Supporting Information

Design, Synthesis, and Biological Evaluation of NAP Isosteres: A Switch from Peripheral to Central Nervous System Acting Mu-Opioid Receptor Antagonists

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# These authors contributed equally.

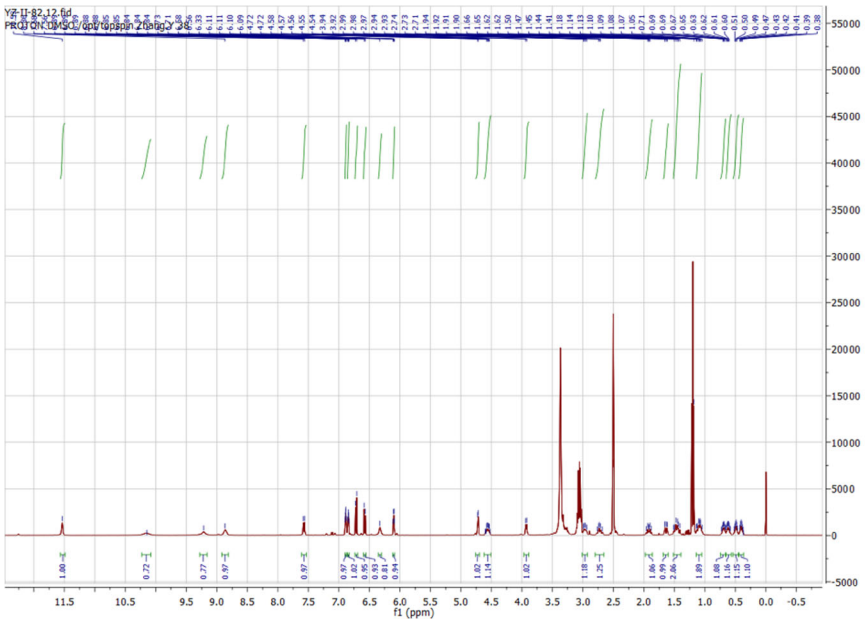
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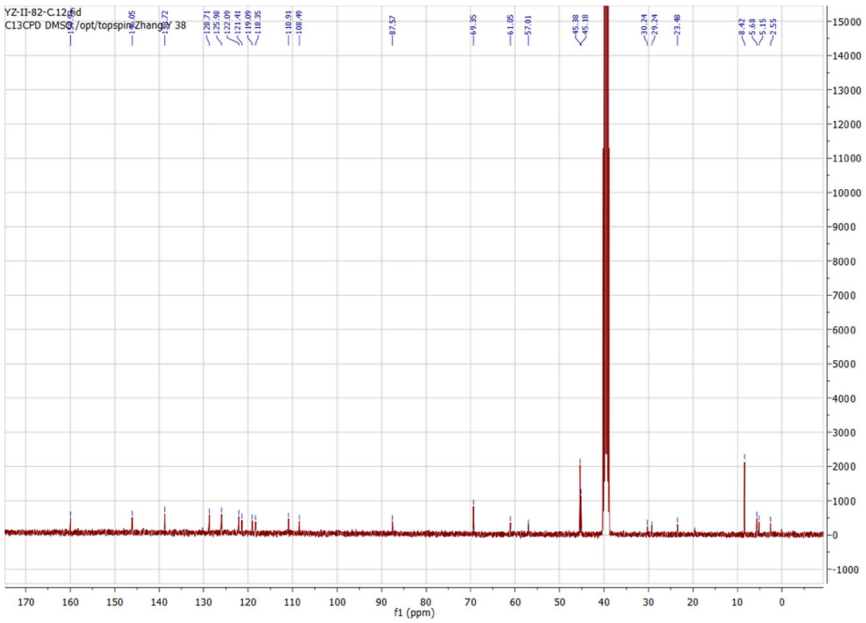
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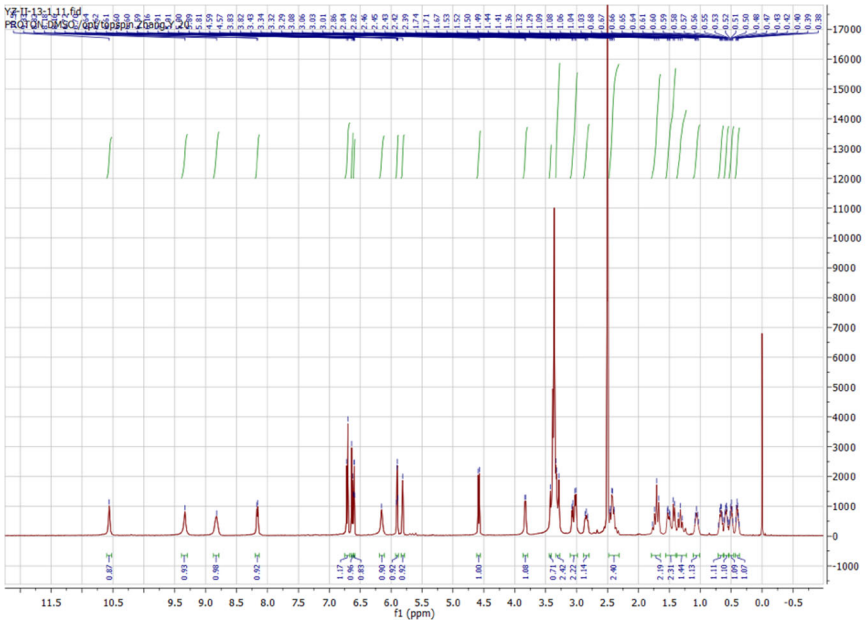
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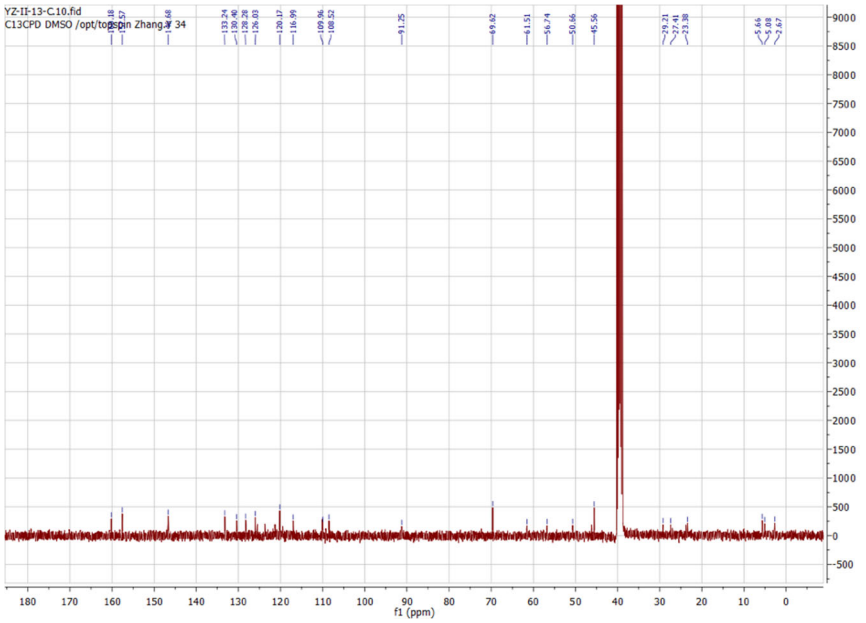
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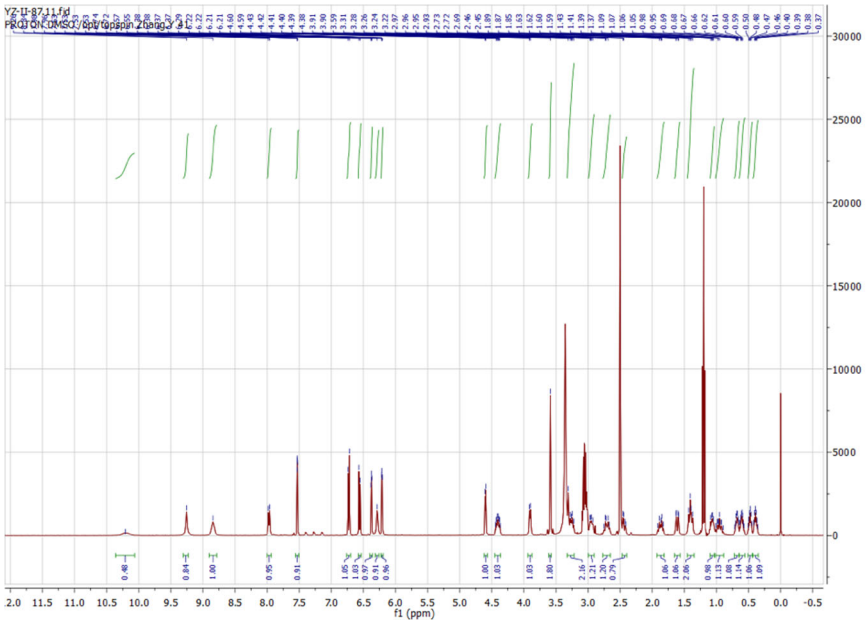


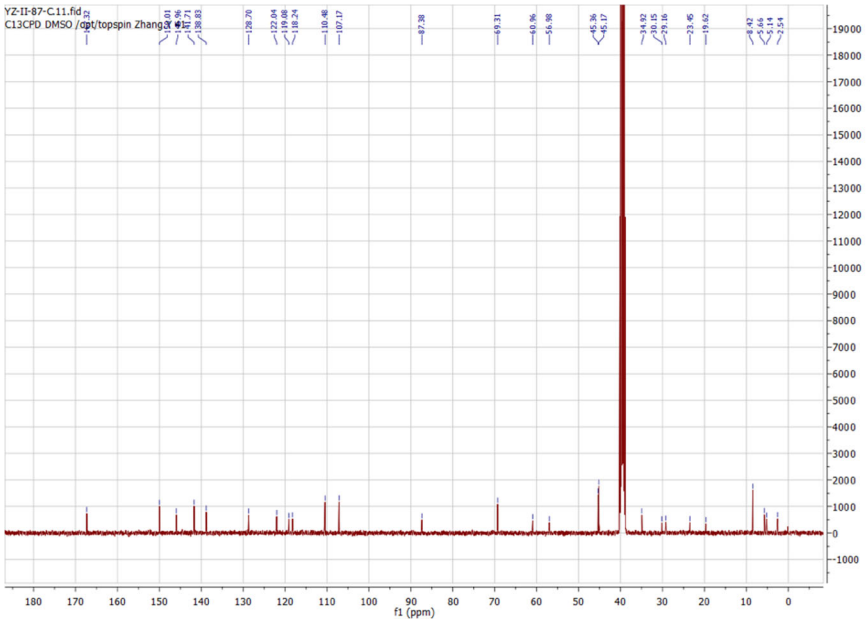
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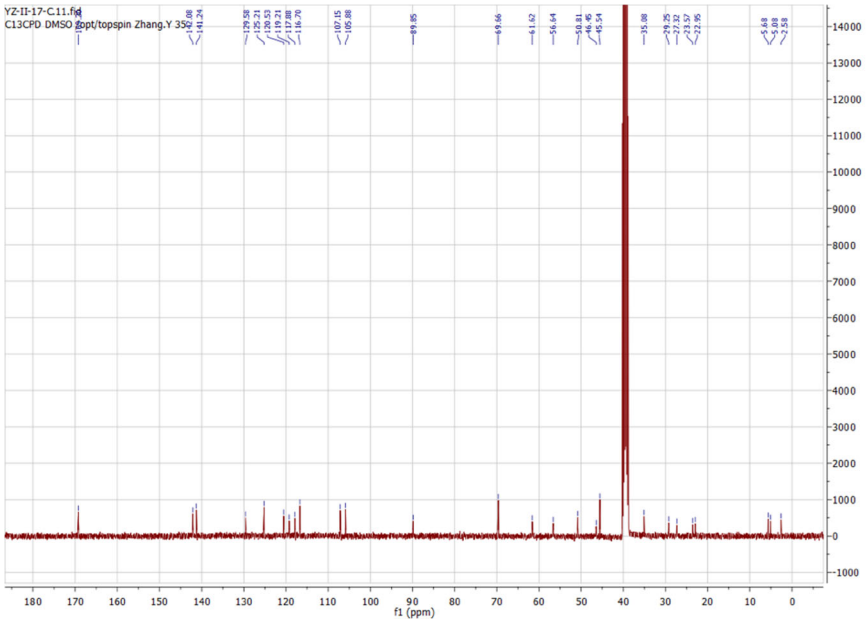
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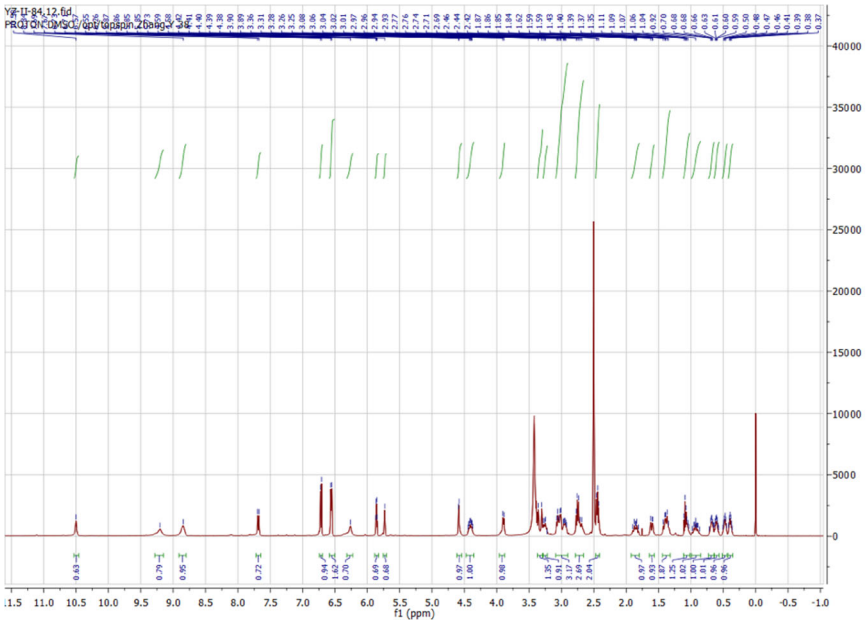


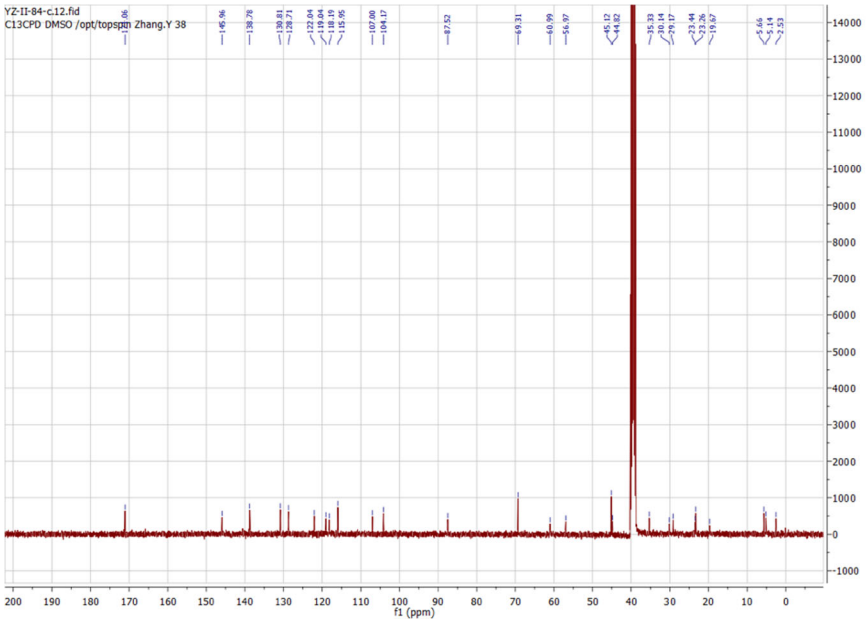
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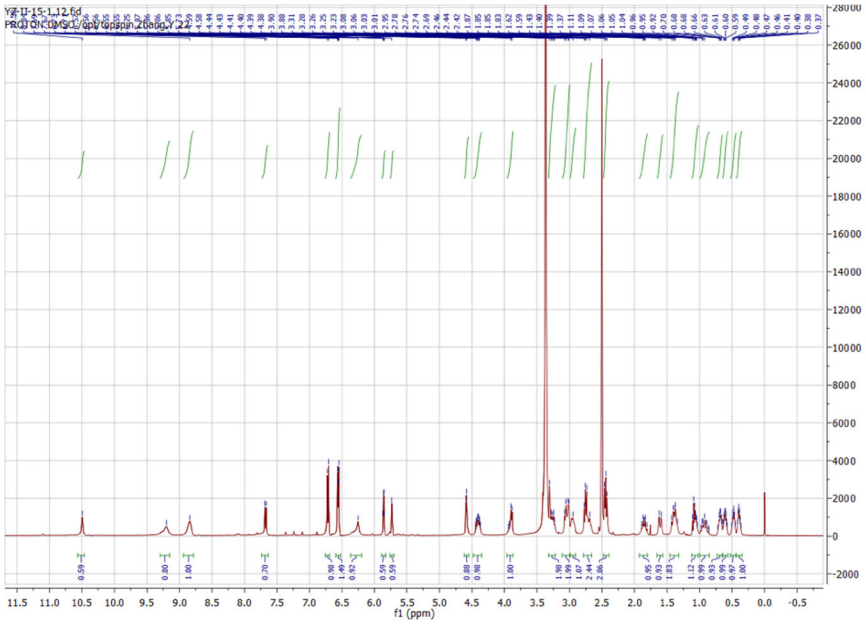


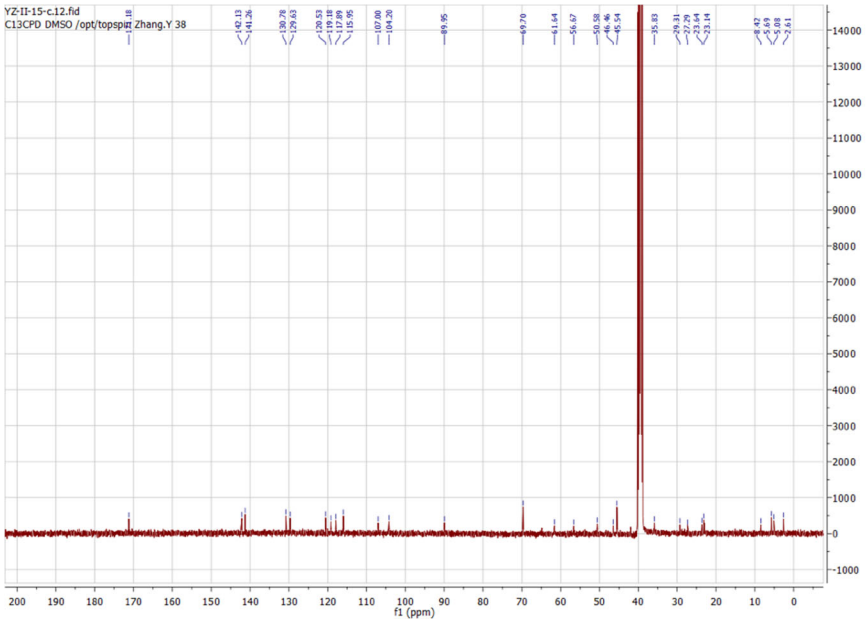
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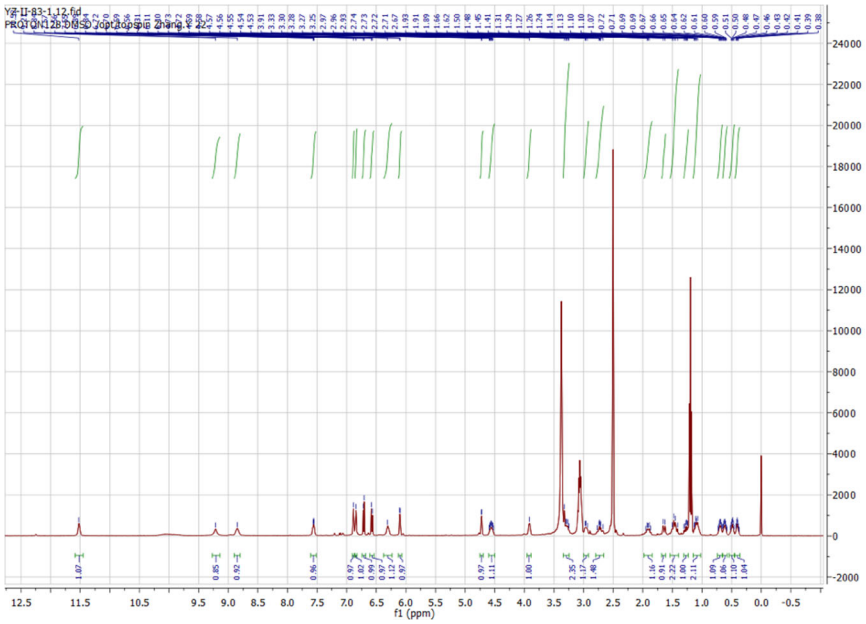


