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Synthesis and Anti-histaminic Evaluation of *N*-Phenyl-(alkyl)-5-(dialkylamino)methyl-2-amino-2-oxazolines

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New *N*- phenyl(alkyl)-5-(dialkylamino)methyl-2-amino-2-oxazolines, 5a–e, have been synthesized from the corresponding 3-phenyl(alkyl)carbamoyl-2-iminooxazolidines 2. A two-stage hydrolysis reaction led finally to the corresponding ring-opened *N*-phenyl(alkyl)-*N'*-[1-{3-(dialkylamino)-propan-2-ol}]ureas 4. The oxazoline ring was regenerated through an intramolecular nucleophilic substitution involving an halogen atom introduced by the reaction of thionyl chloride on 4. Pharmacological properties of 5a–e were evaluated on histaminic and adrenergic receptors in guinea-pig trachea and rat aorta. Compounds 5b and 5e showed a selective anti-histaminic effect on guinea-pig airways, but a significant response was obtained for a concentration $>10^{-6}$ M. No pharmacological activity was obtained with oxazoline 5c whereas oxazolines 5a and 5d seemed to present a non-selective effect on the contractile mechanism of the smooth muscle cell.

Keywords: 2-Amino-2-oxazoline; Adrenergic receptors; Anti-histaminic effect

INTRODUCTION

For several years we have focused our attention mainly on the chemistry of 2-amino-2-oxazolines developed for a biological purpose.[1] Beside the potential of the amidine pharmacophore,[2] these heterocyclic compounds can be regarded as useful either as synthons[3] or as precursors of active ring-opened compounds.[4] Earlier, we found that 5-substituted 2-amino-2-oxazolines presented different pharmacological profiles with respect to the nature of the substituent. The 5-[(1-aryl-4-piperazinyl)methyl]-2-amino-2-oxazolines were developed as antidepressant agents[5] whereas cardiovascular activity was found with 5-(dialkylamino)-methyl-2-amino-2-oxazolines.[6] On the other hand, the general structure of these compounds suggests some pharmacophoric requirements as H_1 receptors antagonists, in comparison with the model recently refined by Timmerman.[7] Hence, we recently reported on the synthesis of some 5-(dialkylamino)-methyl-2-amino-2-oxazolines evaluated as H_1-antagonists.[8]

In this paper we describe preliminary results concerning some 5-(dialkylamino)methyl-2-amino-2-oxazolines structurally characterized by the introduction of an aryl or an alkyl moiety on the exocyclic amino function. As it was not possible to substitute directly the exocyclic nitrogen atom they were synthesized by an original method starting from the 3-phenyl(alkyl)carbamoyl-2-iminooxazolidines **2** obtained by carbamoylation of the amidine function in 2-amino-2-oxazolines.[9] By hydrolysis in acidic medium **2** led to the corresponding 3-phenyl-(alkyl)carbamoyl-5-(dialkylamino)methyl-2-oxazolidinones **3a–e**. That was followed by the opening of the heterocyclic ring leading to *N*-phenyl(alkyl)-*N'*-[1-{3-(dialkylamino)-propan-2-ol}]ureas **4** and then, the cyclic functionality was regenerated through an intramolecular nucleophilic substitution involving an halogen atom introduced by the reaction of thionyl chloride on **4**.

Pharmacological effects of the *N*-phenyl(alkyl)-5-(dialkylamino)methyl-2-amino-2-oxazolines (**5a–e**) were evaluated *in vitro* for their ability to antagonize histamine-induced contraction of guinea-pig trachea. In previous toxicological experiments, an

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erection of adult male mice was observed after *per os* administration with oxazolines. To investigate the mechanism of this surprising observation, *in vitro* experiments were also performed to study the effect of these oxazolines on α-adrenergic receptors of rat aorta.

MATERIALS AND METHODS

General

Microanalyses were carried out at the Service Central d'Analyse CNRS, Vernaison, France and were 0.4% within the theoretical values. Melting points were determined with an SM-LUXPOL Leitz hot-stage microscope and were 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.

Pharmacology

Guinea Pig Tracheal Preparation

Male guinea-pigs (250–350 g, Center of Animal Production, Olivet, France) were killed by a blow on the head and exsanguinated. Trachea were rapidly excised, cleaned of connective tissue and cut into 2–3 mm rings. Each preparation of guinea-pig airways ring was suspended under an initial tension of 2 g in a organ bath filled with warmed (37°C) modified Krebs–Henseleit solution (pH = 7.4) which was gassed with a mixture of 95% O_2 and 5% CO_2. Changes in force were measured isometrically with strain-gauge amplifiers (Cristel, Eybens, France). Data were acquired on-line using Mac Lab system and Chart software (Phymep, Paris, France). After 1 h of equilibration with repeated rinses every 15 min, the resting force was between 1.5 and 2 g. Cumulative concentration-response curves (10^{-8}–3.10^{-4} M) for oxazolines were constructed on precontracted rings with either acetylcholine (10^{-5} M) or histamine (10^{-5} M).

