Electronic Supplementary Material (ESI) for New Journal of Chemistry.

Usnic acid based thiazole-hydrazones as multi-targeting inhibitors of a wide spectrum of SARS-CoV-2 viruses

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Supplementary Material

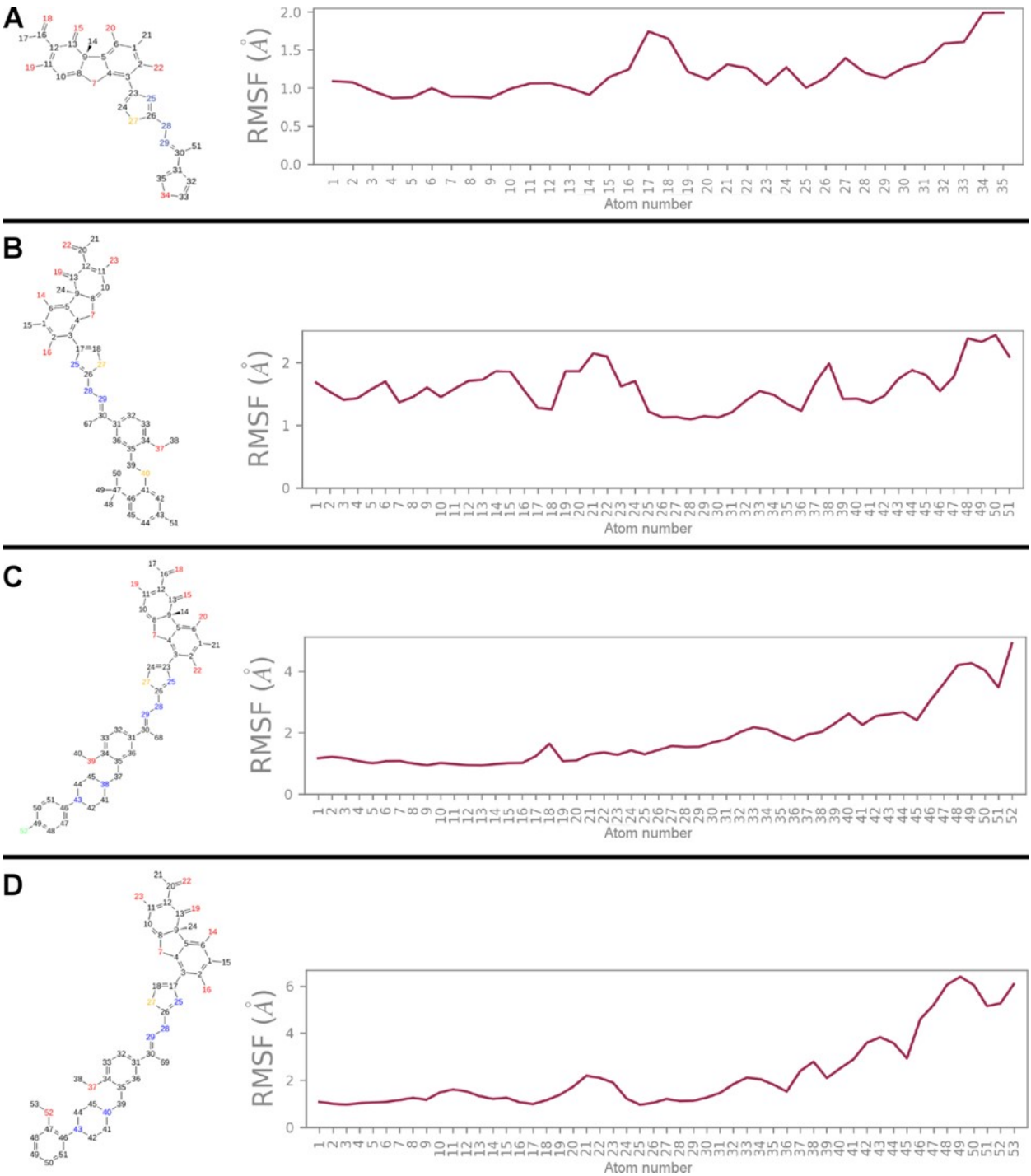


Figure S1 RMSF plots of novel usnic acid derivatives. The position of each atom is indicated by a number for each molecular structure. A - **(+)-7a**, B - **(+) -10g**, C - **(+) -10i**, D - **(-) -10j**.

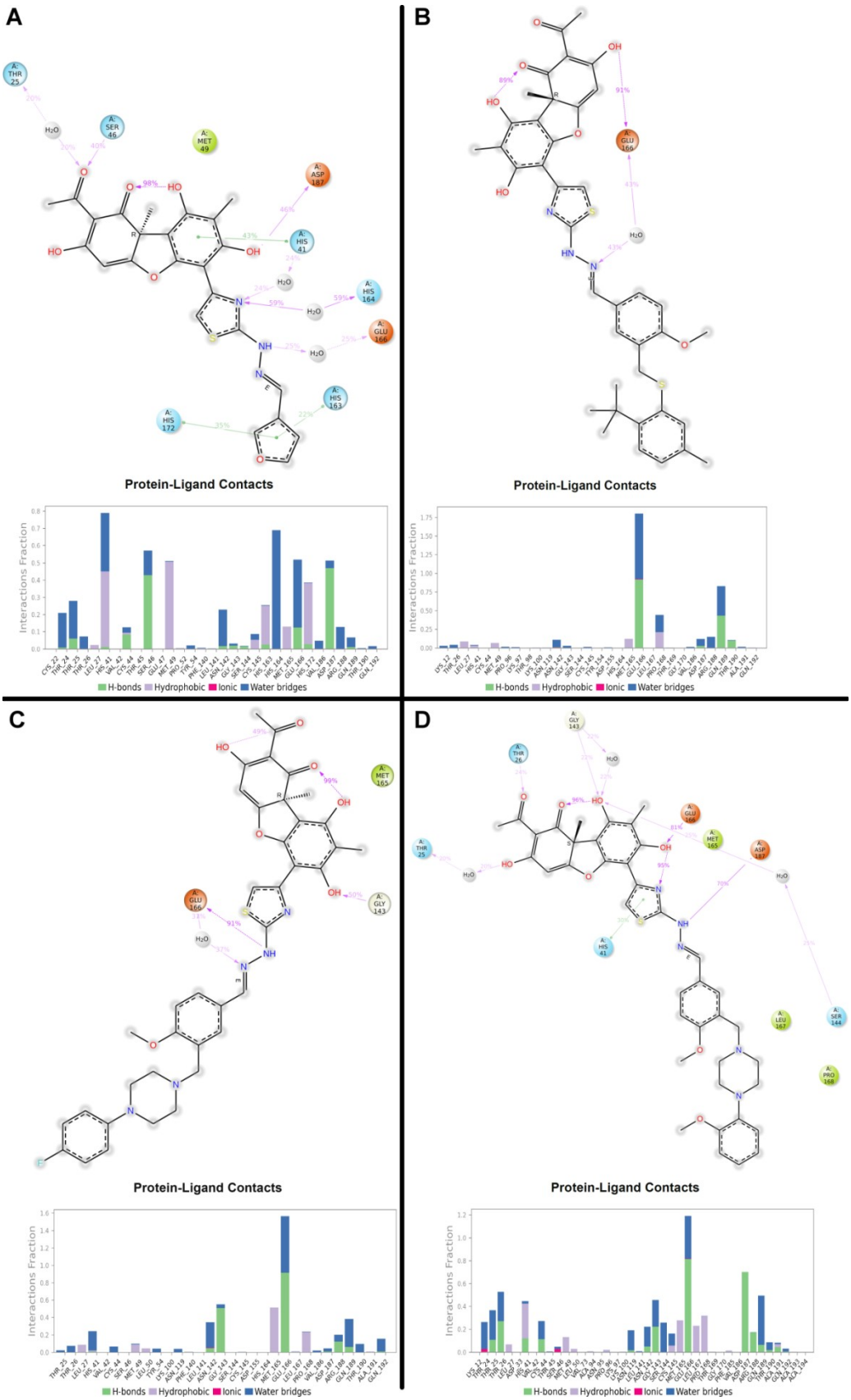


Figure S2 Diagrams of possible interactions of new usnic acid derivatives in the active site of the main protease. The percentage of molecular dynamics simulation time during which the observed interactions existed is given. Purple lines with arrows mark hydrogen bonds, green lines indicate stacking interactions, hydrophobic contacts are possible with individual amino acids without lines. For each molecule, a chart of all possible non-covalent interactions with amino acids of the active site of the main protease is given. A - **(+)-7a**, B - **(+)-10g**, C - **(+)-10i**, D - **(-)-10j**.

