Journal of Molecular Structure 1228 (2021) 129449

Contents lists available at ScienceDirect

Journal of Molecular Structure

journal homepage: www.elsevier.com/locate/molstr

Fenoterol and dobutamine as SARS-CoV-2 main protease inhibitors: A virtual screening study

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A R T I C L E I N F O

Article history:
Received 25 June 2020
Revised 19 September 2020
Accepted 12 October 2020
Available online 13 October 2020

Keywords:
COVID-19
Dobutamine
Drug discovery
Fenoterol
Molecular docking
Virtual screening

A B S T R A C T

Global health is under heavy threat by a worldwide pandemic caused by a new type of coronavirus (COVID-19) since its rapid spread in China in 2019 [1]. Currently, there are no approved specific drugs and effective treatment for COVID-19 infection, but several available drugs are known to facilitate tentative treatment. Since drug design, development and testing procedures are time-consuming [2–5], virtual screening studies with the aid of available drug databases take the initiative at this point and save the time. Besides, drug repurposing strategies promises to identify new agents for the novel diseases in a time-critical fashion. In this study, we used structure based virtual screening method on FDA approved drugs and compounds in clinical trials. As a result of this study we choose three most prominent compounds for further studies. Here we show that these three compounds (dobutamine and its two derivatives) can be considered as promising inhibitors for SARS-CoV-2 main protease and results also demonstrate the possible interactions of dobutamine and its derivatives with SARS-CoV-2 main protease (6W63) [6]. Our efforts in this work directly address current urgency of a new drug discovery against COVID-19.

1. Introduction

Coronaviruses (CoVs) are known to cause mainly respiratory and enteric diseases in humans and animals [7]. They are classified into four genera, alpha, beta, gamma and delta-CoV [8]. As of June 25th, 2020, this newly emerged virus has spread to almost all countries with almost 9,494,571 confirmed cases and over 484,155 global deaths [9]. Currently, very limited information is known about the action mechanism and biology of COVID-19 and there is no vaccine or effective antiviral treatment against COVID-19, yet. Action mechanism of COVID-19 is still a mystery itself, but it was reported that it has the same cell-entry receptor, ACE2 (Angiotensin-Converting Enzyme 2), for infection as SARS-CoV [10,11]. On the other hand, there are growing number of 3D protein structures for COVID-19, generally related to the main protease structure resolved by mostly X-ray diffraction crystallography, available in Protein Data Bank (RCSB PDB).

Previous studies highlighted the importance of drug repurposing studies for certain types of diseases including, Parkinson's, Alzheimer's and Ebola [12–16]. Virtual screening research would replace the time-consuming efforts in identification of new targets for the existing drug molecules as demonstrated in earlier articles [17–19]. It is quite efficient to apply computer-aided drug design techniques to quickly identify promising candidates, especially after the detailed 3D-structures of key virus proteins are resolved. Taking the advantage of a recently deposited crystal structure of SARS-CoV-2 main protease enzyme (M^{pro}) in complex with its natural inhibitor [6], we used virtual screening approach. Structure of the natural ligand (X77) of SARS-CoV-2 main protease (Protein Data Bank (PDB) ID: 6W63) is given in Fig. 1.

Dobutamine (DBT) [1,2-Benzenediol, 4-(2-((3-(4-hydroxyphenyl)-1-methylpropyl)amino)ethyl)-, (±)-] is a beta-1 adrenergic agonist and was first developed as a structural analogue of isoprenaline [20]. DBT revealed that during the early stage of septic shock-induced ARDS, DBT treatment indicated a beneficial effect by relieving pulmonary edema in patients [21]. DBT was also shown to be effective for renal function parameters and it was well tolerated and elicited few side effects, thus, DBT appears to be used safely [22]. Moreover, it acts directly to increase myocardial

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https://doi.org/10.1016/j.molstruc.2020.129449
0022-2860/

Table 1
Docking scores of three hit compounds and natural ligand.