Rat Aorta Preparation

Adult male Wistar rats (250–350 g, Janvier, Genest St Isle, France) were killed by CO_2 asphyxia followed by exsanguination. Descending thoracic aortae were isolated, cleaned of fat and connective tissue and cut into rings measuring 2–3 mm in length. Rings were suspended in the same organ bath used for tracheal preparations and described above. Rings were progressively stretched to a resting tension of 2 g. Cumulative concentration-response curves (10^{-8}–3.10^{-4} M) for oxazolines were constructed on precontracted rings with phenylephrine (3.10^{-6} M).

Drugs and Solutions

Composition of the Krebs–Henseleit solution (mM): NaCl 118.4, KCl 4.7, $CaCl_2$ 2.5, $MgSO_4$ 1.2, KH_2PO_4 1.2, $NaHCO_3$ 25.0, and glucose 11.1. All drugs were purchased from Sigma Chemical Company (St. Louis, MO, USA). Acetylcholine, histamine and phenylephrine were dissolved in distilled water and the oxazolines in either dimethylsulphoxide (DMSO) for oxazoline 5d or ethanol for the other drugs. The final concentrations of the solvent in the organ bath reached 1% vv^{-1} for high concentrations of oxazolines. For a concentration of solvent $>0.1\%$, a non-specific relaxation was observed on precontracted tissue (Table I).

Statistical Analysis of Results

Data were expressed as mean ± s.e.mean of n experiments. E_{max} was defined as the percentage of relaxation from the maximal level of contraction

TABLE I Relaxations induced by oxazolines **5a–e** in guinea-pig trachea and rat aorta, precontracted either with acetylcholine (10^{-5} M) or histamine (10^{-5} M) in trachea and phenylephrine (3.10^{-6} M) in aorta

	Guinea-pig trachea								Rat aorta			
	Acetylcholine				Histamine				Phenylephrine			
	E_{max}		PD_2		E_{max}		PD_2		E_{max}		PD_2	
Compound	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
Control	−32	10	–	–	−43	12	–	–	−21	5	–	–
5a	−218**	68	4.02	0.09	−347***	75	4.00	0.11	−103***	2	4.79	0.14
5d	−226***	35	4.06	0.09	−387***	88	4.63	0.33	−119***	3	4.83	0.08
5b	−49	21	4.40	0.29	−237***	49	5.84	0.16	−33	4	5.64	0.10
5c	−1	10	–	–	−96	36	5.00	0.39	−40	8	5.58	0.39
5e	−10	8	–	–	−226**	62	4.62	0.56	−18	3	5.78	0.29

**$P < 0.01$, ***$P < 0.001$ vs control conditions (DMSO or ethanol alone); $n = 6$ per group.

induced by agonist. To determine agonist potencies from concentration response curves, concentrations producing 50% of maximum effect (EC_{50}) were calculated by fitting curves with the Boltzmann equation. PD_2 values were then determined according to the equation $PD_2 = -\log$ (molar EC_{50}) and compared using Student's t-test ($P < 0.005$ being considered as significant).

Synthesis

General Procedure for the Synthesis of 3-phenyl-(alkyl)carbamoyl-5-(dialkylamino)methyl-2-oxazolidinones (3a–e)

1 M Hydrochloric acid (0.05 mol) was added rapidly to a boiling solution of **2** (0.01 mol) in water (50 mL) and the mixture was refluxed for 2 h. After cooling the solid was collected, washed twice with water and recrystallised.

3-Phenylcarbamoyl-5-(1-phenyl-4-piperazinyl)-methyl-2-oxazolidinone (**3a**)

Hydrochloride m.p. 178°C (ethanol).[10]

3-Propylcarbamoyl-5-(1-phenyl-4-piperazinyl)-methyl-2-oxazolidinone (**3b**)

