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SYNTHESIS OF CHALCONE AND PYRAZOLINE DERIVATIVES WITH ACETOPHENONE AND VERATRALDEHYDE AS PRECURSORS

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ABSTRACT

Chalcones and pyrazolines are heterocyclic compounds with promising biological and pharmaceutical activities. Chalcone and pyrazoline can be found in different sources, such as natural and synthetic compounds. This study aimed to explore the synthesis of chalcone and pyrazoline derivatives with acetophenone and veratraldehyde as precursors. Chalcone was successfully synthesized through the Claissen-Schmidt reaction between acetophenone and veratraldehyde at room temperature 25-30 ºC and mediated by KOH as a base catalyst for 20 hours. The corresponding substituted pyrazoline derivative was also successfully synthesized through a cyclocondensation reaction between the synthesized chalcone and phenylhydrazine as starting materials under reflux conditions at temperatures of 75-80 ºC for 4 hours. The Chalcone A derivative compound obtained was (E)-3-(3,4-dimethoxy phenyl)-1-phenyl prop-2-en-1-one (Chalcone A). The Pyrazoline A derivative compound was obtained as pyrazole compound 5-(3,4-dimethoxy phenyl)-1,3-diphenyl-4,5-dihydro-1H-pyrazole (pyrazoline A). Chalcone A and Pyrazoline A obtained as yellowish and brownish-orange powders in 14.89 % and 66.57 % yields, respectively. The chastities of Chalcone A and Pyrazoline A was 98.55 % and 88.54 %, respectively. A qualitative identification for both synthesized compounds was performed using normal-phase thin-layer chromatography which revealed the R_f value for Chalcone A and Pyrazoline A was 0.43 (in mobile phase ethyl acetate:*n*-hexane 3:1 v/v) and 0.55 (in mobile phase DCM:*n*-hexane 3:1 v/v), respectively. Moreover, the elucidation structure of synthesized compounds using FTIR and GC-MS instruments revealed the structure of synthesized Chalcone A and Pyrazoline A agrees with the theoretical structure of Chalcone A and Pyrazoline A.

Keywords: Synthesis, Chalcone, Pyrazoline, Acetophenone, Veratraldehyde

INTRODUCTION

Chalcones (1,3-diphenyl-2-propen-1-ones) are heterocyclic compounds with two aryl moieties bridged via an α,β-unsaturated carbonyl group. In particular, the chalcone group has a ketoethylenic moiety in its structure: –C=O–CH=CH–. In addition to the ketoethylenic moiety, chalcone derivatives have delocalized π-electrons in their aromatic rings (Elkanzi *et al.*, 2022). Owing to their structure, chalcones and their derivatives possess a wide spectrum of beneficial bioactivities, such as antioxidant, anticancer, antifungal, antimicrobial, antiviral, antimalarial, and antiultraviolet (Puspita, Teruna and Jasril, 2014; Wijayanti *et al.*, 2021; Elkanzi *et al.*, 2022). The physical appearance of chalcones varies from yellow to orange, significantly contributing to the pigmentation of some plants. Chalcones are mainly found naturally in fruits, spices, teas, and soy-based foods (Suma

Wahyuningsih and Mustofa, 2019; Wahyuningsih, Suma and Astuti, 2019; Elkanzi *et al.*, 2022). In addition, chalcones can be found in natural products such as pheromones, plant allelochemicals, and insect hormones (Elkanzi *et al.*, 2022). On the other hand, a wide range of chalcone derivatives can be synthesized by condensing aryl ketones and aromatic aldehydes using various synthetic pathways and versatile conditions because of their simple structure and easy structure construction (Ismiyarto, Matsjeh and Anwar, 2010). In addition, chalcones have become versatile compounds because they are intermediates in the formation of other compounds, such as flavonoid and pyrazoline derivatives (Ismiyarto, Mchalconesnd Anwarusedusp ita, Teruna and Jasril, 2014; Sumaotherncompoundsndsuch as9; Wahyuningsih, Suma and Astuti, 2019). Previous research has focused on the efficient synthesis of chalcones because of their various biological activities.

