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In Silico Investigation on Lovastatin Derivatives against HMGCoA Reductase

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Abstract: -

Background: Hyperlipidemia is a condition where the body has increased levels of lipids, or lipoproteins. Our bodies' main circulating lipid particle is cholesterol. The Mevalonate pathway is the biosynthetic route used for cholesterol, and it is found in the liver.[1] This Mevalonate pathway results in cholesterol. The manufacture of cholesterol is aided by a number of enzymes. A variety of enzymes, including HMG-CoA synthase, HMG-CoA reductase, Farnesyl PP synthase, Lanosterol synthase, and Squalene synthase.[2] The cholesterol-lowering drug lovastatin was first discovered in a strain of *Aspergillus terreus* with the chemical formula $C_{24}H_{36}O_5$ and IUPAC Name: (1S,3R,7S,8S,8aR)-8-{2-[(2R,4R)-4-Hydroxy-6-oxotetrahydro-2H-pyran-2-yl]ethyl}-3,7-dimethyl-1,2,3,7,8,8a-hexahydro-1-naphthalenyl (2S)-2-methylbutanoate.[3] In persons who have heart disease or who are at risk of developing heart disease(cardiovascular disease), lovastatin, a popular HMG-CoA reductase inhibitor, is used along with diet, weight loss, and exercise to lower the risk of heart attack and stroke and to lower the likelihood that heart surgery would be required.[4] Due to adverse effects of lovastatin, such as a consistent rise in serum ALT and AST, GI distress, and dizziness, a new lovastatin derivative with limited adverse effects and high efficacy is required.[5]

Objective: The goal of the current research employed computational methods like docking and in silico ADMET analysis to identify novel lovastatin derivative compounds as HMG-CoA reductase inhibitors with a higher binding affinity as compared to the standard drug lovastatin.

Methods: Virtual screening was used to create molecules, which were then molecular docked with all developed compounds and subjected to ADMET analysis on compounds that were successful.

Results: Utilising virtual screening, compounds were created, and AutoDock Vina 1.5.6 was used for molecular docking in the lovastatin binding site (PDBID: 7CPX) (The active site of HMG-CoA reductase).[6] Seven powerful hits from docking studies were subjected to SwissADME's ADME analysis. Seven substances with the best ADME profiles and greater bioavailability were predicted by ADME analysis.

Conclusion: Exploring the fields of computational and medical research will be made possible by this research work in great detail. Due to this, future experimental investigations with HMGCoA reducatse inhibitors will be made easier to develop.

Keywords: Hyperlipidemia, HMG-CoA reductase inhibitors, Lovastatin, Mevalonate pathway HMG-CoA synthase, docking studies, ADME.

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Graphical Abstract

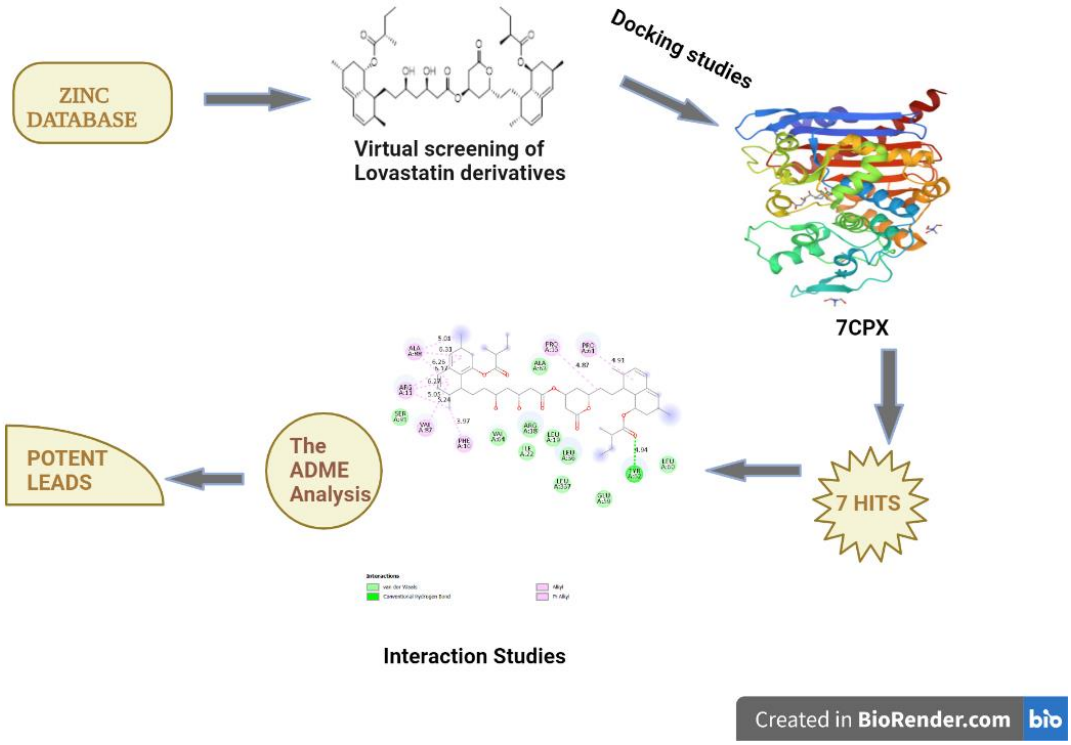


Fig 1: Graphical Abstract

Abbreviation

Abbreviations

ADME = Absorption Distribution Metabolism Excretion Toxicity

PDB = Protein data bank

RMSD = Root mean square deviation

H-Bond = hydrogen bond

BBB = Blood brain barrier

GI = Gastro Intestinal

Log P = Partition co-efficient

Introduction

Hyperlipidemia, also known as hypercholesterolemia is an abnormal rise in our body's lipid or lipoprotein levels. Typically, blood lipid levels rise. A lipid that circulates in our blood is called cholesterol. When the level of cholesterol in the blood rises, it is known as hypercholesterolemia.[7] Since cholesterol is insoluble in water, it is carried in the blood plasma together with other lipoproteins.There are several types of lipoproteins, including Very Low Density Lipoprotein (VLDL), Low Density Lipoprotein (LDL), High Density Lipoproteins (HDL), and Intermediate Density Lipoprotein (IDL).[8]

All lipoproteins carry cholesterol, and LDL cholesterol, sometimes known as bad cholesterol, is typically dangerous. Atherosclerosis and coronary heart disease are both recognised to be caused by it. The liver produces the majority of the cholesterol in our bodies through internal synthesis.[9] Genetic influence and nutritional factors are additional causes. The body uses cholesterol for a variety of processes, including the absorption of lipids and hormones including cortisol, oestrogen, progesterone, and testosterone. In the presence of sunlight, cholesterol aids in the creation of vitamin D.[10] It is crucial for giving cell membranes structural support, acts as an antioxidant, and aids in nerve impulse transmission.