White powder (65%); m.p. 92°C (ethanol). IR (KBr) cm^{-1}: 1695 (NC = O), 1760 (OC = O); ^{1}H-NMR (d_6-DMSO), δ (ppm); J (Hz):7.80 (t, 1H, J = 5.7, CO-N*H*), 7.19 (t, 2H, J = 7.7, *H*-3′ and *H*-5′), 6.91 (d, 2H, J = 8.5, *H*-2′ and *H*-6′), 6.8 (t, 1H, J = 7.2, *H*-4′), 4.91–4.71 (m, 1H, C5-*H*), 3.9 (t, 1H, J = 9.34, C4-H_{2a}), 3.59 (dd, 1H, J = 9.7, 7.2, C4-H_{2b}), 3.17–3.07 (m, 6H, CH_2 $pip_{b\text{-}b'}$, Npip CH_2), 2.69–2.49 (m, 6H, C$H_2pip_{a\text{-}a'}$, CH_2CH$_2$ CH$_3$), 1.45 (sext, 2H, J = 7.2, CH_2-CH$_3$), 0.83 (t, 3H, J = 7.4, CH_3); ^{13}C-NMR (d_6-DMS0), δ (ppm): 154.98 (*C*2), 151.22 (N*C* = O), 150.94 (*C*-1′), 128.87 (*C*-3′ and *C*-5′), 118.81 (*C*-4′), 115.35 (*C*-2′ and *C*-6′), 72.38 (*C*5), 60.07 (Npip-C H$_2$), 53.22 (C H$_2pip_{a\text{-}a'}$), 48.19 (C H$_2$-$pip_{b\text{-}b'}$), 45.85 (*C*4), 41.06 (C H$_2$CH$_2$CH$_3$), 22.45 (C H$_2$-CH$_3$), 11.13 (C H$_3$). Anal. ($C_{18}H_{26}N_4O_3$) C, H, N.

3-Isopropylcarbamoyl-5-(1-phenyl-4-piperazinyl)methyl-2-oxazolidinone (**3c**)

White powder (63%); m.p. 103°C (ethanol). IR (KBr) cm^{-1}: 1695 (NC = 0), 1761 (OC = O); ^{1}H-NMR (d_6-DMSO), δ (ppm); J (Hz): 7.57 (d, 1H, J = 7.5, CO-N*H*), 7.19 (t, 2H, J = 7.8, *H*-3′ and *H*-5′), 6.90 (d, 2H, J = 8.3, *H*-2′ and *H*-6′), 6.75 (t, 1H, J = 7.0, *H*-4′), 4.89–4.75 (m, 1H, C5-*H*), 3.97 (t, 1H, J = 9.4, C4-H_{2a}), 3.81 (sept, 1H, J = 6.7, C*H*$(CH_3)_2$), 3.59(dd, 1H, J = 9.8, 7.2, C4-H_{2b}), 3.12–3.07 (m, 4H, C$H_2pip_{b\text{-}b'}$), 2.76–2.49 (m, 6H, C$H_2pip_{a\text{-}a'}$, Npip-CH_2), 1.11 (d, 6H, J = 6.5, CH_3); ^{13}C-NMR (d_6-DMSO), δ ppm: 155.06 (*C*2), 150.94 (N*C* = O), 150.29 (*C*-1′), 128.83 (*C*-3′ and *C*-5′), 118.76 (*C*-4′), 115.30 (*C*-2′ and *C*-6′), 72.37 (*C*5), 60.02 (Npip-C H$_2$), 53.15 (C H$_2pip_{a\text{-}a'}$), 48.17 (C H$_2pip_{b\text{-}b'}$), 45.72 (C4), 41.60 (C H$(CH_3)_2$), 22.37 (C H$_3$). Anal. (C_{18} H_{26} N_4 O_3): C, H, N.

3-Phenylcarbamoyl-5-[1-(4-fluorophenyl)-4-piperazinyl]methyl-2-oxazolidinone (**3d**)

Hydrochloride m.p. 187°C (ethanol).[10]

3-Phenylcarbamoyl-5-(1-piperidinyl)methyl-2oxazolidinone (**3e**)

White powder (72%); m.p. 141°C (ethanol). IR (KBr) $cm^{-1:}$ 1705 (NC = O), 1765 (OC = O); ^{1}H-NMR ($CDCI_3$), δ (ppm); J (Hz): 9.83 (s, 1H, CO-N*H*), 7.48 (d, 2H, J = 8.0, *H*-2′ and H-6′), 7.30 (t, 2H, J = 7.8, *H*-3′ and *H*-5′), 7.08 (t, 1H, J = 7.4, H-4′), 4.82–4.66 (m, 1H, C5-*H*), 4.13 (dd, 1H, J = 10.4, 8.8, C4-H_{2a}), 3.82 (dd, 1H, J = 10.4, 7.1, C4-H_{2b}), 2.73–2.36 (m, 6H, Npip-CH_2 and CH_2Npip), 1.64–1.29 (m, 6H, CH_2pip); ^{13}C-NMR (d_6-DMSO), δ (ppm): 155.26 (*C*2), 148.92 (*C* = O), 136.98 (*C*-1′), 128.94 (*C*-3′ and *C*-5′), 124.15 (*C*-4′), 119.78 (*C*-2′ and *C*-6′), 72.91 (*C*5), 61.49 (Npip-C H$_2$), 55.35 (*C*2pip and *C*6pip), 46.16 (*C*4), 25.85 (*C*3pip and *C*5pip), 23.81 (*C*4pip). Anal. (C_{16} H_{21} N_3 O_3): C, H, N.

