Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2018, 10(4): 1-9

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Synthesis and Antioxidant Activity of Curcumin Analogues

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ABSTRACT

A study was performed to synthesize curcumin analogues compounds having -Cl group in the aromatic ring, i.e. 2,5-bis(5'-chloro-4'-hydroxy-3'-methoxybenzylidene)cyclopentanone (CHMBC) and 2,5–bis(3'–chloro–4'–hydroxybenzylidene)cyclopentanone (CHBC). These compounds were synthesized by condensation reaction. The purity of the synthesized compounds were determined based on melting point, chromatogram of TLC and HPLC. The structure of CHMBC was characterized by UV-Vis spectrophotometric, IR, ^{1}H-NMR, ^{13}C-NMR and GC-MS. While CHBC was characterized by UV-Vis spectrophotometric, IR, ^{1}H-NMR, and LC-MS. These compounds were tested for their antioxidant activity. The curcumin analogues compounds were poten as an antioxidant.

Keywords: Curcumin analogues; Antioxidant; DPPH; β-carotene bleaching

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INTRODUCTION

Turmeric (*Curcuma longa* L.) has been used as a spice in the foods in Asian countries. Turmeric is used as food coloring agents and preservatives. Turmeric is also used as antidiarrhea, carminative and colagoga. The mayor components contained in turmeric is curcumin (Figure 1a). Curcumin is the yellow pigment, a derivative of polyphenols, which can be obtained by isolation from rhizome of turmeric from familia of Zingiberaceae [1]. Curcumin has a variety of biological activities, including as antioxidant [2]. The antioxidant activity of curcumin is directly related to the phenolic group [3]. Other researchers suggested that the structure responsible for the antioxidant activity of curcumin is a β-diketone group. The existence of hydrogen radical donor from a hydrogen atom of β-diketone group against radical lipid peroxidation is a potential as an antioxidant [4]. Curcumin also have activity as an antiinflammatory [5], anticarcinogenic [6], immunomodulator [7], antiviral [8,9], antiulcer [10] and anticancer [11,12]. In addition, curcumin also have activity as antimutagen, antibacterial, antifungal, antiprotozoal, antihypertensives, antihiperkolesterol [13]. Curcumin is an antiinflammatory and anticancer through the mechanism of antioxidant and prooxidant [14]. Based on the results of these studies, curcumin has broad activity. Therefore, it is important to develop curcumin through modification of its structure by synthesis.

Modification of the structure of curcumin can performed by changing the groups on the aromatic ring and methylene diketone. One of the compounds that resulting from the modification of curcumin is 2,5-bis(4-hydroxy-3-methoxybenzylidene)cyclopentanone. This compound is modified by changing diketone group of curcumin with cyclopentanone. This compounds known as Pentagammavunon-0 (Figure 1b) and has been studied its activity as an antioxidant [15], antiinflammatory and antibacterial [16]. Another modification of curcumin made by changing -OCH_3 group in the aromatic ring with -Cl. One of the compounds that modified in this group is 2,5-bis(3,5-dichloro-4-methoxybenzylidene)cyclopentanone. The replacement of -Cl group with -OCH_3 resulted in the loss of an antioxidant activity, but still potent as antibacterial [16]. The knowledge about the relationship between structure and antioxidant activity of curcumin and its analogues, is an interesting study.

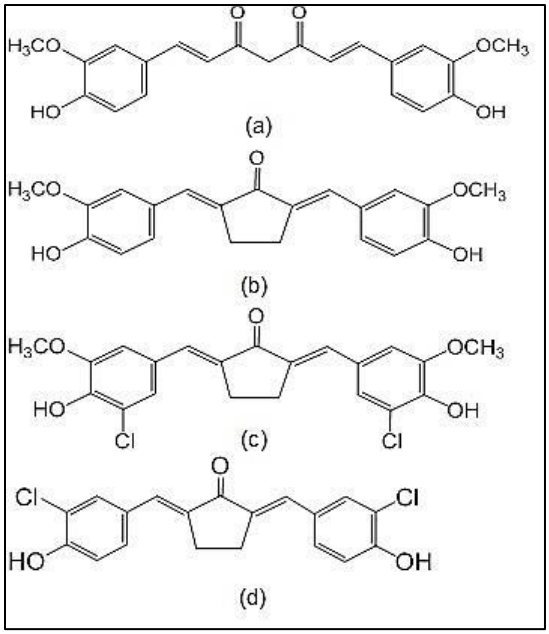


Figure 1: Structures of Curcumin(a), PGV-0 (b), CHMBC (c), CHBC (d)

