Hindawi
Journal of Chemistry
Volume 2021, Article ID 1901484, 7 pages
https://doi.org/10.1155/2021/1901484

Research Article

Identification of Novel SARS-CoV-2 Inhibitors: A Structure-Based Virtual Screening Approach

Abdellah El Aissouq,[1] Oussama Chedadi,[1] Mohammed Bouachrine,[2,3] and Abdelkrim Ouammou[1]

[1]*LIMOME Laboratory, Faculty of Sciences Dhar El Mahraz, Sidi Mohamed Ben Abdellah University, Fez, Morocco*
[2]*MCNS Laboratory, Faculty of Sciences, Moulay Ismail University, Meknes, Morocco*
[3]*EST Khenifra, Sultan Moulay Sliman University, Beni-Mellal, Morocco*

Correspondence should be addressed to Abdelkrim Ouammou; abdelkrim.ouammou@usmba.ac.ma

Received 16 July 2020; Revised 16 September 2020; Accepted 19 December 2020; Published 8 February 2021

Academic Editor: Jo o Paulo Leal

The recent outbreak of the coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) in the last few months raised global health concern. Previous research described that remdesivir and ritonavir can be used as effective drugs against COVID-19. In this study, we applied the structure-based virtual screening (SBVS) on the high similar remdesivir- and ritonavir-approved drugs, selected from the DrugBank database as well as on a series of ritonavir derivatives, selected from the literature. The aim was to provide new potent SARS-CoV-2 main protease (M_{pro}) inhibitors with high stability. The analysis was performed using AutoDock VINA implicated in the PyRx 0.8 tool. Based on the ligand binding energy, 20 compounds were selected and then analyzed by AutoDock tools. Among the 20 compounds, 3 compounds were selected as high-potent anti-COVID-19.

1. Introduction

By the end of 2019, the World Health Organization (WHO) declared a pandemic of a novel coronavirus infection coined COVID-19, caused by SARS-CoV-2 virus. This disease was first detected in the city of Wuhan, China [1, 2], and has quickly spread to more than 216 countries around the world. As of July 1, 2020, and according to WHO report [3], more than 10 million (10 321 689) people were affected by COVID-19, of which more than half a million (507,435) passed away. The contagion rate and death tolls are still increasing, and no confirmed drugs or approved vaccines have yet been discovered. Development of an anti-COVID-19, hence, became a global health emergency.

Currently, there are no targeted therapeutics, and options of effective treatment remain very limited. The clinical candidates that have received attention are remdesivir [4, 5] and ritonavir [6]. Remdesivir is an adenosine triphosphate analog first described in the literature in 2016 as potential treatment for Ebola virus (EBOV) [7]. Ritonavir is an HIV protease inhibitor that interferes with the reproductive cycle of HIV [8]. Although it was initially developed as an independent antiviral agent, it has been shown to possess advantageous properties in combination regimens with low-dose ritonavir and other protease inhibitors.

Accordingly, the process of identification of new antiviral drugs is very complex, expensive, and time-consuming. Thus, computer-aided drug design (CADD) approaches have been recognized as an alternative to overcome this situation [9–11]. Among these approaches, structure-based virtual screening (SBVS) [12–15] by using molecular docking study [16, 17] has become a valuable primary step in the identification of novel lead molecules for the treatment of diseases [9] and proven to be a very efficient tool for antiviral [18] and antibacterial [19] drug discovery. In this study, an SBVS was applied on the high similar remdesivir- and ritonavir-approved drugs that are selected from the DrugBank database as well as on a series of ritonavir

Table 1: The top hit scoring molecules for SARS-CoV-2 M_{pro} inhibitors.

