Available online at www.sciencedirect.com
ScienceDirect
European Journal of Medicinal Chemistry 41 (2006) 1025–1040
EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY
http://france.elsevier.com/direct/ejmech

Original article

QSAR study for a novel series of *ortho* disubstituted phenoxy analogues of α_1-adrenoceptor antagonist WB4101

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Received in revised form 6 April 2006; accepted 14 April 2006
Available online 05 June 2006

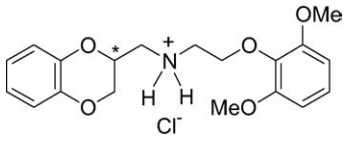
Abstract

On the basis of the affinities at the α_{1a}-, α_{1b}- and α_{1d}-adrenoceptors and the 5-HT_{1A} receptor of a previous series of sixteen 2-[(2-phenoxyethyl)aminomethyl]-1,4-benzodioxanes *ortho* monosubstituted at the phenoxy moiety, a number of *ortho* disubstituted analogues were designed, synthesized in both the enantiomeric forms and tested in binding assays on the same receptors. The affinity values of the new compounds **1**–**11** were compared with those of the enantiomers of the 2,6-dimethoxyphenoxy analogue, the well-known α1 antagonist WB4101, and of the *ortho* monosubstituted derivatives, suggesting some distinctive aspects of the interaction of the phenoxy moiety, in particular with the α_{1a}-AR and the 5-HT_{1A} receptor, of the monosubstituted and the disubstituted compounds. A classical quantitative structure-activity relationship (Hansch) analysis was applied to the whole set of the *S* enantiomers of the *ortho* mono- and disubstituted WB4101 analogues (26 compounds), finding a very good correlation for the α_{1a} affinity. For this latter, a significant parabolic relationship was also found with the volume of the two *ortho* substituents. Diametrically opposite, the same relationships for the 5-HT_{1A} exhibit low or insignificant correlation coefficients.

Keywords: WB4101 analogues; α_1-Adrenoreceptor; 5-HT_{1A} receptor; Binding affinity; QSAR

1. Introduction

Current evidences, based on the acknowledged existence of multiple α_1-adrenoceptor (α_1-AR) subtypes and on their distribution and function [1], indicate that subtype selective α_1 antagonists can represent therapeutic options for lower urinary tract (LUT) syndromes such as bladder overactivity and urinary incontinence [2]. In particular, compounds with selective blocking properties for the α_{1A} and α_{1D} subtypes, the predominating ARs, together with the β_3 subtype, in human LUT, and for the 5-HT_{1A} serotoninergic receptor [3] might be efficacious in relieving symptoms associated with such disorders. In this context, a renewed interest has been taken in investigations devoted to clarifying the pharmacophoric features and to improving both affinity and selectivity of the α_1 antagonist WB4101 (Fig. 1) [4–19], a 2-aminomethyl-1,4-benzodioxane derivative first described in 1965 [20], whose *S* enantiomer we have recently proved to exhibit about nanomolar affinity toward the three different α_1-ARs (α_{1a}, α_{1b} and α_{1d}) and the 5-HT_{1A} receptor with a slight selectivity for α_{1a}- and, to a minor degree, for α_{1d}-ARs [4]. The attractive challenge to modulate the interaction capabilities of this potent α1 antagonist further differentiating its selectivity profile has prompted us to develop series of novel WB4101 analogues. Among these, the *S* naphtho- and tetrahydronaphthodioxane derivatives are significantly more selective for the α_{1a}-AR than (*S*)-WB4101 [4],



WB4101

Fig. 1.

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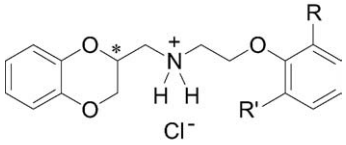
doi:10.1016/j.ejmech.2006.04.004

while the *S* forms of *ortho* monosubstituted phenoxy analogues lose most of the affinity of (*S*)-WB4101 for the α_1-ARs, especially for the α_{1a} and α_{1b} subtypes, but preserve, in some cases, its nanomolar affinity for the 5-HT_{1A} receptor thus acquiring a moderate 5-HT_{1A} selectivity [5]. A classical QSAR analysis, applied to (*S*)-WB4101, its unsubstituted phenoxy analogue and a relatively wide number of *ortho* monosubstituted phenoxyethylaminomethyl derivatives of benzodioxane, has allowed a better insight into some determinants for the affinity spectrum of this class of compounds to be got [5]. Electron rich and/or hydrogen bond accepting atoms or groups are recognized as advantageous *ortho* substituents for the affinities toward the three α_1-ARs and the 5-HT_{1A} receptor by the respective QSARs. Furthermore, the *ortho* dimethoxy substitution has been found important for the interaction with the α_1-ARs, in particular with the α_{1a} and α_{1b} subtypes, but not for the 5-HT_{1A} affinity. In QSAR terms, this is expressed by the relatively low negative incidence of the volume of the two *ortho* substituents or by the largely positive effect of their length in the three α_1 subtype equations. In fact, such a situation inevitably handicaps the α_1 affinities of the derivatives bearing one or two hydrogens as *ortho* substituents in comparison with (*S*)-WB4101. Otherwise, the absence of the volumetric term, combined with the most beneficial effect of the electron-richness, in the 5-HT_{1A} QSAR makes the same derivatives competitive with (*S*)-WB4101 in 5-HT_{1A} affinity.

On the basis of these results, we recently extended our investigations to the novel *ortho* disubstituted phenoxy analogues of WB4101 **1**–**11** (Fig. 2). To design such compounds, among the previously reported *ortho* monosubstitutions at the phenoxy moiety, we selected some of those producing high and/or specific affinity for the 5-HT_{1A} and α_{1d} receptors, namely fluoro, chloro, methyl and *t*-butyl. Intermediate alkyl and alkenyl groups (ethyl, propyl, allyl and isopropyl) were also considered. The same substituent was then introduced into both *ortho* positions to give the *o*-difluoro, *o*-dichloro and *o*-di-*tert*-butyl derivatives **1**–**3** or, alternatively, the two *ortho* positions were occupied by a methoxyl and one of the above substituents yielding the unsymmetrically *ortho* disubstituted compounds **4**–**11**. The interest in these compounds has a duplex nature. Firstly, no 2,6-disubstitution at the phenoxy moiety of WB4101, alternative to that with two methoxyls or methyls [21,22], has been ever considered; secondly, such an investigation naturally tails after that on the *ortho* monosubstituted analogues of WB4101 [5] with the aim of gaining further information on the relationship between the *ortho* disubstitution pattern and the affinity profile of the N-phenoxyethyl derivatives of aminomethylbenzodioxane. Herein we report the synthesis and the binding affinities for the α_{1a}-AR, α_{1b}-AR, α_{1d}-AR and the 5-HT_{1A} receptor of both the enantiomers of compounds **1**–**11** discussing their SAR data, in particular of the *S* isomers, and finally trying a compendious analysis of the results obtained for all the *ortho* mono- and disubstituted phenoxy analogues of WB4101 we have so far characterized.

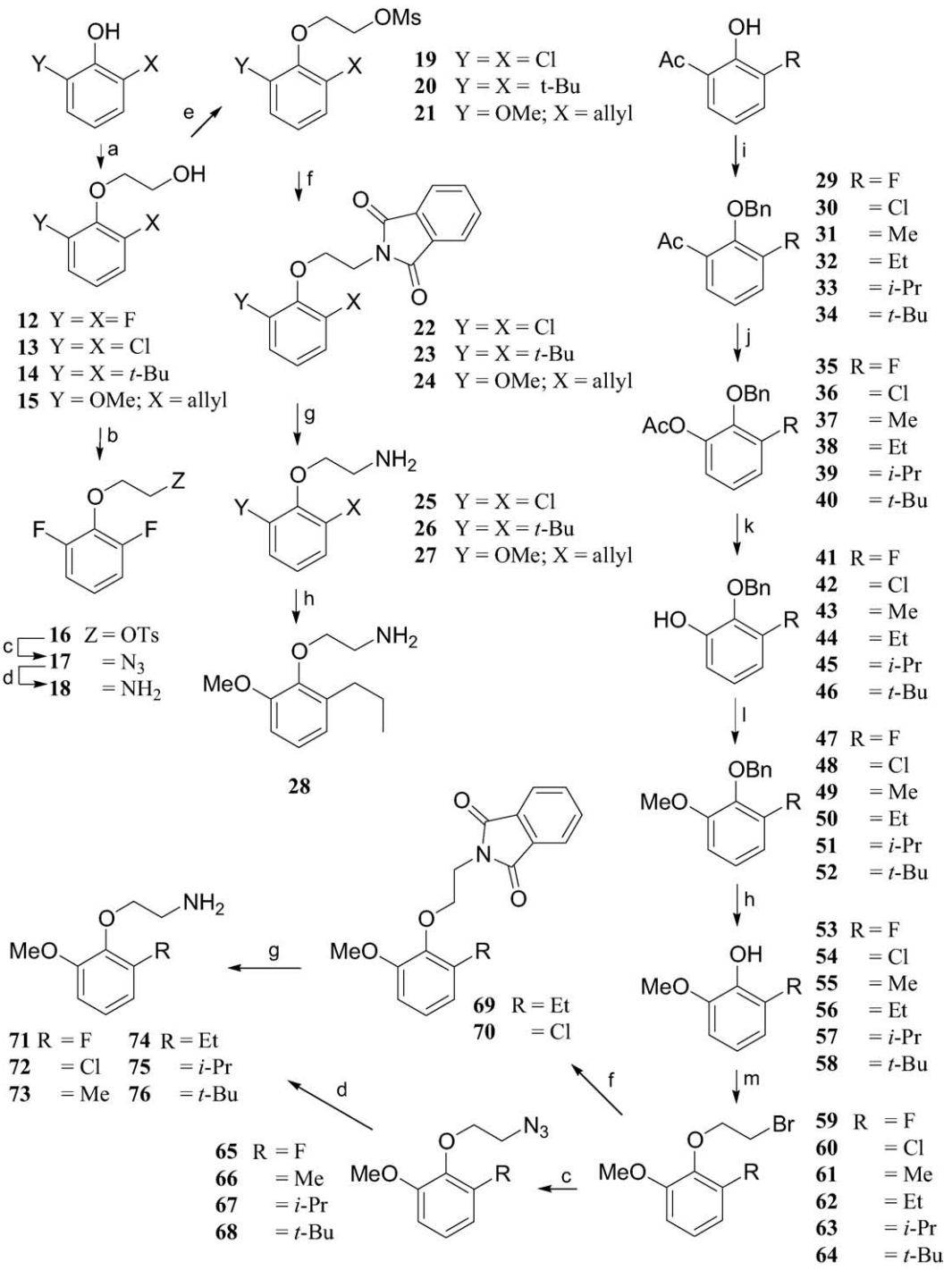


1	R = F	R' = F
2	Cl	Cl
3	*t*-Bu	*t*-Bu
4	OMe	F
5	"	Cl
6	"	Me
7	"	Et
8	"	Pr
9	"	*i*-Pr
10	"	CH_2-CH=CH_2
11	"	*t*-Bu

Fig. 2.

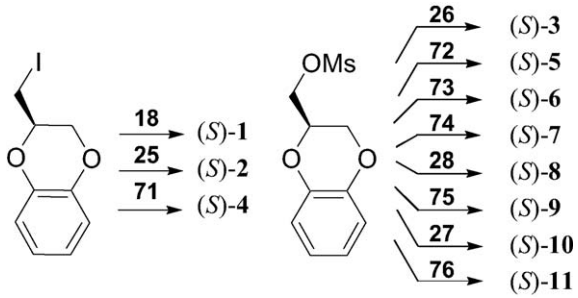
2. Chemistry

The enantiomeric pairs of compounds **1**–**11** were prepared by alkylation of *ortho* disubstituted 2-phenoxyethylamines with the enantiomers of 2-iodomethyl- or 2- mesyloxymethyl-1,4-benzodioxane, in turn obtained according to previously reported procedures [4,18,23,24]. As outlined in Scheme 1, the various 2-phenoxyethylamines were synthesized by different strategies. Those with the same substituent (F, Cl or *t*-Bu) at the *ortho* positions, namely the amines **18**, **25** and **26**, were obtained from the corresponding 2,6-substituted phenols by 2-hydroxyethylation with ethylene carbonate. The resultant ethylene glycols mono-phenyl ethers **12**–**14** were converted into the tosylate **16** and the mesyl esters **19** and **20**. These latter were reacted with potassium phthalimide and submitted to hydrazinolysis to give the dichloro- and di-*t*-butylphenoxyethylamines **25** and **26** respectively, while the tosylate was transformed into azide and reduced to the difluorophenoxyethylamine **18**. For the synthesis of the fenoxyethylamines bearing two different *ortho* substituents, namely the amines **27** and **28** and the amines **71**–**76**, we exploited the Claisen and the Fries rearrangement, respectively. As reported in literature, 2-methoxyphenyl allyl ether underwent, upon heating, allyl migration to give 2-methoxy-6-allylphenol, which was converted into amine **27** by the same pathway as 2,6-dichlorophenol into amine **25**. The allylphenoxyethylamine **27** was then hydrogenated to the propylphenoxyethylamine **28**. Otherwise, in the case of the amines **71**–**76**, the *ortho* methoxy substituent was introduced into the properly 2-substituted phenyl acetates, readily available from the corresponding 2-substituted phenols, by $AlCl_3$ catalyzed conversion into *o*-hydroxyacetophenones followed by: (a) benzylation of the unmasked phenolic moiety; (b) Baeyer–Villiger oxidation of the resultant *o*-benzyloxyacetophenones **29**–**34** to the respective *o*-benzyloxyphenyl acetates **35**–**40**; (c) methanolysis of the ester function; (d) methylation of the resulting *o*-benzyloxyphenols **41**–**46**; (e) hydrogenolytic debenzylation (**53**–**58**); (f) 2-bromoethylation with 1,2-dibromoethane (**59**–**64**). The 6-substituted 2-methoxyphenyl bromoethyl ethers **60** and **62** were converted into phthalimido derivatives yielding, after hydrazinolysis, the 2,6-susbstituted phenoxyethylamines **72** and **74,** respectively. The same two-step transformation



