Research Article

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Computational studies by molecular docking of some antiviral drugs with COVID-19 receptors are an approach to medication for COVID-19

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Abstract: The COVID-19 outbreak is a matter of concern worldwide due to unavailability of promising treatment comprising medication or vaccination till date. The discovery of antiviral drug is of immense importance in the existing spread of novel coronavirus. The goal of the present study was to evolve an opposite antiviral drug against the novel COVID-19 virus. A directly succeeding perspective would be to use the prevailing influential drugs from several antimicrobial and chemotherapeutic agents. The encouraging approach is to identify promising drug molecules and compounds through virtual screening via molecular docking of FDA-approved drugs and some previously synthesized pyridone and **coumarin** derivatives for probable therapeutic outcome. In this conceptual milieu, an effort has been made to propose a computational *in silico* relationship among FDA-approved drugs and coronavirus-associated receptors and proteins. The study results were evaluated on the basis of a dock score by using molecular operating environment. Out of 15 compounds screened, the compounds with the best docking scores toward their targets was **3d**. Therefore, compound **3d** deserves further investigations and clinical trials as a possible therapeutic inhibitor of the COVID-19 caused by the novel SARS-CoV-2.

Keywords: MOE, molecular docking, COVID-19, **pyridones**, **coumarin**

Abbreviations

Binding score energy	It is the energy released when a drug molecule accompanied by a target, resulting in a lowering of the overall energy of the complex
Docking score	It is a procedure to quantify the predictive capability of a docking protocol. While scoring functions are mathematical functions which used to approximately predict the binding affinity between two molecules after they have been docked
PDB	protein data bank
MOE	Molecular operating environment

1 Introduction

Docking process includes both of prediction of ligand conformation and of orientation which means posing within a targeted binding site. The docking studies have two important aims, namely, are accurate structural modeling and correct prediction of activity. Mankind has formerly witnessed the outburst of numerous deadly pathogens such as Zika, Ebola, the Middle East respiratory syndrome (MERS) coronavirus, severe acute respiratory syndrome (SARS) coronavirus, and, currently, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1–5]. The novel COVID-19 pandemic is an ongoing global concern which is also known as the severe acute respiratory syndrome coronavirus spread worldwide [6,7]. The COVID-19 is extremely contagious and potentially fatal disease that can cause mild to severe respiratory tract infections. The COVID-19 outbreak has caused economic and social

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disruptions globally [8,9]. The contagious nature of COVID-19 infection led to the isolation of patients who were subsequently given various treatments [10–12]. The most problematic factor of the pandemic is the rate of transmission. Consequently, the numbers of patients are increasing day by day still with no treatment [13]. Undoubtedly, developing a new drug or vaccine typically takes a long time as it should be intensively tested and ensured to be safe through clinical trials prior to approval for human subjects [14,15]. Although many antiviral drugs and vaccines are undergoing clinical trials against COVID-19, none of them proved their safety and efficacy [16,17]. Currently the COVID-19 is a global pandemic and the situation is not under control [18]. Numerous scientists and researchers are working worldwide to find an efficient means to prevent the pandemic. Due to the unavailability of any approved antiviral drug for COVID-19 treatment, one of the best and fast way to find the antagonist of COVID-19 is through clinically screening the currently available drugs. Hence, repurposing of the clinically available drugs and the available antimicrobials in literature seems to be a faster way to get the target drug [19].

It is the matter of fact that the antimicrobial approach towards the prevention of pandemic could be very effective whereas **coumarins** and **pyridones** are effectively proved as antimicrobials [20–23]. However, some of them also exhibited antitumor, anticancer, analgesic, anti-HIV, antitubercular, and antiviral properties [24–30].

2-pyridone compounds were also shown to be potent nonnucleoside HBV inhibitors [31]. **Coumarin** is a natural compound and is a potential drug candidate owing to its properties of stability, solubility, and low toxicity. There are numerous evidences showing its inhibitory role against infection of various viruses such as HIV, influenza, enterovirus 71, and coxsackievirus A16 [32–35].

Virtual screening is a prevalent modeling tool broadly employed in structure-based drug design [36–40]. It is an imperative means to predict the binding affinity, type of interaction, and the suitable receptor-binding sites among the drug and corresponding receptor by using, for example, scoring functions. In the rational drug design and explicate fundamental biochemical processes, elucidating the binding behavior has an important role [41,42]. In the present study, molecular docking was performed on previously synthesized compounds and drugs mentioned in the clinical protocol of WHO for the treatment of COVID-19. The molecular operating environment (MOE) 2018 modeling program was utilized to predict the binding sites and docking score.

2 Methodology

2.1 Molecular docking method

All docking studies were performed using the MOE program 2018. Structure optimization of the compounds and all drugs that were used as inhibitor agents to COVID-19 was performed by Gaussian 09 program package [45] using the density functional theory with B3LYP [46] and the 6-311++G(d,p) basis sets. The crystal structure of target protein was retrieved from the Protein Data Bank (<http://www.rcsb.org/pdb/>). The Docking score in MOE software was utilizing and accompanied by the five poses for output refinement for final binding poses. Root-mean-square deviation (RMSD) of the compound position compared to the docking, the pose was used in ranking. Both RMSD and the mode of interaction of the native ligand within the structure of the receptor were used as the standard docked model [47–53]. Coronavirus has glycoprotein spikes arranged like a crown. Coronavirus infects its host in three stages. The first stage involves the virus infecting its host by attaching the transmembrane spike-conjugated protein to host through angiotensin-converting protein 2 (ACE 2) within the host so a fancy is formed between S-glycoprotein with ACE-2 with the assistance of transmembrane protease, aminoalkanoic acid 2 (TMPRSS2), produced by host cells. The consequent stage is the replication stage wherein the ribonucleic acid-dependent RNA polymerase (RdRp) is exploited. Coronaviruses are ribonucleic acid viruses that use host cells to replicate. Coronavirus uses RdRp to form new ribonucleic acid copies. The last stage is the maturation stage of virus replication within the host cell by exploiting proteases akin to 3C-like protease (3CLpro) and papain-like protease (PLpro). Some medication is proverbial to be able to inhibit these three processes as well as Arbidol as ACE2 inhibitors, **camostat** mesylate as TMPRSS2 inhibitors, **remdesivir** and antiviral agent as RdRp inhibitors, and **lopinavir** and protease inhibitor as protease inhibitors. **Chloroquine**, **lopinavir**, protease inhibitor, and **remdesivir** are antimicrobials that contain a potential activity against SARS-CoV 2. The target proteins, which are the targets of inhibition, are ACE2, TMPRSS 2, RdRp, 3CLpro, and PLpro [54–57].