	ID	Binding energy (kcal/mol)		Name of drugs
		AutoDock VINA	AutoDock tools	
DrugBank database	DB00503	−7.4	−6.9	Ritonavir
	DB14761	−8.3	−7.3	Remdesivir
	DB12799	−8.9	−8.2	Laniquidar
	DB11796	−8.8	−7.74	Fostemsavir
	DB13345	−9.5	−9.53	Dihydroergocristine
	DB11274	−8.9	−8.21	Dihydro-alpha-ergocryptine
	DB11273	−9.6	−9.21	Dihydroergocornine
	DB14785	−8.7	−8.6	Fenebrutinib
	DB00696	−9.1	−7.69	Ergotamine
	DB14976	−9.5	−8.9	Relacorilant
	DB06290	−8.7	−8.5	Simeprevir
	DB14773	−9.6	−9.4	Lifirafenib
	DB11913	−9.6	−7.97	Methotrexate
	DB00619	−8.8	−9.75	Imatinib
	DB01232	−8.9	−7.73	Saquinavir
	DB14989	−8.7	−8.3	Umbralisib
	DB00762	−9.2	−9.69	Irinotecan
	DB12138	−8.8	−10.08	PF-03715455
Literature database	Mol181	−9.1	−8.9	–
	Mol184	−8.2	−8.58	–
	Mol187	−9.0	−8.75	–
	Mol188	−8.1	−8.45	–

derivatives which are selected from the literature. The docking-based virtual screening approach was performed by using AutoDock VINA implicated in the PyRx 0.8 tool. The aim was to identify new SARS-CoV-2 main protease (M_{pro}) inhibitors with high binding affinity. The top-ranked compounds were then submitted to another screen by using AutoDock 4.2.

2. Materials and Methods

2.1. Protein Structure Preparation. The crystal structure of SARS-CoV-2 M_{pro} (PDB ID : 6LU7) was collected from Protein Data Bank [20]. The ligand was separated from the protein. The polar hydrogen atoms and Kollman charges were added to the protein, and the water molecules were eliminated. The final prepared file was minimized by UCSF Chimera software [21] and saved in PDBQT format for further analysis.

2.2. Dataset Collection and Preparation. To identify the potential drugs against SARS-CoV-2 M_{pro}, an SBVS was performed on the high similar remdesivir- and ritonavir-approved drugs (taken from DrugBank database) [22] as well as on a series of ritonavir analogues (taken from literature) (see Table S1 in Supplementary Materials) [23, 24]. The compounds were imported into OpenBabel within the PyRx 0.8 tool [25] and subjected to energy minimization. The energy minimization was performed with the universal force field (UFF) using the conjugate gradient algorithm. The total number of steps was set to 2000, and the number of steps for update was set to 1. In addition, the minimization was set to stop at an energy difference of less than 0.01 kcal/mol. The minimized compounds were than transformed to PDBQT format for further analysis.

2.3. Structure-Based Virtual Screening (SBVS). In order to identify new potent SARS-CoV-2 M_{pro}, an SBVS using docking simulations was performed on both prepared libraries. The 6LU7 crystal structure was used as receptor and compounds libraries as ligands. The calculation of binding energies was performed using PyRx AutoDock VINA. Firstly, a grid box was set to cover the active site of crystal structure with the following dimension in Å: center (X, Y, Z) = (−9.63, 11.33, 70.50), dimensions (X, Y, Z) = (13.24, 20.25, 13.21) with an exhaustiveness of 8. The top-ranked compounds were then submitted to another screen by using AutoDock 4.2 [26]. Finally, analysis of the finding was performed using Discovery Studio [27] and PyMOL [28] programs.

3. Results and Discussion

3.1. Structure-Based Virtual Screening. In order to find new potential approved drugs for treating SARS-CoV-2 M_{pro}, an SBVS of both selected libraries was performed. AutoDock VINA implicated in the PyRx tool generated 9 different conformations for each ligand which are classified by binding affinity (kcal/mol). The top 20 ranked compounds displaying the free energy of binding in the range −8.7 to −9.6 kcal/mol are presented in Table 1, and the others are presented in Tables S2 and S3 (in Supplementary Materials).

The top hit selected drugs including methotrexate, dihydroergocornine, dihydroergocristine, relacorilant, irinotecan, lifirafenib, ergotamine, laniquidar, saquinavir, dihydro-alpha-ergocryptine, fostemsavir, imatinib, PF-03715455,

