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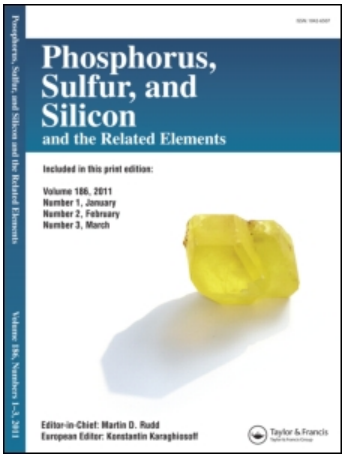


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# Synthesis and Radioprotective Effects of New Phosphorothioates Derived From Naphthylmethylimidazoline and Naphthylethylimidazoline

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# Synthesis and Radioprotective Effects of New Phosphorothioates Derived From Naphthylmethylimidazoline and Naphthylethylimidazoline

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*A number of 2-(1-naphthylmethyl)-2-imidazoline, 2-[1-(1-naphthylethyl]-2-imidazoline, phosphorothioates, and related compounds were prepared for an evaluation as radioprotective agents against γ-rays. In this work, we report the synthesis and evaluation in vivo (radioprotective efficacy and toxicity) of new phosphorothioates. All these derivatives have shown a dose reduction factor between 1.5 and 1.9, which traduces their excellent radioprotective activity. These compounds should present an interest in chimio- and radiotherapy treatments.*

**Keywords** Naphthylmethylimidazoline; naphthylethylimidazoline; phosphorothioates; Radioprotection; WR-2721

## INTRODUCTION

Chemical radioprotection has been a military challenge for the protection of soldiers against exposure to radiations from nuclear devices. For

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the moment, none of the chemicals presenting radioprotective properties offer a sufficient protection to prevent damages caused by a nuclear blast because of the important doses of radiation generated by the atomic blast. On the other hand, these compounds, which have a Dose Reduction Factor (DRF) that is superior to 1.5, present sufficient protection for the application in several other fields (protection of normal tissues during radiotherapy, prevention to exposure to space and radioactive wastes). A large variety of chemical radioprotector agents have been developed in the past for the differential protection of normal tissues versus neoplastic tissues during radiotherapy and also for the protection of military and the civilian personnel from exposure to radiation from a variety of environmental factors, such as nuclear devices and accidental exposure. Several compounds containing phosphorus-sulfur bonds, such as phosphorothioates, have been identified as potential radioprotective agents.[1,2]

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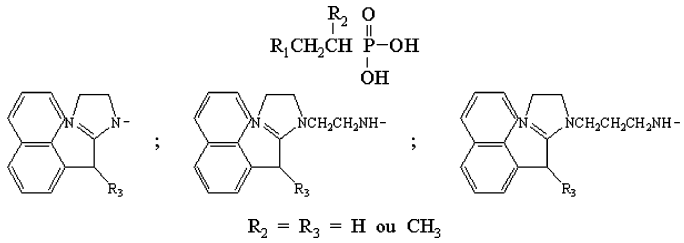
Metallathiazolidines, metalladithioacetals, and phosphorothioates have been tested as potential radioprotector agents, and some of them presented a DRF between 1.5 and 2.[3–7] Some phosphorothioates presented a differential and preferential protection of normal versus tumoral cells.

The WR-2721 ($H_2NCH_2CH_2CH_2NHCH_2CH_2SPO_3X_2$ with X = Li, H) is one of the best currently known radioprotectors. It was the subject of many studies because of its very high radioprotective effect.[8–13] It is currently used for a clinical use (Amifostin, Ethyol®) in spite of its many side effects (vomiting in 25% of the cases, hypotension, etc.). This compound preferentially protects the normal cells because of its weak penetration in the tumor cells. Moreover, the association of WR-2721 with naphthylmethylimidazoline produces a synergy of action for injected amounts to which no toxicity is observed for the two components.[14]

In order to corroborate this idea, we have described the synthesis and radioprotection studies of new phosphorothioate derived from *N*-substituted naphthylmethylimidazoline and naphthylethylimidazoline.

We will be able to show that there is a synergy of action when the coupling is made in a chemical way. We will also compare the phosphorothioates synthesized with their aminothiols metabolites. The structure of these phosphorous derivatives is as depicted in Scheme 1.

The addition of a phosphorothioate moiety to the organic structures makes it possible to obtain, for these molecules, similar properties to those observed with the incorporation of a silicon or germanium atom in the case of organometallic compounds (metallathiazolidines or metalladithioacetals) developed by our laboratory,[15–20] like




**SCHEME 1** Structures of the phosphorus radioprotectors.

- The delayed or prolonged in vivo release of one or more organic substances having radioprotective properties (aminothiols) and
- a fundamental modification of the chemical or biological properties.

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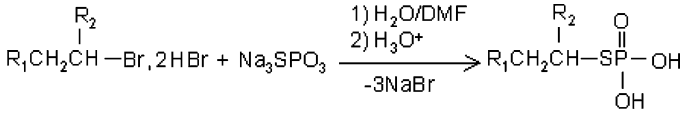
The introduction of a hydrosoluble phosphorus group increases the hydrosolubility and the activity of these molecules by supporting their transport *in vivo*. Moreover, the presence of strongly lipophilic naphthalenic groups supports cellular membranes crossing.

## RESULTS

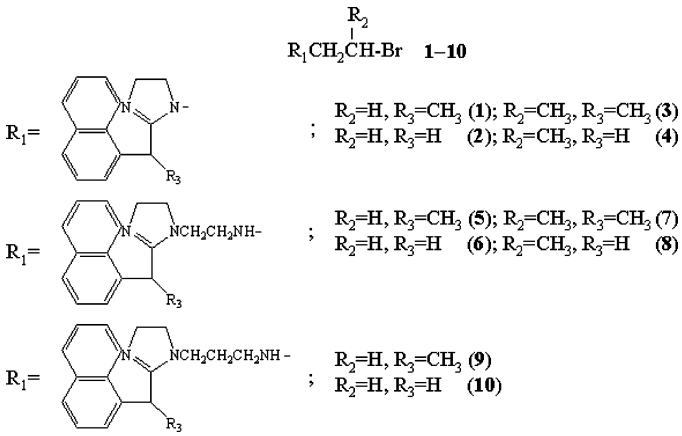
The synthesis of phosphorothioates is shown in Scheme 2. These compounds were obtained by the Piper[9,10] method. Synthesis was achieved by reacting one equivalent of a phosphorylating agent ($Na_3SPO_3$) with one equivalent of *N*-substituted bromide hydrobromide or dihydrobromide derived from naphthylmethylimidazoline or naphthylethylimidazoline in a mixture of water and dimethylformamide at 30°C (Scheme 3). Finally, the reaction mixture was slowly acidified by 3 mL of HBr-$H_2O$ (1 M) solution.

The structures of final compounds (**1–20**) were confirmed by $^1H$,$^{13}C$,$^{31}P$ NMR, mass spectra, and elemental analysis (Scheme 4).

