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A COMBINATORIAL APPROACH TO IDENTIFY NOVEL HIV-PROTEASE (WILD AND MUTANT) INHIBITORS (PIs) USING ZINC DRUG DATABASE

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ABSTRACT: The Human immunodeficiency virus type-1 protease is one of the most important target to highly active anti retrovirus therapy(HAART) for the treatment of all acquired immune deficiency syndrome(AIDS). Protease inhibitor "Darunavir" is most recently included as a PI in the list of HARRT(highly active anti retrovirus therapy), more effective against mutant and wild type simultaneously of Protease with increased no. of H bonding then precursors approved by FDA, So herein we have taken Darunavir as a base structure for virtually identification of more/similar efficient drug like leads then Darunavir using ten different PDB structures (3EM6, 3OXW, 3BVB, 3CYW, 3D1Y, 4DQB, 4DQH, 4DQE, 4DQF, 4DQC & 3EKT) of Protease from PDB database 'RCSB' versus chemical compounds database 'ZINC' using Schrodinger and Discovery Studio software. Using molecular constraint search with similarity coefficient 'Tanimoto', 1,65,000 ligands were extracted and docking analysis were resulted some efficient in docking and in other computational medicinal parameters, we are reporting such lead molecules, and they may further undergo through high end extensive virtual investigation and beyond..

INTRODUCTION: Human immunodeficiency virus (HIV) Is a retrovirus that causes acquired immunodeficiency syndrome (AIDS), a condition of immunity to fail in human body to begin life threatening Infections lifelong. Presently acquired immunodeficiency syndrome(AIDS) is one of the leading cause of death in the world [1, 2]. After rigorous multidisciplinary research worldwide successful development of vaccine is still elusive (Human immunodeficiency virus type-1 protease(HIV-1 PR), a catalytic protein, in a role to cleaves the Gag and Gag-Pol viral poly-proteins, allowing the virus to efficiently infect new host cells. The HIV-1 PR, encoded in the 5' end of the pol gene, is expressed as part of the gag-pol poly-protein. This gene encodes a 99 amino-acids protein.

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Homodimeric of this protein, i.e. protease is a C2-symmetric enzyme consisting 99 amino acid monomer. Each monomer contributes an aspartic acid residue that is essential for catalysis [3]. The two chains of this homodimer form a tunnel with a 'flap" from each protein chain helping to secure the poly-protein in place [3]. The Darunavir and many others inhibitory drugs interact with amino acids in between these dimeric protein flaps.

In HIV-1 Protease inhibitors (PIs) target to disruptanessential function in the life cycle of HIV to breaking up the viral polypeptide into components that can be used to form mature virus particles[4]. Darunavir and other PIs act as non-covalent inhibitor of HIV protease and compete with the natural substrate to occupy the active site. When a protease inhibitor binds, the HIV life cycle is halted as the protein components for new viral particles are not able to produce[3], on this background we induce this work to find out more potent PIs as similar Darunavir like leads against mutant and wild with same efficiencies simultaneously.

Darunavir:

Darunavir is an anti-retroviral drug under the umbrella of Protease inhibitors, which is used for hindering the activity of the virus protease. In the work herein Darunavir is taken as reference molecule and find out 1% of similar molecules of each retrieved file of zinc drug bank(sd file) using similarity coefficient "Tanimoto" in D.S. 2.5 in a single job around 1390 molecules was find out as similar to Darunavir, we performed as like 118 jobs and a total 118x1390 molecules we found out and then perform docking with glide program of Schrodinger.

TABLE:1

PDB	Ligand	Resolution	R value	R free	Mutation
3BVB	Darunavir	1.30	0.170(Obs.)	0.210	D25N
4DQB	Darunavir	1.50	0.170(Obs.)	0.196	WILD
3OXW	Darunavir	1.95	0.175(Obs.)	0.218	150V, A71V
3CYW	Darunavir	1.40	0.169(Obs.)	0.234	I50V
3D1Y	Darunavir	1.05	0.150(Work)	0.174	I54M
4DQC	Darunavir	1.94	0.184(Obs.)	0.196	G16C,238C
4DQE	Darunavir	1.30	0.204(Obs.)	0.219	GI6C, L38C
4DQH	Darunavir	1.79	0.173(Obs.)	0.219	R14C, E65C
3EM6	Darunavir	2.10	0.186(Obs.)	0.240	I50L, A71V
3EKT	Darunavir	1.97	0.211(Obs.)	0.258	L10F, G48V, I54V, V64I, V82A

Protease:

The HIV-1 protease is one of the most important target for antiretroviral therapy used in the treatment of AIDS, this HIV protein has an important key role in viral replication cycle as a catalytic protein. The chemical activity of the HIV-1 protease depends on the two residues in the active site, Asp 25, Asp25', one from each copy of the homodimer. Darunavir interacts with these catalytic aspartates and surrounding backbone of the active site through hydrogen bonds, specifically binding to residues Asp29(B), Asp 30(B), Asp 30(A), Asn 25(B) and Gly27(B). This interaction prohibits viral replication as it competitively inhibits the viral polypeptides from gaining access to the active site and strongly binds to the enzymatic portions of this protein.

Protease inhibitors(PI) were developed to inhibit cleavage function of HIV-1protease by mimicking the reaction intermediates that arises during the hydrolysis of the substrate, disabling the enzyme to cleave the Gag and Gag-Pol viral polyproteins, mutagenic X-ray crystallographic co-complexes ligand-protein structures have been important tools for medicinal chemists to the discovery, design, and optimization of drug candidates [5, 6, 7]. These structural data, along with the computational analysis tools that have been developed to implement structure-based drug design (SBDD), in *in-vitro* analysis high cost and the extensive time frame requirement to find out drug like leads necessarily important, but it make it still impractical to use these conventional methods to evaluate the effect of each mutation in view of the genetic background of HIV-1 protease. In this context computational methods are growing up as a very important tool to medicinal chemist and now popularity of such methodology seeing on floor, fast up-gradation in computation algorithm and better Hardware availability by day, and easy to use, improve the screening analysis much easier, revealing the role of individual mutation and its impact on the protein function, proved to be very successful in computational medicinal chemistry.

As a greater number of X-ray crystal structures become available to medicinal chemists and with the advent of structural genomics [8], computational methods that take advantage of protein-ligand structural data are becoming more critical to the drug design process, in this regard we retrieved following 3EM6, 3OXW, 3BVB, 3CYW, 3D1Y, 4DQB, 4DQH, 4DQE, 4DQF, 4DQC & 3EKT (see **Table 1**) Pbd files from rcsb.org for Protease as target having co-crystalized with inhibitor Darunavir (most recent HIV protease inhibitor to reach the market in 2009) HIV-1 protease is one of the most important drug able target in new drug candidate, a nonpeptidic analogus of Amprenavir,

at the critical change at the terminal tetrahydrofuran (THF) group. Instead of a single THF group, Darunavir contains two THF group fused, form a bis-THF moiety which makes it more effective than Amprenavir. Protease inhibitors restrain the viral maturation by inhibiting the functional and structural proteins formation in virus so HIV produced immature, non-infectious. A single mutation in gene of HIV-PR cause double mutation in enzyme since HIV-PR is homodimeric protein, containing 99 amino acids in each chain with an active site located at the dimer interface.

