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Structural, Electronic, ADME and p450 Analyses of Boron Containing Compounds against Omicron Variant (B.1.1.529) in SARS-CoV-2

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ABSTRACT

Eight boron compounds are investigated in this study. Structural and spectral characterization is done at M062X/6-311G(d) level in the water. Active sites of these compounds are determined using contour plots of frontier molecular orbital, molecular electrostatic potential (MEP) maps and MEP contour.. Electrophilic and nucleophilic attack regions are determined. We aimed to determine whether boron compounds inhibitor used in the treatment of omicron variant of SARS-CoV-2. Since SARS-CoV-2 is a worldwide health problem, anti-viral properties of studied boron compounds were investigated using in silico techniques. Bioavaliability analyses were performed using ADME and p450. It was found that compound B7 can be good drug candidate against omicron variant of SARS-CoV-2.

Keywords: Boron-Imine compounds, SARS-CoV-2_Omicron, p450, ADME, Molecular docking.

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Introduction

In December 2019, the novel coronavirus is broked out in Wuhan, Hubei province of China and it is called as novel coronavirus 2019 (2019-nCoV) or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and appeared as a pandemic threatening the world [1]. To date, many variants of SARS-CoV-2 have been encountered and the threat still continues [1]. To date, seven variants of this virus which are alpha, beta, gamma, delta, omicron, lambda, and mu, are reported and summarized by the world health organization. The most common symptoms of this disease are fever, cough, tiredness, loss of taste and smell. However, the serious symptoms are difficulty breathing, loss of speech or mobility, and chest pain. Currently, many people suffer from this disease, and some end up with death. Additionally, many drugs are used for the treatment of COVID-19 while many vaccines are used for the preventation from SARS-CoV-2. Furthermore, many drug candidates are investigated by researchers [2-6].

Nowadays, the omicron variant of SARS-CoV-2 is the most important threat and many people suffer from this variant. The Omicron variant of SARS-CoV-2 is known as B.1.1.529 variant and has been reported firstly on 24 November 2021 in South Africa [7]. Normally, three genes/proteins of SARS-CoV-2 are reported as the most important ones which are main protease, spike-glycoprotein, and RNA polymerase. However, the spike glycoprotein of the omicron variant of SARS-CoV-2 is not detected at first. In subsequent analyzes, it was reported that the spike protein belonging to the omicron variant was not similar to that of the other variants. Protein structure of omicron variant is shown in Fig. 1.

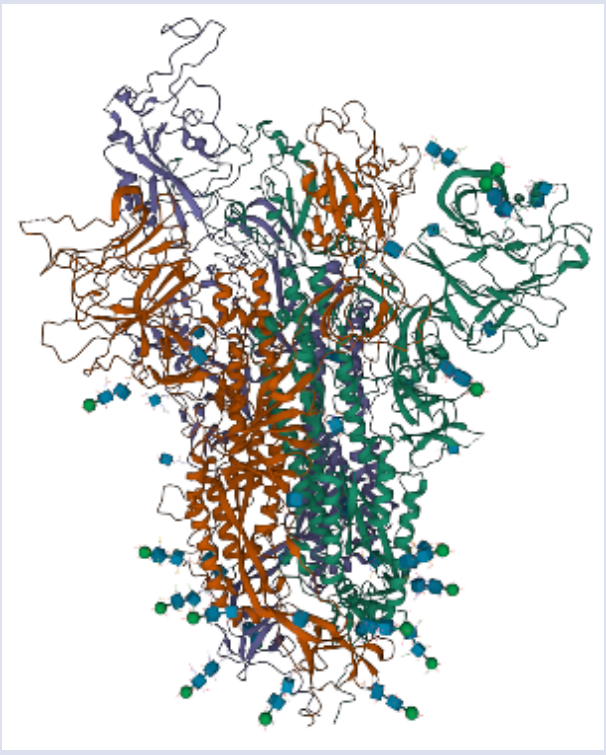


Fig. 1. The protein structure of omicron variant of SARS-CoV-2.

In this study, boron-imine structured compounds are taken into consideration and these compounds have been synthesized by Pasa and co-workers [8]. These compounds are initially optimized at M06-2X/6-311G(d) level in water. In this study, it is accepted that M062X/6-311G(d) level is popular ones for the boron compounds. The Polarizable Continuum Model (PCM) using the integral equation formalism variant (IEF-PCM) model is used to taking of solute – solvent interaction in optimizations. Electronic properties of these boron compounds are investigated using contour diagram of frontier moleculer orbitals, molecular electrostatic potential (MEP) maps and MEP contours. Finally, molecular docking analysis which is the popular analysis in the recent time to determine the biological activity of chemicals are performed between target proteins and selected compounds [9-11]. Target proteins are main protease, RNA polymerase, and spike glycoproteins of SARS-CoV-2. Additionally, alpha and omicron variant of this virus is considered. Finally, selected compounds are found as more inactive against alpha variant of SARS-CoV-2 while they are found as highly active against that of the omicron variant. Compounds B4, B5 and B7 can be good inhibitor candidates in the treatment of the omicron variant of SARS-CoV-2.

Materials and Methods

Optimization

Fully optimization calculations were performed using Gaussian software [12, 13]. Initally, the whole compounds in this study was pre-optimized in universal force field (UFF) molecular mechanic method in order not to waste time and not to encounter errors in future optimization calculations. In subsequent optimization calculations, M06-2X method was used with the 6-311G(d) basis set. Furthermore, IEF-PCM method was used to consider solute-solvent interaction. All calculations were done in the water phase. Furthermore, ChemDraw software was used as utilities throughout the study [14].

