Supporting Document

Poly[(N-acryloyl glycine)-co-(acrylamide)] induced cell growth inhibition in heparanase driven malignancies

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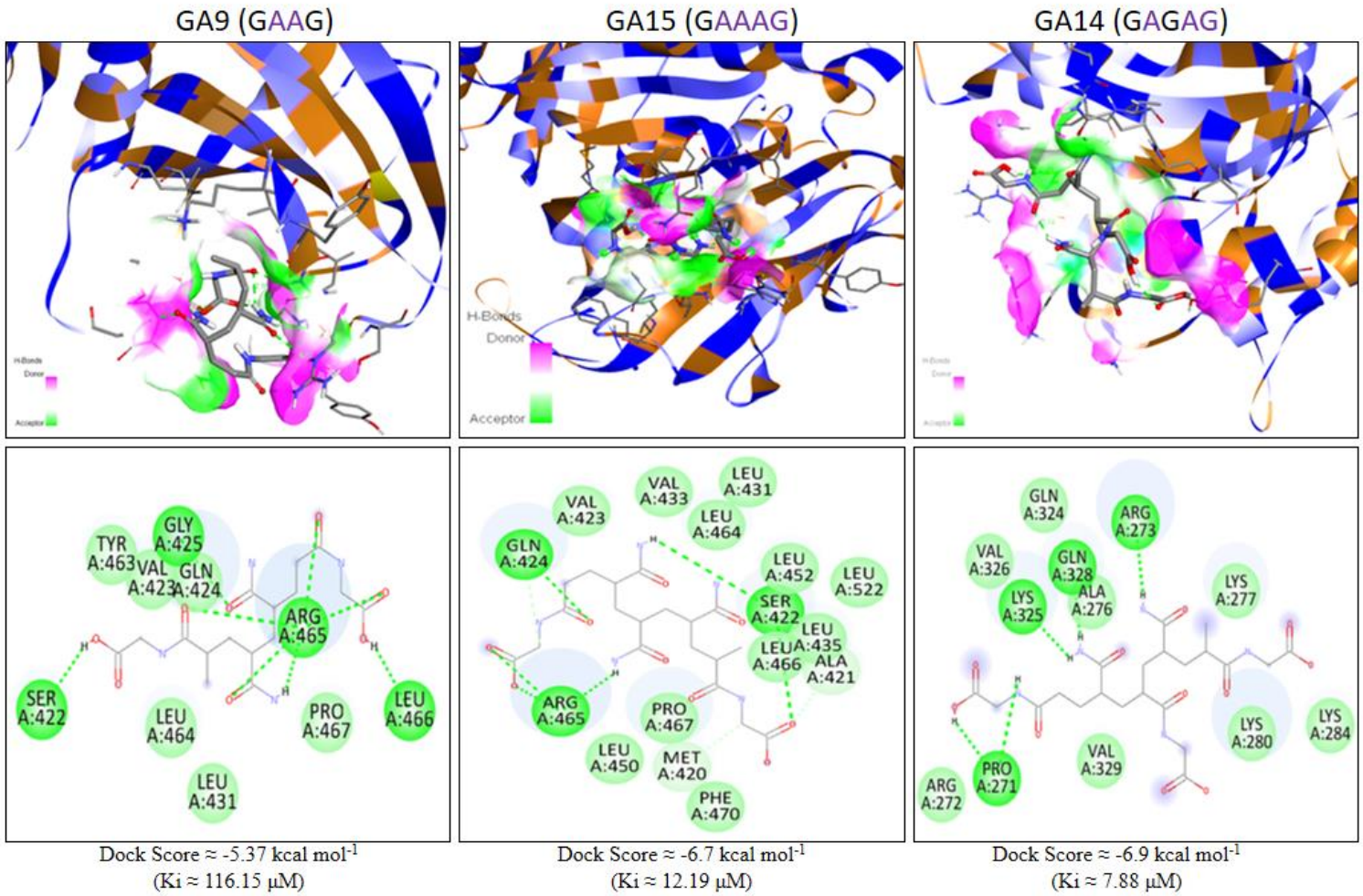

Dock Score ≈ -5.37 kcal mol^{-1} (Ki ≈ 116.15 μM)

Dock Score ≈ -6.7 kcal mol^{-1} (Ki ≈ 12.19 μM)

Dock Score ≈ -6.9 kcal mol^{-1} (Ki ≈ 7.88 μM)

