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Synthesis of new fenmetazole analogues with potential mixed α_2-adrenergic antagonistic activity and noradrenaline-uptake inhibiting properties

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Summary — In the search for new antidepressants with a rapid onset of action, fenmetazole analogues, bearing a second phenyl ring in a position previously shown not to be detrimental to affinity and selectivity for the α_2-adrenoreceptors, were synthesized in an attempt to combine NA-uptake inhibition and blockade of the α_2-adrenoreceptors in the same molecule. Some of the new molecules showed enhanced affinity and selectivity for the α_2-adrenoreceptors compared to fenmetazole. Surprisingly, introduction of a phenyl ring in the structure of fenmetazole changed the agonistic action of the parent compound toward the α_1-adrenoreceptors into an antagonistic effect. However, none of the new derivatives showed *in vitro* NA-uptake inhibitory potency substantially different from the low activity of fenmetazole in this test.

Résumé — Synthèse de nouveaux analogues du fenmétazole visant à combiner un effet antagoniste vis-à-vis des adrénorécepteurs-α_2 avec une action inhibitrice de l'*uptake* de la noradrénaline. *Une série d'analogues du fenmétazole portant un second noyau phényle dans une position dont la substitution avait été reconnue sans effet sur l'affinité et la sélectivité pour les adrénorécepteurs-α_2 a été synthétisée dans le but de trouver de nouveaux antidépresseurs doués d'une entrée en action rapide. Plusieurs des nouvelles molécules ont montré une affinité et une sélectivité pour les adrénorécepteurs α_2 supérieures à celle du fenmétazole. L'introduction d'un second noyau phényle dans la molécule de fenmétazole a changé l'effet agoniste de la molécule de départ vis-à-vis des adrénorécepteurs α_1 en action antagoniste. Aucun nouveau dérivé n'a cependant montré* in vitro *un effet inhibiteur de l'*uptake *de la noradrénaline supérieur à la faible activité du fenmétazole dans ce test.*

α_1- and α_2-adrenoreceptors / NA-uptake inhibition / antidepressant activity / fenmetazole analogues / α_2-antagonism

Introduction

Noradrenaline (NA)-uptake inhibitors are thought to produce their antidepressant activity by increasing NA availability at noradrenergic synapses; however, the increase in intersynaptic NA levels activates a feedback mechanism regulated by α_2-adrenoreceptors, which tends to reduce the release and synthesis of NA [1] and to limit the efficiency of the drugs. The potential interest of combining NA-uptake inhibition with blockade of α_2-adrenoreceptors for achieving antidepressant activity occurring with a rapid onset of action was first suggested by Crews *et al* [2]. In a first attempt to combine both activities in the same molecule, the synthesis of hybrids between reboxetine, an NA-uptake blocker, and idazoxan, an α_2-adrenoreceptor antagonist, was first undertaken [22]. Contrary to our expectations, none of the hybrids prepared showed either activity.

In continuation of this approach, fenmetazole (A) (fig 1), a potential antidepressant [3] with weak α_2-adrenoreceptor properties [4] and low NA-uptake inhibitory potency, was selected as starting molecule. Fenmetazole analogues **I**, **II**, **III** (fig 1) were synthesized. Since at least 2 phenyl rings are present in potent and selective NA-uptake inhibitors [5–7], a second phenyl ring was introduced in the structure of fenmetazole. Substitution by a methoxy group for one of the 2 hydrogen atoms between the oxygen atom and the imidazoline ring of fenmetazole was shown to decrease the α_2-antagonistic property [8]. However, introduction of a methyl group [9] in the same position in phenoxymethyl-2-imidazoline was found to

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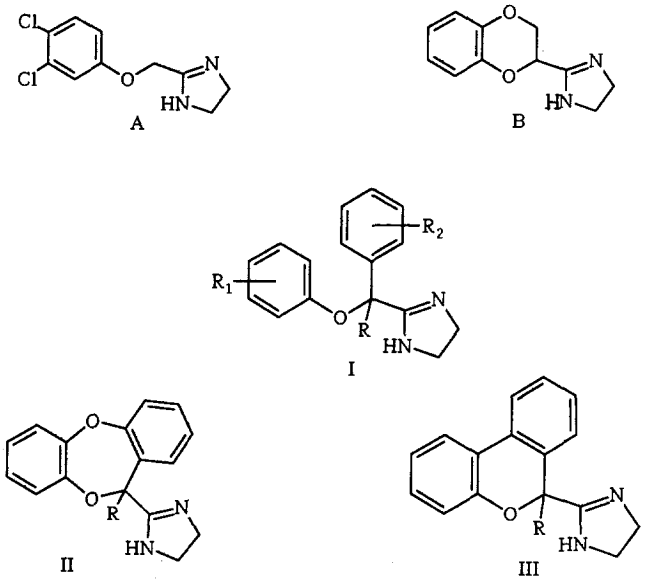
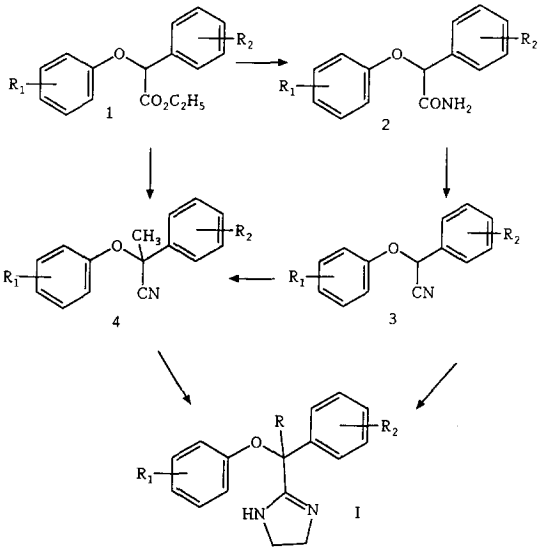


