Supplementary materials

Usnic acid derivative as novel hypoglycemic agent: synthesis and pharmacological evaluation

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Chemistry

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ with solvent resonances (H 7.24, C 76.90 ppm) as internal standards on a Bruker AV-400 spectrometer (operating frequency 400.13 MHz for ^{1}H and 100.61 MHz for ^{13}C). Mass spectra (ionizing-electron energy 70 eV) were recorded on a DFS high-resolution mass spectrometer (Thermo Scientific). Atomic numbering in compounds is given for assignment of resonances in NMR spectra and does not always agree with the nomenclature numbering.

Synthesis of usnic acid enamine derivatives

Compound **2** was synthesized from (+)-UA in according to [1] with the yield of 95%.

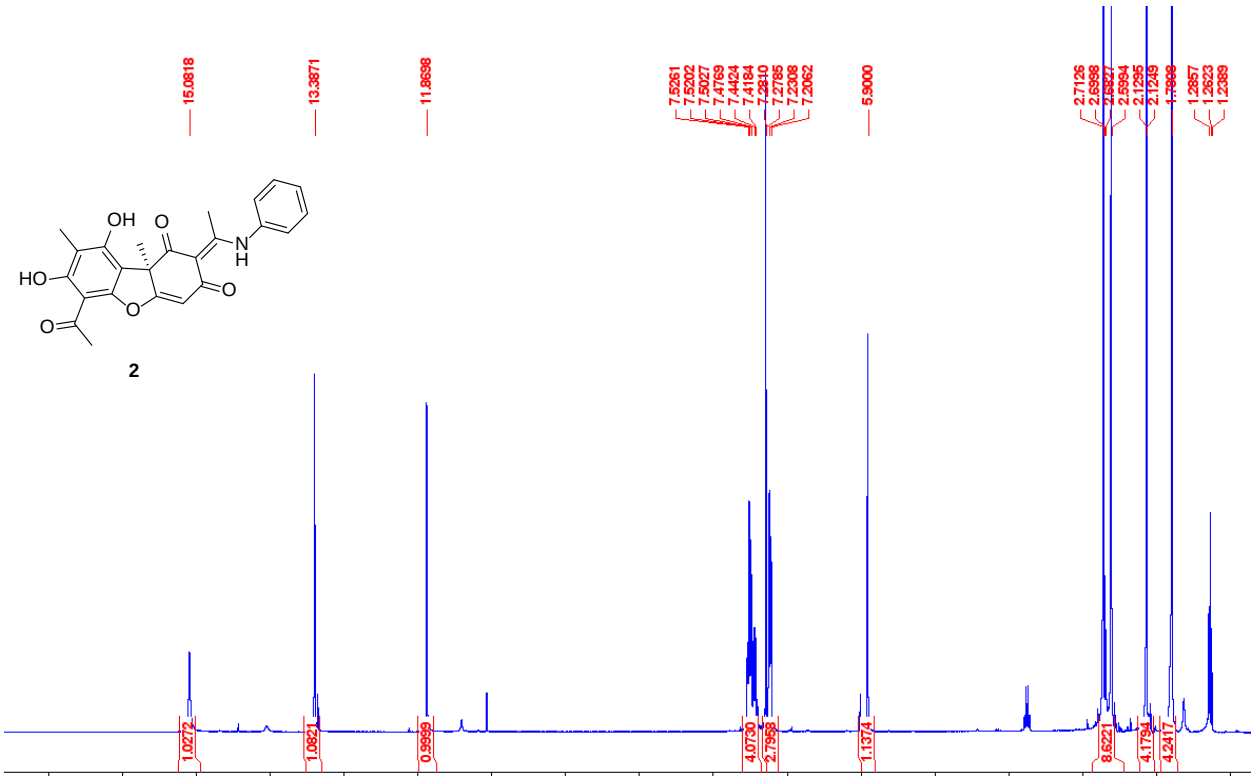


Figure S1. The ^{1}H NMR spectrum of compound **2.**

Compound **3** was synthesized from (+)-UA in according to [2] with the yield of 70%.

