**In silico** identification and validation of triarylchromones as potential inhibitor against main protease of severe acute respiratory syndrome coronavirus 2

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**ABSTRACT**

The ongoing pandemic due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused COVID-19 has emerged as a severe threat to the life of human kind. The identification and designing of appropriate and reliable drug molecule for the treatment of COVID-19 patients is the pressing need of the present time. Among different drug targets, the main protease of SARS-CoV-2 is being considered as the most effective target. In addition to the drug repurposing, different compounds of natural as well as synthetic origins are being investigated for their efficacy against different drug targets of SARS-CoV-2 virus. In that context, the chromone based natural flavonols have also exhibited significant antiviral properties against different targets of SARS-CoV-2. The \textit{in silico} studies presented here discloses the efficacy of triarylchromones (TAC) as potential inhibitor against main protease of SARS-CoV-2. The molecular docking and ADMET study performed using 14 arylchromones which could easily be accessed through simple synthetic protocols, revealed best binding affinities in case of TAC-3 (–11.2 kcal/mol), TAC-4 (–10.5 kcal/mol), TAC-6 (–11.2 kcal/mol), TAC-7 (–10.0 kcal/mol). Additional validation studies including molecular dynamics simulation and binding energy calculation using MMGBSA for protein ligand complex for 100 ns revealed the best binding interaction of TAC-3, TAC-4, TAC-6, TAC-7 against main protease of SARS-CoV-2. Moreover, the in vitro and preclinical validation of identified compounds will help us to understand the molecular mechanisms of regulation of TACs against SARS-CoV-2.

**1. Introduction**

The ongoing pandemic due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has emerged as one of the most contagious disease of last several decades (Rohit et al., 2020; Zheng, 2020; Zhu et al., 2020). Although various structural as well as biological aspects of this virus has already been explored but (Portelli et al., 2020; V’kovski et al., 2020) but several information regarding the specific drug targets, mechanism of action are yet to be established to discover an appropriate drug therapy. SARS-CoV-2 is an enveloped positive-sense RNA viruses, is one of the member viruses of Coronaviridae family and Coronavirus subfamily (Astuti & Ysrafil, 2020; Yang et al., 2020). As per the current data provided by the World Health Organization (WHO), more than 54 millions confirmed cases and approx. 1.3 million deaths have been reported so far across the world since its first report from Wuhan in Dec. 2019, China and respiratory related infection and complications have emerged as one of the major cause of the death (Vincet & Taccone, 2020; https://covid19WHO.int/). Apart from the lower respiratory tract infections, other organs such as kidney, liver, heart have also found to be greatly affected due to the infections due to SARS-CoV-2 virus (Gavriatopoulou et al., 2020; Huang et al., 2020). In order to trounce the existing health crisis, different strategies such as drug repurposing (Guy et al., 2020; Harrison, 2020; Serafin et al., 2020), discovery of new vaccines (Krammer, 2020; Tregoning et al., 2020; https://www.nature.com/articles/d41586-020-03248-7; https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-announce-vaccine-candidate-against) and convalescent plasma therapy (Focosi et al., 2020) are being employed. In that direction, immense efforts are also being made towards the discovery of effective therapeutic agents which could successfully bind with the different drug targets such as the spike (S) protein, enzymes such as proteases, viral RNA etc. and inhibit different steps of the infection (Akaji & Konno, 2020; Coelho et al., 2020; Preeti et al., 2020; Rane et al., 2020; Zhao et al., 2021; Zhu et al., 2020). For examples the spike (S) protein of SARS-CoV-2 interacts with different receptors such as...
Table 1. List of arylchromones as potential drug candidate against main protease of SARS-CoV-2

