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Supplementary Materials

Exploring the Anticancer Potential of *Premna resinosa* (Hochst.) Leaf Surface Extract: Discovering New Diterpenes as Heat Shock Protein 70 (Hsp70) Binding Agents

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Table S1. ^{1}H experimental and calculated NMR chemical shifts for **1a**-**b**, with $^{a}|\Delta\delta|$ (^{1}H) and ^{c}MAE values. Chemical shift data here reported were produced using benzene as reference compound for sp^2 hydrogens, and tetramethylsilane (TMS) for sp^3 hydrogens.

Table S2. ^{13}C experimental and calculated NMR chemical shifts for **1a**-**b**, with $^{a}|\Delta\delta|$ (^{13}C) and ^{b}MAE values. Chemical shift data here reported were produced using benzene as reference compound for sp^2 carbons, and tetramethylsilane (TMS) for sp^3 carbons.

Table S3. ^{1}H experimental and calculated NMR chemical shifts for **4a**-**d**, with $^{a}|\Delta\delta|$ (^{1}H) and ^{c}MAE values. Chemical shift data here reported were produced using benzene as reference compound for sp^2 hydrogens, and tetramethylsilane (TMS) for sp^3 hydrogens.

Table S4. ^{13}C experimental and calculated NMR chemical shifts for **4a**-**d**, with $^{a}|\Delta\delta|$ (^{13}C) and ^{b}MAE values. Chemical shift data here reported were produced using benzene as reference compound for sp^2 carbons, and tetramethylsilane (TMS) for sp^3 carbons.

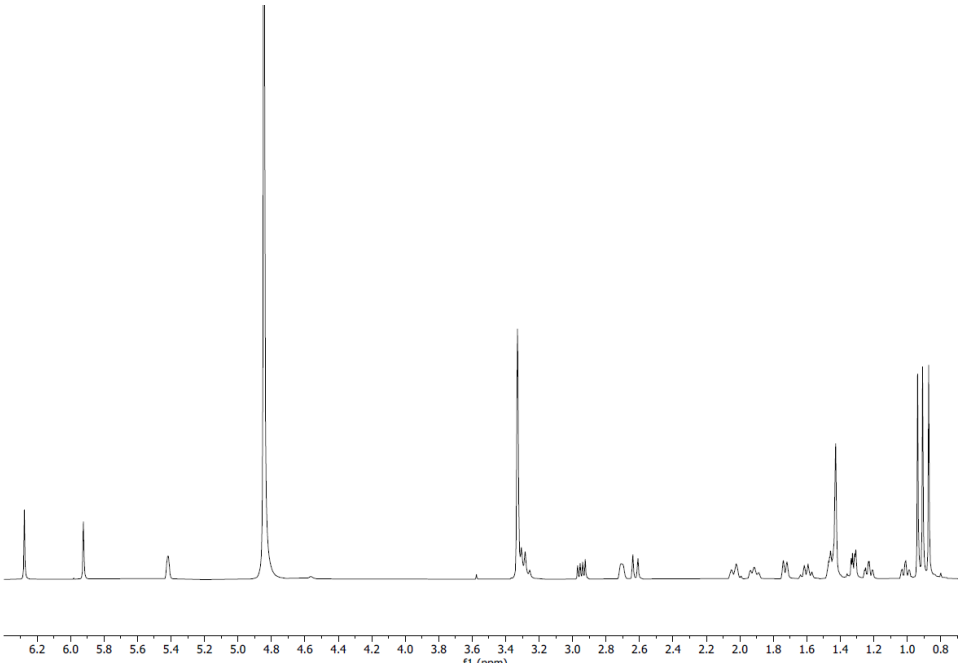

Figure S1. ^{1}H NMR spectrum of compound **1** (CD_3OD, 600 MHz).

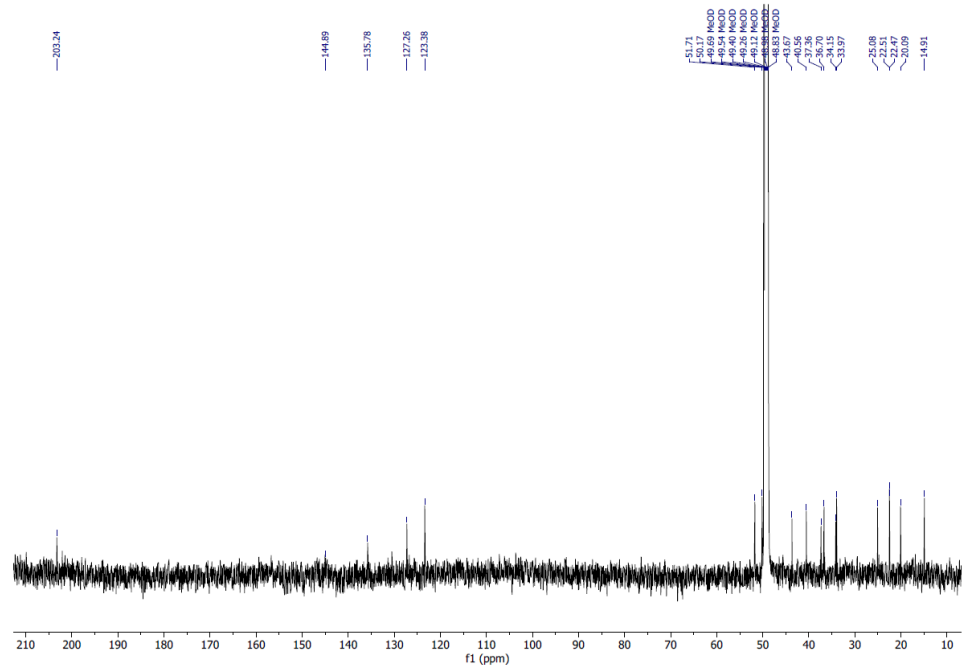

Figure S2. ^{13}C NMR spectrum of compound **1** (CD_3OD, 600 MHz).

