Novel Semisynthetic Derivatives of Bile Acids as Effective Tyrosyl-DNA Phosphodiesterase 1 Inhibitors

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ELECTRONIC SUPPORTING INFORMATION

Table S1. The scores predicted by the four scoring functions for compounds **1a,b, 2a,b, 3a-d, 4a,b-8a,b** and **9a-11a** docked in Tdp1.

Compound	**Scoring Function**				**IC_{50}**
	PLP	**GS**	**CS**	**ASP**	
1a	71.8	56.5	32.7	36.0	0.32±0.11
2a	70.4	58.6	26.7	31.6	0.38±0.12
3a	80.8	60.8	33.9	35.8	0.65±0.16
3c	71.9	49.7	22.9	35.4	0.95±0.05
Fur	45.3	47.6	27.1	33.3	1.23±0.33
1b	75.2	44.6	36.3	33.6	2.65±0.30
2b	74.8	59.5	37.4	35.7	2.6±0.4
3b	80.0	63.5	33.5	34.1	2.7±0.2
3d	72.7	67.9	34.1	37.4	0.48±0.04
4a	41.5	28.2	26.7	28.5	0.43±0.13
4b	65.9	41.9	31.3	28.2	6.7±0.7
5a	62.1	53.9	31.2	27.3	0.42±0.01
5b	66.4	49.7	31.5	27.5	1.3±0.2
6a	64.7	40.3	29.5	27.0	1.00±0.05
6b	66.5	45.8	32.4	28.2	7.6±3.9
7a	63.3	59.4	29.8	30.0	4.08±0.08
7b	63.4	50.1	29.6	32.5	>15
8a	64.5	60.2	30.8	26.8	0.47±0.08
8b	63.5	47.3	33.0	27.2	2.3±0.4
9a	69.4	59.1	31.5	35.0	0.29±0.12
10a	56.9	56.2	25.6	26.8	>15
11a	56.5	61.9	22.1	28.6	>15

Table S2. The calculated molecular descriptors for the bile acid derivatives.

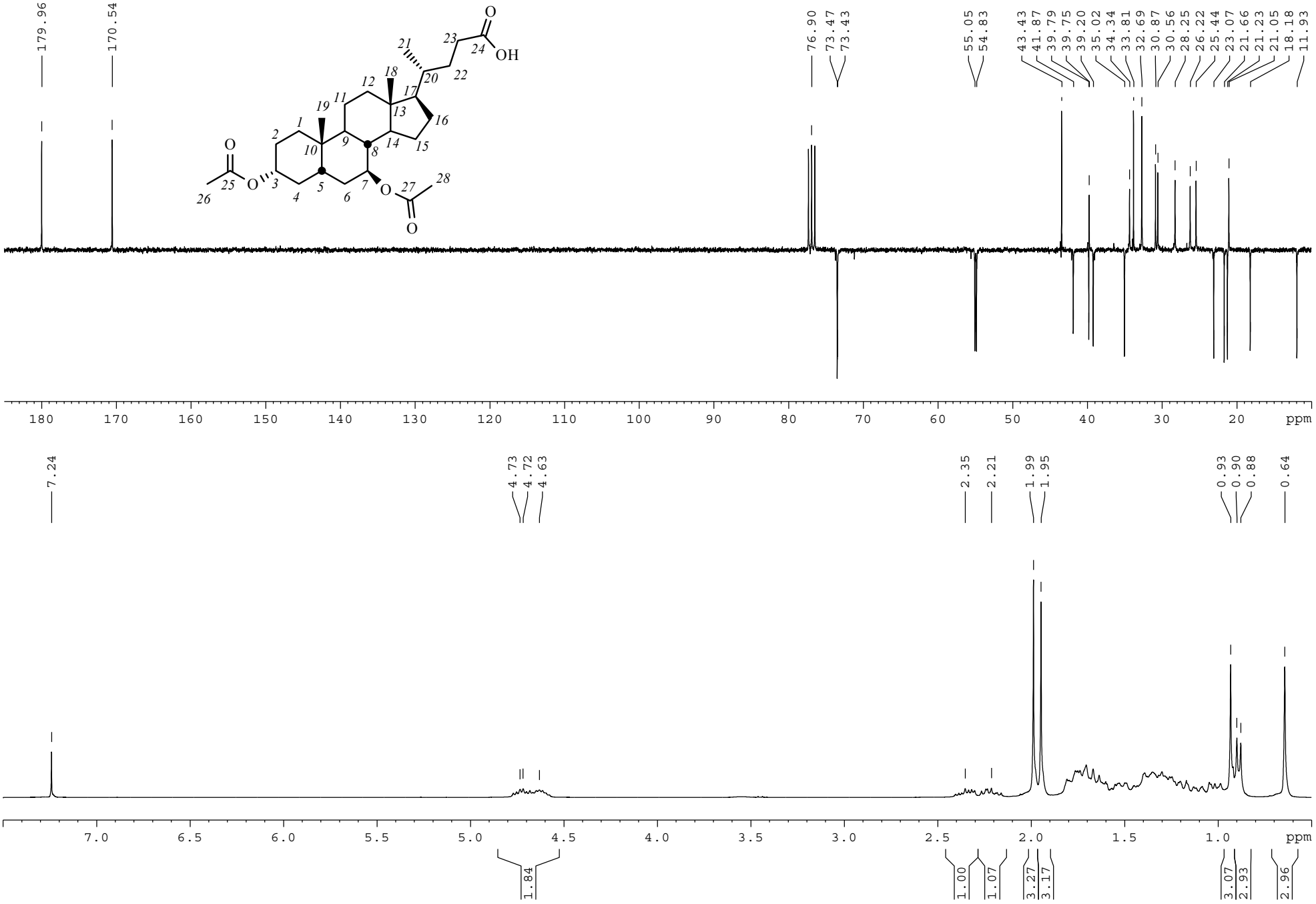
Compound	Molecular Descriptor					
	Mol. weight	**Log P**	**TPSA**	**H bond donor**	**H bond acceptor**	**Rotatable bond**
1a	618.9	5.5	97.5	2	3	11
2a	618.9	5.5	97.5	2	3	11
3a	618.9	5.3	97.5	2	3	11
3c	576.8	5.2	91.4	3	3	9
Fur	304.4	2.9	112.9	4	4	4
1b	534.8	5.0	85.4	4	3	7
2b	534.8	5.0	85.4	4	3	7
3b	534.8	5.0	85.4	4	3	7
3d	576.8	5.2	91.4	3	3	9
4a	551.8	5.7	81.7	1	3	9
4b	467.7	5.4	69.6	3	3	5
5a	630.6	6.5	81.7	1	3	9
5b	546.6	6.2	69.5	3	3	5
6a	565.8	6.1	81.7	1	3	9
6b	481.7	5.9	69.6	3	3	5
7a	552.8	4.4	94.6	1	4	9
7b	468.7	4.1	82.5	3	4	5
8a	609.9	5.7	81.7	1	3	9
8b	525.8	5.4	69.6	3	3	5
9a	708.0	9.0	101.9	2	4	13
10a	588.9	4.7	84.9	1	4	14
11a	589.8	4.0	94.2	1	5	12

Table S3. Criteria of lead-like, drug-like and known drug space (KDS) in terms of molecular descriptors.

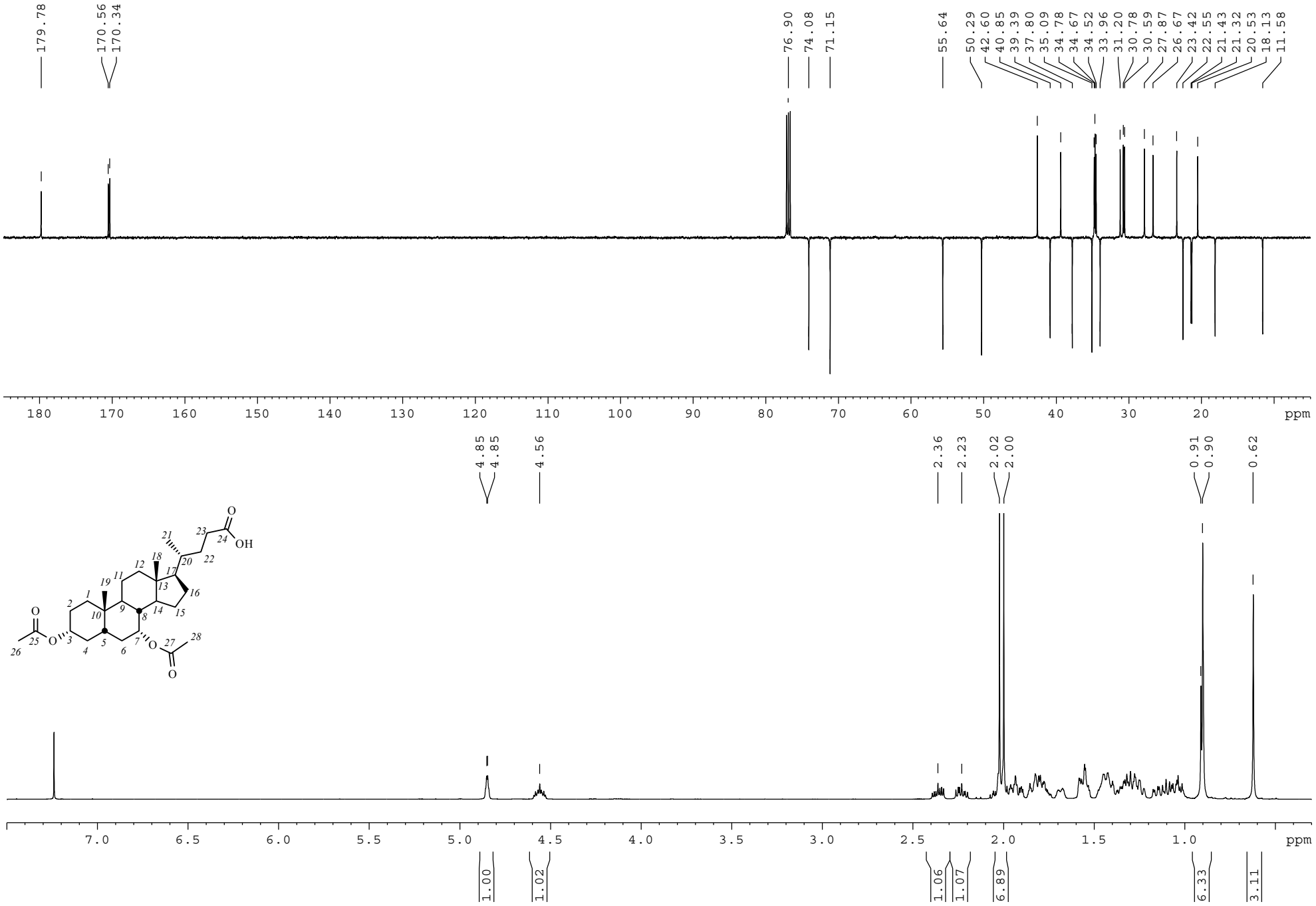
	Lead-like Space	**Drug-like Space**	**Known Drug Space**
Molecular weight (g mol^{-1})	300	500	800
Lipophilicity (Log P)	3	5	6.5
Hydrogen bond donors (HD)	3	5	7
Hydrogen bond acceptors (HA)	3	10	15
Polar surface area ($Å^2$) (PSA)	60	140	180
Rotatable bonds (RB)	3	10	17

From: Zhu, F; Logan, G.; Reynisson J. Wine Compounds as a Source for HTS Screening Collections. A Feasibility Study**.** *Mol. Inf.*, **2012**, *31*, 847 – 855**,** DOI:10.1002/minf.201200103

