# Structure–Activity Relationships in 1,4-Benzodioxan-Related Compounds. 9.<sup>1</sup> From 1,4-Benzodioxane to 1,4-Dioxane Ring as a Promising Template of Novel $\alpha_{1D}$ -Adrenoreceptor Antagonists, 5-HT<sub>1A</sub> Full Agonists, and Cytotoxic Agents<sup>†</sup>

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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  $\alpha_1$ -adrenoreceptor ( $\alpha_1$ -AR) subtypes and 5-HT<sub>1A</sub> receptors, expressed in Chinese hamster ovary and HeLa cell membranes, respectively, and by functional experiments in isolated rat vas deferens ( $\alpha_{1A}$ ), spleen ( $\alpha_{1B}$ ), and aorta ( $\alpha_{1D}$ ). 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  $\alpha_{1D}$ -AR antagonists (compound 14), potential anticancer agents (compound 13), and full 5-HT<sub>1A</sub> receptor agonists (compound 15). In particular, compound 15 may represent a novel lead in the development of highly potent 5-HT<sub>1A</sub> 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  $\alpha_1$ -,  $\alpha_2$ -, and  $\beta$ -adrenoreceptors ( $\alpha_1$ -,  $\alpha_2$ -, and  $\beta$ -ARs<sup>*a*</sup>).<sup>2</sup> Each of these classes is further subdivided into three subtypes, resulting in nine pharmacologically distinct ARs ( $\alpha_{1a/A}$ ,  $\alpha_{1b/B}$ ,  $\alpha_{1d/D}$ ;  $\alpha_{2a/A}$ ,  $\alpha_{2b/B}, \alpha_{2c/C}; \beta_1, \beta_2, \beta_3$ , 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,  $\alpha_{1L}^{3}$ and  $\beta_{4.4}$  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  $\alpha_1$ -AR subtype has a distinct pharmacology and shows discrete tissue distribution.<sup>5</sup>  $\alpha_{1A}$ - and  $\alpha_{1B}$ -AR subtypes play an important role in cardiac development and/or function as well as in blood pressure via vasoconstriction,<sup>6</sup> while the  $\alpha_{1A}$  subtype, dominant in the prostate, bladder neck, and urethra, contributes to the dynamic (phasic) component of increased bladder outlet resistance<sup>7</sup> and together with the  $\alpha_{1D}$  subtype, located in the bladder

\* Corresponding author. Phone: +390737402237. Fax: +390737637345. E-mail: wilma.quaglia@unicam.it. Chart 1. Chemical Structures of WB 4101 (1), Phendioxan (2), and Compound 3



or the spinal cord, mediates lower urinary tract symptoms (LUTS) caused by benign prostatic hyperplasia (BPH).<sup>8</sup> Owing to these effects,  $\alpha_1$ -antagonists were initially developed for the treatment of hypertension and subsequently for symptomatic BPH. At present, while the use of  $\alpha_1$ -antagonists in hypertension is declining,<sup>9</sup>  $\alpha_1$ -antagonists, in particular those selective for  $\alpha_{1A}$ - and/or  $\alpha_{1A}$ -  $+ \alpha_{1D}$ -AR subtypes with respect to the  $\alpha_{1B}$ -AR subtype, are the first-line pharmacotherapeutic approach to BPH,<sup>10</sup> as they are useful for the prompt and effective relief of LUTS, avoiding cardiovascular side effects such as orthostatic hypotension and syncope.<sup>11</sup>

Our research group has long been involved in designing new  $\alpha_1$ -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  $\alpha_1$ -AR subtypes.<sup>12</sup> 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

<sup>&</sup>lt;sup>†</sup> This article is dedicated to Dr. Francesco Gentili.

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<sup>&</sup>lt;sup>*a*</sup> 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.

Chart 2. Chemical Structures of Compounds 4–15



conformationally constrained 1,4-dioxane ring. This investigation was also prompted by our recent study in which the 1,4dioxane 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)<sup>14,15</sup> (Chart 1) or in position 4 of its methylene bioisostere (compound 3)<sup>16</sup> (Chart 1) induced a significant modulation of  $\alpha_1$ -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<sup>17</sup> produced a significant  $\alpha_{1a}$ -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  $\alpha_{1D}$ -AR subtype.<sup>18</sup> These results prompted the design of the 5- or 6-diphenyl derivatives 10-15. In addition, it is well-known that the 5-HT<sub>1A</sub> serotoninergic receptor exhibits a high degree of homology to  $\alpha_1$ -ARs<sup>19</sup> and benzodioxane derivatives,<sup>20</sup> and in particular, **1** and related compounds<sup>21</sup> are effective ligands for the 5-HT<sub>1A</sub> receptor. Therefore, the synthesis of compounds 4-15 (Chart 2) allowed us to investigate the possibility that the increased flexibility of the 1,4dioxane moiety might produce a better or more selective interaction with the 5-HT<sub>1A</sub> receptor versus the  $\alpha_1$ -AR system.

The biological profiles of the novel compounds were assessed using binding assays at human cloned  $\alpha_1$ -adrenoreceptor subtypes and 5-HT<sub>1A</sub> receptors, expressed in Chinese hamster ovary and HeLa cell membranes, respectively, and by functional experiments in isolated rat vas deferens ( $\alpha_{1A}$ ), spleen ( $\alpha_{1B}$ ), and aorta ( $\alpha_{1D}$ ). Moreover, following our recent observation that  $\alpha_{1D}$ - and  $\alpha_{1B}$ -ARs are expressed in PC-3 prostate cancer cells and are involved in the modulation of apoptosis and cell proliferation,<sup>12</sup> 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<sup>22</sup> with allyl alcohol in acidic or basic conditions (17 and 28, respectively) or as previously described in the literature<sup>23,24</sup> (16 and 27), afforded compounds 18, 19, 29, and 30, respectively. Treatment with (1S)-(+)-10-camphorsulfonic acid [(1S)-(+)-10-CSA] in CH<sub>2</sub>Cl<sub>2</sub> 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,<sup>18</sup> or 2-(2,6-dimethoxyphenoxy)ethanamine,<sup>25</sup> in the presence of Et<sub>3</sub>N and EtOCOCI 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 <sup>1</sup>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.<sup>26</sup> In the <sup>1</sup>H NMR spectrum of diastereoisomer 22a, the proton in position 5 at  $\delta$ 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 <sup>1</sup>H NMR spectrum of diastereoisomer **22b**, the situation of the proton in position 5 at  $\delta$  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  $\delta$  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 <sup>1</sup>H NMR spectrum of isomer **33b** the proton in position 6 at  $\delta$  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  $\delta$  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 <sup>1</sup>H NMR spectrum of diastereoisomer **33a**, the situation of the proton in position 6 at  $\delta$  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  $\delta$  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<sup>a</sup>



