Selective, Centrally Acting Serotonin 5-HT$_2$ Antagonists. 2. Substituted 3-(4-Fluorophenyl)-1*H*-indoles

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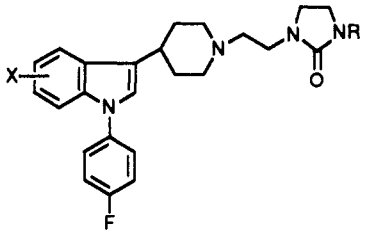
A series of 3-(4-fluorophenyl)-1*H*-indoles substituted in the 1-position with 4-piperidinyl, 1,2,3,6-tetrahydro-4-pyridinyl, and 4-piperazinyl was synthesized. By variation of the substituents in the benzene part of the indole nucleus in 1-[2-[4-[3-(4-fluorophenyl)-1*H*-indol-1-yl]-1-piperidinyl]-ethyl]-2-imidazolidinones, the highest 5-HT$_2$ receptor affinity and selectivity with respect to dopamine D$_2$ 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-HT$_2$ 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-HT$_2$ and D$_2$ 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-HT$_2$ and D$_2$ 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-HT$_2$ 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)-1*H*-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-HT$_2$ receptors compared to the former series. The 1-[2-[4-[2,5-dimethyl-3-(4-fluorophenyl)-1*H*-indol-1-yl]-1-piperidinyl]ethyl]-2-imidazolidinone has high affinity for 5-HT$_2$ receptors (IC$_{50}$ = 3.4 nM) and extremely low affinity for both dopamine D$_2$ receptors (IC$_{50}$ = 6900 nM) and α_1 adrenoceptors (IC$_{50}$ = 2300 nM).

Introduction

The preceding paper[1] within this series discussed the structure–activity relationship in a series of 6-substituted 1-phenyl-3-(4-piperidinyl)-1*H*-indoles, which led to the selective and highly potent serotonin 5-HT$_2$ 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)-1*H*-indoles, which in addition to binding affinity for serotonin 5-HT$_2$ receptors, have strong binding affinity for both dopamine D$_2$ 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]



1 X = 6-Cl, R = 2-propyl
2 X = 5-Cl, R = H

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

The involvement of serotonin receptors in psychiatric disorders, such as anxiety and depression, is discussed in part 1[1] within this series. Selective 5-HT$_2$ antagonists[6] and compounds, which have 5-HT$_2$ antagonistic activity as a main component (e.g. sertindole and related 5-substituted 1-phenyl-3-(4-piperidinyl)-1*H*-indoles),[7] are active

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in animal models predictive of anxiolytic activity. In addition, several clinical studies with the 5-HT_2 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-HT_2 receptors within indole derivatives with 5-HT_2 antagonistic activity.

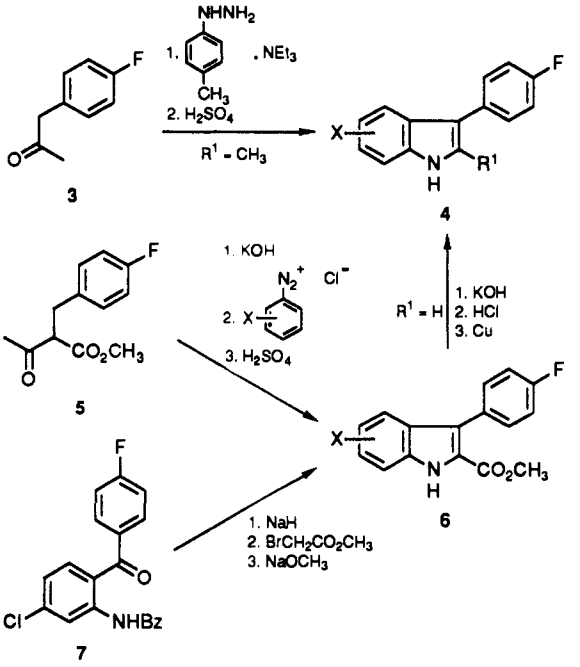
The increase in 5-HT receptor affinity, obtained by interchange of the C-3 atom and the nitrogen atom in the indole nucleus of the hallucinogenic agent dimethyltryptamine,[11] led us to investigation of the pharmacological effects of this isosteric replacement in the series of 1-phenyl-3-(4-piperidinyl)indoles, 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)-1*H*-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-1*H*-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**, $R^1 = CH_3$) was prepared by the Fischer indole synthesis[13] from 4-tolylhydrazine and (4-fluorophenyl)acetone (**3**). The esters **6** used as intermediates in the preparation of 2-unsubstituted indoles (**4**, R^1 = 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 synthesis[14] 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**, R^1 = H) by hydrolysis followed by decarboxylation.[16] The 4-methylindole (**4**, X = 4-CH_3) was prepared by removal of the bromine atom in 7-bromo-4-methylindole (**4**, X = 7-Br, 4-CH_3) 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 $NaBH_4$ 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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Scheme II Synthesis of 1-(4-Piperidinyl)indoles **10** and 1-(1,2,3,6-Tetrahydro-4-pyridinyl)indoles **12** from the Corresponding 1-Unsubstituted Indoles **4**