Lovastatin is a medication used to lower cholesterol levels by inhibiting the enzyme HMG-CoA reductase, which is responsible for the biosynthesis of cholesterol in the liver. In silico investigation involves the use of computer-based methods to simulate and analyze the interactions of small molecules, such as lovastatin derivatives, with target proteins such as HMG-CoA reductase.[11]

One approach to in silico investigation is molecular docking, which predicts the binding mode and affinity of a ligand to a receptor by evaluating the conformational space of the ligand and receptor and estimating their interaction energies. In the case of lovastatin

derivatives, molecular docking can be used to predict their binding modes and affinities to HMG-CoA reductase and identify potential structural modifications that may enhance their binding and inhibitory potency.[12]

Another approach is molecular dynamics simulation, which models the dynamic behavior of a ligand-receptor complex over time by solving the equations of motion for the atoms and molecules in the system. Molecular dynamics simulation can provide insights into the flexibility and stability of the complex and the specific molecular interactions that contribute to its stability or instability.

Furthermore, in silico investigation can also involve quantitative structure-activity relationship (QSAR) analysis, which correlates the structural features of a ligand to its biological activity.[14] QSAR analysis can be used to identify the key structural features of lovastatin derivatives that contribute to their inhibitory potency against HMG-CoA reductase, and to design and optimize new derivatives with improved activity.[15]

Overall, in silico investigation can provide valuable insights into the molecular mechanisms of lovastatin and its derivatives against HMG-CoA reductase, and can guide the design of new and more effective drugs for the treatment of hypercholesterolemia and related diseases.[16]