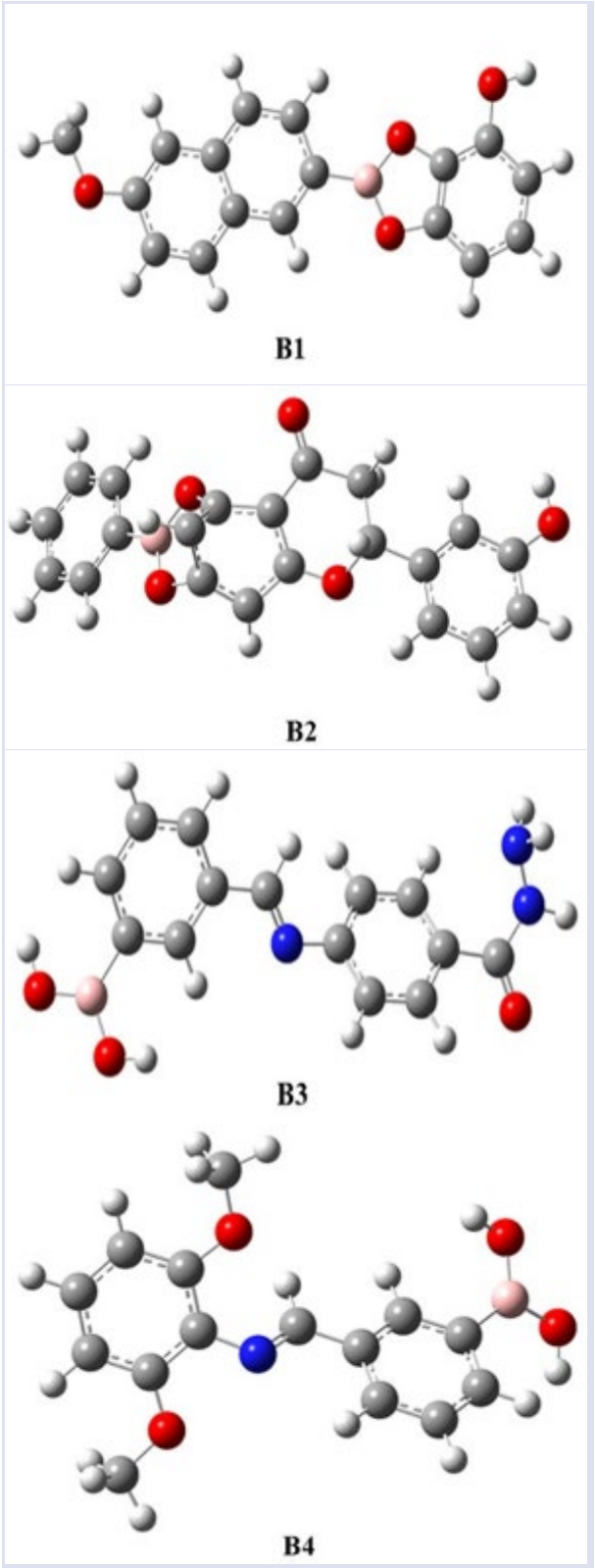
Molecular Docking

Studied compounds were prepared for docking calculation using LigPrep module in Maestro software. Acidity of calculations is selected as 7±2. Then target proteins which are 6NUS [15], 6VSB [16], 6WNP [17] and 7QO7 [18] were prepared using Protein Preperation module. 6NUS, 6VSB and 6WNP are related with alpha variant of SARS-CoV-2 while 7QO7 was related with omicron variant. 6NUS, 6WNP, 6WNP and 7QO7 were related with RNA polymerase, main protease, spike glycoprotein of alpha variant and spike glycoprotein of omicron variant, respectively. The receptor binding domain of them are defined using Grid Generation. Then molecular docking calculations were performed [19-22]. In these calculation four parameters which are docking score (DS), van der Walls energy (E_{vdW}), Coloumb interaction energy (E_{Coul}) and total interaction energy (E_{Total}), were examined and evaluated. ADME and p450 analyses were performed for the studied boron containg compounds.

Results and Discussion

Optimized Structures

The examined compounds are optimized at M06-2X/6-311G(d) level in the water. Optimized structures of them are represented in Fig. 2.



