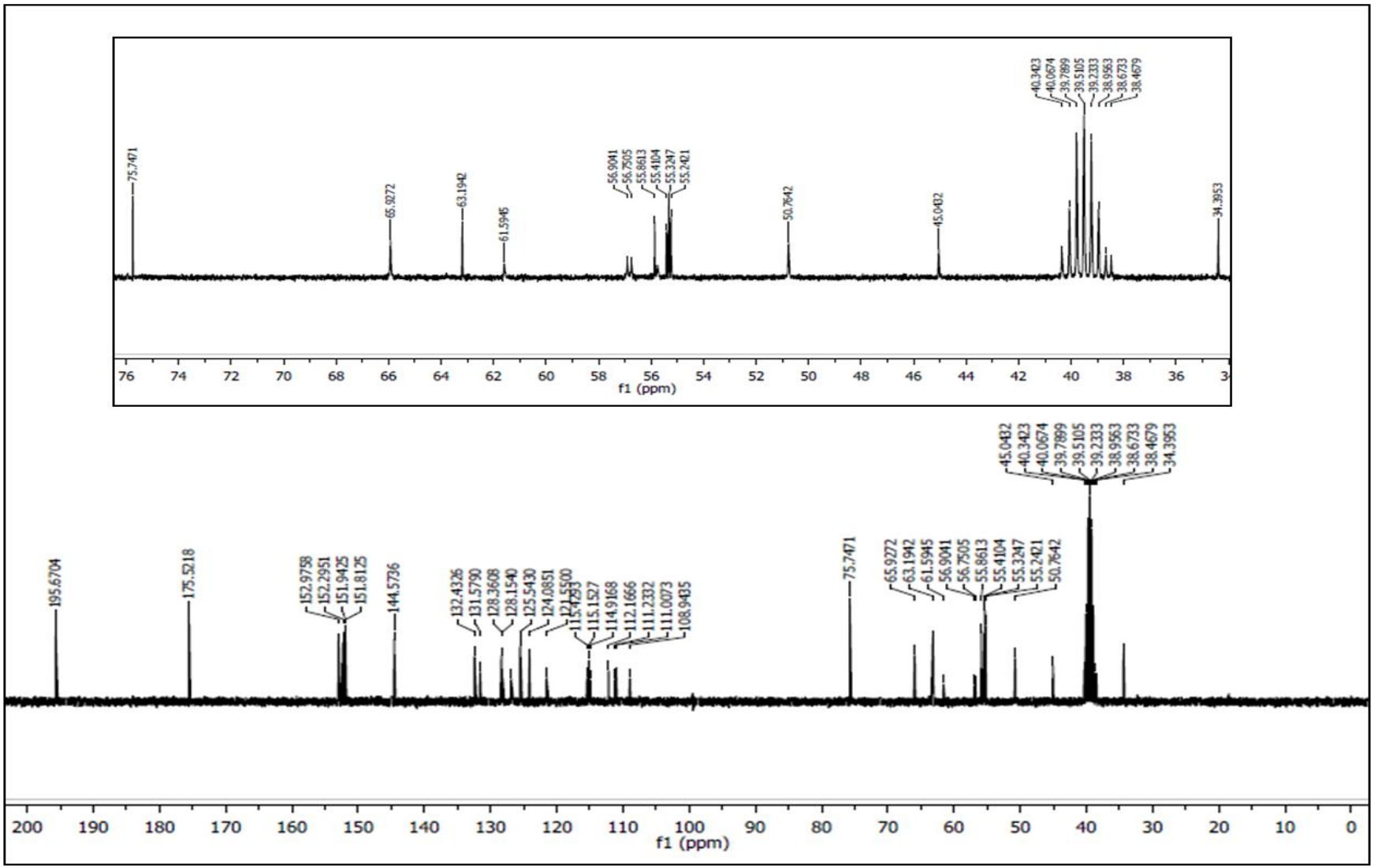


Figure S96. ^{13}C-NMR spectrum of compound **59** in DMSO-d_6.

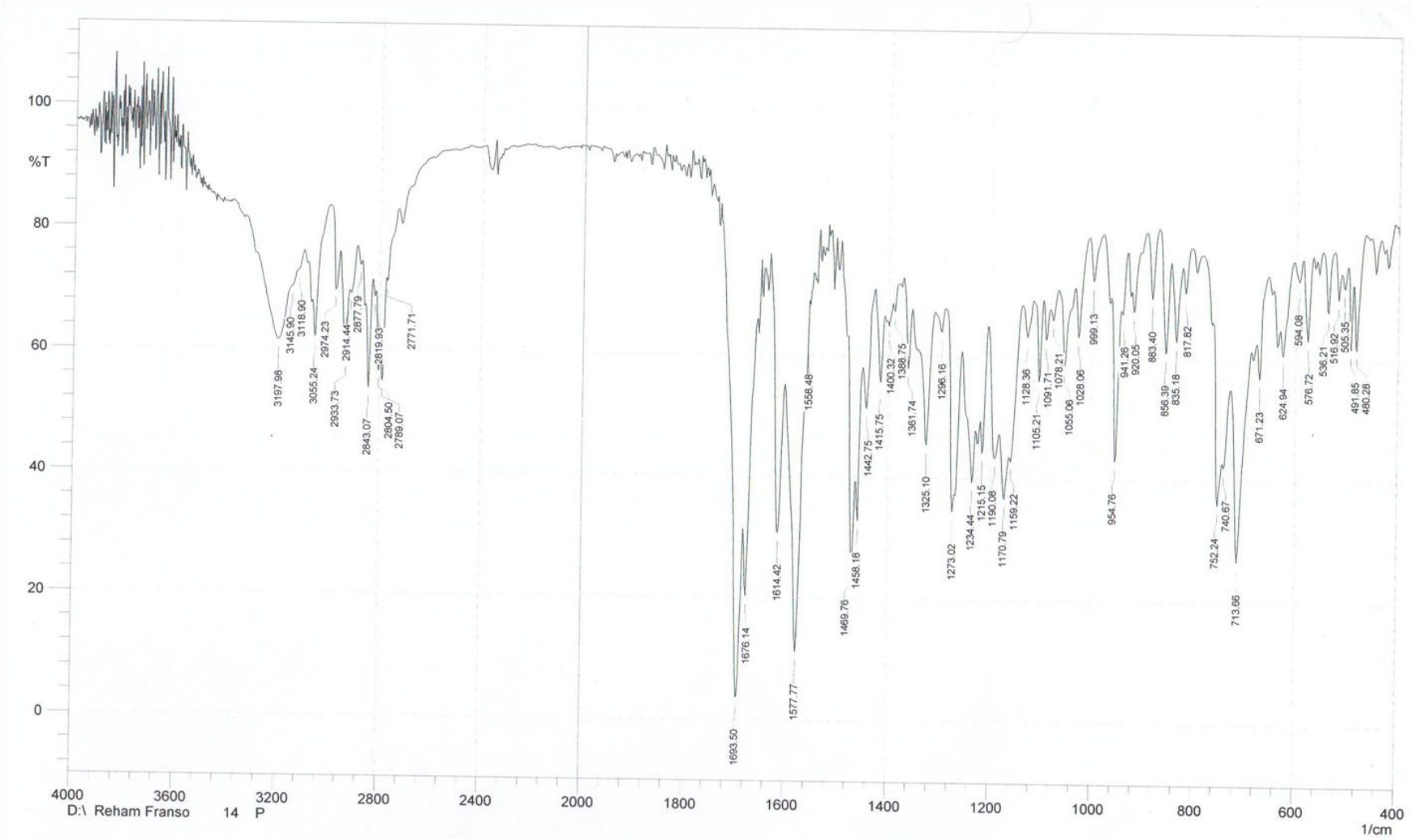


Figure S97. IR spectrum of compound **60** (KBr pellet).

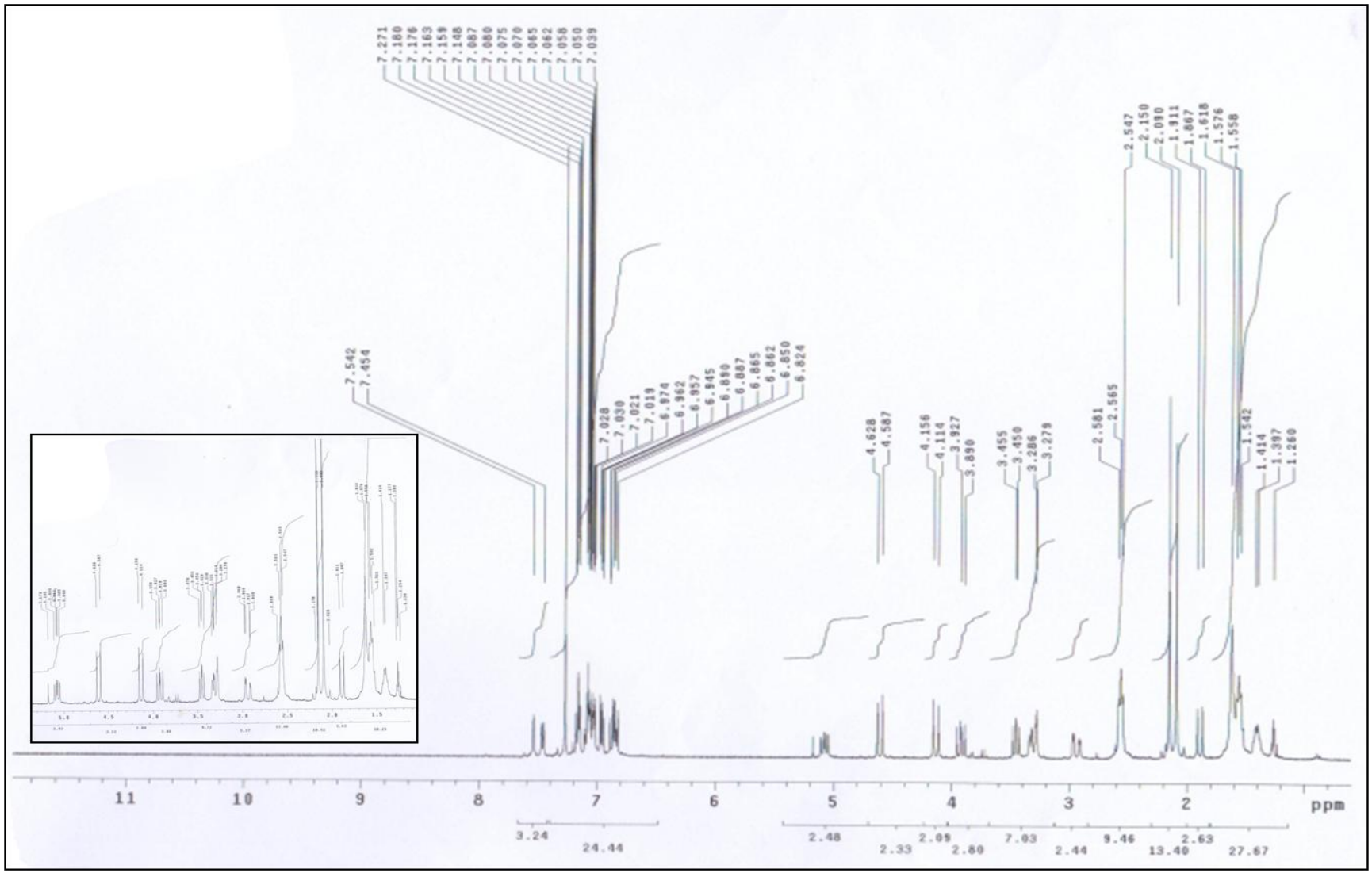


Figure S98. ^{1}H-NMR spectrum of compound **60** in $CDCl_3$.

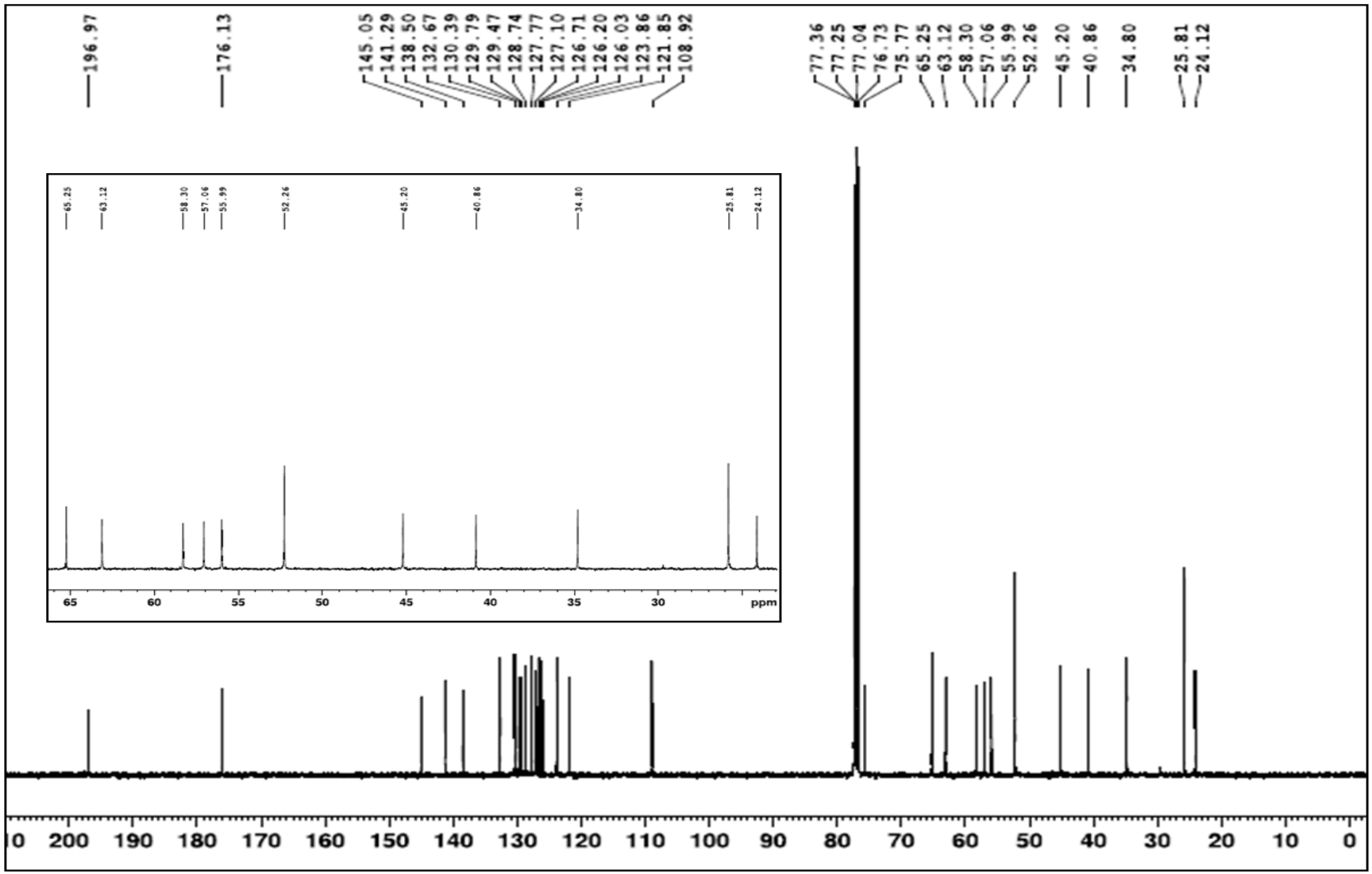


Figure S99. ^{13}C-NMR spectrum of compound **60** in $CDCl_3$.

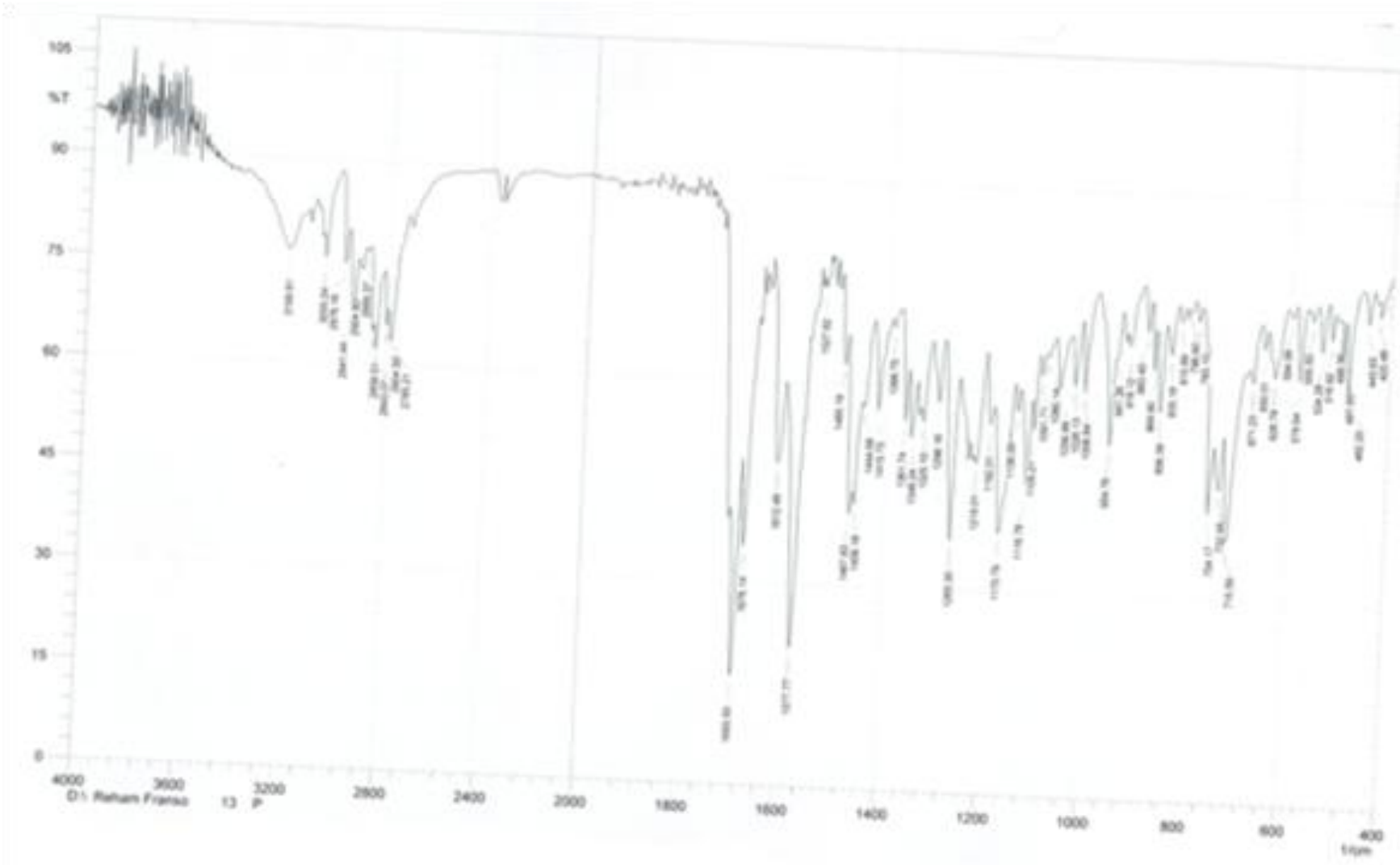


Figure S100. IR spectrum of compound **61** (KBr pellet).

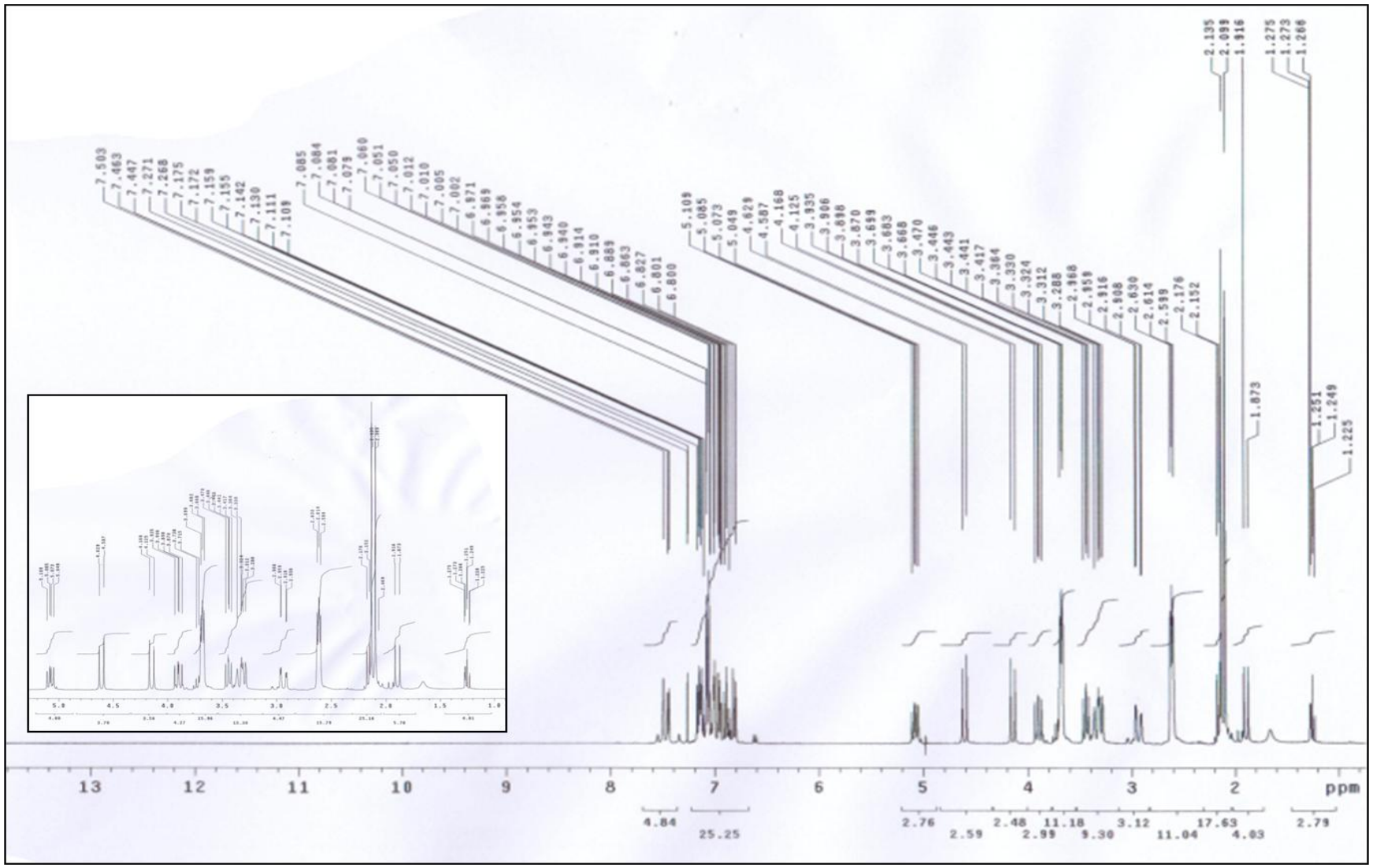


Figure S101. ^{1}H-NMR spectrum of compound **61** in $CDCl_3$.

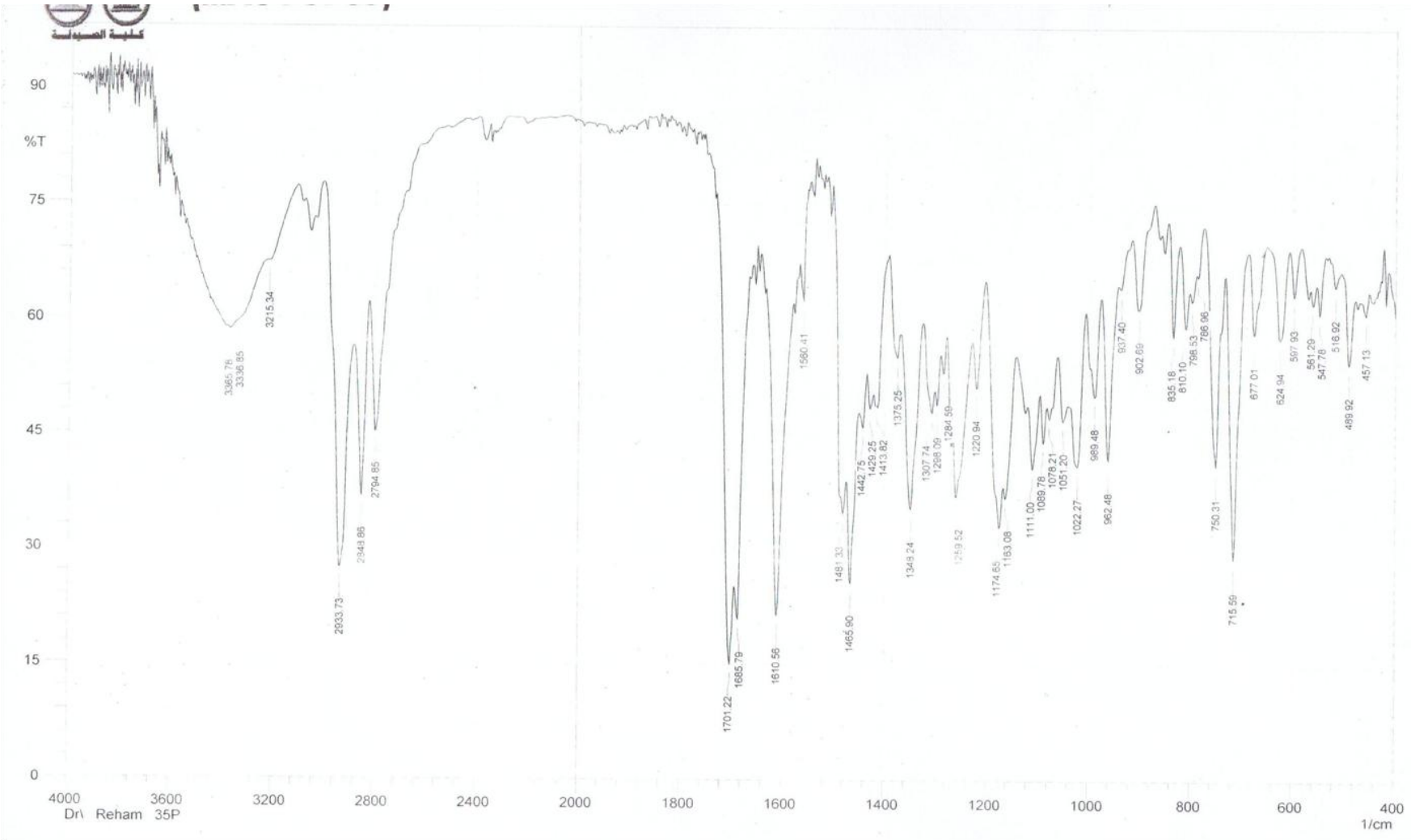


Figure S102. IR spectrum of compound **62** (KBr pellet).

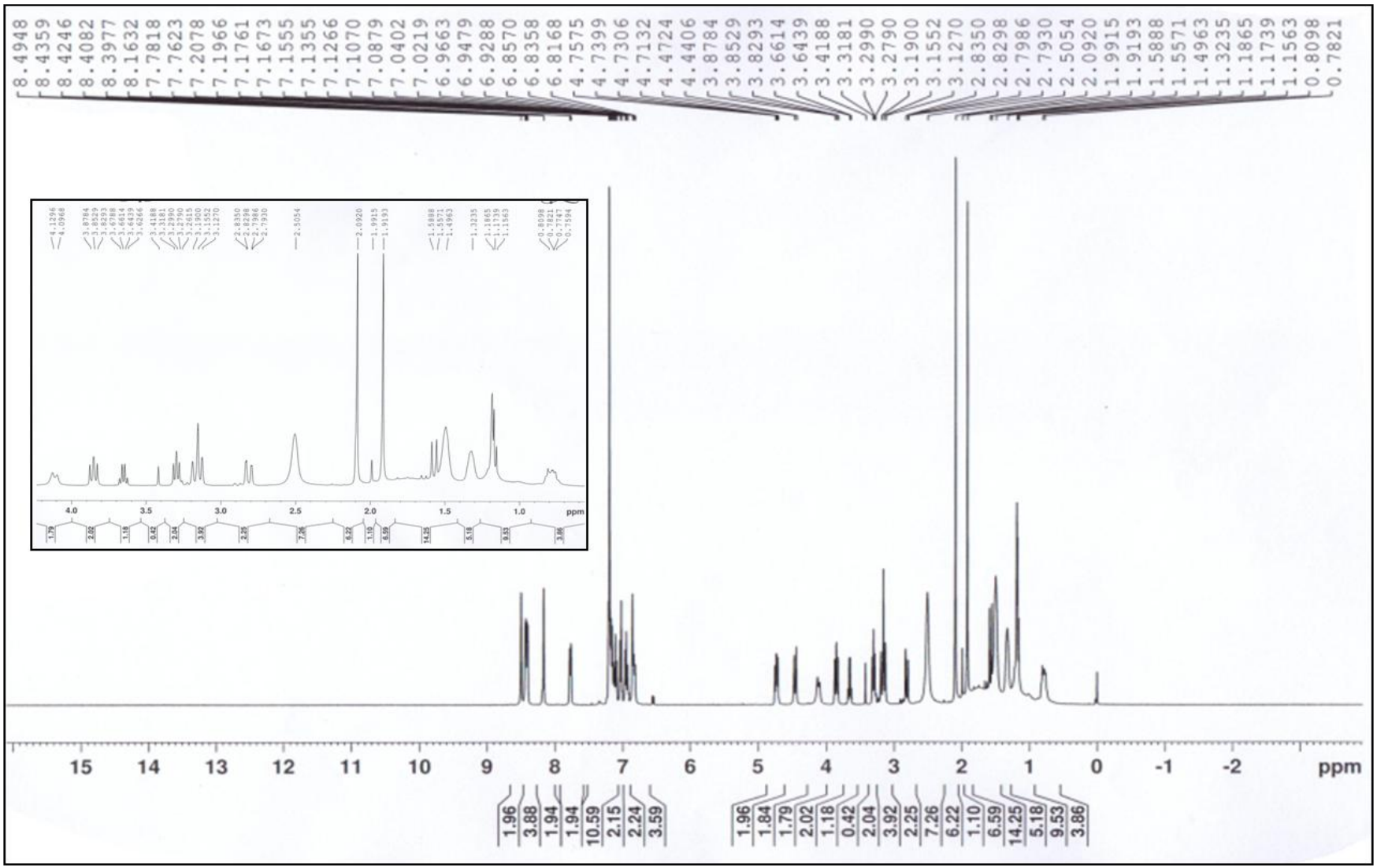


Figure S103. ^{1}H-NMR spectrum of compound **62** in $CDCl_3$.

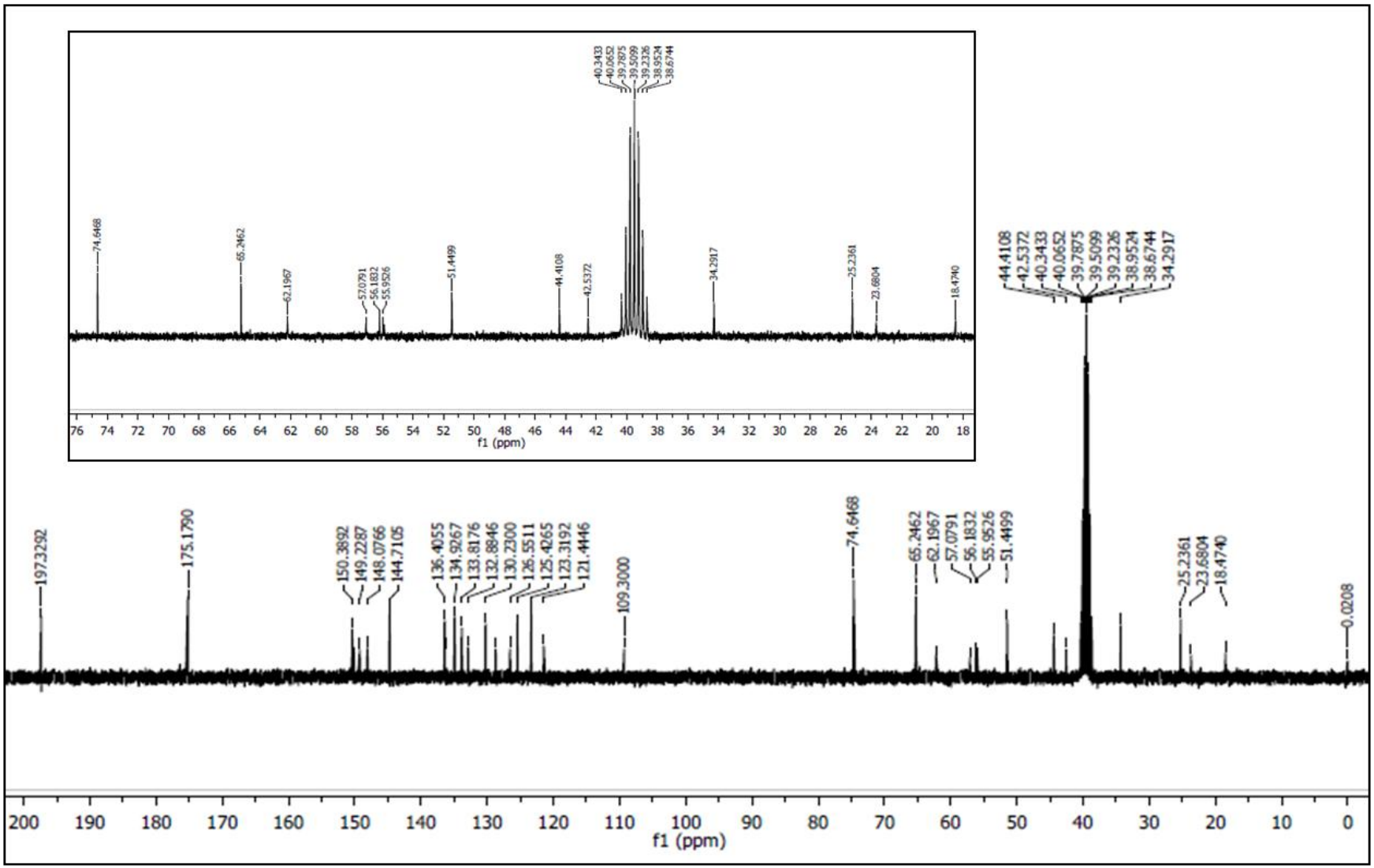


Figure S104. ^{13}C-NMR spectrum of compound **62** in DMSO-d_6.

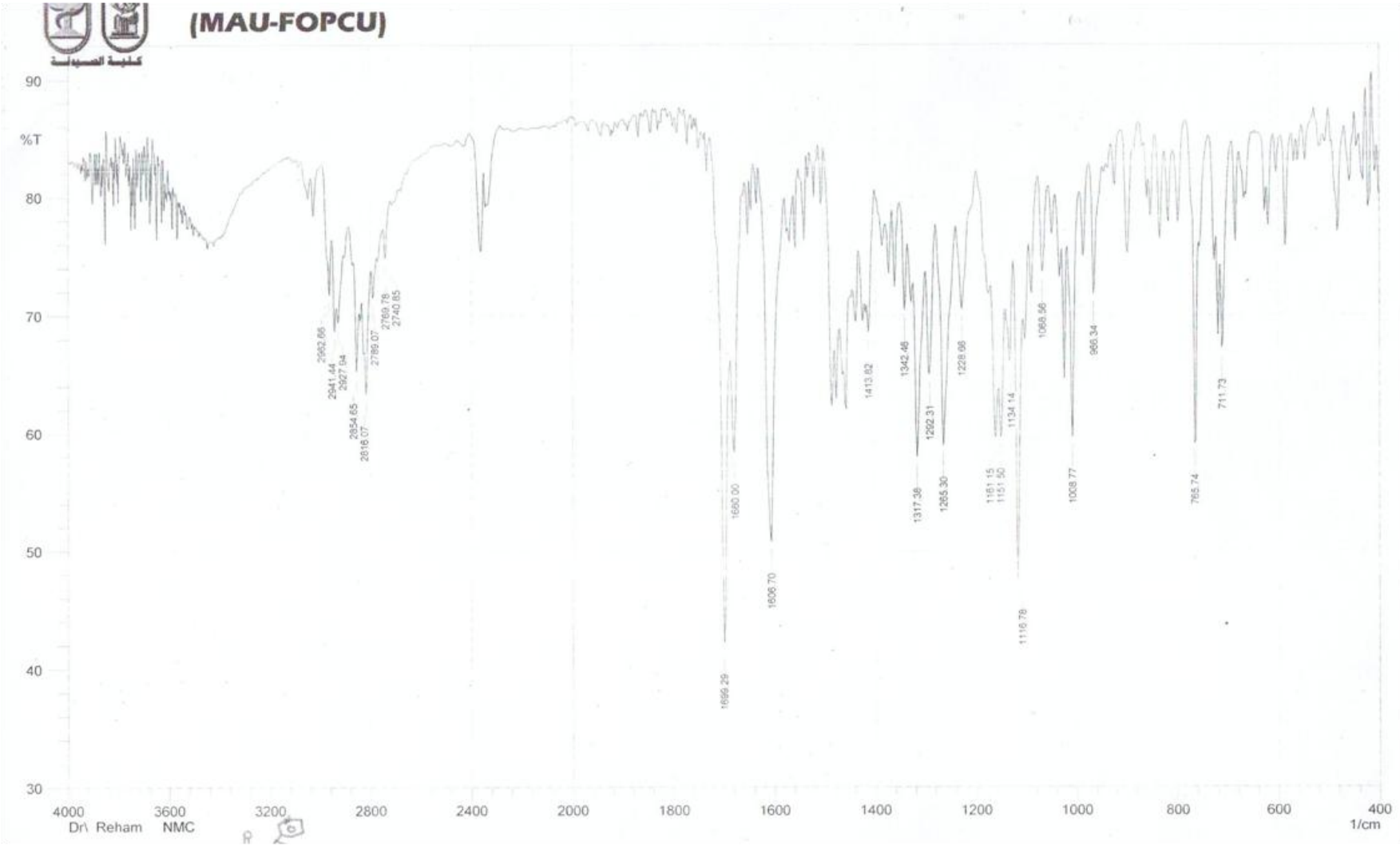


Figure S105. IR spectrum of compound **63** (KBr pellet).

