

**Lupane-type conjugates with aminoacids, 1,3,4- oxadiazole and 1,2,5-oxadiazole-2-oxide derivatives:
synthesis, anti-inflammatory activity and *in silico* evaluation of target affinity**

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Table S1. Anti-inflammatory activity of conjugates in mouse paw edema models

Agent	Dose, mg/kg	Histamine-induced inflammation		Concanavalin A-induced inflammation	
		IEI, %	AIA, %	IEI, %	AIA, %
control	-	32,7±1,1 ####	0	29,8±1,0 ####	0
1	50	27,5±2,8 *###	16,0	24,1±2,8 *###	19
4a	50	23,7±1,8 ***##	27,5	23,3±2,9 ***#	22
4b	50	23,8±1,8 ***##	27,0	16,2±1,5 ***##	45,5
4c	50	21,4±1,1 ***#	34,5	17,4±1,2 ***#	41,5
6a	50	21,9±1,4 ***#	33,0	24,8±1,3 *###	14
7aa	50	21,1±1,5 ***	35,5	23,2±0,9 ***###	20
7ab	50	22,6±1,7 ***#	31,0	20,3±0,9 ***###	30
7ac	50	24,9±2,0 ***##	24,0	13,5±1,0 ***	53,5
6b	50	23,7±1,4 ***#	27,5	21,2±0,6 ***###	29
7ba	50	28,1±2,0 *###	14,0	19,7±0,9 ***###	34
7bb	50	22,6±2,5 ***#	31,0	19,9±2,2 ***##	33
7bc	50	30,9±1,7 ####	5,5	20,6±1,5 ***##	31
6c	50	20,6±2,1 ***	37,0	15,3±1,0 ***#	47

7ca	50	19,6±2,6 ***	40,0	14,7±0,7 ***#	49
7cb	50	20,6±1,5 ***	37,0	16,0±1,0 ***##	44,5
7cc	50	23,9±1,9 ***##	27,0	17,4±1,9 ***##	40
8a	50	23,6 ± 1,8 ***#	28	19,7 ± 2,7***##	34
8b	50	21,7 ± 1,7 ***#	33,5	22,0 ± 1,6 *###	26
8c	50	29,9 ± 1,9 ###	9,0	23,0 ± 2,0 #	23
Ind	50	17,5±1,2 ***	46,5	12,0±0,9 ***	60

IEI inflammation edema index

AIA Anti-inflammatory activity relative to the control

*P <0.05, **P <0.01, ***P <0.001 relative to the control, # P <0.05, ## P <0.01, ### P <0.001 compared with the reference group (indomethacin),

Table S2. Concentrations of half-maximal inhibition (GI₅₀±SEM) of test compounds on immortalized human fibroblasts

Compound	GI ₅₀ ±SEM, uM	Compound	GI ₅₀ ±SEM, uM	Compound	GI ₅₀ ±SEM, uM
doxorubicin	3.15±0.55	7ab	>100	6c	61.41±7.47
1	16.7±2.99	7ac	>100	7ca	>100
4a	>100	6b	>100	7cb	>100
4b	>100	7ba	>100	7cc	>100
4c	>100	7bb	>100	8a	>100
6a	>100	7bc	>100	8b	>100
7aa	>100			8c	>100

All the tested compounds revealed no cytotoxic properties on fibroblasts, while compound 6c showed a slightly cytotoxic effect. Based on the results obtained, one can conclude that the synthesized compounds can be characterized as low toxic

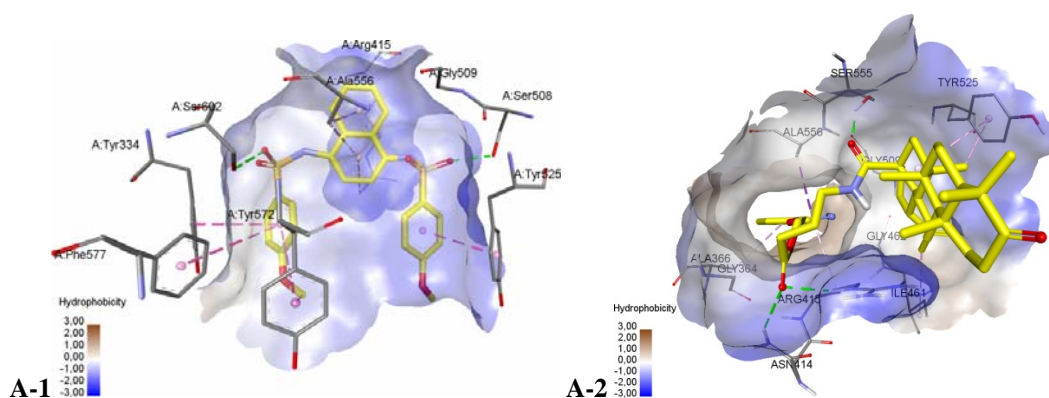


Fig. S1A. Non-covalent interactions of γ -aminobutyric acid ester **7ca** and Cpd16 ligand at the Kelch domain of Keap1. A-1 - Cpd16, A-2 - **7ca**; dotted lines: green - hydrogen bonds, purple - hydrophobic interactions.

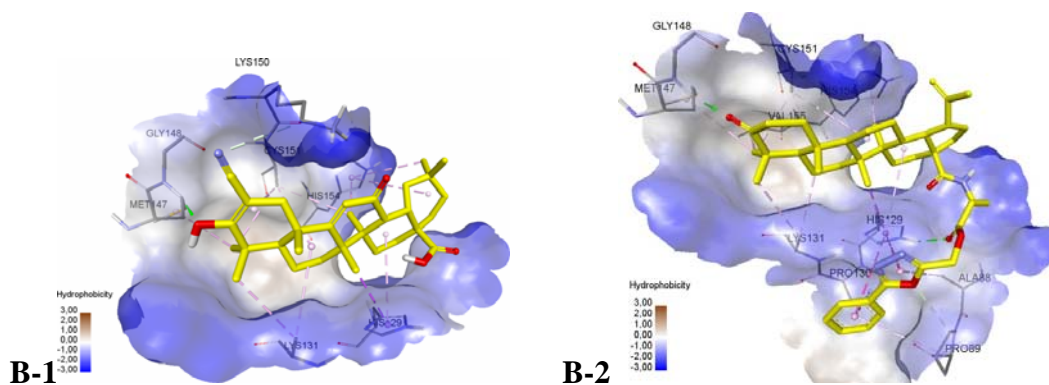


Fig. S1B. Non-covalent interactions of γ -aminobutyric acid ester **7ca** and ligand CDDO in the BTB domain Keap1. B-1 - CDDO, B-2 - **7ca**; dotted lines: green - hydrogen bonds, purple - hydrophobic interactions and stacking.

