Leone (D-6), were utilized in susceptibility testing. Test compounds were dissolved in DMSO and serially diluted with culture media. The uptake of tritiated hypoxanthine was used as an index of inhibition of parasite growth. The compounds described herein were tested against a drug-sensitive strain of *P. berghei* (strain KBG 173) in mice according to methods previously described.[40]

Acknowledgment. This work was done while J.L.V. held a National Research Council Research Associateship at the Walter Reed Army Institute of Research. We are grateful to Dr. A. O. Onabanjo, University of Lagos, Department of Pharmacology, Lagos, Nigeria, for providing the *E. chlorantha* bark. We also thank Drs. Wilbur K. Milhous (WRAIR) and Arba L. Ager, Jr. (University of Miami) for the in vitro and in vivo antimalarial test results, respectively.

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Registry No. 1, 633-65-8; 2, 10605-02-4; 3, 6681-15-8; 4, 549-21-3; 5, 483-15-8; 6, 113975-46-5; 7, 3906-36-3; 8, 522-97-4; 9, 61774-67-2; 10, 113975-47-6.

Graphics Computer-Aided Receptor Mapping as a Predictive Tool for Drug Design: Development of Potent, Selective, and Stereospecific Ligands for the 5-HT_{1A} Receptor

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A conformational study of four 5-HT_{1A} (serotonin) receptor ligands ((*R*-(−)-methiothepin, spiperone, (*S*)-(−)-propranolol, and buspirone) led to the definition of a pharmacophore and a three-dimensional map of the 5-HT_{1A} antagonist recognition site. These models were used to design new compounds and successfully predict their potency, stereospecificity, and selectivity. For example, 8-[4-[(1,4-benzodioxan-2-ylmethyl)amino]butyl]-8-azaspiro[4.5]decane-7,9-dione (1, MDL 72832) has nanomolar affinity (pIC_{50} = 9.14) for the 5-HT_{1A} binding site in rat frontal cortex. As predicted, the *S*-(−) enantiomer of 1 was more active than its *R*-(+) enantiomer (pIC_{50} = 9.21 and 7.66, respectively) and a naphthalene analogue of 1 displayed the expected improved selectivity.

Graphics computer technology that has been developed during the last decade is an important new tool for drug design. It has proven particularly useful in the determination of crystallographic structures and for the theoretical mechanistic studies of the interaction between a substrate and a receptor of known structure.[1] On the other hand, when receptor structure is totally unknown, the graphics computer has generally been used a posteriori to account for structure–activity relationships.

We report here the rational application of the computer-aided receptor mapping technique to the a priori design of a series of novel molecules with high affinity, stereospecificity, and selectivity for a particular receptor. Our objective was the central 5-HT_{1A} receptor subtype.[2] The program was stimulated by the observation that the novel centrally active 5-HT (5-hydroxytryptamine, serotonin) receptor agonist 8-hydroxy-*N*,*N*-di-*n*-propyl-2-aminotetralin (8-OH-DPAT)[3] shows remarkable potency and selectivity for a subtype of the central 5-HT_1 recognition site, designated 5-HT_{1A}.[4] Subsequent work on the behavioral effects of 8-OH-DPAT and 5-MeO-DMT (5-methoxy-*N*,*N*-dimethyltryptamine), as well as the reported clinical properties of buspirone, a compound having a high affinity for the 5-HT_{1A} receptor, strongly suggested that antagonists at this site would have desirable therapeutic potential as novel anxiolytic agents.[5-7] These observations led us to try to design new 5-HT_{1A} receptor antagonists with optimized potency and selectivity.

Table I. Affinity of Compounds Used in Creating Pharmacophore for Central 5-HT recognition Sites in Rat Frontal Cortex

compound	pIC_{50} 5-HT_{1A}	5-HT_{1B}	5-HT_2
8-OH-DPAT	8.52	5.42	5.00
(−)-methiothepin	7.02	6.74	8.20
(+)-methiothepin	6.07	5.49	8.25
spiperone	6.91	6.00	8.67
propranolol	6.77	6.31	5.10
buspirone	7.66	4.90	5.47

Receptor Mapping and Drug Design

The general approach that has been followed was defined by Marshall[8] and can be outlined as follows: (i) critical examination of compounds active or inactive at the target receptor, (ii) graphics computer-aided definition of a pharmacophore, (iii) three-dimensional graphics computer-assisted mapping of the recognition site, and (iv) use of the previously defined pharmacophore and receptor map to design original putative optimized ligands.

In spite of its limitations, this approach proved to be very efficient in the case of the 5-HT_{1A} recognition site, as will be discussed below.

(i) Activity Evaluation. 8-OH-DPAT has been shown to display both high affinity and selectivity for the 5-HT_{1A} recognition site in vitro,[4] and the tritiated analogue has been used to label this site selectively in the brain.[9]

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(2) Pedigo, N.; Yamamura, H.; Nelson, D. *J. Neurochem.* **1981**, *36*, 222.
(3) Arvidsson, L.-E.; Hacksell, U.; Nilsson, J.; Hjorth, S.; Carlsson, A.; Lindberg, P.; Sanchez, D.; Wikstrom, H. *J. Med. Chem.* **1981**, *24*, 921.
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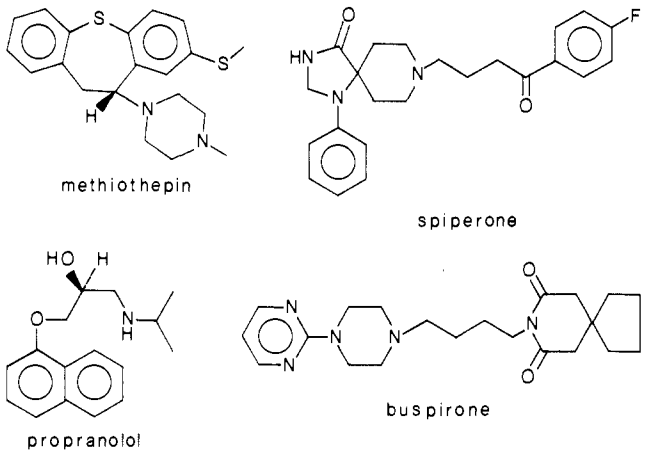
Scheme I



Several pharmacological studies performed with 8-OH-DPAT showed that this compound is an agonist with many central and peripheral actions[10] including effects on the cardiovascular system,[11,12] feeding behavior,[13] sexual activity,[14] the startle response,[15] and body temperature.[16] It has been demonstrated that certain of the behavioral effects are the result of the stimulation of 5-HT_{1A} receptors.[5,17-21] Structure–activity studies among 5-HT_{1A} receptor agonists have been performed, and maps of this site have been proposed.[22,23]

When we initiated this project, 3 years ago, we established the 5-HT_{1A} antagonist properties of four standard molecules: (*R*)-(−)-methiothepin,[24,25a,b] spiperone,[26] (*S*)-(−)-propanolol,[27] and buspirone.[28] These compounds displayed relatively moderate affinity and no selectivity for the 5-HT_{1A} recognition site (Table I). Nevertheless, they clearly interacted with the same site and were assumed, therefore, to contain the same pharmacophore. These four compounds constituted the basis of our structure–activity relationship study.

