

**Identification of FDA Approved Drugs Targeting SARS-CoV-2 by Structure-
Based Drug Repositioning (Version 3)**

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Abstract:

Background: The new strain of Coronaviruses (SARS-CoV-2), and the resulting Covid-19 disease has spread swiftly across the globe after its initial detection in late December 2019 in Wuhan, China, resulting in a pandemic status declaration by WHO within 3 months. Given the heavy toll of this pandemic, researchers are actively testing various strategies including new and repurposed drugs as well as vaccines.

Methods: In the current brief report, we adopted a repositioning approach using in-silico molecular modeling screening using FDA approved drugs with established safety profiles for potential inhibitory effects on Covid-19 virus. We started with structure based drug design by screening more than 2000 FDA approved drugs against Covid-19 virus main protease enzyme (M^{pro}) substrate-binding pocket focusing on two potential sites (central and terminal sites) to identify potential hits based on their binding energies, binding modes, interacting amino acids, and therapeutic indications. In addition, we screened the top hits for both sites for potential covalent binding via nucleophilic thiol attack of Cys 145. We also elucidate the preliminary pharmacophore features for the top candidates using the three strategies bound to Covid-19 virus M^{pro} substrate-binding pocket.

Results: The top hits bound to the central site of M^{pro} substrate-binding pocket include anti-viral drugs such as Darunavir, Nelfinavir and Saquinavir, some of

which are already being tested in Covid-19 patients, in addition to the hypercholesterolemia drug Rosuvastatin and the anti-malarial drug Atovaquone. The top hits bound to the terminal site of M^{pro} substrate-binding pocket include the anti-asthma drug Montelukast and the anti-histaminic Fexofenadine among others. Finally, the top candidates that are predicted to undergo covalent binding were Atovaquone, Mitoxantrone, and Metamizole.

Conclusion: We identify a number of FDA approved drugs with potential activity against SARS-CoV-2 M^{pro} by using structure-based drug repositioning. Our results highlight a number of promising hits based on virtual docking, especially with regards to potential for covalent binding. These results do not confirm or indicate antiviral activity but can rather be used as a starting point for further in vitro and in vivo testing, either individually or in combination.

Introduction

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The new strain for Coronaviruses (CoVs) was identified in late December 2019 named SARS-CoV-2 (Covid-19 virus) resulted in a massive outbreak initially in Wuhan, China and propagated to different nations around the globe. On March 11, World Health Organization (WHO) declared the resulting disease named COVID-19 as a pandemic [1]. Coronavirus cases are estimated at 169,112 with 6,494 death cases as of March 15th 2020 [2]. Clinical efforts to discover potential vaccines and therapeutics are still ongoing with no clear treatment or prophylaxis for COVID-19 in sight. It is safe to say that a sufficient understanding of SARS-CoV-2, and the full clinical picture of the resulting COVID-19 disease will take some time. Similarly, developing and widely distributing effective vaccines or novel antiviral drugs is unlikely to occur during this season, which leaves healthcare systems vulnerable, and risks high mortality rates. Alternatively, drug-repurposing strategies can create viable path towards identification of potential therapeutics with established safety profiles that can be used individually or in combinations for targeting molecular regulators of replication or the survival of SARS-CoV-2. While these strategies are unlikely to provide immunity or cure, they may identify therapeutics that can alter the clinical course of COVID-19, especially in critically ill patients[3-8].

The betacoronavirus genome encodes structural proteins, including the glycosylated spike (S) protein that serves as a major inducer of host immune responses. The spike protein mediates host cell invasion via binding to angiotensin-converting

enzyme 2 (ACE2) (a homolog of angiotensin converting enzyme ACE) which is a membrane bound carboxypeptidase). The cellular invasion process appears to be mediated by priming of S protein facilitated by the host cell-produced serine protease TMPRSS2 . In addition, the viral genome also encodes nonstructural proteins including RNA-dependent RNA polymerase (RdRp), coronavirus main protease (M^{pro}), and papain-like protease (PLpro)[5, 9, 10]. Therefore, targeting ACE2, TMPRSS211, RdRp, M^{pro} , and PLpro, as individual targets, or in combination, is a viable strategy for repurposed drugs. To that end, different drug repurposing efforts have been executed starting with data driven framework coupled with in vitro assays to show the potential of a poly-ADP-ribose polymerase 1 (PARP1) inhibitor, CVL218, currently in a Phase I clinical trial, may serve as a potential drug candidate to inhibit SARS-CoV-2 replication in a dose-dependent manner and with no obvious cytopathic effect. CVL218 showed potential binding affinity of the N-terminal domain of nucleocapsid (N) protein of COVID-19 virus via in-silico analysis [11].

Herein, our structure-based drug design approach is focused on targeting COVID-19 virus M^{pro} based on the elegant work that resulted in solving the crystal structure of COVID-19 M^{pro} in complex with an inhibitory peptide N3 (PDB ID: 6LU7). In particular, that inhibitory peptide binds the substrate-binding pocket of COVID-19 M^{pro} . This domain was the focus of our screen with regards to the potential hydrophobic binding domain and considering the hydrogen bond network. Starting with the published crystal structure provided us with structural insights for the catalytic binding

domain and active druggable sites, elucidating free binding energies with respect to binding affinity and interactions, as shown in figure 1. The purpose of the current study is to accelerate the use of clinically viable approved therapeutics in the setting of a pandemic and highlights some important pharmacophore features for generation of novel molecules that target SARS-CoV-2.

