Molecular insights of protein contours recognition with ligand pharmacophoric sites through combinatorial library design and MD simulation in validating HTLV PR inhibitors

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Supplementary information

Ligand Designing on R- Positions

From these contours are consider for requirement of additional elements in the known inhibitor and ligand rearrangement is done with use of Ligand designer script (Schrodinger) and ChemSketch, the ligand rearrangement position R1, R2, R3, R4 are marked by ligand designer script and attachment of atoms to known inhibitor position by ChemSketch, and ligand prepared through Ligprep.

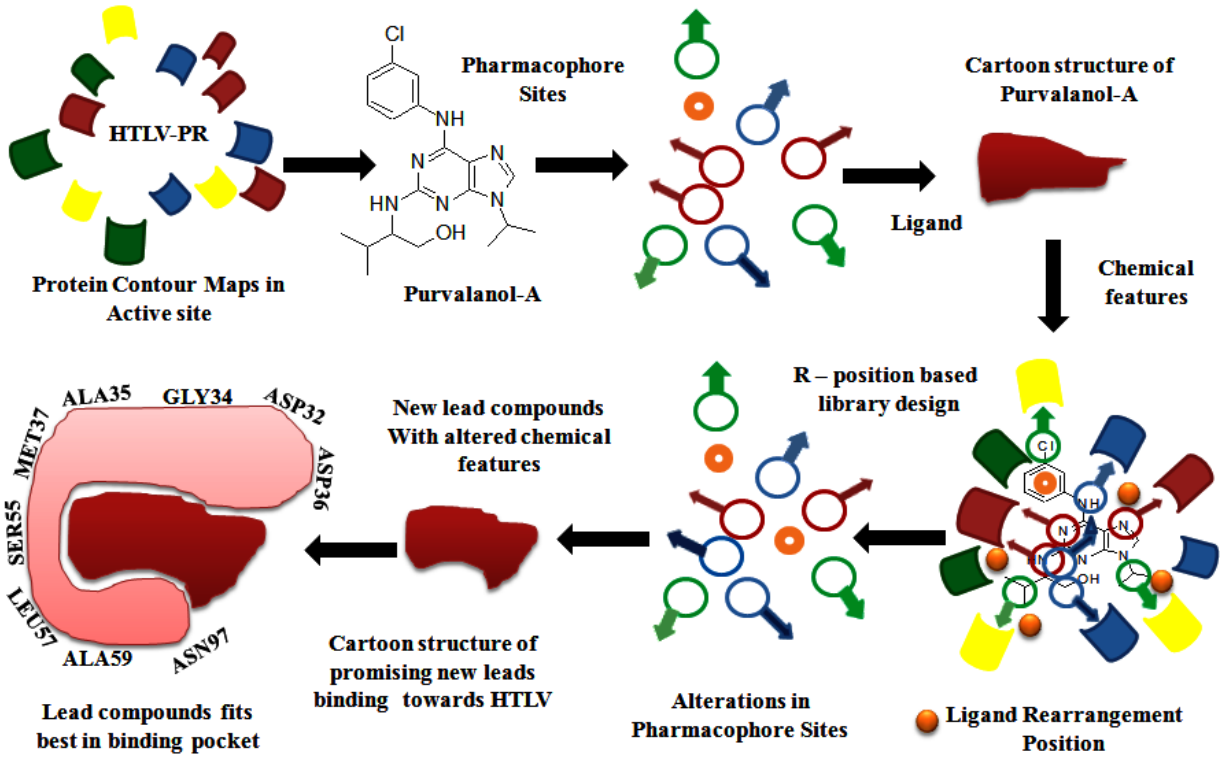

Figure S1. (a), *contours are analyzed for ligand rearrangement with pharmacophore rearrangement*

