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Preliminary communication

Cinnamic acid derived oxazolinium ions as novel cytotoxic agents

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Abstract

Substituted cinnamoyl chlorides, **11**, were converted into (2-hydroxyethyl)-oxazolinium chlorides **14**, *N*,*N*-bis-(2-chloroethyl)amides **16** and (2-chloroethyl)-oxazolinium chlorides **17**. Although derivatives **14** which possess electron-donating substituents (Me or MeO) were more potent than those substituted by electron-withdrawing groups (NO_2, Cl or CF_3), the difference in cytotoxic actin was not significant. Modification of the lipophilic character in a series of alkoxy-substituted derivatives **14** led to more active compounds, where **14t** that possesses a 4-octyloxy-phenyl-substituent was the most potent and displayed cytotoxic activity in the μM range. It is assumed that the oxazolinium salts act as alkylating agents, and undergo nucleophilic attack on the methylene adjacent to the ring oxygen where the oxazolinium ring parallels the aziridinium ring intermediate found in classical alkylating agents. © 2002 Published by Éditions scientifiques et médicales Elsevier SAS.

Keywords: Cinnamic acid; Cytotoxic agents; Oxazolinium salts

1. Introduction

Clinically useful chemotherapeutic nitrogen mustards, **2**, such as mechloretamine, cyclophosphamide, ifosfamide, melphalan and chlorambucil, are commonly prepared from the corresponding substituted-*N*,*N*-bis-(2-hydroxyethyl)amines **1** when treated with $SOCl_2$ or PCl_5. The mechanism by which they elicit their biological activity involves initial intramolecular nucleophilic displacement of a chloride to give reactive aziridinium intermediates **3** that serve as alkylating species (Fig. 1). The potency of the nitrogen mustards is frequently a function of the nucleophilicity of the nitrogen atom [1].

When the R group is strongly electron withdrawing, the nucleophilicity of the nitrogen atom may diminish to a point where the aziridinum intermediate **3** does not form readily and compound **2** thus becomes inactive as an alkylating agent. In the series of *N*,*N*-bis-(2-chloroethyl)anilines, it was shown that deactivation by *p*-NO_2 or *p*-$MeSO_2$ substituents leads to long half life and low potency. However, when the R group is electron donating, the nitrogen atom becomes highly nucleophilic and the aziridinium intermediate **3** forms readily. In such cases the nitrogen mustard **2** may be unacceptably toxic due to a lack of in vivo alkylating selectivity [2], as found in *p*-amino-substituted-aniline mustard. High alkylating potency was also observed with *p*-MeO and *p*-Me substituents [3–5]. In these aniline mustards the antitumour activity parallels toxicity and both properties correlate with the electronic parameters (σ) of the substituents on the phenyl ring and their hydrophobic constants (π). QSAR studies showed the dominant role played by the electronic factor, whereas the role of the hydrophobic character of the substituent is not yet clear [6]. *N*,*N*-bis-(2-chloroethyl)amides **5** of aliphatic acids were prepared from the corresponding acyl chlorides and bis-(2-chloroethyl)amine [7–9]. *N*-Methanesulfonyl-*N*,*N*-bis-(2-iodoethyl)amides were obtained by displacement of the corresponding *N*,*N*-bis-(2-methanesulfonate)sulfonamides with iodide [10]. Amides **5** were reported to be less active as well as less toxic than the corresponding amines due to the diminished nucleophilic character of the nitrogen atom. Although bis-(2-chloroethyl)amides of aromatic acids **5** could have been expected to become alkylating agents upon in vivo hydrolysis to the active *N*,*N*-bis-(2-chloroethyl)amine **6**, they were found to be inactive

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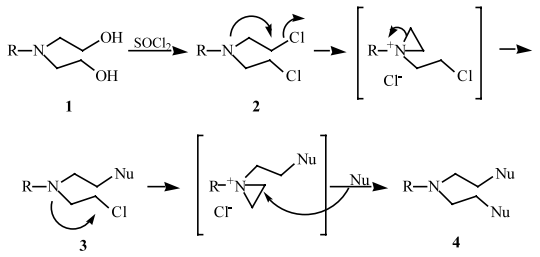


Fig. 1. General mechanism of action of nitrogen mustards.

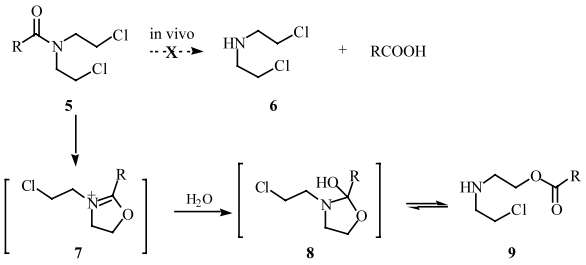


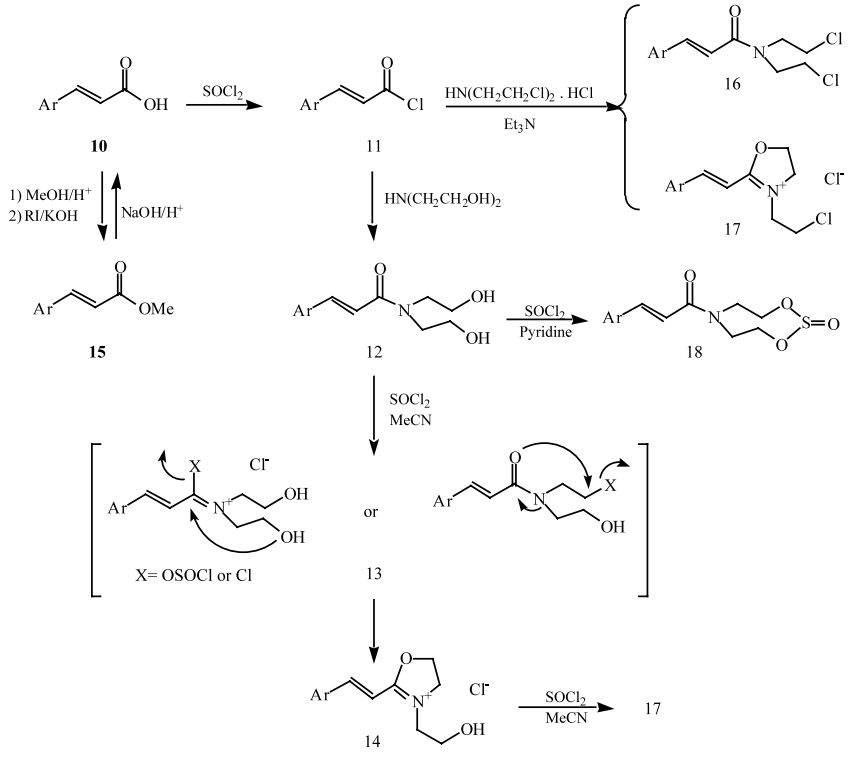
Fig. 2. Rearrangement and deactivation of *N*,*N*-(bis-2-chloroethyl)-arylamides.

since they rearranged to esters **9** via an intermediate oxazolinium ion **7** (Fig. 2). Attempts to obtain stable bis-(2-chloroethyl)amides from the corresponding cinnamic acids failed [11–13]. Thus, a balance between electron withdrawing and donating power of the R group is sought, that will reduce the nucleophilicity of the nitrogen atom, but only to such an extent that it will not impair the formation of a reactive aziridinium ion [14–16].

The aim of these investigations was to evaluate substituted-cinnamyl-bis-(2-chloroethyl)amides as potential alkylating agents, taking advantage of the possibility of modifying the nucleophilicity of the amido nitrogen atom by introducing a variety of electron withdrawing and donating substituents on the aromatic ring.

2. Chemistry

Two alternative pathways have been described for the preparation of *N*,*N*-bis-(2-chloroethyl)amides: (a) treatment of *N*,*N*-bis-(2-hydroxyethyl)amides with thionyl chloride or (b) coupling of an acid chloride with *N*,*N*-bis-(2-chloroethyl)amine. Reaction of a cinnamoyl chloride **11** with diethanolamine gave the corresponding *N*,*N*-bis-(2-hydroxyethyl)cinnamamides **12**, analogs of diol precursors of nitrogen mustards (Fig. 3)



Ar = substituted phenyl substituents

a 2-NO_2, **b** 3- NO_2, **c** 4- NO_2, **d** 2-Cl-5-NO_2, **e** 3-NO_2-4-Cl, **f** 2-CF_3, **g** 3-CF_3, **h** 4- CF_3, **i** 2-Me, **j** 4-Me, **k** 2-MeO, **l** 2-MeO (*cis*), **m** 3-MeO, **n** 4-MeO, **o** 2,4-di-MeO, **p** 3,4,5-tri-MeO, **q** 4-HO, **r** 4-C_3H_7O, **s** 4-C_4H_9O, **t** 4-$C_8H_{17}O$, **u** 4-$C_{12}H_{25}O$, **v** 4-$C_{16}H_{33}O$, **w** 4-$C_{18}H_{37}O$

Fig. 3. Synthesis of *N*,*N*-(bis-2-chloroethyl)-cinnamides (**16**) and oxazolinium salts (**14** and **17**).

