Promising Drug Fondaparinux for the Treatment of COVID-19: an In Silico Analysis of Low Molecular Weight Heparin, Direct Oral Anticoagulant, and Antiplatelet Drug Interactions with Host Protease Furin

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Abstract

**Purpose** As of July 2022, the COVID-19 pandemic has affected over 555 million worldwide confirmed cases and caused more than 6.3 million deaths. The studies showed that the D-dimer levels were increased in non-survivors compared to survivors and heparin treatment has begun to be administered to the patients in severe clinics. As we knew that the entrance of SARS-CoV-2 to the host cell needs to be facilitated by host proteases; we published our hypothesis that heparin as a serine protease inhibitor may block the interaction between spike protein receptor-binding domain and host proteases. In our study, we aimed to investigate the interactions between not only heparins but also other antiplatelet and anticoagulant drugs including fondaparinux.

**Methods** In this study, docking studies were carried out to evaluate the interactions between low molecular weight heparins (LMWHs) (enoxaparin, dalteparin, tinzaparin), direct oral anticoagulant, and antiplatelet drugs with host proteases. Molecular docking studies were performed by using Schrödinger molecular modeling software. 3D structures of the ligands were obtained from the 2D structures by assigning the OPLS-2005 force field using the Maestro 12.7. The 3D crystal structure of the furin complexed with an inhibitor, 2,5-dideoksistreptamin derivative, was extracted from the Protein Data Bank (PDB ID: 5MIM). Docking studies were carried out using the Grid-based Ligand Docking with Energetics module of the Schrödinger Software.

**Results** The docking studies revealed that fondaparinux was the most relevant molecule to interact with furin with a docking score of −12.74. It showed better interaction than the natural ligand of furin with an increased score compared to the docking score of −8.155 of the natural ligand. AnaGA*IsA structure representing LMWH structure has shown a docking score of −11.562 which was also better than the score of the natural ligand of furin.

**Conclusion** Our findings have shown that LMWHs and fondaparinux can be used for their possible antiviral effects in COVID-19 patients. Our results have shown that in accordance with heparin and LMWH, fondaparinux can also be a candidate for “drug repurposing” in COVID-19 therapy, not only because of their anticoagulant but also possible antiviral effects.

**Keywords** COVID-19 · Fondaparinux · Furin · Heparin · Host protease · Low molecular weight heparin · SARS-CoV-2
Introduction

As of July 2022, the COVID-19 pandemic has affected over 555 million worldwide confirmed cases and caused more than 6.3 million deaths [1]. Many clinical studies have shown that the coagulopathy associated with COVID-19 (CAC) is quite different from disseminated intravascular coagulation (DIC) caused by sepsis, and early initiation of unfractionated heparin and low molecular weight heparin (LMWH) provided better prognosis in hospitalized patients [2–5]. As we had previously hypothesized that the positive effects of heparins may not only have been caused by anticoagulant but also antiviral effects [6], and LMWH may have the potential of blocking furin protease during spike protein-ACE2 receptor interactions, we investigated the interactions between furin and heparin, direct oral anticoagulant drugs (edoxaban, apixaban, dabigatran, rivaroxaban, argatroban) and antiplatelet drugs (dipyridamole, acetylsalicylic acid, clopidogrel). Heparin binding is a common feature of some viruses as these pathogens use heparan sulfate proteoglycans (HSPGs) on the glycocalyx of the cell and internalize into the cells [7]. Therefore, heparin and heparan sulfates have been shown to stop the binding of these pathogens to HSPGs and reduce infectivity [7–9]. Recent studies have shown that the spike protein S1 subunit of SARS-CoV-2 also interacts with cellular heparan sulfates; thus, the addition of exogenous heparin leads to inhibition of this binding [10–12]. However, these studies mainly focused on the HSPG binding of spike protein but not on heparin-protease interactions that may be involved in the cellular entrance. SARS-CoV-2 recognizes ACE2 as a receptor through its receptor-binding domain (RBD), however, in addition to receptor binding; protease activators for viral entry are required. Recently Shang et al. have shown that SARS-CoV-2 is activated by not only binding to ACE2 but also the virus depends on host proteases (TMPRSS2, cathepsin, and furin) activation for infectivity [13]. Undoubtedly, COVID-19 patients are complicated by thrombotic events. Although there is not yet a consensus on the dose of heparin in hospitalized COVID-19 patients, studies have shown that these patients benefited from the usage of LMWH after hospitalization [14–16]. Bleeding is less common than clotting in COVID-19 patients, with major bleeding event 1–3% under heparin therapy [14–16]. Emerging clinical data suggest that the use of either prophylactic to intermediate doses of LMWH (e.g., enoxaparin, 40–60 mg daily) in very sick COVID-19 patients is associated with improved outcomes and a better prognosis [17]. Few studies regarding fondaparinux use in COVID-19 patients exist, supporting its equal benefit with LMWH in anticoagulation [18]. In our study, we aimed to evaluate the interactions of the mentioned anticoagulant and antiplatelet drugs with the host protease-furin, to find out their possible antiviral addition to anticoagulant effects.

