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Synthesis and radioprotective study of new siladithioacetals and germadithioacetals

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A series of organosilicon and organogermanium compounds derived from cysteamine, methylcysteamine and 2-[1-(1-naphthyl)ethyl]-2-imidazoline have been prepared and their radiopharmacological properties (radioprotective activity and toxicity) have been determined in mice. A number of these new organometallic derivatives have been found to possess radioprotective activity.

We have also noted a notable decrease of the toxicity and a fairly large increase in the radioprotective activity in comparison with the unsubstituted organic molecules. Copyright © 2003 John Wiley & Sons, Ltd.

KEYWORDS: siladithioacetals; germadithioacetals; toxicity; LD_{50}; naphthylethylimidazoline; radioprotective activity

INTRODUCTION

Several organogermanium compounds are known to possess pharmacological activity.[1–21] Most of them are described as having antitumour, psychotropic, neurotropic, cardiovascular or antiarthritic properties. Organogermanium and organosilicon compounds have also shown radioprotective activity. The great majority of these compounds were metallathiazolidines and metalladithioacetals derived from *N*-substituted cysteamine, methylcysteamine and 2-(1-naphthylmethyl)-2-imidazoline. Many of these compounds have a dose reduction factor (DRF) between 1.4 and 1.75.[22–32]

We have already demonstrated that the substitution of a carbon atom by a germanium or a silicon atom, in certain biologically active molecules such as metallathiazolidines and metalladithioacetals, significantly increases their radioprotective power.[33–35]

We have broadened our work with the synthesis and the study of new siladithioacetals and germadithioacetals derived from 2-[1-(1-naphthyl)ethyl]-2-imidazoline (NEI).

In this paper we report the synthesis, the study of the toxicity and radioprotective activity of the new organosilylated and organogermylated structures shown in Fig. 1; the organic derivatives are shown in Fig. 2.

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EXPERIMENTAL

General procedures

All manipulations were performed under an inert atmosphere of nitrogen or argon using standard Schlenk, 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 Brucker AC-80 spectrometer (80.13 MHz) and ^{13}C NMR spectra on a Brucker 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 (C, H, N) were performed at the *Laboratoire de Microanalyses de l'Ecole Nationale Supérieure de Chimie de Toulouse*.

Synthesis

The sila- and germa-dithioacetals (**1**–**12**) were synthesized by two methods, termed A and B.

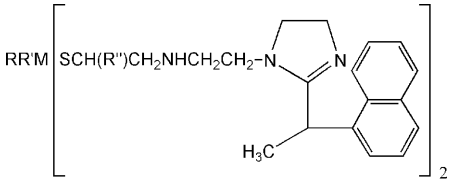


Figure 1. Metalladithioacetals: M = Ge (**1**–**6**), Si (**7**–**12**): R = R′ = *i*-C_5H_{11}, R″ = H (**1**, **7**); R = R′ = *i*-C_5H_{11}, R″ = CH_3 (**2**, **8**); R = R′ = *n*-C_6H_{13}, R″ = H (**3**, **9**); R = R′ = *n*-C_6H_{13}, R″ = CH_3 (**4**, **10**); R = *p*-CH_3–C_6H_4, R′ = CH_3, R″ = H (**5**, **11**); R = *p*-CH_3–C_6H_4, R′ = *CH*$_3$, R″ = CH_3 (**6**, **12**).

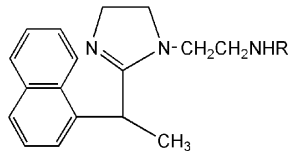


Figure 2. Organic molecules: R = H (**13**); R = CH_2CH_2SH (**14**); R = $CH_2CH(CH_3)SH$ (**15**).

Synthesis of compound 10 (method A)

A solution of dichlorodihexylsilane (0.84 g, 3.10 mmol) in 40 ml of tetrahydrofuran (THF) was added dropwise to a stirred mixture of *N*-substituted methylcysteamine (**15**; 2.12 g, 6.20 mmol) and triethylamine (0.63 g, 6.20 mmol) in 70 ml of THF. The reaction mixture was refluxed for 6 h. After cooling, 30 ml of dry pentane were added with stirring and the solid phase was removed by filtration under an argon atmosphere. The filtrate was concentrated *in vacuo* to afford **10** (2.24 g, 82% yield).

Synthesis of compound 2 (method B)

To a solution of *N*-substituted methylcysteamine (**15**; 3.05 g, 8.93 mmol) in 50 ml of THF was added dropwise with stirring a solution of bis(diethylamino)diisoamylgermane (1.60 g, 4.46 mmol) in 50 ml of anhydrous THF. The mixture was refluxed for 6 h. The volatiles were removed under reduced pressure to afford **2** (4.00 g, 90% yield).

Physicochemical data of derivatives **1**–**12** are reported in Table 1.

Synthesis of organic derivatives

*NEI–$CH_2CH_2NH_2$ (**13**)*

In flask adapted to a Dean–Stark apparatus surmounted by a condenser, diethylenetriamine (108.20 g, 1.05 mol) was added to a solution of 1-naphthyl-2-propanoic acid in 800 ml of xylene. The reaction mixture was refluxed until all the water formed was removed by azeotropic distillation (about 36 h). The cold mixture was allowed to decant and the upper layer was concentrated *in vacuo*, leading to a brown–orange paste; this was stirred overnight at room temperature in 700 ml of diethyl ether. The upper orange layer was concentrated and then fractionally distilled under reduced pressure to obtain **13** (54.27 g, 58% yield); bp = 190–193 °C/0.015 mmHg.

^{1}H NMR ($CDCl_3$; δ, ppm): 0.99 (s, 2H, NH_2); 1.59 (d, 3H, J = 6.9 Hz, C*H*$_3$CH); A_2B_2 syst.: δ_A = 2.62 (2H, CH_2N), δ_B = 3.04 (2H, CH_2N), J_{AB} = 6.0 Hz; A_2B_2 syst.: δ_A = 3.32 (2H, CH_2N), δ_B = 3.79 (2H, CH_2N), J_{AB} = 9.6 Hz; 4.23 (q, 1H, J = 6.9 Hz, C*H*–$C_{10}H_7$); 7.26–7.55 (m, 4H, $C_{10}H_7$); 7.68–7.91 (m, 2H, $C_{10}H_7$); 8.00–8.13 (m, 1H, $C_{10}H_7$).

