TẠP CHÍ KHOA HỌC & CÔNG NGHỆ ĐẠI HỌC DUY TÂN
DTU Journal of Science and Technology 5(54) (2022) 92-98

TRƯỜNG ĐẠI HỌC DUY TÂN
DUYTAN UNIVERSITY

A molecular docking study of natural acridones isolated from the root of *Paramignya trimera*

Nghiên cứu "docking" phân tử cho các hợp chất acridone chiết xuất từ rễ của cây xáo tam phân

Ngo Thi Chinh[a,b*], Dao Duy Quang[a,b]
Ngô Thị Chinh[a,b*], Đào Duy Quang[a,b]

[a]*Institute of Research and Development, Duy Tan University, Da Nang, 550000, Vietnam*
[a]*Viện Nghiên cứu và Phát triển Công nghệ Cao, Trường Đại học Duy Tân, Đà Nẵng, Việt Nam*
[b]*Faculty of Environmental and Natural Science, Duy Tan University, Danang, 550000, Vietnam*
[b]*Khoa Môi trường và Khoa học Tự nhiên, Trường Đại học Duy Tân, Đà Nẵng, Việt Nam*

(Ngày nhận bài: 15/9/2021, ngày phản biện xong: 28/9/2022, ngày chấp nhận đăng: 12/10/2022)

Abstract

A molecular docking study of three natural acridones, namely citrusinine-I, 5-hydroxynoracronycin, and paratrimerin C on a target enzyme DNA polymerase μ (Pol μ), was performed. In addition, the hydrogen peroxide anion (HOO^-), a model radical, and delavirdine, a synthetic drug, are used as ligands for docking on this target protein to investigate the activity of the selected compounds to protect *Pol μ* protein against their harmful effects. The interaction sites and binding energies (ΔG_{bind}) were determined. The results reveal that 5-hydroxynoracronycin (ΔG_{bind}: -5.82 kcal/mol) exhibits a higher binding activity to *Pol μ* protein than the other acridones and HOO^- as well as delavirdine. These acridone compounds illustrated the beneficial effect of protecting *Pol μ* against harmful HOO^- species and commonly-used delavirdine drugs.

Keywords: Molecular docking; acridone; *Paramignya trimera;* polymerase μ.

Tóm tắt

Nghiên cứu docking phân tử của ba acridone tự nhiên là citrusinine-I, 5-hydroxynoracronycin và paratrimerin C trên enzyme đích DNA polymerase μ (Pol μ) đã được thực hiện. Ngoài ra, mô hình của gốc tự do dạng anion hydrogen peroxide (HOO^-), và thuốc tổng hợp delavirdine, cũng được sử dụng làm phối tử gắn vào protein đích này để nghiên cứu khả năng bảo vệ protein *Pol μ* của các hợp chất acridone chống lại các tác hại của các tác nhân này. Các vị trí tương tác và năng lượng liên kết (ΔG_{bind}) đã được xác định. Kết quả cho thấy 5-hydroxynoracronycin (ΔG_{bind}: -5,82 kcal / mol) có thể liên kết với protein *Pol μ* mạnh hơn các hợp chất acridone khác và HOO^- cũng như delavirdine. Các hợp chất acridone này đã chứng minh tác dụng trong việc bảo vệ *Pol μ* chống lại tác hại của các phần tử HOO^- hoạt động và thuốc delavirdine thường sử dụng.

Từ khóa: Docking phân tử; acridone; *Paramignya trimera;* polymerase μ.

[*]*Corresponding Author:* Ngo Thi Chinh, Institute of Research and Development, Duy Tan University, 550000, Da Nang, Viet Nam; Faculty of Environmental and Natural Science, Duy Tan University, Danang, 550000, Vietnam
Email: ngothichinh@duytan.edu.vn

1. Introduction

Paramignya trimera, the local name of "*Xao tam phan*" in Vietnam, has been used as a traditional medicine to treat liver diseases, cancer [1,2], and neuroinflammatory diseases [3]. The antioxidant activity of its root extract was also experimentally investigated by Nguyen's group. [2], in which the acridone derivatives were appreciated. These compounds have also shown several enjoyable biological activities such as antitumor, antimicrobial and antiviral [4,5]. For example, citrusinine-I has potential antiviral activities against herpes simplex virus (HSV) [6]. Recently, we reported the free radical scavenging activity as well as the kinetics of the reactions for theses acridones using density functional theory (DFT) [7]. All compounds have demonstrated their antioxidant in scavenging $HOO^{\bullet}$ radical, and 5-hydroxynoracronycin is the most potential [7].