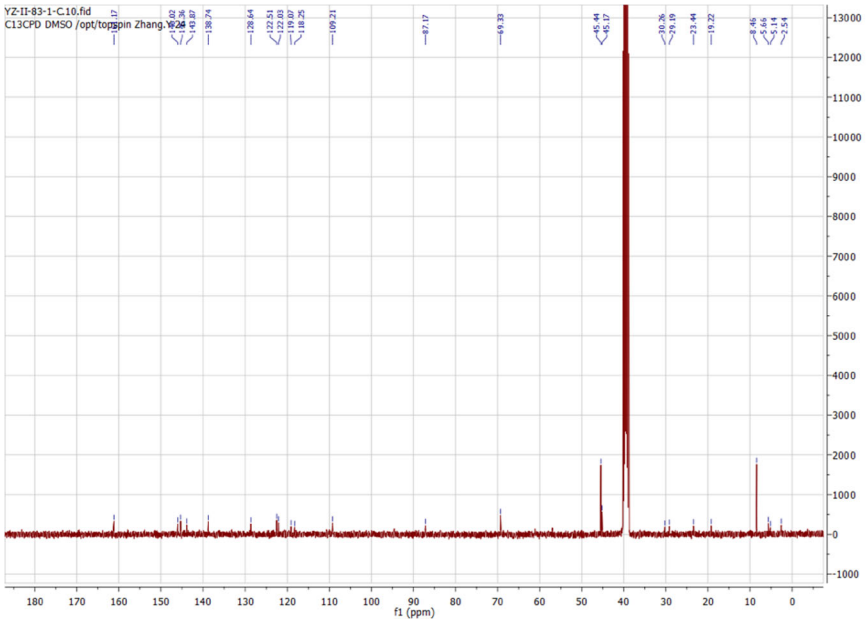
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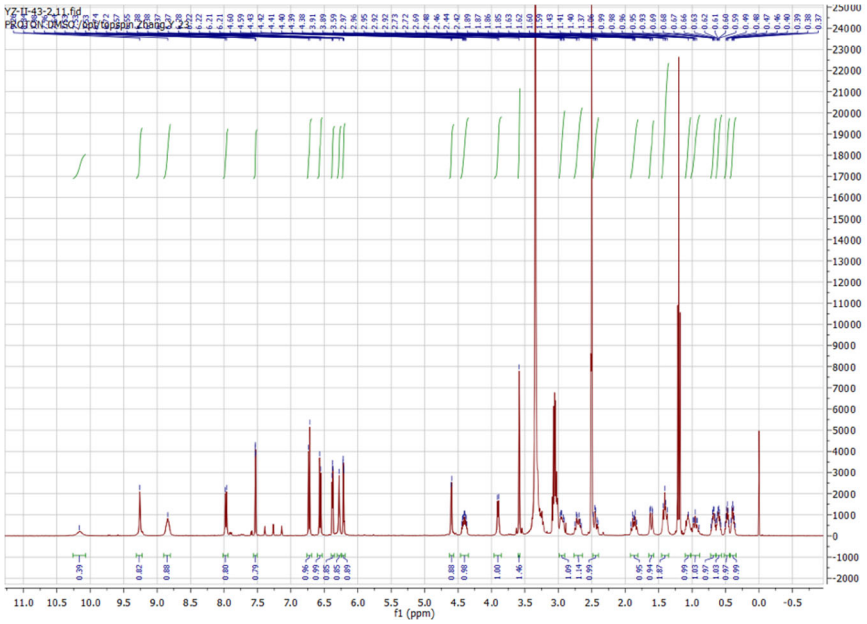


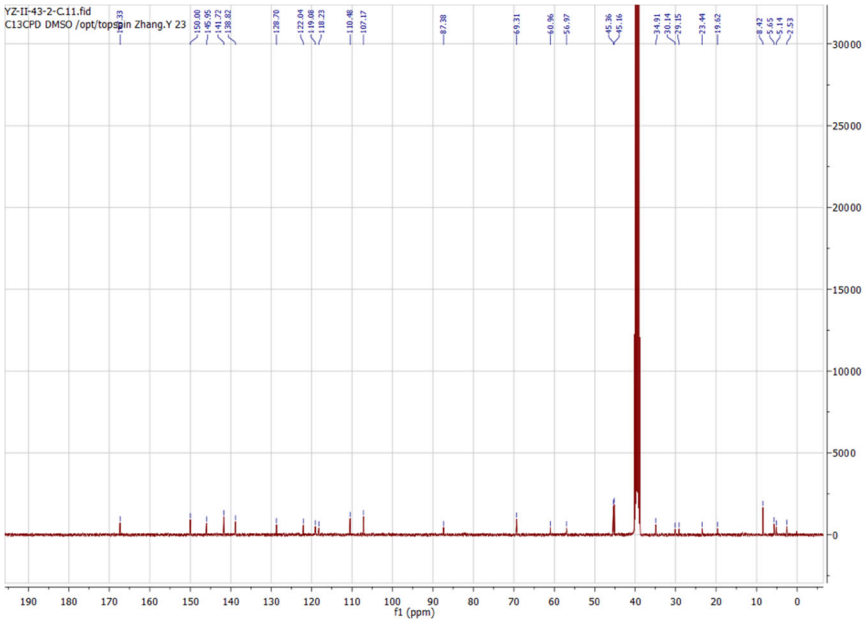
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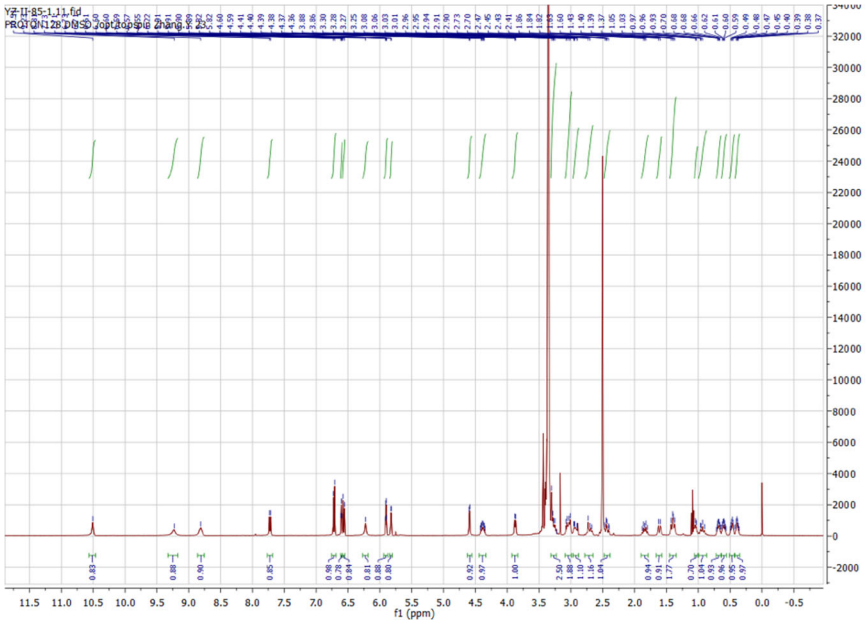


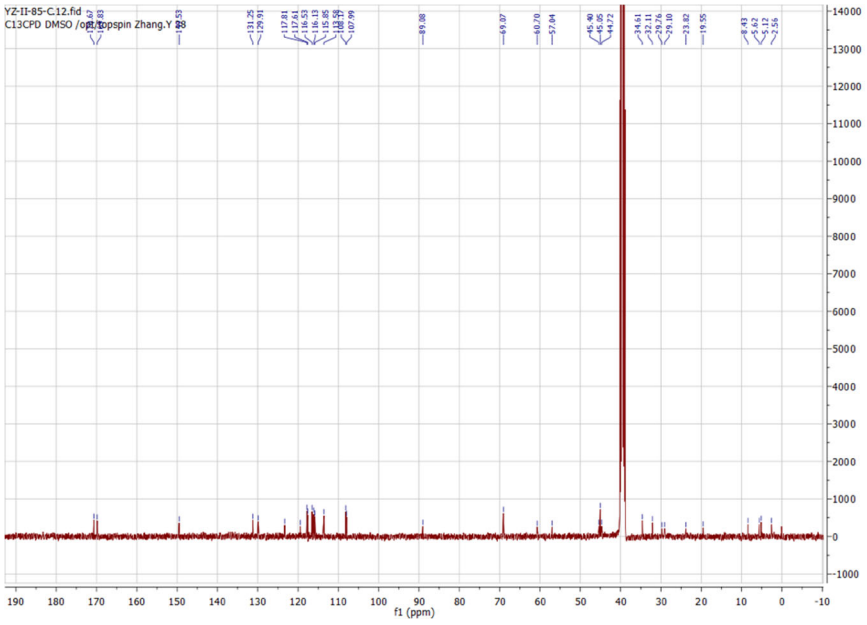
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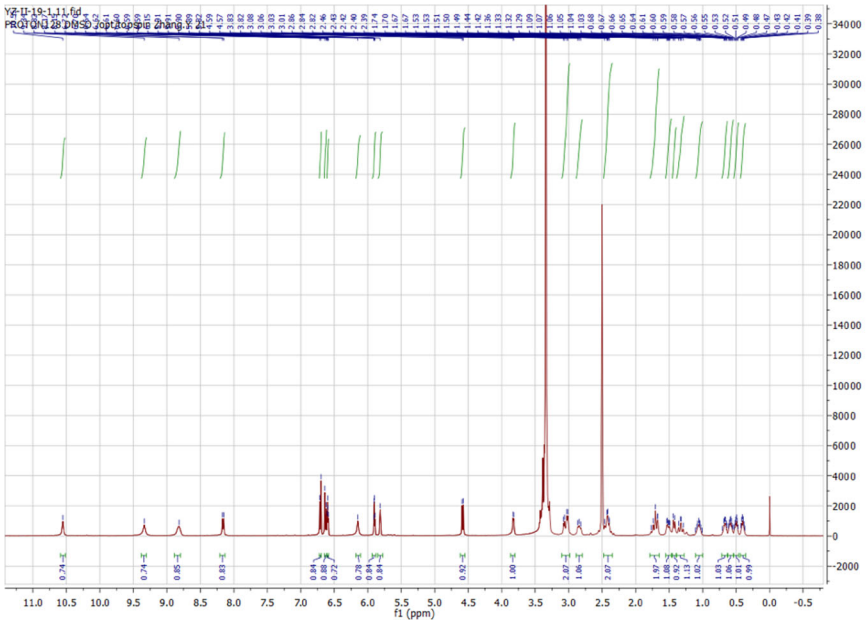


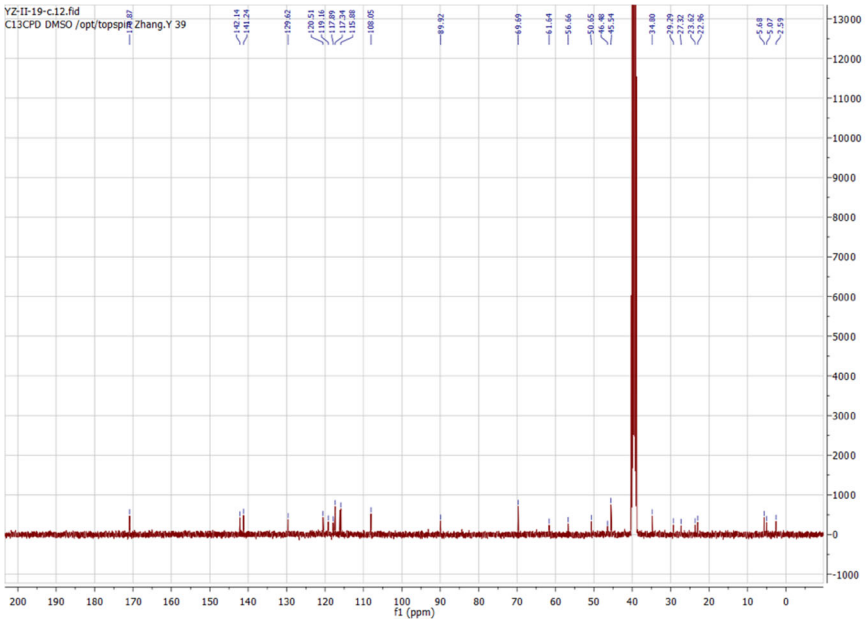
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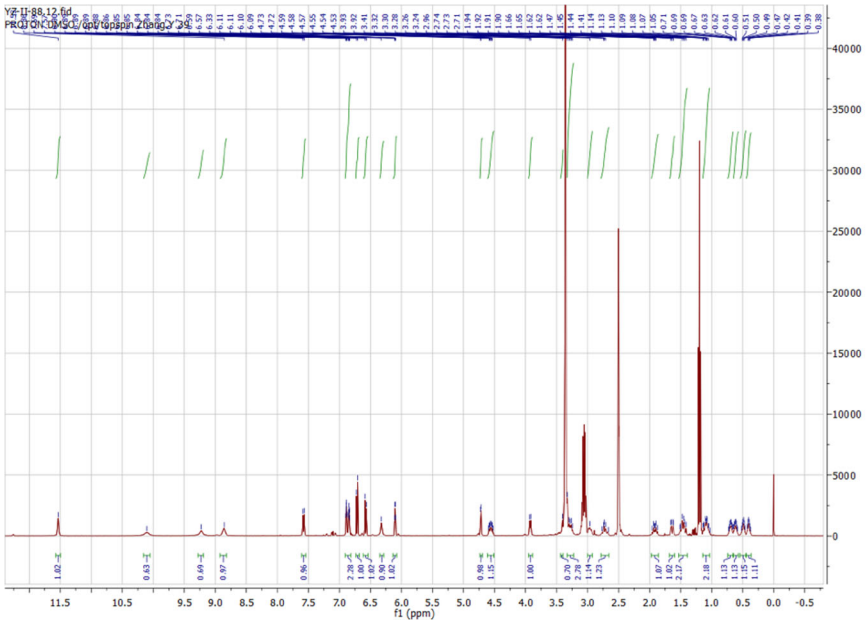


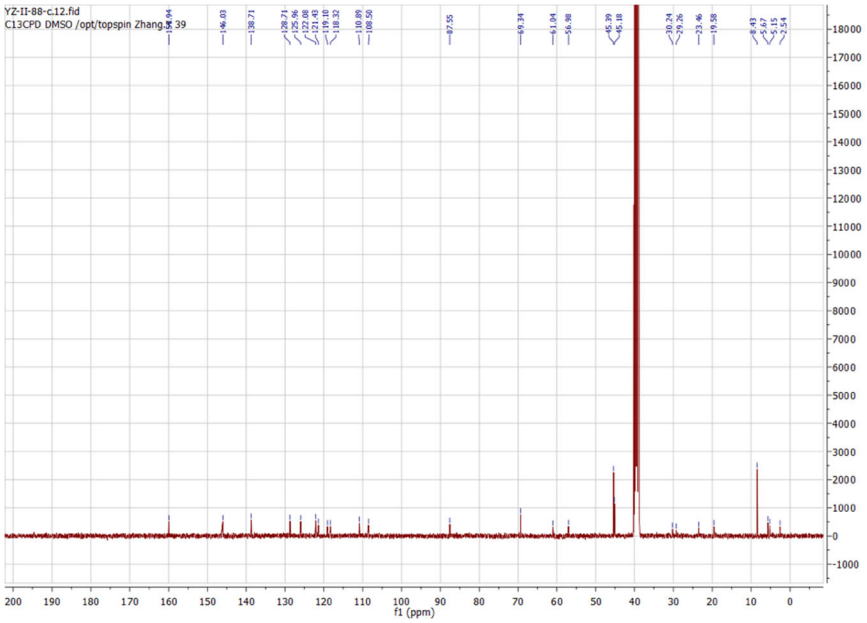
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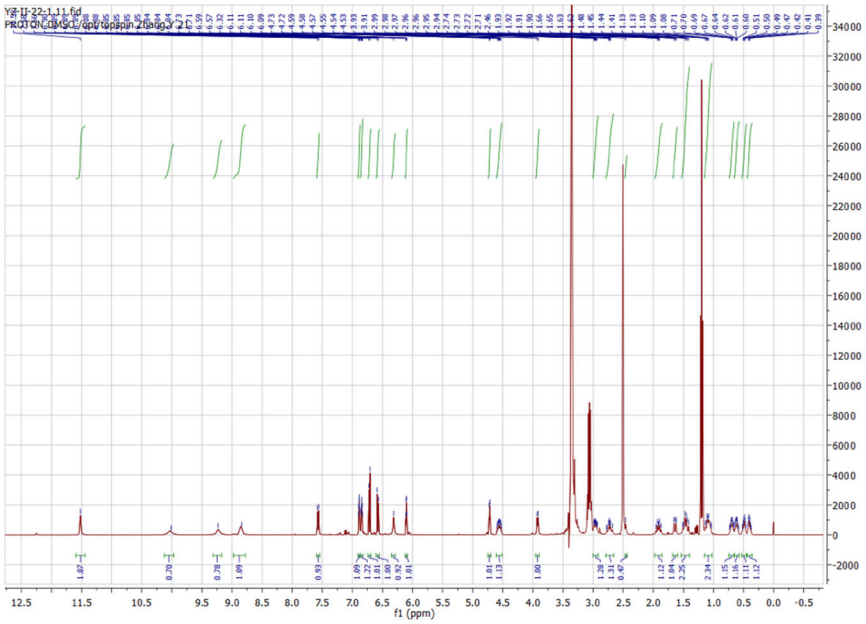


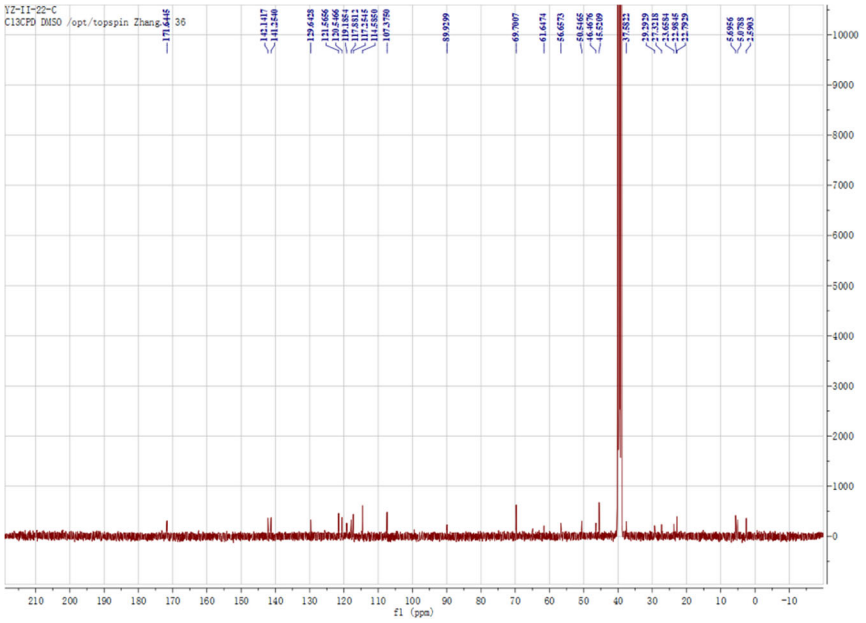
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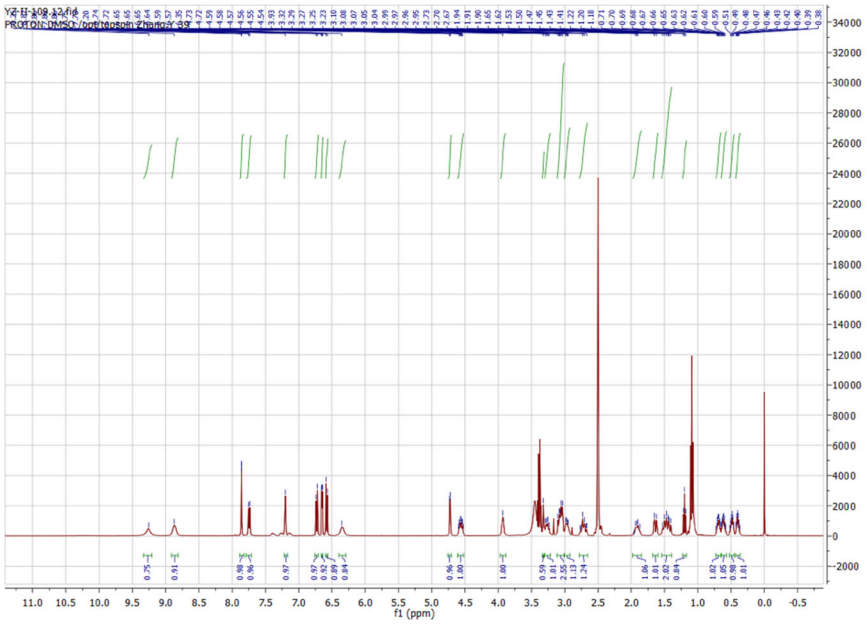


