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Synthesis of New Curcumin Analogues from Kulit Lawang Oils Using the Conventional Method and Microwave

Imanuel Berly Delvis Kapelle[1, 2], Tun Tedja Irawadi[3], Meika Syahbana Rusli[2], Djumali Mangunwidjaja[2], Zainal Alim Mas'ud[3]

[1]Chemistry Department, Mathematic and Natural Science Faculty, Pattimura University, Maluku, Indonesia
[2]Agricultural Industry Technology Department, Agriculture Technology Faculty, Bogor Agricultural Institute, Bogor, Indonesia
[3]Chemistry Department, Mathematic and Natural Science Faculty, Bogor Agricultural Institute, Bogor, Indonesia

Email address:

berly_mollucas@yahoo.com (I. B. D. Kapelle)

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Abstract: Kulit lawang oils are essential oils that are widely available in the Moluccas and oil major component contain eugenol and safrole. Safrole can be converted into value-added products that curcumin analogues. The purpose of this research is to synthesize new compounds curcumin analogues from kulit lawang oils. The steps being taken is isolation safrole, safrole isomerization and oxidation isosafrole produce piperonal. The method synthesis curcumin analogues with piperonal precursor with two methods: conventional and microwave. Results safrole isolation from skin oils mace using alkaline extraction method for 5 hours yield 19.30% were is characterized by GCMS, FTIR and ^{1}H-NMR. Isosafrole proceeds reaction isomerization safrole without the use of solvents for 6 hours at a temperature of 120 ° C obtained yield 77.56% with two products *cis*-isosafrole (15.4%) and *trans*-isosafrole (69.34%) were characterized by GC, FTIR and ^{1}H-NMR. Precursors piperonal which was resulting obtained from the oxidation reaction isosafrol using $KMnO_4$ at temperature < 30 °C obtained yield 65.63% were characterized by GCMS, FTIR and ^{1}H-NMR. Results synthesis curcumin analogues (1,5-Bis-benzo [1,3] dioxol-5-yl-penta-1,4-dien-3-one) in the conventional method using 10% NaOH catalyst for 3 hours at a temperature of 25 °C be obtained yield 78.43% and synthesized using microwave at 140 watts for 2 minutes obtained yield 53.3%.

Keywords: Kulit Lawang Oils, Safrole, Curcumin Analogues

1. Introduction

Kulit lawang oils are one of the potential essential oils and produced in eastern Indonesia especially Maluku and Papua. Plant kulit lawang included in family lauraceae and cinnamon group with characteristics slimy leaves, white wood, brittle and grow wild in the forest. Mace skin oils obtained from the distillation of the bark of lawang (Cinnamomum cullilawan, Blume) with yield 1.49 to 3.80% [14].

In the process of separation kulit lawang oils produces two products: eugenol (69.0%) and safrole (21.0%) [20]. Eugenol and safrole has a different structure, in which the epoxide ring safrole has a very active so it can be used as precursors of synthetic drugs. Safrole at room temperature is a colorless oil, but may turn yellow when exposed to sunlight, but at lower temperatures safrole is white crystal, has an odor sasafras and taste spicy [10,28]. Natural ingredients that have the same epoxide groups with safrole and has anti-cancer activity is piperine [25]. Piperine is an alkaloid compound that has been tested as an anti-tumor activity in vivo method can inhibit 56.8% [6], antioxidant and hepatoprotective effects [18] and can increase the bioavailability [12]. Reactivity of the epoxide group owned by safrole can be used in a way converted into an anti-cancer drug products are derivatives of curcumin analogues.