Ethical approval: The conducted research is not related to either human or animal use.

3 Result and discussion

In silico methods and computational molecular docking studies are effective tools, which are broadly utilized to interpret the molecular aspects of ligand–protein interactions during drug discovery against various prior fatal and emerging diseases including SARS coronavirus [41,42]. In the present study, the virtual screening of numerous previously synthesized 2-pyridone derivatives (**1a–e**) and acetyl **coumarin** derivatives (**2a–e**, **3a–e**) [43,44], which were already reported to have anticancer and antibacterial activities along with the drugs used in WHO COVID-19 treatment protocol, was performed against the human angiotensin-converting enzyme (PDB code = 1O86), SARS-CoV-main *peptidase* (PDB code = 2GTB), *serine protease hepsin* (PDB code = 5CE1), human coronavirus papain-like *proteases* (PDB code = 4OWO), and SARS-Coronavirus NSP12 (PDB code = 6NUR) to discover the most predicated drug–ligand interactions. The obtained parameters contain the docking scores, binding efficiency of ligand, and hydrogen bonding interactions. The results of the molecular docking studies of pyridone and **coumarin** series against the aforementioned proteins were compared with that obtained using different drugs mentioned in the WHO's clinical protocol of COVID-19 treatment such as **Umifenovir**, **chloroquine**, **camostat**, **remdesivir**, **ribavirin**, and **lopinavir**. The topmost compounds were carefully chosen and are presented in Tables 1–6 and Figures 1–5. The study results of the binding score energy of pyridone series represented in Table 2 for compounds **1a–e** are –6.37, –6.54, –6.68, –7.03, and –6.21, respectively. By comparing these scores, one can find that compound **1d** has higher binding score energy than **ribavirin** and it is near to the binding score energy values of **chloroquine**. Also compounds **1a–c** are most active compared to **ribavirin** while this series is of less activity toward 1O86 as compared to references **Umifenovir**, **chloroquine**, **camostat**, **remdesivir**, and **lopinavir**. This means only compound **1d** is the most welcome compound in this series toward 1O86.

The same series was investigated for 2GTB protein, and the binding score energy is represented in Table 4. Compounds **1a–e** showed the binding score energy –6.39, –6.23, –7.21, –6.98, and –6.64, respectively, and this series exhibited higher activity than **ribavirin**. Compound **1c** represented a good activity near the binding score energy value of **Umifenovir** and **camostat** values, and higher than **chloroquine** binding score energy values. By examination of this series for 4OWO in Table 6, it is noticed that they are more active than **ribavirin** only.

The study results of the binding score energy of 5CE1 protein shown in Table 8 indicated that the series is more active than **ribavirin**; while the binding score energy values of compounds **1c**, **1d** are near to **camostat** and **Umifenovir** values. The study results of this series for 6NUR protein is shown in Table 10, demonstrating higher binding score energy values than **Umifenovir**, **chloroquine**, and **ribavirin**.

The interaction between the compounds and the chosen standard antiviral with 1O86 protein is presented in Table 1. Compound **1a** is bonded to Lys 368 by H-acceptor, compound **1b** with GLN281 also by H-acceptor, and compound **1d** is bonded to ARG 124 by H-acceptor; while compounds **1c** and **1e** as well **chloroquine** and **lopinavir** showed no measurable interaction with 1O86 protein.

Similarly, the interaction between the compounds and the chosen standard antivirals with 2GTB protein is given in Table 3, showing that compound **1a** bonded to the receptors at Gly143 like **Umifenovir**, **remdesivir**, and **ribavirin**. While **chloroquine** has no measurable interaction. The interaction between the investigated compounds and the chosen standard antiviral with 4OWO protein in Table 5 revealed that **1b** is bonded with the receptor at GLN at 270(A), TYR 269(A), by H-donor, and TYR 269(A) with pi-interaction, while **1d** is bonded to the receptor by H-acceptor at GLN233(B), **1e** has interactions by H-donor, H-pi, and pi-H at receptor Tyr269(A), 5ring (His172(A), and OH-Tyr269(A), and no similarity was observed in the binding to the receptor like the references antiviral.

The interactions between the compounds and the chosen standard antiviral with 5CE1 protein is illustrated in Table 7. The receptor interacted with the **ribavirin** at GLY 380(A), and the results showed that compounds **1a**, **1b**, and **1d** are bonded to the receptor from the same position and all of them are connected by H-acceptor. Compound **1b** is bonded to the receptor at CYS 381(A), by H-donor like **ribavirin** and **camostat**, while compounds **1a**, **1b**, and **1c** are bonded to the receptor by pi-H at position CYS 349(A) like **chloroquine**, **remdesivir**, and **lopinavir**.

The interactions between the compounds and the chosen standard antiviral with 6NUR protein are represented in Table 9. As a whole, compound **1c** has no measurable interaction. Compounds **1a** and **1b** are bonded to the receptor from ARG 624(A), by H-acceptor like **Umifenovir**, **chloroquine**, **ribavirin**, and **lopinavir**.

Compounds **1a**, **1b**, and **1d** represented interactions with the receptor at ARG 555(A), like **lopinavir** although

Table 1: Interaction table between the compounds and the chosen standard antiviral with 1086 protein

