Knowledge-based structural models of SARS-CoV-2 proteins and their complex with potential drugs

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ABSTRACT

The World Health Organization (WHO) has declared a pandemic of the 2019 novel coronavirus SARS-CoV-2 infection (COVID-19). There is, however, no confirmed anti-COVID-19 therapeutic currently. In order to assist structure-based discovery of repurposing drugs against this disease, knowledge-based models of SARS-CoV-2 proteins were constructed, and the ligand molecules in the template structures were compared with approved/experimental drugs and components of natural medicines. The models suggested several drugs, such as carfilzomib, sinefungin, tecadenoson, and trabodenoson, as potential drugs for COVID-19.

INTRODUCTION

The newly identified coronavirus (SARS-CoV-2) was found to cause severe pneumonia (COVID-19), and rapidly spread across the world from the initial outbreak point in Wuhan, China in late 2019[1, 2]. It became a global health emergency, and the World Health Organization (WHO) has declared a pandemic status of this novel coronavirus outbreak in Mar 11th 2020. Since no approved drug that is specifically targeted to this virus exists at this point of time, drug repositioning/repurposing is thought to be the most effective and feasible approach toward this clear and present threat, and the researchers have initiated studies by employing various means in order to found potential therapeutics [3-11].
SARS-CoV-2 genome was very close to that of the severe acute respiratory syndrome coronavirus (SARS-CoV) [1, 2]. From the past efforts to cure RNA-virus infections, including the experiences from the SARS and Middle East Respiratory Syndrome (MERS) epidemics, several potential target proteins and drugs have been proposed [12, 13]. The 3C-like (main) proteinase, surface glycoprotein [8], and RNA-dependent RNA polymerase are thought to be the most promising targets for anti-COVID-19 therapeutics. For example, the anti-HIV drug lopinavir/ritonavir, which have been proposed to treat SARS [14, 15], is expected to be effective toward SARS-CoV-2 3C-like proteinase [16-18]. Additionally, the anti-viral drug remdesivir is expected to target the RNA-dependent RNA polymerase [19].

The studies of recent drug repositioning/repurposing involve a variety of computational methods, such as network analysis, text mining, machine learning, and structural-based drug repositioning (SBDR) [20-25]. Among these methods, SBDR is most promising to find specific drugs toward a defined target protein, and it prompted the quick structure analyses of SARS-CoV-2 3C-like proteinase and surface glycoprotein [8, 26].

Although structure analyses of many other SARS-CoV-2 proteins would soon follow, predictions of other protein structures with homology/knowledge-based (theoretical) methods would be required until structure analyses are completed, especially for the proteins currently out of focus as drug-targets. In the presented study, therefore, the homology models of SARS-CoV-2 proteins and their ligand complexes
were comprehensively constructed. Also, the structural models of the complex between SARS-CoV-2 proteins and potential drugs were proposed by comparing the ligand molecules of the proteins and the approved, experimental, or natural drugs.

**MATERIALS AND METHODS**

*Homology modeling of SARS-CoV-2 proteins*

The amino acid sequences of SARS-CoV-2 proteins (Table1) were retrieved from the Refseq database at NCBI [27], and structural modeling templates were sought with the SIRD system (http://sird.nagahama-i-bio.ac.jp/sird/), which accepted multiple-query sequences and sought for similar sequences (more than 30% sequence identity to query) with known-structures in the Protein Data Bank (PDB) [28] by using BLAST [29]. This system also sought for the templates of protein complex structures, in which two or more proteins in the multiple-query were associated or any ligand bound to query proteins. The coordinates of template structures were obtained from the PDB [28], and were rendered into the biological quaternary structures.

Initial structural models were constructed by using MODELLER [30]. The models were further refined by iteratively applying molecular dynamics and geometry minimization procedures of PHENIX [31], and manual model modifications on COOT [32]. The model quality was evaluated with MolProbity [33]. The percentages of rotamer outlier, Ramachandran outlier, and crash score were monitored for each model to achieve less than 2%, 0.05%, and 5, respectively.
**Modeling of SARS-CoV-2 protein complexes with potential drugs**

The molecular formula of 8,085 drugs in total were retrieved from KEGG database [34] and DrugBank database [35]. The molecular formula of 5,780 metabolites in total, which have been used for natural medicines (natural drugs) were obtained from KNApSAcK database [36].