All these compounds showed a good radioprotective effect.[20] We decided to calculate the DRF only for three compounds (**16**, **17**, and **20**) that were presenting a low toxicity ($LD_{50} \geq 0.50$ mmol.kg$^{-1}$) and that had good preliminary activity (at least 100% survival for an 8.1 Gy




**SCHEME 2** The synthesis of phosphorothioates.




**SCHEME 3** Structures of hydrobromide organic compounds (**1–10**).

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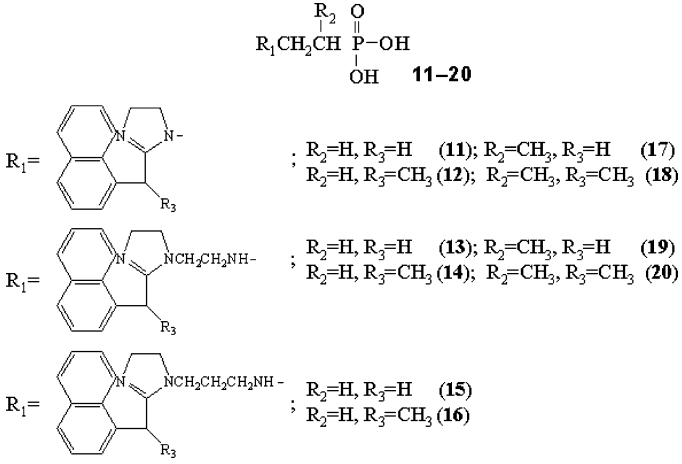
irradiation and 70% for 10.1 Gy) in order to limit the number of animals used. The DRF is the quantitative measurement of the radioprotective power of a substance. It is defined as the ratio of the irradiation doses leading to the death of 50% of the animals, respectively, for protected animals and unprotected ones:

$$\mathrm{DRF} = \frac{\text{irradiation } \mathrm{LD}_{50/30\text{ days}} \text{ (protected animals)}}{\text{irradiation } \mathrm{LD}_{51/30\text{ days}} \text{ (non protected animals)}}.$$




**SCHEME 4** Structures of phosphorus derivatives obtained (**11–20**).

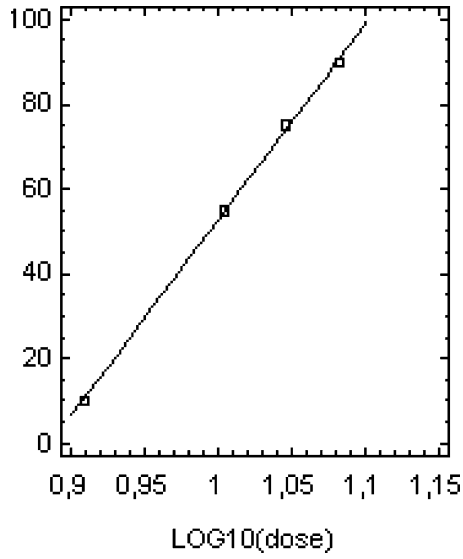



**FIGURE 1** Mortality = f[log(Dose)] for compound **20**.

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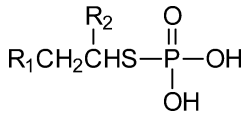
In order to determine the $LD_{50}$ of irradiation, we had to draw the straight line of mortality as a function of the decimal logarithm of the dose (Figure 1). The $LD_{50}$ were determined using STATGRAPHICS Plus 5.1 software and are reported in Table I.

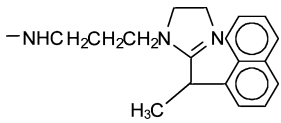
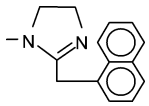
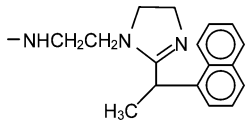
These three compounds have very high DRF (between 1.6 and 1.8). The most active of these three seems to be compound **17**, which is a naphthylmethylimidazoline derivative. The two other compounds have nearly the same DRF.

These three compounds were presenting the same preliminary activity[18] (100% survival for 8.1 Gy irradiation and 70% for 10.1 Gy) but their DRF were different. This traduces the difficulty to extrapolate the DRF of the other phosphorothioates from these three compounds. We can at least try to give a lower and upper limit for their activity:

- $1.5 < DRF < 1.85$ for compounds **11** ($LD_{50/30\ days}$:168 mg/kg), **12** ($LD_{50/30\ days}$:184 mg/kg), **15** ($LD_{50/30\ days}$:150 mg/kg), **16** ($LD_{50/30\ days}$ : 260 mg/kg), **17** ($LD_{50/30\ days}$ : 184 mg/kg), and **20** ($LD_{50/30\ days}$ : 360 mg/kg) because their survival rate, in preliminary tests, were close (100% for 8.1 Gy and $\geq$ 50% at 10.1 Gy);
- $1.3 < DRF < 1.5$ for molecules **14** ($LD_{50/30}$ : 400 mg/kg) and **19** ($LD_{50/30}$ : 150 mg/kg) (80–90% at 8.1 Gy and 70–60% at 10.1 Gy);

**TABLE I The Determination of the DRF of Compounds 16, 17, and 20**



| Compound | $R_1$ | $R_2$ | Correlation Coefficient | Irradiation $LD_{50}$(Gy) | DRF |
|---|---|---|---|---|---|
| Controls | — | — | 0.96996 | $6.22 \pm 0.14$ | — |
| **16** |  | H | 0.98231 | $10.10 \pm 0.25$ | $1.62 \pm 0.08$ |
| **17** |  | $CH_3$ | 0.99995 | $11.44 \pm 0.03$ | $1.84 \pm 0.05$ |
| **20** |  | $CH_3$ | 0.99959 | $9.90 \pm 0.04$ | $1.60 \pm 0.04$ |

- phosphorothioates **13** ($LD_{50/30}$:280 mg/kg) and **18** ($LD_{50/30}$:260 mg/kg) only present a low radioprotective activity.

## DISCUSSION

The aim of this work was to establish a structure-radioprotective activity relation from a limited number of molecules. This analysis highlights the notable radioprotective activity brought by the synthesized phosphorylated compounds. The study of the influence of the various substituents emphasized that the naphthylethylimidazoline derivatives are less toxic and more active than their naphthylmethylimidazoline counterparts. The presence of a methyl group in the $\alpha$ position of the sulphur does not have a systematic influence on toxicity or the radioprotective effect.

The substitution of a proton on the $CH_2$ bridge of the naphthylmethylimidazoline, by an alkyl group, appears thus more favorable in the improvement of the radioprotective properties than that of a proton in the $\alpha$ position of the sulphur. Phosphorothioates have toxicity close to that of the parent aminothiols but, on the other hand, have a higher radioprotective activity. This shows the favorable contribution of phosphorus in the establishment of radioprotective properties.

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This observation highlights the possibility of potentiation of the basic organic substances in the organism of the mouse, thanks to the hydrosoluble phosphorated substituents. Moreover, we found a synergy of action, which appeared also when WR-2721 and naphthylmethylimidazoline were injected simultaneously,[11] by coupling these two in a chemical way.

Among the 10 synthesized compounds and in a preoccupation of saving animals, we carried out the determination of the dose reduction factor only on three derivatives. Compound **17** presents a dose reduction factor of about 1.85 and the phosphorothioates **16** and **20** present a dose reduction factor of approximately 1.60, and we can try to extrapolate the results of the 7 others phosphorated derivatives. Among the 10 molecules, 6 compounds are likely to have a dose reduction factor superior to 1.5, and the phosphorothioate **12** could present a dose reduction factor superior to 1.85 because it offered the best protection during the preliminary tests.

