Supplementary Material

Synthesis, Molecular Modeling and Biological Evaluation of Aza-flavanones as α-Glucosidase Inhibitors

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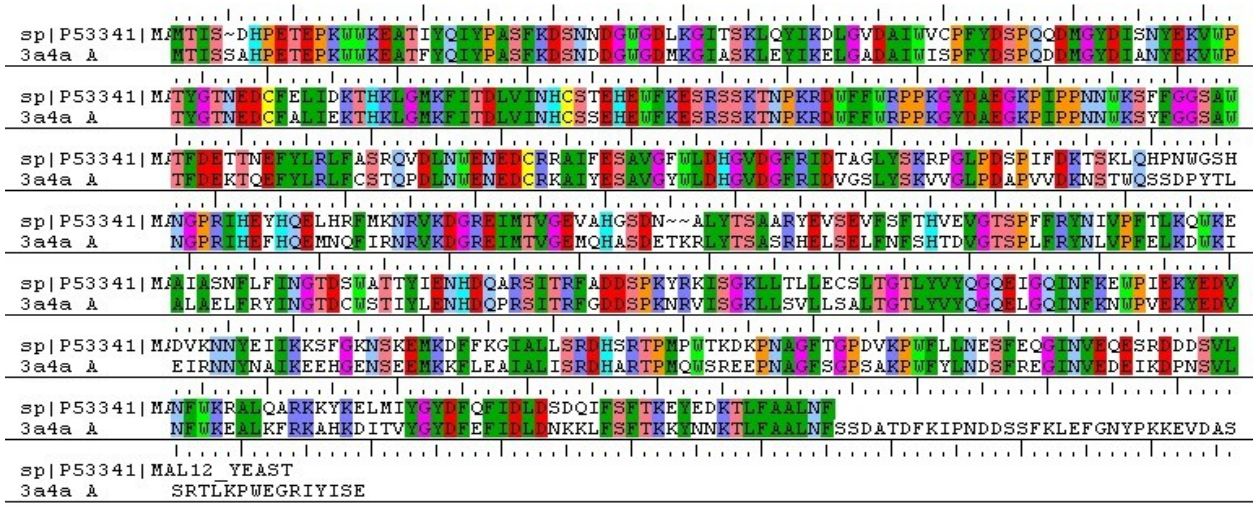

Figure S1. Sequence alignment of α-glucosidase from *S. cerevisiae* and isomaltase from *S. cerevisiae* (PDB ID: 3A4A).