Fig 1. Structures of fenmetazole (A), idazoxan (B), and of fenmetazole analogues **I, II, III** (R = H or CH_3; for R_1 and R_2, see table I).



Scheme 1. Chemical pathways followed for the synthesis of molecules **I**.

enhance selectivity for the α_2-adrenoreceptors (unpublished results). Moreover, the C-2 position of idazoxan (B), a highly potent and selective α_2-adrenoreceptor antagonist similar to fenmetazole, was shown to be the only position in which potency and selectivity toward the α_2-adrenoreceptors were not reduced, and were sometimes increased, upon substitution [10] (for review, see [11]). Therefore, the second phenyl ring of fenmetazole analogues **I** was introduced between the oxygen atom and the imidazoline ring in the basic structure of fenmetazole, in a position corresponding to C-2 in idazoxan.

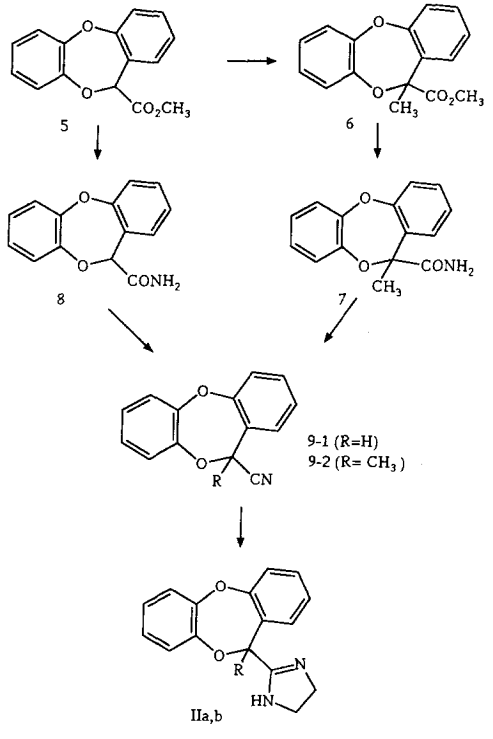
In addition to molecules **I**, other fenmetazole analogues of general structures **II** and **III**, in which the 2 phenyl rings of molecules **I** are linked directly or through an oxygen bridge were also synthesized.

Chemistry

Compounds **I** (table I) were synthesized according to scheme 1.

Esters **1** were prepared as described in [12]. Preparation of amides **2** and nitriles **3** and **4** was performed using conventional methods described in the experimental section. Compounds **I** were obtained by reacting the corresponding nitriles **3** or **4** with ethylenediamine paratoluenesulfonate.

Compounds **II** (table II) were prepared as depicted in scheme 2.



Scheme 2. Chemical pathways followed for the synthesis of molecules **II**.

Table I. Structures and chemical characteristics of compounds **I**. NMR spectra were recorded in $(CD_3)_2SO$ except for $\mathbf{I_d}$ and $\mathbf{I_h}$ for which $CDCl_3/(CD_3)_2SO$ (1/1) was used.

