

Prediction of Enantioseparation of Econazole on the Cyclodextrin Derivatives as Chiral Selectors by Molecular Docking Approach

Dadan Hermawan^{1,*}, Cacu Cacu¹, Nurul Alif Septiorini¹, Ponco Iswanto¹, Uyi Sulaeman¹, Hassan Y Aboul-Enein²

¹ Department of Chemistry, Faculty of Mathematics and Natural Science, Jenderal Soedirman University, Indonesia

² Department of Pharmaceutical and Medical Chemistry, Pharmaceutical and Drug Industries Research Division, National Research Centre (NRC), Dokki, Cairo, Egypt

*Corresponding author. Email: dadan.hermawan@unsoed.ac.id

ABSTRACT

Molecular docking approach has been successfully developed for prediction of enantioseparation of econazole on the cyclodextrin derivatives namely sulfated- β -cyclodextrin (S- 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-Econazole forms more stable interaction with all cyclodextrin derivatives than S-Econazole forms, suggesting that S-econazole will be eluted earlier than R-econazole. In addition, the stability level of cyclodextrin derivatives as chiral selectors was S- β -CD > HP- γ -CD.

Keywords: Cyclodextrin, Enantioseparation, Econazole, Molecular docking.

1. INTRODUCTION

Econazole is an antifungal agent well-known for the potential treatment of several fungal infections in the skin of both humans and animals. This compound has one chiral center, thus leading to two enantiomers. The activity and toxicity of chiralazole drugs might be influenced by stereoisomerism. Based on several reports, there is only one enantiomer that gives good effects [1]. 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) and capillary electrophoresis (CE) [2-4].

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 [5]. Cyclodextrin (CD) is a molecule that has a cyclic torus shape that has an outer surface hydrophilic and a

lipophilic middle cavity that can accommodate various lipophilic ligands. Cyclodextrin is a macromolecule consisting of glucopyranose subunits obtained by enzymatic degradation of starch. Cyclodextrin has a conical shape with a lipophilic center cavity and a hydrophilic surface [6-7]. 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 [8].

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 [9]. The molecular docking method can save time, effort, and the use of solvents or chemicals that pollute the environment [10]. 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 and

receptors complex was obtained. In addition, a more effective ligand can be predicted by calculating the energy interactions of the different ligands [11]. Based on this report, this study aims to analyze the structure of the econazole complex, calculate the binding energy, and determine the most suitable chiral selector to predict the separation of the enantiomers of econazole. 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 [12-15]. 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 [16]. Cyclodextrin shows good enantioselectivity for a wide range of analytes, is 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 [15]. In this study, econazole acts as ligands, and cyclodextrin acts as receptors. Cyclodextrins used for this study are sulfated- β -cyclodextrin (S- β -CD) and hydroxypropyl- γ -cyclodextrin (HP- γ -CD) [17].

2. MATERIALS AND APPARATUS

The crystal structure of S- β -CD and HP- γ -CD were obtained from PubChem (CID: 12049144 and 2733545) in SDF format. The crystal structure of R-Econazole and S-Econazole were obtained from PubChem (CID: 6604378 and 12773795).

A computer with an Operating System (OS) Windows 10 Enterprise 64-bit with processor Intel® Core™ i3-4005U CPU @ 1.70 GHz (4 CPUs), 1.7 GHz and external hard disk 500 GB, RAM 4 GB. The CDs structures were converted into PDB file format using Avogadro software. The structure of Econazole was optimized using the PM3 method implemented in HyperChem software. The AutoDock Vina software was used as a molecular docking tool. Docking results were calculated RMSD using PyMOL software.

2.1. Geometry Optimization

The structure of econazole was geometrically optimized using HyperChem software. The calculation used is semiempirical with PM3 as the method. The structure of econazole and its enantiomers are shown in **Figure 1**.

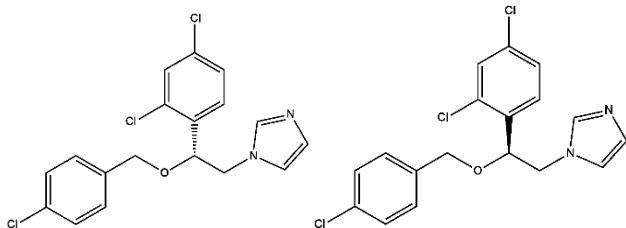


Figure 1 Structure of R-Econazole and S-Econazole.

