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The Search for Potential SARS-CoV-2 Inhibitors Using the *In Silico* Research

Abstract

Aim. Using *in silico* technologies to search for potential SARS-CoV-2 inhibitors among novel tetracyclic ring systems, which are the common core of Crinipellin.

Materials and methods. The study object was new compounds previously synthesized *via* oxidative dearomatization of Crinipellin A. The method of the flexible molecular docking was applied in the study.

Results and discussion. Using the molecular docking, the affinity of five compounds for the receptor-ACE2 SARS-CoV-2 (PDB ID: 7DF4), a spike protein SARS-CoV-2 (PDB ID: 1WNC), a PL protein SARS-CoV-2 (PDB ID: 7CJD) and a reverse transcriptase enzyme SARS-CoV-2 (PDB ID: 6YYT) was studied. The results of the molecular docking obtained suggest that 8,8-dimethyl-5-(phenylsulfonyl)-3,3a,4,5,8,9-hexahydroindeno[3a,4-*b*]furan-2(7*H*)-one may be a potential SARS-CoV-2 inhibitor; it is the basis for its further experimental pharmacological study.

Conclusions. The study constitutes one of the stages of searching for SARS-CoV-2 inhibitors. According to the results obtained, a way to search for potential SARS-COV-2 inhibitors based on Crinipellin A derivatives was proposed. Using the most promising compound with hexahydroindeno[3a,4-b]furan core further studies open up another direction for searching for compounds of SARS-COV-2 inhibitors and will save time and laboratory animals while conducting targeted experimental research.

Keywords: COVID-19 virus; Crinipellin A; flexible molecular docking; SARS-COV-2 inhibitor

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Пошук потенційних інгібіторів SARS-CoV-2 за допомогою *in silico* методів

Анотація

Мета роботи. За використання *in silico* технологій здійснити пошук потенційних інгібіторів SARS-CoV-2 серед нових тетрациклічних кільцевих систем, які є загальним ядром криніпеліну.

Матеріали та методи. Об'єктом дослідження є п'ять нових сполук, одержаних шляхом деароматизації криніпеліну А і синтезованих у попередніх дослідженнях. В *in silico* дослідженнях використано метод гнучкого молекулярного докінгу.

Результати та їх обговорення. Шляхом використання докінгових досліджень вивчено афінітет п'яти сполук до рецептора-ACE2 SARS-CoV-2 (PDB ID:7DF4), spike протеїну SARS-CoV-2 (PDB ID: 1WNC), PL протеїну SARS-CoV-2 (PDB ID: 7CJD) та ферменту зворотної транскриптази SARS-CoV-2 (PDB ID: 6YYT). Одержані результати докінгових досліджень дозволяють стверджувати, що 8,8-диметил-5-(фенілсульфоніл)-3,3a,4,5,8,9-гексагідроіндено[3a,4-*b*]фуран-2(7*H*)-он може бути потенційним інгібітором SARS-COV-2, що є підставою для його подальшого експериментального фармакологічного вивчення.

Висновки. Подане дослідження є одним з етапів пошуку інгібіторів SARS-CoV-2. З огляду на одержані результати запропоновано шлях пошуку потенційних інгібіторів SARS-COV-2 на основі похідних криніпеліну А. Подальші дослідження з використанням найбільш перспективної похідної гексагідроіндено[3a,4-*b*]фурану відкривають ще один напрям пошуку сполук інгібіторів SARS-COV-2 та дають можливість заощадити час і лабораторних тварин у межах виконання цілеспрямованих експериментальних досліджень у майбутньому.

Ключові слова: COVID-19 вірус; криніпелін А; гнучкий молекулярний докінг; інгібітор SARS-COV-2

Conflict of interests: The authors have no conflict of interests to declare.

■ Introduction

Currently, there is no drug that is effective in various forms of the new coronavirus, severe acute respiratory syndrome, coronavirus 2 (SARS-CoV-2). Since there is no efficient approved treatment or SARS-CoV-2 inhibitor drugs, the computational strategy is a promising way and plays a significant role in the pharmaceutical industry for the discovery of new drugs [1].