Scheme 1. Reagents: (a) ethylene carbonate, K_2CO_3, DMF or toluene. (b) TsCl, Py. (c) NaN_3, DMF, H_2O. (d) Hydrazine, PdO, MeOH. (e) MsCl, Et_3N, DCM. (f) Potassium phthalimide, DMF. (g) Hydrazine, 2-methoxyethanol or methanol. (h) H_2-Pd/C, MeOH. (i) Benzyl bromide, tetrabutylammonium bromide, 10% NaOH, DCM. (j) *m*-CPBA, DCM. (k) TsOH or NaOH, MeOH. (l) CH_3I, NaOH, MeOH or EtOH or tetrabutylammonium bromide and DCM. (m) Dibromoethane, KOH, DMSO or tetrabutylammonium bromide and DCM.

from bromo to amino group was accomplished, in the case of the phenoxyethylamines **71**, **73**, **75** and **76**, by reaction with sodium azide and successive reduction of the azido moiety. The final nucleophilic substitutions leading to the *S* isomers of **1**–**11** are illustrated in Scheme 2. The *R* isomers of **1**–**11** were synthesized by the same reactions as their antipodes, but using the 2-substituted 1,4-benzodioxane intermediates with inverted configuration. In particular, compounds **1**, **2** and **4** were prepared by *N*-alkylation of the corresponding primary *ortho* disubstituted 2-phenoxyethylamines **18**, **25** and **71** with enantiopure 2-iodomethyl-1,4-benzodioxane, whereas compounds **3** and **5**–**11** of the respective primary *ortho* disubstituted 2-phenoxyethylamines **26**, **72**–**74**, **28**, **75**, **27** and **76** with enantiopure 2-mesyloxymethyl-1,4-benzodioxane.



Scheme 2. Synthesis of the *S* isomers of compounds **1**–**11**.

3. Results and discussion

Table 1 reports the affinities, expressed as pK_i values (–log K_i, M) , at the three cloned human α_1-AR subtypes and 5-HT_{1A} serotoninergic receptor of the enantiomeric pairs of compounds **1**–**11** and, as comparison terms, of (*S*)- and (*R*)-WB4101.

The affinities of the *S* enantiomers are always higher than those of their antipodes, the eudismic indexes ranging between a maximum of 1.42 and a minimum of 0.52, in the case of the affinities displayed by the enantiomers of **4** for the α_{1d}-AR and the 5-HT_{1A} receptor respectively. Compared to the respective homochiral enantiomers of WB4101, all the *ortho* disubstituted phenoxy derivatives **1**–**11** are less potent, excepting both the enantiomers of **7** at the 5-HT_{1A} receptor. A more detailed analysis of the binding data reveals quite different affinity decreases with respect to the *S* and *R* enantiomers of the 2,6-dimethoxy substituted lead compound depending on the receptor subtype and on the presence of an *ortho* methoxy group. For all the *S* and *R* isomers of **1**–**11**, the maximum affinity diminution was invariably observed at the α_{1d}-AR; at the other three receptors (α_{1a}, α_{1b} and 5-HT_{1A}), the decreases were significantly less pronounced and inter se comparable. Furthermore, a clear-cut boundary distinguishes the group of the methoxy derivatives **4**–**11** from that of the *ortho* symmetrically disubstituted compounds **1**–**3**. In fact, excepting (*S*)-**11** at the α_1-ARs and (*R*)-**6** at the 5-HT_{1A} receptor, it can be stated that all the *S* and *R* methoxy derivatives are more potent, almost always in a significant degree, than the homochiral WB4101 analogues without methoxy substituents. In these two groups, the *t*-butyl derivatives invariably display the lowest affinities, with < 6 pK_i values in the case of the di-*t*-butyl substitution.

Considering the *S* isomers, such trends result in a number of compounds, namely all the methoxy analogues excepting that with an *ortho*-*t*-butyl, which exhibit α_{1a} and α_{1b} affinities very close to those of (*S*)-WB4101 (subnanomolar at the α_{1a}-AR and nearly 10 nanomolar at the α_{1b}-AR). Among the non-methoxy compounds, only the dichloro derivative (*S*)-**2** approximates similar α_{1a} and α_{1b} affinity values. Otherwise, in the case of the α_{1d}-AR, the affinities are from 10-fold to 50-fold lower than that of (*S*)-WB4101 (pK_i 9.29) for the methoxy compounds (*S*)-**4** to (*S*)-**10** and the ratio is largely over 2 orders of magnitude for (*S*)-**11** and all the non-methoxy *S* isomers. Finally, the methoxy derivatives, (*S*)-**11** included, show serotoninergic affinities about 10 nanomolar with the maximum for (*S*)-**7**, whose almost nanomolar 5-HT_{1A} affinity (pK_i 8.86) is similar to that of (*S*)-WB4101 (pK_i 8.61). For the non-methoxy compounds, 29 and 44 nanomolar 5-HT_{1A} affinity values were

Table 1
Experimental affinity constants, expressed as pK_i (–logK_i, M) ± S.E., of the enantiomers of compounds **1**–**11** and of WB4101 for cloned human α_1-adrenoceptor subtypes and 5-HT_{1A} receptor

Phenoxy	Compound	pK_i			
o-substituents		α_{1a}	α_{1b}	α_{1d}	5-HT_{1A}
F,F	(*S*)-**1**	7.56 (± 0.05)	7.04 (± 0.04)	6.88 (± 0.04)	7.53 (± 0.09)
	(*R*)-**1**	6.43 (± 0.07)	6.04 (± 0.10)	< 6	6.94 (± 0.29)
Cl,Cl	(*S*)-**2**	8.22 (± 0.03)	7.28 (± 0.04)	7.15 (± 0.04)	7.36 (± 0.78)
	(*R*)-**2**	7.21 (± 0.04)	6.03 (± 0.10)	< 6 (± 0.08)	6.55 (± 0.11)
t-Bu,*t*-Bu	(*S*)-**3**	< 6	< 6	< 6	< 6
	(*R*)-**3**	< 6	< 6	< 6	< 6
OMe,F	(*S*)-**4**	8.68 (± 0.10)	7.75 (± 0.04)	7.69 (± 0.04)	7.69 (± 0.11)
	(*R*)-**4**	7.33 (± 0.06)	6.35 (± 0.06)	6.27 (± 0.08)	7.17 (± 0.12)
OMe,Cl	(*S*)-**5**	8.94 (± 0.13)	7.74 (± 0.08)	8.39 (± 0.11)	8.26 (± 0.03)
	(*R*)-**5**	7.73 (± 0.06)	6.38 (± 0.05)	7.08 (± 0.07)	6.99 (± 0.02)
OMe,Me	(*S*)-**6**	8.71 (± 0.08)	7.98 (± 0.05)	7.73 (± 0.05)	7.73 (± 0.09)
	(*R*)-**6**	7.61 (± 0.03)	6.73 (± 0.03)	6.46 (± 0.09)	6.86 (± 0.09)
OMe,Et	(*S*)-**7**	8.70 (± 0.09)	8.04 (± 0.04)	8.01 (± 0.03)	8.86 (± 0.05)
	(*R*)-**7**	7.76 (± 0.04)	6.79 (± 0.04)	6.72 (± 0.04)	7.55 (± 0.08)
OMe,Pr	(*S*)-**8**	8.44 (± 0.11)	7.72 (± 0.06)	7.60 (± 0.07)	7.89 (± 0.10)
	(*R*)-**8**	7.58 (± 0.04)	6.87 (± 0.09)	6.56 (± 0.07)	7.06 (± 0.06)
OMe,*i*-Pr	(*S*)-**9**	8.55 (± 0.13)	8.12 (± 0.05)	8.01 (± 0.06)	7.80 (± 0.11)
	(*R*)-**9**	7.72 (± 0.05)	6.99 (± 0.08)	6.80 (± 0.06)	6.93 (± 0.07)
OMe,Allyl	(*S*)-**10**	8.63 (± 0.10)	7.96 (± 0.06)	7.80 (± 0.04)	8.00 (± 0.10)
	(*R*)-**10**	7.66 (± 0.05)	6.91 (± 0.05)	6.66 (± 0.05)	7.04 (± 0.08)
OMe,*t*-Bu	(*S*)-**11**	7.08 (± 0.03)	7.09 (± 0.04)	6.95 (± 0.04)	7.73 (± 0.06)
	(*R*)-**11**	n.d.	n.d.	n.d.	n.d.
OMe,OMe	(*S*)-WB4101 [a]	9.39 (± 0.06)	8.24 (± 0.04)	9.29 (± 0.11)	8.61 (± 0.04)
	(*R*)-WB4101 [a]	7.95 (± 0.04)	7.14 (± 0.06)	7.98 (± 0.08)	7.39 (± 0.03)

[a] Data taken from Ref. [4].

respectively determined in the case of the dihalo derivatives (*S*)-**1** and (*S*)-**2**.

The affinity profiles of the *S* isomers of compounds **1**–**11**, compared to that of (*S*)-WB4101, are characterized by a reduced α_{1a} versus α_{1b} selectivity, with the exception of (*S*)-**5**, and by a moderate α_{1a}/α_{1d} selectivity, of which (*S*)-WB4101 is virtually devoid. Otherwise, the degree of α_{1a}/5-HT_{1A} selectivity of the lead compound is generally maintained and, in the only cases of (*S*)-**7** and (*S*)-**11**, annihilated and reversed respectively.

As stated introducing the paper, compounds **1**–**11** were designed not selecting a number of substituents with maximum variance and minimum covariance in physico-chemical properties, but on the basis of indications provided by the previous SAR analysis of a set of sixteen *ortho* monosubstituted phenoxy analogues of WB4101 (compounds (*S*)-**I**-(*S*)-**XVI** in Table 2) [5]. Such indications restricted the choice to three types of substituent, namely alkyl, alkoxyl and halogen, thus limiting the sampling of the property space. This discouraged a classical Hansch multivariate regression analysis, like that previously performed for compounds (*S*)-**I**-(*S*)-**XVI**. Otherwise, it seemed worthwhile to verify whether parabolic relationships could describe the dependence of the affinities of (*S*)-WB4101 and of compounds (*S*)-**1**, (*S*)-**2** and (*S*)-**4**-(*S*)-**11** at the α_1-AR subtypes and the 5-HT_{1A} receptor on the volume of the two *ortho* substituents, the only parameter, among those selected, which shows a relatively large variation in this series of compounds ((*S*)-**3** was excluded due to its indefinite < 6 pK_i values). For each of the four receptors, the resultant parabolic equation is given in Table 3. The level of significance was judged by the squared correlation coefficient (r^2), the squared cross-validated correlation coefficient (q^2), the standard error of the estimates (SE) and the Fisher significance ratio (*F*). Interestingly, r^2 drops from high values for the α_{1a} and α_{1b} equations, 0.86 and 0.74, respectively, to low ones for the α_{1d} (0.54) and, especially, for the 5-HT_{1A} (0.35) equations and similar trends are also shown by the other statistical parameters. This is consistent with the previously reported QSARs of monosubstituted compounds (*S*)-**I**-(*S*)-**XVI**, which indicate different steric effects of the ortho substituents depending on the considered receptor: (i) a simply negative incidence of the volume on the α_{1a} and, to a minor extent, on the α_{1b} affinity, (ii) a negative incidence of the volume, but counteracted by a largely positive effect of the length, on the α_{1d} affinity and, finally, (iii) no influence of the volume, but only a negative effect of the length in the case of the 5-HT_{1A} receptor.

