http://dx.doi.org/10.5012/bkcs.2014.35.5.1533

Synthesis and Antitumor Activity of New 3-Allylseleno-6-alkoxypyridazines against Breast Cancer MCF-7 Cells

Saet-Byeul Kim, Ji-Hee Lee, Chaewon Kim, and Myung-Sook Park*

*College of Pharmacy, Duksung Women's University, Seoul 132-714, Korea. *E-mail: mspark@duksung.ac.kr*
Received December 10, 2013, Accepted January 2, 2014

Key Words : Alkoxypyridazines, Organoseleniums, Allylselenopyridazines, Antitumor, MCF-7 cells

Organoselenium compounds are useful reagents or synthons in organic synthesis. Over the past few years, synthetic strategies for selenium-containing heterocycles,[1] novel selenium analogs of antioxidants, such as diphenyl diselenide,[2] and Se-methylselenocysteine,[3a] which induces apoptosis through caspase activation in HL-60 cells,[3b] have been reported.

The main components of volatile oils in garlic are sulfur compounds such as allicin. Allicin is responsible for the typical odor of garlic, but it is unstable and converts readily into other compounds. A number of sulfur compounds in garlic have been shown to possess anticarcinogenic activities. Through drug design, a pharmacologically active allylthio group was introduced into a pyridazine ring that is more stable. Various 3-allylthio-6-alkoxypyridazine derivatives (K-compounds) were synthesized by Kwon *et al.*[4] K-Compounds showed especially good antitumor activities.

We have reported on allylthio aralkylaminopyridazines and their anticancer activities.[5-7] In these studies, allylseleno alkoxypyridazines, in which the sulfur atom of K-compounds was replaced with the selenium atom (Figure 1), were designed and synthesized as new organoselenopyridazines.

The isosteric replacement of the sulfur of K-compounds by a selenium atom yields the allylselenopyridazines as target compounds. In order to discover potential anti-tumor organoselenium compounds, we designed new 3-allylseleno-6-alkoxypyridazines **4a-4h**. We synthesized new allylselenopyridazine derivatives that were expected to retain the anticancer activity. Target compounds were synthesized through

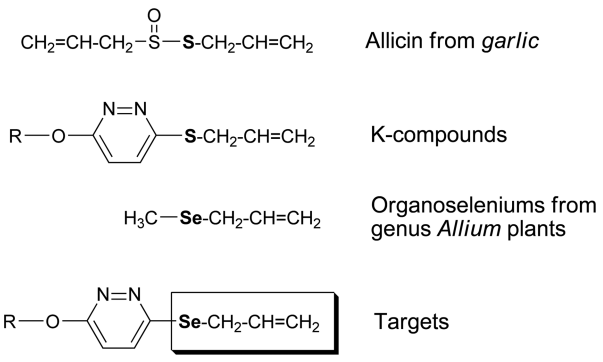
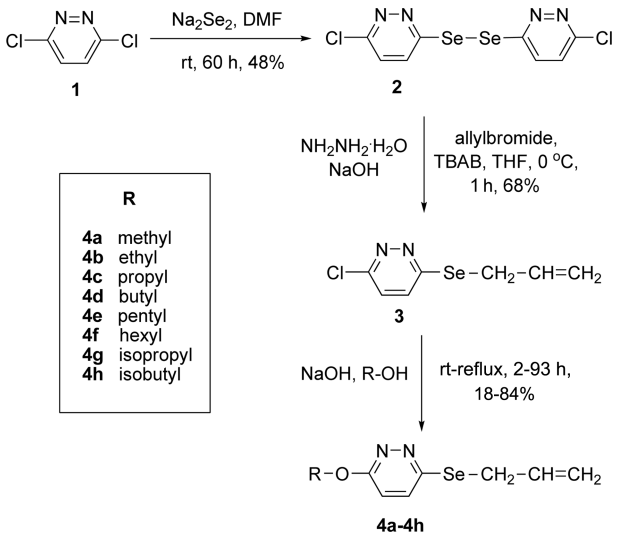


Figure 1. Reported K-compounds and target 3-allyseleno-6-alkoxypyridazines.



