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Molecular Docking Approach for Prediction of Enantioseparation of Miconazole Using Cyclodextrin Derivatives as Chiral Selector

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Abstract. Enantioseparation of miconazole has been successfully predicted based on the molecular docking approach using cyclodextrin derivatives such as sulfated-β-cyclodextrin (S-β-CD), hydroxypropyl-β-cyclodextrin (HP-β-CD) and hydroxypropyl-γ-cyclodextrin (HP-γ-CD) as chiral selectors. Molecular docking was performed using AutoDock Vina software and the root mean square deviation (RMSD) was calculated using PyMol software. Molecular docking shows that R-Miconazole forms more stable interaction with all cyclodextrin derivatives than S-Miconazole forms, suggesting that S-miconazole will be eluted earlier than R-miconazole. In addition, the stability level of cyclodextrin derivatives as chiral selector was HP-β-CD > S-β-CD > HP-γ-CD.

INTRODUCTION

Miconazole is a class of imidazole compounds that are used as an antifungal agent. This drug has been used to treat fungal skin infections such as ringworm, water fleas, tinea versicolor, and candidiasis. This compound has one chiral center and two different enantiomers. The enantiomers have identical physicochemical characteristics but can show differences in pharmacological and toxicological [1]. Based on several reports, there is only one enantiomer that gives good effects while the other one may cause negative effects [2], therefore, the enantiomeric separation of chiral compounds is important to do. One of the most possible methods to separate enantiomers of chiral compounds is High Performance Liquid Chromatography (HPLC).

Chiral separation can be achieved using chiral selectors which clearly distinguish the two enantiomers. Chiral selector changes one of the two enantiomers at different rates into a new compound (kinetics enantioselective) or established a labile molecule at different stability (thermodynamics enantioselective). One of the most widely used chiral selectors is cyclodextrin due to its excellent chiral recognition abilities [3]. However, the HPLC chiral separation can only separate a limited chiral range. Therefore, a preliminary schematic was needed to analyze the three-dimensional structure of compounds to predict the characteristics and functions of these compounds and analyze the actual interactions at the molecular level [4].

Molecular docking is a computational method that has been used to predict the molecular interactions of ligands and receptors. The molecular docking prediction increases accuracy and precision in chiral recognition and also reduces research time since it can be predicted quickly [5]. The molecular docking method can save time, effort, and the use of solvents or chemicals that pollute the environment [6]. This method was performed by placing the ligands systematically on the active site of receptors. The molecular docking method aims to achieve the optimal complex conformation and to predict the interactions of drugs/ligands and receptors, therefore, the best geometry of ligands

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and receptors complex was obtained. In addition, a more effective ligand can be predicted by calculated the energy interactions of the different ligands [7]. Based on this report, the aims of this study are to analyzing the structure of the miconazole complex, calculated the binding energy, and determined the most suitable chiral selector to predicting separation of the enantiomers of miconazole. Chiral selectors commonly used are cyclodextrin and its derivatives. Cyclodextrin is an oligosaccharide composed of six (α-CD), seven (β-CD), and eight (γ-CD) glucose units through α-1,4 glycoside bonds [8]. Cyclodextrin can form an inclusion complex with drugs by inserting drug molecules into the central cavity of cyclodextrin. The inclusion complex formed can improve the solubility, dissolution, stability, and bioavailability of the guest molecule [9]. Cyclodextrin shows good enantioselectivity for a wide range of analytes, transparent to UV light and has good water solubility. In addition, cyclodextrins are available in various ranges, generally, give fast kinetics for the complex formation and breakdown enantiomers, and are relatively cheap [10]. In this study, miconazole acts as ligands, and cyclodextrin acts as receptors. Cyclodextrins used for this study are sulfated-β-cyclodextrin (S-β-CD), hydroxypropyl-β-cyclodextrin (HP-β-CD) and hydroxypropyl-γ-cyclodextrin (HP-γ-CD).

