Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 6, 2021, Pages. 8297 - 8306
Received 25 April 2021; Accepted 08 May 2021.

Docking and Drug Discovery Evaluation of Approved Drugs in Drug Bank Database Against COVID-19

Mohammed Oday Ezzat [1,*],Basma M. Abd Razik [2],Ahmed Oday Ezzat [3]

[1]University of Anbar, 31001,College of Education for Women, Department of Chemistry, Ramadi, Anbar, Iraq
[2]Mustansiriyah University, 10001,College of Pharmacy,Department of Pharmaceutical Chemistry, Baghdad,Iraq
[3]University of Information Technology and Communications, 10001, College of Business Informatics,Department of Informatics System Management, Baghdad,Iraq.
*E-mil: edw.mohamed_oday@uoanbar.edu.iq

Abstract

The approved drugs by the FDA from the drug bank represented a high favorable database in the virtual screening process to discover an efficient medication for COVID-19. In this work, an in-home dataset of 1443 approved drugs by the FDA was virtually screened by docking inside the active site of ACE 2 enzyme and SARS-CoV-2 main protease. The result of some drugs was higher in docking scores than a set of drugs which is currently used as the best available choice in the process for the healing of COVID-19. Moreover, lactose, labetalol, lactulose, and hexoprenaline were bindings at very good docking values at both active sites. These findings led to identifying a hit chemical structure and future modeling study of COVID-19 medication by in-silico drug design and dynamic simulation.

Keywords: SARS-CoV-2 main protease, ACE 2 enzyme, molecular docking, drug design.

1. Introduction

The worldwide prevalence of novel coronavirus (SARS-CoV-2) represents a global pandemic in the last few months produced more than 30 million infections cases and more than 950 thousand approved deaths [1]. In the past decade, several new coronaviruses were isolated and identified. All these types infect a broad range of mammals and birds as of hosts with a recent serious dangerous identification [2]. Recently, the details about the 3D-structures of the SARS-CoV-2 proteins key are resolved and reported. Moreover, the released crystal structure of SARS-CoV-2 protease was already deposited in complex with N3 as a covalent inhibitor. This finding triggers the search processes to identify a better inhibitor with high efficiency and low side effect[3]. The phylogenetic study indicated that the SARS-CoV-2 belonged to the genus beta coronavirus and has approximately 96% of nucleotide sequence similarity with the closest bat coronavirus RaTG13 found in horseshoe bats (Rhinolophus species) in 2013. It shares similarities of 79% with the genome of SARS-CoV and its genome is 89% similar to that of two SARS-like bat viruses [4,5].Angiotensin-converting enzyme 2 (ACE2) is an enzyme located in the lungs, intestines, heart and kidney cell membranes. ACE2 is a function that reduce the blood pressure

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 6, 2021, Pages. 8297 - 8306
Received 25 April 2021; Accepted 08 May 2021.

