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STUDY ON THE SYNTHESIS OF SOME NEW DERIVATIVES OF MALLOAPELTA B ISOLATED FROM *MALLOTUS APELTA*

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SUMMARY

*Six new benzopyran derivatives were synthesized by reduction reaction and Michael reaction from malloapelta B. Their structures were determined as 8-(1'-oxo-butyl)-5,7-dimethoxy-2,2-dimethyl-2H-1-benzopyran (**2**), 8-(1'-oxo-3'(R)-methyl-4'-acetyl-5'-oxo-hexyl)-5,7-dimethoxy-2,2-dimethyl-2H-1-benzopyran (**3**), 8-(1'-oxo-3'(R)-methyl-4'(S/R)-(methyl fomiate)-5'-oxo-hexyl)-5,7-dimethoxy-2,2-dimethyl-2H-1-benzopyran (**4**,**4'**), 8-(1'-oxo-3'(R)-methyl-4'(S/R)-(ethyl formiate)-5'-oxo-hexyl)-5,7-dimethoxy-2,2-dimethyl-2H-1-benzopyran (**5**,**5'**) by spectroscopic data, including two-dimensional NMR techniques and ESI spectrum.*

Keywords: *Malloapelta B; Michael reaction; reduction reaction; 5,7-dimethoxy-2,2-dimethyl-2H-1-benzopyran.*

I - INTRODUCTION

Malloapelta B (**1**), a new benzopyran derivative was isolated from the Vietnamese traditional medicinal plant *Mallotus apelta* (Lour.) Muell.-Arg. [1]. It shows strong cytotoxic effect as well as strong activity against NF-κB activation with IC_{50} value 0.54±0.05 μM. This compound is continued studying further for cancer treatment [2, 3]. To investigate the relations between the structures and their bioactivities as well as probably find new derivatives having stronger bioactivities, we have synthesized a series of its derivatives.

As a part of our research, we report herein six new derivatives synthesized by reduction reaction and Michael reaction. Their structures were determined as 8-(1'-oxo-butyl)-5,7-dimethoxy-2,2-dimethyl-2H-1-benzopyran (**2**), 8-(1'-oxo-3'(*R*)-methyl-4'-acetyl-5'-oxo-hexyl)-5,7-dimethoxy-2,2-dimethyl-2H-1-benzopyran (**3**), 8-(1'-oxo-3'(*R*)-methyl-4'(*S*/*R*)-(methyl formiate)-5'-oxo-hexyl)-5,7-dimethoxy -2,2-dimethyl-2H-1-benzopyran (**4**, **4'**), 8-(1'-oxo-3'(*R*)-methyl-4'(*S*/*R*)-(ethyl formiate)-5'-oxo-hexyl)-5,7-dimethoxy-2,2-dimethyl-2H-1-benzopyran (**5**, **5'**) by the NMR and MS spectra. The relationships between their structures and cytotoxicities will be reported elsewhere.

II - EXPERIMENTAL

Materials and methods

Material

Malloapelta B was isolated from M*allotus apelta* (Lour.) Muell.-Arg.. The reagents were purchased of Aldrich Co. Solvents were distilled prior to use.

General Experimental Procedures

The Electronspray Ionization (ESI) mass spectrum was obtained by using an AGILENT 1100 LC-MSD Trap spectrometer. The ^{1}H-NMR (500 MHz) and ^{13}C-NMR (125 MHz) spectra

were recorded on a Bruker AM500 FT-NMR spectrometer using TMS as the internal standard. Column chromatography (CC) was performed on silica gel (Kieselgel 60, 70-230 mesh and 230-400 mesh, Merck). TLC was performed with Thin layer Art 5562 DC-Alurolle Kieselgel made by Merck Co.

The synthesis of 8-(1'- oxo-butyl)-5,7-dimethoxy-2,2-dimethyl-2H-1-benzopyran (2)

20 mg (0.62 mmol) $NaBH_4$ was added slowly to a solution of 150 mg (0.52 mmol) malloapelta B with 15 ml MeOH in a 40 ml round-flask placed on a magnetic stirrer. The reaction was kept at room temperature for 4 h. The reaction mixture was extracted with mixture $CHCl_3/H_2O$. The $CHCl_3$ extract was separated by column chromatography over silica gel eluted with *n*-hexane-acetone (10:1) to afford 128 mg of the reduced product **2**, yield 85%.

^{1}H-NMR (500 MHz, MeOD), δ (ppm): 5.44 (1H, d, *J* = 10.5 Hz, H-3), 6.56 (1H, d, *J* = 10.5 Hz, H-4), 6.00 (1H, s, H-6), 2.72 (2H, m, H-2'), 1.70 (2H, m, H-3'), 0.95 (3H, t, *J* = 6.5 Hz, H-4'), 3.70 (3H, 7-OCH_3), 3.83 (3H, 5-OCH_3), 1.39 (6H, s, H-11, H-12).

