Supplementary file 1

An integrative computational strategy for antidiabetic drug discovery: from QSAR modeling to retrosynthesis

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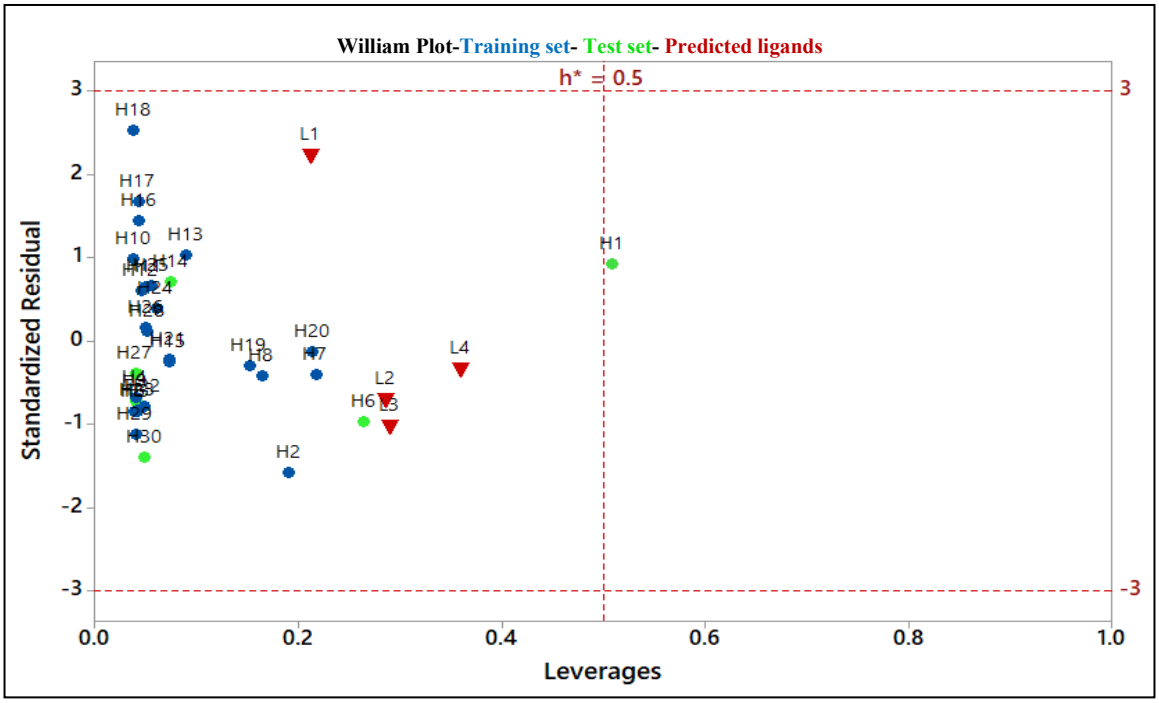