by catalysing the hydrolysis of angiotensin II into angiotensin [6]. Recent article reported the attachment of SARS-CoV-2 to ACE2, however, it still functionalized the maturation of angiotensin. New drug strategy for blocking ACE2 as a host for SARS-CoV-2 is by blocking its binding site to prevent SARS-CoV-2 from hosting[3]. The human angiotensin-converting enzyme 2 (hACE2) is used by both SARS-CoV and SARS-CoV-2 to trigger the spike protein binding and to promote the viral binding to host cells. *In vitro* and *in vivo* studies verified the functionality of hACE2 with the SARS-CoV receptor [7-9].For SARS-CoV, over-expression of ACE2 was demonstrated to increase the severity of the disease in virus-infected mice. This has shown that SARS-CoV in host cells depending on ACE2 is a crucial step [10]. Other SARS-CoV research also reveals that injecting SARS-CoV spike glycoproteins into mice decreases expression levels of ACE2 and exacerbates lung injury [11,12]. Therefore, ACE2 is important as both the SARS-CoV entrance receiver and ACE2 proteins the lungs against injury in the SARS-CoV pathogenesis [9]. Due to the close ties between SARS-CoV spike proteins and SARS-CoV-2, hACE2 's functions in infection are important. The production of molecules that can interact with the hACE2 virus is highly desirable to fight against SARS-CoV-2 without affecting the levels of expression of the ACE2. SARS-CoV-2 spiked glycoprotein structural studies reveal a clear relation between the spike protein and ACE2 and an improved connective affinity than with SARS-CoV [13,14]. Further studies showed that SARS-CoV or SARS-CoV-2 spike protein 193-residue RBD is adequate to connect with ACE2 humans [7,15]. Based on this reality, the SARS-CoV-2 RBD is regarded for the treatment of COVID-19 as a crucial protein model for drug production. Recently, the use of ACE2 protein as a way to block SARS-CoV-2 entry was documented in both computational and experimental studies [16-18]. ACE2 was found to substantially inhibit the infections of the contaminated vascular organoids by SARS-CoV-2. The study has also shown that human recombinant ACE2 decreased the degree of SARS-CoV-2 recuperation in Vero cells by a factor of > 1000 [17]. A further research examined the spike protein binding of hACE2 to produce the molecules that can interfere with the SARS-CoV-2 RBD binding of hACE2. Their findings showed that the nanomolar affinity of a 23-residue peptide hACE2 N-terminal helix (residues 21-43), comparable to that of full length hACE2, could bind to RBD. They also stated that the SARS CoV-2 RBD could not be binding on a 12-residue peptide (Residue 27-38)[9]. One of the important in-silico applications is the computer-aided drug design method, which is used to provide early-stage information about activities of discovered chemical compounds and especially for used as hit drugs[19,20]. Combinatorial chemistry programs are in continuous motion of providing a developed, adequately and efficiently pharmacological activity that informs about novel discovered chemical compounds before further work to design new compounds and proceed to experimental evaluation studies in vitro or in vivo [21]. Recently, many works which were done by combinatorial chemistry methods have shown that the ability of these methods is to identify several potential SARS-CoV-2 antiviral drugs as effective new treatments for other viruses such as HIV and can be used as anti-COVID-19 drugs [22-24]. The drug bank database is an extensive, free access, and online available database containing complete information of most drugs and drug action targets. Drug bank combines both bioinformatics and cheminformatics about drugs resources details such as chemical structure, pharmacological and pharmaceutical properties data with information about drug targets such as sequence structure and proposal pathway in more than 200 data fields[25]. In 2006, the first version of the drug bank database was released with a total of 841 chemical molecules and 113 biotech drugs approved FDA [26]. The latest version (5.1.6) release in 2020 contains 13,563 of drug including 2,627 chemical molecules, 1,373 biologics approved by the

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 6, 2021, Pages. 8297 - 8306
Received 25 April 2021; Accepted 08 May 2021.

FDA. Moreover, it contains 131 nutraceuticals, more than 6,370 experimental (in discovery-phase) drugs and 5,250 non-redundant protein [27]. In pharmacology research, any new chemical compound with potential activity against selective disease could take years of pharmacology evaluation to be approved by the FDA as a drug with free side effects. Because of the urgent need for fast, safe, effective drugs in the fight against COVID-19, the available drugs database is a unique source for virtual screening studies. It become nessessary is to identify a new drug with higher pharmacological efficiency and binding ability to ACE2 and SARS-CoV-2 main protease [28]. In this work, a total of 1443 FDA-approved drugs were virtually screened by docking study inside two active sites (ACE 2 enzyme and SARS-CoV-2 main protease) for determination and specification of promising hit lead compounds in the process for future molecular drug design against COVID-19.