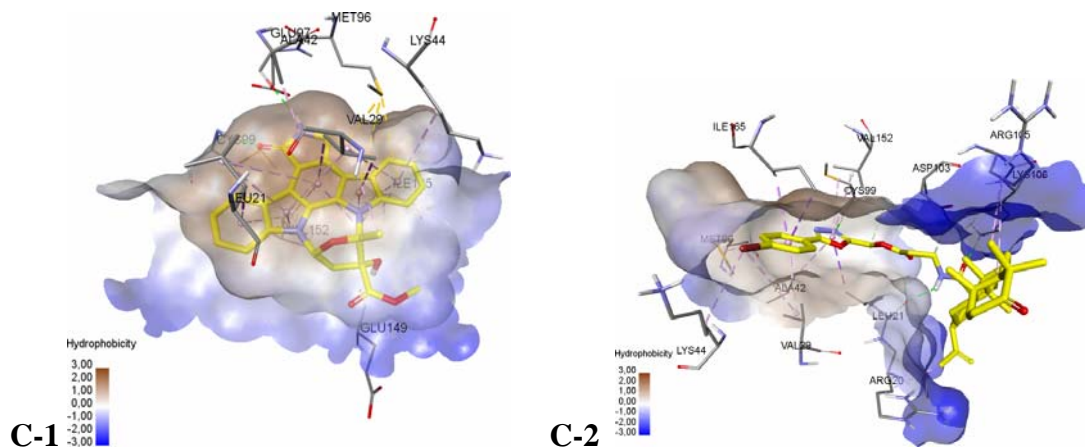
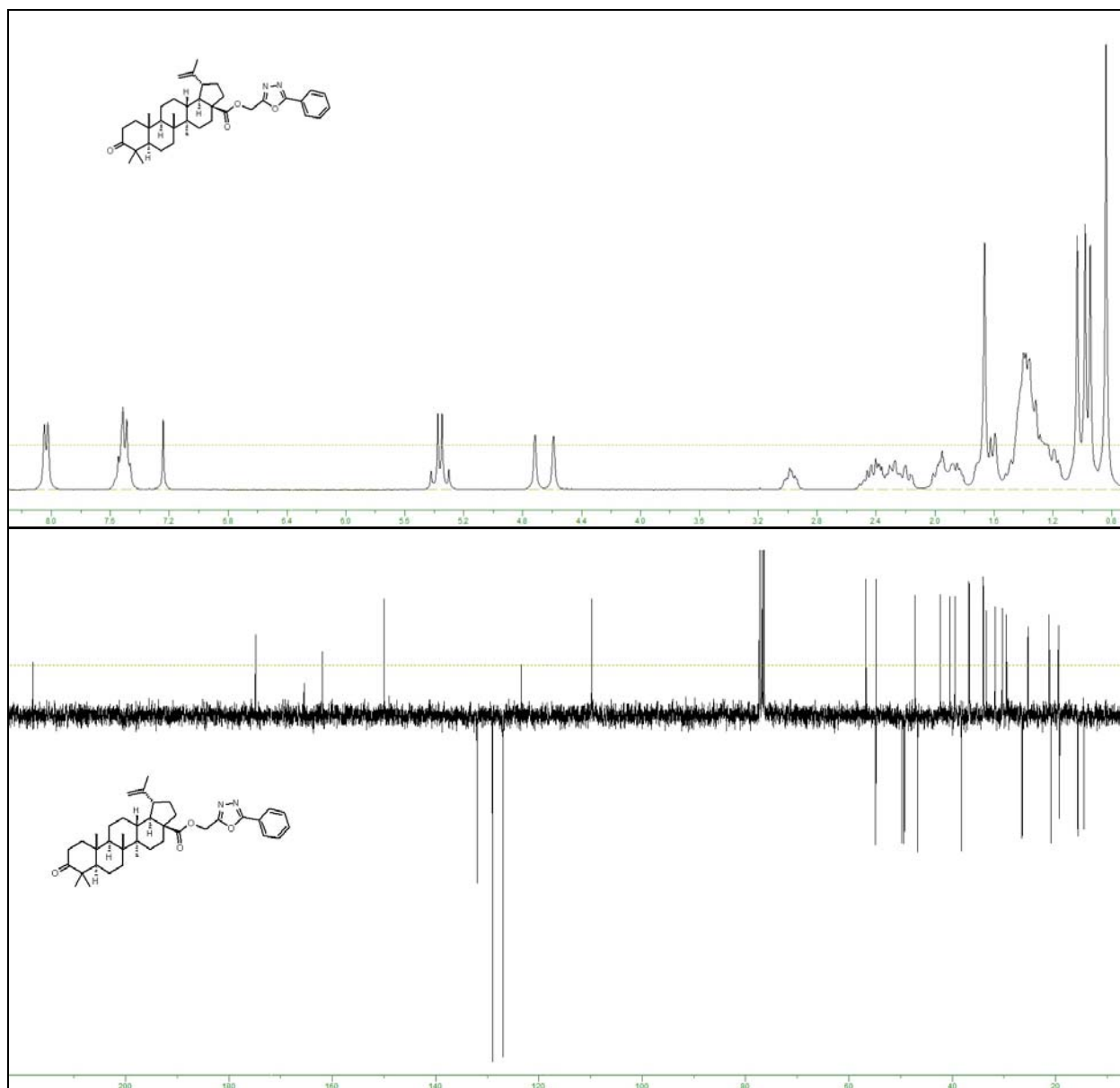


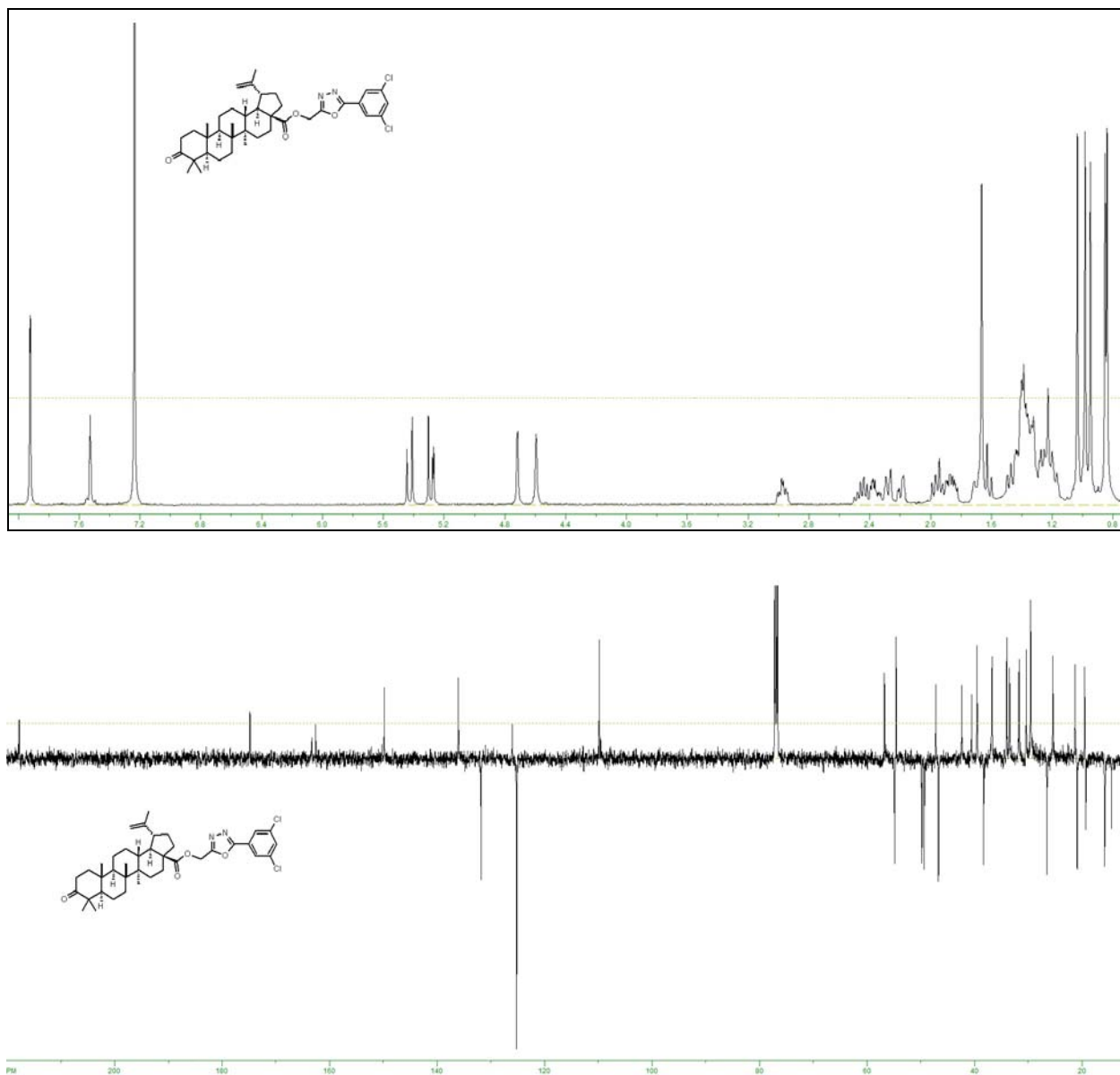
Fig. S1C. Non-covalent interactions of alanine ester **7bc** and ligand K-252A in IKK. C-1 - K-252A, C-2 - **7bc**; dotted lines: green - hydrogen bonds, violet - hydrophobic interactions, yellow - sulfur interactions.