It is reported that heparin binds to several plasma proteins to show its antithrombotic and anticoagulant activity. For example, directly related to the antithrombotic properties, heparin enhances approximately 1000-fold the antithrombin (AT) activity, an endogenous coagulation inhibitor to inhibit the key coagulation proteases: factor Xa and thrombin. Heparin interacts with AT via the ANAGA*ISA (GlcNAc, 6SO3-GlcAGlceNSO3, 3,6SO3*-IdoA2SO3-GlceNSO3, 6SO3) pentasaccharide sequence. Especially in bovine heparin, the natural variant compatible with high affinity for AT, instead of N-acetylation of the first amino sugar residue, having N-sulfation is also present. LMWHs are composed of a mixture of different ranges of fragments, tetra- to hexadecasaccharides, and little higher oligosaccharides. Besides tetrasaccharides, about one out of five chains of LMWHs contain the active sequence ANAGA*ISA [19–21]. Because of these reasons, in this study, we used the ANAGA*ISA sequence for representing the LMWHs for molecular docking studies on furin protease.

Particularly, after the detailed 3D structures of key proteins are resolved, it is quite efficient to use computer-aided drug design techniques to quickly identify promising drug candidates. Molecular docking is one of these techniques. There are various software available for this technique such as Schrodinger, GOLD, FlexX, and Sulflex. Schrodinger software (Glide) is one of the most used programs for molecular docking studies. There are some studies about the accuracy of Glide. Comparisons to published data on rms deviations showed that Glide was approximately twice as accurate as GOLD and FlexX and was also found to be more accurate than the Sulflex method [22, 23]. Besides, we used Schrodinger software in our previous studies several times and our results were found significant. Because of these reasons, we preferred to use this software for this study [24–26].

Herein, molecular docking studies were carried out to understand the possible interactions between LMWHs, fondaparinux, direct oral anticoagulant drugs (edoxaban, apixaban, dabigatran, rivaroxaban, argatroban), warfarin, and antiplatelet drugs (dipyridamole, acetylsalicylic acid, clopidogrel) and a known protease inhibitor camostat mesylate with furin was also investigated.