Analog compounds (homologous) Curcumin is a compound that has the possibility of pharmacological properties similar or even better when compared to the parent compound. Curcumin is a cancer drug from natural ingredients that have been reported to have anti-cancer activity from ginger [19, 31]. Curcumin and curcumin analogues have biological activity as an anti-inflammatory, antioxidant, antitumor, and anti-cancer (gastrointestinal,

breast, ovarian, lung, nerve) [1, 3, 11, 16, 22]. Effectiveness of each compound is influenced by differences in functional groups and structures that affect the physical-chemical properties and pleiotropic effects [2]. Some curcumin analogues with different functional groups in the test activity in vitro and in vivo pharmacokinetics showed that stability the mono-carbonyl analogues and pharmacokinetic profile increased significantly [17]. Based on data screening, quantitative relationship structure reactivity, indicates that substituents which have electron-withdrawing properties in the benzene ring greatly affect the anti-inflammatory properties [33]. Substituents on the carbon atom number-4 on phenol group is the active compound curcumin analogues [32], in the same group also synthesized with different substituents and tested in vitro activity against tumor cells [32], active side of curcumin analogues that provide these results is phenolic and conjugated double bonds [8].

One way to increase the added value of kulit lawang oils is synthesize compounds curcumin analogues as anticancer drugs. Process technology anticancer drugs (curcumin analogues) through several stages of include safrole isolation from kulit lawang oils, safrole isomerization, oxidation and condensation. Safrole can be isolated from kulit lawang oils by using chemical and physical methods. Chemical method using NaOH [13, 20] while the physical method based on the difference in boiling point components. The principle of making isosafrole is isomerization; in which safrole will undergo structural changes due to the influence of the bases so it will happen shift double bond from straight chain approach towards benzene ring in conjugated position. Isomerization reaction mechanism via an intermediate (intermediate) is the formation of a carbocation which is the determinant of the rate of reaction, isomerization results are isosafrole with cis and trans isomers [13]. Safrole isomerization reactions generally use excess alkaline catalyst with process temperatures of 120oC for 6 hours [13] with a reaction without solvent. The oxidation process Isosafrole produces piperonal constitute alkene oxidation reaction, where the products are produced depending on the reaction conditions and the structure of the alkene used. Oxidation reactions performed using KMnO4 as an oxidizing agent in a two-phase system, that is water and the organic phase, then to increase reaction phase transfer catalyst added [20]. Phase transfer catalyst reaction takes place in two stages, the first stage of the transfer of the reactants from the normal phase to the second phase. The second step is the reactions between reactants are transferred to the second phase reactants and the reaction will run continuously until no more reactants to be transferred [21]. Oxidation of the double bond in alkenes dilute KMnO4 will produce diol and two OH groups on the diol compound is located on the same side. Diol formed is further oxidized to ketones, aldehydes or carboxylic acid [4]. In a very strong reaction conditions (75oC, 0.2 M KOH) KMnO4 can decide carbon-carbon double bond in alkenes [23]. This reaction is believed to pass through the formation of an intermediate glycol (1,2-diol) is oxidized further by breaking carbon-carbon bonds [24].

Synthesis of analogues curcumin product is a condensation reaction between two different carbonyl compounds known to the cross aldol condensation. This reactions involving aromatic aldehyde compounds and compounds alkyl or aryl ketone as a reactant known as reaction Claisen-Schmdt. Stages of aldol condensation reaction is divided into two phases: phase addition and dehydration [7]. Piperonal is an aromatic aldehyde compounds that can be reacted with carbonyl compounds other so as to produce curcumin analogues. Synthesis of analogues curcumin through condensation reaction between aromatic aldehydes with carboxylic acids to produce symmetrical [29, 33] and the process can be accelerated by using a microwave [5, 9]. In microwave heating, solvent and solvent particles are heated causing uneven heating [26]. The mechanism of microwave heating is dipolar polarization, interfacial polarization, and conduction mechanism [15].

2. Material and Methods

2.1. Material

Kulit lawang oils from Maluku-Indonesia, NaOH, KOH, $KMnO_4$, CH_3COOH, Na_2SO_4, H_2SO_4, Diethyl ether, petroleum ether, Dichloromethane, Methanol, Tween 80 (Brataco), acetone, and all other chemicals were purchased from Sigma Chemical Co. (USA).

