A REVIEW ON THE RADIOPROTECTIVE ACTIVITY OF ORGANOGERMANIUM AND ORGANOSILICON COMPOUNDS

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Abstract

The present review describes the work carried out during the last 20 years in the field of the radioprotective activity and toxicity of several classes of organosilicon and organogermanium compounds (i.e. metallathiazolidines, metalladithioacetals, metallatranes and germathianes).

1. Introduction

During the 20-year period between 1978 and 1998 the Délégation Générale pour l'Armement and Département de Chimie Pharmacologie, France, sponsored a coordinated antiradiation drug development program. The objective of this program was to develop a drug or combination of drugs with organometallated compounds which could be taken by military personnel or other populations to protect them from the effects of ionizing radiations in a nuclear weapons attack, medical treatments or, in general, all radiation exposition.

During the research program approximately 562 compounds were chemically synthesized and tested in mice for their radioprotective properties.

The vast majority of these compounds were metallathiazolidines, metalladithioacetals of *N*-substituted cysteamine, methylcysteamine, *N*-(2-thioethyl)-1,3-diaminopropane, *N*-substituted cysteamine or methylcysteamine by naphthylmethylimidazoline and *N*-substituted naphthylmethylimidazoline.

120 compounds of these derivatives are characterized by a dose reduction factor (DRF) between 1.3 and 1.75.

The radioprotective activity and toxicity of several classes of organometallated derivatives (silathiazolidines, germathiazolidines, siladithioacetals, germadithioacetals, germatranes, silatranes and germylated sulfides) and their synthesis are reported.

All the biological tests have been performed in the Centre de Recherche du Service de Santé des Armées, La Tronche, France.

2. Sila- and germathiazolidines

Sila- and germathiazolidines of *N*-substituted cysteamine, methylcysteamine, *N*-(2-thioethyl)-1,3-diaminopropane and *N*-substituted cysteamine or methylcysteamine by naphthylmethylimidazoline were prepared according to two methods of heterocyclisation already described in the literature [1-3].

Method A

The action of diorganosilicon and -germanium dichloride [3] (in stoichiometric amounts) on *N*-substituted cysteamine, methylcysteamine, *N*-(2-thioethyl)-1,3-diaminopropane and *N*-substituted cysteamine or methylcysteamine by naphthylmethylimidazoline in refluxing anhydrous tetrahydrofuran in the presence of freshly distilled triethylamine gave by a cyclisation reaction, with elimination of hydrochloric acid from M-Cl and SH and NH [4] groups the corresponding products, Scheme 1.

Scheme 1**Method B**

The reaction of *N*-substituted cysteamine, methylcysteamine, *N*-(2-thioethyl)-1,3-diaminopropane and *N*-substituted cysteamine or methylcysteamine by naphthylmethylimidazoline, in stoichiometric amounts, with the bis(diethylamino)dialkylsilanes or -germanes in anhydrous tetrahydrofuran resulted in the cleavage of M-N bonds by the NH and SH groups (a transamination reaction) [1, 3-5], forming the corresponding sila- and germathiazolidines in good yields, Scheme 2.

Scheme 2

A radioprotective study of metallathiazolidines shows that the silylated and germylated derivatives have a greater biological activity and a lower toxicity than that of the corresponding organic compounds [1] (Table I).

3. Sila- and germadithioacetals

Sila- and germadithioacetals of *N*-substituted cysteamine, methylcysteamine, *N*-(2-thioethyl)-1,3-diaminopropane, *N*-substituted cysteamine and methylcysteamine by naphthylmethylimidazoline and *N*-substituted naphthylmethylimidazoline were also obtained by two methods C and D [10].

Method C

The action of diorganosilicon and -germanium dichloride [3] on two equivalents of *N*-substituted cysteamine, methylcysteamine, *N*-(2-thioethyl)-1,3-diaminopropane, *N*-substituted cysteamine and methylcysteamine by naphthylmethylimidazoline and *N*-substituted naphthylmethylimidazoline in refluxing anhydrous tetrahydrofuran in the presence of freshly distilled triethylamine gave the acyclic derivatives, Scheme 3.

