Structure-Activity Relationships in 1,4-Benzodioxan-Related Compounds. 4.[1] Effect of Aryl and Alkyl Substituents at Position 3 on α-Adrenoreceptor Blocking Activity[2]

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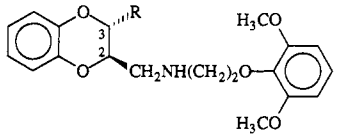
The observation that the insertion of a phenyl ring at position 3 of WB 4101 (1) afforded a potent and selective α_1-adrenoreceptor antagonist, phendioxan (2), prompted us to further investigate that position of the 2,3-dihydro-1,4-benzodioxin moiety. Thus the 3-phenyl of 2 was replaced by methyl, isopropyl, cyclohexyl, or para-substituted phenyl groups either in a cis or a trans relationships affording compounds 3-17 and 58. The structure of these new derivatives was assigned on the basis of the coupling constant of hydrogens at positions 2 and 3 and confirmed by a crystallographic study. The blocking activity and relative selectivity of 3-17 on α_1- and α_2-adrenoreceptors were evaluated in the isolated rat vas deferens. The results were compared with those obtained for 1 and 2. All the compounds, with the exception of isopropyl and cyclohexyl derivatives 5-8, were effective α_1-adrenoreceptor antagonists with a significant α_1/α_2-selectivity. The lipophilic and/or electronic character of para substituents of the 3-phenyl ring does not alter markedly the affinity toward α_1-adrenoreceptors. However, the 3-*p*-tolyl derivative 10 was slightly more potent and even more selective than 2.

WB 4101 {[2-(2,6-dimethoxyphenoxy)ethyl][(2,3-dihydro-1,4-benzodioxin-2-yl)methyl]amine, 1} is a potent and selective α_1-adrenoreceptor antagonist.[3,4] Our research group has previously been involved in designing new α-adrenoreceptor antagonists structurally related to 1 and in studying structure-affinity and structure-selectivity relationships with the goal of developing high-affinity, site-selective ligands for subtypes of the α-adrenoreceptor.[5-9]



1 (WB 4101): R = H
2 (Phendioxan): R = phenyl

A variety of 1 analogues have been studied involving modifications of the benzodioxan ring, the amine function, or the (2,6-dimethoxyphenoxy)ethyl moiety.[6,9-12] Although giving useful information on the structural requirements for an optimal interaction with α-adrenoreceptors, none of these manipulations performed on the structure of 1 has led to a significant improvement of affinity or selectivity for α-adrenoreceptor subtypes. However, in a recent communication[13] we have demonstrated that the insertion of a phenyl ring at the 3-position of 1 affording phendioxan (2) markedly affects the affinity for α_2-adrenoreceptors whereas that for α_1-adrenoreceptors is only slightly decreased. The overall result of this structural modification was a significant improvement in selectivity toward α_1-adrenoreceptors compared to the prototype 1. Thus, the presence of a 3-phenyl ring as in 2 seems to play a crucial role for selectivity and affords the opportunity to examine the effect of various groups and different aromatic substituent parameters such as Hammett's σ and Hansch's π values on both affinity and selectivity for α-adrenoreceptor subtypes. It is known that for relevant quantitative structure-activity relationships at least 12 carefully selected compounds are necessary to obtain a significant two-parameters equation. In the present study, our aim was to determine only whether electronic and/or lipophilic properties of substituents in the para position of the 3-phenyl ring of 2 could exert any favorable effect on α-adrenoreceptor selectivity and affinity rather than assess a quantitative relationship. It seemed this could be determined with a few properly chosen substituents. These were selected to have σ and π values in a positive or negative direction, in all combinations. Comparison of the α-adrenoreceptor blocking activity of these substituted derivatives with the parent compound 2 should reveal the importance, if any, of one or both of these parameters. The compounds used were the chloro ($+\pi$, $+\sigma$) (11 and 12), methyl and ethyl ($+\pi$, $-\sigma$) (9, 10, 13, and 14), acetoxy ($-\pi$, $+\sigma$) (17), and hydroxy and methoxy ($-\pi$, $-\sigma$) (15 and 16) derivatives with either a cis or a trans relationship between the two moieties at positions 2 and 3.

Because only aromatic substituents were inserted at the 3-position of 1, we also examined the effect on α-adrenoreceptor blocking activity of the insertion of an alkyl group as in compounds 3-8.

Chemistry

The structures of the compounds used in the present study are given in Table I. These were synthesized by standard procedures and characterized by ^{1}H NMR and elemental analysis.

The key intermediates were acids 32-44 that were synthesized as shown in Scheme I.

The starting substituted acrylic acid methyl esters were commercially available with the exception of 3-cyclohexyl,[14] 3-(4-ethylphenyl),[15] and 3-(4-hydroxyphenyl) deriv-

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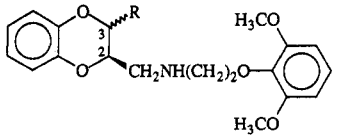
Table I. α_1- and α_2-Adrenoreceptor pA_2 Values in the Isolated Rat Vas Deferens[a]



no.[b]	stereoisomer	R	$J_{2,3}$, Hz[c]	α_1 A_2 against norepinephrine	α_2 pA_2 against clonidine	α_1/α_2[d] selectivity ratio
1		H		9.26 ± 0.04	6.39 ± 0.08	740
2	trans	Ph	7.1[e]	8.39 ± 0.05	4.18 ± 0.06[j]	16000
3	cis	Me	2.4	8.50 ± 0.02	5.70 ± 0.14[k]	630
4	trans	Me	3.2	7.94 ± 0.02	6.46 ± 0.06	30
5	cis	i-Pr	2.3	5.94 ± 0.04[f]	5.76 ± 0.02[k]	2
6	trans	i-Pr	5.5	6.57 ± 0.12[g]	5.94 ± 0.08[k]	4
7	cis	c-C_6H_{11}	2.6	6.20 ± 0.03[f]	<4.52[l]	>50
8	trans	c-C_6H_{11}	4.3	6.09 ± 0.13[f]	<4.52[l]	>40
9	cis	4-MePh	3.0	7.10 ± 0.02[g]	5.24 ± 0.13[k]	73
10	trans	4-MePh	8.0	8.69 ± 0.01	4.37 ± 0.07[j]	21000
11	cis	4-ClPh	2.7	7.09 ± 0.07[h]	4.76 ± 0.03[k]	210
12	trans	4-ClPh	7.9	8.15 ± 0.15[i]	5.17 ± 0.07[k]	1000
13	cis	4-EtPh	2.7	7.23 ± 0.05[h]	<4.52[l]	>500
14	trans	4-EtPh	8.0	7.82 ± 0.01	<4.52[l]	>2000
58	cis	4-HOPh	2.3	–[m]	–[m]	
15	trans	4-HOPh	8.0	7.84 ± 0.01	4.82 ± 0.12[k]	1000
16	trans	4-MeOPh	8.1	8.67 ± 0.02	<4.52[l]	>14000
17	trans	4-AcOPh	8.0	8.12 ± 0.10	4.87 ± 0.05[k]	2600
idazoxan				5.98 ± 0.09	8.01 ± 0.07	0.009

[a] pA_2 values, plus or minus standard error of estimate, were calculated according to Arunlakshana and Schild[28] unless otherwise specified, constraining the slope to −1.[30] pA_2 is defined as the negative logarithm to the base 10 of that dose of antagonist that requires a doubling of the agonist dose to compensate for the action of the antagonist. [b] With the exception of 1 that was a hydrochloride salt, all other compounds were oxalates. [c] Coupling constant between the hydrogens at positions 2 and 3. [d] The α_1/α_2 selectivity ratio is the antilog of the difference between pA_2 values at α_1- and α_2-adrenoreceptors. [e] From ref 13. [f] Calculated according to van Rossum[29] at only one concentration (3 μM) since it was not possible to investigate higher concentrations for the concomitant inhibition of maximum response to norepinephrine. [g] Calculated according to van Rossum[29] at only one concentration (1 μM) since it was not possible to investigate higher concentrations for the concomitant inhibition of maximum response to norepinephrine. [h] Calculated according to van Rossum[29] at only one concentration (0.3 μM) since it was not possible to investigate higher concentrations for the concomitant inhibition of maximum response to norepinephrine. [i] Calculated according to van Rossum[29] at only one concentration (30 nM) since it was not possible to investigate higher concentrations for the concomitant inhibition of maximum response to norepinephrine. [j] Calculated according to van Rossum[29] at 100 μM. [k] Calculated according to van Rossum[29] at only one concentration (30 μM) since it was not possible to investigate higher concentrations owing to the inhibition of twitch responses of electrically stimulated tissue. [l] Inactive up to 30 μM. [m] Not tested.