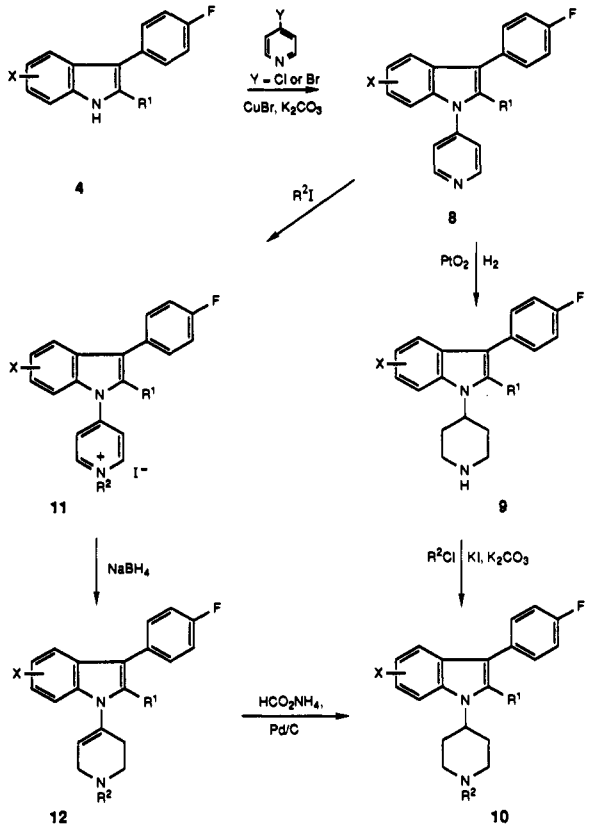
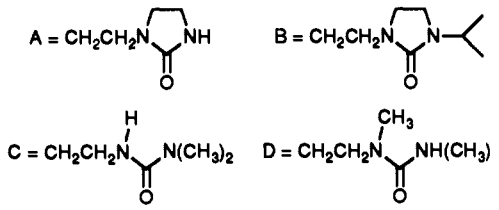


Chart I. Structures of Substituent R^2



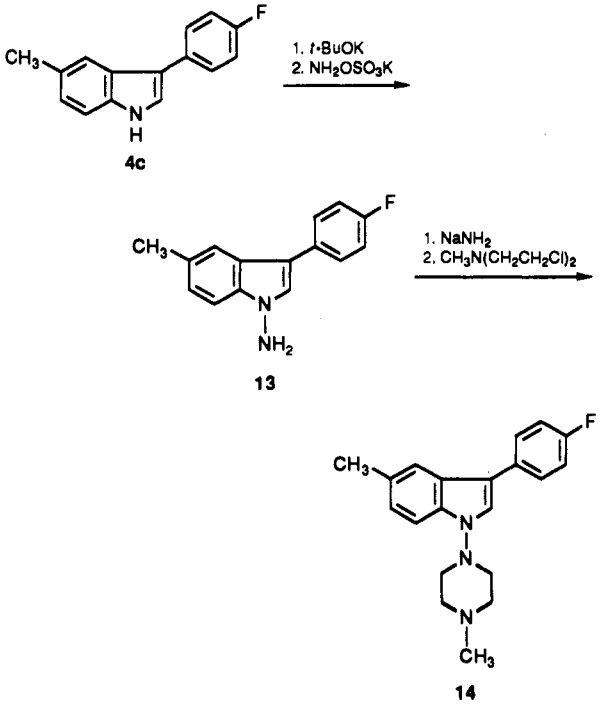
monium formate using palladium as catalyst. This alternative procedure was used for the preparation of 2- and 7-substituted 1-(4-piperidinyl)indoles **10**, since the corresponding 1-(4-pyridinyl)indoles **8** were inert to the catalytic hydrogenation conditions described above.

