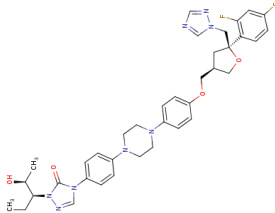
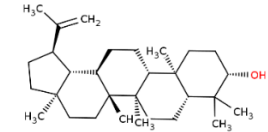
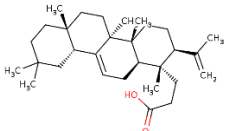
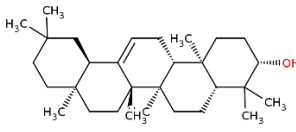
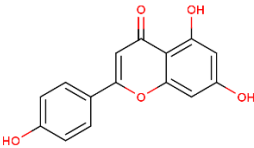


S1. Representing 2D structures of selected compounds

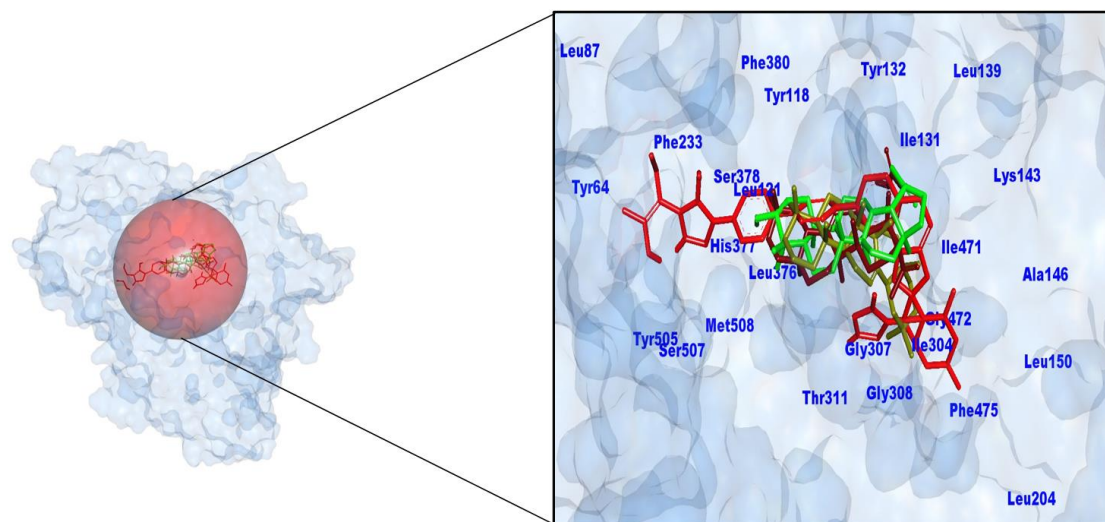
Compounds	PubChem ID	2D Structure
DB01263 (Control Drug) Posaconazole	468595	 <p>The structure of Posaconazole is a complex molecule. It features a central imidazole ring substituted with a propyl group and a 1H-imidazol-2-ylmethyl group. This central core is linked via a piperazine ring to a 4-(4-(2-(4-(1H-imidazol-2-ylmethyl)phenoxy)phenoxy)phenyl)phenoxy group.</p>
Lupeol	259846	 <p>The structure of Lupeol is a pentacyclic triterpene. It consists of five fused six-membered rings. It is substituted with several methyl groups (CH₃) and a terminal vinyl group (CH=CH₂). A hydroxyl group (OH) is attached to one of the rings.</p>
Nyctanthic_acid	12313631	 <p>The structure of Nyctanthic acid is a complex polycyclic molecule. It features a central ring system with multiple methyl groups (CH₃) and a carboxylic acid group (HO-C=O) attached to one of the rings.</p>
beta-Amyrin	73145	 <p>The structure of beta-Amyrin is a pentacyclic triterpene. It consists of five fused six-membered rings. It is substituted with several methyl groups (CH₃) and a hydroxyl group (OH) attached to one of the rings.</p>
Apigenin	5280443	 <p>The structure of Apigenin is a flavone. It consists of a chromone core (a benzene ring fused to a pyrone ring) with a 4-hydroxyphenyl group attached to the 7-position of the pyrone ring. The pyrone ring has a carbonyl group (C=O) and a hydroxyl group (OH) at the 4-position.</p>

