Targeting the Spike: Repurposing mithramycin and dihydroergotamine to Block SARS-CoV-2 Infection.

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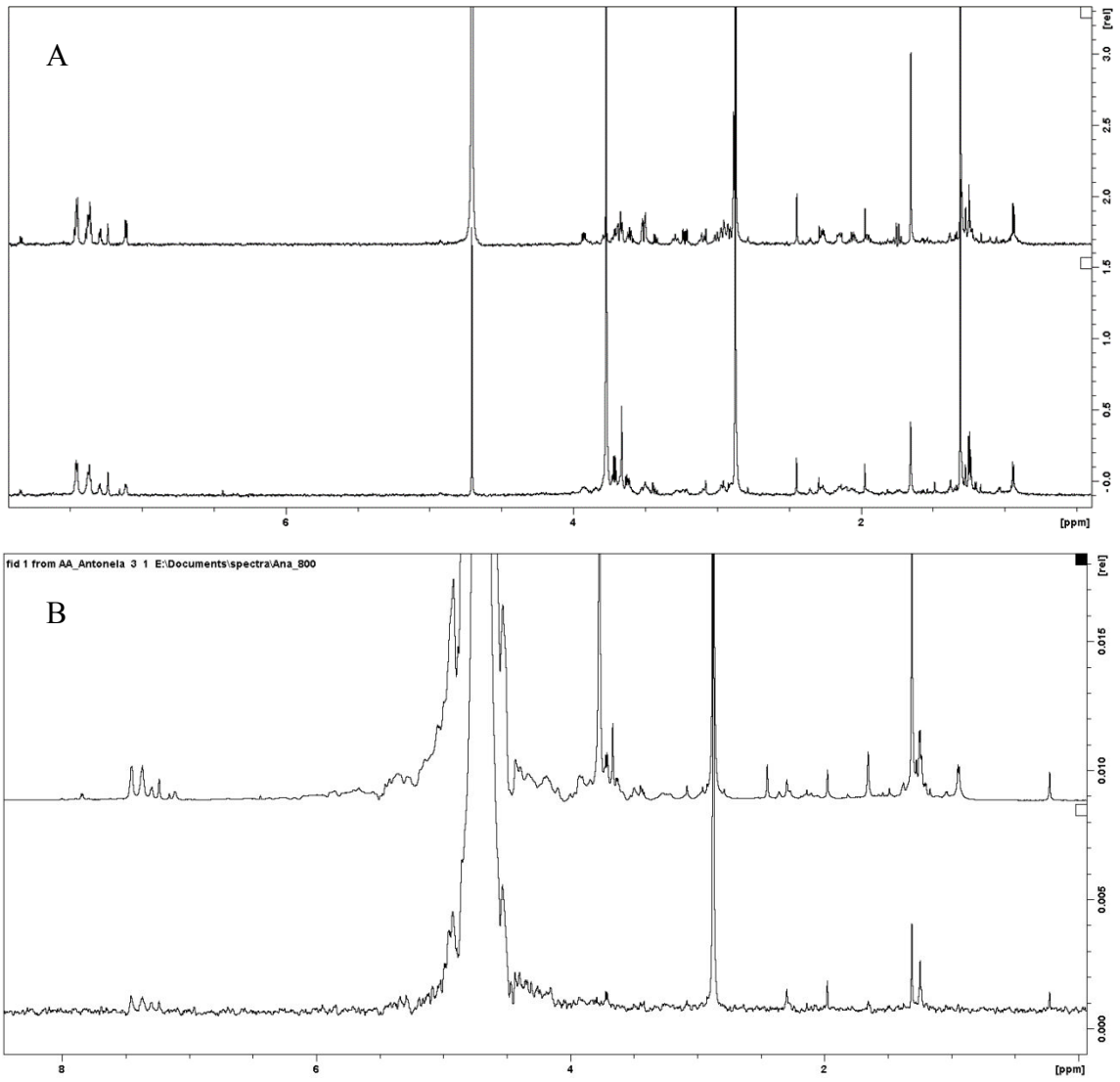

Fig.S1: NMR experiments. **A)** 1H-NMR full spectra of Dihydroergotamine free (above) and in the presence of Spike protein (below) **B)** 1H-STD-NMR experiment (lb=6Hz) of dihydroergotamine in the presence of Spike protein: STD spectrum below and corresponding off-resonance (reference) spectrum on top.