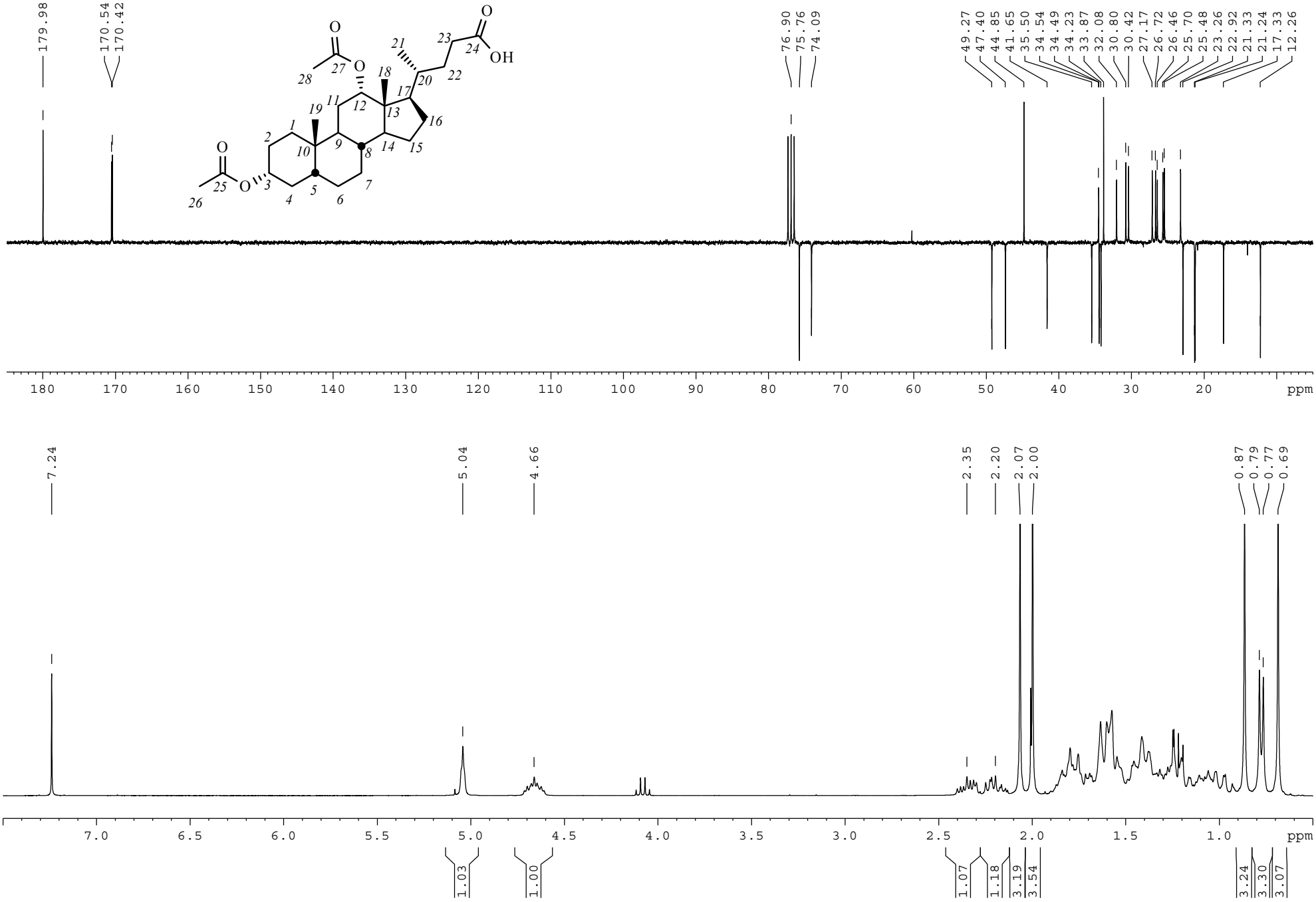
Spectra of Compound **1**, ^{1}H NMR, 300MHz, $CDCl_3$ (bottom); ^{13}C NMR, JMOD, 75MHz, $CDCl_3$ (top)



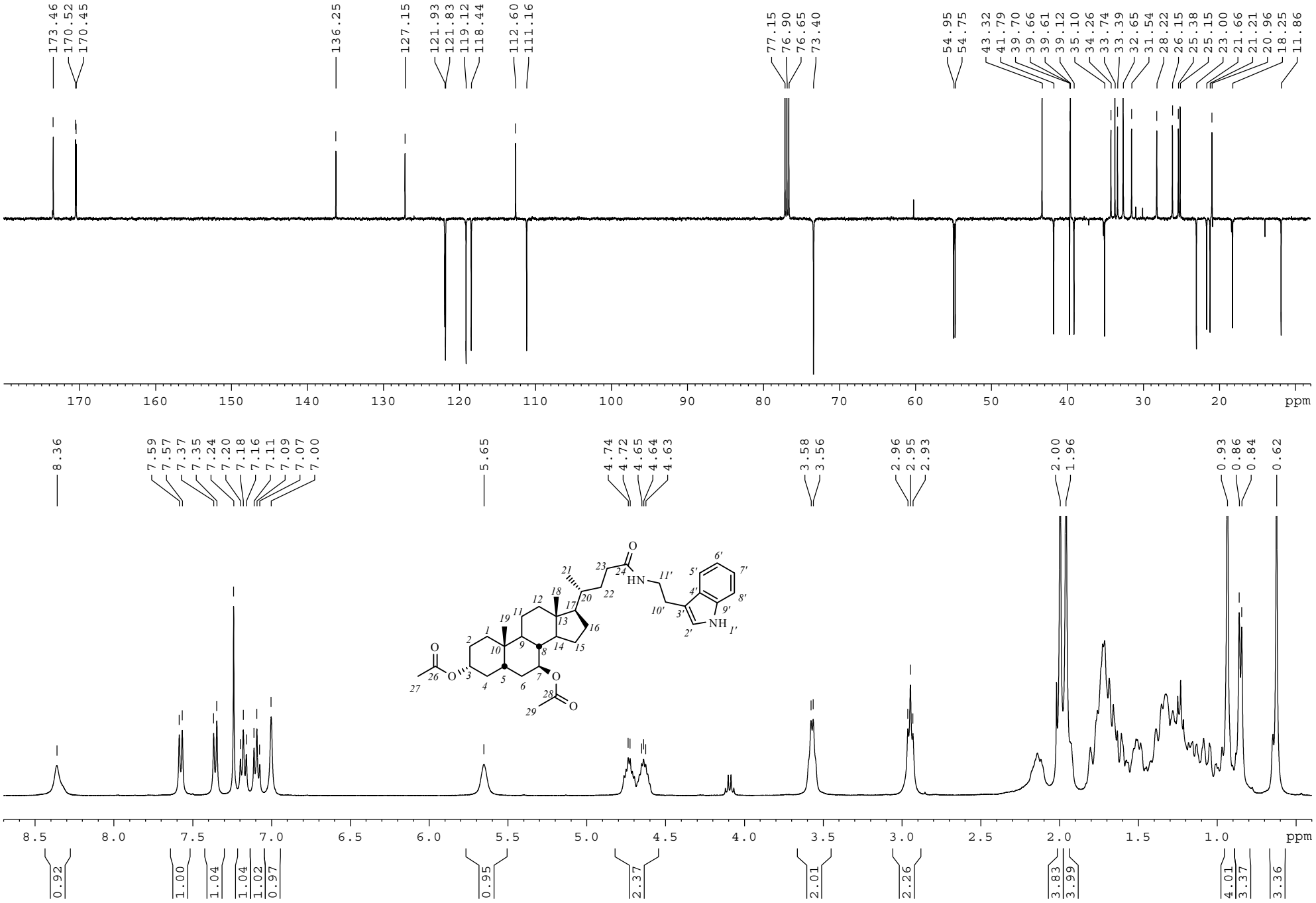
Spectra of Compound **2**, ^{1}H NMR, 500MHz, $CDCl_3$ (bottom); ^{13}C NMR, JMOD, 125MHz, $CDCl_3$ (top)



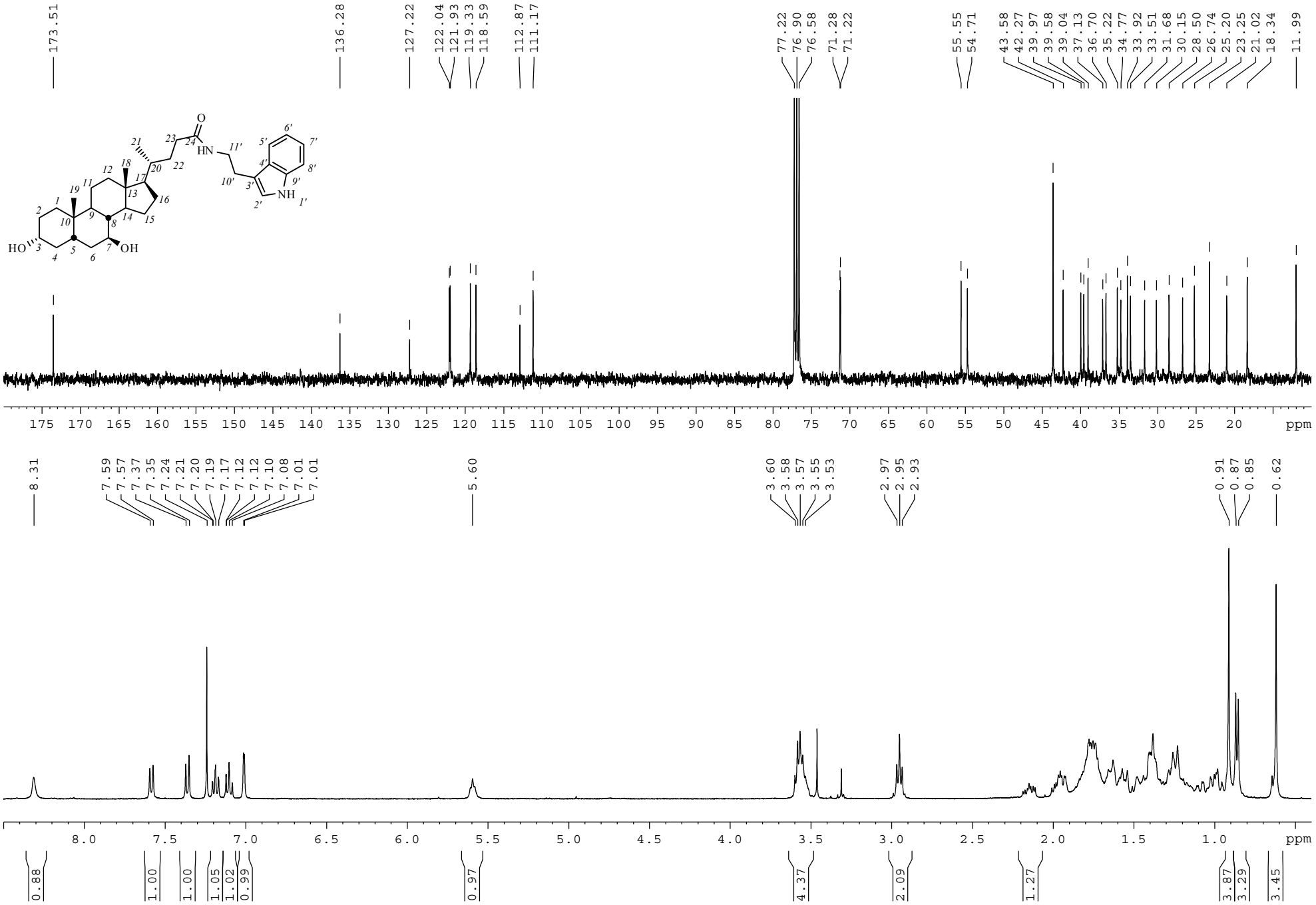
Spectra of Compound **3**, ^{1}H NMR, 300MHz, $CDCl_3$ (bottom); ^{13}C NMR, JMOD, 75MHz, $CDCl_3$ (top)



