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ANTIVIRAL-COVID-19 POTENTIALS OF NOVEL INDOLE AND CEFETAROLINE FOSAMIL ANALOGUES FOR INHIBITION OF 3-CL PROTEASE-SARS/COV-2; BASED ON ANALYSIS OF MOLECULAR DOCKING

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ABSTRACT

The current work focuses on drug development of known approved antibiotics such as **Ceftaroline fosamil** was modified its structural core to obtain a novel ceftaroline fosamil **analogues library** and also a **certain novel indole library** for the inhibition of SARS-CoV-2, **3CL-Proteases enzyme** for against COVID-19, it's a urgent to generate new chemical entities against this virus. As a key enzyme in the life-cycle of corona-virus, the 3C-like main protease (3CLpro or Mpro) is the most attractive for antiviral drug design. Based on a recently solved structure (PDB ID: 6LU7, SARS/CoV-2 3CL Pro, its 99% identical of COVID-19), Reported as., Yu-Chuan Chang et.al.,2020, we were developed the preliminary work of Structure-based drug design for generating potential lead compounds for targeting against the SARS-CoV-2 3CLpro resulted in the, archived three series of derivatives from those library by our structure-based optimization. These three compounds can be used as potential lead candidates for future drug development of the pharmacological interventions against COVID-19.

KEYWORDS: COVID-19, SARS/CoV-2, 3-CL Proteases, Docking and Ceftaroline.

INTRODUCTION

CoVs are enveloped, positive-stranded RNA viruses with nucleocapsid. For addressing pathogenetic mechanisms of SARS-CoV-2, its viral structure, and genome need to be considerations. In CoVs, the genomic structure is organized in a +ssRNA of about 30 kb in length the largest recognized RNA viruses and with a 5′-cap structure and 3′-poly-A tail. Starting from the viral RNA, the synthesis of polyprotein 1a/1ab (pp1a/pp1ab) in the host is realized. The transcription works through the replication-transcription complicated (RCT) organized in double-membrane vesicles and via the synthesis of subgenomic RNAs (sgRNAs) sequences. Of note, transcription termination happens at transcription regulatory sequences, located between the so-called open reading frames (ORFs) that work as templates for the production of subgenomic mRNAs. In the atypical CoV genome, at least six ORFs can be present. Among these, a frameshift between ORF1a and ORF1b guides the production of both pp1a and pp1ab polypeptides that are processed by virally encoded chymotrypsin-like protease (3CLpro) or principal protease (Mpro), as well as one or two papain-like proteases for producing 16 non-structural proteins (nsps). Apart from ORF1a and ORF1b, different ORFs encode for structural proteins, including spike, membrane, envelope, and nucleocapsid proteins.[1] and accessory proteic chains. Different CoVs existing special structural and accessory proteins translated by means of dedicated sgRNAs. Pathophysiology and virulence mechanisms of CoVs, and therefore additionally of SARS-CoV-2 have links to the function of the nsps and structural proteins. For instance, lookup underlined that nsp is able to block the host innate immune response.[7] Among functions of structural proteins, the envelope has a essential role in virus pathogenicity as it promotes viral assembly and release. However, many of these facets (e.g., those of nsp 2, and 11) have not but been described.[1-3]

Among the structural elements of CoVs, there are the spike glycoproteins composed of two subunits (S1 and S2). Homotrimers of S proteins compose the spikes on the viral surface, guiding the link to host receptors.[8] Of note, in SARS-CoV-2, the S2 subunit containing a fusion peptide, a transmembrane domain, and cytoplasmic area is highly conserved. Thus, it could be a goal for antiviral (anti-S2) compounds. On the contrary, the spike receptor binding domain presents solely a 40% amino acid identity with other SARS-CoVs. Other structural factors on which research

must always focus are the ORF3b that has no homology with that of SARS-CoVs and a secreted protein (encoded by ORF8), which is structurally unique from those of SARS-CoV.[1-3]

The 3CLpro has been reported as an alluring target for developing anti-coronaviral drugs: 1) this protease is tremendously conserved in both sequences and 3D structures; 2) 3CLpro is a key enzyme for related virus (including SARS and SARS-CoV-2) replication; 3) it solely exists in the virus, not in humans. Developing specific antiviral capsules targeting 3CLpro of the specific virus has proven significant success; for example, both accepted drugs lopinavir and ritonavir can completely occupy the substrate-binding site of 3CLpro to break down the replication of human immunodeficiency virus (HIV). However, due to the large distinction between HIV and SARS-CoV-2 3CLpro, lopinavir and ritonavir were validated ineffective for inhibiting SARS-Cov-2. On the other hand, the substrate-binding site of 3CLpro is almost the same between the SARS-CoV-2 COVID-19) and SARS as S3 presents. The developed attainable inhibitors and drug-design experience targeting SARS-3CLpro might also be applicable to SARS-CoV-2 (COVID-19).[4-5]

Thus, the present work was focused on the optimization of structure-based drug design for against the SARS/CoV-2, 3CL proteases with newly designed two focused library, one is a Ceftaroline fosamil analogue and second the indole derivatives, resulted in the obtained three potential lead candidate for SARS/CoV-2, 3CL-protease inhibitors and nucleotide analogues for COVID-19. These two identified lead molecule contain the core structure of phenyl sulfo acetamide cap containing the linker of certain beta lactam ring which was connect the thiozole diversity were obtained from the Ceftaroline fosamil library (Shown on Figure: 1-2) and second is a indole derivatives.