| S. no. | Diarylchromone (DAC) | S. no. | Triarylchromone (TAC) |
|--------|-----------------------|--------|-----------------------|
| 1.     | ![Structure 1](image1) | 8.     | ![Structure 8](image8) |
|        | 3,6-bis(4-hydroxyphenyl)-4H-chromen-4-one (DAC-1) |        | 6,8-bis(3,4-dihydroxyphenyl)-3-hydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one (TAC-1) |
| 2.     | ![Structure 2](image2) | 9.     | ![Structure 9](image9) |
|        | 3-hydroxy-2-(4-hydroxyphenyl)-6-(naphthalen-2-yl)-4H-chromen-4-one (DAC-2) |        | 6,8-bis(benzo[d][1,3]dioxol-5-yl)-3-hydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one (TAC-2) |
| 3.     | ![Structure 3](image3) | 10.    | ![Structure 10](image10) |
|        | 6-(4-fluorophenyl)-3-hydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one (DAC-3) |        | 3-hydroxy-2-(4-hydroxyphenyl)-6,8-di(naphthalen-2-yl)-4H-chromen-4-one (TAC-3) |
| 4.     | ![Structure 4](image4) | 11.    | ![Structure 11](image11) |
|        | 2-(4-hydroxyphenyl)-6-(naphthalen-2-yl)-4H-chromen-4-one (DAC-4) |        | 3-hydroxy-2,6,8-tri(naphthalen-2-yl)-4H-chromen-4-one (TAC-4) |
| 5.     | ![Structure 5](image5) | 12.    | ![Structure 12](image12) |
|        | 3-(4-hydroxyphenyl)-6-(naphthalen-2-yl)-4H-chromen-4-one (DAC-5) |        | 3-hydroxy-6,8-bis(4-hydroxybenzyl)-2-(4-hydroxyphenyl)-4H-chromen-4-one (TAC-5) |
| 6.     | ![Structure 6](image6) | 13.    | ![Structure 13](image13) |
|        | 3-hydroxy-6-(4-hydroxyphenyl)-2-(thiophen-2-yl)-4H-chromen-4-one (DAC-6) |        | 3,6,8-tri(naphthalen-2-yl)-4H-chromen-4-one (TAC-6) |

(continued)
angiotensin-converting enzyme 2 (ACE-2), TM protease serine 2 (TMPRSS-2) etc. present on the host cell and facilitates the viral entry (Ali & Vijayan, 2020; Huang et al., 2020). Similarly, proteases such as Mpro or 3CL-protease are also being explored as excellent drug targets due to their involvement in enhancing viral loads and the growth of virus (Wu et al., 2020; Zhang et al., 2020). Despite of the growing understanding about the potential drug targets and fast-track research towards the development of the therapeutic agent, the discovery of appropriate and widely applicable drug therapy is still awaited. Some of the vaccines such as mRNA-1273 and BNT162b2 have exhibited promising results so far (Jackson et al., 2020; Walsh et al., 2020). Except m-RNA based some of these vaccine candidates, no other effective and robust drug therapy could be discovered. Since the surfacing of the first case in China, the efficacy of several natural products as well as FDA-approved drugs of diverse verities has rigorously been investigated. For example, the effectiveness of drugs such as chloroquines, lopinavir, remdisivir, dexamethasone, ivermectin etc. have been investigated so far against COVID-19 but none of these could be established as an effective drug against SARS-CoV-2 (Cao & Yang, 2020; Chaccour et al., 2020; Ferner & Aronson, 2020; Lammers et al., 2020; Wang et al., 2020). Similarly, the efficacy of natural products and phytochemicals against COVID-19 and other viruses has also been explored (Aucoin & Cooley, 2020)}
| S. no. | Compound/ligand | Molecular weight (<500 Da) | Log P (<5) | H-bond donar (5) | H-bond acceptor (<10) | ROF score | Drug likeliness |
|-------|-----------------|---------------------------|------------|-----------------|------------------------|-----------|-----------------|
| 1.    | DAC-1           | 330.33                    | 3.61       | 2               | 4                      | 0         | Yes             |
| 2.    | DAC-2           | 380.39                    | 4.58       | 2               | 4                      | 0         | Yes             |
| 3.    | DAC-3           | 348.32                    | 4.0        | 2               | 5                      | 0         | Yes             |
| 4.    | DAC-4           | 364.39                    | 5.00       | 1               | 3                      | 0         | Yes             |
| 5.    | DAC-5           | 364.39                    | 4.91       | 1               | 3                      | 0         | Yes             |
| 6.    | DAC-6           | 336.36                    | 3.69       | 2               | 4                      | 0         | Yes             |
| 7.    | DAC-7           | 320.30                    | 3.62       | 2               | 5                      | 0         | Yes             |
| 8.    | TAC-1           | 470.43                    | 3.46       | 6               | 8                      | 1         | Yes             |
| 9.    | TAC-2           | 494.45                    | 4.63       | 2               | 8                      | 0         | Yes             |
| 10.   | TAC-3           | 506.55                    | 6.71       | 2               | 4                      | 2         | No              |
| 11.   | TAC-4           | 540.61                    | 7.99       | 1               | 3                      | 2         | No              |
| 12.   | TAC-5           | 466.48                    | 4.59       | 4               | 6                      | 0         | Yes             |
| 13.   | TAC-6           | 524.61                    | 8.38       | 0               | 2                      | 2         | No              |
| 14.   | TAC-7           | 524.61                    | 8.38       | 0               | 2                      | 2         | No              |
In particular, the therapeutic values of chromone as core scaffolds are well established in the literature (Gaspar et al., 2014; Keri et al., 2014). Interestingly chromone scaffold containing phytochemicals such as quercetin, fisetin, etc. which are part of our dietary supplements, have also exhibited their efficacy against different drug targets of SARS-CoV-2 (Derosa et al., 2020; Seri et al., 2020).