This study aims to obtain curcumin analogues compound namely 2,5-*bis*(5'-chloro-4'-hydroxy-3'-methoxybenzylidene)cyclopentanone (CHMBC, Figure 1c) and 2,5-*bis*(3'-chloro-4'-hydroxybenzylidene)cyclopentanone (CHBC, Figure 1d) by condensation reaction. The curcumin analogues synthesized were subjected to in vitro antioxidant activity test.

EXPERIMENTAL SECTION

Materials

Curcumin, linoleic acid, β–carotene and 2,2-diphenyl-1-picrylhydrazyl (DPPH) were purchased from Sigma (Aldrich.Co, USA). 5-chloro-4-hydroxy-3-methoxybenzaldehyde and 3-chloro-4-hydroxybenzaldehyde were synthesized that previously reported [17,18]. Pentagammavunon-0 (PGV-0) were synthesized by researcher. HCl (37%), H_2SO_4, tetrahydrofuran (THF), $AlCl_3$, acetone and cyclopentanone pro synthesis were purchased from E. Merck (Darmstat, Germany). Oxygenated deionized water was purchased from Pharmacy M24, Yogyakarta, Indonesia. All of the reagents used in the experiments were of adequate analytical grade.

Synthesis of CHMBC

The 5-chloro-4-hydroxy-3-methoxybenzaldehyde (0.5 g, 2.68 mmol) was taken in 3.0 mL of THF, followed by the addition of cyclopentanone (0.24 mL, 2.68 mmol). The mixture was stirred, and added with 83 µL of HCl. The stirring processed was continued for 4 hours. The reaction mixture was allowed to stand for 6 days at room temperature without stirring. The product was isolated by washing with 20 mL of cold alcohol to obtain a green-yellow crystal. The crystal was neutralised by the addition of 400 mL cold distilled water. The compound of CHMBC was purified by recrystallization using a solvent mixture of acetone-dichloromethane (1: 1). The product of synthesis was analyzed by thin layer chromatography (TLC) on silica gel plates 60 F_{254} and 1,4-dioxana-methanol (5:8); 1,4-dioxan-methanol (1:1); ethyl acetate-CCl_4 (5:3) etil asetat-CCl_4 (1:1) as a mobile phase.

Synthesis of CHBC

The 3–chloro–4–hydroxybenzaldehyde (0.3 g, 1.92 mmol) was taken in 1.0 mL of THF, followed by the addition of cyclopentanone (0.085 mL, 0.96 mmol). The mixture was stirred, and added with 59 µL of HCl. The stirring processed was continued for 4 hours. The reaction mixture was allowed to stand for 7 days at room temperature without stirring. The product was isolated by washing with 30 mL of cold alcohol to obtain a green-yellow crystal. The crystal was neutralised by the addition of 25 mL cold distilled water. The compound of CHBC was purified by the addition with 8 mL of acetone. Then the mixture was heated on the waterbath. The product of synthesis was

analyzed by thin layer chromatography (TLC) on silica gel plates 60 F_{254}. The mobile phase were ethyl acetate-CCL_4 (5:2) and ethyl acetate-CCL_4 (4:5).

Characterization

The structure of the synthesized compound were characterized using a Perkin Elmer infrared spektrofotometer and a JEOL JNM-ECA 500 spektrofotometer nuclear magnetic resonance. The analysis for carbon of CHMBC was carried out on a ^{13}C-NMR JEOL spektrofotometer nuclear magnetic resonance. The mass of CHMBC was recorded on a QP2010S SHIMADZU gas chromatography mass spectrometry, while CHMBC on a LC-MS mass spectrometry. The purity of these compounds were analysis with a SPD-10A VP Shimadzu high performance liquid chromatography that carried out on a reverse phase C-18 column with methanol as the mobile phase. In addition, the compounds were analysis by TLC and Büchi melting point. The 1800 Shimadzu UV-Vis spectrophotometer was used to recorde the spectra of these compounds.