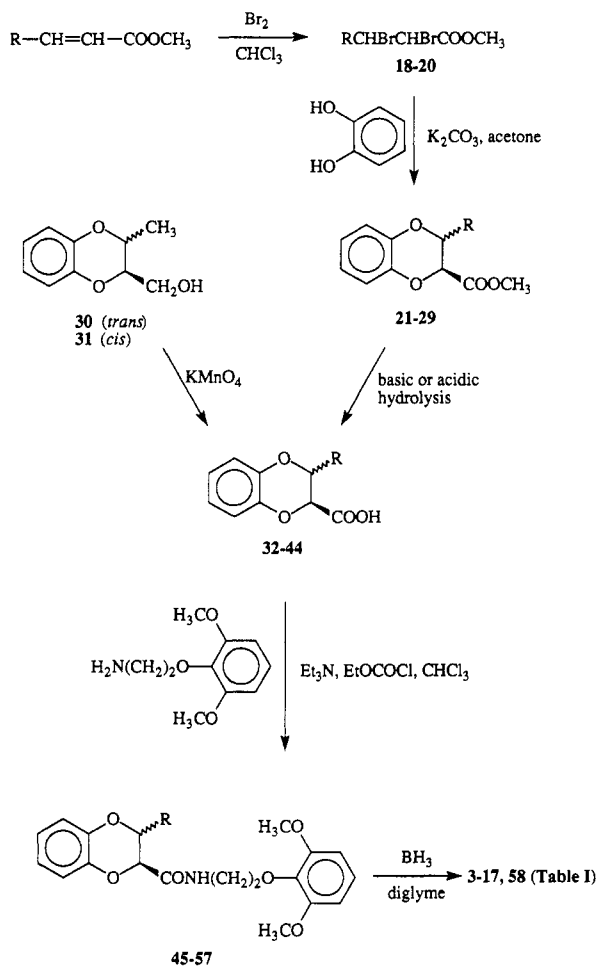
atives.[16] In this last case, the hydroxy function was protected by the tosyl group. Unsaturated esters were transformed by reaction with bromine into the corresponding 2,3-dibromo esters **18–20**, 2,3-dibromo-4-methylpentanoic acid methyl ester,[17] 2,3-dibromo-3-*p*-tolyl-,[18,19] 2,3-dibromo-3-(4-methoxyphenyl)-,[19,20] and 2,3-dibromo-3-(4-chlorophenyl)propionic acid methyl ester.[19] Condensation of the 3-alkyl esters with catechol afforded the corresponding 3-isopropyl (**21** and **22**) and 3-cyclohexyl derivatives (**23** and **24**) as cis and trans isomers through separation by column chromatography. On the contrary different results were obtained with 3-aryl derivatives. Starting from 2,3-dibromo-3-*p*-tolyl-, 2,3-dibromo-3-(4-chlorophenyl)-, and 2,3-dibromo-3-(4-methoxyphenyl)-propionic acid methyl ester only the trans isomers **25**, **26**, and **29**, respectively, were isolated while **19** and **18** afforded **27** and **28**, respectively, as a cis/trans mixture (ratios 1:3 and 1:2, respectively) that could not be separated. Purification by column chromatography of most compounds (**21–29**) was not complete, as revealed by NMR spectra. These compounds were impure for a variable amount of an unidentified material that was, however, easily removed in the following step to the corresponding acids.

With the exception of the basic hydrolysis of trans isomers **25** and **26** that afforded acids **39** and **41**, respectively, both as a cis/trans mixture (ratios 19:81 and 13:87, respectively) owing to a partial inversion of configuration at the 2-carbon, all other esters were hydrolyzed into the corresponding acids **34–38**, **40**, or **42–44** while retaining the same stereochemical relationship between the 2-side chain and the 3-substituent, as revealed by their NMR spectra. Acids **32** and **33** were obtained by oxidation with potassium permanganate of the corresponding alcohols **31** and **30**. A cis/trans mixture (ratio 1:1) of the latter compounds was prepared, as already described,[21] and separated by column chromatography thus allowing us to obtain also the cis isomer **31** that was unknown.

Acids **32–44**, in chloroform, were amidated in the presence of Et_3N and EtOCOCl with (2,6-dimethoxyphenoxy)ethylamine[22] to give corresponding amides **45–57**. Reduction of amides with borane–methyl sulfide complex in dry diglyme gave the corresponding amines with the same stereochemical relationship. Thus, amides **45–50** and **57** gave the expected cis or trans isomers of the corresponding amines whereas amides **52** and **54–56** as cis/trans mixtures afforded the corresponding amines with the same cis/trans ratio between the two isomers that were separated by column chromatography. Acetoxy derivative **17** was obtained easily by acylation of the hydroxy analogue **15** as free base with acetyl chloride.

The stereochemical relationship between the 2-side chain and the 3-substituent in **3–17**, **58**, and as a consequence, in the compounds used for their synthesis was deduced from the coupling constant of hydrogens at the corresponding positions. Thus, in agreement with similar assignments for other 2,3-disubstituted 1,4-benzodioxan derivatives[13,23,24] a trans relationship was assigned to **4**, **6**, **8**, **10**, **12**, **14**, and **15** since the coupling constants were greater than those found for the corresponding cis isomers **3**, **5**, **7**, **9**, **11**, **13**, and **58**. Compounds **16** and **17** were obtained only in one stereochemical relationship between the groups at positions 2 and 3 to which a trans relationship

Scheme I[a]



[a] **20**: R = c-C_6H_{11}; **21, 34, 47**: R = *cis*-i-Pr; **22, 35, 48**: R = *trans*-i-Pr; **23, 36, 49**: R = *cis*-c-C_6H_{11}; **24, 37, 50**: R = *trans*-c-C_6H_{11}; **25, 38, 51**: R = *trans*-4-MePh; **39, 52**: R = 4-MePh; **26, 40, 53**: R = *trans*-4-ClPh; **41, 54**: R = 4-ClPh; **19, 27, 42, 55**: R = 4-EtPh; **18, 28**: R = 4-(4-$MePhSO_3$)Ph; **29, 44, 57**: R = *trans*-4-MeOPh; **32, 45**: R = *cis*-Me; **33, 46**: R = *trans*-Me; **43**: R = 4-HOPh; **56**: R = 4-$EtOCO_2$Ph.

was assigned, since the coupling constant was similar to that found for the other 3-aryl derivatives **8, 10, 12, 14,** and **15** that have a trans relationship. The coupling constants of compounds **3–17** and **58** are reported in Table I together with that of **2**[13] to which a trans relationship was assigned.

However, as the coupling constants of the hydrogens at positions 2 and 3 of 3-alkyl derivatives **3–8** are not very different among cis and trans isomers (for example, compare **3** to **4**; Table I), a stereochemical assignment based only on this parameter may not be safe. Thus, we verified this assignment by evaluating the crystal structure of **30**, the starting material for the synthesis of **4**. It was confirmed that the stereochemical relationship between the 2-hydroxymethyl and the 3-methyl groups in this precursor is trans,[25] as previously suggested.[21]

Pharmacology

The pharmacological profile of compounds **3–17** was evaluated at α_1- and α_2-adrenoreceptors on isolated rat vas deferens tissues.[26,27] To allow comparison of the results, we used the same techniques and statistical evaluation of the bioassays as for other 1,4-benzodioxan-related compounds.[13] WB 4101 (**1**) and phendioxan (**2**) together with idazoxan, a selective α_2-adrenoreceptor antagonist, were used as the standard compounds. α_1-Adrenoreceptor blocking activity was assessed by antagonism of (−)-norepinephrine-induced contractions of the epididymal portion, while α_2-adrenoreceptor blocking activity was determined by antagonism of the clonidine-induced depression of the twitch responses of the field-stimulated prostatic portion of rat vas deferens. The potency of the drugs was expressed as pA_2 values, calculated according to Arunlakshana and Schild[28] or to van Rossum.[29]

Table II. Parameters for the Lipophilic, Electronic, and Steric Properties of *p*-Phenyl Substituents[a]

substituent	π	σ	MR
H	0.00	0.00	0.10
Cl	0.71	0.23	6.03
Me	0.56	−0.17	5.65
Et	1.02	−0.15	10.30
OMe	−0.02	−0.27	7.87
OH	−0.67	−0.37	2.85
AcO	−0.64	0.31	12.47

[a] π, σ, and MR values were taken from ref 31.

Results and Discussion

The pharmacological results at α_1- and α_2-adrenoreceptors of compounds **3–17** are reported in Table I together with those of the standard compounds WB 4101 (**1**) and phendioxan (**2**) for comparison. All compounds, for which at least three different concentrations were investigated, were competitive antagonists as revealed by the slope of the Schild plots that was not significantly different from unity.

An examination of the results observed for the 3-aryl derivatives **9–14** indicates that affinity for α_1-adrenoreceptors varies significantly for a cis or a trans relationship between the groups at positions 2 and 3. Compounds **10, 12,** and **14** were more potent than the corresponding cis isomers **9, 11,** and **13**, in agreement with the results obtained previously with **2** and its corresponding cis isomer.[13]

Our study began with an evaluation of the α-adrenoreceptor blocking properties modification due to replacement of the para hydrogen of the 3-phenyl of **2** by substituents with different lipophilic and electronic character. Substituent constants for a number of parameters are shown in Table II.

It was found that **10** is a potent α_1-adrenoreceptor antagonist with a pA_2 value of 8.69 that was slightly higher than that of the prototype **2** (pA_2 = 8.39). Although less potent than **1**, compound **10** was very selective as revealed by its high selectivity ratio (α_1/α_2 = 21 000) owing to a very low activity toward α_2-adrenoreceptors.

To verify whether the lipophilic properties of the 4-methyl substituent were responsible for the slight increase in affinity, we investigated the 4-ethyl compound **14** ($+\pi$, $-\sigma$). This modification afforded a significant decrease in affinity for α_1-adrenoreceptors and as a consequence a decrease in selectivity that might indicate that too high lipophilicity negatively affects affinity. Thus we investigated less lipophilic substituents such as those in **15** and **16** ($-\pi$, $-\sigma$). The methoxy derivative **16** that has a π value of −0.02 was as active and selective as **10** that has a π value of +0.56. The possibility that hydrophilic groups might increase affinity was ruled out by the observation that **15** was significantly less active than **16**. Our study on para substituents was completed by the

investigation of the chloro ($+\pi$, $+\sigma$) and acetoxy ($-\pi$, $+\sigma$) derivatives **12** and **17** that were only slightly less active, although significantly less selective, than prototype **2**. The overall results obtained with these derivatives clearly indicate that electronic (σ), lipophilic (π), or steric (expressed by molar refractivity, MR) characteristics of 4-substituents have little, if any, effect on α-adrenoreceptor blocking activity when comparison is made with the unsubstituted prototype **2**.

