Supplementary Material (ESI) for Medicinal Chemistry Communications

Electronic Supplementary Information

Synthesis, modeling, and crystallographic study of 3,4-disubstituted-1,2,5-oxadiazoles and evaluation of their ability to decrease STAT3 activity

Dae-Seop Shin,[a] Daniela Masciocchi,[b] Arianna Gelain,[b] Stefania Villa,[b] Daniela Barlocco,*[b] Fiorella Meneghetti,[b] Alessandro Pedretti,[b] Young-Min Han,[a] Dong Cho Han,[a] Mi Young Han,[c] Byoung-Mog Kwon,*[a] Laura Legnani[d] and Lucio Toma*[d]

[a] Laboratory of Chemical Biology and Genomics, Korea Research Institute of Bioscience and Biotechnology, and Department of Biomolecular Science, Korea University of Science and Technology, 52 Uen-Dong Yusung-Ku, Daejeon 305-600, South Korea.

[b] Dipartimento di Scienze Farmaceutiche "Pietro Pratesi", Università degli Studi di Milano, via L. Mangiagalli 25 , 20133 Milano, Italy

[c] Korea Foundation for the Advancement of Science & Creativity, Seoul, Korea

[d] Dipartimento di Chimica Organica, Università degli Studi di Pavia, Via Taramelli 10, 27100 Pavia, Italy

Table S1. Physico-chemical data for compounds **1-3**.

Compd	Eluent	Formula	MW	Yield (%)	MP (°C)
1a	B	$C_{10}H_{10}N_4O_2$	218.21	60	220
1b	A	$C_{11}H_{10}N_4O_4$	262.22	60	200
1c	B	$C_{11}H_{12}N_4O_3$	248.24	31	161
1d	C	$C_{15}H_{12}N_4O_2$	280.28	86	151
1e	B	$C_{16}H_{14}N_4O_2$	294.31	20	154
1f	B	$C_{16}H_{11}F_3N_4O_2$	348.28	70	165
1g	B	$C_{15}H_{11}ClN_4O_2$	314.73	50	220
1h	B	$C_{16}H_{13}ClN_4O_2$	328.75	48	145
1i	B	$C_{18}H_{14}ClF_3N_4O_2$	410.78	54	132
1j	B	$C_{16}H_{11}F_3N_4O_3$	364.28	86	217
1k	B	$C_{24}H_{19}F_3N_4O_3$	468.43	72	90
1l	B	$C_{17}H_{13}F_3N_4O_3$	378.31	65	150
1m	B	$C_{19}H_{15}F_3N_4O_4$	420.34	63	170
1n	B	$C_{20}H_{17}F_3N_4O_4$	434.37	59	118
2a	A	$C_{11}H_{11}N_3O_2$	217.22	90	137
2b	A	$C_{12}H_{11}N_3O_4$	261.23	66	98
2c	B	$C_{11}H_{11}N_3O_3$	233.22	22	133
2d	A	$C_{16}H_{13}N_3O_2$	279.29	58	97
2e	A	$C_{16}H_9ClF_3N_3O_2$	367.71	47	113
3a	D	$C_{10}H_{11}N_3O_3S$	253.28	40	168
3b	D	$C_{11}H_{11}N_3O_5S$	297.29	50	121
3c	D	$C_{10}H_{11}N_3O_4S$	269.28	50	130
3d	D	$C_{15}H_{13}N_3O_3S$	315.35	59	121
3e	D	$C_{15}H_9ClF_3N_3O_3S$	403.76	20	129

Eluent: A petroleum ether/ethyl acetate 9:1; B petroleum ether/ethyl acetate 7:3; C dichloromethane/ petroleum ether/ethyl acetate 7:2.5:0.5; D dichloromethane/methanol 9:1.

Table S2. Relative energy, *in vacuo* and recalculated using the continuum solvent model PCM, equilibrium percentages at 298 K, and significant torsional angles of the B3LYP/6-311+G(d,p) calculated minimum energy conformations of compounds **2d** and **3d**.

	E_{rel} gas phase (kcal/mol)	%	E_{rel} water (kcal/mol)	%	τ_1 (°)	τ_2 (°)	τ_3 (°)	τ_4 (°)	τ_5 (°)
Compd 2d									
2d-1	0.00	45.9	0.41	23.9	174	-14	-125	35	97
2d-2	1.38	4.5	0.80	12.4	-176	-25	8	43	100
2d-3	0.10	38.7	1.80	2.3	173	-14	-109	-46	95
2d-4	1.40	4.3	0.74	13.7	176	19	-9	-43	85
2d-5	1.15	6.6	0.00	47.7	174	87	-126	33	68
Compd 3d									
3d-1	2.52	0.5	1.62	4.1	-119	-179	-106	47	89
3d-2	0.68	11.6	1.43	5.7	73	63	-98	26	81
3d-3	0.63	12.8	1.84	2.9	72	63	-81	-38	80
3d-4	2.58	0.5	2.03	2.1	-127	-63	-109	49	102
3d-5	3.30	0.1	2.89	0.5	61	-78	-109	32	110
3d-6	4.13	0.0	4.67	0.0	62	-85	-89	-34	113
3d-7	2.95	0.3	3.35	0.2	-115	-58	-114	-80	104
3d-8	0.46	16.8	1.10	10.0	-83	179	51	43	88
3d-9	0.35	20.4	1.08	10.4	77	57	-32	43	77
3d-10	0.00	36.8	0.00	63.9	74	57	-36	-38	79
3d-11	3.13	0.2	3.33	0.2	101	-61	-39	44	103

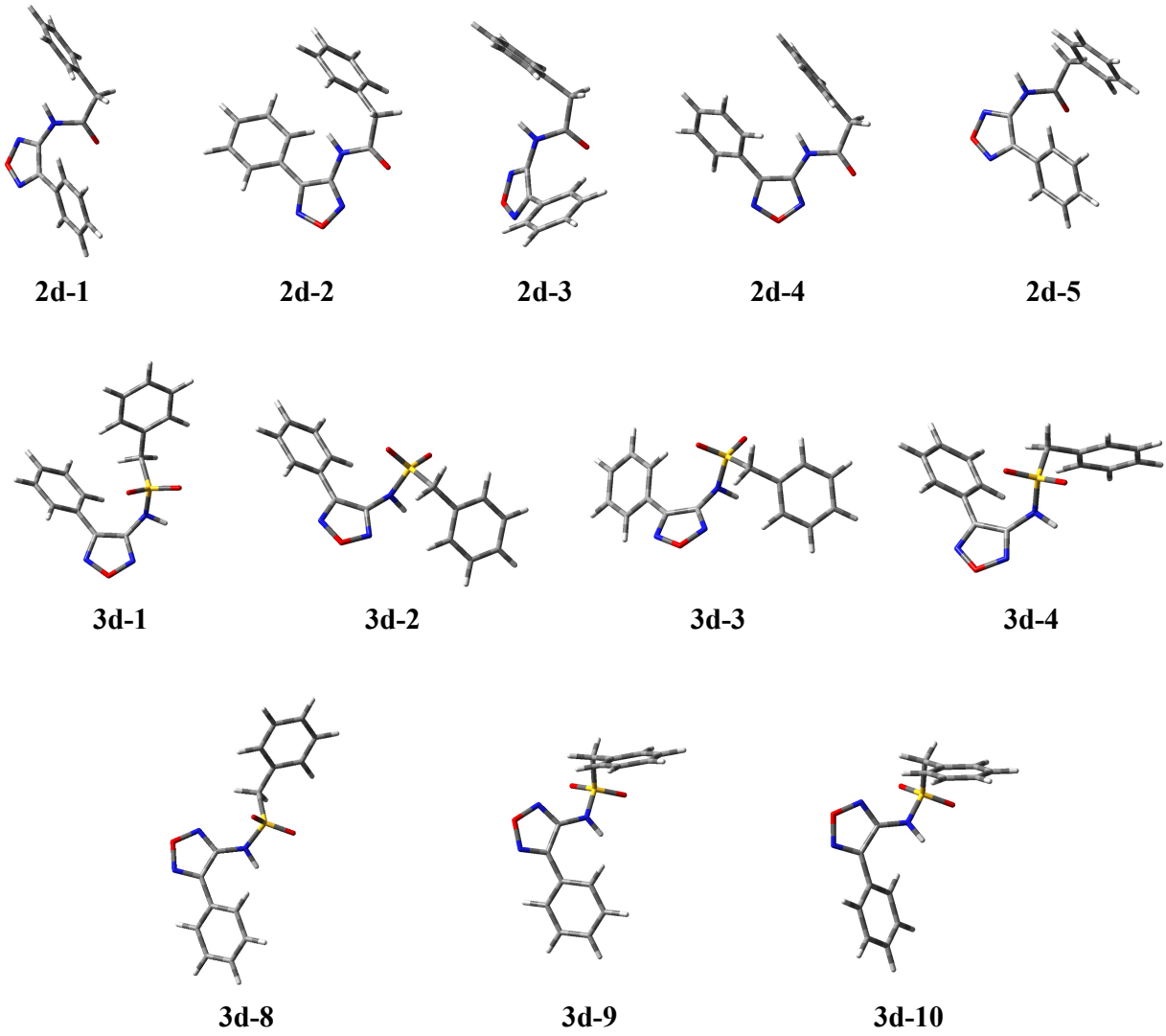


Figure S1. 3D Plot of the populated conformations (P > 1%) of compounds **2d** and **3d**.

Table S4. ^{1}H-NMR Data of Compounds **I** and **1-3** ($CDCl_3$; chemical shift in ppm).

Compd	^{1}H NMR
I	7.15 (s, 1H, NH), 7.55-7.70 (m, 8H, ArH), 9.55 (s, 1H,NH)
I[a]	7.55-7.65 (m, 6H, ArH), 7.70-7.80 (m, 2H, ArH), 9.40 (s, 1H, NH), 9.70 (s, 1H, NH)
1a	2.50 (s, 3H, CH_3), 7.15-7.65 (m, 5H, ArH), 9.00 (br s, 1H, NH), 9.40 (br s, 1H, NH)
1b	4.05 (s, 3H, CH_3), 6.45 (br s, 2H, NH), 7.10-7.40 (m, 5H, ArH)
1c	4.45 (t, 1H, OH), 4.55 (d, 2H, CH_2), 4.80 (d, 2H, C*H*$_2$OH), 7.25-7.40 (m, 5H, ArH), 8.10 (br s, 1H, NH), 10.15 (s, 1H, NH)
1d	6.85 (br s, 1H, NH), 7.10-7.70 (m, 10H, ArH), 9.35 (br s, 1H, NH)
1e	4.55 (br s, 2H, CH_2), 7.10 (br s, 1H, NH), 7.25-7.65 (m, 10H, ArH), 7.75 (br s, 1H, NH)
1f	7.45-7.80 (m, 9H, ArH)
1g[a]	7.05 (t, 1H, ArH), 7.30-7.35 (m, 2H, ArH), 7.40 (d, 2H, ArH), 7.70 (d, 2H, ArH), 7.80 (d, 2H, ArH), 9.24 (s, 1H, NH), 9.28 (s, 1H, NH)
1h	3.25 (s, 3H, N-CH_3), 7.10-7.15 (m, 1H, ArH), 7.25-7.35 (m, 4H, ArH), 7.50 (d, 2H, ArH), 7.60 (br s, 1H, NH), 7.65 (d, 2H, ArH)
1i	2.85 (s, 3H, N-CH_3), 3.40 (s, 3H, N-CH_3), 6.85 (d, 2H, ArH), 7.38 (d, 2H, ArH), 7.55 (s, 4H, ArH)
1j[a]	6.85-6.95 (m, 2H, ArH), 7.55-7.70 (m, 6H, ArH), 9.20 (br s, 1H, NH), 9.72 (s, 1H, OH), 10.15 (br s, 1H, NH)
1k	3.22 (s, 3H, N-CH_3), 5.12 (s, 2H, CH_2), 7.10 (d, 2H, ArH), 7.30-7.60 (m, 9H, ArH), 7.63 (d, 2H, ArH), 7.85 (s, 1H, NH)
1l	3.22 (s, 3H, N-CH_3), 5.42 (br s, 1H, OH), 6.96 (d, 2H, ArH), 7.40-7.65 (m, 6H, ArH), 7.85 (s, 1H, NH)
1m	2.35 (s, 3H, $COCH_3$), 3.23 (s, 3H, N-CH_3), 7.30 (d, 2H, ArH), 7.48 (d, 2H, ArH), 7.55 (d, 2H, ArH), 7.75 (d, 2H, ArH), 7.95 (s, 1H, NH)
1n	2.35 (s, 3H, $COCH_3$), 2.80 (s, 3H, N-CH_3), 3.42 (s, 3H, N-CH_3), 6.85 (d, 2H, ArH), 7.26 (d, 2H, ArH), 7.39 (d, 2H, ArH), 7.62 (d, 2H, ArH)
2a	2.40 (s, 3H, CH_3), 3.80 (s, 2H, CH_2), 7.30-7.50 (m, 5H, ArH)
2b	3.90 (s, 2H, CH_2), 3.95 (s, 3H, OCH_3), 7.35-7.50 (m, 5H, ArH), 8.80 (br s, 1H, NH)
2c	3.20 (br s, 1H, OH), 3.85 (s, 2H, CH_2), 4.80 (s, 2H, C*H*$_2$OH), 7.25-7.55 (m, 5H, ArH), 8.10 (br s, 1H, NH)
2d	3.65 (s, 1H, NH), 3.85 (s, 2H, CH_2), 7.30-7.50 (m, 10H, ArH)
2e	7.45 (d, 2H, ArH), 7.55 (d, 2H, ArH), 7.65 (d, 2H, ArH), 7.75 (d, 2H, ArH)