<sup>*a*</sup> Reagents: (a) HClO<sub>4</sub>, allyl alchool; (b) Na, allyl alchool; (c) *m*-CPBA/CH<sub>2</sub>Cl<sub>2</sub>; (d) (1*S*)-(+)-10-CSA/CH<sub>2</sub>Cl<sub>2</sub>; (e) KMnO<sub>4</sub>/1 N KOH; (f) Et<sub>3</sub>N, EtOCOCl, 2-phenoxyethanamine, or 2-(2-methoxyphenoxy)ethanamine or 2-(2,6-dimethoxyphenoxy)ethanamine/CHCl<sub>3</sub>; (g) BH<sub>3</sub>·MeSMe/THF.

tively. The amination of the iodide derivatives with the suitable amines, 2-phenoxyethanamine, 2-(2-methoxyphenoxy)ethanamine,<sup>18</sup> or 2-(2,6-dimethoxyphenoxy)ethanamine,<sup>25</sup> 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<sub>2</sub>O to afford the corresponding alcohol, whose <sup>1</sup>H 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. [<sup>3</sup>H]Prazosin was used to label cloned human  $\alpha_1$ -ARs expressed in CHO cells.<sup>27</sup> Furthermore, [<sup>3</sup>H]8-OH-DPAT was used to label cloned human 5-HT<sub>1A</sub> receptors expressed in HeLa cells.<sup>28,29</sup>

**Functional Studies.** The pharmacological profiles of compounds **4**–**15** were further determined at  $\alpha_1$ -ARs on different isolated tissues using **1** and BMY-7378 as reference compounds.  $\alpha_1$ -AR subtypes blocking activity was assessed by antagonism of (–)-noradrenaline-induced contraction of rat prostatic vas deferens ( $\alpha_{1A}$ )<sup>30</sup> or thoracic aorta ( $\alpha_{1D}$ )<sup>31</sup> and by antagonism of (–)-phenylephrine-induced contraction of rat spleen ( $\alpha_{1B}$ ).<sup>32</sup> Furthermore, the agonist efficacy of compounds **5b**, **8b**, and **13–15** toward the 5-HT<sub>1A</sub> receptor was assessed by determining the induced stimulation of [<sup>35</sup>S]GTP $\gamma$ S binding in cell membranes from HeLa cells transfected with human cloned 5-HT<sub>1A</sub> receptor<sup>33</sup> 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-quinazoliny1)-4-(1,4-benzo-dioxan-2-ylcarbony1)piperazine (doxazosin)<sup>34</sup> as a comparison, was carried out using the sulforhodamine B (SRB) assay according to the National Cancer Institute protocol.<sup>35</sup> The

#### Scheme 2<sup>*a*</sup>



<sup>*a*</sup> Reagents: (a) Hg(Ac)<sub>2</sub>/AcOH, H<sub>2</sub>O; (b) KI, I<sub>2</sub>/CHCl<sub>3</sub>; (c) 2-phenoxyethanamine or 2-(2-methoxyphenoxy)ethanamine or 2-(2,6-dimethoxyphenoxy)-ethanamine/CH<sub>3</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>2</sub>OH,  $\Delta$ ; (d) Ag<sub>2</sub>O/1,4-dioxane, H<sub>2</sub>O.

antitumor activity was estimated on the basis of the measurements of three parameters: GI<sub>50</sub>, 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<sub>50</sub>, 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<sub>50</sub> concentration, was evaluated by annexin V-FITC binding cytofluorimetric analysis.<sup>36</sup>

# **Results and Discussion**

An analysis of the results reported in Table 1 revealed that all the compounds showed affinity values at  $\alpha_1$ -ARs that were significantly lower than those of **1**, with the exception of compound **14** at  $\alpha_{1D}$  subtype. All the modifications performed were detrimental to  $\alpha_{1b}$  subtype affinity and especially to  $\alpha_{1a}$ -AR affinity, where all compounds showed approximately 100to 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 10fold higher than that of trans **5a** at  $\alpha_{1d}$ -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 **Table 1.** Affinity Constants, Expressed as  $pK_i$ , of Compounds 4–15, WB 4101, BMY-7378, and 8-OH-DPAT for Human Recombinant  $\alpha_1$ -AR Subtypes and 5-HT<sub>1A</sub> Receptor<sup>*a*</sup>



				$pK_i$ , human cloned receptors				
compd	R	$R_1$	$R_2$	$\alpha_{1a}$	$\alpha_{1b}$	$\alpha_{1d}$	5-HT <sub>1A</sub>	
4a (trans)	5-C <sub>6</sub> H <sub>5</sub>	Н	Н	6.27	<6	<6	6.83	
<b>4b</b> (cis)	5-C <sub>6</sub> H <sub>5</sub>	Н	Н	<6	<6	6.45	7.59	
5a (trans)	5-C <sub>6</sub> H <sub>5</sub>	$OCH_3$	Н	6.80	6.55	7.01	7.41	
<b>5b</b> (cis)	$5-C_6H_5$	$OCH_3$	Н	6.36	6.58	7.79	8.46	
6a (trans)	5-C <sub>6</sub> H <sub>5</sub>	$OCH_3$	$OCH_3$	6.29	<6	<6	6.63	
<b>6b</b> (cis)	5-C <sub>6</sub> H <sub>5</sub>	$OCH_3$	OCH <sub>3</sub>	<6	<6	<6	6.59	
7a (trans)	$6-C_6H_5$	Н	Н	6.39	<6	6.81	7.28	
<b>7b</b> (cis)	6-C <sub>6</sub> H <sub>5</sub>	Н	Н	<6	<6	7.14	7.27	
8a (trans)	6-C <sub>6</sub> H <sub>5</sub>	$OCH_3$	Н	7.06	6.52	7.50	8.22	
<b>8b</b> (cis)	6-C <sub>6</sub> H <sub>5</sub>	$OCH_3$	Н	6.70	6.57	7.36	8.38	
9a (trans)	$6-C_6H_5$	$OCH_3$	$OCH_3$	<6	<6	<6	6.38	
<b>9b</b> (cis)	$6-C_6H_5$	$OCH_3$	$OCH_3$	6.33	<6	<6	<6	
10	5,5-(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub>	Н	Н	6.65	6.85	6.90	7.43	
11	$5,5-(C_6H_5)_2$	$OCH_3$	Н	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	$6, 6 - (C_6H_5)_2$	Н	Н	6.77	6.92	8.44	9.23	
14	6,6-(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub>	$OCH_3$	Н	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	

<sup>*a*</sup> Equilibrium dissociation constants ( $K_i$ ) were derived from IC<sub>50</sub> values using the Cheng–Prusoff equation.<sup>50</sup> The affinity estimates were derived from displacement of [<sup>3</sup>H]prazosin and [<sup>3</sup>H]-8-hydroxy-2-(di-*n*-propylamino)tetralin binding for  $\alpha_1$ -ARs and 5-HT<sub>1A</sub> receptor, respectively. Each experiment was performed in triplicate.  $K_i$  values were from two to three experiments, which agreed within  $\pm 20\%$ .