Fig. S1. William plot of CoMSIA/SDHA model

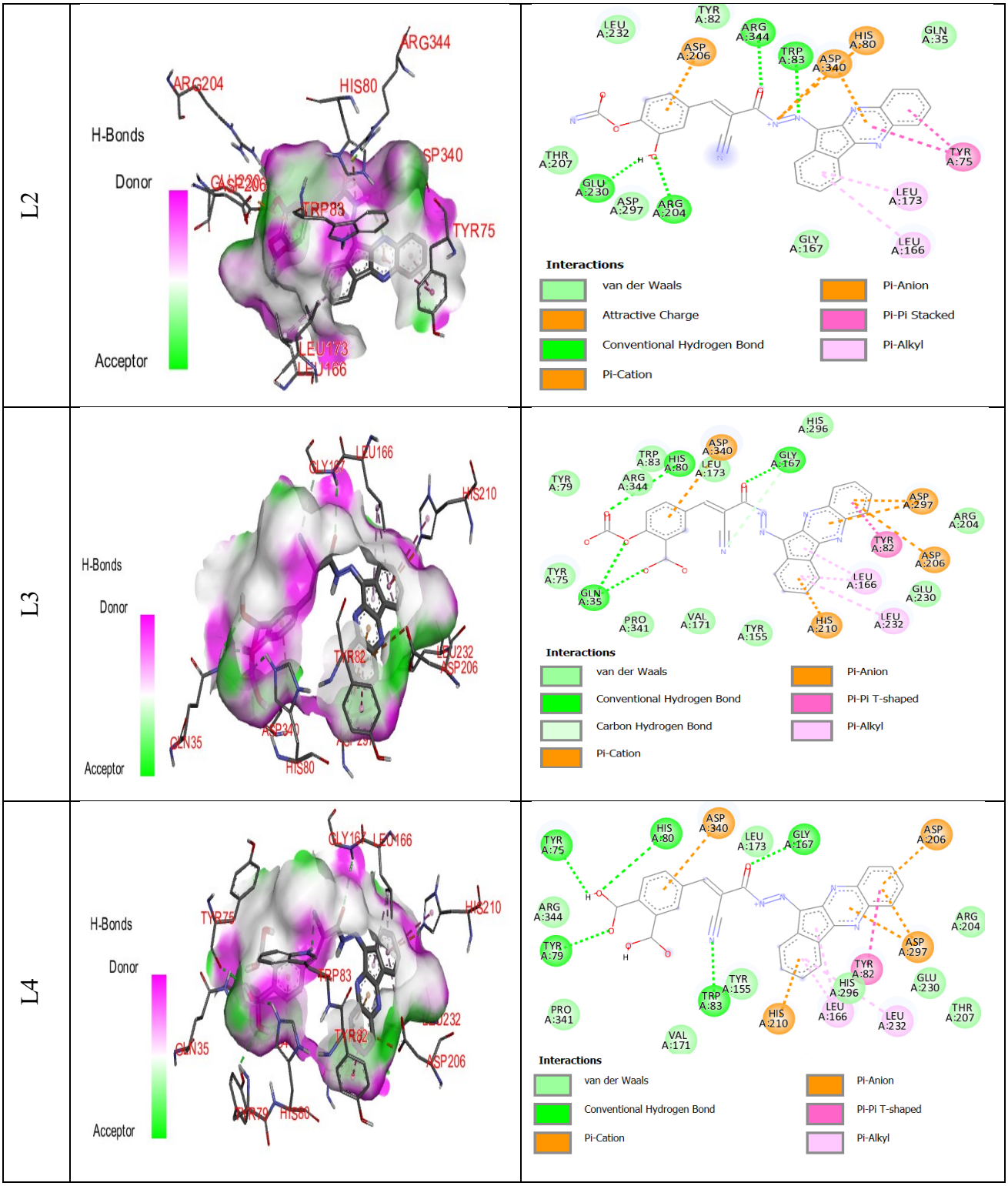


Fig. S2. 2D and 3D interactions of predicted (L2-L4) compounds with α-amylase.

