THEORETICAL STUDY ON CHIRAL RECOGNITION OF VINPOCETINE, KETOCONAZOLE, BROMUCONAZOLE AND PROPICONAZOLE STEREOISOMERS BY TEICOPLANIN AGLYCONE CHIRAL SELECTOR

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DEDICATION

My parents, who raised me and encouraged me,
My husband and my son, who loved, supported and completed me.
My beloved siblings, who were always there for me.
Thank you all for the support and blessings.

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ABSTRACT

Chiral separation has been an important issue as stereochemistry significantly influences the biological activity. In some cases, one stereoisomer may show effectiveness in pharmacology activities while the other may appear toxic. Therefore, it is crucial to develop technology for chiral separation. With the aid of computational tools, a better understanding of the interactions between both drug and fungicide stereoisomers with teicoplanin aglycone (TAG) chiral selector can be achieved before the experiment is conducted. To date, no complexation study of vinpocetine (VP), ketoconazole (KTZ), bromuconazole (BMZ) and propiconazole (PPZ) stereoisomers with TAG chiral selector has been reported. In this study, computational tools were used in the complexation study of drug and fungicide stereoisomers with TAG. This study aimed to give a better understanding of intermolecular interactions such as hydrogen bonding, π-π interaction and hydrophobic interaction between stereoisomers and chiral selector which can assist in chiral separation analysis. Docking simulation was used to find the best conformation of stereoisomers with TAG chiral selector followed by quantum-mechanic calculation representing the second phase of this study at B3LYP/6-31G(d) density functional theory (DFT) level of theory. All the theoretical calculations were performed using GAUSSIAN09 suite. The lower the binding energy, the more stable the interactions of complexes are. The results showed that the stability of inclusion complexes based on binding energy differences obtained from B3LYP/6-31G(d) calculations for VP, KTZ, BMZ and PPZ stereoisomers with TAG chiral selector were in the order of: (3S16R)VP-TAG (|ΔΔE|= 0.00 kcal mol-1) > (3R16R)VP-TAG (|ΔΔE|= 5.94 kcal mol-1) > (3R16S)VP–TAG (|ΔΔE|= 8.27 kcal mol-1) > (3S16S)VP-TAG (|ΔΔE|= 10.59 kcal mol-1); (2R4R)KTZ-TAG (|ΔΔE|= 0.00 kcal mol-1) > (2R4S)KTZ-TAG (|ΔΔE|= 1.43 kcal mol-1) > (2S4R)KTZ–TAG (|ΔΔE|= 6.18 kcal mol-1) > (2S4S)KTZ-TAG (|ΔΔE|= 10.20 kcal mol-1); (2S4S)BMZ-TAG (|ΔΔE|= 0.00 kcal mol-1) > (2S4R)BMZ-TAG (|ΔΔE|= 3.07 kcal mol-1) > (2R4S)BMZ-TAG (|ΔΔE|= 6.71 kcal mol-1) > (2R4R)BMZ-TAG (|ΔΔE|= 10.62 kcal mol-1); (2R4S)PPZ-TAG (|ΔΔE|= 0.00 kcal mol-1) > (2S4S)PPZ-TAG (|ΔΔE|= 2.66 kcal mol-1) > (2S4R)PPZ-TAG (|ΔΔE|= 4.15 kcal mol-1) > (2R4R)PPZ-TAG (|ΔΔE|= 5.92 kcal mol-1), respectively. Results of all binding energy differences of the inclusion complexes between these four drug and fungicide stereoisomers (VP, KTZ, BMZ, PPZ) with TAG chiral selector were considered a measurement of the chiral discrimination together with their interactions such as hydrogen bond, π-π interaction and others. All complexation showed that chiral separation can be achieved using TAG chiral selector. It is expected that the final results from the quantum-mechanic calculation will be useful to further explain the chiral separation analysis at experimental level.

