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Supplementary information

SYNTHESIS, CYTOTOXIC AND ANTIOXIDANT ACTIVITY OF NEW 1,3-DIMETHYL-8-(CHROMON-3-YL)-XANTHINE DERIVATIVES CONTAINING 2,6-DI-TERT-BUTYLPHENOL FRAGMENT

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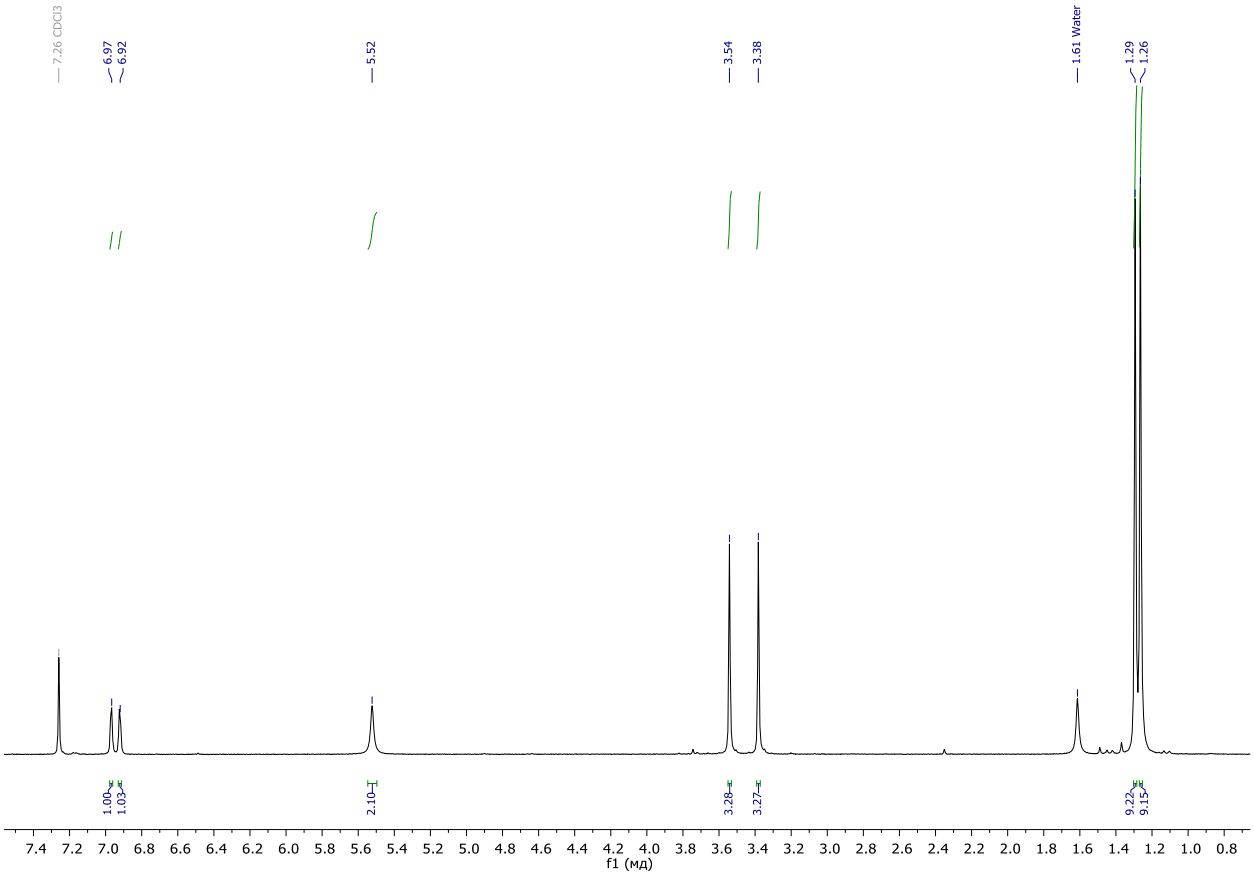


Figure S1. ^{1}H NMR (400 MHz) spectrum of **1** in $CDCl_3$**.**

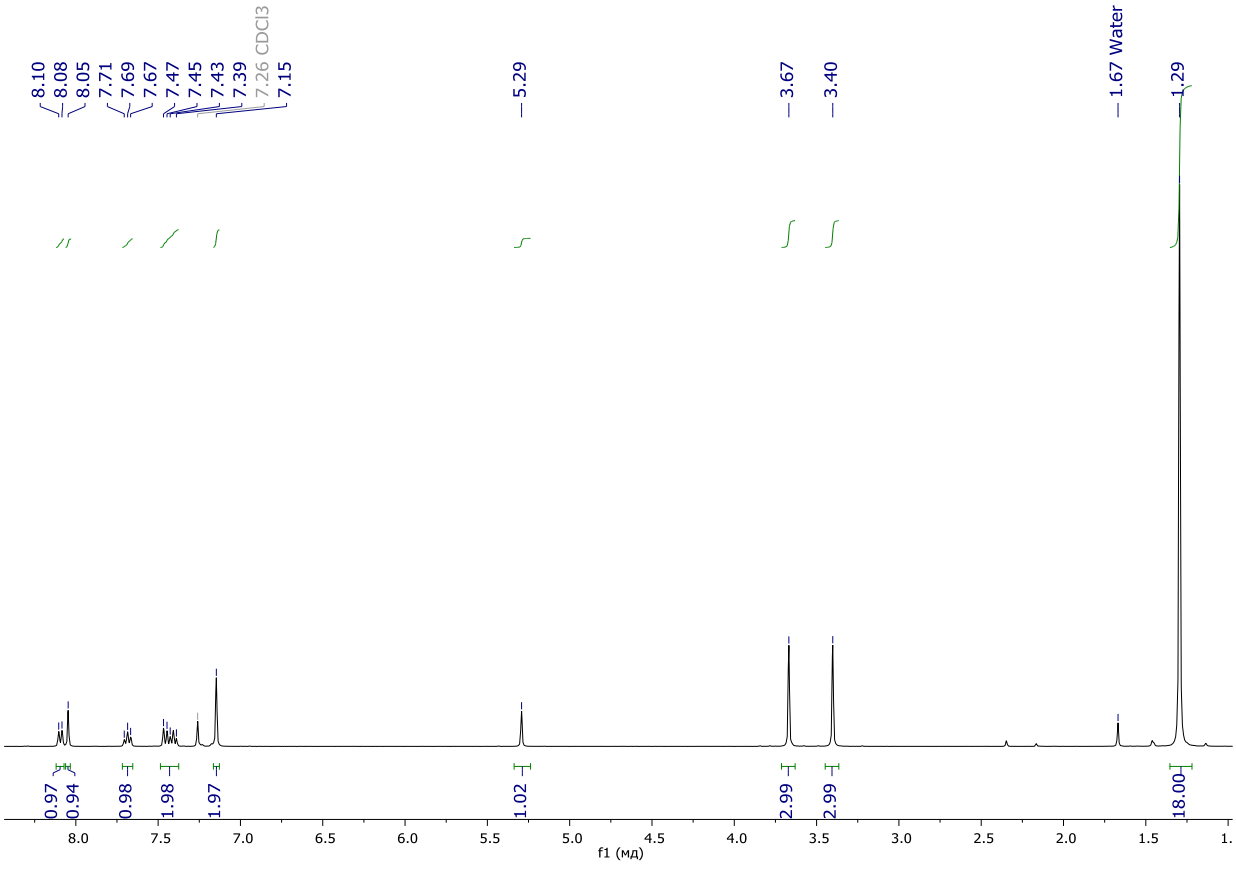


Figure S2. ^{1}H NMR (400 MHz) spectrum of **2** in $CDCl_3$**.**

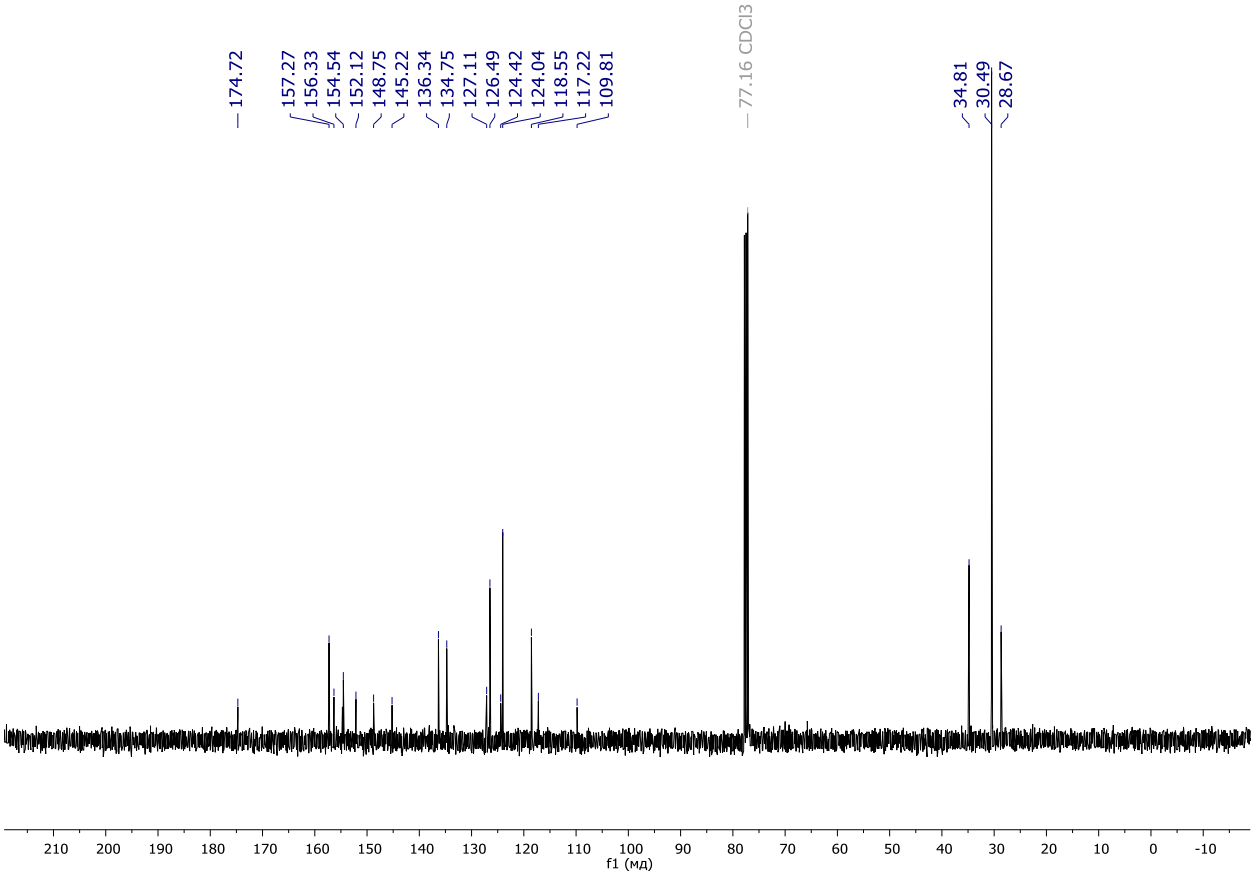


Figure S3. ^{13}C NMR (101 MHz) spectrum of **2** in $CDCl_3$**.**

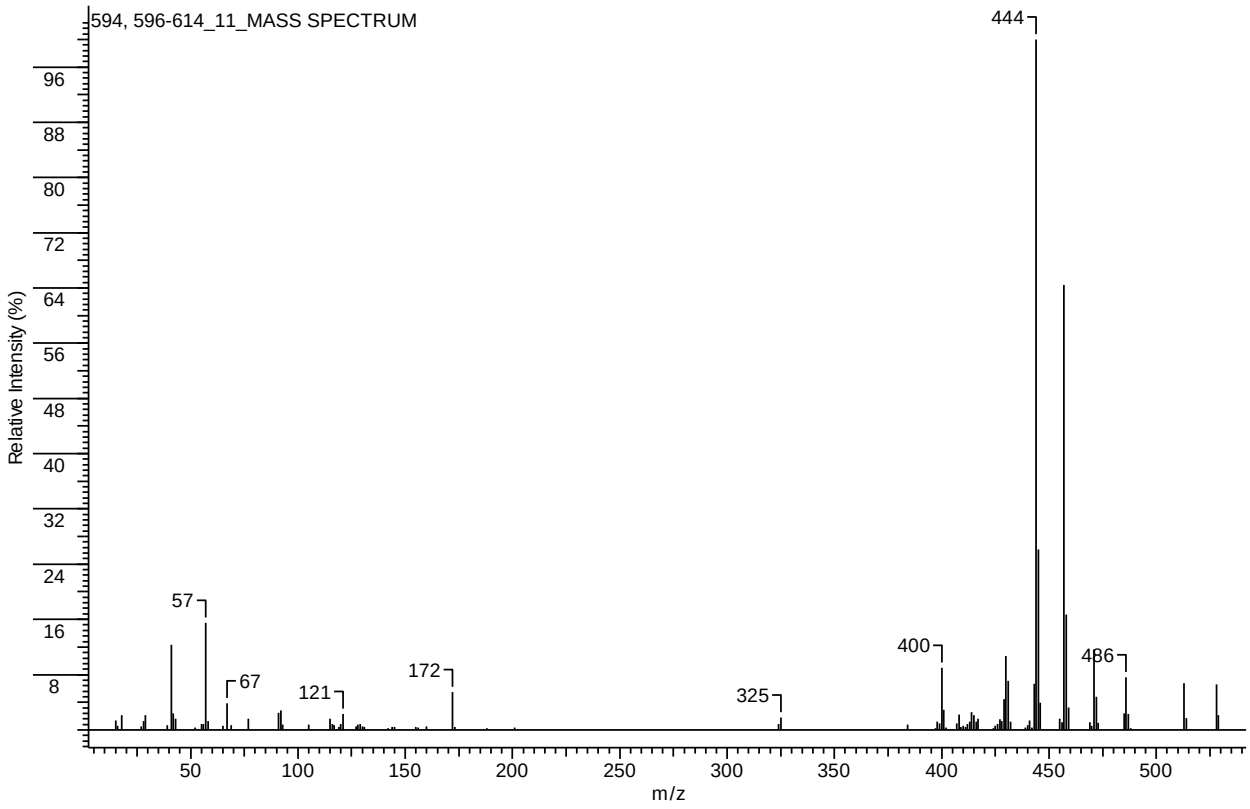


Figure S4. ESI-MS spectrum of **2**.