Table 1
^{1}H-NMR and ^{13}C-NMR chemical shifts of compounds **14**, **16** and **17**

Compound	Solvent	^{1}H-NMR					^{13}C-NMR					
		CH_2N	CH_2OH	CH_2O	$CHCO$	ArC*H*	CH_2N	CH_2OH	CH_2O	$CHCO$	ArC*H*	*C*NO
14r	DMSO	3.08, 3.30	3.71	4.42	6.46	7.78	48.63+50.33	57.15	59.35	115.90	144.98	165.94
14s	DMSO	3.06, 3.29	3.70	4.40	6.47	7.78	45.77+49.15	56.22	59.36	114.50	145.02	166.01
14t	DMSO	3.07, 3.30	3.69	4.40	6.47	7.74	45.53+49.11	56.21	59.37	114.51	145.00	166.03
		CH_2Cl+CH_2N	$CHCO$	ArC*H*			CH_2Cl	CH_2N	$CHCO$	ArC*H*	*C*NO	
16j	$CDCl_3$	3.61–3.94	6.72	7.70			41.79+41.90	50.01+50.06	115.19	144.24	166.94	
16n	$CDCl_3$	3.64–3.92	6.71	7.71			41.72+42.03	50.14+51.18	113.68	143.86	167.40	
16o	$CDCl_3$	3.73–3.96	6.71	7.69			41.9	50.17+51.22	114.12	144.11	167.06	
16p	$CDCl_3$	3.68–3.98	6.76	7.65			41.7	49.86+51.03	115.59	146.10	166.71	
		CH_2N+CH_2Cl	CH_2O	$CHCO$		ArC*H*	CH_2Cl	CH_2N	CH_2O	$CHCO$	ArC*H*	*C*NO
17u	DMSO	3.91–4.5	4.43	6.47		7.81	39.52	47.67+48.19	59.37	114.54	145.22	166.08
17v	$CDCl^3$/ Acetone-d^6	3.6–4.1	4.66	6.36		7.82	37.83	46.10+48.29	58.52	113.54	145.22	165.75
17w	$CDCl^3$/ Acetone-d^6	3.35–3.78	4.60	6.30		7.70	38.33	46.78+48.92	59.22	113.94	146.19	166.76

[17]. Subsequent reaction of **12** with $SOCl_2$ in acetonitrile, in most cases gave mono-chloride products **14**, where only one of the two OH groups was replaced. Attempts to replace the second OH even under drastic conditions including reflux in the presence of an excess of $SOCl_2$, most frequently failed. Only in the single case of **12h** did both OH groups undergo replacement by Cl to give **17h**. Titration of the **17h** showed that one chloride was ionic and the other covalent. Interestingly, the IR spectra (KBr pellets) of the diols **12** showed the presence of two distinct OH absorptions at 3386–3344 and 3288–3245 cm^{-1}, respectively, attributed to two kinds of H-bonded OH groups. The chloride in compounds **14** was also found to be ionic. Compounds **14**, probably because of their ionic character, readily precipitated from the acetonitrile media in the course of the reaction. Other oxazolinium salts have also been reported to precipitate from acetonitrile [18]. The formation of **14** probably took place by cyclisation of an intermediate imido-yl-onium chloride, its chlorosulphite precursor or an amide **13**, involving displacement of chloride or chlorosulphite by one of the OH groups [19], or displacement of the chloride by the amido oxygen. Analogous cyclisations to oxazolines [20] or unstable oxazolinium ions [21,22], as well as a single example of an oxazolinium cinnamyl derivative [23], have been reported. However, when **12b** was treated with $SOCl_2$ in pyridine, an unexpected cyclisation took place to give the eight-membered sulphite **18b**.

The desired *N*,*N*-bis-(2-chloroethyl)-cinnamamides **16** could be prepared by treatment of **11** with *N*,*N*-bis-(2-chloroethyl)amine in the presence of triethylamine and working up the reaction after 0.5 h [24]. However, when the reaction mixtures were stirred for 1–3 h at 50 °C the products obtained were the oxazolinium salts **17** (Fig. 3). Compounds **14**, **16** and **17** were readily distinguished by their characteristic ^{1}H- and ^{13}C-NMR spectra (Table 1). Oxazolinium salts **17** were found to be stable at room temperature for more than 2 years, when stored in sealed vials.

3. Biological data

Biological evaluation of compounds **14** was carried out in the Preclinical Antitumor Drug Discovery Screen of the National Cancer Institute (NCI) [25,26]. The data revealed that the most active compound was **14g**, which was substituted by a CF_3 group at the 3-position. Derivatives substituted with electron withdrawing groups, i.e. NO_2, Cl, CF_3 at the 2- and 4-positions, were the least active. This observation supports the notion that a decrease in electron withdrawing ability by the aromatic substituent would result in an increase in biological activity. In fact, compounds possessing electron-donating substituents were indeed found to be more active than those possessing electron-withdrawing substituents. Several of them were active against one or more tumour cell lines at 10^{-4} M concentration. The most active derivative, **14m**, displayed activity against 31 out of the 56 cell lines evaluated. In general, the highest activity was observed against leukaemia cell lines. Compound **14q** bearing a strong electron donating OH group, displayed poor activity in comparison with derivatives substituted by less polar alkyl or alkoxy groups. This fact may be attributed to the higher hydrophilicity of **14q** that interferes with its ability to cross cell membranes.

Although derivatives possessing Me or MeO substituents were more potent than those substituted by

NO_2, Cl and CF_3 groups, the difference in potency was not significant. When the difference in the activity of compounds possessing electron donating or withdrawing substituents is small, as found in the present case, Topliss' empirical approach suggests modification in their lipophilic character [27]. Therefore, a series of alkoxy oxazolinium salts **14r**–**w** of progressively increasing chain length and lipophilicity of the alkyl group, were prepared. The most active derivative in this series **14t**, having the 4-octyloxy-substituent, displayed activity at 10^{-6} M concentration (Fig. 4), whereas the analogs **14m**, **14r** and **14s** having 4-methoxy, 4-propoxy and 4-butoxy-substituents, respectively, were active only at a maximum of 10^{-5} M concentrations. Subsequent modifications involving elongation of the alkyl chain to 12, 16 and 18 carbons while at the same time replacing the 2-hydroxyethyl-substituent on nitrogen with a 2-chloroethyl group led to compounds less active than **14t**.

4. Conclusions

It may thus be concluded that in this series of oxazolinium derivatives the lipophilic character of the 4-alkoxy-substituent is the controlling factor in cytotoxic activity, and the 4-octyloxy-substituent displayed an optimal balance of electron donating and lipophilic characteristics. It is assumed that the oxazolinium salts act as alkylating agents, and undergo a nucleophilic attack on the methylene adjacent to the ring oxygen. In this respect the oxazolinium ring parallels the aziridinium ring intermediate found in classical alkylating agents.

5. Experimental

5.1. General chemistry

^{1}H-NMR and ^{13}C-NMR spectra were obtained on Bruker AC-200, DPX-300 and DMX-600 spectrometers. For $CDCl_3$ and acetone-d_6 solutions, chemical shifts are expressed in ppm downfield from Me_4Si used as internal standard; for D_2O solutions the HOD peak was taken as δ 4.80 (^{1}H-spectra). Multiplicities in the ^{13}C-NMR spectra were determined by off-resonance decoupling. Mass spectra were obtained on a Finnigan 4021 spectrometer operating in chemical ionisation (CI), desorption chemical ionisation (DCI) or HRMS (high-resolution) modes. Melting points were determined on a Fisher–Johns apparatus. Analyses indicated by the symbols of the elements were within $\pm$0.4% of the theoretical values.

5.1.1. Alkylation of methyl 4-hydroxycinnamate (**15q**) to methyl 4-alkoxycinnamates **15**

5.1.1.1. General procedure. To **15q** (1.7 g, 10 mmol) in 50% KOH (10 mmol, 1.35 mL), CH_2Cl_2 (10 mL), an alkyl iodide (11 mmol) and a surfactant (aliquat or Bu_4N^+ Br^- 1% mole) were added and the mixture was refluxed for 72 h. The organic layer was separated and evaporated to dryness. The residue was extracted (ether–$H_2O \times 3$), washed with brine, dried ($MgSO_4$) and evaporated to give the products as yellow oils, containing some residual alkyl iodide that was removed under high vacuum (yields ca. 75%).

