International Journal of
Molecular Sciences

MDPI

Article

Computational Investigation Identified Potential Chemical Scaffolds for Heparanase as Anticancer Therapeutics

Shraddha Parate [1,†], Vikas Kumar [2,†], Danishuddin [2], Jong Chan Hong [1,*] and Keun Woo Lee [2,*]

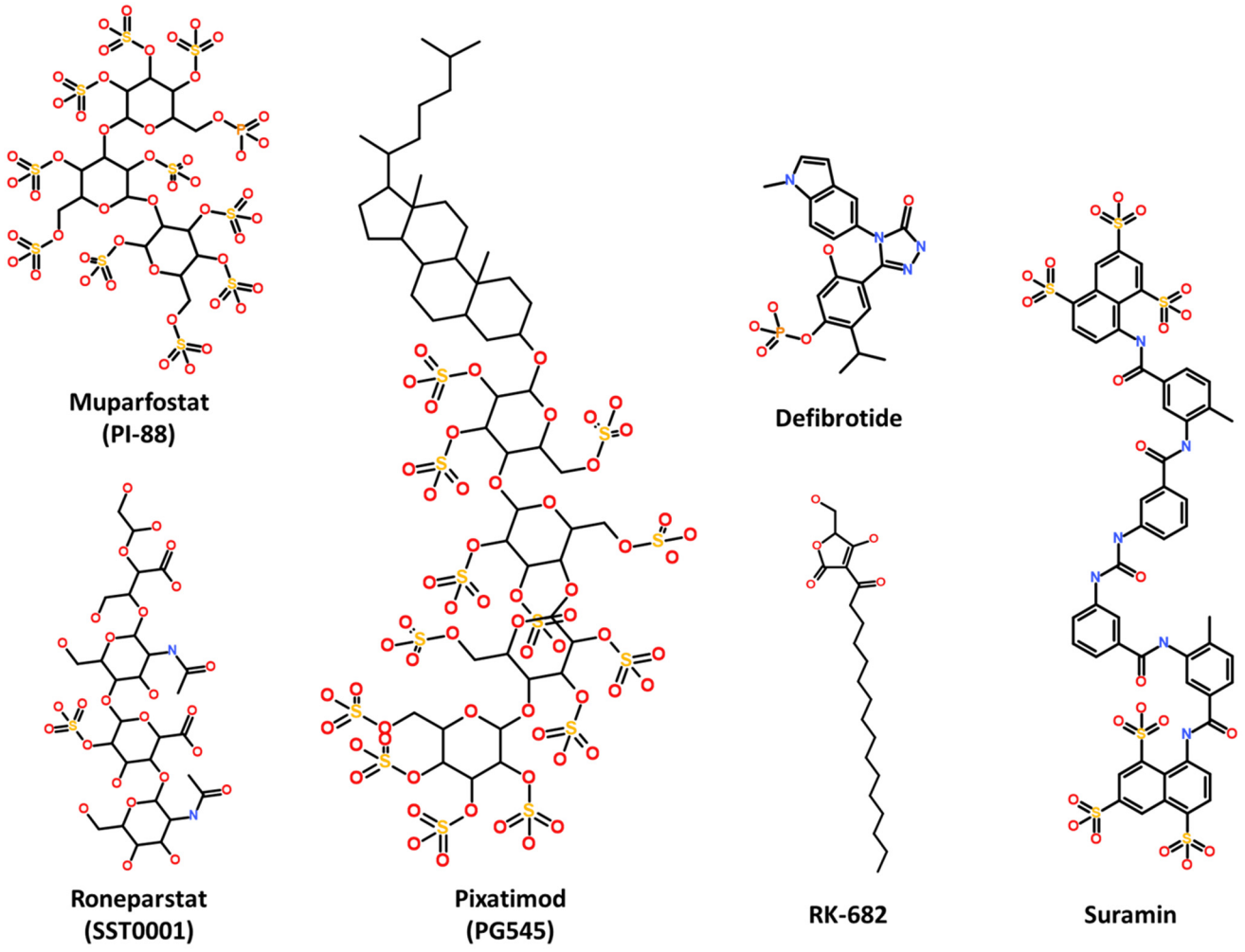

Figure S1. Chemical structures of carbohydrate-based, nucleic acid-based and small molecule Heparanase inhibitors.

