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Identification of Potent Small-Molecule PCSK9 Inhibitors Based on Quantitative Structure-Activity Relationship, Pharmacophore Modeling, and Molecular Docking Procedure

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Abstract

The leading cause of atherosclerotic cardiovascular disease (ASCVD) is elevated low-density lipoprotein cholesterol (LDL-C). Proprotein convertase subtilisin/kexin type 9 (PCSK9) attaches to the domain of LDL receptor (LDLR), diminishing LDL-C influx and LDLR cell surface presentation in hepatocytes, resulting in higher circulating LDL-C levels. PCSK9 dysfunction has been linked to

lower levels of plasma LDLC and a decreased risk of coronary heart disease (CHD). Herein, using virtual screening tools, we aimed to identify a potent small-molecule PCSK9 inhibitor in compounds that are currently being studied in clinical trials. We first performed chemical absorption, distribution, metabolism, excretion, and toxicity (ADMET) filtering of 9800 clinical trial compounds obtained from the ZINC 15 database using Lipinski's rule of 5 and achieved 3853 compounds. Two-dimensional (2D) quantitative structure-activity relationship (QSAR) was initiated by computing molecular descriptors and selecting important descriptors of 23 PCSK9 inhibitors. Multivariate calibration was performed with the partial least square regression (PLS) method with 18 compounds for training to design the QSAR model and 5 compounds for the test set to assess the model. The best latent variables (LV) (LV=6) with the lowest value ofRoot-Mean-Square Error of Cross-Validation (RMSECV) of 0.48 and leave-one-out cross-validation correlation coefficient (R^2CV) = 0.83 were obtained for the QSAR model. The low RMSEC (0.21) with high R^2cal (0.966) indicates the probability of fit between the experimental data and the calibration model. Using QSAR analysis of 3853 compounds, 2635 had a $pIC_{50}<1$ and were considered for pharmacophore screening. The PHASE module (a complete package for pharmacophore modeling) designed the pharmacophore hypothesis through multiple ligands. The top 14 compounds ($pIC_{50}>1$) were defined as active, whereas 9 ($pIC_{50}<1$) were considered as an inactive set. Three five-point pharmacophore hypotheses achieved the highest score: DHHRR1, DHHRR2, and DHRRR1. The highest and best model with survival scores (5.365) was DHHRR1, comprising 1 hydrogen donor (D), 2 hydrophobic groups (H), and 2 rings of aromatic (R) features. We selected the molecules with a higher 1.5 fitness score (257 compounds) in pharmacophore screening (DHHRR1) for molecular docking screening. Molecular docking indicates that ZINC000051951669, with a binding affinity: of -13.2 kcal/mol and 2 H-bonds, has the highest binding to the PCSK9 protein. ZINC000011726230 with energy binding: -11.4 kcal/mol and 3 H-bonds, ZINC000068248147 with binding affinity: -10.7 kcal/mol and 1 H-bond, ZINC000029134440 with a binding affinity: -10.6 kcal/mol and 4 H-bonds were ranked next, respectively. To conclude, the archived molecules identified as inhibitory PCSK9 candidates, and especially ZINC000051951669 may therefore significantly inhibit PCSK9 and should be considered in the newly designed trials.

Introduction

The greatest risk factor for the onset of atherosclerotic cardiovascular disease (ASCVD) events is elevated low-density lipoprotein cholesterol (LDL-C).[1,2] The evidence for a link between hypercholesterolemia and the risk of ASCVD has led to the development of

various guidelines and evidence-based recommendations for lowering lipid levels. These guidelines have changed throughout time to stress lower levels of plasma LDL cholesterol (LDLC) and non-HDL cholesterol (non-HDLC).[3,4] Familial hypercholesterolemia (FH) is an autosomal dominant genetic metabolic disorder defined by severely elevated blood LDL-C and other symptoms, including xanthomas and a history of premature coronary artery disease (CAD).[5] Because the frequency of CAD is exceptionally high in FH patients and the onset is 15-20 years earlier than average, early identification, and therapy to prevent or postpone the development of atherosclerosis are essential. According to various studies, FH heterozygotes are found in 1 in 250-300 people, and even 10% of individuals with acute coronary syndrome may have FH.[6,7] FH is thus one of the most important underlying disorders of CAD from the standpoint of public health.[8]