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## EXPERIMENTAL

All experiments were conducted with strict adherence to the ethical guidelines and approved by a regional committee of ethics in animal experimentation (Midi-Pyrenees, France).

### General Procedures

All manipulations were performed under an inert atmosphere of argon using standard Schlenck, glove box, and high-vacuum-line techniques. All solvents used were freshly dried using standard techniques, and all glassware was oven dried.

$^{1}$H NMR spectra were recorded on a Bruker AC 80 spectrometer operating at 80.13 MHz (chemical shifts ppm relative to internal $Me_4Si$), and $^{13}$C NMR spectra were recorded on an AC 200 spectrometer (50.32 MHz). The multiplicity of the $^{13}$C-NMR signals was determined by the APT technique. Mass spectra under electron impact conditions at 70 and 30 eV were obtained on Hewlett-Packard 5989 and Nermag R10-10H spectrometers. IR and UV spectra were recorded on Perkin-Elmer 1600 FTIR and Lambda-17 spectrophotometers. Melting points were taken uncorrected on a Leitz Biomed hot-plate microscope apparatus or in capillary tubes on a digital electrothermal apparatus. Elemental analyses (C, H, and N) were performed at the Laboratoire de Microanalyse de l'Ecole Nationale Supérieure de Chimie, Toulouse, France.

The general synthesis of compounds (**1–20**) is described below:

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### *Hydrobromide Organic Derivatives 1–10*

A stirred solution of 23.78 mmol of imidazoline in 10 mL of the corresponding bromoalcohol (2-bromoethanol, 2-bromo-1-propanol or 2-(3-bromopropylamino)ethanol) in the presence of 3.12 g (30.80 mmol) of triethylamine was refluxed for 5 h. Hundred mL of a mixture of THF/pentane (3:1) was added, and the precipitate formed was eliminated by filtration. The solvents are removed in vacuo and 20 mL of dry THF were added. After the dropwise addition of 6.36 g (78.48 mmol) of HBr (45% in $CH_3C(O)OH$), the mixture was refluxed for 1 h. After cooling, the solution was concentrated under reduced pressure ($10^{-2}$ mm.Hg) to lead to compounds 1–10.

### *Phosphorothioates Compounds 11–20*

To a suspension of 1.13 g (6.30 mmol) of $Na_3SPO_3$ in 6.5 mL of water, (1 mL/mmol) a solution of 6.30 mmol of *N*-substituted imidazoline hydrobromide was added dropwise with stirring. After total solubilization, 3.25 mL of DMF (half of the volume of water) was added at $-10^{\circ}$C. The mixture was maintained at 30°C during 12 h, and after that time, the reactionnel mixture was slowly acidified by 3 mL of HBr-$H_2O$ (1 M) solution. The solvents were removed under reduced pressure, and the residue was stirred in 20 mL of methanol. The insoluble compounds were removed by filtration. The concentration *in vacuo* ($10^{-2}$ mm.Hg) of the filtrate during 12 h lead to the corresponding phosphorothioates 11–20.

The spectroscopic and physicochemical data of all these compounds (**1–20**) are reported in the following sections.

### *N-(2-Bromoethyl)-2-[1-(1-naphthyl)ethyl]-2-imidazoline*

$^1$H-NMR ($CDCl_3$; $\delta$, ppm): 1.58 (d, 3H, J = 7.0 Hz, C$\underline{H}_3$CH); 2.60–4.63 (m, 9H, $CH_2Br$, $CH_2N$ and C$\underline{H}$-$C_{10}H_7$); 7.11–7.59 (m, 4H, $C_{10}\underline{H}_7$); 7.62–8.11 (m, 3H, $C_{10}\underline{H}_7$). $^{13}$C-NMR ($CDCl_3$; $\delta$, ppm): 21.45 ($\underline{C}H_3CH$); 32.26 ($\underline{C}H_2Br$); 40.84 ($\underline{C}H$-$C_{10}H_7$); 43.14 ($\underline{C}H_2N$); 46.21 ($\underline{C}H_2N$); 49.44 ($\underline{C}H_2N$); 123.43 ($\underline{C}H_{arom.}$); 124.02 ($\underline{C}H_{arom.}$); 125.75 ($\underline{C}H_{arom.}$); 126.01 ($\underline{C}H_{arom.}$); 126.45 ($\underline{C}H_{arom.}$); 126.96 ($\underline{C}H_{arom.}$); 128.65 ($\underline{C}H_{arom.}$); 131.85 ($C_{quat}$); 133.12 ($C_{quat}$); 133.81 ($C_{quat}$); 167.25 (N–$\underline{C}$=N). Mass spectrum: m/z = 329 $[M-1]^+$. Elemental analysis ($C_{17}H_{19}N_2Br$): Calcd. %: C, 61.64; H, 5.78; N, 8.46. Found %: C, 61.61; H, 5.80; N, 8.46. Yield %: 44.

### *N-(2-Bromoethyl)-2-[1-(naphthyl)methyl]-2-imidazoline*

$^1$H-NMR ($CDCl_3$; $\delta$, ppm): 2.60–4.51 (m, 8H, $CH_2Br$ and $CH_2N$); 4.04 (s, 2H, C$\underline{H}_2$-$C_{10}H_7$); 7.24–7.61 (m, 4H, $C_{10}\underline{H}_7$); 7.65–8.09 (m, 3H, $C_{10}\underline{H}_7$). $^{13}$C-NMR ($CDCl_3$; $\delta$, ppm): 32.26 ($\underline{C}H_2Br$); 38.84 ($\underline{C}H_2 - C_{10}H_7$);

40.86 ($\underline{C}H_2N$); 46.81 ($\underline{C}H_2N$); 49.13 ($\underline{C}H_2N$); 123.18 ($\underline{C}H_{arom.}$); 124.36 ($\underline{C}H_{arom.}$); 125.19 ($\underline{C}H_{arom.}$); 125.86 ($\underline{C}H_{arom.}$); 126.37 ($\underline{C}H_{arom.}$); 126.68 ($\underline{C}H_{arom.}$); 128.31 ($\underline{C}H_{arom.}$); 131.12 ($C_{quat}$); 133.17 ($C_{quat}$); 133.86 ($C_{quat}$); 167.38 (N—$\underline{C}$=N). Mass spectrum: m/z = 315 $[M - 1]^+$. Elemental analysis ($C_{16}H_{17}N_2Br$): Calcd. %: C, 60.58; H, 5.40; N, 8.83. Found %: C, 60.56; H, 5.51; N, 8.86. Yield %: 45.

