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Synthesis and pharmacological evaluation of 5-dialkylaminomethyl-2-amino-2-oxazolines as H_1-antagonists

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Abstract

New 5-dialkylaminomethyl-2-amino-2-oxazolines have been synthesized in two steps from the corresponding dialkylamines. They were evaluated in-vitro as H_1-antagonists. Compounds **1c**, **1d** and **1j** significantly antagonized histamine-induced contraction of guinea-pig trachea with a rightward shift of the concentration–response curve to histamine. Compound **1f**, 5-[(4-benzyl-1-piperidinyl)methyl]-2-amino-2-oxazoline, induced an increase in acetylcholine E_{max} (the maximal response to acetylcholine 10^{-3} M) and a shift to the left of the concentration–response curve. The lack of effect of this compound on histamine-induced contraction rules out a non-selective potentiation of the contraction mechanisms. Preliminary structure–activity results were reported partly based on physicochemical results.

Introduction

For several years we have focused our attention mainly on the chemistry of 2-amino-2-oxazolines (Jarry et al 1986, Bosc et al 1992). Recently, we reported the synthesis of 5-[(1-aryl-4-piperazinyl)methyl]-2-amino-2-oxazolines useful either as synthons (Chaimbault et al 1999, Forfar et al 1999) or as precursors of potentially active ring-opened compounds (Bosc & Jarry 1998). 5-Aryl-2-amino-2-oxazolines have been widely investigated for pharmaceutical uses. They are very potent in suppressing appetite, but they cause CNS stimulation and produce sympathomimetic cardiovascular effects (Poos et al 1963).

In this study, we describe the synthesis of a series of 5-dialkylaminomethyl-2-amino-2-oxazolines (**1a**–**l**; Figure 1). The dialkylamino moiety is either a substituted piperidinyl, tetrahydropyridinyl, indolinyl or indolyl ring. The general structure of these compounds is characterized by the presence of pharmacophoric requirements of H_1-receptor antagonists, in comparison with the model recently refined by Ter Laak et al (Battaglia et al 1999, Van der Goot & Timmerman 2000). They were evaluated in-vitro for their ability to antagonize histamine-induced contraction of guinea-pig trachea. Preliminary structure–activity results were reported partly based on physicochemical results.

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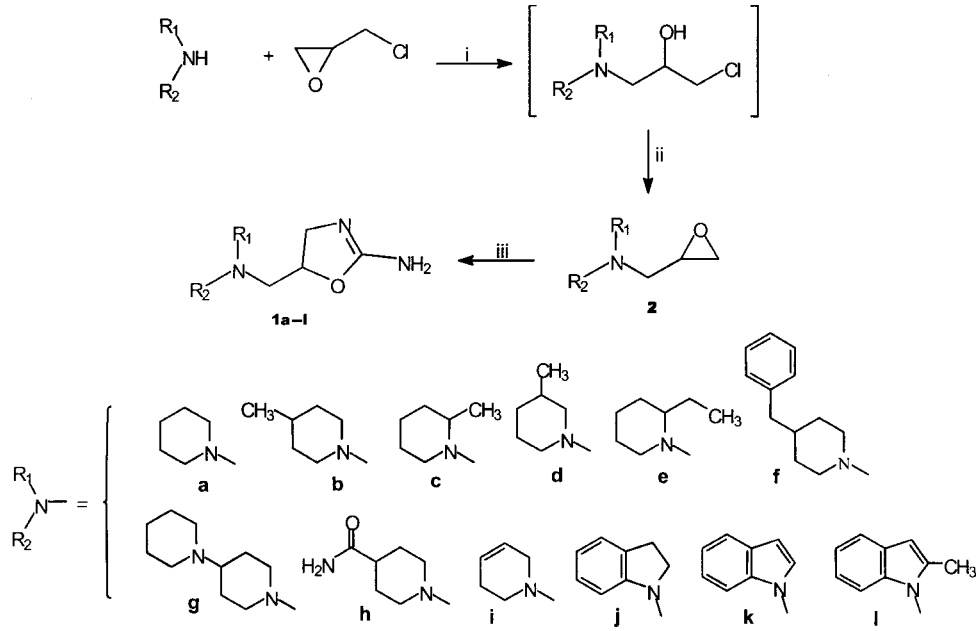

Figure 1 Synthesis of 5-dialkylaminomethyl-2-amino-2-oxazolines. Reagents: I, C_2H_5OH; ii, NaOH, C_2H_5OH; iii, NaNHCN, CH_3OH.

