

# Penapisan virtual berbasis farmakofor sebagai kandidat inhibitor Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) dari Pangkalan Data HerbalDB = Pharmacophore-based virtual screening as Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) candidate inhibitor of HerbalDB Database

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## Abstrak

Penggunaan antibodi monoklonal, seperti alirocumab dan evolocumab sebagai inhibitor PCSK9 telah disetujui oleh U.S. FDA dan European Medicines Agency karena mampu menurunkan kadar LDL. Tetapi, kedua obat ini hanya dapat diadministrasikan secara parenteral sehingga para peneliti masih mencari alternatif lain untuk mengatasi keterbatasan tersebut. Pada penelitian ini, senyawa dari golongan tetrahidroisoquinolin, fenilpiperazin, fenilalanin, dan benzofuran digunakan sebagai training set untuk mendapatkan model farmakofor yang berpotensi sebagai inhibitor PCSK9. Tahapan seperti pembuatan model farmakofor, validasi, optimasi, serta penapisan virtual dilakukan melalui LigandScout. Model farmakofor yang terbangkitkan memiliki skor 0,7031 dengan empat fitur farmakofor, yaitu satu AR, satu H, satu HBA, dan satu HBD. Model farmakofor kemudian dioptimasi menggunakan active set dari ligan terpilih dan decoy set dari DUD-E. Optimasi dengan penambahan feature weight sebesar 0,1 terhadap keempat fitur tersebut memberikan hasil validasi terbaik yang ditunjukkan dengan nilai AUC100%, EF1%, EF5%, sensitivitas, dan spesifitas berturut-turut sebesar 0,93; 34,0%; 6,0%; 1,00; dan 0,79. Hasil penapisan virtual menggunakan model farmakofor tersebut kemudian dievaluasi berdasarkan kaidah Lipinski's Rule of Five dengan KNIME. Sebelas senyawa bahan alam dari HerbalDB yang berpotensi untuk dikembangkan menjadi terapi anti-PCSK9 dalam bentuk sediaan peroral, antara lain morindone, gentisin, mesuaxanthone A, beta-phenethylamine, brazilin, pterofuran, n-cis- feruloyltyramine, bethanidine, 6-methoxykaempferol, gartanin, dan alizarin.

.....The use of alirocumab and evolocumab as PCSK9 inhibitors has been approved by U.S. FDA and European Medicines Agency because of their ability to reduce LDL levels. However, these monoclonal antibodies must be administered parenterally, so researchers are devising alternative strategies to overcome its limitation. In this study, tetrahydroisoquinoline, phenylpiperazine, phenylalanine, and benzofuran compound groups were used as training sets to obtain a pharmacophore model. The process of making a pharmacophore model, validation, optimization, and virtual screening were done using LigandScout. The generated pharmacophore model scored 0.7031 with four pharmacophore features, namely one AR, one H, one HBA, and one HBD. The model was then optimized using the active and decoy set from DUD-E. Optimization by increasing the feature weight by 0,1 to the four features gave the best validation result as indicated by the values of AUC100%, EF1%, EF5%, sensitivity, and specificity are 0.93; 34.0%; 6.0%; 1.00; 0.79 respectively. The virtual screening results using the optimized model were evaluated based on Lipinski's Rule of Five with KNIME. Eleven natural compounds from HerbalDB that may be developed into anti-PCSK9 therapy in oral dosage form were obtained, including morindone, gentisin, mesuaxanthone A, beta-phenethylamine, brazilin, pterofuran, n-cis-feruloyltyramine, bethanidine, 6-methoxykaempferol, gartanin, and alizarin.