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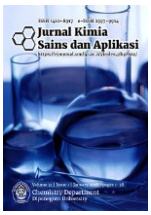

Synthesis and Molecular Docking Study of Dibenzal Monocarbonyl (Curcumin Analog) and Its Potential as Anti-Inflammatory

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Abstract

Curcumin is a naturally occurring substance with a wide range of biological activity. One of the biological activities of curcumin is as an anti-inflammatory. The science of organic synthesis is able to produce substances that are analogous to those found in nature. The synthesis of organic compounds can also be used to change a compound by making it more bioactive. This research focused on synthesizing dibenzal monocarbonyl, a compound similar to curcumin, and examined its interaction with the active site of cyclooxygenase-2 (COX-2) through molecular docking simulations. Dibenzal monocarbonyl was synthesized via an aldol condensation reaction utilizing sodium hydroxide as a catalyst. The synthesized compound was characterized using FTIR and ^{1}H-NMR, achieving a yield of 98.676%. Molecular docking was performed utilizing AutoDock Tools and AutoDock Vina, and each docked compound was visualized through Discovery Studio Visualizer. This compound demonstrated the highest anti-inflammatory activity against COX-2, as indicated by molecular docking studies, with a binding affinity of -8.4 kcal/mol.

1. Introduction

The bioactivity of natural compounds has been reported to be widely found in drug candidate design research [1]. One of the natural compounds that has many biological activities is Curcumin. Some biological activities of curcumin compounds include anticancer, anti-inflammation, antiparasitic, antidiabetic, antiviral, antimicrobial, antioxidant, and antiplasmodial [2]. Organic synthesis is one of the sciences that can create an analog of a compound similar to a natural compound [3]. The synthesis of an organic compound can also be applied to modify a compound by increasing the bioactivity of the compound [4].

Modifying the ß-diketone group of curcumin into a monoketone group is one strategy to increase the bioactivity of the curcumin compound [5]. In addition, several synthesis strategies are also applied in modifying monoketone curcumin analogs, including aldol condensation reactions of aryl aldehydes and ketones in the presence of acid or base catalysts [6]. Substitution on the benzene ring of a curcumin analog also affects its biological activity [2]. One of the tests was carried out by changing substitutions in compounds, one of which was N-dimethylamino, which gave great action as a candidate anti-inflammatory compound [7].

Inflammation serves as a defensive response of the body, signaling disruption or the introduction of foreign entities within the system [8]. This condition has the potential to result in tissue damage. Inflammation is invariably associated with an adverse reaction. It may arise from trauma, exposure to specific chemicals, and heat. Inflammation can involve a range of physiological and pathological processes [9]. Inflammation is categorized into acute and chronic types based on its duration. Numerous studies indicate that inflammation plays a significant role in the progression of various diseases, including diabetes, cancer, autoimmune disorders, and cardiovascular conditions. Acute inflammation typically persists for a period ranging from

minutes to days and is associated with the innate immune response [10]. Acute inflammation arises from the escape of proteins or plasma fluid, accompanied by the movement of leukocytes into extravascular regions [11].

Cyclooxygenase-2 (COX-2) is a key enzyme in fatty acid metabolism, activated by proinflammatory cytokines to produce prostaglandins. In the context of inflammation, COX-2 expression is significantly elevated. Prostaglandins, in turn, promote the proliferation of cancer cells, heighten the likelihood of angiogenesis, suppress apoptosis, and facilitate metastasis [12].

Currently, the discovery of potential compounds that have biological activity is not only carried out at the in vitro and in vivo test stages, but the initial stage of determining potential compounds is also carried out by in silico testing; this aims to accelerate the process of discovering potential compounds as drug candidates [13]. One example of a method used in silico testing is the docking of drug molecules with receptors, which is also called molecular docking [14]. Docking is the procedure in which two molecules are aligned and matched within a three-dimensional space. Currently, the molecular docking approach has been widely used in modern drug design to help understand drug and receptor interactions. The receptor is the active side of the drug's work that plays a role in pharmacological effects. It has been widely reported that computational techniques can support and assist compound design to obtain more potent inhibitors through the receptor drug mechanism [15].

