Sigma J Eng Nat Sci, Vol. 41, No. 3, pp. 457–468, June, 2023

Sigma Journal of Engineering and Natural Sciences
Web page info: https://sigma.yildiz.edu.tr
DOI: 10.14744/sigma.2023.00052

Research Article

Determination of the active molecule as a potential drug against covid-19 virus using molecular docking and hybrid AHP-GRA method

Yunus KAYA[1], Aytaç YILDIZ[2,*]

[1]*Department of Chemistry, Bursa Technical University, Bursa, 16310, Türkiye*
[2]*Department of Industrial Engineering, Bursa Technical University, Bursa, 16310, Türkiye*

ARTICLE INFO

Article history
Received: 26 April 2021
Revised: 15 June 2021
Accepted: 18 July 2021

Keywords:
Covid-19; Favirapiravir; Gaussian; Autodock Vina; AHP; GRA

ABSTRACT

In this study, it is aimed to determine the most effective molecule to be used as an active ingredient against the covid-19 virus among the 15 molecules proposed by adding some electronegative groups to some molecules used in the ebola virus. In the first stage of the study, the proposed molecules are optimized in DFT / B3LYP method and 6-311G ++ (d, p) basis set, dipole moment, entropy, energy of HOMO and LUMO orbitals and band gap energies are calculated. In addition, the interactions of these molecules with the Covid-19 main protease enzyme (PDB no = 6LU7) are examined with the Autodock vina program. Correlation analysis is performed using the IBM SPSS Statistics 23 program with the values obtained from molecular docking and DFT calculations, and it is determined that there is no statistically significant relationship between the band gap factor and free docking energy.
In the second stage of the study, the importance weights of the parameters belonging to the molecules are determined by the Analytical Hierarchy Process (AHP) method. Then, the molecules are ranked by preference using the Gray Relational Analysis (GRA) method. According to the results of the sensitivity analysis performed at the end of the study, it is determined that the 1D6-CN molecule is the most effective molecule to be used as an active ingredient against the covid-19 virus.

Cite this article as: Kaya Y, Yildiz A. Determination of the active molecule as a potential drug against covid-19 virus using molecular docking and hybrid AHP-GRA method. Sigma J Eng Nat Sci 2023;41(3):457–468.

INTRODUCTION

Corona virus, also known as Covid-19, is a deadly virus that causes acute respiratory syndrome that spread from Wuhan, China about a year ago, to the whole world [1]. Drug or vaccine studies that will enable the virus to lose its effect have been studied intensively for more than a year [2-7]. While the favirapiravir molecule is currently used as the drug active ingredient, it is known that this molecule has some side effects, although its effectiveness on the virus is limited [8]. On the other hand, studies on how the virus entered the human body have come to a point, and the structures of enzymes that help it enter the human body have been elucidated [9]. The enzyme whose crystal

***Corresponding author.**
*E-mail address: aytac.yildiz@btu.edu.tr
This paper was recommended for publication in revised form by Regional Editor Azmi Seyhun Kıpçak

structure is determined allows for the intensification of modeling studies.

Density Functional Theory (DFT) attracted a lot of attention especially after Hohenberg and Kohn received the Nobel Prize in 1998, and the number of articles in the literature increased exponentially after 2000. Theoretical optimization, electronic structures, structural and spectroscopic properties of molecules can be reached with this program. In this context, new molecules can be modeled based on molecules with possible drug potential in the literature. In addition, the development of programs such as DFT and autodock vina has increased interest in this field. In this study, some molecules whose effects were investigated against the ebola virus in a study conducted by Rhyma [8] and 15 molecules obtained by adding different substituents to these molecules were used. After obtaining optimized structures of molecules by DFT method, coupling studies with appropriate protein (PDB no = 6LU7) were performed. According to the physicochemical properties of molecules such as dipole moment, entropy, HOMO and LUMO orbital energies and band gap, the relationship between protein binding energies was examined and the effective physicochemical parameters in the molecule was determined upon binding. Then, by using physicochemical parameters that are statistically significant with their protein binding energies, the most effective molecule that can be used as an active ingredient against the covid-19 virus was determined by multi-criteria decision-making methods (AHP, GRA). This study is expected to guide scientists working on drug design in determining the physicochemical properties to be considered in the groups to be added. The work flow of the study is shown in Figure 1.

DFT Study

In this study, 15 different molecules whose general structure is given in Figure 2 were used. Density function theory (DFT/B3LYP) [10] and 6-311++G(d, p) basis set was used in optimization and frequency calculations of molecules. The lack of negative frequency of molecules supports those molecules are optimized in the most accurate geometry. The geometrical parameters, dipole moment, entropy, energy of the highest occupied molecular orbital (HOMO), energy of the lowest unoccupied molecular orbital (LUMO) and band gap energy were determined from output file of optimization and frequency calculations. All calculations were performed with the Gaussian 09 suite program [11].

The 15 molecules optimized using Density Functional Theory (DFT) / B3LYP method and 6-311G++(d, p) basis set were represented in Figure 3. The frequency calculations were performed at same level for accuracy of optimization. Dipole moment, entropy, HOMO and LUMO orbital energies and band gap energy values were listed in Table 1.

Molecular Docking Study

The binding energy for all molecules were calculated by Autodock vina packet program, and given in Table 1. The optimized molecular parameters are used in molecular docking studies. The .pdbqt files were obtained from optimized molecular structures and molecular docking calculations were made with the autodock vina program. The crystal structure of the Covid-19 main protease enzime molecule used has been downloaded from the protein data bank (PDB) (PDB no: 6LU7). For each molecule, the binding types in 24 different conformers were examined and the most suitable binding type was determined (RMSD <2 Å).

