Synthesis of Vanillin Substituted Alkylisatin Derivative

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**Abstract.** This study aims to report the synthesis of a vanillin derivative ethyl 2-(3-(2-(2-(4-formyl-2-methoxyphenoxy)acetyl)-hydrazineylidene)-2-oxoindolin-1-yl)acetate **8** (71% yield) through coupling of 2-(4-formyl-2-methoxy-phenoxy)acetohydrazide **5** and ethyl 2-(2,3-dioxoindolin-1-yl)acetate **7**. The acetohydrazide **5** was obtained in 91% yield from alkylation of vanillin **1** with ethyl chloroacetate **2** followed by the addition of hydrazine hydrate **4**. The alkylation of isatin **6** using ethyl chloroacetate **2** produced the alkylated isatin **7**. The structure of synthesized compounds was established by spectroscopic analysis using 1H/13C NMR, MS, and FTIR.

# INTRODUCTION

Vanillin or 4-hydroxy-3-methoxybenzaldehyde **1** with benzaldehyde framework is responsible for the characteristic of sweet aroma produced by Vanilla species. Vanillin as glucoside is commonly found in vanilla beans and can be isolated from *Vanilla planifolia*, *V. tahitensis*, and *V. pompona*. Vanillin has also been used as an important raw material in the pharmaceutical industry to produce methyldopa, dopamine, and papaverine (**FIGURE 1**) [1].



**FIGURE 1.** Structure of (a) vanillin **1**, (b) methyldopa, (c) dopamine, (d) papaverin

Containing aldehyde, hydroxyl, and ether functional groups attached to the aromatic ring causes vanillin to undergo various chemical reactions [1]. The presence of these three functional groups also makes vanillin show a toxic effect on microorganisms at high concentrations. Condensation of aldehyde group in vanillin followed by substitution produces acetal and mercaptal. The aldehyde group could also be oxidized to produce vanillic acid after protection of the hydroxyl group. Additionally, the esterification or etherification reactions frequently take place in the phenolic hydroxyl group of vanillin [1,2].

Structural transformation through chemical modifications gives vanillin derivatives with diverse bioactivities such as anticancer, antibacterial, antioxidant, neuroprotector, DNA protector, antibiotic enhancer, and anti-quorum sensing [3-6]. The design and development of vanillin derivatives could also be performed through molecular hybridization which combines different organic frameworks and heterocycles [7]. 3-Methoxy-4-((1-(3-(*m*-tolyloxy)propyl)-1H-1,2,3-triazol-4-yl)methoxy)benzaldehyde (78% yield) (**FIGURE 2a**) obtained by combination of 3-methoxy-4-(prop-2-yn-1-yloxy)benzaldehyde and 1-(3-azidopropoxy)-3-methylbenzene shows antibacterial activity against various gram-positive and gram-negative bacteria with minimum inhibitory concentration values ​​of 5 μg/mL [8]. The reaction of vanillin and (4-oxo-4,5-dihydrothiazol-2-yl)amino)benzenesulfonamide afforded (E)-4-((5-(4-hydroxy-3-methoxybenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino)benzenesulfonamide in 82% yield (**FIGURE 2b**). The synthesized compound inhibits MDA-MB-231 and MCF-7 breast cancer cells with a IC50 of 1.56 and 1.52 μM, respectively [4]. A bis-chalcone substituted vanillin namely 1-([1,1'-biphenyl]-2-yl)-3-(3-ethyl-4-hydroxybenzyl)-4-(4-hydroxy-3-methoxybenzyl)pyrrolidine-2,5-dione (83% yield) (**FIGURE 2c**) has promising antifungal activity with an inhibition zone of 22.54 mm against *Candida albicans* and 16.63 mm against *Aspergilus niger* [9]. Combination of biphenyl and vanillin yielded (4-((4'-fluoro-[1,1'-biphenyl]-4-yl)methoxy)-3-methoxy-benzylidene)-3-(4-(tetrahydrofuran-3-yl)phenyl)propanehydrazide (88% yield) (**FIGURE 2d**) possessed anti-inflammatory activities by carrageenan injection with degree of paw thickness 72 mm which is almost similar to sodium diclofenac (75 mm) as a positive control [10].



