

Selective, Centrally Acting Serotonin 5-HT₂ Antagonists. 2. Substituted 3-(4-Fluorophenyl)-1H-indoles

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A series of 3-(4-fluorophenyl)-1H-indoles substituted in the 1-position with 4-piperidinyl, 1,2,3,6-tetrahydro-4-pyridinyl, and 4-piperazinyl was synthesized. By variation of the substituents in the benzene part of the indole nucleus in 1-[2-[4-[3-(4-fluorophenyl)-1H-indol-1-yl]-1-piperidinyl]-ethyl]-2-imidazolidinones, the highest 5-HT₂ receptor affinity and selectivity with respect to dopamine D₂ receptors and α_1 adrenoceptors were obtained by 5-methyl substitution. Different substituents were introduced in the 1-position of the piperidine ring in the 5-methyl-substituted derivative. Thus replacement of the 2-(2-imidazolidinon-1-yl)ethyl side chain with a 2-(1,3-dimethyl-1-ureido)ethyl or methyl substituent resulted in unchanged affinity and selectivity for 5-HT₂ receptors. Replacement with a 2-[3-(2-propyl)-2-imidazolidinon-1-yl]ethyl side chain reduced binding to α_1 adrenoceptors with a factor of four, while affinities for 5-HT₂ and D₂ receptors were retained, compared to the 3-unsubstituted imidazolidinone. Indoles substituted in the 1-position with 4-piperazinyl had generally weaker affinity for both 5-HT₂ and D₂ receptors compared to corresponding 4-piperidinyl- and 1,2,3,6-tetrahydro-4-pyridinyl-substituted indoles. Introduction of a methyl group in the 2-position of the 5-methyl-substituted indole resulted in further increase of selectivity for the 5-HT₂ receptor. Compounds with potent receptor binding also potently inhibited the quipazine-induced head twitch syndrome in rats. The compounds were equally active after oral and subcutaneous administration and showed a long duration of action (>24 h). In general, the derivatives were found to be considerably more potent at 24 h than at 2 h after the administration. The compounds within this series were prepared as analogues of the previously described 1-(4-fluorophenyl)-3-(4-piperidyl)-1H-indoles by interchange of the C-3 carbon atom and the nitrogen atom in the indole nucleus. The pharmacological results indicate that this isosteric replacement results in higher selectivity for 5-HT₂ receptors compared to the former series. The 1-[2-[4-[2,5-dimethyl-3-(4-fluorophenyl)-1H-indol-1-yl]-1-piperidinyl]ethyl]-2-imidazolidinone has high affinity for 5-HT₂ receptors (IC₅₀ = 3.4 nM) and extremely low affinity for both dopamine D₂ receptors (IC₅₀ = 6900 nM) and α_1 adrenoceptors (IC₅₀ = 2300 nM).

Introduction

The preceding paper¹ within this series discussed the structure-activity relationship in a series of 6-substituted 1-phenyl-3-(4-piperidinyl)-1H-indoles, which led to the selective and highly potent serotonin 5-HT₂ antagonist Lu 26-042 (1, Figure 1). These compounds were the result of further development of a series of 5-substituted 1-phenyl-3-(4-piperidinyl)-1H-indoles, which in addition to binding affinity for serotonin 5-HT₂ receptors, have strong binding affinity for both dopamine D₂ receptors and α_1 adrenoceptors.² The atypical neuroleptic sertindole (2, Figure 1), which selectively blocks dopaminergic activity in limbic brain areas in rats after chronic treatment, is a member of this series of compounds.³⁻⁵

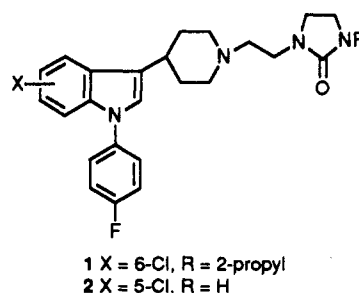


Figure 1. Structure of 1-(4-fluorophenyl)-3-(4-piperidinyl)-1H-indoles.

The involvement of serotonin receptors in psychiatric disorders, such as anxiety and depression, is discussed in part 1¹ within this series. Selective 5-HT₂ antagonists⁶ and compounds, which have 5-HT₂ antagonistic activity as a main component (e.g. sertindole and related 5-substituted 1-phenyl-3-(4-piperidinyl)-1H-indoles),⁷ are active

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in animal models predictive of anxiolytic activity. In addition, several clinical studies with the 5-HT₂ antagonist ritanserin have suggested improvements in dysthymic disorders,⁸ negative symptoms in schizophrenia,⁹ and quality of sleep.¹⁰ These pharmacological and clinical results prompted us to investigate the possibilities of further increasing the selectivity for central 5-HT₂ receptors within indole derivatives with 5-HT₂ antagonistic activity.

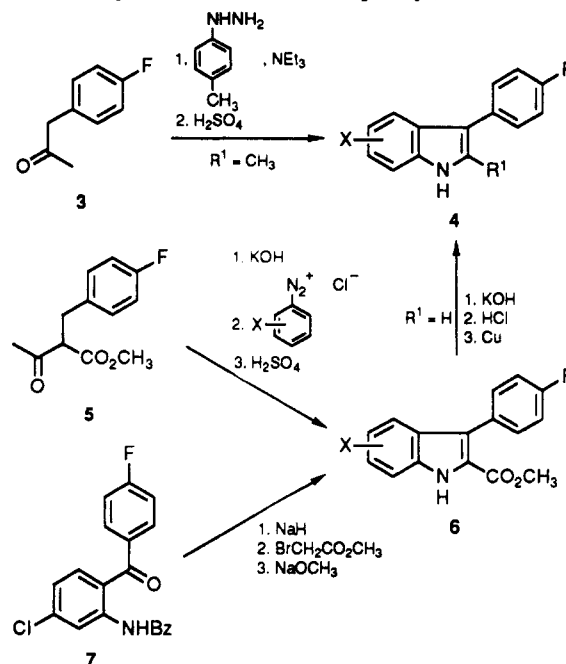
The increase in 5-HT receptor affinity, obtained by interchange of the C-3 atom and the nitrogen atom in the indole nucleus of the hallucinogenic agent dimethyltryptamine,¹¹ led us to investigation of the pharmacological effects of this isosteric replacement in the series of 1-phenyl-3-(4-piperidinyl)indoles, although the two structurally different series of molecules probably bind to two different subtypes of 5-HT receptors. Consequently, in this paper, we discuss the chemical development and structure-activity relationship within a new series of 3-(4-fluorophenyl)-1H-indoles substituted in the 1-position with 4-piperidinyl, 1,2,3,6-tetrahydro-4-pyridinyl, or 4-piperazinyl.

Chemistry

The preparation of 1-(1-methyl-4-piperidinyl)-3-phenyl-1H-indole as intermediate in the synthesis of substituted 2-benzoylaniline is described by Adachi et al.¹² This method, however, is not suitable for preparation of compounds with variation of substituents in the indole nucleus. Thus, we decided to develop new and more versatile methods, which in addition to 1-(4-piperidinyl)indoles (10) afforded 1-(1,2,3,6-tetrahydro-4-pyridinyl)indoles (12) and 1-(4-piperazinyl)indole (14). 1-Unsubstituted indoles (4) are key intermediates in these methods.

The key intermediates 4 were prepared as outlined in Scheme I. The 2-methylindole (4, R¹ = CH₃) was prepared by the Fischer indole synthesis¹³ from 4-tolylhydrazine and (4-fluorophenyl)acetone (3). The esters 6 used as intermediates in the preparation of 2-unsubstituted indoles (4, R¹ = H) were prepared by two routes. Japp-Klingemann reaction of unsubstituted and 2- and 4-substituted anilines with methyl 2-(4-fluorobenzyl)-3-oxobutanoate (5) followed by Fischer indole synthesis¹⁴ afforded the unsubstituted and 7- and 5-substituted esters

Scheme I Synthesis of 3-(4-Fluorophenyl)indoles 4



6, respectively. The 6-chloro-substituted ester (6, X = 6-Cl) was prepared from the 2-benzoylaniline 7 by a modification of the method described by Jones.¹⁵ Esters 6 were converted to the corresponding 2-unsubstituted indoles (4, R¹ = H) by hydrolysis followed by decarboxylation.¹⁶ The 4-methylindole (4, X = 4-CH₃) was prepared by removal of the bromine atom in 7-bromo-4-methylindole (4, X = 7-Br, 4-CH₃) which was prepared from 2-bromo-5-methylaniline by Fischer indole synthesis followed by hydrolysis and decarboxylation as described above. The bromo substituent was introduced to avoid formation of a mixture of 4- and 6-methylindole in the ring closure reaction.

