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Insilico predictions of inhibitors of novel statin structural analogues with HMG-CoA reductase

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ABSTRACT

This paper deals to design a potent drugs for cardiovascular disorders in which HMG Co A is the main target. Objective of our study is to optimize the activity of statin group of drugs against HMG - CoA reductase. : Statin groups like Simvastatin, Lovastatin, Fluvastatin and Atorvastatin are selected for this study. Malegro Virtual Docking (MVD) was used for statin analogues have been designed on the basis of their closest interaction of the native co crystallized protein ligand. All statin analogues have been showed with commercial software Malegro Virtual Docking trial version software and then docked against the target enzyme 1HWA, 1CQP, 1HWI, 1HWKrespectively. Docking studies of designed statin analogues showed conformer generation on all molecules. Similar compounds having 4168, 4144, 158, and 5199conformers are Simvastatin, Lovastatin, Fluvastatin and Atorvastatin respectively. Statins were designed by interaction of hydrogen bond with their respective target site. A molecule showing highest hydrogen bond energy with target was considered as probable potent drug which further needs to be evaluated in laboratory.

Key words: Cardiovascular diseases, HMG-Co A, Statins, Docking studies, Hydrogen bonding.

INTRODUCTION

Hyperlipidemia induces various diseases such as coronary heart disease, which is leading to be a cause for death. In cardiovascular system arteries and veins are the transporters of oxygenated blood throughout the body. Disfunction of these blood vessels results in coronary heart disease [1].The most common reason for this disfunction is the deposition of cholesterol and fatty compounds, which clogs the vessel thus hindering blood supply in different organs of the body and causing strokes, angina attack, hypertension and other cardiovascular disorders [2]. Researchers shows that smoking, alcohol consumption, excessive coffee intake, obesity, prolonged stress state, lack of exercise, diabetic condition are some of the risk factors that increase the chances of different cardiovascular disorders, however are curable and can be controlled [3,4].Currently Statins are almost exclusively used to decrease lipid profiles through inhibiting 3- hydroxyl -3- methyl glutaryl coenzyme A reductase (HMG Co A), a rate limiting enzyme in cholesterol biosynthesis pathway [5]. This reductase catalyses the conversion of HMG-CoA into

mevalonate, which further get converted to isopentenyl pyrophosphste, farnesyl pyrophosphate, squalene, lanosterol and finally to cholesterol [6]. Thus HMG-CoA reductase is identified as the initial rate determining factor in cholesterol biosynthesis thus considered as a target widely accepted for drug development studies of cardiovascular disease [7]. Statin inhibitors are taken for study where statin as a class of drugs used for cholesterol biosynthesis inhibition by inhibiting the activity of HMG-CoA reductase [8]. The HMG-CoA reductase inhibitors have different pharmacokinetic properties and are metabolized differently [9]. The *Insilico* approach for predicting the structure of novel molecules that can inhibit the activity of the disease causing molecule is called as computer aided drug design. This prediction can be done either by keeping in consideration the structure of the disease causing molecule which is often a protein that is called the structure based approach of drug design or by structural analysis of previously known drug molecules that is called analogue based approach of drug design. In this study we optimize the activity of statin group of drugs against HMG - CoA reductase by using four statin molecules. Statins were designed by interaction of hydrogen bond with their respective target site, a molecule showing highest hydrogen bond energy with target was considered as probable potent drug which further needs to be evaluated in laboratory.

EXPERIMENTAL SECTION

A molecule of HMG-Co A reductase with known crystal structure of four chains has been identified and down loaded from the National Centre for Biotechnology and the detail pertaining to the molecular properties of these compound structures has been calculated in detail using the Power MV tool. The inhibitors of the target HMG CoA reductase has been identified as statin groups like Simvastatin, Lovastatin, Fluvastatin and Atorvastatin. These compounds were identified to bind HMG-CoA reductase enzyme according to the statistics of the Protein Data Bank (PDB). The PDB structures were identified and downloaded from http://www.rcsb.org//pdb server with PDB ID include 1CQP, 1HWI, 1HW9 and 1HWK respectively. From the analysis of LIGPLOT obtained from PDBsum, which informs about interaction between ligand and target molecule.