FigS2. NMR ^1H and NMR ^{13}C (Jmod) spectral data of hybrid compounds

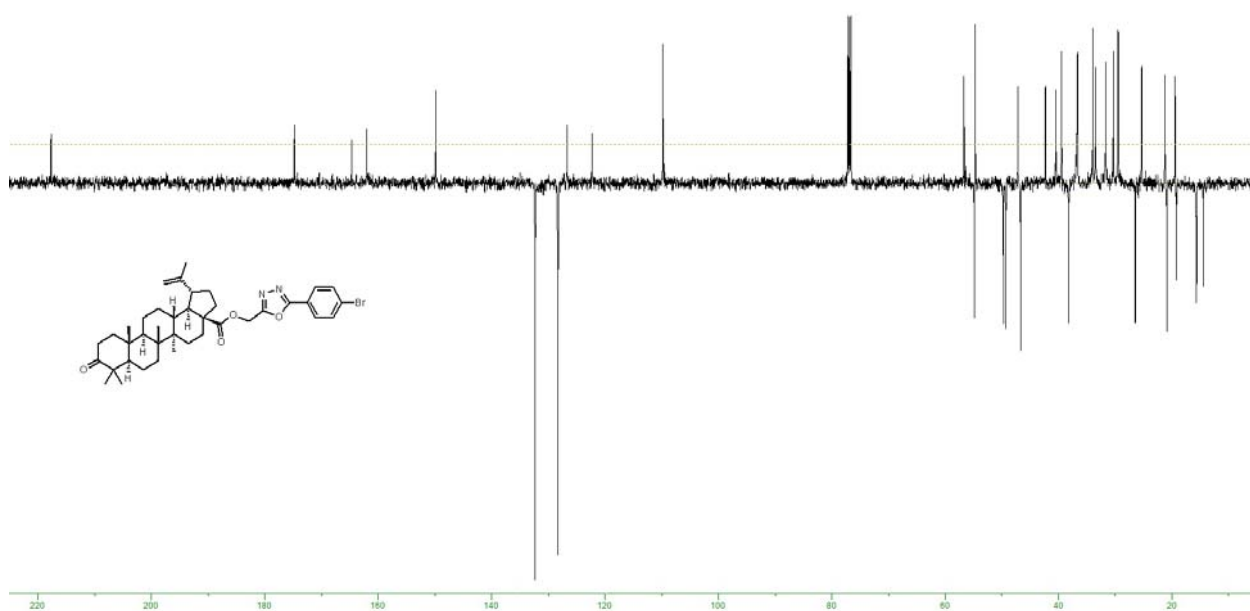
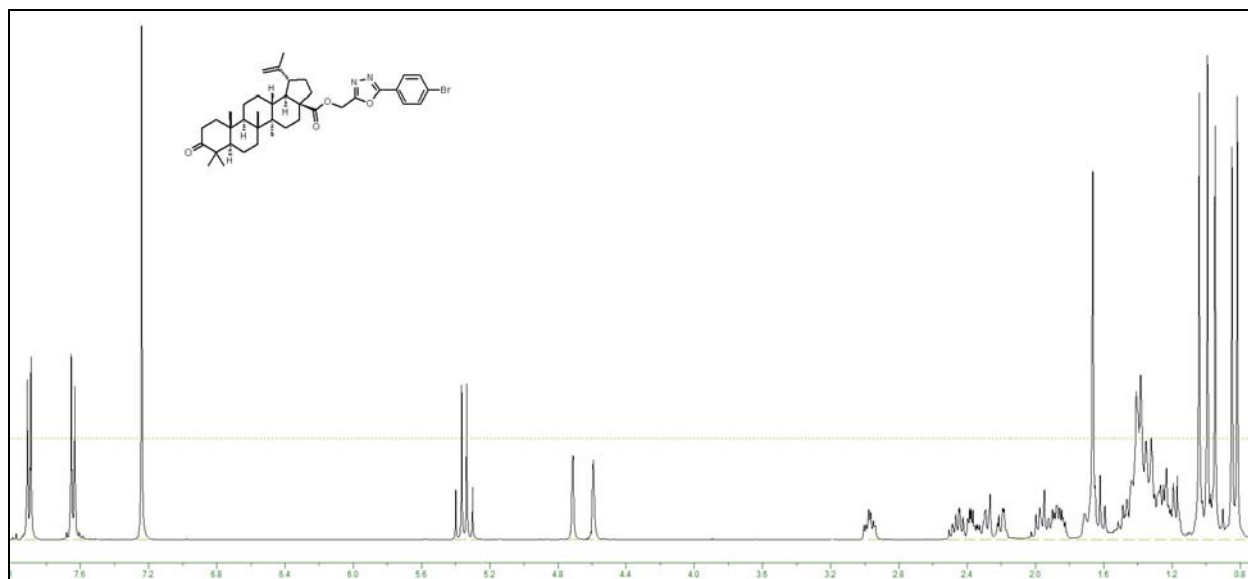
4a