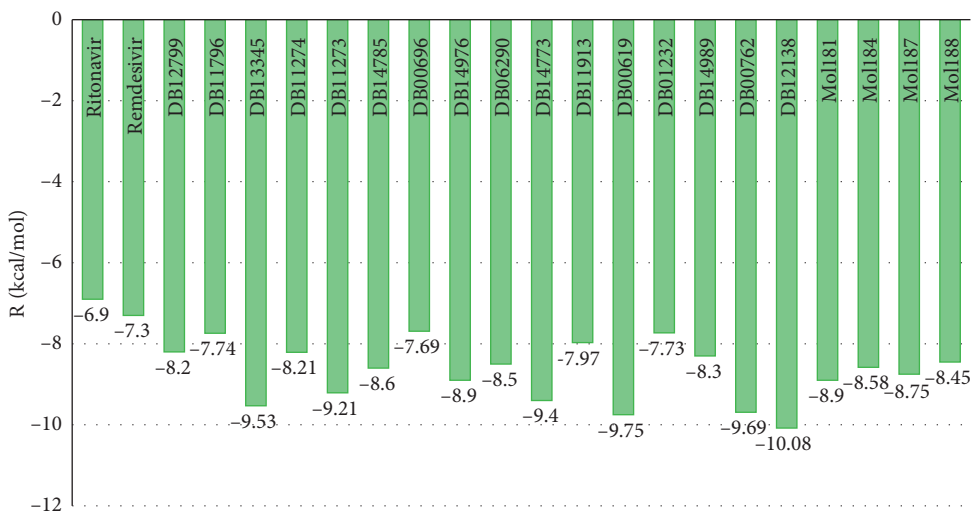


Figure 1: Binding free energy of top 20 ranked compounds and remdesivir and ritonavir drugs.

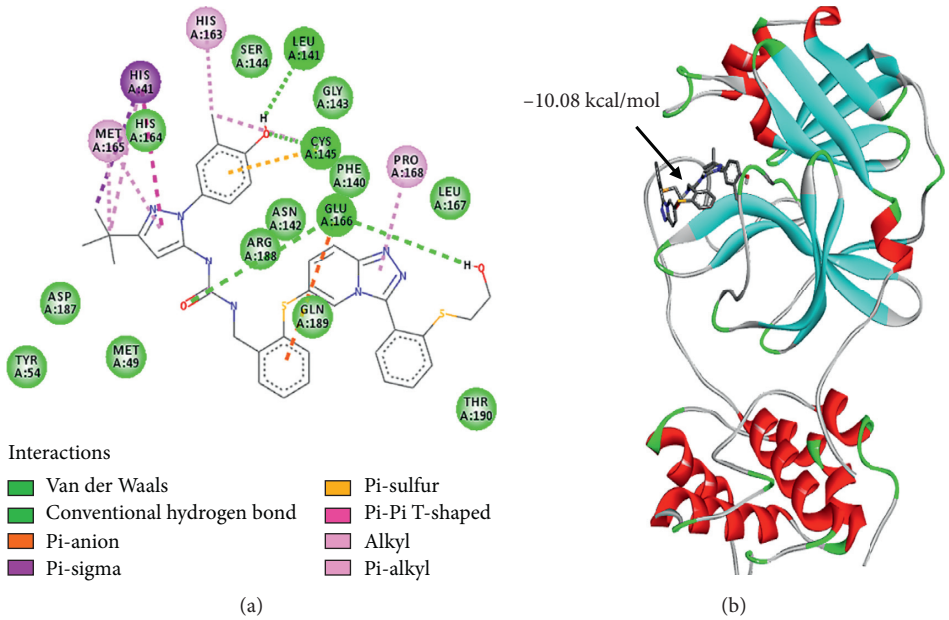


Figure 2: Molecular docking of PF-03715455 drug. (a) 2D view of the binding site interactions. (b) 3D view of the best selected conformation.

fenebrutinib, simeprevir, and umbralisib as well as Mol181, Mol1184, Mol187, and Mol188 were then submitted to another screen by the AutoDock 4.2 tool (Table 1). As shown in Table 1, all selected ligands have a binding free energy greater than remdesivir (−7.3 kcal/mol) and ritonavir (−6.9 kcal/mol) (Figure 1). Similarly, Arul et al. screened the DrugBank database against vital targets of SARS-CoV-2, and among the screened compounds, it was observed that anticancer drugs such as regorafenib, sorafenib, and lifirafenib have a high binding affinity score for the spike protein through molecular docking experiments [29].

3.2. Molecular Interaction and Binding Mode. In order to evaluate the binding site interactions between the screened compounds and the SARS-CoV-2 M_{pro}, PF-03715455, lifirafenib, and Mol181 were selected (Figures 2–4).

