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SYNTHESIS AND ANTICANCER EVALUATION OF CERTAIN γ-ARYLOXYMETHYL-α-METHYLENE-γ-PHENYL-γ-BUTYROLACTONES

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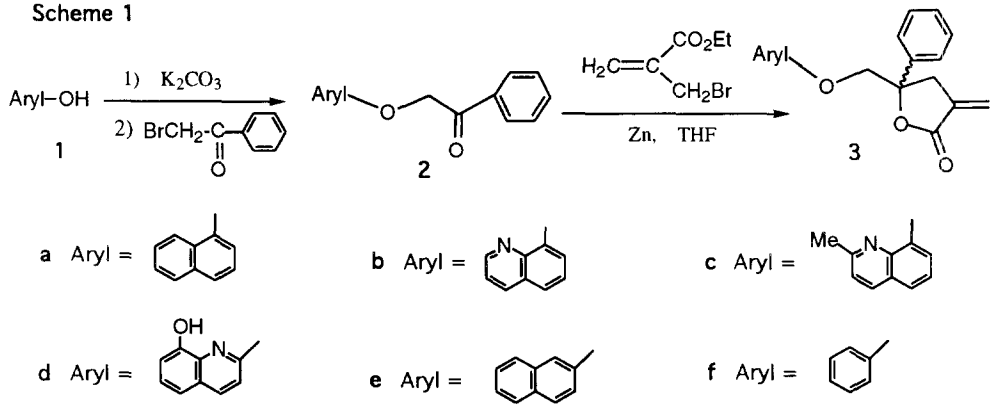
Abstract. Certain γ-aryloxymethyl-α-methylene-γ-phenyl-γ-butyrolactones were synthesized and evaluated for their anticancer activity. These compounds demonstrated a strong growth inhibitory activity against leukemia cell lines but are relatively inactive against non-small cell lung cancers and CNS cancers. The anticancer potency for aryl portion is in an order of quinoline> 8-hydroxyquinoline> 2-methylquinoline>> naphthalene>> benzene.

α-Methylene-γ-butyrolactone is a functional unit in a wide range of natural products especially the cytotoxic sesquiterpenes such as elephantopin, vernolepin, and helenalin.[1-3] A more recent α-methylene-γ-butyrolactone bearing antibiotic is methylenolactocin which possesses a simple chemical structure and significant antibacterial and antitumor activities.[4-6] The structural requirement for the biological activities is O=C-C=CH_2 moiety which acts as an alkylating agent by a *Michael*-type reaction with bionucleophiles.[7] Because of the interesting biological activities and the unique structural feature, a number of possible drug candidates bearing this versatile functionality have been synthesized with a view of developing effective clinical drugs.[8-14] For the past few years, we were particularly interested in synthesizing α-methylene-γ-butyrolactone bearing heterocycles and explored their functions as potential cardiovascular agents.[15-20] To further establish their structure-activity relationships, we report herein the synthesis and anticancer evaluation of certain γ-aryloxymethyl-α-methylene-γ-phenyl-γ-butyrolactones (**3a-f**).

Scheme 1



Synthesis of compounds **3a-d** were previously reported.[16-18] The same synthetic procedures were adopted for the preparation of **3e** and **3f** as illustrated in Scheme 1. Alkylation of **1e** and **1f** respectively

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with 2-bromoacetophenone under basic conditions provided 2-aryloxyacetophenones (**2e**; 84% yield and **2f**: 83% yield) which were then reacted with ethyl 2-(bromomethyl)acrylate and zinc powder in dry tetrahydrofuran (THF) (*Reformatsky*-type condensation) afforded the target compounds, **3e** (89% yield) and **3f** (82% yield).

Table 1. Inhibition of *in Vitro* Cancer Cell Lines by α-Methylene-γ-butyrolactones [Log_{10} GI_{50} (M)] [a]

