In-silico Computational Investigations of AntiViral Lignan Derivatives as Potent Inhibitors of SARS CoV-2

Dipen K. Sureja,* Ashish P. Shah, Normi D. Gajjar, Shwetaba B. Jadeja, Kunjan B. Bodiwala, and Tejas M. Dhameliya*
# Table of Contents

1. 2-D diagrams of Identified Hit Molecules .................................................................2

2. Experimental Section ..................................................................................................5
   2.1 Selection and Preparation of Proteins .................................................................5
   2.2 Preparation of Ligands .......................................................................................5
   2.3 Docking Studies .................................................................................................6
   2.4 Drug Likeliness and ADMET Analysis ...............................................................6
   2.5 Molecular Dynamics (MD) Simulations .............................................................6
   2.6 Availability of Data and Material .......................................................................7
   2.7 Code Availability ...............................................................................................7

3. References ..................................................................................................................8
1. 2-D diagrams of Identified Hit Molecules

Figure S1. The 2D interactions of amino acid residues of PDB ID: 6M2N with (a) clemastatin B and (b) strebluslignanol G.

Figure S2. The 2D interactions of amino acid residues of PDB ID: 6LZG with (a) clemastatin B and (b) diphyllyn.
**Figure S3.** The 2D interactions of amino acid residues of PDB ID: 6W4H with (a) secoisolariciresinol and (b) sesamin.

**Figure S4.** The 2D interactions of amino acid residues of PDB ID: 6WRH with (a) clemastatin B and (b) nordihydroguaiaretic acid.
Figure S5. The 2D interactions of amino acid residues of PDB ID: 6W6Y with (a) savinin and (b) cleistantoxin.

Figure S6. The 2D interactions of amino acid residues of PDB ID: 7BV2 with (a) clemastatin B and (b) silymarin.
2. Experimental Section

2.1 Selection and Preparation of Proteins

The selection of proteins having good resolution has been performed based on a literature survey. The biological targets and PDB selected for the virtual screening includes main protease (PDB: 6M2N), papain-like proteases (PDB: 6W6Y, 6WRH), native spike protein with ACE-2 (PDB: 6LZG), RNA dependent RNA polymerase (PDB: 7BV2), and Non-structural protein 10 and 16 (PDB: 6W4H).

The Protein Data Bank database was used to download the structure of various proteins used in the study.[1] Before docking, the downloaded proteins were prepared using the protein preparation wizard in the Maestro panel of Schrodinger software.[2] The parameters used are briefly summarized as assigning bonds and bond order; adding hydrogen atoms and hydrogen bond optimization; removing crystallographic water molecules and cofactors, and optimizing ionization state corresponding to pH 7. Finally, the OPLS-2005 force field was applied for the energy minimization of protein structure. Further, a receptor grid box of 10 Å × 10 Å × 10 Å at a centroid of the active site was generated with a radius of 20 Å around the co-crystallized ligand present in the crystal structure.[3]

2.2 Preparation of Ligands

Total twenty-seven lignan derivatives possessing antiviral activity were identified from the previous reports. The IUPAC name, biological source, and antiviral activity of lignan derivatives have been presented in Table 1 of main manuscript. The structures were drawn in ChemBioOffice 2018 suite, and IUPAC names and 3D structures of the compounds were generated using the same software. The ligands were built using the build panel of Maestro. LigPrep module was used to prepare and generate the 3D structure of the ligands by addition of hydrogen atoms and ionizing at pH (7 ± 2).[4] The OPLS_2005 force field was applied to minimize energy using the standard energy function, and RMSD cut off 0.01 Å.
2.3 Docking Studies

The low energy conformations of all the ligands were docked into the catalytic domain of targeted protein using Glide, Schrodinger software in an extra precision mode without applying any constraint.[3]

2.4 Drug Likeliness and ADMET Analysis

The QikProp module of Schrodinger software was used to predict the drug-like behavior of the compounds. The compounds were subjected to assess their basic physicochemical properties using Lipinski’s rule of five, including molecular weight, log P, H-bond donors, and H-bond acceptors, along with polar surface area and number of rotatable bonds.[5] Various physicochemical properties of ADMET parameters of the selected lignans and their derivatives were assessed using SwissADME[6] and pkCSM.[7,8] The ADMET properties like water solubility, molar refractivity, CaCO2 cell permeability, intestinal absorption, volume of distribution, fraction unbound, total renal clearance, hepatotoxicity and ability to inhibit the P-glycoprotein were also studied to gain the detailed knowledge about the pharmacokinetic aspects of the selected lignans.

