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Synthesis of Asymmetric Curcumin Analogue (2,6)-2-(3-bromo-4-methoxybenzylidine)-6-(3,4-dimethoxybenzylidine)cyclohexanone with a Base Catalyst

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Abstract

Curcumin analogs are phenolic secondary metabolites that are more stable than curcumin because they do not contain active methylene groups. Generally, these compounds have a symmetric structure, while asymmetric curcumin analogs with higher frequency and potency are rarely synthesized. This study aimed to synthesize asymmetric curcumin analogs from 2-(3,4-dimethoxybenzylidene)cyclohexanone and bromoanisaldehyde. The synthesis was conducted using the Claisen-Schmidt condensation method with a base catalyst in ethanol at 25 °C for 12 hours. The intermediate compound available in the laboratory was characterized using GC-MS, showing a molecular ion (M^+) at m/z 246. Meanwhile, bromoanisaldehyde was characterized by GC-MS and FT-IR, yielding a molecular ion at m/z 215 and a C–Br stretching vibration peak at 812 cm^{-1}. The study yielded a yellow solid weighing 0.13 g (yield percentage: 2.93%) with a melting point of 143-147 °C. UV-Vis, FT-IR, and HR-MS analysis confirmed the successful synthesis and characterization of the asymmetric curcumin analog, as evidenced by the molecular ion (M^+) at m/z 443.06274 in the HR-MS spectrum. However, further analysis, such as ^{1}H-NMR and ^{13}C-NMR, is needed to confirm the structure of the compound. Furthermore, research related to bioactivity testing is crucial for obtaining more stable and effective drug candidates.

Keywords: synthesis, 2-(3,4-dimethoxybenzylidene)cyclohexanone, bromoanisaldehyde, asymmetric curcumin analogs, base catalyst

INTRODUCTION

Curcumin (diferuloylmethane) is the main ingredient of turmeric, and it is in the form of dry powder isolated from the rhizome of Curcuma longa L. The curcumin compound is the natural product that has been most researched because of its varied bioactivity effects, including antiprotozoal, anticancer, antioxidant, antibacterial, anti-inflammatory, antimalarial, antiviral, antidiabetic, and neuroprotective (Urošević et al., 2022). Many people have used turmeric to treat various ailments and prevent oxidative damage from food. The most prominent pharmacological characteristic of curcumin is its antioxidant activity, which can fight free radicals (Purushothaman et al., 2022). Curcumin also holds therapeutic promise for various illnesses, including autoimmune disorders, inflammation, metabolic disorders, cancer, liver disease, neurological disorders, cardiovascular diseases, and lung conditions. (Chainoglou & Hadjipavlou-Litina, 2019).

Curcumin contains symmetrical electronegative oxygen groups with low solubility (11 mg/mL in water). As an oral drug, curcumin has a low bioavailability (1% detected in plasma) (Isnaeni et al., 2021). The quick metabolism, short half-life, restricted circulation, and tissue dispersion of curcumin are further drawbacks. The structure of the curcumin compound is divided into three chromophore parts, with Figure 1 showing that the aromatic parts A and C consist of aromatic rings (symmetric and asymmetric), which function to determine the binding potential between the receptor and the drug compound. On the other hand, pharmacophore B is a dien-dion bond with an active methylene group, causing the instability of curcumin. As a result, pharmacophore B is the part that has the opportunity to experience changes

(modifications) in the structure of curcumin (Mancia et al., 2015).

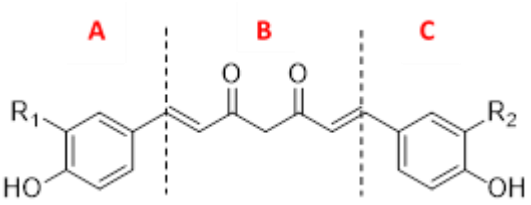

Figure 1. Structure of curcumin analog compounds with three chromophore groups A, B, and C, (1) R_1=R_2=OCH_3 (curcumin), (2) R_1=OCH_3, R_2=H (demethoxycurcumin), (3) R_1=R_2=H (bisdemethoxycurcumin) (Mancia et al., 2015)

Based on this, the researchers synthesized a curcumin analog (Figure 2) by changing the β-diketone group (pharmacophore B) by removing the H-α source on the carbonyl (active methylene group). This aims to ensure that curcumin analogs have a more stable structure to promote apoptosis and anti-metastasis, thereby enhancing bioavailability and bioactivity. One method for creating more potent analogs with the benefit of producing better biological molecules is to use a simpler compound structure (Lu et al., 2023). One of these ongoing interests aims to produce drug-candidate compounds with better oral bioavailability. The method for maximizing drug and target interactions focuses on therapeutic effectiveness and selectivity through heterocyclic curcumin analogs (Ardiansah et al., 2023). Usually, the synthesized curcumin analog compounds are monoketones (monocarbonyls), either half-structured or fully structured.

