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Activity of Isoxazole substituted 9-aminoacridines against SARS CoV-2 main protease for COVID19: A computational approach

Kalirajan Rajagopal[1 *], Gowramma Byran[1], Gomathi Swaminathan[1], Vadivelan Ramachandran[1]

[1.]Department of Pharmaceutical Chemistry, Department of Pharmacology, JSS College of Pharmacy, (JSS Academy of higher education and Research- Deemed University), The Nilgiris (Tamilnadu), India.

ABSTRACT

Coronavirus Disease 2019 (COVID-19), a life-threatening viral disease affected first in china and quickly spread throughout the world in early 2020. So many scientists are rushing to discover novel drugs and vaccines against the coronavirus, and treatments for COVID-19.In the present article, i*n-silico* studies have been performed to explore the binding modes of Isoxazole substituted 9-aminoacridines(**1a-x**) against SARS CoV-2 main protease (PDB id - 5R82) targeting corona virus using Schrodinger suit 2019-4. The docking studies are performed by Glide module, in-silico ADMET screening was performed by qik prop module and the binding energy of ligands was calculated using PRIME MM-GB/SA module. From the results, Isoxazole substituted 9-aminoacridines like **1n,f,c,k,h,a,e,g,b,d** are significantly active against SARS CoV-2 main protease with Glide score more than -5.5 when compared with currently recommended drug for COVID19 Hydroxy chloroquine (G score -5.47) and Co crystallized ligand CID_24701445 (G score -4.4). The docking results of the compounds exhibited similar mode of interactions with COVID19 and the residues THR24, THR25, THR26, SER46, MET49, HIE41, GLN189, ARG189, ASP187, MET168, HIE164, ASN142 and GLY143 play a crucial role in binding with ligands.

Keywords: SARS CoV-2 main protease, COVID19, Acridine, Isoxazole, Docking studies, *In-silico* ADMET, MMGBSA.

1. INTRODUCTION

Coronavirus Disease 2019 (COVID-19), a life-threatening viral disease which was affected first in Wuhan, china and quickly spread throughout the world[1-5]. According to the data from WHO, as on July 2020, more than 16.5 million peoples in the world affected by COVID19, out of these more than 655,000 peoples are died. With more asymptomatic infections being found among COVID-19 cases, it is worthy of consideration, the detail current evidence and understanding of the transmission of SARS-CoV, MERS-CoV, and SARS-CoV-2 and discuss pathogen inactivation methods on coronaviruses is very important[6-10]. In this emergency situation, it is very important to discover novel drugs for the treatment of COVID19.

9-substituted acridines have reported for different pharmacological activities like anticancer[11-13], antimicrobial[14], antioxidant[15], antimalarial[16], analgesic[17], antileishmanial[18], antinociceptive[19], acetyl cholinesterase inhibitors[20] and antiherpes[21] and so forth. Amsacrine which is 9-anilinoacridine derivative was primary DNA-intercalating agent which is more significant and the chromophore intercalates with DNA base pairs[22]. Likewise, isoxazole derivatives also reported for various biological activities[23-28] like antimicrobial, anti-cancer etc.

As a part of our ongoing research on searching the

[*] ***Corresponding author: Kalirajan Rajagopal***
rkalirajan@ymail.com , rkalirajan@jssuni.edu.in
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potent biological molecules against various disease by in-silico and wet lab methods[29-39], we have designed some isoxazole substituted 9-aminoacridines (**1a-x**) against SARS CoV-2 main protease (PDB id - 5R82) targeting corona virus using Schrodinger suit 2019-4. 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 SARS CoV-2 main protease inhibition. The outcomes of the research that the recently designed isoxazole substituted 9-aminoacridines showed significant hindrance with COVID19. These studies will provide the requirement of key structural features in the design of potential drug candidates against COVID19.

2. Materials and Methods

The 3D crystal structure of COVID19 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[40]. The protein was prepared using protein preparation wizard of epic module[41] of Schrödinger suite 2019-4. The protein structure is a monomer, having similar binding sites were removed by deleting waters, refining bond orders and addition of hydrogens. Missing chains and loops are included by[42] using Prime module of Schrödinger suite 2019-4. Protein energy was minimized by 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 in to the binding pocket of SARS CoV-2 main protease by using Glide module of Schrödinger suite 2019-4 in XP (Extra precision) mode[43]. To predict the free energy of binding for the ligands in complex with receptor by 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[44].

3. Results and discussion

Results are summarized in Table 1-3 and Figure 1-5. The results revealed that the COVID19 inhibitory property of the compounds 1a-x. The Chemical-structures of isoxazole substituted 9-aminoacridines(1a-x) are given in the figure 1.