ABSTRAK

Pemisahan kiral merupakan isu penting kerana stereokimia mempengaruhi dengan ketara aktiviti biologi. Dalam beberapa kes, satu stereoisomer boleh menunjukkan keberkesanan dalam aktiviti farmakologi manakala yang satu lagi mungkin toksik. Oleh itu, adalah penting untuk membangunkan teknologi dalam pemisahan kiral. Dengan bantuan alat pengkomputeran, pemahaman yang lebih baik mengenai interaksi antara kedua-dua stereoisomer ubat-ubatan dan racun kulat dengan pemilih kiral teikoplanin aglikon (TAG) boleh dicapai sebelum eksperimen dijalankan. Sehingga kini, tiada kajian kompleks mengenai stereoisomer vinposetin (VP), ketokonazol (KTZ), bromukonazol (BMZ) dan propikonazol (PPZ) dengan pemilih kiral TAG telah dilaporkan. Dalam kajian ini, alat pengkomputeran telah digunakan dalam kajian pengkompleksan stereoisomer ubat-ubatan dan racun kulat dengan TAG. Kajian ini bertujuan untuk memberi pemahaman yang lebih baik mengenai interaksi antara molekul misalnya ikatan hidrogen, interaksi π-π dan interaksi hidrofobik antara stereoisomer dan pemilih kiral yang boleh membantu dalam analisis pemisahan kiral. Simulasi dok telah digunakan untuk mendapatkan konformasi terbaik stereoisomer dengan pemilih kiral TAG diikuti dengan pengiraan mekanik kuantum yang mewakili fasa kedua kajian ini di peringkat teori fungsi kepadatan (DFT) B3LYP/6-31G(d). Semua pengiraan teori telah dilakukan menggunakan suite GAUSSIAN09. Lebih rendah tenaga pengikat, semakin stabil interaksi kompleks. Keputusan menunjukkan bahwa kestabilan kompleks rangkuman berdasarkan keputusan perbezaan tenaga pengikat yang diperoleh daripada pengiraan B3LYP/6-31G(d) bagi stereoisomer VP, KTZ, BMZ dan PPZ dengan pemilih kiral TAG adalah masing-masing dalam urutan: (3S16R)VP-TAG ($|\Delta\Delta E|$= 0.00 kcal mol^{-1}) > (3R16R)VP-TAG ($|\Delta\Delta E|$= 5.94 kcal mol^{-1}) > (3R16S)VP–TAG ($|\Delta\Delta E|$= 8.27 kcal mol^{-1}) > (3S16S)VP-TAG ($|\Delta\Delta E|$= 10.59 kcal mol^{-1}); (2R4R)KTZ-TAG ($|\Delta\Delta E|$= 0.00 kcal mol^{-1}) > (2R4S)KTZ-TAG ($|\Delta\Delta E|$= 1.43 kcal mol^{-1}) > (2S4R)KTZ–TAG ($|\Delta\Delta E|$= 6.18 kcal mol^{-1}) > (2S4S)KTZ-TAG ($|\Delta\Delta E|$= 10.20 kcal mol^{-1}); (2S4S)BMZ-TAG ($|\Delta\Delta E|$= 0.00 kcal mol^{-1}) > (2S4R)BMZ-TAG ($|\Delta\Delta E|$= 3.07 kcal mol^{-1}) > (2R4S)BMZ-TAG ($|\Delta\Delta E|$= 6.71 kcal mol^{-1}) > (2R4R)BMZ-TAG ($|\Delta\Delta E|$= 10.62 kcal mol^{-1}); (2R4S)PPZ-TAG ($|\Delta\Delta E|$= 0.00 kcal mol^{-1}) > (2S4S)PPZ-TAG ($|\Delta\Delta E|$= 2.66 kcal mol^{-1}) > (2S4R)PPZ-TAG ($|\Delta\Delta E|$= 4.15 kcal mol^{-1}) > (2R4R)PPZ-TAG ($|\Delta\Delta E|$= 5.92 kcal mol^{-1}). Keputusan daripada perbezaan semua tenaga pengikat kompleks rangkuman antara keempat-empat stereoisomer ubat-ubatan dan racun kulat (VP, KTZ, BMZ, PPZ) dengan pemilih kiral TAG telah dijadikan pengukur diskriminasi kiral bersama dengan interaksinya misalnya ikatan hidrogen, interaksi π-π dan lain-lain. Semua kompleks menunjukkan bahawa pemisahan kiral boleh dicapai menggunakan pemilih kiral TAG. Dijangkakan bahawa keputusan akhir daripada pengiraan mekanik kuantum akan berguna untuk menerangkan lebih lanjut analisis pemisahan kiral di peringkat eksperimen.

