DESIGN, SYNTHESIS AND *IN SILICO* EVALUATION OF A NEW MOLECULAR PROBE FOR COVALENT MODIFICATION OF HUMAN CYTOCHROMES P450 AND STARD1 PROTEIN

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Steroids play many roles essential for both normal and pathological states of human cells and body [1]. Thus, chemically-modified steroids have found good application as drugs or molecular probes for the process management or monitoring, respectively [2, 3]. We have synthesized a new steroidal diazirine, 17-(methyl(4-(3-(trifluoromethyl)-3H-diazirin-3-yl)benzyl)amino)-androst-5-en-3beta-ol (DAMDz1), using reductive amination followed by nucleophilic substitution. Data from ESI-MS (signal from $[M+H]^+$ ion with m/z 502.4), HPLC-UV (single peak at 205 nm with RT 24.1 min; spectrum with maxima at 220 and 360 nm) and NMR confirm DAMDz1 structure. Free radical photochemistry of diazirine means 365 nm UV irradiation-induced formation of highly reactive triplet carbene, which forms a covalent adduct with amino acid of a protein-of-interest or other biomolecule in the case of co-localization, resulting in photo-crosslinking. Autodock Vina reverse virtual screening allows us to find that DAMDz1 can be bound in the active sites of cytochromes P450 CYP11A1, CYP3A4 and transport protein STARD1 in a proved ligand-like manner with a good affinity (theoretical energy of binding within -13 – -11 kcal/mol). This work impacts on development of photo-affinity probes for various steroid-binding proteins.

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References:

1. Miller W.L., Auchus R.J. Endocr Rev. 2011, 32:81-151
2. Tugaeva K.V. et al. Biochem. Biophys. Res. Commun. 2018, 497: 58-64
3. Budelier M.M. et al. J. Biol. Chem. 2017, 292:9294-9304