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SHORT COMMUNICATION

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Computer modeling of a potential agent against SARS-Cov-2 (COVID-19) protease

Arthur M. Lesk[1] | Arun S. Konagurthu[2] | Lloyd Allison[2] | Maria Garcia de la Banda[2] | Peter J. Stuckey[2] | David Abramson[3]

[1]Department of Biochemistry and Molecular Biology, Pennsylvania State University, University Park, Pennsylvania

[2]Faculty of Information Technology, Monash University, Clayton, Victoria, Australia

[3]Research Computing Centre, The University of Queensland, St Lucia, Queensland, Australia

Correspondence
Arthur M. Lesk, Department of Biochemistry and Molecular Biology, Pennsylvania State University, University Park, PA 16802, USA.
Email: aml25@psu.edu

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Abstract

We have modeled modifications of a known ligand to the SARS-CoV-2 (COVID-19) protease, that can form a covalent adduct, plus additional ligand-protein hydrogen bonds.

KEYWORDS

active-site ligand, COVID-19, modeling

The importance and urgency of developing drugs against COVID-19 elicited great interest on our parts in the newly released structure of the main SARS-CoV-2 protease, containing a small molecule—2-cyclohexyl-~{N}-pyridin-3-yl-ethanamide—in the active site (Protein Data Bank entry 5R84).[1]

This protease is crucial for viral infection—its function is properly to cleave into active components the polyprotein translation of the viral RNA. Ligands that bind to and block the active site can be expected to inhibit the protease and thereby frustrate the virus.

Noticing in 5R84 the proximity of atoms of the ligand to the active site cysteine of the protease (Cys145) reminded us of the approach of Pang *et al*.[2] in developing a human-safe insecticide. Pang *et al*. observed a cysteine in the active site of greenbug *Schizaphis graminum* acetylcholinesterase at a position occupied by a valine in the human homologue. They exploited this sequence difference to design a human-safe inhibitor containing methanethiosulfonate that selectively and irreversibly formed a covalent disulfide bond to the cysteine in the insect enzyme.

This suggested to us an opportunity to model, *in silicio*, analogous modifications of the ligand in 5R84 (and in other structures deposited by the same group at the same time, containing different ligands). By adding a methanethiol (CH_2SH) group to the C12 atom of the ligand, we bring the introduced sulfur atom within covalent bonding distance

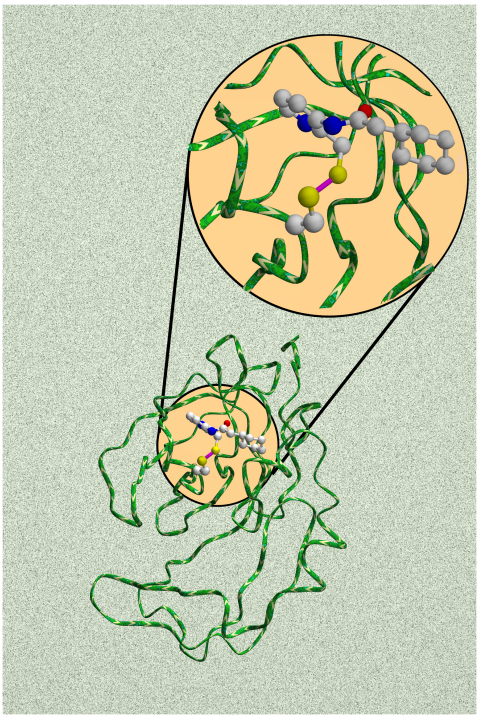

FIGURE 1 Residues 7 to 195 of the SARS-Cov-2 (COVID-19) main protease, binding the modified ligand. The magenta bond is the putative ligand-protein disulfide bond

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of the cysteine with proper stereochemistry (Figure 1). (To achieve this structure with a drug applicable *in vivo*, the ligand would contain not methanethiol but, for instance, methanethiosulfonate as in Pang *et al.*[2]).

In addition, we note that a hydroxyl group added to C6 of the ligand could form a hydrogen bond to the sidechain of His41, and that an amino group added to C11 could form a hydrogen bond to the carbonyl oxygen of Phe140.

It is our hope that these suggestions will contribute to the development of drugs effective against COVID-19.

ORCID

Arthur M. Lesk https://orcid.org/0000-0002-2596-0601

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