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Identification of Novel HMG-CoA Reductase Inhibitors as Potential Antihyperlipidemic Agents Using Computer-Aided Drug Design, Molecular Docking, and In Silico ADMET Analysis

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اكتشاف مثبطات جديدة لإنزيم *HMG-CoA* المختزل كعوامل علاجية محتملة لخفض نسبة الدهون في الدم باستخدام التصميم الدوائي بمساعدة الحاسوب، والالتحام الجزيئي، والتحليل الحاسوبي لخصائص *ADMET*

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Abstract:
Hyperlipidemia is a major metabolic disorder that contributes substantially to the development of cardiovascular diseases and continues to impose a considerable burden on global morbidity and mortality. As the rate-limiting enzyme in the mevalonate pathway, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase plays a central role in cholesterol biosynthesis and remains the principal molecular target of statin therapy. Despite the proven efficacy of statins in lowering serum cholesterol, their clinical application may be restricted by adverse effects, drug interactions, and interindividual variability in treatment response. Consequently, the discovery of novel HMG-CoA reductase inhibitors with improved pharmacological characteristics remains an important objective in drug development. This study employed a computer-aided drug design (CADD) strategy to identify and evaluate new HMG-CoA reductase inhibitor candidates for the management of hyperlipidemia. Structurally optimized molecules were generated from established pharmacophoric features and evaluated through molecular docking to examine their affinity for the enzyme active site. Their drug-likeness and pharmacokinetic characteristics were further investigated using in silico absorption, distribution, metabolism, excretion, and toxicity (ADMET) prediction tools. The docking performance of the designed molecules was compared with that of reference statins. Several candidates demonstrated stronger predicted binding affinities than the reference drug and established favorable interactions with critical catalytic amino acid residues through hydrogen bonding and hydrophobic contacts. Furthermore, the selected lead compounds displayed desirable drug-likeness properties, favorable predicted gastrointestinal

absorption, and acceptable safety profiles. These computational findings identify several promising lead compounds that warrant further investigation as potential antihyperlipidemic agents. Nevertheless, additional experimental studies, including biochemical assays and both in vitro and in vivo studies are required to confirm their biological activity and therapeutic potential.

Keywords: Hyperlipidemia; HMG-CoA reductase; Computer-aided drug design; Molecular docking; In silico ADMET analysis; Statins.

الملخص:

يُعدّ فرط شحميات الدم اضطرابًا أيضيًا رئيسيًا يُسهم بشكل كبير في تطور أمراض القلب والأوعية الدموية، ولا يزال يُشكّل عبئًا كبيرًا على معدلات المراضة والوفيات عالميًا. وباعتباره الإنزيم المُحدِّد لمعدل التفاعل في مسار الميفالونات، يلعب إنزيم HMG-CoA المختزل دورًا محوريًا في تخليق الكوليسترول، ويظل الهدف الجزيئي الرئيسي لعلاج الستاتينات. على الرغم من فعالية الستاتينات المُثبتة في خفض مستوى الكوليسترول في الدم، إلا أن استخدامها السريري قد يكون محدودًا بسبب الآثار الجانبية، والتفاعلات الدوائية، والاختلافات الفردية في الاستجابة للعلاج. ونتيجةً لذلك، يبقى اكتشاف مثبطات جديدة لإنزيم HMG-CoA المختزل ذات خصائص دوائية مُحسَّنة هدفًا هامًا في تطوير الأدوية. استخدمت هذه الدراسة استراتيجية تصميم الأدوية بمساعدة الحاسوب (CADD) لتحديد وتقييم مُرشَّحين جدد لمثبطات إنزيم HMG-CoA المختزل لعلاج فرط شحميات الدم. تم توليد جزيئات مُحسَّنة بنيويًا انطلاقًا من خصائص دوائية معروفة، وخضعت للتقييم باستخدام تقنية الالتحام الجزيئي لدراسة مدى انجذابها للموقع النشط للإنزيم. كما تم التحقق من خصائصها وحركتها الدوائية باستخدام أدوات التنبؤ الحاسوبية للامتصاص والتوزيع والايض والإخراج والسمية (ADMET). وقورن أداء الالتحام للجزيئات المصممة بأداء الستاتينات المرجعية. أظهرت عدة جزيئات مرشحة انجذابًا أقوى للارتباط المتوقع مقارنةً بالدواء المرجعي، وأثبتت تفاعلات إيجابية مع بقايا الأحماض الأمينية التحفيزية الأساسية من خلال الروابط الهيدروجينية والتفاعلات الكارهة للماء. علاوة على ذلك، أظهرت المركبات الرائدة المختارة خصائص دوائية مرغوبة، وامتصاصًا معويًا متوقعًا جيدًا، وملامح أمان مقبولة. تُحدد هذه النتائج الحاسوبية عدة مركبات رائدة واعدة تستحق المزيد من البحث كعوامل محتملة لخفض الدهون في الدم. ومع ذلك، يلزم إجراء دراسات تجريبية إضافية، بما في ذلك التحليلات الكيميائية الحيوية والدراسات المخبرية والحيوية، لتأكيد نشاطها البيولوجي وإمكاناتها العلاجية.