### *N-(2-Bromopropyl)-2-[1-(1-naphthyl)ethyl]-2-imidazoline*

$^1$H-NMR ($CDCl_3$; $\delta$, ppm): 1.38 (d, 3H, J = 5.6 Hz, C$\underline{H}_3$CH); 1.60 (d, 3H, J = 7.1 Hz, C$\underline{H}_3$CH); 2.35–4.52 (m, 8H, CHBr and $CH_2N$ and C$\underline{H}$-$C_{10}H_7$); 7.22–7.65 (m, 4H, $C_{10}\underline{H}_7$); 7.68–8.17 (m, 3H, $C_{10}\underline{H}_7$). $^{13}$C-NMR ($CDCl_3$; $\delta$, ppm): 21.45 ($\underline{C}H_3CH$); 22.35 ($\underline{C}H_3CH$); 32.64 ($\underline{C}HBr$); 39.84 ($\underline{C}H$—$C_{10}H_7$); 43.80 ($\underline{C}H_2N$); 46.14 ($\underline{C}H_2N$); 48.36 ($\underline{C}H_2N$); 123.19 ($\underline{C}H_{arom.}$); 124.01 ($\underline{C}H_{arom.}$); 125.35 ($\underline{C}H_{arom.}$); 125.55 ($\underline{C}H_{arom.}$); 126.02 ($\underline{C}H_{arom.}$); 126.55 ($\underline{C}H_{arom.}$); 128.55 ($\underline{C}H_{arom.}$); 131.24 ($C_{quat}$); 133.75 ($C_{quat}$); 133.99 ($C_{quat}$); 167.74 (N—$\underline{C}$=N). Mass spectrum: m/z = 343 $[M - 1]^+$. Elemental analysis ($C_{18}H_{21}N_2Br$): Calcd. %: C, 62.61; H, 6.13; N, 8.11. Found %: C, 62.56; H, 6.15; N, 8.13. Yield %: 30.

### *1-(2-Bromopropyl)-2-[1-(naphthyl)methyl]-2-imidazoline*

$^1$H-NMR ($CDCl_3$; $\delta$, ppm): 1.36 (d, 3H, J = 5.6 Hz, C$\underline{H}_3$CH); 2.30–4.57 (m, 9H, CHBr, $CH_2N$ and $C\underline{H}_2$—$C_{10}H_7$); 7.06–7.60 (m, 4H, $C_{10}\underline{H}_7$); 7.64–8.12 (m, 3H, $C_{10}\underline{H}_7$). $^{13}$C-NMR ($CDCl_3$; $\delta$, ppm): 22.41 ($\underline{C}H_3CH$); 32.64 ($\underline{C}HBr$); 40.17 ($\underline{C}H_2$-$C_{10}H_7$); 43.64 ($\underline{C}H_2N$); 46.08 ($\underline{C}H_2N$); 48.11 ($\underline{C}H_2N$); 123.36 ($\underline{C}H_{arom.}$); 124.45 ($\underline{C}H_{arom.}$); 125.04 ($\underline{C}H_{arom.}$); 125.75 ($\underline{C}H_{arom.}$); 126.25 ($\underline{C}H_{arom.}$); 126.86 ($\underline{C}H_{arom.}$); 128.31 ($\underline{C}H_{arom.}$); 131.44 ($C_{quat}$); 133.44 ($C_{quat}$); 133.86 ($C_{quat}$); 167.14 (N—$\underline{C}$=N). Mass spectrum: m/z = 329 $[M-1]^+$. Elemental analysis ($C_{17}H_{19}N_2Br$): Calcd. %: C, 61.64; H, 5.78; N, 8.46. Found %: C, 61.66; H, 5.82; N, 8.48. Yield %: 40.

### *1-[N-(2-Bromoethyl)-2-aminoethyl]-2-[1-(1-naphthyl)ethyl]-2-imidazoline*

$^1$H-NMR ($CDCl_3$; $\delta$, ppm): 1.61 (d, 3H, J = 7.0 Hz, C$\underline{H}_3$CH); 2.31–4.54 (m, 14H, $CH_2Br$, $CH_2N$ and C$\underline{H}$-$C_{10}H_7$); 7.01–7.47 (m, 4H, $C_{10}\underline{H}_7$); 7.53–8.03 (m, 3H, $C_{10}\underline{H}_7$). $^{13}$C-NMR ($CDCl_3$; $\delta$, ppm): 22.01 ($\underline{C}H_3CH$); 31.88 ($\underline{C}H_2Br$); 39.98 ($\underline{C}H$-$C_{10}H_7$); 43.35 ($\underline{C}H_2N$); 44.64 ($\underline{C}H_2N$); 45.18 ($\underline{C}H_2N$); 46.14 ($\underline{C}H_2N$); 47.23 ($\underline{C}H_2N$); 123.49 ($\underline{C}H_{arom.}$); 124.54 ($\underline{C}H_{arom.}$); 125.18 ($\underline{C}H_{arom.}$); 126.31 ($\underline{C}H_{arom.}$); 126.97 ($\underline{C}H_{arom.}$); 127.35 ($\underline{C}H_{arom.}$); 128.64 ($\underline{C}H_{arom.}$); 131.27 ($C_{quat}$); 133.35 ($C_{quat}$); 133.64 ($C_{quat}$); 168.69 (N-$\underline{C}$=N). Mass spectrum: m/z = 372 $[M - 1]^+$. Elemental analysis ($C_{19}H_{24}N_3Br$): Calcd. %: C, 60.96; H, 6.46; N, 11.22. Found %: C, 60.99; H, 6.51; N, 11.25. Yield %: 44.

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### 1-[N-(2-Bromoethyl)-2-aminoethyl]-2-(1-naphthylmethyl)-2-imidazoline

$^1$H-NMR ($CDCl_3$; $\delta$, ppm): 2.36–4.59 (m, 13H, $CH_2Br$ and $CH_2N$); 4.11 (s, 2H, $C\underline{H}_2$-$C_{10}H_7$); 7.12–7.67 (m, 4H, $C_{10}\underline{H}_7$); 7.70–8.13 (m, 3H, $C_{10}\underline{H}_7$). $^{13}$C-NMR ($CDCl_3$; $\delta$, ppm): 32.16 ($\underline{C}H_2Br$); 39.54 ($\underline{C}H_2$-$C_{10}H_7$); 42.86 ($\underline{C}H_2N$); 43.31 ($\underline{C}H_2N$); 45.54 ($\underline{C}H_2N$); 46.41 ($\underline{C}H_2N$); 47.13 ($\underline{C}H_2N$); 123.09 ($\underline{C}H_{arom.}$); 124.54 ($\underline{C}H_{arom.}$); 125.01 ($\underline{C}H_{arom.}$); 125.71 ($\underline{C}H_{arom.}$); 126.68 ($\underline{C}H_{arom.}$); 126.97 ($\underline{C}H_{arom.}$); 128.64 ($\underline{C}H_{arom.}$); 131.45 ($C_{quat}$); 133.29 ($C_{quat}$); 133.74 ($C_{quat}$); 167.98 (N–$\underline{C}$=N). Mass spectrum: m/z = 358 $[M - 1]^+$. Elemental analysis ($C_{18}H_{22}N_3Br$): Calcd. %: C, 60.00; H, 6.15; N, 11.66. Found %: C, 60.06; H, 6.20; N, 11.65. Yield %: 45.

