



**INSILICO STUDY OF BINDING PROFILES EVOLUTION OF *PEDALIUM MUREX LINN*
COMPOUNDS TOWARDS HUMAN IMMUNO VIRUS (HIV)**

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ABSTRACT

AIDS (Acquired Immune Deficiency Syndrome), a pandemic disease caused by Human Immuno Deficiency virus (HIV), are pointed out a life threatening virus all over the world. Though there is a considerable research to minimize the mortality rate caused by HIV, but the therapies are limited to the target action, this laid a path to find out the effective target and promising lead to overcome this issue. Using Insilico based molecular docking approach to minimize the effect, the C-C chemokine receptor type (CXCR) is an important target for HIV infection was selected to plot the interaction towards *PEDALIUM MUREX LINN* based compounds through ligand fit module of Accerlys Discovery studio. The compounds 9, 12-octadecadeionic acid, 9-octadecenoic acid have been identified as inhibitors for CXCR, CCR5, gp 120 and gp 41 receptors. It's indicated these two compounds might be considered as a potential lead molecule against selected receptors for HIV infection. Further studies need to be carried out to evaluate the pharmacological efficacy of these inhibitors.

KEYWORDS: HIV, Molecular docking, CXCR, Ligand fit.

INTRODUCTION

The human immunodeficiency virus type 1 (HIV-1) is the primary cause of the acquired immunodeficiency syndrome (AIDS), which is a slow, progressive and degenerative disease of the human immune system.^[1,3] HIV is one of the primary causes of death among adults aged 15–59 years resulting in about 14% of deaths globally in this age group.^[1] Majority of HIV disease in India is due to HIV-1 virus subtype C.^[7] HIV infection begins when there is an interaction between gp120, the trimeric envelope glycoprotein of HIV and CD4- the primary receptor of the host cell.^[4] Ultimately this interaction resulted in the exposure of the coreceptor binding sites of gp120, which in turn facilitate binding of chemokine receptors like CCR5 and CXCR4 present on the CD4 subset.^[3] The gp120 structure, revealed the presence of highly conserved residues located in V3 region that plays major role in the activation of its counterpart CD4^[10] Deletion of most of the V3 residues from gp120 had no effect on CD4 receptor binding, at the same time stabilization of major variable region enables immunogenic response for that specific region.^[3] The gp120 subunit associates with the CD4 receptor and the CCR5 co-receptor, inducing a series of conformational changes in the envelope protein.^[2] With revealing the knowledge of the life circle of HIV, it has been possible to study the binding affinity of some

important targets of HIV receptors and design inhibitors for treatment of AIDS.

MATERIALS AND METHODS

Ligand preparation

The three dimensional structures of compounds 9, 12-octadecadeionic acid, 9-octadecenoic acid and Stigmast-5-en-3-ol were downloaded in .sdf format from Pubchem database. Hydrogen Bonds were added and the energy was minimized using CHARMm force field. Molecular weight, log *P* and number of Hydrogen-bond donors and acceptors for the active principles were observed. All the molecules were tested for Lipinski's drug properties and their two dimensional structures were used for docking.

Protein Preparation

The 3D structure files (Table 1) of the HIV receptor molecules were downloaded from Protein Data bank (PDB). The ligand and crystallographic water molecules were removed from the protein and the chemistry of the protein was corrected for missing hydrogen.

Crystallographic disorders and unfilled valence atoms were corrected using alternate conformations and valence monitor options. Following the above steps of preparation, the protein was subjected to energy minimization using the CHARMm force field.

Table 1. To retrieved the protein of HIV

S.NO	PDB ID	Protein Name
1	3ODU	Structure of the CXCR4 chemokine receptor
2	4MBS	Crystal Structure of the CCR5 Chemokine Receptor
3	3HI1	Structure of HIV-1 gp120 (core with V3)
4	2R5D	Structure of the gp41 N-trimer

This table shows the PDB ID and protein name.

Molecular Docking

Identification of binding cavity

After energy minimization, the binding pockets of the receptor were determined by using “eraser” algorithm using Accelrys Discovery Studio. The algorithm employed to remove the grid points outside the receptor and boundary was framed inside and outside the receptor to open the cavities of the receptor. Each such opened cavity region is identified as a possible binding site. A user-specified size cutoff used to remove sites smaller than the specified volume for further consideration.^[14]

Interaction and Scoring Functions

“LigandFit” protocol on Accelrys Discovery Studio was used to establish the interaction towards the receptor and ligand molecules. Site partitioning approach was followed to sample different parts of the larger binding site for docking. Docking between receptor and ligand was performed in the specified site.

As the result of docking 10 different conformations were obtained for all the compounds, but the top ranked scores among the list was copied from the table browser of the Accelrys Discovery Studio for further ranking and analysis.

The score values of the candidate ligand poses in the binding site are evaluated and prioritized according to the dock score function on the basis of force field approximation, Piecewise Linear Potential function (PLP) Steric and H-bonding intermolecular function, Higher PLP scores indicate stronger receptor-ligand binding (larger pKi values)^[4], LigScore1, LigScore2, Potential of Mean Force (PMF) PMF(developed based on statistical analysis of the 3D structures of protein-ligand complexes, scores are calculated by summing pairwise interaction terms over all interatomic pairs of the receptor-ligand complex, A higher score indicates a stronger receptor-ligand binding affinity)^[8,9] and Jain scores JAIN(sum of five interaction terms namely lipophilic interactions, polar attractive interactions, Polar repulsive interactions, Solvation of the protein and ligand, An entropy term for the ligand).^[5]

RESULTS AND DISCUSSIONS

Molecular docking continues to hold greater promise in the field of computer based drug design which screens small molecules by orienting and scoring them in the binding site of a protein. Interaction and binding energies are the important aspect of molecular docking^[11] which allows ranking the molecules and screening out the low binding or non binding molecules.