It is known that numerous pathological states are often associated with uncontrollable DNA replication. Cancer, autoimmune diseases, and viral/bacterial infections are expensive examples. Inhibiting DNA polymerase, an enzyme responsible for catalyzing the addition of mononucleotides into a growing polymer, presents a fundamental therapeutic approach to these diseases [8]. The molecular docking approach can be used to model the interaction between a small molecule and a protein at the atomic level, which allows us to evaluate biological activities [9]. In order to study the protective activity of polymerase μ (*Pol* μ) vs harmful effects of $HOO^{\bullet}$, molecular docking (MD) is an appropriate approach. Also, analysis is additionally performed for *Pol* μ as the target and a drug compound named delavirdine as a ligand to examine the activity of the selected antioxidants to protect *Pol* μ protein against the harmful effects of this ligand. Delavirdine is a synthetic drug that, in combination with other drugs, is used to treat human immunodeficiency virus (HIV) type 1. It acts as an inhibitor of viral DNA polymerase. Unselective attachment of delavirdine to the human DNA polymerase could induce different harmful effects, mainly when repairing damaged human DNA molecules is impossible.

In this work, we used the AutoDock 4.2 program to study the molecular docking with *Pol* μ protein in water for three natural acridones, namely citrusinine-I [6], 5-hydroxynoracronycin [10], and paratrimerin C [11] (cf. **Figure 1**) isolated from the root of *Paramignya trimera* collected from Khanh Hoa province in Vietnam [11].

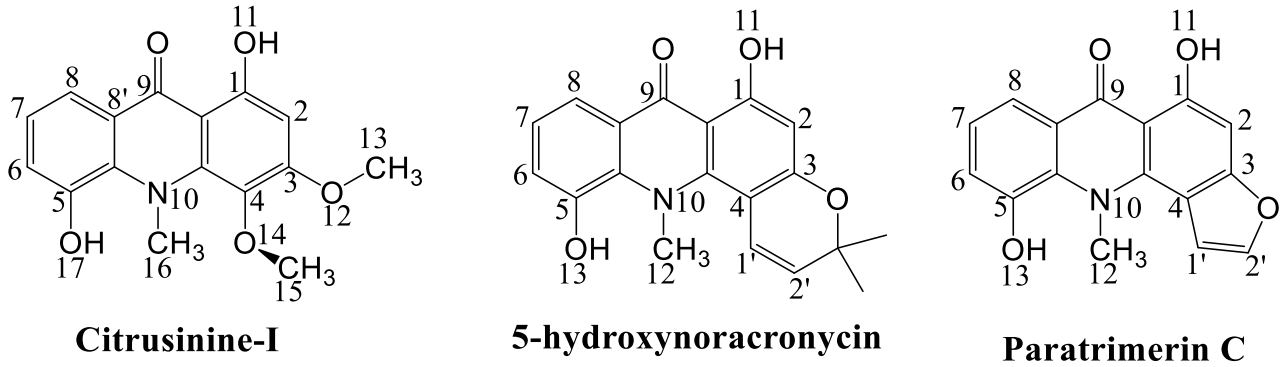

Figure 1: Chemical structures of the acridone compounds

Moreover, the reactive hydrogen peroxide anion (HOO^{-}), a model radical, and delavirdine, a synthetic drug, are also serviced as ligands for docking on this target protein to investigate the activity of the selected compounds to protect *Pol* μ protein against their harmful effects. *Pol* μ consists of a small polypeptide chain containing 494 amino acids [12]. Its primary role is to enable the repair of single-strand and double-strand break (DSB) of DNA molecules [13,14]. The action mechanism is based on its capability to fill small gaps in broken DNA, repairing them by non-homologous end-joining (NHEJ) of broken DNA ends [13].

