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Germaselenazolidines and germadiselenoacetals: syntheses and radioprotective properties†

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A series of organogermanium structures (cyclic or linear) containing selenium has been prepared to be studied in chemical radioprotection. We report the syntheses, characterization and properties of germaselenazolidines and germadiselenoacetals derived from selenocysteamine and methylselenocysteamine. The radioprotective activity was evaluated in mice by intraperitoneal (i.p.) injection. For the selenazolidines, the presence of a methyl group, in the α position of the selenium, decreases the radioprotective efficacy and increases the toxicity, whereas for the diselenoacetals it leads to a reduction of the radioprotective properties and a reduction of the toxicity. Copyright © 2004 John Wiley & Sons, Ltd.

KEYWORDS: germaselenazolidines; germadiselenoacetals; toxicity; LD_{50}; radioprotective activity

INTRODUCTION

Selenium plays a fundamental role as a biological cofactor of glutathion peroxidase, which protects cellular membranes, nucleic acids and proteins against degradation by free radicals.[1–5] Nevertheless, the majority of selenium compounds present toxic effects because of the gaseous or liquid metabolites that are susceptible to being formed.

Our objective in this study was to reduce the toxic effect of organoselenium derivatives by introducing an organogermanium group into the structure. Organogermanium compounds are known to be less toxic, compared with the unsubstituted organic molecules, because they increase the liposolubility of the structure, thereby favoring the crossing of the cellular membranes.

The germaselenazolidines (Fig. 1) and germadiselenoacetals (Fig. 2) have been prepared by reaction of selenocysteamine or methylselenocysteamine with diorganogermanium dichlorides.[6]

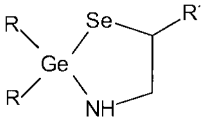

Figure 1. Germaselenazolidines **1–4**: R = n-C_6H_{13}; R′ = H (**1**), R′ = CH_3 (**2**). R = i-C_5H_{11}; R′ = H (**3**), R′ = CH_3 (**4**).

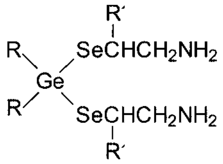

Figure 2. Germadiselenoacetals **5–8**: R = n-C_6H_{13}; R′ = H (**5**), R′ = CH_3 (**6**). R = i-C_5H_{11}; R′ = H (**7**), R′ = CH_3 (**8**).

These organometallic prodrugs permit a slow release, *in vivo*, of antioxidant and active substances. Diselenoacetals contain a potentially available double quantity of active substance compared with their selenazolidine analogs.

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EXPERIMENTAL

General methods

All manipulations were performed under an inert atmosphere of nitrogen or argon using standard Schlenck, glove box and high-vacuum techniques. All solvents used were freshly dried from sodium–benzophenone or $LiAlH_4$ before use. Amines were distilled from potassium hydroxide. IR spectra were recorded on a Perkin–Elmer 1600 FT-IR spectrophotometer. ^1H NMR spectra were recorded on a Bruker AC-80 spectrometer (80.13 MHz) and ^{13}C NMR spectra on a Bruker AC-200 spectrometer (50.32 MHz). Chemical shifts are reported in parts per million relative to internal Me_4Si as reference. Mass spectra under electron impact (EI) conditions at 70 eV were recorded on a Hewlett-Packard 5989 spectrometer. Elemental analyses (carbon, hydrogen, nitrogen) were performed at the Laboratoire de Microanalyse de l'Ecole Nationale Supérieure de Chimie de Toulouse.

