Articles

Effect of Modifications of the Alkylpiperazine Moiety of Trazodone on $5HT_{2A}$ and α_1 Receptor Binding Affinity

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A series of triazolopyridine derivatives (compounds **2a**−**l**) were synthesized in order to explore the effect of modifications of the alkylpiperazine moiety of trazodone (fragment A) on binding affinity for $5HT_{2A}$ and α_1 receptors. All of the synthesized compounds show a decrease of affinity for both $5HT_{2A}$ and α_1 receptors, as compared to trazodone, with the exception of compounds **2b,c** which bear a methyl group in an α position to the aliphatic nitrogen atom N_1. These compounds showed a decrease of affinity only for the α_1 receptor. The stereochemical influence of the piperazine moiety of compound **2c** was also evaluated. Enantiomer (***S***)-**2c** showed the most significant differences between $5HT_{2A}$ and α_1 receptor affinity (IC_{50} values) and among the corresponding functional properties (pA_2 values). Since (***S***)-**2c** cannot generate the metabolite 4-(3-chlorophenyl)piperazine this product was selected for further pharmacological studies.

Introduction

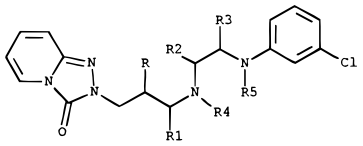
Many of the drugs effective in the treatment of depression and anxiety act on the serotonergic system, either as serotonin reuptake inhibitors or as agonists or antagonists for some subtypes of serotonin receptors.[1] Among the serotonin receptors identified[2] thus far, the $5HT_{1A}$, $5HT_{2A}$, and $5HT_{2C}$ subtypes seem to be involved in anxiety and depression. As an example, ligands specifically acting as $5HT_{1A}$ antagonists or partial agonists or as $5HT_{2A}$ and $5HT_{2C}$ antagonists may act as antidepressant drugs with reduced side effects.[3] Trazodone (**1**) (2-[3-[4-(3-chlorophenyl)-1-piperazinyl]-propyl]-1,2,4-triazolo[4,3-*a*]pyridin-3-one) is a widely used antidepressant drug.[4] Its clinical success has prompted additional investigations. Trazodone has medium to high affinity for several serotonin receptors, in particular $5HT_{2A}$ and the α_1 adrenergic receptor.

Some of the molecules related to trazodone that have been studied[5] have been used for human therapy, e.g., etoperidone[6] and nefazodone.[7] These trazodone analogues are characterized by the same fragment A, with two distinct basic nitrogen atoms: one anilinic (N_4) and the other aliphatic (N_1).

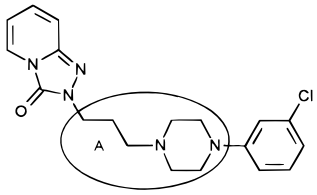
This paper describes the synthesis and properties of a novel series of trazodone analogues (**2a**−**l**) (Table 1) in which the alkylpiperazine moiety (fragment A) has been modified in several ways, while the triazolopyridine and 3-chlorophenyl moieties were held fixed. The following chemical modifications were considered: (a) a small (methyl or ethyl) alkyl group was introduced on each carbon atom of the A fragment (compounds **2a**−**g**); (b) an open chain replaced the piperazine ring (compounds **2h**−**j**); and (c) an oxo group was introduced in the piperazine ring (compounds **2k,l**).

All new molecules were tested for binding affinity to α_1 and $5HT_{2A}$ receptors, to verify how and to what

Table 1. 1,2,4-Triazolo[4,3-*a*]pyridin-3-one Derivatives **2a**−**l**



compd	R	R1	R2	R3	R4	R5
2a	CH_3	H	H	H	$-CH_2-CH_2-$	
2b	H	CH_3	H	H	$-CH_2-CH_2-$	
2c	H	H	CH_3	H	$-CH_2-CH_2-$	
2d	H	H	H	CH_3	$-CH_2-CH_2-$	
2e	H	H	C_2H_5	H	$-CH_2-CH_2-$	
2f	CH_3	H	H	CH_3	$-CH_2-CH_2-$	
2g	H	H	H	CH_3	$-C(CH_3)_2-CH_2-$	
2h	H	H	H	H	H	H
2i	H	H	H	H	CH_3	H
2j	H	H	H	H	H	CH_3
2k	H	H	H	H	$-CH_2-CO-$	
2l	H	H	H	H	$-CH(CH_3)-CO-$	



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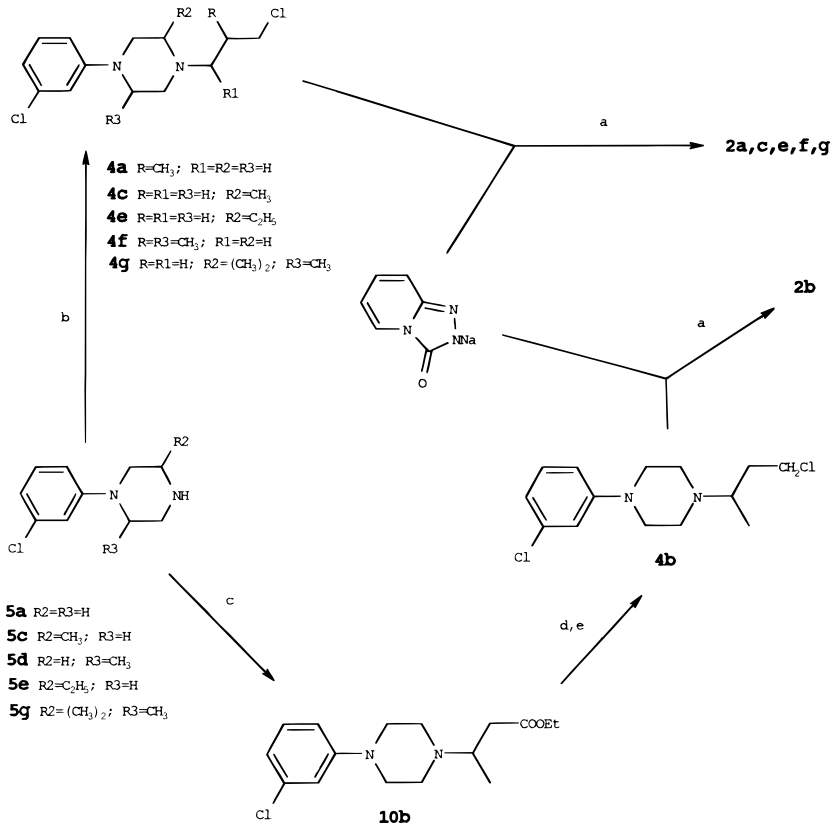
Scheme 1[a]



[a] Reagents and conditions: (a) xylene-isobutyl alcohol (10/1), reflux; (b) $ClCH_2CH(R)CH(R_1)Br$, $(CH_3)_2CO$, 0.6 N NaOH; (c) $CH_3(CH)_2COOEt$, EtOH, EtONa; (d) Red-Al, Et_2O; (e) $SOCl_2$, $CHCl_3$.

extent small chemical modifications in the A fragment can modulate the affinity for the cited receptors. The compounds that showed, in a preliminary binding profile, an affinity value for the $5HT_{2A}$ receptor similar to that of trazodone were then taken into account for further investigations.

Resolution of compound **2c**, which has a methyl substituent on the piperazine ring α to N_1, was also performed. The **2c** enantiomers were tested to evaluate the influence of the stereochemistry of the piperazine moiety on the binding affinity of the above-mentioned receptors and on the related pharmacological activities.

Computer-assisted conformational analyses were carried out on selected compounds to tentatively relate structural modifications with the modulation of binding affinity for $5HT_{2A}$ and α_1 receptors.

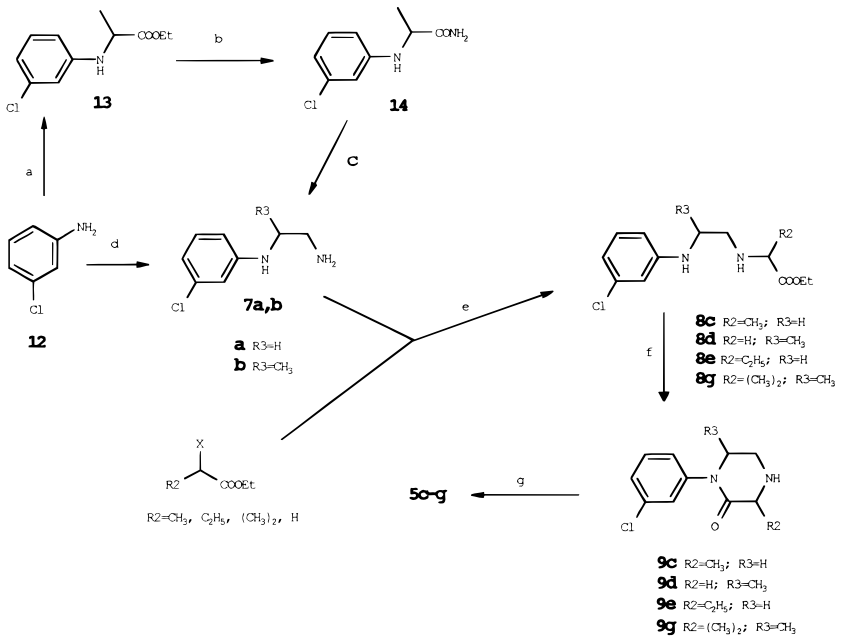
Chemistry

The general synthetic procedure for the preparation of compounds **2a**−**g**, with the exception of **2d**, is based on the N-alkylation of the sodium salt of 1,2,4-triazolo-[4,3-*a*]pyridin-3(2*H*)-one (**3**)[8] with the appropriate 1-(3-halopropyl)-4-(3-chlorophenyl)piperazine **4a**−**g** in a xylene−isobutyl alcohol solution (Scheme 1). Compound **2b** is synthesized, in a slightly different manner, by N-alkylation of the piperazine **5d** with 1-(3-chloropropyl)-1,2,4-triazolo[4,3-*a*]pyridin-3-one[9] in toluene and in the presence of equimolar triethylamine (Scheme 1).