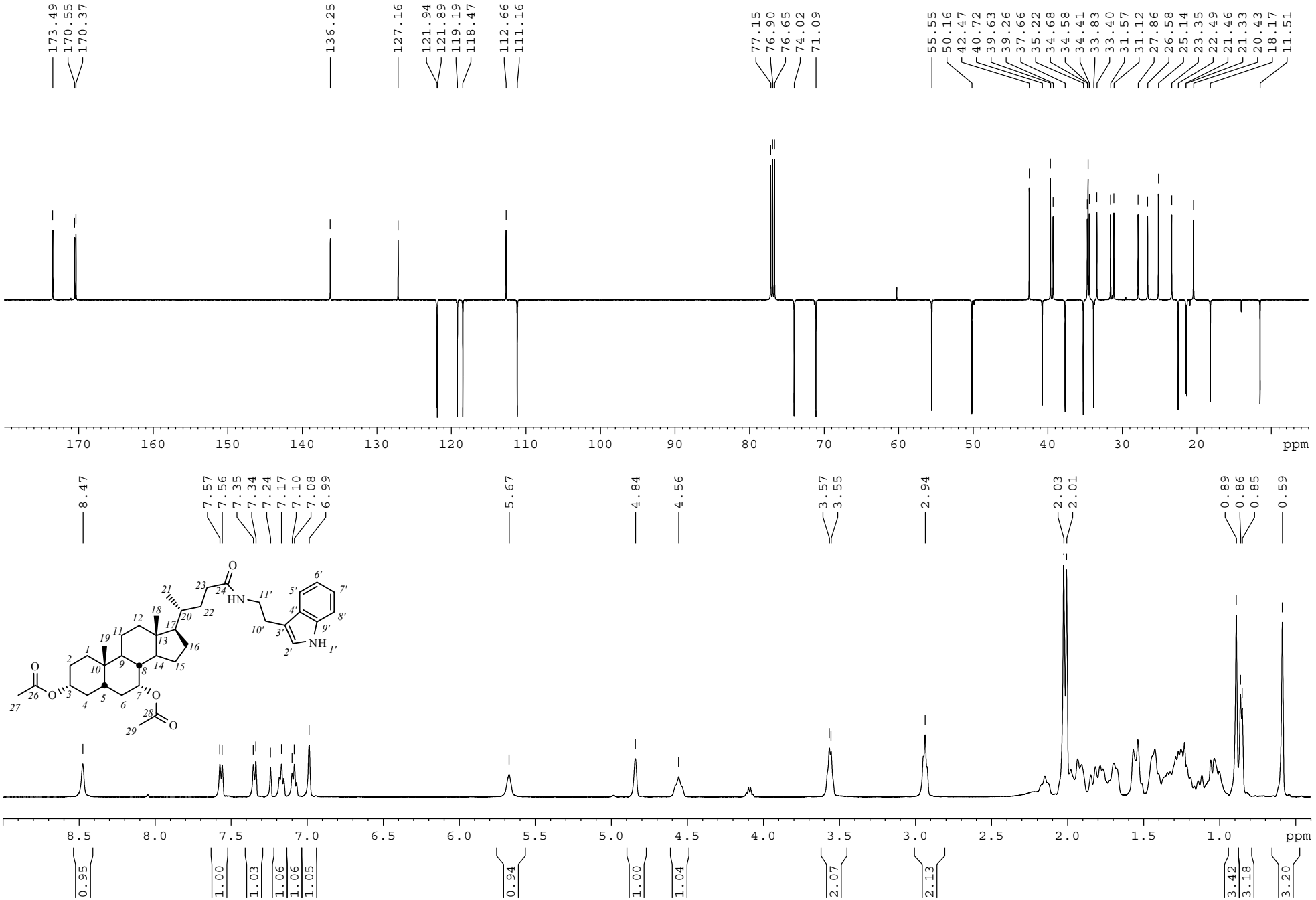
Spectra of Compound **1a**, ^{1}H NMR, 400MHz, $CDCl_3$ (bottom); ^{13}C NMR, JMOD, 125MHz, $CDCl_3$ (top)



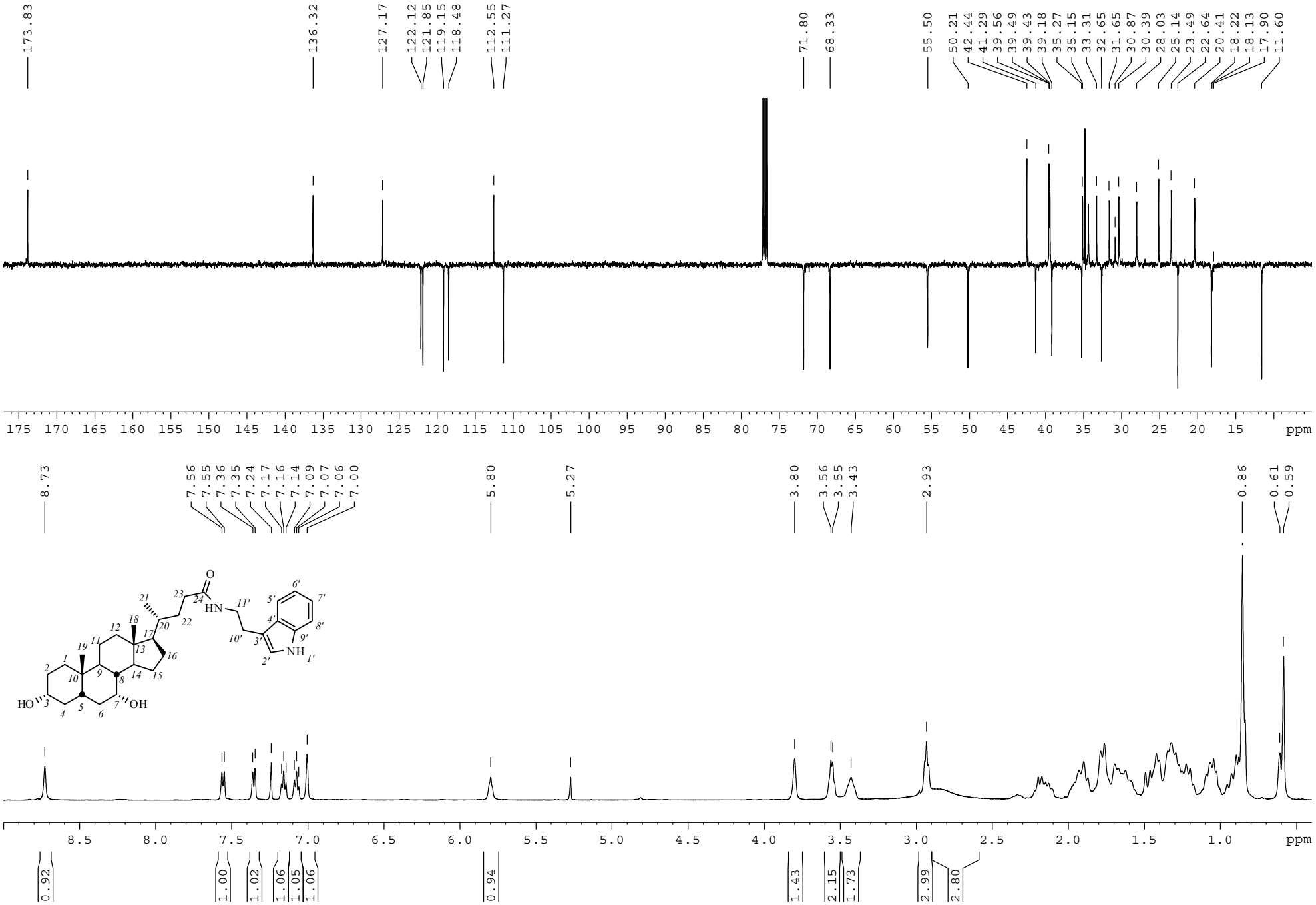
Spectra of Compound **1b**, ^{1}H NMR, 400MHz, $CDCl_3$ (bottom); ^{13}C NMR, BB, 100MHz, $CDCl_3$ (top)



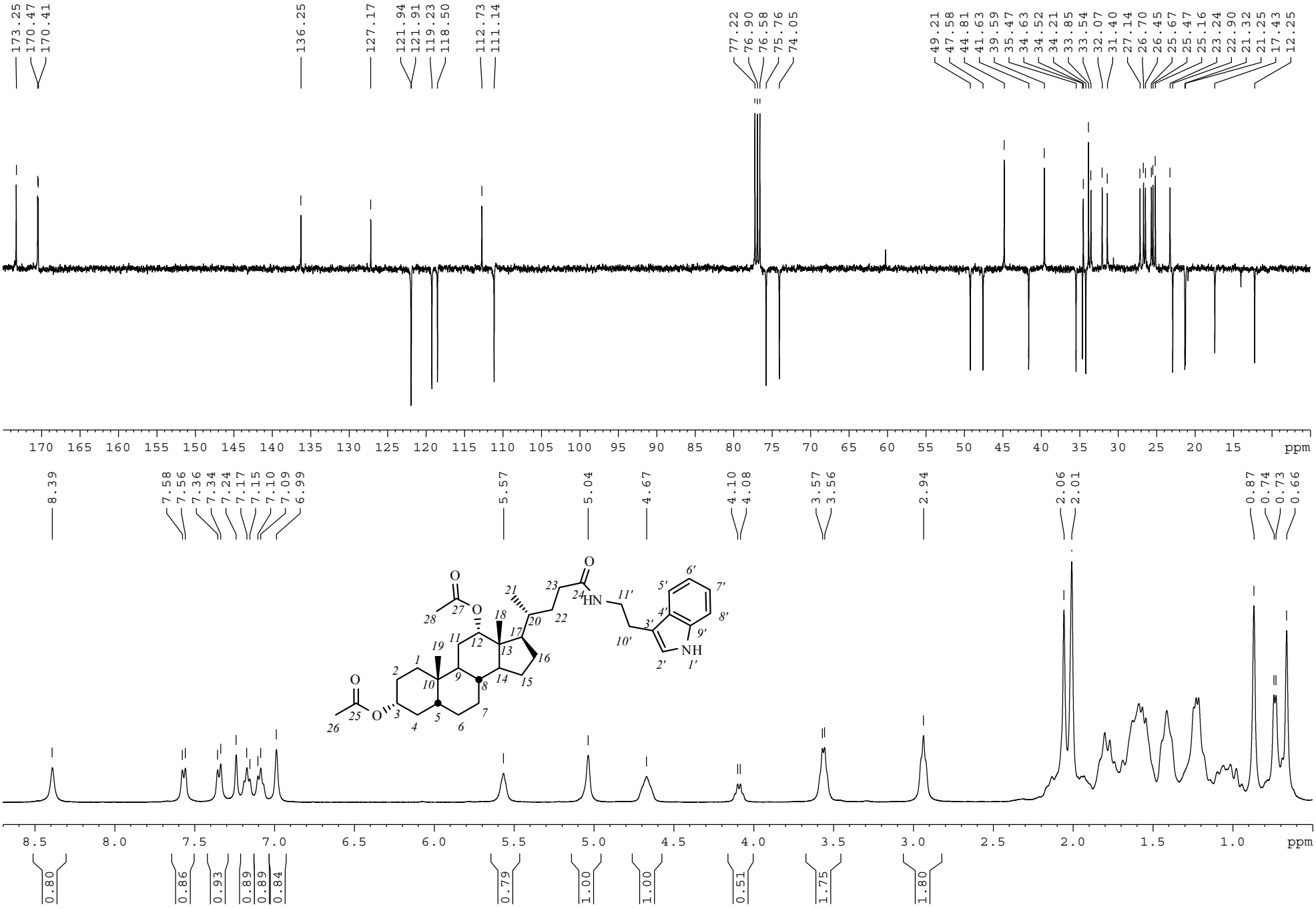
Spectra of Compound **2a**, ^{1}H NMR, 500MHz, $CDCl_3$ (bottom); ^{13}C NMR, JMOD, 125MHz, $CDCl_3$ (top)



