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In silico study and structure-activity relations of glucose-bound coumarin derivatives against the NSP12 protein of SARS-CoV-2

Esra ÇELİK[1a], Mücahit ÖZDEMİR[1b], Bahattin YALÇIN[1c], Baybars KÖKSOY[2d*]

[1]Marmara University, Department of Chemistry, 34722 Istanbul, Turkey.
[2]Bursa Technical University, Department of Chemistry, 16310 Bursa, Turkey

ORCID: [a]0000-0002-7398-9281, [b]0000-0002-0840-4953, [c]0000-0003-4448-1101, [d]0000-0001-7939-5380

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Abstract: In this study, designs of antiviral drug candidates that may be effective against SARS-CoV-2 virus were performed. Molecular docking was used to explore the effect of coumarin and its derivatives, which have antiviral action, on RNA polymerase NSP12, one of the key proteins of the coronavirus. The sugar group on coumarins was selected to increase hydrophilicity, and the amide groups were diversified to investigate selectivity. Coumarins containing 3-(*p*-phenylamidomorpholine), 3-(*p*-phenylamidopiperazine), and 3-(*p*-phenylamidopiperidine) groups had the best docking scores, with binding affinities of -10.1 kcal/mol, -10.1 kcal/mol, and -10.0 kcal/mol, respectively. The pharmacokinetic and toxicokinetic properties of compounds were estimated close to reality using various databases, and their values were close to the target values needed for a compound to become a drug. This study is also thought to give insight to scientists working for the design of SARS-CoV-2 antiviral drugs in terms of the structure activity relationship between coumarin and its functional groups.

Keywords: SARS-CoV-2, COVID-19, Coronavirus, Coumarin, Drug design, Molecular docking.

SARS-CoV-2'nin NSP12 proteinine karşı glukoza bağlı kumarin türevlerinin in silico çalışması ve yapı-aktivite ilişkileri

Özet: Bu çalışmada SARS-CoV-2 virüsüne karşı etkili olabilecek antiviral ilaç adaylarının tasarımları yapılmıştır. Moleküler yerleştirme, antiviral etkiye sahip kumarin ve türevlerinin, koronavirüsün temel proteinlerinden biri olan RNA polimeraz NSP12 üzerindeki etkisini araştırmak için kullanıldı. Kumarinlerdeki şeker grubu, hidrofilisiteyi arttırmak için seçilmiş ve seçiciliği araştırmak için amid grupları çeşitlendirilmiştir. 3-(*p*-fenilamidomorfolin), 3-(*p*-fenilamidopiperazin) ve 3-(*p*-fenilamidopiperidin) gruplarını içeren kumarinler, sırasıyla -10.1 kcal/mol, -10.1 kcal/mol, and -10.0 kcal/mol bağlanma afiniteleriyle en iyi yerleştirme puanlarına sahipti. Bileşiklerin farmakokinetik ve toksikokinetik özellikleri, çeşitli veri tabanları kullanılarak gerçeğe yakın olarak tahmin edildi ve değerleri, bir bileşiğin ilaca dönüşmesi için gereken hedef değerlere yakındı. Bu çalışmanın ayrıca SARS-CoV-2 antiviral ilaçların tasarımı için çalışan bilim insanlarına kumarin ve fonksiyonel grupları arasındaki yapı aktivite ilişkisi açısından fikir vereceği düşünülmektedir.

Anahtar Kelimeler: SARS-CoV-2, COVID-19, Koronavirüs, Kumarin, İlaç tasarımı, Moleküler yerleştirme

*Corresponding Author: baybars.koksoy@btu.edu.tr (B. Köksoy)

