Vietnam Journal of Science and Technology ***61*** *(2) (2023) 174-181*

doi:10.15625/2525-2518/16785

Synthesis and cytotoxic activity of some novel 2’-hydroxychalcones containing murrayafoline A

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Received: 8 December 2021; Accepted for publication: 21 April 2022

Abstract. 2’-Hydroxychalcones and murrayafoline A, a natural compounds isolated from *Glycomis stenocarpa*, have been reported to have the promising anti-cancer activity. In this study, a series of 2'-hydroxychalcones containing murrayafoline A (MuA) **6a-f** were achieved by Claisen-Schmidt condensation of the key intermediate 5'-(1-methoxy-3-methyl-carbazolyl)methyl-2'-hydroxyacetophenone **4** with various aldehydes **5a-f** with purpose of combining activity of two precusors. Their structures were determined by NMR and MS spectral data. Screening for cytotoxicity of compounds showed that compounds **6a-6d** expressed cytotoxic activity, notably compound **6a** displayed activity against all tested cell lines LU-1, Hep-G2, MCF-7, P338, and SW480 with the IC_{50} values ranging from 23.97 to 80.19 μg/mL. Clearly, the substitution at position of N-H group of murrayafoline a led to a decline in the cytotoxicity of the obtained derivatives. This finding suggests the presence of the N-H group might be play a crucial role for the cytotoxicity of the murrayafoline A derivatives.

Keywords: murrayafoline A, 2'-hydroxychalcone, cytotoxicity, chloromethyl, *N*-alkyl, Claisen-Schmidt

Classification numbers: 1.1.2, 1.2.1, 1.2.4

1. INTRODUCTION

Chalcones are a class of the naturally occurring pigments broadly found in the plant kingdom in which 2'-hydroxychalcones (Figure 1) are one of the most important chalcones that has been drawn a great deal of interest by medicinal chemists.

2'-Hydoxychalcones were reported to possess a broad spectrum of bioactivity including antioxidant and soybean lipoxygenase inhibitory [1], anti-inflammatory [2, 3], and anticancer [4, 5] activities. In our previous reports, several types of 2'-hydroxychalcones connecting to nucleosides [6, 7], imidazole, benzotriazole [8], and their bioactivities have been reported. In

the present study, we report the synthesis and cytotoxic activity of novel 2'-hydroxychalcones containing carbazole murrayafoline A, an anti-cancer compound from *Glycosmis sternocapa* [9].

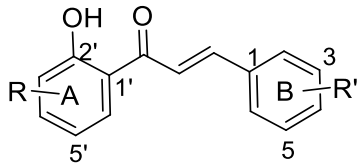


Figure 1. Structure of 2'-hydroxychalcones.

2. MATERIALS AND METHODS

2.1. Materials

Murrayafoline A (MuA) was isolated from the rhizome of *Glycosmis sternocapa* [9]. All chemicals and reaction solvents were purchased from Merck. Melting points were determined in open capillaries on a Shimazu Electrothermal IA 9200 apparatus. NMR spectra were recorded on a Brucker AVANCE 500 MHz spectrometer in DMSO-d_6 at Institute of Chemistry, VAST. Chemical shift (δ) are in ppm relative to TMS, multiplicities are shown as follows: s (singlet), d (doublet), t (triplet), m (multiplet) and coupling constants (*J*) are expressed in hertz (Hz). HRMS was recorded by using an ESI-TOF-MS Agilent 6230 spectrophotometer (MS Varian) at Institute of Chemistry, VAST. ESI-MS was recorded by using an Agilent 1200 Series LCMSD 6310 Ion Trap LC/MS. The reactions accelerated by microwave irradiation were carried out on a 20L 700W microwave oven Electrolux EMM2003W, China. Progress of the reaction was monitored by thin-layer chromatography (TLC) using precoated TLC sheets with ultraviolet (UV) fluorescent silica gel (Merck 60F254) and spots were visualized by UV lamp at 254 nm. Column chromatography was carried out using silica gel (40-230 mesh). The cytotoxic assay was performed according to the protocol as described by Monk and co-workers [10] on five human cancer cell lines including LU-1 (lung cancer), Hep-G2 (liver cancer), MCF-7 (human breast cancer), P338 (murine leukaemia cell), and SW480 (colon cancer).

