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Virtual Screening of Piperidine Based Small Molecules Against COVID-19

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ABSTRACT. COVID-19 was declared a global pandemic in March 2020. Due to urgency with less time, there was a need to explore the potential treatment to address this severe health issue. Drug design and development is a long procedure; therefore, the first approach to speed up the drug development is almost repurposing existing drugs and small molecules. Over past few decades, use of fast and inexpensive computer-aided drug design (CADD) turned out to be a revolution in the pharmaceutical industry. CADD could help to knock out many inactive compounds at different test stages leading to time and money saving. Moreover, it could help to test already existing small molecules for other diseases. Within this work, an in-house library of 210 biologically active compounds was subjected to *in silico* virtual screening against COVID-19. The top 10 compounds from docking studies were further tested for *in silico* ADME prediction using Molinspiration.

KEYWORDS. COVID-19, Corona virus, Piperidine, Virtual screening.

INTRODUCTION. In December 2019, a lot of pneumonia cases infected by some unknown strain of virus were reported in Wuhan.[1] In January 2020, genetic sequencing of samples from patients revealed that it is another type of corona virus. Sequence analysis of suspected 11 patients were done and the results showed a similarity of 94.6 % of Amino Acids (AA) and 80 % of nucleotides (nt) with already known SARS. In February, the Coronavirus Study Group (CSG) of the International Committee on Taxonomy of Viruses officially named the new virus as the novel coronavirus SARS-CoV-2.[2] Subsequently, the resulted corona virus disease has been called COVID-19 putting significant effects on human life systems all around the world.[3, 4] Corona viruses belong to the family of Coronaviridae, divided into four genera: α, β, γ, and δ.[5] The first two groups infect mammals and humans whereas the last two ones infects birds. COVID-19 is a β coronavirus, an oval shaped with 40-140 nm. Like all other coronaviruses, it has crown like features of *S* protein, that's why corona viruses got their name. Corona viruses are not new, first corona virus was isolated from chickens in 1937 and from humans in 1970. Till now, seven types of coronaviruses have been identified that can affect humans. Corona virus is zoonotic virus, more suspects it is bat. There is a debate on zero patient, but it is mainly transmitted through fours ways from person to person.[6]

1) Infected person droplets: when an infected person sneezes, cough the tiny droplets from respiratory tract containing virus directly lands into the respiratory tract of another person.

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2) Aerosol transmission: droplets less than 5 µm could be suspended into air for 3 h, so inhaling in that air probably infect the person.

3) Contaminated surfaces when a person exhales the virus droplets and the droplets land on the surface the surface gets contaminated for couple of hours to multiple days depending on the material. When anyone touches that surface it gets on the hands and gets into body through mouth nose or eyes.

4) Fecal oral route; many studies confirm the presence of virus in infected person feces and urine. That is why who has enforced a high food safety.

To slow down transmission, WHO advised social distancing and frequently hand washing practices.

Ace2 receptors are existed in many organs but first contacting with respiratory tract, so it mainly produces respiratory issues.[5] There are three categories of infected people.

1) Asymptomatic: These are the people who does not produce any noticeable symptoms and go unnoticed.

2) Mild cases who develop dray cough, fever, loss of taste and smell, body aches and weakness. These people will need not much care and would be treated for symptoms.

3) Coming the critical patients who develop severe pneumonia, leading to lung fibrosis. These are the patients who need hospitalization, oxygen and may need ventilators. The main reason for the severity is the cytokine storm an immune response to virus.

COVID-19 has a genome containing a 5'untranslated region (UTR), 12 open reading frames (ORF), 3' UTR and PolyA tail.[7] First ORF contains two third of the genome, which translates into two polypeptides and encodes 16 nonstructural proteins (NSPs). The remaining part of the genome encodes structural proteins.[8] Four of them are most conserved and prominent structural proteins, spike protein (*S*), envelope protein (*E*), membrane protein (*M*) and nucleocapsid protein (*N*). COVID-19 enters to host cell by binding its *S* protein to Ace2 receptor.[9] After binding to receptor, host type 2 trans membrane serine protease, TMPRSS2, helps the virus to get inside the cell. Once the virus gets inside the cell, it will be uncoated and viral genome could be released. As COVID-19 is positive sense RNA virus, it would directly use the cell translation machinery to develop a translation complex. Two main nonstructural proteins like protease 3 chymotrypsin and papain further chop the polyproteins to produce structural proteins for replication assemble, and RNA-dependent RNA polymerase replicate the genome. Once the replication is completed, RNA will be packed into coat and send out. Due to homology of these three proteins with other corona viruses,[10] these are considered potential targets by existing drugs viral entry and immune regulation pathways are also considered alternative pathways to deal COVID-19.[9]