Scheme 1. Synthetic routes for target allylselenoalkoxypyridazines **4a-4h**.

the process of diselenylation, hydrolysis, Se-allylation and alkoxylation of starting material. We tested the ability of these synthetic compounds to inhibit the growth of human breast cancer MCF-7 Cell lines.

Results and Discussion

As a pharmacologically active group, the allylseleno group was introduced into the pyridazine ring in order to prepare new organoselenium compounds. Dichloropyridazinyl diselenide **2** was prepared through diselenylation according to the method of Bhasin *et al.*[9,10]

Elemental selenium suspended in dimethylformamide reacts with 99% hydrazine hydrate in the presence of NaOH at room temperature to give dark green solution containing diselenide anion. The diselenide anion thus formed reacts *in situ* with the 3,6-dichlorpyridazine **1**. Compound **2** was synthesized according to the previously described method.[8a,b]

Dichloropyridazinyl diselenide **2** can be quantitatively reduced to chloropyridazinyl selenolate anion using hydrazine hydrate at room temperature in the presence of NaOH in THF. The anion thus formed reacts readily with allyl bromide to give the 3-allylseleno-6-chloropyridazine **3**. The 3-allylseleno-6-chloropyridazine **3** is an important inter-

Table 1. The optimal conditions alkoxylation for target compounds **4a-4h** and their anti-proliferative activity against cell lines MCF-7 compared to 5-FU in CCK-8 assays

Comp. No.	R	Temp. °C	Time h	IC_{50} μM
4a	methyl	50	23	352.27
4b	ethyl	rt	93	1244.49
4c	propyl	90	2	308.02
4d	butyl	80	16	302.52
4e	pentyl	rt	4	218.55
4f	hexyl	reflux	20	1415.11
4g	isopropyl	rt	6	1099.30
4h	isobutyl	reflux	20	1371.43
5-FU				3670.59

mediate for allylselenopyridazine analogs. These reactions were carried out in the presence of the phase-transfer catalyst NH_4Cl (or TBAB) in an effort to improve the efficiency of the reaction.

The pyridazine NMR peak of **3** appeared at 7.25 and 7.41 ppm, and the allyl peak appeared at 4.0, 5.07, 5.29 and 6.1 ppm. The pyridazine ^{13}C NMR peak appeared at 118.76, 133.90, 155.16 and 158.59 ppm, and the allyl peak appeared at 29.15, 127.71 and 131.24 ppm.

We designed organoselenium analogs of pyridazine in which an allylselenium moiety was introduced at the 3-position of the pyridazine nucleus and the 6-position was substituted with an oxygen (O) atom. Novel 3-allylseleno-6-alkoxypyridazines **4a-4h** were prepared through the alkoxylation of 3-allylseleno-6-chloropyridazine **3** and the related alcohol in order to discover potential antitumor candidates. In Table 1, we summarize the optimal conditions for compounds **4a-4h**. The yields of compounds **4a-4h** were 18-84% and those were identified by NMR.

For investigation of the potential anti-cancer activity of the 8 synthetic compounds, the growth-inhibitory effect of the synthetic compounds was examined against breast cancer (MCF-7) cells.[11] CCK-8 assays were performed on cells treated with various concentrations of the compounds.[12] 5-Fluorouracil (5-FU), which has previously been shown to have anti-proliferative against MCF-7 cells was used as a positive control. We expect that synthesized compounds and 5-FU have similar mechanism of action. The IC_{50} values for these compounds were determined from the concentration range used in this study.

Of the 8 target compounds, four compounds (**4a**, **4c**, **4d** and **4e**) inhibited the growth of breast (MCF-7) cells at standard concentrations (6.25, 25, 100, and 400 μg/mL) (Figure 2). 5-FU, a positive control, showed inhibitory effects on growth of MCF-7 cells at standard concentrations. We further investigated the anti-proliferative activity of compound **4e**, which caused greater inhibition of cell growth than the other compounds. Compound **4e** markedly inhibited MCF-7 cell growth at IC_{50} (218.55 μM) in a dose-dependent manner at a low concentration (6.25 μg/mL). Eight compounds (**4a-4h**) showed higher potency than 5-FU at IC_{50} (3670.59 μM) in inhibiting the growth of MCF-7 cells, suggesting the potential anticancer activity of these compounds (Table 1). The results indicated that compound **4e** had the highest activity towards MCF-7 cells.

