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COMPUTATION DESIGN: NANOSTRUCTURED LIPID CARRIER FORMULA OF PINOSTROBIN

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INTISARI

Nanostructured Lipid Carrier (NLC) berfungsi dalam peningkatan kelarutan dan bioavailabilitas oral dari obat hidrofobik. Penelitian ini dilakukan untuk memperkirakan kelarutan dari pinostrobin dalam berbagai jenis pembawa lipid padat dan cair melalui desain komputasi dan memilih formula NLC yang optimal dengan kandidat pembawa lipid terbaik. Pinostrobin dan semua pembawa lipid ditentukan interaksinya dengan program AutoDockTools. Nilai dari energi bebas ikatan (ΔG), tetapan hambatan (Ki), dan tipe visibiltas interaksi dicatat sebagai hasil penambatan molekul. Visualisasi tipe interaksi ditentukan dengan program BIOVIA Discovery Studio. Hasil penelitian menunjukkan bahwa apokarotenal sebagai pembawa lipid cair yang terbaik dengan nilai ΔG sebesar -3,57 kkal/mol dan Ki sebesar 2,40 mM. Sitosteril alkohol sebagai pembawa lipid padat yang terbaik dengan nilai ΔG sebesar -2,18 kkal/mol dan Ki sebesar 25,35 mM. Apokarotenal dan sitostearil alkohol sebagai kandidat pembawa lipid untuk formula NLC dari pinostrobin.

Kata kunci: komputasi, NLC, pinostrobin

ABSTRACT

Nanostructured Lipid Carrier (NLC) function by increasing the solubility and oral bioavailability of hydrophobic drugs. This study was conducted to estimate the solubility of pinostrobin in various types of solid and liquid lipid carriers through computational design and to select the optimal NLC formula with the best candidate lipid carriers. Pinostrobin and all lipid carriers were determined for their interactions with the AutoDockTools program. The values of the free energy binding (ΔG), the inhibition constant (Ki), and the type of interaction visibility were recorded as a result of the molecular docking. The interaction type of visualization was determined by the BIOVIA Discovery Studio program. The results showed that apocarotenal was the best liquid lipid carrier with a ΔG value of -3.57 kcal/mol and a Ki value of 2.40 mM. Cetostearyl alcohol was the best carrier for solid lipids, with a ΔG value of -2.18 kcal/mol and a Ki value of 25.35 mM. Apocarotenal and cetostearyl alcohol as lipid carrier candidates for the NLC formula of pinostrobin.

***Keywords**: computation, NLC, pinostrobin*

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INTRODUCTION

Nanostructured lipid carriers (NLC) as a method of delivering drugs are of concern to researchers around the world today. It has been used as a solution for oral administration problems with lipophilic drugs (Patil et al., 2022; Tej et al., 2016). The NLC formula was designed with a mixture of solid and liquid lipid carriers (Aryani et al., 2021; Patil et al., 2022; Sharma and Baldi, 2018; Viera et al., 2021). Combining the two lipid carriers aims to lower the melting point and increase drug stability (Albasri et al., 2023; Tej et al., 2016). Some lipids can provide chemical stability for chemically sensitive compounds. Solid lipid carriers (cetostearyl alcohol, cetyl palmitate, glyceryl monostearate, stearic acid, palmitic acid, and tripalmitate) and liquid lipid carriers (apocarotenal, ricinoleic acid, linoleic acid, oleic acid, isopropyl myristate, and ethyl palmitate) had great potential as lipid carriers in NLC (Albasri et al., 2023; Basso et al., 2022; Tenchov et al., 2021). Several factors were considered in selecting a lipid carrier from an NLC formula, including acceptable drug loading and efficiency of liquid lipid solubility, solid lipid solubility that supports controlled drug release and protection from degradation, stability, and uniformity of the formulation. Everything can be adjusted according to the purpose and needs of the user (Basso et al., 2022; Chauhan et al., 2020; Ghasemiyeh and Mohammadi-Samani, 2018).