Compd	*R*	R_1	R_2	*Yield (%)*	mp (°C)	^1H *NMR* δ
$\mathbf{I_a}$	H	H	H	78[a]	123–125	3.40 (bs, 4H, CH_2-CH_2); 5.89 (s, 1H, CH-Ph); 6.9-7.7 (m, 10H, aromatic); 10.52 (bs, 1H, NH)
$\mathbf{I_b}$	H	2-OC_2H_5	H	54[b]	197–200	1.32 (t, 3H, CH_2-CH_3); 3.72 (s, 4H, CH_2-CH_2); 4.05 (q, 2H, CH_2-CH_3); 6.25 (s, 1H, CH-Ph); 6.6-7.7 (m, 9H, aromatic)
$\mathbf{I_c}$	H	3,4-diCl	H	58[b]	188–191	3.60 (s, 4H, CH_2-CH_2); 6.40 (s, 1H, CH-Ph); 7.05 (dd, 1H, aromatic); 7.3-7.7 (m, 7H, aromatic)
$\mathbf{I_d}$	CH_3	H	H	26[b]	167–169	1.80 (s, 3H, CH_3); 3.70 (s, 4H, CH_2-CH_2); 6.7-7.7 (m, 10H, aromatic)
$\mathbf{I_e}$	CH_3	2-OC_2H_5	H	24[b]	130–135	1.35 (t, 3H, CH_2CH_3); 1.80 (s, 3H, CH_3-C); 3.70 (s, 4H, CH_2-CH_2); 4.04 (q, 2H, CH_2-CH_3); 6.7-7.8 (m, 9H, aromatic)
$\mathbf{I_f}$	CH_3	3,4-diCl	H	32[b]	189–192	1.82 (s, 3H, CH_3); 3.72 (s, 4H, CH_2-CH_2); 6.86 (dd, 1H, aromatic); 7.19 (d, 1H, aromatic); 7.3-7.7 (6H, m, aromatic)
$\mathbf{I_g}$	CH_3	H	4-Cl	43[b]	154–160	1.80 (s, 3H, CH_3); 3.65 (s, 4H, CH_2-CH_2); 6.8-7.75 (m, 9H, aromatic)
$\mathbf{I_h}$	CH_3	H	3,4-diOCH_3	13[b]	157–161	2.08 (s, 3H, CH_3); 3.74 (s, 3H, OCH_3); 3.82 (s, 3H, OCH_3); 3.7 (bs, 4H, CH_2-CH_2); 6.6-7.3 (m, 8H, aromatic)

[a]Free base; [b]fumarate

Table II. Structures and chemical characteristics of compounds **II** and **III**. NMR spectra recorded in $(CD_3)_2SO/CDCl_3$ ($\mathbf{II_a}$, $\mathbf{II_b}$) or in $(CD_3)_2SO$ ($\mathbf{III_a}$, $\mathbf{III_b}$).

Compd	*R*	*Yield (%)*	*mp (°C)*	^1H *NMR* δ
$\mathbf{II_a}$	H	57[a]	180–182	3.83 (s, 4H, CH_2-CH_2); 6.60 (s, 1H, O-CH); 6.8-7.5 (m, 8H, aromatic)
$\mathbf{II_b}$	CH_3	47[a]	214–216	1.97 (s, 3H, CH_3); 3.65 (s, 4H, CH_2-CH_2); 6.9-7.6 (m, 8H, aromatic)
$\mathbf{III_a}$	H	47[b]	200–210	3.85 (s, 4H, CH_2-CH_2); 6.60 (s, 1H, O-CH); 6.9-7.9 (m, 8H, aromatic)
$\mathbf{III_b}$	CH_3	48[b]	*	1.98 (s, 3H, CH_3); 3.87 (s, 4H, CH_2-CH_2); 7.0-8.1 (m, 8H, aromatic)

[a]Fumarate; [b]chlorhydrate; *this hydrochloride exists as 2 crystal forms *mp* = 213-220 and then 238-240°C.

The intermediate methyl 11*H*-dibenzo[*b*, *e*][a, d]dioxepine-11-carboxylate **5** was prepared by conventional methods starting from 2-methoxyphenol and 2-fluoro-benzaldehyde, as described in the *Experimental protocols*. **5** was alkylated to give **6** and then transformed into the amide **7** or directly reacted with NH_4OH to afford **8**. Amides **7** and **8** were dehydrated using trifluoroacetic anhydride to give nitriles **9–1** and **9–2**, respectively. Reaction of **9–1** and **9–2** with ethylenediamine paratoluenesulfonate led to the formation of $\mathbf{II_a}$ and $\mathbf{II_b}$, respectively.

Compounds $\mathbf{III_a}$ and $\mathbf{III_b}$ (table II) were sythesized by reacting the corresponding nitriles, prepared according to [13], with ethylenediamine paratoluenesulfonate.

Biology

Molecules **I**, **II** and **III** were assayed *in vitro* to evaluate their affinity and selectivity toward the α_1- and α_2-adrenoreceptors. The ability of compounds with the highest affinity for the α_2-adrenoreceptors to antagonize the inhibitory effect of clonidine on the rat vas deferens and the contractile effect of norepinephrine on the rat anococcygeus was measured to assess respective pre-α_2 and post-α_1 antagonistic activity *in vitro*. The inhibition of NA-and serotonin (5-HT) – uptake was assayed *in vitro* by using rat hypothalamic synaptosomes. Since classical antidepressants have been shown to antagonize the syndrome induced by reserpine in mice [14], the potential antidepressant activity of compounds **I**, **II** and **III** was evaluated *in vivo* by measuring their ability to antagonize reserpine-induced ptosis and hypothermia in the mouse.