In this study, the interaction positions and binding energies for all 3 acridones compounds, HOO- and delavirdine are determined. Moreover, the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) analysis of a polypeptide chain constituted of amino acids Val-Arg-Val-Asp-Leu polypeptide is performed to provide more insight into the interaction mechanisms of the HOO^{-} and the studied compounds to the *Pol* μ.

2. Method

The structure of Pol μ was assumed from Protein Data Bank (PDB ID: 4LZD) [13]. The protein structure was released of water molecules and ligands using BIOVIA Discovery Studio [15]. AutoDock 4.2 program package was used for all docking analyses [16]. Adding Kollman charges and polar hydrogen was performed using AutoDockTools (ADT) graphical user interface. At the physiological pH (approximately 7.4), most of the estimated species are expected to appear in their anionic forms. Therefore, a HOO^{-} anion is used instead of $HOO^{\bullet}$ radical in AutoDock calculations. The protein remained rigid, while the ligand structure's flexibility was considered in the ADT. For partial charges, the Gasteiger method was employed [17]. All calculations for the flexible protein-ligand docking were done using the Lamarckian Genetic Algorithm (LGA) method [18]. The genetic algorithm was parameterized to result in ten possible binding conformations. A grid box with the dimension of (60×60×60) Å and the grid spacing of 1 Å was used.

3. Results and discussion

3.1. Docking positions and Gibbs free energy of binding

Figure 2 displays the docking positions of three studied acridones, delavirdine, and HOO^{-} ligand to Pol μ protein. **Table 1** summarizes bound amino acid, type of interaction during bond formation, and Gibbs free energy of binding (ΔG_{bind}) estimated for all prior binding. The molecules with lower ΔG_{bind} values tend to bind efficiently to the studied protein [9].

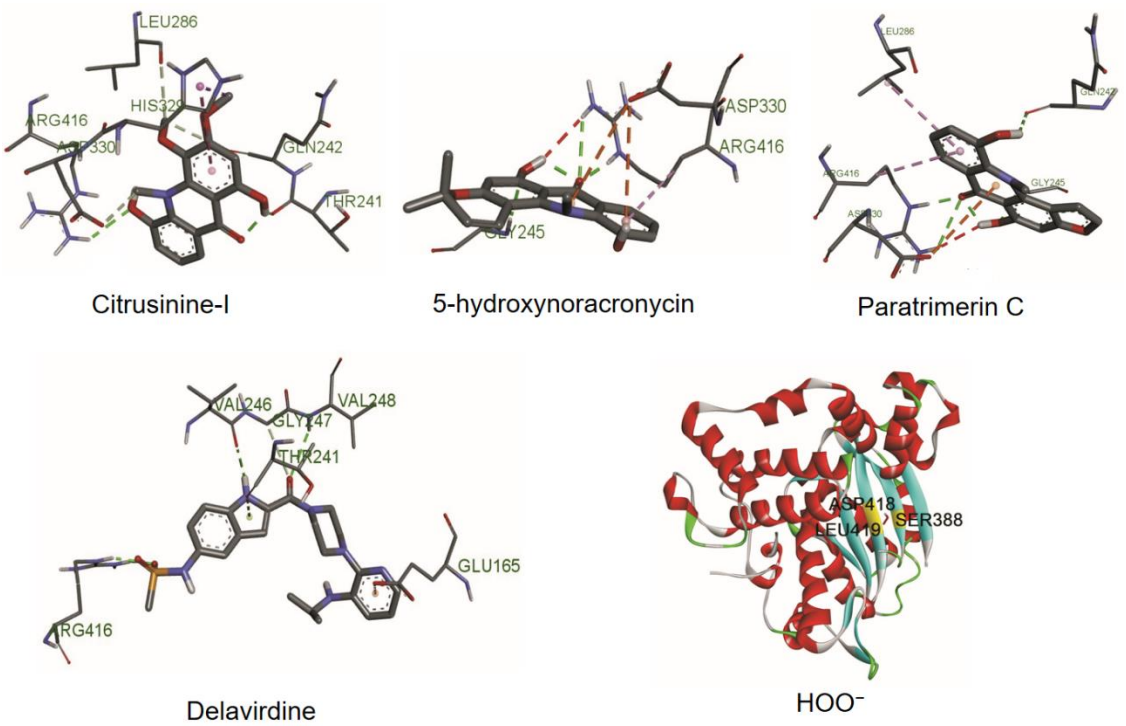

Figure 2. Docking positions of three studied acridones, delavirdine, and HOO− on Pol □ protein