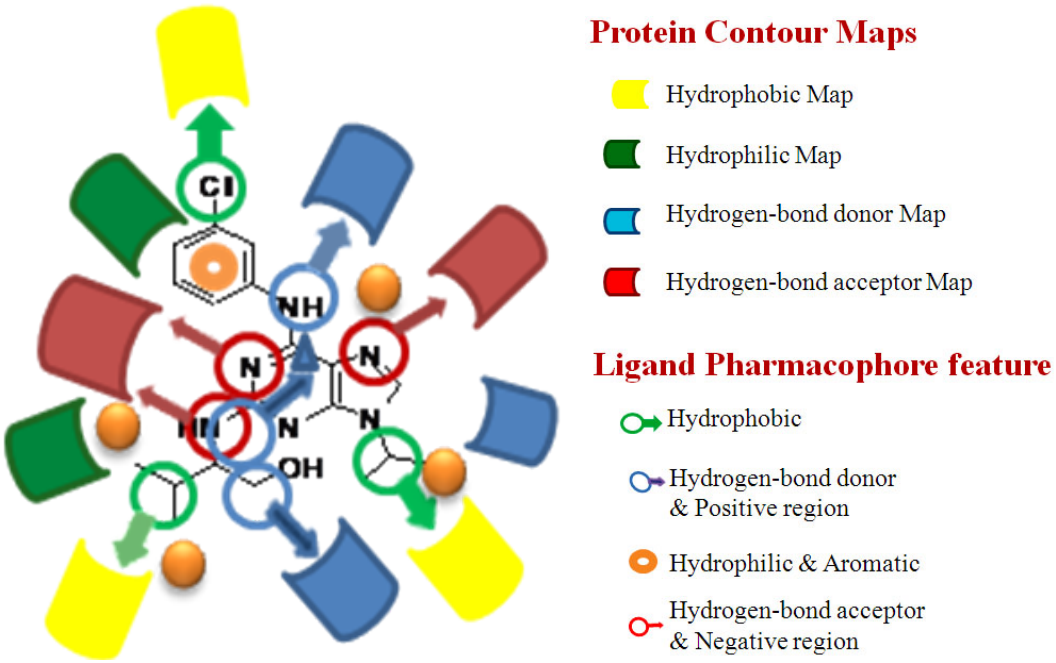

Figure S1 (b). *Represents the cartoon structure of contours with respective pharmacophore, and region of ligand requirement, and orange color spheres represents the ligand requirement and additional atoms attached at that R position.*