2.2. Molecular Docking

Molecular docking was carried out using an 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 that 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 was a parameter in AutoDock Vina that can control some of its comprehensive predictions. 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 [6,19]. 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 = -0.437, Y = 9.514, Z = -8.760, Grid Box size of 20 x 20 x 20 and Grid Spacing 1.000. The HP- γ -CD structure was docked with coordinate value of X = -20.980, Y = 2.342, Z = 67.004, Grid Box size of 18 x 18 x 18 and Grid Spacing 1.000. The docking results should have a Root Mean Square Deviation (RMSD) of less than 3 Å [23].

3. RESULTS

3.1. Geometry Optimization

Geometry optimization can determine the location of atoms in a stable molecular conformation with the lowest energy state to obtain a molecular geometry that is a representation of the molecular structure adopted by compounds in nature.

The first step is ligands and receptors preparation using Avogadro software to change the file format into PDB. Econazole is a ligand that was optimized using HyperChem software by the semiempirical PM3 method, therefore, the most stable structure that has the lowest binding energy was obtained. Econazole enantiomers structures before and after optimization were shown in **Figure 1** and **Figure 2**.

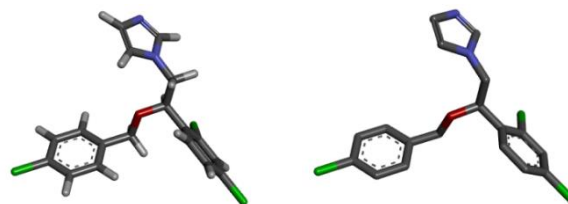


Figure 2 The structure of R-Econazole before and after optimization.

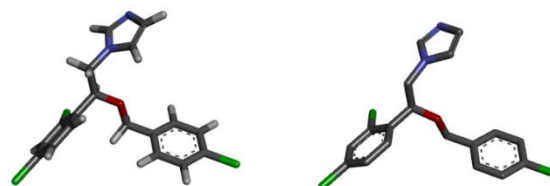


Figure 3 The structure of S-Econazole before and after optimization.

3.2. Molecular Docking

Molecular Docking is a computational simulation used to predict between a drug/ligand and a receptor/protein by attaching a small molecule (ligand) to the active site of the receptor [12]. 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 and receptors complex was obtained. In addition, a more effective ligand can be predicted by calculated the energy interactions of the different ligands [16].

The running process was performed using Autodock Vina software. 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 was a parameter in Autodock Vina that can control some of its comprehensive predictions. 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 [20,23]. In this study, exhaustiveness of 264 was used to obtain a more consistent docking result. 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.

Table 1. RMSD value of the docking results.

Inclusion complex	RMSD value (Å)
S-β-CD/R-Econazole	1.509
S-β-CD/S-Econazole	1.667
HP-γ-CD/R-Econazole	1.642
HP-γ-CD/S-Econazole	2.371

The results of molecular docking are shown the stability of the inclusion complex based on its binding energy (ΔG). Figure 4 shows the structure of S-β-CD/R-Econazole and S-β-CD/S-Econazole complexes. The complex which the econazole is not included in the S-β-CD has ΔG value of S-β-CD/R-Econazole in the range -5.2 to -4.4 Kcal/mol and S-β-CD/S-Econazole in the range -4.7 to -4.2 Kcal/mol. The S-β-CD/R-Econazole complex has a lower binding energy value (-5.2 Kcal/mol) compared to S-β-CD/S-Econazole (-4.7 Kcal/mol). Econazole that does not include the S-β-CD may be caused by the size of the S-β-CD cavity, therefore, the complexes between econazole and S-β-CD could be trapped. The ΔG value of S-β-CD/R-Econazole and S-β-CD/S-Econazole docked using Autodock Vina software are shown

in **Table 2** and **Figure 4**. The negative value of ΔG indicates that the inclusion complex formed is stable [24].

Table 2. The ΔG value of S-β-CD/R-Econazole and S-β-CD/S-Econazole.

