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Synthesis and Anticancer Evaluation of Vitamin K_3 Analogues

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Abstract—Novel vitamin K_3 analogues were synthesized and evaluated for their anticancer activity. Compound **6**, **9**, **10**, **11**, **14**, and (±)**15** demonstrated a strong inhibitory activity against the tumor cells of A-549, Hep G2, MCF7, MES-SA, MES-SA/Dx5, MKN45, SW-480, and TW-039. Compound (±)**15** displayed potent tumor cell cytotoxicity, and compound **14** selectively affected MCF7, even though it did not influence normal cells Detroit551 and WI-38. Compound (±)**15** inhibited MES-SA and MES-SA/Dx5, and this specific result shows that compound (±)**15** may become a good anticancer drug candidate.

Many clinically successful anticancer drugs are either natural products or have been developed from naturally occurring lead compounds.[1] Vitamin K_3 **1** (menadione, 2-methyl[1,4]naphthoquinoline) is currently attracting much attention because of its interesting pharmacological activities.[2–14] Vitamin K_3 has been demonstrated to exhibit inhibit growth and induce cell death in many types of cells both in vitro[15–19] and in vivo.[20,21] Many researchers have demonstrated that vitamin K_3 induced cell death is associated with apoptosis[22–24] and over expression of the c-*myc* gene,[24] which is considered to be closely related to apoptosis.[25–27]

The mechanism by which vitamin K_3 inhibits growth and kills cells is not well understood. Oxidative stress is considered to be a mechanism of action of quinoid compounds such as vitamin K_3, since toxic oxygen species can be generated during redox cycling which involves the quinoid structures.[28–31] Another possible mechanism that determines the toxicity of vitamin K_3 and related quinines is the direct arylation of cellar thiols, leading to the depletion of glutathione and the inhibition of sulfhydryl-dependent proteins.[32–35]

Nishikawa et al. studies of growth inhibition of hepatoma cells induced by vitamin K and its analogues[9] have demonstrated that a 50% growth inhibitory dose of Hep3B cells (Table 1), with compounds as shown in Figure 1. Growth inhibitory activity declined as the length of the side-chain increases. The presence of a sulfur or an oxygen atom at the beginning of the aliphatic side-chain facilitated the growth inhibiting effect of the compounds, as evident when comparing **2** (all-carbon) with **3**, **4**, **5** (thioether) or with **6** (thioethanol) or with **7**, **8** (*O*-ether). The thioethanol derivative **6** was the strongest analogue of all the compounds considered in these studies. According to these studies and the structure–activity relationships, thioether with a hydroxyl group must be involved in this series of analogues. This study describes the synthesis and biological evaluation of new vitamin K_3 analogues.

The compounds were prepared following the method of Borovkov,[36] that employed vitamin K_3 as starting material (Scheme 1).[41] The National Health Research Institute, Division of Biotechnology and Pharmaceutical Research in Taiwan tested in vitro cytotoxicitiy against eight human tumor cell lines and two normal human cell lines (Table 2).[19,37]

The 2-hydroxyethylthio group on 2-(2-hydroxyethylthio)-3-methyl[1,4]naphthoquinone **6** was investigated with respect to the structure–activity relationships. The carbon chain was extended from a two-methylene chain to three-, four-, six- and 11-methylene chains, but the cytotoxic assays revealed that two-, three-, and four-methylene chains exhibit similar cytotoxic potency. Carbon chains longer than a six-methylene chain (**11**

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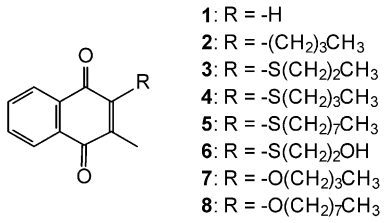
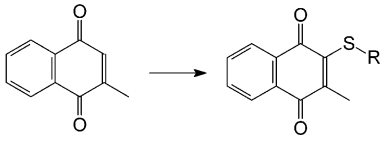
Table 1. The growth inhibitory activity is shown as 50% growth inhibitory dose (μM) for Hep3B cells

Compd	1	2	3	4	5	6	7	8
ID_{50} (μM)	10	78	14	15	100	5.6	55	140



1: R = -H
2: R = -$(CH_2)_3CH_3$
3: R = -$S(CH_2)_2CH_3$
4: R = -$S(CH_2)_3CH_3$
5: R = -$S(CH_2)_7CH_3$
6: R = -$S(CH_2)_2OH$
7: R = -$O(CH_2)_3CH_3$
8: R = -$O(CH_2)_7CH_3$

Figure 1.