Table 1. ΔG_{bind} (kcal/mol) and type of interaction of HOO^-, three acridones and delavirdine with *Pol* μ protein. The interactions of interest (amino acid and type of interaction) are remarked in bold.

Ligand	**Amino acid**	**Type of interaction**	**ΔG_{bind} (kcal/mol)**
HOO^-	Ser 388	Electrostatic interaction	-2.99
	Asp 418	**Electrostatic interaction**	
	Leu 419	Electrostatic interaction	
Citrusinine-I	**Arg 416**	**Conventional hydrogen bond**	-4.49
	Thr 241	Conventional hydrogen bond	
	Asp 330	Carbon hydrogen bond	
	Gln 242	Carbon hydrogen bond	
	Leu 286	Carbon hydrogen bond	
	His 329	π – σ hydrophobic	
	His 329	π – π stacked	
	His 329	π – π stacked	
5-hydroxynoracronycin	Gly 245	Conventional hydrogen bond	**-5.82**
	Arg 416	**Conventional hydrogen bond**	
	Arg 416	**Conventional hydrogen bond**	
	Asp 330	Electrostatic interaction	
	Asp 330	Electrostatic interaction	
	Arg 416	**π – alkyl hydrophobic**	
Paratrimerin C	Gly 245	Conventional hydrogen bond	-5.34
	Arg 416	**Conventional hydrogen bond**	
	Arg 416	**Conventional hydrogen bond**	
	Gln 242	Conventional hydrogen bond	
	Asp 330	Electrostatic interaction	

	Leu 286	π – alkyl hydrophobic	
	Arg 416	**π – alkyl hydrophobic**	
Delavirdine	Val 248	Conventional hydrogen bond	-4.33
	Arg 416	**Conventional hydrogen bond**	
	Arg 416	**Conventional hydrogen bond**	
	Val 246	Conventional hydrogen bond	
	Gly 247	Carbon hydrogen bond	
	Glu 165	π – anion interaction	
	Thr 241	π – lone pair interaction	

It is observed that the most reactive position on *Pol μ* protein for HOO^- attack is Asp418 amino acid with ΔG_{bind} of -2.99 kcal/mol (**Figure 2, Table 1**). In the case of acridones, the reactive positions on protein are determined to be Arg416 which is nearby the Asp418, i.e., the docking position of HOO^- anion (**Table1, Figure 2**). It is worth noting that the investigated compounds can be docked to the protein in the same area as HOO^-. In addition, one observes lower ΔG_{bind} varying from -5.82 to -4.49 kcal/mol for the investigated compounds compared with the ones of HOO^-. The difference in binding energies results from accomplished interaction between ligands and proteins.

Moreover, the bonds of interest between the studied acridones and the protein are mostly conventional hydrogen bonds, or eventually π – alkyl hydrophobic interactions, whereas the HOO^- is linked to the protein by weak electrostatic interactions. Among the three molecule ligands, the most stable interaction configuration is found for 5-hydroxynoracronycin with the lowest ΔG_{bind} of -5.82 kcal/mol (**Table 1**), illustrating the highest activity in linking to the protein. Thus, this molecule shows the highest protective ability against the attack of HOO^- on the *Pol μ* protein.

The calculation algorithm was parameterized to ten most possible binding conformations for docking analysis using delavirdine as a ligand. Neither gives the docking to the amino acids in the sequence from Gln342 to Leu346. However, the docking analysis indicates that there is a possibility for delavirdine to be linked to the Pol μ at the position of Arg416 amino acid by forming a conventional hydrogen bond with the ΔG_{bind} of -4.33 kcal/mol. Thus, delavirdine is linked to Pol μ protein by weaker bonds than the selected acridones with ΔG_{bind} varying from -5.82 to -4.49 kcal/mol. It suggested that all compounds can act as valuable inhibitors against the harmful effect of delavirdine.