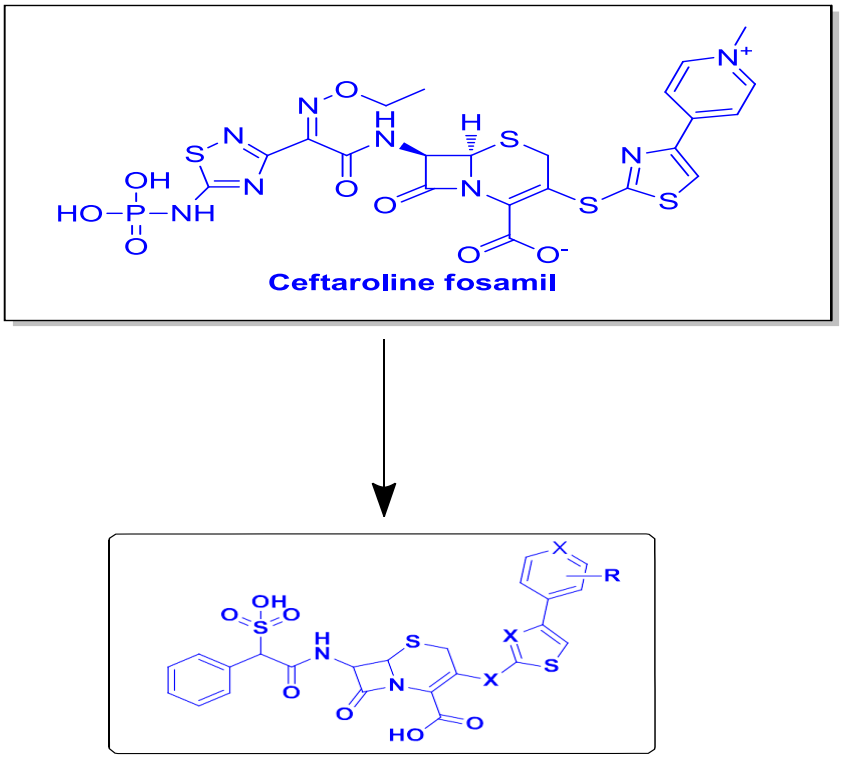


Fig-1: Ceftaroline fosamil analogues library

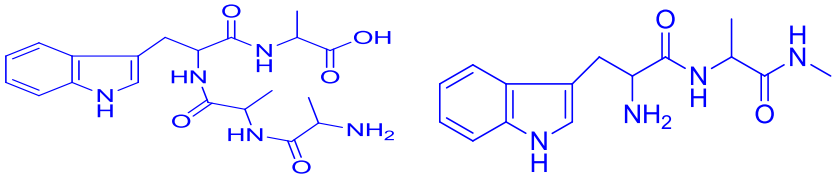


Fig. 2: Newly Designed Indole Derivatives.

MATERIALS AND METHODS

The Proteins/Macromolecules of COVID-19, the SARS/CoV-2 3clpro/Mpro (PDB ID: 6LU7) [Ref] structures were obtained from PDB (https://www.rcsb.org/), in the file format of dot.pdb format. The PDB is an archive for the crystal structures of biological macromolecules from worldwide [Ref]. The 6LU7 protein which contains two chains, A and B, which form a homodimer. Chain A was used for macromolecule preparation. The native ligand for 6LU7 is n-[(5-methylisoxazol-3-yl)carbonyl]alanyl-l-valyl-n~1~-((1r,2z)-4-(benzyloxy)-4-oxo-1-{[(3r)-2-oxopyrrolidin-3-yl]methyl}but-2-enyl)-l-leucinamide.

Active site prediction

A prediction of active site and binding sites of ligand in a protein using CastP. The interaction can be calculated using interaction energy between the protein and a simple Van-der-Waals probe to locate energetically favorable binding sites. Energetically favorable probe sites are clustered according to their spatial proximity and clusters are then ranked according to the sum of interaction energies for sites within each cluster. A probable ligand binding pockets of SARS/CoV-2 (COVID-19) protein is calculated according with geometry accuracy of RMSD and superimposition of the target to its native structure. RMSD depends on the number of equivalent atom pairs of proteins that are compared, which in turn depends upon the maximum allowed distance between atom pairs.[6-7]

Ligand Preparation

The entry point for any chemistry program within drug discovery research is generally the identification of specifically acting low-molecular-weight modulators with an adequate activity in a suitable target assay. The two novel Ligand Library was like Ceftaroline fosamil analogues and Indole derivatives (Shown Fig 1-2) drawn and retrieved from ACD-Chemsketch which is contains totally 30 molecules. The physicochemical and ADMET analysis of all ligands were obtained from molinspiration and Chemicalize data bases.[6-7]

In silico-High Throughput screening

The two novel libraries of ceftaroline fosamil analogues and indole derivatives, Ligand Library which is contains totally 30 molecules were designed based on drug-like properties of their ability is due to the ligand to interact and inhibit the native ligand catalytic site of 3-CL Pro SARS/CoV-2-protein. The ligand structures were designed by using ACD/Chemsketch and saved in .MOL file format. A lead compounds or scaffolds can be identified from diversified compound pool and accelerated screening, a screened pools is focused for bio-targets to inhibit the diseases. We used structural based screening, through molecular docking by using binding and activation to further probe the parent library. The structure of the lead fragments i.e., "the testing ligands" was designed based on the basis of docking studies of ceftaroline fosamil analogues ligand library and indole ligand library with 3-CL Pro SARS/CoV-2-protein. The fragments were identified on the basis of "Lipinski's Rule of Five" and may therefore represent suitable starting point for evolution of good quality lead compounds.[6-7]

Molecular Docking

The two novel designed libraries of ceftaroline fosamil analogues and indole derivatives were used as the initial coordinated for docking with 3-CL Pro SARS/CoV-2-protein and Auto Dock 4.2 is used to check the binding energies of the chosen compounds at the active sites of 3-CL Pro SARS/CoV-2-protein. Grid maps of different grid points, centered on the ligand of the complex structures, were used for receptors respectively, to cover binding pockets. A set of Lamarckian genetic algorithm was used for molecular docking simulations. Population size of 150, mutation rate of 0.02, and crossover rate of 0.8 were set as the parameters. Simulations were performed using up to 2.5 million energy evaluations with a maximum of 27 000 generations. Each simulation was performed 10 times, yielding 10 docked conformations. The lowest energy conformations were regarded as the binding conformations between the ligands and the proteins. Reverse Validation. In this validation process, the complete strategy followed in this study was reversed to ensure that the identified hits really fit the generated models and active sites of both targets. All the parameters required for molecular docking were set as used in actual process.[6-7]

RESULTS AND DISCUSSION

Active Site and Ligand Binding site prediction

According to study of 3-CL Pro SARS/CoV-2-protein RNAs signaling pathway in viral network, there are various sites present in 3-CL Pro SARS/CoV-2-protein. Thus, In this study, we chose 3-chymotrypsin-like protease (3CL-protease), the main protease used to cleave polyproteins into replication-related proteins, and RdRp, the main protein for RNA replication, as the target receptors. The 3CL-protease structure of COVID-19 (PDB ID: 6LU7) was obtained from the RCSB Protein Data Bank, which was recently released on February 5th, 2020. Hence, we can give us a strong structural insight about its mechanism of action and also enable us to trace important target residues for designing drug inhibitors against the 3-CL Pro SARS/CoV-2-protein signaling pathway. The minimized free energy was calculated with electrostatics and van der Waals interactions between residues of complex, the active site and binding site amino acid can be labeled in (Table: 1 & Figure: 2).

