THE SEARCH AND *DE NOVO* DESIGN OF COMPETITIVE LOW-MOLECULAR INHIBITORS OF SARS-COV-2 3-CHYMOTRYPSIN-LIKE PROTEASE WITH ACCEPTABLE PHARMACOKINETIC PROPERTIES

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Introduction: SARS-CoV-2 is a new coronavirus that is believed to have originated at the end of 2019 in the city of Wuhan (the People's Republic of China). As of now, millions of people have died due to pathological disorders caused by this pathogen. 3CLpro is the main protease of SARS-CoV-2, which ensures the processing of two polyproteins (pp1a and pp1ab), which are directly formed as a result of the translation of the viral genome. Accordingly, inhibition of the proteolytic activity of this enzyme is obviously a promising way of countering the reproduction and spread of the new coronavirus.

The aim of this work is the search and *de novo* design of a pool of competitive low-molecular-weight inhibitors of 3CLpro enzymatic activity with pharmacokinetic properties that are likely to be acceptable for systematic use.

Methodology: Initial data were obtained from the RCSB PDB (3CLpro, PDB ID: 6w79) and DrugBank (library of FDA-approved compounds). Their preparation included the removal of all but the target molecules and the generation of possible isomeric forms. Ranking of all FDA-approved medicinal compounds according to their affinity for 3CLpro was performed by virtual screening. One selected compound was analyzed using ADMETlab 2.0. An iterative approach based on molecular dynamics simulation was used to improve its ADMET and affinity. Each of its iterations consisted of three successive stages - the molecular dynamics simulation of the ligand-receptor complex, analysis of the obtained results, and modification of the ligand. Acceptable ligand configurations were selected based on their ADMET (Absorption, Distribution, Metabolism, Excretion, Toxicity) and affinity for the 3CLpro active center (AC).

Results: Among more than 2500 FDA-approved drugs, only Anlotinib showed acceptable affinity parameters for 3CLpro (RMSD: 1.7-2 Å). At the same time, its calculated logP, logD, logS, QED and Tox21 parameters exceeded the values acceptable for medicinal compounds. Further research made it possible to design 15 Anlotinib derivatives: md_a34, md_a49, md_a86, md_a273, md_a388, md_a447, md_a452, md_a508, md_a562, md_a597, md_a603, md_a675, md_a682, md_a690 and md_a711, which are targeted to 3CLpro by two alternative forms of protonation of histidines 41, 163, 164, and 172. All of them have better predicted ADMET parameters than Anlotinib. At the same time, the degree of their affinity to the 3CLpro AC is the same or higher than that of Anlotinib.

Conclusion: Virtual screening identified Anlotinib as the only potential inhibitor among the entire library of FDA-approved medicinal compounds. Due to the unacceptability of its calculated pharmacokinetics, 15 of its structural analogues were designed, which demonstrated a much better calculated ADMET profile. At the same time, the affinity of these substances to the 3CLpro AC was preserved or improved in comparison with Anlotinib.