New Series of Morpholine and 1,4-Oxazepane Derivatives as Dopamine D_4 Receptor Ligands: Synthesis and 3D-QSAR Model

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Since the identification of the dopamine D_4 receptor subtype and speculations about its possible involvement in schizophrenia, much work has been put into development of selective D_4 ligands. These selective ligands may be effective antipsychotics without extrapyramidal side effects. This work describes the synthesis of a new series of 2,4-disubstituted morpholines and 2,4-disubstituted 1,4-oxazepanes with selectivity for the dopamine D_4 receptor. A 3D-QSAR analysis using the GRID/GOLPE methodology was performed with the purpose to get a better understanding of the relationship between chemical structure and biological activity. Inspection of the coefficient plots allowed us to identify that regions which are important for affinity are situated around the two benzene ring systems, a *p*-chlorobenzyl group, and the aliphatic amine belonging to the morpholine or 1,4-oxazepane system. In addition, the size of the morpholine or 1,4-oxazepane ring seems to be important for affinity.

Introduction

Interest in dopamine receptors was reawakened by the discovery, through receptor cloning techniques, that there were not just two classes of dopamine receptors, D_1 and D_2, but two clear subfamilies of each, the D_1-like subfamily (D_1[1−4] and D_5 receptors[5,6]) and the D_2-like subfamily (D_2, D_3, and D_4 receptors[7−9]). Interest in the D_4 receptor as a therapeutic target increased following the discovery that clozapine, an antipsychotic drug with both beneficial effects against positive and negative symptoms of schizophrenia and a very low propensity to induce extrapyramidal motor effects, uniquely showed modest selectivity for D_4 over D_2 receptors.[9]

D_4 receptors are distinctly localized to areas where the dopamine system is thought to serve a role in modulating emotion and cognition[10] and are expressed at low levels in the basal ganglia, suggesting that a selective D_4 receptor ligand might have a low propensity for extrapyramidal side effects. This, together with the indication that the density of D_4 receptors may be upregulated in schizophrenic patients,[11] stimulated the hypothesis that clozapine's action at D_4 receptors may contribute to its status as an unusually effective atypical antipsychotic agent. The enthusiasm for this hypothesis was not dampened by the failure to confirm the elevation of D_4 receptor density in the striatum of postmortem schizophrenic brain.

Altogether this led to remarkably rapid development of a growing number of novel compounds with much greater D_4 selectivity than clozapine. Among the earliest D_4 selective antagonists reported was L-745,870.[12] All of the new D_4 selective compounds exhibited both high D_4 receptor affinity and high selectivity for D_4 sites relative to other dopamine receptor subtypes.[13]

The behavioral effects of several D_4 selective compounds were evaluated in animal models believed to be predictive of antipsychotic activity, as well as models indicative of extrapyramidal side effects. The findings in these models suggested that the compounds might have potential for clinical activity with a low risk of extrapyramidal side effects.[14] However, a number of compounds in this class, including L-745,870 did not show activity in rodent behavioral antipsychotic models.[15]

Clinical trials for D_4 selective drugs moved forward rapidly. The results, however, demonstrated that the selective D_4 receptor antagonist L-745,870 was ineffective as an antipsychotic,[16] and other agents (i.e. NGD 94-1,[17] PNU-101387[18]) that had demonstrated promising results in animal behavioral models, also failed to show evidence of antipsychotic efficacy in clinical trials.

Characterization of a range of antipsychotics in receptor binding assays has shown that clozapine analogues (e.g. quetiapine) do not share the D_4 over D_2 selectivity, and other antipsychotic drugs including remoxipride, risperidone, and sertindole are not D_4 selective, indicating that preferential selectivity for D_4 receptors does not uniquely distinguish atypical from typical antipsychotics.[19−21] Furthermore, many of the atypical agents interact with adrenergic and serotonergic receptors.[22]

The human D_4 receptor protein can be transcribed during its synthesis into different polymorphic variants, creating structural diversity in this receptor that supersedes all other known catecholamine receptors.[23] However, the pharmacological consequences of these structural variants are not well defined. Several genetic linkage studies have tried to associate D_4 receptor polymorphism with specific neuropsychiatric disorders. Unfortunately, no relationship between polymorphism and schizophrenia has been found.[24,25] Other studies have, however, suggested associations between D_4 receptor polymorphism and attention deficit hyperactivity disorder,[26−28] major depressive disorder,[29] and Parkinson's disease.[30] Altogether this indicates that D_4 receptors may have broader implications for human illnesses than has been suggested by the early focus on schizophrenia as a clinical target.

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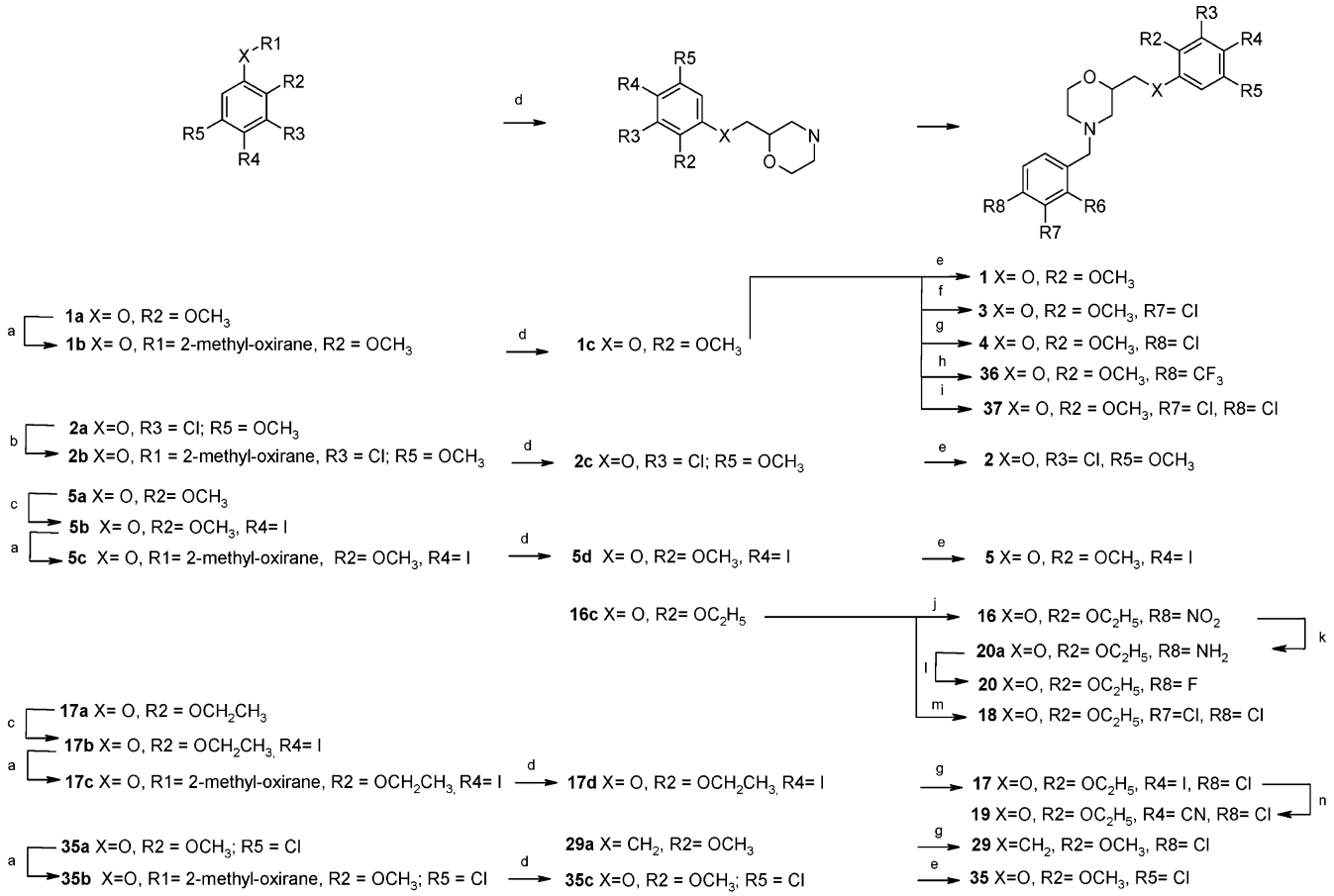
Scheme 1[a]



[a] Reagents: (a) K_2CO_3, epibromohydrin; (b) K_2CO_3, epichlorohydrin; (c) NaI, NaOH, NaOCl, $Na_2S_2O_3$; (d) 2-aminoethylhydrogen sulfate, NaOH; (e) K_2CO_3, benzyl bromide; (f) K_2CO_3, 3-chlorobenzyl chloride; (g) K_2CO_3, 4-chlorobenzyl chloride; (h) K_2CO_3, 4-bromomethyltrifluoromethylbenzene; (i) K_2CO_3, α,3,4-trichlorotoluene; (j) K_2CO_3, 4-nitrobenzyl bromide; (k) Pd/C, H_2; (l) K_2CO_3, 1-chloromethyl-4-fluorobenzene; (m) K_2CO_3, 2,4-dichloro-1-chloromethylbenzene; (n) tetrakis(triphenylphosphine)palladium(0), $Zn(CN)_2$.

Despite the lack of clinical efficacy of selective D_4 ligands so far, the large number of novel compounds of various structures has been very valuable for increasing our understanding of the D_4 receptor. The chemical diversity of these compounds has been particularly helpful for obtaining new information regarding the tertiary structure of the D_4 receptors.

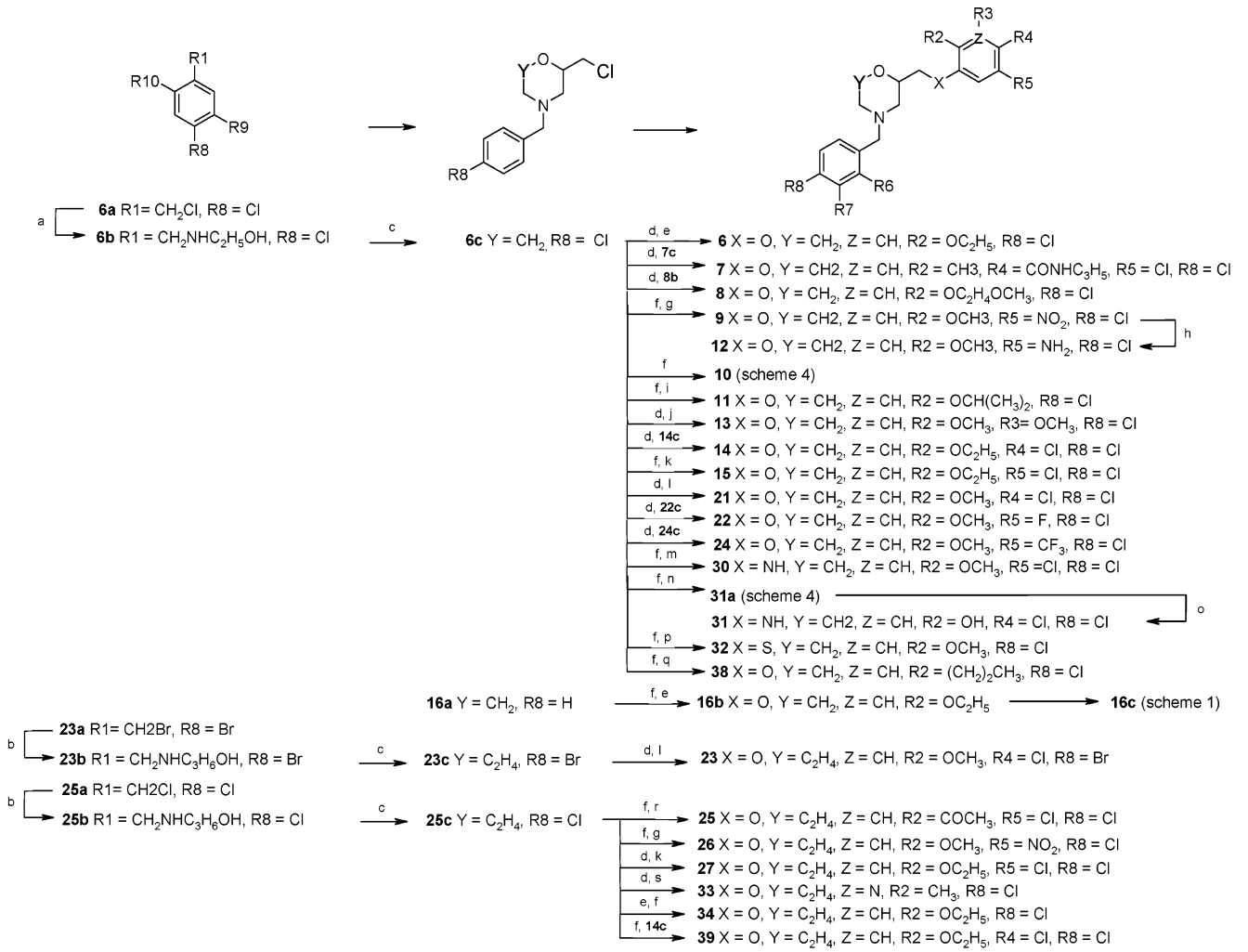
The development of predictive 3D-QSAR models is important both to understand pharmacological data and to predict novel D_4 selective ligands in order to rationalize receptor−ligand interactions of D_4 receptor ligands. A first 3D-QSAR study of D_4 ligands using CoMFA, was performed by Lanig et al..[31] This study used a pharmacophore model similar to the one for the D_4 receptor published by Boström et al.[32] A second 3D-QSAR model was recently published by Boström et al.[33] using CoMFA and CoMSIA methods.

This paper reports the synthesis and binding affinities for a new series of D_4 selective ligands. To explore the three-dimensional structure−activity relationships of these compounds, a 3D-QSAR model was developed based on the structural and biological data using GRID and GOLPE.

Results and Discussion

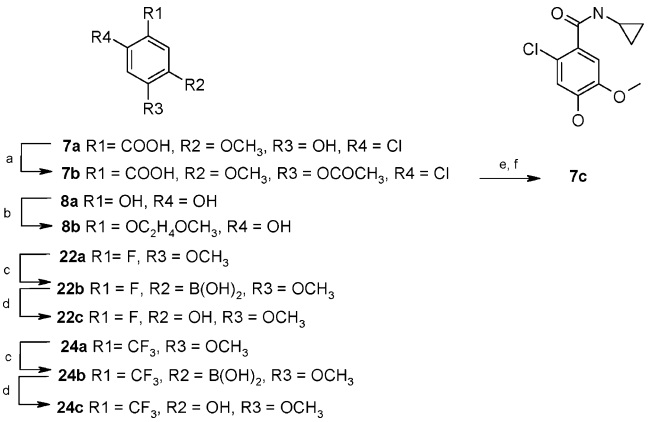
Chemistry. Two general routes toward (±)-2-phenoxymethyl-4-benzylmorpholine derivatives were used. The first was a reaction of a phenol with epibromohydrin, yielding the corresponding 2-phenoxymethyloxirane, followed by a reaction with 2-aminoethylhydrogen sulfate[34] and a benzylation reaction (Scheme 1). The second was a reaction of 2-benzylaminoethanol and epichlorhydrin, followed by dehydration with sulfuric acid, (Scheme 2). The intermediate 4-benzyl-2-chloromethylmorpholine was reacted with a phenol, a potassium alkoxide, and 18-crown-6 ether. The broad scope of this reaction was demonstrated by using also 5-chloroquinolin-8-ol (Scheme 4). The corresponding 2-phenoxymethyl-4-benzyl-1,4-oxazepanes were obtained by an adaptation of the second route using 3-benzylaminopropan-1-ol as precursor (Scheme 2). In cases where the phenols were not commercial available, they could be prepared as follows: 4-iodo-2-methoxyphenol was prepared by an iodination reaction[35] (Scheme 1) and 2-chloro-*N*-cyclopropyl-4-hydroxy-5-methoxybezamide was prepared from its carboxylic acid as precursor by an amidation reaction[36] (Scheme 3). 2-(2-Methoxyethoxy)-phenol (**8b**, Scheme 3) was prepared by a mono methoxyethoxylation of catechol with 2-methoxybromoethane. 4-Chloro-2-ethoxyphenol (**14c**, Scheme 5) was obtained from a chlorination reaction with 4-chloromorpholine. The phenols **22c** and **24c** were obtained from their corresponding phenylboronic acid derivatives **22b** and **24b** by oxidation with hydrogen peroxide (Scheme 3). Anilines **12** and **20a** were prepared by reduction of the nitroaryl group in **9** (Scheme 1) and **16** (Scheme 2),

Scheme 2[a]



[a] Reagents: (a) NaOH, ethanolamine; (b) NaOH, 3-amino-1-propanol; (c) epichlorohydrin, H_2SO_4; (d) EtOK, 18-crown-6 ether; (e) 2-ethoxyphenol; (f) *t*-BuOK, 18-crown-6 ether; (g) 2-methoxy-5-nitrophenol; (h) Pd/C, H_2; (i) 2-isopropoxyphenol; (j) 2,3-dimethoxyphenol; (k) 5-chloro-2-ethoxyphenol; (l) 4-chloro-2-methoxyphenol; (m) 5-chloro-*o*-anisidine; (n) 6-chloro-3*H*-benxazol-2-one; (o) NaOH; (p) 2-methoxybenzenethiol; (q) 2-propylphenol; (r) 5-chloro-2-hydroxyacetophenone; (s) 2-methylpyridin-3-ol.