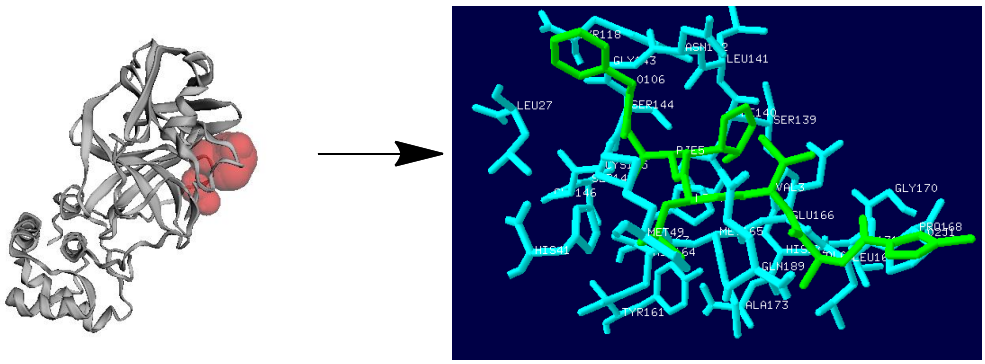
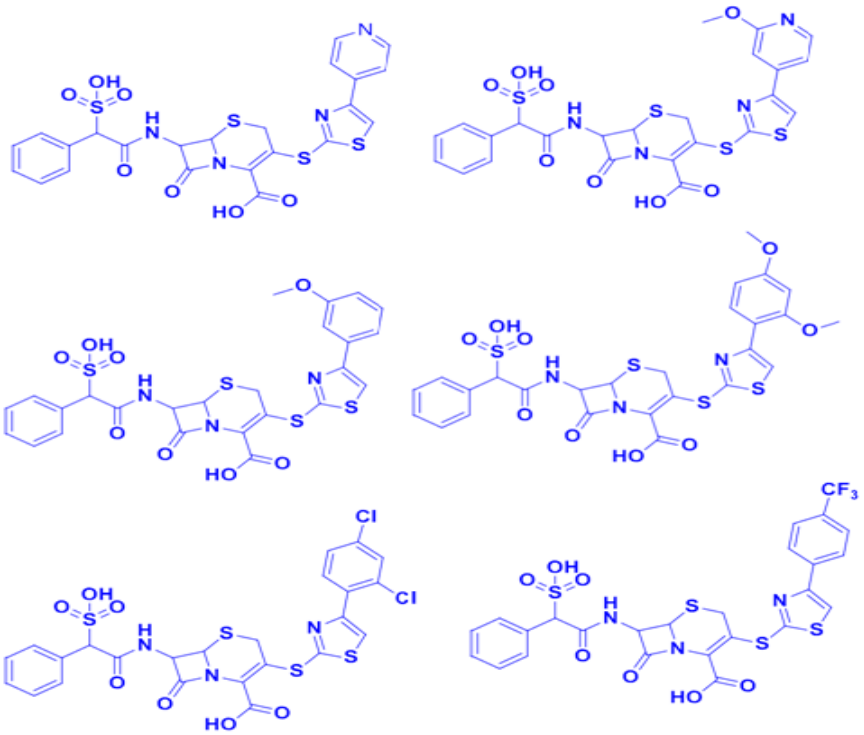


Figure: 3: SARS-CoV-2 active site and ligand binding packets

The right red colour of SARS/CoV-2 3CL-Pro is a ligand binding pocket and left stick indicating the amino acid resedues representing in their ligand binding pocket. The coordinates of modeled structure is calculated based on energy thresholds. We measure predicted site maps onto the ligand coordinates using a RMSD calculations. The clustering of coordinates is 1.6 Å of a ligand atom. A normal energy threshold values is (-1.0 to -1.9 kcal/mol) for retaining methyl binding site but predicted SARS/CoV-2 were varying according the binding energy cut off of 1.4 kcal/mol. active site amino acids were predicted and these amino acids are used for ligand docking studies.

Table 1: SARS/CoV-2 Active site and Ligand Binding sites prediction using CASTp.

Protein Name	SA (Surface Area)	SV (Surface Volume)	Active site Amino acids	
SARS/CoV-2, 3CL Protease PDB ID: 6LU7		224.704	180.763	LEU-27,PRO-39,HIS-41,CYS-44,THR-45,SER-46,ASP-48 MET-49 ,LEU-50 ,TYR-54 ,LEU-141 ,ASN-142, GLY-143 SER-144 CYS-145``HIS-163,164,172,MET-145 GLU-166 LEU-167,PRO-168 ,VAL-171 ,PHE-181 ,VAL-186 ,ASP-187,ARG-188, GLN-189,192