Pyrazole is an extended heterocyclic compound, which is a five-membered ring consisting of two nitrogen atoms in adjacent positions and contains two endocyclic double bonds (Faisal *et al.*, 2019; Kalyani, Sagar, and Dhanashree Student, 2020). Pyrazole and pyrazoline have recently become valuable species because they possess a wide spectrum of anti-inflammatory, antioxidant, anticancer, antidepressant, antifungal, antimicrobial, and antidiabetic properties (Mistry and Desai, 2005; Kasrrouchi *et al.*, 2018; Nurlaili, Jasril and Teruna, 2018). Patent anti-inflammatory drugs that contain pyrazole functional groups, such as Lonozolac (NSAID), celecoxib (NSAID), ramifenazone (NSAID), antipyrine or phenazone, metamizole, aminopyrine or aminophenazone, and phenylbutazone, have already been used clinically to treat inflammatory diseases (Pandya *et al.*, 2017; Kalyani, Sagar and Dhanashree Student, 2020). In addition, pyraclonil (a protoporphyrinogen inhibitor) and pyrazofurin (a DNA/RNA synthesis inhibitor antibiotic) also have a pyrazole moiety in their chemical structures (Pandya *et al.*, 2017). Pyrazoline derivatives can be synthesized chemically through the reaction between chalcone and various hydrazine compounds through a cyclocondensation reaction (Suma, Wahyuningsih and Mustofa, 2019; Wahyuningsih, Suma, and Astuti, 2019).

Chalcone and pyrazoline derivatives can be synthesized under various conditions. The synthesis of chalcone derivatives involving ketone and aldehyde derivatives generally occurs through the Claissen-Schmidt reaction to form chalcone analogs (Bui *et al.*, 2016; Suma, Wahyuningsih, and Mustofa, 2019; Wahyuningsih, Suma, and Astuti, 2019). Meanwhile, the synthesis of pyrazole or pyrazoline derivatives occurs through aldol cyclocondensation between a compound with an α,β-unsaturated moiety from an aldehyde or ketone and hydrazine. Chalcones have α,β-unsaturated moieties in their structure; hence, chalcones can be assigned as an intermediate compound of pyrazoline derivatives and a starting material to react with hydrazine to generate pyrazoles or pyrazoline derivatives (Bhandarkar, 2014; Tanwer *et al.*, 2015; Mohamady *et al.*, 2018). Wahyuningsih and co-workers (2019) reported that the synthesis of chalcone derivatives successfully occurred through Claissen-Schmidt reactions between acetophenone and veratraldehyde derivatives assisted by NaOH 40 % w/v as a catalyst (Wahyuningsih, Suma, and Astuti, 2019). Furthermore, pyrazoline derivatives can be synthesized using chalcone and hydrazine derivatives under reflux conditions (Wahyuningsih *et al.*, 2019). Meanwhile, the synthesis of chalcone and pyrazoline derivatives using acetophenone and veratraldehyde derivatives as precursors assisted by KOH as a base catalyst has not been performed in previous studies.

The exploration of chalcone and pyrazoline synthesis remains attractive because the pharmacological properties of chalcone and pyrazoline derivatives are still being studied and developed. The main objective of this research was to explore the synthesis of chalcone and pyrazoline derivatives using acetophenone and veratraldehyde precursors assisted by KOH as the base catalyst.

RESEARCH METHODS

Equipment and Materials

The equipment used for the synthesis of chalcone and pyrazoline derivatives was glassware from Pyrex, a reflux set, a magnetic stirrer, an electric stove, a Buchner funnel, and Whatman filter paper. Melting points were checked using digital melting point equipment (Electrothermal 9100). Chastity and mass spectra of the compounds were recorded using a GC-MS spectrometer (Shimadzu QP2010S with electron ionization). IR spectra were recorded with a Shimadzu Prestige-21 with KBr plat.

All chemicals and solvents used were of pro-analytical grade and purchased from Merck. The materials for the synthesis of chalcone and pyrazoline derivatives were acetophenone, veratraldehyde, methanol, ethanol, KOH, HCl, glacial acetic acid, *n*-hexane, dichloromethane, ethyl acetate, and aquadest. Thin layer chromatography (TLC) was carried out using aluminum plates (20 × 20 cm; Merck) covered with silica gel 60 F_{254}.

Research Procedure

1. Synthesis of (E)-3-(3,4-dimethoxyphenyl)-1-phenyl prop-2-en-1-one (Chalcone A)

The synthesis of Chalcone A follows the procedure from Wahyuningsih and co-workers (2019) with slight modification. A mixture of acetophenone (1.3 mL, 10 mmol) in 5 mL methanol and 5 mL aqueous KOH 30 % (w/v). Veratraldehyde (1.54 g, 10 mmol) dissolved in 25 mL of methanol was added dropwise and stirred constantly. The reaction mixture was stirred for 2 hours. Then, 10 % (v/v) HCl was added to the mixture dropwise until the pH was 2. The solution mixture was stirred continuously with constant stirring for 20 hours. The progress of the reaction was monitored using TLC with mobile phase ethyl acetate:*n-hexane* 3:1 v/v.