Since replacing a hydrogen at position 3 of **1** with an aryl group affording **2** or its para-substituted analogues **10**, **12**, **14–17** improved selectivity while decreasing affinity for α_1-adrenoreceptors, we wanted to verify whether replacing a hydrogen at position 3 of **1** with an alkyl moiety would afford compounds that could retain hopefully the selectivity displayed by **2** for α_1-adrenoreceptors while leading to an increase in affinity. An examination of the results obtained with 3-alkyl derivatives **3–8** allows some conclusions to be drawn. The stereochemical relationship between the groups at positions 2 and 3 of **3–8** does not seem to play the role observed for 3-aryl derivatives. Among methyl and cyclohexyl derivatives, the cis isomers **3** and **7** were more potent than their corresponding trans isomers **4** and **8**, whereas for isopropyl derivatives the trans isomer **6** was more potent than the cis isomer **5**. However, only the methyl derivatives **3** and **4** were almost as active as **2**, while the selectivity was significantly lower than that of **2** particularly in the case of **4**. It is interesting that methyl and isopropyl groups gave a significant improvement in affinity for α_2-adrenoreceptors compared to **2**, whereas cyclohexyl derivatives **7** and **8** were almost inactive. Evidently α_2-adrenoreceptors are more sensitive than α_1-adrenoreceptors to steric effects.

The biological profile of cyclohexyl derivative **8** may have relevance in comparison to that of the corresponding *p*-tolyl analogue **10**, if one considers that **8** shows quite a low affinity while having overall lipophilicity and steric bulk similar to those of the *p*-tolyl derivative **10** {[π(c-C_6H_{11}) = 2.51; $\pi(C_6H_5)$ + $\pi(CH_3)$ = 1.96 + 0.56 = 2.52] and [MR(c-C_6H_{11}) = 2.67; $MR(C_6H_5)$ - MR(H) + MR-(CH_3) = 2.54 - 0.10 + 0.56 = 3.00]}. Evidently, an aryl group at position 3, although giving a decrease in α_1-affinity likely due to steric hindrance, compared to **1** that bears a hydrogen, is capable of partially contributing to binding at α_1-adrenoreceptors through the formation of a charge-transfer complex that cannot be achieved by alkyl groups for which steric hindrance remains the only effect.

Experimental Section

Chemistry. Melting points were taken in glass capillary tubes on a Buchi SMP-20 apparatus and are uncorrected. IR and NMR spectra were recorded on Perkin-Elmer 297 and Varian VXR 300 instruments, respectively. Chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (TMS), and spin multiplicities are given as s (singlet), d (doublet), t (triplet), q (quartet), dd (double doublet), dt (double triplet), dq (double quartet), or m (multiplet). Although the IR spectra data are not included (because of the lack of unusual features), they were obtained for all compounds reported and were consistent with the assigned structures. The elemental compositions of the compounds agreed to within ±0.4% of the calculated value. When the elemental analysis is not included, crude compounds were used in the next step without further purification. Chromatographic separations were performed on silica gel columns (Kieselgel 40, 0.040–0.063 mm, Merck) by flash chromatography. Petroleum ether refers to the fraction with a boiling point of 40–60 °C. The term "dried" refers to the use of anhydrous sodium sulfate. Compounds were named following IUPAC rules as applied by AUTONOM, a PC software for systematic names in organic chemistry, Beilstein-Institut and Springer-Verlag.

2,3-Dibromo-3-[4-[(4-tolylsulfonyl)oxy]phenyl]propionic Acid Methyl Ester (18). A mechanically stirred mixture of 3-(4-hydroxyphenyl)acrylic acid methyl ester[16] (50 g, 280.6 mmol), K_2CO_3 (279.2 g, 2.02 mol), tosyl chloride (53.5 g, 280.6 mmol; added in two lots at 30-min intervals), and acetone (750 mL) was refluxed for 5 h. Then the mixture was cooled and filtered. Removal of the solvent gave **3-[4-[(4-tolylsulfonyl)oxy]phenyl]acrylic acid methyl ester** that was crystallized from EtOH: 82 g (88% yield), mp 110–112 °C. Bromine (24 g, 150.43 mmol) was added dropwise to a stirred and cooled (0 °C) solution of 3-[4-[(4-tolylsulfonyl)oxy]phenyl]acrylic acid methyl ester (50 g, 150.43 mmol) in chloroform (150 mL). The resulting solution was stirred overnight at room temperature. Removal of the solvent gave a residue that was crystallized from ethyl acetate–petroleum ether: 70 g (95% yield); mp 131–132 °C; ^{1}H NMR ($CDCl_3$) δ 2.48 (s, 3, $CH_3C_6H_4$), 3.90 (s, 3, OCH_3), 4.72 (d, 1, CHBrCO), 5.29 (d, 1, CHBrAr), 6.98–7.73 (m, 8, ArH).

2,3-Dibromo-3-(4-ethylphenyl)propionic Acid Methyl Ester (19). This was obtained in 89% yield following the procedure described for **18** starting from 3-(4-ethylphenyl)acrylic acid methyl ester:[15] mp 89–91 °C (from petroleum ether); ^{1}H NMR ($CDCl_3$) δ 1.27 (t, 3, CH_2CH_3), 2.68 (q, 2, CH_2CH_3), 3.90 (s, 3, OCH_3), 4.87 (d, 1, CHBrCO), 5.35 (d, 1, CHBrAr), 7.19–7.47 (m, 4, ArH).

2,3-Dibromo-3-cyclohexylpropionic Acid Methyl Ester (20). This was obtained in 95% yield following the procedure described for **18** starting from 3-cyclohexylacrylic acid methyl ester:[14] mp 43–45 °C (from petroleum ether); ^{1}H NMR ($CDCl_3$) δ 1.10–2.05 (m, 11, C_6H_{11}), 3.83 (s, 3, OCH_3), 4.37 (dd, 1, $C_6H_{11}CH$Br), 4.51 (d, 1, CHBrCO).

***cis*- and *trans*-3-Isopropyl-2,3-dihydro-1,4-benzodioxin-2-carboxylic Acid Methyl Esters (21 and 22).** A solution of 2,3-dibromo-4-methylpentanoic acid methyl ester[17] (12.5 g, 43.4 mmol) in anhydrous acetone (30 mL) was added dropwise over 15 min to a mechanically stirred mixture of catechol (15.3 g, 138.9 mmol) and anhydrous potassium carbonate (11.525 g, 83.39 mmol) in anhydrous acetone (100 mL) under reflux and N_2. The addition was repeated three times using a total of 46.1 g (333.3 mmol) of potassium carbonate and 50 g (173.6 mmol) of dibromo derivative. After the additions, refluxing was continued for an additional 6 h, and then the mixture was cooled and filtered. The solvent was removed under reduced pressure to give a residue that was taken up in water (60 mL) and extracted with ether (4 × 100 mL). The extracts were washed with cold 2 N NaOH and water and dried. Removal of solvent afforded an oil that was purified by column chromatography using petroleum ether–ethyl acetate (98:2) as the eluting solvent. Crude cis isomer **21** eluted first: 2.99 g (9.1% yield); mp 79–81 °C; ^{1}H NMR ($CDCl_3$) δ 1.08 and 1.16 [2 d, 6, $CH(CH_3)_2$], 2.02 [m, 1, $CH(CH_3)_2$], 3.76 (s, 3, OCH_3), 3.82 (dd, J = 2.3 Hz, 1, 3-H), 4.96 (d, J = 2.3 Hz, 1, 2-H), 6.83–7.00 (m, 4, ArH). NMR spectrum revealed that **21** was contaminated by an unidentified product that was removed in the hydrolysis step.

The second fraction was pure trans isomer **22** as an oil: 2.6 g (7.9% yield); ^{1}H NMR ($CDCl_3$) δ 1.06 and 1.09 [2 d, 6, $CH(CH_3)_2$], 1.99 [m, 1, $CH(CH_3)_2$], 3.79 (s, 3, OCH_3), 4.10 (dd, J = 2.9 Hz, 1, 3-H), 4.81 (d, J = 2.9 Hz, 1, 2-H), 6.85–7.00 (m, 4, ArH).

***cis*- and *trans*-3-Cyclohexyl-2,3-dihydro-1,4-benzodioxin-2-carboxylic Acid Methyl Esters (23 and 24).** These compounds were obtained following the procedure described for **21** and **22** starting from **20** (40.25 g, 125 mmol) and catechol (11.01 g, 100 mmol). The oil obtained (25 g) was purified by column chromatography eluting with petroleum ether–ethyl acetate (97:3). Crude cis isomer **23** eluted first as an oil: 1.8 g (6.5% yield); ^{1}H NMR ($CDCl_3$) δ 0.99–2.30 (m, 11, C_6H_{11}), 3.75 (s, 3, OCH_3), 3.91 (dd, 1, 3-H), 4.95 (d, J = 2.7 Hz, 1, 2-H), 6.83–7.00 (m, 4, ArH). NMR spectrum revealed that **23** was contaminated by an unidentified product that was removed in the hydrolysis step.

The second fraction was pure trans isomer **24** as an oil: 3.7 g (13.4% yield); ^{1}H NMR ($CDCl_3$) δ 1.10–2.03 (m, 11, C_6H_{11}), 3.75 (s, 3, OCH_3), 4.18 (dd, 1, 3-H), 4.88 (d, J = 2.6 Hz, 1, 2-H), 6.83–7.01 (m, 4, ArH).

***trans*-3-*p*-Tolyl-2,3-dihydro-1,4-benzodioxin-2-carboxylic Acid Methyl Ester (25).** A solution of catechol (8.16 g, 74.07 mmol) in methanol (23 mL) was added all at once to a stirred solution of Na (3.41 g, 148.14 mmol) in methanol (56 mL) under N_2. The resulting mixture was heated under reflux for 15 min, and then methyl 2,3-dibromo-3-*p*-tolylpropionic acid methyl ester[18,19] (24.9 g, 74.07 mmol) was added portionwise over 45 min. After the addition, refluxing was continued for an additional 4 h, and the solvent was removed under reduced pressure to give a residue that was taken up in water (30 mL) and extracted with ether (3 × 100 mL). The extracts were washed with cold 10% NaOH and dried. Removal of solvent afforded an oil (22 g) which was purified by column chromatography. Eluting with petroleum ether–ethyl acetate (96:4) gave crude **25**: 2.5 g (11.9% yield); mp 107–110 °C; ^{1}H NMR ($CDCl_3$) δ 2.38 (s, 3, $CH_3C_6H_4$), 3.62 (s, 3, OCH_3), 4.69 (d, J = 6.1 Hz, 1, 2-H), 5.18 (d, J = 6.1 Hz, 1, 3-H), 6.78–7.28 (m, 8, ArH). NMR spectrum revealed that **25** was contaminated by an unidentified product that was removed in the hydrolysis step.

