Serotonin 5-HT_2 Receptor, Dopamine D_2 Receptor, and α_1 Adrenoceptor Antagonists. Conformationally Flexible Analogues of the Atypical Antipsychotic Sertindole

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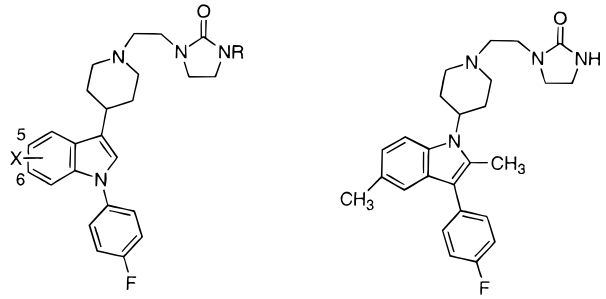
Conformationally flexible analogues of the atypical antipsychotic sertindole (1-[2-[4-[5-chloro-1-(4-fluorophenyl)-1*H*-indol-3-yl]-4-piperidinyl]ethyl]-2-imidazolidinone) were synthesized. Replacement of the 4-piperidinyl ring in sertindole by a 2-(methylamino)ethoxy group or a 2-(methylamino)ethyl group (e.g. 1-[2-[2-[5-chloro-1-(4-fluorophenyl)-1*H*-indol-3-yloxy]ethyl-methylamino]ethyl]-2-imidazolidinone and 1-[3-[[2-[5-chloro-1-(4-fluorophenyl)-1*H*-indol-3-yl]-ethyl]methylamino]propyl]-2-imidazolidinone results in binding affinities for serotonin 5-HT_{2A} and dopamine D_2 receptors, as well as α_1 adrenoceptors, which are very similar to those of sertindole. (Methylamino)alkyl groups of other chain lengths, 3-(methylamino)propyloxy groups, and 2-(methylamino)ethylsulfanyl groups do not have such properties. The capability of the 2-(methylamino)ethoxy group and the 2-(methylamino)ethyl group to replace the 4-piperidinyl ring in sertindole is reflected in molecular modeling studies using recently published receptor-interaction models for 5-HT_2 and D_2 receptors. Structure−affinity investigations concerning the substituents in the indole nucleus and the 2-imidazolidinone ring system in the 2-(methylamino)ethoxy and the 2-(methylamino)ethyl analogues of sertindole have led to high affinity serotonin 5-HT_{2A} receptor antagonists with selectivity versus dopamine D_2 receptors and α_1 adrenoceptors (e.g. 1-[2-[[2-[6-chloro-1-(4-fluorophenyl)-1*H*-indol-3-yloxy]ethyl]methylamino]-ethyl]-2-imidazolidinone and 1-[3-[[2-[6-chloro-1-(4-fluorophenyl)-1*H*-indol-3-yl]ethyl]methylamino]propyl]-2-imidazolidinone). The latter derivative has also high selectivity for 5-HT_{2A} receptors versus serotonin 5-HT_{2C} receptors. Replacement of the basic amino group by nitrogen-containing six-membered rings has led to 5-chloro-1-(4-fluorophenyl)-3-[(4-methylpiperazinyl)-ethoxy]-1*H*-indole, which has high affinity for dopamine D_2, versus low affinity for serotonin 5-HT_{2A} receptors and α_1 adrenoceptors.

Introduction

The development of a new series of 3-substituted 1-(4-fluorophenyl)-1*H*-indoles as potent, centrally acting dopamine D_2 and serotonin 5-HT_2 receptor antagonists has been reported recently.[1] Sertindole (**1a**, Chart 1) is a member of this class of compounds. In several double blind clinical studies sertindole has shown antipsychotic effects comparable to those of the classical antipsychotic haloperidol without inducing extrapyramidal side effects, indicating that sertindole is an atypical antipsychotic.[2] The atypical profile of sertindole is reflected in its pharmacological profile since it selectively blocks dopaminergic activity in the limbic brain areas in rats after chronic treatment.[3,4] *In vitro* sertindole has high affinity for serotonin 5-HT_{2A} and 5-HT_{2C} receptors, dopamine D_2 receptors, and α_1 adrenoceptors. *In vivo* the acute central antidopaminergic and peripheral antiadrenergic effects of sertindole are very weak compared to its very potent and long-lasting antiserotonergic effects.[5]

Extensive structure−activity investigations within the series of 1-(4-fluorophenyl)indoles concerning variations of the substituents in the indole nucleus, changes of the *N*-substituent in the 4-piperidinyl group, and interchange of the C-3 atom and the nitrogen atom in the indole nucleus have led to indoles with high selectivity for serotonin 5-HT_2 receptors versus dopamine D_2 receptors and α_1 adrenoceptors (e.g. Lu 26-042 (**1b**) and Lu 29-066 (**2**), Chart 1).[6,7] The pharmacological effects of these compounds have recently been described in animal models predictive of antipsychotic effects and extrapyramidal side effects.[8]

Chart 1



1a: X = 5-Cl, R = H (sertindole)
1b: X = 6-Cl, R = $CH(CH_3)_2$ (Lu 26–042)

2 (Lu 29–066)

We have recently described the development of a receptor-interaction model for serotonin 5-HT_{2A} receptor antagonists by conformational analysis using molecular mechanics (MM2(91)) and superimposition studies of serotonin 5-HT_{2A} receptor antagonists (Figure 3).[9] Comparison of this model with the receptor-interaction model for dopamine D_2 receptor antagonists developed by Liljefors and Bøgesø[10] suggests a common pharma-

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Table 1. Receptor Binding Affinitites for Reference Compounds

compd	receptor binding:[a] IC_{50} (nM) serotonin 5-HT_{2A} [^{3}H]ketanserin	dopamine D_2 [^{3}H]spiperone	adrenergic α_1 [^{3}H]prazosin
sertindole (**1a**)	0.39	4.1	3.4
Lu 26-042 (**1b**)	1.5	130	70
ritanserin	0.40	12	47
nemonapride	49	0.48	540

[a] The IC_{50} values are the logarithmic mean of at least two determinations. Two full concentration curves were measured using five concentrations of test drug in triplicate (covering three decades). SD-ratios were obtained by calculating the variance of repeated measures of ratios between the first and second IC_{50} determination for a series of 100 drugs. In cases of ratios greater than 3 × SD (99% confidence interval) extra determinations were performed and outliers were discarted. The following 95% confidence ratios (2 × SD-ratio) were calculated: 5-HT_{2A} 2.05; D_2 2.25; α_1 2.20.

cophore for serotonin 5-HT_{2A} and dopamine D_2 receptor antagonists. Antagonists with high selectivity for serotonin 5-HT_{2A} receptors versus dopamine D_2 receptors differ from unselective serotonin 5-HT_{2A} receptor antagonists by having sterical interactions with "forbidden" areas at the dopamine D_2 receptors.[9] Ismaiel *et al.* have recently discussed this model for analogues of the serotonin 5-HT_{2A} antagonists ketanserin and MDL 11,939.[11]

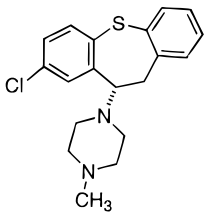
Structural comparisons of sertindole (**1a**) with tricyclic compounds having high affinity for serotonin 5-HT_{2A} and dopamine D_2 receptors (e.g. octoclothepine[9,12] see Chart 2) have previously been described using the receptor-interaction models described above.[9] These comparisons indicate that the 1-(4-fluorophenyl)-1*H*-indole part and the 4-piperidinyl group of sertindole (**1a**) interacts with similar regions of space as do the tricyclic part and the piperazinyl group, respectively, in octoclothepine. Within the series of tricyclic compounds the piperazinyl group has been replaced by conformationally flexible groups, such as the 2-aminoethoxy group in zotepine (see Chart 2).[13,14] These structural characteristics prompted us to study structure−activity relationships for analogues of sertindole (**1a**) in which the 4-piperidinyl ring is replaced by conformationally flexible groups. In the present paper we describe synthesis and structure−activity relationships within series of 5-chloro- and 6-chloro-substituted 1-(4-fluorophenyl)-1*H*-indoles substituted in the 3-position with aminoalkyl, aminoalkoxy, and (aminoalkyl)sulfanyl groups of varying chain lengths. The structure−activity relationships are discussed in relation to the recently published receptor-interaction models for dopamine D_2 and serotonin 5-HT_2 receptor antagonists.

Chemistry

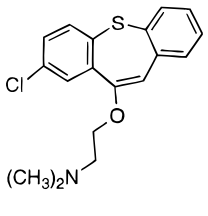
The 5-chloro- and 6-chloro-1-(4-fluorophenyl)-1*H*-indoles with aminomethyl (**5**), 2-aminoethyl (**9** and **10**), 3-aminopropyl (**14**), and 4-aminobutyl (**15**) substituents in the 3-position were prepared as outlined in Scheme 1.

The [(dimethylamino)methyl]- and [(methylamino)methyl]indoles **5a** and **5b** were prepared by reductive amination of 5-chloro-1-(4-fluorophenyl)-1*H*-indol-3-carbaldehyde (**4**) using dimethylamine and methylamine, respectively, in the presence of sodium cyanoborohydride under standard conditions.[15] The 3-indolecarbaldehyde **4** was prepared by Vilsmeier formylation[16−18] of the corresponding 3-unsubstituted indole.[1] Alkylation of [(methylamino)methyl]indole **5b** with 1-(2-chloroethyl)- and 1-(4-chlorobutyl)-2-imidazolidinone afforded **5c** and **5d**, respectively.

Chart 2



S-(+)-octoclothepin



zotepine

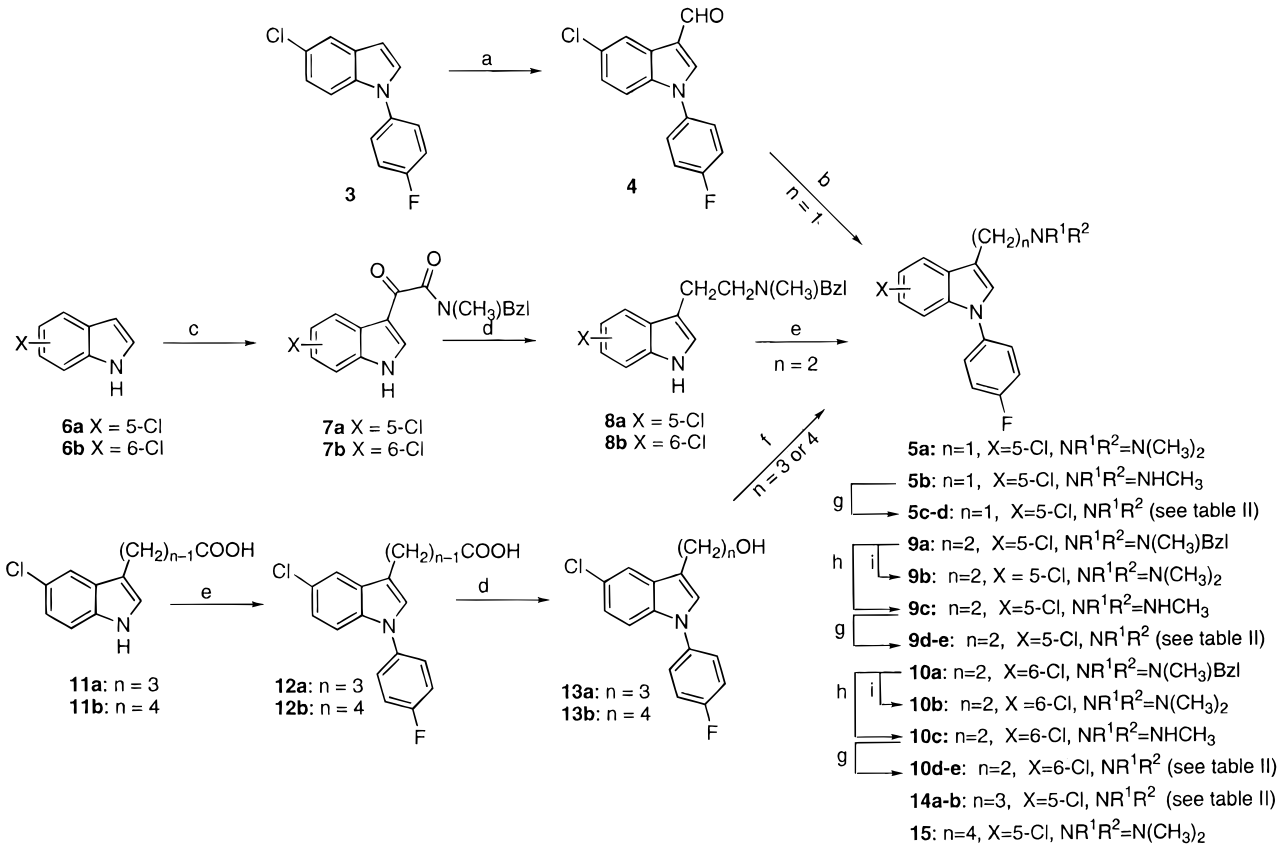
Reaction of indoles **6** with oxalyl chloride and subsequent reaction of the intermediate carboxylic acid chloride with *N*-benzylmethylamine afforded the corresponding amides **7**.[19] Reduction of the amides with lithium aluminum hydride[19] followed by arylation with 4-fluoroiodobenzene under Ullmann conditions afforded the 2-(benzylmethylamino)ethyl derivatives **9a** and **10a**.[20] Treatment of derivatives **9a** and **10a** with methyl chloroformate and subsequent hydrolysis of the intermediate carbamates afforded the corresponding 2-(methylamino)ethyl derivatives **9c** and **10c**, respectively. Reduction of the intermediate carbamates with lithium aluminum hydride afforded dimethylamino derivatives **9b** and **10b**. The (monomethylamino)ethyl derivatives **9c** and **10c** were converted to the corresponding tertiary amines **9d**,**e** and **10d**,**e** by alkylation with substituted 2-chloroethyl- or 3-chloropropyl-2-imidazolidinones as described above for the syntheses of **5c**,**d**.

