Eur. J. Med. Chem. **23** (1988) 511—515

Original paper

Synthesis and pharmacological investigation of the 3-analogs of viminol

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(Received September 21, 1987, accepted May 2, 1988)

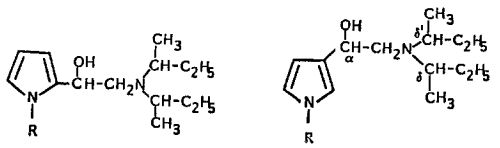
Summary — Some selected stereoisomers of the 3-regioisomer of viminol **1** have been synthesized and studied as potential analgesic and adrenergic agents. In particular, we investigated those compounds possessing the *(R,R)* - or *(S,S)*-configuration at the di-sec.butylamine group and the *R* or *S* configuration at the secondary alcohol. The results indicate that compounds **2**—**5** did not possess the analgesic activity of viminol even if the *(R,R)*-isomers maintain a slight affinity towards opioid receptors. In addition, despite the presence of the ethanolamine moiety, none of the stereoisomers **2**—**5** exhibited an appreciable affinity for the adrenergic receptors.

Résumé — **Synthèse et étude pharmacologique des analogues-3 du viminol.** *Quelques stéréoisomères du régio-3 isomère du viminol* **1** *ont été synthétisés et étudiés comme agents analgésiques et adrénergiques, en particulier les dérivés de configuration* (R,R) *ou* (S,S) *pour le groupe di-sec-butylamine et* R *ou* S *pour l'alcool secondaire. Les composés* **2**—**5** *ne possèdent pas l'activité analgésique du viminol, même si les isomères* (R,R) *présentent une légère affinité vis-à-vis des récepteurs des opioides. De plus, en dépit de la présence de la partie éthanolamine, aucun des stéréoisomères* **2**—**5** *ne révèle d'affinité appréciable pour les récepteurs adrénergiques.*

viminol analogs / analgesic agents / adrenergic agents

Introduction

Viminol **1** is a central analgesic compound which has been the subject of rather extensive pharmacological and toxicological studies [1—7]. This compound has been selected from a series of pyrrole derivatives bearing in position 2 an ethanolamine side chain. According to the reported observations, both central analgesic and adrenergic activities were the main pharmacological properties of these derivatives [8—10]. However, as in the case of viminol, the presence of a tertiary amine group provided compounds with analgesic activity, whereas the adrenergic activity was associated with the presence of a secondary amine group [11]. In addition, the influence of the stereochemistry at the three chiral centers of **1** on the analgesic activity has been the subject of detailed investigation [12—14]. The results indicated that the *(R,R)*-configuration at the di-sec.-butylamine group coupled to the *(S)*-configuration at the secondary alcohol is responsible for the appearance of opioid activity. The aim of the present paper was to extend our knowledge on the structure—activity relationship of such pyrrole derivatives. In particular, we have investigated the influence of a shift of the ethanolamine side chain of **1**, from the 2- to the 3-position, on the analgesic as well as the adrenergic activity. To this purpose, on the basis of our experience with viminol, the four out of eight stereoisomers **2**—**5** were prepared and tested.



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R = o.Cl-C_6H_4-CH_2-

Compound	α	δ	δ'
2	R	R	R
3	S	R	R
4	S	S	S
5	R	S	S

Fig. 1.

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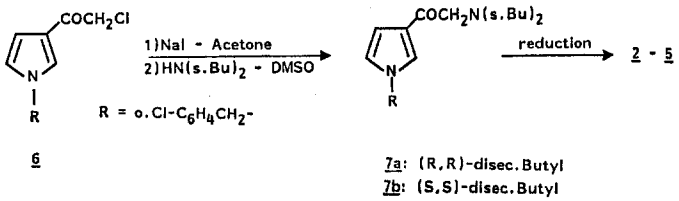
Chemistry

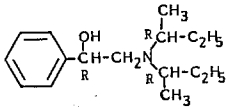


Scheme 1.

The synthetic route to the desired compounds **2**—**5** is reported in Scheme 1. Aminoketones **7** were prepared from α-chloroketone **6** by the sequential reaction with NaI and *(R,R)*- or *(S,S)*-disec.butylamine. Conversion of the aminoketones **7** into the final derivatives **2**—**5** was readily achieved by treatment with different reducing agents. It is worth pointing out the lack of selectivity observed in the reduction of aminoketones **7**. The use of different reagents such as $Zn(BH_4)_2$, $NaBH_4$, Red-Al, K-selectride and DIBAH in the range of temperature $-78 \pm 20°C$ gave invariably an almost equimolar mixture of the two diastereomers. This result sharply differs from that previously reported for the 2-isomers [13] where the proper choice of the reducing agent was crucial for the preferential formation of one of the two diastereomers.