Conversion of the indoles 4 to the corresponding 1-(4-piperidinyl)indoles 10 is described in Scheme II. Copper-catalyzed Ullmann arylation of indoles 4 with 4-chloro- or 4-bromopyridine in *N*-methyl-2-pyrrolidinone (NMP) afforded the corresponding 1-(4-pyridinyl)indoles 8. 4-Bromopyridine was used in the arylation of 2-methyl- and 7-methylindoles, which did not react with 4-chloropyridine, probably due to steric hindrance. It was possible to perform the decarboxylation described above and the arylation with 4-chloropyridine in a one-pot procedure. Catalytic hydrogenation of the 1-(4-pyridinyl)indoles 8 afforded the unsubstituted piperidinylindoles 9. 2-(2-Imidazolidinon-1-yl)ethyl side chains (formulas A and B, Chart I) in compounds 10 were introduced by alkylation of the unsubstituted piperidinylindoles 9 with appropriate alkylating agents. Urea side chains (formulas C and D, Chart I) were introduced by building up the side chain in a straightforward procedure as described previously.¹ Quaternization of 1-(4-pyridinyl)indoles 8 with 1-(2-iodoethyl)-2-imidazolidinone or methyl iodide, followed by reduction with NaBH₄ afforded the corresponding 1-(1,2,3,6-tetrahydro-4-pyridinyl)indoles 12. These compounds were reduced to piperidinylindoles 10 with am-

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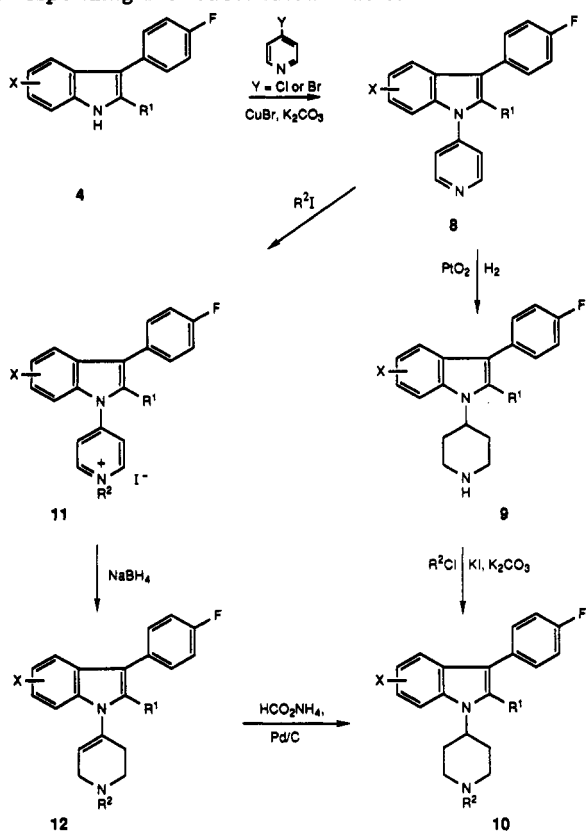
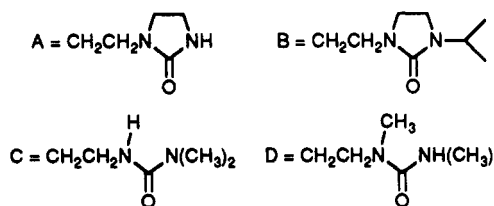
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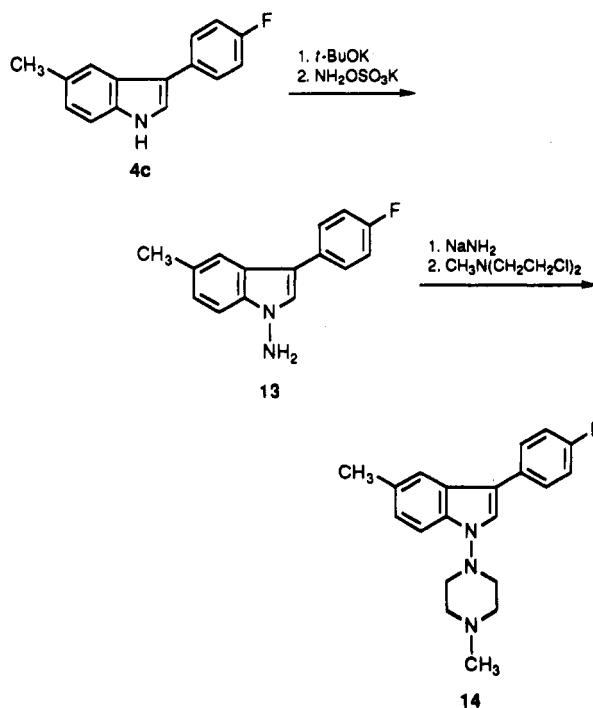
Scheme II Synthesis of 1-(4-Piperidynyl)indoles 10 and 1-(1,2,3,6-Tetrahydro-4-pyridinyl)indoles 12 from the Corresponding 1-Unsubstituted Indoles 4**Chart I.** Structures of Substituent R²

monium formate using palladium as catalyst. This alternative procedure was used for the preparation of 2- and 7-substituted 1-(4-piperidynyl)indoles 10, since the corresponding 1-(4-pyridinyl)indoles 8 were inert to the catalytic hydrogenation conditions described above.

The 1-(4-piperazinyl)indole 14 was prepared from the corresponding indole 4c as outlined in Scheme III. Reaction of 4c with potassium hydroxylamine *O*-sulfate in dimethylformamide¹⁷ afforded a mixture of the desired 1-aminoindole 13 and starting material, due to the deaminating properties of potassium hydroxylamine *O*-sulfate.¹⁸ The aminoindole was easily isolated by chromatography. Reaction with *N,N*-bis(2-chloroethyl)-methylamine and sodium amide in toluene afforded the piperazinylindole 14.

Results and Discussion

The pharmacological test models are described in details in the Experimental Section. Receptor binding affinities

Scheme III. Synthesis of 1-(4-Piperazinyl)indole 14 from the Corresponding 1-Unsubstituted Indole 4c

(dopamine D₂, adrenergic α₁, serotonin 5-HT₂) are reported in Table I. The affinities are compared to the reference compound ritanserin, to the atypical neuroleptic sertindole (2, Figure 1), and to the 5-HT₂ antagonist Lu 26-042 (1, Figure 1). Ritanserin was the first centrally acting 5-HT₂ antagonist identified with considerable selectivity in respect of non-5-HT receptors,¹⁹ and the two latter compounds are members of the previously described series of 1-(4-fluorophenyl)-3-(4-piperidynyl)indoles.^{1,2}

Compound 10a is isosterically related to sertindole (2, Figure 1) by interchange of the C-3 carbon atom and the nitrogen atom in the indole nucleus. By comparing the binding affinities of these two compounds it appears that this isosteric replacement results in a slightly weaker affinity for both 5-HT₂, D₂, and α₁ receptors. The unsubstituted derivative 10b has retained affinity for 5-HT₂ and α₁ receptors, whereas the affinity for D₂ receptors are slightly weakened compared to 10a. Introduction of substituents in the 5-position (10c-f) results in retained 5-HT₂ receptor affinity, while affinities for both D₂ and α₁ receptors are decreased. The highest affinity and selectivity for the 5-HT₂ receptor are obtained by methyl substitution (10e). Methyl substitution in the 4- and 7-positions afforded compounds 10g and 10h with affinity for the three receptors studied similar to that of the 5-fluoro-substituted compound 10c.

Exchange of the 3-unsubstituted imidazolidinone side chain in 10e with the 3-(2-propyl)-substituted imidazolidinone side chain (formula B, Chart I) reduces the affinity for α₁ adrenoceptors by a factor of 4 while the affinity for 5-HT₂ and D₂ receptors is retained (10j). The urea side chains (formulas C and D, Chart I) were designed as open-chain analogues of the imidazolidinone side chains. The 3,3-dimethyl-substituted derivative 10m has a lower selectivity for the 5-HT₂ receptor in respect to D₂ receptors,

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Table I. Substituents and Binding Affinities of 1-(4-Piperidinyl)indoles 10, 1-(1,2,3,6-Tetrahydro-4-pyridinyl)indoles 12, and 1-(4-Piperazinyl)indole 14

compd	substituents ^b			receptor binding ^a		
	X	R ¹	R ² ^c	serotonin 5-HT ₂ [³ H]ketanserin	dopamine D ₂ [³ H]spiperone	adrenergic α ₁ [³ H]prazosin
10a	6-Cl	H	A	1.9	37	11
10b	H	H	A	3.1	120	6.3
10c	5-F	H	A	3.2	250	19
10d	5-Cl	H	A	5.7	410	67
10e	5-CH ₃	H	A	1.6	920	71
10f	5-CF ₃	H	A	9.3	2500	190
10g	4-CH ₃	H	A	7.9	200	34
10h	7-CH ₃	H	A	3.6	370	23
10i	5-CH ₃	CH ₃	A	3.4	6900	2300
10j	5-CH ₃	H	B	2.7	1100	280
10k	5-CH ₃	H	CH ₃	4.5	540	190
10l	5-CH ₃	CH ₃	CH ₃	5.3	2600	2700
10m	5-CH ₃	H	C	2.3	260	89
10n	5-CH ₃	H	D	2.2	1200	54
12a	5-CH ₃	H	A	1.5	280	24
12b	7-CH ₃	H	A	5.8	530	27
12c	5-CH ₃	CH ₃	A	2.8	6300	1000
14	-	-	-	15	3900	500
Lu 26-042 (1)				1.5	130	70
sertindole (2)				0.39	4.1	3.4
ritanserin				0.40	12	47

^a Results are expressed as IC₅₀ values in nM and 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 IC₅₀ 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 discarded. The following 95% confidence ratios (2 × SD ratio) were calculated: D₂ 2.25; α₁ 2.20; 5-HT₂ 2.05. ^b Refer to substituents of structures 10 and 12 in Scheme I. ^c See Chart I for definitions of R².

whereas the 1,3-dimethyl-substituted derivative 10n has similar affinity and selectivity for the 5-HT₂ receptor as 10e. Replacement of the side chains with a methyl group (10k) results in an affinity and selectivity for 5-HT₂ receptors comparable to that of the corresponding imidazolidinone-substituted derivative (10e).