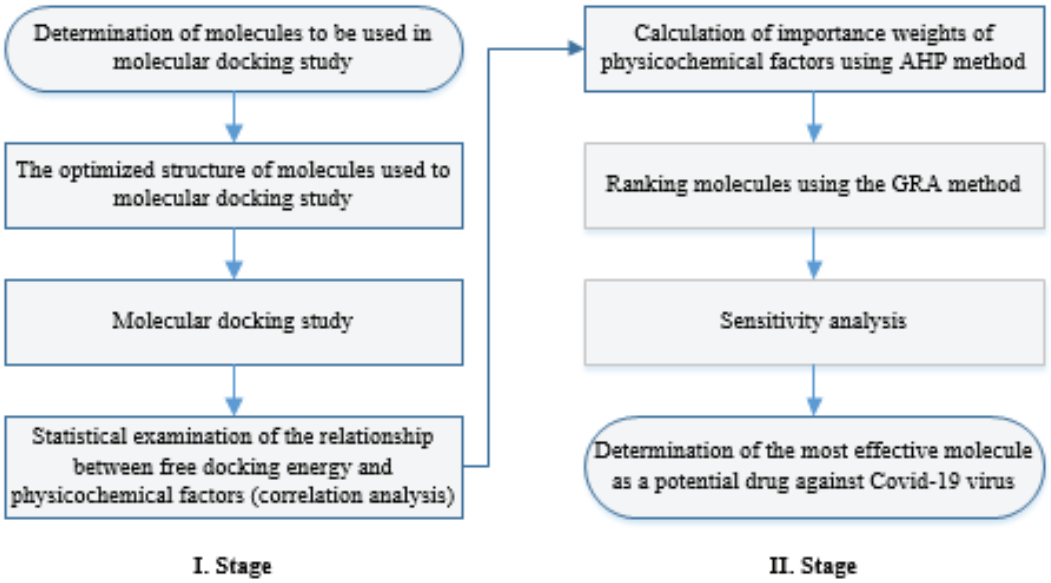

Figure 1. The work flow of the study.

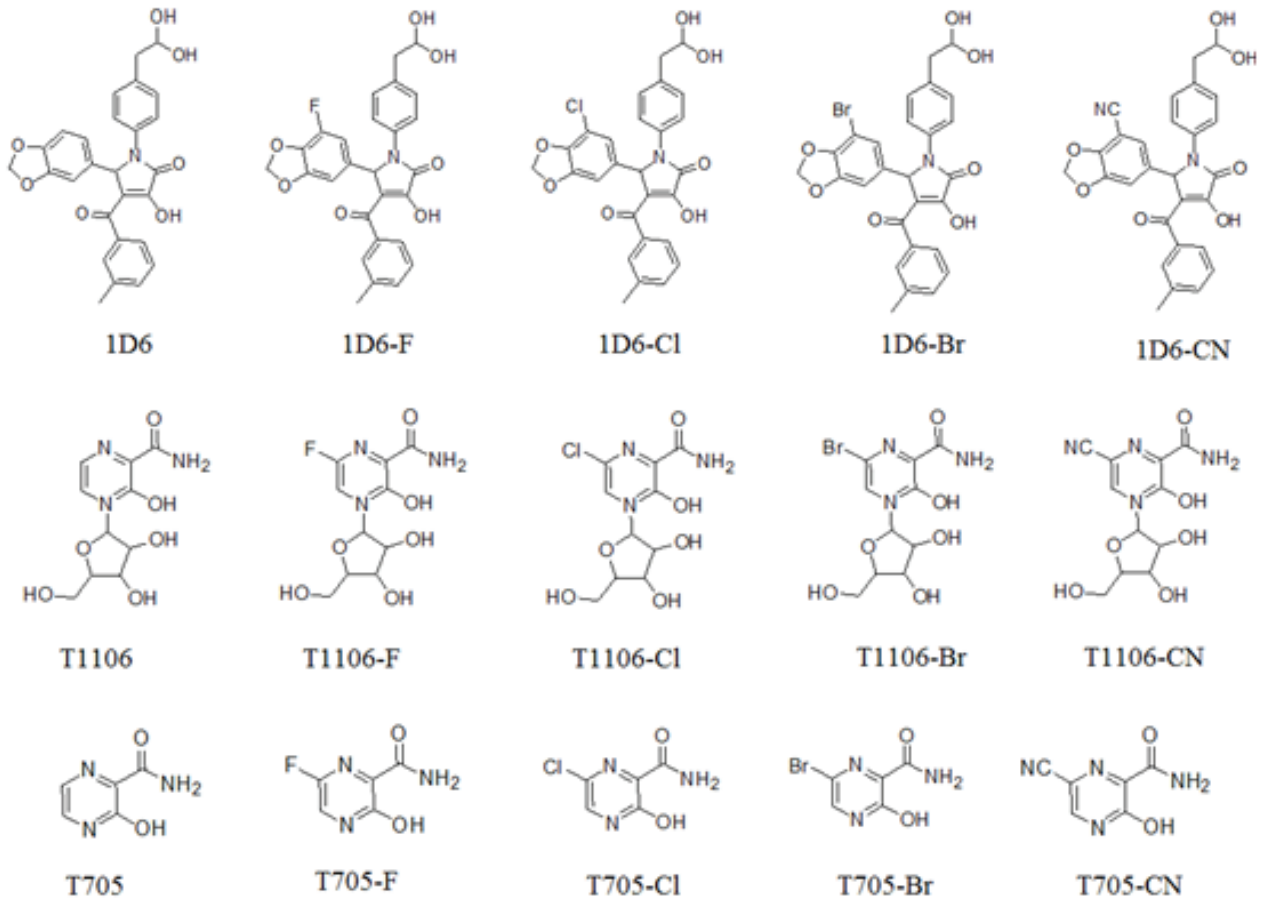

Figure 2. The chemical structure of molecules used to molecular docking study.

