Pergamon

Bioorganic & Medicinal Chemistry 9 (2001) 585–592

BIOORGANIC & MEDICINAL CHEMISTRY

Synthesis and Pharmacological Evaluation of Imidazoline Sites I_1 and I_2 Selective Ligands

Maria Anastassiadou,[a,*] Saïda Danoun,[a] Louis Crane,[a] Geneviève Baziard-Mouysset[a,*] Marc Payard[a,*] Daniel-Henri Caignard,[b] Marie-Claire Rettori[b] and Pierre Renard[b]

[a]*Laboratoire de Chimie Pharmaceutique, Université Paul Sabatier, Faculté de Pharmacie 35, Chemin des Maraîchers, 31062 Toulouse Cedex 4, France*
[b]*Société ADIR. 1, rue Carle Hébert, 92415 Courbevoie Cedex, France*

Received 26 October 1999; accepted 26 September 2000

Abstract—Several series of 2-aryl or heterocyclic-imidazoline compounds have been prepared and evaluated in vitro as imidazoline sites (I_1 and I_2) and α-adrenergic (α_1 and α_2) receptor ligands. Their pK_i values indicate that linkage of the imidazoline moiety at the 2-position with an aromatic substituent dramatically decreases α-adrenergic affinity. I_1 sites are more accessible by phenyl imidazolines substituted by a methyl or a methoxy group at the *ortho* or *meta* position. Indeed, 2-(2′-methoxyphenyl)-imidazoline (**17**) is one of the best I_1 ligands ever reported (pK_i = 8.53 and $I_1/I_2 > 3388$). On the other hand, I_2 selectivity increases in the presence of a methyl group in the *para* position. The original compound, 2-(3′-fluoro-4′-tolyl)-imidazoline (**31**) is a new potent ligand for the I_2 sites with high selectivity (pK_i = 8.53 and $I_2/I_1 > 3388$).

Introduction

Pharmaceutical interest in imidazoline compounds began with the discovery of tolazoline's (**1**) α-adrenergic properties.[1] Subsequently, a large number of related structures with α-adrenergic activity has been synthesized and used in therapeutics.[2–5] Aminoimidazoline derivatives are the most well known imidazoline compounds and are used principally as anti-hypertensive agents.[6]

Since Bousquet and co-workers proposed the concept of imidazoline-preferring sites (*I*),[7] some 15 years ago, the design and synthesis of new molecules binding preferably to *I* sites over α-adrenergic receptors have been brought to practice.[8–12] This new class of imidazoline recognition sites appears to be responsible for a great number of functions in various tissues and species.[13] Recent studies support their involvement in many cardiovascular,[8,13–15] central nervous system (CNS)[16,17] and pancreatic diseases[18–20] and suggest that high *I* selective substances might lead to the development of new antiarhythmic, antihypertensive, antidepressive or antidiabetic drugs with minor lateral effects.[21] The oxazoline rilmenidine, an antihypertensive agent with high selectivity for *I* preferring sites, exhibits lower incidence and intensity of sedation compared with the nonselective compound clonidine and is also potent for α_2-adrenoreceptors.[22] 2-Benzofuranyl-imidazoline (2-BFI),[23] as well as tracizoline[10] and benazoline,[10] have also been described as new selective ligands for *I* sites over α-adrenergic receptors.

To date, two main subclasses of imidazoline recognition sites have been defined: the I_1, binding preferably [^{3}H]-*p*NH$_2$-clonidine and [^{3}H]-clonidine,[24–26] and the I_2, binding preferably [^{3}H]-idazoxan.[27–30] The I_1 participate in blood pressure regulation[13,31,32] whereas the I_2 are mainly associated with the inhibition of the monoamine oxidase (MAO) enzyme in the CNS.[33,34] The antihypertensive effects of rilmenidine and moxonidine, for instance, seem to be due to activation of I_1-binding sites in the rostral ventrolateral medulla (RVLM) of the brain stem.[13,35–37]

As the functional roles of these two imidazoline subsites are different, the design and synthesis of I_1 and I_2 selective ligands are of great significance. Therefore, the aim of the present study was the synthesis and pharmacological evaluation of new *I* sites selective ligands without α-adrenergic affinities, which are selective for one of the two imidazoline sites I_1 or I_2.

*Corresponding author. Tel.: +33-5-6155-1494; fax: +33-5-6225-6881.

0968-0896/01/$ - see front matter
PII: S0968-0896(00)00280-7

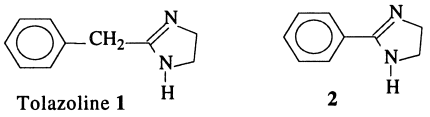
Our research project used as a starting point compound **2**, obtained by removal of the methylene group between the aromatic and imidazoline rings of **1** (Scheme 1). This structural modification resulted in increasing affinity for the imidazoline binding sites while eliminating potency for α-adrenergic receptors, α_1 and α_2 (Table 1).

In an effort to optimize these results, three diverse series of imidazoline compounds have been prepared as shown in Scheme 2.

The first one contains substituted phenyl-imidazolines in the *ortho*, *meta* or *para* position (series **I**). The choice of substituents was made with respect to their steric effects and lipophilic properties (Me, Et, Pr and *i*Pr, Bu, and *t*Bu), or electronic effects (Me, F, OMe...).

As benazoline[10] and 2-BFI[23] were recently described as selective ligands for I_2 sites over α adrenergic receptors, we replaced in the series **II** and **III** the phenyl ring of **2** by a naphthyl group or various heterocycles such as pyridine, pyrazine, furane, thiophene, indole or quinoleine.

All these compounds were tested in vitro as imidazoline binding sites I_1, I_2, and α adrenergic receptors α_1, α_2 ligands (Scheme 2).

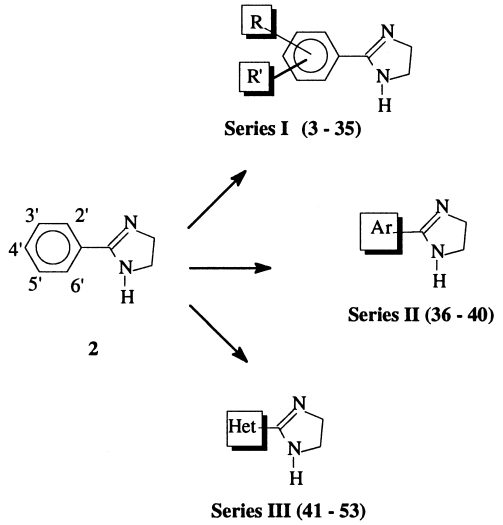


Scheme 1.