By comparing the 5-chloro- and 5-methyl-substituted compounds 10d, 10e, and 10j with the corresponding 6-chloro- and 6-methyl-substituted compounds within the preceding series of 1-(4-fluorophenyl)-3-(4-piperidinyl)-indoles,¹ it appears that the former compounds have a slightly lower affinity for 5-HT₂ receptors, whereas the affinity for D₂ and α₁ receptors is decreased by a factor of 3–10, indicating that the interchange of the C-3 carbon atom and the nitrogen atom in the indole nucleus within 6-substituted 1-(4-fluorophenyl)-3-(4-piperidinyl)indoles results in a higher selectivity for 5-HT₂ receptors.

It has previously been shown² that affinity for 5-HT₂ and D₂ receptors in 1-(4-fluorophenyl)-3-(4-piperidinyl)-indoles is independent of replacement of the piperidinyl group with a 1,2,3,6-tetrahydropyridin-4-yl or a 4-piperazinyl group. The 1,2,3,6-tetrahydropyridin-4-yl compounds 12a and 12b have similar affinities for the three studied receptor types compared to the corresponding 4-piperidinyl compounds 10f and 10h, respectively. In contrast, the 4-piperazinyl compound 14 has slightly weaker affinity than the corresponding 4-piperidinyl compound 10k for both 5-HT₂, α₁, and D₂ receptors. This might be due to electronic or basicity differences between the aniline-like nitrogen atom in the previously reported piperazinyl compounds and the 1-aminoindole nitrogen atom in compound 14.

In the preceding series of 1-(4-fluorophenyl)-3-(4-piperidinyl)indoles methyl substitution in the 2-position of the indole nucleus reduces the affinity for both D₂ and α₁ receptors by a factor of 20–30, whereas the affinity for 5-HT₂ receptors is retained. Similarly, introduction of a

methyl group in the 2-position in the 5-methyl-substituted indole 10f results in retained affinity for 5-HT₂ receptors, whereas the affinity for D₂ and α₁ receptors is reduced by a factor of 8 and 30, respectively (10i, Table I). Replacement of the piperidine group in 10i with a 1,2,3,6-tetrahydro-4-pyridinyl group and replacement of the imidazolidinonyl side chain in 10i with a methyl group result in compounds 12c and 10l, respectively, with similar affinity and selectivity for 5-HT₂ receptors as the former compound. These 2,5-dimethyl-substituted derivatives have accordingly been developed from the previous series of 1-(4-fluorophenyl)-3-(4-piperidinyl)indoles by combination of interchange of the C-3 carbon atom and the nitrogen atom in the indole nucleus with subsequent optimization of the substituent pattern in the indole nucleus. The thus obtained selectivity for the 5-HT₂ receptors is quite outstanding compared to the former compounds (e.g. sertindole and Lu 26-042).

Other structural classes of 5-HT₂ antagonists in addition to affinity for 5-HT₂ receptors have affinity for receptors other than the receptors studied in this paper. Ritanserin has rather high affinity for histamine H₁ receptors¹⁹ and the piperazine derivative LY165163 (PAPP) in addition to 5-HT₂ receptor affinity has affinity for serotonergic 5-HT_{1A} receptors.²⁰ Testing of compound 10i for H₁ and 5-HT_{1A} receptor binding affinity, using [³H]mepyramine and [³H]-8-OH-DPAT as ligands, respectively, resulted in IC₅₀ values greater than 10 000 nM (unpublished results).

In the preceding paper within this series¹ two minimum conformations for the 1-(4-fluorophenyl)-3-(4-piperidinyl)-indoles were suggested. The minimum conformations were determined by molecular mechanics calculation of po-

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Table II. Pharmacological Activity of Selected 1-(4-Piperidinyl)indoles 10

compd	inhibition of quipazine-induced head twitches ^a			inhibition of pergolide-induced rotations ^a at 2 h (sc)
	2 h (sc)	24 h (sc)	24 h (po)	
10a	0.30 (0.11–0.81)	0.68 (0.20–2.31)	NT ^b	9.3 (2.6–32)
10e	0.019 (0.0042–0.085)	0.0081 (0.0034–0.019)	0.0041 (0.00067–0.025)	>24
10i	0.096 (0.041–0.22)	0.0041 (0.00041–0.040)	0.038 (0.014–0.098)	>23
10j	0.062 (0.029–0.13)	0.014 (0.0041–0.047)	0.019 (0.0059–0.060)	>18
10l	0.25 (0.10–0.60)	0.028 (0.0093–0.084)	0.046 (0.017–0.11)	>30
10n	0.036 (0.013–0.093)	0.0021 (0.00043–0.010)	0.0040 (0.0013–0.012)	>22
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
ritanserine	0.10 (0.056–0.18)	0.98 (0.35–2.7)	NT	>21

^a Results are expressed as ED₅₀ values in $\mu\text{mol/kg}$. 95% Confidence limits in brackets. ^b NT: not tested.

tential curves for the rotation of the piperidine ring. The calculations were performed with *N*-methyl derivatives for simplicity. The calculated potential curves for rotation of the chair conformation of the piperidine ring in the unsubstituted 3-(4-fluorophenyl)-1-(1-methyl-4-piperidinyl)indole are qualitatively very similar to that of the 1-(4-fluorophenyl)-3-(1-methyl-4-piperidinyl)indole. The energy of the conformations of 3-(4-fluorophenyl)-1-(1-methyl-4-piperidinyl)indole corresponding to the two minimum-energy conformations suggested for the 1-(4-fluorophenyl)-3-(4-piperidinyl)indoles are calculated to be less than 1 kcal/mol higher than the energy of the global minimum conformation of the former compound (Gundertofte, K., H. Lundbeck A/S, Denmark, personal communication, 1991). These calculations indicate that the higher selectivity for 5-HT₂ receptors obtained within the series of 3-(4-fluorophenyl)-1-(4-piperidinyl)indoles compared to 1-(4-fluorophenyl)-3-(4-piperidinyl)indoles cannot be explained by steric reasons, but is more likely due to differences in the electrostatic potentials around the indole nucleus. A further conformational study of the substituted 4-piperidinyl- and 1,2,3,6-tetrahydro-4-pyridinylindoles, described in this and the preceding paper,¹ and comparison with other structurally unrelated selective and nonselective 5-HT₂ receptor antagonists are in progress.

In Table II are reported some important in vivo pharmacological effects of selected compounds. Quipazine is a 5-HT₂ agonist which induces the characteristic head twitch syndrome in rats.²¹ The 6-chloro derivative 10a inhibited these head twitches with a lower potency than did the corresponding 1-(4-fluorophenyl)indole sertindole. In contrast, the 5-methyl-substituted indoles 10e, 10j, and 10n and the 2,5-dimethyl-substituted indoles 10i and 10l inhibited the head twitches with high potency. Even 24 h after administration of the substances the syndrome was effectively prevented, both after subcutaneous and oral administration. The latter derivatives were in general 2–20 times more efficient 24 h after administration compared to 2 h after the administration. The urea derivative 10n was actually the most potent 5-HT₂ antagonist in vivo within the present series of indoles. Some of the compounds within this series are even more potent centrally acting 5-HT₂ antagonists than the key derivatives sertindole and Lu 26-042 from the previously described 1-(4-fluorophenyl)indole series.^{1,2} In order to confirm the absence of any acute antidopaminergic activity, selective compounds were tested for their ability

to inhibit pergolide-induced (D₂ agonist) contralateral circling in rats with unilateral 6-OHDA lesions.²² This test model is very sensitive to classical dopamine D₂ antagonists. Neuroleptics, such as haloperidol and fluphenazine, are active in the range of 0.01–0.05 $\mu\text{mol/kg}$.⁵ Except for the less selective 6-chloro derivative 10a, none of the tested compounds were able to block the pergolide-induced circling behavior.