***trans*-3-(4-Chlorophenyl)-2,3-dihydro-1,4-benzodioxin-2-carboxylic Acid Methyl Ester (26).** This was prepared following the procedure described for **25** starting from methyl 2,3-dibromo-3-(4-chlorophenyl)propionic acid methyl ester[19] (35 g, 98.18 mmol) and purified by column chromatography. Eluting with petroleum ether–ethyl acetate (95:5) gave an oil that was treated with petroleum ether–ethyl acetate. After cooling, crude **26** was obtained: 3.45 g (11.5% yield); mp 104–110 °C; ^{1}H NMR ($CDCl_3$) δ 3.67 (s, 3, OCH_3), 4.68 (d, J = 6.5 Hz, 1, 2-H), 5.21 (d, J = 6.5 Hz, 1, 3-H), 6.81–7.59 (m, 8, ArH). NMR spectrum revealed that **26** was contaminated by an unidentified product that was removed in the hydrolysis step.

***cis*/*trans*-3-(4-Ethylphenyl)-2,3-dihydro-1,4-benzodioxin-2-carboxylic Acid Methyl Ester (27).** This was prepared following the procedure described for **25** starting from **19** (26.6 g, 75.98 mmol) and purified by column chromatography. Eluting with cyclohexane–ethyl acetate (97:3) gave **27** as a cis/trans mixture (ratio 1:3): oil; 2.6 g (11.4% yield); ^{1}H NMR ($CDCl_3$) δ 1.25 (2 t, 6, CH_2CH_3; cis and trans), 2.66 (2 q, CH_2CH_3; cis and trans), 3.60 (s, 3, OCH_3; cis), 3.62 (s, 3, OCH_3; trans), 4.71 (d, J = 6.5 Hz, 1, 2-H; trans), 5.00 (d, J = 3.2 Hz, 1, 2-H; cis), 5.20 (d, J = 6.5 Hz, 1, 3-H; trans), 5.46 (d, J = 3.2 Hz, 1, 3-H; cis), 6.79–7.59 (m, 16, ArH; cis and trans). NMR spectrum revealed that the cis/trans mixture **27** was contaminated by an unidentified product that was removed in the hydrolysis step.

***cis*/*trans*-3-[4-[(4-Tolylsulfonyl)oxy]phenyl]-2,3-dihydro-1,4-benzodioxin-2-carboxylic Acid Methyl Ester (28).** This was prepared following the procedure described for **25** starting from **18** (30 g, 34.54 mmol) and purified by column chromatography. Eluting with cyclohexane–ethyl acetate (9:1) gave an oil that was treated with ether. After cooling crude **28** was obtained as a cis/trans mixture (ratio 1:2): 2.85 g (18.8% yield); mp 90–99 °C; ^{1}H NMR ($CDCl_3$) δ 2.42 (s, 6, CH_3; cis and trans), 3.52 (s, 3, OCH_3; cis), 3.61 (s, 3, OCH_3; trans), 4.62 (d, J = 6.3 Hz, 1, 2-H; trans), 4.98 (d, J = 3.2 Hz, 1, 2-H; cis), 5.20 (d, J = 6.3 Hz, 1, 3-H; trans), 5.43 (d, J = 3.2 Hz, 1, 3-H; cis), 6.83–7.73 (m, 24, ArH; cis and trans). NMR spectrum revealed that the cis/trans mixture **28** was contaminated by an unidentified product that was removed in the hydrolysis step.

***trans*-3-(4-Methoxyphenyl)-2,3-dihydro-1,4-benzodioxin-2-carboxylic Acid Methyl Ester (29).** A solution of catechol (1.65 g, 14.98 mmol) in dry DMF (5 mL) was added to a stirred solution of $NaOCH_3$ (prepared by dissolving 0.68 g of Na in 20 mL of methanol followed by removal of solvent) in dry DMF (35 mL) under N_2. The resulting mixture was treated dropwise with a solution of 2,3-dibromo-3-(4-methoxyphenyl)propionic acid methyl ester[19,20] (6 g, 17.04 mmol) in dry DMF (7.5 mL) and then heated at 80 °C for 4 h. The solvent was removed under reduced pressure to give a residue that was taken up in water (20 mL) and extracted with ether (3 × 15 mL). The extracts were washed with cold 5% NaOH and dried. Removal of solvent afforded an oil (5 g) which was purified by column chromatography. Eluting with cyclohexane–ethyl acetate (95:5) gave the trans isomer **29** as an oil: 0.65 g (12.5% yield); ^{1}H NMR ($CDCl_3$) δ 3.62 (s, 3, $COOCH_3$), 3.82 (s, 3, OCH_3), 4.68 (d, J = 6.7 Hz, 1, 2-H), 5.18 (d, J = 6.7 Hz, 1, 3-H), 6.79–7.60 (m, 8, ArH). NMR spectrum revealed that **29** was contaminated by an unidentified product that was removed in the hydrolysis step.

***trans*- and *cis*-2-(Hydroxymethyl)-3-methyl-2,3-dihydro-1,4-benzodioxin (30 and 31).** A cis/trans mixture (ratio 1:1) of these compounds was prepared following a procedure already described[21] starting from 3-methyl-2,3-dihydro-1,4-benzodioxin-2-carboxylic acid ethyl ester.[32] The crude mixture of the isomers was separated by column chromatography using cyclohexane–ether (7:3) as the eluting solvent. The trans isomer **30** eluted first: 49% yield; mp 91–92 °C (lit.[21] mp 91–92.5 °C); ^{1}H NMR ($CDCl_3$) δ 1.42 (d, 3, CH_3), 2.03 (t, 1, OH, exchangeable with D_2O), 3.85 (m, 2, CH_2O), 3.98 (m, J = 7.0 Hz, 1, 2-H), 4.18 (five lines, J = 7.0 Hz, 1, 3-H), 6.80–6.95 (m, 4, ArH).

The second fraction was the cis isomer **31** (as an oil): 45% yield; ^{1}H NMR ($CDCl_3$) δ 1.32 (d, 3, CH_3), 2.08 (t, 1, OH; exchangeable with D_2O), 3.78 (m, 2, CH_2O), 4.28 (m, J = 2.7 Hz, 1, 2-H), 4.38 (dq, J = 2.7 Hz, 1, 3-H), 6.82–6.95 (m, 4, ArH).

***cis*-3-Methyl-2,3-dihydro-1,4-benzodioxin-2-carboxylic Acid (32).** A solution of potassium permanganate (1.58 g, 10 mmol) in water (6 mL) was added to a stirred mixture of **31** (0.7 g, 3.88 mmol) in 1 N NaOH (5 mL) such that the temperature was maintained below 10 °C. After 48 h at room temperature the mixture was filtered and the filtrate was acidified with 1 N H_2SO_4 and extracted with chloroform. The extracts were washed with aqueous $NaHCO_3$ solution, and the aqueous layer was acidified with 1 N H_2SO_4. Extraction with chloroform, followed by washing, drying, and evaporation of the solvents, gave **32** as a solid: 0.65 g (86% yield); mp 141–142 °C; ^{1}H NMR ($CDCl_3$) δ 1.41 (d, 3, CH_3), 4.64 (dq, J = 2.8 Hz, 1, 3-H), 4.78 (d, J = 2.8 Hz, 1, 2-H), 6.83–7.02 (m, 4, ArH), 8.84 (br s, 1, COOH).

***trans*-3-Methyl-2,3-dihydro-1,4-benzodioxin-2-carboxylic Acid (33).** This was synthesized via the procedure described for **32** starting from the corresponding trans isomer **30**: 74% yield; mp 132–133 °C; ^{1}H NMR ($CDCl_3$) δ 1.44 (m, 3, CH_3), 4.50 (m, 2, 2-H and 3-H), 6.83–7.00 (m, 4, ArH), 8.80 (br s, 1, COOH).

***cis*-3-Isopropyl-2,3-dihydro-1,4-benzodioxin-2-carboxylic Acid (34).** A solution of **21** (1.94 g, 8.21 mmol) in ethanol (42 mL) was treated with 20% H_2SO_4 (42 mL) and heated under reflux for 3 h. The mixture was concentrated under reduced pressure and then extracted with ether. The extracts were washed with 10% $NaHCO_3$ solution, and the aqueous layer was acidified with 20% HCl. Extraction with ether, followed by washing, drying, and evaporation of the extracts, gave **34**: 0.4 g (27% yield); mp 148–150 °C; ^{1}H NMR ($CDCl_3$) δ 1.09 and 1.18 [2 d, 6, $CH(CH_3)_2$], 2.12 (m, 1, $CH(CH_3)_2$), 3.80 (dd, J = 2.6 Hz, 1, 3-H), 4.98 (d, J = 2.6 Hz, 1, 2-H), 6.86–6.99 (m, 4, ArH), 8.82 (br s, 1, COOH).

***trans*-3-Isopropyl-2,3-dihydro-1,4-benzodioxin-2-carboxylic Acid (35).** This was prepared as described for **34** starting from **22** (1.55 g, 6.56 mmol): 0.45 g (30.6% yield); mp 145–146 °C; ^{1}H NMR ($CDCl_3$) δ 1.05 and 1.07 [2 d, 6, $CH(CH_3)_2$], 2.03 [m, 1, $CH(CH_3)_2$)], 4.11 (dd, J = 2.7 Hz, 1, 3-H), 4.84 (d, J = 2.7 Hz, 1, 2-H), 6.85–6.99 (m, 4, ArH), 8.90 (br s, 1, COOH).