Compound no.	Ligand	Receptor	Interaction	Distance E	(kcal/mol)
1a	N 21	NZ LYS 368 (A)	H-acceptor	3.52	−0.9
1b	N 21	NE2 GLN 281 (A)	H-acceptor	3.30	−0.8
1c	No measurable interaction				
1d	O 20	NH1 ARG 124 (A)	H-acceptor	2.86	−3.8
1e	No measurable interaction				
2a	O 16	ND2 ASN 66 (A)	H-acceptor	3.08	−0.6
	O 20	ND2 ASN 70 (A)	H-acceptor	3.05	−0.6
	6-Ring	ND2 ASN 66 (A)	pi-H	4.29	−1.9
2b	5-Ring	5-Ring HIS 387 (A)	pi-pi	3.67	−0.0
3a	O 16	ND2 ASN 66 (A)	H-acceptor	2.97	−0.9
	6-Ring	ND2 ASN 66 (A)	pi-H	4.24	−1.1
	6-Ring	ND2 ASN 70 (A)	pi-H	4.04	−0.6
3b	5-Ring	6-Ring TRP 357 (A)	pi-pi	3.87	−0.0
2c	Cl 33	O ALA 356 (A)	H-donor	3.11	−1.0
2d	6-Ring	CA TRP 357 (A)	pi-H	4.67	−0.6
2e	O 16	N GLY 404 (A)	H-acceptor	2.90	−0.7
	6-Ring	CB GLU 403 (A)	pi-H	3.64	−0.7
3c	N 20	N ALA 354 (A)	H-acceptor	3.56	−1.2
3d	No measurable interaction				
3e	O 39	ND2 ASN 70 (A)	H-acceptor	2.96	−0.9
	O 40	ND2 ASN 66 (A)	H-acceptor	3.22	−0.9
	6-Ring	CB SER 516 (A)	pi-H	4.63	−0.5
	6-Ring	CE LYS 118 (A)	pi-H	4.24	−0.6
Umifenovir	No measurable interaction				
Chloroquine	No measurable interaction				
Camostat	N 46	OD2 ASP 121 (A)	H-donor	3.02	−0.7
Remdesivir	N 18	O ALA 356 (A)	H-donor	3.28	−1.7
	N 64	O GLY 404 (A)	H-donor	3.02	−1.9
	O 15	N ALA 356 (A)	H-acceptor	3.03	−1.7
	O 46	NH1 ARG 522 (A)	H-acceptor	3.04	−2.4
	O 48	NH2 ARG 522 (A)	H-acceptor	3.05	−2.6
	C 8	5-Ring TRP 357 (A)	H-pi	4.02	−1.0
	6-Ring	CB GLU 403 (A)	pi-H	3.61	−0.6
	6-Ring	CG PRO 407 (A)	pi-H	3.63	−1.2
	5-Ring	CG PRO 407 (A)	pi-H	4.30	−1.0
Ribavirin	5-Ring	NE1 TRP 220 (A)	pi-H	3.56	−0.5
Lopinavir	No measurable interaction				

they are interacted by H-donor, and **lopinavir** is bonded by pi-cation to the receptor. Compound **1a** interacts with the receptor at *SER 682(A)*, by pi-H like **remdesivir**, while **camostat** is bonded to the same position but by H-acceptor interaction. **Camostat** is also bonded to the receptor at *ARG 553* by pi-H while **Umifenovir** is bonded by pi-cation, and compound **1b** is bonded to the same receptor, but compounds **1d** and **1e** are bonded by H-acceptor.

The study results of the **coumarin** series for 1086 protein and the binding score energy are represented in Table 2. From the data obtained in Table 1, it is observed that compounds **2a**, **2b**, **2c**, **2d**, and **2e** have binding score energy values of −6.21, −6.35, −6.69, −6.84, and −6.63,

respectively. It is clear that all of them have higher docking score than **ribavirin**. Compounds **3a**, **3b**, **3c**, **3d**, and **3e** have binding score energy values of −6.08, −6.48, −6.78, −7.08, and −6.63 respectively, and it is noticed that all of them have higher docking score than **ribavirin** while only compound **3d**'s score was near **chloroquine**. Hence, it is concluded that compound **3d** is the most welcomed compound in this series for 1086.

The same series was examined for 2GTB protein and the binding score energy is represented in Table 4. Compounds **2a**, **2b**, **2c**, **2d**, and **2e** have binding score energy values of −6.16, −6.16, −6.29, −7.17, and −6.78 respectively, and it is apparent that all of them scored higher than **ribavirin**. While compound **2d** has binding score

Table 2: Docking score and energy of the compounds and 1086 protein

Compound no.	S	rmsd_refine	E_conf	E_place	E_score1	E_refine	E_score2
1a	-6.37	1.02	-16.27	-66.62	-10.02	-31.98	-6.37
1b	-6.54	2.50	-23.65	-81.96	-8.78	-30.27	-6.54
1c	-6.68	1.14	12.36	-75.69	-8.37	-33.36	-6.68
1d	-7.03	1.43	4.52	-76.10	-8.26	-26.88	-7.03
1e	-6.21	2.92	-27.41	-73.64	-8.72	-29.02	-6.21
2a	-6.21	1.15	23.41	-68.11	-8.85	-25.31	-6.21
2b	-6.35	1.08	20.40	-59.03	-7.31	-27.76	-6.35
3a	-6.08	1.65	-5.45	-57.69	-9.35	-21.97	-6.08
3b	-6.48	1.94	-35.75	-61.15	-8.42	-27.07	-6.48
2c	-6.69	2.16	5.42	-60.47	-8.09	-25.61	-6.69
2d	-6.84	0.87	1.60	-62.11	-8.53	-33.04	-6.84
2e	-6.63	1.74	29.04	-71.02	-7.79	-36.82	-6.63
3c	-6.78	1.34	-45.58	-69.60	-9.10	-32.78	-6.78
3d	-7.08	0.59	-48.41	-70.78	-8.50	-30.15	-7.08
3e	-6.63	1.24	-36.97	-64.11	-8.07	-33.60	-6.63

Compound no.	S	rmsd_refine	E_conf	E_place	E_score1	E_refine	E_score2
Umifenovir	-7.26	1.33	65.41	-93.92	-10.48	-41.11	-7.26
Chloroquine	-7.10	1.64	-45.50	-65.54	-9.39	-37.52	-7.10
Camostat	-7.71	1.80	-116.94	-78.17	-9.95	-34.14	-7.71
Remdesivir	-9.21	1.59	-29.39	-114.79	-9.90	-56.98	-9.21
Ribavirin	-6.17	1.16	149.11	-71.88	-11.60	-24.89	-6.17
Lopinavir	-9.19	2.47	-59.70	-51.38	-9.40	-54.28	-9.19

Table 3: Interaction table between the compounds and the chosen standard antiviral with 2GTB protein

