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

Cheng-Chyi Tzeng,[1,4] Kuan-Han Lee,[2] Tai-Chi Wang,[2] Chein-Hwa Han,[3] and Yeh-Long Chen[1]

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

Methods. The target compounds were synthesized in two steps commencing with aryl-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 GI_{50} indicated that for the aryl portion, potencies of these α-methylene-γ-butyrolactones are in a decreasing order of quinolin-2(1*H*)-one (or 2-hydroxyquinoline, **21**, −5.89) > quinoline (**19**, −5.79) > 2-methylquinoline (**20**, −5.69) > 8-hydroxyquinoline (**17**, −5.64) > 2-naphthalene (**16**, −5.59) > benzene (**15**, −4.90). The same order was obtained for both log TGI and log LC_{50}. However, for the γ-substituent, the potencies are in a decreasing order of biphenyl (**16f–21f**) > phenyl and 4-substituted phenyl (**16b-e–21b-e**) > methyl (**16a–21a**).

Conclusions. Unlike cardiovascular activities of α-methylene-γ-butyrolactones in which a γ-methyl substituent is necessary for vasorelaxing effect while a phenyl or a halogen-substituted phenyl is prefer for the antiplatelet 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(1*H*)-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, antibiotic, and anthelmintic properties (1–3). However, the biological activity of α-methylene-γ-butyrolactones is not only confined to the complex polyfunctional 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 allergenic, 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 (**I**) and evaluated for their cardiovascular activities (15–18). Although the enone ($O = C–C = CH_2$) 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 actitities than a methyl substituent, while a biphenyl counterpart is relatively inactive as a vasorelaxing agent (15–18). Recently, we have reported certain γ-aryloxymethyl-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-aryloxymethyl-α-methylene-γ-butyrolactones. Their structure-activity relationships are also described.

MATERIALS AND METHODS

Melting points were determined on an *Yanaco* micromelting-point apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H 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-(Naphthalen-2-yloxy)-1-(4-Fluorophenyl)ethan-1-one (9c)

2-Naphthol (**2**; 1.44 g, 10 mmol), K_2CO_3 (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 $CHCl_3$ (3 × 20 ml). The organic phase was washed with H_2O, dried (Na_2SO_4), 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. ($C_{18}H_{13}FO_2$) C,H,N. ^{1}H-NMR ($CDCl_3$) δ: 5.33 (2H, s), 7.12–8.14 (11H, m).

2-(Naphthalen-2-yloxy)-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. ($C_{18}H_{13}ClO_2$) C,H,N. ^{1}H-NMR ($CDCl_3$) δ: 5.32 (2H, s), 7.11–8.02 (11H, m).

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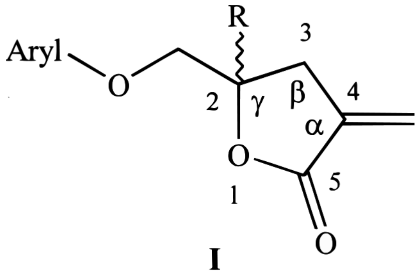
[1] School of Chemistry, Kaohsiung Medical University, Kaohsiung, Taiwan.

[2] Department of Pharmacy, Tajen Institute of Technology, Pingtung, Taiwan.

[3] Department of Pharmacy, Chia Nan College of Pharmacy and Science, Tainan, Taiwan.

[4] To whom correspondence should be addressed. (e-mail: tzengch@cc.kmu.edu.tw)



I

Fig. 1.

2-(Naphthalen-2-yloxy)-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. ($C_{19}H_{16}O_3$) C,H,N. ^{1}H-NMR ($CDCl_3$) δ: 3.87 (3H, s), 5.31 (2H, s), 6.95–8.06 (11H, m).

2-(Naphthalen-2-yloxy)-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. ($C_{24}H_{18}O_2$)C,H,N. ^{1}H-NMR ($CDCl_3$) δ: 5.40 (2H, s), 7.15–8.15 (16H, m).

2-(Naphthalen-1-yloxy)-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. ($C_{19}H_{16}O_3$) C,H,N. ^{1}H-NMR ($CDCl_3$) δ: 3.87 (3H, s), 5.36 (2H, s), 6.76–8.38 (11H, m).

2-(Naphthalen-1-yloxy)-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. ($C_{24}H_{18}O_2$) C,H,N. ^{1}H-NMR ($CDCl_3$) δ: 5.45 (2H, s), 6.79–8.40 (16H, m).