2. Methodology and Computational Method

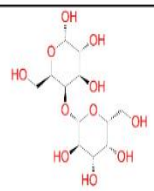
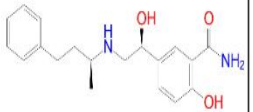
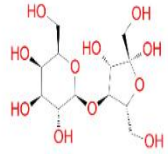
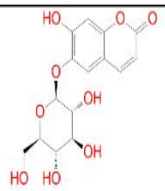
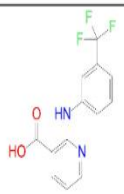
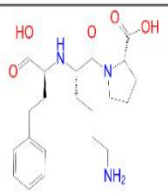
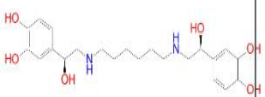
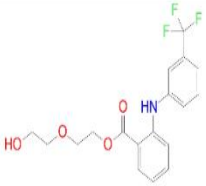
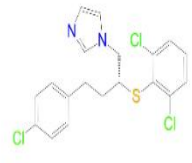
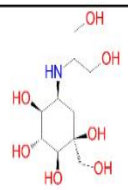
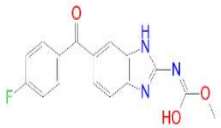
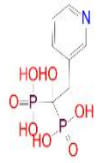
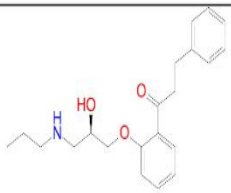
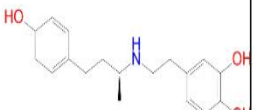
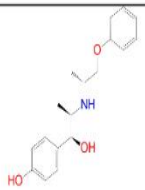
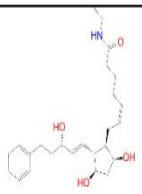
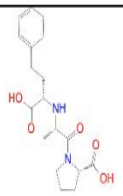
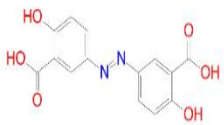
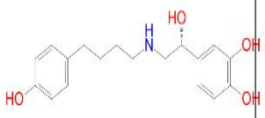
The set of drug database was downloaded from the drug bank website (https://www.drugbank.ca/). Then, it was separated and all approved drugs were isolated as SDF format files. By visual check, all missing and non-complete structures were deleted and the total of selected approved the drug structures and were collected as 1443 compounds by discovery studio (v4.5) (Accelrys Software Inc.). The preparation of all chemical structures conformations was performed by using OpenEye scientific software package[29]. Then, geometry optimization processes run by MMFF94 force field mechanics with the selection of no ionization change and determination of chirality from 3D structure option using OMEGA application. The 3D crystal structure of SARS-CoV-2 main protease and ACE2 were downloaded from protein data bank with PDB codes: 6LU7 and 6M1D, respectively. The preparation processes of both crystals were applied by removing water, ions, and attached ligands using the protein preparation wizard tool with optimization and restrained minimization by MMFF94 force field mechanics. The processes of docking and interaction binding evaluation were performed by using the FRED application at the centre of each active site inside the determined grid with grid box size-adjusted at 50 × 50 × 50 Å and 0.27 partial atomic charge. During the docking process, ligands were adjusted to flexible mode while the receptor kept in rigid mode. The extra precision model with flexible ligand sampling settings was selected for ligands docking. The best-docked orientation and RMSD were saved between protein crystal structures and the automated fragment replacement processes and were used to produce the multiple derivatives of different fragments. All results were collected and exported as an excel file for further interpretation and evaluation.

3. Results and Discussion

Nowadays, the worldly prevalence of infestation cases by a novel coronavirus (2019-nCoV) represented a highly international health concern with the demanded to discover the efficient drug. Because it has already been reported that the characterization of a highly safe and efficient vaccine will take a very long time, most of the scientific efforts now are focused on modelling and discovery of a medication that can be present a proper drug for healing or reduce the infection symptoms. One of the fast and best choices in the process to deliver an effective drug in a short time is the virtual screening of available approved drugs.