As described in Figure 2, the PF-03715455 drug was fixed in the binding pocket of SARS-CoV-2 M_{pro} via conventional hydrogen bond with GLU 166, CYS 145, and LEU 141; hydrophobic interactions (Pi-Sigma, Pi-Pi-T-shaped, Alkyl and Pi-Alkyl) with HIS 41, MET 165, HIS 163, CYS 145, and PRO 168; electrostatic interaction (Pi-anion) with PHE 140; and miscellaneous interaction (Pi-sulfur) with CYS 145.

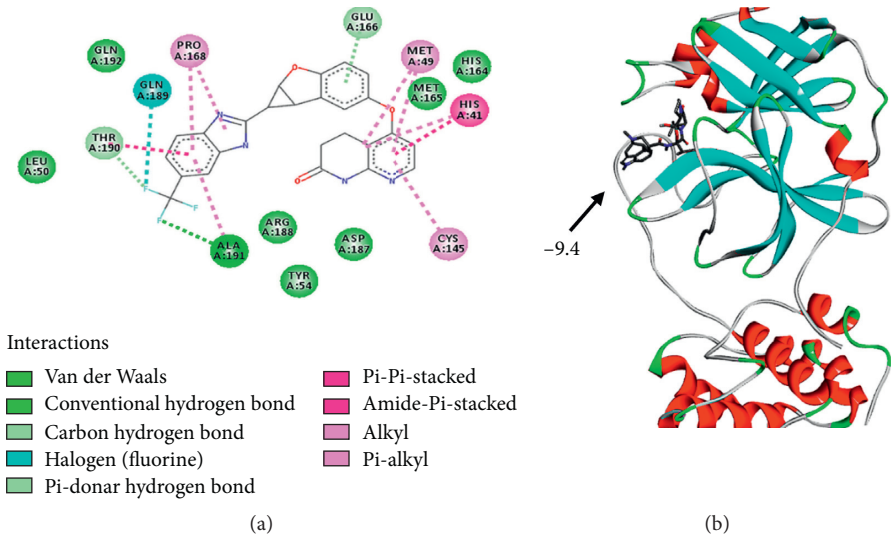


Figure 3: Molecular docking of lifirafenib drug. (a) 2D view of the binding site interactions. (b) 3D view of the best selected conformation.

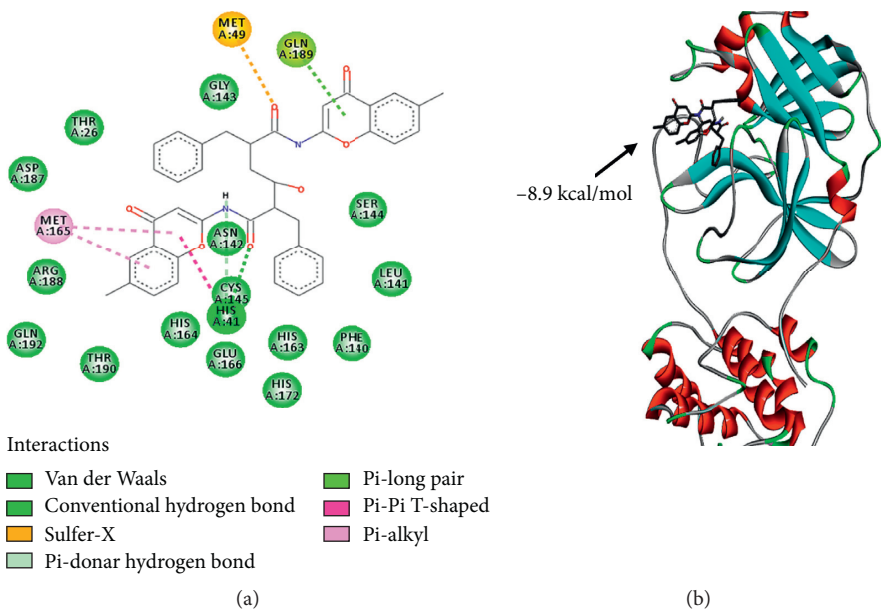
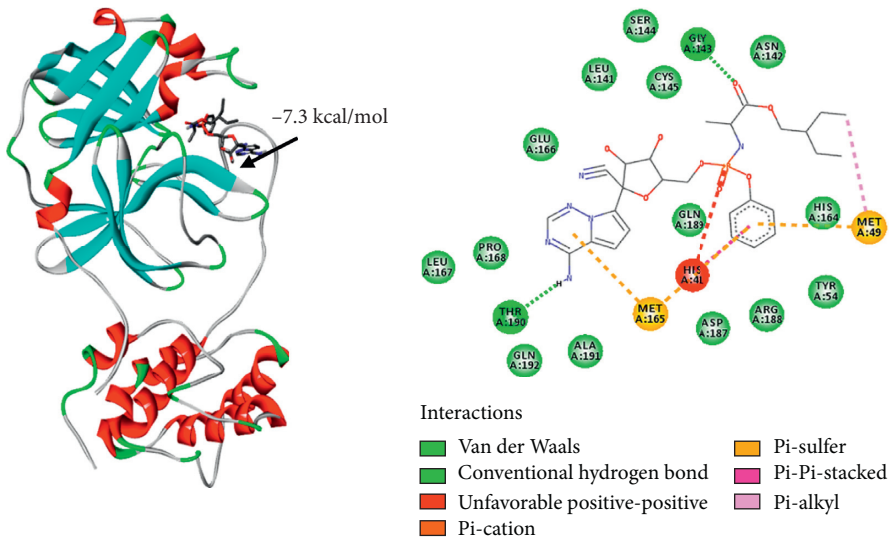