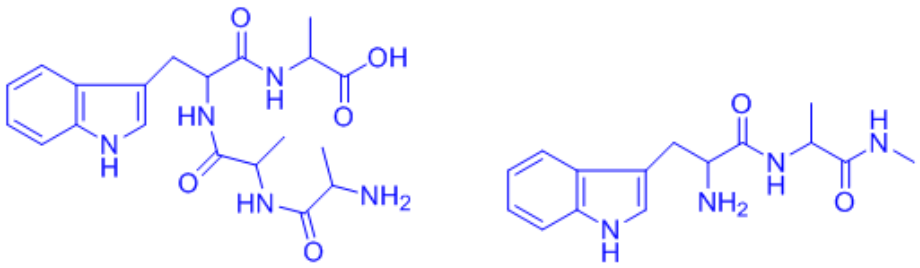
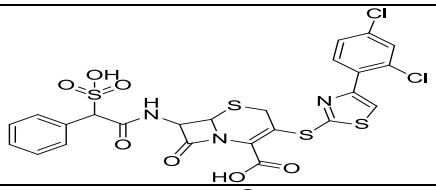
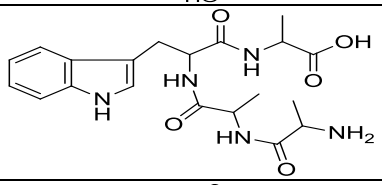
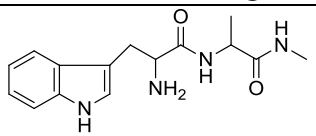


Fig. 4: Most active Hit molecules from docking analysis.

The most active eight hit molecules (shown: Fig-4) were identified from two focused library of rest of 3o molecules based on molecular docking analysis, the libraries which contains the core structure of phenyl sulfo acetic amide cap it was connected with the beta-lactam ring further linked with certain thiozole diversity of whole library called as ceftaroline fosamil analogues in first library, the indole derivatives in second library respectively, which was mainly focused for these novel pharmacophoric chemical space were interacted 3CL-Pro SARS/CoV-2 catalytic site, used for the inhibition of COVID-19.

Table 2: Physico-chemical properties of most active potential Hits.

Ligand No	Structure &IUPAC Name	Mol. Wt.	Log p	R-Bonds	TPSA	N-Violations
Ligand-1a		656	5.76	11	223.45	2
Ligand-2a		417	2.77	9	166.47	1
Ligand-2b		288	0.33	5	100.01	0

The Table-2 shown on generated potential hits from two libraries. (Figure -1-2), totally 30 molecules and their biological properties were analyzed using Hyperchem 7.5 and mole-inspiration Professional in these ligand-1a, ligand-2a and ligand-2b were selected most active hit candidate. Based on a desired Log P value (octonol-water partition coefficient) is no more than 5 (also part of the so-called Lipinski rule-of-five; LogP 5 = 1:100,000 concentration difference between water and octonol phases). Based on Log P values the ligand 1a and 2a having the optimum log p 1-2 for persisting hydrophilic and hydrophobic is shown best molecules is strongly accepting Lipinski rule and it is a best molecule for molecular descriptors studies based on mole-inspiration and Hyperchem 7.5 shown in (Table: 2 & Figure 4)

Molecular Docking

The docking of competitive bioactive molecules of newly designed two focused libraries of ceftaroline analogues and indole derivatives of totally 30 structures onto the conserved domain regions of 3 CL Pro SARS/CoV-2 were performed using Autodock4.2 software package. The 3 CL Pro SARS/CoV-2 was added polar hydrogen atoms and its non-polar hydrogen atoms were merged. For the ligand, non-polar hydrogen atoms were merged with Gustier charges assigned. All rotatable bonds of ligand were set to be rotatable. Docking was performed using genetic algorithm and local search methods. A population size of 150 and 10 millions energy evaluations were used for 100 times searches, with a 80 x 80 x 80 dimension of grid box size and 0.375 Å grid spacing around the domain. Clustering histogram analyses were performed after the docking searches. The best conformations were chosen from the lowest docked energy that populated in the highest number of molecules in a particular cluster with not more than 1.5 Å root-mean-square deviations (RMSD). The H-bond interactions and its binding energy were evaluated for the best affinity by using Pymol molecular visualize. The docking of 3 CL Pro SARS/CoV-2 domains binds with most active ligand such as Ligand-1a, Ligand-2a and Ligand-2b were represented in Figure: 5-10 and Table-4.