Despite the notable effectiveness of statin therapy, there are still considerable deficiencies in the management of hypercholesterolemia and, thus, many people on statin therapy still develop atherosclerosis. Due to severe hypercholesterolemia or poor adherence to existing treatments, some patients have consistently elevated LDL-C levels. Newer, more effective lipid-modifying preparations may provide therapeutic advantages for these patients.9, 10, 11, 12, 13

The discovery of proprotein convertase subtilisin/kexin type 9 (PCSK9) in 2003 opened up the possibility of filling some of the gaps in hypercholesterolemia therapy.[14] PCSK9 consists of 692 aminoacids, with the signal peptide being residues 1-30. The remaining protein is usually split into 3 domains. The prodomain is made up of residues 31-152, the catalytic domain is made up of residues 153-454, and the C-terminal domain is made up of residues 455-692.[15] It is critical to mention, however, that PCSK9 is also present in other organs.[16] PCSK9 attaches to the epidermal growth factor-like repeat A (EGF-A) domain of nascent LDLR in the trans-Golgi apparatus and makes it suitable for lysosomal breakdown.[17] PCSK9 binds to LDLR on the cell surface after being secreted by hepatocytes, forming the LDLR–PCSK9 complex. The endocytic recycling of LDLR for lysosomal breakdown is hampered by this complex.[18,19] These 2 processes work together to diminish LDL-C influx and LDLR cell surface presentation in hepatocytes, resulting in higher circulating LDL-C levels.[20] Gain-of-function mutations in the PCSK9 gene provoke phenotypical FH by reducing the number of LDL receptors (LDLRs) on the hepatocyte surface.[21,22] PCSK9 dysfunction (including loss-of function mutations) has been linked to lower levels of plasma LDLC and a decreased risk of coronary heart disease (CHD) of 88 percent over 15 years of follow-up.[23,24]

Monoclonal antibodies that inhibit the formation of the PCSK9-LDLR complex, antisense oligonucleotides and small interfering

RNA (siRNAs) that reduce PCSK9 gene expression, and synthetic proteins (adnectin) or high-binding affinity mimetic peptides (annexin A2) that bind to PCSK9 and inhibit its interaction with LDLR were all used to investigate the effect of PCSK9 inhibition. However, due to their status as biological products, these medicines could elicit several immune-mediated responses that can culminate in the generation of neutralizing antibodies and ensuing reduction in efficacy. Moreover, their administration is typically by injection, unlike the small molecules commonly administered orally, and the high costs of these therapeutic approaches make prior authorization difficult and may hinder long-term adherence. The development of small-molecule PCSK9 inhibitors, because of their high potential and low cost, has garnered much interest in recent years.[25,26]

Numerous drugs are produced through a series of randomized clinical studies that can be time-consuming, expensive, or fail to demonstrate high inhibition. The use of theoretical approaches as an alternative means for estimating chemical activity might reduce the likelihood of false negatives prior to any testing.[27] Virtual screening is the notion of drug discovery based on a computational strategy for finding new lead compounds for medication development. Therefore *in-silico* approaches can represent a broad and promising approach to discovering a novel target protein with the prediction of its biological activity.[28]

There are 2 basic virtual screenings, including target-based (structure-based) and ligand-based screening.[29] The target-based virtual screening is based on the biological target's 3-dimensional (3D) structure. In this approach, compounds in databases were docked against a protein target to find the best compounds that fit into the target's binding site.[30,31] Another approach (ligand-based) is based on the knowledge of known active chemicals. These compounds were utilized to create a pharmacophore and Quantitative Structure-Activity Relationship (QSAR) models, which specify the structural features that a molecule must possess in order to bind to the target.[32]

In this current work, virtual screening tools were employed to explore a potent small-molecule PCSK9 inhibitor in compounds that are already being studied in clinical trials. Due to their having already passed initial safety studies, these drugs can be accelerated for use as PCSK9 inhibitors.