Table S1 A.a. alignment NTD of S-protein and analysis of biliverdin binding site

Strain	Mutations	Distance from the binding site, Å	Deletion	Distance from the binding site, Å
Delta (B.1.617.2)	T95I G142D Y145H F158G	~ 11 ~ 13 ~ 20 ~ 16	156-157	~ 10-12
Omicron BA.1	T95I	~ 11	143-145	~ 15
Omicron BA 5.2	G142D V213G	~ 13 ~ 18		
Omicron XBB.1.5	H146Q Q183E V213E	~ 25 ~ 15 ~ 18	144	~ 22
Omicron BQ1.1	G142D V213G	~ 13 ~ 18		

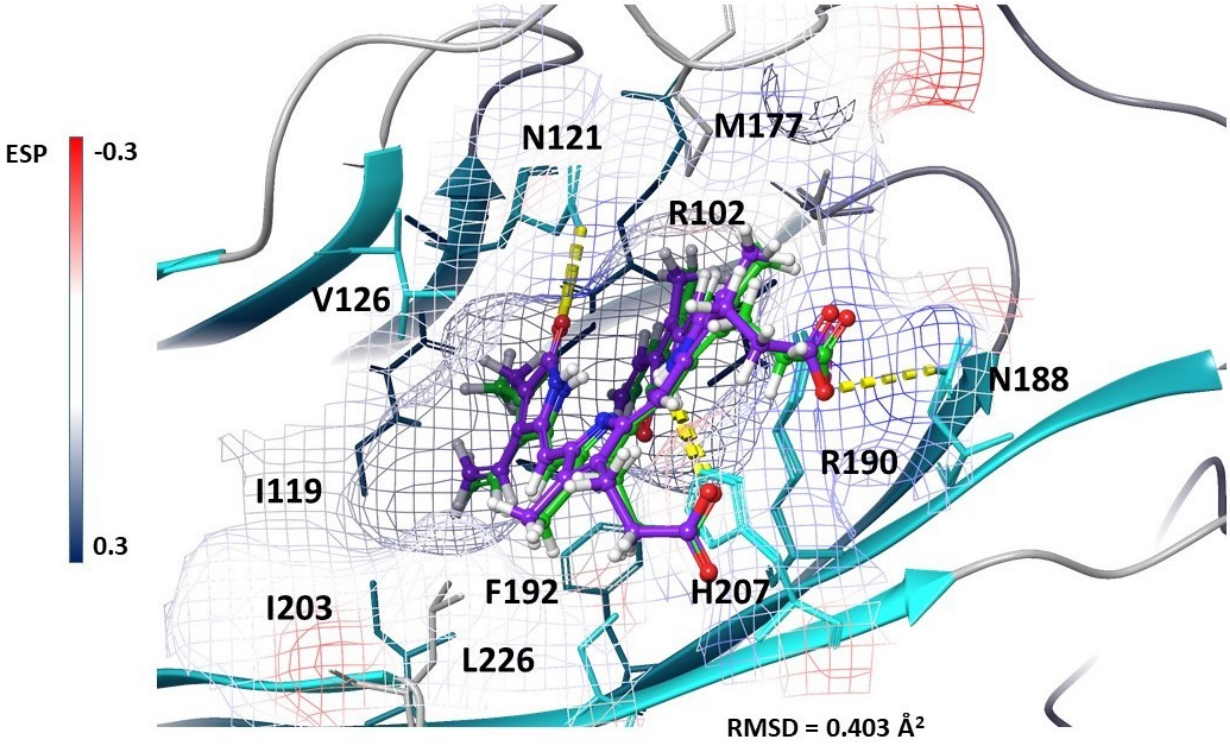


Figure S3 Result of molecular re-docking procedure: green molecule is correspond to geometrical parameters from X-ray complex (PDB ID: 7B62), violet – obtained from re-docking. H-bonds are shown yellow dotted line.

Table S2 S glycoprotein molecular docking and metadynamics results

ID	pIC_{50}	Docking score, kcal/mol	Emodel, kcal/mol	IFD score, kcal/mol	Interactions with a.a.		Pose Score (MD)	ΔG_{bind}, kcal/mol
					H-bond	Others		
(+)-7a	6.19	-9.083	-96.26	-657.16	N121 L101	none	1.18	-91.2
(+)-10g	5.03	-10.278	-109.66	-657.93	N121 L101 Q173	F192 π-π	1.21	-70.5
(+)-10i	5.97	-10.579	-100.47	-654.42	N121 I101	H207 π-π	2.37	-76.3

(+)-10j	5.69	-7.185	-90.02	-653.17	Y170 I101 N99 R190 H207	W104 π-π	1.85	-84.1

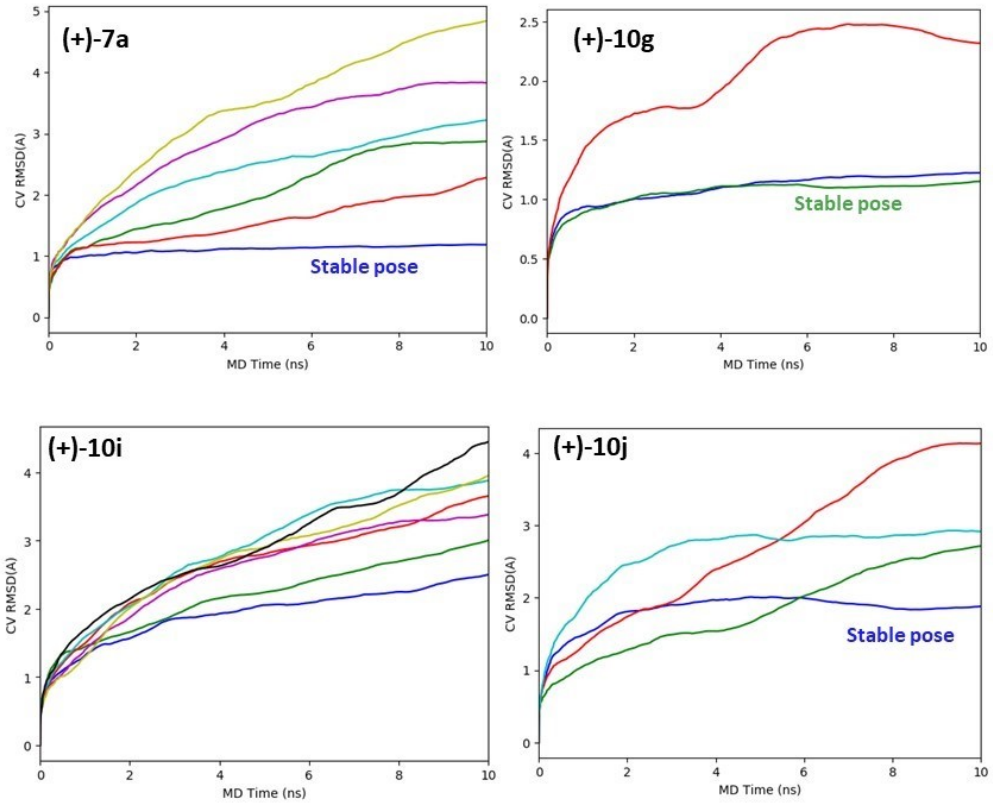
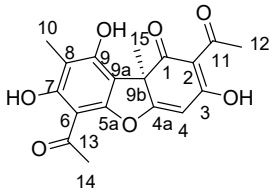


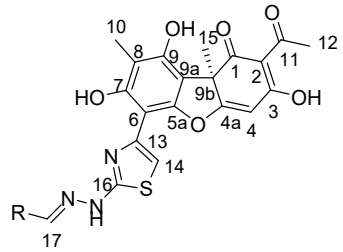
Figure S4 RMSD fluctuation of docking poses of studied compounds

The NMR spectrum of compound 1



NMR ^{1}H (**$CDCl_3$**, δ): 1.74 (3H, s, H-15), 2.09 (3H, s, H-10), 2.64 and 2.66 (6H, s, H-12 and H-14), 5.96 (1H, s, H-4), 11.02 (OH-9), 13.30 (OH-7), 18.84 (OH-3).

The NMR spectra of compounds 7-10



NMR ^{1}H (**$CDCl_3$**, δ): 1.67 (3H, s, H-15), 2.13 (3H, s, H-10), 2.61 (3H, s, H-12), 5.88 (1H, s, H-4).
NMR ^{1}H (**DMSO-*d6***, δ): 1.70 (3H, s, H-15), 2.03 (3H, s, H-10), 2.60 (3H, s, H-12), 6.20 (1H, s, H-4).

Table S3. NMR^{1}H spectra of 16k–16o ($CDCl_3$ for 7a,b, 8b, 9a,b and DMSO-*d6* for 8a,c; δ).