1. INTRODUTION

From December 2019, the SARS-CoV-2 virus, which first appeared in Wuhan, China, has been affecting and endangering people's lives [1]. Acute respiratory syndrome is the most evident impact of coronavirus, but its other effects in the body are also being studied [2]. Headache, cough, fever, loss of taste and smell, and weakness are all frequent SARS-CoV-2 symptoms but still there are symptoms with many other research subjects. Nausea, vomiting, dizziness, diarrhea, redness in the eyes, and vision impairment are some of these symptoms [3, 4]. Additionally, at the person who healing from COVID-19 can observe anxiety and depression as psychology [4]. SARS-CoV-2 genome includes single stranded RNA, Envelope (E), Membrane (M), Spike (S), Nucleocapsid (N) and nonstructural proteins (NSP1-16) [5]. The interaction between spike protein with Ace-2 allows the coronavirus to enter the human cell [6-9]. Human ACE2 enzyme is located on the outer surface of lung arteries, kidneys, and intestine cells and the enzyme has mostly found in the lungs [10]. As the reason that, is scientists think coronavirus mostly effect on lungs. SARS-CoV-2 virus is activated protolithic by host cell proteases after the introduction of the cell [11]. To prevent the coronavirus from entering the cell, vaccinations that produce antibodies have been created. Antiviral medication trials to eliminate SARS-CoV-2 proteins are still ongoing.

Coumarins are seconder metabolites found in plants [12]. Coumarins are naturally existing organic compounds [13]. Coumarin and their derivatives are preferred in biological activity studies because of coumarins excellent pharmacological features [14]. It is also high antioxidant [15] anticoagulant [16], antimicrobial [17], antibacterial [18, 19] and anticancer [20] compounds, are highly preferred in medicine. In addition, coumarins have also been investigated for their effectiveness against pulmonary embolism, which is one of the symptoms of coronavirus [21-23].

The NSP12 protein is attached to RNA catalyzes viral RNA and helps to multiply the coronavirus. Coumarins were shown to attach to amino acids in the NSP12 catalytic domain through non-covalent hydrogen interactions [22]. The coumarin has an inhibitory impact at the conclusion of this contact, and it is estimated in the study that this lowered enzyme activity. In this approach, the coronavirus's fast multiplication in living cells may be avoided, and the coronavirus's potential for severe consequences can be reduced. It is expected that the findings will help to ongoing anti-viral research and that the coronavirus will decrease rather than increase in the cell.

2. MATERIAL AND METHOD

2.1. Molecular docking

Autodock Vina [24] was used to calculate binding affinity for coumarin derivatives (1-8). The X-ray crystal structure of SARS-CoV-2 non-structural protein (PDB code: 7BV2) [25] was resolved using X-ray diffraction method with a resolution factor of 2.50 Å was retrieved from the RCSB Protein Data Bank (https://www.rcsb.org). Automatically the root of each ligand molecule is detected, and torsions were selected. The ligand's torsions were allowed to rotate, and the selected residues were tested. The ligands were docked blindly to see where they would preferentially bind. The amino acids in the active site of NSP-12 and NSP-12 with RNA were determined using BIOVA Discovery Studio Visualizer 2021 [26]. Pre-calculated grid maps were required for running the program, which were calculated using the AutoGrid program. The energy scoring grid box was set to 32x32x32 dimension (x, y, and z) centered at X = 91.692; Y = 92.471; and Z = 103.743 with 0.325 Angstroms grid points spacing assigned. As a docking engine, the Lamarckian Genetic Algorithm was used, with all docking parameters set to default. From 10 conformations obtained through vina calculations, the coumarin derivatives with the lowest energy placement score were chosen. The visualization processes were carried out using the Schrödinger Maestro program [27].

2.2. ADMET predictions

In drug design, determining the pharmacokinetic and toxicokinetic properties of drug candidate molecules prevents multiple experiments, saving both time and cost and making the success rate higher. Absorption, distribution, metabolism, excretion, and toxicity parameters (ADMET) describe the properties that a drug molecule must carry. The SwissADME online database [28] was used to estimate the absorption, distribution, metabolism, and excretion values of coumarin derivatives. The ProTox-II online database [29] was used to estimate toxicity values.

3. RESULTS AND DISCUSSION

3.1. RdRp-NSP12 docking results

Eight targeted-coumarin derivatives were docked by molecular docking study on the NSP12 protein, the RNA polymerase of coronavirus. The docking studies were carried out in two different combinations on the same protein. In the NSP12-encoded docking study, heteroatoms and RNA found in the X-Ray data were extracted and an approach was developed on whether the compounds would only inhibit the polymerase enzyme. All heteroatoms were removed in NSP12 with RNA, and in order to dock for NSP12 without RNA, single stranded RNA was removed from the NSP12 enzyme and the docking study was carried out. Because ligand interactions in the active region where the end part of the RNA interacting with the enzyme is located, in addition to inhibiting NSP12, it causes the RNA Helix to separate from the structure and can stop replication by deactivating the RNA.

