Structure−Activity Relationships in 1,4-Benzodioxan-Related Compounds. 9.[1] From 1,4-Benzodioxane to 1,4-Dioxane Ring as a Promising Template of Novel α_{1D}-Adrenoreceptor Antagonists, 5-HT_{1A} Full Agonists, and Cytotoxic Agents[†]

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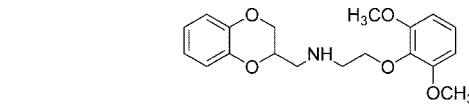
Novel 1,4-dioxane compounds structurally related to WB 4101 (**1**) were prepared in order to investigate the possibility that the quite planar 1,4-benzodioxane template of **1** might be replaced by the less conformationally constrained 1,4-dioxane ring. The biological profiles of the new compounds were assessed using binding assays at human cloned α_1-adrenoreceptor (α_1-AR) subtypes and 5-HT_{1A} receptors, expressed in Chinese hamster ovary and HeLa cell membranes, respectively, and by functional experiments in isolated rat vas deferens (α_{1A}), spleen (α_{1B}), and aorta (α_{1D}). Moreover, the cytotoxic effects of the novel compounds were determined in PC-3 prostate cancer cells. The results showed that the properly substituted 1,4-dioxane nucleus proved to be a suitable scaffold for selective α_{1D}-AR antagonists (compound **14**), potential anticancer agents (compound **13**), and full 5-HT_{1A} receptor agonists (compound **15**). In particular, compound **15** may represent a novel lead in the development of highly potent 5-HT_{1A} receptor full agonists useful as antidepressant and neuroprotective agents.

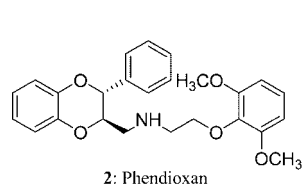
Introduction

The sympathetic nervous system is the main regulator of homeostasis and mediates most of its effects via the α_1-, α_2-, and β-adrenoreceptors (α_1-, α_2-, and β-ARs[a]).[2] Each of these classes is further subdivided into three subtypes, resulting in nine pharmacologically distinct ARs ($\alpha_{1a/A}$, $\alpha_{1b/B}$, $\alpha_{1d/D}$; $\alpha_{2a/A}$, $\alpha_{2b/B}$, $\alpha_{2c/C}$; β_1, β_2, β_3), which have all been cloned, expressed, and sequenced and have been found to be heptahelical (7TM) G-protein-coupled receptors. These nine subtypes do not explain all of the biological responses to native or synthetic AR agonists, leading to the postulation of additional subtypes, namely, α_{1L}[3] and β_4.[4] Because of their widespread expression in many human tissues and their involvement in several physiological processes, ARs have proved to be highly attractive pharmacological targets for the treatment of various pathologies. In particular, each α_1-AR subtype has a distinct pharmacology and shows discrete tissue distribution.[5] α_{1A}- and α_{1B}-AR subtypes play an important role in cardiac development and/or function as well as in blood pressure via vasoconstriction,[6] while the α_{1A} subtype, dominant in the prostate, bladder neck, and urethra, contributes to the dynamic (phasic) component of increased bladder outlet resistance[7] and together with the α_{1D} subtype, located in the bladder or the spinal cord, mediates lower urinary tract symptoms (LUTS) caused by benign prostatic hyperplasia (BPH).[8] Owing to these effects, α_1-antagonists were initially developed for the treatment of hypertension and subsequently for symptomatic BPH. At present, while the use of α_1-antagonists in hypertension is declining,[9] α_1-antagonists, in particular those selective for α_{1A}- and/or α_{1A}- + α_{1D}-AR subtypes with respect to the α_{1B}-AR subtype, are the first-line pharmacotherapeutic approach to BPH,[10] as they are useful for the prompt and effective relief of LUTS, avoiding cardiovascular side effects such as orthostatic hypotension and syncope.[11]

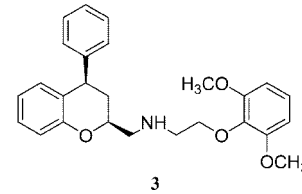
Chart 1. Chemical Structures of WB 4101 (**1**), Phendioxan (**2**), and Compound **3**



1: WB 4101



2: Phendioxan



3

Our research group has long been involved in designing new α_1-AR antagonists structurally related to **1** (WB 4101) (Chart 1) and in studying structure−affinity and structure−selectivity relationships in order to develop high-affinity, subtype-selective ligands for each of the three α_1-AR subtypes.[12] The present study expands on previous structure−activity relationship studies by investigating the possibility that the quite planar 1,4-benzodioxane structure of **1** might be replaced by the less

[†] This article is dedicated to Dr. Francesco Gentili.

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[a] Abbreviations: AR, adrenoreceptor; TM, transmembrane; LUTS, lower urinary tract symptoms; BPH, benign prostatic hyperplasia; CHO, Chinese hamster ovary; PC-3, human prostate cancer cells; SRB, sulforhodamine B; GI, growth inhibition; TGI, total growth inhibition; LC, lethal concentration; PS, phosphatidylserine; MFI, mean fluorescence intensity; K_i, inhibition or dissociation constant; K_b, dissociation constant.

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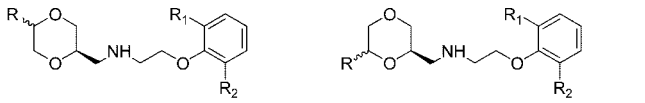
Chart 2. Chemical Structures of Compounds **4**−**15**



4a: R = C_6H_5 (trans); $R_1 = R_2 = H$
4b: R = C_6H_5 (cis); $R_1 = R_2 = H$
5a: R = C_6H_5 (trans); $R_1 = H$; $R_2 = OCH_3$
5b: R = C_6H_5 (cis); $R_1 = H$; $R_2 = OCH_3$
6a: R = C_6H_5 (trans); $R_1 = R_2 = OCH_3$
6b: R = C_6H_5 (cis); $R_1 = R_2 = OCH_3$
10: R = $(C_6H_5)_2$; $R_1 = R_2 = H$
11: R = $(C_6H_5)_2$; $R_1 = H$; $R_2 = OCH_3$
12: R = $(C_6H_5)_2$; $R_1 = R_2 = OCH_3$

7a: R = C_6H_5 (trans); $R_1 = H$; $R_2 = H$
7b: R = C_6H_5 (cis); $R_1 = H$; $R_2 = H$
8a: R = C_6H_5 (trans); $R_1 = H$; $R_2 = OCH_3$
8b: R = C_6H_5 (cis); $R_1 = H$; $R_2 = OCH_3$
9a: R = C_6H_5 (trans); $R_1 = R_2 = OCH_3$
9b: R = C_6H_5 (cis); $R_1 = R_2 = OCH_3$
13: R = $(C_6H_5)_2$; $R_1 = R_2 = H$
14: R = $(C_6H_5)_2$; $R_1 = H$; $R_2 = OCH_3$
15: R = $(C_6H_5)_2$; $R_1 = R_2 = OCH_3$

conformationally constrained 1,4-dioxane ring. This investigation was also prompted by our recent study in which the 1,4-dioxane nucleus proved to be a suitable scaffold for efficacious and selective muscarinic agonists.[13] Considering that the stereochemically defined insertion of a phenyl ring in position 3 of **1** (phendioxan, **2**)[14,15] (Chart 1) or in position 4 of its methylene bioisostere (compound **3**)[16] (Chart 1) induced a significant modulation of α_1-AR subtype selectivity, we designed the cis and trans 5- or 6-phenyl derivatives (compounds **4**−**9**) (Chart 2). Moreover, the enlargement of the 1,4-benzodioxane scaffold of **1** by fusion with an additional benzene ring[17] produced a significant α_{1a}-AR subtype selectivity, and its replacement with a 2,2-diphenyl-1,3-dioxolanyl structure, along with the simultaneous removal of one or two methoxy groups in the 2,6-dimethoxyphenoxy moiety, afforded antagonists selective for the α_{1D}-AR subtype.[18] These results prompted the design of the 5- or 6-diphenyl derivatives **10**−**15**. In addition, it is well-known that the 5-HT_{1A} serotoninergic receptor exhibits a high degree of homology to α_1-ARs[19] and benzodioxane derivatives,[20] and in particular, **1** and related compounds[21] are effective ligands for the 5-HT_{1A} receptor. Therefore, the synthesis of compounds **4**−**15** (Chart 2) allowed us to investigate the possibility that the increased flexibility of the 1,4-dioxane moiety might produce a better or more selective interaction with the 5-HT_{1A} receptor versus the α_1-AR system.

The biological profiles of the novel compounds were assessed using binding assays at human cloned α_1-adrenoreceptor subtypes and 5-HT_{1A} receptors, expressed in Chinese hamster ovary and HeLa cell membranes, respectively, and by functional experiments in isolated rat vas deferens (α_{1A}), spleen (α_{1B}), and aorta (α_{1D}). Moreover, following our recent observation that α_{1D}- and α_{1B}-ARs are expressed in PC-3 prostate cancer cells and are involved in the modulation of apoptosis and cell proliferation,[12] the cytotoxic effects of the new compounds and **1** on this cell line were determined.

Chemistry

The new compounds **4**−**15** were synthesized according to the methods reported in Schemes 1 and 2. Epoxidation of the olefines **16**, **17**, **27**, and **28** (Scheme 1), obtained by opening 2,2-diphenyloxirane[22] with allyl alcohol in acidic or basic conditions (**17** and **28**, respectively) or as previously described in the literature[23,24] (**16** and **27**), afforded compounds **18**, **19**, **29**, and **30**, respectively. Treatment with (1*S*)-(+)-10-camphorsulfonic acid [(1*S*)-(+)-10-CSA] in CH_2Cl_2 led to alcohols **20a/20b**, **21**, **31a/31b**, and **32**. The diastereoisomers of the mixtures **20a/20b** and **31a/31b** were separated by column chromatography. Oxidation of alcohols **20a**, **20b**, **21**, **31a**, **31b**, and **32** to the corresponding acids **22a**, **22b**, **23**, **33a**, **33b**, and **34**, followed by amidation with the suitable amines, 2-phenoxyethanamine, 2-(2-methoxyphenoxy)ethanamine,[18] or 2-(2,6-dimethoxyphenoxy)ethanamine,[25] in the presence of Et_3N and EtOCOCl afforded the amides **24a**, **24b**, **25b**, **26**, **35a**, **35b**, **36a**, **36b**, **37a**, **37b**, and **38**, whose reduction with the borane−methyl sulfide complex in dry THF gave the final amines **5a**, **5b**, **6b**, **12**, **7a**, **7b**, **8a**, **8b**, **9a**, **9b**, and **15**. The stereochemical relationship between the 2-carboxylic function and the 5-phenyl ring in **22a** and **22b** was determined by ^{1}H NMR. The strategy used to identify the individual diastereoisomers was based on the analysis of the coupling constant (*J*) data, as reported for the axial and equatorial protons of 1,4-dioxane.[26] In the ^{1}H NMR spectrum of diastereoisomer **22a**, the proton in position 5 at δ 4.62 ppm showed two coupling constants ($J = 2.56$ Hz and $J = 10.26$ Hz) with the protons in position 6. The presence of a large constant indicated an axial position for such a proton. In addition, the proton in position 2 showed two coupling constants ($J = 3.42$ Hz and $J = 10.69$ Hz) with the protons in position 3. Since one of the constants was large, such a proton was axial. Therefore, the stereochemical relationship between the 2-carboxylic function and the 5-phenyl substituent was trans diequatorial in **22a**.