Figure S1 : *Docking poses for complex of GA9, GA15 and GA14*

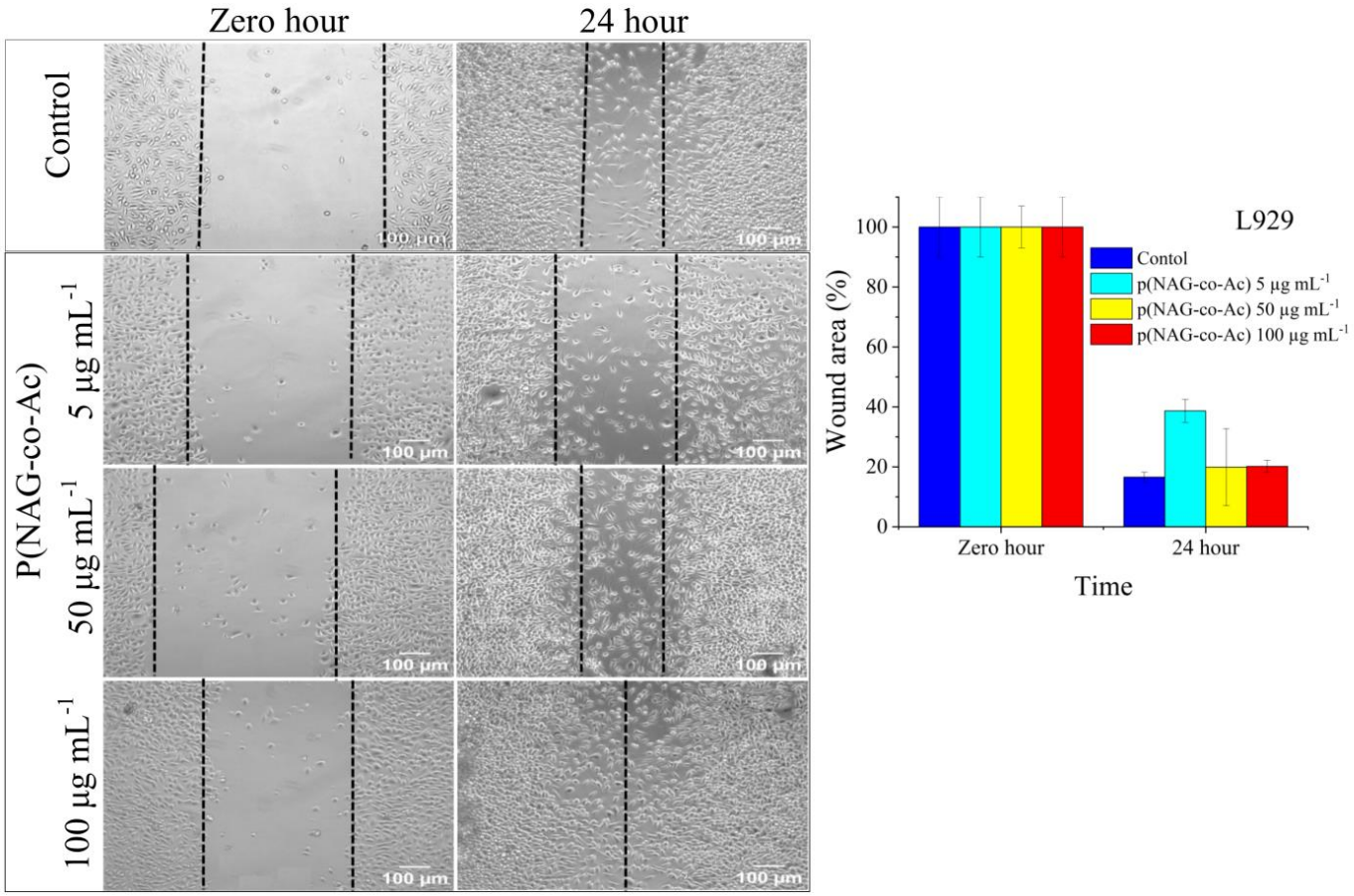

Figure S2: Wound sketch assay on L929 cell line after treatment with p(Nag-co-Ac) hydrogel