5.1.2. Methyl 4-propoxycinnamate (**15r**)

The crude yellow oil obtained was crystallised from EtOH, m.p. 87 °C; ^{1}H-NMR ($CDCl_3$) δ 1.04 (t, 3H, $J = 8$ Hz, *Me*), 1.48 (sextet, 2H, CH_2Me), 3.79 (s, 3H, CO_2*Me*), 3.96 (t, 2H, $J = 8$ Hz, CH_2O), 6.26 (d, 1H, $J = 16$ Hz, *CH*CO_2), 6.84 and 7.47 (AA′XX′ system, $J = 8$ Hz, 4H, *ArH*), 7.65 (d, 1H, $J = 16$ Hz, *ArCH*); ^{13}C-NMR ($CDCl_3$) δ 10.5 (*Me*CH_2), 22.5 (Me*C*H_2), 51.6 (OMe), 69.6 (CH_2O), 114.8 (C-3 and C-3′), 115.1 (*C*HCO_2), 126.9 (C-1), 129.7 (C-2 and C-2′), 144.6 (ArCH), 161.1 (C-4), 167.9 (CO_2); MS (CDI, CH_4) m/z 221 ($[MH]^+$, 100), 189 ($[MH]^+$–MeOH, 20), 179 ($[MH]^+$–C_3H_6, 20); HRMS (DCI, CH_4) Calc. for $C_{13}H_{17}O_3$ ($[MH]^+$): 221.1178. Found: 221.1240.

5.1.3. Methyl 4-butoxycinnamate (**15s**)

^{1}H-NMR ($CDCl_3$) δ 0.89 (t, 3H, $J = 8$ Hz, *Me*), 1.3–1.9 (m, 4H, CH_2CH_2Me), 3.79 (s, 3H, CO_2*Me*), 3.99 (t, 2H, $J = 8$ Hz, CH_2O), 6.30 (d, 1H, $J = 16$ Hz, *CH*CO_2), 6.89 and 7.46 (AA′XX′ system, $J = 8$ Hz, 4H, *ArH*), 7.65 (d, 1H, $J = 16$ Hz, *ArCH*); ^{13}C-NMR ($CDCl_3$) δ 13.8 (*Me*CH_2), 19.2 (Me*C*H_2), 29.4 (CH_2CH_2O), 51.6 (OMe), 67.9 (CH_20), 114.9 (C-3 and C-3′), 115.0 (*C*HCO_2), 126.9 (C-1), 129.7 (C-2 and C-2′), 144.7 (ArCH), 161.1 (C-4), 167.9 (CO_2); MS (CDI, CH_4) m/z 235 ($[MH]^+$, 100), 203 ($[MH]^+$–MeOH, 54), 179 ($[MH]^+$–C_4H_8, 25), 147 ($[MH]^+$–$C_5H_{12}O$, 18); HRMS (DCI, CH_4) Calc. for $C_{14}H_{19}O_3$ ($[MH]^+$): 235.1334. Found: 235.1330.

5.1.4. Methyl 4-octyloxycinnamate (**15t**)

^{1}H-NMR ($CDCl_3$) δ 0.89 (t, 3H, $J = 8$ Hz, *Me*), 1.2–1.44 (m, 10H), 1.82 (quintet, 2H, $J = 8$ Hz, $CH_2CH_2CH_2O$), 3.79 (s, 3H, *Me*), 3.98 (t, 2H, $J = 8$ Hz, CH_2O), 6.3 (d, 1H, $J = 16$ Hz, *CH*CO_2), 6.89 and 7.46 (AA′XX′ system, $J = 8$ Hz, 4H, *ArH*), 7.67 (d, 1H, $J = 16$H, *ArCH*); ^{13}C-NMR ($CDCl_3$) δ 14.1 (*Me*CH_2), 22.6, 26.0, 28.2, 28.7, 29.20 (Me(CH_2)$_5$), 32.8 (CH_2CH_2O), 51.54 (OMe), 68.1 (CH_2O), 114. (C-3 and C-3′), 115.0 (*C*HCO_2), 126.5 (C-1), 129.7 (C-2 and C-2′), 144.8 (Ar*C*H), 161.4 (C-4), 167.8 (CO_2); MS (DCI, CH_4) m/z 291 ($[MH]^+$, 100), 259 ($[MH]^+$

–MeOH, 25), 178 ($[MH]^+$–C_6H_{17}, 30), 113 (C_8H_{17}, 26); HRMS (DCI, CH_4) Calc. for $C_{18}H_{26}O_3$ ($[MH]^+$): 291.1960. Found: 291.1960.

5.1.5. Conversion of methyl 4-hydroxycinnamate (**15q**) to ethyl 4-alkoxycinnamate (**15′**)

5.1.5.1. General procedure. To a stirred solution of Na (20 mmol) in dry EtOH (20 mL), methyl 4-hydroxycinnamate (3.56 g, 20 mmol), and an alkyl bromide (20 mmol) were added. The mixture was refluxed for 24 h, then cooled and extracted (EtOAc–H_2O, Na_2CO_3). The organic layer was dried ($MgSO_4$) and evaporated. The product, purified by silica gel column chromatography (hexane followed by Et_2O), was obtained as a white solid in ca. 95% yield after evaporation of the solvent.

5.1.6. Ethyl 4-dodecyloxycinnamate (**15′u**)

M.p. 53 °C; ^{1}H-NMR ($CDCl_3$) δ 0.90 (t, 3H, $J = 7$ Hz, $Me(CH_2)_{11}$), 1.18–1.50 (m, 18H, Me(CH_2)$_9$), 1.33 (t, 2H, $J = 7$ Hz, CO_2CH_2Me), 1.81 (sextet, 2H, $J = 7$ Hz, OCH_2CH_2), 3.97 (t, 2H, $J = 7$ Hz, OCH_2), 4.25 (q, 2H, $J = 7$ Hz, CO_2CH_2Me), 6.30 (d, 1H, $J = 16$ Hz, $CHCO_2$), 6.88 and 7.45 (AA′XX′ system, 4H, $J = 8$ Hz, ArH), 7.64 (d, 1H, $J = 16$ Hz, ArCH); ^{13}C-NMR ($CDCl_3$) δ 14.1 and 14.3 (two Me), 22.5 (C_{11}), 26.0 and 29.2–29.7 (C_2–C_9), 31.9 (C-$_{10}$), 60.3 (CO_2CH_2Me), 68.1 (CH_2O), 114.8 (C-3 and C-3′), 115.5 ($CHCO_2$), 126.9 (C-1), 129.7 (C-2 and C-2′), 144.3 (ArCH), 161.0 (C-4), 167.4 (CO_2); MS (DCI, CH_4) m/z 361 ($[MH]^+$, 100), 315 ($[MH]^+$–C_2H_6O, 18), 193 ($[MH]^+$–$C_{11}H_{23}$, 27); HRMS (DCI, CH_4) Calc. for $C_{23}H_{37}O_3$ ($[MH]^+$): 361.2743. Found: 361.2760.

5.1.7. Ethyl 4-hexadecyloxycinnamate (**15′v**)

M.p. 59 °C; ^{1}H-NMR ($CDCl_3$) δ 0.88 (t, 3H, $J = 7$ Hz, $Me(CH_2)_{15}$), 1.20–1.32 (m, 26H, Me(CH_2)$_{13}$), 1.33 (t, 2H, $J = 7$ Hz, CO_2CH_2Me), 1.81 (sextet, 2H, $J = 7$ Hz, OCH_2CH_2), 3.97 (t, 2H, $J = 7$ Hz, OCH_2), 4.25 (q, 2H, $J = 7$ Hz, CO_2CH_2Me), 6.30 (d, 1H, $J = 16$ Hz, $CHCO_2$), 6.88 and 7.45 (AA′XX′ system, 4H, $J = 8$ Hz, ArH), 7.64 (d, 1H, $J = 16$ Hz, ArCH); ^{13}C-NMR ($CDCl_3$) δ 14.1 and 14.3 (two Me), 22.7 (C_{15}), 26.0 and 29.1–29.7 (C_2–C_{13}), 31.9 (C_{14}), 60.3 (CO_2CH_2Me), 68.1 (CH_2O), 114.8 (C-3 and C-3′), 115.5 ($CHCO_2$), 126.9 (C-1), 129.6 (C-2 and C-2′), 144.3 (ArCH), 160.94

