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Bioorganic & Medicinal Chemistry 12 (2004) 4937–4951
Bioorganic & Medicinal Chemistry

Structure–affinity studies for a novel series of homochiral naphtho and tetrahydronaphtho analogues of α_1 antagonist WB-4101

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Received 30 April 2004; accepted 28 June 2004
Available online 31 July 2004

Abstract—A number of enantiomeric pairs of naphthodioxane, tetrahydronaphthodioxane and naphthoxy analogues of WB-4101 (**1**) were designed and synthesized in order to improve the selectivity profile of the parent compound, hopefully in favour of the α_{1a}-AR with respect to the other two α_1 subtypes and the 5-HT_{1A} receptor. The new compounds **2**–**8** and, in addition, the two enantiomers of **1** were tested in binding assays on the α_{1a}-AR, α_{1b}-AR, α_{1d}-AR, and the 5-HT_{1A} receptor. Two of them, namely the naphtho- and tetrahydronaphthodioxane derivatives (*S*)-**2** and (*S*)-**3**, showed lower, but significantly more specific α_{1a} affinity than (*S*)-**1**, while the two enantiomers of the 2-methoxy-1-naphthoxy analogue **6** maintained most of the very high α_{1a} affinity of (*S*)-**1** and its α_{1a} versus α_{1b} selectivity slightly increasing the α_{1a}/α_{1d} and $\alpha_{1a}/5HT_{1A}$ affinity ratios. The SAR data were evaluated in the light of known α_1 subtype pharmacophores and of the α_{1a}-AR binding mode of WB-4101 resultant from literature mutagenesis studies disclosing some interesting consonances with these models.
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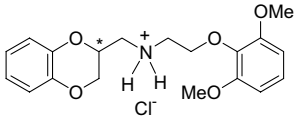
1. Introduction

To date, α_1-adrenergic receptors (α_1-ARs), which are members of the G protein-coupled receptor family, are classified into α_{1A}, α_{1B} and α_{1D} subtypes and the corresponding cloned counterparts α_{1a}, α_{1b} and α_{1d}.[1,2] The design of agents selective for each of these three receptor subtypes has become an attractive challenge for medicinal chemists due to the therapeutic potential of selective α_{1A} and α_{1D} antagonists in the treatment of some urologic disorders.[3] Indeed, relatively recent evidences indicate that α_{1A}- and α_{1D}-ARs, respectively, predominant in human prostate[4] and bladder,[3,5] play a role in lower urinary tract symptoms (LUTS), which have been previously demonstrated to be relieved by α_1 antagonists, nonsubtype-selective, such as Terazosin, Doxazosin, Tamsulosin and Alfuzosin.[6–8]

A variety of structurally unrelated compounds interacts with α_1-AR subtypes, which makes it difficult to determine the structural requisites leading to receptor subtype selectivity. Historically, the first α_1 antagonist to be identified was WB-4101 (**1**),[9] a 2-aminomethyl-1,4-benzodioxane derivative, which was later found to be slightly selective for α_{1A}- and, to a minor degree, for α_{1D}-ARs with respect to α_{1B}-AR and 5-HT_{1A} serotoninergic receptor.[7,10] Over the past decades, many investigations[11–21] have been devoted to improving both affinity and selectivity of this prototype of α_1 antagonists and our researches[22–24] have also contributed to get an insight into some determinants of its binding capacity through the study of several homochiral analogues.



1 (WB 4101)

Keywords: α_1-Antagonist; WB-4101; WB-4101 analogues; α_1-Adrenergic receptor subtypes; 5-HT_{1A} serotoninergic receptor; Binding affinity.
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doi:10.1016/j.bmc.2004.06.040

At present, ligand-based approach to design of subtype selective α_1 antagonists can exploit relatively reliable pharmacophore models,[25–27] generated from a number of different subtype selective antagonists, and be integrated with docking simulations, using the rhodopsin-based models of the AR subtypes,[28] and with the knowledge of the α_1 antagonist binding site resulting from mutagenesis studies.[29,30] These discoveries have allowed the interactions of **1** with the α_1-ARs to be modelled opening new prospects to the rational design of benzodioxane analogues with an improved pharmacological profile.

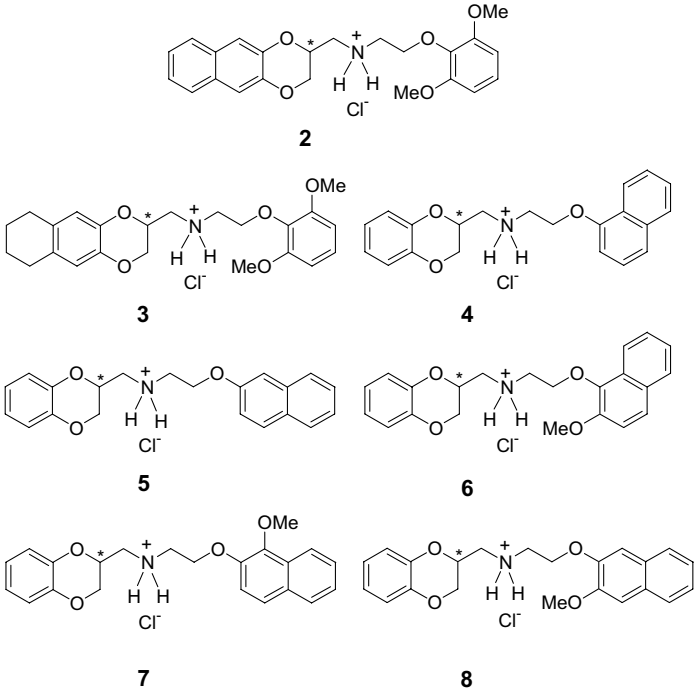
On these bases, we have recently undertaken a study on both the enantiomers of compounds structurally related to **1** aimed at identifying high affinity ligands for α_{1a}-AR with a more pronounced selectivity over the other α_1-AR subtypes and 5-HT_{1A}. The following design approaches have been done: (a) replacement of benzodioxane by a naphthodioxane or a tetrahydronaphthodioxane (compounds **2** and **3**); (b) replacement of 2,6-dimethoxyphenyl by 1- or 2-naphthyl (compounds **4** and **5**); (c) replacement of 2,6-dimethoxyphenyl by *ortho* methoxy substituted 1- or 2-naphthyl (compounds **6**–**8**). Though already described in the literature,[13] the naphthodioxane analogue **2** was included in the series considering that the reported biological data pertain to its racemate and are α_1 and α_2 functional affinities, which provide little, if any, information about binding affinities for α_1-AR subtypes. The rationale of such approaches was to increase the steric hindrance and the hydrophobicity of the benzodioxane or, alternatively, of the dimethoxyphenoxy residue of the lead compound without compromising, but rather modulating the interaction capabilities of these two regions of the ligand, which would be, respectively, involved, according to Perez mutagenesis studies, in conferring α_{1a} selectivity and high α_1 affinity.[29,30]

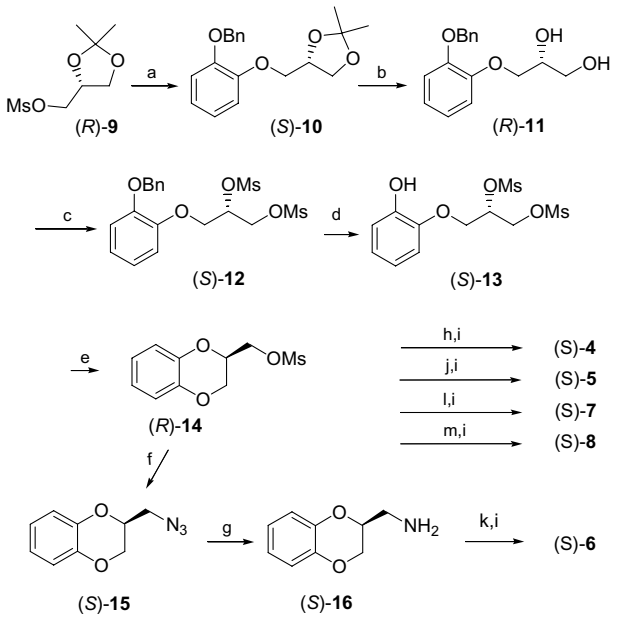
It is common knowledge that aromaticity/hydrophobicity is more important in antagonist than in agonist binding: α_1 agonists generally have one aromatic ring and hydrophilic substituents, while α_1 antagonists are larger molecules with multiple aromatic/hydrophobic moieties.

Of all compounds, including **1**, both the enantiomers have been synthesized and tested in radioreceptor binding assays. Finally, the SAR data have been analyzed applying the pharmacophore models proposed by Bremner and co-workers[27] for the α_1-AR subtypes.

2. Chemistry

The *S* isomers of compounds **4**–**8** were synthesized as outlined in Scheme 1. In detail, the reaction sequence consisted in the following steps: (a) displacement of mesylate from the mesyl ester of (*S*)-glycerol acetonide (*R*)-**9** by 2-(benzyloxy)phenoxide; (b) hydrolysis of the cyclic ketal (*S*)-**10**; (c) mesylation of the resultant *vic*-diol (*R*)-**11**; (d) removal of the benzyl from the phenoxy residue of (*S*)-**12**; (e) intramolecular nucleophilic substitution of the mesylate at C_2 of the glycerol skeleton by the *ortho*-phenoxy moiety to give 1,4-dioxane ring closure [(*R*)-**14**]. (*S*)-**4**, (*S*)-**5**, (*S*)-**7** and (*S*)-**8** were finally obtained by amination of (*R*)-**14** with 1-(2-aminoethoxy)naphthalene (**46**), 2-(2-aminoethoxy)naphthalene (**50**), 1-methoxy-2-(2-aminoethoxy)naphthalene (**37**) and 2-(2-aminoethoxy)-3-methoxynaphthalene (**42**), respectively; (*S*)-**6** was synthesized from the same intermediate (*R*)-**14**, but through three steps: (f) conversion into the azide (*S*)-**15**, (g) reduction with hydrazine to (*S*)-**16**

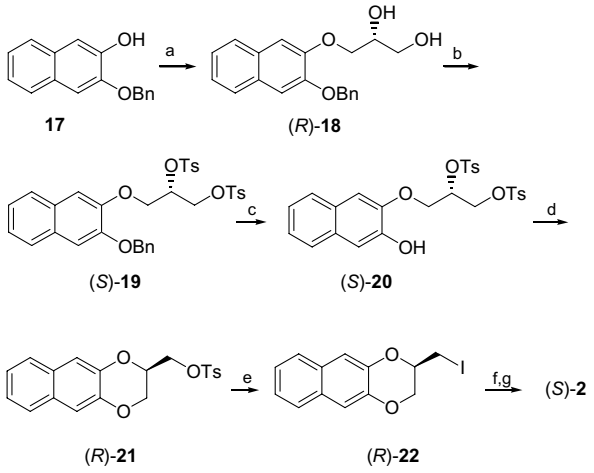




Scheme 1. Reagents and conditions: (a) 2-benzyloxyphenol, KOH, EtOH. (b) HCl. (c) MsCl, TEA. (d) H_2–Pd/C, EtOAc, MeOH. (e) K_2CO_3, acetone. (f) NaN_3, DMF, H_2O. (g) hydrazine, PdO, MeOH. (h) 1-(2-aminoethoxy)naphthalene, 2-propanol. (i) HCl, EtOH. (j) 2-(2-aminoethoxy)naphthalene, 2-propanol. (k) 1-(2-bromoethoxy)-2-methoxynaphthalene, 2-methylpropanol. (l) 1-methoxy-2-(2-aminoethoxy)naphthalene, *n*-butanol. (m) 2-(2-aminoethoxy)-3-methoxynaphthalene, 2-propanol.

and (k) N-alkylation with 1-(2-bromoethoxy)-2-methoxynaphthalene (**54**).

Compound (*S*)-**2** was prepared from (*R*)-**9** as outlined in Scheme 2. Treatment with 3-benzyloxy-2-hydroxynaphthalene (**17**) in the presence of sodium hydroxide and successive hydrolysis of the cyclic ketal afforded (*R*)-**18**, which was ditosylated and debenzylated to give (*S*)-**20**. This latter was converted into (*R*)-2-((tosyloxy)methyl)-2,3-dihydronaphtho[2,3-*b*][1,4]dioxine [(*R*)-**21**] by intramolecular nucleophilic substitution of the tosylate at C_2 of the glycerol skeleton with the naphthoxy moiety. The dihydronaphthodioxine (*R*)-**21** was transformed into iodomethyl derivative (*R*)-**22** and finally submitted to amination with 2-(2,6-dimethoxyphenoxy)ethylamine yielding (*S*)-**2**.