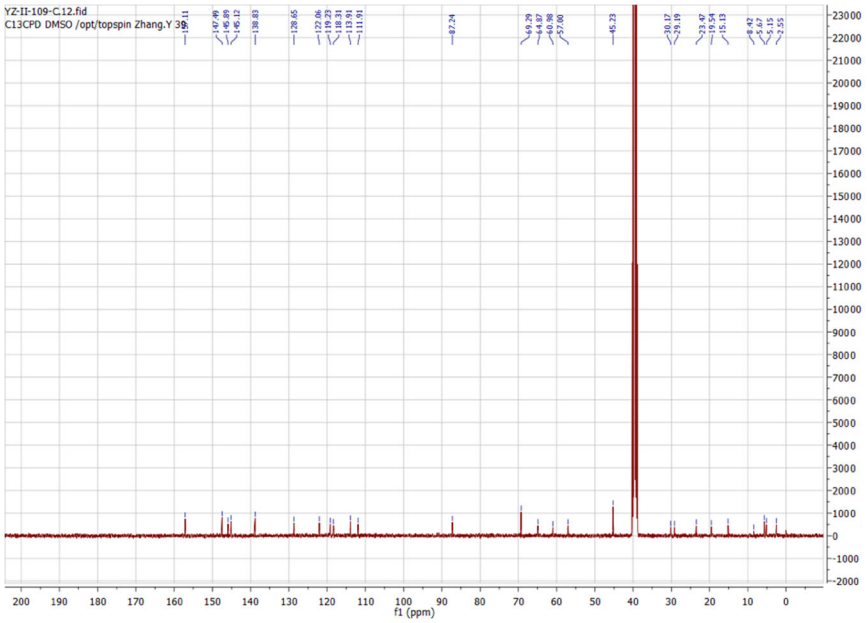
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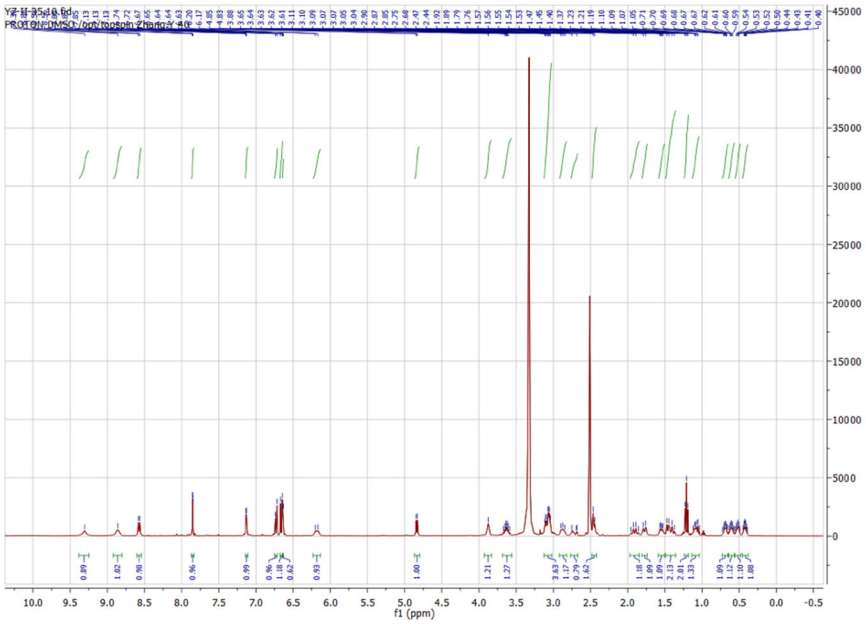


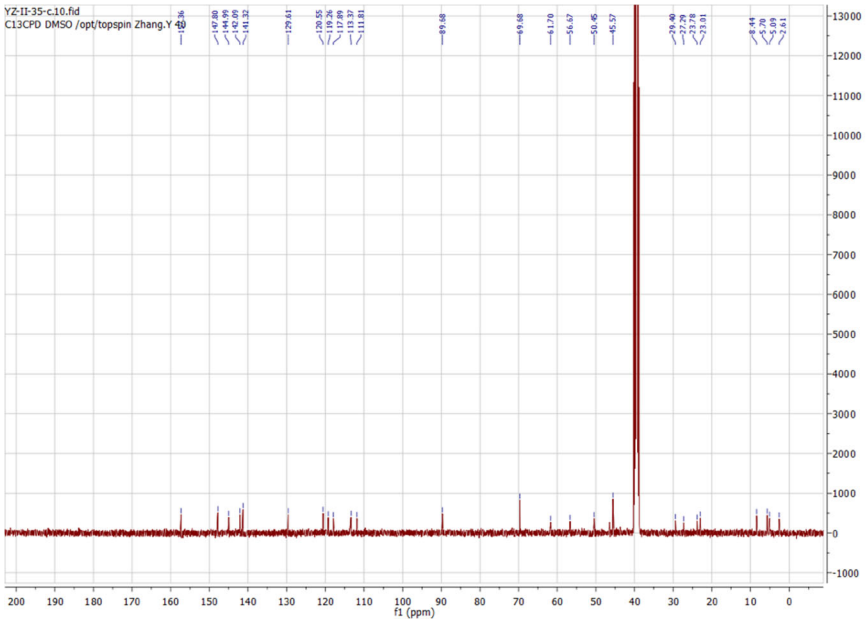
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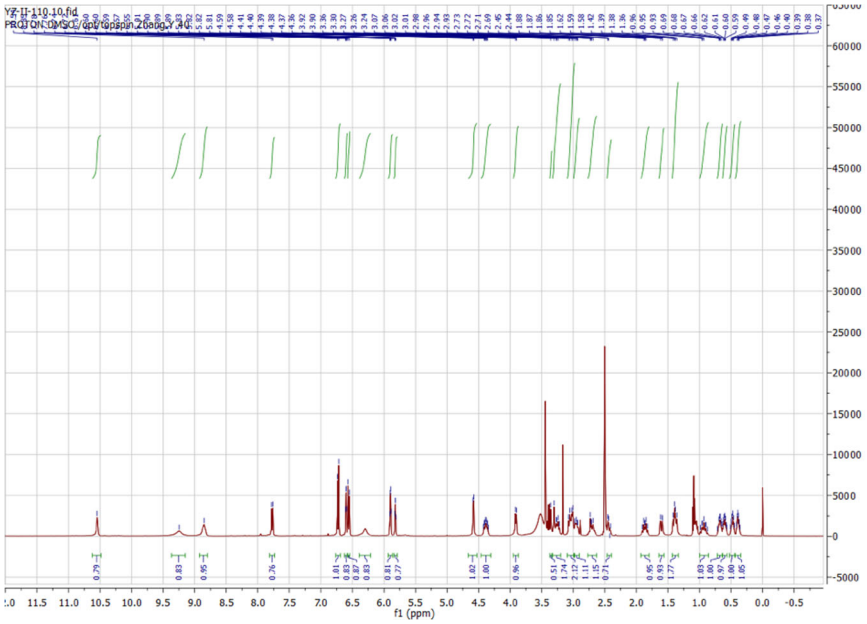


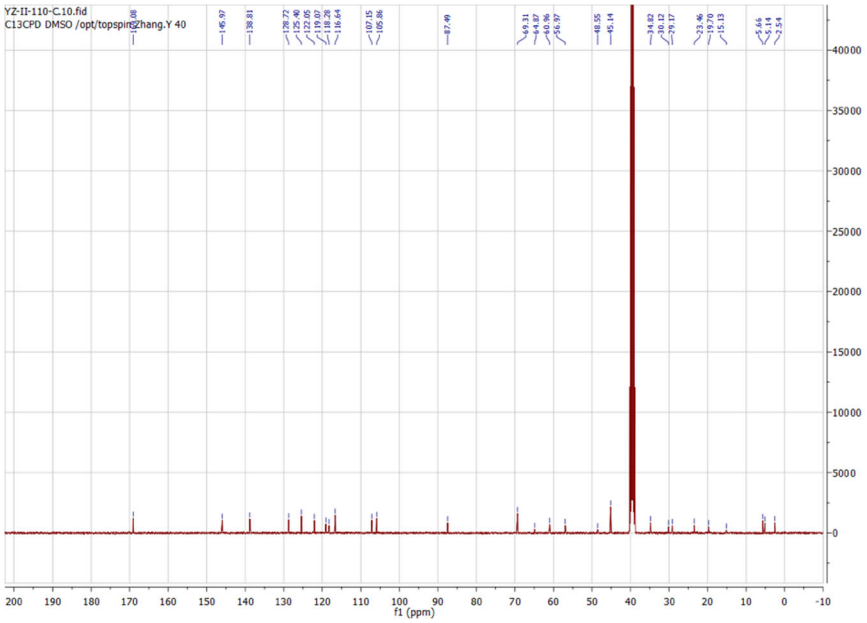
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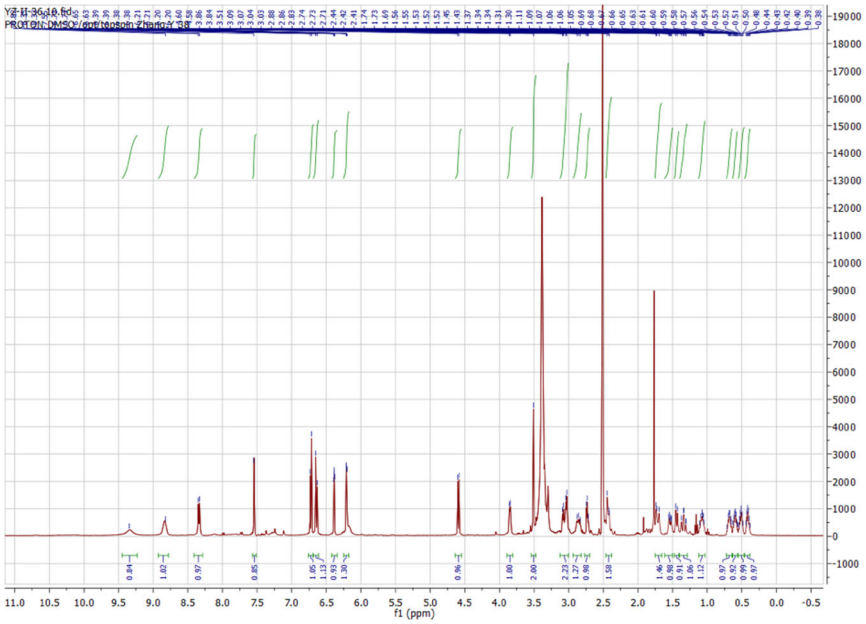


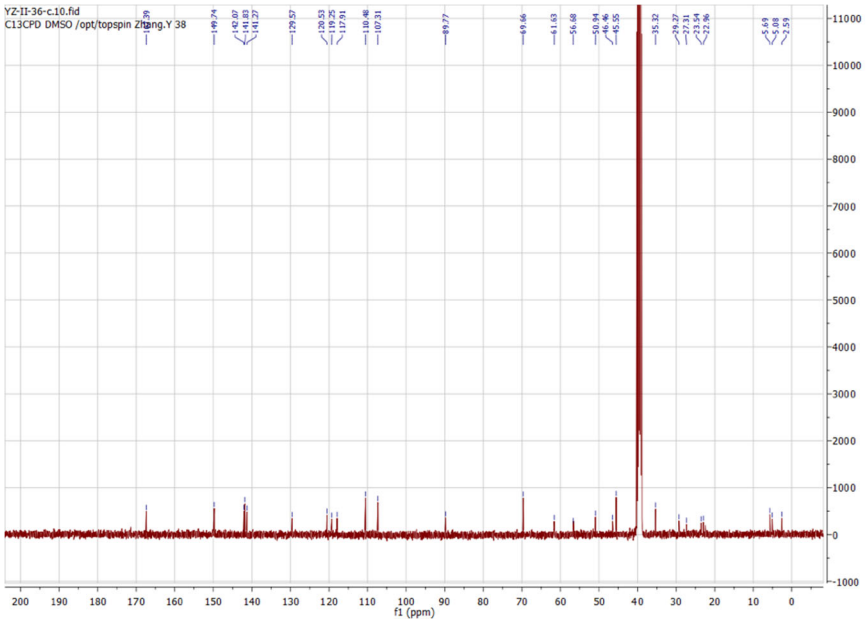
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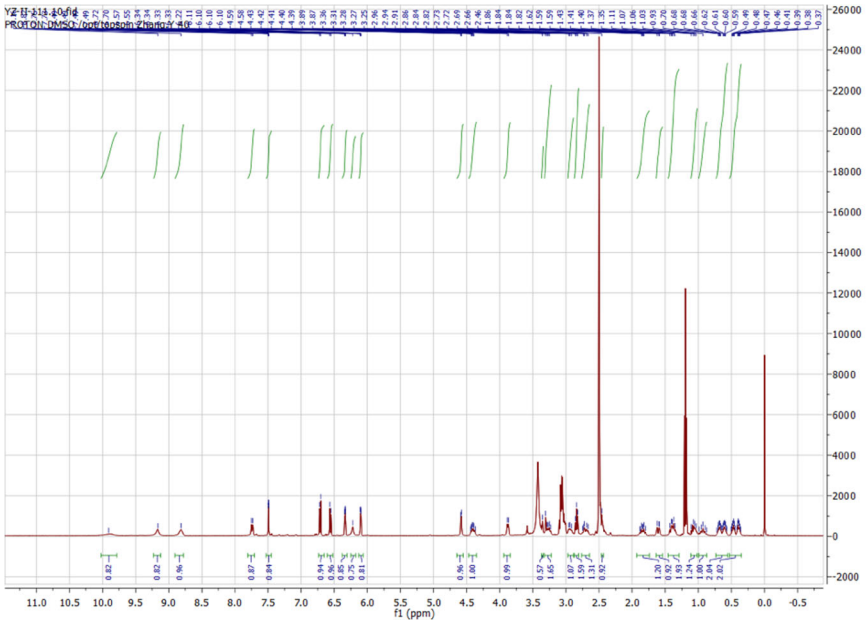


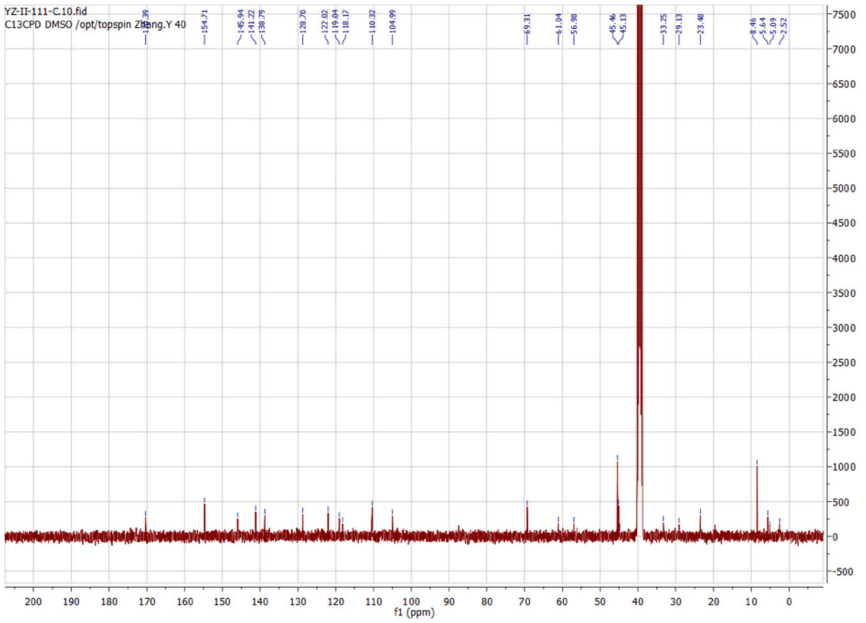
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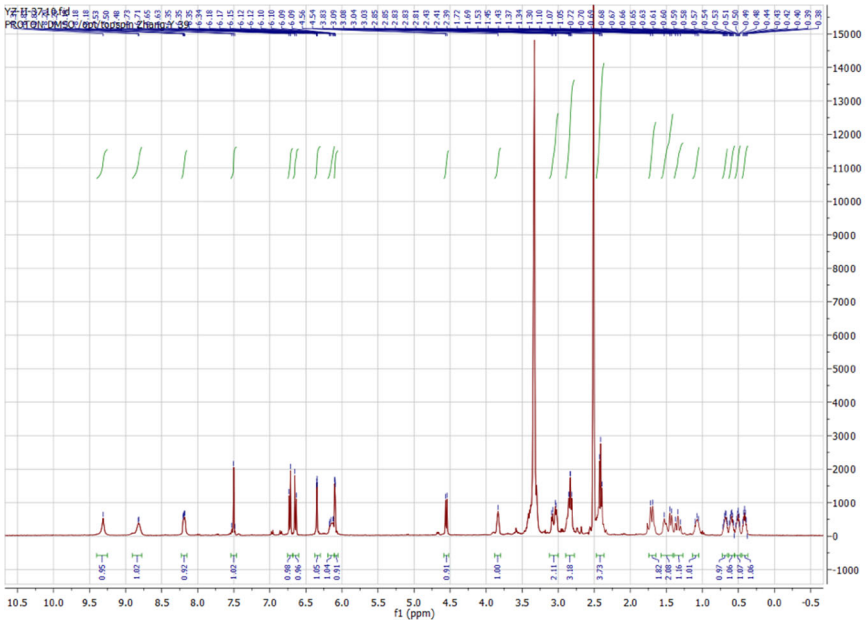


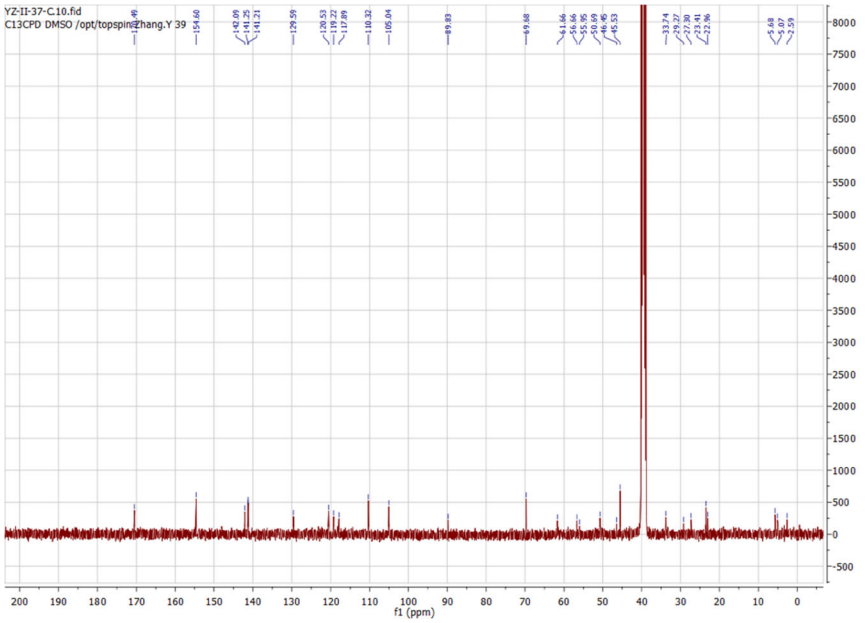
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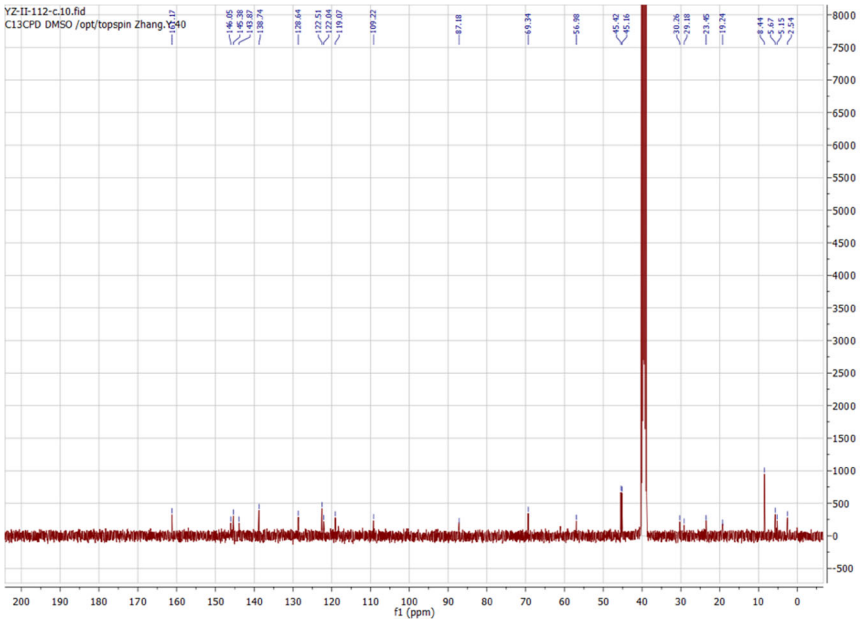
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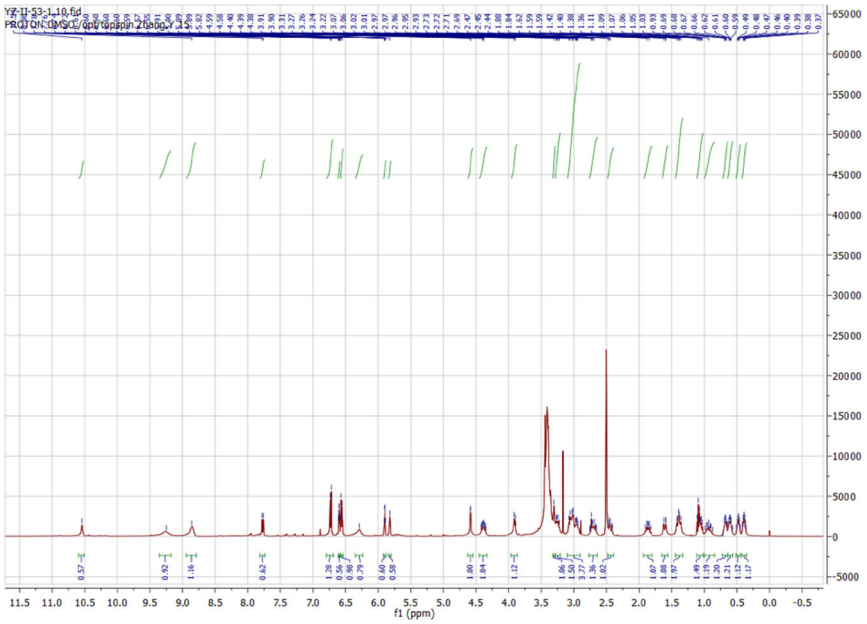