Scheme II

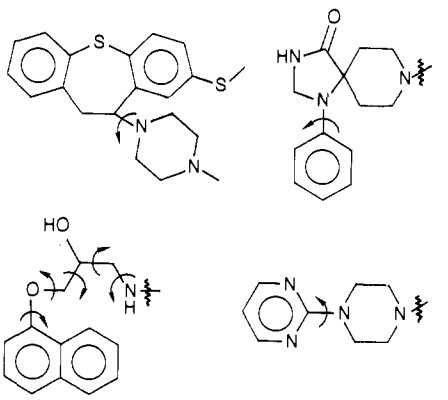


Table II. Fitting Index and Relative Energy of the Active Conformers

compound	torsional angle increment,[a]	global minimal energy,[b] kcal/mol	RMS,[c] Å	ΔE,[d] kcal/mol
(*R*)-(−)-methiothepin	3	3.52	0.000	1.52
buspirone	3	−2.65	0.212	0.28
spiperone	3	4.26	0.183	0.18
(*S*)-(−)-propanolol	30	0.58	0.142	12.36
S-1	3	−0.15	0.202	0.04
R-1	3	−0.15		2.24

[a] Increment chosen to rotate stepwise around the flexible bonds displayed in Scheme II to perform the conformational analysis. [b] Total energy is the sum of bond, bond angle, tortional angle, and van der Waals energy terms (MAXIMIN[33a]). [c] Root mean square index. [d] Difference between the active conformer energy and the global minimum energy.

(ii) Definition of a Pharmacophore. As can be seen in Scheme I, (*R*)-(−)-methiothepin, spiperone, (*S*)-(−)-propranolol, and buspirone have very diverse chemical structures. We hypothesized that the two reference structural features defining the pharmacophore could be the one aromatic ring and one strongly basic nitrogen atom they all have in common. The topographical characterization of the pharmacophore has been performed as follows: models of the four compounds have been built with a VAX 11/750, an Evans & Sutherland PS 300 terminal, and the SYBYL molecular modeling package (Tripos). Crystallographic structures have been utilized for (*S*)-(−)-propranolol,[29] buspirone,[30] spiperone,[31] and methiothepin (derived from octoclothepine and oxyprothepine X-ray structures).[32a,b] For the parts of the starting molecules shown in Scheme II, stable conformations where one aromatic ring and one basic nitrogen atom had the same relative positons in space were sought. For (*R*)-

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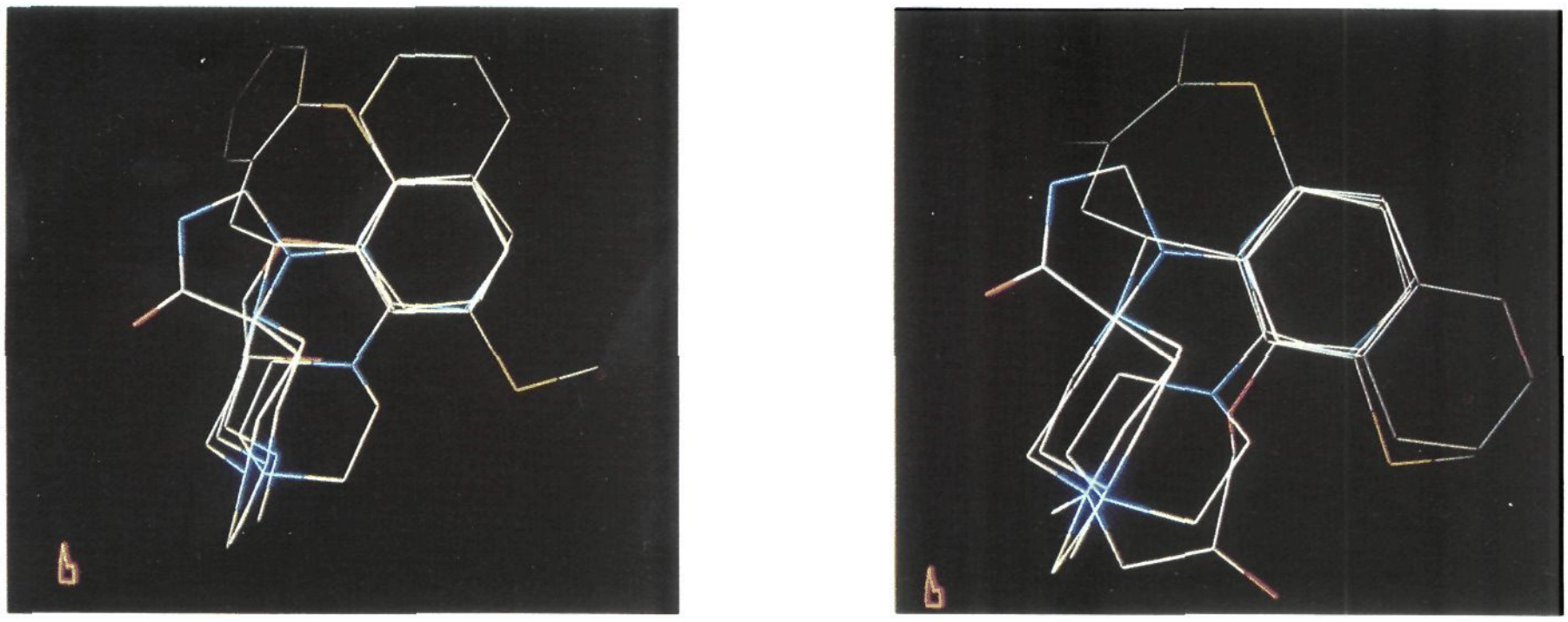

Figure 1. Superimposition of the amino and aromatic moieties of methiothepin, propranolol, spiperone, and buspirone. (a) First possibility for propranolol. (b) Second possibility for propranolol.

