Activity of Thiazine substituted 9-anilinoacridines against Corona virus (COVID19): An In-silico approach

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**ABSTRACT**
Coronavirus Disease 2019 (COVID-19), a life-threatening viral disease affected first in Wuhan, China, and quickly spread to more than 200 countries in the world in the year 2020. So many scientists are trying to discover novel drugs and vaccines for coronavirus and treatment for COVID-19. In the present article, in-silico studies have been performed to explore the binding modes of Thiazine substituted 9-anilinoacridines (1a-z) against SARS CoV 2 main protease (PDB id - 5R82) targeting the coronavirus using Schrodinger suit 2019-4. The molecular docking studies are performed by Glide module, in-silico ADMET screening was performed by Qik prop module, and the binding free energy of ligands was calculated using PRIME MM-GB/SA module of Schrodinger suite 2019-4, Maestro 21.2 version. From the in-silico results, Thiazine substituted 9-anilinoacridines like 1m, 1j, 1s and 1b are significantly active against SARS CoV 2 main protease with Glide score more than -5.4 when compared with the currently recommended drug for COVID19, Hydroxychloroquine (G score -5.47). The docking results of the Thiazine substituted 9-anilinoacridines exhibited similar mode of interactions with COVID19 and the residues GLN19, THR24, THR25, THR26, LEU27, HIE41, SER46, MET49, ASN142, GLN143, HIE164, MET165, ASP187, ARG188 and GLN189, play a crucial role in binding with ligands.

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**INTRODUCTION**
The coronavirus Disease 2019 (COVID-19), a life-threatening viral disease, (Huang et al., 2020; Gu et al., 2020) which affected first in Wuhan, China and spread throughout the world (Holshue et al., 2020; To et al., 2020). According to the data from WHO, as on June 2nd week of 2020, more than 76 lakh people in the world affected by COVID19, out of these more than 4.3 lakhs peoples have died (Lu et al., 2020; Zhou et al., 2020). With more asymptomatic infections being found among COVID-19 cases (Zhou et al., 2020; Huang and Herrmann, 2020), with the details and understanding of the transmission of SARS-CoV, MERS-CoV, and SARS-CoV-2 and discussion of the pathogen inactivation methods are essential (Zhang et al., 2020).

In this emergency, it is necessary to discover novel drugs for the treatment of COVID19 (Chang et al., 2020; Huang et al., 2020) 9-Anilinoacridines have been reported for different pharmacological activities like anti-cancer, (Kapuria et al., 2008; Kallion-
Table 1: Docking studies for Thiazine substituted 9-anilinoacridines (1a-z) with COVID19 (5R82)

| Cpd | Glide score | Lipo philic | EvdW | H Bond | XP Electro | Low MW | Rot Penal | XP Penalties |
|-----|-------------|-------------|------|--------|------------|--------|-----------|--------------|
| 1m  | -6.98       | -6.04       | -1.2 | -0.52  | 0          | 0.15   | 0         |              |
| 1j  | -5.52       | -5.84       | 0    | -0.1   | 0          | 0.15   | 0         |              |
| 1s  | -5.46       | -5.38       | -0.8 | -0.12  | 0          | 0.14   | 0         |              |
| 1b  | -5.43       | -5.09       | -0.7 | -0.22  | 0          | 0.12   | 0         |              |
| 1w  | -5.16       | -5.86       | 0    | 0.05   | 0          | 0.13   | 0         |              |
| 1v  | -5.03       | -4.97       | -0.46| -0.18  | 0          | 0.09   | 0         |              |
| 1h  | -5.03       | -5.61       | -0.36| -0.1   | 0          | 0.15   | 0         |              |
| 1o  | -4.98       | -5.23       | -0.34| -0.01  | 0          | 0.17   | 0         |              |
| 1t  | -4.97       | -5.05       | -0.18| 0.02   | 0          | 0.09   | 0         |              |
| 1l  | -4.94       | -5.82       | 0    | -0.12  | 0          | 0.14   | 0         |              |
| 1q  | -4.91       | -4.99       | -0.1 | -0.08  | 0          | 0.13   | 0         |              |
| 1g  | -4.9        | -5.22       | -0.12| -0.02  | 0          | 0.15   | 0         |              |
| 1r  | -4.86       | -4.82       | -0.64| -0.17  | 0          | 0.14   | 0         |              |
| 1d  | -4.66       | -4.97       | -0.06| 0.06   | 0          | 0.16   | 0         |              |
| 1u  | -4.6        | -5.23       | 0    | 0.02   | 0          | 0.09   | 0         |              |
| 1y  | -4.6        | -5.45       | 0    | 0.01   | 0          | 0.14   | 0         |              |
| 1z  | -4.48       | -5.15       | 0    | 0      | 0          | 0.12   | 0         |              |
| 1e  | -4.47       | -5.56       | -0.1 | -0.04  | 0          | 0.16   | 0         |              |
| 1a  | -4.38       | -4.81       | 0    | -0.02  | 0          | 0.12   | 0         |              |
| 1p  | -4.3        | -5.26       | -0.04| -0.04  | 0          | 0.17   | 0         |              |
| 1c  | -4.3        | -4.85       | -0.18| -0.05  | 0          | 0.12   | 0         |              |
| 1i  | -4.06       | -5.14       | 0    | 0.05   | 0          | 0.15   | 0         |              |
| 1x  | -4.02       | -5.26       | -0.7 | -0.19  | 0          | 0.12   | 0         |              |
| 1k  | -4.02       | -5.2        | 0    | -0.01  | 0          | 0.15   | 0         |              |
| 1n  | -3.76       | -5.18       | -0.02| 0.03   | 0          | 0.15   | 0         |              |
| 1f  | -3.03       | -5          | 0    | 0.12   | 0          | 0.16   | 0         |              |
| Hydroxy | -5.47      | -3.15      | -1.75| -0.69  | -0.38      | 0.5    | 0         |              |