Table 1. pK_i values[a] in bovine brain (I_1), rabbit kidney (I_2) and calf cerebral cortex (α_1 and α_2) for compounds **1** and **2**

Compound	pK_i I_1	pK_i I_2	pK_i α_1	pK_i α_2
Tolazoline **1**	6.64	5.77	5.60	6.74
2	7.49	7.40	< 5.00	< 5.00

[a]Values are the mean of two experiments. The variability is less than 10%.



Scheme 2. Pharmacomodulation of the 2-2-phenyl-Δ-2-imidazoline.

Results

Chemistry

Compounds **3**–**13**, **15**, **18**–**25**, **27**–**30** and **32**–**53** (Tables 2–4) have been synthesized by nucleophilic addition of ethylenediamine (EDA) to the corresponding aromatic nitriles in the presence of catalytic amounts of a sulfur reagent: P_2S_5,[38] but CS_2,[39] or S[40] may be also used (Scheme 3).

The preparation of 2′- or 4′-aromatic halogenated imidazolines has been attempted by addition of EDA to the corresponding nitriles as described above. In this particular case, the formation of the imidazoline moiety does not take place and the reaction observed is an aromatic nucleophilic substitution (SNAr).[42] 2-Amino-ethylamino-benzonitriles have been obtained in this fashion.

For these reasons, the synthesis of compounds **14**, **16**, **26** and **31** has been performed by addition of EDA to the corresponding esters in the presence of trimethylaluminium[43] (Scheme 3). Compound **17** has also been synthesized according to Scheme 3.

Pharmacology

Affinities for compounds of the series **I**, **II** and **III** towards α_1- and α_2-receptors as well as I_1- and I_2-binding sites, were determined from radioligand binding assays. The results obtained are summarized in Tables 2–4. The values are expressed as pK_i affinity constants.

Discussion

The lack of α-adrenergic affinity for almost all of compounds prepared was our first successful result. It seems that linkage of the imidazoline moiety at position 2 with an aromatic substituent generally eliminates α-adrenergic affinity. In addition, 19 of the 53 derivatives prepared show a high selectivity for the *I* sites with affinities reaching the nanomolar scale.

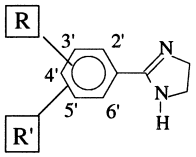
Having accomplished our first goal, we then set out to establish the structural factors that increase potency and selectivity for one *I* subsite over the other.

I_1-binding selectivity

We first examined the influence of different substituents on the phenyl ring of **2**. As shown in Table 2, I_1 sites appear to bind preferably with phenyl-imidazoline analogues substituted with a methyl or a methoxy group in the *ortho* or *meta* positions. Indeed, compounds **3**, **4**, **17**, **18** and **32** are all potent ligands for I_1 binding sites. Compound **17** is the only one of this series also having excellent I_1 selectivity over both I_2 sites and α-adrenergic receptors. Among disubstituted compounds prepared, compound **30** is very selective although its rather average affinity.

With regard to the series **II** and **III** (Tables 3 and 4), the most potent and selective ligand obtained was compound

Table 2. pK_i values[a] in bovine brain (I_1), rabbit kidney (I_2) and calf cerebral cortex (α_1 and α_2) for compounds of series **I**



I
2 - 35

Compound	2′	3′	4′	5′	6′	pK_i I_1	pK_i I_2	pK_i α_1	pK_i α_2	I_1/I_2[b]
2	H	H	H	H	H	7.49	7.40	< 5.00	< 5.00	1.230
3	Me	H	H	H	H	8.21	7.96	< 5.00	< 5.00	1.770
4	H	Me	H	H	H	8.66	8.30	< 5.00	< 5.00	2.290
5	H	H	Me	H	H	5.89	8.04	< 5.00	< 5.00	0.007
6	H	Et	H	H	H	7.31	7.48	< 5.00	< 5.00	0.680
7	H	H	Et	H	H	7.23	7.08	< 5.00	< 5.00	1.410
8	H	H	nPr	H	H	6.22	7.16	< 5.00	< 5.00	0.110
9	H	H	iPr	H	H	5.66	7.09	< 5.00	< 5.00	0.037
10	H	H	Bu	H	H	6.04	6.77	< 5.00	< 5.00	0.180
11	H	H	tBu	H	H	5.05	6.25	< 5.00	< 5.00	0.063
12	Ph	H	H	H	H	6.00	< 5.00	< 5.00	< 5.00	> 10.00
13	H	H	Ph	H	H	6.69	8.00	6.00	< 5.00	0.049
14	F	H	H	H	H	< 5.00	7.00	< 5.00	< 5.00	< 0.010
15	H	F	H	H	H	< 5.00	7.64	< 5.00	< 5.00	< 0.002
16	H	H	F	H	H	7.57	7.43	< 5.00	< 5.00	1.380
17	OMe	H	H	H	H	8.53	5.00	< 5.00	< 5.00	3388
18	H	OMe	H	F	H	7.97	7.75	< 5.00	< 5.00	1.660
19	H	H	OMe	H	H	7.46	8.28	< 5.00	< 5.00	0.150
20	H	H	OPh	H	H	6.34	7.34	5.11	5.26	0.100
21	SMe	H	H	H	H	5.14	< 5.00	< 5.00	< 5.00	> 1.380
22	H	H	SMe	H	H	7.75	8.42	< 5.00	< 5.00	0.210
23	H	H	CF_3	H	H	5.96	7.28	6.89	< 5.00	0.048
24	H	H	OCF_3	H	H	6.04	7.07	< 5.00	< 5.00	0.090
25	H	H	$NHCOCH_3$	H	H	< 5.00	< 5.00	< 5.00	< 5.00	—
26	H	F	F	H	H	7.00	7.00	NT	NT	1.000
27	H	F	H	F	H	5.00	7.11	< 5.00	< 5.00	0.008
28	Cl	H	F	H	H	5.25	5.31	< 5.00	< 5.00	0.871
29	H	Cl	F	H	H	< 5.00	6.77	< 5.00	< 5.00	< 0.017
30	Me	H	H	F	H	7.64	5.30	< 5.00	< 5.00	208
31	H	F	Me	H	H	< 5.00	8.53	< 5.00	< 5.00	< 0.0003
32	F	H	H	Me	H	8.27	8.21	< 5.00	< 5.00	1.150
33	H	*t*Bu	OH	*t*Bu	H	< 5.00	6.57	6.10	5.06	< 0.030
34	Me	CN	H	H	H	7.64	8.30	< 5.00	< 5.00	0.218
35	H	$O–CH_2–O$		H	H	7.46	8.26	< 5.00	< 5.00	0.158