EXPERIMENTAL DETAILS

Materials

The crystal structure of S-β-CD, HP-β-CD, and HP-γ-CD were obtained from PubChem (CID: 12049144, 14049689, and 119174) in sdf format. The R-Miconazole and S-Miconazole crystal structures were obtained from PubChem (CID: 1150344 and 969503).

Instrumentation

A computer with an Operating System (OS) *Windows 10 Home 64-bit* with *processor Intel®* Core™ i3-6006U CPU @ 2.0GHz (4 CPUs), 1.99GHz and external hard disk 500 GB, RAM 4 GB was utilized in this experiment. The CDs structures were converted into pdb file format using Avogadro software. The obtained structures of miconazole were optimized using the PM3 method implemented in HyperChem. The optimized structures of miconazole were used for the molecular docking using Autodock Vina software. The docking results were calculated RMSD using PyMol software and visualized using Discovery Studio software.

Geometry Optimization

The structure of miconazole was geometrically optimized using HyperChem software. The density function used is semiempirical with PM3 as the calculation method. The structure of miconazole and its enantiomers are shown in Fig. 1.

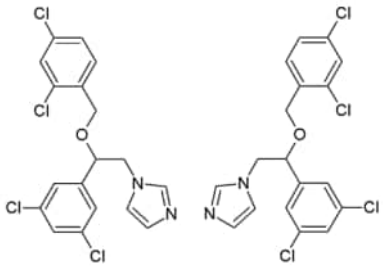

FIGURE 1. Structure of R-Miconazole and S-Miconazole

Molecular Docking

Molecular docking was carried out using automated docking program, AutoDock Vina. Water molecules on the receptor structures are removed to avoid interference during the molecular docking process. Polar hydrogen atoms are added to the structure as only polar atoms will interact with ligands while non-polar hydrogen atoms will be hidden

to increase molecular docking calculation speed. The grid box was determined according to the coordinates of the active site of receptors. This study was conducted using a blind docking process as the grid box parameters are not yet known. The large grid box was arranged so that ligands can rotate freely to find the most stable site on the receptors.

Exhaustiveness is a parameter of Autodock Vina that controls how comprehensive its prediction is. The increase of the exhaustiveness value will be slow down the docking process. However, the higher the exhaustiveness, the higher the probability of a good result of docking. The default value of Autodock Vina exhaustiveness is 8 [7,11]. In this study, exhaustiveness of 264 was used to obtain a more consistent docking result. The S-β-CD structure was docked with coordinate value of X = -3.160, Y = -2.483, Z = -1.514, Grid Box size of 52 x 52 x 52 and Grid Spacing 0.375. The HP-β-CD structure was docked with coordinate value of X = -0.421, Y = -5.367, Z = -2.059, Grid Box size of 60 x 60 x 60 and Grid Spacing 0.375. The HP-γ-CD structure was docked with coordinate value of X = 7.235, Y = 14.629, Z = 2.358, Grid Box size of 52 x 64 x 60 and Grid Spacing 0.375. The docking results should have Root Mean Square Deviation (RMSD) of less than 3 Å [12].

RESULTS AND DISCUSSION

Geometry Optimization

The first step is ligands and receptors preparation using Avogadro software to changes the file format into pdb. Miconazole as a ligand was optimized using HyperChem software by the semiempirical PM3 method, therefore, the most stable structure that has the lowest binding energy was obtained. Miconazole enantiomers structures before and after optimization were shown in Fig. 2 and Fig. 3.

FIGURE 2. The structure of R-Miconazole before and after optimized

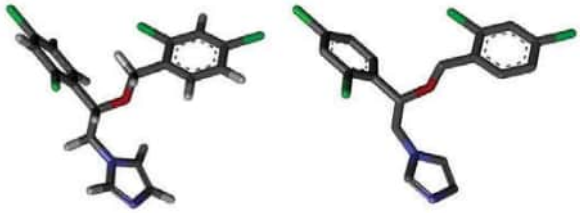

FIGURE 3. The structure of S-Miconazole before and after optimized

Molecular Docking

The running process was performed using Autodock Vina software. The RMSD values of inclusion complexes obtained are shown in Table 1. All of the RMSD values obtained are below 3 Å, this indicates that the ligand structure before and after docking is almost accurate.