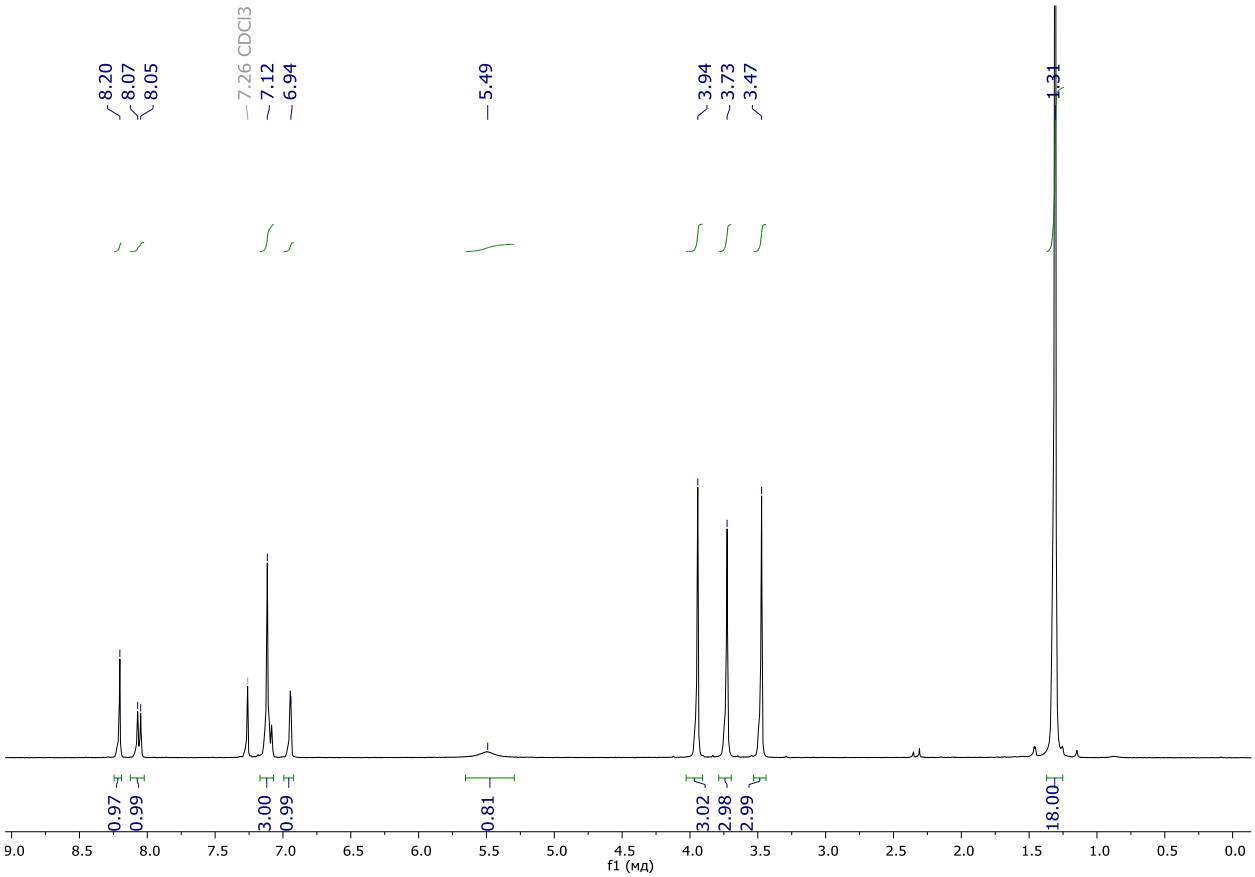


Figure S5. ^{1}H NMR (400 MHz) spectrum of **3** in $CDCl_3$**.**

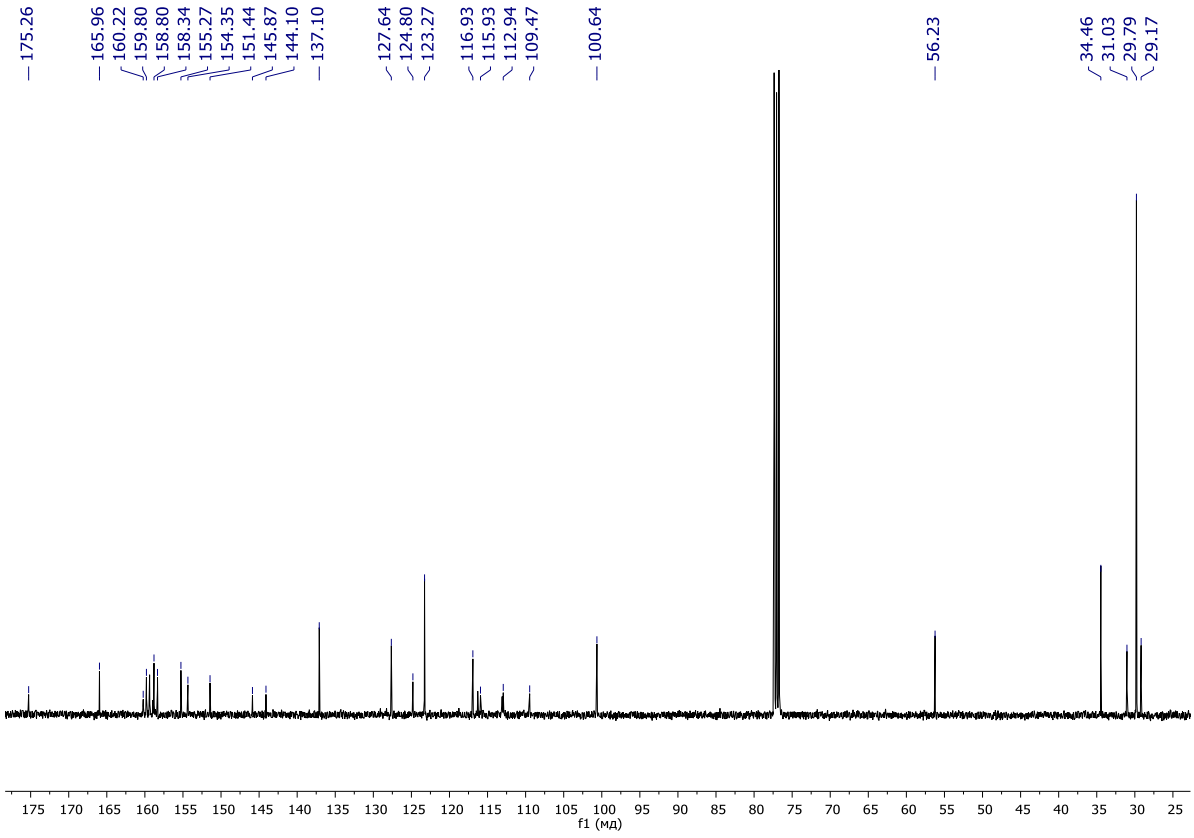


Figure S6. ^{13}C NMR (101 MHz) spectrum of **3** in $CDCl_3$**.**

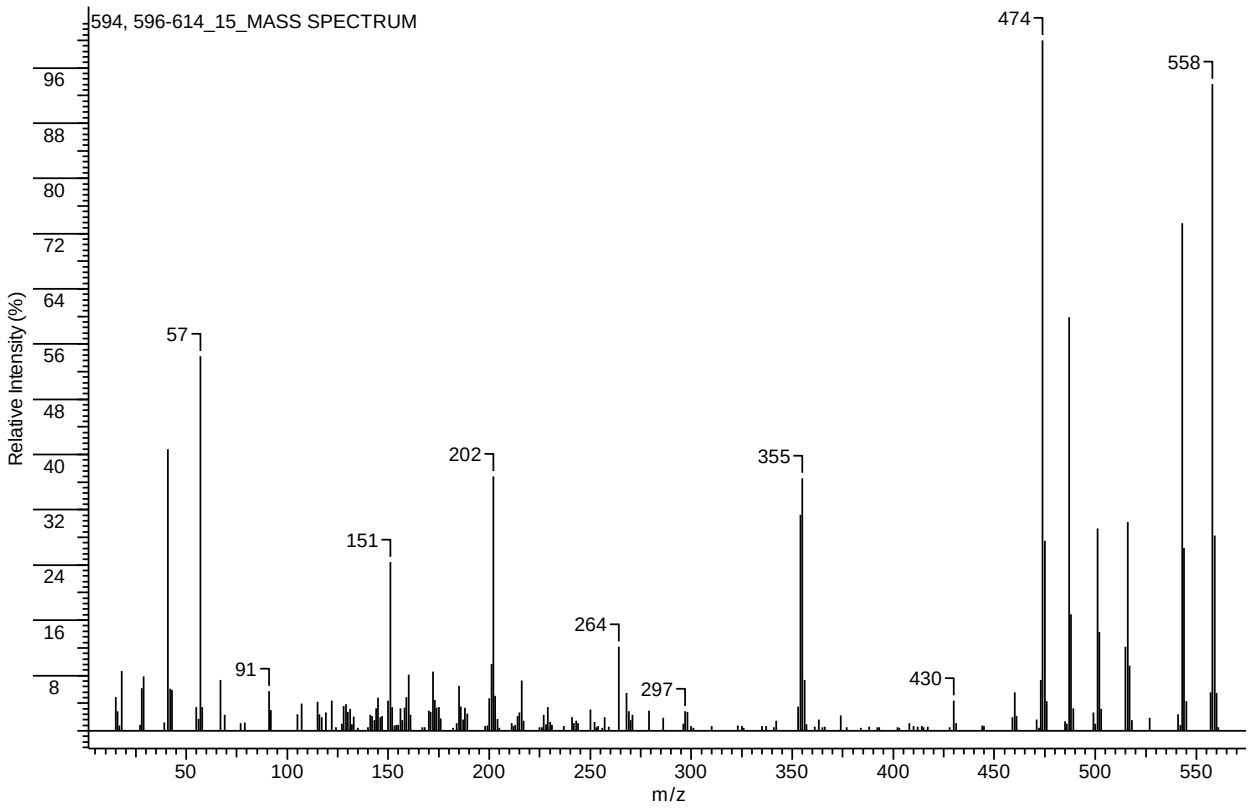


Figure S7. ESI-MS spectrum of **3**.

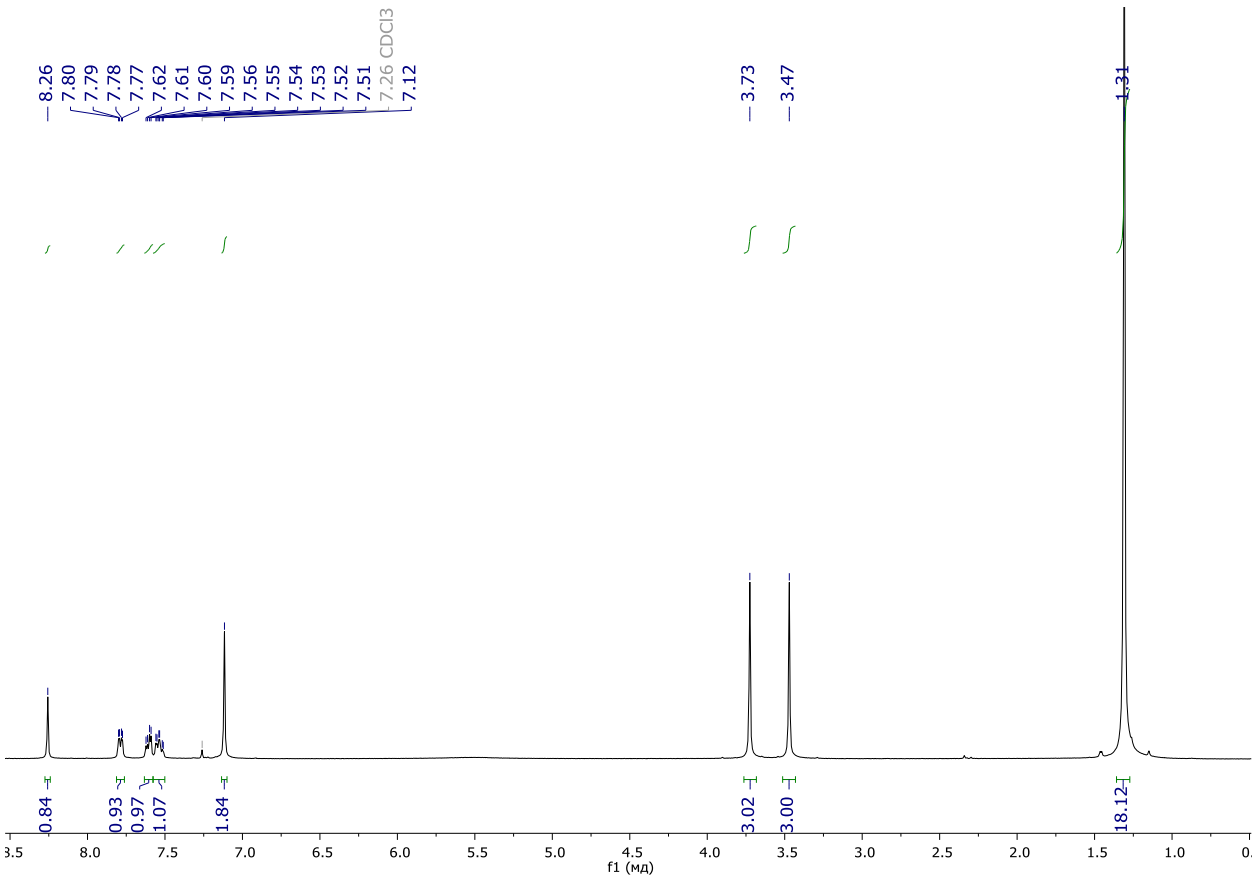


Figure S8. ^{1}H NMR (400 MHz) spectrum of **4** in $CDCl_3$**.**

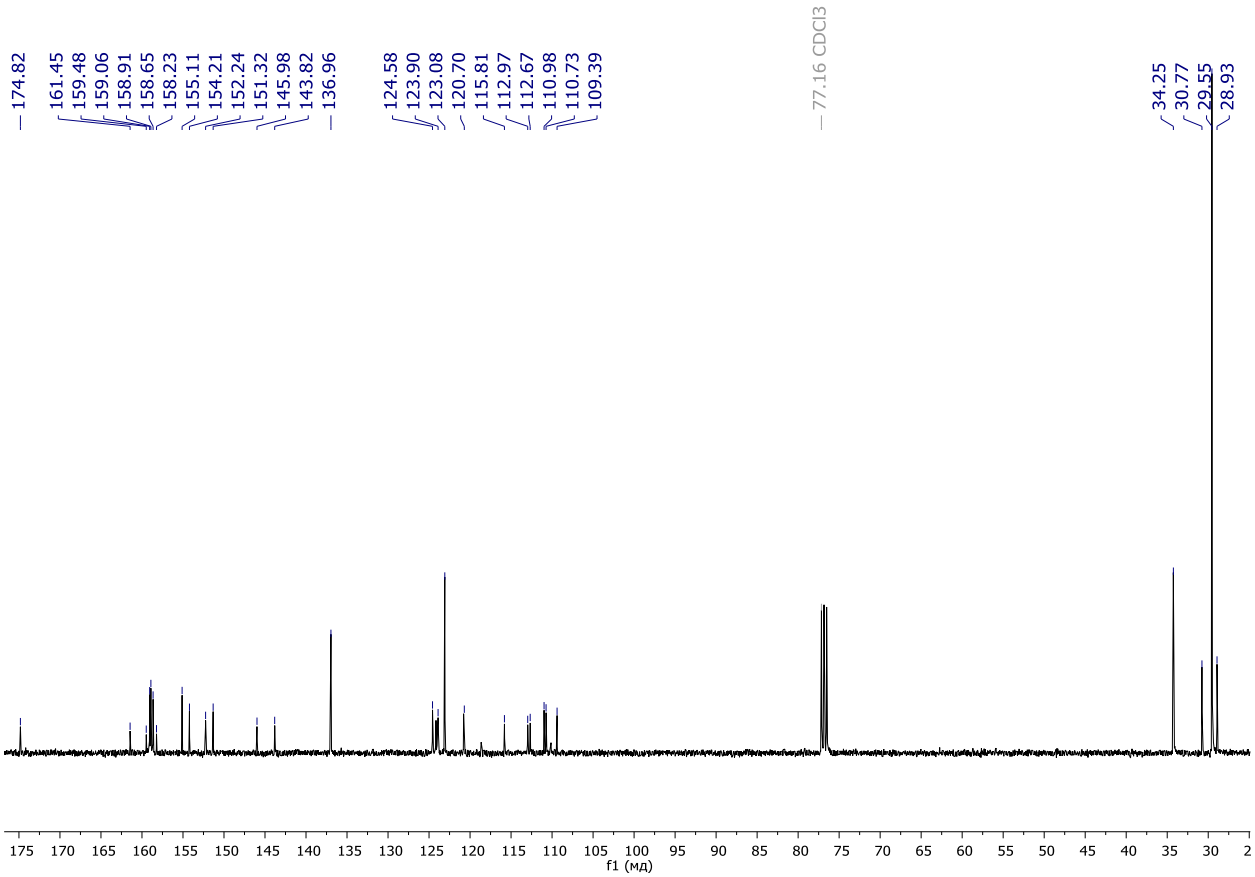


Figure S9. ^{13}C NMR (101 MHz) spectrum of **4** in $CDCl_3$**.**

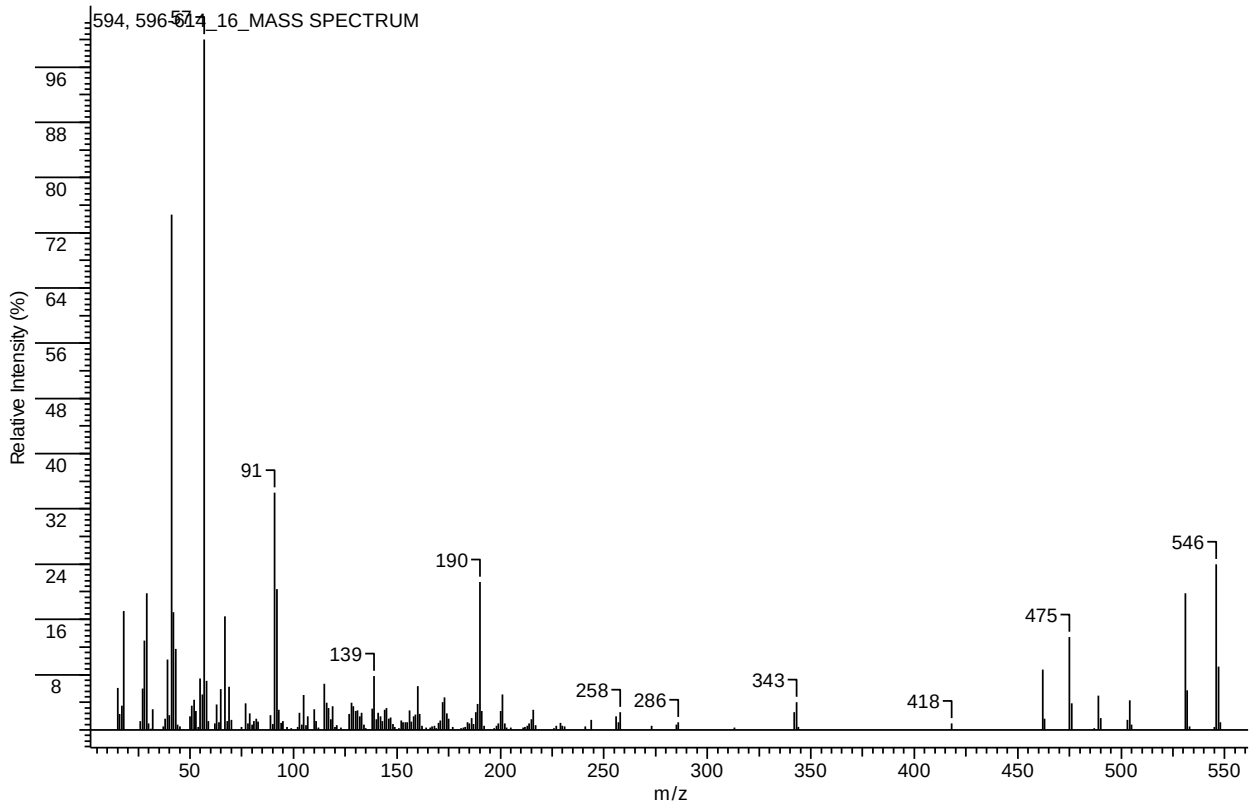


Figure S10. ESI-MS spectrum of **4**.