[a]Values are the mean of two experiments. The variability is less than 10%.
[b]Antilog of the difference between pK_i I_1 and pK_i I_2 values.

38. The affinity of **38** was found to be equal to that of compound **17** while its selectivity is much lower.

It is interesting to observe the difference in affinity between compounds **47** and **48** Substitution of one hydrogen atom in the 3-position of 2-(2-thienyl)-imidazoline by a methyl group increases affinity for both I_1 and I_2 binding sites, although this compound is rather selective for the I_1 binding sites.

I_2-Binding selectivity

For compounds of series **I**, the presence of a methyl group in the *para* position of the phenyl ring, as in compound **5**, resulted in a remarkable increase in I_2 selectivity compared to the *ortho* or *meta* analogues, **3** and **4** (Table 2). In a similar manner, a phenyl group in the *para* position (i.e., compound **13**), shows high potency and good selectivity for the I_2 binding sites. Increase of the alkyl chain length in the *para* position leads to a significant decrease in affinity for I_2 receptors (compounds **7**–**11**) (Table 2).

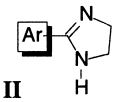
For compounds containing two substituents on the phenyl ring of **2** (series **I**) excellent results have been obtained. Compound **31** is obtained by introduction of a fluoro group in the *meta* position of compound **5** (Table 2). This structural modification leads to an increase in affinity and selectivity for I_2 sites over both I_1 and α-adrenergic receptors. Indeed compound **31** is one of the best I_2 ligands ever reported.

In order to examine if the presence of a phenyl ring is necessary to ensure high affinity and selectivity for I_2 sites, the phenyl ring of **2** has been replaced by other aromatic substituents in the last two series of compounds. These results are reported in Tables 3 and 4.

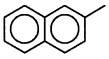
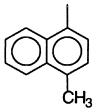
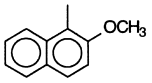
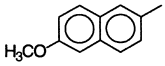
Benazoline (**37**), recently described as a selective ligand for *I* sites, is highly potent for both I_1 and I_2 binding sites. Similar results have been obtained for compound **36**.

As for molecules of the series **III**, the best results were obtained for the quinoline analogues **50** and **51**, for the indolyl derivative **49** as well as for the 2-BFI **52**, another

Table 3. pK_i values[a] in bovine brain (I_1), rabbit kidney (I_2) and calf cerebral cortex (α_1 and α_2) for compounds of series **II**



II
36 - 40

Compound	Ar	pK_i I_1	pK_i I_2	pK_i α_1	pK_i α_2	I_2/I_1[b]
36		8.82	8.82	< 5.00	5.59	1.000
37 Benazoline		8.92	9.18	6.00	6.00	0.550
38		8.54	7.00	< 5.00	6.70	34.67
39		< 5.00	< 5.00	< 5.00	< 5.00	—
40		7.05	7.94	> 5.00	5.46	0.130

[a]Values are the mean of two experiments. The variability is less than 10%.
[b]Antilog of the difference between pK_i I_1 and pK_i I_2 values.

potent ligand for the *I* sites. Although the three of them present a high affinity for the I_2-binding sites, their I_2 selectivity is rather low compared to compounds **5** and **31**.

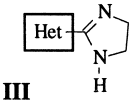
Conclusion

As this has been clarified, 2-phenyl-imidazoline derivatives do not generally bind to α-adrenergic receptors. It is worth noting that 19 of the 53 compounds reported herein show a high affinity and selectivity for the imidazoline binding sites. Among them, compound **17** is one of the best I_1 specific ligands. In a similar manner, the original compound **31** is a new potent ligand for the I_2 binding sites with good selectivity. The naphthyl and heterocyclic compounds **36**–**38** and **50**–**52**, respectively, are highly potent for the *I* sites, even more potent than their phenyl-analogues **17** and **31**, and exhibit rather moderate selectivity. Therefore with respect to other aromatic analogues, phenyl-imidazolines seem to be the most selective derivatives for I_1 and I_2 sites.

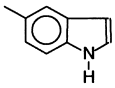
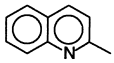
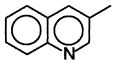
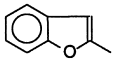
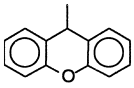
Minor modifications to the structure of the molecules can alter their I_1/I_2 profiles.

With regard to the monosubstituted derivatives **17**–**19** and **21**–**22**, we have concluded that 2-phenyl-imidazolines substituted at the *ortho* position are highly selective for the I_1-subsites, whereas I_2-subsites are more accessible by phenyl derivatives containing the substituent at the *para* position. On the other hand, substitution in the *meta* position of the phenyl ring (compounds **4**, **6** and **18**) results in maintaining potency for both I_1 and I_2 binding sites, but these compounds are less selective.