The structures of the ligand molecules in the known complex structures, as sought in the template-search process, were exhaustively compared with that of the drugs by using COMPLIG [37]. COMPLIG matches molecular graphs, and evaluates the similarity score of two molecules A and B as \(\min\{M(A, B)/M(A), M(A, B)/M(B)\}\), where \(M(A)\) and \(M(B)\) are the total numbers of atoms and bonds in molecules \(A\) and \(B\), respectively, and \(M(A, B)\) is the total number of atoms and bonds matched between molecules \(A\) and \(B\). Both element and chirality, if applicable, should be identical for atoms, and bond order should be identical for bonds to be matched.

Selected drug molecules were built into the protein models by superposing drug molecules to known (original) ligand molecules with COMPLIG. According to the graph matching results, the dihedral angles in the drug molecules were adjusted toward the corresponding angles in the original ligand molecules, and corresponding atoms were superposed between drug and known ligand by fixing the coordinates of the latter. The models of protein - drug complexes were further refined with PHENIX and COOT. The constraints for drug molecules were generated by using the eLBOW application in PHENIX.
RESULTS

Models of SARS-CoV-2 protein

The SARS-CoV-2 genome encodes 11 genes (open reading frames), and the polyprotein from orf1ab is processed into 16 proteins (polypeptides) through cleavages by the papain-like proteinase and 3C-like proteinase activities [1, 12, 38]. As a result of template search, the appropriate structural templates were found for 17 SARS-CoV-2 proteins among a total of 26, and their homology models were constructed (Table 1). The 9 unmodeled proteins included those from very short ORFs, namely, Nsp11 (13 amino acid residues), ORF7b (43 residues), and ORF10 (38 residues) and probable membrane proteins (nsp6, ORF3a, ORF6, M, and ORF8), which were annotated by the SOSUI server [39].

Since a considerable amount of structural studies have already done for SARS-CoV and MERS-CoV proteins, most of the available templates were from these viruses, and they had high-sequence similarity (more than 90%) to SARS-CoV-2 proteins. Two proteins, namely, papain-like proteinase (nsp3) and nucleocapsid phosphoprotein could not be modeled into a single structural model, and separated into 6 and 2 fragments, respectively. As a consequence, the coverage of structural model was lowest (56% of residues) for papain-like proteinase (nsp3).

Third region of papain-like proteinase (nsp3), nsp4, 3C-like proteinase, nsp9, endo-RNase, surface glycoprotein, envelope protein, and C-terminal region of nucleocapsid phosphoprotein were modeled into homo-multimer. As the
hetero-multimeric models, nsp7 and nsp8 were modeled into hetero-16mer, RNA-dependent RNA polymerase, nsp7, and nsp8 were modeled as hetero-tetramer (1:1:2 stoichiometry), 3'-to-5' exonuclease and nsp10 formed hetero-dimer, 2'-O-ribose methyltransferase and nsp10 also formed hetero-dimer, and homo-trimer of surface glycoprotein was modeled in complex with human angiotensin I converting enzyme 2 (ACE2) (Table 1).

Models of SARS-CoV-2 protein with drug

Although the models of SARS-CoV-2 protein would be useful for structure-based virtual screening, potential drugs for these proteins were sought by rather simple knowledge-based method in the presented study. The ligand molecules that were complexed with the homologs of SARS-CoV-2 protein in the PDB were extracted, and structurally similar molecules to the ligands were sought among the approved/experimental drugs retrieved from KEGG database [34] and DrugBank database [35]. Many of the approved drugs, such as morphine, aspirin, or penicillin, have been adapted from natural medicines [40, 41]. The molecules in the natural medicines are expected to serve as argent therapeutics. Therefore, the ligand structures were also compared with the components of natural medicines (natural drugs) registered in the KNApSAcK database [36].

The original ligand molecules and the detected drug molecules were summarized in Table 2. A total of 11 ligand molecules were matched to 21 approved/experimental and 5 natural drugs, and the complex models of the SARS-CoV-2 proteins with several
promising drugs, those with high similarity score or placed in higher ranking, were constructed as follows.