In comparison to ritanserine the key derivative 10i is quite outstanding both with regard to 5-HT₂ receptor selectivity (relative to D₂ and α_1 receptors) in binding studies (Table I) and in vivo 5-HT₂ antagonistic potency (Table II). This compound is at present being further studied in extended pharmacological test models as prototype of an extremely selective 5-HT₂ antagonist.

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. ¹H NMR spectra were recorded at 250 MHz on a Bruker AC 250 spectrometer. Deuterated chloroform (99.8% D) or dimethylsulfoxide (99.9% D) were used as solvents. TMS was used as internal reference standard. Chemical shift values are expressed in ppm values. The following abbreviations are used for multiplicity of NMR signals: s = singlet, d = doublet, t = triplet, q = quartet, h = heptet, dd = double doublet, m = multiplet. Content of water in crystalline compounds was determined by Karl Fischer titration. Microanalyses were performed by Lundbeck Analytical Department and results obtained were within $\pm 0.4\%$ of the theoretical values.

Syntheses of 1-(2-Halogenoethyl)-2-imidazolidinones. 1-(2-Chloroethyl)-2-imidazolidinone was prepared according to literature.^{1,23} 1-(2-Chloroethyl)-2-imidazolidinone was easily converted to 1-(2-iodoethyl)-2-imidazolidinone by using the Finkelstein reaction.²⁴ The preparation of 1-(2-chloroethyl)-3-(2-propyl)-2-imidazolidinone followed the method reported by Costeli and Züst.²⁵

General Procedures for the Synthesis of Methyl 3-(4-Fluorophenyl)-1*H*-indole-2-carboxylates (6). Methyl 5-Methyl-3-(4-fluorophenyl)-1*H*-indole-2-carboxylate (6a). To a solution of *p*-toluidine (119.4 g, 1.1 mol) in concentrated aqueous HCl (0.58 L) was added a solution of NaNO₂ (84.6 g, 1.2 mol) in water (0.5 L) at 0–5 °C during 1.5 h. The reaction mixture was added in one portion to a mixture of methyl 2-(4-fluorobenzyl)-3-oxobutanoate (5) (250 g, 1.1 mol), KOH (220 g, 3.9 mol), water (0.5 L), ethanol (1.25 L), and ice (2 kg) under stirring. After

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reaction for 2 h at room temperature, the reaction mixture was extracted with diethyl ether (2 × 2 L). The combined organic phases were washed with water (3 L) and dried (Na₂SO₄). Evaporation of the solvents afforded the crude 4-tolylhydrazone of methyl 2-oxo-3-(4-fluorophenyl)propanoate (330 g), which was used without further purification.

A mixture of the crude hydrazone, methanol (2.25 L), and concentrated H₂SO₄ (0.1 L) was refluxed for 18 h. The reaction mixture was cooled to room temperature, and a part of the solvents were evaporated in vacuo. The thus obtained solution was cooled to 0 °C, and the precipitated compound was filtered off and dried overnight in vacuo: yield 180 g (58%); mp 151–155 °C; ¹H NMR (CDCl₃) δ 2.40 (s, 3 H), 3.80 (s, 3 H), 7.1–7.2 (m, 3 H), 7.30 (d, 1 H), 7.35 (s, 1 H), 7.50 (dd, 2 H), 9.10 (broad s, 1 H). Anal. (C₁₇H₁₄FN₂) C, H, N.

The following compounds were prepared accordingly: **Methyl 3-(4-fluorophenyl)-1H-indole-2-carboxylate (6b)** was isolated as an oil: ¹H NMR (CDCl₃) δ 3.80 (s, 3 H), 7.10–7.20 (m, 3 H), 7.30–7.50 (m, 2 H), 7.55 (dd, 2 H), 7.60 (d, 1 H), 9.05 (broad s, 1 H).

Methyl 5-Fluoro-3-(4-fluorophenyl)-1H-indole-2-carboxylate (6c): mp 169–170 °C (di-2-propyl ether); ¹H NMR (CDCl₃) δ 3.85 (s, 3 H), 7.10–7.30 (m, 4 H), 7.40 (dd, 2 H), 7.50 (dd, 1 H), 9.05 (broad s, 1 H). Anal. (C₁₆H₁₁F₂NO₂) C, H, N.

Methyl 5-Chloro-3-(4-fluorophenyl)-1H-indole-2-carboxylate (6d): mp 184–186 °C (di-2-propyl ether); ¹H NMR (CDCl₃) δ 3.80 (s, 3 H), 7.15 (t, 2 H), 7.25–7.40 (m, 2 H), 7.50 (dd, 2 H), 7.55 (s, 1 H), 9.10 (broad s, 1 H). Anal. (C₁₆H₁₁ClFNO₂) C, H, N.

Methyl 3-(4-Fluorophenyl)-5-(trifluoromethyl)-1H-indole-2-carboxylate (6e): mp 164–166 °C (methanol); ¹H NMR (CDCl₃) δ 3.85 (s, 3 H), 7.20 (t, 2 H), 7.50 (dd, 2 H), 7.55–7.65 (m, 2 H), 7.85 (s, 1 H), 9.30 (broad s, 1 H). Anal. (C₁₇H₁₁F₄NO₂) C, H, N.

Methyl 3-(4-Fluorophenyl)-7-methyl-1H-indole-2-carboxylate (6f): mp 159–161 °C (di-2-propyl ether); ¹H NMR (CDCl₃) δ 2.50 (s, 3 H), 3.80 (s, 3 H), 7.00–7.20 (m, 4 H), 7.40 (d, 1 H), 7.50 (dd, 2 H), 8.90 (broad s, 1 H). Anal. (C₁₇H₁₄FNO₂) C, H, N.

Methyl 7-Bromo-3-(4-fluorophenyl)-4-methyl-1H-indole-2-carboxylate (6g): mp 112–116 °C (dichloromethane/*n*-heptane, 1:1); ¹H NMR (CDCl₃) δ 2.00 (s, 3 H), 3.75 (s, 3 H), 6.75 (d, 1 H), 7.10 (t, 2 H), 7.40 (d, 1 H), 7.35 (dd, 2 H), 9.00 (broad s, 1 H). Anal. (C₁₇H₁₃BrFNO₂) C, H, N.

Methyl 6-Chloro-3-(4-fluorophenyl)-1H-indole-2-carboxylate (6h). To a suspension of sodium hydride (52.5 g, 1.1 mol) (50% suspension in mineral oil, from which the mineral oil was removed by extraction with dry *n*-heptane) in dry tetrahydrofuran (250 mL) was added a solution of *N*-benzoyl-5-chloro-2-(4-fluorobenzoyl)aniline²⁶ (7) (129 g, 0.36 mol) in dry tetrahydrofuran (500 mL) during 0.5 h at 20 °C (ice cooling). This mixture was stirred for 1 h at room temperature. Then methyl 2-bromoacetate (101 mL, 1.1 mol) was added during 0.5 h at 20 °C (ice cooling), and the mixture was stirred for another 1 h. The solvents were evaporated in vacuo. The remaining oil was diluted with methanol (250 mL), and 5.4 M sodium methoxide in methanol (670 mL) was added carefully. After 1 h at room temperature, the solvents were evaporated in vacuo, and water (500 mL) was added. The thus obtained mixture was extracted with ethyl acetate (2 × 750 mL), and the combined organic phases were washed with brine and dried (Na₂SO₄). Evaporation of the solvents in vacuo afforded the crude title compound, which was purified by column chromatography on silica gel (eluted with ethyl acetate/*n*-heptane 1:3). Pure title compound was obtained by crystallization from heptane (33 g, 30%): mp 194–196 °C; ¹H NMR (CDCl₃) δ 3.85 (s, 3 H), 7.05–7.25 (m, 3 H), 7.40–7.60 (m, 4 H), 9.10 (broad s, 1 H). Anal. (C₁₈H₁₁ClFNO₂) C, H, N.

General Procedures for the Synthesis of 3-(4-Fluorophenyl)-1H-indoles (4). **2,5-Dimethyl-3-(4-fluorophenyl)-1H-indole (4a).** A solution of (4-fluorophenyl)acetone²⁷ (3) (60 g, 0.39 mol), 4-tolylhydrazine, HCl (68.8 g, 0.43 mol), and triethylamine (165 mL, 1.2 mol) in ethanol (600 mL) was refluxed for 18 h. The reaction mixture was cooled to room temperature, the solvents were evaporated in vacuo, and water (500 mL) was added to the remaining oil. The thus obtained mixture was extracted with ethyl acetate (2 × 250 mL). The combined organic phases were washed with brine and dried (Na₂SO₄). Evaporation of the solvents afforded the crude (4-fluorophenyl)acetone tolylhydrazone (100 g) as an oil, which was used without further purification. The crude hydrazone (100 g, 0.39 mol), ethanol (700 mL), and concentrated H₂SO₄ (40 mL) were refluxed for 18 h. After cooling to room temperature, water (500 mL) was added. The thus obtained mixture was extracted with ethyl acetate (2 × 700 mL), the combined organic phases were washed with brine and dried (Na₂SO₄) and the solvents were evaporated in vacuo. The remaining oil was purified by column chromatography on silica gel (eluted with ethyl acetate/*n*-heptane, 1:4) which afforded 75.5 g (80%) of pure 4a as an oil. An analytical sample was crystallized from *n*-heptane: mp 124–128 °C; ¹H NMR (CDCl₃) δ 2.40 (s, 3 H), 2.45 (s, 3 H), 6.95 (d, 1 H), 7.15 (t, 2 H), 7.20 (d, 1 H), 7.35 (s, 1 H), 7.40 (dd, 2 H), 7.70 (broad s, 1 H). Anal. (C₁₆H₁₄FN) C, H, N.

