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Multiple docking of α-, β-, and γ- cyclodextrin with vinpocetine chiral complexes

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ABSTRACT

Cyclodextrin is a compound that is able to form inclusion complexes which modifies the properties of guest ligands such as vinpocetine in order to improve on its physical and chemical characteristics. The molecular docking method of various cyclodextrins with vinpocetine chiral complexes can be used to study on its different binding conformations and orientations which acts as a screening process that is hoped to be able to aid laboratory analysis to synthesize new and more efficient drugs. This study utilizes Autodock 4.2, which is an automatic docking program to study on the complexation reaction of α-, β-, and γ-cyclodextrin with vinpocetine stereoisomers. The docking structures are obtained from PubChem Compound Database and RCSB Protein Data Bank respectively. The aim of this study is to investigate on the most stable complexation formation and study on the different interactions of the complex stereoisomers formed from the simulation of single docking (1:1), and multiple docking (2:1) and (3:1), where one, two, and three different cyclodextrins are docked into a single vinpocetine respectively to study on the orientations, number of conformations, binding energies, and the number of intermolecular hydrogen bonding formations of the cyclodextrins with different stereoisomers of vinpocetine and determining the best possible combination with the lowest binding energies. The lowest binding energy, along with the highest number of conformations indicates that the structure is the most stable chiral complex that is likely to form. For single docking, the trend of binding energy from the least to most stable based on different CD-VP chiral complexes is 3S16S > 3S16R > 3R16S > 3R16R for α-CD, 3S16R > 3S16S > 3R16R > 3R16S for β-CD, 3S16R > 3S16S > 3R16R > 3R16S for γ-CD. For multiple docking in the ratio of 2:1 CD:VP, most complexes form a sandwich conformation with the trend being 3R16R α-CD-γ-CD > 3S16S β-CD-γ-CD > 3S16R β-CD-γ-CD > 3R16S α-CD-γ-CD > 3R16R β-CD-γ-CD > 3S16S α-CD-β-CD > 3R16S β-CD-γ-CD > 3S16R α-CD-γ-CD > 3R16R α-CD-β-CD > 3S16R α-CD-β-CD > 3R16S α-CD-β-CD > 3S16S α-CD-γ-CD. However, multiple docking in the 3:1 ratio of CD:VP show positive energy and are predicted to be unstable.

Keywords: Cyclodextrin, vinpocetine, single docking, multiple docking, chiral complex, Autodock, binding energy.

1. INTRODUCTION

Cyclodextrins (CD), which are also known as Schardinger dextrins, cycloamyloses, cyclomaltoses and cycloglucans, are cyclic oligosaccharides which naturally exists in three different forms namely the α-, β- and γ-cyclodextrin which consists of 6, 7 or 8 glucopiranose units connected with α-1,4 glucosidic bonds with a hydrophilic hydroxyl group on their outer surface and a hydrophobic cavity in their center [1]. The differences between these forms vary in terms of their molecular weight, solubility in water, and in their hollow-diameter, granting them the ability to form inclusion complex with different types of compounds of varying sizes [2].

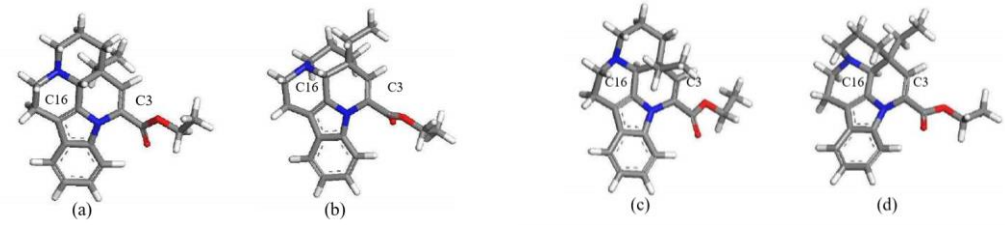

Figure 1 Structure of vinpocetine stereoisomers: (a) 3R-16R, (b) 3R-16S, (c) 3S-16R, (d) 3S-16S [grey = carbon, blue = nitrogen, red = oxygen, white = hydrogen]