2.2. Isolation Safrole

137.42 g kulit lawang oil was added 40 g of NaOH in 300 mL of aquades. The mixture was stirred to form two layers, and then the upper layer was separated. The bottom layer was extracted twice with 100 mL of petroleum ether and added to the top layer, then washed with distilled water until neutral and dried with Na_2SO_4 anhydrous. Petroleum ether was separated using evaporator and conducted distillation at reduced pressure. Product tested by gas chromatography, ^{1}H-NMR and IR.

2.3. Isomerization of Safrole

Into a three-neck flask 500 mL size that has been equipped with a magnetic stirrer, thermometer, cooling tube, blue silica gel and then added 71.56 g (0.44 mol) safrole and 50 g (0.89 mol) KOH. The mixture was refluxed at a temperature of 120 º for 6 hours, and cooled then added 250 mL of aquades and then extracted with diethyl ether. Results dried with Na_2SO_4 and diethyl ether separated using evaporator. Purification was performed using distilled under reduced pressure and purity was tested by GC, the structure was determined by FTIR and ^{1}H-NMR.

2.4. Synthesis of Piperonal

Into a 250 mL three-neck flask included 2,97g (0.02 mol) isosafrol, 100 mL aquades, 2 ml CH_3COOH, 15 ml H_2SO_4 50%, 100 mg twin 80 and 100 mL dichloromethane. Further 9.79 g (0.062 mol) $KMnO_4$ was added about 500 mg every

minute, the temperature is < 30 °C by placing in an ice bath. After $KMnO_4$ added, the flask is heated slowly at 40 °C until the purple color disappeared (15 minutes). The solution is cooled for a few minutes and precipitate MnO_2 filtered using silica gel. Separation of the resulting solution is then poured into a separating funnel and the layers separated. Water layer (upper layer) was extracted with dichloromethane (2 x 30 mL). All organic layers are combined, and then washed with 2 x 30 mL aquades. The organic layer was dried with Na_2SO_4, filtered and evaporated at the evaporator. The residue was added 20% NaOH solution and the mixture was stirred for 30 minutes. Furthermore, the mixture was extracted with dichloromethane, washed with aquades, dried with Na_2SO_4 anhydrous and evaporated back. Recrystallization performed using methanol, the results obtained were analyzed by GC, FTIR, and ^{1}H-NMR.

2.5. Synthesis of Analogues Curcumin by Microwaves Methods

15 g (0.1 mol) piperonal, 2.9 g (0.05 mol) acetone and 10 mL methanol included in Erlenmeyer. The mixture was stirred and included 5 mL of 10% NaOH. The mixture was stirred and put in the microwave at power 140 watts for 2 minutes. The residue was washed with methanol, filtered, and the results were analyzed.

2.6. Synthesis of Analogues Curcumin by Conventional Methods

15 g (0.1 mol) piperonal, 2.9 g (0.05 mol) acetone and 10 mL methanol included in beaker. The mixture was stirred and included 5 mL of 10% NaOH. The mixture was stirred for 3 hours at a temperature of 25 ^{o}C, the residue was washed with methanol, filtered, and the results were analyzed.