In view of the immense therapeutic importance of these chromone containing heterocycles, especially as anti-viral agent, we envisaged that such therapeutic activity could be enhanced by functionalizing the chromone scaffold with appropriate functional groups and moieties. Flavoxate, Pranlukast, Disodium cromoglycate (DSCG) etc. are examples of synthetically produced drugs with chromone scaffold which have displayed excellent efficacy in the treatment of urinary and asthmatic disorders respectively (Gaspar et al., 2014; Reise et al., 2017).

Therefore, the aim of the present in silico study was to investigate the efficacy of newly designed di- and triaryl chromones (Table 1) which could easily be accessed following literature known reaction protocols such as metal-catalyzed cross-coupling and C–H activation reactions (Choi et al., 2016; Kim et al., 2012; Rao & Kumar, 2014), against the SARS-CoV-2 main protease (6LU7) as potential drug target. 6LU7 is the major protease is the major protein in SARS-CoV-2 that has been structured and repositioned in the PDB database recently and is widely accessible around the globe. As shown in Figure 1A, it represents the ribbon structure representation and (B) surface representation of COVID-19 main protease (6LU7) with interacting chain A and B. It is important to underline that compared to the natural product; the synthetic analogues allow the large scale synthesis in relatively short span of time. In addition to that, the pharmacological activities of these could easily be modulated through modification in the substituent.

2. Materials and methods

The SARS-CoV-2 virus main protease (PDB ID- 6LU7) structure was obtained from the RCSB PDB (protein data bank) database (http://www.rcsb.org). Prior to docking or analysis, the solvation parameters, charge assignment, and fragmental volumes to the SARS-CoV-2 main protease was done using the Autodock Tool 4 (ADT) (Morris et al., 2009; Sumit et al., 2020; Vivek et al., 2020). Further optimization of the protein molecule was done using Autodock Tool for the molecular docking (Chandel et al., 2020).

2.1. Ligand preparation

The selected compounds in 3D SDF format were screened in order to select the best hits. The 2D ligand structures were designed using Chemsketch program (Figure 2; Table 2). Avogadro program was used to optimize the ligands.
Babel was used to convert the ligands into the PDB format. The ligands were first optimized and converted to PDBQT format in order to further simplify the process using the PyRx virtual screening tool-python prescription 0.8.

2.2. Compound screening using PyRx program

PyRx software was used for the purpose of molecular screening of all the library of compounds by autodock wizard as the engine for molecular docking (Morris et al., 2008). The ligands were considered to be flexible during the docking period and the protein was considered to be rigid. Auto Grid engine in PyRx was used for the generation of configuration file for the grid parameters. The PyRx application was also used to predict/understand the amino acids residues present in the active site of the protein that interact with the ligands. The results less than 1.0Å in positional root-mean-square deviation (RMSD) were clustered together and considered ideal for identifying the favourable binding. The most negative (highest binding energy) was considered as the best candidate with maximum binding energy (Chandel et al., 2020; Rashmi et al., 2020).

2.3. Analysis and visualization

Pymol version 2.3.4 was used for the visual analysis of the docking site and the validation of results were done using Autodock-Vina (Rauf et al., 2015).

2.4. ADME analysis

The ADME properties (absorption, distribution, metabolism, excretion, and toxicity) of the selected compound were calculated using online Swiss ADME program (Diana et al., 2007). The major parameters for ADMET associated proper-ties includes Lipinski’s rule of five (H bond acceptor, H bond donor, molecular weight, water/octanol partition coefficient), pharmacokinetic properties, the solubility of the drug, and drug likeliness were considered. The values of the observe properties are presented in Table 3.