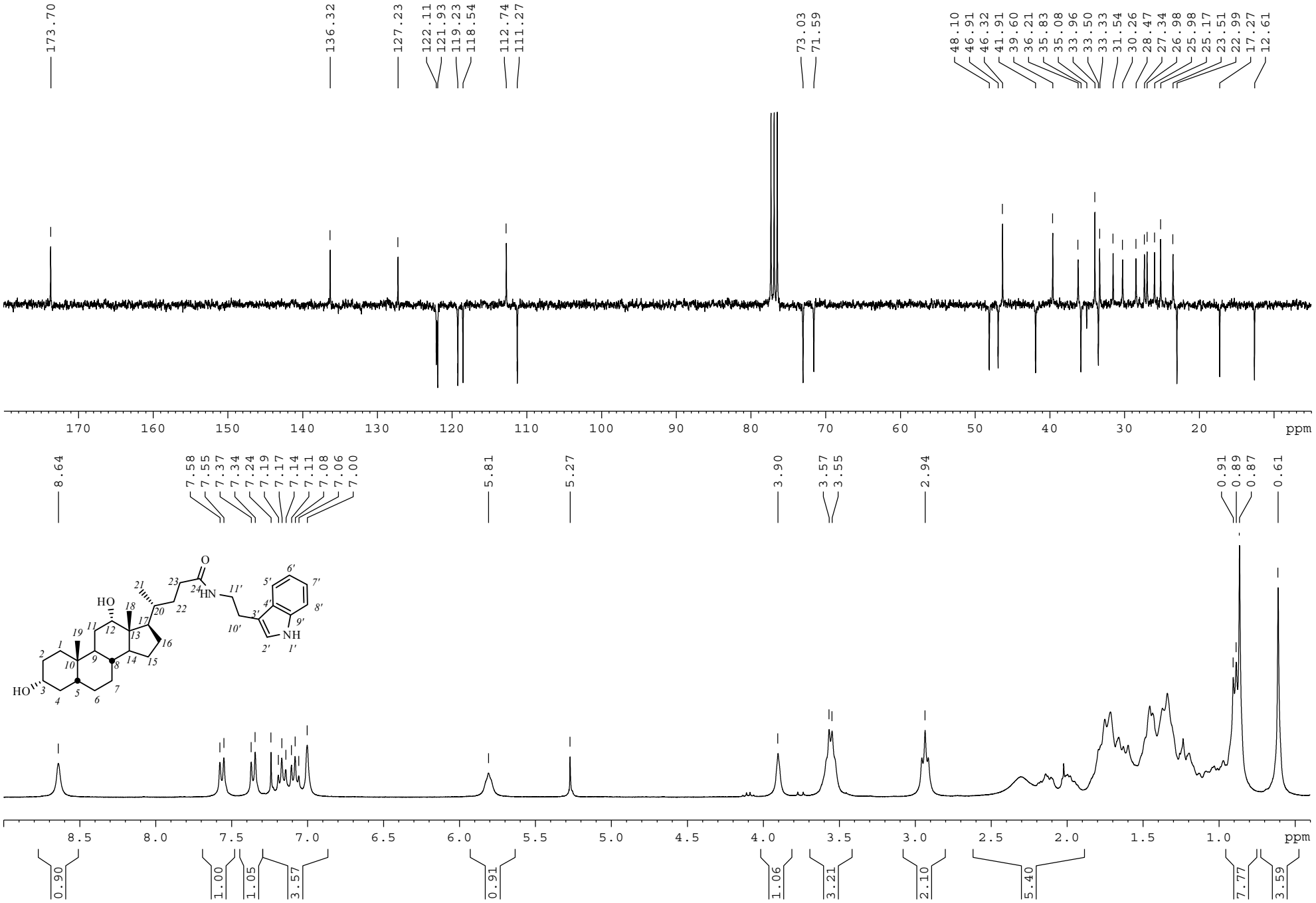
Spectra of Compound **2b**, ^{1}H NMR, 500MHz, $CDCl_3$ (bottom); ^{13}C NMR, JMOD, 125MHz, $CDCl_3$ (top)



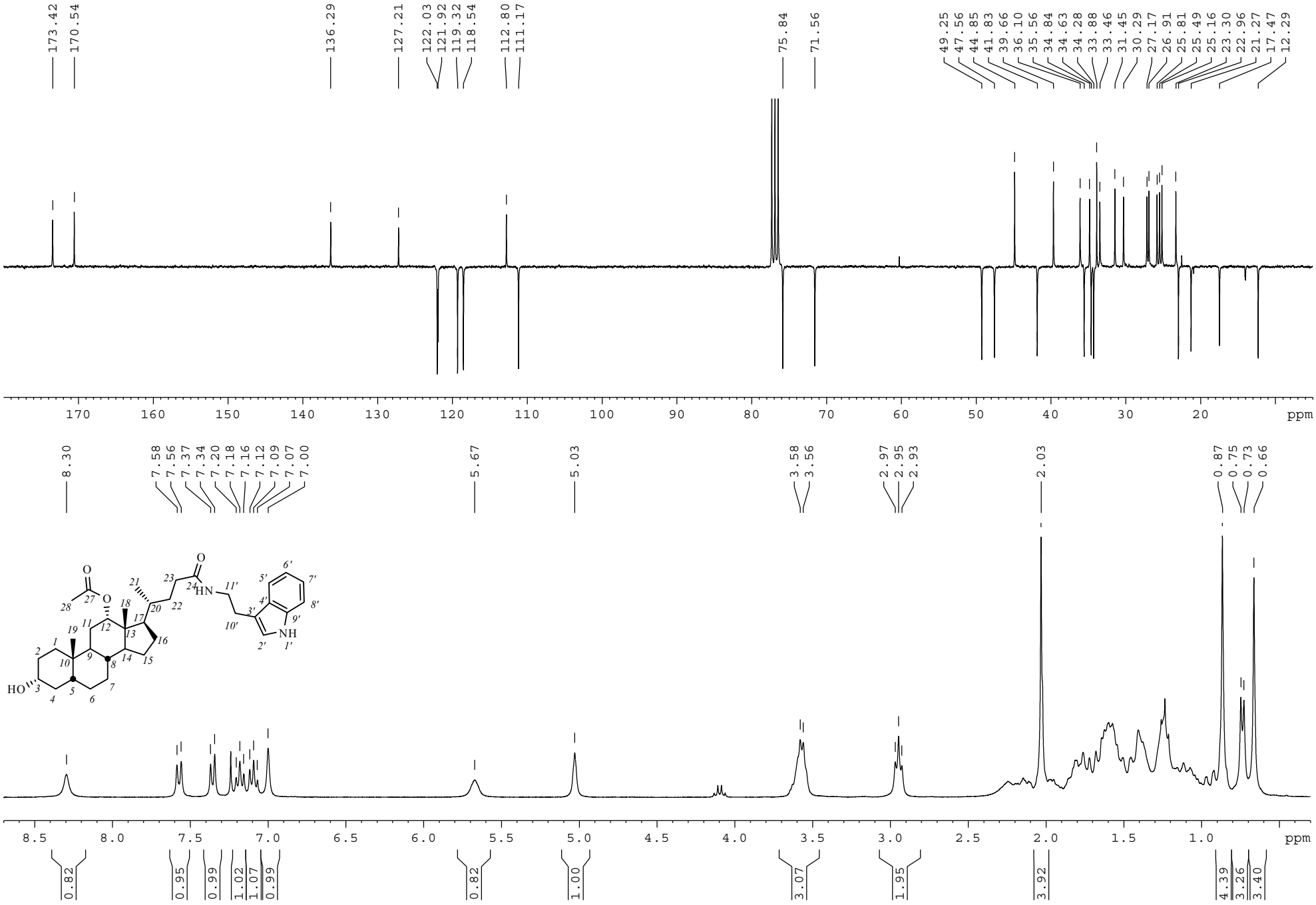
Spectra of Compound **3a**, ^{1}H NMR, 400MHz, $CDCl_3$ (bottom); ^{13}C NMR, JMOD, 100MHz, $CDCl_3$ (top)



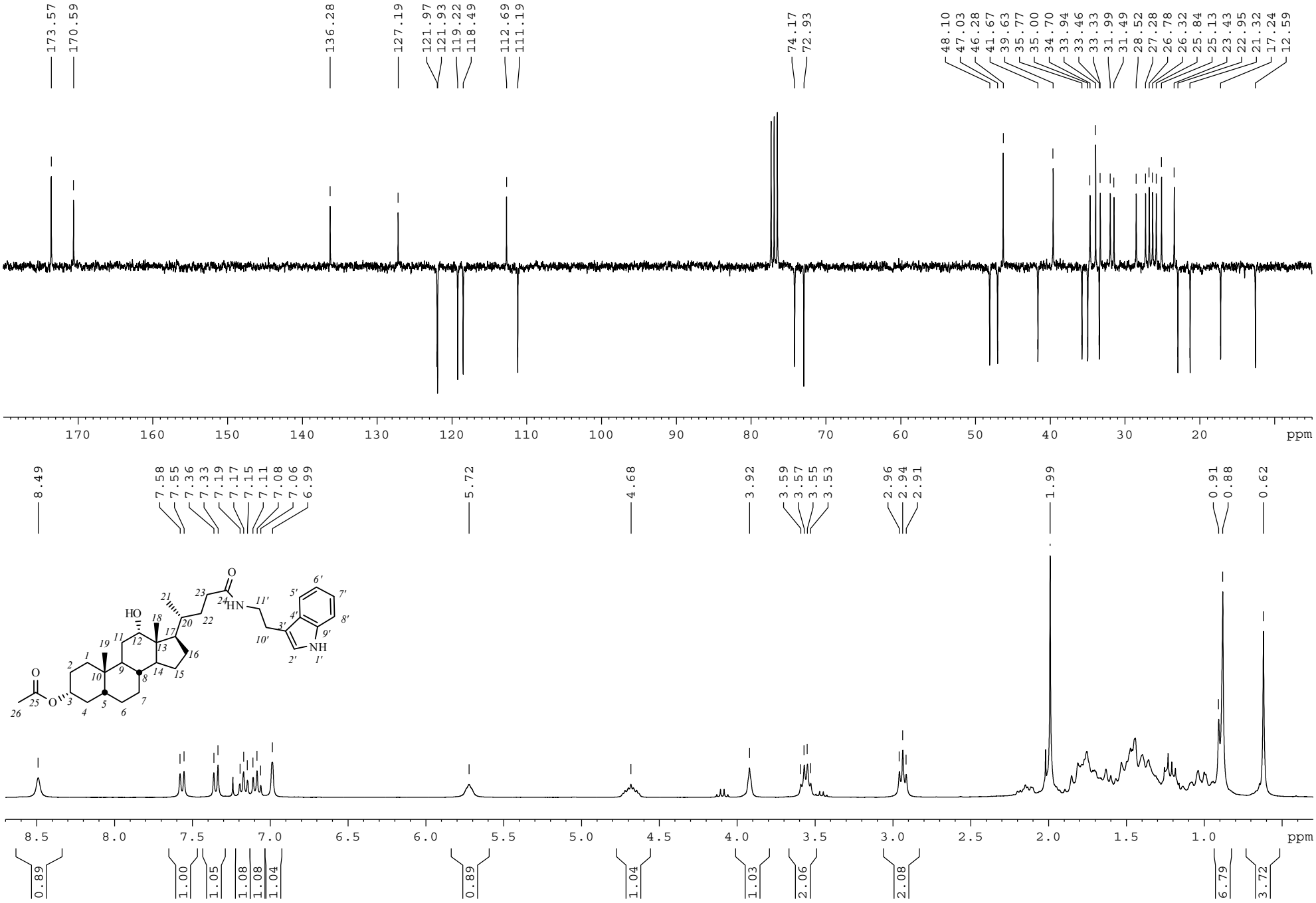
Spectra of Compound **3b**, ^{1}H NMR, 300MHz, $CDCl_3$ (bottom); ^{13}C NMR, JMOD, 75MHz, $CDCl_3$ (top)