The halopropyl derivatives **4a**−**g** are generally prepared by alkylation with 1,3-dihalopropanes of the corresponding key intermediates 1-(3-chlorophenyl)-piperazines **5a**−**g** under reaction conditions suitable to reduce the presence of bis-alkylated products. Compound **4b** is prepared by addition of ethyl crotonate to the commercially available 1-(3-chlorophenyl)piperazine (**5a**) and reduction of the obtained ester **10b** to the corresponding alcohol **11b** which, on reaction with thionyl chloride, yields the desired product (Scheme 1). A very large number of arylpiperazines have been described. Many of them have been investigated for their pharmacological activities, but relatively few C-substituted derivatives on the piperazine ring have been reported.[10]

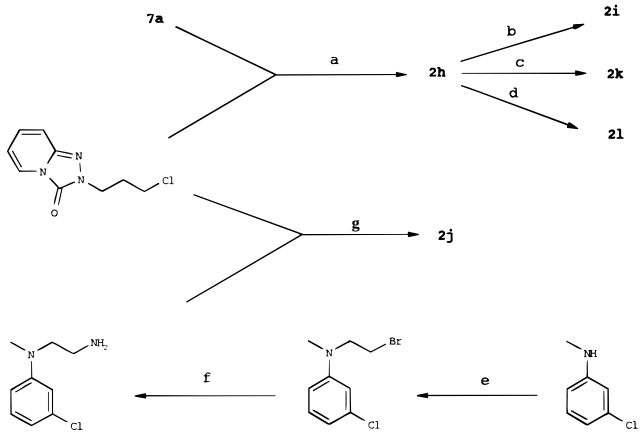
The synthesis of the new 1-(3-chlorophenyl)piperazines **5c**−**g** is achieved by reduction of the corresponding 1-(3-chlorophenyl)piperazinones **9c**−**g** with $LiAlH_4$ or, as an alternative, with $NaBH_4/AlCl_3$ in diglyme. Compounds **9c**,**e** are obtained starting from the common intermediate *N*-(3-chlorophenyl)-1,2-ethanediamine (**7a**)[11] which is synthesized through a procedure suitable to industrial scale-up, by reaction of 3-chloroaniline (**12**) and 2-aminoethanol in an aqueous solution of hydrobromic acid. Compounds **9d,g** are prepared starting from *N*-(3-chlorophenyl)-1-methyl-1,2-ethanediamine (**7b**), synthesized by standard procedures (Scheme 2). After alkylation of **7a** or **7b** with the appropriate haloacetate, the obtained diamino esters **8c**−**g** are cyclized to piperazinones **9c**−**g** directly or through the corresponding acyl chlorides (Scheme 2). The known procedures for the syntheses of piperazinones from diamino esters require thermal or basic cyclization with severe reaction conditions. A new acid aqueous cyclization of the diamino esters **8** that utilizes milder reaction conditions and

Scheme 2[a]



[a] Reagents and conditions: (a) $BrCH(CH_3)CO_2C_2H_5$, $N(C_2H_5)_3$; (b) MeOH, MeONa, NH_3; (c) $LiAlH_4$, Et_2O; (d) HBr, $OH(CH_2)_2NH_2$; (e) toluene, $N(C_2H_5)_3$; (f) 2 N HCl; (g) $LiAlH_4$, Et_2O.

Scheme 3[a]



[a] Reagents and conditions: (a) $(C_2H_5)_3N$, 90 °C, 20 h; (b) C_6H_6, 1.07 N NaOH, $(CH_3)_2SO_4$, t.a., 20 h; (c) $ClCH_2COOEt$, $(C_2H_5)_3N$, 90 °C, $C_6H_5CH_3$, NaH; (d) $BrCH(CH_3)COOEt$, $(C_2H_5)_3N$, 90 °C, 2 h, $C_6H_5CH_3$, NaH; (e) $Br(CH_2)_2Br$, 120 °C, 18 h; (f) 1,3-isoindolinedione, DMF, 80 °C, 5 h, concd HCl; (g) $(C_2H_5)_3N$, 90 °C, 18 h.

provides better yields of compound **9** was recently described.[12]

Compounds **2h,j**, which have an ethylenediamine chain instead of a piperazine ring, are synthesized by alkylation of the diamine **7a** and, respectively, *N*-(3-chlorophenyl)-*N*-methyl-1,2-ethanediamine (**7c**) with 1-(3-chloropropyl)-1,2,4-triazolo[4,3-*a*]pyridin-3-one (Scheme 3). Compound **7c** is prepared according to Gabriel's method[13] by reaction of *N*-(2-bromoethyl)-*N*-methyl-3-chloroaniline with potassium phthalimide and subsequent deprotection of the amine group by hydrazinolysis. Compound **2i** is prepared by alkylation of compound **2h** with dimethyl sulfate in alkaline aqueous medium, while compounds **2k,l** are obtained by alkylation of compound **2h** with ethyl chloroacetate and ethyl 2-bromopropionate, respectively, followed by cyclization of the obtained aminoesters intermediates (Scheme 3).

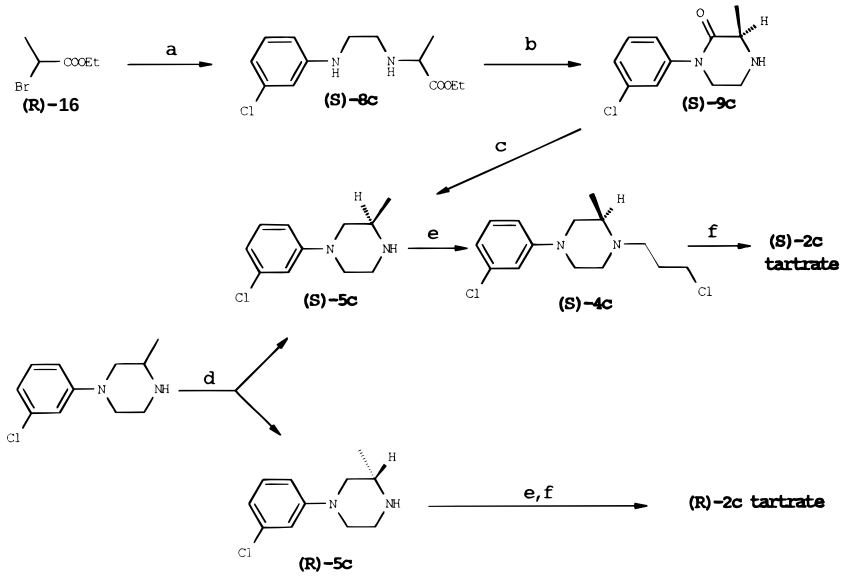
The two enantiomers (***S***)-**2c** and (***R***)-**2c** are obtained by resolution of 2-[3-[4-(3-chlorophenyl)-2-methylpiperazin-1-yl]propyl]-1,2,4-triazolo[4,3-*a*]pyridin-3-one (**2c**), according to the fractional crystallization method.[14] These compounds are also prepared by means of an enantiospecific synthesis, starting with the corresponding piperazines (***S***)-**5c** and (***R***)-**5c** which are obtained by resolution of 1-(3-chlorophenyl)-3-methylpiperazine (**5c**) with (+)-tartaric acid. The synthetic steps from (***S***)-**5c** and (***R***)-**5c** to (***S***)-**2c** and (***R***)-**2c**, respectively, are carried out with retention of configuration of all intermediates. To assign the absolute configuration to the enantiomers of the piperazine key intermediate, 1-(3-chlorophenyl)-3-methylpiperazine (***S***)-**5c** is also prepared with a total stereospecific synthesis, starting with (*S*)-ethyl lactate (**15**) as outlined in Scheme 4. Compound **15** is converted, according to literature,[15] into the corresponding (*R*)- ethyl 2-bromopropionate (**16**), which alkylates the diamine **7a** to give the amino ester (***S***)-**8c**. Both of these reactions take place with Walden inversion at the chiral C atom. Compound (***S***)-**8c** is cyclized in diluted HCl solution, and the obtained piperazinone (***S***)-**9c** is reduced by means of $NaBH_4/AlCl_3$ in diglyme to the corresponding piperazine (***S***)-**5c** without appreciable racemization and with retention of configuration.

Results and Discussion

(1) Binding Affinities and Functional Studies. The synthesized compounds **2a**−**l** were evaluated in vitro in a preliminary binding screening to assess their affinity for the receptors shown in Table 2.

Compounds **2h**−**j**, in which fragment A is an open ethylenic chain, and compounds **2k,l**, in which an oxo function is present on the piperazine moiety, showed a lack of affinity for all receptors taken into account. A rather important loss of affinity was shown by com-

Scheme 4[a]



[a] Reagents and conditions: (a) *N*-(3-chlorophenyl)-1,2-ethanediamine, toluene, $N(C_2H_5)_3$; (b) 2 N HCl; (c) diglyme, $AlCl_3$, $NaBH_4$; (d) optical resolution; (e) 6 N NaOH, acetone, $Cl(CH_2)_3Br$; (f) **1** sodium salt, xylene-isobutyl alcohol (10/1), EtOH, (+)-tartaric acid.

Table 2. Preliminary Binding Studies[a]

	percentage of inhibition at 10^{-7} M						
compd	$5HT_{2A}$	α_1	5HT-R	D_2	NE-R	H_1	σ_1
1	78[b]	49[b]	38[b]	12[b]	0	5[b]	29[b]
2a	52[b]	27[b]	4	3	0	7	34[b]
2b	65[b]	26[b]	63[b]	2	0	31[b]	58[b]
2c	69[b]	37[b]	45[b]	8[b]	2	13[b]	43[b]
2d	34[b]	25[b]	15[b]	0	0	7[b]	68[b]
2e	60[b]	44[b]	20[b]	10[b]	0	14[b]	43[b]
2f	20	7[b]	6	0	0	12[b]	65[b]
2g	40[b]	11[b]	38[b]	3[b]	0	9	81[b]
2h	4[b]	8	10[b]	3[b]	0	0	29[b]
2i	0	10	15	2	4	0	30
2j	0	12[b]	23[b]	4	0	0	65[b]
2k	5[b]	5	2	0	0	2	12
2l	0	2	0	4	0	4	9[b]

[a] The assays were carried out using methods described in the Experimental Section. [b] Data were checked with a verification screen. Differences with respect to the verification screen were less than 20% for inhibition values of 50% and over, higher than 40% for inhibition values from 0 to 50%.