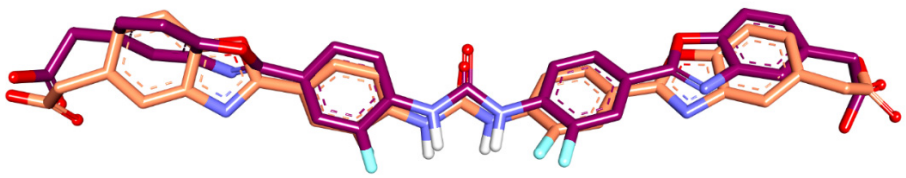

Figure S2. Overlay of the docked pose (orange) of bound ligand with its GS3 Heparanase model conformation (mauve).

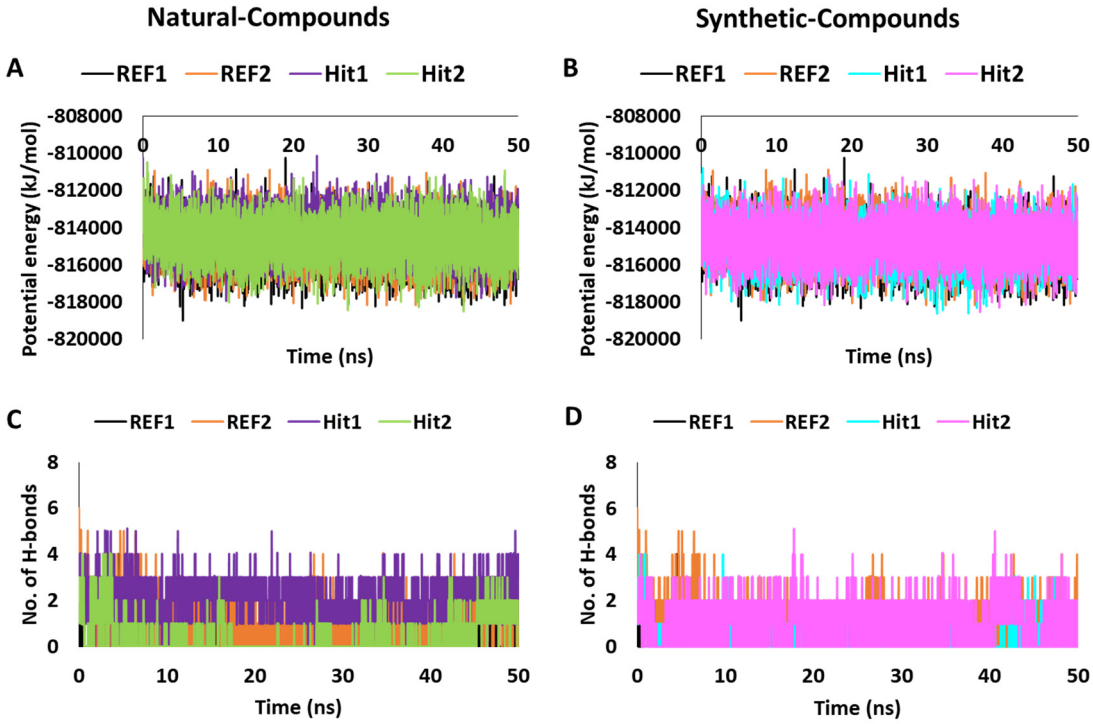

Figure S3. Molecular dynamics simulation analyses plots of Heparanase with the reference (REF) and Hits displaying (A and B) potential energy and (C and D) hydrogen bonds. The left (A and C) and right (B and D) columns represent analysis for natural and synthetic compound hits, respectively.

