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Abstract

Targeting SARS-COV-2 Receptor Binding Domain with Stapled Peptides: An *In-Silico* Study

Luana Janaina de Campos, Martin Conda-Sheridan and Nicholas Palermo

University of Nebraska Medical Center; luana.decampos@unmc.edu (L.J.C.); martin.condasheridan@unmc.edu (M.C.-S.); nick.palermo@unmc.edu (N.P.)

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Abstract: SARS-COV-2 has evolved into a pandemic of unprecedent scale. This coronavirus enters cells by the interaction of the Receptor Binding Domain (RBD) with the human Angiotensin-Converting Enzyme 2 receptor (hACE-2). In this study, we employed a rational structure-based design to propose 22-mer stapled peptides using the structure of the hACE2 α-1 helix as template. These peptides were designed to retain the alfa-helical character of the natural structure, to enhance binding affinity and to display a better solubility profile when compared to other designed peptides available in the literature. We employed different docking strategies (PATCHDOCK and ZDOCK) followed by a double-step refinement process (FIBERDOCK) to rank our peptides, followed by stability analysis/evaluation of the interaction profile of the best docking predictions using a 500 ns Molecular Dynamics (MD) simulation, and a further binding affinity analysis by the Molecular Mechanics/Generalized Born Surface Area (MM/GBSA) method. Our best structure presented a stable profile and could retain important interactions with the RBD even in the presence of the E484K RBD mutation. We predict this peptide can bind the viral RBD with similar potency to the control NYBSP-4 (a 30-mer experimentally proven peptide inhibitor) displaying the advantages of being a smaller peptide. Furthermore, our study provides valuable information for the rational design of double-stapled peptide as inhibitors of SARS-CoV-2 infection.