Vinpocetine (VP), or also known by its chemical name of ethyl apovincaminate is a semisynthetic derivative of the vinca alkaloid Vincamine [3]. It possesses various effects such as enhancing the blood-flow to the cerebral area, acts as an anti-inflammatory agent, as well as neuroprotective effects and has been incorporated as a drug in Eastern Europe for the treatment of cerebrovascular disorders and age-related memory impairment [4]. However, it has a poor solubility in water, has shown to possess pH-dependent solubility, is highly metabolized in the liver, has a low oral availability, and a short eliminate half-life causing it to lose much of its effectiveness and its useful properties and limits its usage for clinical purposes [5]. Besides that, the chiral drug of vinpocetine has 4 different stereoisomers and each may yield different effects due to chiral

compounds' tendency to yield different properties. Cyclodextrins have been used to modify and improve the solubility and dissolution rate of vinpocetine and increases its overall bioavailability through inclusion complex formation [6]. The structures of both compounds are shown in Figure 1 and Figure 2.

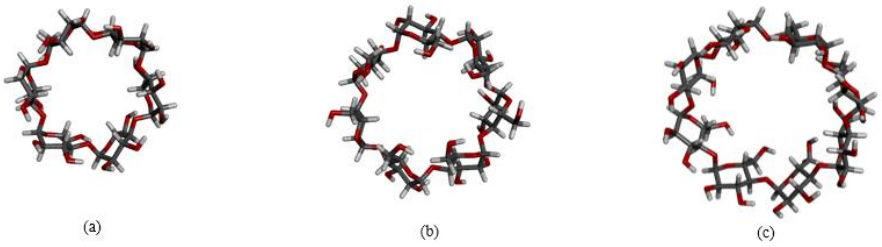

Figure 2 Structures of cyclodextrins: (a) α-cyclodextrin, (b) β-cyclodextrin and (c) γ-cyclodextrin

2. EXPERIMENTAL

The molecular optimization and docking method will primarily be used in the study of this research where the techniques will be used to predict and analyze all of the interaction between the protein receptors and ligands, as well as the contribution of the different types of bonds such as Hydrogen bonding in the energy optimization of the complex structure formations.

This research mainly utilizes the 2D and 3D structures and modelling of natural α-, β-, and γ-cyclodextrin consisting of six, seven, and eight glucopyranose units, respectively. The crystal structures of the different types of cyclodextrins are obtained and extracted from the RCSB Protein Data Bank (PDB code: 1DMB), which is an archive repository specializing in storing information on the 3D structures of biological molecules such as proteins and nucleic acids. The vinpocetine drug molecule and all of its isomers (3R-16R, 3R-16S, 3S-16R, and 3S-16S) are taken from the PubChem Compound Database. All of the structures to be used for modelling and docking are then optimized by semi-empirical method PM3 (Parameterized Model number 3). α-, β-, and γ-cyclodextrin each will be docked molecularly with vinpocetine of a particular stereoisomer structure to test and maximize the interactions of all of the molecules mainly the electrostatic interactions and hydrophobic interactions between the host and the guest molecules using the docking software known as Autodock 4.2. The three hosts of cyclodextrin were assigned with the Kollman and Gasteiger charges while the charges on the vinpocetine were assigned automatically later on. The docking method utilized consist of one method, namely blind docking, where the active sites of the host molecule is undefined. Lamarckian Genetic Algorithm (LGA), which is a search algorithm will be performed afterwards and is utilized in this research [7].

The results of the conformations for the semi-empirical method and the complex structure formed with the lowest energy conformation will be taken as the final structure before proceeding with the next complex formation [8]. The energy levels of α-, β-, and γ-cyclodextrin docked with vinpocetine will be compared and the lowest among the three will be used as the base complex molecule which will be further complexed with the remaining predetermined cyclodextrin in the complex formation reaction where the vinpocetine will be sandwiched between two different cyclodextrins. The energy levels of the sandwich complex are then compared to study on the stability and formation energy of the vinpocetine stereoisomer docked with the different sequences of cyclodextrins. The complexation structures were then further studied and calculated at the Density Functional Theory (DFT) levels by using the Gaussian software [9]. It is then complexed with the last remaining cyclodextrin to see whether a triple docking conformation of cyclodextrin to vinpocetine is theoretically possible based on the simulation results.