By comparing these two sets of data, we can deduce that the two chiral centers are not sufficient to induce a diastereoselectivity; the presence of a bulky group in an adjacent position was necessary.

The configuration at C_α was assigned by comparing the value of the specific rotation of **2** and **3** with that of the model compound 1-phenyl-2-*R,R*-disec.butylamino-1*R*-ethanol **8**. Previously this criterion was successfully applied



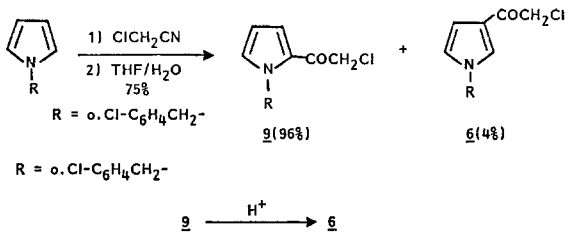
8

Fig. 2.

[13] to the stereoisomers of viminol. Since the specific rotation of **8** ($[\alpha]_D^{20} = -64.8°$) matches that of **2** ($[\alpha]_D^{20} = -73.10°$) and is considerably different from that of **3** ($[\alpha]_D^{20} = +19.87°$), the *R* configuration was attributed to the C_α of derivative **2**. Structures **4** and **5** were attributed by comparing their specific rotations with those measured for **2** and **3**.

We faced some difficulties in the synthesis of the key intermediate **6**. It is well-known [15, 16] that acylation of pyrrole and its *N*-substituted derivatives yields mainly the 2-acyl isomer. As a matter of fact, the reaction of 1-*o*.chlorobenzylpyrrole with chloroacetonitrile gave the 2-isomer contaminated by traces of the 3-isomer (**9**:**6** = 96:4) (Scheme 2).

The few methods available for the synthesis of 3-substituted pyrroles have recently been reviewed [17]. Among the different procedures we attempted, the acid-catalyzed

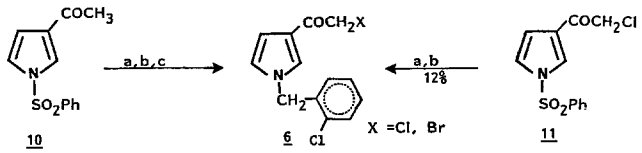


Acid[a]	time, h	% Composition **9**/**6**	% isolated yield of **6**
TFA	36	95/5	4
MsOH	6	4/96	75
TfOH	2	4/96	70

[a]TFA: trifluoroacetic acid; MsOH: methanesulfonic acid; TfOH: trifluoromethanesulfonic acid.

Scheme 2.

rearrangement of **9** proved to be the most efficient method [18]. A dichloroethane solution of **9** was refluxed in the presence of three different acids. The results, reported in Scheme 2, show the dependence of the rearrangement process upon the pK_a of the catalyst. In fact, whereas trifluoroacetic acid is unable to promote the rearrangement, the two sulfonic acids isomerize **9** almost completely and the rate of the process is higher with the more acidic trifluoromethanesulfonic acid. The two isomers were separated by column chromatography and their structure attributed by ^1H NMR. It is noteworthy that **6** and **9** were present in addition to a different pattern of the heteroaromatic protons (see Experimental protocols), a different chemical shift of the protons associated to the CH_2Ar group (5.25 *versus* 5.6 δ); the proximity of this group to the carbonyl moiety in **9** provokes a deshielding effect. Scheme 3 summarizes the other two methods we tested for the synthesis of **6**. In both cases, we took advantage of the well-established ability of the phenylsulfonyl group to yield 3-substituted pyrroles [19—23]. Unfortunately, both the reaction sequences were characterized by a poor overall yield which minimized the synthetic utility of these strategies.



Scheme 3. a: K_2CO_3/MeOH; b: NaH/*o*·Cl—$C_6H_4CH_2Cl$; c: $PhN^+Me_3Br_3^-$ or NBS.