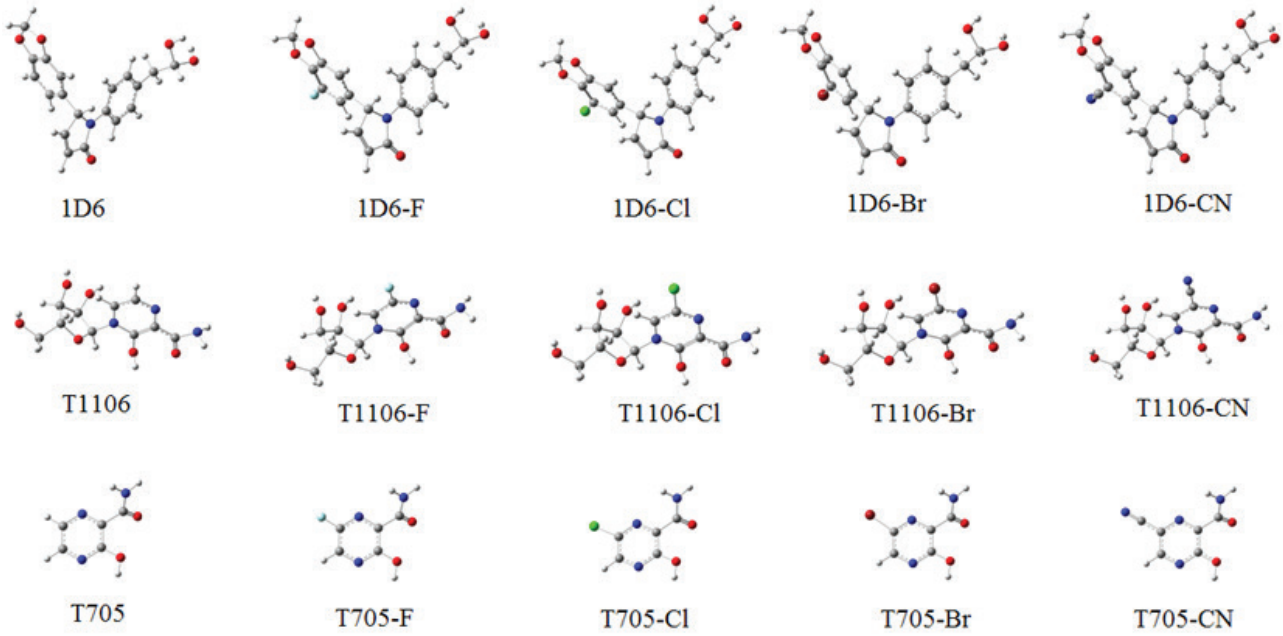

Figure 3. The optimized structure of molecules used to molecular docking study.

Table 1. Dipole moment, electronegativity, entropy, HOMO, LUMO, band gap energy and molecular docking free energy of molecules used to molecular docking study

Molecule	Dipole moment (D)	Entropy (S, J/molK))	Energy of HOMO (eV)	Energy of LUMO (eV)	Band Gap (eV)	Free docking energy (kJ/mol)
1D6	5,0003	147,154	-5,89	-1,59	4,30	-29.71
1D6-F	5,4781	151,249	-5,98	-1,71	4,27	-30.54
1D6-Cl	5,3957	156,404	-5,97	-1,69	4,28	-30.12
1D6-Br	5,4204	157,039	-5,97	-1,70	4,27	-30.12
1D6-CN	7,3652	157,551	-6,10	-1,98	4,12	-31.38
T1106	5,4923	128,147	-5,90	-2,30	3,60	-24.24
T1106-F	5,5190	131,133	-6,09	-2,45	3,64	-25.10
T1106-Cl	5,3942	133,905	-6,08	-2,51	3,57	-25.52
T1106-Br	5,2947	136,579	-6,08	-2,51	3,57	-25.10
T1106-CN	6,5375	138,097	-6,29	-2,97	3,32	-25.52
T705	3,8612	88,967	-7,17	-2,22	4,95	-19.66
T705-F	3,2305	93,164	-7,21	-2,55	4,66	-20.92
T-705-Cl	3,1972	95,986	-7,13	-2,51	4,62	-20.50
T-705-Br	3,0825	98,500	-7,07	-2,56	4,51	-20.08
T-705-CN	4,0545	97,745	-7,66	-2,92	4,74	-20.50

In experimental or theoretical calculations, the drug active ingredient favirapiravir, which is generally used actively against Covid-19 virus, is selected as the reference. The dipole moment value of the favirapiravir (T705-F) molecule was calculated as 3.2305 D. HOMO, LUMO and band gap energies were determined as -7.21, -2.55 and 4.66 eV, respectively. Compared to other molecules in Table 2, the dipole moment is quite low and the band gap energy is quite high. The entropy, which is the most effective parameter for binding in molecular docking calculations, was calculated as 93.164 J / molK for the favirapiravir molecule. Corresponding to these physicochemical parameters, the binding energy was determined as -20.92 kJ / mol. It has been observed that when different substituents are used in the favirapiravir molecule, the binding energies are lower. It has been determined that other molecules similar to the favirapiravir molecule such as T1106 and 1D6 generally exhibit more effective binding properties than favirapiravir.

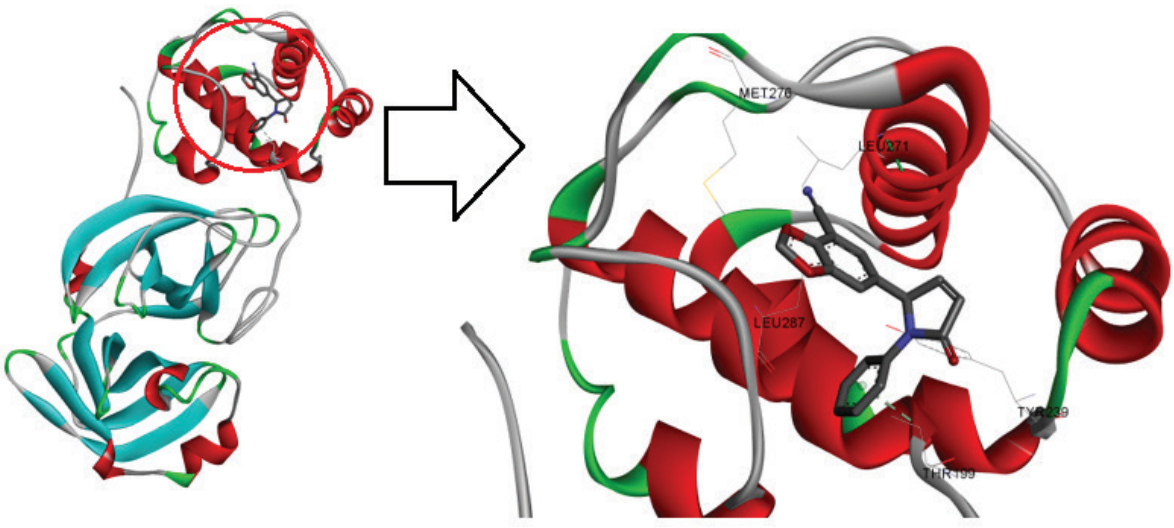

Figure 4. Molecular docking structure of the most favorable docked structure for 1D6-CN in 6LU7.