This study conducted a modified synthesis of organic compounds, focusing on curcumin derivatives that feature an N-dimethylamino substituent on the benzene ring. The research aimed to explore the potential of this compound as an anti-inflammatory agent through molecular docking studies.

2. Experimental

2.1. Materials

All chemical reagents and solvents used in this study were purchased from Merck and were of pro-analytical grade, including benzaldehyde, acetone, 4-dimethylaminobenzaldehyde, ethanol, sodium hydroxide, chloroform, n-hexane, and methanol, without further purification. Thin-layer chromatography was conducted on a 20 × 20 cm aluminum plate coated with silica gel 60 F254 (Merck), and the 3D structure of COX-2 (PDB ID: 4PH9) was utilized.

2.2. Instrumentations

A digital scale (Libror EB 330, Shimadzu) was used to weigh the chemical reagents. Synthetic compounds were filtered using a Büchner funnel. A microwave (SIGMATIC SMO-25SSG) was used to facilitate the synthesis reaction. An FTIR spectrometer (Shimadzu Prestige-21) was used to generate spectra for functional group determination, while a nuclear magnetic resonance (NMR) spectrometer (JEOL JNM-ECA, 500 MHz) was used to analyze the proton signals of the synthesized products, with tetramethylsilane as the internal standard. Molecular docking simulations ran on a system with an AMD Ryzen 5 3500U CPU, Radeon Vega Mobile GFX 2.10 GHz GPU, 8 GB RAM, and Windows 11.

2.3. Synthesis of Dibenzal Monocarbonyl

NaOH (0.4 g, 0.0100 mol) was put into the vessel and dissolved with 2 mL of ethanol. Acetone (0.29 g, 0.0050 mol) was added to the vessel and stirred until mixed. Subsequently, 1.49 g (0.0100 mol) of 4-dimethylamino benzaldehyde was incorporated into the mixture while stirring was maintained. The vessel was then covered with aluminum foil and placed in the microwave for 40 seconds. The product formed was cooled and dried in a desiccator, and the solid was recrystallized using methanol to obtain dibenzal monocarbonyl.

2.4. Molecular Docking Study of Dibenzal Monocarbonyl

The dibenzal monocarbonyl compound is expected to modify its mechanism of action on the COX-2 receptor, as assessed through molecular docking studies. The 3D structures of dibenzal monocarbonyl were geometrically optimized using DFT/B3LYP with a 6-31G basis set [16] in Avogadro and Orca. The crystal structure of COX-2 complexed with ibuprofen as an inhibitor (PDB ID: 4PH9) was obtained from the Protein Data Bank and prepared using Discovery Studio Visualizer.

Molecular docking was performed utilizing AutoDock Tools and AutoDock Vina, with a precision value ranging from 8 to 264. To refine the conformational search, an optimized grid box was established as a parameter [17]. Ibuprofen served as the standard ligand, and a re-docking procedure was conducted to verify the accuracy of the molecular docking technique. The root mean square deviation (RMSD) from re-docking was computed, along with a comparison of binding energies between ibuprofen as the reference ligand and the proposed dibenzal monocarbonyl compound.

3. Results and Discussion

3.1. Synthesis of Dibenzal Monocarbonyl

Dibenzal monocarbonyl was synthesized via a microwave-assisted organic synthesis (MAOS) cyclocondensation reaction (Figure 1), yielding a brick-red solid that appeared greenish-yellow under UV light at 254 nm, with a yield of 98.676%. The FTIR spectrum (Figure 2) (KBr, cm^{-1}) exhibited characteristic absorption bands at 2896 cm^{-1} (C-H aliphatic), 1635 cm^{-1} (C=C alkene), 1600 cm^{-1} (C=O carbonyl), 1549 cm^{-1} (C=C aromatic), 1370 cm^{-1} (C-N tertiary), and 815 cm^{-1} (para-substituted benzene). The ^{1}H-NMR spectrum (500 MHz, $CDCl_3$, ppm) (Figure 3) showed the following signals: δ 3.004 (s, 3H, N-CH_3), δ 6.882 (d, 2H, J = 8 Hz, Ar-H), δ 7.680 (d, 2H, J = 8 Hz, Ar-H), δ 7.498 (s, 1H, C-H alkene), and δ 6.670 (s, 1H, C-H alkene).