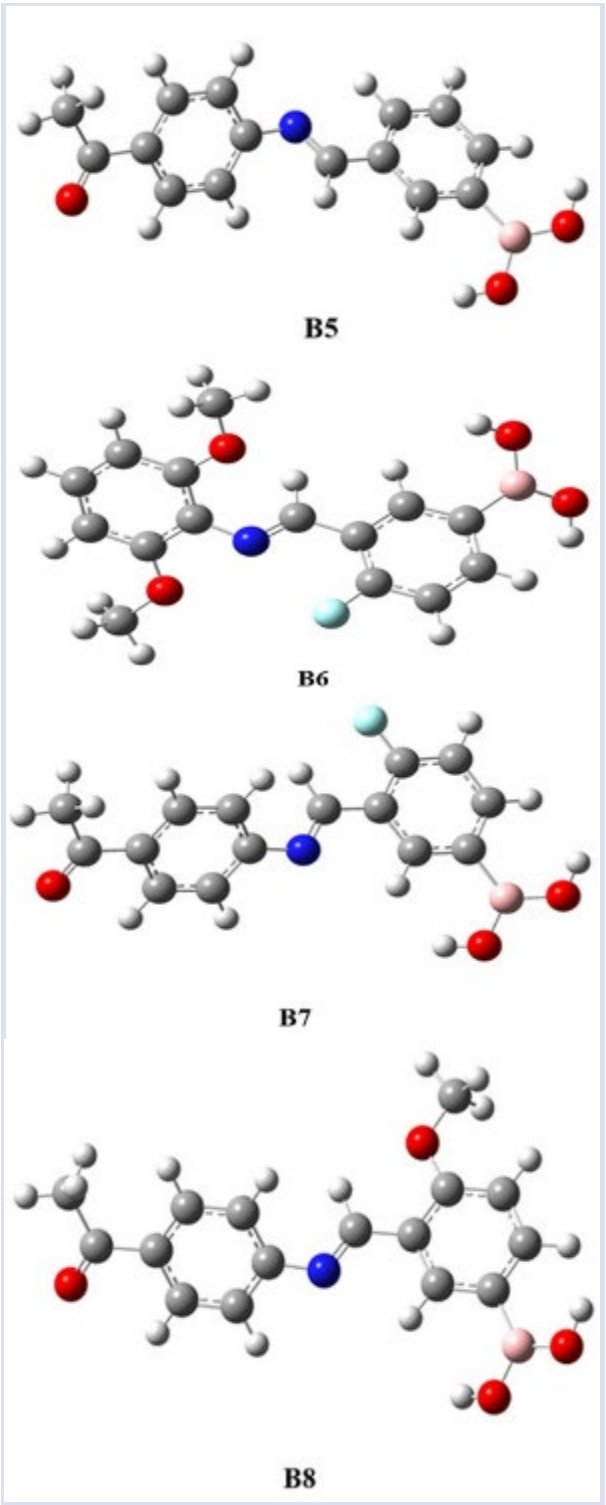


Fig. 2. The optimized structure of studied boron compounds.

According to optimized structures, studied boron compounds are mainly look alike to each other. Only the attached substituents cause the structural branching of the compounds. IR spectrum of studied compounds are calculated and potential energy distribution (PED) analyses of these spectrum are performed. IR spectrum and PED analyses are represented in Fig. 3 and Table 1, respectively.

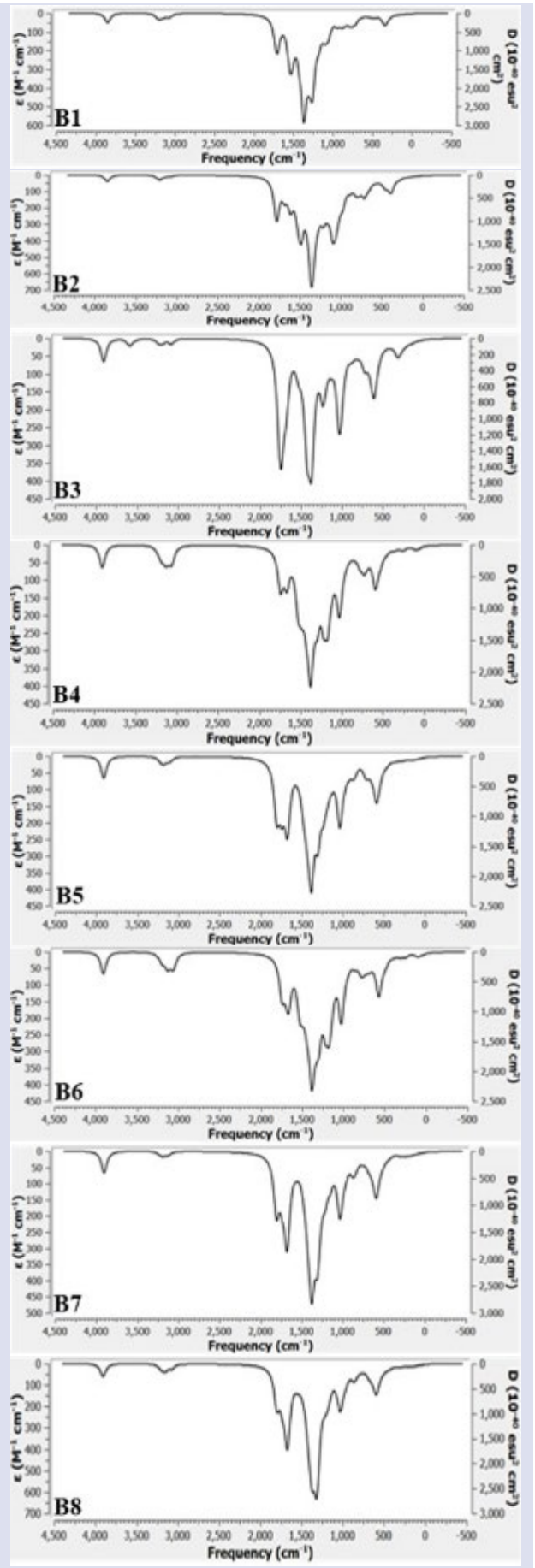


Fig. 3. The IR spectrum of boron compounds.