^{13}C-NMR (125 MHz, MeOD), δ (ppm): 76.7 (s, C-2), 126.6 (d, C-3), 116.4 (d, C-4), 157.6 (s, C-5), 87.8 (d, C-6), 156.5 (s, C-7), 113.6 (s, C-8), 151.5 (s, C-9), 104.2 (s, C-10), 27.7 (q, C-11, C-12), 204.2 (s, C-1'), 47.0 (t, C-2'), 17.6 (t, C-3'), 13.9 (q, C-4'), 55.7 (q, 7-OCH_3), 55.8 (q, 5-OCH_3).

ESI m/z: 291 $[M+H]^+$ ($C_{17}H_{23}O_4$).

The synthesis of 8-(1'-oxo-3'(R)-methyl-4'-acetyl-5'-oxo-hexyl)-5,7-dimethoxy-2,2-dimethyl-2H-1-benzopyran (3)

A mixture of 150 mg (0.52 mmol) *malloapelta B* and acetylacetone in 15ml MeOH added 200 µL NaOH20% was placed on a magnetic stirrer in a 40 ml round-flask. The mixture was maintained at room temperature in 12h. Removal of the solvent afforded a residue that was purified by column chromatography over silica gel eluted with *n*-hexane-acetone (6:1) to give 138 mg product **3**, yield 68%.

^{1}H-NMR (500 MHz, MeOD), δ (ppm): 5.44 (1H, d, J = 10.5 Hz, H-3), 6.55 (1H, d, J = 10.5 Hz, H-4), 5.99 (1H, s, H-6), 1.39 (3H, s, H-11), 1.37 (3H, s, H-12), 2.71 (1H, dd, *J* = 17.0, 8.5 Hz, Ha-2'), 2.74 (1H, dd, *J* = 17.0, 4.0 Hz, Hb-2'), 2.80 (1H, m, H-3'), 3.84 (1H d, *J* = 9.0 Hz, H-4'), 1.01 (3H, d, *J* = 6.5 Hz, H-5'), 2.18 (3H, s, H-7'), 2.19 (3H, s, H-9'), 3.83 (3H, s, 7-OCH_3), 3.78 (3H, s, 5-OCH_3).

^{13}C-NMR (125 MHz, MeOD), δ (ppm): 76.8 (s, C-2), 126.7 (d, C-3), 116.3 (d, C-4), 156.7 (s, C-5), 87.8 (d, C-6), 157.6 (s, C-7), 113.2 (s, C-8), 151.5 (s, C-9), 104.3 (s, C-10), 27.7 (q, C-11, C-12), 202.0 (s, C-1'), 48.7 (t, C-2'), 30.2 (d, C-3'), 73. (d, C-4'), 17.7 (q, C-5'), 204.6 (s, C-6'), 29.7 (q, C-7'), 204.6 (s, C-8'), 29.9 (q, C-9'), 55.7 (q, 7-OCH_3) and 55.7 (q, 5-OCH_3).

ESI m/z: 389 $[M+H]^+$ ($C_{22}H_{29}O_6$).

The synthesis of 8-(1'-oxo-3'(*R*)-methyl-4'-(*S*/*R*)-(methyl formiate)-5'-oxo-hexyl)-5,7-dimethoxy-2,2-dimethyl-2H-1-benzopyran (4,4')

A mixture of 150 mg (0.52 mmol) *malloapelta B* and acetoacetate methyl ester in 15 ml MeOH added 20 mg CH_3ONa was placed on a magnetic stirrer in a 40 ml round-flask. The mixture was maintained at room temperature overnight. Removal of the solvent afforded a residue that was purified by column chromatography over silica gel eluted with *n*-hexane-acetone (4:1) to give 148 mg the mixture of two optical isomers **4** and **4'**, yield 71%.

^{1}H-NMR (500 MHz, MeOD), δ (ppm): 5.43 (d, J = 10.5 Hz, H-3), 6.55 (d, J = 10.5 Hz, H-4), 5.99 (s, H-6), 1.38 (s, H-11), 1.38 (s, H-12), 2.82 - 2.92 (m, H-2'), 2.74 (m, H-3'), 3.56 (d, *J* = 7.5 Hz, H-4')/3.65 (d, *J* = 7.5 Hz, H-4'), 1.05 (3H, s, H-5')/1.06 (3H, s, H-5'), 2.46 (s, H-7'), 3.71 (s, H-9'), 3.78 (s, OCH_3), 3.83 (s, OCH_3).