(–)-methiothepin, spiperone, and (*S*)-(–)-propranolol, two aromatic rings could be considered as putative reference points. In addition, methiothepin and buspirone possessed two basic amino groups. Finally, methiothepin can adopt different conformations by inversion of the sulfur or dimethylene bridges. All the possible reference pairs were taken into consideration to perform the fitting attempt. Before looking for the commonalities in this group of compounds, their possible conformations had to be ascertained. Thus for each compound, rotatable bonds were assigned and a conformational search was performed, allowing the bonds to rotate with a chosen stepwise increment of the dihedral angles. Angle files are thus produced and the internal energy corresponding to each valid conformation was evaluated by a molecular mechanics method (Table II). The fitting attempt has been performed by using the MAXIMIN MULTIFIT program of SYBYL. This method based on molecular mechanics will force the molecular features chosen as reference to an optimized fit at the cost of some conformational energy.[33a,b] The molecules relax to the closest minima, which obviously may not coincide with the global minimum energy. The molecular structural features that have been considered for the matching process are the normal to the aromatic ring (2 Å long vector centered on the phenyl ring centroid) and the basic nitrogen atom. The quality of the superimposition is measured by the root mean square (RMS) index. Among different solutions, one type of pharmacophore emerged from this study as valid in terms of good fit and reasonable intramolecular energy: it was indeed possible to find stable conformations for (*R*)-(–)-methiothepin, spiperone, (*S*)-(–)-propranolol, and buspirone (Table II) which permitted the superimposition of aromatic rings and basic nitrogen atoms, as represented in Figure 1. In this model, the mean distance between the center of the common aromatic nucleus and the nitrogen atom was 5.6 Å, while this nitrogen was lying at 1.6 Å above the plane defined by the reference ring. These features represented the two basic structural parameters necessary for the binding process and defined a possible pharmacophore for

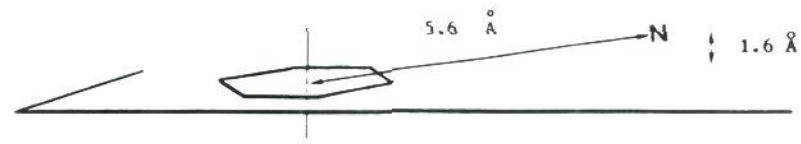

Figure 2. Basic pharmacophore of the 5-HT$_{1A}$ antagonist recognition site.

the 5-HT$_{1A}$ antagonist recognition site (Figure 2).

Although the topography of these two molecular determinants was determined precisely in our model, several possibilities remained concerning the conformation of the (*S*)-(–)-propranolol side chain and the orientation of its naphthyl moiety (Figure 1a,b). Moreover, it should be emphasized that the two chosen primary points of binding are probably not sufficient to stabilize the receptor–ligand complex and additional anchoring groups are almost certainly required. Thus, for instance, the contribution of the side chains (methyl, isopropyl, fluorobenzophenone, and spiroimide belonging to methiothepin, propranolol, spiperone, and buspirone, respectively) has not been considered at this stage of the study although it is unquestionably not negligible. In this respect, it is interesting to note that the first carbon atom of these chains branching the reference nitrogen atom are almost superimposed in our model (Figure 1), pointing thus toward the same region of the receptor.

The pharmacophore described seemed to account for the contribution to affinity of the considered parts of the known 5-HT$_{1A}$ receptor antagonists.

(iii) Receptor Mapping. Using the model outlined above, we defined a van der Waals surface corresponding to the envelope of the superimposed antagonists in their active conformations. This provided us with a volume that in theory corresponded to a zone accessible to ligands in the central 5-HT$_{1A}$ antagonist recognition site (Figure 3).

(iv) Drug Design. In a number of publications, diverse interesting pharmacophores and graphics computer-assisted receptor mapping have been reported, which a posteriori accounted for the activity of a series of ligands.[34a,b,35] In general, and in the particular case of the

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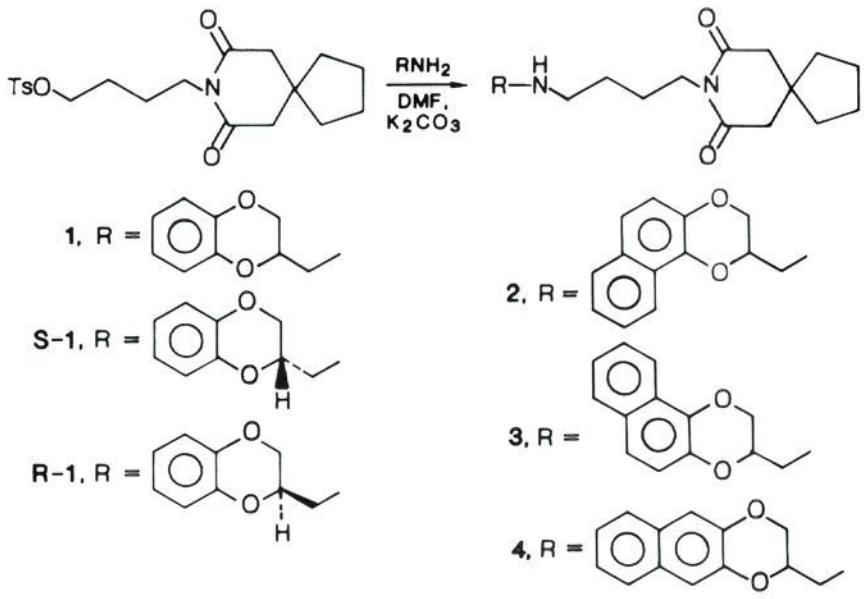
Scheme III



5-HT_{1A} receptor, we were not only interested in rationalizing existing data but we wanted to use the generated model as a predictive tool for drug design. Thus, taking into consideration all the structural information and constraints contained in our model, we designed several original chemical structures that satisfied the above criteria (Figure 3) and for which we predicted a high affinity. All the designed structures belonging to different chemical classes displayed very high affinities with IC_{50} values ranging from 10^{-7} to 10^{-10} M. One of these new lead compounds contained the 2-(aminomethyl)-1,4-benzodioxan moiety and was designed as follows: according to our model, one aromatic ring was required to obtain activity; from Figure 1, it was clear that two heteroatoms substituting the ortho position in this ring were accepted by the receptor since the ether oxygen atom belonging to propranolol and nitrogen atoms belonging to spiperone and buspirone occupied these positions in our model. In addition, the superimposition clearly indicated that it might be possible to incorporate these atoms into a six-membered ring in order to form a 1,4-benzodioxan or a 1,4-benzoxazine system; finally, substitution in position 2 by an aminomethyl group provided us with a structure that matched perfectly the reference structural features, as shown in Figure 4.