***cis*-3-Cyclohexyl-2,3-dihydro-1,4-benzodioxin-2-carboxylic Acid (36).** This was prepared as described for **34** starting from **23** (1.7 g, 6.15 mmol): 0.3 g (23% yield); mp 169–172 °C; ^{1}H NMR ($CDCl_3$) δ 0.98–2.30 (m, 11, C_6H_{11}), 3.90 (dd, J = 2.6 Hz, 1, 3-H), 4.98 (d, J = 2.6 Hz, 1, 2-H), 6.85–7.00 (m, 4, ArH), 7.80 (br s, 1, COOH).

***trans*-3-Cyclohexyl-2,3-dihydro-1,4-benzodioxin-2-carboxylic Acid (37).** A mixture of **24** (3.6 g, 13.03 mmol) and 2 N NaOH (11 mL) was stirred at 70 °C for 2 h. The cooled mixture was extracted with chloroform, and the aqueous layer was acidified with concentrated HCl. Extraction with chloroform, followed by washing, drying, and evaporation of the extracts, gave the trans isomer **37**: 3.1 g (91% yield); mp 149–151 °C; ^{1}H NMR ($CDCl_3$) δ 1.04–2.00 (m, 11, C_6H_{11}), 4.19 (dd, J = 2.3 Hz, 1, 3-H), 4.88 (d, J = 2.3 Hz, 1, 2-H), 6.80–7.00 (m, 4, ArH), 9.70 (br s, 1, COOH).

***trans*- and *cis*/*trans*-3-*p*-Tolyl-2,3-dihydro-1,4-benzodioxin-2-carboxylic Acid (38 and 39).** The trans isomer **38** was prepared by acidic hydrolysis of **25** (2.3 g, 8.09 mmol) as described for **34**: 0.4 g (21.8% yield); mp 169–172 °C; ^{1}H NMR ($CDCl_3$) δ 2.37 (s, 3, $CH_3C_6H_4$), 4.81 (d, J = 6.0 Hz, 1, 2-H), 5.24 (d, J = 6.0 Hz, 1, 3-H), 6.82–7.30 (m, 8, ArH), 8.50 (br s, 1, COOH).

Basic hydrolysis of **25** (1.5 g) as described for **37** afforded **39** as a cis/trans mixture (ratio 19:81): 0.75 g (53% yield); mp 121–124 °C; ^{1}H NMR ($CDCl_3$) δ 2.36 (s, 3, $CH_3C_6H_4$; cis), 2.37 (s, 3, $CH_3C_6H_4$; trans), 4.81 (d, J = 6.0 Hz, 1, 2-H; trans), 5.01 (d, J = 2.4 Hz, 1, 2-H; cis), 5.24 (d, J = 6.0 Hz, 1, 3-H; trans), 5.49 (d, J = 2.4 Hz, 1, 3-H; cis), 6.70–7.31 (m, 16, ArH; cis and trans), 8.50 (br s, 2, COOH; cis and trans).

***trans*- and *cis*/*trans*-3-(4-Chlorophenyl)-2,3-dihydro-1,4-benzodioxin-2-carboxylic Acid (40 and 41).** The trans isomer **40** was prepared as a pink solid by acidic hydrolysis of **26** (3.3 g, 10.83 mmol) as described for **34**: 0.3 g (13.4% yield); mp 160–162 °C; ^{1}H NMR ($CDCl_3$) δ 4.81 (d, J = 5.4 Hz, 1, 2-H), 5.30 (d, J = 5.4 Hz, 1, 3-H), 5.70 (br s, 1, COOH), 6.79–7.39 (m, 8, ArH).

Basic hydrolysis of **26** (1.5 g) as described for **37** afforded **41** (as cis/trans mixture, ratio 13:87) as a solid: 0.7 g (48.9% yield); mp 158–169 °C; ^{1}H NMR ($CDCl_3$) δ 4.81 (d, J = 5.4 Hz, 1, 2-H; trans), 5.04 (d, J = 2.8 Hz, 1, 2-H; cis), 5.30 (d, J = 5.4 Hz, 1, 3-H; trans), 5.50 (d, J = 2.8 Hz, 1, 3-H; cis), 5.55 (br s, 2, COOH; cis and trans), 6.79–7.41 (m, 16, ArH; cis and trans).

***cis*/*trans*-3-(4-Ethylphenyl)-2,3-dihydro-1,4-benzodioxin-2-carboxylic Acid (42).** Basic hydrolysis of **27** (2.2 g, 7.37 mmol) as described for **37** afforded **42** as a cis/trans mixture (ratio 2:8): 1.15 g (55% yield); mp 112–124 °C; ^{1}H NMR ($CDCl_3$) δ 1.27 (2 t, 6, CH_2CH_3; cis and trans), 2.66 (2 q, 4, CH_2CH_3; cis and trans), 4.82 (d, J = 5.5 Hz, 1, 2-H; trans), 5.02 (d, J = 3.0 Hz, 1, 2-H; cis), 5.29 (d, J = 5.5 Hz, 1, 3-H; trans), 5.50 (d, J = 3.0 Hz, 1, 3-H; cis), 6.90–7.60 (m, 16, ArH; cis and trans), 9.70 (br s, 2, COOH; cis and trans).

***cis*/*trans*-3-(4-Hydroxyphenyl)-2,3-dihydro-1,4-benzodioxin-2-carboxylic Acid (43).** A solution of **28** (1.0 g, 2.27 mmol) in methanol (30.7 mL) and 6% KOH (30.7 mL) was stirred under reflux for 1 h. The mixture was acidified with concentrated HCl, and methanol was removed under reduced pressure at 50 °C. The aqueous solution was extracted with ether which in turn was extracted with aqueous $NaHCO_3$ solution, and the aqueous layer was acidified with concentrated HCl. Extraction with ether, followed by washing, drying, and evaporation of the extracts, gave **43** as a cis/trans mixture (ratio 3:7): 0.3 g (48% yield); ^{1}H NMR ($CDCl_3$) δ 4.66 (d, J = 6.4 Hz, 1, 2-H; trans), 4.95 (d, J = 3.4 Hz, 1, 2-H; cis), 5.08 (d, J = 6.4 Hz, 1, 3-H; trans), 5.45 (d, J = 3.4 Hz, 1, 3-H; cis), 6.70–7.83 (m, 16, ArH; cis and trans), 9.50 (br s, 2, COOH; cis and trans).

***trans*-3-(4-Methoxyphenyl)-2,3-dihydro-1,4-benzodioxin-2-carboxylic Acid (44).** This was prepared by acidic hydrolysis of **29** (1.0 g, 2.87 mmol) as described for **34**: 0.2 g (81% yield); ^{1}H NMR ($CDCl_3$) δ 3.80 (s, 3, OCH_3), 4.78 (d, J = 5.4 Hz, 1, 2-H), 5.20 (d, J = 5.4 Hz, 1, 3-H), 6.79–7.58 (m, 8, ArH), 7.72 (br s, 1, COOH).

***cis*- and *trans*-3-Methyl-2,3-dihydro-1,4-benzodioxin-2-carboxylic Acid [2-(2,6-Dimethoxyphenoxy)ethyl]amide (45 and 46). General Procedure Also for the Synthesis of 47–57.** Ethyl chlorocarbonate (0.34 g, 3.04 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **32** (0.6 g, 3.04 mmol) and Et_3N (0.31 g, 3.04 mmol) in chloroform (20 mL), followed after 30 min by the addition of a solution of (2,6-dimethoxyphenoxy)ethylamine[22] (0.6 g, 3.04 mmol) in chloroform (10 mL). The resulting reaction mixture was stirred overnight at room temperature and then washed with 2 N HCl, 2 N NaOH, and finally with water. Removal of dried solvent gave cis amide **45** as a dense oil in 78% yield: ^{1}H NMR ($CDCl_3$) δ 1.20 (d, 3, CH_3), 3.61 (m, 2, NCH_2), 3.88 (s, 6, OCH_3), 4.15 (m, 2, CH_2O), 4.63 (d, J = 2.3 Hz, 1, 2-H), 4.90 (dq, J = 2.3 Hz, 1, 3-H), 6.55–7.07 (m, 7, ArH), 7.82 (t, 1, NH exchangeable with D_2O).

The trans isomer **46** was obtained similarly in 80% yield from **33**: mp 141–143 °C (from ethyl acetate–petroleum ether); ^{1}H NMR ($CDCl_3$) δ 1.50 (d, 3, CH_3), 3.59 (q, 2, NCH_2), 3.81 (s, 6, OCH_3), 4.14 (m, 3, CH_2O and 3-H), 4.28 (d, J = 6.7 Hz, 1, 2-H), 6.55–7.07 (m, 7, ArH), 7.62 (t, 1, NH, exchangeable with D_2O).

***cis*- and *trans*-3-Isopropyl-2,3-dihydro-1,4-benzodioxin-2-carboxylic Acid [2-(2,6-Dimethoxyphenoxy)ethyl]amide (47 and 48).** These compounds were obtained in 90% yield from **34** and **35**, respectively.

47: oil; ^{1} NMR ($CDCl_3$) δ 1.00 [2 d, 6, $CH(CH_3)_2$], 2.14 [m, 1, $CH(CH_3)_2$], 3.58 (m, 2, NCH_2), 3.86 (s, 6, OCH_3), 4.12 (m, 2, CH_2O), 4.30 (dd, J = 2.6 Hz, 1, 3-H), 4.75 (d, J = 2.6 Hz, 1, 2-H), 6.58–7.06 (m, 7, ArH), 7.76 (t, 1, NH, exchangeable with D_2O).

48: mp 85–87 °C; ^{1}H NMR ($CDCl_3$) δ 1.08 [2 d, 6, $CH(CH_3)_2$], 2.10 [m, 1, $CH(CH_3)_2$], 3.55 (m, 2, NCH_2), 3.81 (s, 6, OCH_3), 4.09 (m, 3, CH_2O and 3-H), 4.60 (d, J = 4.9 Hz, 1, 2-H), 6.56–7.02 (m, 7, ArH), 7.53 (t, 1, NH, exchangeable with D_2O).