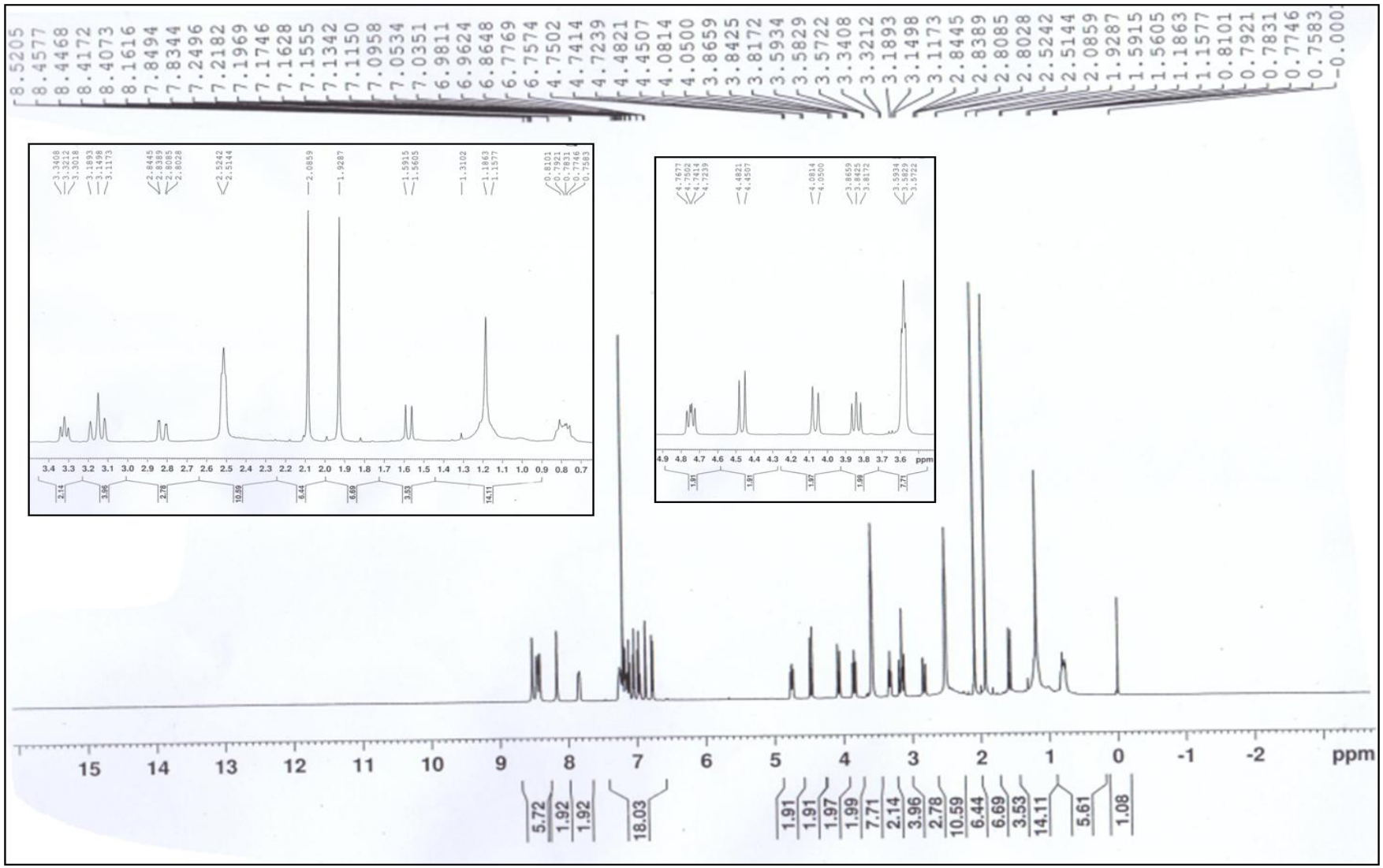


Figure S106. ^{1}H-NMR spectrum of compound **63** in $CDCl_3$.

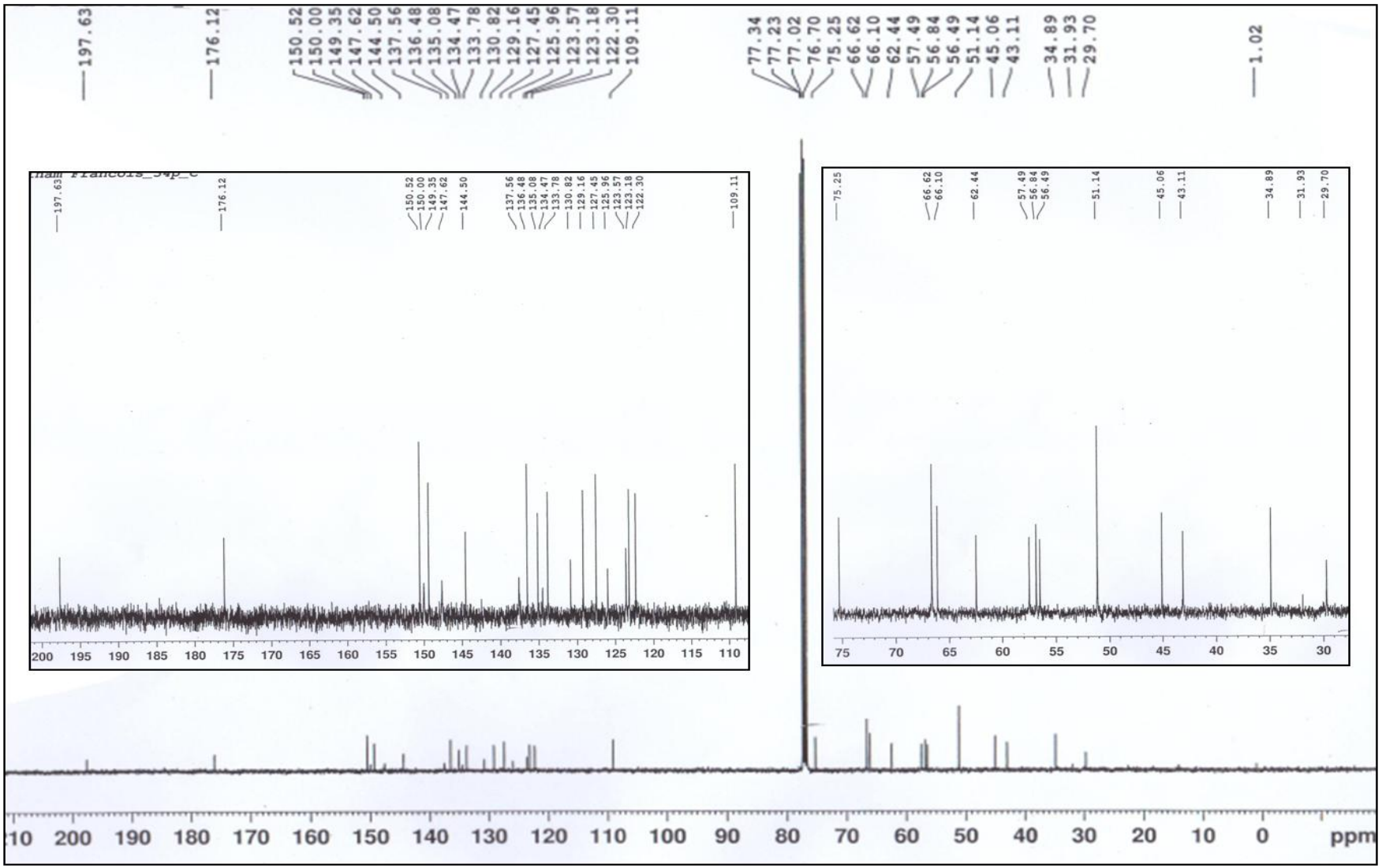


Figure S107. ^{13}C-NMR spectrum of compound **63** in $CDCl_3$.

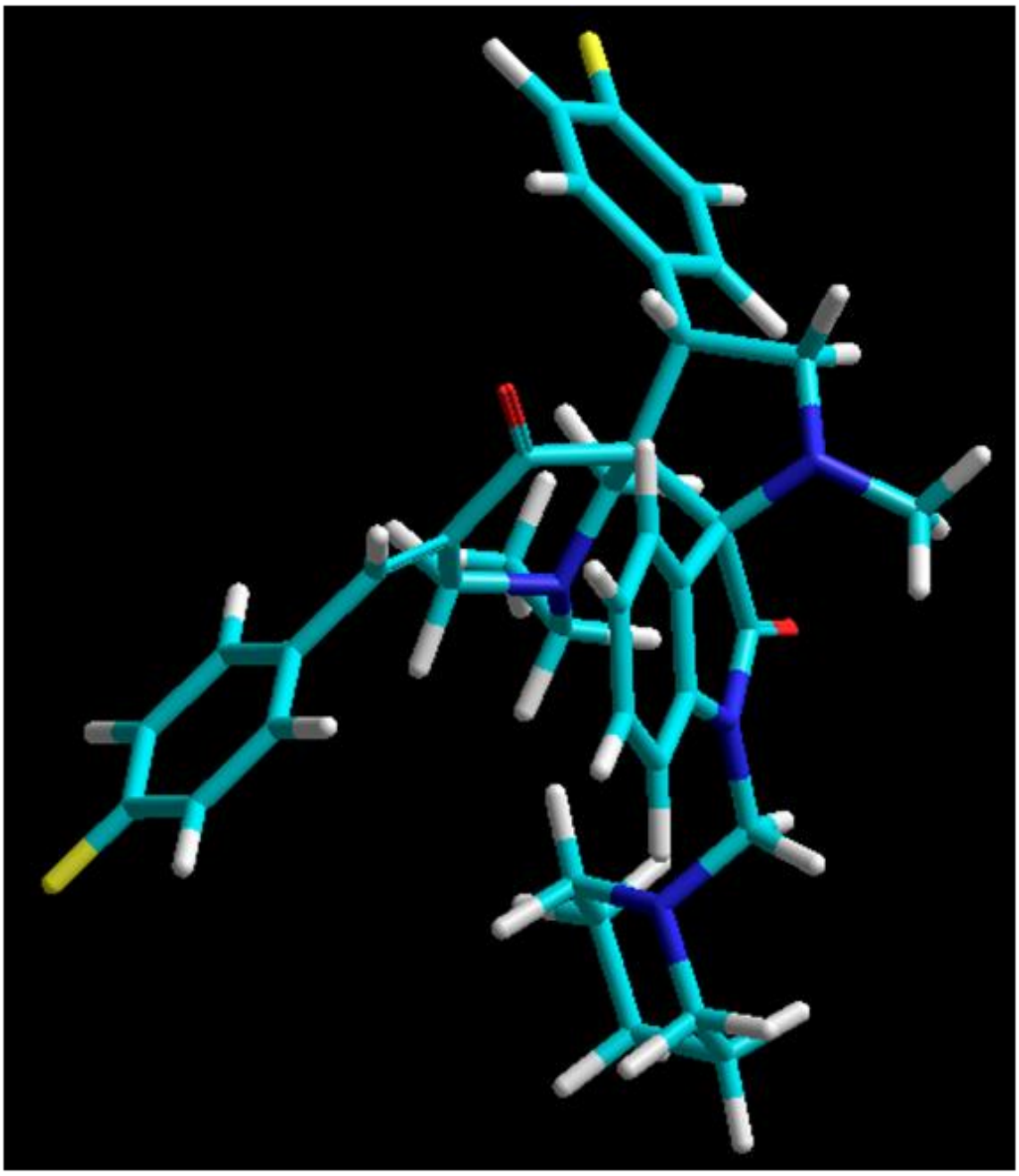


Figure 108. A projection of the optimized structure of compound **46** by semi-empirical AM1.

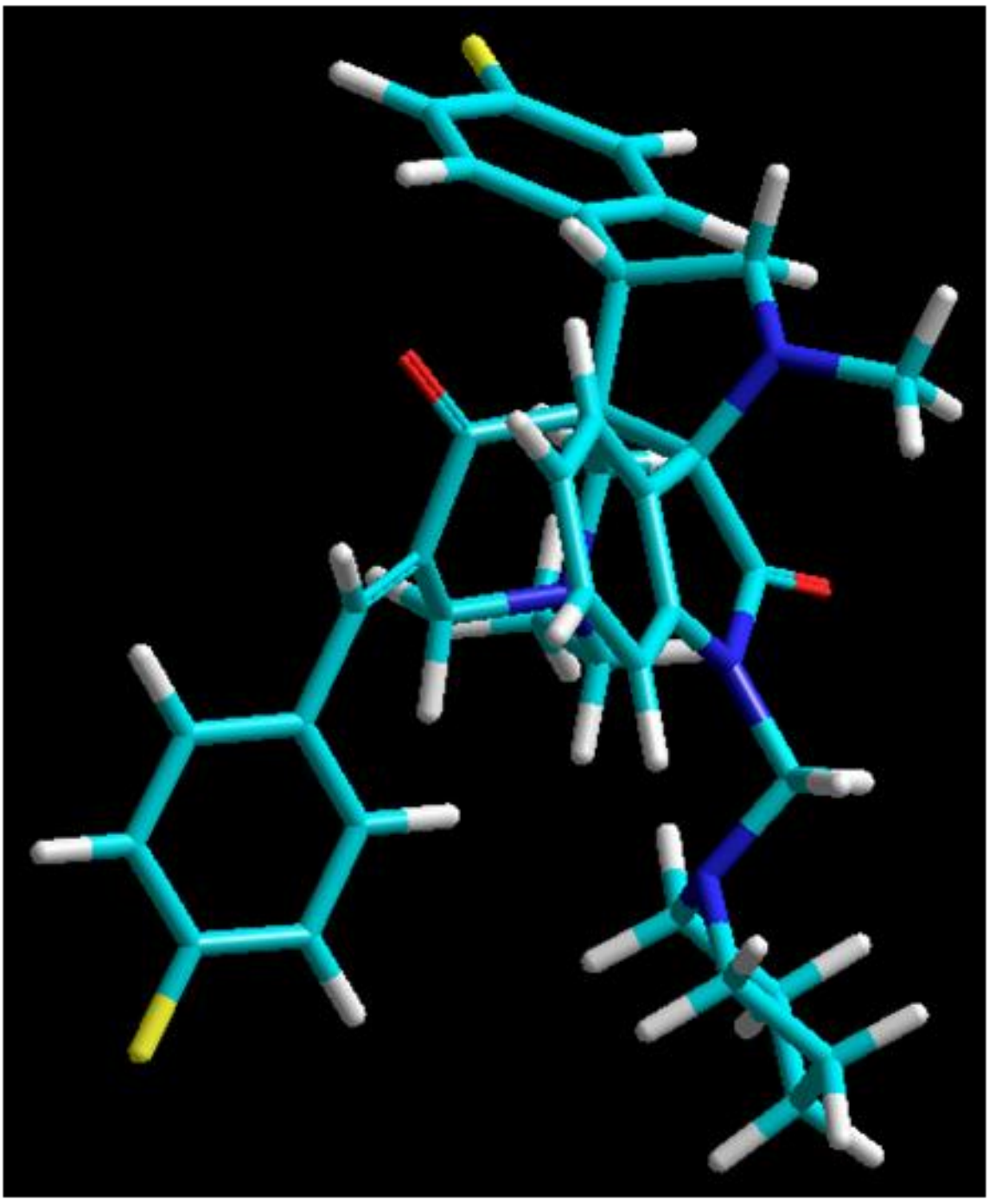


Figure 109. A projection of the optimized structure of compound **46** by semi-empirical PM3.

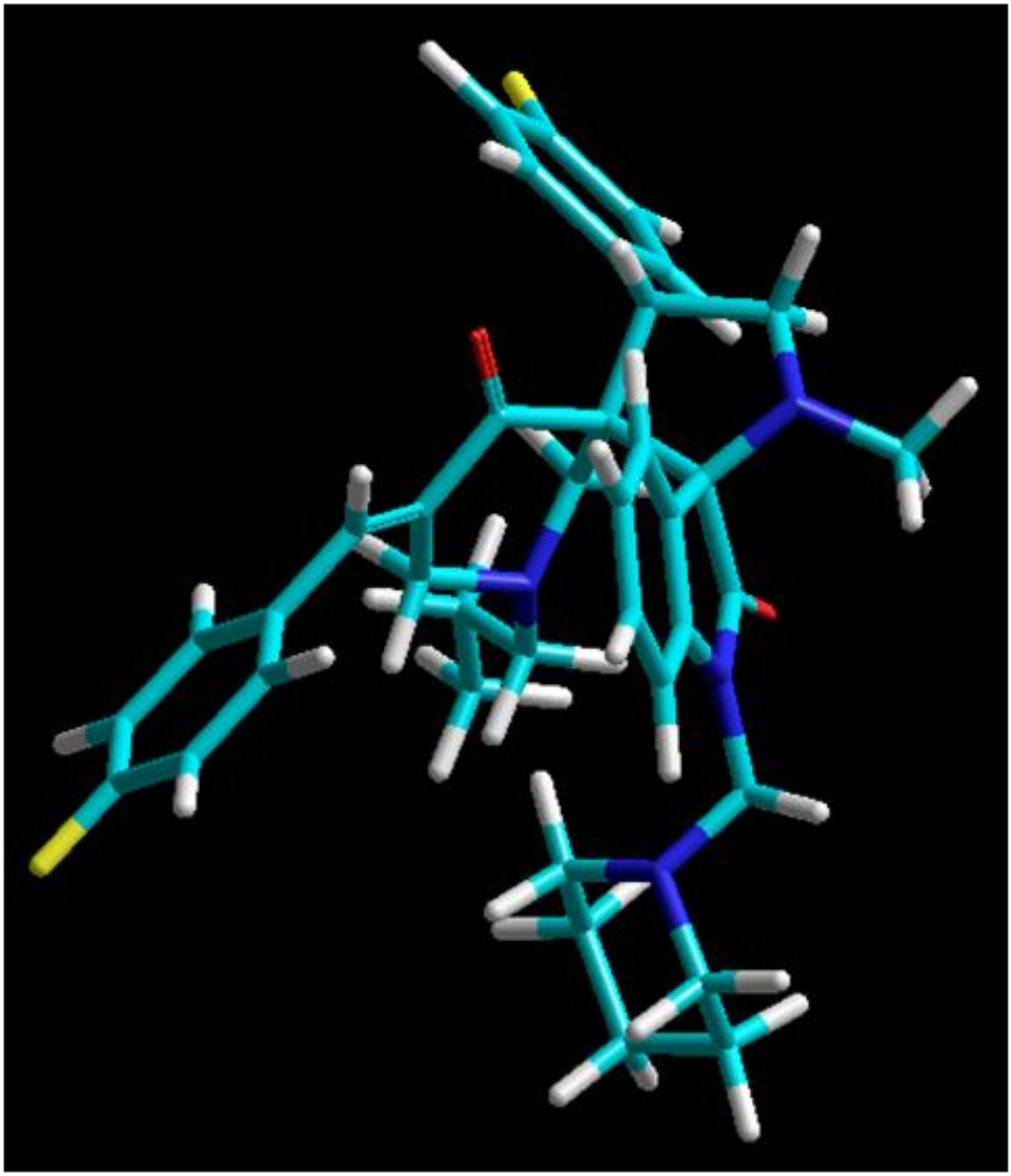


Figure 110. A projection of the optimized structure of compound **48** by semi-empirical AM1.

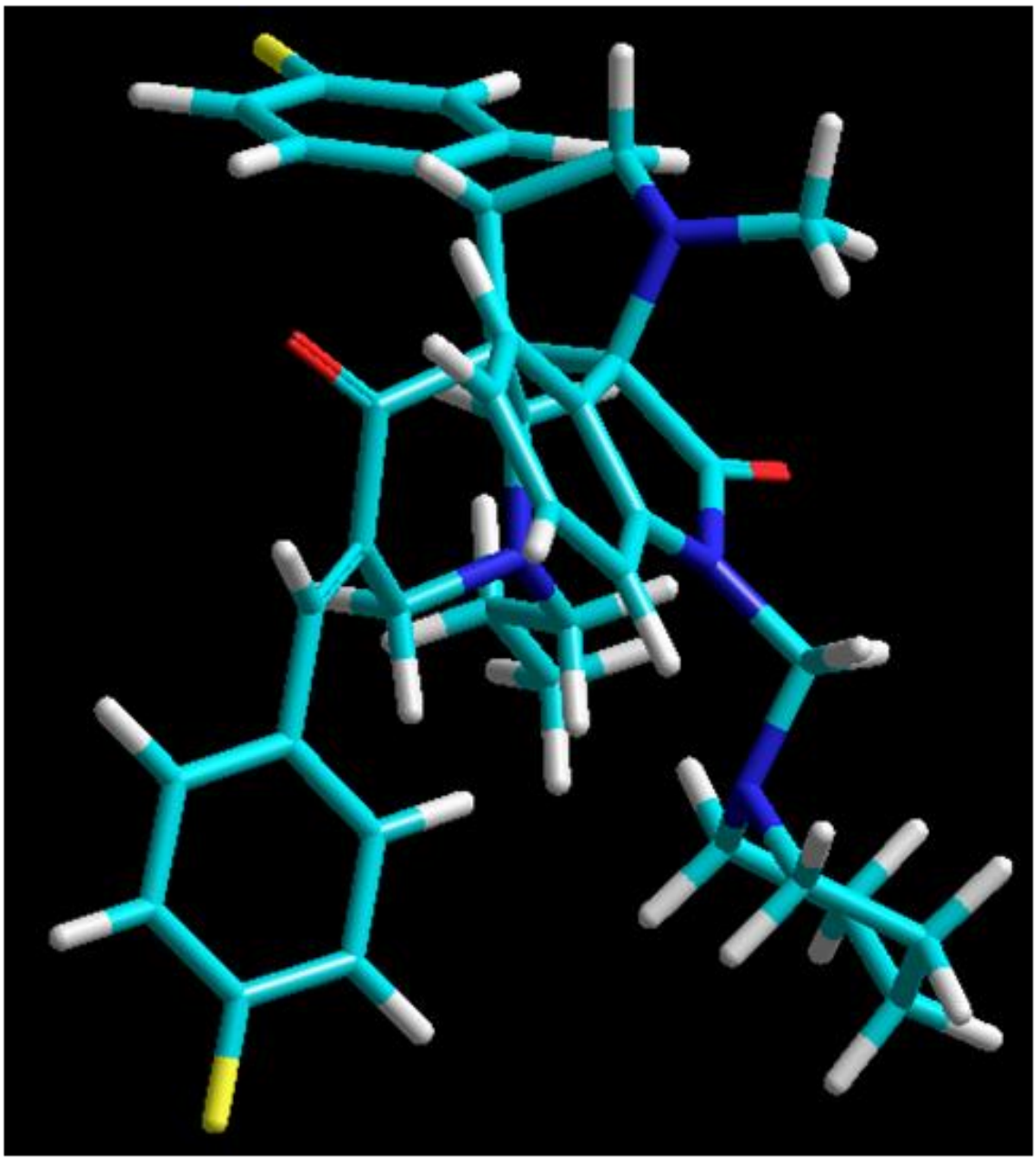


Figure 111. A projection of the optimized structure of compound **48** by semi-empirical PM3.

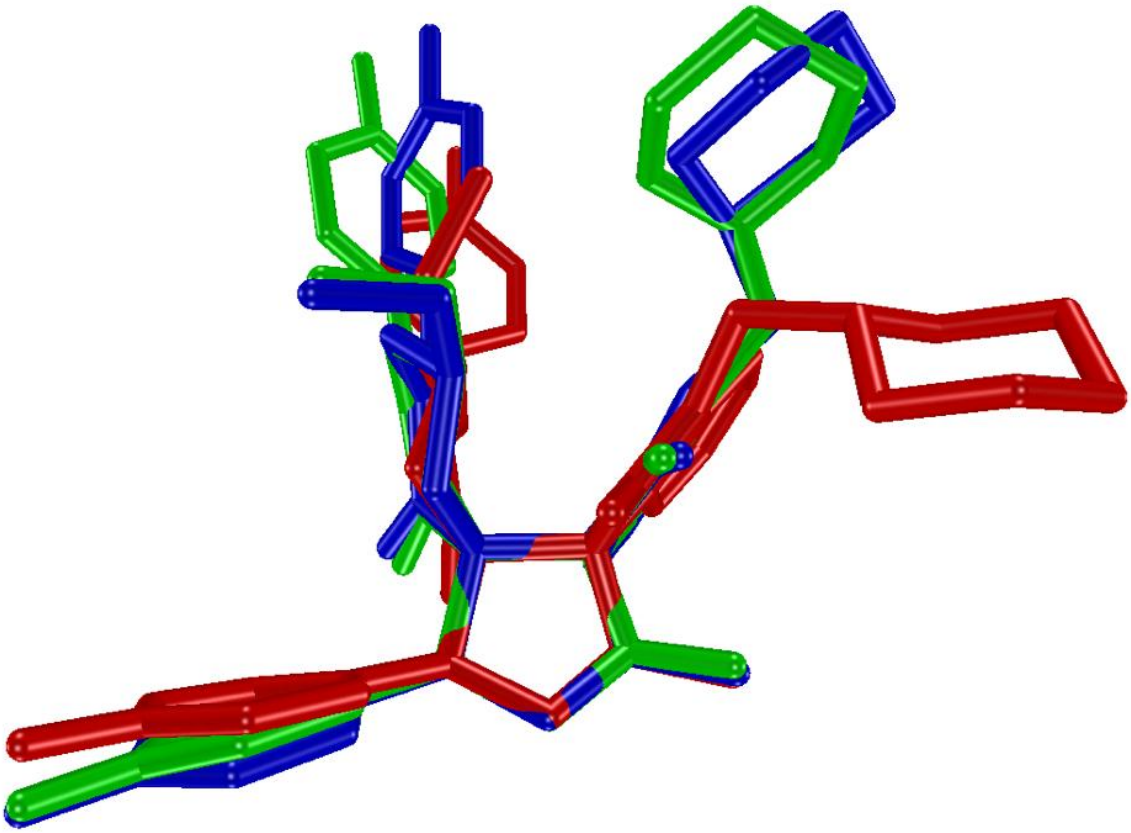


Figure 112. Overlay diagram of compound **46**, drawn so that the central pyrrolidine rings are overlapped (red, X-ray; green, AM1; and blue, PM3).

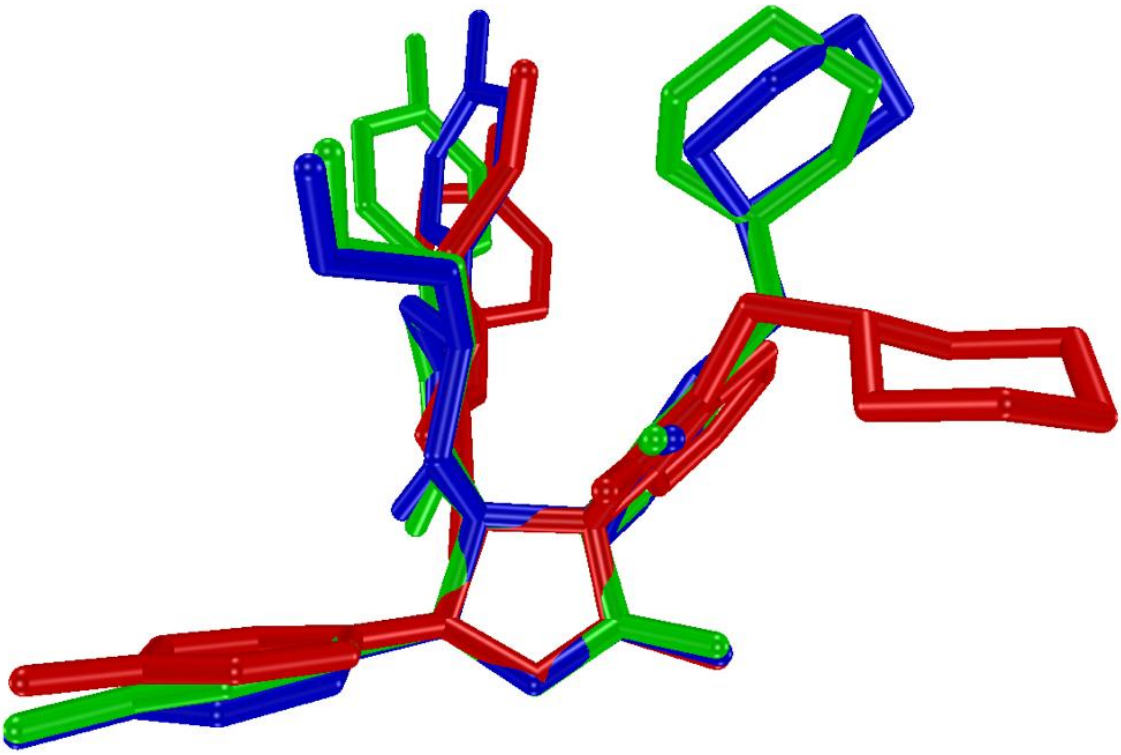
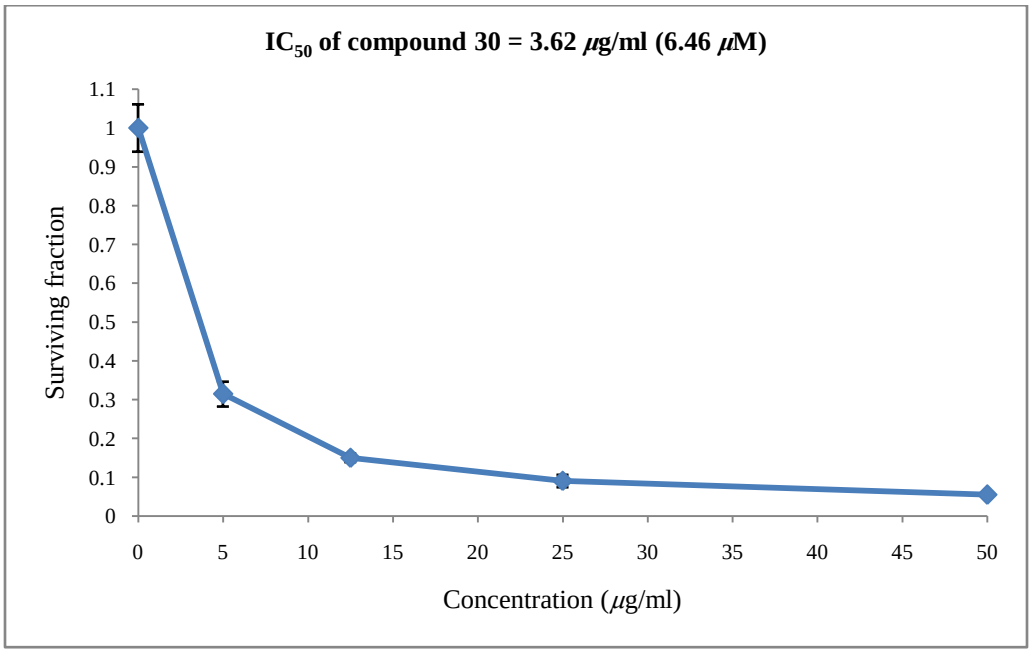
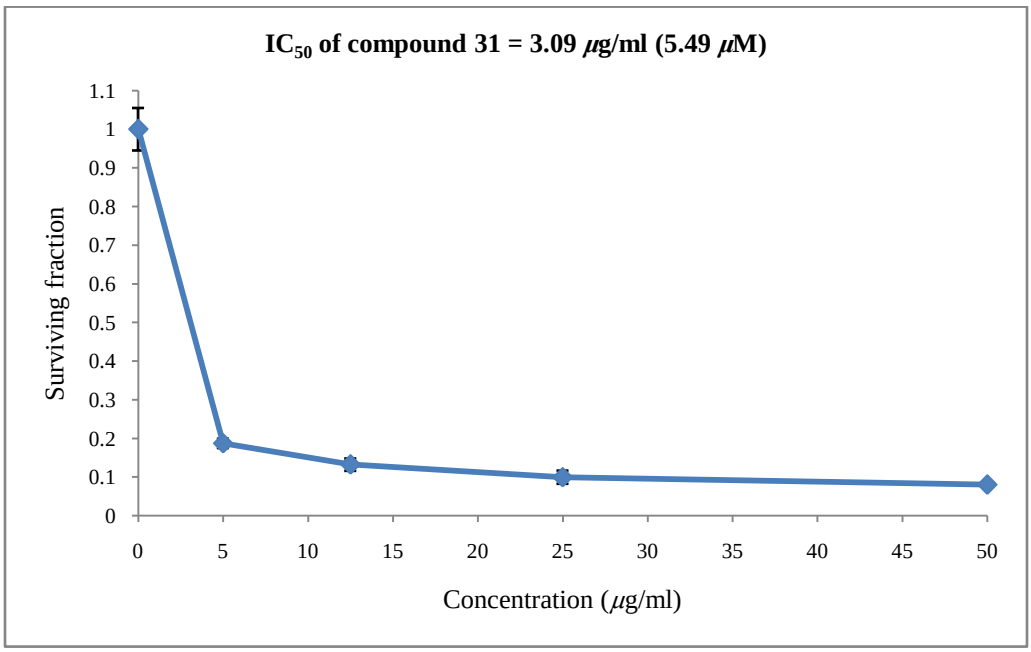
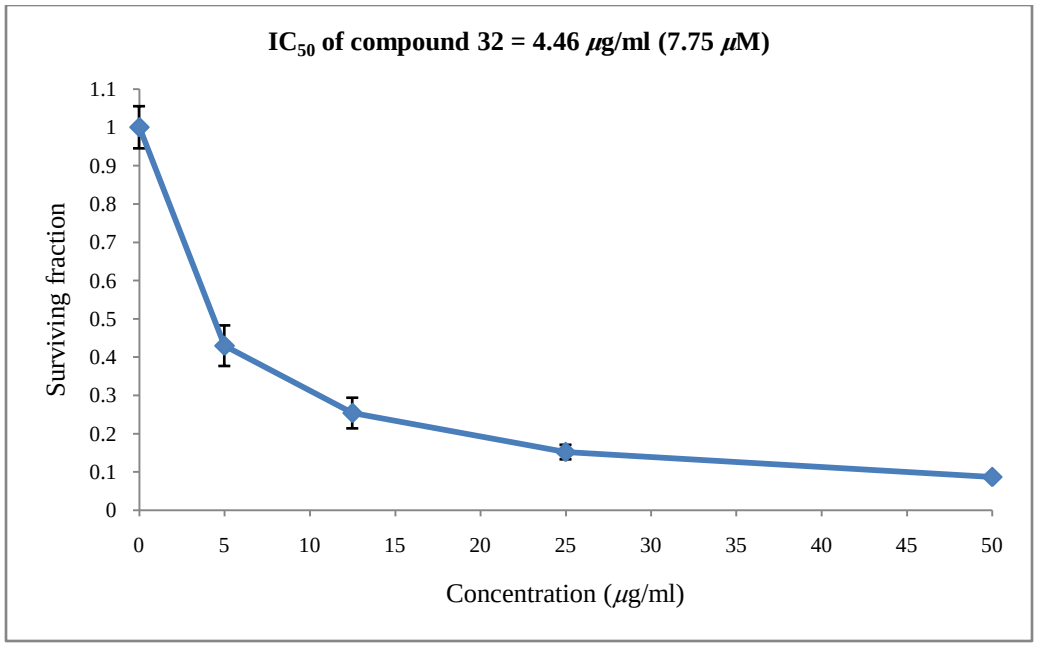
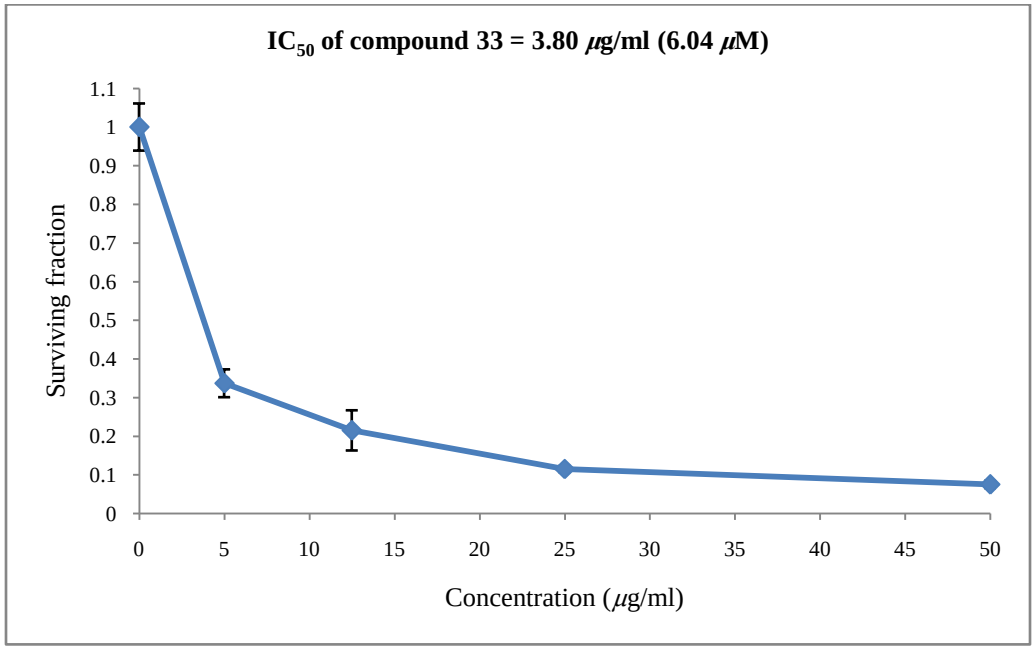


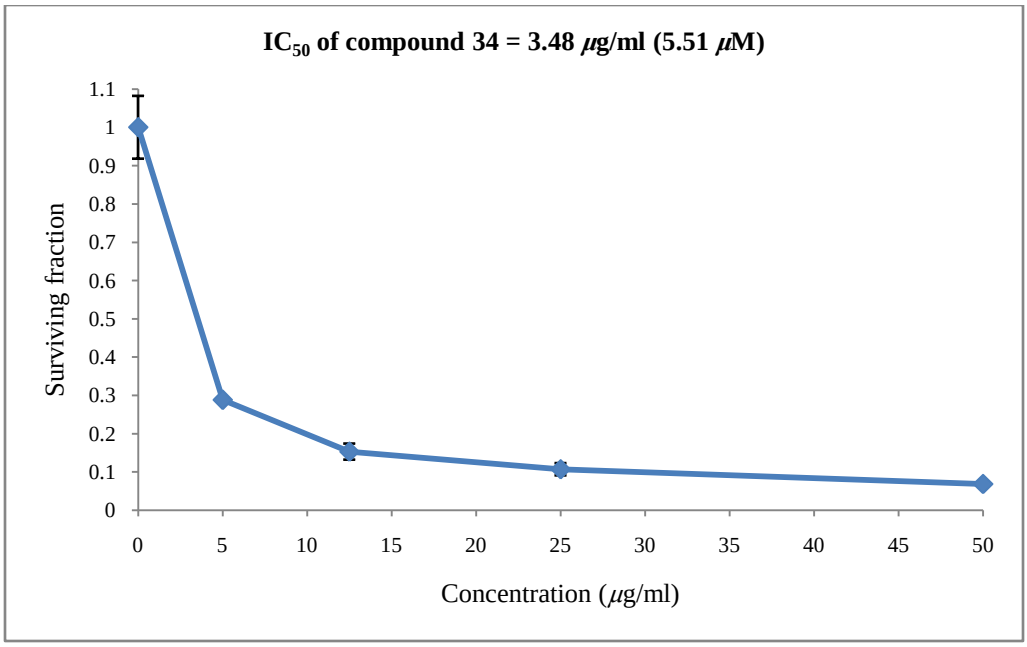
Figure 113. Overlay diagram of compound **48**, drawn so that the central pyrrolidine rings are overlapped (red, X-ray; green, AM1; and blue, PM3).