6: R = $(CH_2)_2OH$
9: R = $(CH_2)_3OH$
10: R = $(CH_2)_4OH$
11: R = $(CH_2)_6OH$
12: R = $(CH_2)_{11}OH$
13: R = $(CH_2)_2CO_2H$
14: R = $CH(CH_3)CH(OH)CH_3$
(±)-15: R = $CH_2CH(OH)CH_3$
(±)-16: R = $CH_2CH(OH)CH_2OH$
17: R = 4-C_6H_4OH

Scheme 1. Reagents and conditions: RSH, $CuSO_4 5H_2O$, ethanol, rt, 30–50%.

and **12**) do not exhibit cytotoxic activity. Compound **17**, but with a phenyl group, also do not exhibit cytotoxic activity. Consequently the binding affinity may be influenced by the steric hindrance in that region. Two hydroxyl groups and a carboxylic group were put on compounds (±)**16** and **13** to enhance the hydrophilic effect but they do not exhibit cytotoxic activity. Surprisingly, compound (±)**15** exhibits strong cytotoxic activity in relation to most tumor cell lines, except that of nasopharyngeal carcinoma (IC_{50} 12.52 μM) toward which it is a little less potent. Comparing compound **6** with compound (±)**15** reveals a methyl group that was extended next to the hydroxyl group on compound (±)**15**. This fine-tuning of the structure may reveal the highly specific selectivity of the receptor. Compound **11** selectively and effectively inhibited MCF7 (breast adenocarcinoma cell line), and did not influence Detroit551 (embryonic skin normal fibroblast) and WI-38 (normal lung fibroblast). Drug resistance to a broad spectrum of chemotherpeutic agents is a major obstacle in the clinical treatment of human cancer.[38–40] Compound (±)**15** inhibited MES-SA (a human uterine sarcoma cell line) and MES-SA/Dx5 [a human MDR (multi-drug resistance) uterine sarcoma cell line]. This specific result shows that compound (±)**15** may become a good anticancer drug.

In summary, we have synthesized 2-(*n*-hydroxyalkylthio)-3-methyl[1,4]naphthoquinones (**6, 9, 10, 11, 14,** (±)**15**). These compounds demonstrated a strong growth inhibitory activity against tumor cell lines. Among them, (±)**15** is the most potent with a mean IC_{50} 5.10 μM. Synthesis and evaluation other types of heterocyclic analogues of (±)**15** are currently under investigation.

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Table 2. IC_{50}(μM)[a] values of tumor cell lines after 72 h continuous exposure to test compounds **6**, **9**–**17**

Tumor type/cell line	6	9	10	11	14	(±)15
A-549[b]	>10	>10	>10	>10	>10	4.74±0.12
Hep G2[c]	8.40±2.72	9.53±0.15	>10	>10	>10	5.59±0.53
MCF7[d]	5.19±0.26	5.16±0.28	5.78±0.15	9.28±3.32	>10	4.61±0.22
MES-SA[e]	>10	>10	>10	>10	>10	7.11±0.67
MES-SA/Dx5[f]	>10	>10	>10	>10	>10	5.10±0.31
MKN45[g]	5.16±0.27	6.40±0.47	6.78±0.55	>10	5.64±0.09	3.92±0.30
SW-480[h]	5.14±0.09	4.85±0.08	4.51±0.10	>10	5.53±0.02	5.19±0.27
TW-039[i]	>10	>10	>10	>10	>10	>10
Detroit551[j]	8.17±1.31	5.26±0.57	7.57±0.57	>10	>10	4.61±0.24
WI-38[k]	7.37±0.09	>10	>10	>10	>10	5.06±0.24

