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ONLINE MOLECULAR DOCKING AND ANALYSIS OF BIOLOGICAL ACTIVITY OF CYANURIC ACID DERIVATIVES

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ОНЛАЙН МОЛЕКУЛЯРНЫЙ ДОКИНГ И АНАЛИЗ БИОЛОГИЧЕСКИЕ АКТИВНОСТИ ПРОИЗВОДНЫХ ЦИАНУРОВОЙ КИСЛОТЫ

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ABSTRACT

This paper presents the results of molecular docking of urea-substituted cyanuric acid products using the online predictive CB-Dock and PASS programs, as well as information about possible areas of their application by biological activity.

АННОТАЦИЯ

В данной работе приведены результаты молекулярного докинга мочевино замещенных продуктов циануровой кислоты с применением онлайн прогнозирующей программы CB-Dock и PASS, а так же сведения об возьможных областей их примения по биологической активности.

Keywords: CB-Dock, PASS, biological activities, cyanuric acid, protein-ligand docking.
Ключевые слова: CB-Dock, PASS, биологические активности, циануровая кислота, стыковка белок-лиганд.

I. Introduction

Previously, we published a synthesis technique, quantum chemical calculations and IR spectroscopy of a urea-substituted cyanuric acid product [1-3]. In this paper, we discuss the prediction results of CB-Dock and PASS online programs, the biological activity of these compounds.

CB-Dock was designed to perform blind docking at predicted locations, rather than on the entire surface of the protein. Therefore, the first step is to detect the intended binding sites (i.e., cavity detection). Since ligand binding sites are usually larger cavities, we select several upper cavities according to the size of the cavity for further analysis (i.e., cavity sorting). Then we calculate the docking center and adjust the size of the docking box. These parameters are necessary for joining molecules using AutoDock Vina (Center and Size). After the docking process is completed, the associated poses are ranked according to the docking score (Dock and Rerank). The first conformation is considered the best binding position, and the corresponding site is the optimal binding site for the requested ligand. Figure 1 shows the CB-Dock workflow.

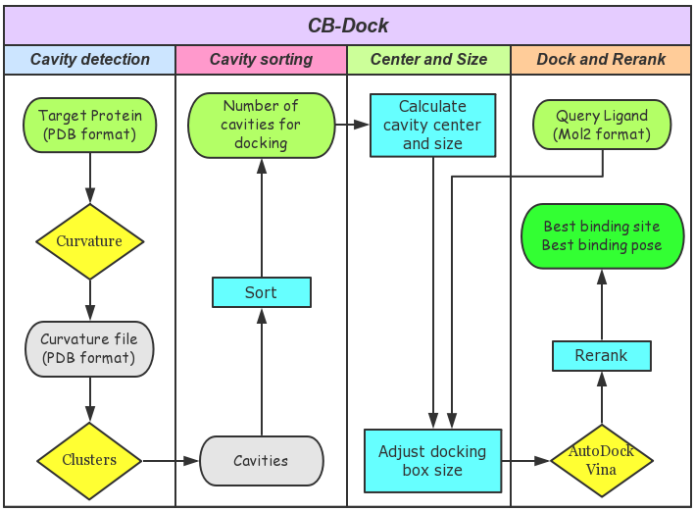


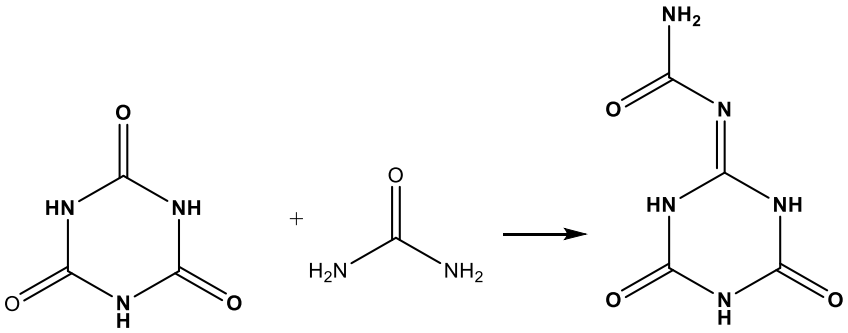
Figure 1. The CB-Dock workflow performing molecular ligand docking

Protein-ligand coupling is widely used to predict ligand binding and affinity. Protein-ligand docking is a powerful tool for computer-assisted drug discovery (or CADD). Currently, there are dozens of commercial and academic tools for protein-ligand docking [3-7]. Most docking tools require a ligand binding region (rotation and translation of the ligand in this region) in advance to find the most favorable binding mode in terms of energy. The binding region is usually represented as a cubic block, so its size and center are crucial for accurate docking, since they define the boundaries of the conformational sampling space. In many application articles, the binding areas are unknown. In order to identify potential interactions between a given protein and a ligand, it is necessary to perform docking on the entire surface of the protein in order to find the most likely binding method. This process is called blind docking [4, 7]. Compared to conventional docking, blind docking is less reliable and stable because the docking space is usually too large for sufficient sampling using a limited number of random searches. Nevertheless, blind docking is especially valuable for detecting unexpected interactions that may occur in unidentified binding modes [7].

II. The experimental part

Synthesis of mono-urea substituted cyanuric acid product.