The crystal structure analysis shows HIV-PR docked with Darunavir in the surrounding pocket of amino acids-Asp-25(A), 30(A), 29(A), 129(B), 130(B), Ala-28(A), 128(B), Gly-48(A), 49(A), 127(B), 148(B), 27(A), 149(B), Leu-123(B), 23(A), Ile-150(B), 182(B), 184(B), 132(B), 50(A), 82(A), 84(A), 32(A), Ser-31(A), Met-76(A), Thr180(B), Val-47(A),, 147(B), Ash-125(B), Arg-8(A), Pro-181(B), 81(A), from literature these amino acids constitutes three regions; catalytic-core(Asp-25(A), Gly-27(A), Ala-28(A), Asp-29(A) and Asp-30(A), flap (Ile-47(A), 54(A), Met-46(A) Phe-53(A), Gly-48(A) ,49(A) 51(A), 52(A) and Ile-50(A)) and the C-terminal region (Pro-81(A), Ile-84(A)). According to literature, Asp-25(A), Gly-27(A), Ala-28(A), Asp-29(A) and Gly-49(A) are known to be highly conserved residue in which a potential protease inhibitor bind effectively.

Experiment:

All following steps- preprocess(default settings), deleting all unnecessary water molecules and other structures except Darunavir, added hydrogen, generated it states, optimization, and minimization (with OPLS2005 force field)with default constraint of the 0.3Å of RMSD and corresponding Grid are generated in these prepared pdbs with the centre defined by the co-crystalized ligand Darunavir with default settings included partial charge and saved all in pre-created directory folder. Ligands extracted as previously mentioned procedure as similar to Darunavir with DS V2.5 in job " find similar molecules" with settings 1% similar molecules to 'Darunavir' with similarity coefficient 'tanimoto' which is very well known accurate similarity measures, remaining are almost default. Similar ligands are prepared for docking jobs in 'ligprep' with force-field OPLS2005 using epik with deselected options 'desalt' and selected 'generate tautomers' and finally with the ligands whose docking score more than Darunavir selectively prepared in 'ligprep' with force field OPLS 2005 using 'ioniser' with included setting as previous, generate default no. of low ring conformations and all combination in default no. and were docked in corresponding grid of pdbs. All docking calculations were performed using the "Extra Precision"(XP) mode of Glide Program with settings including sampling ligands 'flexible', optionally available various protocols for ligands constraints as rewards measure, partial charge of ligands and similarity measures to 'Darunavir' were included, sometime ionized state of ligand (deprotonated/protonated) marginally make influence on the docking scores, sometimes they appear lift up the scores up to the 2 units or more; due to interactions get elevated. All jobs were done on Intel i-7 3770K (unlocked) quad core machine with bios setting 3.9-4.4GHz with G Skill 8GB RAM & Corsair H-70 liquid cooling system. Medicinal parameter were calculated using programme qik prop (table-2-6)

RESULTS AND DISCUSSION:

In our virtual investigation we find the ZINC59485580("L")(((2S,3R,4S,5R,6S)-3,4,5,6-tetrahydroxytetrahydro-2H-pyran-2-yl)methyl L-phenylalaninate) molecule is very fine in docking calculation(-15.34, see Table-3BVB) having 2.5 unit more than to Darunavir("DAR", -12.63) which is likely appreciable to this work.

In other mutant state of protease (see table- 4DQB, 3OXW, 3CYW, 3D1Y, 4DQC, 4DQE, 4DQH, 3EM6 & 3EKT) the D.S. of "L" and other combinatorial structures are better than "DAR". The interactions diagram of ZINC59485580("L") (**Fig1.1(d**) showing very strong interaction network within the protease grid cavity, in the interaction diagram the amino group of phenylalaniate part of the molecule doubly Hydrogen bond (NH_2) donar to ASN(asparagine):25(A) & 25(B), ASN-25(B) also play H-Bond donar to esteric carbonyl of phenylalaninate, and hydroxyl("6S") group at 6^{th} position on (2H)-pyranyl ring to GLY:27(B) and ASP:29(B) respectively also ASP:29(B) play as H-Bond donar to "6S" Hydroxyl group another one to

"5R" Hydroxyl group in addition. These all interaction network make very efficient binding to grid cavity of ZINC59485580. Computed medicinal parameters are not comprehensively supportive, the computed lipophilicity(lip) below to the bottom level, on the another hand, QPPCaco (Predicted apparent Caco-2 cell permeability in nm/sec. Caco-2 cells are a model for the gut blood Barrier, predictions are for non-active transport) and QPPMDCK (Predicted apparent MDCK cell permeability in nm/sec. MDCK cells are considered to be a good mimic for the blood-brain barrier) are also at lower level but QPlogBB (Predicted brain/blood partition coefficient) is in required limit.

Herein in ZINC59485580, we have tried for some modification in its structure by substitution, addition with some appropriate organic moieties, and hetero atom exchange in appropriate sites, outcome of docking of such combinatorial prepared ligands gives some necessary relief in lipophilicity, which is one of the important necessities to identification as a drug like leads, but mentioned above two parameters were remain below to necessities, but all reported molecules are showing computed CNS inactive and computed brain/blood partition coefficient is much supportive to as drug like lead. The importance of the outcomes is that the binding efficacy of all listed molecules are more than Darunavir in docking score in all Pdbs either wild and in various different mutated state Pbds. Entry in each table (3BVB, 4DQB, 3OXW, 3CYW, 3D1Y, 4DQC, 4DQE, 4DQH, 3EM6 & 3EKT) from third row are modified structures of ZINC58485580 and its various properties are tabulated in the table for corresponding Pdbs structures. All modified structures (**Fig 1.3**) are showing good binding affinity with increased lipophilic nature.