Code	Docking score	Glide score	Interactions
Natural Ligand (X77)	−8.938	−9.349	Thr25^{d}, Thr26^{d}, Leu27^{c}, Hie41^{d,e}, Cys44^{c}, Met49^{c}, Pro52^{c}, Tyr54^{c}, Phe140^{c}, Leu141^{c}, Asn142^{d,w}, **Gly143**^{g}, Ser144^{d}, Cys145^{c}, **Hie163**^{d}, His164^{d}, Met165^{c}, **Glu166**^{a}, Leu167^{c}, Pro168^{c}, Hie172^{d}, Asp187^{a}, Arg188^{b}, Gln189^{d}
ZINC000000057278 (DBT)	−8.845	−8.845	Hie41^{d,e}, Cys44^{c}, Met49^{c}, Pro52^{c}, Tyr54^{c}, **Phe140**^{c}, Leu141^{c}, Asn142^{d}, Gly143^{g}, Ser144^{d}, Cys145^{c},**Hie163**^{d}, His164^{d}, Met165^{c}, **Glu166**^{a}, Hie172^{d}, Asp187^{a}, Arg188^{b}, Gln189^{d}
ZINC000000057321 (FNT-SS)	−9.467	−9.489	Hie41^{d}, Cys44^{c}, Met49^{c}, Pro52^{c}, Tyr54^{c}, Phe140^{c}, Leu141^{c}, **Asn142**^{d,e}, Ser144^{d}, Cys145^{c}, **Hie163**^{d}, His164^{d}, Met165^{c}, **Glu166**^{a}, Asp187^{a}, Arg188^{b}, Gln189^{d}, Gln192^{d}
ZINC000000020252 (FNT-RS)	−9.467	−9.489	Hie41^{d,f}, Cys44^{c}, Met49^{c}, Pro52^{c}, Tyr54^{c}, Phe140^{c}, Leu141^{c}, Asn142^{d}, Ser144^{d}, Cys145^{c}, **Hie163**^{d}, His164^{d}, Met165^{c}, **Glu166**^{a}, Asp187^{a}, Arg188^{b}, Gln189^{d}

Bold: H-bond, w: water mediated H-bond, a: negative charge (orange), b: positive charge (cyan), c: Hydrophobic (green), d: Polar (turquoise), e: π-π stacking, f: π-cation, g: glycine

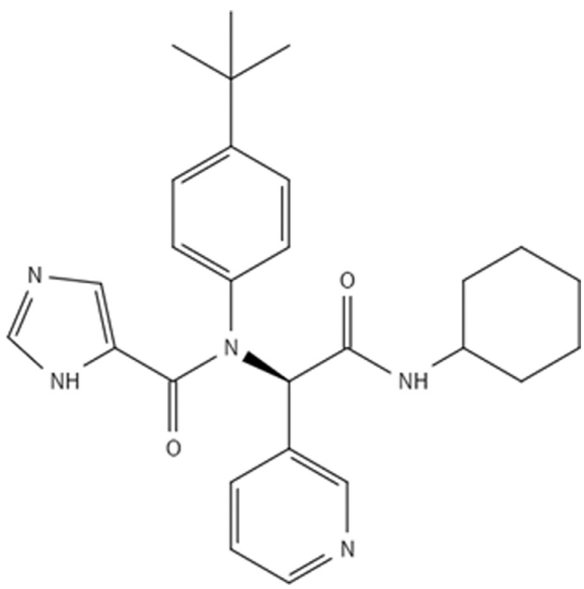

Fig. 1. Structure of natural ligand (X77) of SARS-CoV-2 M^{Pro} (PDB ID: 6W63).

contractility [20] and DBT infusion is generally associated with decreases in pulmonary artery pressure and pulmonary capillary wedge pressure [20,22]. To the best of our knowledge there is no virtual screening study on DBT that inhibits 6W63.

Fenoterol (FNT) [1,3-Benzenediol, 5-(1-hydroxy-2-((2-(4-hydroxyphenyl)-1-methylethyl)amino)ethyl)-] is a known a beta-2 adrenergic agonist drug [23]. In a very recent study performed on the relaxing effect of FNT on the contractions of horse isolated bronchi revealed that, FNT was found to be significantly more effective with respect to clenbuterol [24]. Bernasconi *et al.* showed that FNT is a rapid, powerful, but short-acting bronchodilator [25]. An evaluation of the clinical efficacy by FNT and salbutamol in horses with asthma could be of great interest to assess if they could represent more effective bronchodilators compared to clenbuterol [24]. Up to our knowledge, there is no docking study of FNT into SARS-CoV-2 M^{Pro} (6W63).

2. Methodologies

Structure-based virtual screening method focuses on the therapeutic targets 3D information. Docking procedures are used for the purpose of selecting the hits that exhibit chemical, structural and electronic characteristics. The information of the target protein can be derived from in silico technique or experimental data. We performed docking calculations and ADME properties predictions by Schrödinger 2020 software, with Maestro 12.2 and the Glide and QikProp modules [26–29].