The substituted 3-(1*H*-indol-3-yl)propylamines **14** and 4-(1*H*-indol-3-yl)butylamines **15** were prepared from the corresponding carboxylic acids **12a** and **12b**, respectively, by a straightforward procedure. Lithium aluminum hydride reduction of **12a** and **12b** afforded the corresponding alcohols **13a** and **13b**, respectively, which were subsequently converted to the corresponding mesylates by standard procedures. The mesylates were reacted with appropriate secondary amines resulting in substituted 3-(1*H*-indol-3-yl)propylamines **14** and the 4-(1*H*-indol-3-yl)butylamine **15**. The secondary amines used as reactants were commercially available or were prepared by standard procedures as described in the Experimental Section. Structures of the secondary amines and the amino groups in **14** and **15** are shown in Table 2.

The carboxylic acids **12a** and **12b** used as starting material for the preparation of **14** and **15**, respectively, were prepared by copper-catalyzed Ullmann arylation[20] with 4-fluoroiodobenzene of 3-(5-chloro-1*H*-indol-3-yl)-propanoic acid (**11a**) and 4-(5-chloro-1*H*-indol-3-yl)-butanoic acid (**11b**), respectively, which were prepared as follows. Ethyl 3-[5-chloro-2-(ethoxycarbonyl)-3-indolyl]propanoate and ethyl 4-[5-chloro-2-(ethoxycarbonyl)-3-indolyl]butanoate were prepared according to literature procedures.[21−24] The diesters were hydrolyzed and subsequently decarboxylated to give the desired 3-(5-chloro-1*H*-indol-3-yl)propanoic acid (**11a**) and 4-(5-chloro-1*H*-indol-3-yl)butanoic acid (**11b**), respectively, using standard reaction conditions.[25]

The 5-chloro- and 6-chloro-1-(4-fluorophenyl)-1*H*-indoles (**22**, **23**) with (2-aminoethyl)sulfanyl (**24**) and (3-

Scheme 1[a]



[a] Reaction conditions: (a) DMF, $POCl_3$; (b) $H_2NR^1R^2Cl$, $NaCNBH_3$, 5 Å molecular sieves; (c) (*i*) $(COCl)_2$; (*ii*) $HNCH_3Bzl$; (d) $LiAlH_4$; (e) 4-F-PhI, CuI, K_2CO_3; (f) (*i*) MsCl; (*ii*) HNR^1R^2, $N(CH_2CH_3)_3$; (g) ClR^2, K_2CO_3, KI; (h) (*i*) $ClCO_2CH_3$; (*ii*) HBr, H_2O; (i) (*i*) $ClCO_2CH_3$; (*ii*) $LiAlH_4$.

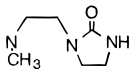
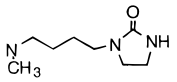
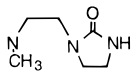
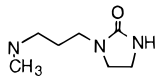
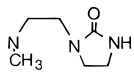
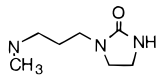
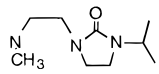
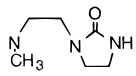
aminopropyl)oxy (**25**) substituents in the 3-position were prepared as outlined in Scheme 2.

The 1-(4-fluorophenyl)-1*H*-indoles substituted in the 3-position with 2-aminoethoxy and (2-aminoethyl)sulfanyl groups **22**, **23**, and **24** were prepared from the corresponding carboxylic acids **17a**, **17b**, and **18**, respectively, by a procedure similar to that described above for the preparation of **14** and **15**. Structures of the amino groups in **22**, **23**, and **24** are shown in Table 3. The preparation of carboxylic acids **17a**, **17b**, and **18** are described in the following.

5-Chloro- and 6-chloro-substituted 2-[1-(4-fluorophenyl)-1*H*-indol-3-yloxy]acetic acids (**17**) were prepared in a two-step procedure from corresponding methyl 1-(4-fluorophenyl)-3-hydroxy-1*H*-indole-2-carboxylates (**16**), which were prepared as described in the literature.[26,27] Alkylation of substituted methyl 1-(4-fluorophenyl)-3-hydroxy-1*H*-indole-2-carboxylates (**16**) with methyl bromoacetate gave the corresponding methyl 2-[1-(4-fluorophenyl)-2-(methoxycarbonyl)-1*H*-indol-3-yloxy]acetates.[26] These diesters were hydrolyzed and subsequently decarboxylated to give the corresponding 2-[1-(4-fluorophenyl)-1*H*-indol-3-yloxy]acetic acids (**17**).

The preparation of 2-(1*H*-indol-3-ylsulfanyl)acetic acids and acetonitriles from 1*H*-indol-3-thiol is described in the literature[28,29] and 1-unsubstituted 1*H*-indol-3-thiols are easily prepared from corresponding indoles according to literature.[30] Consequently, a possible procedure for the preparation of 2-[5-chloro-1-(4-fluorophenyl)-1*H*-indol-3-ylsulfanyl]acetic acid (**18**) is to introduce the 4-fluorophenyl group in 2-(5-chloro-1*H*-indol-3-ylsulfanyl)acetic acid, as described above for the synthesis of **12a** and **12b**. Since the starting material used for this procedure (e.g. 5-chloroindole) is very expensive, we decided to develop a more convenient synthesis for compound **18**. As recently described by Perregaard *et al.* reaction of 1-methylpiperazine with 3-indolinones, generated *in situ*, affords the corresponding 3-(4-methylpiperazinyl)indoles.[1] The reaction mechanism for this reaction is probably the formation of an intermediate hemiaminal, which is converted to the resulting product by elimination of water. In analogy, it would be expected that the reaction of 3-indolinones with alcohols and thiols results in formation of hemiacetals and hemimercaptals, respectively, which similarly eliminate water in the formation of 3-alkoxy- and 3-alkylsulfanyl indoles. Reaction of 5-chloro-2,3-dihydro-1-(4-fluorophenyl)-1*H*-indol-3-one (**27**) with 2-mercaptoacetic acid afforded 2-[5-chloro-1-(4-fluorophenyl)-1*H*-indol-3-ylsulfanyl]acetic acid (**18**). The reaction was performed by heating the reactants at reflux in toluene using a Dean−Stark apparatus with *p*-toluenesulfonic acid as a catalyst, which are standard conditions for the formation of acetals.[31] This convenient procedure for the conversion of 3-indolinones to the corresponding 3-(alkylsulfanyl)indoles and to 3-alkoxyindoles, as described below, has to our knowledge not been described previously. The 5-chloro-2,3-dihydro-1-(4-fluorophenyl)-1*H*-indol-3-one (**27**) used as starting material for these procedures was prepared by deprotection of 3-acetoxy-5-chloro-1-(4-fluorophenyl)indole (**26**) by heating in an

Table 2. Substituents and Receptor Binding Affinitites for 1-(4-Fluorophenyl)indoles **5**, **9**, **10**, **14**, and **15**

				receptor binding[a] IC$_{50}$(nM)		
	substituents[b]			serotonin 5-HT$_{2A}$	dopamine D$_2$	adrenergic α_1
compd	n	X	NR^{1}R^2	[^{3}H]ketanserin	[^{3}H]spiperone	[^{3}H]prazosin
5a	1	5-Cl	$N(CH_3)_2$	12	19	18
5c	1	5-Cl		20	22	23
5d	1	5-Cl		110	20	>100
9b	2	5-Cl	$N(CH_3)_2$	8.9	38	40
9d	2	5-Cl		5.3	25	15
9e	2	5-Cl		1.0	19	14
10b	2	6-Cl	$N(CH_3)_2$	5.5	650	130
10d	2	6-Cl		0.95	590	14
10e	2	6-Cl		1.9	400	54
10f	2	6-Cl		5.8	190	400
14a	3	5-Cl	$N(CH_3)_2$	19	42	73
14b	3	5-Cl		7.8	190	43
15	4	5-Cl	$N(CH_3)_2$	100	4800	310

[a] See footnote a in Table 1. [b] Refer to substituents in structures in Scheme 1.

aqueous solution of sodium sulfite, according to the procedure described by Nenizescu *et al.*[32] By this procedure the product was precipitated directly from the reaction mixture, which is important to avoid oxidative dimerization of the product to indigo type compounds.[33] 3-Acetoxy-5-chloro-1-(4-fluorophenyl)indole (**26**) was prepared as previously described.[1]

The *N*,*N*-dimethyl-3-aminopropyloxy-substituted compound (**25**) was prepared from the corresponding alcohol **21** by conversion to the corresponding mesylate and subsequent reaction with dimethylamine. The alcohol **21** was prepared by reaction of the 3-indolone **27** with 1,3-propanediol in the presence of *p*-toluenesulfonic acid as a catalyst.

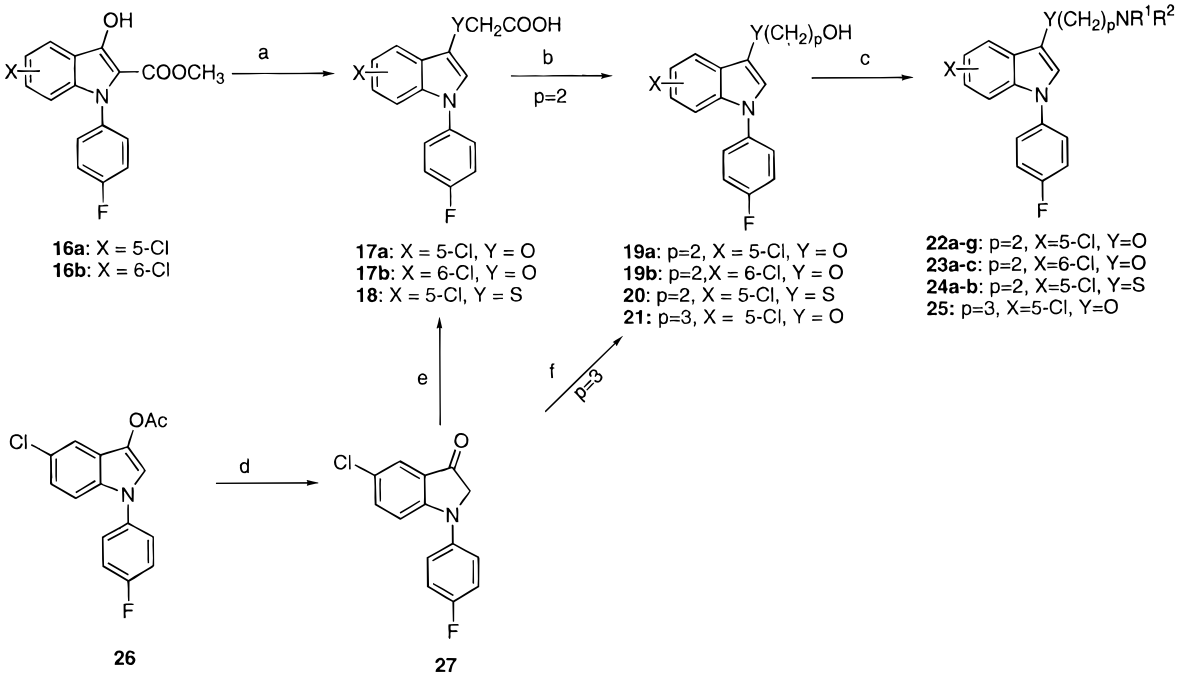
Molecular Modeling Studies

To rationalize the binding affinities obtained for the compounds prepared, molecular modeling studies of selected compounds were performed. The studies were performed on 5-chloro-1-(4-fluorophenyl)-1*H*-indoles substituted in the 3-position with (dimethylamino)methyl, 2-(dimethylamino)ethyl, 3-(dimethylamino)propyl, 2-(dimethylamino)ethoxy, and 2-(dimethylamino)ethylsulfanyl groups (compounds **5a**, **9b**, **14a**, **22a**, and **24a**, respectively, Figure 1). The dimethylamino-substituted compounds were selected as representatives for the corresponding compounds containing amino groups NR^{1}R^2 according to Tables 2 and 3.

The structures of the compounds selected are shown in Figure 1 and the flexible bonds of relevance for the present study are described by indication of the corresponding dihedral angles A (a−b−c−d), B (b−c−d−e), C (c−d−e−f), D (d−e−f−g), and H (h−i−j−k). Since the 3-substituent in the compounds included in the present study is highly flexible, a full conformational analysis by independent driving of all flexible bonds is extremely time consuming. Consequently, the conformational analyses were performed on the basis of the following assumptions.

The internal rotations about the bond connecting the 4-fluorophenyl group to the indole nucleus and about the bonds in the 3-substituent are treated independently. It seems appropriate to assume that the two groups do not interact during the internal rotations because of the large interatomic distance between the two groups. Rotation about the bond connecting the

Scheme 2[a]



[a] Reaction conditions: (a) (*i*) $BrCH_2CO_2CH_3$, K_2CO_3; (*ii*) KOH, H_2O; (*iii*) Cu, NMP; (b) $LiAlH_4$; (c) (*i*) MsCl; (*ii*) HNR^1R^2, $N(CH_2CH_3)_3$; (d) Na_2SO_3, CH_3CH_2OH, H_2O; (e) $HSCH_2CO_2H$, *p*-TSA; (f) $HOCH_2CH_2CH_2OH$, *p*-TSA.

4-fluorophenyl group to the indole nucleus results in two minimum energy conformations, as recently reported for corresponding 3-piperidinyl indoles (e.g. **1a**) corresponding to values of angle H of ±22°.[9]

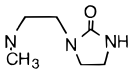
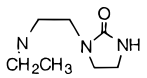
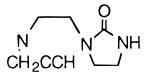
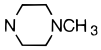
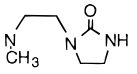
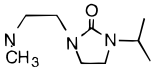
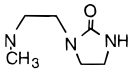
For minimum energy conformations of the compounds included in the present study it seems appropriate that the 3-substituent has a conformation close to a staggered conformation. Eclipsed conformations have calculated conformational energies of 2.7−10.0 kcal/mol.

