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Radioprotective activity of metalladithioacetals derived from *N*-substituted naphthylethylimidazoline

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A number of organosilicon and organogermanium derivatives of *N*-substituted 2-[1-(1-naphthyl)-ethyl]-2-imidazoline have been reported and the toxicity of these compounds has been determined in mice. In this paper we report the evaluation of the radioprotective activity of new sila- and germa-dithioacetals derived from *N*-substituted 2-[1-(1-naphthyl)ethyl]-2-imidazoline. Copyright © 2003 John Wiley & Sons, Ltd.

KEYWORDS: naphthylethylimidazoline; organosilicon compounds; organogermanium compounds; toxicity; radioprotective activity

INTRODUCTION

It is well known that imidazole or imidazoline rings containing compounds induce a large variety of biological effects. For example, medetomidine[1] possesses selective and potent α_2-adrenergic properties. α_2-Adrenergic stimulation is known to mediate biological actions, including hypertension, sedation, antianxiety, analgesia, hypothermia, decreased salivary secretions and mydriasis.[2] The efficiency of this drug is dependent on the naphthalene ring substitution and on the presence of a methyl group attached at the benzylic position.[3]

Some imidazoline compounds, like naphthylmethylimidazoline, have shown a good radioprotective activity in mice. Our group has already demonstrated that the inclusion of some organic radioprotectors into organometallic structures, like sila- and germa-dithioacetals or -thiazolidines, leads to a notable decrease of the toxicity and an increase of the radioprotection.[4–14]

However, the radioprotective action mechanism of naphthylmethylimidazoline remains unclear. Some recent preliminary investigations seem to indicate that, at least *in vitro*, it has no effect on lipidic peroxidation. Perhaps it acts through its vasoconstrictive effects, which can lower the oxygen supply in tissue and hence decrease the radiation-induced lesions.

Another possible explanation of the excellent activity of this first non-sulfur radioprotective compound is its metabolism *in vivo* that forms anti-inflammatory products of the 1-naphthylacetic acid type.[15]

Our objective was to investigate a new series of organosilicon and organogermanium compounds derived from *N*-substituted 2-[1-(1-naphthyl)ethyl]-2-imidazoline. The syntheses, characterization and toxicity in mice of all these derivatives have been the subject of a preliminary report.[16]

EXPERIMENTAL

Evaluation of the radioprotection

Three-month-old male Swiss mice (Janvier, France), 25 g body weight, were used. The radioprotective effect of compounds could be evaluated by determining the dose reduction factor (DRF), defined as the ratio of 50% lethal-dose irradiation on 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 ten mice receiving an intraperitoneal (i.p.) injection of the test compound with a dose equal to one-half of its LD_{50} toxicology 15 min before whole-body irradiation delivered with a dose equal to the LD_{100}/30 days of control mice

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(8.4 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},[17,18] the dose range being determinated 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 and lithium fluoride thermoluminescent dosimeters.

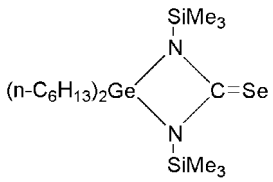
Each irradiation session included three groups of five mice irradiated with an 8.4 Gy dose (according to the date) after an i.p. injection of the solvent alone. A 100% lethality was observed for these lots with a mean survival time equal to 13 days. Furthermore, a group of five unirradiated mice received a test compound with a dose equal to one-half of its LD_{50} toxicology 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.

Syntheses and characterization

The syntheses and the characterization of compounds **1–15** have already been reported.[16]