S2. In silico screening of natural compounds from *Nyctanthes arbor-tristis* posaconazole(DB01263) control drug and the crystal structure of sterol 14-alpha demethylase (CYP51), from the pathogenic yeast *Candida albicans* (PDB:5FSA), *Aspergillus fumigatus* protein farnesyltransferase (PDB: 4LNG) the crystal structure of lanosterol 14-alpha demethylase (PDB:5EQB), and the structure of fungal chitinase from *Aspergillus fumigatus* (PDB:2XUC)).

Complex	Binding Affinity	Complex	Binding Affinity	Complex	Binding Affinity	Complex	Binding Affinity
5fsa_lupeol	-11.5	4lng_beta-Amyrin	-9.0	5eqb_DB01263 (Control Drug)	-11.8	2xuc_Apigenin	-8.4
5fsa_Nyctanthic acid	-10.3	4lng_lupeol	-8.5	5eqb_lupeol	-10.3	2xuc_Quercetin	-8.4
5fsa_beta-Amyrin	-9.8	4lng_DB01263 (Control Drug)	-8.5	5eqb_beta-Sitosterol	-10	2xuc_Kaemferol	-8.2
5fsa_arbortristoside-D	-9.6	4lng_Nyctanthic acid	-8.2	5eqb_arborside-A	-9.9	2xuc_nicotiflorin	-8.1
5fsa_nicotiflorin	-9.5	4lng_Arbortristoside-E	-8.1	5eqb_beta-Amyrin	-9.9	2xuc_Arbortristoside-E	-8.0
5fsa_Arbortristoside-E	-9.4	4lng_beta-Sitosterol	-8.0	5eqb_Nyctanthic acid	-9.7	2xuc_astragalin	-7.9
5fsa_b-sitosterozl	-9.4	4lng_Arborside-B	-7.9	5eqb_Arbortristoside-E	-9.6	2xuc_Arbortristoside-B	-7.5
5fsa_beta-Sitosterol	-9.4	4lng_nicotiflorin	-7.9	5eqb_nicotiflorin	-9.6	2xuc_Arbortristoside-C	-7.4
5fsa_Arbortristoside-C	-9.2	4lng_Arbortristoside-B	-7.8	5eqb_Arbortristoside-C	-9.3	2xuc_arborside-A	-7.4
5fsa_Arbortristoside-B	-9.1	4lng_Arbortristoside-C	-7.8	5eqb_arbortristoside-D	-9.1	2xuc_Arborside-B	-7.3
5fsa_Quercetin	-9	4lng_arborside-A	-7.8	5eqb_Arborside-B	-9	2xuc_Arborside-C	-7.3
5fsa_Arborside-C	-8.9	4lng_arbortristoside-D	-7.6	5eqb_Arborside-C	-8.9	2xuc_arbortristoside-D	-7.3
5fsa_arborside-A	-8.9	4lng_Arborside-C	-7.4	5eqb_astragalin	-8.9	2xuc_beta-Sitosterol	-7.2
5fsa_astragalin	-8.9	4lng_Kaemferol	-7.4	5eqb_Arbortristoside-B	-8.7	2xuc_DB01263 (Control Drug)	-7.2
5fsa_DB01263 (Control Drug)	-8.7	4lng_Apigenin	-7.2	5eqb_Apigenin	-8.2	2xuc_6beta-Hydroxyloganin	-6.8

S3. Showing ligand efficiency data for the selected compounds during their interaction with receptors.