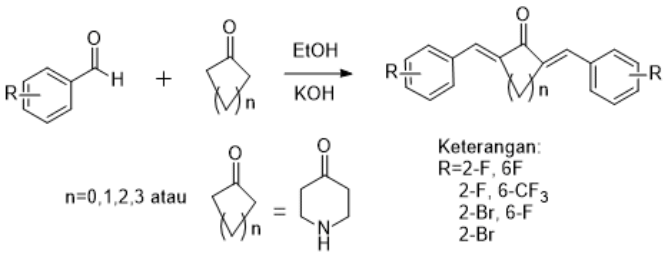

Figure 2. Synthesis of Curcumin Analogues (Yuan et al., 2014)

The synthesis of curcumin analog compounds with one carbonyl group (monocarbonyl) under basic conditions shows that the reactant from benzaldehyde compounds with bromo group substituents has better activity than curcumin compounds, with an IC_{50} of 422 µM (Yuan et al., 2014). The synthesis of curcumin analog compounds with various reactants, namely ketones and benzaldehyde, under acidic conditions, shows that curcumin analog compounds from the reactant in the form of 2,4-dihydroxybenzaldehyde have α-glucosidase enzyme inhibitory activity (IC_{50} 2.8 µM) better than the isolated curcumin compound (IC_{50} 23 µM) (Du et al., 2006). A comparison of the effect of the type of catalyst on the yield of curcumin analog compounds has been carried out, proving that using a sodium hydroxide base catalyst produces a higher yield than an acid catalyst (Liang, Li, et al., 2008; Liang, Yang, et al., 2008). Curcumin analog compounds from ketones (acetone) and benzaldehyde derivatives have been proven to have bioactivity as an antitumor and antioxidant (Li et al., 2015). In addition, the research reported that the synthesis of curcumin analogs using various benzaldehyde and acetone reactants yielded a fairly low inhibitory concentration value, indicating their potential as antioxidants and anticancer agents. One of the compounds is shown in **Figure 3** (Li et al., 2015).

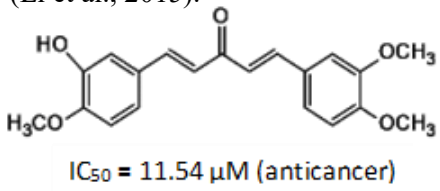

Figure 3. Structure of a curcumin analogue reported to exhibit anticancer activity (Li et al., 2015)

The results of the α-glucosidase inhibitory activity tests on several candidate curcumin analog compounds show that there is good antidiabetic potential in curcumin analogs based on bromovanilin (cyclohexanone) with an IC_{50} of 29.3 µM (Du et al., 2006), as shown in Figure 4. The bromo group in benzaldehyde (the structure of a curcumin analog compound), especially the ortho position, has been proven to increase antidiabetic activity in inhibiting the α-glucosidase enzyme.

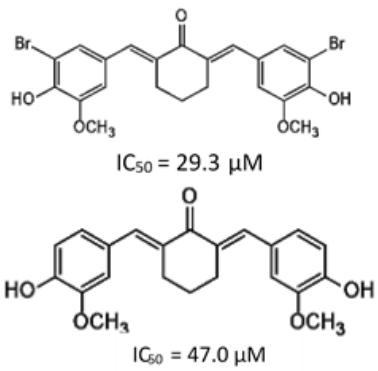

Figure 4. Structure of a curcumin analogue reported to exhibit antidiabetic activity (Du et al., 2006)

The synthesis of symmetrical curcumin analog compounds has been carried out from simple aromatic aldehyde compounds as basic materials, along with testing of their bioactivity and pharmacokinetic properties (Amalraj et al., 2017; Katsori et al., 2011; Lin et al., 2013; Mardianis et al., 2017; Zhang et al., 2015). However, research on synthesizing asymmetric curcumin analog compounds is still limited. Therefore, this research focuses on synthesizing asymmetric curcumin analogs from the intermediate compounds 2-(3,4-dimethoxybenzylidene)cyclohexanone and bromoanisaldehyde. This synthesis uses a mechanism involving the substitution of pharmacophore group B through a Claisen-Schmidt condensation reaction with a base catalyst (KOH). This approach enables the production of a more stable curcumin analogue, which may support further evaluation of its pharmacokinetic and biological properties.