General Procedure for the Synthesis of N-phenyl-(alkyl)-N′-[1-{3-(dialkylamino)-propan-2-ol}]ureas 4a–e

A suspension of **3** (0.01 mol) and 2 M sodium hydroxide (0.02 mol) in water (100 mL) was heated at 100°C for 4 h. After cooling the solid was collected, washed with water and recristallized.

N-phenyl-*N*′-[1-{3-(1-phenyl-4-piperazinyl)propan-2-ol}]urea(**4a**)

M.p. 155° (methanol).[10]

N-propyl-*N*′-[1-{3-(1-phenyl-4-piperazinyl)propan-2-ol}]urea (**4b**)

White powder (74%); m.p. 124°C (C_2CI_4). IR (KB_r) $cm^{-1:}$ 3340 (N-H), 1625 (C = O); ^{1}H- NMR ($CDCl_3$), δ (ppm); J (Hz): 7.23 (t, 2H, J = 7.4, *H*-3′ and *H*-5′), 6.87 (d, 2H, J = 8.1, *H*-2′ and *H*-6′), 6.81 (t, 1H, J = 7.3, *H*-4′), 5.55 (t,1H, J = 5.7, N*H*-CO), 5.42 (t, 1H, J = 5.4, CO-N*H*), 4.02 (s, 1H, O*H*), 3.85–3.76 (m, 1H, C*H*), 3.39 (ddd, 1H, J = 14.1, 6.1, 2.9, CH-CH_{2a}), 3.21–3.05 (m, 7H, CH-CH_{2b}, C$H_2pip_{b\text{-}b'}$, CH_2CH$_2$ CH$_3$), 2.79–2.69 and 2.60–2.49 (2m, 4H, C$H_2pip_{a\text{-}a'}$), 2.42–2.34 (m, 2H, Npip-CH_2), 1.48 (sext, 2H, J = 7.3, CH_2-CH$_3$), 0.89 (t, 3H, J = 7.4, CH_3); ^{13}C-NMR ($CDCl_3$), δ (ppm): 159.67 (*C*O), 151.27 (*C*-1′), 129.26 (*C*-3′ and *C*-5′), 119.98 (*C*-4′), 116.18 (*C*-2′ and *C*-6′), 67.18 (C H), 61.20 (Npip-C H$_2$), 53.49 (*C*2pip and *C*6pip), 49.34 (*C*3pip and *C*5pip), 44.51 (CH-C H$_2$), 42.35 (C H$_2$-CH$_2$-CH$_3$), 23.59 (C H$_2$-CH$_3$), 11.57 (C H$_3$). Anal. ($C_{17}H_{28}N_4O_2$): C, H, N.

N-isopropyl-*N*′-[1-{3-(1-phenyl-4-piperazinyl)propan-2-ol}]urea (**4c**)

White powder (63%); m.p. 139°C (C_2Cl_4). IR (KBr) cm^{-1}: 3335 (N-H), 1622 (C = O); ^{1}H- NMR ($CDCl_3$), δ (ppm); J (Hz): 7.34–7.31 (m, 4H, *H*-3′ and *H*-5′, *H*-2′ and *H*-6′), 7.07–7.00 (m, 1H, CO-N*H*), 6.91–6.81 (m, 1H, *H*-4′), 5.53 (t, 1H, J = 5.8, N*H*-CO), 3.91–3.87

(m, 1H, C*H*), 3.52 (ddd, 1H, J = 14.2, 6.2, 2.9, CH-CH_{2a}), 3.23–3.09 (m, 7H, CH-CH_{2b}, CH_2pip$_{b\text{-}b'}$, C*H*-(CH_3)$_2$, O*H*), 2.84–2.73 and 2.60–2.52 (2m, 4H, CH_2pip$_{a\text{-}a'}$), 2.49–2.41 (m, 2H, Npip-CH_2), 1.18 (d, 6H, J = 6.4, CH_3); ^{13}C-NMR ($CDCl_3$), δ (ppm): 156.54 (*C*O), 138.73 (*C*-1′), 129.21 (*C*-3′ and *C*-5′), 123.6 (*C*-4′), 116.11 (*C*-2′ and *C*-6′), 66.52 (*C*H), 60.71 (Npip-*C*H$_2$), 53.25 (C2pip and *C*6pip), 49.22 (*C*3pip and *C*5pip), 44.07 (CH-*C*H_2), 42.25 (*C*H-(CH_3)$_2$), 21.95 (*C*H$_3$). Anal. ($C_{17}H_{28}N_4O_2$): C, H, N.