The analysis of ligand protein contacts used is based upon the surface complementarity approach developed (R). The complementarity function there in is defined as

$CF = S_l – Si$ -- E

Where
S_{1-} is the sum of all surface areas of legitimate atomic contacts between ligand and receptor.
Si – is the sum of all surface areas of illegitimate atomic contacts and E is the repulsion term [10]. Legitimacy may depend on the hydrophobic and hydrophilic properties of the contacting atoms. Compare the molecular interactions on the basis of the docking results. The docking of the statin groups to the respective target is done using the Molegro Virtual Docking trial version software.

Preparing statin group molecules
In order for the Molegro Virtual Docking (MVD) to be able to perform optimally, the nucleus in the workspace must be properly prepared before the docking begins. The molecule can either be prepared intently in MVD (or) externally by another program (e.g. MOE from CCG or MASTERO from Schrödinger).

Docking
MVD trial version software has been used for docking. Docking is the study for prediction of protein ligand interactions. The docking is based on the identifying the correct poses, ligand energy, Vanderwaals interaction and hydrogen bonding.

RESULTS AND DISCUSSION

The docking study result showed that molecular interaction of statin group with the target 1HW9 ,(Simvastatin) , 1HWI, (Fluvastatin), 1CQP (Lovastatin), 1HWK (Atorvastatin) complex of the catalytic portion of human HMG Co A reductase with statin groups. It was observed that the amino acids are classified as hydrogen bond interaction and other non-covalent interactions. The following table no 1-4 and figure no 1-4 showed hydrogen bond interactions of statin groups binding to the A, B, C and D domains of the target site. Ligand protein contacts are derived with the LPC software [11]. Molecular interaction analysis revealed hydrogen bond interaction in the following manner

Simvastatin has 9 interactions, Lovastatin has 1 hydrogen bond interaction , Fluvastatin has 8 hydrogen bond interaction and Atorvastatin has 10 hydrogen bond interaction .

Table no1: Hydrogen bond interaction for Simvastatin binding to C and D domain

S.No	Start Atom and residue	End Atom and Residue	Distance(Å)
1	NH1 OF ARG 590(C)	O3 OF SIMVASTATIN	3.04
2	NH2 OF ARG 590(C)	O3 OF SIMVASTATIN	2.98
3	CD2 OF ASP 690 (C)	O3 OF SIMVASTATIN	2.92
4	NZ OF LYS 735 (D)	O1A OF SIMVASTATIN	2.87
5	NZ OF LYS 62 (C)	O1BOF SIMVASTATIN	3.18
6	OG OF SER 684 (C)	O1BOF SIMVASTATIN	2.63
7	CE OF GLU 559 (D)	O5 OF SIMVASTATIN	2.87
8	ND2 OF ASN 755 (D)	O5 OF SIMVASTATIN	2.65
9	NZ OF LYS 691 (C)	O5 OF SIMVASTATIN	3.08

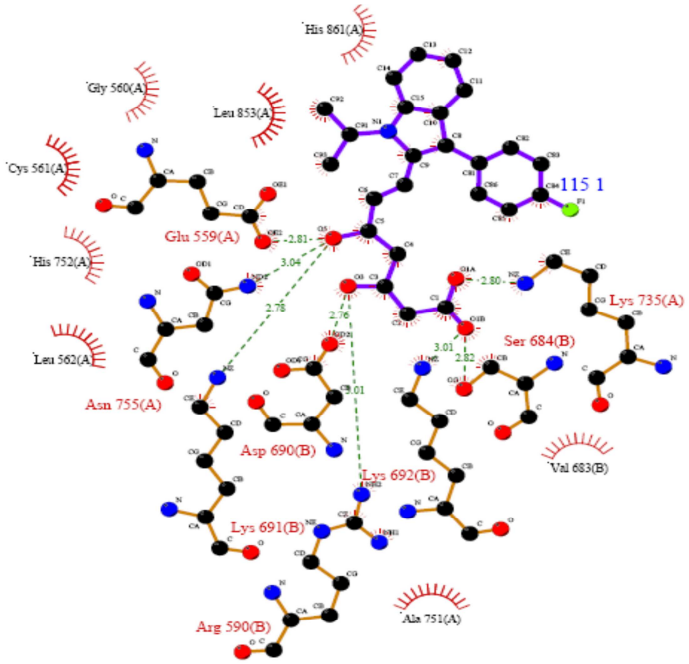


Figure no 1: Interaction of Simvastatin with the target 1HW9 (Complex of the catalytic portion of human HMG-Co a reductase with simvastatin)