Chalcone A was purified using a recrystallization procedure. The synthesized chalcones were dissolved in hot ethanol. The solution was then filtered under hot filter conditions. The filtrate was then immediately cooled in an ice-cold water bath. The reformed crystal of the product was then filtered using a Buchner funnel. The solid product Chalcone A obtained via vacuum filtration. It was dried in an oven for 24 hours and stored in a vacuum desiccator until use. Purified Chalcone A identified using TLC with a mobile phase of ethyl acetate:*n*-hexane 3:1 v/v. Yellow powder, R_f 0.45, m.p 88-92 ºC, yield: 14.89 %, purity: 98.55 %, IR (KBr) ν_{max} (cm^{-1}): 2924 (C–H stretching), 2839 (C–H stretching of $–OCH_3$), 1597 (C=O stretching), 1450 (C=C aromatic stretching), 1388 (–C–H aliphatic bending), 1319 (–C–H bending of methoxy, $–OCH_3$), 1257 and 1141 (C–O ester stretching), and 1026 (=C–H bending). GC-MS Chalcone A (98.55 %, t_R 31.42 minutes, MS: 268 [M^+]).

2. Synthesis of 5-(3,4-dimethoxyphenyl)-1,3-diphenyl-4,5-dihydro-1H-pyrazole (Pyrazoline A)

Chalcone A (0.21 g, 0.76 mmol) was dissolved in ethanol (5 mL), phenylhydrazine (0.8 mL, 0.76 mmol) was heated under reflux with a temperature–75-80 ºC for 4 hours. The reaction progress was monitored using thin-layer chromatography with a mobile phase of DCM:*n*-hexane (3:1 v/v). The product was then precipitated in Erlenmeyer flasks, which were submerged in an ice-cold water bath and refrigerated at 15 °C for 48 hours. The solid Pyrazolin A product was obtained by vacuum filtration and dried in an oven overnight. Purified Pyrazoline A identified using thin-layer chromatography with a mobile phase of DCM:*n*-hexane 3:1 v/v. Brownish-orange solid powder, R_f 0.55, m.p 112-114 ºC, yield: 66.57 %, purity: 88.54 %, IR (KBr) ν_{max} (cm^{-1}): 3055 (C–H aromatic stretching), 3017 (=C–H stretching), 2847 (C–H stretching of methoxy, $–OCH_3$), 1651 (C=N stretching), 1582 and 1450 (C=C aromatic stretching), 1574 (C=C), 1335 (–C–H aliphatic bending), 1319 (–C–H bending of methoxy, $–OCH_3$), 1258 and 1018 (C–O ester stretching), 1134 (C–O ester bending), 849 (aromatic out of plane). GC-MS Pyrazoline A (88.54 %, t_R 42.28 minutes, MS: 358 [M^+]).

RESULTS AND DISCUSSION

The synthesis of chalcone and pyrazoline are interesting compounds because they have various pharmacological activities that are beneficial for health (Karrouchi *et al.*, 2018; Elkanzi *et al.*, 2022). In addition, chalcone can be performed as an intermediate compound to form another compound, for instance, flavonoid and pyrazoline derivatives (Ismiyarto, Matsjeh and Anwar, 2010; Puspita, Teruna and Jasril, 2014; Suma, Wahyuningsih and Mustofa, 2019; Wahyuningsih, Suma and Astuti, 2019). In this work, Chalcone A and

Pyrazoline A derivatives were successfully synthesized under the reaction conditions shown in Figure 1. The physical properties of synthesized Chalcone A and Pyrazoline A are displayed in Table I.

The reaction involving acetophenone and veratraldehyde occurred under base conditions via the Claissen-Schmidt reaction. Chalcones were synthesized by generating carbanion species from the reaction between acetophenone and the potassium hydroxide catalyst. The carbanion species became an excellent donor electron species (nucleophilic) with stable properties owing to resonance and intramolecular conjugation. Meanwhile, veratraldehyde, with a carbonyl moiety from the aldehyde functional group, becomes an electron receiver (electrophilic species) (Ismiyarto, Matsjeh and Anwar, 2010).