13–15 showing affinities significantly higher than the corresponding monosubstituted compounds. Such an increase was **Table 2.** Antagonist Affinities, Expressed as  $pK_b$  Values,<sup>*a*</sup> of Compounds **4–15**, WB 4101, and BMY-7378 at  $\alpha_1$ -ARs on Isolated Rat Vas Deferens ( $\alpha_{1A}$ ), Spleen ( $\alpha_{1B}$ ), and Thoracic Aorta ( $\alpha_{1D}$ ) and Agonist Efficacy, Expressed as  $pD_2$ ,<sup>*b*</sup> of Compounds **5b**, **8b**, **13–15** on 5-HT<sub>1A</sub> Receptor in Comparison to 8-OH-DPAT, 5-CT, and 5-HT<sup>*c*</sup>



					-				
					pKb			binding [ <sup>35</sup> S]GTP	
compd	R	$R_1$	$R_2$	$\alpha_{1A}$	$\alpha_{1B}$	$\alpha_{1D}$	5-HT <sub>1A</sub> pD <sub>2</sub>	% max	
4a (trans)	5-C <sub>6</sub> H <sub>5</sub>	Н	Н	$7.0 \pm 0.07$	$6.97\pm0.13$	$6.56\pm0.16$			
<b>4b</b> (cis)	$5-C_6H_5$	Н	Н	$6.89 \pm 0.08$	$6.68\pm0.06$	$7.05\pm0.07$			
5a (trans)	5-C <sub>6</sub> H <sub>5</sub>	OCH <sub>3</sub>	Н	$7.10 \pm 0.12$	$7.44 \pm 0.09$	$7.48 \pm 0.16$			
<b>5b</b> (cis)	5-C <sub>6</sub> H <sub>5</sub>	OCH <sub>3</sub>	Н	$6.47\pm0.09$	$6.89\pm0.03$	$6.84 \pm 0.16$	7.88	85.5	
6a (trans)	$5-C_6H_5$	OCH <sub>3</sub>	OCH <sub>3</sub>	$7.21 \pm 0.11$	$7.02 \pm 0.10$	$7.26\pm0.09$			
<b>6b</b> (cis)	5-C <sub>6</sub> H <sub>5</sub>	OCH <sub>3</sub>	OCH <sub>3</sub>	$5.96\pm0.10$	$6.70\pm0.02$	$6.08\pm0.06$			
7a (trans)	6-C <sub>6</sub> H <sub>5</sub>	Η	Н	$7.21 \pm 0.11$	$6.88 \pm 0.06$	$6.38\pm0.20$			
<b>7b</b> (cis)	6-C <sub>6</sub> H <sub>5</sub>	Η	Н	$6.72\pm0.06$	$7.12 \pm 0.11$	$6.77\pm0.16$			
8a (trans)	6-C <sub>6</sub> H <sub>5</sub>	OCH <sub>3</sub>	Н	$7.22\pm0.09$	$7.96\pm0.08$	$7.83\pm0.04$			
<b>8b</b> (cis)	6-C <sub>6</sub> H <sub>5</sub>	OCH <sub>3</sub>	Н	$6.57\pm0.01$	$7.40\pm0.07$	$7.20\pm0.08$	7.83	78.1	
9a (trans)	6-C <sub>6</sub> H <sub>5</sub>	OCH <sub>3</sub>	OCH <sub>3</sub>	$5.80\pm0.04$	$5.75\pm0.07$	$7.11\pm0.02$			
<b>9b</b> (cis)	6-C <sub>6</sub> H <sub>5</sub>	$OCH_3$	$OCH_3$	$6.42\pm0.02$	$5.84 \pm 0.07$	$6.55\pm0.06$			
10	$5,5-(C_6H_5)_2$	Η	Н	$6.15 \pm 0.13$	$6.28\pm0.12$	$7.19\pm0.17$			
11	5,5-(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub>	OCH <sub>3</sub>	Н	$6.37\pm0.07$	$6.81\pm0.04$	$7.71 \pm 0.11$			
12	5,5-(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub>	OCH <sub>3</sub>	OCH <sub>3</sub>	$6.08\pm0.05$	$5.74 \pm 0.15$	$7.38\pm0.04$			
13	6,6-(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub>	Η	Н	$6.93\pm0.04$	$7.84 \pm 0.07$	$7.60 \pm 0.12$	9.11	77.1	
14	6,6-(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub>	$OCH_3$	Н	$6.65 \pm 0.14$	$6.86\pm0.06$	$8.32\pm0.17$	9.40	81.5	
15	6,6-(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub>	OCH <sub>3</sub>	OCH <sub>3</sub>	$6.71\pm0.01$	$6.24 \pm 0.13$	$7.22 \pm 0.07$	8.28	106.3	
WB 4101 (1)				$9.51\pm0.06$	$8.16\pm0.09$	$8.80 \pm 0.12$			
BMY-7378				$7.01 \pm 0.08$	$7.48 \pm 0.09$	$8.40\pm0.09$	9.27	26	
8-OH-DPAT							7.60	100	
5-HT							7.30	100	
5-CT							8.45	96	

 ${}^{a}$  pK<sub>b</sub> values were calculated according to van Rossum<sup>51</sup> in the range 0.01–10  $\mu$ M. Each concentration [B] of antagonist was tested four times.  ${}^{b}$  pD<sub>2</sub> values are the negative logarithm of the agonist concentration required to obtain 50% of the maximal stimulation of [ ${}^{35}$ S]GTP $\gamma$ S 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  $\alpha_{1d}$  subtype. In particular, compound 14 displayed the highest affinity for  $\alpha_{1d}$ -AR subtype with a p $K_i$  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  $\alpha_{1a}$  and  $\alpha_{1b}$  subtypes (p $K_i$  of 7.56 and 7.25, respectively), indicating an unfavorable binding to these subtypes. Therefore, favorable  $\alpha_{1d}$  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  $\alpha_1$ -ARs with pK<sub>b</sub> values significantly lower than those of 1, with the exception of compounds 8a and **13** at  $\alpha_{1B}$  and compound **14** at  $\alpha_{1D}$  subtype. The pK<sub>b</sub> 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.<sup>18,37,38</sup> 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  $\alpha$ -ARs, with the exception of trans compound **9a**, which had a higher  $pK_b$ only at  $\alpha_{1D}$  subtype, a lower p $K_b$  at  $\alpha_{1A}$ , and a similar p $K_b$  at  $\alpha_{1B}$  with respect to its corresponding cis diastereoisomer, showing good  $\alpha_{1D}$  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  $\alpha_{1D}$ -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  $\alpha_{1D}$ -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<sub>b</sub> values at  $\alpha_{1A}$  and  $\alpha_{1B}$  subtypes, it proved to be even slightly more selective than BMY-7378 for  $\alpha_{1D}$  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  $\alpha_1$ -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<sup>15,39</sup> 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.