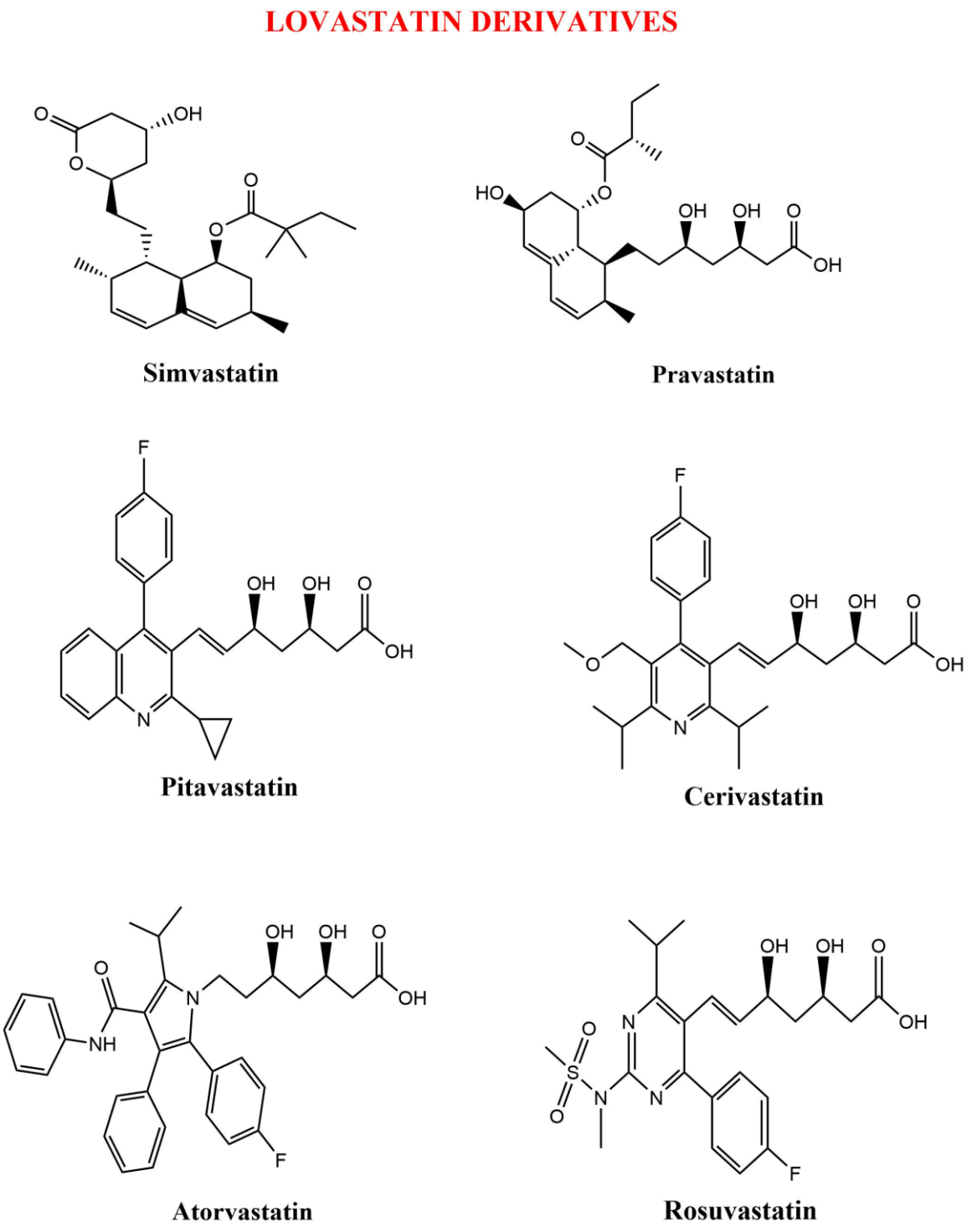


Figure 2: Structures of Lovastatin Derivatives

Methods & Materials

The most widely used method for swiftly identifying the most potent compounds from chemical libraries and screening molecular libraries is in-silico docking.[17] The AutoDock tool Vina 1.5.6 software analyses enzymatic inhibition in terms of binding affinity (Kcal/mol), and the molecules are then evaluated in relation to the best-docked conformation binding affinity score.[18] The ChemBiodraw extreme and ChemBiodraw 3D programmes were used to build the 2D and 3D structures of the chemicals obtained from the ZINC database. The MM2 approach was used to reduce each molecule's energy and increase performance.[19] Additionally, using the AutoDock Vina interface, the derivatives were converted into a readable format. Todiscover HMG-CoA reductase inhibitors, the protein with PDB ID 7CPX was picked and obtained from the protein data bank. Pymol and the Biovia Discovery Studio Visualizer were used to analyse the results of the compounds to reveal the interactions that disclosed the chemical's poses.[20]

COMPUTATIONAL DETAILS

Virtual screening of potential molecules

To build a library of potential molecules having a natural origin, the ZINC small molecule database was searched for commercially accessible chemicals. The ZINC database (www.zinc.docking.org) was used to find 40% of comparable structures, and molecules were downloaded in the structural database file (.sdf) format. Then, Marwin view 18.22 was used to open the zinc database (.sdf) file.[21]

Ligand Preparation

To determine which lovastatin derivative had the highest binding affinity, a library of those compounds was tested. The 2D structures were then created using ChemBioDraw 2D software. Using the ChemBioDraw 3D programme, the ligands were also transformed into three-dimensional structures. Finally, the ligands were saved as.pbd files so that the Autodock Vina software1.5.6 application could examine them.[22]

Validation of Protein for Docking

The ligand structure was determined from the protein (.pdb) file 1Z95 and repeatedly docked with the binding site. The root mean square deviation (RMSD) in the redocked binding sites with the ligands' atoms and crystallographic conformations was used to evaluate the approach's validity and reproducibility.

Molecular Docking Study

By using molecular modelling tools, the created compounds were further examined to identify the most effective HMG-CoA reductase inhibitors. Finding the binding site allowed for the production of the chosen protein, 7CPX.[24] The ligand (198501) was first removed from the protein before it was validated and saved in pdb format. Once again loaded in AutoDock Vina, the protein in pdb format was then prepared for docking investigation by eliminating water and other unnecessary structures, replacing missing atoms, adding polar hydrogen, and finally adding the Kollman charges.[25] Additionally, ligand was created by removing it from the protein, adding the polar hydrogen, finding the root, and then turning it into a file with the pdbqt extension. Lastly, the grid box was generated by keeping the ligand as a centre.[26]

The configuration file “conf.txt” was prepared from the grid output file with the following parameters for x, y, and z co-ordinates as well as size

center_x = 27.744

center_y = 3.191

center_z = 7.791

size_x = 28

size_y = 22

size_z = 26

Additionally, the command "programme files the Scripps Research Institute, vina. exe -config conf.txt -log log.txt" was entered at the command prompt to perform molecular docking using the AutoDock Tool Vina. This created an output file with the docking score and binding affinity (kcal/mol). Similar to this, all proposed compounds were examined, and their binding affinities were tabulated.[27]

2D Interactions for Docking Results

The AutoDock Tool and command prompt were used to determine the binding affinity for each chemical. Seven compounds were discovered to be either equipotent or potent in relation to the commercially available medication Lovastatin after the docking findings were analysed. These seven substances were discovered to have the best binding scores, which fell between -9.2 and -8.7 kcal/mol. To analyse the interactions, these 7 substances were taken into account. The protein and ligand output pdbqt data were converted using Pymol software into pdb format, which was then fed into Discovery Studio Visualizer to produce the 2D interaction file.[28]

ADME and Toxicity Analysis for the Identification of Lead Compounds

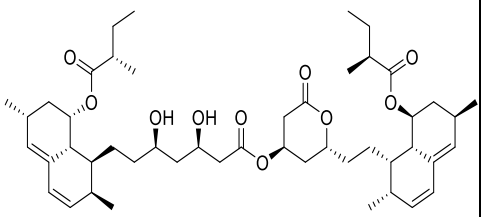
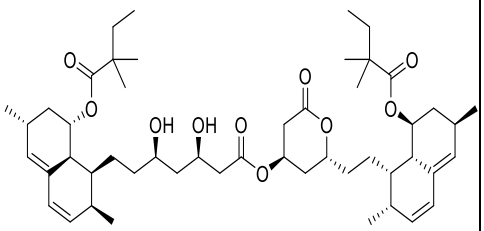
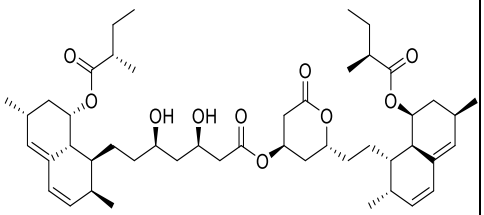
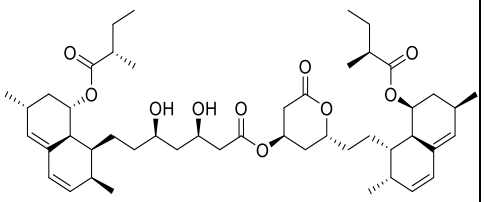
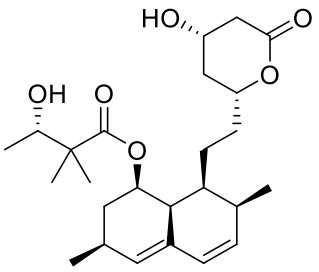
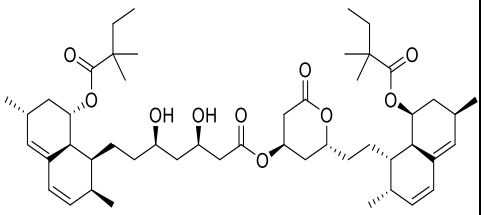
The SwissADME service at http://www.swissadme.ch further screened and assessed each of these hit compounds. Initially, ChemDraw 2D was used to transform each compound into the corresponding smiles ID, which was then copied into the SwissADME webpage. Then, using the BOILED-egg method, the results were predicted in terms of a variety of physicochemical properties, including p-glycoprotein interactions, the Lipinski rule of 5 (drug-likeness), hydrogen bond acceptors, and donors. They were also predicted in terms of drug penetration through the blood-brain barrier and gastrointestinal absorption.[29]