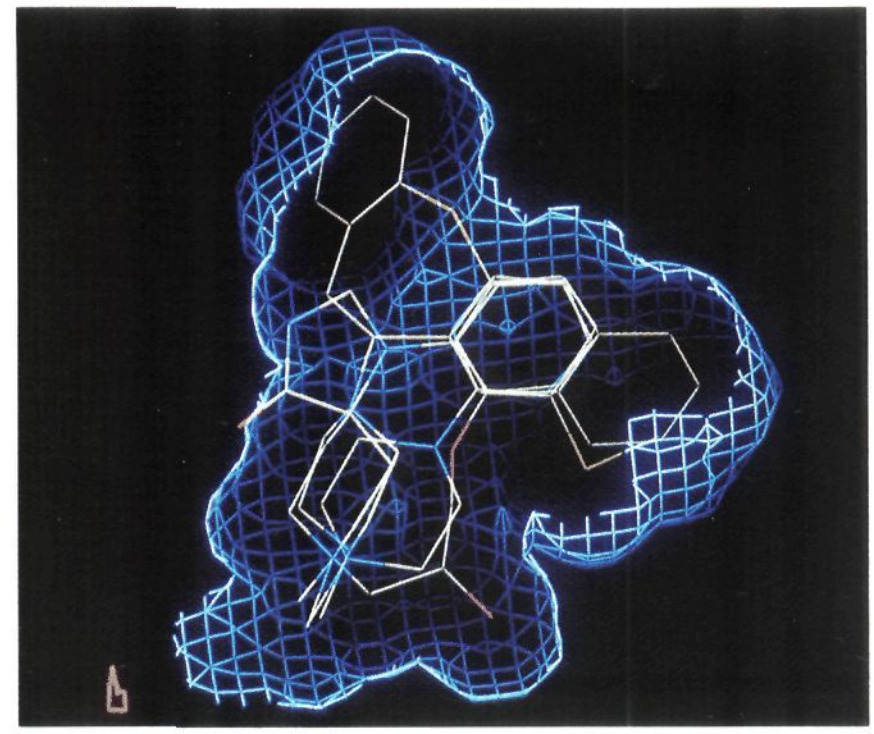


Figure 3. Volume accessible to ligands in the 5-HT_{1A} antagonist recognition site.

Consequently, we predicted that a compound such as 1, combining the designed 2-(aminomethyl)-1,4-benzodioxan moiety with the side chain of buspirone, might display a very high affinity for the 5-HT_{1A} receptor.

Our model was precise enough to encourage us to predict the stereospecificity of the recognition feature. Thus, while the *S* enantiomer of the 2-(aminomethyl)-1,4-benzodioxan moiety fitted perfectly our basic pharmacophore (RMS = 0.20), it was impossible to obtain such a good fit with the *R* enantiomer, as shown in Figure 5. For the *R* enantiomer, if the aromatic ring occupied the "ideal" reference position, it was impossible to find a conformation where the nitrogen atom would be located less than 1.10 Å from the reference nitrogen. Therefore, we predicted that the *S* enantiomer might be more potent than the *R* enantiomer at the 5-HT_{1A} recognition site.

Results and Discussion

Compound 1 (MDL 72832) was prepared according to Scheme III, as previously reported.[36] The separation of

Scheme IV

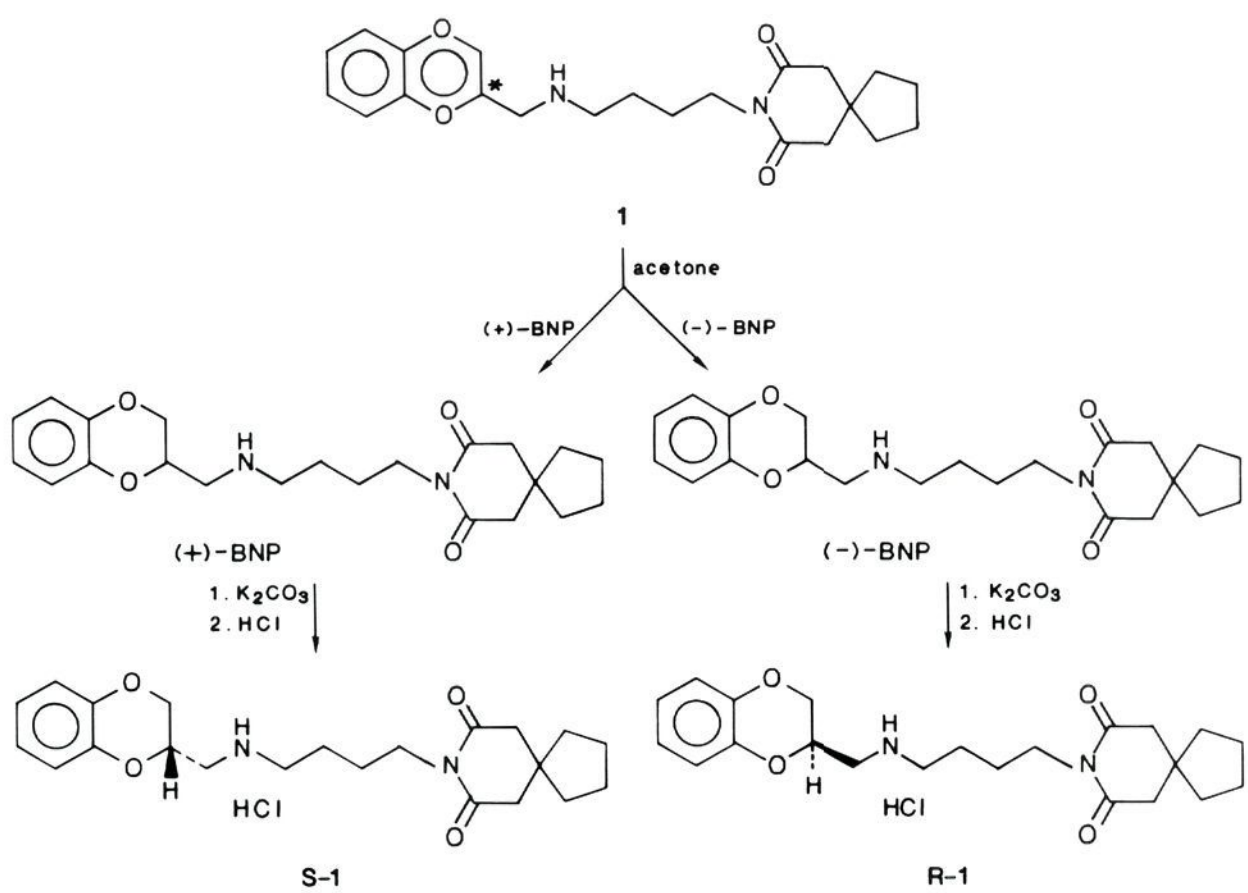


Table III. Affinity of Compound 1 and Its Enantiomers and Naphthyl Isomers for Central Neurotransmitter Recognition Sites in Rat Brain

compound	pIC$_{50}$ ± SEM					
	5-HT$_{1A}$	5-HT$_{1B}$	5-HT$_2$	α_1	α_2	D$_2$
1	9.1 ± 0.1	6.2 ± 0.1	6.2 ± 0.1	7.8 ± 0.1	6.4 ± 0.1	6.8 ± 0.1
S-1	9.2 ± 0.1	6.1 ± 0.4	6.7 ± 0.1	8.0 ± 0.1	6.3 ± 0.1	7.1 ± 0.3
R-1	7.7 ± 0.1	5.3 ± 0.1	6.1 ± 0.1	7.2 ± 0.1	6.2 ± 0.1	5.6 ± 0.3
2	8.3 ± 0.1	6.4 ± 0.2	6.8 ± 0.2	6.1 ± 0.1	<5	6.8 ± 0.3
3	6.1 ± 0.1	5.5 ± 0.1	5.9 ± 0.1	5.2 ± 0.1	<5	6.5 ± 0.1
4	6.5 ± 0.05			5.3 ± 0.1		