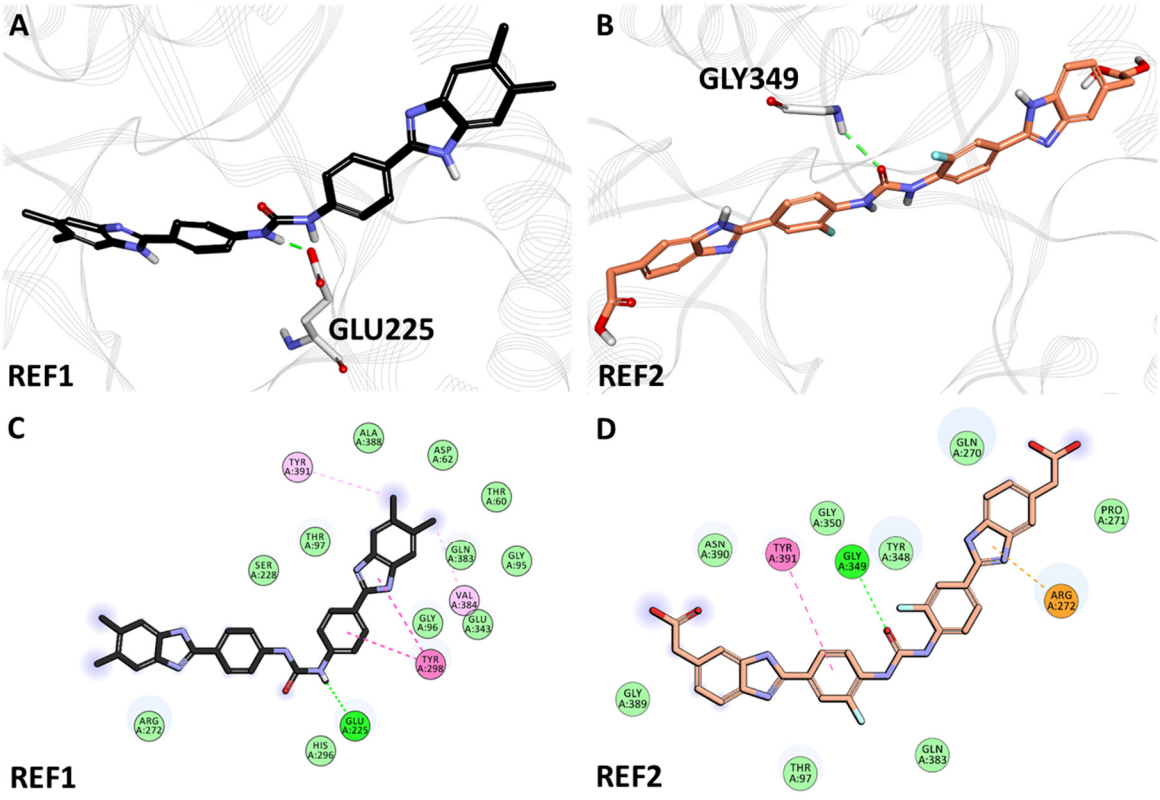

Figure S4. The 3D and 2D intermolecular interactions of reference (REF) compounds (REF1: A and C; REF2: B and D) with the active site residues of Heparanase.