3a[b] 2.25 (s, 3H, CH_3), 4.65 (s, 2H, CH_2), 7.35-7.45 (m, 5H, ArH)

3b 4.00 (s, 3H, OCH_3), 4.70 (s, 2H, CH_2), 7.35-7.45 (m, 5H, ArH), 7.80 (br s, 1H, NH)

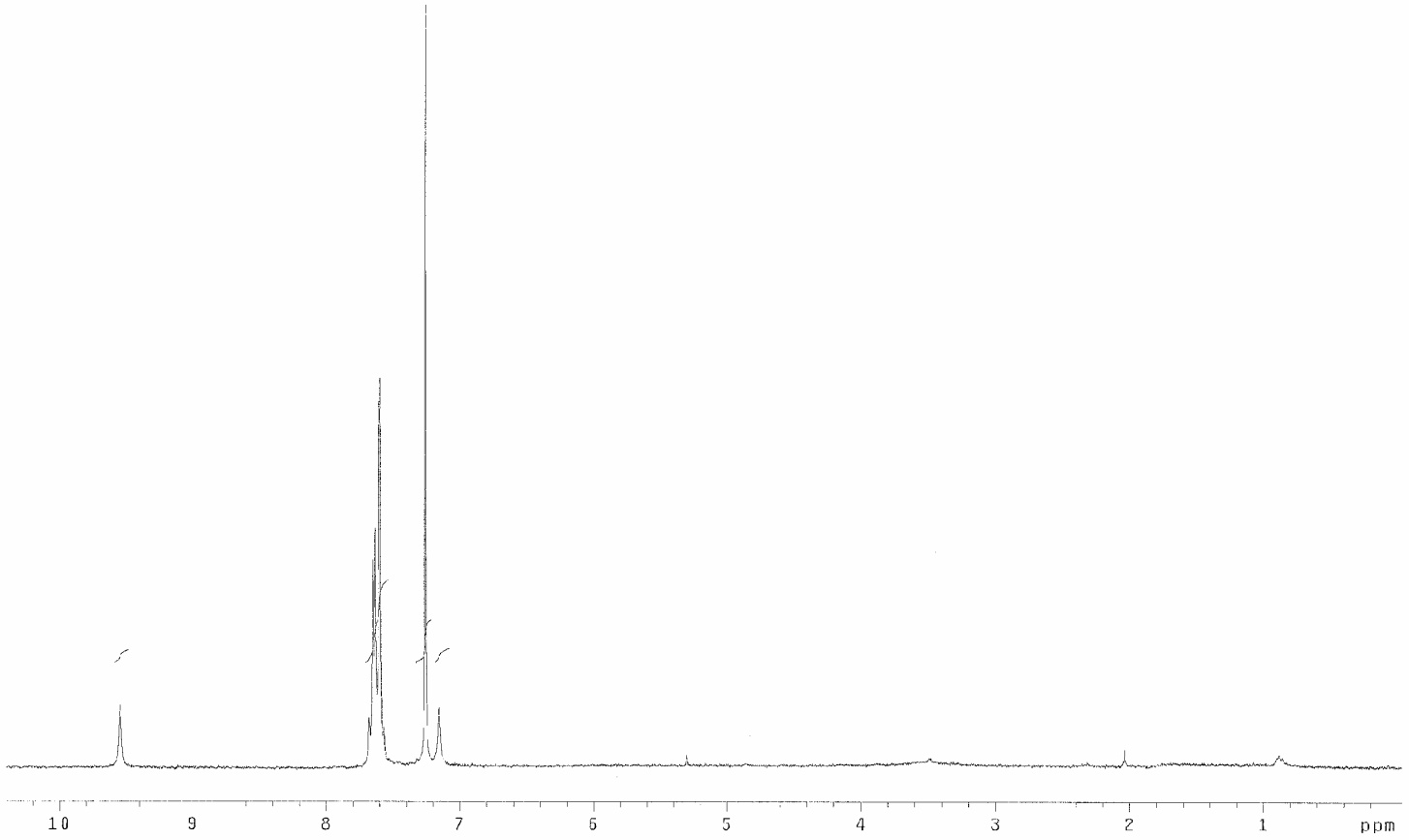
3c[b] 4.45 (s, 2H, CH_2), 4.55 (s, 2H, C*H*$_2$OH), 7.20-7.30 (m, 5H, ArH)

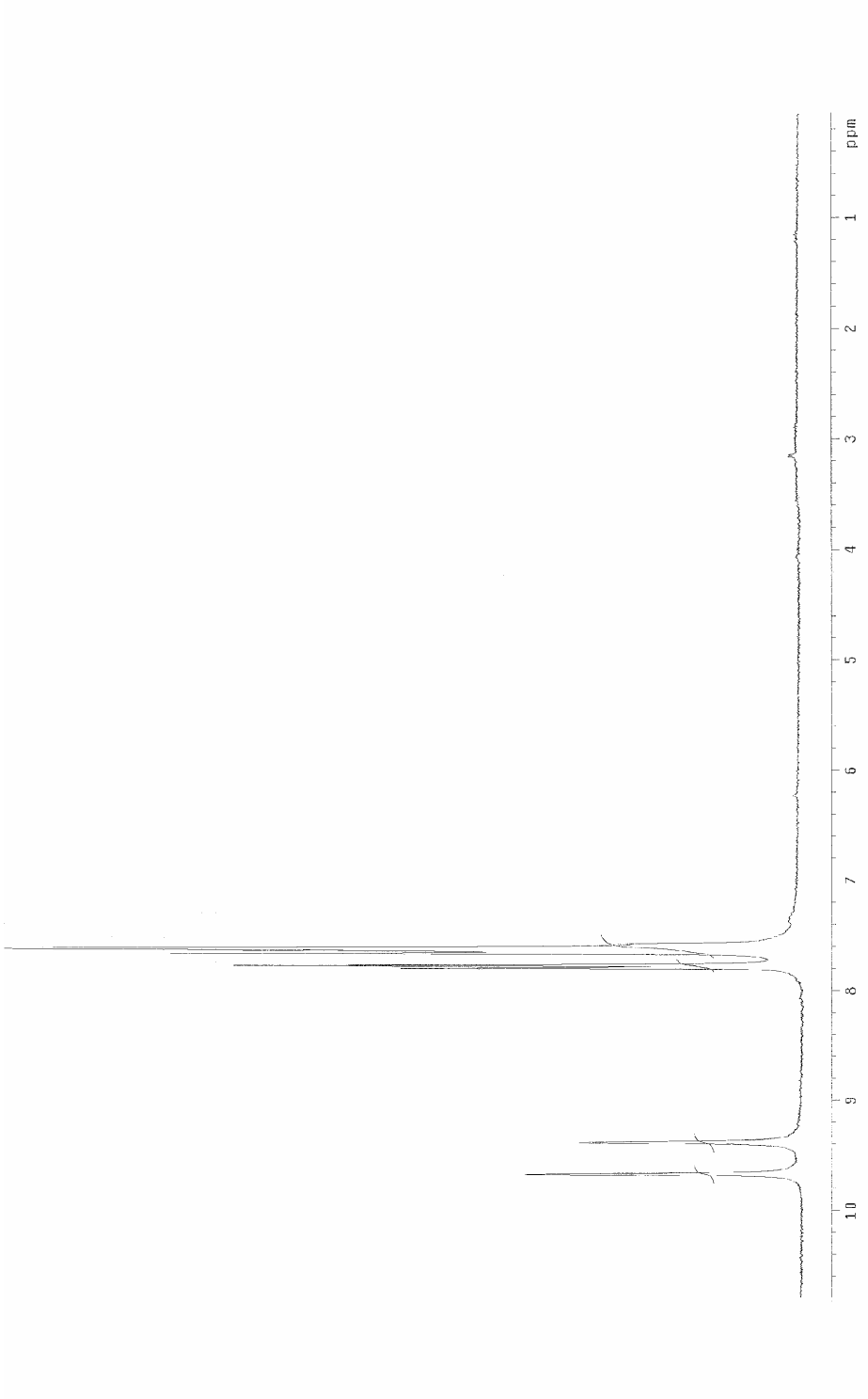
3d 4.75 (s, 2H, CH_2), 7.30-7.65 (m, 10H, ArH)

3e 7.35 (d, 2H, ArH), 7.55 (d, 2H, ArH), 7.75 (d, 2H, ArH), 7.95 (d, 2H, ArH)

[a] DMSO-*d*$_6$; [b] CD_3OD.

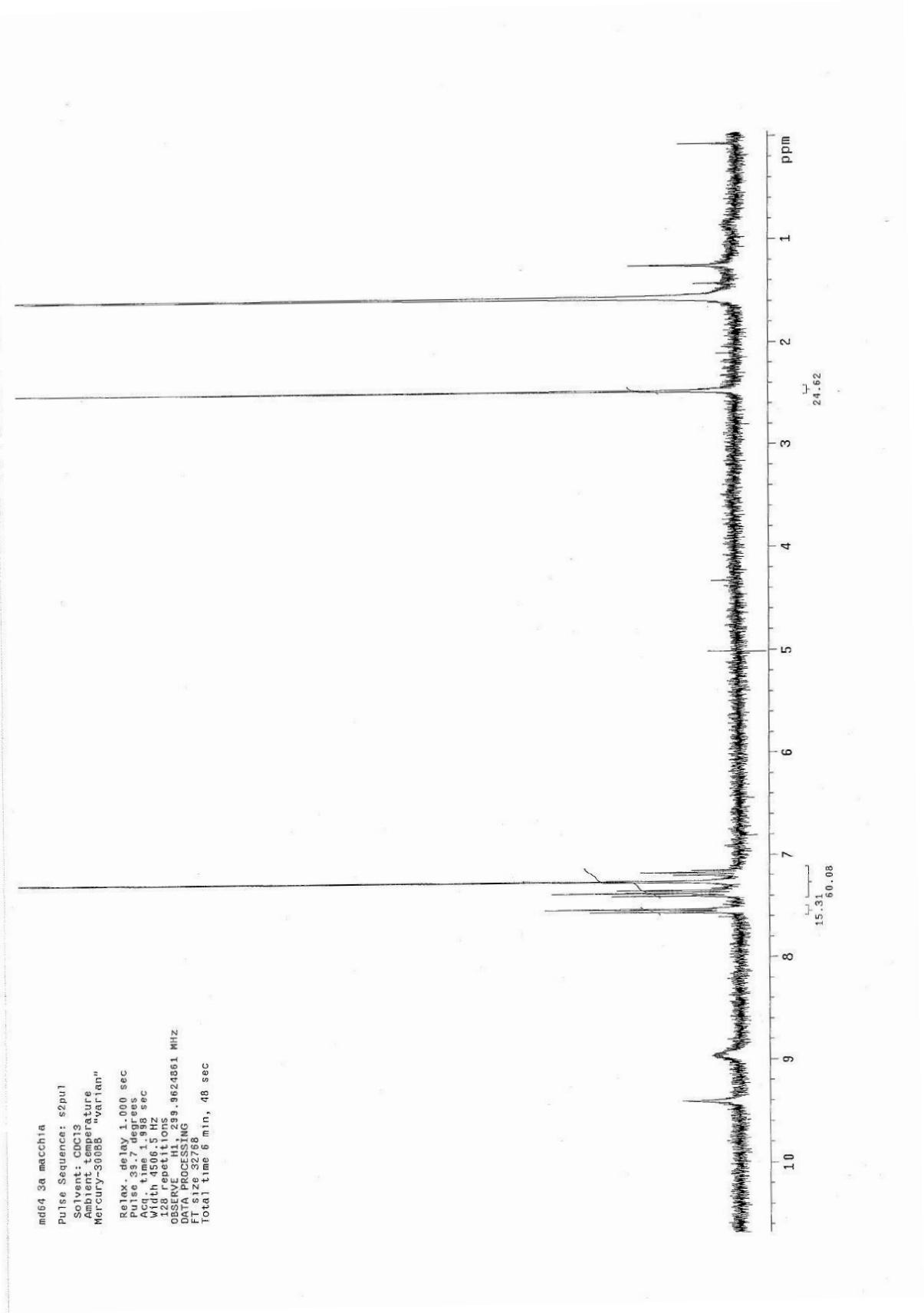
^{1}H NMR Spectrum of compound **I** ($CDCl_3$).