Synthesis of germaselenazolidines 1–4

These compounds were synthesized by a similar method, already described, used for the synthesis of germathiazolidines.[6,7]

Preparation of Li_2Se suspension in tetrahydrofuran

22.45 ml of $LiHBEt_3$ in tetrahydrofuran (THF; 1 M, 22.45 mmol) was added dropwise with stirring to 0.89 g (11.22 mmol) of gray selenium. The mixture was stirred for 1 h at room temperature to give a white suspension of Li_2Se.[8]

Preparation of seleno- or methylseleno-cysteamine

A suspension of 2.30 g (11.22 mmol) of 2-bromoethylamine hydrobromide in 30 ml of anhydrous THF was added dropwise with stirring to a suspension of Li_2Se (11.22 mmol) in THF. The reaction is exothermic. The mixture was stirred at room temperature for 2 h. The yellow solution of 2-aminoethaneselenol obtained was used immediately.

Germaselenazolidine 2

A solution of 1.01 g (7.32 mmol) of methylselenocysteamine and 1.48 g (14.64 mmol) of triethylamine freshly distilled in 80 ml of anhydrous THF was added dropwise with stirring to a solution of 2.30 g (7.32 mmol) of dichlorodihexylgermanium[6] in 30 ml of anhydrous THF. The mixture was stirred for 2.5 h at room temperature. 30 ml of anhydrous pentane was added and the triethylamine hydrochloride formed was filtered. After concentration of the filtrate under vacuum, 10^{-2} mmHg, 2.19 g (yield: 79%) of compound **2** (Fig. 3) were obtained pure as a colorless liquid. The physicochemical data of compounds **1**–**4** are reported in Table 1.

Synthesis of germadiselenoacetals 5–8

These compounds were synthesized using a similar method (already described for germadithioacetals).[7,9]

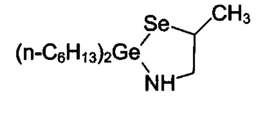


Figure 3. Germaselenazolidine **2**.

Germadiselenoacetal 5

The solutions of selenocysteamine and methylselenocysteamine were prepared as above (e.g. synthesis of germaselenazolidines) and used immediately. To a solution of 1.39 g (11.22 mmol) of 2-aminoethaneselenol and 2.27 g (22.45 mmol) of triethylamine freshly distilled in 80 ml of anhydrous THF was added dropwise, with stirring, a solution of 1.76 g (5.61 mmol) of dihexyldichlorogermanium[6] in 30 ml of anhydrous THF. The mixture was stirred for 2.5 h at room temperature. 30 ml of anhydrous pentane were added and the triethylamine hydrochloride formed was filtered. The concentration under vacuum, 10^{-2} mmHg, of the filtrate leads to 2.44 g (yield: 89%) of pure **5** ($(n\text{-}C_6H_{13})_2Ge(SeCH_2CH_2NH_2)_2$) as a colorless liquid. The physicochemical data of compounds **5**–**8** are reported in Table 1.

Pharmacology: evaluation of the radioprotection

Male Swiss (Janvier, France) mice, age 2.5–3 months and weighing 22–25 g, were used. Compounds were administrated (in a miglyol solution) by an intraperitoneal injection 15 or 90 min before irradiation. The irradiation dose was the $LD_{100/30\ days}$ (the lowest irradiation dose that leads to 100% mortality during the 30 days following the irradiation date) for non-treated control mice (8.1 Gy) or a 2 Gy greater dose. The injected dose of compound was equal to one-half of the LD_{50} toxicity value, which had been determined previously. Whole-body irradiations were performed with a cobalt-60 source. The dose rate was equal to 0.60–0.80 Gy min^{-1} (depending on the irradiation date). During irradiation, 20 animals were placed in a Plexiglas box with 30 cells in a homogeneous field 28.5 cm × 28.5 cm in size. The dosimetry was checked by means of ionization chamber dosimeters. The radiosensitivity of the strain was regularly monitored by the determination of lethality curves. The irradiation $LD_{50/30\ days}$ was equal to 8.1 Gy. The different LD_{50} values were determined by probit analysis.[10,11]

RESULTS AND DISCUSSION

We synthesized the diorganogermadiselenoacetals using a method already described for their diorganogermadithioacetals analogs.[7,9]

The action (in THF) of two equivalents of selenocysteamine or methylselenocysteamine on dialkyldichlorogermaniums,[6] in the presence of freshly distilled triethylamine, leads to the formation of the germadiselenoacetal with elimination of HCl (Scheme 1).