Table no 2: Hydrogen bond interaction for Fluvastatin binding to A and B domain

S .No.	Start Atom and residue	End Atom and Residue	Distance(Å)
1	OE2 OF GLU 559(A)	O5 OF FLUVASTATIN	2.81
2	ND2 OF ASN 755(A)	O5 OF FLUVASTATIN	3.04
3	NZ OF LYS 691(B)	O5 OF FLUVASTATIN	2.78
4	NH2 OF ARG 590(B)	O3 OF FLUVASTATIN	5.01
5	OD2 OF ASP 690(B)	O3 OF FLUVASTATIN	2.76
6	OG OF SER 684(B)	O1B OF FLUVASTATIN	2.82
7	NZ OF LYS 692(B)	O1B OF FLUVASTATIN	3.01
8	NZ OF LYS 735(A)	O1A OF FLUVASTATIN	2.8

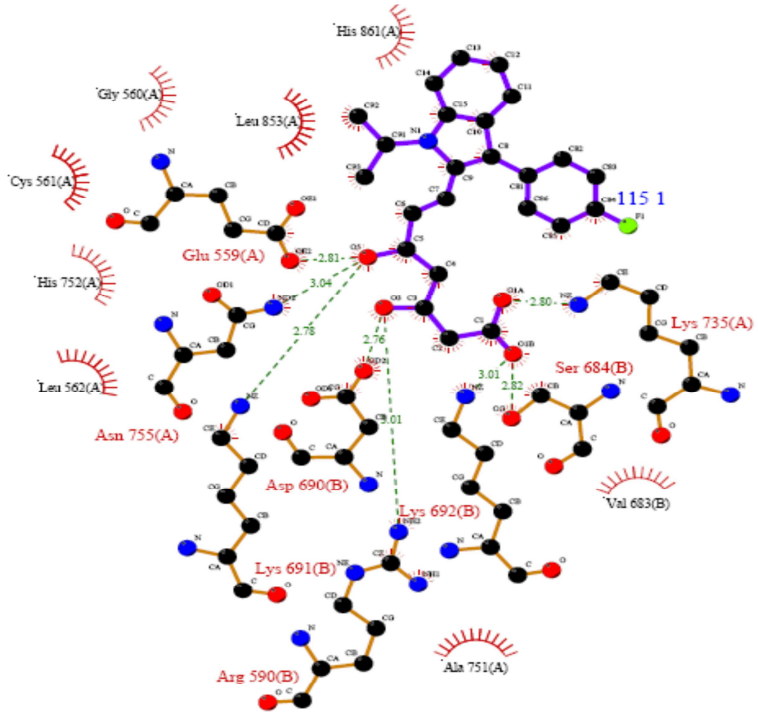


Figure no 2: Interaction of Fluvastatin with the target 1HWI (Complex of the catalytic portion of human HMG-CoA reductase with fluvastatin)

Table no 3: The hydrogen bond interactions for Lovastatin binding to the A and B domains of the target

S.No.	Start Atom and residue	End Atom and Residue	Distance(Å)
1	OH OF TYR 257(A)	O1 OF LOVASTATIN	2.42