Scheme 3

Table I - Radioprotective activity of some selected metallathiazolidines

M = Si									
Cpd [Ref.]	R ₁	R ₂	R ₃	R ₄	LD ₅₀ (mg.kg ⁻¹)	Injected dose (mg.kg ⁻¹)	Irradiation Gy (t, min) ^a	Survival rate %	DRF ^b
1 [1]	CH ₃	C ₆ H ₅	H	H	800	400	10 (15)	93	1.6
						400	10 (120)	90	
						400	12 (15)	70	
						100	10 (15)	16	
2 [1]	CH ₃	C ₆ H ₅	CH ₃	H	750	375	10 (15)	95	1.5
						375	10 (120)	0	
						375	12 (15)	89	
						93.7	10 (15)	75	
3 [1]	C ₂ H ₅	C ₂ H ₅	H	H	1000	500	9.5 (15)	80	1.4
						500	9.5 (120)	90	
						500	11.5 (15)	50	
4 [1]	CH ₃	<i>p</i> -CH ₃ C ₆ H ₄	H	H	1500	750	9.5 (15)	90	1.4
						750	9.5 (120)	70	
						750	11.5 (15)	60	
						187	9.5 (15)	0	
5 [1]	CH ₃	<i>p</i> -CH ₃ OC ₆ H ₄	H	H	1500	750	9.5 (15)	95	1.4
						750	9.5 (120)	60	
						750	11.5 (15)	50	
						187	9.5 (15)	27	
6 [6]	HCl.H ₂ N(CH ₂) ₂ S	HCl.H ₂ N(CH ₂) ₂ S	H	(c)	600	300	7.5 (15)	100	1.6
						300	7.5 (90)	50	
						300	9.5 (15)	90	
						75	7.5 (15)	30	
7 [7]	<i>n</i> -C ₆ H ₁₃	<i>n</i> -C ₆ H ₁₃	H	(d)	250	125	8 (15)	100	1.3
						125	8 (90)	80	
						125	10 (15)	0	
						31.25	8 (15)	0	
8 [7]	<i>n</i> -C ₆ H ₁₃	<i>n</i> -C ₆ H ₁₃	CH ₃	(d)	220	110	8 (15)	80	1.3
						110	8 (90)	90	
						110	10 (15)	0	
						27.5	8 (15)	50	

a: t = time between administration of compound and irradiation.

b: dose reduction factor = (LD₅₀(30 days) treated/LD₅₀(30 days) untreated).