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 dimethylformamide[17] 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 D_2, adrenergic α_1, serotonin 5-HT_2) 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-HT_2 antagonist Lu 26-042 (**1**, Figure 1). Ritanserin was the first centrally acting 5-HT_2 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-piperidinyl)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-HT_2, D_2, and α_1 receptors. The unsubstituted derivative **10b** has retained affinity for 5-HT_2 and α_1 receptors, whereas the affinity for D_2 receptors are slightly weakened compared to **10a**. Introduction of substituents in the 5-position (**10c–f**) results in retained 5-HT_2 receptor affinity, while affinities for both D_2 and α_1 receptors are decreased. The highest affinity and selectivity for the 5-HT_2 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 α_1 adrenoceptors by a factor of 4 while the affinity for 5-HT_2 and D_2 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-HT_2 receptor in respect to D_2 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 IC_{50} 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 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 discarded. The following 95% confidence ratios (2 × SD ratio) were calculated: D_2 2.25; α_1 2.20; 5-HT_2 2.05. [b] Refer to substituents of structures 10 and 12 in Scheme I. [c] See Chart I for definitions of R^2.

whereas the 1,3-dimethyl-substituted derivative **10n** has similar affinity and selectivity for the 5-HT_2 receptor as **10e**. Replacement of the side chains with a methyl group (**10k**) results in an affinity and selectivity for 5-HT_2 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-HT_2 receptors, whereas the affinity for D_2 and α_1 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-HT_2 receptors.

It has previously been shown[2] that affinity for 5-HT_2 and D_2 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-HT_2, α_1, and D_2 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 D_2 and α_1 receptors by a factor of 20–30, whereas the affinity for 5-HT_2 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-HT_2 receptors, whereas the affinity for D_2 and α_1 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 imidazolidinonylethyl side chain in **10i** with a methyl group result in compounds **12c** and **10l**, respectively, with similar affinity and selectivity for 5-HT_2 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-HT_2 receptors is quite outstanding compared to the former compounds (e.g. sertindole and Lu 26-042).

Other structural classes of 5-HT_2 antagonists in addition to affinity for 5-HT_2 receptors have affinity for receptors other than the receptors studied in this paper. Ritanserin has rather high affinity for histamine H_1 receptors[19] and the piperazine derivative LY165163 (PAPP) in addition to 5-HT_2 receptor affinity has affinity for serotonergic 5-HT_{1A} receptors.[20] Testing of compound **10i** for H_1 and 5-HT_{1A} receptor binding affinity, using [^{3}H]mepyramine and [^{3}H]-8-OH-DPAT as ligands, respectively, resulted in IC_{50} values greater than 10 000 nM (unpublished results).

In the preceding paper within this series[1] 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] 2 h (sc)	24 h (sc)	24 h (po)	inhibition of pergolide-induced rotations[a] at 2 h (sc)
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
ritanserin	0.10 (0.056–0.18)	0.98 (0.35–2.7)	NT	>21

[a] Results are expressed as ED_{50} values in μmol/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-HT$_2$ 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-HT$_2$ receptor antagonists are in progress.