A classical quantitative structure-activity relationship (Hansch) study was applied to (*S*)-WB4101 and to its 26 analogs, that is the present *o*-disubstituted derivatives (*S*)-**1**, (*S*)-**2**, (*S*)-**4**-(*S*)-**11** and the previously reported unsubstituted or *o*-monosubstituted derivatives (*S*)-**I**-(*S*)-**XVI**, considering, for these latter, also the contribution of the one or two *ortho* hydrogen atoms. In this case, a variety of substituents was represented and the mass of data was undoubtedly suitable material for a QSAR investigation. First, we maintained the same physicochemical parameters used for the QSAR of (*S*)-

Table 2
Experimental affinity constants, expressed as pK_i (–logK_i, M) ± S.E., of the enantiomers of compounds **I**–**XVI** for cloned human α_1-adrenoceptor subtypes and 5-HT_{1A} receptor [a]

Phenoxy *o*-substituent	Compound	pK_i			
		α_{1a}	α_{1b}	α_{1d}	5-HT_{1A}
H	(*S*)-**I**	7.34 (± 0.05)	7.02 (± 0.03)	7.57 (± 0.08)	8.57 (±0.07)
Me	(*S*)-**II**	7.51 (± 0.04)	7.13 (± 0.05)	7.10 (± 0.05)	8.55 (± 0.04)
Et	(*S*)-**III**	7.58 (± 0.14)	7.06 (± 0.07)	8.01 (± 0.17)	7.26 (± 0.04)
t-Bu	(*S*)-**IV**	6.22 (± 0.04)	6.29 (± 0.08)	6.12 (± 0.04)	7.59 (± 0.03)
CN	(*S*)-**V**	7.06 (± 0.09)	6.05 (± 0.08)	8.17 (± 0.22)	7.15 (± 0.06)
CF_3	(*S*)-**VI**	7.16 (± 0.04)	6.99 (± 0.08)	7.77 (± 0.18)	6.75 (± 0.05)
COMe	(*S*)-**VII**	7.26 (± 0.04)	6.73 (± 0.05)	7.54 (± 0.19)	7.17 (± 0.08)
F	(*S*)-**VIII**	7.47 (± 0.10)	7.27 (± 0.04)	7.16 (±)	8.52 (± 0.02)
Cl	(*S*)-**IX**	7.62 (± 0.07)	7.24 (± 0.29)	8.08 (± 0.32)	7.96 (± 0.04)
SMe	(*S*)-**X**	7.72 (± 0.10)	7.46 (± 0.26)	8.34 (± 0.17)	7.62 (± 0.08)
SOMe	(*S*)-**XI**	7.17 (± 0.07)	6.90 (± 0.04)	7.11 (± 0.11)	7.33 (± 0.04)
SO_2Me	(*S*)-**XII**	6.98 (± 0.15)	7.00 (± 0.04)	6.69 (± 0.06)	6.96 (± 0.04)
NO_2	(*S*)-**XIII**	7.31 (± 0.27)	7.24 (± 0.12)	7.96 (± 0.13)	7.44 (± 0.06)
NHCOMe	(*S*)-**XIV**	7.46 (± 0.19)	6.81 (± 0.14)	7.73 (± 0.03)	8.16 (± 0.43)
NH_2	(*S*)-**XV**	7.26 (± 0.11)	6.88 (± 0.10)	7.88 (± 0.17)	8.06 (± 0.08)
OMe	(*S*)-**XVI**	7.90 (± 0.09)	7.37 (± 0.14)	7.52 (±)	8.67 (± 0.02)

[a] Data taken from Ref. [5].

Table 3
Parabolic relationships between the volume (V) of the *ortho* phenoxy substituents of (*S*)-WB4101, (*S*)-**1**, (*S*)-**2** and (*S*)-**4** -(*S*)-**11** and the affinity for the α_1-ARs and the 5-HT_{1A} receptor. *V* is the sum of the fragmental volume of the two aromatic substituents (data taken from Ref. [25])

Receptor	Equations	*n*	r^2	q^2	S.E.	*F*
α_{1a}	(1) pK_i = 5.92–0.0014V^2 + 0.13V	11	0.858	0.822	0.269	24.16
α_{1b}	(2) pK_i = 5.89–0.0008V^2 + 0.084V	11	0.739	0.673	0.236	11.31
α_{1d}	(3) pK_i = 5.29–0.0012V^2 + 0.118V	11	0.542	0.427	0.519	4.730
5-HT_{1A}	(4) pK_i = 6.54–0.0006V^2 + 0.062V	11	0.346	0.183	0.411	2.123

I-(*S*)-**XVI**, namely the resonance constant of Swain and Lupton (R) [26], the fragmental volume of aromatic substituents (V) [25], the length parameter of Verloop (L) [27] and the ability of accepting H bonds (HBβ) [28]. The resultant four equations, corresponding to the α_{1a}-, α_{1b}- and α_{1d}-AR and to the 5-HT_{1A} receptor, exhibited r^2 values of 0.65, 0.58, 0.41 and 0.36. Compared to the previous corresponding values (0.78, 0.53, 0.71 and 0.85) obtained for (*S*)-**I**-(*S*)-**XVI**, these new correlation coefficients were generally lower and only in the case of the α_{1a} and α_{1b} QSARs they maintained some statistical significance, which was instead completely lost by the equations for the other two receptors. Furthermore, the new α_{1a} QSAR had nearly unchanged coefficients indicating the robustness and the good predictive power of the previous quantitative relationship, constructed on the basis of the α_{1a} affinities of (*S*)-**I**-(*S*)-**XVI**. Consistently with what we had already observed for these latter compounds, a sort of solidarity between α_{1a} and α_{1b} affinity trends in contrast with diverging SAR data for the α_{1d} and 5-HT_{1A} receptors resulted as a consequence of the *o*-disubstitution pattern at the phenoxy moiety. Such a behavior should have been better enlightened by new more significant equations, de novo constructed reselecting physicochemical parameters. For each of the four receptors, the new equation adopted as the final model is given in Table 4. The exclusion of the *o*-monoamino substituted analogue (*S*)-**XV** from the calculation resulted in a remarkable enhancement of the correlation coefficients, probably due to the unique nature of the amino group, among these substituents, of strong hydrogen bond donor, not parametrized by the physicochemical properties represented in the final equations. Therefore, these correlate the affinities of 26 compounds: (*S*)-WB4101, (*S*)-**I**-(*S*)-**XIV**, (*S*)-**XVI**, (*S*)-**1**, (*S*)-**2** and (*S*)-**4**-(*S*)-**11**. The physicochemical parameters, suitably chosen out of 27, and the respective values for each pair of *ortho* substituents are shown in Table 5. As electronic parameters, the resonance and field constants of Swain and Lupton *R* and *F* [26], the Taft σ_R [29] and the Esaki flow intensity I_F [30], indicative of the inductive-field effect, were used, while the fragmental volume of aromatic substituents (*V*) and the length parameter of Verloop (*L*) were employed as steric descriptors. In comparison with the previous equations, constructed for (*S*)-**I**-(*S*)-**XVI** and recalculated including the present disubstituted derivatives without changing the parameters, the QSARs reported in Table 4 exhibit a much better statistic significance, as demonstrated by the r^2 values (0.90, 0.66, 0.59 and 0.67 vs. 0.65, 0.58, 0.41 and 0.36). Partly, this can be ascribed to the presence of squared parameters (V^2 in the three α_1 equations and L^2 in that for the α_{1a} subtype) and of the indicator variable I_{OMe}. This notwithstanding, it is to be underlined the 0.90 value of the α_{1a} squared correlation coefficient, which allows a good prediction of the α_{1a} affinities (Fig. 3). Furthermore, some trends, previously observed for (*S*)-**I**-(*S*)-**XVI**, are confirmed and some new ones are recognized: (i) the α_{1a} and α_{1b} QSARs are similar, but the correlation coefficient is much better for the α_{1a}-AR; (ii) the volumetric term, squared in the three α_1 equations, has a modestly negative incidence on the α_1 affinities, which becomes remarkable for the highest values of *V* only in the α_{1a} and α_{1d} relationships, where it is however counteracted by L; in the 5-HT_{1A} equation, *V*, which is the only steric parameter, is not squared and has a low negative coefficient; (iii) the beneficial effect of the methoxy substituent is parametrized by the new entered indicator variable I_{OMe}, which appears in the three α_1 equations, but not in the 5-HT_{1A} QSAR; (iv) conversely, disappears the HBβ parameter, probably due to the absence of hydrogen bond acceptor substituents, methoxyl excepted, in the new disubstituted WB4101 analogues; (v) electron donor substituents by resonance favor the α_{1a}, α_{1b} and 5-HT_{1A} affinities (see the negative coefficient of *R*), while depress the affinity for the α_{1d}-AR, already modestly advantaged by such substituents in the monosubstituted WB4101 analogues (Table 4).

4. Conclusion

The extension of QSAR analysis from the heterogeneously *o*-monosubstituted WB4101 analogues (*S*)-**I**-(*S*)-**XVI**, to the less representative selection of *o*-disubstituted derivatives (*S*)-**1**-(*S*)-**11** makes the correlation between biological and structural data more difficult. The affinity profiles at the four receptors (α_{1a}, α_{1b}, α_{1d} and 5-HT_{1A}) are less differentiated and the affinity ratios generally less marked than for the monosubstituted analogues. In this context, however, quantitative structure affinity relationships are still able to give relevant information to understanding some determinants of the interaction of these WB4101 related compounds with each of the four receptors, drawing, in particular, interesting distinctions between the α_{1a}-AR and the 5-HT_{1A} receptor. For instance, parallel *ortho* substitutions on (*S*)-**I** and on (*S*)-**XVI** result in parallel shifts in α_{1a} affinity. This is well represented by a plot of the α_{1a} pK_i values for (*S*)-**I** and its *ortho* methyl, ethyl, *t*-butyl, fluoro, chloro and methoxy analogues versus the corresponding *o*-methoxy homologues, that is (*S*)-**XVI**, (*S*)-**6**, (*S*)-**7**, (*S*)-**11**, (*S*)-**4**, (*S*)-**5** and (*S*)-WB4101. Such a plot reveals the existence of a significant linear correlation ($r = 0.944$), suggesting that the *o*-mono-

Table 4
Equations for QSAR of (*S*)-WB4101, (*S*)-**1**, (*S*)-**2**, (*S*)-**4** -(*S*)-**11**, (*S*)-**I**-(*S*)-**XIV** and (*S*)-**XVI** at the α_1-ARs and the 5-HT_{1A} receptor

Receptor	Equation	*n*	r^2	q^2	S.E.	*F*
α_{1a}	(1) pK_i = 6.60–3.46 $10^{-4}V^2$–0.54*R* + 0.53I_{OMe} + 0.032L^2	26	0.896	0.876	0.267	45.19
α_{1b}	(2) pK_i = 7.01–5.09 $10^{-5}V^2$–0.50*R* + 0.53I_{OMe}	26	0.655	0.608	0.340	13.91
α_{1d}	(3) pK_i = 5.89–3.51 $10^{-4}V^2$ + 0.87I_{OMe} + 0.76σ_R + 0.35*L*	26	0.592	0.515	0.444	7.634
5-HT_{1A}	(4) pK_i = 8.66–1.31 *F*–0.87*R*–0.12I_F–0.020*V*	26	0.670	0.608	0.360	10.68

Table 5
Values of the physicochemical parameters [a] used in the QSAR study of *ortho* mono- and disubstituted phenoxy analogues of (*S*)-WB4101

Compound	*o*-Substituent	R [b]	V [c]	L [d]	I_F [e]	F [b]	σ_R [f]	I_{OMe}
(S)-**I**	H, H	0	9.24	4.12	0	0	0	0
(S)-**II**	H, Me	–0.13	22.70	4.93	1.64	–0.04	–0.14	0
(S)-**III**	H, Et	–0.10	36.16	6.17	0.72	–0.05	–0.09	0
(S)-**IV**	H, *t*-Bu	–0.13	63.08	6.17	0.35	–0.07	–0.13	0
(S)-**V**	H, CN	0.19	22.00	6.29	–0.41	0.51	0.19	0
(S)-**VI**	H, CF_3	0.19	31.12	5.36	2.94	0.38	0.19	0
(S)-**VII**	H, Ac	0.20	37.16	6.12	–0.04	0.32	0.19	0
(S)-**VIII**	H, F	–0.34	11.41	4.71	1.32	0.43	–0.45	0
(S)-**IX**	H, Cl	–0.15	20.32	5.58	–1.46	0.41	–0.24	0
(S)-**X**	H, SMe	–0.18	37.70	6.36	–0.65	0.20	–0.20	0
(S)-**XI**	H, SOMe	0.22	42.50	6.17	–1.80	0.59	0.18	0
(S)-**XII**	H, SO_2Me	0.10	47.04	6.17	–1.74	0.54	0.18	0
(S)-**XIII**	H, NO_2	0.16	25.08	5.50	1.40	0.67	0.15	0
(S)-**XIV**	H, NHAc	–0.26	46.03	7.15	–1.88	0.28	-0.26	0
(S)-**XV**	H, NH_2	–0.18	19.53	4.84	0.19	0.02	–0.76	0
(S)-**XVI**	H, OMe	–0.51	27.76	6.04	–3.00	0.26	–0.55	1
(*S*)-**1**	F, F	–0.68	13.58	5.30	2.64	0.86	–0.90	0
(*S*)-**2**	Cl, Cl	–0.30	31.40	7.04	–2.92	0.82	–0.48	0
(*S*)-**3**	*t*-Bu, *t*-Bu	–0.26	116.92	8.22	0.70	-0.14	–0.26	0
(*S*)-**4**	F, MeO	–0.85	38.84	6.63	–1.68	0.69	–1.00	1
(*S*)-**5**	Cl, MeO	–0.66	29.93	7.50	–4.46	0.65	–0.79	1
(*S*)-**6**	Me, MeO	–0.64	41.22	6.85	–1.36	0.22	–0.69	1
(*S*)-**7**	Et, MeO	–0.61	54.68	8.09	–2.28	0.21	–0.60	1
(*S*)-**8**	Pr, MeO	–0.61	68.14	8.09	–2.58	0.21	–0.65	1
(*S*)-**9**	*i*-Pr, MeO	–0.70	58.90	8.12	–2.48	0.23	–0.74	1
(*S*)-**10**	Allyl, MeO	–0.59	68.14	8.90	–2.43	0.20	–0.63	1
(*S*)-**11**	*t*-Bu, MeO	–0.64	81.60	8.09	–2.65	0.19	–0.68	1
(*S*)-**WB4101**	MeO, MeO	–1.02	46.28	7.96	–6.00	0.52	–1.10	2

[a] For each parameter, the reported value is the sum of the contributions of the two substituents in 2 and in 6.
[b] Data taken from Ref. [26].
[c] Data taken from Ref. [25].
[d] Data taken from Ref. [27].
[e] Data taken from Ref. [30].
[f] Data taken from Ref. [29].

substituted WB4101 analogues and the respective *o*-methoxy homologues bind at α_{1a}-AR in a similar fashion with an additive average contribution of *o*-methoxyl to α_{1a} pK_i of about one unit. The additivity of the *ortho* substituent contributions to the α_{1a} affinity is also indicated by the plots of the α_{1a} pK_i values of the difluoro, dichloro and dimethoxy derivatives versus the corresponding monosubstituted analogues and versus the fluoromethoxy, chloromethoxy and dimethoxy derivatives. In these two graphs, the points are only three, but perfectly lying on a straight line ($r = 1$).

