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Synthesis and Application of New Organometallic Compounds of Silicon and Germanium in Chemical Radioprotection

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Several organosilicon and organogermanium compounds possessing radioprotective activity have been synthesized. In this paper, we describe the preparation and study of the pharmacological properties of new organometallic compounds such as metallathiazolidines and metalladithioacetals derived from 1-[*N*-(2-mercaptoethyl)-2-aminoethyl]-2-(1-naphthylmethyl)-2-imidazoline and 1-[*N*-(2-mercaptopropyl)-2-aminoethyl]-2-(1-naphthylmethyl)-2-imidazoline. We have noted a decrease in the toxicity and a rather important increase in the radioprotective activity of these new organometallic derivatives in comparison with the starting organic compounds.

Keywords: organosilicon; organogermanium; metallathiazolidines; metalladithioacetals; toxicity; radioprotective activity; naphthylmethylimidazoline

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INTRODUCTION

The radioprotective activity of organosilicon and organogermanium compounds is now well known and many reports in the literature have been published on the subject.[1–11] This report concerns the synthesis and evaluation in chemical radioprotection of new organosilylated and organogermylated structures, which have been prepared by the condensation of bis(diethylamino)dialkylmetallanes with derivatives **18** or **19**. In this work, we present the study of the toxicity and radioprotective activity of metallathiazolidines and metalladithioacetals (Scheme 1).

EXPERIMENTAL

General methods

All manipulations were carried out under dry nitrogen. Solvents were freshly distilled from sodium/benzophenone before use. IR spectra were recorded on a Perkin-Elmer 1600 FT-IR spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker AC 80 (80.13 MHz) and ^{13}C NMR spectra were recorded on a Bruker AC 200 (50.32 MHz) spectrometer; the multiplicity of the ^{13}C NMR signals was determined by the APT technique and quoted (−) for CH_3 and CH, (+) for CH_2 and (C_{quat}) for quaternary carbon atoms. Mass spectra under electron impact (EI) conditions at 70 and 30 eV were recorded on a Hewlett-Packard 5989A

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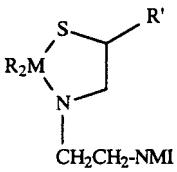
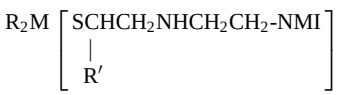
Metallathiazolidines

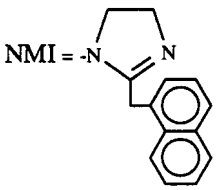


	M = Si		M = Ge	
	R′ = H	R′ = CH_3	R′ = H	R′ = CH_3
R = i – C_5H_{11}	**1**	**2**	**5**	**6**
R = n – C_6H_{13}	**3**	**4**	**7**	**8**

Metalladithioacetals

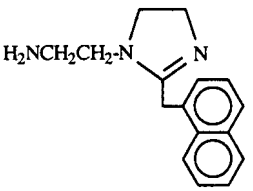


	M = Si		M = Ge	
	R′ = H	R′ = CH_3	R′ = H	R′ = CH_3
R = i – C_5H_{11}	**9**	**10**	**13**	**14**
R = n – C_6H_{13}	**11**	**12**	**15**	**16**



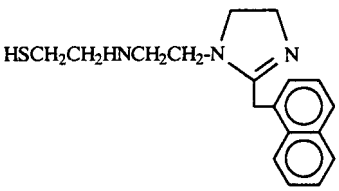
Organic Compounds

1-Aminoethyl-2-(1-naphthylmethyl)-2-imidazoline



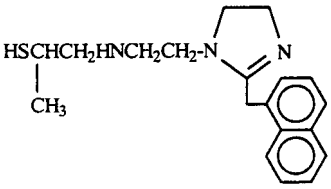
17

1-[*N*-(2-mercaptoethyl)-2-aminoethyl]-2-(1-naphthylmethyl)-2-imidazoline

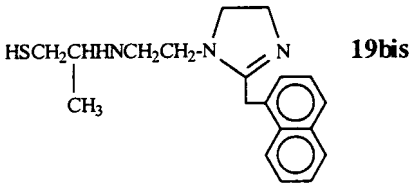


18

1-[*N*-(2-mercaptopropyl)-2-aminoethyl]-2-(1-naphthylmethyl)-2-imidazoline



19



19bis

Scheme 1 The compounds concerned in this study.

spectrometer. Elemental analyses (C, H, N) were performed at the Laboratoire de Microanalyse de l'Ecole Nationale Supérieure de Chimie de Toulouse.

Synthesis of metallathiazolidines 1–8

All these compounds were prepared by a method already described.[1,12–15]

Silathiazolidine 1

Bis(diethylamino)diisoamylsilane (3.04 g, 9.67 mmol) was added dropwise with a syringe to a stirred solution of 1-[*N*-(2-mercaptoethyl)-2-aminoethyl] - 2 - (1 - naphthylmethyl) - 2 -imidazoline **18** (3.03 g, 9.67 mmol) in 70 ml of dry toluene. The reaction mixture was refluxed under nitrogen for 3 h. The volatile material was removed *in vacuo* to afford a brown–orange pasty product corresponding to silathiazolidine **1** (4.10 g, 88%).

Compounds **2**–**8** were prepared similarly from the appropriate bis(diethylamino)dialkylmetallanes and 1-[*N*-(2-mercaptoethyl)-2-aminoethyl]-2-(1-naphthylmethyl)-2-imidazoline or 1-[*N*-(2-mercaptopropyl)-2-aminoethyl]-2-(1-naphthylmethyl)-2-imidazoline.

Metalladithioacetals 9–16

All these compounds were prepared by method already described.[2,13]

Siladithioacetal 9

Bis(diethylamino)diisoamylsilane (1.98 g, 6.29 mmol) was added dropwise with stirring to a solution of 1-[*N*-(2-mercaptoethyl)-2-aminoethyl]-2-(1-naphthylmethyl)-2-imidazoline **18** (3.94 g, 12.57 mmol) in 70 ml of dry toluene. After refluxing for 5 h, the resulting mixture was cooled to room temperature and the volatiles were removed under vaccum to afford **9** (orange pasty product; 4.29 g, 86%).

