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Molecular docking and ADMET analysis of synthetic statins for HMG-CoA reductase inhibition activity

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Hypercholesterolemia is a serious condition that may lead to coronary heart disease, heart attack and stroke raising the rate of morbidity and mortality in hypocholesterolemic patients. Statins are one of the largest selling drugs for hypercholesterolemia. They serve as potential competitive inhibitors of HMG-CoA reductase that catalyzes the rate-limiting step of cholesterol biosynthesis cascade. They can be broadly classified into fermentation-derived, semisynthetic and synthetic statins. For the current study, synthetic statins like fluvastatin, cerivastatin, rosuvastatin were subjected to *in silico* analysis for their competitive binding with HMG-CoA reductase through molecular docking. The molecular interaction between HMG-CoA reductase with statins and their ADMET properties were studied using Maestro suite of Schrödinger software. The results of molecular docking depicted that fluvastatin had the highest docking score while that of rosuvastatin was the least. The prediction of pharmacokinetics of drug performed by QikProp also pointed the efficacy of fluvastatin as a potent inhibitor for HMG-CoA reductase enabling it to be an effective drug to treat hypercholesterolemia among the three synthetic statins.

Keywords: Cerivastatin, Fluvastatin, HMG-CoA reductase, Hypercholesterolemia, Rosuvastatin

Hypercholesterolemia is a serious health condition that may lead to coronary heart disease, heart attack, stroke, and other complications, which raise the rate of morbidity and mortality in the hypocholesterolemic patients[1-3]. Our body can synthesize 50% or more of its own cholesterol requirement through mevalonate pathway and the remaining are obtained from our diet[4]. The conversion of 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) to mevalonate is the rate-limiting step of mevalonate pathway catalyzed by HMG-CoA reductase[1,4].

HMG-CoA reductase is a transmembrane protein, which contains eight domains that are anchored on the membrane of endoplasmic reticulum[5]. The active form of the enzyme has a tightly associated tetramer. The tetrameric structure of the enzyme consists of two catalytic sites formed by monomeric residues in a dimer[6]. Each monomer of HMG-CoA reductase has large and small domains. Both the domains are connected *via* a *cis* loop, which plays a key role in the formation of HMG-CoA binding site[7]. Recently, the regulation of HMG-CoA reductase received much attention that helps to modulate the mevalonate cascade.

Statins are currently prescribed for hyper-cholesterolemia which serves as effective competitive inhibitors of HMG-CoA reductase due to its structural similarity with HMG-CoA. Based on the routes of synthesis, these statins can broadly be classified into three major types, *viz*., fermentation derived, synthetic, and semi-synthetic statins. Lovastatin and compactin are fermentation derived statins whereas simvastatin is a semi-synthetic statin synthesized from lovastatin either by synthetic or enzymatic biotransformation routes[8-10].

A number of synthetic statins are available in the market, such as, cerivastatin, atorvastatin, fluvastatin, pitavastatin, and rosuvastatin, which are more efficient than the fermentation derived statins[10]. These statins are administrated orally, either in the form of hydroxy acid or lactone.

In silico study is a convenient route to investigate those molecules which are difficult to isolate and purify from the fermentation broth. To the best of our knowledge, the molecular docking studies on synthetic statins with HMG-CoA reductase have not been performed so far. Further, it is difficult to find a

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docking study that compares the affinity of different types of statins towards HMG-CoA reductase. Hence, the present study aims to consider important synthetic statins for the docking study. Also, it is a first attempt to compare the binding of HMG-CoA reductase with different statins *in silico* to understand types of interaction at the active site of the enzyme and to elucidate their structure-based functional relationship to develop a novel molecule for hypercholesterolemia.

Materials and Methods

Target Protein

The crystal structure of the protein HMG- CoA reductase (PDB ID: 1HW8) was retrieved from RCSB Protein Data Bank. The protein structure was imported to Maestro software (Schrödinger, LLC, New York) for docking study. The docking studies of statins with HMG-CoA reductase requires the following sequence of steps that are shown in (Fig. 1).