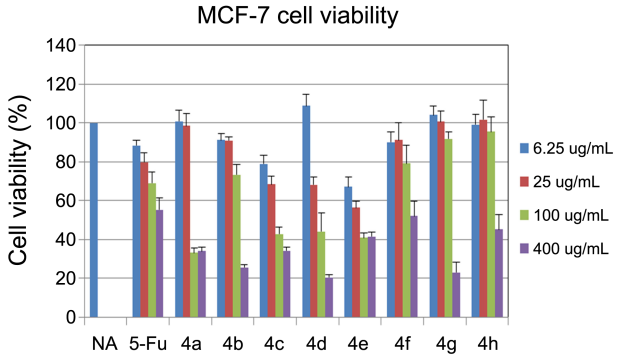


Figure 2. Antitumor activity of synthesized compounds (**4a-4h**) in MCF-7 breast cancer cells.

Finally, a new series of 3-allylseleno-6-alkoxylpyridazines **4a-4h** was synthesized by synthetic route from 3,6-dichloropyridazine for development of new anticancer agents. These new compounds showed anti-proliferative activities against breast cancer (MCF-7) cells in CCK-8 assays, and could be promising candidates for chemotherapy of carcinomas. Among 8 synthesized compounds for inhibiting the growth of these cell lines, compound **4e** showed the highest potency. This result suggests the potential anticancer activity of compound **4e**.

Experimental

Chemicals. Chemicals were supplied by Aldrich, Sigma, Merck, and Tokyo Kasei. Melting points were determined in open capillary tubes on a Büchi 535 melting point apparatus and were uncorrected. NMR spectra were recorded using a Bruker 300 MHz NMR spectrometer. IR spectra were recorded on a Perkin-Elmer 16F PC FT-IR spectrometer using NaCl discs and pellets. Mass fragmentations were recorded using an Agilent 6890 GC and 5973 MS.

Materials and Methods for Bioassays. Cell Line Culture Conditions. MCF-7 breast cancer cells were purchased from the ATCC (Manassas, USA) and maintained at 37 °C in a humidified atmosphere, with 5% CO_2, in MEM (Gibco-BRL Inc.) medium supplemented with 10% fetal bovine serum (Gibco-BRL Inc., Korea).

Anti-proliferative CCK-8 (cell counting kit-8) Assays.[12] The cytotoxic activity of the compounds was determined *in vitro* using the CCK-8 assay kit (Dojindo, Korea). Human breast cancer cells were seeded in 96-well plates at densities of 5000 cells/well with five replicates for each drug concentration and maintained at 37 °C in a 5% CO_2 humidified incubator for 24 h. Control cells were treated with dimethyl sulfoxide (DMSO) equal to the highest percentage of solvent used in the experimental conditions. 5-FU was used as a positive control. The MCF-7 cells were then treated with various concentrations of synthetic compounds (the final

concentrations of **4a-4h** were 6.25, 25, 100, and 400 μg/mL) for 24 h; 10 μL of Cell Counting Kit-8 solution were added to each well (containing 100 μL), and the plates were further incubated for 2.5 h. The absorbance was measured at 450 nm using a micro ELISA reader (ASYS Biotech, Cambridge, BK). The cell viability ratio was calculated as follows: (test group A_{450}/control group A_{450}) × 100%. IC_{50} values were determined from three independent experiments.