The novelty of this study lies in the design and synthesis of an asymmetric curcumin analogue, which has not been widely reported in previous studies (Khor et al., 2019; Zhang et al., 2014). Most existing research focuses on symmetrical analogues, while this study introduces structural asymmetry by combining two different aromatic aldehydes. In addition, the synthesis route used in this study differs from most previous methods, as it employs a stepwise Claisen–Schmidt condensation strategy using preformed intermediates under mild conditions, which has not been commonly applied for this class of compounds. This modification is expected to improve selectivity and potency in biological activity. The aim of this study was to synthesize an asymmetric curcumin analogue (2,6)-2-(3-bromo-4-methoxybenzylidine)-6-(3,4-dimethoxybenzylidine)cyclohexanone, which is expected to be more structurally stable and potentially more effective as a pharmacological agent. However, this study was limited to synthesis, while its bioactivity test will be conducted in further research.

METHODOLOGY

Materials and Instrumentals

The synthesis's materials are of Merck's pro-analysis quality, namely bromoanisaldehyde, potassium hydroxide (KOH), 37% hydrochloric acid (HCl), ethanol, ethyl acetate, n-hexane, plate used for thin-layer chromatography (TLC, Silica Gel 60 F_{254}), universal pH indicator paper, and distilled water. The intermediate compound 2-(3,4-dimethoxybenzylidene)cyclohexanone was synthesized in our laboratory.

The tools used to synthesize asymmetric curcumin analogs were laboratory glassware, a magnetic stirrer, a hot plate, a vacuum desiccator, and an analytical balance (Libror EB330 Shimadzu). A melting point determination tool (Electrothermal 9100), an infrared spectrophotometer (FTIR, Shimadzu Prestige 21), a direct-inlet mass spectrometer (DI-MS type 5973, and Shimadzu QP 2010S), a gas chromatography-mass spectrometer (GC-MS, Shimadzu QP-2010S), a refrigerator, a desiccator, a thermometer, a pH meter, a UV-Vis spectrophotometer (Shimadzu UV-1800), and high-resolution mass spectrometry (LC-HRMS, Thermo Scientific Q Exactive Hybrid Quadropole-Orbitrap Mass Spectrometer) are among the instruments that will be used in the characterization.

Methods

The compound 2-(3,4-dimethoxybenzylidene)cyclohexanone was synthesized in-house and used as an intermediate in this study. The complete synthesis procedure and characterization of this compound will be described in detail in a separate publication. The other reactant was bromoanisaldehyde, which was readily available in the laboratory. Prior to synthesis, both reactants were characterized using GC-MS, and FT-IR analysis was also performed on bromoanisaldehyde. This step was carried out to determine the purity of both reactants.

The synthesis of asymmetric curcumin analog compounds in this study is based on previous research (Li et al., 2015). A total of 1 mmol of the intermediate compound was mixed with one mmol of the bromoanisaldehyde compound. For 30 minutes, the mixture was agitated with a stirrer after being dissolved in 5 mL of ethanol, then 7 mL of 30% KOH (in an aqueous solution) was added and agitated for 12 hours at room temperature; TLC was used to monitor the reaction until all the reactants had reacted. The pH was then adjusted to neutral by adding 0.1 M HCl dropwise until a yellow precipitate appeared. After filtering and washing with cold distilled water, the precipitate was dried. After drying, the precipitate was recrystallized using hot ethanol. The results were dried in a desiccator and weighed, and the melting point was measured and analyzed using an FTIR, DI-MS, and LC-HRMS spectrometer.