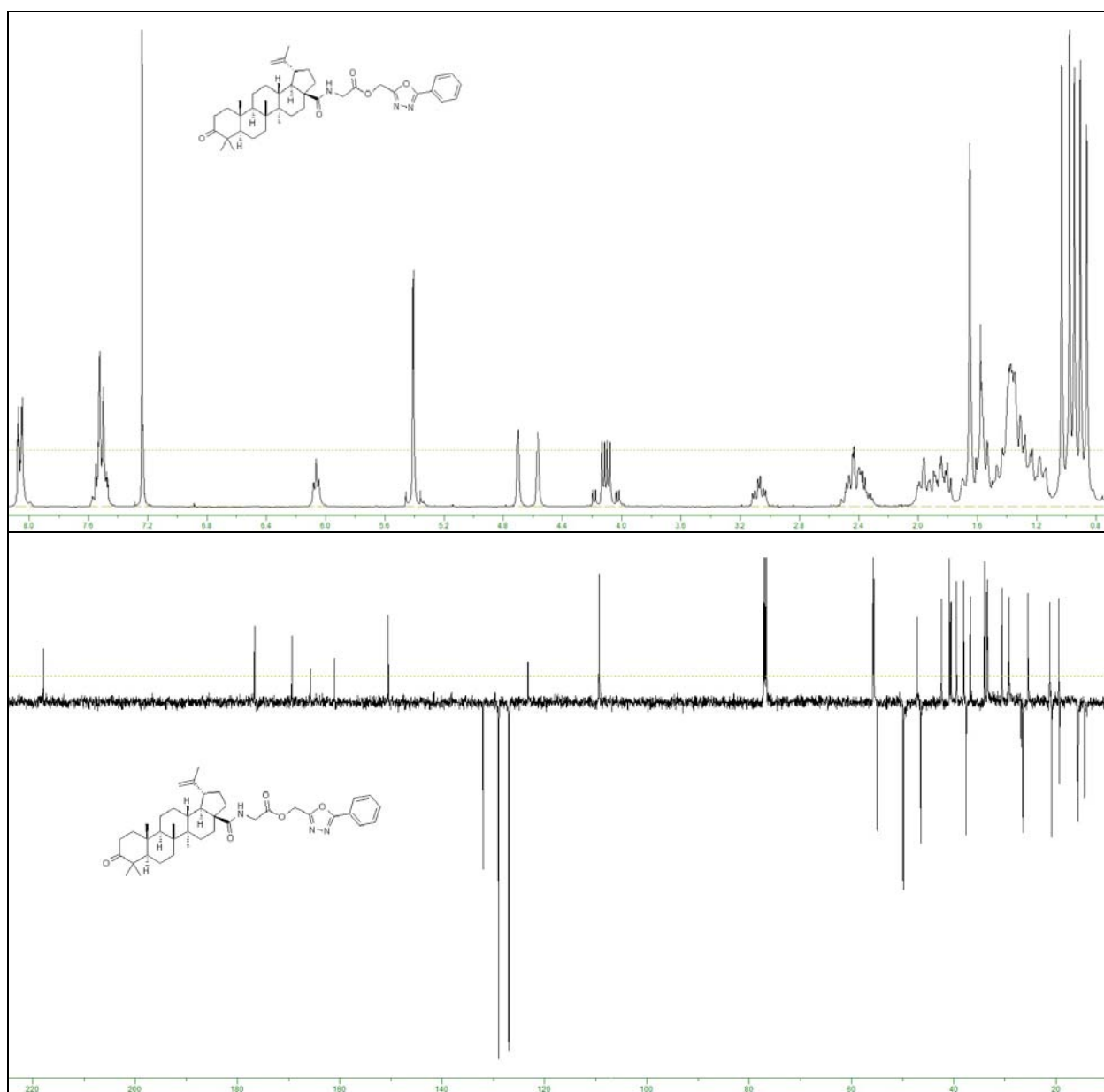
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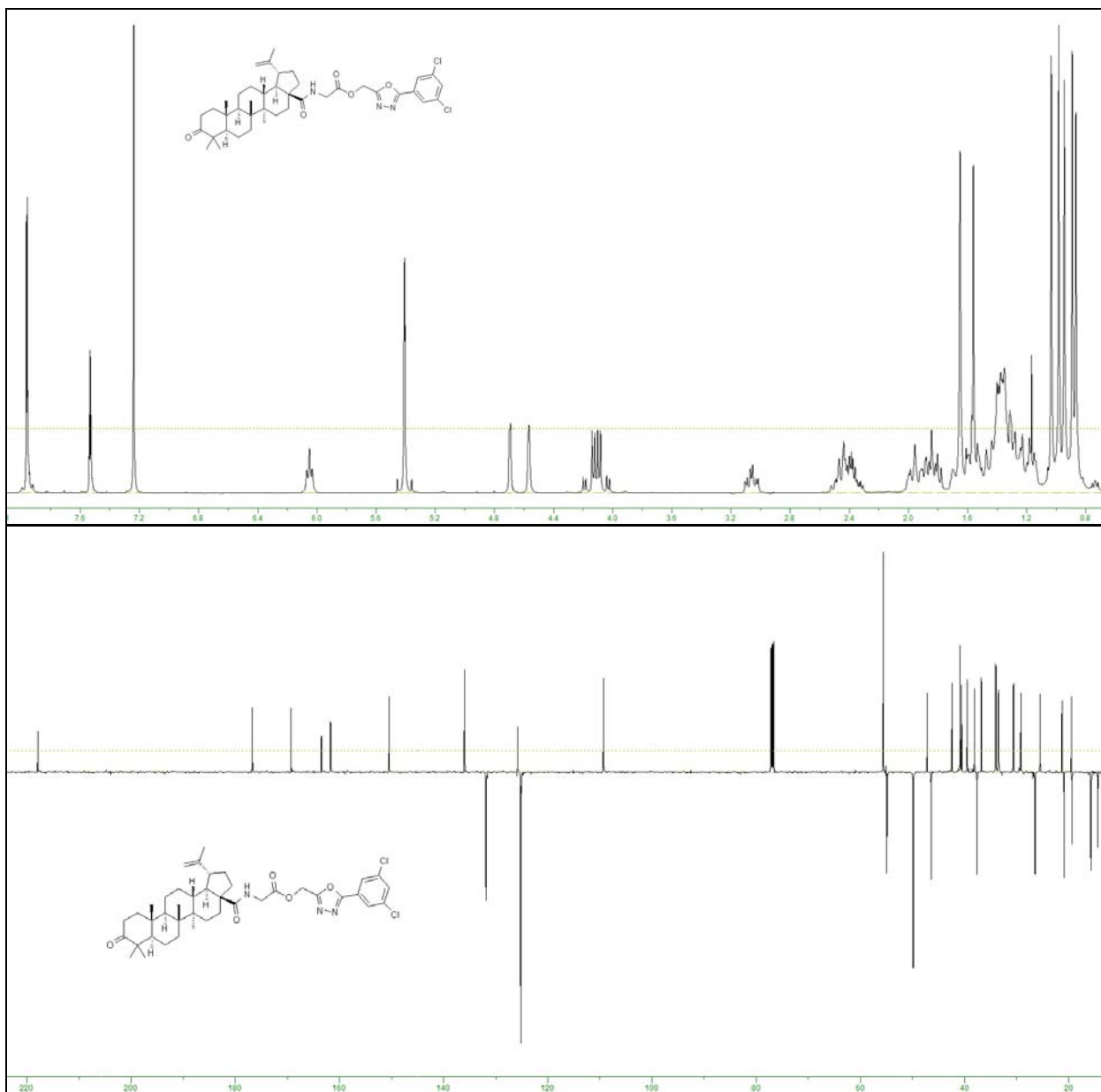
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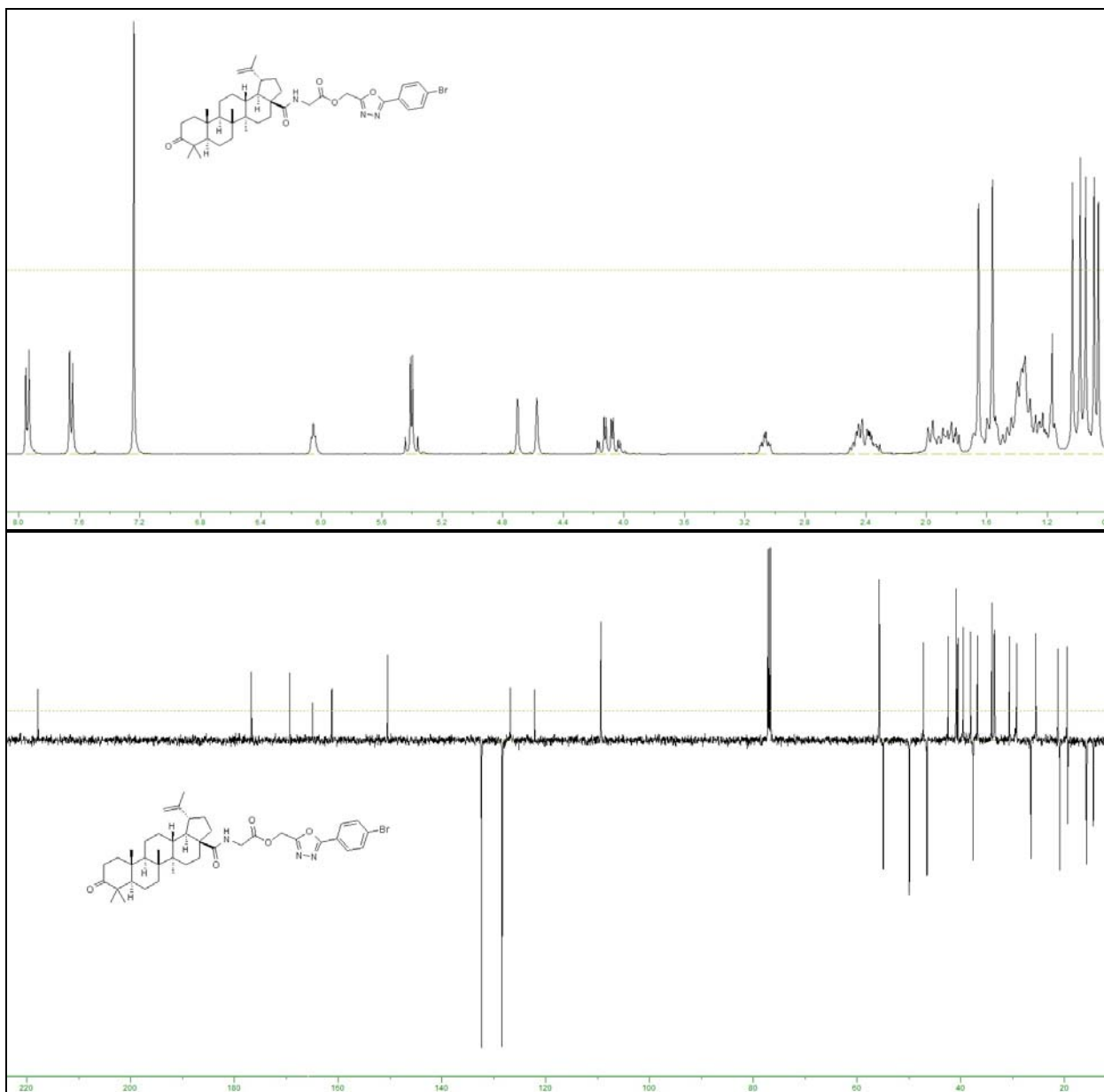