[a] Radioligands used in the binding assays were [^{3}H]-8-OH-DPAT, [^{3}H]-5-HT in the presence of 0.1 μmol of 8-OH-DPAT, [^{3}H]ketanserin, [^{3}H]prazosin, [^{3}H]clonidine, and [^{3}H]domperidone for 5-HT$_{1A}$, 5-HT$_{1B}$, 5-HT$_2$, α_1, α_2, and D$_2$ receptors, respectively.[39,46,49]

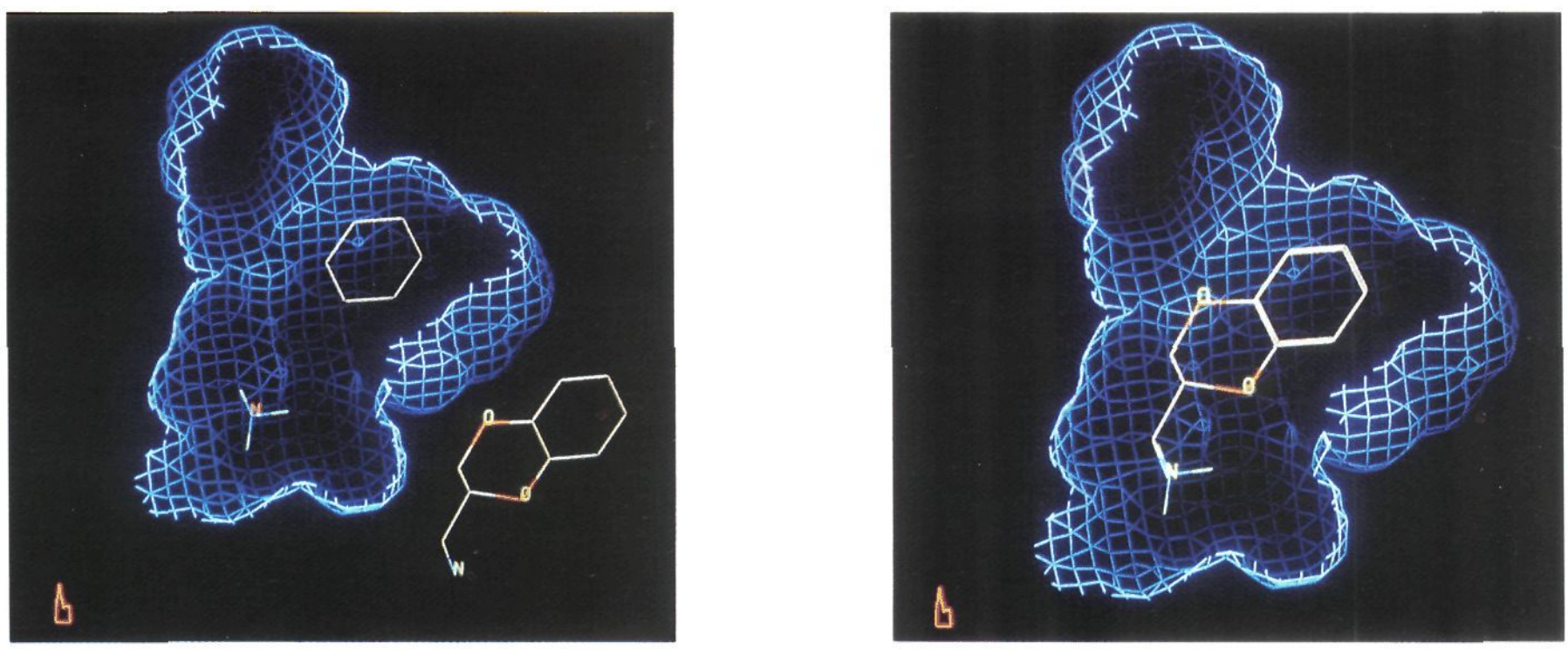


Figure 4. Superimposition of 2-(aminomethyl)-1,4-benzodioxan with the pharmacophore (volume b).

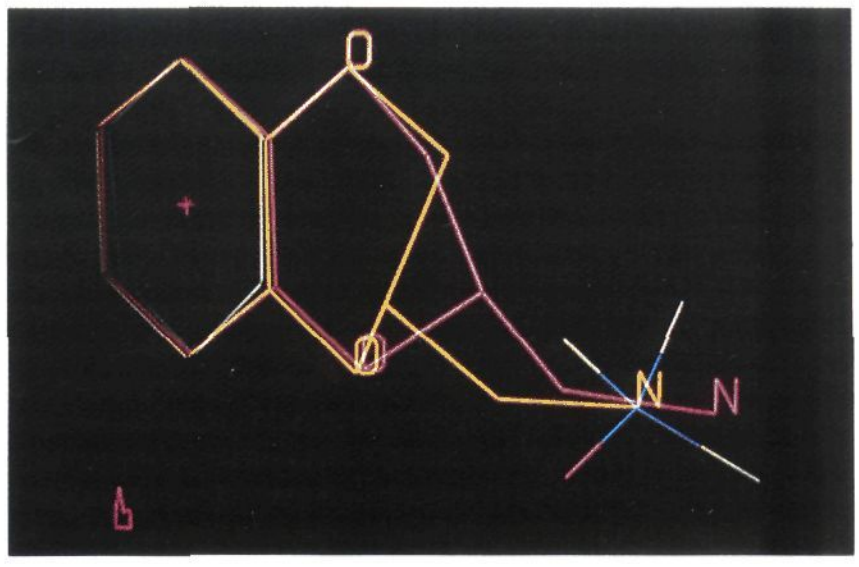


Figure 5. Superimposition of the *S*-(−) enantiomer (yellow) and the *R*-(+) enantiomer (red) of compound 1 with the pharmacophore.

the enantiomers of compound 1 has been achieved by enantioselective crystallization with optically pure binaphthyl phosphoric acid as chiral resolving agent (Scheme IV).[37] Enantiomeric purity was determined by using HPLC techniques (cf. the Experimental Section).