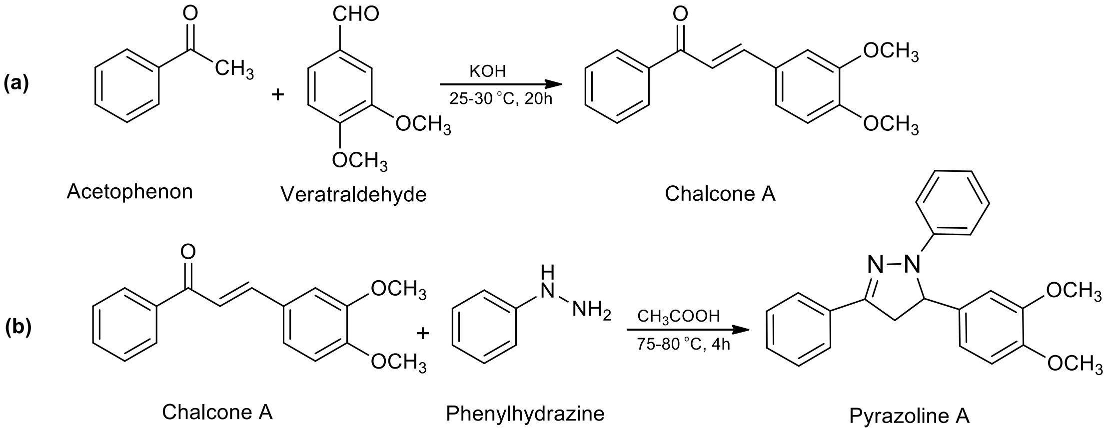


Figure 1. Reaction to Synthesis (a) Chalcone A and (b) Pyrazoline A

Table I. Physical Properties of Synthesized Chalcone A and Pyrazoline A

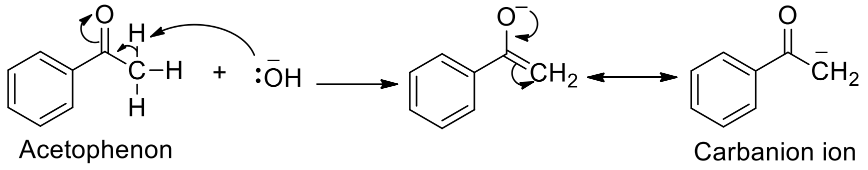
Compound	Molecular formula	Color	Molecular weight	Yield (%)	Chasteness (%)	Melting point (ºC)
Chalcone A	$C_{17}H_{16}O_3$	Yellowish	268	14.89	98.55	88-92
Pyrazoline A	$C_{23}H_{22}O_2N_2$	Brownish-orange	358	66.57	88.54	112-114

The proposed reaction mechanism for the synthesis of Chalcone A illustrated in Figure 2. Nucleophilic addition initiated the reaction, and proton transfer produced a β-hydroxy ketone. Subsequently, the reaction involves the dehydration of water molecules to form an α,β-unsaturated carbonyl. The reaction for the synthesis of Chalcone A complete after 20 hours. In this study, HCl was added dropwise to prevent the Cannizzaro reaction. The Cannizzaro reaction is susceptible to occur because veratraldehyde has Hα in its structure and tends to produce insoluble benzoic acid salts as undesired byproducts (Ismiyarto *et al*., 2001). Fortunately, no Cannizaro reaction occurred, and insoluble benzoic acid salt was not generated.

The synthesized Chalcone A obtained a yellowish powder in a 14.89 % yield, as shown in Figure 3a. The identification of Chalcone A thin-layer chromatography showed an R_f value of 0.43 with a mobile phase of ethyl acetate:*n*-hexane (3:1 v/v), as shown in

Figure 4a. The melting point of the chalcone compound is 88-92 ºC. The MS results revealed the molecular weight of the targeted chalcone. Ion M^+ species with 268 m/z confirmed the desired molecular weight of the synthesized chalcone, which arose with a retention time of 31.42 minutes, and an excellent chastity of 98.55 % of the chalcone was obtained successfully (Figure 6).