Derivatives of Ligand

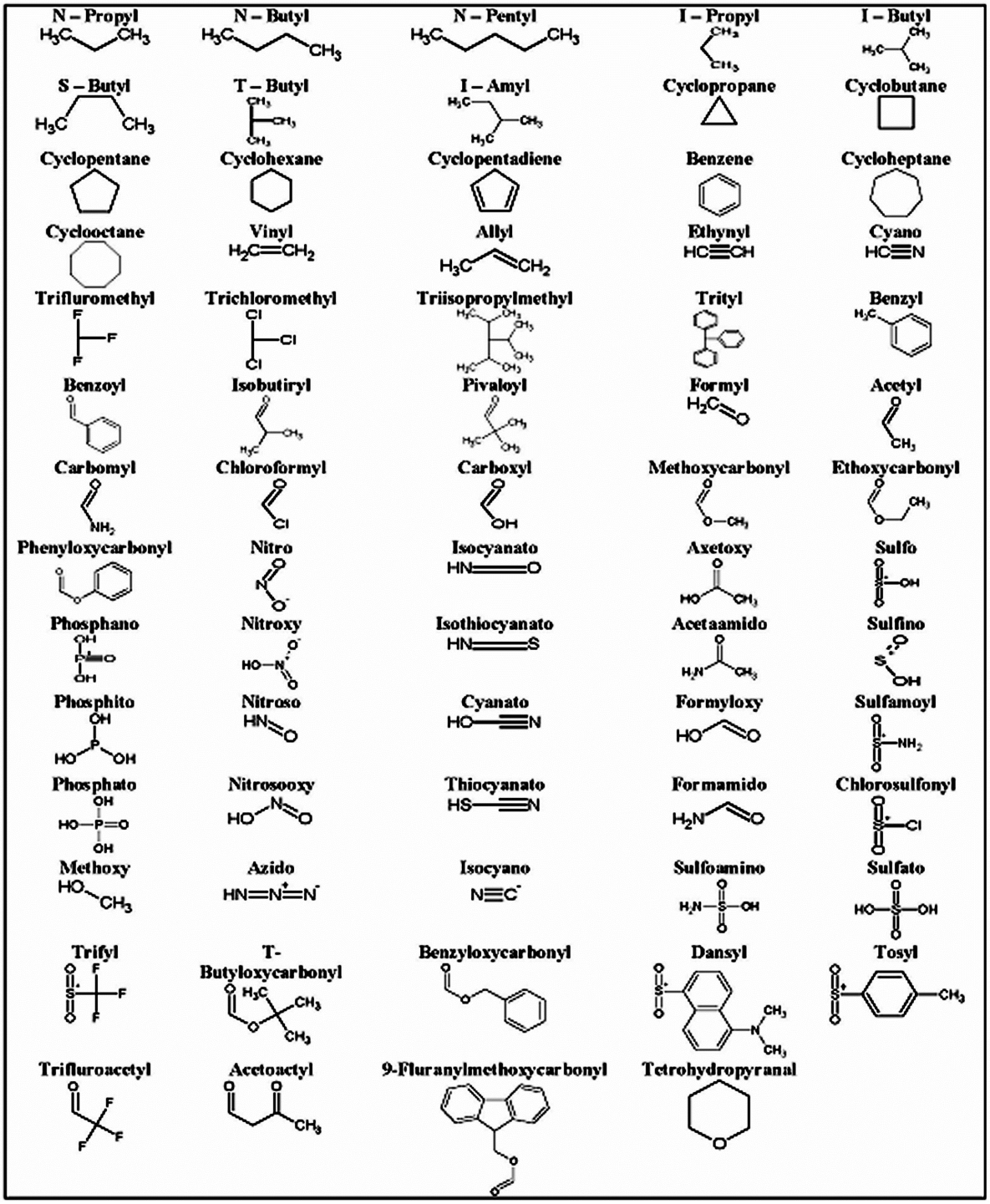

Figure S2. *The known inhibitor Purvalanol-A are added with the* ***Chain structure*** *- N – Propyl, N – Butyl, N – Pentyl, I – Propyl, I – Butyl, S – Butyl, T – Butyl, I – Amyl,* ***Cycle structure*** *– Cyclopropane, Cyclobutane, Cyclopentane, Cyclohexane, Cyclopentadiene, Benzene, Cycloheptane, Cyclooctane.* ***C-groups*** *– Vinyl, Allyl, Ethynyl, Cyano, Triflurомethyl,*

Trichloromethyl, Triisopropylmethyl, Trityl, Benzyl, Benzoyl, Isobutiryl, Pivaloyl, Formyl, Acetyl, Carbomyl, Chloroformyl, Carboxyl, Methoxycarbonyl, Ethoxycarbonyl, Phenyloxycarbonyl. ***Miscellaneous*** *– Nitro, Isocyanato, Acetoxy, Sulfo, Phosphano, Nitroxy, Isothiocyanato, Acetoamido, Sulfino, Phosphito, Nitroso, Cyanato, Formyloxy, Sulfamoyl, Phosphato, Nitrosooxy, Thiocyanato, Formamido, Chlorosulfonyl, Methoxy, Azido, Isocyano, Sulfoamino, Sulfato, Trifyl.* ***Protecting groups*** *- T- Butyloxycarbonyl, Benzyloxycarbonyl, Dansyl, Tosyl, Trifluroacetyl, Acetoactyl, 9-Fluranylmethoxycarbonyl, Tetrohydropyranal in the R^1, R^2, R^3, R^4 position of each inhibitor, and the new leads are obtained and are subjected to Site based molecular docking.*

Active Site Prediction

Active site prediction of crystal structure of HTLV-PR, binding pocket present in between the two monomer chains, Z-Shaped binding pocket, which shows