This work is one of the stages of searching for effective SARS-CoV-2 inhibitors. In this study, we examined five compounds previously synthesized and tested their binding affinity for the human receptor SARS-CoV-2 – ACE2 (PDB ID:7DF4), a spike protein SARS-CoV-2 (PDB ID: 1WNC), a PL protein SARS-CoV-2 (PDB ID:7CJD), a reverse transcriptase SARS-CoV-2 (PDB ID: 6YYT) using the molecular docking research.

■ Materials and methods

Continuing the work in the direction of searching for new antiviral drugs, scientists have synthesized new compounds based on the common core of Crinipellin A *via* oxidative dearomatization [2]. The structures of the test compounds are shown in Figure 1.

The target compounds were designed by chemical modification of the common core of Crinipellin A in such a way that the drug could exhibit the high activity and bioavailability, as well as the low toxicity. The results of predicting their antimicrobial, antiviral, antitumor, antifungal and anti-inflammatory activity and a good pharmacokinetic profile have been confirmed by the data provided by the authors in the article [3].

Ligands were prepared using the MGL Tools 1.5.6 program. The ligand optimization was performed using the Avogadro program.

The analysis of literature data shows that it is the S protein after binding to the ACE2 receptor that determines the penetration of the virus into the cell. This fact indicates that S protein is the main factor in the pathogenesis of COVID-19;

therefore, it is promising for the development *in silico* of specific ligands that can be used as SARS-CoV-2 inhibitors [4–7].

SARS-S engages angiotensin-converting enzyme 2 (ACE2) as the entry receptor and employs the cellular serine protease TMPRSS2 for S protein priming. The SARS-S/ACE2 interface has been elucidated at the atomic level, and it has been found that the efficiency of using ACE2 is a key determining the SARS-CoV transmissibility [8, 9]. The papain-like protease (PLpro) of type 2 coronavirus with a severe acute respiratory syndrome (SARS-CoV-2) plays an essential role in virus replication and immune evasion, representing an attractive drug target. Considering that the PLpro proteases of SARS-CoV-2 and SARS-CoV

2,2-dimethyl-
1,2,3,4,4a,5,7a,8-octahydro-
4,8-ethano-*s*-indacen-
9-one (**1**)

2,2-dimethyl-
1,2,3,4,4a,5,7a,8-octahydrospiro-
[4,8-ethano-*s*-indacene-
10,2'-oxiran]-9-one (**2**)

4,4-dimethyl-
4,5,6a,9,9a,9b-hexahydro-
1*H*-cyclobuta[*d*]-*s*-indacen-
2(3*H*)-one (**3**)

4,5-dihydroxy-
2,2-dimethyldecahydro-
3a,7-ethanocyclopenta-
[2,3]cyclopropa[1,2-*a*]-
pentalen-9-one (**4**)

8,8-dimethyl-5-(phenylsulfonyl)-
3,3a,4,5,8,9-hexahydroindeno[3a,4-*b*]furan-2(7*H*)-one (**5**)

Figure 1. The structural formulas of test compounds

have significant homology, the PLpro inhibitor developed for SARS-CoV is a promising starting point for therapeutic development [10]. The SARS-CoV-2 uses an RNA-dependent RNA polymerase (RdRp) to replicate its genome and transcribe its genes. Therefore, we use the SARS-CoV-2 reverse transcriptase structure in an active form that mimics a replicating enzyme [11].

In the present study, to carry out the docking studies, active macromolecules centers of the human receptor-ACE2 (PDB ID proteins: 7DF4), a spike protein SARS-CoV-2 (PDB ID: 1WNC), a PL protein SARS-CoV-2 (PDB ID: 7CJD), reverse transcriptase SARS-CoV-2 (PDB ID: 6YYT) domains were chosen as biological targets for the antivirus activity from the Protein Data Bank (PDB) [12]. The receptor maps were made in MGL Tools and AutoGrid programs. Water molecules, ions, and the ligand were removed from the PDB file ID: 7DF4, 1WNC, 7CJD, 6YYT.