الكلمات المفتاحية: فرط شحميات الدم؛ إنزيم HMG-CoA المختزل؛ التصميم الدوائي بمساعدة الحاسوب؛ الالتحام الجزيئي؛ التحليل الحاسوبي لخصائص ADMET؛ الستاتينات.

Introduction:

Hyperlipidemia is characterized by abnormal elevations in circulating lipids, including total cholesterol, low-density lipoprotein cholesterol (LDL-C), triglycerides, or combinations of these abnormalities. Persistent dyslipidemia is strongly associated with the initiation and progression of atherosclerosis and is considered one of the most important modifiable risk factors for cardiovascular diseases, including coronary artery disease, myocardial infarction, and ischemic stroke. Despite advances in preventive medicine and lipid-lowering therapies, cardiovascular disease remains the leading cause of death worldwide, emphasizing the continuing need for effective therapeutic interventions aimed at controlling lipid metabolism [1,2].

The biosynthesis of cholesterol involves a sequence of tightly coordinated enzymatic reactions, among which HMG-CoA reductase catalyzes the conversion of HMG-CoA to mevalonate, the committed and rate-limiting step of the pathway. Because this enzyme regulates endogenous cholesterol production, it has become the primary pharmacological target for lipid-lowering agents. Suppression of HMG-CoA reductase activity decreases hepatic cholesterol synthesis, reduces circulating LDL-C concentrations, and lowers the incidence of cardiovascular events [3].

Statins remain the cornerstone of pharmacological treatment for hyperlipidemia owing to their well-established efficacy in reducing LDL-C levels and preventing cardiovascular events. Nevertheless, prolonged statin therapy may be accompanied by undesirable effects, including muscle-related disorders, hepatotoxicity, and clinically significant drug interactions. Furthermore, therapeutic response varies among individuals, and some patients are unable to tolerate statin treatment or fail to achieve optimal lipid control. These limitations highlight the continuing need to discover novel HMG-CoA reductase inhibitors with improved efficacy, safety, and pharmacokinetic characteristics [2,3].

Recent progress in CADD has significantly accelerated the early phases of drug discovery by providing efficient computational strategies for identifying and optimizing bioactive molecules. Modern approaches, including molecular docking, virtual screening, quantitative structure–activity relationship (QSAR) modeling, and machine learning have become indispensable tools for predicting ligand–protein interactions, evaluating molecular properties, and prioritizing compounds before experimental testing [4-8]. These approaches substantially reduce both the time and financial resources required during the drug discovery process while improving the efficiency of lead identification. Several recent

investigations have successfully applied computational methodologies to identify and optimize HMG-CoA reductase inhibitors.

Ancuceanu et al. [4] reported QSAR-based predictive models capable of estimating the inhibitory activity of candidate molecules against HMG-CoA reductase. Similarly, Su et al. [5] employed computational modeling to facilitate the rational design of novel enzyme inhibitors. More recently, Cafiero [9] reported the use of transformer-based artificial intelligence algorithms to generate virtual libraries of candidate HMG-CoA reductase inhibitors, illustrating the growing contribution of artificial intelligence (AI) to medicinal chemistry.