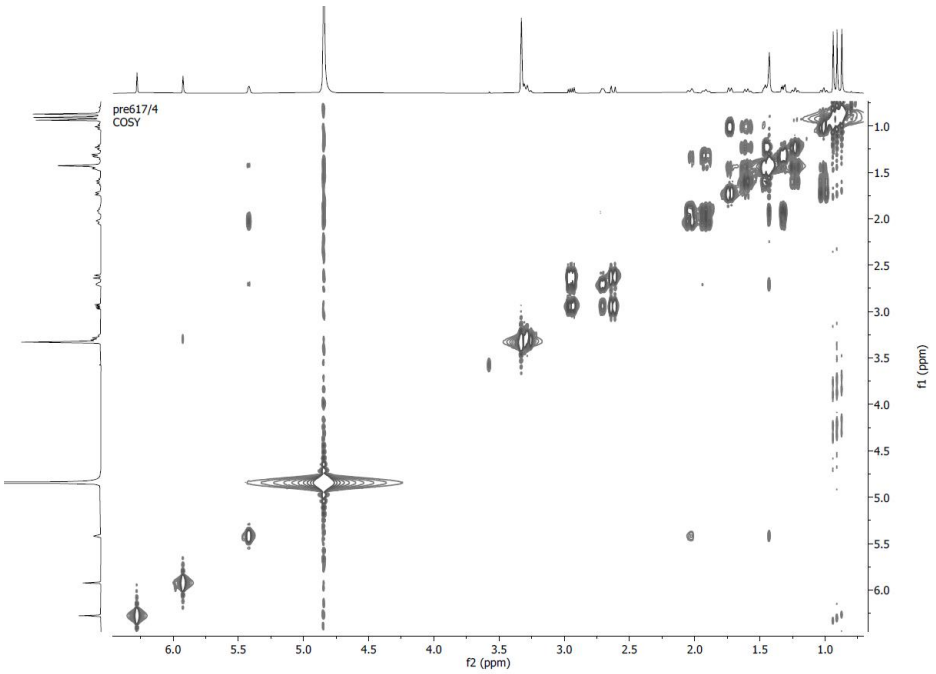

Figure S3. COSY spectrum of compound **1** (CD_3OD, 600 MHz).

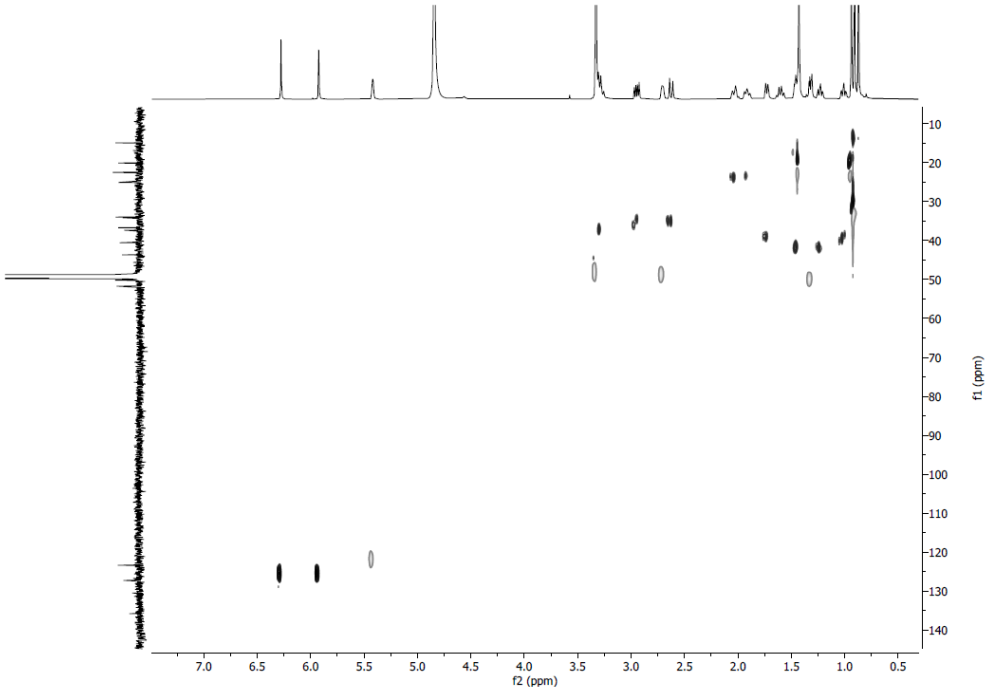

Figure S4. HSQC spectrum of compound **1** (CD_3OD, 600 MHz).