Preparation of HMG-CoA reductase

Originally, the tetrameric protein consists of four monomeric sub-units (Fig. 2). The monomeric chain A and B to form a dimer. Similarly, chains C and D form another dimer, which are identical to each other. The dimeric form of HMG-CoA reductase was used for the docking studies, since, the functional form of HMG-CoA reductase is dimeric in nature[11,12]. Moreover, these dimers are symmetric in nature and are responsible for catalysis of the reaction as observed in original protein structure, where four monomeric subunits of compactin are composed to form a tetrameric protein. Each dimeric unit of the protein is bound with two ligands.

The tetrameric protein was separated into its constituent chains (Chain A & B) and the dimeric unit as chain A was selected for further docking studies. To start docking of protein, it is essential to prepare the protein since the crystal structure obtained from Protein Data Bank consists of issues such as, improper bond orders, missing side chains, *etc*. Hence, the protein preparation process is much helpful in assigning proper bonds, bond order, addition of hydrogen, detection of disulphide bonds and correction of mislabelled elements. Further, the preparation of protein does not have any effect on the geometry of the protein; rather, it checks for any problem in the protein structure and correct those problems. The dimeric form of protein was prepared using protein preparation wizard in the Maestro suite of Schrödinger software for further process.

Sitemap generation

Sitemap tool of the Maestro helped in identification of active sites of a protein. In total four sitemaps were generated by the software for the protein. Similarly, sitemaps were generated for the dimeric form of the protein. The common sitemaps between the tetrameric and dimeric forms of the enzyme were selected for further processing and other site maps were discarded. Out of four sitemaps, two were found to be conserved between the tetrameric and dimeric forms of the enzyme.

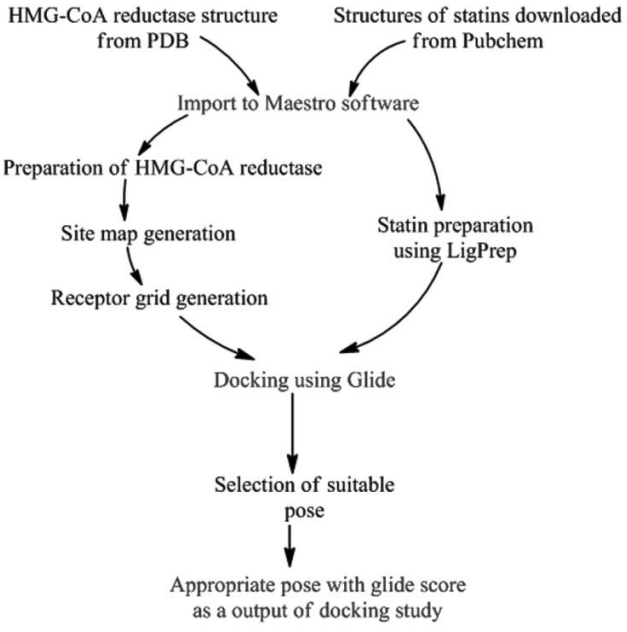

Fig. 1 — Sequential steps involved in the docking study

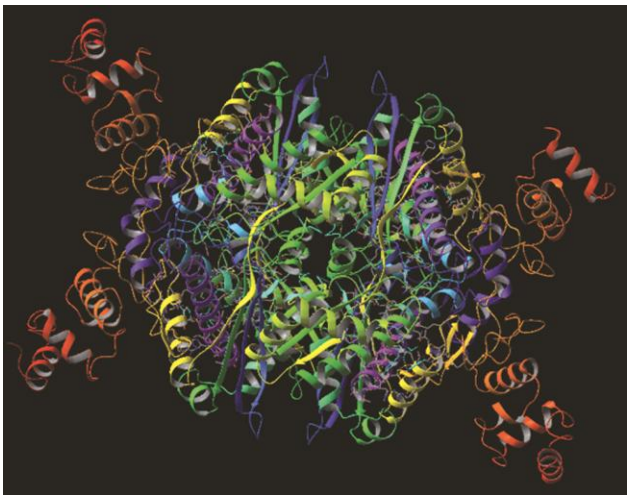

Fig. 2 — Tetrameric structure of HMG-CoA reductase

Receptor grid generation

The receptor grid is the three dimensional boundary for statins to bind with HMG-CoA reductase. The representation of shape and properties of the receptor on a grid provides a more accurate estimate of binding score for the different configurations of a ligand. The receptor grid for the protein was generated by specifying the active site residues using receptor grid generation panel in the glide application of Maestro.