Scheme 3[a]



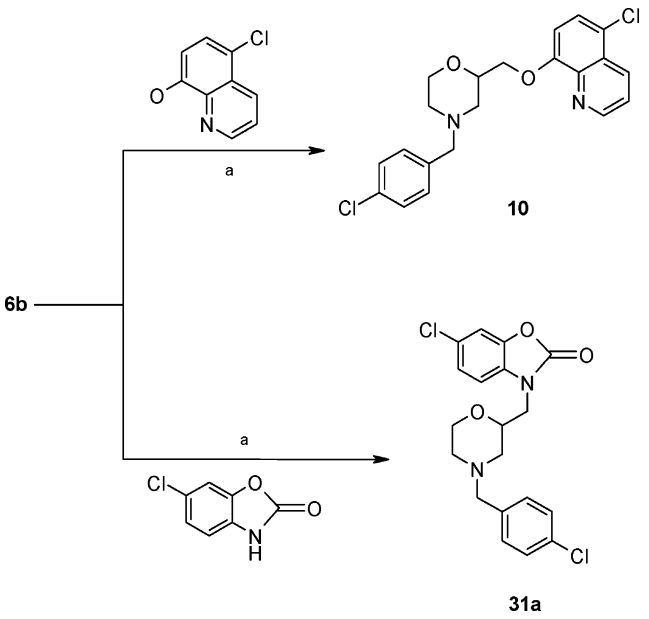
[a] Reagents: (a) acetic acid anhydride; (b) K_2CO_3, 1-bromo-2-methoxyethane; (c) BuLi; (d) H_2O_2; (e) NEt_3, ethyl chloroformate; (f) cyclopropylamine.

respectively, using palladium on carbon under an atmosphere of hydrogen. The same conditions were used to cleave the benzyl group in **16c** and **28** yielding the corresponding des-benzyl derivatives **16d** (Scheme 2) and **29a** (Scheme 6). The iodoaryl compound **17** was converted to the corresponding cyanoaryl compound **19** by a palladium-catalyzed cyanation reaction, using $Zn(CN)_2$ as the cyano source (Scheme 1). The olefin **28** was obtained by a one-pot synthesis from **28b** by a palladium-catalyzed cyclization reaction[37] followed by a palladium-catalyzed Heck reaction (Scheme 6). The amine **31** was prepared by alkaline treatment of the corresponding benzoxazolone **31a** (Scheme 2).

Receptor Binding. As shown in Table 1, the tested compounds inhibited [^{3}H]spiperone binding to human recombinant dopamine $D_{4.2}$ receptors with affinities ranging from low nanomolar to 1.0 micromolar. None of the compounds showed affinity for dopamine D_2 receptors at concentrations up to 10 μM (data not shown).

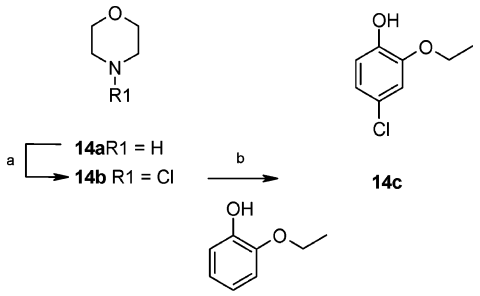
3D-QSAR Analysis. The 3D-QSAR model was based on a training set of 34 molecules (**1**−**34**). To determine the most active enantiomer, the ligands (*S*)-**21**, (R)-**21**, and (S/R)-**21** were synthesized and tested for dopamine D_4 receptor affinity. The (*S*)-enantiomer (Figure 1) and the racemic mixture were found to bind to the D_4 receptor with approximately the same affinity (Table 2), whereas the (*R*)-enantiomer showed low affinity. These biological experiments indicated that the bio-

Scheme 4[a]



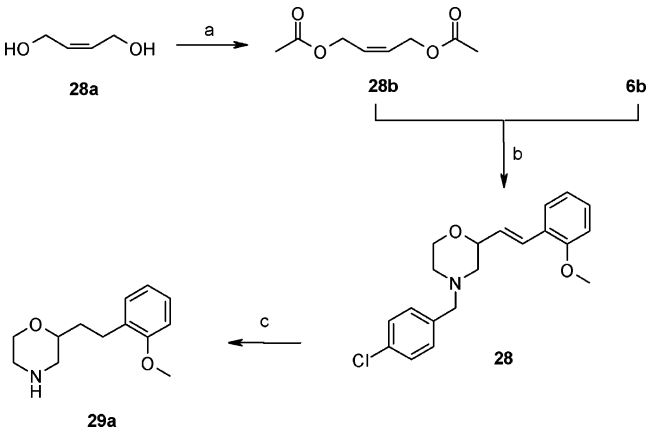
[a] Reagents: (a) *t*-BuOK, 18-crown-6 ether.

Scheme 5[a]



[a] Reagents: (a) NaOCl, − 60 °C.

Scheme 6[a]



[a] Reagents: (a) AcOH, H_2SO_4; (b) 1-iodo-2-methoxy-benzene, $Pd(PPh_3)_4$, NEt_3, N_2; (c) Pd/C, H_2.

active enantiomer of compound **21** was the (*S*)-enantiomer, and therefore only the (*S*)-enantiomer of each ligand **1**−**39** was considered. Compound (*S*)-**15** was chosen as the template because of its high activity.

The geometry optimization of each compound was investigated by systematic conformational search using Tripos.[38] For each molecule, Tripos force field was applied and a conformational analysis was performed for all the rotatable bonds. For the morpholine derivatives, the morpholine ring was used in the chair conformation. For the 1,4-oxazepane derivatives, a conformation analysis of the ring was performed by including ring closure bonds in the molecular description. These bonds were broken during the conformation analysis, allowing the torsional angles to be freely adjusted. A bond length variance of 0.1 Å was used with a bond angle variance of 5°. The energy minimization was carried out with the conjugate gradient minimization algorithm. To optimize the fit of morpholine derivatives and 1,4-oxazepane derivatives to the model, the decisive factors for accommodating the ligands in the model were based on the lowest energy conformation, the lowest RMS values and visual inspection. The quality of superimposition has been measured in terms of RMS values of the fitting points with a range of 0.002 to 0.22 Å.

An optimal superimposition was obtained for the conformations selected (Figure 2). The fitting points used were the sp^3 nitrogen atom and the centers of the two benzene rings. These three points were chosen from the pharmacophore model for dopamine D_4 receptor antagonists described in the literature by Boström et al.[32] The pharmacophore proposed by Bostrom is based on tricyclic ring systems as clozapine and other molecules as butyrophenone with *N*-alkyl substituent. We used three points of this pharmacophore in the aim to obtain a robust and predictive model selective for the binding mode of our data.

In the present study, three probes C3, OH2, and N3+ were chosen based on the supposed possible nature of amino acids forming the binding site. The physicochemical interaction energies between the selected probes and each molecule were calculated with the GRID program. The methyl CH_3 group (C3 probe) was used for investigation of steric interactions, the water molecule (OH2 probe) allowed description of the hydrogen-bonding interactions, and the sp^3 cationic NH_3 group (N3+ probe) was selected to simulate a hydrogen-bond donor. The use of a grid spacing of 1 Å resulted in 40987 variables for each molecule. A Consensus Principal Component Analysis (CPCA)[39] was performed with the purpose of making a probe selection from the molecular structures. For each probe, a score was determined according to the information obtained in the CPCA analysis (Table 3). All of the probes appeared relevant, so they were all taken into consideration when the analysis was started.

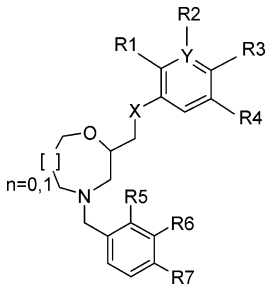
Many of the variables derived from the GRID analysis did not contribute to the correlation between the chemical structure and the biological activity and could be considered as noise, which decreased the quality of the model.[40] To obtain a robust QSAR model, the irrelevant variables were removed using the GOLPE program.

From the 30457 active variables that were automatically selected by GOLPE, an initial pretreatment decreased the number of variables to 14433.

The D-optimal preselection procedure[41] allowed the selection of the most informative variables correlated with the biological activity from an initial PLS model. This procedure reduced the number of variables from 14433 to 1804.

A Smart Region Definition (SRD)[42] algorithm was performed with the aim to select and to group the

Table 1. Structures and Affinities of Dopamine D_4 Ligands



											K_i (μM)	
compd	R1	R2	R3	R4	R5	R6	R7	X	Y	[ ], n =	observed	predictedat
						Training Set						
1	OCH_3	H	H	H	H	H	H	O	C	0	0.85	0.501
2	H	Cl	H	OCH_3	H	H	H	O	C	0	0.92	1.000
3	OCH_3	H	H	H	H	Cl	H	O	C	0	0.65	0.645
4	OCH_3	H	H	H	H	H	Cl	O	C	0	0.032	0.060
5	OCH_3	H	I	H	H	H	H	O	C	0	0.43	0.676
6	OCH_2CH_3	H	H	H	H	H	Cl	O	C	0	0.013	0.026
7	OCH_3	H	$CONHC_3H_5$	Cl	H	H	Cl	O	C	0	0.15	0.204
8	$O(CH_2)_2OCH_3$	H	H	H	H	H	Cl	O	C	0	0.052	0.036
9	OCH_3	H	H	NO_2	H	H	Cl	O	C	0	0.023	0.021
10	H	H	Cl	a	H	H	Cl	O	C	0	0.040	0.033
11	$OCH(CH_3)_2$	H	H	H	H	H	Cl	O	C	0	0.046	0.041
12	OCH_3	H	H	NH_2	H	H	Cl	O	C	0	0.10	0.031
13	OCH_3	OCH_3	H	H	H	H	Cl	O	C	0	1.0	1.000
14	OCH_2CH_3	H	Cl	H	H	H	Cl	O	C	0	0.013	0.005
15	OCH_2CH_3	H	H	Cl	H	H	Cl	O	C	0	0.0029	0.003
16	OCH_2CH_3	H	H	H	H	H	NO_2	O	C	0	0.035	0.026
17	OCH_2CH_3	H	I	H	H	H	Cl	O	C	0	0.024	0.036
18	OCH_2CH_3	H	H	H	Cl	H	Cl	O	C	0	0.29	0.398
19	OCH_2CH_3	H	CN	H	H	H	Cl	O	C	0	0.040	0.017
20	OCH_2CH_3	H	H	H	H	H	F	O	C	0	0.18	0.166
21	OCH_3	H	Cl	H	H	H	Cl	O	C	0	0.0028	0.012
22	OCH_3	H	H	F	H	H	Cl	O	C	0	0.030	0.032
23	OCH_3	H	Cl	H	H	H	Br	O	C	1	0.0020	0.002
24	OCH_3	H	H	CF_3	H	H	Cl	O	C	0	0.25	0.162
25	$COCH_3$	H	H	Cl	H	H	Cl	O	C	1	0.0055	0.003
26	OCH_3	H	H	NO_2	H	H	Cl	O	C	1	0.40	0.398
27	OCH_2CH_3	H	H	Cl	H	H	Cl	O	C	1	0.0093	0.010
28	OCH_3	H	H	H	H	H	Cl	CH	C	0	0.20	0.123
29	OCH_3	H	H	H	H	H	Cl	CH_2	C	0	0.029	0.060
30	OCH_3	H	H	Cl	H	H	Cl	NH	C	0	0.0045	0.005
31	OH	H	Cl	H	H	H	Cl	NH	C	0	0.0054	0.004
32	OCH_3	H	H	H	H	H	Cl	S	C	0	0.061	0.060
33	CH_3		H	H	H	H	Cl	O	N	1	0.083	0.048
34	OCH_2CH_3	H	H	H	H	H	Cl	O	C	1	0.0049	0.008
						Test Set						
35	OCH_3	H	H	Cl	H	H	H	O	C	0	0.070	0.074
36	OCH_3	H	H	H	H	H	CF_3	O	C	0	0.061	0.052
37	OCH_3	H	H	H	H	Cl	Cl	O	C	0	0.032	0.077
38	$(CH_2)_2CH_3$	H	H	H	H	H	Cl	O	C	0	0.032	0.036
39	OCH_2CH_3	H	Cl	H	H	H	Cl	O	C	1	0.0070	0.012

[a] See structure Scheme 4.

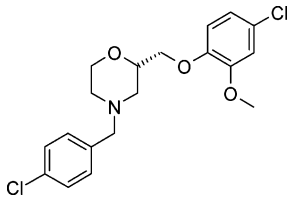


Figure 1. (*S*)-Enantiomer of the 4-(4-chlorobenzyl)-2-(4-chloro-2-methoxyphenoxymethyl)morpholine oxalic acid salt (**21**).

regions of variables of highest importance for the model. These groups were evaluated by Fractional Factorial Design (FFD). This algorithm allowed the extraction of the most relevant variables by building a large number of reduced models similar to the complete model. The SRD variable preselection decreased the number of variables from 1804 to 1725 without reducing the quality of the model, and after FFD (Table 4), 1052 variables were selected, resulting in a significant improvement of the quality of the model ($Q^2 = 0.31$ to $Q^2 = 0.62$). It was concluded that many of the variables contributed to noise and not to the robustness of the predictive model.

Table 2. Enantioselectivity for Compound **21**

conformation	K_i value (μM)
(*S*)	0.0028
(*R*)	1.6
(*S*/*R*)	0.0044

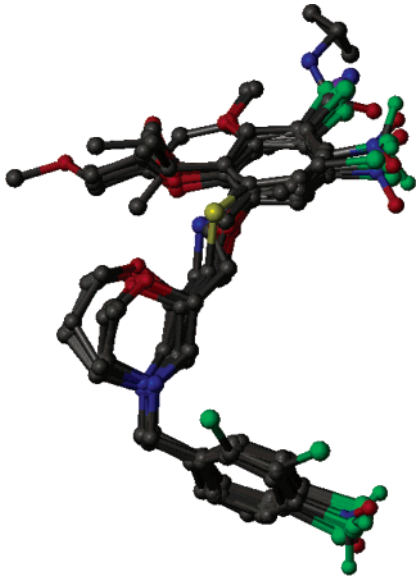


Figure 2. Superimposition of the dopamine D_4 ligands **1**−**39**. For clarity, all hydrogens were removed.

Table 3. Contribution for Each Probe

probe	%
C3	26.6
N3+	38.5
OH2	34.8

Table 4. 3D QSAR Models[a]

	no. of variables	no. of LV'S	R^2	Q^2
initial model	30457	4	0.88	0.31
after pretreatment	14433	4	0.88	0.31
after SRD selection	1725	N.D.	N.D.	N.D.
after FFD selection	1052	4	0.91	0.62

[a] N.D. = data not determined.

An external validation set of five molecules (**35**−**39**), representative of the molecular diversity of our molecules, was applied to test the predictive power of the model. These compounds were selected from a Principal Component Analysis performed by using Golpe program. The experimental and predicted −log(K_i) values for all 39 compounds (Figure 3) showed a good correlation and indicated a good prediction of the affinity of the external set. The predicted values deviated less than half a logarithmic unit from the experimental binding affinities; therefore, it was proposed that the model had enough structural information to be able to predict the test compounds correctly. The quality of the external prediction was shown by the external SDEP value obtained: 0.20 for four components.

Interpretation of Contour Maps. The three-dimensional representation of the GRID/GOLPE data as contour plots illustrates unfavorable and favorable interactions with three different probes C3, N3+, and OH2. As an example, the template molecule **15** is shown for each of the different fields.