Cell Line	3a	3b	3c	3d	3e	3f
Leukemia						
RPMI-8226	-5.64	-7.70*	-8.00*	-7.85*	-5.65	-5.71
SR	-6.64*	-6.61	-6.11	-6.14	-5.48	-5.49
Non-Small Cell Lung Cancer						
NCI-H322M	-4.80#	-4.83#	-4.92	-5.07	-4.89	-4.81
HOP-62	-4.81	-5.29	-5.49	-5.67	-4.74#	-4.83
Colon Cancer						
COLO 205	-5.50	-5.82	-5.65	-5.75	-5.71	-5.76
SW-620	-5.81	-5.97	-5.83	-5.73	-5.72	-5.71
CNS Cancer						
SNB-19	-5.11	-4.92	-4.77#	-4.84#	-4.98	-4.95
U-251	-5.45	-5.67	-5.75	-5.74	-5.55	-4.76#
Melanoma						
LOX IMVI	-5.87	-5.87	-5.84	-5.89	-5.84*	-5.82*
MALME-3M	-5.54	-5.82	-5.77	-5.77	-5.47	-4.98
Ovarian Cancer						
IGROV1	-5.79	-5.81	-5.75	-5.78	-5.81	-4.85
SK-OV-3	-5.13	-5.03	-5.17	-5.15	-5.12	NT[b]
Renal Cancer						
ACHN	-5.36	-5.79	-5.80	-5.82	-5.36	-5.76
TK-10	-4.98	-5.78	-5.68	-5.15	-5.54	-5.50
Prostate Cancer						
PC-3	-5.39	-5.80	-5.53	-5.51	-5.19	-5.67
DU-145	-4.95	-5.42	-5.25	-4.95	-4.92	-4.82
Breast Cancer						
HS-578T	-5.16	-5.83	-5.70	-5.64	-5.41	-4.93
MDA-MB-435	-5.76	-5.67	-5.52	-5.70	-5.54	-5.13
Mean[c]	-5.50	-5.84	-5.71	-5.75	-5.48	-5.32
Range[d]	1.84	2.87	3.23	3.01	1.10	1.06

[a] Data obtained from NCI's *in vitro* disease-oriented tumor cells screen.[21] GI_{50}: Drug molar concentration causing 50% cell growth inhibition.

[b] Not tested.

[c] Mean values over all cell lines tested. The cell lines used in these experiments were leukemia (CCRF-CEM, HL-60 (TB), K-562, MOLT-4, RPMI-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 (COLO 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).

[d] Ratio of the least sensitive cell (#) to the most sensitive cell (*).

The cytotoxicity of **3a-f** against representative cancer cells is outlined in Table 1. Comparison of the mean $\log_{10} GI_{50}$ values of **3a-f**, quinoline derivatives (**3b**,**c** and **d**) are more active than their naphthalene counterparts (**3a** and **e**) which in turn are more active than phenyl derivative, **3f**. Phenyl derivative **3f** exhibited similar potencies to that of cisplatin ($\log_{10} GI_{50}$ = -5.35)[22] and was more cytotoxic than carboplatin ($\log_{10} GI_{50}$ = -3.97).[22] 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 quinoline derivative **3b** exhibits the strongest inhibitory effects with a mean $\log_{10} GI_{50}$ value of -5.84. However, it has low activity against non-small cell lung cancer cell lines such as NCI-H322M with a $\log_{10} GI_{50}$ value of -4.83. Its 2-methyl analogue **3c** is less active (a mean $\log_{10} GI_{50}$ of -5.71) but is more selective in which the ratio of $\log_{10} GI_{50}$ value for the CNS SNB-19 cancer cell (the least sensitive) and the RPMI-8226 leukemia cell (the most sensitive) is 1698 ($10^{3.23}$). The anticancer potency of aryl portion is in an order of quinoline (**3b**, -5.84) > 8-hydroxyquinoline (**3d**, -5.75) > 2-methylquinoline (**3c**, -5.71) >> naphthalene (**3a**, -5.50 and **3e**, -5.48) >> benzene (**3f**, -5.32). However, the order of selectivity (ratio of $\log_{10} GI_{50}$ for the least sensitive to the most sensitive cells) is 2-methylquinoline (**3c**, 3.23) > 8-hydroxyquinoline (**3d**, 3.01) > quinoline (**3b**, 2.87) >> naphthalene (**3a**, 1.84 and **3e**, 1.10) and benzene (**3f**, 1.06).

In summary, we have synthesized certain γ-aryloxymethyl-α-methylene-γ-phenyl-γ-butyrolactones (**3a-f**). These compounds demonstrated a strong growth inhibitory activity against leukemia cell lines. Among them, quinoline derivative **3b** is the most potent with a mean $\log_{10} GI_{50}$ value of -5.84. Synthesis and evaluation of other types of heterocyclic analogues of **3b** are currently under investigation.