RESULTS AND DISCUSSION

The radiopharmacological activities of the metalladithioacetals $^{1}R^{2}RM[SCH(^{3}R)CH_2—NEI]_2$ {[NEI = 2-[1-(1-naphthyl)-ethyl]-2-imidazolyl; $^{1}R = {}^{2}R = n\text{-}C_6H_{13}$, $^{3}R = CH_3$, M = Ge(**1**), Si (**7**); $^{1}R = {}^{2}R = n\text{-}C_6H_{13}$, ^{3}R = H, M = Ge(**2**), Si (**8**); $^{1}R = {}^{2}R = i\text{-}C_5H_{11}$, $^{3}R = CH_3$, M = Ge(**3**), Si (**9**); $^{1}R = {}^{2}R = i\text{-}C_5H_{11}$, ^{3}R = H, M = Ge(**4**), Si (**10**); $^{1}R = p\text{-}CH_3—C_6H_4$, $^{2}R = CH_3$, $^{3}R = CH_3$, M = Ge (**5**), Si (**11**); $^{1}R = p\text{-}CH_3—C_6H_4$, $^{2}R = CH_3$, ^{3}R = H, M = Ge (**6**), Si (**12**)}, selenodiazadihexylgermetane (**13**)



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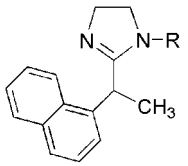
naphthylethylimidazoline derivatives (**14–16**)

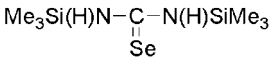


R = H **(14)**
-CH_2CH_2SH **(15)**
-$CH_2CH(CH_3)SH$ **(16)**

Table 1. Survival rate of protected animals 30 days after an 8.4 Gy or a 10.4 Gy irradiation

Compound	Survival rate at 8.4 Gy (%)	Survival rate at 10.4 Gy (%)
1	10	0
2	10	0
3	10	0
4	20	0
5	10	0
6	0	0
7	10	0
8	30	0
9	20	0
10	0	0
11	0	0
12	10	0
13	10	0
14	10	0
15	30	0
16	0	0
17	10	0

and 1,3-bis(trimethylsilyl)selenourea (**17**)



(17)

are reported in Table 1. None of these derivatives has shown a radioprotective activity at 10.4 Gy (LD_{100}/30 days + 2 Gy). Also, compounds **6**, **10**, **11** and **16** present no protection at an 8.4 Gy irradiation dose (LD_{100}/30 days). In fact, on the survival rate histograms (Fig. 1), the 8.4 Gy irradiation dose is superior to the LD_{100}/30 days of unprotected control mice. The real LD_{100} on 30 days seems to be between 8 and 8.15 Gy. This means that the results presented in this paper are under estimated.

A good radioprotection (survival rate of 30% at 8.4 Gy) has been obtained with compounds **8** and **15**, and a quite good survival rate (20%) has been observed with the molecules **4** and **9**. Nine derivatives (compounds **1–3**, **5**, **7**, **12–14** and **17**) offer a weak radioprotective activity (survival rate of 10%).

The comparison between the organic precursor **16**, which has shown zero activity, and its organometallic prodrugs **1**, **3**, **5**, **7** and **9** (survival rate >10%) explain the positive contribution of the organometallic ligands in the radioprotection.

Similarly, a comparison between the organometallic compound **8** and the starting organic derivative **15** shows that the presence of organosilylated or organogermylated groups increases the activity of the organic drug. In fact these organometallic ligands increase the hydrosolubility,

the lipophilicity and the efficiency by favouring their passage through the cellular membranes. These derivatives are generally less toxic than the basic organic compounds. Derivative **8** showed the same radioprotection as **15**, in spite of a lower injected dosage expressed in millimole fraction. Even if organosilylated and organogermylated derivatives show approximately the same toxicity, the silylated derivatives reported in this paper present a