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LIST OF ABBREVIATIONS

ADT	-	AutoDock tool
BE	-	Binding energy
B3LYP	-	(Becke, three parameter, Lee-Yang-Par)
CD	-	Cyclodextrin
CD-EKC	-	Cyclodextrin-modified electrokinetic chromatography
CE	-	Capillary electrophoresis
GA	-	Genetic algorithm
CZE	-	Capillary zone electrophoresis
DFT	-	Density functional theory
dlg	-	Docking log file
HPLC	-	High-performance liquid chromatography
HF	-	Hartree-Fock
EKC	-	Electrokinetic chromatography
GC	-	Gas chromatography
SFC	-	Supercritical fluid chromatography
TLC	-	Thin-layer chromatography
TAG	-	Teicoplanin agylcone
VP	-	Vinpocetine
KTZ	-	Ketoconazole
BMZ	-	Bromuconazole
PPZ	-	Propiconazole
PDB	-	Protein Data Bank
LGA	-	Lamarckian Genetic Algorithm
SE	-	Semi-empirical
RMSD	-	Root mean square deviation

LIST OF SYMBOLS

Å	-	Angstrom
.	-	Alpha
	-	Beta
	-	Gamma
û	-	Delta
Œ	-	Pi
û*E*	-	Binding energy
û ûE	-	Differences in binding energy

CHAPTER 1

INTRODUCTION

1.1 Background of Study

Many chiral compounds exist in two enantiomeric forms, which have same molecular formula but different in structural arrangement (Sekhon, 2010). Chiral compounds are molecules with one or more stereogenic centers. The enantiomers of a chiral compound have same chemical structures, but different in their spatial arrangements of the atoms around the stereogenic center (Sanganyado *et al.*, 2017).

The enantiomeric separation has become a great interest of the most important task in analytical chemistry especially in the clinical, pharmaceutical and agrochemical fields. This has been an issue since the stereochemistry has a significant effect on biological activities (Wan Ibrahim *et al.,* 2007). One enantiomer of a racemic compound may have effective biological activities, while the other can be toxic. This has been a considerable interest in both pharmacological and toxicological evaluations of the enantiomers of chiral drugs (Zhang *et al.,* 2005; Wu *et al.,* 2013). In addition, all conazole fungicides are chiral, which can be an issue in their environmental behavior and toxicity (Garrison *et al.,* 2011). Hence, enantioselective chromatography has become essentially important in analytical tool for chiral analyses to gain pure enantiomers from a wide range of chiral compounds (Zhang *et al.,* 2005).

In view of pharmaceutical drug industries, almost more than half percent of the drugs currently in use are chiral products and 88% of these chiral synthetic drugs are still marketed as racemates with their side-effects (Rentsch, 2002; Nguyen *et al.,*

2006). This problem is raised probably due not only to the high production costs but also the difficulty in chiral separation technique. Hence, the enantioseparation analysis of racemic drugs is essential in order to eliminate unwanted isomer from the preparation so that the right treatment will be given to the patient (Nguyen *et al.*, 2006). On the other hand, chiral fungicides are used in agriculture field for control of many fungal disease of variety crops such as rice, fruits, cereals and others. Thus, there is a concern to potential human and wildlife exposure from its metabolites and residues in the environment, including sediment, water receiving soil runoff and soil (Garrison *et al.*, 2011).

As the production of pure enantiomeric compound and separation of chiral compounds have gained much interest nowadays, enantioselective separation has become one of the most important analytical task (Al-Majed, 2009). Various techniques have been developed for enantioselective separation, which consist of membrane separation, enzyme resolution, chemical recognition and chromatography. All methods vary in term of their abilities for chiral recognition, but are generally time-consuming, involve complicated separation processes and high-cost may limit their use in racemic separation. Hence, it is crucial to develop a simple and effective method for chiral separation (Wu *et al.*, 2013).

