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Synthesis and radioprotective action of silathiazolidines and germathiazolidines

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We report on the synthesis and characterization of new sila- and germa-thiazolidines derived from 2-[1-(1-naphthyl)ethyl]-2-imidazoline. The radioprotective activity was evaluated in mice by intraperitoneal injection. A notable diminution in the toxicity and increase in radioprotective efficacy were shown for the organometallic derivatives compared with the unsubstituted organic precursors. For some of the cyclic compounds, a delay effect was observed tranducing a slow opening *in vivo* of the thiazolidine ring. Copyright © 2004 John Wiley & Sons, Ltd.

KEYWORDS: silathiazolidines; germathiazolidines; naphthylethylimidazoline; toxicity; LD_{50}; radioprotective activity

INTRODUCTION

Many organic and organometallic compounds have been studied and screened in mice for their potential in chemical radioprotection. The most effective radioprotectors developed by our group have been metallathiazolidines and metalladithioacetals. The majority of these compounds have a dose reduction factor between 1.4 and 1.75.[1,2]

The combination of aminothiol radioprotectors with an organometallic group decreases the acute toxicity and increases the radioprotective effect by increasing the radioprotective dose. Thus, this combination increases the efficacy of chemical protection against X- and γ-rays.

The main idea of this investigation was to obtain new effective radioprotective substances in the series of metallathiazolidines containing an aminothiol group and to determine the influence of their organosilicon and organogermanium modifications (Fig. 1) on the radioprotective activity.

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. ^{1}H 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 sila- and germa-thiazolidines

These compounds were synthesized by two methods already described,[3–5] termed A and B.

Synthesis of compound 1 (method A)

To a stirred mixture of *N*-substituted cysteamine (**14**; 1.90 g, 5.56 mmol) and triethylamine (1.13 g, 11.13 mmol) in 70 ml of tetrahydrofuran (THF), a solution of dichlorodihexylgermane (1.75 g, 5.56 mmol) in 40 ml of THF was slowly added. The reaction mixture was refluxed for 6 h, then, after addition of 50 ml of pentane, filtered at room temperature under an argon atmosphere and concentrated *in vacuo* (10^{-2} mmHg) to afford pure **1** (2.59 g; yield: 80%) as a yellow oil.

Synthesis of compound 7 (method B)

To a solution of *N*-substituted cysteamine (**14**; 2.51 g, 7.33 mmol) in 50 ml of THF was added dropwise with

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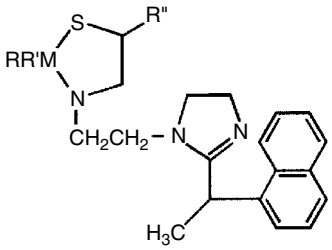


Figure 1. Metallathiazolidines used in this study: M = Ge (**1**–**6**), Si (**7**–**12**); R = R′ = *n*-C_6H_{13}; R″ = H (**1**, **7**); R = R′ = *n*-C_6H_{13}; R″ = CH_3 (**2**, **8**); R = R′ = i-C_5H_{11}; R″ = H (**3**, **9**); R = R′ = i-C_5H_{11}; R″ = CH_3 (**4**, **10**); R = CH_3; R′ = *p*-$CH_3C_6H_4$; R″ = H (**5**, **11**); R = CH_3; R′ = *p*-$CH_3C_6H_4$; R″ = CH_3 (**6**, **12**).

stirring a solution of bis(diethylamino)dihexylsilane (2.40 g, 7.33 mmol) in 50 ml of anhydrous THF. The mixture was refluxed for 6 h. After cooling and addition of 50 ml of anhydrous pentane, the mixture was filtered. The concentration of the solution, at 10^{-2} mmHg, leads to pure **7** (3.30 g; yield: 86%) as a yellow oil. The physicochemical data of the derivatives **1**–**12**, synthesized in this study, are reported in Table 1.

Synthesis of N-substituted 2-[1-(1-naphthyl)ethyl]-2-imidazolines

The synthesis of these *N*-substituted cysteamine and methylcysteamine compounds (Fig. 2) has been described elsewhere.[6]

Pharmacology

Evaluation of the radioprotection

Male Swiss (Janvier, France) mice, age 2.5–3 months and weighing 22–25 g, were used. Compounds were administed, in a miglyol solution, by an intraperitoneal injection 15 or 90 min before irradiation. The irradiation dose was the LD_{100}/30 days 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.