Complex	Delta G kcal/mol	No. of heavy Atoms	Ligand Efficacy (kcal/mol/atom)
Lupeol-5fsa	-11.5	31	-0.37
Nyctanthic acid-5fsa	-10.3	32	-0.32
Beta-amyrin-5fsa	-9.8	31	-0.31
DB01263-5fsa (Control)	-8.7	51	-0.17
Beta-amyrin-4lng	-9.0	31	-0.29
DB01263-4lng (control)	-8.5	51	-0.16
Lupeol-5eqb	-10.3	31	-0.33
DB01263-5eqb (control)	-11.8	51	-0.23
Apigenin-2xuc	-8.4	20	-0.42
DB01263-2xuc	-7.2	51	-0.14



S4. Figure: 3D visualization of active site binding of selected compounds and 5FSA. The left side magnified picture of the binding pocket of 5FSA molecules. The interacting compounds beta-amyrin (olive), DB01263 (red), lupeol (green), and nycanthic acid (maroon) and important amino acid residues in the binding pocket are shown in the right side.

S5. ADME prediction from SwissADME (GI=Gastro intestinal, BBB=Blood Brain Barrier, Pgp=P glycoprotein, CYP=Cytochrome, log K _p = skin permeation)									
Compounds	GI absorption	BBB permeant	Pgp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	log K _p (cm/s)
									negative the log K _p the less skin permeant the molecule
DB01263 (Control Drug)	High	No	Yes	Yes	Yes	Yes	Yes	Yes	-7.32
Lupeol	Low	No	No	No	No	No	No	No	-1.9
Nyctanthic acid	Low	No	No	No	No	Yes	No	No	-2.45
beta-Amyrin	Low	No	No	No	No	No	No	No	-2.41
Apigenin	High	No	No	Yes	No	No	Yes	Yes	-5.80

S6. Drug-likeness prediction from SwissADME server (MW=Molecular Weight, TPSA= total polar surface area, Consensus Log P= average of all predicted Log Po/w)													
Compounds	MW (g/mol)	Rotatable bonds	H-bond acceptors	H-bond donors	TPSA (Å ²)		Lipinski violations	Ghose violations	Veber violations	Egan violations	Muegge violations	Bioavailability Score	Synthetic Accessibility
	MW between 150 and 500 g/mol	no more than 9 rotatable bonds			TPSA between 20 and 130 Å ²							not less than 0.25	normalized between 1 (easy synthesis) and 10 (very difficult synthesis)
DB01263 (Control Drug)	700.78	12	9	1	115.7		2	3	1	0	1	0.17	6.02
Lupeol	426.72	1	1	1	20.23		1	3	0	1	2	0.55	5.49
Nyctanthic acid	440.7	4	2	1	37.3		1	3	0	1	1	0.85	5.73
beta-Amyrin	426.72	0	1	1	20.23		1	3	0	1	2	0.55	6.04
Apigenin	270.24	1	5	3	90.90		0	0	0	0	0	0.55	2.96