In order to study the conformational flexibility of the bond b−c (Figure 1) in the selected compounds separately, conformational analyses were performed on 3-ethyl-, 3-methoxy-, and 3-(methylsulfanyl)-5-chloro-1-(4-fluorophenyl)-1*H*-indoles **28a**, **28b**, and **28c**, respectively. The structures of these compounds, definitions of dihedral angles for flexible bonds, and conformational energy curves for the internal rotations about the bond b−c are shown in Figure 2. The calculations show that bond b−c is highly flexible for the compounds **28a** and **28c**, which have conformational energies lower than 2 kcal/mol for values of angle A (a−b−c−d) in the interval from 45° to 180°. In contrast, the conformational energy curve for **28b** is very steep near the global minimum energy conformation. The global minimum energy conformation for **28b** was found for a value of angle A at 180°.

The conformational analyses of compounds included in the present study were performed by generating input structures with values of dihedral angles A, B, C, and D in all combinations of the following values. In order to search for minimum energy conformations in the interval from 45° to 315° the following input values for angle A were used: ±60°, ±120°, and 180°. The interval from 45° to 315° includes all low energy regions in Figure 2. In order to generate all possible staggered conformations of the 3-substituent the following values for angles B, C, and D were used: ±60° and 180°. For all input structures the value of angle H was 22° corresponding to one of the two symmetrical global minimum energy conformations of the 4-fluorophenyl group relative to the indole nucleus described above. Since some of the input structures are mirror images, the resulting 135 input structures could be reduced to 68. The structures were minimized with full energy minimization except for the dihedral angles A, B, C, and D. The partially minimized structures were subsequently minimized with full energy minimization without any conformational restrictions. Geometries of global minimum energy conformations thus obtained are described in Table 5. Compounds **14a** and **24a** have global minimum energy conformations with the 3-substituent in coiled conformations. In these conformations the dimethylamino group has strong attractive van der Waals interactions with the indole ring system. For these compounds the uncoiled conformer with lowest conformational energy is included in the table.

On the basis of conformational analyses and structural comparisons of sertindole (**1a**) and related indole derivatives an active conformation for sertindole (**1a**) has been suggested.[9] In this study the 2-(2-oxoimidazolidin-1-yl)ethyl group was replaced by a methyl group for simplicity.[9] In Figure 3 the suggested active conformation at the dopamine D_2 and serotonin 5-HT_{2A} receptors for the *N*-methyl analogue (**1a′**) of sertindole (**1a**) is superimposed on three points A, B, and C, representing the recently reported receptor-interaction model for serotonin 5-HT_{2A} receptor antagonists.[9] The three fitting points are the centers of the benzene part of the indole nucleus (A) and the 4-fluorophenyl group (B) and a point 2.8 Å from the basic nitrogen atom in the direction of the lone pair (C). The point C is assumed to simulate a receptor site hydrogen bonding with the nitrogen atom. The distances between the three fitting points in the suggested active conformation for **1a′** are calculated to be 5.3, 7.7, and 8.0 Å for distances AB, AC, and BC, respectively. To rationalize

Table 3. Substituents and Receptor Binding Affinitites for 1-(4-Fluorophenyl)indoles **22**−**25**

					receptor binding[a] IC_{50} (nM)		
	substituents[b]				serotonin 5-HT_{2A}	dopamine D_2	adrenergic α_1
compd	p	X	Y	NR^1R^2	[^{3}H]ketanserin	[^{3}H]spiperone	[^{3}H]prazosin
22a	2	5-Cl	O	$N(CH_3)_2$	4.2	2.9	17
22b	2	5-Cl	O		0.88	5.8	5.7
22c	2	5-Cl	O		18	18	12
22d	2	5-Cl	O		220	190	88
22e	2	5-Cl	O		5.9	2.3	32
22f	2	5-Cl	O		48	27	110
22g	2	5-Cl	O		100	2.4	150
23a	2	6-Cl	O	$N(CH_3)_2$	17	63	170
23b	2	6-Cl	O		2.0	200	41
23c	2	6-Cl	O		6.3	120	600
24a	2	5-Cl	S	$N(CH_3)_2$	42	140	820
24b	2	5-Cl	S		86	790	650
25	3	5-Cl	O	$N(CH_3)_2$	27	24	>100

[a] See footnote a in Table 1. [b] Refer to substituents in structures in Scheme 2.

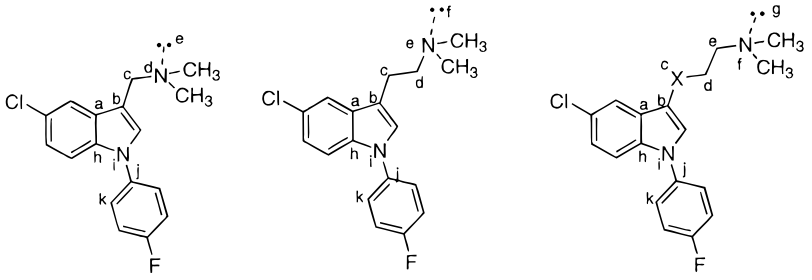


Figure 1. Structures of compounds included in the molecular modeling studies. Flexible bonds are described by indication of corresponding dihedral angles A (a−b−c−d), B (b−c−d−e), C (c−d−e−f), D (d−e−f−g), and H (h−i−j−k).

the receptor binding affinities for dopamine D_2 and serotonin 5-HT_{2A} receptors obtained for the compounds prepared in the present study, these distances are determined for low energy conformers of these compounds.

Since the conformation of the 4-fluorophenyl group relative to the indole nucleus is unaffected by the replacement of the 4-piperidinyl ring with the ring-opened side chains, the distance AB in the low energy conformers of the compounds included in the present study are similar to that of sertindole (**1a**). To study the variation of the distances AC and BC among the low energy conformers obtained in the conformational search procedure described above, these distances were determined for conformers with conformational energies lower than 2.0 kcal/mol. Conformers having distances AC and BC in the intervals 6.7−8.7 and 7.0−9.0 Å, respectively, were superimposed on the suggested receptor active conformation of sertindole (**1a**′). In Figures 4−7 are shown selected least-squares superimpo-

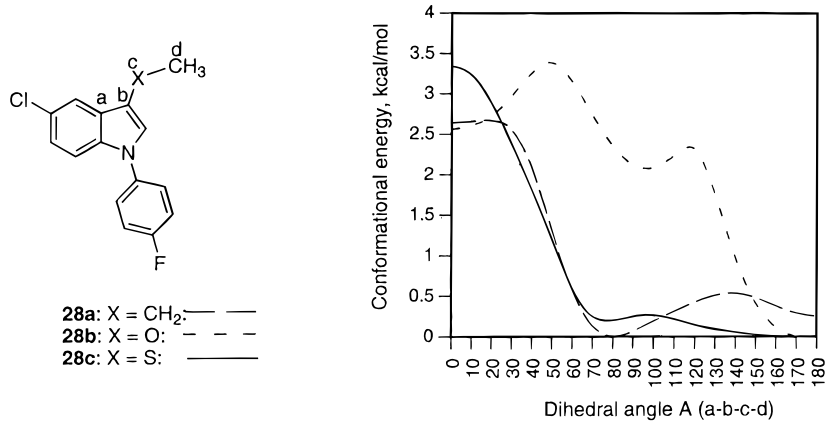


Figure 2. Definition of dihedral angle A (a−b−c−d) in 3-ethyl-, 3-methoxy-, and 3-(methylsulfanyl)-5-chloro-3-(4-fluorophenyl)-1*H*-indoles **28a**−**c** and calculated conformational energy curves for internal rotation about bond b−c.

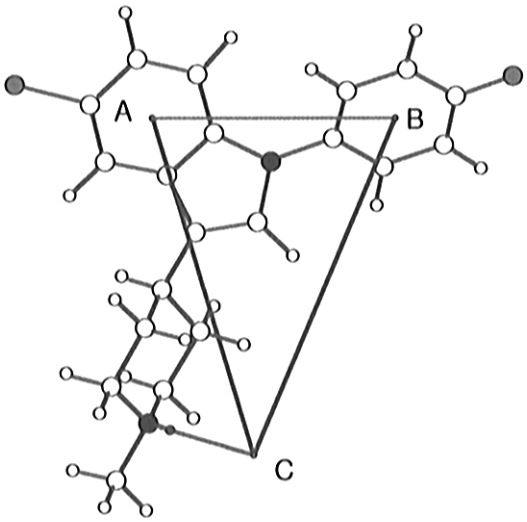


Figure 3. Superimposition of the suggested active conformation of the *N*-methyl analogue **1a′** of sertindole (**1a**) on three points (A, B, and C) representing the recently published receptor-interaction model for 5-HT_2 receptor antagonists.[9]

sitions of the molecules included in the study. Low RMS-values indicate that the relative spatial relationship of the benzene part of the indole nucleus, the 4-fluorophenyl group and the point, which is assumed to simulate a receptor site hydrogen bonding with the nitrogen atom for these conformers, are highly similar to that of the suggested active conformation for **1a′**.

Results and Discussion

The pharmacological test models have been described previously and are described in the Experimental Section referring to relevant references. Receptor binding affinities (serotonin 5-HT_{2A}, dopamine D_2, and adrenergic α_1) for reference compounds and compounds prepared in the present study are reported in Tables 1−3. In Table 1 reference compounds are included for comparison. The atypical antipsychotic sertindole (**1a**, Chart 1) and the 5-HT_2 antagonist Lu 26-042 (**1b**, Chart 1) are members of the previously described series of 1-(4-fluorophenyl)-3-(4-piperidinyl)indoles.[1,6] Ritanserin was the first centrally acting 5-HT_2 antagonist identified with considerable selectivity compared to non-5-HT receptors,[34] and nemonapride is a centrally acting, selective dopamine D_2 antagonist in respect to non-dopamine receptors.[35,36]

The substituted 3-(1*H*-indol-3-yl)propylamine **14b** (Table 2, Scheme 1) is structurally identical to sertindole (**1a**) except that the 4-piperidinyl ring is replaced by a 3-(methylamino)propyl group. This replacement results in reduced receptor binding affinities for both dopamine D_2 receptors, serotonin 5-HT_{2A} receptors, and α_1 adrenoceptors by factors of 10 to 50. Replacement of the methylene group adjacent to the indole nucleus in **14b** by a sulfur or an oxygen atom has pronounced effects on the receptor binding affinities. The former replacement (**24b**) results in reduced affinities for the three receptors by a factor of about 200, compared to sertindole (**1a**), whereas the latter replacement (**22b**) results in receptor binding affinities, which are not significantly different from those of sertindole (**1a**) (Table 3, Scheme 2).

These results are consistent with the molecular modeling studies performed for the *N*,*N*-dimethyl analogues **14a**, **22a**, and **24a** of **14b**, **22b**, and **24b**, respectively. Low RMS-values are obtained by superimposition of selected low energy conformers of the three compounds on the suggested active conformation of the *N*-methyl analogue **1a′** of sertindole (**1a**), indicating that the spatial relationships of the primary pharmacophore elements for these conformers are highly similar to that of **1a′**. In the superimposition of **22a** on the *N*-methyl analogue **1a′** of sertindole (**1a**) in Figure 5, the 2-(dimethylamino)ethoxy side chain occupies the same region of space as the right part of the 4-piperidinyl ring in **1a′** suggesting this conformation as the receptor active conformation for **22a** at the dopamine D_2 and serotonin 5-HT_2 receptors. In superimpositions of low energy conformers of **14a** and **24a** the 3-(dimethylamino)propyl and 2-(dimethylamino)ethylsulfanyl side chains occupy regions of space, which are not occupied by the 4-piperidinyl ring in **1a′** (Figures 4 and 6). This extra volume may lead to steric repulsive interactions with the receptors, and the lower receptor binding affinities obtained for these compounds may be due to such repulsive interactions. Conformers of **14a** and **22a**, in which the 3-substituent has a conformation similar to that of the suggested active conformation of **24a**, have conformational energies higher than 3.0 kcal/mol. This indicates that it is unlikely that these conformers are receptor active conformations of these compounds.

Since the 2-(methylamino)ethoxy group seems to be an excellent replacement group for the 4-piperidinyl ring in **1a**, further structure−affinity investigations were

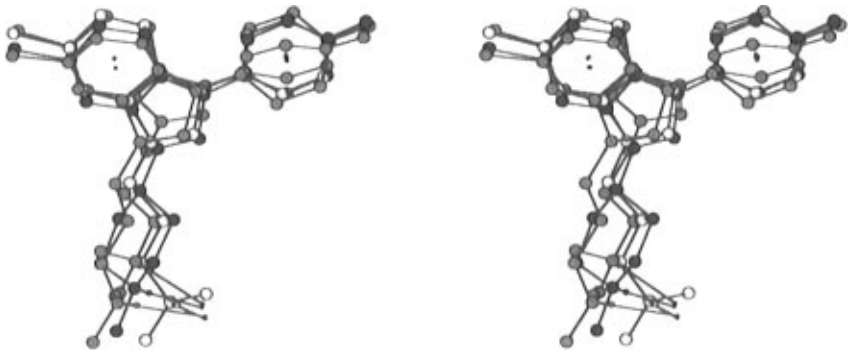


Figure 4. Least-squares superimpositions on the *N*-methyl analog of sertindole **1a′** (blue) of all conformations of **14a** having RMS values lower than 0.4 Å and conformational energy lower than 2 kcal/mol. Characteristics of the three conformers used are as follows (angle A, angle B, angle C, angle D, conformational energy, RMS value): red (−71°, −61°, 177°, 178°, 1.8 kcal/mol, 0.1 Å), yellow (175°, −179°, −172°, 58°, 1.2 kcal/mol, 0.3 Å), and green (112°, −179°, −170°, 59°, 1.2 kcal/mol, 0.2 Å). Hydrogen atoms are omitted for clarity.

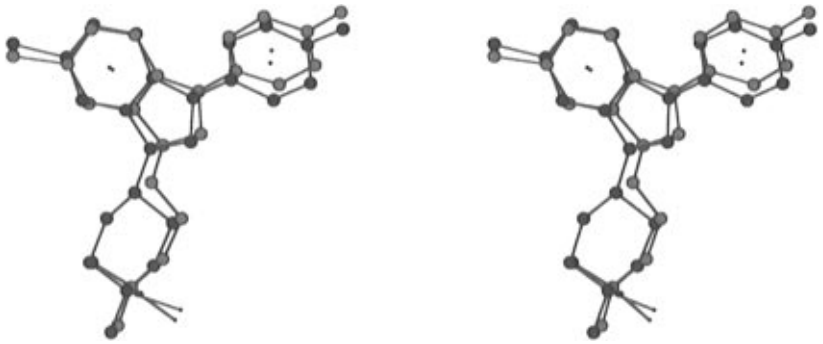


Figure 5. Least-squares superimposition of the suggested active conformation of **22a** on the *N*-methyl analog of sertindole **1a′** (blue). The conformer of **22a** used has conformational energy of 0.6 kcal/mol and the values angles A, B, C, and D are −166°, 180°, −85°, and −59°, respectively. The RMS-value obtained is 0.3 Å. Hydrogen atoms are omitted for clarity.