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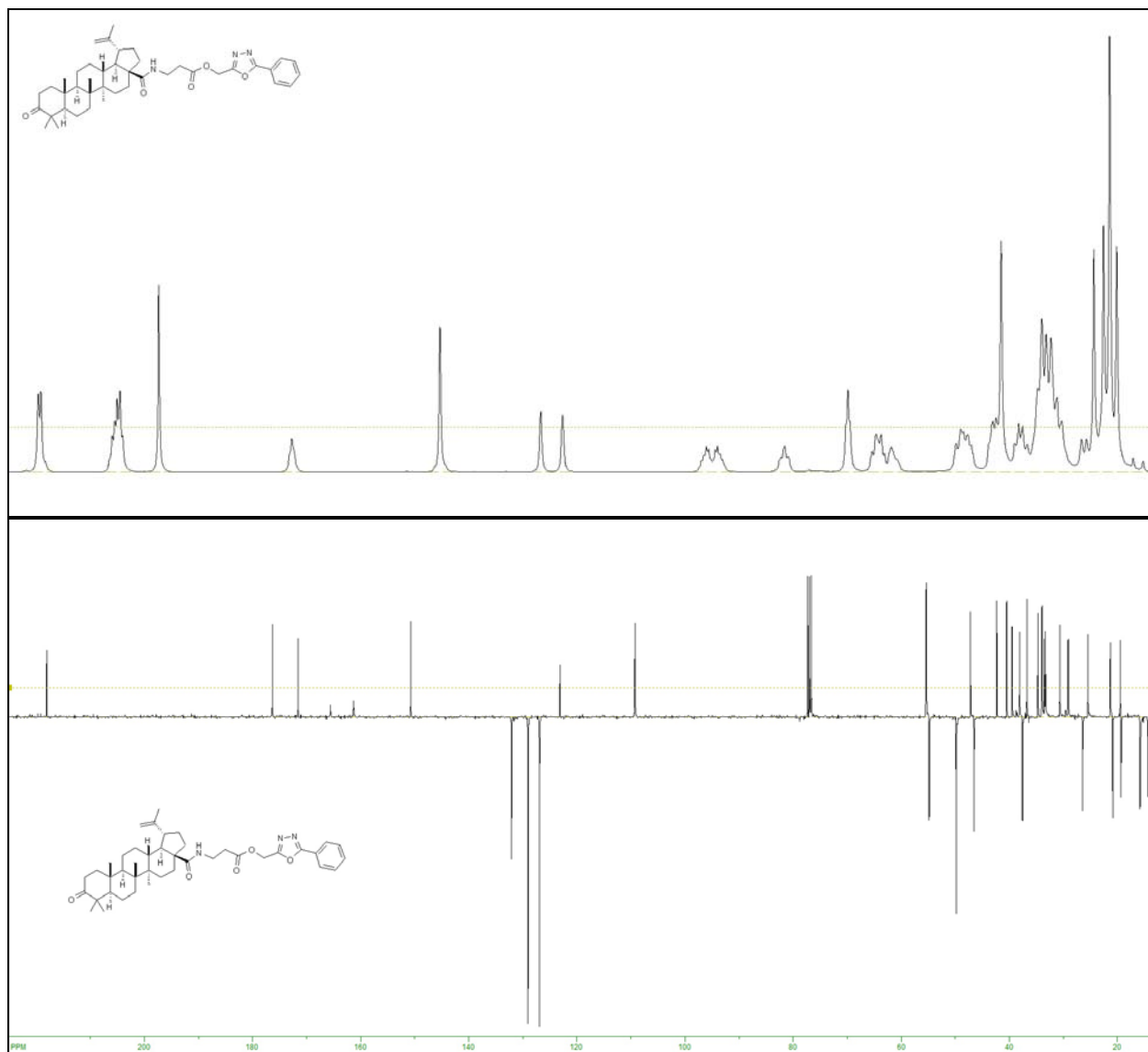
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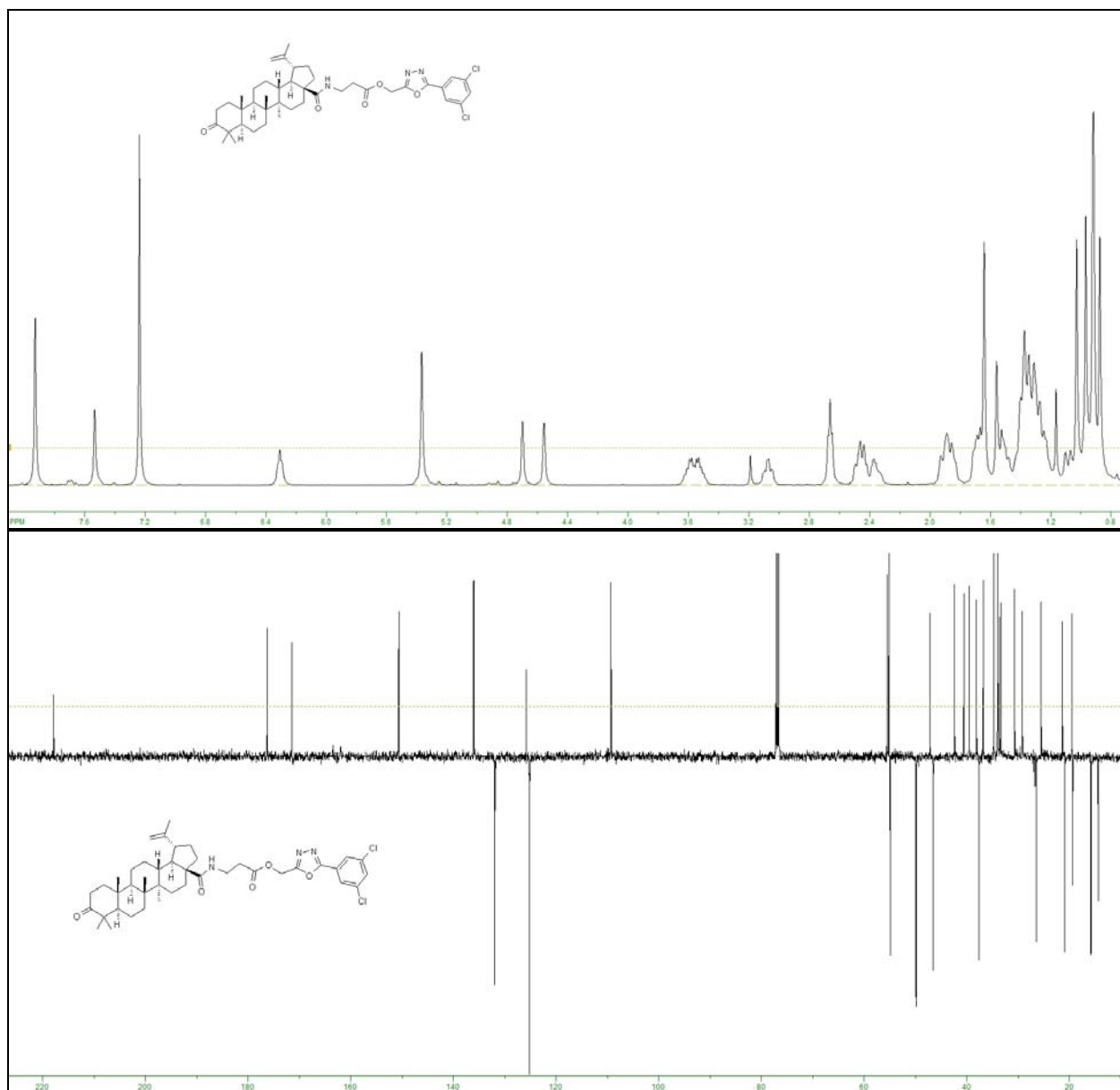