chloroquine (Std)

iemi et al., 1992)
cytotoxic (Wakelin et al., 2003; Kalirajan et al., 2012b), antimicrobial (Nadaraj et al., 2009; Kalirajan et al., 2013), antioxidant (Dickens et al., 2002; Kalirajan et al., 2012b), antimalarial (Anderson et al., 2006), analgesic (Sondhi et al., 2003), antileishmanial (Giorgio et al., 2007), antinociceptive (Llama et al., 1989), acetylcholinesterase inhibitors (Recanatini et al., 2000), larvicidal (Kalirajan et al., 2018b) and antiperhes (Goodell et al., 2006) and so forth.

As a part of our ongoing research (Kalirajan et al., 2011, 2019b) on searching the potent biological molecules against various disease by in-silico (Kalirajan et al., 2017a,b) and wet lab methods Kalirajan et al. (2018a) we have designed some thiazine substituted 9-anilinoacridines (1a-z) against COVID19 (PDB id - 5R82) targeting corona virus using Schrodinger suit 2019-4.

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Figure 1: Chemical structures of Thiazone substituted 9-Anilinoacridines (1a-z)

Figure 2: a - Ligand Interaction of compound 1m with COVID19 (5R82)
b - Ligand Interaction of compound 1j with COVID19 (5R82)
c - Ligand Interaction of compound 1s with COVID19 (5R82)
Table 2: Binding free energy calculation using Prime/MM-GBSA approach

| Compd | dG_Bind | dG_Bind_Coul | dG_Bind_Covalent | dG_Bind_Hbond | dG_Bind_Lipo | dG_Bind_vdW |
|-------|---------|--------------|------------------|---------------|--------------|-------------|
| 1m    | -53.748 | -13.491      | 10.674           | -0.537        | -14.254      | -52.978     |
| 1j    | -47.402 | 1.407        | 3.661            | 1.165         | -13.735      | -56.119     |
| 1s    | -42.170 | 0.679        | 4.804            | 0.408         | -18.541      | -44.855     |
| 1b    | -45.420 | -15.011      | 10.787           | -0.213        | -13.296      | -49.453     |
| 1w    | -44.764 | -2.035       | 1.950            | 2.301         | -16.949      | -52.925     |
| 1v    | -35.345 | -1.584       | 5.497            | 2.100         | -16.438      | -47.083     |
| 1h    | -32.300 | -11.646      | 4.358            | 0.998         | -11.293      | -39.045     |
| 1o    | -27.307 | 6.631        | -7.434           | 2.570         | -11.115      | -43.607     |
| 1t    | -30.589 | 14.031       | -14.378          | 2.461         | -12.713      | -32.359     |
| 1l    | -35.268 | 1.658        | 6.696            | 1.487         | -11.679      | -52.211     |
| 1q    | -31.697 | -16.280      | 4.903            | 0.754         | -13.020      | -37.970     |
| 1g    | -38.980 | -11.544      | 7.913            | 0.659         | -16.233      | -37.431     |
| 1r    | -42.200 | -14.282      | 9.414            | -0.163        | -11.465      | -43.895     |
| 1d    | -33.751 | -9.150       | -5.515           | -0.073        | -8.890       | -34.000     |
| 1u    | -45.388 | -52.323      | 26.903           | -3.544        | -13.946      | -36.914     |
| 1y    | -34.552 | -12.709      | 7.014            | 2.454         | -13.604      | -42.879     |
| 1z    | -41.203 | -8.743       | 10.568           | -0.798        | -16.668      | -43.664     |
| 1e    | -39.409 | -19.185      | 16.716           | 0.693         | -16.006      | -44.954     |
| 1a    | -38.677 | -1.296       | -3.339           | 0.937         | -13.988      | -30.244     |
| 1p    | -52.406 | -28.164      | 24.438           | -1.368        | -19.097      | -53.467     |
| 1c    | -36.992 | -27.370      | 15.020           | 0.176         | -12.909      | -35.820     |
| 1i    | -40.220 | 0.899        | 12.049           | 0.820         | -17.247      | -48.203     |
| 1x    | -29.629 | 10.978       | 0.488            | 2.043         | -16.807      | -41.131     |
| 1k    | -35.141 | 10.209       | 2.636            | 2.205         | -15.882      | -50.573     |
| 1n    | -36.914 | -11.776      | 14.060           | 0.840         | -16.859      | -50.915     |
| 1f    | -18.412 | -2.023       | 4.925            | 0.806         | -12.368      | -40.325     |
| Hydroxy | -26.997 | -4.962       | 2.182            | 0.0111        | -9.289       | -33.062     |