Among these molecules, 1D6-CN molecule has the highest binding energy of -31.18 kJ / mol. It is thought that high dipole moment (7.3652 D) and entropy (157.551 J / molK) values are effective in calculating the binding energy so high. In addition, it is thought that the energy of the HOMO orbital is as high as -6.10 eV and that the band gap energy is calculated at a relatively low value such as 4.12 eV, which is effective in the interaction with the protein molecule. These approaches, which are evaluated between binding energy and physicochemical parameters, will be concretized with statistical studies.

Molecular docking calculations of the 1D6-CN molecule with the highest binding energy among the 15 molecules and the interaction of the conformer with the highest energy among 9 different conformers with the 6LU7 protein are illustrated in Figure 4. Molecular docking studies revealed that the most stable conformers of 1D6-CN are surrounded by amino acids TMET276, LEU271, LEU287, THR199 and TYR239 (within 3.5 Å). In addition, electrostatic interactions were effective in the high binding energy of the 1D6-CN molecule with the protein molecule.

Determination of the Most Effective Molecule Using AHP and GRA Methods

The AHP and GRA methods used in the study are briefly described below in order to determine the most effective molecule to be used as an active ingredient against the covid-19 virus through the data obtained from the molecular docking study.

AHP method

AHP is one of the methods introduced by Thomas L. Saaty [12] in the 1980s and widely used in solving multi-criteria decision-making problems [13]. The method that can be paired both qualitative and quantitative criteria in solving the problem [14] is a basic approach as it improves decision-making learning using consistency measure [15]. In this method, the most suitable solution is reached with less numerical calculations and provides a clear logic between features [16, 17].

It is also very easy to apply [18]. Instead of following complex mathematical methods, AHP uses pairwise comparison matrices and their associated eigenvectors to create appropriate priority sequences of alternatives. AHP is tolerant of different mathematical tools such as linear programming, fuzzy logic etc., which can be taken advantage of to achieve a desired result. Moreover, AHP organically combines qualitative and quantitative methods and divides a decision into a multi-level hierarchical structure. In this way, the thinking processes of decision makers are systematized and simplified [19]. AHP users first transform decision problems into a hierarchy of more easily comprehended sub-problems, each of which can be analyzed independently [15, 20]. Thus, it simplifies the evaluation of all criteria related to decision-making by organizing complex problems in hierarchical order [13]. The AHP model, based on the principle of pairwise comparisons, allows quantitative and qualitative criteria to be evaluated by considering different values for each criterion [15, 17]. Once the hierarchy is established, decision makers systematically evaluate both quantitative and qualitative criteria by comparing them with each other [21]. Therefore, it is a method used by many decision makers thanks to the simplicity, flexibility and ease of use it provides in the solution of the decision problem. Therefore, AHP has been applied to almost all areas involving decision making since its invention [18]. It has contributed to problem solving in various areas and subjects that can be exemplified, such as risk modeling, location analysis, hospital location selection, environmental impact assessment, electrical energy generation, supplier selection [22]. The implementation steps in the AHP method are listed below [23];

Step 1: Defining the problem: Criteria required for the decision and criteria priorities are determined.

Step 2: Creating the hierarchical structure: At the top of the hierarchy is the main goal to be reached. Under it, there are basic criteria and sub-criteria. Alternatives are at the bottom of the hierarchy.

Step 3: Creating pairwise comparison matrices: By using the scale in Table 2 (taking values between 1 and 9), both

Table 2. Importance values of pairwise comparison and their definitions

Value	Definition	Explanation
1	Equal importance	Two activities contribute equally to the objective
3	Moderate importance of one over another	Experience and judgment strongly favor one activity over another
5	Essential of strong importance	Experience and judgment strongly favor one activity over another
7	Very strong importance	An activity is strongly favored and its dominance demonstrated in practice
9	Extreme importance	The evidence favoring one activity over another is of the highest possible order of affirmation
2, 4, 6, 8	Intermediate values between the two adjacent judgments	Indicates intermediate values between two consecutive evaluations.

criteria are compared among themselves and alternatives are compared according to the criteria.

Step 4: Normalizing the pairwise comparison matrices: Each element in the matrix is normalized by dividing it by its column sum.

Step 5: Calculation of the priority vector: Each row sum of the normalized matrix is divided by the size of the matrix and averaged. These values are the weight of importance calculated for each criterion.

Step 6: Calculating the consistency ratio: To determine the consistency of comparisons, the consistency rate (CR) for each matrix must be calculated after the comparison matrices have been constructed. If the CR value is less than 0.10, it can be said that paired comparisons are consistent. If the values are greater than 0.10, there is an inconsistency and, in this case, the decision-making group should review the paired comparisons.

Step 7: Ranking the alternatives: By combining the priority vectors obtained for the criteria, all priorities matrix is obtained. The result vector is obtained by multiplying the priority vector of the decision options with the all-priorities matrix. The decision option with the highest weight in this vector is determined as the decision option to be preferred for the solution of the problem.

Gray relational analysis method

The gray theory was first proposed by Julong Deng in 1982 [24, 25] and is used in a wide variety of fields such as social, economic and industrial systems [26]. Gray theory, which enables modelling and solving of problems that cannot be solved by stochastic or fuzzy decision-making methods, is a frequently used method as a useful theory for cross-system analysis, model building, prediction and decision-making problems [26, 27]. When looking at real life problems, it is very difficult to describe all factors as fully positive or fully negative. Likewise, it is not possible to evaluate all factors as completely specific or completely uncertain [27]. In this context, gray theory is performed to reach an optimum set of parameters to solve this complex relationship between real world problems [25, 28]. In this theory, a system with no uncertainty or excellent knowledge is defined as a white system, a system in which all factors are completely uncertain or no information is defined as a black system, and partially definite and partially uncertain systems are defined as gray or hazy [26, 29]. Gray Relational Analysis (GRA), which is a sub-topic of gray theory, is also mentioned as a decision-making method in the literature. GRA is recommended for problems with multivariate statistics that do not fit any distribution, do not contain sufficient data, and cannot be modeled due to uncertainty [30]. It is used in various engineering applications due to its simplicity and evaluation ability. GRA is a multi-response optimization method that converts a single-target problem into a multi-target response feature function, namely gray relational grade [25, 31]. GRA is a method based on measuring the distance between reference series of a gray system and comparison series. Having the point set topology feature, GRA uses similarity and difference measurements to measure the distance between two points, making a global comparison instead of local to avoid the effects of subjective parameters [26]. The steps of the GRA method are detailed below [32];