The absolute configuration was characterized by preparing the *R* enantiomer of 1 with pure (*R*)-(+)-2-(aminomethyl)-1,4-benzodioxan as the starting material, prepared as described by Nelson et al.[38] The activity of our new compounds has been evaluated by radioligand receptor binding studies with [^{3}H]-8-OH-DPAT as a selective ligand for the 5-HT$_{1A}$ receptor in rat brain membranes as previously described.[39]

As predicted, we indeed observed a very high affinity for compound 1 at the 5-HT$_{1A}$ receptor (pIC$_{50}$ = 9.14, Table III). At the time of its disclosure,[36] this compound was the most active 5-HT$_{1A}$ receptor ligand reported. In addition, this compound was very selective since it displayed only marginal affinity for 5-HT$_{1B}$, 5-HT$_2$, dopamine D$_2$ receptors, and α_2-adrenoceptors (Table III).

Furthermore, as predicted, the *S*-(−) enantiomer of compound 1 (**S-1**) was 36-fold more potent than its *R*-(+) enantiomer (**R-1**). The residual affinity observed for the less active enantiomer can be attributed to the 3.35% of contamination by the most active one (cf. the Experimental Section).

We were thus successful both in designing totally new potent 5-HT$_{1A}$ receptor ligands and in predicting the stereospecificity of the recognition feature.

As can be seen in Table III, compound 1 was very selective for the 5-HT$_{1A}$ site compared with most receptors, but it did display significant affinity for the α_1-adrenoceptor (pIC$_{50}$ = 7.8). This affinity for the α_1-adrenoceptor was not surprising since compounds containing the 2-(aminomethyl)-1,4-benzodioxan moiety are known ligands at these sites.[40,41] According to our model, the stereo-

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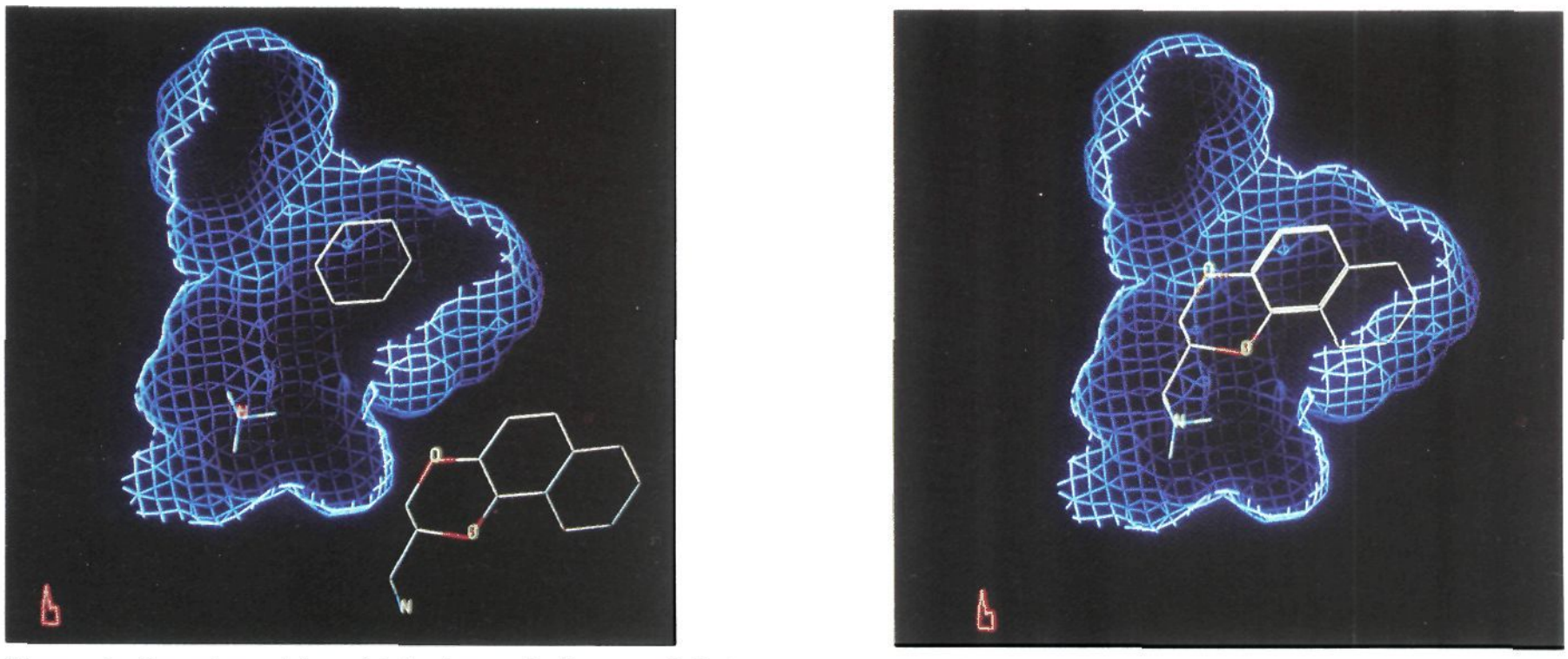

Figure 6. Superimposition of 2-(aminomethyl)-1,4-naphtho[1,2-*b*]dioxan with the pharmacophore (volume b).

