**COV-DOCK server: A web server for COVID-19 ligand-target docking.**

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**Abstract**

**Motivation**

Despite mass level vaccinations and launch of several repurposed drugs, emergence of COVID-19 reinfection has posed a key challenge in front of health authorities across the world. There is an urgent need to find new drugs and the understanding of the COVID-19 target–ligand interactions will play an important role in this direction. Here, we present COV-Dock Server, a web server that predicts the binding modes between COVID-19 targets and the small drug molecules.

**Results**

We collected experimentally solved structures of proteins of SARS-CoV-2. Further, we used predicted structure of experimentally unsolved proteins that were also collected. These structures were prepared for the docking. Next, 257 candidate drugs were docked against these targets using the meta-platform to understand the binding energy distributions. This server provides a free and interactive tool for the prediction of COVID-19 target–ligand interactions and enables drug discovery for COVID-19.

**Keywords:** Bioinformatics, drug repurposing, artificial intelligence, COVID-19, SAR-CoV-2, Molecular Docking.

**Availability and implementation**

COV-DRUGX Software Pipeline: <http://drugx.kamalrawal.in/drugx/> and [www.kamalrawal.in/tools.html](http://www.kamalrawal.in/tools.html)

**Supplementary information**

[Supplementary data](https://sites.google.com/view/drugx-supplementary) are available at our website https://sites.google.com/view/drugx-supplementary

**1. Introduction**

Till date, over 5 million deaths have been reported due to coronavirus disease 2019 (COVID-19). Several clinical trials are going on for the treatment of COVID-19. Currently, 3 drugs and 9 vaccines have been approved by FDA and other regulators which include [Veklury (Remdesivir)](https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-covid-19) ([fda.gov)](https://www.fda.gov/drugs/emergency-preparedness-drugs/coronavirus-covid-19-drugs) and Molnupiravir [Fischer et al., 2021]. The list of approved vaccines are available in [Supplementary Documents](https://sites.google.com/view/drugx-supplementary) on our website.

In the short period of time, most of the structures of SARS-CoV-2 have been released in PDB by different research groups [Kim Y et al., 2020; Lin et al., 2020]. A dedicated database ‘CoV3D’, provides users with comprehensive sets of structures of coronavirus proteins and their complexes with antibodies, receptors, and small molecules [Gowthaman et al., 2021]. Molecular docking has been used extensively for screening of drugs [Yu et al 2020; Rawal et al 2019] and drug repurposing activities [Wang et al., 2020]. Previously, our research group has performed large scale docking against network based proteins for diseases [Jaganadham et al., 2016] and vaccine development [Rawal et al., 2021]. Our free and easy to use computational server shall help those who are interested in drug discovery against COVID-19.

**2. Implementation**

The COV-DOCK server is written in python, HTML, CSS, and JS. Also we used the external libraries such as flask web framework, celery, redis queue, snakemake, obabel, AutoDockFR, AutoDock Vina, and p2rank. For visualization, we have incorporated JSMol (<http://jmol.sourceforge.net/>) in the result page. We have included 23 viral proteins from SARS-COV-2 for docking. These proteins have been reported to be important for virus life [Kong et al., 2020; Peele et al., 2020]. These include spike protein, membrane protein, envelop small membrane protein, nucleocapsid protein, main protease, papain-like protease, nsp3 (207–379), RNA dependent RNA polymerase (RdRp, nsp12/7/8 complex), nsp7, nsp8, nsp12, helicase, nsp14, nsp15 (endoribonuclease), nsp10, nsp16, nsp 16/10 (2′-O-methyltransferase), nsp1, nsp2, nsp4, nsp6, nsp9, ORF3A, ORF6, ORF7A, ORF8 and ORF10. The schematic workflow of the COV-Dock Server is shown in [Supplementary Figure](https://docs.google.com/document/d/1U7ngvJ7ojq9jHnopcJwAXGJqd5wABjqinr7SLRE0DlU/edit?usp=sharing) 1.

Autodock Vina [[Trott and Olson, 20](about:blank)10] is used as a docking engine for docking of small molecules. To transform formats or to generate 3D coordinate for the uploaded files, Open Babel system was utilized [[O'Boyle et al., 2011](about:blank)]. The docking box was defined on the center of native ligand with 40 Å × 40Å × 40Å in length to include the residues of entire cavity in experimental solved structure. For predicted structures, we define according to the information of active sites or binding sites of its homologs of SARS-CoV (details in [Supplementary Information](https://docs.google.com/document/d/1U7ngvJ7ojq9jHnopcJwAXGJqd5wABjqinr7SLRE0DlU/edit?usp=sharing)). We use default parameters of the software.

Since ACE2 and TMPRSS from humans have been considered to be important targets for viral entry [Lan et al., 2020; Fraser et al., 2021], we included them as separate modules under this tool and called COV-Human. Also, incorporating their interacting protein kinases namely AAK1, GAK and JAK1/2 which also play a role in viral endocytosis. These interactions are shown in Figure 2 and 3 in the [Supplementary file](https://docs.google.com/document/d/1U7ngvJ7ojq9jHnopcJwAXGJqd5wABjqinr7SLRE0DlU/edit?usp=sharing).

**3 Usage**

**3.1 Usage of small molecule docking**

Users are allowed to choose any of the COVID-19 (Viral) or Human targets to conduct small molecule docking. For this purpose, only smiles, mol2 or sdf formats are allowed by the server. For the online server, we have provided a single molecule docking option and a batch docking option. In batch docking, users can upload upto 50 molecules in one submitted job. The top 10 models are visualized in 3D by JSMol in the result page. Here, we take the recently launched Molnupiravir drug to dock against 23 viral targets. We find the Molnupiravir display best binding against Viral target Npro (Nucleocapsid Protein). The predicted binding energy of Top 1 ranked binding mode was -8 kcal/mol. Biochemical assays show that the RdRp uses the active form of molnupiravir, β-D-N4-hydroxycytidine (NHC) triphosphate, as a substrate instead of cytidine triphosphate or uridine triphosphate. RdRp is an important target for the development of antiviral drugs against coronaviruses [Dolgin et al., 2021; Cannalire et al., 2020; Tian et al., 2021] Therefore, we used molnupiravir and β-D-N4-hydroxycytidine (NHC) triphosphate to dock against RdRp [Kabinger et al., 2021]. The average binding energy across different targets was -6.326086957 ± 1.214390004 Kcal/mol.

Further, we extracted 256 COVID-19 drugs which are under various stages of drug repurposing studies ([Supplementary Documents](https://sites.google.com/view/drugx-supplementary) on our website) and docked against the viral targets. We found that the distribution of binding energies of these drugs are different from that of control datasets. The control datasets were constructed using strategies like random selection ([Supplementary Documents](https://sites.google.com/view/drugx-supplementary) on our website).

## Conclusions

## An online meta-server, COV-Dock Server, was constructed to predict the binding modes between the targets of COVID-19 and its potential ligands by implementing Autodock Vina as a docking engine. The server provides a user-friendly interface and binding mode visualization for the results, which makes it a useful tool for drug discovery of COVID-19.

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## Author Contributions

## This study was conducted under the overall guidance of KR, who contributed in protocol, critical evaluation of data and manuscript. The pipeline was designed, constructed and validated by RS, R and PS. Manuscript writing was done by R, PP, and PK. All the authors are responsible for the content of the manuscript.

## Competing interests

## The authors declare no competing interests.

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