TABLE: 3BVB

Title	D.S.	XP Lip	rtvFG	CNS	dipole	donorHB	accptHB	QPPCaco	QPlogBB	QPPMDCK	metab	QPlogKhsa	PHOAbs
DAR	-12.63	-7.85	1	-2	10.967	3.5	13.1	451.46	-1.552	209.428	3	-0.199	77.677
L	-15.34	-4.5	2	-2	3.4	6	11.5	11.696	-1.891	4.467	7	-0.909	25.645
16	-14.43	-6.19	2	-2	3.101	5	9.8	36.111	-1.605	15.108	8	-0.351	59.831
15	-13.99	-5.63	2	-2	5.38	5	9.8	44.094	-1.513	18.749	10	-0.183	63.9
16	-13.75	-6.06	2	-2	5.245	5	9.8	34.407	-1.647	14.339	8	-0.363	59.224
15	-13.6	-5.98	2	-2	0.935	5	9.8	38.704	-1.546	16.284	10	-0.184	62.499
32	-13.56	-4.73	2	-2	3.952	5	9.8	32.518	-1.37	14.247	7	-0.612	53.459
16	-13.15	-6.38	2	-2	3.467	5	9.8	40.935	-1.564	17.301	8	-0.346	61.167
54	-13.1	-5.48	2	-2	2.256	5	11.5	27.8	-1.727	14.941	7	-0.641	53.833
36	-12.95	-4.75	2	-2	4.387	5	11.5	31.806	-1.58	14.264	7	-0.77	52.313
14	-13.02	-6.34	2	-2	2.65	5	9.8	42.44	-1.565	17.99	9	-0.249	62.822
12	-12.95	-5.39	2	-2	5.27	5	9.8	38.965	-1.596	16.403	10	-0.266	61.978
40	-12.92	-4.89	2	-2	2.081	5	11.5	39.701	-1.466	16.738	10	-0.63	55.87
12	-12.78	-5.96	2	-2	4.867	5	9.8	37.161	-1.645	15.583	10	-0.281	61.376
36	-12.77	-4.5	2	-2	6.232	5	11.5	42.101	-1.481	23.2	7	-0.752	56.068
32	-12.76	-4.22	2	-2	7.638	5	9.8	32.075	-1.551	17.589	7	-0.58	55.28
11	-12.72	-5.82	2	-2	3.518	5	9.8	46.777	-1.589	19.984	8	-0.46	61.467
31	-12.68	-4.09	2	-2	7.275	5	9.8	34.561	-1.313	19.284	6	-0.665	54.097
34	-12.65	-5.12	2	-2	4.391	5	9.8	27.221	-1.728	14.064	8	-0.325	57.765
32	-12.56	-4.94	2	-2	3.386	5	9.8	33.189	-1.592	18.583	7	-0.582	56.021
32	-12.55	-4.92	2	-2	4.861	5	9.8	26.046	-1.696	14.425	7	-0.584	53.633
11	-12.54	-5.76	2	-2	4.5	5	9.8	39.696	-1.545	16.736	8	-0.461	59.332
31	-12.48	-4.63	2	-2	2.57	5	9.8	50.972	-1.231	30.101	6	-0.694	57.814
43	-12.47	-5.34	2	-2	4.31	5	11.5	28.838	-1.702	15.298	7	-0.641	54.127
10	-12.41	-4.93	2	-2	3.878	5	9.8	44.311	-1.417	18.848	9	-0.44	59.666

(D.S. (Docking Score, kcal/mol), Lip (Lipophilicity), rtvFG (no. of reactive functional groups, 0 – 2), CNS (Predicted central nervous system activity on a –2 (inactive) to +2 (active) scale), Dipole(computed dipole moment, 1.0 – 12.5), donarHB (Estimated number of hydrogen bonds that would be donated by the solute to water molecules in an aqueous solution. Values are averages taken over a number of configurations, so they can be non-integerm, 0.0 – 6.0), accptHB (Estimated number of hydrogen bonds that would be accepted by the solute from water molecules in an aqueous solution. Values are averages taken over a number of configurations, so they can be non-integer, 2.0 – 20.0), QPPCaco(Predicted apparent Caco-2 cell permeability in nm/sec. Caco-2 cells are a model for the gutblood barrier. QikProp predictions are for non-active transport, <25 poor, >500 great), QPlogBB(Predicted brain/blood partition coefficient, –3.0 – 1.2), QPPMDCK(Predicted apparent MDCK cell permeability in nm/sec. MDCK cells are considered to be a good mimic for the blood-brain barrier. QikProp predictions for non-active transport <25 poor, >500 great; metab (Number of likely metabolic reactions, 1-8), QPlogKhsa(Prediction of binding to human serum albumin, –1.5 – 1.5), PHOAbs(Predicted human oral absorption on 0 to 100% scale, >80% is high, <25%ispoor)

4DQB

Title	D.S.	Lip	rtvFG	CNS	dipole	donorHB	accptHB	QPPCaco	QPlogBB	QPPMDCK	metab	QPlogKhsa	PHOAbS
DAR	-10.78	-6.62	1	-2	12.132	3.5	13.1	369.905	-1.671	168.852	3	-0.218	75.545
L	-12.96	-3.4	2	-2	6.040	6	11.5	-8.768	-1.892	3.271	7	-0.928	21.233
16	-12.39	-5.12	2	-2	3.326	5	9.8	53.144	-1.43	22.94	8	-0.381	62.99
14	-11.96	-4.5	2	-2	3.678	5	9.8	37.848	-1.564	15.895	9	-0.271	61.241
16	-11.95	-4.2	2	-2	2.608	5	9.8	75.157	-1.236	33.364	8	-0.284	67.64
41	-11.75	-4.35	2	-2	5.049	5	11.5	43.311	-1.583	25.579	7	-0.656	58.657
16	-11.67	-5.55	2	-2	3.254	5	9.8	38.391	-1.615	16.142	8	-0.357	60.472
32	-11.57	-3.81	2	-2	2.548	5	9.8	42.246	-1.189	21.651	7	-0.602	56.104
46	-11.56	-4.26	2	-2	5.443	5	11.5	51.877	-1.33	30.627	7	-0.706	58.213
31	-11.23	-3.56	2	-2	2.18	5	9.8	40.753	-1.603	22.744	6	-0.651	57.915
16	-11.16	-4.15	2	-2	3.596	5	9.8	45.3	-1.469	19.303	8	-0.345	61.883
36	-11.11	-4.23	2	-2	2.608	5	11.5	39.259	-1.682	22.384	7	-0.746	56.477
11	-11.02	-4.18	2	-2	3.024	5	9.8	36.515	-1.376	15.291	8	-0.474	57.191
44	-10.95	-4.23	2	-2	1.422	5	11.5	36.274	-1.601	20.606	7	-0.779	54.323
36	-10.91	-3.97	2	-1	1.25	5	11.5	71.465	-0.991	43.39	7	-0.761	58.84
32	-10.88	-3.1	2	-2	2.078	5	9.8	54.685	-1.266	31.442	7	-0.602	59.912