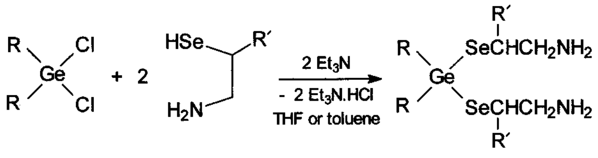
Table 1. Physicochemical data and elemental analyses of compounds **1**–**8**

Compound	Yield (%)	Spectroscopic data and analysis
1	80	R = n-C_6H_{13}; R′ = H ^{1}H NMR ($CDCl_3$; δ, ppm): 0.90 (t, 6H, J = 5.1 Hz, CH_3CH_2); 0.96–1.64 (m, 20H, $(CH_2)_5$); 2.11–2.97 (m, 4H, CH_2CH_2NH); 2.77 (s, 2H, NH) ^{13}C NMR ($CDCl_3$; δ, ppm): 14.13 (CH_3CH_2); 23.47 (CH_2Se); 25.49 (CH_2Ge); 26.44 (CH_3CH_2); 32.17 ($CH_3CH_2CH_2$); 32.79 ($CH_3CH_2CH_2CH_2$); 39.61 (CH_2CH_2Ge); 47.02 (CH_2NH) Mass spectrum: m/z 365 $[M]^{+\bullet}$ Anal. Found: C, 46.11; H, 8.66; N, 3.84. Calc. for $C_{14}H_{31}GeNSe$: C, 46.07; H, 8.56; N, 3.84%
2	79	R = n-C_6H_{13}; R′ = CH_3 ^{1}H NMR ($CDCl_3$; δ, ppm): 0.87–1.63 (m, 29H, C_6H_{13} and CH_3–CH); 2.17–3.04 (m, 3H, $CHCH_2N$); 2.74 (s, 1H, NH) ^{13}C NMR ($CDCl_3$; δ, ppm): 14.11 (CH_3CH_2); 23.34 (CH_3–CH); 25.19 (CH_2Ge); 26.31 (CH_3CH_2); 31.86 ($CH_3CH_2CH_2$); 32.64 ($CH_3CH_2CH_2CH_2$); 38.61 (CHSe); 39.28 (CH_2CH_2Ge); 48.18 (CH_2NH) Mass spectrum: m/z 379 $[M]^{+\bullet}$ Anal. Found: C, 47.49; H, 8.83; N, 3.75. Calc. for $C_{15}H_{33}GeNSe$: C, 47.53; H, 8.78; N, 3.70%
3	74	R = i-C_5H_{11}; R′ = H ^{1}H NMR ($CDCl_3$; δ, ppm): 0.88 (d, 12H, J = 5.3 Hz, $(CH_3)_2CH$); 0.92–1.69 (m, 10H, CH_2CH_2CH); 1.89–2.94 (m, 4H, CH_2CH_2NH); 2.74 (s, 1H, NH) ^{13}C NMR ($CDCl_3$; δ, ppm): 18.93 (CH_2Ge); 21.89 ($(CH_3)_2CH$); 22.99 (CH_2Se); 32.15 ($(CH_3)_2CH$); 38.90 (CH_2CH_2Ge); 47.13 (CH_2NH) Mass spectrum: m/z 337 $[M]^{+\bullet}$ Anal. Found: C, 42.84; H, 8.00; N, 4.14. Calc. for $C_{12}H_{27}GeNSe$: C, 42.78; H, 8.08; N, 4.16%
4	76	R = i-C_5H_{11}; R′ = CH_3 ^{1}H NMR ($CDCl_3$; δ, ppm): 0.86–1.71 (m, 25H, C_5H_{11} and CH_3CH); 2.00–3.01 (m, 3H, $CHCH_2NH$); 2.75 (s, 1H, NH) ^{13}C NMR ($CDCl_3$; δ, ppm): 19.01 (CH_2Ge); 21.91 ($(CH_3)_2CH$); 23.21 (CH_3CH); 32.07 ($(CH_3)_2CH$); 37.86 (CHSe); 39.01 (CH_2CH_2Ge); 47.91 (CH_2NH) Mass spectrum: m/z 351 $[M]^{+\bullet}$ Anal. Found: C, 44.39; H, 8.37; N, 4.03. Calc. for $C_{13}H_{29}GeNSe$: C, 44.49; H, 8.33; N, 3.99%