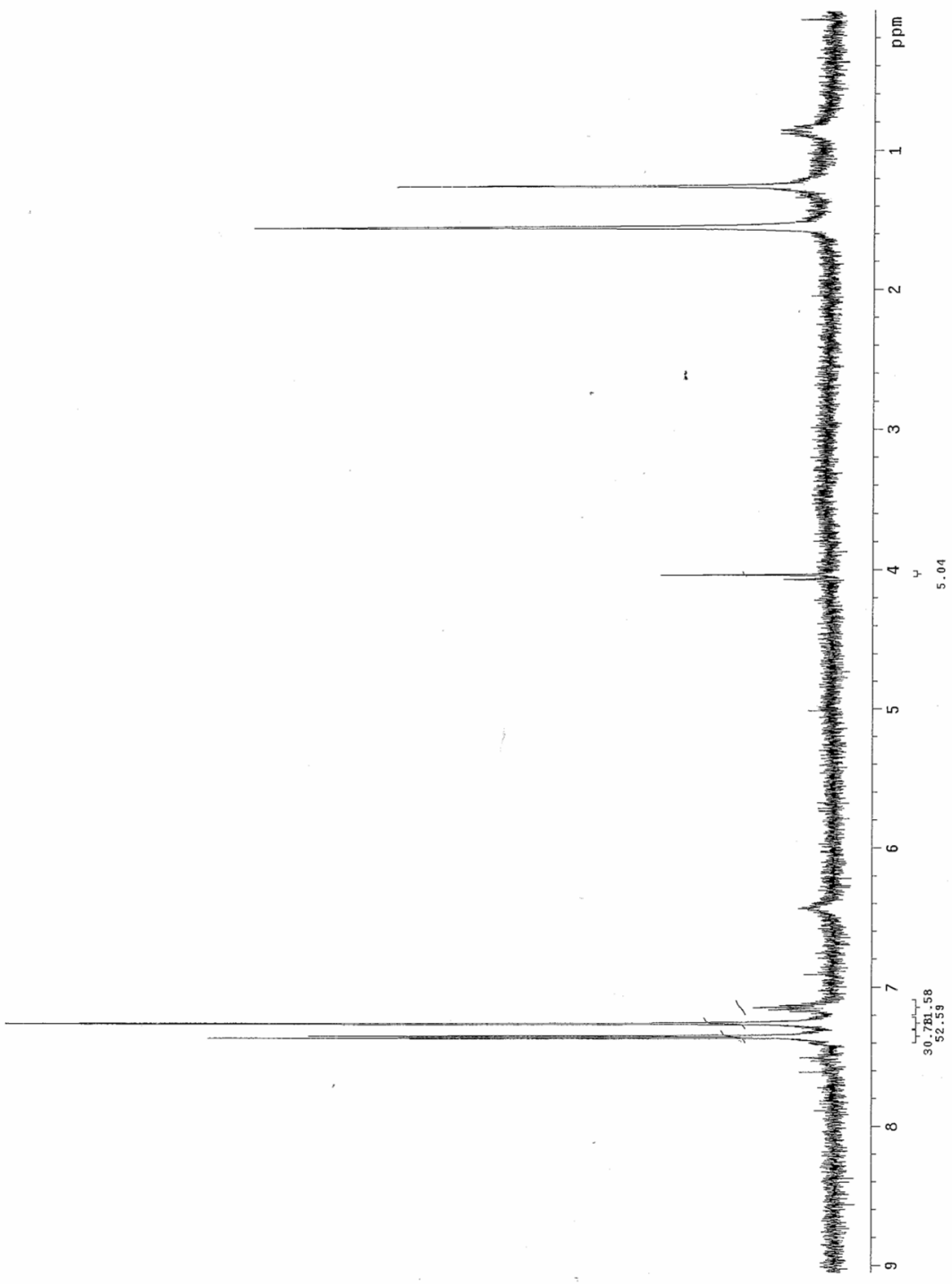


^{1}H NMR Spectrum of compound **I** (DMSO-d_6).