2.2. Methods

*2.2.1. Synthesis of 5'-chloromethyl-2'-hydroxyacetophenone (**3**)*

2'-Hydroxyacetophenone (**1**) was chloromethylated using paraformaldehyde/HCl at 35 ^oC as described by Wong [11]. Intermediate **2** was used for the next step without purification.

*2.2.2. Synthesis of 5'-(1-methoxy-3-methyl-carbazolyl)methylacetophenone (**4**)*

A mixture of murrayafoline A (**3**) (2.11 g, 10 mmol), K_2CO_3 (1.87 g, 13.6 mmol), 5'-chloromethyl-2-hydroxyacetophenone (**2**) (2.76 g, 15.0 mmol) and (1-butyl)triethylammonium bromide (238 mg, 1.0 mmol) in dry dimethylformamide (25 mL) was thoroughly stirred and subjected to microwave irradiation in a microwave oven operating at 50 ^oC with a maximum power output of 250 W for 20 minutes. The mixture was concentrated under reduced pressure and diluted with chloroform (60 mL), then extracted with distilled water (3 times × 30 mL). The organic phase was separated, dried over anhydrous sodium sulfate, concentrated under reduced

pressure to afford crude (**4**). Intermediate (**4**) was purified by column chromatography eluting with *n*-hexane:EtOAc (7:1, v/v).

Yield 46 %, white powder, melting point (mp): 142 – 144 ^{o}C, ESI-MS *m/z:* 360.65 $[M+H]^+$. **^{1}H-NMR** (DMSO-d_6, 500 MHz) δ_H 11.71 (s, 1H, OH), 8.04 (d, *J* = 8.0 Hz, 1H, H-5"), 7.87 (d, *J* = 2.0 Hz, 1H, H-6'), 7.64 (d, *J* = 8.0 Hz, 1H, H-8"), 7.53 (s, 1H, H-4"), 7.39 (t, *J* = 8.0 Hz, 1H, H-7"), 7.19 (dd, J_1 = 2.0 Hz, J_2 = 8.0 Hz, 1H, H-4'), 7.15 (t, *J* = 8.0 Hz, 1H, H-6"), 6.89 (s, 1H, H-2"), 6.80 (d, *J* = 8.0 Hz, 1H, H-3'), 5.77 (s, 2H, 5'-CH_2-9"), 3.94 (s, 3H, 1"-OCH_3), 2.55 (s, 3H, -$COCH_3$), and 2.46 (s, 3H, 3-CH_3). **^{13}C-NMR** (DMSO-d_6, 125 MHz) δ_C 203.6 (C=O), 159.6 (C-2'), 146.1 (C-1"), 140.4 (C-13"), 134.4 (C-4'), 129.8 (C-5'), 129.6 (C-3"), 129.0 (C-6'), 127.2 (C-11"), 125.6 (C-7"), 124.2 (C-10"), 122.5 (C-12"), 120.2 (C-1'), 120.1 (C-8"), 118.9 (C-6"), 117.7 (C-3'), 112.5 (C-4"), 109.8 (C-5"), 109.4 (C-2"), 55.6 (1"-OCH_3), 47.0 (5'-CH_2-9"), 27.6 ($CO\underline{C}H_3$), and 21.2 (3"-CH_3).

*2.2.3.General procedure for the synthesis of 5'-(1-methoxy-3-methyl-N-carbazolyl)methyl-2'-hydroxychalcones **(6a-f)***

To a stirred mixture of 5'-(1-methoxy-3-methyl-carbazolyl) methylacetophenone **(4)** (359 mg, 1.0 mmol) and benzaldehyde derivatives **(5a-f)** (1.1 mmol) in absolute ethanol (15 mL) potassium hydroxide (118 mg, 2.0 mmol) was added. The mixture was stirred at room temperature for 24 hours and the solvent was then removed under reduced pressure. The resulting mixture was dissolved with water, neutralized by 10 % HCl solution and extracted with EtOAc (3 times × 20 mL). The combined extract was dried over anhydrous sodium sulfate and the solvent was then removed under reduced pressure. 5'-(1-Methoxy-3-methyl-*N*-carbazolyl)methyl-2'-hydroxychalcones **(6a-f)** were purified by column chromatography eluting with *n*-hexane:EtOAc.