Antioxidant Activity by β-Carotene Bleaching Method

Antioxidant assay using β-carotene bleaching method was performed according to the procedure that previously reported [19]. A series of concentration of the CHMBC, namely 5, 10, 25, 50 and 100 μM, while CHBC 10, 30, 60, 80 and 100 μM (in ethanol). The activity of the samples were compared with curcumin and PGV-0 with the same concentration to the CHMBC. The β-carotene and linoleic acid emulsion were made by mixing 2 mL of β-carotene (1 mg/mL in chloroform), 30 mg of linoleic acid and 190 mL of Tween 80. The mixture was homogenized to form an emulsion, and then the chloroform was evaporated. The residue was dissolved in 60 mL of oxygenated deionized water (<2 ppm) and the solution was vortexed using ultrasonicator for 4 minutes. Aliquots (2.0 mL) of the β-carotene and linoleic acid emulsion were mixed with 0.2 mL of each concentration series of the sample. Then the mixtures were incubated in a waterbath at 50ºC for 0 and 60 minutes. The absorbance of the emulsions were measured with a UV-Vis spectrophotometer at λ of 450 nm against the blank containing 2.0 mL emulsion of linoleic acid, without β-carotene, and 0.2 mL of the appropriate of sample concentration. For the control solution, 2.0 mL of β-carotene and linoleic acid emulsion was taken and added with 0.2 mL of ethanol. Then this mixtures were incubated at 50ºC for 0 and 60 minutes. The percentage of antioxidant activity was calculated according to the following equation:

$$\% \text{ Antioxidant } = 100 \text{ x } \left[\frac{\text{DRc} - \text{DRs}}{\text{DRc}}\right]$$

Where DRc is degradation rate of control, calculated from ln (a/b)/60; DRs is degradation rate of sample, calculated from (a/b)/60; a and b are absorbance at 0 and 60 minutes. Then, % antioxidant were converted to probit values. Antioxidant activity in this method was also expressed as inhibition concentration (IC_{50}).

Antioxidant Activity by DPPH$^{\cdot}$ Method

Antioxidant assay with radical scavenging activity was determined using stable 2,2-diphenyl-1-pycrylhydrazyl (DPPH) free radical, according to the procedure that previously reported [20]. A series of concentration of the samples 25.000; 50.000; 100.000; 150.000 and 200.000 μM (in methanol) were prepared. A 1.0 mL of each series of the solution was taken and added with 1.0 mL of DPPH (0.15 mM). The mixture was homogenized and allowed to stand in the dark for ± 1.5 hours. Then the absorbance were measured with UV-Vis spectrophotometer at λ of 517 nm against the blank containing 1.0 mL each series of sample solution and 1.0 mL of methanol. The absorbance of control was also being measured (1.0 mL of 0.15 mM DPPH and 1.0 mL of methanol). PGV-0 and curcumin were used as a reference. The concentrations of PGV-0 used were 3.125; 6.250; 12.500; 25.000 and 50.000 μM (in methanol) and those of curcumin are 2.500; 5.000; 10.000; 20.000 and 40.000 μM (in methanol). The inhibition percentage of the DPPH radical (% inhibition DPPH) was calculated according to the following equation:

$$\% \text{ Inhibition DPPH} = \left(\frac{\text{Absorbance of control} - \text{Absorbance of sample}}{\text{Absorbance of control}}\right) \text{ x } 100\ \%$$

Then, % inhibition of DPPH radical was converted to probit values. Antioxidant activity was also expressed as inhibitory concentration (IC_{50}).

Statistical Analysis

All the experiment were repeated three times. The data were calculated as means ± SD. The data of all the assays were analysed by one way ANOVA with significance of 95 % using software SPSS 12. The analysis was followed by t-test to determine weather the mean of a variable differed between the samples. A value of $P < 0.05$ was considered statistically significant.

RESULT AND DISCUSSION

Synthesis of CHMBC and CHBC

The compound of CHMBC was resulted from the condensation reactions between 5-chloro-4-hydroxy-3-methoxybenzaldehyde with cyclopentanone, while CHBC between 3-chloro-4-hydroxybenzaldehyde with cyclopentanone. Carbonyl group of cyclopentanone was protonated in acid condition to form enol. The enol is acts as a nucleophile, then attached to a carbonyl group of electrophilic from 5-chloro-4-hydroxy-3-methoxybenzaldehyde, so 3-chloro-4-hydroxybenzaldehyde with cyclopentanone. The condensation of the two carbonyl compounds were produced a β-hydroxybonyl as an intermediate. Then, the β-hydroxycarbonyl compounds were dehydrated to form α, β-unsaturated. Dehydration of β-hydroxycarbonyl compounds were easy due to the presence of α-proton positions to carbonyl that removable. The reactions are shown in Figure 2. While the physical data of synthesized compounds are shown in Table 1.