3. RESULTS AND DISCUSSION

3.1. Global Minimum Energy of Single Structure of Cyclodextrins and Vinpocetine Stereoisomers

After all of the single structures were geometrically optimized by via Gaussian 09 software as shown in Table 1, the molecular docking simulations were carried out using the optimized structures to obtain a more accurate binding energy value.

3.2. 1:1 Docking of CD:VP Chiral Complex

Based on the bar chart in Figure 3, it can be observed that the binding energies of CD-VP chiral complex are the lowest when vinpocetine stereoisomers are docked to β-cyclodextrin, followed by γ-cyclodextrin and α-cyclodextrin. The sequences of binding energies do not follow a trend where the stability of the structure increases with an increasing number of

glucose units or increase in the molecular mass of the cyclodextrin. The results contain information suggesting that they do not universally behave as a monotonically graded series. This could be due to the symmetrical and asymmetrical structure of the cyclodextrin.

Table 1 Minimum energy of cyclodextrins and vinpocetine stereoisomers after optimization in a.u. unit and kJ mol^{-1} unit

Structure name	Energy (a.u.)	Energy (kJ mol^{-1})
VP 3R16R	- 0.0564	- 148.08
VP 3R16S	- 0.0493	- 129.53
VP 3S16R	- 0.0426	- 111.78
VP 3S16S	- 0.0511	- 134.34
α-cyclodextrin	- 1.9854	- 5212.67
β-cyclodextrin	- 2.3322	- 6123.19
γ-cyclodextrin	- 2.6562	- 6973.85

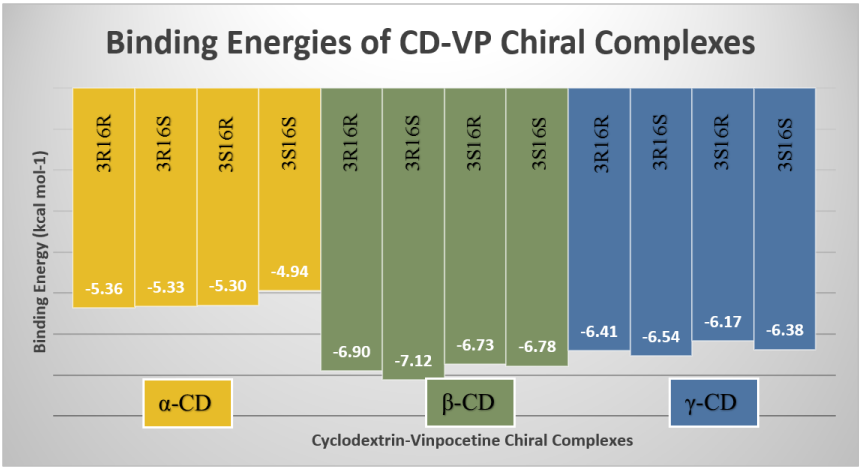

Figure 3 Binding energy comparison obtained from single docking of CD-VP chiral complexes

3.3. 2:1 Docking of CD:VP Chiral Complex

Table 2 Summary of data obtained from every docking simulation of CD-VP-CD sandwich complexes

Cluster	Binding Energy (kcal mol^{-1})	Successful binding	Docking Pose
3S16S αγ-CD	-2.36	Yes	Top
3R16S αβ-CD	-0.90	Yes	Top
3S16R αβ-CD	-0.84	Yes	Top
3R16R αβ-CD	-0.71	Yes	Top
3S16R αγ-CD	-0.71	Yes	Top
3R16S βγ-CD	-0.16	Yes	Bottom
3S16S αβ-CD	-0.13	Yes	Top
3R16R βγ-CD	-0.10	Yes	Bottom
3R16S αγ-CD	0.00	No	Bottom
3S16R βγ-CD	+0.08	No	Bottom
3S16S βγ-CD	+0.10	No	Bottom
3R16R αγ-CD	+0.70	No	Top