Chloroquine and Hydroxychloroquine are already existing used drugs, as their mechanism is to inhibit the endocytosis and viral entry.[9] Arbidol, another drug, inhibits the *S* protein and ACE2 receptor interaction. Lopinavir/ritonavir, another already existing used drug for HIV, inhibits the 3CLprotease activity. Remdesivir, another investigating drug, was being developed by Gilead as multi strain antiviral by inhibiting the activity of RNA dependent polymerase widely being used to treat COVID-19 patients. Both proteases also involve in immune response of host cell making them strong candidate for drug target.[10] PLpro shares 86% identity and 3CLpro shares 96% decoded identity with SARS-CoV. Due to its indispensable role in transcription and replication and having less mutagenesis in main protease as compared to other sites, this gives an edge over other targets. 3CLpro is considered as a favored target for antiviral therapies. 2019-nCoV and SARS-CoV share remarkable 96% sequence identity in their decoded 3Clpro.

Over the past few decades, use of fast and inexpensive computer-aided drug design (CADD) turned out to be revolutionary in pharmaceutical industry.[11] It helps to knock out many inactive compounds at different test stages saving time and money. Moreover, it also helps to test already existing small molecules for other diseases.[4, 12-14] An-Inhouse library of 210 biologically active compoundswas subjected to *in silico* virtual screening against COVID-19.[15, 16] The screening steps showed promising results and authors are repurposing these potential compounds as future drug contenders against COVID-19 examining them *in vitro* and *in vivo*.

METHODOLOGY. Receptor Preparation. The crystal structure of COVID-19 main protease in complex with N3 inhibitor (PDB ID: 6LU7) was retrieved from the Protein Data Bank.[17] The receptor was prepared using Autodock tools,[18] in which hydrogen

atoms were added and charges were assigned. The binding site center of receptor was located at x: -11.683, y: 14.686, z: 65.363, in a grid box of 40*40*40 dimensions with 0.375 angstrom point spacing.

Screening In-house Library. A library of about 210 synthesized compounds[16, 19] of our lab was set up for screening against the prepared receptor of COVID-19 using Autodock vina software.[20] The convention for naming the library compounds was as follows: "Li" for in-house library, PIH/PIO for piperdine hydrazide/oxadiazole depending upon the chemical moieties present in the molecule, and simple numeral for unique naming. The objective was to screen diverse functionalities as possible to find COVID-19 inhibitory potential. The selected series were piperidine based polyfunctional compounds exhibiting sulfonamide, oxadiazole, and hydrazide functional groups. Top 36 compounds were sorted based on binding energies (i.e., stronger than -7.0 kcal/mol) and then processed for re-docking. The selection of compounds was further narrowed for getting top 5 compounds (binding energies stronger than -10.0 kcal/mol) for detailed interaction studies. The .pdbqt files of the in-house library compounds were generated using Raccoon software.[18] The screening studies were performed on Linux platform using Autodock vina.

Table 1: Compounds list sorted according to their binding energy in ascending order after re-docking.