In the ^{1}H NMR spectrum of diastereoisomer **22b**, the situation of the proton in position 5 at δ 4.67 ppm ($J = 2.99$ Hz and $J = 10.26$ Hz) was similar to that of the proton in the same position of diastereoisomer **22a**, indicating an axial position for such a proton. However, the proton in position 2 at δ 4.38 ppm of **22b** showed two small coupling constants ($J = 1.11$ Hz and $J = 2.99$ Hz) with the protons in position 3, indicating an equatorial position for this proton and, consequently, a cis equatorial−axial stereochemical relationship between the 5-phenyl substituent and the 2-carboxylic function.

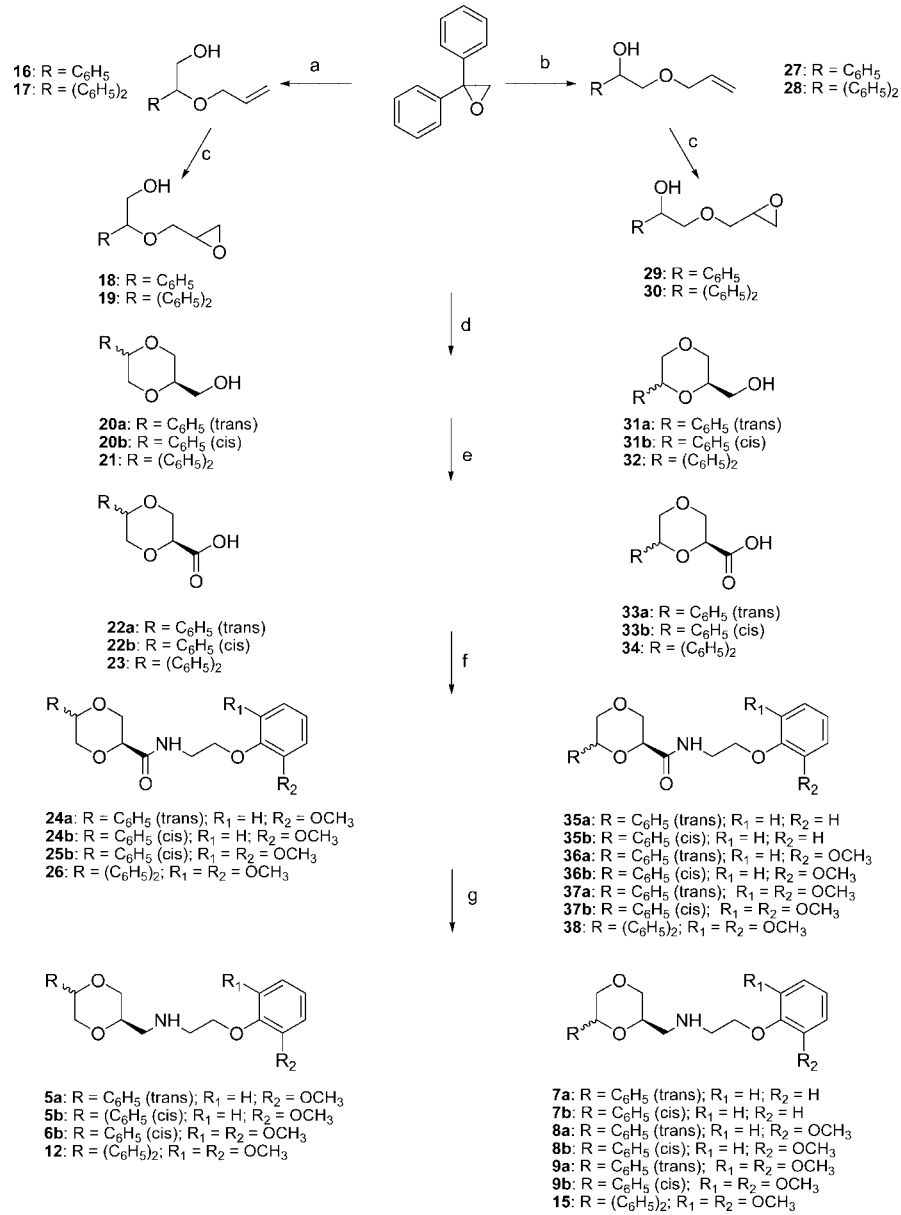
The stereochemical relationship between the 2-carboxylic function and the 6-phenyl ring in **33a** and **33b** was determined by 1D NOE measurements and confirmed by analysis of the coupling constant (*J*) data. In compound **33b**, the irradiation of C2−H caused the NOE effect at C6−H, whereas no NOE effect was observed at C6−H by the irradiation of the same proton in compound **33a**, indicating a cis and trans relationship, respectively, for the two compounds.

Moreover, in the ^{1}H NMR spectrum of isomer **33b** the proton in position 6 at δ 4.78 ppm showed two coupling constants ($J = 2.84$ Hz and $J = 10.44$ Hz) with the protons in position 5. The presence of a large constant indicated an axial position for such a proton. In addition, the proton in position 2 at δ 4.54 ppm showed two coupling constants ($J = 3.20$ Hz and $J = 10.71$ Hz) with the protons in position 3. Since one of the two constants was large, such a proton was axial. Therefore, the stereochemical relationship between the 2-carboxylic function and the 6-phenyl substituent was cis in **33b**.

In the ^{1}H NMR spectrum of diastereoisomer **33a**, the situation of the proton in position 6 at δ 5.16 ppm ($J = 3.13$ Hz and $J = 9.78$ Hz) was similar to that of the proton in the same position of diastereoisomer **33b**, indicating an axial position for such a proton. However, the proton in position 2 at δ 4.52 ppm of **33a** showed two small coupling constants ($J = 1.57$ Hz and $J = 3.91$ Hz) with the protons in position 3, indicating an equatorial position for this proton and, consequently, a trans stereochemical relationship between the 2-carboxylic function and the 6-phenyl substituent.

Compounds **4a**, **4b**, **6a**, **10**, **11**, **13**, and **14** were synthesized according to Scheme 2 starting from the intermediate alcohols **16**, **17**, and **28**, which were subjected to oxymercuration−reduction reaction with mercury(II) acetate, followed by an aqueous solution of iodine and potassium iodide, to afford a mixture of the diastereoisomeric forms **39a/39b**, whose diastereoisomers were separated by column chromatography, **40** and **41**, respec-

Scheme 1[a]



[a] Reagents: (a) $HClO_4$, allyl alchool; (b) Na, allyl alchool; (c) *m*-CPBA/CH_2Cl_2; (d) (1*S*)-(+)-10-CSA/CH_2Cl_2; (e) $KMnO_4$/1 N KOH; (f) Et_3N, EtOCOCl, 2-phenoxyethanamine, or 2-(2-methoxyphenoxy)ethanamine or 2-(2,6-dimethoxyphenoxy)ethanamine/$CHCl_3$; (g) BH_3·MeSMe/THF.

tively. The amination of the iodide derivatives with the suitable amines, 2-phenoxyethanamine, 2-(2-methoxyphenoxy)ethanamine,[18] or 2-(2,6-dimethoxyphenoxy)ethanamine,[25] afforded the final compounds. The structures of the two diastereoisomers **39a** and **39b** were assigned by treating *trans*-2-(iodomethyl)-5-phenyl-1,4-dioxane **39a** with Ag_2O to afford the corresponding alcohol, whose ^1H NMR spectrum was similar to that of the trans isomer **20a** obtained in Scheme 1.

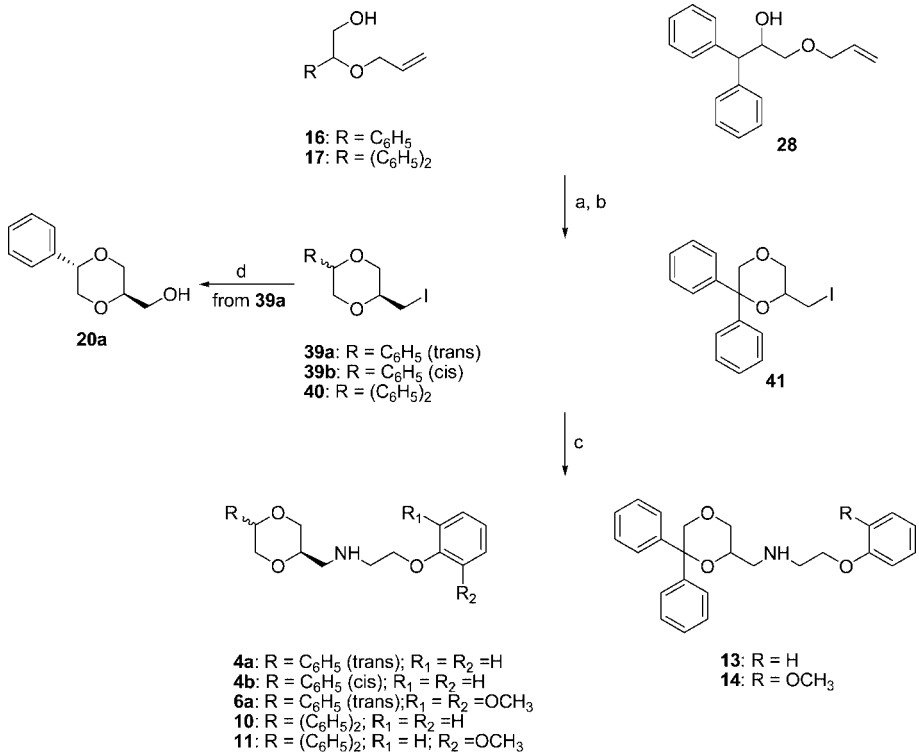
Biology

Binding Experiments. The pharmacological profiles of compounds **4**−**15** were evaluated by radioreceptor binding assays using **1**, 8-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-8-azaspiro[4.5]decane-7,9-dione (BMY-7378) and 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) as reference compounds. [^{3}H]Prazosin was used to label cloned human α_1-ARs expressed in CHO cells.[27] Furthermore, [^{3}H]8-OH-DPAT was used to label cloned human 5-HT_{1A} receptors expressed in HeLa cells.[28,29]

Functional Studies. The pharmacological profiles of compounds **4**−**15** were further determined at α_1-ARs on different isolated tissues using **1** and BMY-7378 as reference compounds. α_1-AR subtypes blocking activity was assessed by antagonism of (−)-noradrenaline-induced contraction of rat prostatic vas deferens (α_{1A})[30] or thoracic aorta (α_{1D})[31] and by antagonism of (−)-phenylephrine-induced contraction of rat spleen (α_{1B}).[32] Furthermore, the agonist efficacy of compounds **5b**, **8b**, and **13**−**15** toward the 5-HT_{1A} receptor was assessed by determining the induced stimulation of [^{35}S]GTPγS binding in cell membranes from HeLa cells transfected with human cloned 5-HT_{1A} receptor[33] using 8-OH-DPAT, 5-hydroxytryptamine (5-HT), and 5-carboxamidotryptamine (5-CT) as reference compounds.

In Vitro Cytotoxic Activity. The in vitro cytotoxic activity of compounds **4**−**15**, and **1** in human PC-3 prostate cancer cells using 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(1,4-benzodioxan-2-ylcarbonyl)piperazine (doxazosin)[34] as a comparison, was carried out using the sulforhodamine B (SRB) assay according to the National Cancer Institute protocol.[35] The

Scheme 2[a]



[a] Reagents: (a) $Hg(Ac)_2$/AcOH, H_2O; (b) KI, $I_2/CHCl_3$; (c) 2-phenoxyethanamine or 2-(2-methoxyphenoxy)ethanamine or 2-(2,6-dimethoxyphenoxy)-ethanamine/$CH_3CH_2OCH_2CH_2OH$, Δ; (d) Ag_2O/1,4-dioxane, H_2O.

