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Identification of novel ligands of human steroid 17α-hydroxylase among modified androstanes and bile acids

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In the present time testing of ligand libraries towards to the range of targets is a standard procedure in the workflow of large pharmaceutical companies and scientific laboratories that design and create effective drugs for various diseases. Today cytochrome P450 enzymes (CYPs) – are important group of drug targets. CYPs are a superfamily of heme-containing enzymes taking part in biotransformation of xenobiotics (including drugs), biosynthesis and metabolism of cholesterol, steroid hormones, fat-soluble vitamins and polyunsaturated fatty acids. Steroid 17α-hydroxylase (CYP17) — is a key human enzyme, taking part in steroid hormone biosynthesis. Mutations of CYP17 gene and changes in CYP17 expression level are associated with congenital adrenal hyperplasia, isolated 17,20-lyase deficiency, polycystic ovary syndrome and Cushing's syndrome. In the present study we performed initial screening of a panel of modified steroids toward human CYP17 to identify novel ligands of the enzyme – perspective high efficient inhibitors.

Recombinant human CYP17 was expressed in the *E. coli* cells, purified and used for the screening of new ligands. *In vitro* screening allowed us to find new CYP17 ligands among modified androstanes and bile acids. All the substances bind in the enzymes' active site like substrates, usually with high or moderate affinity (in comparison to substrates of this enzyme: pregnenolone, progesterone) towards human CYP17, so they could be considered as competitive inhibitors of the enzyme. *In silico* structural insights (docking followed by molecular dynamics simulation) showed that in all cases binding mode of the compounds is quite similar to the binding mode of the "essential" CYP17 ligands, while corresponding "protein-ligand" complexes are quite stable. It was found that long side chain and different modifications does not allow ligand to accept correct pose, which is necessary for hydroxylation.

Analysis of the inhibitory potential of the ligands and identification of possible products of enzymatic reactions are the main tasks of our further work.

Presented results are obtained in the frame of Belarus-Serbia bilateral project „Target-specific screening of new activity modulators of human sterol-hydroxylases" (X18-SRBG002) which is being realized between Institute of Bioorganic Chemistry of NAS of Belarus and University of Novi Sad Faculty of Sciences.