M = Ge									
Cpd [Ref.]	R ₁	R ₂	R ₃	R ₄	LD ₅₀ (mg.kg ⁻¹)	Injected dose (mg.kg ⁻¹)	Irradiation Gy (t, min) ^a	Survival rate %	DRF ^b
9 [1]	CH ₃	C ₆ H ₅	H	H	600	300	9.5 (15)	100	1.6
						300	11.5 (15)	70	
						300	13.5 (15)	40	
						75	9.5 (15)	50	
10 [1]	CH ₃	C ₆ H ₅	CH ₃	H	500	250	9.5 (15)	80	1.75
						250	9.5 (120)	0	
						250	11.5 (15)	70	
						250	13.5 (15)	70	
						250	15.5 (15)	0	
						62.5	9.5 (15)	5	
11 [1]	CH ₃	<i>p</i> -CH ₃ OC ₆ H ₄	H	H	700	350	9.5 (15)	100	1.45
						350	9.5 (120)	20	
						350	11.5 (15)	70	
						87.5	9.5 (15)	13	
12 [1]	CH ₃	<i>p</i> -CH ₃ OC ₆ H ₄	CH ₃	H	600	300	9.5 (15)	95	1.45
						300	9.5 (120)	20	
						300	11.5 (15)	70	
						75	9.5 (15)	20	
13 [1]	C ₆ H ₅	C ₆ H ₅	H	H	400	200	9.5 (15)	90	1.4
						200	11.5 (15)	30	
						100	9.5 (15)	70	
14 [1]	<i>n</i> -C ₄ H ₉	<i>n</i> -C ₄ H ₉	H	H	700	350	9.5 (15)	80	1.45
						350	9.5 (45)	30	
						350	11.5 (15)	70	
15 [1]	<i>n</i> -C ₄ H ₉	<i>n</i> -C ₄ H ₉	CH ₃	H	300	150	9.5 (15)	100	1.4
						150	9.5 (90)	90	
						150	11.5 (15)	30	
						37.5	9.5 (15)	80	
16 [1]	<i>n</i> -C ₅ H ₁₁	<i>n</i> -C ₅ H ₁₁	H	H	1000	500	9.5 (15)	80	1.4
						500	9.5 (120)	10	
						500	11.5 (15)	50	
						125	9.5 (15)	20	
17 [1]	<i>n</i> -C ₅ H ₁₁	<i>n</i> -C ₅ H ₁₁	CH ₃	H	700	350	9.5 (15)	95	1.4
						350	11.5 (15)	60	
						87.5	9.5 (15)	5	
18 [1]	<i>i</i> -C ₅ H ₁₁	<i>i</i> -C ₅ H ₁₁	CH ₃	H	800	400	9.5 (15)	94	1.45
						400	9.5 (120)	22	
						400	11.5 (15)	70	
						400	13.5 (15)	5	
						100	9.5 (15)	0	
19 [8]	CH ₃	C ₆ H ₅	CH ₃	CH ₃ CO	900	450	9 (15)	93	1.35
						450	9 (120)	80	
						450	11 (15)	10	
						112.5	9 (5)	50	
20 [8]	<i>i</i> -C ₅ H ₁₁	<i>i</i> -C ₅ H ₁₁	CH ₃	CH ₃ CO	1000	500	8.5 (15)	100	1.35
						500	8.5 (120)	90	
						500	10.5 (15)	10	
						125	8.5 (15)	80	
						62.5	9 (15)	20	
21 [9]	<i>i</i> -C ₅ H ₁₁	<i>i</i> -C ₅ H ₁₁	H	(a)	800	800	7.75 (15)	80	1.3
						800	7.75 (90)	80	

2 2 [9]	$n\text{-C}_6\text{H}_{13}$	$n\text{-C}_6\text{H}_{13}$	H	(a)	1500	750 750 750 187	7.5 (15) 7.5 (90) 9.5 (15) 7.5 (15)	100 90 0 40	1.5
2 3 [6]	CH_3	$p\text{-CH}_3\text{C}_6\text{H}_4$	H	$(\text{CH}_2)_2$ CONH ₂	> 1500	1000 1000 1000	8.25 (15) 8.25 (90) 10.30 (15)	70 60 20	1.4
2 4 [7]	$i\text{-C}_5\text{H}_{11}$	$i\text{-C}_5\text{H}_{11}$	H	(b)	80	40 40 40 40 10	8 (15) 8 (90) 10 (15) 10 (90) 8 (15)	50 80 0 20 10	1.33
2 5 [9]	$n\text{-C}_6\text{H}_{13}$	$n\text{-C}_6\text{H}_{13}$	CH_3	H	1500	1000 1000 1000	7.5 (15) 7.5 (90) 9.5 (15)	80 90 80	1.5
2 6 [7]	$i\text{-C}_5\text{H}_{11}$	$i\text{-C}_5\text{H}_{11}$	CH_3	(b)	150	75 75 75 75 18.75	8 (15) 8 (90) 10 (15) 10 (90) 8 (15)	30 90 0 0 40	1.3
2 7 [7]	$n\text{-C}_6\text{H}_{13}$	$n\text{-C}_6\text{H}_{13}$	CH_3	(b)	200	100 100 100 25	8 (15) 8 (90) 10 (15) 8 (15)	60 80 30 40	1.3

Method D

The reaction of bis(diethylamino)dialkylsilanes and -germanes with two equivalents of *N*-substituted cysteamine, methylcysteamine, *N*-(2-thioethyl)-1,3-diaminopropane, *N*-substituted cysteamine or methylcysteamine by naphthylmethylimidazoline and *N*-substituted naphthylmethylimidazoline in anhydrous tetrahydrofuran (a cleavage reaction of M-N bonds by the SH group) gave the corresponding organometallated derivatives, Scheme 4.