Materials and Methods

Chemical procedures

Microanalyses were carried out at the Service Central d'Analyse CNRS, Vernaison, France. Melting points were determined with an SM-LUXPOL Leitz hot-stage microscope and are uncorrected. The IR spectra were obtained with a Bruker IFS 25 spectrophotometer. NMR data were recorded with a Bruker AC-200 spectrometer. Chemical shifts (δ ppm) and coupling constants (J Hz) were measured using tetramethylsilane as the internal standard.

General procedure for the preparation of 5-dialkylaminomethyl-2-amino-2-oxazolines (1a–l)

The 1-dialkylamino-2,3-epoxypropanes **2** were obtained by treating an equimolar mixture (0.5 mol) of dialkylamine and epichlorhydrin in 200 mL of ethanol for 3 h. After addition of 20 g (0.5 mol) of NaOH, the mixture was stirred for 15 h. After evaporation of the solvent the residue was dissolved in ether, filtered, washed with water and dried. After evaporation of the ether, the residue was distilled at reduced pressure to yield the corresponding 1-dialkylamino-2,3-epoxypropane. Compound **2** (0.2 mol) was added drop-wise at 20°C to a stirred mixture of monosodium cyanamid salt (12.8 g, 0.2 mol) in 200 mL of methanol. The reaction mixture was stirred for 15 h, then concentrated under reduced pressure. The residue was extracted with ether. The ether phase was washed twice with water and dried. After evaporation of the solvent, the crude 5-dialkylaminomethyl-2-amino-2-oxazolines (**1a**–**l**) were crystallized after trituration with heptane.

*5-[(2-Ethyl-1-piperidinyl)methyl]-2-amino-2-oxazoline (**1e**)*

White powder (27%); mp 114°C; IR (KBr) ν: 1698 cm^{-1} (CN); ^1H NMR ($CDCl_3$) δ: 4.84 (s, 2H, NH_2), 4.67–4.53 (m, 1H, CH), 3.70 (dd, 1H, J = 12.0, 8.8, C2-H_{2a}), 3.27 (dd, 1H, J = 12.0, 7.2, C2-H_{2b}), 2.91–2.79, 2.70–2.49, 2.32–2.12, 1.59–1.18 (4m, 13H, CH_2 pip, C4-H_2, CH_2CH_3), 0.79 (t, 3H, J = 7.4, CH_3); ^{13}C NMR ($CDCl_3$) δ: 161 (C1), 78.45 (C3), 62.14, (C4), 56.38 (CH pip), 52.41 (C2), 57.02, 28.91, 24.70, 23.24 (CH_2 pip), 24 (CH_2CH_3), 10.11 (CH_3). Calculated for $C_{11}H_{21}N_3O$: C, 62.52; H, 10.02; N, 19.89; Found: C, 62.61; H, 10.10; N, 19.83%.

*5[(4-Piperidinyl-1-piperidinyl)methyl]-2-amino-2-oxazoline (**1g**)*

White powder (18%); mp 38.7°C; IR (KBr) ν: 1690 cm^{-1} (CN); ^1H NMR ($CDCl_3$) δ: 4.86 (s, 2H, NH_2), 4.70–4.53 (m, 1H, CH), 3.74 (dd, 1H, J = 12.0, 8.9, C2-H_{2a}), 3.27 (dd, 1H, J = 12.0, 7.4, C2-H_{2b}), 2.59 (dd, 1H, J = 13.5, 8.3, C4-H_{2a}), 2.33 (dd, 1H, J = 13.5,

3.5, C4-H_{2b}), 2.99–2.93, 2.46–2.40, 2.29–2.20, 1.99–1.93, 1.72–1.36 (5m, 19H, CH_2 pip); ^{13}C NMR ($CDCl_3$) δ: 160.8 (*C*1), 78.06 (*C*3), 62.75 (*C*H pip), 62.49 (*C*4), 53.83 (*C*2), 56.56, 27.46, (*C*H_2 pip), 49.99, 26.31, 24.71 (*C*H_2 pip). Calculated for $C_{14}H_{26}N_4O$: C, 63.12; H, 9.84; N, 21.03; Found: C, 63.11; H, 9.90; N, 21.0%.