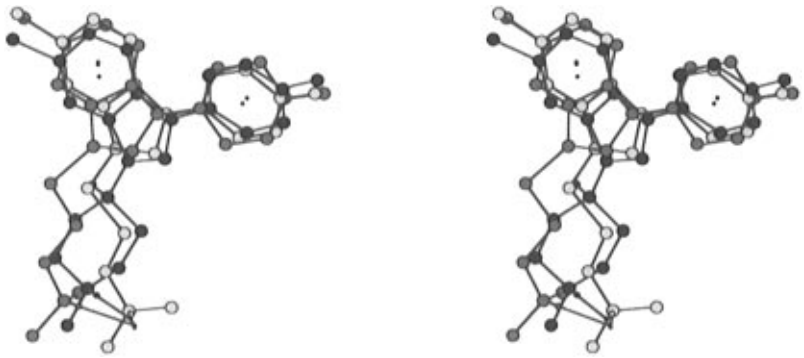


Figure 6. Least-squares superimpositions on the *N*-methyl analog of sertindole **1a′** (blue) of all conformations of **24a** having RMS values lower than 0.4 Å and conformational energy lower than 2 kcal/mol. Characteristics of the two conformers of **24a** used are as follows (angle A, angle B, angle C, angle D, conformational energy, RMS value): yellow (176°, −179°, −172°, 58°, 1.5 kcal/mol, 0.3 Å) and red (117°, −178°, −173°, 57°, 1.6 kcal/mol, 0.3 Å). Hydrogen atoms are omitted for clarity.

performed on indoles substituted by this group. Replacement of the *N*-methyl group in **22b** by other small alkyl groups, such as ethyl and propargyl (**22c** and **22d**), results in reduced affinity for the three receptors studied. The *N*,*N*-dimethyl analogue (**22a**) of **22b** has slightly increased affinity for dopamine D_2 receptors whereas the affinities for serotonin 5-HT_{2A} receptors and α_1 adrenoceptors are slightly reduced. It has previously been shown that corresponding replacement of the 2-(2-oxoimidazolidin-1-yl)ethyl substituent by a methyl group in analogues of sertindole (**1a**) only slightly influences the affinity for 5-HT_2 and D_2 receptors, whereas the *in vivo* activity is highly influenced.[1]

For compounds **22e**−**g** the *N*,*N*-dimethylamino group in **22a** is replaced by nitrogen containing six-membered rings such as 1-piperidinyl (**22e**), 4-morpholinyl (**22f**), and 4-methyl-1-piperazinyl (**22g**) rings, respectively (Table 3). In **22e** the receptor binding affinities are not significantly different from those of the *N*,*N*-dimethylamino compound **22a**, suggesting that lipophilic groups in the areas defined by the piperidinyl ring are well accommodated by the receptors studied. The 4-morpholinyl compound **22f** has reduced affinity for serotonin 5-HT_{2A} and dopamine D_2 receptors and α_1 adrenoceptors by factors of 6−10, compared to compound **22a**. Within series of dopamine D_2 receptor agonists it has been shown that β-oxygen atoms reduce the base strength of amino groups by about 1.5 pK_A units and that the effect is additive.[37] It seems that the basic amino group interacts with a carboxylic acid group at the receptors and that this interaction is essential in order to obtain receptor binding. A sufficiently high base strength of

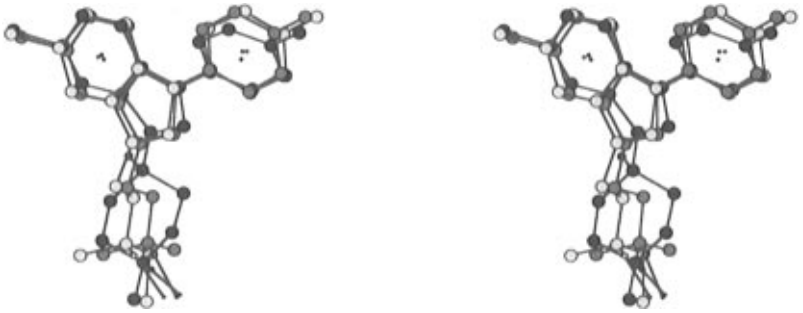


Figure 7. Least-squares superimpositions of the suggested active conformation of **9b** on the *N*-methyl analog of sertindole **1a′** (blue). The conformer of **9b** in red has conformational energy of 0.4 kcal/mol and the values of angles A, B, and C are 95°, 170°, and −57°, respectively. The RMS-values obtained for the superimpositions is 0.2 Å. Hydrogen atoms are omitted for clarity.

the amino group is probably necessary for obtaining this interaction. Possibly the reduced receptor binding affinities obtained for **22f** can be explained by reduced base strength of the amino group as a consequence of the two β-oxygen atoms present in this compound.

For the 2-(4-methyl-1-piperazinyl)ethoxy-substituted derivative **22g** the affinity for D_2 receptors is unchanged, whereas the affinities for serotonin 5-HT_{2A} receptors and α_1 adrenoceptors are reduced by factors of 17 and 5, respectively, compared to the corresponding 1-piperidinyl derivative **22e**. These major changes in receptor binding affinity are the result of the introduction of a further amino group into the molecule. The compound obtained by these rather small structural changes is structurally different from other high affinity dopamine D_2 receptor antagonists with high selectivity versus serotonin 5-HT_{2A} receptors and α_1 adrenoceptors, e.g. the benzamides. The affinity and selectivity for dopamine D_2 receptors are comparable to those of nemonapride (Table 1).

To further explore structure−affinity relationships for analogues of sertindole, in which the piperidinyl group is ring-opened, the chain length of the (dimethylamino)-alkyl substituent in the 3-position was varied from one to four carbon atoms. Apparently the receptor binding affinities for 5-HT_{2A}, D_2, and α_1 receptors are independent of the chain length from one to three carbon atoms (**5a**, **9b**, and **14a**). A chain length of four carbon atoms (**15**) results in significantly reduced receptor binding affinities. Accordingly, the receptor binding affinity is significantly reduced for the 3-(dimethylamino)propoxy derivative **25** having a chain length of four atoms compared to that of the corresponding 2-(dimethylamino)ethoxy derivative **22a**.

Replacement of one of the methyl groups in the 2-(dimethylamino)ethyl derivative **9b** with (2-oxoimidazolidin-1-yl)alkyl groups enhances the receptor binding affinities for the three receptors (**9d** and **9e**), most significantly for compound **9e** with pronounced increase in 5-HT_{2A} receptor affinity. In the methylene (**5c** and **5d**) and propylene series (**14b**) similar replacements result in unimproved binding affinities.

The capability of the 2-(dimethylamino)ethyl group to replace the piperidinyl group in sertindole is reflected in the molecular modeling studies. In Figure 7 is shown superimposition of the suggested active conformation of the 2-(dimethylamino)ethyl derivative **9b** on the suggested active conformation of the *N*-methyl analogue of sertindole (**1a′**). In the superimposition the 3-substituent interacts with similar regions of space as does the piperidinyl group in sertindole.

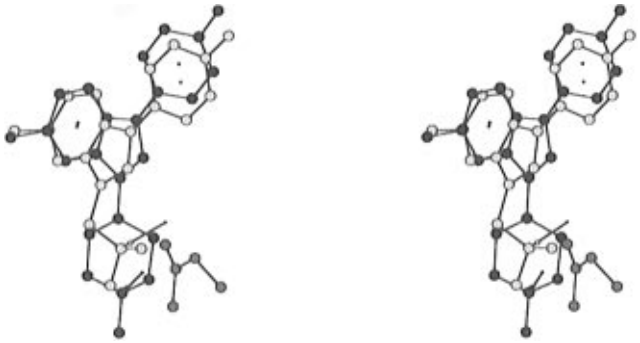


Figure 8. Superimposition of the suggested active conformation of **5a** on fitting points as for the other superimpositions on the *N*-methyl analogue of sertindole (**1a′**) (blue) except that point C is replaced by the carboxylate oxygen atom in the group (red) that is assumed to simulate an aspartate residue at the receptor. In the superimposition of **5a** angle C−C−C−O in the aspartate residue-simulating group has a value of −150°. An optimal interaction between the basic nitrogen atom in **1a′** and the aspartate group is obtained for a value of 120°. The conformer of **5a** has conformational energy of 0.6 kcal/mol, and the values of angles A and B are 135° and 51°, respectively. Hydrogen atoms are omitted for clarity.

Although the (dimethylamino)methyl derivative **5a** has affinity for the 5-HT_{2A} and D_2 receptors, none of its low energy conformers can be fitted into the receptor-interaction model. For this compound the distances between the centers of either of the two benzene rings (A and B) and the point C, which is assumed to simulate a receptor site hydrogen bonding with the basic nitrogen atom, are shorter than in the receptor-interaction model. Similar problems have been discussed in relation to other molecules with high affinity for 5-HT_{2A} and D_2 receptors such as ORG 5222[38] and dexclamol.[10] To further develop the model to accommodate molecules with these geometrical features a carboxylate group is included in the model (indicated in red in Figure 8).[38] The carboxylate group is assumed to simulate the aspartate residue at the receptor, which is believed to interact with the basic amino groups in ligands binding to the receptor.[39,40] Recently a similar approach has been descibed by ter Laak *et al*. for the development of a receptor-interaction model for histamine H_1 receptor antagonists.[41] In Figure 8 superimposition of the suggested active conformation of the (dimethylamino)-methyl derivative **5a** using this extended receptor-interaction model is shown. The fitting points used are as above except that the point C is replaced by the carboxylate oxygen atom. In the superimposition of **5a** angle C−C−C−O in the aspartate residue-simulating group has a value of −150° compared to 120° for an

Table 4. *In Vivo* Pharmacological Activity of Selected Compounds

compd	inhibition of quipazine-induced head twitches:[a] ED_{50} (μmol/kg) 2 h (sc)	24 h (sc)	24 h (po)	inhibition of pergolide-induced rotations:[a] ED_{50} (μmol/kg) 2 h (sc)
10e	4.7 (1.2−18)	8.5 (1.4−53)	NT[b]	NT
22b	0.32 (0.12−0.86)	>9.1	NT	3.6 (2.1−6.1)
22g	NT	NT	NT	0.048 (0.019−0.12)
23b	0.63 (0.27−1.4)	NT	0.25 (0.071−088)	NT
sertindole	0.035 (0.022−0.056)	0.030 (0.014−0.066)	0.039 (0.020−0.078)	3.7 (1.5−8.9)
Lu 26-042	0.11 (0.064−0.18)	0.052 (0.017−0.16)	0.055(0.026−0.12)	>17
ritanserin	0.10 (0.056−0.18)	0.98 (0.35−2.7)	NT	>21
nemonapride	NT	NT	NT	0.0057 (0.0027−0.012)

[a] 95% Confidence limits are stated in brackets. [b] NT: not tested.

optimal fit with the suggested active conformation of the *N*-methyl analogue of sertindole (**1a′**). Further molecular investigations of other 5-HT_{2A} and D_2 receptor antagonists are in progress to study the use of a carboxylate group in the development of 3-D pharmacophores for serotonin 5-HT_{2A} and dopamine D_2 antagonists.

The structure−affinity investigations described above concerning variations of the 3-substituent in sertindole (**1a**) have led to the 2-aminoethyl derivative **9e** and the 2-(dimethylamino)ethoxy derivative **22b** having receptor binding affinities for serotonin 5-HT_{2A} and dopamine D_2 receptors, and for α_1 adrenoceptors similar to those of sertindole (**1a**). For these two key derivatives the structure−affinity relationships concerning changes of the substituents in the indole nucleus and substituents in the 2-imidazolidinone ring system were studied.

It has recently been shown that replacement of the 5-chloro substituent in sertindole (**1a**) with a 6-chloro substituent results in reduced affinity for dopamine D_2 receptors, while the affinity for 5-HT_{2A} receptors is retained.[6] Similar replacement in the 5-chloro-substituted 2-aminoethyl derivative **9e** and the 2-(dimethylamino)ethoxy derivative **22b** result in reduced affinity for dopamine D_2 receptors by factors of 20 and 35, respectively, whereas the affinity for serotonin 5-HT_2 receptors is unaffected (**10e** and **23b**). In addition, we recently described that introduction of a 3-(2-propyl) substituent in the imidazolidinone ring system reduces the affinity for α_1 adrenoceptors by a factor of 3−8, whereas the affinities for dopamine D_2 and serotonin 5-HT_{2A} receptors are not influenced by this replacement.[6] Accordingly, introduction of a 3-(2-propyl) substituent in the imidazolidinone ring system in **10d** and **23b** reduces the affinity for α_1 adrenoceptors by factors of 29 and 15, respectively, resulting in derivatives **10f** and **23c**, respectively. The derivatives **10e**, **10f**, **23b**, and **23c** obtained by these structural changes have high affinity for 5-HT_{2A} receptors with a good selectivity versus dopamine D_2 receptors and α_1 adrenoceptors.

Recently the atypical antipsychotic sertindole (**1a**) and the structurally related 5-HT_2 antagonists Lu 26-042 (**1b**) and Lu 29-066 (**2**) have been reported to have equal affinity for 5-HT_{2A} and 5-HT_{2C} receptors.[8] In contrast, the ring-opened analogues discussed in the present paper have considerably lower affinity for 5-HT_{2C} than for 5-HT_{2A} receptors (personal communication, Kristen Frederiksen, H. Lundbeck A/S).[42] For the 2-aminoethyl derivative **9e** and the 2-(dimethylamino)ethoxy derivative **22b**, IC_{50} values of 31 nM and 14 nM, respectively, were obtained for displacement of [^{3}H]mesulergine from rat 5-HT_{2C} receptors. For the 2-aminoethyl derivative **10e**, which has low affinity for D_2 and α_1 receptors compared to its high affinity for 5-HT_{2A} receptors, an IC_{50} value of 150 nM in the 5-HT_{2C} receptor binding assay was obtained.