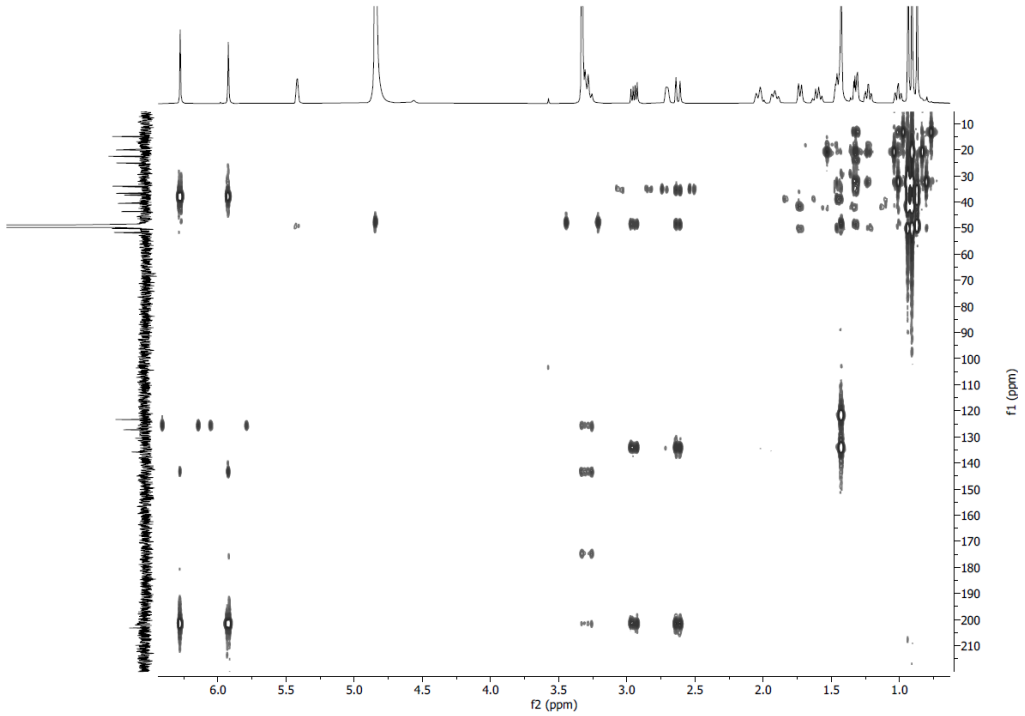

Figure S5. HMBC spectrum of compound **1** (CD_3OD, 600 MHz).

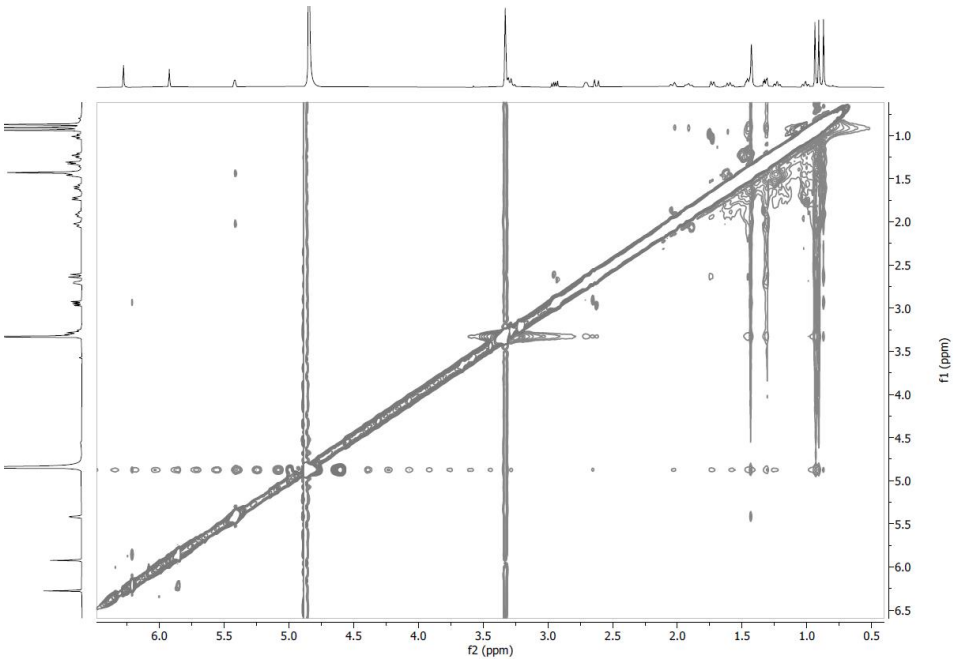

Figure S6. NOESY spectrum of compound **1** (CD_3OD, 600 MHz)

