Electronic Supplementary Material (ESI) for RSC Advances.

Supplementary materials

Structure-based approach: Molecular insight of pyranocumarins against α-glucosidase through computational studies

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Computational detail

Molecular docking

The molecular docking process consists of several stages, those are:

(i) Creation of cluster spheres on the receptor surface using a dot molecular surface (*DMS*) file through the chimera package version 13. Next, the cluster spheres were analyzed using the *sphgen* tool available in the DOCK6 package with a probe radius of 1.4-4.0 Å on the receptor surface. This step aims to generate a clustered spheres file (*sph*).

(ii) Selection of cluster spheres based on the *sph* file previously obtained through the *sphere_selector* tool. Selected cluster spheres focused at a radius of 10.0 Å from the GLC coordinates as a reference.

(iii) Creating a grid-box using the *showbox* and *grid* tools available in the DOCK6 package. In addition, the generation is based on selected cluster sphere coordinates with *bump_overlap*: 0.75 and *dielectric_factor*: 4.

(iv) The minimization process is carried out using functional gird scoring (*internal_energy_rep_exp*: 12 and *internal_energy_cutoff*: 100). This step aims to generate a *min_scored.mol* file which is used as the rmsd reference.

(v) Analysis of interaction energy using flexible conformation with *anchor-and-grow* algorithm (*implex_anchor_max_iterations*: 500 and *simplex_grow_max_iterations*: 500).

Molecular dynamics simulation

The initial coordinates obtained from the molecular docking stage are continued using molecular dynamics simulation through the AMBER22 package. Following are some stages of the molecular dynamics simulation:

(i) The minimization stage is carried out through three main stages: water molecules and sodium ions, ligand-receptor, and the whole system. Some of the parameters used in the minimization process are imin: 1, maxcyc: 1500, ncyc: 500, and cut: 10.

(ii) The heating stage was carried out for 200 ps with harmonic restraint of 30 kcal mol^{-1} (nstlim: 100000, dt: 0.002, tempi: 10.0, temp0: 310.0, and cut: 10.0).

(iii) The first equilibrated stage is carried out in stages for 300 ps harmonic restraint of 30 kcal mol^{-1} (nstlim: 150000, dt: 0.002, tempi: 310.0, temp0: 310.0, and cut: 10.0).

(iv) The second equilibrated stage is carried out in stages for 250 ps harmonic restraint of 20 kcal mol^{-1} (nstlim: 125000, dt: 0.002, tempi: 310.0, temp0: 310.0, and cut: 10.0).

(v) The third equilibrated stage is carried out in stages for 250 ps harmonic restraint of 10 kcal mol^{-1} (nstlim: 125000, dt: 0.002, tempi: 310.0, temp0: 310.0, and cut: 10.0).

(vi) The fourth equilibrated stage is carried out in stages for 500 ps harmonic restraint of 5 kcal mol^{-1} (nstlim: 250000, dt: 0.002, tempi: 310.0, temp0: 310.0, and cut: 10.0).

(vii) The production stage is carried out for 100 ns and each resulting trajectory is saved in 1000 ps (nstlim: 500000, dt: 0.002, tempi: 310.0, temp0: 310.0, and cut: 10.0).

Tables:

Table S1 The average value from conformational dynamics of each system: All parameters were calculated using 100 ns trajectories.

Parameters	**α-Glu**	**PC1-α-Glu**	**PC2-α-Glu**	**PC3-α-Glu**
Energy Total (kcal/mol)	-179222 ± 1557.26	-179099 ± 1563.56	-177613 ± 1550.14	-180626 ± 1571.95
RMSD complex (nm)	0.21 ± 0.03	0.19 ± 0.02	0.23 ± 0.04	0.25 ± 0.06
RoG (nm)	2.42 ± 0.00	2.41 ± 0.00	2.42 ± 0.02	2.42 ± 0.01
B-Factor (nm^2)	35.98 ± 24.36	30.61 ± 19.74	13.83 ± 9.02	11.25 ± 7.14
RMSF (nm)	1.10 ± 0.38	1.02 ± 0.34	0.68 ± 0.23	0.62 ± 0.20

Table S2 Atom contacts detail of each system (The cut value of the first distance is 3.5 Å).