N-phenyl-*N*′-[1-{3-(1-(4-fluorophenyl)-4-piperazinyl) Propan-2-ol}]urea (**4d**)

M.p. 162°C (ethanol).[10]

N-phenyl-*N*′-[1-{3-(1-piperidinyl)propan-2-ol}] urea (**4e**)

White powder (47%); m.p. 146°C (ethanol). IR (KB$_r$) cm^{-1}: 3380, 3318 (N-H), 1680 (C = 0); ^{1}H-NMR ($CDCl_3$), δ (ppm); J (Hz): 7.76 (s, 1H, CO-N*H*), 7.32–6.94 (m, 4H, *H*-3′ and *H*5′, *H*-2′ and *H*-6′), 6.98 (t, 1H, J = 7.1, *H*-4′), 5.98 (t, 1H, J = 5.6, N*H*-CO), 4.12 (s, 1H, O*H*), 3.86–3.74 (m, 1H, C*H*), 3.46 (ddd, 1H, J = 14.1, 6.1, 2.9, CH-CH_{2a}), 3.08 (ddd, 1H, J = 14.1, 6.1, 6.0, CH-CH_{2b}), 2.55–2.46 and 2.35–2.29 (2m, 4H, CH_2-Npip), 2.27 (d, 2H, J = 7.0, Npip-CH_2), 1.51–1.40 (m, 6H, CH_2pip); ^{13}C-NMR ($CDCl_3$), δ (ppm): 156.96 (*C*O), 139.29 (*C*-1′), 129.16 (*C*-3′ and *C*-5′), 123.11 (*C*-4′), 120.24 (*C*-2′ and *C*-6′), 66.61 (*C*H), 61.43 (N$_{pip}$-*C*H$_2$), 54.76 (*C*2pip and *C*6pip), 44.28 (CH-*C*H$_2$), 26.19 (*C*3pip and *C*5pip), 24.28 (*C*4pip). Anal. (C_{15} H_{23} N_3 O_2): C, H, N.

General Procedure for the Synthesis of N-Phenyl-(alkyl)-5-(dialkylamino)methyl-2-amino-2-oxazolines 5a–e

Thionyl chloride (0.1 mol) in methylene chloride (20 mL) was slowly added at 20°C to a solution of **4** (0.1 mol) dissolved in 400 mL of methylene chloride. The mixture was refluxed for 2 h, then the solid was collected and treated with water (200 mL) at 100°C for 30 min. After cooling, 250 mL of a 1 M solution of sodium hydroxide was added. A precipitate appeared, it was collected, washed with water, and recrystallized.

N-phenyl-5-[(1-phenyl-4-piperazinyl)methyl]-2-amino-2-oxazoline (**5a**)

White powder (65%); m.p. 166°C (heptane). IR (KBr) cm^{-1}:1685 (C = N), 1590 (C′-C′); ^{1}H-NMR ($CDCl_3$), δ (ppm); J (Hz): 7.33–7.25 and 7.00–6.87 (2m, 10H, Ar-*H*), 6.15 (s, 1H, N*H*), 4.88–4.72 (m, 1H, C5-*H*), 3.99 (dd, 1H, J = 11.8, 9.0, C4-H$_{2a}$), 3.57 (dd, 1H, J = 11.8, 7.4, C4-H_{2b}), 3.26–3.22 (m, 4*H*, CH_2pip$_{b\text{-}b'}$), 2.80 (dd, 1H, J = 13.5, 8.0, Npip-CH_{2a}), 2.78 (m, 4H, CH_2pip$_{a\text{-}a'}$), 2.61 (dd, 1H, J = 13.5, 3.8, Npip-CH_{2b}); ^{13}C-NMR ($CDCl_3$), δ (ppm):156.96 (*C*2), 151.288 (*C*-1′), 140.69 (*C*-1″), 129.15 (*C*-3′ and *C*-5′), 129.02 (*C*-3″ and *C*-5″), 122.58 (*C*-4″), 119.85 (*C*-4′), 119.33 (*C*-2″ and *C*-6″), 116.11 (*C*-2′and *C*-6′), 76.48 (*C*5), 62.08 (Npip-*C*H$_2$), 54.33 (C4), 53.75 (*C*H$_2$pip$_{a\text{-}a'}$), 49.10 (*C*Hpip$_{b\text{-}b'}$). Anal. ($C_{20}H_{24}N_4O$): C, H, N.