3-Allylseleno-6-chloropyridazine 3. To a vigorously stirred mixture of powdered sodium hydroxide (1.03 g, 26 mmol), tetrabutylammonium bromide (TBAB) (0.34 g, 1.04 mmol), dichloropyridazinyl diselenide **2** (2 g, 5.2 mmol) and distilled THF (30 mL), 99% hydrazine hydrate (0.054 mL, 1.73 mmol) was added dropwise at rt. Stirring was continued for additional 45 min. Allyl bromide (0.86 mL, 10.4 mmol) was added dropwise at 0 °C. Stirring was continued for additional 1 h at 0 °C. Upon completion, the reaction was stopped and the solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate (50 mL). The organic layer was washed with water (50 mL × 4) and then dried over anhydrous Na_2SO_4. After solvent evaporation, the residue was purified by silica gel column chromatography (3:1 v/v, hexane:EtOAc) to afford **3** as a pale yellow liquid. Yield: 68%, mp 78-80 °C. ^{1}H NMR ($CDCl_3$) δ 7.41 (d, J = 9 Hz, 1H, pyridazine), 7.25 (d, J = 9 Hz, 1H, pyridazine), 6.10-6.00 (m, 1H, CH, allyl), 5.29 (d, J = 17.5 Hz, 1H, =CH_2, allyl), 5.07 (d, J = 10.3 Hz, 1H, =CH_2, allyl), 4.00 (d, J = 7.5 Hz, 2H, $SeCH_2$). ^{13}C NMR ($CDCl_3$) δ 158.59, 155.16, 133.90, 118.76 (pyridazine), 131.24, 127.71, 29.15 (allyl). FT-IR (NaCl) cm^{-1} 3032 (aromatic), 1557 (N=N), 765 (C-Se), 706 (C-Cl). GC-MS *m/z* (%) 234 (M+) 219.0 (100.00), 217.0 (48.7), 221.0 (43.9), 153.1 (23.9), 118.1 (23.5).

General Procedure for 3-Allylseleno-6-alkoxypyridazines 4a-4h. To a stirred mixture of powdered sodium hydroxide (83 mg, 2.06 mmol), water and the appropriate absolute alcohol (30 mL), 3-allylseleno-6-chloropyridazine **3** (0.48 g, 2.06 mmol) was added as powder at rt. Metal sodium and related alcohols were useful reagents for generating the alkoxide in the case of long chain alcohols such as butanol, pentanol, hexanol, isopropanol and isobutanol as shown in Table 1. The mixture was stirred for 2-93 h at rt~reflux. Upon completion, the reaction was stopped and the excess alcohol was evaporated under reduced pressure. The residue was dissolved with ethyl acetate (50 mL). The organic layer was washed with water (50 mL × 2) and then dried over anhydrous Na_2SO_4. After solvent evaporation, the residue was purified by silica gel column chromatography (hexane: EtOAc) to afford **4**.

3-Allylseleno-6-methoxypyridazine (4a): Yield: 61%, mp 31-32 °C. ^{1}H NMR ($CDCl_3$) δ 7.32 (d, J = 9 Hz, 1H, CH, pyridazine), 6.80 (d, J = 9 Hz, 1H, CH, pyridazine), 6.12-6.03 (m, 1H, CH, allyl), 5.24 (d, J = 17.7 Hz, 1H, =CH_2, allyl), 5.04 (d, J = 10.2 Hz, 1H, =CH_2, allyl), 4.10 (s, 3H, OCH_3, methyl), 3.96 (d, J = 7.2 Hz, 2H, $SeCH_2$). ^{13}C NMR ($CDCl_3$) δ 163.98, 151.77, 131.83, 117.60 (pyridazine), 134.23, 117.54, 28.75 (allyl), 54.71 (OCH_3). FT-IR (NaCl) cm^{-1} 3080 (aromatic), 2947 (aromatic), 1584 (N=N), 1398 (CH_3), 1008, 916 (allyl double band), 833 (CSe). GC-MS *m/z* (%) 230 (M+), 215.0 (100.0), 230.0 (71.3), 213.0 (50.5), 228.0 (36.0), 149.1 (29.7).

3-Allylseleno-6-ethoxypyridazine (4b): Yield: 18%, Oil. ^{1}H NMR ($CDCl_3$) δ 7.32 (d, J = 9.1 Hz, 1H, CH, pyridazine), 6.77 (d, J = 9.12 Hz, 1H, CH, pyridazine), 6.12-6.03 (m, 1H, CH, allyl), 5.23 (d, J = 16.2 Hz, 1H, =CH_2, allyl), 5.04 (d, J = 9.9 Hz, 1H, =CH_2, allyl), 4.53 (q, J = 7.1 Hz, 2H, OCH_2, ethyl), 3.95 (d, J = 8.5 Hz, 2H, $SeCH_2$), 1.44 (t, J = 7.1 Hz, 3H, CH_3, ethyl). ^{13}C NMR ($CDCl_3$) δ 164.16, 151.79, 132.22, 118.32 (pyridazine), 134.64, 117.94, 28.94 (allyl), 63.56 (OCH_3), 14.89 (ethyl). FT-IR (NaCl) cm^{-1} 3081 (aromatic), 2924 (aromatic), 1583 (N=N), 1306 (CH_2), 1028 (CH_3), 908, 839 (allyl double band), 839 (CSe). GC-MS *m/z* (%) 229.0 (100.0), 135.0 (50.7), 227.0 (50.5), 201.0 (47.1), 199.0 (23.0).