**FIGURE 3.** Structure of vanillin derivatives produced by molecular hybridization

Isatin (1H-indole-2,3-dione) is a "special building block" in the development of biologically active molecules. Isatin with a nitrogen atom N1, two carbonyl groups C2/C3, and aromatic ring has been studied for decades due to the possibility of reactions in almost all positions of its structure [11]. The structure modification as for *N*-acetyl isatin is assumed to work strongly against microorganisms [12]. The derivatives of isatin also show various pharmacological properties [13-14]. As a continuation of the works by our group in the research of active molecules [15-19], the synthesis of vanillin substituted alkylisatin derivative **8** reported herein. The modification includes alkylation of vanillin, substitution of the ester **3** by hydrazine hydrate **4** and reaction of the hydrazide with alkylated isatin **7**.

# EXPERIMENTAL

## General

Melting points were determined with a Fischer John melting point apparatus and are uncorrected. The Fourier-transform infrared (FTIR) spectra were obtained using Shimadzu FTIR-8400S and are reported in cm-1. The NMR spectra (1H, 500 MHz; 13C, 125 MHz) (DMSO-*d6*) were recorded on an Agilent 500 MHz NMR spectrometer using TMS as internal reference (chemical shifts are expressed in *δ* ppm). The electrospray-ionization mass spectra (ESIMS) were measured on a Xevo G2-SQtof.

## Synthesis Ethyl-2-(4-formyl-2-methoxyphenoxy)acetate 3

Vanillin **1** (1.8265 g; 12 mmol) was dissolved in DMF (50 mL) and stirred in an ice bath for 15 minutes. K2CO3 (1.9359 g; 14 mmol) was added and the mixture was stirred for 30 minutes (ice bath). Next, ethyl chloroacetate **2** (2.2 mL; 10 mmol) was added and the reaction mixture was stirred in an ice bath for 2 hours and further at room temperature for 2 hours. After the reaction was complete (TLC monitor), the reaction mixture was poured into cold water [8]. The solid was filtered, washed with cold water, and dried to give a white solid of compound **3** (1.9235 g, 67%). mp 70-72°C. IR (KBr disc) (vmax, cm-1): 2962, 2859, 1749, 1676, 1197, 1139. 1H-NMR (DMSO-*d6*, 500 MHz): *δ* 1.21 (t, *J* = 7 Hz, 3H), 3.86 (s, 3H), 4.18 (q, *J* = 21.5 Hz, 2H), 4.94 (s, 2H), 7.09 (d, *J* = 8.5 Hz, 1H), 7.43 (d, *J* = 1.5 Hz, 1H), 7.51-7.53 (m, 1H), 9.85 (s, 1H). 13C-NMR (DMSO-*d6*, 125 MHz): *δ* 13.4, 54.9, 60.2, 64.4, 109.4, 111.9, 124.9, 129.7, 148.6, 151.7, 167.6, 190.9. HRESIMS [Found: *m*/*z* 239.0918 (M+H)+, calcd for C12H15O5: (M+H)+, 239.0919].

## Synthesis 2-(4-Formyl-2-methoxyphenoxy)acetohydrazide 5

Ethyl-2-(4-formyl-2-methoxyphenoxy)acetate **3** (1.1990 g; 5 mmol) and hydrazine hydrate **4** (0.73 mL; 15 mmol) were dissolved with ethanol (25 mL) in a round bottom flask. The reaction mixture was refluxed for 5 hours [9]. After the reaction completed as monitored by TLC, the reaction mixture was allowed to stand until precipitates formed. The obtained solid was then filtered and dried to produce compound **5** as a yellowish white solid (1.0255 g, 91%). mp 150-152°C. IR (KBr disc) (vmax, cm-1): 3525, 3338, 3255, 2993, 2904, 1676, 1612, 1271, 1134. 1H-NMR (DMSO-*d6*, 500 MHz): *δ* 3.78 (s, 3H), 4.45 (s, 2H), 6.61 (s, 2H), 6.85-6.91 (m, 2H), 7.16 (d, *J* = 2 Hz, 1H), 7.63 (s, 1H), 9.19 (s, 1H). 13C-NMR (DMSO-*d6*, 125 MHz): *δ* 54.7, 66.7, 106.9, 113.1, 117.8, 129.8, 137.7, 146.5, 148.6, 166.1. HRESIMS [Found: *m*/*z* 225.0871 (M+H)+, calcd for C10H13N2O4: (M+H)+, 225.0875].