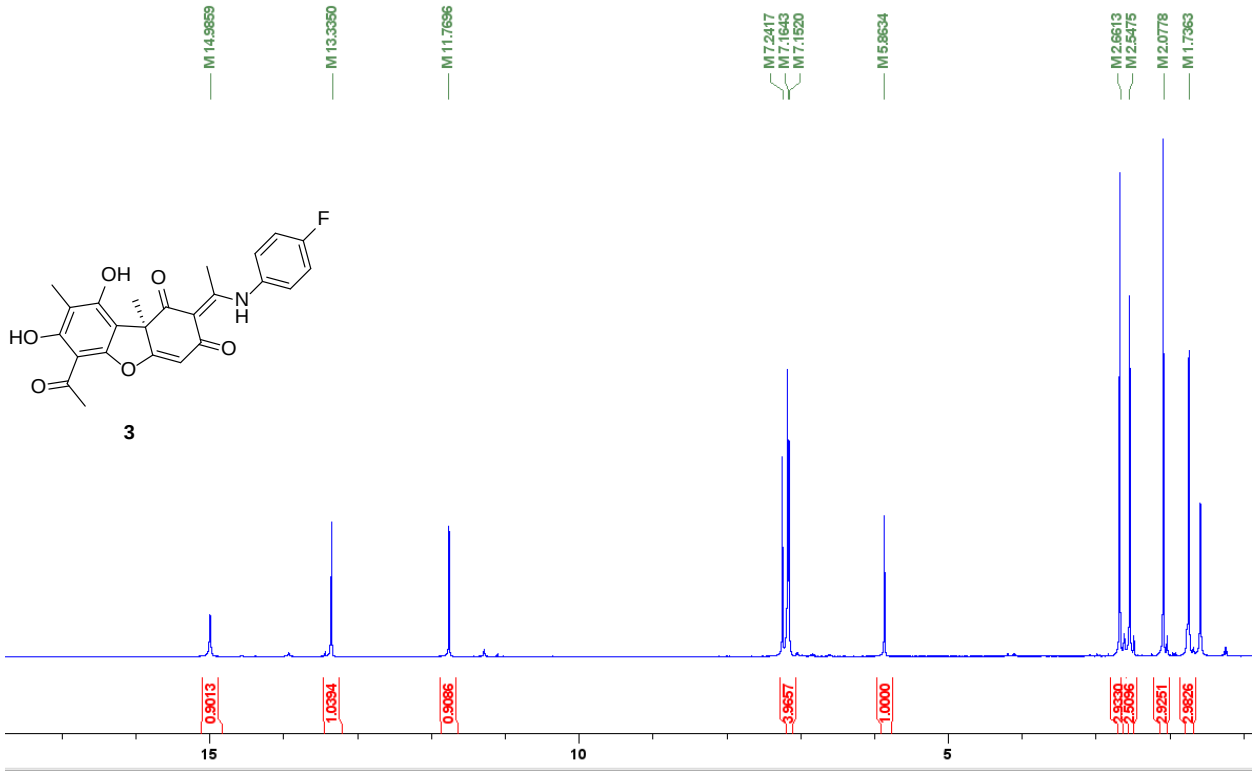


Figure S2. The ^{1}H NMR spectrum of compound **3.**

Compounds **4** and **5** were synthesized from (+)-UA in according to [3] with the yields of 87% each.