3-(4-Fluorophenyl)-7-methyl-1H-indole (4b). A mixture of methyl 3-(4-fluorophenyl)-7-methyl-1H-indole-2-carboxylate (6f) (35.0 g, 0.12 mol), methanol (350 mL), and 1.8 M aqueous NaOH (50 mL) was refluxed for 1 h. Then the solution was cooled to room temperature and acidified with concentrated aqueous HCl to pH = 1. The precipitated product was filtered off and dissolved in ethyl acetate (1000 mL). The resulting solution was dried (Na₂SO₄), and the solvent was evaporated in vacuo. The crude acid was decarboxylated without further purification. A mixture of the crude acid (33.0 g, 0.12 mol), copper (2.5 g), and NMP (500 mL) was refluxed for 5 days. The reaction mixture was cooled to room temperature, and filtered, and water (250 mL) was added. The resulting mixture was extracted with diethyl ether (2 × 400 mL). The combined organic phases were washed with brine (3 × 500 mL) and dried (Na₂SO₄). Evaporation of the solvent and crystallization from diethyl ether afforded 20.9 g (77%) of the title compound: mp 151–153 °C; ¹H NMR (CDCl₃) δ 2.45 (s, 3 H), 7.00–7.20 (m, 2 H), 7.1 (t, 2 H), 7.30 (broad s, 1 H), 7.60 (dd, 2 H), 7.70 (d, 1 H), 8.10 (broad s, 1 H). Anal. (C₁₅H₁₂FN) C, H, N.

The following compound was prepared accordingly: **3-(4-Fluorophenyl)-5-methyl-1H-indole (4c)**: mp 123–126 °C (ethyl acetate/*n*-heptane, 1:3); ¹H NMR (CDCl₃) δ 2.45 (s, 3 H), 7.10 (d, 1 H), 7.15 (t, 2 H), 7.25 (s, 1 H), 7.30 (d, 1 H), 7.60 (dd, 2 H), 7.65 (s, 1 H), 8.10 (broad s, 1 H). Anal. (C₁₅H₁₂FN) C, H, N.

3-(4-Fluorophenyl)-4-methyl-1H-indole (4d). Methyl 7-bromo-3-(4-fluorophenyl)-4-methyl-1H-indole-2-carboxylate (6g) (17.5 g, 0.048 mol) was hydrolyzed and decarboxylated as described above, except that the reaction mixture was worked up before the arylation procedure. This afforded a mixture of two compounds, which were separated by column chromatography on silica gel (eluted with ethyl acetate/*n*-heptane 1:6). The purification gave 3-(4-fluorophenyl)-4-methyl-1H-indole (6c) (3.4 g, 21%) (NMR as described below) and 7-bromo-3-(4-fluorophenyl)-4-methyl-1H-indole (6d) (5.1 g) as an oil. A mixture of the crude 6d (5.1 g, 0.017 mol), ammonium formate (5 g, 0.080 mol), 5% palladium on activated carbon (2.0 g), and methanol (50 mL) was refluxed for 1 h. After cooling to room temperature, the catalyst was filtered off. The solvents were evaporated and water (100 mL) was added. The thus formed mixture was made alkaline by addition of concentrated aqueous NaOH and extracted with diethyl ether (100 mL). The combined organic phases were dried (Na₂SO₄) and the solvent was evaporated. The remaining oil crystallized from diethyl ether and afforded further 3.5 g (29%) of the title compound 6c. An analytical sample was recrystallized from *n*-heptane: mp 80–82 °C; ¹H NMR (CDCl₃) δ 2.25 (s, 3 H),

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(27) (4-Fluorophenyl)acetone was prepared from 4-fluorobenzyl cyanide by the method described for phenylacetone. Julian, P. L.; Olivier, J. J. In *Organic Syntheses*; Blatt, A. H., Ed.; Wiley & Sons: London, 1943; Collect. Vol. 2, pp 391–392.

6.90 (d, 1 H), 7.05 (s, 1 H), 7.05 (t, 2 H), 7.15 (t, 1 H), 7.25 (d, 1 H), 7.40 (dd, 2 H), 8.15 (broad s, 1 H). Anal. (C₁₆H₁₂FN) C, H, N.

General Procedures for the Synthesis of 3-(4-Fluorophenyl)-1-(4-pyridinyl)-1H-indoles (8). 2,5-Dimethyl-3-(4-fluorophenyl)-1-(4-pyridinyl)-1H-indole (8a). 2,5-Dimethyl-3-(4-fluorophenyl)-1H-indole (6a) (50 g, 0.21 mol), 4-bromopyridine hydrochloride (80 g, 0.41 mol), K₂CO₃ (90 g, 0.65 mol), CuBr (10 g), and NMP (750 mL) were refluxed under stirring for 18 h. The reaction mixture was cooled, poured into water (1000 mL), and extracted with diethyl ether (2 × 750 mL). The combined organic phases were washed with brine (3 × 1000 mL), dried (Na₂SO₄), and treated with activated carbon. Evaporation of the diethyl ether afforded the title compound (29.8 g) which was purified by column chromatography on silica gel (eluted with ethyl acetate/*n*-heptane 3:1). The title compound 20.5 g (31%) crystallized from diethyl ether: mp 172–174 °C; ¹H NMR (CDCl₃) δ 2.40 (s, 3 H), 2.45 (s, 3 H), 6.95 (broad d, 1 H), 7.10–7.25 (m, 3 H), 7.35 (m, 3 H), 7.45 (dd, 2 H), 7.70 (broad s, 2 H). Anal. (C₂₁H₁₇FN₂) C, H, N.

The following compound was prepared accordingly: 3-(4-Fluorophenyl)-7-methyl-1-(4-pyridinyl)-1H-indole (8b): mp 98–100 °C (di-2-propyl ether); ¹H NMR (CDCl₃) δ 2.20 (s, 3 H), 7.05–7.30 (m, 5 H), 7.30 (d, 2 H), 7.60 (dd, 2 H), 7.75 (d, 1 H), 8.70 (d, 2 H). Anal. (C₂₀H₁₅FN₂) C, H, N.

3-(4-Fluorophenyl)-5-methyl-1-(4-pyridinyl)-1H-indole (8c). A mixture of methyl 3-(4-fluorophenyl)-5-methyl-1H-indole-2-carboxylate (6a) (180 g, 0.64 mol), methanol (2.5 L), and 1.8 M aqueous NaOH was refluxed for 1.5 h. Then the solution was cooled to room temperature and acidified with concentrated aqueous HCl to pH = 1. The precipitated product was filtered off and dissolved in ethyl acetate (1.0 L). The thus formed solution was dried (Na₂SO₄), and the solvents were evaporated in vacuo. The crude acid (140 g) was decarboxylated without further purification. A mixture of the crude acid (140 g, 0.52 mol), copper (12 g), and NMP (2.5 L) was refluxed for 5 days. The mixture was cooled to room temperature and 4-chloropyridine hydrochloride (140 g, 0.94 mol), K₂CO₃ (287 g, 2.1 mol), and CuBr (35 g) were added. The thus formed mixture was refluxed for 18 h. After cooling to room temperature, water (2.0 L) was added and the mixture was extracted with diethyl ether (2 × 2.5 L). The combined organic phases were washed with brine (2 × 2.5 L) and dried (Na₂SO₄). Evaporation of the solvents afforded 116.9 g (60%) of the title compound: mp 125–127 °C; ¹H NMR (CDCl₃) δ 2.50 (s, 3 H), 7.15 (d, 1 H), 7.20 (t, 2 H), 7.45 (s, 1 H), 7.50 (d, 2 H), 7.55–7.70 (m, 4 H), 8.70 (d, 2 H). Anal. (C₂₀H₁₅FN₂) C, H, N.

The following compounds were prepared accordingly: 6-Chloro-3-(4-fluorophenyl)-1-(4-pyridinyl)-1H-indole (8d) was isolated as an oil: ¹H NMR (CDCl₃) δ 7.20 (t, 2 H), 7.25 (d, 1 H), 7.45 (s, 1 H), 7.50 (broad s, 2 H), 7.60 (dd, 2 H), 7.75 (s, 1 H), 8.80 (d, 1 H), 8.70 (broad s, 2 H).