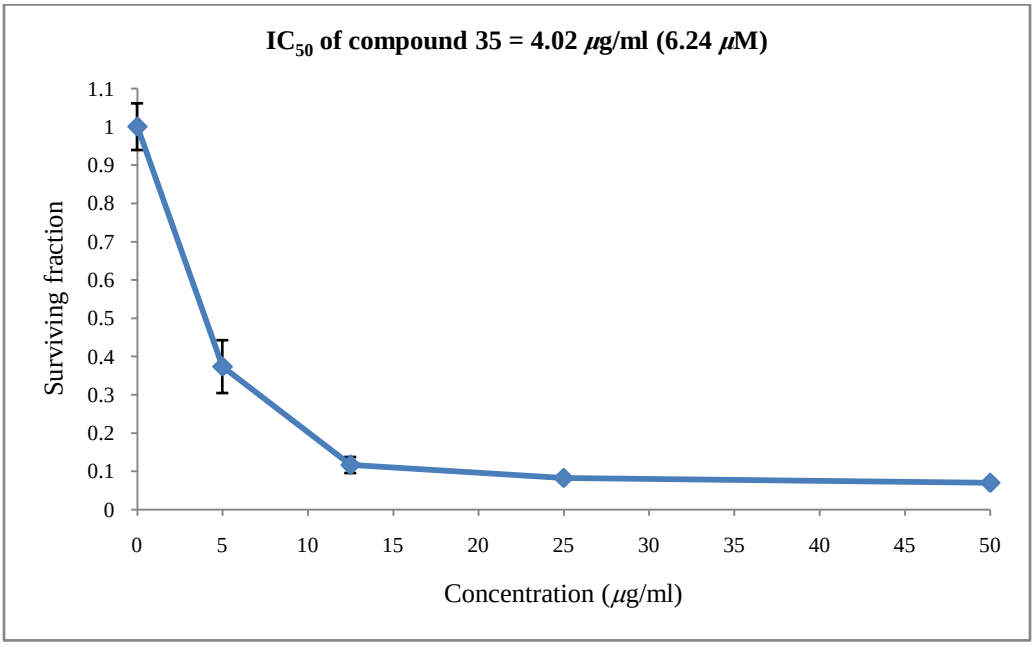

IC50 of compound 30 = 3.62 μg/ml (6.46 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

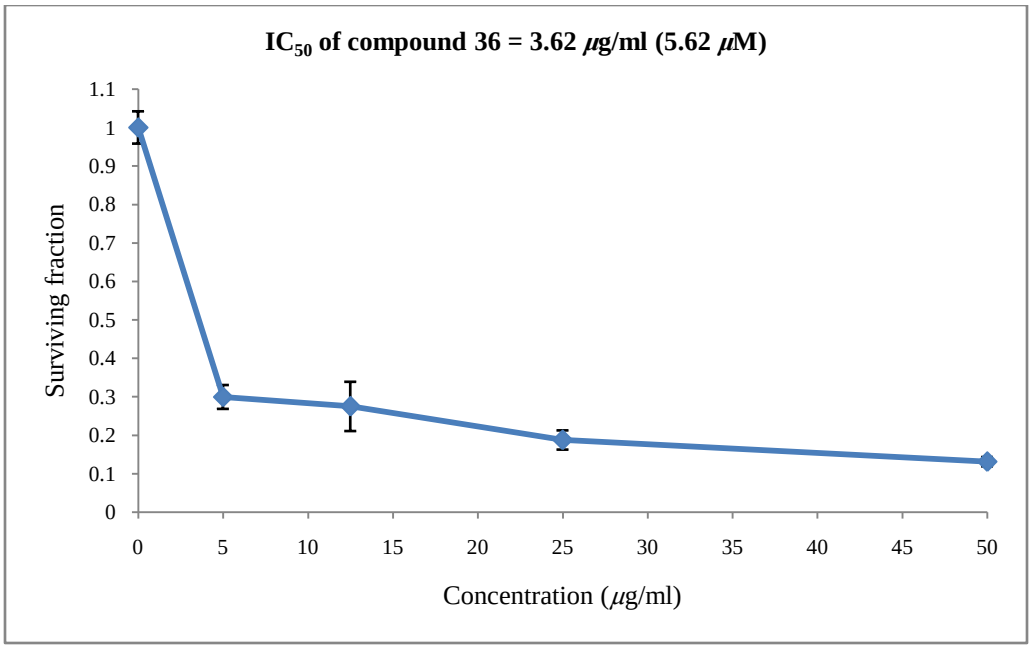

IC50 of compound 31 = 3.09 μg/ml (5.49 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

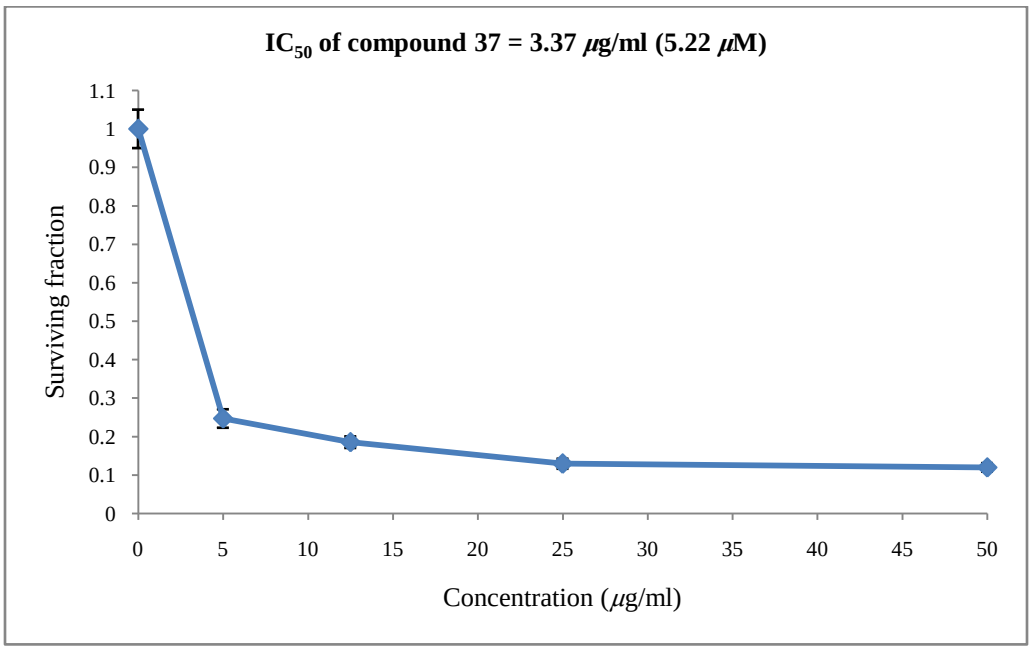

IC50 of compound 32 = 4.46 μg/ml (7.75 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

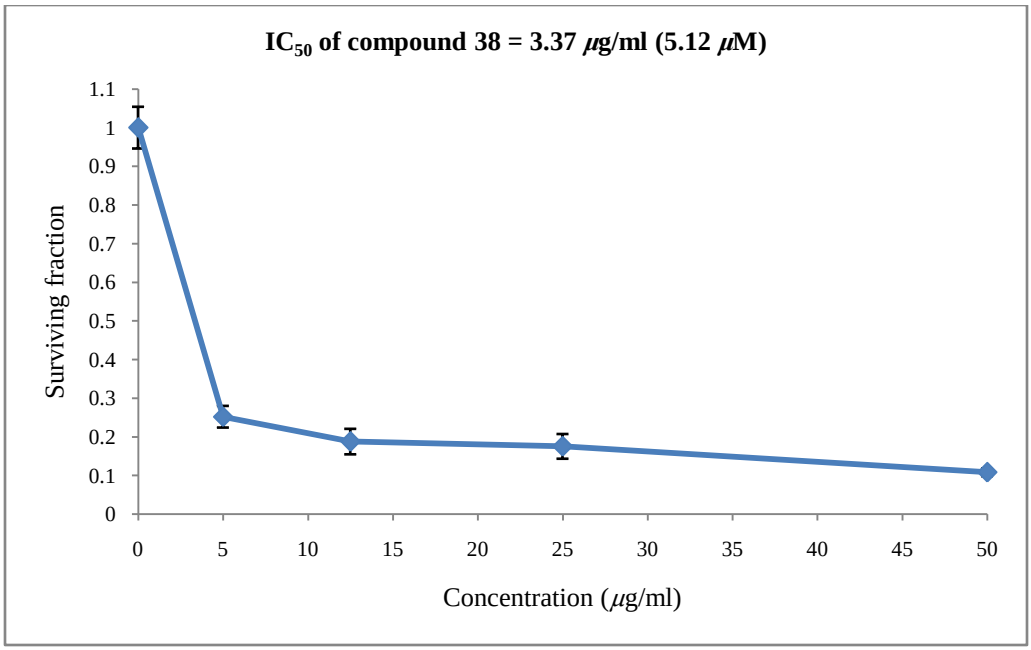

IC50 of compound 33 = 3.80 μg/ml (6.04 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

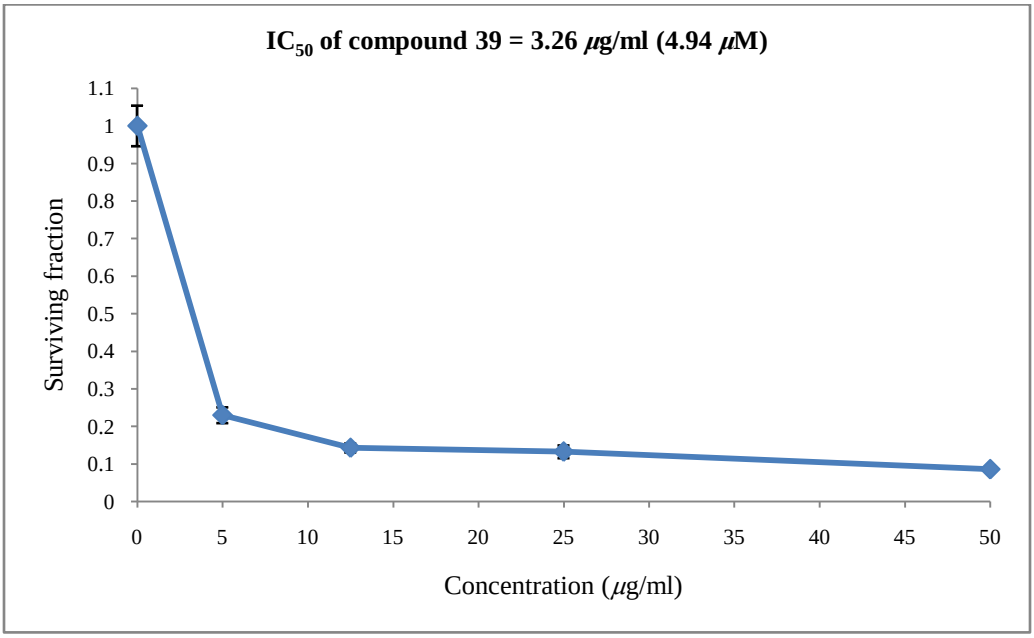

IC50 of compound 34 = 3.48 μg/ml (5.51 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

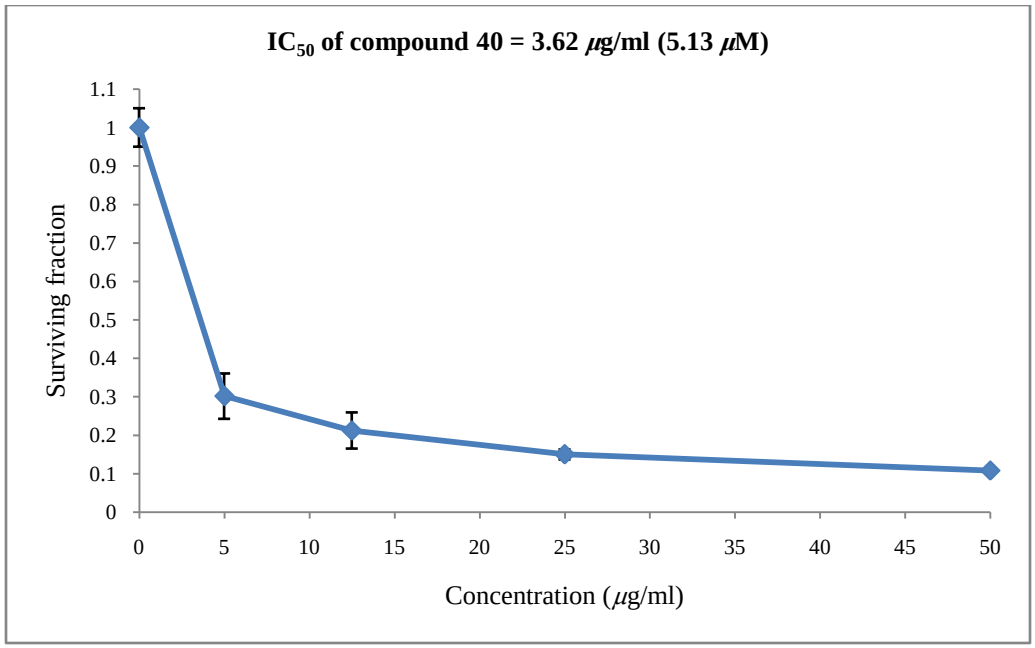

IC50 of compound 35 = 4.02 μg/ml (6.24 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

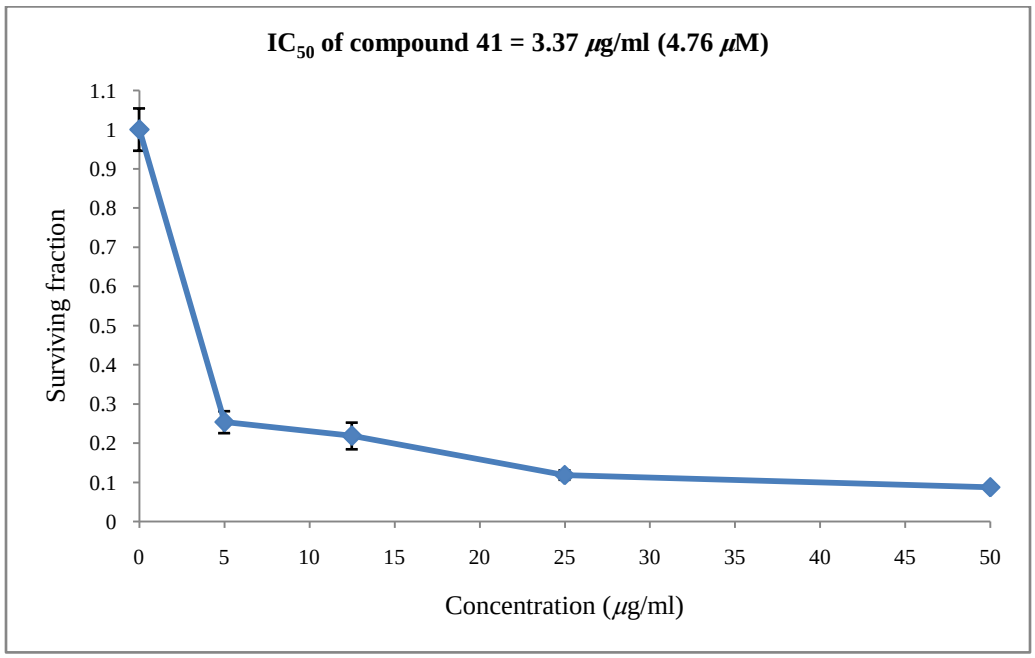

IC50 of compound 36 = 3.62 μg/ml (5.62 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

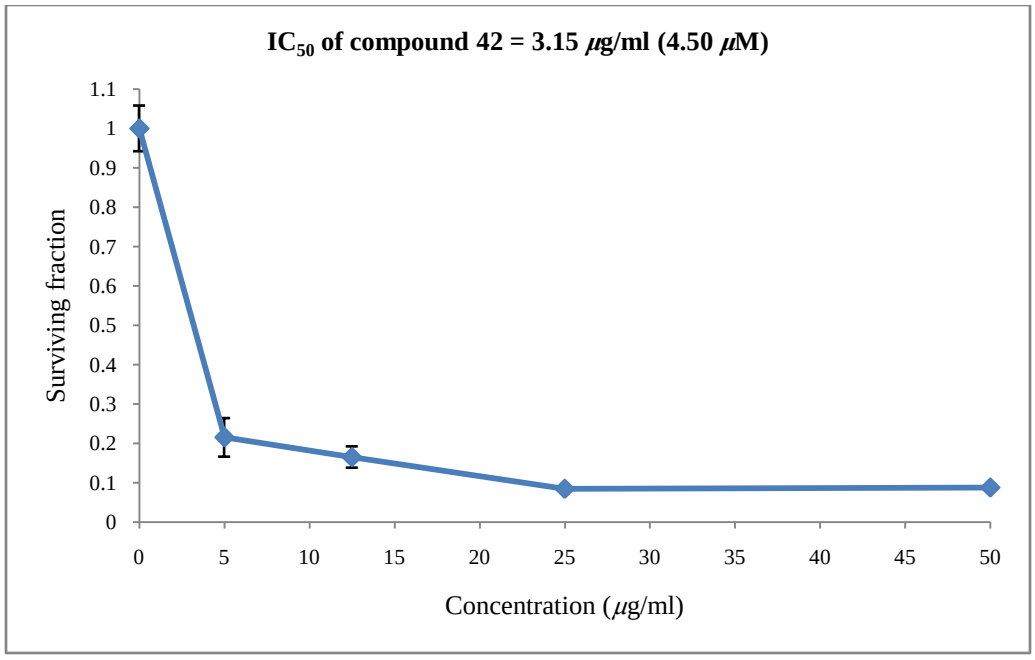

IC50 of compound 37 = 3.37 μg/ml (5.22 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

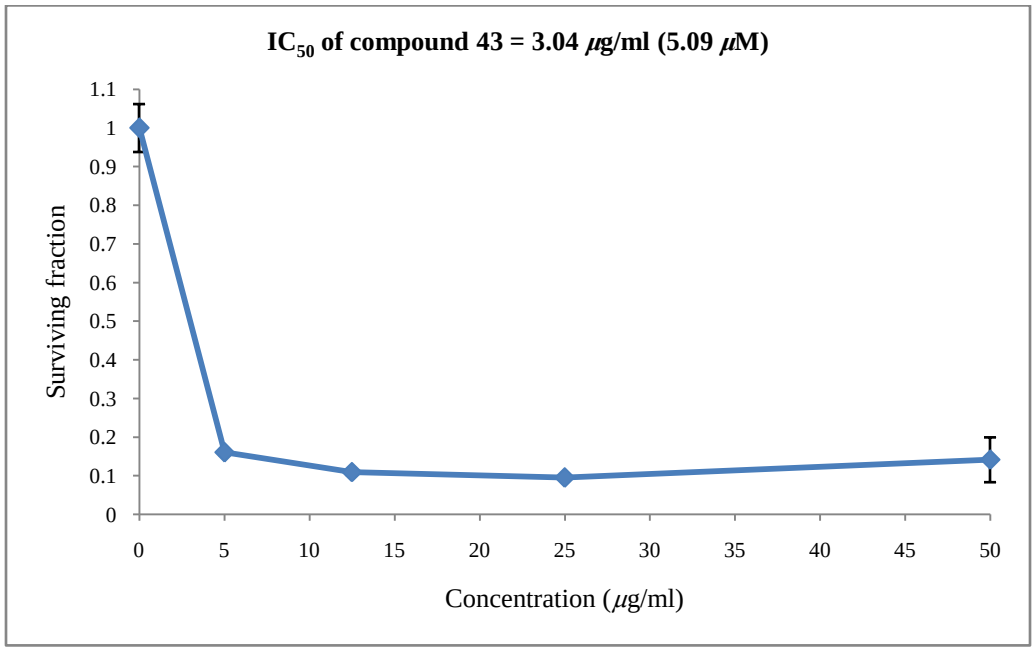

IC50 of compound 38 = 3.37 μg/ml (5.12 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

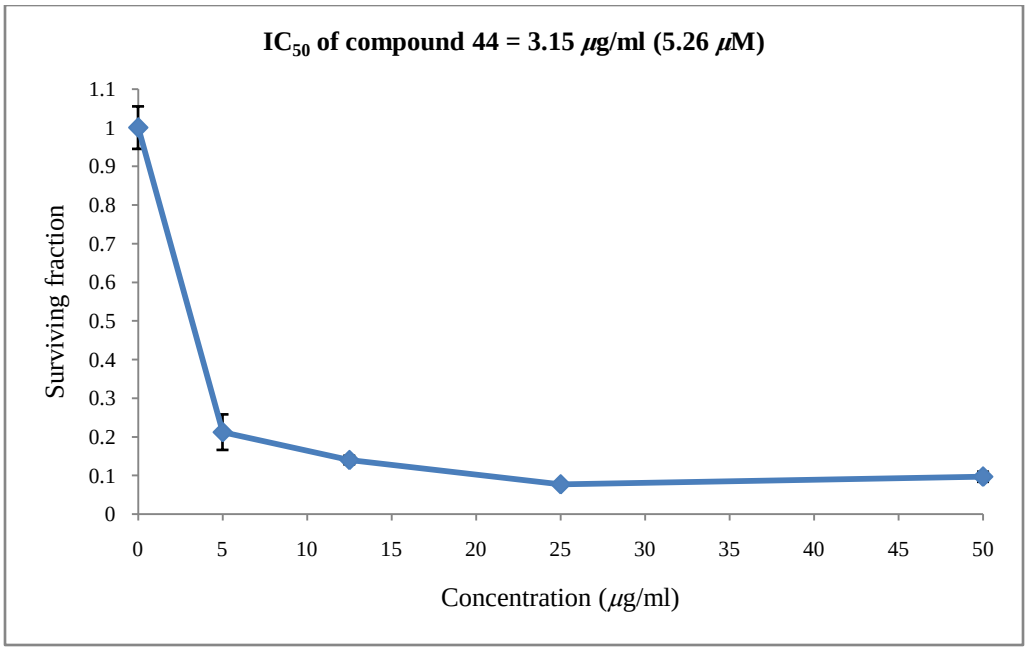

IC50 of compound 39 = 3.26 μg/ml (4.94 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

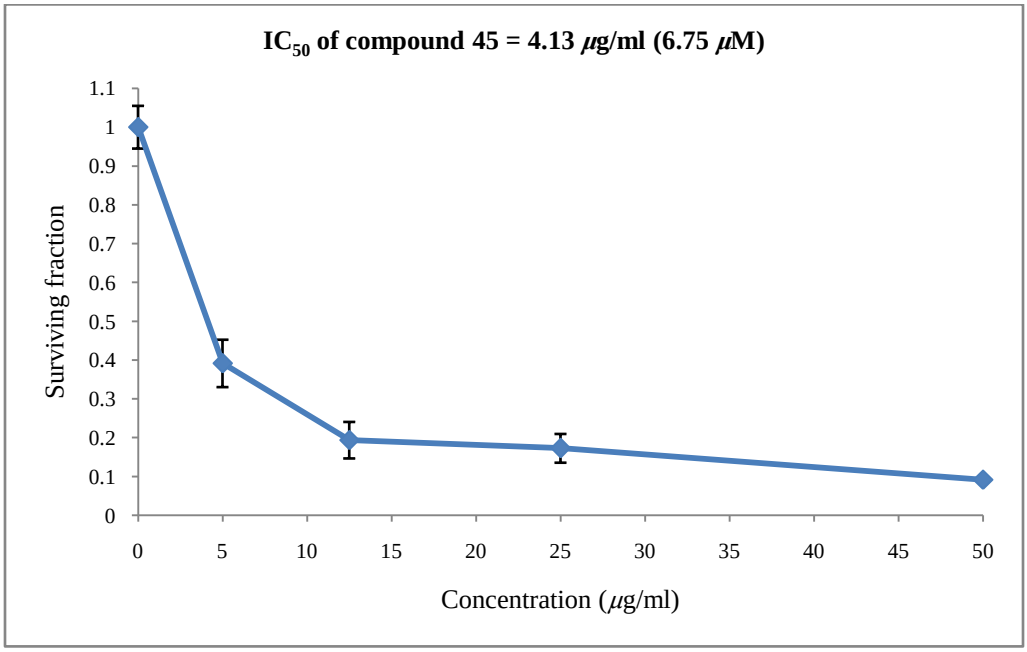

IC50 of compound 40 = 3.62 μg/ml (5.13 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

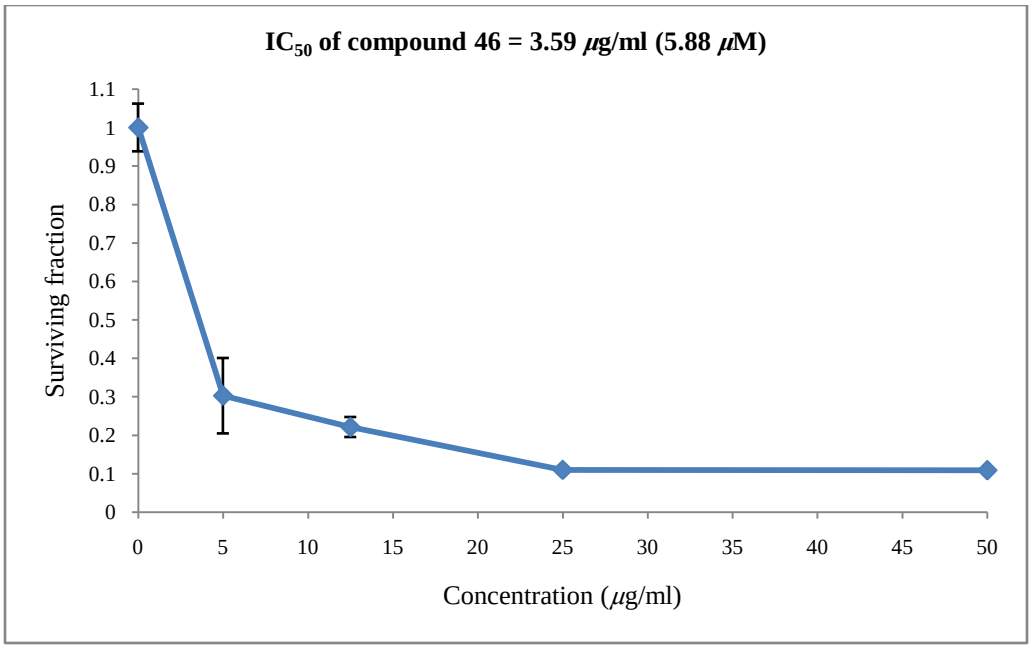

IC50 of compound 41 = 3.37 μg/ml (4.76 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

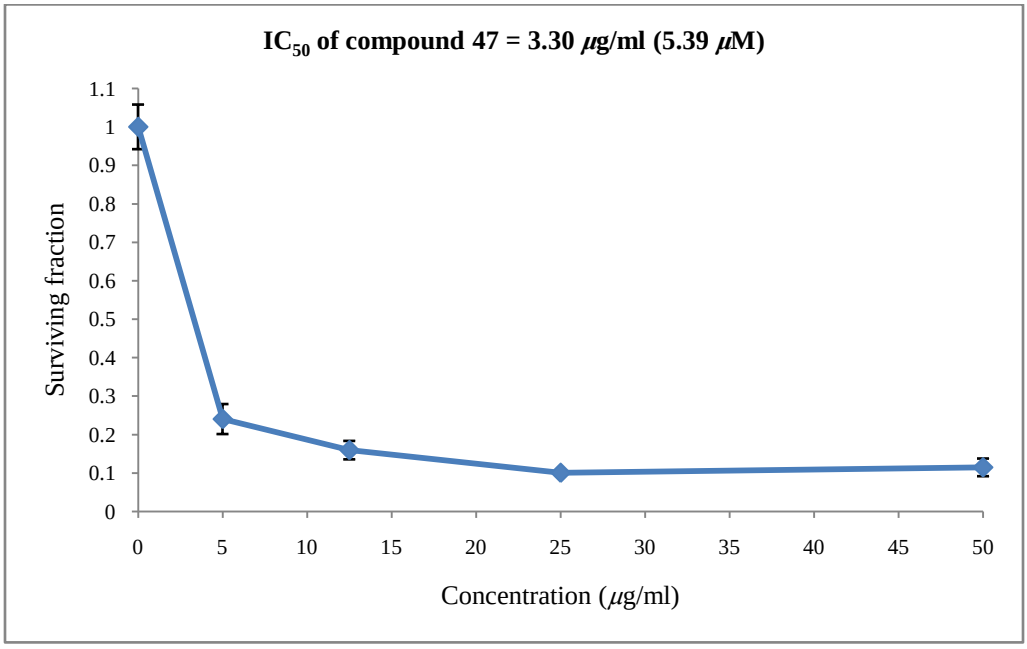

IC50 of compound 42 = 3.15 μg/ml (4.50 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

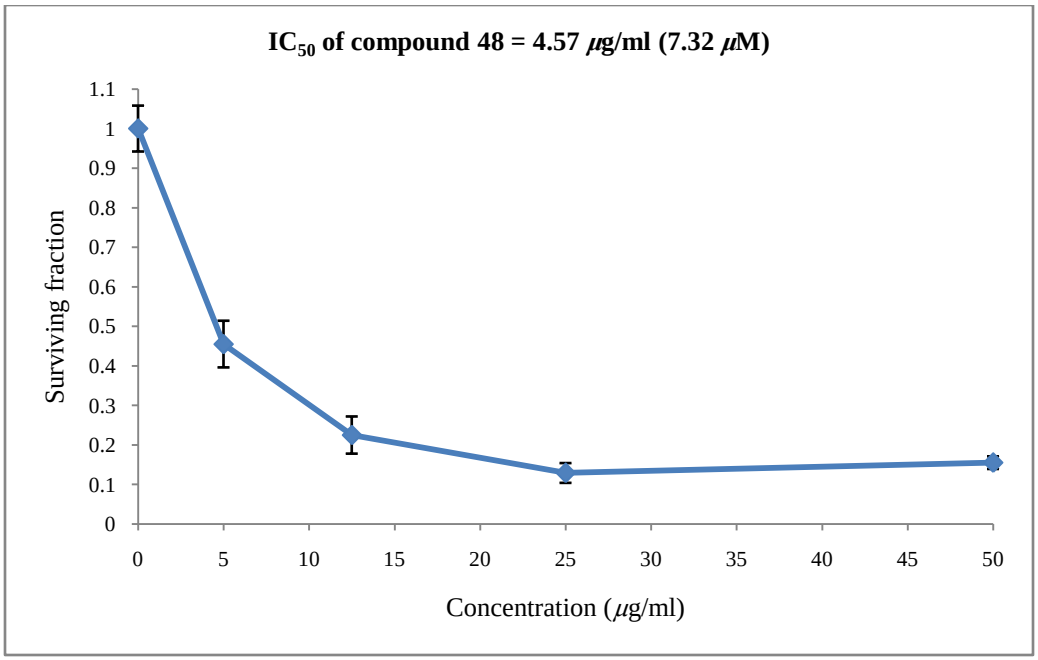

IC50 of compound 43 = 3.04 μg/ml (5.09 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

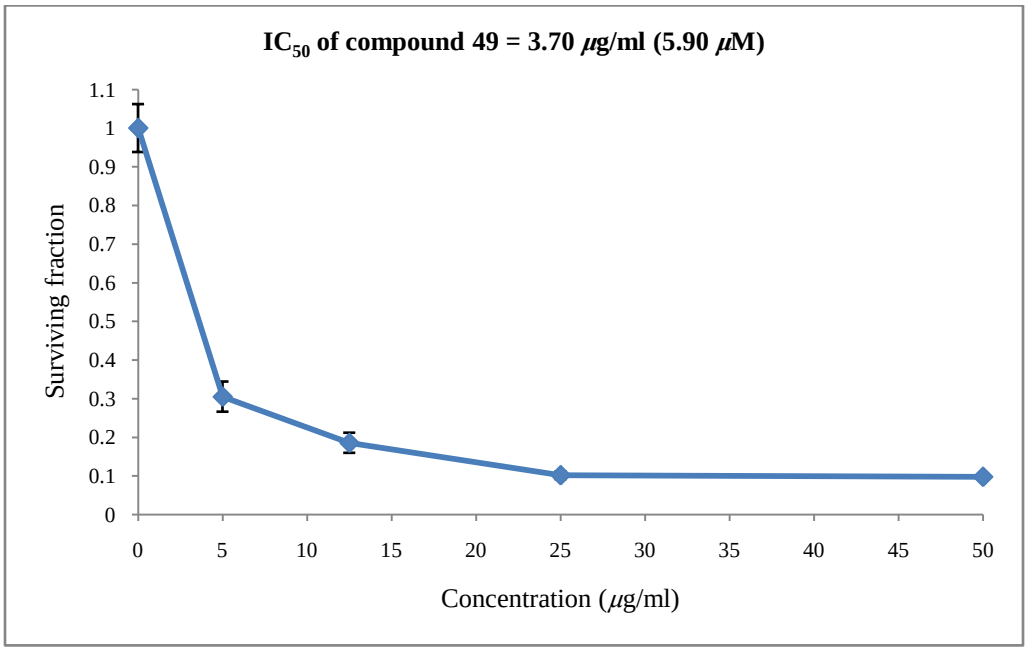

IC50 of compound 44 = 3.15 μg/ml (5.26 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

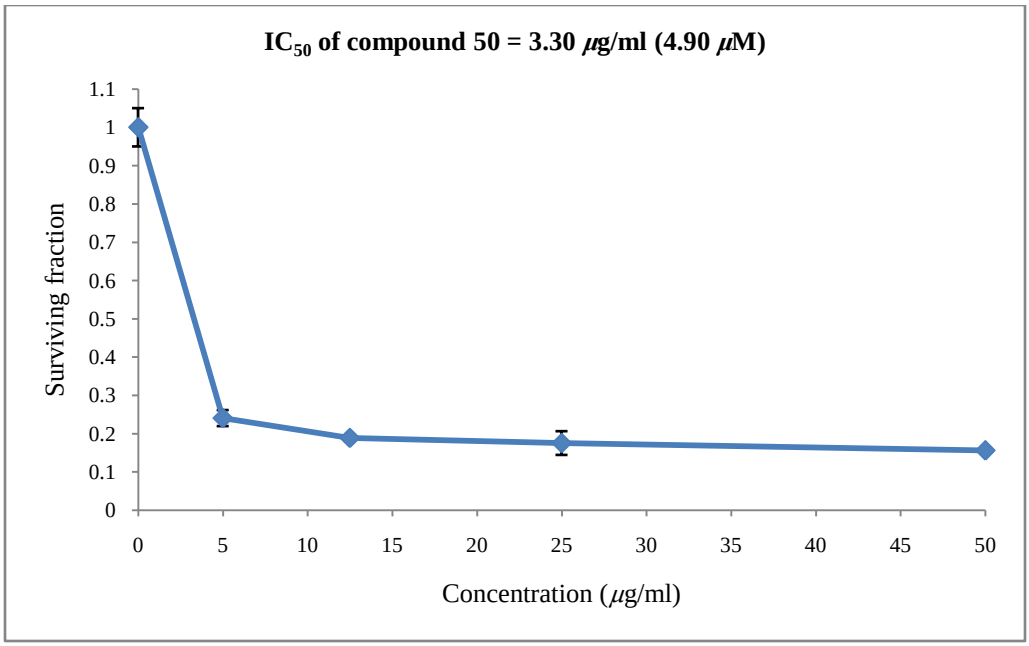

IC50 of compound 45 = 4.13 μg/ml (6.75 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

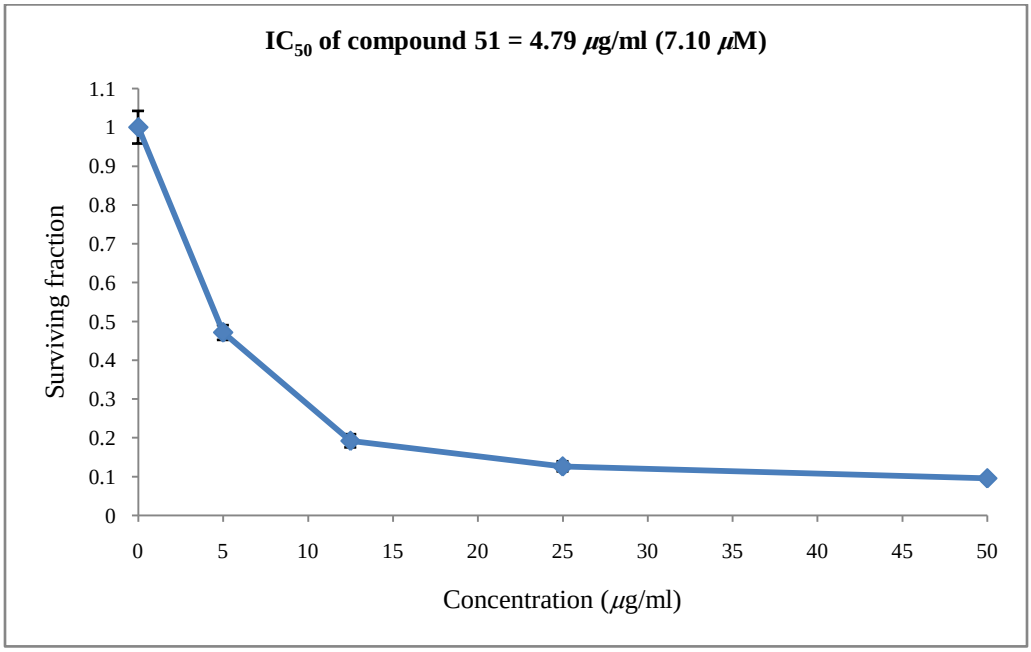

IC50 of compound 46 = 3.59 μg/ml (5.88 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

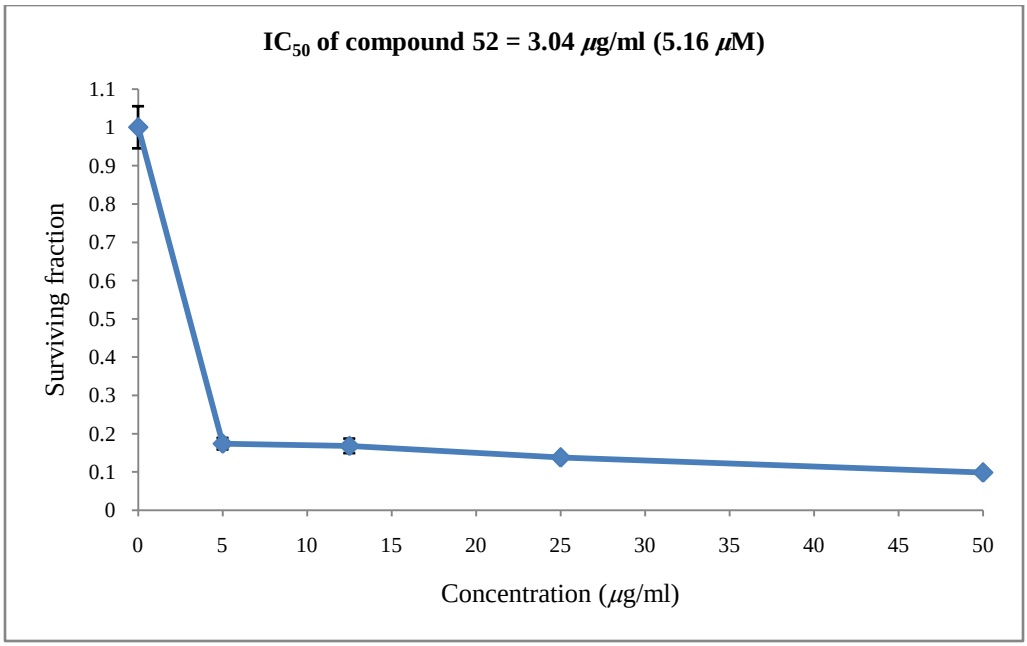

IC50 of compound 47 = 3.30 μg/ml (5.39 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

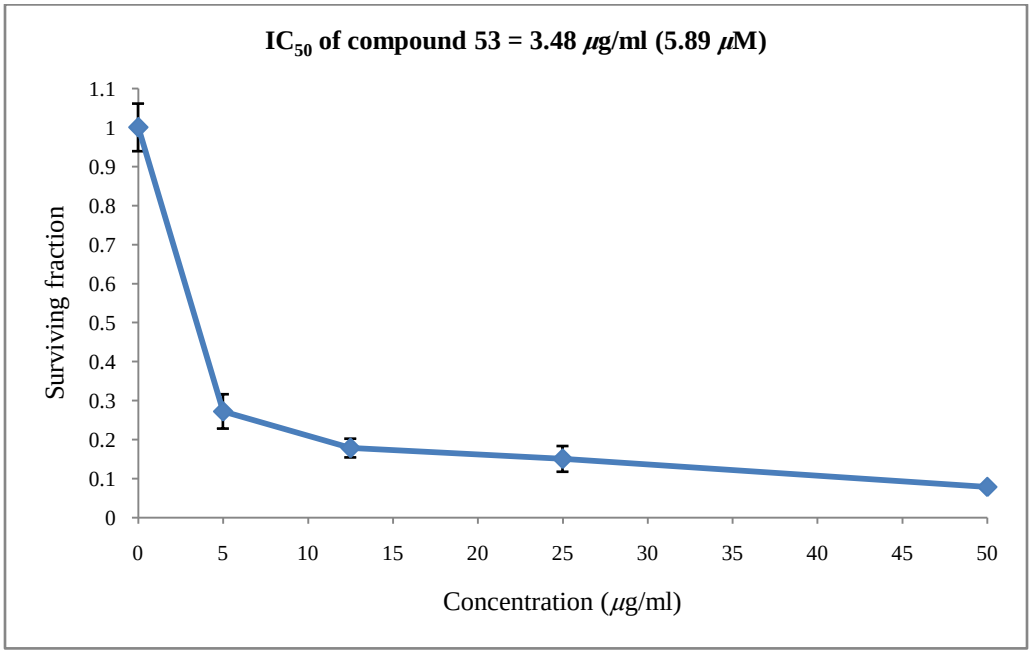

IC50 of compound 48 = 4.57 μg/ml (7.32 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