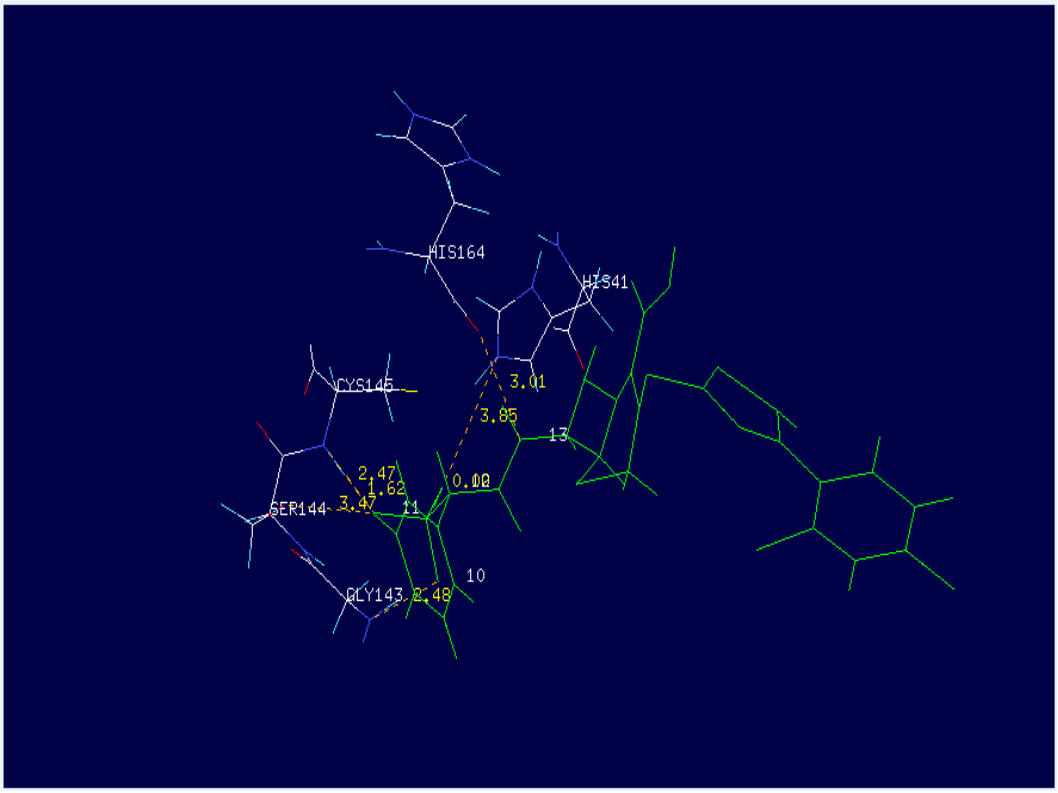


Fig. 5: Intermolecular forces and bonding distances of Ligand-1a (Ceftaroline fosamil analogues) complexed with 3 CL Pro SARS/CoV-2 PDB id: 6LU7. The hydrogen bonds interactions between the ceftaroline fosamil analogue (Ligand-1a) and protein (3 CL Pro SARS/CoV-2) is described below.

The first hydrogen bond is formed between the oxygen (10) atom of drug and Nitrogen atom of Gly 143 residue. The second and third Hydrogen bonds formed between the oxygen (11) atom of drug and the oxygen (OG) atom of Ser 144 and Nitrogen atom of CYS 145 residues. The fourth hydrogen bond is formed between the oxygen-12 (acceptor) atom of drug and Nitrogen (Donor) atom of His-41 residue. The fifth hydrogen bond is formed between the Nitrogen-13 atom (donor) of drug and oxygen atom (acceptor) of His-164 residue.

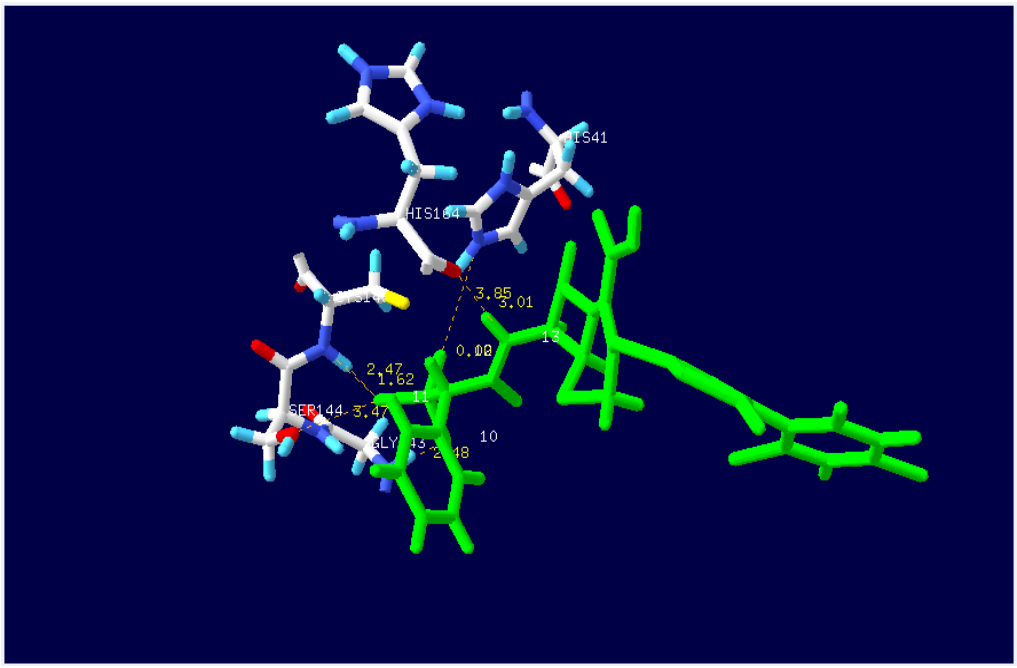


Fig. 6: H- Shown the stic model of H-bonding of Ligand-1a complexed with 3 CL Pro SARS/CoV-2 PDB id: 6LU7.

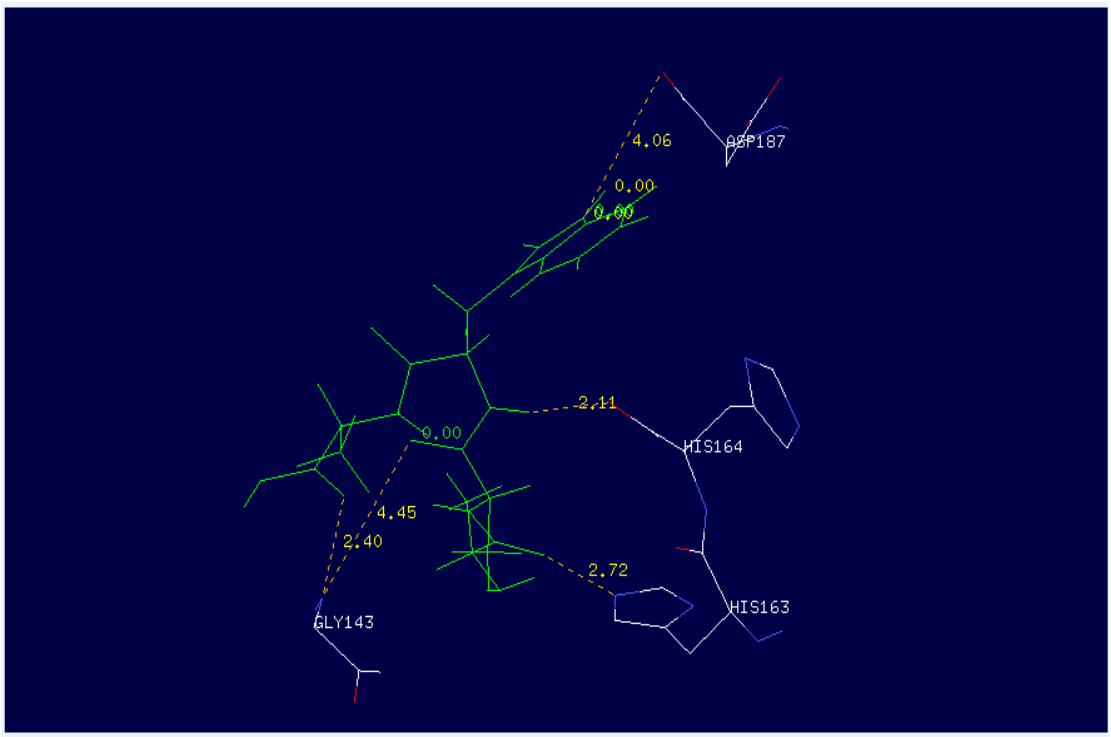


Fig. 7: Intermolecular forces and bonding distances of Ligand-2a (Indole derivatives) complexed with 3 CL Pro SARS/CoV-2 PDB id: 6LU7.