In addition, molecular docking investigations involving both natural products and synthetic compounds have identified several molecules with favorable binding characteristics toward HMG-CoA reductase, further supporting the value of computational approaches in lead discovery [6,7]. Building on these developments, the present study employed molecular docking and in silico ADMET analyses to investigate and test a series of novel HMG-CoA reductase inhibitors. The objective was to identify lead compounds exhibiting strong affinity for the enzyme, favorable physicochemical and pharmacokinetic characteristics, and acceptable safety profiles that could serve as promising candidates for the future development of improved antihyperlipidemic therapies.

Materials and Methods:

The current study used a CADD strategy to design and evaluate novel HMG-CoA reductase inhibitors with potential therapeutic value for the treatment of hyperlipidemia. The computational protocol included ligand design, protein preparation, molecular docking, protein–ligand interaction analysis, drug-likeness evaluation, and in silico prediction of pharmacokinetic and toxicity profiles. The three-dimensional crystal structure of human HMG-CoA reductase was obtained from the Protein Data Bank (PDB). Before docking, the protein receptor structure was optimized using molecular modeling software. All crystallographic water molecules, cofactors, and other unnecessary structural components were removed, while polar hydrogen atoms were subsequently added to complete the receptor model. The prepared protein structure was then subjected to energy minimization to improve its geometric stability before docking calculations.

Novel ligand molecules were designed by incorporating the essential pharmacophoric characteristics of previously reported HMG-CoA reductase inhibitors. Two-dimensional chemical structures were generated using ChemDraw software and subsequently converted into optimized three-dimensional conformations. To obtain energetically stable conformations, all ligands were optimized using the MMFF94 force field before docking simulations. Molecular docking studies were conducted using AutoDock Vina to evaluate the binding affinity of the designed compounds toward the catalytic pocket of HMG-CoA reductase. The docking grid was positioned around the active-site region according to the coordinates of the co-crystallized ligand. Binding affinity was expressed as docking energy (kcal/mol), with more negative values indicating stronger predicted interactions between the ligand and receptor.

The reliability of the docking protocol was verified by re-docking the native ligand into the enzyme active site. A root means square deviation (RMSD) value below 2.0 Å between the experimental and predicted ligand conformations was considered indicative of a valid and reproducible docking procedure. Following docking, the binding orientations of the ligand–protein complexes were visualized using Discovery Studio Visualizer. Hydrogen bonds, hydrophobic interactions, π–π stacking, and electrostatic contacts with catalytic amino acid residues were identified and compared to characterize the binding behavior of each compound. The physicochemical properties of the designed molecules were evaluated using the SwissADME web platform. Drug-likeness was determined according to Lipinski's Rule of Five by assessing molecular weight (MW), lipophilicity (LogP), hydrogen-bond donor (HBD) count, hydrogen-bond acceptor (HBA) count, and topological polar surface area (TPSA).

Pharmacokinetic and toxicity characteristics were predicted using the SwissADME and pkCSM web servers. The evaluated parameters included gastrointestinal (GI) absorption, blood–brain barrier (BBB) permeability, cytochrome P450 (CYP450) enzyme inhibition, hepatotoxicity, mutagenicity, oral bioavailability, and total body clearance. Compounds exhibiting favorable pharmacokinetic behavior and acceptable toxicity predications were considered suitable lead candidates for further investigation. Lead compounds were selected based on an integrated assessment of molecular docking performance, interaction profiles with key catalytic residues, compliance with drug-likeness criteria, and predicted ADMET properties.

Molecules demonstrating strong binding affinity together with favorable pharmacokinetic and safety characteristics were prioritized as potential antihyperlipidemic candidates. Descriptive statistical methods were applied to summarize docking scores and physicochemical characteristics. Continuous variables are presented as mean, standard deviation, and range where appropriate. Comparative

analyses were also conducted to assess the computational performance of the designed compounds relative to the reference HMG-CoA reductase inhibitor.

Results:

The binding performance of ten newly designed HMG-CoA reductase inhibitor candidates was investigated using molecular docking to estimate their affinity for the enzyme's catalytic pocket. The calculated docking scores varied between −7.4 and −10.2 kcal/mol, indicating differences in the interaction strength of the designed molecules with the target enzyme. Among the evaluated candidates, HMR-3**,** HMR-7, and HMR-12 demonstrated the most favorable docking scores of −10.2, −9.8, and −9.6 kcal/mol, respectively. These values were more favorable than the docking score obtained for the reference inhibitor, simvastatin (−8.7 kcal/mol), suggesting that the selected lead compounds possess a higher predicted affinity for the active site of HMG-CoA reductase and may exhibit improved inhibitory potential. A comparison of the docking energies for the lead compounds and the reference drug is presented in Table 1.