Table 4. pK_i values[a] in bovine brain (I_1), rabbit kidney (I_2) and calf cerebral cortex (α_1 and α_2) for compounds of series **III**



III
41 - 53

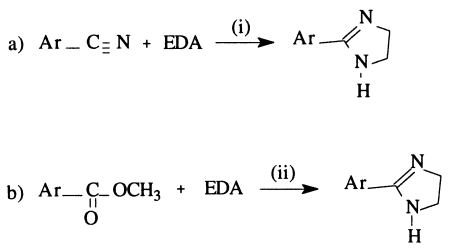
Compound	Het	pK_i I_1	pK_i I_2	pK_i α_1	pK_i α_2	I_2/I_1[b]
41		6.60	6.17	< 5.00	< 5.00	2.700
42		6.00	5.91	< 5.00	< 5.00	1.234
43		5.24	5.18	< 5.00	< 5.00	1.149
44		5.95	5.12	< 5.00	< 5.00	6.760
45		6.39	< 5.00	< 5.00	< 5.00	> 24.5
46		6.24	5.63	< 5.00	< 5.00	4.070
47		6.82	6.44	< 5.00	< 5.00	2.400
48		8.37	7.44	< 5.00	< 5.00	8.510
49		7.28	8.57	< 5.00	5.74	0.050
50		7.34	8.82	5.82	5.74	0.033
51		6.84	8.47	< 5.00	5.68	0.023
52		7.49	8.80	NT	NT	0.050
53		5.13	5.90	5.57	6.40	0.170

[a]Values are the mean of two experiments. The variability is less than 10%.
[b]Antilog of the difference between pK_i I_1 and pK_i I_2 values.

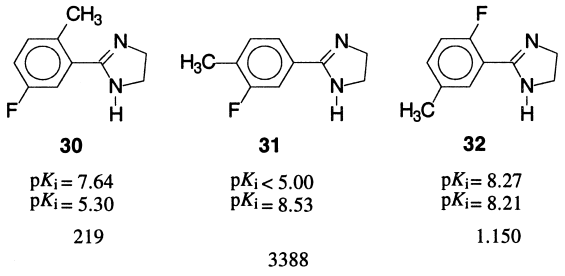
The fluoro-phenyl derivatives **14**–**16** do not obey this rule. Compound **14**, a rather bad ligand for the *I* sites, binds preferably to the I_2 over the I_1 binding sites.

The fluoro and methyl derivatives **30**, **31** and **32** (Table 2) containing exactly the same substituents on the phenyl ring but in different positions, have totally different properties. Compound **30** is high selective for the I_1 sites, **31** for the I_2 ones, while **32** is highly potent for both of them (Scheme 4).

Therefore the variation in I_1/I_2 selectivity seems to be due to the position of the methyl group. Indeed, for



Scheme 3. (a) Synthesis of imidazolines **3**–**13**, **15**, **18**–**25**, **27**–**30**, **32**–**53**. Reagents: (i) P_2S_5. (b) Synthesis of imidazolines **14**, **16**, **17**, **26** and **31**. Reagents: (ii) trimethylaluminium.



Scheme 4.

compound **30** the methyl group is in the *ortho* position, for **31** in the *para* and for **32** in the *meta* position.

In this paper, we have reported new imidazoline-based structures that are outstanding for their affinities and unprecedented I_1 or I_2 selectivities. These compounds will contribute to a better understanding of *I* sites characterization and function.

Experimental

Chemistry

Melting points were determined on a DSC-50 Shimadzu apparatus. Infra-red spectra were recorded on a Perkin–Elmer 983G spectrophotometer. All imidazoline-compounds present the same IR absorption bands towards 3000 cm^{-1} (νCH, CH_2, CH_3) and 3150 cm^{-1} (νNH). ^1H NMR spectra were determined in the indicated solvent with a 200 MHz spectrometer, and peak positions are given as s (singlet), d (doublet), t (triplet), q (quadruplet) or m (multiplet). The microanalyses were performed in the Microanalytical Laboratory of ENSCT in Toulouse, France and the results obtained are within ±0.4% of the theoretical values. Reactions were monitored by thin-layer chromatography (TLC) and product mixtures were purified by column chromatography using silica gel 60 F-254,70–200 mesh. All yields are calculated for analytical pure materials.

2-(2-Tolyl)-4,5-dihydro-1*H*-imidazole (3).[44] A stirred mixture of 2-tolunitrile (2.64 g, 0.02 mol), ethylenediamine (25 mL, 0.37 mol) freshly distilled on KOH, and 0.15 g of P_2S_5 was heated at 120 °C in an oil bath for 4 h. The reaction mixture was then cooled, poured into cold water and extracted with CH_2Cl_2. The organic phase was dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the crude free base was collected and purified by recrystallization from cyclohexane. Yield 89%, mp 90 °C. ^1H NMR ($CDCl_3$) δ 2.48 (s, 3H, CH_3), 3.76 (s, 4H, $2CH_2$), 4.50 (s, 1H, NH), 7.14–7.47 (m, 4H, ArH). Anal. ($C_{10}H_{12}N_2$) C, H, N.

Similarly, compounds **4**,[45] **5**,[46] **6**–**8**, **9**,[41] **10**, **11**,[41] **12**, **13**,[41] **15**,[45] **18**,[47] **19**,[48] **20**, **21**,[49] **22**,[50] **23**–**25**, **27**–**30**, **32**, **33**,[51] **34**, **35**,[48] **36**,[52] **37**,[53] **38**–**40**, **41**,[54] **42**,[54] **43**,[55] **44**,[56] **45**, **46**,[57] **47**,[58] **48**,[59] **49**, **50**,[60] **51**,[61] **52**,[62] and **53** were prepared from the appropriate nitriles as previously described. Physico-chemical data for already known derivatives are in agreement with the literature. For all new compounds prepared, physico-chemical data are reported below.

2-(3′-Ethylphenyl)-4,5-dihydro-1*H*-imidazole (6). Yield 79%, mp < 50 °C. ^1H NMR ($CDCl_3$) δ 1.19 (t, 3H, CH_3), 2.61 (q, 2H, CH_2CH_3), 3.47 (s, 4H, $2CH_2$), 4.05 (s, 1H, NH), 7.27–7.63 (m, 4H, ArH). Anal. ($C_{11}H_{14}N_2$) C, H, N.

2-(4′-Ethylphenyl)-4,5-dihydro-1*H*-imidazole (7). Yield 98%, mp 136 °C. ^1H NMR ($CDCl_3$) δ 1.23 (t, 3H, CH_3), 2.68 (q, 2H, CH_2CH_3), 3.74 (s, 4H, $2CH_2$), 4.70 (s, 1H, NH), 7.22–7.67 (m, 4H, ArH). Anal. ($C_{11}H_{14}N_2$) C, H, N.