3OXW

Title	D.S.	Lip	rtvFG	CNS	dipole	donorHB	accptHB	QPPCaco	QPlogBB	QPPMDCK	metab	QPlogKhsa	PHOAbs
DAR	-10.77	-6.19	1	-2	9.81	3.5	13.1	341.995	-1.61	155.125	3	-0.231	74.087
L	-12.09	-3.3	2	-2	5.443	6	11.5	8.316	-1.869	3.089	7	-0.871	21.650
32	-12.09	-4.72	2	-2	2.41	5	9.8	29.628	-1.664	16.549	7	-0.588	54.914
34	-11.96	-4.37	2	-2	4.881	5	9.8	34.683	-1.525	19.999	8	-0.346	59.6
48	-11.91	-4.4	2	-2	3.056	5	11.5	32.491	-1.292	13.478	7	-0.62	52.402
16	-11.79	-5.15	2	-2	2.694	5	9.8	41.235	-1.612	17.438	8	-0.366	61.129
11	-11.54	-4.58	2	-2	4.095	5	9.8	47.967	-1.488	20.534	8	-0.499	60.76
34	-11.5	-4.51	2	-2	1.487	5	9.8	35.511	-1.652	20.653	8	-0.334	60.569
14	-11.35	-5.54	2	-2	3.249	5	9.8	48.118	-1.369	20.605	9	-0.29	62.84
32	-11.34	-3.95	2	-2	5.911	5	9.8	38.913	-1.465	22.256	7	-0.581	57.383
54	-11.34	-4.53	2	-2	3.358	5	11.5	44.662	-1.477	27.452	7	-0.64	58.515
36	-11.29	-5.1	2	-2	5.022	5	11.5	45.757	-1.566	26.558	7	-0.785	57.135
43	-11.03	-5.06	2	-2	2.754	5	11.5	26.271	-1.772	14.047	7	-0.64	53.379
43	-10.98	-4.67	2	-2	3.983	5	11.5	38.498	-1.521	22.494	7	-0.641	56.847
16	-10.97	-4.78	2	-2	2.834	5	9.8	40.266	-1.621	16.995	8	-0.354	61.057
6	-10.97	-4.65	2	-2	5.123	5	9.8	41.633	-1.51	17.62	8	-0.327	61.462
11	-10.91	-4.68	2	-2	1.937	5	9.8	43.073	-1.551	18.28	8	-0.448	60.57
16	-10.89	-4.92	2	-2	3.079	5	9.8	37.852	-1.65	15.897	8	-0.364	60.331

3CYW

Title	D.S.	Lip	rtvFG	CNS	dipole	donorHB	accptHB	QPPCaco	QPlogBB	QPPMDCK	metab	QPlogKhsa	PHOAbs
DAR	-10.93	-6.98	1	-2	11.128	3.5	13.1	234.585	-1.904	103.21	3	-0.188	71.673
L	-10.21	-3.4	2	-2	6.84	6	11.5	12.0	-1.828	4.612	7	-0.934	24.758
54	-13.37	-5.14	2	-2	1.504	5	11.5	40.632	-1.566	23.325	7	-0.645	57.578
31	-12.67	-3.48	2	-2	3.761	5	9.8	29.717	-1.327	13.519	6	-0.67	51.641
41	-12.38	-5.59	2	-2	4.535	5	11.5	41.775	-1.648	23.969	7	-0.665	58.292
40	-12.3	-4.07	2	-2	3.948	5	11.5	47.736	-1.453	20.428	10	-0.682	57.171
36	-12.26	-5.19	2	-2	4.67	5	11.5	42.168	-1.628	23.822	7	-0.759	56.838
34	-12.25	-5.37	2	-2	2.61	5	9.8	32.146	-1.661	17.875	8	-0.313	59.71
34	-12.22	-5.38	2	-2	2.657	5	9.8	34.076	-1.623	19.234	8	-0.318	60.214
32	-12.12	-3.43	2	-2	4.699	5	9.8	34.543	-1.257	16.813	7	-0.618	53.602
46	-12.05	-5.67	2	-2	3.177	5	11.5	42.55	-1.589	24.788	7	-0.654	58.116
43	-11.99	-5.17	2	-2	3.649	5	11.5	33.081	-1.669	18.539	7	-0.652	55.492
36	-11.96	-5.3	2	-2	4.528	5	11.5	41.316	-1.636	23.578	7	-0.757	56.693
31	-11.91	-4.06	2	-2	2.302	5	9.8	55.327	-1.199	33.445	6	-0.671	59.078
32	-11.86	-5.05	2	-2	3.003	5	9.8	36.574	-1.556	21.658	7	-0.585	57.054
32	-11.8	-4.64	2	-2	3.919	5	9.8	28.385	-1.667	16.171	7	-0.585	54.543
32	-11.79	-4.79	2	-2	3.494	5	9.8	31.897	-1.627	17.836	7	-0.584	55.676
32	-11.7	-3.68	2	-2	4.036	5	9.8	33.512	-1.336	15.092	7	-0.552	54.747
41	-11.7	-3.11	2	-2	4.425	5	11.5	50.114	-1.486	30.189	7	-0.661	59.781

51	-11.62	-4.17	2	-2	4.9	5	11.5	57.982	-1.105	25.206	8	-0.634	58.137
54	-11.55	-5.18	2	-2	6.373	5	11.5	32.665	-1.703	18.04	7	-0.661	55.308
46	-11.5	-5.2	2	-2	5.062	5	11.5	46.855	-1.506	27.711	7	-0.666	58.698
44	-11.38	-5.02	2	-2	4.736	5	11.5	41.608	-1.518	23.809	7	-0.802	55.152
32	-11.32	-4.1	2	-2	3.347	5	9.8	28.339	-1.66	16.419	7	-0.591	54.449
34	-11.23	-5.07	2	-2	6.363	5	9.8	27.806	-1.729	14.469	8	-0.314	58.209
11	-11.13	-4.86	2	-2	5.041	5	9.8	40.563	-1.491	17.131	8	-0.519	58.381
31	-11.07	-4.09	2	-2	2.261	5	9.8	54.047	-1.221	31.654	6	-0.708	58.187