Table (1): Comparative molecular docking scores of the lead compounds and the reference inhibitor against HMG-CoA reductase

Compounds	Binding Energy (kcal/mol)
Reference statin (simvastatin)	-8.7
HMR-3	-10.2
HMR-7	-9.8
HMR-12	-9.6

Analysis of the docking conformations revealed that the selected lead compounds formed stable and favorable interactions within the active pocket of HMG-CoA reductase. Among the evaluated candidates, HMR-3 displayed the most favorable binding pattern, establishing hydrogen bonds with the catalytic residues Lys691, Asp690, and Ser684, together with multiple hydrophobic interactions that likely contributed to its superior docking score. HMR-7 and HMR-12 exhibited similar interaction profiles, indicating their ability to bind stably within the enzyme's catalytic cavity. In addition, the binding orientations of the designed molecules overlapped with the catalytic region occupied by established HMG-CoA reductase inhibitors, suggesting a competitive mode of inhibition. The binding poses and principal protein–ligand interactions of the selected lead compounds are illustrated in Figure 1.

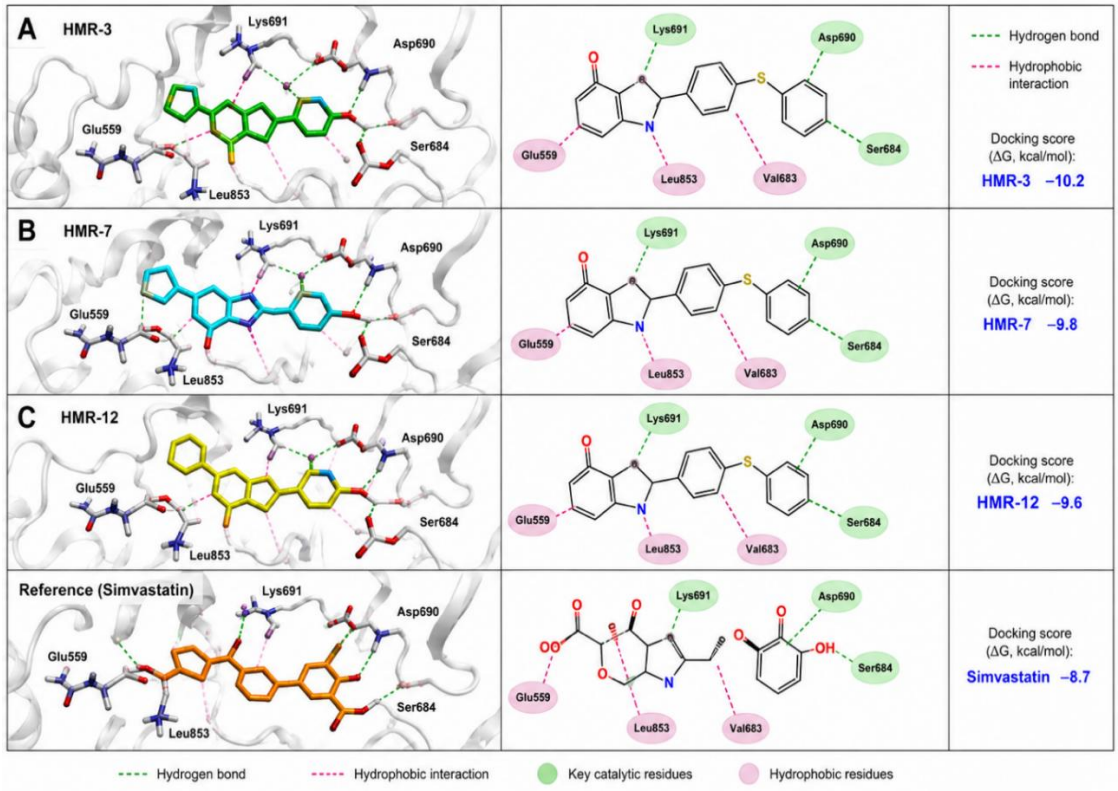

Figure (1): Predicted binding conformations of the lead compounds and their interactions with key catalytic residues of HMG-CoA reductase