[a]IC_{50} is the concentration that induces 50% growth inhibition compared with untreated control cells.
[b]Human lung carcinoma cell line.
[c]Human liver hepatoblastoma cell line.
[d]Mammary gland breast adenocarcinoma cell line.
[e]Human uterine sarcoma cell line.
[f]Human multidrug resistance uterine sarcoma cell line.
[g]Human stomach adenocarcinoma cell line.
[h]Human colon adenocarcinoma cell line.
[i]Human nasopharyngeal carcinoma cell line.
[j]Normal human embryonic skin fibroblast cell line.
[k]Normal human lung fibroblast cell line.

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41. A typical synthesis of **6** is as follows: 2-Mercapto-ethanol (1.5 mL, 21.4 mmol) was added to a solution of 2-methyl[1,4]-naphthoquinone **1** (1 g, 5.8 mmol) in a mixture of methanol (100 mL) and 2-propanol (80 mL). The reaction mixture was stirred for 24 h at room temperature, poured into 300 mL of water, and extracted using ether (3 × 300 mL). The extract was washed with a 10% $CuSO_4$ solution, then water (3 × 300 mL), and dried over $MgSO_4$. The solvent was removed by evaporation to leave a brown residue. Purification by flash chromatography, using 30% ethyl acetate/hexanes to elute, yielded 0.7 g of pure product of 2-(2-hydroxy-ethylthio)-3-methyl[1,4]-naphthaquinone **6**. Yield 47%; mp 79–80 °C. ^{1}H NMR (300.1 MHz, $CDCl_3$) δ2.42 (s, 3H, CH_3), 3.36 (t, 2H, J = 5.7 Hz, CH_2), 3.81 (t, 2H, J = 5.5 Hz, CH_2), 7.71–7.75 (d, 2H, J = 2.5 Hz, ArH), 8.07–8.11 (d, 2H, J = 2.6 Hz, ArH). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ15.6, 37.4, 62.0, 126.7, 126.9, 132.0, 132.6, 133.5, 133.9, 145.7, 148.3, 181.6, 182.3. IR (KBr) 3550, 3066, 2941, 2883, 1871, 1768, 1657, 791 cm^{-1}. FABMS m/z 249 ($M^+ + H$). FABHRMS calcd for $C_{13}H_{13}O_3S$ ($M^+ + H$) 249.0586, found 249.0590. The same synthetic procedures were adopted for the preparation of **9**–**17**. **9**: Yield 38%; mp 49–50 °C. ^{1}H NMR (300.1 MHz, $CDCl_3$) δ1.90 (t, 2H, J = 6.4 Hz, CH_2), 2.36 (s, 3H, CH_3), 3.31 (t, 2H, J = 7.1 Hz, CH_2), 3.81 (t, 2H, J = 8.5 Hz, CH_2), 7.80–7.83 (d, 2H, J = 3.6 Hz, ArH), 8.05–8.12 (d, 2H, J = 2.7 Hz, ArH). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ15.4, 30.8, 33.0, 61.0, 126.6, 126.8, 132.1, 132.9, 133.4, 133.8, 146.6, 147.2, 181.4, 182.2. IR (KBr) 3298, 3184, 2947, 1984, 1957, 1716, 1652, 754 cm^{-1}. FABMS m/z 263 ($M^+ + H$). FABHRMS calcd for $C_{14}H_{15}O_3S$ ($M^+ + H$) 263.0743, found 263.0750. **10**: Yield 45%. Mp 75–76 °C. ^{1}H NMR (300.1 MHz, $CDCl_3$) δ1.64–1.72 (m, 4H, J = 3.5 Hz, CH_2), 2.36 (s, 3H, CH_3), 3.25 (t, 2H, J = 6.0 Hz, CH_2), 3.67 (t, 2H, J = 6.0 Hz, CH_2), 7.61–7.73 (d, 2H, J = 6.0 Hz, ArH), 8.04–8.10 (d, 2H, J = 3.0 Hz, ArH). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ15.3, 27.1, 31.6, 34.1, 62.2, 126.6, 126.8, 132.2, 132.9, 133.4, 133.7, 146.8, 146.8, 181.5, 182.2. IR (KBr) 3348, 3265, 3037, 3010, 2933, 2881, 2850, 1992, 1969, 1716, 1662, 762 cm^{-1}. FABMS m/z 277 ($M^+ + H$). FABHRMS calcd for $C_{15}H_{17}O_3S$ ($M^+ + H$) 277.0899, found 277.0903. **11**: Yield 48%; mp 69–70 °C; ^{1}H NMR (300.1 MHz, $CDCl_3$) δ1.29–1.69 (m, 8H, J = 6.0 Hz, CH_2), 2.35 (s, 3H, CH_3), 3.21 (t, 2H, J = 7.4 Hz, CH_2), 3.63 (t, 2H, J = 6.5 Hz, CH_2), 7.68–7.71 (d, 2H, J = 4.5 Hz, ArH), 8.03–8.11 (d, 2H, J = 5.1 Hz, ArH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ15.3, 25.3, 28.4, 30.6, 32.6, 34.3, 62.9, 126.6, 126.8, 132.1, 133.4, 133.7, 146.7, 147.1, 181.4, 182.3. IR (KBr) 3388, 3326, 3091, 2997, 2931, 2864, 1994, 1965, 1716, 1664, 789 cm^{-1}. FABMS m/z 305 ($M^+ + H$). FABHRMS calcd for $C_{17}H_{21}O_3S$ ($M^+ + H$)