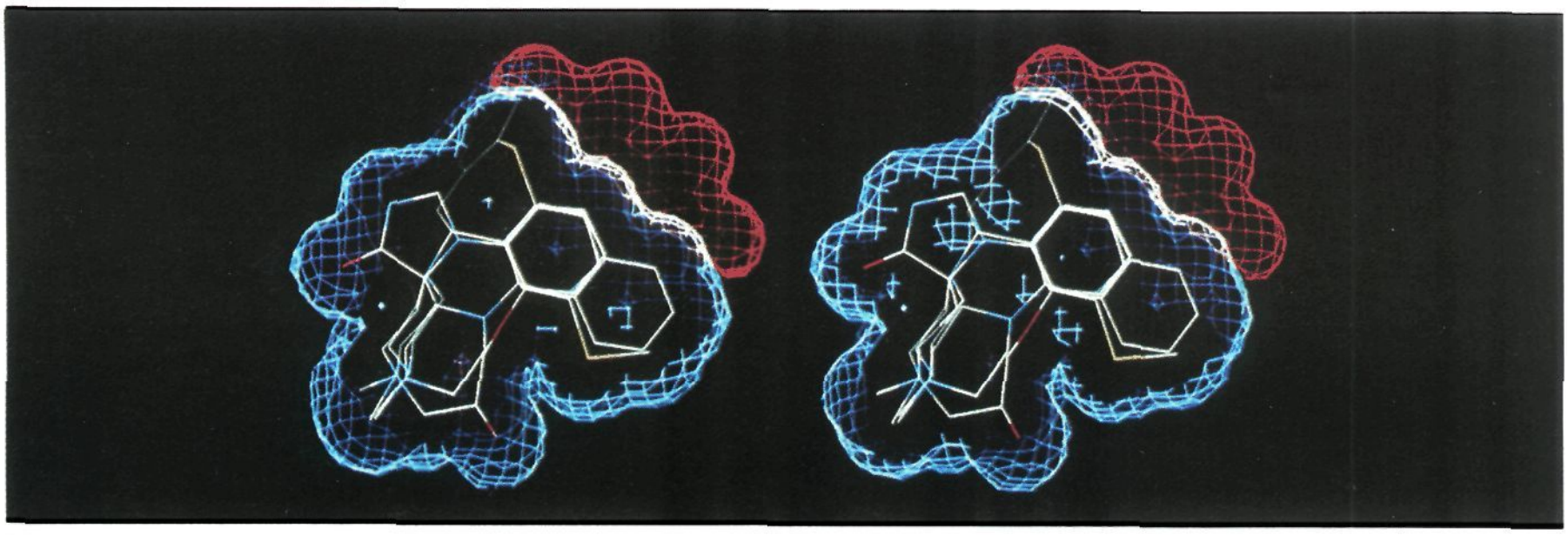

Figure 7. Stereo view of the superimposed antagonists fitting into the volumes accessible (blue) and inaccessible (red) to ligands in the 5-HT_{1A} antagonist recognition site.

chemical requirements of the 5-HT_{1A} and α_1-adrenoceptor are identical,[38] which explains why the affinity ratio remains the same for the *S*-(−) enantiomer **S-1** and the racemate **1**.

To improve the selectivity of compound **1**, we tried to characterize differences between the two sites. Thus, a simple examination of the graphics computer-generated maps of the 5-HT_{1A} receptor and α_1-adrenoceptor (not shown) suggested that naphthyl analogues of **1** would still be accepted by the 5-HT_{1A} receptor (Figure 6) but would not fit into the α_1-adrenoceptor recognition site.[42] We therefore predicted that one of the naphthalene analogues of **1** would display a higher selectivity versus the 5-HT_{1A} receptor than its parent compound.

These molecules have been synthesized according to Scheme *III*, starting from (aminomethyl)naphthodioxan, which has been described previously.[43] Again, as predicted, one of the two isomers (**2**) retained a high affinity for the 5-HT_{1A} recognition site while its affinity for the α_1-adrenoceptor was strongly decreased, leading to a much improved selectivity ratio of 140 (Table III). In addition, the inactivity of **3**, one of the two disymmetrical naphthyl isomers of **1**, permitted selection of model b of Figure 1 as the most valuable, thus removing the original ambiguity about the orientation of the propranolol naphthyl moiety. On the other hand, the inactivity of compounds **3** and **4** led us to define a volume not accessible to ligands (Figure 7) and consequently to a refined model of the 5-HT_{1A} recognition site.

It must be emphasized that buspirone displays both agonist and antagonist properties in different functional assays.[28,44] Interestingly, the conformation of buspirone in the 5-HT_{1A} antagonist recognition site (this study) is different from its conformation in the 5-HT_{1A} agonist recognition site.[23] Thus the torsional angle defined by the four atoms N_{arom}–C_{arom}–N–C is $\theta = -19°$ for the agonist conformer and $\theta = +15°$ for the antagonist conformer. As a result, the height of the nitrogen atom above the plane defined by the aromatic ring, as well as the directions in which the nitrogen lone pairs of electrons point, are different in the two models. This may allow comparison of the active and inactive conformation of the 5-HT_{1A} receptor induced during the fitting process by agonists and antagonists, respectively. Similarly, in functional tests, compound **1** displays both agonist and antagonist properties[45,46] which may be related to a certain conformational

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flexibility. This will be discussed in more detail elsewhere.

Conclusion

We describe here the rational application of computer-aided receptor mapping techniques to the a priori design of a series of novel molecules with very high affinity, stereospecificity, and selectivity for a given receptor. Certain of these compounds exhibit interesting in vitro and in vivo activity, the details of which have been presented in abstract form previously[36,45] and will be described more fully elsewhere.[46-48]

Any pharmacophore or receptor model must be considered circumspect since it invariably relies on several approximations and hypotheses: for example, the ligands are assumed to bind at the same site, the receptor is considered rigid, the modeling process involves approximations of the energy values, and the choice of the important molecular determinants must be judicious. In spite of these limitations, it seems that in the particular case of the 5-HT$_{1A}$ antagonist recognition site our model constitutes a valuable tool since it has permitted both rationalization and prediction of active molecules. Many other analogues of compound **1**, as well as new lead compounds belonging to completely different chemical classes, have been designed by using our model and displayed the expected activity.[46-48] These compounds are currently undergoing biological evaluation.

Experimental Section

Syntheses. Melting points were determined with a Büchi apparatus (capillary method) and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker 90 and Bruker AM-360 spectrometer at 90 and 360 MHz, respectively. Flash chromatography columns were run on silica gel (60 silica gel). Analyses, indicated by elemental symbols, were within ±0.3% of the theoretical values.

8-[4-[(1,4-Benzodioxan-2-ylmethyl)amino]butyl]-8-azaspiro[4.5]decane-7,9-dione (1). 2-(Aminomethyl)-1,4-benzodioxan (0.97 g, 4.8 mmol) was dissolved in dry dimethylformamide (DMF) (5 mL). Potassium carbonate (2 g) was added. *N*-[4-(Tosyloxy)butyl]-3,3-tetramethyleneglutarimide (1.84 g, 4.8 mmol)[36] dissolved in dry dimethylformamide (DMF) (25 mL) was slowly added with stirring and under an inert atmosphere. The mixture was stirred overnight at 120 °C. The solid was filtered off and DMF was distilled under reduced pressure. The oily residue was dissolved in ethyl acetate, washed with H_2O, extracted with 5% HCl basified with potassium carbonate, and extracted with ethyl acetate. This organic solution was finally washed with brine and dried over sodium sulfate and the solvent removed under vacuum, yielding a yellow oil. This crude material was purified by flash chromatography on silica gel (EtOAc/MeOH, 5/1 to 1/1), leading to pure title compound (160 mg). Additional pure product was obtained from the first extracts. The salt was formed in HCl/Et_2O and recrystallized from 2-propanol/ethyl acetate/ether, yielding slightly yellow needles (20%): mp 191 °C. Anal. ($C_{22}H_{30}N_2O_4$·HCl) C, H, N.