No	Contact	Frames	AvgDist (Å)	P_{AC}(%)
PC1-α-Glu				
1	2C=O…ND2(N412)	9979	3.05	92.39
2	2C…O(Y155)	9950	3.10	92.12
3	10aC-O…O(Y155)	8055	3.22	74.58
4	2C=O …O(Y155)	7993	3.23	74.00
5	3C…O(Y155)	4772	3.24	44.18
6	3C...OE2(E408)	2026	3.32	18.75
7	5C-O…CD(R312)	580	3.35	5.37
8	Cl…NH2(R312)	559	3.29	5.17
9	Cl…OG1(T303)	511	3.28	4.73
10	1a’C…OG(G237)	115	3.40	1.06
11	7C...NE2(H277)	64	3.40	0.59
12	3’C…CD(K153)	40	3.38	0.37
13	2’C…O(S154)	22	3.41	0.20
PC2-α-Glu				
1	6C…O(Y155)	5272	3.21	48.81
2	7C…O(Y155)	3852	3.19	35.66
3	8aC…O(Y155)	2387	3.34	22.10
4	1"C=O…NH1(R312)	2064	3.25	19.11
5	7C...OE2(E408)	1458	3.32	13.50
6	6C...OE2(E408)	1339	3.35	12.39
7	3C…OE1(Q276)	1089	3.22	10.08
8	4aC…CE2(Y155)	848	3.23	7.85
9	8bC…N(R312)	796	3.37	7.37
10	2C…OH(Y155)	623	3.32	5.76
11	7’’C...CZ(R312)	620	3.33	5.74
12	3C...NE2(H277)	585	3.32	5.41
13	1a’C…OD1(D239)	552	3.21	5.11
14	Br…OD2(D239)	423	3.33	3.91
15	7’’C…NH2(R312)	414	3.36	3.83
16	3C...CD2(H277)	396	3.39	3.66
17	2C=O...CD2(H277)	224	3.36	2.07
18	3’C…O(L310)	120	3.28	1.11
PC3-α-Glu				
1	3C…O(Y155)	7052	3.15	65.29
2	2C…O(Y155)	5714	3.21	52.90
3	2C=O…O(Y155)	5258	3.22	48.68
4	1a’C…OG(G237)	2364	3.34	21.88
5	2C=O…ND2(N412)	2099	3.08	19.43
6	4’’C…NH1(R312)	1857	3.33	17.19
7	3’’C…NH1(R312)	1353	3.33	12.52
8	3’’C...CZ(R312)	466	3.40	4.31
9	4C...CD(R312)	403	3.41	3.73
10	8bC…OD1(D239)	276	3.35	2.55

Figures:

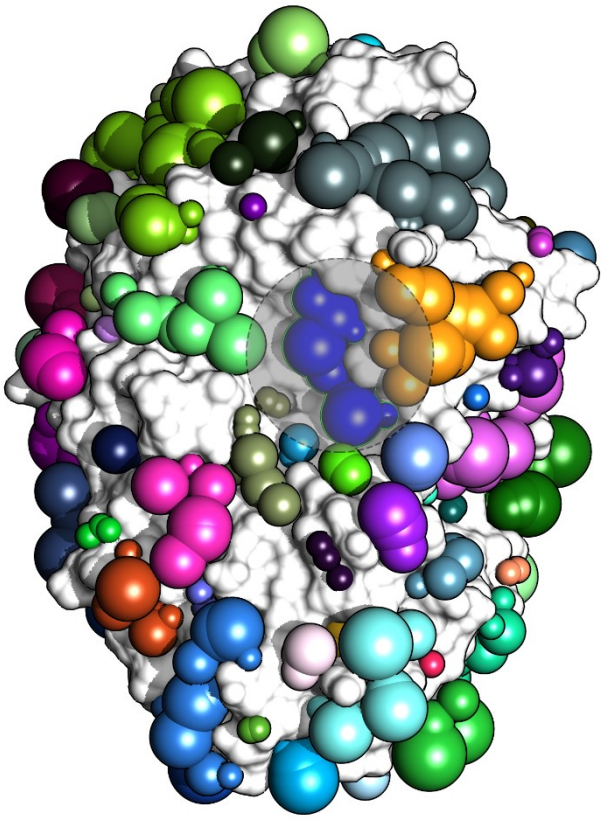

Fig. S1 Cluster spheres visualization on the receptor surface area. The selected cluster spheres (blue color) show the possibility of receptor active sites based on GLC coordinates.