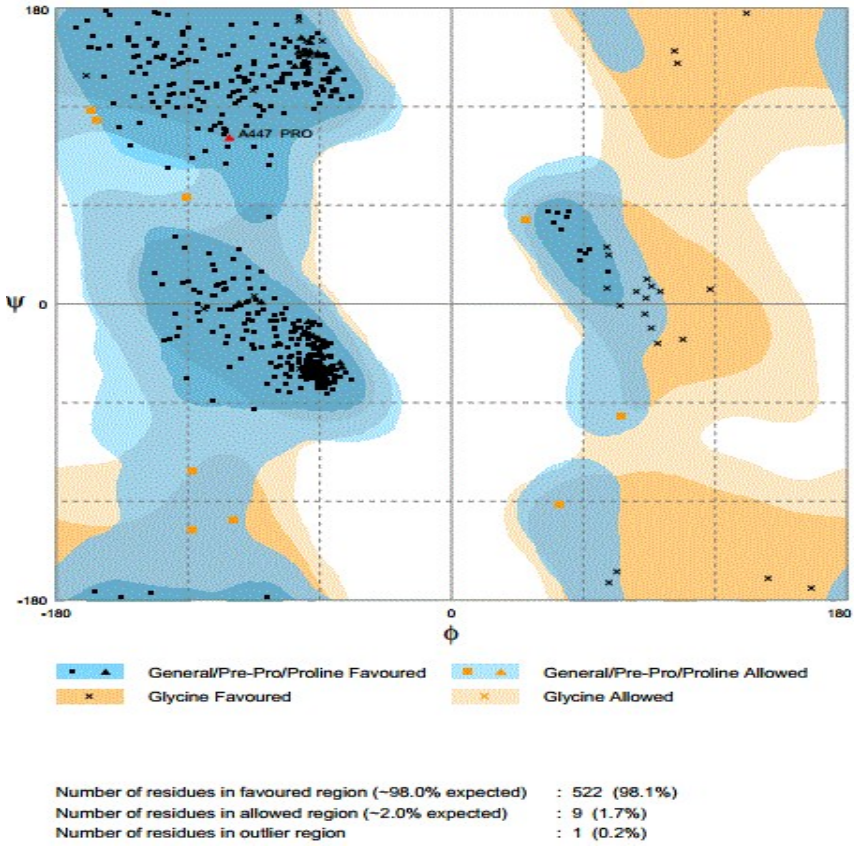

Figure S2. Ramchandran plot analysis for α-glucosidase of *S.cerevisiae* (Baker's *yeast).*

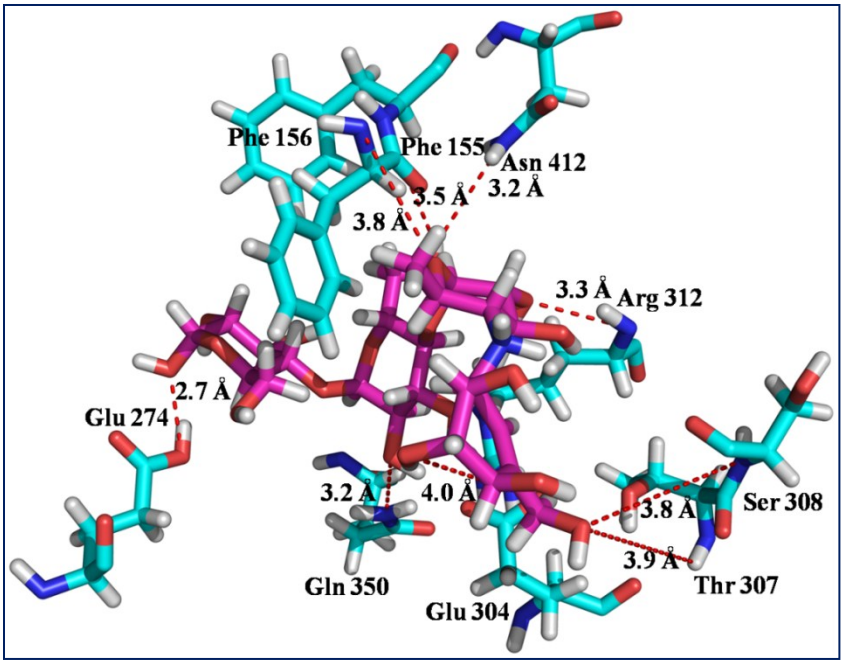

Figure S3. Ligand-protein interactions for Acarbose molecule (magenta colour stick) as revealed from GLIDE docking in the binding site of modeled α-glucosidase. The red dashed lines represent hydrogen bonds. H-bond distances (in Å) between heteroatoms of ligand and amino acid residues are as follows:Phe 155 (3.5), Phe 156 (3.8), Glu 274 (2.7), Glu 304 (4.0), Thr 307 (3.9), Ser 308 (3.8), Arg 312 (3.3), Gln 350 (3.2), Asn 412 (3.2).

Table 5. GLIDE docking results for acarbose and azaflavanones within the binding pocket of α-glucosidase.