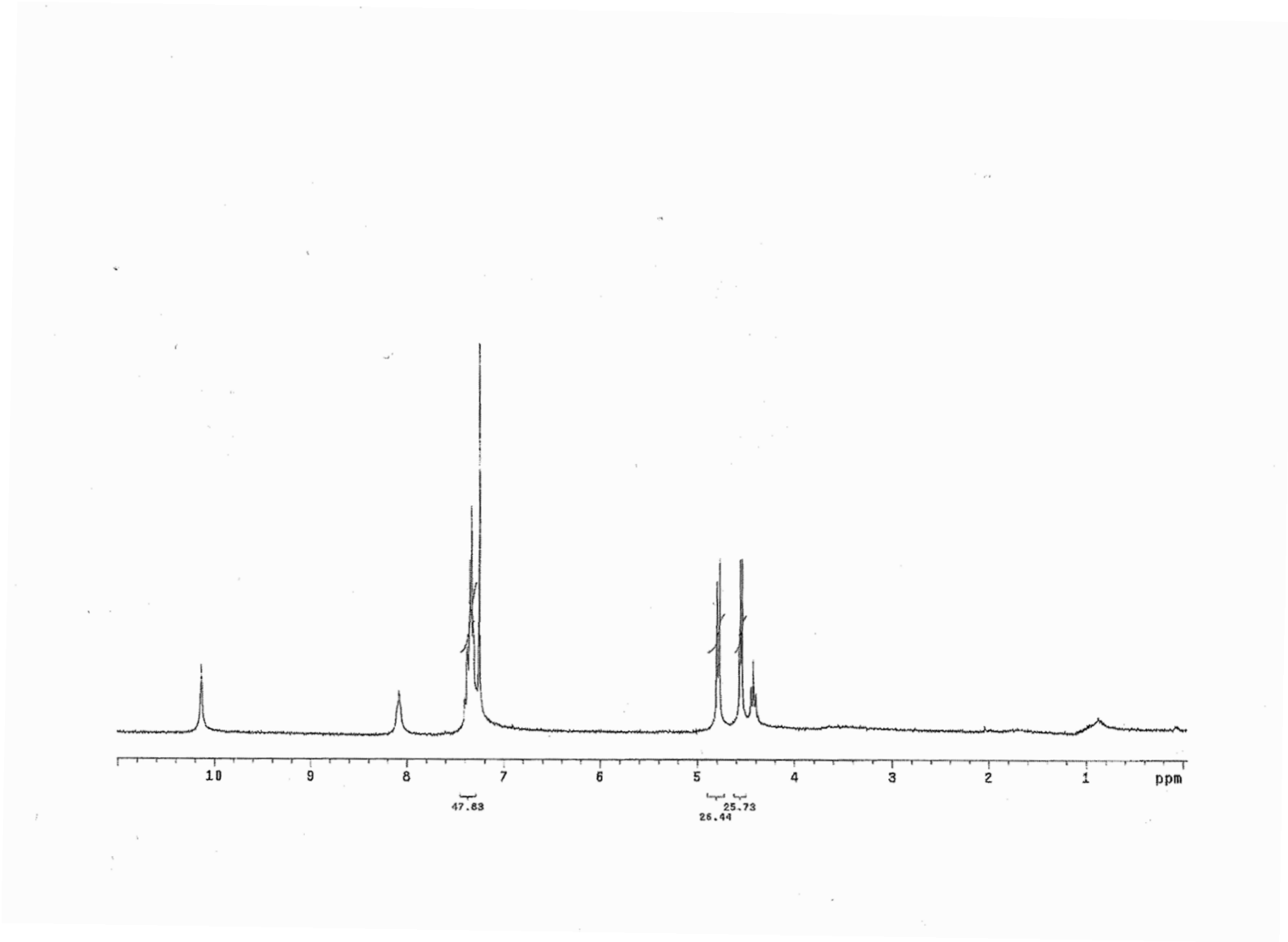
^{1}H NMR Spectrum of compound **1a**



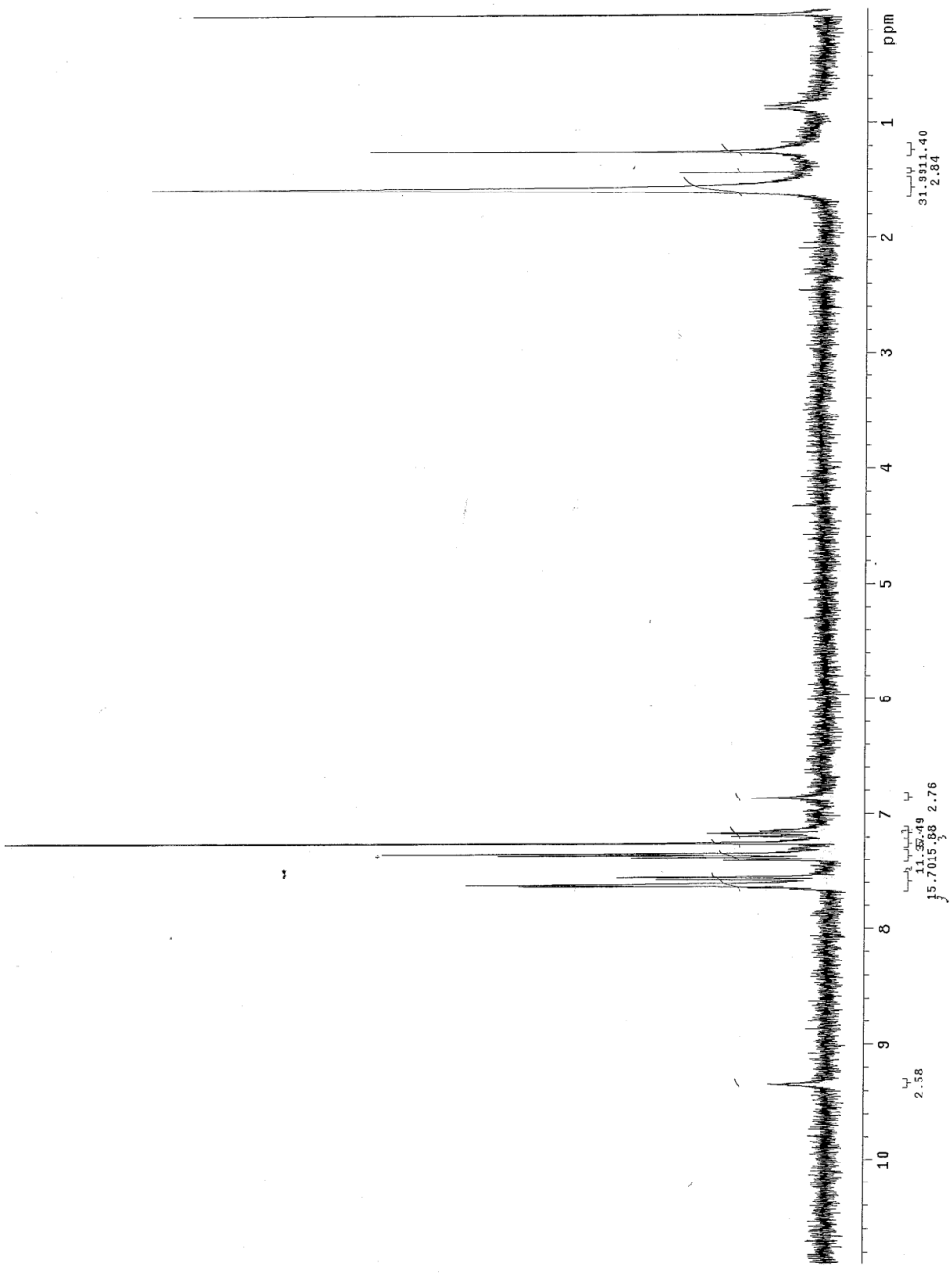
^{1}H NMR Spectrum of compound **1b**



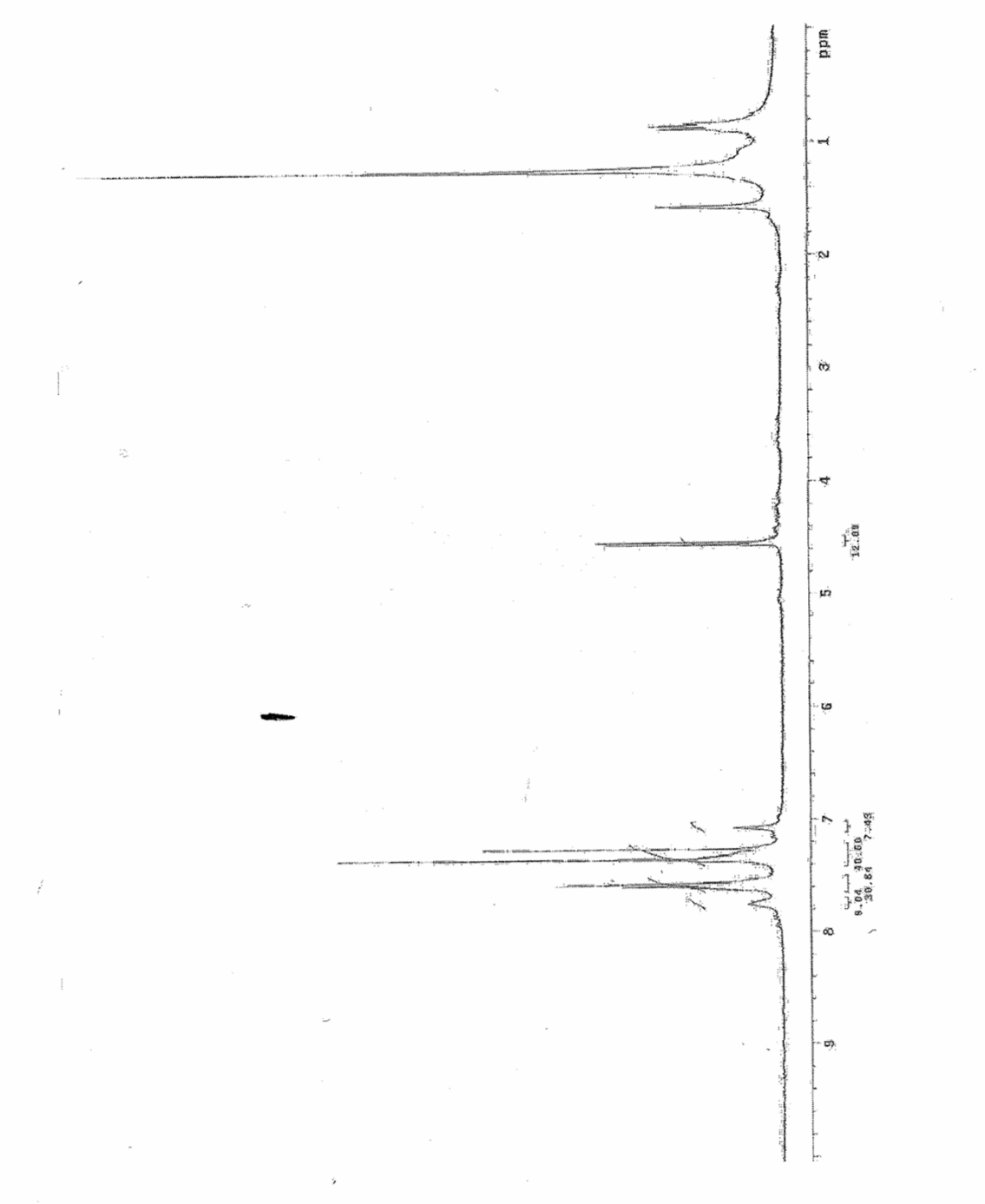
^{1}H NMR Spectrum of compound **1c**



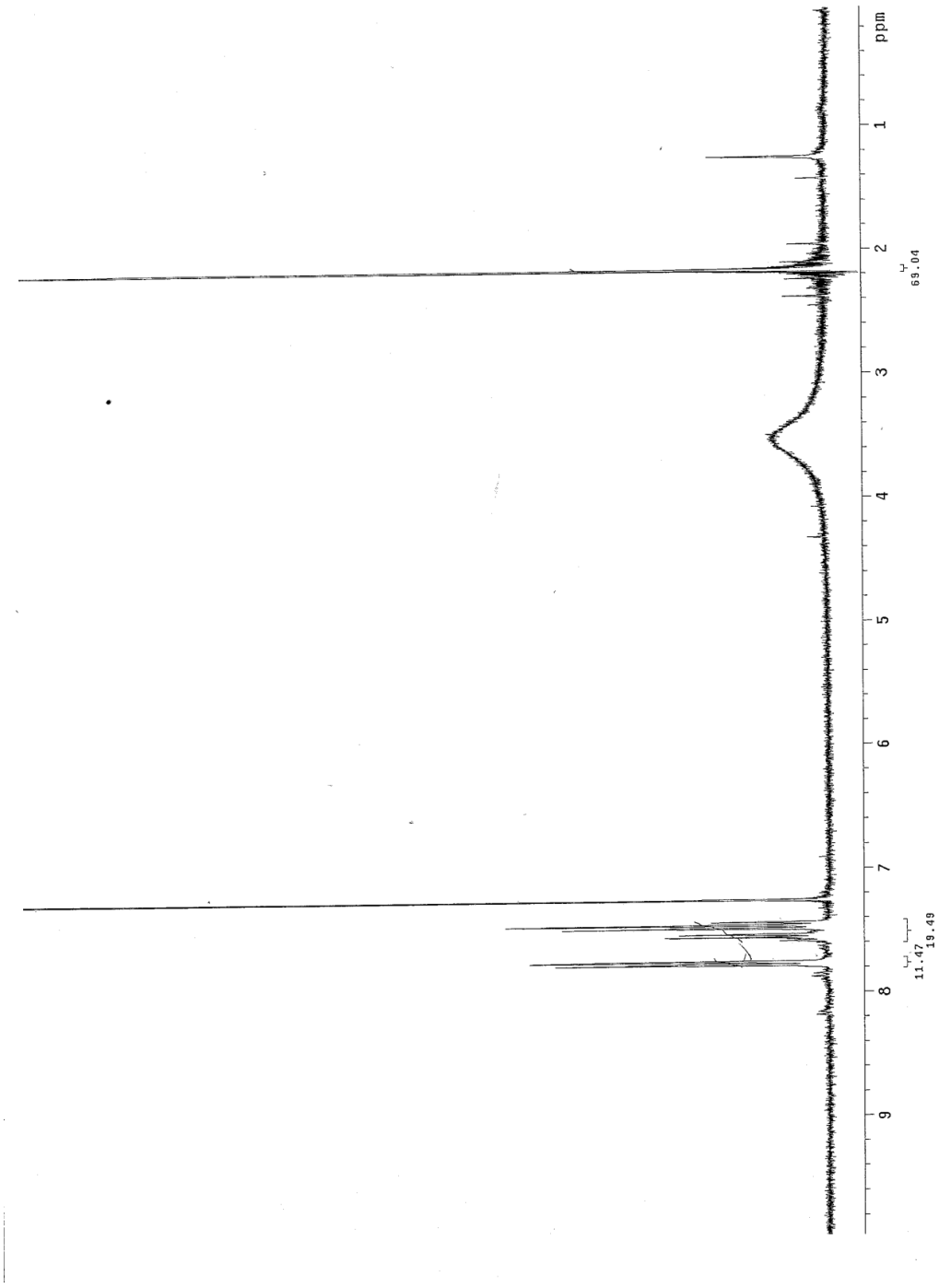
^{1}H NMR Spectrum of compound **1d**



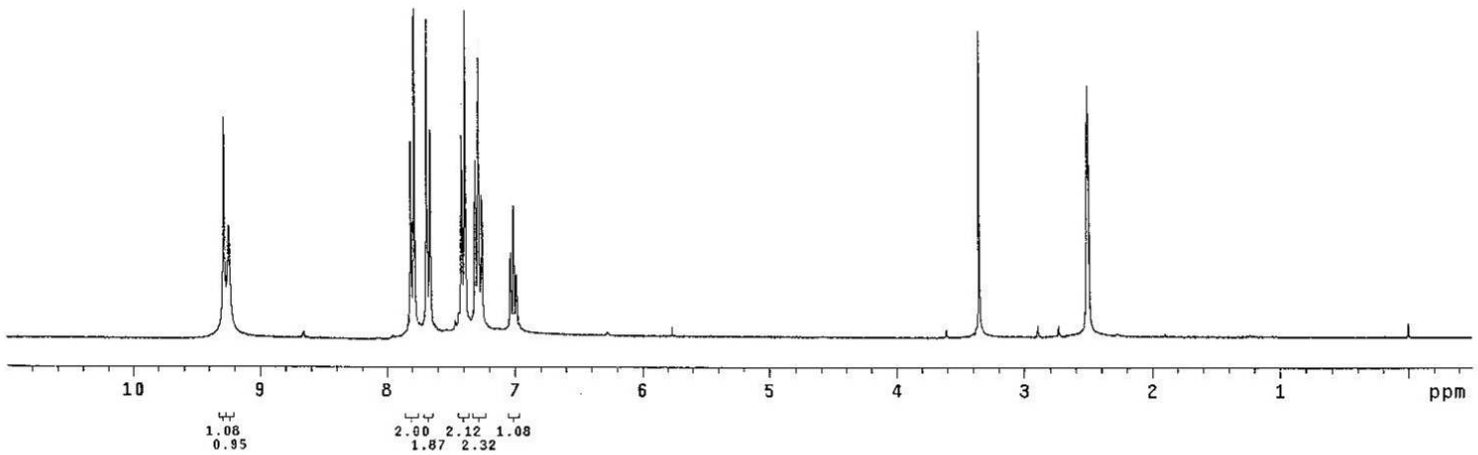