(a) The formation of carbanion species



(b) The formation of Chalcone A

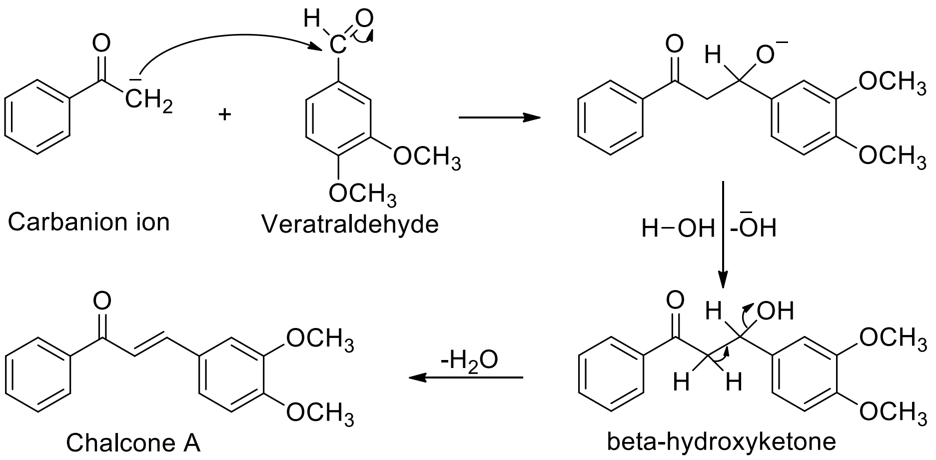


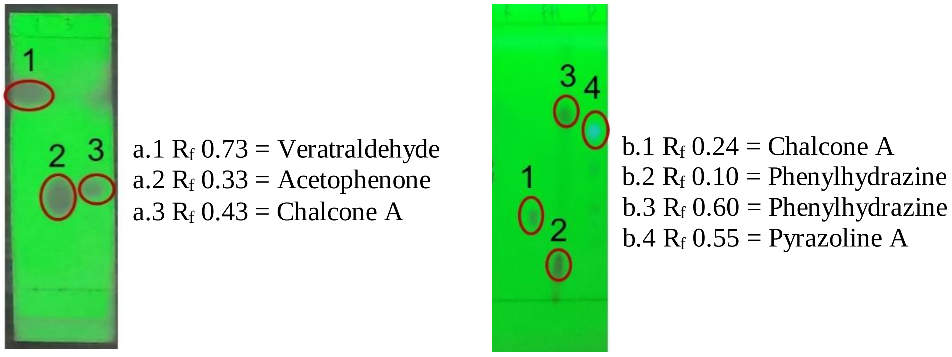
Figure 2. The Proposed Mechanism Reaction to Synthesis Chalcone A

The IR spectra of Chalcone A displayed some important peaks, as shown in Figure 7a. C=C aliphatic stretching and bending bands were observed at 1504 and 1026 cm^{-1}, respectively. In addition, the C–H aldehyde stretching bands at 2850 and 2750 cm^{-1} disappear in Chalcone A's FTIR spectra, confirming that Chalcone A was correctly achieved (Wijayanti *et al.*, 2021).

(a) **(b)**

Figure 3. Powder of synthesized (a) Chalcone A and (b) Pyrazoline A

Another chalcone derivative was successfully synthesized by Wahyuningsih et al. (2019). Wahyuningsih et al. reported (E)-1-(4-chlorophenyl)-3-(3,4-dimethoxyphenyl) prop-2-en-1-one has been done using 4-chloroacetophenon and veratraldehyde, (E)-3-(3,4-dimethoxyphenyl)-1-(4-hydroxyphenyl) prop-2-en-1-one using 4-hydroxyacetophenon and veratraldehyde, and (E)-3-(3,4-dimethoxyphenyl)-1-(2-hydroxyphenyl) prop-2-en-1-one using 2-hydroxy acetophenone and veratraldehyde with NaOH as a catalyst. Each acetophenone derivative was reacted with veratraldehyde to produce a substituted chalcone derivative.



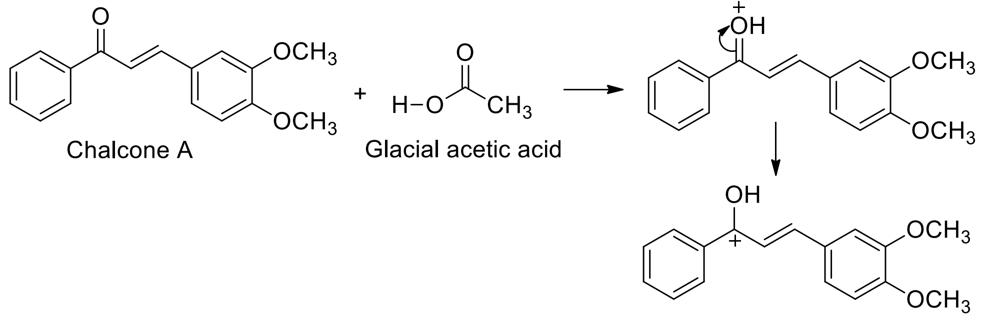
a.1 R_f 0.73 = Veratraldehyde
a.2 R_f 0.33 = Acetophenone
a.3 R_f 0.43 = Chalcone A

b.1 R_f 0.24 = Chalcone A
b.2 R_f 0.10 = Phenylhydrazine
b.3 R_f 0.60 = Phenylhydrazine
b.4 R_f 0.55 = Pyrazoline A