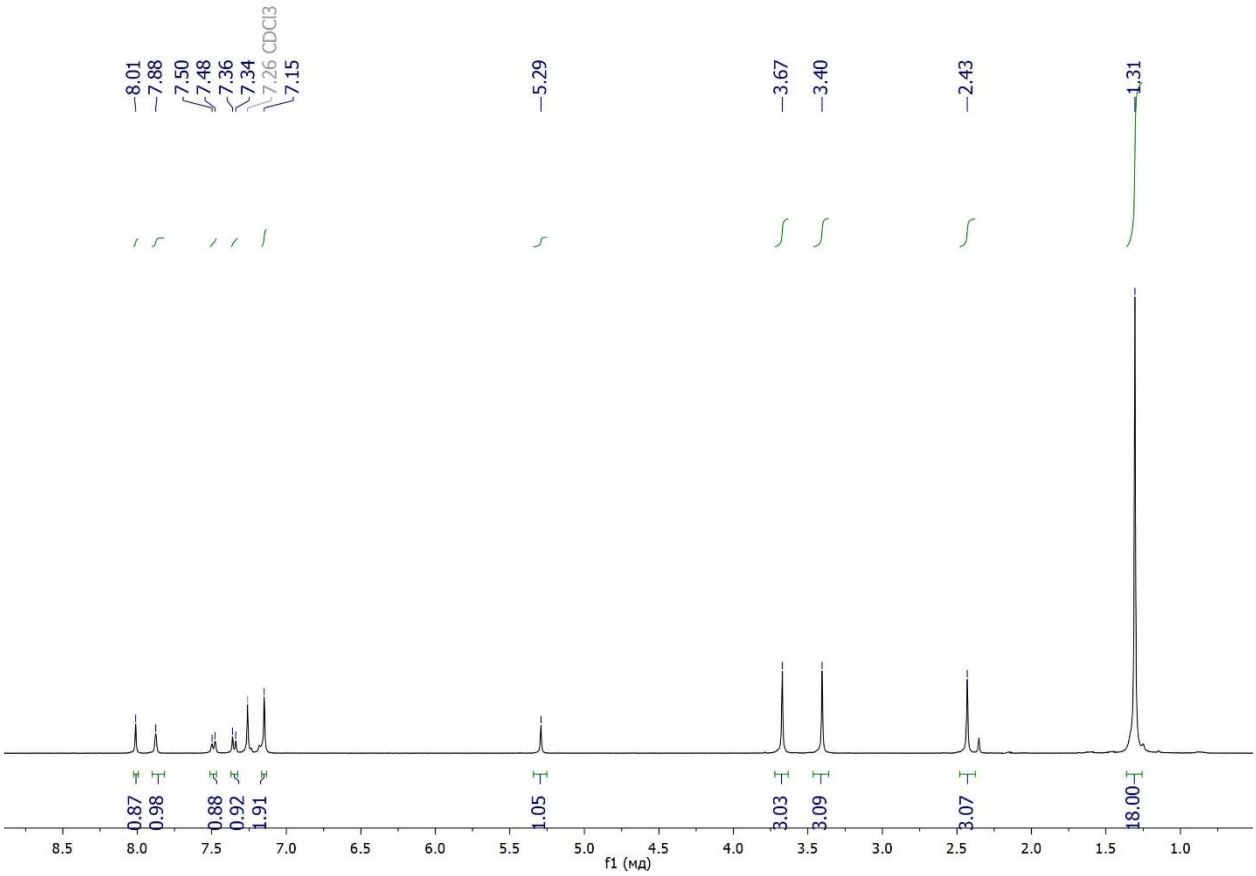


Figure S11. ^{1}H NMR (400 MHz) spectrum of **5** in $CDCl_3$**.**

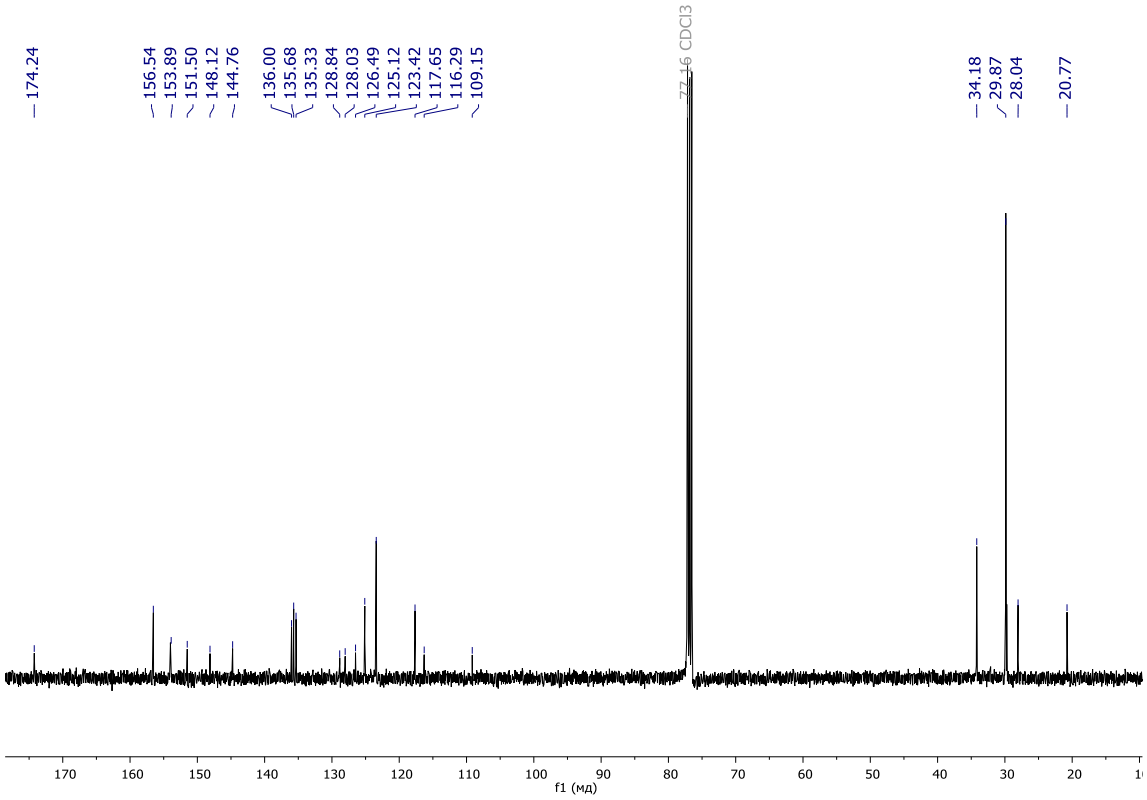


Figure S12. ^{13}C NMR (101 MHz) spectrum of **5** in $CDCl_3$**.**

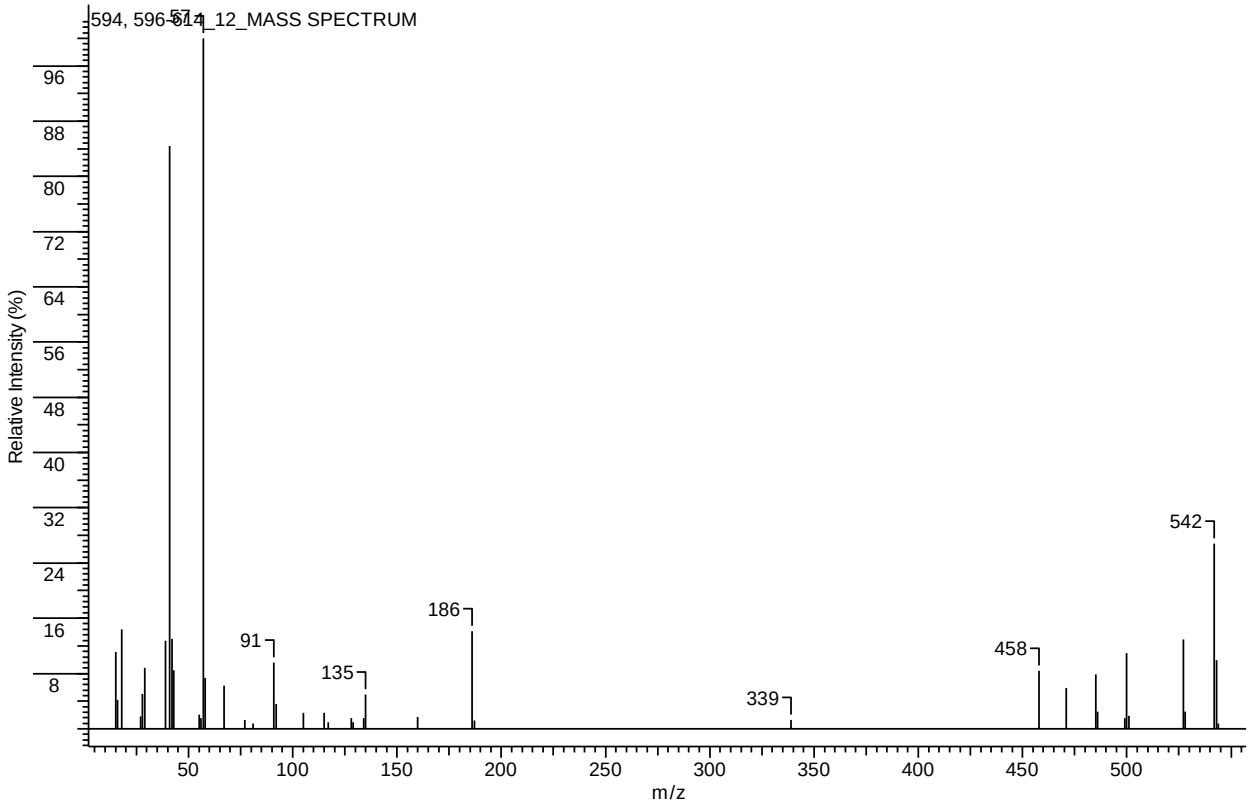


Figure S13. ESI-MS spectrum of **5**.

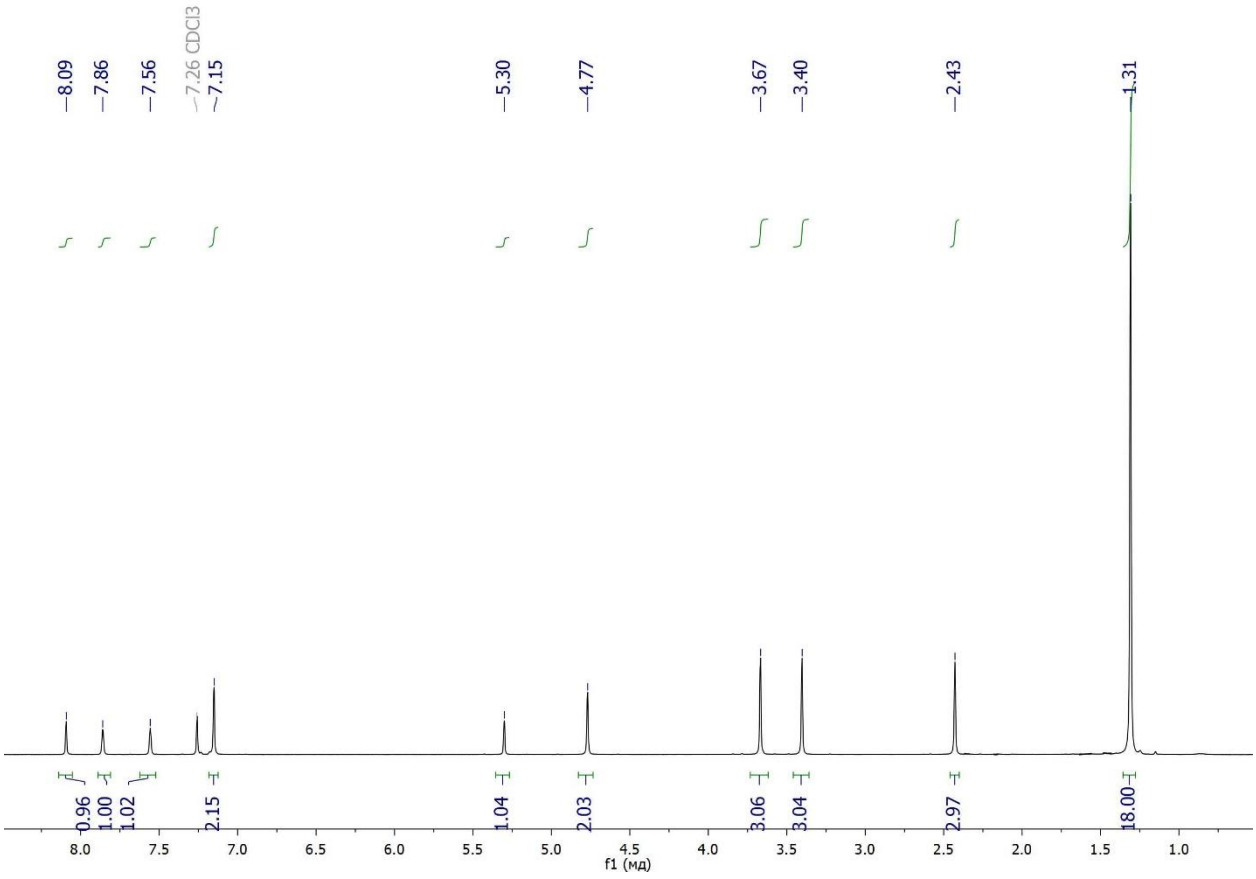


Figure S14. ^{1}H NMR (400 MHz) spectrum of **6** in $CDCl_3$**.**

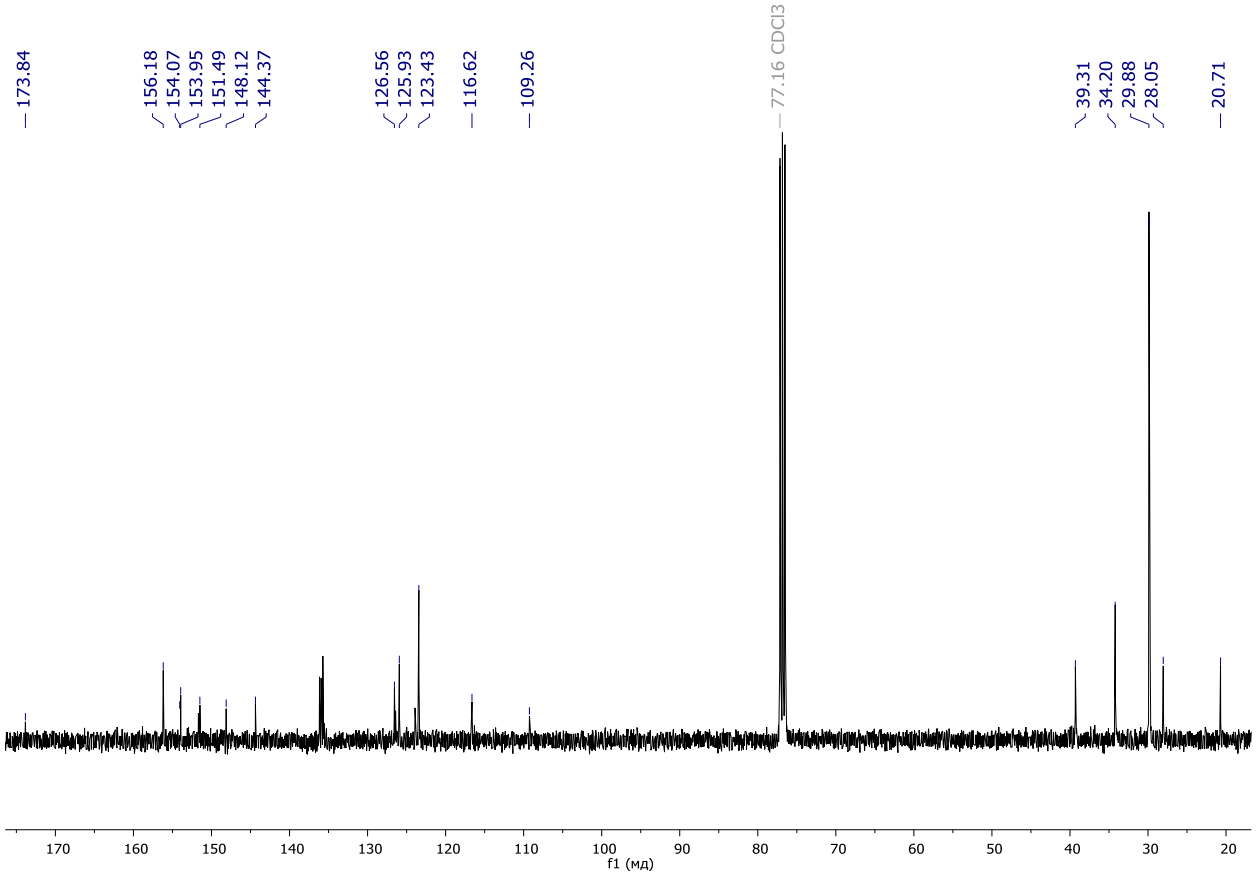


Figure S15. ^{13}C NMR (101 MHz) spectrum of **6** in $CDCl_3$**.**

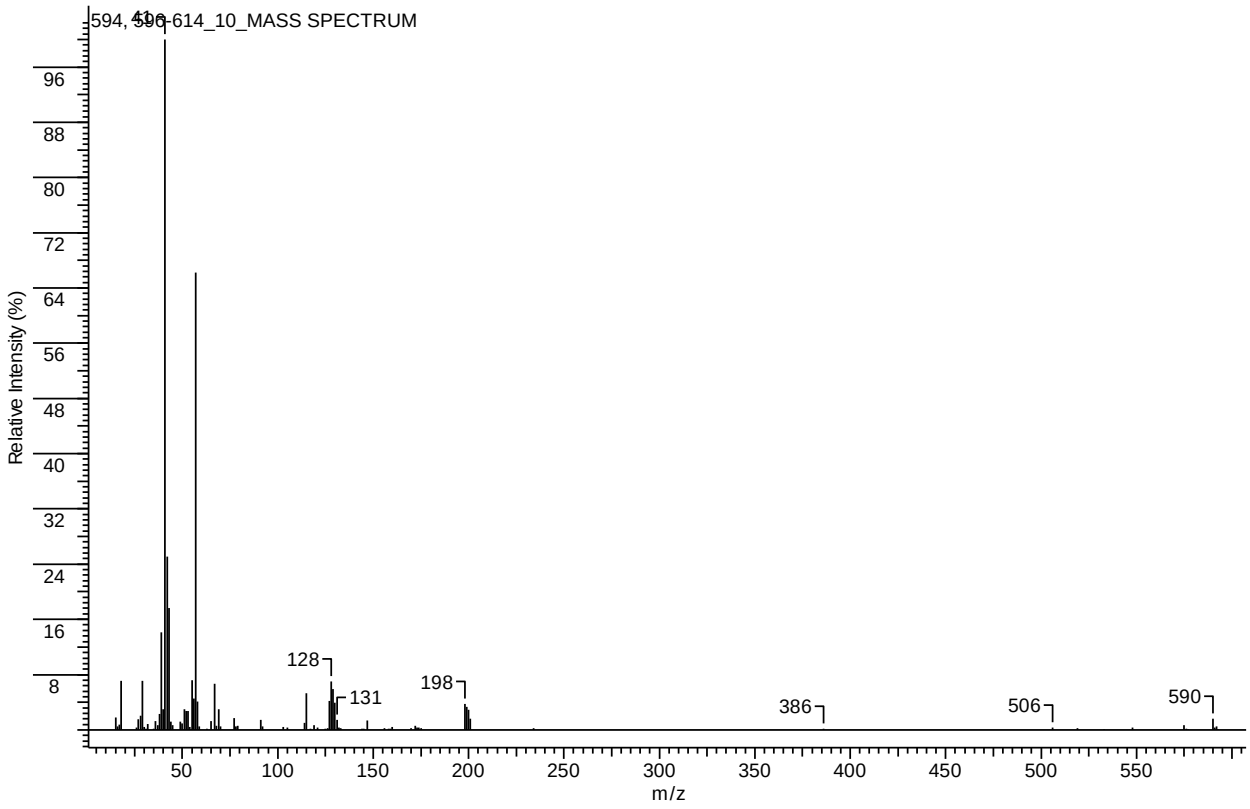


Figure S16. ESI-MS spectrum of **6**.