The first hydrogen bond is formed between the oxygen-10 atom (acceptor) of drug and Nitrogen atom (donor) of Gly 143 residue. The second Hydrogen bonds is formed between the oxygen-22 atom (acceptor)of drug and the Nitrogen atom (donor)of His-163 Residue. The third hydrogen bond is formed between the Oxygen-30 atom (Acceptor) of drug and Nitrogen atom(donor) of Gly-143 residue. The fourth hydrogen bond is formed between the Nitrogen-7(donor) atom of drug and Oxygen atom (acceptor) of Asp-187 residue. The fifth hydrogen bond is formed between the Nitrogen-13 atom (donor) of drug and oxygen atom (acceptor) of His-164 residue.

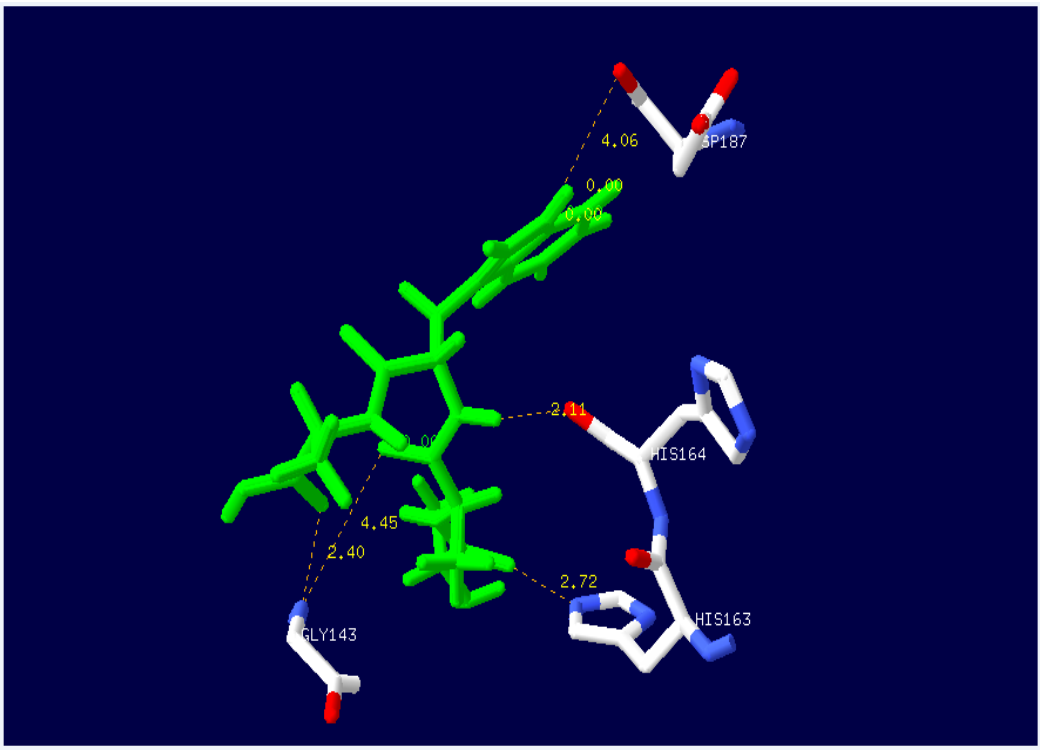


Fig. 8: Shown the stic model of H- bonding of Ligand-2a (Indole derivatives) complexed with 3 CL Pro SARS/CoV-2 PDB id: 6LU7.

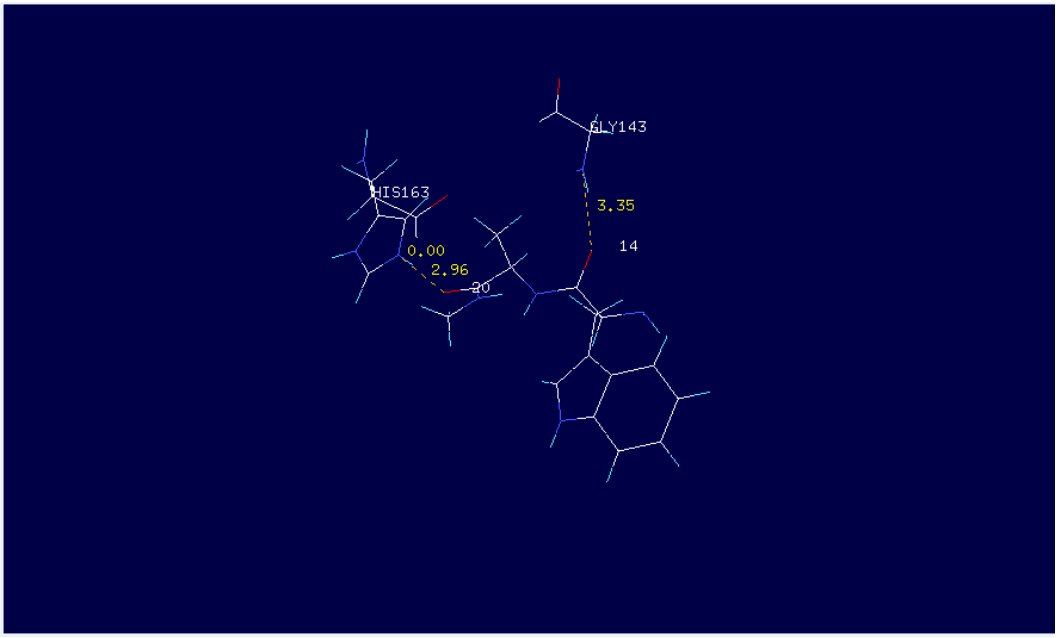


Fig. 9: Intermolecular forces of Ligand-2b (Indole derivatives) complexed with 3 CL Pro SARS/CoV-2 PDB id: 6LU7.