(a) **(b)**

Figure 4. **TLC results of (a) Chalcone A with mobile phase ethyl acetate:n-hexane (3:1 v/v) and (b) Pyrazoline A with Mobile Phase DCM:n-hexane (3:1 v/v) Under UV 254 nm**

(a) The protonation of oxygen atom in carbonyl of Chalcone A by glacial acetic acid



(b) The formation of Pyrazoline A

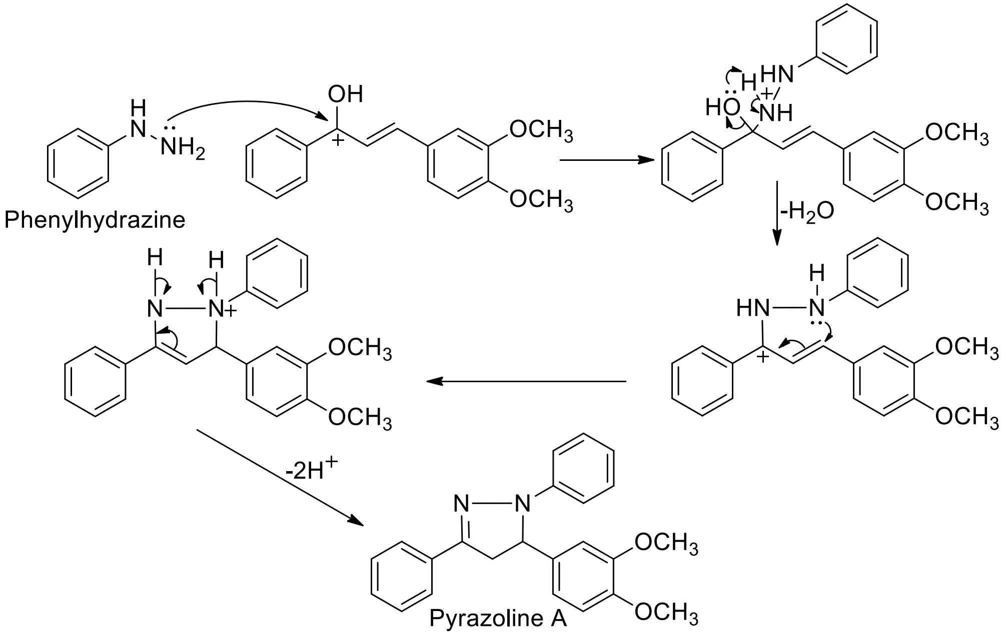


Figure 5. **Proposed Mechanism Reaction to Synthesis Pyrazoline A**

Following confirmation that Chalcone A product had been produced with the expected result, Pyrazoline A successfully synthesized. Chalcone A and phenylhydrazine anhydrate underwent cyclocondensation to generate (5-(3,4-dimethoxy phenyl)-1,3-

diphenyl-4,5-dihydro-1H-pyrazole). As shown in Figure 1b, the reaction for the synthesis of Pyrazoline A assisted by glacial acetic acid as an acid catalyst. Phenylhydrazine became a nucleophilic species since it already has electron-donating properties from nitrogen atoms. Subsequently, the Chalcone A electrophilic species is easily attacked by phenylhydrazine.

The synthesis of Pyrazoline A initiated by oxygen protonation at the carbonyl moiety of chalcone in the presence of glacial acetic acid. Glacial acetic acid provides ion H^+ species and enhances the reactivity to produce carbocations. Then, the carbocations were easily attacked by phenylhydrazine. The proposed reaction mechanism of the cyclocondensation of the carbonyl to produce pyrazole is shown in Figure 5. Overall, Pyrazoline A synthesized at a high temperature (75-80 ºC) for 4 hours under reflux conditions. High temperatures are required to accelerate the formation of five-membered ring (pyrazole) compounds (Suma Wahyuningsih and Mustofa, 2019; Wahyuningsih, Suma and Astuti, 2019).