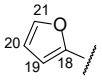
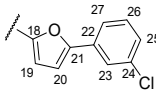
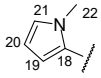
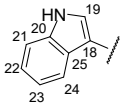
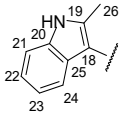
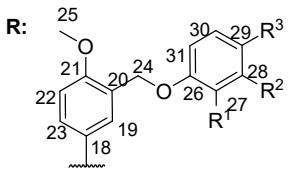
№	7a	7b	8a	8b	8c	9a	9b
							
H-14	s 7.15	s 7.12	s 7.24	s 7.09	s 7.37	s 7.24	s 7.22
H-17	s 7.60	s 7.68	s 7.94	s 7.68	s 8.09	s 8.30	s 8.33
H-19	d 6.65 (J = 2.5 Hz)	d 6.69 (J = 3.3 Hz, AB-system)	s 6.46	m 6.39	s 8.00	m 8.21	
H-20	m 6.45	d 6.66 (J = 3.3 Hz, AB-system)	s 6.14	m 6.11	s 9.17		
H-21	d 7.49 (J = 2.2 Hz)		s 6.92	s 6.72		s 7.45	m 7.34
H-22				s 3.91		m 7.21	m 7.13
		s 7.62				m 7.21	m 7.13
						d 7.83 (J = 2.7 Hz)	m 8.10
		d 7.52 (J = 7.5 Hz)					
		m 7.21–7.30					s 2.51
		m 7.21–7.30					
NH	s 8.88	---	---	bs 8.68	---	s 12.08	s 12.00
NH (HetAr)			s 11.30		s 12.60	s 11.59	s 11.51
OH-3	s 18.77	s 18.76	bs 18.77	s 18.79	---	bs 18.82	bs 18.82
OH-7	bs 12.40	---	s 12.05	---	s 12.71	s 13.03	bs 13.05
OH-9	s 10.26	s 10.26	s 10.28	s 10.28	s 10.31	s 10.30	s 10.31

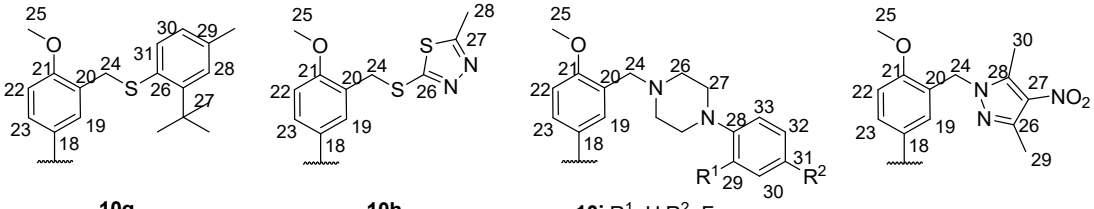
Table S4. NMR[1]H spectra of 17a–17f ($CDCl_3$, δ).



10a R^1=H R^2=H R^3=F
10b R^1=H R^2=F R^3=H
10c R^1=F R^2=H R^3=H
10d R^1=H R^2=Cl R^3=F
10e R^1=F R^2=H R^3=F
10f R^1=H R^2=Me R^3=Cl

№	10a	10b	10c	10d	10e	10f
H-14	s 7.09	s 7.02	m 7.05	s 7.06	s 7.09	s 7.07
H-17	m 7.45–7.65	s 7.81	s 7.68	s 7.64	s 7.60	s 7.69
H-19	m 7.45–7.65	s 7.71	s 7.62	s 7.61	s 7.56	s 7.64
H-22	m 6.82–6.97	d 6.77 (J = 8.6 Hz)	d 6.78 (J = 7.0 Hz)	m 6.82	d 6.51 (J = 7.9 Hz)	m 6.76
H-23	m 7.45–7.65	d 7.44 (J = 8.6 Hz)	d 7.44 (J = 7.0 Hz)	d 7.48 (J = 7.3 Hz)	d 7.48 (J = 8.3 Hz)	d 7.51 (J = 8.3 Hz)
H-24	s 5.00	s 5.07	s 5.09	s 4.97	s 5.00	s 4.99
H-25	s 3.83	s 3.79	s 3.79	s 3.82	s 3.84	s 3.84
H-27	m 6.82–6.97	m 6.90–7.10	s 6.91	m 7.01		d 6.88 (J = 2.4 Hz)
H-28	m 6.82–6.97	m 6.90–7.10	m 7.05		d 6.82 (J = 7.9 Hz)	s 2.34 (Me)
H-29		m 6.90–7.10	m 7.05			
H-30	m 6.82–6.97		m 7.05	m 7.01	t 6.41 (J = 8.4 Hz)	d 7.21 (J = 8.6 Hz)
H-31	m 6.82–6.97	m 6.90–7.10		m 6.82		d 6.83 (J = 8.5 Hz)
NH	bs 8.92	---	bs 9.45	bs 9.45	bs 8.93	bs 9.56
OH-3	s 18.78	s 18.77	s 18.76	s 18.77	s 18.78	s 18.79
OH-7	---	---	---	---	bs 12.21	---
OH-9	s 10.24	s 10.29	s 10.23	s 10.24	s 10.23	s 10.27

Table S5. NMR^{1}H spectra of 17g–17k ($CDCl_3$ for g–j and DMSO-*d6* for k, δ).



10g **10h** **10i** R^1=H R^2=F; **10j** R^1=OMe R^2=H **10k**

№	10g	10k	10i	10j	10k
H-14	s 7.08	s 7.07	s 7.00	s 6.98	s 7.23
H-17	s 7.49	s 7.69	bs 7.98	s 8.13	s 7.26
H-19	s 7.32	s 7.60	bs 7.98	s 8.05	s 7.67
H-22	d 6.76 (J = 8.5 Hz)	m 6.80	d 6.56 (J = 8.0 Hz)	d 6.46 (J = 8.1 Hz)	d 7.08 (J = 8.4 Hz)
H-23	m 7.40	m 7.47	m 7.34	m 6.84-7.03	d 7.50 (J = 8.4 Hz)
H-24	s 4.04	s 4.51	s 4.11	s 4.19	s 5.27
H-25	s 3.77		s 3.61	bs 3.51	s 3.85
H-26			s 3.29	bs 3.51	
H-27	s 1.22 (t-Bu)		s 3.48	m 3.85	
H-28	m 7.23	s 2.73			
H-29	m 7.08		m 6.83–6.94	m 6.84–7.03	s 2.40
H-30	s 2.33 (Me)		m 6.83–6.94	m 3.85 (OMe)	s 2.59
H-31	m 7.32			m 6.84–7.03	
H-32			m 6.83–6.94	m 6.84–7.03	
H-33			m 6.83–6.94	m 6.84–7.03	
NH	bs 9.09		bs 11.22	bs 11.22	bs 12.28
OH-3	s 18.79		bs 18.7	bs 18.76	bs 18.80
OH-7	---		bs 12.64	bs 12.63	bs 12.77
OH-9	s 10.26		s 10.24	s 10.23	s 10.30

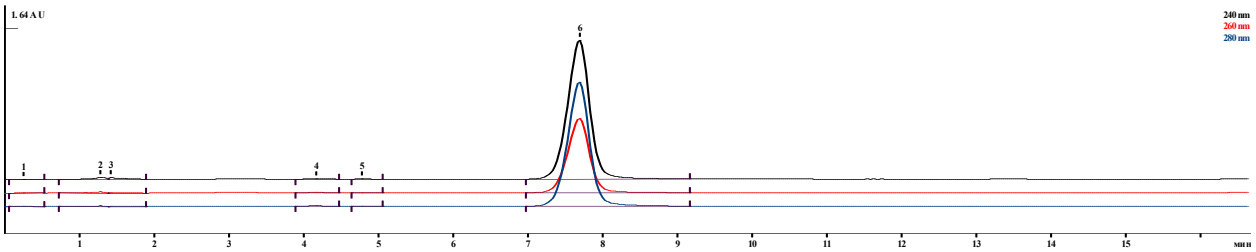


Figure S5 HPLC for compound (99.05% of usnic acid)