The drug-likeness of the selected lead compounds was evaluated by examining their physicochemical properties according to Lipinski's Rule of Five. All three candidates complied with the recommended criteria, indicating favorable characteristics for orally administered drug molecules. Their molecular weights ranged from 418.2 to 445.7 Da, while the calculated LogP values varied between 3.5 and 4.1. The TPSA values of the lead compounds ranged from 79.2 to 92.8 Å², remaining within the range generally associated with good intestinal absorption and favorable oral bioavailability. Furthermore, the numbers of hydrogen-bond donors (HBD) and hydrogen-bond acceptors (HBA) for each compound remained within the accepted limits specified by Lipinski's criteria, supporting their favorable drug-like characteristics. Collectively, these physicochemical findings suggest that the selected lead molecules possess suitable properties for passive membrane diffusion and may represent promising orally active HMG-CoA reductase inhibitors. A summary of the physicochemical characteristics of the lead compounds is presented in Table 2.

Table (2): Physicochemical parameters and drug-likeness characteristics of the selected lead molecules

Physicochemical Parameters of Lead Compounds					
Compounds	**MW (Da)**	**LogP**	**TPSA (Å²)**	**HBD**	**HBA**
HMR-3	432.5	3.7	86.4	3	7
HMR-7	418.2	3.5	79.2	2	6
HMR-12	445.7	4.1	92.8	3	8

MW, molecular weight; LogP, lipophilicity; TPSA, topological polar surface area; HBD, hydrogen-bond donors; HBA, hydrogen-bond acceptors.

The predicted pharmacokinetic and toxicity characteristics of the selected lead compounds are presented in Table 3. The in silico ADMET analysis demonstrated favorable pharmacokinetic characteristics for all three selected candidates. Each compound was predicted to exhibit high GI absorption together with an oral bioavailability score of 0.50, supporting their suitability for oral delivery. None of the lead molecules were predicted to cross the BBB, indicating a low risk of central nervous system exposure. In addition, all compounds were identified as non-inhibitors of CYP450 enzymes, reducing the potential for clinically significant drug–drug interactions. Toxicity prediction indicated no hepatotoxicity and negative mutagenicity for all lead compounds, supporting their favorable safety profiles. The estimated total body clearance values ranged from 0.53 to 0.67 log mL/min/kg, reflecting acceptable elimination characteristics. Collectively, these findings suggest that the selected compounds possess promising pharmacokinetic behavior and safety profiles, supporting their continued development as potential orally active HMG-CoA reductase inhibitors.

Table (3): Predicted in silico ADMET properties of the selected lead compounds

ADMET Parameters	HMR-3	HMR-7	HMR-12
GI absorption	High	High	High
BBB permeability	None	None	None
CYP450 enzyme inhibition	None	None	None
Hepatotoxicity	None	None	None
Mutagenicity	Negative	Negative	Negative
Oral bioavailability score	0.50	0.50	0.50
Total body clearance (log mL/min/kg)	0.67	0.53	0.62

ADMET, absorption, distribution, metabolism, excretion, and toxicity; GI, gastrointestinal; BBB, blood-brain barrier; CYP450, cytochrome P450.

Discussion:

This study employed a CADD approach to identify and evaluate novel HMG-CoA reductase inhibitors with potential therapeutic applications for the treatment of hyperlipidemia. By integrating molecular docking with in silico ADMET evaluation, the study identified several candidate compounds that demonstrated strong binding affinity toward HMG-CoA reductase together with favorable predicted pharmacokinetic properties. These findings are in agreement with recent studies demonstrating the effectiveness of computational approaches in the identification and optimization of HMG-CoA reductase inhibitors [10,11].

One of the most significant outcomes of this study was the identification of compounds HMR-3**,** HMR-7, and HMR-12 as the most promising inhibitor candidates. These compounds produced docking energies that exceeded those of the reference statin, indicating a stronger predicted affinity for the

catalytic pocket of HMG-CoA reductase. These findings are consistent with the study by Samizo and Kaneko [12], who employed computational modeling techniques to identify novel molecules with enhanced inhibitory potential against HMG-CoA reductase.