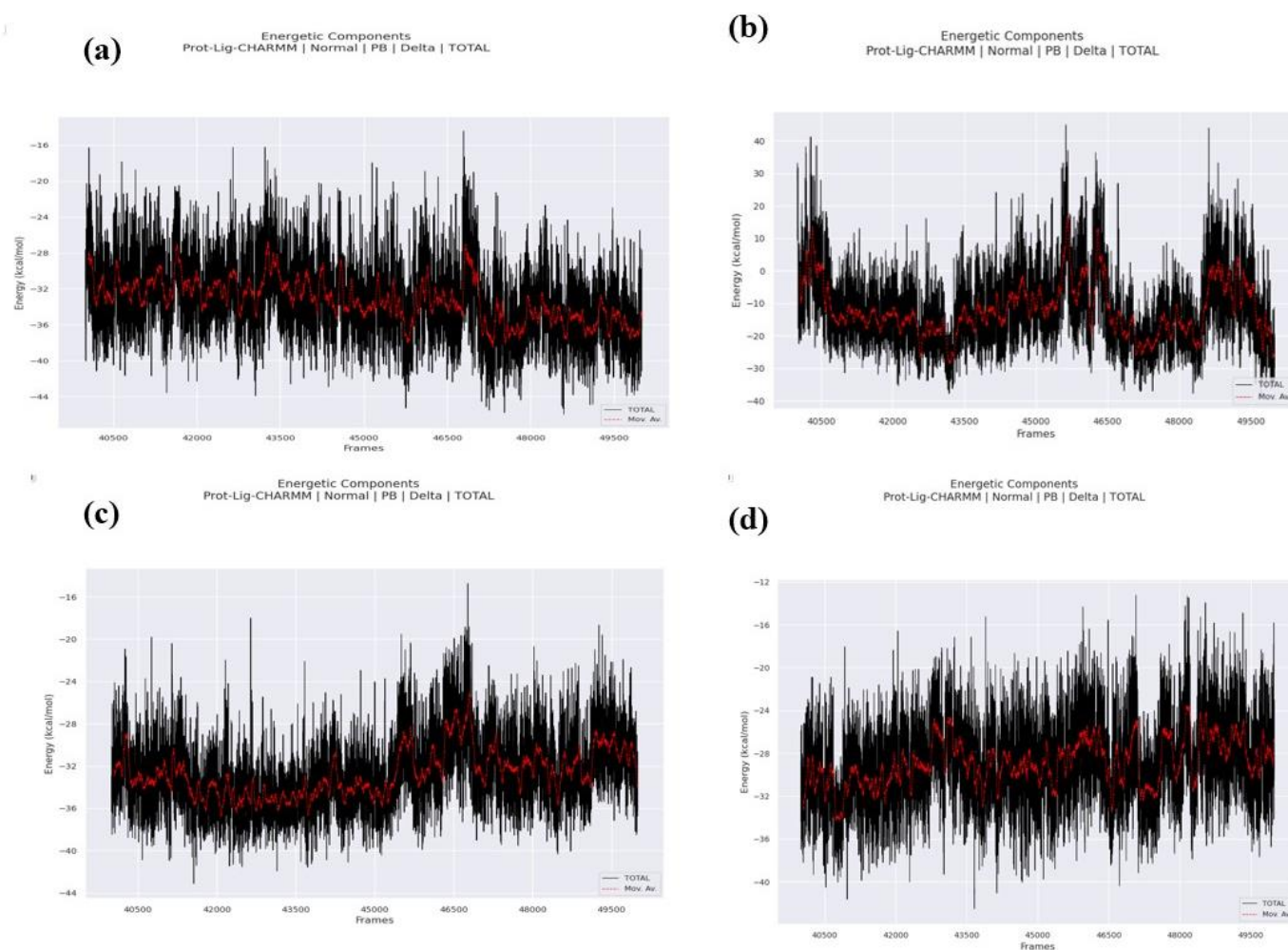
S7: toxicity prediction. Data obtained from pkCSM server										
	AMES toxicity	Max. tolerated dose (Human)	hERG I inhibitor	hERG II inhibitor	Oral Rat Acute Toxicity (LD50)	Oral Rat Chronic Toxicity (LOAEL)	Hepatotoxicity	Skin sensitisation	T. pyriformis toxicity	Minnow toxicity
Standard cut-off	Positive mutagenic	≤ 0.477 log(mg/kg/day)				lowest			> -0.5 log ug/L	Log LC50 < -0.3
DB01263 (Control Drug)	No	0.682	No	Yes	3.076	0.198	Yes	No	0.285	-3.711
Lupeol	No	-0.502	No	Yes	2.563	0.89	No	No	0.316	-1.696
Nyctanthic acid	No	-0.072	No	No	2.503	2.516	Yes	No	0.292	-1.688
beta-Amyrin	No	-0.56	No	Yes	2.478	0.873	No	No	0.383	-1.345
Apigenin	No	0.328	No	No	2.45	2.298	No	No	0.38	2.432