305.1212, found 305.1214. **12**: Yield 8%; mp 71–72 °C. ^{1}H NMR (300.1 MHz, $CDCl_3$) δ1.48–1.70 (m, 18H, CH_2), 2.36 (s, 3H, CH_3), 3.21 (t, 2H, J = 7.2 Hz, CH_2), 3.64 (t, 2H, J = 6.6 Hz, CH_2), 7.69–7.72 (d, 2H, J = 2.1 Hz, ArH), 8.06–8.11 (d, 2H, J = 2.4 Hz, ArH). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ15.3, 15.3, 25.7, 28.8, 29.2, 29.4, 29.5, 29.6, 30.2, 32.8, 33.3, 63.1, 126.6, 126.8, 132.1, 132.8, 133.3, 133.6, 146.6, 147.3, 181.4, 182.3. IR (KBr) 3552, 3072, 2918, 2848, 1867, 1734, 1662, 795 cm^{-1}. FABMS m/z 375 (M^+ + H). FABHRMS calcd for $C_{22}H_{31}O_3S$ 375.1995 (M^+ + H), found 374.1995. **13**: Yield 59%; mp 161–162 °C. ^{1}H NMR (300.1 MHz, $CDCl_3$) δ2.34 (s, 3H, CH_3), 2.78 (t, 2H, J = 7.5 Hz, CH_2), 3.43 (t, 1H, J = 6.8 Hz, CH_2), 7.71–7.82 (d, 2H, J = 3.0 Hz, ArH), 8.08–8.13 (d, 2H, J = 2.1 Hz, ArH). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ15.4, 29.4, 35.2, 126.7, 126.9, 132.1, 132.9, 133.4, 133.8, 146.7, 147.2, 181.4, 182.2, 218.1. IR (KBr) 3028, 2914, 1967, 1869, 1826, 1714, 1662, 1589, 1562, 775 cm^{-1}. FABMS m/z 277 (M^+ + H). FABHRMS calcd for $C_{15}H_{17}O_3S$ (M^+ + H) 277.0899, found 277.0898. **14** (a mixture of isomers): Yield 11%; ^{1}H NMR (300.1 MHz, $CDCl_3$) δ1.21–1.27 (m, 6H, J = 6.3 Hz, CH_3), 2.44 (s, 3H, CH_3), 3.84–3.90 (m, 2H, J = 3.0 Hz, CH), 7.70–7.75 (d, 2H, J = 1.7 Hz, ArH), 7.08–7.10 (d, 2H, J = 2.8 Hz, ArH). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ14.2, 15.6, 15.8, 50.7, 69.9, 126.7, 127.0, 132.1, 132.7, 133.6, 133.9, 145.7, 148.4, 181.6, 182.3. IR (KBr) 2993, 2360, 2341, 1770, 1758, 1660, 844 cm^{-1}. FABMS m/z 277 (M^+ + H). FABHRMS calcd for $C_{15}H_{17}O_3S$ (M^+ + H) 277.0899, found 277.0897. (±)**15**: Yield 43%; mp 39–40 °C. ^{1}H NHR (300.1 MHz, $CDCl_3$) δ1.27 (d, 3H, J = 6.2 Hz, CH_3), 2.41 (s, 3H, CH_3), 3.03–3.10 (q, 1H, J = 8.2 Hz, CH_2), 3.34–3.40 (dd, 1H, J_1 = 12.0, 3.0 Hz CH_2), 3.89 (m, 1H, J = 3.6 Hz, CH), 7.69–7.72 (d, 2H, J = 1.9 Hz, ArH), 8.06–8.10 (d, 2H, J = 2.7 Hz, ArH). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ15.6, 22.2, 29.7, 67.3, 126.7, 127.0, 132.0, 132.6, 133.5, 133.8, 146.0, 148.2, 181.6, 182.3. IR (KBr) 3489, 3410, 3074, 2962, 2925, 2359, 1662, 1589, 746 cm^{-1}. FABMS m/z 263 (M^+ + H). FABHRMS calcd for $C_{15}H_{17}O_3S$ (M^+ + H) 263.0743, found 263.0739. (±)**16**: Yield 73%; mp 117–118 °C. ^{1}H NMR (300.1 MHz, $CDCl_3$) δ2.03 (s, 3H, CH_3), 2.73 (dd, 1H, J = 12.0, 1.8 Hz, CH_2), 3.65 (dd, 1H, J = 12.0, 1.8 Hz, CH_2), 4.40 (dd, 1H, J = 5.7, 1.5 Hz, CH_2), 4.57 (dd, 1H, J = 7.2, 1.2 Hz, CH_2), 5.19 (q, 1H, J = 1.6 Hz, CH), 7.50–7.67 (m, 3H, J = 6.0 Hz, ArH), 8.08 (dd, 1H, J = 10.5, 0.9 Hz, ArH). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ12.1, 32.3, 69.1, 74.6, 126.4, 126.5, 129.5, 129.9, 131.2, 132.5, 138.6, 147.4, 180.2. IR (KBr) 3280, 3074, 2956, 2893, 1979, 1954, 1716, 1649, 762 cm^{-1}. FABMS m/z 261 (M^+ + H- 18). FABHRMS calcd for $C_{14}H_{13}O_3S$ (M^+ + H- 18) 261.0586, found 261.0578. **17**: Yield 65%; mp 180–181 °C; ^{1}H NMR (300.1 MHz, $CDCl_3$) δ2.35 (s, 3H, CH_3), 6.78–6.81 (d, 2H, J = 3.0 Hz, ArH), 7.35–7.38 (d, 2H, J = 6.0 Hz, ArH), 7.69–7.71 (d, 2H, J = 3.0 Hz, ArH), 8.00–8.01 (d, 2H, J = 0.3 Hz, ArH), 8.10–8.12 (d, 2H, J = 6.0 Hz, ArH). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ15.7, 116.1, 116.4, 124.2, 126.7, 127.0, 128.0, 132.0, 132.3, 132.9, 133.8, 155.6, 156.0, 181.0, 183.2. IR (KBr) 3319, 3062, 3041, 3012, 2921, 2854, 1990, 1961, 1716, 1662, 786 cm^{-1}. FABMS m/z 296 (M^+ + 1). FABHRMS calcd for $C_{17}H_{12}O_3S$ (M^+ + H) 296.0508, found 296.0498.