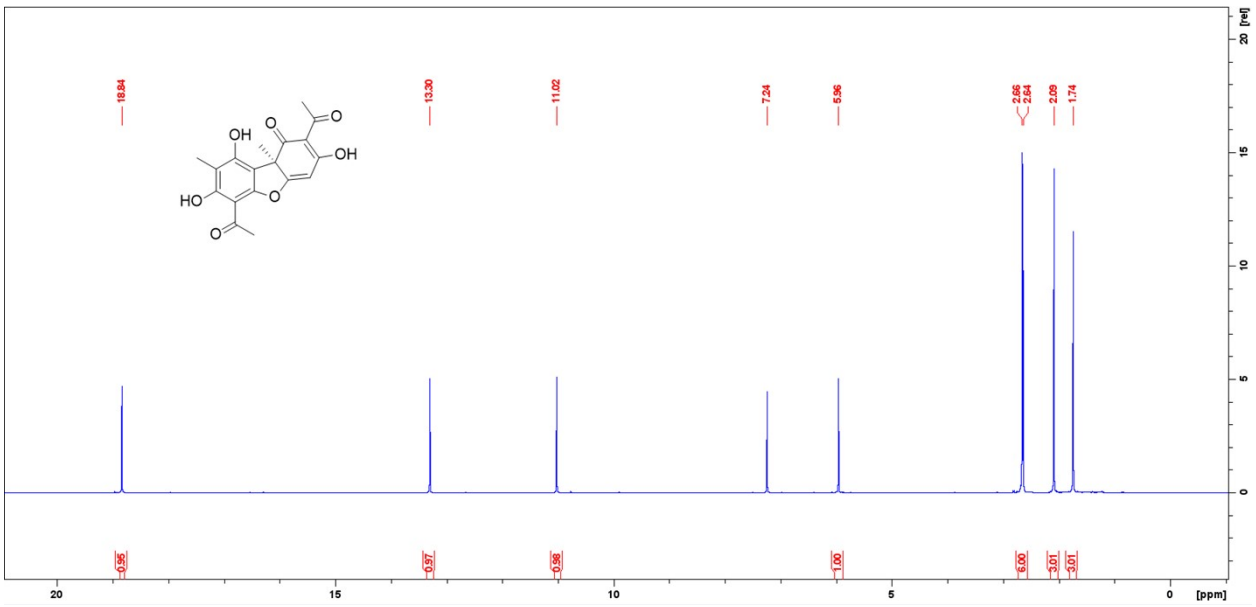


Figure S6: NMR ^{1}H spectrum of **1**

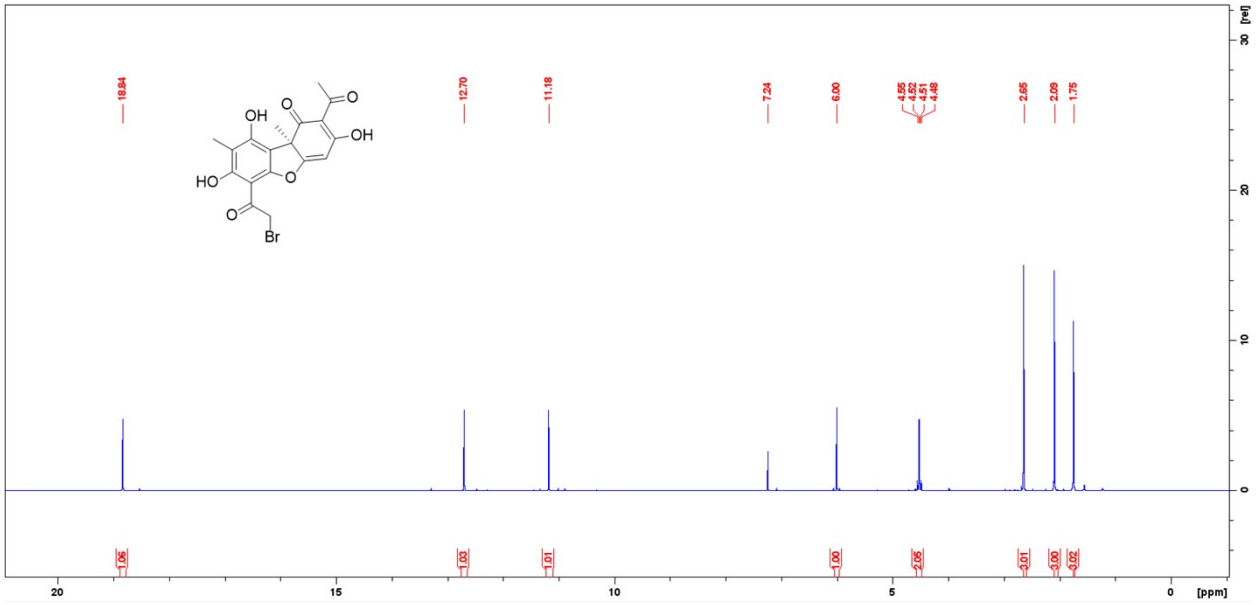


Figure S7: NMR ^{1}H spectrum of **5**

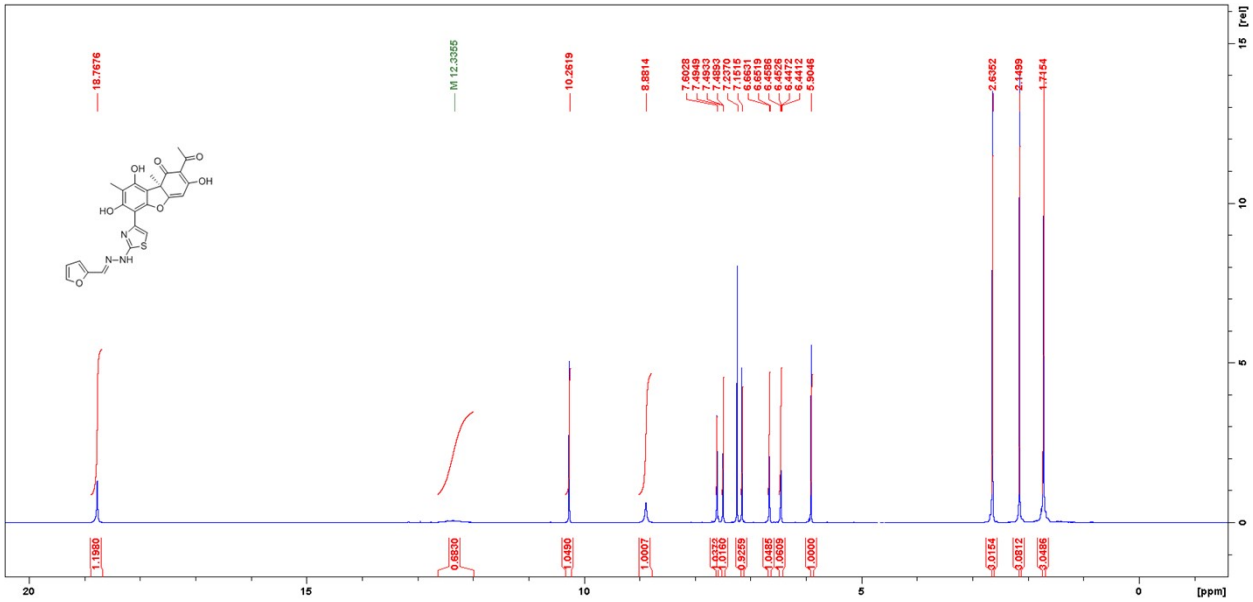


Figure S8: NMR ^{1}H spectrum of **7a**

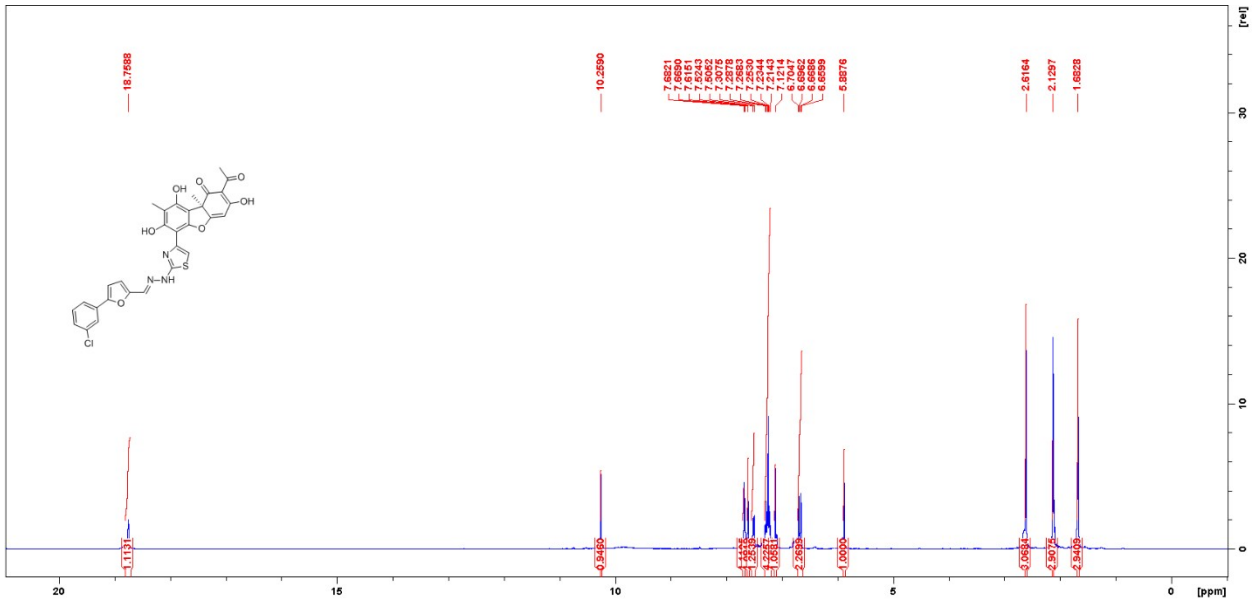


Figure S9: NMR ^{1}H spectrum of **7b**