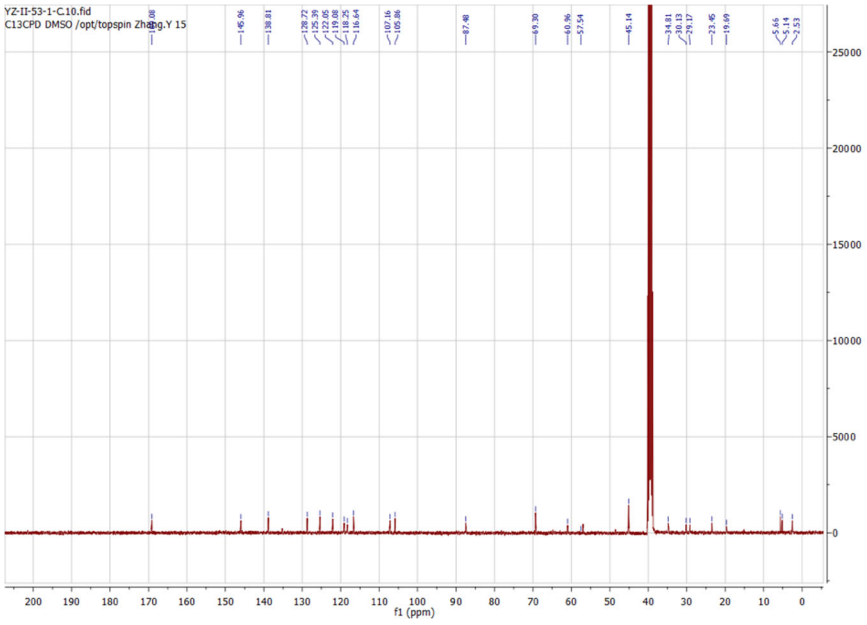
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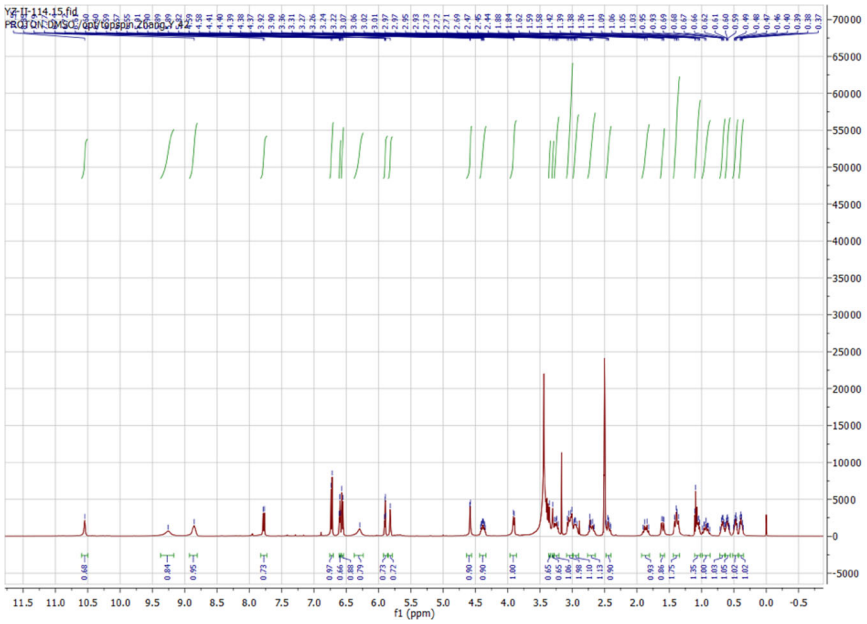


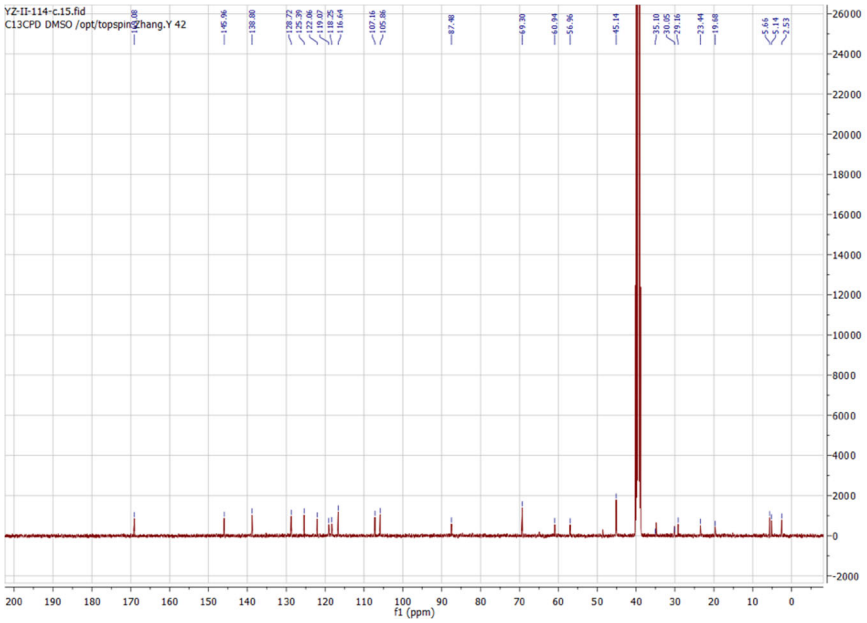
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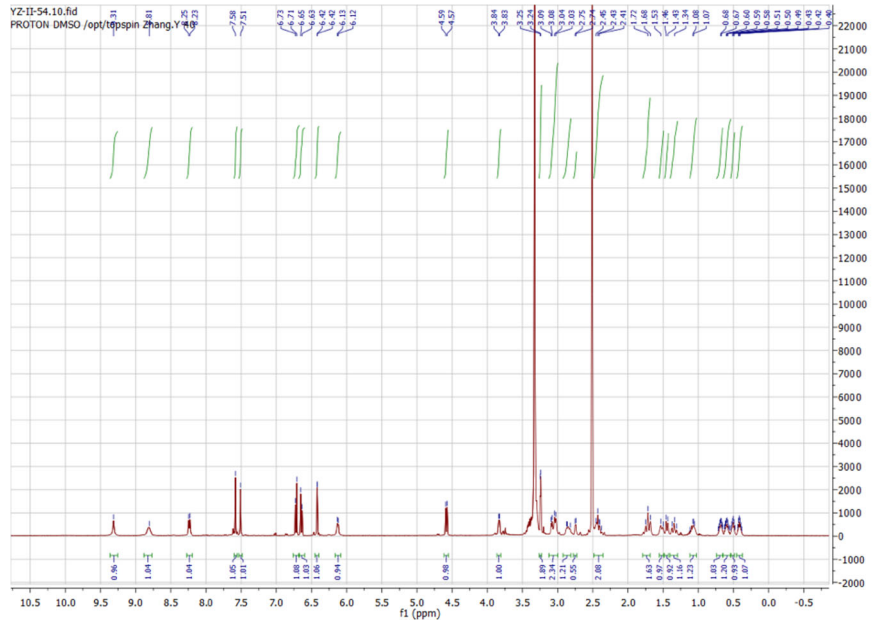


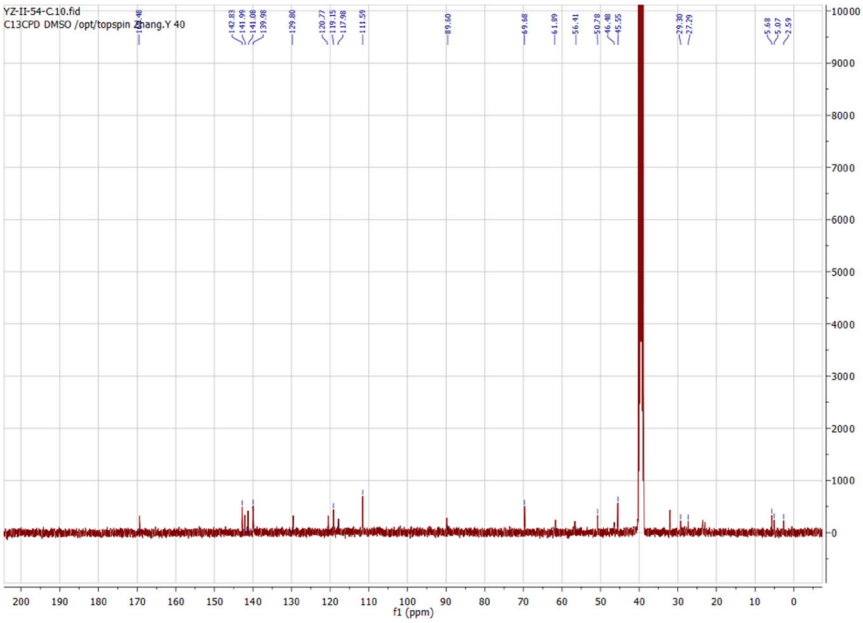
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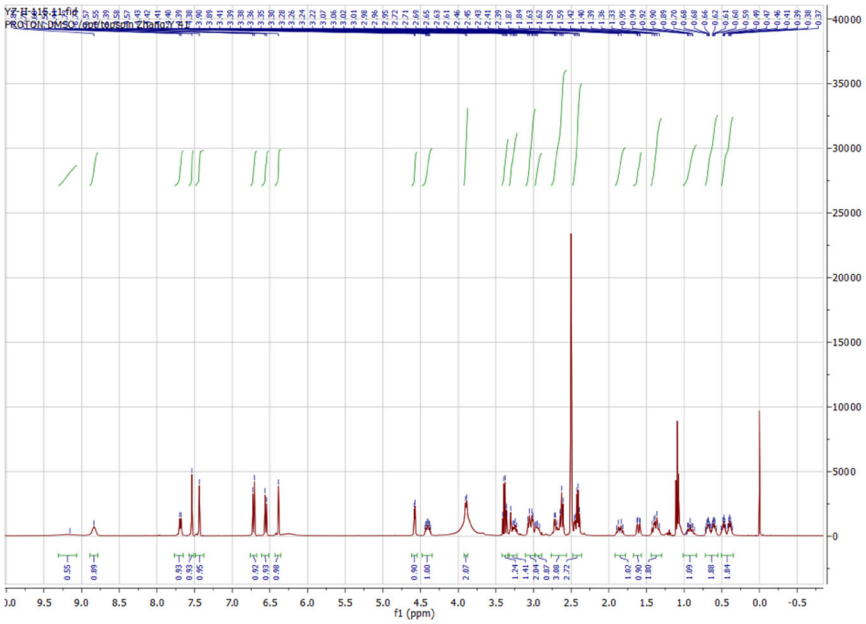


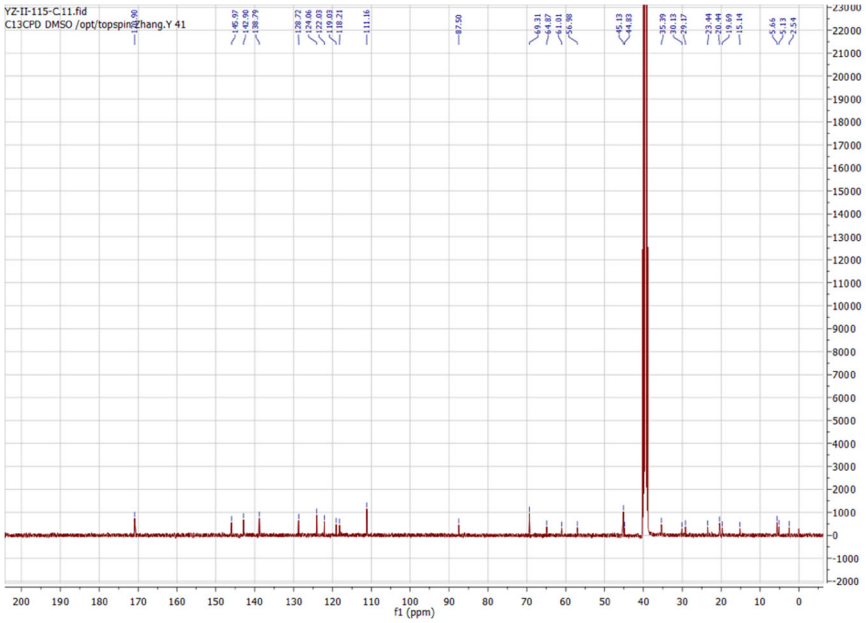
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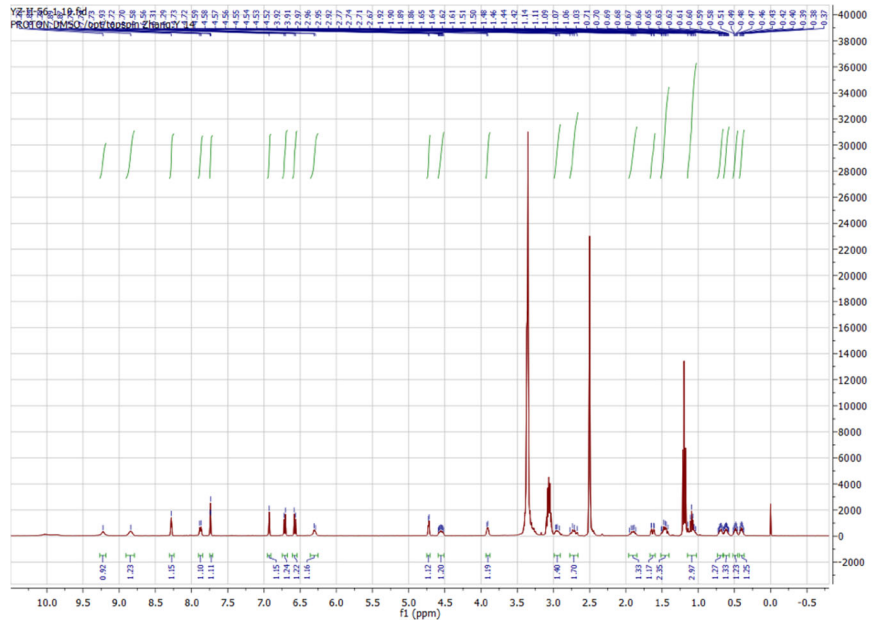


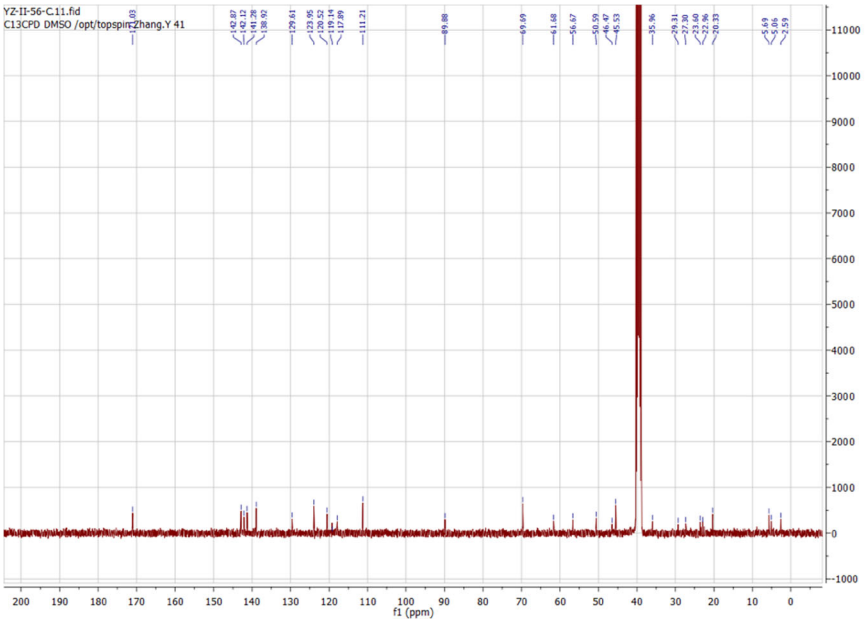
17-Cyclopropylmetyl-3,14β-dihydroxy-4,5α-epoxy-6α-[(3'-furanyl)propanamido]morphinan hydrochloride ***(23)***



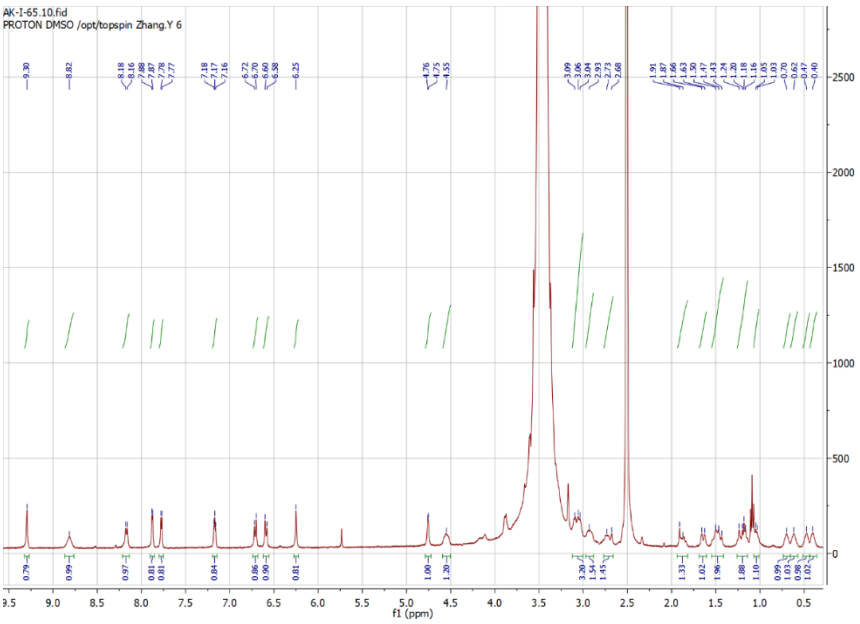


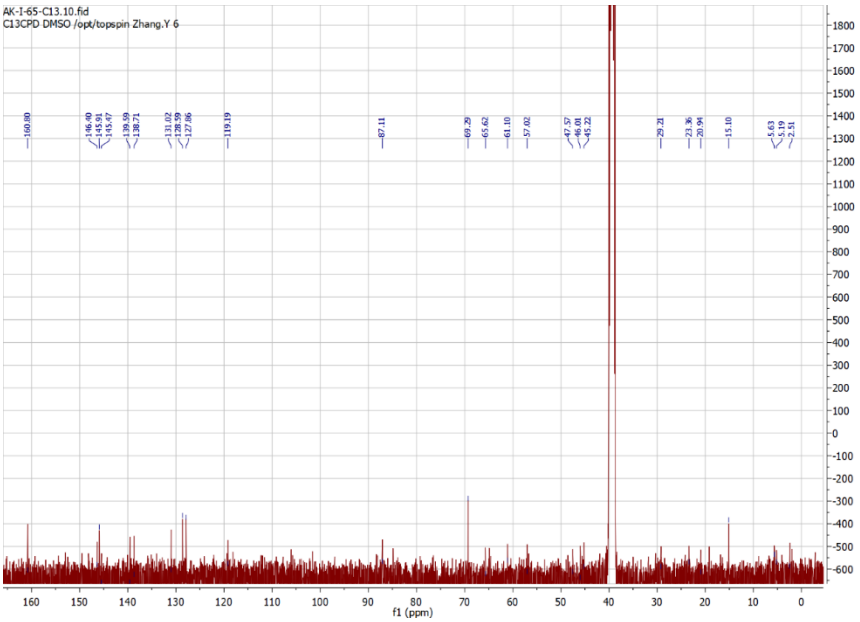
17-Cyclopropylmetyl-3,14β-dihydroxy-4,5α-epoxy-6β-[(3'-furanyl)propanamido]morphinan hydrochloride ***(24)***



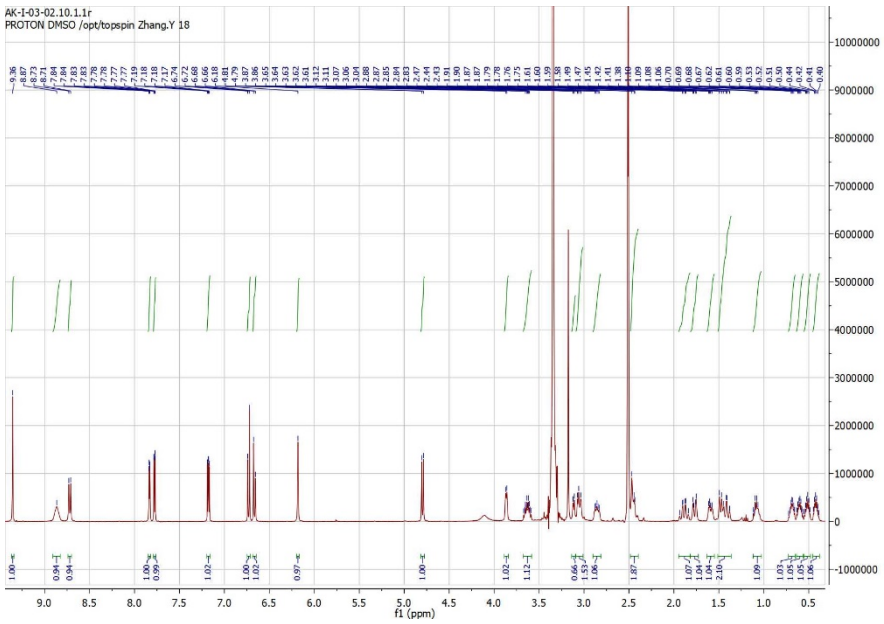


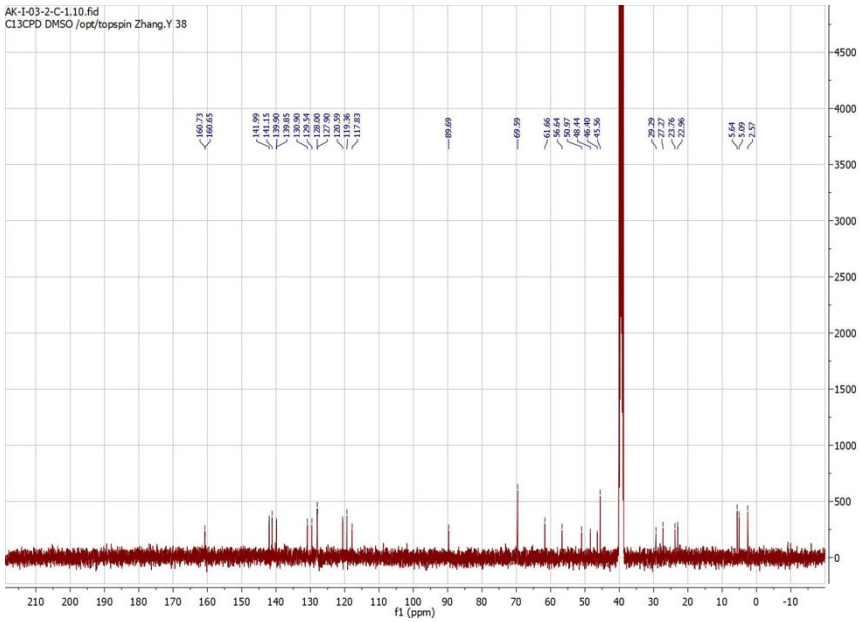
17-Cyclopropylmethyl-3,14β-dihydroxy-4,5α-epoxy-6α-(2′-thienylcarboxamido)morphinan hydrochloride ***(25)***