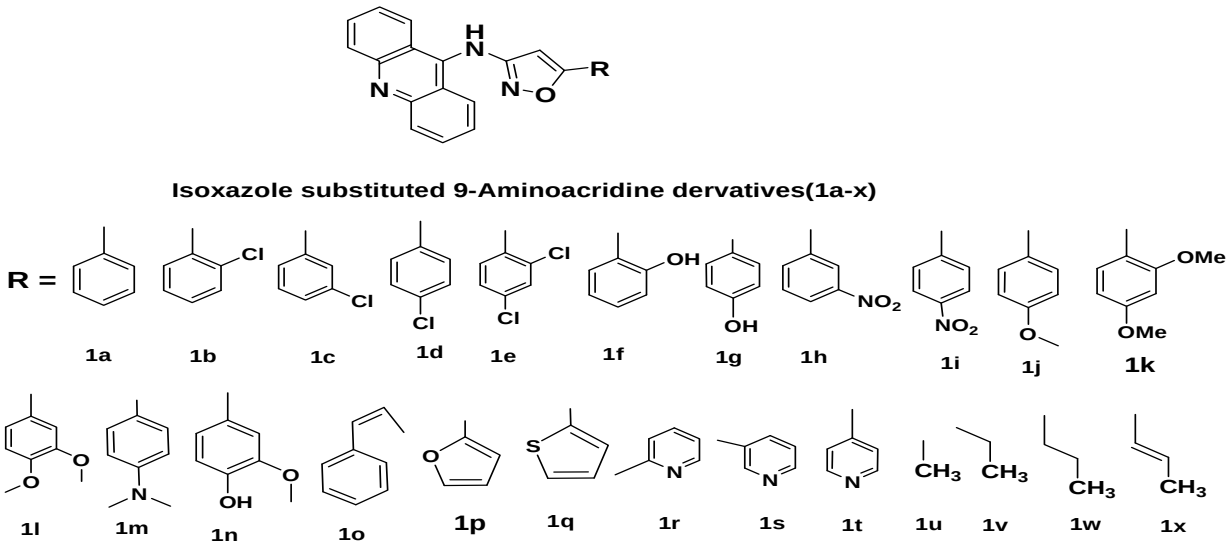

Fig.1. Chemical structures of isoxazole substituted 9-aminoacridines(1a-x)

The docking studies of the ligands to COVID19 protein active sites were performed by the 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) in order to ascertain their inhibitory activity. The analogues show best fit Root Mean Square Difference (rmsd) value of 0.18. As shown in Table 1, it is clearly demonstrated that Isoxazole substituted 9-aminoacridines like **1n,f,c,k,h,a,e,g,b,d** are significantly active against COVID19 with Glide score more than **-5.5** when compared with currently recommended drug for COVID19 Hydroxy chloroquine (G score -5.47) and co-crystallized ligand (G score -4.4). The above compounds have good affinity to the receptor due to more lipophilic character and also due to hydrogen bonding interactions.

The validation of docking studies are performed by redocking of co-crystallized ligand and compounds. All the ligands are binding in the same active site with same orientation.

The results were summarized in the table **1**. The best affinity modes of all the docked compounds with COVID19 (PDB id: 5R82) were shown in figure **2**. Almost all the compounds are docked in the same binding pocket.

The docking results of the compounds exhibited similar mode of interactions with COVID19 and the residues THR24, THR25, THR26, SER46, MET49, HIE41, GLN189, ARG189, ASP187, MET168, HIE164, ASN142 and GLY143 play a crucial role in binding with ligands.The 2D-ligand interaction diagram of compounds **1n,f,c,k** are given in the figures **3a-d.**

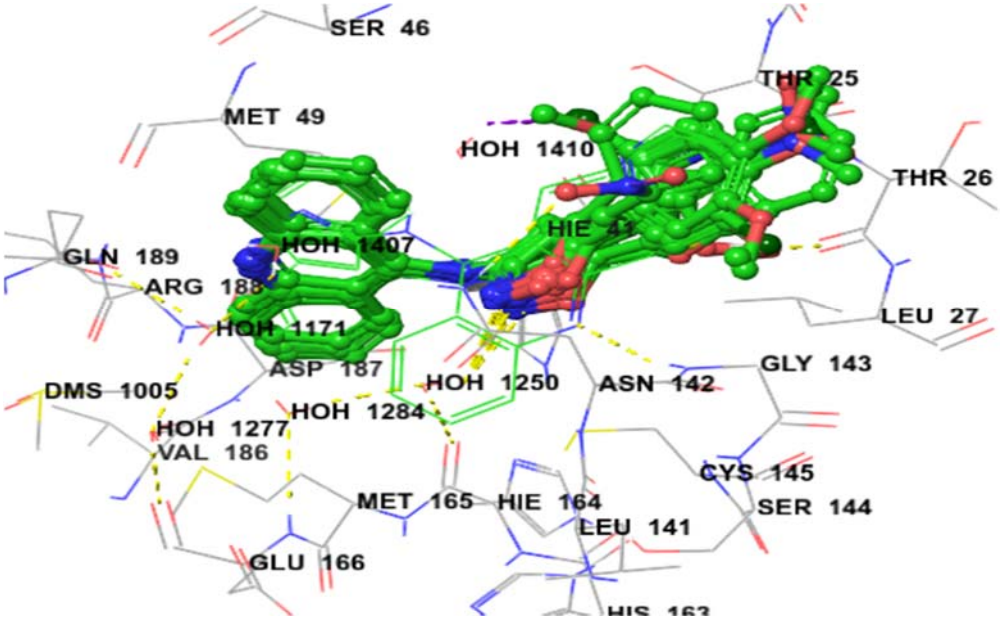

Fig.2.Docked poses of all compounds 1a-x with COVID19 (5R82)