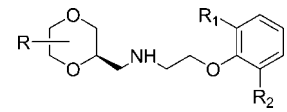
antitumor activity was estimated on the basis of the measurements of three parameters: GI_{50}, the molar concentration of the compound that inhibited 50% net of cell growth; TGI, the molar concentration of the compound that caused total inhibition; and LC_{50}, the molar concentration of the compound that caused 50% net of cell death. Moreover, apoptosis of PC-3 cells, treated with compound **13** at the LC_{50} concentration, was evaluated by annexin V-FITC binding cytofluorimetric analysis.[36]

Results and Discussion

An analysis of the results reported in Table 1 revealed that all the compounds showed affinity values at α_1-ARs that were significantly lower than those of **1**, with the exception of compound **14** at α_{1D} subtype. All the modifications performed were detrimental to α_{1b} subtype affinity and especially to α_{1a}-AR affinity, where all compounds showed approximately 100- to 1000-fold lower affinity than that shown by **1**. This observation indicated that the replacement of the planar condensed aromatic portion of **1** with the pendant phenyl rings inserted in position 5 or 6 of the 1,4-dioxane nucleus altered the optimal molecule geometry, which gave the best interaction with these receptor subtypes.

The stereochemical relationship between the phenyl group in position 5 or 6 and the chain in position 2 did not affect binding to either one of the AR subtypes, the cis diastereoisomers showing affinity values similar to the corresponding trans forms. The only exception was the pair **5a/5b**, in which the cis diastereoisomer **5b** showed an affinity value approximately 10-fold higher than that of trans **5a** at α_{1d}-AR subtype. The insertion of a second phenyl ring in position 5 of the 1,4-dioxane nucleus, which afforded compounds **10**−**12**, did not substantially affect affinity and subtype selectivity with respect to the corresponding monosubstituted derivatives. Instead, the same modification at position 6 was more productive, with the bis-phenyl compounds **13**−**15** showing affinities significantly higher than the corresponding monosubstituted compounds. Such an increase was

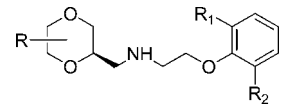
Table 1. Affinity Constants, Expressed as pK_i, of Compounds **4**−**15**, WB 4101, BMY-7378, and 8-OH-DPAT for Human Recombinant α_1-AR Subtypes and 5-HT_{1A} Receptor[a]



				pK_i, human cloned receptors			
compd	R	R_1	R_2	α_{1a}	α_{1b}	α_{1d}	5-HT_{1A}
4a (trans)	5-C_6H_5	H	H	6.27	<6	<6	6.83
4b (cis)	5-C_6H_5	H	H	<6	<6	6.45	7.59
5a (trans)	5-C_6H_5	OCH_3	H	6.80	6.55	7.01	7.41
5b (cis)	5-C_6H_5	OCH_3	H	6.36	6.58	7.79	8.46
6a (trans)	5-C_6H_5	OCH_3	OCH_3	6.29	<6	<6	6.63
6b (cis)	5-C_6H_5	OCH_3	OCH_3	<6	<6	<6	6.59
7a (trans)	6-C_6H_5	H	H	6.39	<6	6.81	7.28
7b (cis)	6-C_6H_5	H	H	<6	<6	7.14	7.27
8a (trans)	6-C_6H_5	OCH_3	H	7.06	6.52	7.50	8.22
8b (cis)	6-C_6H_5	OCH_3	H	6.70	6.57	7.36	8.38
9a (trans)	6-C_6H_5	OCH_3	OCH_3	<6	<6	<6	6.38
9b (cis)	6-C_6H_5	OCH_3	OCH_3	6.33	<6	<6	<6
10	5,5-$(C_6H_5)_2$	H	H	6.65	6.85	6.90	7.43
11	5,5-$(C_6H_5)_2$	OCH_3	H	7.13	7.13	6.99	8.12
12	5,5-$(C_6H_5)_2$	OCH_3	OCH_3	7.05	6.90	6.77	6.64
13	6,6-$(C_6H_5)_2$	H	H	6.77	6.92	8.44	9.23
14	6,6-$(C_6H_5)_2$	OCH_3	H	7.56	7.25	8.94	9.18
15	6,6-$(C_6H_5)_2$	OCH_3	OCH_3	6.47	6.49	7.18	8.85
WB 4101 (**1**)				9.37	8.0	9.29	8.68
BMY-7378				6.42	6.15	8.89	9.43
8-OH-DPAT				<6	<6	<6	8.47

[a] Equilibrium dissociation constants (K_i) were derived from IC_{50} values using the Cheng−Prusoff equation.[50] The affinity estimates were derived from displacement of [^{3}H]prazosin and [^{3}H]-8-hydroxy-2-(di-*n*-propylamino)tetralin binding for α_1-ARs and 5-HT_{1A} receptor, respectively. Each experiment was performed in triplicate. K_i values were from two to three experiments, which agreed within ±20%.

Table 2. Antagonist Affinities, Expressed as pK_b Values,[a] of Compounds **4**−**15**, WB 4101, and BMY-7378 at α_1-ARs on Isolated Rat Vas Deferens (α_{1A}), Spleen (α_{1B}), and Thoracic Aorta (α_{1D}) and Agonist Efficacy, Expressed as pD_2,[b] of Compounds **5b**, **8b**, **13**−**15** on 5-HT_{1A} Receptor in Comparison to 8-OH-DPAT, 5-CT, and 5-HT[c]



				pK_b			binding [^{35}S]GTP	
compd	R	R_1	R_2	α_{1A}	α_{1B}	α_{1D}	5-HT_{1A} pD_2	% max
4a (trans)	5-C_6H_5	H	H	7.0 ± 0.07	6.97 ± 0.13	6.56 ± 0.16		
4b (cis)	5-C_6H_5	H	H	6.89 ± 0.08	6.68 ± 0.06	7.05 ± 0.07		
5a (trans)	5-C_6H_5	OCH_3	H	7.10 ± 0.12	7.44 ± 0.09	7.48 ± 0.16		
5b (cis)	5-C_6H_5	OCH_3	H	6.47 ± 0.09	6.89 ± 0.03	6.84 ± 0.16	7.88	85.5
6a (trans)	5-C_6H_5	OCH_3	OCH_3	7.21 ± 0.11	7.02 ± 0.10	7.26 ± 0.09		
6b (cis)	5-C_6H_5	OCH_3	OCH_3	5.96 ± 0.10	6.70 ± 0.02	6.08 ± 0.06		
7a (trans)	6-C_6H_5	H	H	7.21 ± 0.11	6.88 ± 0.06	6.38 ± 0.20		
7b (cis)	6-C_6H_5	H	H	6.72 ± 0.06	7.12 ± 0.11	6.77 ± 0.16		
8a (trans)	6-C_6H_5	OCH_3	H	7.22 ± 0.09	7.96 ± 0.08	7.83 ± 0.04		
8b (cis)	6-C_6H_5	OCH_3	H	6.57 ± 0.01	7.40 ± 0.07	7.20 ± 0.08	7.83	78.1
9a (trans)	6-C_6H_5	OCH_3	OCH_3	5.80 ± 0.04	5.75 ± 0.07	7.11 ± 0.02		
9b (cis)	6-C_6H_5	OCH_3	OCH_3	6.42 ± 0.02	5.84 ± 0.07	6.55 ± 0.06		
10	5,5-$(C_6H_5)_2$	H	H	6.15 ± 0.13	6.28 ± 0.12	7.19 ± 0.17		
11	5,5-$(C_6H_5)_2$	OCH_3	H	6.37 ± 0.07	6.81 ± 0.04	7.71 ± 0.11		
12	5,5-$(C_6H_5)_2$	OCH_3	OCH_3	6.08 ± 0.05	5.74 ± 0.15	7.38 ± 0.04		
13	6,6-$(C_6H_5)_2$	H	H	6.93 ± 0.04	7.84 ± 0.07	7.60 ± 0.12	9.11	77.1
14	6,6-$(C_6H_5)_2$	OCH_3	H	6.65 ± 0.14	6.86 ± 0.06	8.32 ± 0.17	9.40	81.5
15	6,6-$(C_6H_5)_2$	OCH_3	OCH_3	6.71 ± 0.01	6.24 ± 0.13	7.22 ± 0.07	8.28	106.3
WB 4101 (**1**)				9.51 ± 0.06	8.16 ± 0.09	8.80 ± 0.12		
BMY-7378				7.01 ± 0.08	7.48 ± 0.09	8.40 ± 0.09	9.27	26
8-OH-DPAT							7.60	100
5-HT							7.30	100
5-CT							8.45	96

[a] pK_b values were calculated according to van Rossum[51] in the range 0.01−10 μM. Each concentration [B] of antagonist was tested four times. [b] pD_2 values are the negative logarithm of the agonist concentration required to obtain 50% of the maximal stimulation of [^{35}S]GTPγS binding and were calculated from two to three experiments, which agreed within ±20. [c] 8-OH-DPAT, 8-hydroxy-2-(di-*n*-propylamino)tetralin; 5-HT, 5-hydroxytryptamine; 5-CT, 5-carboxamidotryptamine.

more significant at the α_{1d} subtype. In particular, compound **14** displayed the highest affinity for α_{1d}-AR subtype with a pK_i value of 8.94, which was not significantly different from **1** and BMY-7378. Moreover, the replacement of the condensed benzene ring with two phenyl rings inserted in position 6 of the 1,4-dioxane nucleus, along with the simultaneous removal of one methoxy group in the 2,6-dimethoxyphenoxy moiety, was highly detrimental toward α_{1a} and α_{1b} subtypes (pK_i of 7.56 and 7.25, respectively), indicating an unfavorable binding to these subtypes. Therefore, favorable α_{1d} subtype selectivity was observed.

An analysis of the functional activities, expressed as pK_b and reported in Table 2, revealed that all synthesized compounds behaved as antagonists at α_1-ARs with pK_b values significantly lower than those of **1**, with the exception of compounds **8a** and **13** at α_{1B} and compound **14** at α_{1D} subtype. The pK_b values observed in functional experiments were comparable, in most cases, with the pK_i affinities derived from the binding assays. The discrepancies often observed between functional and binding affinities may not represent an anomaly because in screening procedures a homogeneous population of cloned receptors is used, which can be organized differently from native receptors in functional tissues, and consequently, their biological behavior may not be coincident. Recently other explanations have been considered.[18,37,38] However, although binding and functional data allow similar structure−activity relationships to be deduced, two aspects, concerning the influence of stereochemistry and diphenyl substitution, deserve consideration. The stereochemical relationship between the phenyl ring in position 5 or 6 and the side chain in position 2 seems to affect activity and selectivity differently, depending on the methoxy substitution in the 2,6-dimethoxyphenoxy moiety. In fact, considering the unsubstituted phenoxy derivatives, no significant differences in activity for either one of the AR subtypes were observed between the two diastereoisomers. When one or two methoxy groups were present, the trans diastereoisomers were more potent than the corresponding cis compounds at all the α-ARs, with the exception of trans compound **9a**, which had a higher pK_b only at α_{1D} subtype, a lower pK_b at α_{1A}, and a similar pK_b at α_{1B} with respect to its corresponding cis diastereoisomer, showing good α_{1D} subtype selectivity. With regard to the diphenyl substitution, the insertion of a second phenyl ring in position 5 of the 1,4-dioxane nucleus, obtaining compounds **10**−**12**, seemed to favor a selective α_{1D}-AR profile. However, from the functional data the most interesting result was obtained with compound **14**, whose highest pK_b value of 8.32 for the α_{1D}-AR subtype was not significantly different from that of **1**. Moreover, its functional profile was similar to that displayed by BMY-7378 ($\alpha_{1D} > \alpha_{1B} > \alpha_{1A}$), and because of its lower pK_b values at α_{1A} and α_{1B} subtypes, it proved to be even slightly more selective than BMY-7378 for α_{1D} versus the other two subtypes.