Results and Discussion

The analgesic activity of the new 3-analogs of viminol **2**—**5** was investigated *in vitro* by testing their ability to displace [^{3}H]dihydromorphine from its binding sites and *in vivo* by testing their ability to induce an increase of the mouse pain threshold using the hot plate test. As reported in Table I compounds **2** and **3** were provided with a small

Table I. Inhibition of [^{3}H]dihydromorphine binding and analgesic activity of derivatives **2**—**5**.

Compound	[^{3}H]DHM binding inhibition IC_{50} (μM)[a]	Analgesic activity ED_{50} (mg/kg/i.p.)
2	29	> 25
3	62	>100
4	>300	> 25
5	>300	> 25
Viminol	2	11 (8—15)
Morphine	0.01	1.8 (1.3—2.4)

[a] IC_{50}: μM concentration which is effective in displacing 50% of [^{3}H]dihydromorphine (DHM) binding.

but measurable affinity for [^{3}H]dihydromorphine binding sites, whereas neither compound **4** nor **5** shared the same capacity. However, it has to be pointed out that the affinity of compounds **2** and **3** was about 10 times lower than that of viminol and more than 1000 times lower than that of morphine. As shown in the same Table, none of the stereoisomers tested produced a significant analgesic effect *in vivo*, at least up to subtoxic doses, since the reported doses of 25 mg/kg/i.p. for compounds **2**, **4**, **5** and 100 mg/kg/i.p. for compound **3** represent the highest dose before occurrence of appreciable toxicity. In fact, parallel behavioral studies carried out according to Irwin's procedure indicated that all the tested compounds possessed a higher toxicity with respect to viminol.

Compounds **2**, **4** and **5** exhibited a marked respiratory depression associated with body tremors at 50 mg/kg/i.p., whereas, at doses of 100 mg/kg/i.p., convulsions appeared a few minutes after treatment followed by death within 30—60 min. Compound **3** showed a lower toxicity, since a 2—3-fold increase in the dose was needed to observe the same symptoms as described above; death occurred at about 200 mg/kg/i.p.

The adrenergic activity of the new derivatives **2**—**5** was investigated *in vitro* by testing their abilities to displace [^{3}H]dihydroalprenolol, [^{3}H]prazosin and [^{3}H]clonidine from their binding sites in brain membrane preparations. It is konwn that [^{3}H]dihydroalprenolol labels α_1-receptors and [^{3}H]clonidine labels α_2-receptors. As shown in Table II, viminol by itself did not efficiently displace any ligand we used. Similarly, none of the derivatives **2**—**5** showed an appreciable activity indicating that the positional change of the ethanolamine chain did not improve the adrenergic component of this chemical structure. These results discouraged any further *in vivo* investigation. The present results confirm that the interaction of viminol with the active of the μ opioid receptors is highly stereoselective and requires the presence of the *(R,R)*-configuration at the two sec.butyl groups. In any case, the shift of the lateral chain from the 2- to the 3-position of the pyrrole ring causes a sharp reduction in the opioid activity, associated with the appearance of high toxicity.

Experimental protocols

Chemistry

^{1}H NMR spectra were recorded in $CDCl_3$ solution on a Perkin—Elmer R-600 FT or a Bruker WP-80 spectrometer (Me_4Si as the internal standard). Elemental analyses were carried out with a Carlo Erba Elemental Analyser model 1106. All new compounds gave satisfactory elemental analyses (C, H, N $\leqslant$0.3%).

Rotatory power determinations were carried out at 20°C with a Perkin—Elmer 141 Polarimeter, coupled to a Haake N3-B thermostat. Melting points were determined in open capillaries on a Büchi apparatus and are uncorrected. Thin—layer chromatography (TLC) was carried out on commercial silica gel GF_{254} plates.

(R,R)- and *(S,S)*-disec.butylamine were prepared in the Zambon S.p.a. Laboratories as previously described [13] and had the following specific rotations: *(R,R)*-disec.butylamine: $[\alpha]_D^{20} = -59.16°$ (c = 2.05, Et_2O); *(S,S)*-disec.butylamine: $[\alpha]_D^{20} = +58.79°$ (c = 2.08, Et_2O).

1-o.Chlorobenzyl-2-chloroacetylpyrrole **9**

The acylation of 1-*o*.chlorobenzylpyrrole was carried out as reported previously [13]. An NMR spectrum of the reaction mixture showed the presence of **6** as a by-product (4%).