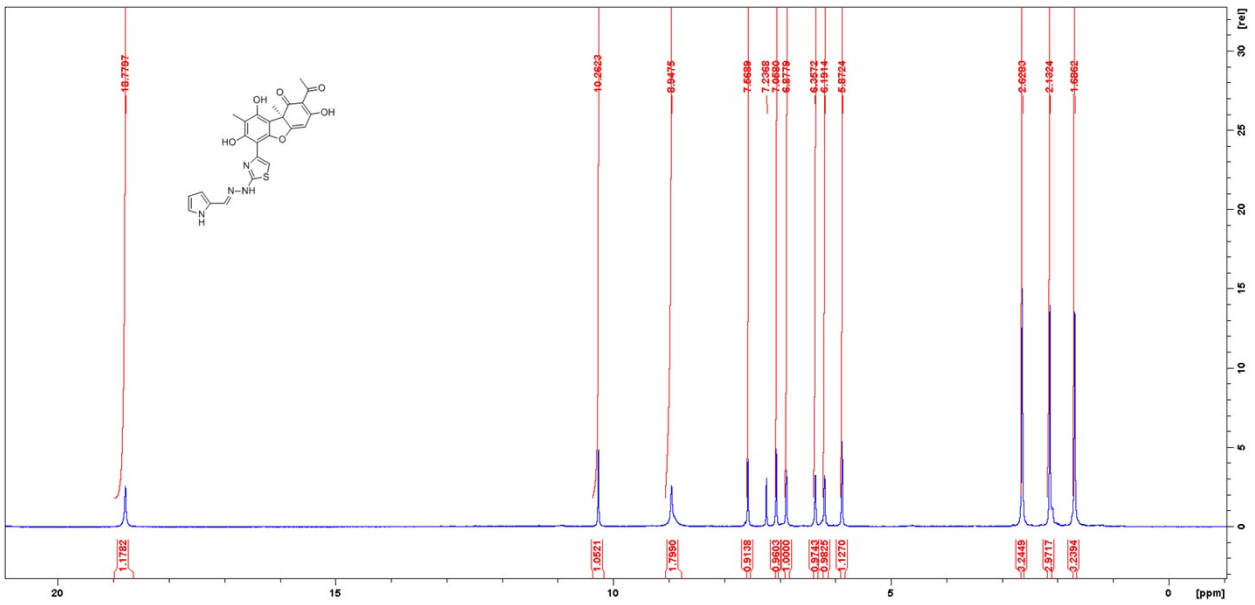


Figure S10: NMR ^{1}H spectrum of **8a**

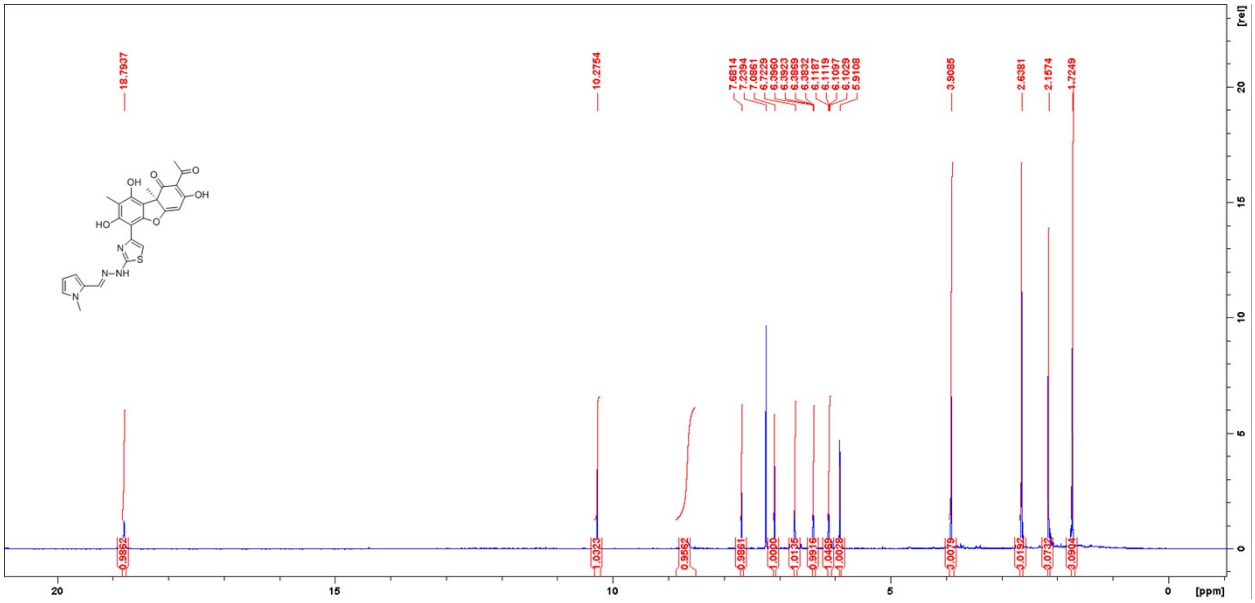


Figure S11: NMR ^{1}H spectrum of **18b**

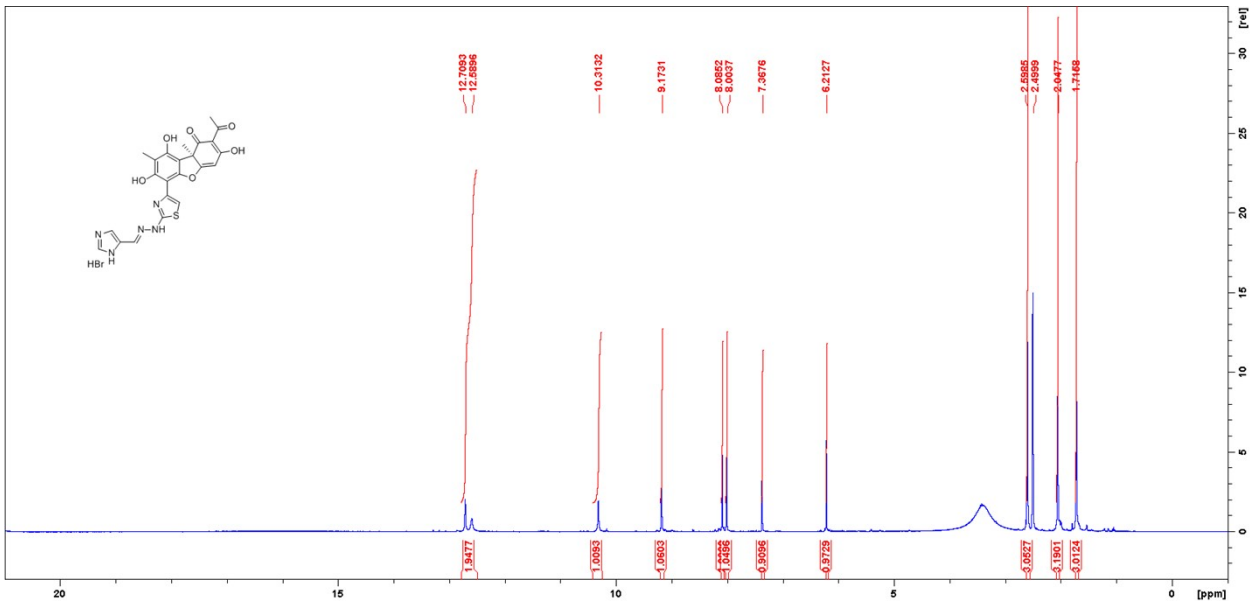


Figure S12: NMR ^{1}H spectrum of **8c**

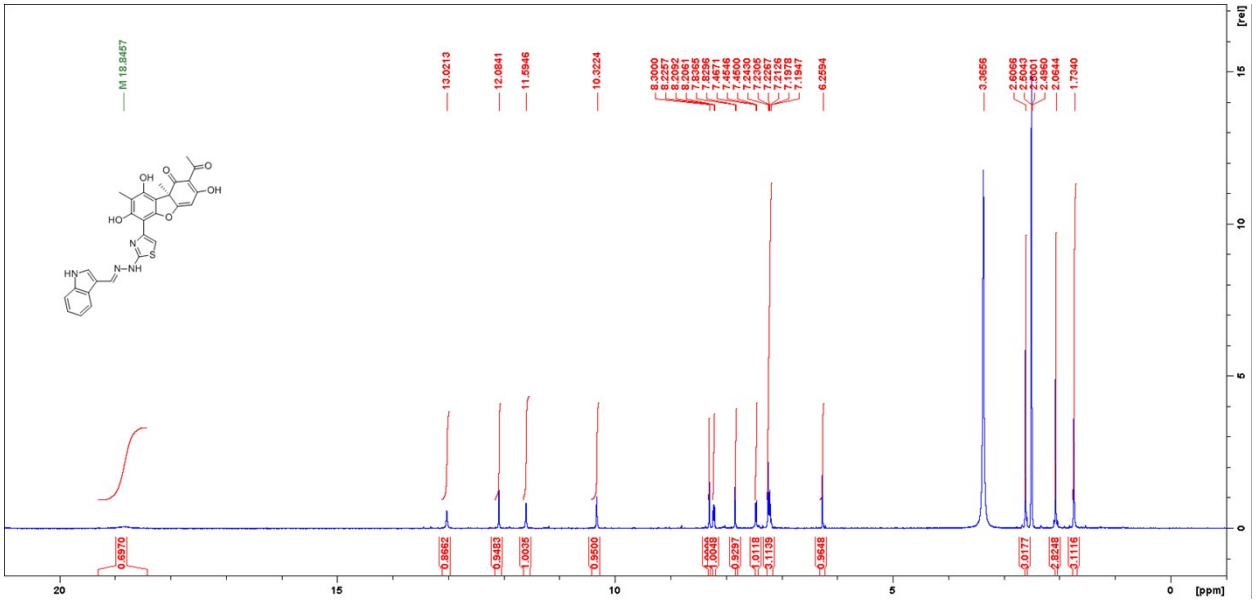