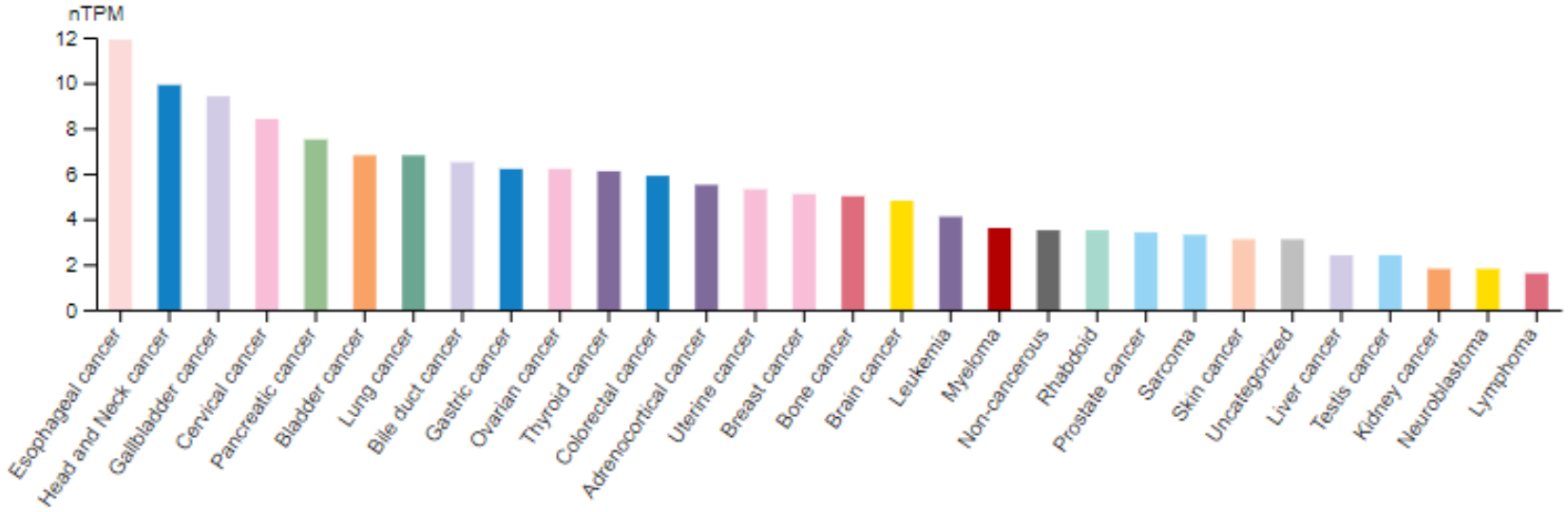

Figure S3: Heparanase gene expression in cancer obtained from Human Protein Atlas

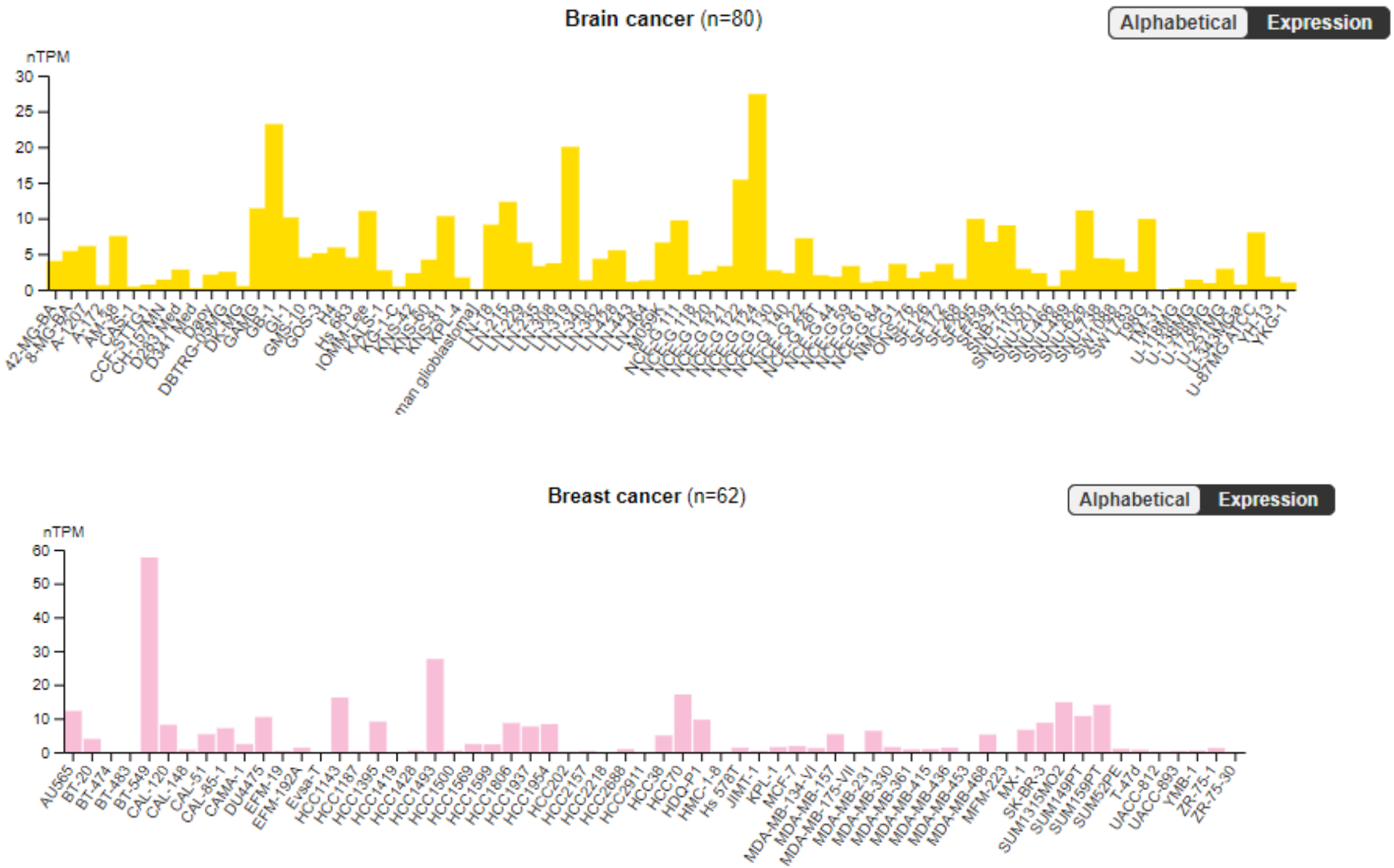

Figure S4. Heparanase gene expression in brain cancer and in breast cancer obtained from Human Protein Atlas