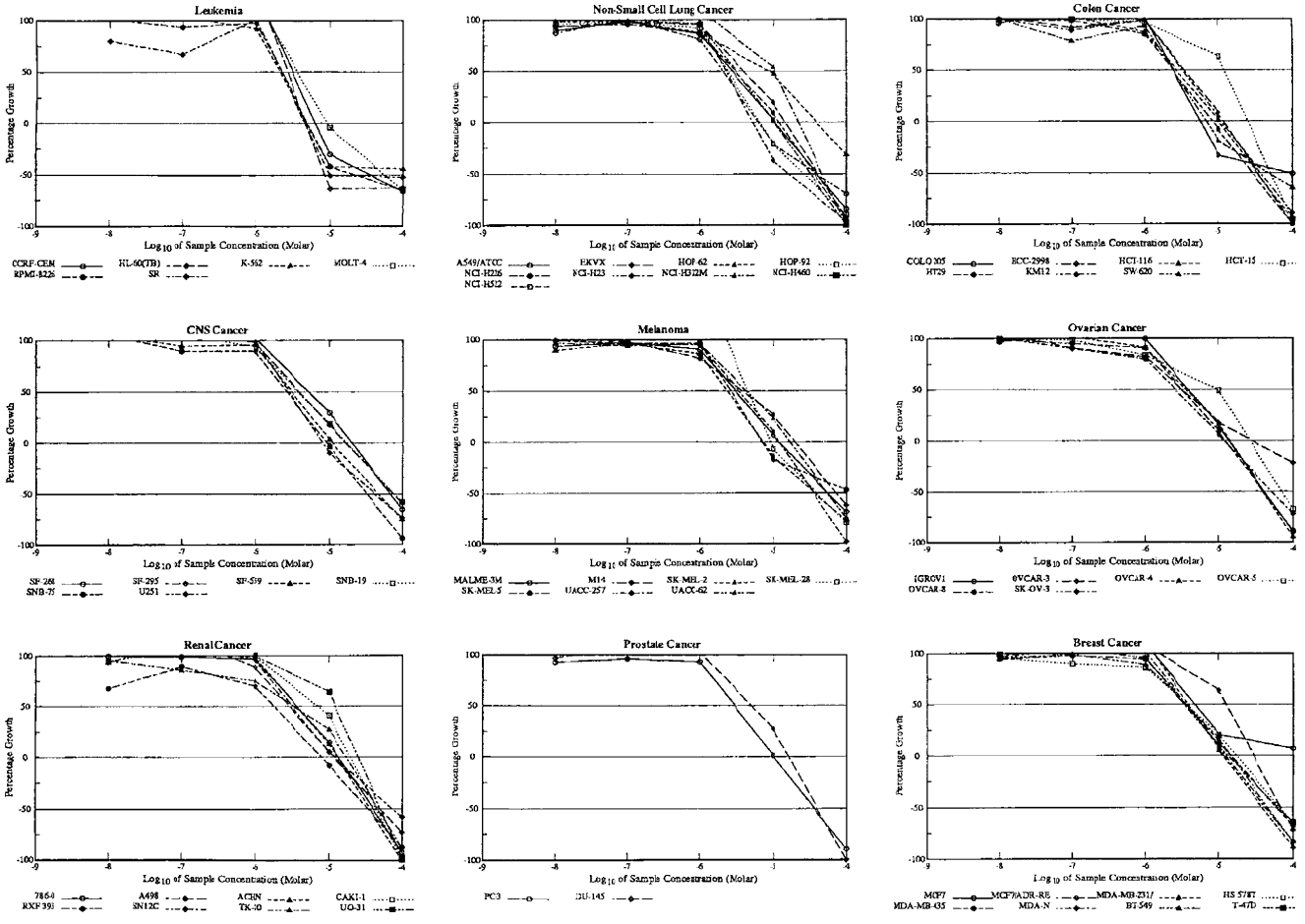


Fig. 4. Dose response curves for 4,5-dihydro-2-[2-(4-octyloxyphenyl)ethene]-3-(2-hydroxyethyl) oxazolinium chloride **14t**.

(C-4), 167.4 (CO_2); MS (DCI, CH_4) m/z 417 ($[MH]^+$, 100), 371 ($[MH]^+$–$MeCH_2OH$, 11), 193 ($[MH]^+$–$C_{16}H_{33}$, 12); HRMS (DCI, CH_4) Calc. for $C_{27}H_{45}O_3$ ($[MH]^+$): 417.3369. Found: 417.3410.

*5.1.8. Ethyl 4-octadecyloxycinnamate (**15′w**)*

M.p. 63 °C; ^{1}H-NMR ($CDCl_3$) δ 0.88 (t, 3H, $J = 7$ Hz, *Me*$(CH_2)_{17}$), 1.21–1.54 (m, 30H, Me(*CH*$_2)_{15}$), 1.34 (t, 2H, $J = 7$ Hz, CO_2CH_2*Me*), 1.78 (sextet, 2H, $J = 7$ Hz, OCH_2*CH*$_2$), 3.98 (t, 2H, $J = 7$ Hz, OCH_2), 4.26 (q, 2H, $J = 7$ Hz, CO_2*CH*$_2$Me), 6.30 (d, 1H, $J = 16$ Hz, $CHCO_2$), 6.89 and 7.47 (AA′XX′ system, 4H, $J = 8$ Hz, ArH), 7.65 (d, 1H, $J = 16$ Hz, ArCH); ^{13}C-NMR ($CDCl_3$) δ 14.0 and 14.3 (two Me), 22.6 (C_{17}), 25.9 and 29.1–29.8 (C_2–C_{15}), 31.8 (C_{16}), 60.2 (CO_2*C*H_2Me), 68.0 (CH_2O), 114.7 (C-3 and C-3′), 115.4 (*C*HCO_2), 126.8 (C-1), 129.6 (C-2 and C-2′), 144.3 (Ar*C*H), 160.9 (C-4), 167.24 (CO_2); MS (DCI, CH_4) m/z 445 ($[MH]^+$, 100), 399 ($[MH]^+$, $MeCH_2OH$, 18), 193 ($[MH]^+C_{18}H_{35}$, 28); HRMS (DCI)CH_4) Calc. for $C_{29}H_{49}O_3$ ($[MH]^+$): 445.3682. Found: 445.3690.

*5.1.9. Hydrolysis of methyl 4-alkoxycinnamates (**15**) to 4-alkoxycinnamic acids **10***

5.1.9.1. General procedure. A methyl 4-alkoxycinnamate (10 mmol) in EtOH (10 mL) was added to NaOH (5 M, 20 mL, 100 mmol). The solution was refluxed for 4 h during which the salt precipitated. The mixture was cooled, acidified (conc. HCl), extracted (EtOAc–H_2O), dried ($MgSO_4$), and evaporated to dryness. The acids were obtained as solids in quantitative yield.

*5.1.10. 4-Propoxycinnamic acid (**10r**)*

M.p. 155 °C; ^{1}H-NMR ($CDCl_3$) δ 1.03 (t, 3H, $J = 8$ Hz, *Me*), 1.82 (sextet, 2H, $J = 8$ Hz, CH_2*CH*$_2$Me), 3.93 (t, 2H, $J = 8$ Hz, OCH_2), 6.42 (d, 1H, $J = 16$ Hz, *CH*CO_2), 6.87 and 7.47 (AA′XX′ system, 4H, $J = 8$ Hz, *ArH*), 7.66 (d, 1H, $J = 16$ Hz, ArCH); ^{13}C-NMR ($CDCl_3$) δ 10.4 (Me), 22.5 (*C*H_2CH_2O), 69.7 (CH_2O), 114.8 (C-3 and C-3′), 116.2 (*C*HCO_2), 129.8 (C-2 and C-2′), 145.2 (Ar*C*H), 161.0 (C-4), 171.8 (CO_2); MS (DCI, CH_4) m/z 207 ($[MH]^+$, 100), 189 ($[MH]^+$–H_2O, 36), 165 ($[MH]^+$–C_3H_6, 9); HRMS (DCI, CH_4) Calc. for $C_{12}H_{15}O_3$ ($[MH]^+$): 207.1021. Found: 207.1020.

*5.1.11. 4-Butoxycinnamic acid (**10s**)*

M.p. 152 °C; ^{1}H-NMR ($CDCl_3$) δ 0.98 (t, 3H, $J = 7$ Hz, *Me*), 1.50 (sextet, 2H, $J = 7$ Hz, CH_2*CH*$_2$Me), 1.79 (quintet, 2H, $J = 16$ Hz, CH_2*CH*$_2CH_2$), 4.00 (t, 2H, $J = 7$ Hz, OCH_2), 6.31 (d, 1H, $J = 16$ Hz, *CH*CO_2), 6.91 and 7.50 (AA′XX′ system, 4H, $J = 8$ Hz, *ArH*), 7.74 (d, 1H, $J = 16$ Hz, Ar*CH*); ^{13}C-NMR ($CDCl_3$) δ 13.82 (Me), 19.20 (Me*C*H_2), 31.25 (*C*H_2CH_2O), 67.89 (CH_2O), 114.38 (C-3 and C-3′) 114.91 (*C*HCO_2), 126.64 (C-1) 130.10 (C-2 and C-2′), 146.82 (Ar*C*H), 161.66 (C-4), 172.16 (CO_2); MS (DCI, CH_4) m/z 221 ($[MH]^+$, 100), 203 ($[MH]^+$–H_2O, 30), 165 ($[MH]^+$–C_4H_8, 12); HRMS (DCI, CH_4) Calc. for $C_{13}H_{17}O_3$ ($[MH]^+$): 221.1178. Found: 221.1140.

