Coronavirus Disease 2019 (COVID-19), a life-threatening viral disease, was discovered first in China and quickly spread throughout the world. According to the data from WHO, as of May 2020, more than 6 million people in the world were affected by COVID19, out of these, around 0.35 million people died. Most of the COVID-19 affected cases are asymptomatic, so it is worthy of consideration, to study the transmission of SARS-CoV, MERS-CoV, and SARS-CoV-2 and also the understanding of the pathogen inactivation methods on coronaviruses is very important [6-10]. The infected patients have severe acute respiratory syndrome by SARS CoV-2 and other symptoms including dry cough, fever, headache, dyspnea and pneumonia with an estimated mortality rate.

Coronavirus Disease 2019 (COVID-19), a life-threatening viral disease, was discovered first in Wuhan, China and quickly spread throughout the world [1-5]. According to the data from WHO, as of May 2020, more than 6 million people in the world were affected by COVID19, out of these, around 0.35 million people died. Most of the COVID-19 affected cases are asymptomatic, so it is worthy of consideration, to study the transmission of SARS-CoV, MERS-CoV, and SARS-CoV-2 and also the understanding of the pathogen inactivation methods on coronaviruses is very important [6-10]. SARS-CoV-2 is a positive-sense single-stranded RNA virus belonging to the β genus of the Coronaviridae family. The SARS-CoV-2 virion consists of at least four (4) structural proteins: Spike (S) protein, membrane (M) protein, envelope (E) protein. The target Main protease (Mpro) is responsible for cleavage of the viral poly-peptide into functional units; and RNA-dependent RNA polyme-rase (RdRp).

Currently, there is no confirmed treatment or vaccine prevention strategy against COVID-19. Due to the urgency of the situation, drug repurposing and identification of novel drugs are widely accepted as the fastest way to identify possible effective therapeutic options. Highly pathogenic coronavirus (SARS CoV-2) and its rapid international spread of disease will become a serious public health emergency [10-16]. The infected patients have severe acute respiratory syndrome by SARS CoV-2 and other symptoms including dry cough, fever, headache, dyspnea and pneumonia with an estimated mortality rate.

Acridine derivatives are mainly reported for various pharmacological activities like anticancer [17-22], antimicrobial [23-24], antioxidant [25-26], antimalarial [27], analgesic [28], antileishmanial [29], antinociceptive [30], acetyl cholinesterase inhibitors [31], antitherpes [32], etc. Anthracene, CK0402, and CK0403 belong to 9-anilinoacridine derivatives, which are DNA-intercalating agents. The modification of 9-anilinoacridines with various heterocyclic sub-
stitutions is permitted for the development of Structure Activity Relationship to afford molecular interactions at the receptor level [33-34]. Similarly, chalcone derivatives also reported for various biological activities [35-38] like antimicrobial, anti-cancer, larvicidal, etc. A previous study by our group reported [39-49] for the synthesis of a series of 9-anilinoacridine derivatives, we have designed some chalcone substituted 9-anilinoacridine analogues by docking studies with Schrödinger suite-2019. The research reveals that the recently designed 9-anilinoacridines (1a-z) showed significant hindrance with COVID19 against coronavirus disease.

2. MATERIALS AND METHODS

2.1. Protein Preparation

The 3D crystal structure of the COVID-19 protein called SARS-CoV-2 main protease receptor co-crystallized with 6-(ethylamino) pyridine-3-carbonitrile (PDB ID: 5R82, Resolution: 1.31 Å) was retrieved from the RSCB protein data bank. The epic module of Schrödinger suite 2019-4 was used to prepare the protein with protein preparation wizard. The protein structure is a monomer with similar binding sites and prepared by removing water, refining bond orders and the addition of hydrogens. Missing chain atoms are included by using the Prime module of Schrödinger suite 2019-4. Protein energy minimization was performed using OPLS3 (Optimized Potentials for Liquid Simulations) molecular force field with RMSD of crystallographic heavy atoms kept at 0.30 Å. A grid box was generated to define the centroid of the active site [50].

