International Journal of ChemTech Research
CODEN (USA): IJCRGG, ISSN: 0974-4290, ISSN(Online):2455-9555
Vol.10 No.1 pp 27-33, 2017

# Synthesis of Piperidine and Morpholine Amides of Ferulic Acid and their Bioactivity against P-388 Leukemia Cells

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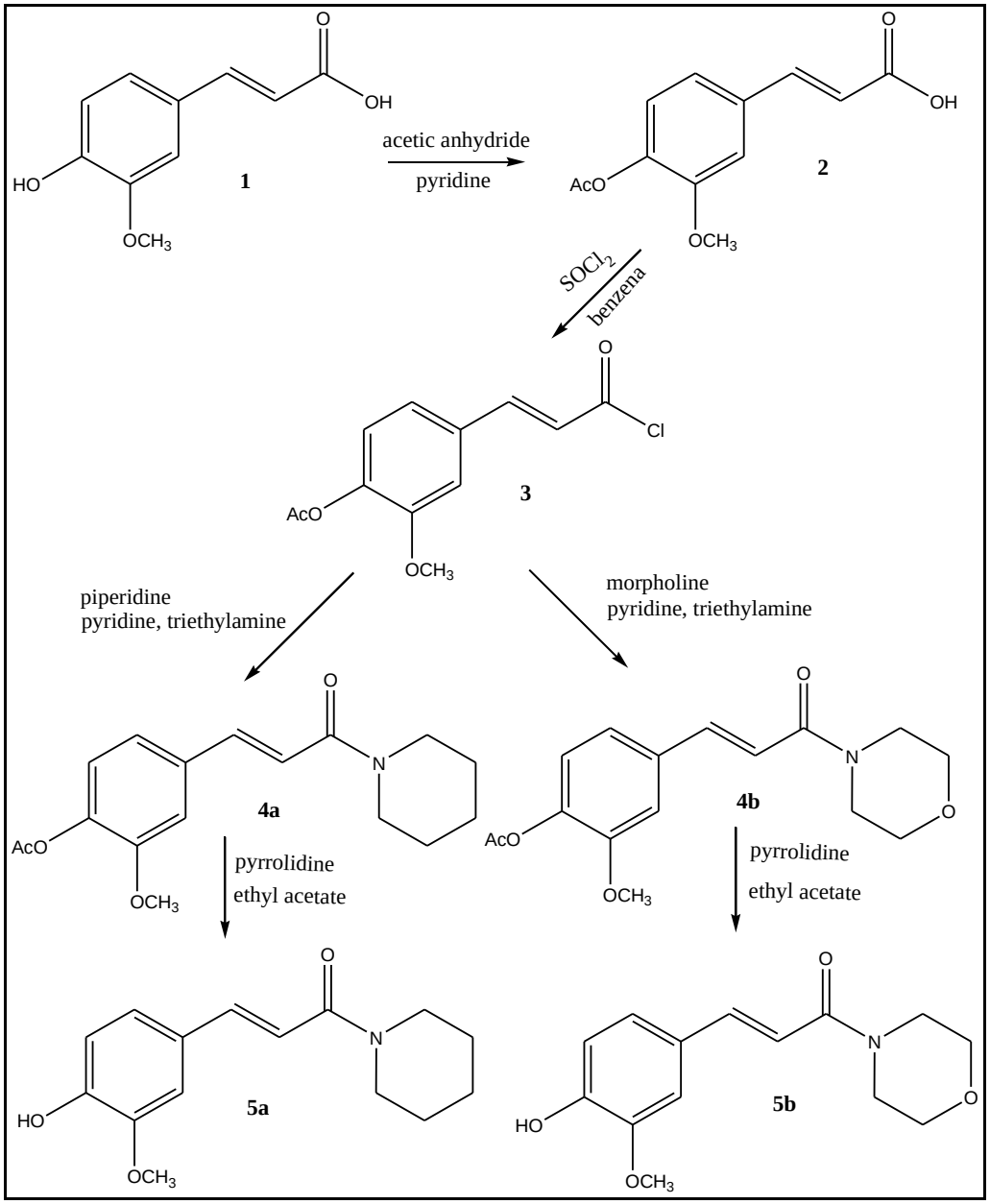
**Abstract :** Synthesis of *N*-feruloylpiperidine (**5a**) and *N*-feruloylmorpholine(**5b**) from ferulic acid through acetylation, chlorination, amidation, and deacetylation reactions have been conducted. The acetylation was carried out using acetic anhydride reagent in pyridine solvent at room temperature for 6 hours. The chlorination was performed with thionyl chloride in benzene solvent by refluxingat 75°C for 4 hours, proceeded by *in situ* amidation using piperidine to synthesize of compound **1** and morpholine to synthesize of compound **2** in the presence of triethylamine and pyridine in dichloromethane solvent at room temperature. The deacetylation was performed using pyrrolidine reagent in ethyl acetate solvent at room temperature for 2 hours giving compounds **5a** and **5b** as yellowish crystalline solids with m.p. of 127-129°C and 151-153°C, respectively. Characterization of these compounds was committed by FTIR spectrophotometer and NMR spectrometer.The bioassay of the both compounds against P-388 leukemia cells gave $IC_{50}$ of46.67 and 57.10 µg/mL, respectively.
**Keywords :** *N*-feruloylpiperidine, *N*-feruloylmorpholine, anticancer, ferulic acid, P-388 leukemia cell.