2,3,4,5-Tetrahydro-2-Methyl-4-Methylene-5-oxo-2-Phenoxymethylfuran (15a)

To a solution of 1-phenoxypropan-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-(bromomethyl)acrylate (0.26 g, 1.3 mmol). The mixture was refluxed under N_2 for 4 h (TLC monitoring). After cooling, it was poured into an ice-cold 5% HCl solution (100 ml) and extracted with CH_2Cl_2 (3 × 50 ml). The CH_2Cl_2 extracts were combined and washed with brine, dried (Na_2SO_4), 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. ($C_{13}H_{14}O_3$) C,H,N. ^{1}H-NMR ($CDCl_3$) 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-Methylene-5-oxo-2-Phenoxymethyl-2-Phenylfuran (15b)

Yield 82%. mp 60-62°C. Anal. ($C_{18}H_{16}O_3$) C,H,N. ^{1}H-NMR ($CDCl_3$) 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-Methylene-2-[(Naphthalen-2-yloxy)methyl]-5-Oxofuran (16a)

Yield 76%. mp 88–89°C. Anal. ($C_{17}H_{16}O_3$) C,H,N. ^{1}H-NMR ($CDCl_3$) 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-Methylene-2-[(Naphthalen-2-yloxy)methyl]-5-oxo-2-Phenylfuran (16b)

Yield 89%. mp 84-86°C. Anal. ($C_{22}H_{18}O_3$) C,H,N. ^{1}H-NMR ($CDCl_3$) 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-Fluorophenyl)-2,3,4,5-Tetrahydro-4-Methylene-2-[(Naphthalen-2-yloxy)methyl]-5-Oxofuran (16c).

Yield 74%. mp 126–127°C. Anal. ($C_{22}H_{17}FO_3$) C,H,N. ^{1}H-NMR ($CDCl_3$) 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-(4-Chlorophenyl)-2, 3, 4,-5-Tetrahydro-4-Methylene-2-[(Naphthalen-2-yloxy)methyl]-5-Oxofuran (16d)

Yield 91%. mp 110–111°C. Anal. ($C_{22}H_{17}ClO_3$) C,H,N. ^{1}H-NMR ($CDCl_3$) 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-Methoxphenyl)-4-Methylene-2-[(Naphthalen-2-yloxy)methyl]-5-Oxofuran (16e)

Yield 86%. mp 99–100°C. Anal. ($C_{23}H_{20}O_4$) C,H,N. ^{1}H-NMR ($CDCl_3$) 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-Methylene-2-[(Naphthalen-2-yloxy)methyl]-5-Oxofuran (16f)

Yield 72%. mp 172–173°C. Anal. ($C_{28}H_{22}O_3$) C,H,N. ^{1}H-NMR ($CDCl_3$) 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-Methoxphenyl)-4-Methylene-2-[(Naphthalen-1-yloxy)methyl]-5-Oxofuran (18e)

Yield 79%. mp 132–133°C. Anal. ($C_{23}H_{20}O_4$) C,H,N. ^{1}H-NMR ($CDCl_3$) 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).

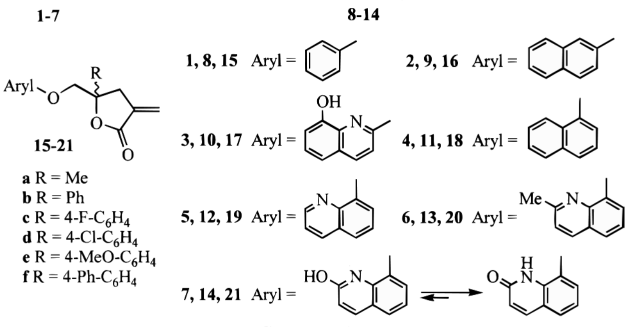
2-(1,1′-Biphenyl-4-yl)-2,3,4,5-Tetrahydro-4-Methylene-2-[(Naphthalen-1-yloxy)methyl]-5-Oxofuran (**18f**)

Yield 84%. mp 161–162°C. Anal. ($C_{28}H_{22}O_3$) C,H,N. ^{1}H-NMR ($CDCl_3$) δ: 3.34 (1H, dt, J = 17.0, 2.9), 3.81 (1H, dt, J = 17.0, 2.2), 4.31, 4.39 (2H, *AB*, J = 10.1), 5.79 (1H, t, J = 2.6), 6.45 (1H, t, J = 2.9), 6.72–8.12 (16H, m).