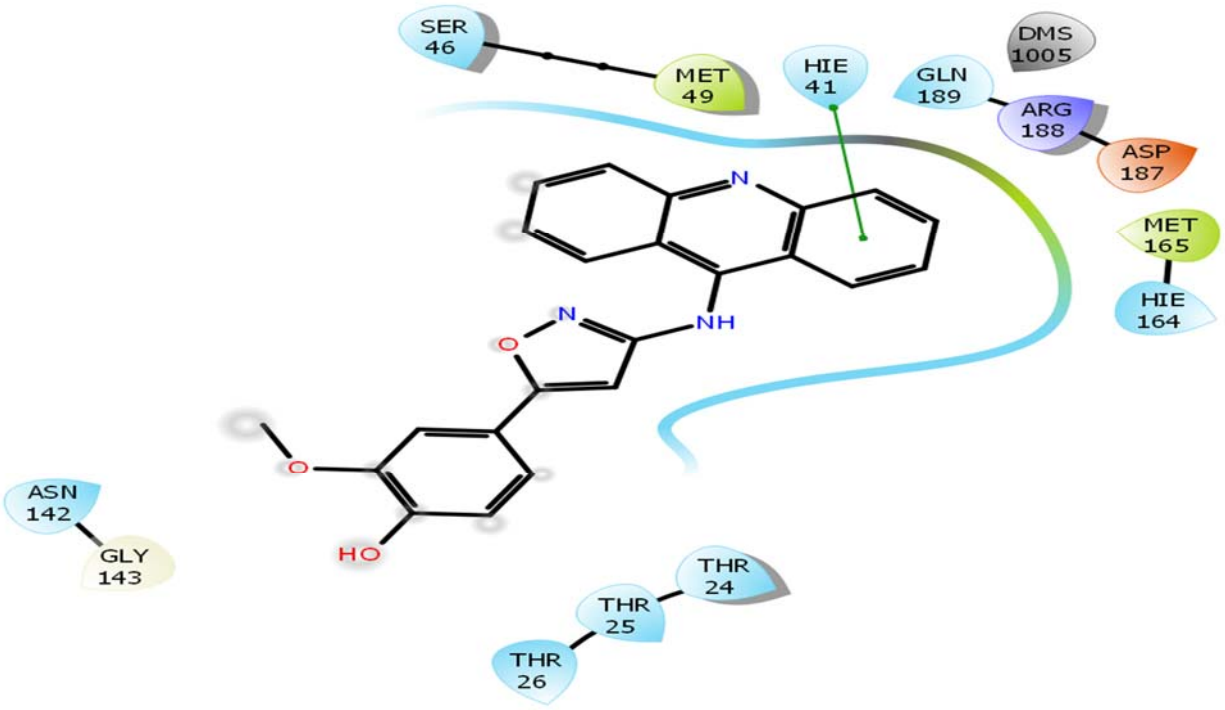

Fig.3.A. Ligand Interaction of compound 1n with COVID19 (5R82)