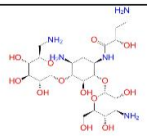
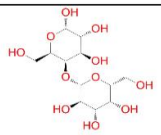
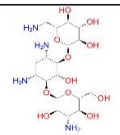
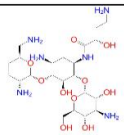
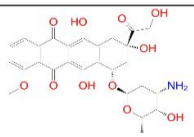
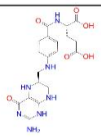
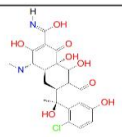
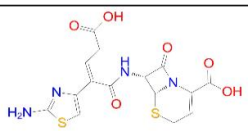
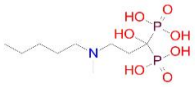
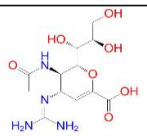
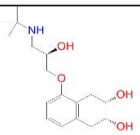
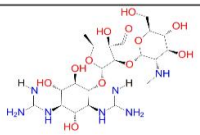
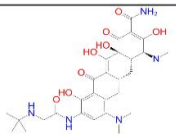
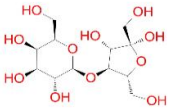
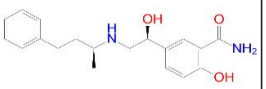
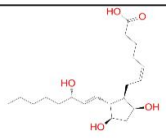
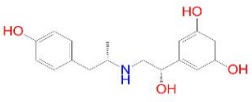
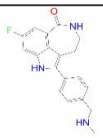
Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 6, 2021, Pages. 8297 - 8306
Received 25 April 2021; Accepted 08 May 2021.

Table 1. The chemical structured, drug bank code and docking binding score of the first 20 active approved drugs inside ACE 2 active site

 DRUGBANK_ID: DB04465 docking score: -10.876	 DRUGBANK_ID: DB00598 docking score: -10.867	 DRUGBANK_ID: DB00581 docking score: -10.689	 DRUGBANK_ID: DB13155 docking score: -10.225
 DRUGBANK_ID: DB04552 docking score: -10.199	 DRUGBANK_ID: DB05239 docking score: -10.083	 DRUGBANK_ID: DB00722 docking score: -10.018	 DRUGBANK_ID: DB08957 docking score: -9.999
 DRUGBANK_ID: DB08984 docking score: -9.949	 DRUGBANK_ID: DB00639 docking score: -9.885	 DRUGBANK_ID: DB04878 docking score: -9.83	 DRUGBANK_ID: DB08974 docking score: -9.807
 DRUGBANK_ID: DB00884 docking score: -9.798	 DRUGBANK_ID: DB01182 docking score: -9.768	 DRUGBANK_ID: DB00841 docking score: -9.698	 DRUGBANK_ID: DB08941 docking score: -9.567
 DRUGBANK_ID: DB00905 docking score: -9.476	 DRUGBANK_ID: DB09477 docking score: -9.43	 DRUGBANK_ID: DB01250 docking score: -9.391	 DRUGBANK_ID: DB01102 docking score: -9.386

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 6, 2021, Pages. 8297 - 8306
Received 25 April 2021; Accepted 08 May 2021.

Table 2. The chemical structured, drug bank code and docking binding score of the first 20 active approved drugs inside SARS-CoV-2 main protease active site

 DRUGBANK_ID: DB00479 docking score: -11.358	 DRUGBANK_ID: DB04465 docking score: -10.345	 DRUGBANK_ID: DB01172 docking score: -9.854	 DRUGBANK_ID: DB06696 docking score: -9.669
 DRUGBANK_ID: DB00997 docking score: -9.638	 DRUGBANK_ID: DB08957 docking score: -9.325	 DRUGBANK_ID: DB00116 docking score: -9.231	 DRUGBANK_ID: DB09093 docking score: -9.166
 DRUGBANK_ID: DB01415 docking score: -9.132	 DRUGBANK_ID: DB00710 docking score: -9.114	 DRUGBANK_ID: DB00558 docking score: -9.086	 DRUGBANK_ID: DB01203 docking score: -8.999
 DRUGBANK_ID: DB01082 docking score: -8.978	 DRUGBANK_ID: DB00560 docking score: -8.95	 DRUGBANK_ID: DB00581 docking score: -8.858	 DRUGBANK_ID: DB00598 docking score: -8.792
 DRUGBANK_ID: DB01160 docking score: -8.776	 DRUGBANK_ID: DB01288 docking score: -8.756	 DRUGBANK_ID: DB12332 docking score: -8.549	 DRUGBANK_ID: DB00938 docking score: -8.543