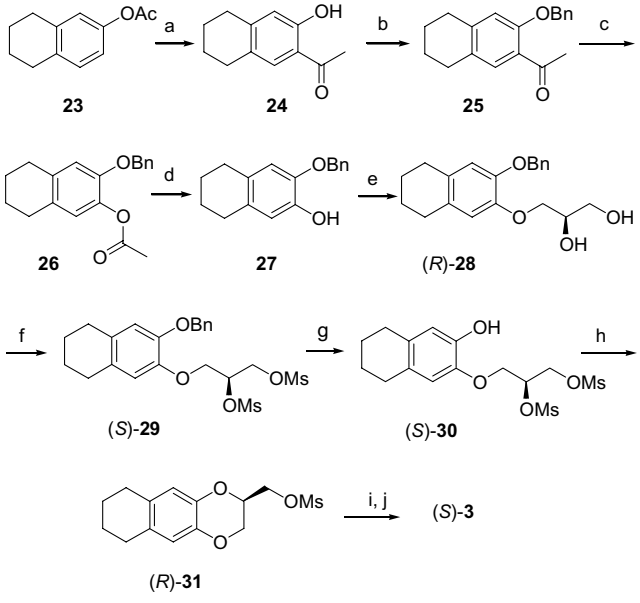


Scheme 2. Reagents and conditions: (a) (*R*)-**9**, NaOH, EtOH; HCl. (b) TsCl, Py. (c) H_2–Pd/C, EtOAc. (d) K_2CO_3, acetone. (e) NaI, acetone. (f) 2-(2,6-dimethoxyphenoxy)ethylamine, 2-propanol. (g) HCl, EtOH.

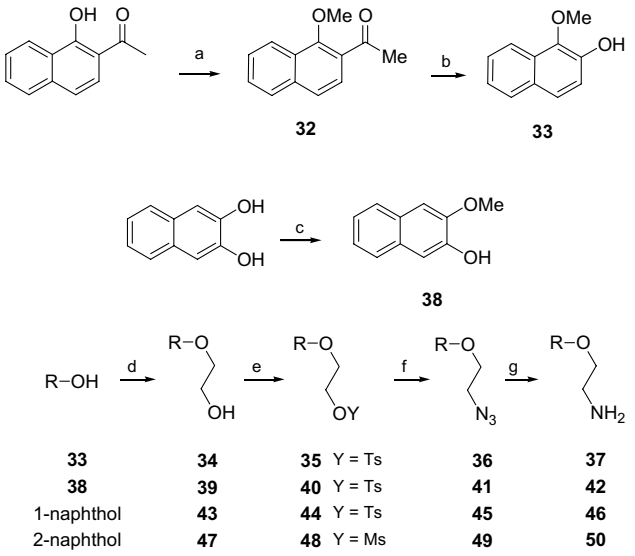
The *S* enantiomer of **3** was synthesized by the strategy illustrated in Scheme 3. Esterification of 5,6,7,8-tetrahydro-2-naphthol with acetyl chloride, followed by Fries rearrangement, afforded **24**, which was benzylated, oxidized to acetate and then submitted to methanolysis to give **27**. Displacement of mesylate substituent of (*R*)-**9** by **27** in the presence of potassium hydroxide and successive hydrolysis of the cyclic ketal led to the diol (*R*)-**28**, which was dimesylated and debenzylated to give (*S*)-**30**. This latter was transformed into (*R*)-2-((mesyloxy)methyl)-2,3,6,7,8,9-hexahydronaphtho[2,3-*b*][1,4]-dioxine [(*R*)-**31**] by intramolecular nucleophilic substitution of mesylate at C_2 of glycerol skeleton. Finally, reaction with 2-(2,6-dimethoxyphenoxy)ethylamine yielded (*S*)-**3**.

The *R* enantiomers of **2**–**8** were synthesized by the same sequence as their antipodes, but using (*S*)-**9**.

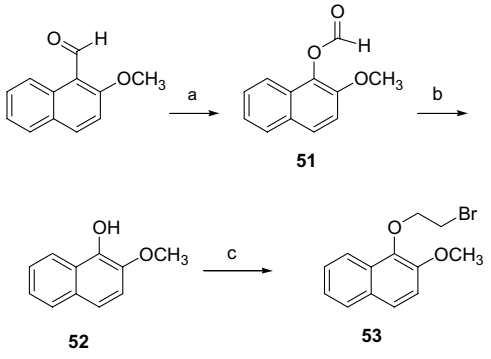
Amines **46**, **50**, **42** and **37** were prepared from 1-naphthol, 2-naphthol, 2-hydroxy-3-methoxynaphthalene (**38**) and 1-methoxy-2-hydroxynaphthalene (**33**), respectively, by treatment with ethylene carbonate and potassium carbonate, tosylation or mesylation of the resultant (2-hydroxy)ethyl derivatives **43**, **47**, **39** and **34**, successive conversion into the corresponding azides **45**, **49**, **41** and **36** and final reduction with hydrazine (Scheme 4). Compound **38** was obtained by treatment of naphthalenediol with dimethyl sulfate, while its position



Scheme 3. Reagents and conditions: (a) $AlCl_3$, 1,2-dichlorobenzene. (b) 2.5 N NaOH, TBAB, benzyl bromide, DCM. (c) *m*-CPBA, CH_2Cl_2. (d) MeOH, 2.5 N NaOH. (e) (*R*)-**9**, KOH, EtOH; MeOH, HCl. (f) MsCl, TEA, DCM. (g) H_2–Pd/C, EtOAc. (h) K_2CO_3, acetone. (i) 2-(2,6-Dimethoxyphenoxy)ethylamine, 2-propanol. (j) HCl, EtOH.



Scheme 4. Reagents and conditions: (a) MeI, KOH, DMSO. (b) *m*-CPBA, CH_2Cl_2; H_2SO_4, MeOH. (c) Me_2SO_4, Me_3COK, 2-methoxyethanol. (d) Ethylene carbonate, K_2CO_3, toluene or DMF. (e) TsCl and Py or MsCl and Et_3N. (f) NaN_3, DMF. (g) Hydrazine, PdO, MeOH.



Scheme 5. Reagents and conditions: (a) *m*-CPBA, CH_2Cl_2. (b) $LiAlH_4$, THF. (c) Dibromoethane, NaH, THF, DMSO.

isomer **33** was synthesized by O-methylation of 1-hydroxy-2-acetonaphthone, followed by the Baeyer–Villiger oxidation of the resultant 1-methoxy-2-acetonaphthone (**32**) to the corresponding naphthyl acetate, which was not isolated, but directly submitted to methanolysis (Scheme 4).

1-(2-Bromoethoxy)-2-methoxynaphthalene (**53**) was obtained by the Baeyer–Villiger oxidation of 2-methoxynaphthaldehyde to the corresponding naphthylformiate **51**, which was submitted to reduction with $LiAlH_4$ to give 2-methoxynaphthol (**52**). This latter was reacted with dibromoethane in the presence of NaH yielding **53** (Scheme 5).

3. Results and discussion

Table 1 reports the affinities, expressed as pK_i values, at the three cloned human α_1-AR subtypes and 5-HT_{1A} serotoninergic receptor, and the selectivities for the α_{1a} subtype with respect to the remaining receptors (α_{1b}, α_{1d} and 5-HT_{1A}).

Considering the binding data, it is possible to observe that almost all the WB-4101 analogues display from moderate to high affinities, but lower than the *S* isomer of the lead compound, which exhibits about nanomolar affinity towards the four different receptors. Only the α_{1a} and α_{1b} affinities (p$K_i\alpha_{1a}$ 8.80 and p$K_i\alpha_{1b}$ 7.80) of (*S*)-**6** approximate those of (*S*)-**1** (p$K_i\alpha_{1a}$ 9.39 and p$K_i\alpha_{1b}$ 8.24). As a consequence of the generalized affinity decrease, the eudismic indexes are relatively small, rarely exceeding the unity, and lower than for **1**, whose *S* enantiomer is 28-, 13-, 20- and 17-fold more potent than the *R* enantiomer towards α_{1a}, α_{1b}, α_{1d} and 5-HT_{1A} receptors, respectively. As shown in Table 1, the affinities of the *S* isomers of compounds **2**–**8** are always higher than those of the corresponding *R* isomers excepting the cases of the low α_{1b} and α_{1d} affinities displayed by the enantiomeric pairs of **2** and **3**.

(*S*)-**1** exhibits 14.1 α_{1a}/α_{1b} and 6.0 α_{1a}/5-HT_{1A} affinity ratios, while its α_{1a} and α_{1d} affinities are nearly equal. Similar selectivity pattern was found for (*R*)-**1**.

The structural modifications performed on the benzodioxane moiety sensibly lowered affinity for α_1-AR subtypes and 5-HT_{1A} receptor, but, what is noteworthy, improved α_{1a} subtype specificity. Indeed, α_{1a}, α_{1b} and 5-HT_{1A} affinities of (*S*)-**2** and (*S*)-**3** were almost equally (about 2 orders of magnitude) decreased with respect to (*S*)-**1**, whereas, for α_{1d}, the loss of affinity ranged between 661-fold and 812-fold. As shown by the affinity ratios reported in Table 1, such a trend slightly improved the α_{1a} versus α_{1b} and 5HT_{1A} selectivities of (*S*)-**1**, while producing moderate, but undeniable α_{1a} versus α_{1d} selectivity, of which (*S*)-**1** is virtually devoid. Therefore, (*S*)-**2** and (*S*)-**3** can be considered ligands with an only moderate α_{1a} affinity, but a significant selectivity over both the other α_1 subtypes and the 5-HT_{1A} receptor. Furthermore, their almost superimposable affinity profiles indicate that the addition of an aromatic or alicyclic residue to the benzodioxane system equally advantages α_{1a} selectivity.

Otherwise, replacement of 2,6-dimethoxyphenyl with naphthyl residues (compounds **4**–**8**) led to averagely higher affinities than those of **2** and **3**, but proved to be detrimental for selectivity, even for that for α_{1a} with regard to α_{1b}, the most marked subtype selectivity shown by (*S*)-**1**. In this series, (*S*)-**6** and (*R*)-**6**, which exhibit nearly nanomolar α_{1a} affinities, constitute an exception, because they maintain the α_{1a}/α_{1b} selectivity of the lead compound while improving the α_{1a}/5-HT_{1A} and α_{1a}/α_{1d} affinity ratios of this latter.

In summary, SAR analysis indicates that the modifications performed on the 2,6-dimethoxyphenyl residue and on the benzodioxane nucleus tend to modulate the ligand α_1-ARs binding affinity and the α_{1a} subtype selectivity, respectively. This trend is consistent with the model of interaction between **1** and α_{1a}-AR antagonist

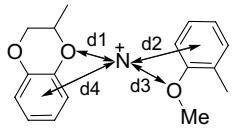
Table 1. Affinity constants, expressed as pK_i ($-\log K_i$, M), and selectivities of the enantiomeric pairs of compounds **1**–**8** for cloned human α_1-adrenoreceptor subtypes and 5-HT_{1A} receptor

Compd	pK_i (±SE)				Affinity ratios		
	α-**1a**	α-**1b**	α-**1d**	5-HT_{1A}	α-**1a**/α-**1b**[a]	α-**1a**/α-**1d**[b]	α-**1a**/5-HT_{1A}[c]
(*S*)-**1**	9.39 (±0.06)	8.24 (±0.04)	9.29 (±0.11)	8.61 (±0.04)	14.1	1.3	6.0
(*R*)-**1**	7.95 (±0.04)	7.14 (±0.06)	7.98 (±0.08)	7.39 (±0.03)	6.5	0.9	3.6
(*S*)-**2**	7.47 (±0.05)	6.05 (±0.04)	6.38 (±0.04)	6.46 (±0.04)	26.3	12.3	10.2
(*R*)-**2**	6.99 (±0.08)	6.37 (±0.04)	6.53 (±0.04)	6.00 (±0.04)	4.2	2.9	9.8
(*S*)-**3**	7.60 (±0.15)	6.24 (±0.03)	6.47 (±0.06)	6.44 (±0.03)	22.9	13.5	14.5
(*R*)-**3**	7.00 (±0.07)	6.40 (±0.05)	6.69 (±0.04)	6.30 (±0.03)	4.0	2.0	5.0
(*S*)-**4**	7.70 (±0.02)	7.19 (±0.03)	8.38 (±0.07)	8.13 (±0.04)	3.2	0.2	0.4
(*R*)-**4**	6.98 (±0.03)	<6	6.74 (±0.06)	7.24 (±0.04)	>9.6	1.7	0.5
(*S*)-**5**	7.29 (±0.04)	6.95 (±0.03)	7.03 (±0.09)	7.41 (±0.06)	2.2	1.8	0.8
(*R*)-**5**	6.66 (±0.05)	<6	6.31 (±0.03)	<6	>4.6	2.2	>4.6
(*S*)-**6**	8.80 (±0.09)	7.80 (±0.07)	8.18 (±0.13)	7.95 (±0.06)	10.0	4.2	7.1
(*R*)-**6**	8.34 (±0.05)	7.07 (±0.07)	7.65 (±0.05)	7.17 (±0.04)	18.6	4.9	14.8
(*S*)-**7**	7.41 (±0.05)	7.28 (±0.05)	7.44 (±0.07)	7.90 (±0.05)	1.3	0.9	0.3
(*R*)-**7**	6.92 (±0.04)	6.57 (±0.07)	6.83 (±0.11)	6.97 (±0.06)	2.2	1.2	0.9
(*S*)-**8**	7.91 (±0.02)	7.58 (±0.03)	7.98 (±0.05)	7.75 (±0.04)	2.1	0.8	1.4
(*R*)-**8**	5.89 (±0.06)	6.76 (±0.04)	6.89 (±0.05)	6.51 (±0.09)	0.1	0.1	0.2