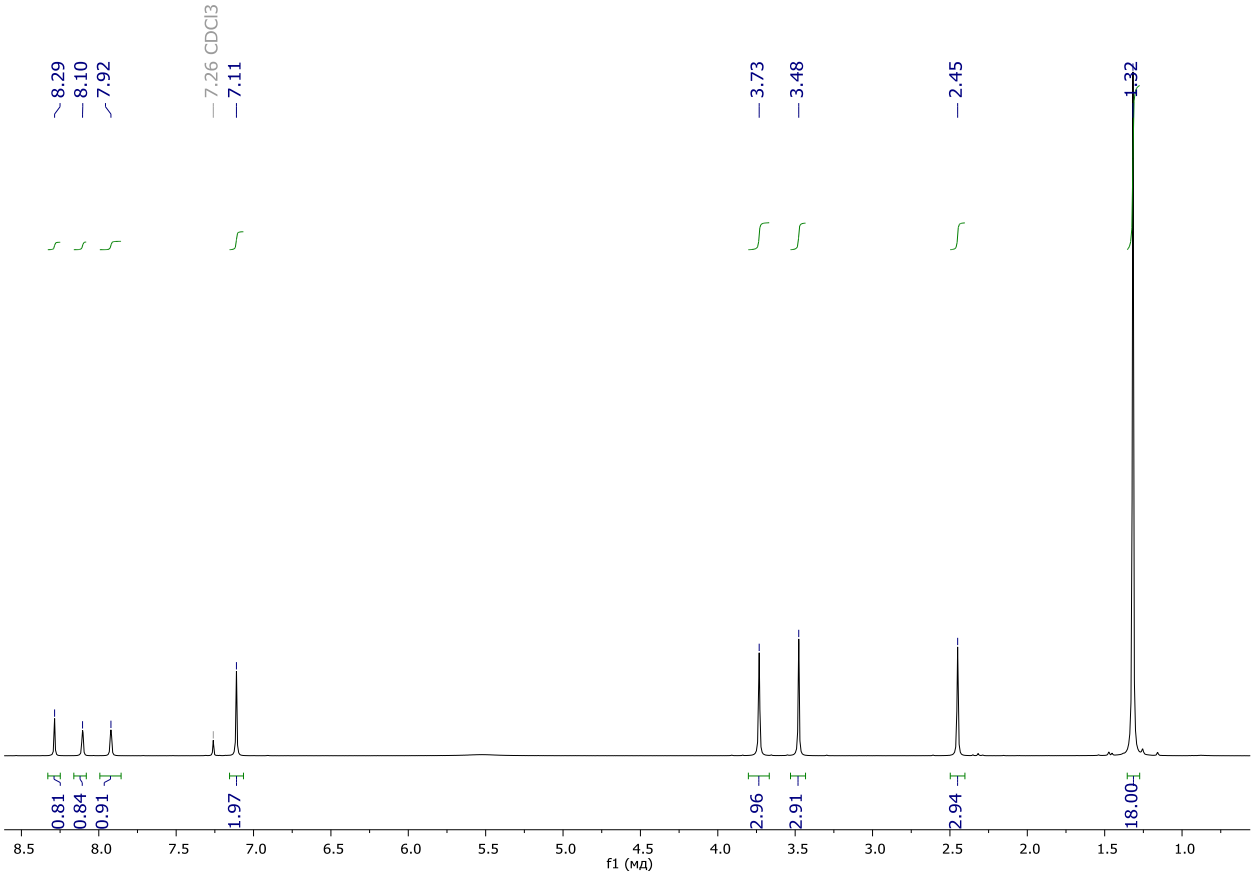


Figure S17. ^{1}H NMR (400 MHz) spectrum of **7** in $CDCl_3$**.**

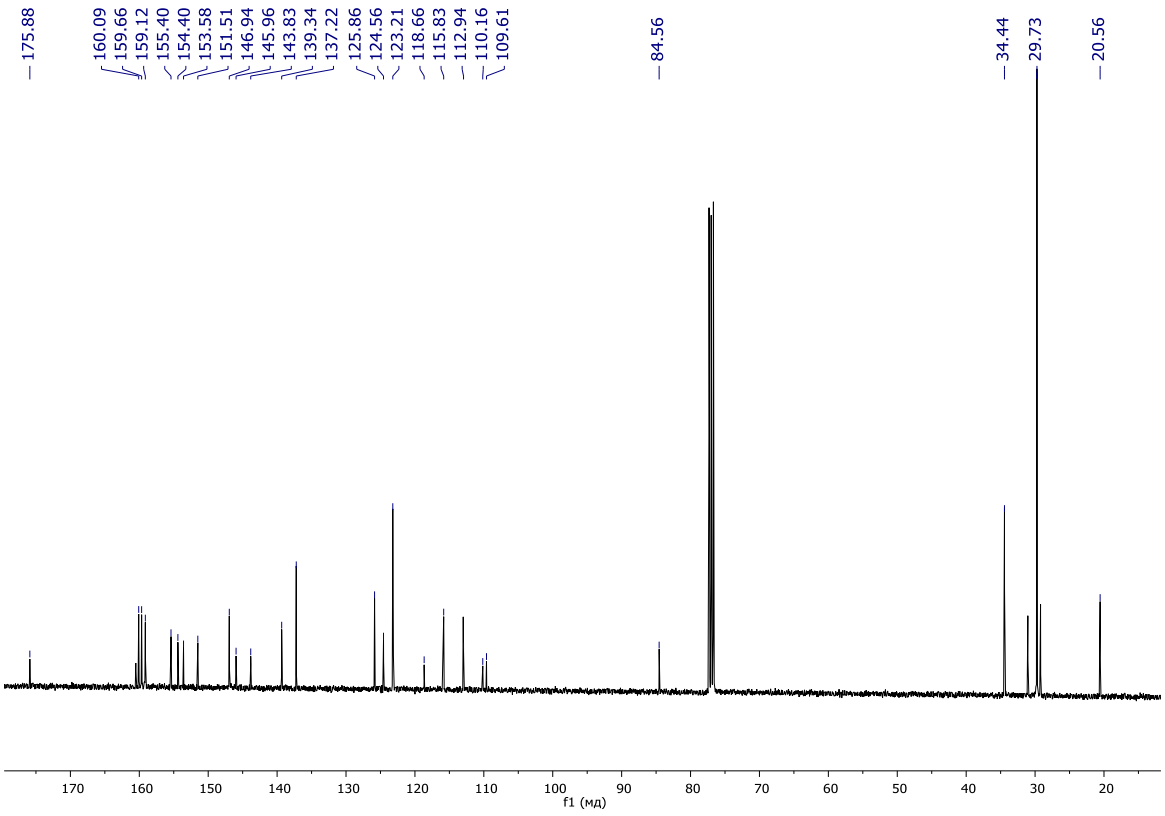


Figure S18. ^{13}C NMR (101 MHz) spectrum of **7** in $CDCl_3$**.**

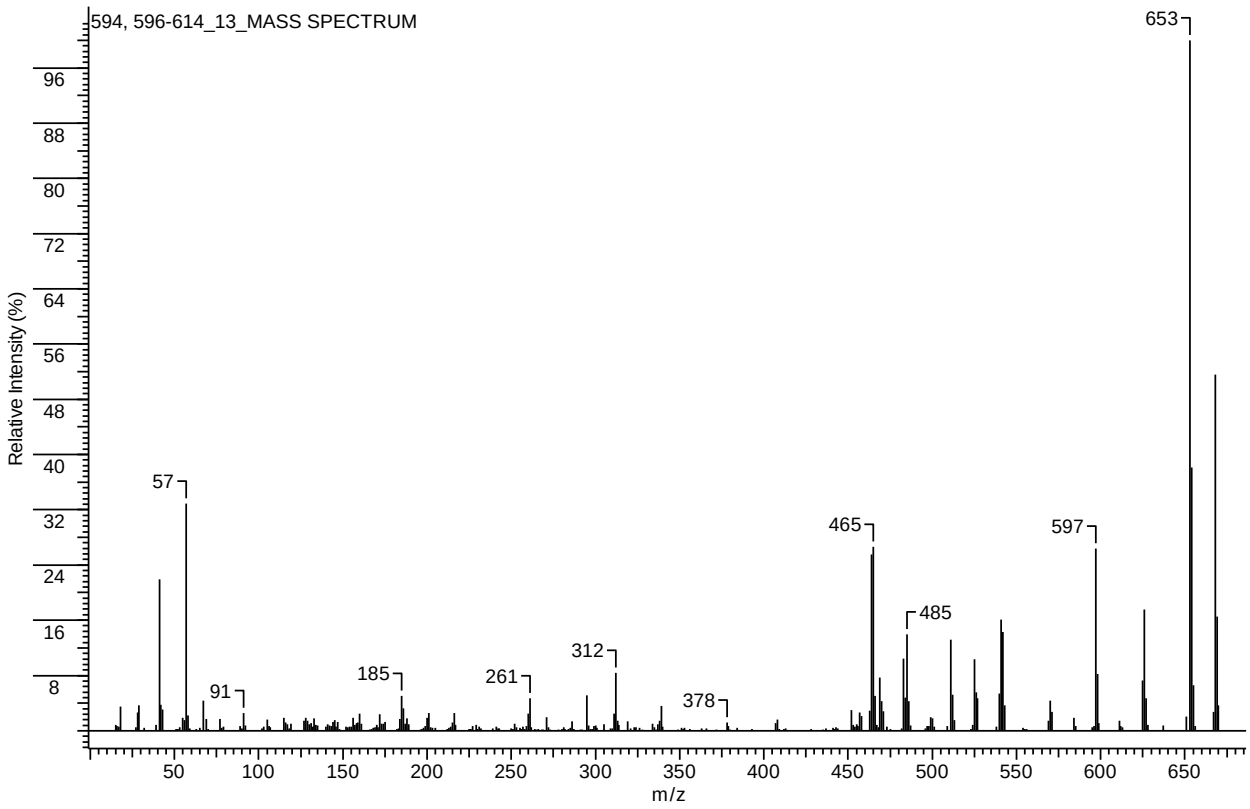


Figure S19. ESI-MS spectrum of **7**.

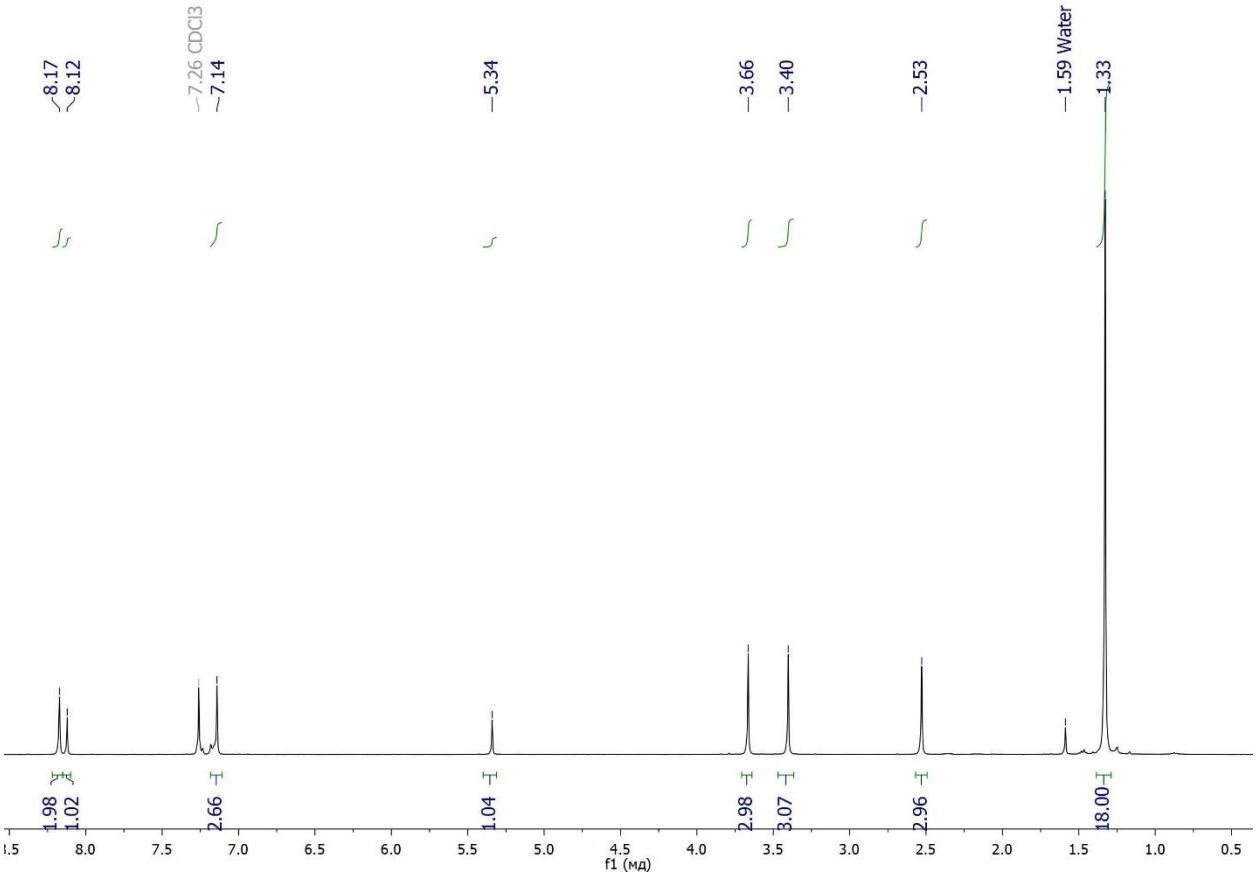


Figure S20. ^{1}H NMR (400 MHz) spectrum of **8** in $CDCl_3$**.**

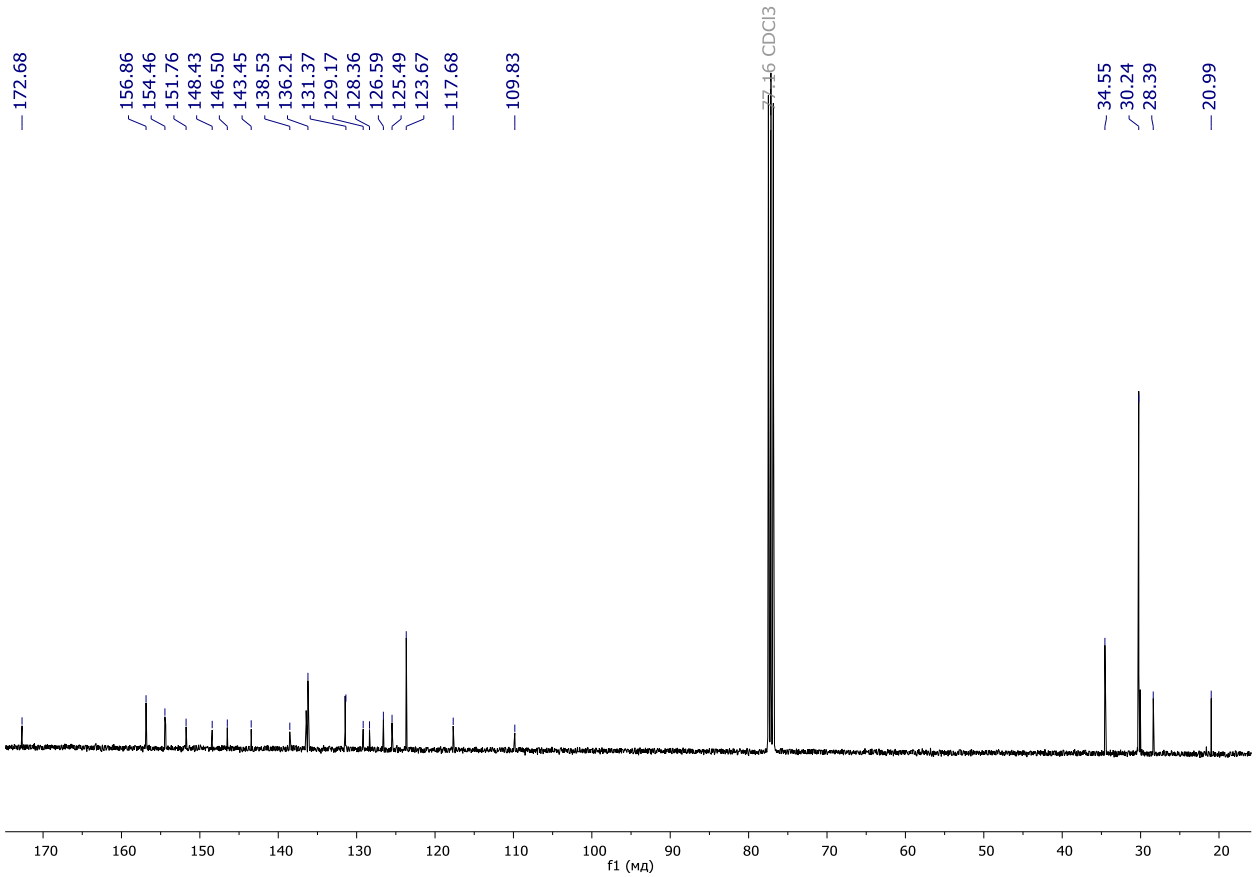


Figure S21. ^{13}C NMR (101 MHz) spectrum of **8** in $CDCl_3$**.**

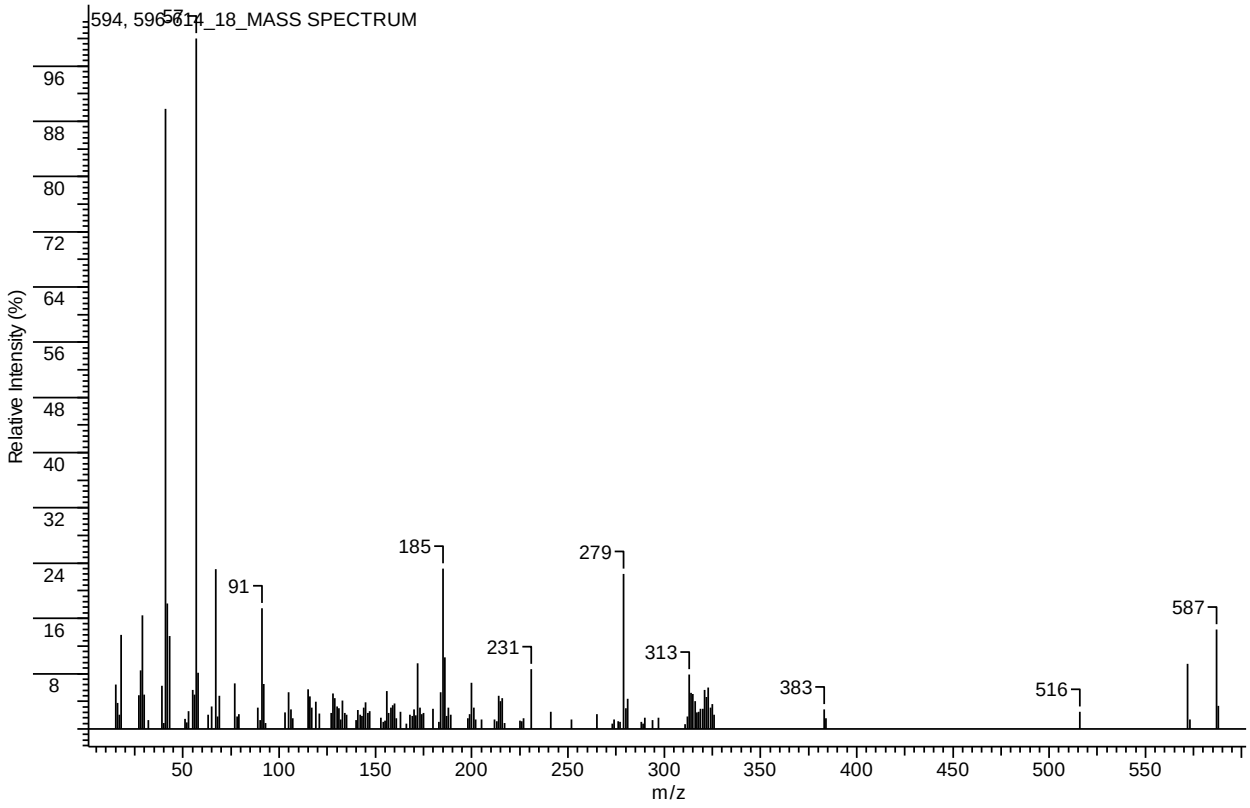


Figure S22. ESI-MS spectrum of **8**.