C3 Contour Maps. The contour maps of PLS coefficients for the C3 probe (Figures 4a and 4b) indicate unfavorable and favorable steric regions. The principal region with high negative value corresponding to A in Figure 4a shows an unfavorable interaction between a substituent in the molecule and the C3 probe which resulted in decreased activity. This effect was clearly

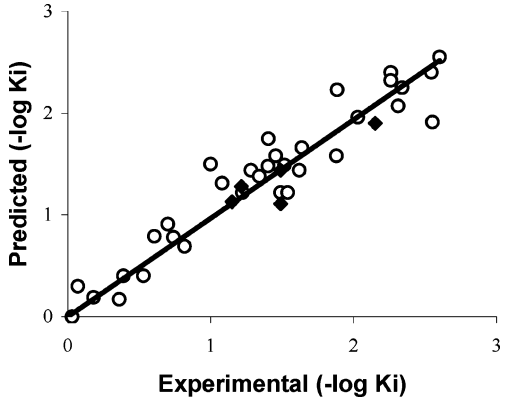


Figure 3. Predicted versus experimental binding affinities (−log K_i) for the 39 dopamine D_4 receptor ligands: ○ = training set; ◆ = test set.

observed by comparing the binding affinities for the *m*-methoxy-substituted compound **13** and the corresponding des-*m*-methoxy compound **4**, which had higher affinity. A similar low D_4 affinity was seen for compound **2**, which had a *m*-chloro substituent. The length of aliphatic chain B (Figure 4a) does not play an important role for the activity. For example, compounds **4**, **6**, **8**, and **11** have different substituents but similar affinity for the dopamine D_4 receptor. These A and B regions belong to a benzene ring system, which is important for binding to the receptor. In area C, corresponding to the positive region (Figure 4b), a favorable interaction between a substituent in the molecule and the C3 probe leads to increased affinity. This indicates that the size of the ring system affects the affinity. The affinity of compound **6** (six-membered ring) was lower, by approximately a factor of 3, compared to compound **34** (seven-membered ring). Another positive region, D in Figure 4b, suggests an important steric contribution in this area. The *p*-chlorobenzyl group present in this region for the majority of compounds seems important for the dopamine D_4 affinity.

N3+ Contour Maps. The coefficient plots generated with the N3+ probe (Figures 5a, 5b) mimic the hydrogen-bond donor energies. Some positive and negative coefficients are positioned in the same areas as the C3 probe. These areas could be considered as steric interactions. Moreover, the unfavorable interaction region present in area E (Figure 5a) reveals that an additional substituent is this position will decrease the affinity.

OH2 Contour Maps. The contour maps for D_4 affinity obtained with the OH2 probe are represented in Figures 6a and 6b. The contribution of the OH2 probe to the PLS model represent the hydrogen bond donating (with the H atom) and the hydrogen bond accepting (with the O atom), but also the steric interaction (van der Waals). It's interesting to notice that the majority of the areas of OH2 probes occupy similar regions in the space as the C3 probe. This indicates that the major effect describes by OH2 probe in of steric nature. The contribution of the OH2 probe in term of hydrogen bonding is minor. In our model, the steric interactions play an essential role in describing the difference affinity of the compounds.

The contour maps obtained from the PLS model allowed the selection of important structural features for selective binding of ligands to the D_4 receptor.

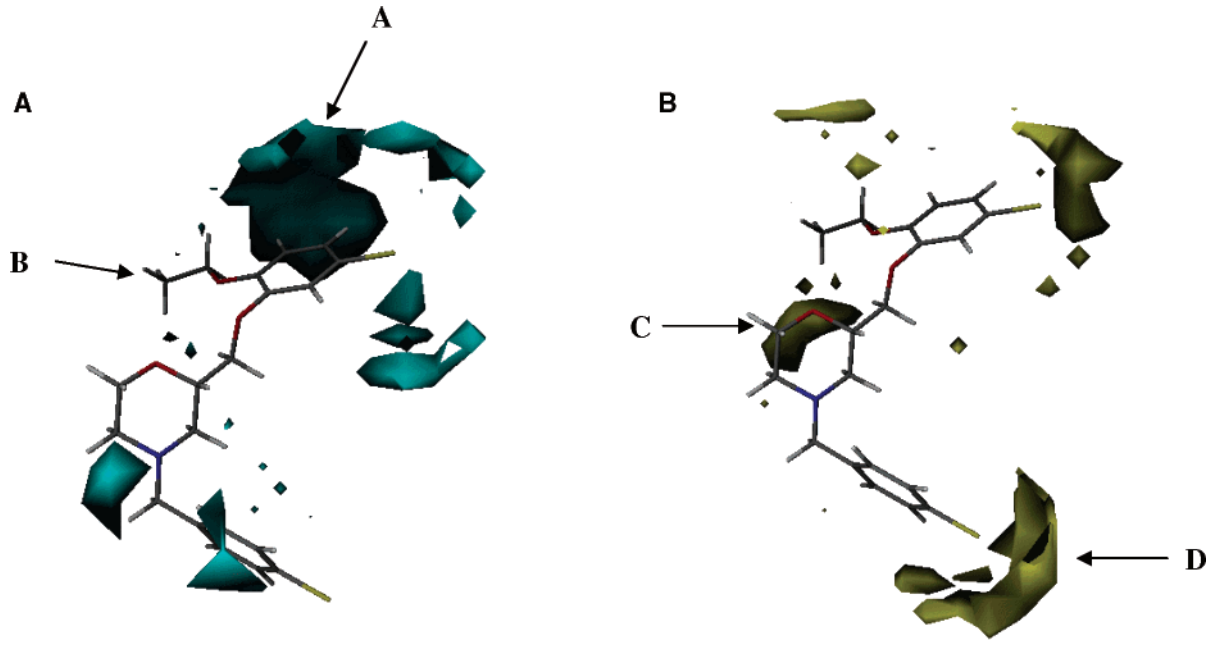


Figure 4. Illustration of the contour maps for dopamine D_4 receptor ligands obtained with the C3 probe. The negative coefficient (Figure 4a) at the −0.0017 kcal/mol level show a principal negative region in area A. The B area represents the aliphatic chain, which has a length unimportant for binding to the receptor. The areas C and D show the principal positive coefficients (Figure 4b) at the 0.0014 kcal/mol level. An unfavorable interaction (positive interaction energy) between a substituent and the probe in regions with negative coefficients will decrease -log(K_i), i.e., reduce the activity of the compound and vice versa for positive coefficients. Compound **15** is shown to illustrate the size of the regions.

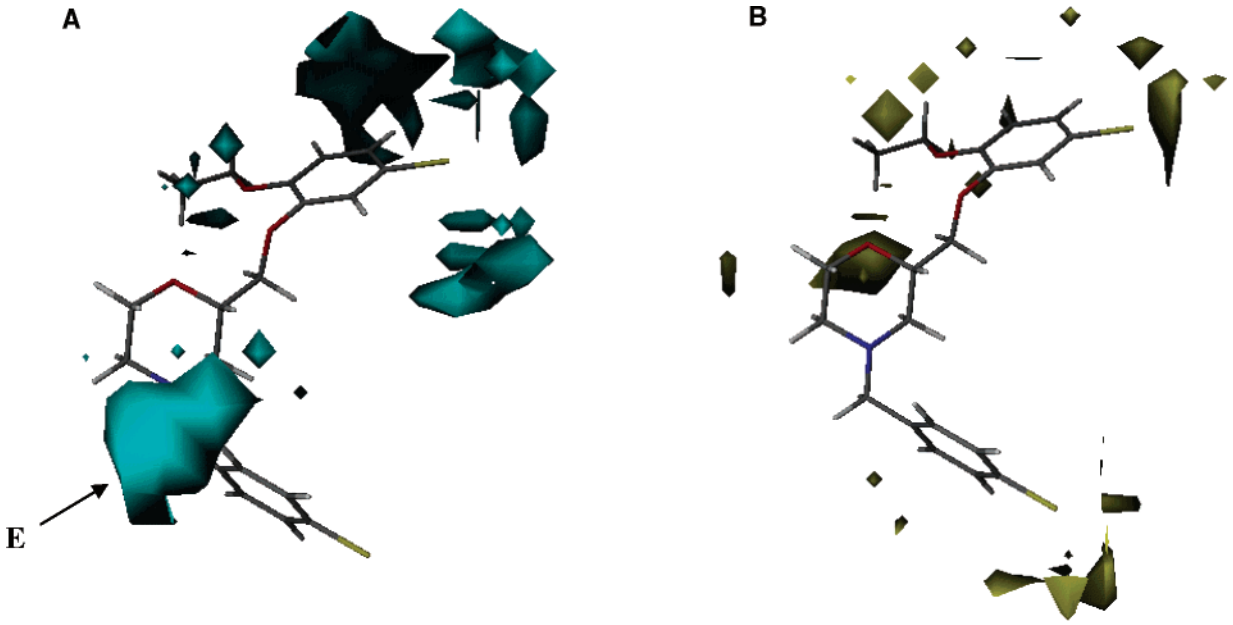


Figure 5. Illustration of the contour maps for dopamine D_4 receptor ligands obtained with the N3+ probe. The negative coefficient (Figure 5a) at the −0.0021 kcal/mol level and the positive coefficient (Figure 5b) at the 0.0016 kcal/mol level are shown. An unfavorable interaction, shown in area E (positive interaction energy) between a substituent and the probe in regions with negative coefficients will decrease -log(K_i), i.e., reduce the activity of the compound and vice versa for positive coefficients. Compound **15** is shown to illustrate the size of the regions.

Recently, a 3D-QSAR study of 25 dopamine D_4 antagonists was published.[31] In this study, the predictive model was performed using CoMFA methodology. The resulting contour maps revealed a favorable steric contribution near to a phenyl group substituted with a bulky electronegative group, which corresponds to area C in our model. The unfavorable steric interaction close to a second benzene ring system is in accordance with the A position in our model. Our model supports the idea that the presence of two π systems should be a prerequisite for high affinity binding. Additional information was obtained from our model regarding another favorable steric contribution in area B, showing that the binding affinity could be dependent on the volume of this area.

An idea of the possible interaction of the ligands with the dopamine D_4 receptors may be gained from the literature. A number of publications suggest that an aromatic ring could interact as an aromatic cluster in the sixth transmembrane segment of the receptor,[43−46]

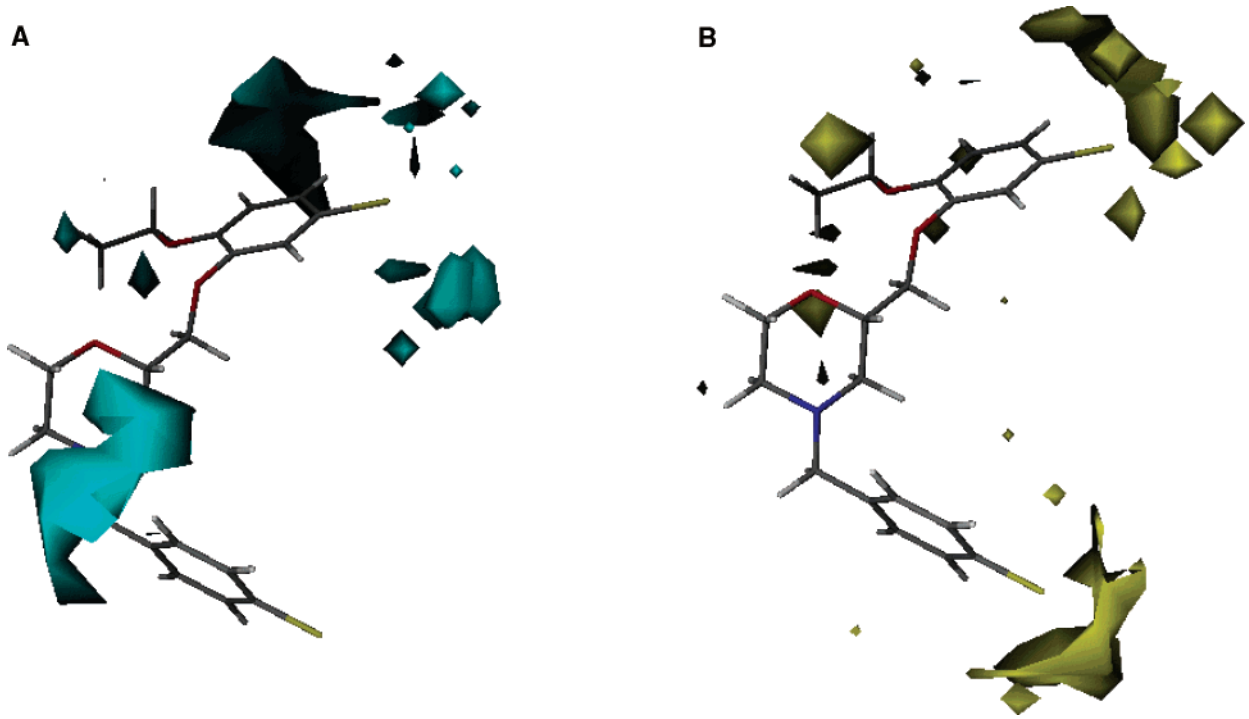


Figure 6. Illustration of the contour maps for dopamine D_4 receptor ligands obtained with the OH2 probe. The negative coefficient (Figure 6a) at the −0.0021 kcal/mol level and positive coefficient (Figure 6b) at the 0.0015 kcal/mol level are shown. An unfavorable interaction (positive interaction energy) between a substituent and the probe in regions with negative coefficients will decrease $-\log(K_i)$, i.e., reduce the activity of the compound and vice versa for positive coefficients. Compound **15** is shown to illustrate the size of the regions.

which is situated close to the conserved serine residues in the fifth transmembrane domain,[47] known to be the molecular determinant for agonist induced signaling.[46,48] Our results correlate with this hypothesis, as area A is unfavorable for the steric field and the length of aliphatic chain B (Figure 4a) does not seem to be important for binding to the receptor.

From our model, the aliphatic amine present in morpholine and in 1,4-oxazepane has an electrostatic interaction. In the literature, this cationic nitrogen might interact with aspartate 114 in the third transmembrane domain.[49−51] This amino acid, conserved in all the dopamine receptors, is very important for ligand−receptor interaction.

The probes show that region D is of great importance, as compound **4** (*p*-chloro substituent) has higher affinity for the D_4 receptor than compound **3** (*m*-chloro substituent). Compounds **1**, **2** and **5**, which lack a *p*-chloro group, also showed lower affinity. These results correlate with recent studies about the active site of the protein,[52−53] where the presence of this second 4-chloro substituted aromatic system seems important for D_4 affinity. In accordance with the study by Schetz et al.,[53] a recognition between the ligand and the phenylalanine 89 in the second transmembrane domain is possible. However, this result should be used with care because the authors showed that different structural classes of compounds may have different binding modes. Following point mutation, the affinity of structural classes is not always affected.

Conclusions

A series of 2,4-disubstituted morpholines and 2,4-disubstituted 1,4-oxazepanes have been synthesized. Thirty-nine compounds were tested for their binding affinity to dopamine D_4 and D_2 receptors. A high selectivity for dopamine D_4 versus D_2 receptor (>10 μM) was found (only D_4 data shown). A 3D-QSAR model of these ligands has been obtained, in which the ligands were described quantitatively with the GRID variables. The model was optimized after selection of the most relevant information with the GOLPE program. The predictability of the final model is represented by a Q^2 of 0.62. GRID plots of PLS coefficients were studied with the purpose of getting a better understanding of the relationship between chemical structure and biological activity. Important regions were identified around both benzene ring systems, where the D region (*p*-chlorobenzyl) is important for the affinity. The aliphatic amine belonging to the morpholine or 1,4-oxazepane group is also important for binding to the D_4 receptor. In accordance with the pharmacophore developed by Boström et al,[32] the three fitting points used are crucial. The two ring systems and the nitrogen atom are necessary for the selectivity of the dopamine D_4 receptor antagonists.[31,32] This information will hopefully aid others in designing new series of selective dopamine D_4 receptor ligands, which could be interesting drug candidates for the treatment of neurological disorders such as schizophrenia.

Experimental Section

Chemistry. Solvents and reagents were purchased from commercial sources and used without further purification unless otherwise stated. ^{1}H NMR spectra were recorded on a Bruker AM 500-MHz spectrometer. Splitting patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (b). The chemical shifts are recorded in parts per million (δ) referenced to tetramethylsilane (TMS).

The uncorrected melting points were determined on a Griffin melting point apparatus. Column chromatography was performed on silica gel (Merck, 0.040−0.063 mm). All moisture-sensitive reactions were performed under nitrogen using oven-dried glassware and with anhydrous solvents. Drying with magnesium sulfate and evaporation gave the product. Elemental analyses were performed by the University of Copenhagen.