[a] Antilog ($pK_i\alpha_{1a} - pK_i\alpha_{1b}$).
[b] Antilog ($pK_i\alpha_{1a} - pK_i\alpha_{1d}$).
[c] Antilog ($pK_i\alpha_{1a} - pK_i$5-HT_{1A}).

binding pocket resulting from Perez mutagenesis studies.[29,30] According to such a model, three consecutive aminoacid residues (Gln 177, Ile 178 and Asn 179) of the second extracellular loop (E2) would interact with the benzodioxane system and account for α_{1a} selectivity, whereas two phenylalanine residues (Phe 308 and Phe 312), set on transmembrane domain 7 (TM7) and strictly conserved among all three α_1-AR subtypes, would be responsible for non subtype selective binding to α_1-ARs through interactions with the 2,6-dimethoxyphenyl fragment of the ligand. Indeed, both the tetrahydronaphthodioxane and naphthodioxane analogues (*S*)-**3** and (*S*)-**2** have markedly lower affinity, but higher specificity for α_{1a}-AR than (*S*)-**1**, suggesting that subtype specific interactions, of apolar nature, with the above three consecutive aminoacid residues set in E2 play a critical role. Conversely, the derivatives modified at the 2,6-dimethoxyphenyl moiety by condensation with an additional benzene maintain a good affinity, but loose subtype selectivity. However, it is to be noticed that the enlargement of the aromatic system in this portion of the ligand molecule doesn't lead to an undiscriminating enhancement of the α_1 affinity as expected on the basis of the proposed involvement of the two phenylalanine residues in the ligand interaction with all the α_1-AR subtypes. The substitution with a 1-naphthyl residue is preferable to that with a 2-naphthyl, where the *para* position to the oxygen atom is not free, as demonstrated by the higher affinities of (*S*)- and (*R*)-**4** with respect to (*S*)- and (*R*)-**5**. Such a trend is confirmed by the series of compounds **6-8**, where the two enantiomers of **6** display the maximum affinities. These results are in agreement with previous observations,[31] which pointed out the deleterious effects of 4-substitution at the 2,6-dimethoxyphenyl moiety. Furthermore, it is evident that the additional presence of an *ortho* positioned methoxy group on the 1-naphthyl fragment favourably contributes to the interaction, as indicated by the fact that

Table 2. Angle (τ, °) and distances ($d1-d4$, Å) between the pharmacophore features of compounds **1**–**8**



Compd	τ[a]	τ min[a]	*d*1	*d*2	*d*3	*d*4
1	125.08	79.09	3.25	5.50	4.83	4.75
2	126.21	91.90	3.20	5.22	4.49	4.41
3	118.51	89.29	2.92	4.98	4.54	4.56
4	109.63	51.60	3.07	5.53	—	—
5	120.99	66.27	2.91	5.26	—	—
6	109.56	57.52	3.06	5.43	4.61	5.02
7	109.64	68.48	3.10	5.19	4.42	4.72
8	123.41	79.09	3.25	5.50	4.83	4.75

[a] HBA–N–A angle determined by *d*1 and *d*2.

(*S*)-**6** displays sensibly higher α_{1a} and α_{1b} affinities than(*S*)-**4** approximating the values of (*S*)-**1**.

To further analyze the SAR data of compounds **2-8**, whose *S* isomers have all $K_i\alpha_{1a} < 100$ nM and, in the case of **2** and **3**, an appreciable α_{1a} specificity, we have applied a pharmacophore model for α_{1a}-AR. Out of those reported in literature, we selected the model developed by Bremner and co-workers,[27] which ensues from four relatively heterogeneous α_{1A} antagonists with α_{1A}/α_{1B} and α_{1A}/α_{1D} selectivities comparable to those of (*S*)-**2** and (*S*)-**3** and is claimed to well predict the α_{1A} affinity of WB-4101, not comprised in the training set. This α_{1A} pharmacophore model includes three features, namely a protonated centre (N), a hydrogen bond acceptor group (HBA) and an aromatic ring (A), defined by a 7.1 Å N–HBA distance, a 5.5 Å N–A distance and a 100° HBA–N–A angle. The fact that the same three features, but in a folded disposition with a 47° angle, also frame the α_{1D} pharmacophore model proposed by the same authors suggests that the conformational profile of the considered compounds could be determinant for the α_{1A}/α_{1D} selectivity. Otherwise, the α_{1A}/α_{1B} selectivity would rest on more solid bases since the α_{1B} pharmacophore model substantially differs from the two others for the presence of four features and, in particular, of a hydrogen bond donor in place of an acceptor.

Table 2 reports the calculated values of the distance between N and dioxane O_1 (*d*1) and between N and the barycentre of the phenyl linked to the oxyethyl chain (*d*2) for compounds **1**–**8**. The same table lists the values of the distance between N and methoxy O (*d*3) and between N and the barycentre of the aromatic ring of the benzodioxane system (*d*4). It is evident that both *d*1 and *d*3, which can be assumed as N–HBA distances, are far from the 7.1 Å value proposed by Bremner. On the contrary, both *d*2 and *d*4 acceptably match with the proposed 5.5 Å N–A distance. Overall, these results indicate that *d*1 and *d*2, or, alternatively, *d*3 and *d*4 are not constructive descriptors to justify the affinity and selectivity profile of the title compounds, in particular of (*S*)-**2**, (*S*)-**3**, (*S*)-**6** and (*R*)-**6**, which would not be able to map the HBA feature of the model. However, consistently with Bremner's models, conformational analysis shows that the two most α_{1a}/α_{1d} selective compounds, that is, (*S*)-**2** and (*S*)-**3**, cannot assume the folded disposition of the three pharmacophore features required for the interaction with the α_{1D} subtype (see the minimum 91.90° and 89.29° HBA–N–A angles in Table 2), what is instead allowed to the other less or not α_{1a}/α_{1d} selective ligands. Significantly, (*S*)-**4**, whose minimum HBA–N–A angle (51.60°) is the most similar to the postulated value of 47°, exhibits a reversed selectivity in favour of α_{1d} with respect to α_{1a} subtype.

4. Conclusions

Although many analogues, mostly racemic, of the potent α_1 antagonist WB-4101 have been investigated over the past years, drawing conclusions on the features relevant to α_1/α_2 selectivity, a few of them have been assayed to evaluate the affinity for the three α_1-AR subtypes and the 5-HT_{1A} receptor. Thus, little is known about their selectivity at this level and the possibility to improve the selectivity of the lead compound, which is just modest excepting the significantly lower α_{1b} affinity compared with those for the other two α_1 subtypes and the 5-HT_{1A} receptor. In this context, the present studies on the enantiomers of WB-4101 and a novel series of homochiral analogues of the same indicate that it is possible to significantly modulate the affinity and selectivity profile of (*S*)-**1** simply fusing a cyclohexane or an additional benzene ring with its benzodioxane or phenoxy moiety. In particular, the naphthodioxane and tetrahydronaphthodioxane derivatives (*S*)-**2** and (*S*)-**3** display a good α_{1a} selectivity with respect to the other two subtypes and the 5-HT_{1A} receptor, while the 2-methoxy-1-naphthyloxy analogue (*S*)-**6** and (*R*)-**6** a very high α_{1a} affinity, little lower than that of (*S*)-**1**, but slightly more specific than this latter. These results are coherent with the α_{1a}-AR binding model for WB-4101 resultant from mutagenesis studies and, to a certain extent, with previously proposed α_1 subtype pharmacophore models.

5. Experimental

5.1. Chemistry

Melting points were measured on Buchi melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded operating at 200 or 300 MHz. Chemical shifts are reported in ppm relative to residual solvent ($CHCl_3$ or DMSO) as internal standard. Signal multiplicity is designed according to the following abbreviations: s = singlet, d = doublet, dd = doublet of doublets, t = triplet, m = multiplet, br s = broad singlet, br t = broad triplet. Optical rotations were determined by a Perkin–Elmer 241 Polarimeter at 25 °C. Elemental analyses (CHN) of the new substances are within 0.40% of theoretical values. Purifications were performed by flash chromatography using silica gel (particle size 40–63 μm, Merck).

(*S*)- and (*R*)-glycerol acetonide were prepared by *Chemi S.p.a.* (Cinisello Balsamo, Milan, Italy) from racemic glycerol acetonide according to the method described in the literature.[32]

5.1.1. (*R*)-1-Mesyloxy-2,3-propanediol acetonide [(*R*)-9]. Prepared from commercially available (*S*)-glycerol acetonide as reported by Jeminet.[33]

5.1.2. (*S*)-1-Mesyloxy-2,3-propanediol acetonide [(*S*)-9]. Prepared from commercially available (*R*)-glycerol acetonide as described for (*R*)-**9**.

5.1.3. (*S*)-3-(2-Benzyloxyphenoxy)-1,2-propanediol acetonide [(*S*)-10]. A solution of 2-benzyloxyphenol (14.7 g, 73.4 mmol) and potassium hydroxide (4.12 g, 73.4 mmol) in ethanol (100 mL) was heated at 70 °C for 30 min and, after adding (*R*)-**9** (22.1 g, 77.2 mmol), refluxed for 24 h. The solvent was evaporated and the residue treated with

diethyl ether (100 mL). The resulting suspension was filtered and the filtrate washed with water, 5% potassium hydroxide, and water again. The organic layer was dried and concentrated to give a residue, which was chromatographed on silica gel. Elution with cyclohexane/ethyl acetate (90:10) afforded 13 g (56%) of (*S*)-**10** as a white solid: mp 36–37 °C; $[\alpha]_D^{25} = +17.4$ (*c* 0.5, ethanol); ^{1}H NMR ($CDCl_3$) δ 1.38 (s, 3H), 1.42 (s, 3H), 3.89–4.07 (m, 2H), 4.08–4.21 (m, 2H), 4.42–4.58 (m, 1H), 5.18 (s, 2H), 6.85–7.00 (m, 4H), 7.32–7.58 (m, 5H).

5.1.4. (*R*)-3-(2-Benzyloxyphenoxy)-1,2-propanediol acetonide [(*R*)-10]. Prepared from (*S*)-**9** as described for (*S*)-**10**: mp 36–37 °C; $[\alpha]_D^{25} = -17.4$ (*c* 0.5, ethanol); ^{1}H NMR identical to that of (*S*)-**10**.

5.1.5. (*R*)-3-(2-Benzyloxyphenoxy)-1,2-propanediol [(*R*)-11]. A suspension of (*S*)-**10** (13 g, 41.3 mmol) in 1 N HCl (65 mL) was heated at 75 °C for 5 h and, after removing acetone by vacuum distillation, cooled to 5 °C and filtered to isolate the precipitate, which was rinsed with water several times and then dissolved in carbon tetrachloride (60 mL). Residual water was removed by azeotropic distillation. After slow cooling to 5 °C, 8.8 g (78%) of (*R*)-**11** crystallized as a white solid: mp 94–95 °C; $[\alpha]_D^{25} = -6.7$ (*c* 0.5, ethanol); ^{1}H NMR ($CDCl_3$) δ 2.5 (t, 1H), 3.21 (d, 1H), 3.89–4.07 (m, 2H), 4.08–4.21 (m, 2H), 4.42–4.58 (m, 1H), 5.10 (s, 2H), 6.85–6.90 (m, 4H), 7.35–7.42 (m, 5H).

5.1.6. (*S*)-3-(2-Benzyloxyphenoxy)-1,2-propanediol [(*S*)-11]. Prepared from (*R*)-**10** as described for (*R*)-**11**: mp 94–95 °C; $[\alpha]_D^{25} = +5.8$ (*c* 0.5, ethanol); ^{1}H NMR identical to that of (*R*)-**11**.