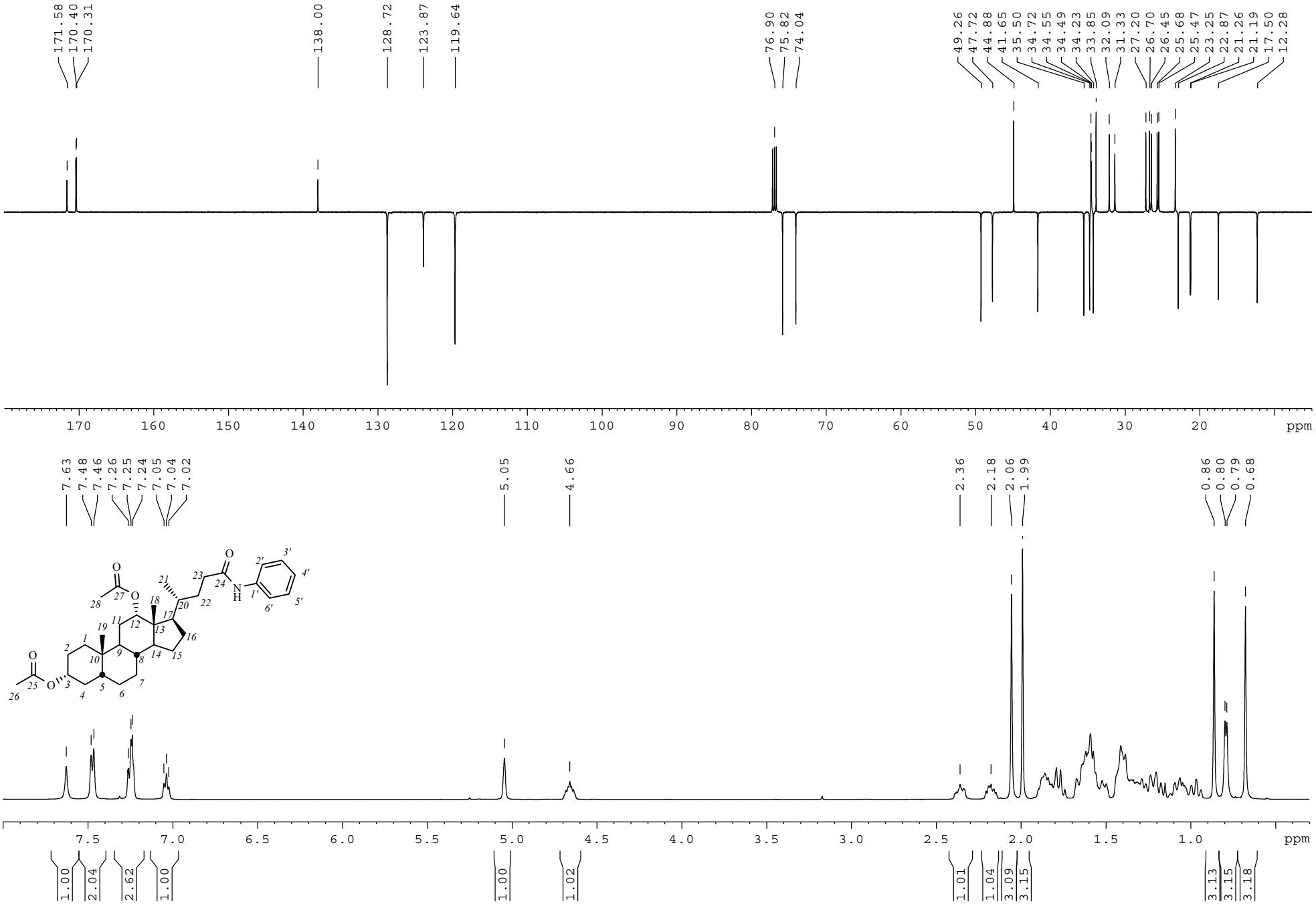
Spectra of Compound **3c**, ^{1}H NMR, 300MHz, $CDCl_3$ (bottom); ^{13}C NMR, JMOD, 75MHz, $CDCl_3$ (top)



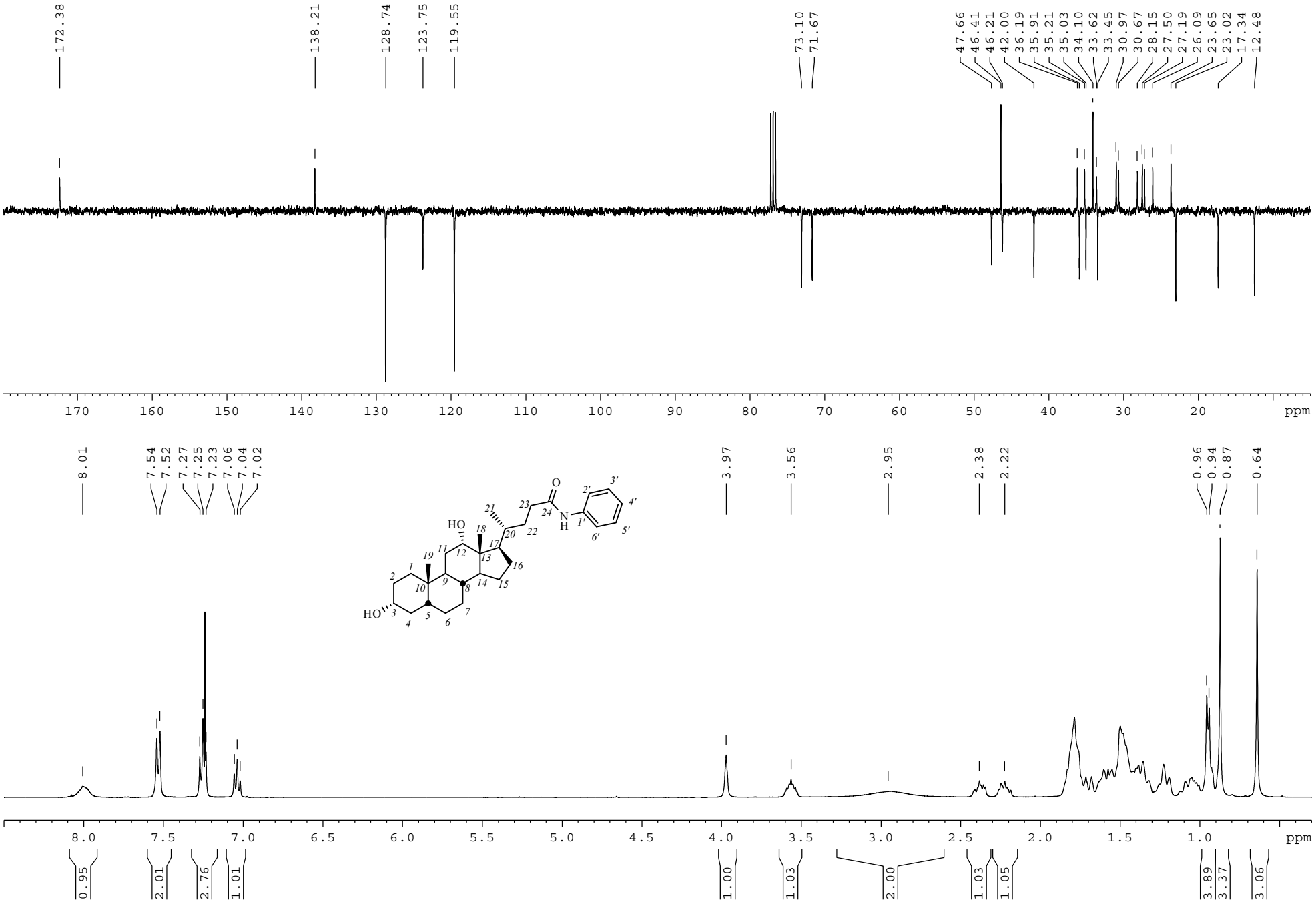
Spectra of Compound **3d**, ^{1}H NMR, 300MHz, $CDCl_3$ (bottom); ^{13}C NMR, JMOD, 75MHz, $CDCl_3$ (top)



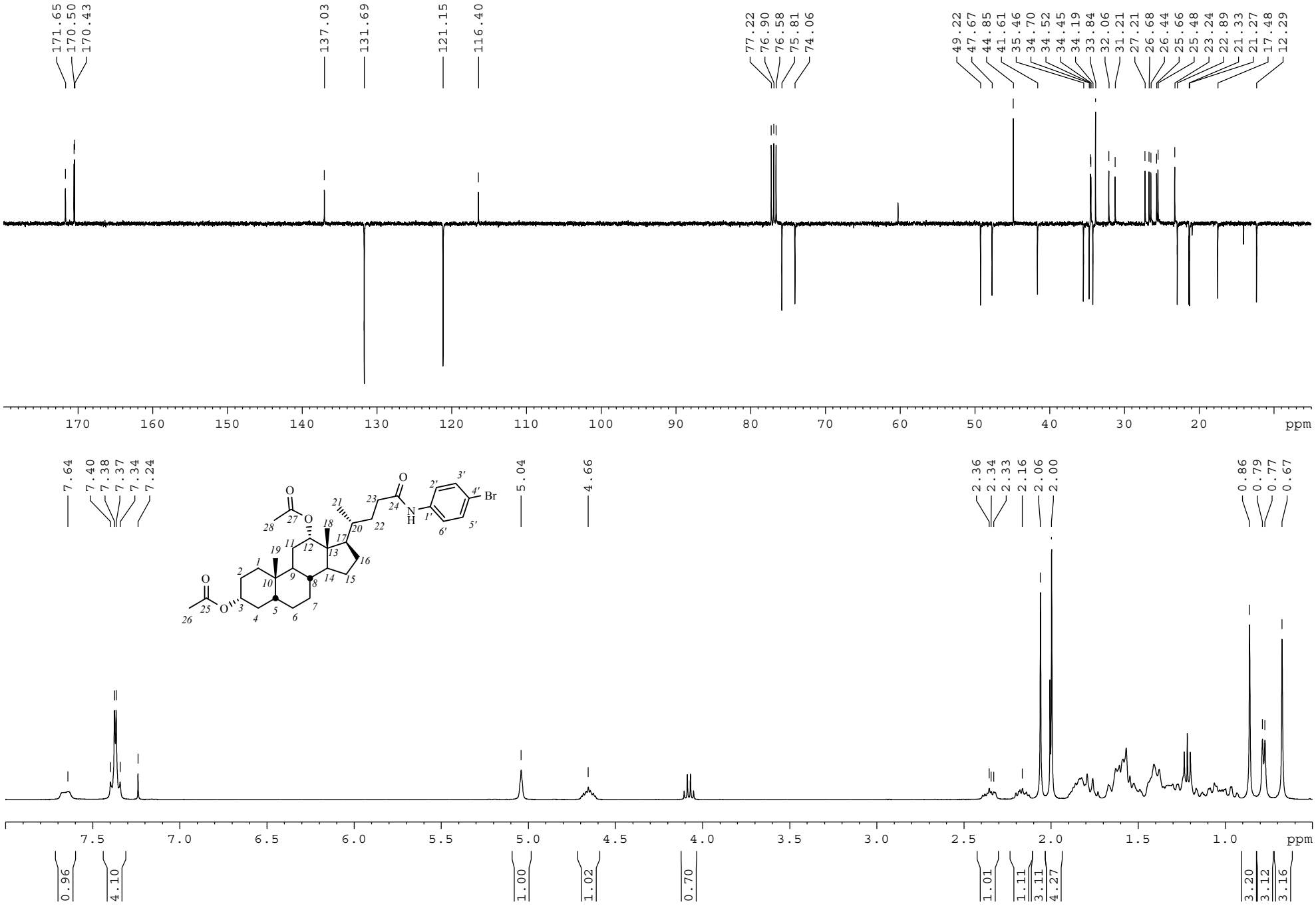
Spectra of Compound **4a**, ^{1}H NMR, 500MHz, $CDCl_3$ (bottom); ^{13}C NMR, JMOD, 125MHz, $CDCl_3$ (top)