RESULTS AND DISCUSSION

Preparation of the α-methylene-γ-butyrolactones is illustrated in Scheme 1. Alkylation of phenol with bromoacetone under basic conditions provided 1-phenoxypropan-2-one (**8a**) (21) which was then reacted with ethyl 2-(bromomethyl)acrylate and zinc powder in dry tetrahydrofuran (THF) (*Reformatsky*-type condensation) to afford 2,3,4,5-tetrahydro-2-methyl-4-methylene-5-oxo-2-phenoxymethylfuran (**15a**) in 73% overall yield. The same synthetic procedure was applied for the synthesis of **15b, 16a-f**, and **18e-f** from their respective ketone precursors (22–24). Synthesis of compounds **17a-f, 18b, 19a-f, 20a-f**, and **21a-f** were previously reported (15–18).

All these compounds were evaluated *in vitro* against 60 human cancer cell lines derived from nine cancer cell types. For each compound, dose-response curves for each cell line were measured with five different drug concentrations, and the molar concentration causing 50% cell growth inhibition (GI_{50}), total cell growth inhibition (TGI, 0% growth), and 50% cell death (LC_{50}, −50% growth) compared with the control was calculated (25). The cytotoxicity of **21a-f** against representative cancer cells is outlined in Table 1. Comparison of the mean log GI_{50} values of **21a-f**, 8-{[2-(1,1′-biphenyl-4-yl)-2,3,4,5-tetrahydro-4-methylene-5-oxofuran-2-yl]methoxy}-quinolin-2(1*H*)-one (**21f**), and its 2-(4-methoxyphenyl) analogue **21e**, having a mean log GI_{50} of −6.27 and −6.15, respectively, are more active than their 2-phenyl, 2-(4-fluorophenyl) and 2-(4-chlorophenyl) counterparts (**21b-d**) which in turn are more active than 2-methyl derivative, **21a**. This finding is interesting, because earlier studies on α-methylene-γ-butyrolactones indicated these compounds also have antiplatelet and vasorelaxing activities, with the γ-phenyl lactones being better antiplatelet agents than their corresponding γ-methyl counterparts and the γ-biphenyl lactones being relatively inactive as vasorelaxing agents (18). Therefore, compounds **21e** and **21f** may be useful in developing α-methylene-γ-butyrolactones anticancer agents that do not have vasorelaxing side effects. Results in Table 1 also show the quinolin-2(1*H*)-one substituted derivatives have a strong growth inhibiting activities against leukemia cell lines, with a log GI_{50} of less than −8.00 (GI_{50} value of less than 0.01 μM) for compound **21e** against RPMI-8226 cell. However, these compounds are relatively inactive against non-small cell lung cancer and CNS cancer cell lines.



Scheme 1.

Table 1. Inhibition of *In Vitro* Cancer Cell Lines by Quinolin-2(1*H*)-one α-Methylene-γ-butyrolactones [Log GI_{50} (M)][a]

Cell Line	**21a**	**21b**	**21c**	**21d**	**21e**	**21f**
Leukemia						
RPMI-8226	−5.85	−6.76	−7.03[b]	−6.91[b]	<−8.00[b]	−7.61[b]
HL-60 (TB)	−6.06[b]	−6.92[b]	−6.60	−6.76	−7.98	−7.61
Non-Small Cell Lung Cancer						
NCI-H322M	−4.83	−4.90[c]	−4.78[c]	−4.91[c]	−4.92[c]	−5.53[c]
HOP-62	−5.11	−5.29	−4.94	−5.38	−5.31	−5.87
Colon Cancer						
COLO 205	−5.68	−5.97	−5.76	−5.92	−6.50	−6.35
SW-620	−5.69	−6.10	−5.63	−5.98	−6.88	−6.91
CNS Cancer						
SF-295	−4.87	−4.96	−4.90	−4.99	−5.34	−5.89
SNB-19	−4.80[c]	−5.19	−5.43	−5.16	−5.35	−5.82
Melanoma						
LOX IMVI	−5.56	6.53	−5.81	−6.42	−6.71	−6.91
MALME-3M	−6.28	−6.91	−5.76	−6.82	−7.96	−7.14
Ovarian Cancer						
IGROV1	−4.97	−5.82	−5.78	−5.79	−5.88	−5.88
SK-OV-3	−4.81	−5.00	−4.82	−5.08	−5.23	−5.63
Renal Cancer						
ACHN	−5.55	−5.83	−5.79	−5.87	−6.14	−6.19
TK-10	−5.40	−5.75	−5.72	−5.79	−5.81	−5.92
Prostate Cancer						
PC-3	−4.90	−5.67	−5.80	−5.41	−5.41	−5.81
DU-145	−5.11	−5.75	−5.31	−5.75	−5.84	−6.04
Breast Cancer						
MCF7	−5.52	−5.96	−6.00	−6.20	−6.70	−6.55
MDA-MB-435	−5.44	−5.93	−5.77	−5.95	−6.31	−6.56
Mean[d]	−5.35	−5.91	−5.75	−5.89	−6.15	−6.27
Range[e]	1.26	2.02	2.25	2.00	3.08	2.08