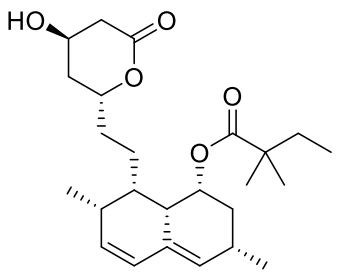
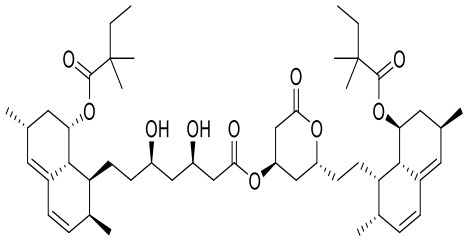
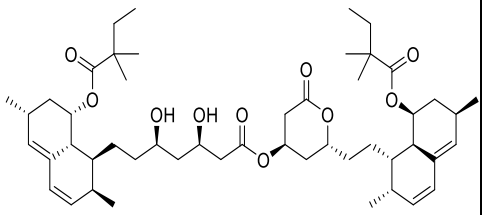
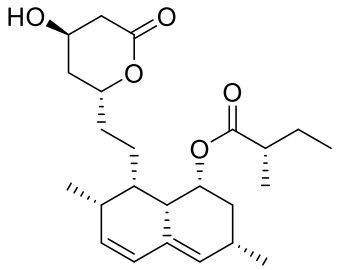
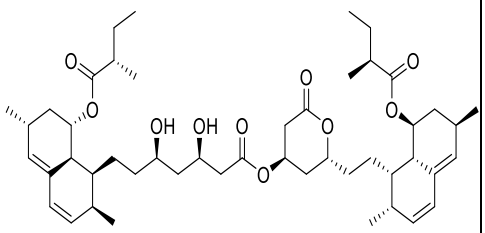
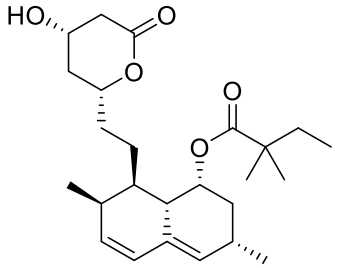
Results

Virtual Screening & Molecular Docking

Initially, a library was created employing a total of 100 designed compounds (EB1-EB100). Then, using the programme AutoDock Vina 1.5.6, molecular docking was carried out at the HMG-CoA reductase active site (PDBID: 7CPX) (lovastatin binding site). The free binding energies reported in kcal/mol for each chemical were examined. When compared to the commercially available drug lovastatin **(binding score -7.0 Kcal/mol),** 7 compounds were shown to exhibit either powerful or equipotent action (binding affinity -9.2 to -8.6 Kcal/mol). Additionally, study showed that compound EB-32 had the highest activity when compared to the reference medication lovastatin (binding affinity = -7.0 kcal/mol). Table 1. To ascertain the interaction with the amino acids of protein given in Table 2 and the top 7 compounds. These seven substances were discovered to be stable in the target receptor's binding pocket with close-by scoring function.

Table 1: The binding affinities of 15 out of the 100 newly discovered compounds

S. NO	Compound Code	Zinc ID	Smiles ID	Structure	Binding Affinity (kcal/mol)
1.	EB-32	ZINC000299872136	CC[C@H](C)C(=O)O[C@H]1C[C@@H](C)C=C2C=C[C@H](C)[C@H](CC[C@@H]3C[C@@H](OC(=O)C[C@H](O)C[C@H](O)CC[C@H]4[C@@H](C)C=CC5=C[C@H](C)C[C@H](OC(=O)[C@@H](C)CC)[C@@H]54)CC(=O)O3)[C@@H]21		-9.2
2.	EB-98	ZINC000299872132	CCC(C)(C)C(=O)O[C@H]1C[C@@H](C)C=C2C=C[C@H](C)[C@H](CC[C@@H](O)C[C@@H](O)CC(=O)O[C@H]3CC(=O)O[C@H](CC[C@@H]4[C@H]5C(=C[C@H](C)C[C@@H]5OC(=O)C(C)(C)CC)C=C[C@@H]4C)C3)[C@@H]21		-9.2
3.	EB-34	ZINC000249686648	CC[C@H](C)C(=O)O[C@H]1C[C@@H](C)C=C2C=C[C@H](C)[C@H](CC[C@@H](O)C[C@@H](O)CC(=O)O[C@H]3CC(=O)O[C@H](CC[C@H]4[C@@H](C)C=CC5=C[C@H](C)C[C@H](OC(=O)[C@@H](C)CC)[C@@H]54)C3)[C@H]21		-9.1
4.	EB-28	ZINC000299872134	CC[C@H](C)C(=O)O[C@H]1C[C@@H](C)C=C2C=C[C@H](C)[C@H](CC[C@@H](O)C[C@@H](O)CC(=O)O[C@H]3CC(=O)O[C@H](CC[C@H]4[C@@H](C)C=CC5=C[C@H](C)C[C@H](OC(=O)[C@@H](C)CC)[C@@H]54)C3)[C@@H]21		-8.9
5.	EB-35	ZINC000255988613	C[C@@H]1C=C2C=C[C@H](C)[C@H](CC[C@@H]3C[C@H](O)CC(=O)O3)[C@@H]2[C@H](OC(=O)C(C)(C)[C@H](C)O)C1		-8.7
6.	EB-47	ZINC000299872133	CCC(C)(C)C(=O)O[C@H]1C[C@@H](C)C=C2C=C[C@H](C)[C@H](CC[C@@H](O)C[C@@H](O)CC(=O)O[C@H]3CC(=O)O[C@H](CC[C@H]4[C@@H](C)C=CC5=C[C@H](C)C[C@H](OC(=O)C(C)(C)CC)[C@@H]54)C3)[C@@H]21		-8.7

