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Original article

Research of potential antidepressant drugs with α_2-adrenoreceptor antagonist and NA-uptake inhibiting properties: synthesis of 2-(1-hydroxy-2-phenoxy-2-phenyl)ethyl-4,5-dihydro-1*H*-imidazole derivatives

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Summary — A series of 2-(1-hydroxy-2-phenoxy-2-phenyl)ethyl-4,5-dihydro-1*H*-imidazole derivatives has been synthesized with the aim of finding potential antidepressant drugs endowed with both NA-uptake and α_2-antagonist properties. The structure of the new compounds was designed by mixing the common elements present in reboxetine and α-aryloxy-benzyl derivatives of ethanolamine, both having NA-uptake inhibitory properties *in vitro*, and in idazoxan, a potent and selective α_2-adrenoreceptor antagonist. The new hybrids allow a good fitting of the common features without the strong steric interactions occurring when the structure of reboxetine is superimposed on that of idazoxan. However, the new derivatives did not display significant interaction with the NA-uptake system and the α_2-adrenoreceptors and proved inactive in the antireserpine test taken as a model of potential antidepressant activity. The possible relationship between the structural changes made in the parent molecules and the complete loss of activity on both systems is discussed.

Résumé — Recherche de nouveaux antidépresseurs visant à combiner l'inhibition de la recapture de la noradrénaline et un effet antagoniste des récepteurs α_2: synthèse de dérivés de l'α-hydroxy-ß-phénoxyphenéthyl-2-imidazoline. *Une série de dérivés de l'α-hydroxy-ß-phénoxyphenéthyl-2-imidazoline (et 2-imidazole) a été préparée en vue de trouver des antidépresseurs potentiels qui combineraient la propriété de bloquer la recapture de la noradrénaline et celle d'antagoniser l'action des adrénorécepteurs α_2. La structure des composés hybrides a été dessinée en retenant les éléments communs à la réboxétine et aux dérivés α-aryloxy-benzyle de l'éthanolamine, en tant qu'inhibiteurs de la recapture de noradrénaline* in vitro, *et à l'idazoxan, un antagoniste puissant des adrénorécepteurs α_2. Les nouveaux dérivés permettent un bon recouvrement des éléments communs sans induire les fortes interactions stériques qui apparaissent lorsque la structure de la réboxétine est superposée à celle de l'idazoxan. Les nouvelles molécules se sont montrées sans effet sur la recapture de la noradrénaline, sans affinité pour les adrénorécepteurs α_2, et inactives dans le test à la réserpine pris comme modèle d'une activité antidépressive potentielle. La relation entre les modifications structurales apportées aux molécules de base et l'absence d'effet des dérivés hybrides est discutée.*

reboxetine / idazoxan / α_2-adrenoreceptor antagonists / NA-uptake inhibitors

Introduction

Today, more than 20 years after the serendipitous observation that depressive symptoms developed in patients treated for hypertension with the biogenic amine-depleting agent reserpine, one of the accepted theories on depression remains that it is caused by a deficiency in brain monoamines due to a dysfunction of noradrenergic and/or serotonergic systems in discrete areas of the brain [1].

According to this hypothesis, antidepressant drugs (ADs) are thought to act primarily by potentiating central monoaminergic synaptic function, the mechanism of action being either inhibition of neuronal monoamine uptake or inhibition of monoamine

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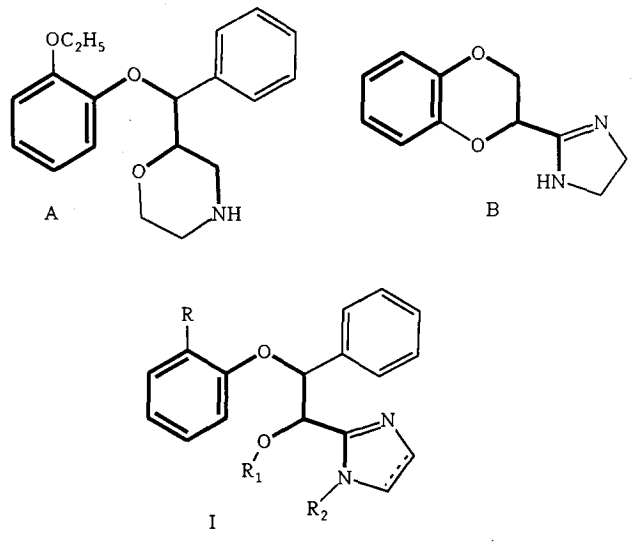
oxidase activity. With regard to ADs thought to elicit antidepressant activity by increasing noradrenaline (NA) availability at noradrenergic synapses, the increase in intersynaptic NA levels activates a feedback mechanism, regulated by pre-synaptic α_2-adrenoreceptors, which tend to reduce the release and synthesis of NA [2] and to limit the efficiency of NA-uptake inhibitors. It has therefore been proposed that NA-uptake inhibitors can only work fully after α_2-adrenoreceptors are desensitized [3]. Using desipramine as a model of NA-uptake blockers, desensitization of α_2-adrenoreceptors was found to occur after 2-3 weeks of administration [4], the delay necessary to achieve a therapeutic effect. On the basis of these observations it has been suggested that compounds with both α_2-adrenoreceptor antagonist and NA-uptake inhibiting properties should have a fast onset of action [5].