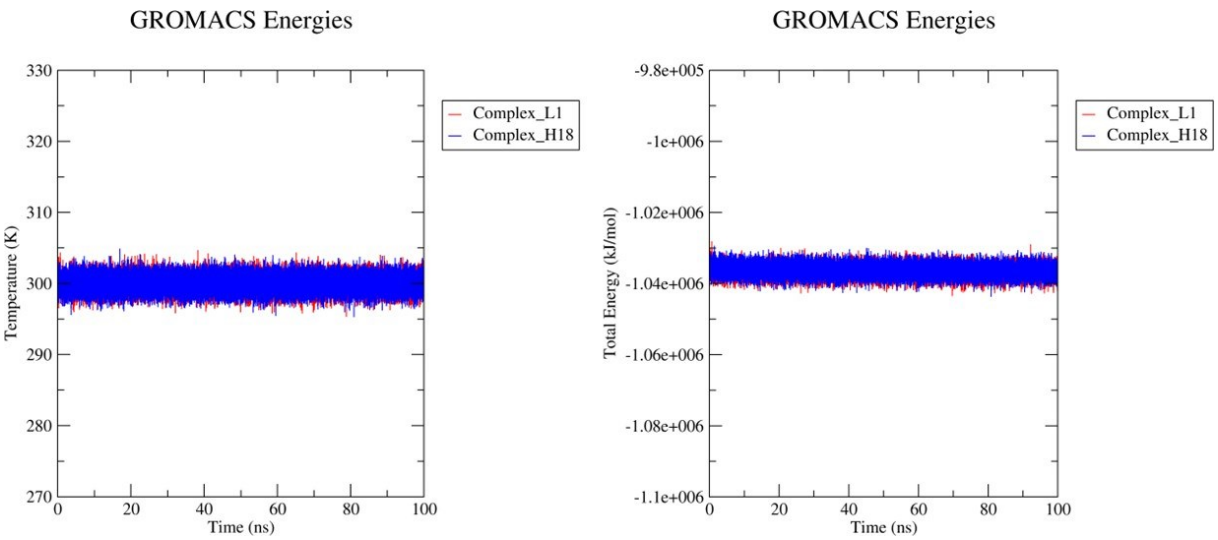


Fig. S3. Stability Analysis of Temperature and Total Energy for Protein-Ligand Complexes (L1 and H18)