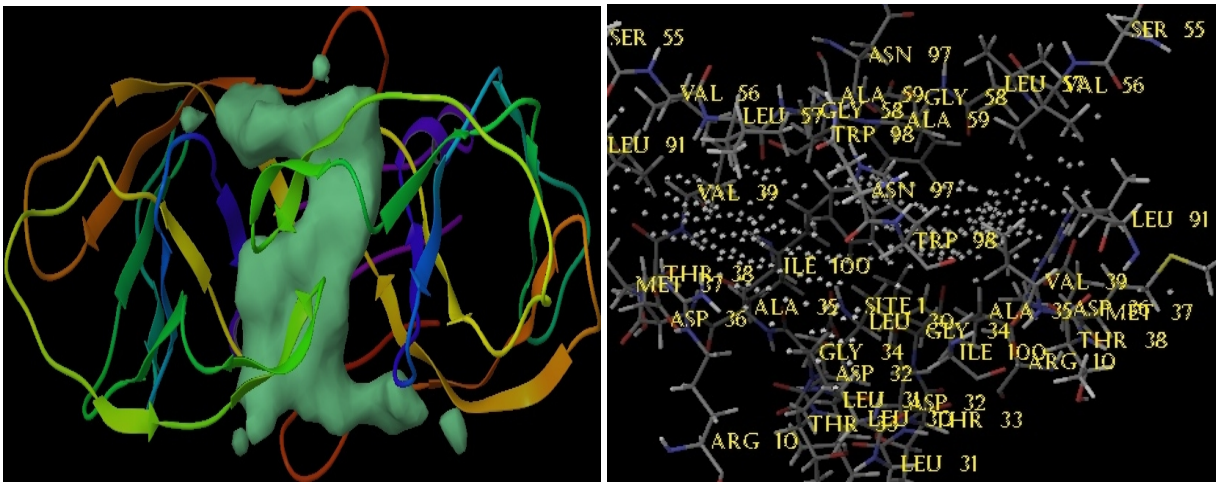

Figure S3. (a) *Represents the Site1 of the crystal structure of 2B7F, showing Z shaped binding pocket, colored in turquoise, present in between the two monomer chain (A and B chain), indicates both chains are to inhibited, by drug (active site binding pocket, resembles to HIV-PR)* **(b)** *The white colored dots indicates the Site1, represents the residues nearby the Site1 which having tendency to interact the ligand atoms, through hydrogen bond interaction.*