Orthostatic hypotension is a common side effect of ADs, often accompanied by a reduction of the vasomotor tone of blood vessels. Conversely, centrally acting α_2-adrenoreceptor antagonists should increase blood pressure, as has actually been found in man with α_2-antagonist idazoxan [6]. Therefore it can be assumed that an AD with both α_2-adrenoreceptor antagonist and NA-uptake inhibiting properties might be a product without major effects on blood pressure.

In a previous paper we reported on α-aryloxy-benzyl derivatives of ethanolamine and morpholine as selective and potent NA-uptake inhibitors *in vitro* [7]. One of the morpholine derivatives, reboxetine **A** (scheme 1), is under clinical investigation as an antidepressant. Reboxetine is a racemic mixture which consists of the RR and SS enantiomers [8].

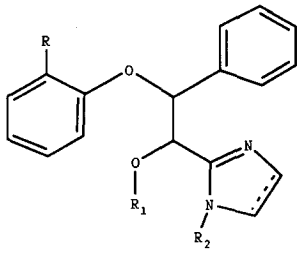


Scheme 1. Structures of reboxetine (A), idazoxan (B) and molecules **I**.

Superimposition of the common elements (thick lines) present in reboxetine **A** and idazoxan **B** (scheme 1), a potent and selective α_2-adrenoreceptor antagonist [9], was found to induce strong steric interactions in the molecule of reboxetine. In addition, the orientation of the N-H bond present in the 2 molecules was different. This might be detrimental for the activity of molecules containing the features common to **A** and **B**, if the orientation of the N-H bond plays a role in the recognition of antagonists by the α_2-adrenoreceptors and/or by the NA-uptake system. By contrast, the superimposition of the common elements present in idazoxan and in molecules **I** (scheme 1), which correspond to an 'open' structure of reboxetine, allowed a good fitting with no apparent steric hindrance, suggesting that hybrids **I** might retain the activity of both parent compounds. However the orientation of the N-H bond in molecules I remains somewhat different from that of the N-H bond in reboxetine.

α-Aryloxy-benzyl derivatives of ethanolamine were shown to display potent antireserpine activity [7] together with NA-uptake inhibitory properties (unpublished data), although less than the morpholine analogues such as reboxetine. Structure I contains the

Table I. 2-(1-Hydroxy-2-phenoxyphenethyl)derivatives of imidazoline and imidazole



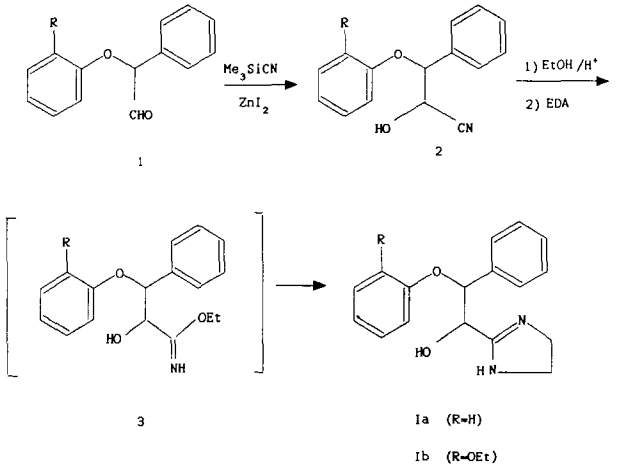
N°	R	R^1	R^2	Δ^a	Configuration	Yield (%)	mp (°C)
I_a	H	H	H	no	RS,SR + RS,RS	53.5	104-115[b]
I_b	OEt	H	H	no	RS,SR + RS,RS	45.6	95-120[c]
I_c	H	Me	H	no	RS,SR	44.6	96-99[b]
I_d	H	Me	H	no	RS,RS	51.0	155-157[d]
I_e	OEt	Me	H	no	RS,SR	56.3	174-177[e]
I_f	OEt	Me	H	no	RS,RS	49.6	153-155[d]
I_g	OEt	Me	Et	no	RS,SR	36.5	106-111[d]
I_h	OEt	Me	Et	no	RS,RS	41.2	123-125[d]
I_i	OEt	Me	H	yes	RS,SR	51.7	115-118[b]
I_j	OEt	Me	H	yes	RS,RS	57.2	160-163[b]
I_k	OEt	Me	Et	yes	RS,SR	55.9	135-137[d]
I_l	OEt	Me	Et	yes	RS,RS	98.0	111-116[d]

a) Refers to the presence of a double bond in position 4 in the imidazole ring; b) base; c) hemifumarate; d) fumarate; e) hydrochloride.

imidazoline ring which is common to many α_2-adrenoreceptor antagonists [10]. Synthesis and biological evaluation of molecules I were performed to examine whether substitution of the imidazoline ring by a moiety present in NA-uptake blockers might confer α_2-adrenoreceptor antagonist properties to a basic structure endowed with NA-uptake inhibitory activity. Since imiloxan, an analogue of idazoxan with a N-ethyl-imidazole residue instead of the imidazoline ring present in idazoxan, though less potent than the parent compound, was shown to be a highly selective α_2-adrenoreceptor antagonist [11], imidazole derivatives of structure I were also synthesized.

