



## 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 2<sup>nd</sup> 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 activi

**Table 1: Docking studies for Thiazine substituted 9-anilinoacridines (1a-z) with COVID19 (5R82)**

Cpd	Glide score	Lipo EvdW	philic	H Bond	XP Electro	Low MW	Rot Penal	XP Penal- ties
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)								

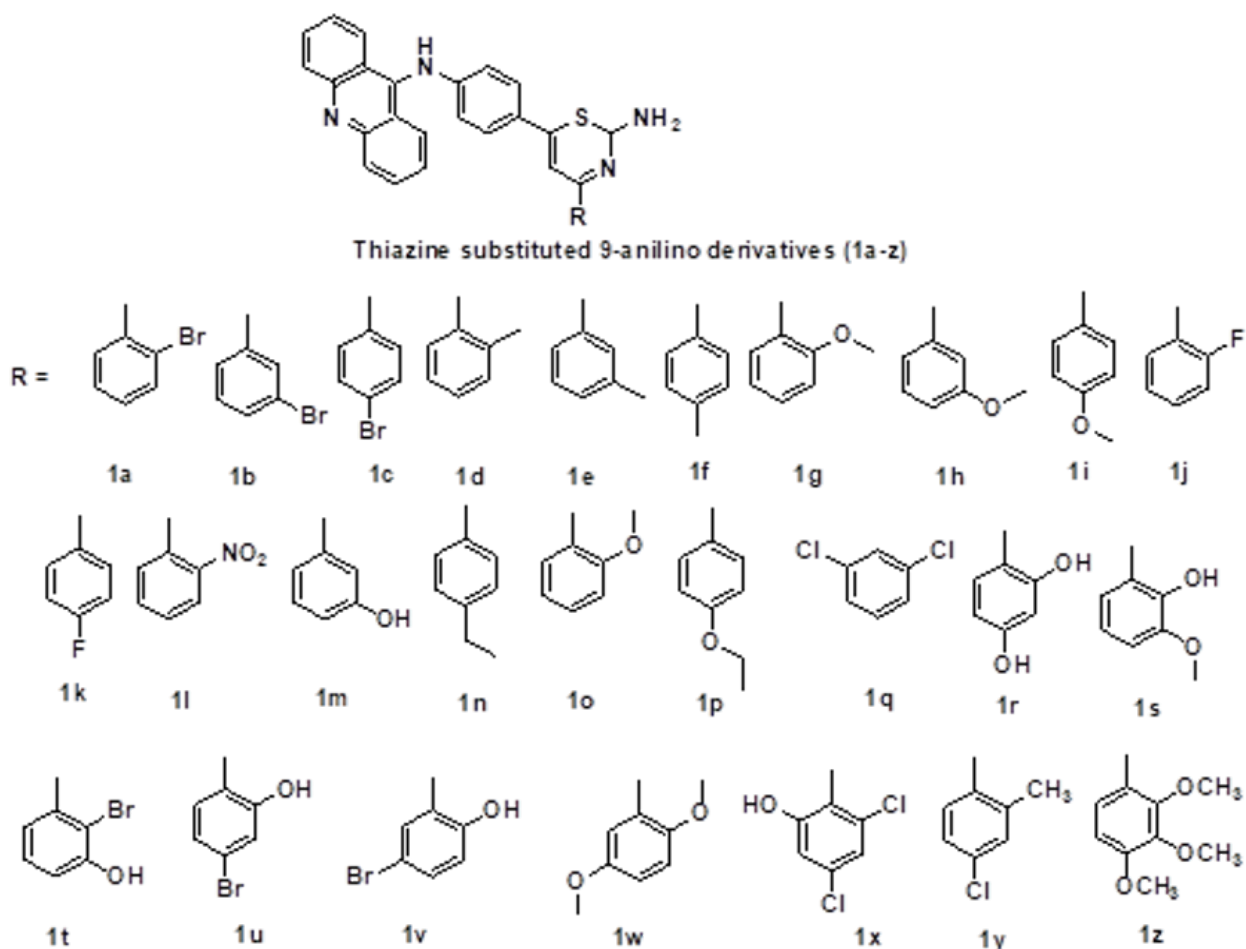
ties like anti-cancer, (Kapuriya *et al.*, 2008; Kallioniemi *et al.*, 1992).