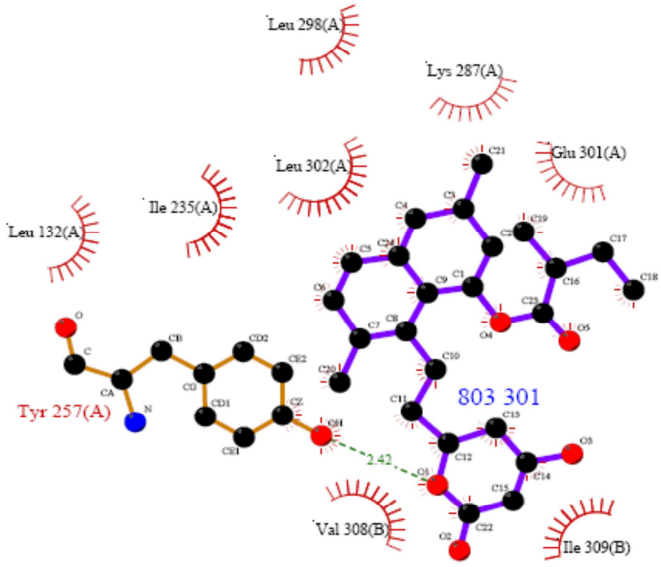


Figure no 3: Interaction of Lovastatin with the target 1CQP (Crystal structure analysis of the complex LFA-1 (CD11A) I Domain / Lovastatin at 2.6 a resolution)

Table no 4: The hydrogen bond interactions for Atorvastatin binding to the A and B domain

S.No.	Start Atom and residue	End Atom and Residue	Distance(Å)
1	OG OF SER 565(A)	O18 OF ATORVASTATIN	2.79
2	OG OF SER 661(B)	F1 OF ATORVASTATIN	3.17
3	NH2 OF ARG 590(B)	O3 OF ATORVASTATIN	2.91
4	OD2 OF ASP 690(B)	O3 OF ATORVASTATIN	2.74
5	NZ OF LYS 735(A)	O1B OF ATORVASTATIN	2.75
6	OG OF SER 684(B)	O1A OF ATORVASTATIN	2.61
7	NZ OF LYS 692(B)	O1A OF ATORVASTATIN	3.12
8	OE2 OF GLU 559(A)	O5 OF ATORVASTATIN	2.87
9	ND2 OF ASN 755(A)	O5 OF ATORVASTATIN	3.14
10	NZ OF LYS 691(B)	O5 OF ATORVASTATIN	2.88

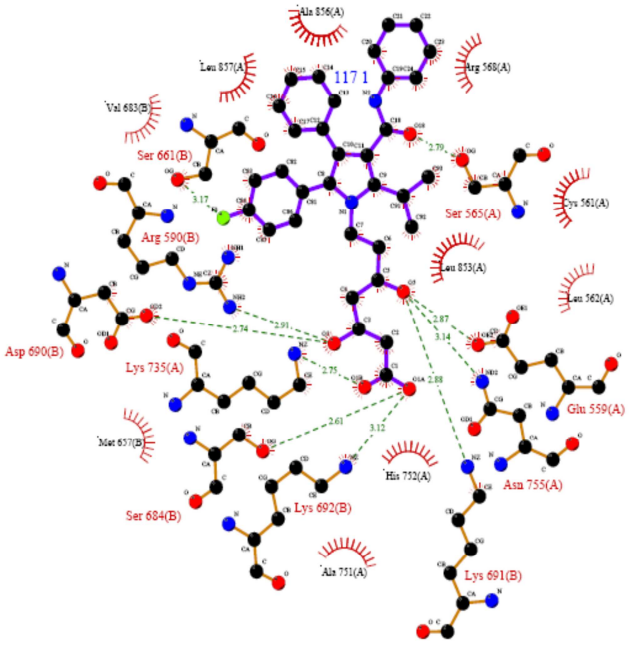
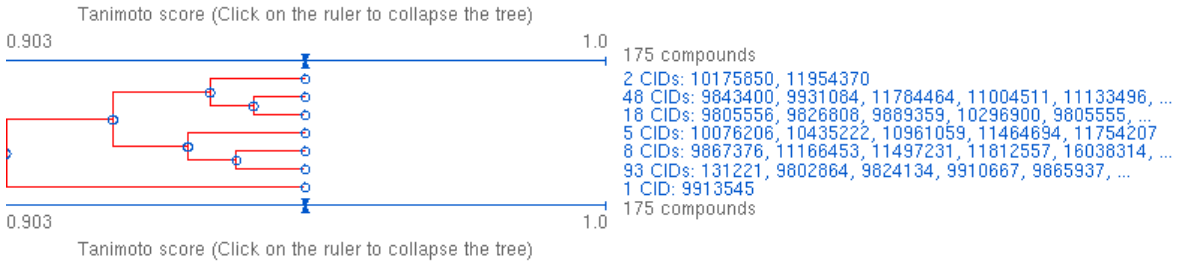