2-(4′-*n*-Propylphenyl)-4,5-dihydro-1*H*-imidazole (8). Yield 70%, mp 130 °C. ^1H NMR ($CDCl_3$) δ 0.92 (t, 3H, CH_3), 1.62 (m, 2H, CH_2CH_3), 2.61 (t, 2H, $ArCH_2$), 3.77 (s, 4H, $2CH_2$), 6.20 (s, 1H, NH), 7.22–7.69 (m, 4H, ArH). Anal. ($C_{12}H_{16}N_2$) C, H, N.

2-(4′-*n*-Butylphenyl)-4,5-dihydro-1*H*-imidazole (10). Yield 61%, mp 101 °C. ^1H NMR ($CDCl_3$) δ 0.90 (t, 3H, CH_3), 1.34 (m, 2H, CH_2CH_3), 1.59 (m, 2H, $CH_2CH_2CH_3$), 2.62 (t, 2H, $ArCH_2$), 3.76 (s, 4H, $2CH_2$), 4.80 (s, 1H, NH), 7.21–7.68 (m, 4H, ArH). Anal. ($C_{13}H_{18}N_2$) C, H, N.

2-(2′-Biphenyl)-4,5-dihydro-1*H*-imidazole (12). Yield 37%, mp 109 °C. ^1H NMR ($CDCl_3$) δ 3.69 (s, 4H, $2CH_2$), 7.41–7.78 (m, 10H, NH + ArH). Anal. ($C_{15}H_{14}N_2$) C, H, N.

2-(4′-Phenoxyphenyl)-4,5-dihydro-1*H*-imidazole (20). Yield 56%, mp 129 °C. ^1H NMR ($CDCl_3$) δ 3.78 (s, 4H, $2CH_2$), 4.75 (s, 1H, NH), 6.99–7.74 (m, 9H, ArH). Anal. ($C_{15}H_{14}N_2O$) C, H, N.

2-(4′-Trifluoromethylphenyl)-4,5-dihydro-1*H*-imidazole (23). Yield 81%, mp 180 °C. ^1H NMR ($CDCl_3$) δ 3.79 (s, 4H, $2CH_2$), 4.55 (s, 1H, NH), 7.63–7.86 (m, 4H, ArH). Anal. ($C_{10}H_9F_3N_2$) C, H, N.

2-(4′-Trifluoromethoxyphenyl)-4,5-dihydro-1*H*-imidazole (24). Yield 77%, mp 150 °C. ^1H NMR ($CDCl_3$) δ 3.60–3.95 (m, 4H, $2CH_2$), 4.70 (s, 1H, NH), 7.23–7.80 (m, 4H, ArH). Anal. ($C_{10}H_9F_3N_2O$) C, H, N.

2-(4′-Acetamidophenyl)-4,5-dihydro-1*H*-imidazole (25). Yield 87%, mp 272 °C. ^1H NMR (DMSO-d_6) δ 2.18 (s, 3H, CH_3), 3.72 (s, 4H, $2CH_2$), 5.54 (s, 1H, Imid NH), 7.72–7.86 (m, 4H, ArH), 10.33 (s, 1H, CONH). Anal. ($C_{11}H_{13}N_3O$) C, H, N.

2-(3′,5′-Difluorophenyl)-4,5-dihydro-1*H*-imidazole (27). Yield 57%, mp 131 °C. ^{1}H NMR ($CDCl_3$) δ 3.77 (s, 4H, $2CH_2$), 4.63 (s, 1H, NH), 6.81–7.25 (m, 3H, ArH). Anal. ($C_9H_8F_2N_2$) C, H, N.

2-(2′-Chloro-4′-fluorophenyl)-4,5-dihydro-1*H*-imidazole (28). Yield 40%, oil. ^{1}H NMR ($CDCl_3$) δ 2.97, 3.16 (2m, 4H, $2CH_2$), 4.93 (s, 1H, NH), 6.46 (m, 1H, $H_{5'}$), 6.59 (m, 1H, $H_{3'}$), 7.35 (m, 1H, $H_{6'}$). Anal. ($C_9H_8ClFN_2$) C, H, N.

2-(3′-Chloro-4′-fluorophenyl)-4,5-dihydro-1*H*-imidazole (29). Yield 41%, mp 109 °C. ^{1}H NMR ($CDCl_3$) δ 3.01, 3.28 (2t, 4H, $2CH_2$), 4.95 (s, 1H, NH), 6.75 (m, 1H, $H_{5'}$), 7.55 (m, 1H, $H_{6'}$), 7.72 (m, 1H, $H_{2'}$). Anal. ($C_9H_8ClFN_2$) C, H, N.

2-(2′-Methyl-5′-fluorophenyl)-4,5-dihydro-1*H*-imidazole (30). Yield 71%, mp 88 °C. ^{1}H NMR ($CDCl_3$) δ 2.41 (s, 3H, CH_3), 3.57 (s, 4H, $2CH_2$), 4.59 (s, 1H, NH), 6.92–7.11 (m, 3H, ArH). Anal. ($C_{10}H_{11}FN_2$) C, H, N.

2-(2′-Fluoro-5′-methylphenyl)-4,5-dihydro-1*H*-imidazole (32). Yield 40%, mp 87 °C. ^{1}H NMR ($CDCl_3$) δ 2.31 (s, 3H, CH_3), 3.74 (s, 4H, $2CH_2$), 5.39 (s, 1H, NH), 6.96–7.86 (m, 3H, ArH). Anal. ($C_{10}H_{11}FN_2$) C, H, N.

2-(3′-Cyano-2′-methylphenyl)-4,5-dihydro-1*H*-imidazole (34). Yield 78%, mp 144 °C. ^{1}H NMR ($CDCl_3$) δ 2.67 (s, 3H, CH_3), 3.78 (s, 4H, $2CH_2$), 4.59 (s, 1H, NH), 7.29–7.65 (m, 3H, ArH). Anal. ($C_{11}H_{11}N_3$) C, H, N.