3. Results and Discussion

3.1. Isolation Safrole

Safrole can be separated from kulit lawang oils by using NaOH. Eugenol and other phenolic components will react with NaOH to form water-soluble salts and formed two layers that can be separated, safrole layer which is not soluble in water are at the top of the mixture. Safrole was then purified using fractionation distills at pressure reduction. In Fraction 2 at temperatures 90-123 ° C / 1 mmHg obtained safrole with yield 19.30%. The properties of the resulting safrole is a clear liquid form, fragrant, insoluble in water but soluble in ethanol, chloroform and ether. Safrole analysis using gas chromatography obtained with a purity of 89.186% safrole. Infrared spectrum of safrole shows absorption bands in the region 3000-2800 cm^{-1} which is the absorption C_{sp3}-H, this was confirmed by the appearance of absorption at 1442.7 cm^{-1} for -CH_2- (methylene). Uptake range of C=C aromatic absorptions appeared at 1608.5 cm^{-1} and is supported by absorption at 3150-3000 cm^{-1} which is the absorption band for =C_{sp2}-H (aromatic). Absorption band at 1247.9 cm^{-1} region and 1041.5 cm^{-1} shows the range of C-O-C (ether) supported by each tape 916.1 cm^{-1} and 808,1cm^{-1}. Analysis and interpretation safrole ^{1}H-NMR spectrum of 60 MHz (δ: ppm) are as follows; δ = 3.2 ppm (d, -CH_2-), δ = 5.0 ppm (d =CH_2), δ = 5.5 to 6.2 ppm (m, = CH-), δ = 5.9 ppm (s, -O-CH_2-O-), δ = 6.8 ppm (m, 3H Ar). Safrole analysis using mass spectrum gives the following description, (m / z): 39, 51, 63, 77, 91, 104, 119, 131, and 162 $[C_{10}H_{10}O_2]^+$ (base peak).

3.2. Isomerization of Safrole

Safrole isomerization into isosafrol can be carried on without solvent system using KOH at 120 °C for 8 hours and obtained yield 77.56%. The properties of the resulting isosafrole is light yellow viscous liquid and fragrant. Analysis using gas chromatography obtained *cis*-isosafrol the 3rd peak with a retention time of 3.375 minutes (15.40%) and *trans*-isosafrole the peak-to-5 with a retention time of 3.700 minutes (69.34%).

Infrared spectrum of isosafrole showed absorption at area 3000-2800 cm^{-1} which is C_{sp3}-H absorption. Absorption range of C = C aromatic appeared at 1608.5 cm^{-1}. Absorption band C_{sp2}-H (aromatic) appears in the area 3150-3000 cm^{-1}, this conclusion is supported by the presence of sharp band with moderate strength at 1490.9 cm^{-1}. Absorption at 1247.9 to 1091.6 cm^{-1} shows the range of the C-O-C. Analysis by ^{1}H-NMR-60 MHz (δ: ppm) are as follows; δ = 1.8 ppm (d, -CH_2), δ = 5.9 ppm (s, -O-CH_2-O-), δ = 6.3 ppm (d, -CH =), δ = 6.7 - 6.9 ppm (d, H Ar).

3.3. Synthesis of Piperonal

Piperonal properties produced in the form of white crystals and fragrant, insoluble in water but soluble in methanol (mp = 56-57 ° C). The results obtained by recrystallization using methanol piperonal to yield 65.63%. Infrared spectrum of piperonal obtained their range C=C aromatic appearing on uptake 1604.7 cm^{-1} is supported by absorption above 3000 cm^{-1} as absorption C_{sp2}-H (aromatic). Absorption area between 3000-2800 cm^{-1} which indicates the absorption C_{sp3}-H are reinforced by the presence of absorption 1448.9 cm^{-1} and 1357.8 cm^{-1} for methylene group (-CH_2-). Aldehyde group is shown by the presence of a weak absorption in the area twins 2711.7 cm^{-1} and 2781.2 cm^{-1} which is very typical for aldehyde compound. This was confirmed by uptake 1689.5 cm^{-1} which shows the carbonyl group. Absorption band 1249.8 cm^{-1}, 1099.3 cm^{-1} and 1037.6 cm^{-1} shows the compound ether (C-O-C). The loss of a double bond isosafrole characterized by loss of absorption areas at 962.4 cm-1.

Analysis by ^{1}H-NMR piperonal yield spectrum with the following peaks (δ: ppm); δ = 5.9 ppm (d, -O-CH_2-O-), δ = 6.9 ppm (d, 1H Ar), δ = 7.2 ppm (d, 2H Ar), δ = 9.9 ppm (d, CH = O). Hints of the data 1H-NMR is a powerful clue oxidation of the double bond isosafrole is δ = 9.9 ppm peak which is the aldehyde proton unprotected because the induction effect of the carbonyl oxygen atom which is electronegative.