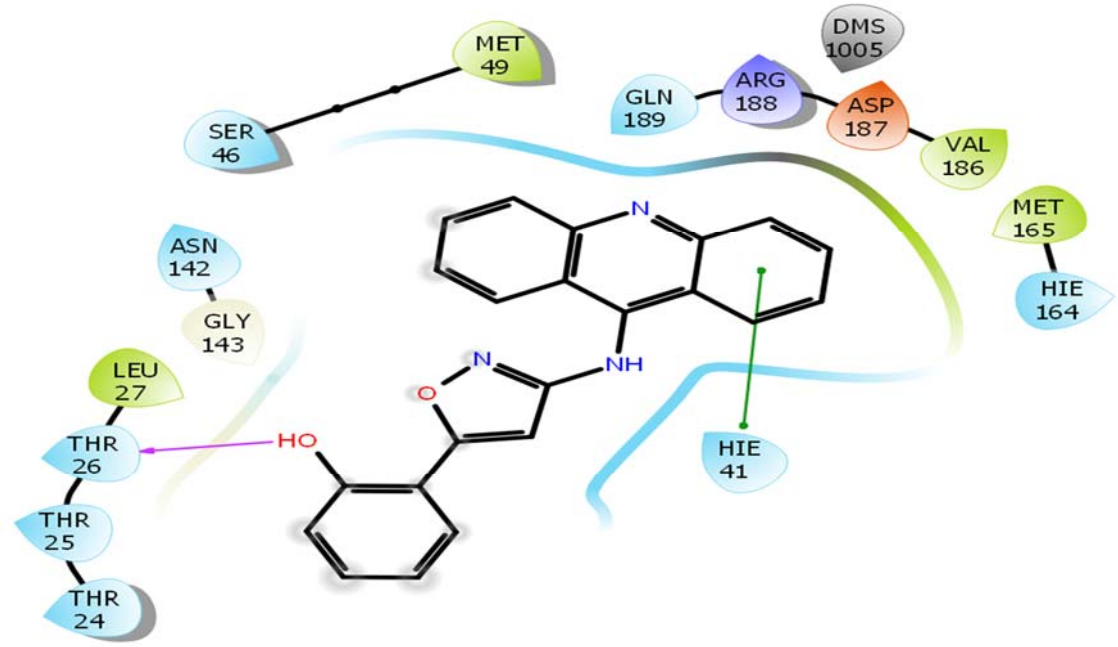

Fig. 3.B. Ligand Interaction of compound 1f with COVID19 (5R82)

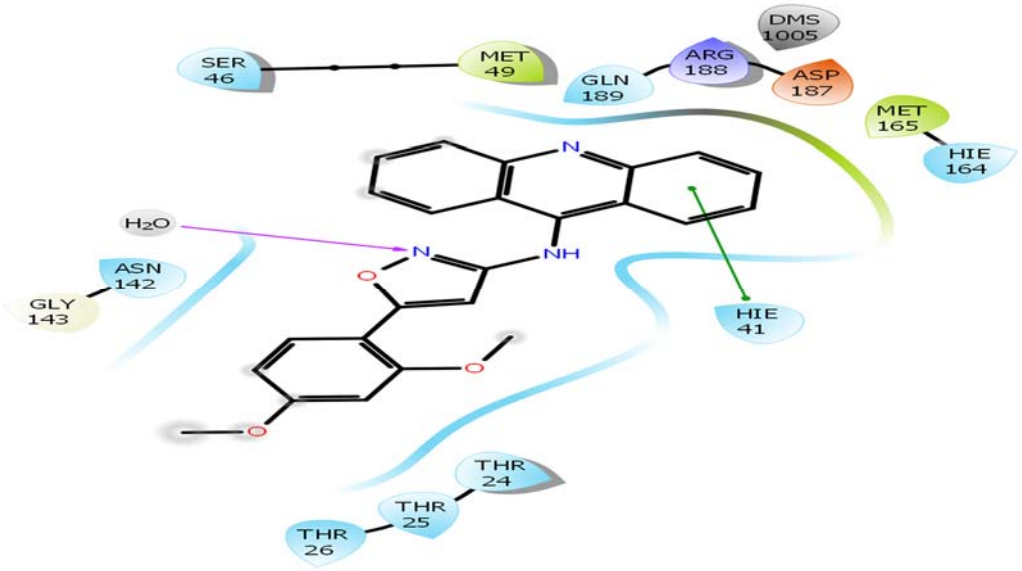

Fig.3.C. Ligand Interaction of compound 1c with COVID19 (5R82)

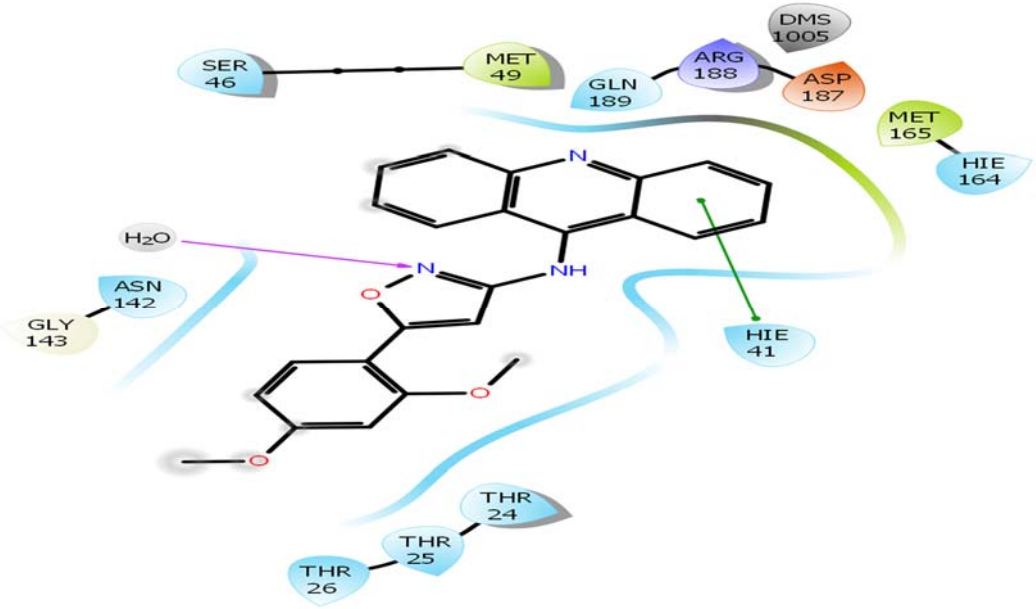

Fig.3.D. Ligand Interaction of compound 1k with COVID19 (5R82)