	Ligand	Receptor	Interaction	Distance E	(kcal/mol)
1a	O 34	SG CYS 44 (A)	H-donor	3.32	-2.4
	N 21	N GLY 143 (A)	H-acceptor	3.12	-0.7
	N 21	OG SER 144 (A)	H-acceptor	3.03	-1.3
	N 21	N CYS 145 (A)	H-acceptor	3.45	-0.6
1b	C 24	SG CYS 44 (A)	H-donor	4.30	-0.5
	O 33	SD MET 165 (A)	H-donor	3.57	-1.0
	6-Ring	NE2 GLN 189 (A)	pi-H	4.31	-0.6
	6-Ring	5-Ring HIS 41 (A)	pi-pi	3.84	-0.0
1c	N 21	NE2 HIS 163 (A)	H-acceptor	3.19	-4.3
1d	6-Ring	NE2 GLN 189 (A)	pi-H	3.80	-1.3
1e	O 20	SG CYS 44 (A)	H-donor	3.62	-1.5
	N 33	OE2 GLU 166 (A)	H-donor	2.99	-1.3
	O 32	NE2 HIS 163 (A)	H-acceptor	3.19	-3.4
	6-Ring	5-Ring HIS 41 (A)	pi-pi	3.95	-0.0
2a	6-Ring	NE2 GLN 189 (A)	pi-H	3.67	-2.8
2b	5-Ring	NE2 GLN 189 (A)	pi-H	4.04	-0.5
	5-Ring	5-Ring HIS 41 (A)	pi-pi	3.81	-0.0
3a	N 20	N GLY 143 (A)	H-acceptor	3.24	-3.4
	6-Ring	NE2 GLN 189 (A)	pi-H	3.71	-4.4
3b	C 9	SG CYS 44 (A)	H-donor	3.61	-0.6
	S 31	SG CYS 145 (A)	H-donor	4.38	-1.0
	N 20	N GLY 143 (A)	H-acceptor	3.04	-4.4
	6-Ring	NE2 GLN 189 (A)	pi-H	4.29	-0.7
	6-Ring	5-Ring HIS 41 (A)	pi-pi	3.93	-0.0
2d	C 9	SG CYS 44 (A)	H-donor	3.64	-0.7

Table 3: continued

	Ligand	Receptor	Interaction	Distance E	(kcal/mol)
2e	O 20	N GLY 143 (A)	H-acceptor	3.18	-2.6
2e	C 21	SD MET 165 (A)	H-donor	3.94	-0.5
	O 20	N GLU 166 (A)	H-acceptor	3.29	-1.1
3c	N 18	N GLY 143 (A)	H-acceptor	3.57	-1.2
	6-Ring	NE2 GLN 189 (A)	pi-H	4.08	-1.5
	6-Ring	5-Ring HIS 41 (A)	pi-pi	3.80	-0.0
3d	N 18	N GLY 143 (A)	H-acceptor	3.30	-2.8
3e	N 20	N GLY 143 (A)	H-acceptor	3.34	-2.7
	6-Ring	NE2 GLN 189 (A)	pi-H	3.71	-2.3
Umifenovir	O 10	N GLY 143 (A)	H-acceptor	2.91	-3.6
Chloroquine	No measurable interactions				
Camostat	N 46	OE1 GLU 166 (A)	H-donor	3.05	-3.1
	N 46	OE2 GLU 166 (A)	H-donor	3.45	-0.6
	O 33	NE2 HIS 163 (A)	H-acceptor	2.83	-0.6
	N 46	OE1 GLU 166 (A)	H-donor	3.05	-3.1
	N 46	OE2 GLU 166 (A)	H-donor	3.45	-0.6
	O 33	NE2 HIS 163 (A)	H-acceptor	2.83	-0.6
Remdesivir	O 46	N GLU 166 (A)	H-acceptor	3.11	-2.0
	N 51	N GLY 143 (A)	H-acceptor	3.15	-0.5
	N 51	OG SER 144 (A)	H-acceptor	2.98	-1.4
	N 51	N CYS 145 (A)	H-acceptor	3.48	-0.5
	6-Ring	5-Ring HIS 41 (A)	pi-pi	3.94	-0.0
Ribavirin	O 1	NE2 HIS 163 (A)	H-acceptor	3.05	-1.8
	O 11	N GLY 143 (A)	H-acceptor	2.95	-1.0
Lopinavir	6-Ring	CG2 THR 25 (A)	pi-H	3.51	-0.5
	6-Ring	NE2 GLN 189 (A)	pi-H	4.16	-0.6

Table 4: Docking score and energy of the compounds and 2GTB protein

Compound no.	S	rmsd_refine	E_conf	E_place	E_score1	E_refine	E_score2
1a	-6.39	0.86	-15.41	-93.48	-12.13	-35.80	-6.39
1b	-6.23	4.35	-27.56	-85.95	-10.81	-27.15	-6.23
1c	-7.21	1.05	13.71	-79.21	-10.20	-39.41	-7.21
1d	-6.98	0.98	3.69	-91.33	-10.55	-35.61	-6.98
1e	-6.64	2.15	-26.64	-73.15	-10.30	-37.62	-6.64
2a	-6.16	0.79	24.13	-63.97	-9.83	-31.93	-6.16
2b	-6.16	1.79	17.64	-67.10	-9.47	-33.34	-6.16
3a	-6.72	0.75	-10.66	-67.50	-10.24	-36.42	-6.72
3b	-6.67	1.34	-31.64	-72.99	-9.69	-36.68	-6.67
2c	-6.29	2.66	6.07	-55.90	-9.17	-31.41	-6.29
2d	-7.17	1.49	6.40	-63.99	-9.16	-35.81	-7.17
2e	-6.78	1.28	32.80	-55.31	-10.23	-35.19	-6.78
3c	-6.85	1.19	-47.33	-84.62	-11.09	-37.93	-6.85
3d	-7.62	2.04	-43.55	-71.67	-9.51	-39.18	-7.62
3e	-7.45	2.23	-35.30	-56.56	-11.05	-38.79	-7.45
Compound no.	S	S	E_conf	E_place	E_score1	E_refine	E_score2
Umifenovir	-7.23	2.36	72.87	-63.18	-10.11	-37.59	-7.23
Chloroquine	-7.03	1.69	-26.96	-52.10	-9.48	-32.28	-7.03
Camostat	-7.37	1.90	-121.50	-62.62	-9.67	-42.81	-7.37
Remdesivir	-8.64	1.39	-43.66	-89.43	-9.74	-47.34	-8.64
Ribavirin	-5.59	1.28	154.07	-75.52	-9.82	-25.79	-5.59
Lopinavir	-8.66	1.81	-60.54	-53.88	-8.62	-50.98	-8.66