***cis*- and *trans*-3-Cyclohexyl-2,3-dihydro-1,4-benzodioxin-2-carboxylic Acid [2-(2,6-Dimethoxyphenoxy)ethyl]amide (49 and 50).** These compounds were obtained from **36** and **37**, respectively.

49: oil; 89% yield; ^{1}H NMR ($CDCl_3$) δ 1.01–1.98 (m, 11, C_6H_{11}), 3.60 (m, 2, NCH_2), 3.88 (s, 6, OCH_3), 4.11 (m, 2, CH_2O), 4.35 (dd, J = 2.7 Hz, 1, 3-H), 4.74 (d, J = 2.7 Hz, 1, 2-H), 6.59–7.07 (m, 7, ArH), 7.78 (t, 1, NH exchangeable with D_2O).

50: 38% yield; mp 93–95 °C (from ethyl acetate–petroleum ether); ^{1}H NMR ($CDCl_3$) δ 1.15–2.03 (m, 11, C_6H_{11}), 3.53 (m, 2, NCH_2), 3.82 (s, 6, OCH_3), 4.08 (m, 2, CH_2O), 4.16 (dd, J = 4.3 Hz, 1, 3-H), 4.68 (d, J = 4.3 Hz, 1, 2-H), 6.55–7.03 (m, 7, ArH), 7.52 (t, 1, NH, exchangeable with D_2O).

***trans*- and *cis*/*trans*-3-*p*-Tolyl-2,3-dihydro-1,4-benzodioxin-2-carboxylic Acid [2-(2,6-Dimethoxyphenoxy)ethyl]amide (51 and 52).** The trans isomer **51** was obtained in 90% yield from **38**: mp 120–122 °C (from ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 2.32 (s, 3, $ArCH_3$), 3.50 (m, 2, NCH_2), 3.85 (s, 6, OCH_3), 4.02 (t, 2, CH_2O), 4.60 (d, J = 6.7 Hz, 1, 2-H), 5.09 (d, J = 6.7 Hz, 1, 3-H), 6.58–7.25 (m, 11, ArH), 7.52 (t, 1, NH, exchangeable with D_2O). Similarly the cis/trans mixture **52** (1:4) was obtained in 80% yield starting from the corresponding cis/trans mixture **39**: mp 106–118 °C; ^{1}H NMR ($CDCl_3$) δ 2.31 (s, 3, $ArCH_3$; cis), 2.32 (s, 3, $ArCH_3$; trans), 3.50 (m, 4, NCH_2; cis and trans), 3.84 (s, 6, OCH_3; cis), 3.85 (s, 6, OCH_3; trans), 4.02 (m, 4, CH_2O; cis and trans), 4.60 (d, J = 6.7 Hz, 1, 2-H; trans), 4.87 (d, J = 2.5 Hz, 1, 2-H; cis), 5.09 (d, J = 6.7 Hz, 1, 3-H; trans), 5.80 (d, J = 2.5 Hz, 1, 3-H; cis), 6.55–7.28 (m, 22, ArH; cis and trans), 7.52 (t, 1, NH, exchangeable with D_2O; trans), 7.72 (t, 1, NH, exchangeable with D_2O; cis).

***trans*- and *cis*/*trans*-3-(4-Chlorophenyl)-2,3-dihydro-1,4-benzodioxin-2-carboxylic Acid [2-(2,6-Dimethoxyphenoxy)ethyl]amide (53 and 54).** The trans isomer **53** was obtained in 55% yield from the corresponding trans isomer **40**: mp 150–151 °C (from ethyl acetate–petroleum ether); ^{1}H NMR ($CDCl_3$) δ 3.50 (m, 2, NCH_2), 3.84 (s, 6, OCH_3), 4.06 (t, 2, CH_2O), 4.57 (d, J = 6.7 Hz, 1, 2-H), 5.10 (d, J = 6.7 Hz, 1, 3-H), 6.58–7.35 (m, 11, ArH), 7.58 (t, 1, NH, exchangeable with D_2O). Similarly the cis/trans mixture **54** (15:85) was obtained in 65% yield starting from **41**: ^{1}H NMR ($CDCl_3$) δ 3.50 (m, 4, NCH_2; cis and trans), 3.77 (s, 6, OCH_3; cis), 3.84 (s, 6, OCH_3; trans), 4.04 (t, 2, CH_2O; trans), 4.12 (m, 2, CH_2O; cis), 4.57 (d, J = 6.7 Hz, 1, 2-H; trans), 4.85 (d, J = 3 Hz, 1, 2-H; cis), 5.10 (d, J = 6.7 Hz, 1, 3-H; trans), 5.82 (d, J = 3 Hz, 1, 3-H; cis), 6.58–7.35 (m, 22, ArH; cis and trans), 7.58 (t, 1, NH, exchangeable with D_2O; trans), 7.62 (t, 1, NH, exchangeable with D_2O; cis).

3-(4-Ethylphenyl)-2,3-dihydro-1,4-benzodioxin-2-carboxylic Acid [2-(2,6-Dimethoxyphenoxy)ethyl]amide (55). This was obtained in 64% yield (oil) as a cis/trans mixture (ratio 1:2) from **42**: ^{1}H NMR ($CDCl_3$) δ 1.20 (t, 3, CH_2CH_3; trans), 1.25 (t, 3, CH_2CH_3; cis), 2.49 (q, CH_2CH_3; cis), 2.62 (q, CH_2CH_3; trans), 3.50 (m, 4, NCH_2; cis and trans), 3.84 (s, 6, OCH_3; trans), 3.88 (s, 6, OCH_3; cis), 4.09 (m, 4, CH_2O; cis and trans), 4.60 (d, J = 6.5 Hz, 1, 2-H; trans), 4.85 (d, J = 3.0 Hz, 1, 2-H; cis), 5.10 (d, J = 6.5 Hz, 1, 3-H; trans), 5.80 (d, J = 3.0 Hz, 1, 3-H; cis), 6.50–7.25 (m, 22, ArH; cis and trans), 7.49 (t, 1, NH, exchangeable with D_2O; trans), 7.52 (t, 1, NH, exchangeable with D_2O; cis).

Carbonic Acid 4-[3-[[2-(2,6-Dimethoxyphenoxy)ethyl]carbamoyl]-2,3-dihydro-1,4-benzodioxin-2-yl]phenyl Ester Ethyl Ester (56). This was obtained in 35% yield (oil) as a cis/trans mixture (ratio 1:2) from **43** using 2 equiv of ethyl chlorocarbonate: ^{1}H NMR ($CDCl_3$) δ 1.40 (2 t, 6, CH_2CH_3; cis and trans), 3.50 (m, 4, NCH_2; cis and trans), 3.73 (s, 6, OCH_3; cis), 3.82 (s, 6, OCH_3; trans), 4.03 (t, 2, CH_2O; trans), 4.10 (m, 2, CH_2O; cis), 4.28 (q, 2, CH_2CH_3; cis), 4.30 (q, 2, CH_2CH_3; trans), 4.61 (d, J = 6.0 Hz, 1, 2-H; trans), 4.85 (d, J = 3.0 Hz, 1, 2-H; cis), 5.21 (d, J = 6.0 Hz, 1, 3-H; trans), 5.85 (d, J = 3.0 Hz, 1, 3-H; cis), 6.54–7.38 (m, 22, ArH; cis and trans), 7.53 (t, 1, NH, exchangeable with D_2O; trans), 7.62 (t, 1, NH, exchangeable with D_2O; cis).

***trans*-3-(4-Methoxyphenyl)-2,3-dihydro-1,4-benzodioxin-2-carboxylic Acid [2-(2,6-Dimethoxyphenoxy)ethyl]amide (57).** This was obtained from **44** and purified by column

chromatography eluting with cyclohexane–ethyl acetate (65:35): 77% yield; mp 116–118 °C; ^{1}H NMR ($CDCl_3$) δ 3.50 (m, 2, NCH_2), 3.78 (s, 3, 4-OCH_3), 3.82 [s, 6, 2,6-$(OCH_3)_2$], 4.04 (t, 2, CH_2O), 4.59 (d, J = 6.7 Hz, 1, 2-H), 5.04 (d, J = 6.7 Hz, 1, 3-H), 6.58–7.29 (m, 11, ArH), 7.52 (t, 1, NH, exchangeable with D_2O).

***cis*-[2-(2,6-Dimethoxyphenoxy)ethyl][(3-methyl-2,3-dihydro-1,4-benzodioxin-2-yl)methyl]amine Oxalate (3). General Procedure for the Synthesis of 3–16 and 58.** A solution of 10 M BH_3·CH_3SCH_3 (0.22 mL) in dry diglyme (1 mL) was added dropwise at room temperature to a solution of **45** (0.9 g, 2.4 mmol) in dry diglyme (40 mL) with stirring under a stream of dry nitrogen with exclusion of moisture. When the addition was completed, the reaction mixture was heated at 120 °C for 12 h. After cooling at 0 °C, excess borane was destroyed by cautious dropwise addition of MeOH (5 mL). The resulting mixture was left to stand for 5 h at room temperature, treated with HCl gas for 10 min, and then heated at 120 °C for 4 h. Removal of the solvent under reduced pressure gave a residue which was dissolved in water. The aqueous solution was basified with NaOH pellets and extracted with chloroform. Removal of dried solvent gave a residue which was purified by column chromatography. Eluting with petroleum ether–ethyl acetate–methanol–32% ammonia (12:2:0.25:0.05) afforded **3** as the free base which was transformed into the oxalate salt and crystallized from EtOH/i-PrOH: 60% yield; mp 187–189 °C; ^{1}H NMR ($CDCl_3$) δ 1.30 (d, 3, CH_3), 2.40 (br s, 1, NH, exchangeable with D_2O), 2.76–3.00 (m, 4, CH_2NCH_2), 3.83 (s, 6, OCH_3), 4.13 (m, 2, CH_2O), 4.33 (m, 1, 2-H), 4.4 (dq, J = 2.4 Hz, 1, 3-H), 6.55–7.02 (m, 7, ArH). Anal. ($C_{20}H_{25}NO_5$·$H_2C_2O_4$) C, H, N.