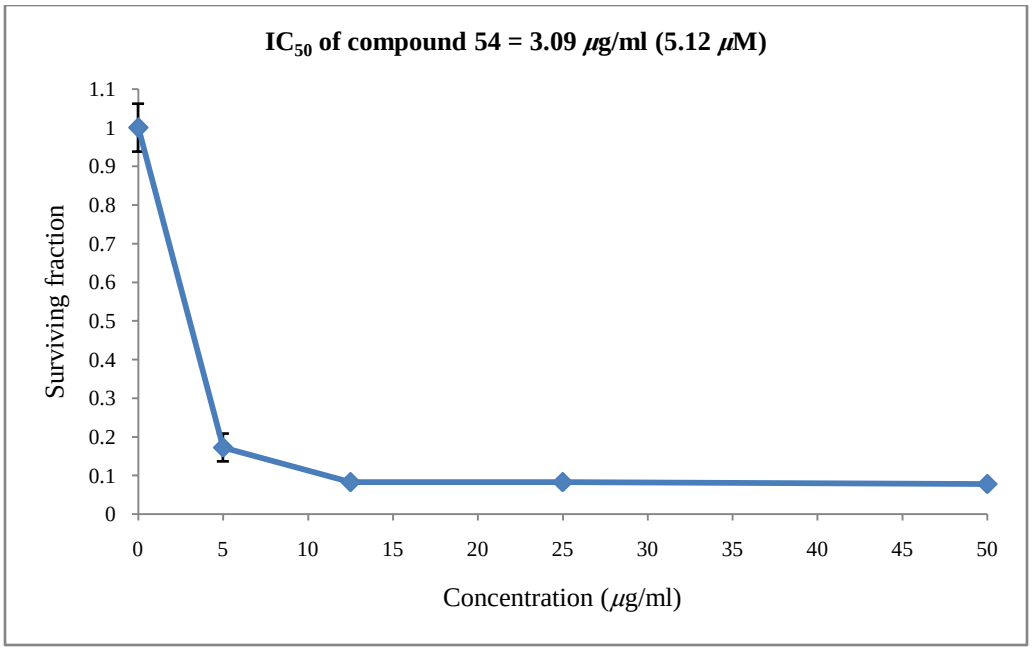

IC50 of compound 49 = 3.70 μg/ml (5.90 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

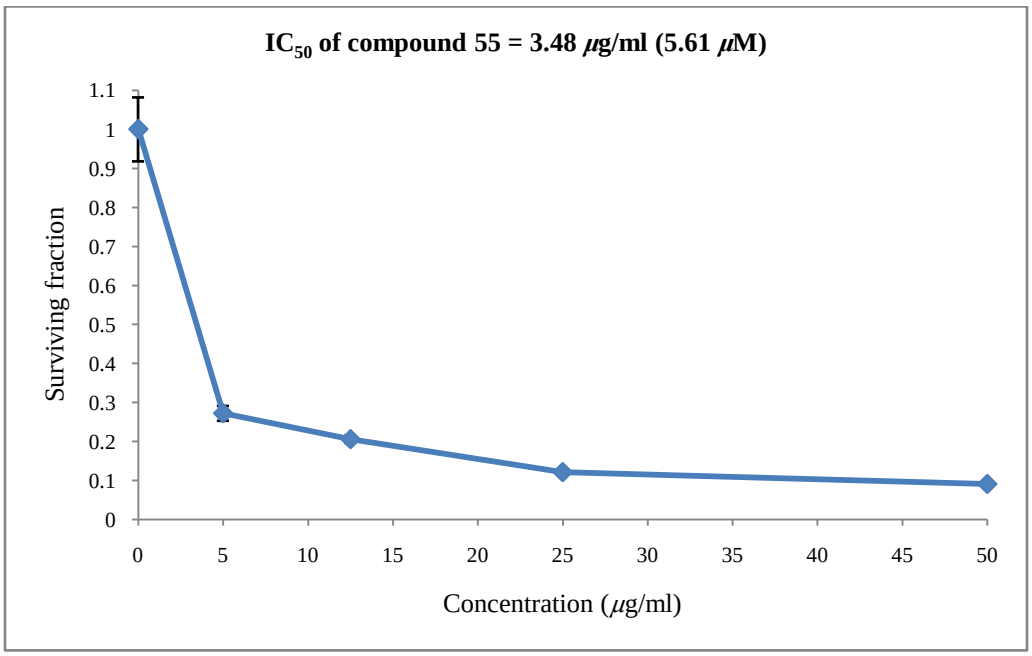

IC50 of compound 50 = 3.30 μg/ml (4.90 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

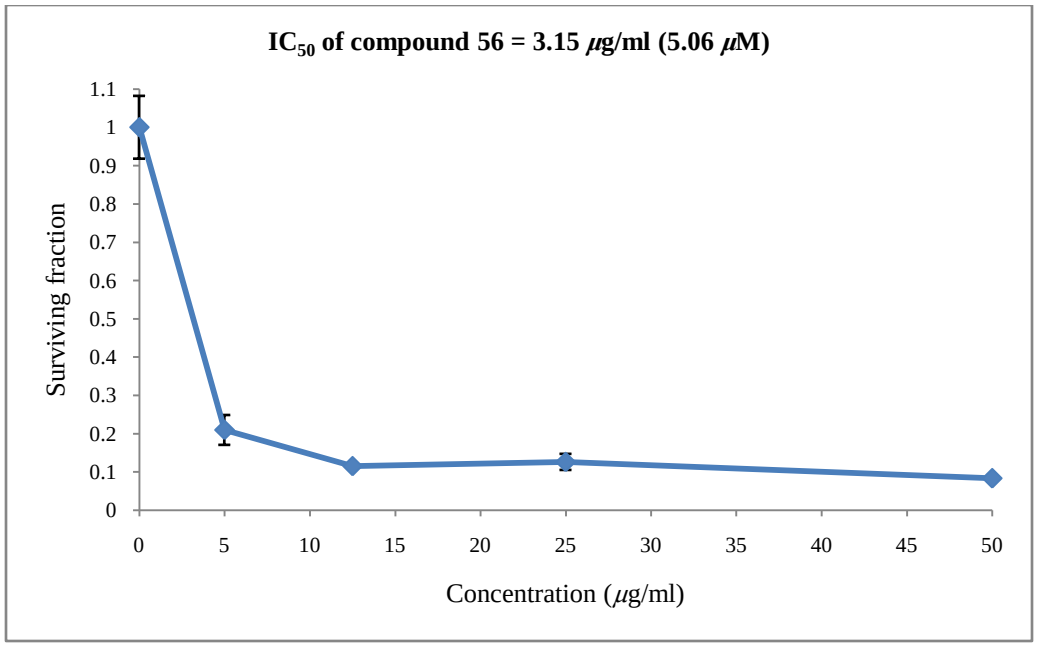

IC50 of compound 51 = 4.79 μg/ml (7.10 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

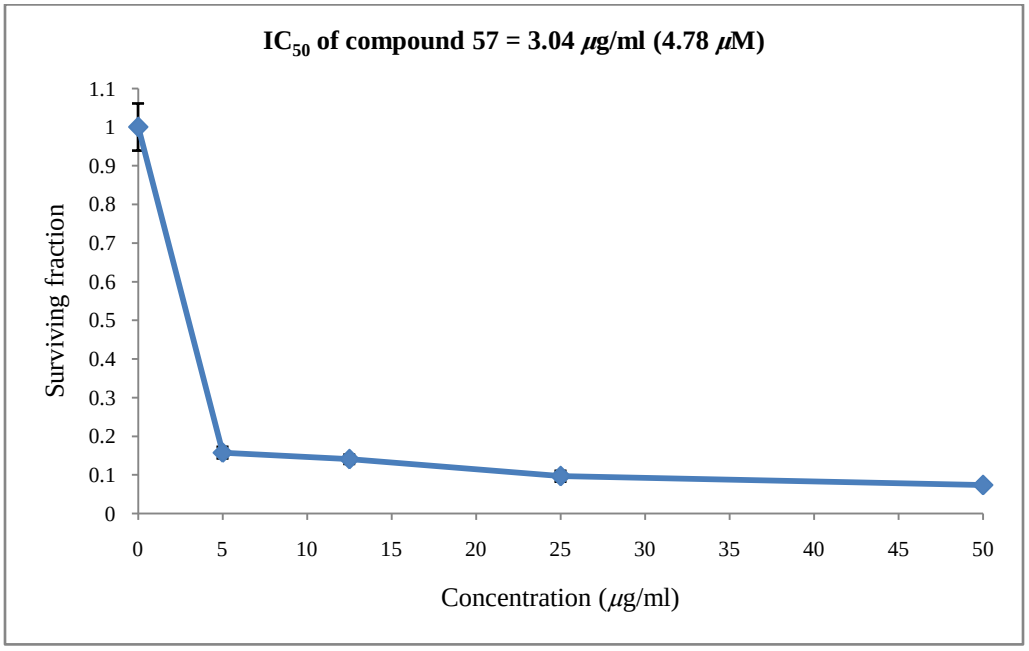

IC50 of compound 52 = 3.04 μg/ml (5.16 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

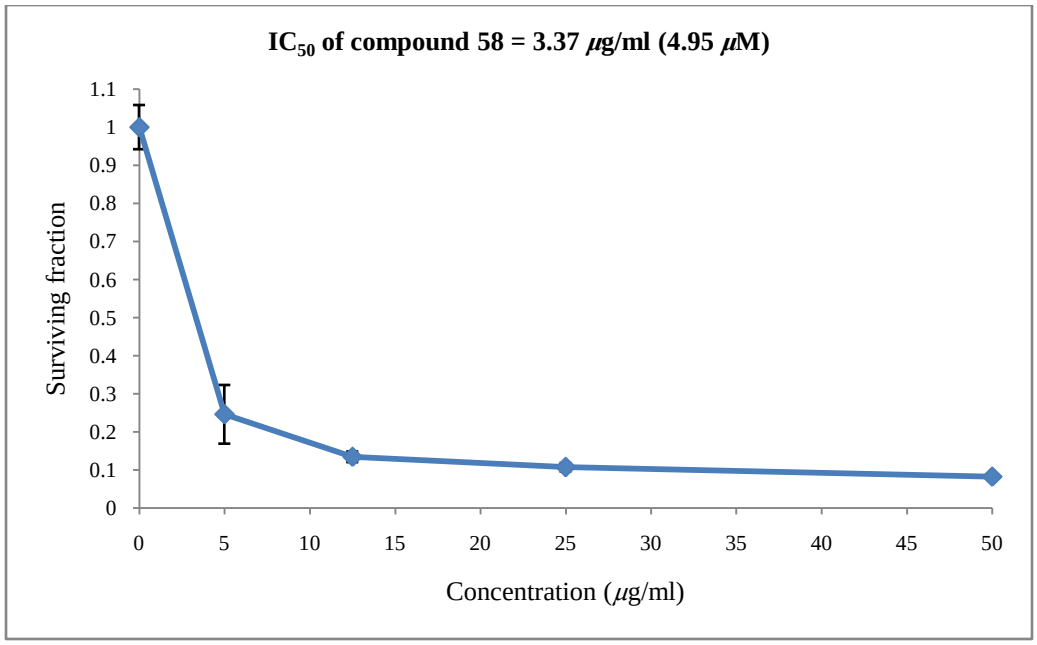

IC50 of compound 53 = 3.48 μg/ml (5.89 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

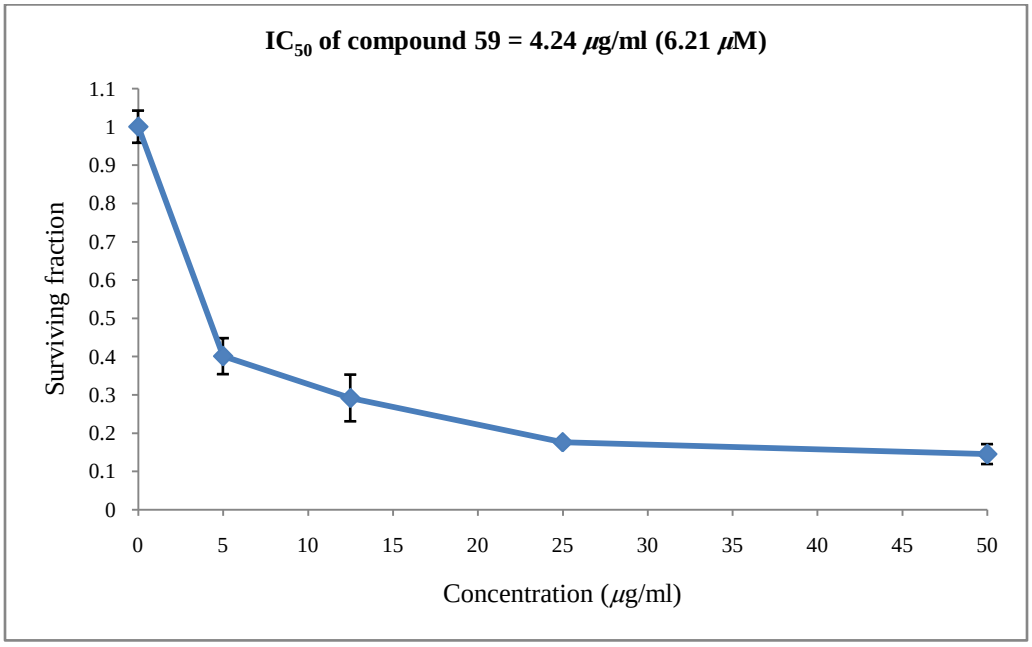

IC50 of compound 54 = 3.09 μg/ml (5.12 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

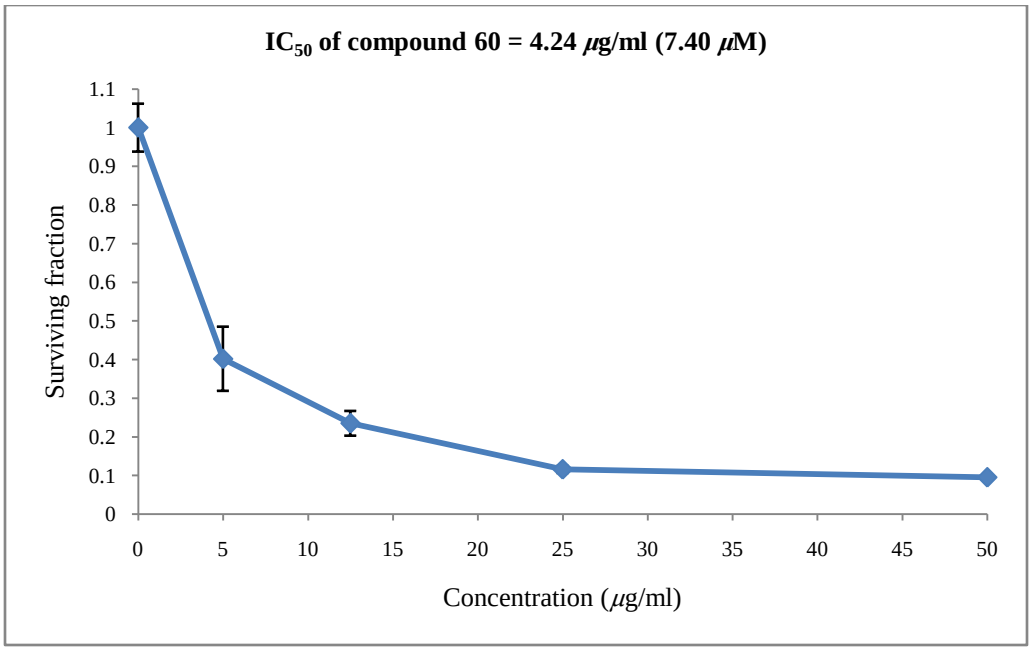

IC50 of compound 55 = 3.48 μg/ml (5.61 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

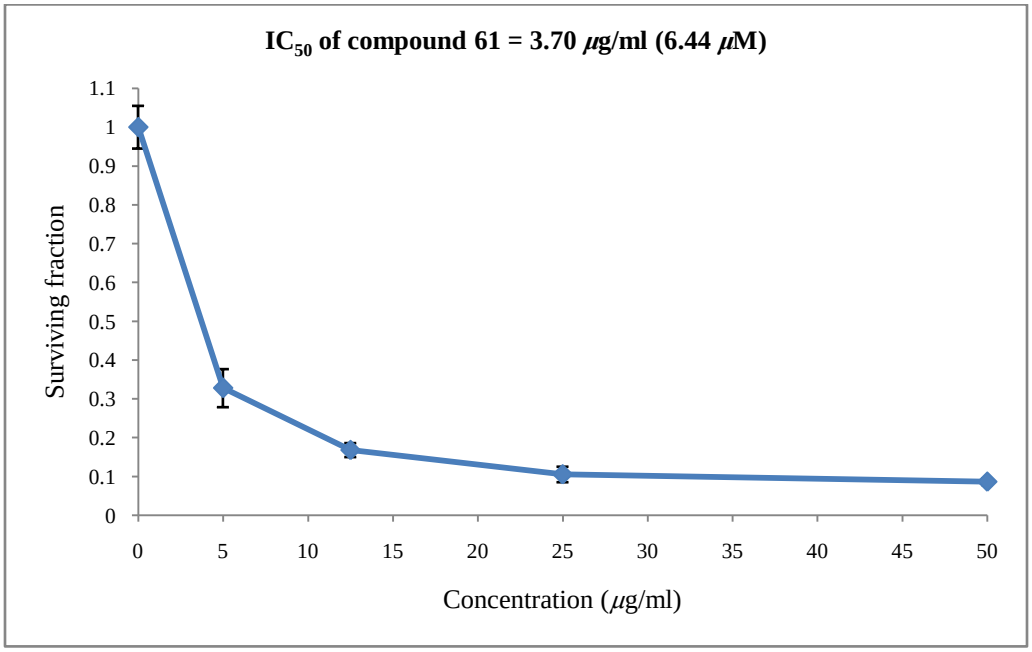

IC50 of compound 56 = 3.15 μg/ml (5.06 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)


IC50 of compound 57 = 3.04 μg/ml (4.78 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)


IC50 of compound 58 = 3.37 μg/ml (4.95 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)


IC50 of compound 59 = 4.24 μg/ml (6.21 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)


IC50 of compound 60 = 4.24 μg/ml (7.40 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)


IC50 of compound 61 = 3.70 μg/ml (6.44 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

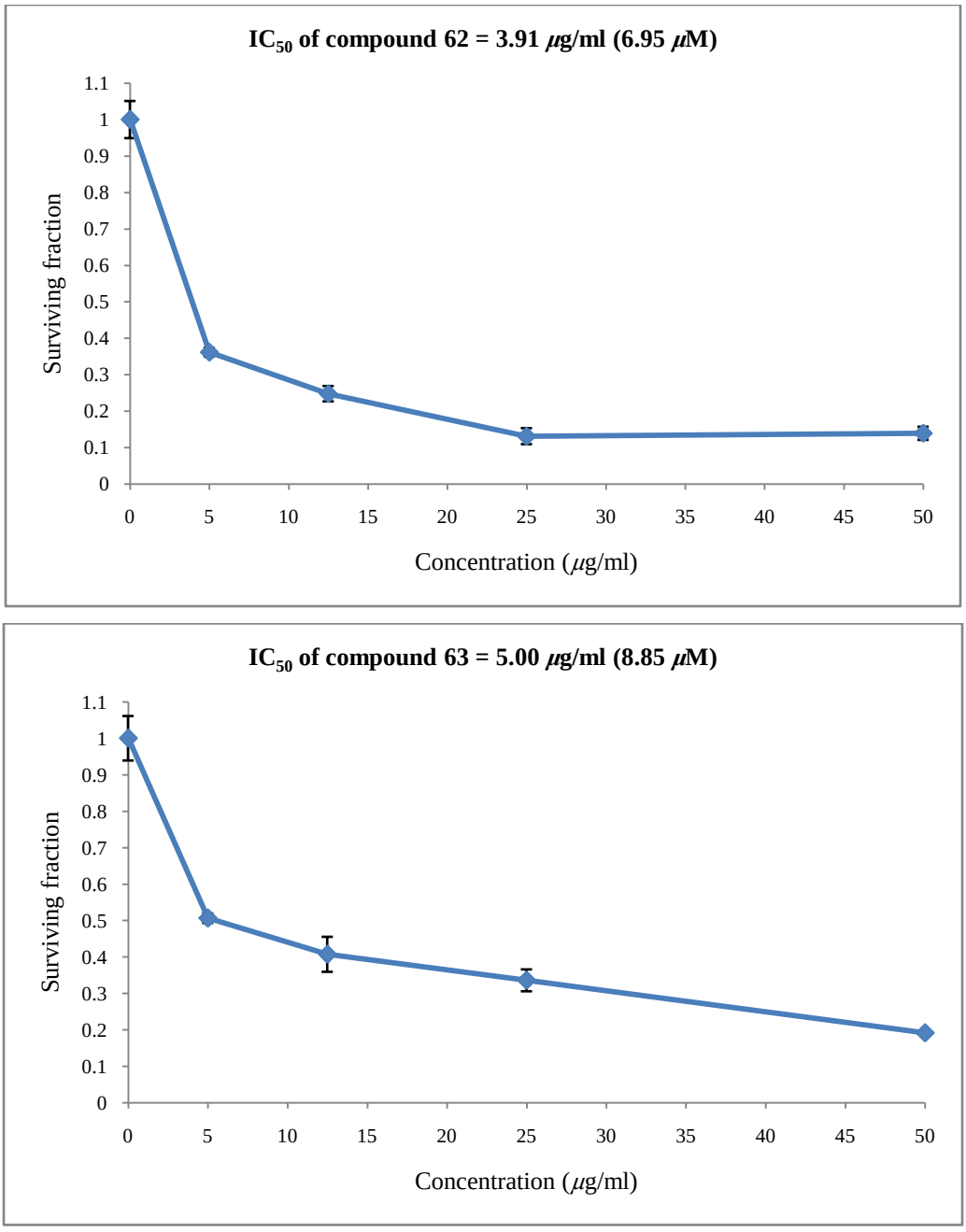
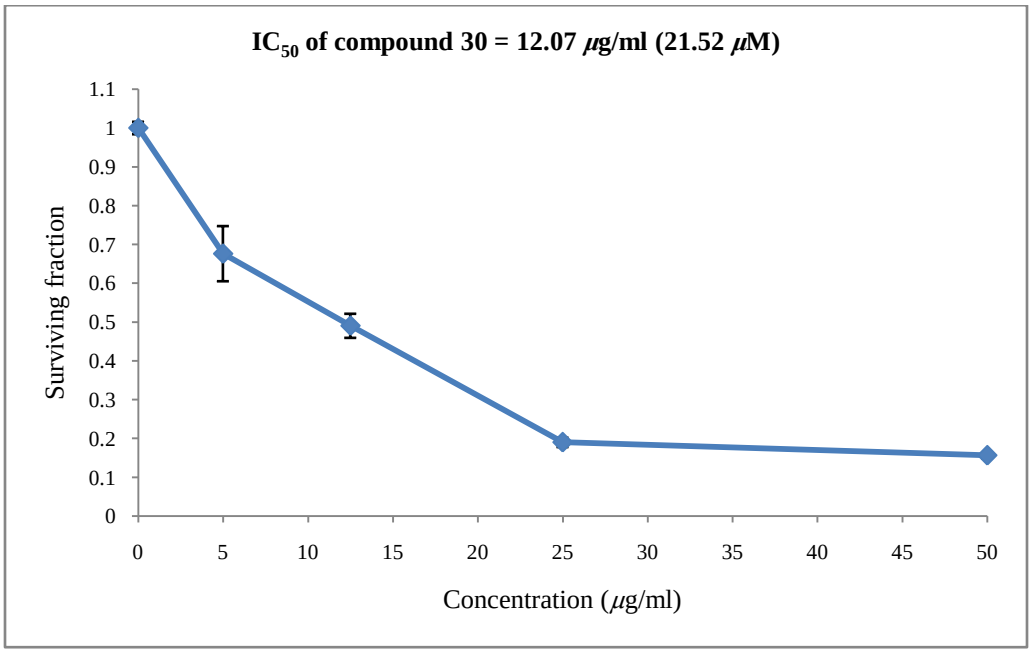
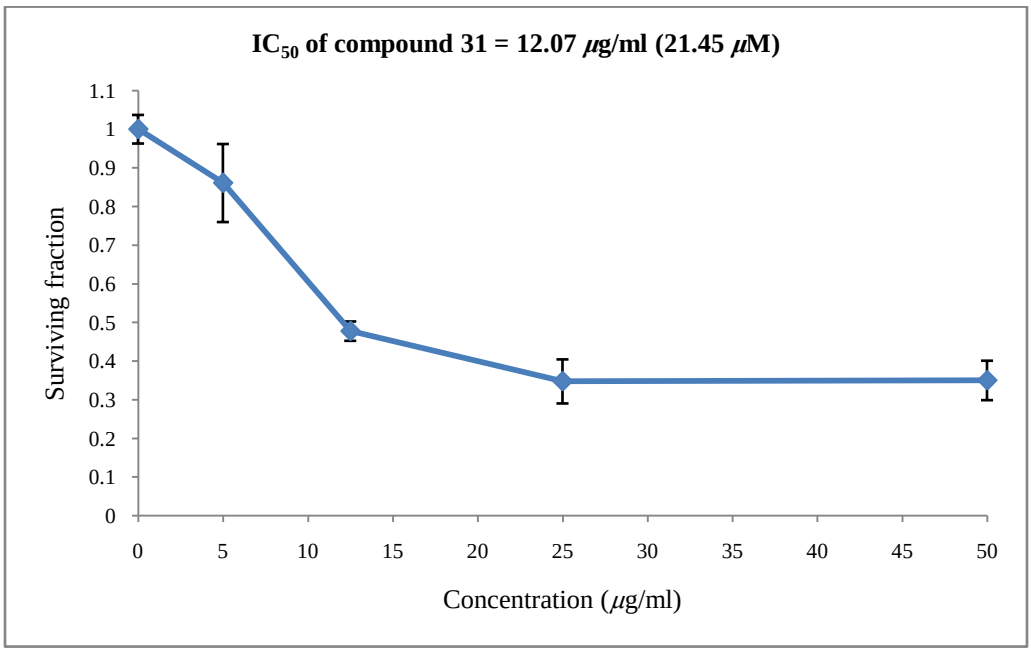
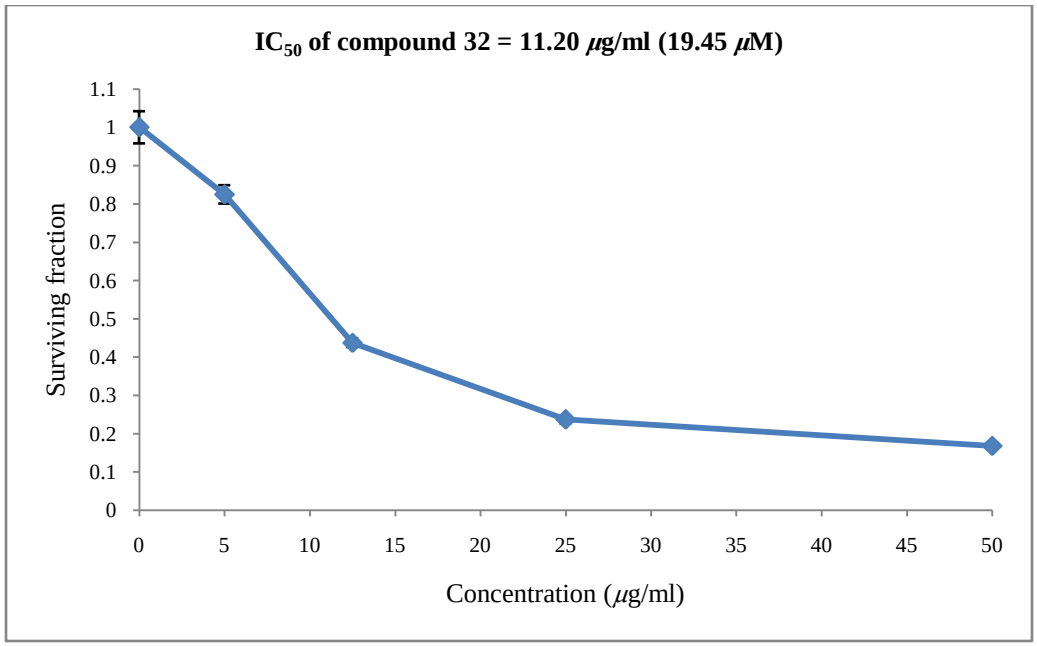
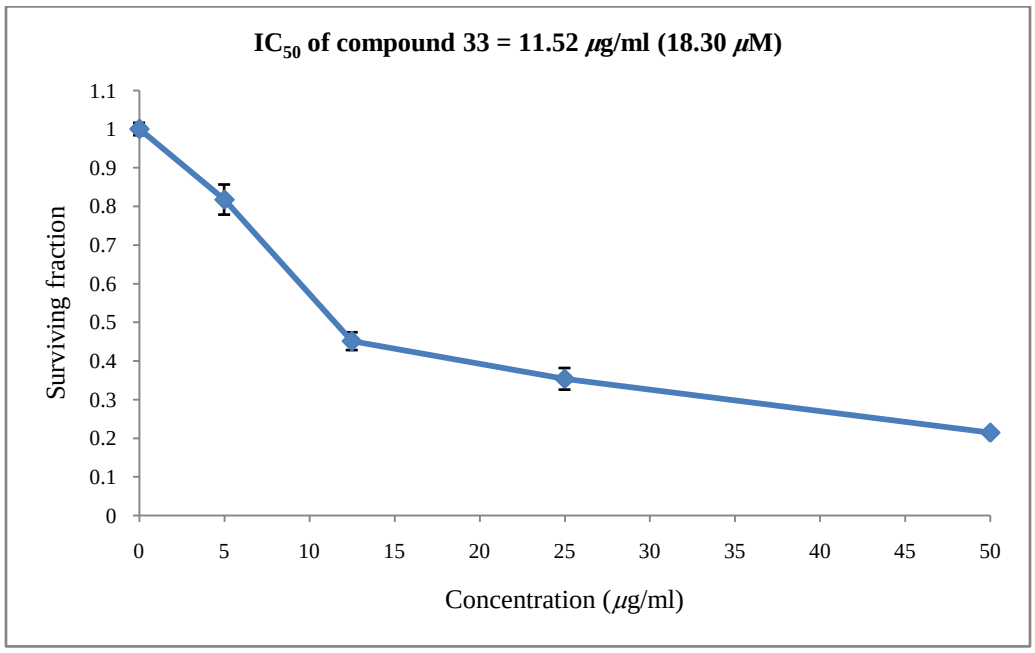


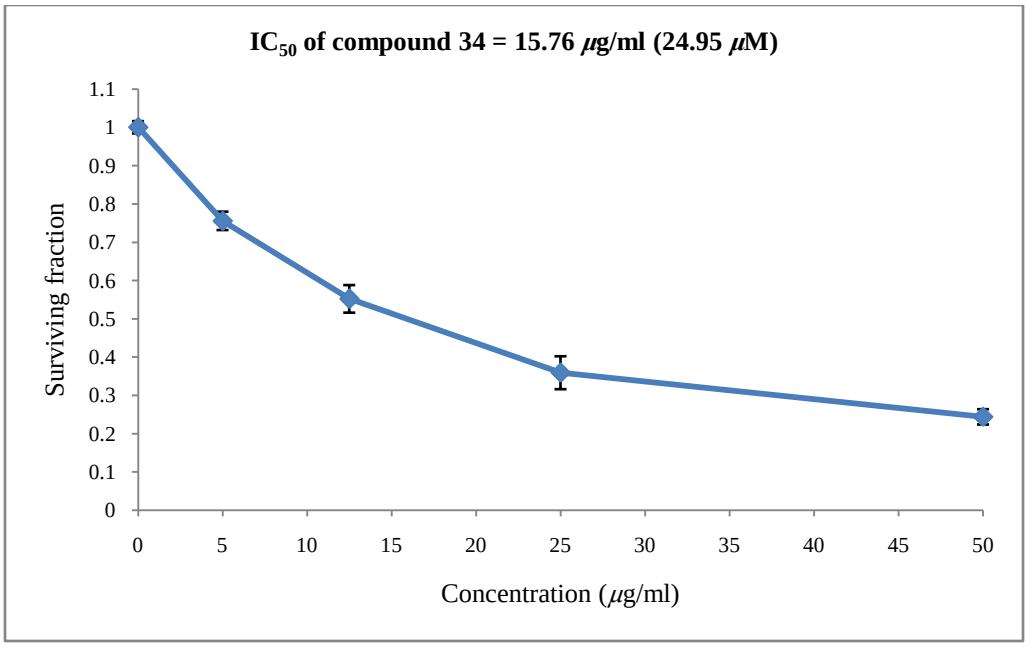
Figure 114. Dose-response curve for the synthesized compounds **30-63** against HeLa (cervical cancer) cell line.

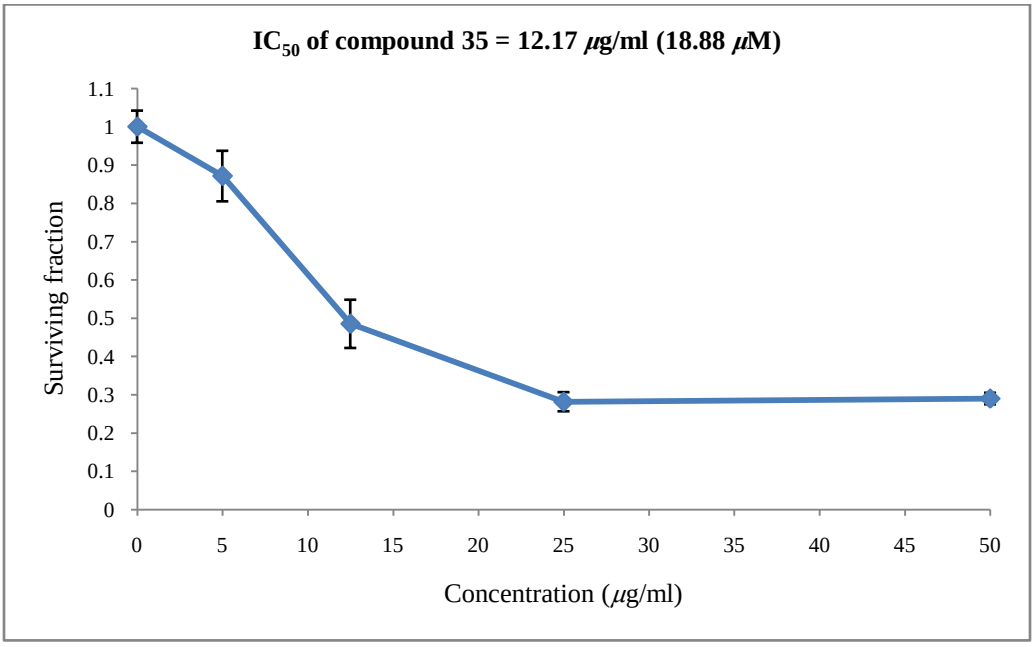

IC50 of compound 30 = 12.07 μg/ml (21.52 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

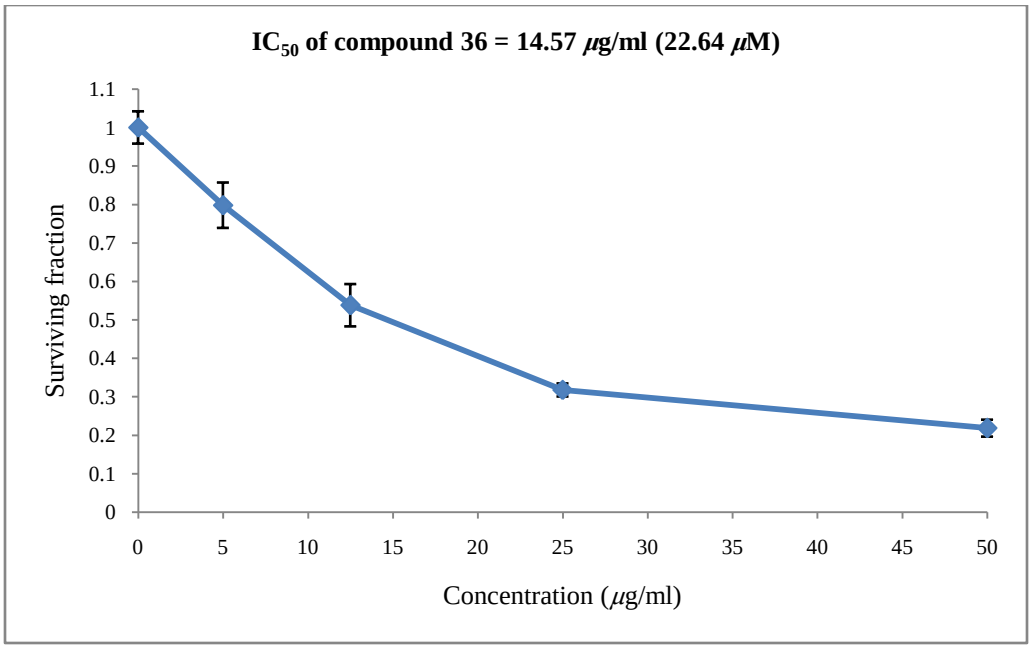

IC50 of compound 31 = 12.07 μg/ml (21.45 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

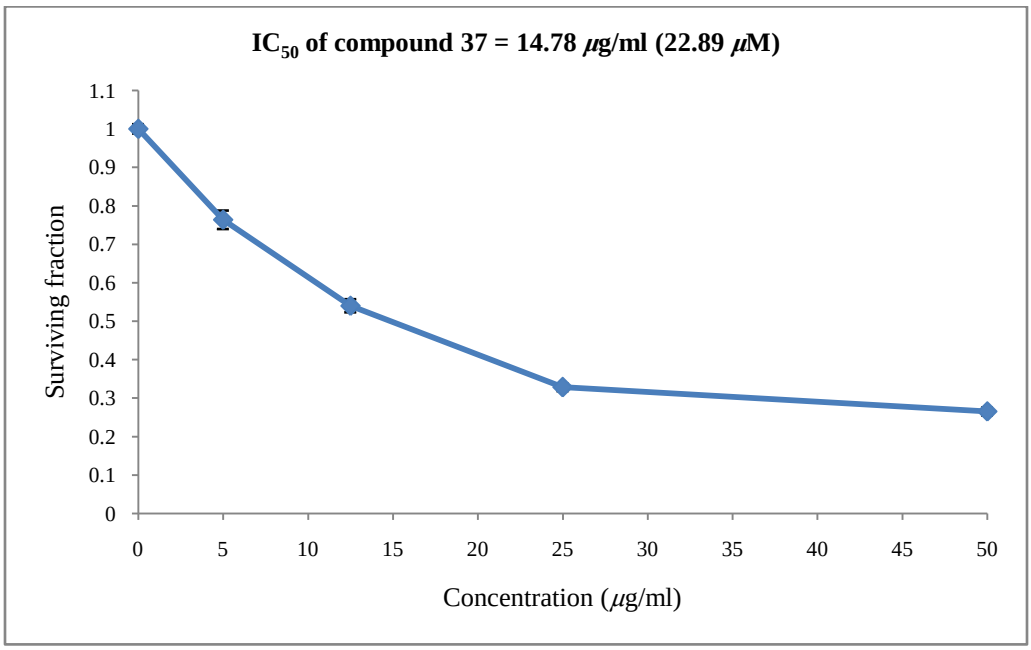

IC50 of compound 32 = 11.20 μg/ml (19.45 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