RESULTS AND DISCUSSION

Intermediate Compounds

The intermediate compound 2-(3,4-dimethoxybenzylidine)cyclohexanone) is available in the laboratory but needs to be analyzed using a GC-MS spectrometer to determine the purity and molecular mass level. In complex mixtures, gas chromatography (GC) analysis is a highly effective method for

identifying chemical components (Watuseke et al., 2024). As shown in Figure 5, one peak is visible in the GC chromatogram with a retention time (t*R*) of 2.45 minutes. The corresponding mass spectrum (Figure 6) shows a molecular ion (M^+) with a base peak at m/z 246. This data shows that the intermediate compound has 100% purity, and the molecular ions produced are by the theoretical molecular mass of the intermediate compound. Therefore, this intermediate compound will be used as the initial reactant, which is then reacted with bromoanisaldehyde to become an asymmetric curcumin compound.

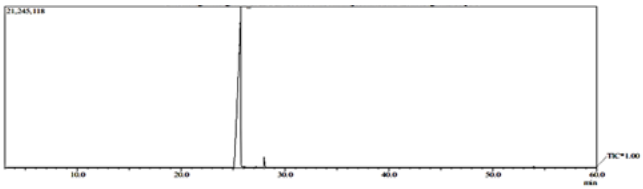

Figure 5. Intermediate Compound Chromatogram

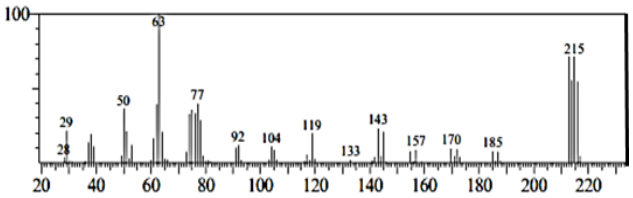

Figure 6. Intermediate Mass Spectrum

Based on the proposed fragmentation pattern, the molecular ion (M^+) with m/z 246 releases methyl and methoxy radicals to produce fragments with m/z 231 and 215. The m/z 215 fragment undergoes further fragmentation by releasing the methoxy cation to form the m/z 187 fragment. The structure of the intermediate compound is shown in Figure 7.

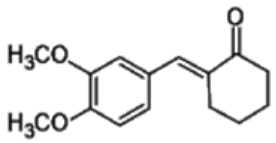

Figure 7. The structure of the intermediate compound

Bromoanisaldehyde Compounds

Another starting material used is the compound bromoanisaldehyde, the ingredients of which are available in the laboratory, so they are not synthetic. The purity level of the bromoanisaldehyde molecule was assessed by GC-MS. The results of GC-MS analysis show that the purity level of the bromoanisaldehyde compound is 100%, with the base peak corresponding to the molecular ion (M^+) at m/z 215 (Figures 8 and 9).

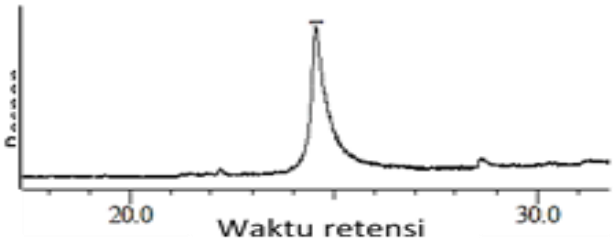

Figure 8. Bromoanisaldehyde chromatogram

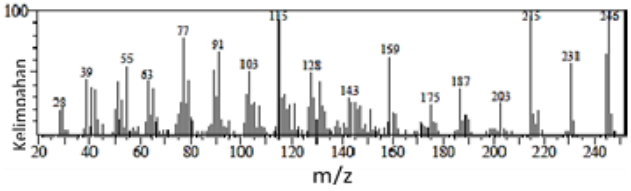

Figure 9. Mass spectrum of bromoanisaldehyde

A material's functional groups and covalent bonds can be identified using Fourier Transform Infrared (FTIR) analysis. The outline of the bioactive chemicals present in a substance can be estimated by determining the functional groups of the molecule or material (SetiyaNingrum et al., 2024). The bromoanisaldehyde compound was analyzed using an FT-IR spectrometer (Table 1 and Figure 10).