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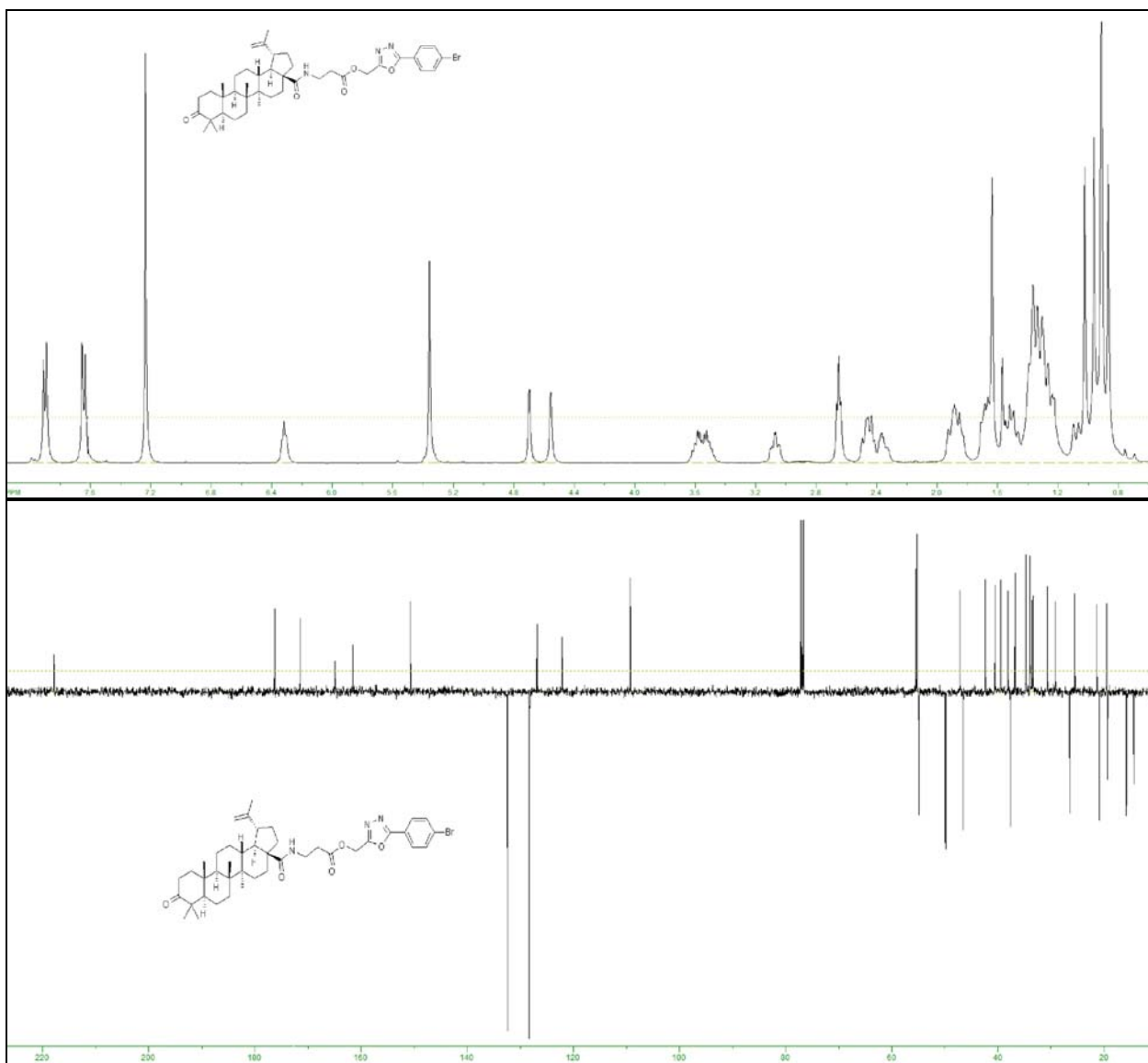
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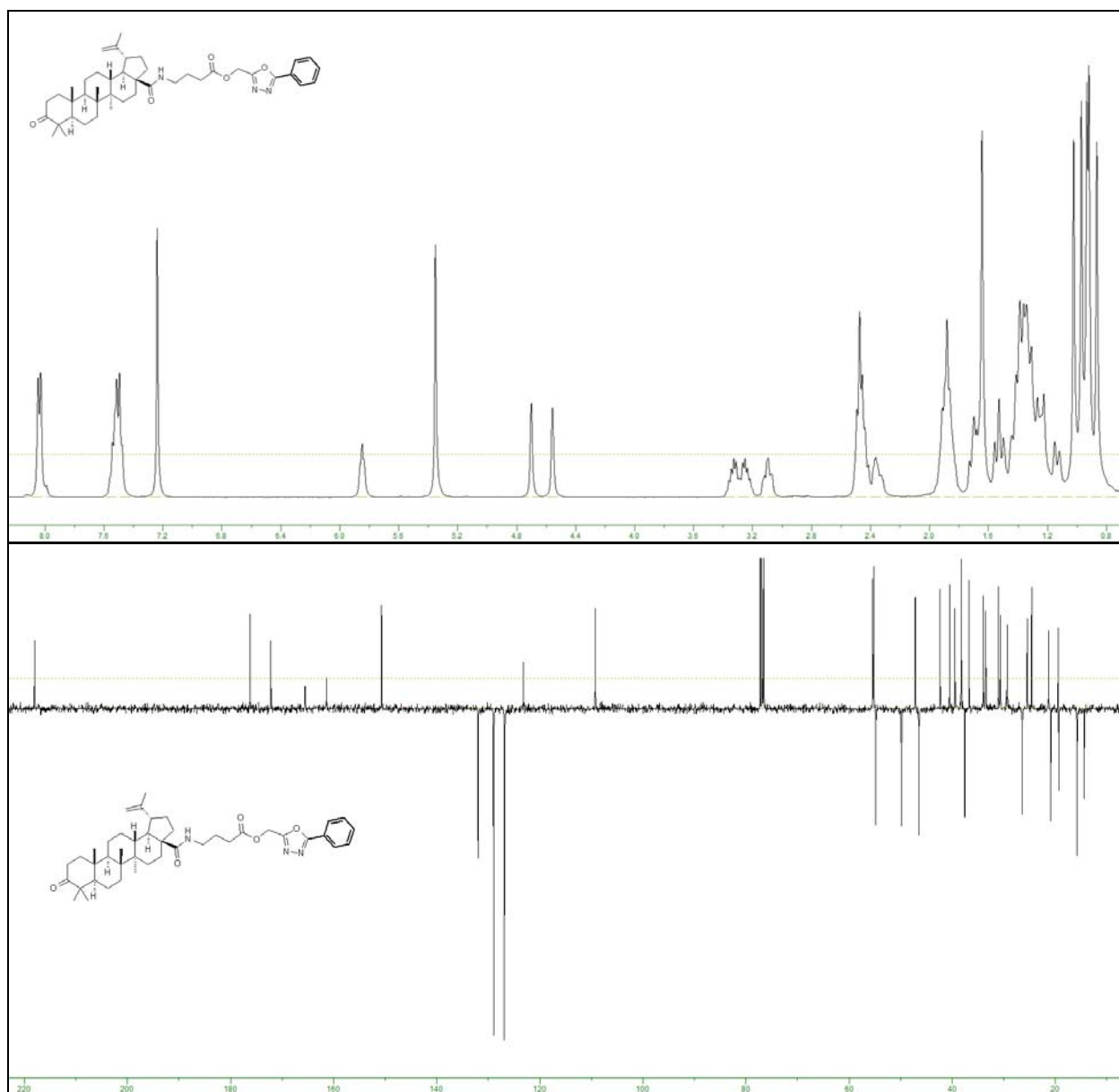