Results and Discussion:

The structural analysis for the peptide ligand N3 co-crystallized along with COVID-19 virus M^{pro} substrate-binding pocket revealed the significance of hydrophobic interactions and hydrogen bond network comprising His163, His164, Glu166, Gln189, and Thr190[8]. We decided to conduct an *in-silico* molecular modeling study for >2000 FDA approved drugs focusing on two potential sites of the M^{pro} substrate-binding pocket based on the co-crystallized peptide N3.

Central site molecular docking:

The central site docking results showed the top 11 hits based on their S score, binding affinity, interacting amino acids, and binding mode to fit the main protease pocket with respect to the reported clinical indication, as shown in Table 1. The rest of the top 100 hits are listed in Table S1.

Our two and three-dimensional analysis for the top hits is shown in figures 2 and

3. Darunavir, a known antiviral with protease inhibitory mode of action [12], showed the best binding affinity in terms of hydrophobic-hydrophobic and hydrogen bond interactions with His163, Glu166, and Thr190 at S score -14.03040 Kcal/mol. The top candidates also included antivirals such as Nelfinavir and Saquinavir at S score ranging from -13.4200 Kcal/mo to -12.0917 Kcal/mol.

The current repurposing study also includes other drugs approved for different clinical indications. For example, Moexipril, an ACE inhibitor [13], showed a proper binding mode via hydrophobic interactions and a hydrogen bond through a carboxylic acid moiety with Gln189 at S score -13.2142 Kcal/mol. Daunorubicin and Mitoxantrone are representatives for anthracene glycosidic chemotherapeutic agents[14, 15]. Daunorubicin showed potential binding affinity via hydrophobic interactions and hydrogen bonding with Asn142 and Glu166. Mitoxantrone showed hydrophobic interactions and a network of hydrogen bonds with His41, His164, Asp187, Thr190, and Gln192. The anthracene derivatives findings suggest that glycoside-based derivatives can target the substrate-binding pocket of COVID-19 virus M^{PRO}. However, administration of chemotherapeutic agents can lead to significant adverse effects and is unlikely to be of any clinical utility in critically ill COVID-19 patients. Metimazole, a pyrazolone based derivative [16], showed a potential binding affinity via hydrogen bonds between a sulphonic acid moiety and His 163 and Ser144 in addition to pi-pi interaction with His41. Although theoretically met-amizole might have clinical utility here, it is also not an ideal candidate due to its association with agranulocytosis, which would be an unwelcomed side effect in

COVID-19 patients. Bepotastine, an anti-histamine [17, 18], exhibited proper binding affinity in the main substrate-binding pocket via hydrophobic interactions and hydrogen bonding through a carboxylic acid moiety with Gln189. Atovaquone, an anti-malarial drug [19] showed a potential binding affinity with no hydrogen bonds with an S score -8.4159 Kcal/ mol. This might complement the current use of chloroquine, another anti-malarial drug, which shares the same scaffold features of atovaquone, to elevate endosomal pH and interfere with ACE2 glycosylation. One of the promising drugs from the current screen that might warrant further investigation is Rosuvastatin, which belongs to the statins class of antihyperlipidemic drugs [20]. We found that Rosuvastatin displayed an excellent binding affinity in terms of free energy with an S score of -12.3096 Kcal/mol. The Rosuvastatin skeleton filled the entire substrate-binding pocket via hydrophobic interactions and hydrogen bonding with Gly143 and Glu166.

In the current report, we show that structure-based drugs design for the top hits elucidated the following preliminary pharmacophore features: (1) The entire pocket needs hydrophobic features or extended phenyl moieties to maintain a proper binding affinity such as in case of anthracene derivatives. (2) A network of hydrogen bonds (whether donors or acceptors) is a significant factor especially with amino acids Glu166, Gln189, His163, and His164. (3) The presence of terminal sulphonic acid and/or carboxylic acid moieties (Bepotastine, Moexipril, Metimazole, and Rosuvastatin) can act as bio-isosteric moieties to the phosphate groups that can be found in antiviral drugs.

Terminal site molecular docking:

The terminal site of M^{pro} substrate-binding pocket results showed the top 8 hits based on their S score, binding affinity, interacting amino acids, and binding mode to fit the terminal portion with respect to the reported clinical indication, as shown in Table 2.

Our two and three-dimensional analysis for the top hits targeting the terminal site is shown in figures 4 and 5. Montelukast, an anti-asthmatic drug, showed the best binding affinity in terms of hydrophobic-hydrophobic and hydrogen bond interactions with Thr24, Ser46, and Gln 189 at S score -11.8226 Kcal/mol. A recent report also showed the binding affinity of Montelukast to the same binding domain[21]. Lisinopril, an ACE inhibitor, showed proper binding mode via hydrophobic interactions and a hydrogen bond through a carboxylic acid and amine moieties with Thr26 and His164, respectively at S score -11.5878 Kcal/mol. Bumetanide, a loop diuretic showed a hydrogen bond network with Ser144, His 163, Glu166, and Gln189; in addition to pi-pi interaction along with His41 at S score -11.3008 Kcal/mol. Fexofenadine, an anti-histaminic, protrudes towards the terminal groove of the protease binding pocket with hydrophobic-hydrophobic interactions and hydrogen bond with Thr26 at S score -10.8085 Kcal/mol. Pirbuterol, another anti-asthma with β 2 adrenergic activity, bound to the terminal site without further protrusion towards the center with hydrogen bonds Thr24, Thr25, and Ser46. Finally,

Bosentan, an endothelin receptor antagonist used for pulmonary arterial hypertension, and quinidine showed hydrophobic interactions with no hydrogen bonds at S score -10.0878 Kcal/mol and -9.0607 Kcal/mol. Although the dimensional size of the terminal site is limited compared to the central site for the M^{pro} substrate-binding domain, the key amino acid residues for binding are Thr24, Thr25, Thr26, and Ser46.