## Introduction

Cinnamic acid derivatives and their anticancer potentials remain underutilized for severaldecades[1]. Many studies evaluated the biological properties of cinnamic acid derivatives (especially hydroxycinnamic acid derivatives) and concluded that some of these derivatives were potent asantimicrobial[2,3], antiviral[4], antioxidant[5,6], antidiabetic[7], and anti-inflamatoryagent[8]. Most of the cinnamic compounds as their esters, amides, aldehydes, and alcoholssignificantly inihibite thegrowth ofone or several bacterial and fungal species[3].Cinnamic acid possesses an $\alpha,\beta$-unsaturated carbonyl moiety, which can be considered as a Michael acceptor, an active moiety was often employed in the design of anticancer drugs[9]. The hydroxycinnamic acid family includes coumaric acid (CoA), caffeic acid (CA), ferulic acid (FA), and sinapic acid (SA).




**1. Ferulic acid**
**2. *O*-acetylferulic acid**
**3. *O*-acetylferuloylchoride**
**4a. *N*-(*O*-acetylferuloyl)piperidine**
**4b. *N*-(*O*-acetylferuloyl)morpholine**
**5a. *N*-feruloylpiperidine**
**5b. *N*-feruloylmorpholine**

**Figure 1.Scheme synthesis of *N*-feruloylpiperidine and *N*-feruloylmorpholine**

FAis a phenolic acid found in seeds and leaves of most plants. FA was first isolated from the genus of*Ferula foetida* by Hlasiwetz Barth in 1866[10].FA, like other phenolic acid (CA and SA) possesses anticancer activity. FA scavenges the free radical, regulates cell growth and proliferation, stimulates cytoprotective enzymes, and inhibits cytotoxic systems in both *in vitro* and *in vivo* experimental models[11]. The esterification and amidationof phenolic acids are practical techniques to improve their antioxidant and antidiabetic activities[12,13].Amide of 4-aminoantipyrine from FA and CA shown antioxidant activity[14], piperidine and morpholineamide from CA gave antioxidant activity against lipid peroxidation[5], andthiazolidine-4-ones amide from FA had antioxidant activity against DPPH and ABTS[15]. Based on these facts, piperidine and morpholine amides of FA have been synthesized via reactions scheme in Figure 1 andtheir anticancer activity againstP-388 leukemia cellshas been tested.

## Experimental Detail

### Chemicals

Ferulic acid was purchased from Sigma Aldrich, piperidine, morpholine, and other chemicals were purchased from Merck,TLC plates (aluminum sheets silica gel 60 $F_{254}$) were purchased from Merck.

### Spectroscopic Measurement

FTIRspectrums were obtained on a Shimadzu Prestige-21 spectrophotometer, $^{1}$H-NMR and $^{13}$C-NMRspectrums were obtained on anA500a Agilent DD2 500 MHz in $CDCl_3$solvent and tetramethylsilane (TMS) as internal standard.

### Bioactivity Assay

Bioactivity of target molecules against P-388 leukemia cellswas performed by MTT method.