^{13}C NMR ($CDCl_3$; δ, ppm): 20.13 (CH_3–CH); 39.46 (CH–$C_{10}H_7$); 40.66 (CH_2N); 50.24 (CH_2N); 50.61 (CH_2N); 52.43 (CH_2N); 123.42 (ar. CH); 125.22 (ar. CH); 125.81 (ar. CH); 126.48 (ar. CH); 126.73 (ar. CH); 127.39 (ar. CH); 128.69 (ar. CH); 132.17 (ar. C_{quat}); 132.33 (ar. C_{quat}); 133.66 (ar. C_{quat}); 169.14 (N–C═N).

IR (cm^{-1}): ν_{NH_2} = 3279, 3360. Mass spectrum: m/z = 266 $[M-1]^+$. Anal. Found: C, 76.44; H, 7.88; N, 15.81. Calc. for $C_{17}H_{21}N_3$: C, 76.37; H, 7.92; N, 15.72%.

*NEI–$CH_2CH_2NHCH_2CH_2SH$ (**14**)*

A solution of **13** (5.50 g, 20.60 mmol) in 60 ml of anhydrous toluene was mixed with a solution of ethylene sulfide (1.42 g, 23.70 mmol) in 20 ml of dry toluene (sealed tube, argon flushed). The mixture was then heated (110 °C in an oven) for 20 h. After cooling, 200 ml of diethyl ether was added and the mixture was cooled to −10 °C for 20 min. After filtration, the solvents were removed *in vacuo* to afford **14** (5.26 g, 78% yield).

^{1}H NMR ($CDCl_3$; δ, ppm): 1.24 (s, 2H, SH and NH); 1.61 (d, 3H, J = 6.8 Hz, C*H*$_3$CH); 2.35–2.75 (m, 4H, CH_2S and CH_2N); A_2B_2 syst.: δ_A = 2.64 (2H, CH_2N), δ_B = 2.97 (2H, CH_2N), J_{AB} = 5.8 Hz; A_2B_2 syst.: δ_A = 3.34 (2H, CH_2N), δ_B = 3.71 (2H, CH_2N), J_{AB} = 8.0 Hz; 4.26 (q, 1H, J = 6.8 Hz, C*H*–$C_{10}H_7$); 7.30–7.52 (m, 4H, $C_{10}H_7$); 7.64–7.87 (m, 2H, $C_{10}H_7$); 7.98–8.17 (m, 1H, $C_{10}H_7$).

^{13}C NMR ($CDCl_3$; δ, ppm): 20.06 (CH_3–CH); 25.03 (CH_2S); 38.11 (CH–$C_{10}H_7$); 41.10 (CH_2NH); 47.21 (CH_2NH); 50.33 (CH_2N); 50.49 (CH_2N); 52.54 (CH_2N); 123.48 (ar. CH); 125.17 (ar. CH); 125.67 (ar. CH); 126.27 (ar. CH); 126.35 (ar. CH); 127.61 (ar. CH); 128.74 (ar. CH); 131.93 (ar. C_{quat}); 132.26 (ar. C_{quat}); 133.89 (ar. C_{quat}); 169.28 (N–C═N).

IR (cm^{-1}): ν_{SH} = 2541, ν_{NH} = 3373. Mass spectrum: m/z = 327 $[M]^{+\bullet}$. Anal. Found: C, 69.59; H, 7.73; N, 12.80. Calc. for $C_{19}H_{25}N_3S$: C, 69.68; H, 7.69; N, 12.83%.

*NEI–$CH_2CH_2NHCH_2CH(CH_3)SH$ (**15**)*

A solution of **13** (6.00 g, 22.40 mmol) in 60 ml of anhydrous toluene was mixed with a solution of propylene sulfide (1.66 g, 22.40 mmol) in 20 ml of dry toluene (sealed tube, argon flushed). The mixture was then heated (110 °C in an oven) for 25 h. After cooling, the concentration under reduced pressure leads to a yellow–orange paste (86% yield) corresponding to **15** (95%) and **15′** (5%) (Scheme 4). Compound **15** was purified by precipitation of **15′** in a toluene–pentane (1/1) solvent mixture. The concentration *in vacuo* of the filtrate leads to **15** (5.66 g, 74% yield).