Table 1. The calculated frequencies (cm^{-1}) in PED Analyses

B1	
3850	STRE(OH)
3180	STRE(CH)
1703	STRE(CC), STRE(CC)
1544	BEND(HCC), BEND(HCH)
1367	STRE(CB)
1293	STRE(CC), BEND(HCC), BEND(HCC)
335	BEND(CCC), BEND(OCC), BEND(CBO), BEND(COC)
B2	
3848	STRE(OH)
3214	STRE(CH)
1781	STRE(OC)
1612	STRE(CC)
1504	BEND(HCC), BEND(CCC)
1361	STRE(CB), BEND(HCC), BEND(HCO)
1218	BEND(HOC), BEND(HCC)
1102	STRE(OC)
815	STRE(CH), TORS(HCCC), OUT(CCOC)
711	BEND(COB), TORS(HCCC), TORS(CCCC)
380	STRE(OC), TORS(HOCC), STRE(CC)
B3	
3906	STRE(OH), STRE(CC)
3585	STRE(NH)
3233	STRE(CH)
3083	STRE(CH)
1762	STRE(OC), BEND(HNH)
1375	STRE(OB), STRE(CB), BEND(HCC)
1234	STRE(CC), STRE(NN), BEND(HNN)
1011	BEND(HNH), TORS(HNNC)
607	STRE(OH), STRE(NC)
309	TORS(HNNC)
B4	
3903	STRE(OH)
3067	STRE(CH)
1742	STRE(NC)
1666	STRE(CC), BEND(CCC)
1377	STRE(OB), STRE(CB)
1214	BEND(HCC)
1033	STRE(OB), BEND(HOB)
781	TORS(HCCC), TORS(CCCC), OUT(OCCC)
592	TORS(HOBC)
B5	
3907	STRE(OH)
3167	(STRE(CH)
1801	STREOC)
1674	STRE(CC)
1378	STRE(OB), STRE(CB)
1301	STRE(CC)
1037	BEND(HOB)
589	TORS(HOBC)
B6	
3905	STRE(OH)
3064	STRE(CH)
1744	STRE(NC)
1688	STRE(CC), BEND(HCC)
1382	STRE(OB), STRE(CB)
1171	STRE(OC), BEND(HCC)
1027	BEND(HOB)
783	TORS(HCCC), OUT(OCCC)
567	TORS(HOBC)
B7	
3904	STRE(OH)
3123	STRE(CH)
1804	STRE(OC)
1678	STRE(CC)
1375	STRE(OB), STRE(CB), BEND(HCC)
1311	STRE(CC), STRE(FC), BEND(HCC)
1036	STRE(OB), BEND(HOB)
875	TORS(HCCC)
592	BEND(OCC), TORS(HOBC)
B8	
3902	STRE(OH)
3074	STRE(CH)
1799	STRE(OC)
1672	STRE(NC), STRE(CC)
1372	STRE(OB), STRE(CB), BEND(HCC)
1321	STRE(CC), STRE(OC)
1034	STRE(OB), BEND(HOB)
852	TORS(HCCC), OUT(OCCC)
592	TORS(HOBC)

Electronic Properties

Electronic properties of chemicals play important role on the determination of interaction mechanism, active site of compounds and molecular effectiveness of compound surface etc. For these aims, different plots of maps can be used and contour diagram of frontier molecular orbitals, molecular electrostatic potential (MEP) maps and MEP contours are calculated for each boron compounds. While contour diagram of frontier molecular orbitals of B1-B8 are represented in Fig. 4.

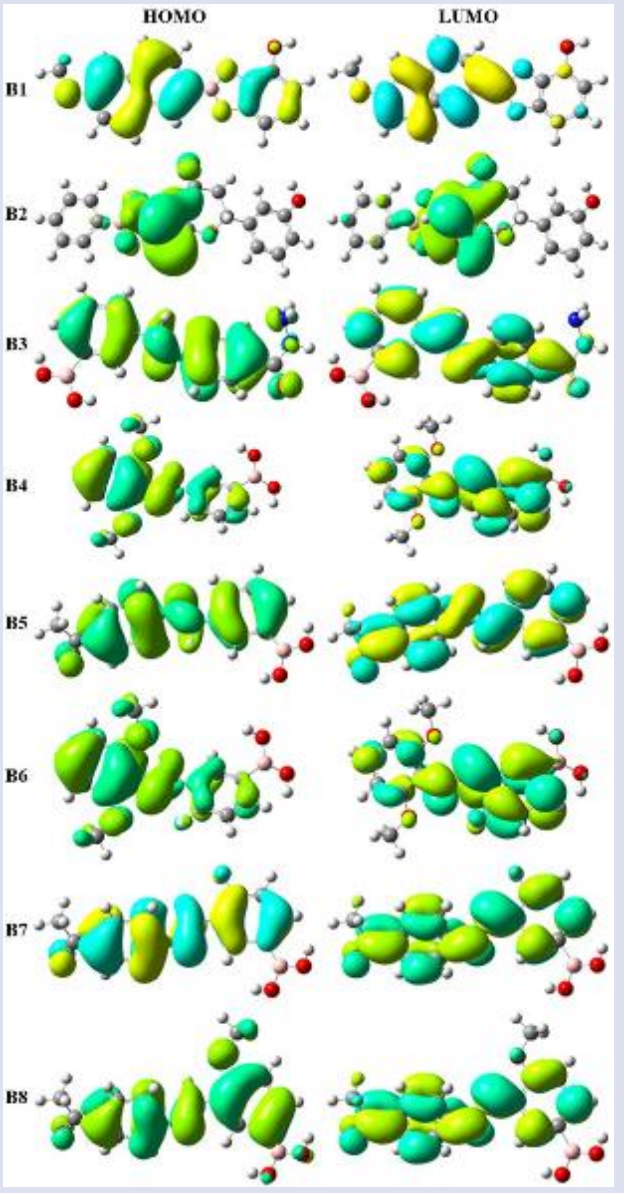


Fig. 4. Contour diagram of frontier molecular orbitals of B1-B8

According to Fig. 4, HOMO electrons are mainly delocalized on the whole structure of the studied compound. In the contour plot of LUMO, electrons could be delocalized on the whole structure. To exmine more detail, MEP maps and contours are calculated and respresented in Fig. 5.