### Synthetic procedures

The conversion of ferulic acids to the corresponding amides in this research were carried out by four steps of reaction: protection of the phenolic hydroxyl groups by acetylation, activation of the carboxylic group by chlorination followed by *in situ* amidation, and deprotection of the phenolic hydroxyl groups by deacetylation reactions**.**

### Protection of the phenolic hydroxyl groups of ferulic acid(synthesis of compound2)

Procedure of this step was adopted from Helm *etal.* (1992)[16]. This method producedcompound **2** as white crystalline solid with m.p. of194-196°C and 77.99 % yield; FTIR (KBr) ν = 3010.88 $cm^{-1}$ (C-H unsaturated), 2943.37 $cm^{-1}$ (C-H aliphatic), 3150.0-2351.23 $cm^{-1}$ (O-H carboxyl),1761.01 $cm^{-1}$ (C=O ester), 1687.71 $cm^{-1}$ (C=O carboxyl), 1631.78 $cm^{-1}$ (C=C olefin), 1600.92 $cm^{-1}$ and 1506.41 $cm^{-1}$ (C=C aromatic),1465.90 and 1371.39 $cm^{-1}$ ($CH_3$), 985.62 $cm^{-1}$ (C-H bend *trans*-olefin), 914.26 and 837.11 $cm^{-1}$ (aromatic 1,2,4-trisubstitution).

### Chlorination and amidation procedure(synthesis of compound 4a and 4b)

This procedure was adopted from Lu and Ralph (1998)[17] and Helm *et al.*, (1992)[16] with slight modification, and amidation was performed *in situ*. The compound **3**were prepared by refluxing a mixture of compound **2** (0.5 g, 2.12 mmol) and thionyl chloride (0.8 mL, 11.0 mmol) in benzene (20 mL) for 4 hours. The result as clear solutions was evaporated to be solid (crude compound **3**).Furthermore, the solid(0.3g) was dissolved in dry dichloromethane (50 mL) and added by related amine(0.3 mL, 3.0mmol of piperidine to synthesize compound **4a**and 0.26 mL, 3.0mmolof morpholine to synthesize of compound **4b**) to which pyridine (0.06 mL) and triethylamine (0.3 mL) were added. The mixture was stirred for 4 hours. The reaction result was washed with aqueous 3% HCl and saturated $NH_4Cl$respectively, drying over anhydride $Na_2SO_4$, and evaporated. The pure amide compounds (**4a**and **4b**) were obtained after purification by gravity column chromatography.

The compound **4a**was obtained as white crystalline solid with m.p. of 121-122°C, 76.3%yield; FTIR (KBr)ν =3064.89and 3012.81 $cm^{-1}$(C-H unsaturated), 2937.59 and 2852.72 $cm^{-1}$ (C-H aliphatic), 1759.08 $cm^{-1}$ (C=O ester), 1649.14 $cm^{-1}$ (C-O amide), 1606.70 $cm^{-1}$ and 1514.12 $cm^{-1}$ (C=C aromatic), 1444.68 and 1369.46 $cm^{-1}$ ($CH_3$), 1257.59 $cm^{-1}$ (C-O phenol), 1219.01 $cm^{-1}$ (C-O ester), 1408.04 and 1307.74 $cm^{-1}$ (C-N), 987.55 $cm^{-1}$ (C-H bend *trans*-olefin), 906.54 and 829.39 $cm^{-1}$ (aromatic 1,2,4-trisubstitution).

The compound **4b**was obtained as white crystalline solid with m.p. of 91-92°C, 58.7 %yield; FTIR (KBr) ν =3120.82 and 3064.89 $cm^{-1}$(C-H unsaturated), 2956.87, 2916.37, and 2856.58 $cm^{-1}$ (C-H saturated), 1761.01 $cm^{-1}$ (C=O ester), 1647.21 $cm^{-1}$ (C=O amide), 1610.56 $cm^{-1}$ and 1512 $cm^{-1}$(C=C aromatic), 1433.11 and 1373.32 $cm^{-1}$ ($CH_3$), 1298.09 $cm^{-1}$ (C-N amide),1259.52 and 1220,54 (C-O phenolic), and 974.05$cm^{-1}$ (C-H bend *trans*-olefin), 906.54 and 829.39 $cm^{-1}$ (aromatic 1,2,4-trisubstitution).