Covalent molecular docking:

Finally, we performed an independent covalent docking study to identify FDA drugs that can target Cys145 within the substrate-binding pocket, especially given that the co-crystallized inhibitor is peptide in nature (α ketoamide) with covalent mode of binding [22]. We screened the top 200 drugs that resulted from the central and terminal molecular docking (top 100 for each) for targeted covalent docking through Cys 145 via DOCKTITE's protocol by Molecular Operating Environment (MOE) [23]. This resulted in identifying 30 drugs that demonstrated possible nucleophilic attack by Cys 145 and undergo covalent docking to generate R and S stereoisomers. Only 9 candidates showed promising binding affinity with respect to S score and covalent binding ability. Our two and three-dimensional analysis for the top 9 covalent hits targeting Cys 145 is shown in figures 6 and 7. By correlating the central and covalent molecular docking, we determined that Atovaquone, Mitoxantrone, and Metamizole showed both promising binding affinity as well as potential covalent binding to Cys 145.

Therefore, screening the FDA approved drug library against the COVID-19 virus M^{pro} substrate-binding pocket can provide valuable insights to fast-track clinical trials for drugs with an established safety profile. Several top hits from our screen, including 3 protease inhibitors, as well as Rosuvastatin, Montelukast, Fexofenadine, Atovaquone, Metamizole, Mitoxantrone, and Pirbuterol can potentially be safely used in COVID-19 patient, however additional studies are needed to determine the antiviral activity against SARS-CoV-2 of these hits.

Materials and Methods:

FDA approved small molecules preparation: The U.S. FDA approved drug database was downloaded (drugbank.ca) and 3D structures were energy minimized using MMFF94 force field.

X-ray crystal structure preparation: Crystal structure of COVID-19 virus M^{pro} co-crystallized with an inhibitor has been resolved and accessed via PDB ID: 6LU7. A box was assigned for docking procedures within the hydrophobic binding domain of the peptide inhibitor.

Structure based *in-silico* screening and scoring: The whole energy minimized

library was enrolled in docking simulations using Molecular Operating Environment (MOE) along with PDB ID: 6LU7. The energy-minimized drugs underwent protonation states to add the missing hydrogens for proper ionization states. MOE docking module used to evaluate the favorable binding conformers based on London dG scoring method to estimate energy profile based on the binding affinity with respect to hydrophobic-hydrophobic interactions, hydrogen bonding, pi-pi interactions, and ionic interactions [24].

Each drug gave 10 possible docked poses. The ideal pose for each drug was selected according to the similarity of its binding mode in the binding pocket to that of the co-crystallized peptide. Two dimensional diagrams were generated using MOE tools, while three dimensional figures were generated using pymol.

Covalent Docking using DOCKTITE:

The covalent docking protocol will filter the top 200 FDA drug candidates combining automated warhead screening to reveal 31 candidates that can undergo nucleophilic attack by Cys 145 based on their chemical structure, nucleophilic side chain attachment with the right configuration (R or S), pharmacophore-based docking, and the chimeric poses will undergo consensus scoring approach using MOE-internal empirical scoring functions and the external knowledge-based scoring function drug score extended (DSX) that consists of distance-dependent pair potentials, novel torsion angle potentials, and newly defined solvent accessible surface-

dependent potentials [25]. The validation step will include pose predictions of 10 protein/ligand complexes with a cut-off mean RMSD of 2 Å.

Conclusion:

In the current report, a structure-based drug repositioning strategy was adopted to repurpose FDA approved drugs targeting COVID-19 M^{pro} substrate-binding pocket which revealed a number of potentially usable drugs that may have clinical utility in COVID-19. Although these are promising findings, these results need further biological in vitro and in vivo validation.

Figures:

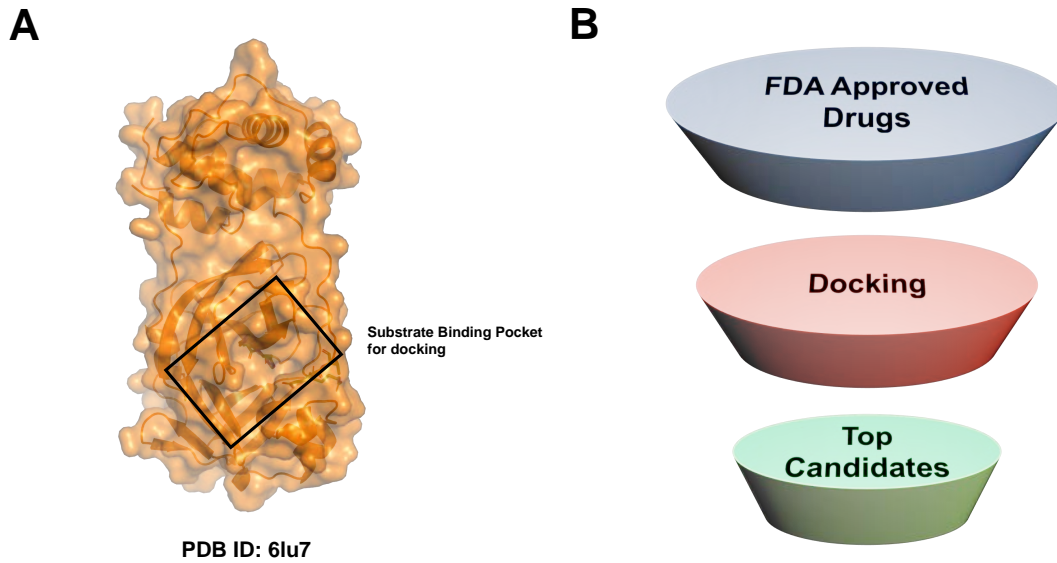


Figure 1. Workflow: **A)** Crystal structure of COVID-19 virus M^{pro} highlighting the substrate binding-pocket which was used for docking. **B)** Schematic diagram for in-silico drug repositioning.

Drug	S score (Kcal / mol)	Clinical Indication
Darunavir	-14.0304	Antiviral
Mitoxantrone	-13.8100	Anticancer
Nelfinavir	-13.4200	Antiviral
Moexpril	-13.2442	Anti-hypertensive
Daunorubicin	-12.5009	Anticancer
Rosuvastatin	-12.3096	Anti-hypercholesterolemia
Saquinavir	-12.0917	Antiviral
Metamizole	-11.6652	Anti-inflammatory
Bepotastine	-10.6350	Anti-histaminic
Benzonatate	-10.4759	Anti-tussive
Atovaquone	-8.1459	Antimalarial

Table 1. List of top 11 drugs docked to the central site of the substrate binding-pocket of COVID-19 virus M^{pro} based on S score.

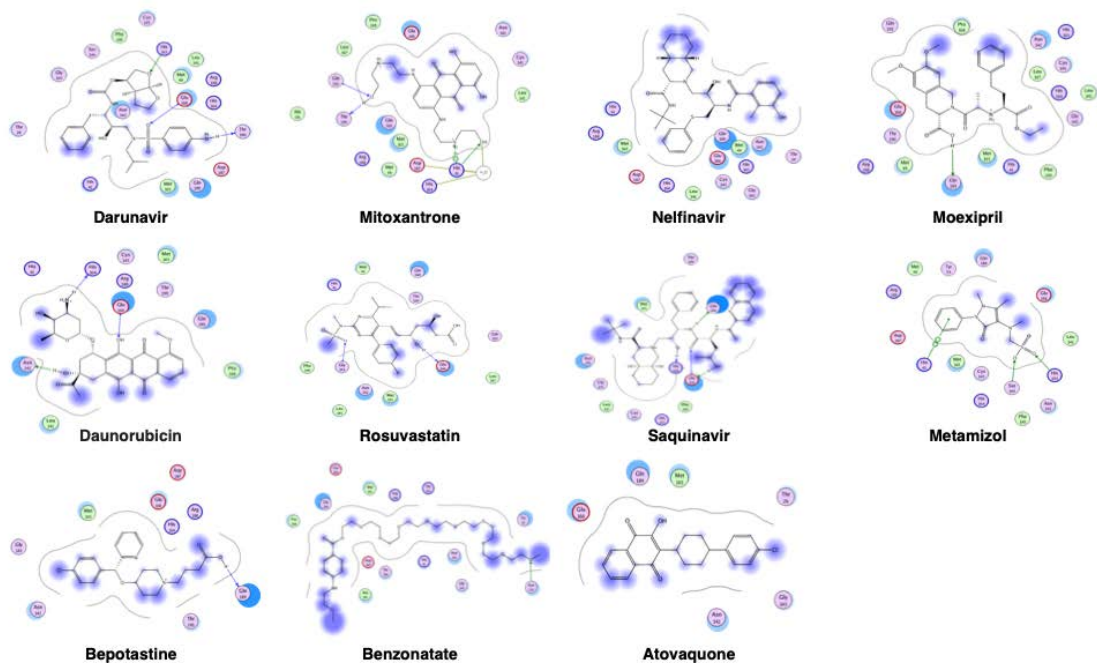


Figure 2. Two-dimensional presentation of docking poses for top 11 candidates targeting the central site of the substrate binding-pocket of COVID-19 virus M^{pro} . Blue arrows are backbone hydrogen bonds and green arrows are the side chain hydrogen bonds.