3-Methoxy-5'-(1-methoxy-3-methyl-carbazolyl)methyl-2'-hydroxychalcone (6a). Yield 75 %, yellow solid, mp: 128 - 130 ^{o}C. ESI-HRMS *m/z* 478.20129 $[M+H]^+$ (calculated for $C_{31}H_{28}NO_4$ 478.20187). **^{1}H-NMR** ($CDCl_3$, 500 MHz) δ_H 12.56 (s, 1H, -OH), 8.04 (d, *J* = 8.0 Hz, 1H, H-5"), 7.70 (d, *J* = 15.5 Hz, 1H, H-*β*), 7.55 (d, *J* = 1.5 Hz, 1H, H-6'), 7.52 (s, 1H, H-4"), 7.39 (m, 2H, H-2, H-7"), 7.32 (m, 2H, H-6, H-6"), 7.21 (dd, J_1 = 1.5 Hz, J_2 = 8.0 Hz, 1H, H-4'), 7.19 (d, *J* = 15.5 Hz, 1H, H-*α*), 7.03 (d, *J* = 8.0 Hz, 1H, H-8"), 6.97 (m, 2H, H-4, H-5), 6.88 (d, *J* = 8.0 Hz, 1H, H-3'), 6.75 (s, 1H, H-2"), 5.78 (s, 2H, 5'-CH_2-9"), 3.89 (s, 3H, 1-OCH_3), 3.84 (s, 3H, 3"-OCH_3), and 2.50 (s, 3H, 3-CH_3). **^{13}C-NMR** ($CDCl_3$, 125 MHz, ppm) δ_C 193.4 (C=O), 162.4 (C-2'), 159.9 (C-3), 146.5 (C-1"), 145.0 (C-*β*), 141.1 (C-13"), 135.8 (C-1), 134.8 (C-4'), 129,9 (C-5'), 129.8 (C-3"), 129.6 (C-6'), 128.0 (C-5), 127.4 (C-11"), 125.7 (C-7"), 125.1 (C-10"), 123.2 (C-12"), 121.1 (C-1'), 120.4 (C-*α*), 120.2 (C-8"), 119.7 (C-6), 119.2 (C-3'), 118.5 (C-6"), 116.4 (C-4), 113.8 (C-2), 112.8 (C-4"), 109.9 (C-5"), 55.7 (1"-$O\underline{C}H_3$), 55.3 (3-$O\underline{C}H_3$), 47.8 (5'-$\underline{C}H_2$-9"), and 21.7 (3"-$\underline{C}H_3$).

4-Methoxy-5'-(1-methoxy-3-methylcarbazolyl)methyl-2'-hydroxychalcone (6b). Yield 81 %, yellow solid, mp: 155 – 157 ^{o}C. ESI-HRMS *m/z* 478.20129 $[M+H]^+$ (calculated for $C_{31}H_{28}NO_4$ 478.20185). **^{1}H-NMR** (DMSO-d_6, 500 MHz) δ_H 12.36 (s, 1H, -OH), 8.08 (s, H-6'), 8.07 (d, *J* = 8.0 Hz, 1H, H-5"), 7.78 (d, *J* = 8.0 Hz, 2H, H-2, H-6), 7.77 (d, *J* = 15.5 Hz, 1H, H-*β*), 7.69 (d, *J* = 8.0 Hz, 1H, H-8"), 7.67 (d, *J* = 15.5 Hz, 1H, H-*α*), 7.55 (s, 1H, H-4"), 7.40 (t, *J* = 8.0 Hz, 1H, H-7"), 7.17 (m, 2H, H-4', H-6"), 7.07 (d, *J* = 8.0 Hz, 2H, H-3, H-5), 6.90 (s, 1H, H-2"), 6.82 (d, *J* = 8.0 Hz, 1H, H-3'), 5.84 (s, 2H, 5'-CH_2-9"), 3.93 (s, 3H, 1"-OCH_3), 3.85 (s, 3H, 4-OCH_3), and 2.46 (s, 3H, 3"-CH_3). **^{13}C-NMR** (DMSO-d_6, 125 MHz, ppm) δ_C 193.0 (C=O), 161.8 (C-2'), 160.6 (C-4), 146.2 (C-1"), 144.8 (C-*β*), 140.5 (C-13"), 134.1 (C-4'), 130.9 (C-2, C-6),