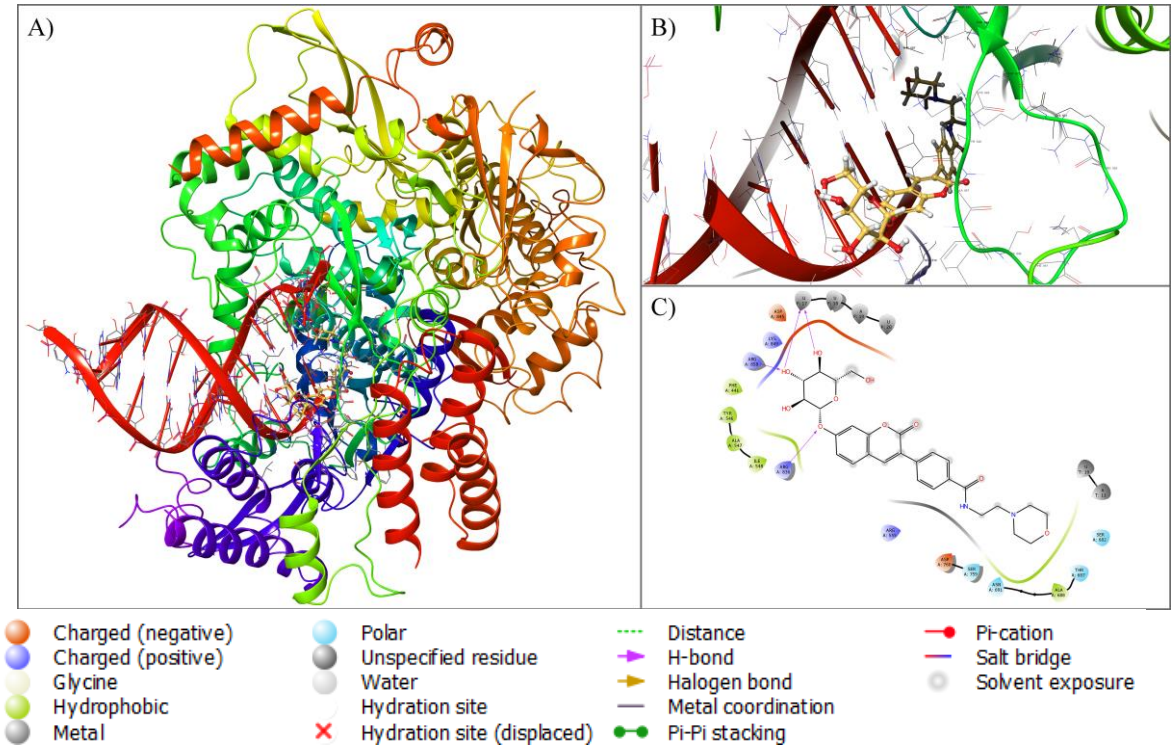


Figure 1. A) General demonstration of NSP12 with RNA and coumarin (**1**) inhibitor. B) Zoomed active site of NSP12 with RNA and coumarin (**1**) inhibitor. C) 2D diagram of coumarin and its interactions with amino acids and nucleobases.