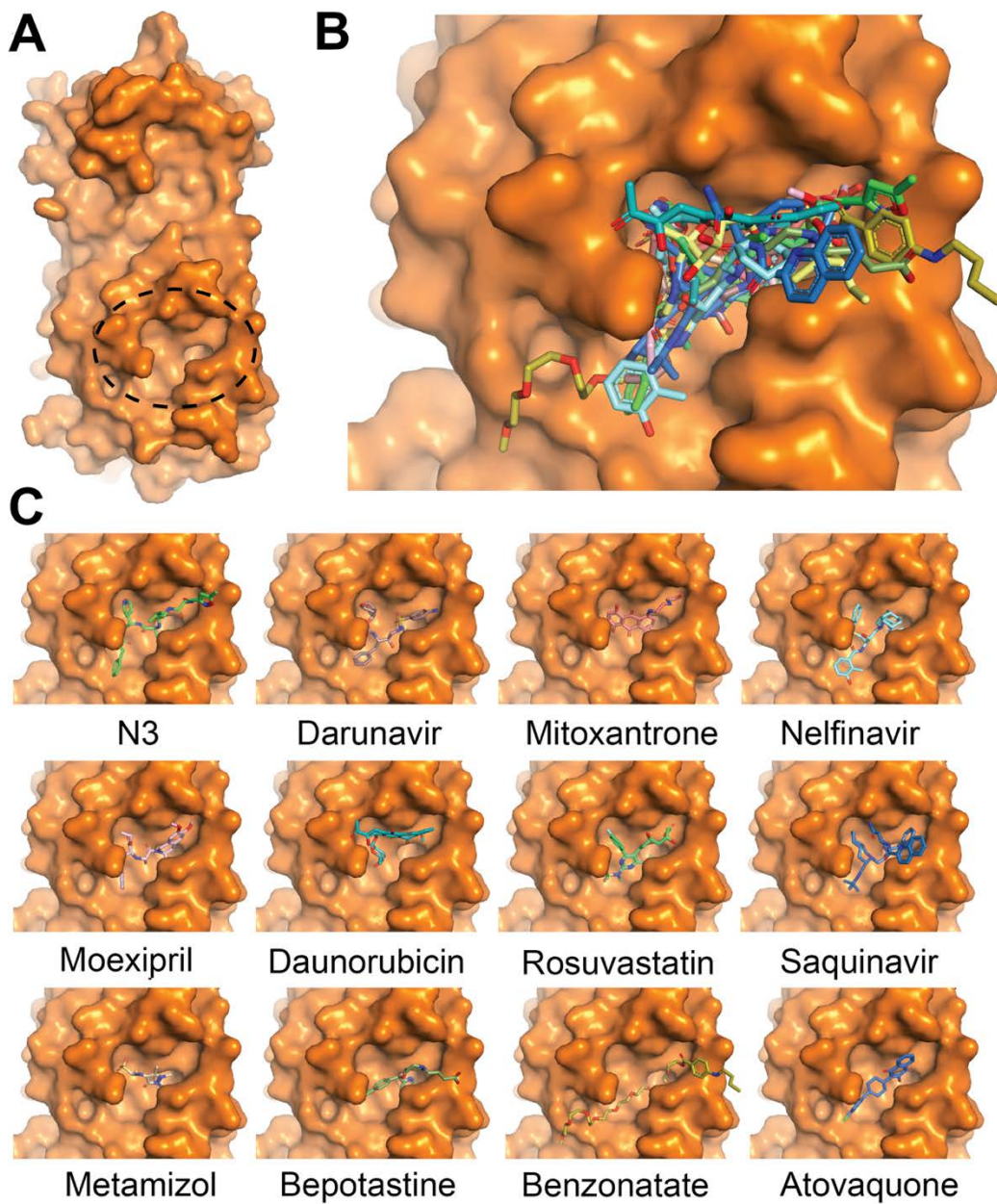


Figure 3. Docked positions to the central site of the substrate binding-pocket of COVID-19 virus M^{pro}: **A)** 3D presentation of the pocket. **B)** Overlaid docked positions of all 11 top hits in addition to the previously co-crystallized inhibitory peptide N3. **C)** Individual docking positions.

Drug	S score (Kcal / mol)	Clinical Indication
Montelukast	-11.8226	Anti-asthma
Lisinopril	-11.5878	Anti-hypertensive
Bumetanide	-11.3008	Anti-hypertensive
Fexofenadine	-10.8085	Anti-histaminic
Adefovir	-10.4470	Antiviral
Pirbuterol	-10.3436	Anti-asthma
Bosnetan	-10.0878	Anti-hypertensive
Quinidine	-9.0607	Anti-malarial

Table 2. List of top drugs docked to terminal site of substrate binding-pocket of COVID-19 virus M^{pro} based on S score.