In Table II are reported some important in vivo pharmacological effects of selected compounds. Quipazine is a 5-HT$_2$ 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-HT$_2$ antagonist in vivo within the present series of indoles. Some of the compounds within this series are even more potent centrally acting 5-HT$_2$ 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 (D_2 agonist) contralateral circling in rats with unilateral 6-OHDA lesions.[22] This test model is very sensitive to classical dopamine D_2 antagonists. Neuroleptics, such as haloperidol and fluphenazine, are active in the range of 0.01–0.05 μmol/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 ritanserin the key derivative **10i** is quite outstanding both with regard to 5-HT$_2$ receptor selectivity (relative to D_2 and α_1 receptors) in binding studies (Table I) and in vivo 5-HT$_2$ antagonistic potency (Table II). This compound is at present being further studied in extended pharmacological test models as prototype of an extremely selective 5-HT$_2$ 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. ^{1}H NMR spectra were recorded at 250 MHz on a Bruker AC 250 spectrometer. Deuterated chloroform (99.8% D) or dimethyl sulfoxide (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 ±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 $NaNO_2$ (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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(22) Arnt, J.; Hyttel, J. Inhibition of SKF 38393- and Pergolide-Induced Circling in Rats with Unilateral 6-OHDA Lesion is Correlated to Dopamine D-1 and D-2 Receptor Affinities in Vitro. *J. Neural. Transm.* **1986**, *67*, 225–240.

(23) Johnston, T. P.; McCaleb, G. S.; Montgomery, J. A. The Synthesis of Antineoplastic Agents. XXXII. *N-Nitrosureas*. *J. Med. Chem.* **1963**, *6*, 669–681.

(24) Ford-Moore, A. H. Benzoylcholine Iodide and Chloride. In *Organic Syntheses*, Rabjohn, N., Ed.; Wiley & Sons: London, 1963; Collect. Vol. 4, pp 84–88.

(25) Costeli, J.; Züst, A. *Ger. Offen.* 2035370, 1971. *Chem. Abstr.* **1971**, *74*, 87985z.

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 (Na_2SO_4). 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 H_2SO_4 (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 ($CDCl_3$) 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. ($C_{17}H_{14}FNO_2$) C, H, N.

The following compounds were prepared accordingly: **Methyl 3-(4-fluorophenyl)-1*H*-indole-2-carboxylate (6b)** was isolated as an oil: ^1H NMR ($CDCl_3$) 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)-1*H*-indole-2-carboxylate (6c): mp 169–170 °C (di-2-propyl ether); ^1H NMR ($CDCl_3$) 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. ($C_{16}H_{11}F_2NO_2$) C, H, N.

Methyl 5-Chloro-3-(4-fluorophenyl)-1*H*-indole-2-carboxylate (6d): mp 184–186 °C (di-2-propyl ether); ^1H NMR ($CDCl_3$) 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. ($C_{16}H_{11}ClFNO_2$) C, H, N.

Methyl 3-(4-Fluorophenyl)-5-(trifluoromethyl)-1*H*-indole-2-carboxylate (6e): mp 164–166 °C (methanol); ^1H NMR ($CDCl_3$) 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. ($C_{17}H_{11}F_4NO_2$) C, H, N.

Methyl 3-(4-Fluorophenyl)-7-methyl-1*H*-indole-2-carboxylate (6f): mp 159–161 °C (di-2-propyl ether); ^1H NMR ($CDCl_3$) 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. ($C_{17}H_{14}FNO_2$) C, H, N.

Methyl 7-Bromo-3-(4-fluorophenyl)-4-methyl-1*H*-indole-2-carboxylate (6g): mp 112–116 °C (dichloromethane/*n*-heptane, 1:1); ^1H NMR ($CDCl_3$) 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. ($C_{17}H_{13}BrFNO_2$) C, H, N.

Methyl 6-Chloro-3-(4-fluorophenyl)-1*H*-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)aniline[26] (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 (Na_2SO_4). 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 ($CDCl_3$) 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. ($C_{16}H_{11}ClFNO_2$) C, H, N.

General Procedures for the Synthesis of 3-(4-Fluorophenyl)-1*H*-indoles (4). 2,5-Dimethyl-3-(4-fluorophenyl)-1*H*-indole (4a). A solution of (4-fluorophenyl)acetone[27] (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 (Na_2SO_4). 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 H_2SO_4 (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 (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/*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 ($CDCl_3$) 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. ($C_{16}H_{14}FN$) C, H, N.