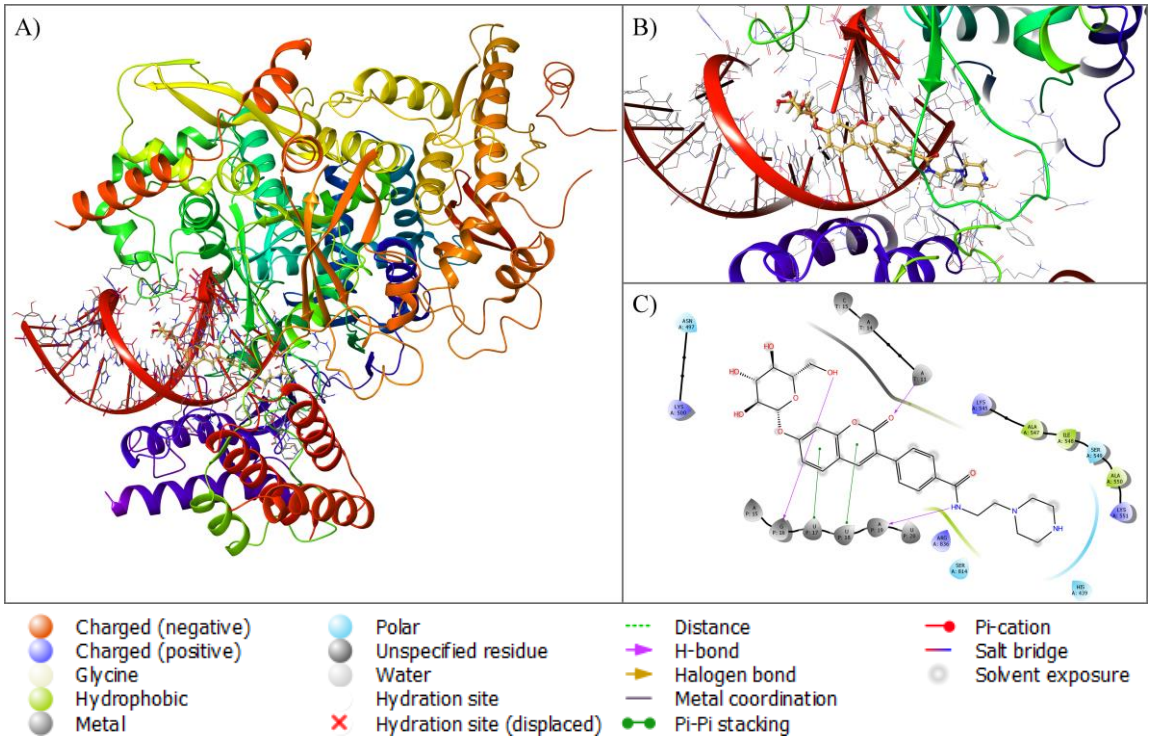
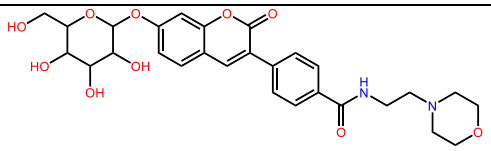
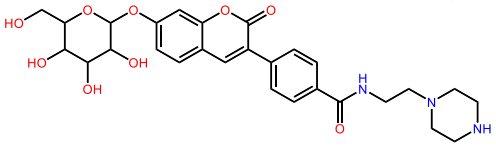
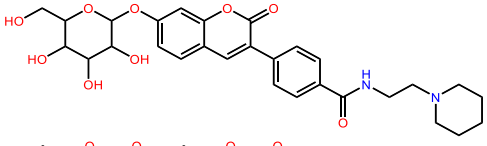
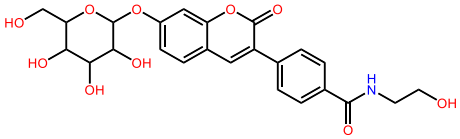
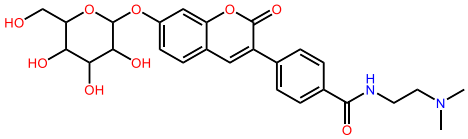
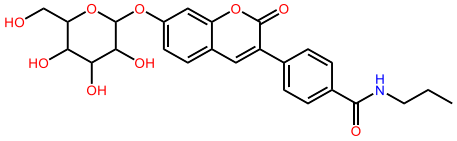
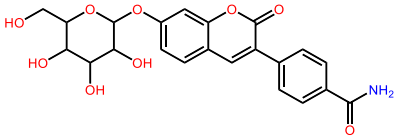
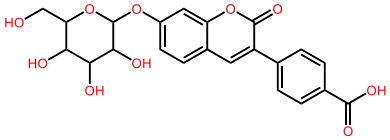
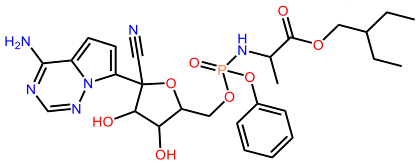
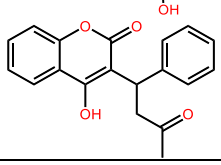


Figure 2. A) General demonstration of NSP12 with RNA and coumarin (**2**) inhibitor. B) Zoomed active site of NSP12 with RNA and coumarin (**2**) inhibitor. C) 2D diagram of coumarin and its interactions with amino acids and nucleobases.