Table 5: Interaction table between the compounds and the chosen standard antiviral with 4OWO protein

	Ligand	Receptor	Interaction	Distance E	(kcal/mol)
1a	O 34	O GLN 270 (A)	H-donor	3.05	−1.1
1b	N 34	O TYR 269 (A)	H-donor	3.01	−3.2
	N 34	6-Ring TYR 269 (A)	H-pi	3.68	−1.0
1c	No measurable interactions				
1d	O 20	NE2 GLN 233 (B)	H-acceptor	3.00	−0.6
1e	N 33	O TYR 269 (A)	H-donor	3.12	−2.1
	N 3	5-Ring HIS 172 (A)	H-pi	4.53	−2.1
	6-Ring	OH TYR 269 (A)	pi-H	4.45	−0.5
2a	5-Ring	CD LYS 158 (A)	pi-H	3.68	−1.6
2b	5-Ring	CD LYS 158 (A)	pi-H	3.65	−0.5
3a	6-Ring	NZ LYS 158 (A)	pi-cation	4.35	−0.6
3b	No measurable interactions				
2c	O 20	N MET 209 (B)	H-acceptor	3.05	−1.3
	6-Ring	CG GLU 162 (A)	pi-H	3.55	−0.6
2d	O 20	NH1 ARG 167 (B)	H-acceptor	3.13	−1.6
	6-Ring	NZ LYS 158 (A)	pi-cation	4.26	−0.5
	6-Ring	NZ LYS 158 (A)	pi-cation	3.94	−8.2
	6-Ring	N MET 209 (B)	pi-H	3.89	−0.6
2e	O 35	N ASP 165 (A)	H-acceptor	2.98	−1.0
3c	6-Ring	6-Ring TYR 265 (A)	pi-pi	3.89	−0.0
3d	N 18	NH1 ARG 167 (B)	H-acceptor	3.53	−0.6
	6-Ring	NZ LYS 158 (A)	pi-cation	3.75	−7.3
3e	6-Ring	NZ LYS 158 (A)	pi-cation	4.55	−0.8
	6-Ring	CB LEU 163 (A)	pi-H	4.35	−0.8
Umifenovir	No measurable interactions				
Chloroquine	6-Ring	N MET 209 (B)	pi-H	3.84	−1.0
	6-Ring	CB MET 209 (B)	pi-H	4.55	−0.5
Camostat	N 49	OG1 THR 302 (A)	H-donor	2.90	−1.8
Remdesivir	N 18	O MET 209 (B)	H-donor	3.13	−2.7
	N 64	O ASP 165 (A)	H-donor	3.43	−1.1
	O 21	NZ LYS 158 (A)	H-acceptor	3.15	−2.5
	5-Ring	NZ LYS 158 (A)	pi-cation	3.94	−0.6
	6-Ring	CD LYS 158 (A)	pi-H	3.51	−0.7
Ribavirin	O 1	O ASN 157 (A)	H-donor	3.08	−0.7
	N 23	O MET 209 (B)	H-donor	2.98	−1.8
	O 11	NH1 ARG 167 (B)	H-acceptor	2.98	−1.8
	5-Ring	CA TYR 208 (B)	pi-H	3.80	−1.1
Lopinavir	N 30	O LEU 163 (A)	H-donor	3.33	−1.1

energy values higher than **chloroquine**. While compounds **3a**, **3b**, **3c**, **3d**, and **3e** have binding score energy values of −6.72, −6.67, −6.85, −7.62, and −7.45, respectively. It is revealed that all of them have higher binding score than **ribavirin**. Furthermore, compounds **3d** and **3e** have binding score energy values higher than **Umifenovir**, **camostat**, and **chloroquine**. This means that compound **3d** is the most active one toward 2GTB protein.

The results of the binding score energy of the same series for 4OWO protein are represented in Table 6. Compounds **2a**, **2b**, **2c**, **2d**, and **2e** have −6.81, −6.96, −6.76, −7.45, and −7.12 respectively, and all of them scored

higher than **ribavirin**. Compounds **3a**, **3b**, **3c**, **3d**, and **3e** have binding score energy values −7.43, −7.34, −7.34, −8.22, and −7.34, respectively. It disclosed that all of them have higher values than **ribavirin**. Moreover, compound **3d** has higher binding score than **chloroquine**. Therefore, compound **3d** appeared as the most active one for 4OWO protein.

The binding score energy results of same series toward 5CE1 protein given in Table 8 exhibited that compounds **2a**, **2b**, **2c**, **2d**, and **2e** have binding score energy values of −6.46, −6.5, −6.74, −7.16, and −6.93, respectively, and compounds **3a**, **3b**, **3c**, **3d**, and **3e** represented docking score of

Table 6: Interaction table between the compounds and the chosen standard antiviral with 4OW0 protein

Compound no.	S	rmsd_refine	E_conf	E_place	E_score1	E_refine	E_score2
1a	−6.60	1.04	−14.69	−90.64	−10.33	−37.54	−6.60
1b	−7.50	0.56	4.93	−89.24	−12.71	−44.58	−7.50
1c	−7.39	1.59	15.44	−71.87	−11.23	−38.11	−7.39
1d	−7.55	1.13	4.90	−87.71	−10.99	−38.90	−7.55
1e	−6.99	2.73	−26.09	−99.80	−10.51	−37.12	−6.99
2a	−6.81	3.16	25.82	−73.59	−9.34	−33.99	−6.81
2b	−6.96	2.03	17.99	−78.37	−10.07	−36.24	−6.96
3a	−7.43	2.55	−11.31	−70.99	−9.87	−37.37	−7.43
3b	−7.34	1.02	−30.37	−70.77	−10.21	−34.92	−7.34
2c	−6.76	1.02	0.91	−84.15	−9.92	−37.08	−6.76
2d	−7.45	1.87	2.22	−71.40	−10.62	−37.53	−7.45
2e	−7.12	1.85	32.33	−79.24	−10.77	−38.91	−7.12
3c	−7.34	1.09	−45.36	−79.77	−10.46	−36.84	−7.34
3d	−8.22	1.19	−45.54	−72.67	−11.35	−38.56	−8.22
3e	−7.34	1.14	−32.54	−72.93	−11.38	−37.08	−7.34