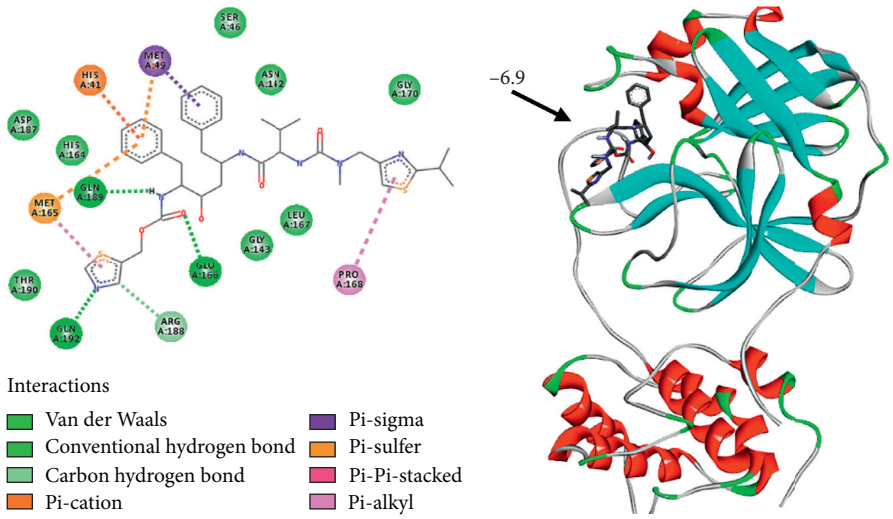
Figure 4: Molecular docking of Mol181. (a) 2D view of the binding site interactions. (b) 3D view of the best selected conformation.

However, lifirafenib (Figure 3) interacted by forming the conventional hydrogen bond interactions with ALA 191; carbon hydrogen bond and Pi-donor hydrogen bond interactions with THR 190 and GLU 166; hydrophobic interactions (Pi-Pi-T-shaped, amide-Pi-stacked, alkyl, and Pi-alkyl) with HIS 41, MET 49, CYS 145, and PRO 168; and halogen (fluorine) interaction with GLN 189. Also, the Mol181 compound (Figure 4) was fixed in the binding pocket of SARS-CoV-2 M_{pro} by forming the same type of interactions, and the most important are the hydrogen bond interactions with CYS 145 and HIS 41 (catalytic dyad residues). From these results, we can conclude that the screened compounds are more likely to be anti-COVID-19 compared to the remdesivir and ritonavir drugs (Figures 5 and 6).



(a) (b)

Figure 5: Molecular docking of remidesivir. (a) 3D view of the best selected conformation. (b) 2D view of the binding site interactions.



(a) (b)

Figure 6: Molecular docking of remidesivir. (a). 2D view of the binding site interactions. (b) 3D view of the best selected conformation.