Ligand preparation

A group of synthetic statins were employed for the current study as listed (Fig. 3) with their PubChem IDs in provided in (Table 1). The structures of statins were obtained from PubChem Compound database available at NCBI (www.ncbi.nlm.nih.gov) and were prepared for docking study using LigPrep application in Maestro software. The ligands employed for docking study should have three-dimensional configurations with realistic bond lengths and bond angles for obtaining the best results. The statins should not have any covalent bonds to the receptor of HMG-CoA reductase. Hence, LigPrep optimize the geometry of statins to check for any problems in the ligand structure and generates the structural variants.

Molecular Docking using Glide

Maestro software provides Glide tool for molecular docking studies to visualize and interpret the molecular level structural interaction between the target protein and ligand. Once the receptor grid is generated, the statins were docked with dimeric form of the protein. The Glide tool has generated different ligand conformations internally. However, a single best pose (confirmation) per ligand was represented as output based on the efficiency of binding. The efficiency of docking was evaluated using Glide (G) score.

Prediction of ADMET Properties

Hypercholesterolemia has been linked to cardiovascular disease, or to be specific to coronary heart disease. The main course of action of statins is reversible inhibition of hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase. Statins may have a similar course of action but they greatly differ in terms of chemical structure and pharmacological attributes which in turn affect their clinical utilities and effectiveness. This difference between different statins and their attributes can be found from their ADMET profiles. ADMET is the abbreviation of pharmacokinetics properties of drugs (absorption, distribution, metabolism, excretion and toxicity) which is generally a pathway of how drug is distributed in the systemic circulation and how the metabolism takes place which is followed by flushing out of drug metabolite from the body. These studies are accompanied with toxicity analysis, which is also an important factor to understand any kind of toxicity associated with the drug molecule leading to certain harmful effects of drug. ADME analysis of synthetic statins was performed using QikProp tool (Schrödinger Inc.) and Toxicity analysis was done using PreADMET, which is a web based service for ADMET prediction. Statins are attributed to being the most effective and safe drug to control hypercholesterolemia. In current analysis, we studied

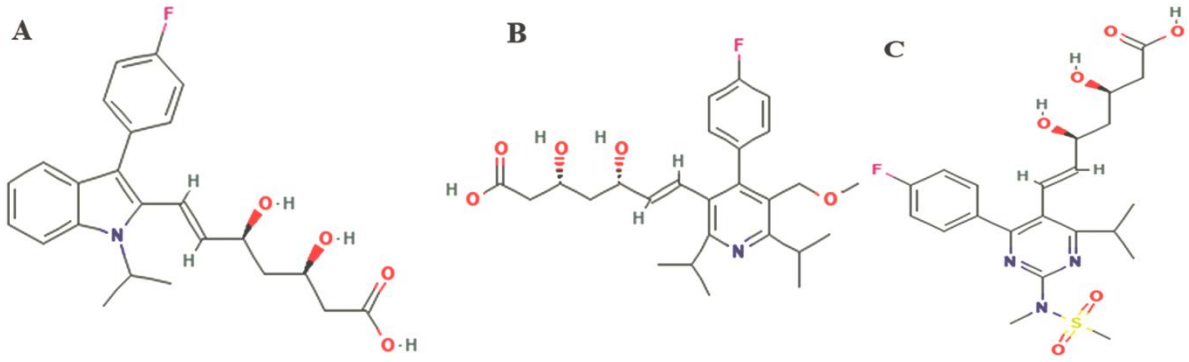

Fig. 3 — Structures of Statins (A) Fluvastatin; (B) Cerivastatin; and (C) Rosuvastatin

Table 1 — Docking scores of different statins

S. No.	Pubchem ID	Statins	Binding amino acid residues	Docking score
1.	446155	Fluvastatin	Arg590, Glu559, Asn658	−7.161
2.	446156	Cerivastatin	Arg590, Asn658, Ser661, Lys691, Asn755	−5.705
3.	446157	Rosuvastatin	Arg590, Asn658, Glu665, His861	−5.688

the following synthetic derivatives of statins namely fluvastatin, cerivastatin and rosuvastatin.