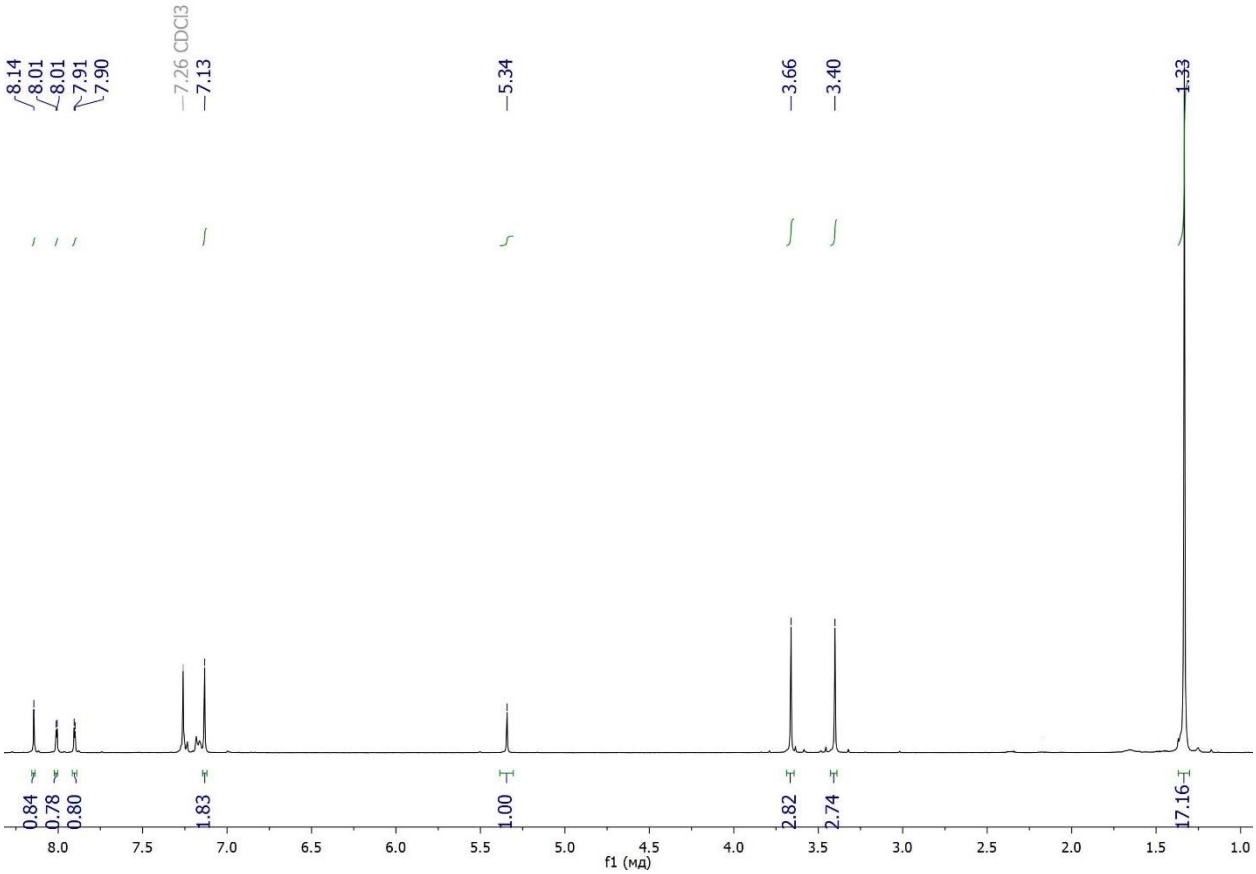


Figure S23. ^{1}H NMR (400 MHz) spectrum of **9** in $CDCl_3$**.**

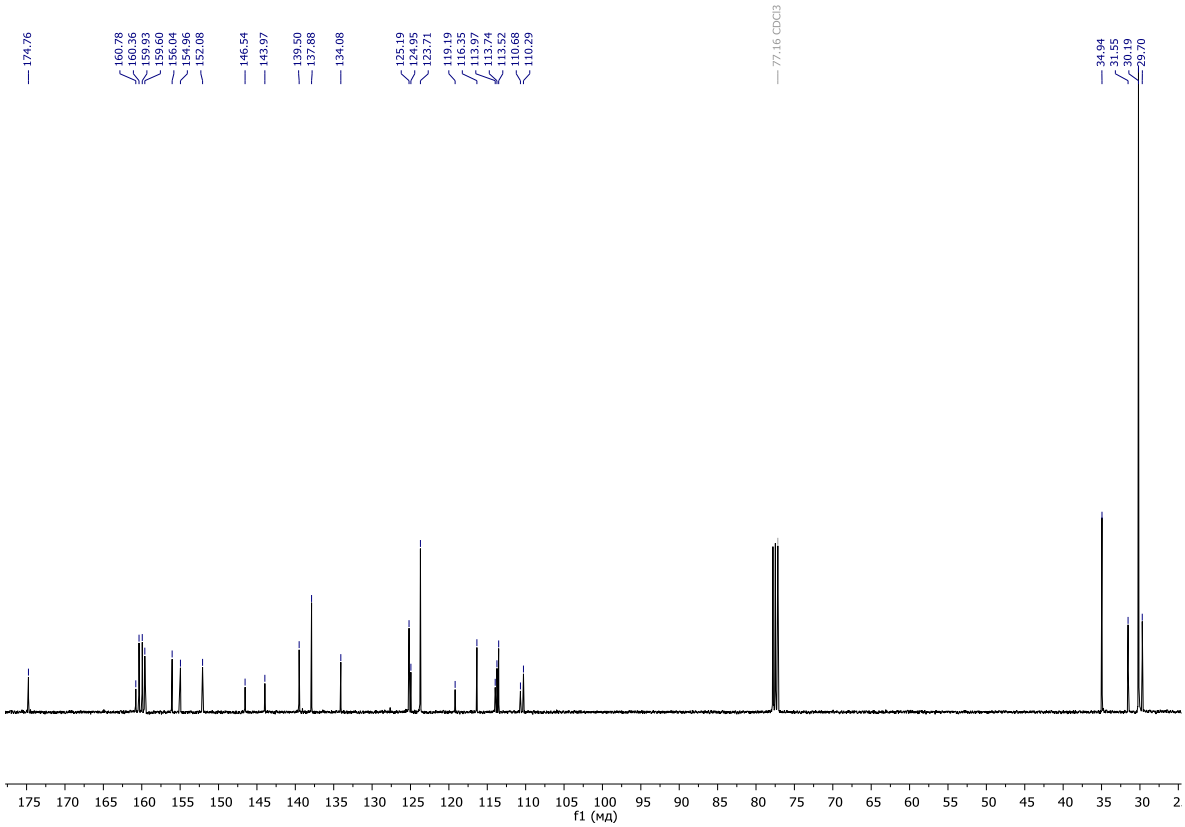


Figure S24. ^{13}C NMR (101 MHz) spectrum of **9** in $CDCl_3$

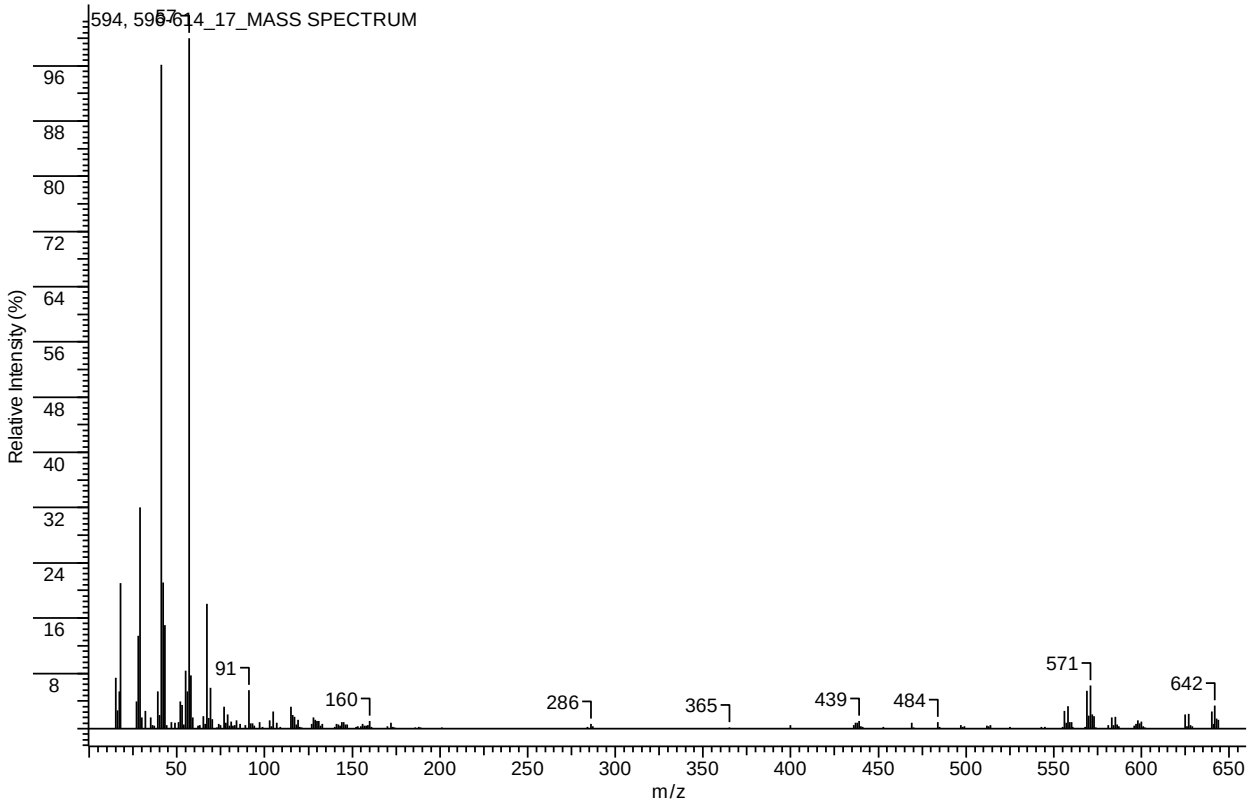


Figure S25. ESI-MS spectrum of **9**.

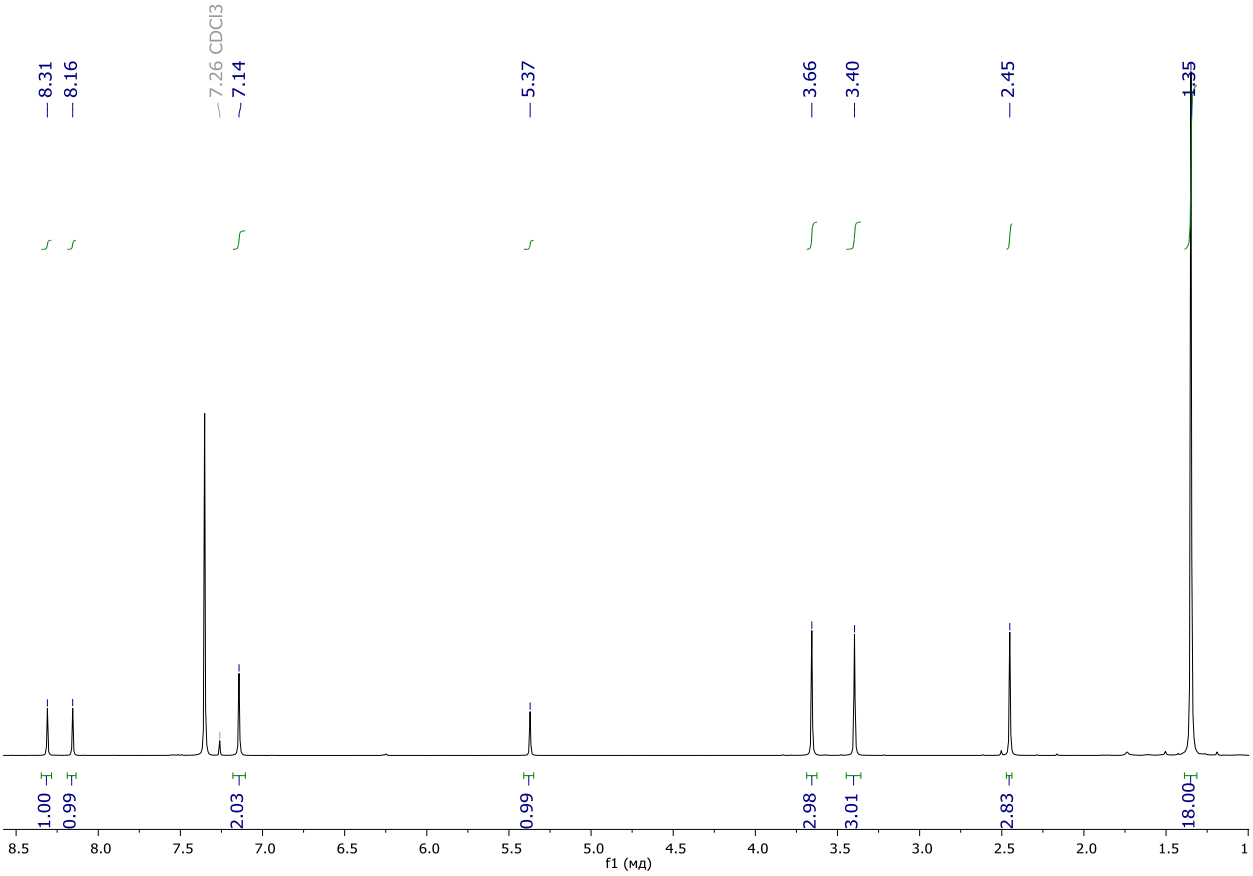


Figure S26. ^{1}H NMR (400 MHz) spectrum of **10** in $CDCl_3$**.**

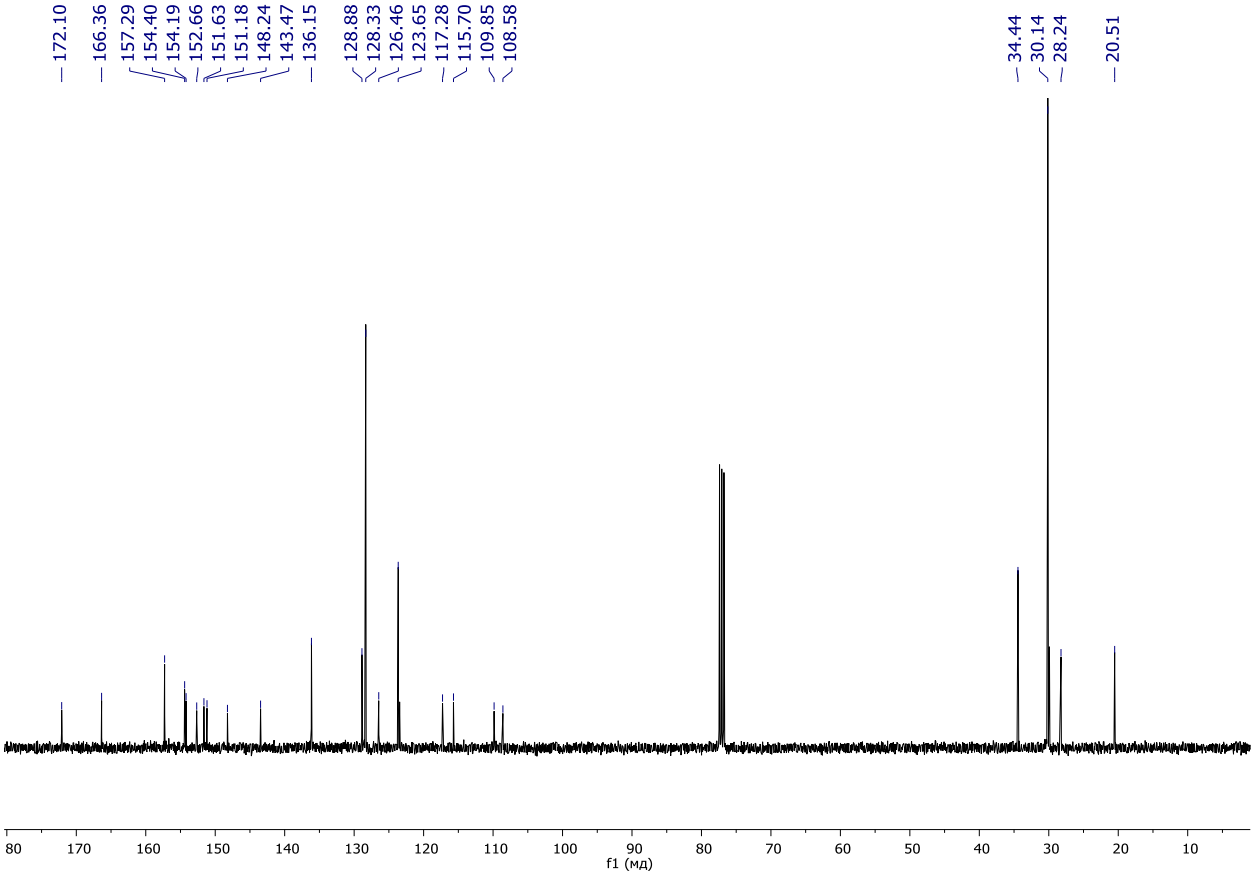


Figure S27. ^{13}C NMR (101 MHz) spectrum of **10** in $CDCl_3$

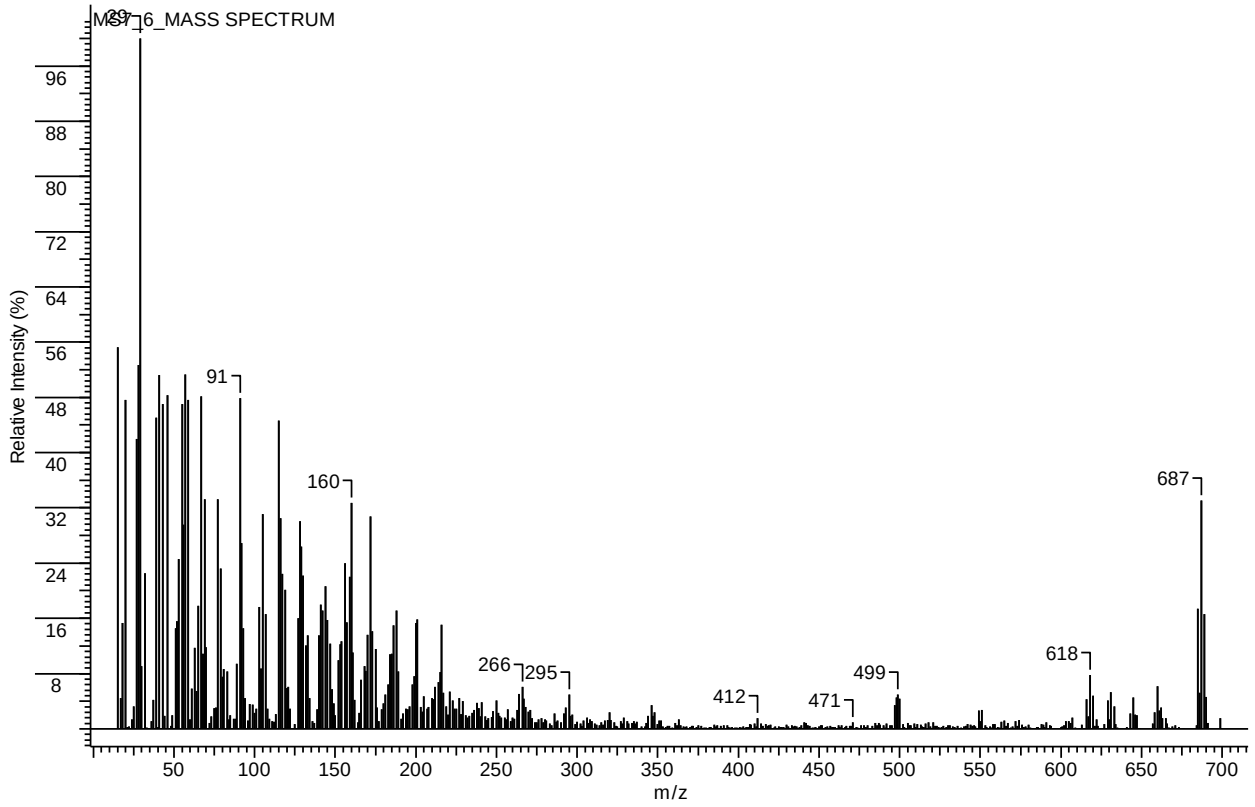


Figure S28. ESI-MS spectrum of **10**.

