Synthesis and Cytotoxic Evaluation of a Series of γ-Substituted γ-Aryloxyethyl-α-methylene-γ-butyrolactones Against Cancer Cells

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Purpose. The main objective of this investigation was to explore the cytotoxic structure-activity relationships of γ-substituted γ-aryl oxyethyl-α-methylene-γ-butyrolactones against cancer cells.

Methods. The target compounds were synthesized in two steps commencing with aryl-α-OH which was treated with a bromomethyl ketone followed by the Reformatsky-type condensation.

Results. Seven types of α-methylene-γ-butyrolactones were evaluated in vitro against 60 human cancer cell lines derived from nine cancer cell types. The average values of log GI50 indicated that for the aryl portion, potencies of these α-methylene-γ-butyrolactones are in a decreasing order of quinolin-2(1H)-one (or 2-hydroxyquinoline, 21, −5.89) > quinoline (19, −5.79) > 2-methylquinoline (20, −5.69) > 8-hydroxyquinoline (17, −5.64) > 2-napthalene (16, −5.59) > benzene (15, −4.90). The same order was obtained for both log TGI and log LC50. However, for the γ-substituent, the potencies are in a decreasing order of biphenyl (16f–21f) > phenyl and 4-substituted phenyl (16e–21e) > methyl (16a–21a).

Conclusions. Unlike cardiovascular activities of α-methylene-γ-butyrolactones in which a γ-aryl substituent is necessary for vasorelaxing effect while a phenyl or a halogen-substituted phenyl is prefer for the platelet activities, a γ-biphenyl substituent proved to be the best for their cytotoxicities against various cancer cell lines tested.

KEY WORDS: α-methylene-γ-butyrolactones; cytotoxicity; quinolin-2(1H)-one; quinoline.

INTRODUCTION

The α-methylene-γ-butyrolactone moiety is a characteristic component of a large number of natural products, especially the sesquiterpene lactones, which possess wide-ranging biological activities, including antitumor, bactericidal, fungicidal, antibacterial, and antihelmintic properties (1–3). However, the biological activity of α-methylene-γ-butyrolactones is not only confined to the complex multifunctional sesquiterpene lactones. For example, the parent α-methylene-γ-butyrolactone (tulipaline A), first isolated from *Erythronium americanum* in 1946, was identified as a substance with allergic, antibiotic, and fungitoxic activities (4–6). Recently, it has also been reported that some natural α-methylene-γ-butyrolactone bearing butanolides, which was isolated from *Litsea akoensis*, also have significant cytotoxicity (7). Due to the unique structural feature as well as interesting biological activities of α-methylene-γ-butyrolactones, their synthesis has attracted renewed attentions (8–10). A number of possible drug candidates bearing this versatile functionality have also been synthesized with the aim of finding effective clinical drugs (11–14). Over the past few years, we were particularly interested in synthesizing α-methylene-γ-butyrolactones (1) and evaluated for their cardiovascular activities (15–18). Although the enone (O = C–C = CH2) component in this type of lactone is essential for their biological activities, by acting as an alkylating agent through a Michael-type reaction with bionucleophiles or sulfhydryl-containing enzymes (19), the substituent at γ-position of the lactone also played an important role for their pharmacological properties. For example, a phenyl group at γ-position contributed more antiplatelet activities than a methyl substituent, while a biphenyl counterpart is relatively inactive as a vasorelaxing agent (15–18). Recently, we have reported certain γ-aryl oxyethyl-α-methylene-γ-phenyl-γ-butyrolactones (I, R = phenyl) as potential anticancer agents (20). To explore the effect of γ-substitution with respect to cytotoxicities of the α-methylene-γ-butyrolactones, we report herein the preparation and evaluation of a series of γ-substituted γ-aryl oxyethyl-α-methylene-γ-butyrolactones. Their structure-activity relationships are also described.

MATERIALS AND METHODS

Melting points were determined on a Yanaco micromelting-point apparatus and are uncorrected. Proton nuclear magnetic resonance (1H NMR) spectra were obtained with a Varian Gemini-200, spectrometer. Chemical shifts were expressed in parts per million (δ) with TMS as an internal standard. Thin-layer chromatography (TLC) was run on precoated (0.2 mm) silica gel 60 F-254 plates manufactured by EM Laboratories, Inc., and short wave UV light (254 nm) was used to detect the UV-absorbing spots. Elemental analyses were carried out on a Heraeus CHN-O-Rapid elemental analyzer and the results were within ±0.4% of theoretical values.