## Synthesis Ethyl-2-(2,3-dioxoindolin-1yl)acetate 7

Isatin **6** (0.44 g; 3 mmol) in a round bottom flask was dissolved in DMF (12.5 mL) and stirred at 0°C (ice bath) for 15 minutes. K2CO3 (0.48 g, 3.5 mmol) was added, and the mixture was further stirred for 30 minutes at 0°C (ice bath). The mixture was added with ethyl chloroacetate **2** (0.53 mL, 5 mmol), and stirring at 0°C (ice bath) was continued for 1 hour followed by stirring at room temperature for 3 hours [8]. The reaction mixture was poured into cold water, filtered, and dried to yield compound **7** as a yellow solid (0.52 g, 74%). mp 147-148°C. IR (KBr disc) (vmax, cm-1): 2952, 1769, 1610, 1468, 1341, 1282, 1170, 1095. 1H-NMR (DMSO-*d6*, 500 MHz): *δ* 1.21 (t, *J* = 7 Hz, 3H), 4.17 (q, *J* = 7 Hz, 2H), 4.61 (s, 2H), 7.16-7.20 (m, 2H), 7.61 (d, *J* = 7 Hz, 1H), 7.68 (t, *J* = 8.5 Hz, 1H). HRESIMS [Found: *m*/*z* 234.0769 (M+H)+, calcd for C12H11NO4: (M+H)+, 234.0766].

## Synthesis Ethyl 2-(3-(2-(2-(4-formyl-2-methoxyphenoxy)acetyl)hydrazineylidene)-2-oxoindolin-1-yl)acetate 8

2-(4-Formyl-2-methoxyphenoxy)acetohydrazide **5** (0.11 g, 0.5 mmol) was dissolved in ethanol (5 mL). Ethyl 2-(2,3-dioxoindolin-1-yl)acetate **7** (0.12 g; 0.5 mmol) was added and the reaction mixture was stirred for a while [9]. Glacial acetic acid (0.06 mL) was added, and reflux was carried out at 70°C for 5 hours. The formed solid was filtered and dried to give compound **8** an orange solid (0.15 g, 71%). mp 313°C (dec). IR (KBr disc) (vmax, cm-1): 3309, 2989, 1669, 1610, 1505, 1416, 1267, 1207, 1028. 1H-NMR (DMSO-*d6*, 500 MHz): *δ* 1.22 (t, *J* = 7 Hz, 3H), 3.91 (s, 3H), 4.17 (q, *J* = 7.5; 10.5 Hz, 2H), 4.60 (s, 2H), 4.66 (s, 2H), 7.08-7.17 (m, 3H), 7.46-7.61 (m,3H), 8.09 (d, *J* = 7.5 Hz, 1H), 8.62 (s, 1H), 11.54 (s, 1H). HRESIMS [Found: *m*/*z* 440.1458 (M+H)+, calcd for C22H22N3O7: (M+H)+, 440.1458].

# RESULTS AND DISCUSSION

The synthesis of vanillin derivative **8** is summarized in **FIGURE 1**. In this study, the derivative **8** was obtained by alkylation of vanillin **1** with ethyl chloroacetate **2** [20], followed by substitution of the product **3** with hydrazine hydrate **4** [9] to give 2-(4-formyl-2-methoxyphenoxy)acetohydrazide **5**. Ethyl-2-(2,3-dioxoindolin-1yl)acetate **7** was prepared from a reaction of isatin **6** with ethyl chloroacetate **2** [15]. Lastly, the reaction of acetohydrazide **5** with alkylated isatin **7** afforded the target **8** [21].



**FIGURE 1.** Synthesis of vanillin derivative **8**. Reagents/conditions: (a) ethyl chloroacetate **2**, K2CO3, DMF, 0°C 2h to rt 2h, 67%; (b) hydrazine hydrate **4**, ethanol, reflux 5 h, 91%; (c) ethyl chloroacetate **2**, K2CO3, DMF, 0°C 1h to rt 3h, 74%; (d) glacial acetic acid (cat.), reflux 5 h, 71%.