Based on Table 2, it can be seen that there are 4 sandwich complexes that fail to bind. These sandwich complexes are α-CD-VP-γ-CD (3R16R), α-CD-VP-γ-CD (3R16S), β-CD-VP-γ-CD (3S16R) and β-CD-VP-γ-CD (3S16S). All of the guest molecules of sandwich complexes mentioned bind at the bottom of host molecules except for α-CD-VP-γ-CD (3R16R) sandwich complex, in which the guest molecule binds at the top of host molecule. We can observe that for α-CD-VP-γ-CD docking simulation, only vinpocetine stereoisomers 3R16R and 3R16S fail to bind while for β-CD-VP-γ-CD docking simulation, only vinpocetine stereoisomers 3S16R and 3S16S fail to bind. Therefore, for docking simulation of α-CD-VP-β-CD, all vinpocetine stereoisomers bind successfully. Failure of sandwich complex docking simulation for these particular vinpocetine stereoisomers can be attributed into a few factors, namely steric hindrance as γ-cyclodextrin is a large molecule to be docked to α-CD-VP and β-CD-VP chiral complex. Another factor may be due to the orientation of vinpocetine stereoisomers, where the functional group present in different stereoisomers are not able to interact well with the functional groups present in the host molecule (α-CD, β-CD) or the guest molecule (γ-CD) itself.