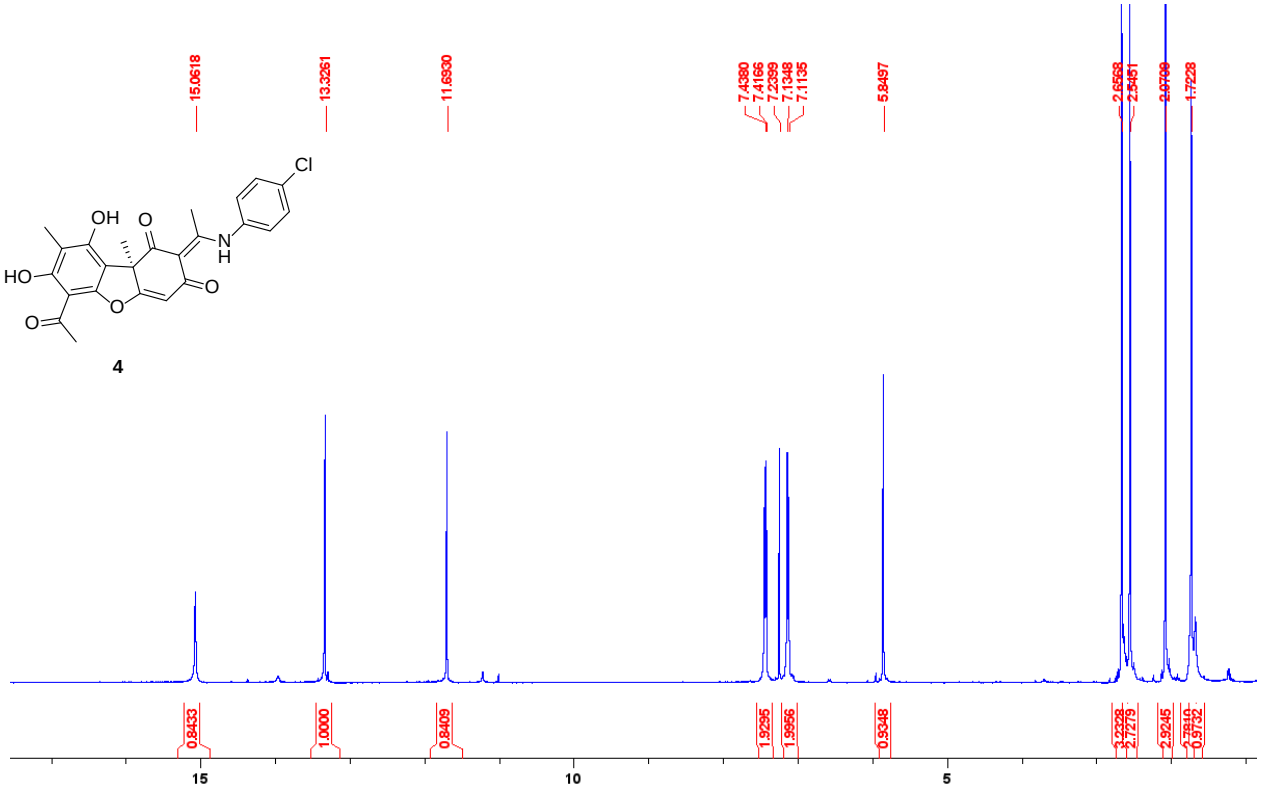


Figure S3. The ^{1}H NMR spectrum of compound **4.**

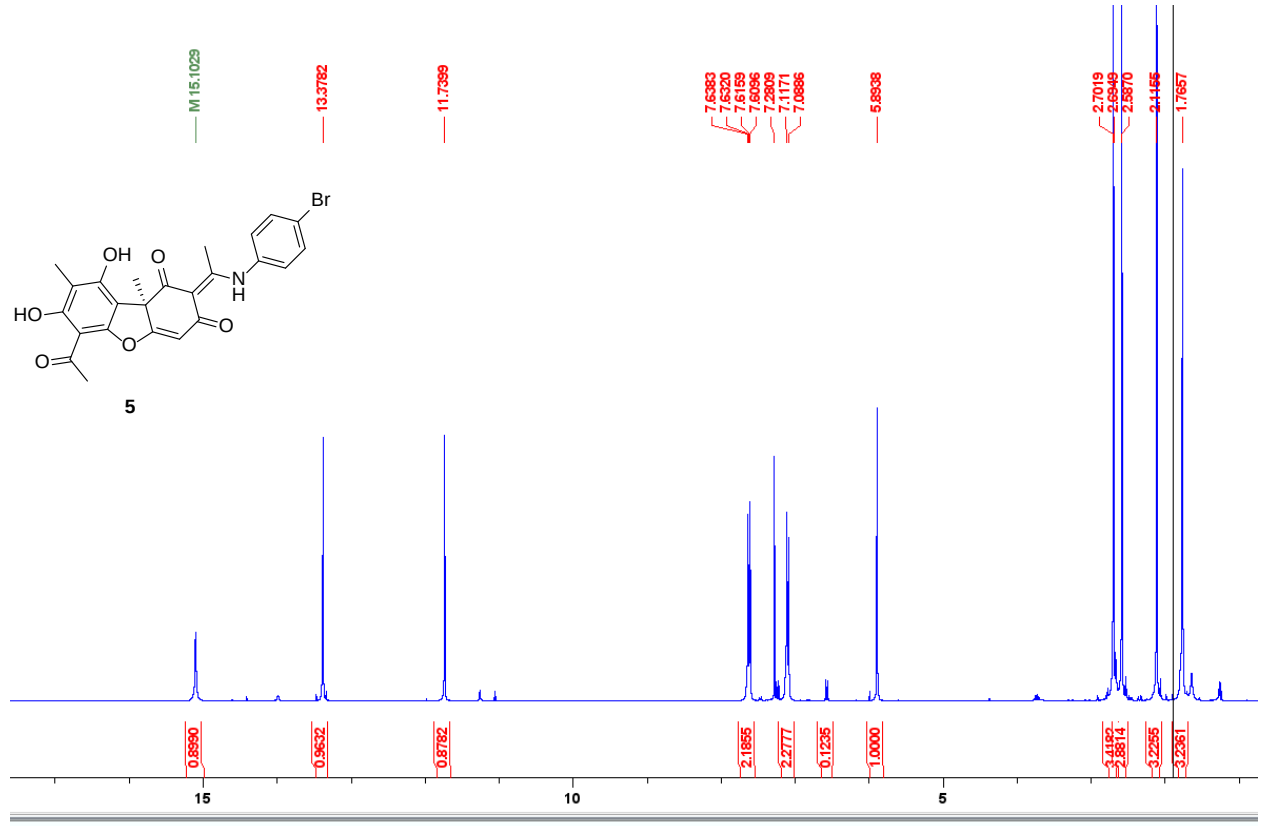


Figure S4. The ^{1}H NMR spectrum of compound **5.**

Synthesis of compounds **6** and **7**

(+)-UA (1 mmol) was treated with appropriate aniline (3 mmol), dissolved in ethanol (12 mL), refluxed on a water bath for 40 h (reaction with 4-trifluoromethylaniline) or 6 h (reaction with 4-methylaniline), cooled, and treated with distilled water (10 mL) and 1M HCl up to pH 5. A white precipitate formed was filtered off, washed with water, and dried in air. The precipitate was separated using column chromatography over silica gel with elution by $CHCl_3$ with an ethyl acetate gradient from 0 to 20% to afford **6** or **7**.

