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

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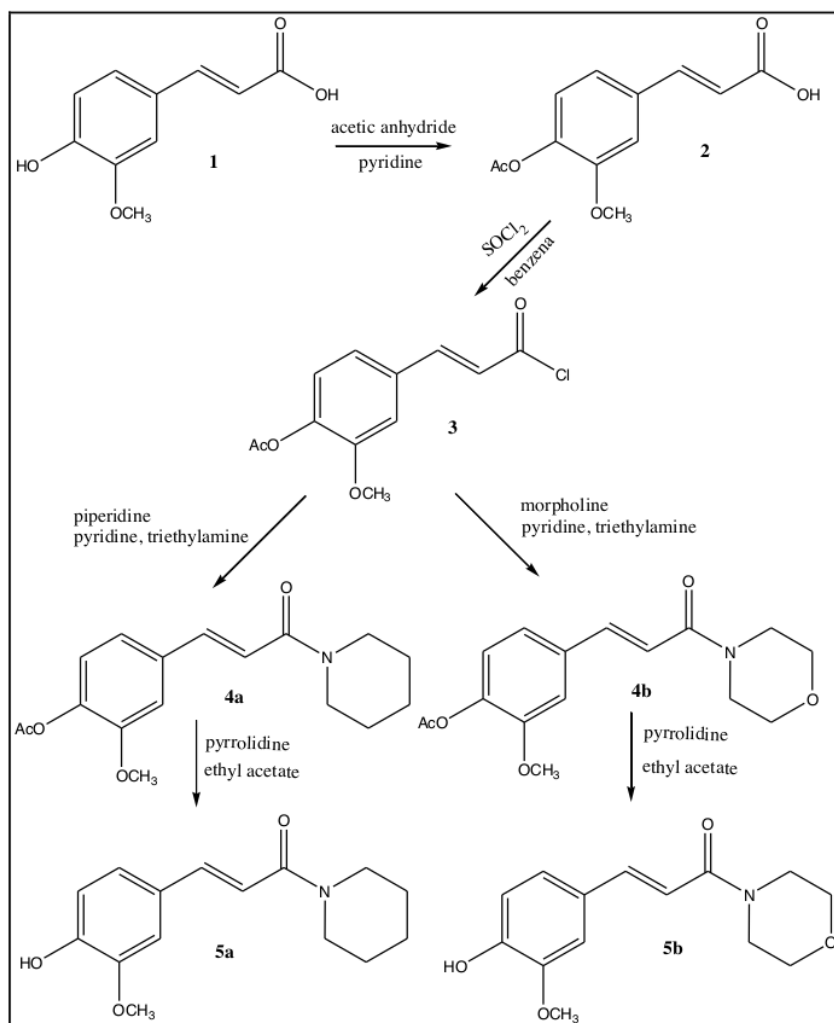
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Abstract : Synthesis of *N*-feruloylpiperidine (**5a**) and *N*-feruloylmorpholine(**5b**) from ferulic acid through acetylation, chlorination, amidation, and deacetylation reactions have been conducted. The acetylation was carried out using acetic anhydride reagent in pyridine solvent at room temperature for 6 hours. The chlorination was performed with thionyl chloride in benzene solvent by refluxing at 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 IC₅₀ of 46.67 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 several decades¹. Many studies evaluated the biological properties of cinnamic acid derivatives (especially hydroxycinnamic acid derivatives) and concluded that some of these derivatives were potent antimicrobial^{2,3}, antiviral⁴, antioxidant^{5,6}, antidiabetic⁷, and anti-inflammatory agent⁸. Most of the cinnamic compounds as their esters, amides, aldehydes, and alcohols significantly inhibit the growth of one or several bacterial and fungal species³. Cinnamic acid possesses an α,β -unsaturated carbonyl moiety, which can be considered as a Michael acceptor, an active moiety was often employed in the design of anticancer drugs⁹. The hydroxycinnamic acid family includes coumaric acid (CoA), caffeic acid (CA), ferulic acid (FA), and sinapic acid (SA).