Table 3. Binding Affinity for $5HT_{2A}$ and α_1 Receptors of Compounds **1** and **2a**−**e**

	IC_{50} (μM)[a]	
compd	$5HT_{2A}$ [^{3}H]ketanserin	α_1 [^{3}H]prazosin
1	0.017 (0.015−0.020)[b]	0.281 (0.174−0.455)[b]
2a	0.094 (0.060−0.147)[b]	0.531 (0.286−0.985)[b]
2b	0.017 (0.014−0.021)[b]	0.627 (0.454−0.866)[b]
2c	0.031 (0.023−0.042)[b]	0.471 (0.338−0.655)[b]
2e	0.169 (0.152−0.187)[b]	0.493 (0.372−0.653)[b]

[a] IC_{50} values were determined, using six concentrations in triplicate, as described in the Experimental Section. [b] The data in parentheses are 95% confidence intervals.

pounds **2d**,**f**,**g**, all bearing at least one methyl group on the piperazine ring in the position β to N_1. For compounds **2a**−**c**,**e**, which showed an inhibition of more than 50% at 10^{-7} M for the $5HT_2$ or α_1 receptors, the IC_{50} values were also determined for the same receptors. The results are shown in Table 3.

Upon this further investigation, all compounds showed a reduction of binding affinity to the α_1 receptor as compared to trazodone. With regard to the $5HT_{2A}$ receptor, compounds **2b**,**c** showed either the same value or a slightly lower value of IC_{50} as compared to trazodone, while compounds **2a**,**e** showed a consistent reduction.

Table 4. Comparison of Binding Affinity IC_{50}[a] and pA_2 Values[b] for Enantiomers of **2c**

	IC_{50} (nM)		pA_2	
compd	$5HT_{2A}$	α_1	rat aorta	rat vas deferens
(*S*)-**2c**	25.4 (22.1−29.4)	981 (841−1140)	8.5 ± 0.6	5.4 ± 0.7
(*R*)-**2c**	234 (80.8−378)	533 (372−764)	7.9 ± 0.7	6.8 ± 0.2

[a] See footnotes of Table 3. [b] pA_2 values were calculated as described in the Experimental Section.

To evaluate the influence of stereochemistry, the two enantiomers (***S***)-**2c** and (***R***)-**2c** of compound **2c** were prepared and IC_{50} values for $5HT_{2A}$ and α_1 receptors were determined (Table 4). The (*S*)-enantiomer showed a consistent reduction of α_1 adrenergic affinity, while the (*R*)-enantiomer showed a marked decrease in affinity to the $5HT_{2A}$ receptor. To investigate the pharmacological meaning of these results, the functional activity of the two products on the adrenergic and serotonergic systems was determined, using in vitro smooth muscle preparations. To investigate the effects of the compounds on α_1 receptors,[16] a cumulative dose−response inhibition curve of rat vas deferens contractions induced by the adrenergic agonist norepinephrine (NE) was determined. The contractile response to serotonin from rat aorta strips was used for functional studies on the serotonergic system.[17]

The results summarized in Table 4 show similar functional effects on the serotoninergic system for the two enantiomers (pA_2 values), while (*S*)-**2c** shows the lowest adrenolytic activity.

(2) Computer-Assisted Molecular Modeling. Three-dimensional molecular models were generated for trazodone (**1**) and the monomethyl derivatives **2a**−**d**. Conformational searches were carried out using the MM2 force field as implemented in SPARTAN[18] to assess the effect of the introduction of one methyl group

on the propyl chain (compounds **2a**,**b**) and, respectively, on the piperazine ring (compounds **2c,d**) with respect to trazodone.

By comparing the total number and relative energy values for all conformers of compounds **1**, and **2a,b**, respectively, it appears that compound **2a** is conformationally restricted when compared to the other two molecules. Therefore, the partial loss of affinity for $5HT_{2A}$ receptors (Table 3) can be explained by stating that the "active" conformation for that receptor is energetically less accessible to **2a** than to **1** and **2b**.

Conformational analyses on compounds **2c**,**d** indicate that the methyl substituent on the piperazine ring does not significantly alter the overall conformational space of these compounds compared to trazodone. Compound **2d**, in which the methyl group is β to N_1, shows a loss of affinity for the $5HT_{2A}$ receptor (Table 2), while **1** and **2c** show very similar binding affinities toward the same receptor. To rationalize these facts, ab initio 3-21G* calculations were performed on compound **2d** using SPARTAN. The results indicate that the additional methyl group on the piperazine ring of **2d** prefers an axial geometry by about 0.5 kcal/mol instead of the equatorial geometry found in **2c**. Therefore, based on these results, there are two alternative hypotheses to explain the loss of affinity of **2d** toward the $5HT_{2A}$ receptor. If the additional methyl group is axial, it may be responsible for steric hindrance inside the binding site cavity; however, if the same methyl group is equatorial either it or the phenyl ring—forced into an orthogonal conformation—could clash with the amino acid residues in the binding cleft.

Conclusions

Simple chemical modifications on the piperazine ring of trazodone (**1**), such as substitution with an ethylenediamine moiety or introduction of an oxo function, cause a loss of affinity toward the α_1 and $5HT_2$ receptors, as shown for compounds **2h**−**l** in preliminary binding tests. Of all compounds (**2a**−**g**) characterized by the introduction of alkyl substituents on the carbon atoms of fragment A, only **2b**,**c** retain an affinity similar to that of trazodone for the $5HT_{2A}$ receptor and a slightly reduced affinity for α_1. All the other compounds show a lower affinity for both receptors.

In general, the position of the carbon to which the methyl group is attached is the most relevant effect of chemical modifications on the binding affinity for the two selected receptors. A methyl group on a carbon atom in the β position to N_1, either on a ring (compounds **2d,f,g**) or on a linear chain (compounds **2e,a**), reduces the affinity particularly for the $5HT_{2A}$ receptor. However, a methyl group on a carbon atom in the α position to N_1 (compounds **2b,c**), although having a minor impact on receptor binding, decreases the affinity, especially for the α_1 receptor.

The (*S*)-enantiomer of **2c** exhibits an interesting balance between adrenergic and serotoninergic activity, showing a reduced adrenolytic activity in comparison to trazodone (**1**) while retaining functional effects on the serotoninergic system. Furthermore, (***S***)-**2c**, although structurally similar to **1**, includes a 2-methyl-4-(3-chlorophenyl)piperazine moiety, and as a consequence, it cannot give rise to 4-(3-chlorophenyl)piperazine (MCPP) as a metabolite, contrary to trazodone and nefazodone. However it is worth noting that there are conflicting opinions, which have not yet been completely clarified, about the relevance of this metabolite in the therapeutic activity of trazodone.[19] Therefore, (***S***)-2-[3-[4-(3-chlorophenyl)-2-methyl-1-piperazinyl]propyl]-1,2,4-triazolo-[4,3-*a*]pyridin-3-one tartrate ((***S***)-**2c**) and its potential metabolite methyl-MCPP ((***S***)-**5c**) have been selected for additional studies that will be reported in future papers.

Experimental Section

Chemistry. Melting points were determined on a Buchi apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AC 100 spectrometer. Chemical shifts (δ) are expressed in parts per million (ppm) relative to the internal standard tetramethylsilane (TMS). IR spectra were determined with a Perkin-Elmer FT-IR System 2000 spectrometer. UV spectra were obtained on a Perkin-Elmer Lamba 38 spectroemter. Elemental analyses for carbon, hydrogen, and nitrogen were determined on a Carlo Erba EA1108 elemental analyzer. The optical purity of enantiomers was determined by an HPLC method using a Chiralcel OD-R (J.T. Baker) analytical column. Optical rotation (α) of pure enantiomers was measured by a Perkin-Elmer 241 polarimeter. Silica gel flash chromatography was performed with Kieselgel 60 (230−400 mesh). Extraction solvents were dried over sodium sulfate.

General Procedure for the Alkylation of 1,2,4-Triazolo[4,3-*a*]pyridin-3(2*H*)-one (3): Compounds 2a−c,e−g. This procedure is described for the synthesis of **2a**.

2-{3-[4-(Chlorophenyl)-1-piperazinyl]-2-methylpropyl}-1,2,4-triazolo[4,3-*a*]pyridin-3(2*H*)-one Hydrochloride (2a). 1-(3-Chlorophenyl)-4-(2-methyl-3-chloropropyl)piperazine (**4a**) (43 g, 0.24 mol) was added to a stirred suspension of 1,2,4-triazolo[4,3-*a*]pyridin-3(2*H*)-one[9] (**3**) sodium salt (22,5 g, 0.16 mol) in a solution of 10:1 xylene-isobutyl alcohol (330 mL), and the reaction mixture was heated at reflux temperature for 8 h. After cooling, the solution was washed with water and evaporated under reduced pressure. The residue was solidified with a solution of 2 N HCl, then filtered, and recrystallized from water to obtain **2a** (35 g, 58% yield). Mp 196−198 °C. IR (KBr, $\nu_{C=O}$): 1710 cm^{-1}. UV (EtOH, λ_{max}): 246 (ϵ = 11 400), 310 (ϵ = 3600) nm. Anal. ($C_{20}H_{25}Cl_2N_5O$) C, H, N, Cl$^-$. As free base, ^{1}H NMR ($CDCl_3$): δ 1.1 (d, J = 7 Hz, 3H, CH_3−CH), 2.5 (m, 7H, CH- and 3CH_2), 3.1 (t, J = 5.5 Hz, 4H, 2CH_2), 4.0 (dd, 2H, CH_2), 6.3−7.3 (m, 7H, ArH), 7.7 (d, 1H, CH triazolopyridine).