2.2. Ligand Preparation

The designed ligands (1a-z) were prepared by using the LigPrep module of Schrodinger suite 2019-4. The structures of designed ligands (1a-z) are shown in Fig. (1). 2D structures were converted to 3D structures, as well as energy minimization and optimized for their geometry, desalted and corrected for their chirality. The ionization and tautomeric states were generated between a pH of 6.8 to 7.2 by using the Epik module. The ligands 1a-z were minimized using Optimized Potentials for Liquid Simulations-3(OPLS-3) force field in Schrodinger suite 2019-4 until an RMSD of 2.0Å was achieved. A single low energy ring confirmation per ligand was generated and the optimized ligands were used for docking analysis.

2.3. MOLECULAR DOCKING STUDIES

All the compounds were docked into the catalytic pocket of COVID-19 by using the Glide module of Schrödinger suite 2019-4 in the XP (Extra precision) mode. The binding modes with significant glide G scores were selected [51-52]. The docking results were analysed by the XP visualizer mode of the Glide module. To predict the free energy of binding for the set of ligands in complex with receptor, post docking energy minimization studies were performed using Prime Molecular Mechanics-Generalized Born Surface Area (MM-GB/SA) of Schrödinger 2019-4. The energy for minimized XP docked pose of ligand receptor complex was calculated using the OPLS3 force field and generalized-Born/surface area (GB/SA) continuum VSGB 2.0 solvent model [53-54].

Fig. (1). Structures of Chalcone substituted 9-Anilinoacridines (1a-z).
3. RESULTS AND DISCUSSION

The results are summarized in Table 1. The best affinity modes of all the docked compounds with COVID-19 (PDB id: 5R82) are shown in Fig. (2). Almost all the compounds are docked in the same binding pocket.

The docking results of the compounds exhibited a similar mode of interactions with COVID-19 and the binding pocket of the residues between THR25 and GLN189. The 2D-ligand interaction diagrams of compounds 1x,a,r,s with COVID-19 (pdb id : 5R82) are shown in Figs. (3a-d). From (Fig. 3a), the amino acid residues THR25, THR26, SER46, HIE41, ASN142, HIE164, GLN189 are making polar region and the amino acids LEU27, MET49, MET169 are making hydrophobic interaction with the ligand. The amino acid HIE 41 is making Pi-Pi staking interaction with acridine moiety. The hydroxyl group is interacted by Hydrogen bonding with the water molecule. The Glide scores are mainly increased due to the lipophilic evidence of the aromatic moiety.

Table 1. Docking studies for Chalcone substituted 9-anilinoacridines with COVID-19 (5R82).

| Cpd | Glide Score | Lipo Philic EvdW | H Bond | XP Electro | Low MW | XP Penal | Rot. Penalties |
|-----|-------------|------------------|--------|------------|--------|---------|--------------|
| 1x  | -5.94       | -4.98            | -1.06  | -0.38      | 0      | 0       | 0.18         |
| 1a  | -5.73       | -5.86            | 0      | -0.06      | 0      | 0       | 0.15         |
| 1r  | -5.63       | -4.6             | 0      | -2         | -0.06  | 0       | 0.23         |
| 1s  | -5.6        | -6.08            | -0.67  | -0.21      | -0.01  | 0       | 0.22         |
| 1t  | -5.44       | -4.65            | -1.14  | -0.37      | 0      | 0       | 0.18         |
| 1h  | -5.31       | -6.05            | -0.48  | -0.17      | -0.07  | 0       | 0.23         |
| 1l  | -5.22       | -5.33            | -0.7   | -0.38      | -0.02  | 0       | 0.22         |
| 1e  | -5.03       | -4.98            | -0.41  | -0.1       | -0.12  | 0       | 0.25         |
| 1m  | -4.97       | -4.98            | -0.39  | -0.04      | -0.11  | 0       | 0.24         |
| 1z  | -4.91       | -5.71            | -0.13  | -0.1       | 0      | 0       | 0.18         |
| 1f  | -4.89       | -4.98            | -0.39  | -0.06      | -0.12  | 0       | 0.25         |
| 1d  | -4.87       | -4.93            | -0.33  | -0.09      | -0.12  | 0       | 0.25         |
| 1w  | -4.84       | -4.92            | -0.58  | -0.11      | 0      | 0       | 0.2          |
| 1q  | -4.75       | -5.04            | -0.22  | -0.07      | 0      | 0       | 0.16         |
| 1g  | -4.72       | -5.17            | -0.39  | -0.1       | -0.07  | 0       | 0.23         |
| 1k  | -4.7        | -4.83            | -0.27  | -0.07      | -0.11  | 0       | 0.19         |
| 1y  | -4.66       | -4.9             | -0.24  | -0.1       | 0      | 0       | 0.21         |
| 1u  | -4.65       | -5.71            | -0.14  | -0.17      | 0      | 0       | 0.18         |
| 1v  | -4.49       | -5.49            | -0.74  | -0.45      | 0      | 1       | 0.18         |
| 1i  | -4.39       | -5.75            | -0.17  | -0.11      | -0.07  | 0       | 0.23         |
| 1o  | -4.35       | -5.55            | 0      | 0.01       | -0.02  | 0       | 0.26         |
| 1n  | -4.32       | -5.58            | -0.12  | -0.07      | -0.07  | 0       | 0.23         |
| 1j  | -4.09       | -4.51            | 0      | -0.06      | -0.11  | 0       | 0.19         |
| 1p  | -3.7        | -4.59            | -0.35  | -0.08      | -0.02  | 0       | 0.26         |
| Hydroxy chloroquine(Std) | -5.47 | -3.15 | -1.75 | -0.69 | -0.38 | 0.5 | 0 |
Fig. (2). Docked poses of all compounds 1a-z with COVID-19 (5R82).