2.5. Molecular dynamics (MD) and molecular simulation (MS) study

Selected complexes were prepared prior to MD simulation in the protein preparation wizard and Prime module of Schrödinger suite (Chandel et al., 2020; Schrödinger, 2020; Schrödinger, 2016; Schrödinger, 2020-1). Removal of steric clashes and strained bonds/angles were done by performing a restrained energy minimization, allowing movement in heavy atoms up to 0.3Å. Extensive 100 ns MD simulation was carried out for both complexes through Desmond (D. E. Shaw Research, New York, NY, 2015) to access the binding stability of compounds with their respective protein complex. The standard fixed-charged force fields were used to optimize the complex. These complexes were solvated in TIP3P water model and 0.15 M NaCl to mimic a physiological ionic
Figure 5. Docking analysis and visualisation of protein–ligand complex (A) Molecular docking analysis between Main protease (PDB ID-6LU7) of SARS-CoV-2 and TAC-6. The protein 6LU7 is represented in 3D ribbon structure (black) and the ligand is represented in light brown colour. The zoom in figure represents surface representation between the active site of the protein and ligand. (B) 2D schematic representation of protein–ligand interaction by LIGPLOT. Hydrogen bonds are indicated using dashed lines between the atoms involved in the interaction. Hydrophobic contacts are represented using red arc with spokes radiating towards the ligand atom in contact.

Figure 6. Docking analysis and visualisation of protein–ligand complex (A) Molecular docking analysis between Main protease (PDB ID-6LU7) of SARS-CoV-2 and TAC-7. The protein 6LU7 is represented in 3D ribbon structure (orange) and the ligand is represented in blue. The zoom in figure represents surface representation between the active site of the protein and ligand. (B) 2D schematic representation of protein–ligand interaction by LIGPLOT. Hydrogen bonds are indicated using dashed lines between the atoms involved in the interaction. Hydrophobic contacts are represented using red arc with spokes radiating towards the ligand atom in contact.
concentration. The full system energy minimization step was done for 100 ps.

The MD simulation was run at constant 300 K temperature, standard pressure (1.01325 bar), within an orthorhombic box with buffer dimensions 10 x 10 x 10 Å³ and NPT ensemble. The energy (kcal/mol) was recorded at interval of 1.2 ps. The protein–ligand complex system was neutralized by balancing the net charge of the system by adding Na⁺ or Cl⁻ counter ions. The Nose–Hoover chain and Martyna–Tobias–Klein dynamic algorithm was used to maintain the temperature of all the systems at 300 K and pressure 1.01325 bar, respectively.

3. Results and discussion

The arylchromones (1–14, Table 1) selected for our purposes could easily be prepared using literature known synthetic protocols mainly under the metal-catalyzed cross-coupling reaction protocols.

The potential drug likeness and efficacy of these functionalyzed chromones were investigated using in silico studies including molecular docking, ADME analysis and molecular dynamics simulation studies which have separately been described in the following sections. Molecular docking study reveals the strength and binding energy of a specific ligand by which a compound interacts with and binds to the active site pocket of a target protein. A compound with lesser binding energy is considered as a possible drug candidate. In order to understand the possible effect of the compounds against main protease 6LU7, molecular docking study of 14 active compounds was performed (Table 2). Docking results...
of main protease 6LU7 with selected 4 compounds (TAC-3, TAC-4, TAC-6, TAC-7) revealed favourable binding energy and were observed to be as the best molecules at the major target site of the protein. The chemical structure of the selected 4 active compounds is shown in Figure 2. The molecular docking study and visualisation of main protease 6LU7 binding TAC-3, TAC-4, TAC-6, and TAC-7 are shown in Figures 3–6, respectively.

Out of the four compounds, TAC-6 exhibited the best docking score (binding energy) i.e. −11.2 Kcal/mol with SARS-CoV-2 Main Protease 6LU7. The 2D schematic representation of protein–ligand interaction is represented by LIGPLOT representing the major amino acid residues of compound 13 binding on the active site pocket of the protein 6LU7 (Figure 5). TAC-3 exhibited (−11.1 kcal/mol) binding energy with main protease 6LU7. TYR118, HIS41, LEU27, HIS163, CYS117, PHE140 are the amino acid residues participating in the interaction at the binding pocket of COVID-19 (Figure 3). The 2D schematic representation of protein–ligand interaction is represented by LIGPLOT representing the major amino acid residues of TAC-3 binding on the active site pocket of the protein 6LU7. TAC-4 exhibited (−10.5 kcal/mol) binding energy with main protease 6LU7. ARG131, PHE134, THR292, ILE200, and PRO132 are the amino acid residues participating in the interaction at the binding pocket of COVID-19 (Figure 4). The 2D schematic representation of protein–ligand interaction is represented by LIGPLOT representing the major amino acid residues of compound 10 binding on the active site pocket of the protein 6LU7. TAC-7

Figure 8. Cα RMSD Plot of complex TAC-3, 4, 6 and 7. Root mean square deviation (RMSD) was carried out for the MD simulation of each system.