Using the procedure described for compound **2a**, the following compounds were obtained (yield 40−70%) from the appropriate **4b,c,e**−**g** halo derivatives.

2-{3-[4-(3-Chlorophenyl)-1-piperazinyl]-1-methylpropyl}-1,2,4-triazolo[4,3-*a*]pyridin-3-one Dihydrochloride Monohydrate (2b). Mp: 196−199 °C. IR (KBr, $\nu_{C=O}$): 1710 cm^{-1}. UV (EtOH, λ_{max}): 245 (ϵ = 11 600), 310 (ϵ = 3690) nm. Anal. ($C_{20}H_{28}Cl_3N_5O_2$) C, H, N, Cl$^-$. As free base, ^{1}H NMR ($CDCl_3$): δ 1.1 (d, J = 7 Hz, 3H, CH_3−CH), 1.9 (m, 2H, CH_2−CH), 2.6 (m, 5H, CH- and 2CH_2), 3.1 (t, 4H, 2CH_2), 4.1 (t, J = 7 Hz, 2H, CH_2), 6.3−7.2 (m, 7H, ArH), 7.8 (d, J = 6.5 Hz, 1H, CH triazolopyridine).

2-{3-[4-(3-Chlorophenyl)-2-methyl-1-piperazinyl]propyl}-1,2,4-triazolo[4,3-*a*]pyridin-3-one Hydrochloride (2c). Mp: 191−192 °C. IR (KBr, $\nu_{C=O}$): 1710 cm^{-1}. UV (EtOH, λ_{max}): 312 (ϵ = 3540), 246 (ϵ = 10 970) nm. Anal. ($C_{20}H_{25}Cl_2N_5O$) C, H, N, Cl$^-$. As free base, ^{1}H NMR ($CDCl_3$ + DMSO): δ 1.1 (d, J = 7 Hz, 3H, CH_3−CH), 1.9−3.5 (m, 11H, aliphatic CH_2 and CH), 4.0 (t, J = 7 Hz, 2H, CH_2), 6.4−7.2 (m, 7H, ArH), 7.8 (d, J = 7 Hz, 1H, CH triazolopyridine).

2-{3-[4-(3-Chlorophenyl)-2-ethyl-1-piperazinyl]propyl}-1,2,4-triazolo[4,3-*a*]pyridin-3-one Hydrochloride (2e). Mp: 180−182 °C. IR (KBr, $\nu_{C=O}$): 1710 cm^{-1}. UV (EtOH, λ_{max}): 323 (ϵ = 3450), 252 (ϵ = 14000) nm. Anal. ($C_{21}H_{27}Cl_2N_5O$) C, H, N, Cl$^-$. As free base, ^{1}H NMR (D_2O): δ 1.1 (t, J = 6.5 Hz, 3H, CH_3−CH_2), 1.6−3.9 (m, 13H, CH_2 and CH), 4.2 (t, J

= 7 Hz, 2H, CH_2), 6.6−7.5 (m, 7H, ArH), 7.9 (d, J = 7 Hz, 1H, CH triazolopyridine).

2-{3-[4-(3-Chlorophenyl)-2-methyl-1-piperazinyl]-2-methylpropyl}-1,2,4-triazolo[4,3-*a*]pyridin-3-one maleate (2f). The reaction mixture from the alkylation of **3** sodium salt with **4f** was worked up as usual, and the raw residue was purified by flash chromatography, eluting with 1:1 hexane/EtOAc. The base thus obtained was dissolved in absolute ethanol, and a solution of equimolar maleic acid was then added to obtain **2f**, which was recrystallized from absolute ethanol. Mp 148−149 °C. UV (EtOH, λ_{max}): 308 (ϵ = 3550), 257 (ϵ = 16 300) nm. Anal. ($C_{25}H_{30}ClN_5O_5$) C, H, N. As free base ^{1}H NMR ($CDCl_3$): due to the presence of two chiral centers, the compound shows all superimposed figures at δ 1.05 (6H, $2CH_3$−CH), 2.1−3.2, (9H, aliphatic), 3.6−4.3 (3H, CH and CH_2), 6.4−7.3 (7H, ArH), 7.8 (1H, CH triazolopyridine).

2-{3-[4-(3-Chlorophenyl)-2,2,3-trimethyl-1-piperazinyl]-propyl}-1,2,4-triazolo[4,3-*a*]pyridin-3-one Hydrochloride Monohydrate (2g). Mp: 205−206 °C. IR (KBr, $\nu_{C=O}$) 1710 cm^{-1}. UV (EtOH, λ_{max}): 312 (ϵ = 3470), 259 (ϵ = 14 900) nm. Anal. ($C_{22}H_{31}Cl_2N_5O_2$) C, H, N, Cl^-. As free base, ^{1}H NMR ($CDCl_3$): δ 1.0 (d, 3H, J = 6.5 Hz, CH_3−CH), 1.6 (d, J = 7 Hz, 6H, $2CH_3$−C), 2.3−4.4 (m, 11H, aliphatic), 6.5−7.4 (m, 7H, Ar−H), 7.7 (d, J = 7 Hz, 1H, CH triazolopyridine). UV (EtOH, λ_{max}): 312 (ϵ = 3470), 259 (ϵ = 14 900) nm. IR (KBr, $\nu_{C=O}$): 1710 cm^{-1}.

Compound **2d** was prepared in an alternative procedure as follows.

2-{3-[4-(3-Chlorophenyl)-3-methyl-1-piperazinyl]propyl}-1,2,4-triazolo[4,3-*a*]pyridin-3-one Hydrochloride (2d). A solution of 1-(3-chlorophenyl)-2-methylpiperazine (**5d**)[20] (6.1 g, 0.029 mol), 2-(3-chloropropyl)-1,2,4-triazolo[4,3-*a*]pyridin-3-one (6.1 g, 0.029 mol), and triethylamine (2.9 g, 0.029 mol) in toluene (100 mL) was refluxed for 18 h. The reaction mixture was washed with water and evaporated under reduced pressure. The remaining residue was purified by flash chromatography (8:2 hexane/EtOAc). The obtained base was transformed into the corresponding hydrochloride which was recrystallized from absolute ethanol to obtain **2d** (5 g, 41% yield). Mp: 179−180 °C. IR (KBr, $\nu_{C=O}$): 1705 cm^{-1}. UV (H_2O, λ_{max}): 249 (ϵ = 8800), 311 (ϵ = 3800) nm. Anal. ($C_{20}H_{25}Cl_2N_5O$) C, H, N, Cl^-. As free base, ^{1}H NMR ($CDCl_3$): δ 1.04 (d, 3H, J = 7 Hz, CH_3−CH), 1.8−3.2 (m, 10H, CH_2), 3.4−3.9 (m, 1H, CH), 4.1 (t, J = 6 Hz, 2H, CH_2), 6.4−7.3 (m, 7H, ArH), 7.7 (d, J = 7 Hz, 1H, CH triazolopyridine).

General Procedure for the Synthesis of Intermediates (Haloalkyl)-3-(chlorophenyl)piperazines 4a,c,e−g. The compounds **4a,c,f,g** were prepared, starting with appropriate dihalopropanes and piperazines, utilizing the same procedure described for **4e.**

4-(3-Chlorophenyl)-1-(3-chloropropyl)-2-ethylpiperazine (4e). 1-(3-Chlorophenyl)-3-ethylpiperazine (**5e**) (6.3 g, 0.028 mol) and 1-bromo-3-chloropropane (6.6 g, 0.042 mol) were added dropwise to a stirred solution of 0.6 N NaOH (10 mL) and acetone (25 mL) at 0 °C. After 48 h at room temperature, under stirring, and 1 h at 50 °C, the reaction mixture was diluted with toluene (30 mL), washed with aqueous 1% HCl (2 × 10 mL), and dried, and the solvent was evaporated under reduced pressure. After purification by flash chromatography eluting with EtOAc, the obtained colorless oil (3.6 g, 45% yield) was used directly in the following step. ^{1}H NMR ($CDCl_3$): δ 1.0 (t, 3H, J = 7.2 Hz, CH_3), 1.1−2.1 (m, 4H, $2CH_2$), 2.3−3.4 (m, 9H, $4CH_2$ and CH), 3.6 (t, 2H, J = 6.5 Hz, CH_2−Cl), 6.7 (m, 3H, ArH), 7.1 (t, 1H, J = 8 Hz, ArH). Anal. ($C_{15}H_{22}Cl_2N_2$) C, H, N.

4-(3-Chlorophenyl)-1-(3-chloro-2-methylpropyl)-3-methylpiperazine (4f). As a colorless oil, purified by flash chromatography eluting with EtOAc in 77% yield. ^{1}H NMR ($CDCl_3$): δ 1.05 (d, d, 6H, J = 7.4, 7.3 Hz, $2CH_3$−CH), 1.9−3.4 (m, 9H, CH_2 and CH), 3.6 (m, 2H, CH_2−Cl), 3.9 (m, 1H, CH−CH_3), 6.7 (m, 3H, ArH), 7.1 (t, 1H, J = 8 Hz, ArH). Anal. ($C_{15}H_{22}Cl_2N_2$) C, H, N.

4-(3-Chlorophenyl)-1-(3-chloropropyl)-2,2,3-trimethylpiperazine (4g). As a colorless oil. Bp: 200 °C (0.4 mmHg), 43% yield. ^{1}H NMR ($CDCl_3$): δ 1.08 (d, s, s, 9H, J = 6.5, CH_3−CH and $2CH_3$−C), 1.75−2.9 (m, 6H, $3CH_2$), 2.9 (s, 2H, CH_2), 3.6 (t, 2H, J = 6.9 Hz, CH_2−Cl), 3.9 (m, 1H, CH−CH_3), 6.7 (m, 3H, ArH), 7.1 (t, 1H, J = 8 Hz, ArH). Anal. ($C_{16}H_{24}Cl_2N_2$) C, H, N.