The formation of ethyl-2-(4-formyl-2-methoxyphenoxy)acetate **3** (67% yield) was performed by reaction of vanillin **1** with ethyl chloroacetate **2** in DMF with the addition of K2CO3 [8]. The reaction involving the substitution of the chlorine atom of ethyl chloroacetate **2** by the nucleophilic hydroxyl group of vanillin **3** was carried out at 0ºC to rt [22,23]. The next reaction of alkylated vanillin **3** with hydrazine hydrate **4** in ethanol afforded 2-(4-formyl-2-methoxyphenoxy)acetohydrazide **5** in 91% yield [9]. The acyl-substitution involves the nucleophilic addition of hydrazine hydrate **4** to ethyl-2-(4-formyl-2-methoxyphenoxy)acetate **3** and the elimination of ethanol [23]. The reaction of isatin **6** and ethyl chloroacetate **2** was done in DMF with the presence of K2CO3 to yield ethyl-2-(2,3-dioxoindolin-1yl)acetate **7** in 74% yield [20,22]. The vanillin derivative ethyl 2-(3-(2-(2-(4-formyl-2-methoxyphenoxy)acetyl)hydrazineylidene)-2-oxoindolin-1-yl)acetate **8** (71% yield) was obtained by coupling 2-(4-formyl-2-methoxyphenoxy)acetohydrazide **5** with ethyl-2-(2,3-dioxoindolin-1yl)acetate **7** in ethanol with a catalytic addition of glacial acetic acid [21]. This reaction is proposed to follow the Wolff-Kishner reaction mechanism [22,23]. The spectroscopic techniques including NMR, FTIR, and HRMS were employed to characterize the structure of all products, and the spectra exhibited the expected signals.

The analytical and spectral data (1H & 13C NMR, FTIR, and HRESIMS) were used to determine the structure of synthesized compounds. The IR spectrum of ethyl-2-(4-formyl-2-methoxyphenoxy)acetate **3**, in addition to the expected absorption bands for the CH aldehyde at 2859 and 2962 cm-1, indicated the presence of bands at 1749, 1676, 1197, 1139 cm-1 corresponding to C=O and C-O groups. The structure of **3** is also supported by the absence of a broad absorption band of the OH group present in the structure of vanillin **1**. The 1H NMR spectrum of **3** displayed the existing aldehyde proton as a singlet at *δ* 9.85 ppm. The methyl and methylene protons appeared as triplet, singlet, quartet, and singlet signals at *δ* 1.21, 3.86, 4.18, and 4.94 ppm, respectively. Analysis of the 13C NMR spectrum 3 demonstrated the presence of new signals for the methyl, methylene, and carbonyl carbons of the ester at *δ* 13.4, 60.2, 64.4, and 167.6 ppm, respectively. The HRESIMS spectrum of ester **3** exhibited a molecular ion peak at *m/z* 239.0918 [M + H]+ corresponding to its relative mass (*m/z* 239.0919). Next, the structure of 2-(4-formyl-2-methoxyphenoxy)acetohydrazide **5** was deduced from its IR spectrum which clearly shows the absorption bands at 3525, 3338, and 3255 cm-1 attributed for the amine group. This is supported by the presence of signals as singlets at *δ* 6.61 and 7.63 ppm correlated to NH2 and NH protons in the 1H NMR spectrum of **5**. The 13C NMR spectrum of **5** revealed the appearance of a signal at *δ* 148.6 ppm fit to amide CONH carbon. The molecular ion peaks at *m/z* 225.0871 [M + H]+ corresponding to the relative mass of **5** (*m/z* 225.0875). Further, ethyl-2-(2,3-dioxoindolin-1yl)acetate **7** was yielded from the reaction of isatin **6** and ethyl chloroacetate **2** and its structure was deducted from the absorption bands in the IR spectrum at 1769, 1282, 1170 cm-1 due to the existence of C=O and C-O bonds. The 1H NMR spectrum of **7** contained signals at *δ* 1.21, 4.17, and 4.61 ppm featured for methyl and methylene protons of alkyl substituent. The mass spectrum (HR-ESI) of alkylated isatin **7** showed a molecular ion peak at *m/z* 234.0769 [M + H]+ calculating for the relative mass of C12H22NO4 (*m*/*z* 234.0766). Finally, the coupling of 2-(4-formyl-2-methoxyphenoxy)acetohydrazide **5** and ethyl-2-(2,3-dioxoindolin-1yl)acetate **7** produced ethyl 2-(3-(2-(2-(4-formyl-2-methoxyphenoxy)acetyl)hydrazineylidene)-2-oxoindolin-1-yl)acetate **8** which its structure was identified from the disappearance of NH2 amine absorption bands present in the precursor **5**. The 1H NMR spectrum of **8** indicated signals at *δ* 8.62 and 11.54 ppm for amine and aldehyde protons. The mass spectrum (HRESIMS) of vanillin derivative **8** presented a molecular ion peak at *m/z* 440.1458 [M + H]+ agree with the relative mass (*m/z* 440.1458). **TABLE 1** and **TABLE 2** display the 1H and 13C NMR data of **3**, **5**, **7**, and **8**.