Fig. (3). a. Ligand Interaction of compound 1x with COVID-19 (5R82). b. Ligand Interaction of compound 1a with COVID-19 (5R82). c. Ligand Interaction of compound 1r with COVID-19 (5R82). d. Ligand Interaction of compound 1s with COVID-19 (5R82).
Fig. (4). Best affinity mode of docked compounds with COVID-19 (5R82).
From the docking study, it was revealed that some of the ligands have shown significant G score values from -5.3 Kcal/mol (compound 1h) to -5.94 Kcal/mol (compound 1x). From the binding modes obtained, it was illustrated that the ligands 1x,a,r,s,t,h showed good hydrophobic, hydrogen bonding and other interactions with different residues THR24 to GLN189 with the active pocket which is shown in Fig. (4). The G-score of the significantly active compounds is mainly due to the polar substitutions in the ortho position of the phenyl ring of chalcone. The compounds which contain a hydroxyl group mainly produce hydrogen bonding with amino acids and water molecules present in the receptor. For example, the ligand 1x exhibited hydrogen bonding interaction with water molecule 1407 and 1171 (H-Bond length 5.71 Å), as shown in Fig. (5). The lipophilic factors are mainly contributed towards G-score, (Fig. 6), because of the aromatic features of acridine rings and substituted phenyl ring of chalcone. The G-Score of the compounds 1a-z is diminished due to the rotational penalties and other penalties.

The ADMET properties for the chalcone substituted 9-anilinoacridines 1a-z can be determined through the in-silico method by using the qikprop module of Schrödinger suite 2016-2. The molecular weight of 1a-z is between 414 and 490 g.mol\(^{-1}\). Estimated no. of hydrogen bond donors of the compounds is in the range of 1-3. Estimated no. of hydrogen bonds acceptors of the compounds is in the range of 3.5-5.75. No. of likely metabolites of the compounds is in the range of 1-5. Prediction of binding to human serum albumin for the compounds is in the range of 0.78 - 1.5. No. of violations of Lipinski’s rule of five is 0-1. % Human oral absorption of the compounds is in the range of 92-100%. Thus,
### Table 2. *In-silico* ADMET screening for the proposed compounds (1a-z).