### 1-[N-(2-Bromopropyl)-2-aminoethyl]-2-[1-(1-naphthyl)ethyl]-2-imidazoline

$^1$H-NMR ($CDCl_3$; $\delta$, ppm): 1.42 (d, 3H, J = 5.6 Hz, $C\underline{H}_3CH$); 1.56 (d, 3H, J = 7.1 Hz, $C\underline{H}_3CH$); 2.17–4.63 (m, 13H, CHBr, $CH_2N$ and $C\underline{H}$-$C_{10}H_7$); 7.11–7.59 (m, 4H, $C_{10}\underline{H}_7$); 7.63–8.14 (m, 3H, $C_{10}\underline{H}_7$). $^{13}$C-NMR ($CDCl_3$; $\delta$, ppm): 22.56 ($\underline{C}H_3CH$); 22.87 ($\underline{C}H_3CH$); 33.14 ($\underline{C}HBr$); 39.65 ($\underline{C}H$-$C_{10}H_7$); 43.80 ($\underline{C}H_2N$); 44.48 ($\underline{C}H_2N$); 45.51 ($\underline{C}H_2N$); 46.19 ($\underline{C}H_2N$); 47.17 ($\underline{C}H_2N$); 123.26 ($\underline{C}H_{arom.}$); 124.54 ($\underline{C}H_{arom.}$); 125.14 ($\underline{C}H_{arom.}$); 125.74 ($\underline{C}H_{arom.}$); 126.62 ($\underline{C}H_{arom.}$); 126.97 ($\underline{C}H_{arom.}$); 128.61 ($\underline{C}H_{arom.}$); 131.01 ($C_{quat}$); 133.56 ($C_{quat}$); 134.77 ($C_{quat}$); 168.13 (N-$\underline{C}$=N). Mass spectrum: m/z = 386 $[M - 1]^+$. Elemental analysis ($C_{20}H_{26}N_3Br$): Calcd. %: C, 61.85; H, 6.75; N, 10.82. Found %: C, 61.90; H, 6.79; N, 10.86. Yield %: 30.

### 1-[N-(2-Bromopropyl)-2-aminoethyl]-2-[1-(1-naphthyl)methyl]-2-imidazoline

$^1$H-NMR ($CDCl_3$; $\delta$, ppm): 1.34 (d, 3H, J = 5.6 Hz, $C\underline{H}_3CH$); 2.14–4.60 (m, 14H, CHBr, $CH_2N$ and $C\underline{H}_2$-$C_{10}H_7$); 6.89–7.48 (m, 4H, $C_{10}\underline{H}_7$); 7.54–8.00 (m, 3H, $C_{10}\underline{H}_7$). $^{13}$C-NMR ($CDCl_3$; $\delta$, ppm): 21.86 ($\underline{C}H_3CH$); 31.82 ($\underline{C}HBr$); 40.24 ($\underline{C}H_2$-$C_{10}H_7$); 43.64 ($\underline{C}H_2N$); 44.23 ($\underline{C}H_2N$); 45.82 ($\underline{C}H_2N$); 46.08 ($\underline{C}H_2N$); 48.11 ($\underline{C}H_2N$); 123.36 ($\underline{C}H_{arom.}$); 124.45 ($\underline{C}H_{arom.}$); 125.04 ($\underline{C}H_{arom.}$); 125.75 ($\underline{C}H_{arom.}$); 126.25 ($\underline{C}H_{arom.}$); 126.86 ($\underline{C}H_{arom.}$); 128.31 ($\underline{C}H_{arom.}$); 131.44 ($C_{quat}$); 133.44 ($C_{quat}$); 133.86 ($C_{quat}$); 167.14 (N-$\underline{C}$=N). Mass spectrum: m/z = 372 $[M - 1]^+$. Elemental analysis ($C_{19}H_{24}N_3Br$): Calcd. %: C, 60.96; H, 6.46; N, 11.22. Found %: C, 61.00; H, 6.51; N, 11.17. Yield %: 40.

### 1-[N-(3-Bromopropyl)-2-aminoethyl]-2-[1-naphthylethyl]-2-imidazoline

$^1$H-NMR ($CDCl_3$; $\delta$, ppm): 1.25 (m, 2H, $CH_2$); 1.61 (d, 3H, J = 7.0 Hz, $C\underline{H}_3CH$); 2.31–4.54 (m, 14H, $CH_2Br$, $CH_2N$ and $C\underline{H}$-$C_{10}H_7$); 7.01–7.47

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(m, 4H, $C_{10}\underline{H}_7$); 7.53–8.03 (m, 3H, $C_{10}\underline{H}_7$). $^{13}$C-NMR ($CDCl_3$; $\delta$, ppm): 22.12 ($\underline{C}H_3CH$); 24.12 ($CH_2$); 32.13 ($\underline{C}H_2Br$); 38.78 ($\underline{C}H$-$C_{10}H_7$); 43.54 ($\underline{C}H_2N$); 44.21 ($\underline{C}H_2N$); 45.24 ($\underline{C}H_2N$); 46.04 ($\underline{C}H_2N$); 47.54 ($\underline{C}H_2N$); 123.31 ($\underline{C}H_{arom.}$); 124.61 ($\underline{C}H_{arom.}$); 125.74 ($\underline{C}H_{arom.}$); 126.09 ($\underline{C}H_{arom.}$); 126.75 ($\underline{C}H_{arom.}$); 127.84 ($\underline{C}H_{arom.}$); 128.16 ($\underline{C}H_{arom.}$); 131.41 ($C_{quat}$); 133.65 ($C_{quat}$); 133.87 ($C_{quat}$); 168.32 (N—$\underline{C}$=N). Mass spectrum: m/z = 386 $[M\text{-}1]^+$. Elemental analysis ($C_{20}H_{26}N_3Br$): Calcd. %: C, 61.85; H, 6.75; N, 10.82. Found %: C, 61.89; H, 6.77; N, 10.84. Yield %: 40.

### *1-[N-(3-Bromopropyl)-2-aminoethyl]-2-[1-naphthylmethyl]-2-imidazoline*

$^1$H-NMR ($CDCl_3$; $\delta$, ppm): 1.34 (m, 2H, $CH_2$); 2.36–4.59 (m, 15H, $CH_2Br$, NH and $CH_2N$); 4.11 (s, 2H, $C\underline{H}_2$-$C_{10}H_7$); 7.12–7.67 (m, 4H, $C_{10}\underline{H}_7$); 7.70–8.13 (m, 3H, $C_{10}\underline{H}_7$). $^{13}$C-NMR ($CDCl_3$; $\delta$, ppm): 24.15 ($CH_2$); 32.19 ($\underline{C}H_2Br$); 39.41 ($\underline{C}H_2$-$C_{10}H_7$); 42.45 ($\underline{C}H_2N$); 43.65 ($\underline{C}H_2N$); 45.98 ($\underline{C}H_2N$); 46.12 ($\underline{C}H_2N$); 47.44 ($\underline{C}H_2N$); 123.31 ($\underline{C}H_{arom.}$); 124.12 ($\underline{C}H_{arom.}$); 125.24 ($\underline{C}H_{arom.}$); 125.85 ($\underline{C}H_{arom.}$); 126.35 ($\underline{C}H_{arom.}$); 126.79 ($\underline{C}H_{arom.}$); 128.54 ($\underline{C}H_{arom.}$); 131.64 ($C_{quat}$); 133.54 ($C_{quat}$); 133.98 ($C_{quat}$); 168.21 (N—$\underline{C}$=N). Mass spectrum: m/z = 372 $[M\text{-}1]^+$. Elemental analysis ($C_{19}H_{24}N_3Br$): Calcd. %: C, 60.96; H, 6.46; N, 11.22. Found %: C, 61.03; H, 6.54; N, 11.21. Yield %: 45.