Compounds **10**–**16** were prepared similarly from the appropriate bis(diethylamino)dialkylmetallane and 1-[*N*-(2-mercaptoethyl)-2-aminoethyl]-2-(1-naphthylmethyl)-2-imidazoline or 1-[*N*-(2-mercaptopropyl)-2-aminoethyl]-2-(1-naphthylmethyl)-2-imidazoline.

1-Aminoethyl-2-(1-naphthylmethyl)-2-imidazoline 17

In a flask adapted to a Dean–Stark apparatus diethylenetriamine (28.99 g, 280.97 mmol) was added to a solution of 1-naphthylacetic acid (52.32 g, 280.97 mmol) in 600 ml of xylene. The mixture was refluxed until all the water formed was removed (about 15 h). The cooled mixture was allowed to decant and the upper phase was concentrated under vaccum leading to a brown–orange paste which was stirred overnight in 700 ml of diethyl ether. The upper orange phase was concentrated and distilled under reduced pressure to obtain 32.30 g (45%) of an orange oily product corresponding to **17**.

1-[*N*-(2-Mercaptoethyl)-2-aminoethyl]-2-(1-naphthylmethyl)-2-imidazoline 18

A solution of 1-aminoethyl-2-(1-naphthylmethyl)-2-imidazoline **17** (5.55 g, 21.91 mmol) in 60 ml of dry toluene was mixed with a solution of ethylene sulphide (1.51 g, 25.19 mmol) in 20 ml of dry toluene (sealed tube, argon-flushed). The reaction mixture was then heated (110 °C oven) for 15 h. After cooling, 40 ml of cold diethyl ether was added with stirring, and filtered to remove a small amount of polyethylene sulphide. The solvent was removed under reduced pressure to give a brown pasty product **18** (5.70 g, 83%).

1-[*N*-(2-Mercaptopropyl)-2-aminoethyl]-2-(1-naphthylmethyl)-2-imidazoline 19

A solution of 1-aminoethyl-2-(1-naphthylmethyl)-2-imidazoline **17** (11.51 g, 45.43 mmol) in 100 ml of dry toluene was mixed with propylene sulphide (3.37 g, 45.43 mmol) (sealed tube, argon-flushed). The reaction mixture was then heated (110 °C oven) for 15 h. Concentration under vaccum gave 14.58 g (98%) of a brown–orange pasty product corresponding to **19** (90%) and **19bis** (10%). Compound **19** was purified by precipitation of **19bis** in toluene/pentane (1:1).

Physicochemical data of all the derivatives **1**–**19** are reported in Table 1.