(±)-2-(2-Methoxyphenyloxymethyl)oxirane (1b). Procedure A. Compound **1b** was prepared from a mixture of 2-methoxyphenol (**1a**) (12.4 g, 100.0 mmol), epibromohydrin (16.4 g, 120.0 mmol), and K_2CO_3 (20.7 g, 149.0 mmol) in THF (125 mL) which was stirred at reflux under N_2 overnight. The mixture was filtered, the solid was extracted with EtOAc, and the filtrate was evaporated. The product was obtained after dissolution in CH_2Cl_2, filtration though silica gel and isolated as an oil. Yield 14.9 g (82%). ^{1}H NMR ($CDCl_3$): δ 6.93 (m, 2H), 6.81 (m, 2H), 4.24 (m, 1H), 3.98 (m, 1H), 3.84 (s, 3H), 3.26 (m, 1H), 2.94 (m, 1H), 2.72 (m, 1H).

(±)-2-(2-Methoxyphenoxymethyl)morpholine (1c). Procedure B. Compound **1c** was prepared according to the literature[54] from a mixture of **1b** (2.00 g, 11.1 mmol), 2-aminoethylhydrogen sulfate (7.80 g, 55.6 mmol), and NaOH (4.40 g, 111.0 mmol) in EtOH (40 mL) and H_2O (15 mL) refluxed for 8 h. The mixture was evaporated. H_2O (100 mL) was added, and the compound was extracted with EtOAc (2 × 50 mL) and isolated as an oil. Yield 2.4 g (100%). ^{1}H NMR ($CDCl_3$): δ 6.90 (m, 4H), 4.18 (m, 1H), 4.06 (m, 1H), 3.93 (m, 1H), 3.84 (s, 3H), 3.68 (m, 1H), 3.56 (m, 2H), 3.12 (d, 1H, J = 8.6 Hz), 2.93 (t, 1H, J = 9.6 Hz), 2.87 (d, 1H, J = 8.6 Hz), 2.78 (t, 1H, J = 9.6 Hz).

(±)-4-Benzyl-2-(2-methoxyphenoxymethyl)morpholine Oxalic Acid Salt (1) Procedure C. Compound **1c** (2.00 g, 11.1 mmol) was mixed with benzyl bromide (1.45 mL, 12.2 mmol), K_2CO_3 (2.30 g, 16.7 mmol) in EtOH (30 mL) and was stirred at reflux for 3.5 h. The mixture was evaporated. H_2O (50 mL) was added, and the product was extracted with EtOAc (2 × 30 mL). The product was obtained by column chromatography with 4% ethanol in CH_2Cl_2. Dissolution in diethyl ether and precipitation with oxalic acid gave a salt that was purified by crystallization from EtOH and then triturated with THF. Yield 0.6 g (22%), mp 132.6 °C. ^{1}H NMR (DMSO-d_6): δ 7.37 (d, 4H,J = 4.1 Hz), 7.32 (bq, 1H, J = 4.1 Hz), 6.89 (m, 4H), 3.90 (m, 4H), 3.75 (m, 2H), 3.71 (s, 3H), 3.59 (t, 1H, J = 10.1 Hz), 2.93 (d, 1H, J = 9.6 Hz), 2.73 (d, 1H, J = 9.6 Hz), 2.30 (m, 1H), 2.19 (m, 1H). Anal. ($C_{19}H_{23}NO_3 \cdot C_2H_2O_4$) C, H, N.

(±)-2-(3-Chloro-5-methoxyphenoxymethyl)oxirane (2b). Compound **2b** was prepared according to procedure A prepared from a mixture of 3-chloro-5-methoxyphenol (**2a**) (5.00 g, 31.5 mmol), epichlorohydrin (4.37 g, 47.3 mmol), and K_2CO_3 (6.52 g, 47.2 mmol) in THF (60 mL). The mixture was evaporated, and H_2O (50 mL) was added. The mixture was extracted with EtOAc (4 × 30 mL). Yield 3.57 g (53%). ^{1}H NMR ($CDCl_3$): δ 6.53 (m, 2H), 6.36 (m, 1H), 4.18 (m, 1H), 3.89 (m, 1H), 3.75 (s, 3H), 3.31 (m, 1H), 2.90 (m, 1H), 2.78 (m, 1H).

(±)-2-(3-Chloro-5-methoxyphenoxymethyl)morpholine (2c). Compound **2c** was prepared according to procedure B using **2b** (3.50 g, 16.3 mmol), 2-aminoethylhydrogen sulfate (11.6 g, 81.5 mmol), and NaOH (6.52 g, 163.0 mmol) in EtOH (80 mL) and H_2O (30 mL), stirred at reflux for 8 h. The mixture was evaporated, and H_2O (50 mL) was added. The compound was extracted with EtOAc (2 × 60 mL) and isolated as an oil. Yield 3.72 g (89%). ^{1}H NMR ($CDCl_3$): 6.57 (m, 2H), 6.40 (m, 1H), 4.18 (m, 1H), 4.03 (m, 2H), 3.80 (m, 3H), 3.62 (m, 2H), 3.47 (m, 1H), 3.33 (m, 1H), 3.18 (m, 1H), 3.08 (m, 1H).

(±)-4-Benzyl-2-(3-chloro-5-methoxyphenoxymethyl)-morpholine Oxalic Acid Salt (2). Compound **2** was prepared according to procedure C using **2c** (3.60 g, 14.0 mmol), benzyl bromide (2.88 g, 16.8 mmol), and K_2CO_3 (5.80 g, 42.0 mmol) in EtOH (40 mL), stirred at reflux for 15 h. Yield 0.67 g (14%), mp 191−192 °C. ^{1}H NMR (DMSO-d_6): δ 7.31 (m, 6H), 6.50 (m, 2H), 3.95 (m, 2H), 3.84 (m, 2H), 3.74 (s, 3H), 3.71 (s, 2H,), 3.59 (t, 1H, J = 10.1 Hz), 2.92 (d, 1H, J = 9.8 Hz), 2.75 (d, 1H, J = 9.8 Hz), 2.30 (m, 1H), 2.17 (m, 1H). Anal. ($C_{19}H_{22}ClNO_3 \cdot C_2H_2O_4$) C, H, N.

(±)-4-(3-Chlorobenzyl)-2-(2-methoxyphenoxymethyl)-morpholine Oxalic Acid Salt (3). Compound **3** was prepared according to procedure C using **1c** (4.26 g, 19.1 mmol), 3-chlorobenzyl chloride (3.38 g, 21.0 mmol), and K_2CO_3 (3.96 g, 28.7 mmol) in EtOH (50 mL), stirred at reflux for 3 h. Yield 0.75 g (9%), mp 132−136 °C. ^{1}H NMR (DMSO-d_6): δ 7.38 (m, 4H), 6.88 (m, 4H), 3.95 (m, 1H), 3.90 (m, 1H), 3.84 (m, 2H), 3.75 (s, 3H), 3.66 (m, 2H), 3.59 (t, 1H, J = 10.0 Hz), 2.93 (d, 1H, J = 9.6 Hz), 2.72 (d, 1H, J = 9.6 Hz), 2.30 (t, 1H, J = 9.6 Hz), 2.18 (t, 1H, J = 9.6 Hz). Anal. ($C_{19}H_{22}ClNO_3 \cdot C_2H_2O_4 \cdot 0.3H_2O$) C, H, N.

(±)-4-(4-Chlorobenzyl)-2-(2-methoxyphenoxymethyl)-morpholine Oxalic Acid Salt (4). Compound **4** was prepared according to procedure C using **1c** (3.67 g, 16.5 mmol), 4-chlorobenzyl chloride (2.92 g, 18.1 mmol), and K_2CO_3 (3.38 g, 24.5 mmol) in EtOH (50 mL) and was stirred at reflux for 3 h. Yield 0.64 g (9%), mp 139−142 °C. ^{1}H NMR (DMSO-d_6): δ 7.42 (d, 2H, J = 7.8 Hz), 7.38 (d, 2H, J = 7.8 Hz), 6.94 (m, 2H), 6.89 (m, 1H), 6.84 (m, 1H), 3.94 (m, 2H), 3.83 (m, 2H), 3.73 (s, 3H), 3.70 (s, 2H), 3.58 (t, 1H, J = 10.1 Hz), 2.93 (d, 1H, J = 9.8 Hz), 2.72 (d, 1H, J = 9.8 Hz), 2.29 (t, 1H, J = 9.8 Hz), 2.18 (t, 1H, J = 9.8 Hz). Anal. ($C_{19}H_{22}ClNO_3 \cdot C_2H_2O_4$) C, H, N.

4-Iodo-2-methoxyphenol (5b). Procedure D. Compound **5b** was prepared according to the literature[35] using guaiacol (**5a**) (50.0 g, 401.0 mmol) and NaI (60.5 g, 401.0 mmol) in MeOH (800 mL), cooled to below 0 °C. NaOH (16.0 g, 401.0 mmol) was added slowly and aqueous NaOCl (15%, 750 mL) was added dropwise during 0.75 h below 0 °C. The mixture was stirred for 10 min at 0 °C and neutralized by adding 4 N HCl (100 mL) at 0 °C. The compound was extracted with diethyl ether (2 × 200 mL). The ether phase was washed with aqueous $Na_2S_2O_3$ (10%, 200 mL) by stirring it overnight. After evaporation of the organic phase, the compound was purified by vacuum distillation. Yield 55.0 g (54%), bp 105−106 °C (0.010 mmHg). ^{1}H NMR ($CDCl_3$): δ 7.18 (m, 1H), 7.09 (m, 1H), 6.67 (d, 1H, J = 6.9 Hz), 5.56 (s, 1H), 3.87 (s, 3H).

(±)-2-(4-Iodo-2-methoxyphenoxymethyl)oxirane (5c). Compound **5c** was prepared according to procedure A from a mixture of **5b** (6.15 g, 24.7 mmol), epibromohydrin (10.1 g, 74.1 mmol), and K_2CO_3 (5.12 g, 37.0 mmol) in DME (100 mL). The mixture was extracted with CH_2Cl_2 (2 × 50 mL). Yield 5.02 g (67%), mp 92−94 °C. ^{1}H NMR ($CDCl_3$): δ 7.18 (m, 1H), 7.12 (m, 1H), 6.68 (d, 1H, J = 7.6 Hz), 4.23 (m, 1H), 3.97 (q, 1H, J = 4.6 Hz), 3.83 (s, 3H), 3.37 (m, 1H), 2.89 (t, 1H, J = 5.8 Hz), 2.73 (m, 1H).

(±)-2-[(4-Iodo-2-methoxyphenoxy)methyl]morpholine (5d). Compound **5d** was prepared according to procedure B using **5c** (3.67 g, 12.0 mmol), 2-aminoethylhydrogen sulfate (8.54 g, 60.2 mmol), and NaOH (4.80 g, 120.0 mmol) in 2-propanol (90 mL) and H_2O (30 mL), stirred at reflux for 8 h. The mixture was evaporated, and H_2O (100 mL) was added. The compound was extracted with CH_2Cl_2 (2 × 60 mL) and isolated as an oil. Yield 3.42 g (81%). ^{1}H NMR ($CDCl_3$): δ 7.23 (m, 1H), 7.17 (m, 1H), 6.70 (m, 1H), 4.17 (m, 1H), 4.07 (m, 2H), 3.87 (s, 3H), 3.80 (m, 2H), 3.68 (m, 1H), 3.42 (m, 1H), 3.20 (m, 1H).

(±)-4-Benzyl-2-(4-iodo-2-methoxyphenoxymethyl)morpholine Oxalic Acid Salt (5). Compound **5** was prepared according to procedure C using **5d** (3.40 g, 9.80 mmol), benzyl bromide (2.00 g, 11.7 mmol), and K_2CO_3 (7.50 g, 53.9 mmol) in EtOH (100 mL), stirred for 15 h at reflux. Yield 1.26 g (24%), mp 160−163 °C. ^{1}H NMR (DMSO-d_6): δ 7.37 (m, 5H), 7.24 (m, 2H), 6.79 (d, 1H, J = 9.4 Hz), 3.95 (m, 2H), 3.84 (m, 2H), 3.75 (s, 3H), 3.71 (s, 2H), 3.61 (t, 1H, J = 9.7 Hz), 2.96 (d, 1H, J = 9.8 Hz), 2.79 (d, 1H, J = 9.8 Hz), 2.33 (t, 1H, J = 9.6 Hz), 2.21 (t, 1H, J = 9.6 Hz). Anal. ($C_{19}H_{22}INO_3 \cdot C_2H_2O_4 \cdot 0.7H_2O$) C, H, N.

2-(4-Chlorobenzylamino)ethanol (6b). Compound **6b** was prepared from a mixture of ethanolamine (56.9 g, 931.0 mmol), NaOH (7.44 g, 186.0 mmol), 2-propanol (50 mL), and 1-chloro-4-chloromethylbenzene (**6a**) (30.0 g, 186.0 mmol),

stirred at reflux for 30 min. After evaporation, H_2O was added (100 mL), and the compound was extracted with CH_2Cl_2 (2 × 50 mL). The compound was purified by vacuum distillation. Yield 27 g (78%), bp 125−126 °C (0.010 mmHg). ^{1}H NMR ($CDCl_3$): δ 7.22 (m, 4H), 3.78 (m, 2H), 3.65 (m, 2H), 2.84 (m, 2H), 1.90 (s, 2H).

(±)-4-(4-Chlorobenzyl)-2-chloromethylmorpholine (6c). Procedure E. Compound **6c** was prepared analogously to the preparation of 4-(4-fluorobenzyl)-2-chloromethylmorpholine as described in the literature,[34,55] from a mixture of **6b** (18.5 g, 100.0 mmol) and epichlorohydrin (90.0 g, 1.00 mol), stirred at 40 °C for 30 min. The excess of epichlorohydrin was evaporated. Concentrated H_2SO_4 (30 mL) was added, and the mixture was heated at 150 °C for 30 min. Ice (300 g) and NaOH (10 g) were added, and the compound was extracted with toluene (3 × 50 mL) as an oil. Yield 14.8 g (57%). ^{1}H NMR ($CDCl_3$): δ 7.25 (m, 4H), 3.89 (m, 1H), 3.74 (m, 1H), 3.68 (m, 1H), 3.52 (m, 1H), 3.48 (m, 2H), 3.44 (m, 1H), 2.81 (d, 1H, J = 9.6 Hz), 2.62 (d, 1H, J = 9.6 Hz), 2.20 (m, 1H), 2.01 (t, 1H, J = 7.6 Hz).

(±)-4-(4-Chlorobenzyl)-2-(2-ethoxyphenoxymethyl)morpholine Oxalic Acid Salt (6). Compound **6** was prepared according to procedure F using **6c** (0.50 g, 1.92 mmol), 2-ethoxyphenol (0.40 g, 5.88 mmol), EtOK (0.33 g, 3.90 mmol), and 18-crown-6 ether (0.10 g, 0.38 mmol) in anhydrous DMF (30 mL) under N_2. Yield 0.090 g (10%), mp 122−127 °C. ^{1}H NMR (DMSO-d_6): δ 7.40 (m, 4H), 6.93 (m, 2H), 6.86 (m, 2H), 4.00 (m, 1H), 3.94 (m, 2H), 3.85 (m, 3H), 3.71 (d, 1H, J = 10.1 Hz), 3.63 (m, 2H), 2.94 (d, 1H, J = 9.6 Hz), 2.75 (d, 1H, J = 9.6 Hz), 2.31 (t, 1H, J = 9.6 Hz), 2.18 (t, 1H, J = 9.6 Hz), 1.23 (t, 3H, J = 6.3 Hz). Anal. ($C_{20}H_{24}ClNO_3 \cdot C_2H_2O_4 \cdot 0.5H_2O$) C, H, N.

4-Acetoxy-2-chloro-5-methoxybenzoic Acid (7b). Compound **7b** was prepared using 2-chloro-4-hydroxy-5-methoxybenzoic acid[36] (**7a**) (10.6 g, 52.3 mmol) and 4-(dimethylamino)-pyridine (1.00 g, 8.00 mmol) in acetic acid anhydride (100 mL). The mixture was stirred at 20 °C for 10 days. The mixture was evaporated and cooled on ice. H_2O (1.0 L) was added, and the mixture was stirred for 3 h. The mixture was filtered and the product washed with H_2O (100 mL). Yield 6.20 g, (48%), mp 137−139 °C. ^{1}H NMR ($CDCl_3$): δ 7.62 (m, 2H), 3.87 (s, 3H), 2.31 (m, 3H).