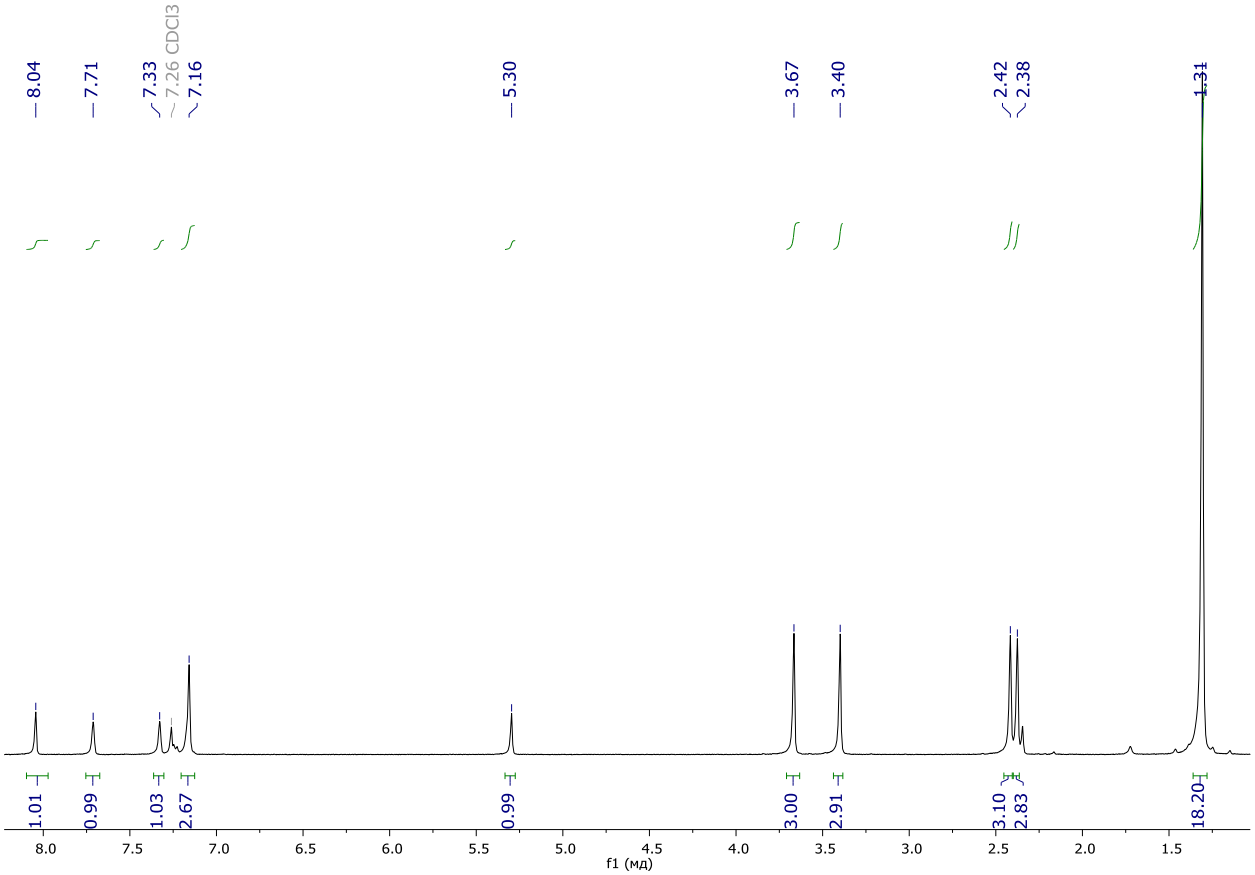


Figure S29. ^{1}H NMR (400 MHz) spectrum of **11** in $CDCl_3$**.**

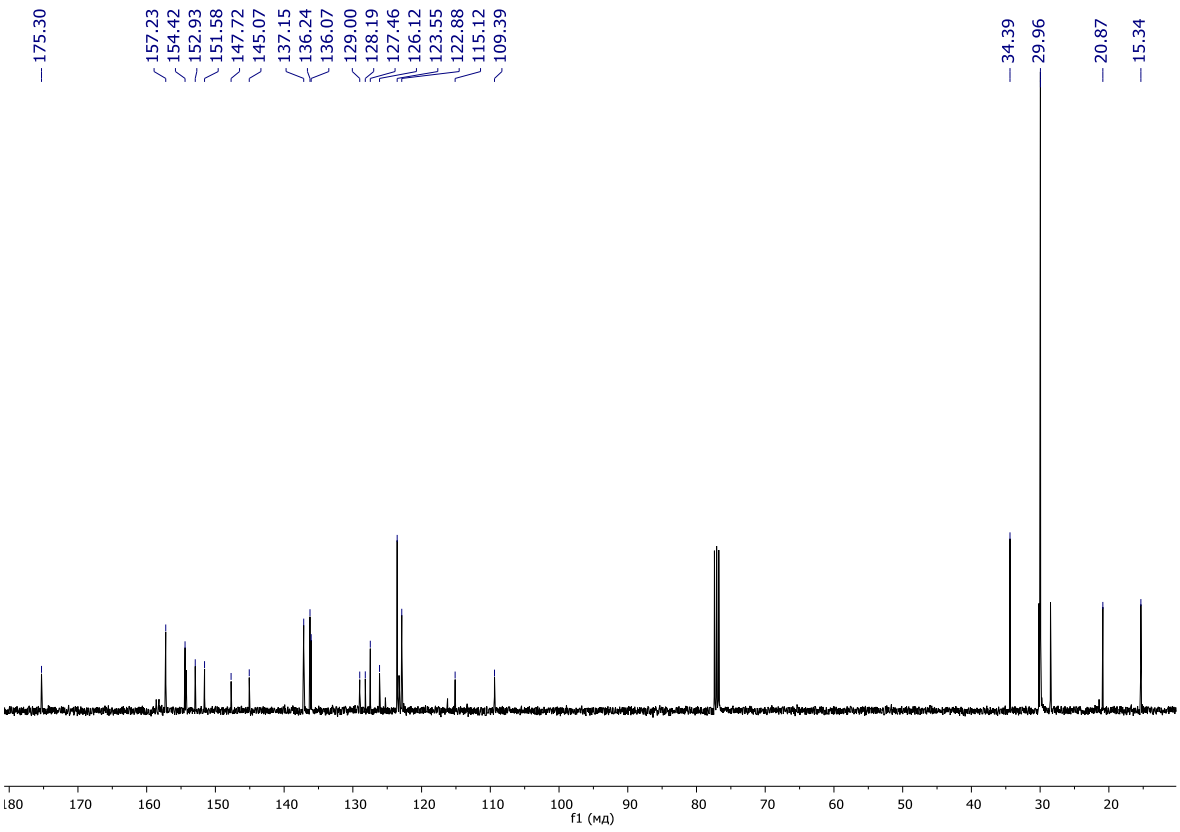


Figure S30. ^{13}C NMR (101 MHz) spectrum of **11** in $CDCl_3$

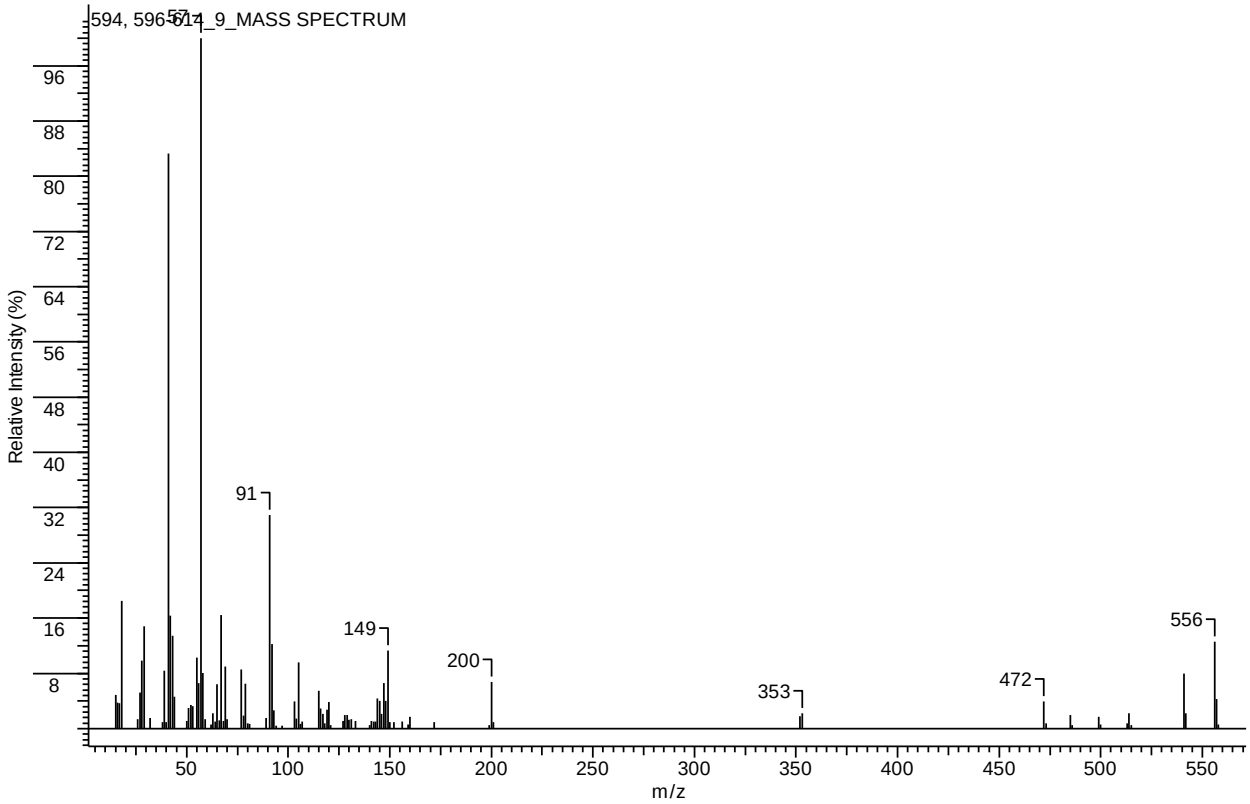


Figure S31. ESI-MS spectrum of **11**.

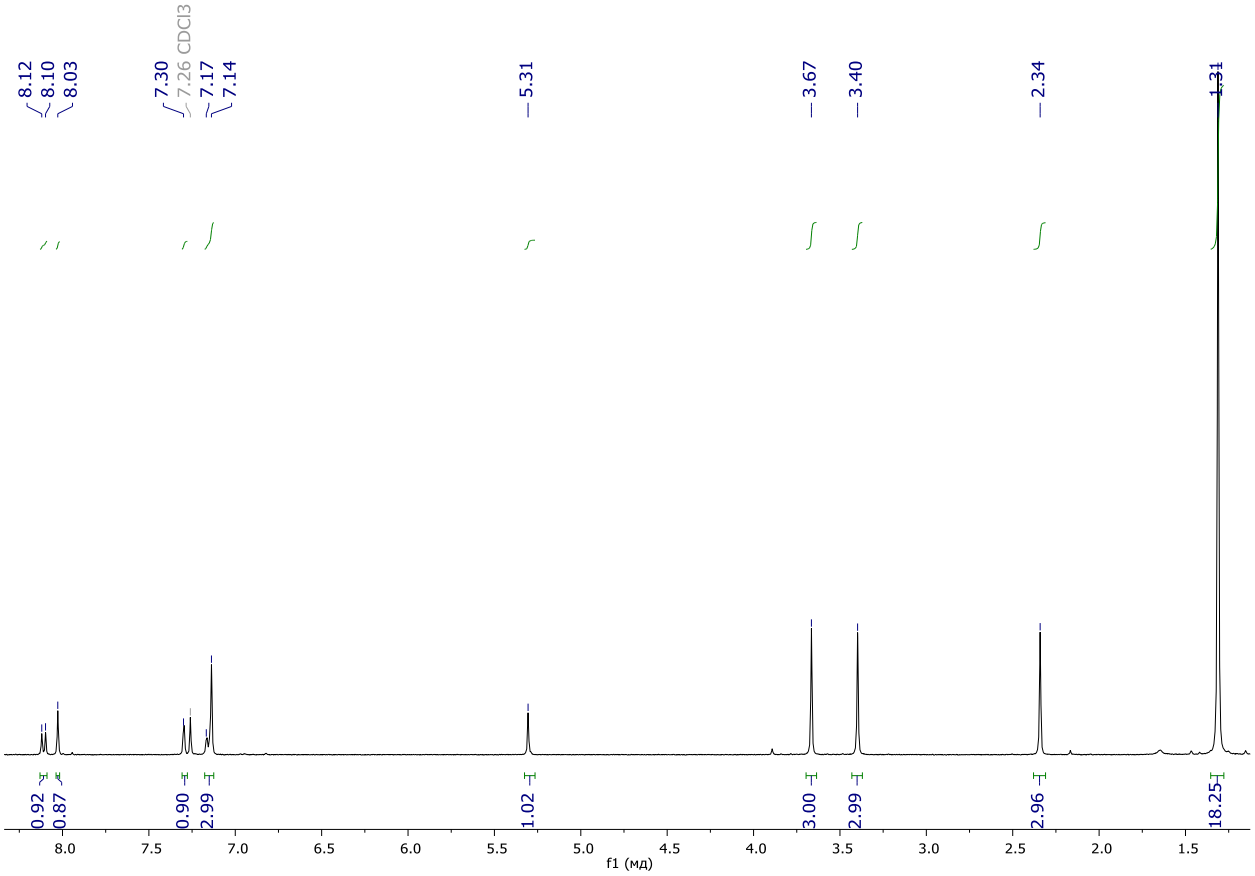


Figure S32. ^{1}H NMR (400 MHz) spectrum of **12** in $CDCl_3$**.**

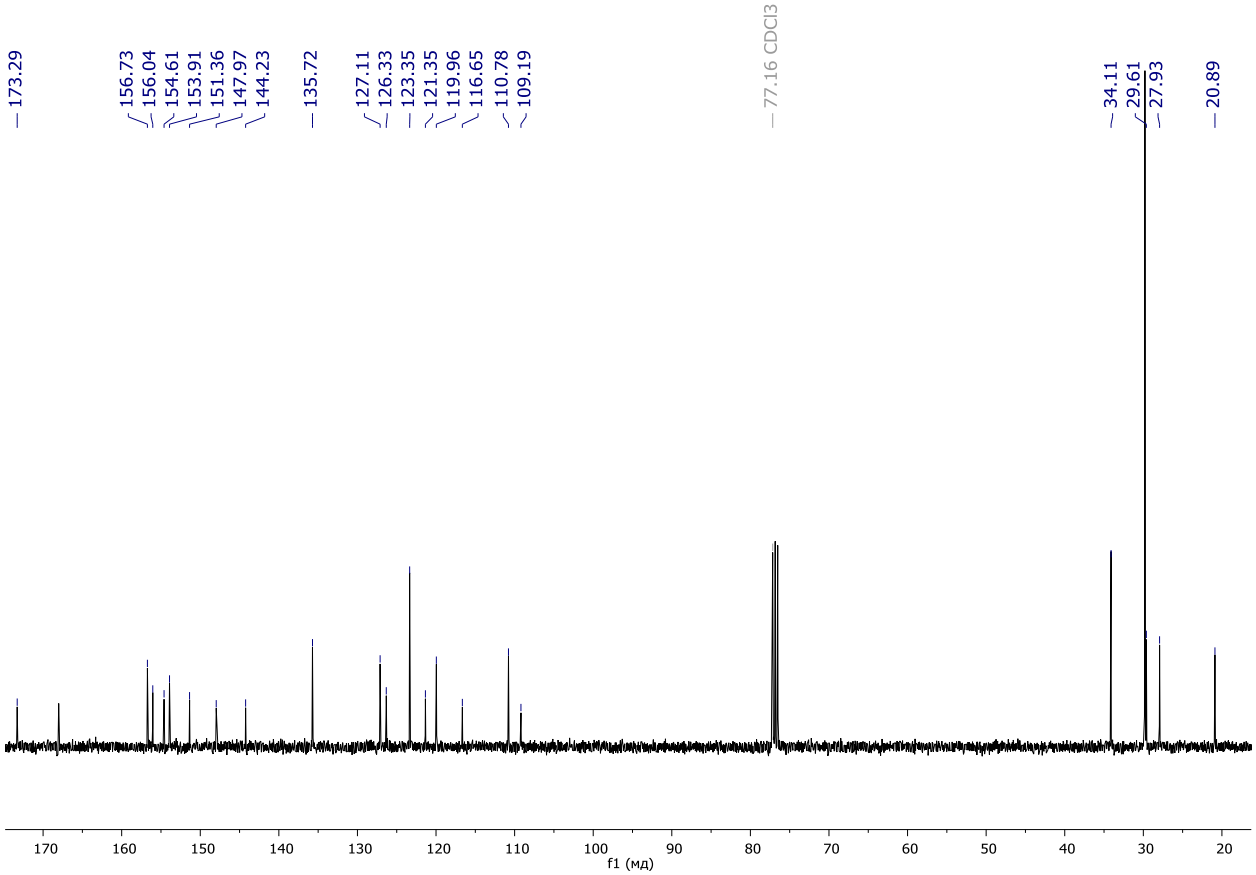


Figure S33. ^{13}C NMR (101 MHz) spectrum of **12** in $CDCl_3$

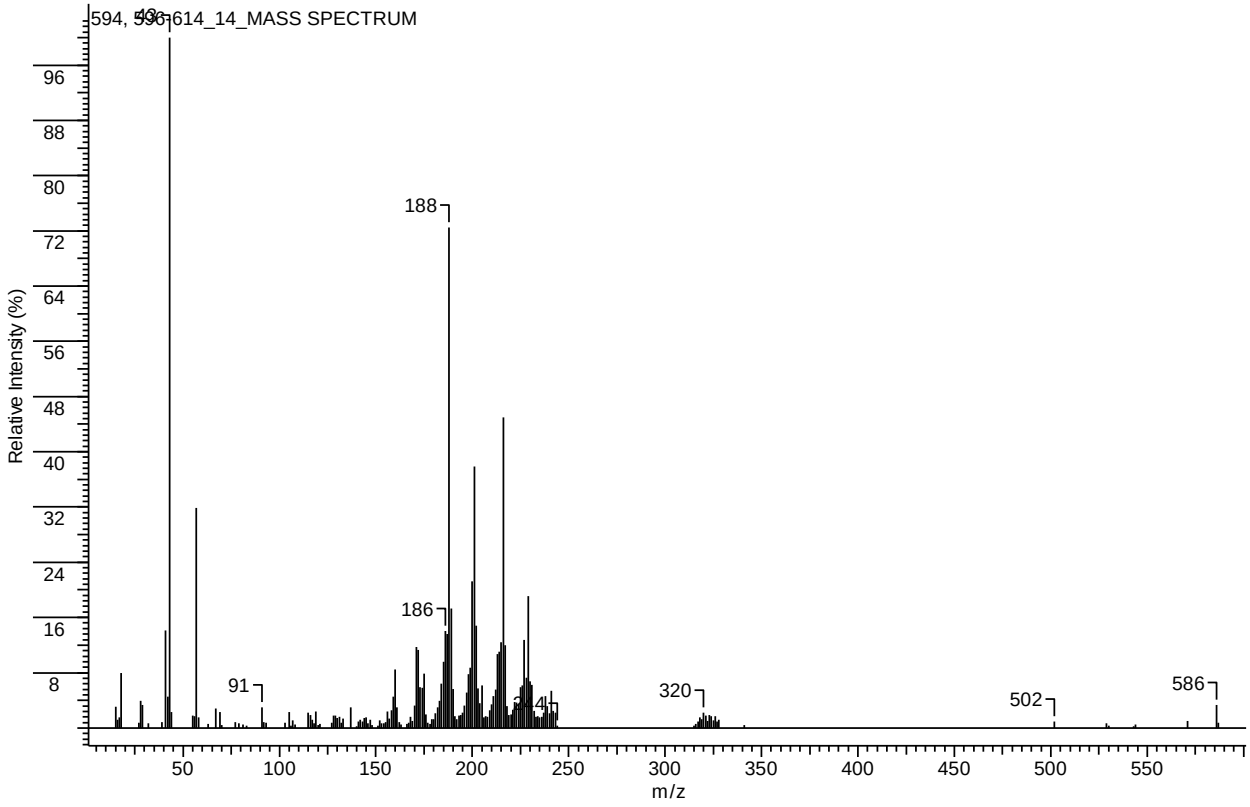


Figure S34. ESI-MS spectrum of **12**.