Results and Discussion

The inhibitory potency of molecules $\mathbf{I}_{a-h}$, $\mathbf{II}_b$, and $\mathbf{III}_b$ toward the NA-uptake system was not substantially different from that of fenmetazole, whereas $\mathbf{II}_a$ and $\mathbf{III}_a$ proved inactive (table III). Surprisingly, the 5-HT uptake inhibitory potency of some derivatives was markedly improved with respect to that of fenmetazole; in particular an IC_{50} value of 6 10^{-8} M was found for $\mathbf{I}_c$. Introduction of an additional methyl group into $\mathbf{I}_c$ ($\mathbf{I}_f$) resulted in a large decrease in 5-HT-uptake inhibitory potency.

The affinity of compounds $\mathbf{I}_{a,d-h}$ and $\mathbf{III}_a$ for the α_2-adrenoreceptors was found to be equal to or higher than that of fenmetazole. $\mathbf{I}_{a,d,h}$, not only showed higher affinity for the α_2-adrenoreceptors than fenmetazole, but also displayed increased selectivity for these receptors, with respect to the α_1-adrenoreceptors, than fenmetazole and idazoxan. Introduction of a phenyl ring in fenmetazole ($\mathbf{I}_c$) did not substantially modify the affinity for the α_2-adrenoreceptors but largely increased selectivity. Addition of a methyl group to $\mathbf{I}_c$ ($\mathbf{I}_f$) resulted in a decrease of selectivity. Interestingly, $\mathbf{I}_d$ was found to be approximately as selective a presynaptic α_2-adrenoreceptor antagonist as idazoxan. It is worth noting that addition of a phenyl ring ($\mathbf{I}_c$) or of a phenyl ring and a methyl group ($\mathbf{I}_f$) to fenmetazole changed the agonistic action of the parent compound toward the α_1-adrenoreceptors into an antagonistic effect. The affinity for the α_2-adrenoreceptors of compounds $\mathbf{I}_a$, $\mathbf{I}_d$ and $\mathbf{I}_h$ did not parallel the antagonistic effect observed in the vas deferens preparation. Thus, p*A*2 values of 8.5, 6.6, 7.4 and 6.6 were found for idazoxan, $\mathbf{I}_a$, $\mathbf{I}_d$ and $\mathbf{I}_h$, respectively, whereas the IC_{50} values in the binding inhibition test were similar. Though this observation remains un-

Table III. *In vitro* reuptake inhibition (NA, 5-HT), affinity for the α-adrenergic receptors, and α_1-, α_2-antagonistic effect of compounds **I**, **II** and **III**, fenmetazole and idazoxan. Between parentheses: number of determinations. –: not determined.

Compds	*Binding inhibition* IC_{50} *(μM)*		*Reuptake inhibition* IC_{50} *(μM)*		*α-Adrenergic antagonism* pA_2 *values (± SD)*	
	α_1	α_2	*NA*	*5-HT*	α_1	α_2
$\mathbf{I}_a$	> 10	0.08	2.5	4.0	< 5.0 (2)	6.6 ± 0.1 (2)
$\mathbf{I}_b$	3.6	1.4	3.2	> 10	–	–
$\mathbf{I}_c$	> 10	0.5	3.5	0.06	5.3 ± 0.1 (2)	6.4 ± 0.5 (2)
$\mathbf{I}_d$	> 10	0.04	4.5	1.6	5.2 ± 0.1 (2)	7.4 ± 0.5 (3)
$\mathbf{I}_e$	> 10	0.2	4.0	2.6	< 5.0 (2)	6.4 ± 0.3 (2)
$\mathbf{I}_f$	2.0	0.2	5.0	3.0	5.1 ± 0.1 (2)	6.4 ± 0.2 (3)
$\mathbf{I}_g$	3.6	0.2	1.0	5.0	< 5.0 (2)	6.3 ± 0.1 (3)
$\mathbf{I}_h$	3.0	0.01	4.1	0.5	5.3 ± 0.4 (2)	6.6 ± 0.1 (2)
$\mathbf{II}_a$	4.7	0.9	> 10	> 10	–	–
$\mathbf{II}_b$	> 10	0.4	7.5	> 10	–	–
$\mathbf{III}_a$	> 10	0.2	> 10	> 10	Agonist	–
$\mathbf{III}_b$	0.5	0.6	8.0	> 10	–	–
Fenmetazole	0.8	0.2	5.5	> 10	Agonist	6.9 ± 0.2 (2)
Idazoxan	2.2	0.03	–	–	6.0 ± 0.1 (4)	8.5 ± 0.4 (4)

explained, it might be that compounds **I** behave as partial agonists of the α_2-adrenoreceptors. As has been shown in the 1,4-benzodioxan series, even minor modifications to the structure of the molecules can alter their agonist/antagonist profiles [10].