2-Chloro-*N*-cyclopropyl-4-hydroxy-5-methoxybenzamide (7c). Compound **7c** was prepared from **7b** (8.60 g, 35.2 mmol) and NEt_3 (8.90 g, 88.0 mmol) in CH_2Cl_2 (100 mL) and cooled to 0 °C. Ethyl chloroformate (7.63 g, 70.3 mmol) was added at 0 °C, and the mixture was stirred for 1 h at room temperature. The mixture was evaporated, and the crude mixture was stirred with cyclopropylamine (6.03 g, 105.0 mmol) in CH_2Cl_2 (100 mL) at reflux overnight. The mixture was washed with H_2O (2 × 200 mL) and evaporated to dryness. The crystalline product was triturated with petroleum ether/CH_2Cl_2 (1:5). Yield 0.57 g (7%), mp 214−216 °C. ^{1}H NMR ($CDCl_3$): δ 7.44 (m, 1H), 6.90 (m, 1H), 5.90 (m, 1H), 3.92 (s, 3H), 2.93 (m, 1H), 1.48 (s, 1H), 0.88 (m, 1H), 0.64 (m, 1H).

(±)-4-(4-Chlorobenzyl)-2[(5-chloro-4-cyclopropylaminocarbonyl-2-methoxyphenoxy)methyl]morpholine Oxalic Acid Salt (7). Compound **7** was prepared according to procedure F using **6c** (0.14 g, 0.60 mmol), anhydrous toluene (10 mL), anhydrous DMF (10 mL), **7c** (0.20 g, 0.80 mmol), EtOK (0.17 g, 2.70 mmol), and 18-crown-6 ether (32.0 mg, 0.10 mmol). The mixture was stirred at reflux for 40 h under N_2. H_2O (80 mL) was added, the mixture filtered, and the crystalline product washed with H_2O (50 mL). Yield 0.09 g, (24%), mp 159−162 °C. ^{1}H NMR ($CDCl_3$): δ 7.57 (m, 4H), 6.83 (s, 1H), 6.63 (s, 1H), 4.05 (m, 1H), 3.96 (m, 1H), 3.90 (m, 1H), 3.80 (s, 3H), 3.73 (bt, 1H), 3.50 (m, 3H), 2.93 (m, 1H), 2.89 (bd, 1H), 2.66 (bd, 1H), 2.23 (bt, 1H), 2.06 (bt, 1H), 1.60 (s, 1H), 0.90 (m, 2H), 0.66 (m, 2H). Anal. ($C_{23}H_{26}Cl_2N_2O_4 \cdot 0.2C_2H_2O_4$) C, H, N.

2-(2-Methoxyethoxy)phenol (8b). Compound **8b** was prepared stirring a mixture of cathecol (**8a**) (10.0 g, 90.8 mmol), 1-bromo-2-methoxyethane (12.6 g, 90.8 mmol), and K_2CO_3 (12.6 g, 90.8 mmol) in EtOH (100 mL) at reflux overnight. The mixture was evaporated, CH_2Cl_2 (200 mL) was added, the mixture was filtered and evaporated, and the product was obtained as an oil. Yield 4.50 g (29%). ^{1}H NMR ($CDCl_3$): δ 6.93 (m, 2H), 6.80 (m, 1H), 6.50 (s, 1H), 4.15 (m, 2H), 3.70 (m, 2H), 3.46 (s, 3H).

(±)-4-(4-Chlorobenzyl)-2-[2-(2-methoxyethoxyphenoxymethyl)]morpholine Oxalic Acid Salt (8). Compound **8** was prepared according to procedure F using **6c** (2.58 g, 9.91 mmol), **8b** (2.50 g, 14.8 mmol), EtOK (1.67 g, 19.8 mmol), and 18-crown-6 ether (0.52 g, 1.98 mmol), stirred in anhydrous DMF (20 mL) for 15 h at 110 °C under N_2. H_2O (50 mL) was added, and the mixture was extracted with diethyl ether (50 mL). The product was purified by column chromatography with 1% MeOH in CH_2Cl_2. Yield 1.20 g (25%), mp 122−127 °C. ^{1}H NMR (DMSO-d_6): δ 7.41 (q, 4H, J = 8.75 Hz), 6.95 (m, 2H), 6.87 (m, 2H), 4.03 (d, 2H, J = 3.37 Hz), 3.97 (m, 1H), 3.91 (m, 1H), 3.85 (m, 2H), 3.75 (d, 1H, J = 10.1 Hz), 3.68 (d, 1H, J = 9.8 Hz), 3.60 (m, 3H), 3.29 (s, 3H), 2.94 (d, 1H, J = 9.5 Hz), 2.73 (d, 1H, J = 9.6 Hz), 2.30 (t, 1H, J = 9.6 Hz), 2.18 (t, 1H, J = 9.6 Hz). Anal. ($C_{21}H_{26}ClNO_4 \cdot C_2H_2O_4 \cdot 0.4H_2O$) C, H, N.

(±)-4-(4-Chlorobenzyl)-2-(2-methoxy-5-nitrophenoxymethyl)morpholine Oxalic Acid Salt (9). Compound **9** was prepared according to procedure F using **6c** (0.66 g, 2.90 mmol), 2-methoxy-5-nitrophenol (0.74 g, 4.40 mmol), *t*-BuOK (0.65 g, 5.80 mmol), and 18-crown-6 ether (0.15 g, 0.60 mmol) in anhydrous toluene (20 mL), stirred for 75 h at reflux under N_2. Yield 0.20 g (14%), mp 176−177 °C. ^{1}H NMR (DMSO-d_6): δ 7.90 (m, 1H), 7.74 (m, 1H), 7.39 (m, 4H), 7.17 (d, 1H, J = 9.2 Hz), 4.10 (m, 2H), 3.90 (s, 3H), 3.84 (s, 2H), 3.65 (m, 2H), 3.59 (t, 1H, J = 9.8 Hz), 2.91 (d, 1H, J = 9.8 Hz), 2.73 (d, 1H, J = 9.8 Hz), 2.28 (m, 1H), 2.17 (t, 1H, J = 9.6 Hz). Anal. ($C_{19}H_{21}ClN_2O_5 \cdot C_2H_2O_4 \cdot 0.3H_2O$) C, H, N.

(±)-4-(4-Chlorobenzyl)-2-(5-chloroquinolin-8-oxymethyl)morpholine Oxalic Acid Salt (10). Compound **10** was prepared according to procedure F using **6c** (0.60 g, 2.30 mmol), 5-chloroquinolin-8-ol (0.72 g, 4.00 mmol), *t*-BuOK (0.66 g, 5.40 mmol), and 18-crown-6 ether (0.14 g, 0.50 mmol) in anhydrous toluene (20 mL), stirred for 75 h at reflux under N_2. Yield 0.42 g (37%), mp 148−150 °C. ^{1}H NMR (DMSO-d_6): δ 8.95 (d, 1H, J = 3.6 Hz), 8.50 (d, 1H, J = 9.5 Hz), 7.73 (q, 1H, J = 3.2 Hz), 7.67 (d, 1H, J = 7.2 Hz), 7.39 (m, 3H), 7.21 (d, 2H, J = 6.5 Hz), 4.32 (m, 2H), 3.98 (m, 1H), 3.88 (d, 1H, J = 9.8 Hz), 3.69 (s, 2H), 3.63 (t, 1H, J = 10.2 Hz), 3.01 (d, 1H, J = 9.8 Hz), 2.73 (d, 1H, J = 9.8 Hz), 2.31 (m, 2H). Anal. ($C_{21}H_{20}Cl_2N_2O_2 \cdot 1.2\ C_2H_2O_4 \cdot 0.3H_2O$) C, H, N.

(±)-4-(4-Chlorobenzyl)-2-(2-isopropoxyphenoxymethyl)morpholine Oxalic Acid Salt (11). Compound **11** was prepared according to procedure F using **6c** (2.00 g, 7.70 mmol), 2-isopropoxyphenol (1.76 g, 11.5 mmol), *t*-BuOK (1.88 g, 15.4 mmol), and 18-crown-6 ether (1.02 g, 3.90 mmol) in anhydrous toluene (30 mL), stirred for 15 h at reflux under N_2. Yield 1.2 g (41%), mp 89−90 °C. ^{1}H NMR (DMSO-d_6): δ 7.38 (q, 4H, J = 8.7 Hz), 6.93 (m, 2H), 6.87 (m, 2H), 4.37 (m, 1H), 3.97 (m, 1H), 3.85 (m, 2H), 3.80 (m, 1H), 3.68 (d, 1H, J = 10.3 Hz), 3.60 (m, 1H), 3.54 (m, 1H), 2.90 (d, 1H, J = 9.6 Hz), 2.76 (d, 1H, J = 9.6 Hz), 2.27 (t, 1H, J = 9.6 Hz), 2.18 (t, 1H, J = 9.6 Hz), 1.00 (m, 6H). Anal. ($C_{21}H_{26}ClNO_3 \cdot C_2H_2O_4$) C, H, N.

(±)-4-(4-Chlorobenzyl)-2-(2-methoxy-5-aminophenoxymethyl)morpholine Oxalic Acid Salt (12). Compound **12** was prepared using compound **9** as its free base (0.85 g, 2.20 mmol) with Pd/C (5%, 0.10 g) in EtOH (20 mL), stirred under hydrogen for 6 h. The product was obtained by column chromatography with 4% EtOH in CH_2Cl_2. Dissolution in diethyl ether and precipitation with oxalic acid gave compound **12**. Yield 70 mg (9%), mp 117.1 °C. ^{1}H NMR (DMSO-d_6): δ 7.41 (q, 4H, J = 9.3 Hz), 6.69 (d, 1H, J = 6.6 Hz), 6.32 (m, 1H), 6.18 (m, 1H), 3.85 (m, 3H), 3.70 (s, 2H), 3.55 (m, 2H), 3.52 (s, 5H), 2.94 (d, 1H, J = 9.6 Hz), 2.75 (d, 1H, J = 9.6 Hz), 2.32 (m, 1H), 2.22 (bt, 1H). Anal. ($C_{19}H_{23}ClN_2O_3 \cdot 2.5C_2H_2O_4 \cdot H_2O$) C, H, N.

(±)-4-(4-Chlorobenzyl)-2-(2,3-dimethoxyphenoxymethyl)morpholine Oxalic Acid Salt (13). Compound **13** was

prepared according to procedure F using **6c** (1.77 g, 11.5 mmol), 2,3-dimethoxyphenol (2.00 g, 7.70 mmol), EtOK (1.88 g, 15.4 mmol), and 18-crown-6 ether (1.02 g, 3.90 mmol) in anhydrous toluene (30 mL), stirred for 72 h at reflux under N_2. Yield 1.0 g (23%), mp 139−141 °C. ^{1}H NMR (DMSO-d_6): δ 7.45 (s, 1H), 7.40 (d, 2H, J = 7.0 Hz), 7.36 (d, 2H, J = 7.0 Hz), 6.94 (t, 1H, J = 7.3 Hz), 6.63 (m, 1H), 3.98 (m, 1H), 3.93 (m, 1H), 3.84 (m, 1H), 3.80 (m, 1H), 3.75 (s, 3H), 3.64 (m, 1H), 3.59 (s, 3H), 3.55 (s, 2H), 2.92 (d, 1H, J = 9.6 Hz), 2.72 (d, 1H, J = 9.6 Hz), 2.29 (m, 1H), 2.18 (m, 1H). Anal. ($C_{20}H_{24}ClNO_4$·$C_2H_2O_4$·0.7H_2O) C, H, N.

4-Chloromorpholine (14b). Compound **14b** was prepared using morpholine (**14a**) (19.7 g, 277.0 mmol) cooled to 10 °C and aqueous NaOCl (10.8 g, 4%, 500 mL) was added, and the mixture was stirred for 5 min. The compound was extracted with diethyl ether (4 × 60 mL) and isolated as an oil. Yield 14.0 g (72%). ^{1}H NMR ($CDCl_3$): δ 3.73 (s, 4H), 3.16 (s, 4H).

4-Chloro-2-ethoxyphenol (14c). Compound **14c** was prepared using 2-ethoxyphenol (2.75 g, 19.9 mmol) cooled in TFA/diethyl ether (2:1) (50 mL) at −60 °C. Compound **14b** (2.66 g, 21.9 mmol) in diethyl ether (50 mL) was added and the mixture stirred at −60 °C for 1 h. The ether phase was washed with H_2O (50 mL), separated, dried, and evaporated. The compound was purified by vacuum distillation. Yield 2.03 g (54%), bp 150 °C (0.40 mmHg). ^{1}H NMR (DMSO-d_6): δ 9.20 (s, 1H), 6.92 (s, 1H), 6.76 (m, 2H), 4.01 (m, 2H), 1.32 (m, 3H).

(±)-4-(4-Chlorobenzyl)-2-(4-chloro-2-ethoxyphenoxymethyl)morpholine Oxalic Acid Salt (14). Procedure F. A mixture of **6c** (1.50 g, 5.80 mmol), **14c** (1.50 g, 8.70 mmol), EtOK (1.30 g, 11.6 mmol), and 18-crown-6 ether (0.30 g, 1.20 mmol) was stirred in anhydrous toluene (30 mL) at reflux for 34 h under N_2. H_2O (20 mL) was added, and the mixture was shaken and separated. Drying and evaporation of the toluene phase was followed by column chromatography on silica gel with 4% EtOH in CH_2Cl_2 as eluent. The free base was dissolved in diethyl ether and precipitated with oxalic acid to give compound **14**. Yield 0.65 g (28%), mp 88−90 °C. ^{1}H NMR (DMSO-d_6): δ 7.38 (d, 2H, J = 7.9 Hz), 7.33 (d, 2H, J = 7.9 Hz), 6.97 (d, 1H, J = 4.5 Hz), 6.93 (s, 1H), 6.87 (m, 1H), 3.96 (m, 2H), 3.86 (m, 1H), 3.80 (d, 1H, J = 10.2 Hz), 3.75 (m, 1H), 3.53 (t, 1H, J = 10.7 Hz), 3.43 (d, 1H, J = 10.9 Hz), 3.25 (s, 2H), 2.72 (d, 1H, J = 9.6 Hz), 2.62 (d, 1H, J = 9.6 Hz), 2.11 (m, 1H,), 1.92 (t, 1H, J = 9.6 Hz), 1.22 (t, 3H, J = 9.6 Hz). Anal. ($C_{20}H_{23}Cl_2NO_3$) C, H, N.

(±)-4-(4-Chlorobenzyl)-2-(5-chloro-2-ethoxyphenoxymethyl)morpholine (15). Compound **15** was prepared according to procedure F using 5-chloro-2-ethoxyphenol (1.70 g, 9.80 mmol), **6c** (1.70 g, 6.60 mmol), *t*-BuOK (1.61 g, 13.2 mmol), and 18-crown-6 ether (0.87 g, 3.30 mmol), stirred in anhydrous DMF (30 mL) for 15 h at 100 °C under N_2. Yield 1.29 g (33%), mp 85−87 °C. ^{1}H NMR ($CDCl_3$): δ 7.44 (s, 4H), 6.84 (m, 3H), 4.29 (m, 3H), 4.14 (m, 3H), 4.04 (m, 3H), 3.65 (d, 1H, J = 10.4 Hz), 3.56 (d, 1H, J = 10.4 Hz), 3.16 (m, 1H), 2.97 (m, 1H), 1.40 (t, 3H, J = 5.8 Hz). Anal. ($C_{20}H_{23}Cl_2NO_3$) C, H, N.

(±)-4-Benzyl-2-(2-ethoxyphenoxymethyl)morpholine (16b). Compound **16b** was prepared according to procedure F using 4-benzyl-2-chloromethylmorpholine (**16a**)[35] (14.0 g, 62.0 mmol), 2-ethoxyphenol (12.8 g, 93.0 mmol), *t*-BuOK (15.1 g, 124.0 mmol), and 18-crown-6 ether (8.19 g, 31.0 mmol), stirred in anhydrous DMF (140 mL) at 110 °C overnight under N_2. Yield 4.76 g (23%). ^{1}H NMR ($CDCl_3$): δ 7.38 (m, 5H), 6.94 (m, 4H), 4.10 (m, 2H), 4.06 (m, 2H), 3.98 (m, 2H), 3.81 (m, 1H), 3.58 (m, 1H), 3.04 (m, 1H), 2.76 (m, 1H), 2.29 (m, 1H), 2.11 (m, 1H), 1.64 (m, 1H), 1.41 (m, 3H).

(±)-2-[(2-Ethoxyphenoxy)methyl]morpholine (16c). Compound **16c** was prepared by stirring a mixture of **16b** (4.75 g, 14.5 mmol) and Pd/C (5%, 500 mg) in EtOH/concentrated HCl (3:1) (40 mL) under an atmosphere of hydrogen. The mixture was filtered and was evaporated. Aqueous sodium hydroxide (50 mL, 4 N) was added, and the mixture was extracted with toluene (2 × 40 mL). The product was isolated as an oil. Yield 3.31 g (96%), mp 176−179 °C. ^{1}H NMR (DMSO-d_6): δ 9.42 (s, 1H), 6.97 (m, 2H), 6.89 (m, 2H), 4.09 (m, 1H), 4.0 (m, 4H), 3.98 (m, 1H), 3.79 (m, 1H), 3.30 (m, 1H), 3.18 (m, 1H), 2.94 (m, 2H), 1.31 (m, 3H).