8-[4-[[(2,3-Dihydronaphtho[1,2-*b*]dioxin-2-yl)methyl]amino]butyl]-8-azaspiro[4.5]decane-7,9-dione (2). According to essentially the same procedure as described for the preparation of compound 1 but with substitution of 2-(aminomethyl)-1,4-naphtho[1,2-*b*]dioxane (0.676 g, 3.1 mmol)[43] for the benzodioxan analogue, 1.53 g of crude oil was obtained. Purification by flash chromatography on silica gel (MeOH/CH_2Cl_2, 5/95) afforded 0.62 g (45.9%) of the pure product. The hydrochloride hemihydrate was recrystallized from MeOH/CH_2Cl_2/*i*-PrOH, mp 228 °C. Anal. ($C_{26}H_{32}N_2O_4$·HCl·$^1/_2H_2O$) C, H, N.

8-[4-[[(2,3-Dihydronaphtho[1,2-*b*]dioxin-3-yl)methyl]amino]butyl]-8-azaspiro[4.5]decane-7,9-dione (3). According to the same method as described for the preparation of compound 1 but starting from 3-(aminomethyl)-1,4-naphtho[1,2-*b*]dioxan (0.5 g, 2.32 mmol),[43] the expected product was obtained (0.49 g, 48.5%) and crystallized as the hydrochloride salt from MeOH/*i*-PrOH/Et_2O: mp 222 °C. Anal. ($C_{26}H_{32}N_2O_4$·HCl) C, H, N.

8-[4-[[(2,3-Dihydronaphtho[2,3-*b*]dioxin-2-yl)methyl]amino]butyl]-8-azaspiro[4.5]decane-7,9-dione (4). According to exactly the same method as described for the preparation of compound 1 but starting from 2-(aminomethyl)-1,4-naphtho[2,3-*b*]dioxan (1.08 g, 5 mmol), the expected product **4** was obtained as pure free base (0.92 g, 42.2%). Recrystallization of the hydrochloride from *i*-PrOH gave white crystals: mp 213 °C. Anal. ($C_{26}H_{32}N_2O_4$·HCl) C, H, N.

(*S*)-(−)- and (*R*)-(+)-8-[4-[(1,4-Benzodioxan-2-ylmethyl)amino]butyl]-8-azaspiro[4.5]decane-7,9-dione (S-1 and R-1). 8-[4-[(1,4-Benzodioxan-2-ylmethyl)amino]butyl]-8-azaspiro[4.5]decane-7,9-dione (1; 0.91 g, 2.35 mmol) was dissolved in a mixture of acetone and 2-propanol. (+)-Binaphthylphosphoric acid (BNP)[37] (0.82 g) dissolved in acetone was added to the previous solution, leading to the formation of white crystals, which were removed by filtration and washed with *i*-PrOH, EtOH, and acetone. The resulting residue was suspended in water and basified with potassium carbonate. The free base so obtained was extracted with ethyl acetate. The organic extract was dried and evaporated, affording the crude optically enriched free base. The remaining traces of BNP, K^+ salt were removed by rapid filtration over silica gel (AcOEt/MeOH, 97/3), yielding the pure free base (0.44 g, 96.7%).

The hydrochloride salt was formed in Et_2O and recrystallized from EtOH, providing white crystals of the expected product: mp 200 °C; $[\alpha]_D$ −44.8° (H_2O, *c* 0.460). Anal. ($C_{22}H_{30}N_2O_4$·HCl) C, H, N.

By following essentially the same procedure but substituting (−)-binaphthylphosphoric acid[37] for (+)-BNP, the remaining enantiomer was obtained: (*R*)-(+)-8-[4-[(1,4-benzodioxan-2-ylmethyl)amino]butyl]-8-azaspiro[4.5]decane-7,9-dione, HCl salt: mp 199 °C; $[\alpha]_D$ +45.1° (H_2O, *c* 0.480). Anal. ($C_{22}H_{30}N_2O_4$·HCl) C, H, N. The optical purity was determined by HPLC (Merck Hibar column, 1400 psi, 1.5 mL/min, CH_2Cl_2/*i*-PrOH, 99.5/0.5) after derivatization with the Mosher reagent: the *R*-(+) enantiomer **R**-1 contained 3.35 ± 0.25% of the *S*-(−) enantiomer, while the *S*-(−) enantiomer **S**-1 contained 2.85 ± 0.20% of the *R*-(+) enantiomer.

Compound **3** made from (*R*)-(+)-2-(aminomethyl)-1,4-benzodioxan prepared as described by Nelson et al.[38] was identical with the *R* enantiomer obtained by resolution.

Binding Experiment. The radioligand receptor binding studies have been performed in rat brain as previously described.[39,46,49] Radioligands used in the binding assays were [^{3}H]-8-OH-DPAT, [^{3}H]-5-HT in the presence of 0.1 μmol of 8-OH-DPAT, [^{3}H]ketanserin, [^{3}H]prazosin, [^{3}H]clonidine, and [^{3}H]domperidone for 5-HT$_{1A}$, 5-HT$_{1B}$, 5-HT$_2$, α_1, α_2, and D_2 receptors, respectively.

Registry No. (±)-1, 113777-33-6; (±)-1·HCl, 113777-40-5; (*S*)-1, 102908-55-4; (*S*)-1·HCl, 102908-56-5; (*R*)-1, 102908-57-6; (*R*)-1·HCl, 102908-58-7; (±)-2, 113777-34-7; (±)-2·HCl, 113777-41-6; (±)-3, 113777-35-8; (±)-3·HCl, 113777-42-7; (±)-4, 113777-36-9; (±)-4·HCl, 113777-43-8; (+)-BNP, 35193-64-7; (−)-BNP, 39648-67-4; (*R*)-methiothepin, 101395-31-7; spiperone, 749-02-0; (*S*)-propranolol, 4199-09-1; buspirone, 36505-84-7; *N*-[4-(tosyloxy)butyl]-3,3-tetramethyleneglutarimide, 102908-67-8; (±)-2-(aminomethyl)-1,4-naphtho[1,2-*b*]dioxan, 113777-37-0; (±)-3-(aminomethyl)-1,4-naphtho[1,2-*b*]dioxan, 113777-38-1; (±)-2-(aminomethyl)-1,4-naphtho[2,3-*b*]dioxan, 113777-39-2; (±)-2-(aminomethyl)-1,4-benzodioxan, 113830-01-6.

Supplementary Material Available: The atomic coordinates of the four compounds defining the pharmacophore (Figure 1b) are available (3 pages). Ordering information is given on any current masthead page.

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