5	89	R = n-C_6H_{13}; R′ = H ^{1}H NMR ($CDCl_3$; δ, ppm): 0.19 (t, 4H, J = 7.1 Hz, CH_2Se); 0.69 (t, 4H, J = 7.1 Hz, CH_2N); 0.85 (t, 6H, J = 5.1 Hz, CH_3CH_2); 1.11–1.70 (m, 20H, $(CH_2)_5$); 2.65 (s, 4H, NH_2) ^{13}C NMR ($CDCl_3$; δ, ppm): 14.10 (CH_3CH_2); 21.65 (CH_2Se); 22.58 (CH_2Ge); 24.90 (CH_3CH_2); 25.76 ($CH_3CH_2CH_2$); 31.41 ($CH_3CH_2CH_2CH_2$); 31.14 (CH_2CH_2Ge); 41.61 (CH_2NH_2) IR. ($CDCl_3$; cm^{-1}): ν_{NH_2} = 3277, 3356 Mass spectrum: m/z 366 $[M - 124]^+$ Anal. Found: C, 39.36; H, 7.91; N, 5.69. Calc. for $C_{16}H_{38}GeN_2Se_2$: C, 39.30; H, 7.83; N, 5.73%
6	82	R = n-C_6H_{13}; R′ = CH_3 ^{1}H NMR ($CDCl_3$; δ, ppm): 0.64 (d, 4H, J = 6.8 Hz, CH_2N); 0.76 (m, 6H, CH_3CH_2); 1.03–1.60 (m, 26H, $(CH_2)_5$ and CH_3–CH); 2.25–2.80 (m, 2H, CHSe); 3.40 (s, 4H, NH_2) ^{13}C NMR ($CDCl_3$; δ, ppm): 14.04 (CH_3CH_2); 22.52 (CH_2Ge); 23.34 (CH_3–CH); 31.34 (CH_3CH_2); 32.07 ($CH_3CH_2CH_2$); 36.65 (CHSe); 37.29 ($CH_3CH_2CH_2CH_2$); 45.93 (CH_2CH_2Ge); 47.89 (CH_2NH_2) IR ($CDCl_3$; cm^{-1}): ν_{NH_2} = 3283, 3364 Mass spectrum: m/z 380 $[M - 138]^+$ Anal. Found: C, 41.90; H, 8.23; N, 5.39. Calc. for $C_{18}H_{42}GeN_2Se_2$: C, 41.81; H, 8.19; N, 5.41%
7	81	R = i-C_5H_{11}; R′ = H ^{1}H NMR ($CDCl_3$; δ, ppm): 0.19 (t, 4H, J = 7.0 Hz, CH_2Se); 0.68 (t, 4H, J = 7.0 Hz, CH_2N); 0.88 (d, 12H, J = 5.5 Hz, $(CH_3)_2CH$); 1.25–1.69 (m, 10H, CH_2CH_2CH); 2.60 (s, 4H, NH_2) ^{13}C NMR ($CDCl_3$; δ, ppm): 18.94 (CH_2Ge); 21.98 ($(CH_3)_2CH$); 23.26 (CH_2Se); 30.38 ($(CH_3)_2CH$); 34.00 (CH_2CH); 42.91 (CH_2NH_2) IR ($CDCl_3$; cm^{-1}): ν_{NH_2} = 3280, 3371 Mass spectrum: m/z 338 $[M - 124]^+$