^{1}H NMR Spectrum of compound **1e**

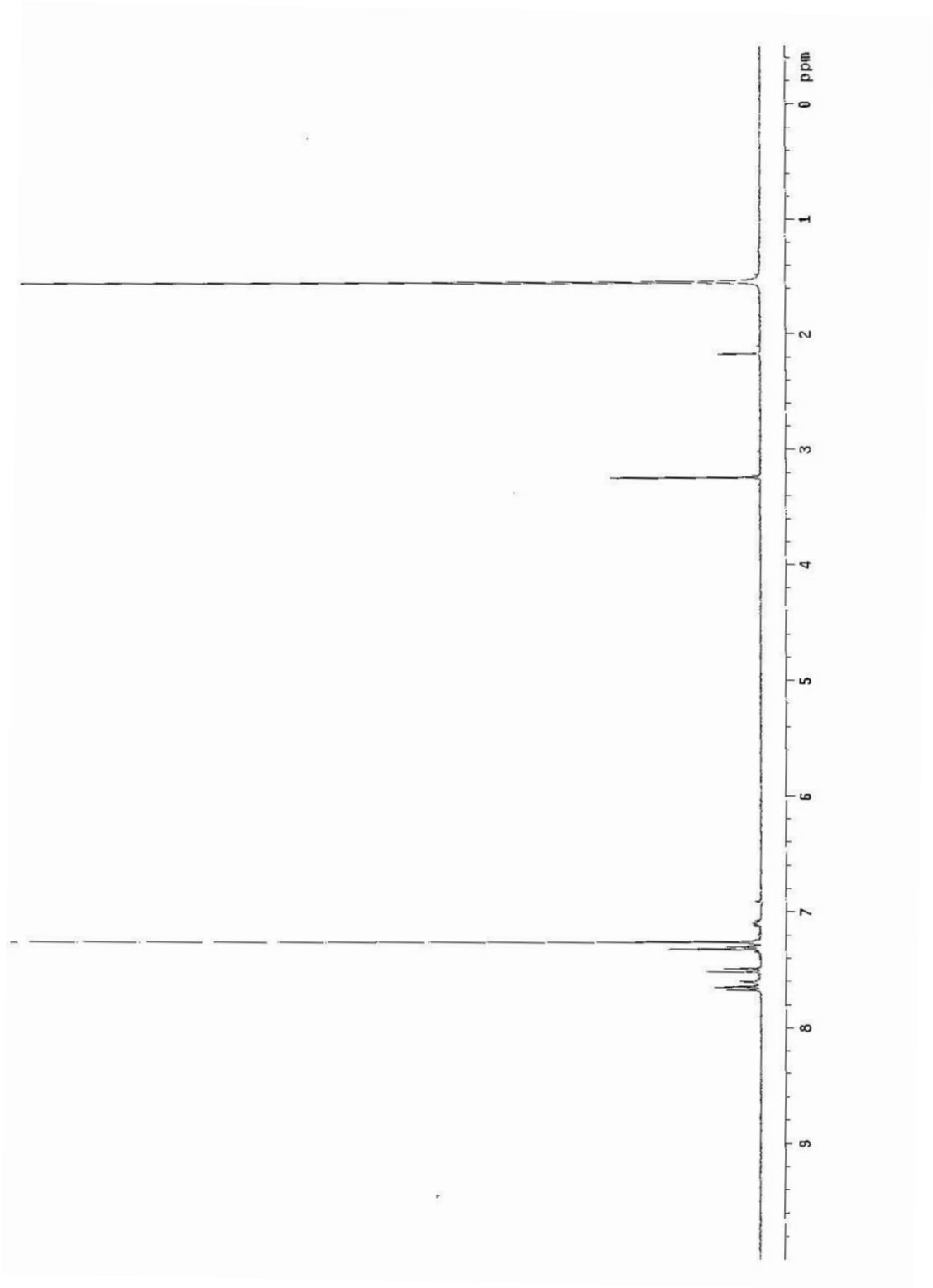


^{1}H NMR Spectrum of compound **1f**



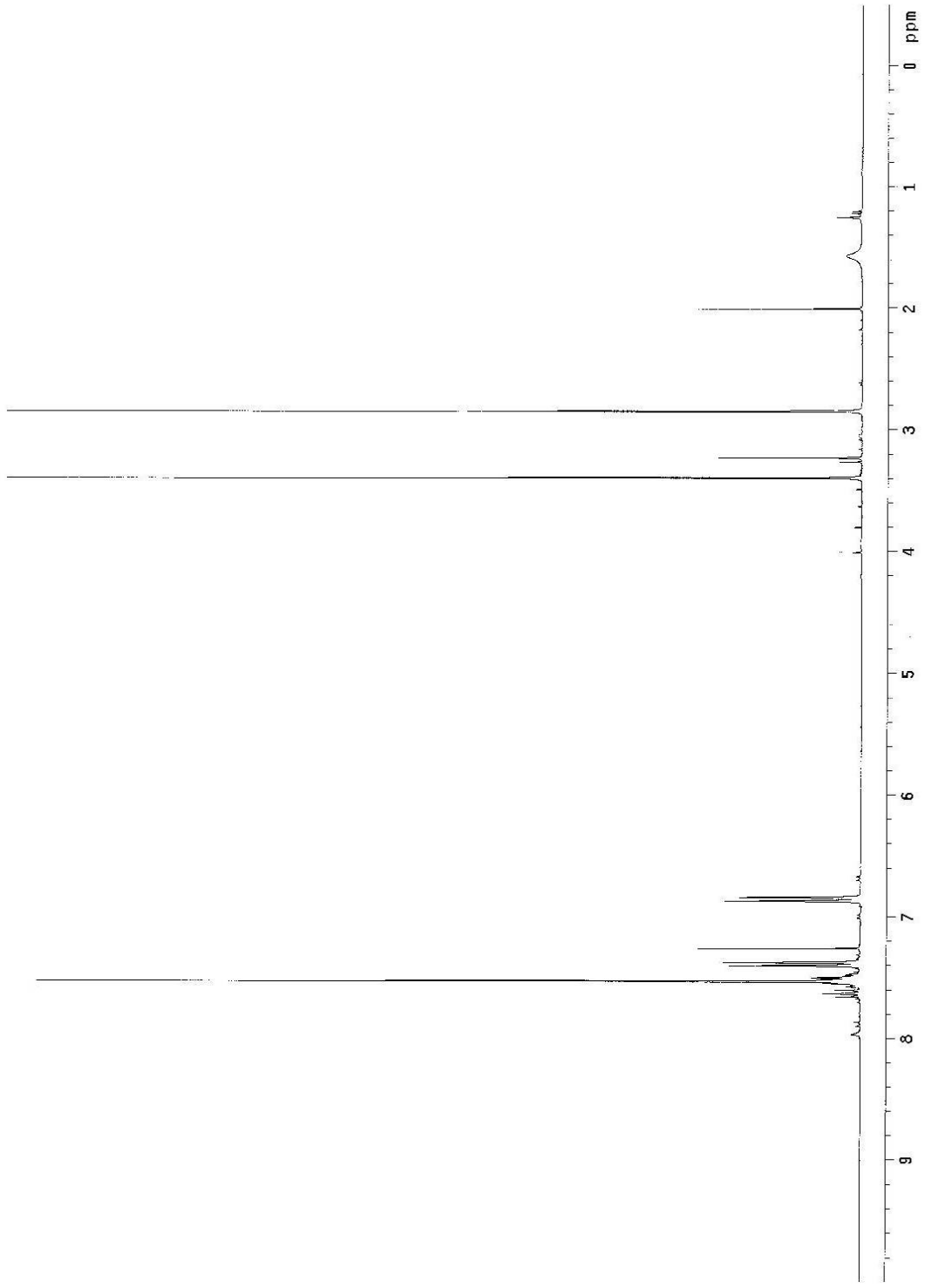
^{1}H NMR Spectrum of compound **1g**



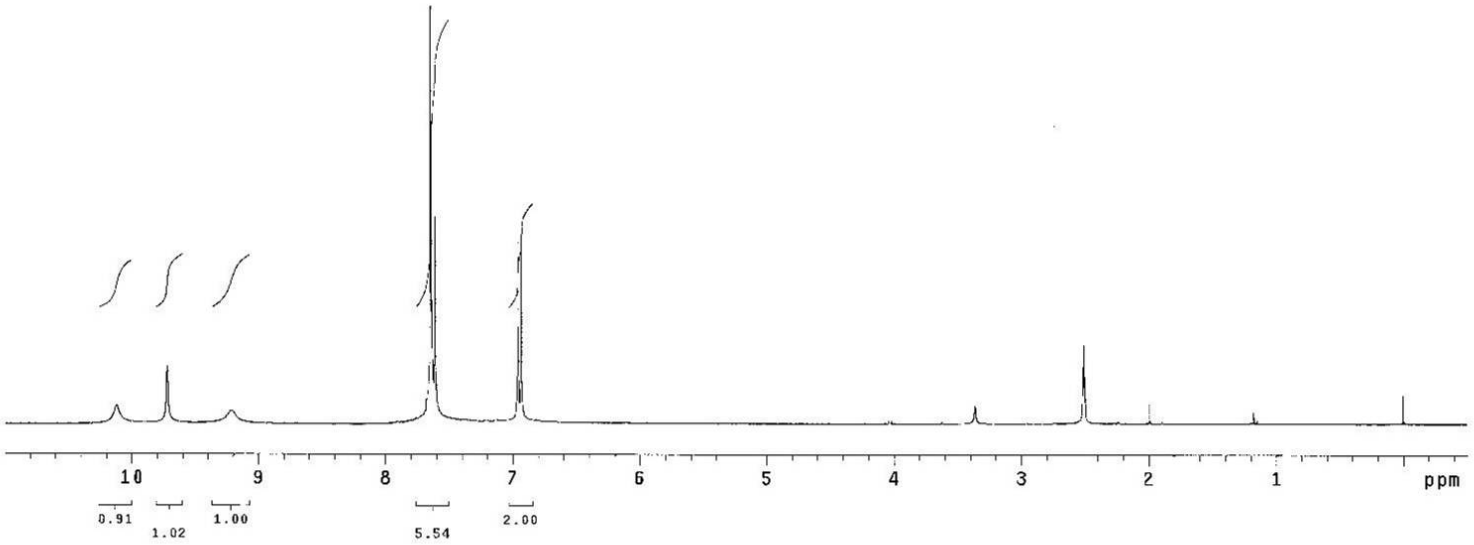


^{1}H NMR Spectrum of compound **1h**

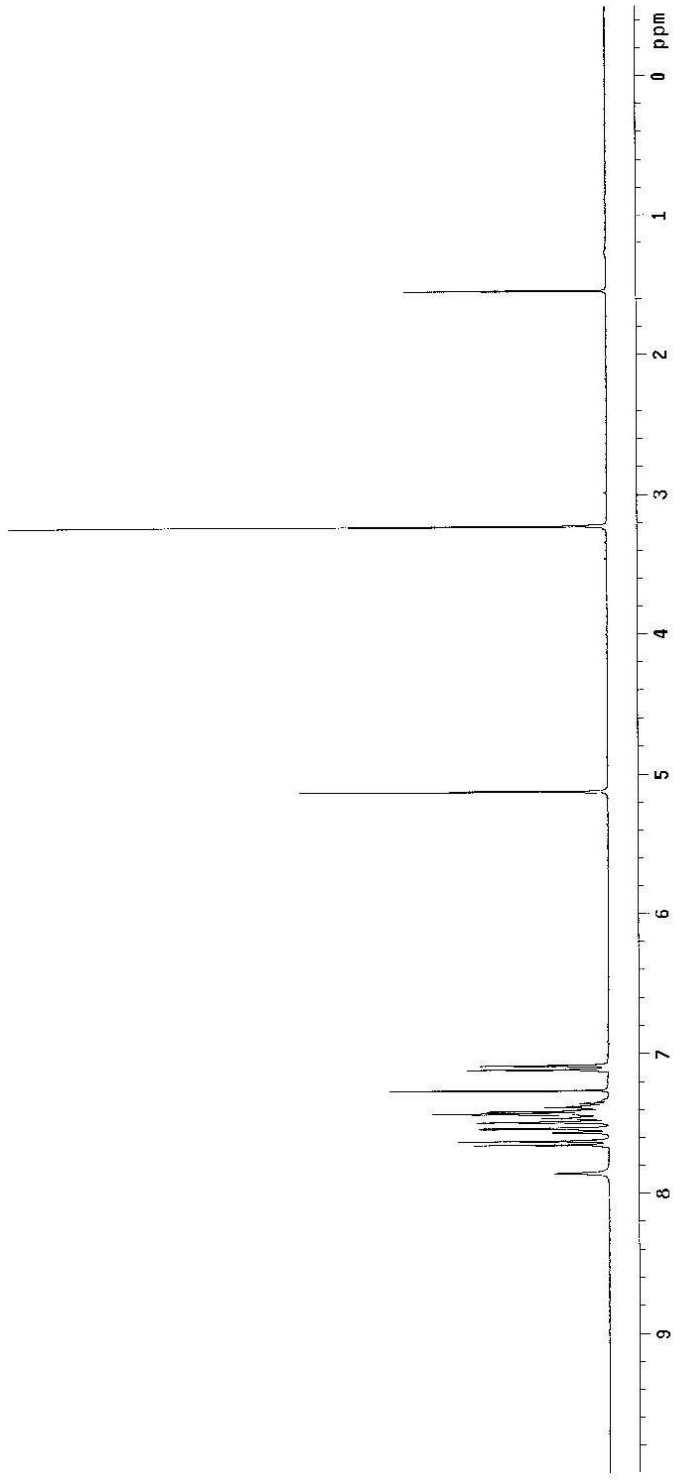
^{1}H NMR spectrum of compound **1i**