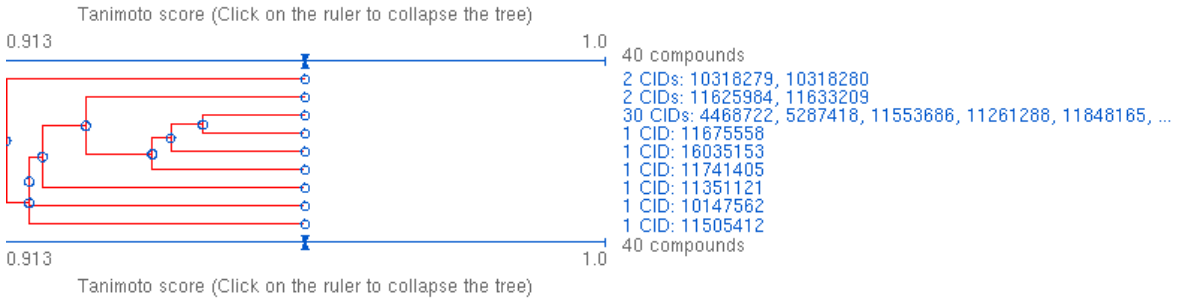
Figure no 4: Interaction of Atorvastatin with the target 1HWK (Complex of the catalytic portion of human HMG-COA reductase with atorvastatin)

Pubchem similarity searches done on a data base approximately 1.3 million compound structures both virtual as well as in stock. The pharmacophoric search result showed that 175 compound similar to Simvastatin, 40 compounds for Fluvastatin, 216 compounds for Lovastatin and 237 compounds for Atorvastatin. These similar compound structures are converted to this 3D format that it becomes suitable for clustering as well as docking. To evaluate the clustering studies details pertaining to the chemical space and the docking results further contradict the level of diversing of the compounds in the chemical space the following clustering data for each statin has been shown in figure -5.

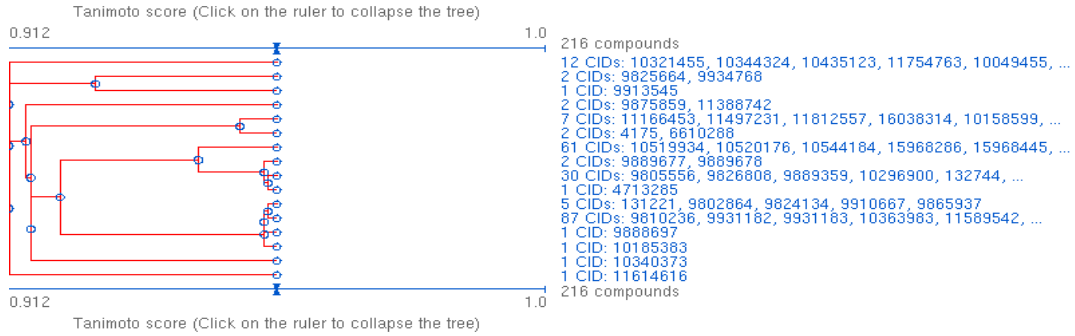
Figure no 5: Clustering Data for Statin groups



