Synthesis and Cytotoxicity of 4-Allyl-2-Methoxyphenol Derivatives

Lingga Kamadatu¹, Mardi Santoso¹

Abstract – 4-Allyl-2-methoxyphenol derivatives was synthesized through the application of methods of Yamaguchi in one pot with a resulting yield of 80-90%. 4-Allyl-2-methoxyphenol derivatives showed good activity in inhibiting the growth of human breast cancer cell MCF-7.

Index Terms – 4-allyl-2-methoxyphenol derivative, cytotoxicity, preparation.

INTRODUCTION

Breast cancer is the second leading cause of death in women are caused by cancer. Development of compounds anti-cancer is still being done to get an anticancer drug with high activity and low side effects. Anti-cancer compounds can be derived from the results of the synthesis and isolation of medicinal plants. [1, 2].

Clave (Syzygium aromaticum (L.) Merr. & Perry) is one of the original Indonesian spice used as seasoning with its main compound is 4-allyl-2-methoxyphenol which are known to have activity in inhibits the growth of cancer cells such as human breast cancer cells (MDA-MB-231; MCF-7 and T47-D). 4-allyl-2-methoxyphenol acetate reported to have activity in inhibiting the growth of cancer cells DU-145 (prostate cancer cells androgen-sensitive) and KB (oral squamous cell carcinoma) [1-5].

Synthesis of 4-allyl-2-methoxyphenol ester is generally conducted through the reaction between 4-allyl-2-methoxyphenol with various acid chlorides and pyridine [4, 6-8]. Yamaguchi method can be used as an alternative method for the synthesis of 4-allyl-2-methoxyphenol ester. This method is reported to have successfully applied to the synthesis of enzyme inhibitors Lux-S acid, thiol esters, and a large ring lactone [9-11].

In this paper reported the application of the method of Yamaguchi in the synthesis of 4-allyl-2-methoxyphenol derivatives (Figure 1) and cytotoxicity studies on breast cancer cells MCF-7 in obtaining new anticancer compound that has high activity and low side effects.

MATERIAL AND METHOD

A. General procedure for the synthesis of 4-allyl-2-methoxyphenol derivatives

A solution of 2,4,6-trichlorobenzoin chloride (0.75 mmol), carboxylic acid (0.75 mmol), triethylamine (0.75 mmol) in dichloromethane was stirred at room temperature for 1 h. 4-Dimethylaminopyridine (0.75 mmol) and 4-allyl-2-methoxyphenol (0.50 mmol) was added to the solution, and the mixture was stirred further at room temperature for 6 h. The product was extracted several times with dichloromethane. The combined extract was wished subsequently with 5% aqueous hydrochloric acid, 5% sodium hydroxide, 10% aqueous sodium bicarbonate, and water, dried over magnesium sulphate and the solvent was removed under reduced pressure to yield the titled compound.

1) 4-allyl-2-methoxyphenyl propionate (a). White solid. Yield: 88% (0.097 g). δH (500 MHz, CDCl3): 1.21 (t, J = 7.8 Hz, 3H, CH3CH2), 2.57 (q, J = 6.5 Hz, 2H, CH2=CH2), 3.36 (d, J = 6.5 Hz, 2H, CH2CH=CH2), 3.76 (s, 3H, OCH3), 5.09-5.14 (m, 2H, CH2CH=CH2), 5.92-6.01 (m, 1H, CH2CH=CH2), 6.75 (d, J = 7.8 Hz, 1H, ArH), 6.87 (s, 1H, ArH), 6.91 (d, J = 7.8 Hz, ArH). δC (125 MHz, CDCl3): 9.55 (CH3CH2), 28.11 (CH2=CH2), 41.05 (CH2CH=CH2), 56.33 (OCH3), 113.92 (ArCH), 116.33 (CH2CH=CH2), 121.66 (ArCH), 123.53 (ArCH), 138.73 (CH2CH=CH2), 139.52 (ArC), 140.52 (ArC), 152.46 (ArC), 174.48 (C=O). MS (EI): m/z 220 (M, 8%), 189 (2), 164 (100), 147 (27), 133 (15), 131 (16), 108 (10), 92 (12), 74 (8), 57 (9), HR-ESI-MS [M+H]+ m/z 221.2643, calculated for C9H8O3, 221.2723.