Compound no.	S	rmsd_refine	E_conf	E_place	E_score1	E_refine	E_score2
Umifenovir	−8.31	3.61	66.94	−93.12	−10.71	−51.37	−8.31
Chloroquine	−7.83	2.09	−44.03	−59.46	−9.80	−40.10	−7.83
Camostat	−8.43	1.71	−120.22	−80.50	−10.85	−41.53	−8.43
Remdesivir	−11.05	2.02	−34.05	−90.49	−10.39	−63.67	−11.05
Ribavirin	−6.14	1.95	150.94	−87.71	−10.41	−29.69	−6.14
Lopinavir	−11.50	2.00	−38.70	−104.83	−10.82	−61.13	−11.50

−6.72, −6.77, −6.69, −7.54, and −7, respectively. All of the docking scores of **coumarin** series are higher than the docking score for **ribavirin**, although compounds **3d** and **3e** afforded higher score than **Umifenovir**; in addition, compound **3d** scored higher than **camostat** and **chloroquine**. The docking score of the same series for 6NUR protein displayed in Table 10 showed that compounds **2a**, **2b**, **2c**, **2d**, and **2e** have binding score energy values of −5.94, −6.06, −6.16, −6.86, and −6.57, respectively, and compounds **3a**, **3b**, **3c**, **3d**, and **3e** represent docking score of −6, −6.17, −6.34, −7.12, and −6.69. All the compounds in this series are showing binding score higher than **ribavirin**, and compounds **3d** and **3e** exhibit higher docking score than **chloroquine** and **Umifenovir**. Conclusively, the study results reveal that compound **3d** emerges as the most effective compound toward all the proteins examined.

Although **3d** has no measurable interactions with the receptors of 1O86 as noticed in Table 1, it actually has a significant docking score and its value is near to **chloroquine** as shown in Table 2. While **3d** is bonded to the receptors of 2GTB, at N-Gly 143(A) by H-acceptor, which seems to be like **remdesivir**, **ribavirin**, and **Umifenovir**;

and all of them are also bonded by hydrogen acceptor (Table 3). The docking score of **3d** proved that it has higher activity than **Umifenovir**, **chloroquine**, **camostat**, and **ribavirin** (Table 4).

It is noticed the interaction between compound **3d** and protein WO40 happens at the same fragment NZ LYS 158 like **remdesivir** by pi-cation, and at the fragment NH1 ARG 167-B like **ribavirin** (Table 6); and it has high docking score values when compared to **chloroquine** and **ribavirin**.

Compound **3d** interacted with 5CE1 at fragments CYS 188(A) by H-donor and GLY 52(A) by H-acceptor, although none of the tested references showed any interactions at these fragments but the tested compound **3d** has a docking score of −7.54, which is higher than that of **Umifenovir**, **chloroquine**, **camostat**, and **ribavirin** (Tables 7 and 8).

The binding site interaction between **3d** and 6NUR happens at ARG 553(A) like **camostat** and SER 682(A) like **remdesivir**, and all of them are bonded by pi-H. The docking score of compounds **3d** is −7.12, which is higher than **Umifenovir**, **chloroquine**, and **ribavirin** (Tables 9 and 10).

Figure 1: Pyridone series, which are docked by MOE and compared with different antiviral drugs [43].

Figure 2: Coumarin compounds 2a–e and 3a–e, which are docked by MOE and compared with different antiviral drugs [44].

3.1 Docking of compounds 1a–e, 2a–e, and 3a–e with 1086 protein by MOE in comparison with different antiviral compounds

Figure 3: 2D-Docking of the compounds and the chosen standard antiviral with 1086 protein.

3.2 Docking of compounds 1a–e, 2a–e, and 3a–e with 2GTB protein by MOE in comparison with different antiviral compounds

Figure 4: 2D-Docking of the compounds and chosen standard antiviral with 2GTB protein.

3.3 Docking of compounds 1a–e, 2a–e, and 3a–e with 4OW0 protein by MOE in comparison with different antiviral compounds

Figure 5: 2D-Docking of the compounds and the chosen standard antiviral with 4OW0 protein.

3.4 Docking of compounds 1a–e, 2a–e, and 3a–e with 5CE1 protein by MOE in comparison with different antiviral compounds

Figure 6: 2D-Docking of the compounds and the chosen standard antiviral with 5CE1 protein.

See Figure 6.

3.5 Docking of compounds 1a–e, 2a–e, and 3a–e with 6NUR protein by MOE in comparison with different antiviral compounds

Figure 7: 2D-Docking of the compounds and the chosen standard antiviral with 6NUR protein.

See Figure 7.

Table 7: Interaction table between the compounds and the chosen standard antiviral with *5CE1* protein

