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Medicinal Chemistry
STUDENT SEMINAR SERIES

Mechanistic insights into nirmatrelvir resistance of SARS-CoV-2 Mpro mutants

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SARS-CoV-2, the pathogen responsible for COVID-19 and long COVID, continues to pose a global health threat and cause considerable economic impact. Resistance to nirmatrelvir, the active agent in Paxlovid and currently the only FDA-approved oral antiviral for COVID-19, increasingly threatens the durability of current therapeutic options. Mutations in the SARS-CoV-2 main protease (Mpro) conferring resistance have been identified in vitro, in circulating strains, and in patients, yet the molecular mechanisms underlying resistance remain poorly understood. This knowledge gap, due to limited insights into the dynamic drug binding process, hinders the development of next-generation Mpro inhibitors with improved resistance profiles. To address these challenges, we leverage the weighted ensemble molecular dynamics simulations to construct a high-resolution dynamic model of nirmatrelvir binding to resistant Mpro mutants. This approach enables us to characterize in detail the binding pathways and key residues involved in drug-target interactions. Analysis of binding free energy landscapes and kinetic profiles further illuminates the dynamic mechanisms of resistance. We systematically refined simulation setups to establish best practices for capturing the ligand binding process using the weighted ensemble strategy, a highly innovative approach that opens new avenues for mechanistic exploration. Insights from this study will support the rational design of Mpro inhibitors with greater resilience to emerging mutations, advancing antiviral strategies against COVID-19 and future coronavirus threats.