Methods

Molecular Docking Studies

Molecular docking studies were performed by using Schrödinger molecular modeling software [27, 28]. Firstly, the ligands shown in Fig. 1 were prepared by using Schrödinger, LigPrep module [29]. 3D structures of the ligands were obtained from the 2D structures by assigning
the OPLS-2005 force field using the Maestro 12.7. LigPrep module can generate the expected ionized forms at significant concentrations corresponding to the pH 7.0 ± 2.0, perform verification, generate variations, and optimize the structures of the ligands. It generates up to 32 different stereochemical structures per ligand. The bond orders and bond angles were assigned after the ligand minimization step. Epik option was used to keep the ligands in the right protonation state in biological conditions. The binding of ligands to the receptors adopts more than one conformation, and the lowest energy conformer is important for docking studies. The 3D crystal structure of the furin complexed with an inhibitor, 2,5-dideoksistreptamin derivative, was extracted from the Protein Data Bank (PDB ID: 5MIM) [30]. Before docking the ligands onto the active site of furin, the protein was prepared using the protein preparation wizard in the Schrödinger software. Hydrogen atoms were added, and the active site of the protein was defined to generate the grid. The grid box was limited to a size of 20 Å in 50.46, −35.68, and −7.92 directions at the active site.

Frequently used empirical scoring function, GlideScore, approximates the ligand binding free energy, and it has many terms, including force field (van der Waals, electrostatic) contributions and penalizing or terms rewarding interactions known to impact on binding of the ligand to the protein. It has been optimized for binding affinity prediction, docking accuracy, and database enrichment. To rank the poses of different ligands, GlideScore should be used. As it simulates a binding free energy, tighter binders were represented as more negative values. GlideScores of −10 or lower usually represent good binding [27, 28].

Our docking procedures were validated by extracting the natural ligand (2,5-dideoksistreptamin derivative) from the binding...
site and re-docking it to the furin structure with the Glide XP (Extra precision mode) mode. Also, before the re-docking process, the natural ligand was minimized with LigPrep module by using OPLS 2005 force field. Glide generates conformations internally and passes these through a series of filters. Glide successfully reproduced the experimental binding conformations of natural ligand in furin with an acceptable root mean square deviation (RMSD) value of 1.01 Å. Then, docking studies were carried out using the Grid-based Ligand Docking with Energetics module of the Schrödinger Software, the ligands were docked into the prepared grid by using “Extra precision mode,” and no constraints were defined. To predict the spatial fit into the active site of the furin, favorable ligand poses were generated, and the best-fit conformations of the ligands were evaluated and minimized to generate glide scores. The hydrogen bonds and other interactions formed with the surrounding amino acids and glide scores were used to determine the binding affinities and best alignment of the compounds at the active site of furin. The results are shown in Table 1.

### Results

In this study, in order to evaluate the interactions between low molecular weight heparins (LMWHs), fondaparinux, direct oral anticoagulant drugs (edoxaban, apixaban, dabigatran, rivaroxaban, argatroban, warfarin), and antiplatelet drugs (dipyridamole, acetylsalicylic acid, clopidogrel) with furin docking studies were carried out. To rank the poses of different ligands, we used GlideScore that simulates a binding free energy. More negative values of GlideScore describe strong interactions; −10 or lower usually represent good binding [27, 28]. The docking studies revealed that fondaparinux was the most relevant molecule to interact with furin. The docking score of fondaparinux with furin was found as −12.74. It showed better interaction than the natural ligand of furin with an increased score compared to the docking score of −8.155 of the natural ligand. AnaGA*IsA structure representing LMWH structure has shown a docking score of −11.562 which was also better than the score of the natural ligand of furin. According to our docking results, fondaparinux and LMWHs showed very strong interactions with the furin.

According to the docking studies, natural ligand (2,5-dideoxistreptamin derivative) revealed H bonds with Asp153, Leu227 (water-mediated), Glu236, Gly255 (water-mediated), Asp264, and Tyr308; pi-pi interactions with His194; and salt bridges with Asp153 and Glu257 (Fig. 2c). The calculated glide energy of 2,5-dideoxistreptamin derivative (natural ligand) was −8.155 kcal/mol. Fondaparinux revealed H bonds with His194, Leu227 (water-mediated), Glu257, Asp258 (water-mediated), and Asn295; salt bridges with His194 and Arg193 (Fig. 2d). LMWHs revealed H bonds with Arg193, His194, S-warfarin, Cys198, Tyr308, Asp153, and Glu255.