This is because the side effects of most approved drugs are already reported after several years of evaluation and investigation which makes it the most saver felid for screening. Further work can be done by modifying and study the possibility of using these drugs as promising hits to discover more efficient drugs with higher pharmacological activities. In contrast, is already have been reported that one of the strategies to fight against COVID-2019 is by targeting the blocking of ACE 2 enzyme active site and stopping the replication process of coronavirus by the highly active compound can bind inside an active site with high docking score. The chemical structure with drug bank code and docking binding score of the first 20 active approved drugs inside ACE 2 and SARS-CoV-2 main protease active sites are listed in Table 1 and Table 2.In most countries, there are several drugs used as the best available choice in the process for healing from COVID-19 symptom and the inhibition of coronavirus replication. Table 3 shows the docking score of these drugs with docking boxes used in this study. By docking score comparison with available drugs in Table 3, the result shows that several drugs from Table 1 and Table 2 were

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 6, 2021, Pages. 8297 - 8306
Received 25 April 2021; Accepted 08 May 2021.

high in the binding score. This result highlighted the fact of the percent of already discovered drugs can be used or modified to give high activity.

Table 3. Docking binding score of the currently used drugs for COVID-19 healing.

Drug Name	Drug Code	ACE 2 Enzyme	SARS-CoV-2 protease
Aliskiren	DB09026	-4.691	-8.328
Atazanavir	DB01072	-3.484	-7.936
Carfilzomib	DB08889	-0.099	-6.724
Ceftolozane	DB09050	-6.065	-7.346
Cobicistat	DB09065	-4.864	-5.189
Dronedarone	DB04855	-6.481	-4.981
Lopinavir	DB01601	-6.806	-5.371
Naloxegol	DB09049	-4.828	-6.038
Pradaxa	DB06695	-5.666	-7.213
Saquinavir	DB01232	-2.309	-5.973
Tessalon	DB00868	-7.659	-5.463
Remdesivir	DB14761	-6.834	-7.428

General screening of results in Table 1 and Table 2 shows that some drugs bind in high binding score drugs at both actives sites and some of them appease two times as in the highest 20 active drugs, Table 4. Interestingly, these findings give a very promising scaffold to focus on these compounds for use as medication or modify and design as a hit compound for higher binding and better pharmacological activity.

Table 4. Docking binding score inside ACE 2 and SARS-CoV-2 protease active sites for the highest 20 drugs.

Drug Code	ACE 2 Enzyme	SARS-CoV-2 protease	Drug Code	SARS-CoV-2 protease	ACE 2 Enzyme
DB04465	-10.876	-10.345	DB00479	-11.358	-5.510
DB00598	-10.867	-8.792	DB04465	-10.345	-10.876
DB00581	-10.689	-8.858	DB01172	-9.854	-5.404
DB13155	-10.225	-8.044	DB06696	-9.669	-4.120
DB04552	-10.199	-7.192	DB00997	-9.638	-6.175
DB00722	-10.018	-8.378	DB08957	-9.325	-9.999
DB08957	-9.999	-9.325	DB00116	-9.231	-8.564
DB08984	-9.949	-6.483	DB09093	-9.166	-3.737
DB04878	-9.830	-6.900	DB01415	-9.132	-5.946

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 6, 2021, Pages. 8297 - 8306
Received 25 April 2021; Accepted 08 May 2021.