Inclusion complex	ΔG (Kcal/mol)	$ \Delta\Delta G $ (Kcal/mol)
S-β-CD/R-Econazole	-5.2	0.5
S-β-CD/S-Econazole	-4.7	

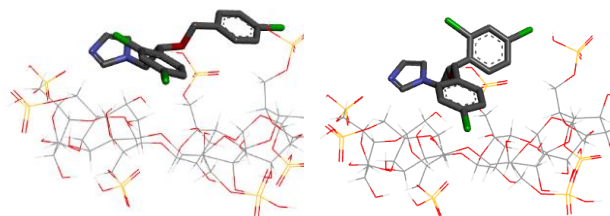


Figure 4 Structure of S-β-CD/R-Econazole and S-β-CD/S-Econazole.

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 $|\Delta\Delta G|$ value is the difference ΔG value of R-Econazole and S-Econazole that describes the enantiomer separation ability to econazole compounds using chiral selector cyclodextrin. The value of $|\Delta\Delta G|$ obtained is 0.5 Kcal/mol. The higher $|\Delta\Delta G|$ value of $|\Delta\Delta G|$, the better separation of chiral compounds. The value of $|\Delta\Delta G|$ indicates that cyclodextrin can be used as a chiral selector to separate the enantiomer of econazole compounds. In this study, the inclusion complex of R-Econazole was lower ΔG values compared to S-Econazole. It causes S-Econazole will be eluted first from the cyclodextrin chiral selector because the stability of S-Econazole is weaker than R-Econazole [25-26].

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-γ-CD/R-Econazole is in the range -4.2 to -3.7 Kcal/mol and HP-γ-CD/S-Econazole is in the range -4.1 to -3.6 Kcal/mol. HP-γ-CD/R-Econazole complex has a lower binding energy value (-4.2 Kcal/mol) compared to HP-γ-CD/S-Econazole (-4.1 Kcal/mol). This complex has $|\Delta\Delta G|$ value in the range 0.1 Kcal/mol. In addition, HP-γ-CD/R-Econazole was a lower ΔG value compared to S-Econazole, therefore, S-Econazole will be eluted first from HP-γ-CD chiral selector. Figure 5 shows the structure of HP-γ-CD/R-Econazole and HP-γ-CD/S-Econazole. The ΔG value of HP-γ-CD/R-Econazole and HP-γ-CD/S-Econazole docked using Autodock Vina software are shown in **Table 3** and **Figure 5**.

Table 3. The ΔG value of HP-γ-CD/R-Econazole and HP-γ-CD/S-Econazole

Inclusion complex	ΔG (Kcal/mol)	$ \Delta\Delta G $ (Kcal/mol)
S-β-CD/R-Econazole	1.509	0.1
S-β-CD/S-Econazole	1.667	

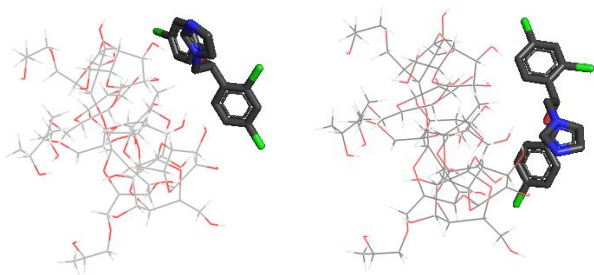


Figure 5 Structure of HP- γ -CD/R-Econazole and HP- γ -CD/S-Econazole

4. DISCUSSION

The molecular docking of econazole and cyclodextrin derivatives showed negative energy and a small number of RMSD. From the docking test, the RMSD value was less than 3 Å, so the prediction was quite accurate. The complexing ability of cyclodextrin was modified by the presence of hydroxypropyl (HP) substituent, therefore, the interaction and complexation energies for S- β -CD are higher than other cyclodextrin derivatives [27-28]. Based on the research that has been done, the use of S- β -CD as a chiral selector for chiral separation of econazole obtained the lowest ΔG value with high affinity and stable complex. It indicates that S- β -CD performed better than HP- γ -CD as a chiral selector for chiral separation of econazole compounds [29-31].