To support the experimental observations and to get an indication of the molecular determinants and stereochemical requirements likely to affect α_1-AR antagonist potency, flexible superimpositions of **15** on **1**, **2**, and **3** were carried out (Figure 1). Considering that the eutomers of **1** and related compounds[15,39] have an (*S*)-configuration at 2-carbon atom, the absolute configuration-(*S*) at this stereogenic center was fixed for compounds **1**, **2**, and **3**, while both enantiomers were considered for **15**. The molecular overlay shown in Figure 1 may indicate that in the case of **15**, but the same also applies to **13** and **14** (superimpositions not shown); both (*S*) and (*R*) enantiomers generated a good overlap with the eutomers of this data set.

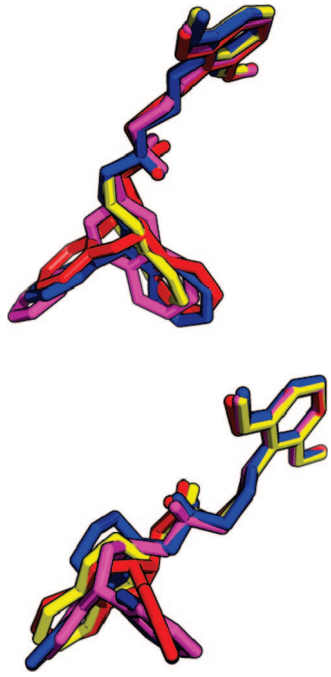


Figure 1. Flexible fit of (*S*)-WB 4101 (**1**), *trans*-(*SS*)-**2**, *cis*-(*SR*)-**3**, and (*S*)-**15** (top) or (*R*)-**15** (bottom). Color codes are as follows: yellow (**1**), red (**2**), magenta (**3**), and blue (**15**). Molecules are rendered with PYMOL available at http://www.pymol.org.

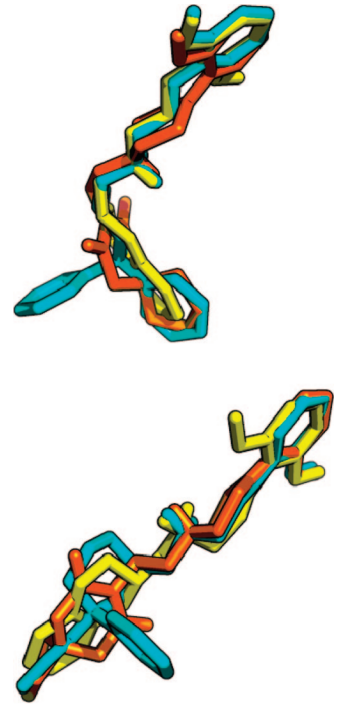


Figure 2. Flexible fit of (*S*)-WB 4101 (**1**), BMY-7378, and (*S*)-**14** (top) or (*R*)-**14** (bottom). Color codes are as follows: yellow (**1**), orange (BMY-7378), and cyan (**14**). Molecules are rendered with PYMOL available at http://www.pymol.org.

Regardless of the absolute configuration of the stereogenic center, it is worth noting that a kind of *reversed-Y* conformation was achieved by the dioxane derivatives that allowed a good fit of the pharmacophoric moieties (i.e., the 6,6-diphenyl group close to the aromatic rings of compounds **2** and **3**, and the aminoalkyl chain). This evidence may suggest that the eudismic ratio for all three 6,6-diphenyldioxane derivatives **13**−**15** should not have a large value but does not exclude the possibility that useful information might come from the synthesis and biological evaluation of the pure enantiomers.

With regard to the 5-HT_{1A} receptor, some interesting observations about structure−affinity relationships may be drawn (Table 1). In fact, among all the 5-phenyl, 6-phenyl, and 5,5-diphenyl derivatives, the presence of a 2-methoxy substituent in the 2-phenoxyethyl moiety was beneficial for high affinity for this receptor. When two phenyl rings were inserted in position 6, the methoxy substitution in the 2-phenoxyethyl moiety did not seem to affect binding to the 5-HT_{1A} receptor. All three derivatives **13**−**15** showed similar nanomolar affinity values. In particular, compounds **13** and **14** showed affinity that was significantly higher than **1** and the reference compound 8-OH-DPAT and similar to BMY-7378.

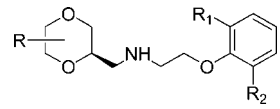
The binding data together with the observation that the three 6,6-diphenyl substituted compounds showed affinity profiles different from that of **1** and overlapping that of BMY-7378 (5-HT_{1A} > α_{1d} > α_{1a} > α_{1b}) allowed us to hypothesize that BMY-7378 and compounds **13**−**15** have a similar binding interaction mode. Moreover, compound **15**, with a low affinity for α_{1d} subtype, displayed a selectivity profile similar to that of 8-OH-DPAT. The better fit of the enantiomers of **14** to BMY-7378 rather than to (*S*)-**1** (Figure 2) might justify the analogies between 6,6-diphenyl-substituted derivatives and BMY-7378. In addition, the different effects of the methoxy substitution in the phenyl group of the side chain of **1**, **13**−**15**, and BMY-7378 on α_1-AR subtype affinity support such an assessment. In fact, it is known that the two methoxy groups at positions 2 and 6 of the phenoxy unit confer optimum affinity in prototype **1**,[40] while in the novel series of compounds only one methoxy group confers the highest affinity at all the α_1-ARs. Similar effects on the affinity at α_1-ARs were instead obtained by the same chemical modification on **14** and BMY-7378. In fact, analogous to what occurred for BMY-7378,[41] removal of the methoxy group of **14**, obtaining **13**, did not alter the α_1-AR profile.

A few compounds (**5b**, **8b**, and **13**−**15**), selected on the basis of the highest affinity shown at the 5-HT_{1A} receptor, were examined in the [^{35}S]GTPγS binding at the human cloned 5-HT_{1A} receptor, and their pD_2 values are reported in Table 2, along with those of the full 5-HT_{1A} receptor agonists 8-OH-DPAT, 5-HT, and 5-CT, which were included for comparison. Among these compounds, **5b**, **8b**, **13**, and **14** proved to be potent partial agonists, with compounds **13** and **14** showing pD_2 values significantly higher than those of the reference compounds. More interestingly, compound **15** was a potent full agonist with a pD_2 value similar to that of 5-CT and significantly higher than those of 5-HT and 8-OH-DPAT. Compound **15** also showed good selectivity for 5-HT_{1A} toward the α_{1A}-, α_{1B}-, and α_{1D}-AR subtypes (binding assays, 240, 229, and 47; functional assays, 37.2, 109.6, and 11.5, respectively), representing a new lead in the design of potent full 5-HT_{1A} agonists significantly selective over α-ARs and structurally unrelated to 5-CT.

With regard to the cytotoxic assays, only the diphenyl-substituted derivatives **10**−**15** were active at low micromolar concentration and were more effective than both lead **1** and doxazosin in suppressing cell growth in PC-3 cells (Table 3). Moreover, the unsubstituted phenoxy moiety or the presence of only one methoxy group seemed to favor PC-3 cell growth inhibition, with compound **13** exhibiting the highest potency (GI_{50} = 1.0 ± 0.09 μM; TGI = 3.9 ± 0.09 μM).

Compound **13** also showed the highest cytotoxic effect (LC_{50} = 6.2 ± 0.8 μM), which was significantly higher than that of

Table 3. Cytotoxic Activity of Compounds **4**−**15** and WB 4101 in Comparison with Doxazosin[a]



compd	R	R_1	R_2	GI_{50}	TGI	LC_{50}
4a (trans)	5-C_6H_5	H	H	177 ± 1.9	252 ± 2.1	>300
4b (cis)	5-C_6H_5	H	H	190 ± 0.7	239 ± 1.7	>300
5a (trans)	5-C_6H_5	OCH_3	H	30.1 ± 0.9	NA[b]	NA[b]
5b (cis)	5-C_6H_5	OCH_3	H	199 ± 1.2	251 ± 2.2	>300
6a (trans)	5-C_6H_5	OCH_3	OCH_3	29 ± 0.5	NA[b]	NA[b]
6b (cis)	5-C_6H_5	OCH_3	OCH_3	199 ± 1.5	251 ± 2.1	>300
7a (trans)	6-C_6H_5	H	H	158 ± 1.4	223 ± 3.0	>300
7b (cis)	6-C_6H_5	H	H	158 ± 1.2	223 ± 2.5	281 ± 2.3
8a (trans)	6-C_6H_5	OCH_3	H	199 ± 1.3	251 ± 3.2	>300
8b (cis)	6-C_6H_5	OCH_3	H	79 ± 1.5	158 ± 2.1	251 ± 3.1
9a (trans)	6-C_6H_5	OCH_3	OCH_3	112 ± 0.6	199 ± 1.8	288 ± 3.1
9b (cis)	6-C_6H_5	OCH_3	OCH_3	79.4 ± 0.8	178 ± 1.9	282 ± 2.8
10	5,5-$(C_6H_5)_2$	H	H	9.9 ± 0.2	19.4 ± 0.5	45.2 ± 1.7
11	5,5-$(C_6H_5)_2$	OCH_3	H	7.8 ± 0.3	16.1 ± 0.6	35.8 ± 1.0
12	5,5-$(C_6H_5)_2$	OCH_3	OCH_3	19.9 ± 0.1	31.6 ± 1.1	40 ± 1.0
13	6,6-$(C_6H_5)_2$	H	H	1.0 ± 0.09	3.9 ± 0.09	6.2 ± 0.8
14	6,6-$(C_6H_5)_2$	OCH_3	H	6.3 ± 0.3	15.4 ± 1.0	35.1 ± 1.2
15	6,6-$(C_6H_5)_2$	OCH_3	OCH_3	25.1 ± 0.4	31.6 ± 1.1	35 ± 1.1
WB 4101 (**1**)				64.56 ± 0.4	199 ± 1.6	>200
doxazosin				26.9 ± 1.3	49.0 ± 2.5	75.8 ± 3.6

[a] In vitro cytotoxic activity in human PC-3 prostate cancer cells was carried out using sulforhodamine B (SRB) assay, according to the National Cancer Institute protocol.[35] GI_{50} represents growth inhibition and is the drug concentration (μM) required to inhibit 50% net of cell growth. Total growth inhibition (TGI) represents the drug concentration (μM) required to inhibit 100% of cell growth. LC_{50} represents the lethal concentration of drug required to kill 50% of the initial cell number. Each quoted value represents the mean of quadruplicate determinations ± standard error ($n = 5$). [b] NA: not active.

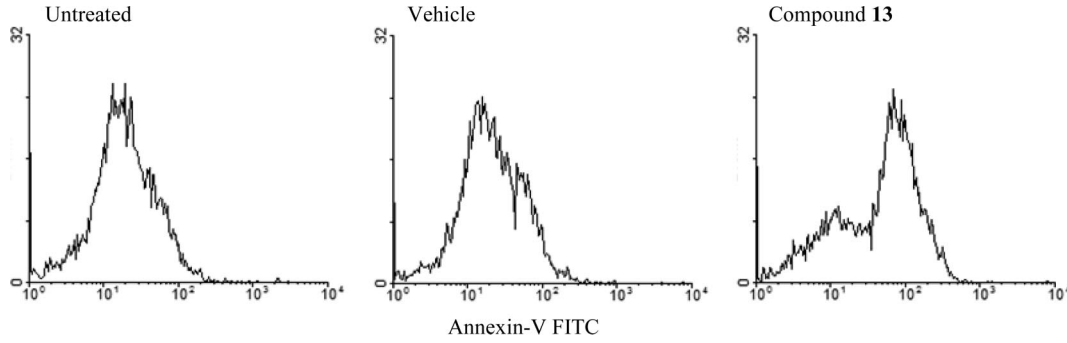


Figure 3. Treatment with compound **13** at the dose corresponding to the LC_{50} markedly induces translocation of PS (MFI of 76.98) in PC-3 cells, whereas very low levels of PS exposure are observed in untreated or vehicle-treated cells (MFI of 30.51 and 35.67, respectively).

