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Computational Design of *1,2,3*-triazole Based Inhibitors of SARS-CoV-2 Main Protease (M^{pro}) †

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Abstract: The SARS-CoV-2 pandemic demands urgent action to obtain new pharmacological treatments, with the main viral protease (M^{pro}) attracting significant scientific attention as a therapeutic target. In this work, we design targeted covalent inhibitors (TCIs) of M^{pro} derived from the *1,2,3*-triazole scaffold. Molecular docking methods were used to evaluate the binding of TCIs to M^{pro}. A training set including reported inhibitors (boceprevir, BCP; IC50: 8 µM and GC376, IC50: 0.15µM) and inactive compounds was used to validate the docking workflow. Inhibitors were also subjected to bioisosteric replacement with *1,2,3*-triazole and further analyzed. The docking workflow reproduced the binding mode of BCP and GC376 to M^{pro}, with the corresponding *1,2,3*-triazole derivatives binding in the reactive pose and exhibiting higher affinity for the catalytic site. Inactive compounds were adequately predicted with non-reactive binding poses. Our results show that obtaining *1,2,3*-triazole based TCIs is a promising strategy for designing potent inhibitors of M^{pro}. This finding supports the bioisosteric replacement of the peptidic bond present in classic M^{pro} peptidomimetic protease inhibitors and, considering the versatility of triazole chemistry, grants the exploration of a wide chemical space for the design of inhibitors.

Keywords: 1,2,3-triazole; SARS-CoV-2 protease inhibitors; molecular modeling; medicinal chemistry.

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Conflicts of Interest

The authors declare no conflict of interest.