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<sub>1A</sub> 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<sub>1A</sub> 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<sub>1A</sub> >  $\alpha_{1d}$  >  $\alpha_{1a}$  >  $\alpha_{1b}$ ) 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  $\alpha_{1d}$  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  $\alpha_1$ -AR subtype affinity support such an assessment. In fact, it is known that the two methoxy groups at positions 2



**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.

and 6 of the phenoxy unit confer optimum affinity in prototype 1,<sup>40</sup> while in the novel series of compounds only one methoxy group confers the highest affinity at all the  $\alpha_1$ -ARs. Similar effects on the affinity at  $\alpha_1$ -ARs were instead obtained by the same chemical modification on **14** and BMY-7378. In fact, analogous to what occurred for BMY-7378,<sup>41</sup> removal of the methoxy group of **14**, obtaining **13**, did not alter the  $\alpha_1$ -AR profile.

A few compounds (5b, 8b, and 13-15), selected on the basis of the highest affinity shown at the 5-HT<sub>1A</sub> receptor, were examined in the  $[^{35}S]GTP\gamma S$  binding at the human cloned 5-HT<sub>1A</sub> receptor, and their  $pD_2$  values are reported in Table 2, along with those of the full 5-HT<sub>1A</sub> 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<sub>1A</sub> toward the  $\alpha_{1A}$ -,  $\alpha_{1B}$ -, and  $\alpha_{1D}$ -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<sub>1A</sub> agonists significantly selective over  $\alpha$ -ARs and structurally unrelated to 5-CT.

With regard to the cytotoxic assays, only the diphenylsubstituted 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<sub>50</sub> =  $1.0 \pm 0.09 \ \mu$ M; TGI =  $3.9 \pm 0.09 \ \mu$ M).

Compound 13 also showed the highest cytotoxic effect (LC<sub>50</sub> =  $6.2 \pm 0.8 \mu$ M), which was significantly higher than that of

Table 3. Cytotoxic Activity of Compounds 4–15 and WB 4101 in Comparison with Doxazosin<sup>a</sup>



<sup>*a*</sup> 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.<sup>35</sup> GI<sub>50</sub> represents growth inhibition and is the drug concentration ( $\mu$ M) required to inhibit 50% net of cell growth. Total growth inhibition (TGI) represents the drug concentration ( $\mu$ M) required to inhibit 100% of cell growth. LC<sub>50</sub> 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). <sup>*b*</sup> 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<sub>50</sub> > 200  $\mu$ M) and doxazosin (LC<sub>50</sub> = 75.8 ± 3.6  $\mu$ M). 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,<sup>42</sup> the effect produced by **5b**, **8b**, and **13–15**, endowed with 5-HT<sub>1A</sub> partial or full agonist activities, was also evaluated in the presence of the 5-HT<sub>1A</sub> antagonist (*S*)-*N-tert*-butyl-3-(4-(2-methoxyphenyl)piperazin-1yl)-2-phenylpropanamide [(*S*)-WAY 100135], which has been reported to have no significant effect on PC-3 cell proliferation.<sup>42</sup> 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<sub>1A</sub> 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.<sup>36</sup> 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.<sup>43</sup> 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  $\alpha_{1D}$ -AR antagonists (compound 14), potential anticancer agents (compound 13), or full 5-HT<sub>1A</sub> receptor agonists (compound 15). The behavior of compound 15 is particularly interesting because the 5-HT<sub>1A</sub> receptor is involved in psychiatric disorders, such as anxiety and depression,<sup>44,45</sup> and 5-HT<sub>1A</sub> agonists may be useful as antidepressants<sup>46,47</sup> and neuropro-

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

To study these aspects in detail, future efforts will be devoted to identifying further structural requirements for selective  $\alpha_1$ -AR and 5-HT<sub>1A</sub> receptor binding sites recognition. In particular, since the enantiomers of 1 have different affinities for  $\alpha_1$ adrenergic and 5-HT<sub>1A</sub> receptors,<sup>39</sup> 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  $\pm 0.4\%$  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<sup>22</sup> (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<sub>2</sub>O (75 mL) and extracted with Et<sub>2</sub>O. The organic phase was washed with H<sub>2</sub>O and dried over Na<sub>2</sub>SO<sub>4</sub>. 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. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  1.85 (br s, 1, OH, exchangeable with D<sub>2</sub>O), 3.82 (d, 2, OCH<sub>2</sub>), 4.35 (s, 2, CH<sub>2</sub>OH), 5.13–5.47 (m, 2, C=CH<sub>2</sub>), 5.98 (m, 1, CH=C), 7.15–7.52 (m, 10, ArH).