From the molecular docking study it was revealed that the ligands have shown agreeable glide G score values from -4.64 Kcal/mol (compound 1x) to -6.39 Kcal/mol (compound 1n). From the binding modes obtained, it was illustrated that the ligands **1n,f,c,k,h,a,e,g** formed hydrogen bonding, hydrophobic and other interactions with different residues THR24 to GLN189 surrounding the active pocket which was shown in figure **4**. The ligand**1f**exhibited hydrogen bonding interaction with THR26 (H-Bond length1.75 A°), residue and with some water molecules are shown in the figure **5**. The presence of aromatic features and different heterocyclic rings majorly contributed towards lipophilic factors.

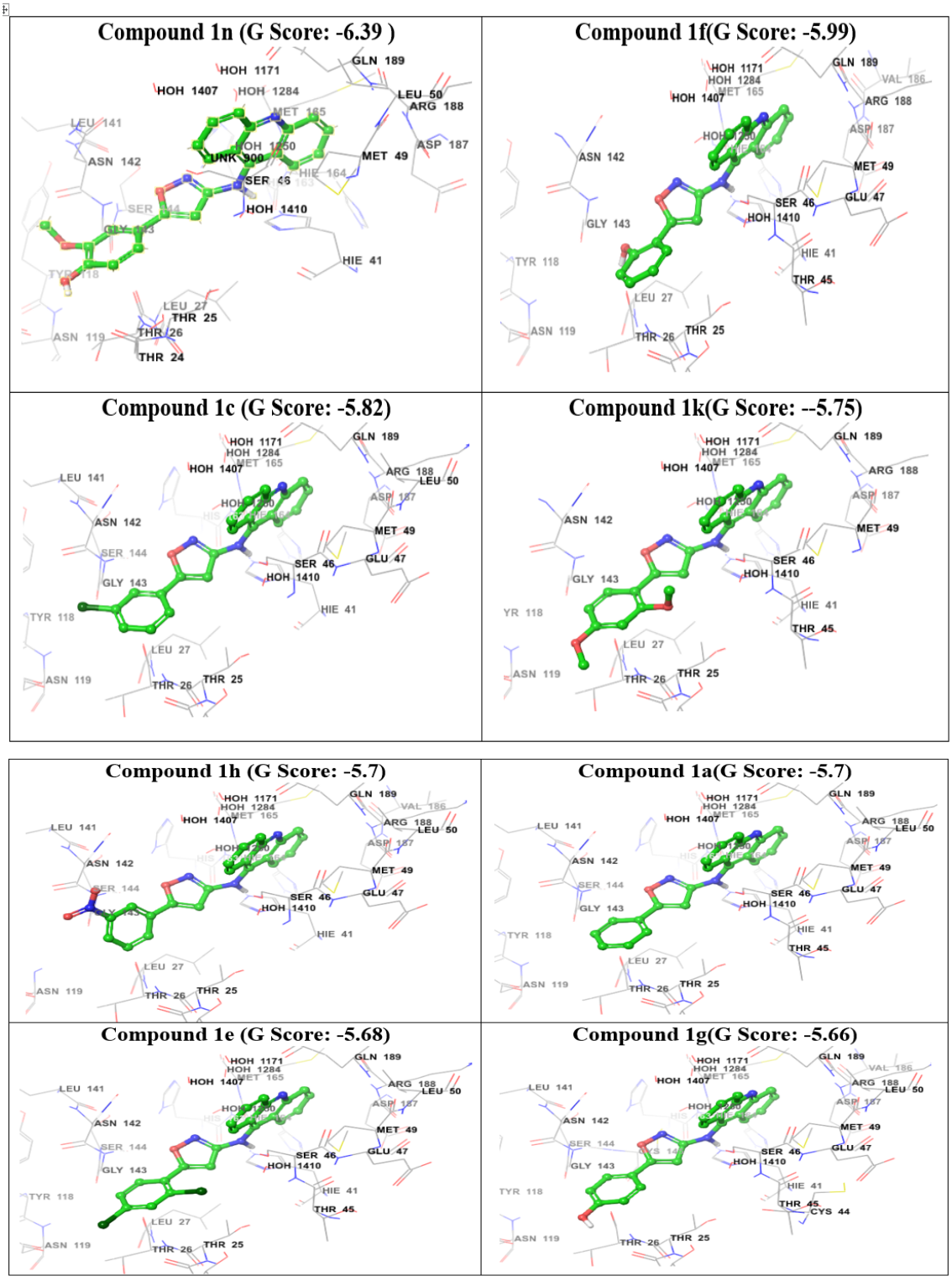

Fig.4. Best affinity mode of docked compounds with COVID19 (5R82)