Figure S13: NMR ^{1}H spectrum of **9a**

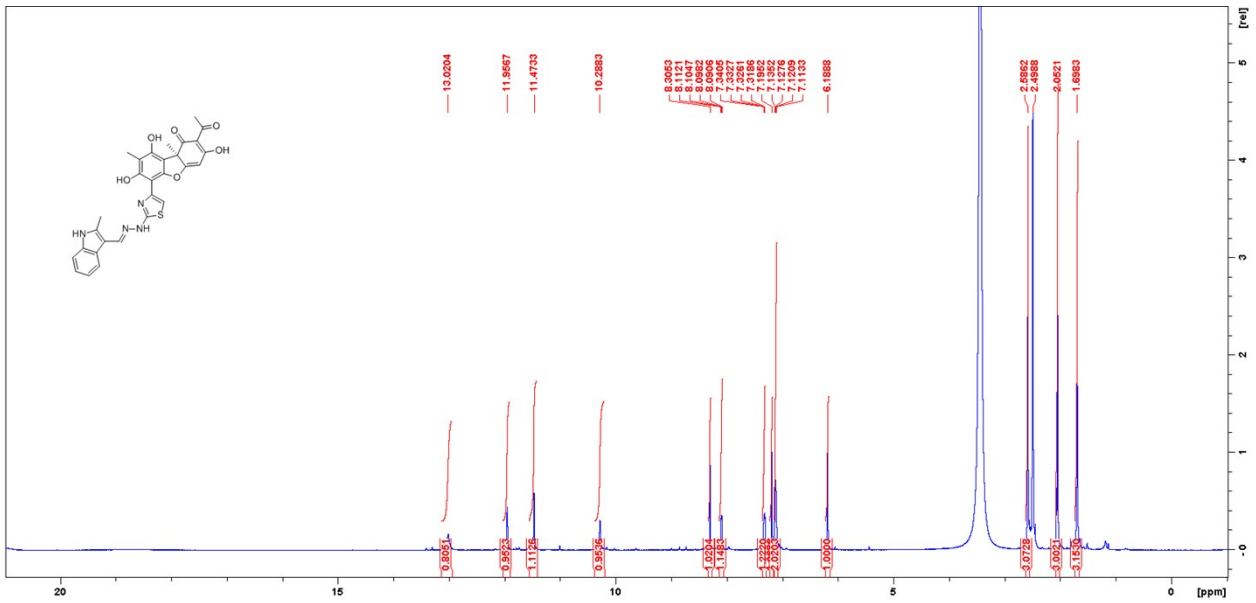


Figure S14: NMR ^{1}H spectrum of **9b**

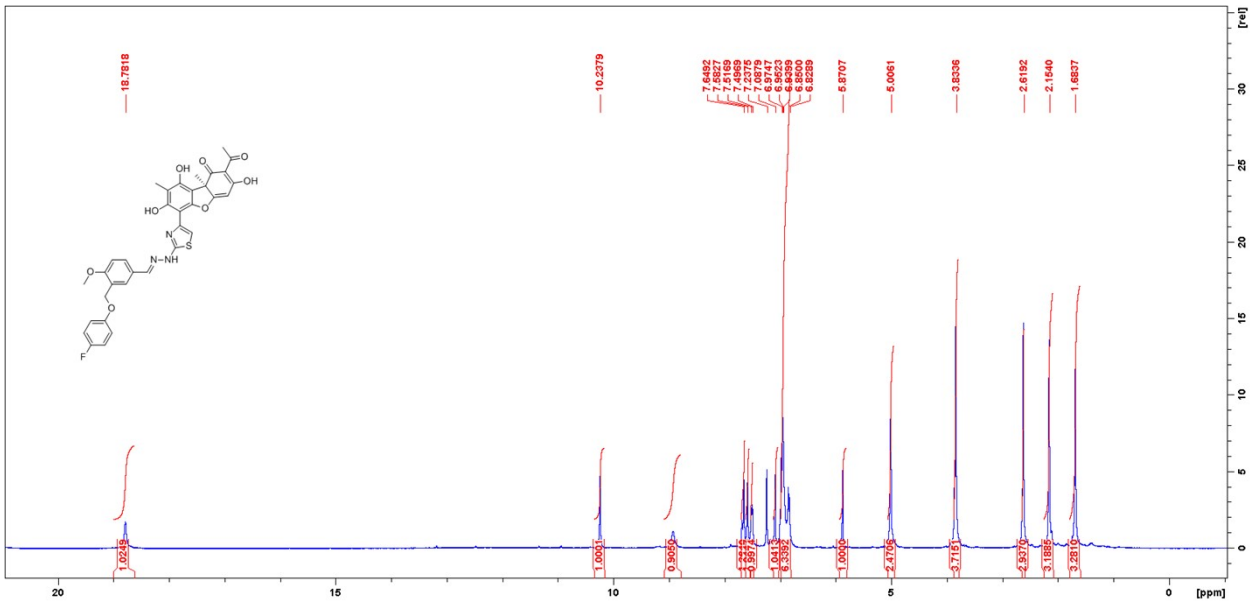


Figure S15: NMR ^{1}H spectrum of **10a**

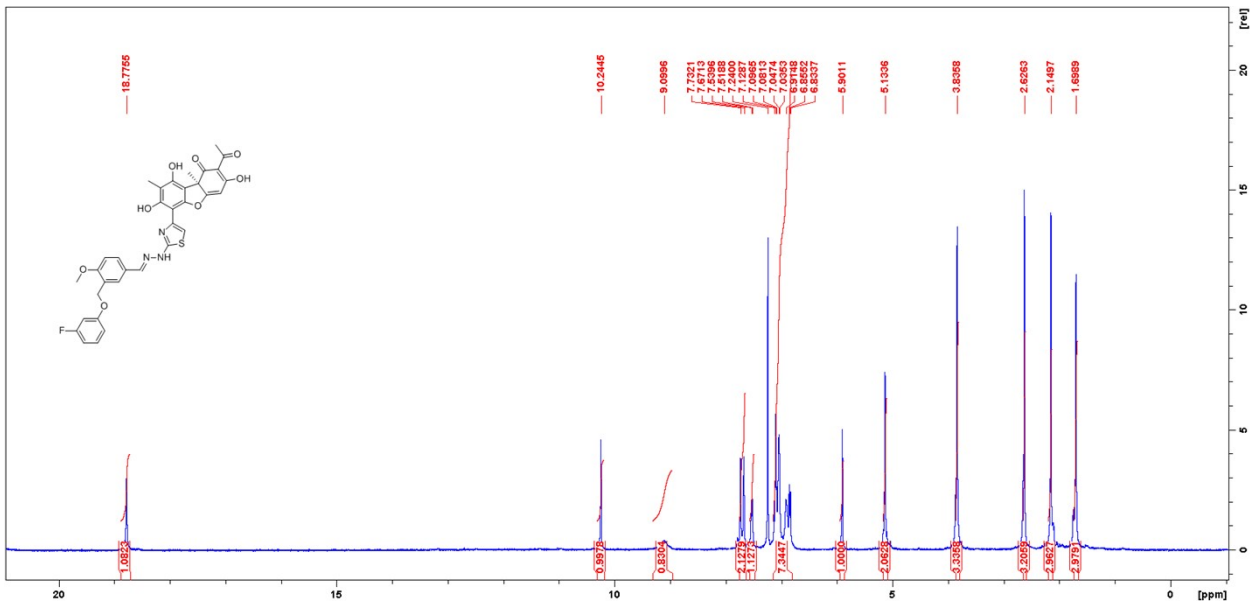


Figure S16: NMR ^{1}H spectrum of **10b**

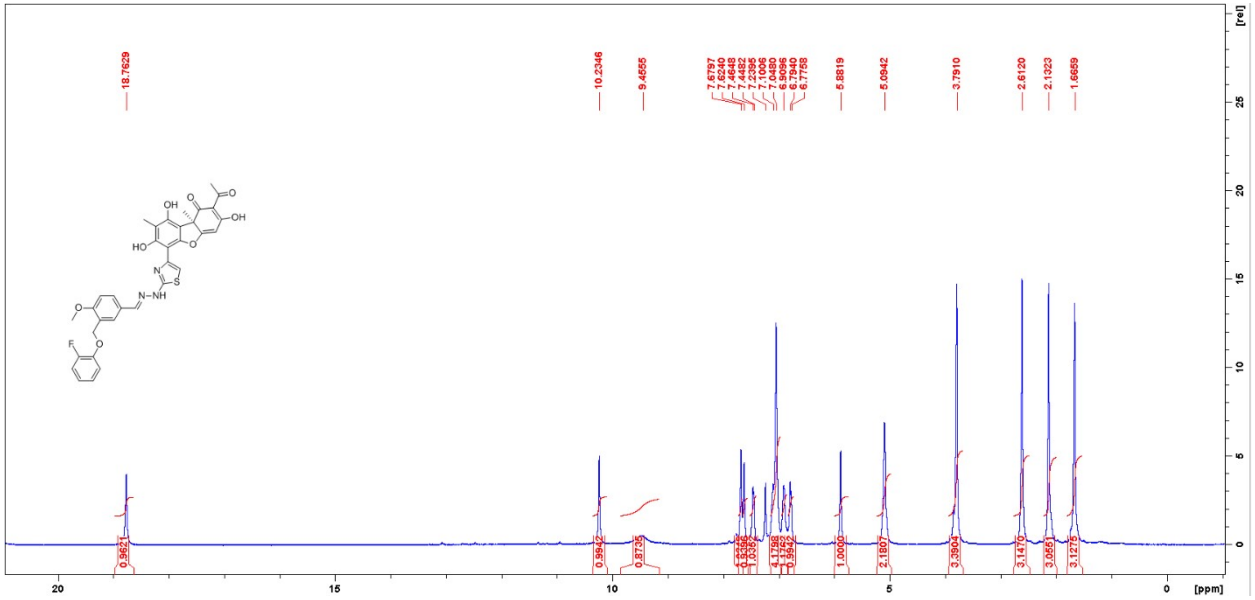