3-(4-Fluorophenyl)-7-methyl-1*H*-indole (4b). A mixture of methyl 3-(4-fluorophenyl)-7-methyl-1*H*-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 (Na_2SO_4), 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 (Na_2SO_4). Evaporation of the solvent and crystallization from diethyl ether afforded 20.9 g (77%) of the title compound: mp 151–153 °C; ^1H NMR ($CDCl_3$) 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. ($C_{16}H_{12}FN$) C, H, N.

The following compound was prepared accordingly: **3-(4-Fluorophenyl)-5-methyl-1*H*-indole (4c)**: mp 123–126 °C (ethyl acetate/*n*-heptane, 1:3); ^1H NMR ($CDCl_3$) 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. ($C_{16}H_{12}FN$) C, H, N.

3-(4-Fluorophenyl)-4-methyl-1*H*-indole (4d). Methyl 7-bromo-3-(4-fluorophenyl)-4-methyl-1*H*-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-1*H*-indole (**6c**) (3.4 g, 21%) (NMR as described below) and 7-bromo-3-(4-fluorophenyl)-4-methyl-1*H*-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 (Na_2SO_4) 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 ($CDCl_3$) δ 2.25 (s, 3 H),

(26) *N*-Benzoyl-5-chloro-2-(4-fluorobenzoyl)aniline was prepared by benzoylation of 5-chloro-2-(4-fluorobenzoyl)aniline prepared as described for 2-(3-chloro-4-methylbenzoyl)aniline. 2,3-Dichloroindone as a Dienophilic Compound. *J. Am. Chem. Soc.* **1959**, *81*, 5641–5646.

(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. ($C_{15}H_{12}FN$) C, H, N.

General Procedures for the Synthesis of 3-(4-Fluorophenyl)-1-(4-pyridinyl)-1*H*-indoles (8). 2,5-Dimethyl-3-(4-fluorophenyl)-1-(4-pyridinyl)-1*H*-indole (8a). 2,5-Dimethyl-3-(4-fluorophenyl)-1*H*-indole (**6a**) (50 g, 0.21 mol), 4-bromopyridine hydrochloride (80 g, 0.41 mol), K_2CO_3 (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 (Na_2SO_4), 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; ^{1}H NMR ($CDCl_3$) 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. ($C_{21}H_{17}FN_2$) C, H, N.

The following compound was prepared accordingly: **3-(4-Fluorophenyl)-7-methyl-1-(4-pyridinyl)-1*H*-indole (8b)**: mp 98–100 °C (di-2-propyl ethyl); ^{1}H NMR ($CDCl_3$) 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. ($C_{20}H_{15}FN_2$) C, H, N.

3-(4-Fluorophenyl)-5-methyl-1-(4-pyridinyl)-1*H*-indole (8c). A mixture of methyl 3-(4-fluorophenyl)-5-methyl-1*H*-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 (Na_2SO_4), 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), K_2CO_3 (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 (Na_2SO_4). Evaporation of the solvents afforded 116.9 g (60%) of the title compound: mp 125–127 °C; ^{1}H NMR ($CDCl_3$) 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. ($C_{20}H_{15}FN_2$) C, H, N.

The following compounds were prepared accordingly: **6-Chloro-3-(4-fluorophenyl)-1-(4-pyridinyl)-1*H*-indole (8d)** was isolated as an oil: ^{1}H NMR ($CDCl_3$) 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), 7.80 (d, 1 H), 8.70 (broad s, 2 H).

3-(4-Fluorophenyl)-1-(4-pyridinyl)-1*H*-indole (8e): mp 115–118 °C (diethyl ether); ^{1}H NMR ($CDCl_3$) 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. ($C_{19}H_{13}FN_2$) C, H, N.

5-Fluoro-3-(4-fluorophenyl)-1-(4-pyridinyl)-1*H*-indole (8f): mp 142–145 °C (diethyl ether); ^{1}H NMR ($CDCl_3$) 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. ($C_{19}H_{12}F_2N_2$) C, H, N.