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 antiherpes (Goodell *et al.*, 2006) and so forth.

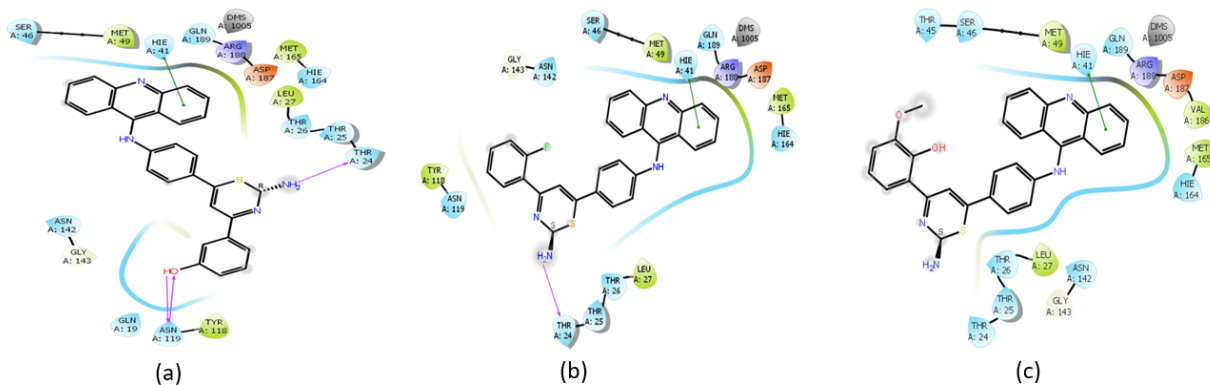
Amsacrine which is a 9-anilinoacridine derivative with primary DNA-inter collating agent, which is more significant and the chromophore intercalates

with DNA base pairs (Rastogi *et al.*, 2002; Kalirajan *et al.*, 2012a). Likewise, thiazine derivatives also reported for various biological activities (Sondhi *et al.*, 2005; Plouvier *et al.*, 1994) like antimicrobial (Kalirajan *et al.*, 2009), anti-cancer (Kalirajan *et al.*, 2019a) analgesic, anti-inflammatory (Sondhi *et al.*, 2005), antimycobacterial (Indumathi *et al.*, 2009)etc.

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.



**Figure 1: Chemical structures of Thiazine 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_Covalen	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	0.0011	-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