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

Compound	Yield (%)	Physical properties and elemental analyses
1	88	R = R′ = *i*-C_5H_{11}; R″ = H; M = Ge ^{1}H NMR ($CDCl_3$; δ, ppm): 0.83 (d, 12H, J = 5.5 Hz, $(CH_3)_2CH$); 0.94 (s, 2H, NH); 0.98–1.53 (m, 10H, CH_2CH_2CH); 1.67 (d, 6H, J = 7.0 Hz, CH_3–CH); 2.15–3.15 (m, 16H, CH_2S and CH_2N); 3.19–3.80 (m, 8H, CH_2N); 4.38 (q, 2H, J = 7.0 Hz, CH–$C_{10}H_7$); 7.23–7.48 (m, 8H, $C_{10}H_7$); 7.53–7.83 (m, 4H, $C_{10}H_7$); 7.90–8.17 (m, 2H, $C_{10}H_7$). ^{13}C NMR ($CDCl_3$; δ, ppm): 17.26 (CH_2S); 18.26 (CH_2Ge); 21.95 (CH_3CH); 22.82 ($(CH_3)_2CH$); 30.23 ($(CH_3)_2CH$); 32.86 (CH_2CH); 41.02 (CH–$C_{10}H_7$); 41.91 (CH_2NH); 46.89 (CH_2NH); 49.98 (CH_2N); 50.26 (CH_2N); 50.62 (CH_2N); 122.33 (ar. CH); 123.33 (ar. CH); 124.32 (ar. CH); 125.48 (ar. CH); 125.72 (ar. CH); 127.68 (ar. CH); 128.87 (ar. CH); 133.53 (ar. C_{quat}); 133.82 (ar. C_{quat}); 134.69 (ar. C_{quat}); 167.88 (N–C=N). IR (cm^{-1}): ν_{NH} = 3369. Mass spectrum: m/z = 541 $[M - 327]^+$. Anal. Found: C, 66.50; H, 8.23; N, 9.77. Calc. for $C_{48}H_{70}GeN_6S_2$: C, 66.43; H, 8.13; N, 9.68%.
2	90	R = R′ = *i*-C_5H_{11}; R″ = CH_3; M = Ge ^{1}H NMR ($CDCl_3$; δ, ppm): 0.81 (d, 12H, J = 5.4 Hz, $(CH_3)_2CH$); 0.91 (s, 2H, NH); 1.03–1.56 (m, 16H, CH_2CH_2CH and CH_3CHS); 1.60 (d, 6H, J = 7.2 Hz, CH_3–CH); 2.22–3.08 (m, 14H, CH_2N and CHS); 3.11–3.86 (m, 8H, CH_2N); 4.26 (q, 2H, J = 7.2 Hz, CH–CH_3); 7.17–7.46 (m, 8H, $C_{10}H_7$); 7.52–7.79 (m, 4H, $C_{10}H_7$); 7.84–8.13 (m, 2H, $C_{10}H_7$). ^{13}C NMR ($CDCl_3$; δ, ppm): 18.86 (CH_2Ge); 21.74 (CH_3CH); 22.02 (CH_3CHS); 23.00 ($(CH_3)_2CH$); 30.17 ($(CH_3)_2CH$); 32.68 (CH_2CH); 41.23 ($SCHCH_3$); 42.21 (CH–$C_{10}H_7$); 42.87 (CH_2NH); 46.79 (CH_2NH); 48.07 (CH_2N); 48.92 (CH_2N); 50.22 (CH_2N); 123.31 (ar. CH); 124.41 (ar. CH); 124.82 (ar. CH); 125.47 (ar. CH); 125.72 (ar. CH); 127.61 (ar. CH); 128.84 (ar. CH); 133.63 (ar. C_{quat}); 133.76 (ar. C_{quat}); 134.73 (ar. C_{quat}); 169.25 (N–C=N). IR (cm^{-1}): ν_{NH} = 3360. Mass spectrum: m/z = 555 $[M - 341]^+$. Anal. Found: C, 67.14; H, 8.31; N, 9.31. Calc. for $C_{50}H_{74}GeN_6S_2$: C, 67.03; H, 8.32; N, 9.38%.
3	87	R = R′ = *n*-C_6H_{13}; R″ = H; M = Ge ^{1}H NMR ($CDCl_3$; δ, ppm): 0.81 (t, 6H, J = 5.7 Hz, CH_3CH_2); 0.94–1.38 (m, 20H, $(CH_2)_5$); 1.50 (d, 6H, J = 6.7 Hz, CH_3–CH); 1.98 (s, 2H, NH); 2.20–3.10 (m, 16H, CH_2N and CH_2S); 3.16–3.80 (m, 8H, CH_2N); 4.42 (q, 2H, J = 6.7 Hz, CH–$C_{10}H_7$); 7.23–7.42 (m, 8H, $C_{10}H_7$); 7.48–7.84 (m, 4H, $C_{10}H_7$); 7.90–8.15 (m, 2H, $C_{10}H_7$). ^{13}C NMR ($CDCl_3$; δ, ppm): 14.06 (CH_3CH_2); 19.92 (CH_3–CH); 22.46 (CH_2S); 23.23 (CH_2Ge); 23.91 (CH_3CH_2); 24.52 ($CH_3CH_2CH_2$); 31.29 ($CH_3CH_2CH_2CH_2$); 31.43 (CH_2CH_2Ge); 38.28 (CH–$C_{10}H_7$); 42.18 (CH_2NH); 47.03 (CH_2NH); 49.28 (CH_2N); 50.23 (CH_2N); 50.71 (CH_2N); 122.31 (ar. CH); 123.35 (ar. CH); 124.51 (ar. CH); 125.43 (ar. CH); 125.95 (ar. CH); 127.73 (ar. CH); 129.06 (ar. CH); 133.67 (ar. C_{quat}); 133.94 (ar. C_{quat}); 134.80 (ar. C_{quat}); 171.12 (N–C=N). IR (cm^{-1}): ν_{NH} = 3370. Mass spectrum: m/z = 569 $[M - 327]^+$. Anal. Found: C, 66.97; H, 8.39; N, 9.44. Calc. for $C_{50}H_{74}GeN_6S_2$: C, 67.03; H, 8.32; N, 9.38%.
4	89	R = R′ = *n*-C_6H_{13}; R″ = CH_3; M = Ge ^{1}H NMR ($CDCl_3$; δ, ppm): 0.72 (t, 6H, J = 5.9 Hz, CH_3CH_2); 1.00–1.51 (m, 26H, $(CH_2)_5$ and CH_3–CHS); 1.61 (d, 6H, J = 6.9 Hz, CH_3–CH); 2.01 (s, 2H, NH); 2.21–3.09 (m, 14H, CHS and CH_2N); 3.14–3.61 (m, 8H, CH_2N); 4.39 (q, 2H, J = 6.9 Hz, CH–$C_{10}H_7$); 7.12–7.44 (m, 8H, $C_{10}H_7$); 7.50–7.65 (m, 4H, $C_{10}H_7$); 7.72–7.94 (m, 2H, $C_{10}H_7$). ^{13}C NMR ($CDCl_3$; δ, ppm): 14.89 (CH_3CH_2); 20.71 (CH_3–CH); 21.53 (CH_3CHS); 23.26 (CH_2Ge); 23.94 (CH_3CH_2); 24.74 ($CH_3CH_2CH_2$); 31.25 ($CH_3CH_2CH_2CH_2$); 32.05 (CH_2CH_2Ge); 41.16 (CH_3CHS); 41.97 (CH–$C_{10}H_7$); 42.68 (CH_2NH); 46.89 (CH_2NH); 48.08 (CH_2N); 49.94 (CH_2N); 50.69 (CH_2N); 123.26 (ar. CH); 124.10 (ar. CH); 124.84 (ar. CH); 125.45 (ar. CH); 126.89 (ar. CH); 127.57 (ar. CH); 128.99 (ar. CH); 132.30 (ar. C_{quat}); 133.70 (ar. C_{quat}); 134.49 (ar. C_{quat}); 169.40 (N–C=N). IR (cm^{-1}): ν_{NH} = 3365. Mass spectrum: m/z = 585 $[M - 341]^+$. Anal. Found: C, 67.64; H, 8.70; N, 9.04. Calc. for $C_{52}H_{78}GeN_6S_2$: C, 67.60; H, 8.51; N, 9.10%.