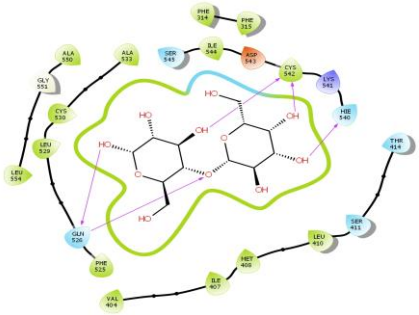
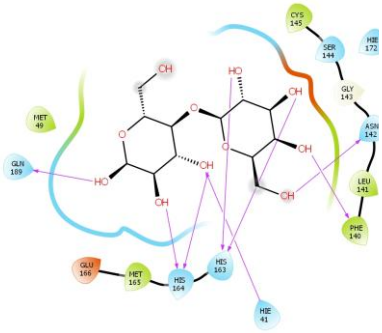
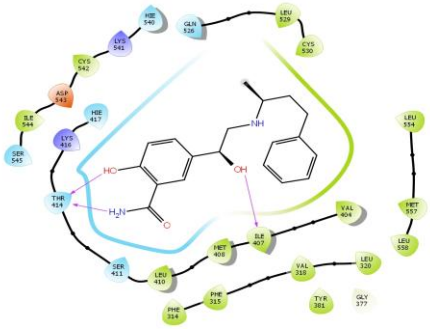
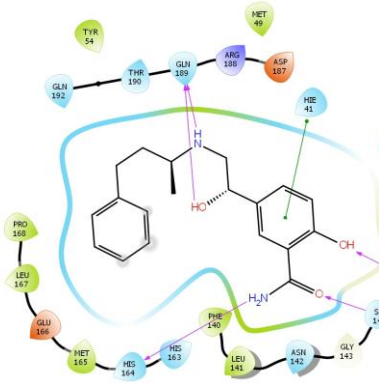
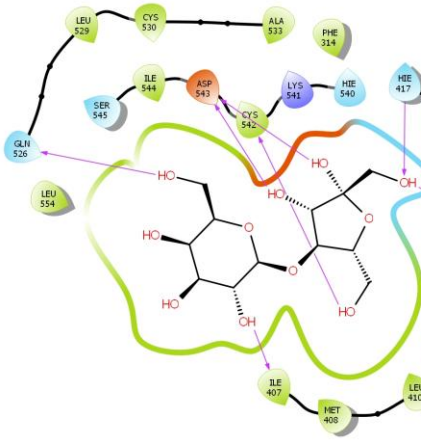
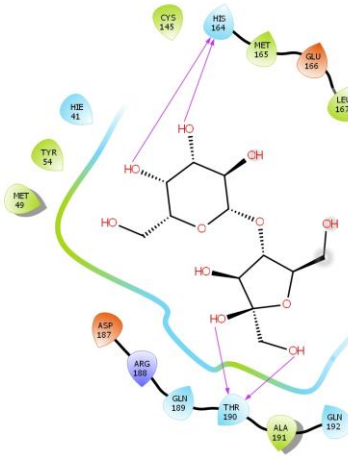
DB00884	-9.798	-8.057	DB00710	-9.114	-7.968
DB01182	-9.768	-7.381	DB00558	-9.086	-8.552
DB00841	-9.698	-7.397	DB01203	-8.999	-6.653
DB08941	-9.567	-6.148	DB01082	-8.978	-5.648
DB00905	-9.476	-6.114	DB00581	-8.858	-10.689
DB09477	-9.430	-7.457	DB00598	-8.792	-10.867
DB01250	-9.391	-7.615	DB01160	-8.776	-0.610
DB01102	-9.386	-7.425	DB01288	-8.756	-5.709
DB00399	-9.381	-7.747	DB12332	-8.549	-6.406
DB06774	-9.365	-6.298	DB00938	-8.543	-8.800
DB00188	-9.308	-8.426	DB04898	-8.531	-4.477