1 (LC_{50} > 200 μM) and doxazosin (LC_{50} = 75.8 ± 3.6 μM). Compounds **4**−**9** and **1** were devoid of cytotoxic activity. Finally, since serotonin has been reported to show an enhancing effect on human PC-3 cell growth,[42] the effect produced by **5b**, **8b**, and **13**−**15**, endowed with 5-HT_{1A} partial or full agonist activities, was also evaluated in the presence of the 5-HT_{1A} antagonist (*S*)-*N*-*tert*-butyl-3-(4-(2-methoxyphenyl)piperazin-1-yl)-2-phenylpropanamide [(*S*)-WAY 100135], which has been reported to have no significant effect on PC-3 cell proliferation.[42] The observation that the inhibitory effects induced by the above compounds on PC-3 cell growth were not reversed by (*S*)-WAY 100135 (data not shown) indicates that their cytotoxic activity was not prevented by the potential proliferative effect because of their efficacy for the 5-HT_{1A} receptor.

A characteristic feature of apoptotic cell death is the loss of phospholipid asymmetry and expression of phosphatidylserine (PS) on the outer layer of the plasma membrane. We analyzed whether treatment for 48 h with compound **13** induced externalization of PS residues from the inner to the outer leaflet of the plasma membrane in PC-3 cells. To this end, PC-3-treated cells were stained with annexin V-FITC and analyzed by flow cytometry.[36] As shown in Figure 3, treatment with compound **13**, at the dose corresponding to the LC_{50}, markedly induced translocation of PS (MFI, 76.98), whereas very low levels of PS exposure were observed in untreated or vehicle-treated cells (MFI, 30.51 and 35.67, respectively). Previous reports have indicated that doxazosin induced apoptosis of PC-3 cells via a death receptor mediated pathway.[43] In this regard, our preliminary results, which showed no change in mitochondrial potential in compound **13**-treated PC-3 cells (data not shown), suggested that this compound seemed to activate a mitochondrial-independent apoptotic pathway. Thus, the ability of compound **13** to induce apoptosis at micromolar doses may be particularly relevant in view of the strong chemoresistance shown by PC-3 cells.

In conclusion, the present study highlights that the less conformationally constrained properly substituted 1,4-dioxane nucleus may be considered a suitable scaffold for building selective α_{1D}-AR antagonists (compound **14**), potential anticancer agents (compound **13**), or full 5-HT_{1A} receptor agonists (compound **15**). The behavior of compound **15** is particularly interesting because the 5-HT_{1A} receptor is involved in psychiatric disorders, such as anxiety and depression,[44,45] and 5-HT_{1A} agonists may be useful as antidepressants[46,47] and neuropro-

tective agents.[48] Since the limited clinical efficacy of the 5-HT_{1A} partial agonists as antidepressants (e.g., buspirone) seems to be related to their low level of intrinsic activity,[49] compound **15** may represent a novel lead in the design of highly potent and efficacious 5-HT_{1A} receptor agonists.

To study these aspects in detail, future efforts will be devoted to identifying further structural requirements for selective α_1-AR and 5-HT_{1A} receptor binding sites recognition. In particular, since the enantiomers of **1** have different affinities for α_1-adrenergic and 5-HT_{1A} receptors,[39] with the intention of verifying the indications that emerged from the flexible superimpositions, the synthesis of the enantiomers of **13**−**15** is already being planned. In addition, it would be of interest to verify whether there is a relationship between stereochemistry and the anticancer activity of compound **13**.

Experimental Section

Chemistry. Melting points were taken in glass capillary tubes on a Büchi SMP-20 apparatus and are uncorrected. IR and NMR spectra were recorded on Perkin-Elmer 297 and Varian EM-390 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), dd (double doublet), t (triplet), q (quartet), or m (multiplet). Mass spectra were obtained using a Hewlett-Packard 1100 MSD instrument utilizing electron-spray ionization (ESI). IR spectral data (not shown because of the lack of unusual features) were obtained for all compounds reported and are consistent with the assigned structures. The microanalyses were performed by the Microanalytical Laboratory of our department. The elemental composition of the compounds agreed to within ±0.4% of the calculated values. Chromatographic separations were performed on silica gel columns (Kieselgel 40, 0.040−0.063 mm, Merck) by flash chromatography. The term "dried" refers to the use of anhydrous sodium sulfate. Compounds were named following IUPAC rules as applied by Beilstein-Institut AutoNom (version 2.1), a software for systematic names in organic chemistry.

2-(Allyloxy)-2,2-diphenylethanol (17). Perchloric acid (70%, 0.75 mL) was added to a stirred solution of 2,2-diphenyloxirane[22] (3.0 g, 15.3 mmol) in allyl alcohol (7.5 mL) at 0 °C. After 0.5 h at room temperature the reaction mixture was poured in H_2O (75 mL) and extracted with Et_2O. The organic phase was washed with H_2O and dried over Na_2SO_4. Removal of dried solvents gave a residue, which was purified by column chromatography, eluting with cyclohexane to afford an oil: 3.1 g; 80% yield. ^{1}H NMR ($CDCl_3$): δ 1.85 (br s, 1, OH, exchangeable with D_2O), 3.82 (d, 2, OCH_2), 4.35 (s, 2, CH_2OH), 5.13−5.47 (m, 2, C=CH_2), 5.98 (m, 1, CH=C), 7.15−7.52 (m, 10, ArH).

2-(Allyloxy)-1,1-diphenylethanol (28). 2,2-Diphenyloxirane[22] (6.3 g, 32.1 mmol) was added dropwise to a stirred solution of freshly cut sodium (0.22 g, 9.56 mmol) in allyl alcohol (22 mL) at room temperature. After 1 h at room temperature the reaction mixture was refluxed for 20 h. Most of the unreacted allyl alcohol was then separated by distillation at atmospheric pressure. After cooling to room temperature, 6 N H_2SO_4 (0.6 mL) was added to the residual solution to neutralize the sodium alloxide, and solvent removal was continued to afford a residual oil, which was purified by column chromatography, eluting with cyclohexane/EtOAc (10:0.05) to give a solid: 6.9 g; 85% yield; mp 29−31 °C. ^{1}H NMR ($CDCl_3$): δ 3.54 (br s, 1, OH, exchangeable with D_2O), 4.02 (s, 2, CH_2O), 4.15 (d, 2, OCH_2), 5.28 (m, 2, C=CH_2), 5.94 (m, 1, CH=C), 7.21−7.53 (m, 10, ArH).

2-(Oxiran-2-ylmethoxy)-2-phenylethanol (18). *m*-Chloroperbenzoic acid (50%) (11.6 g, 33.6 mmol) was added to a solution of **16**[23] (3.0 g, 16.8 mmol) in CH_2Cl_2 (120 mL). After 20 h at room temperature under stirring the reaction mixture was washed with 10% Na_2SO_3, 5% Na_2CO_3, and H_2O. Removal of dried solvents afforded a mixture of the two diastereoisomers as an oil: 2.77 g; 85% yield. ^{1}H NMR ($CDCl_3$): δ 2.42 (br s, 2, OH, exchangeable with D_2O), 2.47−2.85 (four dd, 4, CH_2O cycle), 3.17 (m, 2, CHO cycle), 3.25−3.80 (m, 8, OCH_2 and CH_2OH), 4.48 (two dd, 2, OCHAr), 7.22−7.42 (m, 10, ArH).

2-(Oxiran-2-ylmethoxy)-2,2-diphenylethanol (19). This was obtained following the procedure described for **18** starting from **17** to afford an oil: 50% yield. ^{1}H NMR ($CDCl_3$): δ 1.62 (br s, 1, OH, exchangeable with D_2O), 2.90 (m, 2, CH_2O cycle), 3.24 (m, 1, CHO cycle), 3.43 and 3.64 (two dd, 2, OCH_2), 4.30 (dd, 2, CH_2OH), 7.17−7.50 (m, 10, ArH).

2-(Oxiran-2-ylmethoxy)-1-phenylethanol (29). This was obtained as a mixture of the two diastereoisomers following the procedure described for **18** starting from **27**[24] to afford an oil: 89% yield. ^{1}H NMR ($CDCl_3$): δ 2.61−2.82 (m, 4, CH_2O cycle), 3.07 (br s, 2, OH, exchangeable with D_2O), 3.20 (m, 2, CHO cycle), 3.42−3.90 (m, 8, CH_2OCH_2), 4.90 (m, 2, CHAr), 7.22−8.06 (m, 10, ArH).

2-(Oxiran-2-ylmethoxy)-1,1-diphenylethanol (30). This was obtained following the procedure described for **18** starting from **28** to afford a solid: mp 83−84 °C; 90% yield. ^{1}H NMR ($CDCl_3$): δ 1.60 (br s, 1, OH, exchangeable with D_2O), 2.55 and 2.80 (two dd, 2, CH_2O cycle), 3.16 (m, 1, CHO cycle), 3.52 and 3.90 (two dd, 2, OCH_2), 4.10 (dd, 2, CH_2O), 7.18−7.52 (m, 10, ArH).

***trans*-(5-Phenyl-1,4-dioxan-2-yl)methanol (20a) and *cis*-(5-Phenyl-1,4-dioxan-2-yl)methanol (20b).** A solution of **18** (29.4 g, 151.4 mmol) and (1*S*)-(+)-10-camphorsulfonic acid (3.3 g, 142.1 mmol) in CH_2Cl_2 (1340 mL) was refluxed for 8 h. The reaction mixture was then washed with $NaHCO_3$ saturated solution and dried over Na_2SO_4. Removal of the solvent afforded a residue, which was purified by column chromatography gradient eluent, eluting first with cyclohexane/EtOAc (8:2) and then with cyclohexane/EtOAc (6:4). The trans diastereoisomer **20a** eluted first as a solid: 10.0 g; 34% yield; mp 79−81 °C. ^{1}H NMR ($CDCl_3$): δ 1.93 (t, 1, OH, exchangeable with D_2O), 3.52−4.04 (m, 7, OCH_2 and OCH_2CHCH_2), 4.58 (dd, 1, CHAr), 7.28−7.40 (m, 5, ArH). The second fraction was the cis diastereoisomer **20b** as an oil: 2.0 g; 7% yield. ^{1}H NMR ($CDCl_3$): δ 1.86 (br s, 1, OH, exchangeable with D_2O), 3.67−4.15 (m, 7, OCH_2 and OCH_2CHCH_2), 4.63 (dd, 1, CHAr), 7.25−7.40 (m, 5, ArH).

(5,5-Diphenyl-1,4-dioxan-2-yl)methanol (21). This was obtained following the procedure described for **20** starting from **19**. The residue was purified by column chromatography, eluting with cyclohexane/EtOAc (8:2) to afford a solid: 50% yield; mp 95−97 °C. ^{1}H NMR ($CDCl_3$): δ 1.82 (br s, 1, OH, exchangeable with D_2O), 3.40−3.75 (m, 4, OCH_2 and CH_2OH), 3.88 (m, 1, OCH), 3.79 and 4.69 (two d, 2, CH_2O), 7.11−7.56 (m, 10, ArH).

***cis*-(6-Phenyl-1,4-dioxan-2-yl)methanol (31b) and *trans*-(6-Phenyl-1,4-dioxan-2-yl)methanol (31a).** These were obtained following the procedure described for **20** starting from **29** to afford a mixture of diastereoisomers, which were separated by column chromatography, eluting with cyclohexane/EtOAc (8:2). The cis diastereoisomer **31b** eluted first as a solid: 33% yield; mp 72−73 °C. ^{1}H NMR ($CDCl_3$): δ 2.13 (br s, 1, OH, exchangeable with D_2O), 3.38−3.98 (m, 7, $CH_2OCH_2OCHCH_2$), 4.71 (dd, 1, CHAr), 7.28−7.40 (m, 5, ArH). The second fraction was the trans diastereoisomer **31a** as an oil: 37% yield. ^{1}H NMR ($CDCl_3$): δ 1.68 (br s, 1, OH, exchangeable with D_2O), 3.61−4.16 (m, 7, $CH_2OCH_2OCHCH_2$), 4.87 (dd, 1, CHAr), 7.28−7.48 (m, 5, ArH).