For the receptor-oriented flexible docking the Autodock 4.2 software package was used. To perform calculations in the Autodock 4.2 program the output formats of the receptor and ligand data were converted to a special PDBQT format. In our previous studies, a similar software package and docking parameters were used [12].

The following docking parameters were determined: the maximum RMS tolerance for the conformational cluster analysis – 2 Å; the free energy coefficient for torsional degrees of freedom – 0.2983; the cluster tolerance – 2 Å; the external grid energy – 1000; the maximum initial energy – 0; the maximum number of retries – 10000; the number of individuals in the population – 150; the maximum number of energy evaluations – 2500000; the maximum number of generations – 27000; the number of top individuals to survive to the next generation – 1; the rate of gene mutation – 0.02; the rate of crossover – 0.8; the crossover mode – arithmetic;

the α-parameter of Gauss distribution – 0; the β-parameter of Gauss distribution – 1.

The visual analysis of complexes of substances in the active center of the human receptor-ACE2 (PDB ID: 7DF4), a spike protein SARS-CoV-2 (PDB ID: 1WNC), a PL protein SARS-CoV-2 (PDB ID: 7CJD), a reverse transcriptase SARS-CoV-2 (PDB ID: 6YYT) was performed using the Discovery Studio Visualizer program.

■ Results and discussion

Based on the results of the molecular docking we calculated the scoring function indicating the enthalpy contribution to the value of the free binding energy (Affinity DG) for the best conformation positions; the values of the free binding energy and binding constants (Edoc (kcal mol^{-1}) and Ki (µM micromolar/ mM millimolar) for a definite conformational position of the ligand. It allowed us to evaluate the stability of complexes formed between ligands and the corresponding targets (Table 1).

The inhibitory activity of the test molecules in relation to the biotargets selected can be exhibited by the formation of complexes between them; their stability is provided mainly due to the energetically favorable geometric arrangement of ligands in the active site, as well as the formation of hydrogen bonds, and intermolecular electrostatic and donor-acceptor interactions between them. As a consequence, the thermodynamic probability of this binding is confirmed by negative values of the Affinity DG scoring function (kcal mol^{-1}), the calculated values of the free binding energy Edoc (kcal mol^{-1}), and binding constants Ki (µM).

Hence, further experimental studies are required. The formation of intermolecular interactions, negative values of scoring functions, free binding energy and the calculated binding constants

Table 1. The values of Affinity DG, free binding energy, and binding coefficients for the best conformational positions of the test compounds combined with biotargets (PDB ID: 7DF4, 1WNC, 7CJD, 6YYT)

Molecule	7DF4			1WNC			7CJD			6YYT		
	Affinity DG, kcal mol^{-1}	Edoc kcal mol^{-1}	Ki µM micromolar / mM millimolar	Affinity DG, kcal mol^{-1}	Edoc kcal mol^{-1}	Ki µM micromolar / mM millimolar	Affinity DG, kcal mol^{-1}	Edoc kcal mol^{-1}	Ki µM micromolar / mM millimolar	Affinity DG, kcal mol^{-1}	Edoc kcal mol^{-1}	Ki µM micromolar / mM millimolar
1	-6.9	-5.37	115.63 µM	-5.3	-3.70	1.93 mM	-6.1	-5.74	61.84 µM	-7.0	-5.45	100.60 µM
2	-6.8	-5.66	70.61 µM	-5.1	-3.91	1.36 mM	-7.4	-5.26	139.54 µM	-7.1	-5.13	174.21 µM
3	-7.2	-6.24	26.82 µM	-5.6	-4.78	312.46 µM	-7.1	-6.71	12.13 µM	-7.5	-6.18	29.61 µM
4	-8.3	-6.08	34.89 µM	-5.9	-4.64	399.57 µM	-6.9	-6.13	31.88 µM	-7.5	-5.79	56.83 µM
5	-8.2	-7.00	7.37 µM	-6.2	-5.08	188.85 µM	-7.0	-6.54	16.10 µM	-7.8	-6.84	9.61 µM