N-propyl-5-[(1-phenyl-4-piperazinyl)methyl]-2-amino-2-oxazoline (**5b**)

White powder (12%); m.p. 106°C (heptane). IR (KBr) cm^{-1}: 1675 (C = N), 1600 (C′-C′); ^{1}H-NMR ($CDCl_3$), δ (ppm); J (Hz): 7.25 (t, 2H, J = 7.36, *H*-3′ and *H*-5′), 6.91 (d, 2H, J = 7.9, *H*-2′ and *H*-6′), 6.82 (t, 2H, J = 7.36, *H*-3′ and *H*-4′), 4.80–4.66 (m, 1H, C5-*H*), 3.88 (dd, 1H, J = 12.2, 8.9, C4-H_{2a}), 3.41 (dd, 1H, J = 12.2, 7.5, C4-H_{2b}), 3.24–3.11 (m, 7H, CH_2-CH$_2$-CH$_3$, CH_2pip$_{b\text{-}b'}$,N*H*), 2.74–2.66 (m, 5H, CHpip$_{a\text{-}a'}$, Npip-CH_{2a}), 2.50 (dd, 1H, J = 13.6, 3.4, Npip-CH_{2b}), 1.54 (sext, 2H, J = 7.3, CH_2-CH$_3$), 0.9 (t, 3H, J = 7.4, CH_3); ^{13}C-NMR ($CDCl_3$), δ (ppm): 161.0 (*C*2), 151.02 (*C*-1′), 129.06 (*C*-3′ and *C*-5′), 119.74 (*C*-4′), 116.05 (*C*-2′ and *C*-6′), 77.92 (*C*5), 62.61 (Npip-*C*H$_2$), 56.41 (*C*4), 53.66 (*C*H$_2$pip$_{a\text{-}a'}$), 48.98 (*C*H$_2$pip$_{b\text{-}b'}$), 44.69 (*C*H$_2$CH$_2$-CH$_3$), 22.96 (*C*H$_2$-CH$_3$), 11.22 (*C*H$_3$). Anal. ($C_{17}H_{26}$ N_4 O): C, H, N.

N-isopropyl-5-[(1-phenyl-4-piperazinyl)methyl]-2-amino-2-oxazoline (**5c**)

White powder (14%); m.p. 136°C (heptane). IR (KBr) cm^{-1}: 1685 (C = N), 1605 (C′-C′); ^{1}H-NMR ($CDCl_3$), δ (ppm); J (Hz): 7.24 (t, 2H, J = 7.4, *H*-3′ and *H*-5′), 6.91 (d, 2H, J = 8.6, *H*-2′ and *H*-6′), 6.82 (t, 1H, J = 7.2, *H*-4′), 4.73–4.67 (m, 1H, C5-*H*), 4.02 (S, 1H, N*H*), 3.87 (dd, 1H, J = 12.1, 8.9, C4-H_{2a}), 3.71 (sept, 1H, J = 6.4, C*H* (CH_3)$_2$), 3.41 (dd, 1H, J = 12.1, 7.6, C4-H_{2b}), 3.23–3.18 (m, 4H, CH_2pip$_{b\text{-}b'}$), 2.77–2.66 (m, 5H, CH_2pip$_{a\text{-}a'}$, Npip-CH_{2a}), 2.50 (dd, 1H, J = 13.5, 3.7, Npip-CH_{2b}), 1.42 (d, 6H, J = 6.4, CH_3); ^{13}C-NMR ($CDCl_3$), δ (ppm): 159.72 (C2), 151.26 (C-1′), 129.09 (C-3′ and C-5′), 119.75 (C-4′), 116.08 (C-2′ and C-6′), 77.52 (C5), 62.75 (Npip-*C*H$_2$), 57.14 (C4), 53.68 (*C*H$_2$pip$_{a\text{-}a'}$), 49.04 (*C*H$_2$pip$_{b\text{-}b'}$), 44.80 (*C*H(CH_3)$_2$), 23.18 (*C*H$_3$). Anal. (C_{17} H_{26} N_4 O): C, H, N.

N-phenyl-5-[[1-(4-fluorophenyl)-4-piperazinyl]-methyl]-2-amino-2-oxazoline (**5d**)

White powder (77%); m.p. 162°C (heptane). IR (KBr) cm$^{-1:}$ 1690 (C = N), 1590 (C′-C′); ^{1}H-NMR ($CDCl_3$), δ (ppm); J (Hz): 9.20–9.10 (m; 1H; N*H*)7.23–7.16 and 7.08–6.82 (2m, 4H, *H*-3′ and *H*-5′, *H*-2′ and *H*-6′), 4.76–4.70 (m; 1H; C5-*H*), 3.94 (dd, 1H, J = 11.6, 8.8, C4-H_{2a}),3.52 (dd, 1H, J = 11.6, 7.4, C_4H_{2B}), 3.12–3.05 (m; 4H, CH_2pip$_{b\text{-}b'}$), 2.75 (2dd, 1H, J = 13.5, 7.8, Npip-CH_{2a}), 2.73–2.68 (m; 4H, CH_2pip$_{a\text{-}a'}$), 2.57 (dd, 1H, J = 13.5, 3.8, Npip-CH_{2b}); ^{13}C-NMR ($CDCl_3$), δ (ppm): 158.30 (C-4′), 155.69 (C2), 153.63 (C-1′), 147.87 (C-1″), 128.43 (C-3″ and C-5″), 120.74 (C-2″ and C-6″), 117.1 (C-4″) 115.39 (C-2′ and C-6′), 114.97 (C-3′ and C-5′), 75.31 (C5), 61.76 (Npip-*C*H$_2$), 53.08 (CH$_2$pip$_{a\text{-}a'}$), 48.93 (CH$_2$pip$_{b\text{-}b'}$), 45.70 (C4). Anal. (C_{20} $H_{23}N_4$ O F): C, H, N, F.