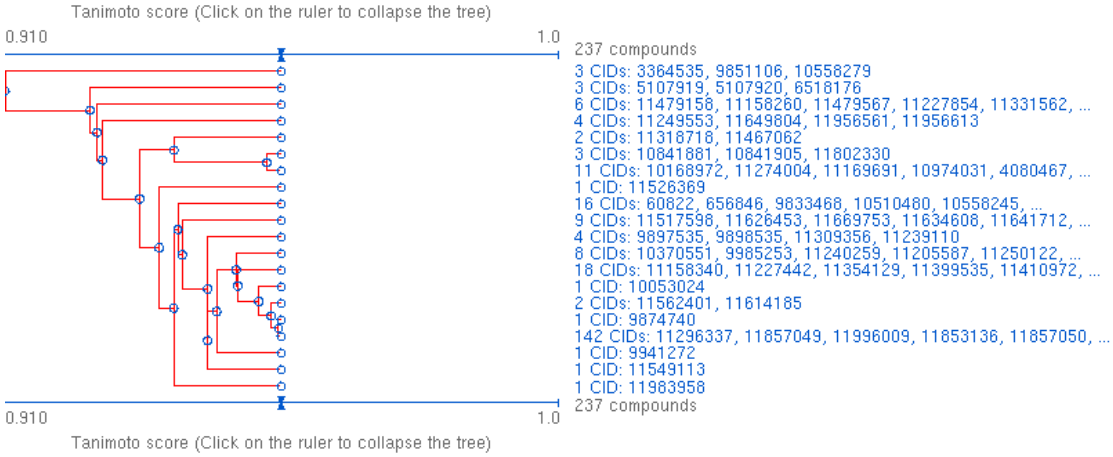
Simvastatin clustering data



Fluvastatin clustering data



Lovastatin clustering data



Atorvastatin Clustering data

The graphical analysis showed in the form of diagrams was a clear indication of the selection pattern. The following figures 6-9 indicated the hydrogen bonding interaction with molecular ID of each statin molecule.

Figure no 6: Hydrogen bond Vs Mol ID (Simvastatin)

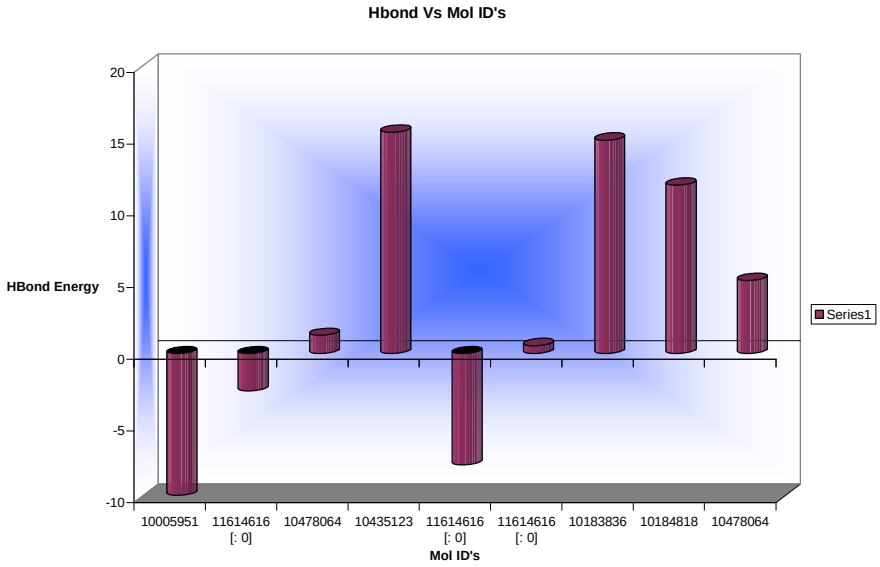


Figure no 7: Hydrogen bond Vs Mol ID (Fluvastatin)