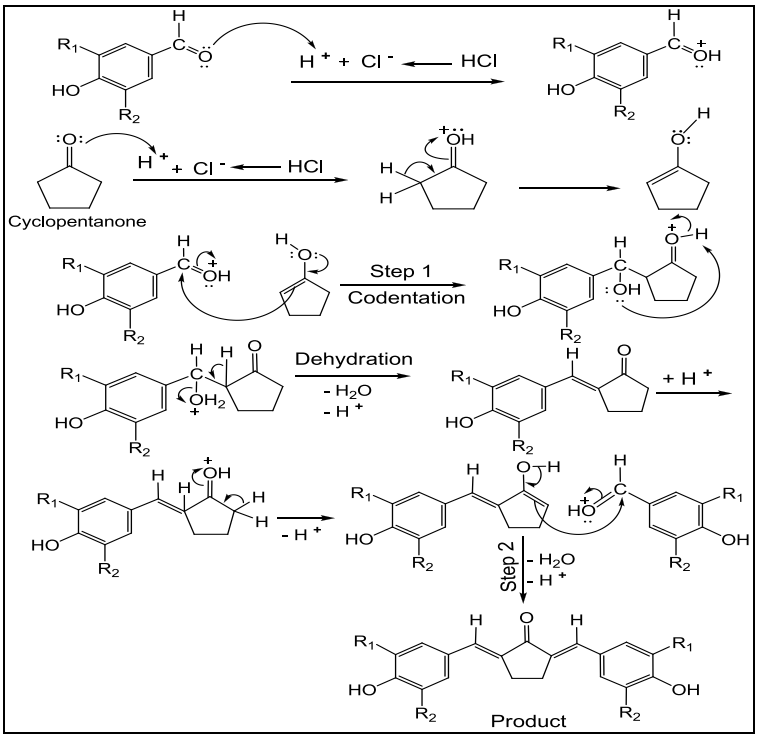


Figure 2: The Mecanism Reaction of Synthesis

Table 1: Physical Data of Synthesized Compounds

Compounds	R1	R2	Colour	Formula, MW	% Yield	Melting Point/°C
CHMBC	OCH3	Cl	Yellowish-green 	$C_{21}H_{18}O_5Cl_2$	49.77	268.0-270.0
CHBC	Cl	H	Yellow-dimly green 	$C_{19}H_{14}O_3Cl_2$	38.13	280.0-284.0

The melting distance of the synthesized compound were 2-4 ºC. Its show that the products were pure. The purity of these compounds were determined based on the results of the analysis using TLC with various mobile phases in different comparisons. The mobile phase were mixture of two kinds of solvents in different comparisons that resulting in spot of top, middle and bottom. The results of this analysis were obtained a single spot and the Rf different with starting material. Its show that the synthesis were successfully and the product pure (Table 2). The purity of the products also based on chromatogram of HPLC analysis. The HPLC analysis at a flow rate of 0.75/min obtained single chromatogram, indicating that the synthesized products were pure.

Table 2: The TLC analysis of Synthesized Compounds read on UV_{254} lamp

	Rf	
Mobile Phase	**Starting Material**	**CHMBC**
1,4-Dioxane-methanol (5:8)	0.75	0.8
1,4-Dioxane-methanol (1:1)	0.65	0.73
Ethyl acetate-CCl_4 (5:3)	0.61	0.54
Ethyl acetate-CCl_4 (1:1)	0.5	0.35
	Starting Material	**CHBC**
Ethyl acetate-CCl_4 (5:2)	0.65	0.63
Ethyl acetate-CCl_4 (4:5)	0.6	0.49

UV-Vis Spectroscopy

Spectrophotometric analysis of the products were resulted 3 peaks for CHMBC and 4 peaks for CHBC. The maximum absorbance synthesized products were longer than their starting materials (5-chloro-4-hydroxy-3-methoxybenzaldehyde and 3-chloro-4-hydroxybenzaldehyde) [17,18]. The UV-Vis spectrophotometric spectrum of Synthesized Compounds is shown in Table 3.