Section snippets

Methods

In the present study, we first performed chemical absorption, distribution, metabolism, excretion, and toxicity (ADMET) filtering; then, the QSAR model was generated for PCSK9 inhibitors to predict and find the highest plogIC_{50} of the molecular library. Subsequently, pharmacophores designed to find hit compounds were then docked with PCSK9 to explore lead compounds. The workflow overview for this research is depicted in Figure 1.…

QSARModel Development Through PLS

After data pre-treatment with S-MLR, 21 PaDEL descriptors remained for the 2D-QSAR model; these were SpMAD_Dzv, ASP-6 minHBd, nRing, ATSC4v, nHaaCH, AATSC7v, VR1_Dzp, SaasC, AATSC4i, SIC2, minHBint7, ATSC7v, AATSC8i, BCUTw-1l, GATS3m, ASP-7, VCH-5, AATSC8e, maxHBint4, and Zagreb, and these were utilized to construct a multivariate calibration QSAR model (Table 2). The description of the descriptors is detailed in Supplementary Table 1.

In QSAR model development, datasets of 23 compounds were…

Discussion

Because PCSK9 is an appealing target for ASCVD therapy development, the prediction of its inhibitors has garnered considerable attention in recent years. This work aimed to build QSAR and pharmacophore models to screen new drugs and perform docking with PCSK9 to explore their interactions with the PCSK9 protein. We used a set of compounds currently being tested in clinical trials to bypass in-vitro experiments and to enhance primary tests for further investigation. We first selected the…

Conclusions

The archived molecules identified as inhibitory PCSK9 small-molecule candidates, and especially ZINC000051951669, may significantly inhibit PCSK9 and should be considered in newly designed trials. However, further in vitro and in vivo work together

with clinical studies are required to validate these findings.…

Ethical Approval

No experimental or clinical work was conducted; no patient data was used. Therefore, no ethical approval was required for this work.…

References (92)

GA Roth *et al.*
Global burden of cardiovascular diseases and risk factors, 1990-2019: update from the GBD 2019 study
J Am Coll Cardiol (2020)

M Banach *et al.*
Optimal use of lipid-lowering therapy after acute coronary syndromes: a position paper endorsed by the International Lipid Expert Panel (ILEP)
Pharmacol Res (2021)

K Dyrbuś *et al.*
The prevalence and management of familial hypercholesterolemia in patients with acute coronary syndrome in the Polish tertiary centre: results from the TERCET registry with 19,781 individuals
Atherosclerosis (2019)

M. Ogura
PCSK9 inhibition in the management of familial hypercholesterolemia

J Cardiol (2018)

AA Momtazi *et al.*

Regulation of PCSK9 by nutraceuticals

Pharmacol Res (2017)

A Sahebkar *et al.*

New LDL-cholesterol lowering therapies: pharmacology, clinical trials, and relevance to acute coronary syndromes

Clin Ther (2013)

M. Farnier

PCSK9: from discovery to therapeutic applications

Arch Cardiovasc Dis (2014)

ØL Holla *et al.*

Role of the C-terminal domain of PCSK9 in degradation of the LDL receptors

J Lipid Res (2011)

S Poirier *et al.*

Dissection of the endogenous cellular pathways of PCSK9-induced low density lipoprotein receptor degradation: evidence for an intracellular route

J Biol Chem (2009)

DW Zhang *et al.*

Binding of proprotein convertase subtilisin/kexin type 9 to epidermal growth factor-like repeat A of low density lipoprotein receptor decreases receptor recycling and increases degradation

J Biol Chem (2007)

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