S8. Data of Poisson Boltzmann complex energy components calculation with \pm SEM (Standard deviation error of the mean) of complexes. Where ΔV_{dwaals} = Van der Waals energy, ΔEEL = Electrostatic molecular energy, ΔEPB = Polar contribution to the solvation energy, $\Delta ENPOLAR$ = Nonpolar contribution of repulsive solute-solvent interactions to the solvation energy, $\Delta EDISPER$ = Nonpolar contribution of attractive solute-solvent interactions to the solvation energy, ΔG_{Gas} =Total gas phase molecular energy, ΔG_{Solv} = Total solvation energy, and ΔG_{Total} =Total binding energy.

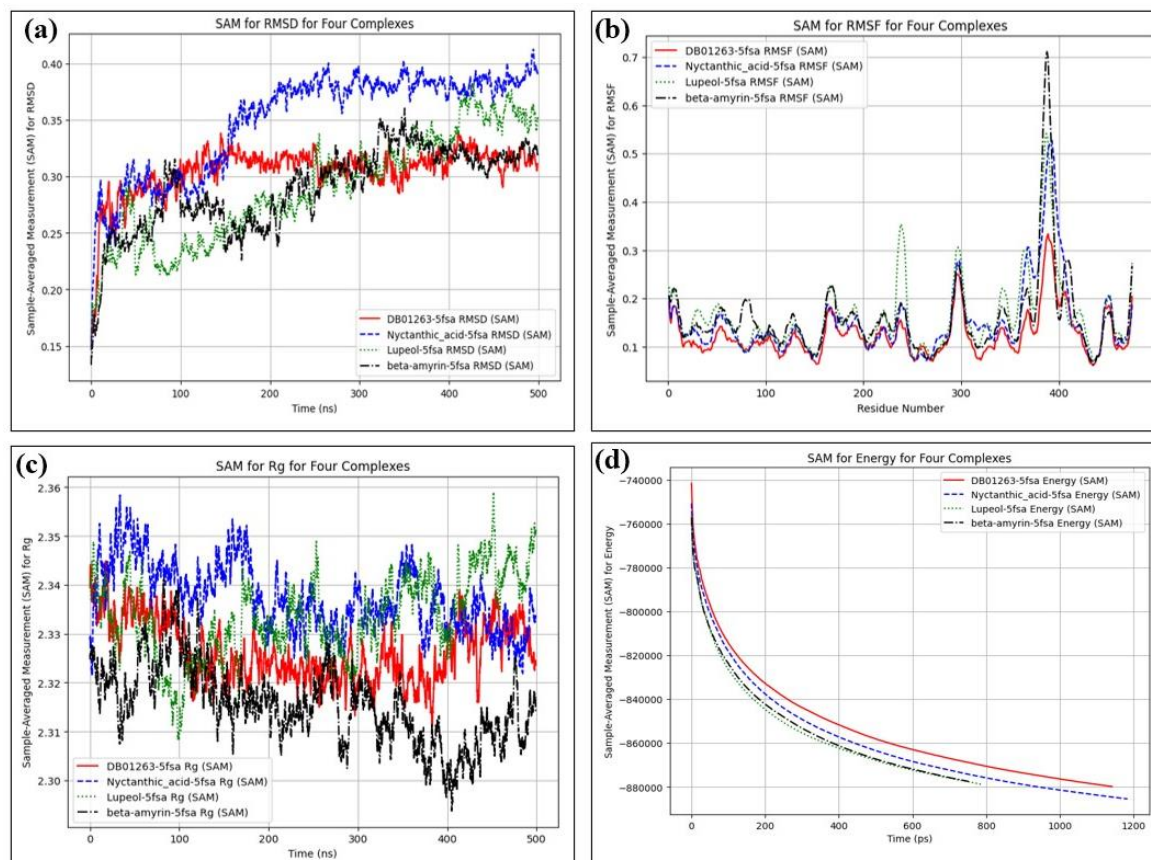
Complex	ΔV_{dwaals}	ΔEEL	ΔEPB	$\Delta ENPOLAR$	$\Delta EDISPER$	ΔG_{Gas}	ΔG_{Solv}	ΔG_{Total}
Lupeol-5fsa	-3516.53 (± 14.50)	-29236.99 (± 51.34)	-6583.40 (± 49.82)	111.40 (± 49.82)	0.00 (± 0.0)	-2837.99 (± 39.20)	-6472.01 (± 39.20)	-9309.00 (± 16.15)
Nyctanthic acid-5fsa	-3496.05 (± 16.47)	-29229.91 (± 70.60)	-6673.27 (± 70.26)	111.74 (± 0.91)	0.00 (± 0.0)	-2771.29 (± 70.57)	-6561.54 (± 69.38)	-9332.83 (± 17.54)
Beta-amyrin-5fsa	-3505.29 (± 14.10)	-29318.03 (± 42.27)	-6616.60 (± 40.86)	111.48 (± 0.95)	0.00 (± 0.00)	-2883.65 (± 37.57)	-6505.12 (± 39.93)	-9388.77 (± 12.60)