4-(3-Chlorophenyl)-1-(3-chloro-2-methylpropyl)piperazine (4a). As a colorless oil, purified by flash chromatography (1:1 hexane/EtOAc) in 57% yield. ^{1}H NMR ($CDCl_3$): δ 1.02 (d, 3H, J = 7 Hz, CH_3−CH), 1.75−2.65 (m, 7H, CH_2 and CH), 3.15 (t, 4H, J = 6.5 Hz, $2CH_2$), 3.6 (m, 2H, CH_2−Cl), 6.7 (m, 3H, ArH), 7.1 (t, 1H, J = 8 Hz, ArH). Anal. ($C_{14}H_{20}Cl_2N_2$) C, H, N. As HCl salt, mp: 178−179 °C.

4-(3-Chlorophenyl)-1-(3-chloropropyl)-2-methylpiperazine (4c). As a colorless oil, in 87% yield. ^{1}H NMR ($CDCl_3$): δ 1.1 (d, 3H, J = 7 Hz, CH_3−CH), 1.9 (q, 2H, J = 7.1 Hz, CH_2), 2.1−3.4 (m, 9H, CH and $4CH_2$), 3.4 (m, 2H, CH_2), 3.6 (t, 2H, J = 7.1 Hz, CH_2−Cl), 6.7 (m, 3H, ArH), 7.1 (m, 1H, ArH). Anal. ($C_{14}H_{20}Cl_2N_2$) C, H, N. As 2HCl salt, mp: 174−176 °C dec.

4-(3-Chlorophenyl)-1-(3-chloro-1-methylpropyl)piperazine (4b). A solution of $SOCl_2$ (15 mL, 0.20 mol) in $CHCl_3$ (50 mL) was added dropwise, under stirring and at reflux temperature, to a solution of 4-(3-chlorophenyl)-1-(3-hydroxy-1-methylpropyl)piperazine (**11b**) (45 g, 0.17 mol) in $CHCl_3$ (200 mL). After 1 h at reflux temperature, the reaction was evaporated under reduced pressure, and the residue was suspended in 2 N NaOH (150 mL) and extracted with diethyl ether. After evaporation of the solvent, the colorless oil obtained (39 g, 82% yield) was used in the following step without further purification. ^{1}H NMR ($CDCl_3$): δ 1.0 (d, 3H, J = 7 Hz, CH_3−CH), 1.8 (m, 2H, CH_2), 2.4−3.1 (m, 5H, CH and $2CH_2$), 3.15 (m, 4H, $2CH_2$), 3.6 (m, 2H, CH_2−Cl), 6.7 (m, 3H, ArH), 7.1 (t, 1H, J = 8 Hz, ArH). Anal. ($C_{14}H_{20}Cl_2N_2$) C, H, N. As 2HCl salt, mp: 160−162 °C dec.

4-(3-Chlorophenyl)-1-(3-hydroxy-1-methylpropyl)piperazine (11b). A solution of the ethyl ester of 3-[4-(3-chlorophenyl)-1-piperazinyl]-3-methylbutanoic acid (**10b**) (49 g, 0.16 mol) in diethyl ether (200 mL) was added dropwise at room temperature to a stirred solution of Red-Al (65 wt % solution of sodium bis(2-methoxyethoxy)aluminum hydride in toluene) (60 mL) in diethyl ether (300 mL). After 2 h at room temperature, the reaction mixture was cooled with ice, and 2 N NaOH solution (80 mL) was added. The organic layer was separated, washed with water, and dried, and the solvent was evaporated under reduced pressure. The residue was recrystallized from hexane to obtain **11b** (40 g, 95% yield). Mp: 86−87 °C. ^{1}H NMR ($CDCl_3$): δ 1.02 (d, 3H, J = 8 Hz, CH_3−CH), 1.3−2.15 (m, 2H, CH_2), 2.4−3.4 (m, 9H, $4CH_2$ and CH), 3.82 (m, 2H, CH_2−OH), 6.7 (m, 3H, ArH), 7.1 (t, 1H, J = 8 Hz, ArH). Anal. ($C_{14}H_{21}ClN_2O$) C, H, N.

Ethyl Ester of 3-[4-(3-chlorophenyl)-1-piperazinyl]-3-methylbutanoic Acid Hydrochloride (10b). 1-(3-Chlorophenyl)piperazine (**5a)** (100 g, 0.5 mol) and ethyl crotonate (60.6 g, 0.53 mol) were added at 60 °C to a stirred 0.04 M solution of EtONa in EtOH (100 mL). After 2 h the reaction mixture was poured into cooled water and extracted with diethyl ether, and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (1:1 hexane/EtOAc) to give **10b** (70 g, 43% yield). As HCl salt, mp: 179−180 °C. ^{1}H NMR (D_2O): δ 1.4 (m, 6H, $2CH_3$), 2.7−4.1 (m, 11H, CH and $5CH_2$), 4.3 (q, 2H, CH_2−CH_3), 6.9−7.5 (m, 4H, ArH). Anal. ($C_{16}H_{24}Cl_2N_2O_2$) C, H, N, Cl^-.

General Procedure for the Synthesis of 1-(3-Chlorophenyl)piperazines 5c,d,e,g. The compounds **5d,e,g** were prepared with the same procedure as described for **5c**, starting with the corresponding piperazinones **9c,d,e,g** as free bases.

1-(3-Chlorophenyl)-3-methylpiperazine hydrochloride (5c). (a) A solution of piperazinone **9c** as free base (33.7 g, 0.15 mol) in 450 mL of diethyl ether was added dropwise, to keep a light reflux (2.5 h), to a suspension of $LiAlH_4$ (11 g, 0.3 mol) in diethyl ether (470 mL). After 3 h at reflux temperature, the reaction mixture was cooled with ice and the metal hydride excess was decomposed by adding dropwise: H_2O (15 mL), 2 N NaOH (15 mL), and H_2O (30 mL). After stirring for 30 min

at room temperature, the filtered solution was evaporated under reduced pressure to obtain **5c** as free base (25.8 g, 82% yield). Bp: 152−153 °C (0.9 mmHg). ^{1}H NMR ($CDCl_3$): δ 1.1 (d, J = 6 Hz, 3H, CH_3−CH), 1.5 (s, 1H, NH), 2.2−3.6 (m, 7H, CH_2 and CH), 6.6−7.2 (m, 4H, ArH). As HCl salt, mp: 181−182 °C. ^{1}H NMR (D_2O): δ 1.36 (d, J = 6 Hz, 3H, CH_3), 2.8−3.8 (m, 7H, CH and CH_2), 6.8−7.4 (m, 4H, ArH). Anal. ($C_{11}H_{16}Cl_2N_2$) C, H, N, Cl^-.

(b) While mantaining a nitrogen atmosphere and keeping the reaction temperature under 50 °C, a solution of **9c** free base (4.9 g, 0.022 mol) and $NaBH_4$ (2.5 g, 0.066 mol) in diglyme (70 mL) was added dropwise to a suspension of $AlCl_3$ (2.9 g, 0.022 mol) in diglyme (10 mL). The reaction mixture was stirred for 1 h at room temperature, then poured into a mixture of ice (150 g) and 37% HCl solution (32 mL), and stirred for an additional 12 h. After being washed with diethyl ether (100 mL), the aqueous solution was basified with 5 N NaOH and then extracted with diethyl ether. The organic solution was evaporated to obtain pure **5c** as free base (3.25 g, 72% yield).

1-(3-Chlorophenyl)-2-methylpiperazine Hydrochloride (5d).[20] The free base was obtained in 58% yield, as an oil. Bp: 112−113 °C (0.4 mmHg). ^{1}H NMR ($CDCl_3$): δ 1.1 (d, J = 6 Hz, 3H, CH_3−CH), 1.6 (s, 1H, NH), 2.7−3.2 (m, 6H, $3CH_2$), 3.7 (m, 1H, CH), 6.7−7.2 (m, 4H, ArH). As HCl salt, mp: 172−174 °C. ^{1}H NMR (D_2O): δ 1.2 (d, J = 7 Hz, 3H, CH_3), 3.4−4.0 (m, 6H, $3CH_2$), 4.1−4.4 (m, 1H, CH), 7.4−7.7 (m, 4H, ArH). Anal. ($C_{11}H_{16}Cl_2N_2$) Cl^-.

1-(3-Chlorophenyl)-3-ethylpiperazine Hydrochloride (5e). Yield: 40%. Mp: 183−184 °C. ^{1}H NMR (D_2O): δ 1.03 (t, J = 7 Hz, 3H, CH_3−CH_2), 1.64−1.79 (m, 2H, CH_2), 2.76−3.75 (m, 7H, $3CH_2$ and CH), 6.90−7.37 (m, 4H, ArH). Anal. ($C_{12}H_{18}Cl_2N_2$) C, H, N, Cl^-.

1-(3-Chlorophenyl)-2,5,5-trimethylpiperazine Hydrochloride (5g). Yield: 45%. Mp: 181−183 °C. ^{1}H NMR (D_2O): δ 1.06 (d, J = 6 Hz, 3H, CH_3−CH), 1.37 (s, 3H, CH_3−C), 1.50 (s, 3H, CH_3−C), 3.01−3.42 (m, 4H, $2CH_2$), 3.90 (m, 1H, CH), 6.67−7.34 (m, 4H, ArH). Anal. ($C_{13}H_{20}Cl_2N_2$) C, H, N, Cl^-.

General Procedure for the Synthesis of 1-(3-Chlorophenyl)piperazinones 9c−e,g. The compounds **9c**,**d** were prepared by cyclocondensation of suitable amino esters **8c,d**. Compounds **9e**,**g** were prepared from amino acids **8e**,**g** by cyclocondensation of the corresponding acid chlorides.