Chemistry

Compounds **I** (table I) with $R^1 = R^2 = H$ were synthesized according to scheme 2.



Scheme 2.

The starting aldehydes **1** were obtained by reduction of the corresponding ethyl esters [12] with diisobutylaluminum hybride (DIBAH) and used without purification for the synthesis of cyanohydrines **2**. Imidazolines $\mathbf{I_a}$ and $\mathbf{I_b}$ were obtained as 50:50 diastereoisomeric mixtures by Pinner reaction by reacting the intermediate iminoethers with ethylenediamine without isolation.

Compounds **I** with R^1 = Me and R^2 = H were obtained following a different route (scheme 3) which enabled the individual synthesis of the single diastereoisomers (the ones actually represented in the scheme are underlined).

Both *cis* and *trans* glycidic acid isomers were separated according to Harada [13]. The acids, but not the corresponding esters, reacted very smoothly with phenolates with 100% regio-and stereoselectivity. Conversion of the acids **4** to nitriles **8** was performed by conventional methods. At variance with the hydroxy derivatives **3**, the methoxyiminoethers **9** were stable crystalline compounds from which the corresponding imidazolines $\mathbf{I_{c-h}}$ were obtained by reaction with ethylenediamine or N-ethyl-ethylenediamine. The imidazoles $\mathbf{I_i}$ and $\mathbf{I_j}$ were prepared from **9** and aminoacetaldehyde dimethyl acetal [14] and $\mathbf{I_k}$ and $\mathbf{I_l}$ by alkylation of $\mathbf{I_i}$ and $\mathbf{I_j}$.

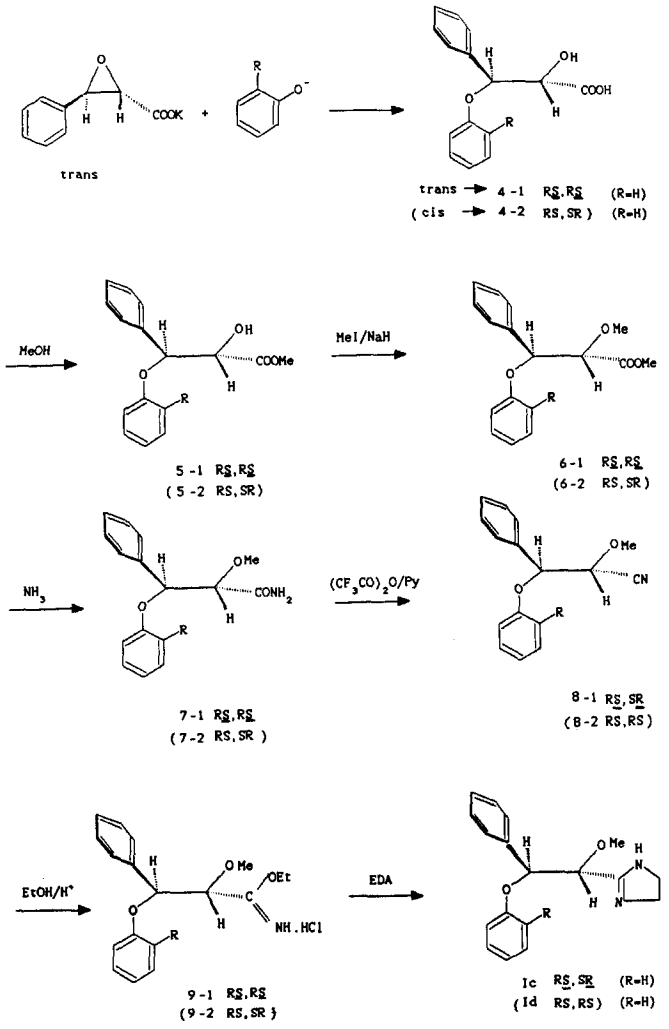
Biology

The potential antidepressant activity of compounds **I** was assayed *in vitro* and *in vivo*. Since classical tricyclic and MAO-inhibitor antidepressants have been shown to antagonize the reserpine-induced syndrome in mice and rats [15], the effect of compounds **I** toward reserpine-induced ptosis and hypothermia was evaluated in mice. The affinity of molecules **I** toward the α_1- and α_2-adrenoreceptors and for the imipramine (IMI) and desipramine (DMI) binding sites was assayed to evaluate their affinity and selectivity toward the adrenergic receptors and their potential as antidepressants, respectively. Imipramine binding has been associated with the neuronal uptake of serotonin (5-HT), whereas desipramine binding has been associated with the neuronal uptake of NA [16]. However, the association between brain desipramine and imipramine binding sites and NA and 5-HT uptake system, respectively, has been questioned [17]. Therefore, the inhibition of NA-and 5-HT-uptake was also assayed *in vitro* by using rat brain synaptosomes.