A high performance liquid chromatography (HPLC) method using cyclodextrin-based Astec Cyclobond as a chiral column has been successfully developed for chiral separation of econazole with $R_s = 2.29$ and analysis time within 9 min. Condition mobile phase composition of acetonitrile: water (0.2% HCOOH) 20:80 (v/v), and UV detection at 220 nm. The calibration curve of econazole was linear with $r^2 = 0.9992$. LOD and LOQ of econazole were 3.31 and 11.03 mg/L, respectively.

5. CONCLUSION

Cyclodextrin derivatives were used to predict chiral separation of econazole compounds, specifically sulfated- β -cyclodextrin (S- β -CD) and hydroxypropyl- γ -cyclodextrin (HP- γ -CD). The results of molecular docking using Autodock Vina shows that R-Econazole has a more stable interaction with all of the cyclodextrin derivatives compared to S-Econazole based on its lower binding energies. These results indicate that S-Econazole will be eluted first followed by R-Econazole. In addition, the stability level of cyclodextrin derivatives as a chiral selector to predicting the separation of econazole is S- β -CD > HP- γ -CD.

AUTHORS' CONTRIBUTIONS

ALL AUTHORS made substantial contributions to CONCEPT and DESIGN, ACQUISITION OF DATA, or ANALYSIS and INTERPRETATION OF DATA; took part in DRAFTING the article or REVISING it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All

the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

ACKNOWLEDGMENTS

The authors would like to acknowledge Universitas Jenderal Soedirman (UNSOED) Indonesia for financial support through Basic Research Grant 2021.

REFERENCES

- [1] J. Zhang, B. Liu, Z. Jiang, Y. Cui, X. Guo. Enantioselective determination of econazole in rat plasma and its application to a pharmacokinetic study, *Analytical Biochemistry*, 2020, vol. 602, pp. 113791. <https://doi.org/10.1016/j.ab.2020.113791>.
- [2] S. Salido-Fortuna, M. Greño, M. Castro-Puyana, M.L. Marina. Amino acid chiral ionic liquids combined with hydroxypropyl- β -cyclodextrin for drug enantioseparation by capillary electrophoresis, *Journal of Chromatography A*, 2019, vol. 1607, pp. 460375. <https://doi.org/10.1016/j.chroma.2019.460375>.
- [3] S. Salido-Fortuna, M. Castro-Puyana, M.L. Marina. Chiral micellar electrokinetic chromatography, *Journal of Chromatography A*, 2020, vol. 1626, pp. 461383. <https://doi.org/10.1016/j.chroma.2020.461383>.
- [4] S. El Deeb, C.F. Silva, C.S.N. Junior, R.S. Hanafi, K.B. Borges. Chiral capillary electrokinetic chromatography: principle and applications, detection and identification, design of experiment, and exploration of chiral recognition using molecular modeling, *Molecules*, 2021, vol. 26, pp. 2841. <https://doi.org/10.3390/molecules26102841>.
- [5] C.S. Nascimento, J.F. Lopes, L. Guimarães, K.B. Borges. Molecular modeling study of the recognition mechanism and enantioseparation of 4-hydroxy propanol by capillary electrophoresis using carboxymethyl- β -cyclodextrin as the chiral selector, *Analyst*, 2014, vol. 139, pp. 3901-3910. <https://doi.org/10.1039/C4AN00223G>.
- [6] V. Suvarna, A. Kajwe, M. Murahari, G.V. Pujar, B.K. Inturi, A.P. Sherje. Inclusion complexes of nateglinide with HP- β -CD and L-Arginine for solubility and dissolution enhancement: preparation, characterization, and molecular docking study, *Journal of Pharmaceutical Innovation*, 2017, vol. 12, no. 2, pp. 168-181. <https://doi.org/10.1007/s12247-017-9275-z>.
- [7] A.P. Sherje, V.M. Kulkarni, N. Manikanta, Y.B. Usha, S. Pritesh, D. Vasanti. Bushan. Inclusion complexation of etodolac with hydroxypropyl-beta-cyclodextrin and auxiliary agents: Formulation characterization and molecular modeling studies, *Molecular Pharmaceutics*, 2017, vol. 14, no. 4, pp. 1231-1242. <https://doi.org/10.1021/acs.molpharmaceut.6b01115>.