Figure S4

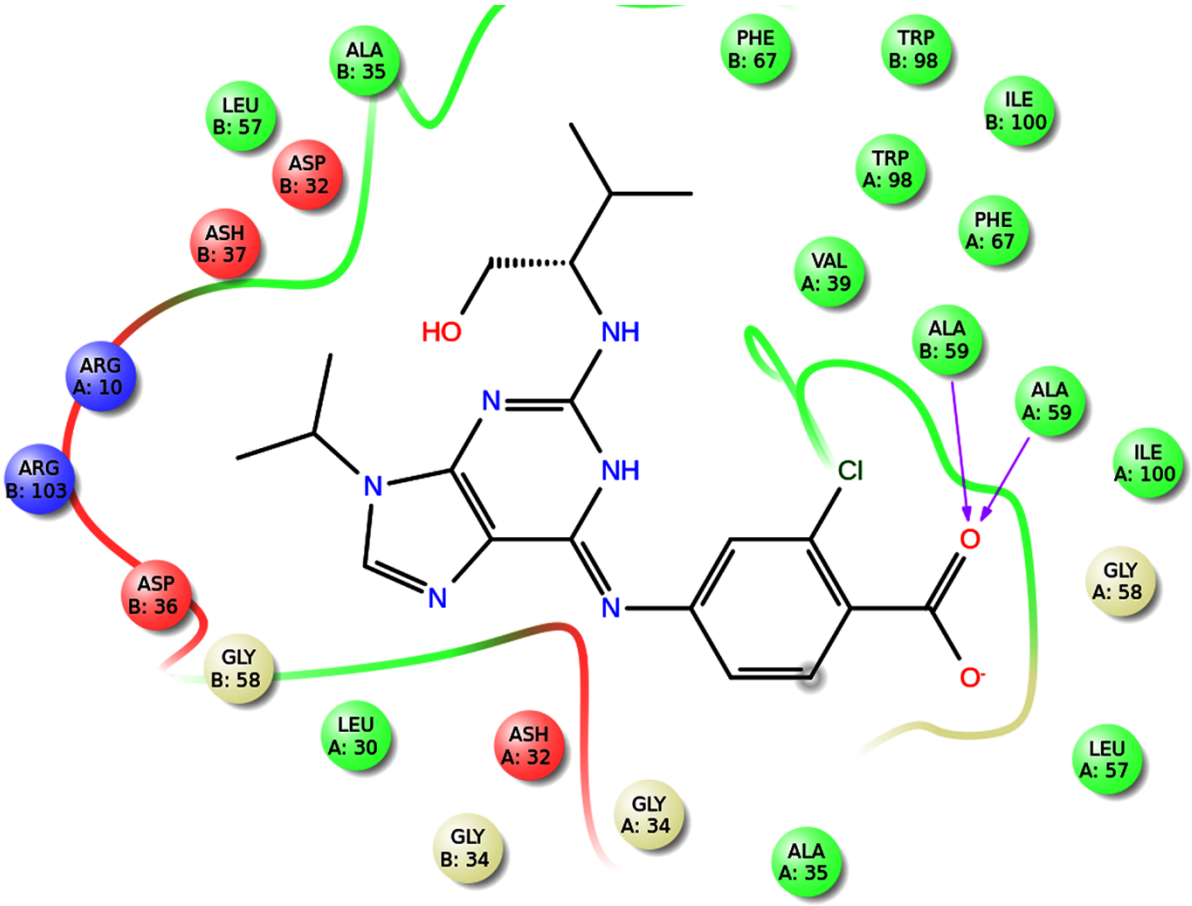

Figure S4: Purvalanol A shows week interactions with the mutant HTLV-1 PR.

Molecular docking results in site based ligand docking

Site obtained from sitemap is used and site based ligand docking is performed, from that the libraries of Purvalanol-A is docked interacted through molecular docking. The top scores of the new leads, which are better than known Purvalanol-A(-6.702560) are given, for knowledge of predicted active site interaction.

Ligand Position	Addition of atoms	Docking score	H-Bonds	Active site
Purvalanol-A R1 Position	Fluroenylmethoxycarbonyl	-8.565992	2	GLY34, LEU57
	Danzyl	-8.366800	2	ARG10
	Carboxyl	-8.148589	2	ASP32, LEU57
	Phospho	-8.079790	2	GLY34, LEU57
	Phosphato	-8.077829	4	GLY34, ASP36, LEU57
	Acetoacetyl	-8.073759	2	ASP36, LEU57
	Cyclopentadiene	-7.982675	2	ASP36, LEU57
	Sulfoamino	-7.916354	4	ASP32, GLY34, ASP36, LEU57
	Nitroso	-7.852271	3	ASP32, GLY34
	Formyloxy	-7.690499	2	ASP36, LEU57
	Sulfamoyl	-7.678700	3	GLY34, ASP36, LEU57
	Phosphito	-7.455105	3	ASP36, LEU57
	Azido	-7.367854	2	GLY34, LEU57
	Tosyl	-7.314779	2	ASP36, LEU57
	Carbamoyl	-7.305788	2	LEU57, LEU30
	Phenyloxycarbonyl	-7.256961	3	ARG10, MET37
	Cyclopentane	-7.219739	2	GLY34, LEU57
	Vinyl	-7.065922	2	ASP36, LEU57
	Benzyloxycarbonyl	-7.029579	2	ARG10, MET37
	Sulfo	-6.999499	3	GLY34, ASP36, LEU57
	Trifluromethyl	-6.990306	1	LEU57
	N-Pentyl	-6.987267	1	GLY34
	Isothiocyanato	-6.979956	2	GLY34, LEU57
	Trifluroacetyl	-6.979547	1	GLY34
	Trichloromethyl	-6.951050	2	GLY34, ASP36
	Sulfato	-6.910771	2	ASP32, GLY34
	Benzyl	-6.892773	2	GLY34, LEU57
	Allyl	-6.866976	1	GLY34
	Isobutiryl	-6.852768	2	ASP36, LEU57

Table S1. Purvalanol-A attached library compounds at R1 position docking results with H-Bond interactions and active site involved in interaction are tabulated.