### *S-2-[2-(1-Naphthylmethyl)-2-imidazoline]ethylthiophosphate*

$^1$H-NMR ($CDCl_3$; $\delta$, ppm): 2.52–4.25 (m, 10H, $CH_2S$, $CH_2N$ and $C\underline{H}_2$-$C_{10}H_7$); 7.02–7.46 (m, 4H, $C_{10}\underline{H}_7$); 7.54–7.93 (m, 3H, $C_{10}\underline{H}_7$); 9.70 (s, 2H, OH). $^{13}$C-NMR ($CDCl_3$; $\delta$, ppm): 28.14 ($\underline{C}H_2S$); 43.44 ($\underline{C}H_2$-$C_{10}H_7$); 44.66 ($\underline{C}H_2N$); 46.21 ($\underline{C}H_2N$); 48.20 ($\underline{C}H_2N$); 122.82 ($\underline{C}H$ arom.); 123.63 ($\underline{C}H$ arom.); 124.19 ($\underline{C}H$ arom.); 125.68 ($\underline{C}H$ arom.); 126.55 ($\underline{C}H$ arom.); 127.54 ($\underline{C}H$ arom.); 128.80 ($\underline{C}H$ arom.); 131.34 (arom. $C_{quat}$); 131.93 (arom. $C_{quat}$); 133.57 (arom. $C_{quat}$); 169.78 (N—$\underline{C}$=N). $^{31}$P-NMR $\{^1H\}$ ($\delta$, ppm): 19.00 ($CDCl_3$); 16.40 ($D_2O$). Mass spectrum: m/z = 332 $[M\text{-}18]^+$. Elemental analysis ($C_{16}H_{19}N_2SO_3P$): Calcd. %: C, 54.85; H, 5.47; N, 8.00. Found %: C, 54.90; H, 5.49; N, 8.00. Yield %: 78.

### *S-2-{2-[1-(1-Naphthyl)ethyl]-2-imidazoline} ethylthiophosphate*

$^1$H-NMR ($CDCl_3$; $\delta$, ppm): 1.54 (d, 3H, J = 7.1 Hz, $C\underline{H}_3CH$); 2.52–4.25 (m, 8H, $CH_2S$ and $CH_2N$); 4.53 (q, 1H, J = 7.1 Hz, $CH_3C\underline{H}$); 7.00–7.41 (m, 4H, $C_{10}\underline{H}_7$); 7.46–7.89 (m, 3H, $C_{10}\underline{H}_7$); 9.86 (s, 2H, OH). $^{13}$C-NMR ($CDCl_3$; $\delta$, ppm): 21.48 ($\underline{C}H_3CH$); 28.45 ($\underline{C}H_2S$); 35.45 ($\underline{C}H$—$C_{10}H_7$); 44.75 ($\underline{C}H_2N$); 46.03 ($\underline{C}H_2N$); 48.42 ($\underline{C}H_2N$); 122.72 ($\underline{C}H$ arom.); 123.12

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(CH arom.); 124.46 (CH arom.); 125.65 (CH arom.); 126.89 (CH arom.); 127.25 (CH arom.); 128.56 (CH arom.); 131.63 (arom. $C_{quat}$); 131.99 (arom. $C_{quat}$); 133.54 (arom. $C_{quat}$); 169.01 (N–C=N). $^{31}$P-NMR {$^{1}$H} ($\delta$, ppm): 15.40 ($CDCl_3$); 16.80 ($D_2O$). Mass spectrum: m/z = 346 $[M-18]^+$. Elemental analysis ($C_{17}H_{21}N_2SO_3P$): Calcd. %: C, 56.03; H, 5.81; N, 7.69. Found %: C, 56.10; H, 5.84; N, 7.74. Yield %: 53.

### *S-2-{(2-Aminoethyl)[2-(1-naphthylmethyl)-2-imidazoline]} ethylthiophosphate*

$^{1}$H-NMR ($CDCl_3$; $\delta$, ppm): 2.12–4.17 (m, 15H, $CH_2S$, $CH_2N$, NH and $CH_2$-$C_{10}H_7$); 7.12–7.49 (m, 4H, $C_{10}H_7$); 7.51–8.06 (m, 3H, $C_{10}H_7$); 10.19 (s, 2H, OH). $^{13}$C-NMR ($CDCl_3$; $\delta$, ppm): 26.74 ($CH_2S$); 44.14 ($CH_2$-$C_{10}H_7$); 44.36 ($CH_2N$); 44.89 ($CH_2N$); 45.21 ($CH_2N$); 46.34 ($CH_2N$); 48.03 ($CH_2N$); 122.65 (CH arom.); 123.25 (CH arom.); 124.07 (CH arom.); 125.23 (CH arom.); 126.62 (CH arom.); 127.55 (CH arom.); 128.85 (CH arom.); 131.09 (arom. $C_{quat}$); 131.87 (arom. $C_{quat}$); 133.57 (arom. $C_{quat}$); 168.86 (N–C=N). $^{31}$P-NMR {$^{1}$H} ($\delta$, ppm): 10.29 ($CDCl_3$); 10.44 ($D_2O$). Mass spectrum: m/z = 375 $[M-18]^+$. Elemental analysis ($C_{18}H_{24}N_3SO_3P$): Calcd. %: C, 54.95; H, 6.15; N, 10.68. Found %: C, 54.90; H, 6.19; N, 10.61. Yield %: 69.

### *S-2-{(2-Aminoethyl)-2-[1-(1-naphthyl)ethyl]-2-imidazoline} ethylthiophosphate*

$^{1}$H-NMR ($CDCl_3$; $\delta$, ppm): 1.60 (d, 3H, J = 6.8 Hz, $CH_3CH$); 2.26–4.25 (m, 13H, $CH_2S$ and $CH_2N$ and NH); 4.56 (q.1H, J = 6.8 Hz, CH-$C_{10}H_7$); 7.10–7.44 (m, 4H, $C_{10}H_7$); 7.51–7.98 (m, 3H, $C_{10}H_7$); 9.90 (s, 2H, OH). $^{13}$C-NMR ($CDCl_3$; $\delta$, ppm): 21.66 ($CH_3CH$); 28.01 ($CH_2S$); 38.86 (CH-$C_{10}H_7$); 43.17 ($CH_2N$); 44.66 ($CH_2N$); 45.74 ($CH_2N$); 46.75 ($CH_2N$); 48.52 ($CH_2N$); 122.88 (CH arom.); 123.25 (CH arom.); 124.85 (CH arom.); 125.35 (CH arom.); 126.45 (CH arom.); 127.65 (CH arom.); 128.58 (CH arom.); 131.25 (arom. $C_{quat}$); 131.75 (arom. $C_{quat}$); 133.24 (arom. $C_{quat}$); 169.22 (N–C=N). $^{31}$P-NMR {$^{1}$H} ($CDCl_3$; $\delta$, ppm): 10.99 ($CDCl_3$); 11.09 ($D_2O$). Mass spectrum: m/z = 389 $[M-18]^+$. Elemental analysis ($C_{19}H_{26}N_3SO_3P$): Calcd. %: C, 56.00; H, 6.43; N, 10.31. Found %: C, 56.03; H, 6.47; N, 10.28. Yield %: 68