| Compound       | Glide score | Interactions                                                                 |
|----------------|-------------|-------------------------------------------------------------------------------|
| 5MIM ligand    | −8.155      | Asp153, Asp154, His194, Cys198, Leu227, Val231, Glu236, Gly255, Trp254, Gly257, Glu258, Asp264, H2O |
| Fondaparinux   | −12.754     | Asp154, Arg193, His194, Cys198, Leu227, Val231, Glu236, His194, Leu227, Asp258, Asn295, Gly255, Asp264, H2O |
| LMWHs          | −12.012     | Arg193, His194, Leu227, Asp228, Gly229, Trp254, Glu257, Asp258, Asn295, Gly255, H2O |
| Edoxaban       | −8.059      | Asp154, Arg185, His194, Leu227, Val231, Glu236, Ser253, Trp254, Gly255, Pro256, Asp264, Gly257, Asn295, H2O |
| Argatroban     | −6.880      | Asp154, Asp154, Asp191, Asn192, His194, Leu227, Asp228, Val231, Glu236, Ser253, Trp254, Gly255, Pro256, Glu257, Asp264, H2O |
| Dipyridamole   | −5.433      | Asp153, Asp153, Asp154, Met189, Asp191, Asp192, Arg193, His194, Leu227, Asp228, Gly229, Ser253, Trp254, Asp258, Gly294, Asn295, H2O |
| Dabigatran     | −5.945      | Asp153, Asp154, Asp154, Asp154, Asp191, Asp192, His194, Leu227, Asp228, Gly229, Ser253, Trp254, Asp258, Gly257, Trp328, Thr365, Asn295, H2O |
| Rivaroxaban    | −4.746      | His194, Leu227, Val231, Glu236, Trp254, Gly255, Pro256, Asn295, Thr365, Gly266, H2O |
| Aspirin        | −3.396      | Leu227, Val231, Glu236, Trp254, Gly255, Tyr308, H2O |
| Clopidogrel    | −3.196      | Leu227, Val231, Glu236, Trp254, Gly255, Pro256, Asp264, Tyr308, H2O |
| R-warfarin     | −3.003      | Asp153, Asp154, Arg185, Asp191, Asn192, His194, Leu227, Asp228, Gly229, Ser253, Trp254, Asn295, Ser368, H2O |
| Apixaban       | −1.736      | Asp153, Asp154, His194, Cys198, Leu227, Val231, Glu236, Ser253, Trp254, Gly255, Pro256, Ser368 |
| S-warfarin     | −1.881      | Leu227, Val231, Glu236, Trp254, Gly255, H2O |

**Bold:** H-bond, w, water-mediated H-bond; a, negative charge; b, positive charge; c, hydrophobic; d, polar; e, π-π stacking; f, salt bridge; g, glycine; h, π-cation interaction.
Leu227, Asp258 (water-mediated), Thr365, and Ser368; salt bridge with Arg193. The calculated glide energy of fondaparinux and LMWHs were found $-12.754$ and $-12.012$, respectively. Another tested compound, edoxaban, was found similar to the natural ligand with a glide score of $-8.059$ and revealed H bonds with Leu227 and Glu236. These three compounds (fondaparinux, LMWHs, and edoxaban) have strong interactions with the furin. Especially fondaparinux and LMWHs were found better interactions than the natural ligand.