2-[1′-(4′-Methylnaphthyl)]-4,5-dihydro-1*H*-imidazole (38). Yield 16%, mp 149 °C. ^{1}H NMR ($CDCl_3$) δ 2.69 (s, 3H, CH_3), 3.75 (s, 5H, NH + $2CH_2$), 7.27–8.65 (m, 6H, ArH). Anal. ($C_{14}H_{14}N_2$) C, H, N.

2-[1′-(2′-Methoxynaphthyl)]-4,5-dihydro-1*H*-imidazole (39). Yield 70%, mp 157 °C. ^{1}H NMR (DMSO-d_6) δ 1.92 (s, 3H, OCH_3), 2.85 and 3.28 (2t, 4H, $2CH_2$), 6.73–7.6 (m, 6H, ArH), 8.15 (s, 1H, NH). Anal. ($C_{14}H_{14}N_2O$) C, H, N.

2-[2′-(6′-Methoxynaphthyl)]-4,5-dihydro-1*H*-imidazole (40). Yield 61%, mp 155 °C. ^{1}H NMR ($CDCl_3$) δ 3.84 (s, 4H, $2CH_2$), 3.91 (s, 3H, OCH_3), 4.85 (s, 1H, NH), 7.13–8.12 (m, 6H, ArH). Anal. ($C_{14}H_{14}N_2O$) C, H, N.

1-Methyl-4,5-bis-[2′-(4′,5′-dihydro-1*H*-imidazolyl)]-imidazole (45). Yield 84%, mp 162 °C. ^{1}H NMR ($CDCl_3$) δ 3.71 (s, 8H, $4CH_2$), 3.99 (s, 3H, CH_3), 5.80 (s, 2H, NH), 7,41 (s, 1H, ArH). Anal. ($C_{10}H_{14}N_6$) C, H, N.

2-(5′-Indolyl)-4,5-dihydro-1*H*-imidazole (49). Yield 60%, mp 181 °C. ^{1}H NMR ($CDCl_3$) δ 2.50 (s, 1H, NH), 3.80 (s, 4H, $2CH_2$), 6.58–8.03 (m, 5H, ArH), 8.60 (s, 1H, NH). Anal. ($C_{11}H_{11}N_3$) C, H, N.

2-(9′-Xanthenyl)-4,5-dihydro-1*H*-imidazole (53). Yield 70%, mp 220 °C. ^{1}H NMR ($CDCl_3$) δ 3.30 (s, 1H, NH), 3.52 (s, 4H, $2CH_2$), 5.41 (s, 1H, CH), 7.04–7.37 (m, 8H, ArH). Anal. ($C_{16}H_{14}N_2O$) C, H, N.

2-(3′-Fluoro-4′-methylphenyl)-4,5-dihydro-1*H*-imidazole (31). A solution of methyl 3-fluoro-4-methyl benzoate (5.34 g, 0.03 mol) in anhydrous toluene (100 mL) was added at 0 °C to a previously prepared solution of trimethylaluminium (3.17 g, 0.044 mol of a 2 M solution in toluene) and ethylenediamine (2.64 g, 0.044 mol) in anhydrous toluene (100 mL). The solution was heated under reflux with stirring for 10 h. On cooling, water (12 mL) was added followed by MeOH (30 mL) and CH_2Cl_2 (30 mL), and the mixture heated again under reflux for 15 min. The $Al(OH)_3$ was then eliminated by filtration and the organic layer was dried over $MgSO_4$ and evaporated in vacuo. The crude product obtained was extracted with CH_2Cl_2. The extracts dried, the solvent removed under reduced pressure and the crude free base was purified by recrystallization from cyclohexane. Yield 83%, mp 161 °C. ^{1}H NMR ($CDCl_3$) δ 2.28 (s, 3H, CH_3), 3.53 (s, 1H, NH), 3.76 (s, 4H, $2CH_2$), 7.15–7.39 (m, 3H, ArH). Anal. ($C_{10}H_{11}FN_2$) C, H, N.

Compounds **14**,[63] **16**,[53] and **17**,[64] were prepared as previously described.

2-(3′,4′-Difluorophenyl)-4,5-dihydro-1*H*-imidazole (26). A stirred mixture of 3,4-difluorothiobenzamide (2.78 g, 0.02 mol) and ethylenediamine (1.8 g, 0.03 mol) freshly distilled on KOH, in toluene (50 mL) was heated under reflux in an oil bath for 4 h. The reaction mixture was then cooled, the solvent was evaporated in vacuo and the crude free base was collected and purified by recrystallization from cyclohexane. Yield 45%, mp 154 °C. ^{1}H NMR ($CDCl_3$) δ 3.77 (s, 5H, NH + $2CH_2$), 7.02–7.65 (m, 3H, ArH). Anal. ($C_9H_8F_2N_2$) C, H, N.

Pharmacology

The affinity for the α_1- and α_2-adrenergic receptors was determined by measurement of [^{3}H]-Prazosin and [^{3}H]-RX 821002 displacement from membrane binding sites of calf cerebral cortex according to the methods previously described by Glossman[65] and Hudson[66]. Non-specific binding was determined with 10^{-5} M of phentolamine for α_1-ARs and with 10^{-5} M of yohimbine for α_2-ARs.

I_1- and I_2-receptors binding assays were performed according to the methods previously described by Steffen[67] and Mac Kinnon.[68]

***I*$_1$-binding sites.** Membranes from bovine adrenal glands (0.6 mg protein/mL) were incubated for 40 min with 4.8 nM [^{3}H]-Clonidine at 22 °C in binding buffer (PBS, EGTA 0.5 mM, $MgCl_2$ 0.5 mM, 0.5% ascorbic acid, pH 7.4) and increasing concentrations of competitors (12 concentrations in DMSO, 10^{-10} to 10^{-5} M) in the presence of 1 μM RX821002 to mask α_2-ARs. Non-specific binding was defined as [^{3}H]-clonidine binding in the presence of 1 μM of S22687-1.

***I*$_2$-binding sites.** Membranes from rabbit kidney cortex (0.5 mg/mL) were incubated for 30 min with 4.7 nM [^{3}H]-Idazoxan at 22 °C in binding buffer (Tris 50 mM, EDTA 1 mM, $MgCl_2$ 2 mM, pH 7.5) and increasing concentrations of competitors (10^{-10} to 10^{-5} M) in the presence of 5 μM of Rauwolscine. 2-BFI was used to define non-specific binding.