*5.1.12. 4-Octyloxycinnamic acid (**10t**)*

M.p. 150 °C; ^{1}H-NMR ($CDCl_3$) δ 0.88 (br t, 3H, $J = 6$ Hz, *Me*), 1.2-1.65 (m, 10H, Me(*CH*$_2)_5$), 1.79 (quintet, 2H, $J = 6$ Hz, OCH_2*CH*$_2$), 3.99 (t, 2H, $J = 6$ Hz, O*CH*$_2$), 6.31 (d, 1H, $J = 16$ Hz, *CH*CO_2), 6.90 and 7.50 (AA′XX′ system, 4H, $J = 8$ Hz, *ArH*), 7.40 (d, 1H, $J = 16$ Hz, Ar*CH*); ^{13}C-NMR ($CDCl_3$) δ 14.08 (*Me*CH_2), 22.64, 25.98, 29.12, 29.21, 29.34 (Me(*C*$H_2)_5$), 31.79 (*C*H_2CH_2O), 68.79 (CH_2O), 114.38 (*C*HCO_2), 114.88 (C-3 and C-3′), 126.55 (C-1), 130.07 (C-2 and C-2′), 146.74 (Ar*C*H), 161.37 (C-4), 172.11 (CO_2); MS (DCI, CH_4) m/z 277 ($[MH]^+$, 100), 259 ($[MH]^+$–H_2O, 26), 165 ($[MH]^+$–C_8H_{16}, 12); HRMS (DCI, CH_4) Calc. for $C_{17}H_{25}O_3$ ($[MH]^+$): 277.1804. Found: 277.1800.

*5.1.13. 4-Dodecyloxycinnamic acid (**10u**)*

M.p. 128 °C; ^{1}H-NMR ($CDCl_3$) δ 0.88 (t, 3H, $J = 7$ Hz, *Me*$(CH_2)_{11}$), 1.85–1.91 (m, 18H, Me(*CH*$_2)_9$), 1.79 (sextet, 2H, $J = 7$ Hz, OCH_2*CH*$_2$), 3.99 (t, 2H, $J = 7$ Hz, OCH_2), 4.25 (q, 2H, $J = 7$ Hz, CO_2*CH*$_2$Me), 6.31 (d, 1H, $J = 16$ Hz, $CHCO_2$), 6.90 and 7.49 (AA′XX′ system, 4H, $J = 8$ Hz, ArH), 7.74 (d, 1H, $J = 16$ Hz, ArCH); ^{13}C-NMR ($CDCl_3$) δ 14.13 (Me), 22.70 (C_{11}), 26.00 and 29.1–29.7 (C_2–C_9), 31.93 (C_{10}), 68.22 (CH_2O), 114.39 (*C*HCO_2H), 114.91 (C-3 and C-3′), 126.58 (C-1), 130.10 (C-2 and C-2′), 146.80 (Ar*C*H), 161.41 (C-4), 172.18 (CO_2H); MS (DCI, CH_4) m/z 333 ($[MH]^+$, 100), 315 ($[MH]^+$–H_2O, 24), 193 ($[MH]^+$–$C_{11}H_{23}$, 7); HRMS (DCI, CH_4) Calc. for $C_{21}H_{33}O_3$ ($[MH]^+$): 333.2430. Found: 333.2420.

*5.1.14. 4-Hexadecyloxycinnamic acid (**10v**)*

M.p. 125 °C; ^{1}H-NMR ($CDCl_3$) δ 0.88 (t, 3H, $J = 7$ Hz, *Me*$(CH_2)_{15}$), 1.30–1.58 (m, 26H, Me*(CH*$_2)_{13}$), 1.85 (sextet, 2H, $J = 7$ Hz, OCH_2*CH*$_2$), 3.99 (t, 2H, $J = 7$ Hz, OCH_2), 6.31 (d, 1H, $J = 16$ Hz, $CHCO_2$), 6.90 and 7.49 (AA′XX′ system, 4H, $J = 8$ Hz, ArH), 7.74 (d, 1H, $J = 16$ Hz, ArCH); ^{13}C-NMR ($CDCl_3$) δ 14.10 (Me), 22.68 (C_{15}), 26.01 and 29.2–29.7 (C_2–C_{13}), 31.93 (C_{14}), 68.25 (CH_2O), 114.30 (*C*HCO_2H), 114.96 (C-3 and C-3′), 126.65 (C-1), 130.07 (C-2 and C-2′), 146.77 (Ar*C*H), 161.43 (C-4), 171.53 (CO_2H); MS (DCI, CH_4) m/z 389 ($[MH]^+$, 100), 371 ($[MH]^+$–H_2O, 18), 193 ($[MH]^+$–$C_{16}H_{33}$, 13); HRMS (DCI, CH_4) Calc. for $C_{25}H_{41}O_3$ ($[MH]^+$): 389.3056. Found: 389.3060.

*5.1.15. 4-Octadecyloxycinnamic acid (**10w**)*

M.p. 119 °C; ^{1}H-NMR ($CDCl_3$) δ 0.88 (t, 3H, $J = 7$ Hz, *Me*$(CH_2)_{17}$), 1.20–1.62 (m, 30H, Me(*CH*$_2)_{15}$), 1.78 (sextet, 2H, $J = 7$ Hz, OCH_2*CH*$_2$), 3.99 (t, 2H, $J = 7$ Hz, OCH_2), 6.31 (d, 1H, $J = 16$ Hz, $CHCO_2$), 6.90 and

7.49 (AA′XX′ system, 4H, $J = 8$ Hz, ArH), 7.73 (d, 1H, $J = 16$ Hz, ArCH); ^{13}C-NMR ($CDCl_3$) δ 14.12 (Me),22.70 (C_{17}), 26.00 and 29.1–29.7 (C_2–C_{15}), 31.94 (C_{16}), 68.22 (CH_2O), 114.09 (*C*HCO_2H), 114.91 (C-3 and C-3′), 126.59 (C-1), 130.06 (C-2 and C-2′), 146.70 (Ar*C*H), 161.40 (C-4), 170.68 (CO_2H); MS (DCI, CH_4) m/z 399 ($[MH]^+$, 100), 165 ($[MH]^+$–$C_{18}H_{35}$, 20); HRMS (DCI, CH_4) Calc. for $C_{27}H_{45}O_3$ ($[MH]^+$): 417.3369. Found: 417.3320.

5.1.16. Cinnamoyl chlorides ***11***

5.1.16.1. General procedure. A solution of a cinnamic acid derivative (8 mmol) and $SOCl_2$ in toluene (13 mL) was heated at 70 °C for 4–24 h. Evaporation of the solution gave ca. 80% of the corresponding acyl chloride.

5.1.17. Cinnamoyl amides ***12***

5.1.17.1. General procedure. A solution of the crude cinnamoyl chloride in dry dioxane (7 mL) was added dropwise (0.5 h) to a stirred, cooled (15 °C) solution of diethanolamine (1.2 g, 16 mmol) in dry dioxane (14 mL). The mixture was further stirred for 24 h, after which most of the solvent was evaporated. The residue was extracted (EtOAc–H_2O $\times 3$), dried ($MgSO_4$) and evaporated. The residue was purified by silica gel column chromatography (EtOAc), to give **12** in yields of ca. 12.5%.

5.1.18. N,N-Bis-(2-hydroxyethyl)-3-(4-propoxyphenyl)-2-propenamide ***(12r)***

M.p. 100 °C; ^{1}H-NMR ($CDCl_3$) δ 1.04 (t, 3H, $J = 7$ Hz, *Me*), 1.82 (sex, 2H, $J = 7$ Hz, CH_2CH_2Me), 3.65 (m, 4H, NCH_2), 3.85 (m, 4H, CH_2OH), 3.93 (t, 2H, $J = 7$ Hz, CH_2O), 6.79 (d, 1H, $J = 16$ Hz, $CHCO_2$), 6.85 and 7.44 (AA′XX′ system, 4H, $J = 8$ Hz, *ArH*), 7.62 (d, 2H, $J = 16$ Hz, Ar*CH*); ^{13}C-NMR ($CDCl_3$) δ 10.49 (Me), 22.52 ($MeCH_2$), 52.32 and 51.36 (NCH_2), 61.54 and 61.28 (CH_2OH) 69.61 (CH_2O), 114.76 (C-3 and C-3′), 114.91 (CH_2O), 127.53 (C-1), 129.57 (C-2 and C-2′), 143.09 (Ar*C*H), 160.67 (C-4), 169.26 (CO); MS (DCI, CH_4) m/z 294 ($[MH]^+$, 100), 276 ($[MH]^+$–H_2O, 24), 252 ($[MH]^+$–C_3H_6, 6), 189 ($[MH]^+$–$C_4H_{11}NO_2$, 59); HRMS (DCI, CH_4) Calc. for $C_{16}H_{24}NO_4$ ($[MH]^+$): 294.1705. Found: 294.1734.