Figure 2. The superposition of molecule **5** and a diagram of intermolecular interactions in the complex with the human receptor-ACE2 (PDB ID: 7DF4)
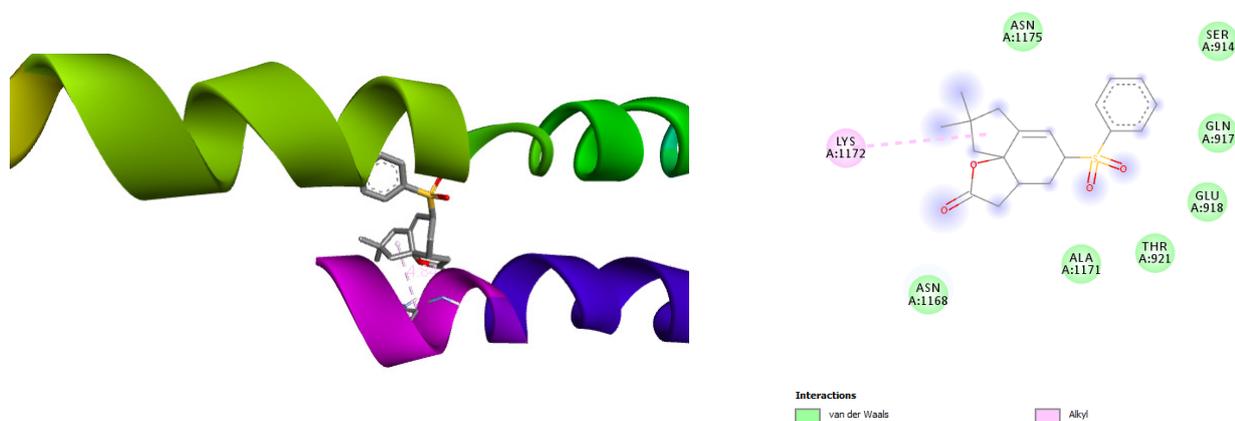
Figure 3. The superposition of molecule **5** and a diagram of intermolecular interactions in the complex with a spike protein SARS-CoV-2 PDB ID: 1WNC

have confirmed that the compounds studied have a significant affinity for the specified biotargets.

As can be seen from the results, molecule **5**, which has the best indicators in relation to all targets selected, is the leader among the compounds under research (the human receptor – ACE2 PDB ID: 7DF4 (Affinity DG = -8.2 kcal mol⁻¹, Edoc = -7.00, Ki = 7.37 μM), a spike protein SARS-CoV-2 PDB ID: 1WNC (Affinity DG = -6.2 kcal mol⁻¹, Edoc = -5.08, Ki = 188.85 μM), a PL protein SARS-CoV-2 PDB ID: 7CJD (Affinity DG = -7.0 kcal mol⁻¹, Edoc = -6.54, Ki = 16.10 μM), a reverse transcriptase SARS-CoV-2 PDB ID: 6YYT (Affinity DG = -7.8 kcal mol⁻¹, Edoc = -6.84, Ki = 9.61 μM)) (Table 1).

For hit compound **5**, a detailed analysis of the geometric location in the active sites of the corresponding targets was performed. This will provide a complete understanding of which fragments of the molecule are involved in binding to biotargets, and will allow giving clear

recommendations for the rational design of future candidates.

Molecule **5** with the human receptor-ACE2 PDB ID: 7DF4 forms a complex due to hydrogen bonds between the oxygen atoms of the sulfonyl group and the carbonyl oxygen of oxolan-2-one with residues of His378 and Asn394 amino acids. Additionally, the complex of the π-π, π-Alk interactions occurring between the phenyl residue and the cyclopentane fragment of the molecule with Phe40 and His401, respectively, is stabilized (Figure 2).

The active molecule complex with a spike protein SARS-CoV-2 PDB ID: 1WNC is formed in the presence of the Alk intermolecular interaction between the cyclopentane fragment of the molecule and the Lys1172, Val171 lysine residue (Figure 3).