Table 1. The docking scores and ligand efficiency values of the coumarins (**1-8**) on NSP12 proteins.

Compound		NSP12+RNA	LE	NSP12	LE
(**1**)		**-10.1**	-0.25	-8.6	-0.21
(**2**)		**-10.1**	-0.25	-7.7	-0.19
(**3**)		**-10.0**	-0.24	-8.6	-0.21
(**4**)		-9.3	-0.26	-8.1	-0.23
(**5**)		-9.6	-0.25	-7.4	-0.20
(**6**)		-9.4	-0.26	-8.0	-0.22
(**7**)		-9.5	-0.29	-8.3	-0.25
(**8**)		-9.3	-0.28	-8.1	-0.25
R1		**-11.20**	-0.27	**-12.61**	-0.30
R2		-7.83	-0.34	-7.88	-0.34

LE: Ligand Efficiency. It is calculated with ΔG / Number of heavy atoms. R1 is remdesivir and R2 is warfarin. R1 and R2 scores are from Ozdemir *et al.* 2020 [22].

Coumarin derivatives (1-3) carrying 3-(*p*-phenylamidomorpholine), 3-(*p*-phenylamidopiperazine), and 3-(*p*-phenylamidopiperidine) have the highest binding affinity scores (Table 1). The effectiveness of these substituents on NSP12 has been reported earlier by Özdemir et al 2020 [22]. Linked sugar groups from the seventh position of coumarins did not increase non-covalent interactions as expected, but this structure would facilitate the dissolution of the target inhibitor in water or blood serum. As the sugar and amide groups increased hydrophilicity, the ligands moved away from the hydrophobic parts and formed non-covalent interactions with both RNA and the critical amino acids in the active site.

The docking score of 3-(*p*-phenylamidomorpholine) carrying coumarin is -8.6 for NSP12, and -10.1 kcal/mol for NSP12+RNA. Arginine amino acid (ARG836) with the oxygen bridge between coumarin and sugar, created an attractive hydrogen-bond interaction (2.78 Å). Again, the arginine amino acid (ARG858) formed a donor hydrogen bond interaction (1.93 Å) with the hydroxy group at the fourth position of the sugar substituent. The hydroxy group in the third position of glucose has a hydrogen bond interaction length of 2.92 Å, whereas the hydroxy group in the fourth position has a hydrogen bond interaction length of 2.25 Å.

The docking score of 3-(*p*-phenylamidopiperazine) carrying coumarin is -7.7 for NSP12 and -10.1 kcal/mol for NSP12 with RNA. Coumarin benzene and alpha pyran rings formed the π-π stacking interactions with pyrimidine-2,4-dione ring of the uracil nucleobases (U:17 and U:18). The amine of the adenine nucleobase (A:11) has strong hydrogen bond interaction (2.42 Å) with carbonyl functional group of coumarin. The guanine nucleobase (G:16) made a strong hydrogen bond interaction (1.88 Å) with the hydroxymethyl group in the sixth position of the glucose. The adenine nucleobase (A:19) with amide group of the coumarin interacted strong hydrogen bond (1.81 Å).

The docking score of 3-(*p*-phenylamidopiperidine)-carrying coumarin is -8.6 for NSP12 and -10.0 kcal/mol for NSP12 with RNA. Coumarin alpha pyran ring made the π-π stacking interactions with pyrimidine-2,4-dione ring of the uracil nucleobases (U:17 and U:18). With the uracil nucleobase (U:18), the hydroxy group at the third position of the glucose group established a hydrogen bond interaction (2.17 Å). The glucose's hydroxymethyl group at the sixth position made a hydrogen bond interaction (2.15 Å) with the guanine (G:16) nucleobase. Coumarins featured in docking analyses exhibited similar interactions. Interactions in RNA-containing NSP-12 are mostly established by nucleobases. This indicates that coumarins can be very effective on its RNA, as well as inhibiting NSP-12, an RNA polymerase.