- | | |
|-----------------------------------------------------|-----------------------------------------------------|
| 1. Ferulic acid | 4b. <i>N</i> -(<i>O</i> -acetylferuloyl)morpholine |
| 2. <i>O</i> -acetylferulic acid | 5a. <i>N</i> -feruloylpiperidine |
| 3. <i>O</i> -acetylferuloylchloride | 5b. <i>N</i> -feruloylmorpholine |
| 4a. <i>N</i> -(<i>O</i> -acetylferuloyl)piperidine | |

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

FA is a phenolic acid found in seeds and leaves of most plants. FA was first isolated from the genus *Ferula foetida* by Hlasiwetz Barth in 1866¹⁰. 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 models¹¹. The esterification and amidation of phenolic acids are practical techniques to improve their antioxidant and antidiabetic activities^{12,13}. Amide of 4-aminoantipyrine from FA and CA shown antioxidant activity¹⁴, piperidine and morpholine amide from CA gave antioxidant activity against lipid peroxidation⁵, and thiazolidine-4-ones amide from FA had antioxidant activity against DPPH and ABTS¹⁵. Based on these facts, piperidine and morpholine amides of FA have been synthesized via reactions scheme in Figure 1 and their anticancer activity against P-388 leukemia cells has 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 F₂₅₄) were purchased from Merck.

Spectroscopic Measurement

FTIR spectra were obtained on a Shimadzu Prestige-21 spectrophotometer, ¹H-NMR and ¹³C-NMR spectra were obtained on an A500a Agilent DD2 500 MHz in CDCl₃ solvent and tetramethylsilane (TMS) as internal standard.

Bioactivity Assay

Bioactivity of target molecules against P-388 leukemia cells was 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 compound 2)

Procedure of this step was adopted from Helm *et al.* (1992)¹⁶. This method produced compound 2 as white crystalline solid with m.p. of 194-196°C and 77.99 % yield; FTIR (KBr) $\nu = 3010.88 \text{ cm}^{-1}$ (C-H unsaturated), 2943.37 cm^{-1} (C-H aliphatic), 3150.0-2351.23 cm^{-1} (O-H carbonyl), 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} (CH₃), 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 compounds 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, 3.0 mmol) of piperidine to synthesize compound 4a and 0.26 mL, 3.0 mmol of 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 NH₄Cl respectively, drying over anhydride Na₂SO₄, 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) $\nu = 3064.89$ and 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} (CH₃), 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) $\nu = 3120.82$ 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} (CH₃), 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)¹⁵ 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 H₂SO₄ (3 x 20 mL) and then saturated NH₄Cl (2 x 20 mL), dried with anhydride Na₂SO₄, 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} (CH₃), 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 819.20 (aromatic 1,2,4-trisubstituted); ¹H NMR (CDCl₃): δ (ppm) = 1.59-1.66 (*m*, 6H, CH₂), 3.57-3.64 (*m*, 4H, 2 x NCH₂), 3.9 (*s*, 3H, CH₃), 6.6 (*bs*, 1H, OH), 6.72 (*d*, 1H, *J*=15.35 Hz, =CH-), 6.89 (*d*, 1H, *J*=3.2 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=); ¹³C NMR (CDCl₃): 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} (CH₃), 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); ¹H NMR (CDCl₃): δ (ppm) = 3.7 (*s*, 8H, CH₂), 3.9 (*s*, 3H, CH₃), 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=); ¹³C NMR (CDCl₃): 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 cells was done at Natural Product Laboratory ITB by MTT method (3-(4,5-dimethyliazol-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 acid¹⁹. However, this method was failed for the conversion of CoA to its amides²⁰. The Failure of this method was due 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 of the hydroxyl of phenolic group.

Protection of hydroxyl of FA was performed using acetic anhydride giving compound **2** as crystalline solid with m.p. of 194-196°C 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 FTIR spectrum.