Sr.No.	Compounds ID	Binding Energy (kcal/mol)	Sr.No.	Compounds ID	Binding Energy (kcal/mol)
1	Li_PIO_114	-7.80	**19**	Li_PIS_141	-7.20
2	Li_PIO_67	-7.60	**20**	Li_PIH_185	-7.10
3	Li_PIO_89	-7.60	**21**	Li_PIO_107	-7.10
4	Li_PIO_95	-7.60	**22**	Li_PIO_61	-7.10
5	Li_PIS_140	-7.60	**23**	Li_PIO_64	-7.10
6	Li_PIO_99	-7.50	**24**	Li_PIO_69	-7.10
7	Li_PIS_144	-7.50	**25**	Li_PIO_77	-7.10
8	Li_PIH_187	-7.40	**26**	Li_PIO_78	-7.10
9	Li_PIH_191	-7.40	**27**	Li_PIS_138	-7.10
10	Li_PIH_189	-7.30	**28**	Li_PIS_39	-7.10
11	Li_PIO_62	-7.30	**29**	Li_HABr1_209	-7.00
12	Li_PIO_66	-7.30	**30**	Li_PIH_184	-7.00
13	Li_PIO_79	-7.30	**31**	Li_PIO_106	-7.00
14	Li_PIO_87	-7.30	**32**	Li_PIO_113	-7.00
15	Li_PIO_101	-7.20	**33**	Li_PIO_59	-7.00
16	Li_PIO_71	-7.20	**34**	Li_PIO_60	-7.00
17	Li_PIO_74	-7.20	**35**	Li_PIO_73	-7.00
18	Li_PIO_76	-7.20	**36**	Li_PIS_35	-7.00

RESULTS & DISCUSSION. The compounds Li_PIO_114, Li_PIO_67 and Li_PIO_89 showed good binding energies stronger than -7 kcal/mol with the main protease target (Table 1 and Figs. 1 and 2) considering for further analysis. The interaction studies of the compound Li_PIO_114 depicted three hydrogen bonds; Lys5 with oxadizole ring (3.07 Å), Arg131 and Thr199 with sulfonamide group (3.36 Å and 3.24 Å). Ser139, Gln127, Glu288, Glu290 and Leu287 were making van der Waals interactions (Figs. 1 and 2 a). Similarly, in case of the compound Li_PIO_67, Phe181 and Cys85 were making hydrogen bond with sulfonamide group (3.36 Å and 3.24 Å), and Glu55 with carbonyl group (2.50 Å). Other residues like Asn84, Gly179, Asn53, Asp187, and Gly183 were involved in hydrophobic interaction with the compound (Figs. 1 and 2 b). Likewise, oxadiazole ring of the compound Li_PIO_67 was contributing to hydrogen bonding with the receptor residue Arg131 (3.82 Å). Lys5 showed hydrogen bonding with sulfonamide group (2.98 Å). Glu290 and Gln127 depicted hydrogen bonding with carbonyl group (2.79 Å and 2.98 Å). The rest residues of the receptor in the ligand vicinity were Asn238, Thr198, Asp289, Leu287, Glu288 and Lys137, making van der Waals interactions with the compound (Figs. 1 and 2 c).