	Ligand	Receptor	Interaction	Distance E	(kcal/mol)
1a	N 3	O GLY 380 (A)	H-donor	2.82	−3.8
	6-Ring	CA CYS 349 (A)	pi-H	4.09	−1.4
1b	N 3	O GLY 380 (A)	H-donor	2.79	−2.4
	N 3	SG CYS 381 (A)	H-donor	3.35	−0.5
	N 9	N GLY 378 (A)	H-acceptor	3.45	−0.5
	6-Ring	CA CYS 349 (A)	pi-H	4.35	−0.6
1c	N 3	O GLY 380 (A)	H-donor	2.82	−4.2
	6-Ring	CA CYS 349 (A)	pi-H	4.12	−0.8
	6-Ring	CG GLN 350 (A)	pi-H	3.76	−0.5
1d	N 3	O GLY 380 (A)	H-donor	2.84	−3.1
1e	6-Ring	CB GLN 350 (A)	pi-H	4.21	−1.0
2a	6-Ring	CA CYS 349 (A)	pi-H	4.18	−0.9
	5-Ring	5-Ring HIS 203 (A)	pi-pi	3.53	−0.0
2b	6-Ring	CA CYS 349 (A)	pi-H	4.25	−0.6
3a	6-Ring	CA CYS 349 (A)	pi-H	4.19	−0.9
	5-Ring	5-Ring HIS 203 (A)	pi-pi	3.58	−0.0
3b	6-Ring	CA CYS 349 (A)	pi-H	4.23	−0.7
	5-Ring	5-Ring HIS 203 (A)	pi-pi	3.66	−0.0
2c	6-Ring CA	CYS 349 (A)	pi-H	4.12	−1.7
2d	C 11	SG CYS 381 (A)	H-donor	4.00	−0.5
2e	6-Ring	CA CYS 349 (A)	pi-H	4.23	−0.6
	6-Ring	CG GLN 350 (A)	pi-H	4.18	−0.5
3c	6-Ring	CA CYS 349 (A)	pi-H	4.23	−0.7
	6-Ring	5-Ring HIS 203 (A)	pi-pi	3.99	−0.0
3d	C 9	SG CYS 188 (A)	H-donor	3.77	−0.5
	O 16	N GLY 351 (A)	H-acceptor	3.05	−2.7
3e	No measurable interactions				
Umifenovir	O 10	OH TYR 301 (A)	H-acceptor	3.05	−2.3
Chloroquine	N 17	OG SER 353 (A)	H-donor	3.06	−0.7
	C 31	5-Ring HIS 203 (A)	H-pi	4.06	−1.3
	6-Ring	CA CYS 349 (A)	pi-H	4.25	−0.9
Camostat	N 49	OD1 ASP 347 (A)	H-donor	3.18	−1.9
Remdesivir	O 21	SG CYS 381 (A)	H-donor	3.72	−0.8
	N 64	O CYS 204 (A)	H-donor	3.07	−1.3
	6-Ring	CA CYS 349 (A)	pi-H	4.23	−0.9
Ribavirin	O 1	O GLY 380 (A)	H-donor	2.97	−0.6
	N 23	OD2 ASP 347 (A)	H-donor	3.13	−3.0
	N 23	SG CYS 381 (A)	H-donor	4.37	−1.1
Lopinavir	C 74	OE2 GLU 252 (A)	H-donor	3.25	−0.5
	O 33	OG SER 353 (A)	H-acceptor	2.82	−2.2
	6-Ring	CA CYS 349 (A)	pi-H	4.25	−0.6
	6-Ring	CA THR 379 (A)	pi-H	4.45	−0.9

Table 8: Docking score and energy of the compounds and 5CE1 protein

Compound no.	S	rmsd_refine	E_conf	E_place	E_score1	E_refine	E_score2
1a	-6.48	1.11	-14.22	-75.53	-9.59	-32.73	-6.48
1b	-6.53	1.83	-20.68	-57.45	-10.08	-36.55	-6.53
1c	-7.05	2.34	9.97	-78.79	-9.52	-35.91	-7.05
1d	-6.73	1.37	6.49	-74.55	-9.82	-35.03	-6.73
1e	-6.43	0.97	-23.66	-67.79	-9.63	-29.24	-6.43
2a	-6.46	1.57	23.37	-60.65	-9.24	-34.86	-6.46
2b	-6.50	1.41	18.86	-63.26	-9.44	-36.39	-6.50
3a	-6.72	1.55	-17.08	-58.77	-10.79	-38.19	-6.72
3b	-6.77	1.16	-35.33	-90.39	-10.52	-38.65	-6.77
2c	-6.74	1.05	1.50	-70.51	-9.54	-36.12	-6.74
2d	-7.16	1.14	4.68	-45.65	-11.42	-37.29	-7.16
2e	-6.93	1.60	32.84	-50.03	-9.70	-36.10	-6.93
3c	-6.93	1.41	-47.84	-88.78	-10.26	-39.89	-6.93
3d	-7.54	1.55	-50.83	-63.86	-10.66	-44.50	-7.54
3e	-7.00	2.79	-37.03	-43.63	-10.07	-37.07	-7.00

Compound no.	S	rmsd_refine	E_conf	E_place	E_score1	E_refine	E_score2
Umifenovir	-6.88	2.06	70.21	-50.29	-9.66	-39.44	-6.88
Chloroquine	-7.28	1.82	-38.19	-62.48	-9.21	-35.43	-7.28
Camostat	-7.47	1.79	-120.35	-62.38	-10.36	-37.85	-7.47
Remdesivir	-8.46	2.09	-28.96	-52.64	-10.44	-51.84	-8.46
Ribavirin	-5.96	1.00	152.47	-64.15	-9.68	-34.52	-5.96
Lopinavir	-8.26	1.81	-67.22	-76.21	-9.74	-50.19	-8.26

Table 9: Interaction table between the compounds and the chosen standard antiviral with 6NUR protein

	Ligand	Receptor	Interaction	Distance E	(kcal/mol)
1a	N 8	NH1 ARG 624 (A)	H-acceptor	3.77	-0.6
	O 20	NE ARG 555 (A)	H-acceptor	3.03	-3.0
	N 21	NZ LYS 545 (A)	H-acceptor	3.19	-1.6
	6-Ring	N THR 556 (A)	pi-H	3.98	-4.9
	6-Ring	N SER 682 (A)	pi-H	4.70	-1.3
1b	C 24	O THR 680 (A)	H-donor	3.32	-0.6
	N 8	NH1 ARG 624 (A)	H-acceptor	3.24	-0.9
	N 9	NH1 ARG 624 (A)	H-acceptor	3.19	-2.8
	N 9	NH2 ARG 624 (A)	H-acceptor	3.36	-0.8
	O 20	NE ARG 555 (A)	H-acceptor	3.05	-5.4
	O 33	NZ LYS 676 (A)	H-acceptor	3.40	-2.4
	6-Ring	NH1 ARG 553 (A)	pi-cation	4.94	-1.2
	6-Ring	N THR 556 (A)	pi-H	3.83	-0.6
	No measurable interactions				
1d	O 20	NH2 ARG 553 (A)	H-acceptor	3.24	-0.8
	N 21	NZ LYS 545 (A)	H-acceptor	3.29	-4.0
	N 21	NH2 ARG 555 (A)	H-acceptor	3.33	-2.6
	6-Ring	N THR 556 (A)	pi-H	4.77	-0.5
	6-Ring	NH1 ARG 624 (A)	pi-cation	3.59	-0.6
1e	N 21	NH1 ARG 553 (A)	H-acceptor	3.31	-3.6
	N 21	NH2 ARG 553 (A)	H-acceptor	3.69	-0.5
	O 32	NZ LYS 676 (A)	H-acceptor	3.00	-9.5
2a	C 21	OD2 ASP 623 (A)	H-donor	3.52	-0.7
	O 20	N THR 556 (A)	H-acceptor	3.13	-0.6
2b	C 21	OD2 ASP 623 (A)	H-donor	3.50	-0.6
	S 30	O ALA 554 (A)	H-donor	3.54	-0.8
	O 20	N THR 556 (A)	H-acceptor	3.12	-0.6