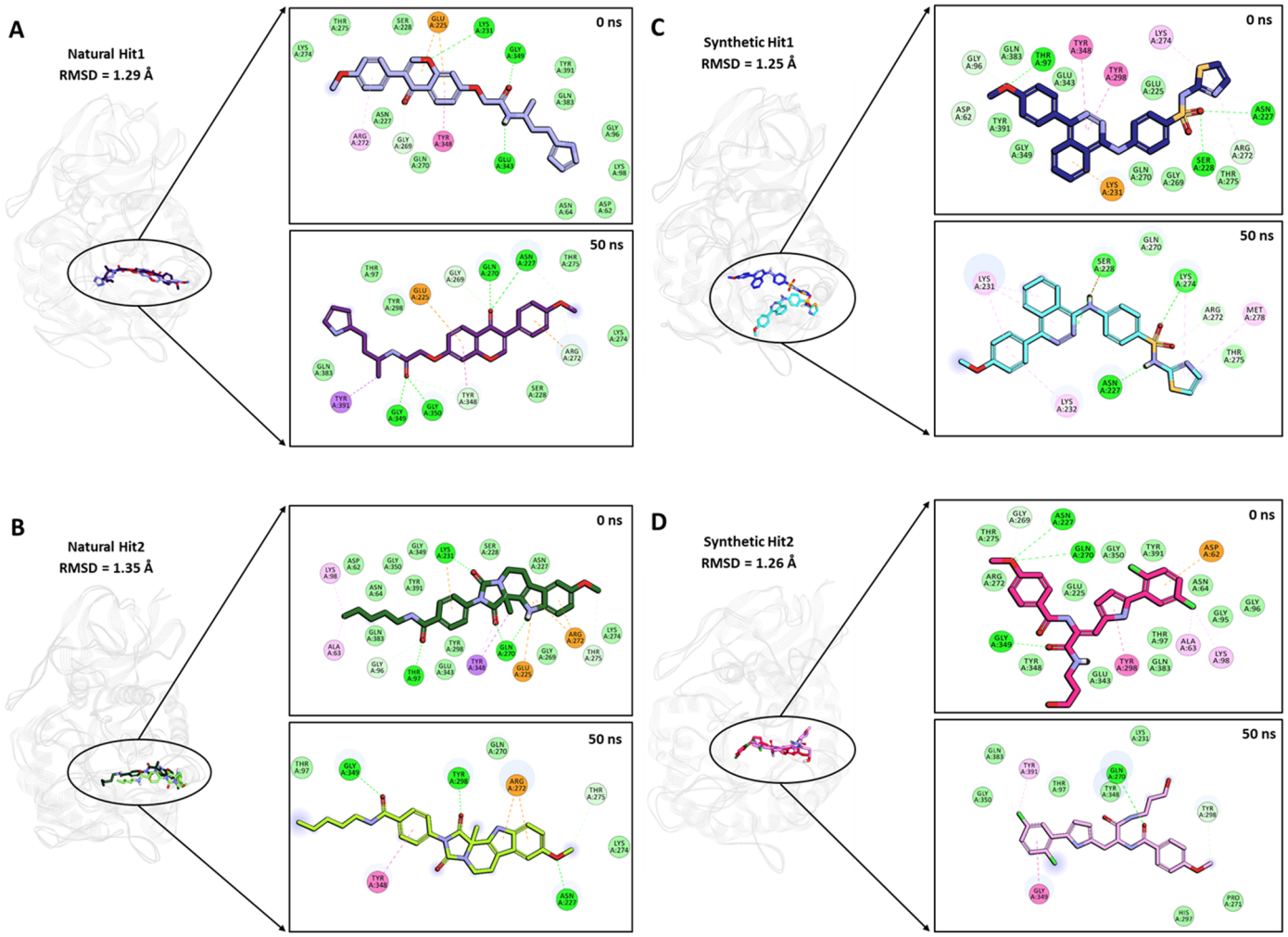

Figure S5. The superimposed complex structures and 2D intermolecular interactions of natural and synthetic compound hits with the catalytic residues of Heparanase at 0 ns and 50 ns.