### *S-2-{(2-Aminopropyl)[2-(1-naphthylmethyl)-2-imidazoline]} ethylthiophosphate*

$^{1}$H-NMR ($CDCl_3$; $\delta$, ppm): 1.25 (m, 2H, $CH_2$); 2.21–4.26 (m, 15H, $CH_2S$, $CH_2N$, NH and $CH_2$-$C_{10}H_7$); 7.08–7.46 (m, 4H, $C_{10}H_7$); 7.58–8.08 (m, 3H, $C_{10}H_7$); 10.02 (s, 2H, OH). $^{13}$C-NMR ($CDCl_3$; $\delta$, ppm): 21.25 ($CH_2$); 27.44 ($CH_2S$); 43.77 ($CH_2$-$C_{10}H_7$); 43.65 ($CH_2N$); 44.89 ($CH_2N$); 45.38 ($CH_2N$); 46.21 ($CH_2N$); 48.25 ($CH_2N$); 122.54 (CH arom.);

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123.75 (CH arom.); 124.24 (CH arom.); 125.68 (CH arom.); 126.35 (CH arom.); 127.75 (CH arom.); 128.75 (CH arom.); 131.02 (arom. $C_{quat}$); 131.75 (arom. $C_{quat}$); 133.35 (arom. $C_{quat}$); 168.44 (N-C=N). $^{31}$P-NMR $\{^1H\}$ ($CDCl_3$; $\delta$, ppm): 9.89 ($CDCl_3$); 10.02 ($D_2O$). Mass spectrum: m/z = 389 $[M-18]^+$. Elemental analysis ($C_{19}H_{26}N_3SO_3P$): Calcd. %: C, 56.00; H, 6.43; N, 10.31. Found %: C, 56.05; H, 6.37; N, 10.39. Yield %: 74.

### *S-2-{(2-Aminopropyl)-2-[1-(1-naphthyl)ethyl]-2-imidazoline} ethylthiophosphate*

$^1$H-NMR ($CDCl_3$; $\delta$, ppm): 1.29 (m, 2H, $CH_2$); 1.60 (d, 3H, J = 6.9 Hz, $CH_3CH$); 2.21–4.34 (m, 13H, $CH_2S$ and $CH_2N$ and NH); 4.59 (q, 1H, J = 6.9 Hz, CH-$C_{10}H_7$); 7.07–7.51 (m, 4H, $C_{10}H_7$); 7.59–8.12 (m, 3H, $C_{10}H_7$); 9.86 (s, 2H, OH). $^{13}$C-NMR ($CDCl_3$; $\delta$, ppm): 21.44 ($CH_2$); 23.01 ($CH_3CH$); 28.24 ($CH_2S$); 36.84 (CH-$C_{10}H_7$); 43.21 ($CH_2N$); 44.44 ($CH_2N$); 45.31 ($CH_2N$); 46.47 ($CH_2N$); 48.68 ($CH_2N$); 122.98 (CH arom.); 123.66 (CH arom.); 124.88 (CH arom.); 125.68 (CH arom.); 126.30 (CH arom.); 127.24 (CH arom.); 128.45 (CH arom.); 131.02 (arom. $C_{quat}$); 131.58 (arom. $C_{quat}$); 133.58 (arom. $C_{quat}$); 168.67 (N–C=N). $^{31}$P-NMR $\{^1H\}$ ($\delta$, ppm): 18.64 ($CDCl_3$); 18.89 ($D_2O$). Mass spectrum: m/z = 403 $[M-18]^+$. Elemental analysis ($C_{20}H_{28}N_3SO_3P$): Calcd. %: C, 56.99; H, 6.70; N, 9.97. Found %: C, 56.94; H, 6.69; N, 9.94. Yield %: 75.

### *1-Methyl-S-2-[2-(1-naphthylmethyl)-2-imidazoline] ethylthiophosphate*

$^1$H-NMR ($CDCl_3$; $\delta$, ppm): 1.25 (d, 3H, J = 5.9 Hz, $CH_3CHS$); 1.94 (m, 1H, CHS); 2.46–4.29 (m, 8H, $CH_2N$ and $CH_2$-$C_{10}H_7$); 6.99–7.41 (m, 4H, $C_{10}H_7$); 7.51–7.89 (m, 3H, $C_{10}H_7$); 9.77 (s, 2H, OH). $^{13}$C-NMR ($CDCl_3$; $\delta$, ppm): 22.32 ($CH_3CHS$); 36.15 ($CH_3CHS$); 43.02 ($CH_2$-$C_{10}H_7$); 44.34 ($CH_2N$); 46.33 ($CH_2N$); 48.65 ($CH_2N$); 122.24 (CH arom.); 123.52 (CH arom.); 124.32 (CH arom.); 125.32 (CH arom.); 126.75 (CH arom.); 127.24 (CH arom.); 128.64 (CH arom.); 131.31 (arom. $C_{quat}$); 131.96 (arom. $C_{quat}$); 133.20 (arom. $C_{quat}$); 167.12 (N–C=N). $^{31}$P-NMR $\{^1H\}$ ($\delta$, ppm): 14.14 ($CDCl_3$); 15.25 ($D_2O$). Mass spectrum: m/z = 346 $[M-18]^+$. Elemental analysis ($C_{17}H_{21}N_2SO_3P$): Calcd. %: C, 56.03; H, 5.81; N, 7.69. Found %: C, 56.11; H, 5.90; N, 7.71. Yield %: 51.

### *1-Methyl-S-2-{2-[1-(1-naphthyl)ethyl]-2-imidazoline} ethylthiophosphate*

$^1$H-NMR ($CDCl_3$; $\delta$, ppm): 1.14 (d, 3H, J = 6.1 Hz, $CH_3CHS$); 1.65 (d, 3H, J = 6.9 Hz, $CH_3CH$); 2.26–4.31 (m, 7H, CHS and $CH_2N$); 4.56 (m, 1H, $CHCH_3$); 6.97–7.44 (m, 4H, $C_{10}H_7$); 7.49–7.98 (m, 3H, $C_{10}H_7$); 9.99 (s, 2H, OH). $^{13}$C-NMR ($CDCl_3$; $\delta$, ppm): 21.43 ($CH_3CH$);

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22.24 (CH$_3$CHS); 36.21 (CHS); 37.44 (CH-C$_{10}$H$_7$); 44.26 (CH$_2$N); 46.09 (CH$_2$N); 47.89 (CH$_2$N); 122.35 (CH arom.); 123.41 (CH arom.); 124.00 (CH arom.); 125.86 (CH arom.); 126.61 (CH arom.); 127.39 (CH arom.); 128.94 (CH arom.); 131.17 (arom. C$_{quat}$); 131.86 (arom. C$_{quat}$); 133.64 (arom. C$_{quat}$); 169.09 (N—C=N). $^{31}$P-NMR {$^1$H} ($\delta$, ppm): 12.19 ($CDCl_3$); 12.33 ($D_2O$). Mass spectrum: m/z = 360 [M −18]$^+$. Elemental analysis ($C_{18}H_{23}N_2SO_3P$): Calcd. %: C, 57.13; H, 6.13; N, 7.40. Found %: C, 57.09; H, 6.17; N, 7.39. Yield %: 42.