Results and Discussion

Compounds **I** did not show any appreciable affinity for α_1- and α_2-adrenoreceptors or for IMI and DMI recognition sites ($IC_{50} \geq 10^{-5}$ M); they also proved inactive as inhibitors of the NA- and 5-HT-uptake *in vitro* ($IC_{50} \geq 10^{-5}$ M) and in the reserpine test ($ED_{50} \geq$ 25 mg/kg, po). Owing to these results we did not deem it interesting to perform further tests.

Substitution of a methyl group for a hydrogen atom in position 3 of idazoxan was shown to result in a dramatic decrease in α_2-adrenoreceptor antagonist activity [18]. Molecular mechanic calculations using data obtained from 2 benzodioxan derivatives with strong α_2-adrenoreceptor antagonist activity, have shown that these molecules can adopt a common orientation of the biologically relevant structural features in which the angle between the mean plane of the benzodioxan ring and the imidazole ring is 45-50° [19]. There is no available information on the possible influence of substitution in position 3 of the benzodioxan ring upon the orientation of the mean plane of



Scheme 3.

the 2 rings. The fact that the open derivatives **I** did not show affinity for the α_2-adrenoreceptors suggests that the presence of a substituent attached to the C atom corresponding to C-3 in idazoxan is detrimental for activity, whatever the structure involved. It is tempting to hypothesize that steric interactions are produced when this position is substituted.

The lack of NA-uptake blocking activity of compounds **I** is more surprising because the corresponding amino alcohols and amino ethers displayed NA-uptake inhibitory activity [7], although to a lesser extent than reboxetine (10-100 times less, unpublished results). This suggests that, at least in the case of molecules **I**, the imidazoline moiety does not behave as a bioisosteric substitute for the amino group.

Experimental protocols

Chemistry

Melting points were determined in open capillaries with a Büchi melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker HX 90 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 $\pm$ 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 3Å molecular sieves. Evaporations were made *in vacuo* (rotating evaporator) and were preceded by drying over sodium sulfate.

2-Hydroxy-3-(2-ethoxyphenoxy)-3-benzenepropanenitrile 2 (R = OEt)

To a mixture of 10.2 g (40 mmol) of **1** (*R* = OEt) and 5.6 ml (44 mmol) of trimethylsilyl cyanide, ZnJ_2 (0.1 g) was added under stirring at room temperature. The reaction was stirred for 24 h, water and ethanol (100:100 ml) were added and the solution stirred for 2 h. After evaporation to dryness and addition of water, the aqueous phase was extracted with ethyl acetate. Removal of the solvent gave a mixture of diastereoisomers (approximately in 1:1 ratio), which was purified by flash-chromatography on a silica-gel column (mobile phase: $CHCl_3$) to give 5.05 g of **2** (*R* = OEt) (44.5%) as a colourless oil. NMR [$(CD_3)_2SO$]: δ 1.32 (3H, t, OCH_2CH_3); 4.00 (2H, q, OCH_2-CH_3); 4.80 (1H, d, CH-CN); 4.98 (1H, d, CH-CN); 5.40 (1H, d, CH-Ph); 5.43 (1H, d, CH-Ph); 6.8-7.6 (9H, m, arom). Anal. $C_{17}H_{17}NO_3$ (C, H, N).

2-Hydroxy-3-phenoxy-3-benzenepropanenitrile 2 (R = H)

Prepared analogously to **2** (*R* = OEt): yield 40.2%: colourless oil. NMR [$(CD_3)_2SO$]: δ 4.85 (1H, d, CH-CN); 4.95 (1H, d, CH-CN); 5.50 (1H, d, CH-Ph); 5.51 (1H, d, CH-Ph). Anal. $C_{15}H_{13}NO_2$ (C, H, N).

2-[1-Hydroxy-2-(2-ethoxyphenoxy)-2-phenyl]ethyl-4,5-dihydro-1H-imidazole hemifumarate I_b

To a stirred solution of 1.1 g (3.9 mmol) of **2** (*R* = OEt) in 30 ml of ethyl ether, 0.68 ml (11.6 mmol) of ethanol was added and a steady stream of gaseous hydrogen chloride was bubbled into the solution for 4 h at room temperature. The solvent was evaporated to dryness to give 1.42 g (100%) of iminoether **3** (*R* = OEt) which was used for the next step without further purification.