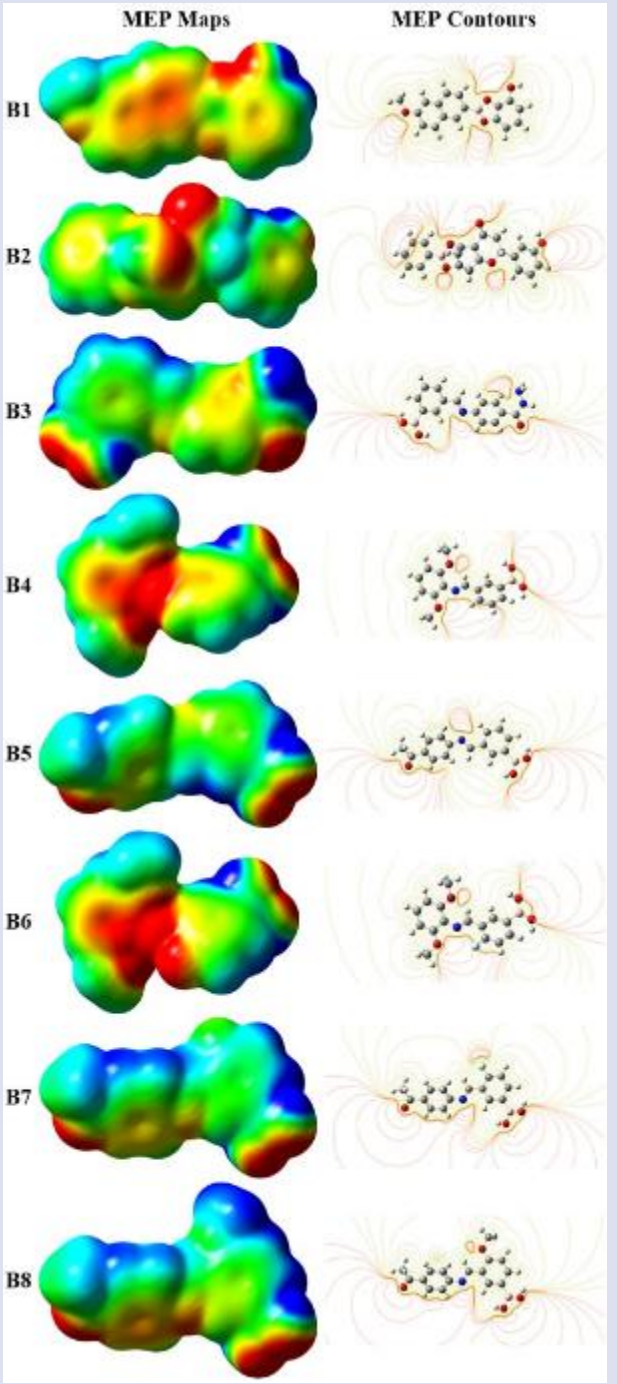


Fig. 5. MEP maps and MEP contours of B1-B8.

Especially, it can be seen easily that π electrons play an essential role in having this feature. MEP maps and contours show the reactive zones on the molecular surface. The reactivity of π electrons is seen easily from MEP maps of related compounds, too. Additionally, reactivity of heteroatoms which are oxygen, nitrogen etc. can be easily seen from MEP contours.

Molecular Docking Analysis

The best method to foresee the biological activity of chemicals is molecular docking calculations. In this study, biological reactivity of studied compounds are investigated against SARS-CoV-2. Especially, alpha and omicron variants are taken into consideration. For this aim, four proteins are selected which are 6NUS, 6VSB, 6WNP and 7QO7. The docking results are summurized and given in Table 2.

Table 2. Summarized docking results

Compounds	6NUS[a]	6VSB[a]	6WNP[a]	7QO7[a]
B1	D	ND	D	D
B2	D	ND	D	D
B3	D	ND	D	D
B4	D	ND	D	D
B5	D	ND	D	D
B6	D	ND	D	D
B7	D	ND	D	D
B8	D	ND	D	D

[a] D: Docked; ND: No Docked

Docking score (DS), van der Walls energy (E_{vdW}), Coulomb interaction energy (E_{Coul}) and total interaction energy (E_{Total}) are given in Table 3.