3-(4-Fluorophenyl)-1-(4-pyridinyl)-1H-indole (8e): mp 115–118 °C (diethyl ether); ¹H NMR (CDCl₃) δ 7.20 (t, 2 H), 7.25–7.40 (m, 2 H), 7.45–7.55 (m, 3 H), 7.60 (dd, 2 H), 7.75 (d, 1 H), 7.90 (d, 1 H), 8.70 (d, 2 H). Anal. (C₁₉H₁₃FN₂) C, H, N.

5-Fluoro-3-(4-fluorophenyl)-1-(4-pyridinyl)-1H-indole (8f): mp 142–145 °C (diethyl ether); ¹H NMR (CDCl₃) δ 7.05 (dd, 1 H), 7.20 (t, 2 H), 7.40–7.55 (m, 4 H), 7.60 (dd, 2 H), 7.70 (dd, 1 H), 8.75 (d, 2 H). Anal. (C₁₉H₁₂F₂N₂) C, H, N.

5-Chloro-3-(4-fluorophenyl)-1-(4-pyridinyl)-1H-indole (8g): mp 162–164 °C (diethyl ether); ¹H NMR (DMSO-*d*₆) δ 7.30 (m, 3 H), 7.75–7.95 (m, 6 H), 8.25 (s, 1 H), 8.75 (d, 2 H). Anal. (C₁₉H₁₂ClFN₂) C, H, N.

3-(4-Fluorophenyl)-1-(4-pyridinyl)-5-(trifluoromethyl)-1H-indole (8h): mp 163–165 °C (diethyl ether); ¹H NMR (CDCl₃) δ 7.20 (t, 2 H), 7.45–7.70 (m, 6 H), 7.80 (d, 1 H), 8.15 (s, 1 H), 8.80 (d, 2 H). Anal. (C₂₀H₁₂F₄N₂) C, H, N.

3-(4-Fluorophenyl)-4-methyl-1-(4-pyridinyl)-1H-indole (8i): mp 100–102 °C (di-2-propyl ether); ¹H NMR (CDCl₃) δ 2.25 (s, 3 H), 7.00 (d, 1 H), 7.10 (t, 2 H), 7.25 (t, 1 H), 7.30 (s, 1 H), 7.45 (dd, 2 H), 7.55 (broad d, 2 H), 7.65 (d, 1 H), 8.75 (broad s, 2 H). Anal. (C₂₀H₁₅FN₂) C, H, N.

General Procedure for the Synthesis of 1-[2-[4-[3-(4-Fluorophenyl)-1H-indol-1-yl]-1,2,3,6-tetrahydropyridin-1-yl]ethyl]-2-imidazolidinones (12a–c). 1-[2-[4-[2,5-Dimethyl-3-(4-fluorophenyl)-1H-indol-1-yl]-1,2,3,6-tetrahydropyridin-1-yl]ethyl]-2-imidazolidinone (12c). A mixture of 2,5-dimethyl-3-(4-fluorophenyl)-1-(4-pyridinyl)-1H-indole (8a) (5.0 g, 0.016 mol), 1-(2-iodoethyl)-2-imidazolidinone (7.6 g, 0.032 mol), and methyl isobutyl ketone (50 mL) was refluxed for 6 h. After cooling to room temperature, the precipitated product was filtered off and dried in vacuo at 70 °C overnight. This afforded 6.3 g of 4-[2,5-dimethyl-3-(4-fluorophenyl)-1H-indol-1-yl]-1-[2-(2-imidazolidinon-1-yl)ethyl]pyridinium iodide. The crude pyridinium iodide (6.3 g, 0.011 mol) was suspended in ethanol (100 mL), and sodium borohydride (2.1 g, 0.055) was added in three portions during 3.5 h. Then the solvent was evaporated in vacuo and water (100 mL) was added. The thus obtained mixture was extracted with dichloromethane (2 × 50 mL). The combined organic phases were washed with brine (100 mL) and dried (MgSO₄). Evaporation of the solvents and purification by column chromatography on silica gel (eluted with ethyl acetate/ethanol 8:1 containing 4% triethylamine) afforded the title compound (2.8 g, 41%). An analytical sample was recrystallized from ethanol: mp 151–153 °C; ¹H NMR (CDCl₃) δ 2.40 (s, 3 H), 2.40–2.50 (m, 2 H), 2.45 (s, 3 H), 2.75 (t, 2 H), 2.90 (t, 2 H), 3.35–3.40 (m, 2 H), 3.50–3.55 (m, 4 H), 3.55–3.65 (m, 2 H), 4.30 (broad s, 1 H), 5.9 (broad s, 1 H), 7.00 (d, 1 H), 7.15 (t, 2 H), 7.20 (d, 1 H), 7.40 (s, 1 H), 7.45 (dd, 2 H). Anal. (C₂₆H₂₉FN₄O) C, H, N.

The following compounds were prepared accordingly: 1-[2-[4-[3-(4-Fluorophenyl)-5-methyl-1H-indol-1-yl]-1,2,3,6-tetrahydropyridin-1-yl]ethyl]-2-imidazolidinone (12a): mp 129–131 °C (diethyl ether); ¹H NMR (CDCl₃) δ 2.45 (s, 3 H), 2.60–2.75 (m, 2 H), 2.75 (t, 2 H), 2.90 (t, 2 H), 3.40–3.50 (m, 2 H), 3.40–3.60 (m, 6 H), 4.65 (broad s, 1 H), 5.9 (broad s, 1 H), 7.00–7.20 (m, 3 H), 7.25 (s, 1 H), 7.45 (d, 1 H), 7.60 (dd, 2 H), 7.65 (s, 1 H). Anal. (C₂₆H₂₇FN₄O) C, H, N.

1-[2-[4-[3-(4-Fluorophenyl)-7-methyl-1H-indol-1-yl]-1,2,3,6-tetrahydropyridin-1-yl]ethyl]-2-imidazolidinone (12b): mp 126–128 °C (diethyl ether); ¹H NMR (CDCl₃) δ 2.45–2.60 (m, 2 H), 2.55 (s, 3 H), 2.80 (t, 2 H), 2.85 (t, 2 H), 3.20–3.30 (m, 2 H), 3.30–3.60 (m, 6 H), 5.25 (broad s, 1 H), 5.9 (broad s, 1 H), 7.00 (d, 1 H), 7.05–7.20 (m, 4 H), 7.55 (dd, 2 H), 7.70 (d, 1 H). Anal. (C₂₆H₂₇FN₄O·0.5H₂O) C, H, N.

General Procedure for the Syntheses of Substituted 3-(4-Fluorophenyl)-1-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indoles (12d,e). The methyl-substituted compounds were prepared as described above for the 2-(2-imidazolidinon-1-yl)-ethyl-substituted compounds, except that the quaternization was performed with iodomethane in acetone at 40 °C overnight. The following compounds were prepared in this manner: 3-(4-Fluorophenyl)-5-methyl-1-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole (12d) was isolated as an oil: ¹H NMR (CDCl₃) δ 2.25 (s, 6 H), 2.60–2.75 (m, 2 H), 2.80 (t, 2 H), 3.15–3.25 (m, 2 H), 5.85–5.95 (m, 1 H), 7.10 (d, 1 H), 7.15 (t, 2 H), 7.20 (s, 1 H), 7.45 (d, 1 H), 7.45 (dd, 2 H), 7.60 (s, 1 H).

2,5-Dimethyl-3-(4-fluorophenyl)-1-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole (12e): mp 98–100 °C (di-2-propyl ether/*n*-heptane, 1:1); ¹H NMR (CDCl₃) δ 2.35 (s, 3 H), 2.40 (s, 3 H), 2.50 (s, 3 H), 2.40–2.50 (m, 2 H), 2.80 (t, 2 H), 3.20–3.30 (m, 2 H), 5.85–5.95 (m, 1 H), 7.00 (d, 1 H), 7.15 (t, 2 H), 7.20 (d, 1 H), 7.40 (d, 1 H), 7.45 (dd, 2 H). Anal. (C₂₂H₂₃FN₂) C, H, N.

General Procedures for the Synthesis of Substituted 3-(4-Fluorophenyl)-1-(4-piperidinyl)-1H-indoles (10). 1-[2-[4-[5-Chloro-3-(4-fluorophenyl)-1H-indol-1-yl]-1-piperidinyl]ethyl]-2-imidazolidinone (10d). 5-Chloro-3-(4-fluorophenyl)-1-(4-pyridinyl)-1H-indole (8g) (3.0 g, 0.0093 mol) was dissolved in acetic acid (100 mL), and PtO₂ (0.3 g) was added. After hydrogenation for 3 days at 3 atm the catalyst was filtered off, the acetic acid was evaporated in vacuo, and water (50 mL) was added. The acidic solution was made alkaline (pH > 9) with concentrated sodium hydroxide and extracted with ethyl acetate (2 × 50 mL). The combined organic phases were successively washed with diluted sodium hydroxide (50 mL), washed with brine, and finally dried (Na₂SO₄). Evaporation of the solvent gave 2.5 g of crude 5-chloro-3-(4-fluorophenyl)-1-(4-piperidinyl)-1H-indole as an oil, which was used without further purification.