Pinostrobin is a bioflavonoid isolated from Bosenbergia pandurata Roxb. rhizome. Its activities include anticancer, antifungal, antibacterial, anti-inflammatory, antioxidant, antiparasitic, antiviral, and antiplatelet (Patel et al., 2016). Research has shown that pinostrobin induces apoptosis in vitro against the T47D cell line (Sukardiman et al., 2014). In addition, pinostrobin is known to play a role in inhibiting the motility of breast cancer cells in the T47D cell line (Jones and Gehler, 2020). Even though it has anti-breast cancer activity, the solubility and dissolution of pinostrobin in water were very low (Murray et al., 2022; Shamsudin et al., 2022). Therefore, in this study, a computational design was developed for the pinostrobin delivery system in the NLC formula.

CADFD (Computer Aided Drug Formulation Design) employs diverse informatics methodologies like molecular dynamics, molecular docking, data analysis, and neural networks to predict the loading of different drugs into their potential carriers (Metwally and Hathout, 2015). Computational design of new Drug Delivery Systems (DDS) by molecular docking is one of the modern ways to determine promising drug formulation designs. The advantages were that it reduced the time and cost required before testing the formula in the laboratory. In addition, they determined molecular and biological properties, reduced the number of compounds tested, filtered materials suitable for the formulation, and improved existing formulas (Bafna et al., 2020; Hessler dan Baringhaus, 2018; Viera et al., 2021). Molecular docking was used in order to predict free energy binding (ΔG) and inhibition constant (Ki) because it was very simple, accurate, and gave high prediction results. In addition, it was used to predict the type of bonding, including conventional hydrogen, ionic, hydrophobic, and van der Waals (Albasri et al., 2023).

Previous research shows that the interaction between curcumin with different solid and liquid lipid carriers has been carried out by molecular docking method. The results showed that the smallest ΔG value, the addition of hydrogen bonds and hydroxyl groups, and the smallest distance from glyceryl monostearate were the selected candidates for solid lipid carrier and oleic acid for liquid lipid carrier in NLC formulation (Albasri et al., 2023). In addition, the selection of lipid carriers of NLC by molecular docking can be used to elucidate the three-dimensional structure, study the molecular and electrostatic properties, and intermolecular interactions between the drug and the carrier which proved that the hydrogen bond between ketoconazole with a mixture of 20% cupuassu fat triacylglycerols, 10% carnauba wax, and 70% caprylic acid triacylglycerols had the lowest affinity energy, -5.3 kcal/mol, the best spatial conformation, and the greatest stability (Vieria et al., 2020).

The main objective of this study is to using molecular docking to predict the solubility of pinostrobin in various lipid carriers and to identify the most effective NLC formula that can minimize the expenses, duration, and labor involved in conducting experiments.

MATERIALS AND METHODS

Materials

A personal computer with NVIDIA®, Core(TM) i7, CPU @ 2.20GHz, and RAM 16 GB was used. The bioinformatic study was performed using software, such as:

a. The ChemOffice 2020 program includes ChemDraw 2D and Chem 3D, which were used to create the molecule's 2D and 3D structures.
b. The AutoDockTools program was used for molecular docking prediction.
c. The Biovia Discovery Studio program was utilized to visualize the docking result.

The molecules included pinostrobin as a ligand, solid lipid carriers (cetostearyl alcohol, cetyl palmitate, glyceryl monostearate, stearic acid, palmitic acid, and tripalmitate), and liquid lipid carriers (apocarotenal, ricinoleic acid, linoleic acid, oleic acid, isopropyl myristate, and ethyl palmitate) as macromolecules.

Methods

Preparation of 2D and 3D structures

Ligands and macromolecules were drawn using ChemDraw 2D and saved in .cdxml format. The 2D structure was copied in the Chem3D program, minimized by MMF94 minimization, and saved in .mol2 format (Widiyana et al., 2016; Widiyana, 2021).

Preparation for molecular docking

Pinostrobin was docked with solid and liquid lipid carriers by the AutoDockTools program. Pinostrobin was used as a ligand, and solid and liquid lipid carriers were used as macromolecules in the docking process. Ligands and macromolecules were saved in .pdbqt format and docked. The center grid box was used: x = -4.997, y = -0.673, and z = -0.214. The result of docking was determined by free energy binding (ΔG), inhibition constant (Ki), and interaction visibility type.

Visualization

The molecular binding ability was visualized by the BIOVIA Discovery Studio program. The type of bond interaction was analyzed and the best-fitting interaction was chosen for maximum solubility.