### *1-Methyl-S-2-{(2-aminoethyl)[2-(1-naphthylmethyl)-2-imidazoline]}ethylthiophosphate*

$^1$H-NMR ($CDCl_3$; $\delta$, ppm): 1.20 (d, 3H, J = 5.9 Hz, CH$_3$CHS); 2.24–4.30 (m, 14H, CHS and CH$_2$N and NH and CH$_2$-C$_{10}$H$_7$); 7.11–7.51 (m, 4H, C$_{10}$H$_7$); 7.59–8.09 (m, 3H, C$_{10}$H$_7$); 10.00 (s, 2H, OH). $^{13}$C-NMR ($CDCl_3$; $\delta$, ppm): 23.31 (CH$_3$CHS); 34.14 (CHS); 43.06 (CH$_2$-C$_{10}$H$_7$); 43.86 (CH$_2$N); 44.66 (CH$_2$N); 45.81 (CH$_2$N); 46.17 (CH$_2$N); 48.54 (CH$_2$N); 122.99 (CH arom.); 123.57 (CH arom.); 124.85 (CH arom.); 125.89 (CH arom.); 126.23 (CH arom.); 127.75 (CH arom.); 128.75 (CH arom.); 131.23 (arom. C$_{quat}$); 131.85 (arom. C$_{quat}$); 133.77 (arom. C$_{quat}$); 169.45 (N—C=N). $^{31}$P-NMR {$^1$H} ($\delta$, ppm): 10.70 ($CDCl_3$); 10.64 ($D_2O$). Mass spectrum: m/z = 389 [M-18]$^+$. Elemental analysis ($C_{19}H_{26}N_3SO_3P$): Calcd. %: C, 56.00; H, 6.43; N, 10.31. Found %: C, 55.94; H, 6.49; N, 10.30. Yield %: 64.

### *1-Methyl-S-2-{(2-aminoethyl)-2[1-(1-naphthyl)ethyl]-2-imidazoline]}ethylthiophosphate*

$^1$H-NMR ($CDCl_3$; $\delta$, ppm): 1.28 (d, 3H, J = 5.8 Hz, CH$_3$CHS); 1.69 (d, 3H, J = 7.0 Hz, CH$_3$CH); 2.19–4.28 (m, 12H, CHS and CH$_2$N and NH); 4.59 (m, 1H, CH-C$_{10}$H$_7$); 7.06–7.49 (m, 4H, C$_{10}$H$_7$); 7.60–8.08 (m, 3H, C$_{10}$H$_7$); 9.89 (s, 2H, OH). $^{13}$C-NMR ($CDCl_3$; $\delta$, ppm): 22.66 (CH$_3$CH); 23.17 (CH$_3$CHS); 33.14 (CHS); 36.44 (CH-C$_{10}$H$_7$); 43.29 (CH$_2$N); 44.66 (CH$_2$N); 45.64 (CH$_2$N); 46.12 (CH$_2$N); 48.64 (CH$_2$N); 122.42 (CH arom.); 123.54 (CH arom.); 124.32 (CH arom.); 125.45 (CH arom.); 126.25 (CH arom.); 127.75 (CH arom.); 128.54 (CH arom.); 131.24 (arom. C$_{quat}$); 131.87 (arom. C$_{quat}$); 133.46 (arom. C$_{quat}$); 169.35 (N—C=N). $^{31}$P-NMR {$^1$H} ($\delta$, ppm):18.49 ($CDCl_3$); 18.64 ($D_2O$). Mass spectrum: m/z = 403 [M-18]$^+$. Elemental analysis ($C_{20}H_{28}N_3SO_3P$): Calcd. %: C, 56.99; H, 6.70; N, 9.97. Found %: C, 57.03; H, 6.59; N, 10.00. Yield %: 59.

### *Radioprotective Activity*

The studies were carried out in mice; Male Swiss albino (age 2.5–3 month; 25–30 g weight at the start of the experiment) were provided by Janvier (Le Genest Saint-Isle, France). They were housed,

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randomly, by 10 in Makrolon type III cages ($33 \times 27 \times 15 cm^3$) and maintained on a 12-h light and dark cycle (8–20 h) in a room with constant temperature ($21 \pm 1^{\circ}C$) and humidity (55%). During the period of at least 7-days quarantine and 30 days of the experiment, except during the irradiation, the mice were maintained on a standard laboratory diet and watered ad libitum.

Whole-body irradiation was performed with a cobalt-60 source. The dose rate, at 1 meter from the source, was between 50.73–52.67 $cGy.min^{-1}$ (depending on the irradiation date).

Irradiation conditions were performed in the morning (between 9 and 12 a.m.). During irradiation, 20 animals were placed in a Plexiglas box with 30 cells in a homogeneous field $28.5 \times 28.5$ $cm^2$ in size. The residence time in the small boxes was limited to the duration of the experiment plus 10 min. The animals were positioned at 1 meter of the source. The dosimeter was checked by means of ionization chamber dosimeters Baldwin-Ionex. The radiosensitivity of the strain was regularly monitored on unprotected animals by the determination of lethality curves. The irradiation $LD_{50/30\,days}$ was equal to 8.1 Gy. The different $LD_{50}$ values were determined by probit analysis.[19,20] For each product tested, 10 animals were exposed to an irradiation dose, which lead to the death of all the control animals within the 30 days following the irradiation ($LD_{100/30days}$), and 10 animals were exposed to a 2 Gy higher dose.

Every day of irradiation, controls are carried out: 5 mice received the miglyol (an inert mixture of fatty acid esters used as a solvent), and 5 untreated mice were irradiated at the $LD_{100/30days}$; for each product tested, survival was followed within 30 days out of 5 mice, which were not irradiated in order to check that there was no long-term toxicity.

Compounds tested were injected intraperitoneally (ip) to the animals 15 min before irradiation. The amount of compound injected was equal to half of his $LD_{50}$ toxicology preliminarily determined; the injected volume was 500 $\mu$L. Mortality was followed twice per day during the 30 days following the exposure.

For each product tested and each irradiation dose, the survival curve according to time was plotted in order to determine the rate of survival at 30 days, average time of survival (ATS, e.g., arithmetic mean of the lifespan of each animal between the beginning and the end of the irradiation), and survival time 50% (ST 50, e.g., for a batch of N animal, the time passed between the beginning of the experiment and the death of the "$N^{th}/2 + 1$" animal).

For the most active three compounds (in order to limit the number of animals used), additional irradiations (20 mice per dose and product) were performed at 7.5, 8.1, 10.1, 11.1, 12.1, 14.1, and 16.1 Gy. For each

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of these 3 products and for irradiated and untreated control animals, by plotting the straight line *mortality = f[log(dose)]*, we have determined the $LD_{50/30days}$ in order to calculate the DRF.

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