To the solution of **3** in 25 ml of ethanol, a solution of 0.26 ml (3.9 mmol) of ethylenediamine in 2 ml of ethanol was added dropwise over 1 h at 0°C. After 4 h, 6 ml of 1 N HCl were added and the solution was evaporated to dryness. The residue was purified by flash chromatography (mobile phase $CHCl_3/CH_3OH$/N HCl: 160/40/4) to obtain 1.1 g of $\mathbf{I_b}$ as a very hygroscopic hydrochloride. The compound was dissolved in water, the solution made basic with 1% NaOH and extracted with ethyl acetate. After evaporation to dryness, the residue was dissolved in methanol and 0.35 g of fumaric acid was added. Precipitation with diethyl ether gave 0.68 g (45.6%) of $\mathbf{I_b}$ hemifumarate as white crystals, mp 95-120°C (ratio of diastereoisomers 50:50). NMR [$(CD_3)_2SO$]: δ 1.33 (3H, m, CH_3); 3.60 (4H, s, N-CH_2-CH_2-N); 3.68 (4H, s, N-CH_2-CH_2-N); 4.03 (2H, q, O-CH_2-); 4.60 (1H, d, *CH*-OH); 4.74 (1H, d, *CH*-OH); 5.48 (1H, d, CH-Ph); 5.62 (1H, d, CH-Ph); 6.70-6.99 (4H, m,

PH-O); 7.20-7.50 (5H, m, Ph-C). Anal. $C_{19}H_{22}N_2O_3 \cdot 1/2\ C_4H_4O_4$ (C, H, N).

3-(1-Hydroxy-2-phenoxy-2-phenyl]ethyl-4,5-dihydro-1H-imidazole $\mathbf{I_a}$

Prepared analogously to $\mathbf{I_b}$; yield 53.5%; white crystals, mp 104-115°C (ratio of diastereoisomers 50:50). NMR ($CDCl_3$): δ 3.57-3.60 (4H, m, N-CH_2-CH_2-N); 4.70 (1H, d, -*CH*-OH); 4.71 (1H, d, *CH*-OH); 5.35 (1H, d, CH-Ph); 5.48 (1H, d, CH-Ph); 6.7-7.5 (10H, m, arom): Anal. $C_{17}H_{18}O_2$ (C, H, N).

(RS, RS) 2-Hydroxy-3-phenoxy-3-benzenepropanoic acid **4–1** *(R = H)*

To a stirred solution of 1.95 g (29.6 mmol) of 85% KOH in 10 ml of water, 4.18 g (44.4 mmol) of phenol were added portionwise at 70°C under nitrogen; then 6.0 g (29.6 mmol) of *trans* potassium phenyl glycidate were added in 20 min. The reaction was kept for 7 h at 70°C and then diluted with water to complete the solution. Addition of 8% HCl gave a white precipitate that was filtered and washed with water to yield 5.1 g (67.1%) of **4–1** (*R* = H) as white crystals, mp 175-180°C. NMR [$(CD_3)_2SO$]: δ 4.20 (1H, d, *CH*-OH); 5.35 (1H, d, CH-Ph); 6.60-7.30 (10H, m, arom). Anal $C_{15}H_{14}O_4$ (C, H).

The following compounds were prepared analogously to **4–1**. (RS, SR) 2-Hydroxy-3-phenoxy-3-benzenepropanoic acid **4–2** (*R* = H); yield 56.5%; mp 137-142°C. Anal $C_{15}H_{14}O_4$ (C, H). (RS, RS) 2-Hydroxy-3-(2-ethoxyphenoxy)-3-benzenepropanoic acid **4–1** (*R* = OEt); yield 57.2%; mp 113-115°C. Anal $C_{17}H_{18}O_5$ (C, H). (RS, SR) 2-Hydroxy-3-(2-ethoxyphenoxy)-3-benzenepropanoic acid **4–2** (*R* = OEt); yield 77.1%; mp 116-121°C. Anal $C_{17}H_{18}O_5$ (C, H).

(RS, RS) Methyl 2-hydroxy-3-phenoxy-3-benzenepropanoate **5–1** *(R = H)*

A solution of 5.0 g (19.3 mmol) of **4–1** (*R* = H) and 0.35 ml of 98% H_2SO_4 in 90 ml of methanol was stirred for 40 h at room temperature. After basification with $NaHCO_3$, the solution was concentrated to dryness, taken up with water and extracted with ethyl acetate. After work-up, 5.25 g (100%) of **5–1** (*R* = H) as a very viscous colourless oil were obtained. NMR ($CDCl_3$): δ 2.95 (1H, d, CH-*OH*); 3.50 (3H, s, $COOCH_3$); 4.35-4.50 (1H, dd, *CH*-OH); 5.25 (1H, d, CH-Ph); 6.50-7.10 (10H, m, arom). Anal $C_{16}H_{16}O_4$ (C, H).

The following compounds were prepared analogously to **5–1**. (RS, SR) Methyl 2-hydroxy-3-phenoxy-3-benzenepropanoate **5–2** (*R* = H); yield 92.2%; mp 72-75°C. Anal $C_{16}H_{16}O_4$ (C, H). (RS, RS) Methyl 2-hydroxy-3-(2-ethoxyphenoxy)-3-benzenepropanoate **5–1** (R = OEt); yield 100%, colourless oil. Anal $C_{18}H_{20}O_5$ (C, H). (RS, SR) Methyl 2-hydroxy-3-(2-ethoxyphenoxy)-3-benzenepropanoate **5–2** (*R* = OEt); yield 87.0%; colourless oil. Anal $C_{18}H_{20}O_5$ (C, H).