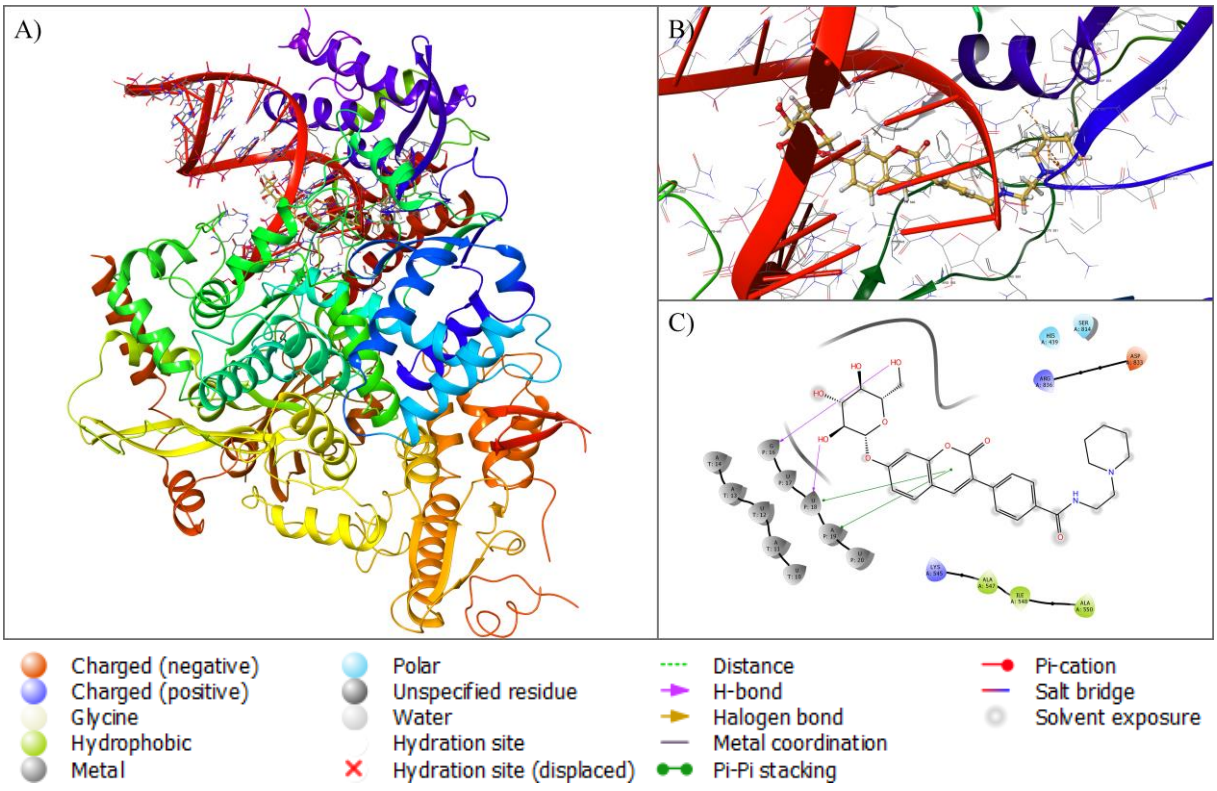


Figure 3. A) General demonstration of NSP12 with RNA and coumarin (**1**) inhibitor. B) Zoomed active site of NSP12 with RNA and coumarin (**1**) inhibitor. C) 2D diagram of coumarin and its interactions with amino acids and nucleobases.

3.2. Pharmacokinetic and toxicokinetic properties

Knowing the behavior of drug components in the body in advance is an approach that provides convenience in drug design. ADMET estimation databases were used to determine the pharmacokinetic and toxicokinetic properties of target coumarin derivatives (1-8). Lipinski mentioned some important criteria for a component to be a drug. Hydrogen bond donors should not exceed 5, hydrogen bond acceptors should not exceed 10, molecular weight should be less than 500 g/mol, and octanol-water partition coefficient (logP)

should not exceed 5 [30]. According to these rules, all coumarins are present in violations for the five important parameters of Lipinski. But violations for compounds 6-8 are only for the topological polar surface area and are negligible.