Results

Molecular docking studies of statins with HMG-CoA reductase

Each statin (ligand) was prepared with possible three-dimensional orientation and hence they were docked separately with the enzyme. The docking score was considered as a parameter to indicate binding efficiency of statins with HMG-CoA reductase. The negative value of docking scores indicated better fitting of ligand into binding site of protein. The docking score for different statins was in the range of −7.161 to −5.688 (Table 1). Synthetic statins, such as, fluvastatin, cerivastatin and rosuvastatin were bound to HMG reductase with the docking scores of −7.161, −5.705 and −5.688, respectively (Table 1).

In addition to four hydrogen bonds and pi-cation interactions, fluvastatin formed a salt bridge with Arg 590, which was not observed with other statins (Fig. 4A). This could be the probable reason for its better docking score. It formed hydrogen bonds with the enzyme *via* amino acids *i.e.* Glu559, Arg590 and Asn658 and had an average bond length of 1.9651 Å. Cerivastatin interacted with a numbers of amino acids at the active site of the enzyme *via* both hydrogen and pi-cation bonds. It bound with Arg590, Asn658, Ser661 and Asn755 (Fig. 4B) *via* hydrogen bonds with the mean bond length of 2.1377 Å. Interestingly, it has two pi-cation interactions with Arg590 and Lys691 of HMG-CoA reductase through the pyridine ring structure and fluorophenyl functional group of cerivastatin with a mean bond length of 2.137 Å (Table 2). Terminal carboxylic group of rosuvastatin formed hydrogen bonds with Arg590, Asn658, Glu665, and His861 (Fig. 4C) with the mean bond length of 2.044 Å.