2-(Naphthalene-2-yl)-1-(4-Fluorophenyl)ethan-1-one (9c)

2-Naphthol (2; 1.44 g, 10 mmol), K2CO3 (1.52 g, 11 mmol), and dry DMF (20 ml) were stirred at r.t. for 30 min. 2-Bromo-4'-fluoroacetophenone (2.39 g, 11 mmol) in dry DMF (10 ml) was added to this solution. The resulting mixture was stirred for 24 h (TLC monitoring), then poured into ice-water (100 ml), and extracted with CHCl3 (3 × 20 ml). The organic phase was washed with H2O, dried (Na2SO4), and evaporated and the crude oil submitted to column chromatography (silica gel, EtOAc/hexane 1:9): 9c (1.99 g, 71%). mp 81–82°C. Anal. (C18H13F2O2) C, H, N. 1H-NMR (CDCl3) δ: 5.33 (2H, s), 7.12–8.14 (11H, m).

2-(Naphthalene-2-yl)-1-(4-Chlorophenyl)ethan-1-one (9d)

From 2 and 2-bromo-4'-chloroacetophenone as described for 9c: 73% yield. mp 110–111°C. Anal. (C18H13ClO2) C, H, N. 1H-NMR (CDCl3) δ: 5.32 (2H, s), 7.11–8.02 (11H, m).
2-(Naphthalen-2-yl)oxy)-1-(4-Methoxyphenyl)ethan-1-one (9e)

From 2 and 2-bromo-4'-methoxyacetophenone as described for 9c: 87% yield. mp 93–94°C. Anal. (C₁₉H₁₆O₃) C.H.N. 1H-NMR (CDCl₃): δ: 3.87 (3H, s), 5.31 (2H, s), 6.95–8.06 (11H, m).

2-(Naphthalen-2-yl)oxy)-1-(1',1'-Biphenyl-4-yl)ethan-1-one (9f)

From 2 and 2-bromo-4'-phenylacetophenone as described for 9c: 68% yield. mp 125–126°C. Anal. (C₂₃H₁₈O₃) C.H.N. 1H-NMR (CDCl₃): δ: 3.87 (3H, s), 5.31 (2H, s), 6.76–8.38 (11H, m).

2-(Naphthalen-1-yl)oxy)-1-(4-Methoxyphenyl)ethan-1-one (11e)

From naphthalen-1-ol (4) and 2-bromo-4'-methoxyacetophenone as described for 9c: 77% yield. mp 90–91°C. Anal. (C₁₉H₁₆O₃) C.H.N. 1H-NMR (CDCl₃): δ: 3.87 (3H, s), 5.36 (2H, s), 6.76–8.38 (11H, m).

2-(Naphthalen-1-yl)oxy)-1-(1',1'-Biphenyl-4-yl)ethan-1-one (11f)

From 4 and 2-bromo-4'-phenylacetophenone as described for 9c: 88% yield. mp 125–126°C. Anal. (C₂₃H₁₈O₃) C.H.N. 1H-NMR (CDCl₃): δ: 5.45 (2H, s), 6.79–8.40 (16H, m).

2,3,4,5-Tetrahydro-2-Methyl-4-Methoxy-5-oxo-2-Phenoxy methylfurin (15a)

To a solution of 1-phenoxypyran-2-one (8a, 0.15 g, 1 mmol) in dry THF (20 ml) were added activated zinc powder (85 mg, 1.3 mmol), hydroquinone (2 mg), and ethyl 2-bromo(methyl)acrylate (0.26 g, 1.3 mmol). The mixture was refluxed under N₂ for 4 h (TLC monitoring). After cooling, it was poured into an ice-cold 5% HCl solution (100 ml) and extracted with CH₂Cl₂ (3 × 50 ml). The CH₂Cl₂ extracts were combined and washed with brine, dried (Na₂SO₄), and evaporated to give a white solid which was crystallized from EtOAc: 15a (0.21 g, 94%), white crystalline solid. mp 71–72°C. Anal. (C₁₈H₁₆O₃) C.H.N. 1H-NMR (CDCl₃): δ: 2.09 (3H, s), 3.28 (1H, dt, J = 17.2, 2.9), 3.72 (1H, dt, J = 17.2, 2.5), 4.46, 4.55 (2H, AB, J = 9.7), 6.20 (1H, t, J = 2.5), 6.82 (1H, t, J = 2.9), 7.40–7.87 (5H, m).

The same procedure was used to convert 8b to 15b, 9a-f to 16a-f, and 11e-f to 18e-f, respectively.

2,3,4,5-Tetrahydro-4-Methoxy-5-oxo-2-Phenoxy methyl-2-Phenyl furan (15b)

Yield 82%. mp 60–62°C. Anal. (C₁₈H₁₆O₃) C.H.N. 1H-NMR (CDCl₃): δ: 3.19 (1H, dt, J = 16.8, 2.9), 3.67 (1H, dt, J = 16.8, 2.4), 4.10, 4.18 (2H, AB, J = 10.1), 5.67 (1H, t, J = 2.6), 6.29 (1H, t, J = 2.9), 6.81–7.49 (10H, m).

