

Dual Inhibition of SARS-CoV-2 PLpro for Enhanced Antiviral Efficacy and Immune Restoration

[Dr. Shailly Tomar, Professor](#)

**Department of Biosciences and Biotechnology
Indian Institute of Technology, Roorkee
Roorkee – 247 667, Uttarakhand, India**

Emerging SARS-CoV-2 variants and drug-resistant mutants threaten current therapies, underscoring the need for more effective antivirals. The papain-like protease (PLpro) is a key viral enzyme involved in replication and immune evasion, making it a promising target. Recognizing the structural and functional similarities between cellular deubiquitinating (DUBs) or deISGylating enzymes and the viral papain-like protease (PLpro), we developed an in-house library of known DUB enzyme inhibitors. Using structure-based identification tools, promising small-molecule DUBs inhibitors were found to bind strongly to the Ubiquitin/ISG15 binding site and the substrate binding cleft of PLpro. Four DUBs inhibitors significantly inhibited the proteolytic activity of purified PLpro and exhibited potent antiviral efficacy against SARS-CoV-2 in a dose-dependent manner. Further, the crystal structures of SARS-CoV-2 PLpro complexed with two inhibitors, Linagliptin and Lithocholic acid, revealed unique interactions within the Ubiquitin/ISG15 binding site (Phe69, His73, Asn128, His175) and the substrate binding cleft, offering insights into their inhibitory mechanisms. Moreover, oral and intraperitoneal administration of Linagliptin in a mouse model of SARS-CoV-2 infection increased survival, reduced lung viral load, and mitigated histopathological damage.

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