Scheme 4

4. Sila- and germatranes

$\text{R-M}(\text{OCH}_2\text{CH}_2)_3\text{N}$

Silatrane and germatranes have been synthesized according to two methods already known in the literature [13-18].

Method E

This method is the simplest and most general.

The reaction of trimethoxymetallanes, $\text{R-M}(\text{OMe})_3$ ($\text{M} = \text{Si}, \text{Ge}$), obtained by the action of tetramethoxymetallanes [10] with cysteamine, methylcysteamine and *N*-(2-thioethyl)-1,3-diaminopropane in the presence of triethanolamine leads to corresponding metallatrane (Scheme 5).

Table II - Radioprotective activity of some selected metalladithioacetals
 $R_1R_2M[S-CH(R_3)-CH_2R_4]_2$

M = Si									
Cpd [Ref.]	R ₁	R ₂	R ₃	R ₄	LD ₅₀ (mg.kg ⁻¹)	Injected dose (mg.kg ⁻¹)	Irradiation Gy (t, min) ^a	Survival rate %	DRF ^b
2 8 [11]	CH ₃	CH ₃	H	NH ₂	800	400	9.5 (15)	100	1.4
						400	9.5 (120)	90	
						400	11.5 (40)	40	
						100	9.5 (15)	33	
2 9 [6]	HCl.H ₂ N(CH ₂) ₂ S	HCl.H ₂ N(CH ₂) ₂ S	H	(c)	500	250	7.5 (15)	60	1.3
						250	7.5 (90)	10	
						250	9.5 (15)	20	
						62.5	7.5 (15)	30	
3 0 [12]	<i>i</i> -C ₅ H ₁₁	<i>i</i> -C ₅ H ₁₁	H	(d)	100	50	7.75 (15)	100	1.4
						50	7.75 (90)	80	
						50	9.75 (15)	10	
						12.5	7.75 (15)	60	
3 1 [12]	<i>n</i> -C ₆ H ₁₃	<i>n</i> -C ₆ H ₁₃	H	(d)	100	50	7.75 (15)	100	1.5
						50	7.75 (90)	100	
						50	9.75 (15)	0	
						12.5	7.75 (15)	50	

a: t = time between administration of compound and irradiation.

b: dose reduction factor = (LD₅₀(30 days) treated/LD₅₀(30 days) untreated).

M = Ge									
Cpd [Ref.]	R ₁	R ₂	R ₃	R ₄	LD ₅₀ (mg.kg ⁻¹)	Injected dose (mg.kg ⁻¹)	Irradiation Gy (t, min) ^a	Survival rate %	DRF ^b
3 2 [9]	(a)	(a)	H	NH ₂	500	250	7.5 (15)	80	1.4
						250	7.5 (90)	70	
						250	9.5 (15)	50	
						62.5	7.5 (15)	0	
3 3 [11]	<i>n</i> -C ₄ H ₉	<i>n</i> -C ₄ H ₉	H	NH ₂	600	300	9.5 (15)	100	1.3
						300	11.5 (15)	10	
3 4 [11]	<i>n</i> -C ₄ H ₉	<i>n</i> -C ₄ H ₉	CH ₃	NH ₂	400	200	9.5 (15)	100	1.3
						200	9.5 (120)	90	
						200	11.5 (15)	20	
						50	9.5 (15)	70	
3 5 [11]	<i>i</i> -C ₅ H ₁₁	<i>i</i> -C ₅ H ₁₁	H	NH ₂	800	400	9.5 (15)	80	1.4
						400	9.5 (120)	50	
						400	11.5 (15)	60	
						100	9.5 (15)	30	
3 6 [11]	<i>i</i> -C ₅ H ₁₁	<i>i</i> -C ₅ H ₁₁	CH ₃	NH ₂	600	300	10 (15)	100	>1.6
						300	12 (15)	95	
3 7 [11]	<i>n</i> -C ₅ H ₁₁	<i>n</i> -C ₅ H ₁₁	CH ₃	NH ₂	800	400	9.5 (15)	100	1.4
						400	9.5 (120)	50	
						400	11.5 (15)	40	
						100	9.5 (15)	40	