Step 1: Construct the data set and construct the decision matrix: The decision matrix, which has alternatives in its rows and indicators in its columns, is represent as *X*. The total alternative number is *m*(i = 1,2,…*m*), and the total indicator number is *n(k=1,2,…n):*

$$X=\begin{bmatrix} x_1(1) & \cdots & x_1(n) \\ \vdots & \ddots & \vdots \\ x_m(1) & \cdots & x_m(n) \end{bmatrix} \quad (1)$$

Step 2: Construct the reference sequence and comparison matrix

$$x_0 = \left(x_0(j),...,x_0(n)\right) \qquad j = 1,2,...,n \quad (2)$$

Step 3: Normalize the data and construct the normalized matrix

If larger sequence values contribute positively, then normalization for "the larger the better" attributes is as follows:

$$x_i(k) = \frac{x_i^0(k) - \min x_i^0(k)}{\max x_i^0(k) - \min x_i^0(k)} \quad (3)$$

where $x_i^0(k)$ is the original value in the row k. in the sequence i. $x_i(k)$ is the value in the row k. in the sequence i after normalization, min $x_i^0(k)$ is the minimum value in the sequence i and max $x_i^0(k)$ is the maximum value in the sequence i.

If smaller sequence values contribute positively, then normalization for "the smaller the better" cost is as follows:

$$x_i(k) = \frac{\max x_i^0(k) - x_i^0(k)}{\max x_i^0(k) - \min x_i^0(k)} \quad (4)$$

Normalization for "the nominal the better" is as follows:

$$x_i(k) = 1 - \frac{\left|x_i^0(k) - x^0\right|}{\max x_i^0(k) - x^0} \quad (5)$$

where x^0 is nominal value.

Step 4: construct the absolute value table and gray relational coefficient matrix

Let k be the row k. on a n-length sequence and $\varepsilon\left(x_0(k), x_i(k)\right)$ be the grey relational coefficient at the point k. calculated using Equations (7), (8), (9) and (10).

$$\Delta=\begin{bmatrix}\Delta_{01}(1) & \cdots & \Delta_{01}(\mathrm{n})\\ \vdots & \ddots & \vdots\\ \Delta_{0\mathrm{m}}(1) & \cdots & \Delta_{0\mathrm{m}}(\mathrm{n})\end{bmatrix} \quad (6)$$

$$\varepsilon\left(x_0(k),x_i(k)\right)=\frac{\Delta_{\min}+\xi\Delta_{\max}}{\Delta_{0i}(k)+\xi\Delta_{\max}} \quad (7)$$

$$\Delta_{0i}(k)=\left|x_0(k)-x_j(k)\right| \quad (8)$$

$$\Delta_{\min}=\min_j\min_k\left|x_0(k)-x_j(k)\right| \quad (9)$$

$$\Delta_{\max}=\max_j\max_k\left|x_0(k)-x_j(k)\right| \quad (10)$$

where $\xi\in(0,1)$ is a coefficient between 0 and 1. The function ξ sets the difference between Δ_{0i} and $\Delta_{\max}$.

Step 5: The grey relational degree is calculated using Eq. (11).

$$\gamma\left(x_0,x_i\right)=\frac{1}{n}\sum_{k=1}^{n}\varepsilon\left(x_0(k),x_i(k)\right) \quad (11)$$

If the weights of criteria are given in advance, grey correlation coefficients are calculated by the multiplying grey relationship coefficients and weights of the criteria.

$$\gamma\left(x_0,x_i\right)=\frac{1}{n}\sum_{k=1}^{n}\varepsilon\left(x_0(k),x_i(k).\left(W_i(k)\right)\right) \quad (12)$$

Findings from AHP and GRA methods

At this stage of the study, firstly, the correlation analysis given in Table 3 was performed through IBM SPSS Statistics 23 program in order to statistically examine the effects of physicochemical parameters of molecules on free docking energy using the data obtained from the docking study.

When Table 3 is examined, it is determined that there is a significant and positive relationship at the 0.01 level between free docking energy and dipole moment, entropy, energy of HOMO and energy of LUMO, but there is no statistically significant relationship between free docking energy and band gap. According to this result, considering the physicochemical parameters of the molecules, the band gap factor was not taken into account in determining which molecule is more effective in using as an active ingredient against the covid-19 virus, using multi-criteria decision-making methods.

Findings from AHP method

In order to determine the most effective molecule to be used as an active ingredient against covid-19 virus, the importance weights of physicochemical parameters were first determined with the AHP method. For this, physicochemical parameters were pairwise compared according to the algorithm of the method by two expert physicochemists according to the scale in Table 2, and the pairwise comparison matrix given in Table 4 was created and the importance weights of the parameters were calculated. The consistency ratio (CR) of the pairewise comparison matrix

Table 3. Correlation analysis

Physicochemical parameters		**Free docking energy**	**Dipole moment**	**Entropy**	**Energy of HOMO**	**Energy of LUMO**	**Band Gap**
Free docking energy	Pearson Correlation	1	,781**	,971**	,839**	,742**	-,360
	Sig. (2-tailed)		,001	,000	,000	,002	,188
Dipole moment	Pearson Correlation	,781**	1	,844**	,765**	,272	-,686**
	Sig. (2-tailed)	,001		,000	,001	,327	,005
Entropy	Pearson Correlation	,971**	,844**	1	,906**	,624*	-,544*
	Sig. (2-tailed)	,000	,000		,000	,013	,036
Energy of HOMO	Pearson Correlation	,839**	,765**	,906**	1	,582*	-,695**
	Sig. (2-tailed)	,000	,001	,000		,023	,004
Energy of LUMO	Pearson Correlation	,742**	,272	,624*	,582*	1	,180
	Sig. (2-tailed)	,002	,327	,013	,023		,522
Band Gap	Pearson Correlation	-,360	-,686**	-,544*	-,695**	,180	1
	Sig. (2-tailed)	,188	,005	,036	,004	,522	

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

Table 4. Paired comparison of molecular physicochemical parameters and their importance weights

Physicochemical parameters	Physicochemical parameters				Importance weights
	Dipole moment	Entropy	Energy of HOMO	Energy of LUMO	
Dipole moment	1	1/2	2	4	0,264
Entropy	2	1	4	8	0,528
Energy of HOMO	1/2	1/4	1	3	0,148
Energy of LUMO	1/4	1/8	1/3	1	0,060

was calculated as 0.008. Since this value is less than 0.10, it has been determined that the paired comparisons are consistent.