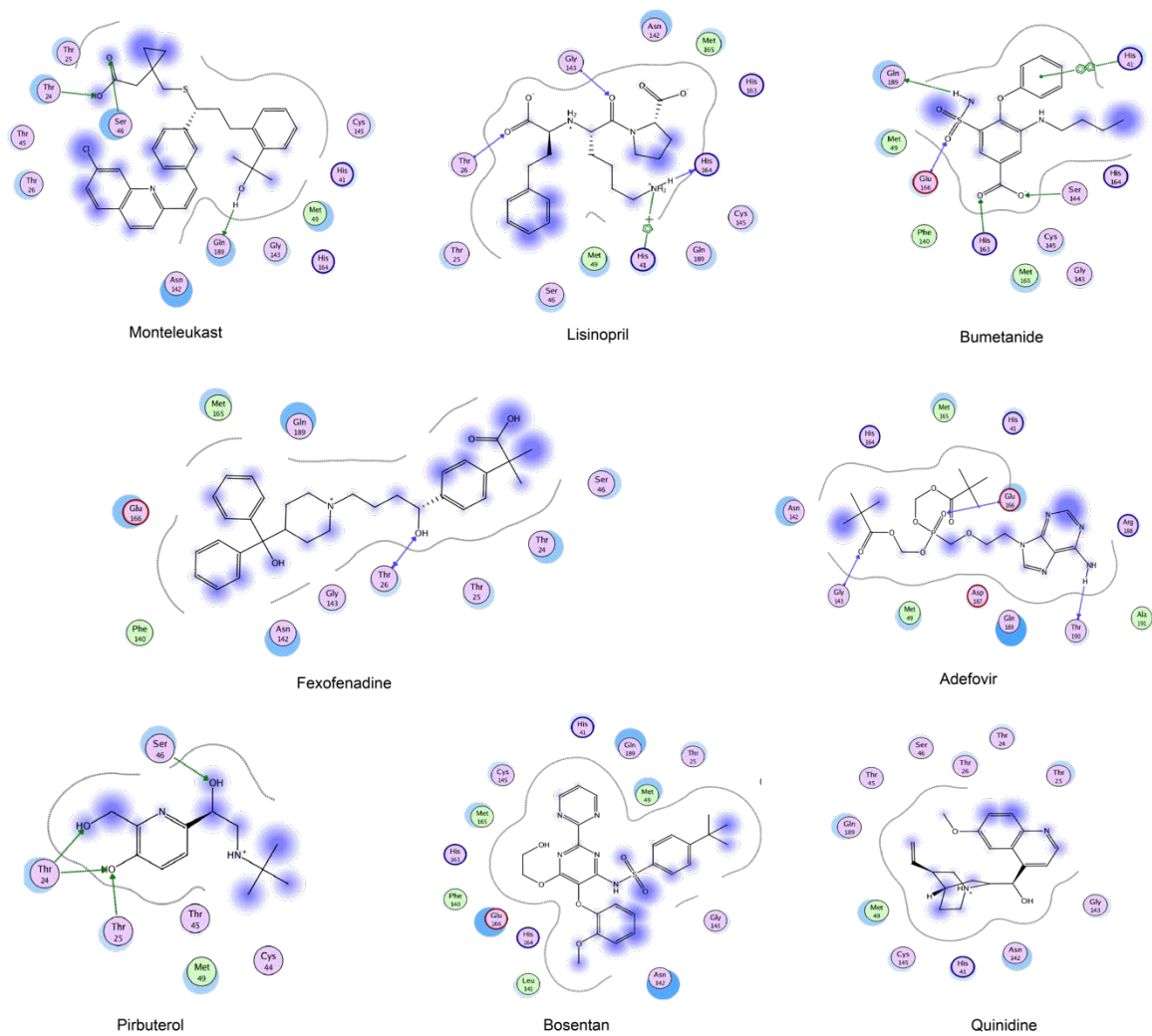


Figure 4. Two-dimensional presentation of docking poses for top 8 candidates targeting terminal site of the substrate binding-pocket of COVID-19 virus M^{PRO}. Blue arrows are backbone hydrogen bonds and green arrows are the side chain hydrogen bonds.