4. Conclusion

In this study, a structure-based virtual screening (SBVS) was applied on the high similar remdesivir- and ritonavir-approved drugs, selected from the DrugBank database as well as on a series of ritonavir derivatives, selected from literature. The SBVS was performed by using AutoDock VINA implicated in PyRx 0.8 software. The top 20 hits based on their highest binding free energy were then verified by using AutoDock tools. Among the top 20 hit selected compounds, PF-03715455, lifirafenib, and Mol181 exhibited the highest binding affinity along with strong and stable interactions with the binding pocket residues of SARS-CoV-2 M_{pro}.

Data Availability

The dataset compounds of this work (format: SDF, MOL2, and PDBQT) are available at https://github.com/ELAISS-OUQ/SARS-CoV-2-inhibitors

Ethical Approval

This study does not involve any study with human or animal subjects.

Conflicts of Interest

The authors declare no conflicts of interest.

Acknowledgments

The authors thank the Moroccan Association of Theoretical Chemistry (MATC) for its relevant help regarding software.

Supplementary Materials

Table S1: chemical structures of ritonavir analogues selected from the literature. From MOL 1 to MOL 177, they are synthetized by Kempf DJ et al., and from Mol178 to Mol188, they are synthetized by Kaye PT et al. The chemical structures of all compounds were designed and optimized using ChemDraw and Chem3D software. Table S2: binding free energy of DrugBank compounds. The calculation was realized using AutoDock VINA, implicated in the PyRx tool. Each drug was calculated using 9 conformations which are classified by binding affinity (kcal/mol). Table S3: binding free energy of ritonavir derivatives. The calculation was realized using AutoDock VINA, implicated in the PyRx tool. Each drug was calculated using 9 conformations which are classified by binding affinity (kcal/mol). (*Supplementary Materials*)

References

[1] L. E. Gralinski and V. D. Menachery, "Return of the coronavirus: 2019-nCoV," *Viruses*, vol. 12, no. 2, pp. 1–8, 2020.

[2] F. Wu, S. Zhao, B. Yu et al., "A new coronavirus associated with human respiratory disease in China," *Nature*, vol. 579, no. 7798, pp. 265–269, 2020.

[3] World Health Organization, *Coronavirus Disease 2019 (COVID-19) Situation Report – 65*, World Health Organization, Geneva, Switzerland, 2020.

[4] E. de Wit, F. Feldmann, J. Cronin et al., "Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection," *Proceedings of the National Academy of Sciences*, vol. 117, no. 12, pp. 6771–6776, 2020.

[5] R. T. Eastman, J. S. Roth, K. R. Brimacombe et al., "Remdesivir: a review of its discovery and development leading to emergency use authorization for treatment of COVID-19," *ACS Central Science*, vol. 6, no. 5, pp. 672–683, 2020.

[6] D. W. Cameron, "Randomised placebo-controlled trial of ritonavir in advanced HIV-1 disease," *Lancet*, vol. 351, no. 9102, pp. 543–549, 1998.

[7] T. K. Warren, R. Jordan, M. K. Lo et al., "Therapeutic efficacy of the small molecule GS-5734 against ebola virus in rhesus monkeys," *Nature*, vol. 531, no. 7594, pp. 381–385, 2016.

[8] M. W. Hull and J. S. G. Montaner, "Ritonavir-boosted protease inhibitors in HIV therapy," *Annals of Medicine*, vol. 43, no. 5, pp. 375–388, 2011.

[9] A. El Aissouq, H. Toufik, M. Stitou, A. Ouammou, and F. Lamchouri, "In silico design of novel tetra-substituted pyridinylimidazoles derivatives as c-jun *N*-terminal kinase-3 inhibitors, using 2D/3D-QSAR studies, molecular docking and ADMET prediction," *The International Journal of Peptide Research and Therapeutics*, vol. 26, no. 3, pp. 1335–1351, 2020.

[10] C. M. Song, S. J. Lim, and J. C. Tong, "Recent advances in computer-aided drug design," *Briefings in Bioinformatics*, vol. 10, no. 5, pp. 579–591, 2009.

[11] S. J. Y. Macalino, V. Gosu, S. Hong, and S. Choi, "Role of computer-aided drug design in modern drug discovery," *Archives of Pharmacal Research*, vol. 38, no. 9, pp. 1686–1701, 2015.

[12] R. P. Gangwal, G. V. Dhoke, M. V. Damre, K. Khandelwal, and A. T. Sangamwar, "Structure-based virtual screening and molecular dynamic simulation studies to identify novel cytochrome bc1 inhibitors as antimalarial agents," *Journal of Computational Medicine*, vol. 2013, Article ID 637901, 9 pages, 2013.