***trans*-[2-(2,6-Dimethoxyphenoxy)ethyl][(3-methyl-2,3-dihydro-1,4-benzodioxin-2-yl)methyl]amine Oxalate (4).** This was obtained from **46** and purified by column chromatography eluting with petroleum ether–ethyl acetate–methanol–32% ammonia (12:2:0.25:0.05). The free base was transformed into the oxalate salt and crystallized from MeOH: 83% yield; mp 228–230 °C; ^{1}H NMR ($CDCl_3$) δ 1.39 (d, 3, CH_3), 2.22 (br s, 1, NH, exchangeable with D_2O), 2.88–3.05 (m, 4, CH_2NCH_2), 3.84 (s, 6, OCH_3), 3.94 (dt, J = 3.2 Hz, 1, 2-H), 4.16 (m, 3, CH_2O and 3-H), 6.57–7.02 (m, 7, ArH). Anal. ($C_{20}H_{25}NO_5$·$H_2C_2O_4$) C, H, N.

***cis*-[2-(2,6-Dimethoxyphenoxy)ethyl][(3-isopropyl-2,3-dihydro-1,4-benzodioxin-2-yl)methyl]amine Oxalate (5).** This was obtained from **47** and purified by column chromatography eluting with cyclohexane–ethyl acetate (6:4). The free base was transformed into the oxalate salt and crystallized from EtOH: 85% yield; mp 173–175 °C; ^{1}H NMR ($CDCl_3$) δ 1.00 and 1.15 [2 d, 6, $CH(CH_3)_2$], 1.87 [m, 1, $CH(CH_3)_2$], 2.40 (br s, 1, NH, exchangeable with D_2O), 2.72–3.00 (m, 4, CH_2NCH_2), 3.75 (dd, J = 2.3 Hz, 1, 3-H), 3.79 (s, 6, OCH_3), 4.08 (m, 2, CH_2O), 4.53 (dt, J = 2.3 Hz, 1, 2-H), 6.53–7.00 (m, 7, ArH). Anal. ($C_{22}H_{29}NO_5$·$H_2C_2O_4$·0.5H_2O) C, H, N.

***trans*-[2-(2,6-Dimethoxyphenoxy)ethyl][(3-isopropyl-2,3-dihydro-1,4-benzodioxin-2-yl)methyl]amine Oxalate (6).** This was obtained from **48** and purified by column chromatography eluting with cyclohexane–ethyl acetate (6:4). The free base was transformed into the oxalate salt and crystallized from EtOH: 76% yield; mp 167–169 °C; ^{1}H NMR ($CDCl_3$) δ 1.00 and 1.10 [2 d, 6, $CH(CH_3)_2$], 2.03 [m, 1, $CH(CH_3)_2$], 2.10 (br s, 1, NH, exchangeable with D_2O), 2.94 (m, 4, CH_2NCH_2), 3.78 (t, J = 5.5 Hz, 1, 3-H), 3.84 (s, 6, OCH_3), 4.14 (m, 2, CH_2O), 4.23 (q, J = 5.5 Hz, 1, 2-H), 6.55–7.02 (m, 7, ArH). Anal. ($C_{22}H_{29}NO_5$·$H_2C_2O_4$) C, H, N.

***cis*-[2-(2,6-Dimethoxyphenoxy)ethyl][(3-cyclohexyl-2,3-dihydro-1,4-benzodioxin-2-yl)methyl]amine Oxalate (7).** This was obtained from **49** and purified by column chromatography eluting with petroleum ether–ethyl acetate (9:6). The free base was transformed into the oxalate salt and crystallized from i-PrOH: 78% yield; mp 180–181 °C; ^{1}H NMR ($CDCl_3$) δ 1.00–2.32 (m, 11, C_6H_{11} and br s, 1, NH, exchangeable with D_2O), 2.75–3.00 (m, 4, CH_2NCH_2), 3.78 (dd, J = 2.6 Hz, 1, 3-H), 3.80 (s, 6, OCH_3), 4.10 (m, 2, CH_2O), 4.54 (dt, J = 2.6 Hz, 1, 2-H), 6.53–7.00 (m, 7, ArH). Anal. ($C_{25}H_{33}NO_5$·$H_2C_2O_4$·0.5H_2O) C, H, N.

***trans*-[2-(2,6-Dimethoxyphenoxy)ethyl][(3-cyclohexyl-2,3-dihydro-1,4-benzodioxin-2-yl)methyl]amine Oxalate (8).** This was obtained from **50** and purified by column chromatography eluting with petroleum ether–ethyl acetate (9:6). The free base was transformed into the oxalate salt and crystallized from i-PrOH: 78% yield. The melting point was indefinite; fusion started at 100 °C and was complete at 119–121 °C: ^{1}H NMR ($CDCl_3$) δ 1.13–1.85 (m, 11, C_6H_{11}), 2.60 (br s, 1, NH, exchangeable with D_2O), 2.95 (m, 4, CH_2NCH_2), 3.80 (t, J = 4.3 Hz, 1, 3-H), 3.83 (s, 6, OCH_3), 4.15 (m, 2, CH_2O), 4.32 (dt, J = 4.3 Hz, 1, 2-H), 6.55–7.02 (m, 7, ArH). Anal. ($C_{25}H_{33}NO_5$·$H_2C_2O_4$·H_2O) C, H, N.

***cis*- and *trans*-[2-(2,6-Dimethoxyphenoxy)ethyl][(3-*p*-tolyl-2,3-dihydro-1,4-benzodioxin-2-yl)methyl]amine Oxalates (9 and 10).** These were obtained from **52** and purified by column chromatography eluting with chloroform–ethyl acetate (97:3). The first fraction was the trans isomer **10** as the free base which was transformed into the oxalate salt and crystallized from EtOH: 54% yield; mp 181–183 °C; ^{1}H NMR ($CDCl_3$) δ 2.11 (br s, 1, NH, exchangeable with D_2O), 2.38 (s, 3, $CH_3C_6H_4$), 2.70–2.84 (m, 4, CH_2NCH_2), 3.85 (s, 6, OCH_3), 4.10 (m, 2, CH_2O), 4.20 (dt, J = 8.0 Hz, 1, 2-H), 4.96 (d, J = 8.0 Hz, 1, 3-H), 6.56–7.32 (m, 11, ArH). Anal. ($C_{26}H_{29}NO_5$·$H_2C_2O_4$) C, H, N.

The second fraction was the cis isomer **9** as the free base which was transformed into the oxalate salt and crystallized from i-PrOH/ether: 27% yield. The melting point was indefinite; fusion started at 75 °C and was complete at 153–156 °C: ^{1}H NMR ($CDCl_3$) δ 2.01 (br s, 1, NH, exchangeable with D_2O), 2.35 (s, 3, $ArCH_3$), 2.50–2.89 (m, 4, CH_2NCH_2), 3.78 (s, 6, OCH_3), 4.01 (m, 2, CH_2O), 4.61 (dt, J = 3.0 Hz, 1, 2-H), 5.28 (d, J = 3.0 Hz, 1, 3-H), 6.52–7.30 (m, 11, ArH). Anal. ($C_{26}H_{29}NO_5$·$H_2C_2O_4$·1.5H_2O) C, H, N.

***cis*- and *trans*-[2-(2,6-Dimethoxyphenoxy)ethyl][[3-(4-chlorophenyl)-2,3-dihydro-1,4-benzodioxin-2-yl]methyl]amine Oxalates (11 and 12).** These were obtained from **54** and purified by column chromatography eluting with petroleum ether–ethyl acetate (1:1). The first fraction was the trans isomer **12** as the free base which was transformed into the oxalate salt and crystallized from EtOH: 52% yield; mp 188–189 °C; ^{1}H NMR ($CDCl_3$) δ 2.28 (br s, 1, NH, exchangeable with D_2O), 2.63–2.91 (m, 4, CH_2NCH_2), 3.85 (s, 6, OCH_3), 4.11 (t, 2, CH_2O), 4.15 (dt, J = 7.9 Hz, 1, 2-H), 5.05 (d, J = 7.9 Hz, 1, 3-H), 6.56–7.40 (m, 11, ArH). Anal. ($C_{25}H_{26}ClNO_5$·$H_2C_2O_4$) C, H, N.

The second fraction was the cis isomer **11** as the free base which was transformed into the oxalate salt and crystallized from EtOH/ether: 26% yield. The melting point was indefinite; fusion started at 92 °C and was complete at 115–117 °C: ^{1}H NMR ($CDCl_3$) δ 1.83 (br s, 1, NH, exchangeable with D_2O), 2.43–2.86 (m, 4, CH_2NCH_2), 3.78 (s, 6, OCH_3), 4.02 (m, 2, CH_2O), 4.60 (dt, J = 2.8 Hz, 1, 2-H), 5.30 (d, J = 2.8 Hz, 1, 3-H), 6.52–7.35 (m, 11, ArH). Anal. ($C_{25}H_{26}ClNO_5$·$H_2C_2O_4$·2.5H_2O) C, H, N.

***cis*- and *trans*-[2-(2,6-Dimethoxyphenoxy)ethyl][[3-(4-ethylphenyl)-2,3-dihydro-1,4-benzodioxin-2-yl]methyl]amine Oxalates (13 and 14).** These were obtained from **55** and purified by column chromatography eluting with cyclohexane–ethyl acetate (7:3). The first fraction was the trans isomer **14** as the free base which was transformed into the oxalate salt and crystallized from EtOH: 64% yield; mp 183–185 °C; ^{1}H NMR ($CDCl_3$) δ 1.26 (t, 3, CH_2CH_3), 2.21 (br s, 1, NH, exchangeable with D_2O), 2.63–2.84 (m, 6, CH_2CH_3 and CH_2NCH_2), 3.84 (s, 6, OCH_3), 4.12 (m, 2, CH_2O), 4.21 (dt, J = 8.0 Hz, 1, 2-H), 5.00 (d, J = 8.0 Hz, 1, 3-H), 6.57–7.38 (m, 11, ArH). Anal. ($C_{27}H_{31}NO_5$·$H_2C_2O_4$) C, H, N.