In the case of the 5-HT_{1A} receptor, attempts at correlation between the same sets of affinity data were completely unsuccessful giving insignificant or nearly null values of *r*.

On the basis of these results and of previous evidences, we can conclude that the interaction of the phenoxy moiety of WB4101 related compounds with the α_{1a}-AR is greatly advantaged by the *ortho* disubstitution. Likely, it stabilizes an extended conformation of the molecule and a proper orientation of the phenyl ring. We don't know if both the *ortho* substituents are involved in the interaction. At any event, if they both have suitable properties, conforming to the present QSAR indications, this should increase the population of bioactive conformers and result in higher affinities. This fact, together with the optimal properties of the methoxy substituent for the α_{1a} interaction, would account for the unequalized potency of WB4101, which has two *o*-methoxy groups. Contrariwise, our analysis suggests that the *ortho* monosubstituted WB4101 analogues and their *ortho* methoxy homologues interact with the 5-HT_{1A} receptor in a different fashion, considering the null correlation between the respective affinities. This would explain why, in the case of this receptor, the contributions of the two *ortho* substituents are not additive, as also indicated by the low correlation coefficient of the respective QSAR here reported, and why properly *o*-monosubstituted WB4101 analogues can compete with this latter and other *o*-disubstituted WB4101 related compounds in 5-HT_{1A} affinity.

5. Experimental protocols

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

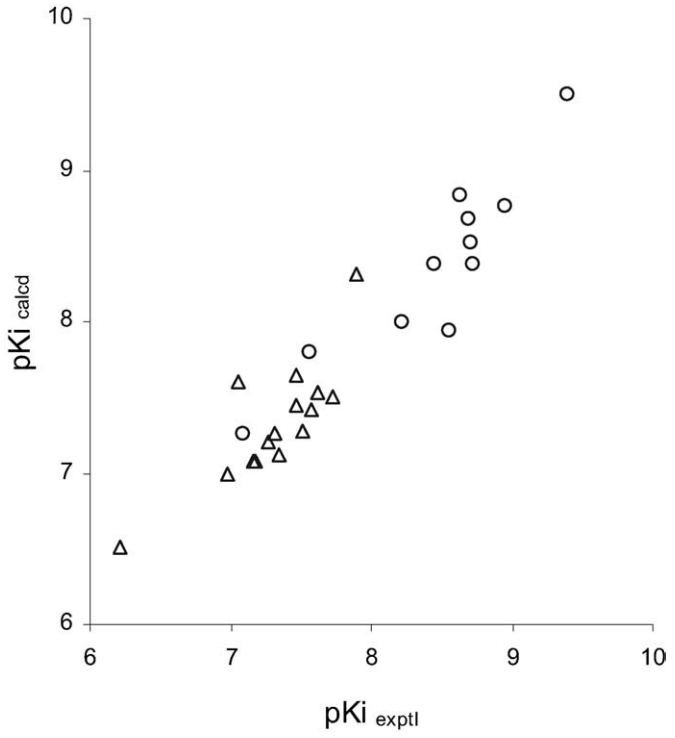


Fig. 3. Relationship between calculated and experimental α_{1a} affinities of (*S*)-**I**-(*S*)-**XIV** and (*S*)-**XVI** (triangles) and of (*S*)-**1**, (*S*)-**2**, (*S*)-**4**-(*S*)-**11** and (*S*)-WB4101 (circles) ($r^2 = 0.90$; $n = 26$).

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).

*5.1.1. 2-(2,6-Difluorophenoxy)ethanol (**12**)*

A mixture of 2,6-difluorophenol (15 g, 115.3 mmol), ethylene carbonate (20.3 g, 230.6 mmol) and potassium carbonate (26.5 g, 185 mmol) in toluene (75 ml) was refluxed for 2 h. After cooling at room temperature, water (40 ml) was added. The aqueous layer was separated and extracted with toluene (3 × 35 ml). The organic phase was treated with 10% NaOH (40 ml), washed with water twice (2 × 30 ml), dried and concentrated to give the crude product which was purified by chromatography on silica gel. Elution with cyclohexane/ethyl acetate (90:10) yielded 20.08 g (83.9%) of **12** as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 2.45 (br s, 1H), 4.05 (m, 2H), 4.25 (m, 2H), 6.80–7.00 (m, 3H). Anal. Calcd for $C_8H_8F_2O_2$ (174.15).

*5.1.2. 2-(2,6-Dichlorophenoxy)ethanol (**13**)*

Prepared from 2,6-dichlorophenol as described for **12** but replacing toluene with DMF. The crude product was isolated (100%) as a yellow oil which was used for the subsequent step without further purification: ^{1}H NMR ($CDCl_3$) δ 2.73 (br s, 1H), 3.94 (m, 2H), 4.18 (m, 2H), 6.95 (t, 1H), 7.25 (m, 2H). Anal. Calcd for $C_8H_8Cl_2O_2$ (207.05).

*5.1.3. 2-(2,6-Di-t-butylphenoxy)ethanol (**14**)*

Prepared from 2,6-di-*t*-butylphenol as described for **12** but replacing toluene with DMF. After chromatography on silica gel (cyclohexane/ethyl acetate 90:10), the product was isolated as a yellow oil (56.9%): ^{1}H NMR ($CDCl_3$) δ 1.44 (s, 18H), 1.97 (br s, 1H), 3.93 (t, 2H), 4.02 (t, 2H), 6.99 (t, 1H), 7.26 (d, 2H). Anal. Calcd for $C_{16}H_{26}O_2$ (250.38).

*5.1.4. 2-(2-Allyl-6-methoxyphenoxy)ethanol (**15**)*

Prepared from 2-allyl-6-methoxyphenol as described for **12** but replacing toluene with DMF. After chromatography on silica gel (cyclohexane/ethyl acetate 80:20), the product was isolated (62.5%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 3.06 (br s, 1H), 3.45 (d, 2H), 3.86 (m, 5H), 4.07 (t, 2H), 5.00–5.09 (m, 2H), 5.88–6.08 (m, 1H), 6.80 (d, 2H), 7.03 (t, 1H). Anal. Calcd for $C_{12}H_{16}O_3$ (208.25).

*5.1.5. 1-Tosyloxy-2-(2,6-difluorophenoxy)ethane (**16**)*

Tosyl chloride (19.3 g, 101.3 mmol) was added drop-wise to a stirred solution of **12** (16.8 g, 97.5 mmol) in pyridine (20 ml) at 0 °C. The resulting mixture was stirred at room temperature for 20 h, diluted with diethyl ether (120 ml) and washed with 10% HCl (120 ml). The aqueous layer was separated and extracted with diethyl ether twice. The organic phases were combined, dried and concentrated to give 21.5 g (67%) of **16** as an oil which was used for the subsequent step without further purification: ^{1}H NMR ($CDCl_3$) δ 2.40 (s, 3H), 4.60–4.80 (m, 4H), 6.80–8.00 (m, 7H). Anal. Calcd for $C_{15}H_{14}F_2O_4S$ (328.34).

*5.1.6. 1-Azido-2-(2,6-difluorophenoxy)ethane (**17**)*

Sodium azide (60 g, 0.92 mol) was added to a stirred solution of **16** in DMF (300 ml) and water (100 ml). The resulting mixture was heated at 90 °C for 5 h. After cooling at room temperature, water (100 ml) was added and the resulting mixture was extracted with hexane (4 × 100 ml). The organic phases were combined, washed with water (30 ml), dried and concentrated to give 14 g of crude product which was purified by chromatography on silica gel. Elution with hexane/ethyl acetate (85:15) yielded 11 g (90%) of **17** as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 3.60 (t, 2H), 4.30 (t, 2H), 6.80–7.05 (m, 3H). Anal. Calcd $C_8H_7F_2N_3O$ (199.16).

*5.1.7. 2-(2,6-Difluorophenoxy)ethylamine (**18**)*

Hydrazine hydrate (20 ml) was added drop-wise to a stirred mixture of **17** (11 g, 63.5 mmol) and PdO (50 mg) in methanol (100 ml) at 65 °C. The reaction mixture was refluxed for 4 h. After cooling at room temperature, PdO was removed by filtration and the resulting solution concentrated to give the crude product, which was purified by chromatography on silica gel. Elution with dichloromethane/methanol (97:3) yielded 4.8 g (50%) of **18** as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.50 (s, 2H), 3.05 (s, 2H), 4.15 (t, 2H), 6.80–7.05 (m, 3H). Anal. Calcd for $C_8H_9OF_2N$ (173.16).

*5.1.8. 1-Mesyloxy-2-(2,6-dichlorophenoxy)ethane (**19**)*

Mesyl chloride (11.13 ml, 143 mmol) was added drop-wise to a stirred solution of **13** (28 g, 136.9 mmol) and TEA (20 ml) in dichloromethane (375 ml) at 0 °C. After 1 h at room temperature, the reaction mixture was washed with a saturated solution of $NaHCO_3$. The aqueous layer was separated and extracted with dichloromethane twice. The organic phases were combined, dried and concentrated to give 34.26 g (87.8%) of **19** as a yellow oil, which was used for the subsequent step without further purification: ^{1}H NMR ($CDCl_3$) δ 3.09 (s, 3H), 4.26 (m, 2H), 4.56 (m, 2H), 6.96 (t, 1H), 7.36 (m, 2H). Anal. Calcd for $C_9H_{10}Cl_2O_4S$ for (285.15).

*5.1.9. 1-Mesyloxy-2-(2,6-di-t-butylphenoxy)ethane (**20**)*

Prepared from **14** as described for **19**. Crystallization from hexane yielded **20** as a light yellow solid (77.1%): m.p. 54.9–55.7 °C; ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 18H), 3.11 (s, 3H), 4.05 (t, 2H), 4.60 (t, 2H), 7.01 (t, 1H), 7.26 (d, 2H). Anal. Calcd for $C_{17}H_{28}O_4S$ (328.47).

*5.1.10. 1-Mesyloxy-2-(2-allyl-6-methoxyphenoxy)ethane (**21**)*

Prepared from **15** as described for **19**. The resulting crude product (91%) was used for the subsequent step without further purification:^{1}H NMR ($CDCl_3$) δ 3.09 (s, 3H), 3.44 (d, 2H), 3.84 (s, 3H), 4.23 (dd, 2H), 4.53 (dd, 2H), 4.99–5.08 (m, 2H), 5.86–6.06 (m, 1H), 6.77–6.81 (dd, 2H), 7.03 (t, 1H). Anal. Calcd for $C_{13}H_{18}O_5S$ (286.35).

*5.1.11. N-[2-(2,6-dichlorophenoxy)ethyl]phthalimide (**22**)*

A solution of **19** (34.26 g, 120 mmol) in DMF (180 ml) was added to a stirred solution of potassium phthalimide (30.5 g, 164.75 mmol) in DMF (400 ml). The resulting mixture was heated at 100 °C for 1.5 h and, after cooling at room temperature, quenched into ice and water (800 ml). The resulting precipitate was isolated, washed with EtOH (50 ml), dried and crystallized from EtOH (100 ml) to give 15.6 g (39%) of **22** as a white solid: m.p. 127 °C; ^{1}H NMR ($CDCl_3$) δ 4.17 (m, 2H), 4.27 (m, 2H), 6.95 (m, 1H), 7.27 (m, 2H), 7.73 (m, 2H), 7.87 (m, 2H). Anal. Calcd for $C_{16}H_{11}Cl_2NO_3$ (336.17).

*5.1.12. N-[2-(2,6-di-t-butylphenoxy)ethyl]phthalimide (**23**)*

Prepared from **20** as described for **22** and isolated after crystallization from EtOH as a white solid (63.9%): m.p. 107.5–108.3 °C; ^{1}H NMR ($CDCl_3$) δ 1.39 (s, 18H), 3.95 (t, 2H), 4.16 (t, 2H), 6.96 (t, 1H), 7.22 (d, 2H), 7.73 (m, 2H), 7.87 (m, 2H). Anal. Calcd for $C_{24}H_{29}NO_3$ (379.49).

*5.1.13. N-[2-(2-allyl-6-methoxyphenoxy)ethyl]phthalimide (**24**)*

Prepared from **21** as described for **22** and isolated after crystallization from EtOH as a white solid (50%): m.p. 76.8–77 °C; ^{1}H NMR ($CDCl_3$) δ 3.32 (d, 2H), 3.63 (s, 3H), 4.09 (t, 2H), 4.20 (t, 2H), 4.86–4.95 (m, 2H), 5.74–5.94 (m, 1H), 6.71 (d, 2H), 6.93 (t, 1H), 7.74 (m, 2H), 7.86 (m, 2H). Anal. Calcd for $C_{20}H_{19}NO_4$ (337.37).