Findings from the GRA method

First, the decision matrix in Table 5 was created using the data obtained from the docking study. In the statistical analysis section, the band gap parameter, which did not show a significant relationship with free docking energy, was not taken into account here. While creating the reference series given in the same table, dipole moment, entropy and energy of HOMO parameters were taken into consideration as the benefit parameter and the max values of the series were taken into consideration. Similarly, energy of LUMO is evaluated as the cost parameter and min values are taken into account.

After the decision matrix was created, the data were normalized using eq. (3) and (4). Here; Dipole moment, entropy and energy of HOMO parameters were evaluated as benefit parameters, and normalized as the "larger the better" situation and the energy of LUMO factor were evaluated as cost criteria and normalized as the "smaller the better" situation. The obtained normalized matrix is given in Table 6.

Then, absolute values were calculated using equation (8), and the gray relational coefficient matrix given in Table 7 was obtained by using eq. (7), (9), (10) and (11).

By using Eq. (12), parameter weights obtained by AHP method and gray relational coefficients were multiplied and weighted gray relational degrees given in Table 8 were obtained. Finally, the preference order of the molecules is made according to the total gray relational degrees.

Table 5. Decision matrix

Molecule	Physicochemical parameters			
	Dipole moment	Entropy	Energy of HOMO	Energy of LUMO
	Max	Max	Max	Min
Reference series	7,3652	157,55	-5,89	-2,97
1D6	5,0003	147,15	-5,89	-1,59
1D6-F	5,4781	151,25	-5,98	-1,71
1D6-Cl	5,3957	156,4	-5,97	-1,69
1D6-Br	5,4204	157,04	-5,97	-1,7
1D6-CN	7,3652	157,55	-6,1	-1,98
T1106	5,4923	128,15	-5,9	-2,3
T1106-F	5,519	131,13	-6,09	-2,45
T1106-Cl	5,3942	133,91	-6,08	-2,51
T1106-Br	5,2947	136,58	-6,08	-2,51
T1106-CN	6,5375	138,1	-6,29	-2,97
T705	3,8612	88,97	-7,17	-2,22
T705-F	3,2305	93,16	-7,21	-2,55
T-705-Cl	3,1972	95,99	-7,13	-2,51
T-705-Br	3,0825	98,5	-7,07	-2,56
T-705-CN	4,0545	97,75	-7,66	-2,92

Table 6. Normalized matrix

	Dipole moment	Entropy	Energy of HOMO	Energy of LUMO
Reference series	1,000	1,000	1,000	1,000
Molecule	Max	Min	Max	Max
1D6	0,448	0,848	1,000	0,000
1D6-F	0,559	0,908	0,949	0,087
1D6-Cl	0,540	0,983	0,955	0,072
1D6-Br	0,546	0,993	0,955	0,080
1D6-CN	1,000	1,000	0,881	0,283
T1106	0,563	0,571	0,994	0,514
T1106-F	0,569	0,615	0,887	0,623
T1106-Cl	0,540	0,655	0,893	0,667
T1106-Br	0,517	0,694	0,893	0,667
T1106-CN	0,807	0,716	0,774	1,000
T705	0,182	0,000	0,277	0,457
T705-F	0,035	0,061	0,254	0,696
T-705-Cl	0,027	0,102	0,299	0,667
T-705-Br	0,000	0,139	0,333	0,703
T-705-CN	0,227	0,128	0,000	0,964

Table 7. Gray relational coefficient matrix

Molecule	Dipole moment	Entropy	Energy of HOMO	Energy of LUMO
1D6	0,475	0,767	1,000	0,333
1D6-F	0,532	0,845	0,908	0,354
1D6-Cl	0,521	0,968	0,917	0,350
1D6-Br	0,524	0,985	0,917	0,352
1D6-CN	1,000	1,000	0,808	0,411
T1106	0,533	0,538	0,989	0,507
T1106-F	0,537	0,565	0,816	0,570
T1106-Cl	0,521	0,592	0,823	0,600
T1106-Br	0,508	0,621	0,823	0,600
T1106-CN	0,721	0,638	0,689	1,000
T705	0,379	0,333	0,409	0,479
T705-F	0,341	0,347	0,401	0,622
T-705-Cl	0,339	0,358	0,416	0,600
T-705-Br	0,333	0,367	0,429	0,627
T-705-CN	0,393	0,364	0,333	0,932
Importance Weight	0,264	0,528	0,148	0,060

In the ranking made according to total gray relational degrees in Table 8, 1D6-CN molecule ranked 1st with a gray relational degree of 0.234, 1D6-Br is ranked 2nd, and T705 molecule ranked last with a gray relational degree of 0.091.

Sensitivity analysis was performed in order to determine whether the rankings in Table 8 changed with the change of parameter weights and to make a more precise evaluation. While performing the sensitivity analysis, one parameter was given the lowest and highest importance weight, while the importance weights of other parameters were not changed. This process was repeated for all parameters and 6 different scenarios were obtained. Then, new rankings were obtained and the results are given in Figure 5.

According to the sensitivity analysis results given in Figure 5, the 1D6-CN molecule ranked first in five scenarios. In the last scenario, T1106-CN molecule ranked first.