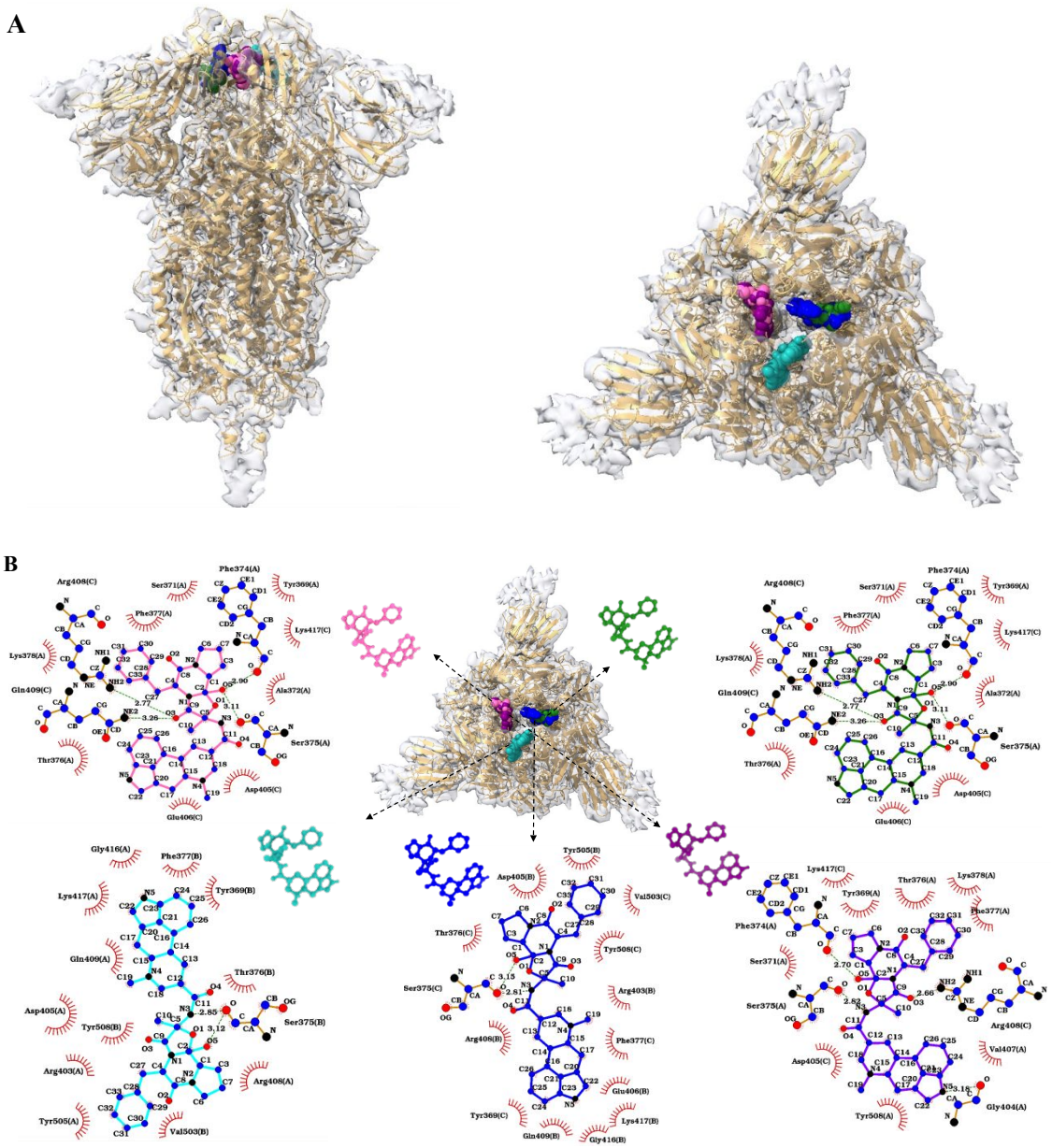

Fig. S2: Representation of docking poses of Dihydroergotamine over the apical region of the RBD-Spike protein with the highest binding affinities (-9.1 kcal/mol) . A) Views of the spike protein from the top and sides (EMDB: 21452). B) Locations in the apical region where the ligand's various conformations interact with RBD**.**