(RS, RS) Methyl 2-methoxy-3-phenoxy-3-benzenepropanoate **6–1** *(R = H)*

To a stirred solution of 5.2 g (19.1 mmol) of **5–1** (*R* = H) and 4.75 ml (76.3 mmol) of methyl iodide in 45 ml of DMF, 0.83 g (19.1 mmol) of 55% NaH in mineral oil was added portionwise in 1 h at 10°C. The reaction mixture was then stirred for a further hour at the same temperature. After work-up, 5.46 g (100%) of crude **6–1** (*R* = H) were obtained as a colourless oil, which was used for the next reaction without further purification. NMR ($CDCl_3$): δ 3.20 (3H, s, CH-O*CH*$_3$); 3.60 (3H, s, $COOCH_3$); 3.95 (1H, d, *CH*-OCH_3); 5.20 (1H, d, CH-Ph); 6.50-7.30 (10H, m, arom). Anal $C_{17}H_{18}O_4$ (C, H).

The following compounds were prepared analogously to **6–1**. (RS, SR) Methyl 2-methoxy-3-phenoxy-3-benzenepropanoate **6–2** (*R* = H); yield 100%; colourless oil. Anal $C_{17}H_{18}O_4$ (C, H). (RS, RS) Methyl 2-methoxy-3-(2-ethoxyphenoxy)-3-benzenepropanoate **6–1** (*R* = OEt); yield 100%; colourless oil. Anal $C_{19}H_{22}O_5$ (C, H). (RS, SR) Methyl 2-methoxy-3-(2-ethoxyphenoxy)-3-benzenepropanoate **6–2** (*R* = OEt); yield 88.4%; colourless oil. Anal $C_{19}H_{22}O_5$ (C, H).

(RS, RS) 2-Methoxy-3-phenoxy-3-benzenepropanamide **7–1** *(R = H)*

A solution of 5.4 g (18.8 mmol) of **6–1** (*R* = H) and 55 ml of 30% NH_4OH in 50 ml of DMF was stirred at room temperature for 36 h in a stoppered flask. The mixture was poured into 600 ml of cold water and the precipitate was filtered and washed with water to give 3.76 g (73.7%) of **7–1** (*R* = H) as white crystals, mp 110-115°C. NMR ($CDCl_3$): δ 3.55 (3H, s, CH-O*CH*$_3$); 4.20 (1H, d, *CH*-OCH_3); 5.60 (1H, d, CH-Ph); 6.70-7.30 (10H, m, arom). Anal $C_{16}H_{17}NO_3$ (C, H, N).

The following compounds were prepared analogously to **7–1**. (RS, SR) 2-Methoxy-3-phenoxy-3-benzenepropanamide **7–2** (*R* = H); yield 74.0%; mp 152-154°C. Anal $C_{16}H_{17}NO_3$ (C, H, N). (RS, RS) 2-Methoxy-3-(2-ethoxyphenoxy)-3-benzenepropanamide **7–1** (*R* = OEt); yield 77.4%; mp 115-118°C. Anal $C_{18}H_{21}NO_4$ (C, H, N). (RS, SR) 2-Methoxy-3-(2-ethoxyphenoxy)-3-benzenepropanamide **7–2** (*R* = OEt); 82.2%; mp 147-149°C. Anal $C_{18}H_{21}NO_4$ (C, H, N).

(RS, SR) 2-Methoxy-3-phenoxy-3-benzenepropanenitrile **8–1** *(R = H)*

To a stirred solution of 3.7 g (13.6 mmol) of **7–1** (*R* = H) and 2.19 ml (27.2 mmol) of pyridine in 40 ml of anhydrous dioxane at 10-15°C, 2.07 ml (14.9 mmol) of trifluoroacetic anhydride were added dropwise in 45 min. After 3 h at room temperature the solution was evaporated to dryness. After work-up, 3.38 g (98.2%) of **8–1** (*R* = H) were obtained as white crystals, mp 86-89°C. NMR ($CDCl_3$): δ 3.40 (3H, s, CH-O*CH*$_3$); 4.15 (1H, d, CH-CN); 5.20 (1H, d, CH-Ph); 6.70-7.40 (10H, m, arom). Anal $C_{16}H_{15}NO_2$ (C, H, N).

The following compounds were prepared analogously to **8–1**. (RS, RS) 2-Methoxy-3-phenoxy-3-benzenepropanenitrile **8–2** (*R* = H); yield 93.6%; mp 71-73°C. Anal $C_{16}H_{15}NO_2$ (C, H, N). (RS, SR) 2-Methoxy-3-(2-ethoxyphenoxy)-3-benzenepropanenitrile **8–1** (*R* = OEt); yield 87.6%; mp 52-54°C. Anal $C_{18}H_{19}NO_3$ (C, H, N). (RS, RS) 2-Methoxy-3-(2-ethoxyphenoxy)-3-benzenepropanenitrile **8–2** (*R* = OEt); yield 100%; colourless oil. Anal $C_{18}H_{19}NO_3$ (C, H, N).