**3C-like proteinase**

3C-like proteinase is involved in the processing of viral polyprotein [42]. This enzyme is one of the most extensively studied drug target, and thus analyzed in complex with various peptide-mimetic inhibitors [43-46]. Unexpectedly, these ligands did not show very high similarity to known drug molecules (Table 2). As a peptide mimetic drug, carfilzomib showed highest score to the template ligand (ligand code AZP) of 3C-like proteinase homolog (Fig. 1A). However, the similarity score between the ligand and the drug was only 0.754. Carfilzomib is the irreversible proteasome inhibitor targeted to the subunits with chymotrypsin-like activity and has been approved for refractory multiple myeloma or Waldenström's macroglobulinemia [47, 48]. A complex model of carfilzomib - SARS-CoV-2 3C-like proteinase was constructed. In the model, carfilzomib formed a parallel β-sheet with His164 – Glu166, and side chains of His41, Cys145, Met165, Leu167, Phe185, and Gln189 contributed major interactions (Figs. 1B and 1C). These residues were conserved between the template (SARS-CoV) and the model (SARS-CoV-2) proteins. Carfilzomib covalently binds to active site threonine through epoxy moiety, and the epoxy moiety is also reactive with thiol group of cysteine [47, 49]. Although a possible covalent linkage between carfilzomib and the catalytic Cys145 of SARS-CoV-2 3C-like proteinase was not explicitly modeled, the epoxy moiety was placed close to the catalytic residue in this model.
**Surface glycoprotein-ACE2 complex**

Surface glycoprotein is used for a viral entrance into the host cell, and its cell-surface receptor is human angiotensin I-converting enzyme 2 (ACE2) [50]. ACE, a homolog of ACE2 sharing 44% amino acid sequence identity, is a major target of hypertension medicating drugs, and several ACE-drug complexes have been reported [51-53]. Lisinopril, enalaprilat, and captopril, which show similar structures to each other (Fig. 2A), have been targeted toward ACE, and approved for hypertension treatments [54-57]. In the structural complex models, these drugs were bound to the protein through a Zn$^{2+}$-coordination with Glu384, His356, and His360 (Figs. 2B and 2C). These residues were conserved between the template (ACE) and the model (ACE2) structures. Although the drug molecules also formed electrostatic interactions with Arg255 and Arg500, these residues were not conserved between ACE and ACE2. The SARS-CoV-2 surface glycoprotein interacted with ACE2 through the receptor-binding domain (RBD), while the bound drugs had no direct interaction to the RBD domain (Fig. 2C).

**2'-O-Ribose methyltransferase**

The complex of 2'-O-ribose methyltransferase (nsp16) and nsp10 is involved in the modification of the viral RNA caps [58]. The structure of 2'-O-ribose methyltransferase subunit was determined in complex with S-adenosyl-L-methionine (ligand code SAM), 7-methyl-guanosine-5'-triphosphate- 5'-guanosine (GTG), and sinefungin (SFG) [59-61]. Among these ligands, S-adenosyl-L-methionine is used for a therapeutic against
depression, liver disorders, fibromyalgia, and osteoarthritis [62], but also is an authentic substrate for this enzyme. Sinefungin is a natural drug produced by *Streptomyces griseolus*, and experimentally used as antibiotics [63-65] (Fig. 3A).

The residues of 2′-O-ribose methyltransferase, Ser74, Asp99, Asn101, Asp130, and Met131, were involved in the major interactions with sinefungin (Figs. 3B and 3C). These residues were conserved among the template proteins (SARS-CoV and betacoronavirus) and SARS-CoV-2.

As the drugs similar to these ligands, several investigational adenosine A1 receptor agonists, namely, tecadenoson, selodenoson, trabodenoson, were found (Fig. 3A). These molecules share adenosine moiety, and this moiety interact with the aforementioned 5 conserved residues in the complex models.