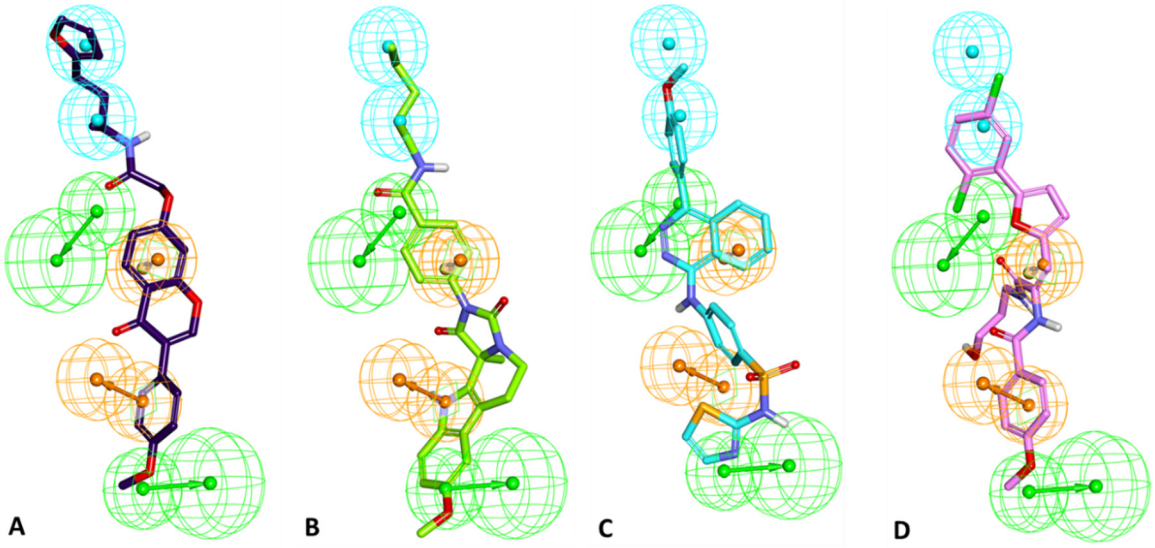

Figure S6. Alignment of identified hits with the pharmacophoric features of Hypo1. Subsections A and B represent Hit1 and Hit2 from natural compounds, whereas subsections C and D denote Hit1 and Hit2 from synthetic compounds of InterBioScreen database, respectively.

Table S1. The docking and binding free energy scores of drug-like natural and synthetic compounds from the InterBioScreen (IBS) database with Heparanase.

IBS ID/REF No.	SMILES ID	Docking Scores		Binding Free Energy Scores
		Goldscore	Chemscore	ΔG_{bind} (kJ/mol)
Natural Drug-Like Compounds				
STOCK1N-75678	COC1=C(C=CC=C1)C(=O)NC2=CC=C(C=C2)C(=O)C3=CC4=C(CCN3C)C=C5OCOC5=C4OC	72.62	-32.54	-67.45
STOCK1N-90022	COC1=C(OC)C=C(C=C1)C2=COC3=CC(=CC=C3C2=O)OCC(=O)NC4=CC5=C(OCCO5)C=C4	70.95	-30.26	-44.12
STOCK1N-71247	COC1=CC=C(C=C1)C2=COC3=CC(=CC=C3C2=O)OCC(=O)NCCC4=C[NH]C5=C4C=CC=C5	70.67	-31.84	-54.42
STOCK1N-21853	COC1=CC2=C([NH]C3=C2CCNC3C4=CC=C(OC)C(=C4)COC5=CC=C(C=C5)[N](=O)=O)C=C1	69.62	-30.54	-39.03
STOCK1N-59679	COC1=CC=C(OC)C(=C1)C2=CC3=C(OC2=O)C=C(OC(=O)C4=CC(=CC(=C4)OC)OC)C=C3	69.31	-33.91	-59.23
STOCK1N-45143	COC(=O)C1=CC=C(COC2=CC3=C(C=C2)C(=O)\C(O3)=C\C4=CC=C(C=C4)C(=O)OC)C=C1	69.20	-34.19	-45.53
STOCK1N-71407	COC1=CC=C2OC(=O)C(=CC2=C1)C3=CC=C(OCC(=O)NC(C)CC4=CC=CO4)C=C3	69.03	-34.03	-68.02
STOCK1N-70463	COC1=CC=C(C=C1)C2=COC3=CC(=CC=C3C2=O)OCC(=O)NC(C)CCC4=CC=CO4	68.95	-32.00	-104.57
STOCK1N-57934	CCCOC(=O)COC1=CC=C2C=C(C(=O)OC2=C1)C3=CC(=O)OC4=C3C=CC(=C4)OC	68.95	-31.80	-51.10
STOCK1N-22579	COC1=CC2=C([NH]C3=C2CCNC3C4=CC=C(OC)C(=C4)COC5=CC=C(NC(C)=O)C=C5)C=C1	68.94	-34.87	-46.94
STOCK1N-90307	CC(=O)C1=CC(=CC=C1)NC(=O)COC2=CC=C3C(=O)C(=C(C)OC3=C2)C4=CC=CC=C4	67.98	-30.17	-55.66
STOCK1N-48729	CCCCCNC(=O)C1=CC=C(C=C1)N2C(=O)N3CCC4=C([NH]C5=C4C=C(OC)C=C5)C3(C)C2=O	67.79	-30.66	-83.75
STOCK1N-67945	CCCCNC(=O)C(C)OC1=CC2=C(C=C1)[N]3C(=C4C(OC)C(=CC=C4C5=NC=CC2=C35)OC)O	67.77	-43.38	-55.81
STOCK1N-36801	COC1=CC=C(C=C1OC)C(=O)OC2=CC=C3C(=O)C(=C(C)OC3=C2)C4=CC(=C(OC)C=C4)OC	67.61	-29.05	-61.54
STOCK1N-68238	COC1C(=CC=C2C3=NC=CC4=C3[N](C(=C12)O)C5=C4C=C(OCC(=O)NCC6=CC=CC=C6)C=C5)OC	67.53	-42.25	-67.13
Synthetic Drug-Like Compounds				
STOCK2S-58608	CC1=CC=C(C=C1)C2=CC=C(OCC(=O)NC3=CC=C(C=C3)[S](=O)(=O)NC4=NC=CS4)C=C2	81.01	-30.43	-53.29
STOCK3S-51955	CC(C)CC1=CC=C(C=C1)C2=CSC(=N2)\C(=C\NC3=CC=C(C=C3)[S](=O)(=O)NC(N)=O)C#N	77.85	-32.04	-59.03
STOCK2S-50669	COC1=CC(=CC=C1OCC2=CC=C(C=C2)C(O)=O)[CH]=[N+]=[NH+][S](=O)(=O)C3=CC=C4C=CC=CC4=C3	77.73	-34.28	-71.35
STOCK1S-47127	COC1=CC(=C(C=C1)C(=O)\C=C\NC2=CC=C(C=C2)[S](=O)(=O)NC3=NC(=CC(=N3)C)C)OC	76.38	-31.12	-73.59
STOCK3S-52245	CCCOC1=CC=C(\C=C\C(=O)NC2=CC=C(C=C2)[S](=O)(=O)NC3=NC(=CC(=N3)C)C)C=C1	75.76	-34.62	-68.04
STOCK3S-49803	CCCOC1=CC=C(\C=C\C(=O)NC2=CC=C(C=C2)[S](=O)(=O)NC3=CC(=NC(=N3)C)C)C=C1	75.17	-34.60	-61.53