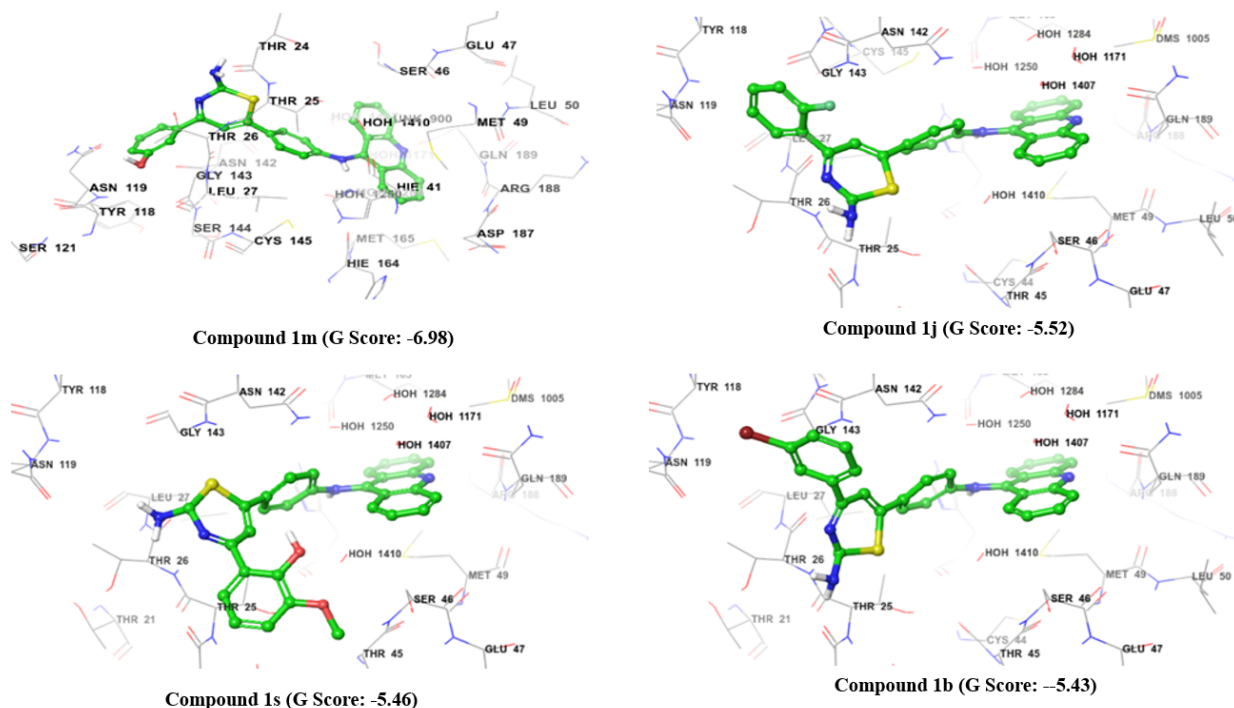


Figure 3: Best affinity mode of docked compounds with COVID19 (5R82)