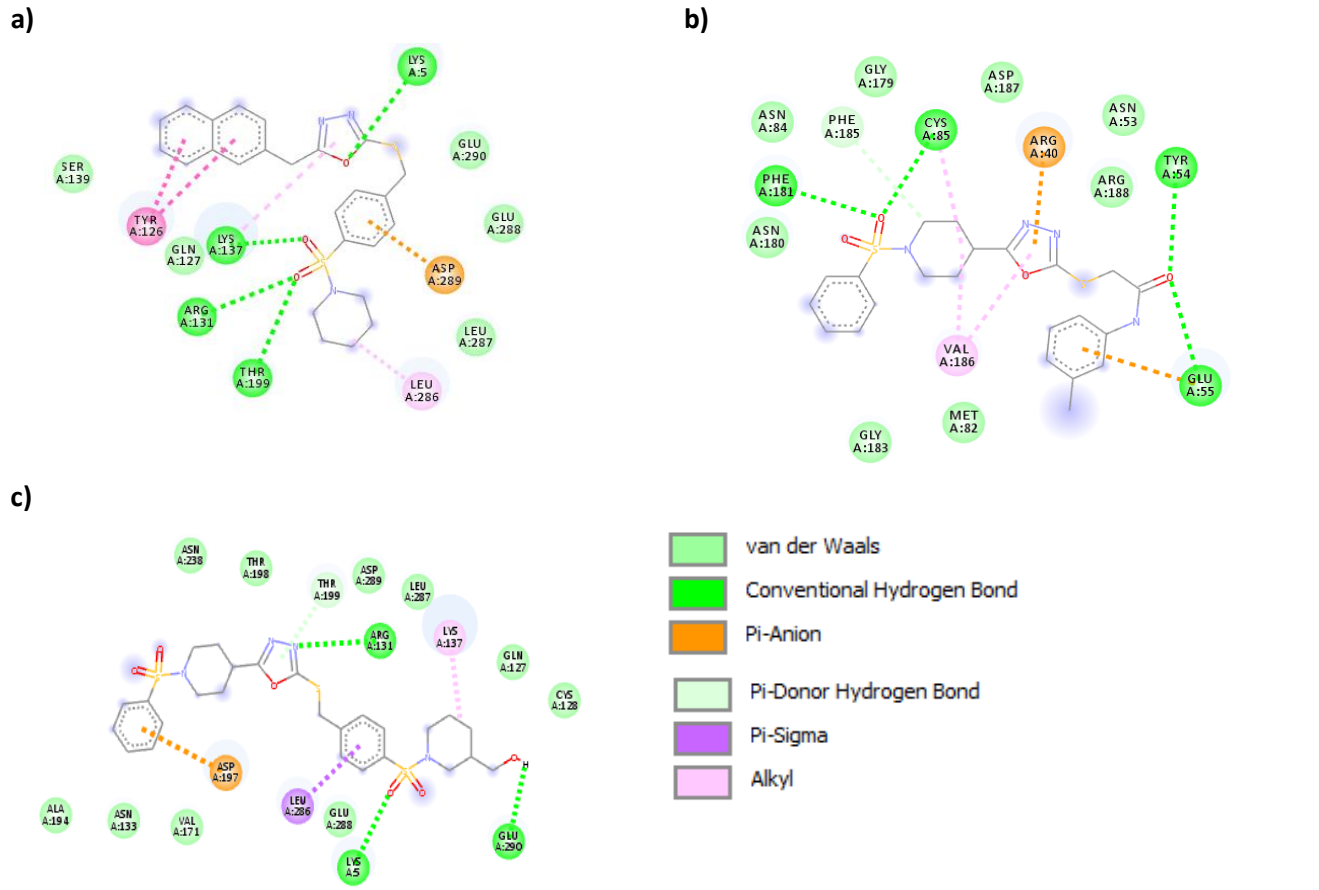

Fig. 1: Interaction diagrams of a) Li_PIO_114, b) Li_PIO_67, and (c) Li_PIO_89, with the COVID-19 receptor, PDB ID: 6lu7.