chloroquine (Std)

Using different modules (Glide, Qikprop and Prime) of Schrödinger suite LLC various computational methods like molecular docking, ADMET screening and binding free energy calculations were performed to find the interactions responsible for COVID19 inhibition. The outcomes of the research that the recently designed Thiazine substituted 9-anilinoacridines showed significant hindrance with COVID19. These studies will provide the requirement of critical structural features in the design of potential drug candidates against COVID19.

MATERIALS AND METHODS

The 3D crystal structure of COVID19 protein called SARS-CoV-2 primary 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 protein was prepared using the protein preparation wizard of an epic module (Sastry et al., 2013) of Schrödinger suite 2019-4. The protein structure is a monomer, having similar binding sites were removed with deleting waters, refining bond orders and addition of hydrogens. Missing chain atoms are included by (Jacobson et al., 2004) using 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.

All the compounds were docked into catalytic pocket
of COVID19 by using Glide module of Schrödinger suite 2019-4 in XP (Extra precision) mode (Friesner et al., 2006; Kalirajan et al., 2012a). The binding methods with best glide G score were selected. To predict the free energy of binding for the set of ligands in complex with receptor a post docking energy minimization study was performed using Prime Molecular Mechanics-Generalized Born Surface Area (MM-GB/SA) of Schrödinger 2019-4. The energy for minimized XP docked pose of the ligand-receptor complex was calculated using the OPLS3 force field and generalized-Born/surface area (GB/SA) continuum VSGB 2.0 solvent model (Li et al., 2011).

RESULTS AND DISCUSSION

Results are summarized in Tables 1 and 2 and Figures 1, 2, 3, 4 and 5. The results revealed that the
COVID19 inhibitory property of the compounds 1a-x. The Chemical-structures of thiazine substituted 9-anilinoacridines (1a-x) are given in Figure 1.

The docking studies of the ligands to COVID19 protein active sites were performed by an advanced molecular docking program Glide module of Schrodinger suite 2019 Maestro-12.2 version for determining the binding affinities of the compounds. The designed analogues were docked towards the COVID19 (PDB id: 5R82) to ascertain their inhibitory activity. The analogues show the best-fit Root Mean Square Difference (RMS) value of 0.18.

As shown in Table 1, it is demonstrated that thiazine substituted 9-anilinoacridines like 1m, j, s, b are significantly active against COVID19 with Glide score more than -5.4 when compared with the currently recommended drug for COVID19 Hydroxychloroquine (G score -5.47). The above compounds have good affinity to the receptor due to more lipophilic character and also due to hydrogen bonding interactions.

The ADMET screening for the molecules can be predicted in-silico by using qikprop module of Schrödinger suite 2019-4. From the in-silico, ADMET screening results of all the compounds are within the recommended values.

Molecular docking was additionally assessed with MM-GBSA free restricting vitality which is identified with the post scoring approach for COVID19 (PDB ID: 5R82) target. From the results of MM-GB/SA studies Table 2 the dG bind values were observed in the range of -22.90 (1h) to -56.797 Kcal/mol (1n) and also dG Coulomb, dG vdw values, dG lipophilic values and the energies are positively contributing towards total binding energy.

The accuracy of docking is confirmed by examining the lowest energy poses predicted by the scoring function. The docking of ligands obtains the Glide score, and MM-GBSA free energy into the coupling pocket is more stable.

CONCLUSIONS

From the results of docking study that the Thiazine substituted 9-anilinoacridines like 1m, j, s, b demonstrated better arrangement at a dynamic site of the COVID19 protein. The in-silico structuring strategy embraced in the present investigation helped for recognizing some lead molecules such as 1m, j, s, b and furthermore may somewhat clarify their beneficial impact for the further determinations like in vitro and in vivo assessments.

Results from the in-silico study revealed that many of the Thiazine substituted 9-anilinoacridines like
1m, j, s, may be useful against COVID19 and are probably going to be helpful after further refinement.

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Conflict of Interest

Nil.

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