Table 3: The UV-Vis Spectroscopy analysis of Synthesized Compounds

Peak Number	Wavelength (nm) CHMBC	Wavelength (nm) CHBC
1	402.8	390.6
2	345.8	265
3	256.7	260.8
4		253.8

Infrared Spectroscopy

Infrared (IR) spectrum of the synthesized compounds showed no peaks at around 2850 and 2750 cm^{-1}, indicating the absence of the aldehyde group and can be used as an indicated that the products were pure. In addition, there were medium intensity peak at 1622.7 (CHMBC) and 1680.2 (CHBC) cm^{-1}, originating from C=O stretching vibration of conjugated group. The existence of the group C=O reinforced with peak at wave number of 1302.6 (CHMBC) and 1361.7 (CHBC) cm^{-1}, showed stretching of C–CO–C group. IR spectrum of CHMBC is shown in Table 4.

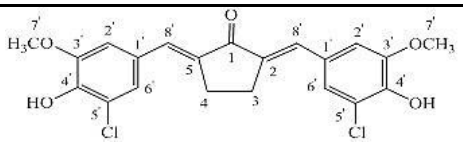
Table 4: The Analysis of IR Spectrum from Synthesized Compounds

Fungtional Groups	Wavenumber (cm^{-1})		Intensity
	CHMBC	**CHBC**	
OH Stretching	3521.4	3465.8	Medium
C–O	1049.1	1052.7	Medium
C–H aliphatic stretching	2374.6; 2345.1	-	Weak
C–H methyl bending and C–H methylene scissoring	1449.3	1413	Strong
C=O stretching conjugated	1622.7	1680.2	Medium
C–CO–C stretching	1302.6	1361.7	Medium
C=C aromatic stretching	1595.1; 1503,9	1595.1; 1499.7	Medium; Strong and Sharp
C–Cl aromatic	1254.4; 1185.6	1255.5; 1168.1	Sharp; Strong and Wide
C–H aromatic bending, in the field	1285.7	1185.4	Strong
Aromatic tetrasubstitution	856.7	994.8	Medium
=C–H aromatic bending, exit field	669.1	699.5	Weak

^{1}H-NMR and ^{13}C-NMR Spectroscopy

Identification of the synthesized products (CHMBC, CHMBC) using ^{1}H-NMR analysis (500 MHz, DMSO-d6) and ^{13}C-NMR (125 MHz, DMSO-*d*6) is presented in Table 5 and 6, respectively.

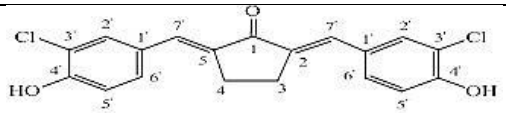
Table 5: The Analysis of ^{1}H-NMR and ^{13}C-NMR Spectra from CHMBC



Number of proton/ carbon	^{1}H-NMR			^{13}C-NMR	
	δ H (ppm)	Signal	Integration	δ C (ppm)	Abundance
1				194.7577	0.04 (1 C)
2 & 5				144.3477	0.11 (2 C)
3 & 4	3.0811	Singlet	2.053 (4 H)	25.7578	0.11 (2 C)
1’				127.0929	0.10 (2 C)
2’	7.3038; J = 1.95	Dublet	1.056 (2 H)	112.8522	0.11 (2 C)
3’				148.5827	0.12 (2 C)
4’				136.097	0.12 (2 C)
5’				124.26	0.11 (2 C)
6’	7.2577; J = 1.95	Dublet	1.071 (2 H)	120.2062	0.09 (2 C)
7’	3.8969	Singlet	3.000 (6 H)	56.2231	0.15 (2 C)
8’	7.3459	Singlet	1.021 (2 H)	131.7762	0.11 (2 C)