The results of molecular docking are shown the stability of the inclusion complex based on its binding energy (ΔG). Fig. 4 shows the structure of S-β-CD/R-Miconazole and S-β-CD/S-Miconazole complexes. The complex which the miconazole is not included in the S-β-CD has ΔG value of S-β-CD/R-Miconazole in the range -4.6 to -4.2 Kcal/mol and S-β-CD/S-Miconazole in the range -4.4 to -3.9 Kcal/mol. The S-β-CD/R-Miconazole complex has a lower binding energy value (-4.6 Kcal/mol) compared to S-β-CD/S-Miconazole (-4.4 Kcal/mol). Miconazole that does not include the S-β-CD may be caused by the size of the S-β-CD cavity, therefore, the complexes between miconazole and S-β-CD could be trapped. The ΔG value of S-β-CD/R-Miconazole and S-β-CD/S-Miconazole docked using Autodock Vina software are shown in Table 2.

TABLE 1. RMSD value of the docking results

Inclusion complex	RMSD value
S-β-CD/R-Miconazole	2.227
S-β-CD/S-Miconazole	1.893
HP-β-CD/R-Miconazole	2.383
HP-β-CD/S-Miconazole	2.389
HP-γ-CD/R-Miconazole	2.941
HP-γ-CD/S-Miconazole	1.964

TABLE 2. The ΔG value of S-β-CD/R-Miconazole and S-β-CD/S-Miconazole

Inclusion complex	ΔG (Kcal/mol)	|ΔΔG| (Kcal/mol)
S-β-CD/R-Miconazole	-4.6	0.2
S-β-CD/S-Miconazole	-4.4	

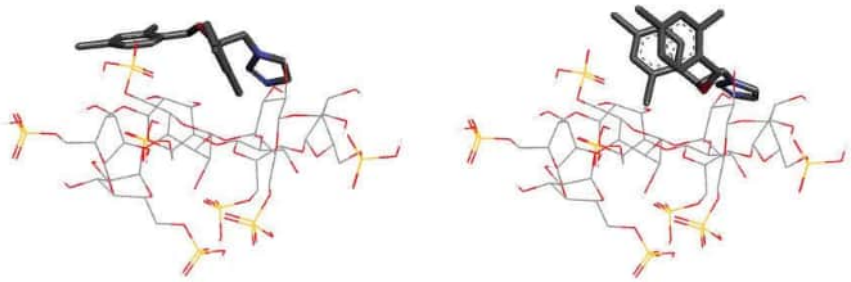

FIGURE 4. Structure of S-β-CD/R-Miconazole and S-β-CD/S-Miconazole

The more negative the ΔG value, the higher affinity between ligands and receptors, therefore, the inclusion complex obtained was more stable. The enantiomer with the highest affinity will spend the most time in the mobile phase while the enantiomer with the least affinity will be eluted first from the column. The |ΔΔG| value is the difference ΔG value of R-Miconazole and S-Miconazole that describes the enantiomer separation ability to miconazole compounds using chiral selector cyclodextrin. The value of |ΔΔG| obtained is 0.2 Kcal/mol. The higher |ΔΔG| value of |ΔΔG|, the better separation of chiral compounds. The value of |ΔΔG| indicates that cyclodextrin can be used as a chiral selector to separating the enantiomer of miconazole compounds. In this study, the inclusion complex of R-Miconazole has lower ΔG values compared to S-Miconazole. It causes S-Miconazole will be eluted first from the cyclodextrin chiral selector because the stability of S-Miconazole is weaker than R-Miconazole.

