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Structure-based Discovery of a Novel Inhibitor of SARS Coronavirus/Host Interactions. David A. Ostrov¹, Jose A. Hernandez Prada¹, Matthew J. Huentelman², Jasenka Zubcevic², Xiaodong Xiao³, Dimiter Dimitrov³, Mohan K. Raizada², Dept. of & Pathology, Immunology & Laboratory Medicine¹, Physiology & Functional Genomics², College of Medicine & Univ. of Florida, McKnight Brain Inst.¹, Gainesville, FL, & Laboratory of Experimental & Computational Biology, CCR, NCI-Frederick, National Institutes of Health³, Frederick, MD.

Angiotensin converting enzyme 2 (ACE2) is considered an important therapeutic target for controlling both cardiovascular diseases and Severe Acute Respiratory Syndrome (SARS) outbreaks. Recently solved high-resolution crystal structures of the apo- and inhibitor-bound forms of ACE2 has provided the basis for a novel molecular docking approach in an attempt to identify ACE2 inhibitors and compounds that block SARS corona virus spike protein-mediated cell fusion. In this study, approximately 140,000 small molecules were screened by *in silico* molecular docking. In this structure-activity relation study, the molecules with the highest predicted binding scores were identified, assayed for ACE2 enzymatic inhibitory activity and for their ability to inhibit SARS corona virus spike protein-mediated cell fusion. This approach identified N-(2-aminoethyl)-1 aziridine-ethanamine as a novel ACE2 inhibitor that also is effective in blocking the SARS corona virus spike protein-mediated cell fusion. Thus, the molecular docking approach resulting in the inhibitory capacity of N-(2-aminoethyl)-1 aziridine-ethanamine provides an attractive small molecule lead compound on which the development of more effective therapeutic agents could be developed to modulate hypertension and for controlling SARS infections.