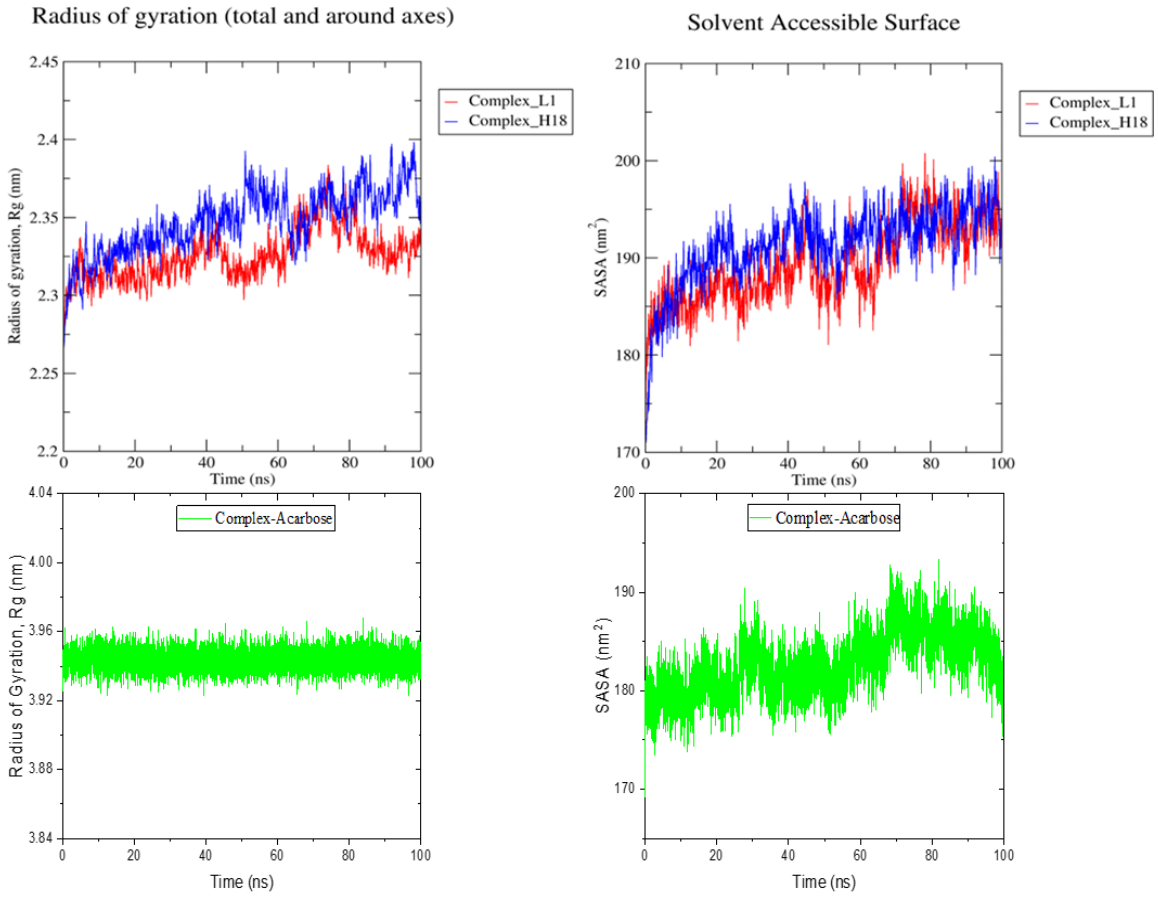


Fig. S4. Rg and SASA of 7TAA-L1, 7TAA-H18 and 7TAA-Acarbose

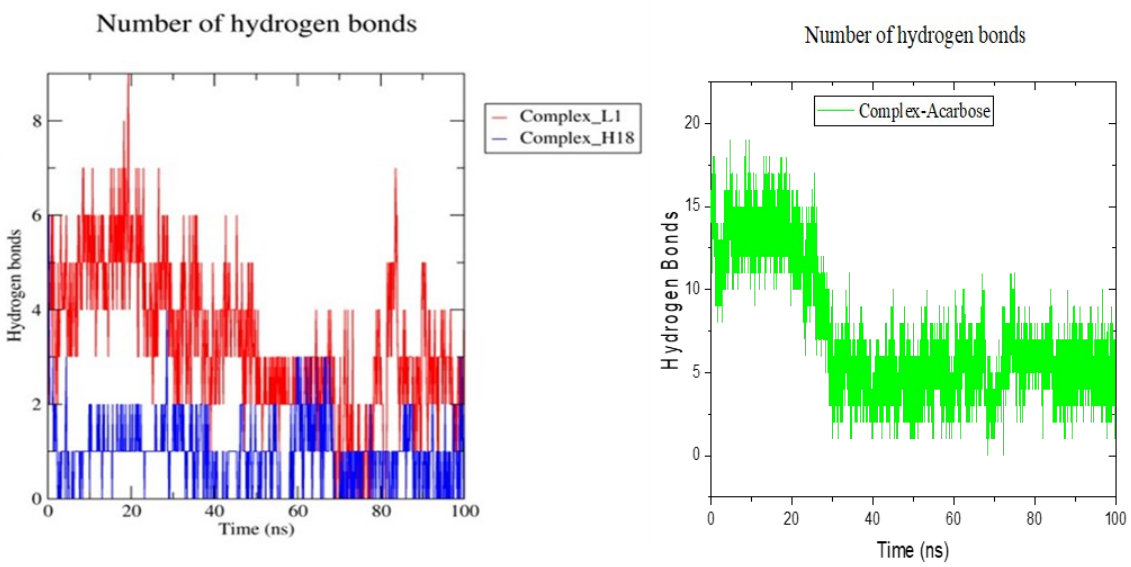