Table 1 Physicochemical data and analyses of derivatives 1–19

Compound	Yield(%)	Physical properties and elemental analyses
1	88	^{1}H NMR ($CDCl_3$; δ, ppm): 0.28–0.62 (m, 4H); 0.80 (d, 12H, J = 5.5 Hz); 0.93–1.37 (m, 6H); 2.44–2.81 (m, 6H); 2.92–3.09 (m, 2H); 3.21–3.44 (m, 2H); 3.66–3.76 (m, 2H); 4.03 (s, 2H); 7.28–7.51 (m, 4H); 7.63–7.84 (m, 2H); 7.94–8.15 (m, 1H). ^{13}C NMR ($CDCl_3$; δ, ppm): 14.30 (+); 22.24 (−); 29.62 (+); 30.66 (−); 32.32 (+); 32.52 (+); 38.85 (+); 46.55 (+); 51.14 (+); 51.26 (+); 52.27 (+); 123.56 (−); 125.50 (−); 125.83 (−); 126.22 (−); 126.39 (−); 127.70 (−); 128.84 (−); 132.05 (C_{quat}); 132.14 (C_{quat}) 133.85 (C_{quat}); 165.86 (C_{quat}). Mass spectrum: m/z = 481 $[M]^{+\cdot}$.
2	84	^{1}H NMR ($CDCl_3$; δ, ppm): 0.33–0.65 (m, 4H); 0.81 (d, 12H, J = 5.5 Hz); 0.87 (d, 3H, J = 5 Hz); 0.94–1.37 (m, 10H); 2.23–3.11 (m, 7H); 3.19–3.46 (m, 2H); 3.67–3.78 (m, 2H); 4.05 (s, 2H); 7.30–7.53 (m, 4H); 7.61–7.91 (m, 2H); 7.95–8.18 (m, 1H). ^{13}C NMR ($CDCl_3$; δ, ppm): 14.18 (+); 21.59 (−); 22.21 (−); 30.79 (−); 32.22 (+); 32.52 (+); 38.86 (+); 41.29 (−); 46.70 (+); 51.08 (+); 51.30 (+); 52.66 (+); 123.48 (−); 125.49 (−); 125.76 (−); 126.23 (−); 126.38 (−); 127.68 (−); 128.83 (−); 132.11 (C_{quat}) 132.21 (C_{quat}); 133.85 (C_{quat}) 165.86 (C_{quat}) Mass spectrum: m/z = 495 $[M]^{+\cdot}$.
3	98	^{1}H NMR ($CDCl_3$; δ, ppm): 0.33–0.59 (m, 4H); 0.86 (t, 6H, J = 5.7 Hz); 1.01–1.21 (m, 16H); 2.46–3.03 (m, 8H); 3.22–3.46 (m, 2H); 3.67–3.77 (m, 2H); 4.04 (s, 2H); 7.29–7.50 (m, 4H); 7.64–7.82 (m, 2H); 7.95–8.17 (m, 1H). ^{13}C NMR ($CDCl_3$; δ, ppm): 14.23 (−); 16.85 (+); 22.67 (+); 23.49 (+); 23.63 (+); 31.61 (+); 32.89 (+); 33.38 (+); 39.65 (+); 47.58 (+); 51.12 (+); 51.31 (+); 52.67 (+); 123.56 (−); 125.50 (−); 125.76 (−); 126.23 (−); 126.38 (−); 127.90 (−); 128.84 (−); 132.04 (C_{quat}); 132.12 (C_{quat}); 133.85 (C_{quat}) 165.90 (C_{quat}) Mass spectrum: m/z = 509 $[M]^{+\cdot}$.
4	98	^{1}H NMR ($CDCl_3$; δ, ppm): 0.31–0.57 (m, 4H); 0.84 (t, 6H, J = 6 Hz); 0.95 (d, 3H, J = 6.6 Hz); 1.21 (m, 16H); 2.21–3.04 (m, 7H); 3.19–3.42 (m, 2H); 3.65–3.75 (m, 2H); 4.02 (s, 2H); 7.31–7.50 (m, 4H); 7.64–7.85 (m, 2H); 7.93–8.16 (m, 1H). ^{13}C NMR ($CDCl_3$; δ, ppm): 14.16 (−); 15.65 (−); 22.60 (+); 23.18 (+); 23.42 (+); 31.54 (+); 37.17 (+); 32.80 (+); 39.79 (+); 41.16 (−); 47.38 (+); 50.97 (+); 51.17 (+); 52.54 (+); 123.41 (−); 125.38 (−); 125.63 (−); 126.12 (−); 126.29 (−); 127.56 (−); 128.71 (−); 132.03 (C_{quat}); 132.15 (C_{quat}); 133.77 (C_{quat}); 165.72 (C_{quat}). Mass spectrum: m/z = 523 $[M]^{+\cdot}$.
5	98	^{1}H NMR ($CDCl_3$; δ, ppm): 0.83 (d, 6H, J = 5.1 Hz); 0.87 (d, 6H, J = 5.3 Hz); 0.98–1.11 (m, 4H); 2.53–2.72 (m, 6H); 2.95–3.06 (m, 2H); 3.20–3.43 (m, 2H); 3.63–3.84 (m, 2H); 4.06 (s, 2H); 7.39–7.54 (m, 4H); 7.59–7.89 (m, 2H); 8.04–8.17 (m, 1H). ^{13}C NMR ($CDCl_3$; δ, ppm): 18.28 (+); 22.14 (−); 27.67 (+); 30.71 (−); 32.23 (+); 32.35 (+); 40.60 (+); 47.62 (+); 50.55 (+); 50.55 (+); 50.74 (+); 52.66 (+); 123.64 (−); 125.42 (−); 125.79 (−); 126.31 (−); 126.45 (−); 127.67 (−); 128.81 (−); 132.07 (+) (C_{quat}); 132.23 (+) (C_{quat}); 133.86 (+) (C_{quat}); 166.12 (+) (C_{quat}). Mass spectrum: m/z = 527 $[M]^{+\cdot}$. Analysis ($C_{28}H_{43}N_3SGe$): Calcd: C, 63.89; H, 8.23; N, 7.98. Found: C, 63.85; H, 8.51; N, 8.81%.
6	98	^{1}H NMR ($CDCl_3$; δ, ppm): 0.85–0.99 (m, 15H); 1.08–1.37 (m, 10H); 2.52–2.85 (m, 4H); 2.95–3.10 (m, 3H); 3.30–3.41 (m, 2H); 3.66–3.78 (m, 2H); 4.04 (s, 2H); 7.33–7.53 (m, 4H); 7.66–7.80 (m, 2H); 8.05–8.19 (m, 1H). ^{13}C NMR ($CDCl_3$; δ, ppm): 18.25 (+); 20.79 (−); 22.14 (−); 30.57 (−); 32.12 (+); 32.20 (+); 40.48 (+); 41.25 (−); 47.46 (+); 50.44 (+); 50.58 (+); 52.43 (+); 123.60 (−); 125.39 (−); 125.77 (−); 126.29 (−); 126.40 (−); 128.22 (−); 129.03 (−); 132.02 (+) (C_{quat}); 132.13 (+) (C_{quat}); 133.82 (+) (C_{quat}); 166.12 (+) (C_{quat}). Mass spectrum: m/z = 541 $[M]^{+\cdot}$. Analysis ($C_{28}H_{45}N_3SGe$): Calcd: C, 62.24; H, 8.39; N, 7.78. Found: C, 62.02; H, 8.44; N, 7.72%.
7	98	^{1}H NMR ($CDCl_3$; δ, ppm): 0.86 (t, 6H, J = 5.7 Hz); 1.23 (m, 20H); 2.54–2.80 (m, 6H); 2.87–3.10 (m, 2H); 3.18–3.46 (m, 2H); 3.66–3.78 (m, 2H); 4.05 (s, 2H); 7.29–7.54 (m, 4H); 7.60–7.89 (m, 2H); 7.98–8.17 (m, 1H). ^{13}C NMR ($CDCl_3$; δ, ppm): 14.15 (−); 14.67 (+); 18.89 (+); 22.62 (+); 24.27 (+); 24.34 (+); 31.04 (+); 31.47 (+); 42.13 (+); 48.27 (+); 50.51 (+); 50.78 (+); 52.72 (+); 123.64 (−); 125.47 (−); 125.77 (−); 126.19 (−); 126.30 (−); 127.60 (−); 128.80 (−); 132.23 (C_{quat}); 132.36 (C_{quat}); 133.85 (C_{quat}); 165.84 (C_{quat}). Mass spectrum: m/z = 555 $[M]^{+\cdot}$. Analysis ($C_{30}H_{47}N_3SGe$): Calcd: C, 65.00; H, 8.54; N, 7.58. Found: C, 65.03; H, 8.86; N, 7.51%.

