Identification of potent small-molecule PCSK9 inhibitors based on quantitative structure-activity relationship, pharmacophore modeling, and molecular docking procedure

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Background: 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 LDL-C and a decreased CHD risk.

Purpose: To identify a potent small-molecule PCSK9 inhibitor in compounds that are currently being studied in clinical trials.

Methods: We first performed chemical absorption, distribution, metabolism, excretion, and toxicity filtering of 9800 clinical trial compounds obtained from the ZINC 15 database using Lipinski’s rule of five 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 five compounds for the test set to assess the model. The best latent variables (LV) (LV=6) with the lowest value of Root-Mean-Square Error of Cross-Validation (RMSECV) of 0.48 and leave-one-out cross-validation correlation coefficient (R²CV)=0.83 were obtained for the QSAR model. The low RMSEC (0.21) with high R²cal (0.966) indicates the probability of fit between the experimental data and the calibration model.

Results: Using QSAR analysis of 3853 compounds, 2635 had a pIC50<1 and were considered for pharmacophore screening. The PHASE module designed the pharmacophore hypothesis through multiple ligands. The top 14 compounds (pIC50>1) were defined as active, whereas nine (pIC50<1) were considered as an inactive set. Three five-point pharmacophore hypotheses achieved the highest score: DHHR1, DHHR2, and DHRR1. The highest and best model with survival scores (5.365) was DHHR1, comprising one hydrogen donor (D), two hydrophobic groups (H), and two rings of aromatic (R) features. We selected the molecules with a higher 1.5 fitness score (257 compounds) in pharmacophore screening (DHHR1) for molecular docking screening. Molecular docking indicates that ZINC000051951669, with a binding affinity: -13.2 kcal/mol and two H-bonds, has the highest binding to the PCSK9 protein. ZINC000011726230 with energy binding: -11.4 kcal/mol and three H-bonds, ZINC000068248147 with binding affinity: -10.7 kcal/mol and one H-bond, ZINC000029134440 with a binding affinity: -10.6 kcal/mol and four H-bonds were ranked next, respectively.

Conclusion: 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.

Figure 1. The six-top docking compound against PCSK9 with lowest binding affinity. A) ZINC000051951669, B) ZINC000011726230, C) ZINC000068248147, D) ZINC000029134440, E) ZINC000000602086, F) ZINC000034630885.