A mixture of 5-chloro-3-(4-fluorophenyl)-1-(4-piperidinyl)-1H-indole (2.5 g, 0.0076 mol), 1-(2-chloroethyl)-2-imidazolidinone (2.1 g, 0.014 mol), K_2CO_3 (1.7 g, 0.012 mol), KI (0.1 g), and methyl isobutyl ketone (250 mL) was refluxed for 18 h. The reaction mixture was cooled, poured into water (100 mL), and extracted with ethyl acetate (2×100 mL). The combined organic phases were dried (Na_2SO_4), and the solvents were evaporated in vacuo. The remaining oil was precipitated from ethyl acetate: 1.8 g (43%); mp 171–174 °C; 1H NMR ($CDCl_3$) δ 2.00–2.20 (m, 4 H), 2.20–2.35 (m, 2 H), 2.60 (t, 2 H), 3.10–3.25 (m, 2 H), 3.40 (t, 2 H), 3.40–3.60 (m, 4 H), 4.20–4.45 (m, 1 H), 4.60 (broad s, 1 H), 7.10 (t, 2 H), 7.20 (d, 1 H), 7.30 (d, 1 H), 7.35 (s, 1 H), 7.50 (dd, 2 H), 7.8 (s, 1 H). Anal. ($C_{24}H_{26}ClFN_4O$) C, H, N.

The following compounds were prepared accordingly: 1-[2-[4-[6-chloro-3-(4-fluorophenyl)-1H-indol-1-yl]-1-piperidinyl]ethyl]-2-imidazolidinone (10a): mp 192–194 °C (2-propanol); 1H NMR ($CDCl_3$) δ 2.00–2.20 (m, 4 H), 2.20–2.35 (m, 2 H), 2.65 (t, 2 H), 3.10–3.25 (m, 2 H), 3.45 (t, 2 H), 3.40–3.60 (m, 4 H), 4.10–4.30 (m, 1 H), 4.50 (broad s, 1 H), 7.10 (t, 2 H), 7.15 (d, 1 H), 7.30 (s, 1 H), 7.40 (s, 1 H), 7.55 (dd, 2 H), 7.75 (d, 1 H). Anal. ($C_{24}H_{26}ClFN_4O$) C, H, N.

1-[2-[4-[3-(4-fluorophenyl)-1H-indol-1-yl]-1-piperidinyl]ethyl]-2-imidazolidinone (10b): mp 172–173 °C (diethyl ether/*n*-heptane, 1:1); 1H NMR ($CDCl_3$) δ 2.00–2.20 (m, 4 H), 2.20–2.40 (m, 2 H), 2.6 (t, 2 H), 3.05–3.30 (m, 2 H), 3.35 (t, 2 H), 3.40–3.60 (m, 4 H), 4.20–4.45 (m, 1 H), 4.70 (broad s, 1 H), 7.05–7.30 (m, 4 H), 7.35 (s, 1 H), 7.40 (d, 1 H), 7.60 (dd, 2 H), 7.85 (d, 1 H). Anal. ($C_{24}H_{27}FN_4O$) C, H, N.

1-[2-[4-[5-fluoro-3-(4-fluorophenyl)-1H-indol-1-yl]-1-piperidinyl]ethyl]-2-imidazolidinone (10c): mp 153–156 °C (ethyl acetate/*n*-heptane, 1:1); 1H NMR ($CDCl_3$) δ 2.00–2.20 (m, 4 H), 2.20–2.40 (m, 2 H), 2.60 (t, 2 H), 3.10–3.25 (m, 2 H), 3.40 (t, 2 H), 3.45–3.60 (m, 4 H), 4.15–4.40 (m, 1 H), 4.70 (broad s, 1 H), 7.00 (dt, 1 H), 7.15 (t, 2 H), 7.35 (dd, 1 H), 7.40 (s, 1 H), 7.50 (dd, 1 H), 7.55 (dd, 2 H). Anal. ($C_{24}H_{26}F_2N_4O$) C, H, N.

1-[2-[4-[3-(4-fluorophenyl)-5-methyl-1H-indol-1-yl]-1-piperidinyl]ethyl]-2-imidazolidinone (10e): mp 186–188 °C (ethanol); 1H NMR ($CDCl_3$) δ 1.95–2.20 (m, 4 H), 2.20–2.40 (m, 2 H), 2.50 (s, 3 H), 2.60 (t, 2 H), 3.10–3.20 (m, 2 H), 3.40 (t, 2 H), 3.45–3.60 (m, 4 H), 4.15–4.40 (m, 1 H), 4.70 (broad s, 1 H), 7.10 (d, 1 H), 7.15 (t, 2 H), 7.30 (s, 1 H), 7.35 (d, 1 H), 7.60 (dd, 2 H), 7.65 (s, 1 H). Anal. ($C_{25}H_{29}FN_4O$) C, H, N.

1-[2-[4-[3-(4-fluorophenyl)-5-(trifluoromethyl)-1H-indol-1-yl]-1-piperidinyl]ethyl]-2-imidazolidinone (10f): mp 182–184 °C (diethyl ether); 1H NMR ($CDCl_3$) δ 2.05–2.20 (m, 4 H), 2.20–2.40 (m, 2 H), 2.60 (t, 2 H), 3.10–3.25 (m, 2 H), 3.40 (t, 2 H), 3.45–3.60 (m, 4 H), 4.20–4.40 (m, 1 H), 4.60 (broad s, 1 H), 7.15 (t, 2 H), 7.40 (s, 1 H), 7.50 (broad s, 2 H), 7.55 (dd, 2 H), 8.10 (s, 1 H). Anal. ($C_{25}H_{26}F_4N_4O$) C, H, N.

1-[2-[4-[3-(4-fluorophenyl)-4-methyl-1H-indol-1-yl]-1-piperidinyl]ethyl]-2-imidazolidinone (10g): mp 163–165 °C (diethyl ether); 1H NMR ($CDCl_3$) δ 1.95–2.20 (m, 4 H), 2.20–2.45 (m, 2 H), 2.25 (s, 3 H), 2.60 (t, 2 H), 3.05–3.20 (m, 2 H), 3.35 (t, 2 H), 3.40–3.60 (m, 4 H), 4.20–4.35 (m, 1 H), 4.60 (broad s, 1 H), 6.60 (d, 1 H), 7.05 (t, 2 H), 7.05–7.20 (m, 2 H), 7.25 (s, 1 H), 7.35 (dd, 2 H). Anal. ($C_{25}H_{29}FN_4O$) C, H, N.

1-[2-[4-[3-(4-fluorophenyl)-5-methyl-1H-indol-1-yl]-1-piperidinyl]ethyl]-3-(2-propyl)-2-imidazolidinone oxalate (10j): mp 175–177 °C (acetone); 1H NMR ($DMSO-d_6$) δ 1.05 (d, 6 H), 2.05–2.40 (m, 4 H), 2.40 (s, 3 H), 2.95–3.50 (m, 10 H), 3.50–3.65 (m, 2 H), 3.75–3.95 (m, 1 H), 4.50–4.70 (m, 1 H), 5.00–6.00 (broad s, 2 H), 7.05 (d, 1 H), 7.30 (t, 2 H), 7.55 (d, 1 H), 7.65 (s, 1 H), 7.70 (dd, 2 H), 7.75 (s, 1 H). Anal. ($C_{28}H_{36}FN_4O \cdot C_2H_2O_4$) C, H, N.

1-[2-[4-[2,5-dimethyl-3-(4-fluorophenyl)-1H-indol-1-yl]-1-piperidinyl]ethyl]-2-imidazolidinone (10i). To a refluxing mixture of 1-[2-[4-[2,5-dimethyl-3-(4-fluorophenyl)-1H-indol-1-yl]-1,2,3,6-tetrahydropyridin-1-yl]ethyl]-2-imidazolidinone (12c) (12 g, 0.028 mol), 5% palladium on activated carbon (5.0), and ethanol (160 mL) was added ammonium formate (17 g, 0.27 mol) during 25 h. The reaction mixture was cooled to room temperature and the catalyst filtered off. The solvents were evaporated and water (100 mL) was added. The thus formed mixture was made alkaline by concentrated NaOH and extracted with ethyl acetate (2×200 mL). The combined organic phases were dried (Na_2SO_4) and the solvent was evaporated. The crude 10i (7.0 g)

was recrystallized from ethanol which gave 4.6 g (38%): mp 188–90 °C; 1H NMR δ 1.80–1.95 (m, 2 H), 2.15–2.35 (m, 2 H), 2.40 (s, 3 H), 2.45 (s, 3 H), 2.50–2.75 (m, 4 H), 3.10–3.25 (m, 2 H), 3.40 (t, 2 H), 3.45–3.65 (m, 4 H), 4.10–4.30 (m, 1 H), 4.40 (broad s, 1 H), 6.95 (d, 1 H), 7.15 (t, 2 H), 7.30 (s, 1 H), 7.40 (dd, 2 H), 7.50 (d, 1 H). Anal. ($C_{26}H_{31}FN_4O$) C, H, N.