5.1.7. (*S*)-3-(2-Benzyloxyphenoxy)-1,2-bis(mesyloxy)propane [(*S*)-12]. Mesyl chloride (7.4 g, 65 mmol) was added dropwise to a stirred solution of (*R*)-**11** (8.8 g, 32 mmol) and TEA (10 mL) in dichloromethane at 0 °C. After 2 h at room temperature, the reaction mixture was washed with 5% $NaHCO_3$, dried and concentrated to give the crude product, which was crystallized from diisopropyl ether yielding 12.4 g (90%) of (*S*)-**12** as a white solid: mp 103 °C; $[\alpha]_D^{25} = -24.3$ (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.90 (s, 3H), 3.03 (s, 3H), 4.24 (m, 2H), 4.48 (m, 2H), 5.03 (s, 2H), 5.15 (m, 1H), 6.90–7.05 (m, 4H), 7.35–7.45 (m, 5H).

5.1.8. (*R*)-3-(2-Benzyloxyphenoxy)-1,2-bis(mesyloxy)propane [(*R*)-12]. Prepared from (*S*)-**11** as described for (*S*)-**12**: mp 102.5 °C; $[\alpha]_D^{25} = +23.0$ (*c* 1, $CHCl_3$); ^{1}H NMR identical to that of (*S*)-**12**.

5.1.9. (*S*)-3-(2-Hydroxyphenoxy)-1,2-bis(mesyloxy)propane [(*S*)-13]. A solution of (*S*)-**12** (13 g, 30.2 mmol) in ethyl acetate (170 mL) and methanol (70 mL) was added with 10% Pd/C (1.2 g) and vigorously shaken under hydrogen at room temperature for 3 h. The catalyst was removed by filtration and the filtrate concentrated to give (*S*)-**11** (9.8 g) as a colourless oil, which was used without purification: $[\alpha]_D^{25} = -5.3$ (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 3.08 (s, 3H), 3.14 (s, 3H) 4.10–4.29 (m, 2H), 4.51 (m, 2H), 5.26 (m, 1H), 6.27 (br s, 1H), 6.84–6.94 (m, 4H).

5.1.10. (*R*)-3-(2-Hydroxyphenoxy)-1,2-bis(tosyloxy)propane [(*R*)-13]. Prepared from (*R*)-**12** as described for (*S*)-**13**: $[\alpha]_D^{25} = +4.5$ (*c* 1, $CHCl_3$); ^{1}H NMR identical to that of (*S*)-**13**.

5.1.11. (*R*)-2-((Mesyloxy)methyl)-1,4-benzodioxane [(*R*)-14]. A mixture of (*S*)-**13** (9.5 g, 27.9 mmol) and potassium carbonate (3.9 g, 30 mmol) in acetone (120 mL) was refluxed for 5 h. After cooling, the reaction mixture was concentrated and the residue treated with ethyl acetate (100 mL) and 10% HCl (60 mL). The organic phase was separated, washed with water, dried, and concentrated to yield a residue, which was crystallized from diisopropyl ether/ethanol (7:1) to give 5.1 g (75%) of (*R*)-**14**: mp 85.4 °C; $[\alpha]_D^{25} = -17.2$ (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 3.09 (s, 3H), 4.20 (dd, 1H), 4.32 (dd, 1H), 4.43–4.55 (m, 3H), 6.89 (s, 4H).

5.1.12. (*S*)-2-((Mesyloxy)methyl)-1,4-benzodioxane [(*S*)-14]. Prepared from (*R*)-**13** as described for (*R*)-**14**: $[\alpha]_D^{25} = +17.3$ (*c* 1, $CHCl_3$); ^{1}H NMR identical to that of (*R*)-**14**.

5.1.13. (*S*)-2-((Azido)methyl)-1,4-benzodioxane [(*S*)-15]. A mixture of (*S*)-**14** (3.0 g, 12.2 mmol) and sodium azide (8 g, 123 mmol) in DMF (130 mL) was heated at 90 °C for 3 h. At the end, the reaction mixture was extracted with dichloromethane for three times. The organic phases were combined, washed with water, dried and concentrated to give the crude product, which was purified by chromatography on silica gel. Elution with cyclohexane/ethyl acetate 80:20 afforded 2.1 g of [(*S*)-**15**] as a yellow oil (91%): $[\alpha]_D^{25} = -16.1$ (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 3.45–3.61 (m, 2H), 4.05 (m, 1H), 4.14 (dd, 1H), 4.38 (m, 1H), 6.81–6.90 (m, 4H).

5.1.14. (*R*)-2-((Azido)methyl)-1,4-benzodioxane [(*R*)-15]. Prepared from (*R*)-**14** as described for (*S*)-**15**: $[\alpha]_D^{25} = +15.6$ (*c* 1, $CHCl_3$); ^{1}H NMR identical to that of (*S*)-**15**.

5.1.15. (*S*)-2-((Amino)methyl)-1,4-benzodioxane [(*S*)-16]. Hydrazine hydrate (6.35 mL) was added dropwise to a stirred mixture of (*S*)-**15** (2.1 g, 10.9 mmol) and PdO (50 mg) in methanol (20 mL). After refluxing for 2 h, the reaction mixture was cooled to room temperature and filtered. The filtrate was concentrated and the resulting crude product treated with 10% HCl until pH = 1. The aqueous layer was alkalized with 40% NaOH until pH = 9 and extracted with dichloromethane. The organic phase was separated, washed with water, dried and concentrated to give 1.59 g of (*S*)-**16** as a yellow oil (88%): $[\alpha]_D^{25} = -55.4$ (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) **δ 1.4 (br s, 1H), 2.94 (m, 2H), 4.0 (m, 1H), 4.12 (m, 1H), 4.28 (dd, 1H), 6.81–6.90 (m, 4H).**

5.1.16. (*R*)-2-((Amino)methyl)-1,4-benzodioxane [(*R*)-16]. Prepared from (*R*)-**15** as described for (*S*)-**16**:

$[\alpha]_D^{25} = +53.7$ (*c* 1, $CHCl_3$); ^1H NMR identical to that of (*S*)-**16**.

5.1.17. 3-Benzyloxy-2-hydroxynaphthalene (17). Potassium carbonate (43.1 g, 0.31 mol) was added in small portions to a solution of 2,3-dihydroxynaphthalene (50 g, 0.31 mol) in DMF (120 mL). The mixture was heated at 50 °C for 30 min. Benzyl chloride (35.7 mL, 0.31 mol) was added dropwise. After heating at 85 °C for 20 h, the solvent was evaporated and the residue treated with dichloromethane and 10% HCl. The organic phase was separated, washed with 10% HCl again and then with water, dried, and concentrated. The resulting residue was purified by chromatography on silica gel. Elution with cyclohexane/ethyl acetate 95:5 afforded 51.45 g (66%) of **17** as a yellow oil: ^1H NMR ($CDCl_3$) δ 5.25 (s, 2H), 5.90 (s, 1H), 7.10–7.58 (m, 9H), 7.60–7.75 (m, 2H). Anal. Calcd for $C_{17}H_{14}O_2$ (250.30).

5.1.18. (*R*)-3-(3-Benzyloxy-2-naphthoxy)-1,2-propanediol [(*R*)-18]. A solution of **17** (13 g, 51.9 mmol) and sodium hydroxide (2.07 g, 51.9 mmol) in ethanol (270 mL) was heated at 70 °C for 15 min and, after adding (*R*)-**9** (14.6 g, 51 mmol), refluxed for 24 h. 5% HCl (150 mL) was added and boiling continued for 4 h. Ethanol was evaporated and the residue treated with ethyl acetate. The aqueous layer was separated and extracted with ethyl acetate again. The combined organic extracts were washed with water, dried, and concentrated. The brownish solid residue was crystallized from methanol yielding 8.1 g (48%) of (*R*)-**18**: mp 127–128 °C; $[\alpha]_D^{25} = -6.45$ (*c* 0.5, ethanol); ^1H NMR ($CDCl_3$) δ 2.50 (br s, 1H), 3.20 (br s, 1H), 3.80 (m, 2H), 4.05–4.35 (m, 3H), 5.20 (s, 2H), 7.10–7.55 (m, 9H), 7.60–7.70 (m, 2H). Anal. Calcd for $C_{20}H_{20}O_4$ (324.38).

5.1.19. (*S*)-3-(3-Benzyloxy-2-naphthoxy)-1,2-propanediol [(*S*)-18]. Prepared from (*S*)-**9** and **17** as described for (*R*)-**18**: mp 131–132 °C; $[\alpha]_D^{25} = +7.0$ (*c* 0.5, ethanol); ^1H NMR identical to that of (*R*)-**18**.

5.1.20. (*S*)-3-(3-Benzyloxy-2-naphthoxy)-1,2-bis(tosyloxy)propane [(*S*)-19]. Tosyl chloride (12.37 g, 65 mmol) was added in small portions to a stirred solution of (*R*)-**18** (8.1 g, 25 mmol) in pyridine (18 mL) at 0 °C. The resulting mixture was stirred at room temperature for 20 h. Ethyl acetate (100 mL) and 10% HCl (90 mL) were added. The organic phase was separated, washed with water, dried, and concentrated to give the crude product, which was crystallized from diethyl ether yielding 11.63 g (74%) of (*S*)-**19** as a white solid: mp 93–96 °C; $[\alpha]_D^{25} = +16.0$ (*c* 0.5, ethyl acetate); ^1H NMR ($CDCl_3$) δ 2.30 (s, 3H), 2.38 (s, 3H), 4.15–4.40 (m, 4H), 4.95 (m, 1H), 5.18 (s, 2H), 7.02 (s, 1H), 7.15–7.50 (m, 12H), 7.60–7.80 (m, 6H). Anal. Calcd for $C_{34}H_{32}O_8S_2$ (632.74).

5.1.21. (*R*)-3-(3-Benzyloxy-2-naphthoxy)-1,2-bis(tosyloxy)-propane [(*R*)-19]. Prepared from (*S*)-**18** as described for (*S*)-**19**: mp 95–95.4 °C; $[\alpha]_D^{25} = -15.8$ (*c* 0.5, ethyl acetate); ^1H NMR identical to that of (*S*)-**19**.

5.1.22. (*S*)-3-(3-Hydroxy-2-naphthoxy)-1,2-bis(tosyloxy)-propane [(*S*)-20]. Prepared from (*S*)-**19** as described for (*S*)-**13** and isolated, after chromatography on silica gel (cyclohexane/ethyl acetate, 70:30), as an orange solid (53%): mp 134–135 °C; $[\alpha]_D^{25} = +7.2$ (*c* 1, chloroform); ^1H NMR ($CDCl_3$) δ 2.42 (s, 6H), 4.25 (m, 4H), 5.09 (m, 1H), 5.99 (br s, 1H), 6.97 (s, 1H), 7.26 (m, 7 H), 7.63 (m, 2H), 7.75 (m, 4H). Anal. Calcd for $C_{27}H_{26}O_8S_2$ (542.62).

5.1.23. (*R*)-3-(3-Hydroxy-2-naphthoxy)-1,2-bis(tosyloxy)-propane [(*R*)-20]. Prepared from (*R*)-**19** as described for (*S*)-**20**: mp 133–135 °C; $[\alpha]_D^{25} = -7.1$ (*c* 1, chloroform); ^1H NMR identical to that of (*S*)-**20**.

5.1.24. (*R*)-2-((Tosyloxy)methyl)-2,3-dihydronaphtho[2,3-*b*][1,4]dioxine [(*R*)-21]. Obtained from (*S*)-**20** as a white solid (99%) following the procedure described for (*R*)-**14**: mp 113–115 °C; $[\alpha]_D^{25} = -9.5$ (*c* 1, chloroform); ^1H NMR ($CDCl_3$) δ 2.43 (s, 3H), 4.15 (m, 1H). 4.20–4.37 (m, 3H), 4.49 (m, 1H), 7.16 (s, 1H), 7.23–7.35 (m, 5H), 7.61 (m, 2H), 7.80 (d, 2H). Anal. Calcd for $C_{20}H_{18}O_5S$ (370.42).

5.1.25. (*S*)-2-((Tosyloxy)methyl)-2,3-dihydronaphtho[2,3-*b*][1,4]dioxine [(*S*)-21]. Prepared from (*R*)-**20** as described for (*R*)-**21**: mp 109–111 °C; $[\alpha]_D^{25} = +8.9$ (*c* 1, chloroform); ^1H NMR identical to that of (*R*)-**21**.