5.1.19. N,N-Bis-(2-hydroxyethyl)-3-(4-butoxyphenyl)-2-propenamide ***(12s)***

M.p. 94 °C; ^{1}H-NMR ($CDCl_3$) δ 0.98 (t, 3H, $J = 7$ Hz, *Me*), 1.49 (sex, 2H, $J = 7$ Hz, CH_2CH_2Me), 1.77 (quintet, 2H, $J = 7$ Hz, ^{13}C-NMR ($CDCl_3$) δ 13.81 (Me), 19.22 ($MeCH_2$), 31.25 (CH_2CH_2O), 51.35 AND 52.29 (NCH_2), 61.20 and 61.37 (CH_2OH), 67.84 (CH_2O), 114.79 (C-3 and C-3′), 115.04 (*C*HCO), 127.59 (C-1), 129.56 (C-2 and C-2′), 143.01 (Ar*C*H), 160.67 (C-4), 169.20 (CO); MS (DCI, CH_4) m/z 308 ($[MH]^+$, 40), 243 ($[MH]^+$–$C_2H_60_2$, 10), 221 ($[MH]^+$–$C_4H_7O_2$, 53), 203 ($[MH]^+$–$C_4H_{11}NO_2$, 19), 179 ($[MH]^+$–$C_5H_7NO_3$,10); HRMS (DCI, CH_4) Calc. for $C_{17}H_{26}NO_4$ ($[MH]^+$): 308.1861. Found: 308.1878.

5.1.20. N,N-Bis-(2-hydroxyethyl)-3-(4-octyloxyphenyl)-2-propenamide ***(12t)***

M.p. 85 °C; ^{1}H-NMR ($CDCl_3$) δ 0.98 (t, 2H, $J = 7$ Hz, *Me*), 1.2–1.43 (m, 10H, $(CH_2)_5Me$), 1.56–1.86 (m, 4H, $OCH_2CH_2CH_2$), 3.61–3.72 (m, 4H, CH_2N), 3.82–3.92 (m, 4H, CH_2OH), 3.97 (t, 2H, $J = 7$ Hz, CH_2O), 6.78 (d, 1H, $J = 16$ Hz, $CHCO_2$), 6.87 and 7.45 (AA′XX′ system, 4H, $J = 8$ Hz, *ArH*), 7.65 (d, 1H, $J = 16$ Hz, Ar*CH*); ^{13}C-NMR ($CDCl_3$) δ 14.07 (Me), 22.65, 26.03, 29.21, 29.22, 29.35 ($Me(CH_2)_5$), 31.81 (CH_2CH_2O), 51.32 and 52.88 (NCH_2), 61,25 and 61.49 (CH_2OH), 68.17 (CH_2O), 114.79 (C-3 and C-3′), 114.94 (*C*HCO), 127.57 (C-1), 129.56 (C-2 and C-2′), 143.10 (Ar*C*H), 160.70 (C-4), 169.24 (CO); MS (DCI, CH_4) m/z 364 ($[MH]^+$, 89), 346 ($[MH]^+$–H_2O, 10), 318 ($[MH]^+$–C_2H_6O, 5), 259 ($[MH]^+$–$C_4H_{11}NO_2$,, 100), 132 ($C_5H_{10}NO_3$); HRMS (DCI, CH_4) Calc. for $C_{21}H_{34}NO_4$ ($[MH]^+$): 364.2488. Found: 364.2500.

5.1.21. N,N-Bis-(2-hydroxyethyl)-3-(4-methoxyphenyl)-2-propenamide ***(12n)***

M.p. 84 °C; ^{1}H-NMR ($CDCl_3$) δ 3.62 (br t, 4H, NCH_2), 3.8 (s, 3H, MeO), 3.83 (br t, 4H, CH_2OH), 6.72 (d, 1H, $J = 16$ Hz, $CHCO_2$), 6.84 and 7.43 (AA′XX′ system, $J = 8$ Hz, ArH), 7.58 (d, 1H, $J = 16$ Hz, ArCH); ^{13}C-NMR ($CDCl_3$) δ 51.30 and 52.28 (NCH_2), 55.34 (MeO), 61.17 and 61.34 (CH_2OH), 114.27 (C-3 and C-3′), 115.25 ($CHCO_2$), 127.63 (C-1), 129.56 (C-2 and C-2′), 142.88 (ArCH), 161.04 (C-4), 169.14 (CO); MS (DCI, CH_4) 266 ($[MH]^+$, 46), 161 ($[MH]^+$–$C_4H_{11}NO_2$, 23); HRMS (DCI, CH_4) Calc. for $C_{14}H_{20}NO_4$ ($[MH]^+$): 266.1392. Found: 266.1400.

5.1.22. N,N-Bis-(2-hydroxyethyl)-3-(4-methylphenyl)-2-propenamide ***(12j)***

M.p. 112 °C; ^{1}H-NMR ($CDCl_3$) δ 2.35 (s, 3H, Me), 3.59–3.69 (m, 4H, NCH_2), 3.80–3.90 (m, 4H, CH_2OH), 6.89 (d, 1H, $J = 16$ Hz, NCH_2), 7.14 and 7.39 (AA′XX′ system, 4H, $J = 8$ Hz, ArH), 7.62 (d, 1H, $J = 16$ Hz, ArCH); ^{13}C-NMR ($CDCl_3$) δ 21.40 (Me), 51.31 and 52.32 (NCH_2), 61.25 and 61.41 (CH_2OH), 116.62 ($CHCO_2$), 127.93 (C-2 and C-2′), 129.53 (C-3 and C-3′), 132.35 (C-1), 140.14 (C-4), 143.24 (ArCH), 169.04 (CNO), MS (DCI, CH_4) 250 ($[MH]^+$, 100), 232 ($[MH]^+$–H_2O, 64), 161 ($[MH]^+$–$C_4H_{11}NO_2$, 40); HRMS (DCI, CH_4) Calc. for $C_{14}H_{20}NO_3$ ($[MH]^+$): 250.1443. Found: 250.1440.

*5.1.23. N,N-Bis-(2-hydroxyethyl)-3-(3-methoxyphenyl)-2-propenamide (**12m**)*

M.p. 60–63 °C; ^{1}H-NMR ($CDCl_3$) 3.60 (br t, 4H, NCH_2), 3.78 (s, 3H, MeO), 3.78–3.86 (m, 4H, CH_2OH), 6.86 (dd, 1H, $J = 8$ Hz, 1 Hz, CH-4), 6.92 (d, 1H, $J = 16$ Hz, NCH_2), 6.99 (br t, 1H, $J = 1$ Hz, CH-2), 7.07 (d, 1H, $J = 8$ Hz, CH-6), 7.24 (t, 1H, $J = 8$ Hz, CH-5), 7.56 (d, 1H, $J = 16$ Hz, ArCH); ^{13}C-NMR ($CDCl_3$) 51.06 and 52.16 (NCH_2), 55.30 (MeO), 60.87 (two CH_2OH), 113.36 (*C*HCO), 115.27 (C-2), 118.10 (C-4), 120.48 (C-6), 136.38 (C-1), 142.94 (Ar*C*H), 159.78 (C-3), 168.62 (CO); MS (DCI, CH_4) m/z 266 ($[MH]^+$, 100), 248 ($[MH]^+$–H_2O, 19) 161 ($[MH]^+$, $C_4H_{11}NO_2$, 43), 106 ($C_4H_{12}NO_2$, 5); HRMS Calc. for $C_{14}H_{20}NO_4$ ($[MH]^+$): 266.1392. Found: 266.1430.

*5.1.24. Oxazolinium salts **14**—cyclisation of an amide upon treatment with $SOCl_2$*

A solution of a substituted propenamide **12** (0.5 mmol), MeCN (15 mL) and $SOCl_2$ (0.15 mL, 2 mmol) was refluxed for 6 h. The mixture was cooled and filtered to give the oxazolidinium salts in quantitative yield.