Purvalanol-A R2 Position	Carboxyl	-9.093357	4	GLY34, ASP36, MET37
	Phosphato	-8.711677	4	ASP32, ASP36, LEU57
	Phosphito	-8.590773	3	ASP32, ASP36, LEU57
	Acetoacetyl	-8.399700	4	ASP32, ASP36, MET37, LEU57
	Cyclopentadiene	-8.179610	1	GLY34
	Benzoyl	-7.972852	1	LEU57
	Thiocyanato	-7.916242	2	GLY34, MET37
	Tosyl	-7.784949	3	ASP32, GLY34, MET37
	Benzyl	-7.701221	2	ASP32, LEU57
	Acetoxy	-7.696410	2	MET37, LEU57
	Trifluroacetyl	-7.669722	2	MET37, LEU57
	T-butyl	-7.585948	1	GLY34
	Danzyl	-7.522937	4	GLY34, GLY58, ALA59
	Butyl	-7.489091	2	ASP32, LEU57
	Isobutyl	-7.459519	1	LEU57
	Fluroenylmethoxycarbonyl	-7.450053	3	ASP36, ALA59
	Formamido	-7.393833	2	GLY34, MET37
	Cyano	-7.350278	2	ASP32, LEU57
	Ethynyl	-7.350278	2	ASP32, LEU57
	Formyloxy	-7.343531	2	MET37, LEU57
	Benzyloxycarbonyl	-7.339480	4	GLY34, LEU57, ALA59
	Sulfoamino	-7.285997	1	MET37
	Chloroformyl	-7.269403	2	ASP32, LEU30
	N – Pentyl	-7.248576	1	GLY34
	Benzene	-7.248576	2	ASP32, GLY34
	Formyl	-7.177764	2	MET37, LEU57
	Acetamido	-7.138717	1	MET37
	Trifyl	-6.986313	3	ASP32, ASP36, LEU57
	Sulfato	-6.971282	2	ASP36, MET37
	Acetyl	-6.952335	2	ASP32, ASP36
	Cyanato	-6.945774	1	GLY34
	I-Amyl	-6.939794	2	GLY34, LEU57
	Pivaloyl	-6.931592	2	ASP32, GLY34
	Ethoxycarbonyl	-6.931443	2	ASP36, LEU57
	Tetrohydropyranal	-6.913617	1	GLY34
	Sulfamoyl	-6.913538	2	ASP32, LEU57
	Trityl	-6.837340	2	GLY34
	Phenyloxycarbonyl	-6.809987	2	GLY34, ALA59
	Cyclobutane	-6.803285	1	ASP32

Table S2. Purvalanol-A attached library compounds at R2 position docking results with H-Bond interactions and active site involved in interaction are tabulated.