*5.1.14. 2-(2,6-Dichlorophenoxy)ethylamine (**25**)*

Hydrazine hydrate (2.95 ml) was added drop-wise to a stirred mixture of **22** (15.6 g, 46.4 mmol) in 2-methoxyethanol (95 ml) at 125 °C. After refluxing for 2 h, 10% HCl was added until pH 3. After cooling at room temperature, the reaction mixture was concentrated, the residue treated with 10% NaOH (70 ml) and washed with dichloromethane. The organic phases were combined, dried and concentrated. Distillation under vacuum (b.p. 110 °C at 1 mbar) of the residue gave 8.5 g (89%) of **25** as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.56 (br s, 2H), 3.07 (t, 2H), 4.03 (t, 2H), 6.95 (t, 1H), 7.25 (d, 2H). Anal. Calcd for $C_8H_9Cl_2NO$ (206.07).

*5.1.15. 2-(2,6-Di-t-butylphenoxy)ethylamine (**26**)*

Prepared from **23** as described for **25**. After distillation under vacuum (b.p. 110 °C at 0.2 mbar), the product was isolated (100%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.44 (s, 20H), 3.16 (t, 2H), 3.81 (t, 2H), 6.98 (t, 1H), 7.25 (d, 2H). Anal. Calcd for $C_{16}H_{27}NO$ (249.39).

*5.1.16. 2-(2-Allyl-6-methoxyphenoxy)ethylamine (**27**)*

Prepared from **24** as described for **25** but replacing 2-methoxyethanol with methanol. The crude product was isolated (100%) and used for the subsequent step without further purification: ^{1}H NMR ($CDCl_3$) δ 1.57 (s, 2H), 3.03 (t, 2H), 3.45 (d, 2H), 3.84 (s, 3H), 3.97 (t, 2H), 5.08 (m, 2H), 5.87–6.07 (m, 1H), 6.80 (d, 2H), 7.00 (t, 1H). Anal. Calcd for $C_{12}H_{17}NO_2$ (207.27).

*5.1.17. 2-(2-Methoxy-6-propylphenoxy)ethylamine (**28**)*

A solution of **27** (4.92 g, 23.7 mmol) in methanol (50 ml) was added with 10% Pd/C (500 mg) and vigorously shaken under hydrogen at room temperature. After removing the catalyst by filtration, the filtrate was concentrated and distilled under vacuum (110 °C at 0.2 mbar) to give 4.91 g (98.8%) of **28** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 3H), 1.63 (m, 4H), 2.62 (t, 2H), 3.04 (t, 2H), 3.83 (s, 3H), 3.96 (t, 2H), 6.79 (dd, 2H), 6.98 (t, 1H). Anal. Calcd for $C_{12}H_{19}NO_2$ (209.28).

*5.1.18. 2-Benzyloxy-3-fluoroacetophenone (**29**)*

Prepared from 2-hydroxy-3-fluoroacetophenone according to the procedure reported in Ref. [19].

*5.1.19. 2-Benzyloxy-3-chloroacetophenone (**30**)*

Prepared from 2-hydroxy-3-chloroacetophenone as described for **29**. After chromatography on silica gel (cyclohexane/ethyl acetate 95:5), the product was isolated (67.1%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 2.55 (s, 3H), 5.02 (s, 2H), 7.15 (t, 1H), 7.38 (m, 3H), 7.48 (m, 3H), 7.56 (dd, 1H). Anal. Calcd for $C_{15}H_{13}ClO_2$ (260.72).

*5.1.20. 2-Benzyloxy-3-methylacetophenone (**31**)*

Prepared from 2-hydroxy-3-methylacetophenone as described for **29**. After chromatography on silica gel (cyclohexane/ethyl acetate 75:25), the product was isolated (77%)

as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 2.33 (s, 3H), 2.59 (s, 3H), 4.85 (s, 2H), 7.10 (t, 1H), 7.34–7.45 (m, 7H). Anal. Calcd for $C_{16}H_{16}O_2$ (240.30).

5.1.21. 2-Benzyloxy-3-ethylacetophenone (32)

Prepared from 2-hydroxy-3-ethylacetophenone as described for **29**. After chromatography on silica gel (toluene), the product was isolated (54%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.28 (t, 3H), 2.62 (s, 3H), 2.75 (q, 2H), 4.87 (s, 2H), 7.16 (t, 1H), 7.30–7.50 (m, 7H). Anal. Calcd for $C_{17}H_{18}O_2$ (254.32).

5.1.22. 2-Benzyloxy-3-i-propylacetophenone (33)

Prepared from 2-hydroxy-3-*i*-propylacetophenone as described for **29**. After chromatography on silica gel (cyclohexane/ethyl acetate 95:5), the product was isolated (87%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.22 (d, 6H), 2.61 (s, 3H), 3.42 (m, 1H), 4.83 (s, 2H), 7.18 (t, 1H), 7.37–7.46 (m, 7H). Anal. Calcd for $C_{18}H_{20}O_2$ (268.35).

5.1.23. 2-Benzyloxy-3-t-butylacetophenone (34)

Prepared from 3-*t*-butyl-2-hydroxyacetophenone as described for **29**. After chromatography on silica gel (toluene) the product was isolated (47.5%) as a solid: m.p. 97.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.32 (s, 9H), 2.62 (s, 3H), 5.16 (s, 2H), 6.97 (d, 1H), 7.35–7.50 (m, 6H), 7.79 (d, 1H). Anal. Calcd for $C_{19}H_{22}O_2$ (282.38).

5.1.24. 2-Benzyloxy-3-fluorophenyl acetate (35)

Prepared from **29** according to the procedure reported in Ref. [19].

5.1.25. 2-Benzyloxy-3-chlorophenyl acetate (36)

Prepared from **30** as described for **35**. The crude product was isolated (100%) as dark oil which was used for the subsequent step without further purification: ^{1}H NMR ($CDCl_3$) δ 2.55 (s, 3H), 5.03 (s, 2H), 7.00 (dd, 1H), 7.07 (t, 1H), 7.29 (dd, 1H), 7.40 (m, 5H). Anal. Calcd for $C_{15}H_{13}ClO$ (276.71).

5.1.26. 2-Benzyloxy-3-methylphenyl acetate (37)

Prepared from **31** as described for **35**. The product was isolated (83.5%) as a yellow oil which was used for the subsequent step without further purification: ^{1}H NMR ($CDCl_3$) δ 2.20 (s, 3H), 2.28 (s, 3H), 4.92 (s, 2H), 6.91–7.09 (m, 3H), 7.36–7.51 (m, 5H). Anal. Calcd for $C_{16}H_{16}O_3$ (256.30).

5.1.27. 2-Benzyloxy-3-ethylphenyl acetate (38)

Prepared from **32** as described for **35**. The product was isolated (96.3%) as a yellow oil which was used for the subsequent step without further purification: ^{1}H NMR ($CDCl_3$) δ 1.25 (t, 3H), 2.20 (s, 3H), 2.70 (q, 2H), 4.95 (s, 2H), 6.90–7.00 (m, 1H), 7.10–7.20 (m, 2H), 7.30–7.50 (m, 5H). Anal. Calcd for $C_{17}H_{18}O_3$ (270.32).

5.1.28. 2-Benzyloxy-3-i-propylphenyl acetate (39)

Prepared from **33** as described for **35**. The crude product was isolated (98%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.19 (d, 6H), 2.18 (s, 3H), 3.36 (m, 1H), 4.93 (s, 2H), 6.92–6.96 (dd, 1H), 7.07–7.18 (m, 2H), 7.36–7.41 (m, 5H). Anal. Calcd for $C_{13}H_{20}O_3$ (226.31).

5.1.29. 2-Benzyloxy-3-t-butylphenyl acetate (40)

Prepared from **34** as described for **35**. Crystallization from methanol gave **40** as a yellow solid (88.3%): m.p. 68.8 °C; ^{1}H NMR ($CDCl_3$) δ 1.29 (s, 9H), 2.29 (s, 3H), 5.07 (s, 2H), 6.90–7.38 (m, 8H). Anal. Calcd $C_{19}H_{22}O_3$ (298.38).

5.1.30. 2-Benzyloxy-3-fluorophenol (41)

Prepared from **35** according to the procedure reported in Ref. [19].

5.1.31. 2-Benzyloxy-3-chlorophenol (42)

A solution of **36** (51.50 g, 186 mmol) and 2.5 N NaOH (83.2 ml) in methanol (520 ml) was stirred for 2 h at room temperature. The solvent was evaporated and the resulting residue added with dichloromethane (400 ml) and washed with water (350 ml). The aqueous layer was treated with 10% HCl (pH 1) and extracted with dichloromethane (4 × 200 ml). The organic phases were combined, dried and concentrated to give 35.69 g (81.7%) of **42** as a dark oil, which was used for the subsequent step without further purification: ^{1}H NMR ($CDCl_3$) δ 5.10 (s, 2H), 5.62 (br s, 1H), 6.85 (m, 1H), 6.97 (m, 2H), 7.41 (m, 5H). Anal. Calcd for $C_{13}H_{11}ClO_2$ (234.68).

5.1.32. 2-Benzyloxy-3-methylphenol (43)

Prepared from **37** as described for **41**. After chromatography on silica gel (cyclohexane/ethyl acetate 80:20), the crude product was isolated (49%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 2.23 (s, 3H), 4.99 (s, 2H), 5.51 (s, 1H), 6.76–6.82 (m, 2H), 6.98 (t, 1H), 7.35–7.52 (m, 5H). Anal. Calcd for $C_{14}H_{14}O_2$ (214.26).

5.1.33. 2-Benzyloxy-3-ethylphenol (44)

Prepared from **38** as described for **41**. After chromatography on silica gel (toluene), **44** was isolated (86%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.34 (t, 3H), 2.79 (q, 2H), 4.96 (s, 2H), 5.74 (s, 1H), 6.80–7.10 (m, 3H), 7.35–7.50 (m, 5H). Anal. Calcd for $C_{15}H_{16}O_2$ (228.29).

5.1.34. 2-Benzyloxy-3-i-propylphenol (45)

Prepared from **39** as described for **41**. After chromatography on silica gel (cyclohexane/ethyl acetate 90:10), the product was isolated (51.6%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.27 (d, 6H), 3.37 (m, 1H), 4.90 (s, 2H), 5.49 (s, 1H), 6.83 (t, 2H), 7.04 (t, 1H), 7.35–7.48 (m, 5H). Anal. Calcd for $C_{16}H_{18}O_2$ (242.31).

5.1.35. 2-Benzyloxy-3-t-butylphenol (46)

Prepared from **40** as described for **41**. After chromatography on silica gel (toluene), the product was isolated (73.4%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 9H), 5.11 (s, 2H), 5.68 (s, 1H), 6.89 (s, 2H), 7.06 (s, 1H), 7.44 (m, 5H). Anal. Calcd for $C_{17}H_{20}O_2$ (254.34).

*5.1.36. 2-Benzyloxy-3-fluoroanisole (**47**)*

Iodomethane (6.1 g, 41.3 mmol) was added drop-wise to a solution of **41** (6 g, 27.5 mmol) and NaOH (1.1 g, 27.5 mmol) in ethanol (60 ml) at room temperature. After 24 h, ethanol was evaporated and the residue treated with 10% HCl (200 ml) and extracted with ethyl acetate (3 × 100 ml). The organic phases were combined, washed with water (10 ml), dried and concentrated to give the crude product, which was purified by chromatography on silica gel. Elution with cyclohexane/ethyl acetate (90:10) afforded 6 g (94%) of **47** as an oil: ^{1}H NMR ($CDCl_3$) δ 3.86 (s, 3H), 5.10 (s, 2H), 6.67–6.72 (m, 2H), 6.92–6.99 (m, 1H), 7.26–7.52 (m, 5H). Anal. Calcd for $C_{14}H_{13}FO_2$ (232.11).

*5.1.37. 2-Benzyloxy-3-chloroanisole (**48**)*

Iodomethane (1.75 ml, 28.1 mmol) was added drop-wise to a solution of **42** (6 g, 25.6 mmol) and tetrabutylammonium bromide (0.84 g, 2.6 mmol) in dichloromethane (60 ml) and 2.5 N NaOH (20.5 ml, 51.1 mmol). The resulting mixture was stirred at room temperature for 7 h. The organic layer was separated, washed with 10% HCl (80 ml) and then with water (80 ml), dried and concentrated to give 6.77 g of the crude product, which was purified by chromatography on silica gel. Elution with cyclohexane/ethyl acetate (90:10) afforded 4.3 g (67.6%) of **48** as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 3.85 (s, 3H), 5.07 (s, 2H), 6.82 (m, 1H), 7.01 (m, 2H), 7.40 (m, 3H), 7.60 (m, 2H).Anal. Calcd for $C_{14}H_{13}ClO_2$ (248.70).

*5.1.38. 2-Benzyloxy-3-methylanisole (**49**)*

Prepared from **43** as described for **47**. After chromatography on silica gel (hexane/ethyl acetate 80:20), the product was isolated (72%) as an oil: ^{1}H NMR ($CDCl_3$) δ 2.23 (s, 3H), 3.88 (s, 3H), 4.99 (s, 2H), 6.76–6.82 (m, 2H), 6.98 (t, 1H), 7.32–7.51 (m, 5H). Anal. Calcd for $C_{15}H_{16}O_2$ (228.29).

*5.1.39. 2-Benzyloxy-3-ethylanisole (**50**)*

Prepared from **44** as described for **47,** but replacing ethanol with methanol. After chromatography on silica gel (toluene), **50** was isolated (48%) as an oil: ^{1}H NMR ($CDCl_3$) δ 1.32 (t, 3H), 2.79 (q, 2H), 3.97 (s, 3H), 5.14 (s, 2H), 6.80–7.00 (m, 2H), 7.10–7.20 (m, 1H), 7.25–7.65 (m, 5H). Anal. Calcd for $C_{16}H_{18}O_2$ (242.31).