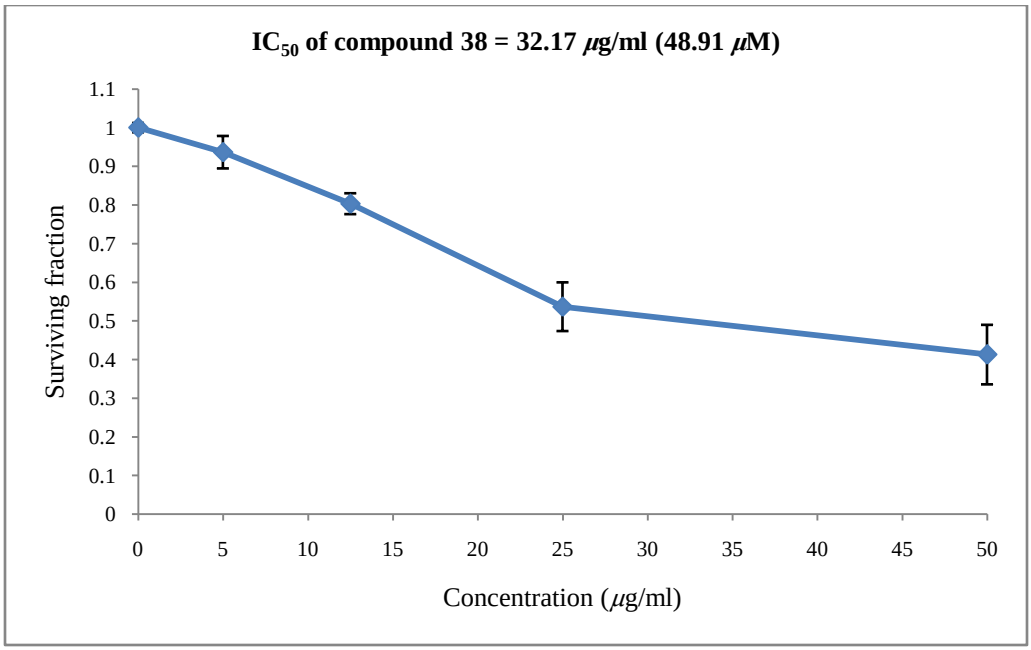

IC50 of compound 33 = 11.52 μg/ml (18.30 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

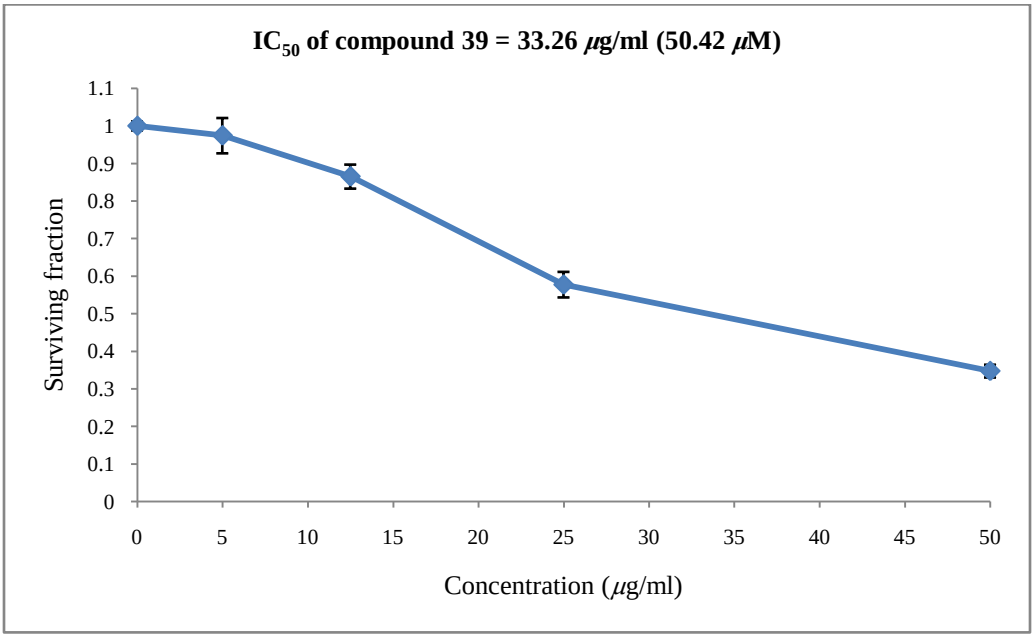

IC50 of compound 34 = 15.76 μg/ml (24.95 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

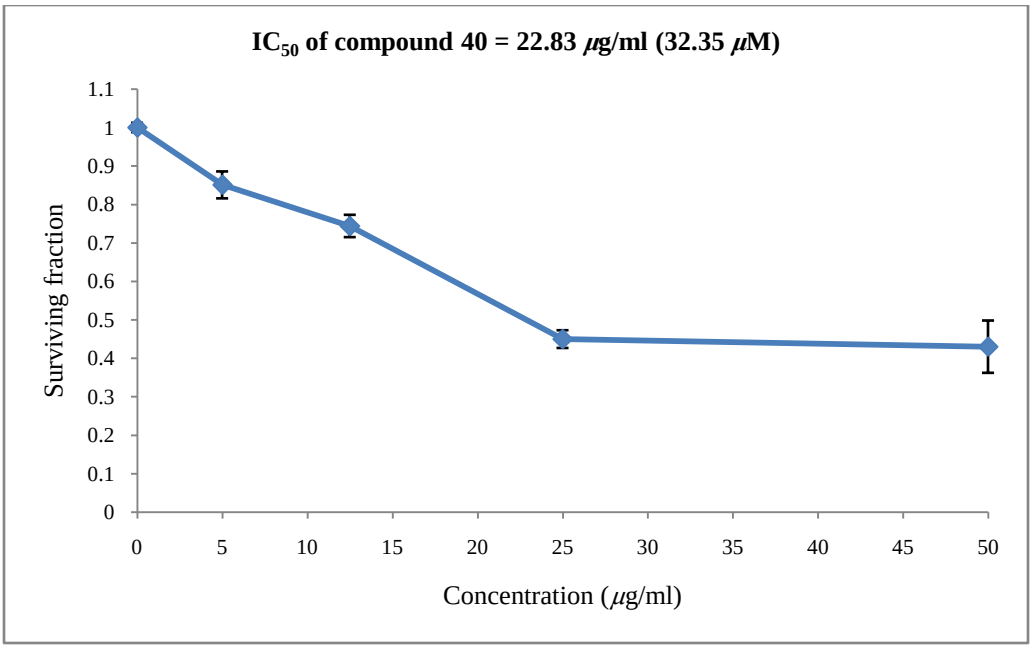

IC50 of compound 35 = 12.17 μg/ml (18.88 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

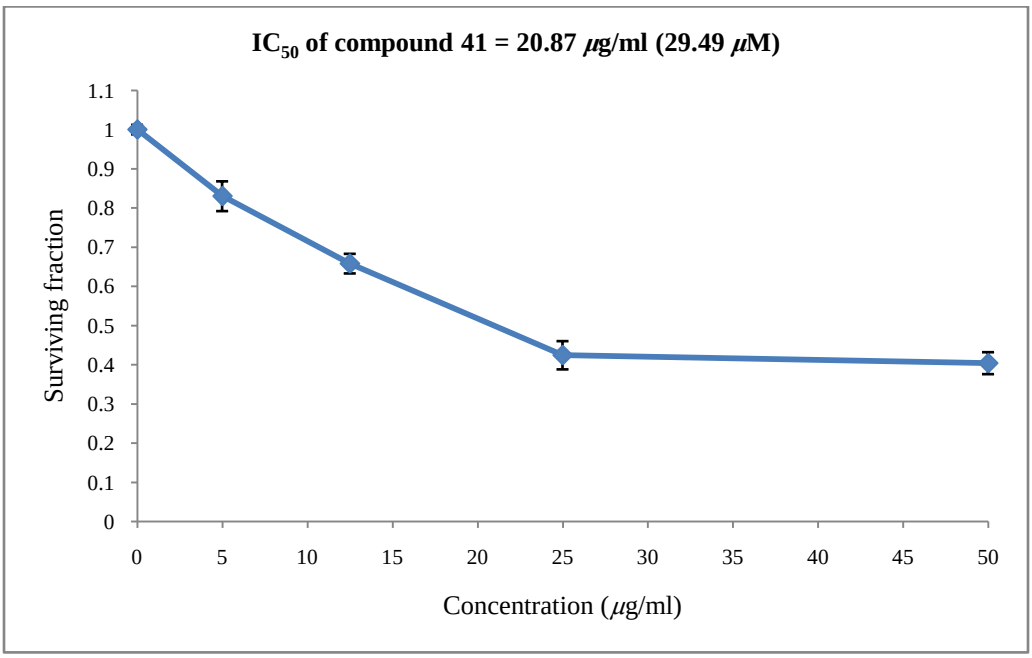

IC50 of compound 36 = 14.57 μg/ml (22.64 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

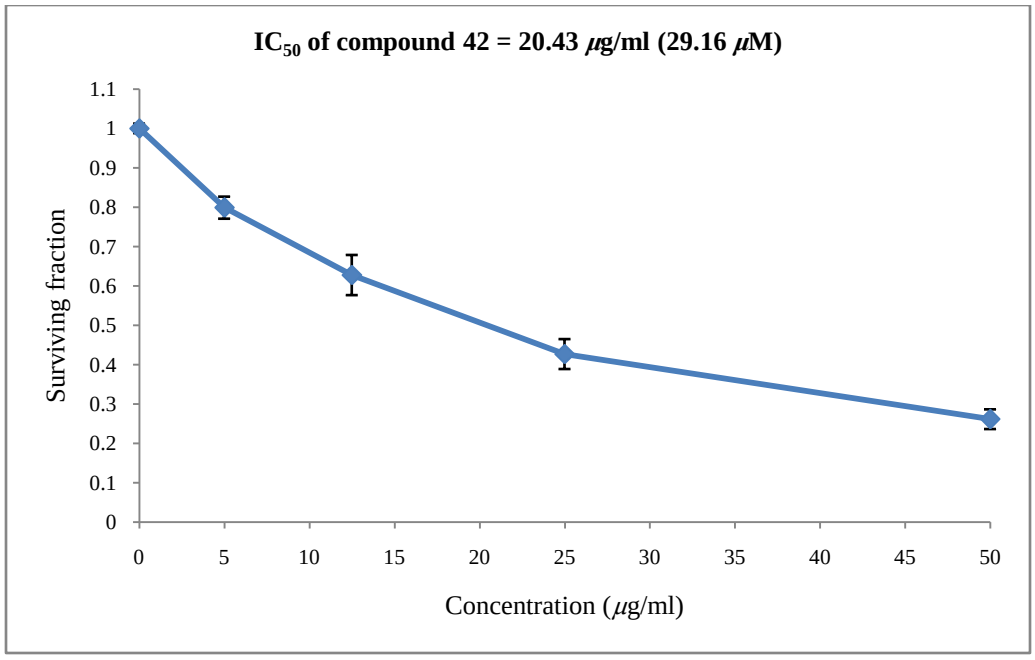

IC50 of compound 37 = 14.78 μg/ml (22.89 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

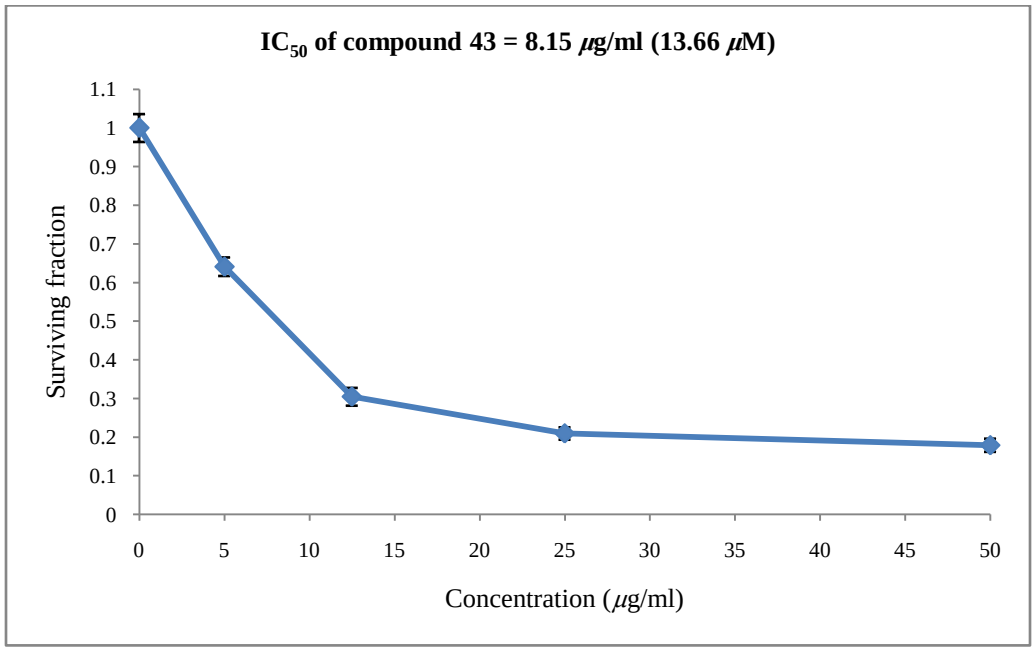

IC50 of compound 38 = 32.17 μg/ml (48.91 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

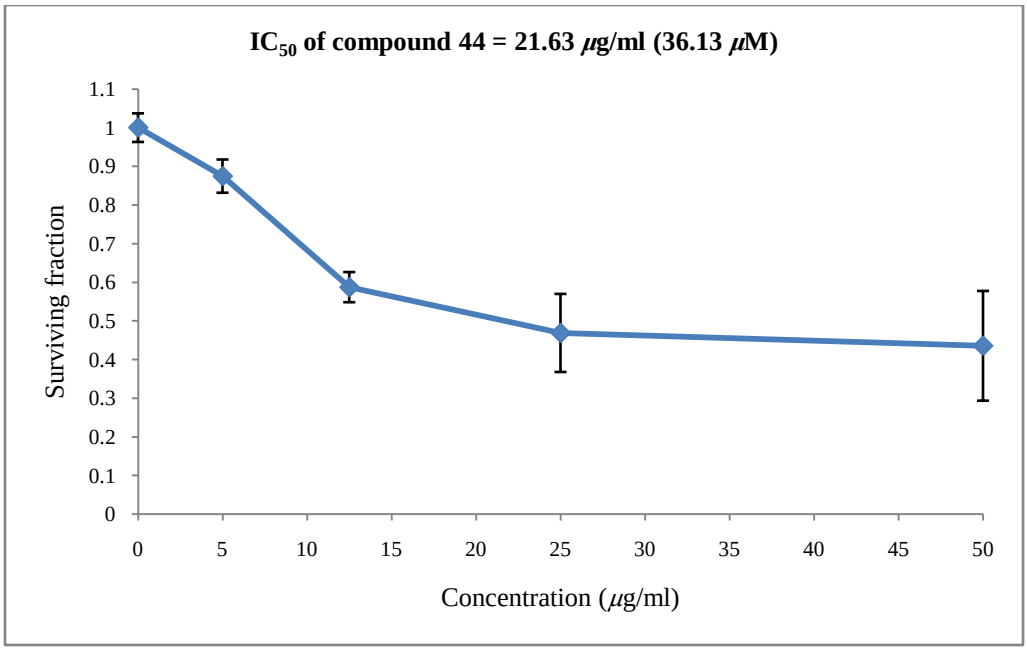

IC50 of compound 39 = 33.26 μg/ml (50.42 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

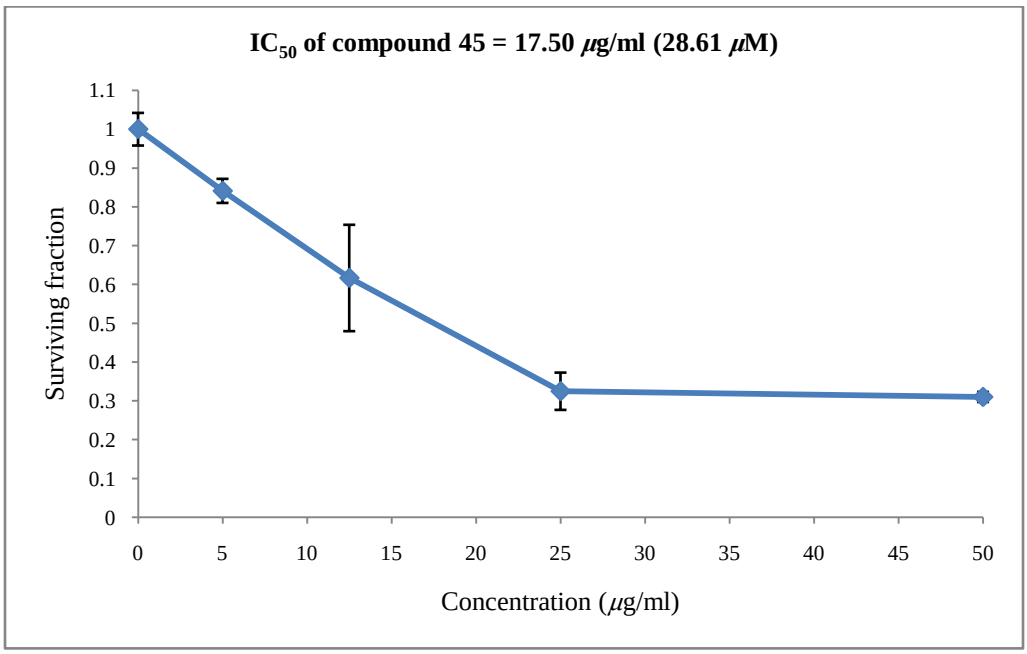

IC50 of compound 40 = 22.83 μg/ml (32.35 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

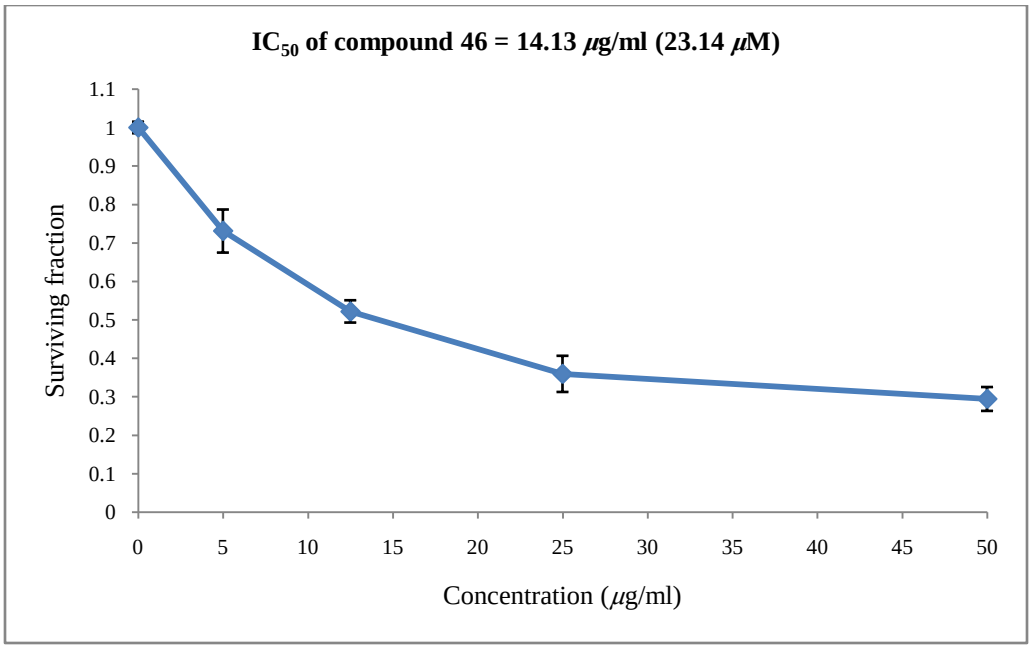

IC50 of compound 41 = 20.87 μg/ml (29.49 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

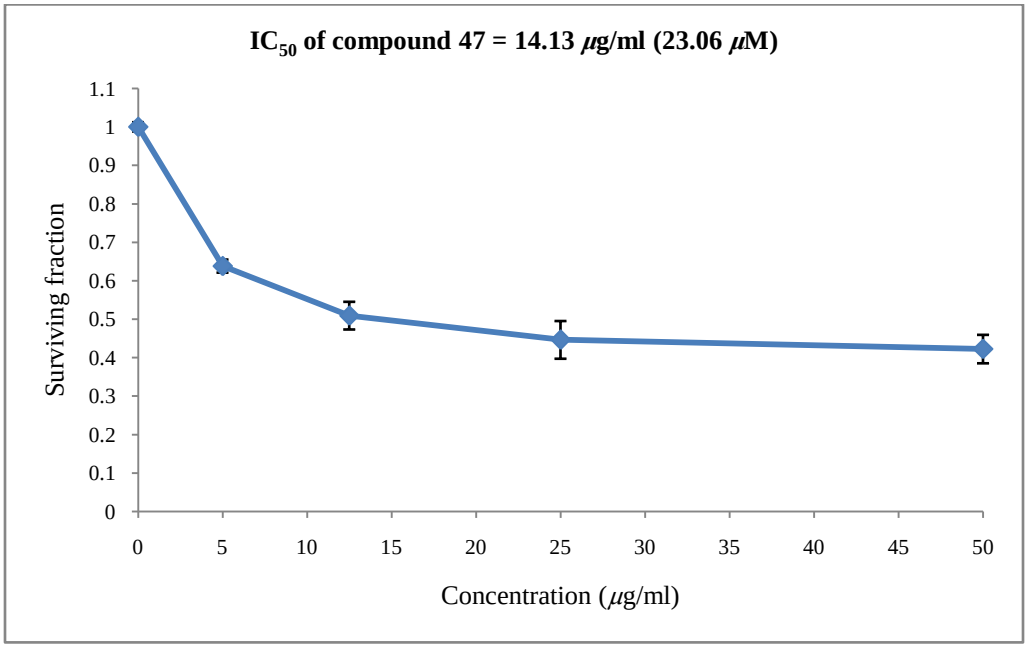

IC50 of compound 42 = 20.43 μg/ml (29.16 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

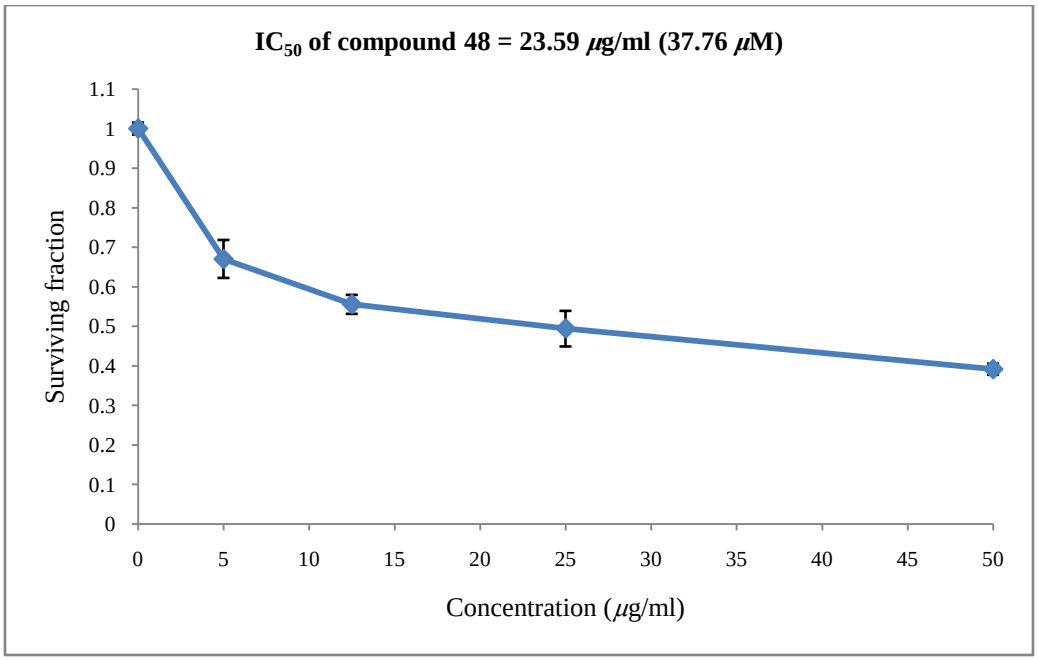

IC50 of compound 43 = 8.15 μg/ml (13.66 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

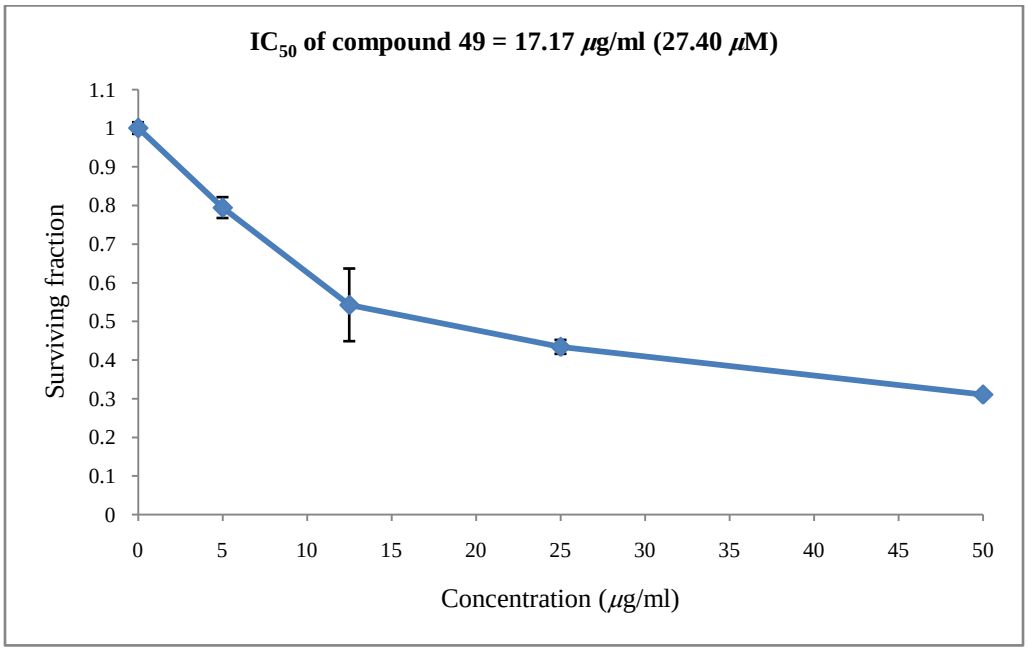

IC50 of compound 44 = 21.63 μg/ml (36.13 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

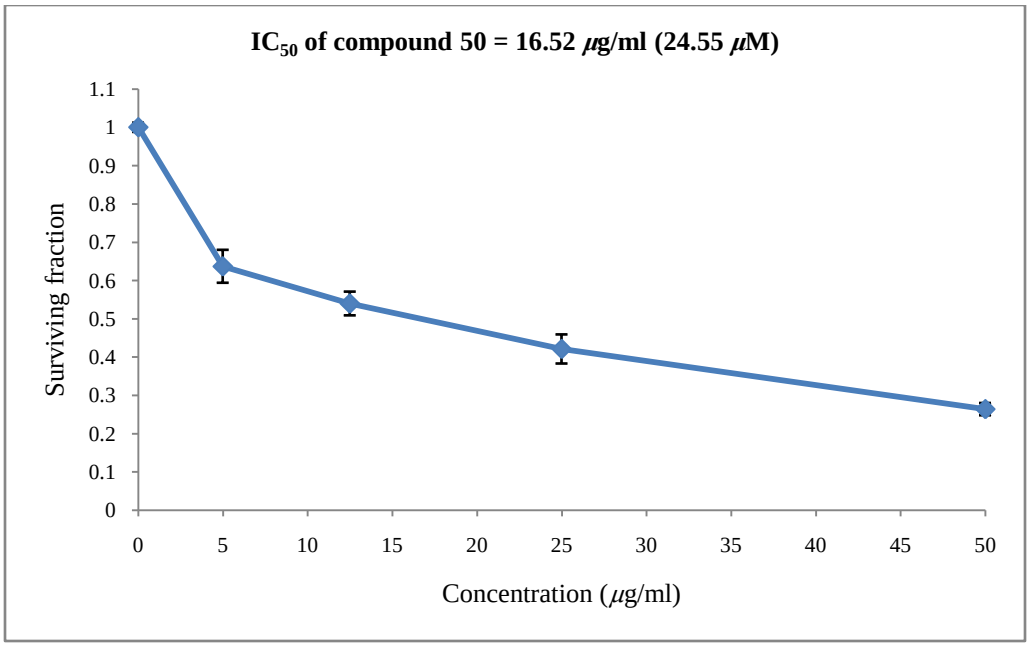

IC50 of compound 45 = 17.50 μg/ml (28.61 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

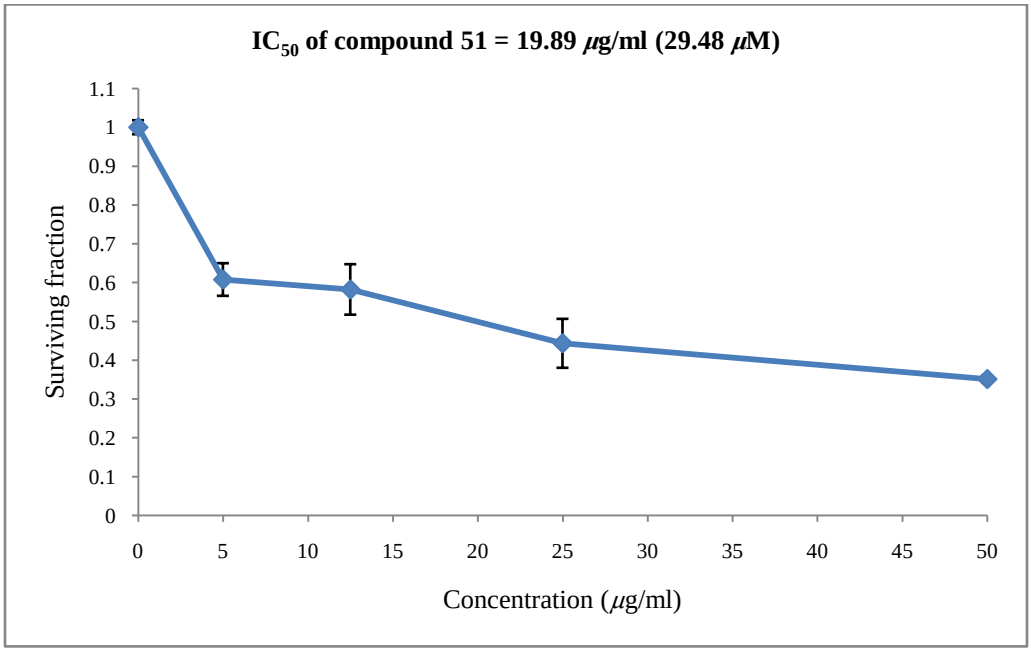

IC50 of compound 46 = 14.13 μg/ml (23.14 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

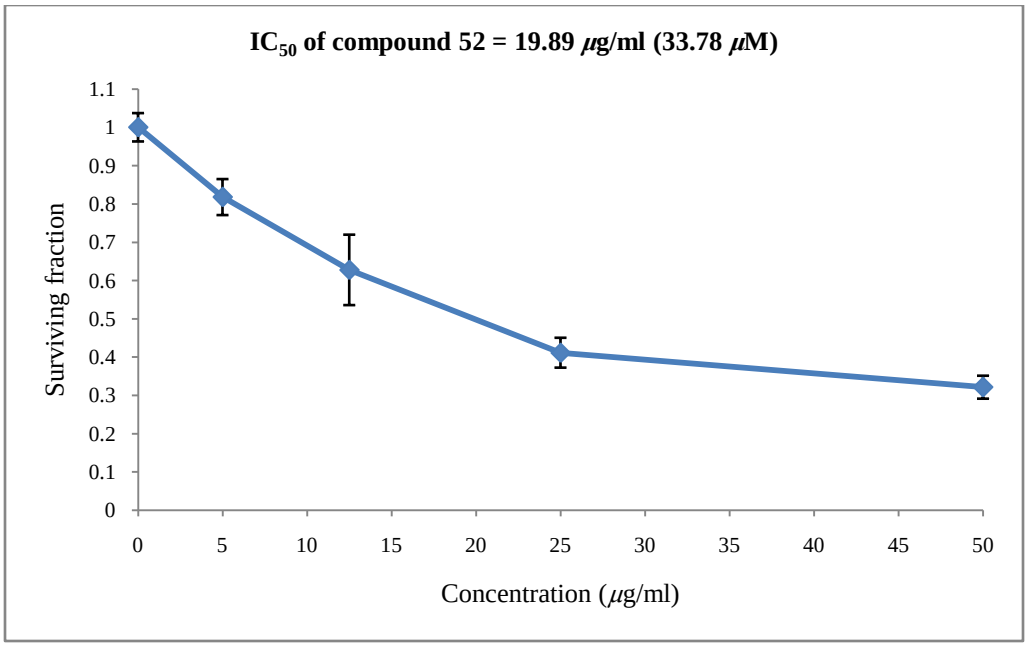

IC50 of compound 47 = 14.13 μg/ml (23.06 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

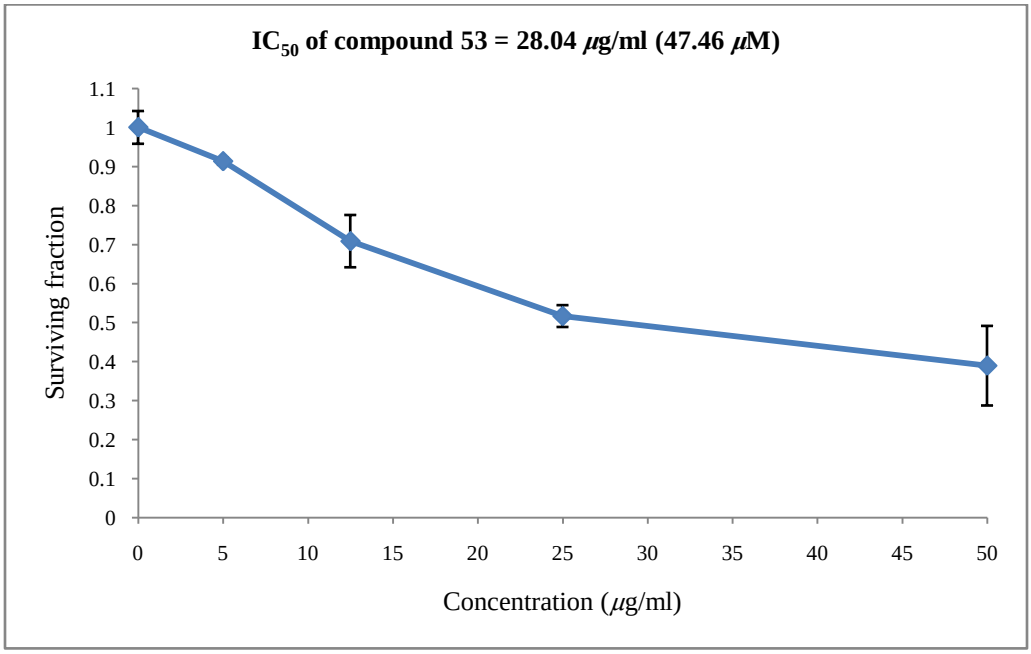

IC50 of compound 48 = 23.59 μg/ml (37.76 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

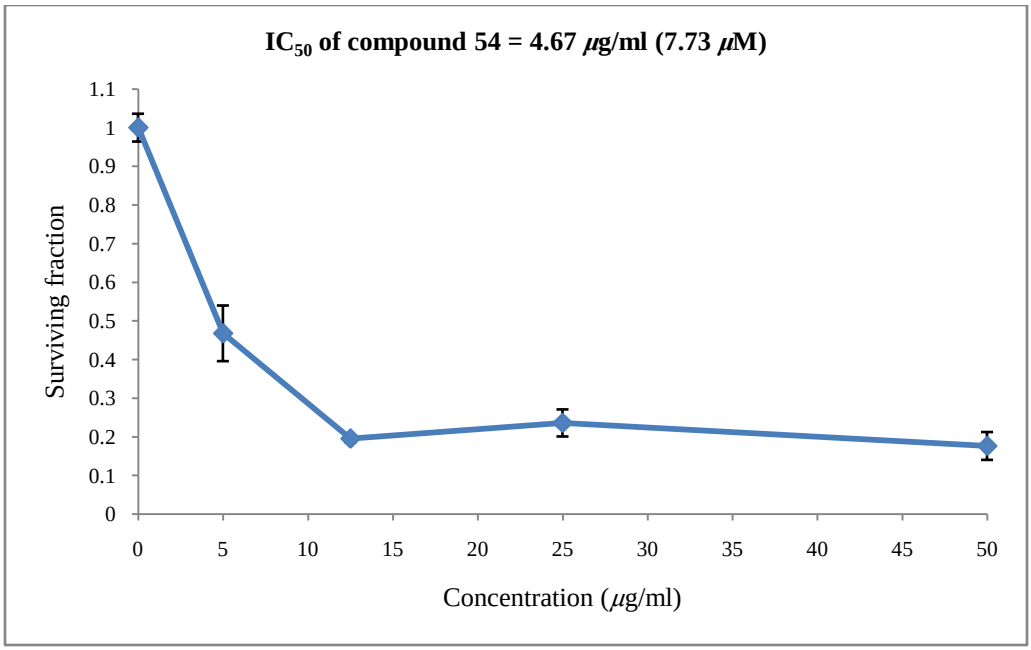

IC50 of compound 49 = 17.17 μg/ml (27.40 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

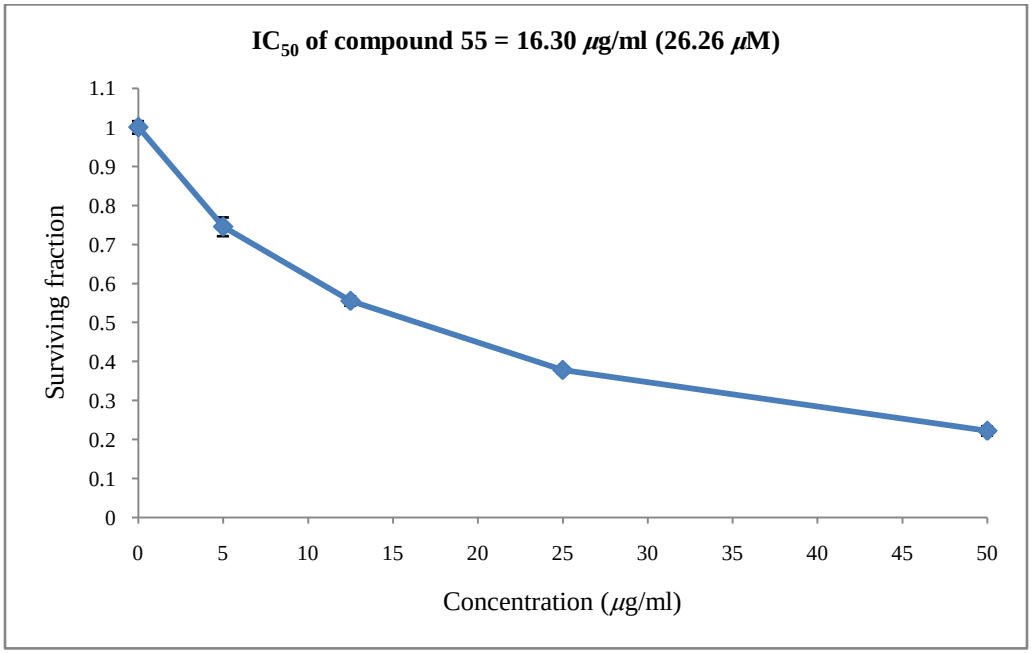

IC50 of compound 50 = 16.52 μg/ml (24.55 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