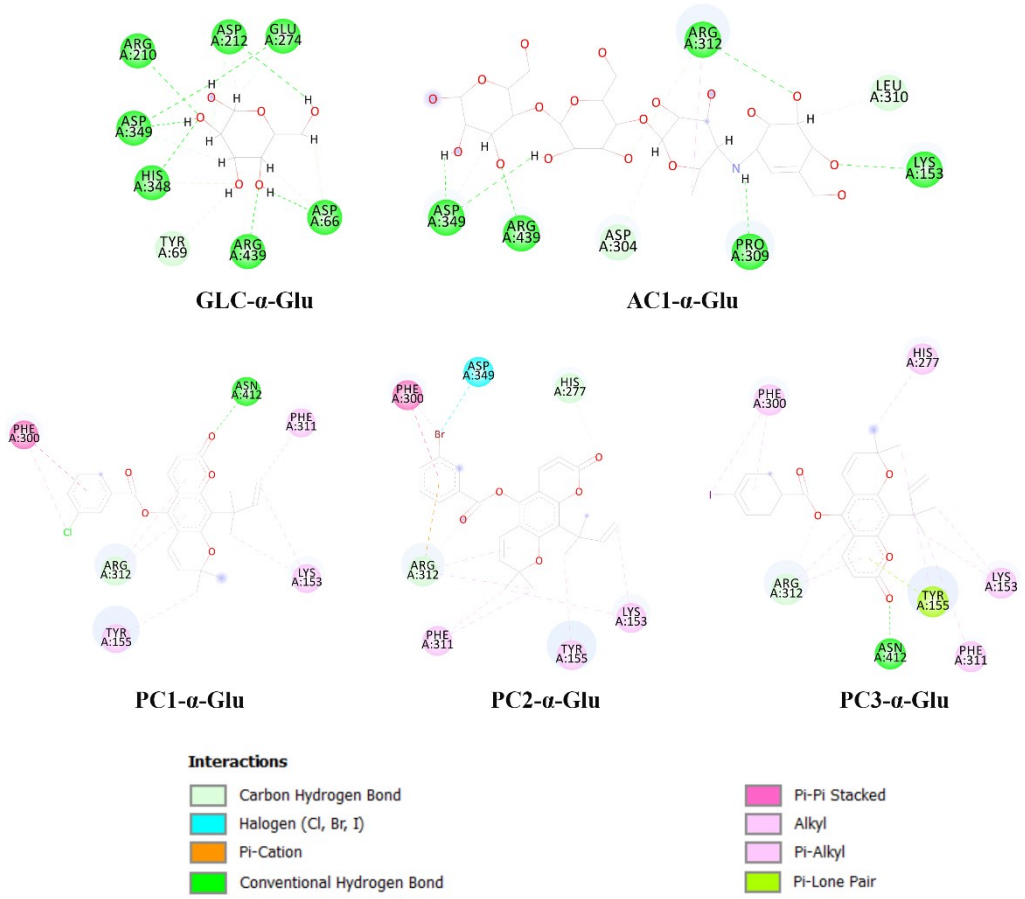

Fig. S2 Docking Analysis: The interaction type of each complex is shown by a 2D-diagram.

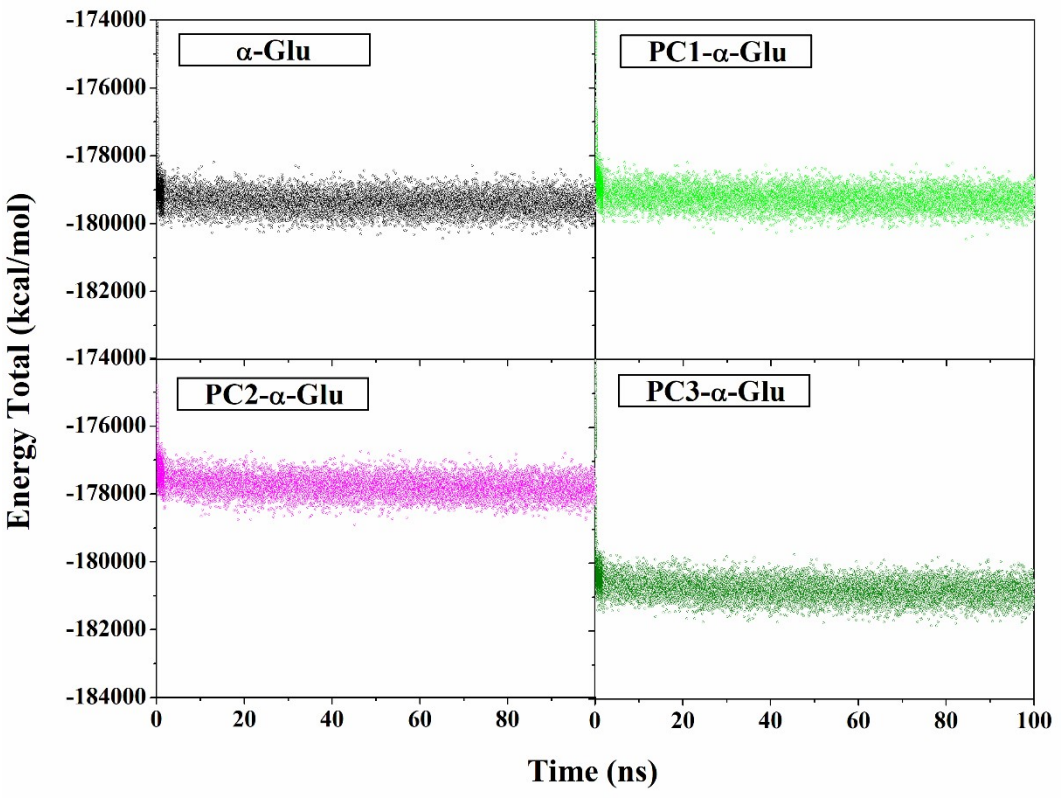

Fig. S3 The energy total of each system was plotted along 100 ns simulation time.