7.	EB-49	ZINC000106106008	CCC(C)(C)C(=O)O[C@@H]1C[C@H](C)C=C2C=C[C@H](C)[C@H](CC[C@@H]3C[C@@H](O)CC(=O)O3)[C@@H]21		-8.7
8.	EB-27	ZINC000299872131	CCC(C)(C)C(=O)O[C@H]1C[C@@H](C)C=C2C=C[C@H](C)[C@H](CC[C@@H]3C[C@@H](OC(=O)C[C@H](O)C[C@H](O)CC[C@H]4[C@@H](C)C=CC5=C[C@H](C)C[C@H](OC(=O)C(C)(C)CC)[C@@H]54)CC(=O)O3)[C@@H]21		-8.6
9.	EB-42	ZINC000257373097	CCC(C)(C)C(=O)O[C@H]1C[C@@H](C)C=C2C=C[C@H](C)[C@H](CC[C@@H](O)C[C@@H](O)CC(=O)O[C@H]3CC(=O)O[C@H](CC[C@H]4[C@@H](C)C=CC5=C[C@H](C)C[C@H](OC(=O)C(C)(C)CC)[C@@H]54)C3)[C@H]21		-8.6
10.	EB-66	ZINC000043772723	CC[C@H](C)C(=O)O[C@@H]1C[C@H](C)C=C2C=C[C@H](C)[C@H](CC[C@@H]3C[C@@H](O)CC(=O)O3)[C@@H]21		-8.6
11.	EB-84	ZINC000299872135	CC[C@H](C)C(=O)O[C@H]1C[C@@H](C)C=C2C=C[C@H](C)[C@H](CC[C@@H](O)C[C@@H](O)CC(=O)O[C@H]3CC(=O)O[C@H](CC[C@@H]4[C@H]5C(=C[C@H](C)C[C@@H]5OC(=O)[C@@H](C)CC)C=C[C@@H]4C)C3)[C@@H]21		-8.6
12.	EB-10	ZINC000003831450	CCC(C)(C)C(=O)O[C@@H]1C[C@H](C)C=C2C=C[C@@H](C)[C@@H](CC[C@@H]3C[C@H](O)CC(=O)O3)[C@@H]21		-8.5

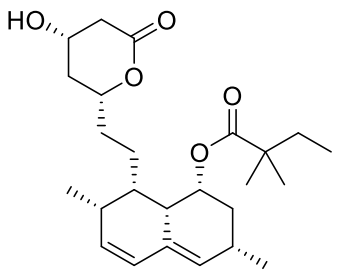
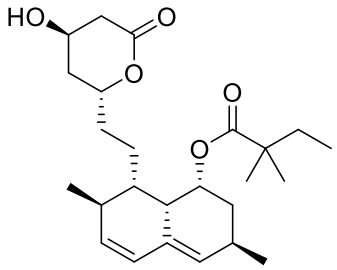
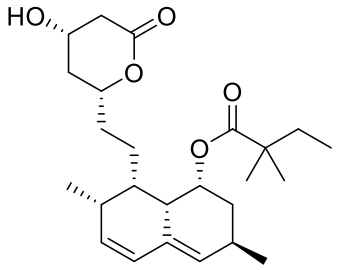
13.	EB-79	ZINC000043772732	CCC(C)(C)C(=O)O[C@@H]1C[C@H](C)C=C2C=C[C@H](C)[C@H](CC[C@@H]3C[C@H](O)CC(=O)O3)[C@@H]21		-8.5
14.	EB-20	ZINC001307301357	CCC(C)(C)C(=O)O[C@@H]1C[C@@H](C)C=C2C=C[C@@H](C)[C@H](CC[C@@H]3C[C@@H](O)CC(=O)O3)[C@@H]21		-8.4
15.	EB-70	ZINC000043772736	CCC(C)(C)C(=O)O[C@@H]1C[C@@H](C)C=C2C=C[C@H](C)[C@H](CC[C@@H]3C[C@H](O)CC(=O)O3)[C@@H]21		-8.4

Table 2: The binding affinity of best ligands along with their H-Bond interactions & other interactions with nearby protein residues in HMG-CoA reductase active pockets

Sr. No	Compound Code	H-Bond Interaction	π- π T shaped Interaction	π- alkyl interaction	π- sulphur interaction
1.	EB-28	SER85 VAL87 ILE86	PRO84 ALA88 ARG11	ALA63 LEU36	--
2.	EB-32	--	--	LEU873 LEU701 PHE891 MET749	--
3.	EB-34	MET745 ASN705 ARG752	PHE764	MET787 MET749 VAL746 PHE891	MET745
4.	EB-35	--	PHE764	LEU873 MET895 PHE891 LEU880	MET787 MET745
5.	EB-47	ASN705	PHE764	LEU701 +MET895	MET787 MET745

				PHE891 LEU880 MET749	
6.	EB-49	MET745 LEU873	PHE764	LEU704 MET749 LEU880 PHE876	--
7.	EB-98	ARG752 PHE764	--	VAL746 PHE891 MET895 MET749	--
8.	Lovastatin	--	--	LEU707 LEU873 PHE764 MET742	--