*5-[(4-Carboxamide-1-piperidinyl)methyl]-2-amino-2-oxazoline (**1h**)*
White powder (17%); mp 202°C; IR (KBr) ν: 1720 (CO), 1668 cm^{-1} (CN); ^{1}H NMR (d_6-DMSO) δ: 7.19 (s, 1H, N*H*), 6.69 (s, 1H, N*H*), 5.74 (s, 2H, NH_2), 4.62–4.48 (m, 1H, C*H*), 3.60 (dd, 1H, J = 12.0, 8.9, C2-H_{2a}), 3.15 (dd, 1H, J = 12.0, 7.1, C2-H_{2b}), 2.86–2.82, 2.49–1.83, 1.59–1.41 (3m, 11H, CH_2 pip, C4-H_2); ^{13}C NMR (d_6-DMSO) δ: 169.3 (*C*O), 159.9 (*C*1), 76.5 (*C*3), 63.2 (*C*4), 53.75 (*C*2), 53.34, 28.59 (*C*H_2 pip), 41.68 (*C*H pip); Calculated for $C_{10}H_{18}N_4O_2$: C, 53.10; H, 7.96; N, 24.78; Found: C, 52.81; H, 7.79; N, 24.52%.

*5-[(1-Indolinyl)methyl]-2-amino-2-oxazoline (**1j**)*
White powder (22%); mp 73°C; IR (KBr) ν: 1684 cm^{-1} (CN); ^{1}H NMR ($CDCl_3$) δ: 7.08–6.44 (m, 4H, *H*-Ar), 4.82–4.72 (m, 1H, C*H*), 4.58–4.52 (m, 2H, NH_2), 3.84 (dd, 1H, J = 12.1, 8.9, C2-H_{2a}), 3.53–2.93 (m, 7H, C2-H_{2b}, N-CH_2, Ar-CH_2); ^{13}C NMR ($CDCl_3$) δ: 160.7 (*C*1), 152.26, 129.58, 127.31, 124.54, 117.99, 106.75 (*C*-Ar), 78.93 (*C*3), 55.81 (*C*4), 54.56 (N-*C*5 indol), 53.84 (*C*2), 28.74 (*C*6 indol). Calculated for $C_{12}H_{15}N_3O$: C, 66.34; H, 6.96; N, 19.34; Found: C, 66.30; H, 6.99; N, 19.31%.

*5-[(1-Indolyl)methyl]-2-amino-2-oxazoline (**1k**)*
White powder (26%); mp 111°C; IR (KBr) ν: 1682 cm^{-1} (CN); ^{1}H NMR ($CDCl_3$) δ: 7.67–7.09 (m, 4H, *H*-Ar), 7.12 (d, 1H, J = 3.1, =C*Ha*), 6.53 (d, 1H, J = 3.1, =C*Hb*), 5.03 (s, 2H, NH_2), 4.91–4.80 (m, 1H, C*H*), 4.32–4.19 (m, 2H, C4-H_2), 3.80 (dd, 1H, J = 12.4, 8.9, C2-H_{2a}), 3.47 (dd, 1H, J = 12.4, 6.26, C2-H_{2b}); ^{13}C NMR ($CDCl_3$) δ: 160.6 (*C*1), 136.28, 128.58, 121.79, 121.12, 119.67, 109.20 (*C*-Ar), 128.06 (=*C*Ha), 101.99 (=*C*Hb), 78.7 (*C*3), 55.44 (*C*4), 49.52 (*C*2). Calculated for $C_{12}H_{13}N_3O$: C, 66.96; H, 6.09; N, 19.52; Found: C, 66.40; H, 6.36; N, 19.31%.