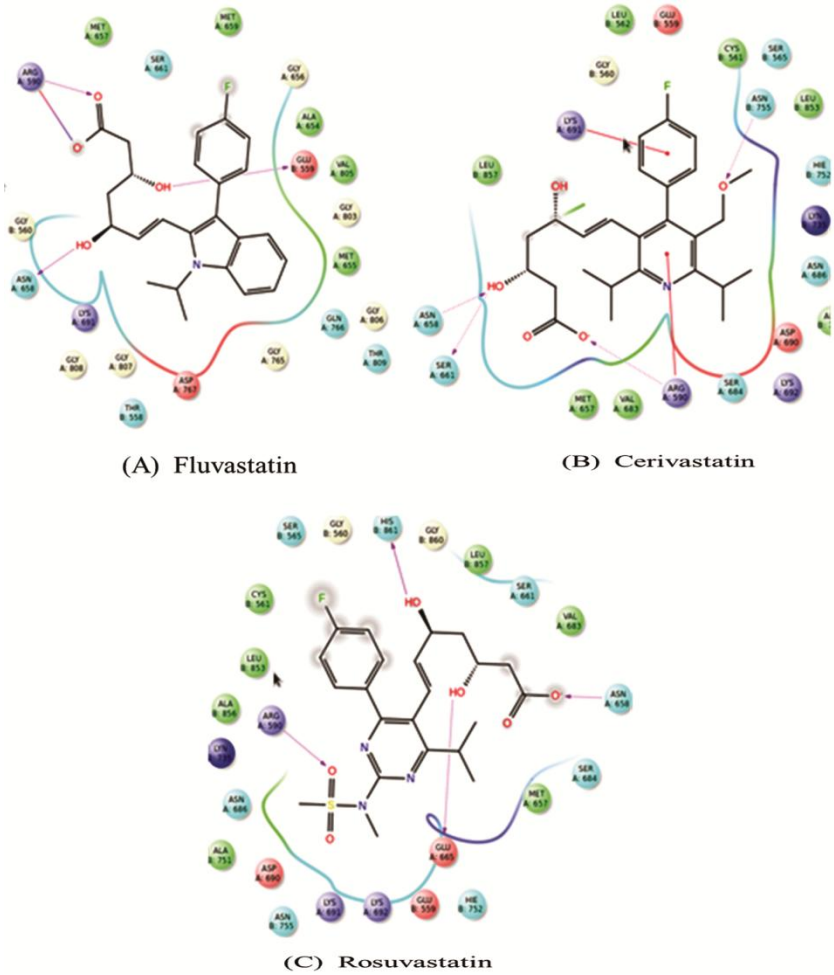

Fig. 4 — Ligand interaction diagram of HMG-CoA reductase with (A) Fluvastatin; (B) Cerivastatin; and (C) Rosuvastatin

ADMET

Absorption and Distribution Profiling

QPlogS, the logarithm of aqueous solubility, is an important indicator of solubility of the drug. If the prediction of CIQPlogS is significantly different from QPlogS then the prediction indicates that solubility of drug is conformation dependent. The dipole moment/constant of a compound also influences the solubility of the compound. Dipole moment of drugs in current studies were found in approximation and are depicted in (Table 3). Assessment of cell permeability by QPPCaco and QPPMDCK data Cell lines for Caco-2 and MDCK used as an *in vitro* model for the prediction of absorption of orally administered drugs in human small intestinal mucosa. Studies on Caco-2 cell lines (at gut-blood barrier) can mimic various process of transport like, transcellular transport, para cellular transport, and some aspect of efflux and active transport. QikProp prediction is used to predict non-active transport of a drug in Caco-2 cell line. MDCK cell lines are used for prediction of absorption of a drug through blood-brain barrier (BBB). QikProp qualitatively predicted the oral absorption of the drug.

Metabolism and Excretion

Metabolism and excretion profiling was predicted to identify whether the drug during metabolism is an inhibitor or substrate of the biological enzymes (Table 4).

Table 2 — Type of interactions between the active site of HMG-CoA reductase and statins

Nature of amino acid	Bond type	Bond length (Å)
Fluvastatin		
Arg590- Charged positive	Salt bridge	4.9074
Glu559- Charged negative	H-bond (side chain)	1.9281
Arg590- Charged positive	H-bond (side chain)	2.0672
Asn658- Polar	H-bond (side chain)	1.9041
Cerivastatin		
Arg590- Charged positive	H-bond (side chain)	2.7620
Arg590- Charged positive	Pi-cation	4.2204
Lys691- Charged positive	Pi-cation	5.9371
Asn658- Polar	H-bond (side chain)	1.8452
Ser661- Polar	H-bond (side chain)	1.9135
Asn755- Polar	H-bond (side chain)	2.1415
Rosuvastatin		
Arg590- Charged positive	H-bond	1.8027
Asn658- Polar	H-bond	2.1233
Glu665- Charged negative	H-bond	2.0766
His861- Polar	H-bond	2.1966

Toxicity

The toxicity analysis is a complex procedure, but there are some descriptors which can predict the toxicity of the compound to a good degree of accuracy. The main descriptors in Qikprop and PreADMET are QPloghERG, Ames test and Rodent Carcinogenicity. In QikProp analysis, QPloghERG is predicted by IC_{50} (Half maximal inhibitory concentration, is a measure of the potency of a substance in inhibiting a specific biological or biochemical function) value for the blockage of hERG K^+ channels.

Table 3 — Comparative Absorption & Distribution Profiling of Statins

Descriptors	Fluvastatin	Cerivastatin	Rosuvastatin	Range
QPlogS (mol/dm^3)	−3.836	−5.252	−3.665	−6.5 - 0.5
CIQPlogS (mol/dm^3)	−6.628	−6.382	−5.336	−6.5 - 0.5
Dipole Moment	5.331	2.896	5.764	1.0 - 12.5
Permeability of CaCO (nm/s)	130.112	107.539	17.484	> 500 – Great <25 - Poor
Permeability of MDCK Cell Lines (nm/s)	105.621	101.712	11.461	> 500 - Great <25 - Poor
Human Oral Absorption (%)	82.792	80.608	64.587	25 - 80
QPlogKhsa	0.643	0.448	−0.357	−1.5 - 1.5
Molecular Weight (Dalton)	411.472	459.557	481.538	130 - 725
QPloghERG	−2.952	−2.97	−2.875	> −5