Figure S17: NMR ^{1}H spectrum of **10c**

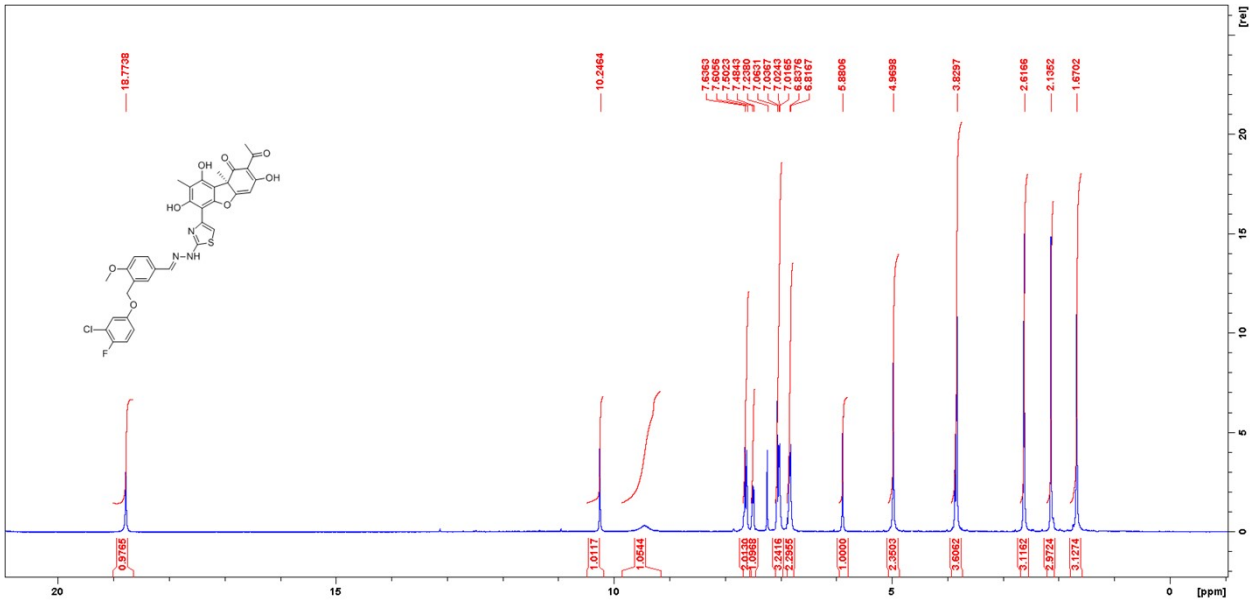


Figure S18: NMR ^{1}H spectrum of **10d**

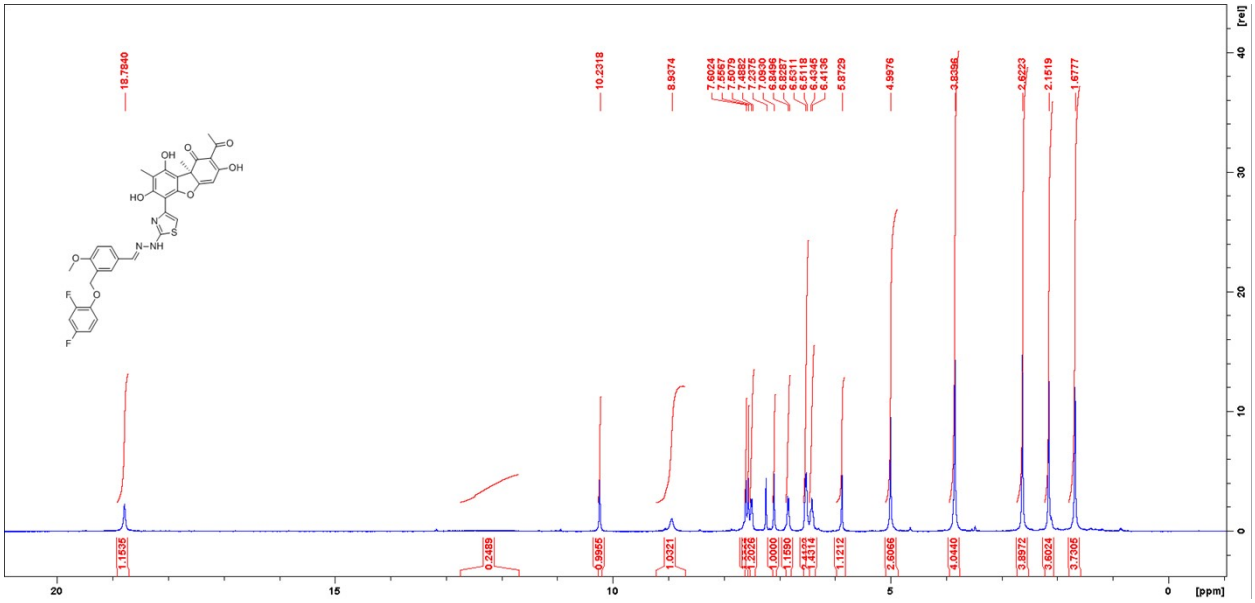


Figure S19: NMR ^{1}H spectrum of **10e**

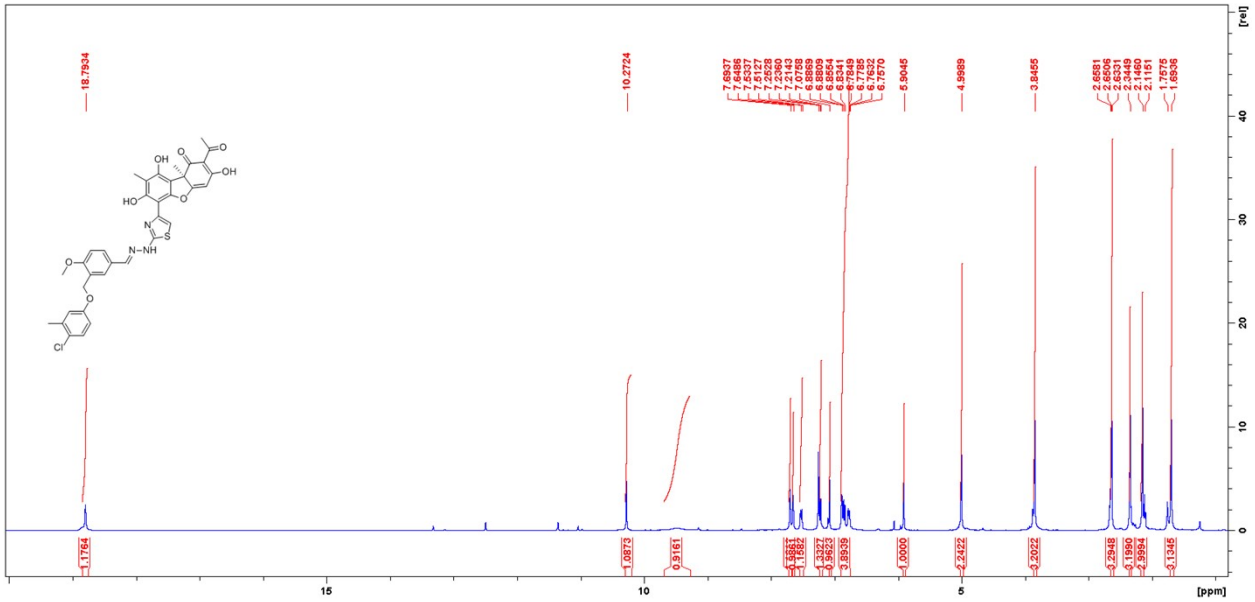


Figure S20: NMR ^{1}H spectrum of **10f**