STOCK1S-95244	COC1=CC=C(C=C1)C2=NN=C(NC3=CC=C(C=C3)[S](=O)(=O)NC4=NC=CS4)C5=C2C=CC=C5	74.92	-30.70	-96.19
STOCK2S-58772	CCOC1=C(OCC)C=C(C=C1)C(=O)NC2=CC=C(C=C2)[S](=O)(=O)NC3=NC(=CC=N3)C	74.53	-31.32	-70.27
STOCK2S-58619	COC1=C(OC)C=C(C=C1)C(=O)NC2=CC=C(C=C2)[S](=O)(=O)NC3=NC(=CC(=N3)C)C	74.29	-31.00	-67.59
STOCK2S-04448	CCN(CC)C(=O)C1=CC=C(C=C1)C2=C3C=CC=CC3=C(NC4=CC=C(C=C4)[S](N)(=O)=O)N=N2	73.30	-36.28	-52.70
STOCK3S-42907	CC1=CC=C(C=C1)C2=N[N+](=C([O-])C3=C2C=CC=C3)CC(=O)NC4=CC=C(C=C4)C(=O)N5CCCCC5	72.48	-36.75	-55.61
STOCK3S-57053	CCCOC1=CC=C(C=C1)C(=O)NC2=CC=C(NC(=O)C3=CC4=C(O3)C=CC=C4)C(=C2)OC	71.47	-35.32	-73.41
STOCK3S-43653	COC1=CC=C(C=C1)C(=O)NC2=CC=C(CC3=CC=C(NC(=O)C4=CC=C(OC)C=C4)C(=C3)O)C=C2O	69.98	-31.57	-52.49
STOCK3S-30539	CCOC1=CC=C(C=C1)C2=C3C=CC=CC3=C(NC4=CC=C(C=C4)[S](N)(=O)=O)N=N2	69.29	-32.09	-59.31
STOCK2S-94267	CC[N]1C(=NN=C1C2=CC=C(C)C=C2)SCC(=O)[NH+]=[N+]=[C](C)C3=CC=C(OC(C)=O)C=C3	69.05	-31.47	-54.27
STOCK3S-72317	COC1=CC=C(NC(=O)C2CC(=O)N(CC3=CC4=C(OCO4)C=C3)C(S2)=NC5=CC=CC=C5)C=C1	67.85	-31.47	-67.31
STOCK3S-52762	CCC(=O)NC1=CC=C(C=C1)C2=NN=C(SCC(=O)C3=CC=C4C=CC=CC4=C3)[N]2C	67.80	-32.05	-54.64
STOCK1S-71515	COC1=CC=C(C=C1)C(=O)N\C(=C\C2=CC=C(O2)C3=C(Cl)C=CC(=C3)Cl)C(=O)NCCCO	67.53	-33.38	-86.80
REF2	OC(=O)CC1=CC2=C(OC(=N2)C3=CC=C(NC(=O)NC4=CC=C(C=C4F)C5=NC6=C(O5)C=CC(=C6)CC(O)=O)C(=C3)F)C=C1	67.43	-24.35	-83.51
REF1	CC1=CC2=C(C=C1C)N=C([NH]2)C3=CC=C(NC(=O)NC4=CC=C(C=C4)C5=NC6=C([NH]5)C=C(C)C(=C6)C)C=C3	55.30	-27.79	-74.61

