Steroidal Pregnanes as 11β-HSD1 Modulators: Insights from Random Forest-Based QSAR and Atomistic Simulations

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Abstract

The enzyme 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) is a validated therapeutic target for Type 2 diabetes mellitus due to its role in local regeneration of active glucocorticoids. Current inhibitors are often limited by their constrained chemical diversity, moderate potency, and off-target effects. The therapeutic potential of steroidal pregnanes in diabetes and metabolic disorders is been widely reported; however, their molecular targets, particularly in glucocorticoid signaling, remain poorly understood. This study explored the interactions of a curated library of steroidal pregnanes with 11β-HSD1 using integrated Machine Learning (ML)-based QSAR, molecular docking, 100 ns Molecular Dynamics (MD) simulations, and MM-GBSA binding free energy calculations. Initial exploratory chemical space analysis of the IC_{50} bioactivity dataset revealed that hydrogen donors, molecular weight, and lipophilicity may contribute to the bioactivity of 11β-HSD1 inhibitors. Evaluation of 42 ML algorithms based on performance metrics revealed Random Forest Regressor (RFR) as a top model for bioactivity predictions. Molecular docking simulation of the top RFR-predicted compounds ($pIC_{50} \geq 6.0$ and $pKi \geq 7.8$) with the active site of 11β-HSD1 identified three compounds (pregnane-3, 20-diol disulphate (P1), 20-Piperidin-2-yl-5α-pregnan-3β,20-diol (P2), and 12,20-di-O-benzoyl-pregnane-3β,12β,14β,20-tetraol (P3)). While the reference carbenoxolone primarily strongly involved peripheral polar contacts to stabilize its orientation, the pregnane scaffolds demonstrated deeper insertion into the hydrophobic catalytic cavity of 11β-HSD1, resulting in enhanced shape complementarity and van der Waals packing. The thermodynamic parameters computed from the MD simulation trajectories revealed both the structural stability and intrinsic conformational flexibility of the 11β-HSD1–pregnane complexes**.** Moreover, the lower MM-GBSA binding energies of P1 (-43.58 kcal/mol) and P3 (-44.95 kcal/mol) as compared with the reference carbenoxolone (-24.19 kcal/mol) indicate high binding affinity and validate the docking scores of the hits. Additionally, the leads exhibited favorable physicochemical and pharmacokinetic profiles. Overall, our findings provide mechanistic insights into ligand binding and highlight key structural features that may account for 11β-HSD1 modulation by steroidal pregnanes, offering a framework for the rational design of pregnane-derived therapeutics.

Keywords: 11β-HSD1 inhibitors, Steroidal pregnanes, Machine learning, Molecular docking, and Dynamics simulation, Antidiabetic drug discovery