### Deprotection of phenolic hydroxyl groups (synthesis of compound 5a and 5b)

Procedure for this step was adopted from Lu and Ralph (1998)[17] with slight modification.Pyrrolidine(1 mL) was added into each compound **4a** and **4b**,the mixture was diluted with 50 mL of ethyl acetate, and stirred for 2 hours.The reaction result was washed with 1 M $H_2SO_4$(3 x 20 mL) and thensaturated$NH_4Cl$ (2 x 20 mL),dried withanhydride $Na_2SO_4$, and evaporated to give compounds **5a** and **5b.**

The compound **5a**was obtained as yellowish crystalline solid with m.p. of 127-129°C, 65.01 %yield; FTIR (KBr)ν = 3360.00 $cm^{-1}$ (O-H phenol),3012.81 $cm^{-1}$ (C-H unsaturated), 2941.44, 2924.09, 2852.72 $cm^{-1}$ (C-H saturated), 1639.49 $cm^{-1}$ (C=O amide), 1598.99 and 1514.12 $cm^{-1}$ (C=C aromatic), 1579.70 $cm^{-1}$(C=C olefin), 1463.97 and 1396.46 $cm^{-1}$ ($CH_3$), 1436.97 $cm^{-1}$ (C-N amide), 1286.52, 1251.80, and 1213.23 $cm^{-1}$(C-O), 979.84 $cm^{-1}$ (C-H bend *trans*-olefin), 850.61 and 819.75 (aromatic 1,2,4-trisubstitution);$^1$H NMR ($CDCl_3$): δ (ppm) = 1,59-1.66(*m*, 6H, $CH_2$), 3.57-3.64 (*m*, 4H, 2 x $NCH_2$), 3.9 (*s*, 3H, $CH_3$), 6.6 (*bs*, 1H, OH), 6.72 (*d*, 1H, *J*=15.35 Hz, =CH-), 6.89 (*d*, 1H, *J*=8.2 Hz, ArH), 6.96 (*d*, 1H, *J*= 1.5 Hz,ArH), 7.04 (*dd*, 1H, *J*=8.2 Hz, 1.5 Hz,ArH), 7.56 (*d*, 1H, *J*=15.3 Hz, -CH=);$^{13}$C NMR ($CDCl_3$): δ (ppm) = 24.7, 25.7, 26.8, 43.5, 47.1, 56, 110, 114.86, 114.96, 121.8, 127.9, 142.7, 146.98, 147.5, 165.8.

The compound **5b**was obtained as yellowish crystalline solid with m.p. of 151-153°C, 74.29 %yield, FTIR(KBr) ν= 3352.28 $cm^{-1}$ (O-H phenolic), 3064.89 $cm^{-1}$ (C-H unsaturated), 2987.74, 2912.51, and 2870.08 $cm^{-1}$ (C-H saturated), 1649.14 $cm^{-1}$ (C=O amide), 1597.06 and 1517.98 $cm^{-1}$ (C=C aromatic), 1450.47 and 1363.67 $cm^{-1}$ ($CH_3$), 1411.89 $cm^{-1}$ (C-N amide), 1269.16 and 1230.58 (C-O), 974.5 $cm^{-1}$ (C-H bend *trans*-olefin), 866.04 and 808.17 $cm^{-1}$ (aromatic 1,2,4-trisubstitution);$^1$H NMR ($CDCl_3$): δ (ppm) = 3.7 (*s*, 8H,$CH_2$), 3.9 (*s*, 3H, $CH_3$), 6.7 (*d*, 1H, *J*=15.3Hz, =CH-), 6.9 (*d*, 1H, *J*=8.2 Hz, ArH), 6.97 (*s*, 1H, ArH), 7.07 (*d*, 1H, *J*=8Hz, ArH), 7.62 (*d*, 1H, *J*=15.3 Hz, -CH=); $^{13}$C NMR ($CDCl_3$): δ (ppm) = 42.62, 46.36, 56.06, 66.96, 110.07, 113.81, 114.97, 122.09, 127.64, 143.64, 146.93, 147.71, 166.03.

**Anticancer bioassay (MTT Method)**

Bioassay of compounds **5a** and **5b**against P-388 leukemia cellswas done at Natural Product Laboratory ITB by MTT method (3-(4,5-dimethyltiazol-2-yl)-2,5-difeniltetrazolium bromide)[18].