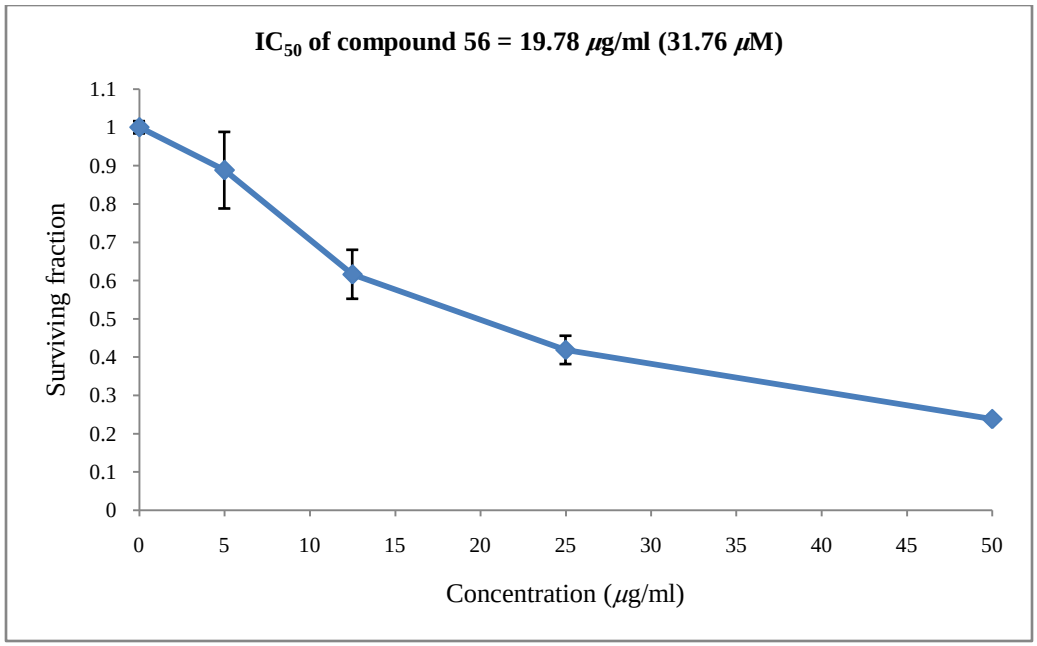

IC50 of compound 51 = 19.89 μg/ml (29.48 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

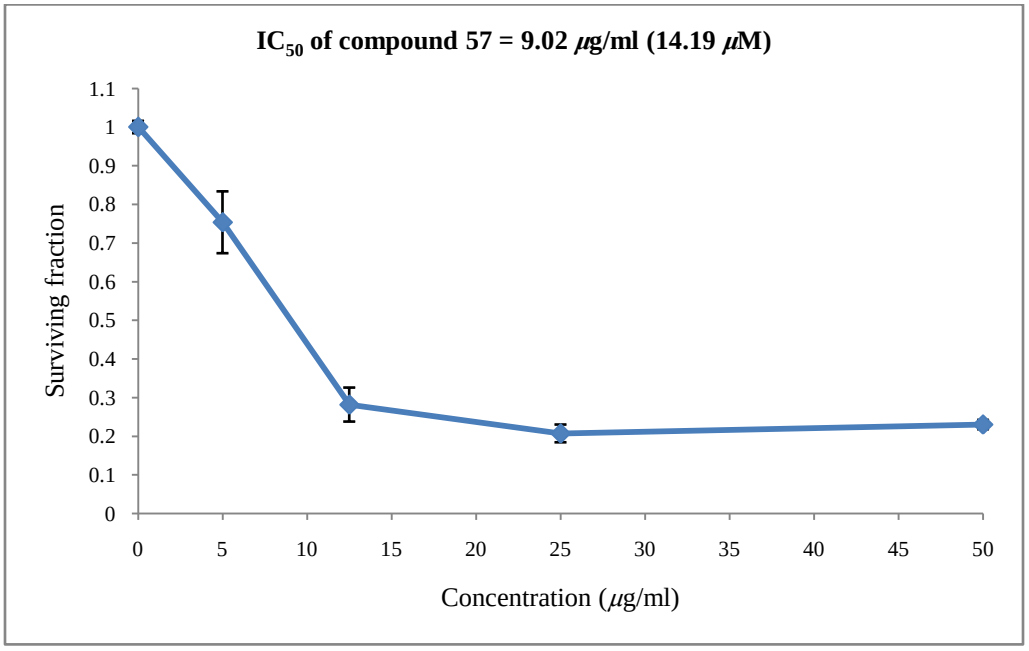

IC50 of compound 52 = 19.89 μg/ml (33.78 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

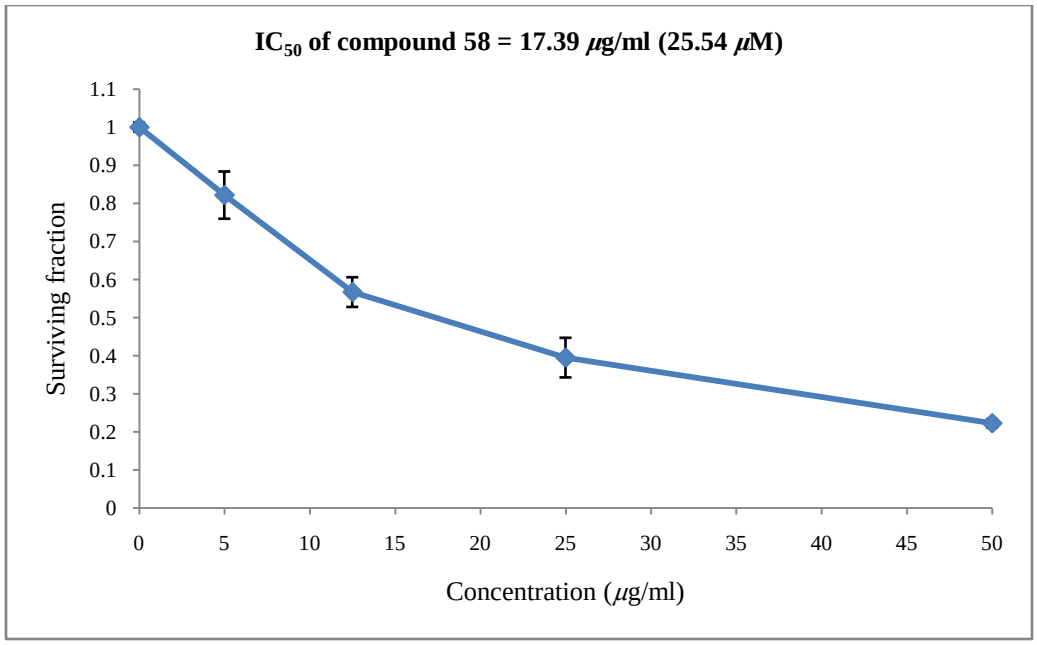

IC50 of compound 53 = 28.04 μg/ml (47.46 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

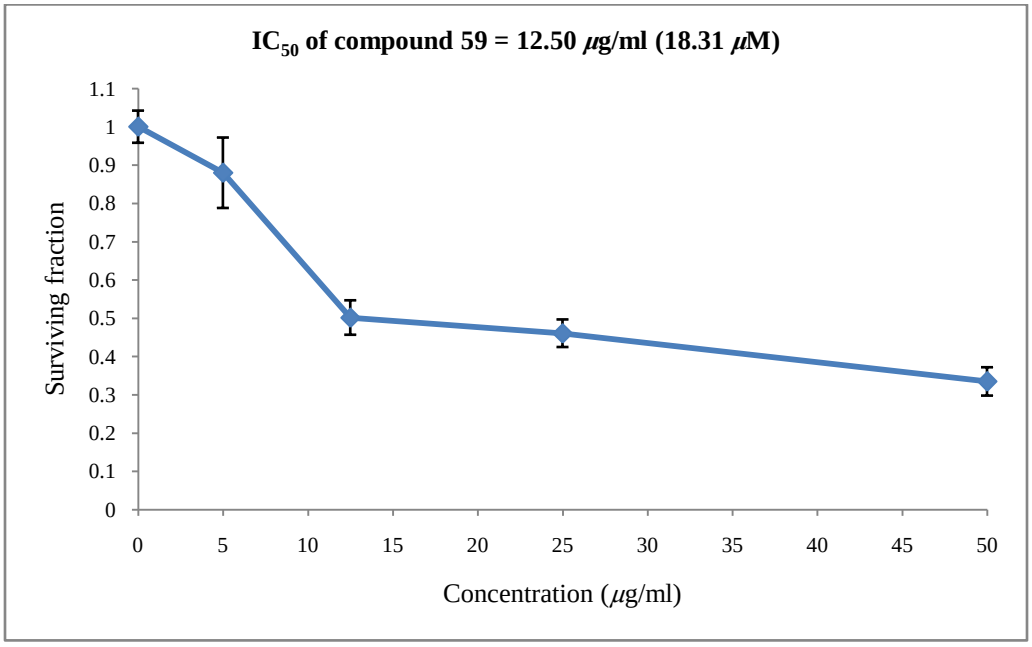

IC50 of compound 54 = 4.67 μg/ml (7.73 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

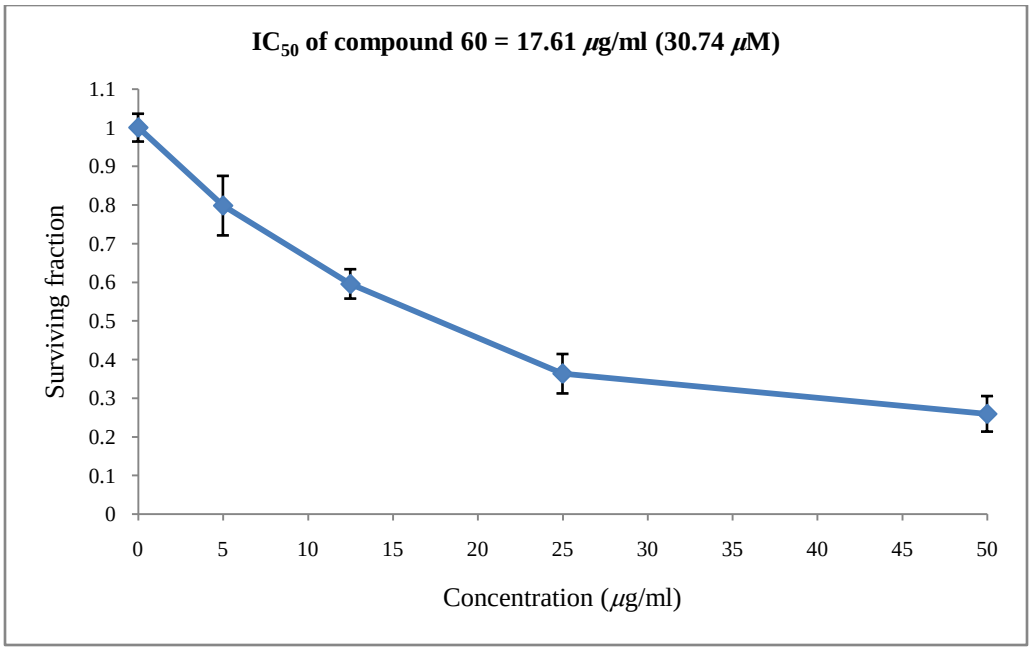

IC50 of compound 55 = 16.30 μg/ml (26.26 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

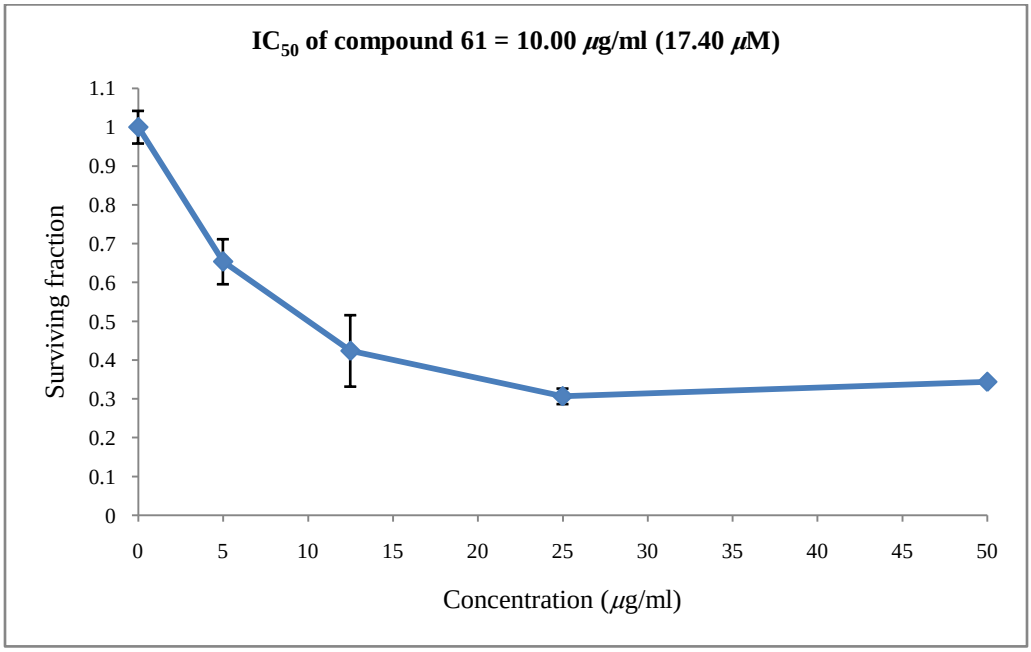

IC50 of compound 56 = 19.78 μg/ml (31.76 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)


IC50 of compound 57 = 9.02 μg/ml (14.19 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)


IC50 of compound 58 = 17.39 μg/ml (25.54 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)


IC50 of compound 59 = 12.50 μg/ml (18.31 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)


IC50 of compound 60 = 17.61 μg/ml (30.74 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)


IC50 of compound 61 = 10.00 μg/ml (17.40 μM)
Surviving fraction
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
45
50
Concentration (μg/ml)

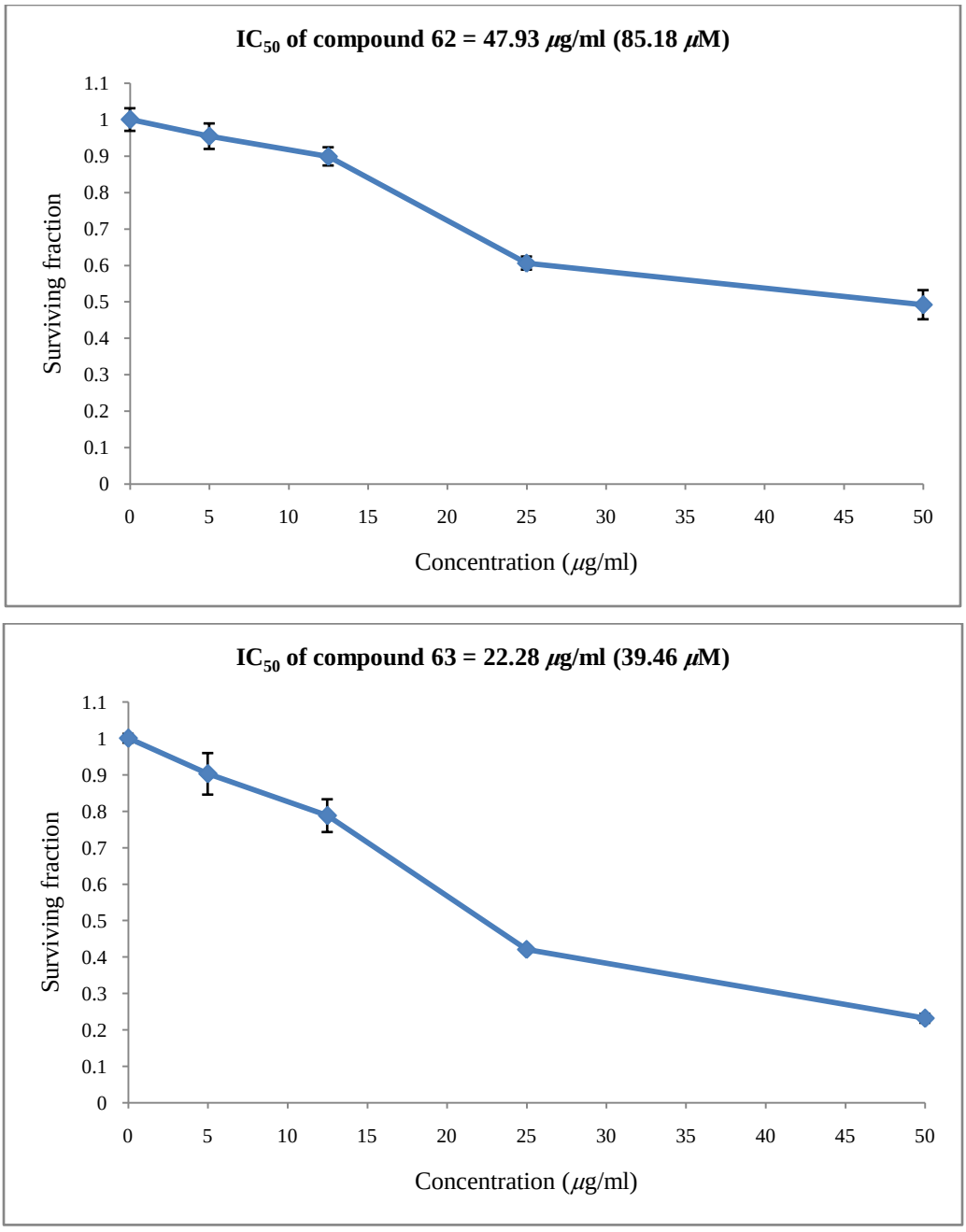


Figure 115. Dose-response curve for the synthesized compounds **30-63** against HepG2 (liver cancer) cell line.

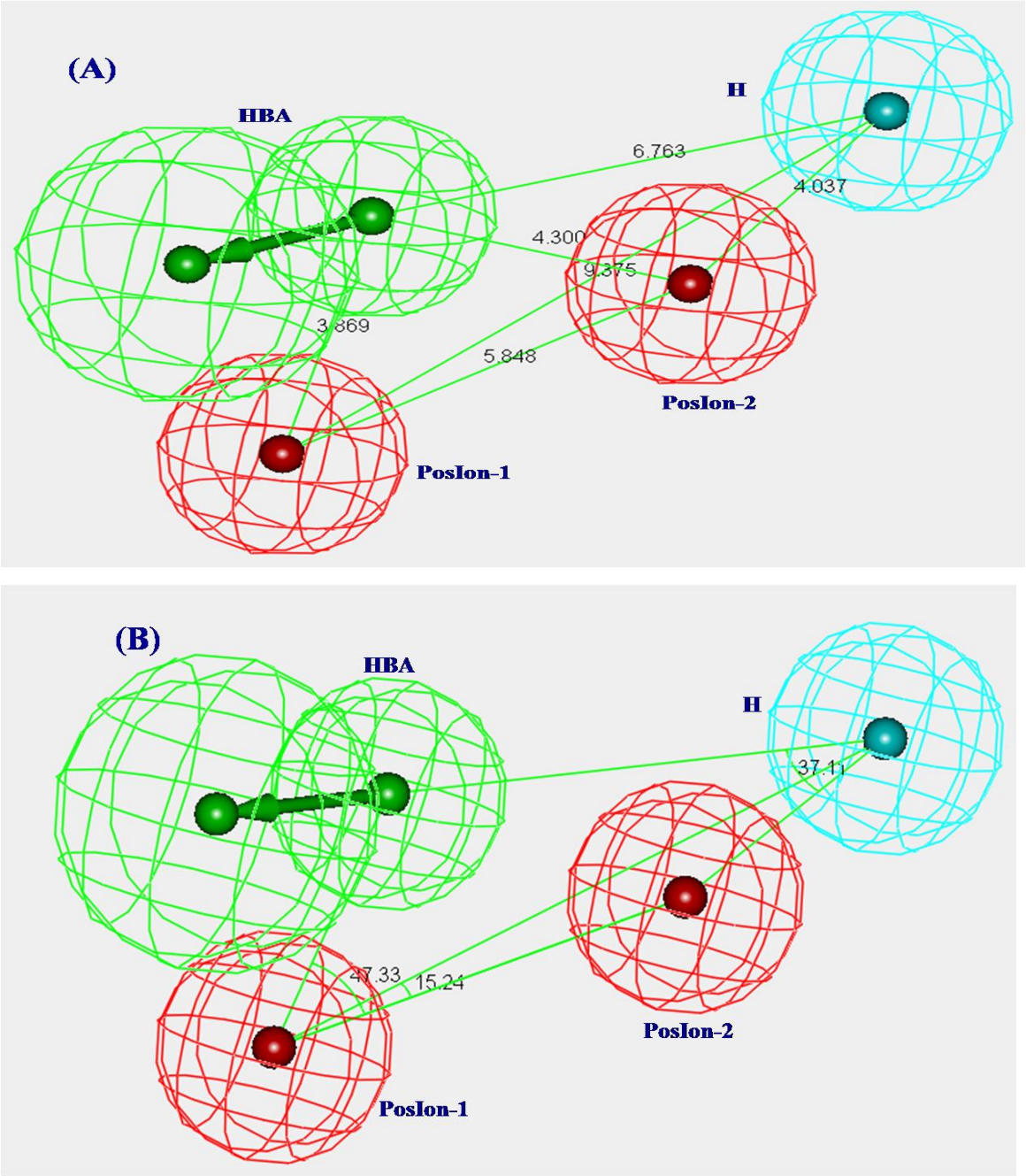
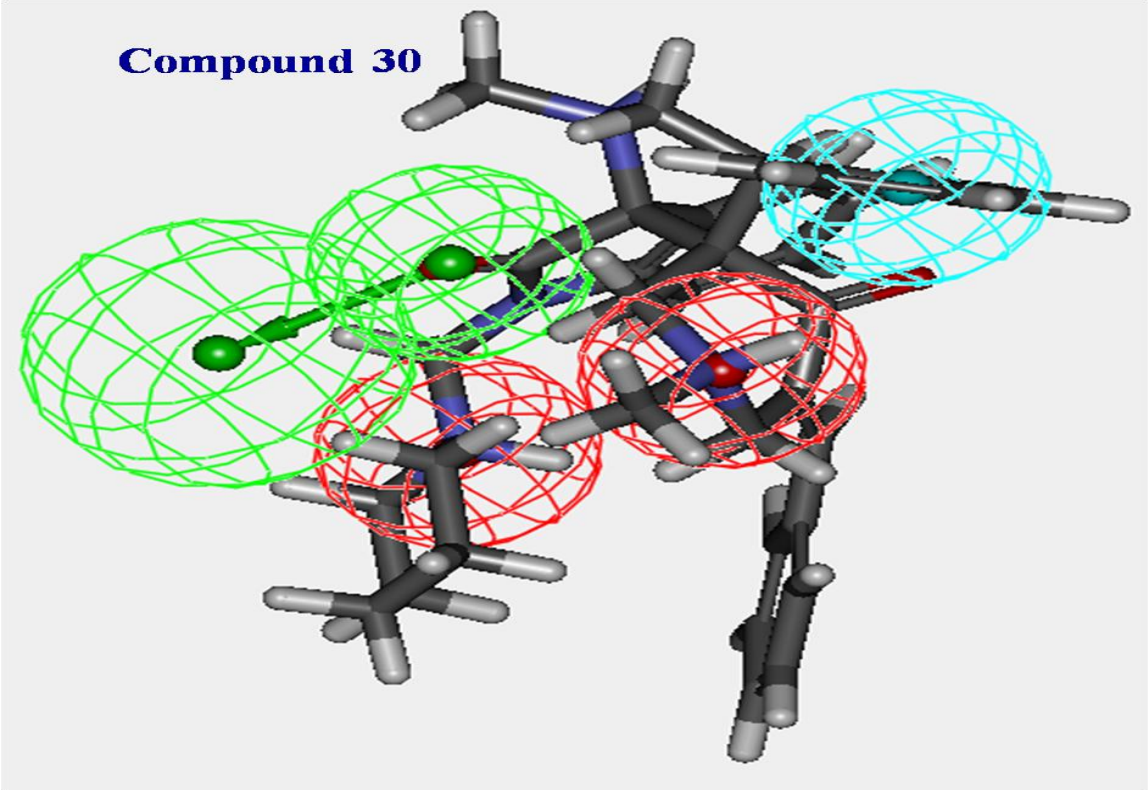
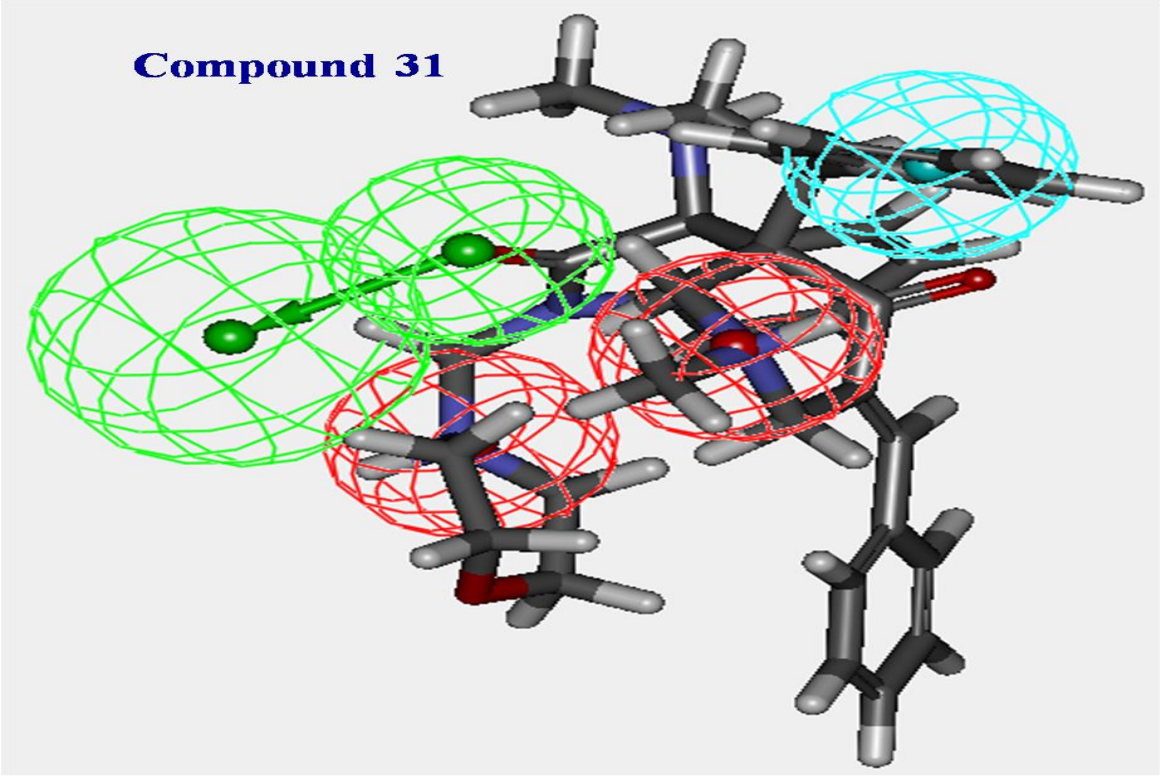


Figure S116. (A) Constraint distances "H – PosIon-1 = 9.375, H – PosIon-2 = 4.037, H – HBA = 6.763, PosIon-1 – PosIon-2 = 5.848, PosIon-1 – HBA = 3.869, PosIon-2 – HBA = 4.300 Å" and (B) constraint angles "H – PosIon-1 – PosIon-2 = 15.24, H – PosIon-1 – HBA = 47.33, PosIon-2 – H – PosIon-1 = 37.11 °" of the generated 3D-pharmacophore for the synthesized bio-active spiro-compounds **30-63** against HeLa (cervical carcinoma) cell line which contains two positive ionizables (PosIon-1, PosIon-2; red), one hydrophobic (H; light blue) and one hydrogen bonding acceptor (HBA; green).