RESULTS AND DISCUSSION

Pinostrobin and lipid carriers were determined for minimization energy by ChemDraw. The smallest amout of total potential energy was obtained from the process. The molecules with the smallest total potential energy showed high intermolecular stability (Nusantoro and Fadlan, 2021). The results of determining the energy minimization of macromolecules obtained values of -29.622 to 73.323 kcal/mol. Stearic acid has the lowest minimization energy compared to other molecules at -29.622 kcal/mol. It means the stability of stearic acid is higher than that of other macromolecules. The minimization energy is shown in Table 1.

The results of molecular docking between pinostrobin and solid lipid carriers (Figure 1) and liquid lipid carriers (Figure 2) were known from the interaction visibility type and bond distance visualization by the BIOVIA Discovery Studio program. The interaction visibility type and bond distance between pinostrobin and cetostearyl alcohol, such as: a conventional hydrogen (1.78 Å), four hydrophobic pi-alkyls (3.65–4.64 Å), and two hydrophobic alkyls (3.95-4.29 Å). The interaction visibility type and bond distance between pinostrobin and cetyl palmitate, such as: a conventional hydrogen (1.77 Å), five hydrophobic pi-alkyls (3.69-5.20 Å), and two hydrophobic alkyls (3.83-4.49 Å). The interaction visibility type and bond distance between pinostrobin and glyceryl monostearate, such as: a conventional hydrogen (1.78 Å), four hydrophobic pi-alkyls (3.61-4.67 Å), and two hydrophobic alkyls (3.79-4.26 Å). The interaction visibility type and bond distance between pinostrobin and stearic acid, such as: a conventional hydrogen (1.78 Å), four hydrophobic pi-alkyls (3.63-4.58 Å), and two hydrophobic alkyls (3.86-4.37 Å). The interaction visibility type and bond distance between pinostrobin and palmitic acid, such as: a conventional

hydrogen (1.78 Å), four hydrophobic pi-alkyls (3.74-5.07 Å), and two hydrophobic alkyls (3.91-4.33 Å). The interaction visibility type and bond distance between pinostrobin and tripalmitate, such as: a conventional hydrogen (1.78 Å), three hydrophobic pi-alkyls (3.43-4.75 Å), and one hydrophobic alkyl (3.99 Å). The interaction visibility type and bond distance between pinostrobin and apocarotenal, such as: eight hydrophobic pi-alkyls (3.78-5.43 Å), one hydrophobic pi-sigma (3.35 Å), three hydrophobic alkyls (3.65–4.18 Å), and a conventional hydrogen (1.78 Å). The interaction visibility type and bond distance between pinostrobin and ricinoleic acid, such as: a conventional hydrogen bond (2.07 Å), six hydrophobic pi-alkyls (3.67-5.41 Å), and two hydrophobic alkyls (4.53-4.74 Å). The interaction visibility type and bond distance between pinostrobin and linoleic acid, such as: a conventional hydrogen (1.78 Å), five hydrophobic pi-alkyls (4.22-5.44 Å), two hydrophobic pi-sigma (3.56-3.59 Å), and two hydrophobic alkyls (3.86-4.12 Å). The interaction visibility type and bond distance between pinostrobin and oleic acid, such as: a conventional hydrogen (1.77 Å), six hydrophobic pi-alkyls (3.55-5.34 Å), and two hydrophobic alkyls (3.59-5.21 Å). The interaction visibility type and bond distance between pinostrobin and isopropyl myristate, such as: a conventional hydrogen (1.79 Å), four hydrophobic pi-alkyls (3.68-4.52 Å), and two hydrophobic alkyls (3.73-4.09 Å). The interaction visibility type and bond distance between pinostrobin and ethyl palmitate, such as: a conventional hydrogen bond (1.77 Å), four hydrophobic pi-alkyls (3.63-4.55 Å), and two hydrophobic alkyls (3.82-4.41 Å).