The following compounds were prepared accordingly: 1-[2-[4-[3-(4-fluorophenyl)-7-methyl-1H-indol-1-yl]-1-piperidinyl]ethyl]-2-imidazolidinone (10h): mp 141–144 °C (diethyl ether); 1H NMR ($CDCl_3$) δ 2.00–2.35 (m, 6 H), 2.60 (t, 2 H), 2.75 (s, 3 H), 3.10–3.25 (m, 2 H), 3.40 (t, 2 H), 3.40–3.60 (m, 4 H), 4.45 (broad s, 1 H), 4.70–4.85 (m, 1 H), 6.95–7.05 (m, 2 H), 7.10 (t, 2 H), 7.35 (s, 1 H), 7.55 (dd, 2 H), 7.70 (d, 1 H). Anal. ($C_{25}H_{29}FN_4O \cdot 0.2H_2O$) C, H, N.

3-(4-fluorophenyl)-5-methyl-1-(1-methyl-4-piperidinyl)-1H-indole fumarate (10k): mp 170–172 °C (ethanol); 1H NMR ($DMSO-d_6$) δ 1.90–2.30 (m, 4 H), 2.40 (s, 3 H), 2.50 (s, 3 H), 2.45–2.55 (m, 4 H), 3.10–3.25 (m, 2 H), 4.35–4.60 (m, 1 H), 6.60 (s, 2 H), 7.05 (d, 1 H), 7.25 (t, 2 H), 7.50 (d, 1 H), 7.60 (s, 1 H), 7.70 (dd, 2 H), 7.75 (s, 1 H). Anal. ($C_{21}H_{23}FN_2 \cdot C_4H_4O_4$) C, H, N.

2,5-Dimethyl-3-(4-fluorophenyl)-1-(1-methyl-4-piperidinyl)-1H-indole (10l): mp 110–112 °C (*n*-heptane); 1H NMR ($CDCl_3$) δ 1.75–2.00 (m, 2 H), 2.05–2.30 (m, 2 H), 2.35 (s, 6 H), 2.40 (s, 3 H), 2.60–2.80 (m, 2 H), 3.00–3.20 (m, 2 H), 4.10–4.30 (m, 1 H), 6.95 (d, 1 H), 7.10 (t, 2 H), 7.30 (s, 1 H), 7.40 (dd, 2 H). Anal. ($C_{22}H_{26}FN_2$) C, H, N.

The following urea derivatives were prepared as described previously¹ from the corresponding unsubstituted piperidinylindoles 9 prepared as described above: 1-[1-[2-(3,3-dimethyl-1-ureido)ethyl]-4-piperidinyl]-3-(4-fluorophenyl)-5-methyl-1H-indole (10m): mp 126–128 °C (diethyl ether); 1H NMR ($CDCl_3$) δ 1.90–2.40 (m, 6 H), 2.50 (s, 3 H), 2.60 (t, 2 H), 2.95 (s, 6 H), 3.05–3.15 (m, 2 H), 3.30–3.45 (m, 2 H), 4.15–4.35 (m, 1 H), 4.95 (broad s, 1 H), 7.05–7.15 (m, 3 H), 7.25 (s, 1 H), 7.30 (d, 1 H), 7.55 (dd, 2 H), 7.65 (s, 1 H). Anal. ($C_{26}H_{31}FN_4O$) C, H, N.

1-[1-[2-(1,3-dimethyl-1-ureido)ethyl]-4-piperidinyl]-3-(4-fluorophenyl)-5-methyl-1H-indole hydrochloride (10n): mp 204–205 °C (acetone); 1H NMR ($CDCl_3$) δ 2.20–2.35 (m, 2 H), 2.45 (s, 3 H), 2.75–3.35 (m, 6 H), 2.80 (s, 3 H), 3.00 (s, 3 H), 3.75–3.95 (m, 4 H), 4.25–4.45 (broad s, 1 H), 4.45–4.60 (m, 1 H), 7.05–7.15 (m, 3 H), 7.30 (d, 1 H), 7.35 (s, 1 H), 7.55 (dd, 2 H), 7.65 (s, 1 H). Anal. ($C_{26}H_{31}FN_4O \cdot HCl \cdot 0.65H_2O$) C, H, N.

Synthesis of 3-(4-fluorophenyl)-5-methyl-1-(1-methyl-4-piperazinyl)-1H-indole (14). 1-Amino-3-(4-fluorophenyl)-5-methyl-1H-indole (13). Potassium *tert*-butoxide (7.5 g, 0.067 mol) was added to a solution of 3-(4-fluorophenyl)-5-methyl-1H-indole (4c) (15 g, 0.067 mol) in DMF during 15 min at 0–5 °C. Then a suspension of potassium hydroxylamine-*O*-sulfonate in DMF (prepared by addition of potassium *tert*-butoxide (7.5 g, 0.067 mol) to a suspension of hydroxylamine-*O*-sulfonic acid (7.6 g, 0.067 mol) in DMF (100 mL) during 0.5 h at 0–5 °C) was added slowly at 0–5 °C. After reaction at 0 °C for 1 h the mixture was poured onto ice and extracted with diethyl ether (2×250 mL). The combined organic phases were washed with brine (3×250 mL) and dried (Na_2SO_4). Evaporation of the solvents afforded a mixture of the title compound and the starting material, which were separated by column chromatography on silica gel (eluted with ethyl acetate/*n*-heptane 1:3). This afforded starting material (9.0 g, 60%) and the title compound which crystallized from diethyl ether (4.3 g, 27%): mp 116–120 °C; 1H NMR ($CDCl_3$) δ 2.50 (s, 3 H), 4.70 (s, 2 H), 7.05–7.20 (m, 3 H), 7.25 (s, 1 H), 7.30 (d, 1 H), 7.55 (dd, 2 H), 7.60 (s, 1 H). Anal. ($C_{15}H_{13}FN_2$) C, H, N.

3-(4-fluorophenyl)-5-methyl-1-(1-methyl-4-piperazinyl)-1H-indole (14). To a mixture of 1-amino-3-(4-fluorophenyl)-5-methyl-1H-indole (13) (1 g, 0.0042 mol) and toluene (20 mL) was added a 50% suspension of sodium amide in xylene (1.0 mL, 0.012 mol). After reaction for 15 min at room temperature a solution of *N,N*-bis(2-chloroethyl)methylamine (0.8 g, 0.0051 mol) in toluene (5 mL) was added slowly and the mixture was refluxed for 3 h. After cooling to room temperature, the solvents were evaporated in vacuo and water (100 mL) was added. The mixture was extracted with ethyl acetate (2×50 mL), and the combined organic phases were dried (Na_2SO_4). Evaporation of the solvents in vacuo and purification by column chromatography on silica

gel (eluted with ethyl acetate/ethanol 4:1 containing 4% triethylamine) afforded pure 14 (1.0 g, 74%) as an oil. An analytical sample crystallized from *n*-heptane: mp 105–107 °C; ¹H NMR (CDCl₃) δ 2.40 (s, 3 H), 2.45 (s, 3 H), 2.70 (broad s, 4 H), 3.25 (t, 4 H), 7.10 (broad d, 1 H), 7.15 (t, 2 H), 7.45 (s, 1 H), 7.50 (d, 1 H), 7.55 (dd, 2 H), 7.50 (broad s, 1 H). Anal. (C₂₀H₂₂FN₃O) C, H, N.

Pharmacological Test Methods. Animals. Male Wistar rats (Mol:Wist, SPF, 170–270 g) were used. We have recently described the handling procedures in details.⁵

Calculations. ED₅₀ values were calculated by log-probit analyses. IC₅₀ values were estimated from concentration–effect curves using a log-concentration scale. Details are available from the references cited in the description of specific test methods below.

Antagonism of Quipazine-Induced Head Twitches. The experimental details are given by Arnt et al.²¹ 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.²² Contralateral circling is induced in 6-OHDA-lesioned rats in response to administration of pergolide (0.05 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 1 week before and 1 week after the test session for each rat (at least four rats per dose).

Receptor Binding. DA D₂ Receptors. Affinity of test compounds to dopamine D₂ receptors was estimated by their ability to displace [³H]spiperone from rat striatal membranes as described by Hyttel.²⁸

5-HT₂ Receptors. Affinity of test compounds to serotonin 5-HT₂ receptors was estimated by their ability to displace [³H]-ketanserin from rat cortical membranes as described by Hyttel.²⁸

α₁ Adrenoceptors. Affinity of test compounds to α₁ adrenoceptors was estimated by their ability to displace [³H]prazosin from whole rat brain membranes as described by Skarsfeldt and Hyttel.²⁹

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