Table S1: Bioactivity score of (a) homopolymer of n-acryloyl glycine (b) Linear hetro- polymer of n-acryloyl glycine and acrylamide and (c) cross-linked homopolymer and (d) cross-linked hetropolymer represent p(NAG-co-Ac) polymer.

Sr.No	p(NAG-co-Ac) random series	Protease inhibitor	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Enzyme inhibitor
1	G1	-1.97	-2.23	-1.72	-2.82	-2.34	-1.62
2	G2	0.26	-0.06	-0.1	-0.74	-0.36	0.06
3	G3	0.41	0.1	-0.1	-0.39	-0.1	0.39
4	G4	0.29	0.07	-11	-0.29	-0.07	0.04
5	G5	0.17	-0.14	-0.76	-0.63	-0.48	-0.36
6	G6	-0.61	-1.17	-2.29	-1.97	-1.91	-1.6
7	G7	-2.21	-2.94	-3.58	-3.55	-3.53	-3.26
8	G8	-3.52	-3.66	-3.78	-3.79	-3.77	-3.52
9	G9	-3.78	-3.9	-3.94	-3.96	-3.85	-3.91
10	G10	-3.85	-3.96	-3.99	-4	-4	-3.97
11	G11	-3.92	-3.83	-3.83	-3.66	-3.87	-3.67
12	A1	-3.74	-3.83	-3.83	-3.66	-3.87	-3.67
13	A2	-0.64	-1.02	-0.71	-1.48	-1.46	-0.65
14	A3	-0.12	-0.4	-0.34	-0.74	-0.68	-0.22
15	GA1	0.16	-0.45	-0.33	-1.19	-0.97	-0.15
16	GA4.1	0.38	0.02	-0.17	-0.57	-0.27	0.09
17	GA2	0.54	0.14	-0.11	-0.33	-0.07	0.1
18	GA3	0.5	0.13	-0.15	-0.41	-0.14	0.08
19	GA4	0.5	0.13	-0.15	-0.41	-0.14	0.08
20	GA5	0.41	0.1	-0.08	-0.24	-0.04	0.07

21	GA6	0.38	0.1	-0.11	-0.29	-0.1	0.06
22	GA7	0.45	0.11	-0.13	-0.27	-0.05	0.07
23	GA8	0.45	0.11	-0.13	-0.27	-0.05	0.07
24	GA9	0.44	0.11	-0.13	-0.33	-0.11	0.07
25	GA10	0.32	0.06	-0.36	-0.28	-0.15	-0.06
26	GA11	0.3	0.06	-0.38	-0.33	-0.19	-0.07
27	GA12	0.3	0.06	-0.38	-0.33	-0.19	-0.07
28	GA13	0.33	0.09	-0.16	-0.25	-0.09	0.05
29	GA14	0.33	0.09	-0.16	-0.25	-0.09	0.05
30	GA15	0.37	0.1	-0.11	-0.28	-0.09	0.06
31	GA16	0.44	0.1	-0.13	-0.27	-0.05	0.06
32	GA17	0.32	0.08	-0.2	-0.25	-0.09	0.04
33	D1	0.28	0.06	0.05	-0.58	-0.03	0.2
34	D2	0.42	0.18	-0.03	-0.28	0.04	0.13
35	D3	0.32	0.14	0.01	-0.31	-0.06	0.1
36	D4	0.17	0	-0.39	-0.38	-0.23	-0.14
37	D5	-0.24	-0.62	-1.5	-1.31	-1.22	-1
38	D6	-1.28	-1.93	-3.07	-2.89	-2.85	-1.28
39	D7	-2.83	-3.37	-3.66	-3.67	-3.65	-3.55
40	D8	-3.59	-3.71	-3.81	-3.82	-3.81	-3.75
41	D9	-3.76	-3.83	-3.89	-3.9	-3.9	-3.85
42	D10	-3.85	-3.9	-3.95	-3.96	-3.96	-3.92
43	D11	-3.81	-3.87	-3.92	-3.93	-3.93	-3.88
44	D12	-3.75	-3.83	-3.89	-3.9	-3.9	-3.85
45	D13	-3.68	-3.77	-3.86	-3.86	-3.87	-3.81
46	D14	-3.58	-3.7	-3.81	-3.81	-3.82	-3.75
47	D15	-2.79	-3.37	-3.67	-3.66	-3.67	-3.55
48	D16	-1.96	-2.77	-3.56	-3.51	-3.51	-3.16
49	D17	-1.19	-1.91	-3.14	-2.88	-2.9	-2.45
50	D18	-0.11	-0.59	-1.54	-1.22	-1.23	-0.94