(*continued overleaf*)

Table 1. (*Continued*)

Compound	Yield (%)	Physical properties and elemental analyses
5	89	R = *p*-CH_3–C_6H_4; R′ = CH_3; R″ = H; M = Ge ^{1}H NMR ($CDCl_3$; δ, ppm): 0.99 (s, 2H, NH); 1.15 (s, 3H, CH_3Ge); 1.64 (d, 6H, J = 7.0 Hz, CH_3–CH); 2.33 (s, 3H, *p*-CH_3); 2.18–3.14 (m, 16H, CH_2N and CH_2S); 3.21–3.80 (m, 8H, CH_2N); 4.41 (q, 2H, J = 7.0 Hz, CH–$C_{10}H_7$); 7.12–8.14 (m, 18 H, C_6H_4 and $C_{10}H_7$). ^{13}C NMR ($CDCl_3$; δ, ppm): 8.93 (CH_3Ge); 17.36 (CH_2S); 21.64 (*p*-CH_3); 21.99 (CH_3–CH); 41.16 (CH–$C_{10}H_7$); 41.64 (CH_2NH); 45.64 (CH_2NH); 49.06 (CH_2N); 50.04 (CH_2N); 50.31 (CH_2N); 121.98 (ar. CH); 123.06 (ar. CH); 124.10 (ar. CH); 125.21 (ar. CH); 125.66 (ar. CH); 127.44 (ar. CH); 128.71 (ar. CH); 129.74 (ar. CH); 131.85 (ar. CH); 133.58 (ar. C_{quat}); 133.89 (ar. C_{quat}); 134.41 (ar. C_{quat}); 134.77 (ar. C_{quat}); 140.06 (ar. C_{quat}); 171.04 (N–*C*═N). IR (cm^{-1}): ν_{NH} = 3358. Mass spectrum: m/z = 505 $[M - 327]^+$. Anal. Found: C, 66.24; H, 7.11; N, 9.99. Calc. for $C_{46}H_{58}GeN_6S_2$: C, 66.43; H, 7.03; N, 10.10%.
6	86	R = *p*-CH_3–C_6H_4; R′ = CH_3; R″ = CH_3; M = Ge ^{1}H NMR ($CDCl_3$; δ, ppm): 0.97 (s, 2H, NH); 1.13 (s, 3H, CH_3Ge); 1.26 (d, 6H, J = 6.8 Hz, CH_3CHS); 1.65 (d, 6H, J = 7.1 Hz, CH_3–CH); 2.32 (s, 3H, *p*-CH_3); 2.09–3.07 (m, 14H, CH_2N and CHS); 3.12–3.83 (m, 8 H, CH_2N); 4.48 (q, 2H, J = 7.1 Hz, CH–$C_{10}H_7$); 7.09–8.15 (m, 18 H, C_6H_4 and $C_{10}H_7$). ^{13}C NMR ($CDCl_3$; δ, ppm): 8.88 (CH_3–Ge); 21.59 (*p*-CH_3); 21.87 (CH_3–CH); 22.12 (CH_3CHS); 41.12 (CH–CH_3); 41.21 (CH–$C_{10}H_7$); 41.56 (CH_2NH); 45.39 (CH_2NH); 49.00 (CH_2N); 49.89 (CH_2N); 50.24 (CH_2N); 122.06 (ar. CH); 122.94 (ar. CH); 124.03 (ar. CH); 125.11 (ar. CH); 125.56 (ar. CH); 127.09 (ar. CH); 128.81 (ar. CH); 129.68 (ar. CH); 131.74 (ar. CH); 133.64 (ar. C_{quat}); 133.97 (ar. C_{quat}); 134.32 (ar. C_{quat}); 134.83 (ar. C_{quat}); 139.88 (ar. C_{quat}); 169.96 (N–*C*═N). IR (cm^{-1}): ν_{NH} = 3363. Mass spectrum: m/z = 519 $[M - 341]^+$. Anal. Found: C, 66.91; H, 7.35; N, 9.89. Calc. for $C_{48}H_{62}GeN_6S_2$: C, 67.05; H, 7.27; N, 9.77%.