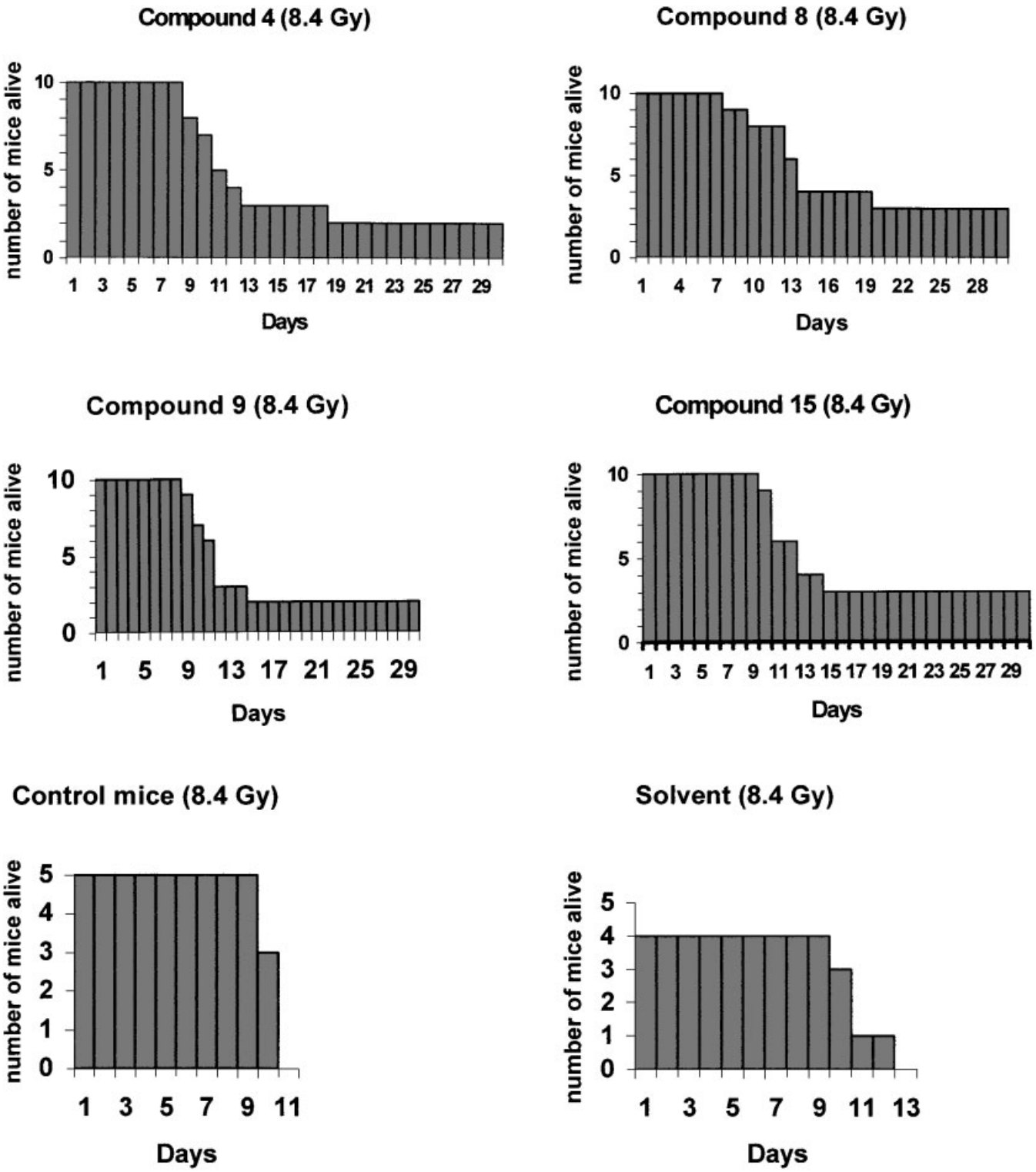


Figure 1. Radioprotective evaluation of compounds **4, 8, 9** and **15** at 8.4 Gy.

greater radioprotective activity than that of the germylated homologues.

Male Swiss mice were injected i.p. with solutions of the test compound (**4, 8, 9** and **15**) in miglyol at a dose equal to one-half of their LD_{50} toxicology 15 min before γ-irradiation at 8.4 Gy from ^{60}Co. The radioprotective evaluation was determined 30 days after irradiation (LD_{100}/30 days for control mice).

CONCLUSION

The results presented in this paper confirm the positive contribution of germanium and silicon in the radioprotection field in agreement with previous work[4–14] and the interesting biological activity of organogermanium and organosilicon compounds.[19–24] We also observed that organometallated groups decrease the toxicity of the basic organic molecules to which they are attached.

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