The complex with a PL protein SARS-CoV-2 PDB ID: 7CJD is formed by the participation of a hydrogen bond and the Alk intermolecular
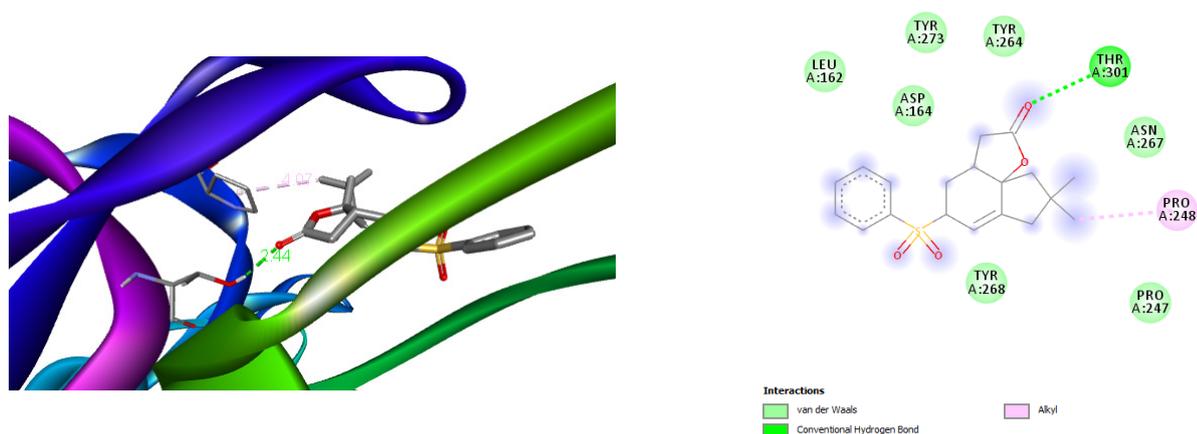
Figure 4. The superposition of molecule **5** and a diagram of intermolecular interactions in the complex with a PL protein SARS-CoV-2 PDB ID: 7CJD
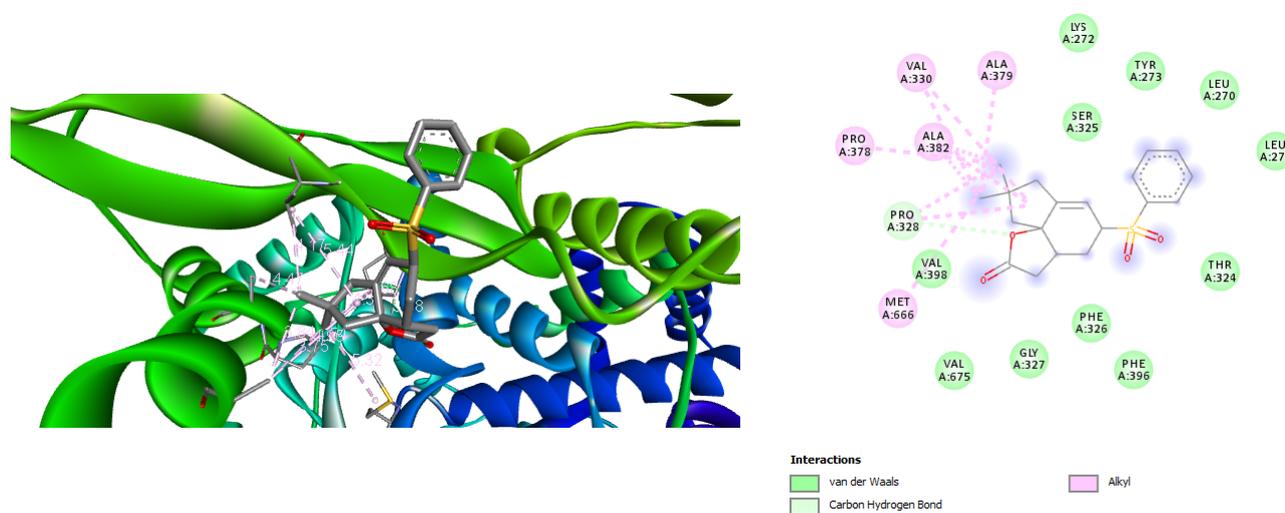
Figure 5. The superposition of molecule **5** and a diagram of intermolecular interactions in the complex with a reverse transcriptase SARS-CoV-2 (PDB ID: 6YYT)

interaction between the carbonyl oxygen atom of oxolan-2-one and the metal substitute with the Thr301 and Pro248 threonine residues, respectively (Figure 4).