(±)-2-(2-Ethoxyphenoxymethyl)-4-(4-nitrobenzyl)morpholine Oxalic Acid Salt (16). Compound **16** was prepared according to procedure C using **16c** (3.00 g, 11.0 mmol), 4-nitrobenzylbromide (2.37 g, 11.0 mmol), and K_2CO_3 (1.52 g, 11.0 mmol), stirred in DMF (30 mL) for 4 h at 80 °C. Yield 1.10 g (27%), mp 113−114 °C. ^{1}H NMR (DMSO-d_6): δ 8.23 (d, 2H, J = 9.8 Hz), 7.33 (d, 2H, J = 9.8 Hz), 6.92 (m, 2H), 6.85 (m, 2H), 4.0 (m, 1H), 3.93 (m, 2H), 3.83 (m, 3H), 3.74 (d, 1H, J = 11.0 Hz), 3.66 (d, 1H, J = 11.0 Hz), 3.59 (m, 1H), 2.92 (d, 1H, J = 9.6 Hz), 2.72 (d, 1H, J = 9.6 Hz), 2.29 (m, 1H), 2.18 (t, 1H, J = 9.6 Hz), 1.18 (t, 3H, J = 5.8 Hz). Anal. ($C_{20}H_{24}N_2O_5$·$C_2H_2O_4$·0.4H_2O) C, H, N.

2-Ethoxy-4-iodophenol (17b). Compound **17b** was prepared according to procedure D using 2-ethoxyphenol (**17a**) (20.0 g, 144.0 mmol), NaI (21.7 g, 144.0 mmol), NaOH (5.80 g, 144.0 mmol), aqueous NaOCl (10.8 g, 4%, 267 mL), and EtOH (500 mL), stirred 1.5 h at −10 °C. Aqueous $Na_2S_2O_3$ (10%, 200 mL) was added, and the pH was adjusted to 7 with HCl (1 N). The product was precipitated and was filtered. Yield 26.2 g (69%), mp 88−91 °C. ^{1}H NMR (DMSO-d_6): δ 9.22 (s, 1H), 7.13 (m, 1H), 7.06 (m, 1H), 6.60 (m, 1H), 3.97 (m, 2H), 1.30 (m, 3H).

(±)-2-(2-Ethoxy-4-iodophenoxymethyl)-oxirane (17c). Compound **17c** was prepared according to procedure A using compound **17b** (15.0 g, 56.8 mmol), epibromohydrin (23.0 g, 171.0 mmol), and K_2CO_3 (11.7 g, 85.2 mmol) in DME (200 mL), stirred at reflux overnight. Yield 11.3 g (62%). ^{1}H NMR ($CDCl_3$): δ 7.21 (m, 1H), 7.16 (m, 1H), 6.68 (m, 1H), 4.22 (m, 1H), 4.02 (m, 2H), 3.98 (m, 1H), 3.83 (s, 3H), 3.30 (m, 1H), 2.91 (m, 1H), 2.73 (m, 1H).

(±)-2-[(2-Ethoxy-4-iodophenoxy)methyl]morpholine (17d). Compound **17d** was prepared according to procedure B using compound **17c** (5.16 g, 16.1 mmol), aminohydrogensulfate (11.3 g, 80.5 mmol), and NaOH (6.45 g, 161.0 mmol) in 2-propanol/H_2O (3:1) (200 mL), stirred at reflux for 8 h. The product was isolated as an oil. Yield 3.96 g (67%). ^{1}H NMR ($CDCl_3$): δ 7.23 (m, 1H), 7.18 (m, 1H), 6.71 (m, 1H), 4.41 (m, 1H), 4.20 (m, 1H), 4.06 (m, 3H), 3.81 (m,1H), 3.66 (m, 1H), 3.59 (m, 1H), 3.40 (m, 1H), 3.23 (m, 1H), 1.47 (m, 3H).

(±)-4-(4-Chlorobenzyl)-2-(2-ethoxy-4-iodophenoxymethyl)morpholine Oxalic Acid Salt (17). Compound **17** was prepared according to procedure C using **17d** (3.90 g, 10.7 mmol), 4-chlorobenzyl chloride (2.07 g, 12.9 mmol), and K_2CO_3 (8.13 g, 58.9 mmol) in EtOH (100 mL), stirred at reflux for 3 h. Yield 1.58 g (11%), mp 86−90 °C. ^{1}H NMR (DMSO-d_6): δ 7.37 (m, 2H), 7.32 (m, 2H), 7.17 (m, 2H), 6.76 (m, 1H), 4.0 (m, 1H), 3.94 (m, 2H), 3.86 (m, 2H), 3.80 (d, 1H, J = 10.3 Hz), 3.74 (m, 1H), 3.52 (m, 1H), 3.40 (m, 1H), 2.78 (d, 1H, J = 9.7 Hz), 2.62 (m, 1H), 2.10 (t, 1H, J = 9.7 Hz), 1.93 (t, 1H, J = 9.7 Hz), 1.22 (t, 3H, J = 5.47 Hz). Anal. ($C_{20}H_{23}ClINO_3$·0.3H_2O) C, H, N.

(±)-4-(2,4-Dichlorobenzyl)-2-(2-ethoxyphenoxymethyl)-morpholine Oxalic Acid Salt (18). Compound **18** was prepared as procedure C by stirring **16d** (0.27 g, 1.10 mmol), 2,4-dichloro-1-chloromethylbenzene (0.22 g, 1.10 mmol), and K_2CO_3 (0.15 g, 1.10 mmol) in DMF (10 mL) for 3 h at 80 °C. Yield 0.21 g (48%), mp 141−143 °C. ^{1}H NMR (DMSO-d_6): δ 7.60 (m, 1H), 7.53 (d, 1H, J = 7.5 Hz), 7.42 (m, 1H), 6.93 (m, 2H), 6.86 (m, 2H), 4.0 (m, 1H), 3.94 (m, 2H), 3.87 (m, 3H), 3.66 (d, 1H, J = 9.6 Hz), 3.58 (m, 2H), 2.91 (d, 1H, J = 9.6 Hz), 2.71 (d, 1H, J = 9.6 Hz), 2.29 (bt, 1H), 2.17 (t, 1H, J = 9.6 Hz), 1.22 (t, 3H, J = 6.3 Hz). Anal. ($C_{22}H_{27}Cl_2NO_8$) C, H, N.

(±)-4-[4-(4-Chlorobenzyl)-morpholin-2-ylmethoxy]-3-ethoxybenzonitrile Oxalic Acid Salt (19). Compound **19** was prepared by using compound **17** as its free base (1.00 g, 2.10 mmol), tetrakis(triphenylphosphine)palladium(0) (0.35 g, 0.30 mmol), and $Zn(CN)_2$ (0.17 g, 1.40 mmol) in anhydrous DMF (15 mL), stirred for 4 h at 80 °C under N_2, followed by addition of H_2O (20 mL). The precipitate and the mother liquor were extracted with EtOAc (2 × 30 mL), dried, and evaporated to dryness. The crude product was further purified by fractional crystallization from EtOH and then triturated with

diethyl ether. Dissolution in diethyl ether and precipitated with oxalic acid gave compound **19**. Yield 30 mg (9%), mp 132−138 °C. ^{1}H NMR (DMSO-d_6): δ 7.39 (m, 6H), 7.10 (m, 1H), 4.09 (m, 1H), 4.01 (m, 2H), 3.95 (m, 1H), 3.85 (d, 2H, J = 6.2 Hz), 3.73 (d, 1H, J = 11.3 Hz), 3.61 (q, 2H, J = 10.2 Hz), 2.92 (d, 1H, J = 9.6 Hz), 2.77 (d, 1H, J = 9.6 Hz), 2.31 (t, 1H, J = 9.6 Hz), 2.16 (t, 1H, J = 9.6 Hz), 1.25 (m, 3H). Anal. ($C_{21}H_{23}ClN_2O_3 \cdot C_2H_2O_4 \cdot 1.9H_2O$) C, H, N.

(±)-4-[2-(2-Ethoxyphenoxymethyl)morpholin-4-ylmethyl]phenylalanine Oxalic Acid Salt (20a). Compound **20a** was prepared by stirring a mixture of compound **16** (2.72 g, 7.30 mmol) in EtOH (40 mL) and Pd/C (5%, 300 mg) under an atmosphere of hydrogen. The product was isolated as an oil. Yield 0.94 g (37%). ^{1}H NMR ($CDCl_3$): δ 6.92 (m, 8H), 4.70 (m, 1H), 4.18 (m, 1H), 4.10 (m, 4H), 4.05 (m, 1H), 3.94 (m, 1H), 3.39 (m, 2H), 3.19 (m, 1H), 3.09 (m, 3H), 1.44 (m, 3H).

(±)-2-(2-Ethoxyphenoxymethyl)-4-(4-fluorobenzyl)morpholine Oxalic Acid Salt (20). Compound **20** was prepared according to the procedure C by using **20a** (0.49 g, 2.10 mmol), 1-chloromethyl-4-fluorobenzene (0.30 g, 2.10 mmol), and K_2CO_3 (0.29 g, 2.10 mmol) in EtOH (20 mL, 99%), stirred 4 h at reflux. Yield 0.77 g (85%), mp 139−141 °C. ^{1}H NMR (DMSO-d_6): δ 7.42 (t, 2H, J = 7.5 Hz), 7.20 (t, 2H, J = 7.5 Hz), 6.94 (bt, 2H), 6.87 (m, 2H), 4.01 (m, 1H), 3.95 (m, 2H), 3.90 (m, 2H), 3.83 (m, 1H), 3.77 (m, 1H), 3.70 (m, 1H), 3.60 (t, 1H, J = 10.4 Hz), 3.00 (d, 1H, J = 9.8 Hz), 2.82 (d, 1H, J = 9.8 Hz), 2.38 (m, 1H), 2.25 (m, 1H), 1.24 (t, 3H, J = 5.8 Hz). Anal. ($C_{20}H_{24}FNO_3 \cdot C_2H_2O_4 \cdot 0.15H_2O$) C, H, N.

(S)-4-(4-Chlorobenzyl)-2-(4-chloro-2-methoxyphenoxymethyl)morpholine Oxalic Acid Salt (21). Compound (*S*)-**21** was prepared according to procedure F from (*S*)-**6c** (1.00 g, 3.80 mmol), 4-chloro-2-methoxyphenol (0.91 g, 5.80 mmol), EtOK (0.64 g, 7.60 mmol), and 18-crown-6 ether (0.50 g, 1.90 mmol), stirred in anhydrous toluene (20 mL) at reflux for 20 h under N_2. Yield 1.05 g (72%), mp 139−142 °C. ^{1}H NMR (DMSO-d_6): δ 7.40 (m, 4H), 7.01 (m, 1H), 6.94 (m, 1H), 6.89 (m, 1H), 3.93 (m, 2H), 3.84 (m, 2H), 3.75 (s, 3H), 3.65 (m, 1H), 3.58 (m, 2H), 2.91 (d, 1H, J = 9.8 Hz), 2.74 (d, 1H, J = 9.8 Hz), 2.30 (bt, 1H), 2.15 (bt, 1H). Anal. ($C_{19}H_{21}Cl_2NO_3 \cdot C_2H_2O_4 \cdot 0.5H_2O$) C, H, N.

(±)-4-(4-Chlorobenzyl)-2-(4-chloro-2-methoxyphenoxymethyl)morpholine Oxalic Acid Salt (±)-(21). Compound (±)-**21** was prepared according to the procedure of compound (*S*)-**21** using (±)-**6c** as starting material. Yield 0.51 g (35%), mp 138−140 °C. ^{1}H NMR (DMSO-d_6): δ 7.39 (m, 4H), 7.01 (m, 1H), 6.94 (m, 1H), 6.89 (m, 1H), 3.95 (m, 2H), 3.83 (m, 2H), 3.75 (s, 3H), 3.65 (m, 1H), 3.57 (m, 2H), 2.90 (d, 1H, J = 9.8 Hz), 2.74 (d, 1H, J = 9.8 Hz), 2.28 (bt, 1H), 2.14 (bt, 1H). Anal. ($C_{19}H_{21}Cl_2NO_3 \cdot C_2H_2O_4 \cdot 0.5H_2O$) C, H, N.

(R)-4-(4-Chlorobenzyl)-2-(4-chloro-2-methoxyphenoxymethyl)morpholine Oxalic Acid Salt (21). Compound (*R*)-**21** was prepared according to the procedure of compound (*S*)-**21** using (*R*)-**6c** as starting material. Yield 0.57 g (39%), mp 149−151 °C.^{1}H NMR (DMSO-d_6): δ 7.39 (m, 4H), 7.01 (m, 1H), 6.94 (m, 1H), 6.89 (m, 1H), 3.94 (m, 2H), 3.82 (m, 2H), 3.75 (s, 3H), 3.65 (m, 1H), 3.56 (m, 2H), 2.89 (d, 1H, J = 9.8 Hz), 2.73 (d, 1H, J = 9.8 Hz), 2.27 (bt, 1H,), 2.14 (bt, 1H). Anal. ($C_{19}H_{21}Cl_2NO_3 \cdot C_2H_2O_4 \cdot 0.5H_2O$) C, H, N.

5-Fluoro-2-methoxyphenylboronic Acid (22b). Procedure G. Compound **22b** was prepared using 4-fluoroanisole (**22a**) (22.9 g, 181.0 mmol) dissolved in anhydrous THF (200 mL) and cooled to −60 °C under N_2. *n*-Butyllithium in cyclohexane (100 mL, 2 M) was added at −60 °C and the mixture stirred for 5 h at −60 °C. Triisopropyl borate (47.8 g, 254.0 mmol) was added at −70 °C and the mixture stirred for 1 h at −70 °C and at room-temperature overnight. Aqueous HCl (250 mL, 1 M) was added. The aqueous phase was extracted with diethyl ether (2 × 100 mL), and the combined ether phase was extracted with aqueous NaOH (2 × 100 mL, 1 M). The aqueous phase was made acidic by addition of concentrated HCl at 0 °C. The precipitated solid was isolated by filtration and triturated with CH_2Cl_2/*n*-heptane. Yield 9.00 g (30%), mp 156−158 °C. ^{1}H NMR ($CDCl_3$): δ 7.56 (m, 1H), 7.15 (m, 1H), 6.88 (m, 1H), 5.95 (m, 2H), 3.94 (m, 3H).

5-Fluoro-2-methoxyphenol (22c). Compound **22c** was prepared using **22b** (6.00 g, 35.3 mmol) in EtOH (100 mL) and aqueous H_2O_2 (7.1 mL, 35%), stirred at reflux 2 h. The mixture was evaporated. H_2O (50 mL) was added, and the mixture was extracted with EtOAc (2 × 50 mL). The product was isolated as an oil. Yield 3.82 g (63%). ^{1}H NMR ($CDCl_3$): δ 6.76 (m, 1H), 6.70 (m, 1H, 6.56 (m, 1H), 5.80 (s, 1H), 3.86 (s, 3H).

(±)-4-(4-Chlorobenzyl)-2-(5-fluoro-2-methoxyphenoxymethyl)morpholine Oxalic Acid Salt (22). Compound **22** was prepared according to procedure F using **6c** (1.00 g, 3.90 mmol), **22c** (0.99 g, 5.80 mmol), EtOK (0.66 g, 7.80 mmol), and 18-crown-6 ether (1.03 g, 3.90 mmol) in anhydrous toluene (10 mL), stirred at reflux for 15 h under N_2. Yield 0.37 g (21%), mp 155−157 °C. ^{1}H NMR (DMSO-d_6): δ 7.42 (d, 2H, J = 7.1 Hz), 7.38 (d, 2H, J = 7.1 Hz), 6.90 (m, 2H), 6.68 (bt, 1H), 3.95 (m, 2H), 3.83 (m, 2H), 3.69 (m, 3H), 3.65 (m, 2H), 3.58 (t, 1H, J = 9.6 Hz), 2.92 (d, 1H, J = 9.6 Hz), 2.73 (d, 1H, J = 9.6 Hz), 2.30 (t, 1H, J = 9.6 Hz), 2.17 (t, 1H, J = 9.6 Hz). Anal. ($C_{19}H_{21}ClFNO_3 \cdot C_2H_2O_4 \cdot 0.1H_2O$) C, H, N.