N-PHENYL-5-[(1-PIPERIDINYL)METHYL]-2-AMINO-2-OXAZOLINE (**5e**)

White powder (67%); m.p. 118°C (heptane). IR (KBr) $cm^{-1:}$ 1682 (C = N), 1590 (C′-C′); ^{1}H-NMR ($CDCl_3$), δ (ppm); J (Hz): 7.32–7.20 (m, 4H, *H*-2′, *H*-3′, *H*-5′ and *H*-6′), 6.99–6.91 (m, 1H, *H*-4′), 6.1 (s, 1H, N*H*), 4.81–4.67 (m, 1H, C5-*H*), 3.92 (dd, 1H, J = 11.5, 9.1, C4-H_{2a}), 3.49 (dd, 1H, J = 11.5, 7.4, C_4-H_{2b}), 2.67 (dd, 1H, J = 13.5, 7.8, Npip-CH_{2a}), 2.50–2.41(m, 5H, CH_2Npip, Npip-CH_{2b}), 1.63–1.39 (m, 6H, CH_{2pip}); ^{13}C-NMR ($CDCl_3$), δ (ppm): 156.66 (C2), 136.61 (C-1′), 128.91 (C-3′ and C-5′), 122.15 (C-2′ and C-6′), 118.87 (C-4′), 77.09 (C5), 63.16 ($N_{pip}C\,H_2$), 5.08 (C4, C2pip and C6pip), 25.85 (C3pip and C5pip), 24.12 (C4pip). Anal. ($C_{15}H_{21}N_3O$): C, H, N.

RESULTS

Synthesis

For the synthesis of target heterocycles **5**, the reaction sequences outlined in Figure 1 were followed. As the two nitrogen atoms of 2-amino-2-oxazolines are potent nucleophilic centres it is difficult to promote a monosubstitution on the amidine moiety. Moreover, alkylation of ambident nucleophiles with similar sites often resulted in problems of uncertain regiochemistry.[11] Consequently, the reaction pathway was based on the reactivity of 2-amino-2-oxazolines towards aryl(alkyl)isocyanates giving, under particular conditions,[9] the corresponding 3-aryl(alkyl)carbamoyl-2-iminooxazolidines. Hence, 2-iminooxazolidines (**2a**–**e**) were used as starting material for the preparation of **5a**–**e**. They were easily hydrolyzed in acidic medium to the corresponding 2-oxazolidinones (**3a**–**e**). 2-Oxazolidinones were characterized in the IR by a strong *v*(CO) near 1745 cm^{-1}. The opening of the oxazolidinone ring was achieved in basic medium by heating during 3 h. The resulting *N*-phenyl(alkyl)-*N*′-[1-{substituted}-propan-2-ol)]ureas (**4a**–**e**) were assigned by ^{1}H NMR. The OH was found at 4.10 ppm, while the neighbouring CH appeared as a multiplet at 3.70 ppm. For **4b**, the two NH were found at 5.42 ppm as a triplet (J = 5.4 Hz) for the NH-propyl and at 5.55 ppm as a triplet (J = 5.7 Hz) for the other NHCO.

The reaction of **4a**–**e** with thionyl chloride and the subsequent treatment with boiling water, followed

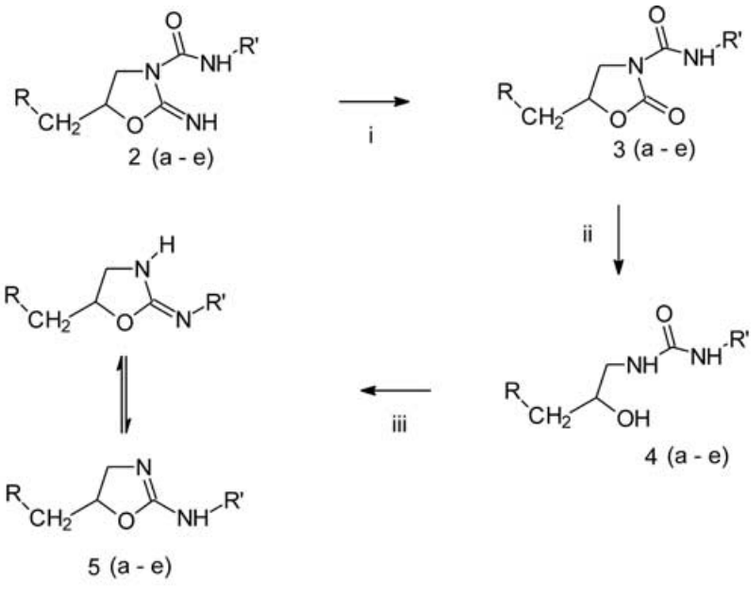

FIGURE 1 Reagents (i) H_3O^+, H_2O; (ii) OH^-, H_2O; (iii) $SOCl_2$.