Fig. S5. Number of hydrogen bonds of 7TAA-L1, 7TAA-H18 and 7TAA-Acarbose

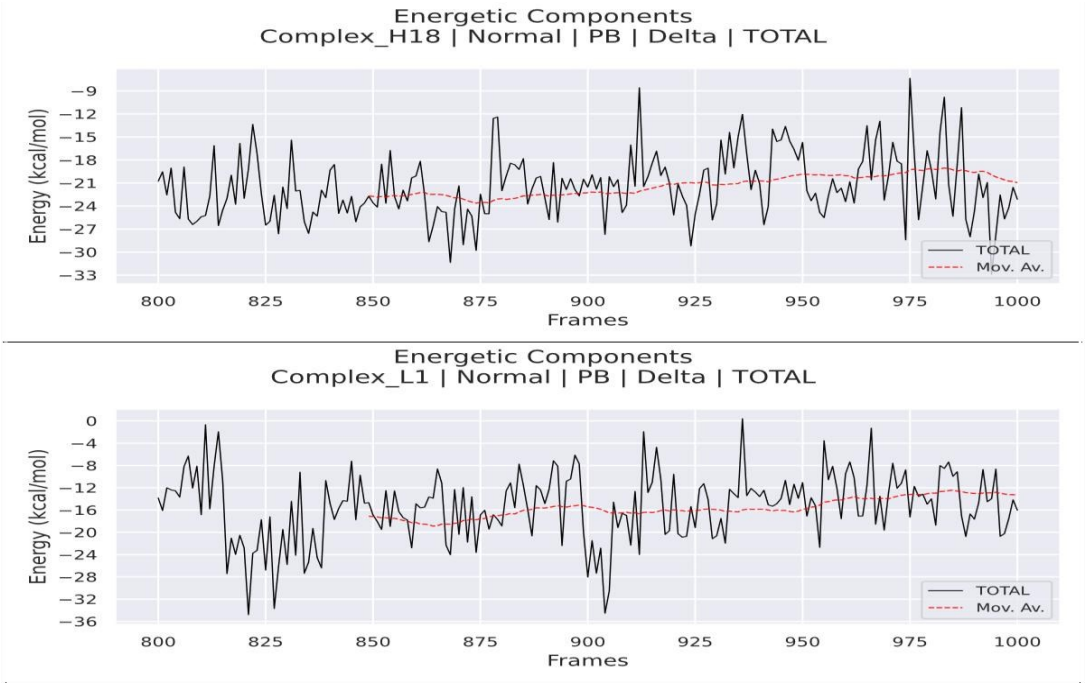


Fig. S6. Dynamic Energetic Analysis of Protein-Ligand Complexes (L1 and H18)