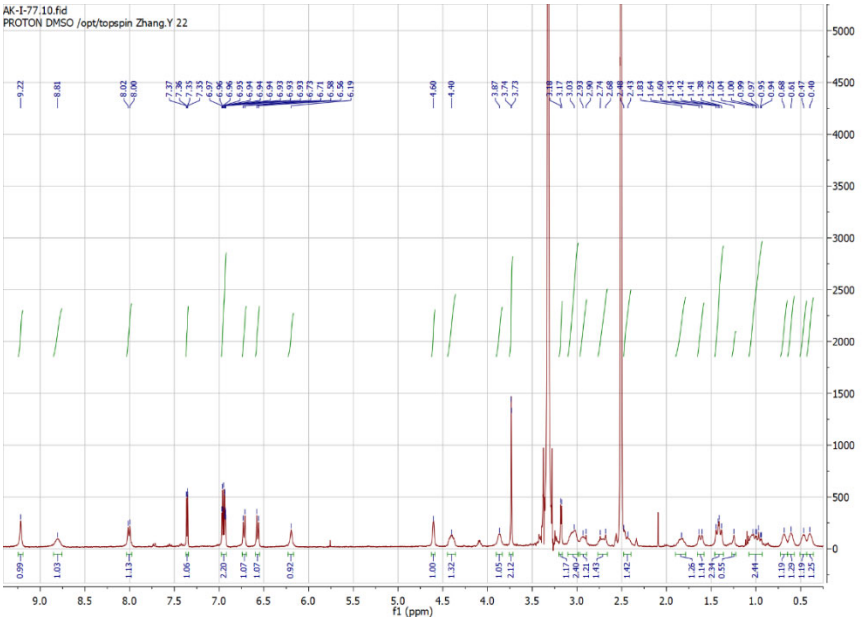


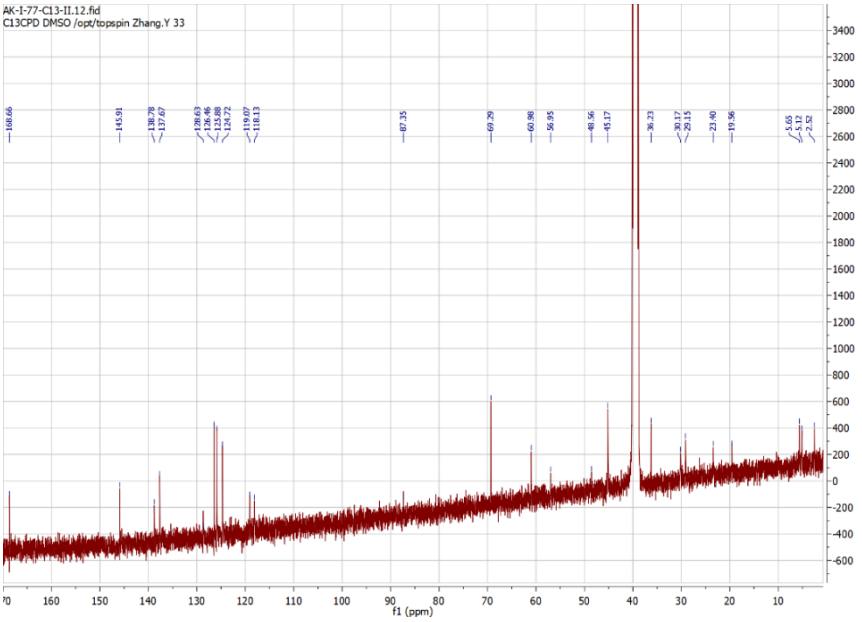
17-Cyclopropylmethyl-3,14β-dihydroxy-4,5α-epoxy-6β-(2′-thienylcarboxamido)morphinan hydrochloride ***(26)***



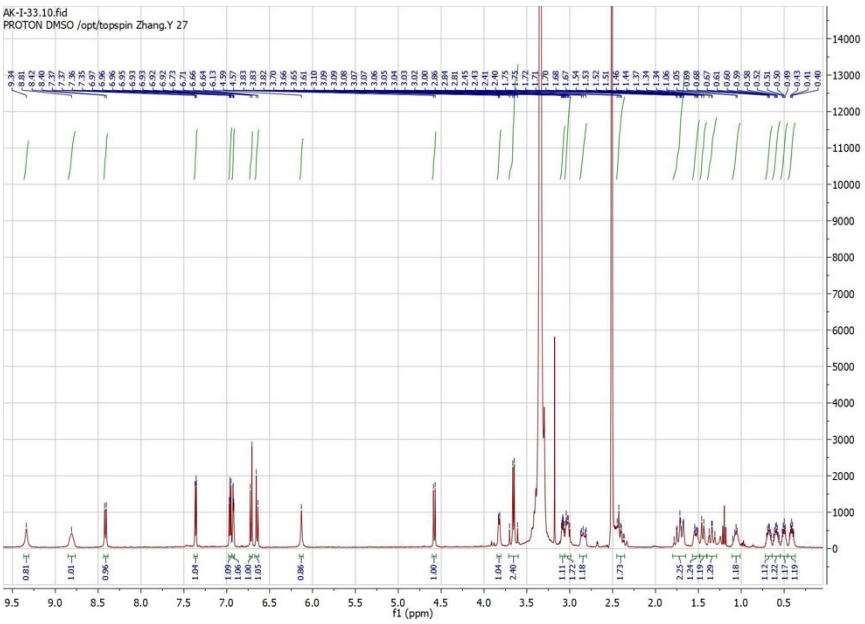


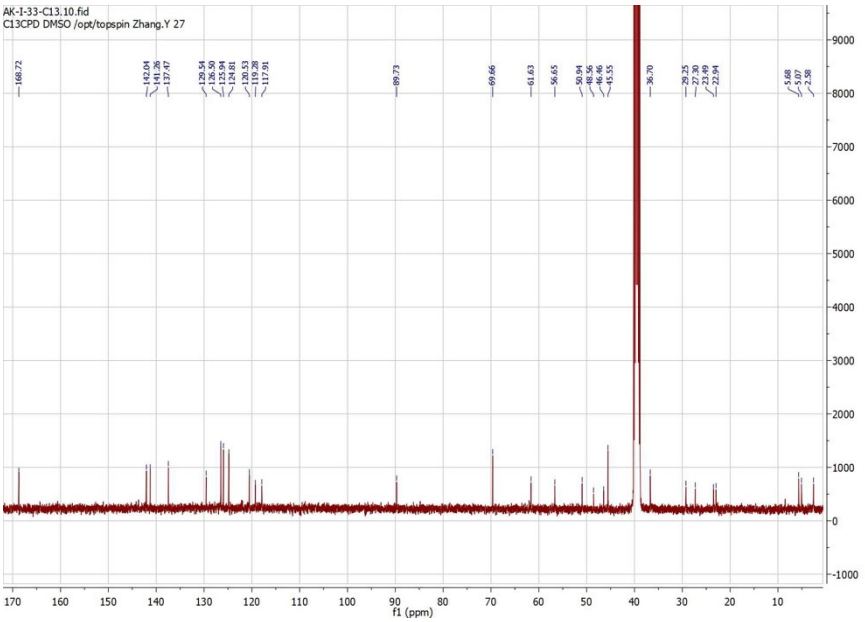
17-Cyclopropylmethyl-3,14β-dihydroxy-4,5α-epoxy-6α-(2′-thienylacetamido)morphinan hydrochloride ***(27)***



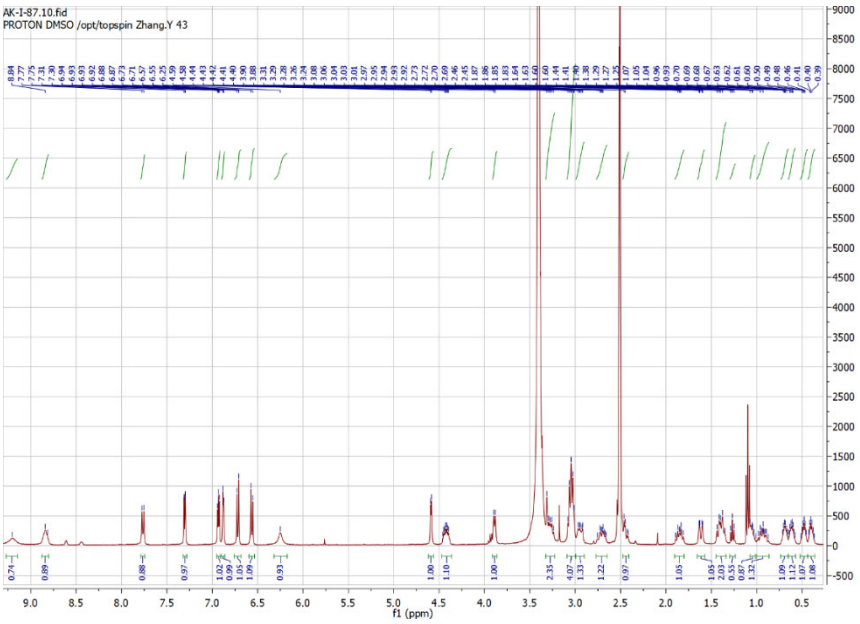


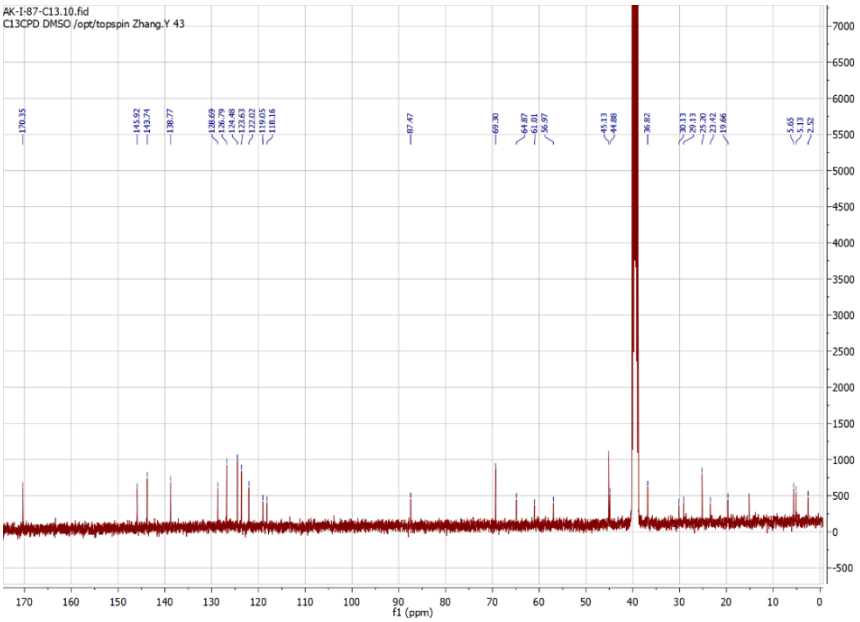
17-Cyclopropylmethyl-3,14β-dihydroxy-4,5α-epoxy-6β-(2′-thienylacetamido)morphinan hydrochloride ***(28)***



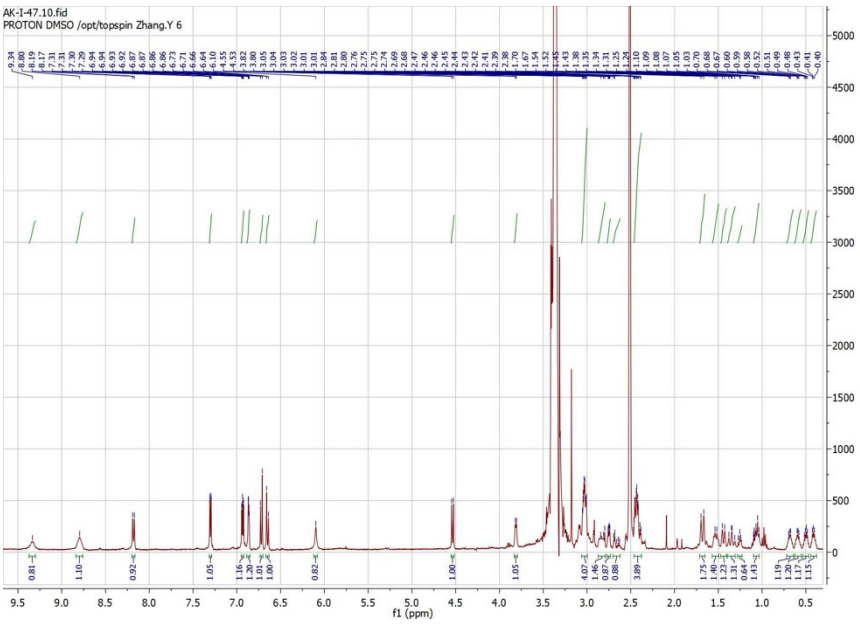


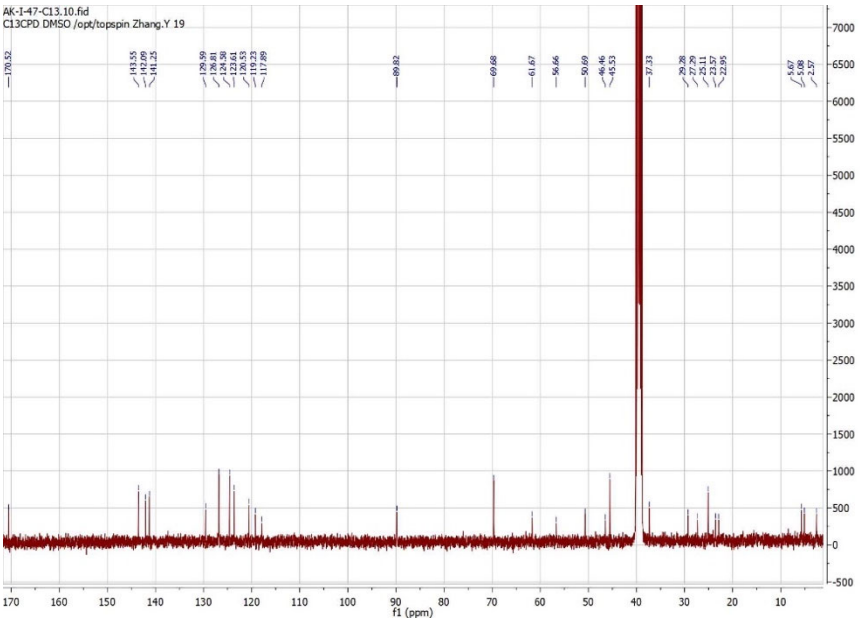
17-Cyclopropylmethyl-3,14β-dihydroxy-4,5α-epoxy-6α-[3′-(thiophen-2″yl)propanamido]morphinan hydrochloride ***(29)***



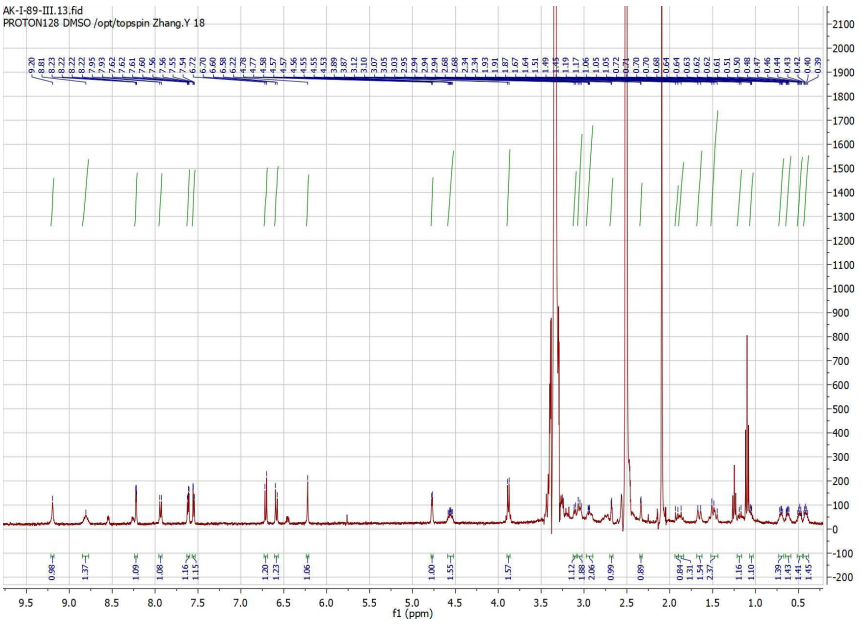


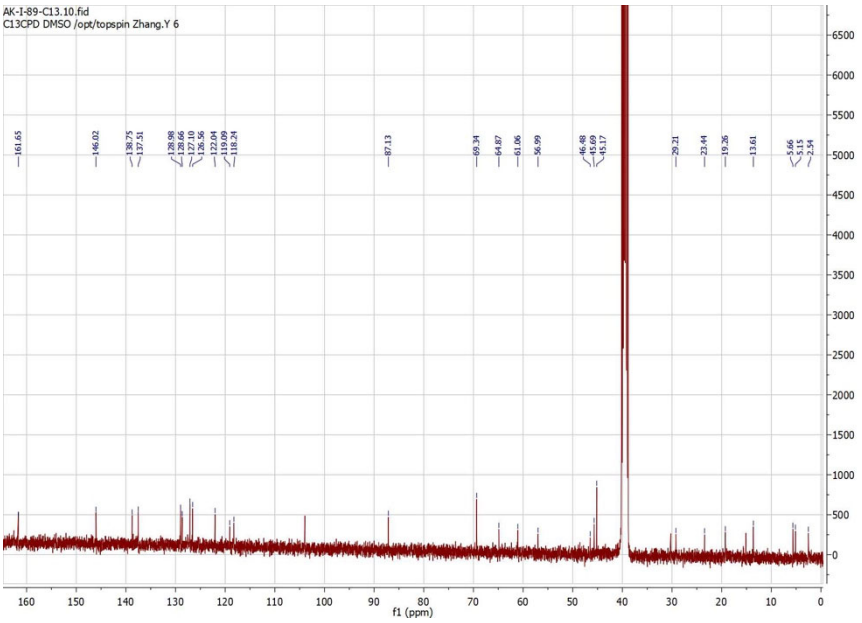
17-Cyclopropylmethyl-3,14β-dihydroxy-4,5α-epoxy-6β-[3′-(thiophen-2″-yl)propanamido]morphinan hydrochloride ***(30)***



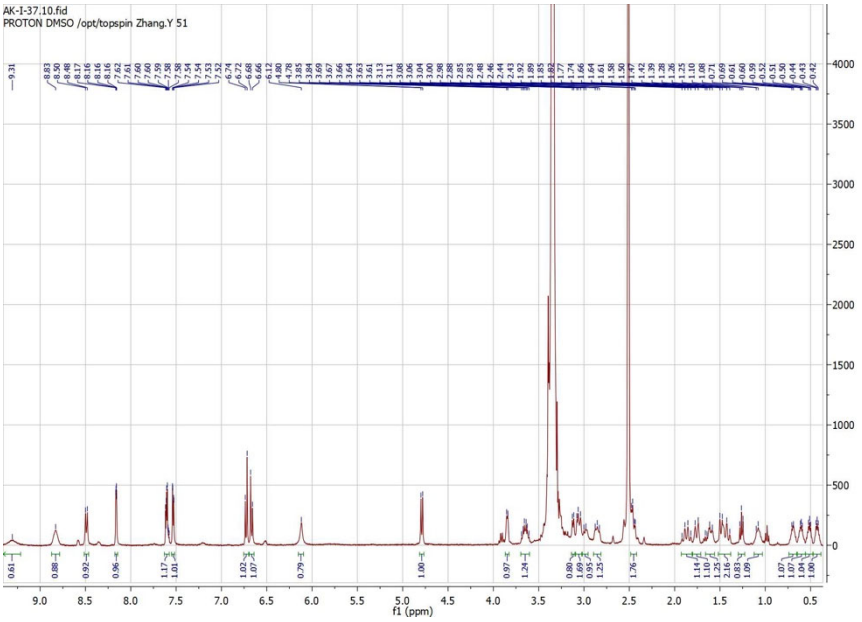


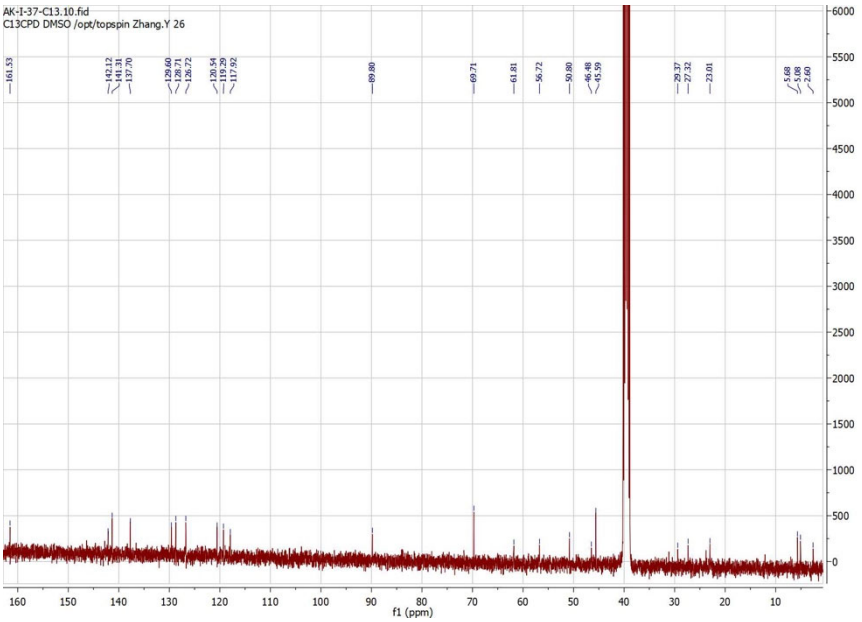
17-Cyclopropylmethyl-3,14β-dihydroxy-4,5α-epoxy-6α-(3′-thienylcarboxamido)morphinan hydrochloride ***(31)***