**TABLE 1.** 1H NMR data of **3**, **5**, **7** and **8**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Proton** | **Chemical Shifts (*δ*) (ppm)** | | | |
| **(3)** | (**5**) | (**7**) | (**8**) |
| -COOCH2C**H**3 | 1.21 (t, *J*=7 Hz, 3H) |  | 1.21 (t, *J*=7 Hz, 3H) | 1.22 (t, *J*=7 Hz, 3H) |
| -COOC**H**2CH3 | 4.18 (q, *J*=21.5 Hz, 2H) |  | 4.17 (q, *J*=7 Hz, 2H) | 4.17 (q, *J*=7.5; 10.5 Hz, 2H) |
| -OC**H**2CO | 4.94 (s,2H) |  | 4.61 (s, 2H) | 4.60 (s, 2H) |
| -OC**H**2CONH |  | 4.45 (s, 2H) |  | 4.66 (s, 2H) |
| -OC**H**3 | 3.86 (s, 3H) | 3.78 (s, 3H) |  | 3.91 (s, 3H) |
| Ar H | 7.09 (d, *J*=8.5 Hz, 1H)  7.43 (d, *J*=1.5 Hz)  7.51-7.53 (m, 1H) | 6.85-6.90 (m, 2H) | 7.16-7.20 (m, 2H) | 7.08-7.17 (m, 3H) |
| 7.16(d, *J*=2 Hz, 1H) | 7.61 (d, *J*=7 Hz, 1H) | 7.46-7.61 (m,3H) |
|  | 7.68 (t, *J*=8.5 Hz, 1H) | 8.09 (d, *J*=7.5 Hz, 1H) |
| -C**H**O |  | 9.19 (s, 1H) |  | 8.62 (s, 1H) |
| -N**H**2 |  | 6.61 (s, 2H) |  |  |
| -N**H** |  | 7.63 (s, 1H) |  | 11.54 (s, 1H) |

Table 2. Comparison 13C NMR data of (**3**) and (**5**)

|  |  |  |
| --- | --- | --- |
| **Carbon** | **Chemical Shifts (*δ*) (ppm)** | |
| (**3**) | (**5**) |
| -COOCH2C**H**3 | 13.4 |  |
| -COOC**H**2CH3 | 60.2 |  |
| -OCH2**C**O | 167.6 | 148.6 |
| -OC**H**2CO | 64.4 | 66.7 |
| -OC**H**3 | 54.9 | 54.7 |
| -Ar C | 109.4  111.9  124.9  129.7 | 106.9  133.1  117.8  129.8  137.7  146.4 |
| 148.6  151.7 |
| -C**H**O | 190.9 | 166.1 |

# CONCLUSION

The vanillin derivative, ethyl 2-(3-(2-(2-(4-formyl-2-methoxyphenoxy)acetyl)-hydrazineylidene)-2-oxoindolin-1-yl)acetate **8** was successfully synthesized in 71% yield through coupling of 2-(4-formyl-2-methoxy-phenoxy)acetohydrazide **5** and ethyl 2-(2,3-dioxoindolin-1-yl)acetate **7**.

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