S.No	Ligand id	Docking score	Interactions		
			H- bonds	π - π	Hydrophobic
1	Acarbose	-8.41	Phe 155, Phe 156, Glu 274, Glu 304, Thr 307, Ser 308, Arg 312, Gln 350, Asn 412	-	Phe 155, Phe 156, Phe 175, Ala 276, Phe 300, Phe 309, Phe 310, Phe 311, Tyr 313
2	5a	-7.09	Lys 153, Arg 312, Tyr 313, Asn 412	His 237	Phe 155, Pro 238, Ala 276, Phe 300, Pro 309, Phe 310, Phe 311, Tyr 313
3	5b	-6.77	Lys 153, Arg 312	His 237	Phe 155, Pro 238, Phe 300, Pro 309, Phe 311
4	5c	-6.64	Arg 312, Tyr 313, Asn 412	-	Phe 155, Phe 156, Leu 174, Pro238, Pro 309, Phe 310, Tyr 313
5	5d	-5.44	Asp 408	-	Phe 155, Phe 175, Phe 300, Phe 311, Tyr 313
6	5e	-5.24	Asn 412	-	Phe 155, Pro 238, Phe 311, Tyr 313
7	5f	-4.78	Phe 155, Phe 156		Phe 155, Phe 156, Phe 175, Phe 300
8	5g	-7. 98	Lys 153, Arg 312, Tyr 313, Asn 412	His 237	Phe 155, Phe 156, Leu 174, Phe 175, Leu 216, Pro 238, Ala 276, Phe 300, Val 303, Pro 309, Phe 310, Phe 311, Tyr 313
9	5h	-6.88	Lys 153, Arg 312, Tyr 313, Asn 412	Phe 155, His 237	Phe 155, Phe 156, Pro 238, Ala 276, Phe 300, Pro 309, Phe 310, Phe 311, Tyr 313
10	5i	-6.50	Lys 153, Arg 312, Arg 439	-	Phe 155, Pro 238, Phe 300, Pro 309, Phe 311
11	5l	-5.01	Lys 153, Arg 312	-	Phe 155, Pro 238, Phe 300, Phe 311
12	5n	-4.23	Phe 155		Phe 155, Pro 238, Phe 311
13	5o	-4. 55	Phe 155		Phe 155, Pro 238, Phe 300, Phe 311
14	5p	-6.02	Lys 153, Arg 312	His 237	Phe 155, Pro 238, Phe 300, Pro 309, Phe 310, Phe 311
15	5q	-5.63	Lys 153, Arg 312	His 237	Phe 155, Pro 238, Phe 300, Pro 309, Phe 311
16	5r	-7.43	Lys 153, Arg 312, Tyr 313, Asn 412	His 237	Phe 155, Phe 156, Leu 174, Phe 175, Leu 216, Pro 238, Ala 276, Phe 300, Pro 309, Phe 310, Phe 311, Tyr 313
17	5t	-4.16	Arg 312		Phe 155, Phe 156, Phe 300, Phe 311
18	5v	-5.22	Arg 312	-	Phe 155, Phe 156, Phe 175, Phe310, Phe 311, Tyr 313
19	5w	-7.21	Lys 153, Arg 312, Tyr 313	His 237	Phe 155, Leu 174, Phe 175, Pro 238, Ala 276, Phe 300,

					Pro 309, Phe 310, Phe 311, Tyr 313
20	Voglibose	-6.32	Phe 155, Phe 156, Glu 304, Asp 349, Gln 350, Asp 408, Asn 412	-	Phe 155, Phe 156, Phe 175, Ala 276, Phe 300, Val 303, Tyr 313
21	Miglitol	-6.04	Phe 155, Arg 210, Glu 304, Asp 349, Gln 350, Asp 408		Phe 155, Phe 156, Phe 175, Phe 300, Tyr 313

Prime MM/GBSA binding energy calculations

The MM/GBSA (Molecular mechanics/generalized born surface area) analysis was used to calculate ligand-binding energies based on docking complex, using the MM/GBSA technology available in Prime module of Schrodinger software. The protein ligand complexes obtained from molecular docking were subjected to MM/GBSA calculations. The relative binding free energy ΔG_{bind} was estimated according to following equation:

$$\Delta G_{bind} = E_{complex}\text{ (minimized) - [}E_{ligand}\text{(unbound, minimized) + } E_{receptor}\text{(unbound, minimized)]}$$

Where ΔG_{bind} is the calculated relative free energy which includes both ligand and receptor strain energy.$E_{complex}$ (minimized) is the MM/GBSA energy of the minimized complex, and E_{ligand} (unbound, minimized) is the MM/GBSA energy of the ligand after removing it from the complex and allowing it to relax. $E_{receptor}$ (unbound, minimized) is the MM/GBSA energy of protein after separating it from the ligand.

Table 6. Binding energies (ΔG_{bind}) obtained for some of synthesized aza-flavanone derivatives and other known glucosidase inhibitors.

S.No	Ligand ID	Binding energy (kcal/mol)
1	**Acarbose**	-82.20
2	**5a**	-40.36
3	**5g**	-48.60
4	**5h**	-40.64
5	**5r**	-43.69
6	**5w**	-44.47
7	**Miglitol**	-42.02
8	**Voglibose**	-39.34