**2-(Allyloxy)-1,1-diphenylethanol (28).** 2,2-Diphenyloxirane<sup>22</sup> (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<sub>2</sub>SO<sub>4</sub> (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. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  3.54 (br s, 1, OH, exchangeable with D<sub>2</sub>O), 4.02 (s, 2, CH<sub>2</sub>O), 4.15 (d, 2, OCH<sub>2</sub>), 5.28 (m, 2, C=CH<sub>2</sub>), 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<sub>2</sub>Cl<sub>2</sub> (120 mL). After 20 h at room temperature under stirring the reaction mixture was washed with 10% Na<sub>2</sub>SO<sub>3</sub>, 5% Na<sub>2</sub>CO<sub>3</sub>, and H<sub>2</sub>O. Removal of dried solvents afforded a mixture of the two diastereoisomers as an oil: 2.77 g; 85% yield. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  2.42 (br s, 2, OH, exchangeable with D<sub>2</sub>O), 2.47-2.85 (four dd, 4, CH<sub>2</sub>O cycle), 3.17 (m, 2, CHO cycle), 3.25-3.80 (m, 8, OCH<sub>2</sub> and CH<sub>2</sub>OH), 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. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  1.62 (br s, 1, OH, exchangeable with D<sub>2</sub>O), 2.90 (m, 2, CH<sub>2</sub>O cycle), 3.24 (m, 1, CHO cycle), 3.43 and 3.64 (two dd, 2, OCH<sub>2</sub>), 4.30 (dd, 2, CH<sub>2</sub>OH), 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**<sup>24</sup> to afford an oil: 89% yield. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  2.61–2.82 (m, 4, CH<sub>2</sub>O cycle), 3.07 (br s, 2, OH, exchangeable with D<sub>2</sub>O), 3.20 (m, 2, CHO cycle), 3.42–3.90 (m, 8, CH<sub>2</sub>OCH<sub>2</sub>), 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. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  1.60 (br s, 1, OH, exchangeable with D<sub>2</sub>O), 2.55 and 2.80 (two dd, 2, CH<sub>2</sub>O cycle), 3.16 (m, 1, CHO cycle), 3.52 and 3.90 (two dd, 2, OCH<sub>2</sub>), 4.10 (dd, 2, CH<sub>2</sub>O), 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 (1S)-(+)-10-camphorsulfonic acid (3.3 g, 142.1 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1340 mL) was refluxed for 8 h. The reaction mixture was then washed with NaHCO3 saturated solution and dried over Na<sub>2</sub>SO<sub>4</sub>. 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. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  1.93 (t, 1, OH, exchangeable with  $D_2O$ ), 3.52-4.04 (m, 7, OCH<sub>2</sub> and OCH<sub>2</sub>CHCH<sub>2</sub>), 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. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  1.86 (br s, 1, OH, exchangeable with D<sub>2</sub>O), 3.67-4.15 (m, 7, OCH<sub>2</sub> and OCH<sub>2</sub>CHCH<sub>2</sub>), 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. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  1.82 (br s, 1, OH, exchangeable with D<sub>2</sub>O), 3.40–3.75 (m, 4, OCH<sub>2</sub> and CH<sub>2</sub>OH), 3.88 (m, 1, OCH), 3.79 and 4.69 (two d, 2, CH<sub>2</sub>O), 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. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  2.13 (br s, 1, OH, exchangeable with D<sub>2</sub>O), 3.38–3.98 (m, 7, CH<sub>2</sub>OCH<sub>2</sub>OCHCH<sub>2</sub>), 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. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  1.68 (br s, 1, OH, exchangeable with D<sub>2</sub>O), 3.61–4.16 (m, 7, CH<sub>2</sub>OCH<sub>2</sub>OCHCH<sub>2</sub>), 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. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  1.84 (br s, 1, OH, exchangeable with D<sub>2</sub>O), 3.53–3.83 (m, 5, OCH<sub>2</sub>CHCH<sub>2</sub>), 3.64 and 4.61 (two d, 2, CH<sub>2</sub>O), 7.20–7.58 (m, 10, ArH).

*trans*-5-Phenyl-1,4-dioxane-2-carboxylic Acid (22a). A solution of KMnO<sub>4</sub> (3.25 g, 20.6 mmol) in H<sub>2</sub>O (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<sub>2</sub>SO<sub>4</sub> and extracted with CHCl<sub>3</sub>. After evaporation of the dried solvent, the

residue was crystallized from EtOAc/petroleum ether: 0.92 g; 40% yield; mp 165–167 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  3.62 (dd J = 10.26, 11.97 Hz, 1, 6-CH<sub>2</sub>), 3.81 (dd, J = 10.69, 11.54 Hz, 1, 3-CH<sub>2</sub>), 4.07 (dd, J = 2.56, 11.97 Hz, 1, 6-CH<sub>2</sub>), 4.35 (dd, J = 3.42, 11.54 Hz, 1, 3-CH<sub>2</sub>), 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<sub>2</sub>O), 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. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  3.84 (dd J = 2.99, 11.97 Hz, 1, 6-CH<sub>2</sub>), 4.07 (dd, J = 10.26, 11.97 Hz, 1, 6-CH<sub>2</sub>), 4.11 (dd, J = 3.85, 11.97 Hz, 1, 3-CH<sub>2</sub>), 4.38 (dd, J = 1.11, 2.99 Hz, 1, 2-CH), 4.51 (dd, J = 1.11, 11.97 Hz, 1, 3-CH<sub>2</sub>), 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<sub>2</sub>O).

**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. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  3.72 (dd, 1, 3-CH<sub>2</sub>), 3.95 (d, 1, 6-CH<sub>2</sub>), 4.15 (dd, 1, 3-CH<sub>2</sub>), 4.41 (dd, 1, 2-CH), 4.66 (d, 1, 6-CH<sub>2</sub>), 6.87 (br s, 1, COOH, exchangeable with D<sub>2</sub>O), 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. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  3.55 (dd J = 9.78, 11.53 Hz, 1, 5-CH<sub>2</sub>), 3.92 (dd, J = 11.73, 3.13 Hz, 1, 5-CH<sub>2</sub>), 3.95 (dd, J = 3.91, 11.73 Hz, 1, 3-CH<sub>2</sub>), 4.36 (dd, J = 1.57, 11.73 Hz, 1, 3-CH<sub>2</sub>), 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<sub>2</sub>O).

*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. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  3.46 (dd J = 10.44, 11.90 Hz, 1, 5-CH<sub>2</sub>), 3.61 (dd, J = 10.71, 11.54 Hz, 1, 3-CH<sub>2</sub>), 3.89 (dd, J = 2.84, 11.90 Hz, 1, 5-CH<sub>2</sub>), 4.23 (dd, J = 3.20, 11.54 Hz, 1, 3-CH<sub>2</sub>), 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<sub>2</sub>O).

**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. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  3.62 (d, 1, 5-CH<sub>2</sub>), 3.68 (dd, 1, 3-CH<sub>2</sub>), 4.21 (dd, 1, 3-CH<sub>2</sub>), 4.35 (dd, 1, 2-CH), 4.61 (d, 1, 5-CH<sub>2</sub>), 7.08 (br s, 1, COOH, exchangeable with D<sub>2</sub>O), 7.27–7.54 (m, 10, ArH).

*trans-N*-(2-(2-Methoxyphenoxy)ethyl)-5-phenyl-1,4-dioxane-2carboxamide (24a). Et<sub>3</sub>N (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<sub>3</sub> (30 mL) at 0 °C. After 30 min a solution of 2-(2methoxyphenoxy)ethanamine<sup>18</sup> (0.58 g, 3.46 mmol) in CHCl<sub>3</sub> (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<sub>2</sub>SO<sub>4</sub>. Removal of the solvent gave a solid, which was crystallized from EtOAc/cyclohexane: 0.95 g; 77% yield; mp 100–102 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  3.52–3.78 (m, 4, NCH<sub>2</sub> and cycle), 3.90 (s, 3, OCH<sub>3</sub>), 4.0 (dd, 1, cycle), 4.23 (dd, 1, cycle), 4.15 (t, 2, CH<sub>2</sub>OAr), 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<sub>2</sub>O).