Purvalanol-A R3 Position	Phenyloxycarbonyl	-10.208523	2	GLY34, MET37
	Phosphato	-10.028146	5	ASP32, GLY34, ASP36
	Chloroformyl	-9.967000	3	ASP32, GLY34, MET37
	Cycloheptane	-9.265767	1	ASP36
	Trifluroacetyl	-9.141660	4	ASP32, GLY34, ASP36, MET37
	Phosphito	-9.085907	2	ASP36, LEU57
	Acetamido	-9.036692	2	ASP32, GLY34, ASP36, MET37
	Nitroxy	-8.934191	3	ASP32, GLY34, MET37
	Acetyl	-8.867921	3	ASP32, GLY34, ASP36
	Benzene	-8.831860	1	GLY34
	T – Butyl	-8.777912	2	ASP32, GLY34
	Trichloromethyl	-8.622579	2	ASP32, GLY34
	Sulfino	-8.548162	1	MET37
	Benzoyl	-8.519988	1	MET37
	Sulfato	-8.468488	2	GLY34, MET37
	Formamido	-8.308966	2	GLY34, MET37
	Benzyl	-8.303546	1	ASP36
	Formyl	-8.228145	3	ASP32, GLY34, MET37
	Chlorosulfonyl	-8.218263	3	ASP32, GLY34, ASP36
	Sulfoamino	-8.214180	4	ASP32, GLY34, LEU57
	T- Butyloxycarbonyl	-8.123968	1	GLY34
	Isobutiryl	-7.854320	2	ASP32, MET37
	Acetoacetyl	-7.813852	3	ASP32, GLY34, MET37
	Benzyloxycarbonyl	-7.777628	2	ASP32, MET37
	Thiocyanato	-7.722379	2	ASP32, GLY34
	Trifluromethyl	-7.335328	2	ASP32, MET37
	Phosphano	-7.330417	4	GLY34, SER55, LEU57, GLN62
	Acetoxy	-7.312448	3	ASP32, GLY34, MET37
	S-Butyl	-7.277311	1	ASP32
	Cyclooctane	-7.258960	1	ASP36
	Formyloxy	-7.135790	2	ASP32, ASP36
	Cyano	-7.097047	2	ASP32, MET37
	Carboxyl	-7.035752	2	GLY34, MET37
	N – Propyl	-6.986083	1	GLY34
	Tosyl	-6.969499	2	ASP36, MET37

Table S3. Purvalanol-A attached library compounds at R3 position docking results with H-Bond interactions and active site involved in interaction are tabulated.

Purvalanol-A R4 Position	Formyl	-9.792020	4	ASP32, ASP36, LEU57
	Carboxyl	-9.295359	5	ASP32, ASP36, MET37, LEU57
	Fluroenylmethoxycarbonyl	-9.221705	4	ASP32, ASP36, ALA59
	Benzyloxycarbonyl	-9.017948	4	ASP32, ASP36, ALA59
	Phenyloxycarbonyl	-8.812543	4	GLY34, LEU57, ALA59
	Phosphito	-8.773525	4	ASP36, MET37, LEU57
	Ethynyl	-8.645007	3	ASP32, GLY34, LEU57
	Acetoacetyl	-8.627168	2	ASP36, LEU57
	Phosphato	-8.520319	4	GLY34, ASN97, ALA99
	Trityl	-8.129960	5	ASP32, GLY34, LEU57
	Cycloheptane	-8.075769	2	ASP36, ALA59
	Propyl	-8.070831	3	ASP32, GLY34
	Cyano	-7.983771	3	ASP32, ASP36, LEU57
	Formyloxy	-7.838598	2	ASP32, MET37
	Phosphano	-7.792247	3	ASP32, GLY34, MET37
	Cyanato	-7.768998	3	ASP32, LEU57
	Danzyl	-7.686912	1	GLY34
	Acetoxy	-7.674101	3	ASP32, MET37
	Sulfino	-7.611824	3	ASP32, ASP36, LEU57
	Sulfato	-7.574927	2	ASN97, ALA99
	Thiocyanato	-7.434632	2	ASP32, LEU57
	Allyl	-7.430779	2	GLY34
	Cyclopropane	-7.304613	2	ASP32, GLY34
	Chloroformyl	-7.242689	2	GLY34, LEU57
	Cyclopentane	-7.212437	1	LEU57
	Vinyl	-7.148030	2	ASP32, GLY34
	Tosyl	-7.145920	2	ALA59
	T-Butyl	-7.077889	1	ALA59
	Benzyl	-6.989732	2	ASP36, ALA59
	T- Butyloxycarbonyl	-6.955697	3	ASP36, ALA59
	N – Pentyl	-6.953860	2	ALA59

Table S4. Purvalanol-A attached library compounds at R4 position docking results with H-Bond interactions and active site involved in interaction are tabulated.