2,3,4,5-Tetrahydro-2-Methyl-4-Methoxy-2-[(Naphthalen-2-yl)methyl]-5-Oxofuran (16a)

Yield 76%. mp 88–89°C. Anal. (C₁₇H₁₆O₃) C.H.N. 1H-NMR (CDCl₃): δ: 1.60 (3H, s), 2.78 (1H, dt, J = 17.1, 2.8), 3.23 (1H, dt, J = 17.1, 2.6), 4.03, 4.12 (2H, AB, J = 9.7), 5.67 (1H, t, J = 2.5), 6.30 (1H, t, J = 2.9), 7.09–7.79 (7H, m).

2,3,4,5-Tetrahydro-4-Methoxy-2-[(Naphthalen-2-yl)methyl]-5-Oxofuran (16b)

Yield 89%. mp 84–86°C. Anal. (C₁₇H₁₆O₃) C.H.N. 1H-NMR (CDCl₃): δ: 3.23 (1H, dt, J = 16.8, 2.9), 3.71 (1H, dt, J = 16.8, 2.5), 4.22, 4.30 (2H, AB, J = 10.1), 5.70 (1H, t, J = 2.5), 6.33 (1H, t, J = 2.9), 7.06–7.74 (12H, m).

2,4,5-Tetrahydro-4-Methoxybenzo[b]furan (16c)

Yield 74%. mp 126–127°C. Anal. (C₁₇H₁₆O₃) C.H.N. 1H-NMR (CDCl₃): δ: 3.19 (1H, dt, J = 16.8, 2.9), 3.69 (1H, dt, J = 16.8, 2.4), 4.19, 4.27 (2H, AB, J = 10.1), 5.71 (1H, t, J = 2.4), 6.34 (1H, t, J = 2.8), 7.06–7.78 (11H, m).

2,3,4,5-Tetrahydro-2-(4-Methoxyphenyl)-4-Methoxy-2-[(Naphthalen-2-yl)methyl]-5-Oxofuran (16d)

Yield 91%. mp 110–111°C. Anal. (C₂₃H₂₀O₄) C.H.N. 1H-NMR (CDCl₃): δ: 3.17 (1H, dt, J = 16.9, 2.9), 3.69 (1H, dt, J = 16.9, 2.6), 4.18, 4.26 (2H, AB, J = 10.1), 5.71 (1H, t, J = 2.4), 6.33 (1H, t, J = 2.8), 7.05–7.78 (11H, m).

2,3,4,5-Tetrahydro-2-(4-Methoxyphenyl)-4-Methoxy-2-[(Naphthalen-1-yl)methyl]-5-Oxofuran (16e)

Yield 86%. mp 99–100°C. Anal. (C₂₃H₂₀O₄) C.H.N. 1H-NMR (CDCl₃): δ: 3.19 (1H, dt, J = 16.8, 2.9), 3.67 (1H, dt, J = 16.9, 2.4), 3.83 (3H, s), 4.17, 4.27 (2H, AB, J = 10.2), 5.69 (1H, t, J = 2.4), 6.31 (1H, t, J = 2.9), 6.94–7.77 (11H, m).

2-(1',1'-Biphenyl-4-yl)-2,3,4,5-Tetrahydro-4-Methoxy-2-[(Naphthalen-2-yl)methyl]-5-Oxofuran (16f)

Yield 72%. mp 172–173°C. Anal. (C₂₅H₂₂O₃) C.H.N. 1H-NMR (CDCl₃): δ: 3.27 (1H, dt, J = 17.1, 2.9), 3.74 (1H, dt, J = 17.1, 2.4), 4.29, 4.37 (2H, AB, J = 10.1), 5.72 (1H, t, J = 2.4), 6.35 (1H, t, J = 2.7), 7.12–7.76 (16H, m).

2,3,4,5-Tetrahydro-2-(4-Methoxyphenyl)-4-Methoxy-2-[(Naphthalen-1-yl)methyl]-5-Oxofuran (18e)

Yield 79%. mp 132–133°C. Anal. (C₂₅H₂₂O₃) C.H.N. 1H-NMR (CDCl₃): δ: 3.28 (1H, dt, J = 16.9, 2.9), 3.75 (1H, dt, J = 16.9, 2.2), 3.84 (3H, s), 4.23, 4.31 (2H, AB, J = 10.1), 5.76 (1H, t, J = 2.6), 6.42 (1H, t, J = 2.9), 6.69–8.10 (11H, m).