Compound 30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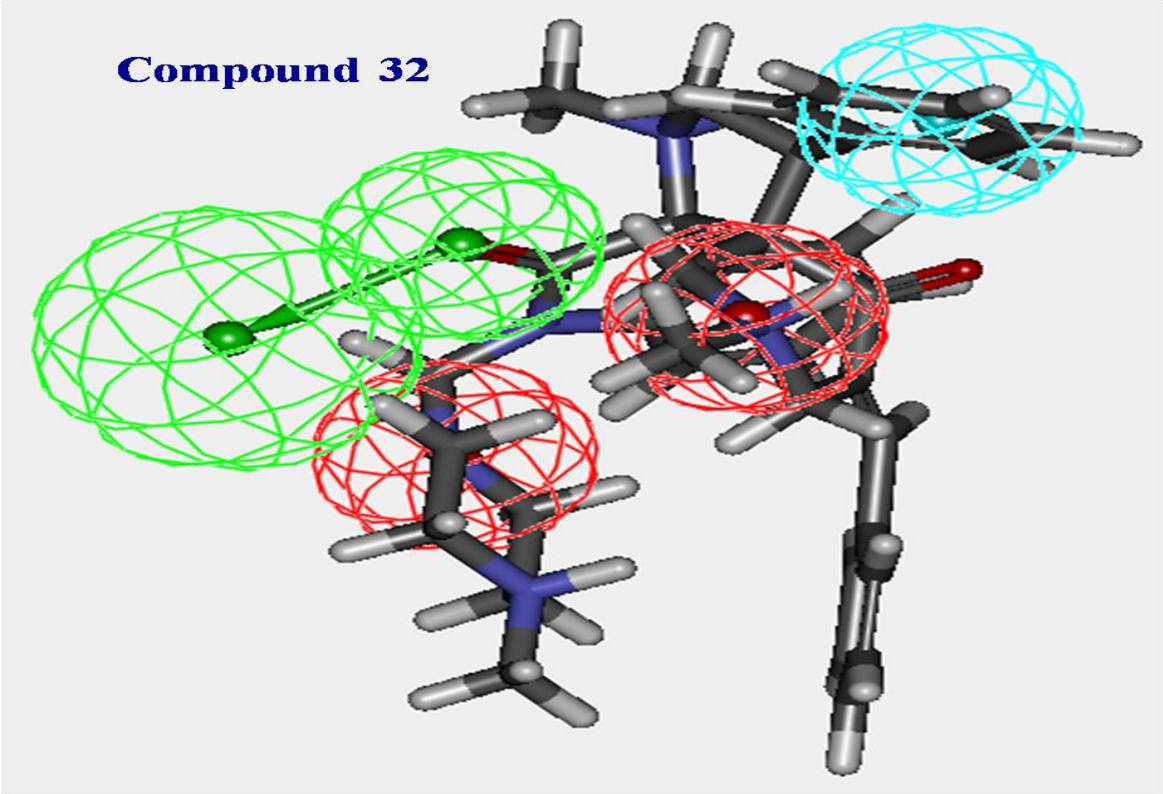
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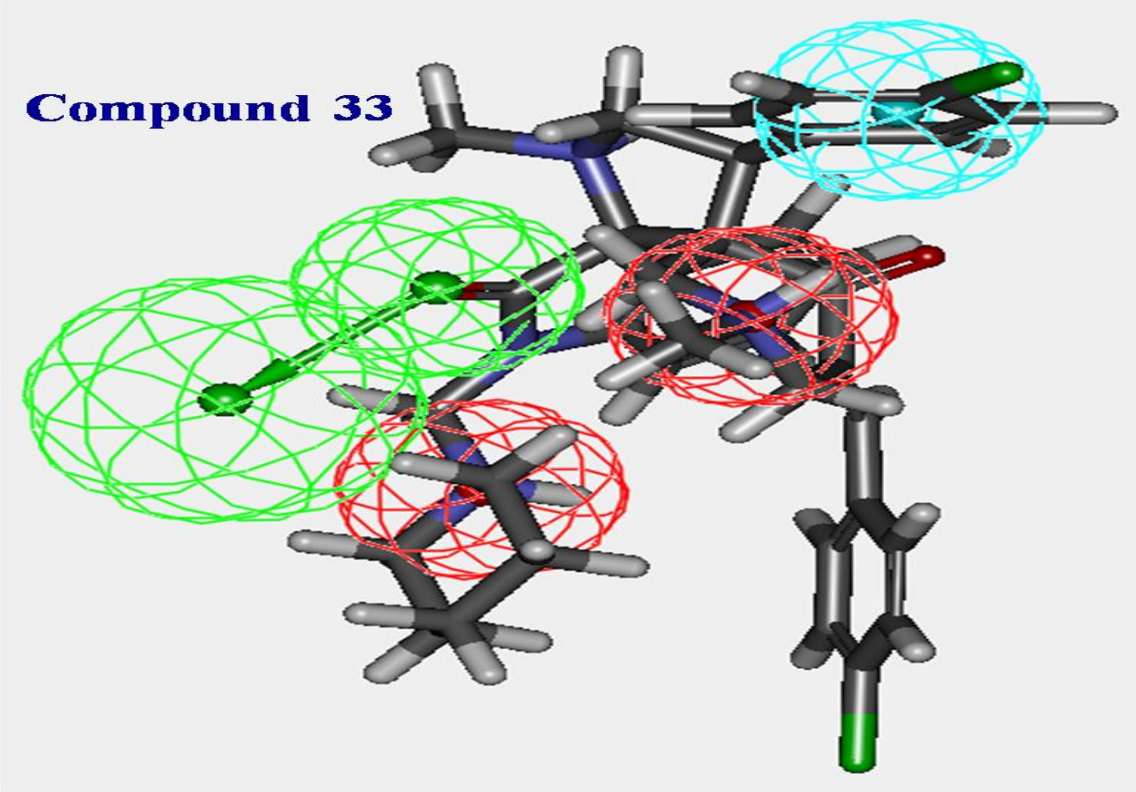
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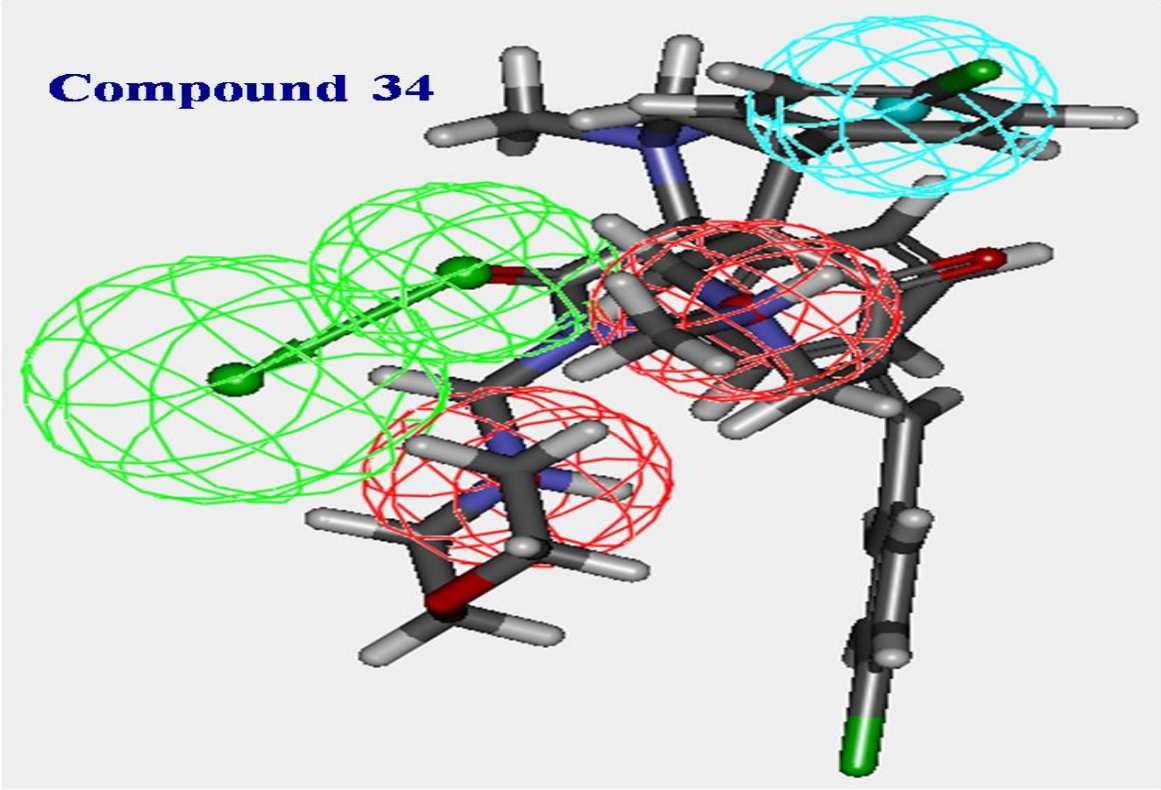
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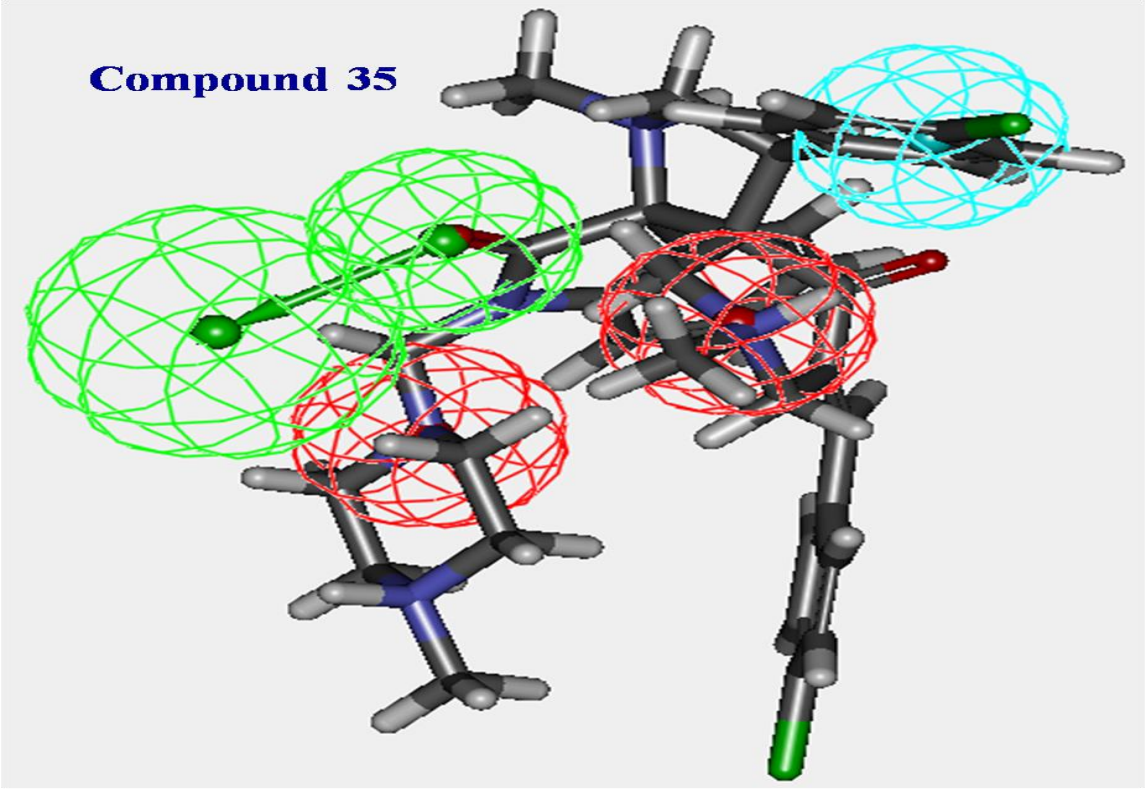
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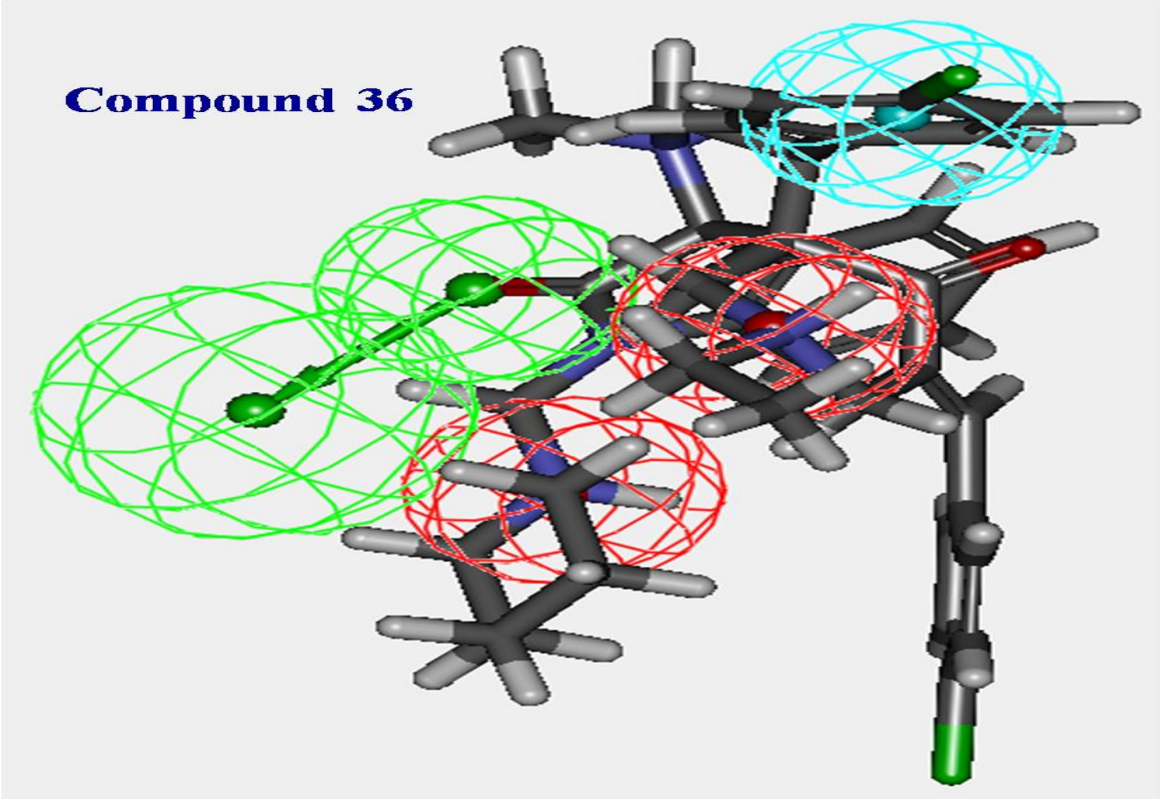
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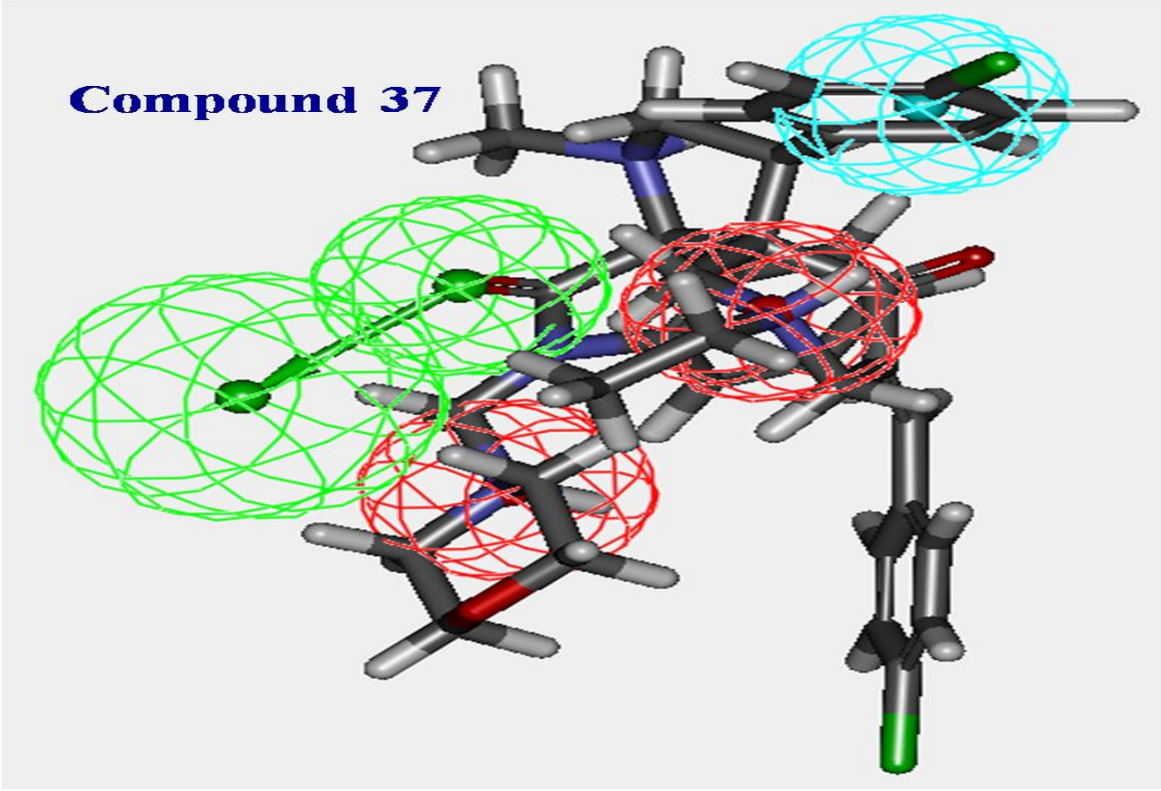
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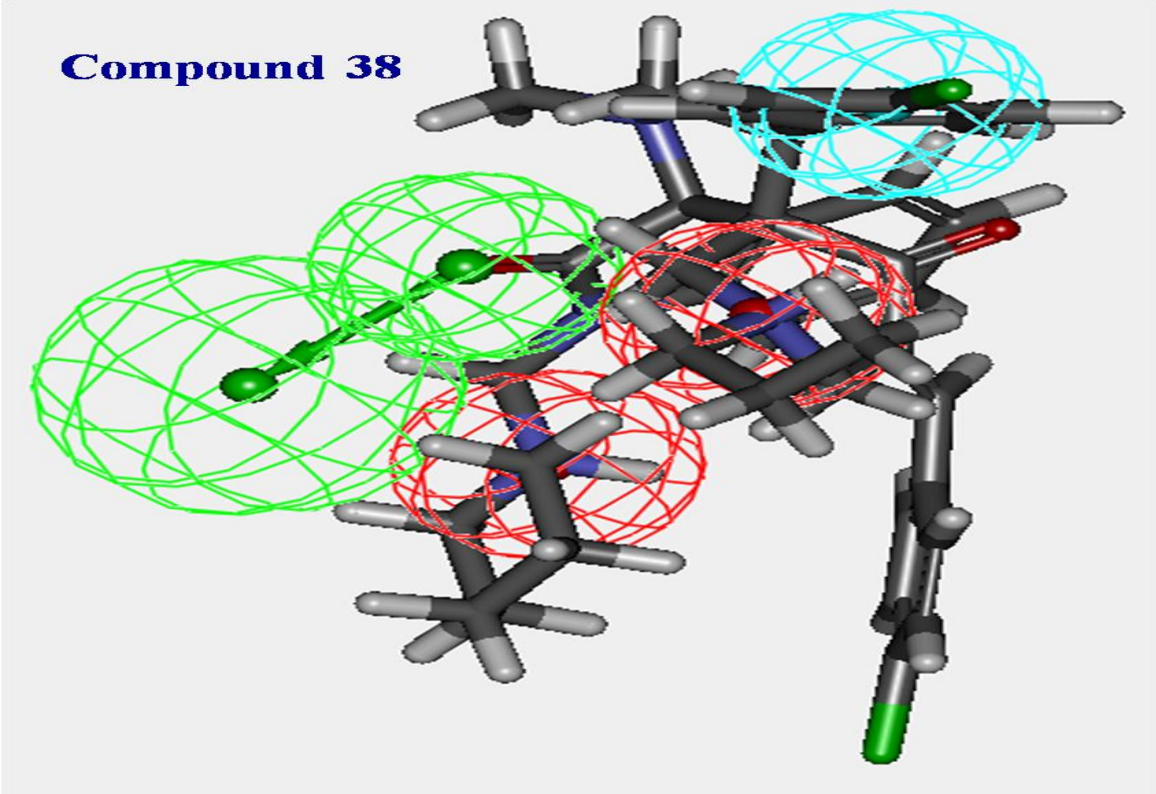
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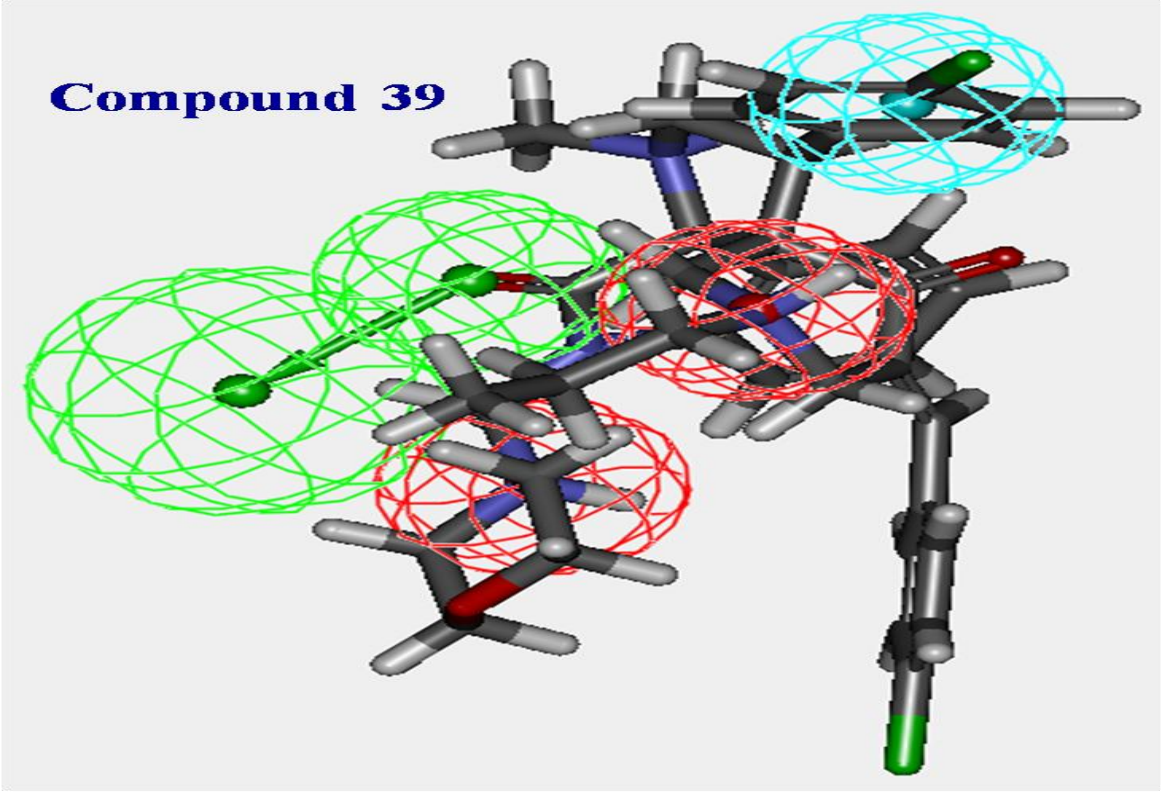
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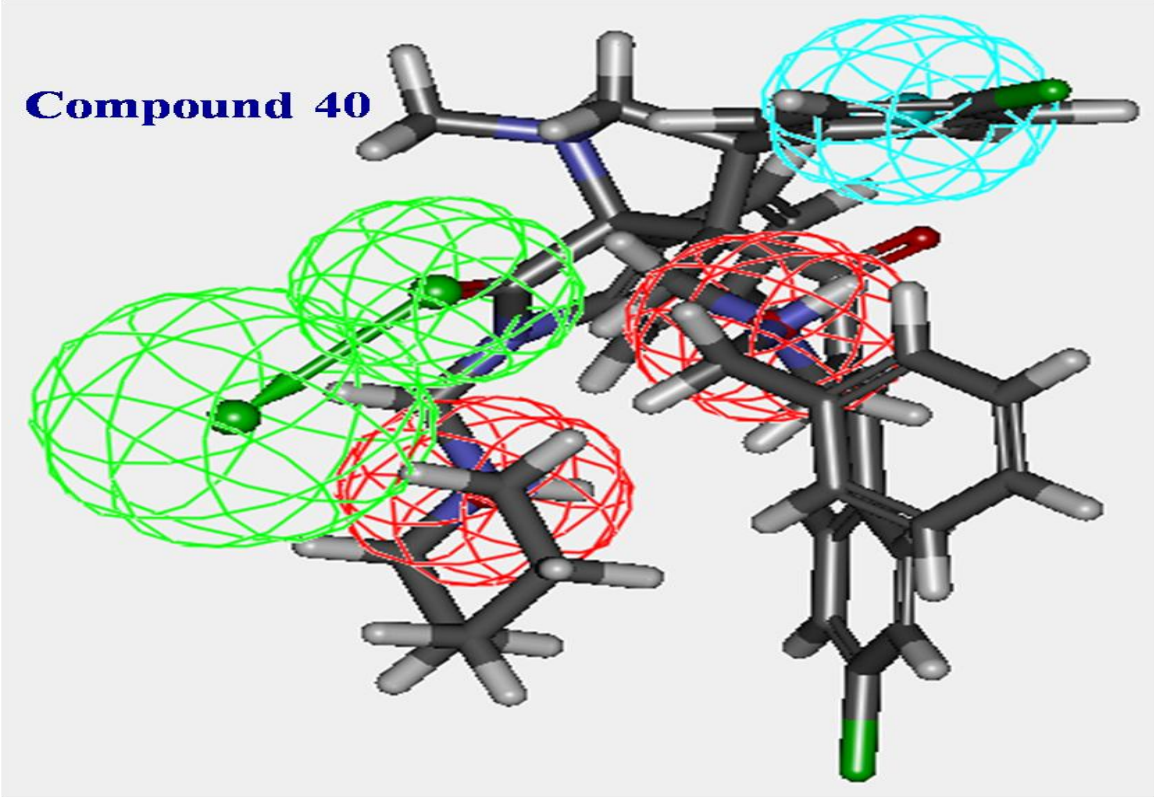
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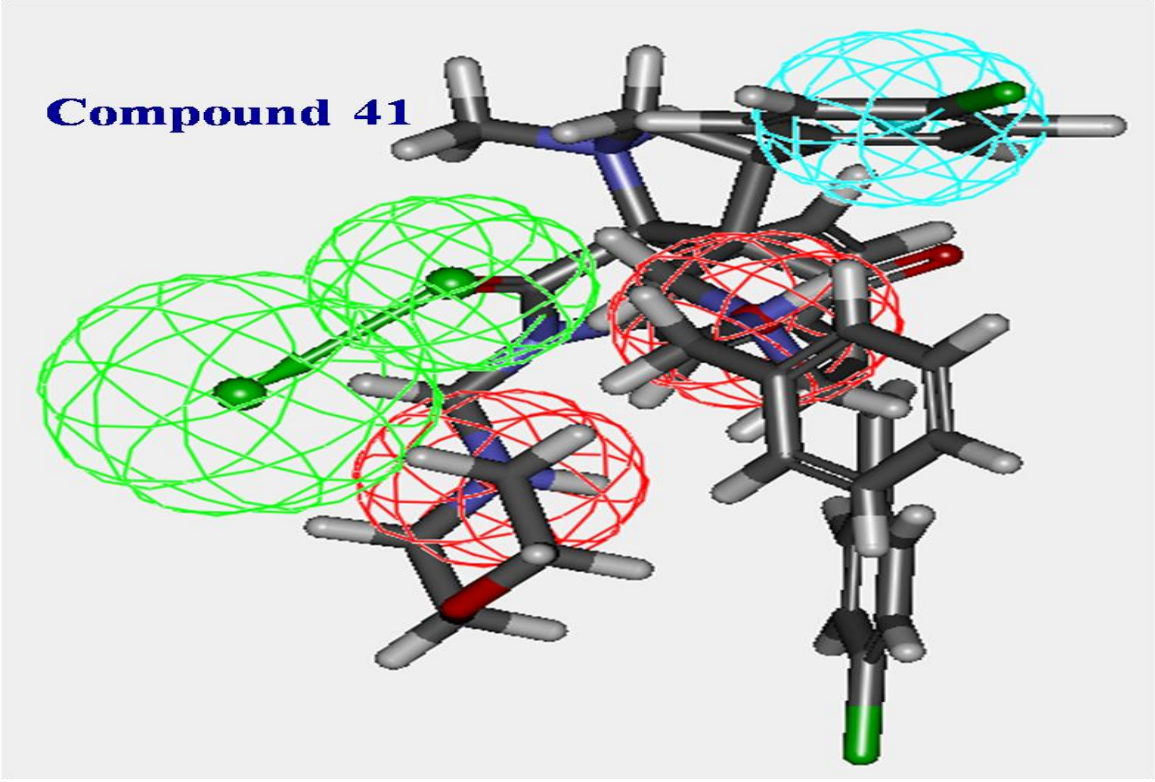
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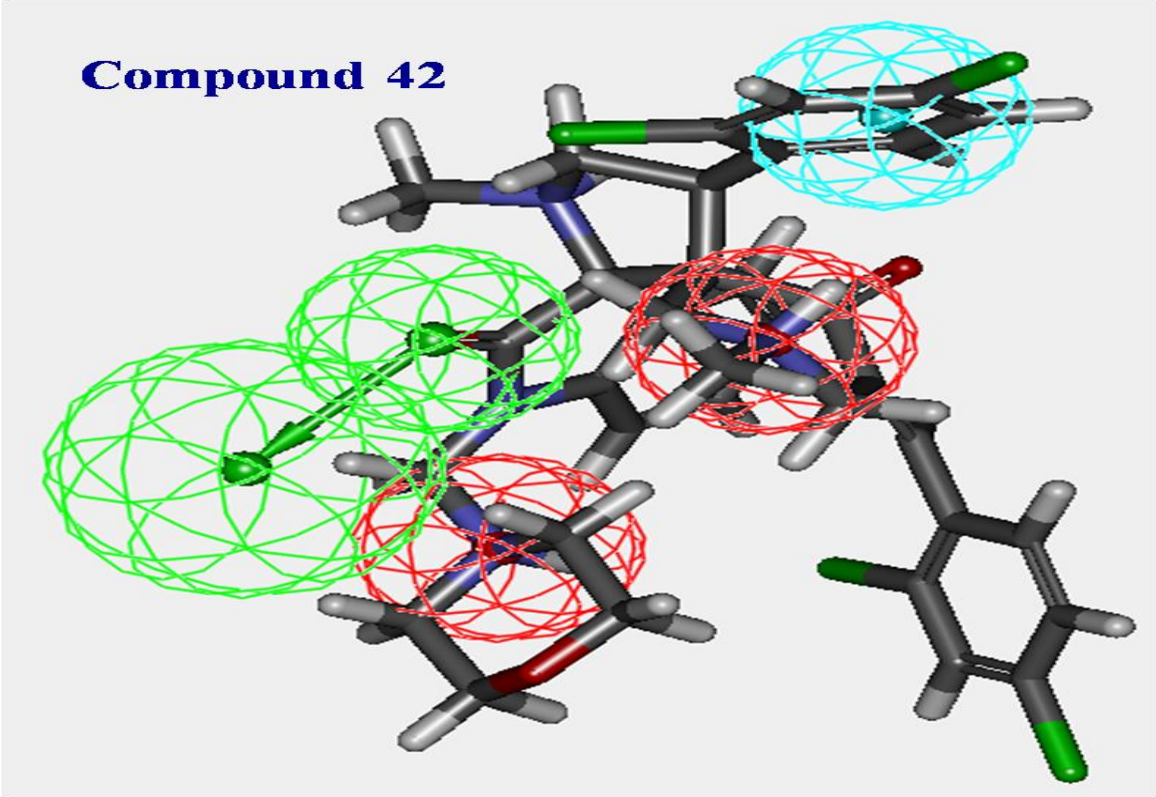
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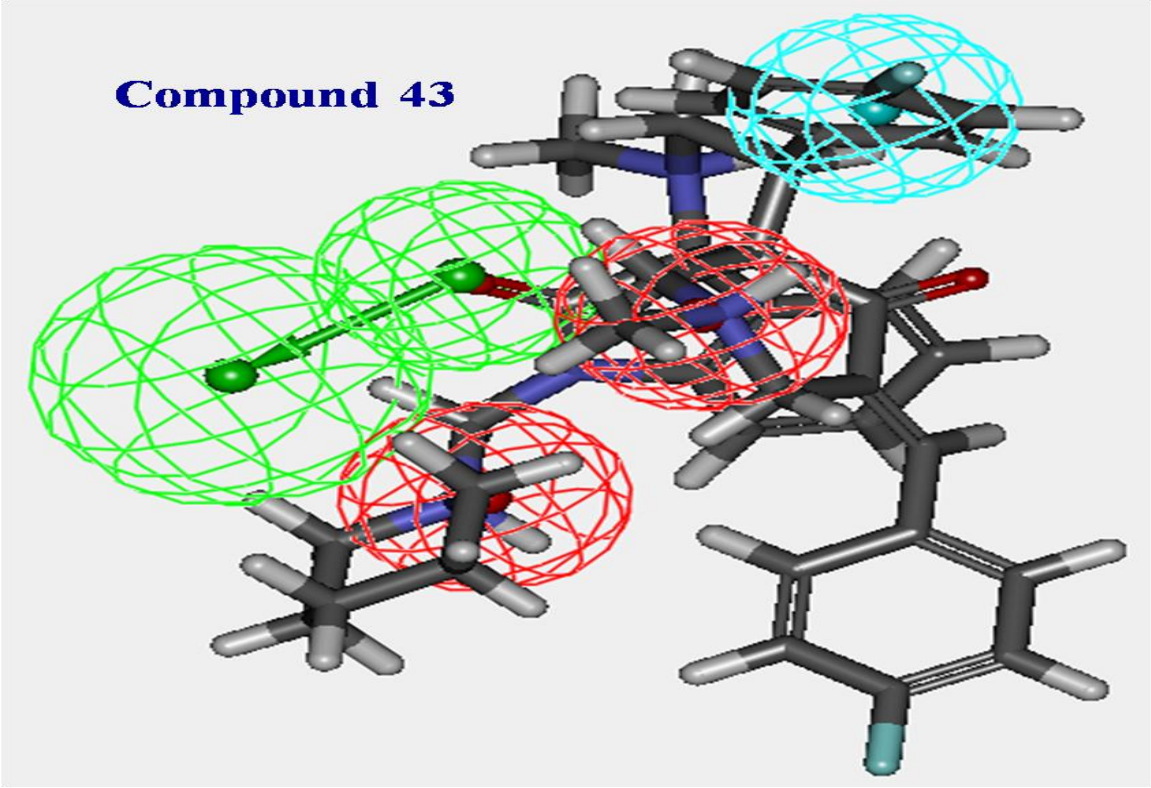
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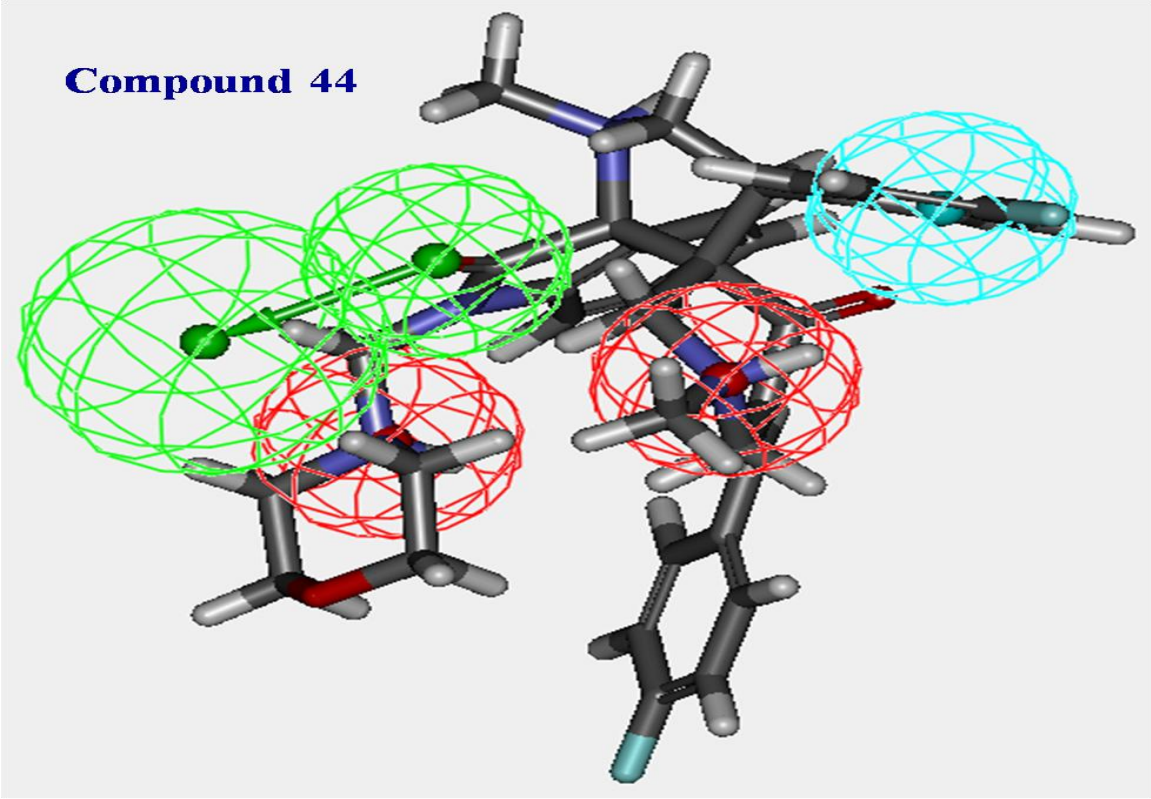
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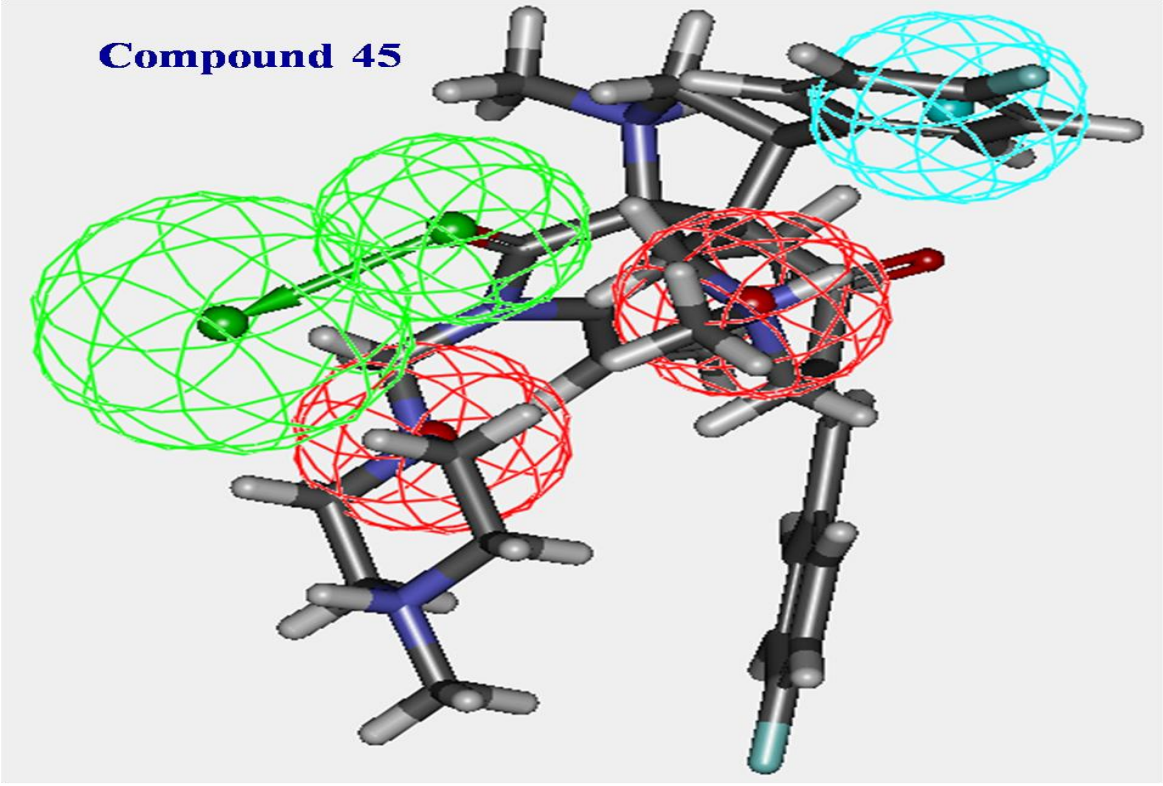
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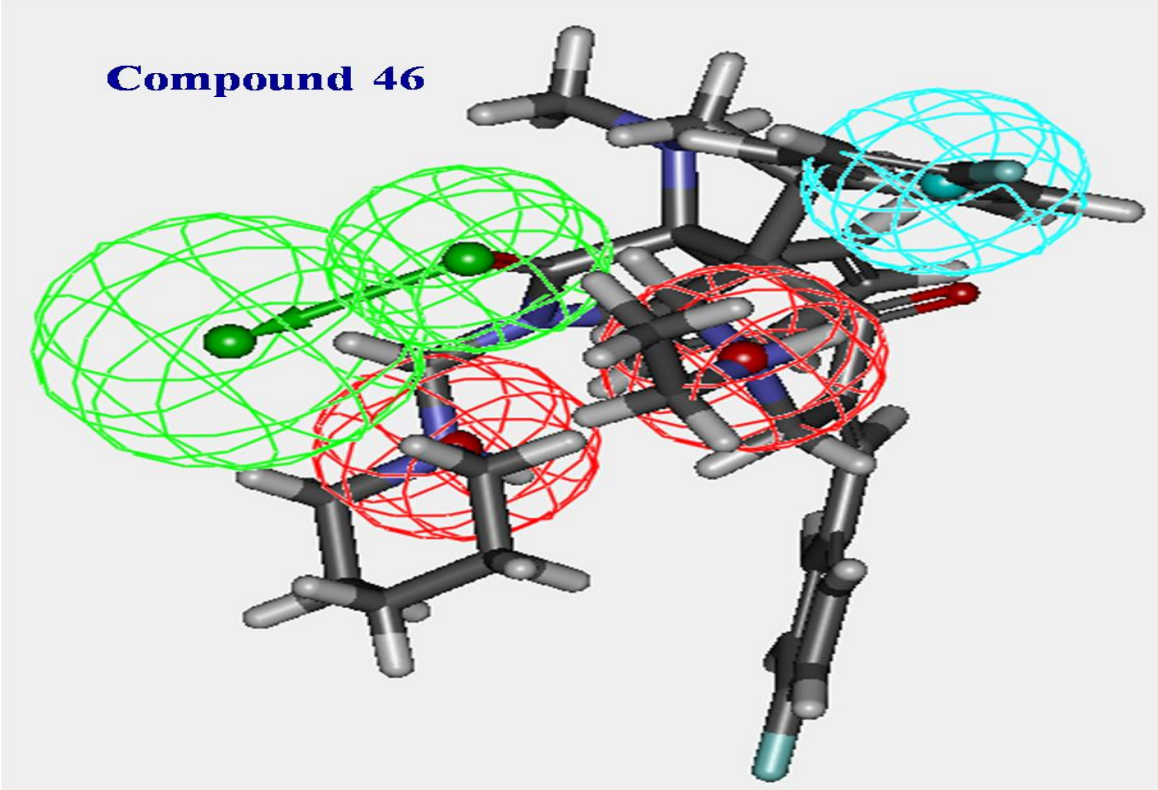
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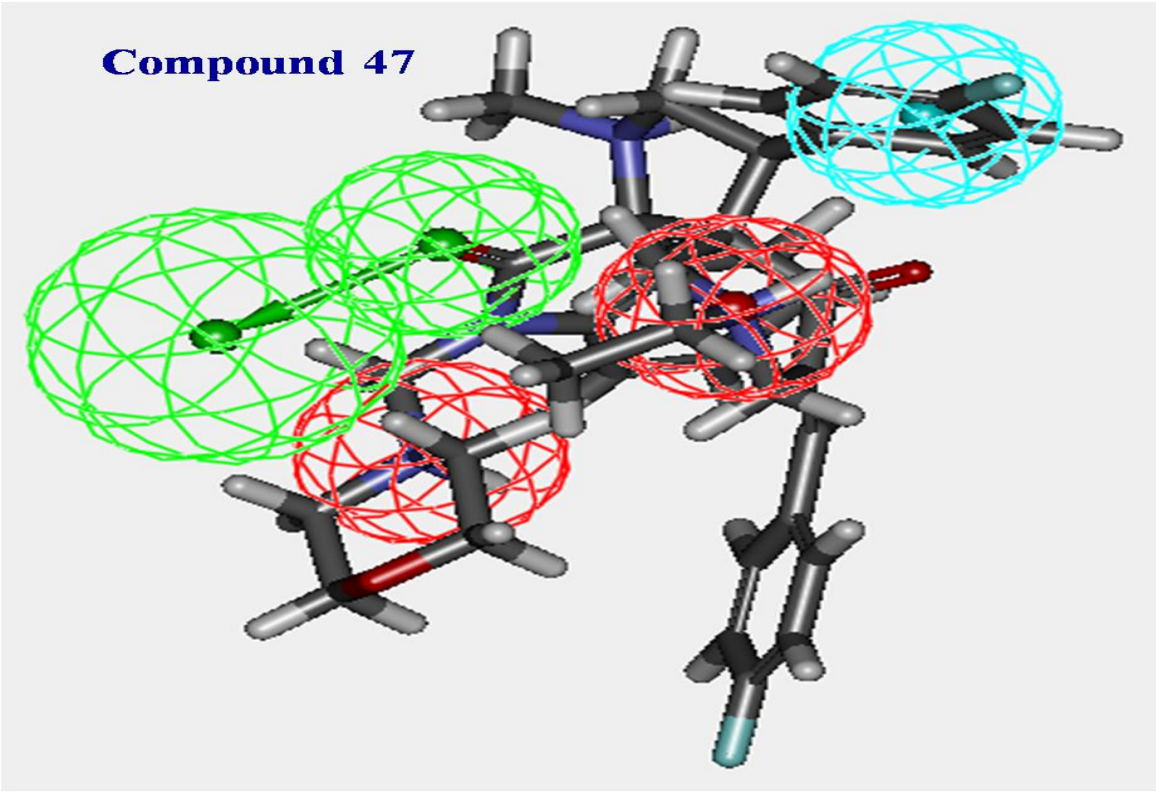