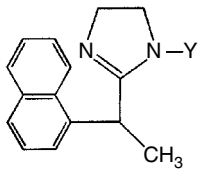


Figure 2. The *N*-substituted 2-[1-(1-naphthyl)ethyl]-2-imidazolines used in this study: Y = H (NEI, **13**); Y = $CH_2CH_2NHCH_2CH_2SH$ (**14**): Y = $CH_2CH_2NHCH_2CH(CH_3)SH$ (**15**).

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.[7,8]

RESULTS AND DISCUSSION

Silathiazolidines and germathiazolidines constitute the two major classes of radioprotectors. In our studies, we have found 2-(1-naphthylmethyl)-2-imidazoline (NMI) to be a potent radioprotector. The introduction of a methyl group; at the benzylic position 1, to give 2-[1-(1-naphthyl)ethyl]-2-imidazoline (NEI; **13**), leads to a compound with a good radioprotective effect.[9,10]

The present study was directed to investigate the effects of structural modification of 2-[1-(1-naphthyl)ethyl]-2-imidazoline as radioprotector. It has been shown previously[11] that certain imidazole derivatives possess potent and selective antagonist activity on α_2-adrenergic receptors.

Herein, we investigate the *N*-substitution of the imidazoline ring of **13** with an aminothiol group to give **14** and **15** and the introduction of an organometallic group to lead to sila- and germa-thiazolidines. We compare the activity of organometallic compounds with those of unsubstituted organic derivatives.

Synthesis of metallathiazolidines

These sila- and germa-thiazolidines were prepared using two heterocyclization methods previously described in the literature.[3–5]

Method A

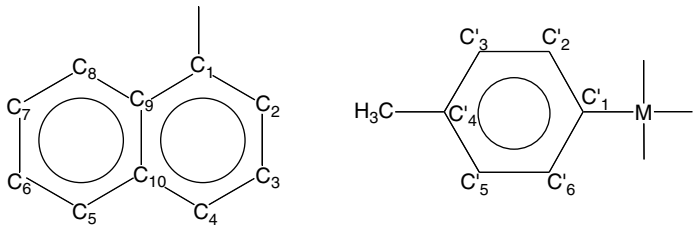
The action of diorganosilicon and diorganogermanium dichlorides[5] (in stoichiometric amounts) on *N*-substituted 2-[1-(1-naphthyl)ethyl]-2-imidazoline (**14** or **15**) in refluxing anhydrous THF in the presence of freshly distilled triethylamine gave, by a dehydrohalogenation reaction between M–Cl, SH and NH groups, the cyclic derivatives in good yields (Scheme 1).

Method B

The reaction of *N*-substituted 2-[1-(1-naphthyl)ethyl]-2-imidazoline, in stoichiometric amounts, with the bis(diethylamino)diorgano-silanes or -germanes in refluxing anhydrous THF resulted in a cleavage reaction of M–N (M = Si, Ge) bonds by the SH group and NH groups (transamination reaction)[3] forming the corresponding sila- and germa-thiazolidines in good yields (Scheme 1).

Analysis of the results, reported in Table 2, shows that the organometallated derivatives described have a lower toxicity and a greater radioprotective activity than that of the basic organic derivatives.