[a] Data obtained from NCI's *in vitro* disease-oriented tumor cells screen. GI_{50}: Drug molar concentration causing 50% cell growth inhibition.

[b] The most sensitive cell.

[c] The least sensitive cell.

[d] Mean values over all cell lines tested. These cell lines are: leukemia (CCRF-CEM, HL-60 (TB), K-562, MOLT-4, PRMI-8226, and SR); non-small cell lung cancer (A549/ATCC, EKVX, HOP-62, HOP-92, NCI-H226, NCI-H23, NCI-H322M, and NCI-H522); colon cancer (COLC 205, HCC-2998, HCT-116, HCT-15, HT29, KM12, and SW-620); CNS cancer (SF-268, SF-295, SF-539, SNB-19, SNB-75, and U251); melanoma (LOX IMVI, MALME-3M, M14, SK-MEL-2, SK-MEL-28, SK-MEL-5, and UACC-257); ovarian cancer (IGROV1, OVCAR-3, OVCAR-4, OVCAR-5, OVCAR-8, and SK-OV-3); renal cancer (786-0, A498, ACHN, CAKI-1, RXF 393, SN12C, TK-10, and UO-31); prostate cancer (PC-3 and DU-145); and breast cancer (MCF7, MCF7/ADR-RES, MDA-MB-231/ATCC, HS 578T, MDA-MB-435, MDA-N and T-47D).

[e] Difference in log GI_{50} value for the least sensitive cell and the most sensitive cell.

The log GI_{50}, log TGI, and log LC_{50} of different compounds, expressed in the form of mean graph midpoint values, are listed in Table 2. Comparison of the log GI_{50} mean graph midpoints of **16a-f** shows the γ-substituted biphenyl compound, 2-(1,1′-biphenyl-4-yl)-2,3,4,5-tetrahydro-4-methylene-2-[(naphthalen-2-yloxy)methyl]-5-oxofuran (**16f**), with a GI_{50} of −5.72, is more active than its 2-phenyl analogues **16b-e** which in turn are more

Table 2. Mean Values of the α-Methylene-γ-butyrolactones in the *In Vitro* Disease-Oriented Anticancer Screen[a]

Compd.	Log GI_{50}	Log TGI	Log LC_{50}	Range
15a	−4.48	−4.05	−4.01	1.05
15b	−5.32	−4.82	−4.34	1.06
Average	−4.90	−4.44	−4.18	1.06
16a	−5.37	−4.84	−4.37	1.01
16b	−5.48	−5.00	−4.52	1.10
16c	−5.54	−5.01	−4.45	2.68
16d	−5.61	−5.05	−4.54	1.73
16e	−5.63	−5.18	−4.79	1.55
16f	−5.72	−5.23	−4.68	1.55
Average	−5.59	−5.05	−4.56	1.60
17a	−5.52	−4.98	−4.37	2.07
17b	−5.75	−5.32	−4.72	3.01
17c	−5.66	−5.22	−4.56	2.31
17d	−5.60	−5.05	−4.59	2.57
17e	−5.58	−4.97	−4.47	2.48
17f	−5.75	−5.19	−4.77	2.26
Average	−5.64	−5.12	−4.58	2.45
18b	−5.50	−4.98	−4.59	1.84
18e	−5.77	−5.30	−4.66	2.00
18f	−5.73	−5.33	−4.71	1.81
Average	−5.67	−5.20	−4.65	1.88
19a	−5.44	−4.89	−4.24	1.74
19b	−5.84	−5.29	−4.53	2.87
19c	−5.74	−5.36	−4.89	1.95
19d	−5.83	−5.42	−4.87	1.65
19e	−5.93	−5.23	−4.61	1.59
19f	−5.93	−5.50	−4.91	1.61
Average	−5.79	−5.28	−4.68	1.90
20a	−5.44	−4.91	−4.30	1.52
20b	−5.71	−5.30	−4.63	3.23
20c	−5.62	−5.06	−4.54	1.71
20d	−5.72	−5.14	−4.60	1.52
20e	−5.77	−5.35	−4.79	1.95
20f	−5.88	−5.47	−5.06	1.92
Average	−5.69	−5.21	−4.65	1.98
21a	−5.35	−4.86	−4.32	1.26
21b	−5.91	−5.54	−5.07	2.02
21c	−5.75	−5.35	−4.52	2.25
21d	−5.89	−5.48	−4.98	2.00
21e	−6.15	−5.59	−5.03	3.08
21f	−6.27	−5.78	−5.26	2.08
Average	−5.89	−5.43	−4.86	2.12