Enantioselective separation compounds can be achieved by chiral recognition known as chiral selector. Back then, many chiral selectors have been used in enantioselective recognition which include macrocyclic antibiotics, cellulose and cyclodextrin (Wu *et al.*, 2013). Among these, macrocyclic antibiotics chiral selectors (vancomycin, teicoplanin, teicoplanin aglycone, etc) had proven to be tremendously suitable for enantioresolution of racemic compounds (Al-Majed, 2009).

Prior to this, teicoplanin appears to be the latest chiral selector used in enantioselective separation analysis. Teicoplanin chiral selector is a macrocyclic glycopeptide antibiotic that is produced from actinoplanes and is proven to be an excellent chiral selector for enantioselective recognition mechanism. It is easily dissolved in aqueous solutions within a broad pH range because of the excellent structural properties of aglycones that can form a hydrophobic semi-rigid basket-

shaped cleft with a single acidic carboxylic acid group (COOH) and the only basic primary amine. Besides, it promotes chiral selectivity towards the chiral analytes through several interactions. Other than aglycone, it also contains many stereogenic centers, aromatic rings and macrocyclic rings. In addition, teicoplanin offers more hydrophobic interactions compared to other chiral selectors since it has a long fatty acid chain in the D-glucosamines group. Various interactions can be formed between racemates and teicoplanin as a result from these unique structures of teicoplanin, for instance hydrogen bonding, hydrophobic, steric repulsion, dipole–dipole and ionic π-π interaction. Hence, teicoplanin can excellently be used for chiral recognition of many racemic compounds (Wu *et al.*, 2013). The difference between teicoplanin aglycone (TAG) and teicoplanin is that TAG does not contain the sugar chains (Al-Majed, 2009).

TAG is the most promising chiral selector in the world to date. It has been effectively used for enantioseparation of carboxylic acids, underivatised amino acids and many other compounds. Its superb capabilities as chiral selector is due to its semi-rigid basket-like aglycone that is formed from four fused macrocyclic rings with hydroxyl and phenolic-group together with two potentially charged groups, a carboxylic acid group and a primary amine (Bechtold *et al.*, 2007).

In this study, the interactions of drugs (vinpocetine and ketoconazole) and fungicides (bromuconazole and propiconazole) with TAG chiral selector were investigated using molecular docking and quantum chemical calculation. Computational study is expected to give a better understanding about the molecular interactions (i.e hydrogen bonding and π-π interactions) between the chiral selector with both drug and fungicide stereoisomers before conducting any experiments.

1.2 Problem Statement

The separation of enantiomers has become a great interest especially in both the pharmaceutical and agrochemical science fields. This has been an issue since stereochemistry has significant effects on biological activities such as toxicology,

pharmacokinetics, pharmacology and metabolism (Wan Ibrahim *et al.*, 2007). One enantiomer of a racemic compound may have effective biological activities, while the other can be toxic. Therefore it is vital to have safe enantioseparation techniques in order to eliminate the undesirable isomer from the preparation and to find the accurate therapeutic mechanism for the pharmaceutical drug industry and also agrochemical used (Nguyen *et al.*, 2006).

Enantiomer drugs have become increasingly significant over the past 20 to 30 years. About more than half of the drugs currently in use are chiral compounds. For this purpose, the U.S Food and Drug Administration (FDA) has also recommended an assessment on the development of synthesis and analysis methods on enantioseparation when synthesizing a new drug (Bernal *et al.*, 2002; Zhang *et al.*, 2005). Meanwhile, chiral fungicides are used in agriculture field for control of many fungal diseases of various crops such as rice, fruits and cereals. Chirality is expected to play an essential role in the triazole fungicide bioactivities. Therefore, there is a concern related to potential human and wildlife exposure from its metabolites and residues in the environment, including sediment and water receiving soil runoff (Garrison *et al.*, 2011).