DB01263-5fsa Control	-3539.68 (± 23.90)	-29329.69 (± 21.83)	-6566.63 (± 30.02)	112.37 (± 1.43)	0.00 (± 0.00)	-2924.00 (± 43.11)	-6454.26 (± 28.97)	-9378.26 (± 23.37)
Beta-amyrin-4lng	-3197.03 (± 3.78)	-26827.71 (± 10.61)	-5690.68 (± 9.24)	96.62 (± 0.11)	0.00 (± 0.00)	-1620.23 (± 11.91)	-5594.06 (± 9.21)	-7214.29 (± 7.91)
DB01263-4lng control	-3216.62 (± 4.57)	-26691.47 (± 16.20)	-5877.54 (± 14.08)	97.96 (± 0.11)	0.00 (± 0.00)	-1346.25 (± 16.11)	-5779.58 (± 14.01)	-7125.83 (± 9.32)
Lupeol-5eqb	-3829.89 (± 3.15)	-32883.07 (± 18.19)	-5741.76 (± 14.30)	128.11 (± 0.14)	0.00 (± 0.00)	-4480.15 (± 17.80)	-5613.66 (± 14.30)	-10093.81 (± 9.67)
DB01263-5eqb control	-3747.49 (± 4.02)	-32802.43 (± 15.01)	-5808.12 (± 10.17)	134.80 (± 0.14)	0.00 (± 0.00)	-4554.78 (± 16.21)	-5673.33 (± 10.11)	-10153.05 (± 9.33)
Apigenin-2xuc	-2185.12 (± 6.06)	-17562.72 (± 8.41)	-6184.42 (± 12.22)	69.86 (± 0.11)	0.00 (± 0.00)	2867.01 (± 7.50)	-6114.57 (± 12.20)	-3247.56 (± 13.93)
DB01263-2xuc	-2251.51 (± 14.15)	-17713.00 (± 33.87)	-6309.22 (± 30.54)	67.32 (± 0.49)	0.00 (± 0.00)	3049.20 (± 64.45)	-6241.89 (± 30.05)	-3192.70 (± 36.31)

S9. Data of MMPBSA-based free energy calculation components with \pm SEM (Standard deviation error of the mean) of ligand-receptor of complexes.