129.9 (C-5'), 129.0 (C-3"), 128.8 (C-6'), 127.3 (C-11"), 126.9 (C-1), 125.6 (C-7"), 124.3 (C-10"), 122.5 (C-12"), 120.3 (C-8"), 120.2 (C-1'), 119.0 (C-*α*), 118.7 (C-6"), 117.8 (C-3'), 114.5 (C-3, C-5), 112.6 (C-4"), 109.9 (C-5"), 109.4 (C-2"), 55.7 (1'-O$\underline{C}$H$_3$), 55.4 (4-O$\underline{C}$H$_3$), 47.0 (5'-$\underline{C}$H$_2$-9"), and 21.3 (3"-$\underline{C}$H$_3$).

3,4,5-Trimethoxy-5'-(1-methoxy-3-methyl-carbazolyl)methyl-2'-hydroxychalcone (6c). Yield 76 %, yellow solid, mp: 150 – 152 ^{o}C. ESI-MS *m/z* 538.26 [M+H]$^{+}$. **^{1}H-NMR** (DMSO-*d*$_6$, 500 MHz) δ_H 12.14 (s, 1H, -OH), 8.11 (d, *J* = 2.0 Hz, 1H, H-6'), 8.05 (d, *J* = 8.0 Hz, 1H, H-5"), 7.76 (m, 2H, H-*α*, H-*β*), 7.68 (d, *J* = 8.0 Hz, 1H, H-8"), 7.53 (s, 1H, H-4"), 7.39 (t, *J* = 8 Hz, 1H, H-7"), 7.16 (m, 4H, H-2, H-6, H-4', H-6"), 6.86 (s, 1H, H-2"), 6.83 (d, *J* = 8.0 Hz, 1H, H-3'), 5.84 (s, 2H, 5'-CH$_2$-9"), 3.94 (s, 3H, 1"-OCH$_3$), 3.88 (s, 6H, 3-OCH$_3$, 5-OCH$_3$), 3.75 (s, 3H, 4-OCH$_3$), and 2.45 (s, 3H, 3"-CH$_3$). **^{13}C-NMR** (DMSO-*d*$_6$, 125 MHz, ppm) δ_C 193.1 (C=O), 160.2 (C-2'), 153.1 (C-3, C-5), 146.2 (C-1"), 145.0 (C-*β*), 140.4 (C-13"), 140.2 (C-4), 134.1 (C-4'), 129.9 (C-5'), 129.0 (C-3"), 128.9 (C-6'), 127.2 (C-11"), 129.9 (C-1), 125.6 (C-7"), 124.2 (C-10"), 122.5 (C-12"), 121.2 (C-1'), 120.1 (C-8"), 121.0 (C-*α*), 118.9 (C-6"), 117.8 (C-3'), 112.5 (C-4"), 109.9 (C-5"), 109.4 (C-2"), 106.8 (C-2, C-6), 60.2 (4-O$\underline{C}$H$_3$), 56.2 (3-O$\underline{C}$H$_3$, 5-O$\underline{C}$H$_3$), 55.6 (1"-O$\underline{C}$H$_3$), 47.0 (5'-$\underline{C}$H$_2$-9"), and 21.2 (3"-$\underline{C}$H$_3$).