*5.1.25. 4,5-Dihydro-2-[2-(4-propoxyphenyl)ethene]-3-(2-hydroxyethyl)-oxazolinium chloride (**14r**)*

^{1}H-NMR (DMSO) δ 0.98 (t, 3H, $J = 6$ Hz, *Me*), 1.76 (sextet, 2H, $J = 6$ Hz, CH_2CH_2Me), 3.08 (t, 2H, $J = 5.4$ Hz, NCH_2), 3.30 (br t, 2H, NCH_2), 3.71 (t, 2H, $J = 4.7$ Hz, CH_2OH), 3.98 (t, 2H, $J = 6.5$ Hz, CH_2OAr), 4.42 (m, 2H, CH_2O), 6.48 (d, 1H, $J = 16$ Hz, $CHCO_2$), 6.99 and 7.68 (AA′XX′ system, 4H, $J = 8$ Hz, *ArH*), 7.80 (d, 2H, $J = 16$ Hz, Ar*CH*); ^{13}C-NMR (DMSO) δ 10.21 (Me), 22.22 ($MeCH_2$), 48.63 and 50.33 (NCH_2), 57.15 (CH_2OH), 59.35 (CH_2O), 70.38 (CH_2OAr), 115.08 (C-3 and C-3′), 115.90 (*C*HCO), 127.69 (C-1), 130.04 (C-2 and C-2′), 144.98 (Ar*C*H), 162.45 (C-4), 165.94 (CNO); MS (FAB) m/z 313 ($[MH]^+$, 1.3), 294 ($[MH]^+$–H_2O, 26).

*5.1.26. 4,5-Dihydro-2-[2-(4-butoxyphenyl)ethene]-3-(2-hydroxyethyl)-oxazolinium chloride (**14s**)*

^{1}H-NMR (DMSO) δ 0.92 (t, 3H, $J = 6$ Hz, *Me*), 1.43 (sextet, 2H, $J = 6$ Hz, CH_2CH_2Me), 1.70 (quintet, 2H, $J = 7$ Hz, CH_2CH_2O), 3.06 (t, 2H, $J = 5.4$ Hz, NCH_2), 3.29 (br t, 2H, NCH_2), 3.70 (m, 2H, CH_2OH), 4.0 (t, 2H, $J = 6.4$ Hz, CH_2OAr), 4.40 (br t, 2H, $J = 5$ Hz, CH_2O), 5.32 (t, 1H, $J = 8$ Hz, OH), 6.46 d, 1H, $J = 16$ Hz, *CH*CNO), 6.97 and 7.66 (AA′XX′ system, 4H, $J = 8$ Hz, *ArH*), 7.78 (d, 1H, $J = 16$ Hz, Ar*CH*); ^{13}C-NMR (DMSO) δ 13.57 (Me), 22.40 ($MeCH_2$), 30.53 ($MeCH_2CH_2$) 45.77 and 49.15 (NCH_2), 56.22 (CH_2OH), 59.36 (CH_2O), 67.28 (CH_2OAr), 114.50 (*C*HCO), 114.78 (C-3 and C-3′), 127.69 (C-1), 130.10 (C-2 and C-2′), 145.02 (Ar*C*H), 160.65 (C-4), 166.01 (CNO); MS (FAB) m/z 326 ($[MH]^+$, 0.5), 308 ($[MH]^+$–H_2O, 3).

*5.1.27. 4,5-Dihydro-2-[2-(4-octyloxyphenyl)ethene]-3-(2-hydroxyethyl)-oxazolinium chloride (**14t**)*

^{1}H-NMR (DMSO) δ 0.87 (br t, 3H, *Me*), 1.20-1.37 (m, 12H, $(CH_2)_6Me$), 3.07 and 3.30 (t, 4H, $J = 6$ Hz, NCH_2), 3.69 (quintet, 2H, $J = 6$ Hz, CH_2OH), 4.02 (t, 2H, CH_2OAr), 4.40 (t, 2H, $J = 6$ Hz, CH_2O), 4.97 (t, 1H, $J = 6$ Hz, OH), 6.47 (d, 1H, $J = 16$ Hz, *CH*CNO) 6.99 and 7.68 (AA′XX′ system, 4H, $J = 8$ Hz, *ArH*), 7.74 (d, 1H, $J = 16$ Hz, Ar*CH*); ^{13}C-NMR (DMSO) δ 13.86 (Me), 22.40, 25.37, 28.46, 28.55, 28.61 ($Me(CH_2)_5$) 31.13 (CH_2CH_2O) 45.53 and 49.11 (NCH_2), 56.21 (CH_2OH), 59.37 (CH_2O), 67.58 (CH_2OAr), 114.51 (*C*HCO), 114.79 (C-3 and C-3′), 126.27 (C-1), 130.10 (C-2 and C-2′), 145.00 (Ar*C*H), 160.66 (C-4), 166.03 (CNO); MS (FAB) m/z 382 ($[MH]^+$, 3), 364 ($[MH]^+$–H_2O, 13).

*5.1.28. N,N-Bis-(2-chloroethyl)-3-(substituted-phenyl)-2-propenamides (**16**)*

5.1.28.1. General procedure. A solution of an cinnamoyl chloride **11** (3 mmol) in dry $CHCl_3$ (7 mL) was added dropwise (20 min) to a stirred solution of bis-(2-chloroethyl)amine hydrochloride (625 mg, 3.5 mmol) and Et_3N (1 mL, 7 mmol) in dry $CHCl_3$ (7 mL). The mixture was further stirred for 0.5 h and was then extracted with dilute HCl, H_2O and dilute $NaHCO_3$. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated to dryness. The corresponding amides **16** were obtained as oils in 60–85% yield.

*5.1.29. N,N-Bis-(2-chloroethyl)-3-(4-methylphenyl)-2-propenamide (**16j**)*

^{1}H-NMR ($CDCl_3$) δ 3.61–3.94 (m, 8H, four CH_2), 6.72 (d, 1H, $J = 16$ Hz, CHCNO), 7.17 and 7.41 (AA′XX′ system, 4H, $J = 8$ Hz, ArH), 7.70 (d, 1H, $J = 16$ Hz, ArCH); ^{13}C-NMR ($CDCl_3$) δ 41.79 and 41.90 (CH_2Cl), 50.01 and 50.06 (CH_2N), 55.39 (Me), 115.19 (*C*HCO), 127.93 (C-2 and C-2′), 129.59 (C-3 and C-3′), 132.07 (C-1), 140.39 (C-4), 144.24 (Ar*C*H), 166.94 (CNO); MS (DCI, CH_4) m/z 286 ($[MH]^+$, 14), 232 ($[MH]^+$–HCl, 10), 161 ($[MH]^+$–$C_4H_8Cl_2N$, 100), 142 ($C_4H_8Cl_2N$, 6); HRMS (DCI, CH_4) Calc. for $C_{14}H_{18}Cl_2NO$ ($[MH]^+$): 286.0765. Found: 286.0700.

*5.1.30. N,N-Bis-(2-chloroethyl)-3-(4-methoxyphenyl)-2-propenamide (**16n**)*

^{1}H-NMR ($CDCl_3$) δ 3.64–3.92 (m, 8H, four CH_2), 3.84 (s, 3H, MeO), 6.71 (d, 1H, $J = 16$ Hz, CHCNO), 6.91 and 7.49 (AA′XX′ system, 4H, $J = 8$ Hz, ArH), 7.71 (d, 1H, $J = 16$ Hz, ArCH); ^{13}C-NMR ($CDCl_3$) δ 41.72 and 42.03 (CH_2Cl), 50.14 and 51.18 (NCH_2), 113.68 (*C*HCO), 114.32 (C-3 and C-3′), 127.57 (C-1), 129.62 (C-2 and C-2′), 143.86 (Ar*C*H), 161.21 (C-4), 167.10 (CNO); MS (DCI, CH_4) m/z 302 ($[MH]^+$, 47), 266 ($[MH]^+$–HCl, 18), 161 ($[MH]^+$–$C_4H_8Cl_2N$, 100);

HRMS (DCI, CH_4) Calc. for $C_{14}H_{18}Cl_2NO_2$ ($[MH]^+$): 302.0715. Found: 302.0640.