| Compounds | Mol. Wt. | Dipole | Donor HB | Acceptor HB | QPlog HERG | # metab | QPlog Khsa | Rule of Five | % Human Oral Absorption |
|-----------|---------|--------|----------|-------------|------------|--------|------------|--------------|-----------------------|
| 1a        | 479.375 | 2.234  | 1        | 3.5         | -8.037     | 2      | 1.353      | 1            | 100                   |
| 1b        | 479.375 | 2.162  | 1        | 3.5         | -8.1       | 1      | 1.372      | 1            | 100                   |
| 1c        | 479.375 | 1.656  | 1        | 3.5         | -8.059     | 1      | 1.371      | 1            | 100                   |
| 1d        | 414.506 | 0.418  | 1        | 3.5         | -7.984     | 3      | 1.367      | 1            | 100                   |
| 1e        | 414.506 | 0.862  | 1        | 3.5         | -8.029     | 3      | 1.39       | 1            | 100                   |
| 1f        | 414.506 | 1.232  | 1        | 3.5         | -8.035     | 3      | 1.391      | 1            | 100                   |
| 1g        | 430.505 | 1.917  | 1        | 4.25        | -8.096     | 3      | 1.247      | 1            | 100                   |
| 1h        | 430.505 | 1.453  | 1        | 4.25        | -8.025     | 2      | 1.231      | 1            | 100                   |
| 1i        | 430.505 | 1.989  | 1        | 4.25        | -8.032     | 3      | 1.235      | 1            | 100                   |
| 1j        | 418.469 | 2.728  | 1        | 3.5         | -8.034     | 2      | 1.258      | 1            | 100                   |
| 1k        | 418.469 | 2.003  | 1        | 3.5         | -8.007     | 1      | 1.269      | 1            | 100                   |
| 1l        | 445.476 | 6.759  | 1        | 4.5         | -8.097     | 2      | 1.166      | 1            | 92.83                 |
| 1m        | 416.478 | 1.523  | 2        | 4.25        | -7.998     | 2      | 1.005      | 1            | 100                   |
| 1n        | 428.532 | 1.196  | 1        | 3.5         | -8.109     | 3      | 1.511      | 1            | 100                   |
| 1o        | 444.532 | 1.889  | 1        | 4.25        | -8.276     | 3      | 1.392      | 1            | 100                   |
| 1p        | 444.532 | 2.132  | 1        | 4.25        | -8.328     | 3      | 1.391      | 1            | 100                   |
| 1q        | 469.369 | 2.916  | 1        | 3.5         | -7.87      | 2      | 1.454      | 1            | 100                   |
| 1r        | 432.478 | 2.39   | 3        | 5           | -7.863     | 4      | 0.78       | 0            | 100                   |
| 1s        | 446.504 | 3.43   | 2        | 5           | -7.904     | 4      | 1.021      | 1            | 100                   |
| 1t        | 495.374 | 3.394  | 2        | 4.25        | -7.908     | 3      | 1.122      | 1            | 100                   |
| 1u        | 495.374 | 0.265  | 2        | 4.25        | -7.923     | 3      | 1.137      | 1            | 100                   |
| 1v        | 495.374 | 1.752  | 2        | 4.25        | -7.922     | 3      | 1.137      | 1            | 100                   |
| 1w        | 460.531 | 0.66   | 1        | 5           | -7.989     | 4      | 1.252      | 1            | 100                   |
| 1x        | 485.368 | 2.231  | 2        | 4.25        | -7.824     | 3      | 1.226      | 1            | 100                   |
| 1y        | 448.951 | 2.011  | 1        | 3.5         | -7.88      | 3      | 1.489      | 1            | 100                   |
| 1z        | 490.557 | 4.052  | 1        | 5.75        | -7.779     | 5      | 1.214      | 1            | 100                   |

**Recommended values**: 130-725 1 - 12.5 0 - 6 2-20 -2-6.5 0-1.5 max 4 >80% is high <25% is poor.

**Abbreviations**: MW- Molecular weight of the molecule, Dipole - Dipole moment, donorHB - Estimated number of hydrogen bonds that would be donated by the solute to water molecules in an aqueous solution, acceptHB - Estimated number of hydrogen bonds that would be accepted by the solute from water molecules in an aqueous solution, QPlogPo/w - Predicted octanol/water partition coefficient, #metab- Number of likely metabolic reactions, QPlogKhsa- Prediction of binding to human serum albumin, Rule Of Five Number of violations of Lipinski’s rule of five, % Human Oral absorption- Predicted human oral absorption on 0 to 100% scale.

Almost all the ADMET properties of the compounds are within the recommended values. The results of the ADMET properties for the compounds 1a-z are shown in Table 2.

Molecular docking was additionally assessed with MM-GBSA free restricting vitality, which is identified with the post scoring approach for COVID-19 (PDB ID: 5R82) target and the values are shown in Table 3. From the results of MM-GB/SA studies, the dG bind values were observed in the range of -27.21 (1m) to -51.73 Kcal/mol (1s) and also dG Coulomb, dG vdw values, dG lipophilic values and the energies were positively contributing towards total binding energy. The accuracy of docking was confirmed by examining the lowest energy poses predicted by the scoring function. The Glide score and MM-GBSA free energy were obtained by the docking of ligands into the coupling pocket were more stable.