There is a signal dublet from CHMBC at chemical shift (δ) of 7,3038 dan 7,2577 ppm show that the present of 2 H from $H_{2'}$ and H from $H_{6'}$. It show that hydrogens in this compound were interaction of each other, namely *meta* coupling. Another signal appear at δ 3,8969 and 3,0811 ppm. It show that the present of protons from -OCH_3 and $H_2C–CH_2$ (cyclopentane). The protons in the ring of benzene from CHBC not equivalen, therefore there are tree proton area that different. Two protons (2H from $H_{2'}$) appear dublet of dublet, so interaction of each other, namely *meta* coupling (mc) with protons of $H_{6'}$ and *para* coupling (pc) with protons of $H_{5'}$. Two protons (2H from $H_{5'}$) appear dublet of dublet, so interaction of each other, namely *ortho* coupling (oc) with protons of $H_{6'}$ and *para* coupling with protons of $H_{2'}$. Two protons (2H from $H_{6'}$) appear dublet of dublet too, there is interaction of each other, namely *ortho* coupling with protons of $H_{5'}$ and *meta* coupling with protons of $H_{2'}$. Two area of protons are signal singlet that come from α,β-unsaturated and cyclopentane.

Table 6: The analysis of ^{1}H-NMR spectra from CHBC



Number of proton	δ H (ppm)	Signal	Integration
2 H from $H_{7'}$	73,613	Singlet	1,022
2 H from $H_{2'}$	7,1356; *J* = 1,95; mc	Dublet of dublet	1,572
2 H from $H_{5'}$	6,9664; *J* = 6,45; oc	Dublet of dublet	1,000
2 H from $H_{6'}$	7,5403; *J* = 8,40; oc	Dublet of dublet	1,597
	J = 1,95; mc		
4 H from H_3 and H_4	31,353	Singlet	2,308

Mass Spectrometry

The analysis of CHMBC using GC-MS (EI-MS) obtained molecular ions and fragmentation at m/z 404 ($M^{+\bullet}$base peak), 385 , 370 , 352 , 196 and 192 (Figure 3). While CHBC was analysis by LC-MS (ESI-MS). Based on thus analysis, the molecular weight of CHBC are 360.91 and 363.65. It show that this compound is isotop (Figure 4). The fragmentation of ESI-MS analysis this compound is shown in Table 7. Based on the results of spectroscopic studies (UV-Vis, IR, ^{1}H-NMR, ^{13}C-NMR) and mass spectrometry (GC-MS, LC-MS), the synthesized compounds corresponds to structure of CHMBC and CHBC.

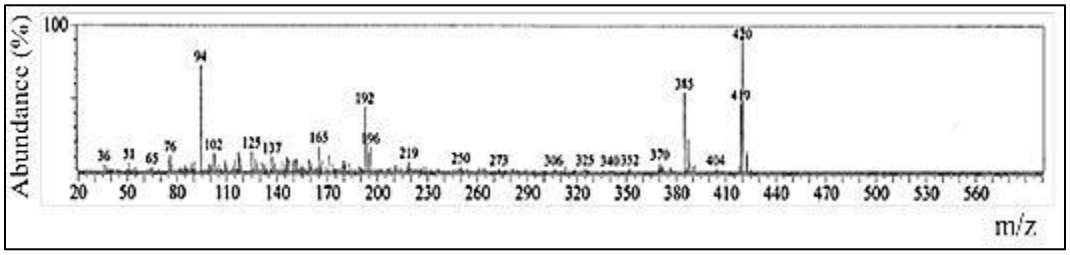


Figure 3: The Mass spectrum of CHMBC

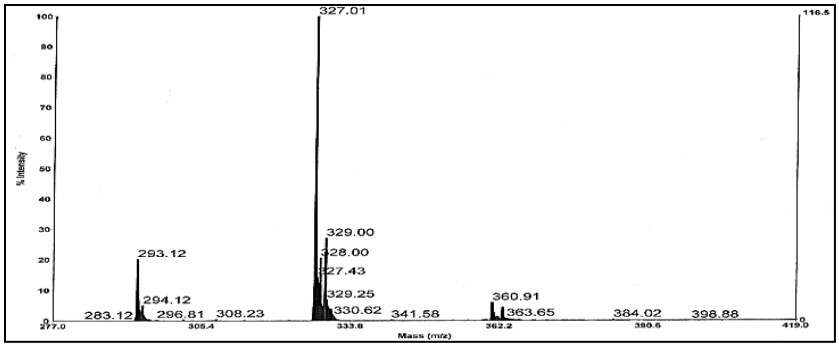


Figure 4: The Mass spectrum of CHBC

Table 7: The Fragmentation of ESI-MS Analysis from CHBC

Positive Ionisation		Negative Ionisation	
Ions/Fragments	**m/z**	**Ions/Fragments**	**m/z**
M [Cl^{35}]	360,91	[M – H – Cl^{37} – OH]$^-$	308,23
M [Cl^{37}]	363,65	[M – H – 2 O – Cl^{35}]$^-$	293,12
[M + H + Na]	384,02		
[M + H – Cl^{35}]$^+$	329,00		
[M + H – Cl^{37}]$^+$	327,01 (base peak)		