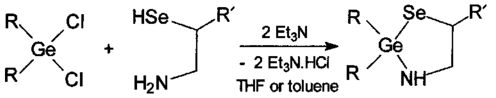
(*continued overleaf*)

Table 1. (*Continued*)

Compound	Yield (%)	Spectroscopic data and analysis
		Anal. Found: C, 36.51; H, 7.40; N, 5.99. Calc. for $C_{14}H_{34}GeN_2Se_2$: C, 36.48; H, 7.43; N, 6.07%
8	80	R = i-C_5H_{11}; R′ = CH_3 ^{1}H NMR ($CDCl_3$; δ, ppm): 0.65 (d, 4H, *J* = 6.8 Hz, CH_2N); 0.88 (m, 12 H, (CH_3)$_2$CH); 1.22–1.70 (m, 16H, CH_2CH_2CH and CH_3CH); 2.66 (s, 2H, CHSe); 3.15 (s, 4H, NH_2) ^{13}C NMR ($CDCl_3$; δ, ppm): 18.99 (CH_2Ge); 22.04 ((CH_3)$_2$CH); 23.61 (CH_3CH); 30.33 ((CH_3)$_2$CH); 34.09 (CH_2CH); 35.24 (CHSe); 47.93 (CH_2NH_2) IR ($CDCl_3$; cm^{-1}): $\nu_{NH_2} = 3277, 3361$ Mass spectrum: *m/z* 352 $[M - 138]^+$ Anal. Found: C, 39.24; H, 7.86; N, 5.70. Calc. for $C_{16}H_{38}GeN_2Se_2$: C, 39.30; H, 7.83; N, 5.73%



Scheme 1.



Scheme 2.

Germaselenazolidines were prepared similarly, using one equivalent of selenocysteamine or methylselenocysteamine (Scheme 2).[6,7]

The objective of this work was to incorporate organoselenium groups into organometallic structures such as germaselenazolidines and germadiselenoacetals so as to decrease their toxicity and increase their radioprotective activity. Table 2 summarizes the radiation protection obtained in mice after intraperitoneal administration (in a miglyol solution) of the organogermanium derivatives described. Generally, these organometallic compounds have a lower toxicity and a greater radioprotective activity than that of the starting organic derivatives.

Some of the organometallic compounds possess a good radioprotective activity, whereas all the organic basic derivatives are inactive. This shows that the germanium supports vectorization, *in vivo*, of the protective organic compound.

Moreover, the presence of the germanium atom allows a very significant fall in the acute toxicity of the germanium prodrugs compared with their organic precursors. Indeed, selenocysteamine and methylselenocysteamine are very toxic

Table 2. Toxicity and radioprotective properties of compounds **1**–**4**

Compound	R	R′	LD_{50}(mg kg^{-1})[mmol kg^{-1}]	Irradiation		Survival %
				Dose (Gy)	Time[a] (min)	
1	*n*-C_6H_{13}	H	224 [0.61]	8.1	15	30
				8.1	90	50
2	*n*-C_6H_{13}	CH_3	200 [0.53]	8.1	15	30
				8.1	90	40
3	i-C_5H_{11}	H	255 [0.76]	8.1	15	40
				8.1	90	60
4	i-C_5H_{11}	CH_3	236 [0.67]	8.1	15	40
				8.1	90	50
5	*n*-C_6H_{13}	H	260 [0.53]	8.1	15	20
6	*n*-C_6H_{13}	CH_3	300 [0.58]	8.1	15	0
7	i-C_5H_{11}	H	150 [0.33]	8.1	15	0
8	i-C_5H_{11}	CH_3	185 [0.38]	8.1	15	0
$HSeCH_2CH_2NH_2.HCl$			17 [0.11]	8.1	15	0
$HSeCH(CH_3)CH_2NH_2.HCl$			10 [0.06]	8.1	15	0

[a] Time between the administration of the compound by intraperitoneal injection and irradiation.