3-Allylseleno-6-propoxypyridazine (4c): Yield: 84%, mp 53-54 °C. ^{1}H NMR ($CDCl_3$) δ 7.32 (d, J = 9 Hz, 1H, CH, pyridazine), 6.78 (d, J = 9 Hz, 1H, CH, pyridazine), 6.12-6.03 (m, 1H, CH, allyl), 5.23 (d, J = 18 Hz, 1H, =CH_2, allyl), 5.03 (d, J = 9.9 Hz, 1H, =CH_2, allyl), 4.42 (t, J = 6.9 Hz, 2H, OCH_2, propyl), 3.95 (d, J = 7.5 Hz, 2H, $SeCH_2$), 1.90-1.78 (m, 2H, CH_2, propyl), 1.05 (t, J = 7.5 Hz, 3H, CH_3, propyl). ^{13}C NMR ($CDCl_3$) δ 163.98, 151.35, 131.83, 117.56 (pyridazine), 134.28, 117.68, 28.56 (allyl), 68.94, 22.18, 10.42 (propyl). FT-IR (NaCl) cm^{-1} 3086 (aromatic), 2962 (aromatic), 1590 (N=N), 1382 (CH_2), 1188 (CH_3), 926, 839 (allyl double band), 839 (CSe). GC-MS *m/z* (%) 258 (M+), 201.0 (100.0), 258.1 (78.9), 243.0 (71.7), 135.1 (57.3), 199.0 (49.2).

3-Allylseleno-6-butoxypyridazine (4d): Yield: 24%. Oil. ^{1}H NMR ($CDCl_3$) δ 7.31 (d, J = 9 Hz, 1H, pyridazine), 6.77 (d, J = 9 Hz, 1H, pyridazine), 6.12-6.03 (m, 1H, CH, allyl), 5.23 (d, J = 16.8 Hz, 1H, =CH_2, allyl), 5.04 (d, J = 9.9 Hz, 1H, =CH_2, allyl), 4.46 (t, J = 6.6 Hz, 2H, OCH_2), 3.95 (d, J = 7.5 Hz, 2H, $SeCH_2$), 1.84-1.75 (m, 2H, CH_2, butyl), 1.52-1.44 (m, 2H, CH_2, butyl), 0.97 (t, J = 7.4 Hz, 3H, CH_3, butyl). ^{13}C NMR ($CDCl_3$) δ 164.36, 151.74, 132.20, 118.06 (pyridazine), 134.67, 117.94, 28.93 (allyl), 67.61, 31.27, 19.56, 14.20 (butyl). FT-IR (NaCl) cm^{-1} 3080 (aromatic), 2958 (aromatic), 1583 (N=N), 1379 (CH_2), 1129 (CH_3), 988, 915 (allyl double band), 832 (CSe). GC-MS *m/z* (%) 272 (M+) 257.0 (100.0), 201.0 (96.4), 135.1 (73.1), 255.1 (50.1), 199.0 (47.7).