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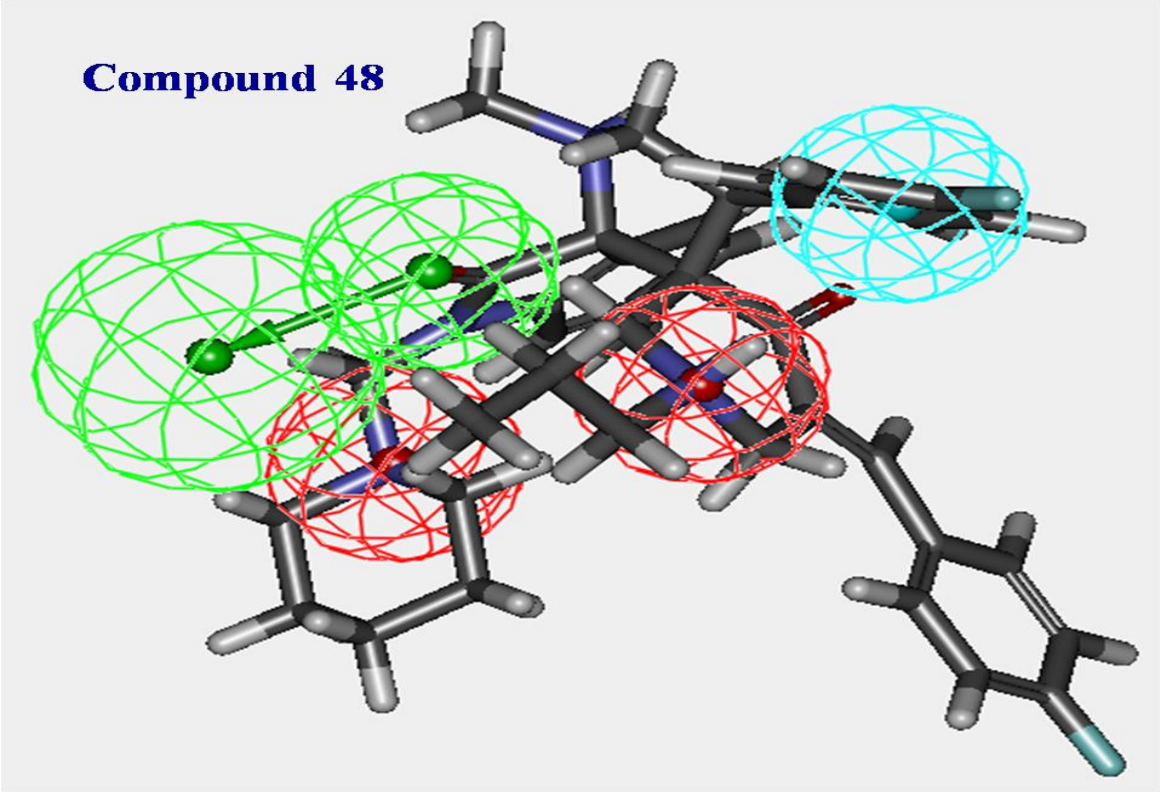
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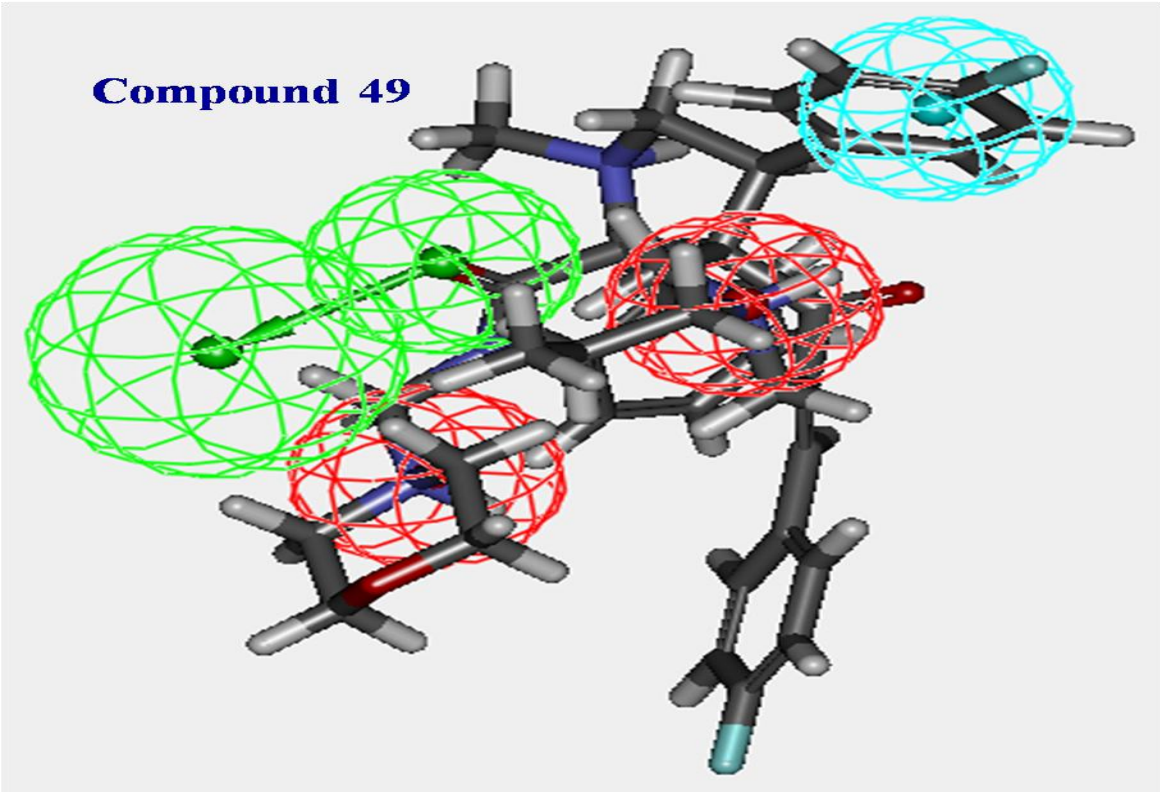
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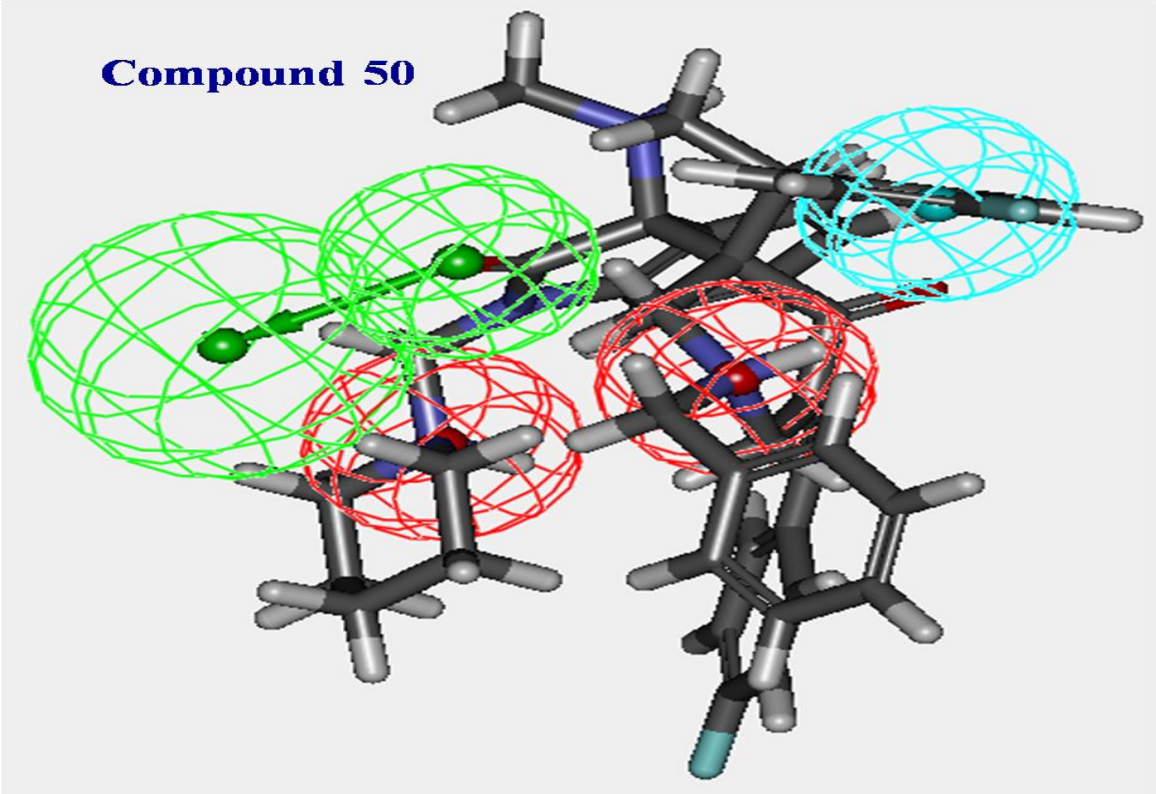
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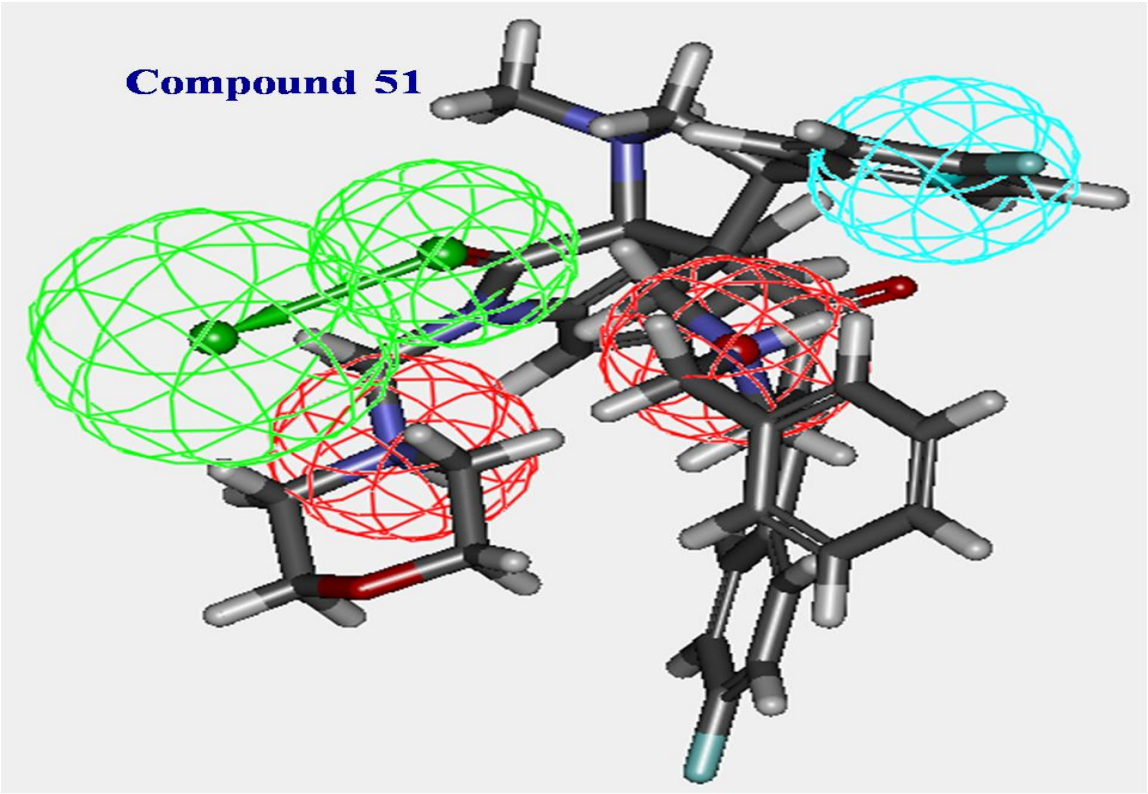
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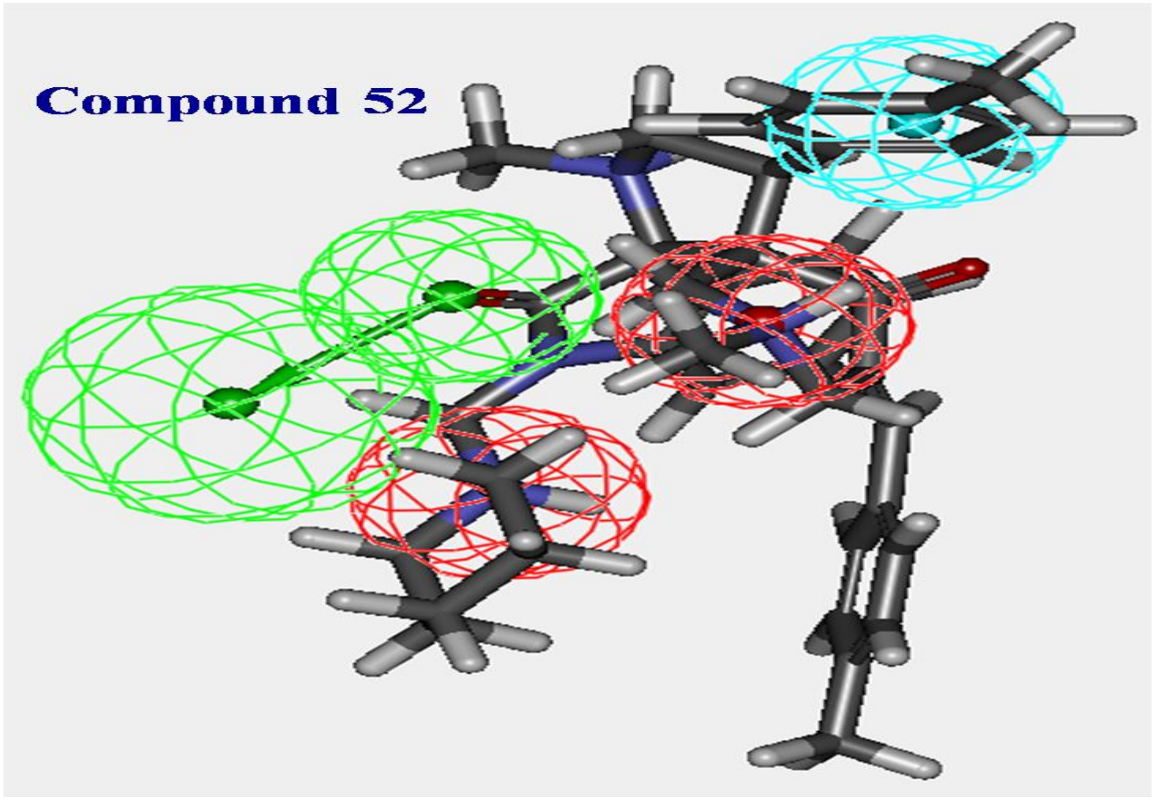
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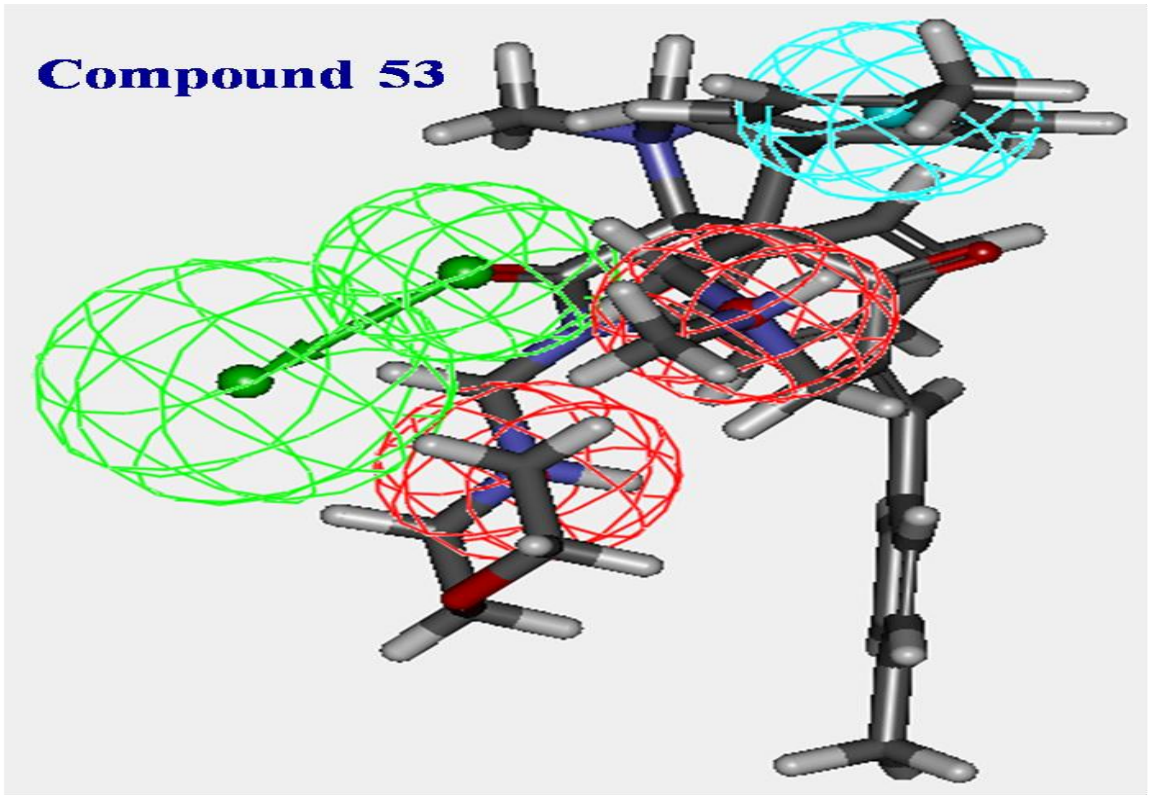
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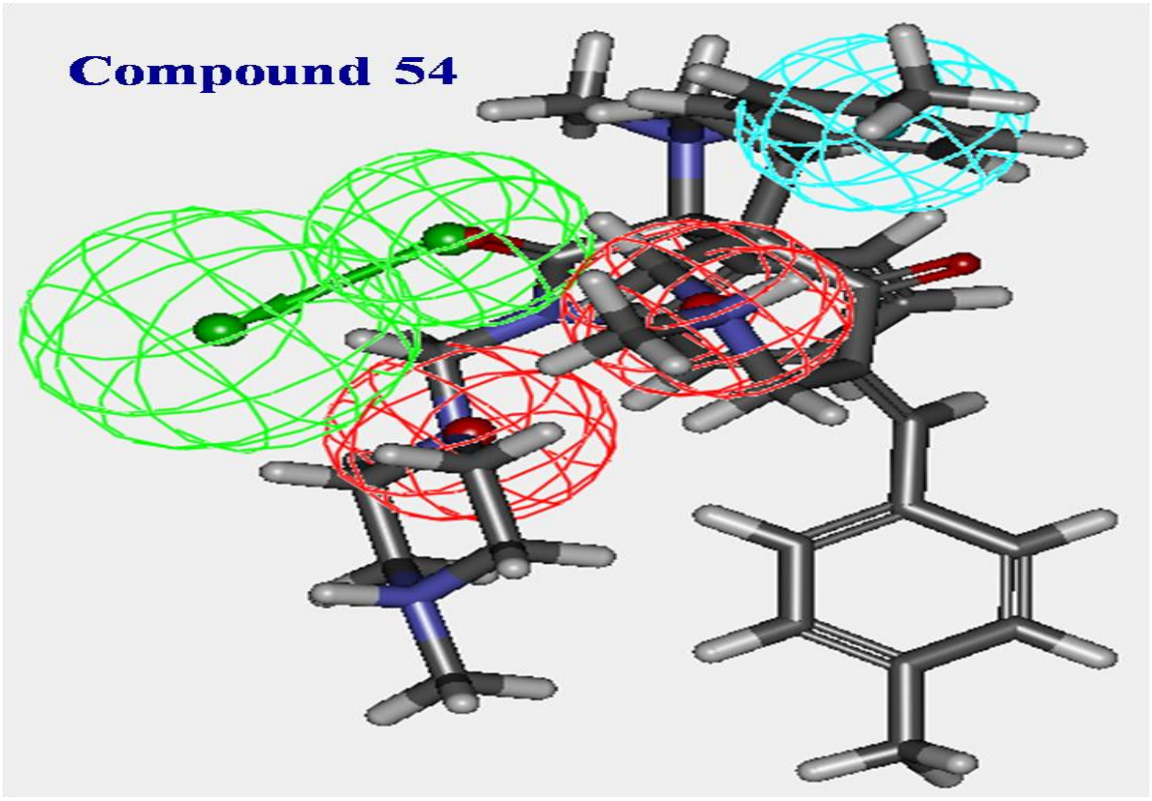
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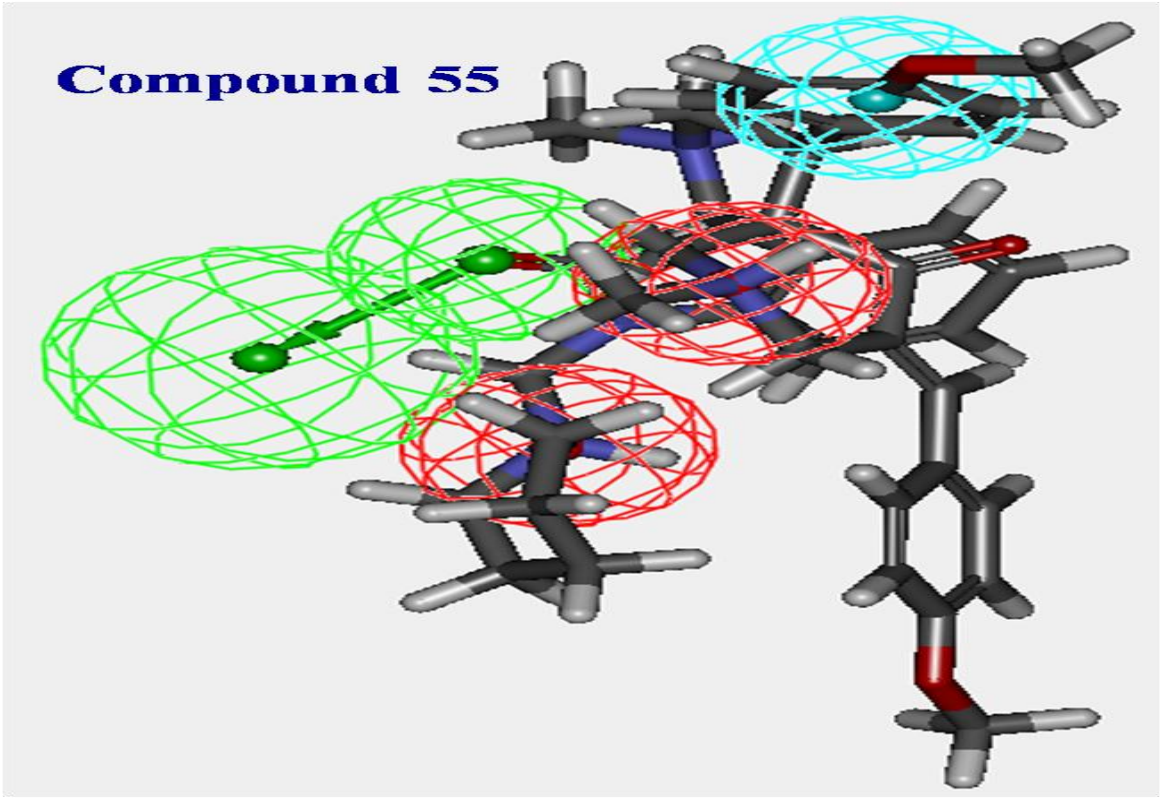
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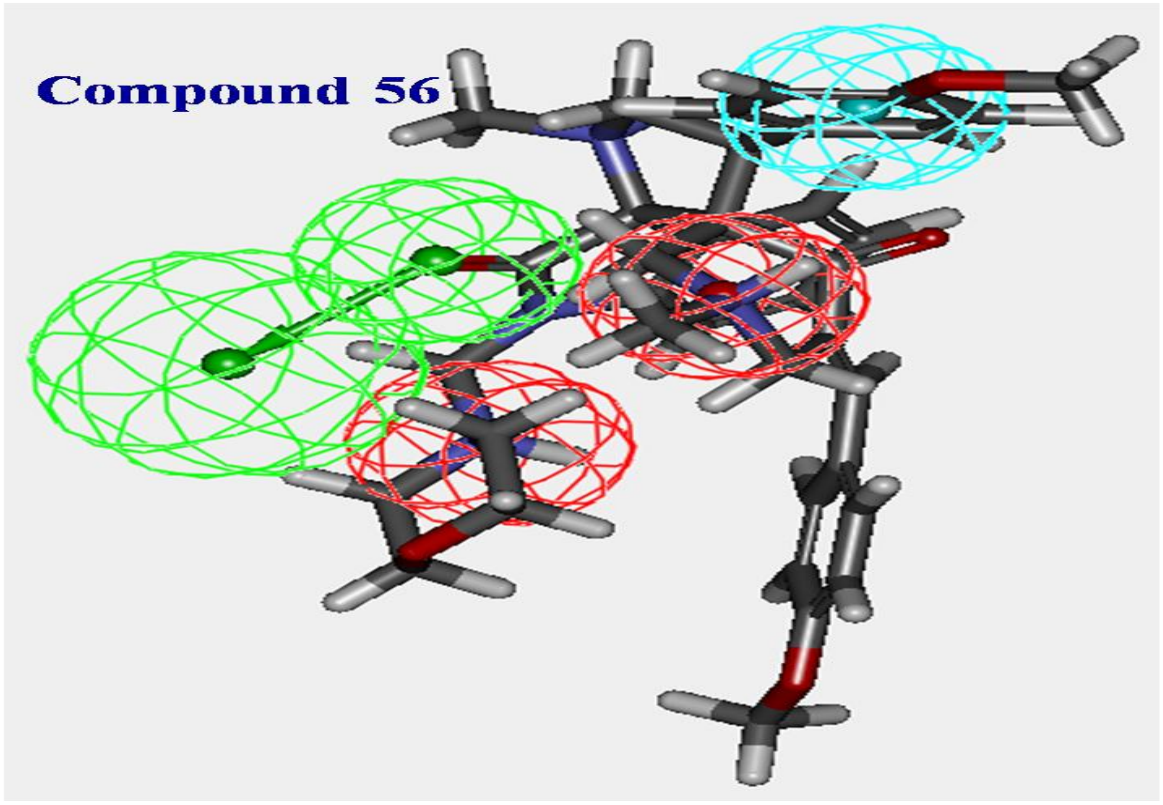
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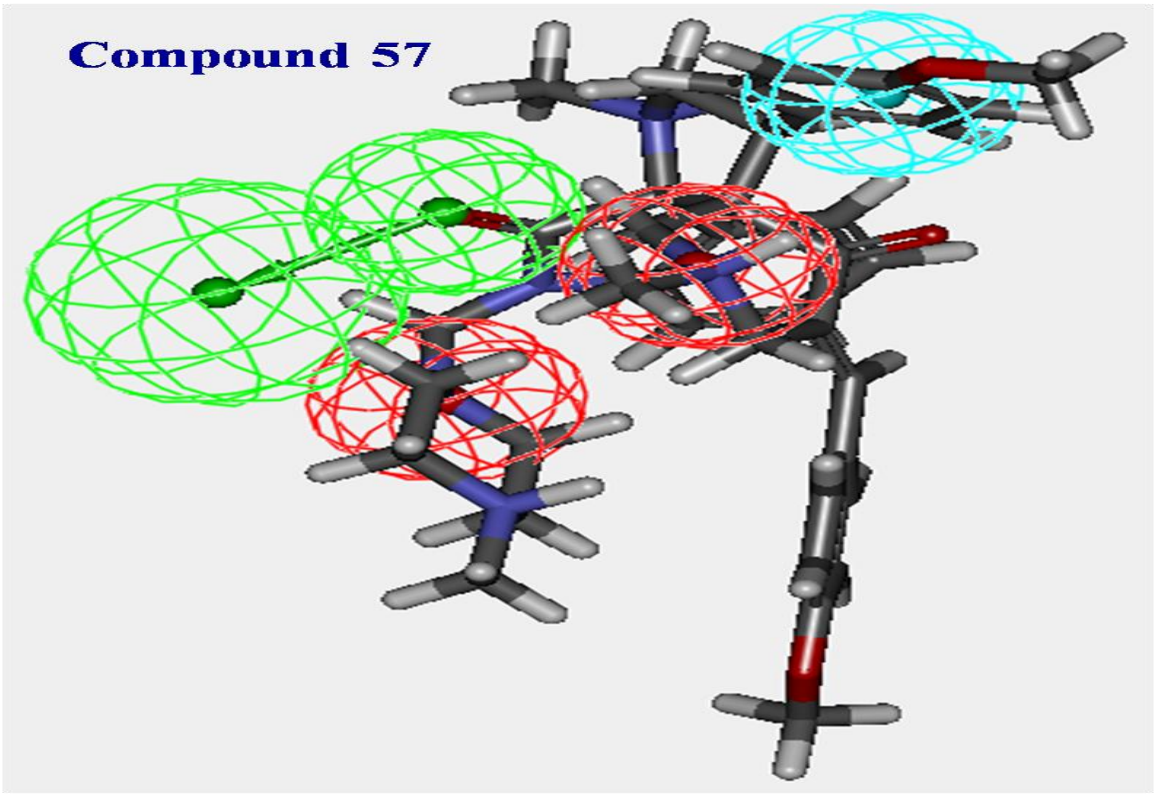
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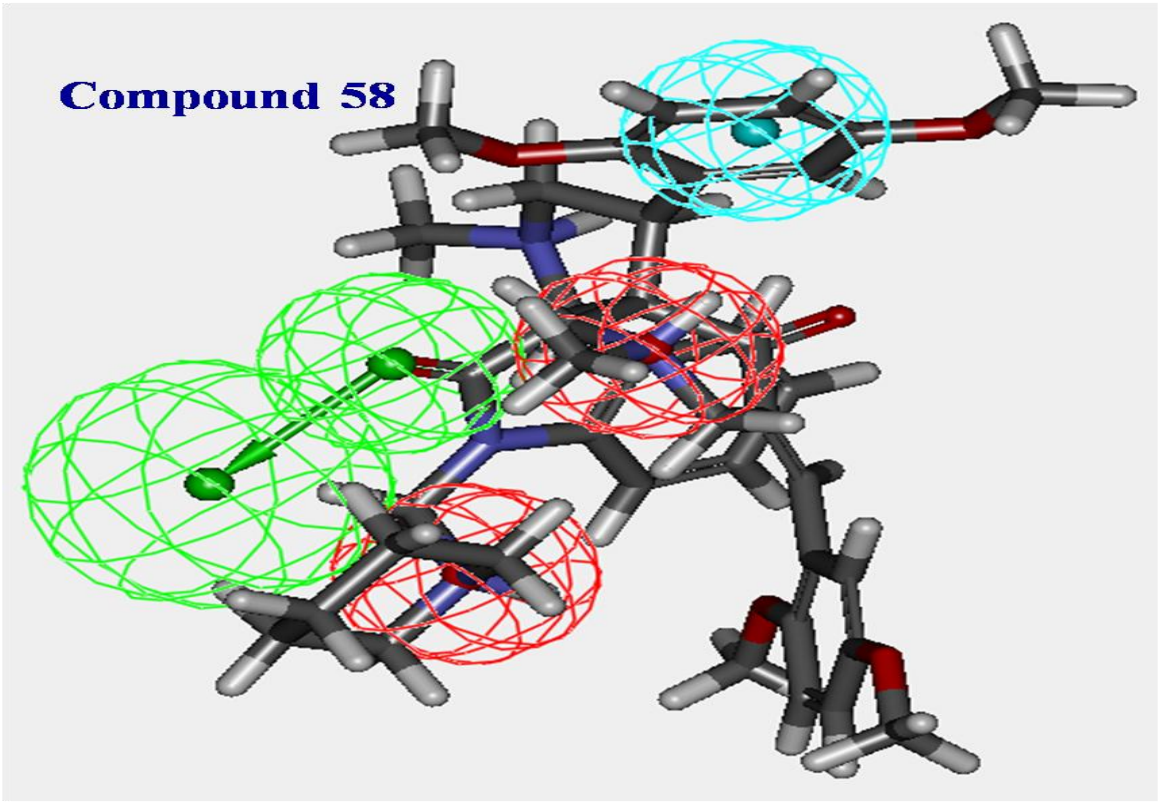
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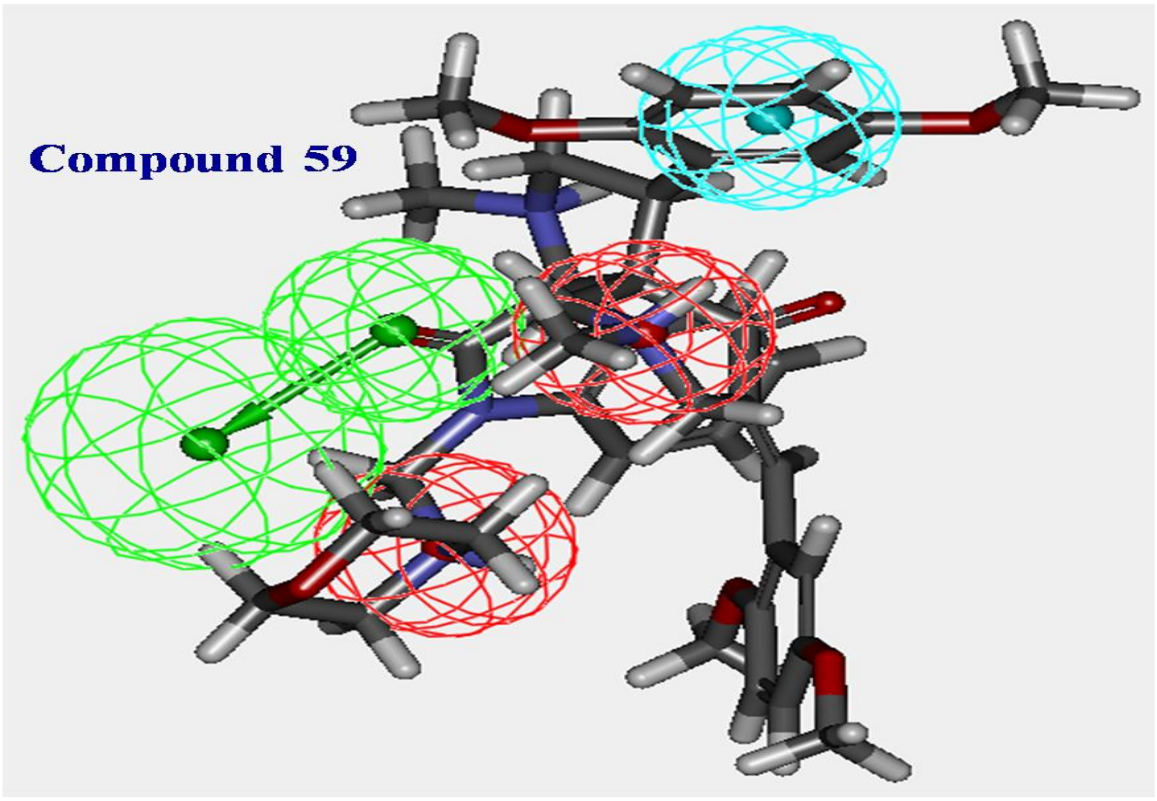
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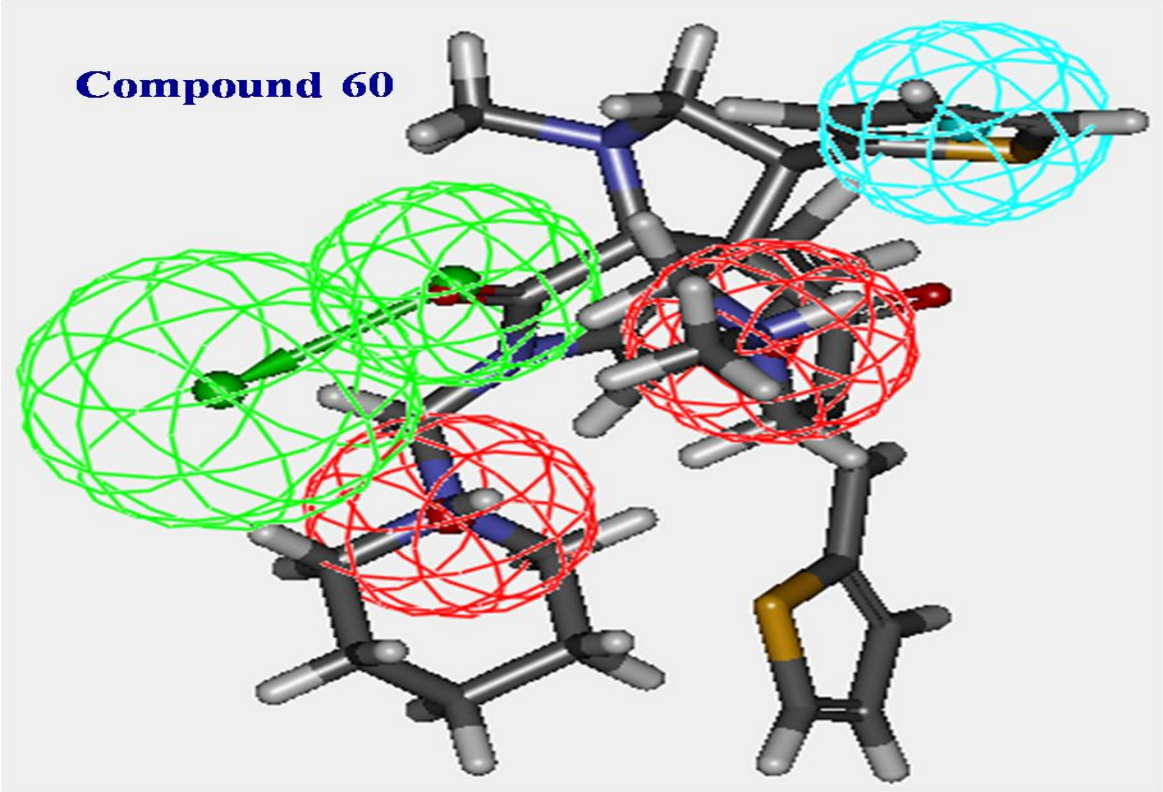
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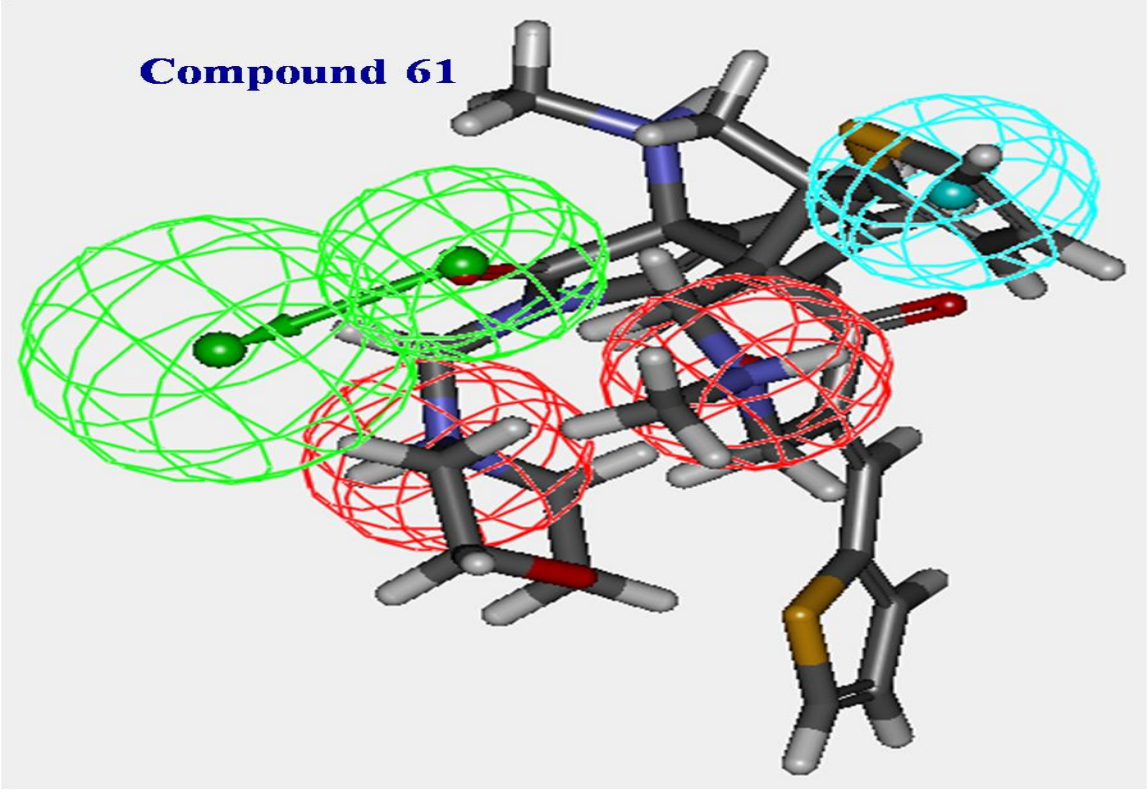
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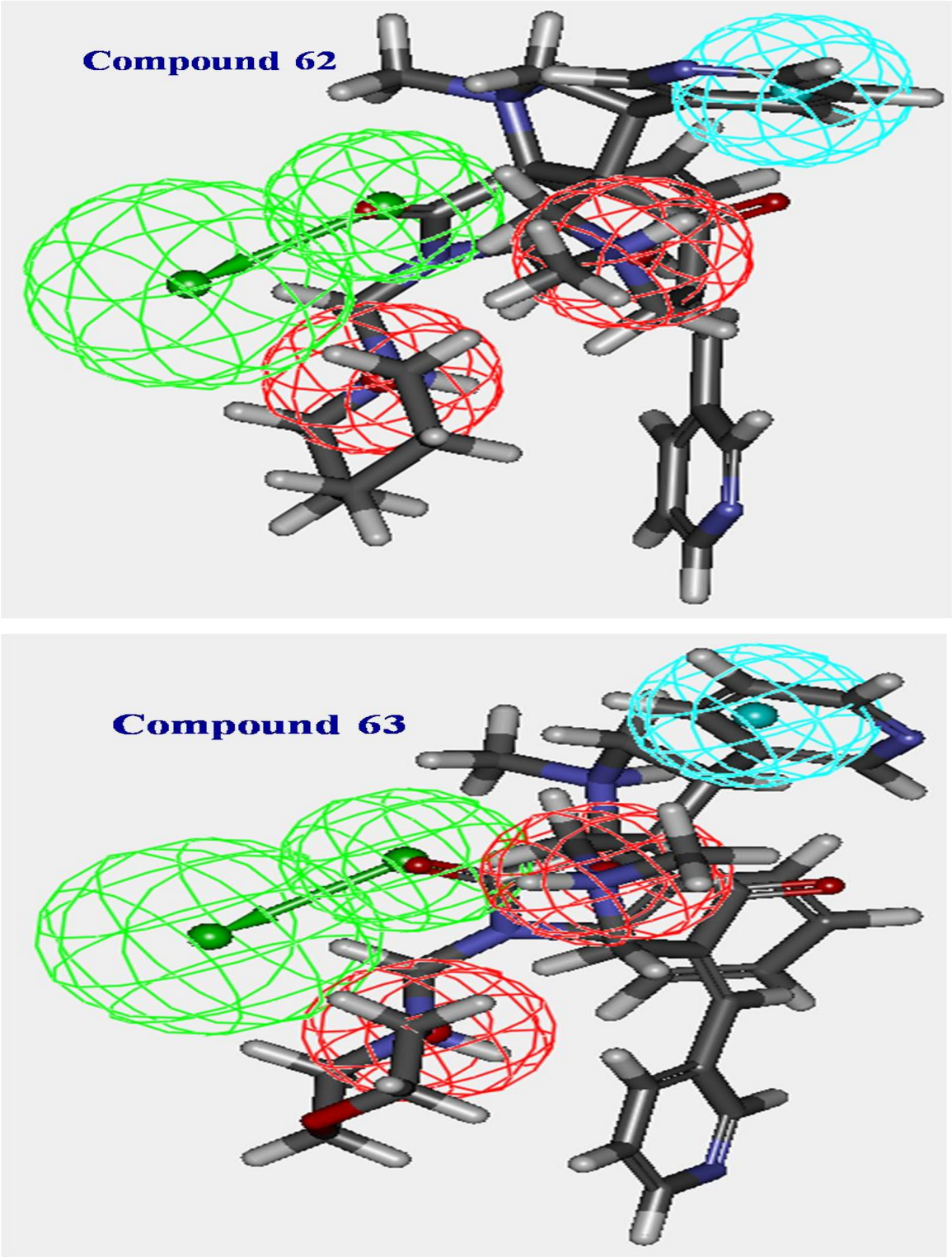

Figure S117. 3D-pharmacophore mapped on the synthesized bio-active spiro-compounds **30-63** against HeLa (cervical carcinoma) cell line.