Molecule **5** forms a hydrogen bond with the Pro328 proline residue due to the oxygen atom of the oxolan-2-one fragment in the active site of a reverse transcriptase SARS-CoV-2 PDB ID: 6YYT. The stabilization of the complex is provided by Alk interactions with the Pro328, Pro378, Met666, Val330, Ala382, Ala379 residues (Figure 5).

The values of interatomic distances in active sites between fragments of molecule **5** and amino acid residues shown in the diagrams (Figures 2–5), categories and types of intermolecular interactions are given in Table 2.

Among all the molecules tested, compound **5** has the best affinity for biotargets (PDB ID: 7DF4, 1WNC, 7CJD, 6YYT). This is evidenced by the formation of a number of intermolecular interactions between them, the negative values of scoring functions, the free binding energy, and the calculated values of binding constants.

The final stage of molecular docking results is to provide certain recommendations for the rational design of future drug candidates. These recommendations can be provided on the basis of the results of the calculated evaluation functions obtained and a detailed analysis of the geometric location of the tested ligands in the active site of the target. This approach of using docking data provides information on the participation in the creation of appropriate intermolecular contacts of certain atoms, pharmacophore groups, functional groups of the test compounds with amino acid residues of the site. The binding energy of each individual contact is included in the total free energy of binding, which is the main marker for predicting the affinity for a specific target.

Table 2. The values of interatomic distances, categories and types of intermolecular interactions of molecule 16 in active biotarget sites (PDB ID: 7DF4, 1WNC, 7CJD, 6YYT).

7DF4 Distance, Å	7DF4 Category	7DF4 Types	1WNC Distance, Å	1WNC Category	1WNC Types	7CJD Distance, Å	7CJD Category	7CJD Types	6YYT Distance, Å	6YYT Category	6YYT Types
2.30	Hydrogen Bond	Conventional Hydrogen Bond				2.44	Hydrogen Bond	Conventional Hydrogen Bond	3.68	Hydrogen Bond	Carbon Hydrogen Bond
2.91	Hydrogen Bond	Conventional Hydrogen Bond							4.68	Hydrophobic	Alkyl
4.41	Hydrophobic	π-π Stacked							5.44	Hydrophobic	Alkyl
									4.47	Hydrophobic	Alkyl
									4.95	Hydrophobic	Alkyl
			4.84	Hydrophobic	Alkyl	4.07	Hydrophobic	Alkyl	3.84	Hydrophobic	Alkyl
									3.7484	Hydrophobic	Alkyl
4.66	Hydrophobic	Pi-Alkyl							4.17	Hydrophobic	Alkyl
									4.34	Hydrophobic	Alkyl
									4.54	Hydrophobic	Alkyl
									5.32	Hydrophobic	Alkyl

Using the results of calculation obtained and visualization of molecular docking, it is possible to provide recommendations for the rational designing of future SARS-CoV-2 inhibitors, namely:

- creation of basic rigid systems using the example of tetracyclic ring frameworks;
- saturation of such a system with hydrogen acceptors, in particular oxygen- and sulfur-containing groups in the form of carbonyl fragments, sulfonyl and hydroxyl groups, that enables the formation of intermolecular donor-acceptor interactions with amino acid residues of the active center;

- introduction of hydrophobic inclusions in the form of methyl and phenyl fragments in order to form stabilizing contacts of the formed "molecule-target" complex.

■ Conclusions

According to the results obtained, we have proposed a way to search for potential SARS-COV-2 inhibitors based on Crinipellin A derivatives. Using the most promising compound **5** further studies open up another direction for searching for compounds of SARS-COV-2 inhibitors.

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