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Molecular Insights into the 5α-Reductase Inhibitors: Quantitative Structure Activity Relationship, Pre-Absorption, Distribution, Metabolism, and Excretion and Docking Studies

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Abstract : 5-Alpha-reductases (5AR), a membrane bound, NADPH dependent enzyme and convert male hormone testosterone (T) into more potent androgen dihydrotestosterone (DHT). DHT is the required for the development and function of male sex organs, but its overproduction has been found to be associated with physiological conditions like Benign Prostatic Hyperplasia (BPH). Thus the inhibition of 5ARs could be a key target for the treatment of BPH. In present study, 2D and 3D Quantitative Structure Activity Relationship (QSAR) pharmacophore models have been generated for 5AR based on known inhibitory concentration (IC_{50}) values with extensive validations. The four featured 2D pharmacophore based PLS model correlated the topological interactions (–OH group connected with one single bond) (SsOHE-index); semi-empirical (Quadrupole2) and physicochemical descriptors (Mol. wt, Bromines Count, Chlorines Count) with 5AR inhibitory activity, and has the highest correlation coefficient (r^2 = 0.98, q^2 =0.84; F = 57.87, pred r^2 = 0.88). Internal and external validation was carried out using test and proposed set of compounds. The contribution plot of electrostatic field effects and steric interactions generated by 3D-QSAR showed interesting results in terms of internal and external predictability. The well validated 2D Partial Least Squares (PLS) and 3D k-nearest neighbour (kNN) models were used to search novel 5AR inhibitors with different chemical scaffold. To gain more insights into the molecular mechanism of action of these steroidal derivatives, molecular docking and in silico absorption, distribution, metabolism, and excretion (ADME) studies were also performed. Studies have revealed the hydrophobic and hydrogen bonding of the ligand with residues Alanine (ALA) 63A, Threonine (THR) 60A, and Arginine (ARG) 456A of 4AT0 protein at the hinge region. The results of QSAR, molecular docking, in silico ADME studies provide guideline and mechanistic scope for the identification of more potent 5-Alpha-reductase inhibitors (5ARI).

Keywords : 5α-reductase inhibitor, benign prostatic hyperplasia, ligands, molecular docking, QSAR
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