5.1.26. (*R*)-2-(Iodomethyl)-2,3-dihydronaphtho[2,3-*b*][1,4]-dioxine [(*R*)-22]. A mixture of (*R*)-**21** (3.05 g, 8.2 mmol) and sodium iodide (13.6 g, 90 mmol) in acetone (40 mL) was refluxed for 18 h. The solvent was evaporated and the residue treated with 10% HCl and ethyl acetate. The aqueous layer was separated and extracted with ethyl acetate. The organic phases were combined, washed with a saturated aqueous solution of sodium metabisulfite (50 mL), dried, and concentrated to give 2.43 g (91%) of (*R*)-**22** as a pale yellow solid: mp 73–74 °C; $[\alpha]_D^{25} = -7.3$ (*c* 1, chloroform); ^1H NMR ($CDCl_3$) δ 3.38 (d, 2H), 4.24 (dd, 1H), 4.35–4.50 (m, 2H), 7.30 (m, 4H), 7.66 (m, 2H).

5.1.27. (*S*)-2-(Iodomethyl)-2,3-dihydronaphtho[2,3-*b*][1,4]dioxine [(*S*)-22]. Prepared from (*S*)-**21** as described for (*R*)-**22**: mp 66–68 °C; $[\alpha]_D^{25} = +6.9$ (*c* 1, chloroform); ^1H NMR identical to that of (*R*)-**22.**

5.1.28. 2-Acetoxy-5,6,7,8-tetrahydronaphthalene (23). Acetyl chloride (28.9 mL, 0.37 mol) was added stepwise to a cool solution of 5,6,7,8-tetrahidro-2-naphthol (50 g, 0.337 mol) and pyridine (29.9 mL) in dichloromethane (250 mL) keeping the temperature under 5 °C. The reaction mixture was stirred at room temperature for 2 h, treated with 10% HCl (150 mL), washed with water (100 mL), dried, and concentrated to give 64 g of **23** as an oil, which was used for the subsequent step without further purification: ^1H NMR ($CDCl_3$) δ 1.80 (m, 4H), 2.29 (s, 3H), 2.77 (m, 4H), 5.28 (s, 2H), 6.82 (m, 2H), 7.07 (m, 1H).

5.1.29. 3-Acetyl-5,6,7,8-tetrahydro-2-naphthol (24). A solution of **23** (64 g) in 1,2-dichlorobenzene (64 mL)

was added with aluminium trichloride (45 g) and heated at 100 °C for 5 h. After cooling, dichloromethane (200 mL) was added and the resulting mixture was poured into frozen 10% HCl (250 mL). The organic phase was separated, washed with water, dried, and concentrated. After distillation of dichlorobenzene under vacuum, the green residue was crystallized from methanol (300 mL) to give 42.1 g (66%) of **24** as a light yellow solid: mp 71–72 °C; ^{1}H NMR ($CDCl_3$) δ 1.78 (m, 4H), 2.58 (s, 3H), 2.75 (m, 4H), 6.68 (s, 1H), 7.40 (s, 1H), 11.96 (s, 1H).

5.1.30. 2-Benzyloxy-3-acetyl-5,6,7,8-tetrahydronaphthalene (25). At room temperature, 2, 5 N NaOH (440 mL) was added to a stirred solution of benzyl bromide (39.4 mL, 0.33 mol), TBAB (9.2 g) and **24** (42.1 g, 0.22 mol) in dichloromethane (400 mL). The reaction mixture was stirred at room temperature for 4 h. Afterwards, the organic phase was separated, treated with 10% HCl (100 mL), washed with water (50 mL), dried, and concentrated to give the crude product. Crystallization from methanol (250 mL) afforded 44.1 g (71%) of **25** as a white solid: mp 94–95 °C; ^{1}H NMR ($CDCl_3$) δ 1.78 (m, 4H), 2.58 (s, 3H), 2.76 (m, 4H), 5.11 (s, 2H), 6.72 (s, 1H), 7.34–7.45 (m, 5H), 7.50 (s, 1H).

5.1.31. 2-Benzyloxy-3-acethoxy-5,6,7,8-tetrahydronaphthalene (26). 3-Chloroperbenzoic acid (62.8 g) was added to a solution of **25** (44 g, 160 mmol) in dichloromethane (400 mL) at 0 °C. The reaction mixture was stirred at room temperature for 20 h. The progress of the reaction was monitored by ^{1}H NMR analysis observing the shifting of the acetyl signal from 2.58 to 2.26 δ. At the end of the reaction, the mixture was filtered and washed with a saturated solution of sodium bicarbonate and with water. The organic phase was dried and concentrated to give 46.5 g of **26** as a yellow oil, which was used for the subsequent step without further purification: ^{1}H NMR ($CDCl_3$) δ 1.78 (m, 4H), 2.26 (s, 3H), 2.70 (m, 4H), 5.04 (s, 2H), 6.71 (s, 1H), 6.76 (s, 1H), 7.35–7.47 (m, 5H).

5.1.32. 3-Benzyloxy-5,6,7,8-tetrahydro-2-naphthol (27). A solution of crude **26** (46 g, 0.155 mol) in methanol (240 mL) was added with 2, 5 N NaOH (80 mL) and stirred at room temperature for 5 h. After addition of HCl 10% until pH 1, a brownish solid was formed, which was isolated by filtration. The solid was crystallized twice from cyclohexane to give 29 g of **27** as a yellow solid: mp 75–76 °C; ^{1}H NMR ($CDCl_3$) δ 1.78 (m, 4H), 2.68 (m, 4H), 5.06 (s, 2H), 6.63 (s, 1H), 6.66 (s, 1H), 7.37–7.45 (m, 5H).

5.1.33. (*R*)-3-(3-Benzyloxy-5,6,7,8-tetrahydro-2-naphthoxy)-1,2-propanediol [(*R*)-28]. A solution of 3-benzyloxy-2-naphthol **27** (15 g, 59.0 mmol) and potassium hydroxide (3.9 g, 60 mmol) in ethanol (200 mL) was heated at 70 °C for 30 min and, after adding (*2R*)-1-mesyloxy-2,3-propanediol acetonide [(*R*)-**9**] (12.6 g, 60 mmol), refluxed for 24 h. The solvent was evaporated and the residue treated with methanol (70 mL) and HCl 1 N (70 mL). The resulting suspension was heated at 75 °C for 3 h. The methanol was evaporated under vacuum and the residue was extracted with dichloromethane. The organic phase was dried and concentrated to give the crude product, which was purified by chromatography on silica gel. Elution with dichloromethane/methanol 98/2 afforded 11.4 g (59%) of (*R*)-**28** as a solid: mp 95–96 °C; $[\alpha]_D^{25} = -6.5$ (*c* 0.5 ethanol); ^{1}H NMR ($CDCl_3$) δ 1.76 (m, 4 H), 2.35 (t, 1H), 2.66 (m, 4H), 3.17 (d, 1H), 3.68 (m, 2H), 4.02 (m, 2H), 4.12 (dd, 1H), 5.04 (s, 2H), 6.65 (s, 2H), 7.31–7.45 (m, 5H).

5.1.34. (*S*)-3-(3-benzyloxy-5,6,7,8-tetrahydro-2-naphthoxy)-1,2-propanediol [(*S*)-28]. Prepared from (*S*)-**9** and **27** as described for (*R*)-**28**: mp 123–124 °C; $[\alpha]_D^{25} = +5.2$ (*c* 0.5, ethanol); ^{1}H NMR identical to that of (*R*)-**28**.

5.1.35. (2*S*)-3-(3-Benzyloxy-5,6,7,8-tetrahydro-2-naphthoxy)-1,2-bis(mesyloxy)propane [(*S*)-29]. Prepared from (*R*)-**28** as described for (*S*)-**12** and isolated after crystallization from diisopropyl ether as a white solid (87%): mp 126–127 °C; $[\alpha]_D^{25} = -16.1$ (*c* 1, chloroform); ^{1}H NMR ($CDCl_3$) 1.75 (m, 4H), 2.64 (m, 4H), 2.90 (s, 3H), 3.05 (s, 3H), 4.20 (m, 2H), 4.40–4.55 (m, 2H),4.98 (m, 2H), 5.05 (m, 1H), 6.58 (s, 1H), 6.65 (s, 1H).

5.1.36. (*R*)-3-(3-Benzyloxy-5,6,7,8-tetrahydro-2-naphthoxy)-1,2-bis(mesyloxy)propane [(*R*)-29]. Prepared from (*S*)-**28** as described for (*S*)-**29**: mp 125–126 °C; $[\alpha]_D^{25} = +15.7$ (*c* 1, chloroform); ^{1}H NMR identical to that of (*S*)-**29**.

5.1.37. (*S*)-3-(3-Hydroxy-5,6,7,8-tetrahydro-2-naphthoxy)-1,2-bis(mesyloxy)propane [(*S*)-30]. Prepared from (*S*)-**29** as described for (*S*)-**13** and isolated as a white solid (95%): mp 114 °C; $[\alpha]_D^{25} = +4.7$ (*c* 1, chloroform); ^{1}H NMR ($CDCl_3$) δ 1.75 (m, 4H), 2.64 (m, 4H), 3.10 (s, 3H), 3.14 (s, 3H), 4.18–4.22 (m, 2H), 4.48–4.53 (m, 2H), 5.25 (m, 1H), 6.53 (s, 1H), 6.63 (s, 1H).

5.1.38. (*R*)-3-(3-Hydroxy-5,6,7,8-tetrahydro-2-naphthoxy)-1,2-bis(mesyloxy)propane [(*R*)-30]. Prepared from (*R*)-**29** as described for (*S*)-**30**: mp 112–113 °C; $[\alpha]_D^{25} = -4.8$ (*c* 1, chloroform); ^{1}H NMR identical to that of (*S*)-**30**.

5.1.39. (*R*)-2-((Mesyloxy)methyl)-2,3,6,7,8,9-hexahydronaphtho[2,3-*b*][1,4]dioxine [(*R*)-31]. Prepared from (*S*)-**30** as described for (*R*)-**14** and isolated as a white solid (78%): mp 81 °C; $[\alpha]_D^{25} = -13.8$ (*c* 1, chloroform); ^{1}H NMR ($CDCl_3$) δ 1.67 (m, 4H), 2.58 (m, 4H), 3.02 (s, 3H), 4.02 (dd, 1H), 4.19 (dd, 1H), 4.34 (m, 3H), 6.52 (s, 2H).

5.1.40. (*S*)-2-((Mesyloxy)methyl)-2,3,6,7,8,9-hexahydronaphtho[2,3- *b*][1,4]dioxine[(*S*)-31]. Prepared from (*R*)-**30** as described for (*R*)-**31**: mp 79.0 °C; $[\alpha]_D^{25} = +13.5$ (*c* 1, chloroform); ^{1}H NMR identical to that of (*R*)-**31**.

5.1.41. 1-Methoxy-2-acetonaphthone (32). Iodomethane (16.2 mL, 260 mmol) was added dropwise to a solution of 1-hydroxy-2-acetonaphthone (24.2 g, 130 mmol) and potassium hydroxide (8 g, 143 mmol) in DMSO (250 mL) at room temperature. After 18 h, water (200 mL) and diethyl ether (50 mL) were added. The

aqueous layer was separated and extracted with diethyl ether twice. The organic phases were combined, dried, and concentrated to give the crude product, which was purified by chromatography on silica gel. Elution with cyclohexane/ethyl acetate (95:5) afforded 24.1 g (93%) of **32** as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 2.78 (s, 3H), 4.13 (s, 3H), 7.49–7.65 (m, 3H), 7.74 (d, 1H), 7.86 (m, 1H), 8.23 (m, 1H).

5.1.42. 1-Methoxy-2-hydroxynaphthalene (33). 3-Chloroperbenzoic acid (61.75 g) was added to a solution of **32** (24 g, 120 mmol) in dichloromethane (400 mL) at 0 °C. The reaction mixture was stirred at room temperature for 20 days, repeating the addition of 3-chloroperbenzoic acid (10 g) every five days. The progress of the reaction was monitored by ^{1}H NMR analysis observing the shifting of the acetyl signal from 2.8 to 2.4 δ. At the end of the reaction, the mixture was washed with a saturated solution of sodium bicarbonate. The organic phase was dried and concentrated. The residue was dissolved in methanol (120 mL) and concentrated sulfuric acid (4 mL) was added. After stirring over-night at room temperature, the solvent was removed and the residue treated with brine and diethyl ether. The aqueous layer was separated and extracted with diethyl ether twice. The organic phases were combined, dried, and concentrated to give the crude product, which was purified by chromatography on silica gel. Elution with cyclohexane/ethyl acetate (95:5) afforded 13.5 g (65%) of **33** as a yellow solid: mp 92–93 °C; ^{1}H NMR ($CDCl_3$) δ 3.98 (s, 3H), 5.80 (s, 1H), 7.23 (d, 1H), 7.30 (d, 1H), 7.48 (t, 1H), 7.57 (d, 1H), 7.79 (d, 1H), 7.94 (d, 1H). Anal. Calcd for $C_{11}H_{10}O_2$ (174.20).