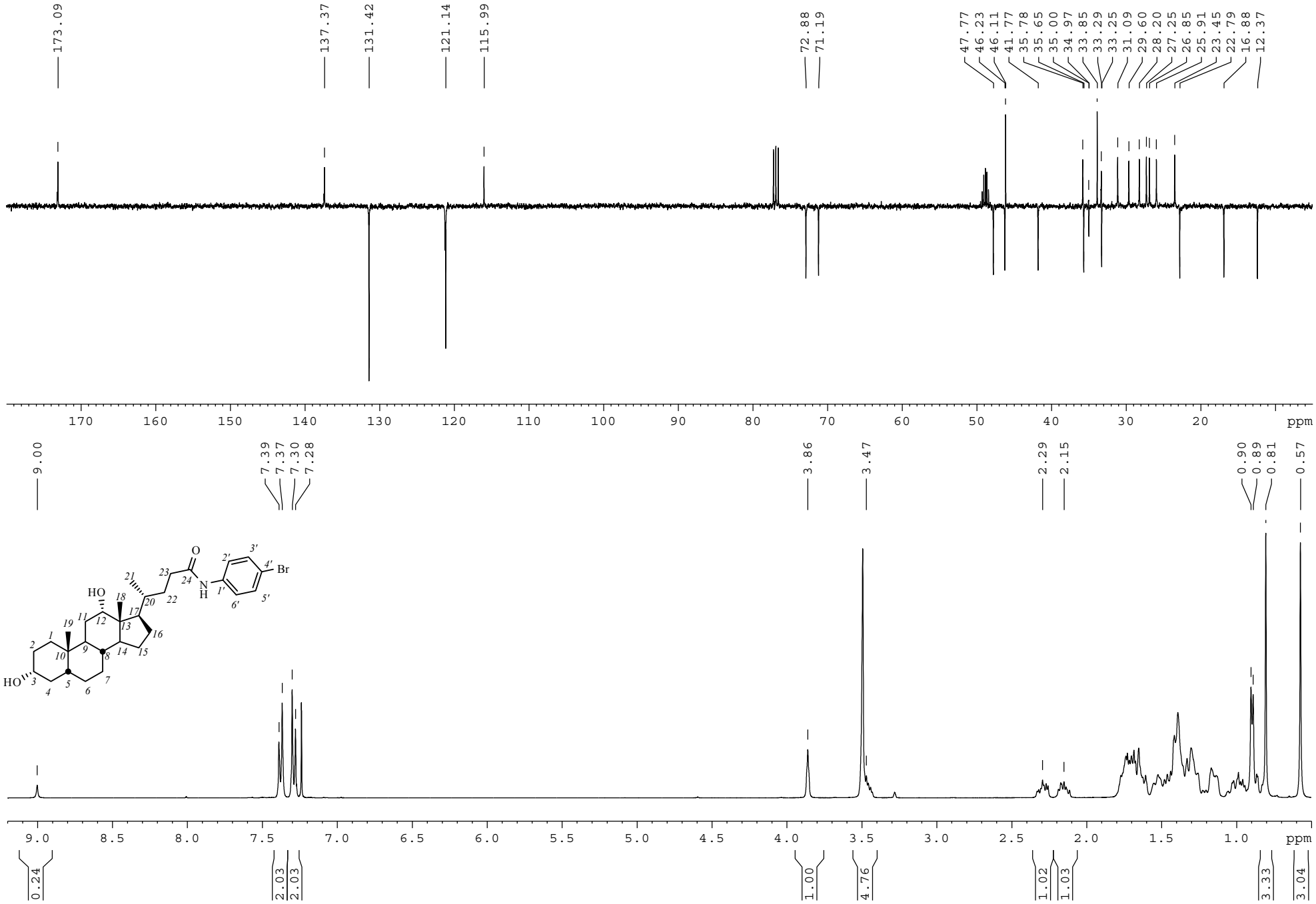
Spectra of Compound **4b**, ^{1}H NMR, 400MHz, $CDCl_3$ (bottom); ^{13}C NMR, JMOD, 100MHz, $CDCl_3$ (top)



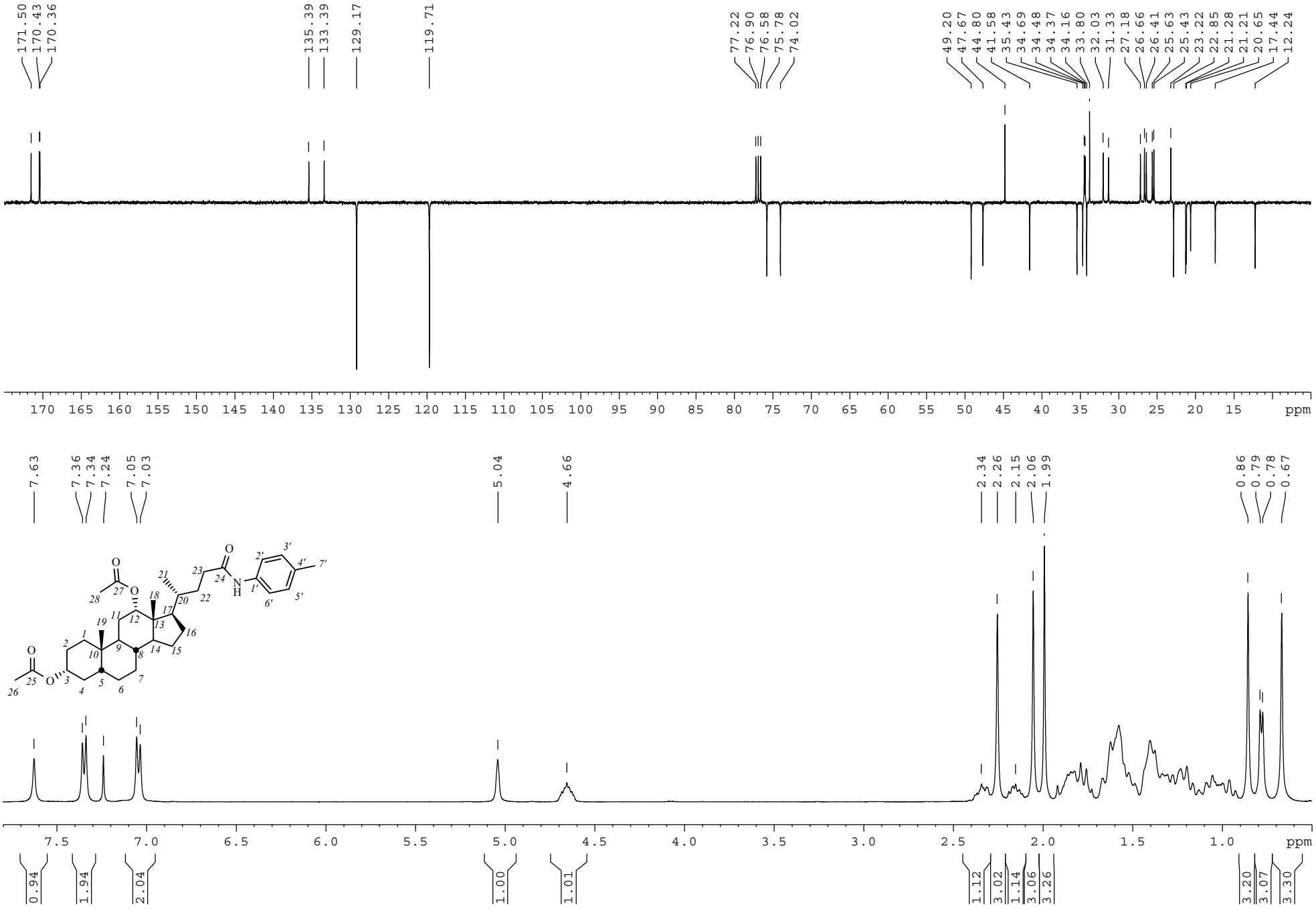
Spectra of Compound **5a**, ^{1}H NMR, 400MHz, $CDCl_3$ (bottom); ^{13}C NMR, JMOD, 100MHz, $CDCl_3$ (top)



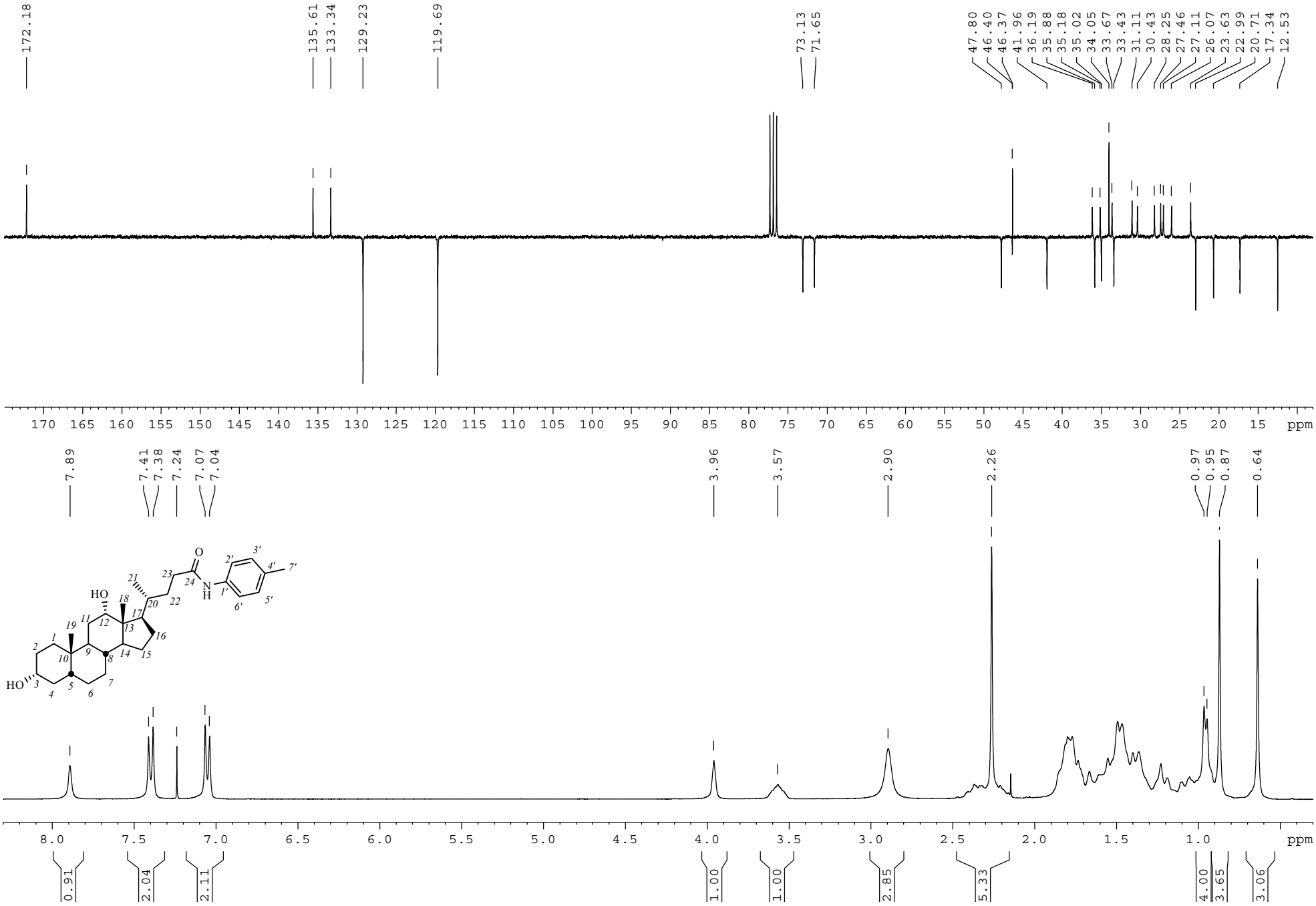
Spectra of Compound **5b**, ^{1}H NMR, 400MHz, $CDCl_3$+CD_3OD (bottom); ^{13}C NMR, JMOD, 100MHz, $CDCl_3$+CD_3OD (top)