Table 1 Continued

Compound	Yield(%)	Physical properties and elemental analyses
8	98	^{1}H NMR ($CDCl_3$; δ ppm): 0.86–1.06 (m, 9H); 1.17–1.27 (m, 20H); 2.55–3.10 (m, 7H); 3.25–3.39 (m, 2H); 3.66–3.76 (m, 2H); 4.05 (s, 2H); 7.30–7.54 (m, 4H); 7.62–7.89 (m, 2H); 7.96–8.17 (m, 1H). ^{13}C NMR ($CDCL_3$; δ ppm): 14.15 (−); 15.46 (−); 22.61 (+); 23.36 (+); 24.20 (+); 31.43 (+); 31.58 (+); 32.25 (+); 40.64 (+); 41.32 (−); 48.19 (+); 50.59 (+); 50.79 (+); 52.75 (+); 123.89 (−); 125.48 (−); 125.78 (−); 126.29 (−); 126.45 (−); 127.60 (−); 128.81 (−); 132.07 (C_{quat}); 132.24 (C_{quat}); 133.87 (C_{quat}); 165.90 (C_{quat}). Mass spectrum: $m/z = 569$ $[M]^{+\cdot}$. Analysis ($C_{31}H_{49}N_3SGe$): Calcd: C, 65.51; H, 8.69; N, 7.39. Found: C, 64.01; H, 8.83; N, 7.76%.
9	86	^{1}H NMR ($CDCL_3$; δ ppm): 0.33–0.62 (m, 4H); 0.81 (d, 12H, $J = 5.74$ Hz); 0.90 (s, 2H); 1.03–1.27 (m, 6H); 2.43–2.82 (m, 12H); 2.96–3.11 (m, 4H); 3.31–3.42 (m, 4H); 3.67–3.77 (m, 4H); 4.05 (s, 4H); 7.34–7.53 (m, 8H); 7.60–7.89 (m, 4H); 8.05–8.17 (m, 2H). ^{13}C NMR ($CDCl_3$; δ ppm): 14.30 (+); 22.21 (−); 29.62 (+); 30.66 (−); 32.38 (+); 32.64 (+); 40.81 (+); 47.44 (+); 50.57 (+); 50.78 (+); 52.72 (+); 123.84 (−); 125.50 (−); 125.81 (−); 126.33 (−); 126.40 (−); 127.69 (−); 128.83 (−); 132.14 (C_{quat}); 132.23 (C_{quat}); 133.86 (C_{quat}); 165.86 (C_{quat}). IR (cm^-): $\nu_{NH} = 3360$. Mass spectrum: $m/z = 481$ $[M-313]^{+\cdot}$.
10	81	^{1}H NMR ($CDCl_3$; δ ppm): 0.31–0.61 (m, 4H); 0.78 (d, 12H, $J = 5.7$ Hz); 0.84 (d, 6H, $J = 5$ Hz); 0.92 (s, 4H); 1.01–1.34 (m, 6H); 2.19–3.39 (m, 18H); 3.62–3.73 (m, 4H); 4.01 (s, 4H); 7.30–7.49 (m, 8H); 7.56–7.86 (m, 4H); 8.01–8.13 (m, 2H). ^{13}C NMR ($CDCl_3$; δ ppm): 14.15 (+); 21.61 (−); 22.23 (−); 30.62 (−); 32.23 (+); 32.35 (+); 40.56 (+); 41.27 (−); 47.50 (+); 50.50 (+); 50.70 (+); 52.69 (+); 123.65 (−); 125.45 (−); 125.77 (−); 126.28 (−); 126.37 (−); 127.65 (−); 128.79 (−); 132.11 (C_{quat}); 132.24 (C_{quat}); 133.83 (C_{quat}); 165.49 (C_{quat}). IR (cm^-): $\nu_{NH} = 3373$. Mass spectrum: $m/z = 495$ $[M-327]^{+\cdot}$. Analysis ($C_{48}H_{70}N_6S_2Si$): Calcd: C, 70.02; H, 8.57; N, 10.21. Found: C, 67.19; H, 8.85; N, 9.93%.
11	83	^{1}H NMR ($CDCl_3$; δ ppm): 0.23–0.59 (m, 4H); 0.86 (t, 6H, $J = 6$ Hz); 0.92 (s, 2H); 1.20 (m, 16H); 2.44–2.81 (m, 12H); 2.93–3.10 (m, 4H); 3.17–3.40 (m, 4H); 3.65–3.76 (m, 4H); 4.04 (s, 4H); 7.29–7.53 (m, 8H); 7.67–7.89 (m, 4H); 7.96–8.17 (m, 2H). ^{13}C NMR ($CDCl_3$; δ ppm): 14.23 (−); 16.84 (+); 22.67 (+); 23.27 (+); 23.36 (+); 31.52 (+); 31.60 (+); 32.39 (+); 40.61 (+); 47.59 (+); 50.56 (+); 50.77 (+); 52.73 (+); 123.63 (−); 125.49 (−); 125.80 (−); 126.23 (−); 126.31 (−); 127.68 (−); 128.82 (−); 132.13 (C_{quat}); 132.24 (C_{quat}); 133.85 (C_{quat}); 165.88 (C_{quat}). IR (cm^-): $\nu_{NH} = 3379$. Mass spectrum: $m/z = 509$ $[M-313]^{+\cdot}$.
12	73	^{1}H NMR ($CDCl_3$; δ ppm): 0.33–0.59 (m, 4H); 0.85 (t, 6H, $J = 6$ Hz); 0.93 (s, 2H); 1.02–1.38 (m, 16H); 1.19 (d, 6H, $J = 6.3$ Hz); 2.24–3.44 (m, 18H); 3.67–3.77 (m, 4H); 4.05 (s, 4H); 7.34–7.54 (m, 8H); 7.68–7.89 (m, 4H); 7.95–8.16 (m, 2H). ^{13}C NMR ($CDCl_3$; δ ppm): 14.21 (−); 16.74 (+); 20.80 (−); 22.67 (+); 23.28 (+); 31.67 (+); 32.26 (+); 32.39 (+); 40.62 (+); 41.28 (−); 46.75 (+); 50.58 (+); 50.79 (+); 52.90 (+); 123.84 (−); 125.48 (−); 125.81 (−); 126.23 (−); 126.36 (−); 127.69 (−); 128.84 (−); 132.05 (C_{quat}); 132.23 (C_{quat}); 133.86 (C_{quat}); 166.19 (C_{quat}). IR (cm^{-1}): $\nu_{NH} = 3381$. Mass spectrum: $m/z = 523$ $[M-327]^{+\cdot}$. Analysis ($C_{50}H_{74}N_6S_2Si$): Calcd: C, 70.54; H, 8.76; N, 9.87. Found: C, 68.73; H, 9.03; N, 9.79%.
13	98	^{1}H NMR ($CDCl_3$; δ ppm): 0.89 (d, 12H, $J = 5.5$ Hz); 0.92 (s, 2H); 1.16–1.51 (m, 10H); 2.53–2.79 (m, 12H); 2.96–3.12 (m, 4H); 3.17–3.42 (m, 4H); 3.67–3.78 (m, 4H); 4.06 (s, 4H); 7.35–7.55 (m, 8H); 7.69–7.91 (m, 4H); 8.04–8.16 (m, 2H). ^{13}C NMR ($CDCl_3$; δ ppm): 17.40 (+); 18.26 (+); 22.14 (−); 30.53 (−); 32.36 (+); 33.46 (+); 40.80 (+); 47.61 (+); 50.58 (+); 50.76 (+); 52.87 (+); 123.63 (−); 125.43 (−); 125.80 (−); 126.32 (−); 126.43 (−); 127.68 (−); 128.82 (−); 132.05 (C_{quat}); 132.21 (C_{quat}); 133.85 (C_{quat}); 166.15 (C_{quat}). IR (cm^{-1}): $\nu_{NH} = 3367$. Mass spectrum: $m/z = 527$ $[M-313]^{+\cdot}$. Analysis ($C_{46}H_{66}N_6S_2Ge$): Calcd: C, 65.79; H, 7.92; N, 10.01. Found: C, 64.24; H, 8.34; N, 9.65%.