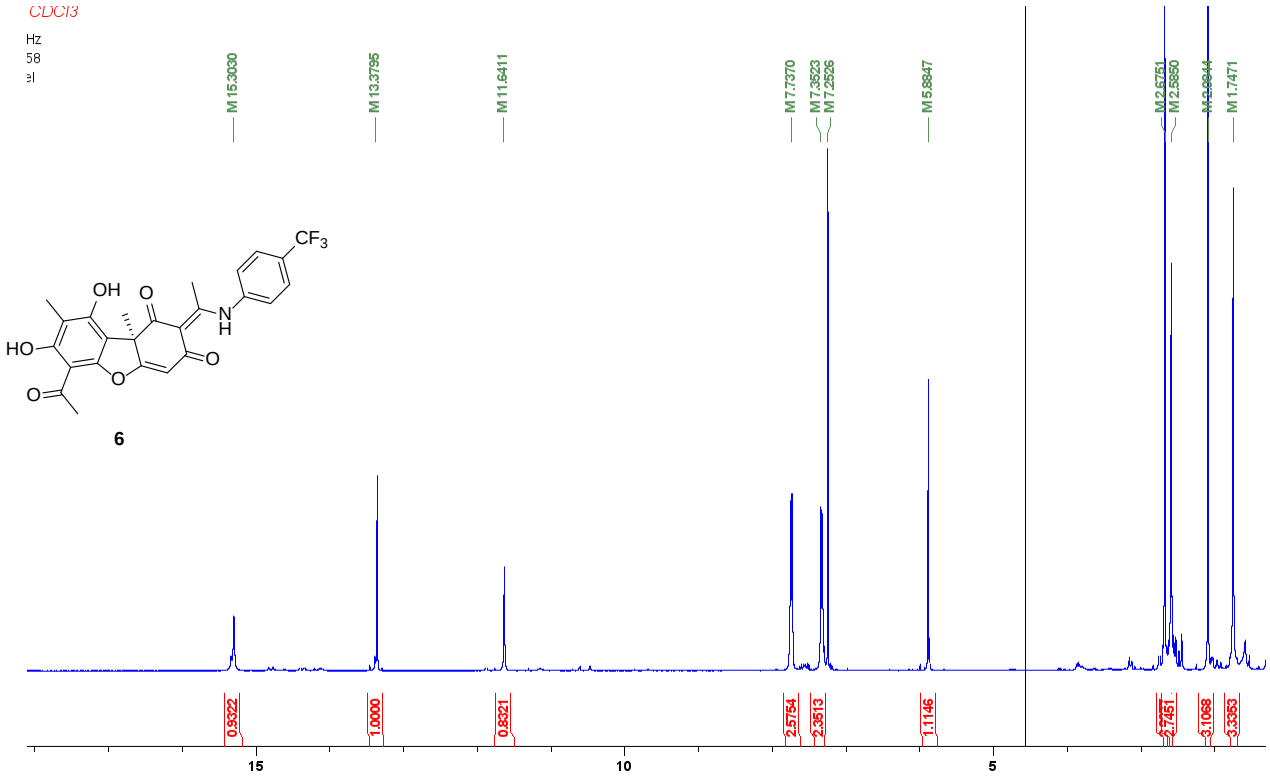


Figure S5. The ^{1}H NMR spectrum of compound 6.