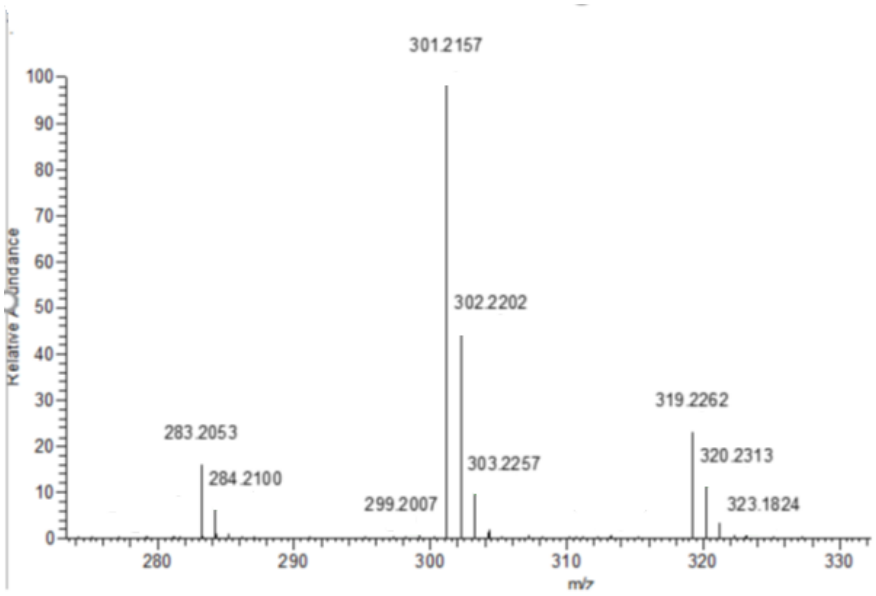

Figure S7. HRESIMS of compound **1.**

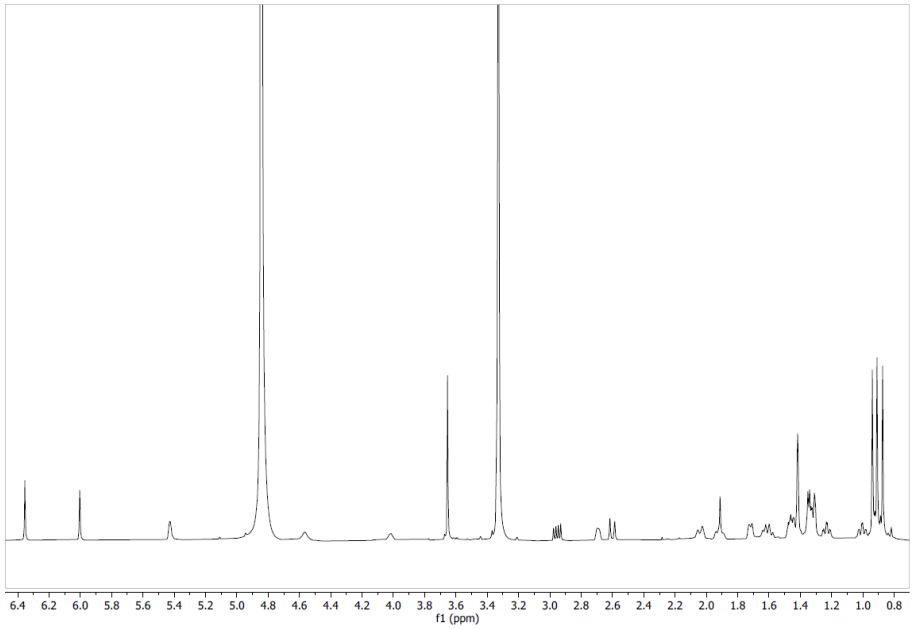

Figure S8. ^{1}H NMR spectrum of compound **2** (CD_3OD, 600 MHz).

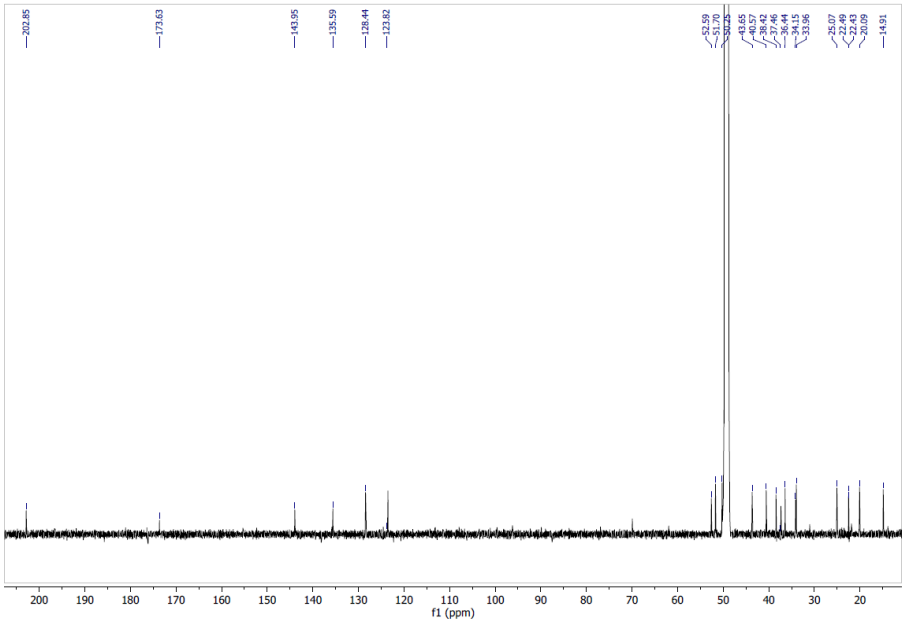

Figure S9. ^{13}C NMR spectrum of compound **2** (CD_3OD, 600 MHz).

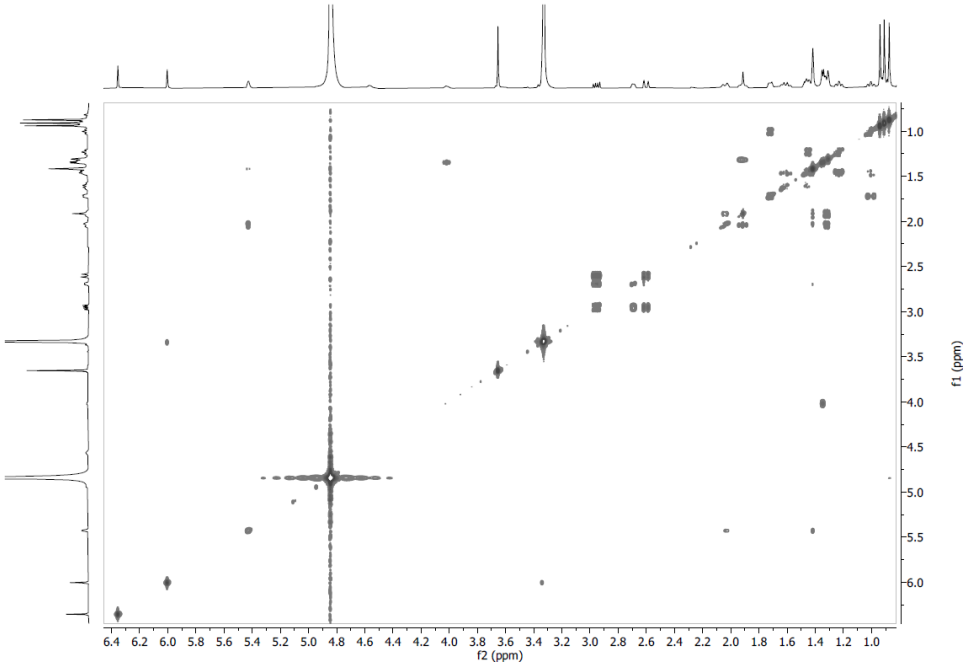

Figure S10. COSY spectrum of compound 2 (CD_3OD, 600 MHz).