3-(4-Bromobenzylamino)propan-1-ol (23b). Compound **23b** was prepared using 3-amino-1-propanol (60.1 g, 800.0 mmol), NaOH (6.08 g, 152.0 mmol), 4-bromobenzyl bromide (**23a**) (40.0 g, 160.0 mmol), and 2-propanol (400 mL), stirred for 30 min at reflux. The mixture was evaporated, and CH_2Cl_2 (250 mL) was added following by filtration. The product was isolated as an oil. Yield 12.5 g (32%). ^{1}H NMR (DMSO-d_6): δ 7.50 (m, 2H), 7.30 (m, 2H), 4.56 (m, 1H), 3.73 (s, 2H), 3.46 (m, 2H), 2.60 (m, 2H), 1.63 (m, 2H).

(±)-4-(4-Bromobenzyl)-2-chloromethyl[1,4]oxazepane (23c). Compound **23c** was prepared according to procedure E using **23b** (12.0 g, 49.5 mmol), epichlorohydrin (45.8 g, 495.0 mmol), and concentrated H_2SO_4 (19 mL). The product was isolated as an oil. Yield 2.75 g (17%). ^{1}H NMR ($CDCl_3$): δ 7.46 (m, 2H), 7.13 (m, 2H), 3.91 (m, 1H), 3.81 (m, 1H), 3.63 (s, 3H), 3.50 (m, 1H), 3.43 (m, 1H), 2.93 (m, 1H), 2.76 (m, 1H), 2.61 (m, 2H) 1.93 (m, 2H).

(±)-4-(4-Bromobenzyl)-2-(4-chloro-2-methoxyphenoxymethyl)[1,4]oxazepane Oxalic Acid Salt (23). Compound **23** was prepared according to procedure F using **23c** (2.70 g, 8.50 mmol), 4-chloro-2-methoxyphenol (2.03 g, 12.8 mmol), EtOK (1.40 g, 17.0 mmol), and 18-crown-6 ether (2.25 g, 8.50 mmol) in anhydrous toluene (25 mL), stirred at reflux for 15 h under N_2. Yield 0.56 g (13%), mp 132−136 °C. ^{1}H NMR (DMSO-d_6): δ 7.54 (d, 2H, J = 6.8 Hz), 7.36 (d, 2H, J = 6.8 Hz), 7.00 (m, 1H), 6.90 (m, 2H), 4.04 (m, 1H), 3.96 (s, 2H), 3.92 (m, 1H), 3.81 (m, 2H), 3.73 (s, 3H), 3.70 (m, 1H), 3.13 (m, 1H), 3.04 (m, 1H), 2.89 (bt, 1H), 2.80 (bt, 1H) 1.92 (m, 2H). Anal. ($C_{20}H_{23}BrClNO_3 \cdot C_2H_2O_4$) C, H, N.

5-Trifluoromethyl-2-methoxyphenylboronic Acid (24b). Compound **24b** was prepared according to procedure G using 1-methoxy-4-trifluoromethylbenzene (**24a**) (8.00 g, 45.4 mmol) and anhydrous THF (80 mL). *n*-Butyllithium in hexanes (20 mL, 2.5 M) was added at −30 °C followed by triisopropyl borate (12.0 g, 63.6 mmol) at −70 °C under N_2. Yield 8.1 g (82%), mp 149−151 °C. ^{1}H NMR (DMSO-d_6): δ 7.94 (m, 1H), 7.74 (m, 1H), 7.14 (d, 1H, J = 8.3 Hz), 3.86 (m, 3H).

2-Methoxy-5-trifluoromethylphenol (24c). Compound **24c** was prepared using **24b** (5.00 g, 22.7 mmol) in ethanol (50 mL) and aqueous H_2O_2 (30%, 4.54 mL). The mixture was stirred at reflux for 2.5 h. H_2O (50 mL) was added, and the compound was extracted with EtOAc (2 × 50 mL). The product was isolated as an oil. Yield 3.57 g (82%). ^{1}H NMR ($CDCl_3$): δ 7.17 (m, 1H), 7.14 (d, 1H, J = 7.6 Hz), 6.90 (d, 1H, J = 7.6 Hz), 5.71 (s, 1H), 3.90 (m, 3H).

(±)-4-(4-Chlorobenzyl)-2-(2-methoxy-5-trifluoromethylphenoxymethyl)morpholine Oxalic Acid Salt (24). Compound **24** was prepared according to procedure F using **6c** (0.45 g, 1.70 mmol), **24c** (0.49 g, 2.60 mmol), EtOK (0.28 g, 3.40 mmol), and 18-crown-6 ether (0.45 g, 1.70 mmol) in anhydrous toluene (10 mL), stirred at reflux for 90 h under N_2. Yield 0.43 g (61%), mp 145−147 °C. ^{1}H NMR (DMSO-d_6): δ 7.39 (m, 4H), 7.28 (m, 1H), 7.22 (m, 1H), 7.12 (d, 1H, J = 7.5 Hz), 4.02 (d, 2H, J = 4.6 Hz), 3.86 (m, 2H), 3.80 (s, 3H), 3.61 (m, 3H), 2.92

(d, 1H, J = 9.8 Hz), 2.67 (d, 1H, J = 9.8 Hz), 2.30 (m, 1H), 2.03 (m, 1H). Anal. ($C_{20}H_{21}ClF_3NO_3$) C, H, N.

3-(4-Chlorobenzylamino)propan-1-ol (25b). Compound **25b** was prepared using 3-amino-1-propanol (116 g, 1.55 mol), NaOH (13.6 g, 310.0 mmol), 4-chlorobenzyl chloride (**25a**) (50.0 g, 310.0 mmol), and 2-propanol (100 mL), stirred for 30 min at reflux. CH_2Cl_2 (500 mL) was added, and the mixture was stirred at reflux for 30 min. The mixture was filtered and the product collected by vacuum distillation. Yield 18 g (29%), bp 128−130 °C (0.030 mmHg). ^{1}H NMR ($CDCl_3$): δ 7.20 (m, 4H), 3.80 (m, 4H), 2.83 (m, 2H), 1.75 (m, 2H).

(±)-4-(4-Chlorobenzyl)-2-chloromethyl[1,4]oxazepane (25c). Compound **25c** was prepared according to procedure E using **25b** (13.5 g, 67.8 mmol), epichlorohydrin (62.7 g, 678.0 mmol), and concentrated H_2SO_4 (21 mL). The product was isolated as an oil. Yield 8.94 g (48%). ^{1}H NMR ($CDCl_3$): δ 7.34 (m, 4H), 3.96 (m, 2H), 3.87 (m, 1H), 3.71 (m, 2H), 3.51 (m, 2H), 2.98 (m, 1H), 2.81 (m, 1H), 2.67 (m, 2H), 1.90 (m, 2H).

(±)-1-(4-Chloro-2[4-(4-chlorobenzyl)[1,4]oxazepan-2-ylmethoxy]phenyl)ethanone Oxalic Acid Salt (25). Compound **25** was prepared according to procedure F using **25c** (2.00 g, 7.30 mmol), 5-chloro-2-hydroxyacetophenone (1.87 g, 11.0 mmol), *t*-BuOK (1.63 g, 14.6 mmol), and 18-crown-6 ether (1.93 g, 7.30 mmol) in anhydrous toluene (30 mL), stirred at reflux for 40 h under N_2. Yield 0.10 g (5%), mp 148−151 °C. ^{1}H NMR (DMSO-d_6): δ 7.54 (m, 2H), 7.42 (d, 2H, J = 7.6 Hz), 7.22 (d, 2H, J = 7.6 Hz), 7.15 (m, 1H), 4.09 (m, 1H), 4.01 (m, 2H), 3.93 (s, 2H), 3.84 (m, 1H), 3.73 (m, 1H), 3.05 (m, 2H), 2.88 (m, 1H), 2.78 (m, 1H), 2.40 (s, 3H), 1.94 (m, 2H). Anal. ($C_{21}H_{23}Cl_2NO_3 \cdot C_2H_2O_4$) C, H, N.

(±)-4-(4-Chlorobenzyl)-2-(2-methoxy-5-nitrophenoxymethyl)[1,4]oxazepane Oxalic Acid Salt (26). Compound **26** was prepared according to procedure F using **25c** (2.00 g, 7.30 mmol), 2-methoxy-5-nitrophenol (1.86 g, 11.0 mmol), *t*-BuOK (1.63 g, 14.6 mmol), and 18-crown-6 ether (1.93 g, 7.30 mmol) in anhydrous toluene (50 mL), stirred at reflux for 75 h under N_2. Yield 0.62 g (20%), mp 140−143 °C. ^{1}H NMR (DMSO-d_6): δ 7.91 (m, 1H), 7.71 (m, 1H), 7.41 (m, 4H), 7.16 (m, 1H), 3.87 (s, 3H), 3.71 (m, 7H), 2.93 (m, 4H), 1.92 (bd, 2H). Anal. ($C_{20}H_{23}ClN_2O_5 \cdot 1.5C_2H_2O_4$) C, H, N.

(±)-4-(4-Chlorobenzyl)-2-(5-chloro-2-ethoxyphenoxymethyl)[1,4]oxazepane Oxalic Acid Salt (27). Compound **27** was prepared according to procedure F using **25c** (1.37 g, 5.00 mmol), 5-chloro-2-ethoxyphenol (1.30 g, 7.50 mmol), EtOK (0.84 g, 10.0 mmol), and 18-crown-6 ether (1.32 g, 5.00 mmol) in anhydrous toluene (50 mL), stirred at reflux for 15 h under N_2. Yield 0.94 g (46%), mp 122−125 °C. ^{1}H NMR (DMSO-d_6): δ 7.41 (m, 4H), 6.92 (m, 3H), 4.03 (m, 1H), 3.95 (m, 5H), 3.84 (m, 2H), 3.75 (m, 1H), 3.05 (m, 2H), 2.85 (m, 2H), 1.92 (m, 2H), 1.27 (m, 3H). Anal. ($C_{21}H_{25}Cl_2NO_3 \cdot C_2H_2O_4$) C, H, N.

1,4-Di-(acetoxy)but-2-ene (28b). Compound **28b** was prepared using but-2-ene-1,4-diol (**28a**) (40.0 g, 454.0 mmol) and AcOH (109 g, 1.81 mol). Concentrated H_2SO_4 (1 mL) was added dropwise, and the mixture was stirred at reflux for 3 h. The excess of AcOH was evaporated. Diethyl ether was added, and the organic phase was washed with H_2O (2 × 50 mL) and once with aqueous $NaHCO_3$ (50 mL). The mixture was dried, and the compound was obtained by evaporation. The product was isolated as an oil. Yield 50.8 g (64%). ^{1}H NMR ($CDCl_3$): δ 5.76 (m, 2H), 4.67 (d, 4H, J = 4.8 Hz), 2.06 (m, 6H).

(±)-4-(4-Chlorobenzyl)-2-[2-(2-methoxyphenyl)-vinyl]-morpholine Oxalic Acid Salt (28). Compound **28** was prepared using **6b** (2.00 g, 10.7 mmol), **28b** (2.78 g, 16.1 mmol), NEt_3 (3.26 g, 32.3 mmol), and $Pd(PPh_3)_4$ (0.31 g, 0.27 mmol) in anhydrous THF (20 mL), stirred at reflux under N_2 for 5 h according to Uozumi et al.[38] DMF (10 mL) was added with *N*,*N*-diisopropylethylamine (2.78 g, 21.5 mmol) and 2-iodoanisole (3.78 g, 16.1 mmol) and the mixture stirred at 130 °C for 15 h. The product was obtained by column chromatography with 4% EtOH in CH_2Cl_2. Dissolution in diethyl ether and precipitation with oxalic acid gave compound **28**. Yield 1.0 g (21%), mp 178−180 °C. ^{1}H NMR (DMSO-d_6): δ 7.42 (q, 4H, J = 7.3 Hz), 7.38 (s, 1H), 7.23 (t, 1H, J = 7.3 Hz), 6.97 (d, 1H, J = 8.4 Hz), 6.89 (t, 1H, J = 8.4 Hz), 6.83 (m, 1H), 5.22 (m, 1H), 4.16 (m, 1H), 3.91 (d, 1H, J = 10 Hz), 3.79 (s, 3H), 3.71 (m, 2H), 3.64 (t, 1H J = 10 Hz), 2.91 (d, 1H, J = 9.6 Hz), 2.80 (d, 1H, J = 9.6 Hz), 2.38 (t, 1H, J = 9.8 Hz), 2.16 (t, 1H, J = 9.8 Hz). Anal. ($C_{20}H_{22}ClNO_2 \cdot C_2H_2O_4$) C, H, N.

(±)-2-[2-(2-Methoxyphenyl)ethyl]morpholine (29a). Compound **29a** was prepared using **28** (0.40 g, 1.20 mmol) in EtOH (10 mL) and Pd/C (5%, 100 mg), stirred for 1.5 h under H_2. The mixture was filtered and evaporated. Aqueous K_2CO_3 (30 mL, 1 M) was added. The mixture was extracted with EtOAc (2 × 20 mL), filtered, and evaporated to dryness. The product was obtained by column chromatography on silica gel with 20% EtOH in CH_2Cl_2 as eluent and isolated as an oil. Yield 0.99 g (100%). ^{1}H NMR ($CDCl_3$): δ 7.16 (m, 1H), 7.10 (m, 1H), 6.83 (m, 2H), 3.94 (m, 2H), 3.82 (s, 3H), 3.74 (m, 1H), 3.59 (m, 1H), 3.05 (m, 1H), 2.98 (m, 1H), 2.95 (m, 1H), 2.79 (m, 1H) 2.75 (m, 1H), 2.65 (m, 1H), 1.73 (m, 2H).

(±)-4-(4-Chlorobenzyl)-2-[2-(2-methoxyphenyl)ethyl]-morpholine Oxalic Acid Salt (29). Compound **29** was prepared according to procedure C using **29a** (0.99 g, 4.50 mmol), *p*-chlorobenzyl chloride (0.72 g, 4.50 mmol), and K_2CO_3 (0.62 g, 4.50 mmol), stirred in DMF (20 mL) for 3 h at 50 °C. Yield 0.12 g (8%), mp 167−169 °C. ^{1}H NMR (DMSO-d_6): δ 7.43 (d, 2H, J = 6.6 Hz), 7.36 (d, 2H, J = 6.6 Hz), 7.16 (t, 1H, J = 6.6 Hz), 7.07 (d, 1H, J = 7 Hz), 6.92 (d, 1H, J = 7 Hz), 6.84 (t, 1H, J = 6.6 Hz), 3.84 (d, 1H, J = 11 Hz), 3.74 (s, 3H), 3.69 (m, 2H), 3.51 (t, 1H, J = 11 Hz), 3.41 (m, 1H), 2.84 (m, 1H), 2.70 (m, 1H), 2.65 (m, 1H) 2.59 (m, 1H), 2.36 (m, 1H), 2.10 (m, 1H) 1.59 (m, 2H). Anal. ($C_{20}H_{24}ClNO_2 \cdot C_2H_2O_4 \cdot 0.4H_2O$) C, H, N.

(±)-4-(4-Chlorobenzyl)-morpholin-2-ylmethyl-(5-chloro-2-methoxyphenyl)amine Oxalic Acid Salt (30). Compound **30** was prepared according to procedure F using **6c** (2.00 g, 7.70 mmol), 5-chloro-*o*-anisidine (3.64 g, 20.0 mmol), *t*-BuOK (1.73 g, 10.0 mmol), and 18-crown-6 ether (0.40 g, 1.50 mmol) in anhydrous toluene (30 mL), stirred at reflux for 15 h under N_2. Yield 0.29 g (10%), mp 169−171 °C. ^{1}H NMR (DMSO-d_6): δ 7.46 (m, 1H), 7.38 (m, 4H), 6.76 (m, 1H), 6.53 (m, 1H), 5.08 (m, 1H), 3.85 (m, 1H), 3.76 (s, 3H), 3.71 (m, 1H), 3.57 (m, 2H), 3.19 (m, 1H), 3.05 (m, 1H), 2.89 (bd, 1H), 2.78 (m, 2H), 2.34 (bt, 1H), 2.17 (bt, 1H). Anal. ($C_{19}H_{22}Cl_2N_2O_2 \cdot C_2H_2O_4 \cdot H_2O$) C, H, N.