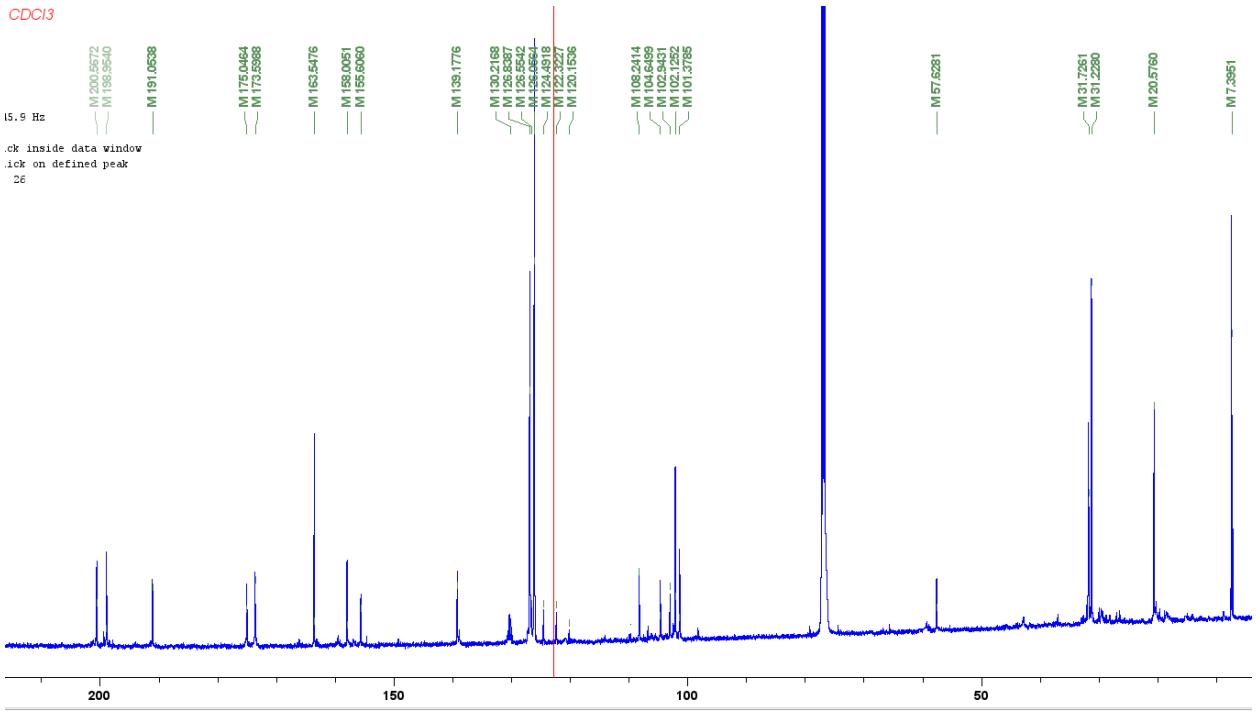
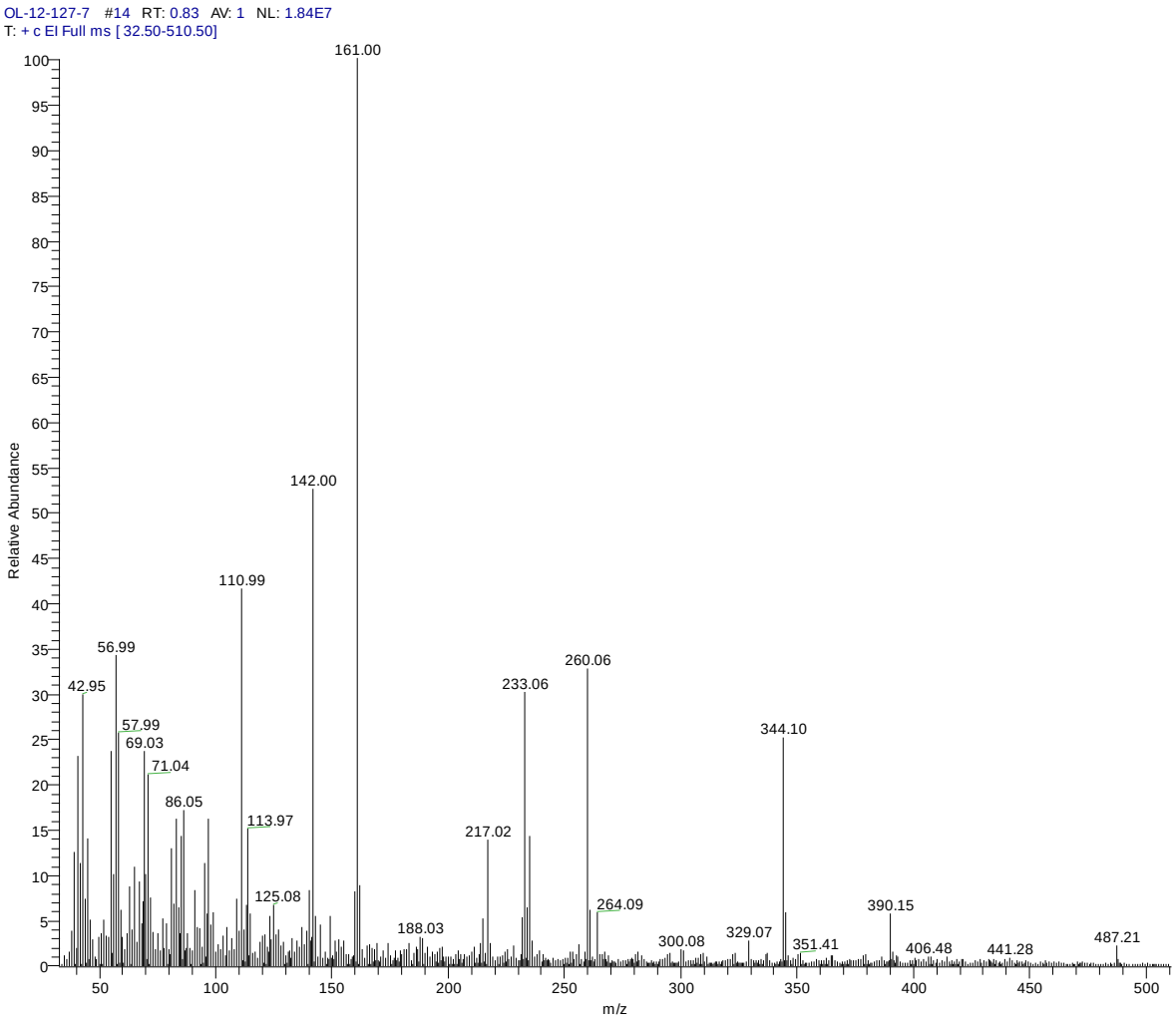