The plant *pedalium murex l* was reported for good anti microbial activity^[12] was selected and 23 chemical constituents were identified through GC-MS technique. Four receptor molecules (Table 1) were selected for this study was docked and the Ligand-docking score was compared (table 2).

After docking process the validation of result was carried to select an inhibitor which suitable for all the given receptor molecules. From this result, a suitable multi target inhibitor was selected, 9, 12-octadecadienoic acid had Dock score-12.205 with 2RD5 (3-Hydrogne bonds) shown in the figure1, dock score 26.75 with 3ODU (1-Hydrogne bond) and dock score 31.885 with 3HI4 (1-Hydrogne bond), in the mean time 9, 12-octadecadienoic acid had low dock score 8.89 with 4MBS but possess 3 Hydrogen bonds was also considered to be a inhibitor because H-bond interaction towards the receptor and lower the bond length are two important criteria which support good interaction of the ligand-Receptor complex.^[15]

There was no conformational pose found for tetradecanoic acid, propenoic acid and stigmast-5-en-3-ol. The different scoring and binding energies of the compounds were shown in the table 2.

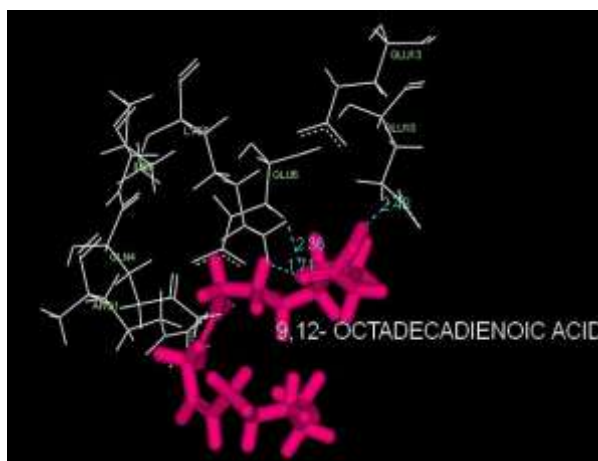


Fig 1: Compound 9, 12-octadecadienoic docked with gp41 N-trimer protein.

Hydrogen bonds are visible with bond length in green color.

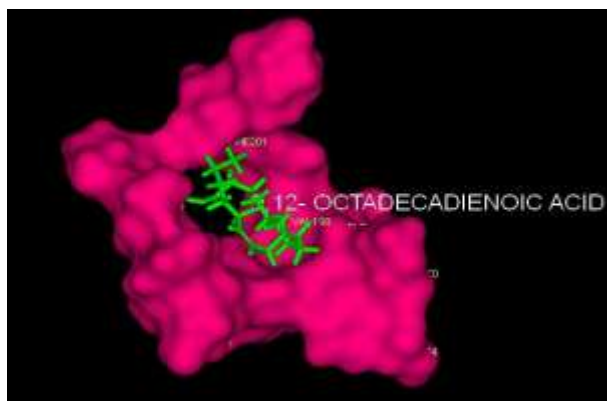


Fig 2. CXCR4 chemokine receptor docked with 9, 12-octadecadienoic acid.

It shows surface area of CXCR4 protein is pink color and ligand is green color.

Hydrogen Bonds Profiles

The hydrogen bonds formed between the compounds and receptor molecules were shown in the figure 1. The more number of H-bond interaction towards the receptor and lower the bond length are two important criteria which support good interaction of the ligand-receptor complex.^[15] The participating atoms of the amino acids and ligand molecule are shown in the table 3.

Table 2. Summary of docking information of the Top ranked poses of compounds

S. No	Compound with Protein PDB ID	Lig_score 1	Lig_score 2	-PLP1	-PLP2	JAIN	-PMF	Dock Score
1	9,12-octadecadienoic acid-2RD5	2.22	2.51	24.33	26.24	-2.91	46.1	12.205
2	9,12-octadecadienoic acid-3ODU	1.68	3.78	24.9	21.91	-2.51	85.75	26.75
3	9,12-octadecadienoic acid-3HI4	1.78	3.24	69.84	69.32	-0.55	16.81	31.885
4	9-octadecadienoic acid-4MBS	1.76	1.16	48.15	53.81	3.36	91.29	8.89

Table 3. Hydrogen Bond interactions between the receptor and the ligand

S.No	Compound with Protein PDB ID	Hydrogen bonds with atom	Ligand Atom	Distance Length (Å)
1	9,12-octadecadienoic acid-2RD5	LYS8:HZ1	O2	2.36
		LYS8:HZ3	O2	1.71
		GLU10:OE1	H52	2.48
2	9,12-octadecadienoic acid-3ODU	SER263:OG	H52	1.82
3	9,12-octadecadienoic acid-3HI4	LYS117: O	H52	2.07
4	9-octadecadienoic acid-4MBS	ARG 126:HH22	O2	2.06
		ARG 140:HH12	O1	2.48
		ARG140:HH22	O2	2.11

This table shows interaction of protein and ligand formed hydrogen bonds with atoms.

CONCLUSION

Molecular docking plays a vital role in ligand screening and lead molecule identification against target receptor; the same technique was carried out to find effective inhibitor towards CXCR4 chemokine receptor, CCR5 Chemokine Receptor, HIV-1 gp120 and gp41 N-trimer receptors. In this present study 9, 12-octadecadienoic acid and 9-octadecadienoic acid had good binding affinity towards selected receptors and found to be more suitable inhibitor molecules. Thus 9, 12-octadecadienoic acid and 9-octadecadienoic acid can be treated as a potential inhibitor of HIV receptors, thus can be considered as a good drug for AIDS and suggested for further clinical testing.

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