1-(3-Chlorophenyl)-3-methylpiperazin-2-one Hydrochloride (9c). A suspension of the ethyl ester of *N*-[2-(3-chlorobenzenamino)ethyl]alanine (**8c**) (55.2 g, 0.2 mol) in 2 N HCl solution was heated at reflux temperature for 5 h. After cooling, K_2CO_3 (110.4 g, 0.8 mol) was added and the oil was extracted with dichloromethane (3 × 100 mL) to obtain **9c** as free base (33.1 g, 73% yield). Bp: 180−182 °C (0.4 mmHg). ^{1}H NMR ($CDCl_3$): δ 1.40 (d, J = 6 Hz, 3H, CH_3−CH), 1.90 (s, 1H, NH), 3.0−3.95 (m, 5H, $2CH_2$ and CH), 7.1−7.5 (m, 4H, ArH). As HCl salt, mp: 181−183 °C. Anal. ($C_{11}H_{14}Cl_2N_2O$) Cl^-.

1-(3-Chlorophenyl)-2-methylpiperazin-6-one (9d). Following the same procedure described for **9c**, an oil was obtained in 52% yield. ^{1}H NMR ($CDCl_3$): δ 1.09 (d, J = 6 Hz, 3H, CH_3−CH), 2.09 (s, 1H, NH), 2.94−3.28 (m, 2H, CH_2), 3.65 (s, 2H, CH_2−CO), 3.75−4.05 (m, 1H, CH), 7.02−7.45 (m, 4H, ArH). Anal. ($C_{11}H_{13}ClN_2O$) C, H, N.

1-(3-Chlorophenyl)-3-ethylpiperazin-2-one Hydrochloride (9e). $SOCl_2$ (4.2 mL, 0.058 mol) was added to a solution of *N*-[2-(3-chlorobenzamino)ethyl]aminobutyric acid (**8e**) (10 g, 0.039 mol) in $CHCl_3$ (100 mL). The reaction mixture was heated at reflux temperature for 2 h, then cooled, and evaporated. A solution of the residue in toluene (100 mL) and triethylamine (10.8 mL, 0.078 mol) was heated at 60 °C for 4 h, then cooled, and filtered; the solution evaporated to obtain **9e** as free base (6.6 g, 83.4% yield). Bp: 195−200 °C (0.3 mmHg). As HCl salt, Mp: 149−152 °C. ^{1}H NMR (DMSO): δ 1.07 (t, J = 7 Hz, 3H, CH_3), 1.67−2.30 (m, 2H, CH_2), 3.32−4.8 (m, 5H, $2CH_2$ and CH), 7.2−7.6 (m, 4H, ArH), 10.3 (s, 1H, NH). Anal. ($C_{12}H_{16}Cl_2N_2O$) C, H, N, Cl^-.

1-(3-Chlorophenyl)-2,5,5-trimethylpiperazin-6-one (9g). Following the same procedure described for **9e,** an oil was obtained. Bp: 160−162 °C (0.2 mmHg), 65% yield. ^{1}H NMR ($CDCl_3$): δ 1.05 (d, J = 7 Hz, 3H, CH_3−CH), 1.42 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 1.75 (s, 1H, NH), 2.8−3.5 (m, 2H, CH_2), 3.7−4.0 (m, 1H, CH), 6.9−7.4 (m, 4H, ArH). Anal. ($C_{13}H_{17}ClN_2O$) C, H, N.

General Procedure for the Synthesis of 1-(3-Chlorophenyl)ethanediamino Esters or Acids (8c−e,g). The compounds were prepared by alkylation with a halo ester, of the suitable benzene ethanediamines **7a**,**b**, as described for **8c**. For **8e**,**g**, the corresponding acids were isolated by hydrolysis of the reaction mixture.

Ethyl Ester of *N*-[2-(3-Chlorobenzamino)ethyl]alanine Hydrochloride (8c). At room temperature, ethyl 2-bromopropionate (52.17 g, 0.29 mol) was added dropwise to a solution of *N*-(3-chlorophenyl)ethanediamine (**7a**) (35.4 g, 0.21 mol) and triethylamine (31.5 g, 0.31 mol) in toluene (250 mL). The reaction mixture was then heated at reflux temperature for 6 h, cooled, and washed with water (2 × 100 mL), and the organic phase was separated. After extraction with 2 N HCl (3 × 80 mL), KOH (40 g) was added to the aqueous solution and the oil was extracted with toluene (3 × 75 mL) to obtain **8c** as free base (44 g, 70% yield). ^{1}H NMR ($CDCl_3$): δ 1.25 (m, 6H, $2CH_3$), 2.74−3.36 (m, 5H, $2CH_2$ and CH), 4.15 (q, J = 7 Hz, 2H, CH_2), 6.35−7.2 (m, 4H, ArH). Anal. ($C_{13}H_{19}ClN_2O_2$) C, H, N. As HCl salt, mp: 108−110 °C.

Ethyl Ester of *N*-[2-(3-chlorobenzamino)propyl]glycine (8d). From **7b**, as an oil, in 75% yield. ^{1}H NMR ($CDCl_3$): δ 1.20 (m, 6H, $2CH_3$), 1.85 (s,1H, NH), 2.70 (d, J = 7 Hz, 2H, CH_2), 3.42 (s, 2H, CH_2−CO), 3.5 (m, 1H, CH), 4.22 (q, J = 7 Hz, 2H, CH_2), 6.4−7.4 (m, 4H, ArH). Anal. ($C_{13}H_{19}ClN_2O_2$) C, H, N.

***N*-[2-(3-Chlorobenzamino)ethyl]aminobutyric Acid (8e).** From **7a**, in 53% yield. Mp: 207−208 °C. ^{1}H NMR (DMSO): δ 1.0 (t, J = 7 Hz, 3H, CH_3−CH_2), 1.92 (m, 2H, CH_2), 2.90−3.60 (m, 4H, $2CH_2$), 3.70 (t, J = 6 Hz, 1H, CH), 6.42−7.18 (m, 4H, ArH), 9.8 (s broad, 1H, COOH). Anal. ($C_{12}H_{17}ClN_2O_2$) C, H, N.

***N*-[2-(3-Chlorobenzenamino)propyl]aminoisobutyric Acid (8g).** From **7b**, in 40% yield. Mp: 205−210 °C. ^{1}H NMR (CD_3COOD): δ 1.22 (d, J = 6 Hz, 3H, CH_3−CH), 1.49 (s, 6H, $2CH_3$), 2.90−3.22 (m, 2H, CH_2), 3.62−4.03 (m, 1H, CH), 6.5−7.2 (m, 4H, ArH). Anal. ($C_{13}H_{19}ClN_2O_2$) C, H, N.

***N*-(3-Chlorophenyl)-1,2-ethanediamine (7a).**[11] At room temperature and with stirring, a 47% HBr solution (101.5 mL, 0.88 mol) was added dropwise to a mixture of 3-chloroaniline (56 g, 0.44 mol) and ethanolamine (26.6 g, 0.44 mol). Water was removed by heating the solution to 168−171 °C (1 h). The reaction mixture was then kept at this temperature for 6 h, cooled, diluted with H_2O (100 mL), basified with 6 N NaOH solution (180 mL) and stirred at room temperature for an additional 8 h. The oil was extracted with toluene (3 × 90 mL), the organic phase evaporated, and the residue distilled to give **7a** (40.5 g, 54.5% yield). Bp 116−121 °C (0.1 mmHg) (lit.[11] bp 118−125 °C, 0.1 mmHg).

Ethyl Ester of 2-(3-Chlorobenzamino)propanoic Acid (13). While stirring, the ethyl ester of 2-bromopropanoic acid (25 g, 0.14 mol) was added dropwise into a mixture of 3-chloroaniline (15.8 g, 0.13 mol) and triethylamine (10.1 mL, 0.25 mol). The reaction mixture was heated at 100 °C for 12 h, cooled, diluted with toluene (100 mL), and washed with H_2O. The organic phase was then evaporated at reduced pressure to obtain a residue which was distilled to give **13**[21] (24.5 g, 87% yield). Bp: 132−135 °C (0.7 mmHg). Mp: 37−38 °C. ^{1}H NMR ($CDCl_3$): δ 1.1−1.5 (m, 6H, $2CH_3$), 3.9−4.4 (m, 4H, CH, CH_2 and NH), 6.4−7.2 (m, 4H, ArH).

2-(3-Chlorobenzamino)propanamide (14). NH_3 was bubbled for 8 h into a cooled (ice−water bath) 0.05 M solution of MeONa in MeOH (200 mL) in which **13** (32 g, 0.14 mol) was dissolved. After standing at room temperature for 12 h, the reaction mixture was concentrated to one-half volume and poured into H_2O (200 mL). The precipitate was filtered and recrystallized to obtain **14 (**24 g, 89% yield). Mp: 121−122 °C. ^{1}H NMR ($CDCl_3$ + DMSO): δ 1.46 (d, J = 7 Hz, 3H, CH_3), 3.79 (m, 1H, CH), 5.12 (d, J = 5 Hz, 1H, NH), 6.4−7.2 (m, 6H, ArH and NH_2).

2-(3-Chlorobenzamino)propanamine (7b). At room temperature, a solution of **14** (10 g, 0.05 mol) in THF (100 mL) was added dropwise to a suspension of $LiAlH_4$ (6.8 g, 0.18 mol) in diethyl ether (150 mL). The reaction mixture was heated to reflux temperature and then cooled. The excess of $LiAlH_4$ was decomposed as previously described. After filtration, the organic phase was evaporated and the residue was distilled to obtain **7b** (6.7 g, 73% yield). Bp: 125−130 °C (0.5 mmHg). ^{1}H NMR ($CDCl_3$): δ 1.1 (d, s, J = 6 Hz, 5H, CH_3 and NH_2), 2.52−2.95 (m, 2H, CH_2), 3.3−3.55 (m, 1H, CH), 3.8 (br s, 1H, NH), 6.4−7.2 (m, 4H, ArH). Anal. ($C_9H_{13}ClN_2$) C, H, N.