Table 1 Continued

Compound	Yield(%)	Physical properties and elemental analyses
14	98	^{1}H NMR ($CDCl_3$; δ ppm): 0.81(d, 12H); 0.86 (d, 6H); 0.97 (s, 2H); 1.13–1.44 (m, 10H); 2.47–2.69 (m, 10H); 2.78–3.17 (m, 4H); 3.22–3.38 (m, 4H); 3.63–3.73 (m, 4H); 4.02 (s, 4H); 7.31–7.51 (m, 8H); 7.56–7.86 (m, 4H); 8.02–8.15 (m, 2H). ^{13}C NMR ($CDCl_3$; δ ppm): 18.23 (+); 20.77 (−); 22.14 (−); 30.52 (−); 32.26 (+); 33.37 (+); 40.50 (+); 41.23 (−); 47.46 (+); 50.43 (+); 50.59 (+); 52.61 (+); 123.62 (−); 125.36 (−); 125.71 (−); 126.22 (−); 126.40 (−); 127.57 (−); 128.72 (−); 132.02 (C_{quat}) 132.23 (C_{quat}) 133.78 (C_{quat}); 165.95 (C_{quat}). IR (cm^{-1}): ν_{NH} = 3369. Mass spectrum: m/z = 541 $[M-327]^{+\cdot}$. Analysis ($C_{48}H_{70}N_6S_2Ge$): Calcd: C, 66.43; H, 8.13; N, 9.68. Found: C, 64.76; H, 8.42; N, 9.43%.
15	98	^{1}H NMR ($CDCl_3$; δ ppm): 0.86 (t, 6H, J = 5.7 Hz); 0.92 (s, 2H); 1.25 (m, 20H); 2.56–2.72 (m, 12H); 2.96–3.11 (m, 4H); 3.16–3.42 (m, 4H); 3.66–3.78 (m, 4H); 4.06 (s, 4H); 7.34–7.54 (m, 8H); 7.61–7.90 (m, 4H); 8.04–8.16 (m, 2H). ^{13}C NMR ($CDCl_3$; δ ppm): 14.16 (−); 19.93 (+); 22.63 (+); 23.36 (+); 24.69 (+); 31.39 (+); 31.59 (+); 32.66 (+); 40.64 (−); 47.65 (+); 50.60 (+); 50.81 (+); 52.76 (+); 123.64 (−); 125.02 (−); 125.80 (−); 126.31 (−); 126.45 (−); 127.68 (−); 128.83 (−); 132.08 (+); 132.25 (+); 133.87 (+); 166.14 (+). IR (cm^-): ν_{NH} = 3366. Mass spectrum: m/z = 555 $[M-313]^{+\cdot}$. Analysis ($C_{48}H_{70}N_6S_2Ge$): Calcd: C, 66.43; H, 8.13; N, 9.68. Found: C, 66.37; H, 8.29; N, 10.41%.
16	99	^{1}H NMR ($CDCl_3$; δ ppm): 0.85 (t, 6H, J = 5.7 Hz); 0.91 (s, 2H); 1.21 (d, 6H); 1.17–1.35 (m, 20H); 2.55–2.79 (m, 8H); 2.84–3.09 (m, 6H); 3.16–3.39 (m, 4H); 3.64–3.75 (m, 4H); 4.04 (s, 4H); 7.32–7.52 (m, 8H); 7.59–7.87 (m, 4H); 8.03–8.15 (m, 2H). ^{13}C NMR ($CDCl_3$; δ ppm): 14.16 (−); 20.77 (−); 22.58 (+); 23.36 (+); 24.66 (+); 31.38 (+); 31.58 (+); 32.22 (+); 40.59 (+); 41.24 (−); 47.55 (+); 50.55 (+); 50.75 (+); 52.67 (+); 123.69 (−); 125.51 (−); 125.76 (−); 126.31 (−); 126.36 (−); 127.68 (−); 128.80 (−); 132.05 (C_{quat}); 132.23 (C_{quat}); 133.86 (C_{quat}); 165.92 (C_{quat}) IR (cm^-): ν_{NH} = 3365. Mass spectrum: m/z = 569 $[M-327]^{+\cdot}$. Analysis ($C_{50}H_{74}N_6S_2Ge$): Calcd: C, 67.03; H, 8.32; N, 9.38. Found C, 66.34; H, 8.58; N, 9.61%.
17	45	B.p. = 184–186 °C /0.02 mm Hg. ^{1}H NMR ($CDCl_3$; δ ppm): 0.92 (s, 2H); A_2B_2 System: δ_A = 2.48 (2H), δ_B = 2.91 (2H), J_{AB} = 6 Hz; A_2B_2 System: δ_A = 3.19 (2H), δ_B = 3.68 (2H), J_{AB} = 9 Hz; 4.01 (s, 2H); 7.54–7.30 (m, 4H); 7.86–7.59 (m, 2H); 8.09–7.99 (m, 1H). ^{13}C NMR ($CDCl_3$; δ ppm): 32.28 (+); 40.57 (+); 50.53 (+); 50.69 (+); 52.60 (+); 123.60 (−); 125.40 (−); 125.79 (−); 126.42 (−); 126.65 (−); 127.66 (−); 128.81 (−); 132.06 (C_{quat}); 132.21 (C_{quat}); 133.85 (C_{quat}); 166.12 (C_{quat}). IR (cm^{-1}): ν_{NH2} = 3281.3362. Mass spectrum: m/z = 252 $[M-1]^{+\cdot}$. Analysis ($C_{16}H_{19}N_3$): Calcd: C, 75.85; H, 7.56; N, 16.58. Found C, 75.82; H, 7.75; N, 17.16%.
18	83	^{1}H NMR ($CDCl_3$; δ ppm): 1.09 (s, 2H,); 2.43–2.70 (m, 4H); A_2B_2 System: δ_A = 2.58 (2H), δ_B = 3.00 (2H), J_{AB} = 6.2 Hz; A_2B_2 System: δ_A = 3.29 (2H), δ_B = 3.75 (2H), J_{AB} = 8.8 Hz; 4.04 (s, 2H); 7.33–7.53 (m, 4H); 7.66–7.81 (m, 2H); 8.03–8.08 (m, 1H). ^{13}C NMR ($CDCl_3$; δ ppm): 24.88 (+); 32.29 (+); 40.55 (+); 47.53 (+); 50.51 (+); 50.67 (+); 52.60 (+); 123.62 (−); 125.42 (−); 125.81 (−); 126.32 (−); 126.42 (−); 127.67 (−); 128.81 (−); 132.05 (C_{quat}); 132.20 (C_{quat}); 133.84 (C_{quat}); 166.14 (C_{quat}). IR (cm^{-1}): ν_{SH} = 2543; ν_{NH} = 3369. Mass spectrum: m/z = 313 $[M]^{+\cdot}$. Analysis ($C_{18}H_{23}N_3S$): Calcd: C, 68.97; H, 7.39; N, 13.40. Found: C, 68.94; H, 7.52; N, 14.07%.
19	88	^{1}H NMR ($CDCl_3$; δ ppm): 1.1 (s, 2H); 1.17 (d, 3H, J = 6.6 Hz); 2.38–2.94 (m, 7H); 3.14–3.42 (m, 2H); 3.65–3.91 (m, 2H); 4.04 (s, 2H). ^{13}C NMR ($CDCl_3$; δ ppm): 20.79 (−); 22.40 (+); 22.90 (−); 32.35 (+); 35.78 (−); 40.59 (+); 41.52 (−); 47.56 (+); 50.56 (+); 50.75 (+); 52.64 (+); 123.63 (−); 125.44 (−); 125.82 (−); 126.34 (−); 126.44 (−); 127.70 (−); 128.84 (−); 132.04 (C_{quat}); 132.19 (C_{quat}), 133.85 (C_{quat}); 166.21 (C_{quat}), IR (cm^{-1}): ν_{SH} = 2539; ν_{NH} = 3364. Mass spectrum: m/z = 327 $[M]^{+\cdot}$. Analysis ($C_{19}H_{25}N_3S$): Calcd: C, 69.68; H, 7.69; N, 12.83. Found. C, 68.78; H, 7.81; N, 12.73%.