0.001 mol (0.129 g) of cyanuric acid was added to a suspension of 0.001 mol (0.129 g) of urea in 50 ml of water. The reaction mixture was boiled for one hour. The reaction mixture was left for 2 days at room temperature. After 2 days, the fallen crystals were filtered out, washed with a small amount of methanol, acetone and hexane. After recrystallization, 0.15876 g (84%) of 1-(4,6-dioxo-1,3,5-triazinane-2-ylidene) urea (L1) with T. plav was obtained from methanol. 252oC.



Similarly, di-, tri-urea substituted cyanuric acid products were synthesized.

III. Results and discussion

In order to identify potential interactions between a given protein and a ligand, it is necessary to perform docking on the entire surface of the protein in order to find the most likely binding method. This process is called blind docking [4,8.10]. Compared to conventional docking, blind docking is less reliable and stable because the docking space is usually too large for sufficient sampling using a limited number of random searches. Nevertheless, blind docking is especially valuable for detecting unexpected interactions that may occur in unidentified binding modes [9,11].

During the docking processing, a progress bar appeared showing the task status. When the processing was completed (after about 3 minutes), the web page was updated with the results. Table 1 lists the Vina scores, the cavity dimensions, the docking centers and the intended cavity dimensions.

Table 1.

Results after docking completion

CyM1 -- 3ij2

Vina score	Cavity size	Center			Size		
		x	y	z	x	y	z
-12.4	2493	-10	62	1	25	31	17
-11.1	2380	4	68	28	26	28	17
-11.1	1081	-19	85	9	23	17	17
-10.8	1105	-6	67	14	28	23	17
-9.8	1206	8	47	13	17	17	25

CyM2 -- 3ij2

Vina score	Cavity size	Center			Size		
		x	y	z	x	y	z
-10	2493	-10	62	1	25	31	18
-9.7	2380	4	68	28	26	28	18
-9.4	1081	-19	85	9	18	18	18
-8.9	1105	-6	67	14	28	18	18
-7.9	1206	8	47	13	18	18	25

After selecting the ligand in the table, the structure is visualized in interactive 3D graphics (Fig. 2).

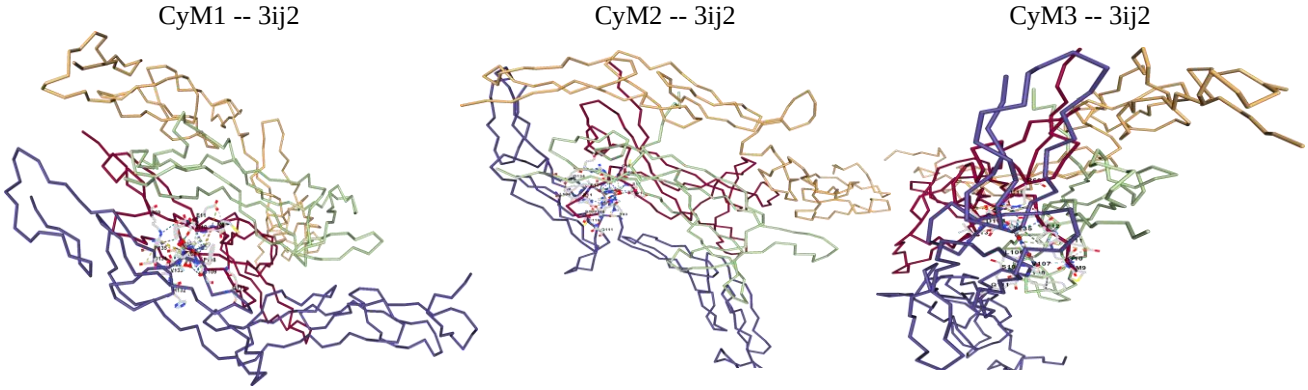


Figure 2. Structures after molecular docking of urea substituted cyanuric acid products

In our example, the upper binding method with a Vina score for the CyM1 ligand is -12.4, but all ligands have an equal binding cavity (i.e., 2493). And for CyM2 ligands, Vina scores are -10 and CyM3 Vina scores are -8.5 respectively.

Table 2.

The value of cavity sizes and Vina scores for CyM1- CyM3 ligands

CyM1		CyM2		CyM3	
Vina score	**Cavity size**	**Vina score**	**Cavity size**	**Vina score**	**Cavity size**
-12.4	2493	-10	2493	-8.5	2493
-11.1	2380	-9.7	2380	-7.9	1105
-11.1	1081	-9.4	1081	-7.8	2380
-10.8	1105	-8.9	1105	-7.7	1206
-9.8	1206	-7.9	1206	-7.6	1081

№	Biological activity	Activity/ Inactivity	Urea Substituted Cyanuric acid products		
			CyM1	CyM2	CyM3
1	Leukopoiesis stimulator [12]	P_a	0,683	0,683	0,660
		P_i	0,008	0,008	0,010
2	NADPH peroxidase inhibitor [13]	P_a	0,696	0,696	0,793
		P_i	0,028	0,028	0,013
3	Pterine deaminase inhibitor [14]	P_a	0,858	0,858	0,843
		P_i	0,003	0,003	0,003
4	Dimethylarginine inhibitor	P_a	0,749	0,749	0,825
		P_i	0,010	0,010	0,005
5	Treatment of phobic disorders	P_a	0,714	0,714	0,806
		P_i	0,070	0,070	0,032

IV. Conclusion

We have previously studied the obtained new compounds by quantum chemical and physico-chemical methods [1-3], in this article their biological properties are studied. Using the PASS online program, conclusions were drawn about the additional biomedical potential of compounds by comparing the results of bioactivity predictions with data determined experimentally in scientific publications [12-14].

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