Table 4 — Metabolism Profile

	Names	Fluvastatin	Cerivastatin	Rosuvastatin
Metabolism				
	CYP2C19 inhibition	Inhibitor	Inhibitor	Non
	CYP2C9 inhibition	Inhibitor	Inhibitor	Inhibitor
	CYP2D6 inhibition	Non	Non	Non
	CYP2D6 substrate	Non	Non	Non
	CYP3A4 inhibition	Inhibitor	Inhibitor	Non
	CYP3A4 substrate	Substrate	Substrate	Weakly

Discussion

Molecular docking is a technique which helps in identification of binding sites of ligand with the protein[18,19]. It is also used to find out potential ligands for a given target protein. In the current study, synthetic statins, namely, fluvastatin, cerivastatin, and rosuvastatin were used as ligands to study their interaction with HMG-CoA reductase. Some of the amino acids, such as, Arg590 and Asn658 were the conserved residues found at the active site of HMG-CoA reductase that interacted with most of the statins as observed from docking studies (Fig. 4). The guanidinium group of positively charged amino acid, Arg590, formed hydrogen bonds with the sulfone group of rosuvastatin and the terminal carboxylate group of HMG-CoA like moiety of statins, *viz*., cerivastatin and fluvastatin. The polar amino acid, Asn658, also formed hydrogen bonds with the hydroxy group of HMG like moiety of statins, such as cerivastatin, fluvastatin, and rosuvastatin. Lys691 is another common positively charged amino acid found at the *cis* loop of HMG-CoA reductase that formed pi-cation interaction with the fluorophenyl ring structure of cerivastatin. Other amino acids, such as Glu559, Ser661, Glu665, Asn755, and His861 were found at the active site of HMG-CoA reductase.

Istvan and Deisenhofer (2001) observed that the following amino acids, serine (Ser648), lysine (Lys691 and 692), and aspartate (Asp690) at the cis-loop of HMG-CoA reductase interacted with HMG-CoA-like moieties of statins through polar interactions. Carbonell and Freire (2005) reported that the sulfonyl group in rosuvastatin formed hydrogen bonds with the hydroxyl group of Ser565[11]. These results, to some extent, ascertained the accuracy of the prediction of the active site and docking results of the present work. Some hydrophobic amino acids are found at the active site of the enzyme and they could play a key role in bringing those statins towards the active site of the enzyme by hydrophobic interactions.

Tabernero *et al*. (2003) reported the importance of HMG-CoA like moiety of statins in binding with HMG-CoA reductase. Moreover, they have also reported crucial role of hydrophobic interaction between active site of the enzyme and the hydrophobic regions (decalin ring and butyryl side chain) of statins. The simple sulfonamide structure in rosuvastatin formed a hydrogen bond with positively charged amino acids *via* a carbonyl group. It showed that the carbonyl group present at HMG-CoA like moiety and sulfonyl group are found to be crucial in the binding of statins[20].

Overall, the present study showed the importance of functional groups, such as HMG-CoA like moiety and high electron density chains, such as, sulfone group, fluorophenyl group, and pi-conjugated ring structures, to develop next generation statins molecules with improved efficiency.

Hypercholesterolemia has been linked to cardiovascular disease or coronary heart disease. The main course of action of statins is reversible inhibition of hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase. Synthetic statins may have a similar course of action but they greatly differ in terms of a chemical structure and pharmacological attributes which in turn affect their clinical utilities and effectiveness. This difference between different statins and their attributes can be found from their ADMET profiles.