Table 1. FT-IR spectrum of bromoanisaldehyde

Functional Group	Wavenumber (cm^{-1})
Carbonyl group (C=O)	1696
Double bond in aromatic ring (C=C aromatic)	1597 and 1555
Carbon-oxygen bond in ether group (C-O ether)	1273 and 1187
Carbon-bromine bond (C-Br)	812

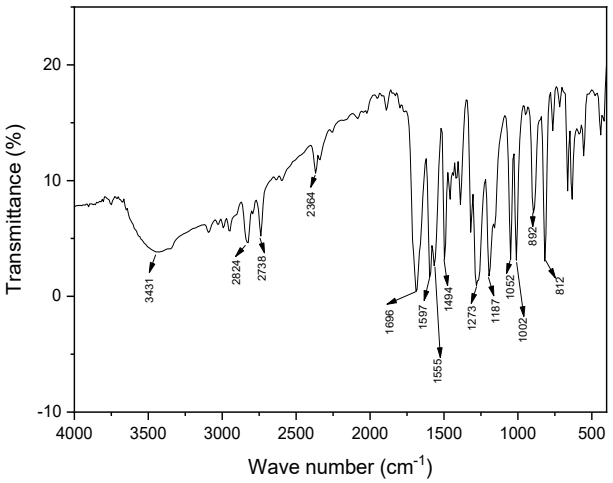

Figure 10. FT-IR spectrum of bromoanisaldehyde

The FT-IR spectrum shows that the C-Br group's vibration absorption is at the absorption peak of 812 cm^{-1}. The C=O group's vibration is absorbed at a wave number of 1696 cm^{-1}. Vibrational absorption of the C=C group on the aromatic ring is represented by the absorption peaks at 1597 and 1555 cm^{-1}. C-O ether absorption is defined by the absorption peaks at 1273 and 1187 cm^{-1}.

Synthesis of Asymmetric Curcumin Analogs

Synthesis of asymmetric curcumin analog compounds was carried out through an aldol condensation reaction between the starting material intermediate compound (2-(3,4-dimethoxybenzylidine)cyclohexanone) and bromoanisaldehyde with a base catalyst. The aldol condensation reaction is influenced by reaction kinetic factors such as the basic nature of the reactants (intermediate compounds and bromoanisaldehyde), namely the acidity of the alpha hydrogen (Hα), which is more acidic than the hydrogen attached to the carbon atom, resulting in Cα having a negative charge (nucleophile). However, the negative character of Cα is still weak, so it is necessary to add a catalyst. The catalyst in this reaction increases the reaction speed without undergoing permanent changes by reducing the activation energy (E_{akt}). Finally, the number of reactants that react increases and produces reaction products more quickly. This research used the KOH compound as a base catalyst, which will take Hα and form enolate ions.

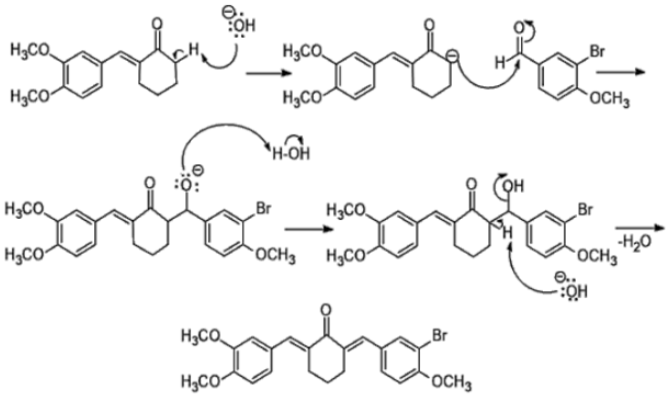

Figure 11. *Claisen-Schmidt* Mechanism Reaction

Theoretically, the intermediate compound structure has Hα and the carbonyl group. The carbonyl group will attract electrons, causing the electron density on the carbon atom to decrease and the bond between carbon and Hα to become weaker, so that Hα is acidic and easily separated. The KOH catalyst will take the Hα and form a reactive enolate ion because it carries a negative charge and is more nucleophilic than the neutral enol. The easier it is for Hα to escape, the easier it is for enolate ions to form, so that the reaction occurs quickly. The enolate ion will act as a nucleophile and add the carbonyl carbon (C) to the aromatic aldehyde compound (bromoanisaldehyde), and a β-hydroxy ketone compound is produced. This compound undergoes further dehydration to produce an unsaturated α,β-ketone compound, an asymmetric curcumin analog compound. The reaction mechanism of the *Claisen–Schmidt* condensation involved in the synthesis process is illustrated in Figure 11.

Characterization of asymmetric curcumin analog compounds

The product obtained was a yellow solid weighing 0.13 g (yield percentage: 2.93%) with a melting point of 143-147 °C. The TLC results using the eluent ethyl acetate: *n*-hexane showed the same R*f* value (the same spot between the product and the intermediate compound). Based on analysis using a TLC scanner, the R*f* results are shown in Figure 12, located in the interval 0.47-0.68.