- [8] D.K. Pratoko. Molecular docking of piper longum (L.) phytochemicals to cyclooxygenase-2 (cox-2) receptors as anti-inflammatory, *Chemistry Progress*, 2012, vol. 5, pp. 31-36.
- [9] S.R. Arsad. H. Maarof, W.A.W. Ibrahim, H.Y. Aboul-Enein. Theoretical and molecular docking study of ketoconazole on heptakis (2,3,6-tri-O-methyl)- β -cyclodextrin as chiral selector, *Chirality*, 2016, vol. 28, pp. 209214. <https://doi.org/10.1002/chir.22554>.
- [10] Y. Liu, L. Cai, J. Lun, M. Zhao, X. Guo. Enantiomeric separation and molecular docking study of seven imidazole antifungal drugs on a cellulose tris-(3,5-dimethyl phenyl carbamate) chiral stationary phase, *New Journal of Chemistry*, 2020, vol. 44, pp. 18337-18346. <https://doi.org/10.1039/D0NJ03657A>.
- [11] H. Setiawan, M.I. Irawan. Study of ligand placement approach in protein using genetic algorithm, *Jurnal Sains dan Seni* 2017, vol. 6, pp. 68-72
- [12] T. Rostinawati, Y.C. Sumirtapura, Elfahmi, D.S. Retnoningrum. Determination of -cyclization activity of wild-type cyclodextrin glucosyltransferase, H43K, P84Y, Y93F, Y188L, and S468F from *Bacillus* sp. A2-5a against soluble starch, *Pharmauho*, 2016, vol. 2, pp. 1-5.
- [13] M. Wei, X. Yang, P. Watson, F. Yang, H. Liu. Development of QSAR model for predicting the inclusion constants of organic chemicals with α -cyclodextrin, *Environmental Science and Pollution Research Environ*, 2018, vol. 25, pp. 17565–17574. <https://doi.org/10.1007/s11356-018-1917-2>.
- [14] I.M. Le-Deygen, A.A. Skuredina, I.V. Uporov, E.V. Kudryashova, Thermodynamics and molecular insight in guest–host complexes of fluoroquinolones with β -cyclodextrin derivatives, as revealed by ATR-FTIR spectroscopy and molecular modeling experiments, *Analytical and Bioanalytical Chemistry*, 2017, vol. 409, pp. 6451–6462. <https://doi.org/10.1007/s00216-017-0590-5>.
- [15] D. Chantasart, P. Rakkaew. Preparation and characterization of dry β -cyclodextrin-based ternary complexes of haloperidol and lactic acid for drug delivery, *Journal of Drug Delivery Science and Technology*, 2019, vol. 52, pp. 73–82. <https://doi.org/10.1016/j.jddst.2019.04.011>.
- [16] I. Makmur, A. Halim, M.D. Oktavia, H. Anggraeni. Amlodipine Besylate- β -cyclodextrin inclusion complex by kneading method, *Jurnal Farmasi Higea*, 2018, 10, pp. 60-75.
- [17] A.C. Illapakurthy, Y.A. Sabnis, B.A. Avery, M.A. Avery, C.M. Wyandt. Interaction of artemisinin and its related compounds with hydroxypropyl- β -cyclodextrin in solution state: Experimental and molecular-modeling studies, *Journal of Pharmaceutical Sciences*, 2003, vol. 92, no. 3, pp. 649–655. <https://doi.org/10.1002/jps.10319>.
- [18] B. Varghese, F.O. Suliman, A. Al-Hajri, N.S.S. Al Bishri, N. Al-Rwashda. Spectral and theoretical study on complexation of sulfamethoxazole with β - and HP β -cyclodextrins in binary and ternary systems, *Spectrochimica Acta Part A: Molecular Spectroscopy*, 2018, vol. 190, pp. 392–401. <https://doi.org/10.1016/j.saa.2017.09.060>.
- [19] S. Wren, T.A. Berger, K.S. Boos, H. Engelhardt, E.R. Adlard, I.W. Davies, K.D. Altria, R. Stock. The use of cyclodextrins as chiral selectors, *Chromatographia*, 2001, vol. 54, pp. 59-77. https://doi.org/10.1007/978-3-322-83141-5_5.
- [20] S. Forli, R. Huey, M.E. Pique, M.F. Sanner, D.S. Godsell, A.J. Olson. Computational protein-ligand docking and virtual drug screening with the AutoDock suite, *Nature Protocols*, 2016, vol. 11, pp. 905-919. <https://doi.org/10.1038/nprot.2016.051>.
- [21] A.N. Jain, A. Nicholls. Recommendations for evaluation of computational methods, *Journal of Computer-Aided Molecular Design*, 2008, vol. 22, pp. 133-139. <https://doi.org/10.1007/s10822-008-9196-5>.
- [22] A.A. Pratama, Y. Rifai, A. Marzuki. Molecular docking of the compound 5.5'-dibromomethylsesamin, *Majalah Farmasi dan Farmakologi*, 2017, vol. 21, pp. 67-69.
- [23] V. Barillaro, G. Dive, P. Bertholet, B. Evrard, L. Delattre, Z. Eric, G. Piel, Theoretical and experimental investigations on miconazole/cyclodextrin/acid complexes: molecular docking studies, *International Journal of Pharmaceutics*, 2007, vol. 342, pp. 152-160. <https://doi.org/10.1016/j.ijpharm.2007.05.003>.
- [24] E.S. Nurhidayah, A.L. Ivansyah, M.A. Martoprawiro, M.A. Zulfikar. A molecular docking study to predict enantioseparation of some chiral carboxylic acid derivatives by methyl- β -cyclodextrin, *Journal of Physics: Conference Series*, 2018, vol. 1013, pp. 012203. [doi :10.1088/1742-6596/1013/1/012203](https://doi.org/10.1088/1742-6596/1013/1/012203).
- [25] V. Aiassa, C. Garnerio, M.R. Longhi, and A. Zoppi. Cyclodextrin multicomponent complexes: Pharmaceutical applications, *Pharmaceutics*, 2021, vol. 13, no. 7, pp. 1099. <https://doi.org/10.3390/pharmaceutics13071099>.
- [26] S. Alshehri, S.A. Syed, A.J. Mohammad, A. Mohammad, Z.H. Mohammad, A. Afzal, M.W. Abdul. Host-guest complex of β -cyclodextrin and pluronic F127 with Luteolin: Physicochemical characterization, anti-oxidant activity, and molecular modeling studies, *Journal of Drug Delivery Science and Technology*, 2020, vol. 55, pp. 101356. <https://doi.org/10.1016/j.jddst.2019.101356>.
- [27] C.V. Bui, T. Rosenau, H. Hettegger. Polysaccharide- and β -cyclodextrin-based chiral selectors for enantiomer resolution: recent developments and applications, *Molecules*, 2021, vol. 26, pp. 4322. <https://doi.org/10.3390/molecules26144322>.