**DISCUSSION**

In the presented study, the knowledge-based models of SARS-CoV-2 proteins were constructed by homology modeling and comparison of the known ligands with drugs. Since a considerable number of structure analyses have already reported for coronavirus proteins including those of SARS-CoV, 66% (17/26) of the SARS-CoV-2 proteins could be modeled based on highly similar (85% sequence identity and 89% coverage on average) templates (Table 1).

Several drugs were suggested to bind to the SARS-CoV-2 targets (Table 2). The procedure employed in the presented study should largely limit the extent of search (because depend on the presence of ligands in known complex structures). However, it
is noteworthy that the binding of suggested drugs to the homologous proteins of the SARS-CoV-2 targets would be probable because of the presence of structural evidences.

The complex models were constructed for several high-scored and/or high-ranked drugs. Unexpectedly, no drug was detected for one of the most promising drug targets, 3C-like proteinase, with a similarity score higher than 0.8. In the previous study, the score more than 0.8 was suggested to be required for highly similar interactions between ligand and protein [37]. It implied that the inhibitors bound to the 3C-like proteinase in the known structures are considerably deviated from most of the approved protease-targeted drugs. For example, the anti-HIV drug lopinavir/ritonavir, which was expected to target SARS-CoV-2 3C-like proteinase [16-18], showed only limited similarity (score 0.513) to the known ligand (ligand code AXP) of SARS-CoV 3C-like proteinase (Fig. 2A). One possible reason of the low similarity to drugs is that the protease inhibitors tend to have higher-molecular weight and thus their molecular structures showed large variety. Another reason would be that a majority of the protease inhibitory drugs are targeted toward serine or zinc proteases [66, 67]. Also, the expected drug lopinavir/ritonavir has been designed for HIV-protease, which is aspartic protease. These proteases are structurally distinct from 3C-like proteinase known to be a cysteine protease. This observation implies that structure optimizations would likely be required for repurposed drugs for SARS-CoV-2 3C-like proteinase. Consequently, the presented study suggested carfilzomib, which has been targeted toward threonine protease and approved for multiple myeloma treatment [47, 48], as a marginally resembling drug.
The model showed, however, carfilzomib fit well into the active site by forming considerable stabilizing interactions and no severe steric hinderance (Fig. 1C).

Another potential target is the complex of surface glycoprotein and ACE2 to prevent virus entry into the cell [68, 69]. Many hypertension drugs are targeted to ACE, and the presented study highlighted the approved drugs, namely, lisinopril, enalaprila, and captopril, as potential ligands for ACE2. An expectation in advance was to find a drug that bound to ACE2 and also interfered the interactions between surface glycoprotein and ACE2. However, as the models revealed, the drug-binding site of ACE2 existed inside a deep cleft in the center of ACE2 molecule, and the ligands do not interact directly with the surface glycoprotein (Fig. 2C). Also, most of the drugs are targeted toward ACE (not ACE2), and ACE and ACE2 diverge considerably in their amino acid sequences (44% identity). Therefore, effects of the ACE drugs on preventing surface glycoprotein - ACE2 interactions would not be highly promising.

Another target presented results highlighted was 2’-O-ribose methyltransferase (nsp16) – nsp10 complex, which is less focused as a target of drug repurposing. 2’-O-ribose methyltransferase is required to finalize the cap structure, 7MeGpppA2OMe, of coronavirus RNAs by transferring a methyl group to 2’ OH group of ribonucleotide from S-adenosyl-L-methionine [70, 71]. The cap structure is essential for viral mRNAs to be translated and escape from innate immune system in the host cell. Thus, inhibition of this enzyme might prevent virus propagation. Despite the overall sequence identities between templates (SARS-CoV or Human betacoronavirus) and SARS-CoV-2 enzymes were relatively low (~66%), the residues interacting with the drugs were conserved.
Among the suggested drugs for this enzyme, sinefungin is a naturally occurring and verified inhibitor of 2'-O-ribose methyltransferase. Since a toxicity was detected [72], however, appreciation of this natural drug should be carefully considered. Although tecadenoson has been examined in a clinical trial for atrial fibrillation, and passed phase II test, final results were not formally reported at this point of time [73]. Trabodenoson was designed for treating ocular hypertension and primary open-angle glaucoma [74], but had failed in the phase III clinical trial test due to lack of superiority over placebo. Selodenoson was designed to control heart rate [75], and it seems still in a developmental stage. Since tecadenoson and trabodenoson appeared to have cleared the phase I tests, these drugs would worth examining against COVID-19.