($10 < LD_{50} < 17\ \mathrm{mg\,kg^{-1}}$ and $0.06 < LD_{50} < 0.11\ \mathrm{mmol\,kg^{-1}}$ respectively), whereas their germanium derivatives are 3–11 times less toxic ($150 < LD_{50} < 300\ \mathrm{mg\,kg^{-1}}$ and $0.33 < LD_{50} < 0.76\ \mathrm{mmol\,kg^{-1}}$ respectively). In fact, the germanium prodrugs make it possible to inject the organic derivatives in more significant amounts, thus allowing radioprotective activity.

For the cyclic structures, as was observed in the case of germathiazolidine,[12] the methyl group in α position to the selenium atom seems to lead to an increase in the acute toxicity, which also leads to an appreciable fall in the radioprotective efficacy. The cyclic structures also make it possible to obtain a delay effect; i.e. here, the compound injected causes the maximum of its effect within a time ranging between 15 and 90 min. Conversely, in the case of the linear structures, the presence of a methyl group in α position to the selenium atom causes a reduction in the acute toxicity, just as observed in the case of sulfur.[13]

Moreover, for the linear structures **5**–**8**, and conversely with the cyclic derivatives **1**–**4**, the derivative with the *n*-hexyl group is less toxic and more active than the derivative with the i-amyl group. We thus note that the contribution brought by the i-amyl and *n*-hexyl vectors is reversed when we pass from a cyclic structure to a linear structure.

CONCLUSIONS

In summary, this analysis shows equivalent behavior between the germaselenazolidines and the germadiselenoacetals with regard to toxicity. However the cyclic structures are characterized by a radioprotective character that is definitely more marked.

The study of the effect of the different substituents on the activity of the organometallic compounds has shown that the presence of a methyl group in α position to the selenium atom has a different influence on the toxicity and the radioprotective activity, according to whether the compound is cyclic or linear in nature. Indeed, for the selenazolidines, the presence of methyl decreases the radioprotective efficacy and increases the toxicity, whereas for the diselenoacetals it leads to a reduction of the radioprotective properties and a reduction in the toxicity. In much the same way, the nature of the group led to opposited effects, with regard to toxicity and radioprotective power, between the linear or cyclic structures.

The presence of organogermanium substituents, which increase the hydrosolubility, and the presence of organic ligands, which increase the liposolubility and biological activity of these molecules, permits a very significant improvement in their radioprotective properties and favors their passage through the cellular membranes.

The results presented confirm the positive contribution of germanium in chemical radioprotection in agreement with previous work[14–18] and the interesting biological activity of organogermanium compounds in different fields.[19–37]