Table 8. Weighted gray relational degree and ranking

Molecule	Dipole moment	Entropy	Energy of HOMO	Energy of LUMO	Total gray relational degree	Ranking
1D6	0,125	0,405	0,148	0,020	0,175	5
1D6-F	0,140	0,446	0,134	0,021	0,185	4
1D6-Cl	0,138	0,511	0,135	0,021	0,201	3
1D6-Br	0,138	0,520	0,135	0,021	0,204	2
1D6-CN	**0,264**	**0,528**	**0,119**	**0,025**	**0,234**	**1**
T1106	0,141	0,284	0,146	0,031	0,150	9
T1106-F	0,142	0,298	0,120	0,034	0,149	10
T1106-Cl	0,137	0,313	0,122	0,036	0,152	8
T1106-Br	0,134	0,328	0,122	0,036	0,155	7
T1106-CN	0,190	0,337	0,102	0,060	0,172	6
T705	0,100	0,176	0,060	0,029	0,091	15
T705-F	0,090	0,183	0,059	0,037	0,093	14
T-705-Cl	0,090	0,189	0,061	0,036	0,094	13
T-705-Br	0,088	0,194	0,063	0,038	0,096	12
T-705-CN	0,104	0,192	0,049	0,056	0,100	11

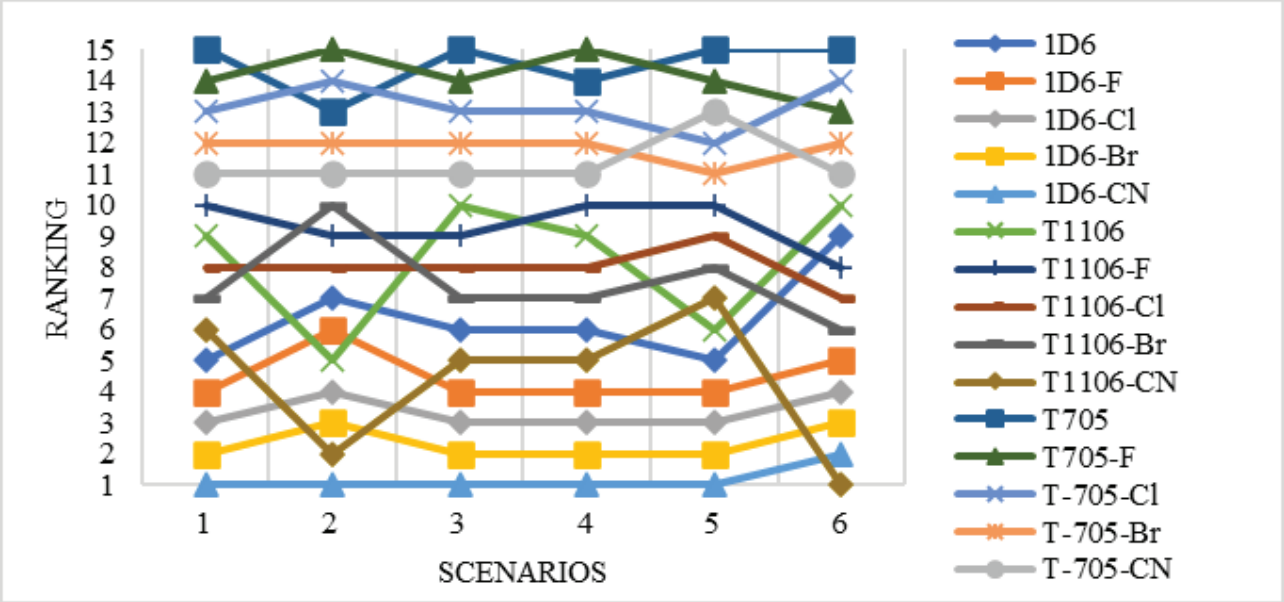

Figure 5. Sensitivity analysis.

On the other hand, the 1D6-Br molecule, ranked second, except for scenarios where the lowest weight of importance was given to the entropy factor (0.06) and the energy of LUMO factor to the highest weight. When Figure 4 is examined, it is thought that it may be beneficial to choose the 1D6-CN molecule as the most effective molecule to be used as an active ingredient against the covid-19 virus in drug design.

CONCLUSION AND DISCUSSION

The viral drug studies continue against the covid-19 virus, which we have been fighting for about a year. In this context, effective drug active ingredient studies are still interesting experimentally and theoretically. In this context, this study includes the theoretical calculation and statistical study results of 15 molecules obtained by adding substituents to some molecules previously used in the ebola

virus. Physicochemical parameters such as dipole moment, entropy, HOMO, LUMO and band gap energies were calculated by optimizing the 15 molecule DFT / B3LYP / 6-311G ++ (d, p) method and basis set.

In addition, docking studies of the molecules were carried out and the relationship between physicochemical parameters and their binding energies was statistically analyzed and the molecule suitable for being the drug active ingredient was determined. According to the docking results obtained, 1D6-CN molecule with a binding energy of -31.18 kJ / mol has the highest interaction. The dipole moment of this molecule was calculated as 7.3652 D and its entropy 157.551 J / molK.

In the second stage of the study, multi-criteria decision-making methods were used to determine the most effective molecule as a drug active ingredient against the covid-19 virus. AHP method, which is one of these methods, was used to determine the importance weights of the physicochemical parameters of the molecules. The most effective molecule was determined using the GRA method. According to the result obtained from the study, the 1D6-CN molecule was determined as the most effective molecule that can be used as an active ingredient against the covid-19 virus. The determination of the 1D6-CN molecule as the most effective molecule according to the results obtained from both the docking study and multi-criteria decision-making methods has shown that it will be beneficial to use this molecule in drugs against the covid-19 virus. According to these results, it shows that the molecules can be synthesized in the experimental environment and their effect against the Covid-19 virus can be started to tested in vivo and in vitro environment. In addition, statistical studies have determined the physicochemical parameters that are decisive on the mechanism of action, and it is thought that it will also be beneficial for molecular designs.

As a result, it is thought that the methods used in the study and the results obtained will guide both researchers and drug designers.

AUTHORSHIP CONTRIBUTIONS

Authors equally contributed to this work.

DATA AVAILABILITY STATEMENT

The authors confirm that the data that supports the findings of this study are available within the article. Raw data that support the finding of this study are available from the corresponding author, upon reasonable request.

CONFLICT OF INTEREST

The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

ETHICS

There are no ethical issues with the publication of this manuscript.