*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. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  3.68–4.20 (m, 8, NCH<sub>2</sub>, CH<sub>2</sub>OAr and cycle), 3.71 (s, 3, OCH<sub>3</sub>), 4.50–4.66 (two dd, 2, cycle), 6.80–7.41 (m, 9, ArH), 7.22 (br t, 1, NH, exchangeable with D<sub>2</sub>O).

*cis-N*-(2-(2,6-Dimethoxyphenoxy)ethyl)-5-phenyl-1,4-dioxane-2carboxamide (25b). This was obtained following the procedure described for 24a starting from 22b and 2-(2,6-dimethoxyphenoxy)ethanamine.<sup>25</sup> The residue was purified by column chromatography, eluting with cyclohexane/EtOAc (7:3) to afford a solid: 43% yield; mp 111–112 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  3.62 (q, 2, NCH<sub>2</sub>), 3.78-4.20 (m, 6, CH<sub>2</sub>OAr and cycle), 3.82 (s, 6, OCH<sub>3</sub>), 4.63 (two dd, 2, cycle), 6.55-7.42 (m, 8, ArH), 7.83 (br t, 1, NH, exchangeable with D<sub>2</sub>O).

*N*-(2-(2,6-Dimethoxyphenoxy)ethyl)-5,5-diphenyl-1,4-dioxane-2carboxamide (26). This was obtained following the procedure described for 24a starting from 23 and 2-(2,6-dimethoxyphenoxy)ethanamine.<sup>25</sup> The residue was purified by column chromatography, eluting with cyclohexane/EtOAc (8:2) to afford a solid: 52% yield; mp 168–170 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  3.52–4.67 (m, 7, NCH<sub>2</sub>, CH<sub>2</sub>OAr, and cycle), 3.82 (s, 6, OCH<sub>3</sub>), 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<sub>2</sub>O).

*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. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  3.60–4.35 (m, 8, NCH<sub>2</sub>, CH<sub>2</sub>OAr, 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<sub>2</sub>O).

*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. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  3.41 (m, 2, cycle), 3.70 (q, 2, NCH<sub>2</sub>), 3.88 (dd, 1, cycle), 4.05 (t, 2, CH<sub>2</sub>OAr), 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<sub>2</sub>O).

*trans-N*-(2-(2-Methoxyphenoxy)ethyl)-6-phenyl-1,4-dioxane-2carboxamide (36a). This was obtained following the procedure described for 24a starting from 33a and 2-(2-methoxyphenoxy)ethanamine.<sup>18</sup> The residue was purified by column chromatography, eluting with cyclohexane/EtOAc (7:3) to afford an oil: 57% yield. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  3.60–4.34 (m, 8, NCH<sub>2</sub>CH<sub>2</sub>OAr and cycle), 3.63 (s, 3, OCH<sub>3</sub>), 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<sub>2</sub>O).

*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.<sup>18</sup> The residue was purified by column chromatography, eluting with cyclohexane/EtOAc (7:3) to afford an oil: 60% yield. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  3.32–4.34 (m, 8, NCH<sub>2</sub>, CH<sub>2</sub>OAr, and cycle), 3.68 (s, 3, OCH<sub>3</sub>), 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<sub>2</sub>O).

*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.<sup>25</sup> The residue was purified by column chromatography, eluting with cyclohexane/EtOAc (7.5:2.5) to afford an oil: 35% yield. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  3.40–4.35 (m, 8, NCH<sub>2</sub>, CH<sub>2</sub>OAr, and cycle), 3.62 (s, 6, OCH<sub>3</sub>), 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<sub>2</sub>O).

*cis-N-*(2-(2,6-Dimethoxyphenoxy)ethyl)-6-phenyl-1,4-dioxane-2carboxamide (37b). This was obtained following the procedure described for 24a starting from 33b and 2-(2,6-dimethoxyphenoxy)ethanamine.<sup>25</sup> The residue was purified by column chromatography, eluting with cyclohexane/EtOAc (7.5:2.5) to afford an oil: 66% yield. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  3.38–4.40 (m, 8, NCH<sub>2</sub>, CH<sub>2</sub>OAr, and cycle), 3.66 (s, 6, OCH<sub>3</sub>), 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<sub>2</sub>O).

*N*-(2-(2,6-Dimethoxyphenoxy)ethyl)-6,6-diphenyl-1,4-dioxane-2carboxamide (38). This was obtained following the procedure described for 24a starting from 34 and 2-(2,6-dimethoxyphenoxy)ethanamine.<sup>25</sup> The residue was purified by column chromatography, eluting with cyclohexane/EtOAc (7.5:2.5) to afford an oil: 70% yield. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  3.51–4.26 (m, 8, NCH<sub>2</sub>, CH<sub>2</sub>OAr, and cycle), 3.77 (s, 6, OCH<sub>3</sub>), 4.62 (d, 1, cycle), 6.57–7.57 (m, 13, ArH), 7.82 (br t, 1, NH, exchangeable with D<sub>2</sub>O).