Figure S6. The ^{13}C NMR spectrum of 6

Tsource=70˚C

Tprobe=200˚C



m/z	Intensity	Relative
38.92	2280049.0	12.39
40.93	4239947.0	23.04
41.93	2070071.0	11.25
42.91	3801182.0	20.65
42.95	5488568.0	29.82
44.93	2559688.0	13.91
54.96	4342001.0	23.59
55.97	1825745.0	9.92
56.99	6289048.0	34.17
57.99	4723693.0	25.66
64.99	1994334.0	10.84
67.01	1691037.0	9.19
69.03	4332771.0	23.54
70.04	1843445.0	10.02
71.04	3859336.0	20.97
81.03	2370156.0	12.88
83.05	2974649.0	16.16

85.06	2625202.0	14.26
86.05	3128839.0	17.00
95.03	2055204.0	11.17
97.05	2958526.0	16.07
110.99	7642964.0	41.52
111.06	1902124.0	10.33
113.97	2752228.0	14.95
142.00	9667840.0	52.53
161.00	18405888.0	100.00
217.02	2550429.0	13.86
233.06	5527386.0	30.03
235.04	2622106.0	14.25
260.06	6022581.0	32.72
264.09	1067559.0	5.80
265.08	212051.0	1.15
266.28	200981.0	1.09
267.29	254636.0	1.38
269.01	186844.0	1.02
280.30	216666.0	1.18
281.31	262172.0	1.42
283.05	186202.0	1.01
294.32	204165.0	1.11
295.33	240003.0	1.30
300.08	322370.0	1.75
301.07	282063.0	1.53
308.34	206560.0	1.12
309.35	243187.0	1.32
322.36	203376.0	1.10
323.37	228962.0	1.24
329.07	491632.0	2.67
336.38	213336.0	1.16
337.39	231708.0	1.26
344.10	4615915.0	25.08
345.10	1074160.0	5.84
350.40	204603.0	1.11
351.41	229985.0	1.25
364.42	185939.0	1.01
378.43	195256.0	1.06
379.44	221719.0	1.20
390.15	1027397.0	5.58
391.15	257616.0	1.40
392.46	187399.0	1.02
487.21	395741.0	2.15
488.21	105762.0	0.57

M^+ calc **m/z= 487.1237 $(C_{25}H_{20}O_6N_1F_3)^{+\cdot}$**

M^+ meas **m/z= 487.1238**

Figure S7. The DFS spectrum of 6.