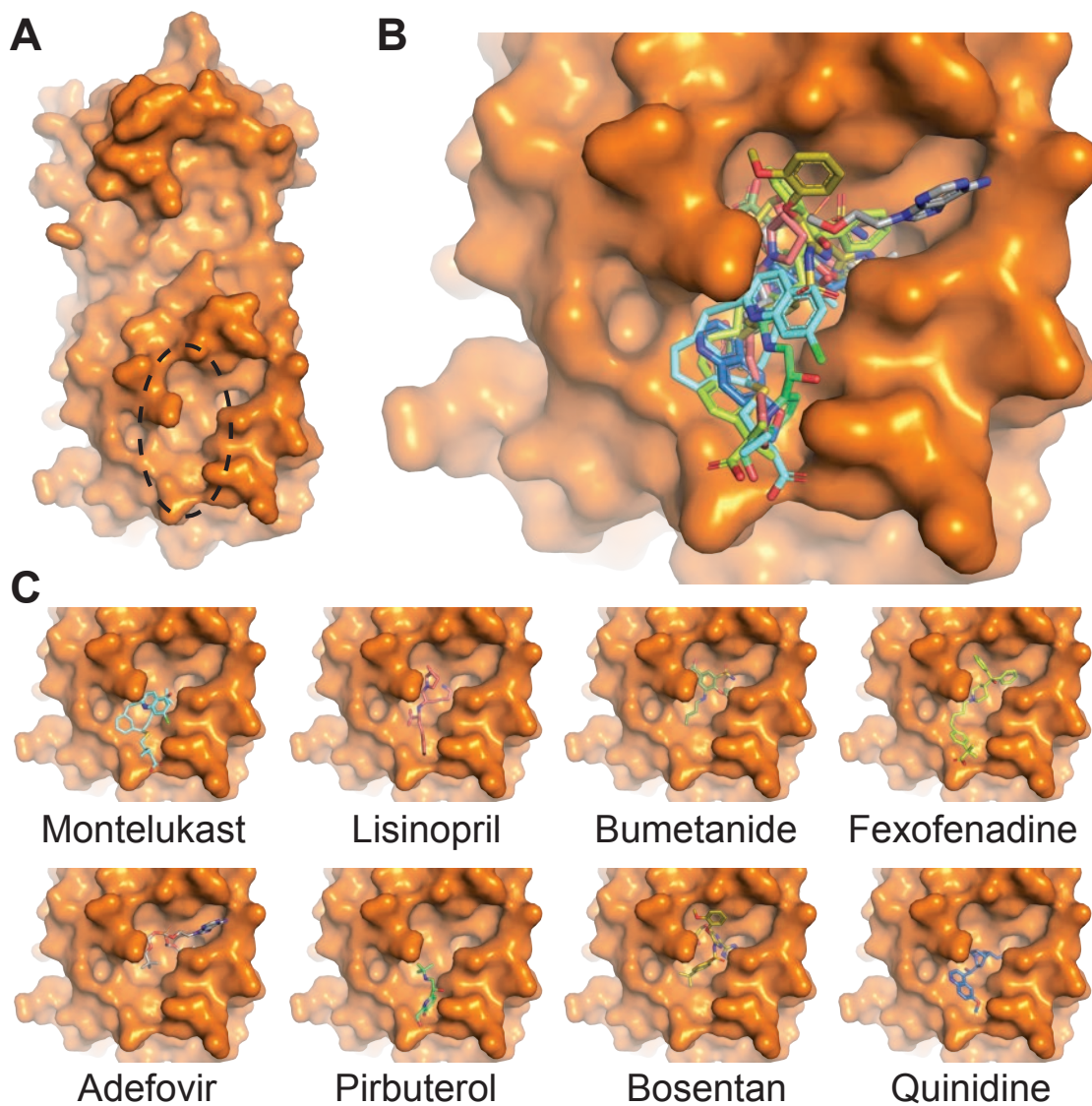


Figure 5. Docked positions to the terminal site of the substrate binding-pocket of COVID-19 virus M^{pro} **A)** 3D presentation of the pocket. **B)** Overlaid docked positions of all 8 top hits in addition to the previously co-crystallized inhibitory peptide N3. **C)** Individual docking positions.

Drug	Stereogenic center orientation	S score (Kcal / mol)	Clinical Indication
Dronedarone	R	-12.8752	Anti-arrythmia
Mitoxantrone	R	-11.6140	Anticancer
Tipranavir	S	-11.3686	Antiviral
Idarubicin	R	-10.1043	Anticancer
Atovaquone	R	-8.8177	Anti-malarial
Ouabin	S	-8.4562	Anticancer
Entacapone	R	-8.2882	COMT inhibitor
Metamizole	R	-8.2165	Anti-inflammatory
Mebendazole	R	-7.5352	Anti-parasite

Table 3. List of top drugs docked covalently to Cys 145 of COVID-19 virus M^{pro} substrate-binding pocket showing the configuration of nucleophilic attack and S score.

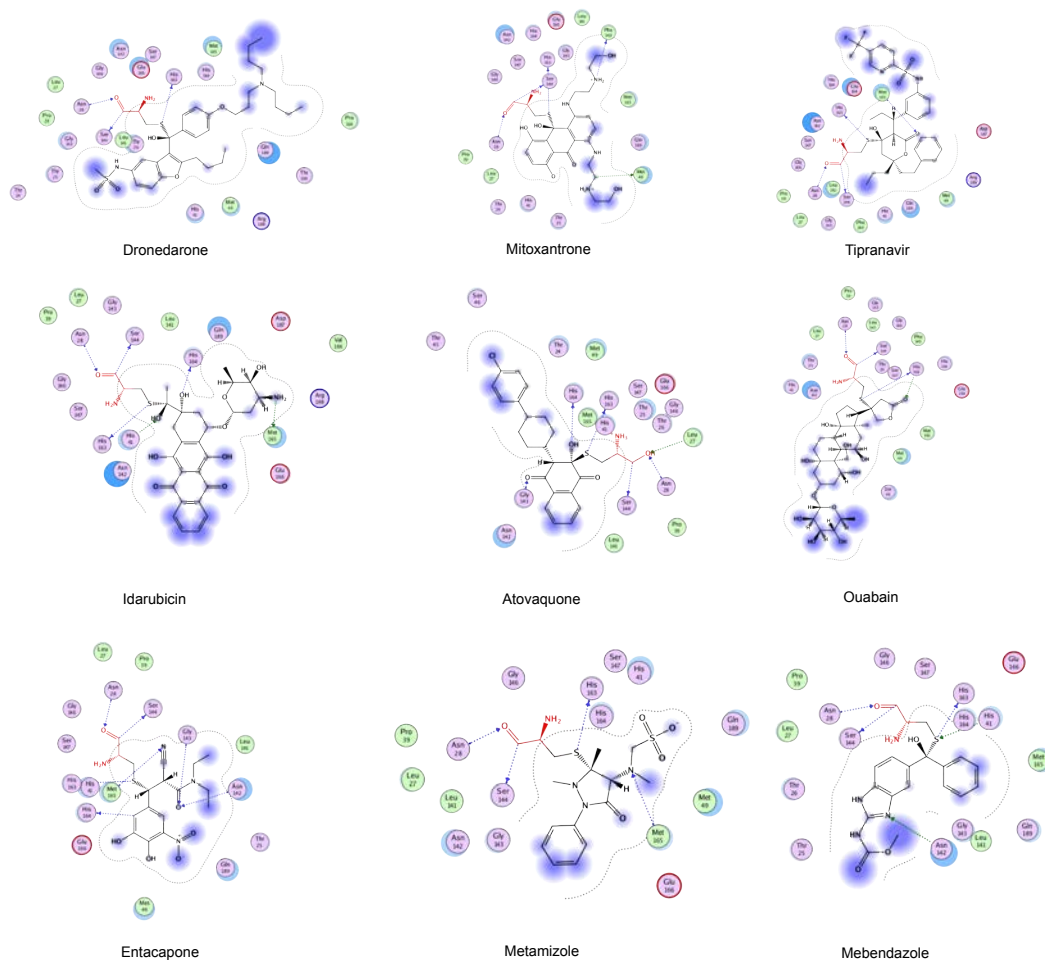


Figure 6. Two-dimensional presentation of covalent docking poses for top 9 candidates targeting Cys 145 of protease domain. Blue arrows are backbone hydrogen bonds and green arrows are the side chain hydrogen bonds.