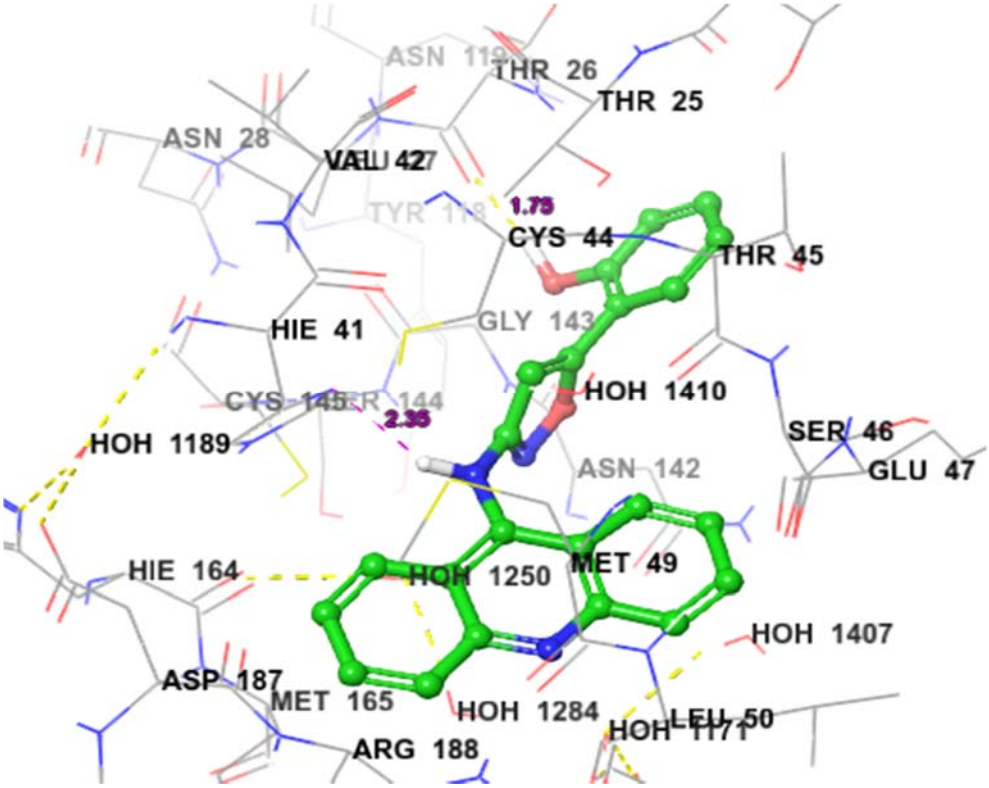

Fig. 5. Hydrogen bonding interaction of compound 1f with COVID19 (5R82)

The ADMET screening for the molecules can be predicted *in-silico* by using qikprop module of Schrödinger suite 2019-4. The results of the ADMET properties for compounds are shown in Table-**2**. From the Table-**2**, *in-silico* ADMET screening results of most the compounds are within the recommended values. The molecular weight between 275.3 and 406.27. Evaluated number of hydrogen bond donors of the molecules are in the range of 1-2. Evaluated number of hydrogen bonds acceptors of most of the compounds are in the range of 3 –5.85. The Prediction of binding to human serum albumin between 0.3 and 1.2. The most of the compounds have QPlogP values are between 3.5 and 5.85. A number of likely metabolites of the compounds are in the range of 0-2. A number of violations of Lipinski's rule of five is 0-1. The compounds have % Human oral absorption in the scope of 94-100%. So from the *in-silico* ADMET screening results of most the compounds are within the recommended values except few parameters of some compounds.

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 and the values are shown in the Table **3**. From the results of MM-GB/SA studies the dG bind values were observed in the range of -22.90 (1h) to -56.797 Kcal/mol (1n) and also dG coulomb, dGvdw 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 Glide score and MM-GBSA free energy are obtained by the docking of ligands into the coupling pocket are more stable.

4. Conclusion

From the results of docking study that the isoxazole substituted 9-aminoacridines like 1n,f,c,k,h,a,e,g,b,d demonstrated better arrangement at dynamic site of the COVID19 protein. The in-silico structuring strategy embraced in the present investigation helped for recognizing some lead molecules such as 1n,f,c,k,h,a,e,g,b,d and furthermore may somewhat clarify their useful impact for the further determinations like in vitro and in vivo assessments. Results from the in-silico study, revealed that many of the isoxazole substituted 9-aminoacridines like 1n,f,c,k,h,a,e,g,b,dmay be useful against COVID19 and are probably going to be helpful after further refinement.