Table 1 Continued

Compound	Yield(%)	Physical properties and elemental analyses
19bis	10	^{1}H NMR ($CDCl_3$; δ, ppm): 1.1 (s, 2H); 1.34 (d, 3H, J = 6.5 Hz); 2.85–3.10 (m, 7H); 3.14–3.42 (m, 2H); 3.65–3.91 (m, 2H); 4.04 (s, 2H). ^{13}C NMR ($CDCl_3$; δ, ppm): 20.79 (−); 22.40 (+); 22.90 (−); 32.35 (+); 35.78 (−); 40.59 (+); 41.52 (−); 47.56 (+); 50.56 (+); 50.75 (+); 52.64 (+); 123.63 (−); 125.44 (−); 125.82 (−); 126.34 (−); 126.44 (−); 127.70 (−); 128.84 (−); 132.04 (C_{quat}); 132.19 (C_{quat}); 133.85 (C_{quat}); 166.21 (C_{quat}) IR (cm^{-1}): ν_{SH} = 2538; ν_{NH} = 3364. Mass spectrum: m/z = 327 $[M]^+$. Analysis ($C_{19}H_{25}N_3S$): Calcl: C, 69.68; H, 7.69; N, 12.83. Found: C, 68.78; H, 7.81; N, 12.73%.

PHARMACOLOGY

Among the three reference compounds, **18** had no activity, **17** a low and delayed activity and **19 a** slightly better one. On the whole, germa- and sila-thiazolidines **1, 3, 4, 5, 6** and **8** had a lower toxicity and a higher activity. Silathiazolidines had the lowest toxicity, but in spite of a higher injected dose, they were not more radioprotective than the corresponding germanium derivatives. Like most thiazolidine compounds, they showed a sustained radioprotective activity. The metalladithioacetals were slightly less active, except compound **16**, which was equally efficient. They also showed a sustained action. The silicon derivatives were also less toxic than the germanium ones. It is interesting to note that derivative **5** had one of the highest activities in spite of the lowest injected dose.

These results confirm:

(1) the sustained effect of heterocyclic compounds and particularly of thiazolidines which act through the release of cysteamine[16] ($HSCH_2CH_2NH_2$), which is considered as the reference radioprotector;
(2) the positive contribution of germanium and silicon towards decreasing the toxicity and increasing the radioprotective activity. They allow a higher penetration inside the cell and a better diffusion in the body. Moreover, their low electronegativity, their great covalent radius and the presence of empty *d* orbitals can lead to a decrease in free-radical-induced chemical lesions.

RADIOPROTECTIVE EVALUATION

Three-month-old male CDI mice (Charles River, France), 25 g body weight, were used.