[a] GI_{50}: Drug molar concentration causing 50% cell growth inhibition. TGI: Drug concentration causing total cell growth inhibition (0% growth). LC_{50}: Drug concentration causing 50% cell death (−50%). The concentration shown are mean values of the average sensitivity of 60 cell lines toward the test agent.

active than the 2-methyl counterpart, **16a** (log $GI_{50} = -5.37$). Similar results were obtained for compounds **17a-f, 19a-f, 20a-f**, and **21a-f** in which the 2-biphenyl derivatives (**17f, 19f, 20f**, and **21f**) always possess the strongest cytotoxicity among each individual groups. Although the log GI_{50} values of individual compound within each group varies, comparison of the average values for each group indicated that the cytotoxicity is in a decreasing order of quinolin-2(1*H*)-one (**21**, −5.89) > quinoline (**19**, −5.79) > 2-methylquinoline (**20**, −5.69) > 8-hydroxyquinoline (**17**, −5.64) > 2-naphthalene (**16**, −5.59) > benzene (**15**, −4.90). The same order was obtained for both log TGI and log LC_{50}. The observed higher potency of quinoline derivatives than their naphthalene counterparts is probably due to a higher affinity of quinoline with DNA strands, an action of mechanism similar to that of antimalarial chloroquine whose activity was attributed by the intercalation of quinoline portion into DNA (26). Under such circumstances, the quinoline became a carrier of the alkylating α-methylene-γ-butyrolactone, thus reducing the chance of its reaction with other cell components and resulted in the enhancement of the anticancer potency. The present results also show that the constitutional isomers **16b,e,f** and **18b,e,f** respectively, also possess comparable cytotoxicity. The selective cytotoxicity of the compounds being evaluated in the present study (as represented by their average range of log GI_{50} values) show in a decreasing order of 8-hydroxyquinoline (**17**, 2.45) > quinolin-2(1*H*)-one (**21**, 2.12) > 2-methylquinoline (**20**, 1.98) > quinoline (**19**, 1.90) > 2-naphthalene (**16**, 1.60) > benzene (**15**, 1.06).

CONCLUSIONS

We have synthesized certain γ-substituted γ-aryloxymethyl-α-methylene-γ-butyrolactones and evaluated for their cytotoxicities. These compounds demonstrated a strong growth inhibitory activity against leukemia cell lines but are relatively inactive against non-small cell lung cancers and CNS cancers. The α-methylene-γ-butyrolactone moiety may be considered as the determinant pharmacophore for their activities, while the substituents which included both aryl group and γ-substituent, are important and play a modulatory role in which the aryl group is prefer to be quinolin-2(1*H*)-one and γ-substituent prefer to be a biphenyl. Among these α-methylene-γ-butyrolactones, 8-{[2-(1,1′-biphenyl-4-yl)-2,3,4,5-tetrahydro-4-methylene-5-oxofuran-2-yl]methoxy}quinolin-2(1*H*)-one (**21f**) is the most potent with a mean log GI_{50} value of −6.27. The relatively low activity of **21f** as a vasorelaxing agent compared to that of their γ-methyl and γ-phenyl counterparts (**21a** and **21b**) (18) can be advantageous because vasorelaxing effects will otherwise become side effects when these compounds are used as anticancer agents.

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