3 8 [11]	CH ₃	C ₆ H ₅	CH ₃	NH ₂	600	300 300 300 75	9.5 (15) 9.5 (120) 11.5 (15) 9.5 (15)	90 20 90 45	>1.5
3 9 [11]	CH ₃	<i>p</i> -CH ₃ -C ₆ H ₄	CH ₃	NH ₂	800	400 400 400 100	9.5 (15) 9.5 (120) 11.5 (15) 9.5 (15)	85 70 60 33	1.5
4 0 [8]	<i>i</i> -C ₅ H ₁₁	<i>i</i> -C ₅ H ₁₁	CH ₃	NH(CH ₂) ₃ NH ₂	300	150 150 150 37.5	9 (15) 9 (120) 11 (15) 9 (15)	87 40 40 90	1.4
4 1 [9]	<i>i</i> -C ₅ H ₁₁	<i>i</i> -C ₅ H ₁₁	H	(b)	900	450 450 450 112.5	7.75 (15) 7.75 (90) 9.75 (15) 7.75 (15)	50 80 0 50	1.3
4 2 [9]	<i>n</i> -C ₆ H ₁₃	<i>n</i> -C ₆ H ₁₃	H	(b)	800	400 400 400 100	7.5 (15) 7.5 (90) 9.5 (15) 7.5 (15)	100 80 0 50	1.5
4 3 [6]	<i>i</i> -C ₅ H ₁₁	<i>i</i> -C ₅ H ₁₁	H	NH(CH ₂) ₂ CONH ₂	> 1500	1000 1000 1000	8.25 (15) 8.25 (90) 10.25 (15)	100 90 30	1.4
4 4 [6]	<i>n</i> -C ₆ H ₁₃	<i>n</i> -C ₆ H ₁₃	H	NH(CH ₂) ₂ CONH ₂	> 1500	1000 1000	8.25 (15) 8.25 (90)	90 20	1.3
4 5 [12]	<i>i</i> -C ₅ H ₁₁	<i>i</i> -C ₅ H ₁₁	H	(c)	80	50 50 50 50 50 50 12.5	7.75 (15) 7.75 (90) 7.75 (180) 9.75 (15) 9.75 (90) 11.75 (15) 7.75 (15)	100 100 90 70 0 30 80	1.7
4 6 [12]	<i>n</i> -C ₆ H ₁₃	<i>n</i> -C ₆ H ₁₃	H	(c)	150	75 75 75 18.75	7.75 (15) 7.75 (90) 9.75 (15) 7.75 (15)	90 100 10 70	1.4
4 7 [9]	<i>n</i> -C ₆ H ₁₃	<i>n</i> -C ₆ H ₁₃	CH ₃	NH ₂	800	800 800 800	7.5 (15) 7.5 (90) 9.5 (15)	100 70 90	≥1.6
4 8 [7]	<i>n</i> -C ₆ H ₁₃	<i>n</i> -C ₆ H ₁₃	CH ₃	(d)	160	80 80 80 80 20	8 (15) 8 (90) 10 (15) 10 (90) 8 (15)	60 100 10 0 50	1.3

Scheme 5

Method F

The second method of synthesis of silatranes and germatranes includes of methoxymetallatranes. Thus, methoxymetallatranes obtained by the reaction of tetramethoxymetallanes with triethanolamine gave a condensation reaction with cysteamine, methylcysteamine and *N*-(2-thioethyl)-1,3-diaminopropane affording the metallatranes (Scheme 6).