Several structure determinations of SARS-CoV-2 proteins, e.g., endoRNase (PDB IDs 6vww and 6vw01) and nucleocapsid phosphoprotein (6vyo), have been reported after the modeling of the presented study have been executed. Although many of the other proteins should be under analyses undoubtedly, it would take considerable time before all structures of potential targets are experimentally elucidated. During the period until the structural determinations, theoretical models might be useful. The presented structural models are freely available from the BINDS webpage (https://www.binds.jp/SARS-CoV-2/) and also deposited in the BSM-Arc repository (BSM00015) [76].

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**AUTHOR CONTRIBUTIONS**

M.O., S.K., and T.S. conceived and designed the study. A.H., C.S. S.N. M.S. and T.S. constructed the models. A.H., C.S. and T.S. wrote the manuscript. All authors commented on the manuscript.

**DECLARATION OF INTERESTS**

The authors declare no competing interests.
| Gene       | Protein Name | Length | Model template | PDB ID     | Identity (%) | Coverage (%) | Model description | Region | Interacting protein | Model | Ligand | Rotamer outlier (%) | Ramachandran outlier (%) | Clash score |
|------------|--------------|--------|----------------|------------|--------------|--------------|-------------------|--------|---------------------|-------|--------|---------------------|--------------------------|-------------|
| orf1ab     | Leader protein | 180    | monomer(A) | 2hsxA     | 85.3         | 66.7         | monomer(A) | A: 10 - 129 | 0.97 | 0.455 |
|           | nsp2         | 638    | n.a.         | 2hsxA     | 85.3         | 66.7         | monomer(A) | A: 10 - 129 | 0.97 | 0.455 |
|           | papain-like proteinase (nsp3) | 1945 | monomer(A) | 2hsxA | 85.3 | 66.7 | monomer(A) | A: 10 - 129 | 0.97 | 0.455 |
|           | nsp4         | 500    | homo-dimer(A, B) | 2hsxA | 85.3 | 66.7 | monomer(A) | A: 10 - 129 | 0.97 | 0.455 |
|           | 3C-like proteinase | 306    | homo-dimer(A, C) | 2hsxA | 85.3 | 66.7 | monomer(A) | A: 10 - 129 | 0.97 | 0.455 |
|           | nsp6         | 290    | n.a.         | 2hsxA     | 85.3         | 66.7         | monomer(A) | A: 10 - 129 | 0.97 | 0.455 |
|           | nsp7         | 83     | homo-dimer(A, C) | 2hsxA | 85.3 | 66.7 | monomer(A) | A: 10 - 129 | 0.97 | 0.455 |
|           | nsp8         | 198    | hetero-tetramer(E, F, G, H, S, T, U, V) | 2hsxA | 85.3 | 66.7 | monomer(A) | A: 10 - 129 | 0.97 | 0.455 |
|           | nsp9         | 113    | homo-dimer(A, B) | 2hsxA | 85.3 | 66.7 | monomer(A) | A: 10 - 129 | 0.97 | 0.455 |
|           | nsp10        | 139    | hetero-dimer(B) | 2hsxA | 85.3 | 66.7 | monomer(A) | A: 10 - 129 | 0.97 | 0.455 |
|           | RNA-dependent RNA polymerase | 932 | hetero-tetramer(A) | 2hsxA | 85.3 | 66.7 | monomer(A) | A: 10 - 129 | 0.97 | 0.455 |
|           | helicase     | 601    | monomer(A) | 2hsxA | 85.3 | 66.7 | monomer(A) | A: 10 - 129 | 0.97 | 0.455 |
|           | 3'-5' Exonuclease | 527    | hetero-dimer(A) | 2hsxA | 85.3 | 66.7 | monomer(A) | A: 10 - 129 | 0.97 | 0.455 |
|           | Endo-RNase   | 346    | homo-hexamer(A, B, C, D, E, F) | 2hsxA | 85.3 | 66.7 | monomer(A) | A: 10 - 129 | 0.97 | 0.455 |
|           | 2'-O-Ribose methyltransferase | 298    | hetero-dimer(A) | 2hsxA | 85.3 | 66.7 | monomer(A) | A: 10 - 129 | 0.97 | 0.455 |
|           | nsp11        | 13     | n.a.         | 2hsxA     | 85.3         | 66.7         | monomer(A) | A: 10 - 129 | 0.97 | 0.455 |
Table 1. Continued