51	D19	0.35	0.04	-0.46	-0.38	-0.27	-0.12
52	D20	0.2	-0.18	-0.9	-0.72	-0.64	-0.44
53	D21	0.45	0.15	-0.16	-0.27	-0.07	0.05
54	D22	0.5	0.17	-0.06	-0.29	-0.07	0.07
55	D23	0.44	0.13	-0.06	-0.33	-0.12	0.01
56	D24	0.45	0.19	-0.09	-0.43	-0.09	0.08
57	D25	0.41	0.17	-0.07	-0.32	-0.18	0.07
58	D26	0.26	0.07	-0.16	-0.25	-0.09	0.01

Table S2: DFT calculation for (a) homopolymer of n-acryloyl glycine (b) Linear hetro- polymer of n-acryloyl glycine and acrylamide and (c) cross-linked homopolymer and (d) cross-linked hetropolymer represent p(NAG-co-Ac) polymer, changes in dipole moment and Intramolecular hydrogen bonding in different solvent

			molecular weight (g/mol)	hERG beta (ADMET)	Free energy in Vaccume (Fc)(Eh)	Dipole moment in gas (μ'c) (Debye)	Free energy in gas (Fw)(Eh)	Dipole moment in gas (μ'w) (Debye)	Free energy in ethanol (Fe)(Eh)	Dipole moment in ethanol (μ'e) (Debye)	Intramolcular hydrogen bonding in water (Kcal/mol)	Intermolecular hydrogen bonding energy in ethanol (Kcal/mol)	Intramolcular hydrogen bonding in hexane(Kcal /mol)	Intramolcular hydrogen bonding in chcl3(Kcal /mol)
1		Glycine			-284.073	5.59	-284.091	7.27	-284.090	7.21	-11.25	-10.84		
2	G1	N-Acryloyl glycine (G)			-475.029	1.93	-475.053	1.95	-475.052	1.95	-14.98	-14.45		
3	G2	GG			-951.319	3.00	-951.366	3.34	-951.365	3.33	-29.84	-28.80		
4	G3	GGG			-1424.991	2.95	-1425.057	6.68	-1425.055	6.51	-41.58	-40.10		
5	G4	GGGG			-1899.644	5.45	-1899.711	8.67	-1899.708	8.50	-41.81	-40.23		
6	G5	GGGGG			-2374.251	7.74	-2374.332	13.92			-50.42			
7	G6	GGGGGG			-2848.880	3.83	-2848.962	4.77	-2848.959	4.82	-51.69	-49.79		

8	GA1	GA	202.21	3.78(safe)	-722.795	4.53	-722.830	5.47	-722.829	5.44	-21.98	-21.21		
10	GA4.1	AAG	273.29	3.88(safe)	-969.822	5.50	-969.864	7.55	-969.863	7.46	-26.79	-25.84		
11	GA2	GGA	331.33	4.24(safe)	-1197.432	3.85	-1197.479	11.04	-1197.477	10.86	-29.59	-28.47		
12	GA3	AGG	331.33	4.25(safe)	-1197.431	8.49	-1197.487	8.66	-1197.486	8.59	-35.10	-34.25		
13	GA4	GAG	331.33	4.25(safe)	-1197.410	4.77	-1197.457	7.12	-1197.456	6.99	-30.02	-28.92		
14	GA5	GGGA			-1672.050	5.32	-1672.108	9.62	-1672.106	9.43	-36.44	-35.02		
15	GA6	GGAG	460.44	4.42(safe)	-1672.059	12.59	-1672.111	24.98	-1672.109	24.44	-32.82	-31.45		
16	GA7	GGAA	402.40	4.31(safe)	-1444.450	6.66	-1444.494	10.51	-1444.492	10.31	-27.34	-26.37		
17	GA8	GAGA			-1444.421	6.04	-1444.486	9.39	-1444.483	8.70	-40.77	-39.19		
18	GA9	GAAG			-1444.429	15.96	-1444.492	22.31	-1444.490	22.04	-40.04	-38.54		
19	GA10	GGGGA			-2146.682	6.28	-2146.735	10.70	-2146.733	10.44	-33.37	-32.08		
20	GA11	GGGAG	589.56	4.51(safe)	-2146.657	14.84	-2146.741	24.30	-2146.738	23.72	-52.65	-50.54		
21	GA12	GGAGG	589.56		-2146.640	13.87	-2146.719	20.97	-2146.716	20.52	-49.35	-47.45		