^{1}H NMR: 4.42 (s, 2H, CH_2Cl); 5.64 (s, 2H, CH_2Ar); 6.21 (t, 1H, H-4); 6.62 (t, 1H, H-3); 6.8—7.5 (m, 5H, 4 Ar and H-5).

Isomerization of **9**

A. 1.5 g (5.6 mmol) of **9** and 5 ml (0.056 mol) of triflic acid in 1,2-dichloroethane (25 ml) were refluxed until TLC showed the disappearance of the starting material (1.5 h). The reaction mixture was poured onto ice and made alkaline with solid K_2CO_3. After the usual work-up, the residue was crystallized from diisopropylether and gave **6** as colorless prisms, mp: 83—85°C. Yield: 70%; R_F (cyclohexane—ethyl acetate, 4:1) = 0.25. The ratio **9**/**6** reported in Scheme 2 was deduced from the NMR spectrum of the reaction mixture.

Table II. Inhibition (IC_{50}[a] values) of [^{3}H]dihydroalprenolol, [^{3}H]prazosin and [^{3}H]clonidine binding in rat cerebral cortex membrane preparations.

Compound	[^{3}H]Dihydroalprenolol binding (μM)	[^{3}H]Prazosin binding (μM)	[^{3}H]Clonidine binding (μM)
2	147	98	>300
3	>300	>300	>300
4	>300	>300	>300
5	>300	>300	>300
Viminol	250	180	>300
Isoproterenol	0.2	n.d.	n.d.
Norepinephrine	n.d.	0.8	n.d.
Clonidine	n.d.	n.d.	0.008

[a] IC_{50}: μM concentration which is effective in displacing 50% of specific ligand binding. n.d.: not determined.

B. The same conditions were used in the isomerization of **9** (1.5 g, 5.6 mmol) with methanesulfonic acid. The starting material disappeared after 6 h.

C. The use of trifluoroacetic acid as the catalyst did not evidence any appreciable isomerization even after a long period of time (36 h).

1-o.Chlorobenzyl-3-chloroacetylpyrrole **6**

A. 5 g (17.6 mmol) of 1-phenylsulfonyl-3-chloroacetylpyrrole [22] were treated with K_2CO_3 (3 g) in methanol (40 ml). The mixture was stirred at RT (room temperature) until the disappearance of the starting material (10 h), then poured into water and extracted with $CHCl_3$. The crude product was purified by column chromatography (SiO_2—cyclohexane/ethyl acetate, 7:3) and gave 0.5 g (20%) of 3-chloroacetylpyrrole which was crystallized from toluene as colorless prisms; mp: 132°C dec. R_F (cyclohexane—ethyl acetate, 3:2) = 0.43.

^{1}H NMR ($CDCl_3$): 4.53 (s, 2H, CH_2Cl); 6.6—7.0 (m, 2H, H-4 and H-5); 7.62 (m, 1H, H-2); 8.5—9.3 (bs, 1H, NH).

B. A solution of 3-chloroacetylpyrrole (0.5 g, 3.5 mmol) in 30 ml of anhydrous tetrahydrofuran (THF) was added dropwise to 0.17 g (7 mmol) of 99% NaH in 20 ml anhydrous THF. The mixture was stirred at RT until the evolution of gas ceased and then reacted with 0.9 ml (7 mmol) of *o*.chlorobenzylchloride. The reaction mixture was poured into water, extracted with ether and subjected to the usual work-up. 1-*o*.Chlorobenzyl-3-chloroacetylpyrrole was purified by column chromatography (cyclohexane/ethyl acetate, 4:1). Yield: 60%.

^{1}H NMR ($CDCl_3$): 4.45 (s, 2H, CH_2Cl); 5.25 (s, 2H, CH_2Ar); 6.7 (m, 2H, H-4 and H-5); 6.9—7.2 (m, 5H, 4 Ar and H-2).

1-o.Chlorobenzyl-3-acetylpyrrole

This compound was prepared from 1-phenylsulfonyl-3-acetylpyrrole [20] with the method described above for **6**. Overall yield: 54%. The mp of the intermediate 3-acetylpyrrole (111—112°C) agrees with that previously reported [19]. 1-*o*.Chlorobenzyl-3-acetylpyrrole: colorless liquid, R_F (cyclohexane/ethyl acetate, 7:3) = 0.35.

^{1}H NMR: 2.35 (s, 3H, MeCO); 5.15 (s, 2H, CH_2Ar); 6.65 (m, 2H, H-4 and H-5); 6.9—7.1 (m, 5H, 4 Ar and H-2).