Table 3. The molecular docking results

Comp.	DS[a]	E_{vdW}[a]	E_{Coul}[a]	E_{Total}[a]
6WNP				
B1	-4.025	-18.607	-2.412	-21.019
B2	-4.459	-23.707	-4.969	-28.675
B3	-3.999	-18.383	-10.056	-28.440
B4	-3.459	-20.045	-4.633	-24.678
B5	-4.175	-19.363	-6.274	-25.637
B6	-3.208	-17.640	-6.718	-24.358
B7	-4.387	-19.878	-7.344	-27.222
B8	-3.961	-16.111	-10.001	-26.112
6NUS				
B1	-4.970	-25.791	-2.226	-28.017
B2	-4.061	-30.073	-3.423	-33.496
B3	-5.026	-32.006	-4.806	-36.812
B4	-4.589	-30.838	-5.315	-36.153
B5	-5.814	-24.050	-9.323	-33.373
B6	-4.566	-28.114	-7.157	-35.271
B7	-4.338	-31.376	-2.472	-33.847
B8	-5.581	-31.039	-6.366	-37.405
7QO7				
B1	-6.490	-35.881	-1.848	-37.729
B2	-6.389	-43.435	-2.425	-45.860
B3	-6.092	-39.063	-1.179	-40.242
B4	-7.258	-31.499	-10.517	-42.016
B5	-7.018	-37.780	-2.730	-40.509
B6	-5.399	-31.124	-3.888	-35.012
B7	-7.352	-39.375	-1.904	-41.278
B8	-6.657	-36.210	-4.512	-40.722

[a] in kcal/mol

According to obtained results, studied boron compounds are more effective against omicron variant than alpha variant of SARS-CoV-2.

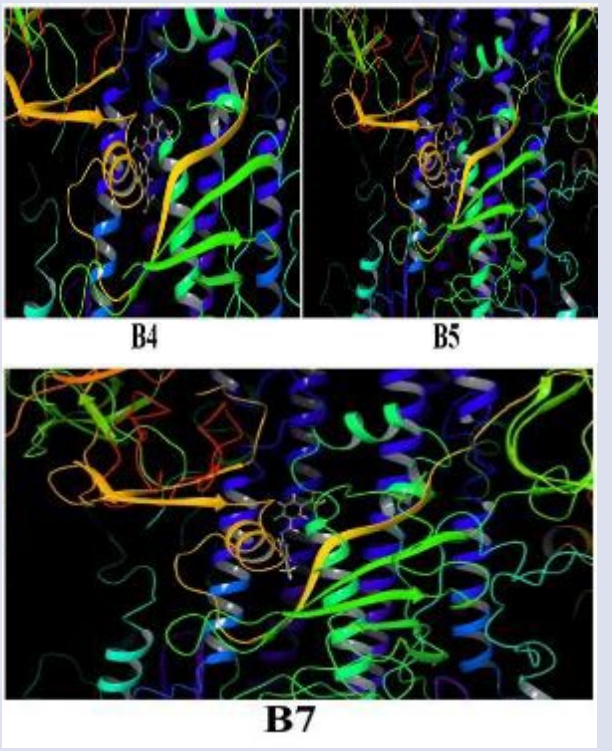
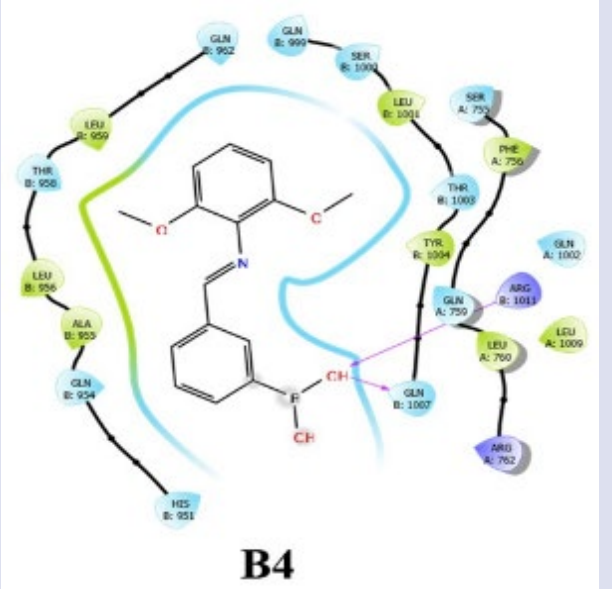


Fig. 6. Docking structure of B4, B5 and B7 compounds

Especially, docking score in alpha variant are so small. However, this case is not same in omicron variant. The docking score is the first parameter due to the fact that it shows the key-lock harmony between inhibitor candidate and target protein. In obtained results, the docking score of B4, B5 and B7 is better than the other in omicron variant of SARS-CoV-2. Their interaction energies are better, too. The complex structure of B4, B5 and B7 with 7QO7 are represented in Fig. 6. Additionally, interaction maps of them are represented in Fig. 7.