Figure 9. Protein–ligand RMSD plot: (A) complex TAC-3, (B) complex TAC-4, (C) complex TAC-6, and (D) complex TAC-7. Root mean square deviation (RMSD) plots of the protein–ligand complexes against the simulation time of 100 ns. The ligand TAC-3, TAC-4, TAC-6 and TAC-7 are shown in the red colour and the protein main protease (6LU7) side chain is shown in the blue colour.
exhibited (~10.0 Kcal/mol) binding energy with main protease 6LU7. PHE291, GLN127, ARG4, and LYS5 are the amino acid residues participating in the interaction at the binding pocket of COVID-19 (Figure 6). The 2D schematic representation of protein–ligand interaction is represented by LIGPLOT representing the major amino acid residues of TAC-4 binding on the active site pocket of the protein 6LU7. The molecular docking study in our study showed the inhibitory potential of 4 compounds, ranked by affinity ($\Delta G$); TAC-6 > TAC-3 > TAC-4 > TAC-7.

3.1. ADME calculations

Next, to get an insight about the drug-likeness properties of the lead compounds, all the 14 compounds were screened for ADME properties using swiss ADME programme and the results are shown in Table 3. The major criteria to understand the drug likeness properties of a particular compound involves Lipinski’s rule of five (ROF) and if a specific lead compound with a certain pharmacological and biological activity has chemical and physical properties would make it a likely orally active drug in humans. Lipinski’s rule of five suggests the molecular properties which are critical in order to understand the drug's pharmacokinetics in the human body for example absorption, distribution, metabolism, and excretion (ADME).

An ideal drug following Lipinski’s rule of five criteria are (i) molecular mass of a compound less than 500 Daltons, (ii) no more than 5 hydrogen bond donors, (iii) no more than 10 hydrogen bond acceptors, (iv) an octanol-water partition coefficient log P not greater than 5. Three or more than 3 violations of the Lipinski’s rule do not fit into the criteria of drug likeliness and ideally it is not generally considered for further drug discovery. However, it is very important to mention that Lipinski’s rule of five is not applicable to certain class of natural products and drugs which are substrates of biological transporters such as antibodies and proteins and antibodies and are successfully FDA approved and widely distributed in the market. Although in our study, all the four triarylchromones (TAC 3, 4, 6 and 7) are not following Lipinski’s rule of five. However, the selected compounds docked against main protease 6LU7 have been validated using molecular dynamics simulation studies and the results revealed that the selected lead compounds were identified as the most suitable target against SARS-CoV-2 main protease 6LU7. Therefore, this preliminary screening process of potential compounds would facilitate in providing the fast in silico analysis towards development of therapeutic agent against SARS-CoV-2 (COVID-19).

3.2. Molecular dynamics (MD) simulation

All four complexes (complex TAC-3, TAC-4, TAC-6, and TAC-7) were simulated for 100 ns and the final structure exhibited good stereochemical geometry of the residues as analyzed by Ramachandran map (Figure 7A–D). The proteins in all four complexes were stabled with only 1–3 residues in outlier region. Both complex TAC-3 and complex TAC-7 have only one residue (Asp33) in outlier region while complex TAC-4 and complex TAC-6 have 3 (Asp33, Asn84, Tyr154) and 2 (Asp33, Asn84), respectively. It was found that Asp33 is the most common residue lie in outlier region in all four complexes. These number of residues in favoured, additional allowed, generously allowed and outlier region along with their percentage given in Table 4.

The Ramachandran plot showed good stereochemical geometry of residues of protein for all four complexes.

Figure 10. Ligand RMSF: (A) complex TAC-3, (B) complex TAC-4, (C) complex TAC-6, and (D) complex TAC-7. The Y axis represents the RMSF values in molecular distance unit, i.e. Angstrom (Å) while the X axis indicates the specific position of the residue.
The binding free energy for these four docked complexes were also calculated by MMGBSA as given in Table 5 where compound in complex TAC-3 has lowest binding free energy of −78 kcal/mol among all compounds. This generalized Born model and solvent accessibility method of force field optimization to elicit free energies from structural information circumventing the computational complexity of free energy simulations. Molecular dynamics simulation study of all four complexes for 100 ns was done to analyze the stability of docked ligand within the binding pocket where ligand interacted with active domain of proteins through water bridges, hydrophobic interactions, salt bridge and H-bonds. The Cα RMSD is not deviated so much in all four complexes (Figure 8).