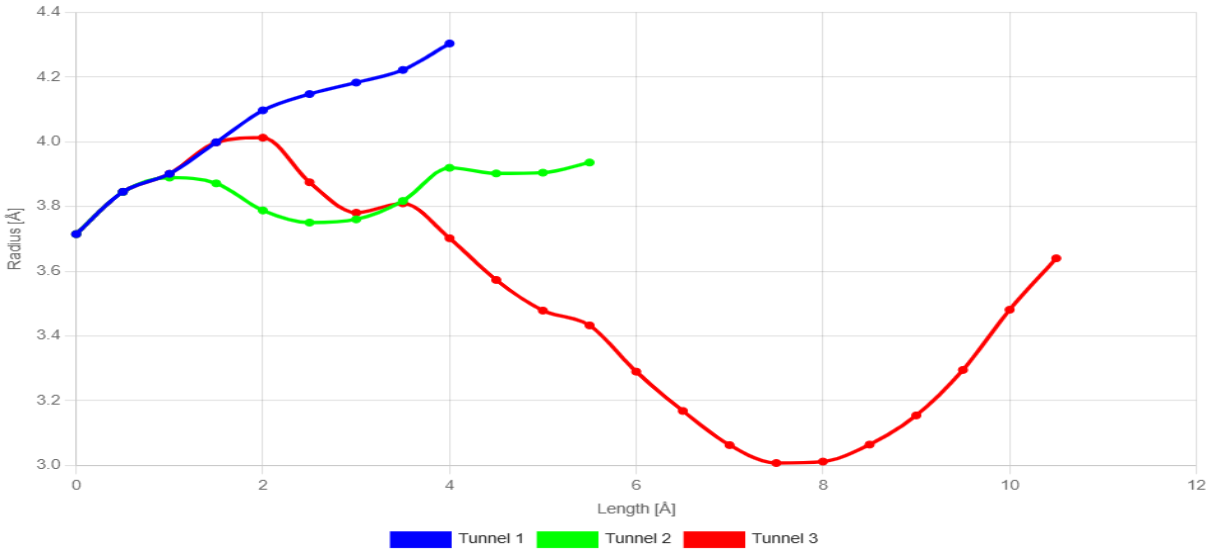


Fig. S7. radius of the tunnel as a function of its length

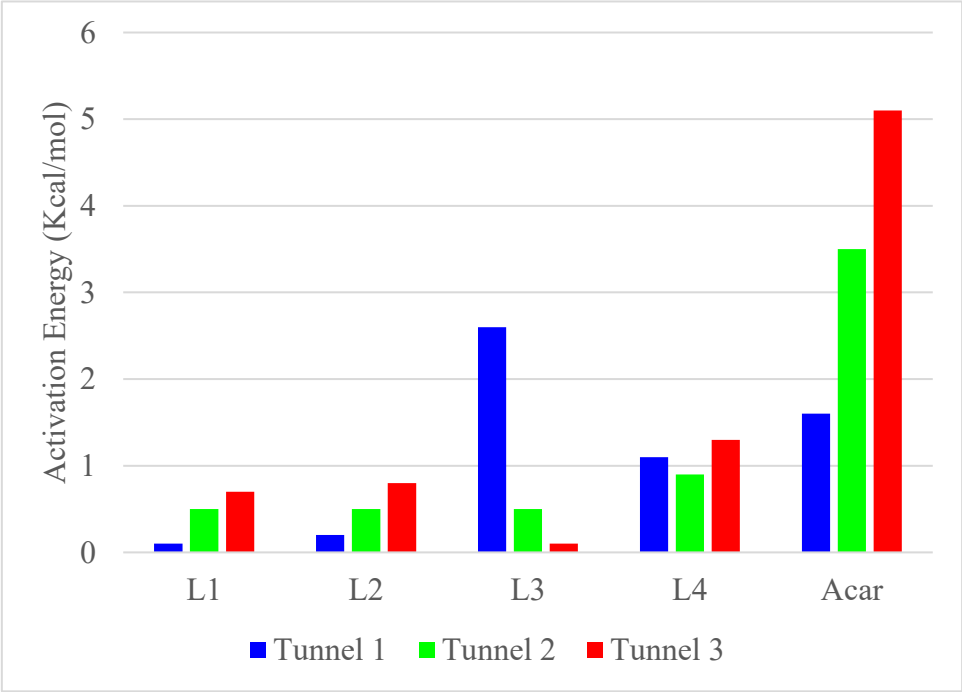
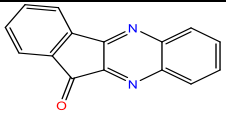
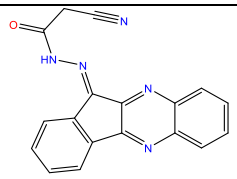
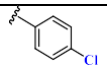
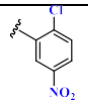
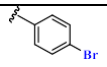
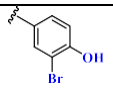
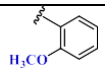
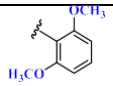
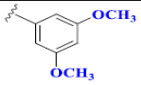
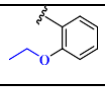
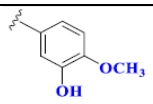
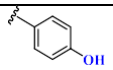
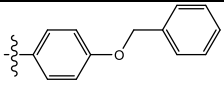


Fig. S8. Acarbose's and developed inhibitors' activation energy for transport tunnels.

Table S1. A dataset comprising molecular structures along with their corresponding experimental activity values

Code	Intermediate	α-Amylase Inhibitory activity IC_{50} (μM)	pIC_{50}
H1		33.48	4.475

H2		41.40	4.383
R			
H3		51.64	4.287
H4		44.88	4.348
H5		49.20	4.308
H6		19.10	4.719
H7		15.05	4.822
H8		16.70	4.777
H9		46.45	4.333
H10		7.56	5.121
H11		19.50	4.710
H12		19.25	4.716
H13		18.77	4.727
H14		21.44	4.669
H15		43.14	4.365
H16		5.22	5.282
H17		3.85	5.415
H18		2.34	5.631
H19		55.43	4.256

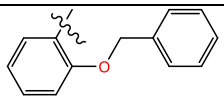
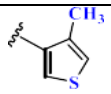
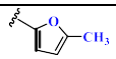
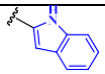
H20		54.16	4.266
H21		42.2	4.375
H22		56.43	4.248
H23		50.19	4.299
H24		12.38	4.907
H25		10.44	4.981
H26		20.46	4.689
H27		35.21	4.453
H28		21.36	4.670
H29		57.3	4.242
H30		24.26	4.615

Table S2. Molecular Dynamics Simulation Parameters for Protein-Ligand Complexes

Protein-Ligand Complex		**Complex L1**	**Complex H18**	**Complex Acarbose**
MD Simulation Type		Conventional All-atom MD simulation		
Parametrization Forcefield		Charmm36m (Charmm-gui Solution Builder)		
System Solvation	Water Model	TIP3P water molecule		
	PBC Box	10 Å extended from the protein		
System Neutralization	Sodium ions	106	106	106
	Chloride ions	82	82	82
Nstep Energy Minimization		Not exceeding 1000 Kj/mol/nm		

System Equilibration	NVT and NPT ensemble
MD Simulation time, nstep	100 ns (50000000 nstep)
MD Simulation Temperature	300K
Gromacs Software Version	2024.5