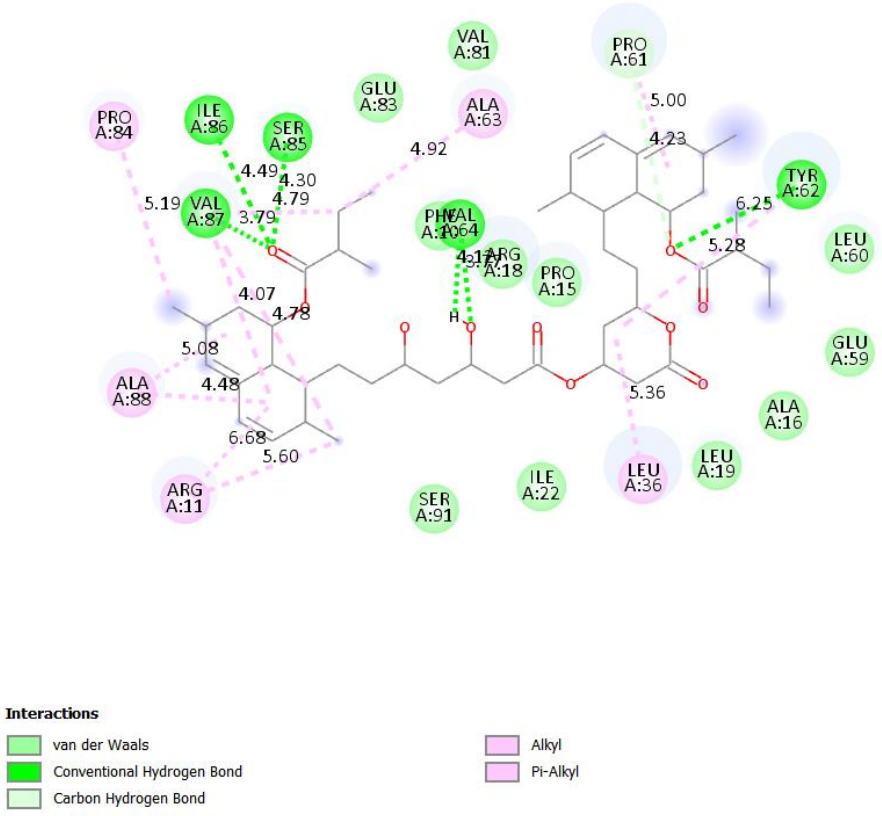


Figure 2: Interaction of EB-28 in the active site of androgen receptors

As depicted in figure 2, EB-28 with the binding affinity (-8.9 Kcal/mol) was found to have multiple type of interactions with protein residues in the active site of HMG-CoA reductase. EB-28 has the three H-bond interactions with residues like SER85, VAL87&ILE86, It has been noticed that compound EB-28 also has π- π T shaped interaction with ALA88, PRO84&ARG11. It has π-alkyl type of interactions with ALA63, LEU36 with no π-sulphur interaction.

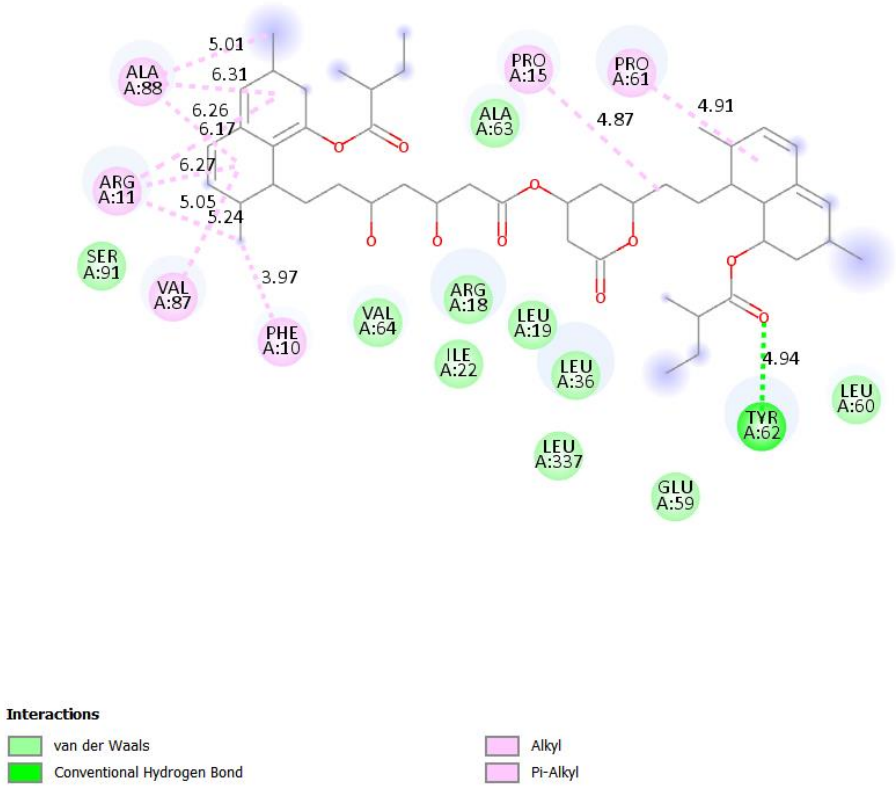


Figure 3: Interaction of EB-32 in the active site of HMG-CoA reductase

EB-32 and EB-98 have the highest binding affinities and same score of -9.2Kcal/mol. And it was found to have multiple type of interactions with protein residues in the active site of HMG-CoA reductase. It has been noticed that compound EB-32 has π-alkyl type of interactions with LEU873, LEU701, PHE891, MET749. Although, compound EB-32 was the most potent compound but it was interesting to see that there was no other type of interactions (like H-bond interaction, π- π T shaped, π-sulphur interactions) was seen with compound EB-32 which were common with other compounds.