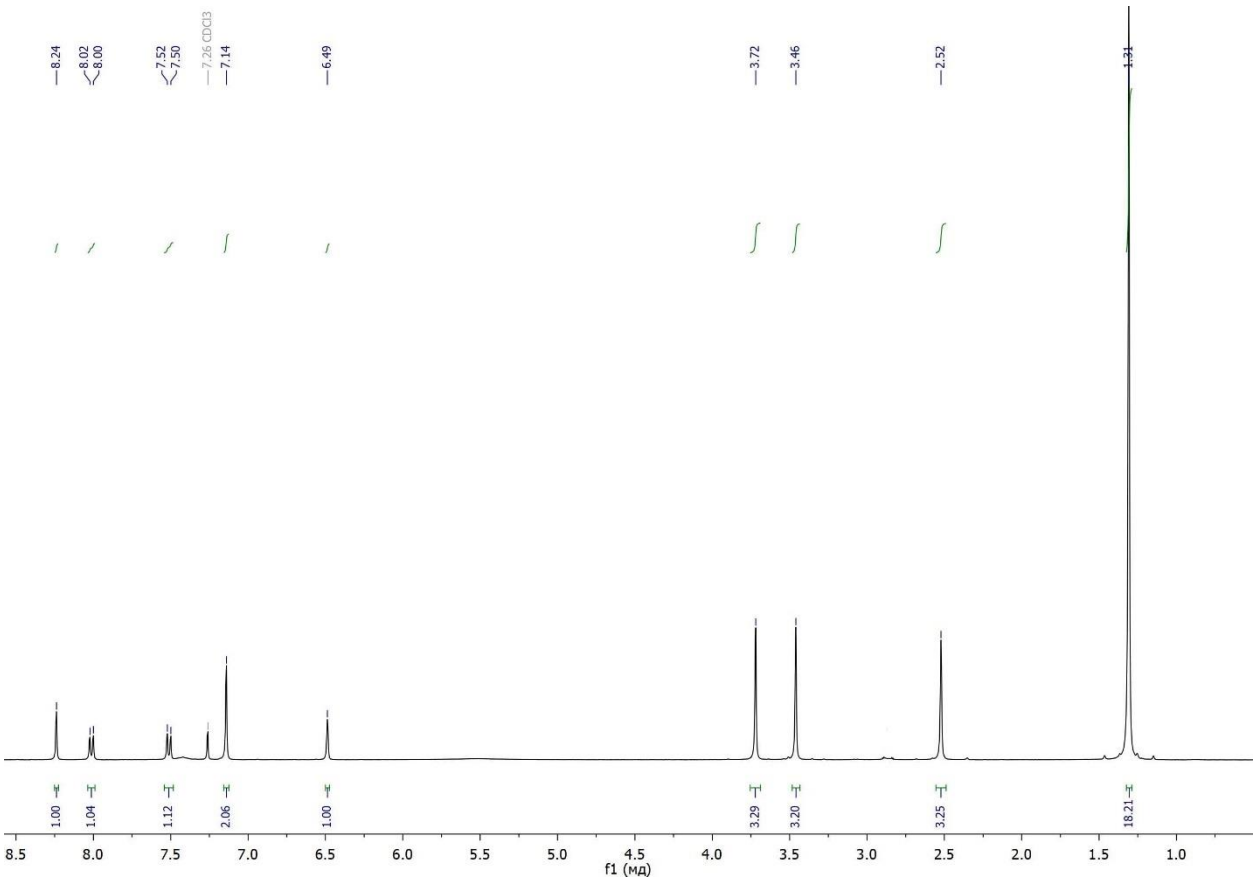


Figure S35. ^{1}H NMR (400 MHz) spectrum of **13** in $CDCl_3$**.**

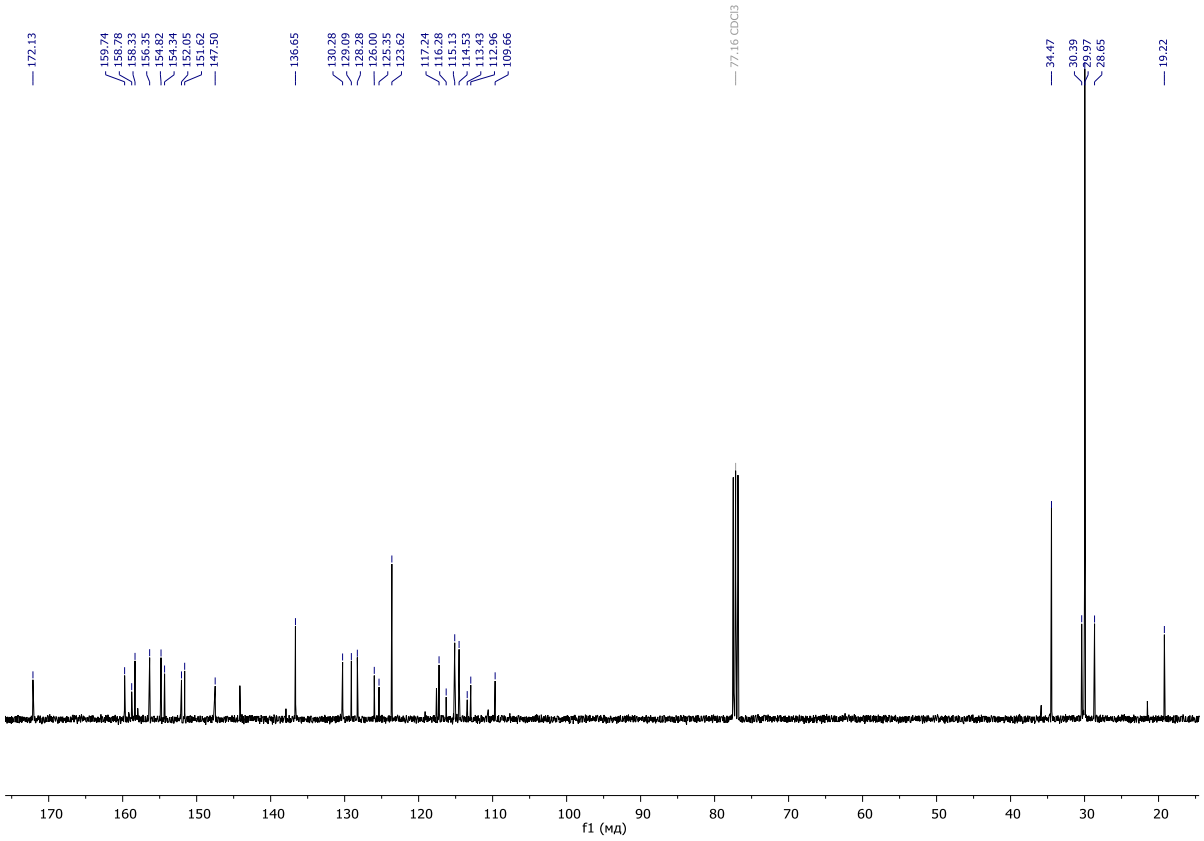


Figure S36. ^{13}C NMR (101 MHz) spectrum of **13** in $CDCl_3$

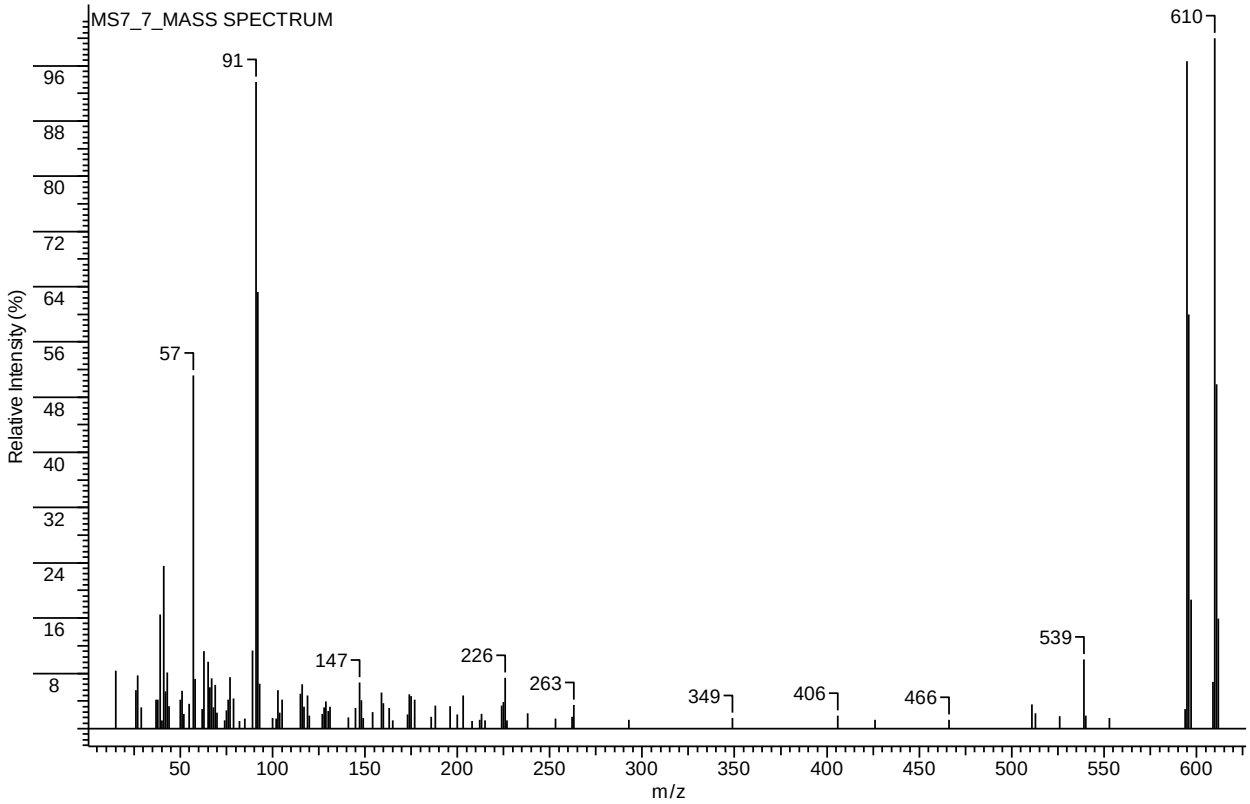


Figure S37. ESI-MS spectrum of **13**.

Table S1. Crystal data and structure refinement parameters for **2**.

	2
Formula unit	$C_{30}H_{32.5}N_4O_{5.25}$
Formula weight	533.10
Crystal system	Monoclinic
Space group	$P2_1/c$
Z	4
a, Å	9.7391(8)
b, Å	25.2387(19)
c, Å	11.2459(9)
β, °	93.420(2)
V, Å3	2759.3(4)
Dcalc (g cm−1)	1.283
Linear absorption, μ (cm−1)	0.89
F(000)	1130
2Θmax, °	60
Reflections measured	31316
Independent reflections	8343
Observed reflections [I > 2σ(I)]	4584

Parameters	403
R1	0.0647
wR2	0.1593
GOF	1.016
Δρmax/Δρmin (e Å−3)	0.301/-0.368

Table S2. Bond lengths for **2.**

Atom	Atom	Length/Å	Atom	Atom	Length/Å
O5	C20	1.371(2)	C19	C18	1.397(3)
O2	C4	1.229(2)	C19	C23	1.544(3)
O1	C3	1.226(2)	C4	C5	1.416(3)
N3	C2	1.379(2)	C27	C29	1.546(3)
N3	C3	1.373(3)	C27	C30	1.534(3)
N3	C6	1.465(3)	C27	C28	1.542(3)
N1	C17	1.448(2)	C1	C8	1.478(4)
N1	C5	1.394(3)	C23	C25	1.539(3)
N1	C1	1.354(3)	C23	C26	1.544(3)
N2	C2	1.358(3)	C23	C24	1.540(3)
N2	C1	1.343(2)	C15	C10	1.394(4)
O4	C16	1.226(3)	C15	C16	1.473(4)
N4	C3	1.401(3)	C15	C14	1.392(4)
N4	C4	1.415(3)	C9	C8	1.344(4)
N4	C7	1.470(3)	C9	O3	1.342(4)
C21	C20	1.411(3)	C8	C16	1.463(4)
C21	C22	1.398(3)	C10	C11	1.401(4)
C21	C27	1.542(3)	C10	O3	1.379(3)
C20	C19	1.413(3)	C11	C12	1.385(5)
C17	C22	1.373(3)	C14	C13	1.373(4)
C17	C18	1.377(3)	C12	C13	1.385(5)
C2	C5	1.372(3)			

Table S3. Bond Angles for **2.**

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C2	N3	C6	121.12(18)	C2	C5	C4	123.46(18)
C3	N3	C2	119.68(16)	C21	C27	C29	109.32(17)
C3	N3	C6	119.13(17)	C30	C27	C21	111.47(17)
C5	N1	C17	128.65(17)	C30	C27	C29	110.92(16)
C1	N1	C17	125.07(17)	C30	C27	C28	106.38(18)
C1	N1	C5	106.17(16)	C28	C27	C21	110.97(16)
C1	N2	C2	103.19(16)	C28	C27	C29	107.70(18)
C3	N4	C4	126.62(18)	N1	C1	C8	121.50(18)
C3	N4	C7	116.32(17)	N2	C1	N1	113.22(18)
C4	N4	C7	117.01(17)	N2	C1	C8	125.28(19)
C20	C21	C27	122.63(16)	C25	C23	C19	110.31(18)

C22	C21	C20	117.29(18)	C25	C23	C26	111.03(17)
C22	C21	C27	120.07(18)	C25	C23	C24	106.17(19)
O5	C20	C21	115.13(17)	C26	C23	C19	111.26(18)
O5	C20	C19	122.19(18)	C24	C23	C19	111.22(17)
C21	C20	C19	122.67(17)	C24	C23	C26	106.7(2)
C22	C17	N1	119.33(18)	C10	C15	C16	119.4(3)
C22	C17	C18	121.72(17)	C14	C15	C10	118.9(3)
C18	C17	N1	118.88(17)	C14	C15	C16	121.6(3)
C17	C22	C21	120.53(19)	O3	C9	C8	125.1(3)
N2	C2	N3	125.66(17)	C9	C8	C1	121.0(3)
N2	C2	C5	112.80(17)	C9	C8	C16	120.7(3)
C5	C2	N3	121.53(19)	C16	C8	C1	118.2(2)
C20	C19	C23	123.34(17)	C15	C10	C11	121.4(3)
C18	C19	C20	116.91(18)	O3	C10	C15	122.8(3)
C18	C19	C23	119.74(18)	O3	C10	C11	115.9(4)
C17	C18	C19	120.83(18)	O4	C16	C15	123.4(3)
O1	C3	N3	121.97(19)	O4	C16	C8	122.5(3)
O1	C3	N4	120.8(2)	C8	C16	C15	114.1(3)
N3	C3	N4	117.18(17)	C12	C11	C10	118.4(3)
O2	C4	N4	120.64(19)	C13	C14	C15	119.7(3)
O2	C4	C5	127.89(19)	C11	C12	C13	120.1(3)
N4	C4	C5	111.46(17)	C14	C13	C12	121.5(3)
N1	C5	C4	131.92(17)	C9	O3	C10	117.8(2)
C2	C5	N1	104.62(17)				

Table S4. Comparison of selected bond distances (Å) of compound **2** determined theoretically (from DFT calculation) and experimentally (from crystal structure).

Bond	B3LYP	EXPT	Bond	B3LYP	EXPT
O5-C20	1.37013	1.371(2)	C19-C18	1.39443	1.397(3)
O2-C4	1.22434	1.229(2)	C19-C23	1.54936	1.544(3)
O1-C3	1.22244	1.226(2)	C4-C5	1.43293	1.416(3)
N3-C2	1.37238	1.379(2)	C27-C29	1.54830	1.546(3)
N3-C3	1.38695	1.373(3)	C27-C30	1.54825	1.534(3)
N3-C6	1.46497	1.465(3)	C27-C28	1.54830	1.542(3)
N1-C17	1.43914	1.448(2)	C1-C8	1.47017	1.478(4)
N1-C5	1.39422	1.394(3)	C23-C25	1.55139	1.539(3)
N1-C1	1.36671	1.354(3)	C23-C26	1.55155	1.544(3)
N2-C2	1.35314	1.358(3)	C23-C24	1.54311	1.540(3)
N2-C1	1.33593	1.343(2)	C15-C10	1.39915	1.394(4)
O4-C16	1.22754	1.226(3)	C15-C16	1.47675	1.473(4)
N4-C3	1.40223	1.401(3)	C15-C14	1.40494	1.392(4)
N4-C4	1.42046	1.415(3)	C9-C8	1.35543	1.344(4)
N4-C7	1.46893	1.470(3)	C9-O3	1.33847	1.342(4)
C21-C20	1.41494	1.411(3)	C8-C16	1.46974	1.463(4)
C21-C22	1.39609	1.398(3)	C10-C11	1.39476	1.401(4)
C21-C27	1.54678	1.542(3)	C10-O3	1.37392	1.379(3)
C20-C19	1.41768	1.413(3)	C11-C12	1.38558	1.385(5)
C17-C22	1.38754	1.373(3)	C14-C13	1.38324	1.373(4)
C17-C18	1.38535	1.377(3)	C12-C13	1.40391	1.385(5)
C2-C5	1.37909	1.372(3)			

Table S5. Comparison of selected angles (°) of compound **2** determined theoretically (from DFT calculation) and experimentally (from crystal structure).

Bond	B3LYP	EXPT	Bond	B3LYP	EXPT
C2-N3-C6	120.240	121.12(18)	C2-C5-C4	122.554	123.46(18)
C3-N3-C2	119.529	119.68(16)	C21-C27-C29	110.382	109.32(17)
C3-N3-C6	120.226	119.13(17)	C30-C27-C21	110.315	111.47(17)
C5-N1-C17	126.780	128.65(17)	C30-C27-C29	110.206	110.92(16)
C1-N1-C17	127.010	125.07(17)	C30-C27-C28	107.081	106.38(18)
C1-N1-C5	105.924	106.17(16)	C28-C27-C21	111.708	110.97(16)
C1-N2-C2	104.598	103.19(16)	C28-C27-C29	107.049	107.70(18)
C3-N4-C4	127.238	126.62(18)	N1-C1-C8	124.642	121.50(18)
C3-N4-C7	115.021	116.32(17)	N2-C1-N1	112.529	113.22(18)
C4-N4-C7	117.741	117.01(17)	N2-C1-C8	122.823	125.28(19)
C20-C21-C27	122.236	122.63(16)	C25-C23-C19	110.568	110.31(18)
C22-C21-C20	117.098	117.29(18)	C25-C23-C26	111.219	111.03(17)
C22-C21-C27	120.664	120.07(18)	C25-C23-C24	106.148	106.17(19)
O5-C20-C21	115.835	115.13(17)	C26-C23-C19	110.850	111.26(18)
O5-C20-C19	121.482	122.19(18)	C24-C23-C19	111.673	111.22(17)
C21-C20-C19	122.683	122.67(17)	C24-C23-C26	106.218	106.7(2)
C22-C17-N1	119.376	119.33(18)	C10-C15-C16	120.463	119.4(3)
C22-C17-C18	120.762	121.72(17)	C14-C15-C10	118.200	118.9(3)
C18-C17-N1	119.860	118.88(17)	C14-C15-C16	121.331	121.6(3)
C17-C22-C21	121.142	120.53(19)	O3-C9-C8	124.978	125.1(3)
N2-C2-N3	125.565	125.66(17)	C9-C8-C1	118.059	121.0(3)
N2-C2-C5	111.886	112.80(17)	C9-C8-C16	119.996	120.7(3)
C5-C2-N3	122.549	121.53(19)	C16-C8-C1	121.672	118.2(2)
C20-C19-C23	122.669	123.34(17)	C15-C10-C11	121.971	121.4(3)
C18-C19-C20	117.132	116.91(18)	O3-C10-C15	121.312	122.8(3)
C18-C19-C23	120.199	119.74(18)	O3-C10-C11	116.717	115.9(4)
C17-C18-C19	121.174	120.83(18)	O4-C16-C15	122.680	123.4(3)
O1-C3-N3	122.368	121.97(19)	O4-C16-C8	123.373	122.5(3)
O1-C3-N4	120.831	120.8(2)	C8-C16-C15	113.932	114.1(3)
N3-C3-N4	116.802	117.18(17)	C12-C11-C10	118.630	118.4(3)
O2-C4-N4	121.423	120.64(19)	C13-C14-C15	120.538	119.7(3)
O2-C4-C5	127.264	127.89(19)	C11-C12-C13	120.634	120.1(3)
N4-C4-C5	111.313	111.46(17)	C14-C13-C12	120.027	121.5(3)
N1-C5-C4	132.355	131.92(17)	C9-O3-C10	119.172	117.8(2)
C2-C5-N1	105.061	104.62(17)			

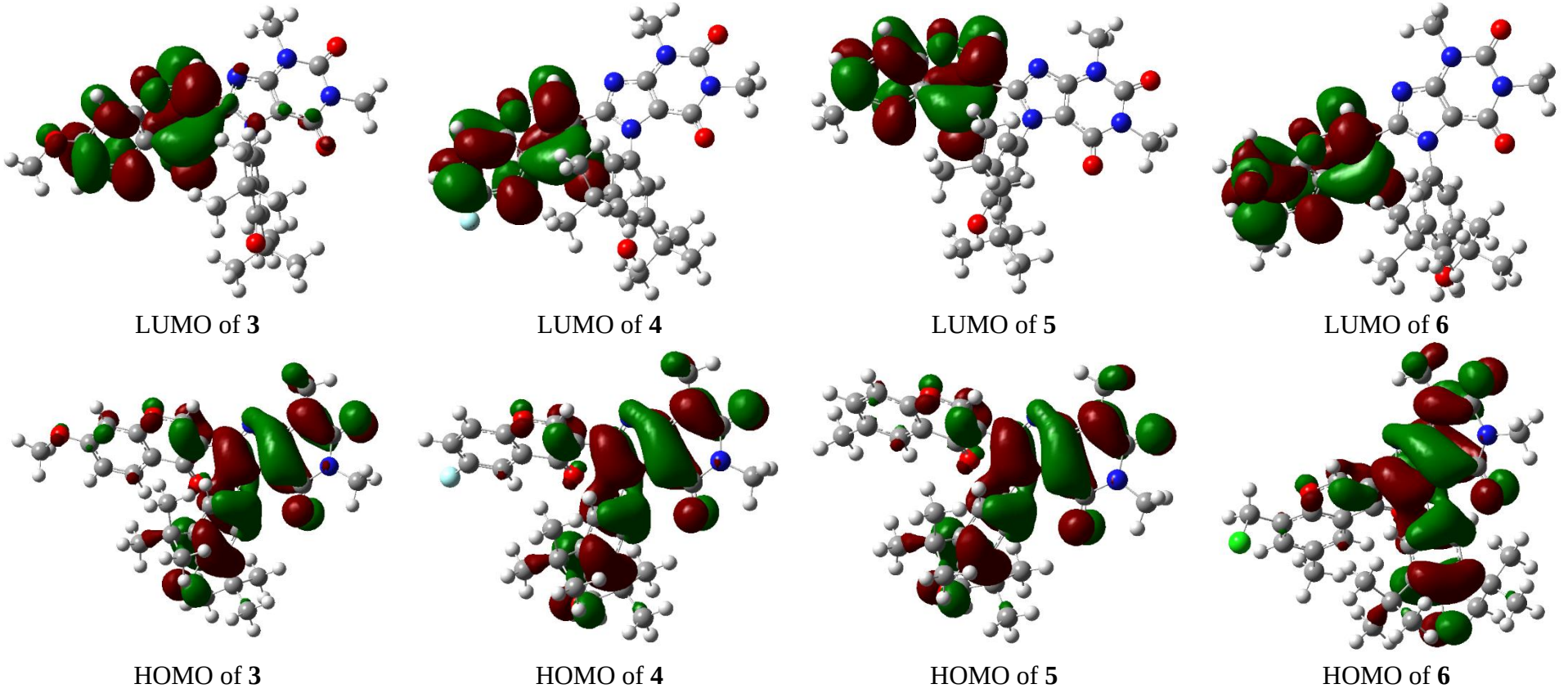


Figure S38. Visualization of HOMO/LUMO for compounds **3-6**

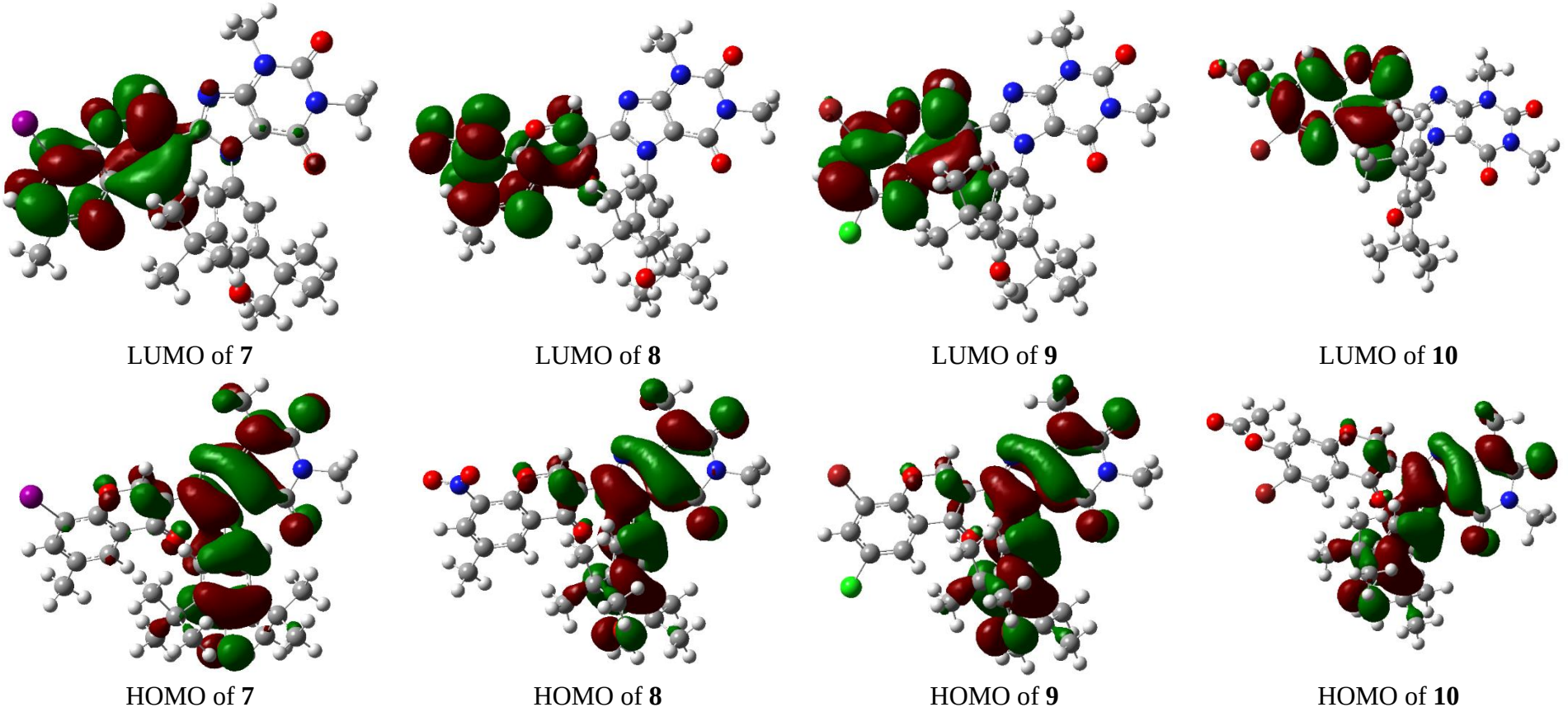
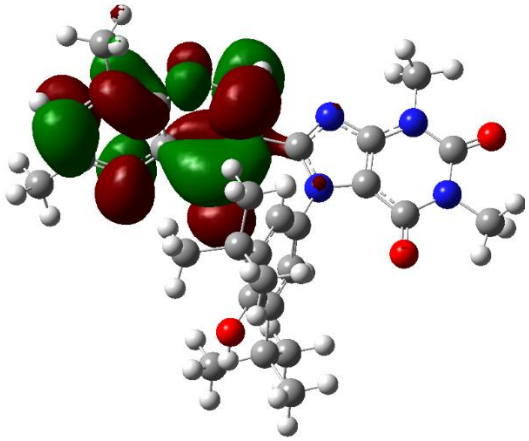
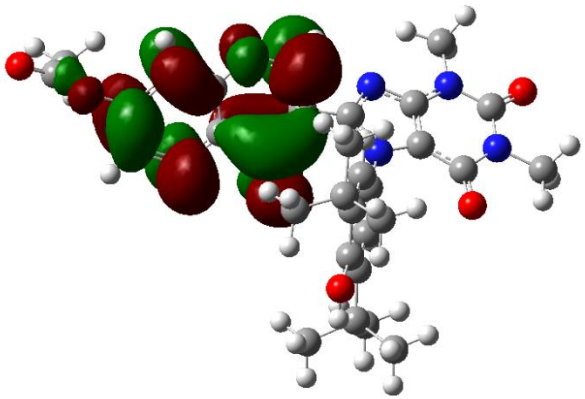


