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Identification of new druggable binding sites of Sars-Cov-2 nsp10, nsp14, and nsp16 proteins by using computational alanine scanning mutagenesis

SARS-CoV-2 is the etiological agent for the novel coronavirus disease 2019 (COVID- 19) global pandemic. Coronavirus replicates in host cell cytoplasm via a large membrane-associated RNA replication/transcription machinery comprising at least sixteen virus-encoded non-structural proteins (nsp1 to nsp16) [1]. Among non-structural proteins nsp10, nsp14 and nsp16 are the key components of RNA methylation process [2-4]. Accordingly, the design of peptide and peptidomimetics capable of inhibiting the interaction of nsp10 with its partner proteins nsp14 and/or nsp16 represents a promising approach for the development of new anti-viral drugs. In the frame of a multidisciplinary project (PRIN2022 Prot. 2022MBK24T), in order to identify the druggable binding sites of Sars-Cov-2 nsp10, nsp14, and nsp16 proteins, we performed hotspot prediction by means of computational alanine scanning (CAS) mutagenesis experiments on all available experimentally determined Sars-CoV-2 nsp10, nsp14, and nsp16 structures. The structures were clustered according to the protein conformational/functional state and the effect of each mutation on the binding affinity (mutation energy, ΔΔGmut) was calculated together with the root means square fluctuation (RMSF) value of each predicted hot spot residue. The predicted hot regions may include binding sites for alternative or simultaneous ligands, according to the protein functional state, providing important information to drive the design strategy.

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