Antioxidant Activity by β-Carotene Bleaching Method

The β-carotene bleaching method is based on inhibition percentage of the linoleic acid radical. The reaction starts with the formation of linoleic acid radical, which initiated by oxygenated deionized water. Then, free radical degrade β-carotene. The sample which have antioxidant power will neutralize this free radical by donating an electron, so that it prevents degradation of β-carotene. The samples undergo resonance after donated its electron and forming a complex with linoleic acid radical, so that it was stable. The mecanism of sample as an antioxidant is following reaction of vitamin E with free radical DPPH [21]. The reaction mecanism of antioxidant by β-carotene bleaching method is shown in Figure 5.

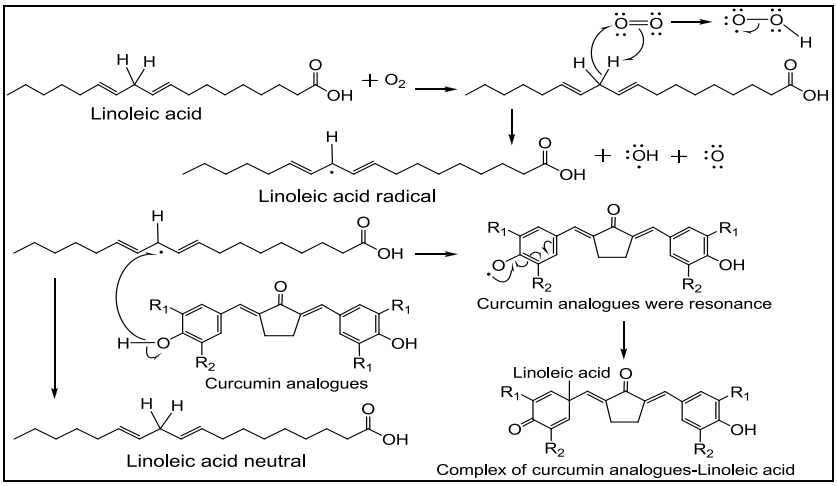


Figure 5: Antioxidant Reaction Mecanism by β-Carotene Bleaching Method

It can be seen that an increase in absorbance of the solution corresponds to the increasing concentration of sample; after beeing incubated for 60 minutes compared 0 menit (Figure 6). It showed that the samples potential as an antioxidant. The antioxidant power of CHMBC was higher, than curcumin and PGV-0 (Table 8). While the antioxidant power of CHBC was lower than curcumin and PGV-0. The antioxidant power of CHMBC was higher than CHBC. The IC_{50} of CHMBC, CHBC, PGV-0 and curcumin were significantly different from each other (P value < 0.05). The molecular of CHMBC was larger than that of CHBC, PGV–0 and curcumin. The compound with a large molecular, is easier to scavenge free radical of linoleic acid.

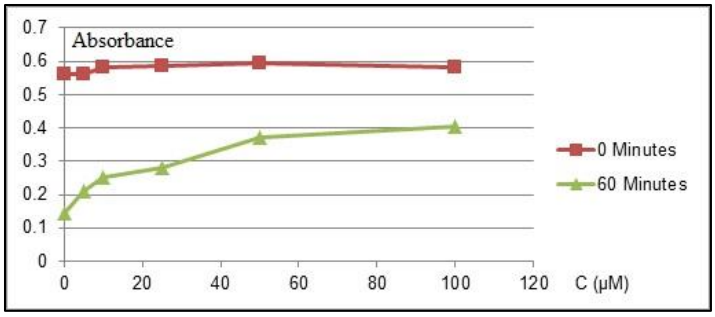


Figure 6: The Absorbance of CHMBC after Incubated of 0 and 60 Minute

Antioxidant Activity by DPPH· Method

The antioxidant activity of samples are also determined by DPPH assay. This method was based on the measurement of the lost of the violet color of the DPPH radical after reaction with samples. The antioxidant potency of CHMBC and CHBC were lower than that of PGV-0 and curcumin (Table 8).