3-Allylseleno-6-pentoxypyridazine (4e): Yield: 47%. mp 46-48 °C. ^{1}H NMR ($CDCl_3$) δ 7.29 (d, J = 9.1 Hz, 1H, pyridazine), 6.74 (d, J = 9.1 Hz, 1H, pyridazine), 6.12-5.98 (m, 1H, CH, allyl), 5.21 (d, J = 18 Hz, 1H, =CH_2, allyl), 5.01 (d, J = 9.9 Hz, 1H, =CH_2, allyl), 4.42 (t, J = 6.7 Hz, 2H, OCH_2), 3.92 (d, J = 7.5 Hz, 2H, $SeCH_2$), 1.84-1.74 (m, 2H, CH_2, pentyl), 1.43-1.32 (m, 4H, CH_2, pentyl), 0.90 (t, J = 6.9 Hz, 3H, CH_3, pentyl). ^{13}C NMR ($CDCl_3$) δ 164.12, 151.51, 131.97, 117.83 (pyridazine), 134.44, 117.71, 28.71 (allyl), 67.66, 28.71, 28.26, 22.58, 14.19 (pentyl). FT-IR (NaCl) cm^{-1} 3080 (aromatic), 2952 (aromatic), 1589 (N=N), 1380 (CH_2), 1128 (CH_3), 995, 919 (allyl double band), 840 (CSe). GC-MS *m/z* (%) 286 (M+), 201.0 (100.0), 217.1 (78.9), 286.1 (59.5), 199.0 (50.3), 153.1 (43.8).

3-Allylseleno-6-hexoxypyridazine (4f): Yield: 24%. Oil, ^{1}H NMR ($CDCl_3$) δ 7.31 (d, J = 9.1 Hz, 1H, pyridazine), 6.76 (d, J = 9.1 Hz, 1H, pyridazine), 6.12-6.00 (m, 1H, CH, allyl), 5.23 (d, J = 16.9 Hz, 1H, =CH_2, allyl), 5.03 (d, J = 9.9 Hz, 1H, =CH_2, allyl), 4.45 (t, J = 6.7 Hz, 2H, OCH_2), 3.95 (d, J = 7.3 Hz, 2H, $SeCH_2$), 1.85-1.78 (m, 2H, CH_2, hexyl), 1.45-1.26 (m, 6H, CH_2, hexyl), 0.90 (t, J = 4.6 Hz, 3H, CH_3, hexyl). ^{13}C NMR ($CDCl_3$) δ 164.15, 151.52, 132.00, 117.84 (pyridazine), 134.45, 117.71, 28.99 (allyl), 67.70, 31.70, 28.74, 25.80, 22.76, 14.20 (hexyl). FT-IR (NaCl) cm^{-1} 3080 (aromatic), 2954 (aromatic), 1579 (N=N), 1380 (CH_2), 1129 (CH_3), 995, 916 (allyl double band), 833 (CSe). GC-MS *m/z* (%) 300 (M+), 234.2 (100.0), 150.1 (66.4), 85.2 (54.7), 117.1 (40.0), 55.1 (23.4).

3-Allylseleno-6-isopropoxypyridazine (4g): Yield: 38%, mp 53-54 °C, ^{1}H NMR ($CDCl_3$) δ 7.31 (d, J = 9.1 Hz, 1H, CH, pyridazine), 6.72 (d, J = 9.1 Hz, 1H, CH, pyridazine), 6.12-6.03 (m, 1H, CH, allyl), 5.55-5.46 (m, 1H, OCH_2, isopropyl), 5.23 (d, J = 16.9 Hz, 1H, =CH_2, allyl), 5.03 (d, J = 9.9 Hz, 1H, =CH_2, allyl), 1.40 (d, J = 6.1 Hz, 6H, CH_3×2, isopropyl). ^{13}C NMR ($CDCl_3$) δ 163.79, 151.30, 132.26, 118.52 (pyridazine), 134.64, 117.90, 28.91 (allyl), 70.20, 22.27, 22.15 (isopropyl). FT-IR (NaCl) cm^{-1} 3081 (aromatic), 2925 (aromatic), 1582 (N=N), 1028, 908 (allyl double band), 838 (CSe). GC-MS *m/z* (%) 256 (M+), 201.0 (100.0), 258.0 (70.1), 199.0 (63.2), 135.1 (40.1), 243.0 (37.6).