- [28] S.M. Omar, F. Ibrahim, A. Ismail. Formulation and evaluation of cyclodextrin-based nanosponges of griseofulvin as pediatric oral liquid dosage form for enhancing bioavailability and masking bitter taste, *Saudi Pharmaceutical Journal*, 2020, vol. 28, pp. 349–361. <https://doi.org/10.1016/j.jsps.2020.01.016>.
- [29] V. Suvarna, S. Thorat, U. Nayak, A. Sherje, M. Murahari. Host-guest interaction study of Efavirenz with hydroxypropyl- β -cyclodextrin and L-arginine by computational simulation studies: Preparation and characterization of supramolecular complexes, *Journal of Molecular Liquids*, 2018, vol. 259, pp. 55–64. <https://doi.org/10.1016/j.molliq.2018.02.131>.
- [30] T. Bíró, Z. Aigner. Current approaches to use cyclodextrins and mucoadhesive polymers in ocular drug delivery—a mini-review, *Scientia Pharmaceutica*, 2019, vol. 15, pp. 87. <https://doi.org/10.3390/scipharm87030015>.
- [31] M. Sillion, A. Fifere, A.L. Lungoci, N.L. Marangoci, S.A. Ibanescu, R. Zonda, A. Rotaru, M. Pinteala. Mass spectrometry as a complementary approach for noncovalently bound complexes based on cyclodextrins, *Advancements of Mass Spectrometry in Biomedical Research*, 2019, pp. 685–701. https://doi.org/10.1007/978-3-030-15950-4_41.