2.1. Structure based virtual screening

X-ray crystallographic structure of SARS-CoV-2 M^{Pro} and its non-covalent inhibitor (X77) complex (PDB: 6W63) was retrieved from Protein Data Bank (www.rcsb.org) and prepared for docking process. In order to prepare the enzyme, we used the protein preparation wizard module. We chose OPL5-2005 force field for minimization and pH = 7.0 to minimize hydrogen atoms. Bond orders were assigned, with zero order bonds to disulfide bonds and metals as well. For virtual screening study, approximately 9,000 commercially available compounds (FDA approved drugs and compounds in clinical trials) were taken from ZINC database [30,31]. All these ligands were prepared by using Schrödinger, LigPrep module [26]. The bond angles and bond orders were assigned after ligand minimization step. In order to keep the ligands in the right protonation state in biological conditions, epik option was used. After the preparation of ligands and enzyme, we generated the grid for docking process. The active site of SARS-CoV-2 M^{Pro} was defined for generating the grid in Maestro. The grid box was limited to the size of 10 Å at the active site. First, docking procedure was validated by extracting the nature ligand, X77 from the binding site and re-docking it to SARS-CoV-2 M^{Pro} by using the Glide SP (standard precision glide docking) module [27,28]. Glide generates conformations internally and passes these through a series of filters. Glide had successfully reproduced the experimental binding conformations of X77 in SARS-CoV-2 M^{Pro} with an acceptable root-mean-square deviation (RMSD) value of 0.678 Å. Docking studies were carried out using high throughput virtual screening (HTVS) option, standard- precision (SP screening) and extra-precision (XP screening) mode of Glide module respectively. We considered ring conformations, nitrogen inversions, input partial charges and, for amides, a penalty for nonplanar conformations was applied. Epik state penalties were added to docking scores. We did not use any similarities or constraints for the docking calculations. The compounds were re-docked via post processing. The best pose was output based on Glide score. After visual inspection, we retained FNT and DBT together with one isomer of FNT as two potential inhibitor candidates. Docking scores of FNT and DBT, plus one isomer of FNT, and natural ligand were shown in Table 1.

2.2. ADME/Tox analysis

In order to obtain an efficient collection of hit molecules, in silico ligand filtration was also done for screening compounds by employing Lipinski “Rule of Five” [32] and ADME properties using QikProp module of Schrödinger Software [26]. Calculated ADME properties predictions of the selected hit compounds were shown in Table 2. This analysis includes, brain/blood partition coefficient (QPlog BB), aqueous solubility (QPlog S), total solvent accessible surface area (SASA), octanol/water partition coefficient (QPlog

Table 2
QikProp Properties Predictions of three hit compounds*

Code	Molecular weight(g mol^{-1})	Volume(Å^3)	Percent human oral absorp-tion(%)	SASA(Å^3)	QPlog BB	QPlog S	QPlog Po/w	QPPMDCK (nm/s)	Rule of five
DBT	301.385	1078.865	73.825	635.032	−1.374	−3.058	2.472	28.362	0
FNT-SS	303.357	947.614	63.004	504.590	−1.005	−0.484	0.858	23.431	0
FNT-RS	303.357	1025.878	57.754	591.912	−1.686	−1.783	1.034	9.784	0

* SASA: Solvent accessible surface area; QPlogBB: Predicted brain/blood partition coefficient; QPlogS: Predicted aqueous solubility; QPlogPo/w: Predicted octanol/water partition coefficient; QPPMDCK: Predicted apparent MDCK (Madin-Darby canine kidney) cell permeability.