Substitution of one hydrogen atom in phenoxymethyl-2-imidazoline [15] by a phenyl ring ($\mathbf{I_a}$) considerably decreased affinity for the α_1-adrenoreceptors (IC_{50} = 0.04 μM (α_1) and 0.06 μM (α_2) for phenoxymethyl-2-imidazoline in binding inhibition tests). In addition the agonistic action of the parent compound toward the α_1-adrenoreceptors (ED_{50} = 6.9 10^{-7} M) was changed into an antagonistic effect (see $\mathbf{I_a}$ in table III). Substitution of the phenoxy moiety of molecules **I** was found to result in a decrease of affinity and antagonistic property toward the α_2-adrenoreceptors ($\mathbf{I_c}$ compared to $\mathbf{I_a}$ and $\mathbf{I_e}$ and $\mathbf{I_f}$ compared to $\mathbf{I_d}$), in keeping with the effect of substitution of the phenyl ring in idazoxan [4].

Linkage of the 2 phenyl rings in molecules $\mathbf{I_a}$ and $\mathbf{I_d}$, either through an oxygen atom or directly, to give compounds $\mathbf{II_{a,b}}$ and $\mathbf{III_{a,b}}$, respectively, resulted in decreased affinity for the α_2-adrenoreceptors compared to the parent compounds $\mathbf{I_a}$ and $\mathbf{I_d}$.

Molecules **I**, **II** and **III** proved unable to antagonize the syndrome induced by reserpine in the mouse; the only exception was $\mathbf{III_a}$, for which an ED_{50} value of 2.9 mg/kg (ptosis and hypothermia) was found after oral administration. Under the same conditions, fenmetazole gave ED_{50} values of 1 mg/kg (ptosis) and 4.8 mg/kg (hypothermia). Though $\mathbf{III_a}$ showed very low affinity for the α_1-adrenoreceptors in binding inhibition test ($IC_{50} > 10^{-5}$ M), it displayed potent α_1-agonistic activity in the anacoccygeus preparation (ED_{50} = 8.1 10^{-8} M), superior to that of fenmetazole (ED_{50} = 2.7 10^{-6} M). It can be asked whether the α_1-agonistic activity of $\mathbf{III_a}$ and fenmetazole may account for the antireserpine effect seen after acute administration in mice (for an extensive discussion of the possible role of α_1-adrenoreceptors in depression, see [16]).

In conclusion, introduction of a phenyl ring ($\mathbf{I_c}$) or of a phenyl ring plus a methyl group ($\mathbf{I_f}$) in fenmetazole did not dramatically modify affinity for the α_2-adrenoreceptors, but changed the α_1-agonistic effect of the parent compound into an antagonistic activity. In $\mathbf{I_d}$, the α_2-antagonistic activity was enhanced compared to fenmetazole. However, none of the molecules synthesized displayed NA-uptake inhibitory potency superior to that of fenmetazole. It might be that the second phenyl ring was introduced in a position not favourable for NA-uptake inhibition, or that the imidazoline ring does not behave as a bioisosteric substitute for the amino group present in potent NA-uptake inhibitors, or that the imidazoline ring should be linked to the phenoxybenzyl moiety by one or 2 methylenes for achieving potent NA-uptake inhibition [5–7].

Experimental protocols

Chemistry

Melting points (*mp*) were determined in open capillaries with a Büchi melting point apparatus and are uncorrected. ^{1}H-NMR spectra were recorded in a Bruker WP 80 SY spectrometer. Chemical shifts are reported in parts per million (δ) relative to internal Me_4Si. Elemental analyses were performed by our analytical laboratory and agreed with theoretical values within ± 0.4%. Common reagent-grade chemicals and starting materials were purchased from commercial sources and were used as received. Drying of solvents was performed by storage on 3 Å molecular sieves. Evaporation was performed *in vacuo* (rotating evaporator) and were preceded by drying over sodium sulfate.

*Preparation of molecules **I***

*2-(2-Ethoxyphenoxy)-2-benzeneacetamide (**2**, R_1 = 2-OC_2H_5, R_2 = H, scheme 1)*
The solution of 20 g (0.066 mol) of **1** ($R_1 = OC_2H_5$, R_2 = H) and 170 ml of 30% NH_4OH in 150 ml of DMF was stirred at room temperature (rt) for 24 h in a stoppered flask. The mixture was poured into 1500 ml of cold H_2O. The solid which precipitated was filtered, washed with water and finally dried to yield 15.8 g (88%) of **2** ($R_1 = OC_2H_5$, R_2 = H) as white crystals; *mp* = 146–149°C. NMR ($CDCl_3$) δ: 1.35 (t, 3H, OCH_2CH_3), 3.95 (q, 2H, OCH_2CH_3), 5.25 (s, 1H, CH-Ph), 6.6–7.4 (m, 9H, aromatic). Anal $C_{16}H_{17}NO_3$ (C, H, N). Analogously, the following compounds **2** (R_1, R_2; *mp*; yield) were obtained: (H, H; 151–152°C, 85%); (3,4-diCl, H; 103–105°C; 92%); (H, 4-Cl; 145–147°C; 68%); (H, 3,4-diOCH_3; 153–154°C; 84%).