Scheme 6

Table III - Radioprotective activity of some selected metallatranes
YHN-CH₂-CH(R)-SM(OCH₂CH₂)₃N

Cpd [Ref.]	M	R	Y	LD ₅₀ (mg.kg ⁻¹)	Injected dose (mg.kg ⁻¹)	Irradiation Gy (t, min) ^a	Survival rate %	DRF ^b
49 [10]	Si	H	H.HCl	600	300	9.75 (15)	80	1.3
					300	11.75 (15)	10	
					75	9.75 (15)	40	
50 [10]	Ge	H	H.HCl	700	350	9.75 (15)	80	1.4
					350	9.75 (120)	0	
					350	11.75 (15)	40	
					87.5	9.75 (15)	0	
51 [10]	Ge	H	H ₂ N(CH ₂) ₃	300	150	9.5 (15)	60	1.4
					150	9.5 (120)	0	
					150	11.5 (15)	40	
					37.5	9.5 (15)	10	
52 [10]	Ge	H	2 HCl.H ₂ N(CH ₂) ₃	900	450	9.5 (15)	100	1.45
					450	9.5 (120)	20	
					450	11.5 (15)	30	
					112.5	9.5 (15)	70	
53 [10]	Ge	CH ₃	H.HCl	1500	1000	10 (15)	80	1.5
					1000	10 (120)	0	
					1000	12 (15)	70	

5. Germylated sulfides

Table IV - Radioprotective activity of germylated sulfides

Cpd [Ref.]	R	LD ₅₀ (mg.kg ⁻¹)	Injected dose (mg.kg ⁻¹)	Irradiation Gy (t, min) ^a	Survival rate %	DRF ^b
54 [9]	CH ₃	1000	500	7.5 (15)	100	1.6
			500	7.5 (90)	50	
			500	9.5 (15)	80	
			125	7.5 (15)	10	
55 [10]	H	800	800	9.5 (15)	100	≥ 1.5
			800	11.5 (15)	90	

The syntheses of these compounds were realized by the action of NaSH on $\{[\text{HCl} \cdot \text{H}_2\text{NCH}_2\text{CH}(\text{R})\text{S}]_2\text{GeCl}_2$ ($\text{R} = \text{H}, \text{CH}_3$) [10] in anhydrous pyridine, Scheme 7.

Scheme 7

6. Diisoamylidithiagermocane

$(i\text{-C}_5\text{H}_{11})_2\text{Ge}(\text{SCH}_2\text{CH}_2)_2\text{S}$

This compound was obtained by the reaction of 2,2'-thiodiethanethiol with diisoamylgermyldichloride [3], in equimolar amount, in anhydrous tetrahydrofuran and in the presence of freshly distilled triethylamine, Scheme 8.

Scheme 8

Table V - Radioprotective activity of diisoamylidithiagermocane

Cpd [Ref.]	LD ₅₀ (mg.kg ⁻¹)	Injected dose (mg.kg ⁻¹)	Irradiation Gy (t, min) ^a	Survival rate %	DRF ^b
5 6 [6]	>1500	1000	7.5 (15)	60	1.3
		1000	7.5 (90)	50	
		250	7.5 (15)	60	

7- Di-*n*-hexylpyridinooxathiagermolane

This product was prepared by action of dichlorodi-*n*-hexylgermanium [3] on 2-thio-3-pyridinol in refluxing anhydrous tetrahydrofuran in the presence of freshly distilled triethylamine, Scheme 9.