^{13}C-NMR (125 MHz, MeOD), δ (ppm): 76.88/76.91 (s, C-2), 126.69/126.69 (d, C-3), 116.30/116.31 (d, C-4), 156.65/156.68 (s, C-5), 87.80/87.86 (d, C-6), 157.60/157.60 (s, C-7), 113.21/113.28 (s, C-8), 151.54/151.54 (s, C-9), 104.24/104.24 (s, C-10), 27.65/27.65 (q, C-11), 27.70/27.70 (q, C-12), 202.06/202.17 (s, C-1'),

48.71/48.96 (t, C-2'), 29.38/29.44 (d, C-3'), 64.25/63.97 (d, C-4'), 17.28/17.84 (q, C-5'), 29.64/29.44 (q, C-7'), 52.07/52.12 (q, C-9'), 55.68/5.68 (q, 7-OCH_3), 55.80/55.80 (q, 5-OCH_3).

ESI m/z: 405 $[M+H]^+$ ($C_{22}H_{29}O_7$).

The synthesis of 8-(1'-oxo-3'(*R*)-methyl-4' (*S*/*R*)-(ethylformiate)-5'-oxo-hexyl)-5,7-dimethoxy-2,2-dimethyl-2H-1-benzopyran (5,5')

A mixture of 150 mg (0.52 mmol) *malloapelta B* and acetoacetate ethyl ester in 15 ml C_2H_5OH added 200 µL NaOH 20% was placed on a magnetic stirrer in a 40 ml round-flask. The mixture was maintained at room temperature in 14 h. Removal of the solvent afforded a residue that was purified by column chromatography over silica gel eluted with *n*-hexane-acetone (4:1) to give 152 mg the mixture of two optical isomers **5** and **5'**, yield 70%.

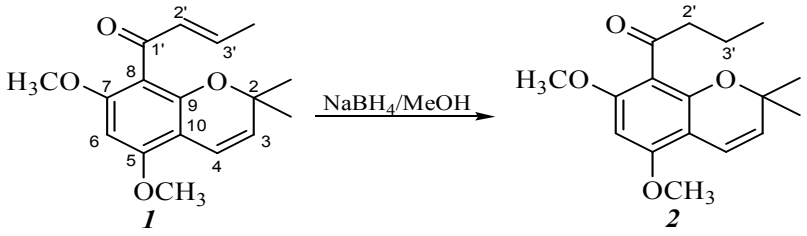
^{1}H-NMR (500 MHz, MeOD), δ (ppm): 5.45 (d, *J* = 10.5 Hz, H-3), 6.56 (d, J = 10.5 Hz, H-4), 5.99 (s, H-6), 2.83 - 2.92 (m, H-2'), 2.74 (m, H-3'), 3.52 (d, J = 7.5 Hz, H-4')/3.60 (d, *J* = 7.5 H-4'), 1.05 (d, *J* = 6.5 Hz, H-5')/1.06 (d, *J* = 6.5 Hz, H-5'), 2.24 (s, H = 7'), 4.17 (q, *J* = 6.5 Hz, H-9'), 1.26 (t, *J* = 6.5 Hz, H-10'), 3.77 (s, 7-OCH_3), 3.83 (s, 5-OCH_3).

^{13}C-NMR (125 MHz, MeOD), δ (ppm): 76.81/76.82 (s, C-2), 126.69/126.69 (d, C-3), 116.30/116.80 (d, C-4), 156.63/156.67 (s, C-5), 87.80/87.80 (d, C-6), 157.09/157.09 (s, C-7), 113.26/113.34 (s, C-8), 151.51/151.51 (s, C-9), 104.24/104.24 (s, C-10), 27.65/27.65 (q, C-11), 27.70/27.70 (q, C-12), 202.13/202.21 (s, C-1'), 48.77/48.99 (t, C-2'), 29.40/29.57 (d, C-3'), 64.30/64.48 (d, C-4'), 17.35/17.80 (q, C-5'), 203.36/203.38 (s, C-6'), 29.30/29.34 (q, C-7'), 169.10/169.16 (s, C-8'), 61.10/61.09 (t, C-9'), 14.12/14.13 (q, C-10'), 55.79/55.79 (q, OCH_3), 56.00/56.00 (s, OCH_3).

ESI m/z: 419 $[M+H]^+$ ($C_{23}H_{31}O_7$).