*2-(2-Ethoxyphenoxy)-2-benzeneacetonitrile (**3**, R_1 = 2-OC_2H_5, R_2 = H, scheme 1)*
To a stirred solution of 15 g (0.055 mol) of **2** (R_1 = 2-OC_2H_5, R_2 = H) and 8.9 ml (0.11 mol) of pyridine in 150 ml of anhydrous dioxane at 10–15°C, 8.6 ml (0.06 mol) of trifluoroacetic anhydride were added dropwise within 1 h. After 3 h at rt, the solution was evaporated. The residue was taken up with ethyl acetate, washed with water, dried and evaporated to dryness to yield 13.5 g (97%) of **3** (R_1 = 2-OC_2H_5, R_2 = H) as a white solid; mp = 73–75°C. NMR ($CDCl_3$) δ: 1.40 (t, 3H, OCH_2CH_3), 4.00 (q, 2H, OCH_2CH_3), 5.80 (s, 1H, CH-Ph), 6.7-7.5 (m, 9H, aromatic). Anal $C_{16}H_{15}NO_2$ (C, H, N). Analogously, the following compounds **3** (R_1, R_2; *mp*; yield) were obtained: (H, H; 55–58°C; 96%); (3,4-diCl, H; 68–69°C; 94%); (H, 4-Cl; oil; 98%); (H, 3,4-diOCH_3; oil; 98%).

*2-(2-Ethoxyphenoxy)-2-benzenepropanenitrile (**4**, R_1 = OC_2H_5, R_2 = H, scheme 1)*
To a stirred solution of 2.53 g (0.01 mol) of **3** (R_1 = 2-OC_2H_5, R_2 = H) and 2.5 ml (0.04 mol) of methyliodide in 20 ml of anhydrous DMF, 0.5 g (0.011 mol) of 55% NaH were added portionwise within 1 h at 10–15°C. After 1 h at the same temperature, the mixture was cautiously poured into ice-water and extracted with ethyl acetate. The organic phase was washed with H_2O, dried and evaporated to give 2.6 g (90%) of **4** (R_1 = 2-OC_2H_5, R_2 = H) as a colourless oil pure enough to be further used without purification. NMR ($CDCl_3$) δ: 1.40 (t, 3H, OCH_2CH_3), 1.95 (s, 3H, CH_3-C-Ph), 3.90 (q, 2H, OCH_2CH_3); 6.5-7.5 (m, 9H, aromatic). Analogously, the following compounds **4** (R_1, R_2; yield) were obtained: (H, H; 98%); (3,4-di Cl; 92%); (H, 4-Cl; 85%); (H, 3,4-diOCH_3; 89%).

General procedure for the preparation of 2-(phenoxyphenylmethyl)-4,5-dihydro-1H-imidazole (R = H) and 2-(1-phenoxyphenyl)ethyl-4,5-dihydro-1H-imidazole (R = CH_3) derivatives ***I_{a-h}*** *(table I)*

The solution of 0.01 mol of ethylenediamine paratoluenesulphonate and 0.01 mol of the appropriate nitrile was heated at 135–145°C under vigourous stirring for 5 h. After cooling and addition of H_2O, the solution was basified with potassium carbonate and extracted with ethyl acetate. The organic layer was washed with H_2O, dried and evaporated to give a residue which was purified on a silica gel column by flash chromatography (mobile phase: $CHCl_3/CH_3OH$/30% NH_4OH, 193/7/0.3, v/v/v) to give $\mathbf{I_{a-h}}$. The free bases $\mathbf{I_{b-h}}$ were treated with the stoichiometric amount of fumaric acid in methanol to give the fumarates (physical data and yields are given in table I).

Preparation of compounds ***IIa,b***

*Methyl 11H-dibenzo[b,e][1,4]dioxepine-11-carboxylate (**5**, scheme 2)*

To a stirred slurry of 32.7 g (0.75 mol) of 55% NaH in 300 ml of anhydrous DMF kept under nitrogen, 93.1 g (0.75 mol) of 2-methoxyphenol were added dropwise. After 30 min at room temperature 79 ml (0.75 ml) of 2-fluorobenzaldehyde in 20 ml of DMF were added; the mixture was heated at 70°C for 8 h. After cooling to 0°C and addition of H_2O, the solution was extracted with ethyl acetate. The organic layer was washed with H_2O, dried and evaporated to yield 128 g (75%) of 2-(2-methoxyphenoxy)benzaldehyde as an oil, used in the next step without purification. NMR ($CDCl_3$) δ: 3.60 (s, 3H, OCH_3), 6.4-7.7 (m, 8H, aromatic); 10.50 (s, 1H, CHO).