|   |   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|---|
| S | YP_009724390.1 | Surface glycoprotein | 1273 | 6vsbA | 100.0 | 88.6 | homo-trimer(A, B, C) | A, B, C: 13 - 1140 | EAL | 1.63 | 0.08 | 5.83 |
|   |   |   |   |   |   |   |   |   |   |   |
|   |   |   |   |   |   |   |   |   |   |   |
| E | YP_009724391.1 | ORF3a protein | 275 | n.a. |   |   |   |   |   |   |   |
| M | YP_009724393.1 | Membrane glycoprotein | 222 | n.a. |   |   |   |   |   |   |   |
| ORF6 | YP_009724394.1 | ORF6 protein | 61 | n.a. |   |   |   |   |   |   |   |
| ORF7a | YP_009724395.1 | ORF7a protein | 121 | 1yo4A | 91.4 | 90.7 | homo-pentamer(A, B, C, D, E) | A, C, D, E: 5 - 68 B: 1 - 68 | 1.67 | 0 | 4.63 |
| ORF7b | YP_009725296.1 | ORF7b protein | 43 | n.a. |   |   |   |   |   |   |   |
| ORF8 | YP_009724396.1 | ORF8 protein | 121 | n.a. |   |   |   |   |   |   |   |
| N | YP_009724397.2 | Nucleocapsid phosphoprotein | 419 | 1sskA | 81.6 | 39.1 | monomer(A) | A: 20 - 183 | 1.56 | 0 | 4.88 |
|   |   |   |   | 2jw8B | 95.8 | 30.1 | homo-dimer(A, B) | A: 243 - 367 B: 242 - 367 | 0.48 | 0 | 3.31 |
| ORF10 | YP_009725255.1 | ORF10 protein | 38 | n.a. |   |   |   |   |   |   |   |

1. "Protein" indicates Refseq IDs of SARS-CoV-2 proteins, and also serves as the model identifiers. "Model template": "Identity" and "Coverage" show amino acid sequence identity and coverage of the template structure ("PDB ID") to the corresponding SARS-CoV-2 proteins. "Model": "Model description" and "Interacting protein" show chain ID(s) of the corresponding and bounding proteins, respectively. "Region" shows chain ID(s) and the start and end residue numbers of modeled region. "Ligand" shows the names or PDB codes of ligands in the template or models structures. "Rotamer outlier", "Ramachandran outlier", and "Clash score" show the parameters of the models.
| Ligand name                          | Ligand code | Protein name                        | Protein sources                  | PDB IDs    | Score | Drug name | DB codes          |
|-------------------------------------|-------------|-------------------------------------|----------------------------------|------------|-------|-----------|-------------------|
| S-adenosyl-L-methionine             | SAM         | 2'-O-Ribose methyl transferase (nsp16) | SARS-CoV, Human betacoronavirus  | 5c8t, 3r24, 5yni, 5ynm, 5yn6 | 1.000 | Ademetionine | D07128, C00052045, D05846 |
| Sinefungin                          | SFG         | 2'-O-Ribose methyl transferase (nsp16) | SARS-CoV, Human betacoronavirus  | 2xyr, 5ynn, 5ynp, 5ynb | 1.000 | Sinefungin   | C00052045, D05846 |
| 7-Methyl-Guanosine-5'-Triphosphate-5'-Guanosine | GTG   | 2'-O-Ribose methyl transferase (nsp16) | Human betacoronavirus            | 5yni, 5ynn | 0.788 | Nadide     | D00002 |
| Ace-Ser-Ala-Val-ALC-His-H            | n.a         | 3C-like proteinase                   | SARS-CoV                         | 3avz       | n.d.  |           |                   |
| N-[(5-methylisoxazol-3-yl)carbonyl]alanyl-L-valyl-N-1-((1R,2Z)-4-(benzyloxy)-4-oxo-1-[[3R-2-oxopyrroolidin-3-yl][methyl]but-2-enyl]-L-leucinamide | n.a     | 3C-like proteinase                   | SARS-CoV-2                       | 6lu7       | n.d.  |           |                   |
| C4Z inhibitor                        | n.a         | 3C-like proteinase                   | SARS-CoV                         | 3vb5       | n.d.  |           |                   |
Table 2. Continued