22	GA13	GGAAG	531.52	4.47(safe)	-1919.048	3.36	-1919.118	7.81	-1919.115	7.67	-43.70	-42.11		
23	GA14	GAGAG	531.52	4.47(safe)	-1919.042	9.71	-1919.115	14.15	-1919.113	14.01	-45.95	-44.23		
24	GA15	GAAAG	473.48	4.41(safe)	-1691.419	8.99	R				0.00	1061365.53		
25	GA16	GGGGGA	718.67	4.64(safe)	-2621.240	6.97	-2621.333	9.69	-2621.329	9.51	-58.02	-55.77		
26	GA17	GGGAGG	718.67	4.64(safe)	-2595.339	3.25	-2595.390	3.96	-2595.391	4.75	-32.07	-32.39		
27	GA18	GAGGAG	660.63	4.54(safe)	-2368.721	4.41								
25	D1	D-G	247.29		-823.083	1.92	-823.108	2.83	-823.107	2.79	-15.87	-15.30		
26	D2	G-D-G	364.40		-1260.846	2.45	-1260.897	2.17			-32.18	791180.93		
27	D3	GG-D-G	479.49		-1694.985	2.24	-1695.049	3.88	-1695.047	3.76	-40.20	-38.78		
28	D4	GGDGG	594.57		-2130.338	9.55	-2130.417	12.93	-2130.414	12.79	-49.53	-47.66		
29	D5	GGGDGG	709.66	4.73(safe)	-2565.674	6.22								
30	D6	GGGDGGG	824.75	4.86 (safe)	-3000.995	6.03								
	D7	GAGDGAG	764.79	4.75 safe	-2702.911	17.27	-2703.007	22.41	-2703.003	21.76	-60.18	-57.85		

31	D18	GAGDGGA												
32	D19	GAGDGA	610.62	4.82 (safe)	-2170.756	6.01	-2170.831	9.13			-46.65			
33	D20	GAGDGG	651.63	4.77(safe)	-2338.114	6.42	-2338.190	10.97	-2338.187	10.79	-47.43	-45.63		
34	D21	GADGG	536.54	4.77 (safe)	-1902.748	4.89	-1902.816	8.21	-1902.814	8.04	-42.92	-41.34		
35	D22	GADGA	478.50	4.7(safe)	-1675.144	8.72	-1675.213	10.89	-1675.210	10.77	-43.13	-41.55		
36	D24	ADG	306.36	4.1(safe)	-1032.056	5.99	-1032.092	7.95	-1032.091	7.82	-22.68	-21.96		
37	D25	GADG	407.42	4.68 (safe)	-1428.145	5.41	-1428.198	6.63	-1428.196	6.57	-33.08	-31.89		
38	D26	GGADG	537.52	4.74(safe)	-1922.568	7.87	-1922.644	11.92	-1922.641	11.82	-47.45	-45.62		

Table S3: HOMO LUMO energy difference with increase in size of monomer to polymer and in presence of cross linker

	HOMO (eV)	LUMO (eV)	Band gap (eV)	Chemical hardness (η)	Chemical softness (σ)	Electronegativity (χ)	Electrophilicity (ω)
D1	-6.097	-1.079	5.018	2.509	0.398565165	3.588	2.565513
D2	-6.5	-0.379	6.121	3.0605	0.326743996	3.4395	1.932717
D3	-6.53	-0.414	6.116	3.058	0.327011118	3.472	1.971024
D4	-6.473	-0.657	5.816	2.908	0.343878955	3.565	2.185218
D5			0	0		0	

D6				0		0	
D7	-6.398	-0.302	6.096	3.048	0.32808399	3.35	1.840961
D18			0	0	#DIV/0!	0	
D19	-6.356	-0.527	5.829	2.9145	0.343112026	3.4415	2.031896
D20	-6.473	-0.46	6.013	3.0065	0.332612673	3.4665	1.99844
D21	-6.424	-0.378	6.046	3.023	0.330797221	3.401	1.913133
D22	-6.428	-0.357	6.071	3.0355	0.329435019	3.3925	1.895743
D24	-6.448	-0.314	6.134	3.067	0.326051516	3.381	1.863574
D25	-6.496	-0.567	5.929	2.9645	0.337325013	3.5315	2.103473
D26	-6.58	-0.716	5.864	2.932	0.34106412	3.648	2.269424
Glycine	-6.881	0.535	7.416	3.708	0.269687163	3.173	1.357596
G1	-7.143	-1.137	6.006	3.003	0.333000333	4.14	2.853746
G2	-7.018	-0.106	6.912	3.456	0.289351852	3.562	1.835626
G3	-6.919	0.017	6.936	3.468	0.288350634	3.451	1.717042
G4	-6.98	-0.546	6.434	3.217	0.310848617	3.763	2.200834
G5	-6.988	-0.418	6.57	3.285	0.304414003	3.703	2.087094
G6	-6.867	-0.48	6.387	3.1935	0.313136058	3.6735	2.112823
GA1	-6.881	0.074	6.955	3.4775	0.287562904	3.4035	1.665537
GA2	-6.888	-0.148	6.74	3.37	0.296735905	3.518	1.83625
GA3	-7.018	-0.031	6.987	3.4935	0.286245885	3.5245	1.777888
GA4	-6.829	-0.219	6.61	3.305	0.302571861	3.524	1.878756
GA4.1	-6.793	-0.042	6.751	3.3755	0.296252407	3.4175	1.730011
GA5	-6.92	-0.543	6.377	3.1885	0.313627097	3.7315	2.183486
GA6	-6.966	-0.228	6.738	3.369	0.296823983	3.597	1.920215
GA7	-6.766	-0.196	6.57	3.285	0.304414003	3.481	1.844347
GA8	-6.783	0.013	6.796	3.398	0.294290759	3.385	1.686025
GA9	-6.883	-0.016	6.867	3.4335	0.291247998	3.4495	1.732787
GA10	-6.89	-0.414	6.476	3.238	0.308832613	3.652	2.059466
GA11	-6.949	-0.115	6.834	3.417	0.292654375	3.532	1.825435