Similarly, Agosto et al. [13] reported that several phytochemicals derived from natural sources formed stable interactions and demonstrated strong binding affinity toward the enzyme active site, further supporting the reliability of molecular docking as a lead identification tool. Detailed analysis of the protein–ligand complexes revealed that the lead compounds established multiple hydrogen bonds together with extensive hydrophobic interactions involving key catalytic amino acid residues. These intermolecular interactions are recognized as critical determinants of binding stability and inhibitory activity and have been consistently reported in previous computational investigations of HMG-CoA reductase inhibitors [14,15].

The interaction patterns observed in the present study indicate that the designed compounds may inhibit HMG-CoA reductase through binding modes comparable to those of currently available statins, thereby supporting their potential as competitive enzyme inhibitors. Assessment of the physicochemical properties demonstrated that most of the designed molecules complied with Lipinski's Rule of Five, indicating favorable properties for oral drug development. Compliance with these criteria indicates an appropriate balance between molecular size, lipophilicity, hydrogen-bonding capacity, and overall drug-likeness, all of which are essential during the early stages of drug development. These observations are consistent with previous reports emphasizing the importance of drug-likeness screening in improving the efficiency of lead optimization [16,17].

The in silico ADMET analysis further supported the therapeutic potential of the lead compounds by predicting favorable pharmacokinetic behavior and acceptable safety profiles. All selected candidates demonstrated high gastrointestinal absorption, satisfactory oral bioavailability, minimal predicted interactions with major CYP450 enzymes, and low risks of hepatotoxicity and mutagenicity. Recent drug discovery studies have successfully used similar computational methods to prioritize compounds with favorable pharmacokinetic characteristics before experimental validation [18,19].

Recent developments in AI and machine-learning technologies have further transformed modern drug discovery by improving the identification and optimization of novel therapeutic molecules. Lionta et al. and Vamathevan et al. [20,21] highlighted the increasing contribution of AI-driven computational models to medicinal chemistry research. Combining these advanced computational techniques with molecular docking and ADMET prediction may further enhance the efficiency of identifying next-generation HMG-CoA reductase inhibitors with improved therapeutic potential.

In summary, the computational analyses identified several promising HMG-CoA reductase inhibitor candidates with favorable binding characteristics, acceptable drug-likeness, and predicted pharmacokinetic properties. These findings suggest that the selected lead compounds represent attractive candidates for further development as potential antihyperlipidemic agents.

Conclusion and Future Research:

The present study used a CADD workflow to identify and test novel HMG-CoA reductase inhibitors with potential antihyperlipidemic activity. The computational analyses demonstrated that several designed compounds exhibited high binding affinity to the enzyme active site, with docking scores that were comparable to or exceeded those of the reference statin. Protein–ligand interaction analysis further revealed stable hydrogen-bonding networks and hydrophobic contacts involving key catalytic residues, supporting the predicted inhibitory potential of the lead compounds. Evaluation of the physicochemical and pharmacokinetic properties indicated that the selected molecules possessed favorable drug-like characteristics and satisfactory ADMET profiles.

The predicted high GI absorption, good oral bioavailability, low toxicity risk, and minimal CYP450 enzyme interactions suggest that these compounds may have suitable pharmacological properties for further development. Among the investigated candidates, HMR-3 demonstrated the most favorable overall profile, combining the strongest binding affinity with desirable predicted pharmacokinetic characteristics. Collectively, these computational findings suggest that the identified compounds represent attractive lead molecules for the development of next-generation HMG-CoA reductase inhibitors with potential antihyperlipidemic activity. Nevertheless, the conclusions of this study are based exclusively on computational predictions. Therefore, additional investigations, including molecular dynamics (MD) simulations, chemical synthesis, biochemical enzyme inhibition studies, and comprehensive in vitro and in vivo evaluations, are required to verify the biological activity, safety, and therapeutic efficacy of these compounds. Overall, this study provides a valuable platform for future medicinal chemistry research and supports the continued development of innovative antihyperlipidemic agents targeting HMG-CoA reductase.

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