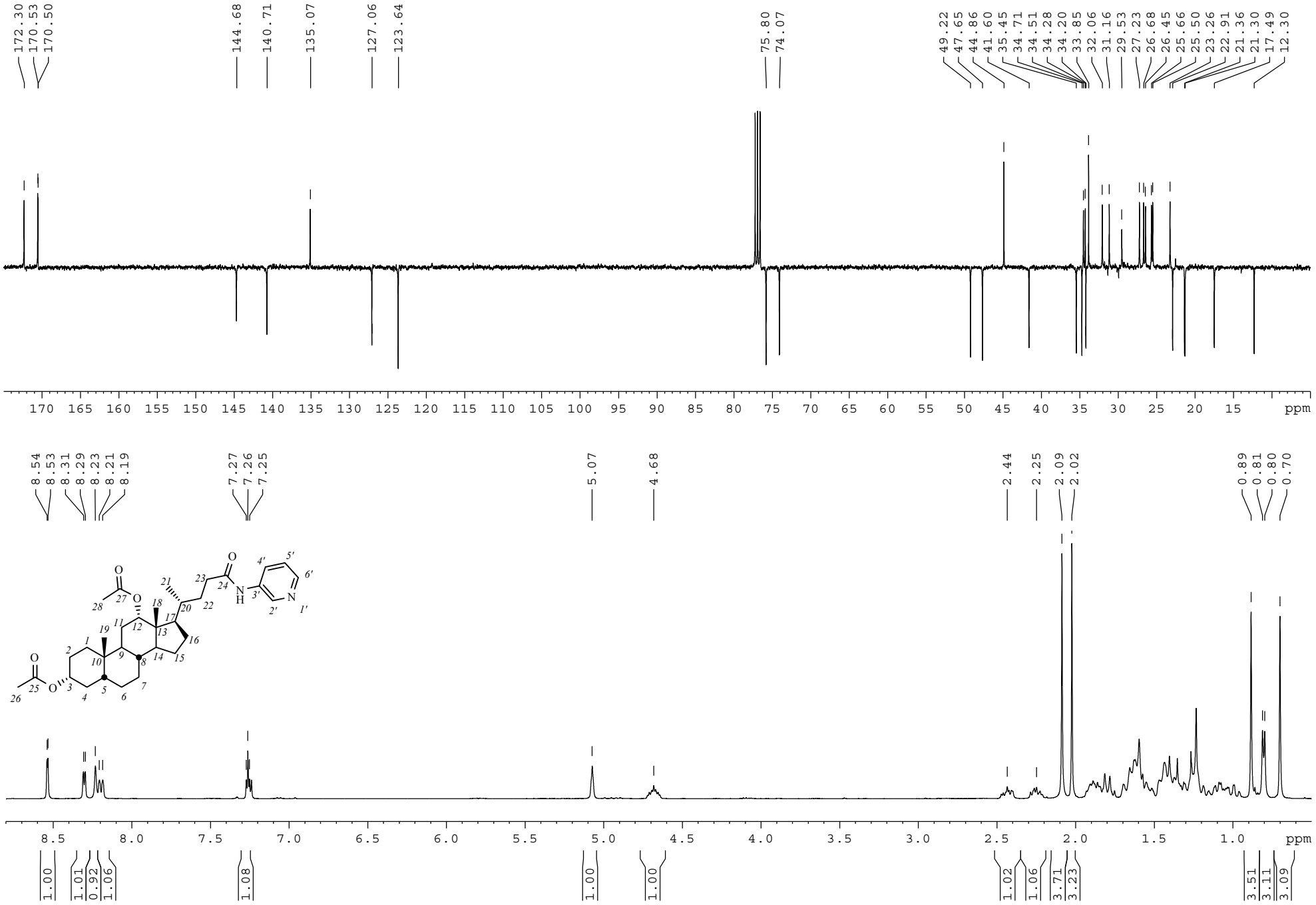
Spectra of Compound **6a**, ^{1}H NMR, 400MHz, $CDCl_3$ (bottom); ^{13}C NMR, JMOD, 100MHz, $CDCl_3$ (top)



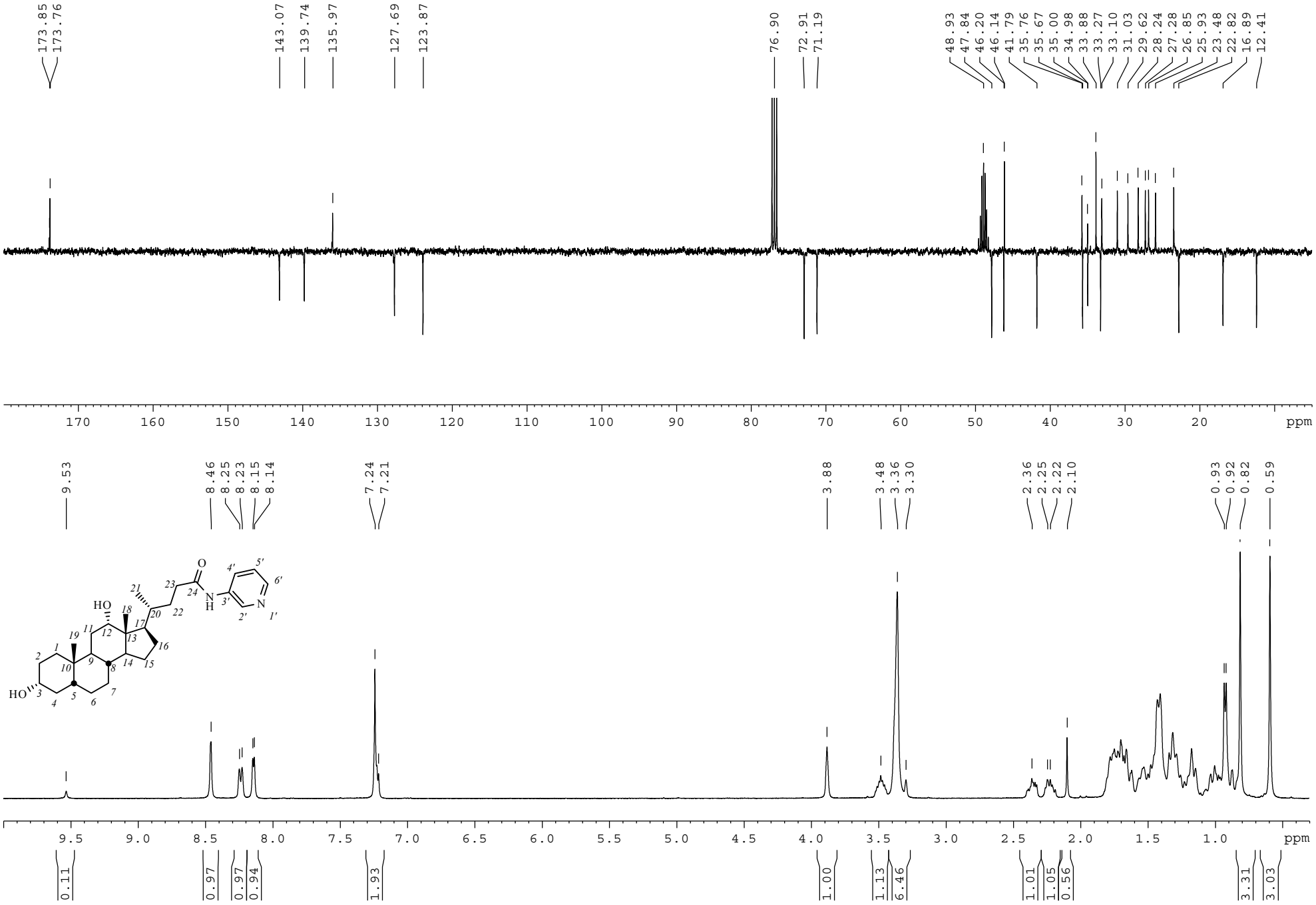
Spectra of Compound **6b**, ^{1}H NMR, 300MHz, $CDCl_3$ (bottom); ^{13}C NMR, JMOD, 75MHz, $CDCl_3$ (top)



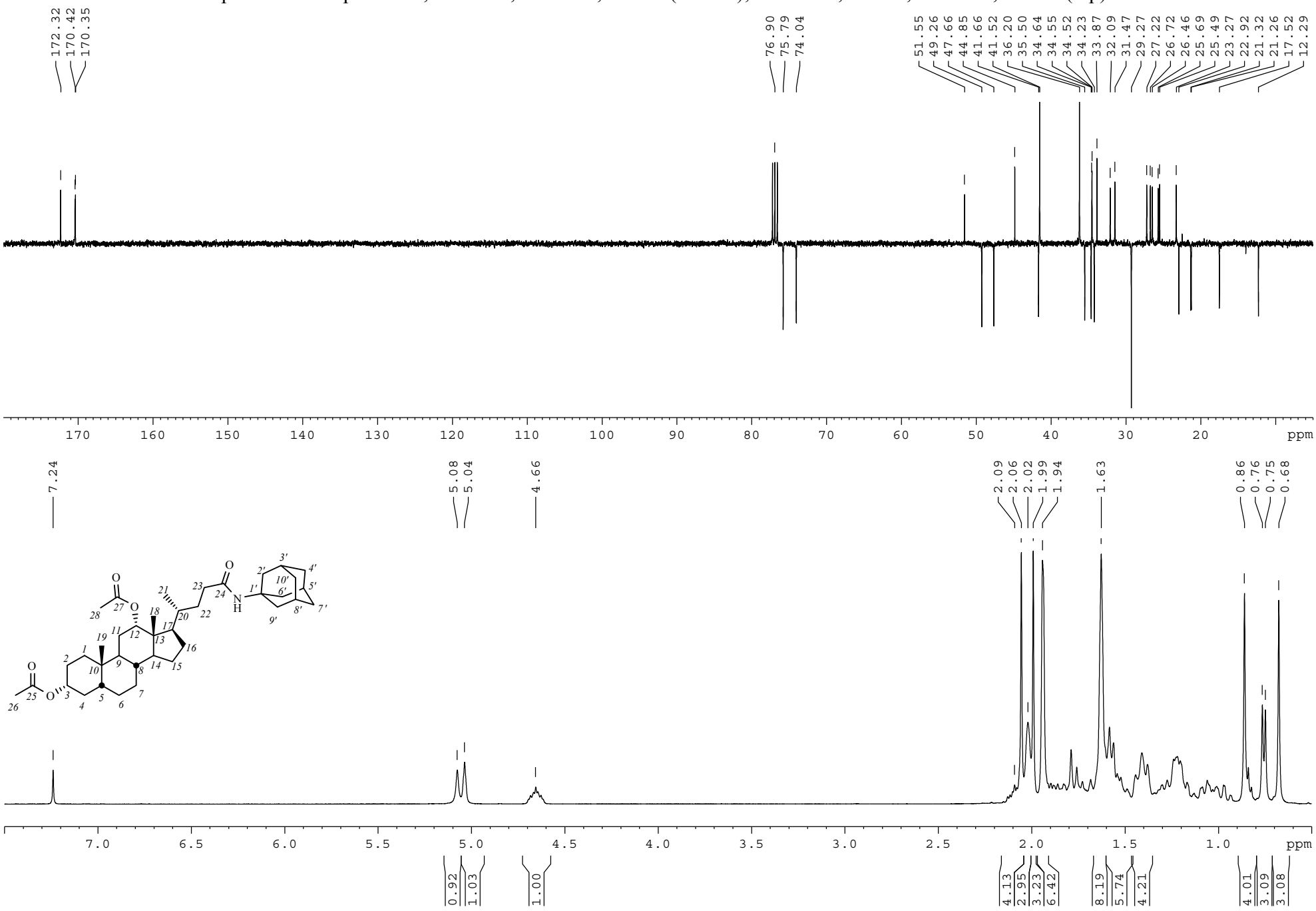
Spectra of Compound **7a**, ^{1}H NMR, 400MHz, $CDCl_3$ (bottom); ^{13}C NMR, JMOD, 100MHz, $CDCl_3$ (top)