GA12	-6.881	-0.56	6.321	3.1605	0.316405632	3.7205	2.189862
GA13	-6.787	-0.098	6.689	3.3445	0.298998356	3.4425	1.771686
GA14	-6.74	0.002	6.742	3.371	0.296647879	3.369	1.683501
GA15	-6.738	0.048	6.786	3.393	0.294724433	3.345	1.64884
GA16	-6.712	-0.592	6.12	3.06	0.326797386	3.652	2.179265
GA17	-7.475	-3.996	3.479	1.7395	0.574877838	5.7355	9.455579

Table S4: protein ligand interaction with heparanase PDBID-7PRT

S.No.		Ligands	Lowest binding energy (kcal mol-1)	Estimated inhibition constant (Ki)	H bond	Interacting Residue (non hydrogen bond)
Reference Molecules						
1		*Cyclophellitol*	-4.65	829.53 uM	SER422 (2.036,1.901), GLN424(1.828), ARG465(2.135,1.928)	
2		*Roneparstat*	-1.36	100.76mM	ASP183(2.204), ARG382(1.989)	ILE185,PHE385.LEU408,TYR 404,SER407,TRP365,LYS411, LEU398,LEU182
Ligands						
1		*Glycine*	-4.09	1.00 mM	**H(1)** Lys232(1.79),	GLU225, Ser228
2	G1	*N-Acryloylglycine (G)*	-5.16	166.36uM	**H(3)** LYS538(1.851), LYS473(1.849,1.699)	PRO469,ALA537
3	G2	*GG*	-4.53	479.91 uM	**H(3) LYS280**(1.916), LYS284(1.725), LYS277(1.812)	

4	G3	*GGG*	-4.52	487.79uM	H(6) LYS232(1.703), **ARG272**(1.915), THR275(2.129,1.828,1.946), LYS274(2.236)	ASN227,GLN276,ARG273
5	G4	*GGGG*	-5.46	99.29 uM	H (7) LYS277(2.073),LYS284(1.865),ARG273(2.059,1.852,1.819)**, LYS280**(2.054)	
6	G5	*GGGGG*	-7.76	2.05uM	LYS325(2.169,2.134,1.836), **ARG272**(2.063), **LYS280**(1.928,1.926), **ARG273**(2.207)	ALA276
7	G6	*GGGGGG*	-7.62	2.62 uM	AG273(2.159,2.094,1.895), LYS325(2.22), **LYS280**(2.079,1.995), LYS284(1.996), LYS277(1.863)	
8	GA1	*G-A*	-4.73	339.9uM	**H (4)** VAL433(2.183,1.925), VAL423(2.019), ARG374(2.215)	MET420,ALA421,SER422,LEU371,TYR434,LEU431
9	GA4.1	*A-A-G*	-5.18	159.74uM	**H(4)** ARG465(2.208, 2.121, 2.063, 2.002), **GLN424(**2.003)	LEU452,LEU466,PRO467
10	GA2	G-G-A	-5.57	81.94 uM	MET512(2.114), ASN496(2.149), LYS514(1.858,1.791)	LEU498,LEU495
11	GA3	*A-G-G*				

12	GA4	*G-A-G*	-4.4	597.59uM	LYS411(1.885),VAL380(2.086),ARH382(2.115,1.747),PHE385(1.889),PHE386(2.042)	VAL384
13	GA5	*G-G-G-A*	-5.05	199.39uM	SER422(2.007,1.693),GLN424(2.235,2.013)	LEU452,LEU464,ARG465,VAL433,VAL423
14	GA6	*G-G-A-G*	-5.11	178.43 uM	SER422(2.206),ARG465(2.001,1.693),GLN424(2.19,1.825)	VAL423,LEU466,LEU452,PRO467,LEU450,PHE470,ILE534
15	GA7	*G-G-A-A*		689.02uM	**LYS280**(1.977,1.952),LYS325(2.153),GLN328(1.971),VAL329,ALA276,ARG273,SER332	HIS458,PHE527
16	GA8	*G-A-G-A*	-4.56	451.4uM	LYS412(1.78),VAL380(1.752),LYS411(2.0,1.861,2.14)	VAL414,PHE410,ASN439,VAL379
17	GA9	*G-A-A-G*	-5.37	116.15uM	GLN424(2.062),GLY425(2.144),ARG465(2.092,2.08,2.024)	SER422,VAL423,LE464,LEU466,TYR463