3D1Y

Title	D.S.	Lip	rtvFG	CNS	dipole	donorHB	accptH	QPPCaco	QPlogBB	QPPMDCK	metab	QPlogKhsa	PHOAbs
DAR	-7.23	-4.7	1	-2	8.333	3.5	13.1	428.108	-1.611	197.744	3	-0.154	77.984
L	-11.35	-3.1	2	-2	4.082	6	11.5	5.415	-2.275	1.943	7	-0.970	17.059
16	-11.72	-4.06	2	-2	5.239	5	9.8	43.92	-1.567	18.668	8	-0.352	61.878
16	-11.72	-4.05	2	-2	5.567	5	9.8	43.512	-1.459	18.481	8	-0.347	61.479
10	-11.37	-3.46	2	-2	2.087	5	9.8	73.78	-1.064	32.704	9	-0.476	63.234
51	-11.27	-3.86	2	-2	3.462	5	11.5	41.033	-1.407	17.345	8	-0.689	54.804
36	-11.17	-3.79	2	-2	3.253	5	11.5	36.162	-1.671	17.544	7	-0.768	54.683
36	-11.02	-3.37	2	-2	4.131	5	11.5	40.993	-1.623	23.48	7	-0.767	56.394
46	-10.87	-3.71	2	-2	3.89	5	11.5	39.201	-1.589	22.44	7	-0.671	56.841
14	-10.82	-3.64	2	-2	4.28	5	9.8	42.021	-1.557	17.797	9	-0.246	62.718
54	-10.77	-3.67	2	-2	3.748	5	11.5	59.635	-1.096	35.313	7	-0.632	59.633
40	-10.67	-4.15	2	-2	3.492	5	11.5	38.01	-1.61	15.969	10	-0.653	55.709
11	-10.66	-3.96	2	-2	3.824	5	9.8	44.692	-1.587	19.023	8	-0.475	60.672
32	-10.66	-3.88	2	-2	2.721	5	9.8	35.444	-1.556	20.618	7	-0.576	56.804
16	-10.6	-3.88	2	-2	4.09	5	9.8	34.861	-1.585	14.544	8	-0.367	59.093
41	-10.59	-3.72	2	-2	2.179	5	11.5	54.122	-1.194	32.169	7	-0.633	59.414
32	-10.59	-2.74	2	-2	2.913	5	9.8	25.521	-1.484	12.53	7	-0.593	51.799
44	-10.54	-3.54	2	-2	1.551	5	11.5	40.444	-1.533	20.574	7	-0.814	54.335
11	-10.5	-3.96	2	-2	2.614	5	9.8	37.241	-1.69	15.62	8	-0.479	58.962
43	-10.4	-3.33	2	-2	2.229	5	11.5	36.54	-1.534	22.099	7	-0.625	56.613
36	-10.38	-3.67	2	-2	6.158	5	11.5	38.304	-1.352	21.061	7	-0.731	54.366
32	-10.36	-3.37	2	-2	2.511	5	9.8	53.138	-1.093	32.68	7	-0.55	59.625
32	-10.35	-4.11	2	-2	4.173	5	9.8	38.202	-1.487	22.008	7	-0.608	56.776
48	-10.27	-4.11	2	-2	0.84	5	11.5	37.115	-1.528	15.563	7	-0.652	54.906
32	-10.19	-2.91	2	-2	2.4	5	9.8	44.864	-1.421	26.619	7	-0.604	58.51
31	-10.17	-3.43	2	-2	2.165	5	9.8	47.724	-1.224	22.98	6	-0.701	56.259
14	-10.1	-4.26	2	-2	5.434	5	9.8	48.697	-1.459	20.872	9	-0.256	63.822

4DQC

Title	D.S.	Lip	rtvFG	CNS	dipole	donorHB	accptHB	QPPCaco	QPlogBB	QPPMDCK	metab	QPlogKhsa	PHOAbs
DAR	-10.64	-6.54	1	-2	11.617	3.5	13.1	314.074	-1.84	141.482	3	-0.087	76.332
L	-11.62	-3.0	2	-2	6.848	6	11.5	8.693	-1.754	3.241	7	-0.842	21.771
11	-11.57	-4.65	2	-2	3.432	5	9.8	38.793	-1.673	16.324	8	-0.46	59.661
31	-11.19	-3.41	2	-2	2.238	5	9.8	51.414	-1.212	30.155	6	-0.665	58.295
54	-11.13	-4.23	2	-2	3.091	5	11.5	40.364	-1.466	21.555	7	-0.661	56.504
11	-11.01	-4.36	2	-2	3.695	5	9.8	70.413	-1.213	31.094	8	-0.46	64.434
44	-10.99	-3.51	2	-2	2.83	5	11.5	72.48	-1.162	43.362	7	-0.814	59.525
16	-10.94	-4.13	2	-2	4.346	5	9.8	40.406	-1.258	17.059	8	-0.419	58.409
43	-10.9	-4.29	2	-2	3.859	5	11.5	39.687	-1.528	22.819	7	-0.655	56.93
16	-10.77	-4.18	2	-2	2.43	5	9.8	70.793	-1.054	31.275	8	-0.395	64.308
36	-10.76	-3.83	2	-2	3.3	5	11.5	59.722	-1.337	29.014	7	-0.728	59.373
54	-10.65	-4.23	2	-2	4.824	5	11.5	39.424	-1.59	23.685	7	-0.619	57.87
36	-10.65	-3.47	2	-2	3.537	5	11.5	71.228	-1.24	43.555	7	-0.774	60.799
16	-10.64	-5.26	2	-2	1.893	5	9.8	40.673	-1.59	17.181	8	-0.351	61.116
31	-10.62	-3.36	2	-2	2.521	5	9.8	54.619	-1.205	32.845	6	-0.693	58.565

4DQE

Title	D.S.	Lip	rtvFG	CNS	dipole	donorHB	accptHB	QPPCaco	QPlogBB	QPPMDCK	metab	QPlogKhsa	PHOAbs
DAR	-9.28	-5.72	1	-2	13.06	3.5	13.1	408.387	-1.631	187.916	3	-0.207	76.797
L	-11.58	-3.8	2	-2	6.086	6	11.5	8.815	-1.816	3.291	7	-0.871	21.895
16	-12.74	-4.51	2	-2	5.621	5	9.8	48.745	-1.47	20.895	8	-0.376	62.265