| Ligand | PDB ID | Protein | Source | Template | Source Organism | Source PDB | Template Organism | Template PDB | Scoring |
|--------|--------|---------|--------|----------|----------------|------------|-------------------|------------|---------|
| Ac-ESTLQ-H | n.a | 3C-like proteinase | SARS-CoV | 3snd | Magnesium pidolate | D08263 | 0.783 | 0.779 | 0.779 | 0.775 | C00030099 | C00030100 | C00032442 |
| (5S,8S,14R)-Ethyl 11-(3-Amino-3-Oxopropyl)-8-Benzyl-14-Hydroxy-5-Isobutyl-3,6,9,12-Tetraoxo-1-Phenyl-2-Oxa-4,7,10,11-Tetraazapentadecan-15-Oate | AZP | 3C-like proteinase | SARS-CoV | 2gfb | Carfilzomib | D08880 | 0.754 | 0.779 | 0.779 | 0.775 | |
| 1-((2S)-2-(((1S)-1-Carboxy-3-Phenylpropyl)Amino)Propanyl)-L-Proline | EAL | ACE | Human | 1uze | Enalaprilat | D03769 | 1.000 | 0.932 | 0.926 | 0.925 | 0.918 | D00362 | D00621 | D03775 | D00362 |
| [N2-((S)-1-Carboxy-3-Phenylpropyl)-L-Lysyl-L-proline | LPR | ACE somatic isoform | Human | 1o86 | Lisinopril | D00362 | 1.000 | 0.932 | 0.896 | 0.867 | 0.857 | D03769 | D07892 | D03440 | D03775 |
| L-Captopril | X8Z | ACE | Human | 4c2p | Captopril | D00251 | 1.000 | 0.853 | 0.851 | 0.795 | 0.795 | D08565 | D07215 | C0007421 | D01809 |

*"Protein source" and "PDB ID" are the source organisms and PDB of the template structures, respectively. "Ligand code" is HETATM code in PDB. "DB code" is headed by D and C for the IDs of the molecules in KEGG and KNApSAcK, respectively.
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**Figure 1. 3C-like proteinase – carfilzomib model**

(A) Formula of (5s, 8s, 14r)-ethyl 11-(3-amino-3-oxopropyl)-8-benzyl-14-hydroxy-5-isobutyl-3, 6, 9, 12-tetraoxo-1-phenyl-2-oxa-4, 7, 10, 11-tetraazapentadecan-15-oate (template ligand with ligand code AZP), carfilzomib, and lopinavir/ritonavir. (B) Overall structure of the model. (C) Close view of the carfilzomib binding-site. Hydrogen-bonds are shown in yellow lines.
Figure 2. Surface glycoprotein – ACE2 – lisinopril/enalaprilat/captopril model

(A) Formula of lisinopril (ligand code LPR), enalaprilat (EAL), and captopril (X8Z).

(B) Overall structure of the model. (C) Close view of the lisinopril/enalaprilat/captopril binding-site. Hydrogen-bonds are shown in yellow lines. Lisinopril, enalaprilat, and captopril were superposed and the carbon-atoms were colored light-blue, gray, and magenta, respectively.
Figure 3. 2’-O-Ribose methyltransferase (nsp16) – nsp10 – sinefungin/tecadenoson/selodenoson/trabodenoson model

(A) Formula of sinefungin (ligand code SFG), tecadenoson, selodenoson, and trabodenoson. (B) Overall structure of the model. (C) Close view of the binding-site for sinefungin (SFG) and trabodenoson. Hydrogen-bonds are shown in yellow lines.