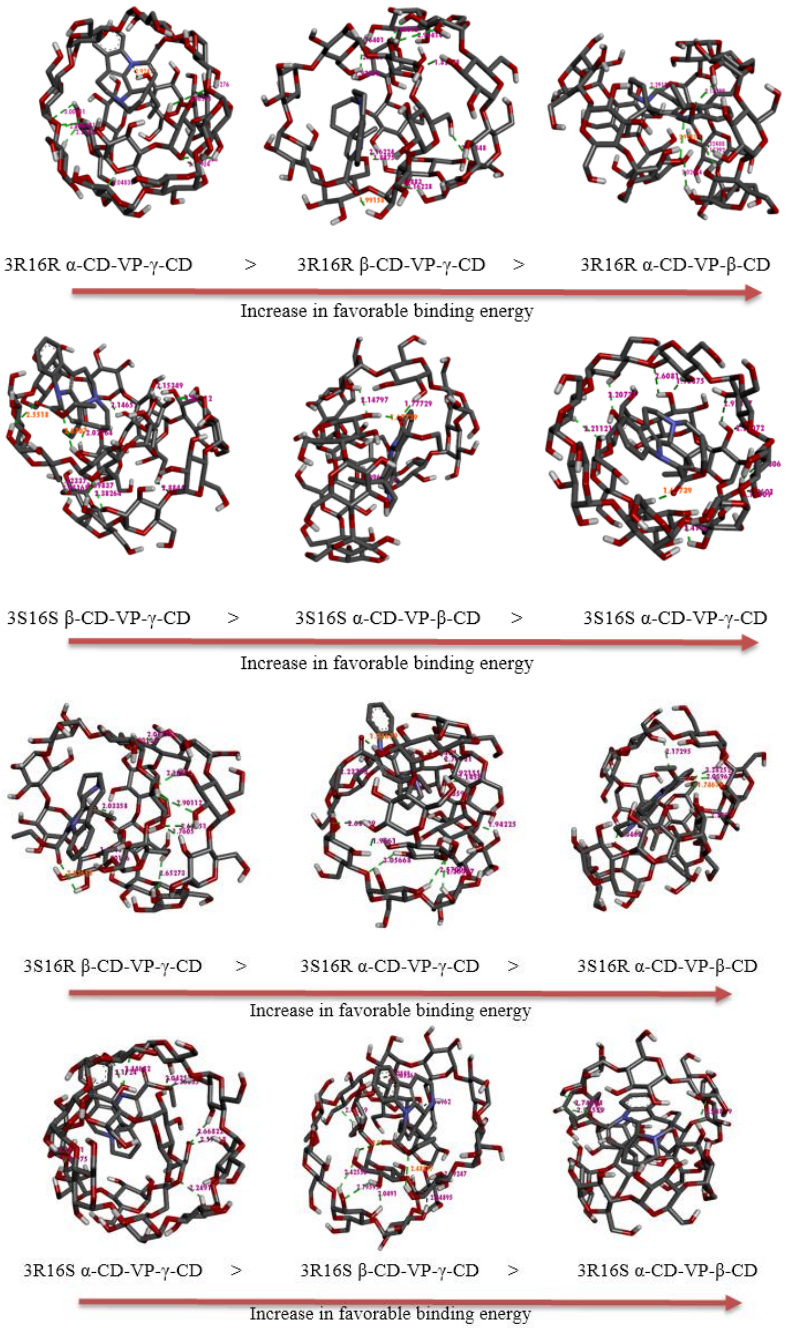

Figure 4 Lowest to highest binding energy for vinpocetine stereoisomers docked in a 2:1 ratio of Cyclodextrin : Vinpocetine

Based on Figure 4 above, it can be generalized that docking simulation of β-CD-VP-γ-CD sandwich complex produced the highest binding energy, followed by docking simulation of α-CD-VP-β-CD sandwich complex and α-CD-VP-γ-CD sandwich complex, which produced the lowest binding energy. The analysis made can be attributed to the functional groups available in both the host and guest molecules, as well as interactions between the host and guest molecules upon docking. The structure of cyclodextrin itself possess many hydrogen (H) atoms at the rim of its cavity, as well as oxygen (O) atoms. Therefore, intermolecular and intramolecular hydrogen bonds, van der Waals forces or electrostatic forces may form between different types of cyclodextrins and also with vinpocetine, which possess O atom and nitrogen (N) atom in its structure. It can be deduced that the binding energy possessed by the sandwich complexes that bind successfully ranges from -0.10 kcal mol^{-1} to -2.36 kcal mol^{-1} while the range of binding energy of sandwich complexes that fail to bind is from +0.00 kcal mol^{-1} to +0.70 kcal mol^{-1}. The most favorable structure with the lowest binding energy is the α-CD-VP-γ-CD (3S16S) sandwich complex while the least favorable structure with the highest binding energy is α-CD-VP-γ-CD (3R16R).

3.4. 3:1 Docking of CD:VP Chiral Complex

Blind triple docking of α-cyclodextrin, β-cyclodextrin, and γ-cyclodextrin with vinpocetine was carried out in order to see whether the triple docking process along with the orientation is theoretically possible. The grid map size was set to 120 × 120 × 120 Å. Table 3 below shows all of the data obtained from the triple docking simulations of αβγ-CD-VP sandwich complexes.

Table 3 Summary of data obtained from triple docking simulation of αβγ-CD-VP sandwich complexes

Cluster	αβγ-CD 3R16R	αβγ-CD 3R16S	αβγ-CD 3S16R	αβγ-CD 3S16S
Binding energy (kcal mol^{-1})	+1.28	+0.25	+1.01	+0.37
Number of conformations	2	1	1	3
H-bonds formed	5	8	5	4
Successful binding	No	No	No	No