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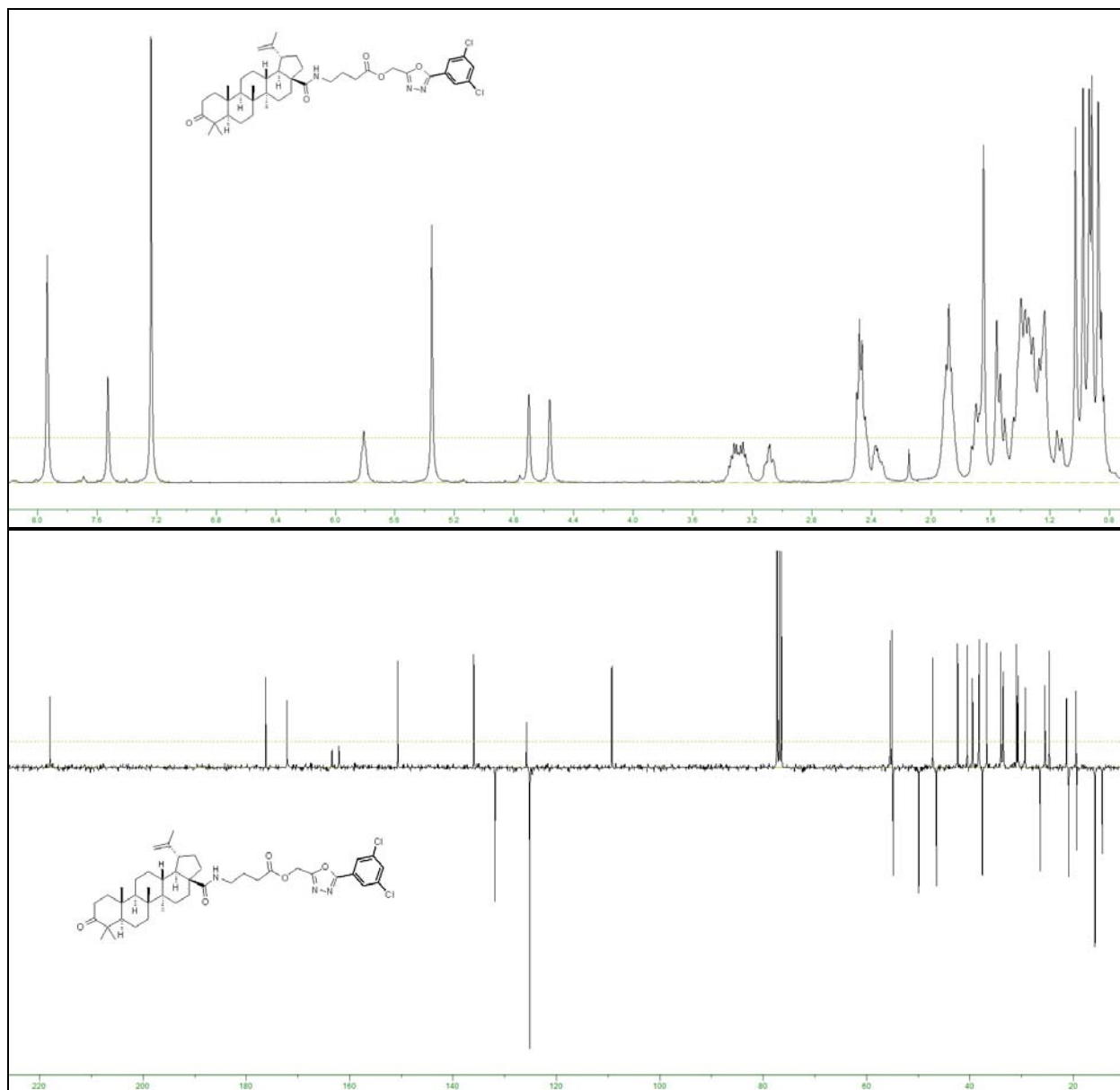
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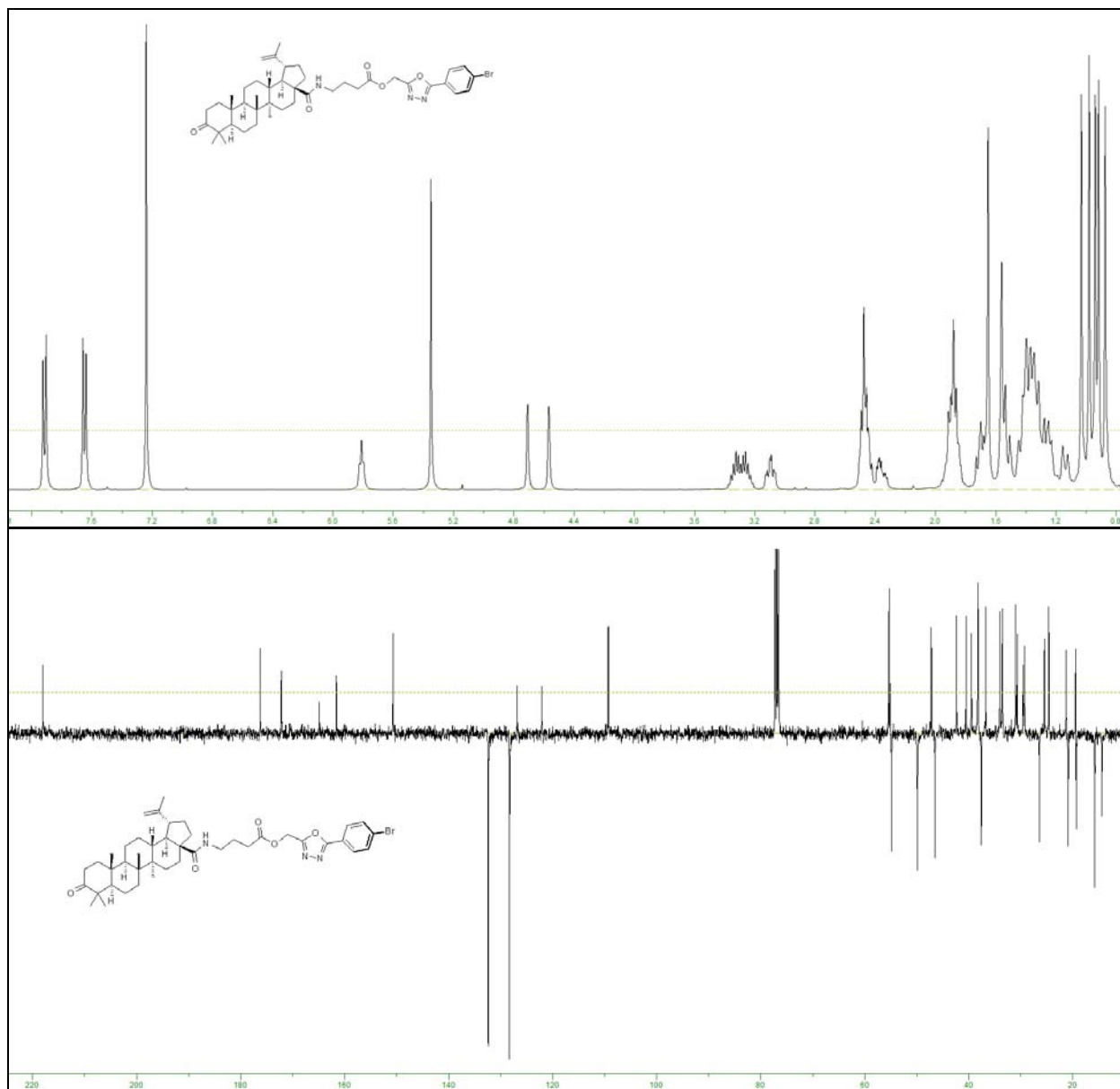