Table 9: continued

	Ligand	Receptor	Interaction	Distance E	(kcal/mol)
3a	6-Ring	NH1 ARG 624 (A)	pi-cation	3.91	-0.8
3b	6-Ring	NH1 ARG 624 (A)	pi-cation	3.94	-0.9
2c	6-Ring	NH1 ARG 624 (A)	pi-cation	3.83	-2.4
	6-Ring	NH2 ARG 624 (A)	pi-cation	4.71	-0.5
2d	O 16	N THR 556 (A)	H-acceptor	2.98	-2.0
	6-Ring	CD ARG 553 (A)	pi-H	4.40	-0.9
	6-Ring	N SER 682 (A)	pi-H	4.47	-1.4
2e	C 21	OD2 ASP 623 (A)	H-donor	3.60	-0.6
	O 20	N THR 556 (A)	H-acceptor	3.11	-0.6
3c	6-Ring	NH1 ARG 624 (A)	pi-cation	3.91	-0.8
3d	O 16	N THR 556 (A)	H-acceptor	2.96	-2.1
	6-Ring	CD ARG 553 (A)	pi-H	4.38	-0.9
	6-Ring	N SER 682 (A)	pi-H	4.46	-1.5
3e	O 16	N THR 556 (A)	H-acceptor	3.15	-1.0
	6-Ring	NH1 ARG 624 (A)	pi-cation	3.98	-0.8
Umifenovir	5-Ring	NH1 ARG 553 (A)	pi-cation	3.46	-1.1
	6-Ring	NH1 ARG 624 (A)	pi-cation	3.53	-1.1
Chloroquine	CL 1	NZ LYS 621 (A)	H-acceptor	3.48	-1.1
	N 34	NH1 ARG 624 (A)	H-acceptor	3.37	-2.7
Camostat	O 11	N SER 682 (A)	H-acceptor	3.00	-0.6
	6-Ring	CD ARG 553 (A)	pi-H	4.04	-0.6
Remdesivir	N 64	O THR 680 (A)	H-donor	3.34	-1.1
	O 15	NZ LYS 621 (A)	H-acceptor	2.89	-9.3
	6-Ring	CB SER 682 (A)	pi-H	3.71	-0.9
Ribavirin	C 6	OD2 ASP 623 (A)	H-donor	3.31	-1.0
	N 23	OE2 GLU 665 (A)	H-donor	3.25	-1.4
	O 8	NH1 ARG 624 (A)	H-acceptor	2.79	-2.1
	O 26	NZ LYS 676 (A)	H-acceptor	2.91	-2.1
	5-Ring	CB ALA 558 (A)	pi-H	3.54	-0.9
Lopinavir	6-Ring	NE ARG 555 (A)	pi-cation	4.52	-1.7
	6-Ring	NH2 ARG 555 (A)	pi-cation	4.26	-2.1
	6-Ring	NH1 ARG 624 (A)	pi-cation	3.60	-1.1
	6-Ring	CA SER 681 (A)	pi-H	4.46	-0.5

Table 10: Docking score and energy of the compounds and 6NUR protein

Compound no.	S	rmsd_refine	E_conf	E_place	E_score1	E_refine	E_score2
1a	-6.19	0.92	-11.33	-138.94	-12.14	-23.58	-6.19
1b	-6.70	1.36	6.12	-102.83	-12.48	-28.03	-6.70
1c	-6.88	2.38	23.19	-56.84	-11.39	-30.46	-6.88
1d	-6.40	1.53	11.56	-63.71	-10.14	-15.32	-6.40
1e	-6.26	1.24	-26.82	-84.84	-10.15	-33.66	-6.26
2a	-5.94	1.38	26.20	-57.22	-9.38	-29.97	-5.94
2b	-6.06	0.99	17.81	-66.62	-9.75	-30.92	-6.06
3a	-6.00	1.71	-10.63	-64.41	-10.80	-23.99	-6.00
3b	-6.17	1.73	-29.09	-58.52	-10.26	-25.11	-6.17
2c	-6.16	1.05	5.21	-73.01	-9.54	-31.32	-6.16
2d	-6.86	1.08	5.26	-62.29	-10.72	-28.95	-6.86
2e	-6.57	1.58	33.15	-63.19	-9.77	-34.42	-6.57
3c	-6.34	1.87	-44.54	-57.46	-10.78	-27.65	-6.34
3d	-7.12	1.52	-46.93	-53.15	-9.62	-28.17	-7.12
3e	-6.69	2.16	-32.68	-75.00	-11.01	-32.78	-6.69

Table 10: continued

Compound no.	S	rmsd_refine	E_conf	E_place	E_score1	E_refine	E_score2
Umifenovir	−6.54	2.05	64.49	−50.30	−9.62	−36.26	−6.54
Chloroquine	−6.82	3.10	−43.44	−54.45	−8.96	−32.20	−6.82
Camostat	−7.19	1.97	−121.40	−70.96	−11.20	−40.19	−7.19
Remdesivir	−8.42	2.60	−46.00	−85.37	−10.72	−50.77	−8.42
Ribavirin	−5.48	1.23	150.97	−72.87	−12.19	−12.27	−5.48
Lopinavir	−8.83	1.59	−49.27	−30.42	−9.80	−42.16	−8.83

4 Conclusion

The purpose of this study is to gauge the binding affinity of the active compounds within the target protein that plays a task in the method of virus entry in host cells, virus replication, and therefore the *in silico* process of virus maturation in host cells. Of the 15 compounds of two prepared series of 2-pyridone derivatives and coumarin derivatives, It has been thought that compound no. **3d** was the foremost profit one. Compound **3d** showed higher activities toward *2GTB*, *4OWO*, *5CEI*, and *6NUR* over **Umifenovir**, **chloroquine**, **camostat**, **ribavirin**, and generally **remdesivir**. Hopefully, this analysis will contribute to the discovery of a drug for the COVID-19 antiviral.

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