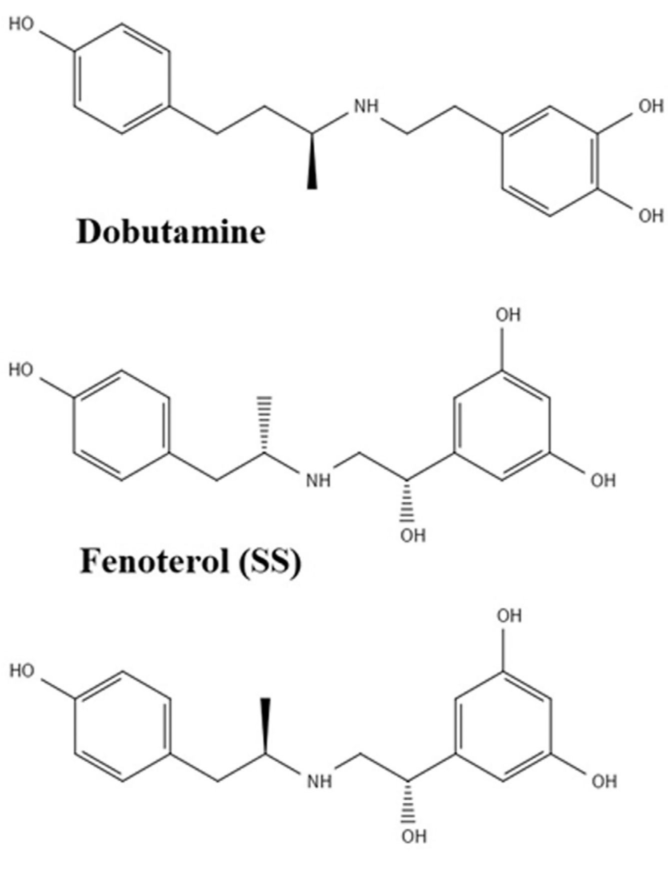

Fig. 2. Structures of SARS-CoV-2 M^{Pro} inhibitor candidate compounds.

Po/w), predicted apparent MDCK cell permeability (QPPMDCK), Lipinski's "Rule of Five" violations, and human oral absorption.

3. Results

Structure-based virtual screening method focus on the therapeutic targets 3D information. For the purpose of selecting the hits that exhibit chemical, structural and electronic characteristics, docking procedures are used [29]. In order to test the action mechanism of various FDA approved drugs exist in ZINC database, we used structure based virtual screening method by using Schrödinger software and found that DBT (ZINC000000057278), FNT (SS isomer) (ZINC000000057321) and its stereoisomer FNT (RS isomer) (ZINC000000020252), inhibit SARS-CoV-2 M^{Pro}. Structures of these hit compounds are demonstrated in Fig. 2. Ligand filtration was also done for screening compounds by employing Lipinski's [32] "Rule of Five" and Absorption, Distribution, Metabolism and Excretion (ADME) properties using QikProp [26,32] module. Docking scores and QikProp Properties Predictions of all candidate compounds are shown in Tables 1 and 2, respectively. According to docking results, docking scores of all three compounds were found between −9.467 and −8.845. We found that FNT-SS and FNT-RS have same docking scores and these values are better than X77. DBT seemed to have higher docking score (–8.845) than X77 (–8.938). Almost all the pharmacokinetic properties conducted by QikProp were within acceptable range. Three top compounds are with good inhibiting profile and exhibit suitable ADME/Tox (toxicity) properties for SARS-CoV-2 M^{Pro}. To the best of our knowledge, there are not any docking studies on FNT (SS and RS) for inhibition purpose of COVID-19 structure (6W63), although they are approved by FDA. In our opinion, these candidates need to be rapidly confirmed whether they might be used as a drug against COVID-19.

After we figured out that natural ligand of SARS-CoV-2 M^{Pro} showed H-bond with Asn142, Gly143, Hie163 and Glu166 in active site, we next evaluated our docking results and found similarity that all three compounds showed H-bonds with Hie163, and Glu166 which are the important residues for the SARS-CoV-2 M^{Pro} inhibition. Our findings revealed that DBT interacts via H-bonds towards Phe140, Hie163, Glu166, π-π interaction with Hie41. Besides, FNT-SS showed H-bonds towards Hie163 and Glu166 and water mediated H-bond with Asn142 whereas FNT-RS showed H-bonds with Hie163 and Glu166 and a π-cation interaction Hie41 (Fig. 3). From docking results, we determined that our hit compounds are in strong interactions with SARS-CoV-2 M^{Pro} and particularly FNT-SS and -RS showed stronger interactions the than X77, natural ligand. Docking scores of both FNT-SS and -RS are -9.467 and this is better than docking score of X77 (Table 1). Thus, both FNT compounds might be promising inhibitors of SARS-CoV-2 M^{Pro}.