*5.1.40. 2-Benzyloxy-3-i-propylanisole (**51**)*

Prepared from **45** as described for **47**. After chromatography on silica gel (cyclohexane/ethyl acetate 90:10), the product was isolated (78.4%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.18 (d, 6H), 3.39 (m, ,1H), 3.89 (s, 3H), 5.02 (s, 2H), 6.79–6.89 (m, 2H), 7.08 (t, 1H), 7.33–7.52 (m, 5H). Anal. Calcd for $C_{17}H_{20}O_2$ (256.34).

*5.1.41. 2-Benzyloxy-3-t-butylanisole (**52**)*

Prepared from **46** as described for **47**, but replacing ethanol with methanol. The crude product was isolated (88.8%) and used for the subsequent step without further purification: ^{1}H NMR ($CDCl_3$) δ (s, 9H), 3.93 (s, 3H), 5.16 (s, 2H), 6.86 (dd, 2H), 6.97 (br s, 1H), 7.30–7.55 (m, 5H). Anal. Calcd for $C_{18}H_{22}O_2$ (270.37).

*5.1.42. 2-Fluoro-6-methoxyphenol (**53**)*

A solution of **47** (6 g, 25.8 mmol) in methanol (60 ml) was added with 10% Pd/C (250 mg) and vigorously shaken under hydrogen at room temperature. The catalyst was removed by filtration and the filtrate concentrated to give **53**, which was purified by chromatography on silica gel. Elution with cyclohexane/ethyl acetate (95:5) yielded 3 g (82%) of **53** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 3.90 (s, 3H), 5.40 (s, 1H), 6.64–6.78 (m, 3H). Anal. Calcd for $C_7H_7FO_2$ (142.04).

*5.1.43. 2-Chloro-6-methoxyphenol (**54**)*

Prepared from **48** as described for **53**. After chromatography on silica gel (cyclohexane/ethyl acetate 80:20), **54** was isolated (87.2%) as a solid: m.p. 52.9 °C; ^{1}H NMR ($CDCl_3$) δ 3.89 (s, 3H), 5.85 (br s, 1H), 6.78 (m, 2H), 6.93 (m, 1H). Anal. Calcd for $C_7H_7ClO_2$ (158.58).

*5.1.44. 2-Methyl-6-methoxyphenol (**55**)*

Prepared from **49** as described for **53**. The crude product was isolated (77%) as yellow oil and used without further purification: ^{1}H NMR ($CDCl_3$) δ 2.27 (s, 3H), 3.88 (s, 3H), 5.68 (br s, 1H), 6.72–6.75 (m, 3H). Anal. Calcd. for $C_8H_{10}O_2$ (138.16).

*5.1.45. 2-Ethyl-6-methoxyphenol (**56**)*

Prepared from **50** as described for **53**. The crude product was isolated (92%) as a yellow oil and used for the subsequent step without further purification: ^{1}H NMR ($CDCl_3$) δ 1.32 (t, 3H), 2.80 (q, 2H), 3.92 (s, 3H), 5.84 (s, 1H), 6.75–6.90 (m, 3H). Anal. Calcd for $C_9H_{12}O_2$ (152.19).

*5.1.46. 2-i-Propyl-6-methoxyphenol (**57**)*

Prepared from **51** as described for **53**. After chromatography on silica gel (cyclohexane/ethyl acetate 80:20), **57** was isolated (79%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.24 (d, 6H), 3.32 (m, 1H), 3.88 (s, 3H), 5.74 (s, 1H), 6.70–6.77 (m, 1H), 6.82–7.26 (m, 2H). Anal. Calcd for $C_{10}H_{14}O_2$ (166.22).

*5.1.47. 2-t-Butyl-6-methoxyphenol (**58**)*

Prepared from **52** as described for **53**. The crude product was isolated (95.4%) as a red oil and used for the subsequent step without further purification: ^{1}H NMR ($CDCl_3$) δ 1.36 (s, 9H), 3.93 (s, 3H), 5.40–5.80 (s, 1H), 6.91–6.97 (m, 3H). Anal. Calcd for $C_{11}H_{16}O_2$ (180.24).

*5.1.48. 2-(2-Fluoro-6-methoxyphenoxy)-1-bromoethane (**59**)*

Dibromoethane (15.8 g, 84 mmol) was added drop-wise to a solution of **53** (3 g, 21 mmol) and KOH (4.8 g, 84 mmol) in DMSO (30 ml). The resulting mixture was stirred for 24 h and then treated with 10% HCl (100 ml) and extracted with diethyl ether (3 × 50 ml). 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 (90:10) afforded 4 g (76%) of **59** as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 3.60 (t, 2H), 3.85 (s, 3H), 4.36 (t, 2H), 6.65–6.80 (m, 2H), 6.84–7.08 (m, 1H). Anal. Calcd for $C_9H_{10}BrFO_2$ (248.96).

*5.1.49. 2-(2-Chloro-6-methoxyphenoxy)-1-bromoethane (**60**)*

Prepared from **54** as described for **59**. After chromatography on silica gel (toluene), **60** was isolated (85.2%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 3.70 (t, 2H), 3.81 (s, 3H), 4.22 (t, 2H), 7.05 (m, 3H). Anal. Calcd for $C_9H_{10}BrClO_2$ (265.53).

*5.1.50. 2-(2-Methyl-6-methoxyphenoxy)-1-bromoethane (**61**)*

Prepared from **55** as described for **59**. The crude product was isolated (98.6%) by distillation under vacuum (100 °C at 0.2 mbar) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 2.31 (s, 3H), 3.64 (t, 2H), 3.84 (s, 3H), 4.27 (t, 2H), 6.77 (d, 2H), 6.93 (t, 1H). Anal. Calcd for $C_{10}H_{13}BrO_2$ (245.11).

*5.1.51. 2-(2-Ethyl-6-methoxyphenoxy)-1-bromoethane (**62**)*

Dibromoethane (18.80 ml, 0.218 mol) was added drop-wise to a solution of **56** (8.3 g, 0.054 mol), KOH (12.24 g, 0.218 mol) and tetrabutylammonium bromide (3.33 g, 10.3 mmol) in dichloromethane (110 ml) and water (90 ml). The resulting mixture was stirred for 24 h and then treated with 10% HCl (60 ml). The aqueous layer was extracted with dichloromethane (3 × 70 ml). The organic phases were combined, washed with water, dried and concentrated to give 13.5 g (96.4%) of **62**, which was used for the subsequent step without further purification: ^{1}H NMR ($CDCl_3$) δ 1.22 (t, 3H), 2.72 (q, 2H), 3.67 (t, 2H), 3.85 (s, 3H), 4.28 (t, 2H), 6.70–6.90 (m, 2H), 6.95–7.10 (m, 1H). Anal. Calcd for $C_{11}H_{15}BrO_2$ (259.14).

*5.1.52. 2-(2-i-Propyl-6-methoxyphenoxy)-1-bromoethane (**63**)*

Prepared from **57** as described for **59**. Distillation under vacuum (110 °C at 0.3 mbar) gave **63** (51.3%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.22 (d, 6H), 3.46 (m, 1H), 3.62 (t, 2H), 3.85 (s, 3H), 4.27 (t, 2H), 6.76 (d, 1H), 6.87 (d, 1H), 7.05 (t, 1H). Anal. Calcd for $C_{12}H_{17}BrO_2$ (273.17).

*5.1.53. 2-(2-t-Butyl-6-methoxyphenoxy)-1-bromoethane (**64**)*

Prepared from **58** as described for **62**. After chromatography on silica gel (toluene), **64** was isolated (73.3%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 9H), 3.65 (t, 2H), 3.90 (s, 3H), 4.32 (t, 2H), 6.80–7.00 (m, 3H). Anal. Calcd for $C_{13}H_{19}BrO_2$ (287.19).

*5.1.54. 2-(2-Fluoro-6-methoxyphenoxy)ethylazide (**65**)*

A mixture of **59** (4 g, 16 mmol) and sodium azide (10.5 g, 16 mmol) in DMF (60 ml) and water (30 ml) was heated at 90 °C for 5 h. After cooling at room temperature, water (30 ml) was added and the resulting mixture extracted with *n*-hexane (7 × 20 ml). The organic phases were combined, washed with water, dried and concentrated to give 3.35 g (98%) of **65** as an oil, which was used without further purification: ^{1}H NMR ($CDCl_3$) δ 3.50 (t, 2H), 3.90 (s, 3H), 4.20 (t, 2H), 6.65–6.79 (m, 2H), 6.90–7.06 (m, 1H). Anal. Calcd for $C_9H_{10}FN_3O_2$ (211.06).

*5.1.55. 2-(2-Methyl-6-methoxyphenoxy)ethylazide (**66**)*

Prepared from **61** as described for **65**. The crude product was isolated (80%) as a yellow oil and used without further purification: ^{1}H NMR ($CDCl_3$) δ 2.31 (s, 3H), 3.57 (t, 2H), 3.85 (s, 3H), 4.11 (t, 2H), 6.77 (d, 2H), 6.97 (t, 1H). Anal. Calcd for $C_{10}H_{13}N_3O_2$ (207.23).

*5.1.56. 2-(2-i-Propyl-6-methoxyphenoxy)ethylazide (**67**)*

Prepared from **63** as described for **65**. The crude product was isolated (91.5%) as a yellow oil and used without further purification: ^{1}H NMR ($CDCl_3$) δ 1.23 (q, 6H), 3.42 (m, 1H), 3.59 (t, 2H), 3.86 (s, 3H), 4.13 (t, 2H), 6.75–6.89 (m, 2H), 7.05 (t, 1H). Anal. Calcd for $C_{12}H_{17}N_3O_2$ (235.28).

*5.1.57. 2-(2-t-Butyl-6-methoxyphenoxy)ethylazide (**68**)*

Prepared from **64** as described for **65**. The crude product was isolated (94.2%) as a yellow oil and used without further purification: ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 9H), 3.61 (m, 2H), 3.89 (s, 3H), 4.17 (m, 2H), 6.90–7.0 (m, 3H). Anal. Calcd for $C_{13}H_{19}N_3O_2$ (249.31).

*5.1.58. N-[2-(2-ethyl-6-methoxyphenoxy)ethyl]phthalimide (**69**)*

A solution of phthalimide (12.55 g, 67.7 mmol) in DMF was added drop-wise to **62** (13.5 g, 52.1 mmol) in DMF (48 ml). The mixture was refluxed for 3 h and, after cooling at room temperature, quenched into ice and water (300 ml). The resulting precipitate was isolated yielding 12.98 g (76.7%) of **69** as a white solid: m.p. 81–82.4 °C; ^{1}H NMR ($CDCl_3$) δ 1.05 (t, 3H), 2.52 (q, 2H), 3.65 (s, 3H), 4.10–4.30 (m, 4H), 6.60–6.80 (m, 2H), 6.90–7.00 (m, 1H), 7.70–7.80 (m, 2H), 7.80–7.90 (m, 2H). Anal. Calcd for $C_{19}H_{19}NO_4$ (325.36).

*5.1.59. N-[2-(2-chloro-6-methoxyphenoxy)ethyl]phthalimide (**70**)*

Prepared from **60** as described for **69** and isolated (100%) as a white solid: m.p. 94.4 °C; ^{1}H NMR ($CDCl_3$) δ 3.60 (s, 3H), 4.15 (t, 2H), 4.25 (t, 2H), 6.70 (dd, 1H), 6.93 (m, 2H), 7.70 (m, 2H), 7.90 (m, 2H). Anal. Calcd. for $C_{17}H_{14}ClNO_4$ (331.75).

*5.1.60. 2-(2-Fluoro-6-methoxyphenoxy)ethylamine (**71**)*

Hydrazine hydrate (7 ml) was added to a stirred mixture of **65** (3.35 g, 15.8 mmol) and PdO (60 mg) in methanol at 65 °C. After refluxing for 5 h, PdO was removed by filtration and the filtrate was concentrated. The residue was treated with a saturated solution of NaCl and dichloromethane (30 ml). The aqueous layer was separated and extracted with dichloromethane again. The organic phases were combined, washed with water, dried and concentrated. Distillation under vacuum (110 °C at 0.2 mbar) of the residue gave 2.5 g (85%) of **71** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.60 (s, 2H), 2.95 (t, 2H), 3.83 (s, 3H), 4.10 (t, 2H), 6.71–6.78 (m, 2H), 6.82–6.99 (m, 1H). Anal. Calcd for $C_9H_{12}FNO_2$ (185.06).

*5.1.61. 2-(2-Chloro-6-methoxyphenoxy)ethylamine (**72**)*

Hydrazine hydrate (1.88 ml) was added drop-wise to a stirred solution of **70** (4.26 g, 12.8 mmol) in 2-methoxyethanol

(26 ml) at 125 °C. After refluxing for 3 h, 10% HCl was added (pH 3). After cooling, the precipitate was removed and the filtrate was concentrated. The resulting residue was dissolved in dichloromethane (100 ml) and treated with 10% HCl. The aqueous layer was separated, treated with 2.5 N NaOH and extracted with dichloromethane (4 × 50 ml). The organic phases were combined, washed with a saturated solution of NaCl, dried and concentrated to give 2.04 g (78.7%) of **72** as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.73 (br s, 2H), 3.02 (t, 2H), 3.85 (s, 3H), 4.05 (t, 2H), 6.80 (m, 1H), 6.97 (m, 2H). Anal. Calcd for $C_9H_{12}ClNO_2$ (201.65).