III - RESULTS AND DISCUSSION

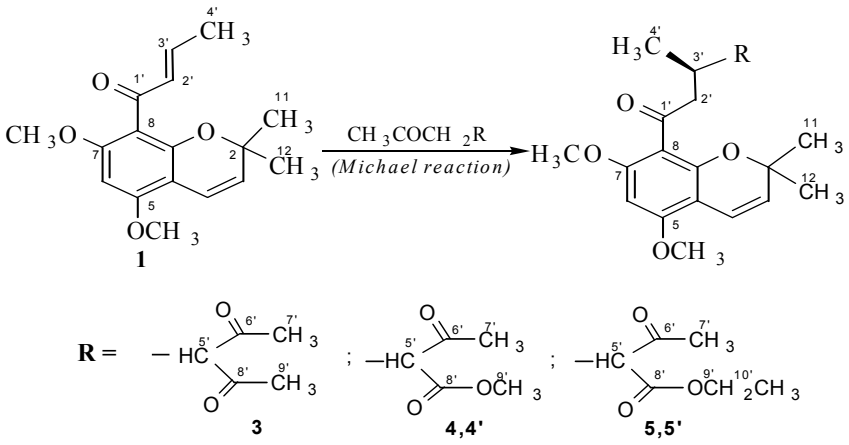
Compound **2** was obtained as white crystals from the reduction reaction after being purified by column chromatography over silica gel. The synthetic process [4, 5] was illustrated as scheme 1.



Scheme 1

The NMR spectra of **2** were similar to those of **1**, except for the absence of the double bond signals at C-2' and C-3', and the additional of two methylene signals at δ_C 47.0/17.6 and δ_H 2.72 (m)/1.70 (m) in the NMR spectra of **2**. These changes were further confirmed by analysis of the proton-coupling constants and by the appearance of a quasi ion peak at *m/z* 291 [M+H] ($C_{17}H_{22}O_4$ + H) in the positive ESI spectrum of **2**. Consequently, the structure of **2** was 8-(1'-oxo-butyl)-5,7-dimethoxy-2,2-dimethyl-2H-1-benzopyran.

Compounds **3**, **4/4'**, **5/5'** were obtained as white crystals by Michael reaction with acetylacetone, acetoacetate methyl ester, and acetoacetate ethyl ester as agents of the reactions, respectively. The synthetic process of these compounds [4, 5] was illustrated as scheme 2.



Scheme 2

The ^{1}H-NMR of **3** exhibited two doublets at δ 5.44 and 6.55 (J = 10.5 Hz), which were assigned to H-3 and H-4, respectively. A singlet of H-6 was at δ 5.99, two quaternary methyl groups at δ 1.37 and 1.39 as the singles, two methoxyl groups were at 3.78 and 3.83. The acetoacetyl group was determined to connect at C-3' from the appearance of two methyl groups at δ 2.18 and 2.19, and a methine proton at δ 3.84 (d, J = 9.0 Hz). In addition, the methyl group at δ 1.01 as a doublet (J = 6.5 Hz) also confirmed the acetoacetyl group attached to C-3'. The ^{13}C-NMR and DEPT spectra of **3** showed signals of 22 carbons. The two acetyl groups were confirmed at δ 204.6, 29.7/29.9. The methylene and methine carbons at δ 48.7 and 30.2, respectively evidenced the absence of the double bond. Furthermore, the ESI exhibited a quasi ion peak at m/z 389 [M+H], correspond to the molecular formula of $C_{22}H_{28}O_6$. From the above data, compound **3** was determined to be 8-(1'-oxo-3'(*R*)-methyl-4'-acetyl-5'-oxo-hexyl)-5,7-dimethoxy-2,2-dimethyl-2H-1-benzopyran.

Compounds **4/4'** and **5/5'** were obtained as two racemics, which were confirmed by the analysis of NMR data. All the NMR spectra of **4/4'** and **5/5'** were similar to those of **3**, except for the more appearance of the methoxy group (δ_C 52.12/52.07 and δ_H 3.71) instead of the methyl carbon at δ_C 29.9/δ_H 2.19). The stereochemistry at C-3' of **4/4'** and **5/5'** were suggested to be (*R*) by comparing the chemical shifts and proton coupling constants of **4/4'** and **5/5'** with those of 6-(methyl 1′-oxo-3′-hydroxy-butyl ether)-5,7-dimethoxy-2,2-dimethyl-2H-1-benzopyran and 6-(1′-oxo-3′-hydroxy-butyl)-5,7-dimethoxy-2,2-dimethyl-2H-1-benzopyran [6], and with the similar structure reported in the literature [7]. In addition, the ESI spectra of **4/4'** and **5/5'** showed the ion peaks at m/z 405 $[M+H]^+$ and 419 $[M+H]^+$ corresponding to the molecular formula of $C_{22}H_{28}O_7$ and $C_{23}H_{30}O_7$, respectively. Thus, compound **4/4'**was determined to be a racemic of 8-(1'-oxo-3'(*R*)-methyl-4'(*S*/*R*)-(methyl formiate)-5'-oxo-hexyl)-5,7-dimethoxy-2,2-dimethyl-2H-1-benzopyran and **5/5'** was a racemic of 8-(1'-oxo-3'(*R*)-methyl-4'(*S*/*R*)-(ethyl formiate)-5'-oxo-hexyl)-5,7-dimethoxy-2,2-dimethyl-2H-1-benzopyran.

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