Table S2. The entropic distribution of the total binding free energy scores for reference (REF) inhibitors and selected potential hits from InterBioScreen (IBS) database against Heparanase.

Ligands (IBS ID/REF No.)	van der Waals (kJ/mol)	Electrostatic (kJ/mol)	Polar solvation (kJ/mol)	SASA energy (kJ/mol)	Binding free energy ΔG_{bind} (kJ/mol)
Natural Compound Hits					
Hit1 (STOCK1N-70463)	-169.280 +/- 18.050	-86.216 +/- 15.175	171.068 +/- 26.205	-20.150 +/- 1.812	-104.579 +/- 20.649
Hit2 (STOCK1N-48729)	-147.049 +/- 24.361	-21.267 +/- 19.495	103.627 +/- 44.940	-19.062 +/- 2.438	-83.751 +/- 26.469
Synthetic Compound Hits					
Hit1 (STOCK1S-95244)	-163.420 +/- 16.897	-35.954 +/- 14.820	121.494 +/- 29.609	-18.313 +/- 1.647	-96.193 +/- 23.866
Hit2 (STOCK1S-71515)	-133.337 +/- 16.571	-44.788 +/- 20.534	107.469 +/- 45.892	-16.150 +/- 2.029	-86.806 +/- 26.536
Reference Inhibitors					
REF1	-135.600 +/- 13.852	-77.120 +/- 17.869	155.337 +/- 37.648	-17.230 +/- 2.079	-74.612 +/- 20.900
REF2	-173.780 +/- 16.684	-71.717 +/- 31.611	182.920 +/- 59.166	-20.942 +/- 2.278	-83.519 +/- 31.504

Table S3. Assessment of anti-cancer drug sensitivity prediction for reference (REF) inhibitors and identified hits generated by PaccMann.

Cancer Types	Natural Compound Hits (IC50)(μM)		Synthetic Compound Hits (IC50)(μM)		Reference Inhibitors (IC50)(μM)		Cell Lines
	Hit1 (STOCK1N-70463)	Hit2 (STOCK1N-48729)	Hit1 (STOCK1S-95244)	Hit2 (STOCK1S-71515)	REF1	REF2	
Ovarian cancer	0.528	0.556	0.522	0.599	0.562	0.569	A2780
Lung cancer	0.564	0.581	0.573	0.624	0.604	0.592	A549
Breast cancer	0.582	0.549	0.598	0.633	0.614	0.601	MCF-7
Ewing's sarcoma	0.548	0.567	0.557	0.611	0.593	0.583	SK-ES-1
Multiple myeloma	0.539	0.562	0.547	0.608	0.580	0.584	MM1S
Hepatocellular carcinoma	0.534	0.523	0.518	0.611	0.541	0.526	HepG2