*5.1.62. 2-(2-Methyl-6-methoxyphenoxy)ethylamine (**73**)*

Prepared from **66** as described for **71**. Distillation under vacuum (90 °C at 0.3 mbar) gave **73** (69.3%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.76 (br s, 2H), 2.25 (s, 3H), 2.98 (t, 2H), 3.78 (s, 3H), 3.91 (t, 2H), 6.72 (d, 2H), 6.91 (t, 1H). Anal. Calcd for $C_{10}H_{15}NO_2$ (181.23).

*5.1.63. 2-(2-Ethyl-6-methoxyphenoxy)ethylamine (**74**)*

Prepared from **69** as described for **72**. Distillation under vacuum (105 °C at 0.5 mbar) gave **74** (72%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.23 (t, 3H), 1.63 (br s, 2H), 2.67 (q, 2H), 3.04 (t, 2H), 3.83 (s, 3H), 3.96 (t, 3H), 6.78 (m, 1H), 6.99 (m, 1H). Anal. Calcd for $C_{11}H_{17}NO_2$ (195.26).

*5.1.64. 2-(2-i-Propyl-6-methoxyphenoxy)ethylamine (**75**)*

Prepared from **67** as described for **71**. Distillation under vacuum (100 °C at 0.2 mbar) gave **75** (79.2%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.22 (d, 6H), 1.74 (br s, 2H), 3.05 (t, 2H), 3.37 (m, 1H), 3.83 (s, 3H), 3.95 (t, 2H), 6.75 (d, 1H), 6.84 (d, 1H), 7.03 (t, 1H). Anal. Calcd for $C_{12}H_{19}NO_2$ (209.28).

*5.1.65. 2-(2-t-Butyl-6-methoxyphenoxy)ethylamine (**76**)*

Prepared from **68** as described for **71**. Distillation under vacuum (120 °C at 0.3 mbar) gave **76** (74.3%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 9H), 1.87 (br s, 2H), 3.07 (t, 2H), 3.86 (s, 3H), 4.01 (t, 2H), 6.75–7.00 (m, 3H). Anal. Calcd for $C_{13}H_{21}NO_2$ (223.31).

*5.1.66. (S)-2-[((2-(2,6-difluorophenoxy)ethyl)amino)methyl]-1,4-benzodioxane hydrochloride [(**S**)-**1**]*

A solution of (*R*)-2-iodomethyl-1,4-benzodioxane (650 mg, 2.36 mmol) and **18** (800 mg, 4.62 mmol) in 2-propanol was refluxed for 18 h. After cooling at room temperature, the solvent was removed and dichloromethane and a saturated aqueous solution of $NaHCO_3$ were added. The aqueous layer was separated and extracted with dichloromethane again. 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 (80:20) afforded 320 mg (42%) of (*S*)-2-[((2-(2,6-difluorophenoxy) ethyl)amino)methyl]-1,4-benzodioxane as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 2.05 (s, 1H), 2.95–3.10 (m, 4H), 3.95–4.10 (dd, 1H), 4.20–4.40 (m, 4H), 6.75–7.05 (m, 7H). The secondary amine was dissolved in ethanol (3 ml) and 5 N HCl/EtOH (1 ml) was slowly added. The resulting precipitate was isolated and dried yielding 180 mg (21.3% based on the starting amount of (2R)-2-iodomethyl-1,4-benzodioxane) of (*S*)-**1** as a white solid: m.p. 178–182 °C; $[\alpha]_D^{25} = -56.3$ (*c* 1, methanol); ^{1}H NMR (DMSO-d_6) δ 3.20–3.50 (m, 5H), 4.05–4.20 (m, 1H), 4.30–4.55 (m, 3H), 4.70 (m, 1H), 6.80–6.95 (m, 4H), 7.05–7.15 (m, 3H), 9.60 (br s, 1H). Anal. Calcd for $C_{17}H_{18}ClF_2NO_3$ (357.78).

*5.1.67. (R)-2-[((2-(2,6-difluorophenoxy)ethyl)amino)methyl]-1,4-benzodioxane hydrochloride [(**R**)-**1**]*

Prepared from (*S*)-2-iodomethyl-1,4-benzodioxane and **18** as described for (*S*)-**1**: m.p. 178–182 °C; $[\alpha]_D^{25} = +58.2$ (*c* 1, methanol); ^{1}H NMR identical to that of (*S*)-**1**.

*5.1.68. (S)-2-[((2-(2,6-dichlorophenoxy)ethyl)amino)methyl]-1,4-benzodioxane hydrochloride [(**S**)-**2**]*

Prepared from (*R*)-2-iodomethyl-1,4-benzodioxane (1 g, 3.62 mmol) and **25** (2.98 g, 14.48 mmol) as described for (*S*)-**1** but replacing 2-propanol with 2-methyl-1-propanol and refluxing for 48 h. After chromatography on silica gel (dichloromethane/methanol 98:2), the secondary amine was isolated as a yellow oil: $[\alpha]_D^{25} = -26.77$ (*c* 1, chloroform); ^{1}H NMR ($CDCl_3$) δ 2.00 (br s, 1H), 2.98–3.13 (m, 4H), 4.14 (m, 1H), 4.19 (m, 2H), 4.32–4.40 (m, 2H), 6.86 (m, 4H), 7.00 (t, 1H), 7.29 (d, 2H). Subsequent treatment with HCl/EtOH yielded (*S*)-**2** (31.4% based on the starting amount of (*R*)-2-iodomethyl-1,4-benzodioxane) as a white solid: m.p. 174.5 °C; $[\alpha]_D^{25} = -52.6$ (*c* 1, methanol); ^{1}H NMR (DMSO-d_6) δ 3.54–3.43 (m, 4H), 4.16 (dd, 1H), 4.35–4.47 (m, 3H), 4.80 (m, 1H), 6.95 (m, 4H), 7.27 (t, 1H), 7.57 (d, 2H), 9.76 (m, 2H). Anal. Calcd for $C_{17}H_{18}Cl_3NO_3$ (390.23).

*5.1.69. (R)-2-[((2-(2,6-dichlorophenoxy)ethyl)amino)methyl]-1,4-benzodioxane hydrochloride [(**R**)-**2**]*

Prepared from (*S*)-2-iodomethyl-1,4-benzodioxane and **25** as described for (*S*)-**2**: m.p. 173.5 °C; $[\alpha]_D^{25} = +53.0$ (*c* 1, methanol); ^{1}H NMR identical to that of (*S*)-**2**.

*5.1.70. (S)-2-[((2-(2,6-di-t-butylphenoxy)ethyl)amino)methyl]-1,4-benzodioxane hydrochloride [(**S**)-**3**]*

A mixture of (*R*)-2-mesyloxymethyl-1,4-benzodioxane (0.98 g, 4.01 mmol) and **26** (2 g, 8.02 mmol) in 2-methyl-1-propanol (5 ml) was refluxed for 24 h. After cooling at room temperature, dichloromethane and a saturated aqueous solution of $NaHCO_3$ were added. The aqueous layer was separated and extracted with dichloromethane again. 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 (70:30) afforded 1.38 g (86.8%) of (*S*)-2-[((2-(2,6-Di-*t*-butylphenoxy)ethyl)amino) methyl]-1,4-benzodioxane as a yellow oil: $[\alpha]_D^{25} = -25.6$ (*c* 1, chloroform); ^{1}H NMR ($CDCl_3$) δ 1.44 (s, 18H), 1.68 (s, 1H), 2.99 (m, 2H), 3.13 (t, 2H), 3.89 (t, 2H), 4.01–4.11 (dd, 1H), 4.29–4.34 (m, 2H), 6.87 (m, 4H), 4.98 (t, 1H), 7.25 (d, 2H). The secondary amine was dissolved in ethanol (5 ml) and 2.2 N HCl/EtOH (2.5 ml) was slowly added. The solvent was evaporated and the residue crystallized from ethyl acetate

(20 ml). The resulting precipitate was dried yielding 910 mg of (S)-**3** (52% based on the starting amount of (*R*)-2-mesyloxymethyl-1,4-benzodioxane) as a white solid: m.p. 176.5 °C; $[\alpha]_D^{25} = -50.1$ (*c* 1, methanol); ^{1}H NMR (DMSO-d_6) δ 1.44 (s, 18H), 3.25–3.65 (m, 4H), 4.01–4.16 (m, 3H), 4.40–4.45 (dd, 1H), 4.76 (br s, 1H), 6.87 (m, 4H), 6.98 (t, 1H), 7.25 (d, 2H), 9.6 (br s, 1H), 10.06 (br s, 1H). Anal. Calcd for $C_{25}H_{36}NO_3Cl$ (434.02).

*5.1.71. (R)-2-[((2-(2,6-di-t-butylphenoxy)ethyl)amino)methyl]-1,4-benzodioxane hydrochloride [(**R**)-**3**]*

Prepared from (*S*)-2-mesyloxymethyl-1,4-benzodioxane and **26** as described for (*S*)-**3**: m.p. 172.9 °C; $[\alpha]_D^{25} = +49.8$ (*c* 1, methanol); ^{1}H NMR identical to that of (*S*)-**3**.

*5.1.72. (S)-2-[((2-(2-fluoro-6-methoxyphenoxy)ethyl)amino)methyl]-1,4-benzodioxane hydrochloride [(**S**)-**4**]*

Prepared from (*R*)-2-iodomethyl-1,4-benzodioxane (1.2 g, 4.34 mmol) and **71** (1.18 g, 6.37 mmol) as described for (*S*)-**1** but replacing 2-propanol with 2-methyl-1-propanol and refluxing for 24 h. After chromatography on silica gel (dichloromethane/methanol 98:2), the secondary amine was isolated as a yellow oil: $[\alpha]_D^{25} = +26.6$ (*c* 1, chloroform); ^{1}H NMR ($CDCl_3$) δ 2.05 (br s, 1H), 2.80–3.12 (m, 4H), 3.85 (s, 3H), 4.05–4.12 (m, 1H), 4.15–4.23 (m, 2H), 4.26–4.39 (m, 2H), 6.80–6.52 (m, 5H), 6.65–7.00 (m, 7H). Subsequent treatment with HCl/EtOH yielded (S)-**4** (23.4% based on the starting amount of (*R*)-2-iodomethyl-1,4-benzodioxane) as a white solid: m.p. 111 °C; $[\alpha]_D^{25} = +53.90$ (*c* 1, methanol); ^{1}H NMR (DMSO-d_6) δ 3.38–3.58 (m, 4H), 3.80 (s, 3H), 4.12–4.29 (m, 1H), 4.32–4.40 (m, 2H), 4.42–4.58 (m, 1H), 4.75–4.82 (m, 1H), 6.85–7.00 (m, 6H), 7.10–7.20 (m, 1H), 9.60 (br s, 2H). Anal. Calcd for $C_{18}H_{21}ClFNO_4$ (369.58).

*5.1.73. (R)-2-[((2-(2-fluoro-6-methoxyphenoxy)ethyl)amino)methyl]-1,4-benzodioxane hydrochloride [(**R**)-**4**]*

Prepared from (*S*)-2-iodomethyl-1,4-benzodioxane and **71** as described for (*S*)-**4**: m.p. 111 °C; $[\alpha]_D^{25} = -48.3$ (*c* 1, methanol); ^{1}H NMR identical to that of (S)-**4**.

*5.1.74. (S)-2-[((2-(2-chloro-6-methoxyphenoxy)ethyl)amino)methyl]-1,4-benzodioxane hydrochloride [(**S**)-**5**]*

Prepared from (*R*)-2-mesyloxymethyl-1,4-benzodioxane (0.637 g, 2.61 mmol) and **72** (1.05 g, 5.21 mmol) as described for (*S*)-**3**. After chromatography on silica gel (cyclohexane/ethyl acetate 60:40), the secondary amine was isolated as a dark oil: $[\alpha]_D^{25} = -27.2$ (*c* 1, chloroform); ^{1}H NMR ($CDCl_3$) δ 1.90 (br s, 1H), 2.99 (m, 4H), 3.85 (s, 3H), 4.06 (dd, 1H), 4.15 (m, 2H), 4.30 (m, 2H), 6.85 (m, 5H), 6.97 (m, 2H). Subsequent treatment with HCl/EtOH yielded (*S*)-**5** (32% based on the starting amount of (*R*)-2-mesyloxymethyl-1,4-benzodioxane) as a white solid: 136.5 °C; $[\alpha]_D^{25} = -54.2$ (*c* 1, methanol); ^{1}H NMR (DMSO-d_6) δ 3.40 (m, 4H), 3.81 (s, 3H), 4.08 (dd, 1H), 4.20 (m, 2H), 4.36 (dd, 1H), 4.69 (m, 1H), 6.88 (m, 4H), 7.08 (m, 3H), 9.40 (br s, 2H). Anal. Calcd for $C_{18}H_{21}Cl_2NO_4$ (386.27).

*5.1.75. (R)-2-[((2-(2-chloro-6-methoxyphenoxy)ethyl)amino)methyl]-1,4-benzodioxane hydrochloride [(**R**)-**5**)]*

Prepared from (*S*)-2-mesyloxymethyl-1,4-benzodioxane and **72** as described for (*S*)-**5**: m.p. 136.5 °C; $[\alpha]_D^{25} = +46.8$ (*c* 1, methanol); ^{1}H NMR identical to that of (*S*)-**5**.

