Combined structure- and ligand-based virtual screening: In the search of novel 11beta-hydroxysteroid dehydrogenase inhibitors for the treatment of metabolic syndrome

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Background and Aims. 11beta-hydroxysteroid dehydrogenase type 1 (11B\text{HSD1}) catalyzes the conversion of inactive cortisone to active cortisol in a NADPH dependent manner within cells of key metabolic tissues. Excess cortisol elevates blood glucose levels by increasing glucose production in liver, and by inhibiting uptake and disposal of glucose in muscle and adipose tissues, leading to insulin resistance and metabolic syndrome. Recently solved crystal structures of human 11B\text{HSD1} provide a source of structural information for the identification of novel 11B\text{HSD1} selective inhibitors using virtual screening, a complementary tool to in vitro screening to effectively identify novel bioactive compounds.

Material and Methods. An initial structural alignment of 18 crystal structures of human 11B\text{HSD1} in complex with ligands was used as starting point. Proteins were prepared using Accelrys Discovery Studio v2.1 (Accelrys Inc). The OpenNCI database containing near 260,000 compounds was filtered by ADME/Tox constraints with FILTER. Multiple conformations for each compound in the database were generated by OMEGA. Shape-based searching was performed using vROCS. Rigid docking of the conformer database was performed with FRED using the ChemGauss3 scoring function.

Results. Clustering of the co-crystallized ligands using structural fingerprints identify 4 main binding modes or clusters. The top 1000 ranked compounds resulting from the docking procedure on each cluster center protein were filtered based on docked ligand poses that satisfy essential binding features from previously obtained structure-based pharmacophore models. Finally, 40 compounds were requested to the Developmental Therapeutics Program at NCI/NIH. The biological evaluation of the selected compounds was performed in LS14 differentiated cell culture expressing 11B\text{HSD1} using cortisone as substrate. The cortisol produced was quantified by HPLC/MS/MS and the percent inhibition expressed as a percentage decrease relative to control is reported. New scaffolds displaying biological percentage inhibition in the order of 30-70% and activity within de micromole range were identified. Analog design and structure-activity relationships for lead optimization are currently ongoing.

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