3-Allylseleno-6-isobutoxypyridazine (4h): Yield: 31%. Oil, ^{1}H NMR ($CDCl_3$) δ 7.33 (d, J = 9.0 Hz, 1H, pyridazine), 6.79 (d, J = 9.0 Hz, 1H, pyridazine), 6.14-6.00 (m, 1H, CH, allyl), 5.23 (d, J = 16.9 Hz, 1H, =CH_2, allyl), 5.03 (d, J = 9.9 Hz, 1H, =CH_2, allyl), 4.24 (d, J = 6.6 Hz, 2H, OCH_2), 3.95 (d, J = 7.5 Hz, 2H, $SeCH_2$), 2.20-2.07 (m, 1H, CH, isobutyl), 1.02 (d, J = 6.7 Hz, 6H, CH_3×2, isobutyl). ^{13}C NMR ($CDCl_3$) δ 164.41, 151.70, 132.18, 118.00 (pyridazine), 134.65, 117.88, 28.88 (allyl), 73.87, 28.18, 19.52 (isobutyl). FT-IR (NaCl) cm^{-1} 3081 (aromatic), 2925 (aromatic), 1583 (N=N), 1006, 911 (allyl double band), 833 (CSe). GC-MS *m/z* (%) 272 (M+), 201.0 (100.0), 272.1 (65.8), 199.0 (60.8), 257.0 (50.8), 135.1 (42.0).

Acknowledgments. This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT and Future Planning (No 2012050022).

References

1. Garud, D. R.; Koketsu, M.; Ishihara, H. *Molecules* **2007**, *12*, 504.
2. Rosa, R. M.; Moura, D. J.; Silva, A. C. R.; Saffi, J.; Henriques, J. A. P. *Mutation Res.* **2007**, *631*, 44.
3. (a) Andreadou, I.; Menge, W. M. P. B.; Commandeur, J. N. M.; Worthington, E. A.; Vermeulen, N. P. E. *J. Med. Chem.* **1996**, *39*, 2040. (b) Kim, T.; Jung, U.; Cho, D. Y.; Chung, A. S. *Carcinogenesis* **2001**, *22*, 559.
4. (a) Lee, J. I.; Park, H.; Yun, Y. S.; Kwon, S. K. *J. Korean Chem. Soc.* **2001**, *45*, 386. (b) Kwon, S. K.; Kim, M. K. *Yakhak Hoeji* **2002**, *46*, 89. (c) Kwon, S. K. *Yakhak Hoeji* **2002**, *46*, 155. (d) Kwon, S. K.; Moon, A. R. *Arch. Pharm. Res.* **2005**, *4*, 391. (e) Jung, M. Y.; Kwon, S. K.; Moon, A. *Eur. J. Cancer* **2001**, *37*, 2104.
5. Park, E. H.; Park, M. S. *J. Korean Chem. Soc.* **2007**, *51*, 244.
6. Lee, M. S.; Kim, E. S.; Moon, A.; Park, M. S. *Bull. Korean Chem. Soc.* **2009**, *30*, 83.
7. (a) Won, Y. H.; Park, M. S. *Arch. Pharm. Res.* **2010**, *33*, 189. (b) Kim, C.; Park, E. H.; Park, M. S. *Bull. Korean Chem. Soc.* **2013**, *34*, 3317.
8. (a) Lee, S. H.; Park, M. S. *Yakhak Hoeji* **2011**, *55*, 32. (b) Lee, S. H.; Kim, S. B.; Park, M. S. *J. Korean Chem. Soc.* **2011**, *55*, 546.
9. (a) Bhasin, K. K.; Singh, J. *J. Organometal. Chem.* **2002**, *658*, 71. (b) Bhasin, K. K.; Bhandal, B. S.; Singh, J.; Singh, N.; Singh, K.; Singh, N.; Singh, P. *Synth. Commun.* **2002**, *32*, 1319.
10. Bhasin, K. K.; Singh, N.; Kumar, R.; Deepali, D. G.; Mehta, S. K.; Klapoetke, T. M.; Crawford, M. J. *J. Organometal. Chem.* **2004**, *689*, 3327.
11. Yoon, D. H.; Ji, M. K.; Ha, H. J.; Park, J.; Kang, P.; Lee, W. K. *Bull. Korean Chem. Soc.* **2013**, *34*, 1899.
12. Jung, J. H.; Kim, E. J., Chung, H. K.; Park, H. J.; Jeong, S. Y.; Choi, E. K. *Int. J. Oncol*. **2012**, *40*, 385.