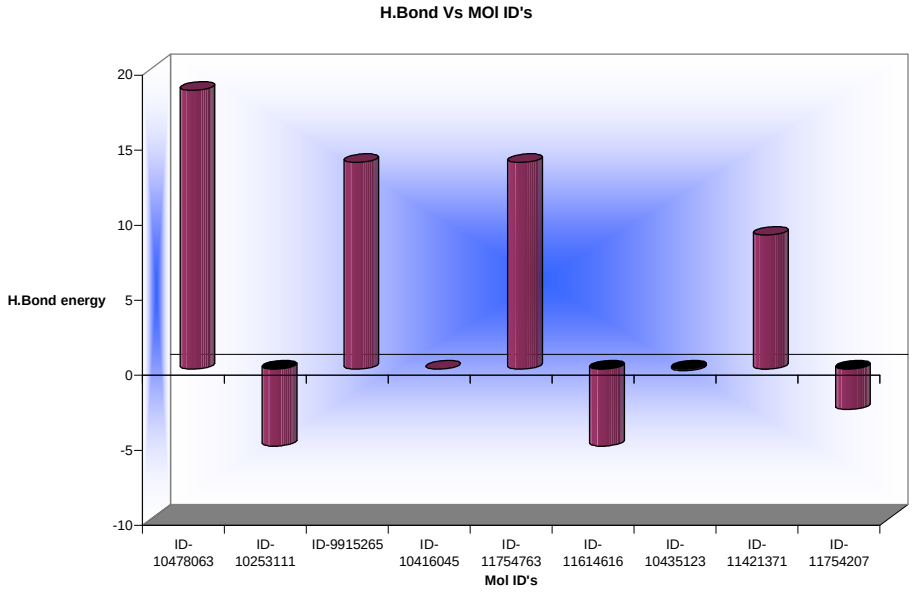


Figure no 8: Hydrogen bond Vs Mol ID (Lovastatin)

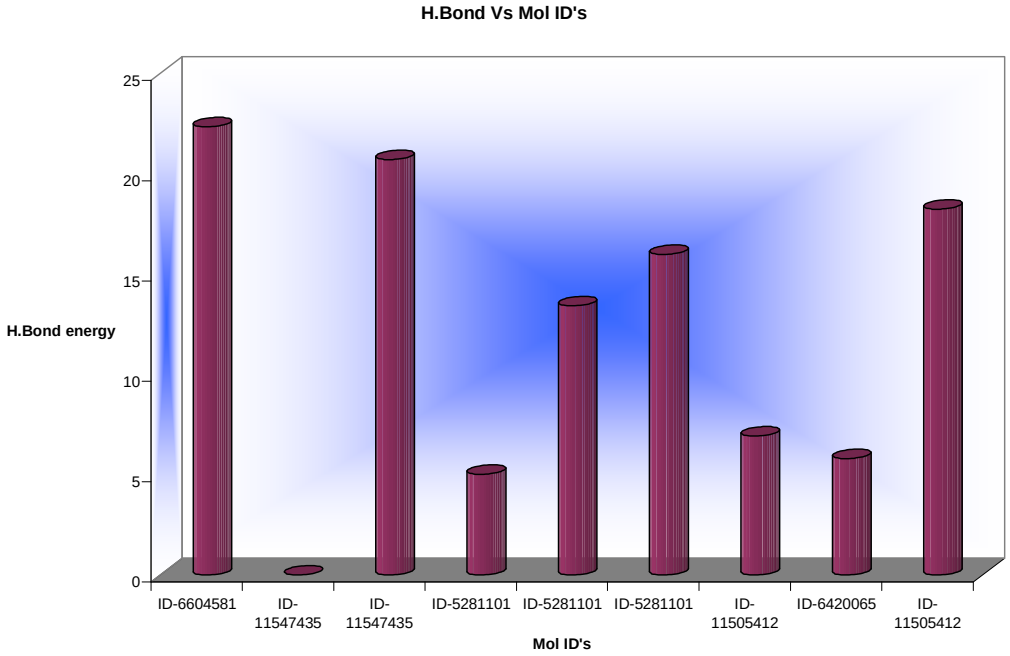
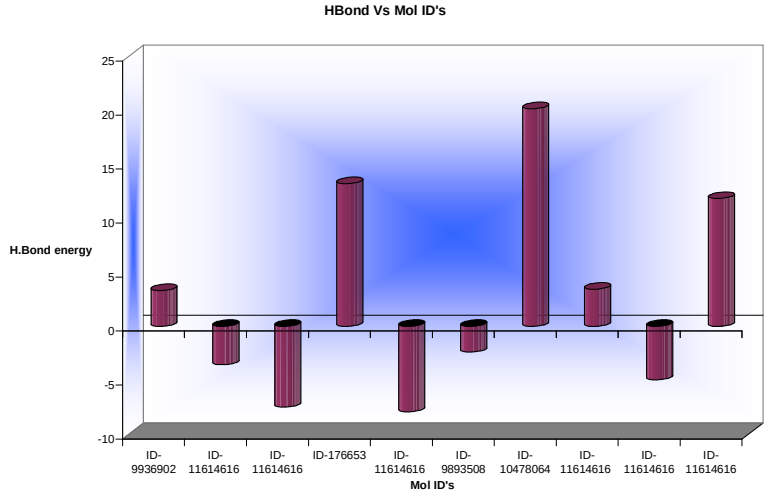


