Acetamido-Propanoic Acid Derived Compounds as Protease Inhibitors to Target Coronaviruses

Arun HS Kumar¹ and Vikram Sharma²

ABSTRACT
Background: Coronavirus infection as evolved into a major pandemic and is currently being treated using established antiviral agents developed for other similar viruses. Considering the frequent mutations rate in this virus, novel drugs will be necessary for effective treatment in future. Hence this study evaluated the potential of acetamido-propanoic acid derived compounds as viral protease inhibitors. Materials and Methods: Using cheminformatics approach novel acetamido-propanoic acid derived compounds were designed and their binding efficacy against the Coronavirus 2019 (Covid-19) protease was tested using in silico pharmacology. Results: STGYC compounds had physico-chemical features favourable for developing them for potential clinical use. The binding efficacy of STGYC compounds against Covid-19 protease was similar to that of favipiravir, which currently being reported to be effective in treating coronavirus infection. Conclusion: STGYC compounds shown favourable features to be further evaluated and developed as viral protease inhibitors.

Key words: Protease inhibitors, SARS-CoV-2, Pandemic, Coronavirus, Covid-19, Antiviral drugs.

INTRODUCTION
The last decade as witnessed major epidemics from coronavirus infections, which are known to cause respiratory and enteric symptoms.¹⁻³ Coronaviruses with their genome size ranging from 27-34 kilobases are the largest among the RNA viruses and are enveloped with a positive sense single stranded RNA and nucleocapsid of helical symmetry.¹⁻³ The coronaviruses enters the host cells by attaching to the cell surface receptor using its spike proteins, which is a key step in the coronavirus infectivity. In addition to the coronavirus spike proteins, its envelope, matrix, nucleocapsid and other non-structural proteins are involved in various stages of viral replication and pathogenesis.¹⁻³ Hence several of these viral proteins have been targeted to develop antiviral drugs. Several broad spectrum antiviral drugs are available to treat viral infections albite with varying efficacy (http://drugvirus.info/).¹⁻³ Among these antiviral drug categories, the protease inhibitors are widely used and to best of our knowledge, protease inhibitors have been the first line of drugs to treat the current pandemic of the novel coronavirus of 2019 (Covid-19).¹⁻³,⁶,⁷ Hence in this work using the reported crystal structures of covid-19, an in silico pharmacological approach was used to develop novel inhibitors of covid-19 protease.¹⁻³

MATERIALS AND METHODS
The protein data bank (https://www.rcsb.org/) was screened for the reported crystal structures of Covid-19 proteins. Of the nine reported crystal structures of covid-19 proteins until 15th March 2020, seven were shortlisted in our analysis. PDB files of the reported protein crystal structures were downloaded. VADAR version 1.8 (http://vadar.wishartlab.com/) was used for the structural and stereochemical analysis of the protein structures. Using a cheminformatics approach novel Acetamido-propanoic acid derived compounds were designed and assessed in the ChemDraw software. Molecular docking was performed to reveal the interactions of novel ligands against the target protein i.e., Covid-19 protease using AutoDock Vina and the docked protein-ligand complex were visualised using the PyMOL v 1.8.2.0 software.¹⁻³

RESULTS
The seven Covid-19 protein structures analysed are listed in Table 1. The molecular weight of the proteins and the best peptide sequences which may find application in antibody generation were identified in the VADAR screening. The structural analysis was focused at evaluating the relative proportion of helix, beta-sheet, coil, turns and the hydrogen-bonds (HBonds) (Figure 1). The total accessible surface area (ASA), ASA of the protein backbone and sidechains are reported in Figure 2. The volume of the protein structures analysed in summarised in Figure 3.

A representative of acetamido-propanoic acid derived compounds is shown in Figure 4a. These compounds are code named as STGYC compounds. The general physico-chemical characteristics of the

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Table 1: List and details of the covid-19 protein crystal structures evaluated

<table>
<thead>
<tr>
<th>PDB file ID</th>
<th>Details</th>
<th>M Wt</th>
<th>Antigenic Sequence</th>
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<tbody>
<tr>
<td>5R80</td>
<td>Crystal Structure of COVID-19 main protease in complex with Z18197050</td>
<td>33522.64</td>
<td>TVNVLAWLYA</td>
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<td></td>
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<td>PLTQDHVDVL</td>
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<td>VLDMCASLKE</td>
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<td>6M03</td>
<td>Crystal structure of COVID-19 main protease in apo form</td>
<td>33797.96</td>
<td>GKVEGMVQV</td>
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<td>GNVQLRVIGH</td>
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<tr>
<td>6VW1</td>
<td>Structure of 2019-nCoV chimeric receptor-binding domain complexed with its receptor human ACE2</td>
<td>181354.5</td>
<td>STIEEQAKTF</td>
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<tr>
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<td>LFYQQSLASW</td>
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<td>6VYO</td>
<td>Crystal structure of RNA binding domain of nucleocapsid phosphoprotein from SARS coronavirus 2</td>
<td>54732.61</td>
<td>IIWVATEGAL</td>
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<td>6W01</td>
<td>Crystal Structure of NSP15 Endoribonuclease from SARS CoV-2 in the Complex with a Citrate</td>
<td>77760</td>
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<td>LTVFDDGRVD</td>
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<td>6W02</td>
<td>Crystal Structure of ADP ribose phosphatase of NSP3 from SARS CoV-2 in the complex with ADP ribose</td>
<td>35650.16</td>
<td>ADPIHSLRVC</td>
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<td>EDIQKLKASY</td>
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<td>6Y84</td>
<td>COVID-19 main protease with unliganded active site (2019-nCoV, coronavirus disease 2019, SARS-CoV-2)</td>
<td>33522.64</td>
<td>SGFRKMAFPS</td>
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</table>

Figure 1: Ramachandran plots of the seven protein crystal structures. Graph represents the relative proportion of helix, beta-sheet, coil, turns and the hydrogen-bonds (HBonds) in the protein structure.

Figure 2: The total accessible surface area (ASA), ASA of the protein backbone and sidechains of the seven covid-19 proteins.

Figure 3: Volume of the seven covid-19 proteins.

STGYC compounds is summarised in Table 2. Two of the STGYC compounds (STGYC 7126 and 7126A) were docked against the crystal structure of Covid-19 protease (PDB ID 6Y84) and their binding affinities are compared with that of the standard compounds i.e., Favipiravir and Lopinavir/Ritonavir (Table 3). The ligand bound to its receptor site on the Covid-19 protease is shown in the Figure 4B.
favipiravir, which is reported to be effective in treating COVID-19 infection. The binding affinity and the physico-chemical properties of the STGY compounds were within the favourable range for them to further develop for clinical use. Considering the highly mutating nature of the coronaviruses including the COVID-19,[2, 3] it is necessary to have alternatives such as the STGY compounds as potential viral protease inhibitors. We have also included in this study the structural and stereo-chemical features of 7 COVID-19 proteins, which are potentially targetable. In further studies we will look at the feasibility of STGY compounds to target these alternate COVID-19 targets using the in silico described here.

In summary, STGY compounds have favourable features to be developed as protease inhibitors for future clinical application.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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ABBREVIATIONS

RNA: Ribonucleic acid
COVID-19: Illness caused by SARS-CoV-19 virus
HBond: Hydrogen Bonds
ASA: Accessible surface area

REFERENCES