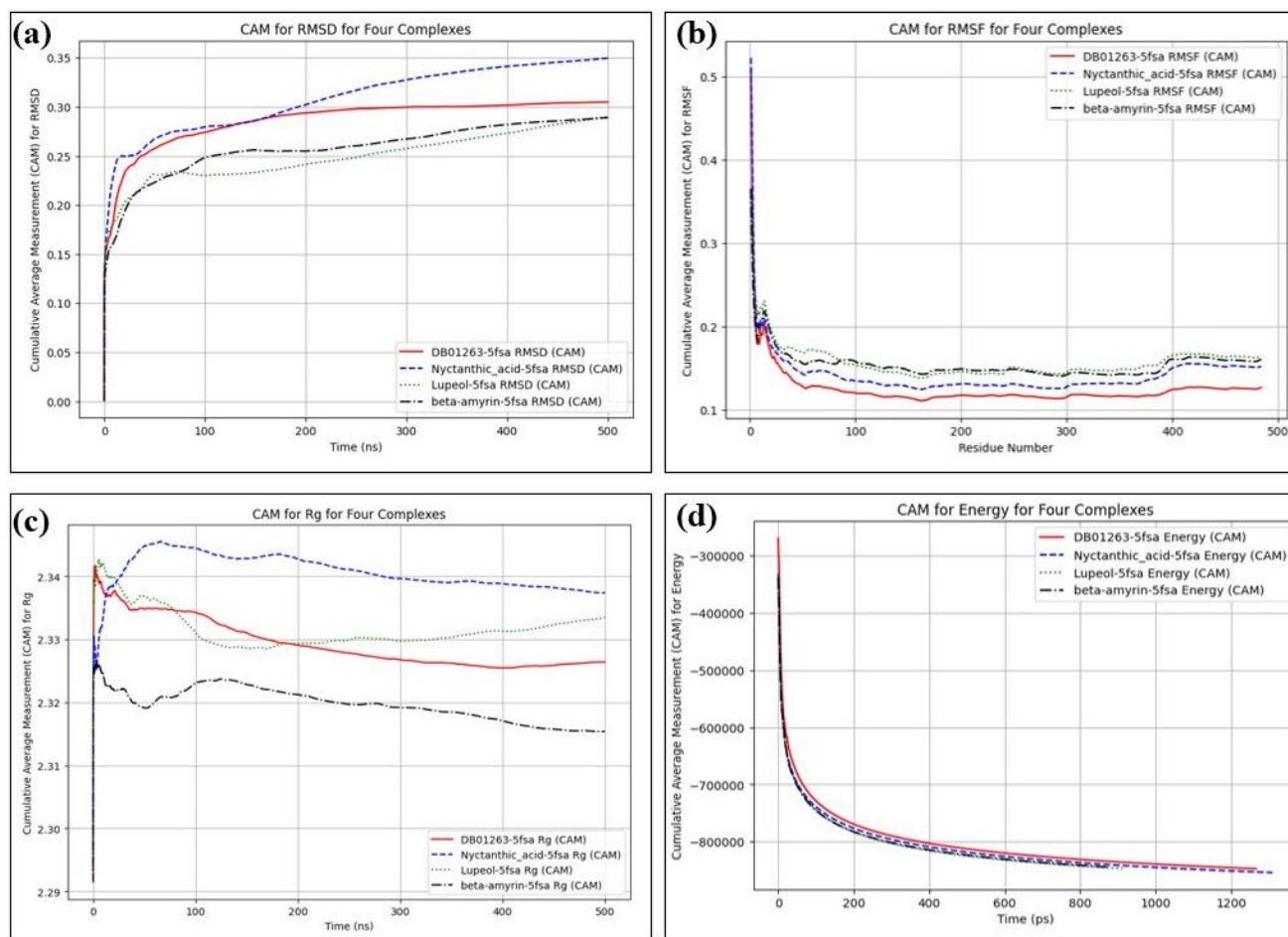
Complex	ΔV_{dwaals}	ΔEEL	ΔEPB	$\Delta ENPOLAR$	$\Delta EDISPER$	ΔG_{Gas}	ΔG_{Solv}	ΔG_{Total}
Lupeol-5fsa	-49.12 (± 1.03)	4.34 (± 0.77)	23.33 (± 1.10)	-4.90 (± 0.03)	0.00 (± 0.00)	-44.78 (± 0.48)	18.43 (± 1.11)	-26.35 (± 0.74)
Nyctanthic acid-5fsa	-45.75 (± 0.74)	-22.51 (± 0.84)	41.62 (± 1.36)	-5.04 (± 0.04)	0.00 (± 0.00)	-68.26 (± 0.36)	36.57 (± 1.36)	-31.69 (± 1.57)
Beta-amyrin-5fsa	-45.91 (± 0.48)	0.24 (± 0.87)	23.20 (± 0.52)	-5.00 (± 0.03)	0.00 (± 0.00)	-46.67 (± 0.77)	18.20 (± 0.54)	-28.47 (± 0.58)
DB01263-5fsa control	-79.07 (± 1.71)	-57.09 (± 3.44)	131.29 (± 3.50)	-7.52 (± 0.09)	0.00 (± 0.00)	-136.16 (± 4.12)	123.72 (± 3.54)	-12.45 (± 4.93)
Beta-amyrin-4lng	-40.74 (± 0.28)	-4.30 (± 0.32)	-19.29 (± 0.24)	-4.07 (± 0.01)	0.00 (± 0.00)	-45.03 (± 0.41)	15.22 (± 0.23)	-29.81 (± 0.38)
DB01263-4lng control	-21.80 (± 0.36)	115.91 (± 1.18)	-101.00 (± 1.63)	-2.67 (± 0.05)	0.00 (± 0.00)	94.11 (± 1.34)	-103.67 (± 1.60)	-9.56 (± 0.50)
Lupeol-5eqb	-49.90 (± 0.24)	-0.57 (± 0.31)	26.78 (± 0.43)	-5.01 (± 0.01)	0.00 (± 0.00)	-50.46 (± 0.39)	21.76 (± 0.43)	-28.70 (± 0.44)
DB01263-5eqb control	-69.90 (± 0.36)	-107.61 (± 0.86)	146.31 (± 1.05)	-7.43 (± 0.02)	0.00 (± 0.00)	-177.51 (± 0.94)	138.88 (± 1.04)	-38.63 (± 0.71)
