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Active-learning driven chemical space exploration and relative binding affinity estimation of SARS-CoV-2 PLpro inhibitors using FEP+

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The global pandemic, initiated by the SARS-CoV-2 virus and emerging in 2020, has profoundly influenced humanity, resulting in 772.4 million confirmed cases and approximately 7 million fatalities as of December 2023. The resultant negative impacts of travel restrictions and lockdowns have highlighted the critical need for enhanced preparedness for future pandemics. This study primarily addresses this need by traversing chemical space to design inhibitors targeting the SARS-CoV-2 papain-like protease (PLpro). Pathfinder-based retrosynthesis analysis was employed to synthesize analogues of the hit, GRL-0617 using commercially available building blocks through the substitution of the naphthalene moiety. A total of 10 models were developed using active learning QSAR methods, which demonstrated robust statistical performance, including an R2 > 0.70, Q2 > 0.64, standard deviation < 0.30, and RMSE < 0.31 on average across all models. Subsequently, 35 potential compounds were prioritized for FEP+ calculations. The FEP+ results indicated that compound 45 was the most active in this series, with a ΔG of -7.28 ± 0.96 kcal/mol. Compound 5 exhibited a ΔG of -6.78 ± 1.30 kcal/mol. The inactive compounds in this series were compound 91 and compound 23, with a ΔG of -5.74 ± 1.06 and -3.11 ± 1.45 kcal/mol, respectively. The integrated strategy implemented in this study is anticipated to provide significant advantages in multiparameter lead optimization efforts, thereby facilitating the exploration of chemical space while conserving and/or enhancing the efficacy and property space of synthetically aware design concepts. Consequently, the outcomes of this research are expected to substantially contribute to preparedness for future pandemics and their associated variants of SARS-CoV-2 and related viruses, primarily by delivering affordable therapeutic interventions to patient populations in resource-limited and underserved settings.

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