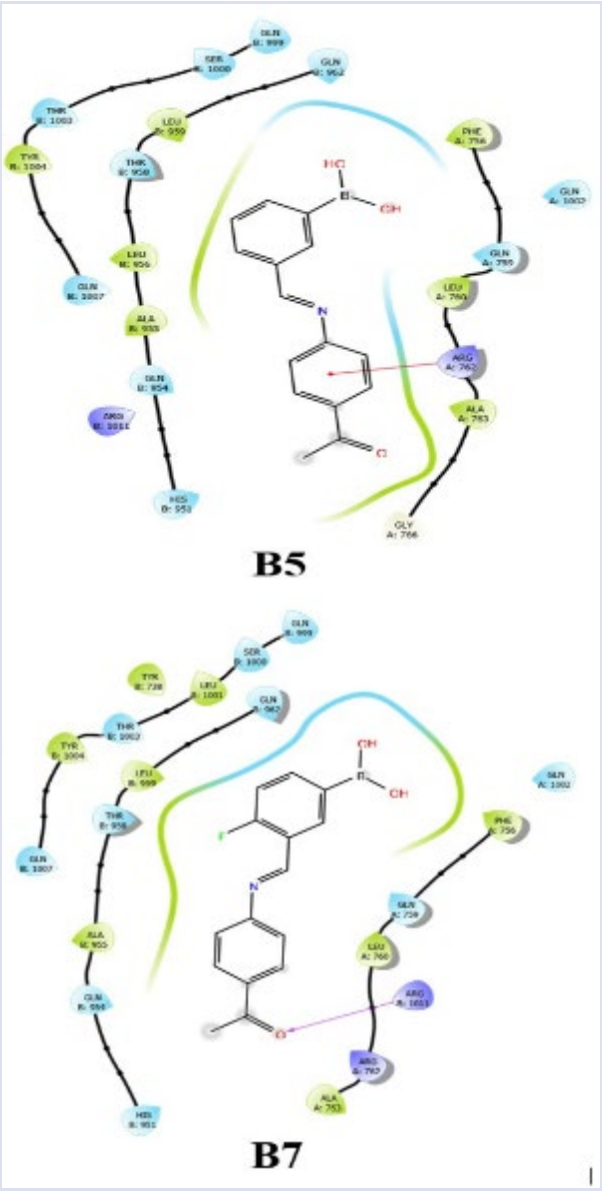


Fig. 7. Interaction maps of B4, B5 and B7 with spike glycoprotein of omicron variant of SARS-CoV-2.

As a result, B4, B5 and B7 compounds can be effective against omicron variant of SARS-CoV-2. The further analyses should be done in detail to today's problem to fight COVID19

ADME Analysis

ADME is an abbreviation for "absorption, distribution, metabolism and excretion" in pharmacokinetics and pharmacology and describes the localization of a pharmaceutical compound within an organism. The whole criterias affect drug levels and drug exposure kinetics to tissues and so affect the performance and pharmacological activity of the drug candidates. QikProp descriptors of studied boron containing compounds are calculated using Maestro 12.8 software to determine the ADME properties. However atomic properties of boron is changed as any special atom to calculate the parameters. QikProp parameters are given in Table 4.

Table 4. Calculated QikProp parameters of studied boron compounds for ADME analyses

Parameters[a]	B1	B2	B3	B4	B5	B6	B7	B8	RV[b]
Stars	0	1	1	0	1	0	1	0	0-5
Amine	0	0	0	0	0	0	0	0	0-1
rtvFG	1	1	2	1	1	1	1	1	0-2
SASA	521.9	627.1	543.1	558.4	547.0	567.5	552.8	586.4	300.0-1000.0
FOSA	98.0	76.7	15.4	196.6	97.3	195.1	94.0	186.3	0.0-750.0
FISA	56.1	104.5	243.3	103.2	163.2	109.0	163.0	162.5	7.0-330.0
PISA	367.7	445.9	284.4	258.6	286.5	231.9	258.6	237.6	0.0-450.0
WPSA	0	0	0	0	0	31.5	37.2	0	0.0-175.0
donorHB	1	1	5	2	2	2	2	2	0.0-6.0
AccptHB	3	5	7.4	5.9	6.4	5.9	6.4	7.2	2.0-20.0
QPpolrz	32.0	40.7	28.0	29.2	28.9	29.9	29.1	30.9	13.0-70.0
QPPCaco	2907.5	1011.8	48.9	1041.0	280.7	916.4	282.0	284.9	<25 poor >500 great
QPlogBB	-0.1	-0.5	-2.2	-0.9	-1.4	-0.9	-1.3	-1.5	-3.0- 1.2
QPPMDCK	1568.1	501.0	19.0	516.7	125.3	669.6	201.4	127.3	<25 poor >500 great
QPlogKp	-1.1	-1.8	-4.2	-1.7	-2.9	-1.9	-2.9	-2.9	-8.0- -1.0
metab	2	4	0	2	0	2	0	1	1-8
QPlogKhsa	0.4	0.5	-0.7	-0.3	-0.4	-0.2	-0.3	-0.4	-1.5- 1.5
Percent Human-Oral Absorption	100	100	58.1	94.2	79.7	94.4	80.8	80.5	>80% is high <25% is poor
PSA	47.6	75.1	121.2	65.9	85.4	68.5	85.3	91.5	7.0- 200.0
RuleOfFive	0	0	0	0	0	0	0	0	Max is 4
RuleOfThree	0	1	0	0	0	0	0	0	Max is 3

[a] Stars: Number of property or descriptor values that fall outside the 95% range of similar values for known drugs; Amine: Number of non-conjugated amine groups; rtvFG: Number of reactive functional groups; SASA: Total solvent accessible surface area; FOSA: Hydrophobic component of the SASA; FISA: Hydrophilic component of the SASA; PISA: π (carbon and attached hydrogen) component of the SASA; WPSA: Weakly polar component of the SASA; donorHB: Estimated number of hydrogen bonds that would be donated; AccptHB: Estimated number of hydrogen bonds that would be accepted; QPpolrz: Predicted polarizability in cubic angstroms; QPPCaco: Predicted apparent Caco-2 cell permeability in nm/sec; QPlogBB: Predicted brain/blood partition coefficient; QPPMDCK: Predicted apparent MDCK cell permeability in nm/sec; QPlogKp: Predicted skin permeability; metab: Number of likely metabolic reactions; QPlogKhsa: Prediction of binding to human serum albumin; PercentHuman-OralAbsorption: Predicted human oral absorption on 0 to 100% scale; PSA: Van der Waals surface area of polar nitrogen and oxygen atoms; RuleOfFive: Number of violations of Lipinski's rule of five; RuleOfThree: Number of violations of Jorgensen's rule of three.
[b] RV: Recommended Value