Table 1. Physicochemical data and analysis of compounds **1**–**12**



Compound	Yield (%)	Spectroscopic data and analysis
1	80	R = R′ = *n*-C_6H_{13}; R″ = H; M = Ge ^{1}H NMR ($CDCl_3$; δ, ppm): 0.86 (t, 6H, J = 5.6 Hz, CH_3CH$_2$); 1.23–1.52 (m, 20H, (CH_2)$_5$); 1.66 (d, 3H, J = 7.1 Hz, CH_3CH); 2.52–2.80 (m, 6H, CH$_2$N and CH$_2$S); 2.84–3.09 (m, 2H, CH$_2$N); 3.16–3.48 (m, 2H, CH$_2$N); 3.63–3.80 (m, 2H, CH$_2$N); 4.51 (q, 1H, J = 7.1 Hz, CH–$C_{10}H_7$); 7.27–7.53 (m, 4H, $C_{10}H_7$); 7.60–7.88 (m, 2H, $C_{10}H_7$); 7.93–8.15 (m, 1H, $C_{10}H_7$) ^{13}C NMR ($CDCl_3$; δ, ppm): 14.15 (*C*H$_3$CH$_2$); 14.74 (*C*H$_2$CH$_2$Ge); 18.94 (*C*H$_2$Ge); 20.63 (*C*H$_3$–CH); 22.57 (CH$_3$*C*H$_2$); 24.27 (CH$_3$*C*H$_2$CH$_2$CH$_2$); 24.39 (CH$_3$CH$_2$*C*H$_2$CH$_2$); 31.14 (*C*H$_2$S); 34.72 (*C*H–$C_{10}H_7$); 42.19 (*C*H$_2$N); 48.35 (*C*H$_2$N); 50.33 (*C*H$_2$N); 50.69 (*C*H$_2$N); 53.08 (*C*H$_2$N); 123.41 (C_8); 125.47 (C_6); 125.86 (C_7); 126.08 (C_4); 126.39 (C_2); 127.51 (C_3); 128.80 (C_5); 132.39 (C_9); 132.51 (C_{10}); 133.71 (C_1); 168.89 (N–*C* = N) Mass spectrum: m/z 569 $[M]^{+\cdot}$. Anal. Found: C, 65.41; H, 8.58; N, 7.44. Calc. for $C_{31}H_{49}GeN_3S$: C, 65.50; H, 8.69; N, 7.39%
2	78	R = R′ = *n*-C_6H_{13}; R″ = CH_3; M = Ge ^{1}H NMR ($CDCl_3$; δ, ppm): 0.84–1.09 (m, 9H, CH_3CH$_2$ and CH_3CHS); 1.13–1.34 (m, 20H, (CH_2)$_5$); 1.63 (d, 3H, J = 6.8 Hz, CH_3–CH); 2.51–3.07 (m, 7H, C*H*S and CH_2N); 3.14–3.41 (m, 2H, CH_2N); 3.60–3.73 (m, 2H, CH_2N); 4.56 (q, 1H, J = 6.8 Hz, CH–$C_{10}H_7$); 7.26–7.58 (m, 4H, $C_{10}H_7$); 7.63–7.92 (m, 2H, $C_{10}H_7$); 7.99–8.21 (m, 1H, $C_{10}H_7$) ^{13}C NMR ($CDCl_3$; δ, ppm): 14.15 (*C*H$_3$CH$_2$); 15.53 (*C*H$_3$–CHS); 20.58 (*C*H$_3$CH); 22.63 (*C*H$_2$Ge); 23.29 (*C*H$_2$CH$_2$Ge); 24.31 (CH$_3$*C*H$_2$CH$_2$CH$_2$); 31.36 (CH$_3$CH$_2$*C*H$_2$); 31.56 (CH$_3$*C*H$_2$); 34.76 (*C*H–$C_{10}H_7$); 40.60 (*C*H$_2$N); 41.25 (*C*H$_3$CHS); 48.24 (*C*H$_2$N); 50.61 (*C*H$_2$N); 50.84 (*C*H$_2$N); 52.66 (*C*H$_2$N); 123.80 (C_8); 125.36 (C_6); 125.82 (C_7); 126.36 (C_4); 126.59 (C_2); 127.46 (C_3); 128.64 (C_5); 132.00 (C_9); 132.36 (C_{10}); 133.79 (C_1); 168.39 (N–*C* = N) Mass spectrum: m/z 583 $[M]^{+\cdot}$. Anal. Found: C, 66.09; H, 8.97; N, 7.18. Calc. for $C_{32}H_{51}GeN_3S$: C, 65.99; H, 8.83; N, 7.21%
3	81	R = R′ = *i*-C_5H_{11}; R″ = H; M = Ge ^{1}H NMR ($CDCl_3$; δ, ppm): 0.85 (d, 12H, J = 5.3 Hz, (CH_3)$_2$CH); 0.94–1.31 (m, 10H, CH_2CH_2C*H*); 1.66 (d, 3H, J = 7.0 Hz, CH_3–CH); 2.48–2.76 (m, 6H, CH$_2$S and CH$_2$N); 2.88–3.09 (m, 2H, CH_2N); 3.18–3.44 (m, 2H, CH_2N); 3.57–3.89 (m, 2H, CH_2N); 4.60 (q, 1H, J = 7.0 Hz, CH–$C_{10}H_7$); 7.26–7.59 (m, 4H, $C_{10}H_7$); 7.61–7.94 (m, 2H, $C_{10}H_7$); 8.06–8.21 (m, 1H, $C_{10}H_7$) ^{13}C NMR ($CDCl_3$; δ, ppm): 18.31 (*C*H$_2$Ge); 20.81 (*C*H$_3$CH); 22.19 ((*C*H$_3$)$_2$CH); 27.73 (*C*H$_2$CH); 30.83 ((CH$_3$)$_2$*C*H); 32.14 (*C*H$_2$S); 34.65 (*C*H–$C_{10}H_7$); 40.81 (*C*H$_2$N); 46.96 (*C*H$_2$N); 50.34 (*C*H$_2$N); 50.79 (*C*H$_2$N); 52.81 (*C*H$_2$N); 123.56 (C_8); 125.28 (C_6); 125.81 (C_7); 126.18 (C_4); 126.38 (C_2); 127.41 (C_3); 128.63 (C_5); 132.11 (C_9); 132.41 (C_{10}); 133.98 (C_1); 169.09 (N–*C* = N) Mass spectrum: m/z 541 $[M]^{+\cdot}$. Anal. Found: C, 64.28; H, 8.45; N, 7.84 Calc. for $C_{29}H_{45}GeN_3S$: C, 64.46; H, 8.39; N, 7.78%
4	83	R = R′ = i-C_5H_{11}; R″ = CH_3; M = Ge ^{1}H NMR ($CDCl_3$; δ, ppm): 0.83–0.98 (m, 15H, (CH_3)$_2$CH and CH_3CHS); 1.06–1.39 (m, 10H, CH_2CH_2C*H*); 1.66 (d, 3H, J = 6.9 Hz, CH_3–CH); 2.46–2.83 (m, 4H, CH$_2$N); 2.90–3.12 (m, 3H, CH_2N and C*H*S); 3.24–3.43 (m, 2H, CH$_2$N); 3.60–3.78 (m, 2H, CH$_2$N); 4.58 (q, 1H, J = 6.9 Hz, CH–CH$_3$); 7.26–7.55 (m, 4H, $C_{10}H_7$); 7.62–7.83 (m, 2H, $C_{10}H_7$); 7.90–8.13 (m, 1H, $C_{10}H_7$)