3.4. Synthesis of Analogues Curcumin (1,5-Bis-benzo[1,3]dioxol-5-yl-penta-1,4-dien-3-one)

Product condensation piperonal with acetone obtained yellow crystals for both methods, but the product by conventional methods have greater yield when compared with microwave method is 78.43 % (mp = 191 °C) and 53.3 % (mp = 180 °C). Condensation reaction using conventional methods to produce analog of curcumin better. In terms of reaction time, the microwave method is better but has a weakness for volatile solvents, in this case methanol. Heating by using microwaves can increase the reaction rate of 10 to 1000 times if compared to conventional heating [27]. On heating by microwaves, the solvent will reach a boiling point very quickly and superheating events, namely the achievement of a higher boiling point rather than the actual boiling point when compared to conventional heating. Therefore, the time required for the reaction becomes shorter, because the solvent molecules are located between reactant molecules experience a temperature increase dramatically and will create a much faster reaction.

The synthesis of analogues of curcumin used basic catalysts is NaOH, because under alkaline conditions will form the enolate anion is more reactive than the enol form produced by the acid catalyst. Analogues curcumin 1,5-Bis-benzo [1,3] dioxol-5-yl-penta-1,4-dien-3-one can be obtained by condensation of acetone with two equivalent piperonal. The reaction begins with hydroxide ions in NaOH removes a proton from the carbon α the acetone molecules to form an enolate ion. Enolate ions will act as the nucleophilic in addition reaction with piperonal molecules produce an alkoxide ion. Alkoxide ion will accept a proton from water to form aldol [24]. The mechanism of the reaction between piperonal, acetone, and NaOH is estimated as follows:

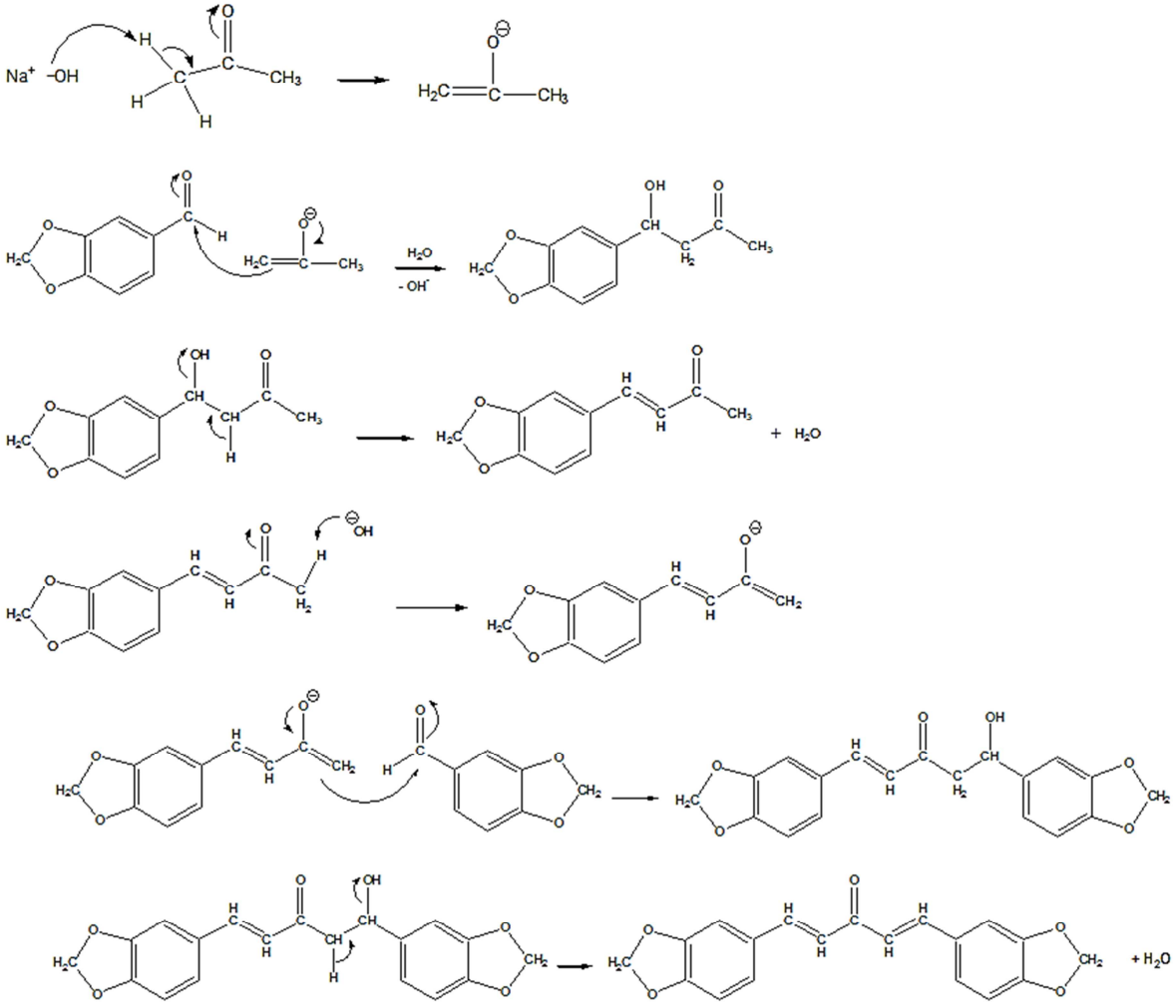

Figure 1. *Mechanism Reaction Synthesis of analogues curcumin (1,5-Bis-benzo[1,3]dioxol-5-yl-penta-1,4-dien-3-one).*

The results of identification using LC-ESI MS to conventional methods obtained product at a retention time 3:38 minutes (Figure 2) and to methods of microwave tR = 2.98 min (Figure 3). The value of m / z molecular ion and ion fragments of curcumin analogues with conventional methods were detected for the $[M]^+ = 323$; [M+Na] = 345; [2M+Na] = 667; [3M+Na] = 990 (Figure 4). The value of m / z molecular ion and ion fragments of curcumin analogues with micro wave method were detected for the $[M]^+ = 323$; [M + Na] = 345; [2M + Na] = 667; $[3M + Na]^+ = 991$ (Figure 5). From these data it can be concluded that the obtained target compound with a molecular weight of 322 g / mol.