The radioprotective effect of compounds was evaluated by determining the dose reduction factor (DRF), defined as the ratio of 50% lethal-dose irradiation 30 days (LD_{50}/30 days) of injected mice to that of control mice. Initially the survival rate was determined 30 days after irradiation in different groups of 10 mice receiving an intraperitoneal (i.p.) injection of the test compound with a dose equal to half or one-eighth of its LD_{50} 15 or 90 min before whole-body irradiation delivered with a dose equal to the LD_{100}/30 days of control mice (7.5, 7.75 or 8 Gy according to the irradiation date), or with a dose equal to this dose + 2 Gy. When necessary, other irradiation doses were tested in order to evaluate the irradiation LD_{50} of protected mice by the Kraber method (calculated or graphic).[17]

The radiosensitivity of the strain was regularly monitored by the determination of lethality curves of males and females. The LD_{50}/30 days was between 6.5 ± 0.3 and 6.75 ± 0.3 Gy according to the date ($P < 0.05$) Under these conditions significant protection was observed with a DRF value superior to 1.15.

The toxicity was evaluated by a Probit analysis of the LD_{50},[18,19] the dose range being determined in a preliminary study. Five groups of 10 mice were then injected with different doses within this range.

Whole-body irradiations were performed with a ^{60}Co γ-ray source (6×10^{13} Bq). The dose rate was equal to 0.2–0.3 Gy min^{-1}. For the exposure, mice were positioned inside a Plexiglass 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 and lithium fluoride thermoluminescent dosimeters.

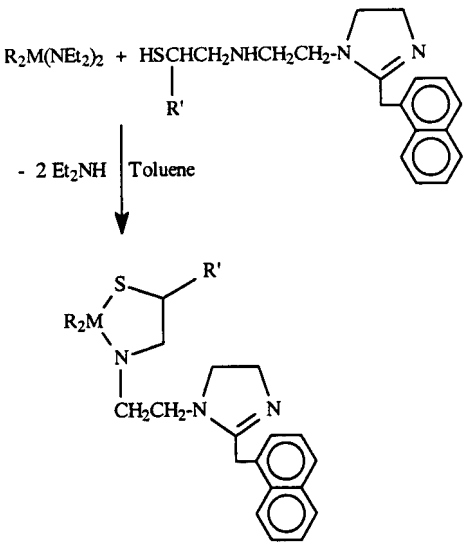
Each irradiation session included a group of 10 mice irradiated with 7.5, 7.75 or 8 Gy according to the date after intraperitoneal injection of the solvent alone. A 100% lethality was always observed with a mean survival time equal to 11 ± 1 days. Furthermore, a group of eight unirradiated mice received the test compound with a dose equal to half of its

LD_{50} 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 metallathiazolidines

These compounds were prepared according to the method of heterocyclization already described in the literature.[1,12–15] The reaction of **18** and **19**, in stoichiometric amounts, with the bis(diethylamino)dialkylmetallanes in anhydrous toluene resulted in cleavage of M–N bonds (M = Si, Ge) by the NH and SH groups, forming the corresponding metallathiazolidines in good yields (Scheme 2).



Scheme 2

Synthesis of metalladithioacetals

The reaction of 2 equiv. of **18** or **19** with bis(diethylamino)dialkylmetallanes in anhydrous toluene, a cleavage reaction of M–N bonds (M = Si, Ge) by the SH groups,[2,13–15] gave the corresponding metalladithioacetals (Scheme 3) in quantitative yields.

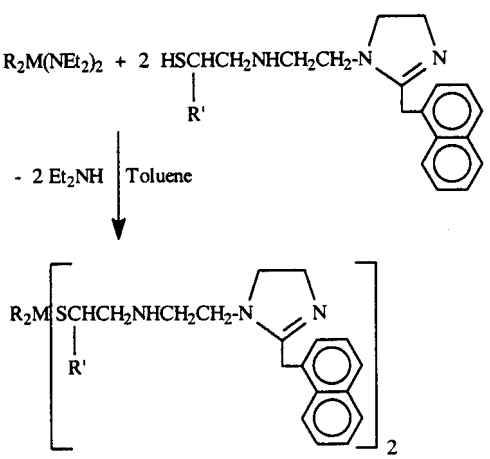
Synthesis of organic compounds

Compounds **18** and **19** were obtained by the reaction of stoichiometric amounts of 1-aminoethyl-2-(1-naphthylmethyl)-2-imidazoline with ethylene sulphide or propylene sulphide in toluene (100 °C) (i.e. by a cleavage of the C–S bond by NH_2 group)[20] (Scheme 4).

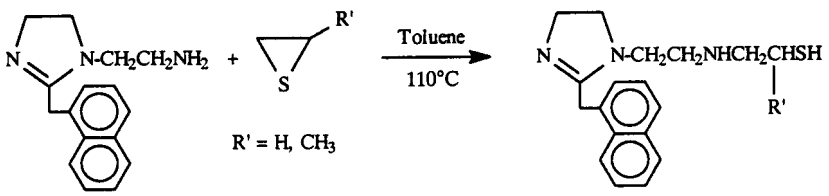
Tables 2 and 3 summarize the radiation protection and toxicity in mice after intraperitoneal administration of metallathiazolidines **1**–**8** and metalladithioacetals **9**–**16** as discussed. The compounds **1, 3, 4, 6, 8** and **16** showed a high radioprotective activity (DRF = 1.25–1.33) and lower toxicity in comparison with the starting organic compounds **18** and **19** (Table 4). Derivatives **1** and **3** showed a much greater radioprotective activity and lower toxicity than that of compound **18**. At an $LD_{50}/2$ of approximately 125 mg kg^{-1}, **3** protected 100% and 80% of mice when it was injected 15 and 90 min, respectively, before irradiation at 8 Gy. At an $LD_{50}/2$ of approximately 110 mg kg^{-1}, **4** protected 80% and 90% of mice when it was injected 15 and 90 min, respectively, before irradiation at 8 Gy.

At an $LD_{50}/2$ of approximately 75 mg kg^{-1}, **6** protected 90% of mice when it was injected 90 min before irradiation at 8 Gy. At an $LD_{50}/2$ of approximately 100 mg kg^{-1}, **8** protected 60% and 80% of mice when it was injected 15 and 90 min, respectively, before irradiation at 8 Gy.