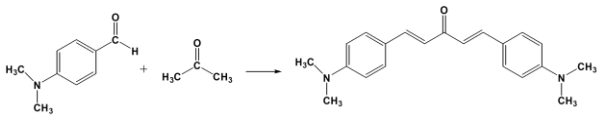

Figure 1. Scheme of synthesis of dibenzal monocarbonyl

Table 1. Molecular docking results of dibenzal monocarbonyl

Compound	Binding affinity (kcal/mol)	Interaction
Native ligand (Ibuprofen)	-7.6	H Bond: TYR356 Salt Bridge: ARG121 Van der Waals: PHE382, GLY527, SER531, LEU353, MET523, VAL524, LEU360, LEU532, SER354, VAL 117 Pi-Sigma: VAL350 Pi-Alkyl: TYR386, TRP388, ALA528 Pi-Cation: ARG121
Test ligand (Dibenzal monocarbonyl)	-8.4	Pi-Sigma: ALA528 Amide- PI stacked: GLY527 Alkyl and Pi Alkyl: VAL89, VAL117, TYR116, TYR386, LEU353, VAL350, TRP388, VAL524

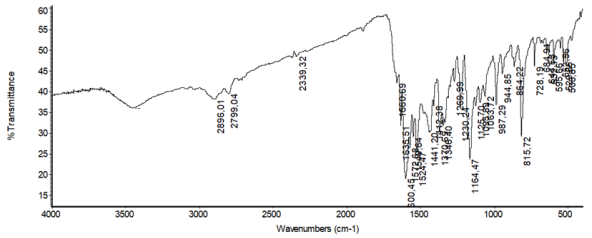

Figure 2. FTIR spectrum of dibenzal monocarbonyl

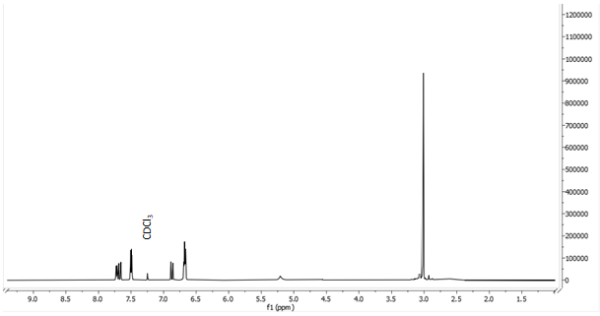

Figure 3. ^{1}H-NMR spectrum of dibenzal monocarbonyl

Dibenzal monocarbonyl was successfully synthesized with a yield of 98.676%. The structure of the monocarbonyl was identified using FTIR and H-NMR spectrometry. FTIR analysis confirmed the presence of a C=O carbonyl group at 1600 cm^{-1} [5]. Absorption observed at wavenumbers ranging from 1360 to 1310 cm^{-1} suggests the presence of a C-N tertiary bond. The spectrum reveals an absorption peak at 1370.68 cm^{-1}. Furthermore, the absence of absorption in the region of 3500 to 3100 cm^{-1}, where tertiary amines lack N-H bonds, further supports the presence of tertiary amines [18]. The typical absorption of aromatic C=C is also shown in the area of 1635 cm^{-1}. Substituted benzene in the para position was observed in the absorption range of 850-800 cm^{-1}, with an additional absorption detected at 815.72 cm^{-1}, which further substantiated the synthesis of the compound featuring para-substituted benzene [19].

Furthermore, the structure of the synthesized compound through ^{1}H-NMR spectroscopy, which identified the number and type of hydrogen atoms. The yield of the compound is associated with distinct absorbance observed in some areas of chemical shift (δ). A peak at δ 3.004 ppm appears as a singlet with six hydrogen atoms, indicating a methyl group (-CH_3) attached to a nitrogen atom. This results in a higher chemical shift than typical methyl absorption. The singlet pattern suggests no adjacent protons, reinforcing the structural assignment.

In the region of δ 6.882 ppm, a doublet absorption corresponding to two hydrogen atoms indicates the presence of aromatic C-H bonds. The para-substituted benzene structure exhibits two pairs of ortho-coupled protons, producing two doublet signals with a *J* value of 8-10 Hz. The spectra also reveal a doublet absorption near δ 7.680 ppm. Additionally, the absorption peaks at δ 6.670 ppm and δ 7.498 ppm confirm the presence of C-H alkene bonds. The variation in chemical shifts between these alkene protons can be attributed to differences in their surrounding environments.