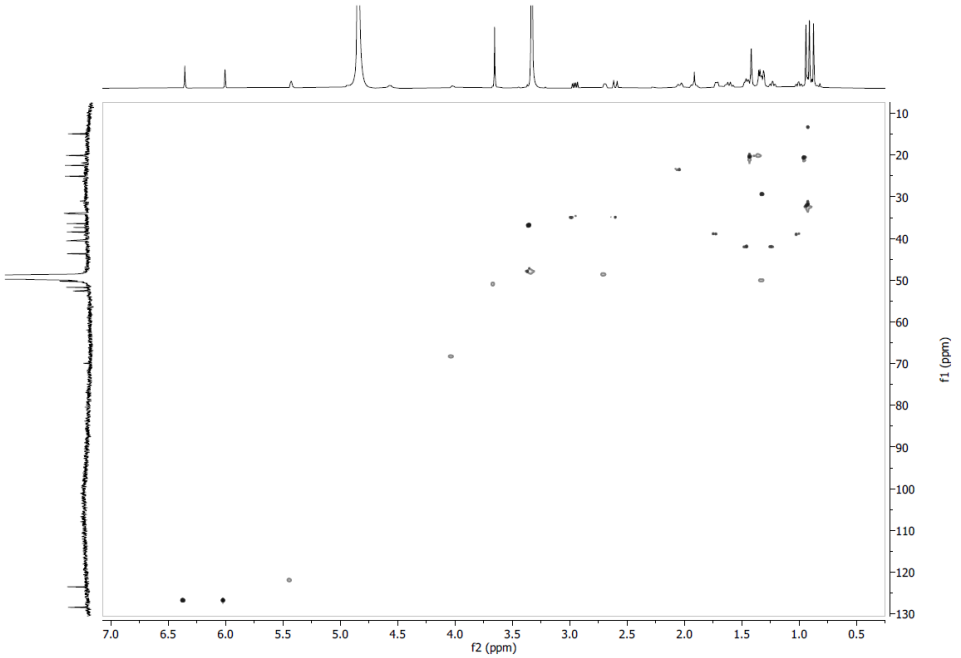

Figure S11. HSQC spectrum of compound **2** (CD_3OD, 600 MHz).

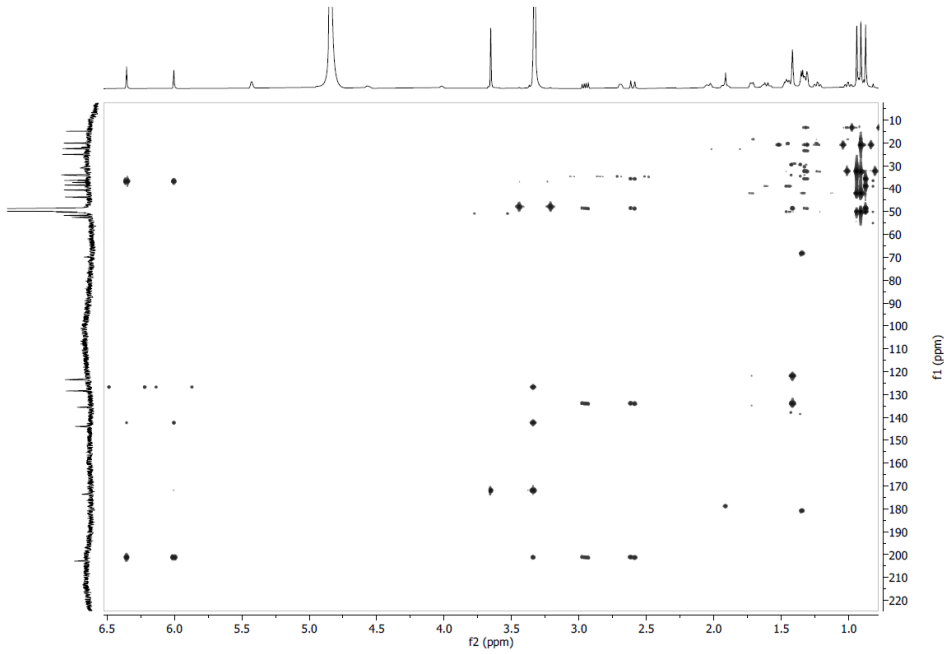

Figure S12. HMBC spectrum of compound 2 (CD_3OD, 600 MHz).