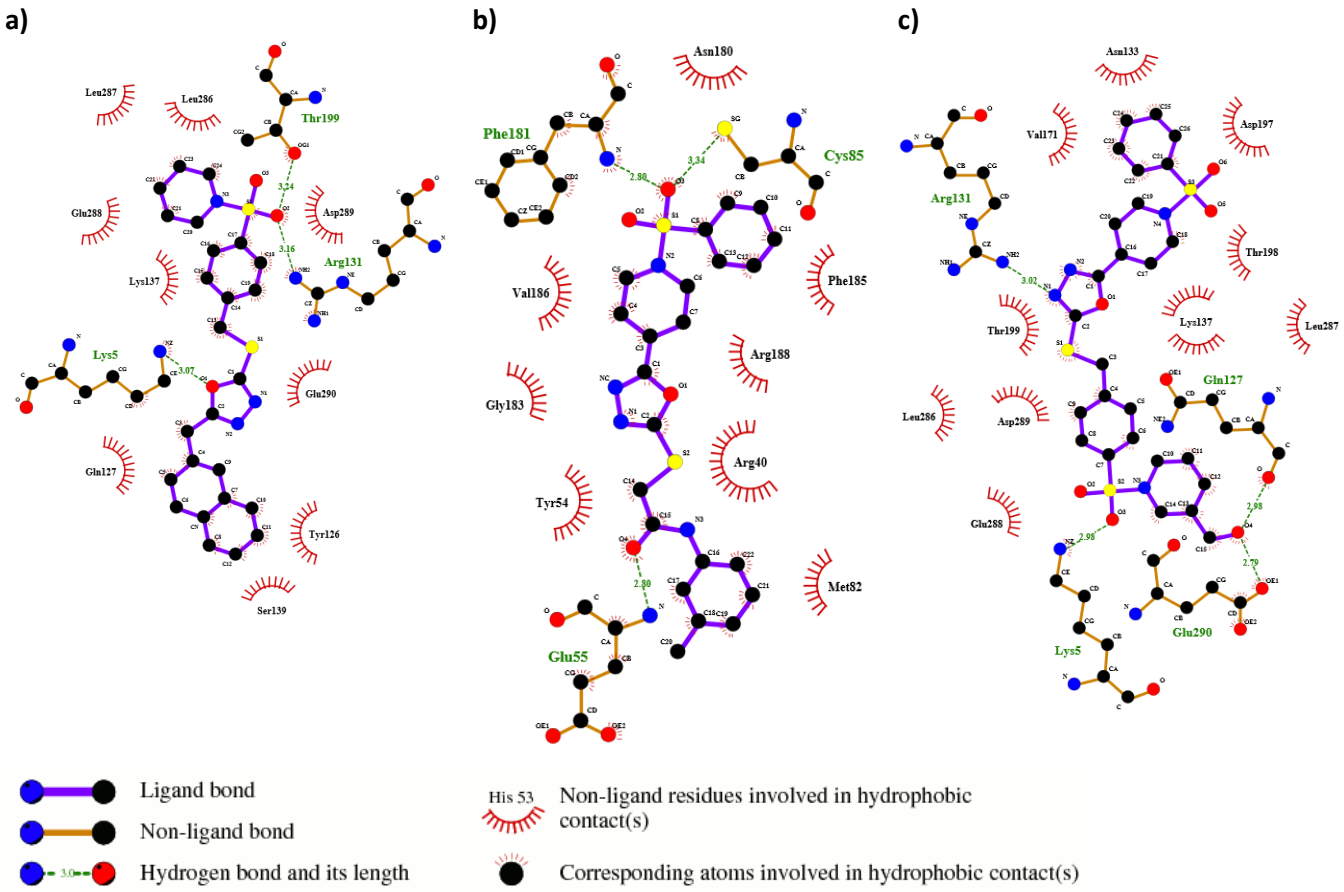

Fig. 2: Interaction diagrams of a) Li_PIO_114, b) Li_PIO_67, and (c) Li_PIO_89, with the COVID-19 receptor, PDB ID: 6lu7.

Table 2: *In silico* ADME predictions.

Sr.No.	Compound ID	miLogP	TPSA	natoms	MW	nON	nOHNH	nrotb
1	Li_PIO_114	5.12	76.30	33	479.63	6	0	7
2	Li_PIO_67	2.70	105.40	32	472.59	8	1	7
3	Li_PIO_89	2.52	133.91	39	592.76	10	1	9
4	Li_PIO_95	2.50	76.30	29	427.36	6	0	6
5	Li_PIS_140	4.60	75.71	30	430.57	6	1	6
6	Li_PIO_99	2.71	160.46	37	547.62	12	1	11
7	Li_PIS_144	3.27	95.94	29	418.51	7	2	6
8	Li_PIH_187	3.00	112.65	31	465.60	8	2	6
9	Li_PIH_191	2.96	112.65	32	473.58	8	2	6
10	Li_PIH_189	1.57	129.72	33	497.64	9	2	7

milogP: LogP (octanol/water partition coefficient), TPSA: Molecular Polar Surface Area, MW: Molecular Weight, nON: number of Hydrogen bond acceptors, nOHNH: number of Hydrgogen bond donors, nrotb: Number of Rotatable Bonds.

The top 10 compounds from docking studies were further tested for *in silico* ADME prediction using Molinspiration (http://www.Molinspiration.com//cgi-bin/properties), which employs Lipinski's "Rule of 5" to check the drug likeliness properties (Table 2). The compound Li_PIO_99 slightly more molecular weight; other compounds showed optimal ADME properties.

CONCLUSION. In this virtual screening of in-house small molecule library, initially 210 piperidine based polyfunctional compounds were screened against COVID-19. The top 36 compounds were sorted based on binding energies (stronger than -7.0 kcal/mol) and then processed for re-docking. The selection of compounds was further narrowed for getting top 5 compounds for detailed interaction studies (binding energy stronger than -10.0 kcal/mol). The docking studies against COVID-19 protease (PDB ID: 6lu7) revealed that the compounds Li_PIO_114, Li_PIO_67 and Li_PIO_89 could show promising binding potential with the receptor. These hit compounds were further tested for *in silico* ADME predictions, which employs Lipinski's "Rule of 5" to check the drug likeliness properties. The compound Li_PIO_99 was slightly more molecular weight; other compounds showed optimal ADME properties.

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