32	-11.42	-3.28	2	-2	1.265	5	9.8	42.541	-1.45	25.958	7	-0.582	58.462
41	-11.27	-4.69	2	-2	3.801	5	11.5	30.576	-1.772	17.72	7	-0.636	55.746
16	-11.21	-4.91	2	-2	2.365	5	9.8	43.904	-1.506	18.661	8	-0.399	60.938
34	-11.15	-4.51	2	-2	6.597	5	9.8	26.764	-1.666	15.507	8	-0.333	57.428
11	-11.14	-4.04	2	-2	3.16	5	9.8	39.964	-1.485	16.858	8	-0.452	59.193
16	-11.04	-5.16	2	-2	3.442	5	9.8	45.017	-1.557	19.173	8	-0.347	62.198
44	-11.04	-3.57	2	-1	2.421	5	11.5	78.377	-0.886	49.794	7	-0.795	58.422
36	-10.85	-4.22	2	-2	1.085	5	11.5	38.807	-1.668	22.362	7	-0.727	56.632
32	-10.7	-3.39	2	-2	4.066	5	9.8	34.578	-1.239	16.392	7	-0.63	53.156
11	-10.69	-4.69	2	-2	3.07	5	9.8	37.482	-1.701	15.729	8	-0.474	59.137
32	-10.65	-3.4	2	-2	2.354	5	9.8	55.142	-1.251	31.757	7	-0.619	59.615
34	-10.44	-4.07	2	-2	4.532	5	9.8	28.114	-1.636	16.71	8	-0.354	57.691
41	-10.43	-3.95	2	-2	1.186	5	11.5	42.76	-1.636	24.833	7	-0.632	59.065
48	-10.4	-4.33	2	-2	4.325	5	11.5	39.874	-1.605	16.817	7	-0.679	55.682
31	-10.29	-3.3	2	-2	2.128	5	9.8	48.67	-1.289	26.427	6	-0.682	57.567
46	-10.27	-4.35	2	-2	2.73	5	11.5	44.745	-1.547	25.003	7	-0.646	58.517
31	-10.21	-3.2	2	-2	4.409	5	9.8	38.343	-1.335	21.743	6	-0.662	55.471
51	-10.21	-3.86	2	-2	5.754	5	11.5	51.642	-1.364	22.24	8	-0.697	57.344
32	-10.17	-4.17	2	-2	0.467	5	9.8	35.519	-1.286	18.69	7	-0.584	54.923
31	-10.15	-3.23	2	-2	2.149	5	9.8	48.351	-1.243	27.873	6	-0.667	57.656
32	-9.94	-3.53	2	-2	4.887	5	9.8	43.497	-1.123	22.961	7	-0.583	56.39
32	-9.91	-4.52	2	-2	2.742	5	9.8	33.039	-1.542	19.079	7	-0.601	55.46
11	-9.87	-4.6	2	-2	7.804	5	9.8	25.369	-1.728	10.315	8	-0.487	54.618
48	-9.86	-4.38	2	-2	3.902	5	11.5	34.462	-1.653	14.364	7	-0.644	54.776
32	-9.86	-3.13	2	-2	1.641	5	9.8	48.432	-1.28	27.224	7	-0.583	58.781
54	-9.84	-4.59	2	-2	3.039	5	11.5	33.268	-1.67	18.447	7	-0.66	55.412
11	-9.82	-3.97	2	-2	3.987	5	9.8	71.388	-1.189	31.56	8	-0.466	64.384
32	-9.76	-4.53	2	-2	2.39	5	9.8	31.033	-1.617	18.655	7	-0.582	55.535
32	-9.7	-4.1	2	-2	3.271	5	9.8	36.591	-1.261	19.294	7	-0.578	55.24
43	-9.69	-4.62	2	-2	2.436	5	11.5	41.512	-1.545	24.144	7	-0.607	58.347
11	-9.67	-4.81	2	-2	5.139	5	9.8	40.636	-1.506	17.164	8	-0.475	59.326
11	-9.6	-4.33	2	-2	3.973	5	9.8	52.577	-1.44	22.676	8	-0.463	62.196
46	-9.56	-4.01	2	-2	3.273	5	11.5	33.614	-1.63	19.357	7	-0.628	55.967
44	-9.53	-3.44	2	-2	3.387	5	11.5	51.62	-1.354	27.555	7	-0.797	56.617
41	-9.52	-4.09	2	-2	1.565	5	11.5	33.65	-1.744	18.953	7	-0.667	56.137
31	-9.52	-4.06	2	-2	2.924	5	9.8	31.533	-1.51	18.125	6	-0.694	53.651
48	-9.51	-3.76	2	-2	4.006	5	11.5	35.06	-1.534	14.633	7	-0.647	54.303
45	-9.44	-3.38	2	-2	6.119	5	11.5	29.608	-1.588	15.229	7	-0.716	52.734
32	-9.36	-3.13	2	-2	2.469	5	9.8	45.57	-1.358	24.558	7	-0.58	58.435
31	-9.36	-3.45	2	-2	1.572	5	9.8	24.576	-1.597	12.742	6	-0.677	51.184
54	-9.29	-3.49	2	-2	1.769	5	11.5	64.126	-1.199	35.458	7	-0.644	60.744

4DQH

Title	D.S.	Lip	rtvFG	CNS	dipole	donorHB	accptHB	QPPCaco	QPlogBB	QPPMDCK	metab	QPlogKhsa	PHOAbs
DAR	-11.37	-6.69	1	-2	12.22	3.5	13.1	342.66	-1.689	156.079	3	-0.182	75.27
L	-8.842	-3.7	2	-2	6.164	6	11.5	18.542	-1.633	7.351	7	-0.905	29.544
11	-11.74	-4.36	2	-2	1.828	5	9.8	61.677	-1.293	26.946	8	-0.447	63.365
41	-11.34	-4.56	2	-2	4.972	5	11.5	50.814	-1.489	30.139	7	-0.641	60.313
16	-11.21	-4.26	2	-2	2.752	5	9.8	39.236	-1.643	16.526	8	-0.359	60.779
16	-11.13	-4.86	2	-2	3.662	5	9.8	52.97	-1.433	22.859	8	-0.387	62.872
11	-11.08	-4.69	2	-2	4.055	5	9.8	45.119	-1.515	19.22	8	-0.496	60.195
16	-11.07	-4.5	2	-2	4.37	5	9.8	41.143	-1.362	17.396	8	-0.332	60.519

3EM6

Title	D.S.	Lip	rtvFG	CNS	dipole	donorHB	accptHB	QPPCaco	QPlogBB	QPPMDCK	metab	QPlogKhsa	PHOAbs
DAR	-9.93	-6.44	1	-2	12.215	3.5	13.1	338.236	-1.706	153.283	3	-0.258	74.037
L	-10.45	-3.4	2	-2	6.751	6	11.5	16.427	-1.637	6.449	7	-0.931	27.266
46	-12.75	-5.08	2	-2	2.591	5	11.5	30.037	-1.677	16.707	7	-0.638	54.637
36	-12.17	-4.73	2	-2	3.687	5	11.5	41.473	-1.592	23.456	7	-0.738	56.815
32	-11.63	-3.55	2	-2	3.782	5	9.8	31.787	-1.293	15.102	7	-0.63	52.513
41	-11.59	-4.84	2	-2	3.853	5	11.5	42.211	-1.591	24.19	7	-0.651	58.366
36	-11.53	-4.5	2	-2	4.64	5	11.5	52.959	-1.447	30.961	7	-0.785	58.264
32	-11.5	-3.69	2	-2	3.479	5	9.8	31.566	-1.393	13.154	7	-0.584	53.619
31	-11.28	-3.68	2	-2	4.614	5	9.8	35.055	-1.34	14.993	6	-0.69	53.116
34	-11.08	-4.53	2	-2	1.695	5	9.8	37.221	-1.6	21.215	8	-0.354	60.503
54	-10.91	-5.27	2	-2	5.02	5	11.5	30.033	-1.698	14.96	7	-0.689	53.542
31	-10.84	-3.68	2	-2	4.034	5	9.8	35.182	-1.328	14.811	6	-0.686	53.098
54	-10.84	-5.17	2	-2	2.414	5	11.5	38.969	-1.622	21.98	7	-0.655	57.145
32	-10.77	-3.48	2	-2	3.124	5	9.8	29.876	-1.437	12.447	7	-0.578	53.315

46	-10.67	-4.94	2	-2	2.934	5	11.5	42.699	-1.593	24.421	7	-0.653	58.128
48	-10.58	-4.99	2	-2	2.929	5	11.5	24.628	-1.898	9.99	7	-0.634	52.086
45	-10.51	-4.4	2	-2	5.116	5	11.5	26.648	-1.789	13.776	7	-0.755	52.121
44	-10.41	-3.94	2	-2	3.3	5	11.5	52.147	-1.057	30.988	7	-0.758	55.426
41	-10.38	-4.86	2	-2	2.94	5	11.5	41.742	-1.609	24.374	7	-0.657	58.281
43	-10.32	-5.29	2	-2	2.002	5	11.5	31.785	-1.736	17.573	7	-0.614	55.842
48	-10.14	-4.56	2	-2	3.941	5	11.5	36.079	-1.646	15.094	7	-0.631	55.507
36	-10.08	-4.73	2	-2	2.959	5	11.5	30.23	-1.821	15.869	7	-0.733	54.086
12	-10	-4.4	2	-2	7.27	5	9.8	36.507	-1.644	15.287	10	-0.293	61.001