In Table 4 some important *in vivo* pharmacological effects for selected compounds are reported. To determine the serotonin 5-HT_{2A} antagonistic effects of the compounds their ability to inhibit the quipazine-induced (5-HT_2 agonist) head twitch syndrome in rats was determined.[43] The antidopaminergic effects were reflected in their ability to inhibit pergolide-induced (D_2 agonist) contralateral circling in rats with unilateral 6-OHDA lesions.[44]

For sertindole very potent and very long lasting antiserotonergic effects *in vivo* have been reported. For 2-(dimethylamino)ethoxy derivative **22b**, having a receptor-binding profile similar to that of sertindole (**1a**), the antiserotonergic effects are about ten times weaker than for sertindole (**1a**) and of a shorter duration compared to sertindole. The antidopaminergic effects *in vivo* are of similar potency as for sertindole. For the selective 5-HT_{2A} receptor antagonists **10e** and **23b**, long lasting antiserotonergic effects are obtained in vivo. The effects are about 10−100 times weaker than the effects obtained for the previously reported selective serotonin 5-HT_2 receptor antagonist Lu 26-042. The selective dopamine D_2 receptor antagonist **22g** has potent antidopaminergic effects *in vivo*.

Conclusion

Replacement of the 4-piperidinyl ring in sertindole (**1a**) by a 2-(methylamino)ethoxy group (**22b**) or a 2-(methylamino)ethyl group (**9d** and **9e**) results in binding affinities for serotonin 5-HT_{2A} and dopamine D_2 receptors, as well as α_1 adrenoceptors, which are very similar to those of **1a**, indicating that these groups are excellent replacements for the 4-piperidinyl ring in sertindole (**1a**). (Methylamino)alkyl groups of other chain lengths, 3-(methylamino)propyloxy groups, and 2-(methylamino)ethylsulfanyl groups do not have such properties.

The capability of the 2-(methylamino)ethoxy group (**22b**) and the 2-(methylamino)ethyl group (**9d** and **9e**) to replace the 4-piperidinyl ring in sertindole (**1a**) is reflected in molecular modeling studies using the recently published receptor-interaction models for 5-HT_2 and D_2 receptors. Low energy conformers of 2-(methylamino)ethoxy and 2-(methylamino)ethyl derivatives are well accommodated into the model, and the 2-(methylamino)ethoxy and 2-(methylamino)ethyl groups occupy similar regions of space as do the piperidinyl group in the suggested active conformation of sertindole (**1a**).

Structure−affinity investigations concerning the substituents in the indole nucleus and the 2-imidazolidi-

none ring system in the 2-(methylamino)ethoxy derivative **22b** and the 2-(methylamino)ethyl derivatives **9d** and **9e** have led to high affinity serotonin 5-HT_{2A} receptor antagonists with selectivity versus dopamine D_2 receptors and α_1 adrenoceptors (e.g. **10e**, **10f**, **23b**, and **23c**). In addition the 2-(methylamino)ethyl derivative **10e** has high selectivity for 5-HT_{2A} receptors compared to serotonin 5-HT_{2C} receptors.

The antiserotonergic effects obtained *in vivo* for the 2-(methylamino)ethyl and 2-(methylamino)ethoxy derivatives prepared in the present study are generally weaker than the effects obtained for corresponding piperidinyl derivatives such as sertindole (**1a**) and Lu 26-042 (**1b**).

Replacement of the amino group in **22b** by nitrogen-containing six-membered rings has led to the structurally new selective dopamine D_2 receptor antagonist **22g**. This derivative has potent antidopaminergic effects in *vivo*.

Experimental Section

All reactions were carried out under a positive pressure of nitrogen. Melting points were determined on a Büchi SMP-20 apparatus and are uncorrected. ^{1}H NMR spectra were recorded at 250 MHz on a Bruker AC 250 spectrometer. Deuterated chloroform (99.8% D) or deuterated dimethyl sulfoxide (99.9% D) were used as solvents. TMS was used as internal reference standard. Chemical shift values are expressed in ppm-values. Mass spectra were obtained on a Quattro MS-MS system from VG Biotech, Fisons Instruments, Manchester, GB. The MS-MS system was connected to a HP 1050 modular HPLC system. A volume of 20−50 μL of the sample (0.1−0.05 mg/mL) dissolved in a mixture of acetonitrile: water:acetic acid = 250:250:1 (v/v/v) was introduced via the autosampler at a flow of 30 μL/min into the electrospray source. Spectra were obtained at two sets of standard operating conditions: one to obtain molecular weight information (MH^+) and another to obtain fragmentation in the source (high cone voltage). The background was subtracted. The relative intensities of the molecular ions obtained in the fragmentation spectrum are given. If the relative intensity of the MH^+ ion not is given this ion was only obtained in the molecular weight spectra. Content of water in crystalline compounds was determined by Karl Fischer titration. Microanalyses were performed by Lundbeck Analytical Department and results obtained were within 0.4% of the theoretical values for all crystalline products.

Syntheses of Substituted of 1-(Chloroalkyl)-2-imidazolidinones and 1-[2-(Alkylamino)ethyl]-2-imidazolidinones. 1-(2-Chloroethyl)-2-imidazolidinone, 1-(3-chloropropyl)-2-imidazolidinone, 1-(2-chloroethyl)3-(2-propyl)-2-imidazolidinone, and 1-(3-chloropropyl)-3-(2-propyl)-2-imidazolidinone were prepared according to the literature.[6,45,46] **1-[2-(Methylamino)ethyl]-2-imidazolidinone Hydrochloride.** A mixture of 1-(2-chloroethyl)imidazolidinone (5.0 g) and a 33% solution of methylamine in ethanol was heated in a sealed tube at 80 °C for 18 h. After cooling to room temperature the volatile products were evaporated, affording 5.0 g (81%) of an oil which was used for the preparation of **14**, **22**, **23**, and **24** without further purification: ^{1}H NMR (DMSO-d_6) δ 2.55 (s, 3 H), 3.00 (t, 2 H), 3.20−3.45 (m, 6 H), 6.5 (broad s, 1 H).

The following compounds were prepared accordingly. **1-[2-(Ethylamino)ethyl]-2-imidazolidinone hydrochloride:** ^{1}H NMR (DMSO-d_6) δ 1.15 (t, 3 H), 2.65−3.05 (m, 4 H), 3.15−3.45 (m, 6 H), 6.50 (broad s, 1 H).

1-[2-(3-Propynylamino)ethyl]-2-imidazolidinone hydrochloride: ^{1}H NMR (DMSO-d_6) δ 3.10−3.4 (m, 9), 3.70 (t, 2 H), 6.5 (broad s, 1 H).

1-[2-(Methylamino)ethyl]-3-(2-propyl)-2-imidazolidinone hydrochloride: ^{1}H NMR ($CDCl_3$) δ 1.1 (d, 6 H), 2.65 (s, 3 H), 3.05 (t, 2 H), 3.30−3.55 (m, 6 H), 4.05 (h, 1 H), 6.90 (broad s, 2 H).

5-Chloro-1-(4-fluorophenyl)indole-3-carbaldehyde (4). Phosphorus oxychloride (12.5 g, 0.081 mol) was added to *N*,*N*-dimethylformamide (29.5 g, 0.19 mol) at 0−5 °C. After stirring for 10 min a solution of 5-chloro-1-(4-fluorophenyl)indole (**3**) (20 g, 0.081 mol) in *N*,*N*-dimethylformamide (50 mL) was added at 0−5 °C. The reaction mixture was stirred for 0.5 h and subsequently poured into ice. The resulting mixture was made alkaline with concentrated NaOH and after stirring for 1 h at room temperature the mixture was extracted with diethyl ether (2 × 250 mL). The combined organic phases were dried (Na_2SO_4), the solvents were evaporated, and the remaining oil was purified by column chromatography on silica gel (eluted with ethyl acetate/heptane 1:1) affording pure title compound 20.1 g (90%), which crystallized from heptane: mp 152−154 °C; ^{1}H NMR ($CDCl_3$) δ 7.20−7.35 (m, 4 H), 7.50 (dd, 2 H), 7.85 (s, 1 H), 8. 35 (s, 1 H), 10.05 (s, 1 H). Anal. ($C_{15}H_9ClFNO$) C, H, N.

***N*,*N*-Dimethyl-5-chloro-1-(4-fluorophenyl)-1*H*-indol-3-ylmethylamine Maleate (5a).** A mixture of 5-chloro-1-(4-fluorophenyl)indole-3-carbaldehyde (**4**) (2.5 g, 0.0091 mol), dimethylamine hydrochloride (1.5 g, 0.018 mol), 3 Å molecular sieves (5 g), and methanol (50 mL) was stirred at room temperature for 1 h. Sodium cyanoborohydride (0.6 g, 0.095 mol) was added, and the mixture was stirred for 24 h at room temperature. Further 3 Å molecular sieves (5 g) and sodium cyanoborohydride (0.6 g, 0.095 mol) were added, and the mixture was stirred for further 24 h at room temperature. The precipitate was filtered off, and the solvents were evaporated. The remaining oil was purified by column chromatography on silica gel (eluted with ethyl acetate/heptane 1:1 containing 4% triethylamine) affording pure title compound as an oil (2.1 g, 76%). The maleate of **5a** was crystallized from ethanol: mp 174−177 °C; ^{1}H NMR (DMSO-d_6) δ 2.80 (s, 6 H), 4.50 (s, 2 H), 6.05 (s, 2 H), 7.30 (broad d, 1 H), 7.40−7.55 (m, 3 H), 7.70 (dd, 2 H), 7.95 (s, 1 H), 8.10 (broad s, 1 H); MS (*m*/*z*) 303 (MH^+), 258 (20), 223 (61), 222 (100), 162 (70), 127 (61). Anal. ($C_{17}H_{16}ClFN_2 \cdot C_4H_4O_4$) C, H, N.

The following compound was prepared accordingly. ***N*-Methyl-5-chloro-1-(4-fluorophenyl)-1*H*-indol-3-ylmethylamine hydrochloride (5b):** mp 236−238 °C (acetone); ^{1}H NMR (DMSO-d_6) δ 2.55 (s, 3 H), 4.35 (s, 2H), 7.25 (broad d, 1 H), 7.40−7.55 (m, 3 H), 7.65 (dd, 2 H), 7.95 (s, 1 H), 8.05 (broad s, 1 H); MS (*m*/*z*) 289 (MH^+, 1), 258 (14), 223 (45) 222 (100), 162 (62) 127 (28). Anal. ($C_{16}H_{14}ClFN_2 \cdot HCl$) C, H, N.

***N*-Benzyl-*N*-methyl-2-[5-chloro-1-(4-fluorophenyl)-1*H*-indol-3-yl]ethylamine (9a).** To a solution of 5-chloroindole (**6a**) (20 g, 0.13 mol) in dry diethyl ether (200 mL) was added a solution of oxalyl chloride (20 g, 0.16 mol) in dry diethyl ether (200 mL) at 0−5 °C. After stirring for 0.5 h at 0−5 °C was added a solution of benzylmethylamine (24 g, 0.20 mol) in dry diethyl ether at 0−5 °C, and triethylamine was slowly added to pH at 8−9. Water and ethyl acetate (500 mL) was added, and the organic phase was washed with brine and dried (Na_2SO_4). Evaporation of the solvents afforded the crude *N*-benzyl-*N*-methyl-2-(5-chloro-1*H*-indol-3-yl)-2-oxoacetamide (**7a**) (19.1 g) as an oil. A solution of the crude **7a** (20.1 g, 0.058 mol) in dry tetrahydrofuran (200 mL) was added to a suspension of lithium aluminum hydride (5.4 g, 0.14 mol) in tetrahydrofuran (100 mL). After heating at reflux for 2.5 h the reaction mixture was cooled to 0 °C and treated with water (6 mL) and 4 N aqueous NaOH (6 mL). The precipitate was filtered off and extracted with dichloromethane (3 × 200 mL). The combined organic phases were dried (Na_2SO_4), and the solvents were evaporated. The remaining oil was purified by column chromatography on silica gel (eluted with ethyl acetate) affording *N*-benzyl-*N*-methyl-2-(5-chloro-1*H*-indol-3-yl)ethylamine (**8a**) (16 g) as an oil: ^{1}H NMR ($CDCl_3$) δ 2.30 (s, 3 H), 2.65−2.80 (m, 2 H), 2.85−3.00 (m, 2 H), 3.60 (s, 2 H), 6.95 (broad s, 1 H), 7.05−7.20 (m, 2 H), 7.15−7.35 (m, 5), 7.45 (broad s, 1 H), 8.35 (broad s, 1 H). A mixture of *N*-benzyl-*N*-methyl-2-(5-chloro-1*H*-indol-3-yl)ethylamine (**8a**) (16 g, 0.054 mol), 4-fluoroiodobenzene (14.3 g, 0.064 mol), K_2CO_3 (11.1 g, 0.080 mol) and 1-methyl-2-pyrrolidinone (200 mL) was heated at 165 °C for 8 h. After cooling to room temperature, water (250 mL) was added and the thus formed mixture was extracted with diethyl ether (2 × 300 mL). The combined

organic phases were washed with brine (3 × 500 mL) and dried (Na_2SO_4). Evaporation of the solvent afforded an oil that was purified by column chromatography on silica gel (eluted with ethyl acetate/heptane 1:3) affording pure title compound **9a** as an oil: 13.7 g (26%) ^{1}H NMR ($CDCl_3$) δ 2.35 (s, 3 H), 2.70−2.80 (m, 2 H), 2.90−3.00 (m, 2 H), 3.60 (s, 2 H), 7.05−7.40 (m, 12 H), 7.55 (broad s, 1 H).