**CONCLUSION**

From the results of the docking study, the chalcone substituted 9-anilinoacridines like 1x,a,r,s demonstrated better arrangement at a dynamic site of the COVID-19 protein. The in-silico structuring strategy embraced in the present investigation helped for recognizing some lead molecules such as 1x,a,r,s and furthermore, may somewhat clarify their useful impact for further determinations like *in vitro* and *in vivo* assessments. Results from the in-silico study revealed that...
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Table 3. Binding free energy calculation using the Prime/MM-GBSA approach.

| Compd | MMGBSA_dG_Bind | MMGBSA_dG_Bind_Coulomb | MMGBSA_dG_Bind_Covalent | MMGBSA_dG_Bind_Hbond | MMGBSA_dG_Bind_Lipo | MMGBSA_dG_Bind_vdW |
|-------|----------------|-------------------------|--------------------------|----------------------|---------------------|---------------------|
| 1x    | -41.7118       | -19.8012                | 14.7544                  | -1.7465              | -13.4021            | -36.9959            |
| 1a    | -46.1948       | -1.9833                 | 0.8683                   | 0.2607               | -17.0654            | -48.8353            |
| 1r    | -37.7339       | -37.9524                | 17.2256                  | -1.2058              | -10.8127            | -35.1776            |
| 1s    | -51.7347       | -37.1426                | 16.7489                  | -0.6954              | -15.8816            | -40.3132            |
| 1t    | -44.2135       | -6.5753                 | 11.0821                  | 0.9335               | -17.6131            | -48.5997            |
| 1h    | -34.1986       | 13.06704                | -2.0889                  | 2.3342               | -18.1744            | -44.5451            |
| 1l    | -44.3474       | -4.8198                 | 8.8167                   | 0.8790               | -15.6018            | -50.0159            |
| 1e    | -50.088        | 9.3217                  | 5.2962                   | 1.1282               | -18.5420            | -47.8738            |
| 1m    | -27.2082       | -5.2366                 | -5.4233                  | 0.9976               | -9.1627             | -32.9882            |
| 1z    | -54.7570       | -14.8355                | -0.2392                  | 0.4727               | -16.6383            | -43.9280            |
| 1f    | -29.5722       | -15.2603                | 2.72677                  | 0.8809               | -9.5453             | -33.9117            |
| 1d    | -30.4468       | -3.1099                 | -3.5493                  | 1.4691               | -8.7914             | -34.2431            |
| 1w    | -45.3033       | -34.3787                | 7.7789                   | 0.1408               | -12.1577            | -34.8301            |
| 1q    | -40.9959       | -16.57348               | 13.203                   | 0.8163               | -16.8225            | -45.2267            |
| 1g    | -41.9792       | -7.8755                 | 3.7845                   | 1.0351               | -15.6967            | -45.0998            |
| 1k    | -40.5187       | 2.2724                  | 3.1117                   | -0.0513              | -11.5765            | -35.3478            |
| 1y    | -37.2317       | -10.5121                | 2.2761                   | -0.8012              | -9.3400             | -33.9486            |
| 1u    | -48.3246       | -25.7633                | 10.7455                  | 0.8694               | -14.5589            | -45.8813            |
| 1v    | -48.8581       | 3.4566                  | 2.7829                   | 1.357                | -15.8008            | -53.5403            |
| 1i    | -39.0579       | -6.8311                 | 6.9959                   | 2.0103               | -16.4265            | -46.2939            |
| 1o    | -36.6079       | -0.2583                 | -2.1928                  | 2.48533              | -15.7793            | -41.6399            |
| 1n    | -50.4160       | -20.5983                | 16.0928                  | -0.7659              | -18.7972            | -44.9817            |
| 1j    | -30.4440       | 2.7013                  | 1.6967                   | 1.6586               | -12.9087            | -38.8273            |
| 1p    | -42.7862       | -3.67424                | 8.3296                   | 0.9366               | -17.5742            | -47.1647            |
| Hydroxy Chloroquine (std) | -26.9975 | -4.9621 | 2.1824 | 0.0011 | -9.2894 | -33.0622 |

many of the chalcone substituted 9-anilinoacridines like 1x, a, r, s may be useful against COVID-19 and are probably going to be helpful after further refinement.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are basis of this research.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

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