TABLE 3. The ΔG value of HP-β-CD/R-Miconazole and HP-β-CD/S-Miconazole

Inclusion complex	ΔG (Kcal/mol)	|ΔΔG| (Kcal/mol)
HP-β-CD/R-Miconazole	-5.1	0.3
HP-β-CD/S-Miconazole	-4.8	

Following the same approach, the ΔG value of the inclusion complex was obtained from the docking process using Autodock Vina. The ΔG value of HP-β-CD/R-Miconazole is in the range -5.1 to -4.5 Kcal/mol and HP-β-CD/S-Miconazole in the range -4.8 to -4.3 Kcal/mol. HP-β-CD/R-Miconazole complex has a lower binding energy value (-5.1 Kcal/mol) compared to HP-β-CD/S-Miconazole (-4.8 Kcal/mol). Similar to the S-β-CD/Miconazole complex, this inclusion complex has |ΔΔG| value in the range 0.3 Kcal/mol. In addition, HP-β-CD/R-Miconazole has a lower ΔG value compared to S-Miconazole, therefore, S-Miconazole will be eluted first from HP-β-CD chiral selector. Fig. 5 shows the structure of HP-β-CD/R-Miconazole and HP-β-CD/S-Miconazole. The ΔG value of HP-β-CD/R-Miconazole and HP-β-CD/S-Miconazole docked using Autodock Vina software are shown in Table 3.

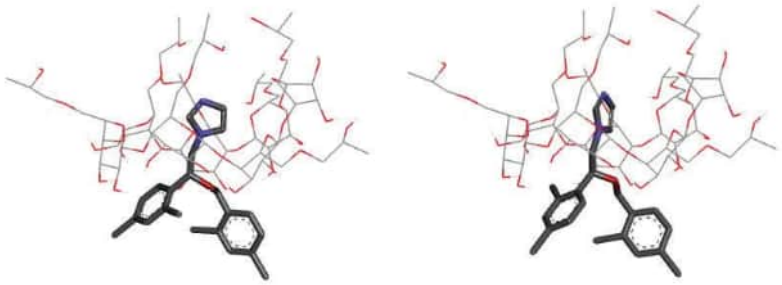

FIGURE 5. Structure of HP-β-CD/R-Miconazole and HP-β-CD/S-Miconazole

The ΔG value of HP-γ-CD/Miconazole complex was obtained from the docking process using Autodock Vina. The ΔG value of HP-γ-CD/R-Miconazole is in the range -4.4 to -4.0 Kcal/mol and HP-γ-CD/S-Miconazole in the range -4.3 to -3.8 Kcal/mol. HP-γ-CD/R-Miconazole complex has a lower binding energy value (-4.3 Kcal/mol) compared to HP-γ-CD/S-Miconazole (-4.4 Kcal/mol). This complex has |ΔΔG| value in the range 0.1 Kcal/mol. In addition, HP-γ-CD/R-Miconazole has a lower ΔG value compared to S-Miconazole, therefore, S-Miconazole will be eluted first from HP-γ-CD chiral selector. Fig. 6 shows the structure of HP-γ-CD/R-Miconazole and HP-γ-CD/S-Miconazole. The ΔG value of HP-γ-CD/R-Miconazole and HP-γ-CD/R-Miconazole docked using Autodock Vina software are shown in Table 4.

TABLE 4. The ΔG value of HP-γ-CD/R-Miconazole and HP-γ-CD/S-Miconazole

Inclusion complex	ΔG (Kcal/mol)	|ΔΔG| (Kcal/mol)
HP-γ-CD/R-Miconazole	-4.4	0.1
HP-γ-CD/S-Miconazole	-4.3	