Scheme 9

8. Pharmacology: evaluation of radioprotection

Male CD1 mice (Charles River, France), 25 g body weight, were used. The compounds were injected intraperitoneally 15, 90, 120 or 180 min before irradiation. The irradiation dose was LD₁₀₀/30 days for untreated mice (7.5, 7.75, 8, 8.25 or 8.3 Gy, according to the irradiation date) or a

2 Gy greater dose. When necessary, other irradiation doses (between 8.5-13.5 Gy were tested in order to evaluate the irradiation LD₅₀/30 days of protected mice. The injected dose of the compound was equal to one-half or one-eighth of the LD₅₀ value which had been determined previously. The radioprotective effect was evaluated by the Dose Reduction Factor (DRF), which is the ratio between the LD₅₀/30 days of treated mice and that of control mice (between 6.5 and 6.75 Gy, according to the date).

Table VI - Radioprotective activity of di-*n*-hexylpyridinoxathiagermolane

Cpd [Ref.]	LD ₅₀ (mg.kg ⁻¹)	Injected dose (mg.kg ⁻¹)	Irradiation Gy (t, min) ^a	Survival rate %	DRF ^b
5 7 [6]	800	400	7.5 (15)	40	1.3
		400	7.5 (90)	50	
		400	9.5 (15)	0	
		100	7.5 (15)	20	

Irradiation was applied using a cobalt-60 source at the dose rate of 0.3-0.4 Gy.min⁻¹ according to the date. During irradiation, animals were placed in a Plexiglass box with 30 cells in a homogeneous field, 28.5 x 28.5 cm in area. Dosimetry was checked with an ionisation chamber dosimeter. The different LD₅₀ values were determined by probit analysis.

9. Conclusion

The objective of this work was to incorporate potentially radioprotective organic groups in organometallic structures such as metallathiazolidines, metalladithioacetals, metallatranes and germathianes so as to decrease their toxicity and increase their radioprotective activity.

Tables I through VI summarize the radiation protection obtained in mice after intraperitoneal administration in miglyol solution of the organosilylated and organogermylated derivatives described. Generally, these organometallic compounds have a lower toxicity and a radioprotective activity equal to or greater than that of the starting organic derivatives (namely cysteamine [19], methylcysteamine [10] and *N*-substituted cysteamine or methylcysteamine [6, 9] and *N*-substituted naphthylmethylimidazoline [7, 12]). We have to underline that in some cases this great radioprotective activity was obtained with organosilylated or organogermylated derivatives injected in lower doses, expressed in mmol fraction, than those used for starting organic compounds.

The analysis of the toxicity and powerful radioprotective effect of all compounds presented in Table I shows that the metallathiazolidines have generally a good radioprotective activity and lower toxicity compared with starting organic derivatives.

Several compounds in this series (**1**, **2**, **6**, **9** and **10**) exhibit a dose reduction factor (DRF) of 1.5–1.75.

The LD₅₀ dose of each compound indicated that they were weakly toxic (500-1500 mg.kg⁻¹).

-Derivative **1** (DRF = 1.6; LD₅₀ = 800 mg.kg⁻¹) at one-half of LD₅₀ (the maximum tolerated dose, MTD) this product protects 93 % and 90 % of mice at 10 Gy 15 or 120 minutes after injection and 70 % survival at 12 Gy 15 minutes before irradiation. At one-eighth of the LD₅₀, there was a 16 % survival at a dose of 10 Gy.

-Derivative **2** (DRF = 1.5; LD₅₀ = 750 mg.kg⁻¹) at one-half of LD₅₀ 95 % and 89 % protection were obtained at doses of 10 and 12 Gy. At one-eighth of the LD₅₀, there was still 75 % survival at a dose of 10 Gy.

-Derivative **6** (DRF = 1.6; LD₅₀ = 600 mg.kg⁻¹) at one-half of LD₅₀ 100 % and 90 % survival were obtained at doses of 7.5 and 9.5 Gy and 50 % survival was observed at a dose of 7.5 Gy. At one-eighth of the LD₅₀, there was a 30 % survival at a dose of 7.5 Gy.

