Drug Design for inhibition of the main protease and papain-like protease of the SARS-CoV-2 causing COVID19

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Since the outbreak of the global pandemic of the coronavirus disease 2019 (COVID19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) over 754 million cases and over 6.8 million deaths have been reported globally.[1] With seven different vaccines and eight medicines authorized for the use in the European Union (EU), as well as a vaccination rate of 82.4% (primary course) in the EU adult population, the pandemic seems to be largely under control.[2,3] However, with constantly mutating SARS-CoV-2 variants contributing to increased transmission and higher antibody resistance towards current vaccines, there remains the need for medicines that effectively target also new variants with minimal side effects.[4] The main protease (3CL^{pro}) and the papain-like protease (PL^{pro}) are both critical for the replication of the SARS-CoV-2 virus, since they process together sixteen non-structural proteins.[5] In previous *in silico* studies, we have already screened over 1 Mio compounds including approved and under investigation drugs, as well as natural products against the active site of 3CL^{pro}.[6] We then investigated the inhibition activity of the most promising candidates from the *in silico* studies and additionally several African plant extracts against the 3CL^{pro} in the wet lab with promising results.[7] In order to increase the selection and diversity of potential lead compounds in the fight against COVID19, our next step includes the computational design of D-peptides against the active sites of 3CL^{pro} and PL^{pro} considering the cleavage site consensus sequence of the substrate polypeptides. D-peptides are considerably more resistant to proteolytic degradation than L-peptides, which is why they are promising for oral drug treatment.[8] The aim of this project is to identify potential inhibitors of 3CL^{pro} and PL^{pro} using molecular docking and dynamics (MD) simulations followed by *in vitro* and *in cell* testing.

[1] Weekly epidemiological update on COVID-19 – 8 February 2023, https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports, June 2022

[2] European Medicines Agency - COVID-19 vaccines and treatments, https://www.ema.europa.eu/en, February 2023

[3] Country overview report: week 5 2023, https://covid19-country-overviews.ecdc.europa.eu, February 2023

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