2) b) 4-allyl-2-methoxyphenyl butanoate (b). Colourless oil. Yield: 86% (0.1008 g). δH (500 MHz, CDCl3): 1.07 (t, J = 7.5 Hz, 3H, CH3CH2), 1.81 (m, 2H, CH2=CH2), 2.57 (t, J = 7.5 Hz, 2H, CH2CH=CH2), 3.39 (d, J = 6.5 Hz, 2H, CH2CH=CH2), 3.81 (s, 3H, OCH3), 5.09-5.14 (m, 2H, CH2CH=CH2), 5.93-6.01 (m, 1H, CH2CH=CH2), 6.78 (d, J = 8.4 Hz, 1H, ArH), 6.80 (s, 1H, ArH), 6.95 (d, J = 8.4 Hz, ArH). δC (125 MHz, CDCl3): 13.65 (CH2CH3), 18.65 (CH2CH3), 35.95 (CH2CH2CH3), 40.15 (CH2CH2CH3), 55.81 (OCH3), 112.76 (ArCH), 116.17 (CH2CH=CH2), 120.70 (ArCH), 122.59 (ArCH), 137.17 (CH2CH=CH2), 138.12 (ArC), 138.90 (ArC), 150.97 (ArC), 171.93 (C=O). MS (EI): m/z 234 (M, 8%), 164 (100), 147 (27), 131 (16), 108 (10), 91 (12), 71 (8), 51 (9), HR-ESI-MS [M+H]+ m/z 235.2355, calculated for C10H12O4, 235.2389.

3) c) 4-allyl-2-methoxyphenyl isobutanoate (c). Colourless oil. Yield: 86% (0.1018 g). δH (500 MHz, CDCl3): 1.34 (d, J = 7.2 Hz, 6H, CH(CH3)2), 2.84 (m, 1H, CH(CH3)2), 3.39 (d, J = 6.5 Hz, 2H, CH2CH=CH2), 3.80 (s, 3H, OCH3), 5.09-5.14 (m, 2H, CH2CH=CH2), 5.93-6.02 (m, 1H, CH2CH=CH2), 6.77 (d, J = 7.8 Hz, 1H, ArH), 6.79 (s, 1H, ArH), 6.94 (d, J = 7.8 Hz, ArH). δC (125 MHz, CDCl3): 19.15 (CH(CH3)2), 34.04 (CH(CH3)2), 40.17 (CH2CH=CH2), 55.89

¹Lingga Kamadatu and Mardi Santoso are with Department of Chemistry, Faculty of Mathematics and Natural Sciences, Institut Teknologi Sepuluh Nopember, Surabaya. Email: heidenling@gmail.com; tsv09@yahoo.com.
B. Synthesis of 4-allyl-2-methoxyphenol derivatives

Synthesis of 4-allyl-2-methoxyphenol derivatives was performed using the Yamaguchi esterification method. The reaction involved the carboxylic acid with triethylamine in dichloromethane at room temperature to produce triethylammonium propionate which was then reacted with 2,4,6-trichlorobenzoin chloride to form a mixed anhydride. The second stage of the reaction involved the reaction of 4-allyl-2-methoxyphenol as nucleophiles with mixed anhydride and 4-dimethylaminopyridine to produce 4-allyl-2-methoxyphenyl propionate, 4-allyl-2-methoxyphenyl butanoate and 4-allyl-2-methoxyphenyl isobutanoate with good yield results (80-90%).

B. Cytotoxicity assay

Cytotoxicity assay performed with MTT assay, to see the activity of 4-allyl-2-methoxyphenol derivatives against human breast cancer cells MCF-7 in vitro. Breast cancer cells were given treatment varying concentrations of 4-allyl-2-methoxyphenol derivatives (6.25, 12.5, 25, 50, 100, 200 μg/mL). From the results obtained that the 4-allyl-2-methoxyphenyl propionate, 4-allyl-2-methoxyphenyl butanoate and 4-allyl-2-methoxyphenyl isobutanoate able to inhibit the growth of human breast cancer cells MCF-7. The IC₅₀ were 0.400 μg/mL, 5.73 μg/mL and 1.29 μg/mL for MCF-7, respectively. This indicates that 4-allyl-2-methoxyphenol derivatives has cytotoxicity against human breast cancer cells MCF-7. 4-allyl-2-methoxyphenol derivatives has the best activity better than 4-allyl-2-methoxyphenol (IC₅₀ 1.5 μM) [1].

4-allyl-2-methoxyphenol derivatives showed good activity in inhibiting the growth of human breast cancer cell MCF-7. The IC₅₀ were 0.400 μg/mL, 5.73 μg/mL and 1.29 μg/mL for MCF-7, respectively. The results showed that 4-allyl-2-methoxyphenol derivatives has the potential to be developed as an anti-breast cancer.

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REFERENCES