1-o.Chlorobenzyl-3-bromoacetylpyrrole

A. 0.25 g (1.2 mmol) of 1-*o*.chlorobenzyl-3-acetylpyrrole, 0.212 g (1.2 mmol) of NBS and a spatula tip of dibenzoyl peroxide in CCl_4 (20 ml) were stirred at 0°C. When the TLC showed the disappearance of the starting material, the mixture was filtered, the solvent removed under vacuum and the residue purified by column chromatography. 19 mg of 1-*o*.chlorobenzyl-3-bromoacetylpyrrole were collected as a brown oil.

^{1}H NMR: 4.22 (s, 2H, CH_2Br); 5.30 (s, 2H, CH_2Ar); 6.7—7.0 (m, 2H, H-4 and H-5); 7.1—7.7 (m, 5H, 4 Ar and H-2). The NMR spectra of different fractions showed the presence of the acetyl group accompanied by a modification of the heteroaromatic pattern.

B. 0.25 g (1.2 mmol) of **10** and 0.451 g (1.2 mmol) of phenyltrimethylammonium perbromide in anhydrous THF were stirred at −5°C until TLC showed the disappearance of the starting material (30 min). The mixture was poured into water and extracted with ether; the organic layer was dried over anhydrous Na_2SO_4 and the solvent removed under vacuum. Chromatography of the residue gave results superimposible onto those obtained with Method A.

Synthesis of 2—5

Chloroketone **6** (4 g, 16.4 mmol) was reacted with an acetone solution (25 ml) of NaI (13 g, 0.08 mol) at RT; the reaction was completed in a few minutes. The crude iodoketone was reacted with *(R,R)*-disec.butylamine or *(S,S)*-disec.butylamine (5.7 ml, 33 mmol) in dimethylsulfoxide (DMSO) (40 ml) at RT. The mixture was then poured into water, extracted with ether and the organic layer dried over Na_2SO_4. After removal of the solvent, 3.84 g of aminoketone **7a** (or **7b**) were collected (65% overall yield). To a stirred solution of **7a** (3.84 g, 10.7 mmol) in EtOH (50 ml), solid $NaBH_4$ (1.2 g) was added portionwise at RT. The progress of the reaction was monitored by TLC until the disappearance of the starting material (6 h). After the usual work-up, column chromatography (cyclohexane/ethyl acetate, 4:1) of the residue yielded 1.31 g of **2** and 1.97 g of **3**.

The $NaBH_4$ reduction of **7b** gave results superimposible onto those reported above.

The reduction of **7a** was also carried out with the following reducing agents: $Zn(BH_4)_2$ at RT, Red-Al at 0°C, K-selectride at −78°C and DIBAH at −78°C. In all cases the ratio **2**:**3** was similar to that observed in the corresponding reduction with $NaBH_4$ (40:60).

2 and **4** NMR: 0.8—1.8 (m, 16H, 4Me and $2CH_2$); 2.4—3.4 (m, 5H, CH_2N, 2CHN and OH); 4.53 (dd, 1H, *CH*OH; J_a = 3.8 Hz and J_b = 10.0 Hz); 5.15 (s, 2H, CH_2Ar); 6.20 (dd, 1H, H-4; $J_{2,4}$ = 1.6 Hz and $J_{4,5}$ = 3.5 Hz); 6.7—7.0 (m, 3H, H-5, H-2 and 1 Ar); 7.10—7.7 (m, 3H, Ar).

3 and **5** NMR: 0.7—1.2 (m, 12H, 4Me); 1.2—1.8 (m, 4H, $2CH_2CH_3$); 2.4—3.01 (m, 4H, CH_2N and 2CHN); 3.5 (bs, 1H, OH); 4.62 (dd, 1H, *CH*OH; J_a = 4.0 Hz, J_b = 10.0 Hz); 5.15 (s, 2H, CH_2Ar); 6.25 (dd, 1H, H-4; $J_{2,4}$ = 1.5 Hz, $J_{4,5}$ = 3.6 Hz); 6.6—7.0 (m, 3H, H-2, H-5 and 1 Ar); 7.1—7.6 (m, 3H, Ar.).

Specific rotations: **2**: $[\alpha]_D^{20} = -73.10°$ (c = 0.658, $CHCl_3$); **3**: $[\alpha]_D^{20} = +19.85°$ (c = 0.770, $CHCl_3$); **4**: $[\alpha]_D^{20} = +73.68°$ (c = 0.722, $CHCl_3$); **5**: $[\alpha]_D^{20} = -20.16°$ (c = 0.853, $CHCl_3$).