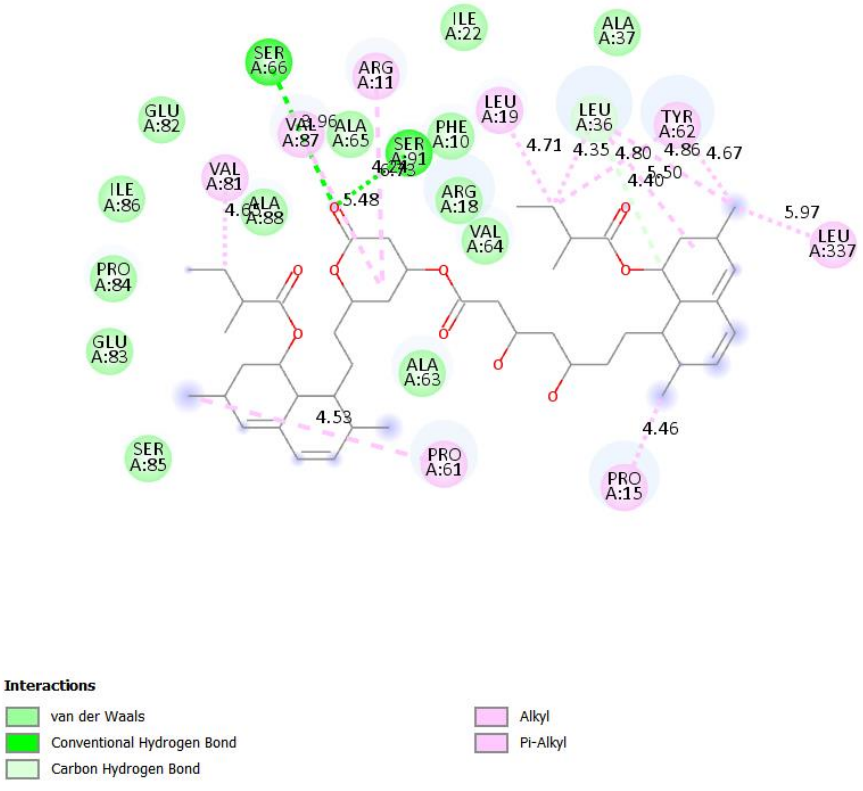


Figure 4: Interaction of EB-34 in the active site of HMG-CoA reductase

Compound EB-34 has the binding affinity of -7.6 Kcal/mol with multiple interaction which is presented in Figure 4. Although, it has same binding affinity but there was no H-bond interaction was found in the EB-34. But π- π T shaped interaction was found with the residue PHE764. Moreover, this compound has also shown π-alkyl interaction with same residue as shown by compound EB-34 i.e. LEU873, LEU701, PHE891, MET749. Interestingly, this compound has shown two π-sulfur type of interaction with residues like MET787 & MET757.

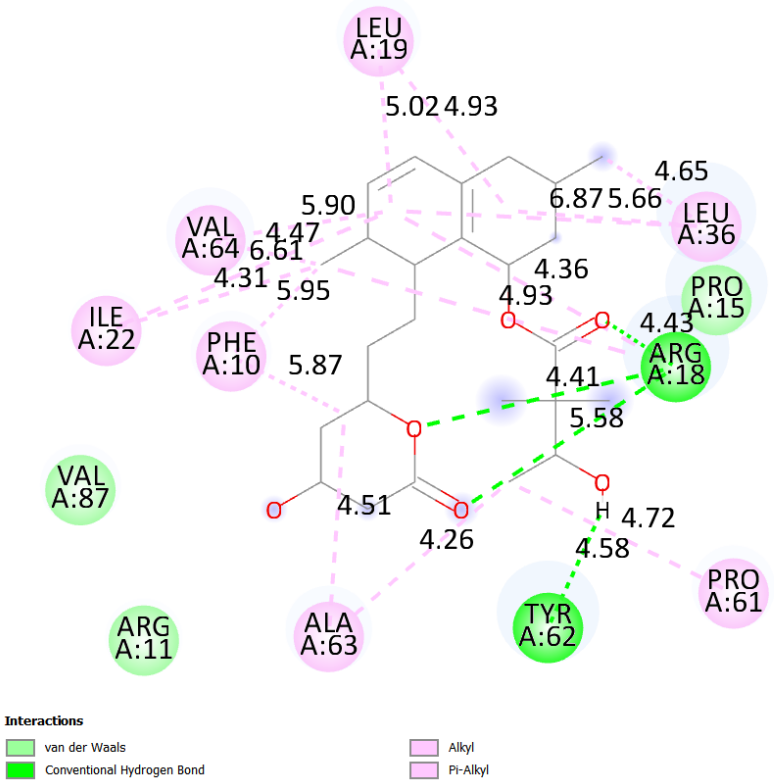


Figure 5: Interaction of EB-35 in the active site of HMG-CoA reductase

Figure 5 presenting the interactions of compound EB-35 which has been found to have same binding score as compare to EB-35. But SEB-35 has shown one H-bond interaction with amino acid residue ASN705. Moreover, it has shown one π- π T shaped interaction with PHE764 and multiple π-alkyl interaction with LEU701, MET895, PHE891 & LEU880. EB-35 has also shown two π-sulphur type of interactions with same residues as shown by EB-35.

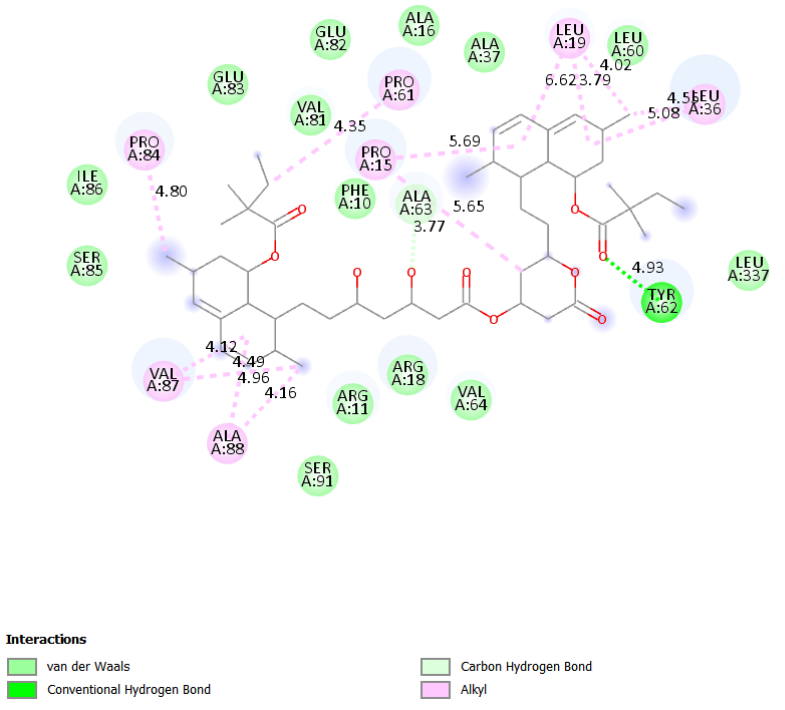


Figure 6: Interaction of EB-98 in the active site of androgen receptors

Figure 6. Presenting the interactions of compound EB-47 which has been found to have same binding score as compare to EB-98. But EB-47 has shown one H-bond interaction with amino acid residue ASN705. Moreover, it has shown one π- π T shaped interaction with PHE764 and multiple π-alkyl interaction with LEU701, MET895, PHE891 & LEU880. EB-47 has also shown two π-sulphur type of interactions with same residues as shown by EB-47.