**Discussion**

SARS-CoV-2, a single-stranded RNA virus that is characterized by Spike (S) proteins projecting from the virion surface, has two subunits (S1 and S2) at its spike protein. The S1 subunit has a receptor-binding domain (RBD) and interacts with the host cell receptor which is angiotensin-converting enzyme (ACE2). As soon as the S2 subunit occurs, it forms a fusion between the virus and host cell membranes. SARS-CoV has shown that the proteolytic action of host proteases is very important for the viral entry to the host cell. While the binding to host cell receptor is the first step of infection, the entrance of the virus into the cell is dependent on the cleavage of the S1–S2 subunits to expose S2 for fusion to the cell membrane [13]. A few studies recently have enlightened the cellular heparan sulfates (HS) and receptor-binding domain (RBD) of the spike protein. Clausen et al. have shown that the ectodomain of spike protein interacts with cell surface HS through the RBD. In this study, they have shown that heparin enhances the open confirmation of the RBD to bind to ACE2. Unfractionated heparin,

![Docking poses alignment of the natural ligand of 5MIM, fondaparinux, and LMWHs.](image)
non-anticoagulant heparin, heparin lyases, and lung heparan sulfate potently blocked spike protein binding and/or infection by pseudotyped and authentic SARS-CoV-2 virus [12]. The results made them suggest that manipulation of heparan sulfate or inhibition of viral adhesion by exogenous heparin may provide new therapeutic options. Tandon et al. pseudotyped SARS-CoV-2 spike glycoprotein on a third-generation lentiviral vector (pLV) and infected HEK293T cells. They showed that pLV-S particles were efficiently neutralized by different concentrations of UFH, enoxaparin, 6-O-desulfated heparin, and 6-O-desulfated enoxaparin [11]. Relevant but another hypothesis that anticoagulants may be interfering with the spike binding via host protease inhibition, in our study, we evaluated the interactions with host protease-furin with anticoagulant and antiplatelet drugs.

The shape, depth, and charge of furin protease are well known, and it has a canyon-like narrow crack. In many species, the active site pocket of furin is conserved; it is reported that the catalytic site residues of furin include Asp153, His194, Ser253, Pro256, Asn295, and Ser368. Besides, Asp153, Ser253, and Ser368 are known as a catalytic triad that is important for the mechanism of action of furin [31, 32]. According to the docking studies, fondaparinux and LMWHs have strong interactions with the active site residues including the catalytic triad; their calculated glide energies were found −12.754 and −12.012, respectively. The glide scores of these compounds were found better than the natural ligand of 5MIM structure. Fondaparinux and LMWHs interfered directly with the catalytic competent conformation of the catalytic triad. Thus, the strong H-bonds between Asp153, His194, and Ser368 of the catalytic triad of furin might be disrupted, and the respective proton shuttle mechanism could be inhibited. It can be concluded that they might have significant inhibitory activities on furin.

Although we have clinical experience that heparin and LMWH have effects of improving the prognosis of COVID-19 patients, there are few studies regarding the use of fondaparinux [18, 33]. Fondaparinux is a synthetic molecule recommended as LMWH in prophylaxis and treatment of venous thromboembolism and can be used as an alternative to heparin in heparin-induced thrombocytopenia (HIT) [34]. Although fondaparinux was previously shown to bind to the adeno-associated virus with its sulfated groups, as far as we know, this is the first study showing the antiviral possible effect of fondaparinux on SARS-CoV-2 [35]. It has been shown that both heparins, LMWHs, and fondaparinux show anti-inflamatory effects during infections [36, 37].

Our results have shown that like heparin and LMWH, fondaparinux can also be a candidate for “drug repurposing” in COVID-19 therapy not only because of its anticoagulant but also possible antiviral effects. However, these results are a good starting point to new clinical studies where fondaparinux could be directly compared with other anticoagulant agents to see whether the affinity of the receptor has a clinical translation and application in everyday practice and whether it provides more benefits than other agents or not.

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Author Contribution FBBA implemented the hypothesis of the study and designed the study. TB and KB performed the conceptualization and methodology of the study. TB, KB, and SDE made the investigation and software analysis. TB and FBBA wrote and edited the manuscript.

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Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code Availability Not applicable.

Declarations

Ethics Approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Conflict of Interest The authors declare that they do not have any competing interests.

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