Table I. Minimize the energy of the ligand and lipid carrier

Compounds	Minimize Energy (kcal/mol)
Pinostrobin	48.932
Solid Lipids	
Cetostearyl alcohol	-4.434
Cetyl palmitate	-31.933
Glyceryl monostearate	18.833
Stearic acid	-29.622
Palmitic acid	-29.219
Tripalmitate	-20.357
Liquid Lipids	
Apocarotenal	73.323
Ricinoleic acid	-4.698
Oleic acid	-16.381
Linoleic acid	-2.997
Isopropyl myristate	-7.778
Ethyl palmitate	-13.733

Molecular docking results such as free energy binding (ΔG) and inhibition constants (Ki) were performed through the AutoDockTools program. ΔG is used to indicate bonding stability and Ki to determine binding affinity. The lowest ΔG value means greater ligand contact with macromolecules at a certain pose (Albasri et al., 2023; Aryani et al., 2021). The lowest Ki value indicated a smaller ligand concentration was needed to inhibit solubility. The lowest ΔG and Ki values have the highest solubility prediction (Gupta et al., 2018; Pratama, 2020; Albasri et al., 2023). The docking molecule results showed a ΔG value in the range of -2.13 to -3.57 kcal/mol and a Ki value of 27.25-2.40 mM (Table II). The interaction between pinostrobin and apocarotenal as a liquid lipid carrier showed the lowest ΔG and Ki values, respectively, -3.57 kcal/mol and 2.40 mM. The lowest ΔG and Ki values indicate higher stability and binding affinity for pinostrobin and apocarotenal. It means pinostrobin has the highest solubility in apocarotenal as a liquid lipid carrier

compared to others. Visualization results in Table III from the BIOVIA Discovery Studio program reported that a conventional hydrogen bond was produced between pinostrobin as an H-donor and apocarotenal as H-acceptors in the OH-H bond type, which demonstrates the basis for solubilization in a biomolecular structure.