From Table 4, four drugs with drug bank codes DB04465, DB00598, DB00581 and DB08957 show a very high binding ability inside both active sites. These results refer to the novel finding of the ability of these drugs (colored in Table 4). By code referencing in the drug bank website, these codes are referring to lactose, labetalol, lactulose and hexoprenaline, respectively. All these compounds are safe to use and already reported side effects and a fact that both lactose and lactulose are kinds of sugar. Lactose is a composed disaccharide of galactose and glucose represent around 2–8% of milk while lactulose is a non-absorbable compound used for the treatment of constipation complication and hepatic encephalopathy. Inside ACE 2 enzyme and SARS-CoV-2 protease active sites each drug interacts and binds by multi bonds with deferent surrounding amino acids related with the chemical structure specification of each drug Table5. For lactose, inside ACE 2 enzyme it shows five H-bonds with its hydroxyl groups as: two with each of GLN526 & CYS542, and one with HIE540. At the same time, lactose shows eight H-bonds inside SARS-CoV-2 protease active site as: two with each of HIS163 & HIS164, one with each of HIE41, PHE140, ASN142, and GLN189. In contrast, labetalol shows three H-bonds inside the ACE 2 site as: Two H-bonds between hydroxyl and amine group with THR414 while it interacts by one H-bond between hydroxyl and ILE407. Furthermore, Labetalol as it a medical chemical compound used for the treatment of high blood pressure and management of angina, and both are related to the ACE 2 action mechanism. Moreover, inside the SARS-CoV-2 site, labetalol shows one Pi-Pi stacking interaction between an aromatic ring with HIE41 and five H-bonds as: two between GLN189 with amine and hydroxyl group, one between HIS164 with an amine, one between SER144 with a ketone, and one between CYS145 with a hydroxyl group. Because of the chemical structure of lactulose with eight hydroxyl groups, it shows seven H-bonds inside the ACE 2 site as: two between hydroxyl group with THR414 and HIE417, two between ASP543 with a hydroxyl group, one with each of ILE407, GLN526, and CYS542. Moreover, inside the SARS-CoV-2 site, lactulose shows four H-bonds as: two bonds between both of HIS164 & THR190 with four different hydroxyl groups. The fourth drug, hexoprenaline shows six H-bonds inside the ACE 2 site as: two between GLN522 with amine and hydroxyl group, one bond with each of THR414, THR445, HIE540, and ASP543. Finally, inside the

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 6, 2021, Pages. 8297 - 8306
Received 25 April 2021; Accepted 08 May 2021.

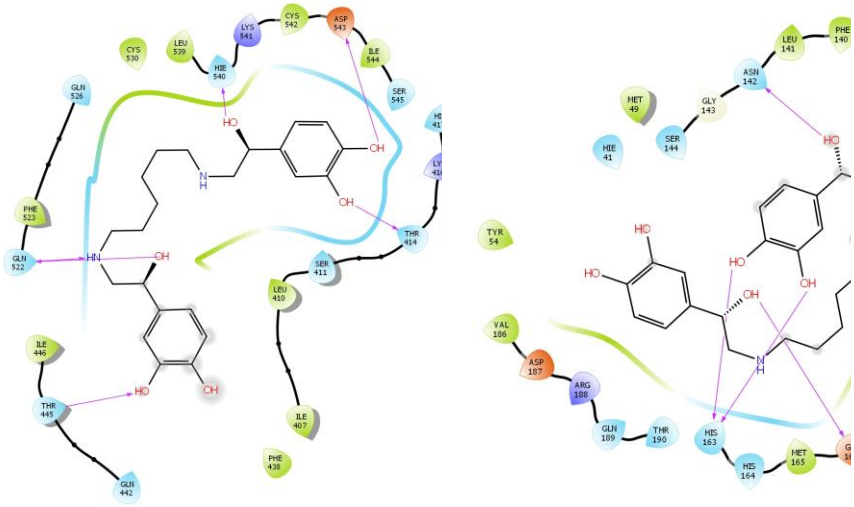
SARS-CoV-2 site, hexoprenaline shows only three H-bonds as: two between HIS160 with two hydroxyl groups and one between GLU166 with one hydroxyl group.

Table 5. Lactose, labetalol, lactulose, and hexoprenaline in 2D views inside ACE 2 enzyme and SARS-CoV-2 protease active sites.

Drug Name	ACE 2 Enzyme	SARS-CoV-2 protease
Lactose		
Labetalol		
Lactulose		

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 6, 2021, Pages. 8297 - 8306
Received 25 April 2021; Accepted 08 May 2021.

Hexoprenaline



In Table 4, there are more interesting results that appear about drugs under codes DB00598, DB13155, DB04552, DB00722, DB00116, and DB00558 show a very promising activity with a good range of binding score at both active sites. All these chemical scaffold representative very promising lead compounds can be used as hits for future molecular drug design with further pharmacological activity prediction.

4. Conclusion

The new strategy in the fight against the corona pandemic is based on targeting the inhibition of both ACE2 and SARS-CoV-2 main protease by compounds with the high binding affinity and high pharmacological efficiency as a promising drug. The approved drug database represented a portentous source with fast and less said searching for promising drug or hit lead drug. The results of this work were the specification of four drugs lactose, labetalol, lactulose and hexoprenaline which were shown a very high binding ability inside both active sites. Furthermore, several approved drugs show a very promising activity with a good range of binding scores at both active sites. All these findings can be used as hit lead compounds for further search and design of new COVID-19 drugs.