3.2. Molecular Docking Study of Dibenzal Monocarbonyl

Molecular docking studies were carried out to determine the interaction, calculate the binding affinity of the native ligand, and test the ligand on the active site of the COX-2 receptor. The interaction visualization of native ligand (ibuprofen) and dibenzal monocarbonyl on the active site of the COX-2 receptor is shown in Figure 4.

The docking method was validated between native ligand and protein structures to obtain a small RMDS value of 2 Å. Figure 5 is the RMDS value obtained, namely 1.272 Å, which indicates a positive method validity with excellent resolution [5]. The results of molecular docking between the native ligand and the test ligand and the interaction between amino acids and ligands are presented in Table 1. The binding affinity obtained shows that the test ligand compound has a lower binding affinity value than the native ligand in the form of ibuprofen. A low binding affinity value of the test ligand also indicates higher stability of the ligand-receptor complex within the active site of the COX-2 receptor [20].

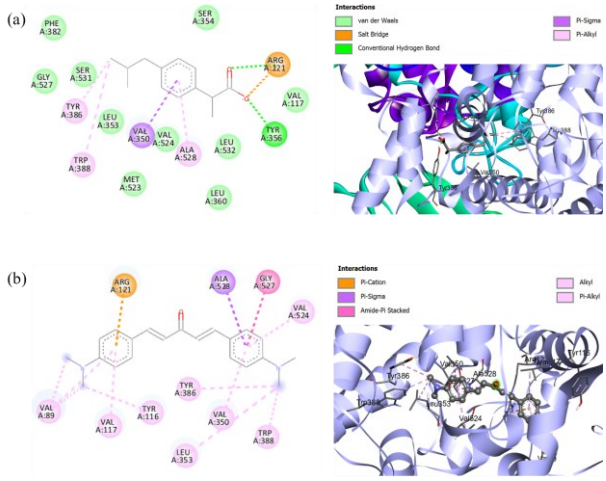

Figure 4. Visualization of the interaction between (a) the native ligand and the receptor, and (b) the test ligand and the receptor

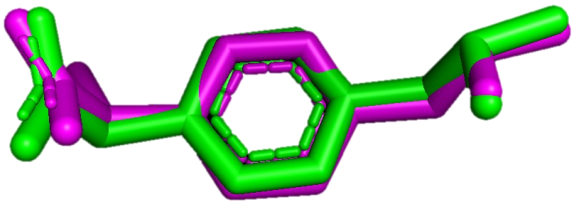

Figure 5. Overlapping visualization of the native ligand (ibuprofen) and the re-docked ligand, with an RMSD value of 1.272 Å

Several key amino acids involved in ligand binding to the COX-2 receptor include ARG121, TYR356, and VAL117 [7]. The test ligands interact with these key amino acids within the COX-2 molecule. Additionally, the stability of the test ligand-receptor complex is reinforced by interactions with other amino acids. The dimethyl substituent in the test ligand structure forms alkyl and π- alkyl interactions with VAL89, VAL117, TYR116, TYR386, LEU353, VAL350, TRP388, and VAL524. Meanwhile, the aromatic ring establishes π-cation, π-sigma, and amide-π stacked interactions with ARG121, ALA528, and GLY527.

However, the pharmacological activity of the compound cannot be solely explained by its binding affinity. Therefore, further experimental validation is necessary, including both in vitro and in vivo studies. As an initial step, molecular docking plays a crucial role in developing and designing new drugs.

4. Conclusion

Based on the results of this study, the dibenzal monocarbonyl compound was successfully synthesized, with its structure confirmed through IR spectroscopy and ^{1}H-NMR analysis. Molecular docking analysis demonstrated that the synthetic compound, serving as the test ligand, exhibited potential anti-inflammatory activity, achieving an affinity score of -8.4 kcal/mol, which surpasses that of the standard ligand, ibuprofen (-7.6 kcal/mol). Therefore, further experimental validation through in vitro and in vivo studies is necessary to comprehensively assess the anti-inflammatory properties of dibenzal monocarbonyl.

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