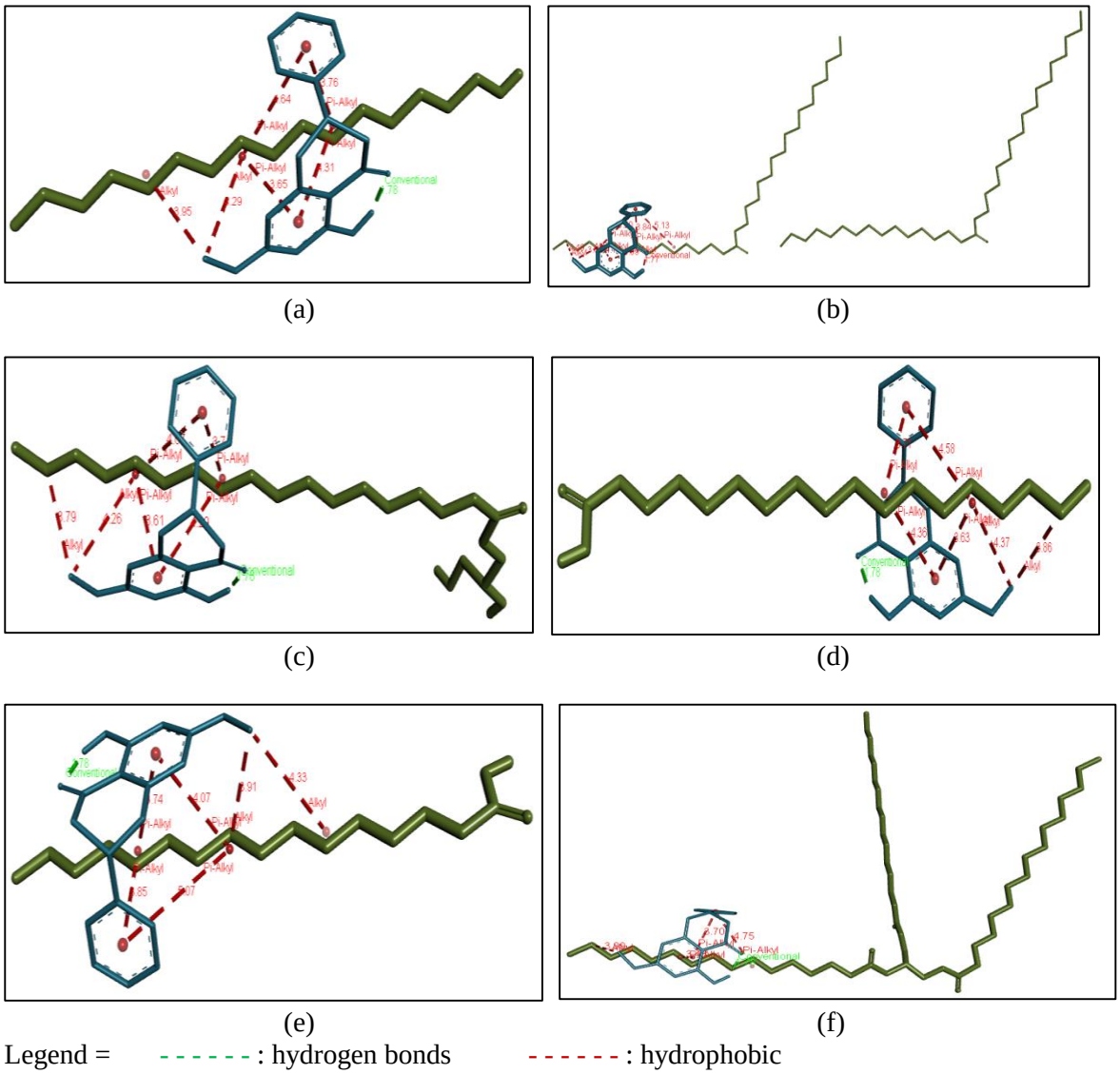

Figure 1. Interaction visibility type of pinostrobin (blue) and solid lipids (green), such as: (a) cetostearyl alcohol, (b) cetyl palmitate, (c) glyceryl monostearate, (d) stearic acid, (e) palmitic acid, and (f) tripalmitate

The strong conventional hydrogen bonds played a major role in the solubility process between pinostrobin and apocarotenal. The conventional hydrogen bond distance of 1.78 Å indicates a higher affinity and solubility than the other bond types available (less than 3000 Å) (Albasri et al., 2023). This indicates that the existence of this interaction increases the binding affinity and solubility of pinostrobin and apocarotenal. There were eight pi-alkyl bonds and three alkyl bonds, which provided stability to the system in their interactions. The pi-sigma bond added to the stability of the interaction. In addition, cetostearyl alcohol has been known to have the lowest ΔG and Ki values of -2.18 kcal/mol and 25.35 mM, respectively, compared to other solid lipid carriers.

Between pinostrobin and cetostearyl alcohol, there were several bonds that affect solubility: a conventional hydrogen, four hydrophobic pi-alkyls, and two hydrophobic alkyls, allowing solubility. Therefore, cetostearyl alcohol can be combined with apocarotenal to become a candidate lipid carrier in the NLC formula.