It suggests the structural stability of protein in all four complexes but ligand RMSD plot showed least deviation in ligand in complex TAC-3 as compare to other three complex TAC-4, 6, and 7 (Figure 9A–D). Ligand RMSD indicates how stable the ligand is with respect to the protein and its binding pocket. The plot (Figure 9A–D) show the RMSD of a ligand when the protein–ligand complex is first aligned on the protein backbone of the reference and then the RMSD of the ligand is measured. The similarly, ligand root mean square fluctuation (RMSF) is also least fluctuating for ligand within complex TAC-3 among all complexes (Figure 10A–D). It indicates conformational stability of compound in complex TAC-3. The RMSF is useful for characterizing local changes along...
the protein chain. TAC-3 showed less fluctuations than others, indicates that the ligand is stable in TAC-3 complex along the protein chain during simulation. The molecular dynamic study strongly validated the molecular docking data of protein ligand interaction for complex TAC-3 as compare to other complexes. It is very clear after trajectory analysis that ligand in complex TAC-3 is very stable than others. Figure 11A shows protein RMSF of ligand–protein complex interacting with binding site residues of protein where Thr25, Thr26, His41, Met49, Leu50, Phe140, Leu141, Asn142, Gly143, Ser144, Cys145, His163, His164, Met165, Glu166, Leu167, Pro168, His172, and Ala191 residues are interacting to compound shown by green lines matching the residue index, while the pink and blue bands indicate protein secondary structures helices and β-strands, respectively.

Figure 12. Complex TAC-4: (A) RMSF plot of residue number and C-alpha of spike protein at 100 ns simulation. It predicts the fluctuations of the C-alpha atoms; residues are shown in three letter code with their respective number in green colour belong to binding site residues interacting to compound shown in green line. (B) The histogram of protein–ligand contact over the course of the trajectory (C) A timeline representation of the interactions and contacts (salt bridge, hydrophobic, ionic, water bridges) with compound. The top panel shows the total number of specific contacts the protein–ligand complex in each trajectory frame. The bottom panel shows binding site residues interact with the ligand in each trajectory frame.
The type of interaction between compound and protein can be seen in Figure 11B where 3 kinds of interaction between ligand and protein such as H-bond (green), water bridge (blue), and hydrophobic interaction (grey) can be seen. There was no ionic interaction in complex. The bottom panel of Figure 11C shows the total number of contacts, the protein makes with the ligand over the course of the trajectory. While the bottom panel shows which residues interact with the ligand in each trajectory frame. Some residues make more than one specific contact with the ligand, which is represented by a darker shade of orange, according to the scale to the right of the plot. Even binding free energy after MD simulation was further calculated and found that ligand in TAC-3 has lowest binding energy over others (Table 4). Moreover, TAC-4 (Figure 12A–C), TAC-6

![Figure 13. Complex TAC-6: (A) RMSF plot of residue number and C-alpha of spike protein at 100 ns simulation. It predicts the fluctuations of the C-alpha atoms; residues are shown in three letter code with their respective number in green colour belong to binding site residues interacting to compound shown in green line. (B) The histogram of protein–ligand contact over the course of the trajectory (C) A timeline representation of the interactions and contacts (salt bridge, hydrophobic, ionic, water bridges) with compound. The top panel shows the total number of specific contacts the protein–ligand complex in each trajectory frame. The bottom panel shows binding site residues interact with the ligand in each trajectory frame.](image-url)
(Figure 13A–C) and TAC-7 (Figure 14A–C) also showed strong stability at the active site of the protein (main protease of SARS-CoV-2).

4. Conclusion

The identification of potent/effective molecules against infectious diseases including COVID-19 are always appreciable. As we already know by now, COVID-19 has hugely impacted the socio-economic status of the several countries across the world. In this situation, the identification of an effective and reliable drug molecule against COVID-19 targeting through main protease of SARS-CoV-2 will help us to develop potential therapeutic approach which could save millions of people globally. In this in silico study, we have identified triarylchromones (TAC) derivatives as potent inhibitors
against main protease of SARS-CoV-2 which can be further tested against the SARS-CoV-2 at in vitro and in vivo model for the development of therapeutic approach for COVID-19.

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Disclosure statement

The authors declare no conflict of interest.

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