3EKT

Title	D.S.	Lip	rtvFG	CNS	dipole	donorHB	accptHB	QPPCaco	QPlogBB	QPPMDCK	metab	QPlogKhsa	PHOAbs
DAR	-10.93	-4.71	2	-2	2.515	7	9.6	23.438	-1.112	10.476	5	0.102	39.888
L	-11.10	-2.7	2	-2	7.249	6	11.5	14.369	-1.925	5.580	7	-0.973	27.036
32	-12.34	-4.17	2	-2	4.849	5	9.8	50.003	-1.325	30.641	7	-0.573	59.906
54	-12.29	-3.83	2	-2	4.373	5	11.5	49.607	-1.164	27.855	7	-0.644	57.541
46	-12.28	-3.84	2	-2	4.373	5	11.5	49.618	-1.164	27.861	7	-0.644	57.542
36	-12.13	-4.54	2	-2	5.873	5	11.5	38.39	-1.652	21.566	7	-0.737	56.187
41	-11.99	-4.61	2	-2	5.994	5	11.5	60.238	-1.379	37.597	7	-0.644	61.831
48	-11.96	-4.71	2	-2	6.312	5	11.5	40.368	-1.557	17.042	7	-0.654	56.043
32	-11.93	-4.54	2	-2	4.849	5	9.8	50.007	-1.325	30.645	7	-0.573	59.907
36	-11.89	-4.52	2	-2	5.873	5	11.5	38.389	-1.652	21.565	7	-0.737	56.186
44	-11.89	-4.61	2	-2	5.89	5	11.5	38.392	-1.544	21.568	7	-0.787	54.501
41	-11.87	-3.96	2	-2	5.222	5	11.5	42.596	-1.632	26.302	7	-0.617	59.392
31	-11.72	-4.8	2	-2	4.648	5	9.8	49.996	-1.272	30.635	6	-0.668	58.472
31	-11.47	-4.66	2	-2	4.649	5	9.8	50.001	-1.272	30.639	6	-0.668	58.473
46	-11.16	-4.56	2	-2	3.783	5	11.5	24.058	-1.819	12.234	7	-0.624	52.605
48	-11.02	-4.81	2	-2	2.732	5	11.5	26.894	-1.317	10.987	7	-0.608	50.487

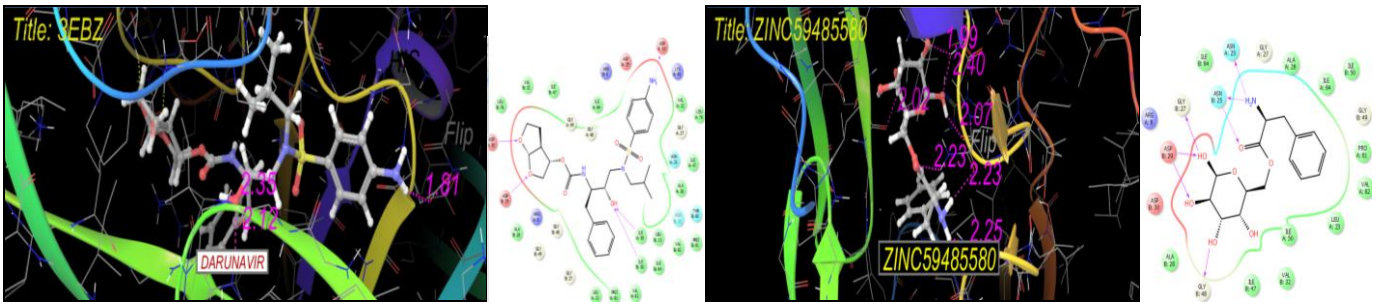
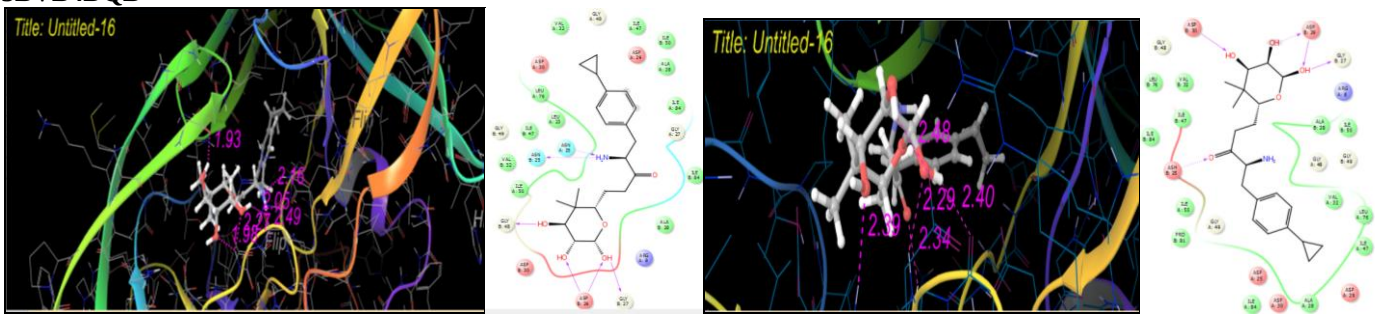
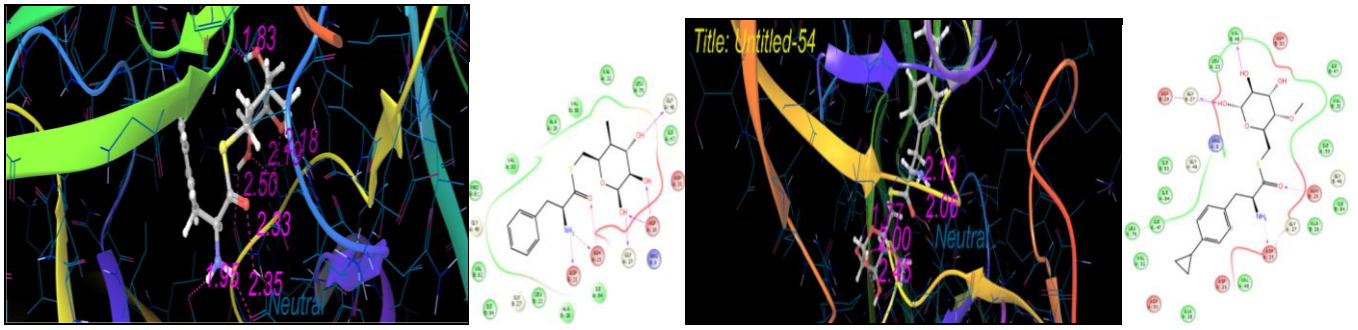


FIG. 1.1(A) DARUNAVIR DOCKED IN PDB 3BGR, (B) ITS INTERACTION DIAGRAM (C) ZINC59485580 (“L”) DOCKED IN PDB 3BGR (D) ITS CORRESPONDING INTEACTION DIAGRAM