5.1.43. 1-Methoxy-2-(2-hydroxyethoxy)naphthalene (34). A mixture of **33** (8.5 g, 48.8 mmol), ethylene carbonate (8.53 g, 96.9 mmol) and potassium carbonate (13.5 g, 97 mmol) in toluene (160 mL) was refluxed over-night. After cooling to room temperature, water was added. The aqueous layer was separated and extracted with toluene twice. The organic phases were combined, dried, and concentrated to give a brown oil (10 g), which was purified by chromatography on silica gel. Elution with cyclohexane/ethyl acetate (80:20) yielded 8 g (75%) of **34** as a solid: mp 64–65 °C; ^{1}H NMR ($CDCl_3$) δ 1.80 (br s, 1H), 3.95 (m, 2H), 4.03 (s, 3H), 4.28 (t, 2H), 7.28 (d, 1H), 7.44 (m, 2H), 7.60 (d, 1H), 7.79 (d, 1H), 8.10 (d, 1H). Anal. Calcd for $C_{13}H_{14}O_3$ (218.25).

5.1.44. 1-Methoxy-2-(2-tosyloxyethoxy)naphthalene (35). Tosyl chloride (6.8 g, 35.7 mmol) was added in small portions to a stirred solution of **34** (7.8 g, 35.7 mmol) in pyridine (9 mL) at 0 °C. The resulting mixture was stirred at room temperature over-night, diluted with dichloromethane (30 mL), and washed with 10% HCl. The aqueous layer was separated and extracted with dichloromethane twice. The organic phases were combined, dried, and concentrated. The resulting crude product (13 g) was crystallized from diethyl ether yielding 9.05 g (68%) of **35** as a white solid: mp 78–79 °C; ^{1}H NMR ($CDCl_3$) 2.42 (s, 3H), 3.93 (s, 3H), 4.38 (m, 4H), 7.14 (d, 1H), 7.26–7.55 (m, 5H), 7.80 (m, 3H), 8.10 (d, 1H). Anal. Calcd for $C_{20}H_{20}O_5S$ (372.44).

5.1.45. 1-Methoxy-2-(2-azidoethoxy)naphthalene (36). A mixture of **35** (8.95 g, 24 mmol) and sodium azide (15.6 g, 240 mmol) in DMF (130 mL) was heated at 90 °C for 2 h. After cooling, water (30 mL) and ethyl acetate (150 mL) were added. The aqueous layer was separated and extracted with ethyl acetate twice. The organic phases were combined, washed with water, dried, and concentrated to give the crude product, which was purified by chromatography on silica gel. Elution with cyclohexane/ethyl acetate (70:30) afforded 5.37 g (92%) of **36** as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 3.66 (t, 2H), 4.06 (s, 3H), 4.31 (t, 2H), 7.27 (d, 1H), 7.38–7.56 (m, 2H), 7.60 (d, 1H), 7.81 (d, 1H), 8.17 (d, 1H).

5.1.46. 1-Methoxy-2-(2-aminoethoxy)naphthalene (37). Hydrazine hydrate (22.4 mL) was added dropwise to a stirred mixture of **36** (7.47 g, 30.7 mmol) and PdO (86 mg) in methanol (160 mL) at 65 degrC. After refluxing for 2 h, the reaction mixture was cooled to room temperature and filtered. The filtrate was concentrated and the resulting crude product purified by chromatography on silica gel. Elution with dichloromethane/methanol (98:2) gave 4.46 g (67%) of **37** as an oil: ^{1}H NMR ($CDCl_3$) δ 1.95 (br s, 2H), 3.15 (t, 2H), 4.01 (s, 3H), 4.19 (t, 2H), 7.24 (d, 1H), 7.41 (t, 1H), 7.49 (t, 1H), 7.57 (d, 1H), 7.78 (d, 1H), 8.11 (d, 1H).

5.1.47. 2-Hydroxy-3-methoxynaphthalene (38). 95% Potassium *tert*-butoxide (14.8 g, 125 mmol) was added in small portions to a solution of 2,3-dihydroxynaphthalene (20 g, 125 mmol) in 2-methoxyethanol (100 mL). After dimethyl sulfate (15.8 g, 125 mmol) was added dropwise, the reaction mixture was heated at 80 °C over-night. 40% NaOH (15 mL) and water (25 mL) were added dropwise at 80 °C. After cooling to room temperature, the solvent was removed and the residue treated with 10% HCl (50 mL) and dichloromethane (20 mL). The aqueous layer was separated and extracted with dichloromethane twice. The organic phases were combined, washed with water, dried, and concentrated to give the crude product, which was purified by chromatography on silica gel. Elution with cyclohexane/ethyl acetate (85:15) afforded 18.2 g (84%) of **38** as a white solid: mp 108–109 °C; ^{1}H NMR ($CDCl_3$) δ 4.03 (s, 3H), 5.92 (br s, 1H), 7.12 (s, 1H), 7.33 (m, 3H), 7.65 (m, 2H). Anal. Calcd for $C_{11}H_{10}O_2$ (174.20).

5.1.48. 2-(2-Hydroxyethoxy)-3-methoxynaphthalene (39). Prepared from **38** as described for **34** but replacing toluene with DMF. After chromatography on silica gel (cyclohexane/ethyl acetate 60:40), the product was isolated as a yellow oil (70%): ^{1}H NMR ($CDCl_3$) δ 3.61 (m, 1H), 3.99 (s, 3H), 4.02 (m, 2H), 4.15 (m, 2H), 7.08 (s, 1H), 7.11 (s, 1H), 7.31 (m, 2H), 7.64 (m, 2H).

5.1.49. 2-(2-Tosyloxyethoxy)-3-methoxynaphthalene (40). Prepared from **39** as described for **35** and isolated, after chromatography on silica gel (cyclohexane/ethyl acetate 70/30), as a white solid (51%): mp 88–89 °C; ^{1}H NMR ($CDCl_3$) δ 2.40 (s, 3H), 3.95 (s, 3H), 4.32 (m, 2H), 4.46 (m, 2H), 7.05 (s, 1H), 7.11 (s, 1H), 7.33 (m, 4H), 7.65 (m, 2H), 7.84 (d, 2H). Anal. Calcd for $C_{20}H_{20}O_5S$ (372.44).

5.1.50. 2-(2-Azidoetoxy)-3-methoxynaphthalene (41). Prepared from **40** as described for **36**. After chromatography on silica gel (cyclohexane/ethyl acetate 80:20), the product was isolated as a white solid (98%): mp 65–66 °C; ^{1}H NMR ($CDCl_3$) δ 3.65 (m, 2H), 3.95 (s, 3H), 4.25 (m, 2H), 7.05 (s, 1H), 7.09 (s, 1H), 7.34 (m, 2H), 7.65 (m, 2H). Anal. Calcd for $C_{13}H_{13}N_3O_2$ (243.27).

5.1.51. 2-(2-Aminoethoxy)-3-methoxynaphthalene (42). Hydrazine hydrate (25 mL) was added dropwise to a stirred mixture of **41** (9.07 g, 37.3 mmol) and PdO (96 mg) in methanol (100 mL) at 65 °C. After refluxing for 90 min, the reaction mixture was filtered and the filtrate concentrated. The residue was treated with dichloromethane (30 mL) and 10% HCl (20 mL). The organic layer was separated and extracted with 10% HCl twice. The acidic aqueous phases were combined, made alkaline with 10% sodium hydroxide (100 mL), and extracted with dichloromethane several times. The organic extracts were combined, dried, and concentrated to give 4.9 g (60%) of **42** as a viscous yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.90 (br s, 2H), 3.21 (t, 2H), 3.98 (s, 3H), 4.15 (t, 2H), 7.13 (br s, 2H), 7.33 (m, 2H), 7.65 (m, 2H).

5.1.52. 1-(2-Hydroxyethoxy)naphthalene (43). Prepared from 1-naphthol as described for **34** and isolated as a yellow oil (83%): ^{1}H NMR ($CDCl_3$) δ 2.95 (br s, 1H), 4.08 (m, 2H), 4.17 (m, 2H), 6.77 (d, 1H), 7.35 (t, 1H), 7.52 (m, 3H), 7.85 (m, 1H), 8.35 (m, 1H).

5.1.53. 1-(2-Tosyloxyethoxy)naphthalene (44). Prepared from **43** as described for **35** and isolated as a white solid (64%): mp 99–100 °C; ^{1}H NMR ($CDCl_3$) δ 2.42 (s, 3H), 4.33 (m, 2H), 4.53 (m, 2H), 6.69 (d, 1H), 7.20–7.60 (m, 6H), 7.59 (d, 1H), 7.84 (d, 2H), 8.02 (d, 1H). Anal. Calcd for $C_{19}H_{18}O_4S$ (342.41).

5.1.54. 1-(2-Azidoethoxy)naphthalene (45). Prepared from **44** as described for **36**. Hexane/water extraction and concentration of organic phases gave **45** as a yellow oil (92%): ^{1}H NMR ($CDCl_3$) δ 3.65 (t, 2H), 4.21 (t, 2H), 6.77 (d, 1H), 7.46 (t, 1H), 7.60 (m, 3H), 7.92 (m, 1H), 8.45 (m, 1H).

5.1.55. 1-(2-Aminoethoxy)naphthalene (46). Prepared from **45** as described for **37** and identically isolated as an oil (56%): ^{1}H NMR ($CDCl_3$) δ 1.65 (br s, 2H), 3.21 (t, 2H), 4.14 (t, 2H), 6.80 (d, 1H), 7.40–7.60 (m, 4H), 7.81 (m, 1H), 8.29 (m, 1H).

5.1.56. 2-(2-Hydroxyethoxy)naphthalene (47). Prepared from 2-naphthol as described for **34** and isolated, after chromatography on silica gel (cyclohexane/ethyl acetate 60:40), as a yellow solid (62%): mp 76–77 °C; ^{1}H NMR ($CDCl_3$) δ 2.36 (br s, 1H), 4.11 (m, 2H), 4.19 (m, 2H), 7.22–7.26 (m, 2H), 7.32–7.50 (m, 2H), 7.72–7.80 (m, 3H). Anal. Calcd for $C_{12}H_{12}O_2$ (188.23).

5.1.57. 2-(2-Mesyloxyethoxy)naphthalene (48). Prepared from **47** as described for (*S*)-**12**. Crystallization from methanol yielded **48** (96%) as a white solid (96%): mp 114–115 °C; ^{1}H NMR ($CDCl_3$) 3.12 (s, 3H), 4.37 (m, 2H), 4.65 (m, 2H), 7.15 (m, 2 H), 7.41 (m, 2H), 7.76 (m, 3H). Anal. Calcd for $C_{13}H_{14}O_4S$ (266.31).

5.1.58. 2-(2-Azidoethoxy)naphthalene (49). Prepared from **48** as described for **36** and isolated, after chromatography on silica gel (cyclohexane/ethyl acetate 85/15), as a white solid (83%): mp 75–76 °C; ^{1}H NMR ($CDCl_3$) δ 3.67 (t, 2H), 4.27 (t, 2H), 7.10 (m, 2H), 7.44 (m, 2H), 7.77 (m, 3H). Anal. Calcd for $C_{12}H_{11}N_3O$ (213.24).

5.1.59. 2-(2-Aminoethoxy)naphthalene (50). Prepared from **49** as described for **37** and isolated, after chromatography on silica gel (dichloromethane/methanol 90:10), as a low-melting solid (75%): ^{1}H NMR ($CDCl_3$) δ 1.74 (s, 2H), 3.09 (t, 2H), 4.04 (t, 2H), 7.12 (m, 2H), 7.45 (m, 2H), 7.75 (m, 3H).

5.1.60. 2-Methoxynaphthoformiate (51). 3-Chloroperbenzoic acid (16.7 g, 96 mmol) was added to a solution of 2-methoxynaphthaldeyde (9 g, 48.3 mmol) and ethylacetate (90 mL) at 0 °C. The reaction mixture was stirred at room temperature for 40 h. The progress of the reaction was monitored by ^{1}H NMR analysis observing the lost of the aldehyde signal. At the end of the reaction the ethylacetate was evaporated under vacuum. The residue was diluted with dichloromethane filtrated and washed twice with a saturated solution of sodium bicarbonate and with water. The organic phase was dried and concentrated to give 9.0 g of **51** (91.8%) as violet oil. ^{1}H NMR ($CDCl_3$) δ 3.96 (s, 3H), 7.36–7.40 (m, 2H), 7.52 (t, 1H), 7.76–7.87 (m, 1H), 8.45 (s, 1H).