(*continued overleaf*)

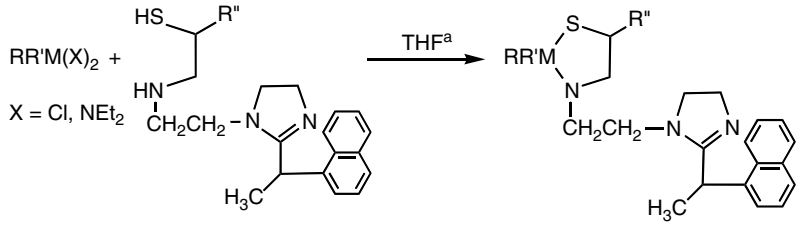
Table 1. (*Continued*)

Compound	Yield (%)	Spectroscopic data and analysis
		^{13}C NMR ($CDCl_3$; δ, ppm): 18.20 (CH_2Ge); 20.66 (CH_3CH); 20.97 (CH_3CHS); 22.24 (($CH_3)_2CH$); 30.63 (($CH_3)_2CH$); 30.89 (CH_2CH); 34.61 ($CH–C_{10}H_7$); 40.26 (CH_2N); 41.08 ($CH–C_{10}H_7$); 47.66 (CH_2N); 50.41 (CH_2N); 50.63 (CH_2N); 52.39 (CH_2N); 123.59 (C_8); 125.18 (C_6); 125.69 (C_7); 126.17 (C_4); 126.51 (C_2); 128.00 (C_3); 129.11 (C_5); 132.01 (C_9); 132.26 (C_{10}); 133.92 (C_1); 169.03 (N–*C* = N) Mass spectrum: *m*/*z* 555 $[M]^{+\cdot}$. Anal. Found: C, 65.06; H, 8.51; N, 7.52. Calc. for $C_{30}H_{47}GeN_3S$: C, 64.99; H, 8.54; N, 7.58%
5	81	R = *p*-$CH_3–C_6H_4$; R′ = CH_3; R″ = H; M = Ge ^{1}H NMR ($CDCl_3$; δ, ppm): 1.13 (s, 3H, CH_3Ge); 1.63 (d, 3H, J = 6.8 Hz, CH_3–CH); 2.33 (s, 3H, p-CH_3); 2.51–2.79 (m, 6H, CH_2N and CH_2S); 2.83–3.11 (m, 2H, CH_2N); 3.14–3.49 (m, 2H, CH_2N); 3.59–3.82 (m, 2H, CH_2N); 4.54 (q, 1H, J = 6.8 Hz, $CH–C_{10}H_7$); 7.19–8.23 (m, 11H, C_6H_4 and $C_{10}H_7$) ^{13}C NMR ($CDCl_3$; δ, ppm): 8.89 ($CH_3–Ge$); 20.61 (CH_3CH); 21.62 (*p*-CH_3); 32.09 (CH_2S); 34.79 ($C_{10}H_7–CH$); 41.08 (CH_2N); 47.12 (CH_2N); 50.42 (CH_2N); 50.84 (CH_2N); 52.70 (CH_2N); 122.12 (C'_3 and C'_4); 123.21 (C'_2 and C'_6); 124.03 (C_8); 125.11 (C_6); 125.69 (C_7); 127.28 (C_4); 128.59 (C_2); 129.66 (C_3); 131.97 (C_5); 133.64 (C_9); 133.94 (C'_1); 134.36 (C_{10}); 134.86 (C_1); 139.94 (C'_4); 169.18 (N–*C* = N) Mass spectrum: *m*/*z* 505 $[M]^{+\cdot}$. Anal. Found: C, 64.47; H, 6.58; N, 8.27. Calc. for $C_{27}H_{33}GeN_3S$: C, 64.31; H, 6.60; N, 8.33.
6	77	R = *p*-$CH_3–C_6H_4$; R′ = CH_3; R″ = CH_3; M = Ge ^{1}H NMR ($CDCl_3$; δ, ppm): 1.12 (s, 3H, CH_3Ge); 1.15 (d, 3H, J = 6.9 Hz, CH_3CHS); 1.65 (d, 3H, J = 7.2 Hz, CH_3–CH); 2.33 (s, 3H, *p*-CH_3); 2.45–2.81 (m, 5H, CH_2N and CHS); 2.85–3.09 (m, 2H, CH_2N); 3.12–3.44 (m, 2H, CH_2N); 3.50–3.80 (m, 2H, CH_2N); 4.58 (q, 1H, J = 7.2 Hz, $CH–C_{10}H_7$); 7.15–8.15 (m, 11 H, C_6H_4 and $C_{10}H_7$) ^{13}C NMR ($CDCl_3$; δ, ppm): 8.91 ($CH_3–Ge$); 20.48 (CH_3–CH); 21.51 (*p*-CH_3); 21.99 (CH_3CHS); 35.08 ($CH–C_{10}H_7$); 37.61 ($CH–CH_3$); 41.13 (CH_2N); 46.98 (CH_2N); 50.31 (CH_2N); 50.98 (CH_2N); 52.75 (CH_2N); 122.01 (C'_3 and C'_5); 123.21 (C'_2 and C'_6); 124.19 (C_8); 124.97 (C_6); 125.59 (C_7); 127.14 (C_4); 128.51 (C_2); 129.62 (C_3); 132.09 (C_5); 133.56 (C_9); 134.03 (C'_1); 134.41 (C_{10}); 134.97 (C_1); 140.31 (C'_4); 168.97 (N–*C* = N) Mass spectrum: *m*/*z* 519 $[M]^{+\cdot}$. Anal. Found: C, 64.94; H, 6.79; N, 8.06. Calc. for ($C_{28}H_{35}GeN_3S$): C, 64.89; H, 6.81; N, 8.11