[13] P. Srinivasan, P. Chella Perumal, and A. Sudha, "Discovery of novel inhibitors for Nek6 protein through homology model assisted structure based virtual screening and molecular docking approaches," *The Scientific World Journal*, vol. 2014, Article ID 967873, 9 pages, 2014.

[14] Y. Wang, R. Han, H. Zhang et al., "Combined ligand/structure-based virtual screening and molecular dynamics simulations of steroidal androgen receptor antagonists," *BioMed Research International*, vol. 2017, Article ID 3572394, 18 pages, 2017.

[15] W. Wang, D. Wan, D. Liao et al., "Identification of potent chloride intracellular channel protein 1 inhibitors from traditional Chinese medicine through structure-based virtual screening and molecular dynamics analysis," *BioMed Research International*, vol. 2017, Article ID 4751780, 18 pages, 2017.

[16] Z. Liu, J. Zhao, W. Li et al., "Molecular docking of potential inhibitors for influenza H7N9," *Computational and Mathematical Methods in Medicine*, vol. 2015, Article ID 480764, 8 pages, 2015.

[17] R. Dubey, A. K. Tewari, V. P. Singh et al., "Molecular docking study of conformational polymorph: building block of crystal chemistry," *The Scientific World Journal*, vol. 2013, Article ID 309710, 6 pages, 2013.

[18] F. R. S. Santos, D. A. F. Nunes, W. G. Lima et al., "Identification of zika virus NS2B-NS3 protease inhibitors by structure-based virtual screening and drug repurposing approaches," *Journal of Chemical Information and Modeling*, vol. 60, no. 2, pp. 731–737, 2020.

[19] S. Nirwan, V. Chahal, and R. Kakkar, "Structure-based virtual screening, free energy of binding and molecular dynamics simulations to propose novel inhibitors of Mtb-MurB oxidoreductase enzyme," *Journal of Biomolecular Structure and Dynamics*, vol. 1102, pp. 1–16, 2020.

[20] X. Liu, B. Zhang, Z. Jin, H. Yang, and Z. Rao, "The crystal structure of COVID-19 main protease in complex with an inhibitor N3, PDB release," 2020.

[21] E. F. Pettersen, T. D. Goddard, C. C. Huang et al., "UCSF chimera?a visualization system for exploratory research and analysis," *Journal of Computational Chemistry*, vol. 25, no. 13, pp. 1605–1612, 2004.

[22] D. S. Wishart, Y. D. Feunang, A. C. Guo et al., "DrugBank 5.0: a major update to the drug bank database for 2018," *Nucleic Acids Research*, vol. 46, no. D1, pp. D1074–D1082, 2018.

[23] D. J. Kempf, H. L. Sham, K. C. Marsh et al., "Discovery of ritonavir, a potent inhibitor of HIV protease with high oral bioavailability and clinical efficacy," *Journal of Medicinal Chemistry*, vol. 41, no. 4, pp. 602–617, 1998.

[24] P. T. Kaye, M. A. Musa, A. T. Nchinda, and X. W. Nocanda, "Novel heterocyclic analogues of the HIV-1 protease inhibitor, ritonavir," *Synthetic Communications*, vol. 34, no. 14, pp. 2575–2589, 2004.

[25] J. Duncan, "Small-molecule library screening by docking with PyRx," *Methods in Molecular Biology*, vol. 1263, pp. 243–250, 2015.

[26] O. Trott and A. J. Olson, "Software news and update autoDock vina : improving the speed and accuracy of docking with a new scoring function , efficient optimization , and multi-threading," *Journal of Computational Chemistry*, vol. 31, no. 2, pp. 455–461, 2009.

[27] BIOVIA - Scientific Enterprise Software for Chemical Research, "Material Science R&D," 2020, https://www.3dsbiovia.com.

[28] L. Schrodinger, *The PyMOL Molecular Graphics System, Version 2.2.0*, Schrödinger, Inc., Karnataka, India, 2015.

[29] S. Dallakyan, A. J. Olson, and J. Jeyakanthan, "Small-molecule library screening by docking with PyRx," *Methods in Molecular Biology (Clifton, N.J.)*, vol. 1263, pp. 243–250, 2015.