Acknowledgements

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REFERENCES

1. Galan P, Preziozi P, Triol I. *Cahiers de Nutrition et de Diététique* 1997; **32**: 359.
2. Willett WC, Stampfer MJ, Hunter D. *The Epidemiology of Selenium and Human Cancer*. Royal Society of Chemistry: Cambridge, 1991; 141.
3. Lederer J. *Sélénium et Vitamine E: Les Deux Pompiers de l'Organisme*, Nauwalaerts: Maloine, 1986.
4. Simonoff M, Simonoff G. *Le Sélénium et la Vie*. Masson: Paris, 1991.
5. Dubois F, Belleville F. *Pathol. Biol.* 1988; **36**: 1017.
6. Lesbre M, Mazerolles P, Satgé J. In *The Organic Compounds of Germanium*. John Wiley: New York, 1973.
7. Satgé J, Cazes A, Bouchaut M, Fatôme M, Sentenac-Roumanou H, Lion C. *Eur. J. Med. Chem.* 1982; **17**: 433.
8. Gladysz JA, Hornby JL, Garbe JE. *J. Org. Chem.* 1978; **43**: 1204.
9. Fatôme M, Sentenac-Roumanou H, Lion C, Satgé J, Fourtinon M, Rima G. *Eur. J. Med. Chem.* 1984; **19**: 119.
10. Bonet-Maury P, Patti F. *J. Radiol. Electrol. Arch. Electr. Med.* 1979; **31**: 455.
11. Finney DJ. *Probit Analysis*. Cambridge University Press: Cambridge, 1947.
12. Célariès B, Amourette C, Lion C, Rima G. *Appl. Organometal. Chem.* 2004; **18**: in press.
13. Célariès B, Amourette C, Lion C, Rima G. *Appl. Organometal. Chem.* 2003; **17**: 561.
14. Célariès B, Amourette C, Lion C, Rima G. *Appl. Organometal. Chem.* 2003; **17**: 135.
15. Célariès B, Rima G, Court L, Lion C, Roman V, Laval JD. *Metal-Based Drugs* 2001; **8**: 199.
16. Célariès B, Court L, Lion C, Rima G, Roman V. *Main Group Met. Chem.* 2001; **25**: 58.
17. Rima G, Satgé J, Dagiral R, Lion C, Fatôme M, Roman V, Laval JD. *Appl. Organometal. Chem.* 1999; **13**: 583.
18. Rima G, Satgé J, Dagiral R, Lion C, Sentenac-Roumanou H, Fatôme M, Roman V, Laval JD. *Metal-Based Drugs* 1999; **6**: 49.
19. Kakimoto N, Matsui M, Takada T, Akida M. *Heterocycles* 1985; **23**: 2681.
20. Tacke R, Becker B, Berg D, Brandes W, Dutzmann S, Schaller K. *J. Organometal. Chem.* 1992; **438**: 45.
21. Lukevics E, Germane S, Ignatovich L. *Appl. Organometal. Chem.* 1992; **6**: 543.
22. Anger F, Anger JP, Guillou L, Papillon A. *Appl. Organometal. Chem.* 1992; **6**: 267.
23. Tacke R, Reichel D, Jones PG, Hou X, Waelbroeck M, Gross J, Mutschler E, Lambrecht G. *J. Organometal. Chem.* 1996; **521**: 305.
24. Lukevics E, Veveris V, Dirnens V. *Appl. Organometal. Chem.* 1997; **11**: 805.
25. Lukevics E, Ignatovich L, Germane S. *Khim. Geterotsikl. Soed.* 1995; **10**: 1412.
26. Lukevics E, Ignatovich L. *Main Group Met. Chem.* 1994; **1**: 133.

27. Lukevics E, Gar T, Ignatovich L, Mironov F. *Biological Activity of the Germanium-Containing Compounds*. Zinatne: Riga, Russia, 1990.
28. Li F, Zhang Z, Gao H. *Metal-Based Drugs* 1996; **5**: 241.
29. Ignatovich L, Zarina D, Shestakova I, Germane S, Lukevics E. *Metal-Based Drugs* 2001; **8**: 211.
30. Lukevics E, Ignatovich L. *Chem. Org. Germanium Tin Lead Compd.* 2002; **2**: 1653.
31. Lukevics E, Ignatovich L, Shestakova I. *Appl. Organometal. Chem* 2003; **17**: 898.
32. Gerber GB, Léonard A. *Mutat. Res.* 1997; **387**: 141.
33. Xueqing S, Zhiqiang Y, Qinglan X, Jinshan L. *J. Organometal. Chem.* 1998; **566**: 103.
34. Yu B, Wu J, Zhou X. *Chung-Hua-Wai-Ko-Tsa-Chih* 1995; **33**: 167.
35. Satoh M, Iwaguchi TI. *Antitumor Activity of New Novel Organogermanium Compounds*. Cancer and Chemotherapy Publ.: Japan, 1979; 79–83.
36. Ishida W, Suzuki F, Asho H, Hayashi Y. Antitumor effects of organo-germanium compounds (Ge-132) in mouse tumors. In *Proceedings of the Annual Meeting of the Japan Cancer Association II*, 1979; 193.
37. Jao SW, Lee W, Ho YS. *Dis. Colon Rectum* 1990; **33**: 99.