7	86	R = R′ = n-C_6H_{13}; R″ = H; M = Si ^{1}H NMR ($CDCl_3$; δ, ppm): 0.94 (t, 6H, J = 5.8 Hz, CH_3CH_2); 1.10–1.38 (m, 20H, $(CH_2)_5$); 1.65 (d, 3H, J = 7.0 Hz, CH_3CH); 2.50–2.78 (m, 6H, CH_2N and CH_2S); 2.82–3.07 (m, 2H, CH_2N); 3.14–3.46 (m, 2H, CH_2N); 3.61–3.80 (m, 2H, CH_2N); 4.53 (q, 1H, J = 7.0 Hz, $CH–C_{10}H_7$); 7.24–7.52 (m, 4H, $C_{10}H_7$); 7.58–7.84 (m, 2H, $C_{10}H_7$); 7.89–8.13 (m, 1H, $C_{10}H_7$) ^{13}C NMR ($CDCl_3$; δ, ppm): 7.88 (CH_2Si); 14.10 (CH_3CH_2); 20.66 (CH_3–CH); 23.30 (CH_3CH_2); 25.74 (CH_2CH_2Si); 26.08 ($CH_3CH_2CH_2CH_2$); 26.45 ($CH_3CH_2CH_2$); 31.17 (CH_2S); 34.68 ($CH–C_{10}H_7$); 42.14 (CH_2N); 48.63 (CH_2N); 50.11 (CH_2N); 50.76 (CH_2N); 53.29 (CH_2N); 123.45 (C_8); 125.25 (C_6); 125.63 (C_7); 126.35 (C_4); 126.51 (C_2); 127.36 (C_3); 128.14 (C_5); 132.32 (C_9); 132.41 (C_{10}); 133.33 (C_1); 169.55 (N = *C* = N) Mass spectrum: *m*/*z* 523 $[M]^{+\bullet}$. Anal. Found: C, 71.10; H, 9.45; N, 8.00. Calc. for: $C_{31}H_{49}N_3SSi$ C, 71.07; H, 9.43; N, 8.02%
8	82	R = R′ = *n*-C_6H_{13}; R″ = CH_3; M = Si ^{1}H NMR ($CDCl_3$; δ, ppm): 0.86–1.10 (m, 9H, CH_3CH_2 and CH_3CHS); 1.12–1.36 (m, 20H, $(CH_2)_5$); 1.65 (d, 3H, J = 6.9 Hz, CH_3–CH); 2.50–3.10 (m, 7H, *CH*S and CH_2N); 3.13–3.43 (m, 2H, CH_2N); 3.56–3.71 (m, 2H, CH_2N); 4.53 (q, 1H, J = 6.9 Hz, $CH–C_{10}H_7$); 7.23–7.56 (m, 4H, $C_{10}H_7$); 7.60–7.90 (m, 2H, $C_{10}H_7$); 7.94–8.17 (m, 1H, $C_{10}H_7$) ^{13}C NMR ($CDCl_3$; δ, ppm): 7.86 (CH_2Si); 14.11 (CH_3CH_2); 21.53 ($CH_3–CHS$); 21.68 (CH_3CH); 23.45 (CH_2CH_2Si); 24.25 ($CH_3CH_2CH_2CH_2$); 31.12 ($CH_3CH_2CH_2$); 31.64 (CH_3CH_2); 34.25 ($CH–C_{10}H_7$); 40.55 (CH_2N); 41.14 (CH_3CHS); 48.47 (CH_2N); 50.27 (CH_2N); 50.52 (CH_2N); 52.85 (CH_2N); 123.21 (C_8); 125.58 (C_6); 125.84 (C_7); 126.55 (C_4); 126.97 (C_2); 127.31 (C_3); 128.52 (C_5); 132.12 (C_9); 132.56 (C_{10}); 133.55 (C_1); 169.39 (N–*C* = N) Mass spectrum: *m*/*z* 537 $[M]^{+\bullet}$. Anal. Found: C, 71.49; H, 9.61; N, 7.80. Calc. for: $C_{32}H_{51}N_3SSi$ C, 71.45; H, 9.56; N, 7.81.