The following compound was prepared in a similar way. ***N*-Benzyl-*N*-methyl-2-[6-chloro-1-(4-fluorophenyl)-1*H*-indol-3-yl]ethylamine (10a): 10a** was isolated as an oil. ^{1}H NMR ($CDCl_3$) δ 2.35 (s, 3H), 2.75 (m, 2 H), 3.00 (m, 2 H), 3.60 (s, 2 H), 7.05−7.40 (m, 12 H), 7.45 (d, 1 H).

***N,N*-Dimethyl-2-[6-chloro-1-(4-fluorophenyl)-1*H*-indol-3-yl]ethylamine Oxalate (10b).** A mixture of *N*-benzyl-*N*-methyl-2-[6-chloro-1-(4-fluorophenyl)-1*H*-indol-3-yl]ethylamine (**10a**) (5.7 g, 0.014 mol), methyl chloroformate (1.6 g, 0.017 mol), K_2CO_3 (2.4 g, 0.017 mol), and 1,1,1-trichloroethane (70 mL) was heated at reflux for 1.5 h, and the precipitate was filtered off. Evaporation of the solvents afforded crude *N*-methyl-*N*-(methoxycarbonyl)-2-[6-chloro-1-(4-fluorophenyl)-1*H*-indol-3-yl]ethylamine (3.2 g) as an oil. A solution of the crude *N*-(methoxycarbonyl)-2-[6-chloro-1-(4-fluorophenyl)-1*H*-indol-3-yl]ethylamine (3.2 g, 0.0089 mol) in tetrahydrofuran (50 mL) was added to a suspension of lithium aluminum hydride (0.5 g, 0.014 mol) in tetrahydrofuran (50 mL). After reflux for 2 h the reaction mixture was cooled to 0 °C and carefully treated with water (0.5 mL), 4 N aqueous NaOH (0.5 mL), and then water (0.5 mL). The resulting mixture was filtered and dried (Na_2SO_4). Evaporation of the solvents afforded the title compound as an oil (2.6 g, 59%), which was crystallized as its oxalate from acetone: mp 155−156 °C (acetone); ^{1}H NMR (DMSO-d_6) δ 2.85 (s, 6 H), 3.10−3.25 (m, 2 H), 3.30−3.40 (m, 2 H), 7.20 (broad d, 1 H), 7.40 (t, 2 H), 7.45 (s, 1 H), 7.55−7.65 (m, 3 H), 7.75 (d, 1 H); MS (*m*/*z*) 317 (MH^+, 5), 272 (36), 237 (70) 236 (52). Anal. ($C_{18}H_{18}ClFN_2 \cdot C_2H_2O_4$) C, H, N.

The following compound was prepared in a similar way. ***N,N*-Dimethyl-2-[5-chloro-1-(4-fluorophenyl)-1*H*-indol-3-yl]ethylamine maleate (9b):** mp 170−172 °C (ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 2.90 (s, 6 H), 3.20−3.30 (m, 2 H), 3.30−3.45 (m, 2 H), 6.30 (s, 2 H), 7.15−7.30 (m, 4 H), 7.35 (d, 1 H), 7.40 (dd, 2 H), 7.60 (broad s, 1 H); MS (*m*/*z*) 317 (MH^+, 11), 272 (72), 237 (46), 236 (27). Anal. ($C_{18}H_{18}ClFN_2 \cdot C_4H_4O_4$) C, H, N.

***N*-Methyl-2-[5-chloro-1-(4-fluorophenyl)-1*H*-indol-3-yl]-ethylamine Maleate (9c).** A mixture of *N*-benzyl-*N*-methyl-2-[5-chloro-1-(4-fluorophenyl)-1*H*-indol-3-yl]ethylamine (**9a**) (13.7 g, 0.026 mol), methyl chloroformate (2.9 g, 0.031), K_2CO_3 (4.2 g, 0.031), and 1,1,1-trichloroethane (150 mL) was heated at reflux for 2 h and the precipitate was filtered off. Evaporation of the solvents afforded crude *N*-methyl-*N*-(methoxycarbonyl)-2-[5-chloro-1-(4-fluorophenyl)-1*H*-indol-3-yl]-ethylamine (12.2 g) as an oil. A mixture of the crude *N*-(methoxycarbonyl)-2-[5-chloro-1-(4-fluorophenyl)-1*H*-indol-3-yl]ethylamine (12.2 g, 0.034) and 47% hydrobromic acid (150 mL) was heated at reflux for 14 h. The reaction mixture was poured into ice, made alkaline with concentrated NaOH and extracted with diethyl ether (2 × 200 mL). The combined organic phases were washed with brine and dried (Na_2SO_4). Evaporation of the solvents afforded pure title compound **9c** as an oil (7.9 g, 52%), which was crystallized as its maleate salt from ethyl acetate: mp 171−173 °C (ethyl acetate); ^{1}H NMR (DMSO-d_6) δ 2.65 (s, 3 H), 3.05−3.20 (m, 2 H), 3.20−3.30 (m, 2 H), 6.05 (s, 2 H), 7.20 (broad d, 1 H), 7.45 (t, 2 H), 7.50 (s, 1 H), 7.60 (dd, 2 H), 7.65 (s, 1 H), 7.80 (broad s, 1 H); MS (*m*/*z*) 303 (MH^+), 237 (82) 236 (100). Anal. ($C_{17}H_{16}FClN_2 \cdot C_4H_4O_4$) C, H, N.

The following compound was prepared in a similar way. ***N*-Methyl-2-[6-chloro-1-(4-fluorophenyl)-1*H*-indol-3-yl]-ethylamine hemioxalate (10c):** ^{1}H NMR (DMSO-d_6) δ 2.50 (s, 3 H), 3.05 (broad s, 4 H), 7.05 (dd, 1 H), 7.35 (t, 2 H), 7.40 (broad s, 1 H), 7.45 (s, 1 H), 7.55 (dd, 2 H), 7.65 (d, 1 H); MS (*m*/*z*) 303 (MH^+), 272 (100), 237 (33). Anal. ($C_{17}H_{16}FClN_2 \cdot 0.5C_2H_2O_4 \cdot 0.3H_2O$) C, H, N.

General Procedure for the Preparation of Tertiary Amines 5c,d, 9d,e, and 10d−f from the Corresponding Secondary Amines 5b, 9c, and 10c, Respectively. 1-[2-[[2-[6-Chloro-1-(4-fluorophenyl)-1*H*-indol-3-yl]ethyl]-methylamino]ethyl]-3-(2-propyl)-2-imidazolidinone Oxalate (10f). A mixture of *N*-methyl-2-[6-chloro-1-(4-fluorophenyl)-1*H*-indol-3-yl]ethylamine (2.0 g, 0.0066 mol), 1-(2-chloroethyl)-3-(2-propyl)imidazolidin-2-one (1.4 g, 0.0073 mol), K_2CO_3 (1.4, 0.0099 mol), KI (0.3 g), and methyl isobutyl ketone (100 mL) was refluxed for 18 h. The reaction mixture was cooled and poured into water and extracted with ethyl acetate. The combined organic phases were dried (Na_2SO_4), and the solvents were evaporated *in vacuo*. The remaining oil was purified by column chromatography on silica gel (eluted with ethyl acetate/ethanol 3:1 containing 4% triethylamine) affording pure title compound (**10f**) (1.5 g, 50%) as an oil. The title compound was crystallized as its oxalate salt from acetone: 172−173 °C (acetone); ^{1}H NMR (DMSO-d_6) δ 1.0 (d, 6 H), 2.80 (s, 3 H), 3.05−3.50 (m, 12 H), 3.90 (qui, 1 H), 7.20 (broad d, 1 H), 7.45 (t, 2 H), 7.50 (s, 1 H), 7.55 (s, 1 H), 7.60 (dd, 2 H), 7.75 (d, 1 H); MS (*m*/*z*) 457 (MH^+, 23), 272 (48), 198 (71), 155 (100). Anal. ($C_{25}H_{30}ClFN_4O \cdot C_2H_2O_4$) C, H, N.

1-[2-[[5-Chloro-1-(4-fluorophenyl)-1*H*-indol-3-ylmethyl]methylamino]ethyl]-2-imidazolidinone (5c): mp 141−143 °C (ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 2.30 (s, 3 H), 2.60 (t, 2 H), 3.25−3.50 (m, 6 H), 3.70 (s, 2 H), 4.50 (broad s, 2 H), 7.10−7.25 (m, 4 H), 7.35 (d, 1 H), 7.40 (dd, 2 H), 2.80 (broad s, 1 H); MS (*m*/*z*) 401 (MH^+, 3), 258 (64), 223 (100), 222 (80), 162 (60). Anal. ($C_{21}H_{22}ClFN_4O$) C, H, N.

1-[4-[[5-Chloro-1-(4-fluorophenyl)-1*H*-indol-3-ylmethyl]methylamino]butyl]-2-imidazolidinone oxalate (5d): mp 155−157 °C (acetone); ^{1}H NMR (DMSO-d_6) δ 1.80−1.95 (m, 4 H), 2.80 (s, 3 H), 3.10−3.35 (m, 6 H), 3.35−3.50 (m, 2H), 4.60 (s, 2 H), 6.65−6.75 (m, 1 H), 7.20 (broad d, 1 H), 7.35−7.50 (m, 3 H), 7.60 (dd, 2 H), 7.70 (dd, 1 H), 7.80 (broad s, 1 H); MS (*m*/*z*) 429 (MH^+), 258 (100), 223 (27), 141 (91). Anal. ($C_{23}H_{26}ClFN_4O \cdot C_2H_2O_4$) C, H, N.

1-[2-[[2-[5-Chloro-1-(4-fluorophenyl)-1*H*-indol-3-yl]ethyl]methylamino]ethyl]-2-imidazolidinone maleate (9d): mp 137−139 °C; ^{1}H NMR (DMSO-d_6) δ 2.95 (s, 3 H), 3.10−3.55 (m, 12 H), 6.05 (s, 2 H), 6.65 (broad s, 1 H), 7.25 (broad d, 1 H), 7.40−7.55 (m, 3 H), 7.60 (dd, 2 H), 7.65 (s, 1 H), 7.65 (broad s, 1 H); MS (*m*/*z*) 415 (MH^+), 272 (33), 237 (28), 113 (100). Anal. ($C_{22}H_{24}ClFN_4O \cdot C_4H_4O_4$) C, H, N.

1-[3-[[2-[5-Chloro-1-(4-fluorophenyl)-1*H*-indol-3-yl]ethyl]methylamino]propyl]-2-imidazolidinone hydrochloride (9e): mp 171−173 °C (acetone); ^{1}H NMR ($CDCl_3$) δ 2.10−2.30 (m, 2 H), 2.90 (s, 3 H), 3.05−3.60 (12 H), 4.60 (broad s, 1 H), 7.15−7.35 (m, 5 H), 7.40 (dd, 2 H), 7.60 (broad s, 1 H); MS (*m*/*z*) 429 (MH^+, 2), 272 (34), 237 (20), 127 (100), 99 (44). Anal. ($C_{23}H_{26}ClFN_4O \cdot HCl$) C, H, N.

1-[2-[[2-[6-Chloro-1-(4-fluorophenyl)-1*H*-indol-3-yl]ethyl]methylamino]ethyl]-2-imidazolidinone hydrochloride (10d): mp 213−16 °C (ethanol); ^{1}H NMR (DMSO-d_6) δ 2.90 (broad s, 3 H), 3.15−3.65 (m, 12 H), 6.60 (broad s, 1 H), 7.20 (broad d, 1 H), 7.45 (t, 2 H), 7.50 (broad s, 1 H), 7.60 (s, 1 H), 7.65 (dd, 2 H), 7.85 (d, 1 H), 10.60 (broad s, 1 H); MS (*m*/*z*) 415 (MH^+, 11), 113 (100). Anal. ($C_{22}H_{24}ClFN_4O \cdot HCl$) C, H, N.

1-[3-[[2-[6-Chloro-1-(4-fluorophenyl)-1*H*-indol-3-yl]ethyl]methylamino]propyl]-2-imidazolidinone oxalate (10e): mp 112−114 °C (acetone); ^{1}H NMR (DMSO-d_6) δ 1.75−1.95 (m, 2 H), 2.80 (s, 3 H), 3.00−3.40 (m, 12 H), 6.40 (broad s, 1 H), 7.20 (broad d, 1 H), 7.40 (t, 2 H), 7.45 (s, 1 H), 7.60 (s, 1 H), 7.60 (dd, 2 H), 7.75 (d, 1 H); MS (*m*/*z*) 429 (MH^+, 8), 272 (72), 237 (22) 127 (100), 99 (68). Anal. ($C_{23}H_{26}ClFN_4O \cdot C_2H_2O_4$) C, H, N.

3-[5-Chloro-1-(4-fluorophenyl)-1*H*-indol-3-yl]propanol (13a). A mixture of 3-[5-chloro-1*H*-indol-3-yl]propanoic acid[23,24] (**11a**) (17.5 g, 0.078 mol), 4-fluoroiodobenzene (20.8 g, 0.094 mol), CuI (2.4 g), K_2CO_3 (21.6 g, 0.16 mol), and *N*-methyl-2-pyrrolidinone (0.20 L) was heated at 165 °C for 7 h. The reaction mixture was cooled to room temperature, and water (0.25 L) was added. After the mixture was acidified with concentrated hydrochloric acid it was extracted with diethyl ether (2 × 0.30 L). The combined organic phases were washed with brine (3 × 0.40 L) and dried (Na_2SO_4). Evaporation of the solvents afforded the crude acid **12a** (26 g) as an oil. The

oil was dissolved in dry diethyl ether and added to a suspension of lithium aluminum hydride (15 g, 0.40 mol) in dry diethyl ether (0.20 L) over 30 min. After reflux for further 2 h the reaction mixture was cooled to 0 °C and carefully treated with water (15 mL), 4 N aqueous NaOH (15 mL), and then water (75 mL). The resulting mixture was filtered and dried (Na_2SO_4). Evaporation of the solvents afforded the title compound as an oil (17.6 g, 74%). An analytical sample was crystallized from heptane: mp 67−69 °C; ^{1}H NMR ($CDCl_3$) δ 1.55 (broad s, 1 H), 2.00 (qui, 2 H), 2.90 (t, 2 H), 3.75 (t, 2 H), 7.10 (s, 1 H), 7.15 (broad d, 1 H), 7.20 (t, 2 H), 7.35 (d, 1 H), 7.40 (dd, 2 H), 7.60 (broad s, 1 H). Anal. ($C_{17}H_{15}ClFNO$) C, H, N.