Figure no 9: Hydrogen bond Vs Mol ID (Atorvastatin)



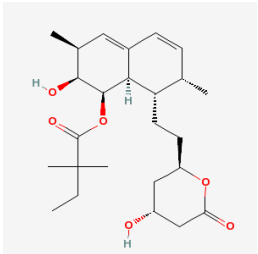
The docking results showed in all statin groups had negative affinity energy and share a high negative energy with minimum electro static energy of zero. For Simvastatin molecules showed H bond energy of 1.23and 31 heavy atom and a molecular weight of 434.566 which is clearly less than 500 and gets classified as drug like molecule. For Lovastatin the molecular weight of 592.997 which is slightly more than 500 and would be made acceptable as a drug candidate if slight modification in its side chain are made after the first study of bioactivity. For Fluvastatin the molecular weight of 613 which is clearly greater than 500 hence in later stages of drug development the molecule levels to be refined before it enters the pre clinical trials. For Atorvastatin, the molecular weight of 540.644 which is slightly higher than and levels to be refined to make less than 500 so that drug likes properties are satisfied. The docking validation results were reported in table-5.

Table no 5: Docking validation result for statin groups

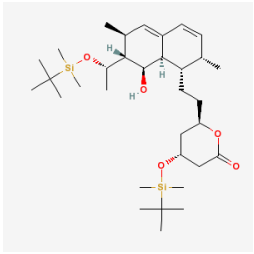
Compound name	Ligand	Affinity	Protein Vdw	H-bond	Molecular weight	Docking score
Simvastatin	10478064	-229.105	603.653	1.2783	434.566	9993.8
Lovastatin	10416045	-314.13	500.15	0	592.997	9994.1
Fluvastatin	11505412	-243.578	942.025	18.2323	613.653	7384.39
Atorvastatin	9893508	-254.245	526.597	-2.3821	540.644	9995.69

The docking interpretation was obvious that the molecular compounds structures that had good *Insilico* presence for the suit of target have to be refined to fit the LIPINRKI barrier as well as be a good drug candidate in the drug discovery cycle. The above mention molecular compounds structures were shown in figure -10.

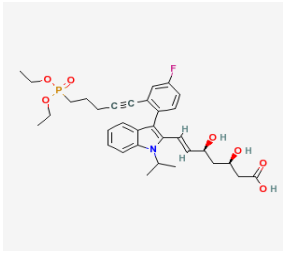
Figure no 10: Structure and Mol ID of refined Statin groups



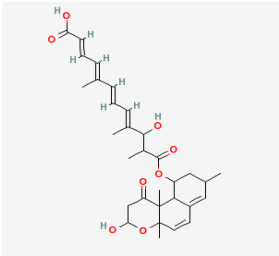
10478064.mol



10416045.mol



11505412.mol



9893508 .mol

CONCLUSION

Computer aided drug design is no longer merely a promising techniques. It is a practical and realistic way of helping the medicinal chemistry. Still drugs must be synthesized and tested by the computational techniques can contribute a clear molecular rationale and above all provide a spur to the imagination. The need to perform not only lead identification but also even optimization as well as lead validation is of extreme importance. Binding affinity optimization was done by *Insilico* designing of structural analogues of statin and predicting their interactions with HMG CoA target by docking studies. Statin structural analogues has shown positive results in docking validation analysis and has shown best binding affinity with target.

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