Acknowledgement

This work was supported by the French pharmaceutical industry 'Laboratoires ADIR'.

References

1. Sanders, J.; Miller, D.; Patil, P. N. *J. Pharmacol. Exp. Ther*. **1975**, *195*, 362.
2. Caroon, J. M.; Clarc, R. D.; Kluge, A. F.; Olah, R.; Repke, D. B.; Unger, S. H.; Michel, A. D.; Whiting, R. L. *J. Med. Chem*. **1982**, *28*, 666.
3. Chapleo, C. B.; Myers, P. L.; Butler, R. C. M.; Doxey, J. C.; Roach, A. G.; Smith, C. F. C. *J. Med. Chem*. **1983**, *26*, 823.
4. Halsta, D. J.; Luttinger, D.; Perrone, M. H.; Silbernagel, M. J.; Ward, S. J.; Haubrich, D. R. *J. Med. Chem*. **1987**, *30*, 1555.
5. Clark, R. D.; Berger, J.; Garg, P.; Weinhardt, K. K.; Spedding, M.; Kilpatrick, A. T.; Brown, C. M.; Mackinnon, A. C. *J. Med. Chem*. **1990**, *33*, 596.
6. (i) Castáner, J. *Drugs Future*, **1977**, *2*, 351; (ii) Castáner, J. *Drugs Future*, **1984**, *9*, 66; (iii) Mannhold, R. *Drugs Future*, **1992**, *17*, 526.
7. Bousquet, P.; Feldman, J.; Schwartz, J. *J. Pharmacol. Exp. Ther*. **1984**, *230*, 232.
8. Austin Yu, M. D.; William, H.; Frishman, M. D. *J. Clin. Pharmacol*. **1996**, *36*, 98.
9. Pilets, J. E.; Zhu, H.; Chikkala, D. N. *J. Pharmacol. Exp. Ther*. **1996**, *279*, 694.
10. Pigini, M.; Bousquet, P.; Carotti, A.; Dontenwill, M.; Giannella, M.; Moriconi, R.; Piergentili, A.; Quaglia, W.; Tayebati, S. K.; Brasili, L. *Bioorg. Med. Chem*. **1997**, *5*, 833.
11. Carrieri, A.; Brasili, L.; Leonetti, F.; Pigini, M.; Giannella, M.; Bousquet, P.; Carotti, A. *Bioorg. Med. Chem*. **1997**, *5*, 843.
12. Pigini, M.; Bousquet, P.; Brasili, L.; Carrieri, A.; Cavagna, R.; Dontenwill, M.; Gentili, F.; Giannella, M.; Leonetti, F.; Piergentili, A.; Quaglia, W.; Carotti, A. *Bioorg. Med. Chem*. **1998**, *6*, 2245.
13. Molderings, G. J. *Drugs Future* **1997**, *22*, 757.
14. Meeley, M. P.; Ernsberger, P.; Granata, A. R.; Reis, D. J. *Life Sci*. **1986**, *38*, 1119.
15. Wenzel, R. R.; Spieter, L.; Qui, S.; Shaw, S.; Luscher, T. F.; Noll, G. *Hypertension* **1998**, *32*, 1022.
16. Ernsberger, P. R.; Damon, T. H.; Graff, L.; Schaefer, S. G.; Christen, M. O. *J. Pharmacol. Exp. Ther*. **1993**, *264*, 172.
17. Piletz, J. E.; Halaris, A.; Ernsberger, P. R. *Crit. Rev. Neurobiol*. **1994**, *9*, 29.
18. Chan, S. *Clin. Sci*. **1993**, *85*, 671.
19. Rondu, F.; Le Bihan, G.; Wang, X.; Lamouri, A.; Touboul, E.; Dive, G.; Bellahsene, T.; Pfeiffer, B.; Renard, P.; Guardiola-Lemaitre, B.; Manechez, D.; Penicaud, L.; Ktorza, A.; Godfroid, J. J. *J. Med. Chem*. **1997**, *40*, 3793.
20. Ernsberger, P. R.; Ishizuka, T.; Liu, S.; Farrell, C. J.; Bedol, D.; Koletsky, R. J.; Friedman, J. E. *J. Pharmacol. Exp. Ther*. **1999**, *288*, 139.
21. Bousquet, P.; Bricca, G.; Dontenwill, M.; Feldman, J.; Belcourt, A.; Tibirica, E. *Thérapie* **1992**, *47*, 525.
22. Van Zwieten, P. A.; Thoolen, M. J. M. C.; Jonkman, F. A. M.; Willfert, B.; De Jong, A.; Timermans, P. B. *Arch. Int. Pharmacoclin. Ther*. **1986**, *279*, 130.
23. Nutt, D. J.; French, N.; Handley, S.; Hudson, A.; Husbands, S.; Jackson, H.; Jordan, S.; Lalies, M. D.; Lewis, J.; Lione, L.; Mallard, N.; Pratt, J. *Ann. N. Y. Acad. Sci*. **1995**, *763*, 125.
24. Ernsberger, P. R.; Meeley, M. P.; Mann, J. J.; Reis, D. J. *Eur. J. Pharmacol*. **1987**, *134*, 1.
25. Molderings, G. J.; Moura, D.; Fink, K.; Bönisch, H.; Göthert, M. *Naunyn-Schmiedeberg's Arch. Pharmacol*. **1993**, *348*, 70.
26. Bricca, G.; Greney, H.; Zang, J.; Dontenwill, M.; Stuszman, J.; Belcourt, A.; Bousquet, P. *Eur. J. Pharmacol*. **1994**, *266*, 25.
27. Coupry, I.; Podevin, R. A.; Dausse, J. P.; Parini, A. *Biochem. Biophys. Res. Commun*. **1987**, *147*, 1055.
28. Parini, A.; Coupry, I.; Graham, R. M.; Uzielli, I.; Atlas, D.; Lainer, S. M. *J. Biol. Chem*. **1989**, *264*, 11874.
29. Lauchaud-Pettiti, V.; Podevin, R. A.; Chretien, Y.; Parini, A. *Eur. J. Pharmacol*. **1991**, *206*, 23.
30. Molderings, G. L.; Kundt, L.; Göthert, M. *Naunyn-Schmiedeberg's Arch. Pharmacol*. **1994**, *350*, 252.
31. Ernsberger, P. R.; Westbrooks, K. L.; Christen, M. O.; Schaefer, S. G. *J. Cardiovasc. Pharmacol*. **1992**, *20*, S1.
32. Dubar, M.; Pillon, G. *Ann. N. Y. Acad. Sci*. **1995**, *763*, 642.
33. Raddatz, R.; Parini, A.; Lanier, S. M. *J. Biol. Chem*. **1995**, *270*, 27961.
34. Limon-Boulez, I.; Tesson, F.; Gargalidis-Moudanos, C.; Parini, A. *J. Pharmacol. Exp. Ther*. **1996**, *276*, 359.
35. Tibirica, E.; Feldman, J.; Mermet, C.; Monassier, L.; Gonon, I.; Bousquet, P. *Eur. J. Pharmacol*. **1991**, *209*, 213.
36. Ernsberger, P. R.; Damon, T. H.; Graff, L. M.; Schafer, S. G.; Christen, M. O. *J. Pharmacol. Exp. Ther*. **1993**, *264*, 172.
37. Head, G. H. *Ann, N. Y. Acad. Sci*. **1995**, *763*, 531.
38. Korshin, E. E.; Sabirova, L. I.; Akhadullin, A. G.; Levin, Y. A. *Russian Chem. Bull*. **1994**, *43*, 431.
39. Corbel, J. C.; Uriac, P.; Huet, J.; Martin, C. A. E.; Advenier, C. *Eur. J. Med. Chem*. **1995**, *30*, 3.
40. Doyle, T. J.; Haseltine, J. *J. Heterocycl. Chem*. **1994**, *31*, 1417.
41. Levesque, G.; Gressier, J. C.; Proust, M. *Synthesis* **1981**, *12*, 963.
42. Tidwell, R. R.; Jones, S. K.; Geratz, J. D.; Ohemeng, K. A.; Cory, M. *J. Med. Chem*. **1990**, *33*, 1252.
43. Neef, G.; Eder, U.; Sauer, G. *J. Org. Chem*. **1981**, *46*, 2824.
44. Dupin, P.; Viloria-Vera, D. A.; De Savignac, A.; Lattes, A.; Sutter, B.; Haicour, P. *Ann. Univ. Ferrara*, **1980**, *7*, 301.
45. Klem, R. E.; Skinner, H. F.; Walba, H.; Isensee, R. W. *J. Heterocycl. Chem*. **1970**, *7*, 403.
46. Limatibul, S.; Watson, J. W. *J. Org. Chem*. **1971**, *36*, 3803.
47. Graser, F. (BASF A.G.) Perylenetetracarboxylic acid and diimide dyes; Pat.ent 2616486; *Chem. Abstr*. **1977**, *88*, 75307.
48. Takeuchi, K.; Akatsuka, K.; Goto, K.; Kasuya, Y. *J. Pharmacobio-Dyn*. **1986**, *9*, 375.
49. Hagen, H.; Fly, H. *Justus. Liebig Ann. Chem*. **1975**, *1*, 1994.
50. McClelland, W. *J. Chem. Soc*. **1930**, 1095.
51. Koshelev, V. N.; Kelatev, V. I.; Belov, N. V.; Malova, O. V.; Osipov, S. L.; Spirkin, V. G. *Khim. Tekhnol. Topl. Masel*. **1995**, *1*, 19.
52. Harfenist, M.; Soroko, F. E.; Mc Kenzie, G. M. *J. Med. Chem*. **1978**, *21*, 405.
53. Pigini, M.; Brasili, L.; Cassinelli, A.; Giardina, D.; Gulini, U.; Quaglia, W.; Melchiorre, C. *Eur. J. Med. Chem*. **1987**, *22*, 273.
54. Upshall, D. G. *Teratology* **1972**, *5*, 287.
55. Sawa, N. *Nippon Kagaku Zasshi* **1968**, *89*, 780.
56. Forks, H.; Janowiec, M. *Acta. Pol. Pharm*. **1982**, *39*, 79.
57. Isagulyants, V. I.; Anufrieva, N. M.; Frolov, V. I.; Adzhiev, A. Y. *Prevrashch Geterotsikl Soedin* **1976**, *206*.
58. Mc Farland, J. W.; Conover, L. H.; Howes, H. L.; Lynch, J. C.; Chisholm, D. R.; Austin, W. C.; Cornwel, R. L.; Danilewicz, J. C.; Courtney, W.; Morgan, D. H. *J. Med. Chem*. **1969**, *12*, 1066.