18	GA10	GGGGA	-6	39.88 uM	LYS352(2.215),LYS284(1.869),**LYS280(2.082,1.759),**GLN328(2.145)	VAL329,LYS277,ARG283,LYS325,ALA276
19	GA11	GGGAG	-4.52	489.68 uM	ARG481(2.127),LYS514(1.79),THR461(2.04,2.0),ALA526(1.966),LYS477(2.115)	PRO525,LEU479,ASN496
20	GA12	GGAGG	-5.93	44.91uM	ARG273(2.134,1.811),LYS277(1.87,1.682),LYS280(1.983),LYS284(1.866)	LYS274
21	GA13	GGAAG	-6.26	25.68uM	ARG465(2.079,1.89,1.877), TYR463(2.199),SER422(2.093),LYS462(2.029)	LEU464,PRO467,GLN424,ALA421,VAL423
22	GA14	GAGAG	-6.96	7.88 uM	GLN328(1.891),LYS325(1.91), LYS284(1.892),**LYS280**(2.053),ARG273(2.149)	PRO271,VAL329,ALA276,LYS277
23	GA15	GAAAG	-6.7	12.19uM	ARG465(2.028,2.004,1.93),**SER422**(2.149,1.992),GLN424(2.129)	VAL423,VAL433,MET420,PRO467,LEU452,LEU466,LEU435,ALA421
24	GA16	GGGGGA	-3.31	3.75mM	ARG273, ARG 273, **LYS 280**	
25	GA17	GGGAGG	-6.46	18.25uM	ARG273(2.218,1.929,1.873), **LYS280**(1.766),LYS284(1.918),LYS277(1.975,1.844)	SER281

26	*D1*	D-G	-6.83	9.8 uM	GLN424(2.131),ARG465(2.074,1.982)	LEU464,LEU452
27	*D2*	G-D-G	-7.59	274.09 nM	Lys 280 () Lys 325	ARG273, PRO271, LYS325, ARG272, Lys284, ALA276
28	*D3*	GG-D-G	-9.04	235nM	LYS274(2.199,1.826),LYS231(2.107,1.957), **ARG272**(1.802),LYS277(1.849)	SER228,LEU230,PHE236,ASN227,ARG273
29	*D4*	GGDGG	-11.08	7.53 nM	**LYS231(2.217,2.083),LYS232**(1.913),LEU230(2.076),**ARG272**(1.946,1.939),LYS274(1.758)	VAL329, ALA276, PRO271,ARG272
30	*D5*	GGGDGG	-10.72	13.87nm	**ARG272**(2.063),ARG273(2.207),LYS325(2.169,2.134,1.836), lys277, lys280' lys280	SER332,VAL329, PRO271,
31	*D6*	GGGDGGG	-8.39	705.85 nM	**LYS231**(1.798,1.763),ASN227(1.826),LYS274(1.941,1.799),**ARG272**(2.182,1.973)	ARG273,SER228,LEU230
32	*D7*	GAGDGAG	-5.67	69.31µM	**ARG273**(2.063,1.724),**LYS325**(1.882),**LYS280**(1.981),**GLN328**(2.229)	VAL329,ALA276,ARG272,PRO271

33	*D18*	GAGDGGA	-7.66	2.43 µM	**ARG273**(1.895),**LYS325**(2.058),**LYS280(**2.224, 2.18), LYS277 (2.175)	SER332, GLN 328, PRO271
34	*D20*	GAGDGG	-7.6	2.7uM	LYS277(2.122), **LYS280(**2.045, 2.232), LYS 325 (2.17)	GLN328, PRO 271
35	*D21*	GADGG	-8.22	940.4 nM	LYS277(1.916),LYS325(1.979),LYS284(2.177),PRO271 (2.132)**,LYS280**(1.933)	SER281,SER332,VAL329,ALA276,**ARG273**
36	*D22*	GADGA	-6.68	12.66 uM	ARG374(2.182,2.031,1.919), ALA421(2.175),VAL433(1.9 421.839)	MET420,MET375,ALA421,VAL433,LEU371,ARG432,LEU431
37	*D24*	ADG	-5.8	55.81 µM	SER422, TYR463	ALA421, VAL423, TYR463, LYS462, PRO467
38	*D25*	GADG	-6.68	12.7 µM	GLN424(1.951),**SER422**(2.127),ARG465(1.909,1.631)	ALA421,VAL423,VAL433,LEU452,LEU466,PRO467