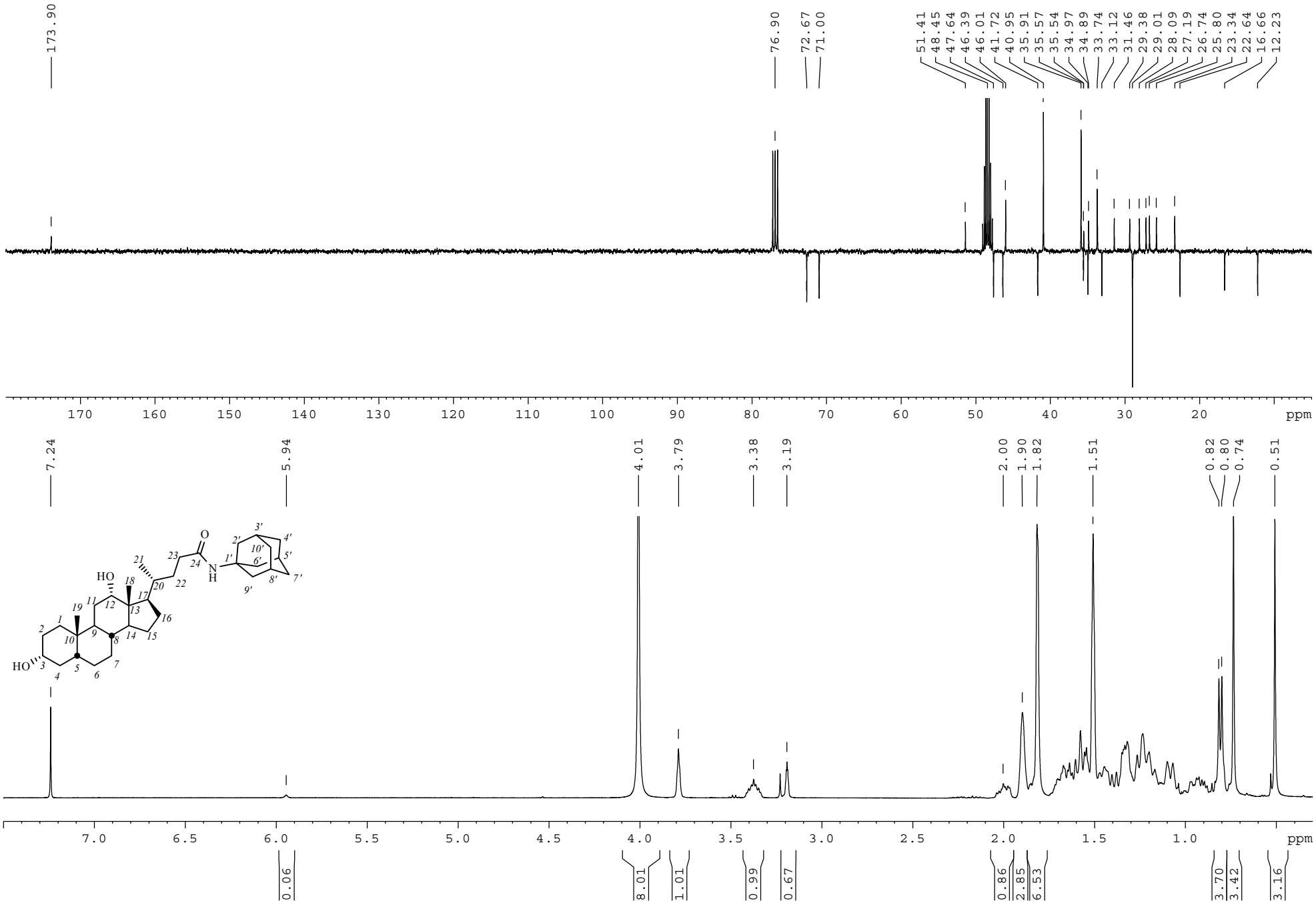
Spectra of Compound **7b**, ^{1}H NMR, 400MHz, $CDCl_3$+CD_3OD (bottom); ^{13}C NMR, JMOD, 100MHz, $CDCl_3$+CD_3OD (top)



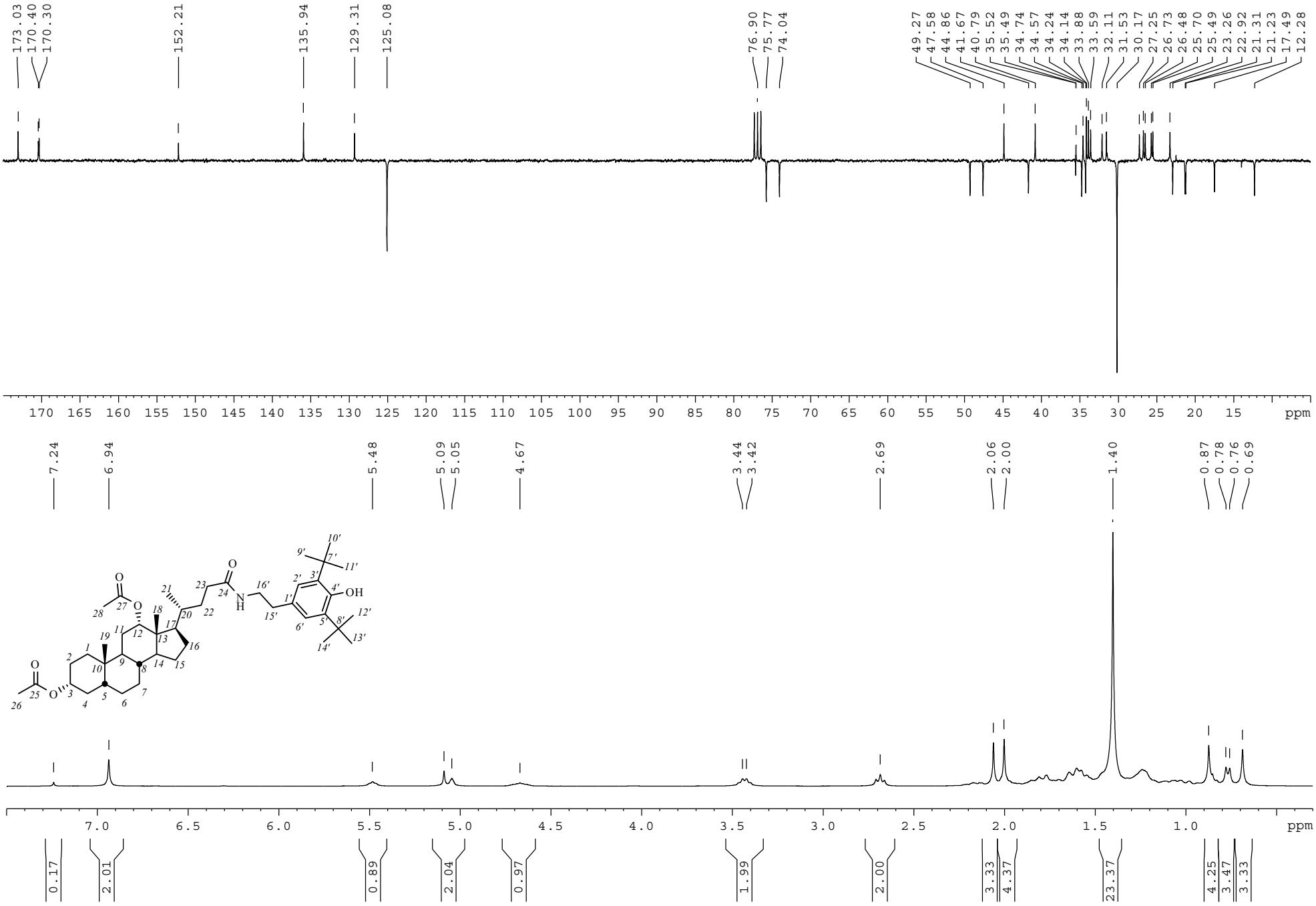
Spectra of Compound **8a**, ^{1}H NMR, 400MHz, $CDCl_3$ (bottom); ^{13}C NMR, JMOD, 100MHz, $CDCl_3$ (top)



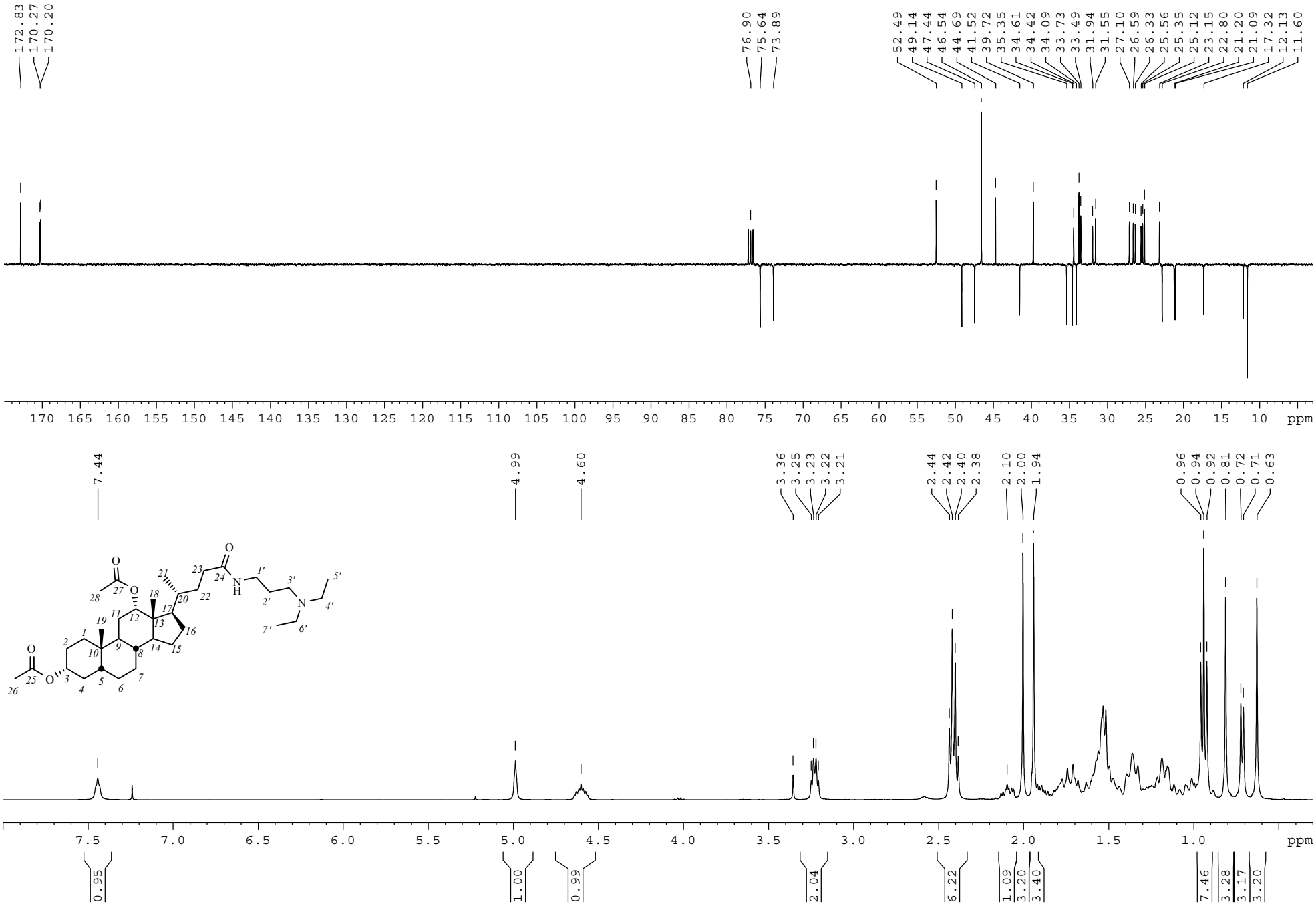
Spectra of Compound **8b**, ^{1}H NMR, 400MHz, $CDCl_3$+CD_3OD (bottom); ^{13}C NMR, JMOD, 100MHz, $CDCl_3$+CD_3OD (top)



Spectra of Compound **9a**, ^{1}H NMR, 300MHz, $CDCl_3$ (bottom); ^{13}C NMR, JMOD, 75MHz, $CDCl_3$ (top)



Spectra of Compound**10a**, ^{1}H NMR, 400MHz, $CDCl_3$ (bottom); ^{13}C NMR, JMOD, 100MHz, $CDCl_3$ (top)



Spectra of Compound **11a**, ^{1}H NMR, 400MHz, $CDCl_3$ (bottom); ^{13}C NMR, JMOD, 100MHz, $CDCl_3$ (top)