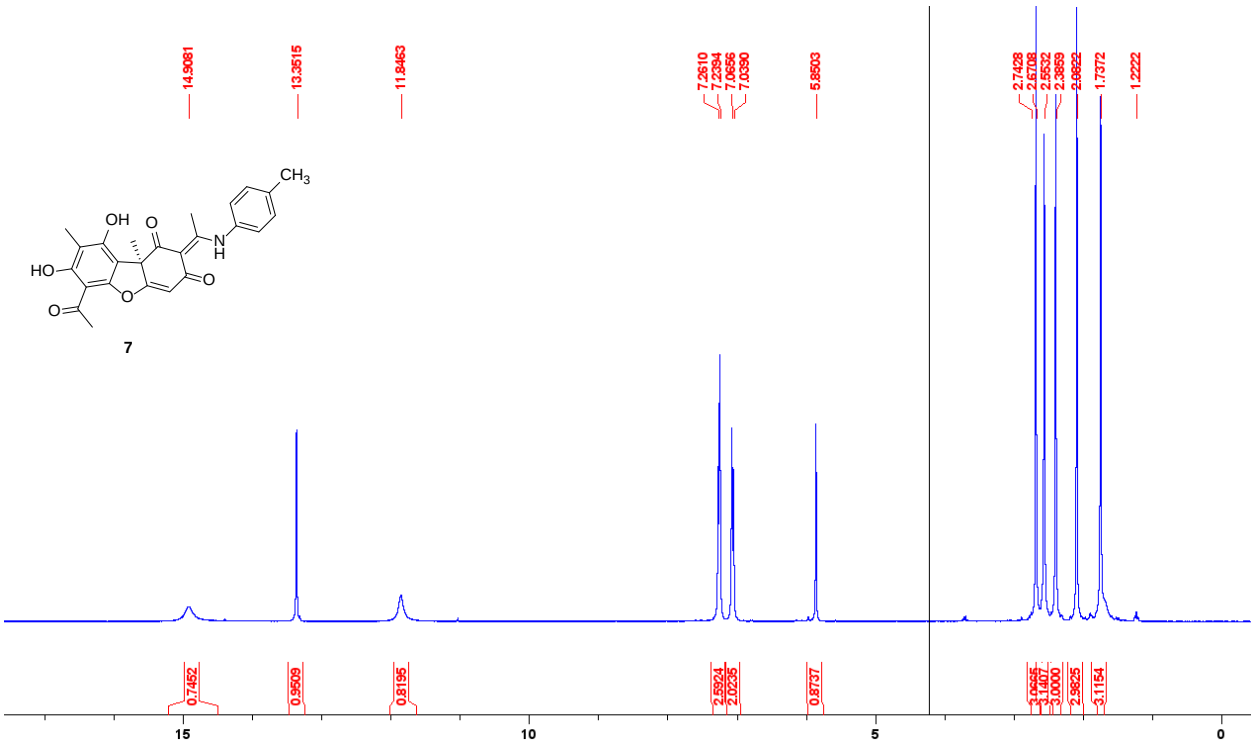


Figure S8. The ^{1}H NMR spectrum of compound **7.**

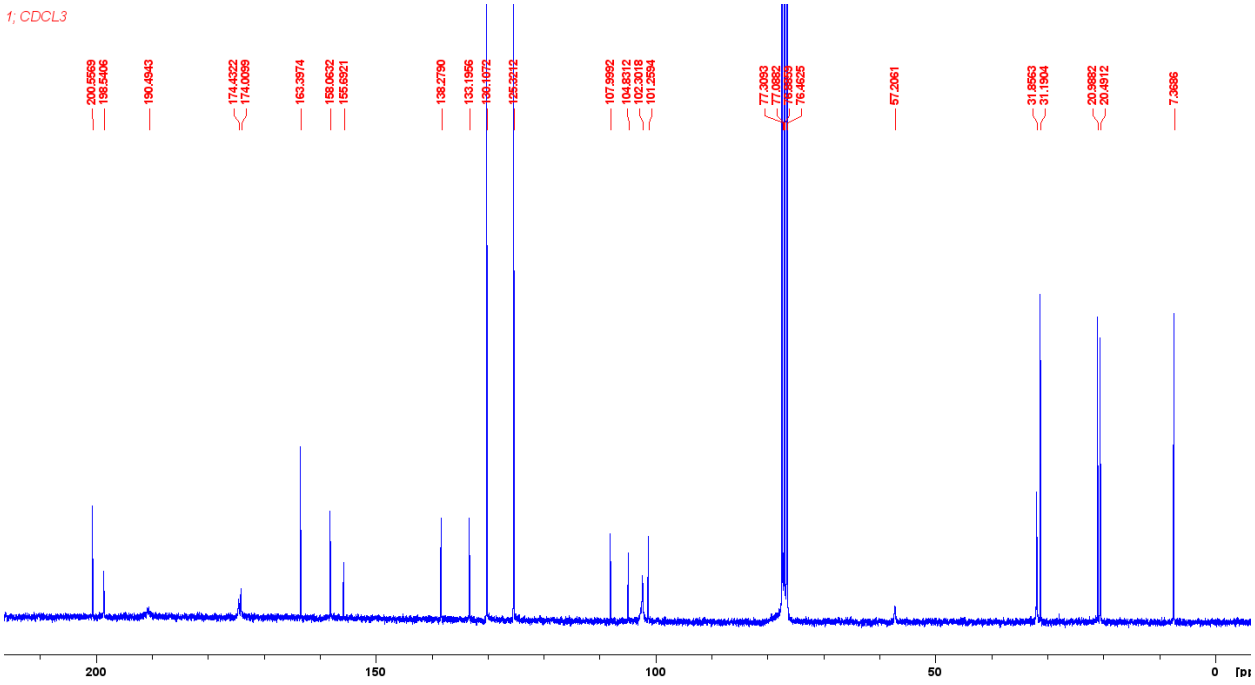
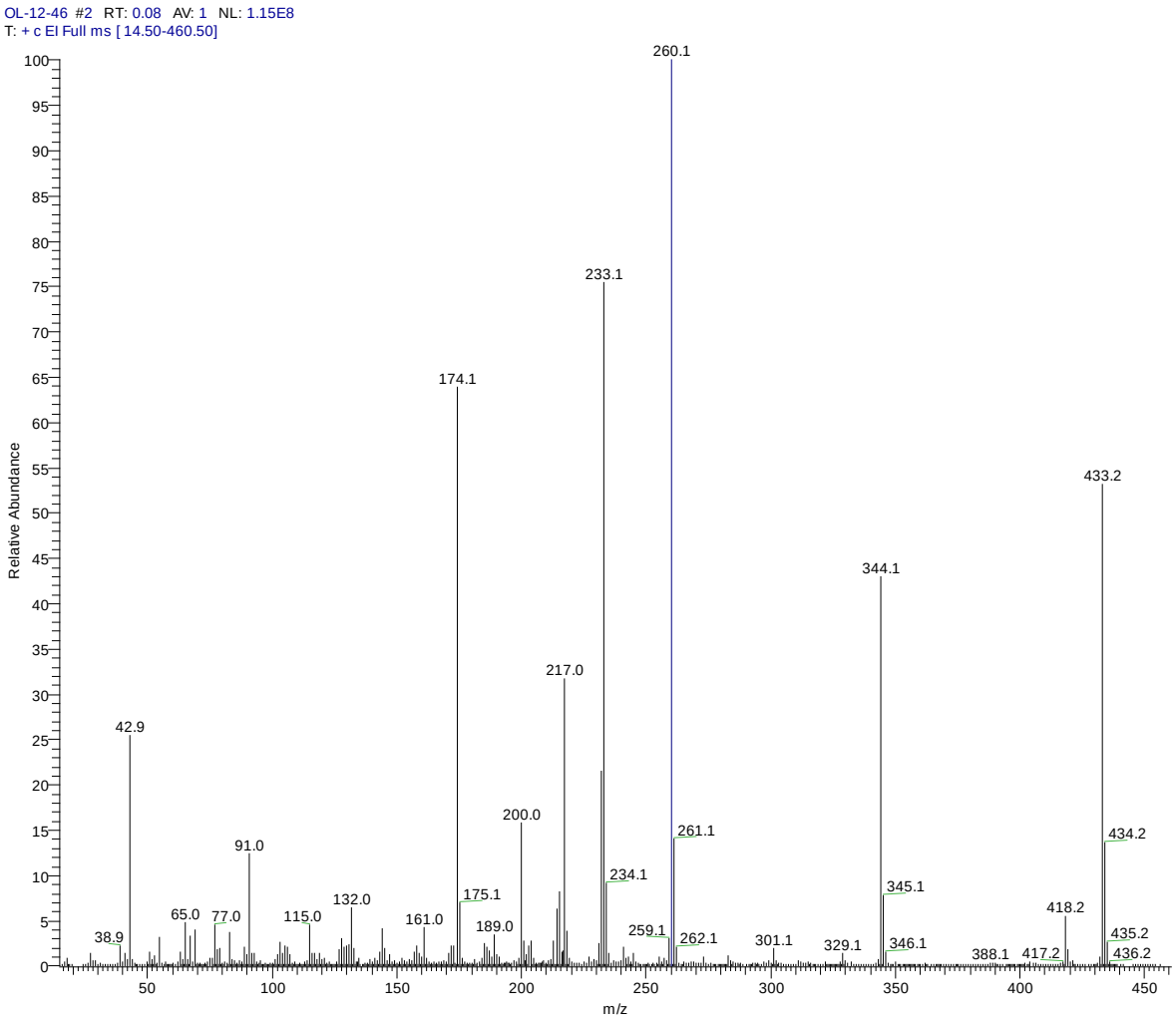