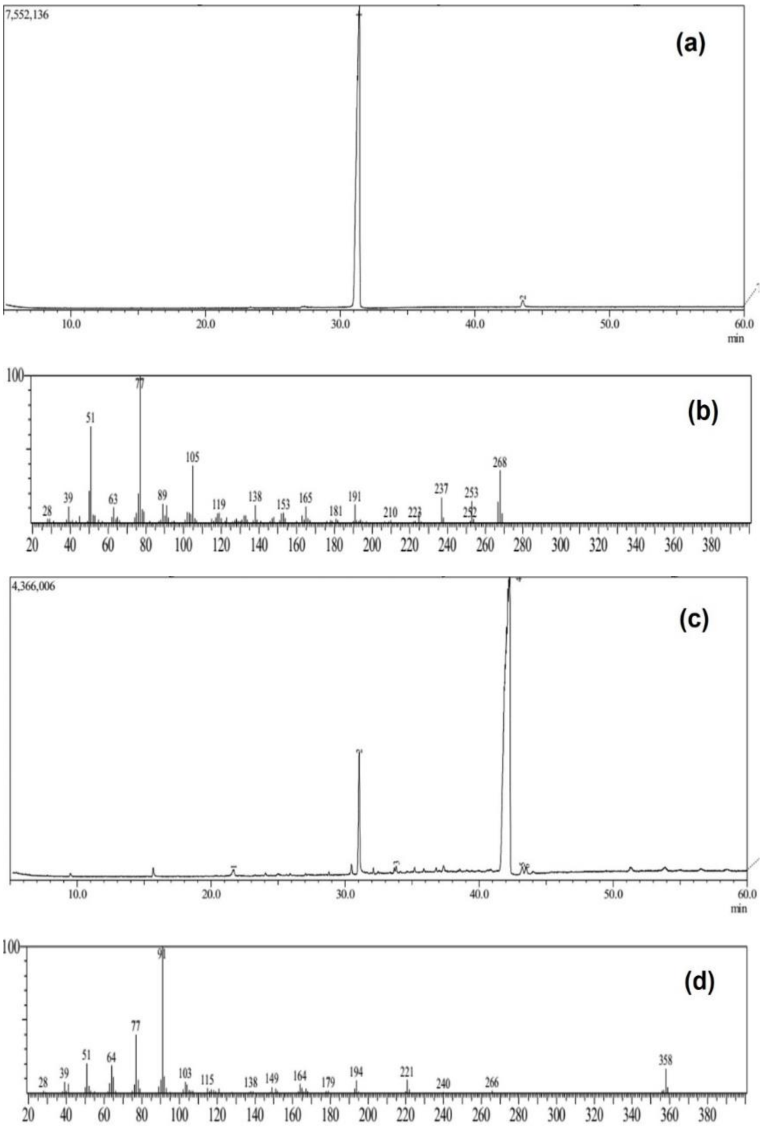


Figure 6. GC Spectra of (a) Chalcone A, (b) MS Spectra of Chalcone A, (c) GC Spectra of Pyrazoline A, and (d) MS Spectra of Pyrazoline A

In this work, pyrazoline was obtained as a brownish-orange powder in 66.57 % yield. The target compound was identified by thin-layer chromatography. The R_f value of the pyrazoline compound was 0.55 with mobile phase DCM:*n*-hexane (3:1 v/v), and gave a blue spot under UV 254 nm, as shown in

Figure **4**b. Generally, *bis*-(pyrazole) and *bis*-(pyrazoline) derivatives give blue spots under UV 254 nm, as mentioned in a previous report by Pinto et al. (2003). The melting point of pyrazoline compound was 112-114 ºC. The MS results revealed the molecular weight of the targeted pyrazoline. A typical ion M^+ value of 358 m/z represents the desired molecular weight of the synthesized pyrazoline, which arose at a retention time of 42.27 minutes and a fascinating chastity result of 88.54% pyrazoline was obtained, as displayed in Figure 6c and Figure **6**d.