5. References

[1] Chan JF W, Yuan S, Kok KH, To KKW, Chu H and Yang J 2020. *Lancet.***395** 514.
[2] Chen Y, Liu Q and Guo D. 2020 *J Med Virol*. **92** 418.,
[3] Yan R, Zhang Y, Li Y, Xia L, Guo Y and Zhou Q.2020 *Sci.(*80-).**27**;367(6485):1444.
[4] Lu R, Zhao X, Li J, Niu P, Yang B and Wu H.2020 *Lancet*.**395** 565.
[5] Xu X, Chen P, Wang J, Feng J, Zhou H and Li X. 2020 *Sci China Life Sci*.**63** 457.
[6]. Hamming I, Timens W, Bulthuis M, Lely A, Navis G and van Goor H.2004*J. Pathol.* **203** 631.
[7] Wong SK, Li W, Moore MJ, Choe H and Farzan M2004 *J Biol Chem*. **279** 3197.
[8] Kuba K, Imai Y, Ohto-Nakanishi T and Penninger JM.2010 *Pharmacol Ther.***128**119.
[9] Zhang H, Penninger JM, Li Y, Zhong N and Slutsky AS.2020 *Intensive Care Med.***46** 586.
[10] Yang X, Deng W, Tong Z, Liu Y, Zhang L and Zhu H 2007 *Comp Med*.**57** 450.
[11] Imai Y, Kuba K, Rao S, Huan Y, Guo F and Guan B2005 *Nature*. **436** 112.
[12] Kuba K, Imai Y, Rao S, Gao H, Guo F and Guan B2005 *Nat Med.* **11** 875.
[13] Walls AC, Park Y-J, Tortorici MA, Wall A, McGuire AT and Veesler D. 2020 *Cell***98** 151.

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 6, 2021, Pages. 8297 - 8306
Received 25 April 2021; Accepted 08 May 2021.

[14] Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CL and Abiona O 2020*Science***367**1260.
[15] Liu H, Lupala C, Li X, Lei J, Chen H and Qi J2020*bioRxiv*.**561** 8.
[16] Zhang G, Pomplun S, Loftis AR, Loas A and Pentelute BL.2020 *bioRxiv*.**318**12.
[17] Monteil V, Kwon H, Prado P, Hagelkrüys A, Wimmer RA, Stahl M, et al. 2020*Cell***97** 6.
[18] Huang X, Pearce R and Zhang Y. 2020*bioRxiv*.**607**9.
[19] Yu W and Jr ADM 2017 *Computer-Aided Drug Design Methods'*. *Antibiot Methods Protoc.* Chapter 5 , p:85–106.
[20] Ezzat MO and Abd Razik BM2020*Acta Pharm Sci*. **20** 1.
[21] Zhou Y, Hou Y, Shen J, Huang Y, Martin W and Cheng F.2020 *Cell Discov.***6**1.
[22] Wan Y, Shang J, Graham R, Baric RS and Li F.2020 *J Virol.***94**7.
[23] Krylov A, Windus TL, Barnes T, Marin-Rimoldi E, Nash JA and Pritchard B2018 J *Chem Phys*. **149**180901.
[24] Dong L, Hu S and Gao J. 2020*Today Technol*.**14**58.
[25] Wishart DS, Knox C, Guo AC, Cheng D, Shrivastava S and Tzur D2008 *Nucleic Acids Res*. **36**901.
[26] Wishart DS, Knox C, Guo AC, Shrivastava S, Hassanali M and Stothard P2006 *Nucleic Acids Res*.**34**668.
[27] Wishart DS, Feunang YD, Guo AC, Lo EJ, Marcu A and Grant JR2018 *Nucleic Acids Res.***46**1074.
[29] Hawkins PCD, Skillman AG and Nicholls A2007 *J Med Chem*. **50**74.