Next, we investigated, pharmacokinetic properties of these prominent compounds by performing QikProp Properties Predictions which was implemented in Schrödinger software with the recommended values and range. Based on these predictions, the human oral absorption percentage of DBT was found to be ~74%. However, FNT-SS and RS showed medium range oral absorption with the value of ~58-63%. For tested inhibitor candidate compounds, the partition coefficient (QPlog Po/w) was within the recommended range of 0.86-2.47. Brain/blood partition coefficient (QPlog BB) and total solvent accessible surface area (SASA) were also found to be within satisfactory range. Violations of Lipinski's "Rule of Five" were also calculated and none of the compounds violate this rule, thus indicating their potential as drug-like molecules [32,33]. Additionally, DBT is in the acceptable range for predicted apparent Madin-Darby canine kidney (MDCK) cell permeability (QPMDCK) value of 28.362 whereas FNT-SS (23.431) and -RS (9.784) exhibit poor mimic for permeability in blood-brain barrier compared to DBT. Here, QPPMDCK is predicted apparent MDCK cell permeability in nm/s and poor means <25 and great means >500 [22]. Predicted aqueous solubility values (QPlog S) were also found as acceptable. QikProp pharmacokinetic properties predictions of the hit compounds were presented in Table 2.

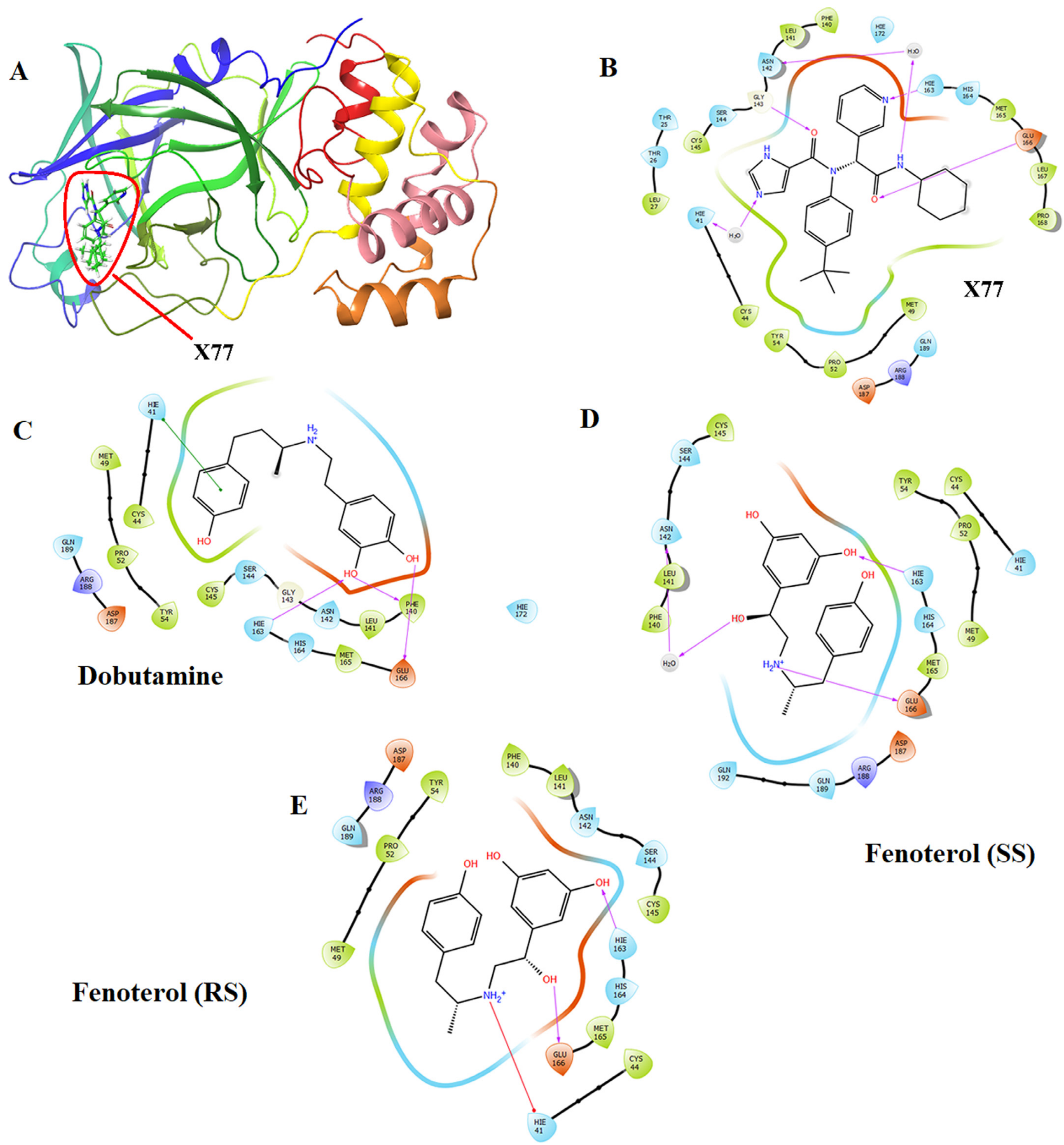

Fig. 3. Visualization of SARS-CoV-2 M^{Pro} enzyme binding modes in the active site (A) and docked position with compounds X77 (B), DBT (C), FNT-SS (D) and FNT-RS (E). Different colors show the expected interactions: negative charge (orange), positive charge (cyan), hydrophobic (green), polar (turquoise). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

4. Discussion

This global threat showed that our current options against this virus are quite limited. Even though there are increasing number of efforts, no drugs can treat effectively this virus currently. Discovering a broad-spectrum drug/(s) that may be used for COVID-19 is still a challenging marathon. Given the fact that drug development and registration progress is time-consuming, drug repurposing against COVID-19 and other diseases is the quickest way to open the way towards treatment for such infectious diseases.

In order to contribute to discovery of potential COVID-19 drugs as soon as possible, we first screened thousands of compounds and extracted two main structures, FNT (SS and RS) and DBT for one certain SARS-CoV-2 M^{Pro} (6W63). Docking results revealed that

X77 was seen to be H-bonded via Gly143, Hie163, Glu166 in active site of the protein. Similarly, all hit compounds showed H-bonds with Hie163, and Glu166, which are the important residues for the SARS-CoV-2 M^{Pro} (Fig. 3). Based on our docking work, DBT and FNT are in strong interactions with the enzyme and we figured out that FNT-SS and RS interacted with main protease stronger than natural ligand, with the docking score of -9.467 which is better than X77's docking score of -8.938. Here, we propose that, particularly FNT-SS and RS can be considered as the best two SARS-CoV-2 M^{Pro} inhibitors rather than DBT. Although the docking score of DBT is higher than the X77, meaning not better than any of FNT isomers, it still can be considered as a potential treatment against COVID-19 since it also has a close docking value to X77.