To stirred solution of 47.5 g (1.12 mol) of LiCl in 450 ml of H_2O, 144 g (2.24 mol) of KOH 85% were slowly added. When all the KOH dissolved, 128 g (0.56 mol) of 2-(2-methoxyphenoxy)benzaldehyde was added dropwise, followed by 50.3 ml (0.56 mol) of bromoform. The reaction mixture was heated at 40–45°C for 48 h and then concentrated under vacuum. The residue was diluted with water, which was washed with ethyl acetate, then acidified with 23% HCl and extracted with ethyl acetate. The organic phase was dried and evaporated. The residue was purified on silica gel column by flash chromatography (mobile phase: benzene/ethyl acetate/acetone/acetic acid, 130/24/20/12, v/v) to give 108.7 g of 2-(2-methoxyphenoxy)-α-hydroxybenzeneacetic acid (72%) as a colourless oil. NMR ($CDCl_3$) δ: 3.60 (s, 3H, OCH_3), 5.30 (s, 1H, *CH*-OH), 6.3-7.3 (m, 8H, aromatic). Anal $C_{15}H_{14}O_5$ (C, H).

To the solution of 115 g (0.42 mol) of the preceding compound in 290 ml glacial acetic acid, 290 ml of a 33% solution of HBr in acetic acid was added. The reaction mixture was refluxed for 8 h, then cooled to rt, poured into water, and extracted with ethyl acetate. After drying, ethyl acetate was evaporated to yield 135.4 g (100%) of 2-(2-hydroxyphenoxy)-α-bromobenzeneacetic acid as a dark oil, used for the next step without purification. NMR ($CDCl_3$) δ: 5.70 (s, 1H, CHBr), 6.4-7.5 (m, 8H, aromatic), 7.8 (bs, 2H, COOH+OH).

To the solution of 135 g (0.42 mol) of the preceding compound in 300 ml of methanol, 14 ml of 96% H_2SO_4 were added and the solution stirred at rt for 40 h. 50 g of $NaHCO_3$ were then added and the reaction mixture was evaporated to dryness. The residue was taken up in ethyl acetate, which was washed with H_2O, dried and evaporated. Purification of the residue on silica gel column by flash chromatography (mobile phase: ethyl acetate/hexane, 40/60, v/v) gave 91.5 g (64.8%) of methyl 2-(2-hydroxyphenoxy)-α-bromobenzeneacetate as a colourless oil. NMR ($CDCl_3$) δ: 3.75 (s, 3H, OCH_3), 5.80 (s, 1H, CHBr), 6.5-7.7 (m, 8H, aromatic). Anal $C_{15}H_{13}BrO_4$ (C, H, Br).

To the suspension of 11.8 g (0.27 mol) of 55% NaH in 1400 ml of anhydrous DMF, 91.5 g (0.27 mol) of the preceding compound in 60 ml of DMF were added under nitrogen.

The reaction mixture was stirred for 3 h at rt then poured into cold water and extracted with ethyl acetate. The organic phase was dried and evaporated. The solid residue was triturated with methanol, filtered and finally dried under vacuum to give 45.4 g (65%) of **5** as a white solid, *mp* = 80–82°C. NMR ($CDCl_3$) δ: 3.79 (s, 3H, OCH_3), 5.77 (s, 1H, O-CH-Ph), 6.8-7.5 (m, 8H, aromatic). Anal $C_{15}H_{12}O_4$ (C, H).

*Methyl 11-methyl-11H-dibenzo[b,e][1,4]dioxepine-11-carboxylate (**6**, scheme 2)*

To the stirred solution of 2 g (0.0078 mol) of **5** and 1.9 ml (0.03 mol) of methyl iodide, 0.37 g (0.0086 mol) of 55% NaH was added portionwise at rt within 1 h. The mixture was stirred for an additional hour, poured into H_2O and extracted with ethyl acetate. The organic layer was washed with H_2O, dried and evaporated to yield 2.1 g (100%) of **6** as a white solid; *mp* 121–125°C. NMR ($CDCl_3$) δ: 1.95 (s, 3H, CH_3), 3.60 (s, 3H, OCH_3), 6.6-7.3 (m, 8H, aromatic). Anal $C_{16}H_{14}O_4$ (C, H).