(RS, RS) Ethyl[(1-methoxy-2-phenoxy-2-phenyl)ethyl]imidoate hydrochloride **9–1** *(R = H)*

A steady stream of gaseous hydrogen chloride was bubbled through a stirred solution of 2.0 g (7.89 mmol) of **8–1** (*R* = H) in 40 ml of anhydrous diethyl ether and 1.38 ml (23.6 mmol) of ethanol for 7 h at room temperature. The solution was evaporated to dryness, the residue taken up with diethyl ether and filtered to give 2.3 g (87.1%) of **9–1** (*R* = H) as white crystals, mp 129-131°C. NMR[$(CD_3)_2SO$]: δ 1.20 (3H, t, CH_2-*CH*$_3$); 3.34 (3H, s, OCH_3); 4.48 (2H, q, *CH*$_2$-CH_3); 4.69 (1H, d, *CH*-OCH_3); 5.60 (1H, d, CH-Ph); 6.70-7.60 (10H, m, arom). Anal $C_{18}H_{21}NO_3 \cdot HCl$ (C, H, N, Cl).

The following compounds were prepared analogously to **9–1**. (RS, SR) Ethyl[(1-methoxy-2-phenoxy-2-phenyl)ethyl]-imidoate hydrochloride **9–2** (*R* = H); yield 85.5%; mp 132-134°C. Anal $C_{18}H_{21}NO_3 \cdot HCl$ (C, H, N, Cl). (RS, RS) Ethyl[(1-methoxy-2-(2-ethoxyphenoxy)-2-phenyl)ethyl]imidoate hydro-

chloride **9–1** (*R* = OEt); yield 76.4%; mp 120-122°C. Anal $C_{20}H_{25}NO_4$. HCl (C, H, N, Cl). (RS, SR) Ethyl[(1-methoxy-2-(2-ethoxyphenoxy)-2-phenyl)ethyl] imidoate hydrochloride **9–2** (*R* = OEt); yield 81.4%; mp 133-136°C. Anal $C_{20}H_{25}NO_4$. HCl (C, H, N, Cl).

(RS, SR) 2-(1-Methoxy-2-phenoxy-2-phenyl)ethyl-4,5-dihydro-1H-imidazole $\mathbf{I_c}$

A solution of 0.334 ml (5 mmol) of ethylenediamine in 2 ml of ethanol was added over 1 h to a stirred solution of 1.68 g (5 mmol) of **9–1** (*R* = H) in 30 ml of ethanol at 0-10°C. After 4 h at 0-10°C, 10 ml of 1 N HCl were added and the solution was concentrated to dryness. The residue was purified by flash chromatography (mobile phase $CHCl_3/CH_3OH$/N HCl: 155/45/4.5) to obtain $\mathbf{I_c}$ as a very hygroscopic solid. The hydrochloride was dissolved in water, the solution made basic with 1% NaOH and extracted with ethyl acetate. Evaporation of the solvent gave 0.66 g (44.6%) of $\mathbf{I_c}$ as a white solid, mp 96-99°C. NMR [$(CD_3)_2SO$]: δ 3.17 (3H, s, OCH_3; 3.40 (4H, bs, N-CH_2-CH_2-N); 4.12 (1H, d, *CH*-OCH_3); 5.50 (1H, d, CH-Ph); 6.8-7.6 (10H, m, arom). Anal $C_{18}H_{20}N_2O_2$ (C, H, N).

The following compounds were prepared analogously to $\mathbf{I_c}$. (RS, RS) 2-(1-Methoxy-2-phenoxy-2-phenyl)ethyl-4,5-dihydro-1*H*-imidazole fumarate $\mathbf{I_d}$. Anal $C_{18}H_{20}N_2O_2 \cdot C_4H_4O_4$. (RS, SR) 2-[1-Methoxy-2-(2-ethoxyphenoxy)-2-phenyl]ethyl-4,5-dihydro-1*H*-imidazole hydrochloride $\mathbf{I_e}$. Anal $C_{20}H_{24}N_2O_3 \cdot HCl$ (C, H, N, Cl). (RS, RS) 2-[1-Methoxy-2-(2-ethoxyphenoxy)-2-phenyl]ethyl-4,5-dihydro-1*H*-imidazole fumarate $\mathbf{I_f}$. Anal $C_{20}H_{24}N_2O_3 \cdot C_4H_4O_4$ (C, H, N). (RS, SR) 1-Ethyl-2-[1-methoxy-2-(2-ethoxyphenoxy)-2-phenyl]ethyl-4,5-dihydro-1*H*-imidazole fumarate $\mathbf{I_g}$. Anal $C_{22}H_{28}N_2O_3 \cdot C_4H_4O_4$ (C, H, N). (RS, RS) 1-Ethyl-2-[1-methoxy-2-(2-ethoxyphenoxy)-2-phenyl]ethyl-4,5-dihydro-1*H*-imidazole fumarate $\mathbf{I_h}$. Anal $C_{22}H_{28}N_2O_3 \cdot C_4H_4O_4$ (C, H, N). For yields and mp values, see table I).