Table 8: Antioxidant Properties of CHMBC, CHBC, PGV–0 and Curcumin

Name	DPPH Assay Mean of IC50 ± SD (µM)	β–carotene Bleaching Method Mean of IC50 ± SD (µM)
CHMBC	177.03 ± 0.17	38.27 ± 1.36
CHBC	176.42 ± 2.52	176.69 ± 0.52
PGV-0	32.54 ± 0.84	48.74 ± 0.52
Curcumin	19.09 ± 0.04	42.29 ± 0.70

The IC_{50} of CHMBC, CHBC, PGV-0 and curcumin were significantly different from each other ($p = 0.000 < 0.05$). The functional groups of CHMBC is more bulky than PGV–0 and curcumin. Thus it would be more difficult to donate electron to the free radical DPPH compared with PGV-0 and curcumin. In addition, the compound of CHMBC and CHBC contains -Cl group. It is a strong electron withdrawing group. The existence of electrons drawn out (negative induction by -Cl group) was reduced electron density around the OH group, so the donation of electrons to free radical DPPH also reduced. As a result, the antioxidant powers were also lower than PGV-0 and curcumin that without -Cl group. The reaction mechanism of antioxidant with DPPH assay is following reaction of vitamin E to the DPPH [21]. The samples donate electron to DPPH and forming radical species. A molecul of free radical DPPH is violet color. Then, samples undergo resonance and formed complex with DPPH. While DPPH is forming $DPPH_2$ which yellow color. This molecul is neutral. The reaction mecanism of antioxidant with DPPH assay is shown in Figure 7.

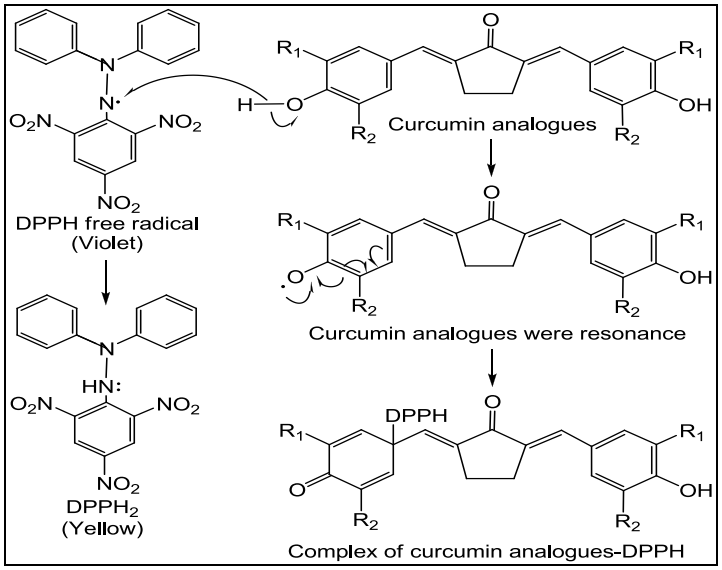


Figure 7: Antioxidant Reaction Mecanism by DPPH Assay

CONCLUSION

The condensation reaction between 5-chloro-4-hydroxy-3-methoxybenzaldehyde and 3-chloro-4-hydroxybenzaldehyde with cyclopentanone were produced 2,5-*bis*(5'-chloro-4'-hydroxy-3'-methoxybenzylidene)cyclopentanone (CHMBC) and 2,5–*bis*(3'–chloro–4'–hydroxybenzylidene)cyclopentanone (CHBC), respectively. The in vitro antioxidant assays demonstrated that curcumin analogues have antioxidant activity, either by DPPH radical scavenging activity and β-carotene bleaching method. The potency of antioxidant activity of CHMBC was more higher than that CHBC, curcumin and pentagamavunon-0 (PGV-0) that measure by the β-carotene bleaching method. While antioxidant activity of curcumin analogues using DPPH radical scavenging assay was lower than that PGV-0 and curcumin.

ACKNOWLEDGEMENT

Authors thanks to the Directorate of Higher Education Indonesia (DIKTI) on the graduate program BPPS scholarship. Authors also thanks to LIPI in Serpong, Indonesia that has helped an elusidation of the structure of the synthesized compound.

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