Identification of novel 11?-HSD1 inhibitors by combined ligand- and structure-based virtual screening

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11 beta-hydroxysteroid dehydrogenase type 1 (11?-HSD1) converts cortisone to cortisol in a NADPH dependent manner. Overexpression of 11?-HSD1 in key metabolic tissues is related to the development of type 2 diabetes, obesity, hypertension and metabolic syndrome. Using crystal structures of human 11?-HSD1 in complex with inhibitors as source of structural information, a combined ligand and structure-based virtual screening approach was implemented to identify novel 11?-HSD1 inhibitors. A selected group of compounds was identified in silico and further evaluated in cell-based assays for cytotoxicity and 11?-HSD1 mediated cortisol production inhibitory capacity. The expression of 11?-HSD1 and 11?-HSD2 in human LS14 adipocytes was assessed during differentiation. Biological evaluation of 39 compounds in adipocytes and steroids quantification by

HPLC-MS/MS identify 4 compounds that exhibit 11?-HSD1 mediated cortisol production inhibitory activity with potencies in the micromolar range. Two