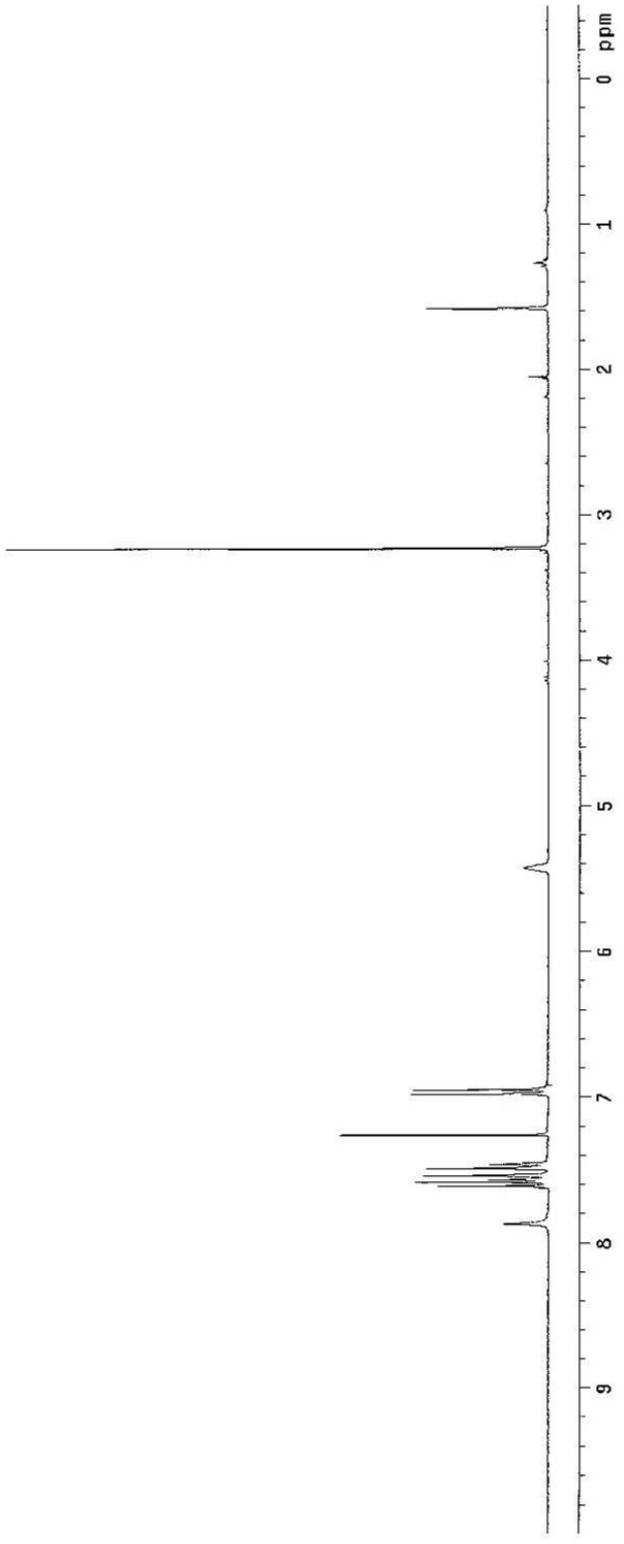
^{1}H NMR spectrum of compound **1j**



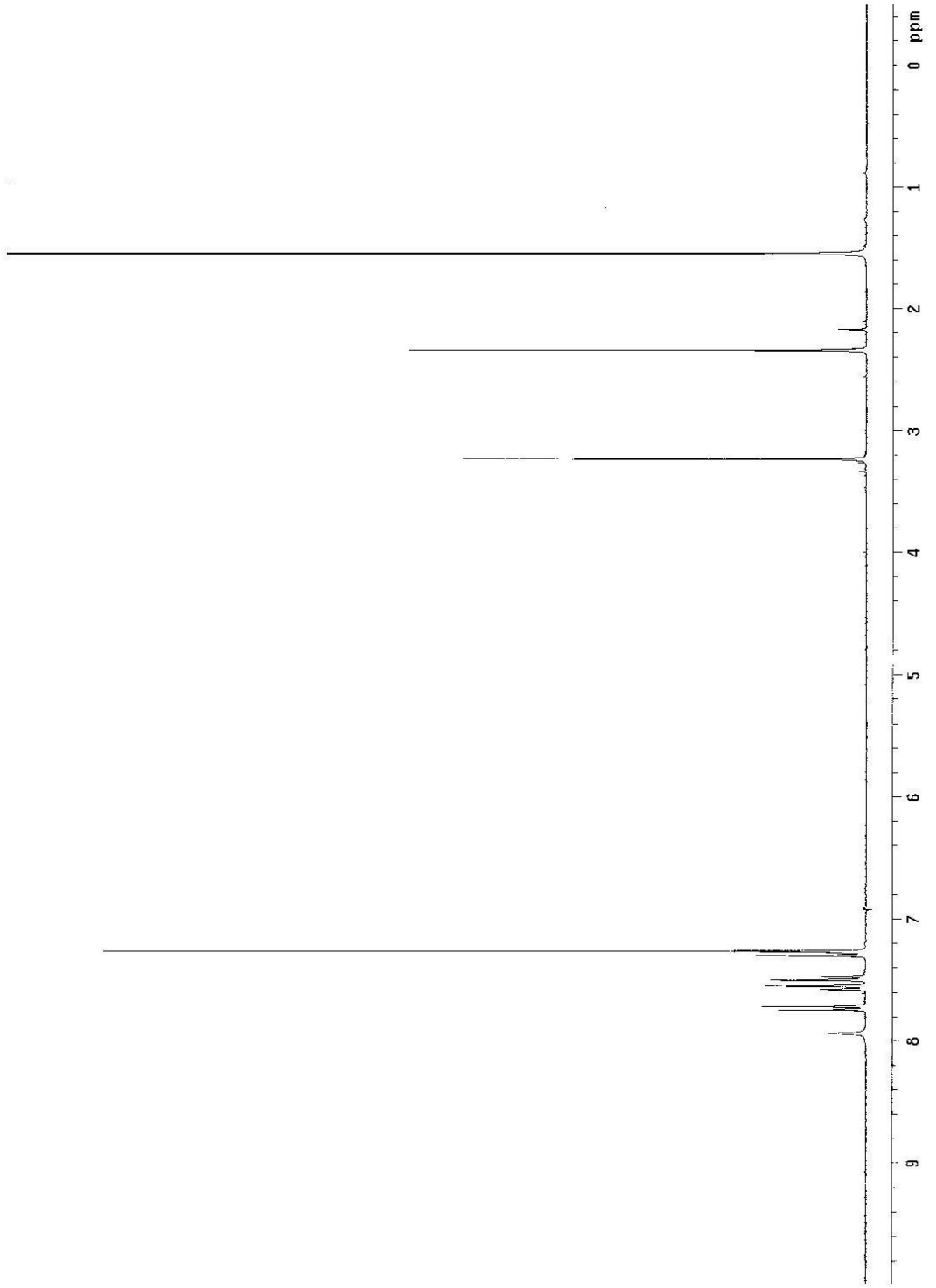
^{1}H NMR spectrum of compound **1k**



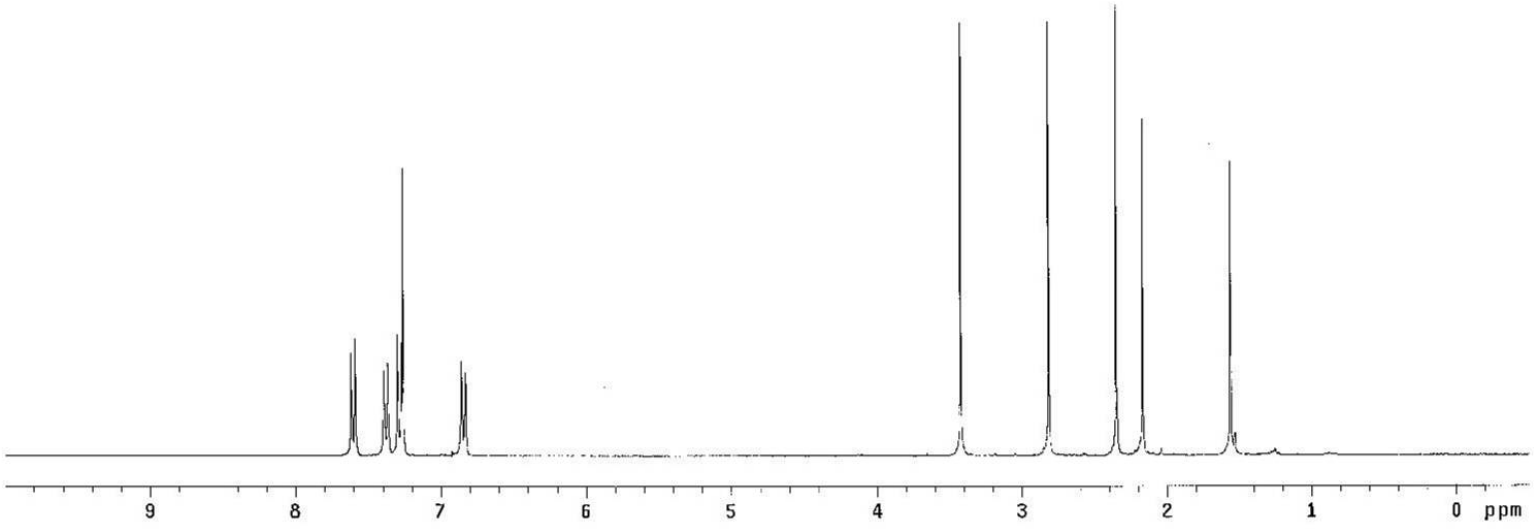
^{1}H NMR spectrum of compound **11**



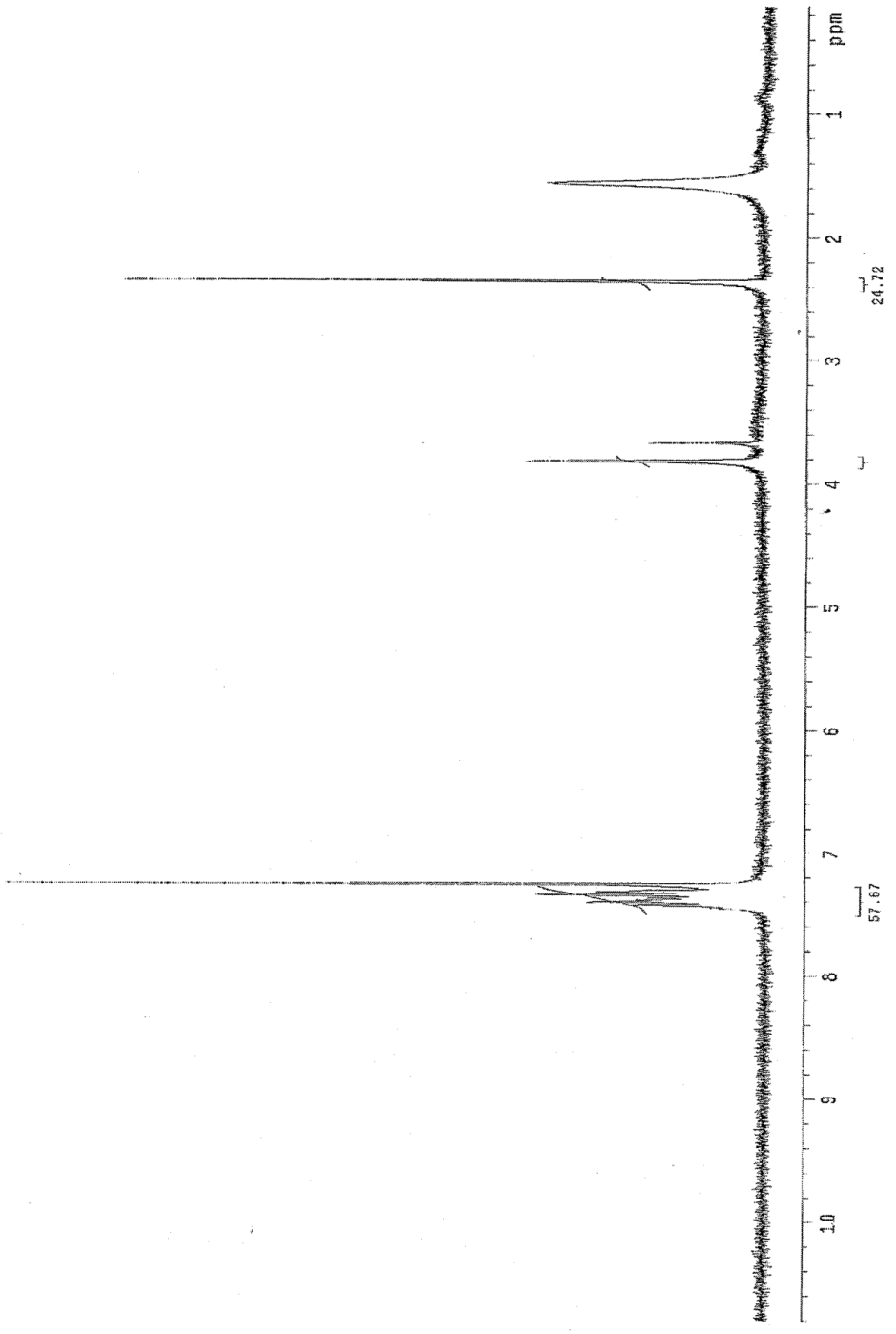
^{1}H NMR spectrum of compound **1m**