*11-Methyl-11H-dibenzo[b,e][1,4]dioxepine-11-carboxamide (**7**, scheme 2)*

The mixture of 2.1 g (0.0077 mol) of **6** in 50 ml of KOH/ethanol 0.5 N was refluxed for 4 h. After cooling, the reaction mixture was concentrated, diluted with H_2O, which was washed with diethyl ether, and acidified with 23% HCl. The precipitate was filtered, washed with H_2O, and dried at 50°C. The white solid was dissolved in 7 ml of thionyl chloride and refluxed for 3 h. The solution was then added dropwise to an excess of 30% NH_4OH and the mixture stirred for 2 h at rt. The solid formed was filtered and washed with isopropyl ether to give 1.82 g (92%) of **7** as a white solid; *mp* = 152°C (dec). NMR ($CDCl_3$) δ: 1.70 (s, 3H, CH_3), 6.5-7.4 (m, 8H, aromatic). Anal $C_{15}H_{13}NO_3$ (C, H, N).

*11H-Dibenzo[b,e][1,4]dioxepine-11-carboxamide (**8**, scheme 2)*

The solution of 0.5 g (0.00195 mol) of **5** in 10 ml of DMF and 10 ml of 30% NH_4OH was stirred for 16 h at rt in a stoppered flask. The mixture was poured into cold H_2O and the resulting white solid was filtered, washed with H_2O and dried under vacuum to give 0.28 g (61%) of **8** as white crystals; *mp* = 140–145°C. NMR ($CDCl_3 + (CD_3)_2SO$ 1:1) δ: 5.97 (s, 1H, O-CH-Ph), 5.8-7.5 (m, 8H, aromatic), 7.6 (bs, 2H, NH_2). Anal $C_{14}H_{11}NO_3$ (C, H, N).

*11H-Dibenzo[b,e][1,4]dioxepine-11-carbonitrile (**9–1**, scheme 2)*

To the stirred solution of 2.3 g (0.0095 mol) of **8** and 1.5 ml of pyridine in 40 ml of anhydrous dioxane, 1.45 ml (0.001 mol) of trifluoroacetic anhydride was added dropwise within 45 min at 10–15°C. After 5 h at rt the mixture was concentrated, diluted with ethyl acetate, which was washed with H_2O, dried and evaporated to dryness. The residue was purified by flash chromatography on silica gel column (mobile phase: hexane/ethyl acetate, 70/30, v/v) to give 2 g (91%) of **9–1** as an oil. NMR ($CDCl_3$) δ: 6.05 (s, 1H, O-CH-CN), 6.7-7.3 (m, 8H, aromatic). Anal $C_{14}H_9NO_2$ (C, H, N). **9–2** was prepared analogously from **7** and obtained as white crystals; *mp* = 85°C (dec). NMR ($CDCl_3$) δ: 2.15 (s, 3H, CH_3), 6.8-7.4 (m, 8H, aromatic). Anal $C_{15}H_{11}NO_2$ (C, H, N).

2-(11H-Dibenzo[b,e][1,4]dioxepin-11-yl)-4,5-dihydro-1H-imidazole $\mathbf{II_a}$ *and 2-(11-methyl-11H-dibenzo[b,e][1,4]dioxepin-11-yl)-4,5-dihydro-1H-imidazole* $\mathbf{II_b}$ *(scheme 2)*

$\mathbf{II_a}$ and $\mathbf{II_b}$ were prepared using the general procedure described for the preparation of **I**. Physical data and yields are given in table II.

Preparation of compounds $\mathbf{III_{a,b}}$

2-(6*H*-Dibenzo[*b,d*]pyran-6-yl)-4,5-dihydro-1*H*-imidazole $\mathbf{III_a}$ and 2-(6-methyl-6*H*-dibenzo[*b,d*]pyran-6-yl)-4,5-dihydro-1*H*-imidazole $\mathbf{III_b}$ were synthesized from the corresponding nitriles, which were obtained as described in [12], using the method described for the preparation of **I**. Physical data and yields are given in table II.

Biological evaluation

The affinity for the α_1- and α_2-adrenergic receptors was determined using [^{3}H] prazosin [17] and [^{3}H] yohimbine [18], as radioligands, respectively. The uptake of 5-HT and NA into rat hypothalamic synaptosomes was measured according to [19]. The reserpine antagonism test was performed in male mice as described by Rubin *et al* [20]. The presynaptic (α_2) and postsynaptic (α_1) α-adrenoreceptor antagonistic properties of compounds **I**, **II** and **III** were evaluated as described by Stillings *et al* [10], except that NA was used instead of phenylephrine in the rat anococcygeus preparation. Results are expressed as pA_2 values according to Arunlakshana and Schild [21]. The postsynaptic α_1-adrenoreceptor agonist activity of $\mathbf{III_a}$, fenmetazole and phenoxymethyl-2-imidazoline was determined according to [10].

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