Table 1. (*Continued*)

Compound	Yield (%)	Spectroscopic data and analysis
9	84	R = R′ = i-C_5H_{11}; R″ = H; M = Si ^{1}H NMR ($CDCl_3$; δ, ppm): 1.05 (d, 12H, J = 5.5 Hz, (CH_3)$_2$CH); 1.19–1.45 (m, 10H, CH_2CH_2CH); 1.64 (d, 3H, J = 7.0 Hz, CH_3–CH); 2.39–2.71 (m, 6H, CH_2S and CH_2N); 2.76–3.00 (m, 2H, CH_2N); 3.08–3.40 (m, 2H, CH_2N); 3.51–3.84 (m, 2H, CH_2N); 4.46 (q, 1H, J = 7.0 Hz, CH–$C_{10}H_7$); 7.22–7.49 (m, 4H, $C_{10}H_7$); 7.52–7.89 (m, 2H, $C_{10}H_7$); 7.91–8.17 (m, 1H, $C_{10}H_7$) ^{13}C NMR ($CDCl_3$; δ, ppm): 7.76 (CH_2Si); 21.03 (CH_3CH); 22.31 ((CH_3)$_2$CH); 27.45 (CH_2CH); 31.83 ((CH_3)$_2$CH); 32.12 (CH_2S); 35.13 (CH–$C_{10}H_7$); 40.75 (CH_2N); 44.96 (CH_2N); 49.47 (CH_2N); 50.45 (CH_2N); 52.85 (CH_2N); 123.48 (C_8); 125.58 (C_6); 125.95 (C_7); 126.28 (C_4); 126.35 (C_2); 127.52 (C_3); 128.83 (C_5); 132.25 (C_9); 132.66 (C_{10}); 133.74 (C_1); 169.12 (N–C=N) Mass spectrum: m/z 495 $[M]^{+\bullet}$. Anal. Found: C, 70.28; H, 9.15; N, 8.39. Calc. for: $C_{29}H_{45}N_3SSi$ C, 70.25; H, 9.15; N, 8.47 %
10	82	R = R′ = i-C_5H_{11}; R″ = CH_3; M = Si ^{1}H NMR ($CDCl_3$; δ, ppm): 0.89–1.13 (m, 15H, (CH_3)$_2$CH and CH_3CHS); 1.16–1.45 (m, 10H, CH_2CH_2CH); 1.64 (d, 3H, J = 7.0 Hz, CH_3–CH); 2.39–2.80 (m, 4H, CH_2N); 2.86–3.08 (m, 3H, CH_2N and CHS); 3.15–3.47 (m, 2H, CH_2N); 3.56–3.83 (m, 2H, CH_2N); 4.56 (q, 1H, J = 7.0 Hz, CH–CH_3); 7.21–7.57 (m, 4H, $C_{10}H_7$); 7.63–7.80 (m, 2H, $C_{10}H_7$); 7.86–8.13 (m, 1H, $C_{10}H_7$) ^{13}C NMR ($CDCl_3$; δ, ppm): 7.71 (CH_2Si); 21.76 (CH_3CH); 21.97 (CH_3CHS); 22.14 ((CH_3)$_2$CH); 30.56 ((CH_3)$_2$CH); 30.85 (CH_2CH); 34.54 (CH–$C_{10}H_7$); 40.74 (CH_2N); 41.63 (CH–$C_{10}H_7$); 47.52 (CH_2N); 50.68 (CH_2N); 50.99 (CH_2N); 52.55 (CH_2N); 123.35 (C_8); 125.35 (C_6); 125.78 (C_7); 126.23 (C_4); 126.52 (C_2); 128.42 (C_3); 129.56 (C_5); 132.14 (C_9); 132.85 (C_{10}); 133.78 (C_1); 169.07 (N–C=N) Mass spectrum: m/z 509 $[M]^{+\bullet}$. Anal. Found: C, 70.61; H, 9.24; N, 8.26. Calc. for: $C_{30}H_{47}N_3SSi$ C, 70.67; H, 9.29; N, 8.24 %