-Derivative **9** (DRF = 1.6; LD₅₀ = 600 mg.kg⁻¹) at one-half of LD₅₀ 100 %, 70 % and 40 % survival were obtained at doses of 9.5, 11.5 and 13.5 Gy. At one-eighth of the LD₅₀, there was a 50 % survival at a dose of 9.5 Gy.

-Derivative **10** (DRF = 1.75; LD₅₀ = 500 mg.kg⁻¹) at one-half of LD₅₀ 80 %, 70 % and 70 % survival were obtained at doses of 9.5, 11.5 and 13.5 Gy.

The analysis of the results reported in Table II shows that the siladithioacetals and germadithioacetals **31**, **36**, **38**, **39**, **42**, **45** and **47** have an important radioprotective activity (DRF between 1.5-1.7).

-Derivative **31** (DRF = 1.5; LD₅₀ = 100 mg.kg⁻¹) at one-half of LD₅₀ 100 % protection was observed at a dose of 7.75 Gy. At one-eighth of the LD₅₀, there was still 50 % survival at a dose of 7.75 Gy.

-Derivative **36** (DRF > 1.6; LD₅₀ = 600 mg.kg⁻¹) at one-half of LD₅₀ 100 % and 95 % survival were obtained at doses of 10 and 12 Gy.

-Derivative **38** (DRF > 1.5; LD₅₀ = 600 mg.kg⁻¹) at one-half of LD₅₀ 90 % survival was observed at doses of 9.5 or 11.5 Gy. At one-eighth of the LD₅₀, there was 45 % survival at a dose of 9.5 Gy.

-Derivative **39** (DRF = 1.5; LD₅₀ = 800 mg.kg⁻¹) at one-half of LD₅₀ 85 %, 70 % and 60 % survival were obtained at doses of 9.5 and 11.5 Gy. At one-eighth of the LD₅₀, there was 33 % survival at a dose of 9.5 Gy.

-Derivative **42** (DRF = 1.5; LD₅₀ = 800 mg.kg⁻¹) at one-half of LD₅₀ 100 % and 80 % survival were observed at a dose of 7.5 Gy. At one-eighth of the LD₅₀, there was still 50 % survival at a dose of 7.5 Gy.

-Derivative **45** (DRF = 1.7; LD₅₀ = 80 mg.kg⁻¹) at LD₅₀/1.6 100 % and 90 % survival were observed at a dose of 7.75 Gy. 70 % and 30 % survival were also obtained at doses of 9.75 and 11.75 Gy. At LD₅₀/6.4, there was still 80 % survival at dose of 7.75 Gy.

-Derivative **47** (DRF > 1.6; LD₅₀ = 800 mg.kg⁻¹) the administration of this product at of LD₅₀ protects 100 % and 70 % of mice at a dose of 7.5 Gy and 90 % survival was obtained at a dose of 9.5 Gy.

At last, it is important to note the significant radioprotective activity of organogermylated sulfides **54** and **55** (DRF = 1.5-1.6).

-Derivative **54** (DRF = 1.6; LD₅₀ = 1000 mg.kg⁻¹) at the MTD this product protects 100 % and 80 % of mice at doses of 7.5 and 9.5 Gy, it also protects 50 % of mice at a dose of 7.5 Gy.

-Derivative **55** (DRF (1.5; LD₅₀ = 800 mg.kg⁻¹) at of LD₅₀ 100 % and 90 % protection were observed at doses of 9.5 and 11.5 Gy.

In short, several organosilylated and organogermylated compounds present a good radioprotective activity compared with the starting organic derivatives due to the presence in these molecules of organometallic groups which increase the hydrosolubility and by the presence of organic ligands which increase the liposolubility and biological activity of these molecules, thereby favouring their passage through the cellular membranes.

The results presented in this paper confirm the positive contribution of germanium and silicon in this field in agreement with previous works [1, 6-12, 20-22] and the interesting biological activity of organosilicon and organogermanium compounds in different fields [23-44].

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