The following compound was prepared in a similar way. **4-[5-Chloro-1-(4-fluorophenyl)-1*H*-indol-3-yl]butanol (13b):** mp 80−82 °C (heptane/ethanol); ^{1}H NMR ($CDCl_3$) δ 1.35 (broad s, 1 H), 1.60−1.90 (m, 4 H), 2.80 (t, 2 H), 3.70 (t, 2 H), 7.10 (s, 1 H), 7.15 (broad d, 1 H), 7.20 (t, 2 H), 7.35 (d, 1 H), 7.40 (dd, 2 H), 7.60 (broad s, 1 H). Anal. ($C_{18}H_{17}ClFNO$) C, H, N.

2-[5-Chloro-1-(4-fluorophenyl)-1*H*-indol-3-yloxy]ethanol (19a). A mixture of methyl 5-chloro-1-(4-fluorophenyl)-3-hydroxy-1*H*-indol-2-carboxylate[1] (**16a**) (200 g, 0.62 mol), methyl 2-bromoacetate (125 g, 0.81 mol), K_2CO_3 (112 g, 0.81 mol), and acetone (2.0 L) was refluxed for 18 h. The mixture was cooled to room temperature and filtered, and the solvents were evaporated *in vacuo*. To the remaining oil (270 g) were added methanol (1.5 L) and 3 N aqueous KOH (0.6 L). After reflux for 1 h the solution was cooled to room temperature and acidified by concentrated hydrochloric acid. The crystalline product was filtered off and dissolved in ethyl acetate and dried (Na_2SO_4). Evaporation of the solvents afforded 2-[2-carboxy-5-chloro-1-(4-fluorophenyl)-1*H*-indol-3-yloxy]acetic acid (**17a**) (240 g) as an oil, which was decarboxylated without further purification. A mixture of the crude dicarboxylic acid, copper (15 g), and *N*-methyl-2-pyrrolidinone was refluxed for 1.5 h. The mixture was cooled to room temperature, and water (2.0 L) was added. The precipitated product was filtered off and dissolved in ethyl acetate (1.5 L). The solution was washed with brine (3 × 1 L) and dried (Na_2SO_4). Evaporation of the solvents afforded the crude carboxylic acid (**17a**) (223 g), which was dissolved in dry diethyl ether (1.5 L). The solution was added to a suspension of lithium aluminum hydride (70 g, 1.9 mol) in dry diethyl ether (1.0 L) over 45 min. After reflux for additional 0.5 h the reaction mixture was cooled to 0 °C and carefully treated with water (70 mL), 4 N aqueous NaOH, and then water (300 mL). The reaction mixture was filtered and dried (Na_2SO_4). Evaporation of the solvents afforded the crystalline title compound (110 g, 55%). An analytical sample was recrystallized from diethyl ether: mp 118−120 °C; ^{1}H NMR ($CDCl_3$) δ 2.35 (broad s, 1 H),4.0 (t, 2 H), 4.15 (t, 2 H), 6.85 (s, 1 H), 7.10 (broad d, 1 H), 7.15 (t, 2 H), 7.40 (dd, 2 H), 7.65 (broad s, 1 H). Anal. ($C_{16}H_{13}ClFNO_2$) C, H, N.

The following compound was prepared accordingly. **2-[6-Chloro-1-(4-fluorophenyl)-1*H*-indol-3-yloxy]ethanol (19b):** mp 97−98 °C (diethyl ether); ^{1}H NMR ($CDCl_3$) δ 4.00 (t, 2 H), 4.15 (t, 2 H), 6.80 (s, 1 H), 7.10 (d, 1 H), 7.20 (t, 2 H), 7.40 (s, 1 H), 7.35 (dd, 2 H), 7.60 (d, 1 H). Anal. ($C_{16}H_{13}ClFNO_2$) C, H, N.

5-Chloro-2,3-dihydro-1-(4-fluorophenyl)-1*H*-indol-3-one (27). To a mixture of $Na_2SO_3 \cdot 7H_2O$ (90 g, 0.36 mol) and water (1.8 L) was added ethanol (1.5 L) and 3-acetoxy-5-chloro-1-(4-fluorophenyl)-1*H*-indole (prepared according to literature procedures[1,47,48]) (**26**) (60 g, 0.20 mol) at 60 °C. The resulting mixture was refluxed for 1 h, and after stirring at room temperature for further 18 h the precipitate was filtered off, washed with water (300 mL) at 60 °C, and dried *in vacuo* overnight at 60 °C affording the title compound (44.3 g, 85%): mp 99−101 °C; ^{1}H NMR ($CDCl_3$) δ 4.20 (s, 2 H), 7.10 (s, 1 H), 7.10 (t, 2 H), 7.25 (dd, 2 H), 7.40 (broad d, 1H), 7.60 (broad s, 1 H). Anal. ($C_{14}H_9ClFNO$) C, H, N.

2-[5-Chloro-1-(4-fluorophenyl)-1*H*-indol-3-ylsulfanyl]ethanol (20). A mixture of 5-chloro-2,3-dihydro-1-(4-fluorophenyl)-1*H*-indol-3-one (**27**) (25.0 g, 0.10 mol), mercaptoacetic acid (25 g, 0.27 mol), *p*-toluenesulfonic acid (5.0 g), and toluene (500 mL) was refluxed for 18 h. Evaporation of the solvents afforded the crude 2-[5-chloro-1-(4-fluorophenyl)-1*H*-indol-3-ylsulfanyl]acetic acid (**18**), which was isolated as an oil and used without further purification. A solution of the crude acid in dry tetrahydrofuran (200 mL) was added to a suspension of lithium aluminum hydride (7.5 g, 0.20 mol) in dry tetrahydrofuran (200 mL) during 15 min. After reflux for 1 h the reaction mixture was cooled to 0 °C and carefully treated with water (5 mL) and 28% aqueous NaOH (5 mL). The precipitate was filtered off and extracted with dichloromethane (3 × 500 mL). The combined organic phases were dried ($MgSO_4$), and the solvents were evaporated affording the title compound (**20**) as an oil (25 g). Purification by column chromatography on silica gel (eluted with ethyl acetate/heptane 1:2) afforded the pure title compound (**20**) (12 g, 40%) as an oil. An analytical sample was crystallized from ether/heptane (1:2): mp 85−86 °C; ^{1}H NMR ($CDCl_3$) δ 2.10−2.50 (broad s, 1 H), 2.95 (t, 2 H), 3.70 (t, 2 H), 7.20 (broad d, 1 H), 7.25 (t, 2 H), 7.35 (d, 1 H), 7.40 (dd, 2 H), 7.45 (s, 1 H), 7.80 (broad s, 1 H). Anal. ($C_{16}H_{13}ClFNOS$) C, H, N.

3-[6-Chloro-1-(4-fluorophenyl)-1*H*-indol-3-yloxy]propanol (21). To a refluxing solution of 1,3-propandiol (8.7 g, 0.115 mol) and *p*-toluenesulfonic acid (2.5 g) in toluene (150 mL) was added a solution of 5-chloro-2,3-dihydro-1-(4-fluorophenyl)-1*H*-indol-3-one (**27**) (6 g, 0.023 mol) in toluene (100 mL) over 25 min. After reflux for further 10 min the solvents were evaporated. Purification by column chromatography on silica gel (eluted with ethyl acetate/heptane 1:1) afforded the title compound (**21**) (2.4 g, 33%) as an oil: ^{1}H NMR (DMSO-d_6) δ 1.95 (m, 2 H), 3.65 (m, 2 H), 4.15 (t, 2 H), 4.60 (t, 1 H), 7.20 (broad d, 1 H), 7.30−7.55 (m, 4 H), 7.55−7.65 (m, 3 H).

General Procedure for the Conversion of Alcohols 13a, 13b, 19a, 19b, 20, and 21 to Corresponding Amines 14, 15, 22, 23, 24, and 25, Respectively. 1-[2-[2-[5-Chloro-1-(4-fluorophenyl)-1*H*-indol-3-yloxy]ethylmethylamino]-ethyl]-2-imidazolidinone Maleate (22b). To a solution of 2-[5-chloro-1-(4-fluorophenyl)-1*H*-indol-3-yloxy]ethanol (**19a**) (4.8, 0.016 mol) and triethylamine (5 mL) in dichloromethane (50 mL) a solution of methanesulfonyl chloride (1.9 mL, 0.025 mol) in dichloromethane (16 mL) was added at 0−5 °C over 0.5 h. After stirring for 3 h at room temperature the reaction mixture was washed with water (2 × 100 mL) and dried (Na_2SO_4), and the solvents were evaporated *in vacuo*. Excess of methanesulfonyl chloride was removed by concentrating the remaining oil with toluene *in vacuo* several times. The crude methansulfonate of **19a** (6.0 g, 0.016 mol) was used without further purification. A mixture of the crude methansulfonate, 2-[(methylamino)ethyl]-2-imidazolidinone (4.9 g, 0.034 mol), K_2CO_3 (4.0 g, 0.029 mol), and methyl isobutyl ketone was refluxed for 18 h. After cooling to room temperature, water (100 mL) was added, and the resulting mixture was extracted with ethyl acetate (2 × 100 mL). The combined organic phases were washed with water (100 mL) and brine (100 mL) and dried (Na_2SO_4). Evaporation of the solvents and purification by column chromatography on silica gel (eluted with ethyl acetate/ethanol 5:1 containing 4% triethylamine) afforded the title compound (4.2 g, 61%) as an oil. The title compound crystallized as its maleate from ethyl acetate: mp 183−185 °C; ^{1}H NMR (DMSO-d_6) δ 2.85 (s, 3 H), 3.20−3.55 (m, 8 H), 3.65 (broad s, 2 H), 4.40 (broad t, 2 H) 6.05 (s, 2 H), 6.65 (broad s, 1 H), 7.2, (broad d, 1 H, 7.45 (t, 2 H), 7.55 (d, 1 H), 7.69 (7.55, 1 H), 7.60 (dd, 2 H), 7.70 (broad s, 1 H); MS (*m*/*z*) 431 (MH^+, 2), 170 (33), 113 (100). Anal. ($C_{22}H_{24}ClFN_4O_2 \cdot C_4H_4O_4$) C, H, N.

The following compounds were prepared accordingly. ***N*,*N*-Dimethyl-3-[5-chloro-1-(4-fluorophenyl)-1*H*-indol-3-yl]-propylamine fumarate (14a):** mp 172−173 °C (ethanol); ^{1}H NMR (DMSO-d_6) δ 2.00 (qui, 2 H), 2.50 (s, 6 H), 2.65−2.90 (m, 4 H), 6.50 (s, 2 H), 7.20 (broad d, 1 H), 7.40 (t, 2 H), 7.45 (d, 1 H), 7.55 (s, 1 H), 7.60 (dd, 2 H), 7.70 (broad s, 1 H); MS (*m*/*z*) 331 (MH^+, 37), 286 (71), 258 (100), 251 (62). Anal. ($C_{19}H_{20}ClFN_2 \cdot C_4H_4O_4$) C, H, N.

1-[2-[[3-[5-Chloro-1-(4-fluorophenyl)-1*H*-indol-3-yl]-propyl]methylamino]ethyl]-2-imidazolidinone fumarate (14b): mp 132−134 °C (ethanol); ^{1}H NMR (DMSO-d_6) δ 180−2.00 (m, 2 H), 2.40 (s, 3 H), 2.55−2.80 (m, 6 H), 3.15−3.25 (m, 4 H), 3.30−3.40 (m, 2 H), 6.30 (s, 1 H), 6.60 (s, 2 H), 7.20 (broad

Table 5. Global Minimum Energy Conformations for Compounds Included in the Molecular Modeling Study. For Compounds Having Global Minimum Energy Conformations with the 3-Substituent in a Coiled Conformation, the Conformation and Conformational Energy of the Uncoiled Conformation with Lowest Energy Is Indicated

compd	dihedral angles A	B	C	D	conformational energy, kcal/mol	conformer
5a	60°	−54°	−	−	0.0	global minimum (uncoiled)
9b	69°	52°	55°	−	0.0	global minimum (uncoiled)
14a	100°	−72°	63°	−53°	0.0	global minimum (coiled)
	76°	178°	55°	−56°	0.8	local minimum (uncoiled)
22a	−172°	−179°	−170°	58°	0.0	global minimum (uncoiled)
24a	105°	−84°	66°	−52°	0.0	global minimum (coiled)
	120°	−63°	−172°	57°	1.0	local minimum (uncoiled)

Table 6. Forcefield Parameters Added to the MM2(91) Force-Field[a]

	atom types	*V*1	*V*2	*V*3
Torsional Parameters (kcal/mol)				
$C(sp^3)-C(sp^2)-C(sp^2)-N(sp^2)$	(1−2−2−40)	0.	15.	0.
$O(sp^3)-C(sp^2)-C(sp^2)-N(sp^2)$	(6−2−2−40)	0.	15.	0.
$N(sp^3)-C(sp^3)-C(sp^3)-S\ (sp^3)$	(8−1−1−15)	0.	0.	0.35
$C(sp^2)-C(sp^2)-C(sp^2)-S(sp^3)$	(2−2−2−15)	0.	16.25	0.
$S(sp^3)-C(sp^2)-C(sp^2)-N(sp^2)$	(15−2−2−40)	0.	16.25	0.
$H-C(sp^2)-C(sp^2)-S(sp^3)$	(5−2−2−15)	0.	16.25	0.
$C(sp^2)-C(sp^2)-S(sp^3)-C(sp^3)$	(2−2−15−1)	−1.8	1.	−0.7
$H-C(sp^3)-S(sp^3)-C(sp^2)$	(5−1−15−2)	0.	0.	0.5
$C(sp^3)-C(sp^3)-S(sp^3)-C(sp^2)$	(1−1−15−2)	0.0	0.0	0.5

	atom types	I_0 (Å)	k (mdyn Å^{-1})
Bond Length and Stretching Constant			
$C(sp^2)-S(sp^3)$	(2−15)	1.765	4.0

	atom types	θ_0 (deg)	k_θ (mdyn Å rad^{-2})
Bond Angles and Bending Constants			
$S(sp^3)-C(sp^2)-C(sp^2)$	(2−2−15)	120.0	0.5
$C(sp^3)-S(sp^3)-C(sp^2)$	(1−15−2)	94.0	0.6
$C(sp^2)-S(sp^3)$ out-of-plane	(2−15)		0.05

[a] The constants were chosen in analogy with parameters for similar combinations of atoms in the standard forcefield parameter list or in analogy with parameters for similar combinations of atoms published by Kao *et al*.[52]

s, 1 H), 7.40 (t, 2 H), 7.45 (d, 1 H), 7.55 (s, 1 H), 7.60 (dd, 2 H), 7.70 (broad s, 1 H); MS (*m*/*z*) 429 (MH^+, 20), 286 (4), 113 (100). Anal. ($C_{23}H_{26}ClFN_4O\cdot C_4H_4O_4$) C, H, N.