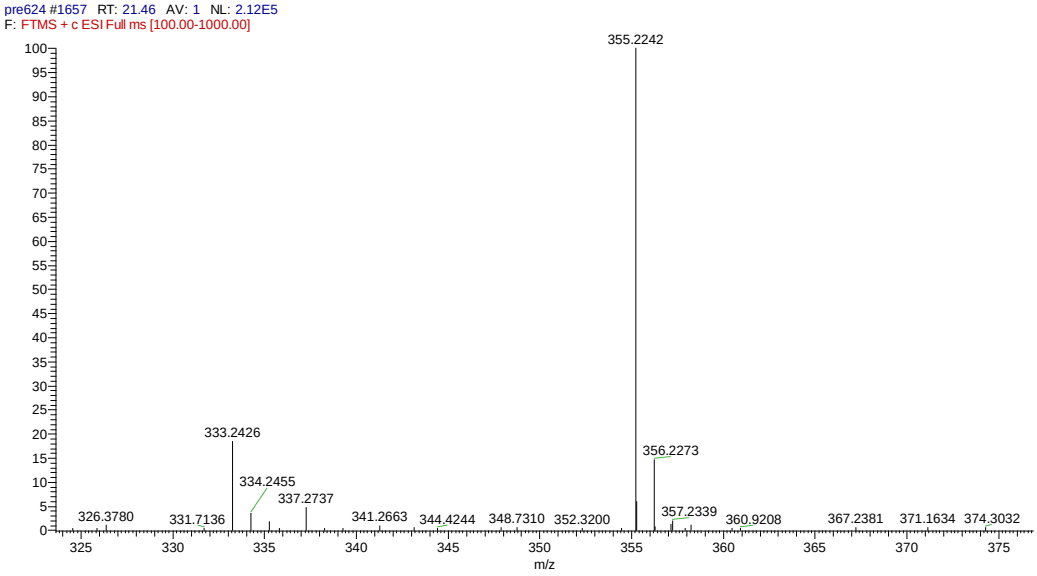

Figure S13. HRESIMS of compound **2.**

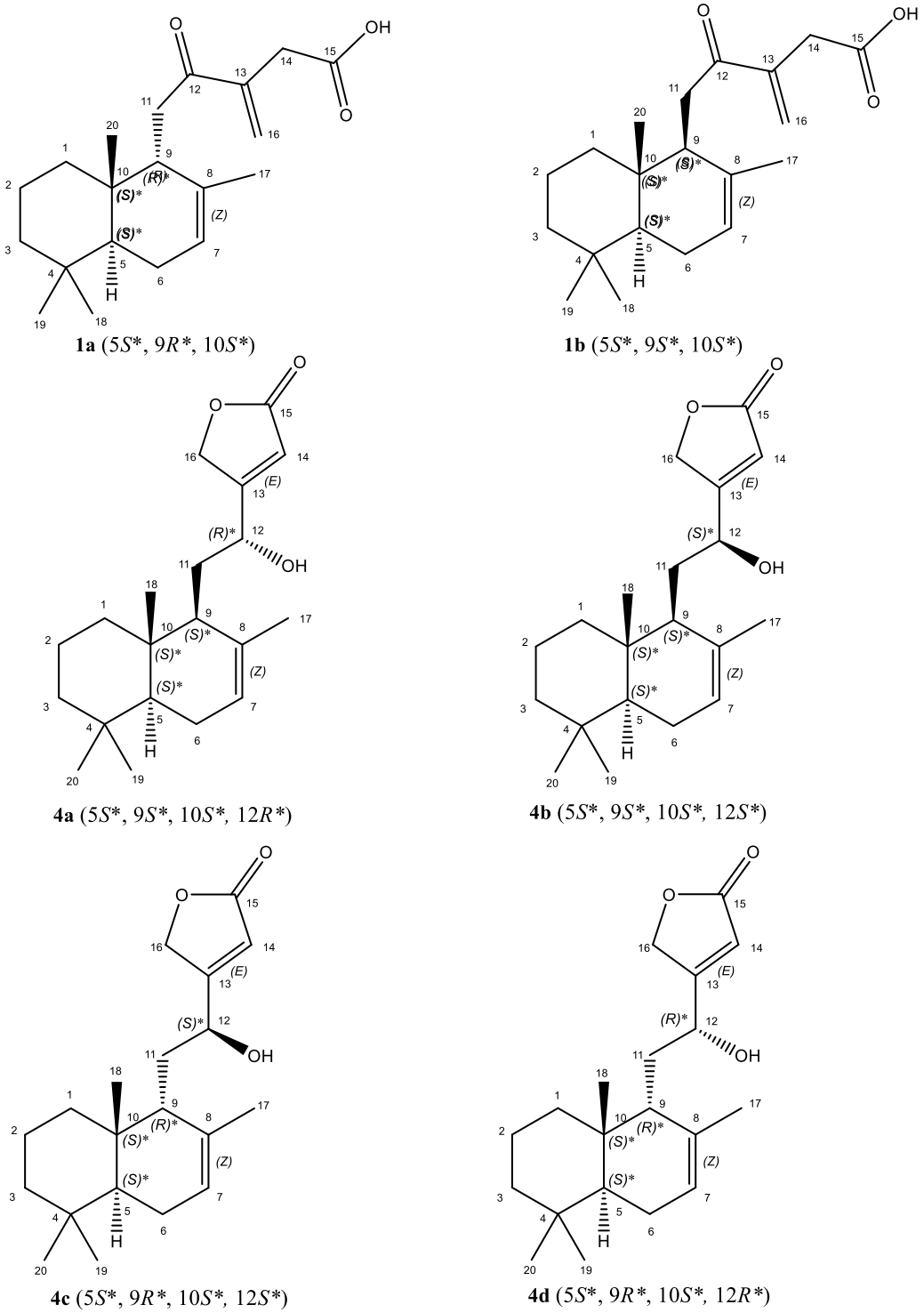

Figure S14. 2D structures of investigated stereoisomers of **1** and **4**.

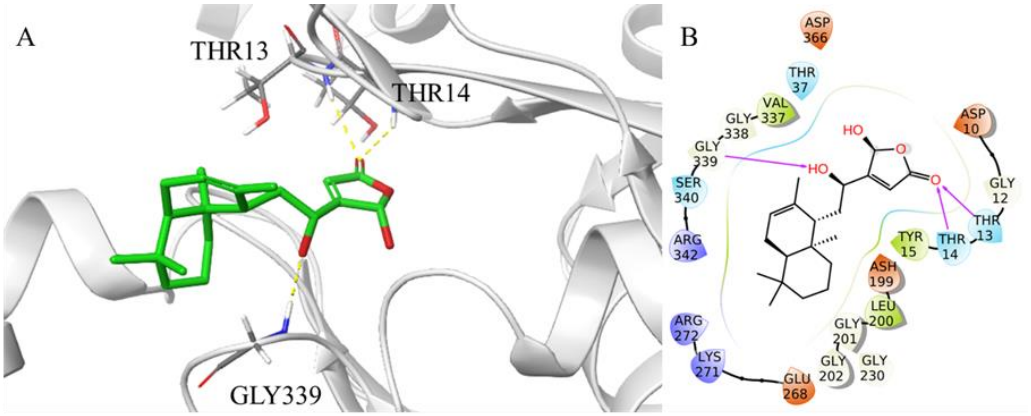

Figure S15. Binding pose and interaction of **3** docked to Hsp70 ATP binding site. (**A**) The protein is reported as grey ribbons and residues are colored by atom types; the ligand is reported as green capped sticks; H-bonds are presented as yellow dotted lines. (**B**) The ligand is surrounded by the protein residues represented as follows: the negatively charged residues are indicated in red, polar residues are in cyan, hydrophobic residues are shown in green; H-bonds are depicted as purple arrows.