(6,6-Diphenyl-1,4-dioxan-2-yl)methanol (32). This was obtained following the procedure described for **20** starting from **30**. The residue was purified by column chromatography, eluting with cyclohexane/EtOAc (9:1) to afford a solid: 60% yield; mp 114−115 °C. ^{1}H NMR ($CDCl_3$): δ 1.84 (br s, 1, OH, exchangeable with D_2O), 3.53−3.83 (m, 5, OCH_2CHCH_2), 3.64 and 4.61 (two d, 2, CH_2O), 7.20−7.58 (m, 10, ArH).

***trans*-5-Phenyl-1,4-dioxane-2-carboxylic Acid (22a).** A solution of $KMnO_4$ (3.25 g, 20.6 mmol) in H_2O (15 mL) was added dropwise to a stirred mixture of **20a** (2.16 g, 11.1 mmol) in 1 N KOH (15 mL) such that the temperature was maintained below 10 °C. After 18 h at room temperature the mixture was filtered over Celite, MeOH was added, and the solvent was concentrated under vacuum. The resulting aqueous solution was acidified with 6 N H_2SO_4 and extracted with $CHCl_3$. After evaporation of the dried solvent, the

residue was crystallized from EtOAc/petroleum ether: 0.92 g; 40% yield; mp 165−167 °C. ^{1}H NMR ($CDCl_3$): δ 3.62 (dd J = 10.26, 11.97 Hz, 1, 6-CH_2), 3.81 (dd, J = 10.69, 11.54 Hz, 1, 3-CH_2), 4.07 (dd, J = 2.56, 11.97 Hz, 1, 6-CH_2), 4.35 (dd, J = 3.42, 11.54 Hz, 1, 3-CH_2), 4.41 (dd, J = 3.42, 10.69 Hz, 1, 2-CH), 4.62 (dd, J = 2.56, 10.26 Hz, 1, 5-CH), 5.91 (br s, 1, COOH, exchangeable with D_2O), 7.31−7.41 (m, 5, ArH).

***cis*-5-Phenyl-1,4-dioxane-2-carboxylic Acid (22b).** This was obtained following the procedure described for **22a** starting from **20b**: 93% yield. ^{1}H NMR ($CDCl_3$): δ 3.84 (dd J = 2.99, 11.97 Hz, 1, 6-CH_2), 4.07 (dd, J = 10.26, 11.97 Hz, 1, 6-CH_2), 4.11 (dd, J = 3.85, 11.97 Hz, 1, 3-CH_2), 4.38 (dd, J = 1.11, 2.99 Hz, 1, 2-CH), 4.51 (dd, J = 1.11, 11.97 Hz, 1, 3-CH_2), 4.67 (dd, J = 2.99, 10.26 Hz, 1, 5-CH), 7.30−8.28 (m, 5, ArH), 9.61 (br s, 1, COOH, exchangeable with D_2O).

5,5-Diphenyl-1,4-dioxane-2-carboxylic Acid (23). This was obtained following the procedure described for **22a** starting from **21**: 82% yield; mp 188−190 °C. ^{1}H NMR ($CDCl_3$): δ 3.72 (dd, 1, 3-CH_2), 3.95 (d, 1, 6-CH_2), 4.15 (dd, 1, 3-CH_2), 4.41 (dd, 1, 2-CH), 4.66 (d, 1, 6-CH_2), 6.87 (br s, 1, COOH, exchangeable with D_2O), 7.20−7.54 (m, 10, ArH).

***trans*-6-Phenyl-1,4-dioxane-2-carboxylic Acid (33a).** This was obtained following the procedure described for **22a** starting from **31a**: 54% yield; mp 110−112 °C. ^{1}H NMR ($CDCl_3$): δ 3.55 (dd J = 9.78, 11.53 Hz, 1, 5-CH_2), 3.92 (dd, J = 11.73, 3.13 Hz, 1, 5-CH_2), 3.95 (dd, J = 3.91, 11.73 Hz, 1, 3-CH_2), 4.36 (dd, J = 1.57, 11.73 Hz, 1, 3-CH_2), 4.52 (dd, J = 1.57, 3.91 Hz, 1, 2-CH), 5.16 (dd, J = 3.13, 9.78 Hz, 1, 6-CH), 7.30−8.36 (m, 5, ArH), 8.43 (br s, 1, COOH, exchangeable with D_2O).

***cis*-6-Phenyl-1,4-dioxane-2-carboxylic Acid (33b).** This was obtained following the procedure described for **22a** starting from **31b**: 54% yield; mp 117−120 °C. ^{1}H NMR ($CDCl_3$): δ 3.46 (dd J = 10.44, 11.90 Hz, 1, 5-CH_2), 3.61 (dd, J = 10.71, 11.54 Hz, 1, 3-CH_2), 3.89 (dd, J = 2.84, 11.90 Hz, 1, 5-CH_2), 4.23 (dd, J = 3.20, 11.54 Hz, 1, 3-CH_2), 4.54 (dd, J = 3.20, 10.71 Hz, 1, 2-CH), 4.78 (dd, J = 2.84, 10.44 Hz, 1, 6-CH), 7.30−8.12 (m, 5, ArH), 8.61 (br s, 1, COOH, exchangeable with D_2O).

6,6-Diphenyl-1,4-dioxane-2-carboxylic Acid (34). This was obtained following the procedure described for **22a** starting from **32**: 52% yield; mp 197−199 °C. ^{1}H NMR ($CDCl_3$): δ 3.62 (d, 1, 5-CH_2), 3.68 (dd, 1, 3-CH_2), 4.21 (dd, 1, 3-CH_2), 4.35 (dd, 1, 2-CH), 4.61 (d, 1, 5-CH_2), 7.08 (br s, 1, COOH, exchangeable with D_2O), 7.27−7.54 (m, 10, ArH).

***trans*-*N*-(2-(2-Methoxyphenoxy)ethyl)-5-phenyl-1,4-dioxane-2-carboxamide (24a).** Et_3N (0.35 g, 3.46 mmol) and EtOCOCl (0.38 g, 3.46 mmol) were added to a solution of **22a** (0.72 g, 3.46 mmol) in dry $CHCl_3$ (30 mL) at 0 °C. After 30 min a solution of 2-(2-methoxyphenoxy)ethanamine[18] (0.58 g, 3.46 mmol) in $CHCl_3$ (10 mL) was added and the reaction mixture was left at room temperature for 3 h. The solution was then washed with 2 N HCl and 2 N NaOH, and the organic phase was dried over Na_2SO_4. Removal of the solvent gave a solid, which was crystallized from EtOAc/cyclohexane: 0.95 g; 77% yield; mp 100−102 °C. ^{1}H NMR ($CDCl_3$): δ 3.52−3.78 (m, 4, NCH_2 and cycle), 3.90 (s, 3, OCH_3), 4.0 (dd, 1, cycle), 4.23 (dd, 1, cycle), 4.15 (t, 2, CH_2OAr), 4.41 (dd, 1, cycle), 4.58 (dd, 1, cycle), 6.88−7.48 (m, 9, ArH), 7.27 (br t, 1, NH, exchangeable with D_2O).

***cis*-*N*-(2-(2-Methoxyphenoxy)ethyl)-5-phenyl-1,4-dioxane-2-carboxamide (24b).** This was obtained following the procedure described for **24a** starting from **22b**. The residue was purified by column chromatography, eluting with cyclohexane/EtOAc (7:3) to afford an oil: 42% yield. ^{1}H NMR ($CDCl_3$): δ 3.68−4.20 (m, 8, NCH_2, CH_2OAr and cycle), 3.71 (s, 3, OCH_3), 4.50−4.66 (two dd, 2, cycle), 6.80−7.41 (m, 9, ArH), 7.22 (br t, 1, NH, exchangeable with D_2O).

***cis*-*N*-(2-(2,6-Dimethoxyphenoxy)ethyl)-5-phenyl-1,4-dioxane-2-carboxamide (25b).** This was obtained following the procedure described for **24a** starting from **22b** and 2-(2,6-dimethoxyphenoxy)-ethanamine.[25] The residue was purified by column chromatography, eluting with cyclohexane/EtOAc (7:3) to afford a solid: 43% yield; mp 111−112 °C. ^{1}H NMR ($CDCl_3$): δ 3.62 (q, 2, NCH_2), 3.78−4.20 (m, 6, CH_2OAr and cycle), 3.82 (s, 6, OCH_3), 4.63 (two dd, 2, cycle), 6.55−7.42 (m, 8, ArH), 7.83 (br t, 1, NH, exchangeable with D_2O).

***N*-(2-(2,6-Dimethoxyphenoxy)ethyl)-5,5-diphenyl-1,4-dioxane-2-carboxamide (26).** This was obtained following the procedure described for **24a** starting from **23** and 2-(2,6-dimethoxyphenoxy)-ethanamine.[25] The residue was purified by column chromatography, eluting with cyclohexane/EtOAc (8:2) to afford a solid: 52% yield; mp 168−170 °C. ^{1}H NMR ($CDCl_3$): δ 3.52−4.67 (m, 7, NCH_2, CH_2OAr, and cycle), 3.82 (s, 6, OCH_3), 4.26 (dd, 1, cycle), 4.68 (d, 1, cycle), 6.54−7.46 (m, 13, ArH), 7.52 (br t, 1, NH, exchangeable with D_2O).

***trans*-*N*-(2-Phenoxyethyl)-6-phenyl-1,4-dioxane-2-carboxamide (35a).** This was obtained following the procedure described for **24a** starting from **33a** and 2-phenoxyethanamine. The residue was purified by column chromatography, eluting with cyclohexane/EtOAc (8.5:1.5) to afford a solid: 63% yield; mp 123−125 °C. ^{1}H NMR ($CDCl_3$): δ 3.60−4.35 (m, 8, NCH_2, CH_2OAr, and cycle), 4.42 (dd, 1, cycle), 4.78 (dd, 1, cycle), 6.82−7.42 (m, 10, ArH), 7.13 (br t, 1, NH, exchangeable with D_2O).

***cis*-*N*-(2-Phenoxyethyl)-6-phenyl-1,4-dioxane-2-carboxamide (35b).** This was obtained following the procedure described for **24a** starting from **33b** and 2-phenoxyethanamine. The residue was purified by column chromatography, eluting with cyclohexane/EtOAc (9:1) to afford a solid: 61% yield; mp 95−97 °C. ^{1}H NMR ($CDCl_3$): δ 3.41 (m, 2, cycle), 3.70 (q, 2, NCH_2), 3.88 (dd, 1, cycle), 4.05 (t, 2, CH_2OAr), 4.32 (dd, 1, cycle), 4.40 (dd, 1, cycle), 4.75 (dd, 1, cycle), 6.82−7.53 (m, 10, ArH), 7.13 (br t, 1, NH, exchangeable with D_2O).

***trans*-*N*-(2-(2-Methoxyphenoxy)ethyl)-6-phenyl-1,4-dioxane-2-carboxamide (36a).** This was obtained following the procedure described for **24a** starting from **33a** and 2-(2-methoxyphenoxy)-ethanamine.[18] The residue was purified by column chromatography, eluting with cyclohexane/EtOAc (7:3) to afford an oil: 57% yield. ^{1}H NMR ($CDCl_3$): δ 3.60−4.34 (m, 8, NCH_2CH_2OAr and cycle), 3.63 (s, 3, OCH_3), 4.45 (dd, 1, cycle), 4.84 (dd, 1, cycle), 6.81−7.40 (m, 9, ArH), 7.42 (br t, 1, NH, exchangeable with D_2O).