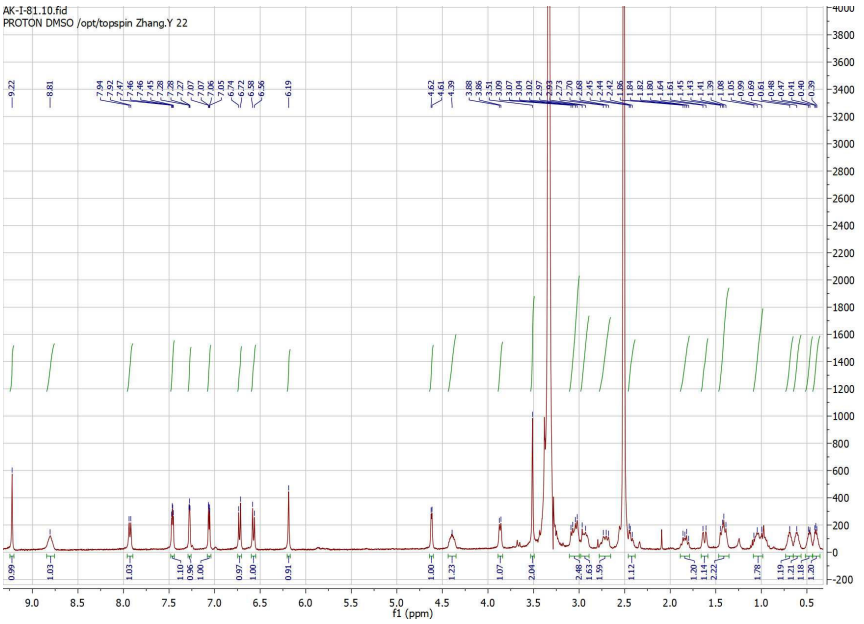


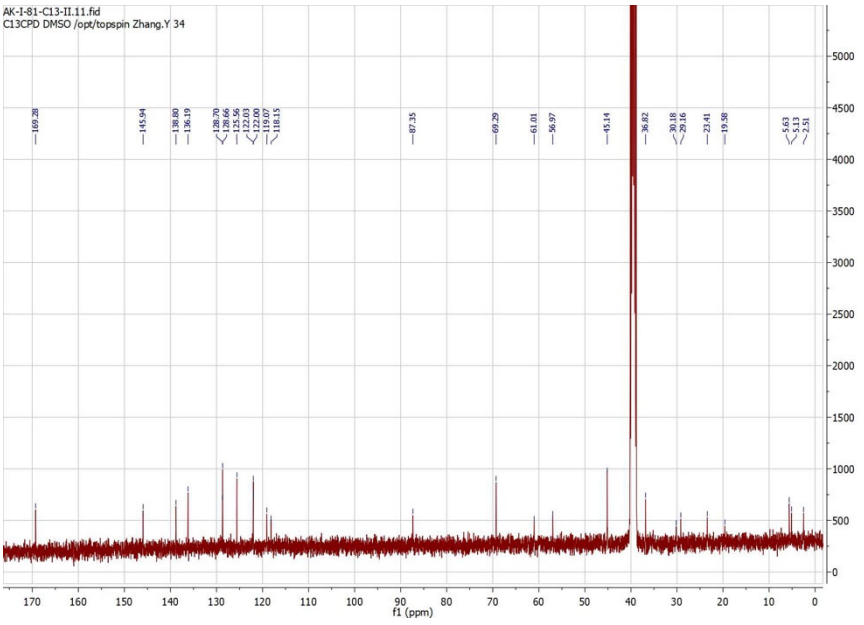
17-Cyclopropylmethyl-3,14β-dihydroxy-4,5α-epoxy-6β-(3′-thienylcarboxamido)morphinan hydrochloride ***(32)***



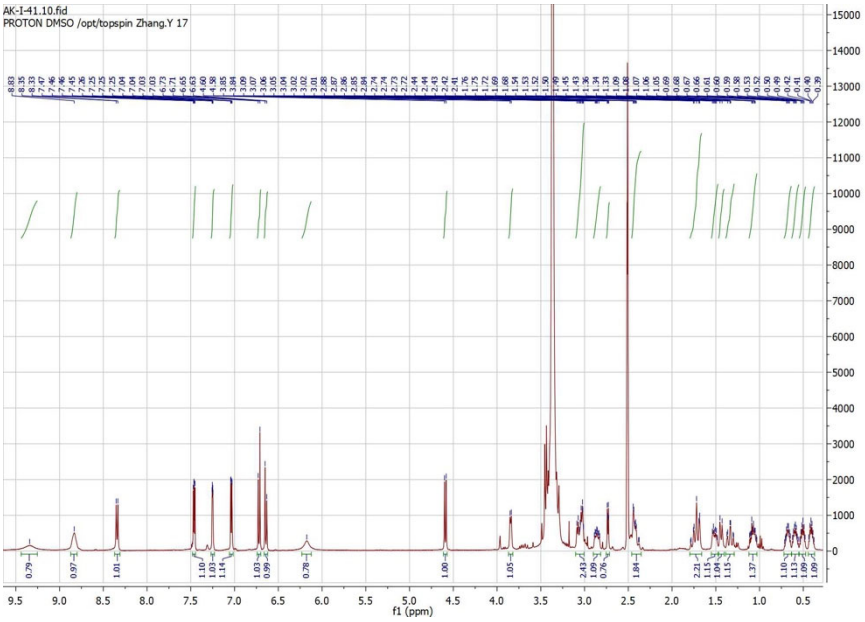


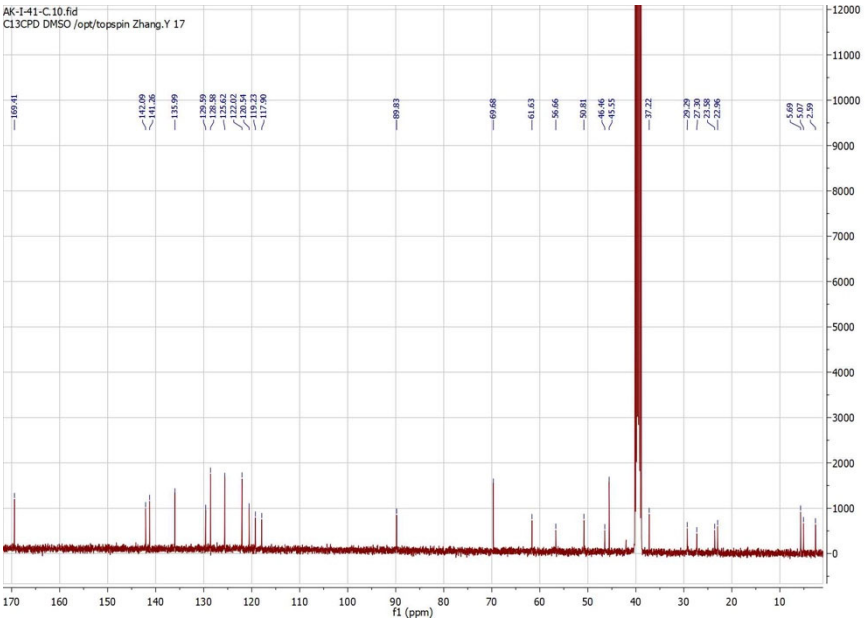
17-Cyclopropylmethyl-3,14β-dihydroxy-4,5α-epoxy-6α-(3′-thienylacetamido)morphinan hydrochloride ***(33)***



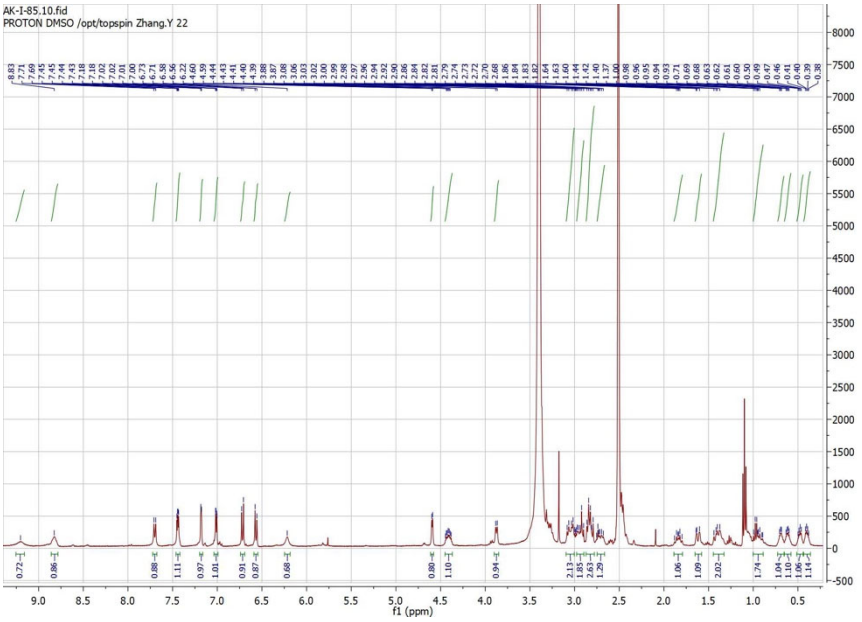


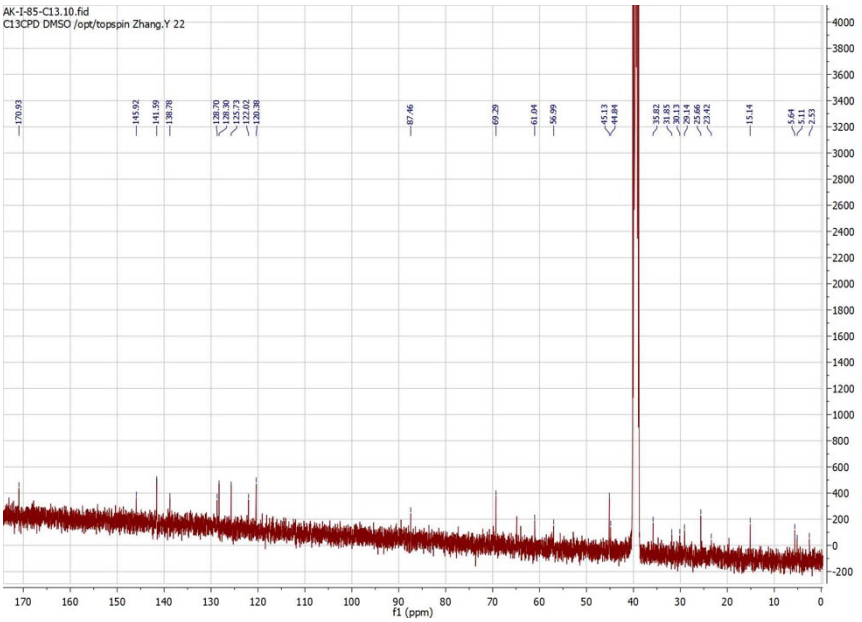
17-Cyclopropylmethyl-3,14β-dihydroxy-4,5α-epoxy-6β-(3′-thienylacetamido)morphinan hydrochloride ***(34)***



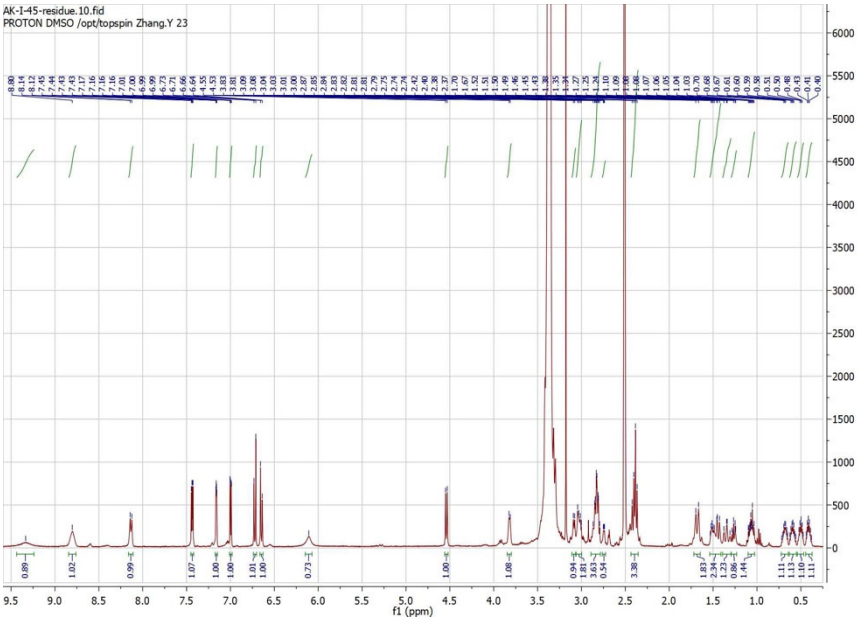


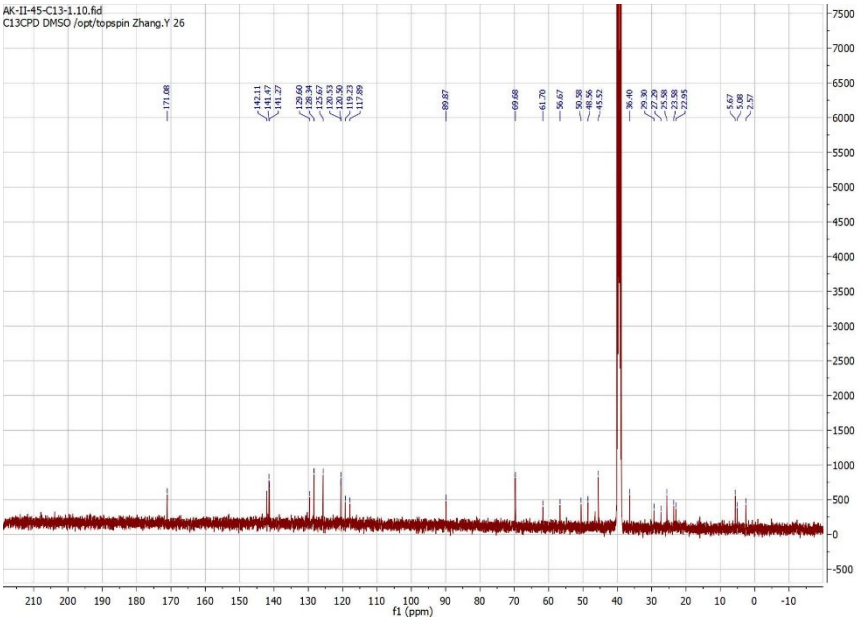
17-Cyclopropylmethyl-3,14β-dihydroxy-4,5α-epoxy-6α-[3′-(thiophen-3″-yl)propanamido]morphinan hydrochloride ***(35)***





17-Cyclopropylmethyl-3,14β-dihydroxy-4,5α-epoxy-6β-[3′-(thiophen-3″ yl)propanamido]morphinan hydrochloride ***(36)***





2. Purity data of final compounds.

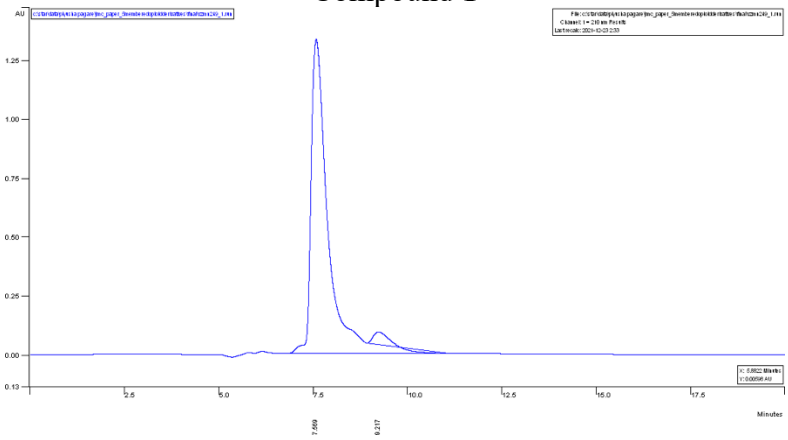
HPLC System: Varian Prostar 210;
Column: Microsorb-MV100-5 C18 (250 * 4.6 mm);
Injection Volume: 5 μL;
Sample Concentration: 1mg/mL;
Single Wavelength: 210 nm

Table S1. HPLC Analysis of Target Compounds.

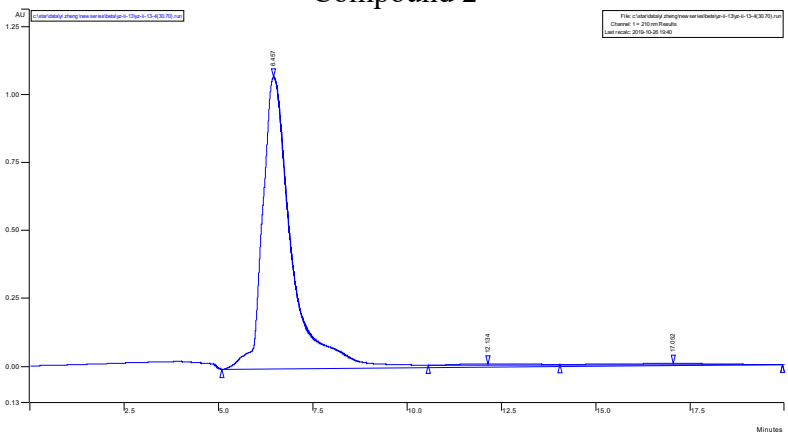
Compound	System	Retention Time (min)	Purity (%)
1	water/acetonitrile (30/70) with 0.01% trifluoroacetic acid at 0.8 mL/min for 20 minutes	7.56	97.72
2	water/acetonitrile (30/70) with 0.01% trifluoroacetic acid at 0.5 mL/min for 20 minutes	6.45	96.98
3	water/acetonitrile (30/70) with 0.01% trifluoroacetic acid at 0.8 mL/min for 20 minutes	7.51	99.84
4	water/acetonitrile (30/70) with 0.01% trifluoroacetic acid at 0.8 mL/min for 20 minutes	7.34	97.71
5	water/acetonitrile (30/70) with 0.01% trifluoroacetic acid at 0.8 mL/min for 20 minutes	7.58	99.65
6	water/acetonitrile (30/70) with 0.01% trifluoroacetic acid at 0.5 mL/min for 20 minutes	6.44	98.97
7	water/acetonitrile (30/70) with 0.01% trifluoroacetic acid at 0.5 mL/min for 20 minutes	6.43	99.20
8	water/acetonitrile (30/70) with 0.01% trifluoroacetic acid at 0.8 mL/min for 20 minutes	7.24	96.13
9	water/acetonitrile (30/70) with 0.01% trifluoroacetic acid at 0.5 mL/min for 20 minutes	6.50	95.14
10	water/acetonitrile (30/70) with 0.01% trifluoroacetic acid at 0.5 mL/min for 20 minutes	6.46	99.86
11	water/acetonitrile (30/70) with 0.01% trifluoroacetic acid at 0.5 mL/min for 20 minutes	6.41	96.13
12	water/acetonitrile (30/70) with 0.01% trifluoroacetic acid at 0.5 mL/min for 20 minutes	6.32	96.93
13	water/acetonitrile (30/70) with 0.01% trifluoroacetic acid at 0.8 mL/min for 20 minutes	7.72	100
14	water/acetonitrile (30/70) with 0.01% trifluoroacetic acid at 0.5 mL/min for 20 minutes	6.31	98.05
15	water/acetonitrile (30/70) with 0.01% trifluoroacetic acid at 0.8 mL/min for 20 minutes	4.84	96.72
16	water/acetonitrile (30/70) with 0.01% trifluoroacetic acid at 0.8 mL/min for 20 minutes	7.45	97.44
17	water/acetonitrile (30/70) with 0.01% trifluoroacetic acid at 0.5 mL/min for 20 minutes	6.24	97.59