The second fraction was the cis isomer **13** as the free base which was transformed into the oxalate salt and crystallized from EtOH/ether: 16% yield. The melting point was indefinite; fusion started at 80 °C and was complete at 168–170 °C: ^{1}H NMR ($CDCl_3$) δ 1.23 (t, 3, CH_2CH_3), 2.20 (br s, 1, NH, exchangeable with D_2O), 2.52–2.90 (m, 6, CH_2CH_3 and CH_2NCH_2), 3.78 (s, 6, OCH_3), 4.04 (m, 2, CH_2O), 4.60 (dt, J = 2.7 Hz, 1, 2-H), 5.24 (d, J = 2.7 Hz, 1, 3-H), 6.53–7.33 (m, 11, ArH). Anal. ($C_{27}H_{31}NO_5$·$H_2C_2O_4$·1.5H_2O) C, H, N.

***cis*- and *trans*-[2-(2,6-Dimethoxyphenoxy)ethyl][[3-(4-hydroxyphenyl)-2,3-dihydro-1,4-benzodioxin-2-yl]methyl]amine Oxalates (58 and 15).** These were obtained from **56** and purified by column chromatography eluting with cyclohexane–ethyl acetate–ethanol (6:1.5:0.35). The first fraction was the trans isomer **15** as the free base (mp 147–152 °C) which was transformed into the oxalate salt and crystallized from i-PrOH/ether: 40% yield. The melting point was indefinite; fusion started at 96–99 °C and was complete at 182–183 °C: ^{1}H NMR (DMSO-d_6) δ 2.23

(br s, 1, NH, exchangeable with D_2O), 2.59 (m, 4, CH_2NCH_2), 3.72 (s, 6, OCH_3), 3.88 (t, 2, CH_2O), 4.20 (dt, J = 8.0 Hz, 1, 2-H), 4.90 (d, J = 8.0 Hz, 1, 3-H), 6.60–7.26 (m, 11, ArH), 9.58 (s, 1, OH, exchangeable with D_2O). Anal. ($C_{25}H_{27}NO_6 \cdot H_2C_2O_4 \cdot H_2O$) C, H, N.

The second fraction was the cis isomer **58** as the free base which was transformed into the oxalate salt and crystallized from i-PrOH/ether: 11% yield. The melting point was indefinite; fusion started at 80 °C and was complete at 162–164 °C: ^{1}H NMR ($CDCl_3$) δ 2.40 (br s, 1, NH, exchangeable with D_2O), 2.84–3.15 (m, 4, CH_2NCH_2), 3.88 (s, 6, OCH_3), 4.13 (m, 2, CH_2O), 5.02 (dt, J = 2.3 Hz, 1, 2-H), 5.25 (d, J = 2.3 Hz, 1, 3-H), 6.55–7.25 (m, 11, ArH). Anal. ($C_{25}H_{27}NO_6 \cdot H_2C_2O_4 \cdot H_2O$) C, H, N.

***trans*-[2-(2,6-Dimethoxyphenoxy)ethyl][[3-(4-methoxyphenyl)-2,3-dihydro-1,4-benzodioxin-2-yl]methyl]amine Oxalates (16).** This was obtained from **57** and purified by column chromatography eluting with petroleum ether–ethyl acetate–ethanol (12:3:0.4). The free base was transformed into the oxalate salt and crystallized from EtOH/ether: 86% yield; mp 183–185 °C; ^{1}H NMR ($CDCl_3$) δ 2.30 (br s, 1, NH, exchangeable with D_2O), 2.64–2.88 (m, 4, CH_2NCH_2), 3.82 (s, 3, 4-OCH_3), 3.84 [s, 6, 2,6-$(OCH_3)_2$], 4.10 (m, 2, CH_2O), 4.20 (dt, J = 8.1 Hz, 1, 2-H), 4.92 (d, J = 8.1 Hz, 1, 3-H), 6.52–7.38 (m, 11, ArH). Anal. ($C_{26}H_{29}NO_6 \cdot H_2C_2O_4 \cdot 0.5H_2O$) C, H, N.

Acetic Acid *trans*-4-[3-[[[2-(2,6-Dimethoxyphenoxy)ethyl]amino]methyl]-2,3-dihydro-1,4-benzodioxin-2-yl]-phenyl Ester Oxalate (17). Acetyl chloride (0.1 mL, 1.4 mmol) was added to a stirred solution of **15** as free base (0.1 g, 0.23 mmol) in acetic acid (2 mL). After being stirred overnight at room temperature, the solution was cooled at 0 °C and excess acetyl chloride destroyed by cautious addition of water. The resulting solution was basified with 3 N NaOH and extracted with ether. The extracts were washed with 2 N NaOH and dried. Removal of solvent gave a residue which was purified by column chromatography. Eluting with cyclohexane–ethyl acetate–ethanol (12:3:0.4) afforded **17** as the free base which was transformed into the oxalate salt and crystallized from EtOH: 82% yield; mp 195–196 °C; ^{1}H NMR ($CDCl_3$) δ 2.25 (br s, 1, NH, exchangeable with D_2O), 2.32 (s, 3, $COCH_3$), 2.67–2.92 (m, 4, CH_2NCH_2), 3.83 (s, 6, OCH_3), 4.12 (t, 2, CH_2O), 4.21 (dt, J = 8.0 Hz, 1, 2-H), 5.06 (d, J = 8.0 Hz, 1, 3-H), 6.54–7.50 (m, 11, ArH). Anal. ($C_{27}H_{29}NO_7 \cdot H_2C_2O_4 \cdot 0.5H_2O$) C, H, N.

Biology. Functional Antagonism in Isolated Rat Vas Deferens. Male albino rats (175–200 g) were killed by a sharp blow on the head, and both vasa deferentia were isolated, freed from adhering connective tissue and transversely bisected. Prostatic, 12 mm in length, and epididymal portions, 14 mm in length, were prepared and mounted individually in baths of 20-mL working volume containing Krebs solution of the following composition (mM): NaCl, 118.4; KCl, 4.7; $CaCl_2$, 2.52; $MgSO_4$, 1.2; KH_2PO_4, 1.2; $NaHCO_3$, 25.0; glucose, 11.1. $MgSO_4$ concentration was reduced to 0.6 mM when twitch response to field stimulation was studied. The medium was maintained at 37 °C and gassed with 95% O_2–5% CO_2. The loading tension used to assess α_1- or α_2-blocking activities was 0.4 or 0.5–0.8 g, respectively, and contractions were recorded by means of force transducers connected to a two-channel Gemini 7070 polygraph.

Field stimulation of the tissue was carried out by means of two platinum electrodes, placed near the top and bottom of the vas deferens, at 0.1 Hz using square pulses of 3-ms duration at voltage of 10–35 V. The stimulation voltage was fixed throughout the experiments. Propranolol hydrochloride (1 μM) and cocaine hydrochloride (10 μM) were present in the Krebs solution throughout the experiments outlined below to block β-adrenoreceptors and neuronal uptake mechanisms, respectively.

The α_1-adrenoreceptor blocking activity was determined on the epididymal portion of the vas deferens. The tissues were allowed to equilibrate for at least 1 h before addition of any drug. Norepinephrine dose–response curves were obtained cumulatively, the first one being discarded and the second one taken as a control. After incubation with the antagonist for 30 min, a third dose–response curve was obtained. Responses were expressed as a percentage of the maximal response obtained in the control curve. Parallel experiments, in which tissues did not receive any antagonist, were run in order to correct for time-dependent changes in agonist sensitivity.[33] It was generally verified that the third dose–response curve was identical to the second because the change in dose–ratio was less than 2, which usually represents a minimal correction.

The antagonist potency of compounds at α_1-adrenoreceptors was expressed in terms of their dissociation constants.

The α_2-adrenoreceptor blocking activity was assessed on the prostatic portion of the vas deferens by antagonism to clonidine which inhibits twitch responses of the field-stimulated vas deferens by acting on the α_2-adrenoreceptor.[34,35] The tissues were allowed to equilibrate for at least 1 h before addition of any drug. A first clonidine dose–response curve, taken as control, was obtained cumulatively avoiding the inhibition of more than 90% of twitch responses. Under these conditions it was possible to obtain a second dose–response curve which was not significantly different from the first one. Thus, after incubation with antagonist for 30 min, a second dose–response curve was obtained and dose–ratio (DR) values were determined from the concentration causing 50% inhibition of the twitch response in the absence and presence of antagonist. Parallel experiments, in which tissues did not receive any antagonist, were run in order to correct for time-dependent changes in agonist sensitivity and to determine concentration of agonist causing 100% inhibition of twitch responses. The results are expressed as dissociation constants.

The dissociation constants (pA_2 values, Table I) were determined by Schild plots[28] obtained from the dose ratios at the EC_{50} values of the agonists calculated at three antagonist concentrations. Each concentration was tested five times, and Schild plots were constrained to slope −1, as required by theory.[30] When applying this method, it was always verified that the experimental data generated a line whose derived slope was not significantly different from unity ($p > 0.05$). Compounds **5–9** and **11–13** were tested at only one concentration, in the range 0.03–0.3 μM, when determining α_1-adrenoceptor blocking activity because it was not possible to investigate higher concentrations for the concomitant inhibition of maximum response to norepinephrine. Similarly compounds **2**, **3**, and **5–17** were tested at only one concentration when determining α_2-adrenoreceptor blocking activity because of their low affinity for this receptor. In these cases, pA_2 values were calculated according to van Rossum.[29] Data are presented as the mean ±SE of n experiments. Differences between mean values were tested for significance by student's t-test.

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