*5.1.76. (S)-2-[((2-(2-methyl-6-methoxyphenoxy)ethyl)amino)methyl]-1,4-benzodioxane hydrochloride [(**S**)-**6**)]*

Prepared from (*R*)-2-mesyloxymethyl-1,4-benzodioxane (1.28 g, 5.25 mmol) and **73** (1.90 g, 10.5 mmol) as described for (*S*)-**3**. After chromatography on silica gel (cyclohexane/ethyl acetate 1:1), the free amine was isolated as an oil: $[\alpha]_D^{25} = -30.3$ (*c* 1, chloroform); ^{1}H NMR ($CDCl_3$) δ 1.94 (br s, 1H), 2.29 (s, 3H), 2.90–3.09 (m, 4H), 3.83 (s, 3H), 4.01–4.11 (m, 3H), 4.30–4.35 (m, 2H), 6.74–7.00 (m, 7H). Subsequent treatment with HCl/EtOH afforded (S)-**6** (51% based on the starting amount of (*R*)-2-mesyloxymethyl-1,4-benzodioxane) as a white solid: m.p. 142.7 °C; $[\alpha]_D^{25} = -58.2$ (*c* 1, methanol); ^{1}H NMR (DMSO-d_6) δ 2.27 (s, 3H), 3.43–3.46 (m, 4H), 3.82 (s, 3H), 4.11–4.21 (m, 3H), 4.46 (dd, 1H), 4.81 (m, 1H), 6.80–7.07 (m, 7H), 9.63 (br s, 2H). Anal. Calcd for $C_{19}H_{24}ClNO_4$ (765.39).

*5.1.77. (R)-2-[((2-(2-methyl-6-methoxyphenoxy)ethyl)amino)methyl]-1,4-benzodioxane hydrochloride [(**R**)-**6**)]*

Prepared from (*S*)-2-mesyloxymethyl-1,4-benzodioxane and **73** as described for (*S*)-**6**: m.p. 142.7 °C; $[\alpha]_D^{25} = +58.6$ (*c* 1, methanol); ^{1}H NMR identical to that of (*S*)-**6**.

*5.1.78. (S)-2-[((2-(2-ethyl-6-methoxyphenoxy)ethyl)amino)methyl]-1,4-benzodioxane hydrochloride [(**S**)-**7**]*

Prepared from (*R*)-2-mesyloxymethyl-1,4-benzodioxane (1 g, 4.09 mmol) and **74** (1.59 g, 8.19 mmol) as described for (*S*)-**3**. After chromatography on silica gel (dichloromethane/methanol 9:/5), the free amine was isolated as an oil: $[\alpha]_D^{25} = -30.3$ (*c* 1, chloroform); ^{1}H NMR ($CDCl_3$) δ 1.22 (t, 3H), 2.67 (q, 2H), 3.05–3.11 (m, 4H), 3.20–3.35 (br s, 1H), 3.84 (s, 3H), 4.03–4.12 (m, 3H), 4.31–4.44 (m, 2H), 6.75–7.02 (m, 7H). Subsequent treatment with HCl/EtOH yielded (*S*)-**7** (37.4% based on the starting amount of (*R*)-2-mesyloxymethyl-1,4-benzodioxane) as a white solid: m.p. 225 °C; $[\alpha]_D^{25} = -57.2$ (*c* 1, methanol); ^{1}H NMR (DMSO-d_6) δ 1.18 (t, 3H), 2.65 (q, 2H), 3.30–3.60 (m, 4H), 3.82 (s, 3H), 4.10–4.35 (m, 3H), 4.45 (d, 1H), 4.81 (m, 1H), 6.83–7.10 (m, 7H), 9.50 (m, 2H). Anal. Calcd for $C_{20}H_{26}ClNO_4$ (379.42).

*5.1.79. (R)-2-[((2-(2-ethyl-6-methoxyphenoxy)ethyl)amino)methyl]-1,4-benzodioxane hydrochloride [(**R**)-**7**]*

Prepared from (*S*)-2-mesyloxymethyl-1,4-benzodioxane and **74** as described for (*S*)-**7**: m.p. 225 °C; $[\alpha]_D^{25} = +56.5$ (*c* 1, methanol); ^{1}H NMR identical to that of (*S*)-**7**.

*5.1.80. (S)-2-[((2-propyl-6-methoxyphenoxy)ethyl)amino)methyl]-1,4-benzodioxane hydrochloride [(**S**)-**8**]*

Prepared from (*R*)-2-mesyloxymethyl-1,4-benzodioxane (1.17 g, 4.78 mmol) and **28** (2 g, 9.56 mmol) as described for (*S*)-3. After chromatography on silica gel (cyclohexane/

ethyl acetate 1:1), the secondary amine was isolated as a yellow oil: $[\alpha]_D^{25} = -33.3$ (*c* 1, chloroform); ^{1}H NMR ($CDCl_3$) δ 0.99 (t, 3H), 1.61 (m, 2H), 1.94 (br s, 1H), 2.62 (t, 2H), 3.03 (m, 4H), 3.84 (s, 3H), 4.07 (m, 3H), 4.35 (m, 2H), 6.70–7.05 (m, 7H). Subsequent treatment with HCl/EtOH afforded (*S*)-**8** (41.5% based on the starting amount of (*R*)-2-mesyloxymethyl-1,4-benzodioxane) as a white solid: m.p. 120.8 °C; $[\alpha]_D^{25} = -56.4$ (*c* 1, methanol); ^{1}H NMR (DMSO-d_6) δ 0.94 (t, 3H), 1.57 (m, 2H), 2.61 (t, 2H), 3.40–3.46 (m, 4H), 3.82 (s, 3H), 4.21 (m, 3H), 4.44 (dd, 1H), 4.82 (m, 1H), 6.94 (m, 7H), 9.57–9.88 (br s, 2H). Anal. Calcd for $C_{21}H_{28}ClNO_4$ (393.44).

*5.1.81. (R)-2-[((2-propyl-6-methoxyphenoxy)ethyl)amino) methyl]-1,4-benzodioxane hydrochloride [(**R**)-**8**]*

Prepared from (*S*)-2-mesyloxymethyl-1,4-benzodioxane and **28** as described for (*S*)-**8**: m.p. 120.6 °C; $[\alpha]_D^{25} = +56.0$ (*c* 1, methanol); ^{1}H NMR identical to that of (*S*)-**8**.

*5.1.82. (S)-2-[((2-i-propyl-6-methoxyphenoxy)ethyl)amino) methyl]-1,4-benzodioxane hydrochloride [(**S**)-**9**]*

Prepared from (*R*)-2-mesyloxymethyl-1,4-benzodioxane (0.87 g, 3.58 mmol) and **75** (0.87 g, 3.58 mmol) as described for (*S*)-**3**. After chromatography on silica gel (cyclohexane/ethyl acetate 1:1), the secondary amine was isolated as an oil: $[\alpha]_D^{25} = -26.8$ (*c* 1, chloroform); ^{1}H NMR ($CDCl_3$) δ 1.22 (d, 6H), 1.85 (br s, 1H), 2.93–3.09 (m, 4H), 3.37 (m, 1H), 3.83 (s, 3H), 4.02–4.11 (m, 3H), 4.29–4.35 (m, 2H), 6.73–6.87 (m, 6H), 7.04 (t, 1H). Subsequent treatment with HCl/EtOH yielded (*S*)-**9** (46% based on the starting amount of (*R*)-2-mesyloxymethyl-1,4-benzodioxane) as a white solid: m.p. 138.9 °C; $[\alpha]_D^{25} = -54.4$ (*c* 1, methanol); ^{1}H NMR (DMSO-d_6) δ 1.18 (d, 6H), 3.30–3.60 (m, 5H), 3.81 (s, 3H), 4.10–4.25 (m, 3H), 4.43 (dd, 1H), 4.78 (m, 1H), 6.88–6.99 (m, 6H), 7.11 (t, 1H), 9.73 (br s, 2H). Anal. Calcd for $C_{21}H_{28}ClNO_4$ (393.44).

*5.1.83. (R)-2-[((2-i-propyl-6-methoxyphenoxy)ethyl)amino) methyl]-1,4-benzodioxane hydrochloride [(**R**)-**9**]*

Prepared from (*S*)-2-mesyloxymethyl-1,4-benzodioxane and **75** as described for (*S*)-**9**: m.p. 139.4 °C; $[\alpha]_D^{25} = +53.3$ (*c* 1, methanol); ^{1}H NMR identical to that of (*S*)-**9**.

*5.1.84. (S)-2-[((2-allyl-6-methoxyphenoxy)ethyl)amino) methyl]-1,4-benzodioxane hydrochloride [(**S**)-**10**]*

Prepared from (*R*)-2-mesyloxymethyl-1,4-benzodioxane (1.10 g, 4.52 mmol) and **27** (1.34 g, 6.46 mmol) as described for (*S*)-**3**. After chromatography on silica gel (cyclohexane/ethyl acetate 1:1), the secondary amine was isolated as an oil: $[\alpha]_D^{25} = -28.2$ (*c* 1, chloroform); ^{1}H NMR ($CDCl_3$) δ 1.97 (s, 1H), 3.02 (m, 4H), 3.45 (d, 2H), 3.84 (s, 3H), 4.10 (m, 3H), 4.35 (m, 2H), 5.08 (dd, 2H), 5.88–6.08 (m, 1H), 6.77–7.05 (m, 7H). Subsequent treatment with HCl/EtOH yielded (*S*)-**10** (25% based on the starting amount of (*R*)-2-mesyloxymethyl-1,4-benzodioxane) as a white solid: m.p. 102.3 °C; $[\alpha]_D^{25} = -55.6$ (*c* 1, methanol); ^{1}H NMR (DMSO-d_6) δ 3.42 (m, 6H), 3.83 (s, 3H), 4.20 (m, 3H), 4.42 (dd, 1H), 4.79 (m, 1H), 5.05 (m, 2H), 6.00 (m, 1H), 6.94 (m, 7H), 9.48–9.80 (br s, 2H). Anal. Calcd for $C_{21}H_{26}ClNO_4$ (391.43).

*5.1.85. (R)-2-[((2-allyl-6-methoxyphenoxy)ethyl)amino) methyl]-1,4-benzodioxane hydrochloride [(**R**)-**10**]*

Prepared from (*S*)-2-mesyloxymethyl-1,4-benzodioxane and **27** as described for (*S*)-**10**: m.p. 102.5 °C; $[\alpha]_D^{25} = +55.2$ (*c* 1, methanol); ^{1}H NMR identical to that of (*S*)-**10**.

*5.1.86. (S)-2-[((2-t-butyl-6-methoxyphenoxy)ethyl)amino) methyl]-1,4-benzodioxane hydrochloride [(**S**)-**11**]*

Prepared from (*R*)-2-mesyloxymethyl-1,4-benzodioxane (1 g, 4.1 mmol) and **76** (1.82 g, 8.15 mmol) as described for (*S*)-**3**. After chromatography on silica gel (cyclohexane/ethyl acetate 1:1), the secondary amine was isolated as an oil: $[\alpha]_D^{25} = -23.3$ (*c* 1, chloroform); ^{1}H NMR ($CDCl_3$) δ 1.32 (s, 9H), 2.03 (br s, 1H), 2.97 (m, 2H), 3.08 (t, 2H), 3.88 (s, 3H), 4.05 (dd, 1H), 4.13 (t, 2H), 4.28–4.35 (m, 2H), 6.80–6.94 (m, 7H). Subsequent treatment with HCl/EtOH gave (*S*)-**11** (35% based on the starting amount of (*R*)-2-mesyloxymethyl-1,4-benzodioxane) as a white solid: m.p. 137 °C; $[\alpha]_D^{25} = -49.2$ (*c* 1, methanol); ^{1}H NMR (DMSO-d_6) δ 1.31 (s, 9H), 3.35–3.50 (m, 4H), 3.82 (s, 3H), 4.05–4.20 (m, 1H), 4.35–4.50 (m, 3H), 4.70–4.85 (m, 1H), 6.85–7.00 (m, 7H), 9.70 (br s, 2H). Anal. Calcd for $C_{22}H_{30}ClNO_4$ (407.47).

*5.1.87. (R)-2-[((2-t-butyl-6-methoxyphenoxy)ethyl)amino) methyl]-1,4-benzodioxane hydrochloride [(**R**)-**11**]*

Prepared from (*S*)-2-mesyloxymethyl-1,4-benzodioxane and **76** as described for (*S*)-**11**: m.p. 137 °C; $[\alpha]_D^{25} = +45.8$ (*c* 1, methanol); ^{1}H NMR identical to that of (*S*)-**11**.

5.2. Biology

5.2.1. Binding assays

The pharmacological profile of both the *S* and *R* enantiomers of compounds **1**–**11** 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. [31][1]) 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 (from 0.3 to 1000 nM depending on the affinity). Prazosin 1 μM was used to determine non-specific binding.

Binding studies at 5-HT_{1A} receptor 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 1 μM was used to determine non-specific 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 was 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. Statistics

The descriptors were selected out of 27 molecular parameters, mainly taken from [32]. They were chosen to parameterize both electronic and steric properties of substituents. In order to account for the effect of methoxyl group, a de novo constant was added indicating its presence. The models were manually obtained using a step-wise regression method by which further parameters were progressively included in QSARs in addition to the best single parameter correlating with affinity so as to maximize r^2 without exceeding the number of 4 parameters in each model. The statistical analyses were carried out using Analyse-It 1.68 (Analyse-It software, Ltd).

Acknowledgements

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

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