5.1.61. 2-Methoxynaphthol (52). $LiAlH_4$ (1.9 g, 50 mmol) was suspended in anhydrous THF (20 mL) under N_2 and a solution of **51** (10 g, 50 mmol) in THF was added dropwise. After 4 h, the reaction was quenched into frozen 10% HCl (50 mL) and extracted with dichloromethane (100 mL). The organic phase was separated, washed with water, dried and concentrated to give 8.53 g of crude **52** as a yellow oil, which was purified by chromatography on silica gel. Elution with toluene afforded 4.0g of **52** (47%)as green solid: mp 53.38 °C; ^{1}H NMR ($CDCl_3$) δ 4.0 (s, 3H), 6.05 (s, 1H) 7.27 (d, 1H) 7.41 (m, 3H) 7.75 (d, 1H) 8.15 (d, 1H).

5.1.62. 1-(2-Bromoethoxy)-2-methoxynaphthalene (53). Sodium hydride (1 g, 39.6 mmol) was suspended in THF anhydrous (5 mL) under N_2 atmosphere, and the mixture was cooled at 0 °C. DMSO (5 mL) was joined and **52** (5.5 g, 31.5 mmol) diluted with THF/DMSO (1/1; 30 mL) was added dropwise keeping the temperature under 20°C. At the end, the reaction mixture was quenched into frozen 10% HCl and dichloromethane was added (100 mL). The organic phase was separated, washed with water, dried and concentrated to give the crude product, which was purified by chromatography on silica gel. Elution with cyclohexane/ethylacetate (70:30) afforded 1.78 g (30%) of **53** as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 3.73 (t, 2H), 3.98 (s, 3H), 4.47 (t, 2H), 7.25 (d, 1H), 7.38 (t, 1H), 7.50 (t, 1H), 7.63 (d, 1H) 7.79 (d, 1H), 8.25 (d, 1H).

5.1.63. (*S*)-2-[((2-(2,6-Dimethoxyphenoxy)ethyl)amino)-methyl]-2,3-dihydronaphtho[2,3-*b*][1,4]dioxine hydrochloride [(*S*)-2]. A solution of (*R*)-**22** (1.2 g, 3.7 mmol) and 2-(2,6-dimethoxyphenoxy)ethylamine (1.47 g, 7.45 mmol) in 2-propanol (30 mL) was refluxed for 48 h. After cooling to room temperature, 10% NaOH and ethyl acetate were added. The aqueous layer was separated and extracted with ethyl acetate again. The organic phases were combined, dried, and concentrated to give a residue, which was purified by chromatography on silica gel. Elution with dichloromethane/methanol (95:5) afforded 0.89 g (61%) of (*2S*)-2-[((2-(2,6-dimethoxyphenoxy)-ethyl)amino)methyl]-2,3-dihydronaphtho[2,3-*b*][1,4]dioxine as an oil: $[\alpha]_D^{25} = -43.0$ (*c* 1, chloroform);); ^{1}H NMR ($CDCl_3$) δ 2.20 (br s, 1H), 2.93–3.10 (m, 4H), 3.85 (s, 6H), 4.15 (m, 3H), 4.40 (m, 2H), 6.61 (d, 2H), 7.00 (t, 1H), 7.29 (m, 4H), 7.64 (m, 2H). The secondary amine was dissolved in ethanol (20 mL) and 2 N HCl/EtOH (4 mL) was added. The solution was filtered and the filtrate concentrated to give a residue, which was crystallized from 2-propanol yielding 0.53 g (33%, based on the starting amount of (*R*)-**22**) of (*S*)-**2** as a white solid: mp 161 °C; $[\alpha]_D^{25} = -60.5$ (*c* 1, ethanol); ^{1}H NMR (DMSO-d_6) δ 3.38 (m, 2H), 3.56 (m, 2H), 3.83 (s, 6H), 4.19–4.40 (m, 3H), 4.55 (m, 1H), 4.90 (m, 1H), 6.75 (d, 2H), 7.11 (t, 1H), 7.36 (m, 2H), 7.45 (m, 2H), 7.78 (m, 2H), 9.20 (br s, 1H), 9.40 (br s, 1H). Anal. Calcd for $C_{23}H_{26}ClNO_5$ (431.91).

5.1.64. (*R*)-2-[((2-(2,6-Dimethoxyphenoxy)ethyl)amino)-methyl]-2,3-dihydronaphtho[2,3-*b*][1,4]dioxine hydrochloride [(*R*)-2]. Prepared from (*S*)-**22** and 2-(2,6-dimethoxyphenoxy)ethylamine as described for (*S*)-**2**: mp 160 °C; $[\alpha]_D^{25} = +59.0$ (*c* 1, ethanol) ($[\alpha]_D^{25} = +43.3$ (*c* 1, chloroform) for the free amine); ^{1}H NMR identical to that of (*S*)-**2**. Anal. Calcd for $C_{23}H_{26}ClNO_5$ (431.91).

5.1.65. (*S*)-2-[((2-(2,6-Dimethoxyphenoxy)ethyl)amino)-methyl]-2,3,6,7,8,9-hexahydro naphtho[2,3-*b*][1,4]dioxine hydrochloride [(*S*)-3]. A solution of (*R*)-**31** (1.2 g, 4.0 mmol) and 2-(2,6-dimethoxyphenoxy)ethylamine (0.79 g, 4.0 mmol) in 2-methyl-1-propanol (6 mL) was refluxed for 48 h. After cooling to room temperature, 10% $NaHCO_3$ and ethyl acetate were added. The aqueous layer was separated and extracted with ethyl acetate again. The organic phases were combined, dried, and concentrated to give a residue, which was purified by chromatography on silica gel. Elution with cyclohexane/ethyl acetate (80:20) afforded 0.940 g (58.8%) of (*2S*)-2-[((2-(2,6-dimethoxyphenoxy)ethyl)amino)methyl]-2,3,6,7,8,9-hexahydronaphtho[2,3-*b*][1,4]dioxine as a solid: mp 75–76 °C; $[\alpha]_D^{25} = -24.3$ (*c* 1, chloroform);); ^{1}H NMR ($CDCl_3$) δ 1.74 (m, 4H), 2.55 (br s, 1H) 2.65 (m, 4H), 2.88–3.00 (m, 4H), 3.84 (s, 6H), 3.98–4.05 (m, 1H), 4.14 (m, 2H), 4.27 (m, 2H), 6.58 (m, 4H), 6.99 (t, 1H). The secondary amine was dissolved in ethanol (5 mL) and 2 N HCl/EtOH (4 mL) was added. The resulting precipitate was isolated, rinsed with ethanol, and dried yielding 0.634 g (62%, based on the starting amount of (*R*)-**31**) of (*S*)-**3** as a white solid: mp 203–204 °C; $[\alpha]_D^{25} = -43.7$ (*c* 1, methanol); ^{1}H NMR (DMSO-d_6) δ 1.65 (m, 4H), 2.59 (m, 4H), 3.30–3.45 (m, 4 H), 3.76 (s, 6H), 4.03 (dd, 1H),4.12 (m, 2H), 4.30 (dd 1H), 4.65 (m, 1H), 6.57 (s, 2H), 6.69 (d, 2H), 7.04 (t, 1H), 9.05 (br s, 1H), 9.52 (br s, 1H). Anal. Calcd for $C_{23}H_{30}ClNO_5$ (435.94).

5.1.66. (*R*)-2-[((2-(2,6-Dimethoxyphenoxy)ethyl)amino)-methyl]-2,3,6,7,8,9-hexahydronaphtho[2,3-*b*][1,4]dioxine hydrochloride [(*R*)-3]. Prepared from (*S*)-**31** and 2-(2,6-dimethoxyphenoxy)ethylamine as described for (*S*)-**3**: mp 202.5 °C; $[\alpha]_D^{25} = +43.2$ (*c* 1, methanol) ($[\alpha]_D^{25} = +22.9$ (*c* 1, chloroform) for the free amine); ^{1}H NMR identical to that of (*S*)-**3**. Anal. Calcd for $C_{23}H_{30}ClNO_5$ (435.94).

5.1.67. (*S*)-2-[((2-(1-Naphthoxy)ethyl)amino)methyl]-1,4-benzodioxane hydrochloride [(*S*)-4]. A mixture of (*R*)-**14** (880 mg, 3.60 mmol) and **46** (678 mg, 3.62 mmol) in 2-propanol (10 mL) was refluxed for 36 h. The solvent was evaporated and the residue treated with 10% NaOH (30 mL) and ethyl acetate (30 mL). The aqueous layer was separated and extracted with ethyl acetate. The organic phases were combined, washed with water, dried, and concentrated to give a residue, which was purified by chromatography on silica gel. Elution with dichloromethane/methanol (98:2) afforded 600 mg of (*2S*)-2-[((2-(1-naphthoxy)ethyl)amino)methyl]-1,4-benzodioxane as a yellow oil: $[\alpha]_D^{25} = -21.8$ (*c* 1, chloroform); ^{1}H NMR ($CDCl_3$) δ 2.01 (br s, 1H), 3.05 (m, 2H), 3.23 (t, 2H), 4.06 (dd, 1H), 4.20–4.40 (m, 4H), 6.82–6.92 (m, 5H), 7.34–7.52 (m, 4H), 7.82 (m, 1H), 8.27 (m, 1H). The secondary amine was dissolved in a mixture of ethanol (5 mL) and ethyl acetate (5 mL), and 4.6 N HCl/EtOH (1 mL) was added. The resulting precipitate was isolated, rinsed with ethanol, and dried yielding 360 mg (27%, based on the starting amount of (*R*)-**14**) of (*S*)-**1** as a white solid: mp 191.2–192.5 °C; $[\alpha]_D^{25} = -58.4$ (*c* 1, methanol); ^{1}H NMR (DMSO-d_6) δ 3.44 (m, 2 H), 3.65 (m, 2H), 4.16 (dd, 1H), 4.47–4.57 (m, 3H), 4.87 (m, 1H), 6.94 (m, 4H), 7.04 (d, 1H), 7.43–7.61 (m, 4H), 7.92 (dd, 1H), 8.49 (d, 1H), 9.99 (br s, 2H). Anal. Calcd for $C_{21}H_{22}ClNO_3$ (371.86).

5.1.68. (*R*)-2-[((2-(1-Naphthoxy)ethyl)amino)methyl]-1,4-benzodioxane hydrochloride [(*R*)-4]. Prepared from (*S*)-**14** and **46** as described for (*S*)-**4**: mp 190.5–191.5 °C; $[\alpha]_D^{25} = +58.4$ (*c* 1, methanol) ($[\alpha]_D^{25} = +22.6$ (*c* 1, $CHCl_3$) for the free amine); ^{1}H NMR identical to that of (*S*)-**4**. Anal. Calcd for $C_{21}H_{22}ClNO_3$ (371.86): C, 67.83; H, 5.96; N, 3.77; Cl, 9.53. Found: C, 67.71; H, 5.91; N, 3.71; Cl, 9.59.

5.1.69. (*S*)-2-[((2-(2-Naphthoxy)ethyl)amino)methyl]-1,4-benzodioxane hydrochloride [(*S*)-5]. A mixture of (*R*)-**14** (2.42 g, 9.89 mmol) and **50** (1.85 g, 9.89 mmol) in 2-propanol (10 mL) was refluxed for 48 h. (*2S*)-2-[((2-(2-Naphthoxy)ethyl)amino)methyl]-1,4-benzodioxane was isolated as described for (2*S*)-2-[((2-(1-naphthoxy)ethyl)amino)methyl]-1,4-benzodioxane in 46% yield (1.51 g) as a white solid: mp 111–112 °C; $[\alpha]_D^{25} = -34.4$ (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) 1.68 (br s, 1H), 3.01 (m, 2H), 3.14 (t, 2H), 4.06 (dd, 1H), 4.19–4.34 (m, 4H), 6.85 (m, 4H), 7.17 (m, 2H), 7.38 (m, 2H), 7.75 (m, 3H). The secondary amine was dissolved in ethyl acetate (10 mL), and 2 N HCl/EtOH (4 mL) was added. The

resulting precipitate was isolated, rinsed with ethyl acetate, and dried yielding 1.2 g (33%, based on the starting amount of (*R*)-**14**) of (*S*)-**5** as a white solid: mp 244–245 °C; $[\alpha]_D^{25} = -46.1$ (*c* 1, DMSO); ^{1}H NMR (DMSO-d_6) δ 3.37 (m, 2H), 3.57 (m, 2H), 4.14 (dd, 1H), 4.43 (m, 3H), 4.72 (m, 1H), 6.94 (m, 4H), 7.26 (m, 1H), 7.51 (m, 3H), 7.89 (m, 3H), 9.32 (br s, 2H): Anal. Calcd for $C_{21}H_{22}ClNO_3$ (371.86).