Polar surface areas are used in prediction of absorption, and compounds with large areas cannot penetrate the blood brain barrier, and as the polar surface grows, it becomes difficult for compounds to penetrate the cell membrane. All coumarin derivatives (1-8) are above the threshold value as TPSA. Due to the sugar groups that bind from the seventh position of coumarins, they have the high-water solubility. Not all coumarins can penetrate the blood-brain barrier due to the large topological polar surfaces but can be the substrate of *p*-glycoprotein with an important role in drug absorption. The warfarin drug is also a P-gp substrate. All Coumarins are not metabolized by CYP enzymes and are determined that they are not inhibitors that may exhibit side effects or toxicity.

The average similarity of the coumarins to the other compounds used for toxicokinetic estimates is 60%. The prediction accuracy is average 70%. On the toxicity scale from 1 to 6, 1 means highly toxic and 6 means non-toxic. Toxicity class of coumarin derivatives (1-8) estimated as 4. Coumarin derivatives are inactive for hepatotoxicity, carcinogenicity, cytotoxicity, and mitochondrial membrane potential values. As immunotoxicity, compounds 1, 3, 5, 7 and 8 are inactive, while compounds 2, 4 and 6 are active. The propyl piperazine (compound 2 functional group), propanol (compound 4 functional group) and propyl (compound 6 functional group) groups are thought to enhance immunotoxicity. Benzoic acid (compound 8 functional group) has been shown to have mutagenic effect compared to benzamide. All these ADMET features give an idea that the designed coumarin compounds may be the drug candidate.

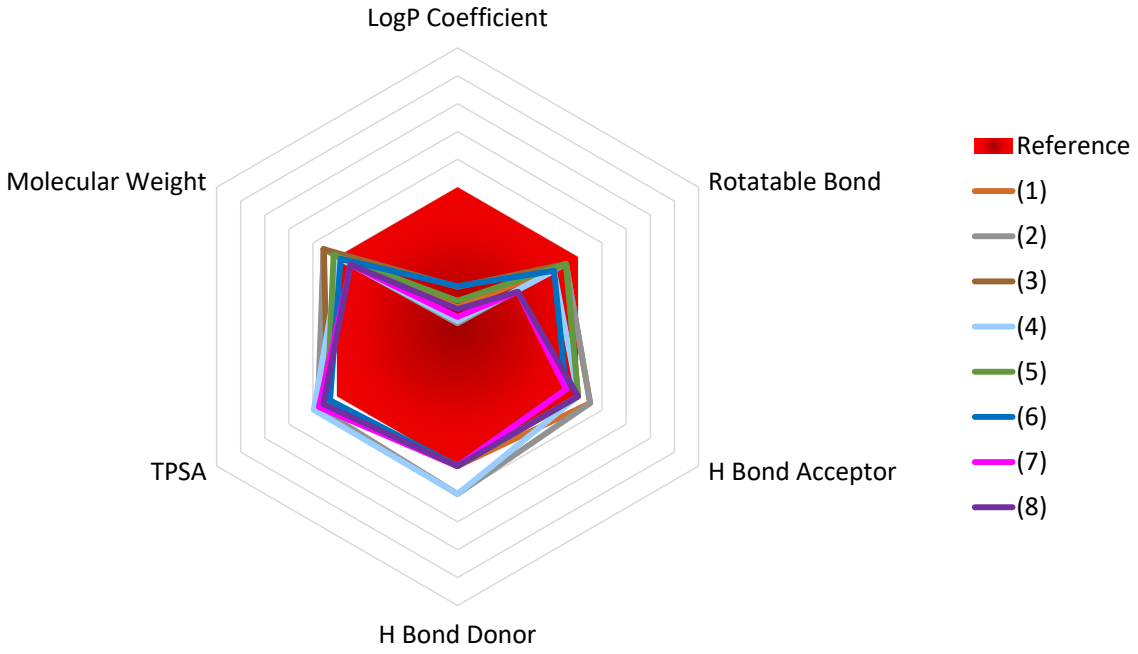


Figure 4. The radar chart of designed coumarins (**1-8**) for logP coefficient, molecular weight, topological polar surface area, hydrogen bond donor, hydrogen bond acceptor, rotatable bond values. Reference values according to Lipinski's rule of five, logP value should be between 0.2-5; rotatable bond value should be between 0-10; hydrogen bond acceptor value should be between 0-10; hydrogen bond donor value should be between 0-5; topological polar surface area value should be between 20-150; molecular weight value should be between 150-500.