Figure S9. The ^{13}C NMR spectrum of **7**

Tsource=70˚C

Tprobe=250˚C



m/z	Intensity	Relative
42.9	29094656.0	25.37
54.9	3483748.0	3.04
65.0	5320831.0	4.64
67.0	3623530.0	3.16
69.0	4499410.0	3.92
77.0	5111967.0	4.46
83.0	4086479.0	3.56
91.0	14037248.0	12.24
103.0	2904379.0	2.53
105.0	2474059.0	2.16
115.0	5132121.0	4.48
128.0	3277621.0	2.86
130.0	2384000.0	2.08
131.0	2624815.0	2.29
132.0	7217669.0	6.29
144.0	4646695.0	4.05

161.0	**4773413.0**	**4.16**
172.0	**2492124.0**	**2.17**
173.0	**2414981.0**	**2.11**
174.1	**73205248.0**	**63.84**
175.1	**7879124.0**	**6.87**
185.0	**2759213.0**	**2.41**
189.0	**3856314.0**	**3.36**
200.0	**18016768.0**	**15.71**
201.0	**3059666.0**	**2.67**
203.0	**2393414.0**	**2.09**
204.1	**2994379.0**	**2.61**
213.0	**3112948.0**	**2.71**
214.0	**7137848.0**	**6.22**
215.0	**9333504.0**	**8.14**
217.0	**36211200.0**	**31.58**
218.0	**4300197.0**	**3.75**
231.1	**2684158.0**	**2.34**
232.1	**24475392.0**	**21.34**
233.1	**86436096.0**	**75.38**
234.1	**10307072.0**	**8.99**
259.1	**3388540.0**	**2.95**
260.1	**114672640.0**	**100.00**
261.1	**15982848.0**	**13.94**
344.1	**49152512.0**	**42.86**
345.1	**8761600.0**	**7.64**
418.2	**6185619.0**	**5.39**
433.2	**60917504.0**	**53.12**
434.2	**15455488.0**	**13.48**
435.2	**2865484.0**	**2.50**

Вычисление элементных составов

M^+ calc **m/z= 433.1520 $(C_{25} H_{23} O_6 N_1)^{+\cdot}$**
M^+ meas **m/z= 433.1521**

Figure S10. The DFS spectrum of 7.

1 Zakharenko A, Sokolov D, Luzina O, Sukhanova M, Khodyreva S, Zakharova O, Salakhutdinov N, Lavrik O. Influence of Usnic Acid and its Derivatives on the Activity of Mammalian Poly(ADP-ribose)polymerase 1 and DNA Polymerase β. Med Chem, 2012; 8: 883-893. doi: 10.2174/1573406411309050013

2 Sokolov DN, Zarubaev VV, Shtro AA, Luzina OA, Komarova NI, Salakhutdinov NF, Kiselev OI. Anti-viral activity of (-)- and (+)-usnic acids and their derivatives against influenza virus A(H1N1)2009. Bioorg Med Chem Lett, 2012; 22: 7060-7064. doi: 10.1016/j.bmcl.2012.09.084

3 Tazetdinova AA, Luzina OA, Polovinka MP, Salakhutdinov NF, Tolstikov GA. Amino-derivatives of usninic acid. Chem Nat Compd. 2009; 45: 800-804. https://doi.org/10.1007/s10600-010-9502-z