Acknowledgments

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Table 1. Docking studies for Isoxazole substituted 9-aminoacridines(1a-x) with COVID19 (5R82)

Cpd	Glide score	Lipophilic EvdW	H Bond	XP Electro	Low MW	XP Penalties	Rot Penal
1n	-6.39	-5.65	-0.78	-0.09	-0.22	0	0.17
1f	-5.99	-5.13	-1.23	-0.49	-0.32	0	0.2
1c	-5.82	-5.57	-0.28	-0.08	-0.26	0	0.18
1k	-5.75	-5.56	-0.24	-0.09	-0.18	0	0.16
1h	-5.7	-5	-0.53	-0.17	-0.23	0	0.17
1a	-5.7	-5.21	-0.38	-0.11	-0.38	0	0.21
1e	-5.68	-5.48	-0.22	0.01	-0.15	0	0.15
1g	-5.66	-5.38	-0.37	-0.17	-0.32	0	0.2
1b	-5.54	-5.32	-0.24	-0.05	-0.26	0	0.18
1d	-5.5	-5.32	-0.22	-0.02	-0.26	0	0.18
1i	-5.49	-5.28	-0.29	-0.02	-0.23	0	0.17
1w	-5.47	-4.82	-0.46	-0.1	-0.49	0	0.26
1q	-5.47	-5.08	-0.28	-0.13	-0.36	0	0.21
1j	-5.46	-5.33	-0.24	-0.04	-0.28	0	0.18
1p	-5.46	-5	-0.37	-0.15	-0.41	0	0.23
1v	-5.26	-4.54	-0.41	-0.13	-0.5	0	0.19
1m	-5.21	-5.6	-0.22	-0.09	-0.23	0	0.17
1t	-5.15	-5.13	-0.17	-0.05	-0.37	0	0.21
1s	-5.12	-5.28	-0.66	-0.11	-0.37	0	0.21
1l	-4.96	-5.12	0	-0.1	-0.18	0	0.16
1u	-4.95	-4.46	-0.3	-0.06	-0.5	0	0.2
1r	-4.87	-4.75	-0.43	-0.14	-0.37	0	0.21
1o	-4.81	-5.24	-0.52	-0.18	-0.29	0	0.25
1x	-4.64	-3.51	-0.7	-0.2	-0.5	0	0.26
Hydroxy chloroquine (Std)	-5.47	-3.15	-1.75	-0.69	-0.38	0.5	0
CID_24701445_Co-ligand	-4.4	-2.88	-0.7	-0.21	0.5	0.29	0.29

Table 2. *In-silico* ADMET screening for Isoxazole substituted 9-aminoacridines

Compounds	Mol. Wt.	Donor HB	Accpt HB	QPlogKhsa	QPlog o/w	#metab	Rule of Five	%Human Oral Absorption
1a	337.38	1	3	0.869	4.88	0	0	100
1b	371.825	1	3	0.936	5.124	0	1	100
1c	371.825	1	3	0.991	5.378	0	1	100
1d	371.825	1	3	0.989	5.377	0	1	100
1e	406.27	1	3	1.099	5.848	0	1	100
1f	353.379	2	3.75	0.641	4.224	1	0	100
1g	353.379	2	3.75	0.662	4.094	1	0	100
1h	382.378	1	4	0.826	4.182	1	0	94.046
1i	382.378	1	4	0.83	4.194	1	0	94.091
1j	367.406	1	3.75	0.886	4.99	1	0	100
1k	397.432	1	4.5	0.869	5.008	2	1	100
1l	397.432	1	4.5	0.92	5.159	2	1	100
1m	380.448	1	4	1.037	5.303	1	1	100
1n	383.406	2	4.5	0.68	4.339	2	0	100
1o	363.418	1	3	1.155	5.884	0	1	100
1p	327.342	1	3.5	0.604	4.23	1	0	100
1q	343.402	1	3	0.794	4.79	1	0	100
1r	338.368	1	4	0.647	4.229	1	0	100
1s	338.368	1	4.5	0.541	3.944	2	0	100
1t	338.368	1	4.5	0.542	3.944	2	0	100
1u	275.309	1	3	0.398	3.505	1	0	100
1v	289.336	1	3	0.506	3.847	1	0	100
1w	303.363	1	3	0.627	4.231	1	0	100
1x	301.347	1	3	0.627	4.17	1	0	100
Hydroxy chloroquine(std)	335.876	2	5.7	1.085	3.369	5	0	93.213
Recommended values	130-725	0– 6	2-20	-2-8.5	-2-6.5	1 – 8	max 4	>80% is high <25% is poor

MW- Molecular weight of the molecule,

donorHB - Estimated number of hydrogen bonds that would be donated by the solute to water molecules in an aqueous solution.

accptHB- Estimated number of hydrogen bonds that would be accepted by the solute from water molecules in an aqueous solution

QPlogKhsa- Prediction of binding to human serum albumin.

QPlogPo/w - Predicted octanol/water partition coefficient.

#metab- Number of likely metabolic reactions.

RuleOfFiveNumber of violations of Lipinski's rule of five.

%Human- Oral absorption- Predicted human oral absorption on 0 to 100% scale.