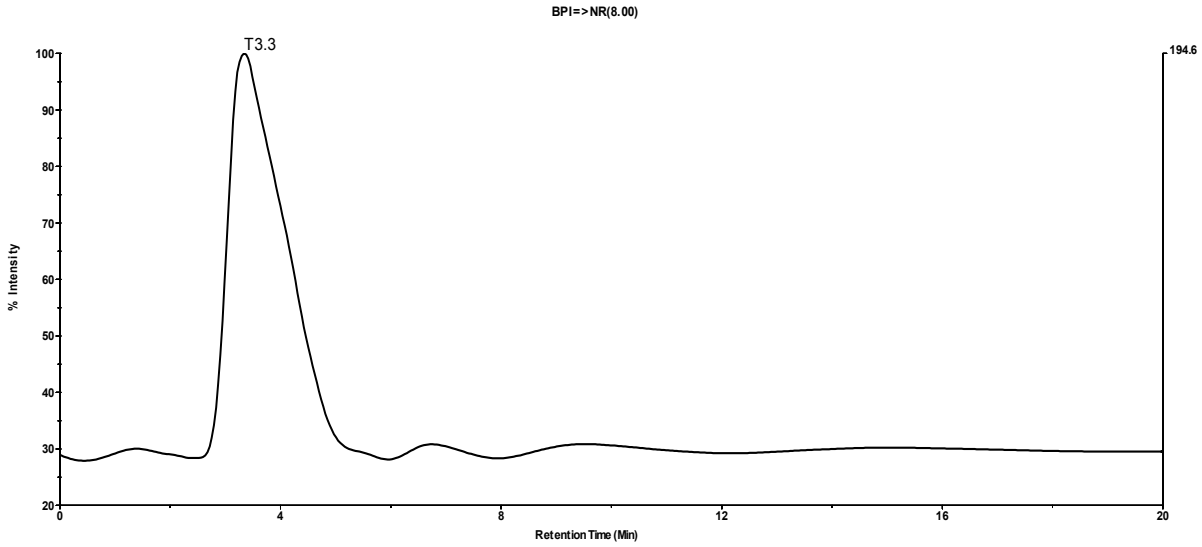

Figure 2. *Retention time conventional methods.*

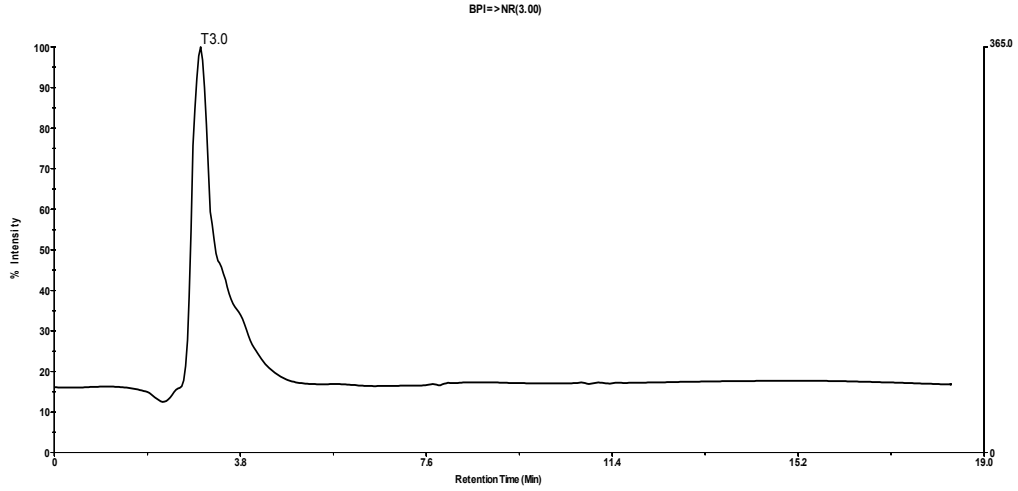

Figure 3. *Retention time microwaves methods.*

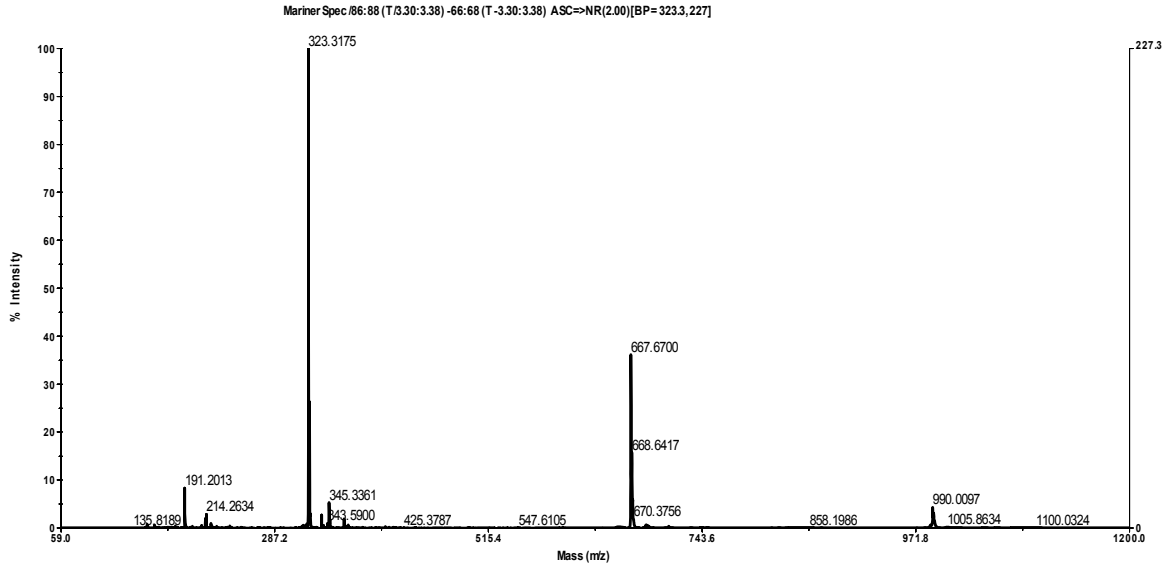

Figure 4. *Spectrum MS conventional methods.*

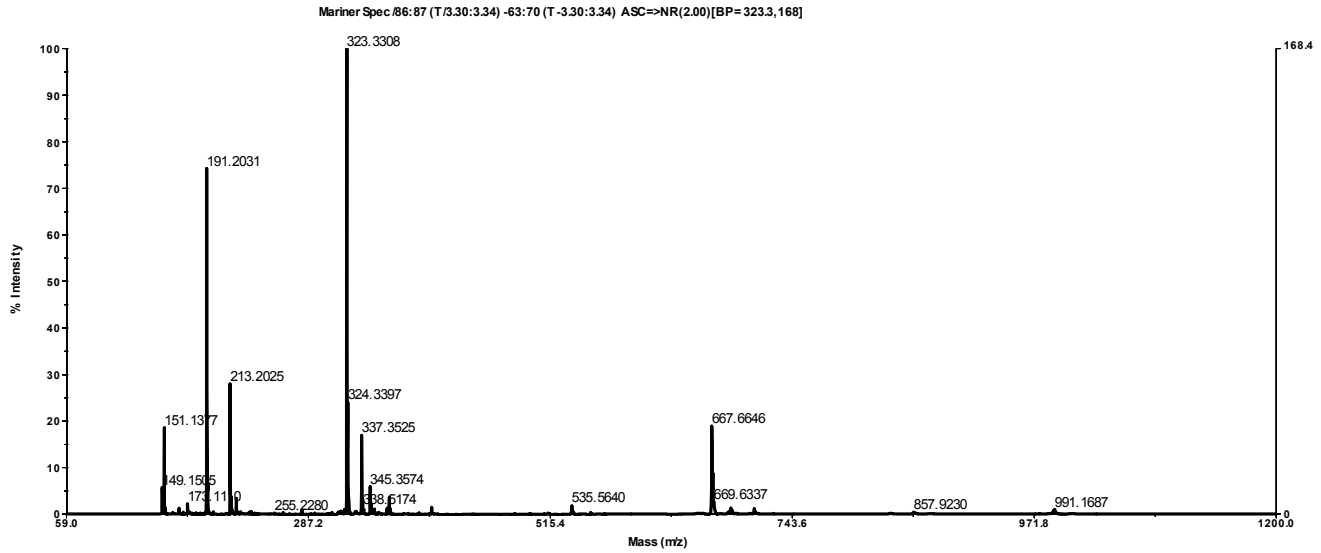

Figure 5. *Spectrum MS microwaves methods.*

4. Conclusions

Curcumin analogues (1,5-Bis-benzo [1,3] dioxol-5-yl-penta-1,4-dien-3-one) can be synthesized using precursor piperonal and acetone under alkaline conditions using conventional method (78.43%) and microwave (53.3%). The solvent used in the condensation process greatly affect yield results. Precursor piperonal obtained from the oxidation reaction isosafrole using $KMnO_4$ generate yield 65.63%. Purification using silica gel and climate control in the oxidation process may increase yield results. Isosafrol results isomerization without using a solvent to produce yield of 77.56%. Safrole isolated from kulit lawang oils using alkaline extraction method produce yield of 19.3%. Percent alkaline were added for the extraction must be proportional to the eugenol percent contained in the oil.

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