(RS, SR) 2-[1-Methoxy-2-(2-ethoxyphenoxy)-2-phenyl]ethyl-1H-imidazole $\mathbf{I_i}$

To a stirred solution of 1.65 g (4.3 mmol) of **9–1** (*R* = OEt) in 16 ml of ethanol, 0.53 ml (4.9 mmol) of aminoacetaldehyde dimethyl acetal were added at room temperature. After 4 h the solution was evaporated to dryness, 21 ml of 4N HCl were added to the residue and the mixture was stirred at room temperature for 24 h. The solution was basified with 2N NaOH and extracted with ethyl acetate. After work-up and purification of the crude material by flash-chromatography (mobile phase $CHCl_3/CH_3OH$: 200/4), 0.75 g (51.7% of $\mathbf{I_i}$ was obtained as white crystals, mp 115-118°C. NMR ($CDCl_3$): δ 1.61 (3H, t, OCH_2CH_3); 3.28 (3H, s, OCH_3); 4.20 (2H, q, OCH_2CH_3); 4.71 (1H, d, *CH*-OCH_3); 5.71 (1H, d, CH-Ph); 6.6-7.3 (11H, m, arom). Anal $C_{20}H_{22}N_2O_3$ (C, H, N).

(RS, RS) 2-[1-Methoxy-2-(2-ethoxyphenoxy)-2-phenyl]ethyl-1H-imidazole $\mathbf{I_j}$

Prepared analogously to $\mathbf{I_i}$: yield 57.2%: white solid, mp 160-163°C. NMR ($CDCl_3$: δ 1.60 (3H, t, OCH_2CH_3), 3.12 (3H, s, OCH_3); 4.21 (2H, q, OCH_2-CH_3); 4.68 (1H, d, *CH*-OCH_3); 5.22 (1H, d, CH-Ph); 6.6-7.4 (11H, m, arom). Anal $C_{20}H_{22}N_2O_3$ (C, H, N).

(RS, SR) 1-Ethyl-2-[1-methoxy-2-(2-ethoxyphenoxy)-2-phenyl]ethyl-1H-imidazole fumarate $\mathbf{I_k}$

To a stirred solution of 0.77 g (2.27 mmol) of $\mathbf{I_i}$ in 18 ml of DMF, 0.109 g (2.5 mmol) of 55% sodium hydride in mineral oil was added in 2 portions at 0°C and the temperature was allowed to rise to room temperature. After 30 min the solution was cooled again to 0°C and 0.193 ml (2.4 mmol) of ethyl iodide was added dropwise over 15 min. The mixture was stirred for 30 min at room temperature, poured into water, extracted with benzene and evaporated to dryness. The residue, 0.83 g, was dissolved in methanol (20 ml) together with 0.26 g of fumaric acid and the solution evaporated to dryness. The residue was ground with diethyl ether to give 0.6 g (55.9%) of $\mathbf{I_k}$ as a white solid, mp 135-137°C. NMR [$(CD_3)_2SO$]: δ 1.27 (3H, t, N-CH_2-CH_3); 1.35 (3H, t, OCH_2CH_3; 3.02 (3H, s, OCH_3); 3.87 (2H, q, OCH_2CH_3); 4.16 (2H, q, N-CH_2-CH_3); 4.77 (1H, d, *CH*-OCH_3); 5.64 (1H, d, CH-Ph); 6.75-7.35 (11H, m, arom). Anal $C_{22}H_{26}N_2O_3 \cdot C_4H_4O_4$ (C, H, N).

(RS, RS) 1-Ethyl-2-[1-methoxy-2-(2-ethoxyphenoxy)-2-phenyl]ethyl-1H-imidazole fumarate $\mathbf{I_l}$

Prepared analogously to $\mathbf{I_k}$; yield 98.0%, white solid, mp 111-116°C. NMR [$(CD_3)_2SO$]: δ 1.02 (3H, t, N-CH_2-CH_3); 1.33 (3H, t, O-CH_2CH_3); 3.29 (3H, s, OCH_3); 3.87 (2H, q, N-CH_2-CH_3); 4.05 (2H, q, OCH_2CH_3); 4.82 (1H, d, *CH*-OCH_3); 5.69 (1H, d, CH-Ph); 6.7-7.3 (11H, m, arom.). Anal $C_{22}H_{26}N_2O_3 \cdot C_4H_4O_4$ (C, H, N).

Pharmacology

Compounds **I** were tested for their α_1, α_2, IMI and DMI receptor affinity using [^{3}H]prazosin[20], [^{3}H]yohimbine[21], [^{3}H]imipramine[22] and [^{3}H]nortryptiline[23] as radioactive ligands, respectively. The NA-and 5-HT-uptake inhibition tests were performed according to Ross and Renyi [24] using rat hypothalamic synaptosomes. The reserpine antagonism test was performed in male mice as described by Rubin *et al* [25].

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