*5.1.31. N,N-Bis-(2-chloroethyl)-3-(2,4-dimethoxy-phenyl)-2-propenamide (**16p**)*

^{1}H-NMR ($CDCl_3$) δ 3.73–3.96 (m, 8H, four CH_2), 3.92 (s, 3H, *p*-MeO), 3.93 (s, 3H, *m*-MeO) 6.71 (d, 1H, $J = 16$ Hz, CHCNO), 6.88 (d, 1H, $J = 8$ Hz, H-5), 6.88 (d, 1H, $J = 8$ Hz, H-2), 7.15 (dd, 1H, $J = 8$ Hz, 2 Hz, H-6), 7.69 (d, 1H, $J = 16$ Hz, ArCH); ^{13}C-NMR ($CDCl_3$) δ 41.9 (two CH_2Cl), 50.17 and 51.22 (NCH_2), 56.01 (two MeO), 110.40 (C-2), 111.27 (C-5), 114.12 (*C*HCO), 122.01 (C-6), 127.94 (C-1), 144.11 (Ar*C*H), 149.26 (C-4), 151.00 (C-3), 167.06 (CNO); MS (DCI, CH_4) *m*/*z* 332 ($[MH]^+$, 4), 296 ($[MH]^+$–HCl, 2), 190 ($[MH]^+$–$C_4H_8Cl_2N$, 100); HRMS (DCI, CH_4) Calc. for $C_{15}H_{20}Cl_2NO_3$ ($[MH]^+$): 332.0820. Found: 332.0820.

*5.1.32. N,N-Bis-(2-chloroethyl)-3-(3,4,5-trimethoxy-phenyl)-2-propenamide (**16p**)*

^{1}H-NMR ($CDCl_3$) δ 3.68–3.98 (m, 8H, four CH_2), 3.87 (s, 3H, *p*-MeO), 3.88(s, 6H, two *m*-MeO), 6.75 (s, 2H, C-2 and C-5), 6.76 (d, 1H, $J = 16$ Hz, CHCNO), 7.65 (d, 1H, $J = 16$ Hz, ArCH); ^{13}C-NMR ($CDCl_3$) δ 41.7 (two CH_2Cl), 49.86 and 51.03 (NCH_2), 56.12 (three MeO), 105.14 (C-2 and C-6), 115.59 (*C*HCO), 130.33 (C-4), 146.10 (Ar*C*H), 153.32 (C-3 and C-5), 166.71 (CNO); MS (DCI, CH_4) *m*/*z* 362 ($[MH]^+$, 4), 221 ($[MH]^+$–$C_4H_9Cl_2N$, 100); HRMS (DCI, CH_4) Calc. for $C_{16}H_{22}Cl_2NO_4$ ($[MH]^+$, 362.0926. Found: 332.0910.

*5.1.33. Oxazolidinium chlorides **17***

5.1.33.1. General procedure. A cinnamoyl chloride **11** (8 mmol) in $CHCl_3$ (10 mL) was added dropwise to a solution of bis-(2-chloroethyl)amine hydrochloride (1.43 g, 8 mmol), Et_3N (2.8 mL, 20 mmol) in $CHCl_3$ (10 mL). The mixture was stirred for 0.5–1 h at r.t. then extracted (HCl 3N, $NaHCO_3$). The organic layer was washed with brine, dried ($MgSO_4$) and heated for 1–3 h at 50 °C. Evaporation of the solvent gave the corresponding product **17** in ca. 70% yield.

*5.1.34. 4,5-Dihydro-2-[2-(4-dodecyloxyphenyl)ethene]-3-(2-chloroethyl)-oxazolinium chloride (**17u**)*

^{1}H-NMR (DMSO) δ 0.85 (t, 3H, $J = 7$ Hz, *Me*), 1.28–1.47 (m, 18H, $(CH_2)_9$Me), 1.70 (quintet, 2H, $J = 7$ Hz, CH_2CH_2O), 3.91–4.5 (m, 8H, NCH_2CH_2Cl, CH_2OAr, NCH_2CH_2O), 4.43 (t, 2H, $J = 7$ Hz, NCH_2CH_2O), 6.47 (d, 1H, $J = 16$ Hz, *CH*CNO), 6.97 and 7.67 (AA′XX′ system, 4H, $J = 8$ Hz, *ArH*), 7.81 (d, 1H, $J = 16$ Hz, Ar*CH*); ^{13}C-NMR (DMSO) δ 13.95 (Me), 22.09 (C_{11}), 25.45 and 28.6–29.0 (C_2–C_9), 31.30 (C_{10}), 39.52 (CH_2Cl), 47.67 and 48.19 (NCH_2), 59.37 (CH_2O), 67.67 (CH_2OAr) 114.54 (*C*HCO), 114.87 (C-3 and C-3′), 126.43 (C-1), 130.20 (C-2 and C-2′), 145.22 (Ar*C*H), 160.76 (C-4), 166.08 (CNO).

*5.1.35. 4,5-Dihydro-2-[2-(4-hexadecyloxyphenyl)-ethene]-3-(2-chloroethyl)-oxazolinium chloride (**17v**)*

^{1}H-NMR ($CDCl_3$/acetone-d_6) δ 0.88 (t, 3H, $J = 7$ Hz, *Me*), 1.13–1.54 (m, 28H, $(CH_2)_9$Me), 1.79 (quintet, 2H, $J = 7$ Hz, CH_2CH_2O), 3.56 (m, 2H, CH_2Cl), 3.56–4.10 (m, 4H, two NCH_2), 4.14 (t, 2H, $J = 7$ Hz, CH_2OAr), 4.66 (br t, 2H, NCH_2CH_2O), 6.36 (d, 1H, $J = 16$ Hz, *CH*CNO), 6.89 and 7.54 (AA′XX′ system, 4H, $J = 8$ Hz, *ArH*), 7.82 (d, 1H, $J = 16$ Hz, Ar*CH*); ^{13}C-NMR ($CDCl_3$/acetone-d_6) δ 13.12 (Me), 21.83 (C_{15}), 25.21 and 28.1–30.0 (C_2–C_{13}), 31.30 (C_{14}), 37.83 (CH_2Cl), 46.10 and 48.29 (NCH_2), 58.52 (CH_2O), 67.32 (CH_2OAr) 113.54 (*C*HCO), 114.12 (C-3 and C-3′), 126.06 (C-1), 129.27 (C-2 and C-2′), 145.22 (Ar*C*H), 160.59 (C-4), 165.75 (CNO).

*5.1.36. 4,5-Dihydro-2-[2-(4-octadecyloxyphenyl)ethene]-3-(2-chloroethyl)-oxazolinium chloride (**17w**)*

^{1}H-NMR ($CDCl_3$/acetone-d_6) δ 0.78 (t, 3H, $J = 7$ Hz, *Me*), 1.02–1.43 (m, 30H, $(CH_2)_{15}$Me), 1.78 (quintet, 2H, $J = 7$ Hz, CH_2CH_2O), 3.35–3.78 (m, 6H, two NCH_2 and CH_2Cl), 3.88 (t, 2H, $J = 7$ Hz, CH_2OAr), 4.60 (br t, 2H, NCH_2CH_2O), 6.30 (d, 1H, $J = 16$ Hz, *CH*CO), 6.80 and 7.43 (AA′XX′ system, 4H, $J = 8$ Hz, *ArH*), 7.70 (d, 1H, $J = 16$ Hz, Ar*CH*); ^{13}C-NMR ($CDCl_3$/acetone-d_6) δ 14.07 (Me), 22.64 (C_{17}), 25.96 and 29.1–29.6 (C_2–C_{15}), 31.87 (C_{16}), 38.33 (CH_2Cl), 46.78 and 48.92 (NCH_2), 59.22 (CH_2O), 68.11 (CH_2OAr) 113.94 (*C*HCO), 114.78 (C-3 and C-3′), 126.56 (C-1), 129.94 (C-2 and C-2′), 146.19 (Ar*C*H), 161.27 (C-4), 166.76 (CNO).

*5.1.37. 1-(2-oxo-2λ_4-[1,3,2,6]dioxathiazocan-6-yl)-3-(3-nitro-phenyl)-Propenone (**18**)*

To a solution of **12b** (100 mg, 0.35 mmol) [9] in dry pyridine (2 mL) $SOCl_2$ (53.8 μL, 0.73 mmol) was added. The mixture was stirred for 3 days at r.t., it was then filtered and the filtrate was extracted with CH_2Cl_2. The organic phase was washed with water, separated, dried ($MgSO_4$) and evaporated to give an orange residue that after a few hours under high vacuum it solidified, 27 mg (23% yield). ^{1}H-NMR (DMSO) δ 3.60 (m, 1H), 3.75 (m, 1H), 4.0 (m, 4H), 4.70 (m, 2H), 6.91 (d, 1H, $J = 11$ Hz, Hα), 7.60 (t, 1H, $J = 6$ Hz, H4), 7.80 (d, 1H, $J = 11$ Hz, Hβ), 7.81 (t, 1H, $J = 6$ Hz, H5), 8.21 (t, 1H, $J = 6$ Hz, H5), 8.40 (br s, 1H, H2). MS (CI, butane) *m*/*z* 327 ($[MH]^+$, 100), 297 ($[MH]^+$–H_2CO, 2), 281 ($[MH]^+$–EtOH, 4), 263 ($[MH]^+$–SO_2, 5).

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