18	water/acetonitrile (30/70) with 0.01% trifluoroacetic acid at 0.8 mL/min for 20 minutes	7.70	99.80
19	water/acetonitrile (30/70) with 0.01% trifluoroacetic acid at 0.8 mL/min for 20 minutes	4.76	97.49
20	water/acetonitrile (30/70) with 0.01% trifluoroacetic acid at 0.5 mL/min for 20 minutes	6.41	97.12
21	water/acetonitrile (30/70) with 0.01% trifluoroacetic acid at 0.8 mL/min for 20 minutes	4.80	96.01
22	water/acetonitrile (30/70) with 0.01% trifluoroacetic acid at 0.8 mL/min for 20 minutes	7.50	98.73
23	water/acetonitrile (30/70) with 0.01% trifluoroacetic acid at 0.8 mL/min for 20 minutes	4.88	100
24	water/acetonitrile (30/70) with 0.01% trifluoroacetic acid at 0.5 mL/min for 20 minutes	6.43	97.61
25	water/acetonitrile (30/70) with 0.01% trifluoroacetic acid at 0.5 mL/min for 30 minutes	6.49	97.47
26	water/acetonitrile (30/70) with 0.01% trifluoroacetic acid at 0.5 mL/min for 30 minutes	6.41	99.82
27	water/acetonitrile (30/70) with 0.01% trifluoroacetic acid at 0.5 mL/min for 30 minutes	6.67	97.70
28	water/acetonitrile (30/70) with 0.01% trifluoroacetic acid at 0.5 mL/min for 30 minutes	6.52	96.39
29	water/acetonitrile (30/70) with 0.01% trifluoroacetic acid at 0.5 mL/min for 30 minutes	6.71	98.46
30	water/acetonitrile (30/70) with 0.01% trifluoroacetic acid at 0.5 mL/min for 30 minutes	6.73	97.48
31	water/acetonitrile (30/70) with 0.01% trifluoroacetic acid at 0.5 mL/min for 30 minutes	5.64	96.98
32	water/acetonitrile (30/70) with 0.01% trifluoroacetic acid at 0.5 mL/min for 30 minutes	6.22	98.85
33	water/acetonitrile (30/70) with 0.01% trifluoroacetic acid at 0.5 mL/min for 30 minutes	6.46	97.35
34	water/acetonitrile (30/70) with 0.01% trifluoroacetic acid at 0.5 mL/min for 30 minutes	6.29	98.08
35	water/acetonitrile (30/70) with 0.01% trifluoroacetic acid at 0.5 mL/min for 30 minutes	6.85	96.47
36	water/acetonitrile (30/70) with 0.01% trifluoroacetic acid at 0.5 mL/min for 30 minutes	6.66	99.50

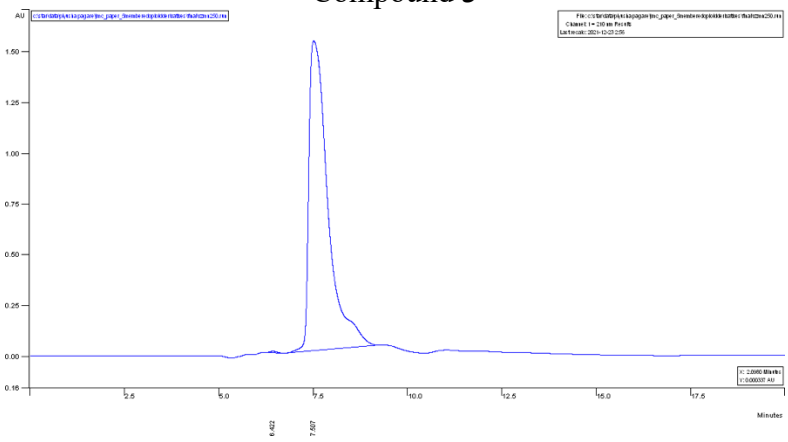
Compound **1**



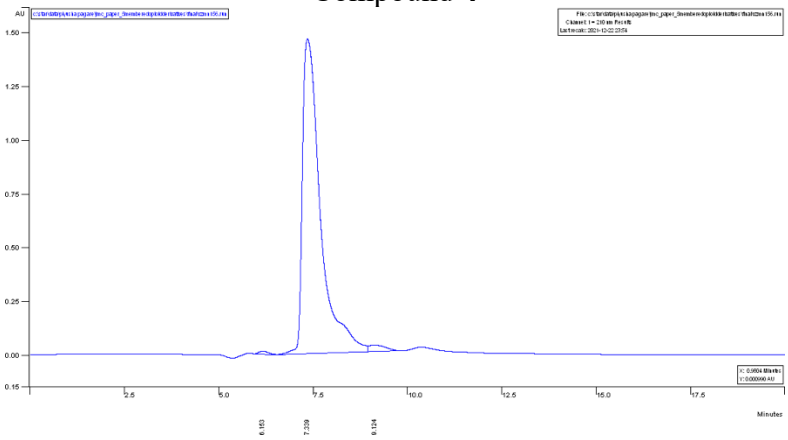
Compound **2**



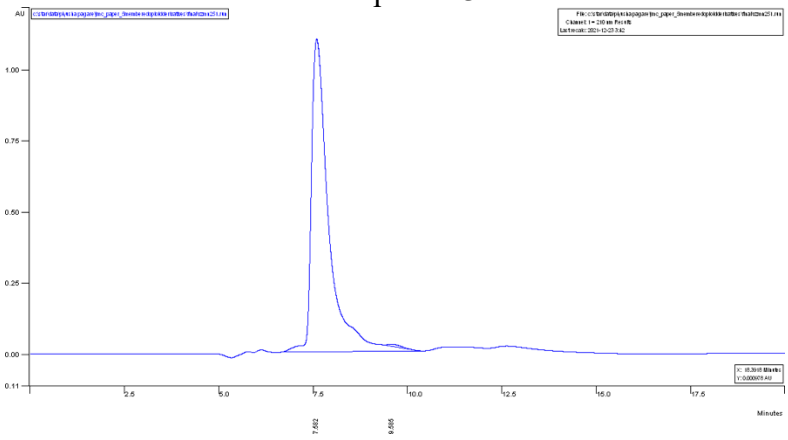
Compound **3**



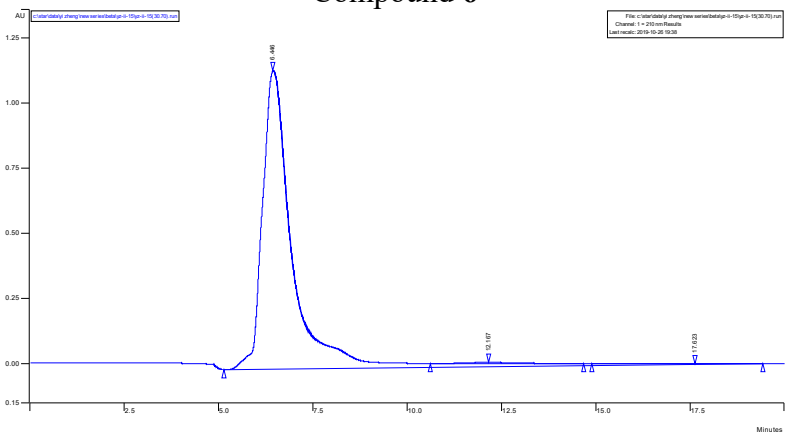
Compound **4**



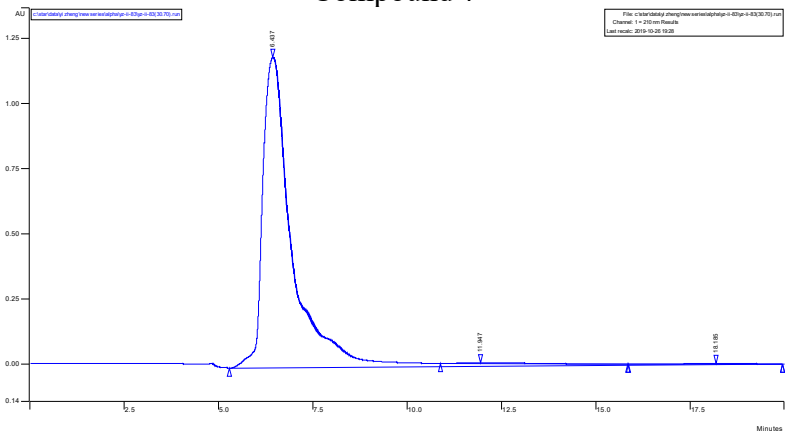
Compound **5**



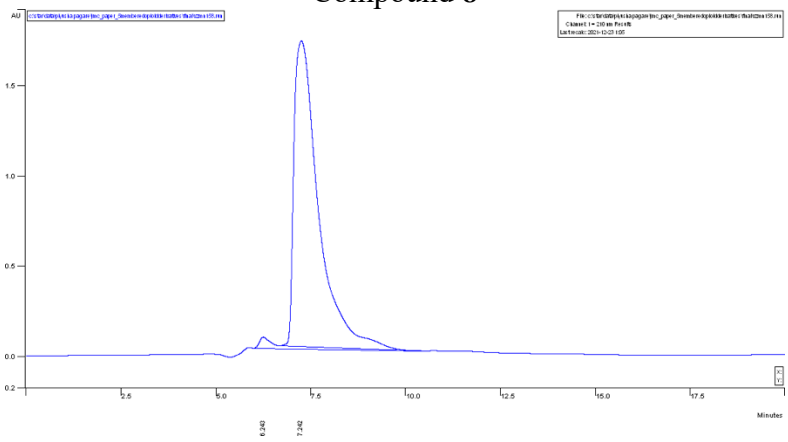
Compound **6**



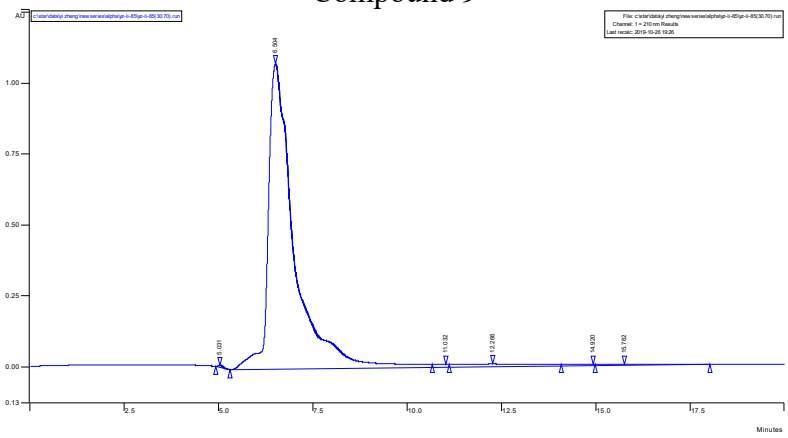
Compound **7**



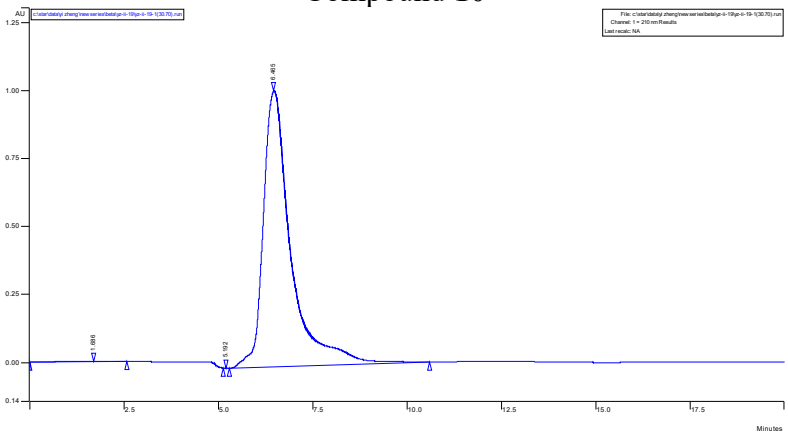
Compound **8**



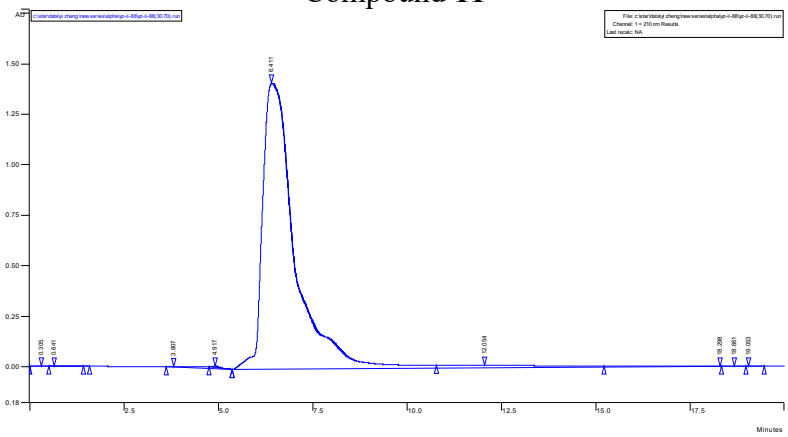
Compound **9**



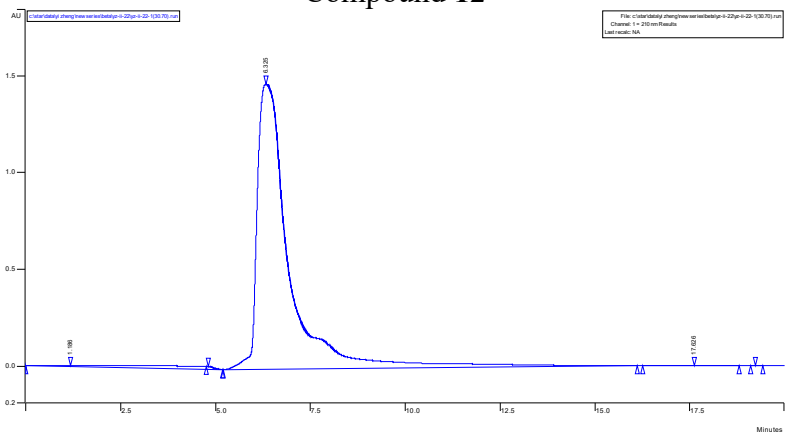
Compound **10**



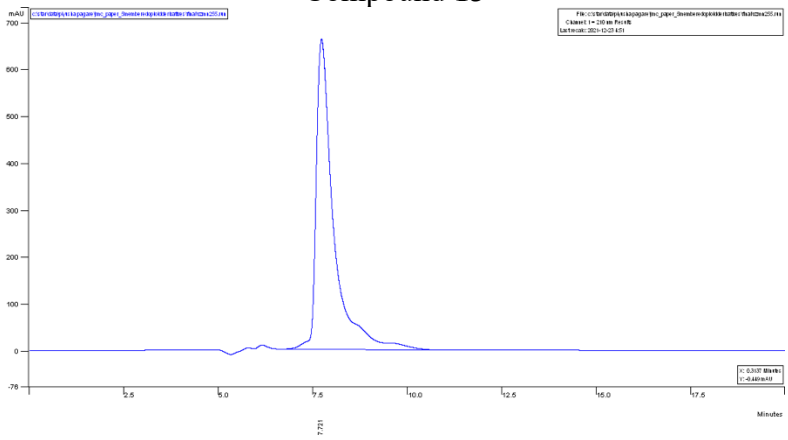
Compound **11**



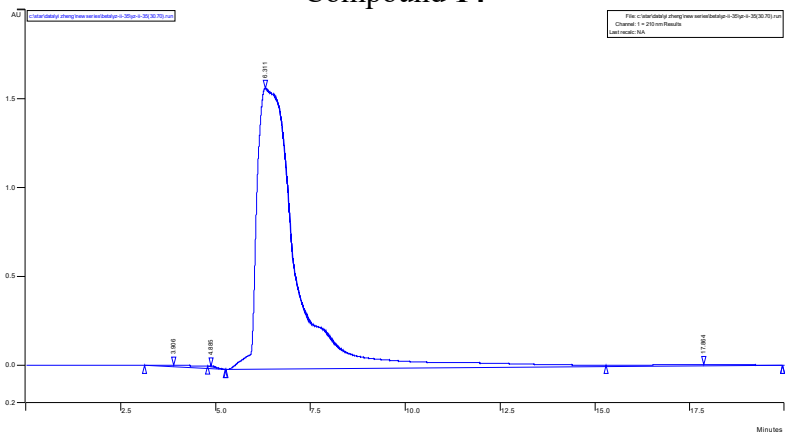
Compound **12**



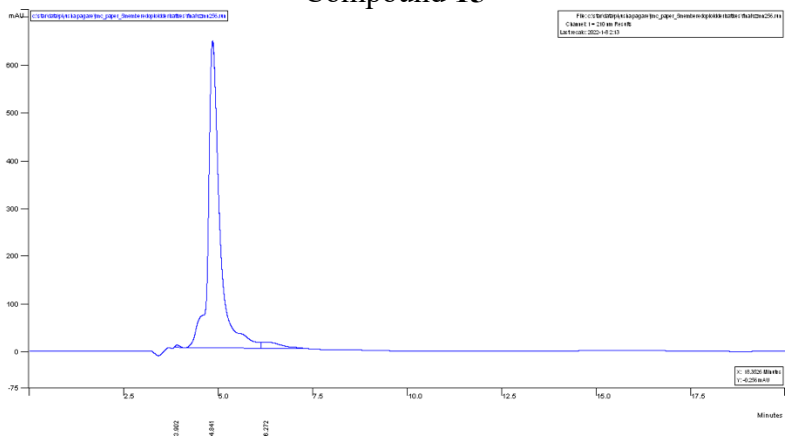
Compound **13**



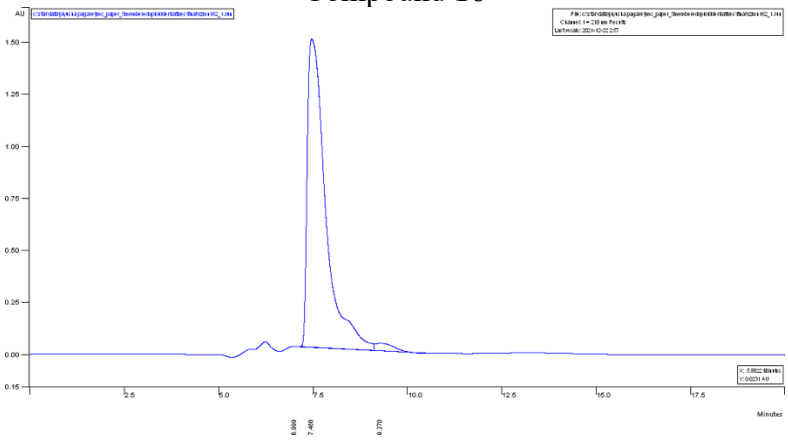
Compound **14**



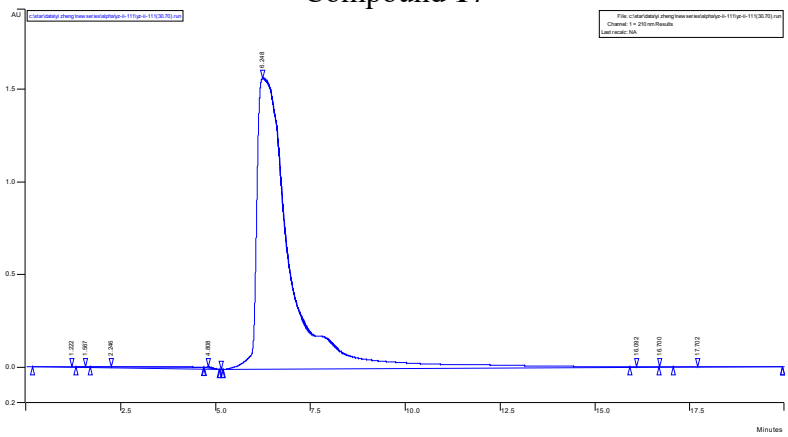
Compound **15**



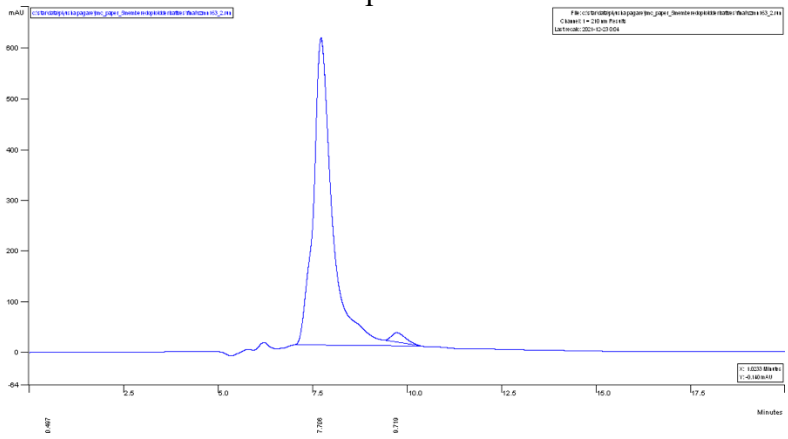
Compound **16**



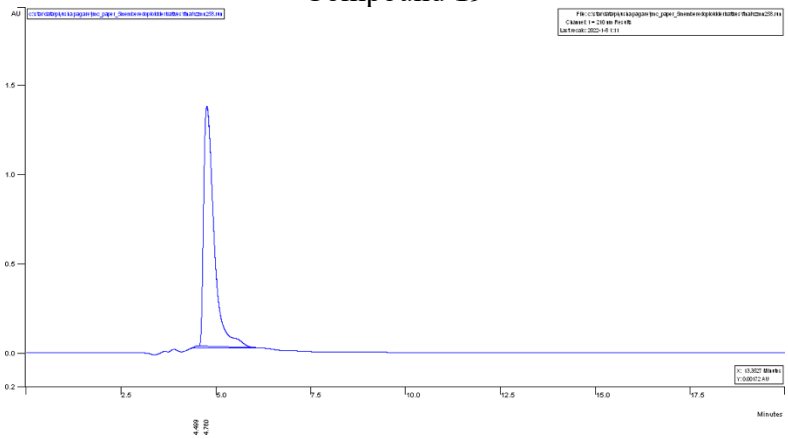
Compound **17**



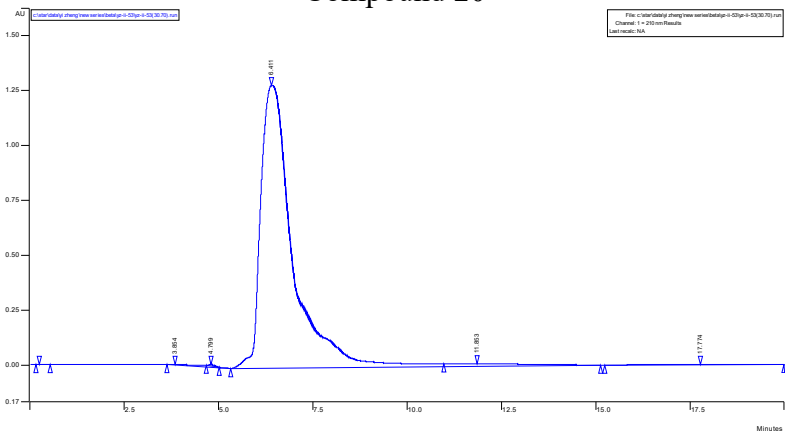
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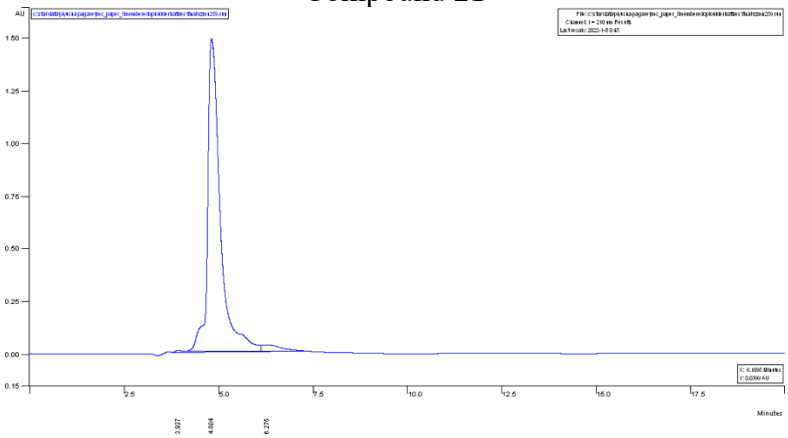
Compound **19**