59. Houliha, W. J.; Cheon, S. H.; Parrino, V. A.; Handley, D. A.; Larson, D. A. *J. Med. Chem.* **1993**, *36*, 3098.
60. Hudson, A. L.; Husbands, S.; Lewis, J. W.; Nutt, D. J. *Br. J. Pharmacol.* **1994**, *112*, S320.
61. Gaedcke, F.; Zymalkowski, F. *Arch. Pharm. (Weinheim Ger.)* **1979**, *312*, 812.
62. Chapleo, C. B.; Myers, P. L.; Butler, R. C. M.; Davis, J. A.; Doxey, C. *J. Med. Chem.* **1984**, *27*, 570.
63. Beger, J.; Wagner, G. *Z. Chem.* **1981**, *21*, 5184.
64. Bergman, J.; Brynolf, A. *Tetrahedron Lett.* **1989**, *30*, 2979.
65. Glossman, H.; Homung, R.; Presek, P. *J. Cardiovasc. Pharmacol.* **1980**, *2*, S303.
66. Hudson, A. L.; Mallard, N. J.; Tyacke, R.; Nutt, D. J. *Mol. Neuropharmacol.* **1992**, *1*, 219.
67. Steffen, G.; Dendorfer, A.; Dominiack, P. *Ann. N. Y. Acad. Sci.,* **1995**, *763*, 157.
68. MacKinnon A. C.; Stewart, M.; Olvermann, H. J.; Spedding, M.; Brown, C. *Eur J. Pharmacol.* **1993**, *232*, 79.