***cis*-*N*-(2-(2-Methoxyphenoxy)ethyl)-6-phenyl-1,4-dioxane-2-carboxamide (36b).** This was obtained following the procedure described for **24a** starting from **33b** and 2-(2-methoxyphenoxy)-ethanamine.[18] The residue was purified by column chromatography, eluting with cyclohexane/EtOAc (7:3) to afford an oil: 60% yield. ^{1}H NMR ($CDCl_3$): δ 3.32−4.34 (m, 8, NCH_2, CH_2OAr, and cycle), 3.68 (s, 3, OCH_3), 4.40 (dd, 1, cycle), 4.72 (dd, 1, cycle), 6.81−7.56 (m, 9, ArH), 7.83 (br t, 1, NH, exchangeable with D_2O).

***trans*-*N*-(2-(2,6-Dimethoxyphenoxy)ethyl)-6-phenyl-1,4-dioxane-2-carboxamide (37a).** This was obtained following the procedure described for **24a** starting from **33a** and 2-(2,6-dimethoxyphenoxy)-ethanamine.[25] The residue was purified by column chromatography, eluting with cyclohexane/EtOAc (7.5:2.5) to afford an oil: 35% yield. ^{1}H NMR ($CDCl_3$): δ 3.40−4.35 (m, 8, NCH_2, CH_2OAr, and cycle), 3.62 (s, 6, OCH_3), 4.51 (dd, 1, cycle), 4.95 (dd, 1, cycle), 6.42−7.47 (m, 8, ArH), 7.89 (br t, 1, NH, exchangeable with D_2O).

***cis*-*N*-(2-(2,6-Dimethoxyphenoxy)ethyl)-6-phenyl-1,4-dioxane-2-carboxamide (37b).** This was obtained following the procedure described for **24a** starting from **33b** and 2-(2,6-dimethoxyphenoxy)-ethanamine.[25] The residue was purified by column chromatography, eluting with cyclohexane/EtOAc (7.5:2.5) to afford an oil: 66% yield. ^{1}H NMR ($CDCl_3$): δ 3.38−4.40 (m, 8, NCH_2, CH_2OAr, and cycle), 3.66 (s, 6, OCH_3), 4.44 (dd, 1, cycle), 4.78 (dd, 1, cycle), 6.47−7.55 (m, 8, ArH), 7.68 (br t, 1, NH, exchangeable with D_2O).

***N*-(2-(2,6-Dimethoxyphenoxy)ethyl)-6,6-diphenyl-1,4-dioxane-2-carboxamide (38).** This was obtained following the procedure described for **24a** starting from **34** and 2-(2,6-dimethoxyphenoxy)-ethanamine.[25] The residue was purified by column chromatography, eluting with cyclohexane/EtOAc (7.5:2.5) to afford an oil: 70% yield. ^{1}H NMR ($CDCl_3$): δ 3.51−4.26 (m, 8, NCH_2, CH_2OAr, and cycle), 3.77 (s, 6, OCH_3), 4.62 (d, 1, cycle), 6.57−7.57 (m, 13, ArH), 7.82 (br t, 1, NH, exchangeable with D_2O).

***trans*-2-(2-Methoxyphenoxy)-*N*-((5-phenyl-1,4-dioxan-2-yl)methyl)ethanamine (5a).** A solution of 10 M $BH_3 \cdot CH_3SCH_3$ (0.9 mL) in dry THF (3 mL) was added dropwise at room temperature to a stirred solution of **24a** (0.95 g, 2.66 mmol) in dry THF (50 mL) under a stream of dry nitrogen with exclusion of moisture. When the addition was completed, the reaction mixture was heated at reflux temperature for 8 h. After the mixture was cooled to 0 °C, excess borane was destroyed by cautious dropwise addition of EtOH (5 mL). The resulting mixture was left to stand overnight at room temperature, cooled to 0 °C, acidified with concentrated HCl, and then heated to 60 °C for 1 h. Removal of the solvent under reduced pressure gave a residue, which was dissolved in H_2O. The aqueous solution was basified with 2 N NaOH and extracted with $CHCl_3$. Removal of dried solvents gave a residue, which was purified by column chromatography, eluting with $CHCl_3$/EtOH (9.5:0.5) to afford an oil: 0.84 g; 92% yield. ^{1}H NMR ($CDCl_3$): δ 2.25 (br s, 1, NH, exchangeable with D_2O), 2.80−3.18 (m, 4, CH_2NCH_2), 3.48−4.25 (m, 7, CH_2OAr and cycle), 3.88 (s, 3, OCH_3), 4.58 (dd, 1, cycle), 6.83−7.42 (m, 9, ArH). MS (ESI): m/z = 344.1 ($M + H^+$). The free base was transformed into the oxalate salt and crystallized from MeOH: mp 206−207 °C. Anal. ($C_{20}H_{25}NO_4 \cdot H_2C_2O_4$) C, H, N.

***cis*-2-(2-Methoxyphenoxy)-*N*-((5-phenyl-1,4-dioxan-2-yl)methyl)ethanamine (5b).** This was obtained following the procedure described for **5a** starting from **24b**: 78% yield. ^{1}H NMR ($CDCl_3$): δ 1.68 (br s, 1, NH, exchangeable with D_2O), 2.78−3.35 (m, 4, CH_2NCH_2), 3.72−4.24 (m, 7, CH_2OAr and cycle), 3.83 (s, 3, OCH_3), 4.65 (dd, 1, cycle), 6.83−7.44 (m, 9, ArH). MS (ESI): m/z = 344.1 ($M + H^+$). The free base was transformed into the oxalate salt and crystallized from MeOH: mp 223−225 °C. Anal. ($C_{20}H_{25}NO_4 \cdot H_2C_2O_4$) C, H, N.

***cis*-2-(2,6-Dimethoxyphenoxy)-*N*-((5-phenyl-1,4-dioxan-2-yl)methyl)ethanamine (6b).** This was obtained following the procedure described for **5a** starting from **25b**: 76% yield. ^{1}H NMR ($CDCl_3$): δ 1.89 (br s, 1, NH, exchangeable with D_2O), 2.75−3.32 (m, 4, CH_2NCH_2), 3.74−4.28 (m, 7, CH_2OAr and cycle), 3.85 (s, 6, OCH_3), 4.66 (dd, 1, cycle), 6.53−7.48 (m, 8, ArH). MS (ESI): m/z = 374.1 ($M + H^+$). The free base was transformed into the oxalate salt and crystallized from EtOH: mp 198−199 °C. Anal. ($C_{21}H_{27}NO_5 \cdot H_2C_2O_4$) C, H, N.

2-(2,6-Dimethoxyphenoxy)-*N*-((5,5-diphenyl-1,4-dioxan-2-yl)methyl)ethanamine (12). This was obtained following the procedure described for **5a** starting from **26**: 56% yield; mp 83−85 °C. ^{1}H NMR ($CDCl_3$): δ 1.99 (br s, 1, NH, exchangeable with D_2O), 2.52−2.92 (m, 4, CH_2NCH_2), 3.32−4.18 (m, 7, CH_2OAr and cycle), 3.81 (s, 6, OCH_3), 3.73 (d, 1, cycle), 4.64 (d, 1, cycle), 6.52−7.52 (m, 13, ArH). MS (ESI): m/z = 450.2 ($M + H^+$). The free base was transformed into the oxalate salt and crystallized from EtOH: mp 190−191 °C. Anal. ($C_{27}H_{31}NO_5 \cdot H_2C_2O_4$) C, H, N.

***trans*-2-Phenoxy-*N*-((6-phenyl-1,4-dioxan-2-yl)methyl)ethanamine (7a).** This was obtained following the procedure described for **5a** starting from **35a**: 96% yield. ^{1}H NMR ($CDCl_3$): δ 1.90 (br s, 1, NH, exchangeable with D_2O), 2.80−3.38 (m, 4, CH_2NCH_2), 3.66−4.20 (m, 7, CH_2OAr and cycle), 4.87 (dd, 1, cycle), 6.82−7.49 (m, 10, ArH). MS (ESI): m/z = 314.1 ($M + H^+$). The free base was transformed into the oxalate salt and crystallized from EtOH: mp 209−210 °C. Anal. ($C_{19}H_{23}NO_3 \cdot H_2C_2O_4$) C, H, N.

***cis*-2-Phenoxy-*N*-((6-phenyl-1,4-dioxan-2-yl)methyl)ethanamine (7b).** This was obtained following the procedure described for **5a** starting from **35b**: 81% yield. ^{1}H NMR ($CDCl_3$): δ 1.80 (br s, 1, NH, exchangeable with D_2O), 2.68−3.08 (m, 4, CH_2NCH_2), 3.32−4.11 (m, 7, CH_2OAr and cycle), 4.68 (dd, 1, cycle), 6.81−7.42 (m, 10, ArH). MS (ESI): m/z = 314.1 ($M + H^+$). The free base was transformed into the oxalate salt and crystallized from MeOH: mp 212−213 °C. Anal. ($C_{19}H_{23}NO_3 \cdot H_2C_2O_4$) C, H, N.

***trans*-2-(2-Methoxyphenoxy)-*N*-((6-phenyl-1,4-dioxan-2-yl)methyl)ethanamine (8a).** This was obtained following the procedure described for **5a** starting from **36a**: 82% yield. ^{1}H NMR ($CDCl_3$): δ 2.55 (br s, 1, NH, exchangeable with D_2O), 2.87−3.43 (m, 4, CH_2NCH_2), 3.58−4.27 (m, 7, CH_2OAr and cycle), 3.68 (s, 3, OCH_3), 4.87 (dd, 1, cycle), 6.81−7.48 (m, 9, ArH). MS (ESI): m/z = 344.1 ($M + H^+$). The free base was transformed into the oxalate salt and crystallized from EtOH: mp 178−179 °C. Anal. ($C_{20}H_{25}NO_4 \cdot H_2C_2O_4$) C, H, N.

***cis*-2-(2-Methoxyphenoxy)-*N*-((6-phenyl-1,4-dioxan-2-yl)methyl)ethanamine (8b).** This was obtained following the procedure described for **5a** starting from **36b**: 70% yield. ^{1}H NMR ($CDCl_3$): δ 1.93 (br s, 1, NH, exchangeable with D_2O), 2.72−3.08 (m, 4, CH_2NCH_2), 3.32−4.18 (m, 7, CH_2OAr and cycle), 3.78 (s, 3, OCH_3), 4.68 (dd, 1, cycle), 6.83−7.36 (m, 9, ArH). MS (ESI): m/z = 344.1 ($M + H^+$). The free base was transformed into the oxalate salt and crystallized from EtOH: mp 162−164 °C. Anal. ($C_{20}H_{25}NO_4 \cdot H_2C_2O_4$) C, H, N.

***trans*-2-(2,6-Dimethoxyphenoxy)-*N*-((6-phenyl-1,4-dioxan-2-yl)methyl)ethanamine (9a).** This was obtained following the procedure described for **5a** starting from **37a**: 80% yield. ^{1}H NMR ($CDCl_3$): δ 1.99 (br s, 1, NH, exchangeable with D_2O), 2.81−3.27 (m, 4, CH_2NCH_2), 3.70−4.24 (m, 7, CH_2OAr and cycle), 3.75 (s, 6, OCH_3), 4.87 (dd, 1, cycle), 6.52−7.45 (m, 8, ArH). MS (ESI): m/z = 374.1 ($M + H^+$). The free base was transformed into the oxalate salt and crystallized from EtOH: mp 150−152 °C. Anal. ($C_{21}H_{27}NO_5 \cdot H_2C_2O_4$) C, H, N.