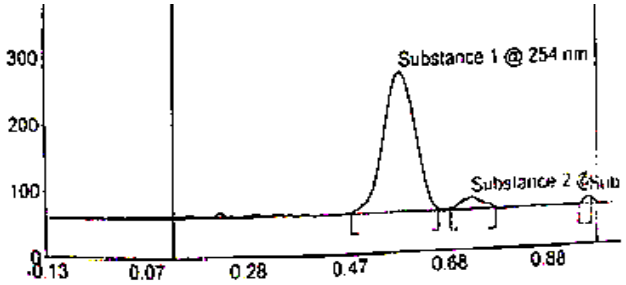

Figure 12. TLC scanner for asymmetric curcumin analog compounds

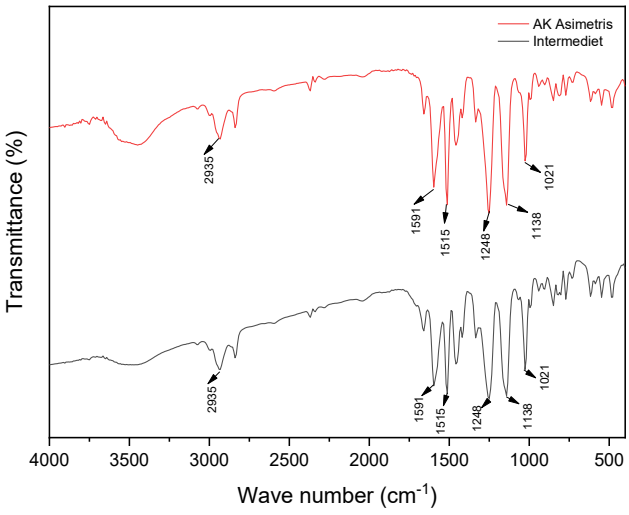

Figure 13. FT-IR spectrum of asymmetric and intermediate curcumin analog compounds

The results of FTIR spectrometer analysis between intermediate compounds and asymmetric curcumin analogs show that there are identical wave number absorptions (**Figure 13**), namely the Csp^2-H functional group at wave numbers 2931-2932 cm^{-1}, aromatic C=C at wave numbers 1597 and 1512 cm^{-1}, and C-O ether at wave numbers 1249 and 1141 cm^{-1}. The FTIR spectra of the intermediate and final products show very similar absorption patterns. This similarity is due to the presence of the same main functional groups in both compounds, such as aromatic C=C, Csp^2–H, and ether C–O, which remain present after the condensation reaction. This analysis reveals that no significant differences were observed in the FTIR spectra, including the appearance or disappearance of specific groups, as the reaction that occurs is the addition of another aromatic group (bromoanisaldehyde), which exhibits similar IR absorption characteristics to those of the groups in the intermediate compound. Thus, structural changes cannot be detected sensitively by FTIR. Therefore, confirmation of the target compound's formation was strengthened by analysis using a UV-Vis spectrometer and HR-MS.

The subsequent analysis utilizes a UV-Vis spectrometer operating in the range of 330–500 nm, and a UV-Vis spectrum is obtained as shown in Figure 13. UV-Vis spectrum analysis aims to provide information regarding the presence of chromophores and wavelength (λ) in the compounds being tested; chromophores can be benzene rings or conjugated double bonds. The analysis shows that the intermediate compound has a maximum absorption of 0.756 at a maximum wavelength of 360 nm. The asymmetric curcumin analog compound has a maximum wavelength of 364 nm with a maximum absorption of 0.585. Based on analysis with a UV-Vis spectrometer shown in **Figure 14**, it indicates that both compounds have chromophore groups such as aromatic, carbonyl groups, or conjugated double bonds (alkene in aromatic), which are capable of absorbing radiation in the visible wavelength region. This analysis shows that a slight bathochromic shift occurred in the synthesized compound. This is possibly due to methoxy and bromo groups as auxochromes, which are bound to the benzene nucleus as chromophore groups. The reaction between the two starting materials forms a longer conjugated double bond where electrons experience delocalization, and the energy required for electronic transitions becomes higher, so the wavelength absorbed will be greater than the starting material (intermediate compound, λ 360 nm).