## Result and Discussion

Theoretically, the conversion of carboxylic group to amide can be performed directly using a catalyst like as in the conversion 3-phenylbutanoic acid with benzylamine catalyzed boric acid[19]**.** However, this method was failed for the conversion of CoA to its amides[20]. The Failure of this method wasdue to the existence of phenolic groups in the CoA. Since the structure of FA is analog with CoA, the conversion of FA to its amide requires protection ofthe hydroxyl of phenolic group.

Protection of hydroxyl of FA was performed using acetic anhydridegiving compound **2** as crystalline solid with m.p. of 194-196ºC and 78.0% yield. The success of this reaction was indicated with the appearance of carbonyl absorption of acetyl group accompanied the loss of hydroxyl absorption of phenolic group on FTIRspectrum.

To perform the amidation reaction of carbonyl groups, activation wasrequired by conversion them into acid halide using thionyl chloride in dry benzene. However, the product of this reaction wasmore unstable to be isolated from the mixture product, so the amidation reaction with piperidine and morpholine were conducted *in situ*givingcompound **4a** and **4b,** respectively. The compound **4a** was obtained as white crystalline solid with m.p. of121-122ºC and 76.31% yield, and the **4b** was obtained as white crystalline solid with m.p.of 91-92ºC and 58.70% yield. The decrease of melting point of the product in this step is a logical consequence of the decrease in polarityof compounds. To convince that the products were the molecular target (**4a** and **4b**), the both products were characterized using FTIR spectrophotometer. This case was indicated by FTIR spectra of both compounds in which absorptionpeaksof C-N appearat 1408.04 and 1433.11 $cm^{-1}$accompanied by the loss of hydroxyl absorption of carboxylicgroup. These facts was corroborated with the shift of wavenumber of carbonyl group absorption from 1687.71 to 1649.14 $cm^{-1}$and 1647.21 for both compounds(**4a** and **4b**), respectively.

The final step of the synthesis targetin this research was deprotection of phenolic group via deacetylation reaction using pyrrolidine in ethyl acetate solvent. The compound **5a** was obtained as yellowish crystalline solid with m.p.of 127-129ºC and 65.0% yield, and the compound **5b** was obtained as yellowish crystalline solid with m.p.of151-153ºC and 74.3% yield.

Characterization of thetarget compounds (**5a** and **5b**) with FTIR gave spectra in which hydroxyl absorption reappear at 3360.00 and 3352.28 $cm^{-1}$,respectively, accompanied by the loss of carbonyl absorption from acetyl group. The later fact greatly indicated the absence of acetyl group in the both compounds.

FTIR data of the both target compounds were corroborated with NMR data. In the $^{1}$H-NMR spectrumof compound **5a**, peaks created from saturated systemwere found in δ of 1.5876 - 1.6574 ppm and 3.5672 - 3.6409 ppmrepresenting ten protons that came from piperidine group. Similarly, in the spectrum of compound **5b**,peaksin δof3.6000 - 3.7090 ppm representing eight protons that came from morpholine group. The presence of those peaks indicated that the compounds **5a** and **5b** have been boundwith piperidine and morpholine groups, respectively.

In the $^{13}$C-NMR spectra, peaks corresponding to saturated carbon were also found inboth compounds. Five peaks in δ of 24.703, 25.707, 26.830, 43.508, and 47.100 ppmwere created from piperidine group, and the two peaks in δ of 46.360 and 66.960 ppm were createdmorpholine group.

All the data of FTIR, $^{1}$H-NMR, and $^{13}$C-NMRspectrawhich could be identified (Table 1) match with compound **5a** and **5b**, so the both compoundswere success to be synthesized via acetylation, chlorination, amidation, and deacetylation reactions sequentially.