Note that derivatives **5, 12, 13, 14, 15** and **16** have a greater radioprotective activity and a lower toxicity, in spite of lower injected dosages in the case of the metallated derivatives (expressed in mmol fractions, on an average 0.156 mmol) compared with **18** (0.40 mmol) and **19** (0.24 mmol).

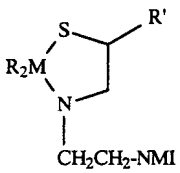


Scheme 3



Scheme 4

Table 2 Radioprotective activity of sila- and germa-thiazolidines



Compound	M	R	R′	LD_{50} (mg kg^{-1}) (LD_{50} mmol)	Injected dose (mg kg^{-1})	Irradiation (Gy) (*t*, min)[a]	Survival rate (%)	DRF[b]
1	Si	i−C_5H_{11}	H	225	112.5	8 (15)	40	
				(0.47)	112.5	10 (15)	0	
					112.5	8 (90)	70	1.25
					28.12	8 (15)	0	
2	Si	i−C_5H_{11}	CH_3	225	112.5	8 (15)	50	
				(0.45)	112.5	10 (15)	10	1.2
					112.5	8 (90)	60	1.2
					28.12	8 (15)	50	1.2
3	Si	n−C_6H_{13}	H	250	125	8 (15)	100	
				(0.49)	125	10 (15)	0	1.3
					125	8 (90)	80	1.25
					31.25	8 (15)	0	
4	Si	n−C_6H_{13}	CH_3	220	110	8 (15)	80	
				(0.42)	110	10 (15)	0	1.25
					110	8 (90)	90	1.3
					27.5	8 (15)	50	1.18
5	Ge	i−C_5H_{11}	H	80	40	8 (15)	50	
				(0.15)	40	10 (15)	0	1.2
					40	8 (90)	80	
					40	10 (90)	20	1.33
					10	8 (15)	10	
6	Ge	i−C_5H_{11}	CH_3	150	75	8 (15)	30	
				(0.28)	75	10 (15)	0	
					75	8 (90)	90	
					75	10 (90)	0	1.3
					18.75	8 (15)	40	
7	Ge	n−C_6H_{13}	H	175	87.5	8 (15)	20	
				(0.31)	87.5	10 (15)	0	1.1
					87.5	8 (90)	40	
8	Ge	n−C_6H_{13}	CH_3	200	100	8 (15)	60	
				(0.35)	100	10 (15)	30	1.25
					100	8 (90)	80	1.3
					25	8 (15)	40	

[a] *t* = time between administration of compound and irradiations.
[b] Dose reduction factor = $LD_{50\ (30\ days)}$, treated/$LD_{50\ (30\ days)}$ untreated.

Table 3 Radioprotective activity of sila- and germa-dithioacetals

$$R_2M\left[\begin{array}{l} SCHCH_2NHCH_2CH_2\text{-}NMI \\ \quad | \\ \quad R' \end{array}\right]_2$$

Compound	M	R	R′	LD_{50} (mg kg^{-1}), (LD_{50} mmol)	Injected dose (mg kg^{-1})	Irradiation (Gy) (*t*, min)[a]	Survival rate (%)	DRF[b]
9	Si	i−C_5H_{11}	H	200	100	8 (15)	20	
				(0.25)	100	10 (15)	20	
					100	8 (90)	40	1.15
					25	8 (15)	20	
10	Si	i−C_5H_{11}	CH_3	150	75	8 (15)	30	
				(0.18)	75	10 (15)	0	
					75	8 (90)	40	1.15
					18.75	8 (15)	20	
11	Si	n−C_6H_{13}	H	175	87.5	8 (15)	60	
				(0.21)	87.5	10 (15)	20	1.2
					87.5	8 (90)	60	1.2
					21.9	8 (15)	0	
12	Si	n−C_6H_{13}	CH_3	125	62.5	8 (15)	40	
				(0.15)	62.5	10 (15)	0	
					62.5	8 (90)	60	1.2
					15.63	8 (15)	50	1.2
13	Ge	i−C_5H_{11}	H	150	75	8 (15)	20	
				(0.18)	75	10 (15)	10	1.2
					75	8 (90)	40	
					18.75	8 (15)	10	
14	Ge	i−C_5H_{11}	CH_3	125	62.5	8 (15)	60	
				(0.14)	62.5	10 (15)	0	1.2
					62.5	8 (90)	56	1.2
					15.6	8 (15)	30	
15	Ge	n−C_6H_{13}	H	120	60	8 (15)	30	
				(0.14)	60	10 (15)	0	1.1
					60	8 (90)	20	
					15	8 (15)	10	
16	Ge	n−C_6H_{13}	CH_3	160	80	8 (15)	60	
				(0.18)	80	10 (15)	10	
					80	8 (90)	100	
					80	10 (90)	0	1.3
					20	8 (15)	50	

a,b see Table 2

CONCLUSIONS

In conclusion, the radioprotective activity by intraperitoneal administration in mice of metal-lathiazolidines and metalladithioacetals is more potent than that of the starting organic derivatives **18** and **19**.

Once more, the results reported in this paper confirm the positive contribution of silicon and germanium in chemical radioprotection. We also observed that silicon and organogermanium groups decrease the toxicity of the organic molecules to which they are linked

This is in agreement with our previous work[1–11]

Table 4 Radioprotective activity of organic compounds

Compound	LD_{50} (mg kg^{-1}) (LD_{50}, mmol)	Injected dose (mg kg^{-1})	Irradiation (Gy) (*t*, min)[a]	Survival rate (%)	DRF[b]
17	175	100	7.75 (15)	0	
	(0.69)	100	9.75 (15)	0	
		100	7.75 (90)	70	1.2
		25	7.75 (15)	10	
18	125	60	7.75 (15)	50	1.1
	(0.40)	60	7.75 (90)	50	1.1
19	80	40	7.75 (15)	70	
	(0.24)	40	9.75 (15)	0	1.15
		40	7.75 (90)	90	1.25
		10	7.75 (15)	30	

a,b See Table 2

and confirms the interesting biological activity of organosilicon and organogermanium compounds in different fields.[21–37]

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