by a neutralization with sodium hydroxide, gave the desired *N*-phenyl(alkyl)-5-(dialkylamino)methyl-2-amino-2-oxazolines (**5a**–**e**). A recent paper highlighted the mechanism of the oxazoline ring closure.[12] The heterocyclisation is supposed to progress through a two steps reaction. First, a non-isolated intermediate compound is formed by conversion of **4** to the corresponding alkyl halide, followed by an intramolecular nucleophilic substitution on the carbon atom of the carbamide. The IR and NMR spectra of compounds **5a**–**e** were in agreement with the proposed structures. In the ^{1}H NMR spectra, the protons at C-4 and C-5 formed a characteristic ABX system, the NpipCH_2 methine proton was found at about 4.75 ppm. The position of the signal for the exchangeable NH depends on the nature of the lateral chain. The tautomerism equilibrium of the amidine moiety has an influence on the physicochemical behaviour of *N*-phenyl-(alkyl)-5-(dialkylamino)methyl-2-amino-2-oxazolines (**5a**–**e**). Indeed the measured pKa values for the amidine basic centre range from 4.64 to 5.60 compared to the values near 8.8 for the corresponding non substituted 5-substituted 2-amino-2-oxazolines indicating an important decrease in basicity.[13]

Pharmacological Studies (Table I)

Compounds **5a** and **5d** induced a concentration-dependent relaxation in guinea-pig trachea precontracted either with acetylcholine or histamine. Maximal relaxations were two to three times greater compared to the level of precontraction induced by the agonist. This considerable relaxing response was also observed in rat aorta precontracted with phenylephrine. Moreover, PD_2 values showed a very low affinity of these compounds in both types of preparations employed.

Oxazolines **5b** and **5e** induced a significant relaxation in guinea-pig trachea precontracted with histamine and sensitivities, expressed as PD_2 values, were significantly higher for **5b** than those determined for **5e**. However, these two oxazolines had no relaxing effect in trachea precontracted with acetylcholine and also in rat aorta precontracted with phenylephrine. The last compound **5c** induced no change of the precontractile responses in guinea-pig trachea and rat aorta.

DISCUSSION

The present study was designed to test the pharmacological effects of *N*-phenyl(alkyl)-5-(dialkylamino)methyl-2-amino-2-oxazolines (**5a**–**e**) in precontracted trachea with histamine or acetylcholine, in order to evaluate the selectivity of these compounds on histaminic receptors. Moreover, preliminary toxicological experiments have shown a significant erection of adult male mice after *per os* administration with some oxazolines. It was then decided to investigate the effect of **5a**–**e** on α-adrenergic receptors in rat aorta, which is a tissue with a large density of adrenergic receptors.

At high concentrations, oxazolines **5a** and **5d** induced a complete relaxation in guinea-pig trachea precontracted either with acetylcholine or histamine, and in rat aorta precontracted with phenylephrine. This result suggests that this spectacular relaxing effect cannot be considered as a specific activity on a receptor structure. It is supported by the fact that at the end of the experiment carried out with **5a** and **5d**, the contractile response to phenylephrine in rat aorta was partially abolished. Consequently, it can be proposed that these oxazolines may be toxic on the smooth muscle activity (data not shown).

Compounds **5b** and **5e** demonstrated a relaxing effect when guinea-pig trachea was precontracted with histamine, suggesting a selective anti-histaminic activity. However, this pharmacological property was observed for high concentrations and the plateau of the concentration-response curve was not reached (data not shown). To avoid solubility difficulties encountered with the compounds, a higher concentration was not investigated.

In terms of structure–activity relationships, the phenyl group found in compounds **5a**, **5d** and **5e** seemed to be involved in the noticed relaxant effect. However, the relaxant response of compounds **5b** and **5e** was only observed in the presence of precontraction induced by histamine, and may suggest a specific effect. Compared to **5e**, oxazoline **5b** seemed to be more potent on the histaminic receptor, but this should be confirmed by binding experiments which evaluate affinities for H_1-receptors.

In conclusion, compounds **5b** and **5e** showed a selective anti-histaminic property on guinea-pig airways, but this effect was observed at a relatively too high concentration compared with other available anti-histaminic tools to deserve further investigation.

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