trans-2-(2-Methoxyphenoxy)-N-((5-phenyl-1,4-dioxan-2-yl)methyl)ethanamine (5a). A solution of 10 M BH<sub>3</sub>·CH<sub>3</sub>SCH<sub>3</sub> (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<sub>2</sub>O. The aqueous solution was basified with 2 N NaOH and extracted with CHCl<sub>3</sub>. Removal of dried solvents gave a residue, which was purified by column chromatography, eluting with CHCl<sub>3</sub>/EtOH (9.5:0.5) to afford an oil: 0.84 g; 92% yield. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  2.25 (br s, 1, NH, exchangeable with D<sub>2</sub>O), 2.80-3.18 (m, 4, CH<sub>2</sub>NCH<sub>2</sub>), 3.48-4.25 (m, 7, CH<sub>2</sub>OAr and cycle), 3.88 (s, 3, OCH<sub>3</sub>), 4.58 (dd, 1, cycle), 6.83–7.42 (m, 9, ArH). MS (ESI): m/z = 344.1 (M + H<sup>+</sup>). The free base was transformed into the oxalate salt and crystallized from MeOH: mp 206-207 °C. Anal. (C<sub>20</sub>H<sub>25</sub>NO<sub>4</sub>· H<sub>2</sub>C<sub>2</sub>O<sub>4</sub>) 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. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  1.68 (br s, 1, NH, exchangeable with D<sub>2</sub>O), 2.78–3.35 (m, 4, CH<sub>2</sub>NCH<sub>2</sub>), 3.72–4.24 (m, 7, CH<sub>2</sub>OAr and cycle), 3.83 (s, 3, OCH<sub>3</sub>), 4.65 (dd, 1, cycle), 6.83–7.44 (m, 9, ArH). MS (ESI): *m/z* = 344.1 (M + H<sup>+</sup>). The free base was transformed into the oxalate salt and crystallized from MeOH: mp 223–225 °C. Anal. (C<sub>20</sub>H<sub>25</sub>NO<sub>4</sub>·H<sub>2</sub>C<sub>2</sub>O<sub>4</sub>) 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. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  1.89 (br s, 1, NH, exchangeable with D<sub>2</sub>O), 2.75–3.32 (m, 4, CH<sub>2</sub>NCH<sub>2</sub>), 3.74–4.28 (m, 7, CH<sub>2</sub>OAr and cycle), 3.85 (s, 6, OCH<sub>3</sub>), 4.66 (dd, 1, cycle), 6.53–7.48 (m, 8, ArH). MS (ESI): *m/z* = 374.1 (M + H<sup>+</sup>). The free base was transformed into the oxalate salt and crystallized from EtOH: mp 198–199 °C. Anal. (C<sub>21</sub>H<sub>27</sub>NO<sub>5</sub>•H<sub>2</sub>C<sub>2</sub>O<sub>4</sub>) 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. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  1.99 (br s, 1, NH, exchangeable with D<sub>2</sub>O), 2.52–2.92 (m, 4, CH<sub>2</sub>NCH<sub>2</sub>), 3.32–4.18 (m, 7, CH<sub>2</sub>OAr and cycle), 3.81 (s, 6, OCH<sub>3</sub>), 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<sup>+</sup>). The free base was transformed into the oxalate salt and crystallized from EtOH: mp 190–191 °C. Anal. (C<sub>27</sub>H<sub>31</sub>NO<sub>5</sub>•H<sub>2</sub>C<sub>2</sub>O<sub>4</sub>) 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. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  1.90 (br s, 1, NH, exchangeable with D<sub>2</sub>O), 2.80–3.38 (m, 4, CH<sub>2</sub>NCH<sub>2</sub>), 3.66–4.20 (m, 7, CH<sub>2</sub>OAr and cycle), 4.87 (dd, 1, cycle), 6.82–7.49 (m, 10, ArH). MS (ESI): *m*/*z* = 314.1 (M + H<sup>+</sup>). The free base was transformed into the oxalate salt and crystallized from EtOH: mp 209–210 °C. Anal. (C<sub>19</sub>H<sub>23</sub>NO<sub>3</sub>•H<sub>2</sub>C<sub>2</sub>O<sub>4</sub>) 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. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  1.80 (br s, 1, NH, exchangeable with D<sub>2</sub>O), 2.68–3.08 (m, 4, CH<sub>2</sub>NCH<sub>2</sub>), 3.32–4.11 (m, 7, CH<sub>2</sub>OAr and cycle), 4.68 (dd, 1, cycle), 6.81–7.42 (m, 10, ArH). MS (ESI): *m*/*z* = 314.1 (M + H<sup>+</sup>). The free base was transformed into the oxalate salt and crystallized from MeOH: mp 212–213 °C. Anal. (C<sub>19</sub>H<sub>23</sub>NO<sub>3</sub>•H<sub>2</sub>C<sub>2</sub>O<sub>4</sub>) 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. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  2.55 (br s, 1, NH, exchangeable with D<sub>2</sub>O), 2.87–3.43 (m, 4, CH<sub>2</sub>NCH<sub>2</sub>), 3.58–4.27 (m, 7, CH<sub>2</sub>OAr and cycle), 3.68 (s, 3, OCH<sub>3</sub>), 4.87 (dd, 1, cycle), 6.81–7.48 (m, 9, ArH). MS (ESI): *m/z*  = 344.1 (M + H<sup>+</sup>). 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. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  1.93 (br s, 1, NH, exchangeable with D<sub>2</sub>O), 2.72–3.08 (m, 4, CH<sub>2</sub>NCH<sub>2</sub>), 3.32–4.18 (m, 7, CH<sub>2</sub>OAr and cycle), 3.78 (s, 3, OCH<sub>3</sub>), 4.68 (dd, 1, cycle), 6.83–7.36 (m, 9, ArH). MS (ESI): *m/z* = 344.1 (M + H<sup>+</sup>). The free base was transformed into the oxalate salt and crystallized from EtOH: mp 162–164 °C. Anal. (C<sub>20</sub>H<sub>25</sub>NO<sub>4</sub>·H<sub>2</sub>C<sub>2</sub>O<sub>4</sub>) 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. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  1.99 (br s, 1, NH, exchangeable with D<sub>2</sub>O), 2.81–3.27 (m, 4, CH<sub>2</sub>NCH<sub>2</sub>), 3.70–4.24 (m, 7, CH<sub>2</sub>OAr and cycle), 3.75 (s, 6, OCH<sub>3</sub>), 4.87 (dd, 1, cycle), 6.52–7.45 (m, 8, ArH). MS (ESI): *m/z* = 374.1 (M + H<sup>+</sup>). The free base was transformed into the oxalate salt and crystallized from EtOH: mp 150–152 °C. Anal. (C<sub>21</sub>H<sub>27</sub>NO<sub>5</sub>·H<sub>2</sub>C<sub>2</sub>O<sub>4</sub>) 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. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  2.05 (br s, 1, NH, exchangeable with D<sub>2</sub>O), 2.82–3.02 (m, 4, CH<sub>2</sub>NCH<sub>2</sub>), 3.32–4.27 (m, 7, CH<sub>2</sub>OAr and cycle), 3.72 (s, 6, OCH<sub>3</sub>), 4.72 (dd, 1, cycle), 6.50–7.41 (m, 8, ArH). MS (ESI): *m/z* = 374.1 (M + H<sup>+</sup>). The free base was transformed into the oxalate salt and crystallized from 2-PrOH: mp 183–184 °C. Anal. (C<sub>21</sub>H<sub>27</sub>NO<sub>5</sub>•H<sub>2</sub>C<sub>2</sub>O<sub>4</sub>) 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. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$ 2.02 (br s, 1, NH, exchangeable with D<sub>2</sub>O), 2.62–2.97 (m, 4, CH<sub>2</sub>NCH<sub>2</sub>), 3.50–4.20 (m, 6, CH<sub>2</sub>OAr and cycle), 3.80 (s, 6, OCH<sub>3</sub>), 4.62 (d, 1, cycle), 6.54–7.58 (m, 13, ArH). MS (ESI): *m/z* = 450.2 (M + H<sup>+</sup>). The free base was transformed into the oxalate salt and crystallized from 2-PrOH: mp 151–153 °C. Anal. (C<sub>27</sub>H<sub>31</sub>NO<sub>5</sub>·H<sub>2</sub>C<sub>2</sub>O<sub>4</sub>) 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<sub>2</sub>O (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<sub>2</sub>O (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<sub>3</sub> (16 mL). A solution of I<sub>2</sub> (4.73 g, 18.6 mmol) in CHCl<sub>3</sub> 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<sub>2</sub>SO<sub>3</sub> and 10% KI and dried over Na<sub>2</sub>SO<sub>4</sub>. 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. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  3.15 (d, 2, CH<sub>2</sub>I), 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. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  3.50–4.18 (m, 7, CH<sub>2</sub>I, 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. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  3.05 (d, 2, CH<sub>2</sub>I), 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. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  3.19 (d, 2, CH<sub>2</sub>I), 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<sub>3</sub>. 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. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  2.0 (br s, 1, NH, exchangeable with D<sub>2</sub>O), 2.75–3.12 (m, 4, CH<sub>2</sub>NCH<sub>2</sub>), 3.47–4.09 (m, 5, cycle), 4.12 (t, 2, CH<sub>2</sub>OAr), 4.57 (dd, 1, cycle), 6.87–7.39 (m, 10, ArH). MS (ESI): *m/z* = 314.1 (M + H<sup>+</sup>). The free base was transformed into the hydrochloride salt and crystallized from 2-PrOH: mp 216–217 °C. Anal. (C<sub>19</sub>H<sub>23</sub>NO<sub>3</sub>•HCl• 0.5H<sub>2</sub>O) 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. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  1.98 (br s, 1, NH, exchangeable with D<sub>2</sub>O), 2.80–3.20 (m, 4, CH<sub>2</sub>NCH<sub>2</sub>), 3.23–4.0 (m, 5, cycle), 4.13 (t, 2, CH<sub>2</sub>OAr), 4.67 (dd, 1, cycle), 6.86–7.52 (m, 10, ArH). MS (ESI): *m*/*z* = 314.1 (M + H<sup>+</sup>). The free base was transformed into the oxalate salt and crystallized from MeOH: mp 226–228 °C. Anal. (C<sub>19</sub>H<sub>23</sub>NO<sub>3</sub>•H<sub>2</sub>C<sub>2</sub>O<sub>4</sub>) 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:<sup>25</sup> 19% yield. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  2.05 (br s, 1, NH, exchangeable with D<sub>2</sub>O), 2.79–3.0 (m, 4, CH<sub>2</sub>NCH<sub>2</sub>), 3.47–4.30 (m, 7, CH<sub>2</sub>OAr and cycle), 3.88 (s, 6, OCH<sub>3</sub>), 4.60 (dd, 1, cycle), 6.55–7.43 (m, 8, ArH). MS (ESI): m/z = 374.1 (M + H<sup>+</sup>). The free base was transformed into the oxalate salt and crystallized from 2-PrOH: mp 167–169 °C. Anal. (C<sub>21</sub>H<sub>27</sub>NO<sub>5</sub>•H<sub>2</sub>C<sub>2</sub>O<sub>4</sub>•0.5H<sub>2</sub>O) 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. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  1.98 (br s, 1, NH, exchangeable with D<sub>2</sub>O), 2.62–3.08 (m, 4, CH<sub>2</sub>NCH<sub>2</sub>), 3.44 (dd, 1, cycle), 3.66–4.01 (m, 3, cycle), 4.08 (t, 2, CH<sub>2</sub>OAr), 4.67 (d, 1, cycle), 6.88–7.58 (m, 15, ArH). MS (ESI): *m/z* = 390.2 (M + H<sup>+</sup>). The free base was transformed into the oxalate salt and crystallized from EtOH: mp 223–225 °C. Anal. (C<sub>25</sub>H<sub>27</sub>NO<sub>3</sub>• H<sub>2</sub>C<sub>2</sub>O<sub>4</sub>) 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:<sup>18</sup> 45% yield; mp 102–103 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  2.22 (br s, 1, NH, exchangeable with D<sub>2</sub>O), 2.62–3.08 (m, 4, CH<sub>2</sub>NCH<sub>2</sub>), 3.39 (dd, 1, cycle), 3.68–4.01 (m, 3, cycle), 3.86 (s, 3, OCH<sub>3</sub>), 4.11 (t, 2, CH<sub>2</sub>OAr), 4.62 (d, 1, CH<sub>2</sub>O), 6.84–7.56 (m, 14, ArH). MS (ESI): m/z = 420.2 (M + H<sup>+</sup>). The free base was transformed into the oxalate salt and crystallized from MeOH: mp 214–216 °C. Anal. (C<sub>26</sub>H<sub>29</sub>NO<sub>4</sub>•H<sub>2</sub>C<sub>2</sub>O<sub>4</sub>) 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. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  1.62 (br s, 1, NH, exchangeable with D<sub>2</sub>O), 2.70–3.10 (m, 4, CH<sub>2</sub>NCH<sub>2</sub>), 3.50–4.20 (m, 6, CH<sub>2</sub>OAr and cycle), 4.62 (d, 1, cycle), 6.86–7.60 (m, 15, ArH). MS (ESI): *m/z* = 390.2 (M + H<sup>+</sup>). The free base was transformed into the oxalate salt and crystallized from EtOH: mp 154–156 °C. Anal. (C<sub>25</sub>H<sub>27</sub>NO<sub>3</sub>•H<sub>2</sub>C<sub>2</sub>O<sub>4</sub>•0.25H<sub>2</sub>O) 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:<sup>18</sup> 45% yield. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  2.38 (br s, 1, NH, exchangeable with D<sub>2</sub>O), 2.66–3.12 (m, 4, CH<sub>2</sub>NCH<sub>2</sub>), 3.51–4.19 (m, 4, cycle), 3.73 (s, 3, OCH<sub>3</sub>), 4.13 (t, 2, CH<sub>2</sub>OAr), 4.63 (d, 1, cycle), 6.63–7.60 (m, 14, ArH). MS (ESI): *m/z* = 420.2 (M + H<sup>+</sup>). The free base was transformed into the oxalate salt and crystallized from 2-PrOH: mp 112–113 °C. Anal. (C<sub>26</sub>H<sub>29</sub>NO<sub>4</sub>• H<sub>2</sub>C<sub>2</sub>O<sub>4</sub>•0.5H<sub>2</sub>O) C, H, N. *trans*-(5-Phenyl-1,4-dioxan-2-yl)methanol (20a). A suspension of Ag<sub>2</sub>O (2.12 g, 9.2 mmol) in H<sub>2</sub>O (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 <sup>1</sup>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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