To perform the amidation reaction of carbonyl groups, activation was required by conversion them into acid halide using thionyl chloride in dry benzene. However, the product of this reaction was more unstable to be isolated from the mixture product, so the amidation reaction with piperidine and morpholine were conducted *in situ* giving compound **4a** and **4b**, respectively. The compound **4a** was obtained as white crystalline solid with m.p. of 121-122°C and 76.31% yield, and the **4b** was obtained as white crystalline solid with m.p. of 91-92°C and 58.70% yield. The decrease of melting point of the product in this step is a logical consequence of the decrease in polarity of 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 absorption peaks of C-N appear at 1408.04 and 1433.11 cm^{-1} accompanied by the loss of hydroxyl absorption of carboxylic group. These facts were 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 target in 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 127-129°C and 65.0% yield, and the compound **5b** was obtained as yellowish crystalline solid with m.p. of 151-153°C and 74.3% yield.

Characterization of the target 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 latter 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 $^1\text{H-NMR}$ spectrum of compound **5a**, peaks created from saturated system were found in δ of 1.5876 - 1.6574 ppm and 3.5672 - 3.6409 ppm representing ten protons that came from piperidine group. Similarly, in the spectrum of compound **5b**, peaks in δ of 3.6000 - 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 bound with piperidine and morpholine groups, respectively.

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

All the data of FTIR, $^1\text{H-NMR}$, and $^{13}\text{C-NMR}$ spectra which could be identified (Table 1) match with compound **5a** and **5b**, so the both compounds were successful 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 ($^{\circ}\text{C}$)	Yield (%)	FTIR ν (cm^{-1})	$^1\text{H-NMR}$ δ (ppm)	$^{13}\text{C-NMR}$ 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 <i>trans</i> -olefin), 850.61 and 819.75 (aromatic 1,2,4-trisubstitution)	1.59-1.66 (<i>m</i> , 6H, CH_2), 3.20-3.64 (<i>m</i> , 4H, 2 x NCH_2), 7.9 (<i>s</i> , 3H, CH_3), 6.6 (<i>bs</i> , 1H, OH), 6.72 (<i>d</i> , 1H, $J=15.35$ Hz, =CH-), 6.89 (<i>d</i> , 1H, $J=8.2$ Hz, ArH), 6.96 (<i>d</i> , 1H, $J=1.5$ Hz, ArH), 7.04 (<i>dd</i> , 1H, $J=8.2$ Hz, 1.5 Hz, ArH), 7.56 (<i>d</i> , 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 <i>trans</i> -olefin), 866.04 and 808.17 (aromatic 1,2,4-trisubstitution)	3.7 (<i>s</i> , 8H, CH_2), 3.9 (<i>s</i> , 3H, CH_3), 6.7 (<i>d</i> , 1H, $J=15.3$ Hz, =CH-), 6.9 (<i>d</i> , 1H, $J=8.2$ Hz, ArH), 6.97 (<i>s</i> , 1H, ArH), 7.07 (<i>d</i> , 1H, $J=8$ Hz, ArH), 7.62 (<i>d</i> , 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 46.67 and 57.10 $\mu\text{g/mL}$, respectively. Comparing to bioactivity of analog compounds previously

synthesized, namely *p*-coumaryl morpholine with IC_{50} of 19.35 $\mu\text{g/mL}$ ²¹, it was clear that both compounds **5a** and **5b** are less active than *p*-coumaryl morpholine compound.

The main difference between *p*-coumaric and ferulic skeleton is the presence of methoxy. In ferulic skeleton, there is a methoxy group in the *ortho* position of the hydroxyl group, but there is none in the *p*-coumaric skeleton. Pursuant to the IC_{50} value of both compounds, it can be supposed that the presence of a methoxy group in the *ortho* position of the hydroxyl group of the cinnamic skeleton aggravates their activity against P-388 leukemia cells. This is understandable because the presence of a methoxy group in the *ortho* position of the hydroxyl group creates intramolecular hydrogen bonding. This bonding causes the hydrogen of the hydroxyl group to be released as a 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 a yellowish crystalline solid with m.p. of 127-129°C, and the compound **5b** as a yellowish crystalline solid with m.p. of 151-153°C. Compound **5a** and **5b** gave IC_{50} values of 46.67 and 57.10 $\mu\text{g/mL}$, respectively, against P-388 leukemia cells.

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