Table 3. Binding free energy calculation using 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
1n	-56.7968	-23.5154	2.4804	-1.8585	-10.9638	-40.0530
1f	-53.4693	-36.973	10.0153	-3.5311	-15.3509	-34.2833
1c	-47.3019	-11.948	10.2109	-1.0722	-13.2933	-45.2213
1k	-43.9099	-15.814	2.2821	0.3468	-13.1878	-40.3116
1h	-22.8992	6.9013	-2.0890	1.7164	-11.3424	-31.7120
1a	-49.1943	-30.712	5.8477	-1.7633	-13.6913	-31.6009
1e	-42.2462	-25.773	-0.4271	0.5160	-10.2413	-34.5282
1g	-46.7504	-36.282	4.1380	-0.6984	-11.9709	-27.1283
1b	-50.9684	-32.433	5.3735	-0.8809	-14.1885	-32.4094
1d	-47.7638	-32.581	9.3811	-1.57074	-10.6278	-30.9074
1i	-41.5192	-16.310	7.1774	0.1748	-11.0601	-41.2056
1w	-18.7796	-4.4731	0.8444	1.1242	-7.2195	-33.4287
1q	-44.1846	0.6761	-2.0777	1.1035	-11.8353	-42.0376
1j	-30.3496	-24.485	4.6831	0.2354	-12.5731	-33.7760
1p	-41.1950	-12.571	1.4255	0.1776	-11.0097	-36.9079
1v	-38.7516	-6.2809	4.3009	-0.8058	-10.4623	-35.3600
1m	-37.5011	-24.428	3.8591	0.2568	-9.5163	-34.8443
1t	-43.1380	-35.158	10.6070	-1.0321	-10.5935	-31.661
1s	-50.5496	-27.102	17.2451	-1.0286	-17.0153	-41.0016
1l	-46.3071	-17.765	-0.1487	1.0456	-9.0579	-44.2125
1u	-37.9464	-14.893	1.4122	-1.1176	-6.2972	-30.8720
1r	-39.5155	-18.112	0.2818	-0.0504	-11.9452	-33.9023
1o	-38.3410	-14.036	10.5528	-0.1116	-11.5826	-40.0713
1x	-39.1372	-1.2618	11.6664	-0.1053	-15.1498	-34.6229
Hydroxy Chloroquine (std)	-26.9975	-4.9621	2.1824	0.0011	-9.2894	-33.0622

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نشاط Isoxazole استبدال Aminoacridines−9 ضد السارس CoV−2 بروتياز الرئيسية ل COVID19: نهج حسابي

كاليراجان راجاغوبال[1] *، غوراما بيران[1]، غوماثي سواميناثان[1] و فاديلان راماشاندران[1]

[1] قسم الكيمياء الصيدلانية، كلية JSS للصيدلة، أكاديمية JSS للتعليم العالي والبحوث، أوتي − 643001، نيلغيريس (تاميلنادو)، الهند.

ملخص

مرض فيروس كورونا 2019 (COVID-19)، وهو مرض فيروسي مهدد للحياة يتأثر أولا في الصين وينتشر بسرعة في جميع أنحاء العالم in في أوائل عام2020. الكثير من cientists يسارعون لاكتشاف الأدوية واللقاحات الجديدة ضد الفيروس التاجي ، والعلاجات ل COVID - 19. أنان هذه المادة، وقدأجريت دراسات ط نسيليكو لاستكشاف طرق ملزمة من Isoxazole استبدال aminoacridines (1a-x−9) ضد السارس CoV-2 protease الرئيسية (PDB id - 5R82) استهداف فيروس كورونا باستخدام دعوى Schrodinger 2019-4. يتم إجراء دراسات الإرساء بواسطة وحدة Glide ، وتم إجراء فحص ADMET في silico بواسطة وحدة دعامة qik وتم حساب الطاقة الملزمة لليغند باستخدام وحدة PRIME MM-GB / SA. من النتائج، Isoxazole استبدال aminoacridines−9 مثل n1، f، c، k، h، a،e،g،b،d نشطة بشكل ملحوظ ضد سارس CoV-2 protease الرئيسية مع الإنزلاق درجة أكثر من −−5.5 بالمقارنة مع المخدرات الموصى بها حاليا ل COVID19 هيدروكسي الكلوروكين (G النتيجة −5.47) وشركاه بلورة ليغاند G) CID_24701445 النتيجة −4.4). أظهرت نتائج الالتحام للمركبات طريقة مماثلة من التفاعلات مع COVID19 والمخلفات THR24، THR25، THR26، SER46، MET49، HIE41، GLN189، ARG189، ASP187، MET168، HIE164، ASN142 و GLY143 تلعب دورا حاسما في الربط مع ليغاندس.

الكلمات الدالة: سارس (CoV−2)،(COVID19)

****المؤلف المراسل: كاليراجان راجاغوبال***

rkalirajan@ymail.com , rkalirajan@jssuni.edu.in

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