5.1.70. (*R*)-2-[((2-(2-Naphthoxy)ethyl)amino)methyl]-1,4-benzodioxane hydrochloride [(*R*)-5].. Prepared from (*S*)-**14** and **50** as described for (*S*)-**5**: mp 244–245 °C; $[\alpha]_D^{25} = +46.1$ (*c* 1, DMSO) ($[\alpha]_D^{25} = +33.9$ (*c* 1, $CHCl_3$) for the free amine); ^{1}H NMR identical to that of (*S*)-**5**. Anal. Calcd for $C_{21}H_{22}ClNO_3$ (371.86).

5.1.71. (*S*)-2-[((1-Naphthoxy-2-methoxy)ethyl)amino)-methyl]-1,4-benzodioxane hydrochloride [(*S*)-6]. A mixture of *S*-**14**, 2-aminomethyl-1,4-benzodioxane, (401.6 mg, 1.99 mmol) and **54** (280 mg, 0.996 mmol) in 2-methylpropanol (4 mL) was refluxed for 4 h. The solvent was evaporated and the residue treated with 10% HCl (5 mL) and dichloromethane (10 mL). The aqueous layer was separated and extracted with dichloromethane. The organic phases were combined, washed with water, dried and concentrated to give a residue, which was purified by chromatography on silica gel. Elution with cyclohexane/ethylacetate/2-methyl-1-propanol (1:1:0.3) afforded 320 mg of (2*S*)-2-[((1-naphthoxy-2-methoxy)ethyl)amino)methyl]-1,4-benzodioxane as a yellow oil: $[\alpha]_D^{25} = -27.5$ (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.19 (br s, 1H), 2.96–3.13 (m, 4H), 3.98 (s, 3H), 4.07 (q, 1H), 4.25–4.38 (m, 4H), 6.82–6.93 (m, 4H), 7.27–7.38 (m, 2H), 7.46 (t, 1H), 7.60 (d, 1H), 7.78 (d, 1H), 8.12 (d, 1H). The secondary amine was dissolved in EtOH (5 mL) and 1.39 N HCl/EtOH (3 mL) was added. The resulting precipitate was isolated, rinsed with ethanol, and dried yielding 120 mg (15% based on the starting amount of (*S*)-**14**) of (*S*)-**6** as a white solid: mp 164 °C; $[\alpha]_D^{25} = -46.5$ (*c* 1, ethanol); ^{1}H NMR (DMSO-d_6) δ 3.35–3.50 (m, 4H), 3.92 (s, 3H), 4.08–4.14 (m, 1H), 4.31–4.42 (m, 3H), 4.74–4.77 (m, 1H), 6.85–6.95 (m, 4H), 7.38 (m, 1H), 7.50 (m, 2H), 7.74 (d,1H), 7.86 (d, 1H), 8.10 (d, 1H), 9.46 (br s, 1H), 9.76 (br s, 1H).

5.1.72. (*R*)-2-[((1-Naphthoxy-2-methoxy)ethyl)-amino)-methyl]-1,4-benzodioxane hydrochloride[(*R*)-6]. Prepared from (*R*)-**14** and **54** as described for (*S*)-**6**: mp 162 °C; $[\alpha]_D^{25} = +43.5$ (*c* 1, ethanol) ($[\alpha]_D^{25} = +25.4$ (*c* 1, $CHCl_3$) for the free amine); ^{1}H NMR identical to that of (*S*)-**6**.

5.1.73. (*S*)-2-[((2-(1-Methoxy-2-naphthoxy)ethyl)amino)-methyl]-1,4-benzodioxane hydrochloride [(*S*)-7]. A solution of (*R*)-**14** (769 mg, 3.15 mmol) and **37** (1.37 g, 6.3 mmol) in *n*-butanol (30 mL) was refluxed for 48 h. (2*S*)-2-[((2-(1Methoxy-2-naphthoxy)ethyl)amino)methyl]-1,4-benzodioxane was isolated as described for (2*S*)-2-[((2-(1-naphthoxy)ethyl)amino)methyl]-1,4-benzodioxane in 50% yield (570 mg) as a viscous oil: $[\alpha]_D^{25} = -25.3$ (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.75 (br s, 1H), 3.01 (t, 2H), 3.15 (t, 2H), 4.02 (s, 3H), 4.05–4.11 (m, 1H), 4.25–4.40 (m, 4H), 6.86 (m, 4H), 7.20–7.55 (m, 3H), 7.58 (d, 1H), 7.78 (d, 1H), 8.12 (d, 1H). The secondary amine was dissolved in ethanol (10 mL), and 2 N HCl/EtOH (5 mL) was added. The solvent was evaporated and the resulting residue crystallized from ethyl acetate (20 mL) yielding 450 mg (36%, based on the starting amount of (*R*)-**14**) of (*S*)-**7** as a white solid: mp 154–155 °C; $[\alpha]_D^{25} = -44.3$ (*c* 1, ethanol); ^{1}H NMR (DMSO-d_6) δ 3.40 (m, 2H), 3.57 (m, 2H), 3.97 (s, 3H), 4.18 (m, 1H), 4.40–4.60 (m, 3H), 4.76 (m, 1H), 6.95 (br s, 4H), 7.35–7.60 (m, 3H), 7.75 (d, 1H), 7.93 (d, 1H), 8.06 (d, 1H), 9.50 (br s, 1H), 9.70 (br s, 1H). Anal. Calcd for $C_{22}H_{24}ClNO_4$ (401.89).

5.1.74. (*R*)-2-[((2-(1-Methoxy-2-naphthoxy)ethyl)amino)-methyl]-1,4-benzodioxane hydrochloride [(*R*)-7]. Prepared from (*S*)-**14** and **35** as described for (*S*)-**7**: mp 155–156 °C; $[\alpha]_D^{25} = +44.7$ (*c* 1, ethanol) ($[\alpha]_D^{25} = +24.6$ (*c* 1, $CHCl_3$) for the free amine); ^{1}H NMR identical to that of (*S*)-**7**. Anal. Calcd for $C_{22}H_{24}ClNO_4$ (401.89).

5.1.75. (*S*)-2-[((2-(3-Methoxy-2-naphthoxy)ethyl)amino)-methyl]-1,4-benzodioxane hydrochloride [(*S*)-8]. A mixture of (*R*)-**14** (884 mg, 3.62 mmol) and **42** (787 mg, 3.62 mmol) in 2-propanol (10 mL) was refluxed for 36 h. Crude (2*S*)-2-[((2-(3-methoxy-2-naphthoxy)ethyl)-amino)methyl]-1,4-benzodioxane was isolated as described for (2*S*)-2-[((2-(1-naphthoxy)ethyl)amino)-methyl]-1,4-benzodioxane and purified by chromatography on silica gel. Elution with dichloromethane/methanol (95:5) afforded 365 mg (28%) of the secondary amine as a white solid: mp 107–108 °C; $[\alpha]_D^{25} = -29.0$ (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.80 (br s, 1H), 3.01 (t, 2H), 3.18 (t, 2H), 3.99 (s, 3H), 4.06 (dd, 1H), 4.23–4.34 (m, 4H), 6.86 (m, 4H), 7.13 (s, 1H), 7.16 (s, 1H), 7.34 (m, 2H), 7.67 (m, 2H). Anal. Calcd for $C_{22}H_{23}NO_4$ (365.43). (2*S*)-2-[((2-(3-Methoxy-2-naphthoxy)ethyl)amino)methyl]-1,4-benzodioxane was dissolved in ethyl acetate (10 mL), and 2 N HCl/EtOH (2 mL) was added. The resulting precipitate was isolated, rinsed with ethyl acetate, and dried yielding 395 mg (27%, based on the starting amount of (*R*)-**14**) of (*S*)-**8** as a white solid: mp 155–156 °C; $[\alpha]_D^{25} = -45.2$ (*c* 1, ethanol); ^{1}H NMR (DMSO-d_6) δ 3.41 (m, 2H), 3.55 (m, 2H), 3.93 (s, 3H), 4.15 (dd, 1H), 4.43 (m, 3H), 4.78 (m, 1H), 6.64 (m, 4H), 7.39 (m, 4H), 7.80 (m, 2H), 9.73 (br s, 2H). Anal. Calcd for $C_{22}H_{24}ClNO_4$ (401.88).

5.1.76. (*R*)-2-[((2-(3-Methoxy-2-naphthoxy)ethyl)amino)-methyl]-1,4-benzodioxane hydrochloride [(*R*)-8]. Prepared from (*S*)-**14** and **42** as described for (*S*)-**8**: mp 154–155 °C; $[\alpha]_D^{25} = +45.2$ (*c* 1, ethanol) ($[\alpha]_D^{25} = +27.9$ (*c* 1, $CHCl_3$) for the free amine); ^{1}H NMR identical to that of (*S*)-**8**. Anal. Calcd for $C_{22}H_{24}ClNO_4$ (401.88).

5.2. Biology

Binding assays. The pharmacological profile of both the *S* and *R* enantiomers of compounds **1**–**8** was assessed by measuring their affinities for α_{1a}, α_{1b}, α_{1d} AR-subtypes and 5-HT_{1A} serotoninergic receptor with in vitro binding studies.

Briefly, membranes derived from Chinese Hamster Ovary (CHO) cells expressing α_1-AR subtypes (prepared

as described by Testa et al.[34]) were resuspended in Tris–HCl, 50 mM, pH = 7.7 containing 10 μM pargyline and 0.1% ascorbic acid, and incubated for 30 min at 25 °C with 0.5 nM [^{3}H]-Prazosin (NEN, 80.5 Ci/mmol) in the absence or presence of different concentrations of the tested compounds. Prazosin 1 μM was used to determine nonspecific binding.

Binding studies at 5-HT_{1A} receptors were carried out using crude membrane preparations from rat hippocampus, which were resuspended in Tris–HCl 50 mM (pH = 7.7, 10 μM pargyline and 4 mM $CaCl_2$) and incubated for 30 min at 25 °C with 1 nM [^{3}H]-8-OH-DPAT, in the absence or presence of different concentrations of the tested compounds. 5-HT_{1A} 1 μM was used to determine nonspecific binding.

Incubations were stopped by rapid filtration, through GF/B fiber filters, which were then washed, dried and counted in a LK1214 rack β liquid scintillation spectrometer.

At least three different experiments, in triplicate, were carried out for each compound and usually each compound was tested simultaneously on the different α_1-AR subtypes. Prazosin or 5-HT_{1A} were always tested in parallel, as reference drugs. The % inhibitory effects obtained in the different experiments were pooled together and the inhibition curves were analyzed using the 'one-site competition' equation built into GraphPad Prism 4.0 (GraphPAD Software, San Diego, CA). This analysis gives the IC50 (i.e. the drug concentration inhibiting specific binding by 50%), calculated with the relative standard error. K_i values were then calculated by IC50 using the Cheng and Prusoff equation in which the K_d of [^{3}H]-Prazosin for α_{1a}, α_{1b}, α_{1d} AR-subtypes were 0.4, 0.4 and 0.7 nM, respectively, whereas the K_d of [^{3}H]-8-OH-DPAT for 5-HT_{1A} receptors was 1.2 nM.

5.3. Computational methods

Compounds **1**–**8** were considered in protonated form and *S* configuration. Their molecules were built using the *ChemNote* module in the Quanta/CHARMM package (*MSI*, Burlington, USA). After a preliminary minimization to discard high-energy intramolecular interactions, the overall geometry and the atomic charges were optimized using *MOPAC6.0* (keywords: 'AM1', 'PRECISE', 'GEO-OK'). The conformational analysis was carried out by a MonteCarlo procedure able to produce 1000 conformers randomly rotating the flexible torsions automatically detected by the program. All the obtained geometries were optimized to avoid high-energy rotamers. The 1000 conformers were clustered according to their similarity to discard the redundant ones (two geometries are considered as 'different' if they differ more than 60° in one torsion). For each group the lowest energy geometry was considered only. The *d*1–*d*4 distances and the τ angle of pharmacophore models were calculated averaging the corresponding measures of all the lowest energy conformers for each analyzed compound, while τ minimum indicates the lowest angle value for each compound in this analysis.

Acknowledgement

Financial support provided by the Italian Ministero dell'Istruzione, dell'Università e della Ricerca Scientifica is gratefully acknowledged.

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