4- Isopropyl -5'-(1-methoxy-3-methyl-carbazolyl)methyl-2'-hydroxychalcone (6d). Yield 76 %, yellow solid, mp: 121 – 123 ^{o}C. ESI-MS *m/z* 490.41 [M+H]$^{+}$. **^{1}H-NMR** (DMSO-*d*$_6$, 500 MHz) δ_H 8.08 (d, *J* = 2.0 Hz, 1H, H-6'), 8.07 (d, *J* = 8.0 Hz, 1H, H-5"), 7.74 (m, 4H, H-2, H-6, H-6", H-7"), 7.69 (d, *J* = 8.0 Hz, 1H, H-8"), 7.56 (s, 1H, H-4"), 7.41 (d, *J* = 8.0 Hz, 2H, H-3, H-5), 7.40 (d, *J* = 15.5 Hz, 1H, H-*β*), 7.17 (m, 1H, H-4'), 7.16 (d, *J* = 15.5 Hz, 1H, H-*α*), 6.90 (s, 1H, H-2"), 6.83 (d, *J* = 8.0 Hz, 1H, H-3'), 5.84 (s, 2H, 5'-CH$_2$-9"), 3.93 (s, 3H, 1"-OCH$_3$), 2.97 (m, 1H, 4-C$\underline{H}$(CH$_3$)$_2$), 2.46 (s, 3H, 3"-CH$_3$), and 1.25 (d, *J* = 6.5 Hz, 6H, 4-CH(C$\underline{H}_3$)$_2$). **^{13}C-NMR** (DMSO-*d*$_6$, 125 MHz, ppm) δ_C 193.0 (C=O), 160.4 (C-2'), 151.9 (C-4), 146.2 (C-1"), 144.6 (C-*β*), 140.5 (C-13"), 134.2 (C-4'), 132.0 (C-1), 129.9 (C-5'), 129.1 (C-2, C-6), 129.0 (C-3"), 128.8 (C-6'), 127.0 (C-11"), 127.0 (C-3, C-5), 125.6 (C-7"), 124.2 (C-10"), 122.5 (C-12"), 120.7 (C-*α*), 120.6 (C-1'), 120.1 (C-8"), 118.9 (C-6"), 117.8 (C-3'), 112.6 (C-4"), 109.9 (C-5"), 109.4 (C-2"), 55.7 (1"-OCH$_3$), 47.0 (5'-CH$_2$-9), 33.4 (4-$\underline{C}$H(CH$_3$)$_2$), and 23.5 (4-CH($\underline{C}$H$_3$)$_2$).

4-Methyl-5'-(1-methoxy-3methyl-carbazolyl)methyl-2'-hydroxychalcone (6e). Yield 79 %, yellow solid, mp: 186 – 188 ^{o}C. ESI-HRMS *m/z* 462.20689 [M+H]$^{+}$ (calculated for $C_{31}H_{28}NO_3$ 462.20637). **^{1}H-NMR** (DMSO-*d*$_6$, 500 MHz) δ_H 12.2 (s, 1H, -OH), 8.08 (s, 1H, H-6'), 8.06 (d, *J* = 8.0 Hz, 1H, H-5"), 7.74 (s, 2H, H-4', H-8"), 7.68 (m, 2H, H-*α*, H-*β*), 7.55 (s, 1H, H-4"), 7.39 (t, *J* = 8.0 Hz, 1H, H-7"), 7.32 (d, *J* = 8.0 Hz, 2H, H-2, H-6), 7.17 (m, 2H, H-3", H-5"), 6.89 (s, 1H, H-2"), 6.83 (d, *J* = 8.0 Hz, 1H, H-3'), 5.84 (s, 2H, 5'-CH$_2$-9"), 3.93 (s, 3H, 1"-OCH$_3$), 2.46 (s, 3H, 3"-CH$_3$), and 2.38 (s, 3H, 4-CH$_3$). **^{13}C-NMR** (DMSO-*d*$_6$, 125 MHz, ppm) δ_C 193.1 (C=O), 160.6 (C-2'), 144.7 (C-*β*), 146.2 (C-1"), 141.3 (C-13"), 140.5 (C-4), 134.3 (C-4'), 131.6 (C-1), 130.7 (C-5'), 129.1 (C-3"), 129.7 (C-2, C-6), 129.0 (C-3, C-5), 128.9 (C-6'), 127.3 (C-11"), 125.6 (C-7"), 124.3 (C-10"), 122.7 (C-12"), 120.5 (C-*α*), 120.2 (C-8"), 120.2 (C-1'), 119.0 (C-6"), 117.9 (C-3'), 112.6 (C-4"), 110.0 (C-5"), 109.5 (C-2"), 55.7 (1"-O$\underline{C}$H$_3$), 47.1 (5'-$\underline{C}$H$_2$-9"), 21.3 (3"-CH$_3$), and 21.1 (4-$\underline{C}$H$_3$).