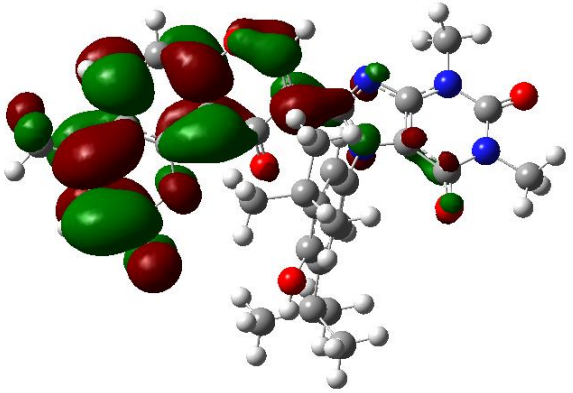
Figure S39. Visualization of HOMO/LUMO for compounds **7-10**



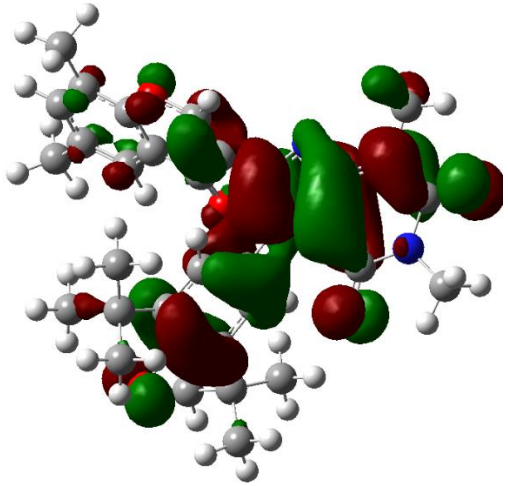
LUMO of **11**



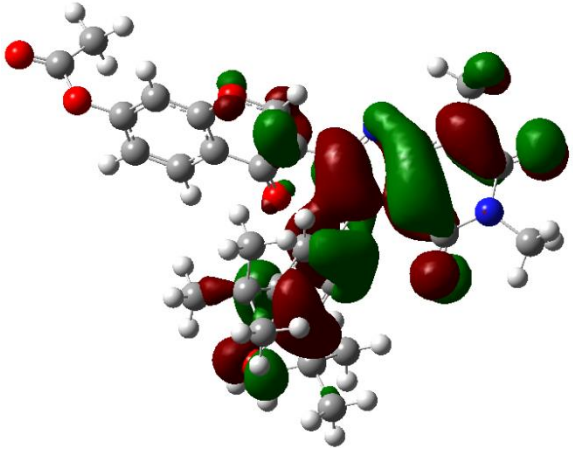
LUMO of **12**



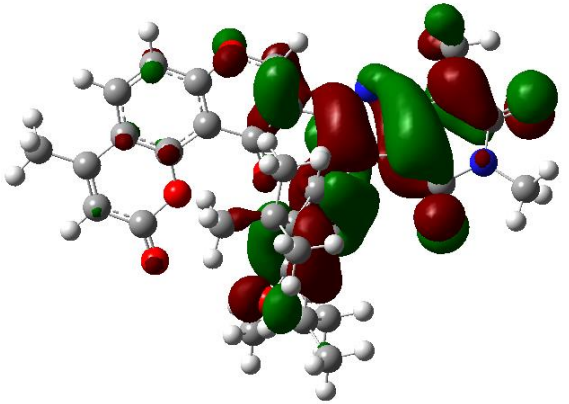
LUMO of **13**



HOMO of **11**



HOMO of **12**



HOMO of **13**

Figure S40. Visualization of HOMO/LUMO for compounds **11-13**

Table S6. Calculated molecular descriptors for compounds **2-7**

	2	**3**	**4**	**5**	**6**	**7**
E_{HOMO} (eV)	-6,1097	-6,08773	-6,11903	-6,09127	-6,11495	-5,87385
E_{LUMO} (eV)	-2,04929	-1,95514	-2,18181	-2,00494	-2,17446	-1,97228
Energy gap (eV)	4,060485	4,132595	3,937217	4,086336	3,940483	3,901571
Ionization potential, IP (eV)	6,109776	6,087734	6,119028	6,091272	6,114946	5,873853
Electron affinity (eV)	2,049291	1,955139	2,18181	2,004936	2,174463	1,972282
Electronegativity, χ (eV)	4,079533	4,021437	4,150419	4,048104	4,144704	3,923068
Chemical hardness, η (eV)	2,030243	2,066298	1,968609	2,043168	1,970241	1,950785
Chemical softness, S (eV^{-1})	0,492552	0,483957	0,507973	0,489436	0,507552	0,512614
Electrophilicity index, ω (eV)	4,09867	3,913268	4,375165	4,01023	4,35951	3,944683
Chemical potential, μ (eV)	-4,07953	-4,02144	-4,15042	-4,0481	-4,1447	-3,92307

Table S7. Calculated molecular descriptors for compounds **8-13**

	8	**9**	**10**	**11**	**12**	**13**
E_{HOMO} (eV)	-6,14243	-6,09182	-6,09807	-6,10978	-6,11957	-6,13454
E_{LUMO} (eV)	-2,95951	-2,41447	-2,35351	-1,95051	-2,16086	-2,27705
Energy gap (eV)	3,182917	3,677349	3,744561	4,159262	3,958714	3,857488
Ionization potential, IP (eV)	6,142429	6,091816	6,098075	6,109776	6,119572	6,134538
Electron affinity (eV)	2,959512	2,414468	2,353514	1,950513	2,160857	2,27705
Electronegativity, χ (eV)	4,550971	4,253142	4,225794	4,030144	4,140215	4,205794
Chemical hardness, η (eV)	1,591459	1,838674	1,87228	2,079631	1,979357	1,928744
Chemical softness, S (eV^{-1})	0,628354	0,54387	0,534108	0,480854	0,505215	0,518472
Electrophilicity index, ω (eV)	6,507028	4,919092	4,768874	3,905035	4,330036	4,58555
Chemical potential, μ (eV)	-4,55097	-4,25314	-4,22579	-4,03014	-4,14021	-4,20579

Table S8. The predicted types of biological activity for compounds **2-13**

Type of biological activity	Compound											
	2	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Lipid metabolism regulator	0,725	0.733	0,579	0,689	0.494	0,521	0.499	0,552	0.718	0,545	0,870	0.656
Histidine kinase inhibitor	0,713	0.692	0,665	0,688	0.599	0,598	0.587	0,643	0.649	0,631	0,700	0.626
Antiallergic	0,676	0.687	0,659	0,661	0.602	0,486	0.569	0,493	0.576	0,666	0,662	0.644
Lipid peroxidase inhibitor	0,441	0.529	0,312	0,466	0.302	0,198	0.361	0.572	0.450	0,474	0,633	0.608
Antiparkinsonian	0,433	0.390	0,426	0,404	0.348	0,219	0.264	0,362	0.255	0,365	0,352	0.287
General pump inhibitor	0,420	0.435	0,366	0,401	0.315	-	-	-	-	0,372	0,364	0.533
Antiinflammatory	0,372	0.384	0,396	0,382	0.343	0,240	0.269	0,357	0.401	0,450	0,487	0.494
Diuretic	0,331	0.277	0,226	0,313	0.277	0,277	0.300	0,305	0.334	0,285	0,331	0.275
Immunomodulator	0,331	0.265	0,295	0,307	0.295	0.154	0.200	0,199	0.244	0,372	0,332	0.285
Cardioprotectant	0,308	0.325	0,290	0,336	-	0,298	0.244	-	-	0,330	0,264	-
Antioxidant	0,233	0.263	0,194	0,230	0.198	0,168	0.185	0,169	0.235	0,266	0,276	0.258
Spasmolytic	0,231	0.236	-	0,202	-	-	-	-	-	0,190	0,207	0.259
Vasodilator	0,226	0.245	-	0,196	-	-	-	-	-	0,183	0,289	-
Cytostatic	0,196	0.218	-	-	-	-	-	-	-	-	0,234	-
Lipoxygenase inhibitor	0,166	0.172	0,165	0,168	0.136	0,106	0.122	0,126	0.151	0,183	0,178	0.119
MAO inhibitor	0,147	0.191	0,134	0,163	-	-	-	0,109		0,132	0,124	0.185
Cyclooxygenase inhibitor	0,139	0.156	0,230	0,165	0.099	-	-	0,112	0.154	0,212	0,196	0.167
Antiischemic, cerebral	-	0.337	0,385	0,360	0.362	-	-	-	-	0,343	0,420	0.319

Table S9. Drug-Likeness of compounds **2-13**

Соединение	MW[1]	HBD[2]	HBA[3]	MR[4]	TPSA, Å[2 5]	MLOGP[6]	Rotatable bonds	Bio-availability	Lipinski rule	Veber rule
2	528.6	1	6	154.15	112.26	3.08	4	0.55	+	+
3	558.62	1	7	160.65	121.49	2.77	5	0.55	+	+
4	546.59	1	7	154.11	112.26	3.45	4	0.55	+	+
5	542.63	1	6	159.12	112.62	3.27	4	0.55	+	+
6	591.10	1	6	168.88	112.26	3.65	5	0.55	+	+
7	668.52	1	6	171.84	112.26	3.91	4	0.55	+	+
8	587.62	1	8	167.94	158.08	2.41	5	0.17	+	-
9	641.94	1	6	166.87	112.26	4.09	4	0.55	+	+
10	665.53	1	8	173.35	138.56	3.49	6	0.17	-	+
11	556.65	1	6	164.09	112.26	3.46	4	0.55	+	+
12	586.63	1	8	165.65	138.56	2.94	6	0.17	-	+
13	610.66	1	8	175.16	142.47	3.15	4	0.17	+	-

[1] *Molecular weight g/mol*
[2] *Number of H-bond donors*
[3] *Number of H-bond acceptors*
[4] *Molar Refractivity*
[5] *Topological Polar Surface Area*
[6] *Log* $P_{octanol/water}$

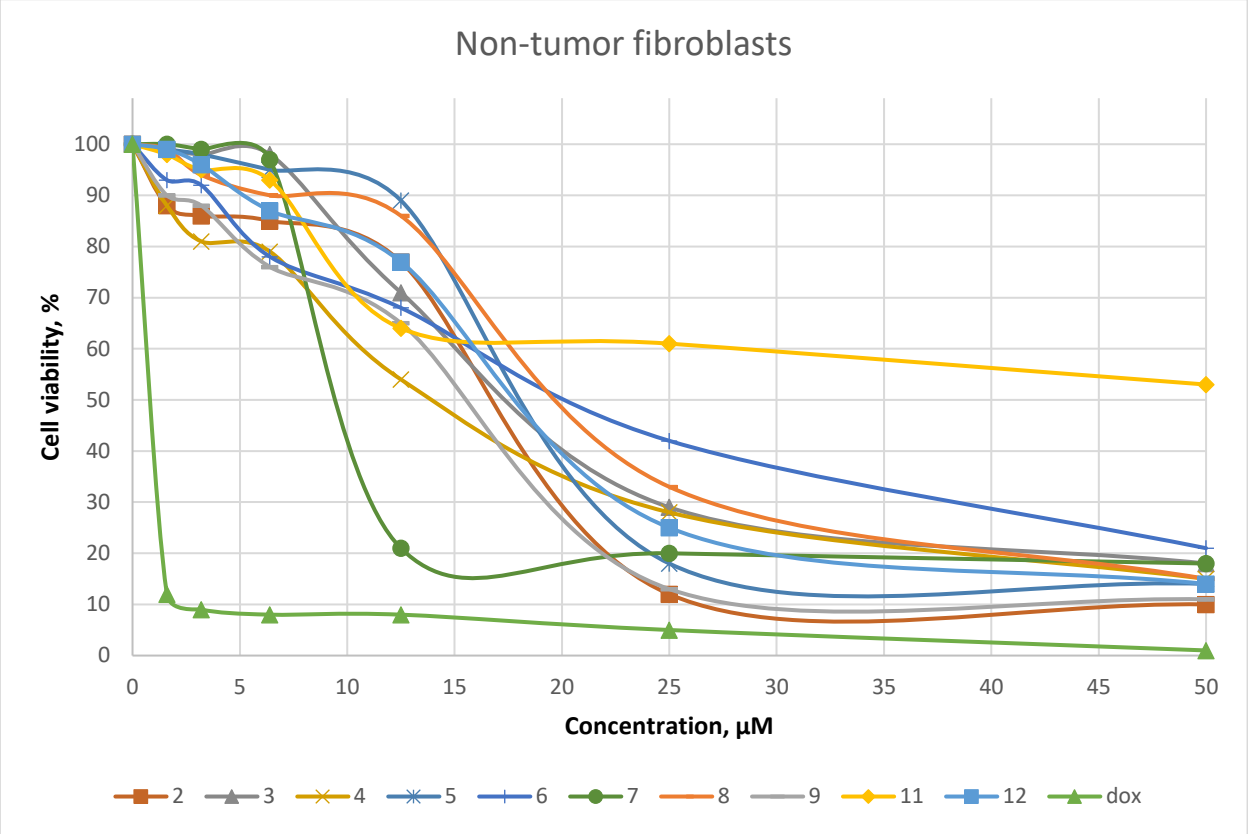


Figure S41. The dependence of the survival of non-tumor fibroblasts on the concentration of compounds **2-9, 11, 12**

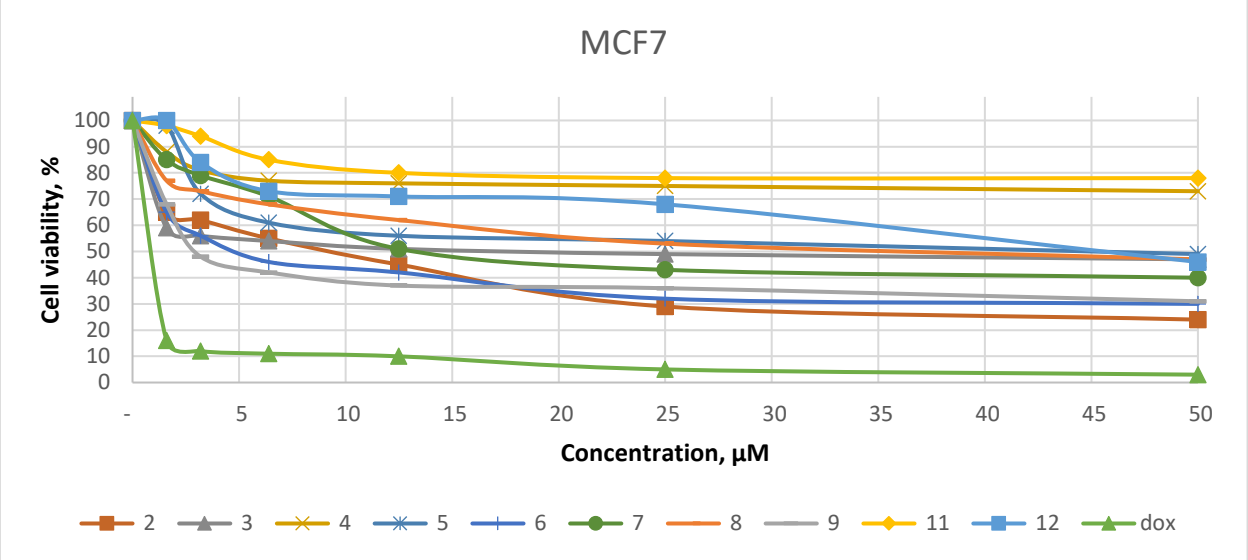


Figure S42. Dependence of the survival of breast adenocarcinoma cells on the concentration of compounds **2-9, 11, 12**

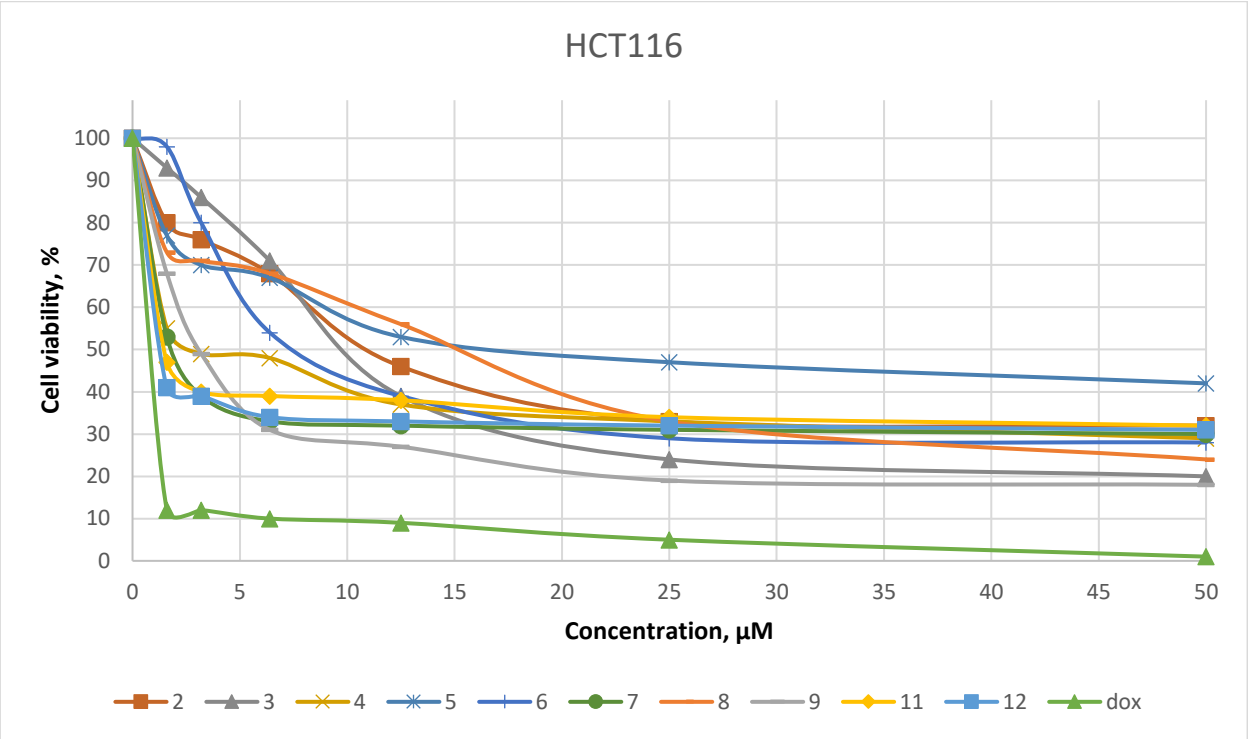


Figure S43. Dependence of the survival of colon adenocarcinoma cells on the concentration of compounds **2-9, 11, 12**