(±)-6-Chloro-3-[4-(4-chlorobenzyl)-morpholin-2-ylmethyl]-3*H*-benzoxazol-2-one (31a). Compound **31a** was prepared according to procedure F using **6c** (8.00 g, 30.8 mmol), 6-chloro-3*H*-benzoxazol-2-one (6.26 g, 37.0 mmol), *t*-BuOK (7.00 g, 61.6 mmol), and 18-crown-6 ether (8.00 g, 30.8 mmol) in anhydrous DMF (100 mL), stirred at 110 °C for 24 h under N_2. Yield 1.68 g (11%), mp 167−170 °C. ^{1}H NMR (DMSO-d_6): δ 7.46 (m, 1H), 7.33 (m, 4H), 7.16 (m, 1H), 7.13 (m, 1H), 3.88 (m, 1H), 3.80 (m, 2H), 3.75 (m, 1H), 3.48 (m, 2H), 3.43 (m, 1H), 2.78 (m, 1H), 2.53 (m, 1H), 2.08 (m, 1H) 1.19 (m, 1H).

(±)-5-Chloro-2-[4-(4-chlorobenzyl)-morpholin-2-ylmethyl]amino)phenol Oxalic Acid Salt (31). Compound **31** was prepared by mixing **31a** (1.50 g, 3.80 mmol) and aqueous NaOH (3.80 mL, 4 N) in DME (7.60 mL) at 50 °C for 1 h. The product extracted with EtOAc (2 × 30 mL) was obtained by column chromatography with 4% EtOH in CH_2Cl_2. Dissolution in diethyl ether and precipitated with oxalic acid gave compound **31**. Yield 1.05 g (61%), mp 177−179 °C. ^{1}H NMR (DMSO-d_6): δ 7.41 (d, 2H, J = 6.5 Hz), 7.37 (d, 2H, J = 6.5 Hz), 6.61 (m, 1H), 6.48 (m, 1H), 6.40 (m, 1H), 4.86 (m, 1H), 3.85 (d, 1H, J = 10 Hz), 3.68 (s, 3H), 3.55 (t, 2H, J = 10 Hz), 3.18 (m, 1H), 3.03 (m, 1H), 2.89 (d, 1H, J = 9.6 Hz), 2.75 (d, 1H, J = 9.6 Hz), 2.31 (bt, 1H) 2.17 (bt, 1H). Anal. ($C_{18}H_{20}Cl_2N_2O_2 \cdot C_2H_2O_4$) C, H, N.

(±)-4-(4-Chlorobenzyl)-2-(2-methoxy-phenylsulfanylmethyl)morpholine Oxalic Acid Salt (32). Compound **32** was prepared according to procedure F using **6c** (1.00 g, 3.80 mmol), 2-methoxybenzenthiol (0.80 g, 5.80 mmol), *t*-BuOK (0.92 g, 7.60 mmol), and 18-crown-6 ether (0.50 g, 1.90 mmol) in anhydrous toluene (10 mL), stirred at reflux for 15 h under N_2. Yield 0.71 g (60%), mp 101−103 °C. ^{1}H NMR (DMSO-d_6): δ 7.46 (s, 2H), 7.40 (m, 1H), 7.33 (m, 1H), 7.18 (m, 2H), 6.96

(d, 1H, J = 7.2 Hz), 6.91 (t, 1H, J = 7.2 Hz), 3.82 (m, 1H), 3.77 (s, 3H), 3.56 (m, 2H), 3.50 (m, 2H), 2.95 (t, 2H, J = 5.8 Hz), 2.90 (m, 1H), 2.67 (d, 1H, J = 7.5 Hz), 2.23 (bt, 1H), 2.05 (bt, 1H). Anal. ($C_{19}H_{22}ClNO_2S \cdot C_2H_2O_4 \cdot H_2O$) C, H, N.

(±)-4-(4-Chlorobenzyl)-2-(2-methyl-pyridin-3-yloxymethyl)[1,4]oxazepane Oxalic Acid Salt (33). Compound **33** was prepared according to procedure F using **25c** (2.70 g, 10.0 mmol), 2-methylpyridin-3-ol (2.20 g, 20.0 mmol), EtOK (1.68 g, 20.0 mmol), and 18-crown-6 ether (2.60 g, 10.0 mmol) in anhydrous toluene (100 mL), stirred at reflux for 75 h under N_2. Yield 1.15 g (16%), mp 60−61 °C. ^{1}H NMR (DMSO-d_6): δ 7.81 (m, 1H), 7.29 (m, 2H), 7.10 (m, 2H), 7.04 (m, 2H), 3.98 (m, 3H), 3.82 (m, 1H), 3.68 (m, 2H), 3.51 (m, 1H), 3.08 (m, 2H), 2.88 (m, 1H), 2.76 (m, 1H), 2.03 (s, 3H), 1.85 (m, 1H) 1.71 (m, 1H). Anal. ($C_{19}H_{23}ClN_2O_2 \cdot C_2H_2O_4 \cdot H_2O$) C, H, N.

(±)-4-(4-Chlorobenzyl)-2-(2-ethoxyphenoxymethyl)[1,4]-oxazepane Oxalic Acid Salt (34). Compound **34** was prepared according to procedure F using **25c** (1.00 g, 3.65 mmol), 2-ethoxyphenol (0.76 g, 5.47 mmol), *t*-BuOK (0.82 g, 7.30 mmol), and 18-crown-6 ether (0.19 g, 0.73 mmol) in anhydrous toluene (10 mL), stirred at reflux for 75 h under N_2. The final product was obtained as an oil. Yield 0.60 g (44%). ^{1}H NMR ($CDCl_3$): δ 7.35 (m, 2H), 7.28 (m, 2H), 6.96 (m, 4H), 4.15 (m, 1H), 4.04 (m, 4H), 3.92 (m, 2H), 3.74 (m, 2H), 3.10 (bd, 1H), 2.85 (s, 1H), 2.72 (m, 2H), 2.03 (s, 1H), 1.92 (m, 1H), 1.43 (m, 3H). Anal. ($C_{21}H_{26}ClNO_3 \cdot C_2H_2O_4 \cdot H_2O$) C, H, N.

(±)-2-(5-Chloro-2-methoxyphenoxy)oxirane (35b). Compound **35b** was prepared according to procedure A using 5-chloro-2-methoxyphenol (**35a**) (1.00 g, 6.30 mmol), epibromohydrin (2.60 g, 18.9 mmol), and K_2CO_3 (1.30 g, 9.50 mmol) in DME (75 mL). The product was isolated as an oil. Yield 1.23 g (92%). ^{1}H NMR ($CDCl_3$): δ 6.90 (m, 2H), 6.76 (m, 1H), 4.25 (m, 1H), 3.99 (m, 1H), 3.84 (s, 3H), 3.25 (m, 1H), 2.93 (m, 1H), 2.71 (m, 1H).

(±)-2-[(5-Chloro-2-methoxyphenoxy)methyl]morpholine (35c). Compound **35c** was prepared according to procedure B using **35b** (1.20 g, 5.60 mmol), 2-aminoethyl-hydrogen sulfate (3.95 g, 28.0 mmol), and NaOH (2.24 g, 56.0 mmol) in 2-propanol (30 mL) and H_2O (10 mL). The product was isolated as an oil. Yield 0.94 g (65%). ^{1}H NMR ($CDCl_3$): δ 6.89 (m, 3H), 4.20 (m, 1H), 4.10 (m, 2H), 3.88 (s, 3H), 3.82 (m, 2H), 3.69 (m, 1H), 3.59 (m, 1H), 3.40 (m, 1H), 3.11 (m, 1H).

(±)-4-Benzyl-2-(5-chloro-2-methoxyphenoxymethyl)-morpholine Oxalic Acid Salt (35). Compound **35** was prepared according to procedure C using **35c** (0.94 g, 3.70 mmol), benzyl bromide (0.76 g, 4.40 mmol), and K_2CO_3 (0.76 g, 20.3 mmol) in EtOH (20 mL), stirred at reflux for 3 h. Yield 0.15 g (10%), mp 166−168 °C. ^{1}H NMR (DMSO-d_6): δ 7.36 (m, 5H), 6.97 (m, 3H), 3.96 (d, 2H, J = 3.4 Hz), 3.84 (m, 2H), 3.75 (s, 3H), 3.71 (m, 2H), 3.58 (t, 1H, J = 10.0 Hz), 2.93 (d, 1H, J = 9.6 Hz), 2.75 (d, 1H, J = 9.6 Hz), 2.32 (bt, 1H), 2.19 (bt, 1H). Anal. ($C_{19}H_{22}ClNO_3 \cdot C_2H_2O_4 \cdot 0.2H_2O$) C, H, N.

(±)-2-(2-Methoxyphenoxymethyl)-4-(4-trifluoromethylbenzyl)morpholine Oxalic Acid Salt (36). Compound **36** was prepared according to procedure C using **1c** (2.00 g, 9.00 mmol), 4-bromomethyltrifluoromethylbenzene (2.58 g, 10.8 mmol), and K_2CO_3 (6.84 g. 49.5 mmol) in EtOH (50 mL), stirred at reflux for 3.5 h. Yield 0.43 g (10%), mp 101−108 °C. ^{1}H NMR (DMSO-d_6): δ 7.71 (s, 2H), 7.58 (s, 2H), 6.91 (m, 4H), 3.76 (m, 10H), 2.90 (s, 1H), 2.70 (s, 1H), 2.28 (s, 1H), 2.16 (s, 1H). Anal. ($C_{20}H_{22}F_3NO_3 \cdot C_2H_2O_4 \cdot 1.1H_2O$) C, H, N.

(±)-4-(3,4-Dichlorobenzyl)-2-(2-methoxyphenoxymethyl)morpholine Oxalic Acid Salt (37). Compound **37** was prepared according to procedure C using **1c** (2.10 g, 9.40 mmol), α,3,4-trichlorotoluene (2.20 g, 11.3 mmol), and K_2CO_3 (7.15 g, 51.7 mmol) in ethanol (50 mL), stirred for 3.5 h. Yield 0.34 g (7.7%), mp 140−143 °C. ^{1}H NMR (DMSO-d_6): δ 7.60 (d, 2H, J = 7.5 Hz), 7.36 (m, 1H), 6.90 (m, 4H), 3.96 (m, 1H), 3.90 (m, 1H), 3.82 (m, 1H), 3.71 (s, 4H), 3.64 (s, 2H), 3.58 (t, 1H, J = 10.3 Hz), 2.90 (d, 1H, J = 9.8 Hz), 2.72 (d, 1H, J = 9.8 Hz), 2.29 (m, 1H), 2.18 (t, 1H, J = 9.8 Hz). Anal. ($C_{21}H_{23}Cl_2NO_7$) C, H, N.

(±)-4-(4-Chlorobenzyl)-2-(2-propylphenoxymethyl)morpholine Oxalic Acid Salt (38). Compound **38** was prepared according to procedure F using **6c** (2.00 g, 7.70 mmol), 2-propylphenol (1.57 g, 11.5 mmol), *t*-BuOK (1.73 g, 15.4 mmol), and 18-crown-6 ether (0.40 g, 1.50 mmol) in anhydrous toluene (25 mL), stirred at reflux for 15 h under N_2. Yield 0.86 g (31%), mp 158−161 °C. ^{1}H NMR (DMSO-d_6): δ 7.39 (m, 4H), 7.11 (t, 1H, J = 6.8 Hz), 7.08 (d, 1H, J = 6.8 Hz), 6.89 (d, 1H, J = 8.5 Hz), 6.84 (t, 1H, J = 6.8 Hz), 4.02 (m, 1H), 3.86 (m, 2H), 3.73 (d, 1H, J = 9.8 Hz), 3.61 (d, 2H, J = 9.8 Hz), 2.93 (d, 1H, J = 9.6 Hz), 2.75 (d, 1H, J = 9.6 Hz), 2.51 (s, 2H), 2.40 (m, 1H), 2.30 (t, 1H, J = 9.6 Hz), 2.17 (t, 1H, J = 9.6 Hz) 1.43 (m, 2H), 0.79 (t, 3H, J = 4.6 Hz). Anal. ($C_{21}H_{26}ClNO_2 \cdot C_2H_2O_4 \cdot 0.2H_2O$) C, H, N.

(±)-4-(4-Chlorobenzyl)-2,4-chloro-2-ethoxyphenoxymethyl[1,4]oxazepane Oxalic Acid Salt (39). Compound **39** was prepared according to procedure F using **25c** (2.00 g, 7.30 mmol), **14c** (1.26 g, 7.30 mmol), *t*-BuOK (1.63 g, 14.6 mmol), and 18-crown-6 ether (0.96 g, 3.70 mmol) in anhydrous toluene (30 mL), stirred at reflux for 15 h under N_2. Yield 0.80 g (20%), mp 77−80 °C. ^{1}H NMR (DMSO-d_6): δ 7.43 (m, 7H), 3.75 (s, 2H), 3.48 (s, 2H), 3.40 (m, 2H), 2.62 (m, 2H), 2.61 (m, 2H), 2.06 (m, 3H), 2.01 (m, 2H), 1.62 (m, 3H). Anal. ($C_{21}H_{25}Cl_2NO_3 \cdot C_2H_2O_4$) C, H, N.

In Vitro Inhibition of [^{3}H]Spiperone Binding to $D_{4.2}$ Dopamine Receptors (human recombinant). Tissue preparation: Frozen membranes from Chinese Hamster Ovary cells transfected with the human recombinant dopamine $D_{4.2}$ receptor (Research Biochemical International, D-195). Membranes were suspended in 10 mM Tris-HCl (pH 7.2) containing 2 mM EDTA, and stored tightly sealed at −80 °C.

Assay: The membranes were thawed and diluted in incubation buffer (50 mM Tris-HCl, pH 7.4, containing 120 mM NaCl, 5 mM KCl, 5 mM $MgCl_2$, and 1 mM EDTA), in a ratio of 0.25 mL of membranes to 4.75 mL of incubation buffer. Aliquots of 100 μL of diluted membranes were added to 100 μL of test solution and 50 μL of [^{3}H]spiperone (0.5 nM, final concentration). Finally, 750 μL of incubation buffer was added, and the assay mixture was incubated for 60 min at 25 °C. Nonspecific binding was determined using haloperidol (1 μM, final concentration). After incubation, the assay was terminated by rapid filtration over GF/C glass fiber filters (presoaked in 0.1% polyethyleneimine for at least 20 min) and then washed twice with 5 mL of ice cold 50 mM Tris-HCl in 0.9% NaCl at pH 7.4. The amount of radioactivity on the filters was determined by conventional liquid scintillation counting.

Computational Chemistry. Conformational Analysis. The partial charges were calculated with the Gasteiger−Hückel method from Tripos.[38] The conformational analysis of the nonprotonated compounds was performed using the systematic search as implemented by Tripos. Low energy conformations were established from molecular mechanics minimization using Tripos force field and a dielectric constant of 1.0. The termination used was the gradient with 0.05 kcal/mol.

Molecular Alignment. The fitting points used were the sp^3 nitrogen atom and the center of both benzene ring systems.

GRID Calculations. The descriptive steric, electrostatic, and hydrogen-bonding interactions represented by the Lennard−Jones energy, the Coulombic energy, and a hydrogen-bonding term, respectively, were calculated using GRID (version 20).[56] The analysis was performed using a grid spacing of 1 Å. The grid dimensions were (Å): X_{min}/X_{max}, 0.0/22.0; Y_{min}/Y_{max}, 12.0/14.0; Z_{min}/Z_{max}, 14.0/7.0.

GOLPE Analysis. The partial least-squares (PLS) models were calculated using GOLPE (version 4.5.12).[57]

Variable Pretreatments. GOLPE automatically rejects variables having a total sum of square (SS) less than 10^{-7}. Afterward, an advanced pretreatment was performed: variables with a standard deviation lower than 0.02 were defined as inactive variables. Absolute values lower than 0.01 kcal/mol were set to zero.

D Optimal Variable Preselection. Each time 50% of the variables were selected. Each selection was preceded by calculation of a new PLS model including only the last selected variables. The selection procedure was repeated three times,

with a reduction of the number of variables from 7216, 3608, to 1804, respectively.

Variable Preselection SRD. A number of seeds (1366) was selected after D optimal design criterion in the weight space. Since groups of variables may represent the same structural information as a single variable, the variables were grouped together according to the SRD grouping algorithm, with a critical distance of 1.0 Å and a collapsing distance of 2.0 Å.

Variable Selection FFD. The obtained groups of variables were used in the FFD variable selection procedure. The model was built by removing the variables according to the FFD design and using 20% of dummies.

Cross-Validation. The model was validated by using the random group cross-validation approach. Thus, the ligands were randomly assigned to five groups, each one containing an equal number of ligands. The models were built keeping one of these groups out of the analysis until all the ligands had been kept out once. The formation of the groups and the validation was repeated 20 times.

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Supporting Information Available: Elemental analyses data. This material is available free of charge via the Internet at http://pubs.acs.org.

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