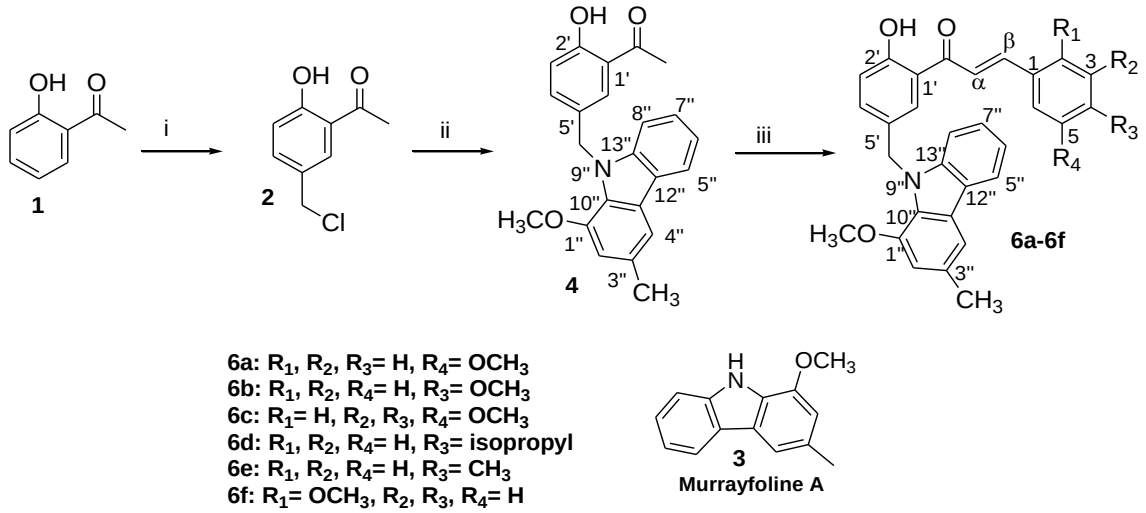
2-Methoxy-5'-(1-methoxy-3-methyl-carbazolyl)methyl-2'-hydroxychalcone (6f). Yield 57 %, yellow solid, mp: 148 - 150 ^{o}C. ESI-HRMS *m/z* 478.02129 [M+H]$^{+}$ (calculated for $C_{31}H_{28}NO_4$ 478.20186). **^{1}H-NMR** (DMSO-*d*$_6$, 500 MHz) δ_H 12.19 (s, 1H, -OH), 8.07 (s, 1H, H-6'), 8.05 (d, *J* = 8.0 Hz, 1H, H-5"), 8.00 (s, 1H, H-3), 7.81 (d, *J* = 8.0 Hz, 1H, H-6), 7.74 (d, *J* = 16.0 Hz, 1H, H-*α*), 7.67 (d, *J* = 8.0 Hz, 1H, H-8"), 7.55 (s, 1H, H-4"), 7.49 (t, *J* = 8.0 Hz, 1H, H-4'), 7.39 (t, *J* = 8.0 Hz, 1H, H-7"), 7.21 (d, *J* = 8.0 Hz, H-6"), 7.13 (m, 3H, H-*β*, H-4, H-5), 6.89 (s, 1H, H-2"),