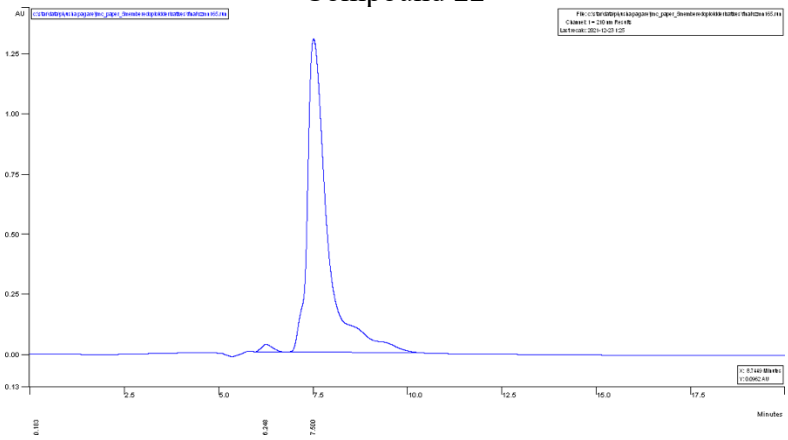
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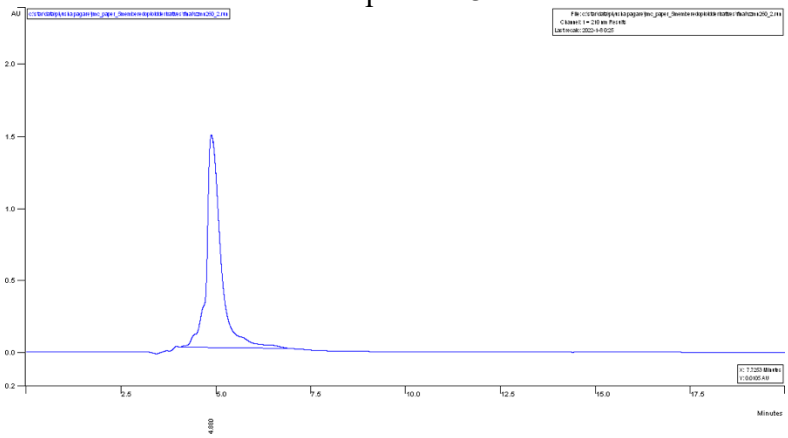
Compound **21**



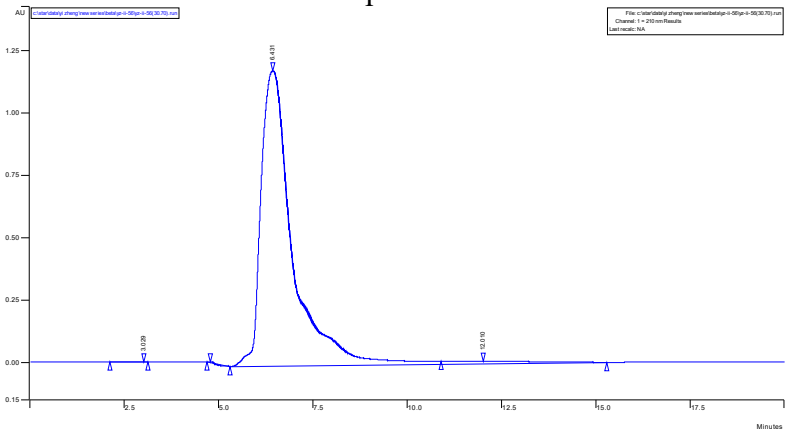
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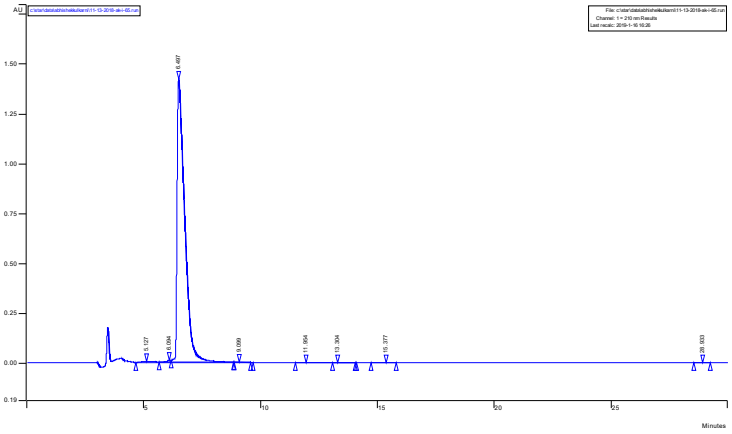
Compound **23**



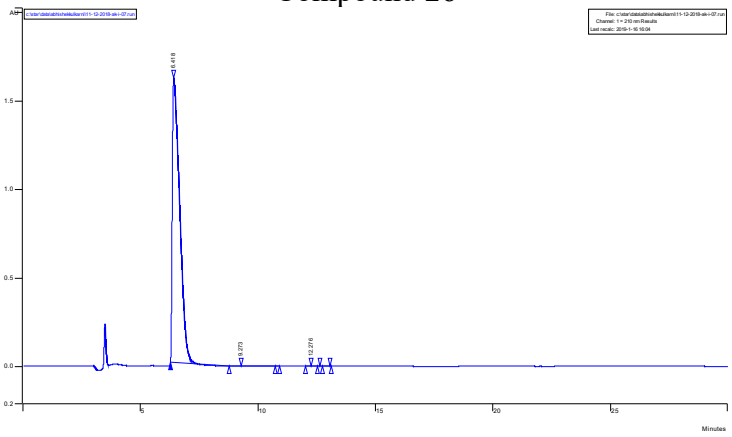
Compound **24**



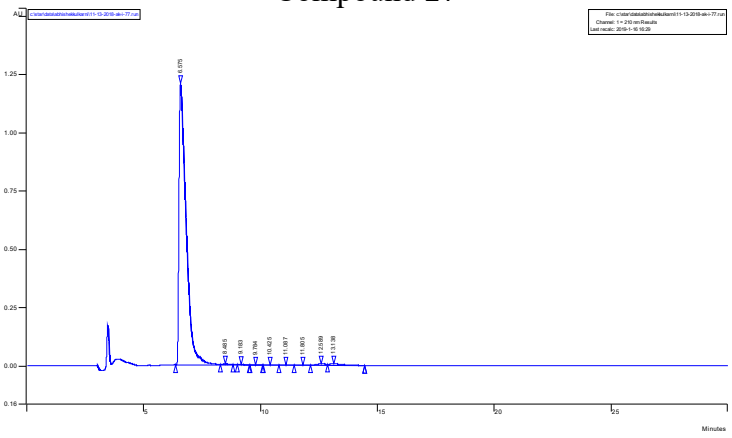
Compound **25**



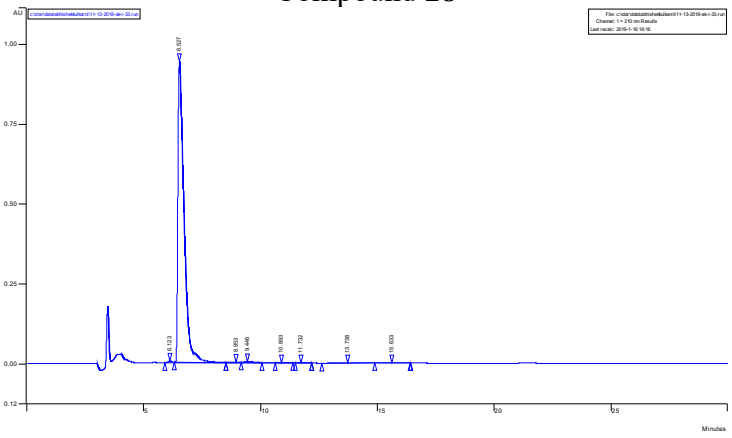
Compound **26**



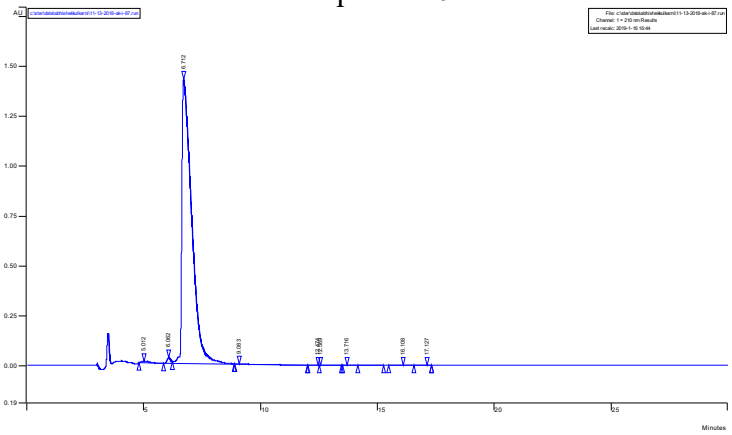
Compound **27**



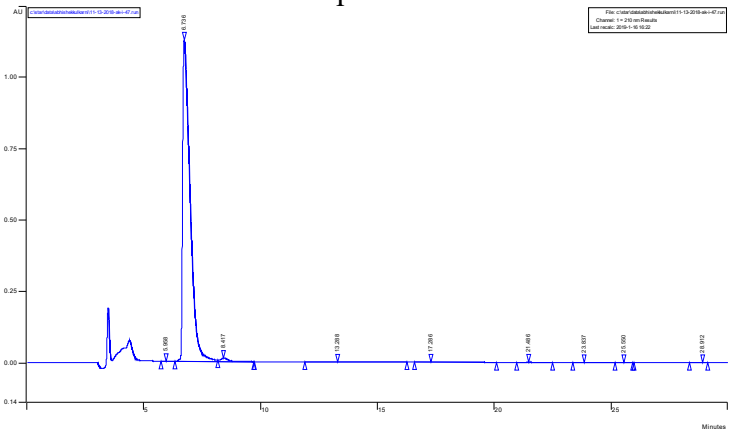
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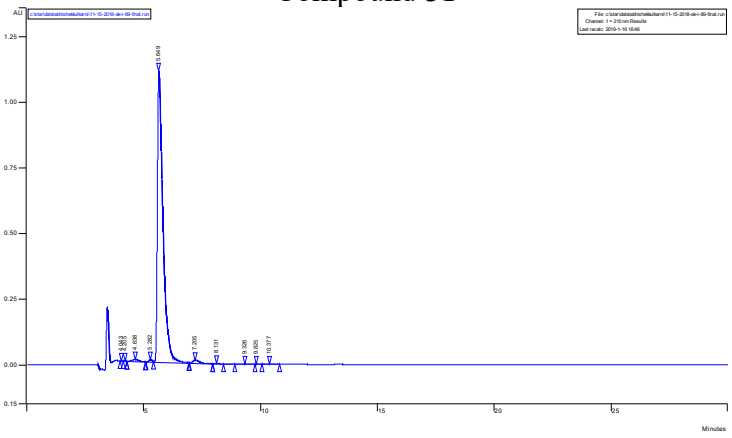
Compound **29**



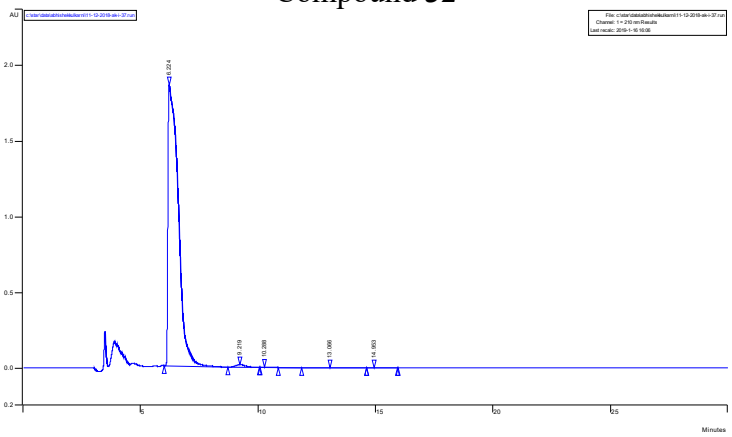
Compound **30**



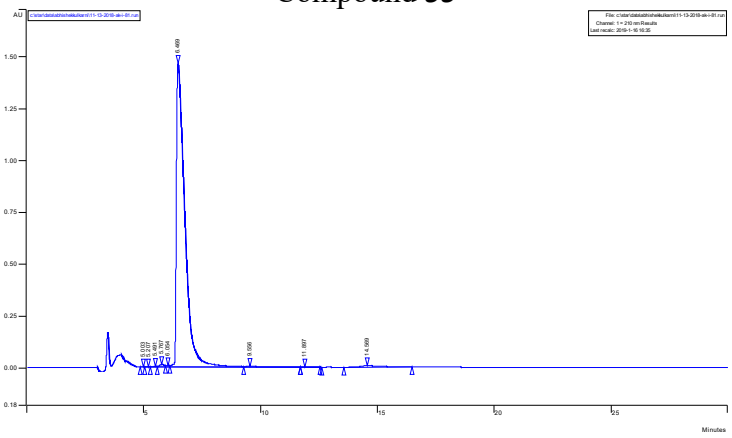
Compound **31**



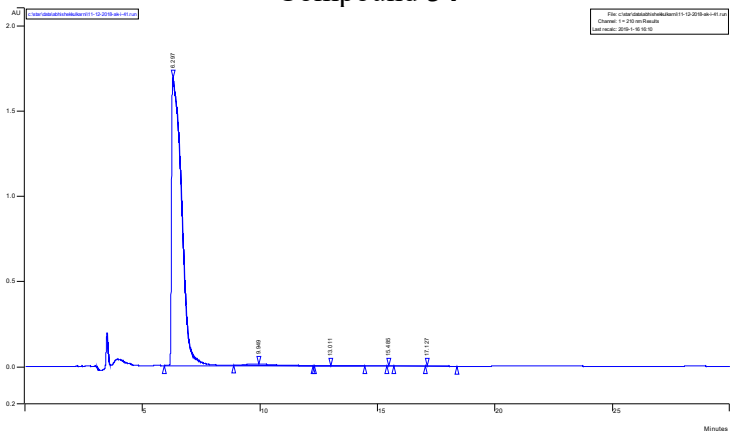
Compound **32**



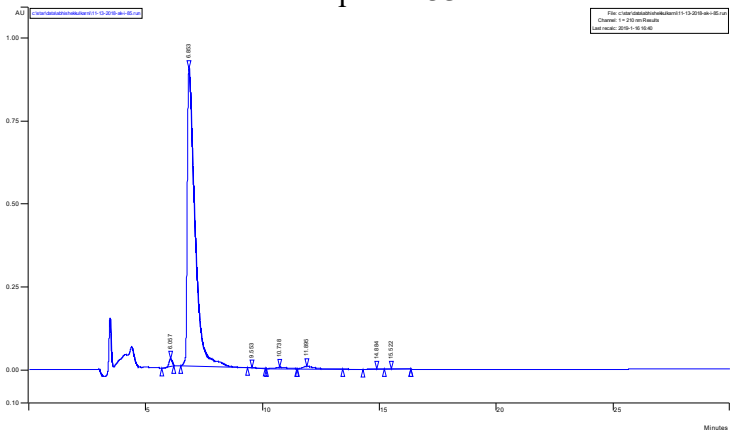
Compound **33**



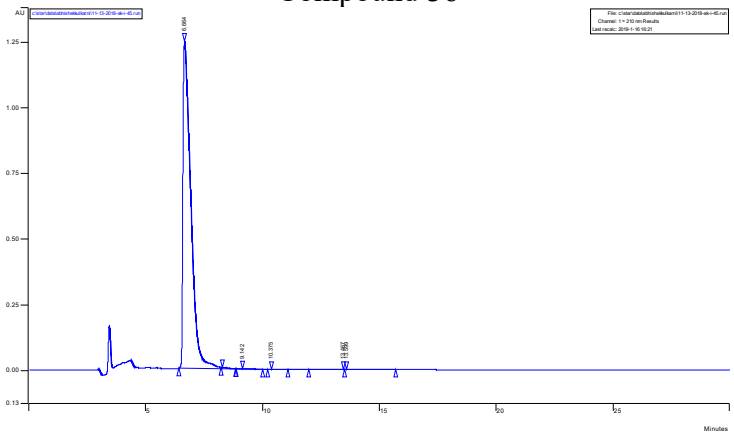
Compound **34**



Compound **35**



Compound **36**



3. **Table S2.** In-silico physicochemical properties prediction of final compounds

Compound	Mol.wt.	cLogP	pKa (Base)	cLogD (pH 7.4)	HBD	HBA	TPSA
NAP	447.54	1.18	7.17	0.98	3	7	94.39
1	435.52	1.71	7.39	1.35	4	7	97.82
2	435.52	1.71	7.39	1.35	4	7	97.82
3	449.54	1.88	7.35	1.02	4	7	97.82
4	449.54	1.88	7.35	1.02	4	7	97.82
5	463.57	2.31	7.37	1.50	4	7	97.82
6	463.57	2.31	7.37	1.50	4	7	97.82
7	435.52	1.71	7.36	0.94	4	7	97.82
8	435.52	1.71	7.36	0.94	4	7	97.82
9	449.54	1.88	7.36	1.01	4	7	97.82
10	449.54	1.88	7.36	1.01	4	7	97.82
11	463.57	2.31	7.37	1.50	4	7	97.82
12	463.57	2.31	7.37	1.50	4	7	97.82
13	436.50	1.99	7.35	1.44	3	7	95.17
14	436.50	1.99	7.35	1.44	3	7	95.17
15	450.53	2.22	7.35	1.50	3	7	95.17
16	450.53	2.22	7.35	1.50	3	7	95.17
17	464.55	2.47	7.37	1.87	3	7	95.17
18	464.55	2.47	7.37	1.87	3	7	95.17
19	436.50	1.99	7.30	1.51	3	7	95.17
20	436.50	1.99	7.30	1.51	3	7	95.17
21	450.53	2.22	7.36	1.50	3	7	95.17
22	450.53	2.22	7.36	1.50	3	7	95.17
23	464.55	2.47	7.37	1.87	3	7	95.17
24	464.55	2.47	7.37	1.87	3	7	95.17
25	452.57	2.77	7.34	2.11	3	6	110.27
26	452.57	2.77	7.34	2.11	3	6	110.27
27	466.59	2.65	7.34	1.92	3	6	110.27
28	466.59	2.65	7.34	1.92	3	6	110.27
29	480.62	3.04	7.37	2.40	3	6	110.27
30	480.62	3.04	7.37	2.40	3	6	110.27
31	452.57	2.77	7.34	2.11	3	6	110.27
32	452.57	2.77	7.34	2.11	3	6	110.27
33	466.59	2.65	7.36	1.92	3	6	110.27
34	466.59	2.65	7.36	1.92	3	6	110.27
35	480.62	3.04	7.37	2.39	3	6	110.27
36	480.62	3.04	7.37	2.39	3	6	110.27

Mol.wt., molecular weight; HBD, hydrogen bond donor; HBA, hydrogen bond acceptor; TPSA, total polar surface area.
Data generated using ACD/Percepta v2020.2.0.

4. **Table S3.** CNS-MPO and LLE calculations of most potent compounds

Compound	CNS-MPO[a]	LLE[b]
NLX	5.5	7.01
NAP	4.4	8.25
1	4.2	7.78
14	4.4	7.53
15	4.3	7.01
16	4.3	7.42
25	3.8	6.66
26	3.8	6.85
31	3.8	6.65
32	3.82	6.83

a. Values calculated using the CNS-MPO calculator
b. LLE = $pK_{i\,(MOR)}$- cLogP