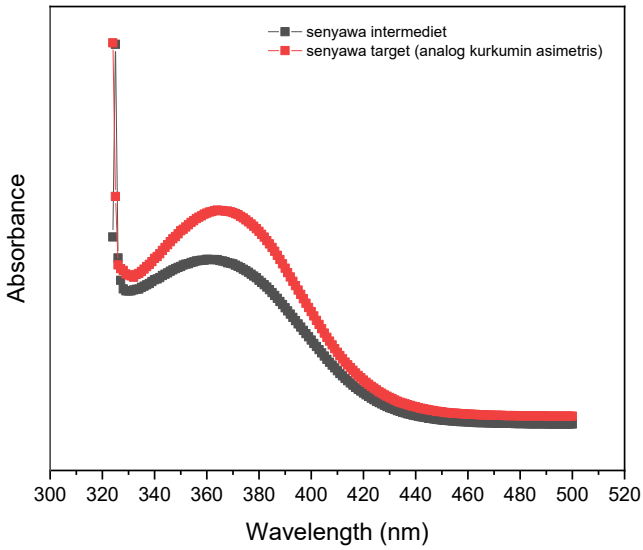

Figure 14. UV-Vis Spectrum

The next analysis uses a GC-MS and DI-MS spectrometer to determine the compound's purity level and the target molecule's mass. However, when injected into the instrument, the solid sample sublimes, so it does not get the desired results. The asymmetric curcumin analog compound was then analyzed using HRMS to determine the molecular mass of the target compound (Figure 15).

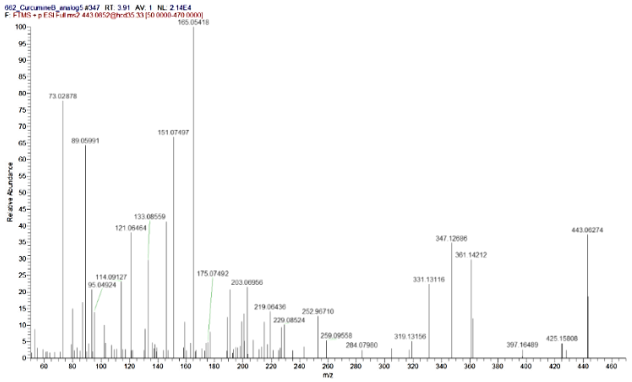

Figure 15. HR-MS spectrum

At m/z 443.06274, the HR-MS spectrum of the asymmetric curcumin analogue shows a molecular ion peak corresponding to the formula $C_{23}H_{23}BrO_4$ ($[M+H]^+$), while the theoretical value is 443.063635. The mass difference between the observed and theoretical peaks is 0.000895 Da, or 0.895 mDA, which is well within the acceptable error range of less than 3 mDA as recommended by the Journal of the American Chemical Society (JACS) (Gasella et al., 2015; Rahmawati et al., 2018; Setiawan et al., 2015). This shows that the asymmetric curcumin analog compound has been successfully synthesized according to the expected target.

Based on the results of UV-Vis spectroscopy, FT-IR, and high-resolution mass spectrometry (HR-MS) data analysis, the asymmetric curcumin analog compound synthesized from intermediate compounds and bromoanisaldehyde in this study is in accordance with the expected target compound, namely the asymmetric curcumin compound (2,6)-2-(3—bromo-4-methoxybenzylidine)-6-(3,4-dimethoxybenzylidine)cyclohexanone. These analytical methods provided preliminary evidence supporting the formation of the target compound. However, to confirm the complete molecular structure, further analysis using nuclear magnetic resonance (^{1}H-NMR and ^{13}C-NMR) is required. This will be addressed in a subsequent study as part of ongoing research. Furthermore, it is necessary to conduct in vitro and silico assessment tests as an alpha-amylase enzyme inhibitor (Natsir et al., 2024).

CONCLUSION

This study successfully achieved its objective by synthesizing an asymmetric curcumin analog compound, namely (2,6)-2-(3-bromo-4-methoxybenzylidene)-6-(3,4-dimethoxybenzylidene)cyclohexanone, from 2-(3,4-dimethoxybenzylidene)cyclohexanone and bromoanisaldehyde using a base catalyst (KOH). Structural characterization through UV-Vis spectroscopy, FTIR, and HR-MS confirmed that the synthesized compound corresponds to the expected target molecule. Although the spectral data strongly support the proposed structure, further analysis using ^{1}H-NMR and ^{13}C-NMR is necessary to confirm the atom connectivity and provide a complete structural elucidation.

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