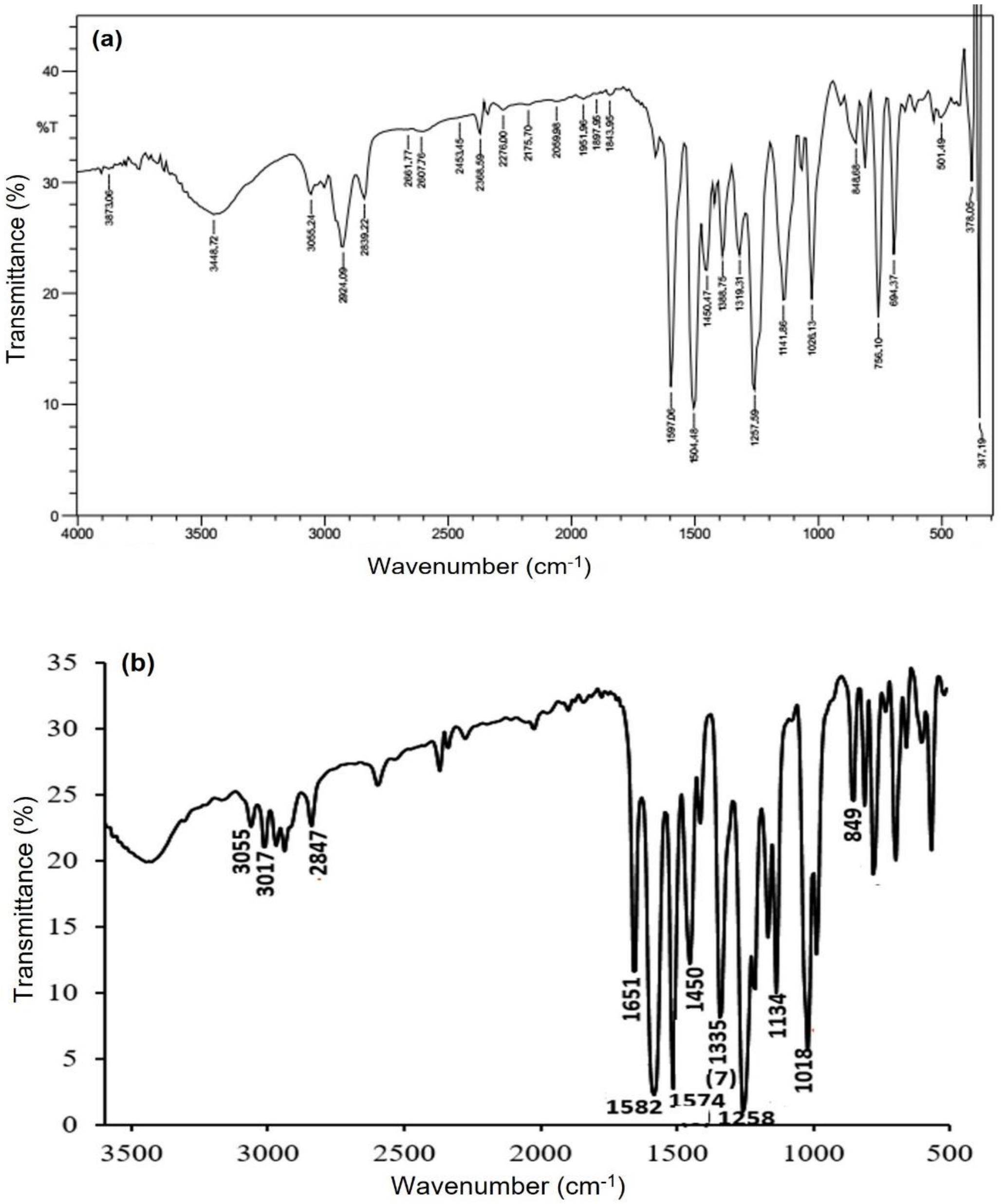


Figure 7. IR Spectra of (a) Chalcone A and (b) Pyrazoline A

The presence of C=N aliphatic stretching and bending bands arose at 1597 cm^{-1} and C–N at 1142 cm^{-1}, respectively, as shown in Figure 7, confirming the formation of a pyrazoline ring. The synthesis of pyrazoline derivatives using chalcone and phenylhydrazine with glacial acetic acid to produce *N*-phenylpyrazoline derivatives gave typical IR spectra for C=N aliphatic stretching emerges at 1597-1651 cm^{-1} (Suma, Wahyuningsih and Mustofa, 2019; Wahyuningsih, Suma and Astuti, 2019). Meanwhile, C=C aromatic stretching appears at 1574 cm^{-1}. C–O ester stretching was observed at 1258 and 1018 cm^{-1} (Pavia *et al*., 2015). Finally, the elucidation of the structure of synthesized Chalcone A and Pyrazoline A through GC-MS and FTIR analysis data met the theoretical structure of Chalcone A and Pyrazoline A. Synthesized chalcone and pyrazoline warrants further bioactivity investigation in the pharmaceutical field.

CONCLUSION

In this study, chalcone derivative (E)-3-(3,4-dimethoxy phenyl)-1-phenyl prop-2-en-1-one was synthesized successfully using acetophenone and veratraldehyde compounds as precursors under base conditions with KOH as the catalyst. In addition, the synthesized chalcone was used as the starting material for the formation of the pyrazoline derivative 5-(3,4-dimethoxy phenyl)-1,3-diphenyl-4,5-dihydro-1H-pyrazole through a cyclocondensation reaction with phenylhydrazine under acidic conditions with glacial acetic acid as the catalyst.

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All the authors agree to publish this research and declare that there are no conflicts of interest to disclose.

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