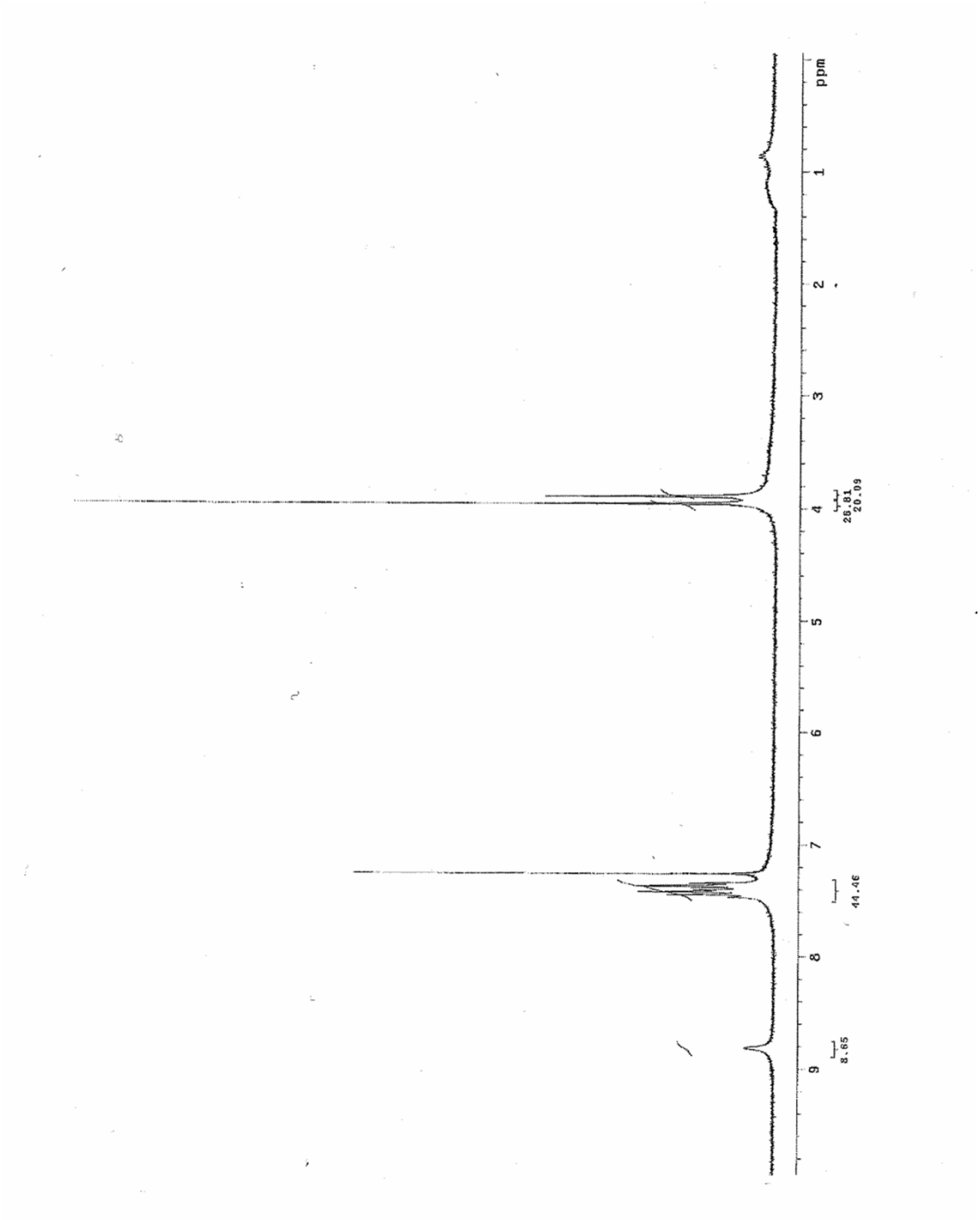
^{1}H NMR spectrum of compound **1n**



^{1}H NMR spectrum of compound **2a**

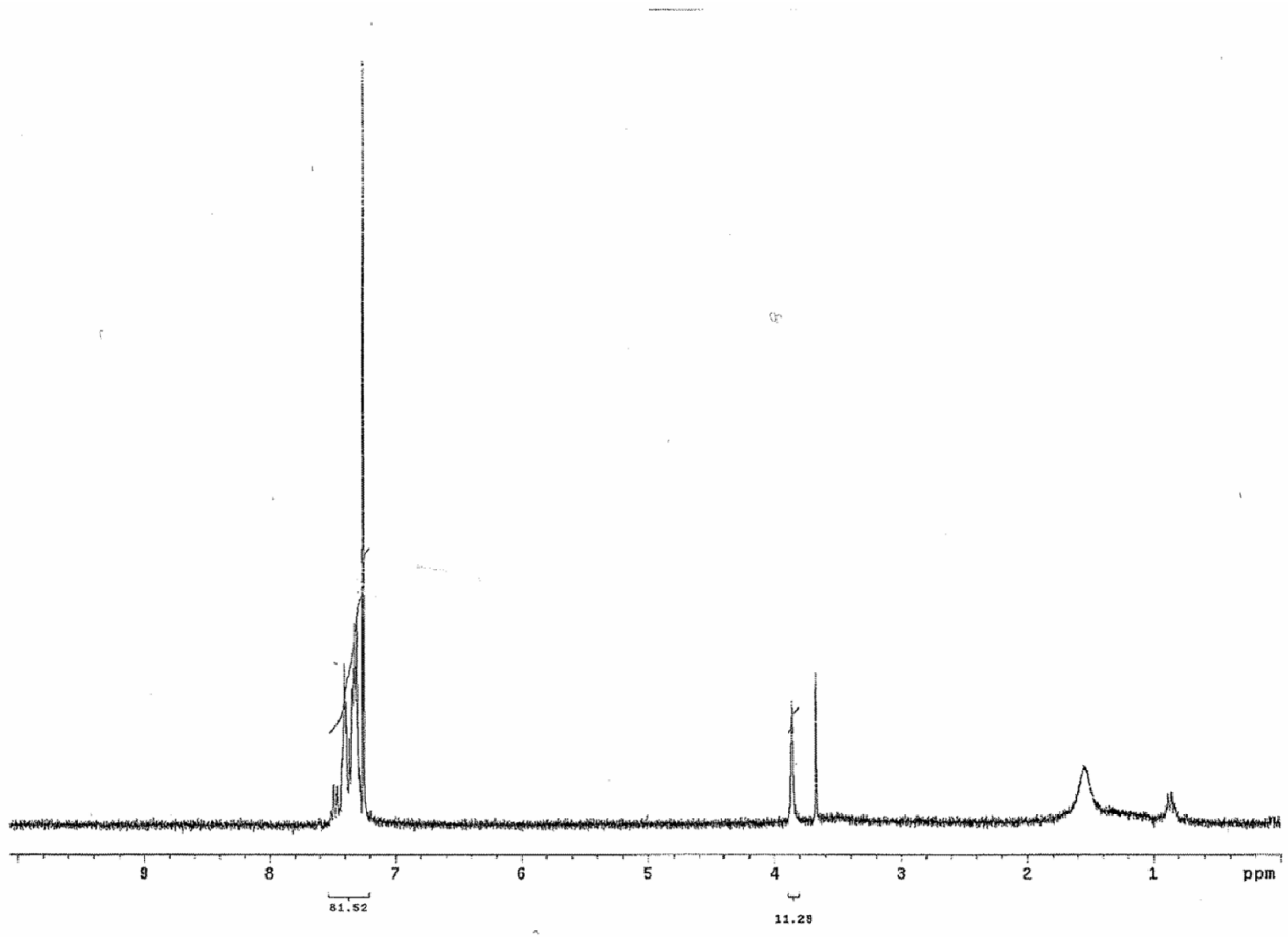


^{1}H NMR spectrum of compound **2b**

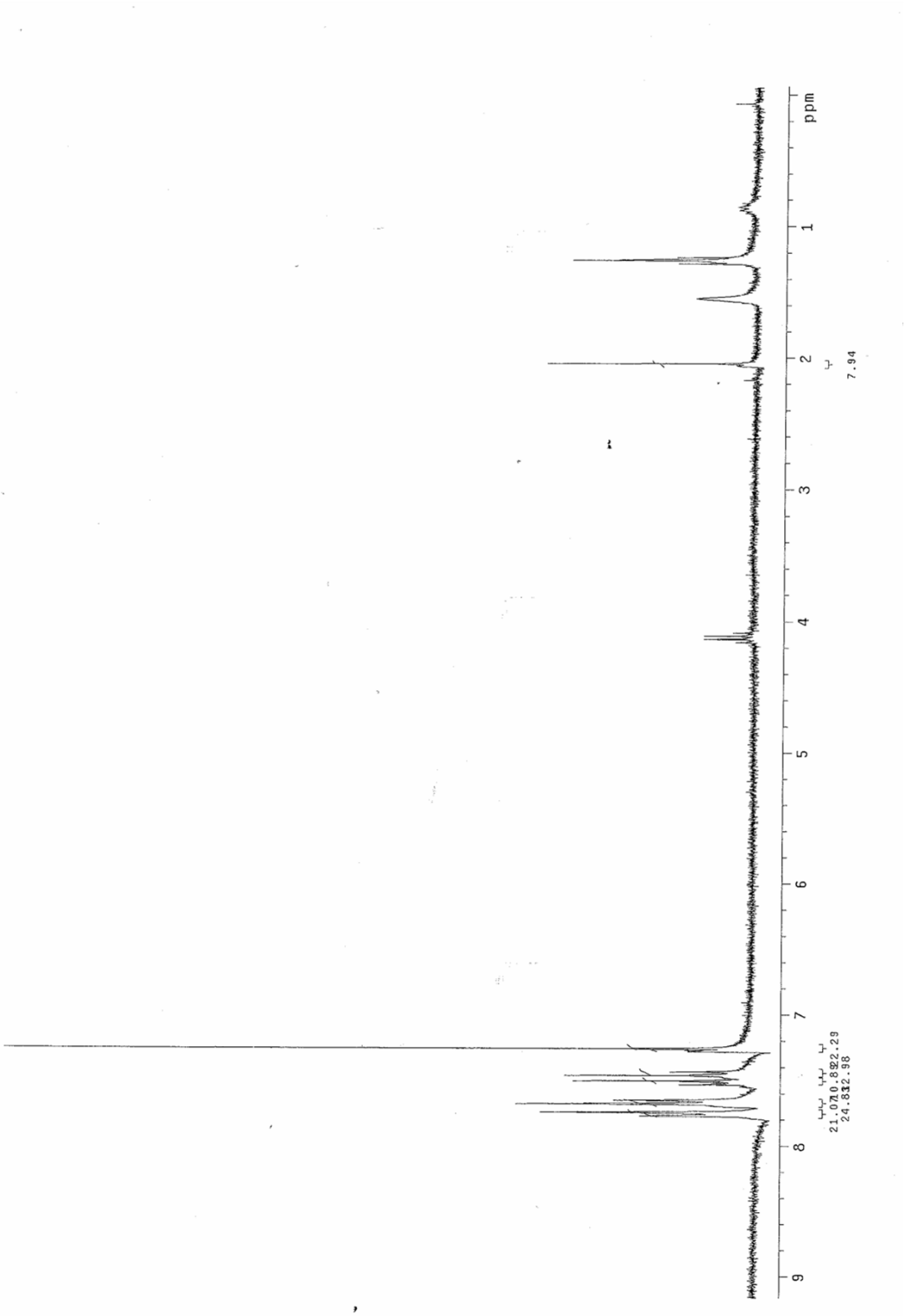


^{1}H NMR spectrum of compound **2c**

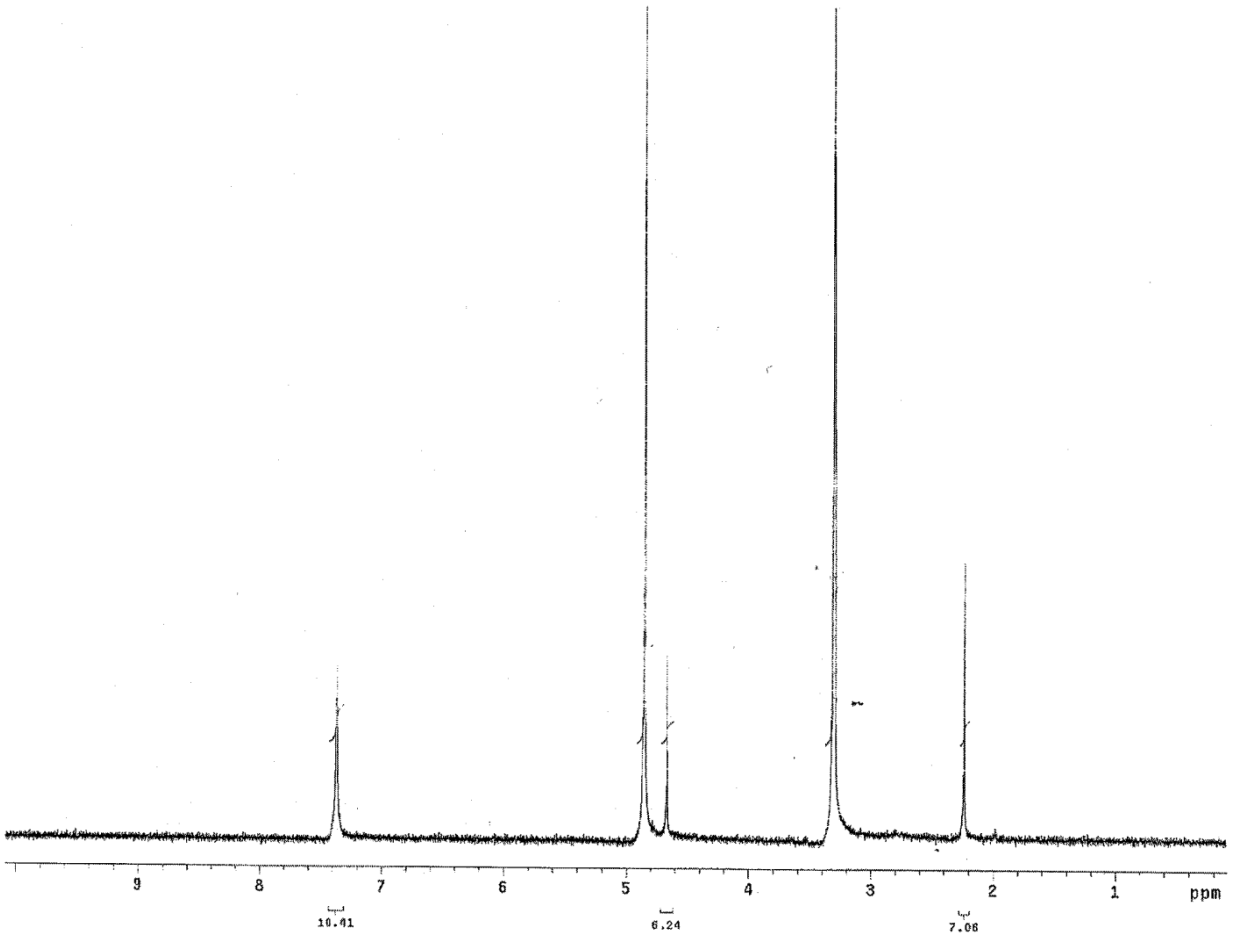
^{1}H NMR spectrum of compound **2d**