**Table 1.FTIR and NMR spectral data of compounds 5a and 5b**

| Compound | mp ($^{0}$C) | Yield (%) | FTIR ν ($cm^{-1}$) | $^{1}$HNMR δ (ppm) | $^{13}$CNMR δ (ppm) |
|---|---|---|---|---|---|
| **5a** | 127-129 | 65.01 | 3360.00 (O-H phenol), 3012.81 (C-H unsaturated), 2941.44, 2924.09, 2852.72 (C-H saturated), 1639.49 (C=O amide), 1598.99 and 1514.12 (C=C aromatic), 1579.70 (C=C olefin), 1463.97 and 1396.46 ($CH_3$), 1436.97 (C-N amide), 1286.52, 1251.80, and 1213.23(C-O), 979.84 (C-H bend *trans*-olefin), 850.61 and 819.75 (aromatic 1,2,4-trisubstitution) | 1,59-1.66 (*m*, 6H, $CH_2$), 3.57-3.64 (*m*, 4H, 2 x $NCH_2$), 3.9 (*s*, 3H, $CH_3$), 6.6 (*bs*, 1H, OH), 6.72 (*d*, 1H, *J*=15.35 Hz, =CH-), 6.89 (*d*, 1H, *J*=8.2 Hz, ArH), 6.96 (*d*, 1H, *J*= 1.5 Hz,ArH), 7.04 (*dd*, 1H, *J*=8.2 Hz, 1.5 Hz,ArH), 7.56 (*d*, 1H, *J*=15.3 Hz, -CH=) | 24.7, 25.7, 26.8, 43.5, 47.1, 56, 110, 114.86, 114.96, 121.8, 127.9, 142.7, 146.98, 147.5, 165.8. |
| **5b** | 151-153 | 74.29 | 3352.28 (O-H phenolic), 3064.89 (C-H unsaturated), 2987.74, 2912.51, and 2870.08 (C-H saturated), 1649.14 (C=O amide), 1597.06 and 1517.98 (C=C aromatic), 1450.47 and 1363.67 ($CH_3$), 1411.89 (C-N amide), 1269.16 and 1230.58 (C-O), 974.5 (C-H bend *trans*-olefin), 866.04 and 808.17 (aromatic 1,2,4-trisubstitution) | 3.7 (*s*, 8H,$CH_2$), 3.9 (*s*, 3H, $CH_3$), 6.7 (*d*, 1H, *J*=15.3Hz, =CH-), 6.9 (*d*, 1H, *J*=8.2 Hz, ArH), 6.97 (*s*, 1H, ArH), 7.07 (*d*, 1H, *J*=8Hz, ArH), 7.62 (*d*, 1H, *J*=15.3 Hz, -CH=) | 42.62, 46.36, 56.06, 66.96, 110.07, 113.81, 114.97, 122.09, 127.64, 143.64, 146.93, 147.71, 166.03. |

Bioactivity assay of both synthesized compounds **5a** and **5b** against P-388 leukemia cell gave $IC_{50}$ value of 46.67and 57.10µg/mL,respectively. Comparing to bioactivity of analog compounds previously

synthesized, namely *p*-coumaryl morpholine with $IC_{50}$of19.35 µg/mL[21],it was clear that both compounds **5a** and **5b**are less activethan *p*-coumaryl morpholine compound.

The main different between *p*-coumaric and ferulic skeleton is the present of methoxy. In ferulic skeleton, there is methoxy group in *ortho* position of hydroxyl group, but there is no in *p*-coumaric skeleton. Persuant to the $IC_{50}$ value of both compounds, it can be supposed that the present of methoxy group in *ortho* position of hydroxyl group of cinnamic skeleton aggravate their activity against P-388 leukemia cell. This is understandable because the presence of methoxy group in *ortho* position of hydroxyl group create intramolecular hydrogen bonding. This bonding caused the hydrogen of hydroxyl is sluggish to be released as hydrogen radical.

## Conclusion

The compounds **5a** and **5b** can be synthesized from FA via acetylation, chlorination and amidation *in situ*, and deacetylation. By this method, the compound **5a**was obtained as yellowish crystalline solid with m.p.of127-129°C, and the compound **5b** as yellowish crystalline solid with m.p. of151-153°C. Compound **5a** and **5b** gave $IC_{50}$ values of46,67 and 57.10 µg/mL, respectively against P-388 leukemia cell.

## Acknowledgements

The authors gratefully acknowledge the financial support from Rector of Hasanuddin University. The authors also would like to thankthe staff of Integrated Laboratory, Chemistry Department, Faculty of Mathematic and Natural Sciences of Hasanuddin University in assistance to take FTIR spectra; Chemistry Laboratory of ITB for assisting in $^{1}$H-NMR and $^{13}$C-NMRmeasurements; and Natural Product Laboratory of Chemistry Department, Faculty of Mathematic and Natural Sciences of ITB for assisting in bioactivity assay of samples.

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