REFERENCES

[1] Trott O, Olson AJ. AutoDock Vina: Improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. J Comput Chem 2010;31:455–461. [CrossRef]

[2] Stigler RD, Hoffmann B, Abagyan R, Schneider-Mergener J. Soft docking an L and a D peptide to an anticholera toxin antibody using internal coordinate mechanics. Structure 1999;7:663–670. [CrossRef]

[3] Abele E, Lukevics E. Recent advances in the chemistry of oximes. Org Prep Proced Int 2000;32:235–264. [CrossRef]

[4] Menziani MC, De Rienzo F, Cappelli A, Anzini M, De Benedetti PG. A computational model of the 5-HT3 receptor extracellular domain: search for ligand binding sites. Theor Chem Acc 2001;106:98–104. [CrossRef]

[5] Hetényi C, Körtvélyesi T, Penke B. Mapping of possible binding sequences of two beta-sheet breaker peptides on beta amyloid peptide of Alzheimer's disease. Bioorg Med Chem 2002;10:1587–1593. [CrossRef]

[6] Zhu X, Shi D. Synthesis and biological activities of novel thiophosphoryl oximates containing thiazole and 1, 2, 3triazole rings. Chinese J Chem 2009;27:565–568. [CrossRef]

[7] Dittmar M, Lee JS, Whig K, Segrist E, Li M, Jurado K, et al. Drug repurposing screens reveal fda approved drugs active against SARS-Cov-2. Microbiology 2020;35:108959. [CrossRef]

[8] Rhyman L, Tursun M, Abdallah HH, Choong YS, Parlak C, Kharkar P, et al. Theoretical investigation of the derivatives of favipiravir (T-705) as potential drugs for Ebola virus. Phys Sci Rev 2018;3:20170198. [CrossRef]

[9] Bakowski MA, Beutler N, Chen E, Nguyen TTH, Kirkpatrick MG, Parren M, et al. Oral drug repositioning candidates and synergistic remdesivir combinations for the prophylaxis and treatment of COVID-19. Nature Commun 2020 Article 153403. [CrossRef]

[10] Becke AD. Density-functional thermochemistry III. The role of exact exchange. J Chem Phys 1993;98:5648. [CrossRef]

[11] Frisch MJ, Trucks GW, Schlegel HB. Gaussian 09, revision D.01. Wallingford CT: Gaussian, Inc, 2009.

[12] Saaty TL. The analytic hierarchy process. 1st ed. McGraw-Hill: New York; 1980. [CrossRef]

[13] Sedghiyan D, Ashouri A, Maftouni N, Xiong Q, Rezaee E, Sadeghi S. Prioritization of renewable energy resources in five climate zones in Iran using AHP, hybrid AHP-TOPSIS and AHP-SAW methods. Sustain Energy Technol Assess 2021;44:101045. [CrossRef]

[14] Kadak EG. The place of AHP technique in performance evaluation and its application in the pharmaceutical distribution sector in Turkey. Master Thesis. Adana: Cukurova University; 2006.
[15] Solangi YA, Longsheng C, Shah SAA. Assessing and overcoming the renewable energy barriers for sustainable development in Pakistan: An integrated AHP and fuzzy TOPSIS approach. Renew Energy 2021;173:209–222. [CrossRef]
[16] Ramnath RA, Thyla PR, Harishsharran AKR. Machining parameter selection in milling epoxy granite composites based on AHP. Mater Today 2021;42:319–324. [CrossRef]
[17] Shahnazari A, Pourdej H, Kharage MD. Ranking of organic fertilizer production from solid municipal waste systems using analytic hierarchy process (AHP) and VIKOR models. Biocatal Agric Biotechnol 2021;32:101946. [CrossRef]
[18] Aksoy B, Gursoy M. Evaluation of location selection process of logistics villages using analytic hierarchy process and electre methods: a case study for Turkey. Sigma J Eng Nat Sci 2020;38:1897–1910.
[19] Han Y, Wang Z, Lu X, Hu B. Application of AHP to road selection. ISPRS Int J Geoinf 2020;9:86. [CrossRef]
[20] Enis OS. Denetim evreninin belirlenmesinde alternatif bir yöntem: Analitik hiyerarşi prosesi. Denetisim 2010;4:8–16. [Turkish]
[21] Ozyoruk B, Ozcan EC. Application of analytical hierarchy process in the supplier selection: An example from automotive sector. Süleyman Demirel Univ J Econ Adm Sci 2008;13:133–144.
[22] Caner HI, Aydin CC. Shipyard site selection by raster calculation method and AHP in GIS environment, İskenderun, Turkey. Mar Policy 2021;127:104439. [CrossRef]
[23] Saaty TL. Theory and applications of the analytic network process. 3rd ed. USA: RWS Publications; 2005.
[24] Li X, Wang Z, Zhang L, Zou C, Dorrell DD. State-of-health estimation for Li-ion batteries by combing the incremental capacity analysis method with grey relational analysis. J Power Sources 2019;410:106–114. [CrossRef]
[25] Babbar A, Sharma A, Singh P. Multi-objective optimization of magnetic abrasive finishing using grey relational analysis. Mater Today 2022;50:570–575. [CrossRef]
[26] Kocak D. Green growth dynamics in OECD countries: an application of gray relational analysis. Grey Syst Theory Appl 2020;10:545–563. [CrossRef]
[27] Kursun B, Kurt U, Guvercin S, Okten K, Akgul S, Yildiz A. An application for the failure mode and effects analysis integrated with the grey relational analysis. Trakya Univ J Eng Sci 2016;17:35–44.
[28] Yildiz A, Ozbek A. Selection of socks export markets for Turkey using multicriteria decision making methods. Sigma J Eng Nat Sci 2020;38:1897–1910.
[29] Pandya VJ, Rathod PP. Optimization of mechanical properties of green composites by gray relational analysis. Mater Today 2020;27:19–22. [CrossRef]
[30] Yaser EM, Shunmugesh K. Multi-objective optimization of milling process parameters in glass fibre reinforced polymer via grey relational analysis and desirability function. Mater Today 2019;11:1015–1023. [CrossRef]
[31] Baranitharan P, Ramesh K, Sakthivel R. Multi-attribute decision-making approach for Aegle marmelos pyrolysis process using TOPSIS and Grey Relational Analysis: Assessment of engine emissions through novel Infrared thermography. J Clean Prod 2019;234:315–328. [CrossRef]
[32] Julong D. Introduction to grey system theory. J Grey Syst 1989;1:1–24.