***cis*-2-(2,6-Dimethoxyphenoxy)-*N*-((6-phenyl-1,4-dioxan-2-yl)methyl)ethanamine (9b).** This was obtained following the procedure described for **5a** starting from **37b**: 73% yield. ^{1}H NMR ($CDCl_3$): δ 2.05 (br s, 1, NH, exchangeable with D_2O), 2.82−3.02 (m, 4, CH_2NCH_2), 3.32−4.27 (m, 7, CH_2OAr and cycle), 3.72 (s, 6, OCH_3), 4.72 (dd, 1, cycle), 6.50−7.41 (m, 8, ArH). MS (ESI): m/z = 374.1 ($M + H^+$). The free base was transformed into the oxalate salt and crystallized from 2-PrOH: mp 183−184 °C. Anal. ($C_{21}H_{27}NO_5 \cdot H_2C_2O_4$) C, H, N.

2-(2,6-Dimethoxyphenoxy)-*N*-((6,6-diphenyl-1,4-dioxan-2-yl)methyl)ethanamine (15). This was obtained following the procedure described for **5a** starting from **38**: 66% yield. ^{1}H NMR ($CDCl_3$): δ 2.02 (br s, 1, NH, exchangeable with D_2O), 2.62−2.97 (m, 4, CH_2NCH_2), 3.50−4.20 (m, 6, CH_2OAr and cycle), 3.80 (s, 6, OCH_3), 4.62 (d, 1, cycle), 6.54−7.58 (m, 13, ArH). MS (ESI): m/z = 450.2 ($M + H^+$). The free base was transformed into the oxalate salt and crystallized from 2-PrOH: mp 151−153 °C. Anal. ($C_{27}H_{31}NO_5 \cdot H_2C_2O_4$) C, H, N.

***trans*-2-(Iodomethyl)-5-phenyl-1,4-dioxane (39a) and *cis*-2-(Iodomethyl)-5-phenyl-1,4-dioxane (39b).** A solution of mercury(II) acetate (6.33 g, 19.9 mmol) in H_2O (25 mL) and acetic acid (0.025 mL) was added to a stirred solution of **16**[23] (4.42 g, 24.8 mmol). The reaction mixture was heated to reflux for 45 min, then allowed to stand overnight at room temperature. After the reaction mixture was filtered, a solution of KI (4.0 g, 24.2 mmol) in H_2O (26 mL) was added to the filtrate and ((5-phenyl-1,4-dioxan-2-yl)methyl)mercury(II) iodide separated as an oil, which was dissolved in $CHCl_3$ (16 mL). A solution of I_2 (4.73 g, 18.6 mmol) in $CHCl_3$ was added, and the reaction mixture was heated to boiling and then allowed to stand at room temperature for 18 h. The organic phase was washed with 10% Na_2SO_3 and 10% KI and dried over Na_2SO_4. The evaporation of the solvent in vacuo afforded a mixture of the two diastereoisomers, which were separated by column chromatography, eluting with cyclohexane/EtOAc (99:1). The trans isomer **39a** eluted first: 5.3 g; 56% yield. ^{1}H NMR ($CDCl_3$): δ 3.15 (d, 2, CH_2I), 3.50−3.78 (m, 3, cycle), 3.99 (dd, 1, cycle), 4.17 (dd, 1, cycle), 4.58 (dd, 1, cycle), 7.28−7.42 (m, 5, ArH). The second fraction was the cis isomer **39b** as a solid: 2.2 g; 23% yield; mp 43−45 °C. ^{1}H NMR ($CDCl_3$): δ 3.50−4.18 (m, 7, CH_2I, cycle), 4.65 (dd, 1, cycle), 7.28−7.53 (m, 5, ArH).

5-(Iodomethyl)-2,2-diphenyl-1,4-dioxane (40). This was obtained following the procedure described for **39** starting from **17**: 47% yield; mp 170−172 °C. ^{1}H NMR ($CDCl_3$): δ 3.05 (d, 2, CH_2I), 3.35 (dd, 1, cycle), 3.78−3.94 (m, 3, cycle), 4.63 (d, 1, cycle), 7.13−7.52 (m, 10, ArH).

6-(Iodomethyl)-2,2-diphenyl-1,4-dioxane (41). This was obtained following the procedure described for **39** starting from **28**: 28% yield; mp 76−79 °C. ^{1}H NMR ($CDCl_3$): δ 3.19 (d, 2, CH_2I), 3.44−3.63 (m, 3, cycle), 3.92 (dd, 1, cycle), 4.60 (d, 1, cycle), 7.12−7.57 (m, 10, ArH).

***trans*-2-Phenoxy-*N*-((5-phenyl-1,4-dioxan-2-yl)methyl)ethanamine (4a).** A solution of **39a** (0.5 g, 1.6 mmol) and 2-phenoxyethanamine (1.13 g, 9.0 mmol) in 2-ethoxyethanol (10 mL) was heated to reflux for 5 h. Removal of the solvent under reduced pressure gave a residue, which was dissolved in water. The aqueous solution was basified with NaOH and extracted with $CHCl_3$. Removal of dried solvents gave a residue, which was purified by column chromatography, eluting with EtOAc to afford a solid: 0.21 g; 40% yield; mp 37−39 °C. ^{1}H NMR ($CDCl_3$): δ 2.0 (br s, 1, NH, exchangeable with D_2O), 2.75−3.12 (m, 4, CH_2NCH_2), 3.47−4.09 (m, 5, cycle), 4.12 (t, 2, CH_2OAr), 4.57 (dd, 1, cycle), 6.87−7.39 (m, 10, ArH). MS (ESI): m/z = 314.1 ($M + H^+$). The free base was transformed into the hydrochloride salt and crystallized from 2-PrOH: mp 216−217 °C. Anal. ($C_{19}H_{23}NO_3 \cdot HCl \cdot 0.5H_2O$) C, H, N.

***cis*-2-Phenoxy-*N*-((5-phenyl-1,4-dioxan-2-yl)methyl)ethanamine (4b).** This was obtained following the procedure described for **4a** starting from **39b**: 33% yield. ^{1}H NMR ($CDCl_3$): δ 1.98 (br s, 1, NH, exchangeable with D_2O), 2.80−3.20 (m, 4, CH_2NCH_2), 3.23−4.0 (m, 5, cycle), 4.13 (t, 2, CH_2OAr), 4.67 (dd, 1, cycle), 6.86−7.52 (m, 10, ArH). MS (ESI): m/z = 314.1 ($M + H^+$). The free base was transformed into the oxalate salt and crystallized from MeOH: mp 226−228 °C. Anal. ($C_{19}H_{23}NO_3 \cdot H_2C_2O_4$) C, H, N.

***trans*-2-(2,6-Dimethoxyphenoxy)-*N*-((5-phenyl-1,4-dioxan-2-yl)-methyl)ethanamine (6a).** This was obtained following the procedure described for **4a** starting from **39a** and 2-(2,6-dimethoxyphenoxy)-ethanamine:[25] 19% yield. ^{1}H NMR ($CDCl_3$): δ 2.05 (br s, 1, NH, exchangeable with D_2O), 2.79−3.0 (m, 4, CH_2NCH_2), 3.47−4.30 (m, 7, CH_2OAr and cycle), 3.88 (s, 6, OCH_3), 4.60 (dd, 1, cycle), 6.55−7.43 (m, 8, ArH). MS (ESI): m/z = 374.1 ($M + H^+$). The free base was transformed into the oxalate salt and crystallized from 2-PrOH: mp 167−169 °C. Anal. ($C_{21}H_{27}NO_5 \cdot H_2C_2O_4 \cdot 0.5H_2O$) C, H, N.

***N*-((5,5-Diphenyl-1,4-dioxan-2-yl)methyl)-2-phenoxyethanamine (10).** This was obtained following the procedure described for **4a** starting from **40**: 36% yield. ^{1}H NMR ($CDCl_3$): δ 1.98 (br s, 1, NH, exchangeable with D_2O), 2.62−3.08 (m, 4, CH_2NCH_2), 3.44 (dd, 1, cycle), 3.66−4.01 (m, 3, cycle), 4.08 (t, 2, CH_2OAr), 4.67 (d, 1, cycle), 6.88−7.58 (m, 15, ArH). MS (ESI): m/z = 390.2 ($M + H^+$). The free base was transformed into the oxalate salt and crystallized from EtOH: mp 223−225 °C. Anal. ($C_{25}H_{27}NO_3 \cdot H_2C_2O_4$) C, H, N.

***N*-((5,5-Diphenyl-1,4-dioxan-2-yl)methyl)-2-(2-methoxyphenoxy)-ethanamine (11).** This was obtained following the procedure described for **4a** starting from **40** and 2-(2-methoxyphenoxy)ethanamine:[18] 45% yield; mp 102−103 °C. ^{1}H NMR ($CDCl_3$): δ 2.22 (br s, 1, NH, exchangeable with D_2O), 2.62−3.08 (m, 4, CH_2NCH_2), 3.39 (dd, 1, cycle), 3.68−4.01 (m, 3, cycle), 3.86 (s, 3, OCH_3), 4.11 (t, 2, CH_2OAr), 4.62 (d, 1, CH_2O), 6.84−7.56 (m, 14, ArH). MS (ESI): m/z = 420.2 ($M + H^+$). The free base was transformed into the oxalate salt and crystallized from MeOH: mp 214−216 °C. Anal. ($C_{26}H_{29}NO_4 \cdot H_2C_2O_4$) C, H, N.

***N*-((6,6-Diphenyl-1,4-dioxan-2-yl)methyl)-2-phenoxyethanamine (13).** This was obtained following the procedure described for **4a** starting from **41**: 55% yield. ^{1}H NMR ($CDCl_3$): δ 1.62 (br s, 1, NH, exchangeable with D_2O), 2.70−3.10 (m, 4, CH_2NCH_2), 3.50−4.20 (m, 6, CH_2OAr and cycle), 4.62 (d, 1, cycle), 6.86−7.60 (m, 15, ArH). MS (ESI): m/z = 390.2 ($M + H^+$). The free base was transformed into the oxalate salt and crystallized from EtOH: mp 154−156 °C. Anal. ($C_{25}H_{27}NO_3 \cdot H_2C_2O_4 \cdot 0.25H_2O$) C, H, N.

***N*-((6,6-Diphenyl-1,4-dioxan-2-yl)methyl)-2-(2-methoxyphenoxy)-ethanamine (14).** This was obtained following the procedure described for **4a** starting from **41** and 2-(2-methoxyphenoxy)-ethanamine:[18] 45% yield. ^{1}H NMR ($CDCl_3$): δ 2.38 (br s, 1, NH, exchangeable with D_2O), 2.66−3.12 (m, 4, CH_2NCH_2), 3.51−4.19 (m, 4, cycle), 3.73 (s, 3, OCH_3), 4.13 (t, 2, CH_2OAr), 4.63 (d, 1, cycle), 6.63−7.60 (m, 14, ArH). MS (ESI): m/z = 420.2 ($M + H^+$). The free base was transformed into the oxalate salt and crystallized from 2-PrOH: mp 112−113 °C. Anal. ($C_{26}H_{29}NO_4 \cdot H_2C_2O_4 \cdot 0.5H_2O$) C, H, N.

***trans*-(5-Phenyl-1,4-dioxan-2-yl)methanol (20a).** A suspension of Ag_2O (2.12 g, 9.2 mmol) in H_2O (7 mL) was added to a solution of **39a** (2.8 g, 9.2 mmol) in 1,4-dioxane (30 mL), and the mixture was refluxed for 48 h. After filtration and evaporation of the solvent, the residue was purified by column chromatography, eluting with cyclohexane/EtOAc (6:4) to afford a solid: 75% yield; mp 79−81 °C. The ^{1}H NMR results were similar to the results of the same product obtained from **18**.

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Supporting Information Available: Experimental details for in vitro assays and molecular modeling; elemental analysis results for compounds **4**−**15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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