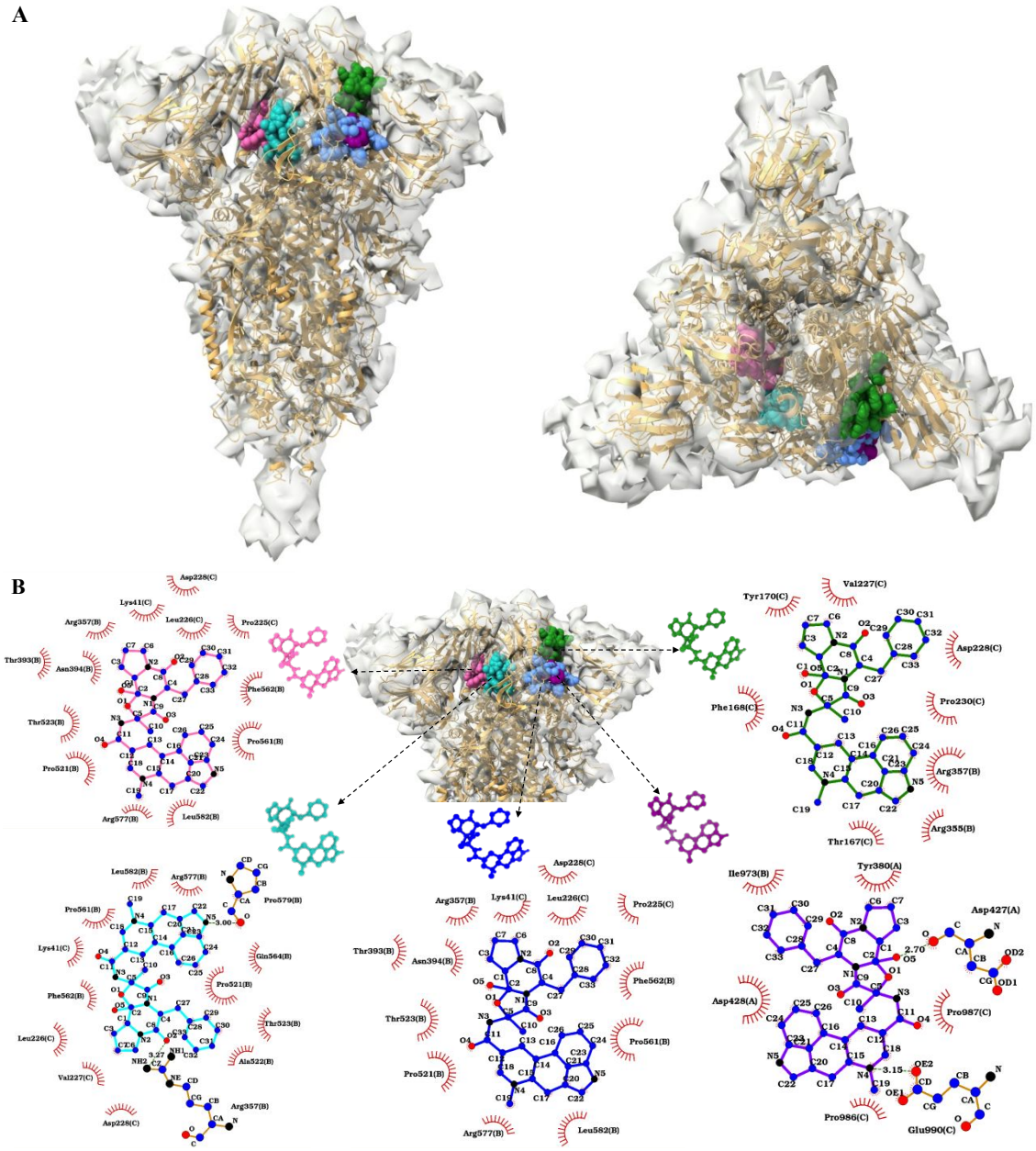

Fig. S3: Representation of docking poses of Dihydroergotamine over the lateral region of the RBD-Spike protein with the highest binding affinities (-9.4 kcal/mol) . A) Views of the spike protein from the top and sides (EMDB: 21452). B) Locations in the apical region where the ligand's various conformations interact with RBD