3BVB4DQB



3OXW **3CYW**



3D1Y **4DQC**

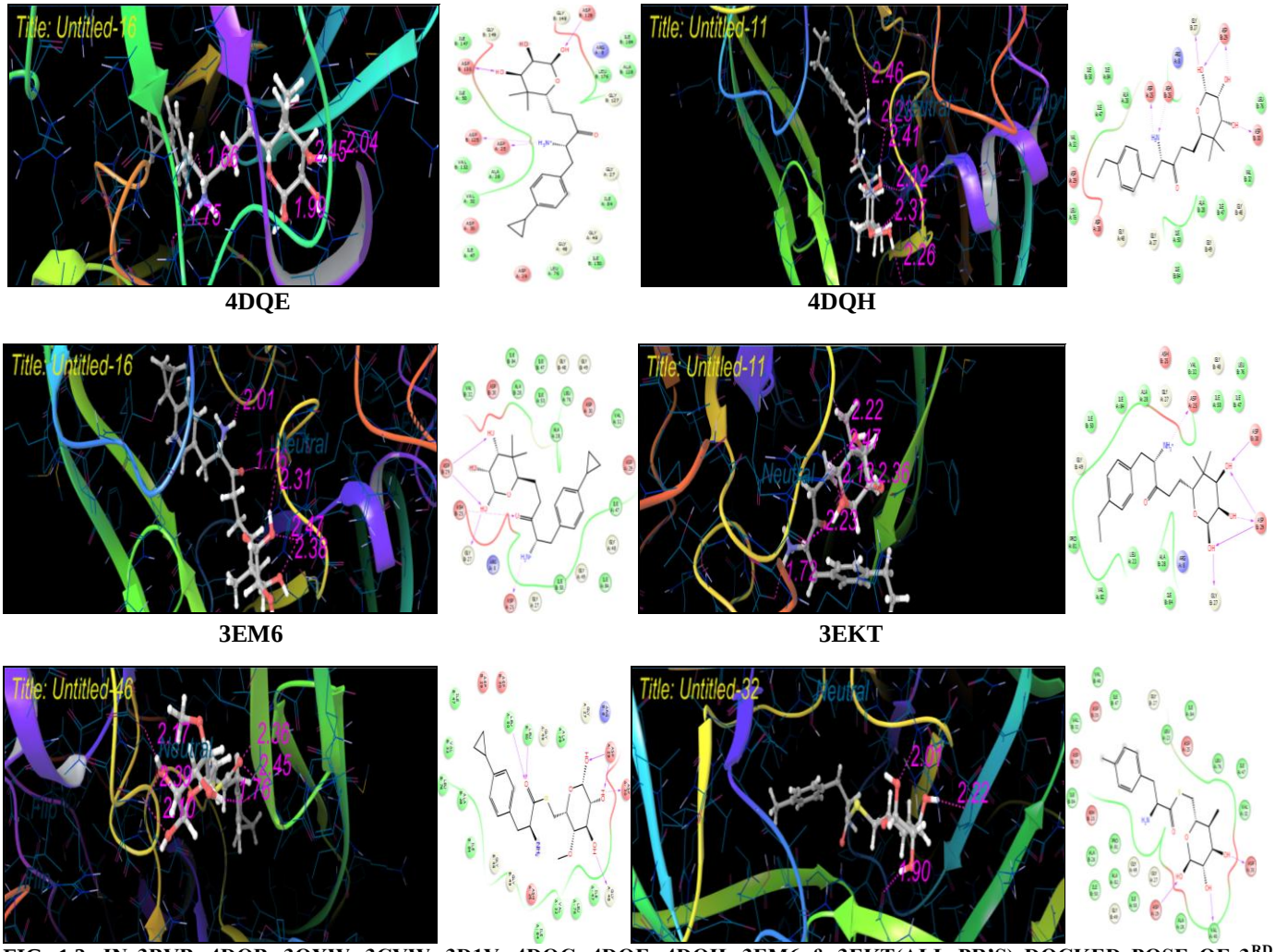


FIG. 1.2: IN 3BVB, 4DQB, 3OXW, 3CYW, 3D1Y, 4DQC, 4DQE, 4DQH, 3EM6 & 3EKT(ALL PR'S) DOCKED POSE OF 3RD ENTRY LIGAND IN EACH TABLE OF CORRESPONDING PDBS AND ITS CORRESPONDING INTERACTION DIAGRAM ON RIGHT SIDE.

CONCLUSION: In this work, we have tried to recognized some more/similar potent drug like leads instead 'Darunavir' with effective binding capacity, we have used ten different RT crystallographic structures with either different mutagenic level or wild type for better identification/verification for our results, modified and original structure showing effective binding capacity to respective grid cavity of protease, showing some fine computed properties, therefore, this study verify the importance of small drug like molecules libraries as like 'ZINC. docking.org'and their use certainly help scientific groups to enhance their capabilities in drug discovery with reducing time, including drug discovery process prior synthesis. Herein identified molecules may further investigate instead "in silico" the more advanced level to the work needed in forward to look much better.

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REFERENCES:

1. Ivetac, A.; McCammon, J.A. "Elucidating the Inhibition Mechanism of HIV-1 Non-Nucleoside Reverse Mechamism of Inhibitors through Multicopy Molecular Dynamics Simulations" Journal of Molecular Biology 2008; 388 (3): 644–658.
2. Rituraj and Alam. IJPSR "virtual screening of novel hiv-rt nnrt inhibitors using zinc database" 2014; V5(7): 2947-2954.
3. Goodsell, D.S. & Olson, A.J. Structural Symmetry and Protein Function. Ann. Rev. Biophys. Biomol. Struct. 29, 105-153, 2000.
4. Mittal, S., Bandaranayake, R. M. et al "Structural and Thermodynamic Basis of Amprenavir/Darunavir and Atazanavir Resistance in HIV-1 Protease with Mutations at Residue 50" J. Virology. 2013; 87, 4176-4184.

5. V Pawar, D Lokwani, S Bhandari, D Mitra, S Sabde, K Bothara, A Madgulkar: Design of potential reverse transcriptase inhibitor containing Isatin nucleus using molecular modeling studies. Bioorganic & Medicinal Chemistry 2010; 18(9): 3198–3211.
6. Aboye T., Ha H., Majumder S., Christ F.,Debyser Z., Shek htman A., Neamati N.,Camarero J.Design of a Novel Cycl otide-Based CXCR4 Antagonist with Anti-Human Immun odeficiency Virus (HIV)-1 Activity. Journal of Medicinal Chemistry. 2012; 55, 10729-10734.
7. A Herschhorn and A Hizi: Virtual Screening, Identification, and Biochemical Characterization of Novel Inhibitors of the Reverse Transcriptase of Human Immunodeficiency Virus Type-1 J. Med. Chem. 2008; 51, 5702–5713.
8. Stevens, R. C.; Yokoyama, S.; Wilson, I. A. Global efforts in structural genomics. Science 2001; 294, 89-92.

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