6.84 (d, J = 8.0 Hz, 1H, H-3'), 5.83 (s, 2H, 5'-CH_2-9"), 3.92 (s, 3H, 1"-OCH_3), 3.85 (s, 3H, 2-OCH_3), and 2.45 (s, 3H, 3"-CH_3). **^{13}C-NMR** (DMSO-d_6, 125 MHz) δ_C 193.1 (C=O), 160.5 (C-2'), 158.5 (C-2), 146.2 (C-1"), 140.5 (C-13"), 139.2 (C-6), 134.3 (C-4'), 132.9 (C-β), 130.1 (C-5'), 129.1 (C-3"), 128.7 (C-4), 128.6 (C-6'), 127.3 (C-11"), 125.7 (C-7"), 124.3 (C-10"), 122.6 (C-12"), 122.5 (C-1), 121.5 (C-α), 120.8 (C-1'), 120.7 (C-3), 120.2 (C-8"), 119.0 (C-3'), 117.9 (C-6"), 112.6 (C-2"), 109.9 (C-5"), 109,5 (C-5); 55.7 (1"-O<u>C</u>H_3), 55.8 (2-OCH_3), 47.1 (5'-CH_2-9"), and 21.3 (3"-<u>C</u>H_3).

3. RESULTS AND DISCUSSION

3.1. Synthesis of new 2'-hydroxychalcones containing murrayafoline A

The synthesis of chalcones **6a-f** was started from commercial 2'-hydroxyacetophenone (**1**) (Scheme 1). 5'-Chloromethyl-2'-hydroxyacetophenone (**2**) was obtained in 79 % yield by chloromethylation of **1** with paraformaldehyde in HCl at 35 ^oC as described by Wong [11]. Compound **2** was then *N*-alkylated with murrayafoline A under microwave to give 5'-(1-methoxy-3-methylcarbazolyl)methylacetophenone (**4)** in a yield of 46 %. Spectral data of **4** were agreed well with its structure.



6a: R_1, R_2, R_3= H, R_4= OCH_3
6b: R_1, R_2, R_4= H, R_3= OCH_3
6c: R_1= H, R_2, R_3, R_4= OCH_3
6d: R_1, R_2, R_4= H, R_3= isopropyl
6e: R_1, R_2, R_4= H, R_3= CH_3
6f: R_1= OCH_3, R_2, R_3, R_4= H

Schemes 1: Preparation of 5'-(1-methoxy-3-methyl-N-carbazolyl)methyl-2'-hydroxychalcones **6a-f**
Reagents and conditions: i, paraformaldehyde, HCl, 35 ^oC; ii, MuA **3**, K_2CO_3, DMF, MW 250 W, 20 min; iii, aldehydes **5a-5f**, KOH, EtOH.

In the final step, the chalcones **6a-f** (57 - 81 % yields) were prepared in by Claisen-Schmidt condensation of **4** with various aldehydes: 3-methoxy benzaldehyde (**5a**), 4-methoxy benzaldehyde (**5b**), 3,4,5-trimethoxy benzaldehyde (**5c**), 4-isopropyl benzaldehyde (**5d**), 4-methyl benzaldehyde (**5e**) and 2-methoxy benzaldehyde (**5f)** in ethanol, catalyzed by KOH at room temperature. The structures of chalcones **6a-f** were elucidated by 1D, 2D-NMR, and MS data. Among these derivatives, chalcone **6c** was selected to be an example for determination of structures **(6a-f)**. The ^{1}H-NMR spectrum of **6c** showed the presence of murrayafoline A moiety by signals of the protons: Two singlets at δ_H 7.53 and 6.86 attributed to H-4" and H-2",

respectively. A signal at δ_H 7.39 (*J* = 8.0 Hz) was assigned to H-7", signal of H-6" (δ_H 7.16) was overlapped with signals of H-2, H-6 and H-4'. The resonances of H-5" and H-8" arose two doublets (*J* = 8.0 Hz) at δ_H 8.05 and 7.68, respectively. Assignment of carbons in murrayafoline A moiety was further supported by analysis of HSQC and HMBC spectra. Specially, the connection of murrayafoline A with 2'-hydroxychacone was confirmed by HMBC correlation between 9"-CH2-(δ_H 5.84) and C-6' (δ_C 128.9), C-5' (δ_C 129.9), C-4' (δ_C 134.1) of ring A and C-13" (δ_C 140.4) of murrayafoline A (Figure 2).