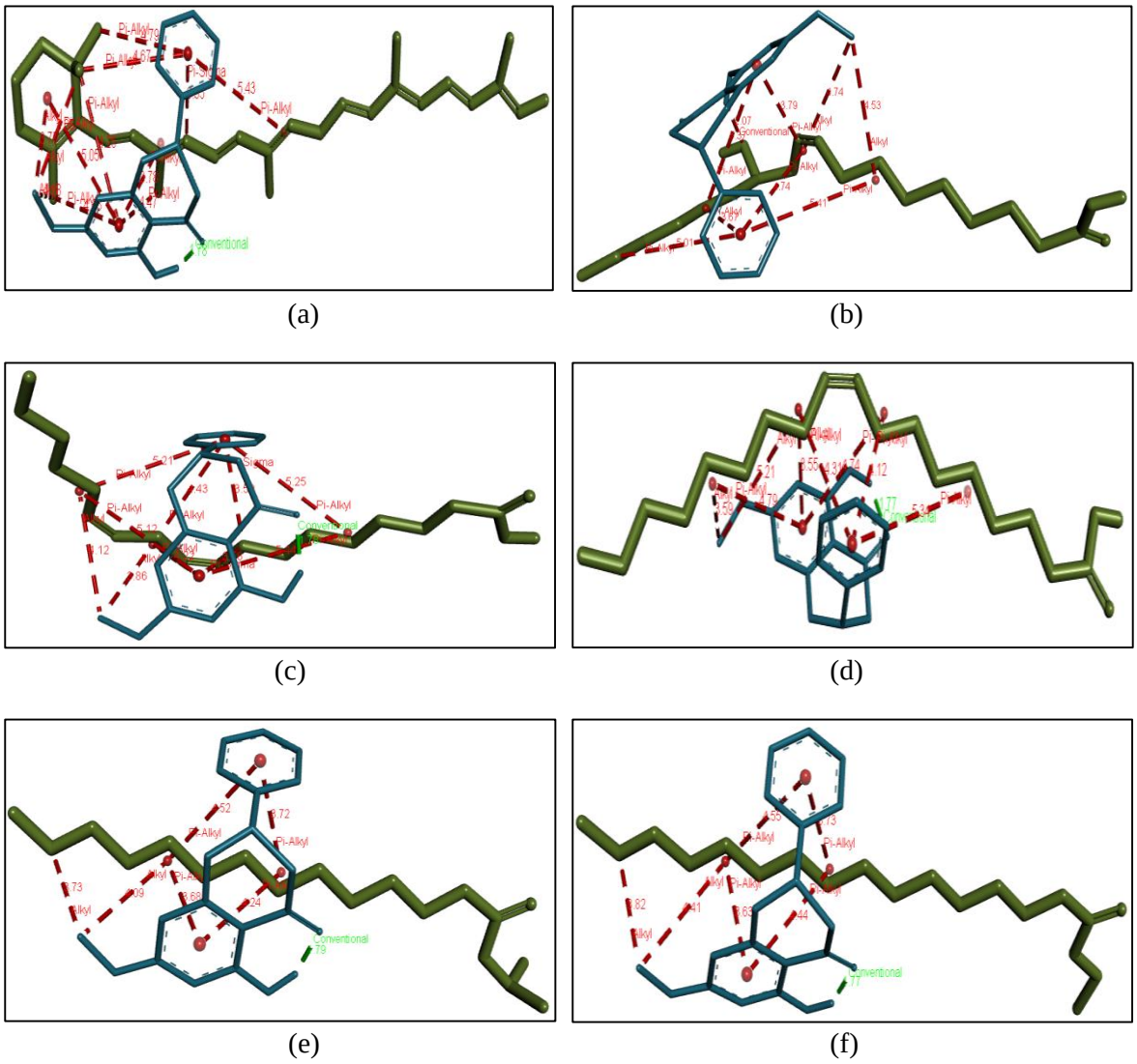

Figure 2. Interaction visibility type of pinostrobin (blue) and liquid lipids (green), such as: (a) apocarotenal, (b) ricinoleic acid, (c) linoleic acid, (d) oleic acid, (e) isopropyl myristate, and (f) ethyl palmitate

Table II. Molecular docking results of pinostrobin solubility in lipid carriers

Lipid Carriers	ΔG (kcal/mol)	Ki (mM)
Solid Lipids		
Cetostearyl alcohol	-2.18	25.35
Cetyl palmitate	-2.17	24.76
Glyceryl monostearate	-2.15	26.59
Stearic acid	-2.14	26.93
Palmitic acid	-2.14	27.09
Tripalmitate	-2.13	27.25
Liquid Lipids		
Apocarotenal	-3.57	2.40
Ricinoleic acid	-3.54	2.55
Linoleic acid	-3.13	5.12
Oleic acid	-2.61	12.27
Isopropyl myristate	-2.41	27.01
Ethyl palmitate	-2.13	27.23

Table III. Interaction visibility type of pinostrobin and apocarotenal

Distance (Å)	Interaction visibility type
5.43	Hydrophobic pi-alkyl
4.79	Hydrophobic pi-alkyl
4.67	Hydrophobic pi-alkyl
3.78	Hydrophobic pi-alkyl
4.47	Hydrophobic pi-alkyl
4.25	Hydrophobic pi-alkyl
5.05	Hydrophobic pi-alkyl
4.66	Hydrophobic pi-alkyl
3.65	Hydrophobic alkyl
4.18	Hydrophobic alkyl
3.75	Hydrophobic alkyl
3.35	Hydrophobic pi-sigma
1.78	Conventional hydrogen

CONCLUSIONS

The findings of molecular docking showed that apocarotenal was the best liquid lipid carrier, with the smallest ΔG (-3.57 kcal/mol) and Ki (2.40 mM) values of all types of lipid carriers, strong stability and affinity, and the highest solubility prediction of pinostrobin. Cetostearyl alcohol was chosen as a solid lipid carrier compared to other solid lipid carriers with the lowest ΔG (-2.18 kcal/mol) and Ki (25.35 mM) values. Apocarotenal and cetostearyl alcohol can be used as lipid carriers for NLC formula candidates for pinostrobin.

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