According to Table 4, calculated parameters are in the good agreement with the recommended value for each parameters. These parameters reveal the druglikeness properties of the investigated compounds. Especially, these compounds have skin permeability, MDCK cell permeability, Caco-2 cell permeability, brain/blood permeability. Additionally, some compounds can be taken part in metabolic reactions which it is undesirable. In such cases, the dose of the drugs taken into the body should be adjusted. According to all results in Section 3.5 and 3.6, **B5 and B7** is the most significant drug candidates for the SARS-CoV-2. However, p450 metabolism analyzes are required for a clearer prediction and the affinities of the compounds (B4, B5 and B7) against CYP enzymes should be investigated.

p450 Analyses

p450 metabolism analysis is so critical for the drug desing processes. It is vital to investigate the interaction of the designed drugs with CYP enzymes, which are cytochrome p450 enzymes.

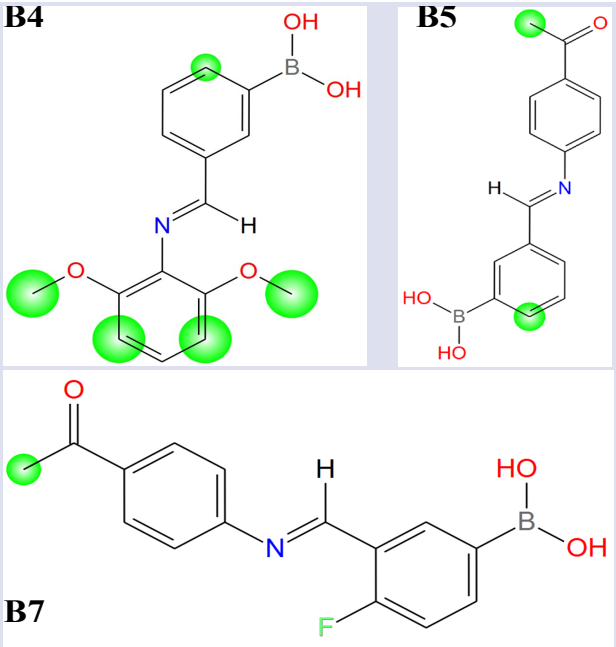


Fig. 8. The overall SOM score of B4, B5 and B7

CYP enzymes have been identified in animals, plants, fungi, protists, bacteria, and archaea, as well as in viruses. However, it is known that it is not found in some living things, although it is rare. It is known that there are more than 300000 CYP proteins. CYP enzymes are essential for the metabolism of many medications. Three CYP enzymes are so important and the most known ones which are CYP2C9, CYP2D6 and CYP3A4 and they metabolize ninty percent of drugs. p450 metabolism prediction can be done by in silico techniques. In this study, p450 metabolism analyses of synthesized boron compound are performed against CYP2C9. It is seen that each compound inhibits the CYP2C9. Overall SOM score of B4, B5 and B7 compounds against the CYP2C9 is represented in Fig. 8. The docking results of B4, B5 and B7 compounds are given in Table 5.

Table 5. The docking results against CYP2C9

Compound	DS[a]	E_{vdW}[a]	E_{Coul}[a]	E_{Total}[a]
B4	-6.242	-29.436	-7.957	-37.393
B4	-6.831	-24.896	-8.228	-33.124
B4	-6.772	-30.584	-8.036	-38.619
B5	-6.748	-40.903	-0.600	-41.502
B5	-5.955	-25.085	-5.737	-30.822
B7	-6.154	-35.734	-6.130	-41.864

[a] in kcal/mol

According to Fig. 8, the results are displayed as green circles, in which the radius is proportional to the score. Larger scores mean higher reactivity. The most reactive compound is found as B4 while B7 is the least reactive one. These results are agreement with docking results given in Table 5. While more than one binding pattern of the B4-labeled compound to CYP2C9 is determined, this value is two in B5 and one in B7. While the strongest key-lock compatibility is observed in B4, this value of B7 is in the middle level among the results. The docking structure of B7 with CYP2C9 is represented in Fig. 9.

Fig. 9. The complex structure between B7 and CYP2C9.

Conclusion

Eight boron compounds were investigated. Firstly, these compounds were fully optimized M06-2X/6-311G(d) level in water. IR spectrum of them were calculated to characterization of these structure. Electronic properties of studied compounds were investigated contour plots of frontier molecular orbitals, MEP maps and MEP contours. Especially active atoms and zones on the structure were determined in detail. Biological activity of these compounds were examined against SARS-CoV-2. Alpha variant and omicron variant were taken into consideration. Four proteins were selected which are 6NUS, 6VSB, 6WNP and 7QO7. The 7QO7 protein belongs to the omicron variant, while the others belong to the alpha variant. The results obtained show that the investigated compounds did not exhibit the desired effect against the alpha variant, but were highly effective against the omicron variant. In particular, B4, B5 and B7 compounds were found to be highly effective against the omicron variant. ADME properties and p450 analyses of related compounds are performed. As a result, B7 is found as the best drug candidate against Omicron variant of SARS-CoV-2.

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Conflicts of interest

There are no conflicts of interest in this work.

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