7	87	R = R′ = *i*-C_5H_{11}; R″ = H; M = Si ^{1}H NMR ($CDCl_3$; δ, ppm): 1.01 (d, 12H, J = 5.5 Hz, (CH_3)$_2$CH); 1.14 (s, 2H, NH); 1.25–1.60 (m, 10H, CH_2CH_2CH); 1.68 (d, 6H, J = 7.0 Hz, CH_3–CH); 2.19–3.18 (m, 16H, CH_2S and CH_2N); 3.14–3.77 (m, 8H, CH_2N); 4.41 (q, 2H, J = 7.0 Hz, CH–$C_{10}H_7$); 7.17–7.44 (m, 8H, $C_{10}H_7$); 7.49–7.81 (m, 4H, $C_{10}H_7$); 7.86–8.13 (m, 2H, $C_{10}H_7$). ^{13}C NMR ($CDCl_3$; δ, ppm): 7.81 (CH_2Si); 17.24 (CH_2S); 21.89 (CH_3CH); 22.06 ((CH_3)$_2$CH); 31.73 ((CH_3)$_2$CH); 32.09 (CH_2CH); 40.21 (CH–$C_{10}H_7$); 41.71 (CH_2NH); 46.64 (CH_2NH); 49.46 (CH_2N); 50.32 (CH_2N); 50.75 (CH_2N); 122.74 (ar. CH); 123.49 (ar. CH); 124.45 (ar. CH); 125.36 (ar. CH); 125.87 (ar. CH); 127.38 (ar. CH); 128.71 (ar. CH); 133.34 (ar. C_{quat}); 133.69 (ar. C_{quat}); 134.57 (ar. C_{quat}); 166.77 (N–*C*═N). IR (cm^{-1}): ν_{NH} = 3366. Mass spectrum: m/z = 495 $[M - 327]^+$. Anal. Found: C, 69.97; H, 8.49; N, 10.16. Calc. for $C_{48}H_{70}N_6S_2Si$: C, 70.02; H, 8.57; N, 10.21%.
8	87	R = R′ = *i*-C_5H_{11}; R″ = CH_3; M = Si ^{1}H NMR ($CDCl_3$; δ, ppm): 1.02 (d, 12H, J = 5.4 Hz, (CH_3)$_2$CH); 1.11 (s, 2H, NH); 1.15–1.59 (m, 16H, CH_2CH_2CH and CH_3CHS); 1.66 (d, 6H, J = 7.1 Hz, CH_3–CH); 2.15–3.16 (m, 14H, CH_2N and CHS); 3.11–3.80 (m, 8H, CH_2N); 4.44 (q, 2H, J = 7.1 Hz, CH–$C_{10}H_7$); 7.18–7.49 (m, 8H, $C_{10}H_7$); 7.53–7.81 (m, 4H, $C_{10}H_7$); 7.85–8.12 (m, 2H, $C_{10}H_7$). ^{13}C NMR ($CDCl_3$; δ, ppm): 7.69 (CH_2Si); 21.79 (CH_3CH); 22.11 (CH_3CHS); 22.19 ((CH_3)$_2$CH); 31.66 ((CH_3)$_2$CH); 32.20 (CH_2CH); 40.03 (SCHCH_3); 40.31 (CH–$C_{10}H_7$); 41.64 (CH_2NH); 46.59 (CH_2NH); 48.89 (CH_2N); 50.40 (CH_2N); 50.85 (CH_2N); 122.61 (ar. CH); 123.21 (ar. CH); 124.63 (ar. CH); 125.42 (ar. CH); 125.81 (ar. CH); 127.51 (ar. CH); 128.57 (ar. CH); 133.46 (ar. C_{quat}); 133.78 (ar. C_{quat}); 134.33 (ar. C_{quat}); 167.08 (N–*C*═N). IR (cm^{-1}): ν_{NH} = 3369. Mass spectrum: m/z = 509 $[M - 341]^+$. Anal. Found: C, 70.39; H, 8.75; N, 9.84. Calc. for $C_{50}H_{74}N_6S_2Si$: C, 70.54; H, 8.76; N, 9.87%.
9	84	R = R″ = *n*-C_6H_{13}; R″ = H; M = Si ^{1}H NMR ($CDCl_3$; δ, ppm): 0.95 (t, 6H, J = 5.9 Hz, C$H_3$$CH_2$); 1.10–1.36 (m, 20H, ($CH_2$)$_5$); 1.50 (d, 6H, J = 6.9 Hz, CH_3–CH); 1.74 (s, 2H, NH); 2.14–3.09 (m, 16H, CH_2N and CH_2S); 3.13–3.78 (m, 8H, CH_2N); 4.48 (q, 2H, J = 6.9 Hz, CH–$C_{10}H_7$); 7.17–7.40 (m, 8H, $C_{10}H_7$); 7.44–7.81 (m, 4H, $C_{10}H_7$); 7.86–8.12 (m, 2H, $C_{10}H_7$).