11	79	R = p-CH_3–C_6H_4; R′ = CH_3; R″ = H; M = Si ^{1}H NMR ($CDCl_3$; δ, ppm): 0.67 (s, 3H, CH_3Si); 1.57 (d, 3H, J = 6.7 Hz, CH_3–CH); 2.33 (s, 3H, p-CH_3); 2.42–2.71 (m, 6H, CH_2N and CH_2S); 2.79–3.05 (m, 2H, CH_2N); 3.10–3.42 (m, 2H, CH_2N); 3.46–3.77 (m, 2H, CH_2N); 4.56 (q, 1H, J = 6.7 Hz, CH–$C_{10}H_7$); 7.19–8.16 (m, 11H, C_6H_4 and $C_{10}H_7$) ^{13}C NMR ($CDCl_3$; δ, ppm): 1.83 (CH_3Si); 21.42 (CH_3CH); 21.84 (p-CH_3); 32.15 (CH_2S); 34.86 ($C_{10}H_7$–CH); 41.52 (CH_2N); 47.04 (CH_2N); 50.25 (CH_2N); 50.85 (CH_2N); 52.42 (CH_2N); 122.44 (C'_3 and C'_5); 123.56 (C'_2 and C'_6); 124.41 (C_8); 125.33 (C_6); 125.95 (C_7); 127.45 (C_4); 128.51 (C_2); 129.24 (C_3); 131.44 (C_5); 133.45 (C_9); 133.78 (C'_1); 134.56 (C_{10}); 134.96 (C_1); 139.55 (C'_4); 168.75 (N–C=N) Mass spectrum: m/z 459 $[M]^{+\bullet}$. Anal. Found: C, 70.53; H, 7.26; N, 9.11. Calc. for: $C_{27}H_{33}N_3SSi$ C, 70.54; H, 7.23; N, 9.14%
12	81	R = p-CH_3–C_6H_4; R′ = CH_3; R″ = CH_3; M = Si ^{1}H NMR ($CDCl_3$; δ, ppm): 0.72 (s, 3H, CH_3Si); 1.17 (d, 3H, J = 6.6 Hz, CH_3CHS); 1.61 (d, 3H, J = 7.1 Hz, CH_3–CH); 2.32 (s, 3H, p-CH_3); 2.43–2.74 (m, 5H, CH_2N and CHS); 2.79–3.02 (m, 2H, CH_2N); 3.10–3.44 (m, 2H, CH_2N); 3.49–3.76 (m, 2H, CH_2N); 4.57 (q, 1H, J = 7.1 Hz, CH–$C_{10}H_7$); 7.15–8.17 (m, 11 H, C_6H_4 and $C_{10}H_7$) ^{13}C NMR ($CDCl_3$; δ, ppm): 1.89 (CH_3Si); 21.48 (CH_3CH); 21.73 (p-CH_3); 22.32 (CH_3CHS); 35.45 (CH–$C_{10}H_7$); 37.74 (CH–CH_3); 41.85 (CH_2N); 46.75 (CH_2N); 50.01 (CH_2N); 50.55 (CH_2N); 52.52 (CH_2N); 122.21 (C'_3 and C'_5); 123.25 (C'_2 and C'_6); 124.24 (C_8); 124.53 (C_6); 125.25 (C_7); 127.02 (C_4); 128.57 (C_2); 129.58 (C_3); 132.52 (C_5); 133.85 (C'_1); 134.14 (C_9); 134.74 (C_{10}); 135.55 (C_1); 140.55 (C'_4); 168.65 (N–C=N) Mass spectrum: m/z 473 $[M]^{+\bullet}$. Anal. Found: C, 71.03; H, 7.41; N, 8.84. Calc. for: $C_{28}H_{35}N_3SSi$ C, 70.99; H, 7.45; N, 8.87%