Table S3. External validation of the CoMSIA-SDHA model

Parameters	CoMSIA-value	Threshold	Comment
r^2_{pred}	0.910	> 0.6	validated
r^2_0	0.857	Near to r^2_{pred}	validated
r'^2_0	0.866	Near to r^2_{pred}	validated
k	1.004	0.85≤ k ≤ 1.15	validated
k'	0.996	0.85≤ k' ≤ 1.15	validated
$\frac{(r^2 - r^2_0)}{r^2}$	0.059	< 0.1	validated
$\frac{(r^2 - r'^2_0)}{r^2}$	0.049	< 0.1	validated
r^2_m	0.635	> 0.5	validated
r'^2_m	0.636	> 0.5	validated
$\overline{r^2_m}$	0.718	> 0.5	validated
Δr^2_m	0.132	< 0.2	validated
$Q^2_{F_1}$	0.997	> 0.7	validated
Q^2_{F2}	0.743	> 0.7	validated

Table S4. Physicochemical properties and synthetic accessibility of designed inhibitors

Molecules	Molecular Weight	Log P	Rotatable Bonds	H-bond Acceptor	H-bond Donor	Lipinski validation	Synthetic accessibility
Rule	< 500	< 5	< 10	< 10	< 5		
L1	449.426	3.202	3	8	4	Yes	2.871
L2	476.452	3.125	4	8	4	Yes	3.064
L3	507.462	3.058	5	9	4	No	3.058

L4	493.479	2.052	5	9	5	Yes	3.113
Acarbose	645.608	-8.721	13	19	14	No	5.756

Table S5. Summary of molecular docking findings

Ligands	Affinity (kcal/mol)	Amino acid residues	Category	Type of interactions
H18	-9.4	His 210	Hydrogen bond	Conventional (Acceptor)
		Arg 344	Hydrogen bond	Conventional (Acceptor)
		Tyr 82	Hydrophobic	Pi-Pi Stacked
		Trp 83	Hydrophobic	Pi-Pi T-Shaped
		Val 171	Hydrophobic	Pi-Alkyl
		Leu 173	Hydrophobic	Pi-Alkyl
		Leu 232	Hydrophobic	Pi-Alkyl
		Glu 230	Electrostatic	Pi-anion
		Asp 297	Electrostatic	Pi-anion
		Asp 340	Electrostatic	Salt bridge
L1	-13.2	His 122	Hydrogen bond	Conventional (Acceptor)
		Asp 206	Hydrogen bond	Conventional (Donor)
		Asp 297	Hydrogen bond	Conventional (Donor)
		Asp 168	Electrostatic	Pi-anion
		Asp 297	Electrostatic	Pi-anion
		Asp 340	Electrostatic	Pi-anion
		Tyr 75	Hydrophobic	Pi-Pi Stacked
L2	-10.2	Trp 83	Hydrogen bond	Conventional (Acceptor)
		Glu 230	Hydrogen bond	Conventional (Donor)
		Arg 204	Hydrogen bond	Conventional (Acceptor)
		Arg 344	Hydrogen bond	Conventional (Acceptor)
		Asp 206	Electrostatic	Pi-anion
		Asp 297	Electrostatic	Pi-anion
		His 80	Electrostatic	Pi-cation
		Asp 340	Electrostatic	Attractive charge
		Tyr 75	Hydrophobic	Pi-Pi Stacked
		Leu 166	Hydrophobic	Pi-Alkyl
		Leu 173	Hydrophobic	Pi-Alkyl
L3	-14.5	Gln 35	Hydrogen bond	Conventional (Acceptor)
		His 80	Hydrogen bond	Conventional (Acceptor)
		Gly 167	Hydrogen bond	Conventional (Acceptor)
		Asp 206	Electrostatic	Pi-anion
		Asp 297	Electrostatic	Pi-anion
		Asp 340	Electrostatic	Pi-anion
		His 210	Electrostatic	Pi-cation
		Tyr 82	Hydrophobic	Pi-Pi T-Shaped
		His 210	Hydrophobic	Pi-Pi T-Shaped
		Leu 166	Hydrophobic	Pi-Alkyl
		Leu 232	Hydrophobic	Pi-Alkyl
L4	-14.0	Tyr 75	Hydrogen bond	Conventional (Donor)
		Tyr 79	Hydrogen bond	Conventional (Acceptor)
		His 80	Hydrogen bond	Conventional (Acceptor)
		Trp 83	Hydrogen bond	Conventional (Acceptor)
		Gly 167	Hydrogen bond	Conventional (Acceptor)
		Asp 206	Electrostatic	Pi-anion
		Asp 297	Electrostatic	Pi-anion
		Asp 340	Electrostatic	Pi-anion
		His 210	Electrostatic	Pi-cation
		Tyr 82	Hydrophobic	Pi-Pi T-Shaped
		His 210	Hydrophobic	Pi-Pi T-Shaped
		Leu 166	Hydrophobic	Pi-Alkyl
		Leu 232	Hydrophobic	Pi-Alkyl