Apigenin-2xuc	-14.37 (± 0.40)	-13.54 (± 0.58)	20.18 (± 0.82)	-1.75 (± 0.05)	0.00 (± 0.00)	-27.91 (± 0.92)	18.44 (± 0.77)	-9.48 (± 0.36)
DB01263-2xuc	-40.99 (± 0.82)	244.08 (± 1.63)	-217.52 (± 1.68)	-4.64 (± 0.03)	0.00 (± 0.00)	203.09 (± 1.91)	-222.16 (± 1.68)	-19.07 (± 0.43)



S10. Molecular Mechanics Poisson–Boltzmann Surface Area (MMPBSA) binding free energy analysis over a 500 ns molecular dynamics (MD) simulation. The total binding energy fluctuations are represented in black, with the moving average shown in red. (A) Beta-amyrin-5fsa, (B) Control (DB01263)-5fsa, (C) Lupeol-5fsa, and (D) Nyctanthic acid-5fsa. The energy values (kcal/mol) indicate the stability and affinity of ligand binding throughout the simulation.



S11. 2D representation of Sample-Averaged Measurement (SAM) analysis for molecular dynamics simulations of four selected protein-ligand complexes. (A) SAM for RMSD over 500 ns. (B) SAM for RMSF across amino acid residues. (C) SAM for Rg over 500 ns. (D) SAM for Energy over simulation time.



S12: 2D representation of Cumulative Average Measurement (CAM) analysis for molecular dynamics simulations of four selected protein-ligand complexes. (A) CAM for RMSD over 500 ns. (B) CAM for RMSF across amino acid residues. (C) CAM for Rg over 500 ns. (D) CAM for Energy over simulation time.