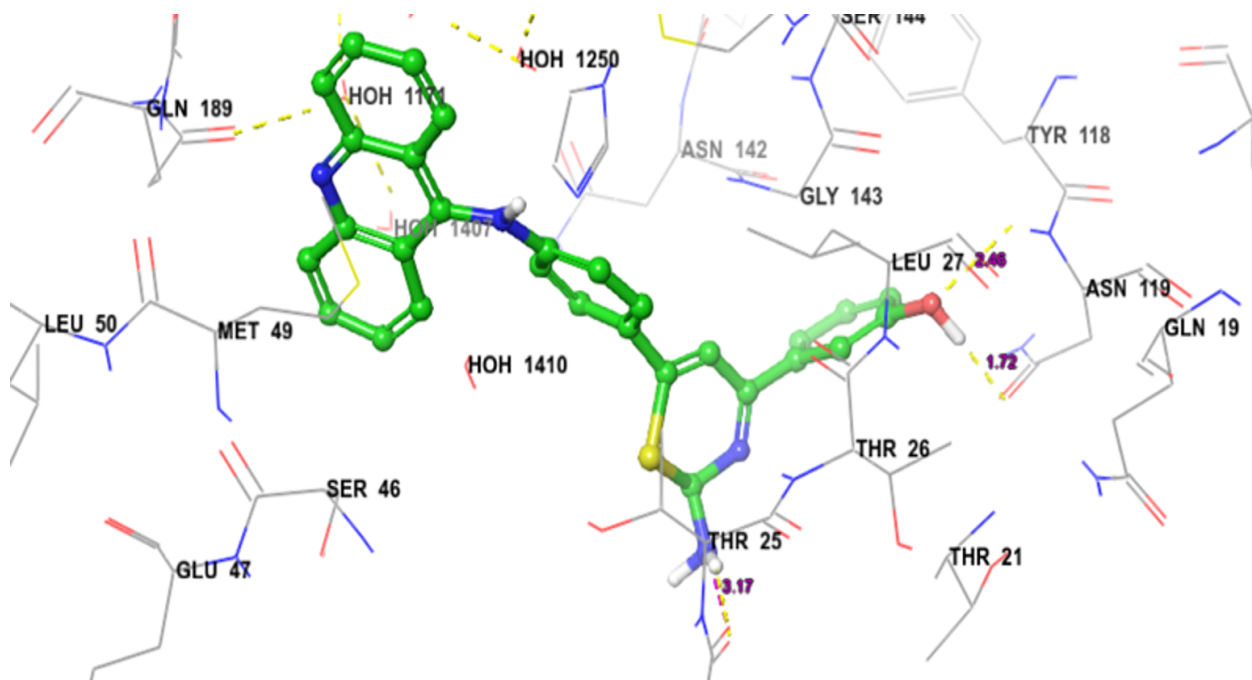


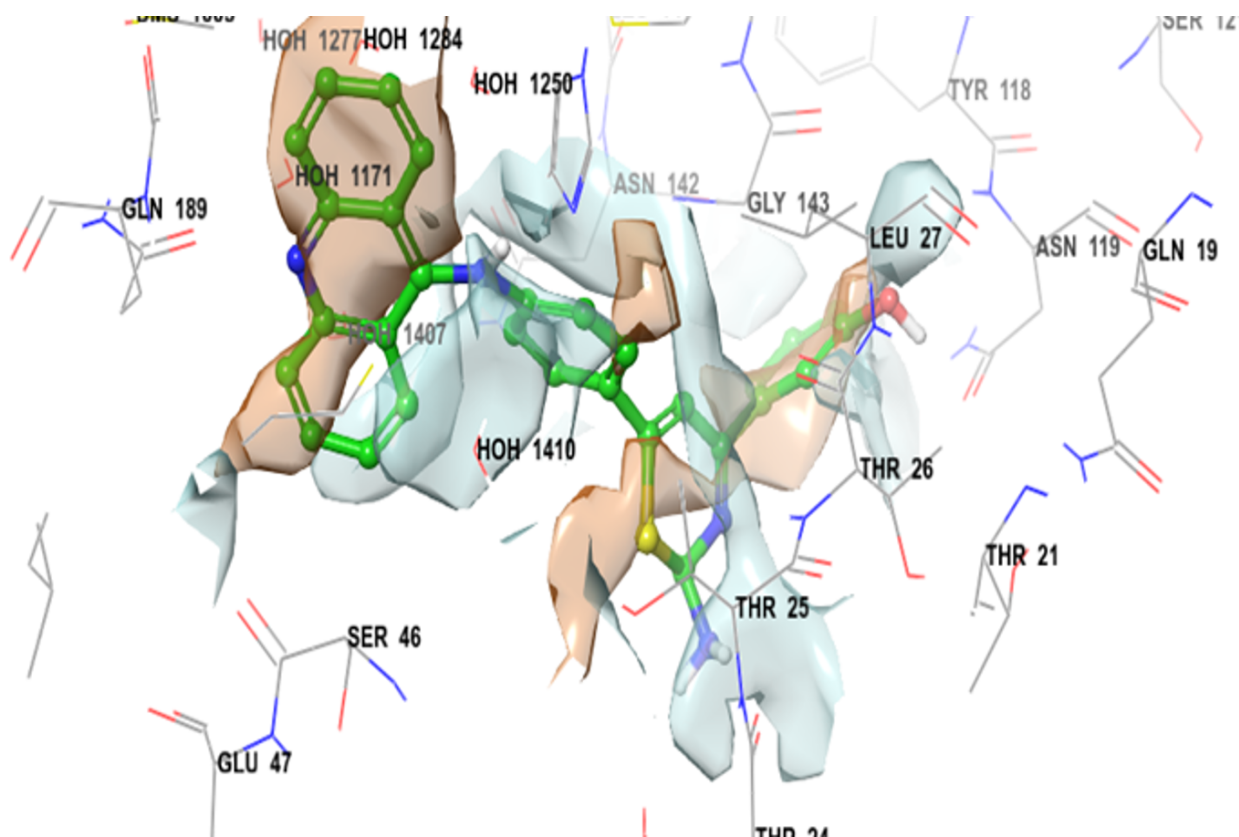
Figure 4: Hydrogen bonding interaction of compound 1m with COVID19 (5R82)

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



**Figure 5: 5Hydrophilic/lipophilic map of compound 1m with COVID19 (5R82)**

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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Nil.

#### Conflict of Interest

Nil.

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