*5-[(2-Methyl-1-indolyl)methyl]-2-amino-2-oxazoline (**1l**)*
White powder (29%); mp 88°C; IR (KBr) ν 1698 cm^{-1} (CN); ^{1}H NMR ($CDCl_3$) δ: 7.55–7.04 (m, 4H, *H*-Ar), 6.27 (s, 1H, =C*H*), 4.95 (s, 2H, NH_2), 4.93–4.81 (m, 1H, C*H*), 4.24 (dd, 1H, J = 15.4, 8.3, C4-H_{2a}), 4.11 (dd, 1H, J = 15.4, 4.3, C4-H_{2b}), 3.83 (dd, 1H, J = 12.5, 8.8, C2-H_{2a}) ; 3.51 (dd, 1H, J = 12.5, 6.15, C2-H_{2b}), 2.43 (d, 3H, J = 0.8, CH_3); ^{13}C NMR ($CDCl_3$) δ: 160.53 (*C*1), 136.80, 128.10, 120.71, 119.83, 119.61, 108.80 (*C*-Ar), 136.49 (=*C*-CH_3), 100.66 (=*C*H), 78.65 (*C*3), 55.38 (*C*4), 46.62 (*C*2), 12.98 (*C*H_3). Calculated for $C_{13}H_{15}N_3O$: C, 68.10; H, 6.59; N, 18.33; Found: C, 68.40; H, 6.36; N, 18.30%.

Pharmacological procedures

Guinea-pigs of either sex, 250–400 g were killed by a blow on the head and exsanguinated. Trachea were rapidly removed and cut into rings. Each set of guinea-pig airways rings was suspended under an initial tension of 2 g in Krebs-Henseleit solution, bubbled with 95% O_2–5% CO_2 and maintained at 37°C. Changes in force of contraction were measured isometrically with strain-gauge amplifiers. Digital signal acquisition enabling treatment of pharmacological data was performed using the Mac Lab system and the chart 3.5.6 program (Phymep, Paris, France). Krebs solution was composed of (mM): NaCl 4.7; $CaCl_2$ 1.9; $MgSO_4$ 1.2; KH_2PO_4 1.2; $NaHCO_3$ 25; glucose 11.5.

After 1 h of equilibration with washing every 15 min, the resting load was between 1 and 2 g. Under these conditions, the responses obtained were reproducible. Cumulative concentration–response curves to histamine dihydrochloride (10^{-7}–10^{-3} M) or acetylcholine (10^{-8}–10^{-3} M) were performed after 10 min incubations with the tested compounds at 10^{-6} M. The E_{max} and $-$logEC50 were determined from cumulative concentration response curves. E_{max} was defined as the maximal response to histamine or acetylcholine 10^{-3} M. $-$logEC50 was defined as the $-$log concentration of acetylcholine or histamine which induces 50% of the maximal response. Results are expressed as mean $\pm$ s.e.m. Statistical comparison with the paired control was performed using paired Student's *t*-test with $P < 0.05$ being considered significant.

Drugs were acetylcholine chloride and histamine dihydrochloride (Sigma, St Louis, MO). Depending on the requirement, drugs were dissolved in distilled water or ethanol and then diluted in Krebs solution.

Results

Chemistry

For the synthesis of target heterocycles, the reaction sequences outlined in Figure 1 were followed. Treatment of appropriate dialkylamines with epichlorhydrin in

ethanol led to the 1-dialkylamino-2,3-epoxypropanes, **2**, via 1-chloro-3-dialkylaminopropan-2-ols (Heywood & Phillips 1958, Jarry et al 1986). The epoxydes, **2**, were converted into the corresponding 5-dialkylaminomethyl-2-amino-2-oxazolines **1a**–**l** by condensation with monosodium cyanamid salt performed in methanol. The IR and NMR spectra of all compounds were in agreement with the proposed structures. In the ^{1}H NMR spectra, the protons at C-2 and C-3 formed a characteristic ABX system, the C-5 methine H was found at about 5 ppm.

Different substituents or heterocycle moieties were defined to increase the lipophilicity of the molecules in comparison with the non-substituted compound **1a**. On the other hand, the amidine function in the 2-amino-2-oxazoline ring represents a basic centre predominantly protonated at physiological pH, capable of an H-bonding interaction with any potential receptor. The measured pK_a values range from 8.81 to 9.75 for the amidine basic centre (Demontes-Mainard et al 1992).