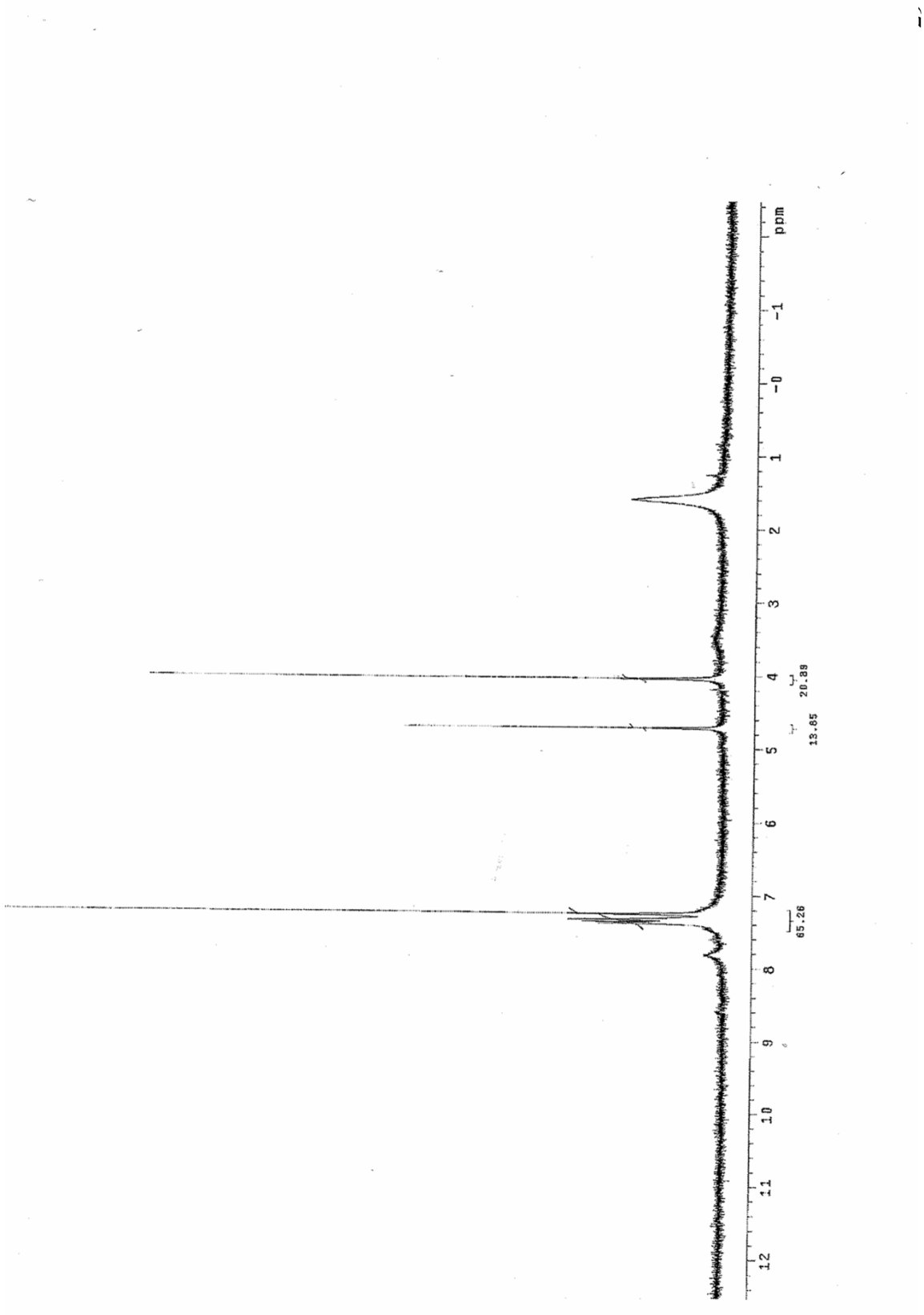
^{1}H NMR spectrum of compound **2e**



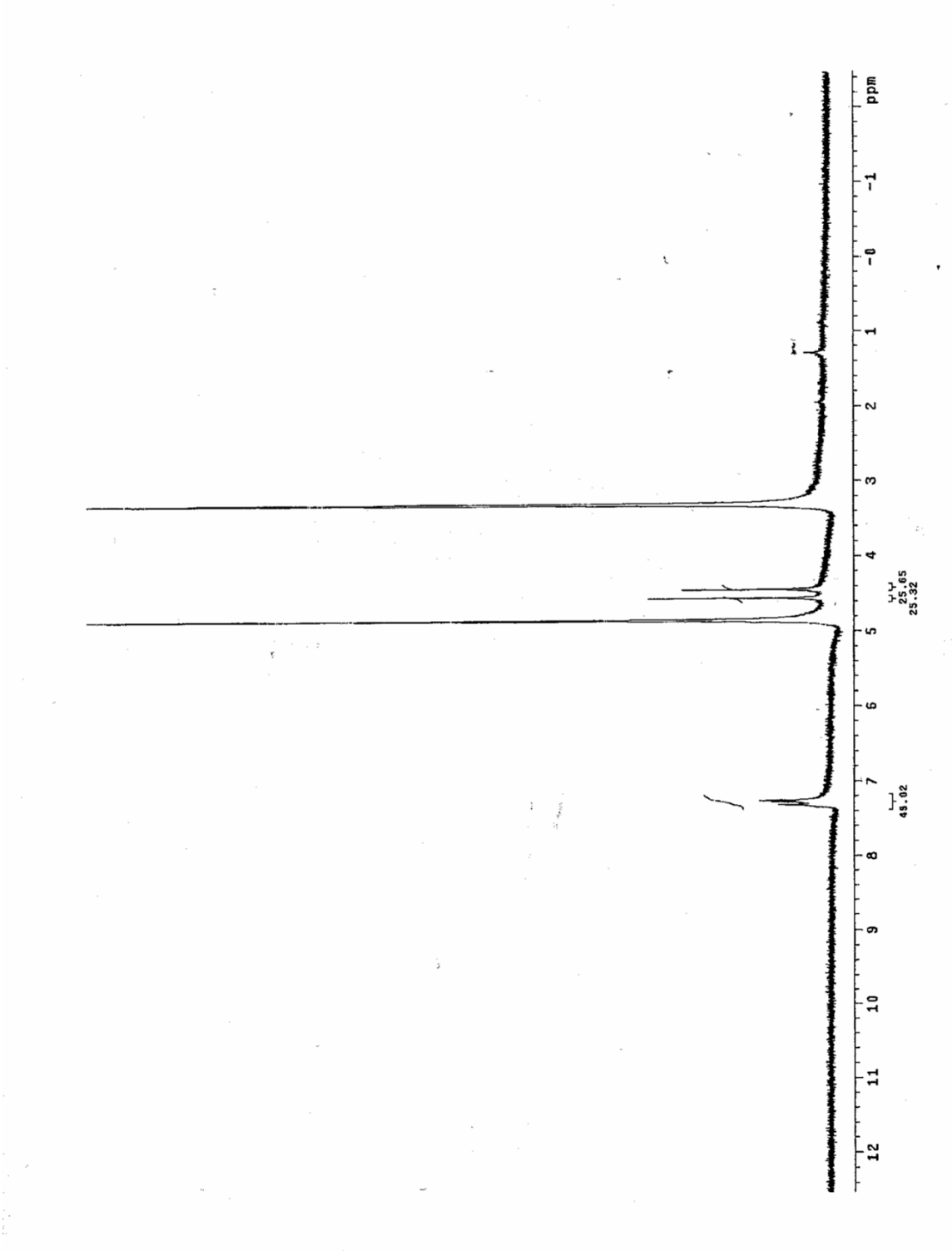
^{1}H NMR spectrum of compound **3a**



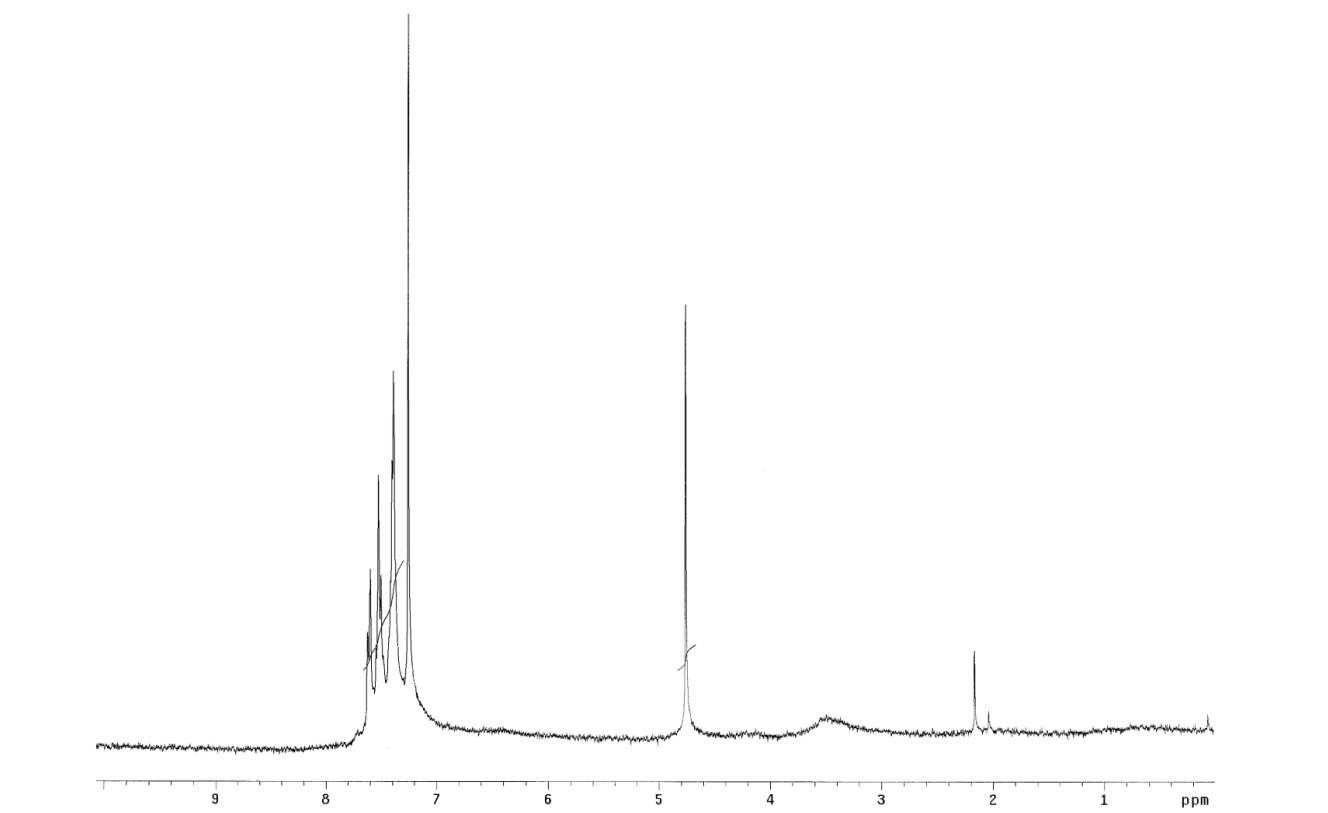
^{1}H NMR spectrum of compound **3b**



^{1}H NMR spectrum of compound **3c**



^{1}H NMR spectrum of compound **3d**



^{1}H NMR spectrum of compound **3e**