2-(3-{[2-(3-Chloroanilino)ethyl]amino}propyl)-1,2,4-triazolo[4,3-*a*]pyridin-3-one Hydrochloride (2h). A mixture of **7a** (3.4 g, 0.02 mol), 2-(3-chloropropyl)triazolo[4,3-*a*]pyridin-3-one[9] (4.2 g, 0.02 mol), and triethylamine (20.2 g, 0.2 mol) was heated at 90 °C for 20 h, then diluted with water (10 mL), and extracted with diethyl ether (2 × 10 mL). The residue of the combined organic layers (6.9 g) was purified by flash chromatography (9:1 $CHCl_3$/MeOH) to obtain **2i** as free base (4.2 g, 61% yield). As HCl salt, mp: 189−191 °C. ^{1}H NMR (DMSO): δ 2.2−2.4 (m, 2H, CH_2), 2.9−3.2 (m, 4H, $2CH_2$), 3.2−3.6 (m, 2H, CH_2), 4.05 (t, J = 7 Hz, 2H, CH_2), 6.4 (m, 1H, NH), 6.5−7.3 (m, 7H, ArH), 7.9 (d, J = 7 Hz, 1H, CH triazolopyridine), 9.3 (broad s, 1H, NH). IR (KBr, ν_{max}): 1700, 3320 cm^{-1}. UV (H_2O, λ_{max}): 246 (ϵ = 13360), 305 (ϵ = 4700) nm. Anal. ($C_{17}H_{21}Cl_2N_5O$) C, H, N, Cl^-.

2-(3-{[2-(3-Chloroanilino)ethyl]methylamino}propyl)-1,2,4-triazolo[4,3-*a*]pyridin-3-one Hydrochloride (2i). At room temperature, compound **2h** (1.53 g, 0.004 mol) was added to a stirred mixture of benzene (10 mL) and 1.07 N NaOH (15 mL). Dimethyl sulfate (1 g, 0.008 mol) was then added dropwise; and, after 20 h at room temperature, the organic phase was separated, washed with water, and evaporated under reduced pressure. The residue (1.6 g) was purified by flash chromatography (9:1 $CHCl_3$/MeOH), and the obtained base was transformed into the corresponding hydrochloride **2i** (1.3 g, 82% yield). Mp: 160−162 °C. ^{1}H NMR (D_2O): δ 2.2−2.4 (m, 2H, CH_2), 3.1 (s, 3H, CH_3), 3.2−3.7 (m, 6H, $3CH_2$), 4.1 (t, J = 7 Hz, 2H, CH_2), 6.5−7.5 (m, 7H, ArH), 7.7 (d, J = 7 Hz, 1H, CH triazolopyridine). IR (KBr, ν_{max}): 1700, 3320 cm^{-1}. UV (H_2O, λ_{max}): 246 (ϵ = 13 000), 305 (ϵ = 4650) nm. Anal. ($C_{18}H_{23}Cl_2N_5O$) C, H, N, Cl^- .

***N*$_1$-(3-Chlorophenyl)-*N*$_1$-methyl-1,2-ethanediamine Dihydrochloride (7c). (a)** *N*-methyl-3-chloroaniline (7.01 g, 0.05 mol) was heated in 1,2-dibromoethane (46.5 g, 0.25 mol) at 120 °C for 18 h. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in water (20 mL), basified with 6 N NaOH, and extracted with diethyl ether. The obtained oil was distilled to yield 4.4 g of *N*-(2-bromoethyl)-*N*-methyl-3-chloroaniline, bp: 120−125 °C (0.5 mmHg), which was reacted with equimolar 1,3-isoindolinedione potassium salt (3.28 g) in DMF solution (30 mL). After 5 h at 80 °C, the stirred reaction mixture was poured into water and the oil was extracted with diethyl ether. The solvent was evaporated, and the residue was purified by flash chromatography (2:1 hexane/EtOAc) to yield 2.6 g of 2-[2-(*N*-methyl-3-chloroanilino)ethyl]-1,3-isoindolinedione. Mp: 86−88 °C. ^{1}H NMR ($CDCl_3$): δ 2.95 (s, 3H, CH_3), 3.5−3.95 (m, 4H, $2CH_2$), 6.4−7.1 (m, 4H, ArH), 7.55−7.9 (m, 4H, ArH).

(b) A suspension of the above-described product (10.6 g, 0.034 mol) in concentrated HCl (40 mL) and water (6 mL) was heated at reflux temperature for 10 h. The reaction mixture was cooled then filtered. The resultant aqueous solution was basified to obtain an oil which was extracted with diethyl ether. The organic phase was washed with $NaHCO_3$ solution and then evaporated to give a residue which was distilled. The fraction (3.6 g) at bp 93−95 °C was converted to the dihydrochloride salt **7c**. Mp 232−234 °C dec. Anal. ($C_9H_{15}Cl_3N_2$) Cl^-. As free base, ^{1}H NMR ($CDCl_3$): δ 1.1 (s, 2H, NH_2), 2.7−2.95 (m, 7H, $2CH_2$ and CH_3), 6.4−7.2 (m, 4H, ArH).

2-(3-{[2-(3-Chloro(methyl)anilino)ethyl]amino}propyl)-1,2,4-triazolo[4,3-*a*]pyridin-3-one Hydrochloride (2j). A mixture of 2-(3-chloropropyl)-1,2,4-triazolo[4,3-*a*]pyridin-3-one[9] (13.4 g, 0.063 mol) and **7c** as free base (11.7 g, 0.063 mol) in triethylamine (64 g, 0.63 mol) was heated at 90 °C for 18 h. The reaction mixture was diluted with water and extracted with diethyl ether to give, after removal of the solvent, a residue which was purified by flash chromatography (9:1 $CHCl_3$/MeOH). The obtained **2j** base (7.3 g, 35% yield) was converted to the hydrochloride salt. Mp 185−186 °C. ^{1}H NMR (DMSO): δ 2.0−2.35 (m, 2H, CH_2), 2.7−3.35 (m, 11H, $4CH_2$ and CH_3), 4.05 (t, J = 6 Hz, 2H, CH_2), 6.5−7.3 (m, 7H, ArH), 7.8 (d, J = 7 Hz, 1H, CH triazolopyridine), 9.3 (broad s, 1H, NH). IR (KBr, ν_{max}): 1720, 3460 cm^{-1}. UV (H_2O, λ_{max}): 246 (ϵ = 15 000), 305 (ϵ = 4800) nm. Anal. ($C_{18}H_{23}Cl_2N_5O\cdot{}^1/_2H_2O$) C, H, N.

2-{3-[4-(3-Chlorophenyl)-3-oxo-1-piperazinyl]propyl}-1,2,4-triazolo[4,3-*a*]pyridin-3-one Hydrochloride (2k). At 90 °C and with stirring, ethyl chloroacetate (1.46 g, 0.11 mol) was added dropwise to a mixture of **2h** as freebase (3.75 g, 0.011 mol) and triethylamine (2.2 g, 0.02 mol). After 2 h, the reaction mixture was poured into water and the resultant oil was extracted with diethyl ether. Removal of the solvent left a residue which was then dissolved in toluene (30 mL) in the presence of NaH (0.2 mg), and the reaction mixture was refluxed for 1 h. After being washed with water and evaporation of the organic solvent, the residue was dissolved in ethanol and converted to the hydrochloride salt (2.6 g, 62% yield). Mp 210−212 °C. ^{1}H NMR (D_2O): δ 2.3−2.7 (m, 2H, CH_2), 3.4−4.4 (m, 10H, $5CH_2$), 6.9−7.6 (m, 7H, ArH), 7.8 (d, 1H, CH triazolopyridine). IR (KBr, $\nu_{C=O}$): 1690 cm^{-1}. UV (H_2O, λ_{max}): 264 (ϵ = 3780), 316 (ϵ = 3430) nm. Anal. ($C_{19}H_{21}Cl_2N_5O_2$) C, H, N.

2-{3-[4-(3-Chlorophenyl)-2-methyl-3-oxo-1-piperazinyl]propyl}-1,2,4-triazolo[4,3-*a*]pyridin-3-one Hydrochloride (2l). Following the same procedure described for **2k**, but starting with **2h** (3.1 g, 0.009 mol) and ethyl 2-bromopropionate (2.44 g, 0.009 mol), **2l** (1.9 g, 49% yield) was obtained. Mp: 243−245 °C. ^{1}H NMR (D_2O): δ 1.7 (d, J = 8 Hz, 3H, CH_3), 2.3−2.7 (m, 2H, CH_2), 3.4−4.5 (m, 9H, $4CH_2$ and CH), 6.7−7.6 (m, 7H, ArH), 7.85 (d, 1H, CH triazolopyridine). IR (KBr, $\nu_{C=O}$): 1680, 1720 cm^{-1}. UV (H_2O, λ_{max}): 264 (ϵ = 3840), 316 (ϵ = 3600) nm. Anal. ($C_{20}H_{23}Cl_2N_5O_2$) C, H, N.

Optical Resolution of 2-{3-[4-(3-Chlorophenyl)-2-methyl-1-piperazinyl]propyl}-1,2,4-triazolo[4,3-*a*]pyridin-3-one (2c). (a) A suspension of **2c** as free base (12.5 g, 0.032 mol) and naturally occurring (+)-tartaric acid (4.8 g, 0.032 mol) in ethanol (125 mL) was heated at 60 °C until dissolution and then slowly cooled at room temperature. The precipitate was filtered and recrystallized twice from ethanol (3 × 50 mL) to yield 4.7 g of (***S***)-**2c** (+)-tartrate salt. Mp: 151−152 °C. $[\alpha]^{25}_D$ +14.2° (c = 1, methanol). Anal. ($C_{24}H_{30}ClN_5O_7$) C, H, N. After the salt was partitioned between 5% K_2CO_3 solution and $CHCl_3$, the organic layer was washed with water and evaporated to obtain (***S***)-**2c** free base (3.1 g). Mp: 63−65 °C. $[\alpha]^{25}_D$ +32° (c = 1, ethanol). As HCl salt, mp: 122−124 °C (hygroscopic).