Table 1. (*Continued*)

Compound	Yield (%)	Physical properties and elemental analyses
		^{13}C NMR ($CDCl_3$; δ, ppm): 7.86 (CH_2Si); 14.09 (CH_3CH_2); 20.02 (CH_3–CH); 22.51 (CH_2S); 23.24 (CH_3CH_2); 23.43 (CH_2CH_2Si); 31.80 ($CH_3CH_2CH_2$); 32.22 ($CH_3CH_2CH_2CH_2$); 39.00 (CH–$C_{10}H_7$); 42.36 (CH_2NH); 47.23 (CH_2NH); 49.34 (CH_2N); 50.12 (CH_2N); 50.67 (CH_2N); 122.48 (ar. CH); 123.24 (ar. CH); 124.31 (ar. CH); 125.65 (ar. CH); 125.99 (ar. CH); 127.58 (ar. CH); 128.87 (ar. CH); 133.53 (ar. C_{quat}); 133.87 (ar. C_{quat}); 134.64 (ar. C_{quat}); 169.52 (N–*C*=N). IR (cm^{-1}): $\nu_{NH} = 3361$. Mass spectrum: $m/z = 523$ $[M - 327]^+$. Anal. Found: C, 70.65; H, 8.81; N, 9.90. Calc. for $C_{50}H_{74}N_6S_2Si$: C, 70.54; H, 8.76; N, 9.87%.
10	82	R = R′ = *n*-C_6H_{13}; R″ = CH_3; M = Si ^{1}H NMR ($CDCl_3$; δ, ppm): 0.91 (t, 6H, $J = 5.7$ Hz, CH_3CH_2); 1.10–1.48 (m, 26H, $(CH_2)_5$ and CH_3–CHS); 1.62 (d, 6H, $J = 7.2$ Hz, CH_3–CH); 1.89 (s, 2H, NH); 2.17–3.11 (m, 14H, CHS and CH_2N); 3.16–3.66 (m, 8H, CH_2N); 4.43 (q, 2H, $J = 6.9$ Hz, CH–$C_{10}H_7$); 7.15–7.47 (m, 8H, $C_{10}H_7$); 7.53–7.69 (m, 4H, $C_{10}H_7$); 7.73–7.99 (m, 2H, $C_{10}H_7$). ^{13}C NMR ($CDCl_3$; δ, ppm): 7.86 (CH_2Si); 14.11 (CH_3CH_2); 20.65 (CH_3–CH); 21.74 (CH_3CHS); 23.38 (CH_3CH_2); 23.49 (CH_2CH_2Si); 31.74 ($CH_3CH_2CH_2$); 32.28 ($CH_3CH_2CH_2CH_2$); 39.12 (CH–$C_{10}H_7$); 40.26 (CH_3CHS); 42.51 (CH_2NH); 46.65 (CH_2NH); 48.39 (CH_2N); 49.29 (CH_2N); 50.56 (CH_2N); 123.34 (ar. CH); 124.21 (ar. CH); 124.96 (ar. CH); 125.38 (ar. CH); 126.75 (ar. CH); 127.64 (ar. CH); 129.13 (ar. CH); 132.03 (ar. C_{quat}); 133.58 (ar. C_{quat}); 134.34 (ar. C_{quat}); 168.99 (N–*C*=N). IR (cm^{-1}): $\nu_{NH} = 3363$. Mass spectrum: $m/z = 537$ $[M - 341]^+$. Anal. Found: C, 71.14; H, 8.89; N, 9.61. Calc. for $C_{52}H_{78}N_6S_2Si$: C, 71.02; H, 8.94; N, 9.56%.
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); 1.01 (s, 2H, NH); 1.60 (d, 6H, $J = 7.2$ Hz, CH_3–CH); 2.31 (s, 3H, *p*-CH_3); 2.09–3.17 (m, 16H, CH_2N and CH_2S); 3.22–3.81 (m, 8H, CH_2N); 4.46 (q, 2H, $J = 7.2$ Hz, CH–$C_{10}H_7$); 7.09–8.14 (m, 18 H, C_6H_4 and $C_{10}H_7$). ^{13}C NMR ($CDCl_3$; δ, ppm): 1.79 (CH_3Si); 17.24 (CH_2S); 21.31 (*p*-CH_3); 22.14 (CH_3–CH); 40.61 (CH–$C_{10}H_7$); 41.26 (CH_2NH); 45.09 (CH_2NH); 48.42 (CH_2N); 49.52 (CH_2N); 50.45 (CH_2N); 122.24 (ar. CH); 123.24 (ar. CH); 124.14 (ar. CH); 125.25 (ar. CH); 125.65 (ar. CH); 127.26 (ar. CH); 128.35 (ar. CH); 129.65 (ar. CH); 131.56 (ar. CH); 133.25 (ar. C_{quat}); 133.65 (ar. C_{quat}); 134.36 (ar. C_{quat}); 134.62 (ar. C_{quat}); 140.32 (ar. C_{quat}); 169.87 (N–*C*=N). IR (cm^{-1}): $\nu_{NH} = 3363$. Mass spectrum: $m/z = 459$ $[M - 327]^+$. Anal. Found: C, 70.24; H, 7.39; N, 10.74. Calc. for $C_{46}H_{58}N_6S_2Si$: C, 70.18; H, 7.43; N, 10.68%.
12	83	R = *p*-CH_3–C_6H_4; R′ = CH_3; R″ = CH_3; M = Si ^{1}H NMR ($CDCl_3$; δ, ppm): 0.70 (s, 3H, CH_3Si); 1.03 (s, 2H, NH); 1.24 (d, 6H, $J = 6.6$ Hz, CH_3CHS); 1.61 (d, 6H, $J = 7.2$ Hz, CH_3–CH); 2.31 (s, 3H, *p*-CH_3); 2.13–3.22 (m, 14H, CH_2N and CHS); 3.20–3.83 (m, 8 H, CH_2N); 4.48 (q, 2H, $J = 7.2$ Hz, CH–$C_{10}H_7$); 7.09–8.15 (m, 18 H, C_6H_4 and $C_{10}H_7$). ^{13}C NMR ($CDCl_3$; δ, ppm): 1.86 (CH_3Si); 21.33 (*p*-CH_3); 21.71 (CH_3–CH); 22.23 (CH_3CHS); 40.14 (CH–CH_3); 40.80 (CH–$C_{10}H_7$); 41.23 (CH_2NH); 44.75 (CH_2NH); 48.52 (CH_2N); 49.35 (CH_2N); 50.02 (CH_2N); 122.33 (ar. CH); 122.65 (ar. CH); 123.25 (ar. CH); 124.45 (ar. CH); 125.52 (ar. CH); 127.23 (ar. CH); 128.25 (ar. CH); 129.32 (ar. CH); 131.36 (ar. CH); 133.52 (ar. C_{quat}); 133.95 (ar. C_{quat}); 134.25 (ar. C_{quat}); 134.63 (ar. C_{quat}); 139.63 (ar. C_{quat}); 169.66 (N–*C*=N). IR (cm^{-1}): $\nu_{NH} = 3366$. Mass spectrum: $m/z = 473$ $[M - 341]^+$. Anal. Found: C, 70.91; H, 7.65; N, 10.26. Calc. for $C_{48}H_{62}N_6S_2Si$: C, 70.71; H, 7.66; N, 10.31%.

15. ^{1}H NMR ($CDCl_3$; δ, ppm): 1.19 (s, 2H, SH and NH); 1.21 (d, 3H, $J = 6.6$ Hz, CH_3CHS); 1.60 (m, 3H, CH_3CH); 2.29–3.50 (m, 9H, CHS and CH_2N); 3.54–3.97 (m, 2H, CH_2N); 4.36 (m, 1H, CH–$C_{10}H_7$); 7.23–7.51 (m, 4H, $C_{10}H_7$); 7.64–7.87 (m, 2H, $C_{10}H_7$); 7.93–8.14 (m, 1H, $C_{10}H_7$).