It would only be possible to use all these compounds after clinical tests are complete and the simulation results are validated. Moreover, since there are much more crystallographic structures of this virus, increasing daily, it is important to focus on new crystallographic structures of COVID-19 together with their natural ligands in order to further understand its action mechanism and nature.

Even though our calculations demonstrated that FNT-SS and RS inhibit COVID-19 better, further computational, experimental and clinical research should be performed. Most importantly, since there is still no effective drug and vaccine against this virus, we suggest that our results open up a new direction for further research on the way to design new potential drugs, specifically like FNT and DBT, against COVID-19.

5. Conclusion

COVID-19 is now a global concern and since there is a lack of proper and effective medication, it is urgent and necessary to find and evaluate treatment methods more rapidly. At this step, computational methods play a crucial role and they pave the way to find leading candidate compounds to be used as drugs for COVID-19 as well as other diseases. Here, we used virtual screening techniques and identified three FDA approved hit drugs as potential inhibitors for 6W63, SARS-CoV-2 main protease enzyme, by using extensive ZINC database. Based on molecular docking approach in our work, dobutamine and fenoterol would be possible candidates against COVID-19. We have obtained satisfactory results providing that natural ligand X77 and two possible ligands, dobutamine and fenoterol, exhibit inhibition on SARS-CoV-2 main protease enzyme (6W63). It was observed that the binding ability of dobutamine and fenoterol was better compared to natural ligand X77. We have been able to find that all our compounds fit at the active site of the 6W63 and showed hydrogen bonds with the surrounded amino acids in the cavity.

As a conclusion, these candidates could be promising inhibitors of SARS-CoV-2 M^{Pro} and they also need to be rapidly confirmed by experimental study. Besides, we suggest that the present findings can be led to design new and more potent drugs against COVID-19.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Kayhan Bolelli: Data curation, Resources, Software, Visualization, Writing - original draft. **Tugba Ertan-Bolelli:** Conceptualization, Data curation, Resources, Software, Visualization, Writing - original draft. **Ozan Unsalan:** Data curation, Funding acquisition, Software, Writing - original draft, Writing - review & editing. **Cisem Altunayar-Unsalan:** Conceptualization, Writing - original draft.

Acknowledgements

We acknowledge Rita Podzuna of Schrödinger for supplying one-month fully operational evaluation of Schrödinger suite.

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