3.2. HOMO and LUMO analysis

To evaluate why the HOO^- species' docking positions differ from those of the studied compounds, we employed the density functional density (DFT) approaches to simulate a polypeptide chain constituted of amino acids Val-Arg-Val-Asp-Leu was optimized. The chosen order of amino acids in the polypeptide chain agrees with the *Pol μ*, *i.e.,* Val415-Arg416-Val417-Asp418-Leu419. The structural optimization was performed at the DFT/M05-2X/6-31+G(d) level of theory. The HOMO and LUMO distributions of the optimized Val-Arg-Val-Asp-Leu polypeptide chain provide more insight into the interaction mechanisms of the reactive oxygen species and the four studied compounds to the Pol μ (**Figure 3**).

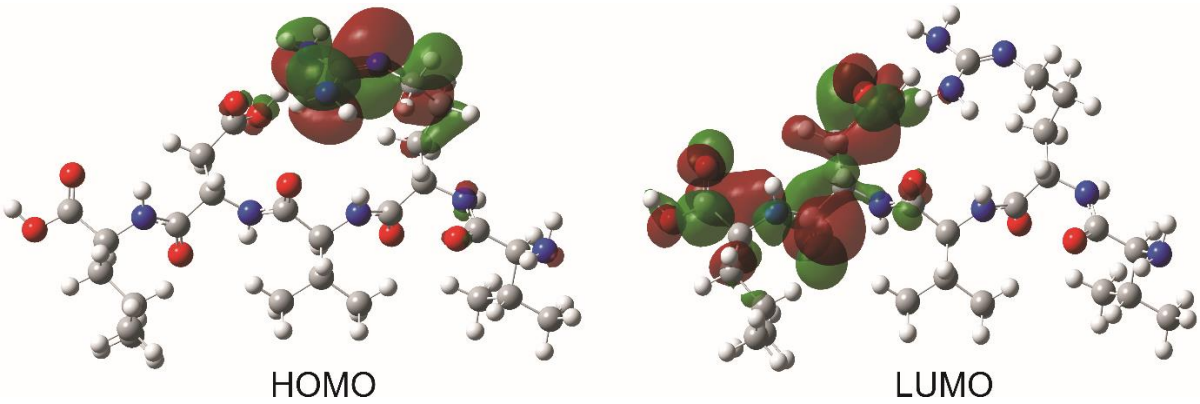

Figure 3. The HOMO and LUMO distributions of Val-Arg-Val-Asp-Leu polypeptide chain.

It is observed that HOMO is found over the side chain of Arg416, which is the most preferred attacking position on protein for the studied compounds. On the other hand, LUMO is determined over the peptide bond between Asp418 and Leu419 and covers the side chains of those amino acids, which is the interacting position for HOO^-. It is worth noting that the studied compounds are docked at the HOMO location, while HOO^- is linked at the LUMO site. This observation indicates that these two ligands form chemical bonds with the protein *via* two different mechanisms. Indeed, the studied compounds act as electron acceptors, while HOO^- acts as an electron donor. And the obtained results suggest that a potential way to protect the protein is to inactivate the reactive oxygen species before they can link to the protein.

4. Conclusions

The molecular docking study has been performed for the acridone derivatives in water with *Pol* μ. The results illustrate that the interacting positions for acridone compounds and delavirdine are found at Arg416 amino acid, next to the docking position for HOO^- (Asp418). The HOMO and LUMO analysis of an example polypeptide chain of amino acids Val-Arg-Val-Asp-Leu demonstrate that acridones and delavirdine are docked at the HOMO location, while HOO^- is linked at the LUMO site. Based on the binding energy and the corresponding interactions, we conclude that three acridones could protect the *Pol* μ protein against the harmful influence of HOO^- and delavirdine. Notably, the 5-hydroxynoracronycin represents the highest protective activity with the lowest ΔG_{bind} of -5.82 kcal/mol.

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