Pharmacology

All 5-dialkylaminomethyl-2-amino-2-oxazolines, **1a**–**l**, were tested as H_1-receptor antagonists. Significant results are summarized in Table 1. No effect was observed for any compound on baseline tension. Compounds **1c**, **1d** and **1j** significantly antagonized histamine-induced contraction of guinea-pig trachea with a rightward shift of the concentration–response curve to histamine. This antagonism was selective of histamine since no antagonistic effect of these compounds on acetylcholine-induced contraction was observed.

Compound **1f** induced an increase in acetylcholine E_{max} and a shift to the left of the concentration–response curve. However, the increase of the maximal response to acetylcholine induced by **1f** makes it unlikely that the potentiation is due to cholinesterase inhibition. Indeed in that case, only a leftward shift of the acetylcholine concentration–response curve is observed without change in the maximal response. Moreover, the lack of effect of this compound on histamine-induced contraction rules out a non-selective potentiation of the contraction mechanisms.

The other tested 2-amino-2-oxazolines induced no change of either acetylcholine or histamine concentration–response curves.

Discussion

In terms of structure–activity relationships only preliminary results were attained, the number of tested compounds being too limited to draw a definitive conclusion. No activity was found for the non-substituted piperidinyl compound **1a**, nor for the related tetrahydropyridine **1i**, suggesting an influence of the substitution on the piperidinyl ring. Of the 5-piperidinyl-

Table 1 Effect of 5-dialkylaminomethyl-2-amino-2-oxazolines **1a**–**l** on guinea-pig trachea, determined from the cumulative response curves to histamine (10^{-7}–10^{-3} M histamine dihydrochloride) or acetylcholine (10^{-8}–10^{-3} M).

Compound	Histamine		Acetylcholine	
	E_{max}	−log EC50	E_{max}	−log EC50
Control	1911 ± 106 (n = 25)	5.36 ± 0.07	2098 ± 173 (n = 28)	5.55 ± 0.12
1a	1811 ± 377	5.18 ± 0.12	2377 ± 406	5.17 ± 0.37
1b	1940 ± 280	5.32 ± 0.06	2774 ± 367	5.89 ± 0.18
1c	1389 ± 49*	4.99 ± 0.17*	2609 ± 401	5.03 ± 0.49
1d	1508 ± 168*	5.08 ± 0.15*	2932 ± 266	5.11 ± 0.42
1e	2392 ± 365	5.57 ± 0.13	3324 ± 467	5.77 ± 0.47
1f	1363 ± 335	5.77 ± 0.31	2516 ± 243*	6.65 ± 0.37*
1g	1794 ± 239	4.22 ± 0.04	1772 ± 684	5.59 ± 0.94
1h	1958 ± 439	4.06 ± 0.13	1853 ± 321	4.54 ± 0.54
1i	1602 ± 89*	5.34 ± 0.11	2931 ± 344	5.24 ± 0.37
1j	1424 ± 171	3.75 ± 0.23*	2021 ± 368	5.50 ± 0.56
1k	1562 ± 273	5.52 ± 0.19	1262 ± 302	5.46 ± 1.14
1l	1160 ± 152	5.35 ± 0.40	1464 ± 440	5.56 ± 0.31

*$P < 0.05$ vs paired control; n = 6 per group.

methyl-2-amino-2-oxazolines, only a methyl and a benzyl substituent were found to favour antagonism of the histamine-induced contraction. These results could be estimated in terms of lipophilicity (**1f**, log P = 2.38; **1i,** log P = 0.19) (Péhourcq et al 2000). Moreover, the substitution position on the piperidinyl ring was found to have influence in the three methyl-substituted isomers **1b**, **1c** and **1d**.

The two related compounds **1k** and **1l**, on the other hand, were poorly active, in contrast to their hydrogenated counterpart **1j**, that induced an increase in acetylcholine E_{max} and a shift to the left of the concentration–response curve. These results cannot be simply estimated in terms of lipophilicity.

In conclusion, a mild antihistaminic effect of some 5-dialkylaminomethyl-2-amino-2-oxazolines (**1a**–**l**) was noticed during this study. Nevertheless, this was observed at a relatively too high concentration (10^{-6} M), compared with other available antihistaminic tools, to deserve further investigation.

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