The first hydrogen bond is formed between the oxygen-14 atom (acceptor) of drug and Nitrogen atom (donor) of Gly 143 residue. The second Hydrogen bonds is formed between the oxygen-20 atom (acceptor)of drug and the Nitrogen atom (donor)of His-163 Residue.

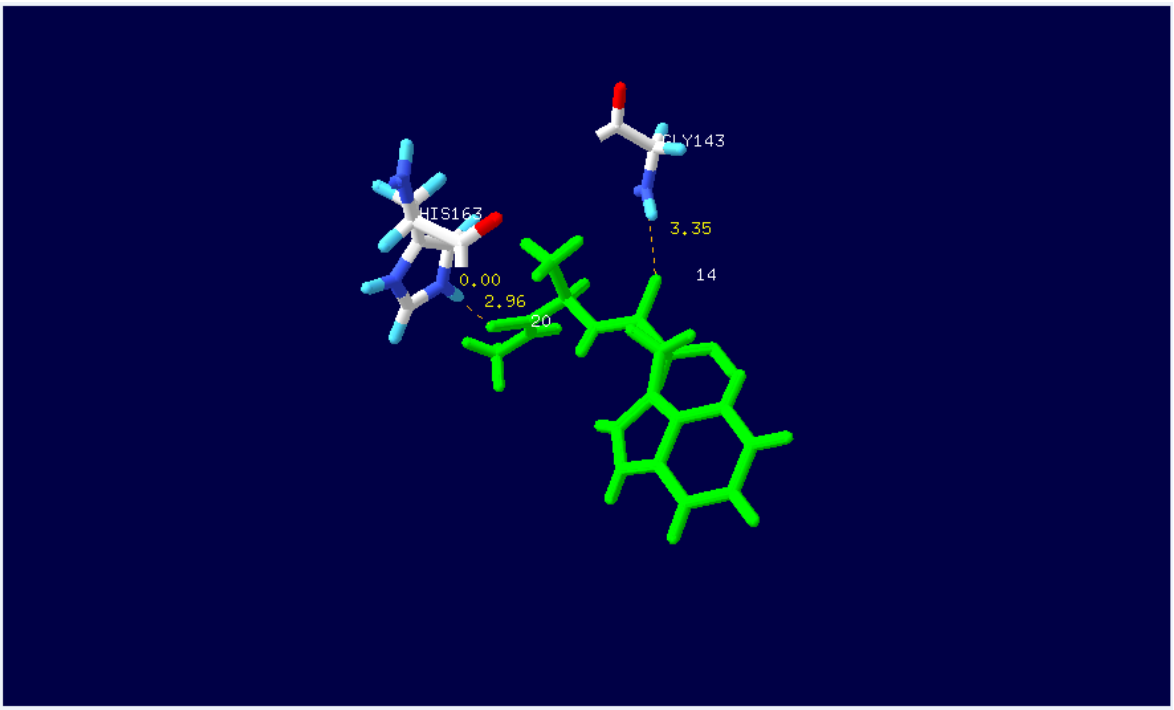


Fig. 10: Shown on stic model of H- bonding of Ligand-2b (Indole derivatives) complexed with 3 CL Pro SARS/CoV-2 PDB id: 6LU7.

Table 4: Docking Scores and Interactions.

Molecules	Docking score	No of H Bonds	Interaction Residues	H-Bond Energy
Ligand-1a	-9.34	5	His-41, HIS-164, Cys-145 Ser-144, Gly-143	11.37
Ligand-2a	-9.13	4	His-164, HIS-163, Gly-143, ASP-187	13.16
Ligand-2b	-8.56	2	GLY-143,HIS-163	15.63

DISCUSSION

In the concluding weeks of 2019, an outbreak of novel coronavirus (COVID-19) infections occurred in Wuhan, China. As of February 14, 2020, is in dire need of finding potential therapeutic agents. Currently no proven antiviral agent available, medical professionals have resorted to supportive care to contain the infection. In this study, we used structure based drug design by our molecular docking strategies to develop the anti-covid-19 through newly designed two focused library such as **Ceftaroline fosamil analogue and indol derivatives of totally 30 molecular structure** were used as protease inhibitors and nucleotide analogues for COVID-19. The evaluation was made on docking scores calculated by Autodock-4.2. Preliminary results suggested that the best docking scores and the comparison of the docking sites of three ligands such as **first, Ligand-1a, IUPAC Name:** 3-((4-(2,4-dichlorophenyl)thiazol-2-yl)thio)-8-oxo-7-(2-phenyl-2-sulfoacetamido)-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, and **second, Ligand-2a, IUPAC Name:** 2-(2-(2-(2-aminopropanamido)propanamido)-3-(1H-indol-3-yl)propanamido)propanoic acid, and **third, Ligand-2b, IUPAC Name:** 2-amino-3-(1H-indol-3-yl)-N-(1-(methylamino) -1-oxopropan-2-yl)propanamide, shows a near perfect dock in the overlap regions of the protein pocket, the active sites inferred from the proteins of SARS coronavirus are compatible with the docking site of 3CL Proteases/SARS/CoV-2 (COVID-19), PDB ID-6LU7, the explanation of 3-chymotrypsin-like protease (3CL-protease), the main protease used to cleave polyproteins into replication-related proteins, and RdRp, the main protein for RNA replication, as the target receptors. The 3CL-protease structure of COVID-19 (PDB ID: 6LU7) was obtained from the RCSB Protein Data Bank, which was recently released on February 5th, 2020.

A molecular docking study by Autodock-4.2 Version was performed to calculate of binding energy and H-bond interaction, H-bond donor and acceptors, hydrobhobicity and lipobobicity at all two focused library, totally 30 molecular structures were separately docked with 3CL Proteases/SARS/CoV-2. In order to gain functional and structural insight into the mechanism of most active lead compounds, molecular docking simulation was performed by the aid of autodock docking software. Docking simulation is a popular approach for the preliminary screening in structure based drug design.