^{13}C NMR ($CDCl_3$; δ, ppm): 20.11 (CH_3–CH); 20.81 (CH_3–CHS); 35.84 (CHS); 38.24 (CH–$C_{10}H_7$); 40.66 (CH_2N); 47.11 (CH_2N); 50.56 (CH_2N); 50.81 (CH_2N); 52.39 (CH_2N); 123.39 (ar. CH); 124.88 (ar. CH); 125.61 (ar. CH); 126.20 (ar. CH); 126.51 (ar. CH); 127.39 (ar. CH); 128.63 (ar. CH); 132.23 (ar. C_{quat}); 132.31 (ar. C_{quat}); 133.94 (ar. C_{quat}); 170.11 (N–*C*=N).

IR (cm^{-1}): $\nu_{SH} = 2536$, $\nu_{NH} = 3371$. Mass spectrum: $m/z = 341$ $[M]^{+\bullet}$, $m/z = 280$ $[M - 61]^+$. Anal. Found: C, 70.29; H, 8.03; N, 12.26. Calc. for $C_{20}H_{27}N_3S$: C, 70.34; H, 7.97; N, 12.30%.

15′. ^{1}H NMR ($CDCl_3$; δ, ppm): 1.19 (s, 2H, SH and NH); 1.43 (d, 3H, $J = 6.5$ Hz, CH_3CHN); 1.60 (m, 3H, CH_3CH); 2.35–3.56 (m, 9H, CH_2S, CH_2N and CHN); 3.58–4.03 (m, 2H, CH_2N); 4.36 (m, 1H, CH–$C_{10}H_7$); 7.23–7.51 (m, 4H, $C_{10}H_7$); 7.64–7.87 (m, 2H, $C_{10}H_7$); 7.93–8.14 (m, 1H, $C_{10}H_7$).

^{13}C NMR ($CDCl_3$; δ, ppm): 20.12 (CH_3–CH); 22.51 (CH_2S); 23.08 (CH_3–CHN); 38.26 (CH–$C_{10}H_7$); 41.69 (CHN); 47.13 (CH_2N); 50.61 (CH_2N); 50.82 (CH_2N); 52.43 (CH_2N); 123.41 (ar. CH); 124.87 (ar. CH); 125.58 (ar. CH); 126.16 (ar. CH); 126.51 (ar. CH); 127.40 (ar. CH); 128.64 (ar. CH); 132.25 (ar. C_{quat}); 132.33 (ar. C_{quat}); 133.93 (ar. C_{quat}); 170.09 (N–C═N).

IR (cm^{-1}): $\nu_{SH} = 2541$, $\nu_{NH} = 3369$. Mass spectrum: $m/z =$ 341 $[M]^{+\bullet}$, $m/z = 294$ $[M - 47]^+$. Anal. Found: C, 70.38; H, 8.00; N, 12.21. Calc. for $C_{20}H_{27}N_3S$: C, 70.34; H, 7.97; N, 12.30%.

PHARMACOLOGY

Evaluation of the radioprotection

Three-month-old male Swiss mice (Janvier, France), 25 g body weight, were used. Initially, the survival rate was determined 30 days after irradiation in different groups of ten mice receiving an intraperitoneal (i.p.) injection of the test compound with a dose equal to one-half of its LD_{50} toxicity 15 min before whole-body irradiation delivered with a dose

Table 2. Toxicity and radioprotective activity of compounds **1**–**15**

Compound	LD_{50} (mg kg^{-1}) [mmol kg^{-1}]	Injected dose (mg kg^{-1})	Irradiation (Gy) [t (min)][a]	MST 30 (days)[b]	ST_{50} (days)[c]	Survival rate (%)
1	280	140	8.1 [15]	16.4	14	20
	[0.323]		10.1 [15]	8.9	10	0
2	>300	150	8.1 [15]	19	14	30
	[0.335]		10.1 [15]	10.4	10	0
3	510	255	8.1 [15]	4.7	1	0
	[0.569]		10.1 [15]	3.5	1	0
4	>300	150	8.1 [15]	19.7	13	40
	[>0.325]		10.1 [15]	9	9	0
5	184	92	8.1 [15]	18.3	13	50
	[0.221]		10.1 [15]	7.7	1	0
6	200	100	8.1 [15]	16.2	11	40
	[0.233]		10.1 [15]	17.1	12	40
7	225	112.5	8.1 [15]	3.9	1	0
	[0.273]		10.1 [15]	4.4	1	0
8	210	105	8.1 [15]	18	10	40
	[0.247]		10.1 [15]	10	10	0
9	90	45	8.1 [15]	17.2	13	20
	[0.106]		10.1 [15]	10.3	10	0
10	130	65	8.1 [15]	14.6	12	10
	[0.148]		10.1 [15]	10.7	11	0
11	80	40	8.1 [15]	16.2	13	10
	[0.102]		10.1 [15]	11	11	0
12	212	106	8.1 [15]	7.8	4	0
	[0.260]		10.1 [15]	6.9	7	0
13	160	80	8.1 [15]	18.8	16	40
	[0.598]		10.1 [15]	5.4	8	0
14	>300	150	8.1 [15]	6.2	3	0
	[>0.916]		10.1 [15]	6.8	5	0
15	212	106	8.1 [15]	2.5	1	0
	[0.621]		10.1 [15]	3.6	1	0

[a] t is the time between administration of the compound and irradiation.
[b] MST is the mean survival time of the animals during the 30 days following the irradiation.
[c] ST_{50}, the median survival time, is the time spent between the start of the experiment and the death of 50% + 1 animals of the lot.

equal to the LD_{100}/30 days of control mice (8.1 Gy according to the irradiation date), or with a 2 Gy greater dose.

The toxicity was evaluated by a probit analysis of the LD_{50},[36,37] the dose range being determined in a preliminary study. Four groups of ten mice were then injected with different doses within this range.

Whole-body irradiations were performed with a ^{60}Co γ-ray source. The dose rate was equal to 0.58 Gy min^{-1} (according to the irradiation date). For the exposure, mice were positioned inside a Plexiglas box divided into 30 cells in a homogeneous 28.5 cm × 28.5 cm field. The dosimetry was carried out by means of ionization chamber dosimeters.