2.5 Molecular Dynamics (MD) Simulations

Hit molecules, obtained from the manual analysis of the docking results and druggability analysis, were selected for MD simulation using GROMACS 2020.1[9,10] software. CHARMM36 as an all-atom force field[11] and CGenFF server were used to generate the topology were applied.[12,13] After the energy minimization process, solvation with TIP3P water model and neutralization by Na⁺ and Cl⁻ ions were carried out along with the thermal equilibration using canonical (NVT) and pressure equilibration using isobaric-isothermal (NPT) ensemble for 100 ps. These were followed by the final MD run of 10 ns to study their time-dependent stability analysis of the ligand-receptor complexes.
2.6 Availability of Data and Material

The protein and ligand required for molecular modelling have been retrieved from RCSB PDB and PubChem, respectively. The preparation of protein, ligands, and prediction of ADMET properties has been performed using AutoDock Vina, OpenBabel, SwissADME/pKCSM, respectively. The 3D-images of docked compounds with the ligands have been presented using Biovia Discovery Studio. To study the stability of ligands into the ligand-protein complexes, GROMACS 2020.1 have been used from www.zenodo.org.

2.7 Code Availability

The present work does not involve any deposition of newly reported crystal structures.
3. References

[1] “Protein Data Bank,” can be found under https://www.rcsb.org/, (accessed March 1, 2022).

[2] Protein Preparation Wizard; Epik, Schrödinger, LLC, New York, NY, 2020; Impact, Schrödinger, LLC, New York, NY, 2020; Prime, Schrödinger, LLC, New York, NY, 2020.

[3] Schrödinger Release 2020-3: Glide, Schrödinger, LLC, New York, NY, 2020.

[4] Schrödinger Release 2020-3: LigPrep, Schrödinger, LLC, New York, NY, 2020.

[5] Schrödinger Release 2020-3: QikProp, Schrödinger, LLC, New York, NY, 2020.

[6] A. Daina, O. Michielin, V. Zoete, Sci. Reports 2017, 7, 42717.

[7] “pkCSM: Pharmacokinetic properties,” can be found under http://biosig.unimelb.edu.au/pkcsms/prediction, (accessed September 19, 2021).

[8] D. E. V. Pires, T. L. Blundell, D. B. Ascher, J. Med. Chem. 2015, 58, 4066–4072.

[9] M. J. Abraham, Berk Hess, E. Lindahl, D. van der Spoel, “GROMACS 2020.1 (Manual Version 2020.1) Zenodo,” can be found under http://doi.org/10.5281/zenodo.4054996, 2020.

[10] M. J. Abraham, T. Murtola, R. Schulz, S. Páll, J. C. Smith, B. Hess, E. Lindah, SoftwareX 2015, 1–2, 19–25.

[11] J. Huang, S. Rauscher, G. Nawrocki, T. Ran, M. Feig, B. L. De Groot, H. Grubmüller, A. D. MacKerell, Nat. Methods 2016, 14, 71–73.

[12] K. Vanommeslaeghe, E. Hatcher, C. Acharya, S. Kundu, S. Zhong, J. Shim, E. Darian, O. Guvench, P. Lopes, I. Vorobyov, A. D. Mackerell, J. Comput. Chem. 2010, 31, 671–690.

[13] W. Yu, X. He, K. Vanommeslaeghe, A. D. MacKerell, J. Comput. Chem. 2012, 33, 2451–2468.