Acarbose	-18.3	Gln 35	Hydrogen bond	Conventional
		Trp 83	Hydrogen bond	Conventional
		His 122	Hydrogen bond	Conventional
		Arg 204	Hydrogen bond	Conventional
		Asp 206	Hydrogen bond	Conventional
		Lys 209	Hydrogen bond	Conventional
		His 210	Hydrogen bond	Conventional
		Glu 230	Hydrogen bond	Conventional
		Gly 234	Hydrogen bond	Conventional
		His 296	Hydrogen bond	Conventional
		Asp 297	Hydrogen bond	Conventional
		Asp 340	Hydrogen bond	Conventional
		Arg 344	Hydrogen bond	Conventional

Table S6. Thermodynamic Properties of Protein-Ligand Complexes (L1, H18 and Acarbose) Over 100 ns MD Simulation

System	Temperature Average (K)	Standard Deviation	Total Energy Average (Kj/Mol)	Standard Deviation
L1	299	1.065	-1.037×10^6	1.644×10^3
H18	299	1.063	-1.036×10^6	1.657×10^3
Acarbose	299	1.063	-1.036×10^6	1.687×10^3

Table S7. RMSD Average and standard deviation of studied complexes

System	L1	H18	Acarbose
RMSD Average (nm)	0.198	0.250	0.312
Standard Deviation	0.028	0.05	0.07

Table S8. The structural characteristics of the calculated tunnels.

Tunnel	Bottleneck radius (Å)	Length (Å)	Distance to surface (Å)	Curvature	Throughput	Number of residues
1	3.70	4.00	3.60	1.10	0.95	20
2	3.70	5.40	4.90	1.10	0.94	23
3	3.00	9.90	5.00	2.00	0.90	20

Table 4 Compounds under study as they move through receptor tunnels.

Studied ligands	Energy [kcal/mol]	Tunnel 1	Tunnel 2	Tunnel 3

L1	E_{max}	-6.6	-7.1	-7.3
	E_a	0.1	0.5	0.7
L2	E_{max}	-4.7	-7.1	-6.8
	E_a	0.2	0.5	0.8
L3	E_{max}	-7.4	-7.3	-7.2
	E_a	2.6	0.5	0.1
L4	E_{max}	-7.1	-7.1	-6.9
	E_a	1.1	0.9	1.3
Acarbose	E_{max}	-8.4	-7	-7
	E_a	1.6	3.5	5.1

Table S10. Tunnels developed in the 7TAA receptor transport the BE of L1, L2, L3, L4, and acarbose molecules.

Ligand	Tunnel	E_a (kcal/mol)	K_i (h^{-1}) /A	IC_{50} (μM)	BE (h^{-1} μM^{-1}) × A
L1	1	0.1	3060.79	0.087	3.53×10^{4}
	2	0.5	1599.41	0.087	1.84×10^{4}
	3	0.7	1156.17	0.087	1.33×10^{4}
L2	1	0.2	2602.35	1.758	1.48×10^{3}
	2	0.5	1599.41	1.758	9.10×10^{2}
	3	0.8	983.01	1.758	5.59×10^{2}
L3	1	2.6	52.98	0.390	1.36×10^{2}
	2	0.5	1599.41	0.390	4.10×10^{3}
	3	0.1	3060.79	0.390	7.85×10^{3}
L4	1	1.1	604.158	0.126	4.80×10^{3}
	2	0.9	835.771	0.126	6.64×10^{3}
	3	1.3	436.731	0.126	3.47×10^{3}
Acarbose	1	1.6	268.41	14.650	1.83×10
	2	3.5	12.30	14.650	8.40×10^{-1}
	3	5.1	0.92	14.650	6.26×10^{-2}