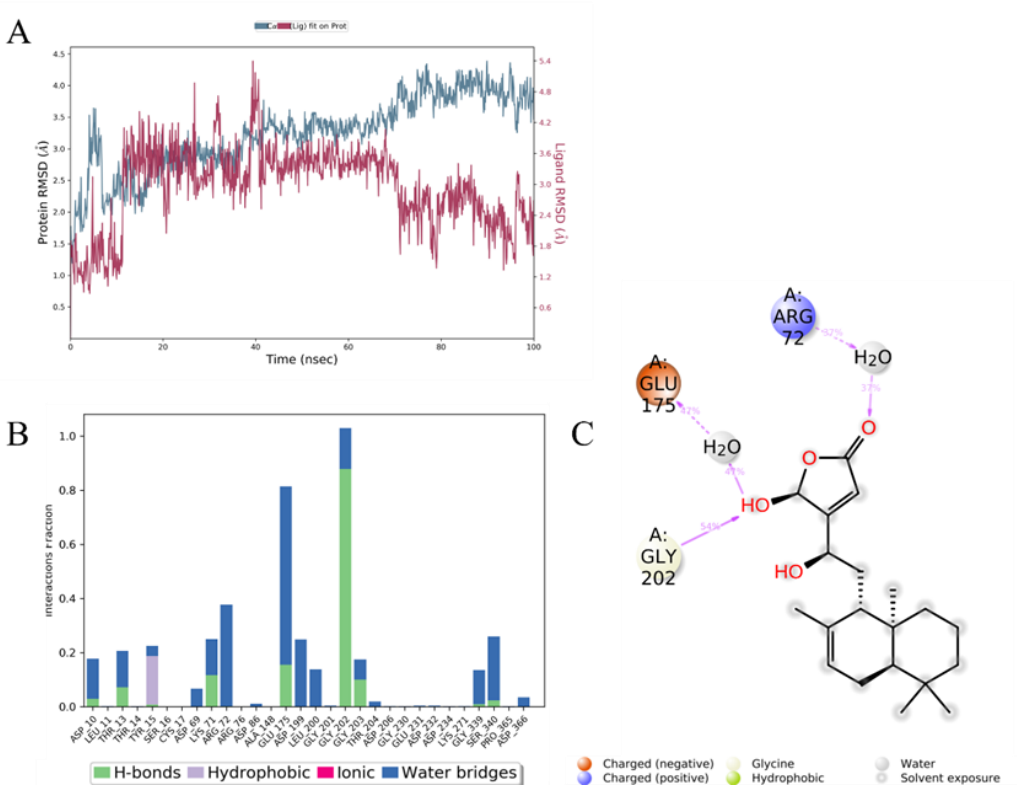

Figure S16. Molecular dynamic simulation results. (**A**) Root-mean square deviation (RMSD) plot for **3**/Hsp70 complex along 100 ns molecular dynamics simulation related to Cα positions of residues belonging to the protein backbone (blue) and the ligand (purple). (**B**) Protein-ligand interactions (or 'contacts') plot for **3**/Hsp70 complex along 100 ns molecular dynamics simulation. Contacts are categorized into four types: hydrogen bonds, hydrophobic, ionic and water bridges. (**C**) Ligand atom interactions with the protein residues. Interactions that occur more than 30.0% of the simulation time in the selected trajectory (0.00 through 100.00 ns), are shown.

Table S1. ^{1}H experimental and calculated NMR chemical shifts for 1**a**-**b**, with [a]|Δδ|(^{1}H) and [c]MAE values. Chemical shift data here reported were produced using benzene as reference compound for sp^2 hydrogens, and tetramethylsilane (TMS) for sp^3 hydrogens.

^{1}H	δ_{exp}(^{1}H), ppm	δ_{calc}(^{1}H), ppm		|Δδ| (^{1}H), ppm	
Position	**exp_1**	**calc_1a**	**calc_2b**	**calc_1a**	**calc_1b**
1	1.74	1.00	1.64	0.74	0.10
1	1.01	0.87	0.99	0.14	0.02
2	1.46	1.68	1.69	0.22	0.23
2	1.5	1.22	1.32	0.28	0.18
3	1.46	1.19	1.24	0.27	0.22
3	1.24	1.32	1.36	0.08	0.12
5	1.33	1.38	1.38	0.05	0.05
6	1.96	2.07	2.03	0.11	0.07
6	2.05	2.07	2.13	0.02	0.08
7	5.43	5.37	5.75	0.06	0.02
9	2.71	2.56	2.81	0.15	0.10
11	2.94	3.32	2.95	0.38	0.01
11	2.63	2.31	2.61	0.32	0.02
14	3.3	3.17	3.22	0.13	0.08
16	5.94	6.14	6.46	0.20	0.52
16	6.3	6.43	6.75	0.13	0.11
17	1.46	1.61	1.34	0.15	0.12
18	0.93	0.97	0.98	0.04	0.05
19	0.96	0.87	0.88	0.09	0.08
20	0.87	1.09	0.98	0.22	0.11
MAE				0.19	0.11

Table S2. ^{13}C experimental and calculated NMR chemical shifts for **1a**-**b**, with [a] $|\Delta\delta|$ (^{13}C) and [b] MAE values. Chemical shift data here reported were produced using benzene as reference compound for sp^2 carbons, and tetramethylsilane (TMS) for sp^3 carbons.