For the silathiazolidines (**7**–**12**), a good survival rate has been observed (between 10 and 40%), for an 8.1 Gy irradiation, 15 min after injection, and these compounds are still active 90 min after irradiation (until 70% of survival rate). This induces a slow opening of the ring and a slow liberation of the active molecule. Generally, their activity 90 min after injection is greater than that at 15 min. The thiazolidine ring permits one to obtain a delayed effect for compounds **7**–**9** (i.e. the maximum effect appears between 15 and 90 min) and a prolonged effect for compounds **10** and **12** (the maximum effect is reached between 0 and 15 min and remains close to the maximum at least 90 min after injection). All the compounds



Scheme 1. Silathiazolidines and germathiazolidines preparation. [a] When X = Cl: with Et_3N and elimination of 2 $Et_3N \cdot HCl$; when X = NEt_2: with elimination of 2 Et_2NH.

Table 2. Toxicity and radioprotective activity of compounds 1–12

Compound	Injected Dose (mg kg^{-1})	LD_{50} (mg kg^{-1}) [mmol kg^{-1}]	Irradiation (Gy) [t(min)][a]	Survival rate (%)
1	150	>300 [0.53]	8.1 [15]	0
2	300	600 [1.03]	8.1 [15]	0
3	75	150 [0.28]	8.1 [15]	0
4	300	600 [1.08]	8.1 [15]	0
5	75	150 [0.30]	8.1 [15]	0
6	75	150 [0.29]	8.1 [15]	0
7	150	300 [0.573]	8.1 [15]	30
			8.1 [90]	70
8	150	300 [0.557]	8.1 [15]	20
			8.1 [90]	30
9	300	600 [1.210]	8.1 [15]	10
			8.1 [90]	30
10	75	150 [0.294]	8.1 [15]	40
			8.1 [90]	30
11	75	150 [0.326]	8.1 [15]	10
			8.1 [90]	0
12	75	150 [0.316]	8.1 [15]	30
			8.1 [90]	20
14	150	>300 [>0.916]	8.1 [15]	50
15	106	212 [0.621]	8.1 [15]	0

[a] t: time between administration of the compound and irradiation.

described in this paper have a nil radioprotective activity for a 10.1 Gy irradiation.

Compounds **3**, **4**, **9** and **10** display a similar structure; the toxicity of these derivatives may be partly attributed to the naphthylethylimidazoline part. The substitution may modulate the toxicity slightly.

Although the organosilylated and organogermylated derivatives both show approximately the same toxicity (Table 2), the silicon-containing molecules (**7**–**12**) described in this paper seem to present a higher radioprotective activity than their germylated homologues (**1**–**6**).

CONCLUSIONS

In short, the radioprotective activity of organometallic compounds can be increased, compared with unsubstituted organic derivatives, by the presence of organometallic groups; these groups increase the hydrosolubility, the lipophilicity and the activity of these molecules, thereby favouring their passage through the cellular membranes. These derivatives are generally less toxic and more active than the basic organic derivatives.

The results presented in this paper confirm the positive contribution of germanium and silicon in the radioprotection field, in agreement with previous work[1,2] and the interesting biological activity of organogermanium and organosilicon compounds.[12–19] We also observed that organometallated groups decrease the toxicity of the basic organic molecules to which they are attached.

The organometallic derivatives derived from NEI described in this paper are slightly less toxic, but also less active, than their NMI analogues studied previously.[1] In

order to understand these observations, we undertook to study their action mechanism *in vitro*. These studies will enable us to make elucidate the action mechanism of these organometallic compounds *in vivo*, which may be similar to that described for WR-2721.[20,21]

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