ADME Analysis

These top 7 compounds were found to interact with important residues and had good binding in the HMG-CoA reductase active site. The ADME study of these compounds were therefore predicted as these physicochemical qualities are crucial in determining the compound's fate. Table 3 lists the physicochemical characteristics of the seven hit compounds, including their molecular weight, H-bond acceptors, H-bond donors, and Log P value. Additionally, predictions for hit compounds include GI absorption, BBB penetrations, the number of Lipinski violations, and synthetic accessibility. The results showed that all seven of the hit compounds had drug-like characteristics and had no violations of Lipinski's rule of five. The remaining hit compounds, with the exception of EB-32, EB-98, EB-34, EB-28 and EB-47, all have at least one violation of the lead likeness property. These seven top-performing substances have all demonstrated high GI absorption without BBB penetration. All of the hits had a bioavailability of 0.55, which was comparable to that of the medication lovastatin. All of the identified compounds had effective Log P values between 3.33 and 8.00, indicating that their lipophilicity and hydrophilicity characteristics are at their peak. These hits were discovered to have excellent and efficient synthetic accessibility, demonstrating the ability of these compounds to be synthesised. All of these substances had demonstrated a strong propensity to inhibit the CYP1A2, CYP2C9, and CYP3A4 enzymes. The CYP2C19 and CYP2D6 enzymes were discovered to metabolise the drugs, however.

Table 3: Drug likeness property of hit compounds using SwissADME

Sr. No	Compound Code	Binding Affinity (kcal/mol)	MW	#H-bond acceptors	#H-bond donors	Consensus Log P	GI absorption	BBB permeant	Lipinski #violations	Bioavailability Score	Leadlikeness #violations	Synthetic Accessibility
1.	EB-32	-9.2	809.08	10	2	7.28	Low	No	2	0.17	3	8.95
2.	EB-98	-9.2	837.13	10	2	7.88	Low	No	2	0.17	3	9.14
3.	EB-34	-9.1	809.08	10	2	7.44	Low	No	2	0.17	3	8.95
4.	EB-28	-8.9	809.08	10	2	7.39	Low	No	2	0.17	3	8.95
5.	EB-35	-8.7	434.57	6	2	3.33	High	No	0	0.55	2	5.91
6.	EB-47	-8.7	837.13	10	2	8.00	Low	No	2	0.17	3	9.14
7.	EB-49	-8.7	418.57	5	1	4.18	High	No	0	0.55	2	5.8
8.	Lovastatin	-7.0	404.54	5	1	3.88	High	Yes	0	0.55	2	5.76

Table 4: Pharmacokinetic toxicity Properties

Sr. No	Compound Code	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
1	EB-32	No	-0.397	No	No	5.04	1.699	Yes	No	0.285	-0.873
2	EB-98	No	-0.449	No	No	4.191	2.239	Yes	No	0.285	-1.024
3	EB-34	No	-0.429	No	No	4.063	2.281	Yes	No	0.285	-0.954
4	EB-28	No	-0.429	No	No	4.063	2.281	Yes	No	0.285	-0.954
5	EB-35	No	-0.096	No	No	2.315	2.05	No	No	0.421	1.314
6	EB-47	Yes	-0.426	No	Yes	4.047	2.214	Yes	No	0.285	-1.188
7	EB-49	No	-0.141	No	No	2.14	0.445	No	No	0.55	0.227
8	Lovastatin	No	-0.492	No	No	2.181	0.017	No	No	0.572	0.329

Discussion

Virtual screening was done on all the 100 compounds obtained from the ZINC database, after which 15 lovastatin derivatives were included in this article.[30] It was demonstrated that all of these compounds were better suited to the HMG-CoA reductase active binding region when the molecules were docked into the lovastatin binding site (PDBID: 7CPX). Additional analysis based on the docking data revealed that 7 compounds have more effective binding to the receptor's active site when compared to the drug lovastatin.[31] Additionally, due to hydrophobic contacts, hydrogen bond interactions, and electrostatic interactions in the lovastatin binding site (PDBID: 7CPX), the compounds were stabilized and substantially more likely to prevent the action of the HMG-CoA reductase enzyme. The ADME study was then performed on the 7 hits, and it was predicted that each of these hit compounds would have drug-likeness properties. The highest Log P values for these compounds came from 4-5 H-bond donors and 1 H-bond acceptor. Additionally, these compounds have a significant possibility of inhibiting the CYP1A2, CYP2C9, and CYP3A4 enzymes, a high GI absorption, and a low BBB penetration.

Conclusion

The in silico investigation of lovastatin derivatives against HMG-CoA Reductase has provided insights into the potential efficacy of these compounds as cholesterol-lowering drugs. Through computational methods such as molecular docking and molecular dynamics simulations, the binding affinity and stability of these derivatives to the target enzyme HMG-CoA reductase have been evaluated. Based on the results of these simulations, some of the lovastatin derivatives have shown promising interactions with HMG-CoA Reductase active site, suggesting that they may be effective inhibitors of the enzyme. However, further experimental validation is needed to confirm these findings and determine the actual effectiveness of these compounds in vivo.[32]

Overall, the in silico investigation of lovastatin derivatives against HMG-CoA Reductase has provided valuable information for guiding the design and optimization of new cholesterol-lowering drugs, and has the potential to contribute to the development of more effective treatments for hypercholesterolemia and related diseases.

Conflict of Interest

The authors declared no potential conflict of interest.

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