Table 3. The pharmacokinetic and toxicokinetic properties of coumarins in this study (**1**-**8**).

Properties	Coumarin derivatives							
	(**1**)	(**2**)	(**3**)	(**4**)	(**5**)	(**6**)	(**7**)	(**8**)
Molweight (g/mol)	556.56	555.58	554.59	487.46	514.52	485.48	443.40	444.39
Number of atoms	72	73	74	60	67	62	53	52
Heavy atoms	41	40	40	35	37	35	32	32
Number of bonds	76	77	78	63	70	65	56	55
Rotatable bonds	9	9	9	8	9	8	5	5
H-Bond acceptors	11	11	10	10	10	9	9	10
H-Bond donors	5	6	5	6	5	5	5	5
Dipole moment (D)[a]	7.04	6.74	6.82	6.24	6.81	6.97	6.90	5.24
Molar refractivity	144.88	150.51	148.60	121.03	132.38	124.68	110.16	109.02
TPSA (Å^2)	171.16	173.96	161.93	178.92	161.93	158.69	172.68	166.89
Log $P_{o/w}$	0.69	-0.12	1.43	0.20	0.93	1.45	0.35	0.63
Water solubility	Soluble	Soluble	Soluble	Soluble	Soluble	Soluble	Soluble	Soluble
GI absorption	Low	Low	Low	Low	Low	Low	Low	Low
BBB permeant	No	No	No	No	No	No	No	No
P-gp substrate	Yes	No	No	Yes	Yes	Yes	No	No
CYP1A2 inhibitor	No	No	No	No	No	No	No	No
CYP2C19 inhibitor	No	No	No	No	No	No	No	No
CYP2C9 inhibitor	No	No	No	No	No	No	No	No
CYP2D6 inhibitor	No	No	No	No	No	No	No	No
CYP3A4 inhibitor	No	No	No	No	No	No	No	No
Log K_p (cm/s)	-9.46	-9.66	-8.58	-9.29	-8.94	-8.15	-9.13	-8.68
Lipinski rules	No	No	No	No	No	Yes	Yes	Yes
Toxicity class[b]	4	4	4	4	4	4	4	4
Hepatotoxicity	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive
Carcinogenicity	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive
Immunotoxicity	Inactive	Active	Inactive	Active	Inactive	Active	Inactive	Inactive
Mutagenicity	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Active
Cytotoxicity	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive
MMP[c]	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive

[a] Dipole moment estimated by Avogadro program.

[b]The toxicity class consists of six numbers. Number 1 means toxic; number 6 means non-toxic.

[c]MMP: Mitochondrial Membrane Potential.

4. CONCLUSION

In this study, the effect of coumarin and its derivatives, whose antiviral activity is known, on RNA polymerase NSP12, one of the important proteins of the SARS-CoV-2 virus, was investigated by molecular docking. In general, NSP12 with RNA scores were lower due to a decrease in the NSP12 catalytic region cavity. The best NSP12+RNA docking scores are 3-(*p*-phenylamidomorpholine), 3-(*p*-phenylamidopiperazine) and 3-(*p*-phenylamidopiperidine) groups carrying coumarins and binding affinities are -10.1 kcal/mol, -10.1 kcal/mol, and -10.0 kcal/mol, respectively. Ligand efficiency suggests that coumarin derivatives in this study may be the potential NSP12 inhibitors. Research on the NSP12 protein of coumarins can be increased with in vivo/in vitro studies. This study is also expected to provide insight into the inhibiting effect of coumarin and its derivatives on scientists working on antiviral treatments for SARS-CoV-2.

5. CONFLICT OF INTEREST

The authors declare no competing financial interest.

Ethical Approval: Ethics Approval is not required for this study.

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