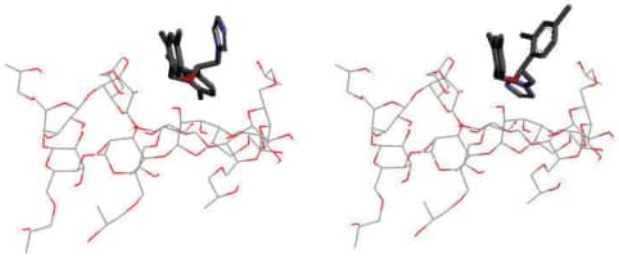

FIGURE 6. Structure of HP-γ-CD/R-Miconazole and HP-γ-CD/S-Miconazole

The complexing ability of cyclodextrin was modified by the presence of hydroxypropyl (HP) substituent, therefore, the interaction and complexation energies for HP-β-CD are higher than other cyclodextrin derivatives. In contrast to HP-γ-CD, the complexation energies, deformation, and interaction in HP-γ-CD are weak as the large cavity in HP-γ-CD prevents the fit between host and guest molecules [13-16]. Based on the research that has been done, the use of HP-β-CD as a chiral selector for chiral separation of miconazole obtained the lowest ΔG value with high affinity and stable complex. It indicates that HP-β-CD performed better than S-β-CD and HP-γ-CD as a chiral selector for chiral separation of miconazole compounds.

CONCLUSION

Cyclodextrin derivatives can be used to predict chiral separation of miconazole compounds, specifically sulfated-β-cyclodextrin (S-β-CD), hydroxypropyl-β-cyclodextrin (HP-β-CD), and hydroxypropyl-γ-cyclodextrin (HP-γ-CD). The results of molecular docking using Autodock Vina shows that R-Miconazole has a more stable interaction with all of the cyclodextrin derivatives compared to S-Miconazole based on its lower binding energies. These results

indicate that S-Miconazole will be eluted first followed by R-Miconazole. In addition, the stability level of cyclodextrin derivatives as a chiral selector to predicting the separation of miconazole is HP-β-CD>S-β-CD>HP-γ-CD.

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REFERENCES

1. E. Sanganyado, Z. Lu, Q. Fu, D. Schlenk, and J. Gan, Water Res. **124**, 527–542 (2017).
2. R. Chang. *General Chemistry: The Essential Concepts, 3rd Edition*. (McGraw-Hill, New York, 2014).
3. C. S. Nascimento, J. F. Lopes, L. Guimarães, and K. B. Borges, Analyst. **139**, 3901-3910 (2014).
4. D. K. Pratoko, Chem. Prog. **5**, 31-36 (2012).
5. S. R. Arsad, H. Maarof, W. A. W. Ibrahim, and H. Y. Aboul-Enein, Chirality. **28**, 209-214 (2016).
6. Y. Liu, L. Cai, J. Lun, M. Zhao, and X. Guo, New J. Chem., **44**, 18337-18346 (2020).
7. H. Setiawan and M. I. Irawan, Jurnal Sains dan Seni ITS. **6**, 68-72 (2017).
8. T. Rostinawati, Y. C. Sumirtapura, Elfahmi, and D. S. Retnoningrum, Pharmauho. **2**, 1-5 (2016).
9. I. Makmur, A. Halim, M. D. Oktavia, and H. Anggraeni, Jurnal Farmasi Higea, **10**, 60-75 (2018).
10. S. Wren, T. A. Berger, K.S. Boos, H. Engelhardt, E. R. Adlard, I. W. Davies, K. D. Altria, and R. Stock. Chromatographia, **54**, 59-77 (2001).
11. S. Forli, R. Huey, M. E. Pique, M. F. Sanner, D. S. Godsell, and A. J. Olson, Nat. Prot. **11**, 905-919 (2016).
12. A. N. Jain and A Nicholls, J. Comput. Aided. Mol. **22**, 133-139 (2008).
13. V. Barillaro, G. Dive, P. Bertholet, B. Evrard, L. Delattre, Z. Eric, and G. Piel, Int. J. Pharm. **342**, 152-160 (2007).
14. S. Yusri, H. Sutanto, and M.Nasikin, AIP Conf Proc. 020006-1-020006-6 (2021).
15. S. Priya, B. S. Bharathi, G. B. Veerakanellore, T. Stalin, J. Mol. Struct. **1160**, 1–8 (2018).
16. N. R. Azhari, N. Yahaya, F. Bukhari, M. Suah, S. Prabu, B. Y. Hui, M. S. Shahriman, N. N. M. Zain, Chirality. **44**, 18337–18346 (2020).

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