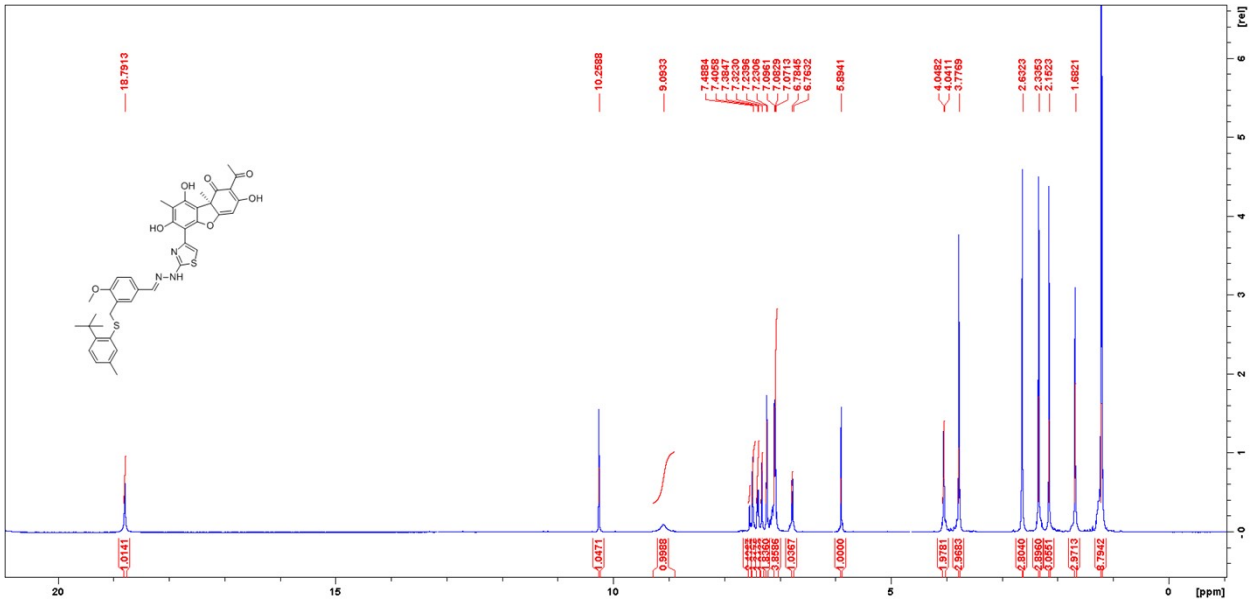


Figure S21: NMR ^{1}H spectrum of **10g**

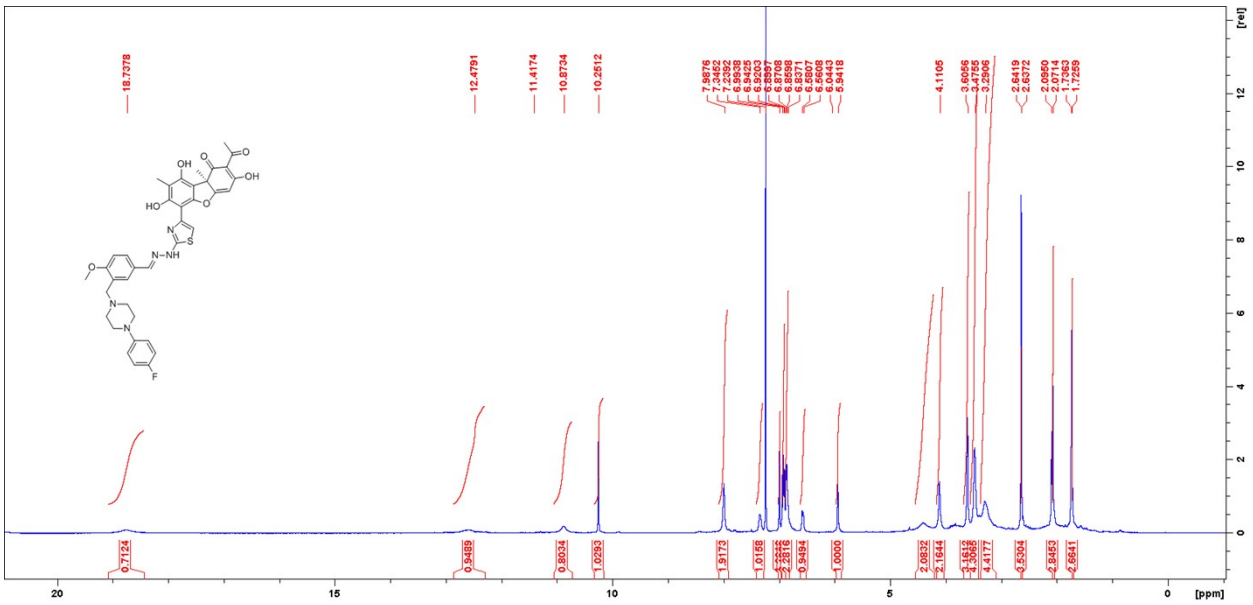


Figure S22: NMR ^{1}H spectrum of **10i**

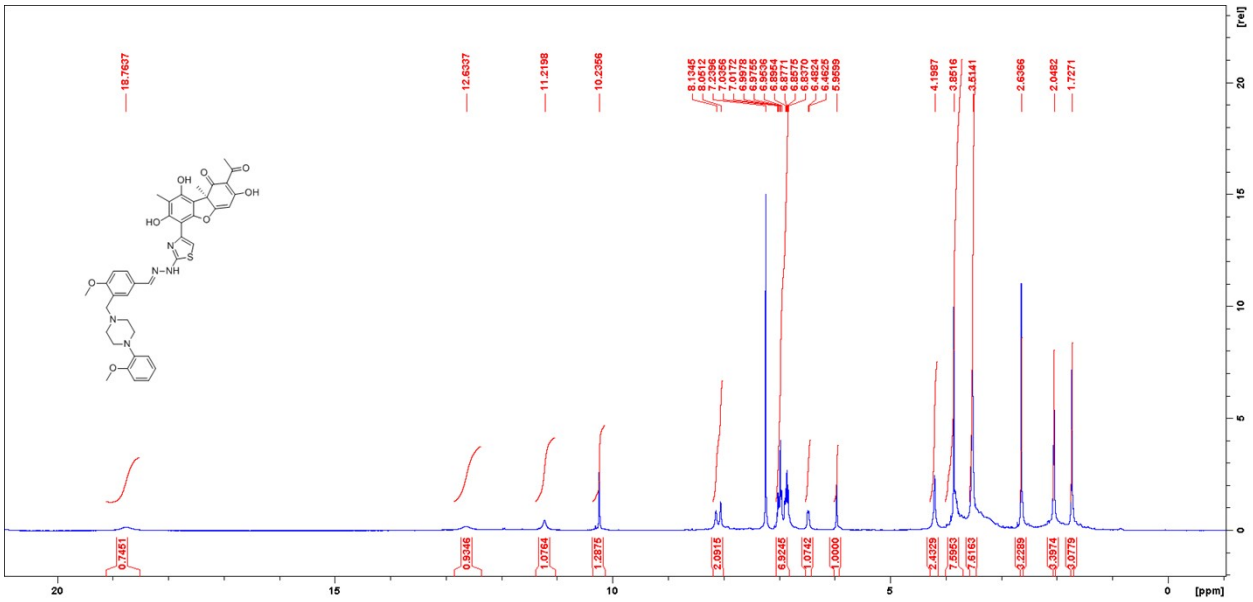


Figure S23: NMR ^{1}H spectrum of **10j**

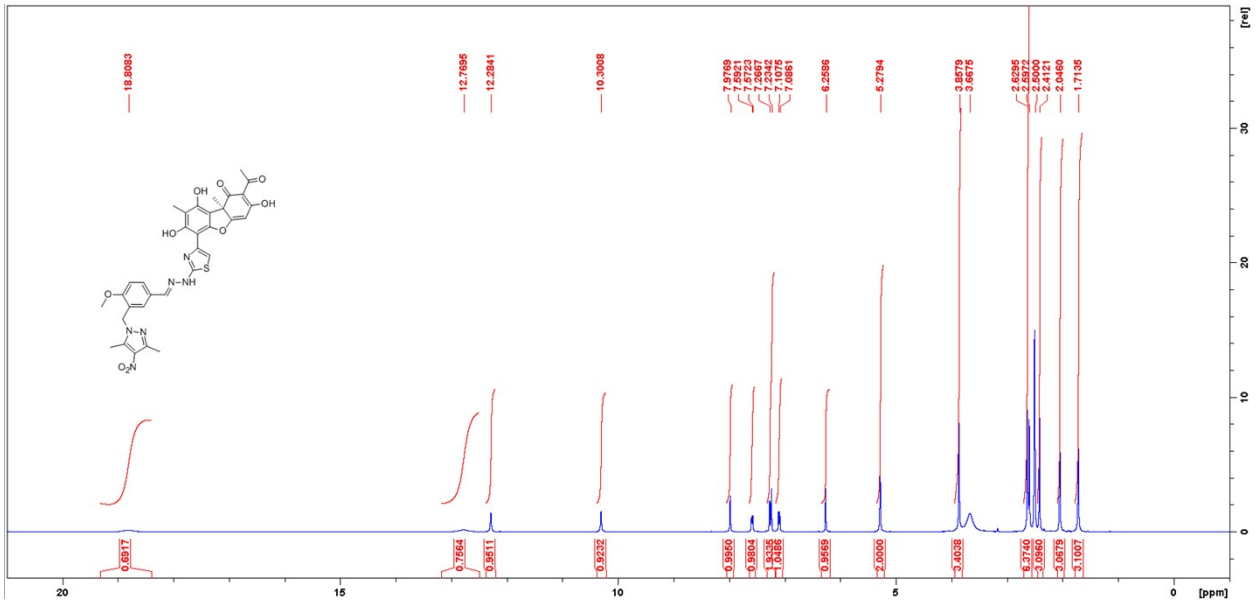


Figure S24: NMR ^{1}H spectrum of **10k**