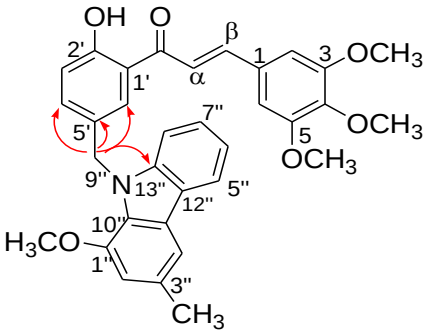


Figure 2. The key HMBC correlations of derivative **6c**.

3.2. Bioactive assays

The cytotoxic activity of **6a-f** was evaluated according to the method described by Monk and co-workers [10]. Chalcones **6a-f** exhibited much weaker activity than that of murayafoline A (Table 1). Among them, only chalcone **6a** containing three methoxy groups in ring B was found to show moderate cytotoxic activity against all tested cancer cell lines. Activity of chalcone **6c**, **6d** indicated that 3-methoxy or 4-isopropyl substituents of aldehydes could be useful for activity against MCF-7, P-338 and SW480 cell lines. Substituents 4-methyl and 2-methoxy of chalcones **6e**, **6f** in ring B did not improve their cytotoxic activity. In addition, the results also confirmed the important role of the N-H group in murrayafoline A for its cytotoxic activity.

Table 1. Cytotoxic activity of the synthesized 2'-hydroxychalcones containing murrayafoline A.

No	**Compounds**	**IC_{50} (µg/mL)**				
		LU-1	**HepG2**	**MCF7**	**P388**	**SW480**
1	6a	47.83 ± 1.07	68.22 ± 2.38	80.19 ± 4.01	23.97 ± 7.46	24.43 ± 3.48
2	6b	>100	>100	59.48 ± 3.40	19.09 ± 1.46	68.81 ± 2.13
3	6c	>100	>100	63.33 ± 3.07	23.45 ± 1.40	>100
4	6d	>100	>100	96.62 ± 5.20	44.46 ± 0.24	56.17 ± 1.74
5	6e	>100	>100	>100	>100	>100
6	6f	>100	>100	>100	>100	>100
7	Murrayafoline A	19.68 ± 2.93	8.73 ± 0.17	16.90 ± 2.17	4.21 ± 0.50	4.35 ± 1.21
8	Ellipticine*	0.57 ± 0.15	0.51 ± 0.11	0.38 ± 0.07	0.29 ± 0.05	0.48 ± 0.02

* Ellipticine was used as a positive control.

4. CONCLUSIONS

Three reactions including chloromethylation, *N*-alkylation and Claisen Schmidt condensation were used to conjugate 2'-hydroxyacetophenone and murrayafoline A to six new 2'-hydroxychalcones. Their cytotoxic activity against LU-1, HepG2, MCF-7, P338, and SW480 human cancer cell lines was evaluated and discussed. The results confirmed that the N-H group of murrayafoline A was the required functional group for its cytotoxicity. This is a useful suggestion for orientation in the design of the murrayafoline A derivatives.

Acknowledgements. The present research was supported by Vietnam Academy of Science and Technology (VAST) via the project: VAST04.02/15-16.

Credit authorship contribution statement. Le Duc Anh: Investigation, formal analysis. Luu Van Chinh: Supervision, formal analysis and writing the manuscript. Truong Ngoc Hung: Investigation, formatting and submitting the final manuscript. Nguyen Manh Cuong: Providing material (murrayafoline A). Pham Hong Ngoc: Investigation.

Declaration of competing interest. The authors declare no conflict of interests.

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