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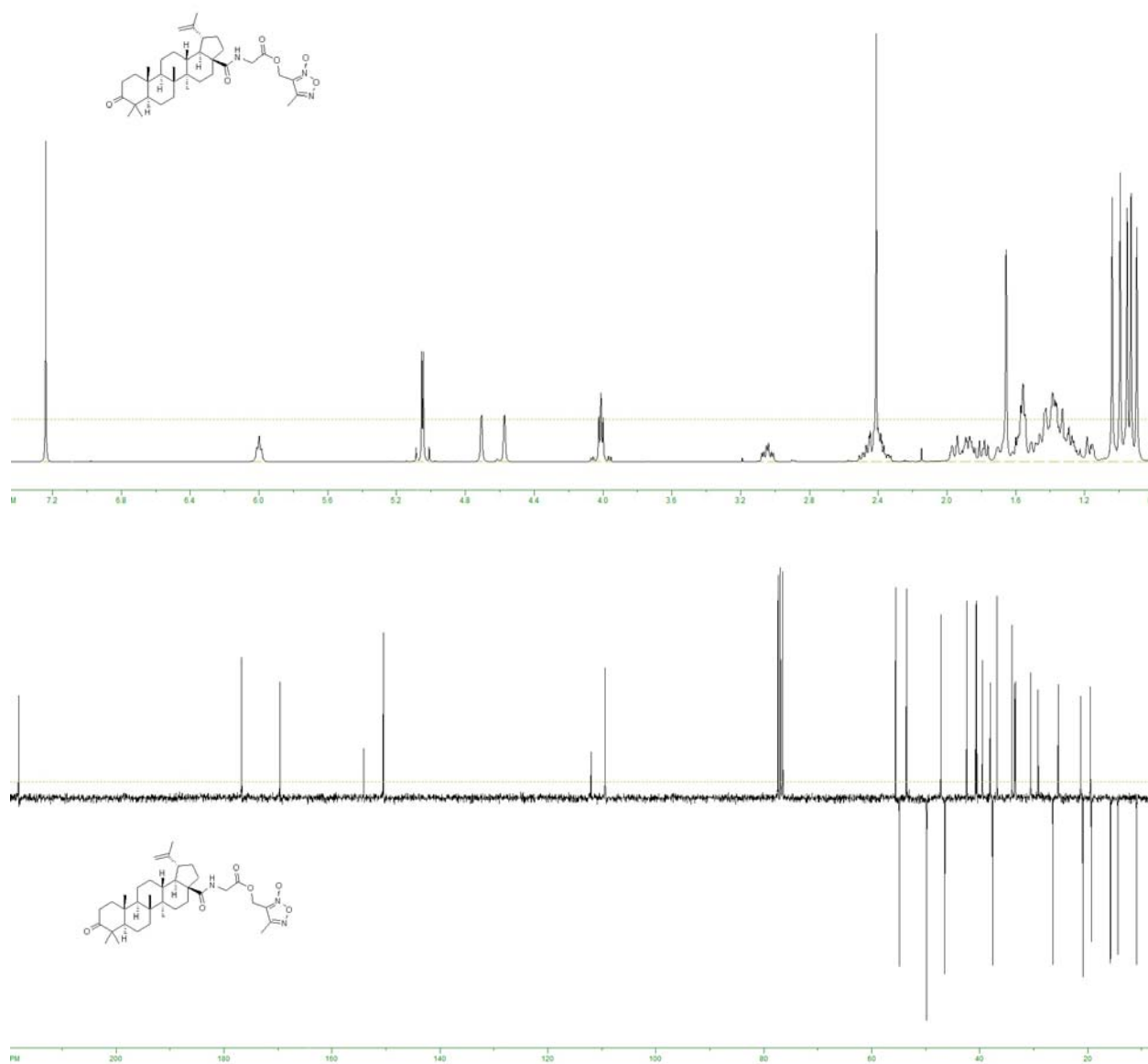
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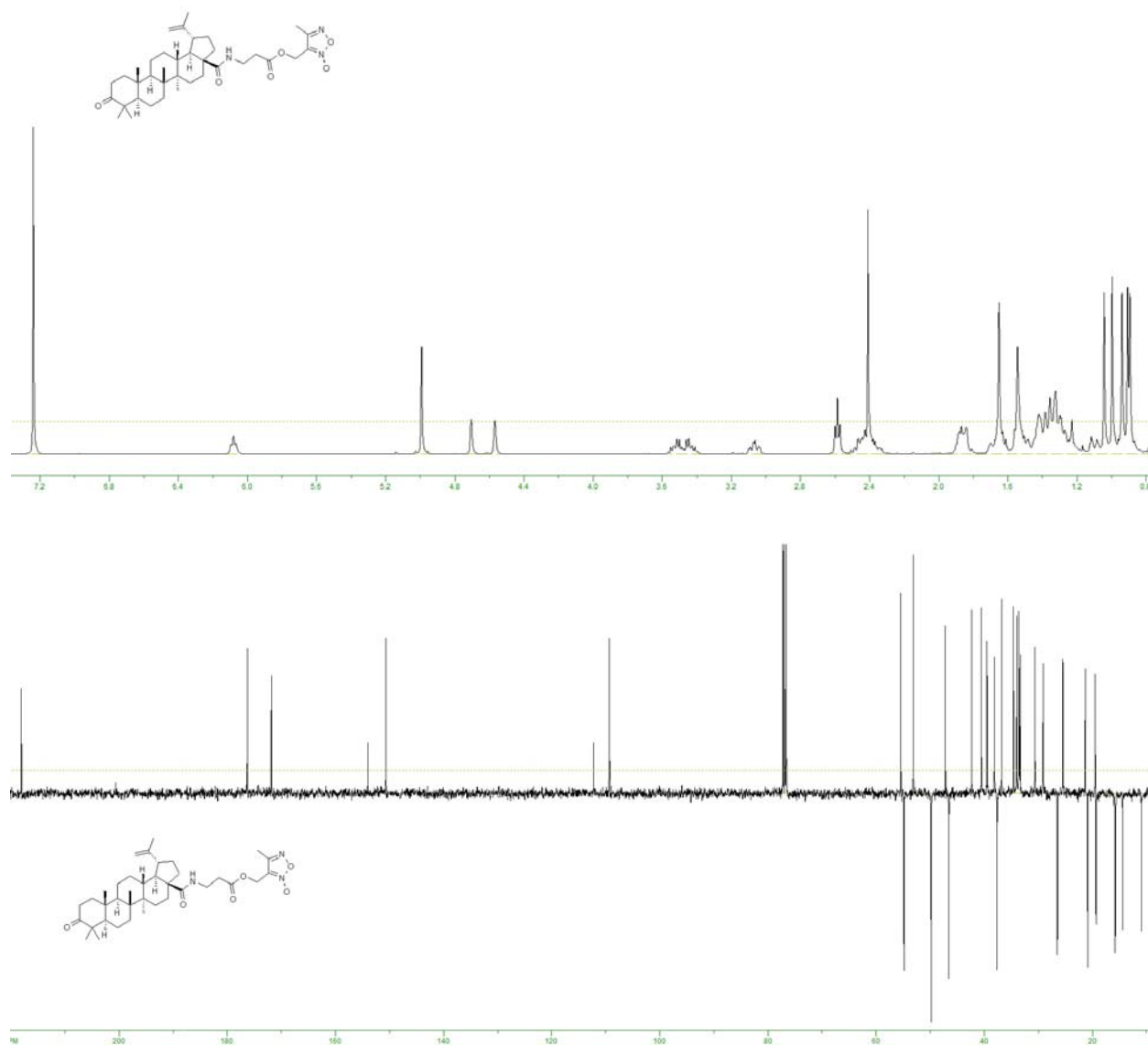
7cc



8a



8b



8c