^{13}C	δ_{exp}(^{13}C), ppm	δ_{calc}(^{13}C), ppm		$\|\Delta\delta\|$ (^{13}C), ppm	
Position	**exp_1**	**calc_1a**	**calc_1b**	**calc_1a**	**calc_1b**
1	38.7	37.6	39.8	1.1	1.1
2	18.0	20.8	20.9	2.8	2.9
3	41.7	42.1	41.7	0.4	0.0
4	33.0	33.8	34.2	0.8	1.2
5	50.1	42.1	49.6	8.0	0.5
6	23.5	26.5	26.2	3.0	2.7
7	122.0	126.3	126.3	4.3	4.3
8	134.0	138.9	138.9	4.9	4.9
9	48.6	47.1	49.0	1.5	0.4
10	36.0	37.8	37.5	1.8	1.5
11	35.0	39.7	36.9	4.7	1.9
12	203.0	201.3	201.3	1.7	1.7
13	144.0	144.8	144.8	0.8	0.8
14	37.2	39.5	38.6	2.3	1.4
15	174.5	171.2	171.2	3.3	3.3
16	125.5	134.5	134.5	9.0	9.0
17	21.1	24.1	23.8	3.0	2.7
18	32.0	33.6	33.9	1.6	1.9
19	21.0	23.1	22.9	2.1	1.9
20	13.0	22.8	16.7	9.8	3.7
MAE				3.3	2.4

Table S3. ^{1}H experimental and calculated NMR chemical shifts for **4a**-**d**, with [a]|Δδ|(^{1}H) and [c]MAE values. Chemical shift data here reported were produced using benzene as reference compound for sp^2 hydrogens, and tetramethylsilane (TMS) for sp^3 hydrogens.

^{1}H	δ_{exp}(^{1}H), ppm	δ_{calc}(^{1}H), ppm				|Δδ| (^{1}H), ppm			
Position	**exp_4**	**calc_4a**	**calc_4b**	**calc_4c**	**calc_4d**	**calc_4a**	**calc_4b**	**calc_4c**	**calc_4d**
1	0.87	1.02	1.11	1.71	1.54	0.15	0.24	0.84	0.67
1	1.76	1.75	1.71	1.33	1.17	0.01	0.05	0.43	0.59
2	1.42	1.36	1.36	1.43	1.35	0.06	0.06	0.01	0.07
2	1.6	1.72	1.71	1.81	1.78	0.12	0.11	0.21	0.18
3	1.45	1.37	1.37	1.44	1.37	0.08	0.08	0.01	0.08
3	1.21	1.24	1.25	1.35	1.27	0.03	0.04	0.14	0.06
5	1.25	1.36	1.38	1.65	1.64	0.11	0.13	0.40	0.39
6	1.91	2.03	2.05	2.22	2.15	0.12	0.14	0.31	0.24
6	2.02	2.15	2.13	2.16	2.10	0.13	0.11	0.14	0.08
7	5.48	5.46	5.49	5.67	5.53	0.02	0.01	0.19	0.05
9	1.87	2.38	2.28	1.72	1.51	0.51	0.41	0.15	0.36
11	1.71	1.61	1.56	2.01	1.96	0.16	0.15	0.24	0.19
11	1.77	1.46	1.82	1.83	1.60	0.25	0.05	0.12	0.11
12	4.71	4.60	4.44	5.44	4.91	0.11	0.27	0.73	0.20
14	6.05	5.72	5.70	5.68	5.72	0.33	0.35	0.37	0.33
16	5.01	4.89	4.90	4.91	4.91	0.12	0.11	0.10	0.10
16	5.03	4.86	4.93	4.90	4.95	0.17	0.10	0.13	0.08
17	1.78	1.70	1.66	1.87	1.79	0.08	0.12	0.09	0.01
18	0.89	0.86	0.87	0.91	0.87	0.03	0.02	0.02	0.02
19	0.93	0.97	0.99	1.01	0.98	0.04	0.06	0.08	0.05
20	0.83	0.93	0.97	1.04	1.04	0.10	0.14	0.21	0.21
MAE						0.13	0.13	0.23	0.19

Table S4. ^{13}C experimental and calculated NMR chemical shifts for **4a**-**d**, with [a] $|\Delta\delta|$ (^{13}C) and [b] MAE values. Chemical shift data here reported were produced using benzene as reference compound for sp^2 carbons, and tetramethylsilane (TMS) for sp^3 carbons.

^{13}C	δ_{exp}(^{13}C), ppm	δ_{calc}(^{13}C), ppm				$\|\Delta\delta\|$ (^{13}C), ppm			
Position	**exp_4**	**calc_4a**	**calc_4b**	**calc_4c**	**calc_4d**	**calc_4a**	**calc_4b**	**calc_4c**	**calc_4d**
1	39.0	39.3	39.5	37.5	36.0	0.3	0.5	1.5	3.0
2	18.4	20.8	20.8	20.9	20.9	2.4	2.4	2.5	2.5
3	42.0	41.6	41.6	42.3	42.2	0.4	0.4	0.3	0.2
4	36.4	34.2	34.0	34.5	34.1	2.2	2.4	1.9	2.3
5	50.1	49.5	49.8	45.2	42.0	0.6	0.3	4.9	8.1
6	23.4	26.3	26.4	26.7	26.9	2.9	3.0	3.3	3.5
7	122.3	127.5	127.4	130.2	129.0	5.2	5.1	7.9	6.7
8	134.8	138.4	138.3	140.8	138.9	3.6	3.5	6.0	4.1
9	50.3	49.6	52.3	51.0	51.5	0.7	2.0	0.7	1.2
10	36.0	37.9	38.9	38.2	38.7	1.9	2.9	2.2	2.7
11	33.3	35.2	32.8	36.5	40.7	1.9	0.5	3.2	7.4
12	69.1	70.0	71.3	69.9	69.7	0.9	2.2	0.8	0.6
13	176.0	179.9	178.8	179.8	179.5	3.9	2.8	3.8	3.5
14	114.5	117.0	117.3	115.8	116.5	2.5	2.8	1.3	2.0
15	176.5	172.5	172.6	172.9	172.8	4.0	3.9	3.6	3.7
16	71.5	70.3	70.5	69.9	70.1	1.2	1.0	1.6	1.4
17	21.4	23.6	24.5	25.2	25.7	2.2	3.1	3.8	4.3
18	32.0	33.8	33.9	33.9	33.3	1.8	1.9	1.9	1.3
19	21.0	23.1	22.9	23.6	23.0	2.1	1.9	2.6	2.0
20	13.0	15.9	15.5	23.6	22.8	2.9	2.5	10.6	9.8
MAE						2.2	2.3	3.2	3.5