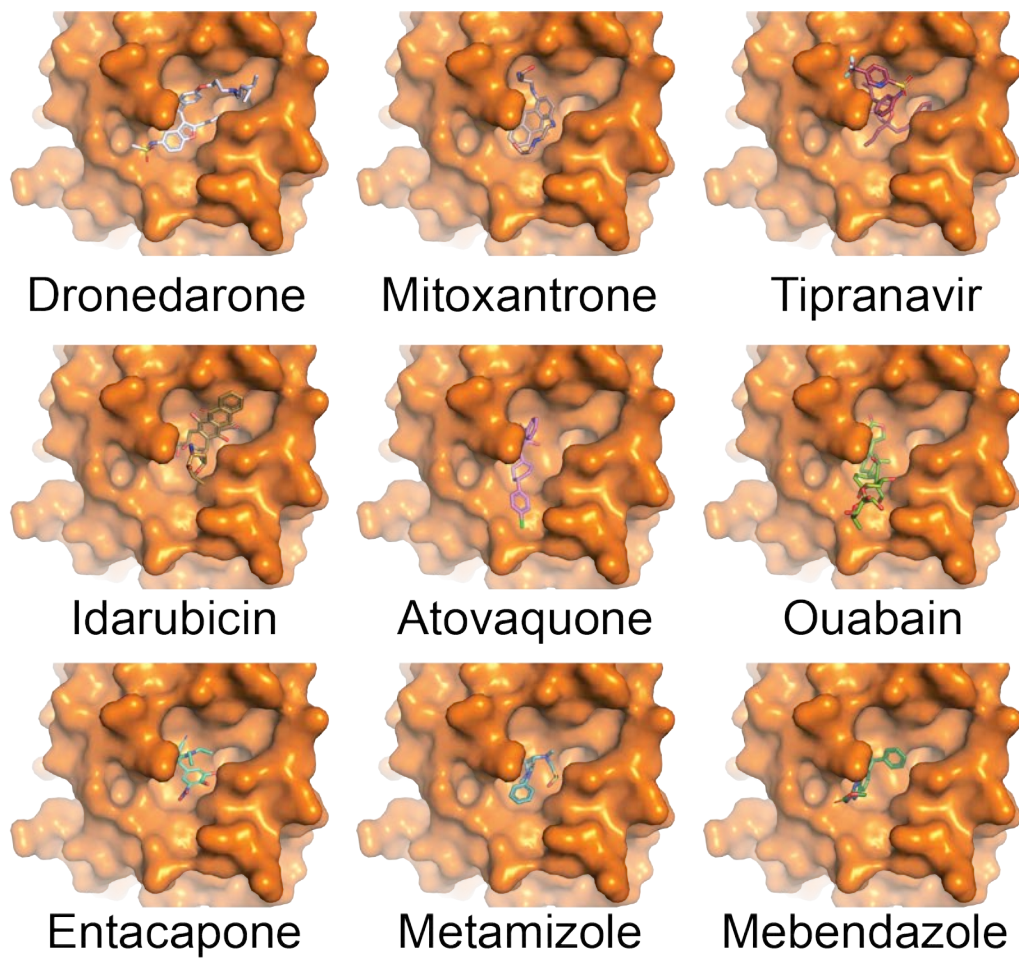


Figure 7. Docked positions for the covalently bound candidates targeting Cys 145 of COVID-19 virus M^{pro}.

Supporting Information:

Table S1. List of the remaining top 100 drugs bound to the central site of the substrate binding pocket based on S score.

Drug	S score (Kcal / mol)
Dipiverfin	-8.1378
Defroxamine	-8.1225
Dobutamine	-8.1108
Metipanolol	-8.0286
Ziprosidone	-8.0030
Cladribine	-7.9624
Almitrine	-7.9462
Epoprostenol	-7.8723
Famciclovir	-7.8672
Fluvastatine	-7.8443
Ticonazole	-7.8416
Delviradine	-7.8185
Methantheline	-7.7925

Drug	S score (Kcal / mol)
Mefloquine	-7.7520
Diatrizoate	-7.6401
lloperidone	-7.6082
Sapropterin	-7.5764
Vincristine	-7.5485
Oxamniquine	-7.54058
Teniposide	-7.5293
Abacavir	-7.4897
Zoledronic acid	-7.4834
Etoposide	-7.4235
Carbetocin	-7.4149
Adefovir	-7.3944
Desoximetasone	-7.3692
Timolol	-7.3641
Loratadine	-7.2958
variconazole	-7.2894
Tipranvir	-7.2732

Drug	S score (Kcal / mol)
Chloroquine	-7.2639
Indometacin	-7.2021
Meloxicam	-7.2002
Labetolol	-7.2001
Deslanoside	-7.1533
Leflunomide	-7.1231
Pimozide	-7.0937
Repaglinide	-7.0160
Furosemide	-6.9690
Candoxatril	-6.8322
Indapamide	-6.8165
Lansoprazole	-6.8003
Simvastatin	-6.7121
Cilizapril	-6.6663
Fosinopril	-6.4010
Donedarone	-6.2281
Indinavir	-6.2012

Drug	S score (Kcal / mol)
Paricalcitol	-6.1779
Imodium	-6.1374
Bexarotene	-6.0809
Clofarabine	-6.0798
Betamethasone	-5.9249
Bricodar	-5.7965
Nafareline	-5.7426
Mebendazol	-5.7426
Levocabastine	-5.6281
Losartan	-5.3706
Omapatrilate	-5.3388
Cidofovir	-5.1052
Flecainide	-4.9986

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