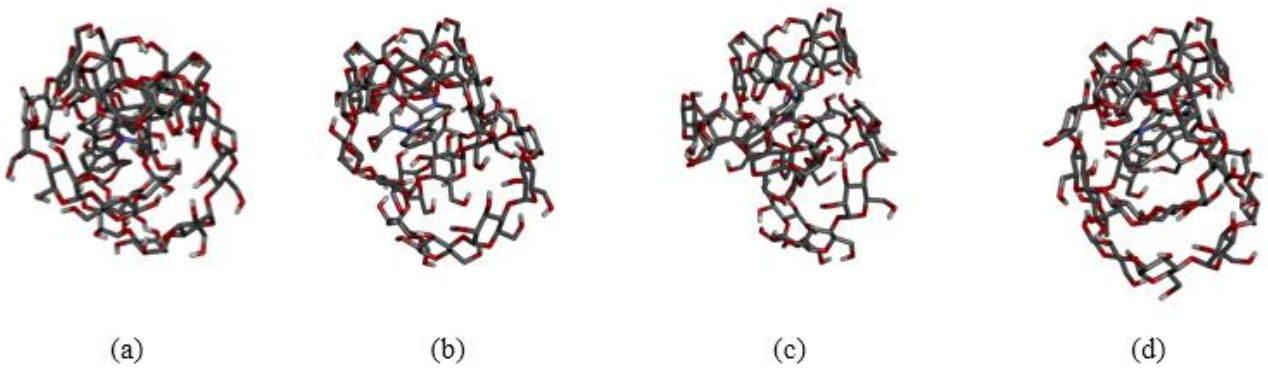

Figure 5 Structure of α-CD-β-CD-γ-CD-VP complexes. (a) 3R16R, (b) 3R16S and (c) 3S16R, (d) 3S16S [grey = carbon, blue = nitrogen, red = oxygen, white = hydrogen]

Based on Table 3, it is clear that none of the triple docking sequences of cyclodextrins with the vinpocetine is successful since all of the binding energies obtained were positives, indicating that the binding is highly unlikely to occur. From the structures in Figure 5, the three cyclodextrins orientate itself in such a way that two of the cyclodextrins bind to the vinpocetine, forming a sandwich complex, while the third cyclodextrin binds to either end of the two cyclodextrins. This could be due to the size restraint of the hollow center of the cyclodextrin or due to the lack of free elements in the vinpocetine to bind to the third cyclodextrin. The more intramolecular hydrogen bonds formation indicates that the structure is stable with lower binding energies. The H-bonds formed may be from the sandwiched complex of two of the cyclodextrins, and not to the third one, indicating that the sandwich structure of cyclodextrin and vinpocetine complex is favorable.

4. CONCLUSION

The molecular docking method is a screening process to determine theoretically, the most stable complexes with the lowest binding energies to be produced in the laboratory synthesis in order to improve on the characteristics and properties of vinpocetine as a drug. The optimized energies of the vinpocetine stereoisomer molecules follow the sequence from the highest to the lowest minimum energy 3S16R > 3R16S > 3S16S > 3R16R. In the single docking complex formation of the 1:1 ratio of cyclodextrin : vinpocetine, it was observed that the trend of increasing favourable binding energy based on the different chiral complexes formed is: 3S16S > 3S61R > 3R16S > 3R16R for α-CD, 3S16R > 3S16S > 3R16R > 3R16S for β-CD, 3S16R > 3S16S > 3R16R > 3R16S for γ-CD. In multiple docking, for the formation of sandwiched complexes, it is observed that the trend of increasing favourable binding energy is 3R16R α-CD-VP-γ-CD > 3S16S β-CD-VP-γ-CD > 3S16R β-CD-VP-γ-CD > 3R16S α-CD-VP-γ-CD > 3R16R β-CD-VP-γ-CD > 3S16S α-CD-VP-β-CD > 3R16S β-CD-VP-γ-CD > 3S16R α-CD-VP-γ-CD > 3R16R α-CD-VP-β-CD > 3S16R α-CD-VP-β-CD > 3R16S α-CD-VP-β-CD > 3S16S α-CD-VP-γ-CD. Based on the results and the structures obtained, the complexation forms a sandwich complex where the vinpocetine compound is bonded in between two of the cyclodextrin compounds at both top and bottom. The lower binding energy, along with the higher number of conformations, as well as the higher number of intermolecular H-bond present indicates that the complexation formation is possible and that the complex formed is stable. For triple docking, where all three types of cyclodextrins are bonded to different isomers of vinpocetine, the trend of increasing favourable binding energy is α-CD-β-CD-γ-CD-VP 3R16R > α-CD-β-CD-γ-CD-VP 3S16R > α-CD-β-CD-γ-CD-VP 3S16S > α-CD-β-CD-γ-CD-VP 3R16S. None of the triple docking complexes obtained were successful since all of them possess positive binding energy indicating that the complex is unstable and highly unlikely to occur.

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