***N,N*-Dimethyl-4-[5-chloro-1-(4-fluorophenyl)-1*H*-indol-3-yl]butylamine maleate (15):** mp 131−133 °C (ethyl acetate); ^{1}H NMR (DMSO-d_6) δ 1.70−2.95 (m, 4 H), 2.80 (s, 6 H), 2.75−2.85 (m, 2 H), 3.00−3.15 (m, 2 H), 6.25 (s, 2 H), 7.10−7.25 (m, 4 H) 7.35 (d, 1 H), 7.40 (dd, 2 H), 7.55 (broad s, 1 H); MS (*m*/*z*) 345 (MH^+, 15), 300 (85), 265 (100). Anal. ($C_{20}H_{22}ClFN_2\cdot C_4H_4O_4$) C, H, N.

***N,N*-Dimethyl-2-[5-chloro-1-(4-fluorophenyl)-1*H*-indol-3-yloxy]ethylamine sesquifumarate (22a):** mp 165−167 °C (ethanol); ^{1}H NMR (DMSO-d_6) δ 2.60 (s, 6 H), 3.15 (t, 2 H), 4.30 (t, 2 H), 6.60 (s, 3 H), 7.20 (broad d, 1 H), 7.40 (t, 2 H), 7.45 (s, 1 H), 7.50 (d, 1 H), 7.60 (dd, 2 H), 7.65 (broad s, 1 H); MS (*m*/*z*) 333 (MH^+), 72 (100). Anal. ($C_{18}H_{18}ClFN_2O\cdot 1.5(C_4H_4O_4)$) C, H, N.

1-[2-[[2-[5-Chloro-1-(4-fluorophenyl)-1*H*-indol-3-yloxy]ethyl]ethylamino]ethyl]-2-imidazolidinone maleate (22c): mp 155−157 °C (ethyl acetate); ^{1}H NMR (DMSO-d_6) δ 1.30 (t, 3 H), 3.20−3.55 (m, 10 H), 3.55−3.80 (m, 2 H), 4.35−4.50 (m, 2 H), 6.05 (s, 2 H), 6.65 (s, 1 H), 7.25 (broad d, 1 H), 7.40 (t, 2 H), 7.50 (d, 1 H), 7.55 (s, 1 H), 7.60 (dd, 2 H), 7.70 (broad s, 1 H); MS (*m*/*z*) 445 (MH^+, 3), 184 (41), 113 (100). Anal. ($C_{23}H_{26}ClFN_4O_2\cdot C_4H_4O_4$) C, H, N.

1-[2-[[2-[5-Chloro-1-(4-fluorophenyl)-1*H*-indol-3-yloxy]ethyl]-3-propynylamino]ethyl]-2-imidazolidinone oxalate (22d): mp 139−141 °C (acetone); ^{1}H NMR (DMSO-d_6) δ 2.75 (t, 2 H), 3.00 (t, 2 H), 3.10−3.30 (m, 5 H), 3.40 (t, 2 H), 3.65 (broad s, 2 H), 4.15 (t, 2 H), 6.25 (broad s, 1 H),7.20 (broad d, 1 H), 7.40 (t, 2 H), 7.45 (s, 1 H), 7.50 (d, 1 H), 7.55 (broad s, 1 H), 7.60 (dd, 2 H); MS (*m*/*z*) 455 (MH^+, 3), 194 (41), 113 (100). Anal. ($C_{24}H_{24}ClFN_4O_2\cdot C_2H_2O_4$) C, H, N.

5-Chloro-1-(4-fluorophenyl)-3-(2-(1-piperidinyl)ethoxy)-1*H*-indole (22e): mp 82−84 °C (*n*-heptane); ^{1}H NMR ($CDCl_3$) δ 1.40−1.55 (m, 2 H), 1.55−1.70 (m, 4 H), 2.50 (t, 4H), 2.85 (t, 2 H), 4.15 (t, 2 H), 6.85 (s, 1 H), 7.15 (broad d, 1 H), 7.20 (t, 2 H), 7.30 (d, 1 H), 7.40 (dd, 2 H), 7.65 (broad s, 1 H); MS (*m*/*z*) 373 (MH^+, 1), 260 (2), 112 (100). Anal. ($C_{21}H_{22}ClFN_2O$) C, H, N.

5-Chloro-1-(4-fluorophenyl)-3-(2-(4-morpholinyl)-ethoxy)-1*H*-indole maleate (22f): mp 185−187 °C (ethyl acetate); ^{1}H NMR (DMSO-d_6) δ 3.15−3.40 (m, 4 H), 3.40−3.60 (m, 2 H), 3.75−3.95 (m, 4 H), 4.40 (t, 2 H), 6.10 (s, 2 H), 6.25 (broad d, 1 H), 7.40 (t, 2 H), 7.50 (d, 1 H), 7.55 (s, 1 H), 7.60 (dd, 2 H), 7.70 (broad s, 1 H); MS (*m*/*z*) 375 (MH^+, 2), 114 (100). Anal. ($C_{20}H_{20}ClFN_2O_2\cdot C_4H_4O_4$) C, H, N.

5-Chloro-1-(4-fluorophenyl)-3-[(4-methylpiperazinyl)-ethoxy]-1*H*-indole dimaleate (22g): mp 196−198 °C (ethyl acetate); ^{1}H NMR (DMSO-d_6) δ 2.70−3.40 (m, 8 H), 2.80 (s, 3 H), 2.95 (t, 2 H), 4.20 (t, 2 H), 6.15 (s, 4 H), 7.20 (broad d, 1 H), 7.40 (t, 2 H), 7.45 (s, 1 H), 7.50 (d, 1 H), 7.55 (broad s, 1 H), 7.60 (dd, 2 H); MS (*m*/*z*) 388 (MH^+, 4), 127 (100). Anal. ($C_{21}H_{23}ClFN_3O\cdot 2(C_4H_4O_4)$) C, H, N.

***N,N*-Dimethyl-2-[6-chloro-1-(4-fluorophenyl)-1*H*-indol-3-yloxy]ethylamine (23a):** mp 66−68 °C (*n*-heptane); ^{1}H NMR ($CDCl_3$) δ 2.40 (s, 6 H), 2.80 (t, 2 H), 4.10 (t, 2 H), 6.80 (s, 1 H), 7.10 (d, 1 H), 7.20 (t, 2 H), 7.35 (broad s, 1 H), 7.40 (dd, 2 H), 7.60 (d, 1 H); MS (*m*/*z*) 333 (MH^+), 72 (100). Anal. ($C_{18}H_{18}ClFN_2O$) C, H, N.

1-[2-[[2-[6-Chloro-1-(4-fluorophenyl)-1*H*-indol-3-yloxy]-ethyl]methylamino]ethyl]-2-imidazolidinone (23b): mp 100−102 °C (diethyl ether); ^{1}H NMR ($CDCl_3$) δ 2.40 (s, 3 H), 2.65 (t, 2 H), 2.90 (t, 2 H), 3.30−3.40 (m, 4 H), 3.45−3.60 (m, 2 H), 4.10 (t, 2 H), 4.50 (broad s, 1 H), 6.80 (s, 1 H), 7.10 (broad d, 1 H), 7.20 (t, 2 H), 7.35 (broad s, 1 H), 7.40 (dd, 2 H), 7.60 (d, 1 H); MS (*m*/*z*) 431 (MH^+, 3), 170 (65), 113 (100). Anal. ($C_{22}H_{24}ClFN_4O_2$) C, H, N.

1-[2-[[2-[6-Chloro-1-(4-fluorophenyl)-1*H*-indol-3-yloxy]-ethyl]methylamino]ethyl]-3-(2-propyl)-2-imidazolidinone oxalate (23c): mp 165−167 °C (acetone); ^{1}H NMR (DMSO-d_6) δ 1.00 (d, 6 H), 2.80 (s, 3 H), 3.10−3.55 (m, 10 H), 3.90 (h, 1 H), 4.40 (m, 2 H), 7.15 (broad d, 1 H), 7.40 (t, 2 H), 7.45 (s, 1 H), 7.50 (broad s, 1 H), 7.60 (dd, 2 H), 7.65 (d, 1 H); MS (*m*/*z*) 473 (MH^+, 10), 212 (62), 155 (100). Anal. ($C_{25}H_{30}ClFN_4O_2\cdot C_2H_2O_4$) C, H, N.

***N,N*-Dimethyl-2-[5-chloro-1-(4-fluorophenyl)-1*H*-indol-3-ylsulfanyl]ethylamine hydrochloride (24a):** mp 200−202 °C (acetone); ^{1}H NMR (DMSO-d_6) δ 2.70 (s, 6 H), 3.05−3.30 (m, 4 H), 7.30 (dd, 1 H), 7.45 (t, 2 H), 7.55 (d, 1 H), 7.75 (broad s, 1 H), 7.70 (dd, 2 H), 8.10 (s, 1 H); MS (*m*/*z*) 349 (MH^+, 1), 276 (100), 104 (34), 58 (64). Anal. ($C_{18}H_{18}ClFN_2S\cdot HCl$) C, H, N.

1-[2-[[2-[5-Chloro-1-(4-fluorophenyl)-1*H*-indol-3-ylsulfanyl]ethylmethyl]amino]ethyl]-2-imidazolidinone (24b): mp 65−67 °C (acetone); ^{1}H NMR ($CDCl_3$) δ 2.95 (s, 3 H), 3.35−3.75 (m, 15 H), 4.90 (s, 1 H), 7.35 (t, 2 H), 7.40 (bd, 1 H), 7.50 (d, 1 H), 7.65 (d, 1 H), 7.75 (s, 1 H), 7.85 (broad s, 1 H); MS (*m*/*z*) 447 (MH^+, 4), 276 (100), 202 (13), 113 (51). Anal. ($C_{22}H_{24}ClFN_4OS\cdot HCl\cdot 0.85H_2O$) C, H, N.

***N,N*-Dimethyl-2-[5-chloro-1-(4-fluorophenyl)-1*H*-indol-3-yloxy]propylamine maleate (25):** mp 122−124 °C (ethyl acetate/diethyl ether); ^{1}H NMR (DMSO-d_6) δ 2.20−2.40 (m, 2 H), 2.90 (s, 6 H), 3.30−3.40 (m, 2 H), 4.10 (t, 2 H), 6.20 (s, 2 H), 6.85 (s, 1 H), 7.10−7.25 (m, 3 H), 7.30 (d, 1 H), 7.40 (dd, 2

H), 7.60 (broad s, 1 H); MS (*m*/*z*) 347 (MH^+), 86 (52), 58 (100). Anal. ($C_{19}H_{20}ClFN_2O \cdot C_4H_4O_4$) C, H, N.

Pharmacological Test Methods. Receptor Binding. Dopamine D_2 Receptors and Serotonin 5-HT_2 Receptors. Affinity of test compounds to dopamine D_2 receptors was estimated by their ability to displace [^{3}H]spiperone from rat striatal membranes and the affinity of test compounds to serotonin 5-HT_2 receptors was estimated by their ability to displace [^{3}H]ketanserin from rat cortical membranes as described by Hyttel.[49]

α_1 Adrenoceptors. Affinity of test compounds to α_1 adrenoceptors was estimated by their ability to displace [^{3}H]-prazosin from whole rat brain membranes as described by Skarsfeldt and Hyttel.[50]

Antagonism of Quipazine-Induced Head Twitches. The experimental details are given by Arnt et al.[43] Test compounds were injected sc or po to rats 2 or 24 h before quipazine (15 μmol/kg, sc). Head twitches were counted 30−40 min after the quipazine treatment. The number of head twitches in the drug treated group (at least four animals per dose) was expressed in percent of the number of head twitches in a quipazine-treated control group.

Antagonism of Pergolide-Induced Circling Behavior in Rats with Unilateral 6-OHDA Lesions. This test method is described in detail by Arnt and Hyttel.[44] Contralateral circling is induced in 6-OHDA lesioned rats in response to administration of pergolide (0.050 μmol/kg, sc). Test compounds were injected sc 2 h before pergolide. The effect of individual doses of test drugs is calculated as percent of the mean effect of control sessions one week before and one week after the test session for each rat (at least four rats per dose).

Computational Methods. Conformational energies and energy-minimized geometries were calculated using the molecular mechanics program MM2(91) developed by Allinger and co-workers.[51,53] In addition to standard force field parameters, constants listed in Table 6 were chosen in analogy with parameters for similar combinations of atoms in the MM2-(91) force field parameter list or in analogy with parameters reported by Kao *et al*.[52] As in previous work, all calculations were done on the unprotonated amines with unshared electron pairs represented by a pseudoatom.[10] Conformational energy curves were calculated by using the driver option implemented in MM2(91) with an angle increment of 10° and with full energy minimization except the dihedral angle(s) used as driving angle(s). The construction of input structures for MM2(91) and the studies on molecular superimposition were done by means of the molecular modeling program MacMimic.[53] Fitting points used in the superimpositions were the centers of the two benzene rings (e.g. the benzene part of the indole nucleus (A) and the 4-fluorophenyl group (B)) and a point 2.8 Å from the basic nitrogen atom in the direction of the lone pair (C). The point C is assumed to simulate a receptor site hydrogen bonding with the nitrogen atom.

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