Each irradiation session included three groups of five mice irradiated with an 8.1 Gy dose (according to the date) after an i.p. injection of the solvent alone. A 100% lethality at this dose was observed for these lots, with a mean survival time equal to 13 days. Furthermore, a group of five unirradiated mice received a test compound with a dose equal to one-half of its LD_{50} toxicity in order to check for toxic lethality among the injected and irradiated mice. For all the compounds, these animals were alive 30 days after injection.

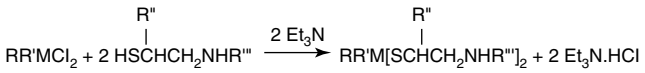
RESULTS AND DISCUSSION

Synthesis of metalladithioacetals

Metalladithioacetals of *N*-substituted cysteamine and methylcysteamine were prepared according to the two methods A and B already described in the literature.[23,38]

Method A

The action of the dichlorodiorganometallanes on 2 mol of *N*-substituted cysteamine or methylcysteamine in refluxing anhydrous THF in the presence of triethylamine gave the acyclic derivatives (Scheme 1) in yields of 75–90%.



Scheme 1.

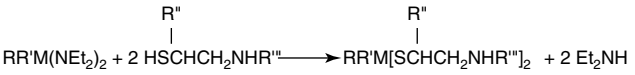
Method B

The reaction of 2 mol of *N*-substituted cysteamine or methylcysteamine with the bis(diethylamino)diorganometallanes in refluxing anhydrous THF, a cleavage reaction of M–N (M = Si, Ge) bonds by the SH groups,[23,38–40] gave the corresponding metallated derivatives (Scheme 2) in yields of 80–95%.

Synthesis of ligands

*Synthesis of **13***

This compound was prepared according to the method already described in the literature.[33] The condensation between the carboxylic acid and the diethylenetriamine in xylene leads to the imidazoline derivative **13** (Scheme 3) in yield of 60%.



Scheme 2. M = Ge (**1**–**6**), Si (**7**–**12**): R = R′ = *i*-C_5H_{11}, R″ = H (**1**, **7**); R = R′ = *i*-C_5H_{11}, R″ = CH_3 (**2**, **8**); R = R′ = *n*-C_6H_{13}, R″ = H (**3**, **9**); R = R′ = *n*-C_6H_{13}, R″ = CH_3 (**4**, **10**); R = *p*-CH_3–C_6H_4, R′ = CH_3, R″ = H (**5**, **11**); R = *p*-CH_3–C_6H_4, R′ = CH_3, R″ = CH_3 (**6**, **12**).

*Synthesis of **14** and **15***

These compounds have been prepared by reaction of the appropriate amine with ethylene or propylene sulfide, in toluene, by cleavage of the C–S bond by NH_2 groups[41] (Scheme 4). Yields lie between 65 and 80%.

CONCLUSIONS

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

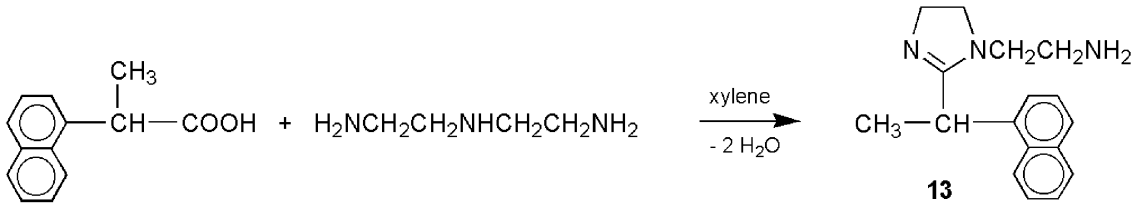
For example, with compounds **2**, **4**, **6** and **8**, a good survival rate has been observed, 30%, 40%, 40% and 40% respectively, for an 8.1 Gy irradiation, but only compound **6** offers protection for a 10.1 Gy irradiation (40%). This is in contrast to compound **15**, which provided no protection, even at 8.1 Gy. This means that the organometallic ligands provide a high contribution to the radioprotection.

Six derivatives (compounds **2**, **4**, **5**, **6**, **8** and **13**) offer good protection at 8.1 Gy (survival rate >30%), but only one (compound **6**) provides good protection at 10.1 Gy. Four derivatives provided weak protection (survival rate <20%), namely compounds **1**, **9**, **10** and **11**. Compounds **3**, **7**, **12**, **14** and **15** gave no radioprotective activity.

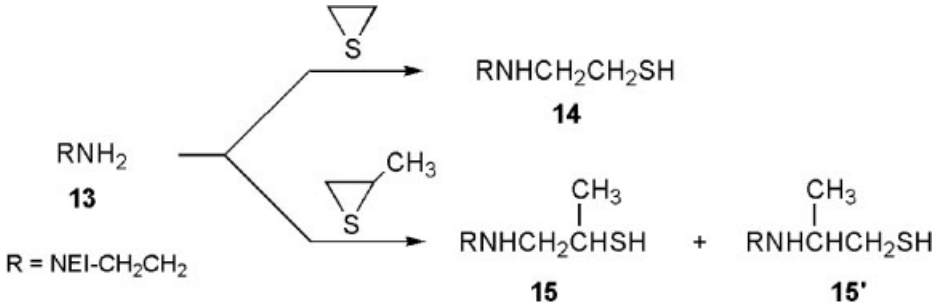
Even if organosilylated and organogermylated derivatives show approximately the same toxicity, the germanium-containing molecules described in this paper seem to present a higher radioprotective activity than their silicon-containing homologues.

In short, the radioprotective activity of metalladithioacetals derived from *N*-substituted cysteamine and methylcysteamine can be increased, compared with unsubstituted organic derivatives. This is achieved by the presence of organometallic groups, which 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



Scheme 3.



Scheme 4.

field, in agreement with previous work,[22–35] and the interesting biological activity of organogermanium and organosilicon compounds.[42–53] We also observed that organometallated groups decrease the toxicity of the basic organic molecules to which they are attached.

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