By performing docking simulation, information on feasible conformations of the ligand within the protein binding site can be obtained. This information can also reflect the nature and quality of the interaction. In our study, the grid box for docking simulation was built with enough size to enable probing into the binding with 3CL Proteases/SARS/CoV-2 is the first human protein whose three dimensional X-ray crystal structure is broadly used in molecular docking studies to expose the binding properties of COVID-19 inhibitors.

The Ligand-1a, Ligand-2a and Ligand-2b which displayed superior COVID-19 inhibitory activity in 3CL Proteases/SARS/CoV-2 enzymes, which possessed highest docking activity among the various selected and designed compounds. This simulation may assist to reveal binding orientation and interaction of these molecules with amino acid residues composing active site gorge in these 3CL Proteases/SARS/CoV-2 enzymes.

The ligand-protein interactions of Ligand-1a, Ligand-2a and Ligand-2b indicated that hydrogen bonding, hydrophobic and mild polar interactions are the three major interactions incorporating the attachment of this ligand to 3CL Proteases/SARS/CoV-2 enzymes. In brief, **Ligand-1a** at 3CL Proteases/SARS/CoV-2 enzymes active site represented 5-H-Bond interactions of binding affinity of Fitness is 84.32, S(hb_ext) is 11.37, S(vdw_ext) is 55.42, S(hb_int) is 0.00, S(int) is -3.24 and **ligand-2a** having 5 H-bond interactions of Fitness is 67.56, S(hb_ext) is 15.77, S(vdw_ext) is 50.12, S(hb_int) is 0.00, S(int) is -17.13 and finally **Ligand-2b** having 2 H-bond interactions of Fitness is 56.47, S(hb_ext) is 15.63, S(vdw_ext) is 39.07, S(hb_int) is 0.00, S(int) is -12.88 respectively, which was shown the strong interaction with the target enzyme. The ligand–protein interactions were predicted by using Pymol. The most active potential anti-viral 3CL Proteases/SARS/CoV-2 inhibitor was identified after the detailed analysis of the ligand–protein interactions. Binding interactions of all compounds have been observed thoroughly and the compound showing the best interactions among all has been identified as lead compound. These three above said lead ligands have been identified as the most active from the set of 30 ligands. These three ligands have shown strong hydrogen bonding and hydrophobic interactions with the target protein than the rest of the ligands. Along with their strong interactions, values and docking score were shown in Table 4 and Figure 5-10. After analyzing them on the basis of their interactions and docking values, these three molecules has been identified as the potential lead candidate drugs for the inhibitory activity of 3CL Proteases/SARS/CoV-2 for against COVID-19, which may give to the concern in its safety and efficacy for furthered to development of the pre-clinical pharmacological therapeutics for COVID-19.

CONCLUSION

Demonstrated the utility of in-silico structure-based drug design, we were able to achieve the novel ceftaroline fosamil analogues and indole derivatives chemical space for 3 CL Pro SARS/Cov-2 (COVID-19) family in these first, ligand 1a, IUPAC Name: 3-((4-(2,4-dichlorophenyl)thiazol-2-yl)thio)-8-oxo-7-(2-phenyl-2-sulfoacetamido)-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid & second, Ligand-2a, IUPAC Name: 2-(2-(2-(2-aminopropanamido) propanamido)-3-(1H-indol-

3-yl)propanamido)propanoic acid and third Ligand-2b, IUPAC Name: 2-amino-3-(1H-indol-3-yl)-N-(1-(methylamino)-1-oxopropan-2-yl)propanamide shown remarkable anti-viral-COVID-19 potentials based on inhibition of SSARS/CoV-2 activity through binding and activation.

REFERENCES

1. Chang, Y.; Tung, Y.; Lee, K.; Chen, T.; Hsiao, Y.; Chang, H.; Hsieh, T.; Su, C.; Wang, S.; Yu, J.; Shih, S.; Lin, Y.; Lin, Y.; Tu, Y.E.; Tung, C.; Chen, C. Potential Therapeutic Agents for COVID-19 Based on the Analysis of Protease and RNA Polymerase Docking. Preprints, 2020, 2020020242 (doi: 10.20944/preprints202002.0242.v1).
2. Bowen Tang, Fengming He, Dongpeng Liu, Meijuan Fang, Zhen Wu,Dong Xu. AI-aided design of novel targeted covalent inhibitors against SARS-CoV-2. doi: https://doi.org/10.1101/2020. 03.03.972133.
3. Khaerunnisa, S.; Kurniawan, H.; Awaluddin, R.; Suhartati, S.; Soetjipto, S. Potential Inhibitor of COVID-19 Main Protease (Mpro) From Several Medicinal Plant Compounds by Molecular Docking Study. Preprints, 2020, 2020030226 (doi: 10.20944/preprints202003.0226.v1).
4. Li, Guangdi & Clercq, Erik. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). Nature Reviews Drug Discovery. 19. 10.1038/d41573-020-00016-0, 2020.
5. B.Robson.Computers and viral diseases. Preliminary bioinformatics studies on the design of a synthetic vaccine and a preventative peptidomimetic antagonist against the SARS-CoV-2 (2019-nCoV, COVID-19) coronavirus., j.comp biomed.2020.103670.
6. Rajaganapathy Kaliyaperumal, Manjunatha P. Mudugal, Prashantha C Nagaraja, Nageena Taj., Exploration of Novel Sulpho Tyrosine Based Unnatural Amino Acid Chemical Space for Allosteric Site of Human Shp2 Protein Tyrosine Phosphatase; A Computational Approach., Journal of Drug Design and Medicinal Chemistry, 2018; 4(3): 22-34.
7. K Rajaganapathy, R Manavalan, K Kannan, V K Kalaichelvan Histone Deacetylase Inhibitor Based Novel Lead Molecules and its Analogues: A Molecular Docking Ap-proach Inventi Impact: Molecular Modeling, 2014; 1.