Pharmacology

[^{3}H]Dihydromorphine ([^{3}H]DHM) binding assay

The binding of [^{3}H]DHM to opiate receptors was performed on rat brain membranes as described by Mack *et al.* [24]. Male Sprague—Dawley rats weighing 170—250 g were sacrificed by decapitation; striata were rapidly removed at 4°C. Tissue was homogenized in approximately 10 vol of 50 mM Tris (pH 7.4) and then centrifuged at 50 000 × *g* for 30 min. After preincubation of the striatal membranes in 50 mM Tris at 25°C for 60 min, [^{3}H]DHM (specific activity 85.1 Ci/mmol) was added to give a final concentration of 2 nM, in the absence and in the presence of different concentrations of new compounds. Non-specific binding was estimated in the presence of 10^{-5} M naloxone. After incubation, samples were filtered through Whatman GF/B glass fiber filters under vacuum. The filters were then washed twice with 5 ml of Tris buffer and the radioactivity was measured by liquid scintillation spectrometry in 20 ml of Filtercount scintillation cocktail (Packard) with an efficiency of about 60%.

Hot plate test

The analgesic effect was determined according to the method described by Eddy *et al.* [25]. Male Albino Swiss CD/1 mice weighing 20—22 g were used. The tested compounds were administered intraperitoneally at different doses. The reaction time was determined before and 10, 20, 30, 45 and 60 min after administration. The reaction time represents the time in seconds from contact with the plate (51°C) until hind paw lick or jump occurred. The mice were removed as soon as they reacted or, if they failed to react, after 30 s.

Behavioral observation

Behavioral alteration of groups of 6 mice was studied according to the method described by Irwin [26]. Male Albino Swiss CD/1 mice were used. Animals were deprived of food for 18 h prior to the experiments. The test compounds were administered intraperitoneally at different doses. After treatment, the animals were replaced in their home cage and their behavior was compared to that of vehicle-treated mice. Detailed observation of mice was performed 30, 90, 150 and 300 min after drug administration using a standardized procedure. Mortalities were recorded during a 7 day post treatment period.

[^{3}H]Dihydroalprenolol ([^{3}H]DHA) binding assay

Adrenergic receptor binding was measured in membrane preparations from rat cerebral cortex as described by U'Prichard *et al.* [27] using [^{3}H]DHA as the specific ligand (specific activity 55 Ci/mmol). Tissue homogenates were incubated at 25°C for 20 min with [^{3}H]DHA (final concentration 1 nM) in 50 mM Tris-HCl buffer (pH 8) in the absence and in the presence of different concentrations of new compounds. Non-specific binding was defined as the non-displaceable binding obtained in the presence of 10 μM (D,L)-alprenolol. Samples were filtered under vacuum through Whatman GF/B glass fiber filters and rinsed 4 times with 4 ml of ice cold 50 mM Tris-HCl buffer. The radioactivity was counted by liquid scintillation spectrometry in 15 ml of Filtercount with an efficiency of about 60%.

[^{3}H]Prazosin and [^{3}H]clonidine binding assays

The experiments were performed according to the method described by Greengrass and Brenner [28]. Male Sprague—Dawley rats (250 g)

were killed by decapitation. Rat cerebral cortex was rapidly removed and homogenized in 20 vol (w/v) of ice cold 50 mM Tris-HCl buffer (pH 7.7), at 25°C. Homogenates were centrifuged twice for 10 min at 50 000 × *g* with resuspension of the pellet in fresh buffer. [^{3}H]-Prazosin (spec. act. 26 Ci/mmol) or [^{3}H]clonidine (spec. act. 20 Ci/mmol) was added to the tubes up to a final concentration of 0.5 nM, in the absence and in the presence of various concentrations of the new compounds; the tubes were then incubated at 25°C for 30 min. The incubation was termined by rapid filtration under vacuum through Whatman GF/B glass fiber filters. The filters were rinsed 3 times with 5 ml of ice cold 50 mM Tris buffer. The filters were placed in vials containing 10 ml of Filtercount scintillation cocktail (Packard) and the radioactivity was measured by liquid scintillation spectrometry with an efficiency of about 45%.

Acknowledgment

This work has been supported by 'Ministero della Publica Istruzione', Rome.

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