The solubility of any drug can either be conformation-dependent or conformation independent which is determined by the difference in values of QPlogS and CIQPlogS. Fluvastatin exhibited a significant difference in values of QPlogS and CIQPlogS (2.792) compared to cerivastatin, and rosuvastatin and hence it can be concluded that the solubility of fluvastatin was dependent on its conformation. The dipole of fluvastatin, cerivastatin and rosuvastatin was 5.331, 2.896, and 5.764, respectively. These values are within the range of 1.0−12.5 which is recommended for a molecule to act as a suitable drug. High dipole value means that the molecule is highly soluble in an aqueous medium and hence they are less likely to be administered orally. From the results of dipole, it can be inferred that rosuvastatin is highly soluble among the three synthetic statins. QPPCaco and QPPMDCK are parameters that determine the permeability of a likely drug across the gut-blood barrier and blood-brain barrier, respectively. From Table 3 it can be seen that fluvastatin has the highest permeability in Caco and MDCK cells among the three synthetic statins whereas rosuvastatin has very poor permeability. The percentage of human oral absorption is high for fluvastatin (82.792%) and least for rosuvastatin (64.587). This can be correlated with the value of dipole for the synthetic statins.

Binding to human serum albumin (HSA) determined the distribution of drugs inside the body. This also helps in solubilisation and uniform distribution of the drug in tissues. From the data of

Table 5 — Toxicity Analysis

	Names	Fluvastatin	Cerivastatin	Rosuvastatin
Ames test		Mutagen	Mutagen	Mutagen
	TA100-10 RLI	−ve	−ve	−ve
	TA100-NA	−ve	−ve	−ve
	TA1535-10 RLI	−ve	+ve	+ve
	TA1535-NA	+ve	−ve	−ve
Carcinogenicity				
	Carcinogenicity (mouse)	−ve	−ve	−ve
	Carcinogenicity (rat)	+ve	−ve	−ve
hERG_inhibition		High risk	Medium risk	Ambiguous

QPlogHSA, it can be predicted that fluvastatin has the highest binding to HAS than cerivastatin and rosuvastatin. The IC_{50} value of any drug is predicted by its efficiency to block HERG K^+ channels. From Table 3, it can be observed that there is no significant difference between the QPlogHERG values of fluvastatin and cerivastatin whereas that of rosuvastatin is least.

The metabolic profile of the three statins showed that instead of having comparatively lower inhibitory activity, rosuvastatin has shown the least interference as non-inhibitor and weak substrate for metabolic enzymes. Hence it is less likely to have side effects. The toxicity study for all three compounds is found to be negative for most of the descriptors and risk factors are also found in approximation for all the drugs. Results for fluvastatin are found with high risk for hERG inhibition hence the study confined the drugs with potential inhibitory effect for HMG-CoA but can have certain to side effects as per toxicity profiling (Table 5).

The results of molecular docking and pharmacokinetics profiles of three synthetic statins with HMG-CoA reductase indicate that fluvastatin binds strongly with amino acids at the active site of HMG-CoA. The absorption profile considered that fluvastatin is better absorbed compared to the remaining two statins. But it might have certain side effects as pointed out by the metabolism and toxicity profile of fluvastatin. On the other hand, rosuvastatin has shown the least risk of side effects with poor interactions with HMG-CoA reductase. The development of suitable analogues of rosuvastatin which have better interactions with HMG-CoA reductase can be a suitable option for enhancing the efficacy of rosuvastatin as an improved drug candidate.

Conclusion

Hypercholesterolemia has been linked to cardiovascular disease or coronary heart disease. Statins, potential inhibitors of HMG-CoA reductase, can be explored as suitable drug candidates for treatment of hypercholesterolemia. In the current work, synthetic statins, namely, fluvastatin, cerivastatin and rosuvastatin were studied for their interaction with HMG-CoA reductase. The three-dimensional molecular interactions between statins and HMG-CoA reductase were mimicked using Schrödinger software to understand the structural based functionality of statins and molecular mechanism of interactions at the active site of the enzyme. From molecular docking interactions and ADME predictions it can be concluded that fluvastatin is the most suitable drug among the three synthetic statins whereas rosuvastatin is found with comparatively weaker interaction and pharmacokinetics. This kind of studies with the help of computer-aided drug discovery tools help in the identification of target-ligand interaction at the molecular level, hence give a deeper insight for further optimization of the drug molecule with better pharmacokinetics profiling.

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Conflict of interest

All authors declare no conflict of interest.

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