(b) The mother liquor from the isolation of (***S***)-**2c** was concentrated to dryness and the solid partitioned between 5% K_2CO_3 solution and $CHCl_3$. The residue (5.7 g) from the organic layer was added to equimolar (−)-tartaric acid in ethanol (80 mL), and the suspension was heated at reflux temperature for 10 min. After cooling, the salt was filtered, recrystallized from water, and then recrystallized from ethanol, to yield, after decomposition of the tartrate, 3.2 g of (***R***)-**2c** free base. $[\alpha]^{25}_D$ − 28° (c = 1, ethanol).

Enantiospecific Synthesis of (*S*)-2-{3-[4-(3-Chlorophenyl)-2-methyl-1-piperazinyl]propyl}1,2,4-triazolo-[4,3-*a*]pyridin-3-one (+)-tartrate ((*S*)-2c). Following the procedure described for the racemic **2c**, but starting with the enantiomer (***S***)-**4c** (3.5 g, 0.012 mol), (***S***)-**2c** free base (4.2 g, 89% yield) was obtained. Mp: 65−66 °C. $[\alpha]^{25}_D$ +32° (c = 1, ethanol). To a solution of the described free base (4.2 g, 0.011 mol) in ethanol (50 mL) was added (+)-tartaric acid (1.63 g, 0.011 mol), and the suspension was heated at reflux temperature for 10 min. After cooling and dilution with ethanol (20 mL), the precipitate was filtered to obtain 5.4 g of (***S***)-**2c** (+)-tartrate. Mp 151−152 °C. $[\alpha]^{25}_D$ +14.2° (c = 1, methanol).

(*S*)-4-(3-Chlorophenyl)-1-(3-chloropropyl)-2-methylpiperazine ((*S*)-4c). To a stirred solution of 6 N NaOH (20 mL) and acetone (44 mL) cooled at 5 °C were added dropwise 1-bromo-3-chloropropane (8.4 g, 0.054 mol) and, afterward, (*S*)-**5c** (9.4 g, 0.045 mol). After 12 h at room temperature, the reaction mixture was diluted with toluene (50 mL) and the aqueous phase was separated. After extraction of the organic phase with 6 N HCl, the aqueous solution was basified and the oil extracted with EtOAc. The residue of the organic solvent was purified by flash chromatography eluting with EtOAc to obtain an oil (10.5 g, 83% yield), $[\alpha]^{25}_D$ +47.6° (*c* = 1, ethanol).

(*S*)-1-(3-Chlorophenyl)-3-methylpiperazine ((*S*)-5c). (a) By Optical Resolution of Racemic Piperazine 5c. A suspension of **5c** (29.1 g, 0.138 mol) and (+)-tartaric acid (21 g, 0.140 mol) in H_2O (175 mL) was heated at 60 °C until dissolution. After spontaneous cooling at room temperature for 12 h, the solid which precipitated was filtered and recrystallized from H_2O (130 mL) to obtain (*S*)-**5c** (+)-tartrate (12 g, 48% yield). Mp: 150−152 °C. The salt was suspended in 10% NaOH (30 mL) with stirring for 30 min, and the oil was extracted with dichloromethane (3 × 15 mL). The combined organic layers were evaporated to obtain (*S*)-**5c** free base as an oil (6.9 g, 98.5% yield). $[\alpha]^{25}_D$ −14.7° (*c* = 1, ethanol).

(b) By Stereospecific Synthesis. Under a nitrogen atmosphere, while stirring and mantaining a reaction temperature of less than 45 °C, a solution of $NaBH_4$ (3.42 g, 0.09 mol) and piperazinone (*S*)-**9c** (6.8 g, 0.03 mol) in diglyme (100 mL) was added dropwise to a suspension of $AlCl_3$ (3.99 g, 0.03 mol) in diglyme (14 mL). After 1 h, the reaction mixture was poured into ice (210 g) and concentrated HCl (45 mL), stirred for 14 h at room temperature, and then heated for 2 h at 50 °C; 5 N NaOH (95 mL) was added, and the oil was extracted with dichloromethane (2 × 50 mL). The residue of the combined organic layers was distilled to obtain (*S*)-**5c** as free base (4.2 g). Bp: 143−145 °C (0.4 mmHg). $[\alpha]^{25}_D$ − 14.1° (*c* = 1, ethanol).

(*R*)-1-(3-Chlorophenyl)-3-methylpiperazine ((*R*)-5c). The mother liquor from the isolation of enantiomer (*S*)-**5c**, described above, was basified with 5% K_2CO_3, and the oil was extracted with dichloromethane. Evaporation of the solvent afforded a residue (3.6 g) which was suspended in water (25 mL). Then (−)-tartaric acid (2.55 g) was added. The mixture was refluxed until dissolution and then cooled, and the salt was filtered and recrystallized from ethanol to obtain (*R*)-**5c** (−) tartrate (5.5 g). Mp 149−150 °C. The corresponding base showed $[\alpha]^{25}_D$ +14.5° (*c* = 1, ethanol).

(*R*)-2-{3-[4-(3-Chlorophenyl)-2-methyl-1-piperazinyl]-propyl}-1,2,4-triazolo[4,3-*a*]pyridin-3-one (+)-tartrate ((*R*)-2c). The compound was prepared following the same procedure described for the enantiomer (*S*)-**2c**, with retention of configuration and starting from the enantiomer (*R*)-**5c**. The (*R*)-**2c** (+)-tartrate was decomposed to give the corresponding base. $[\alpha]^{25}_D$ −25.2° (*c* = 1, toluene).

(*S*)-Ethyl Ester of *N*-[2-(3-Chlorobenzenamino)ethyl]-alanine Maleate ((*S*)-8c). Triethylamine (10.7 mL, 0.077 mol) was added dropwise to a stirred solution of **7a** (8.7 g, 0.051 mol) and (*R*)-ethyl 2-bromopropionate (**16**)[15] (9.26 g, 0.051 mol; $[\alpha]^{20}_D$ +44.3°, neat) in toluene (90 mL) at 60 °C. The reaction mixture was then refluxed for 11 h, cooled, and extracted with 2 N HCl solution. The aqueous layer was basified, and the oil was extracted with dichloromethane to yield 10 g of residue after evaporation of the solvent. Equimolar maleic acid was added to the solution of the raw (*S*)-**8c** free base (10 g) in 2-propanol (100 mL) and the mixture was heated at reflux temperature for 10 min. After cooling, the solid was filtered and recrystallized twice from 2-propanol to yield 2.5 g of (*S*)-**8c** maleate. $[\alpha]^{25}_D$ −18.1° (*c* = 1, ethanol).

(*S*)-1-(3-Chlorophenyl)-3-methylpiperazin-2-one Hydrochloride ((*S*)-9c). A solution of (*S*)-**8c** (2 g) in 2 N HCl solution (20 mL) was heated at reflux temperature for 3 h. After cooling, the reaction mixture was basified with K_2CO_3 and extracted with dichloromethane (2 × 10 mL). The residue of the organic phase was purified by flash chromatography eluting with $CHCl_3$ to yield 1.5 g of (*S*)-**9c**. $[\alpha]^{25}_D$ −50.8 (*c* = 1, ethanol).

Molecular Modeling. All molecular mechanics and quantum mechanics calculations were carried out under vacuum and on neutral species, on a Silicon Graphics Indigo R4000 workstation using the software package SPARTAN.[18] In particular, each 3D structure was optimized using the MM2 force field as implemented in the above-mentioned software package. Since corrections for conjugated systems are currently not included in this implementation, the TYPE50 keyword was invoked to assign appropriate atom types and parameters to aromatic carbons. Default values were used for all other keywords. Each time the energy convergence criterion (i.e., 0.00001 kcal/mol) was first met, a second minimization was automatically started to ensure proper convergence. Only one of two enantiomeric forms was arbitrarily chosen for molecules with one asymmetric carbon atom.

Biology: Receptor Binding. The receptors affinity was estimated at Nova Screen Laboratories[22] by the ability of the tested compounds to displace selective radioligands. The assays were carried out using the following: for $5HT_{2A}$—rat cortical membranes, [^{3}H]ketanserin (1.0 nM) as radioligand and methysergide as reference compound; for α_1—rat cortical membranes, [^{3}H]prazosin (0.5 nM) and prazosin; for 5HT-R—rat forebrain membranes, [^{3}H]citalopram (0.7 nM) and imipramine; for D_2—rat striatal membranes, [^{3}H]sulpiride (3.0 nM) and sulpiride; for NE-R—rat cortical membranes, [^{3}H]-desmethylimipramine (3.0 nM) and desipramine; for H_1—bovine cerebellar membranes, [^{3}H]pyrilamine (2.0 nM) and triprolidine; for σ_1—pig brain membranes, [^{3}H]-(+)-pentazocine (3.0 nM) and (+)-3-PPP.

In the preliminary binding assay, the results are expressed as inhibition percentage compared to results without drug (Table 2) and represent the average of duplicate tubes at each tested concentration in a single experiment. For the selected compounds (inhibition > 50% at 10^{-7} M) the binding affinities for $5HT_{2A}$ and α_1 are expressed as IC_{50} values (Tables 3 and 4), which were calculated based on three replicates at six different concentrations of the tested compounds in a single experiment.

Rat Vas Deferens. Male Sprague−Dawley rats weighing 200−300 g were used. According to Bonaccorsi[23] and Tayo,[24] isometric contractions of 3−4 different preparations of vas deferens were recorded with a Ugo Basile microdynamometer recorder. Cumulative contractile dose−response curves were obtained by a stepwise increase in concentrations of agonist (L-noradrenaline HCl; Fluka) as soon as a steady response to the preceding dose was obtained. Tested compounds were added 2 min before agonist. The pA_2 of the curves was calculated by the Schild Plot analysis.[25]

Rat Aorta Strips. Male Sprague−Dawley rats weighing 200−300 g were used. In agreement with Patil et al.,[26] isometric contractions of 3−7 different preparations of aorta strips were recorded with a Ugo Basile microdynamometer recorder. Cumulative contractile dose−response curves were obtained by stepwise increase in concentration of the agonist (serotonin creatinin sulfate; Sigma), as soon as a steady response to the preceding dose was obtained. Tested compounds were added 2 min before agonist. The pA_2 of the curves were calculated by the Schild plot analysis.[24]

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