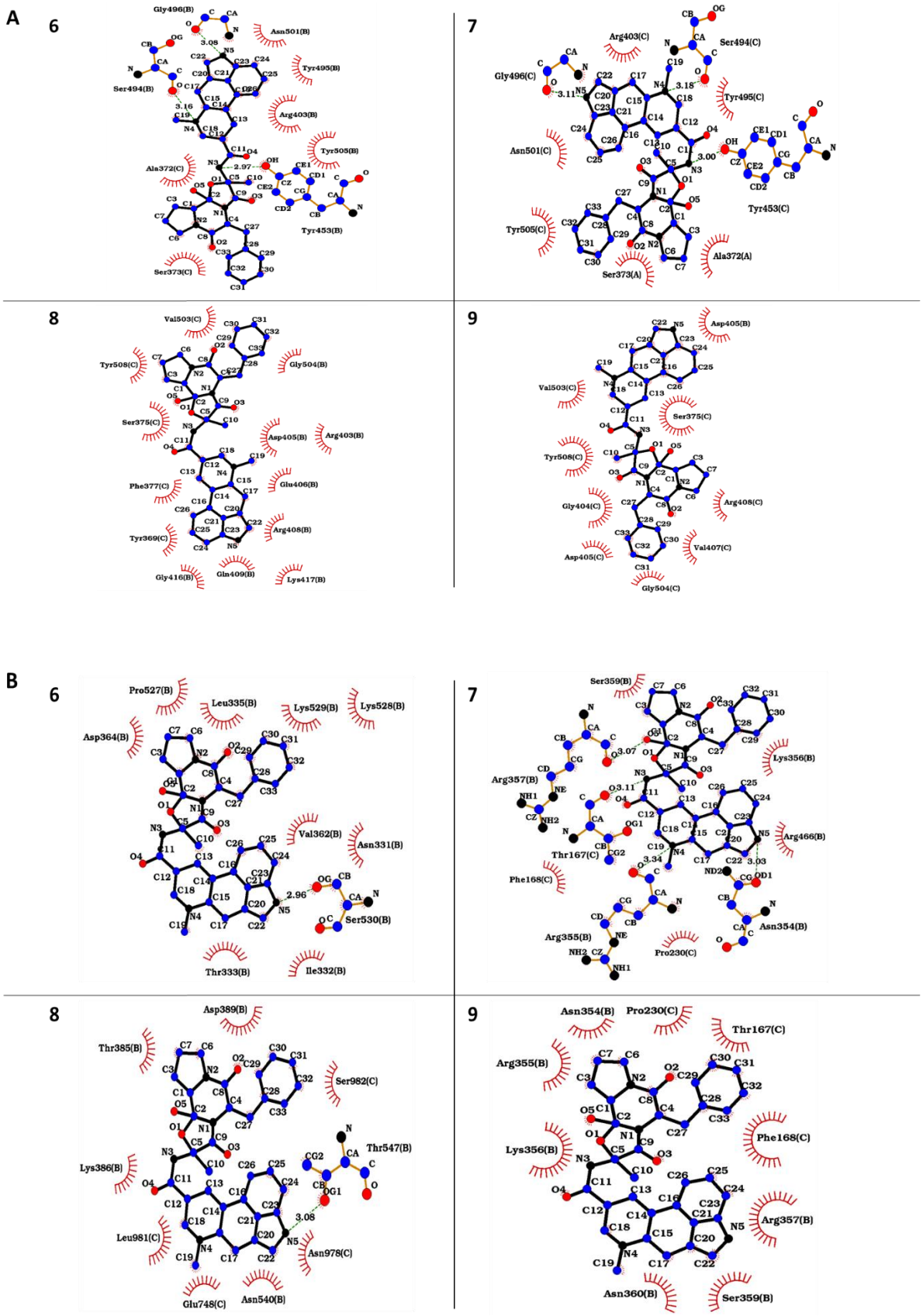

Fig. S4: 2D Plot of the remaining docking poses of Dihydroergotamine: A) over the apical region where the ligand's various conformations interact with RBD (from left to right -8.6, -8.6, -8.5, -8.4 kcal/mol); B) over the lateral region where the ligand's various conformations interact with RBD (from left to right -9.3, -9.0, -9.0, -8.9 kcal/mol).

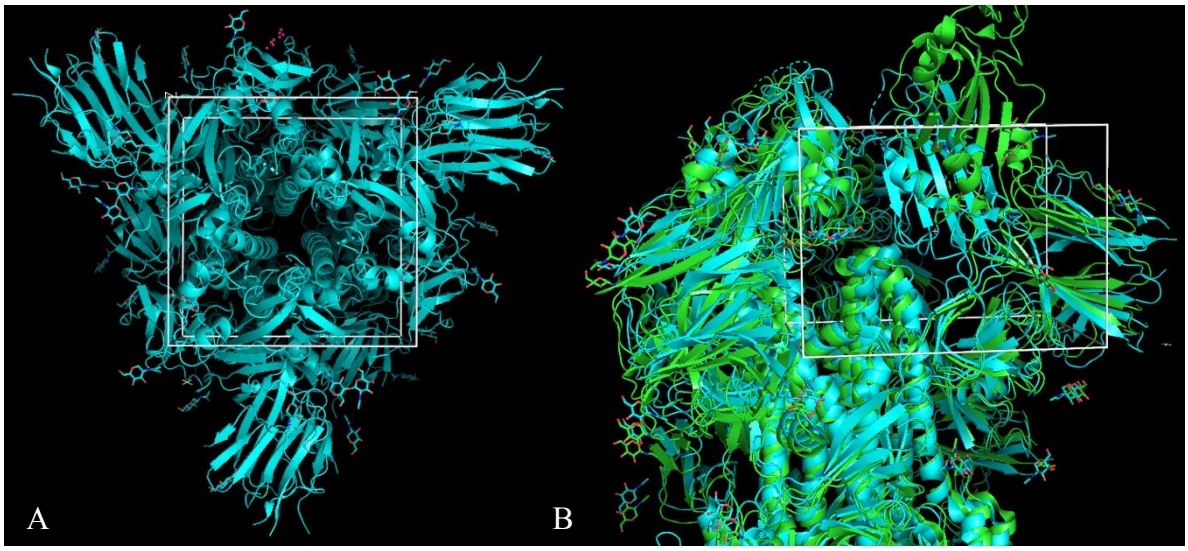

Fig S5: Schematic Representation of Docking Search Grids. (a) Depiction of the apical search grid used for the docking simulations, delineated by a cube with dimensions 47x47x47 nm, centered on the apical region of the SARS-CoV-2 spike protein. (b) Illustration of the lateral search grid for docking studies, defined by a cuboidal area of 52x44x38 nm, encompassing the lateral domain of the spike protein. In green we show the open configuration while in blue the closed one. These grids indicate the specific regions targeted during our in silico docking analyses, providing spatial context to our simulation approach.