All chiral recognition methods vary in term of their abilities, but are generally time-consuming, involving complicated separation processes, using big volumes of solvents and high-costing, thus limiting their use in racemic separation. Hence, it is crucial to develop a simple, effective and cost-saving method for chiral separation (Wu *et al.*, 2013). In this study, molecular docking and theoretical quantum chemical calculation were used to investigate the inclusion of drug and fungicide stereoisomers with TAG. This microcyclic antibiotics teicoplanin compound with semi-rigid aglycone basket shaped provide hydrophobic sites, hydrogen bonding site, dipolar sites and π-interaction sites in which offer a broad enantioselectivity. They can be used in all chromatographic modes. However, to the best of our knowledge, studies concerning this type of molecule as compared to other chiral selector such as cyclodextrin is still scarce. Our work therefore, extended the computational study of vinpocetine, ketoconazole, bromuconazole and propiconazole with TAG as chiral selector.

This molecular level investigation will give a better understanding of the intermolecular interactions (hydrogen bonding, π-π interaction, hydrophobic and ionic interactions) between drug and fungicide stereoisomers with TAG chiral selector, which later can assist in chiral separation analysis at the experimental level.

1.3 Objectives of Study

The aim of this study is to investigate the interactions of vinpocetine, ketoconazole, bromuconazole and propiconazole with macrocyclic antibiotic chiral selector TAG using computational tools via docking studies and quantum chemical calculations.

The objectives of this study are:

i. To investigate the best active site positions in the receptor binding pockets of TAG chiral selector.

ii. To predict the preferable complex interactions and their best orientation formed by using docking studies.

iii. To compare the effectiveness of TAG as a chiral selector for vinpocetine, ketoconazole, bromuconazole and propiconazole enantioseparation.

1.4 Scope of Study

In this study, investigation of the best active site interactions formed among the drug and fungicide stereoisomers based on hydrogen bonding and binding energy formation were performed using docking simulation, and quantum chemical calculation involving density functional theory (DFT) method.

The structures of the drugs (vinpocetine and ketoconazole) and fungicides (bromuconazole and propiconazole), and TAG chiral selector crystal structures were extracted from PubChem database and Protein Data Bank (PDB) website, respectively, and modified using Discovery Studio Client 3.5 (Accelrys, BIOVIA,

San Diego CA). Vinpocetine is a drug compound that has been used worldwide to facilitate cerebral metabolism by enhancing oxygen and glucose uptake, while ketoconazole is a drug compound that has been commonly used in fungal infection associated with the increase use of cancer chemotherapy, AIDS and organ transplant. On the other hand, bromuconazole and propiconazole is a chiral triazole fungicide, one of the major classes of pesticides used to protect against fungal decay which are frequently used in the agriculture and lumber industry and extensively used in agriculture as an antiseptic sprayed on the foliar appearance, respectively.

The prediction of preferable interactions between these stereoisomers with TAG chiral selector and their best orientation of inclusion complexes formed with overall minimum binding energy were accomplished by docking studies simulation involving blind and fixed docking. At blind docking step, one hundred (100) possible random binding interactions were generated and results were saved in docking log file (dlg file). The best conformations of two clusters from dlg file were selected to perform fixed docking and all docking procedure was done using Autodock 4.2 software (Morris *et al.*, 2009). Next, the accuracy and stabilization of some complexes from docking results were calculated using quantum-mechanic calculation at B3LYP/6-31G(d) level of theory. All the theoretical calculations were performed using GAUSSIAN09 suite.

1.5 Significance of Study

Chirality has gained much interest in many analytical chemistry tasks especially in the field of agrochemical sciences and pharmaceutical drug development. Most chiral compounds display differently in their biological activities even though they have the same chemical structures. In some cases, one enantiomer may show effectiveness in pharmacological activities while the other may appear toxic. Thus, it is very crucial to develop more advanced method in chiral separation. Here, with the aid of computational tools, a better understanding of the interactions between drug and fungicide stereoisomers and TAG chiral selectors can be achieved before conducting an experiment. The advantages are time and cost-saving and no

complicated separation processes involved. Finally, improvement on the separation of the stereoisomers is expected to enhance the efficacy in therapeutic use of drugs and the safety exposure of these fungicides to human and wildlife.

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