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References and Notes

1. Lee, K. H.; Hall, I. H.; Mar, E. C.; Starnes, C. O.; Elgebaly, S. A.; Waddell, T. G.; Hadgraft, R. I.; Ruffner, C. G.; Weidner, I. *Science* **1977**, *196*, 533-535.
2. Spring, O.; Albert, K.; Gradmann, W. *Phytochemistry* **1981**, *20*, 1883-1885.
3. Hoffmann, H. M. R.; Rabe, J. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 94-110.
4. Park, B. K.; Nakagawa, M.; Hirota, A.; Nakayama, M. *J. Antibiot.* **1988**, *41*, 751-758.
5. Zhu, G.; Lu, X. *J. Org. Chem.* **1995**, *60*, 1087-1089.

6. Maiti, G.; Roy, C. *J. Chem. Soc., Perkin Trans. 1* **1996**, 403-404.
7. Kupchan, S. M.; Fessler, D. C.; Eakin, M. A.; Giacobbe, T. J. *Science* **1970**, *168*: 376-378.
8. Petragnani, N.; Ferraz, H. M. C.; Silva, G. V. J. *Synthesis* **1985**, 157-183.
9. Lee, K. K.; Rice, G. K.; Hall, I. H.; Amarnath, V. *J. Med. Chem.* **1987**, *30*, 586-588.
10. Sanyal, U.; Mitra, S.; Pal, P.; Chakraborti, S. K. *J. Med. Chem.* **1986**, *29*, 595-599.
11. Huang, B. R.; Lee, K.H.; Hwang, L. C.; Han, C. H.; Chen, Y. L.; Tzeng, C. C.; Chen, C. F. *Chin. Pharm. J.* **1991**, *43*, 447-455.
12. Huang, B. R.; Lee, K.H.; Tseng, T. L.; Wang, H. M.; Chen, C. F.; Tzeng, C. C. *Kaohsiung J. Med. Sci.* **1993**, *22*, 2206-2208.
13. Kim, J. C.; Kim, J. A.; Kim, S. H.; Park, J. H.; Kim, S. H.; Choi, S. K.; Park, W. W. *Arch. Pharmacol. Res.* **1996**, *19*, 235-239.
14. Kim, J. C.; Kim, J. A.; Park, J. H.; Kim, S. H.; Kim, S. H.; Choi, S. K.; Park, W. W. *Arch. Pharmacol. Res.* **1997**, *20*, 253-258.
15. Chen, Y. L.; Wang, T. C.; Liang, S. C.; Teng, C. M.; Tzeng, C. C. *Chem. Pharm. Bull.* **1996**, *44*, 1591-1595.
16. Chen, Y. L.; Wang, T. C.; Lee, K. H.; Chang Y. L.; Teng, C. M.; Tzeng, C. C. *Helv. Chim. Acta* **1996**, *79*, 651-657.
17. Wang, T. C.; Chen, Y. L.; Liou, S. S.; Chang Y. L.; Teng, C. M.; Tzeng, C. C. *Helv. Chim. Acta* **1996**, *79*, 1620-1626.
18. Liou, S. S.; Zhao, Y. L.; Chang Y. L.; Teng, C. M.; Tzeng, C. C. *Chem. Pharm. Bull.* **1997**, *45*, 1777-1781.
19. Tzeng, C. C.; Wang, T. C.; Chen, Y. L.; Wang, C. J.; Chang Y. L.; Teng, C. M. *Helv. Chim. Acta* **1997**, *80*, 1161-1168.
20. Tzeng, C. C.; Zhao, Y. L.; Chen, Y. L.; Liou, S. S.; Wang, T. C.; Chang Y. L.; Teng, C. M. *Helv. Chim. Acta* **1997**, *80*, 2337-2344.
21. Monks, A.; Scuderio, D.; Skehan, P.; Shoemaker, R.; Paull, K.; Vistica, D.; Hose, C.; Langlay, J.; Cronise, P.; Vaigro-Wolff, A.; Gray-Goodrich, M.; Campbell, H.; Mayo, J.; Boyd, M. *J. Natl. Cancer Inst.* **1991**, *83*, 757-766.
22. Anderson, W. K.; Kasliwal, R.; Houston, D. M.; Wang, Y. S.; Narayanan, V. L.; Haugwitz, R. D.; Plowman, J. *J. Med. Chem.* **1995**, *38*, 3789-3797.