5-Chloro-3-(4-fluorophenyl)-1-(4-pyridinyl)-1*H*-indole (8g): mp 162–164 °C (diethyl ether); ^{1}H 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. ($C_{19}H_{12}ClFN_2$) C, H, N.

3-(4-Fluorophenyl)-1-(4-pyridinyl)-5-(trifluoromethyl)-1*H*-indole (8h): mp 163–165 °C (diethyl ether); ^{1}H NMR ($CDCl_3$) 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. ($C_{20}H_{12}F_4N_2$) C, H, N.

3-(4-Fluorophenyl)-4-methyl-1-(4-pyridinyl)-1*H*-indole (8i): mp 100–102 °C (di-2-propyl ether); ^{1}H NMR ($CDCl_3$) 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. ($C_{20}H_{15}FN_2$) C, H, N.

General Procedure for the Synthesis of 1-[2-[4-[3-(4-Fluorophenyl)-1*H*-indol-1-yl]-1,2,3,6-tetrahydropyridin-1-yl]ethyl]-2-imidazolidinones (12a–c). 1-[2-[4-[2,5-Dimethyl-3-(4-fluorophenyl)-1*H*-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)-1*H*-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)-1*H*-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 ($MgSO_4$). 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; ^{1}H NMR ($CDCl_3$) 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. ($C_{26}H_{26}FN_4O$) C, H, N.

The following compounds were prepared accordingly: **1-[2-[4-[3-(4-Fluorophenyl)-5-methyl-1*H*-indol-1-yl]-1,2,3,6-tetrahydropyridin-1-yl]ethyl]-2-imidazolidinone (12a)**: mp 129–131 °C (diethyl ether); ^{1}H NMR ($CDCl_3$) 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. ($C_{26}H_{27}FN_4O$) C, H, N.

1-[2-[4-[3-(4-Fluorophenyl)-7-methyl-1*H*-indol-1-yl]-1,2,3,6-tetrahydropyridin-1-yl]ethyl]-2-imidazolidinone (12b): mp 126–128 °C (diethyl ether); ^{1}H NMR ($CDCl_3$) 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. ($C_{26}H_{27}FN_4O \cdot 0.5H_2O$) C, H, N.

General Procedure for the Syntheses of Substituted 3-(4-Fluorophenyl)-1-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1*H*-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)-1*H*-indole (12d)** was isolated as an oil: ^{1}H NMR ($CDCl_3$) 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)-1*H*-indole (12e): mp 98–100 °C (di-2-propyl ether/*n*-heptane, 1:1); ^{1}H NMR ($CDCl_3$) 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. ($C_{22}H_{23}FN_2$) C, H, N.

General Procedures for the Synthesis of Substituted 3-(4-Fluorophenyl)-1-(4-piperidinyl)-1*H*-indoles (10). 1-[2-[4-[5-Chloro-3-(4-fluorophenyl)-1*H*-indol-1-yl]-1-piperidinyl]ethyl]-2-imidazolidinone (10d). 5-Chloro-3-(4-fluorophenyl)-1-(4-pyridinyl)-1*H*-indole (**8g**) (3.0 g, 0.0093 mol) was dissolved in acetic acid (100 mL), and PtO_2 (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 (Na_2SO_4). Evaporation of the solvent gave 2.5 g of crude 5-chloro-3-(4-fluorophenyl)-1-(4-piperidinyl)-1*H*-indole as an oil, which was used without further purification.

A mixture of 5-chloro-3-(4-fluorophenyl)-1-(4-piperidinyl)-1*H*-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; ^{1}H 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)-1*H*-indol-1-yl]-1-piperidinyl]ethyl]-2-imidazolidinone (10a)**: mp 192–194 °C (2-propanol); ^{1}H 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)-1*H*-indol-1-yl]-1-piperidinyl]ethyl]-2-imidazolidinone (10b): mp 172–173 °C (diethyl ether/*n*-heptane, 1:1); ^{1}H 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)-1*H*-indol-1-yl]-1-piperidinyl]ethyl]-2-imidazolidinone (10c): mp 153–156 °C (ethyl acetate/*n*-heptane, 1:1); ^{1}H 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-1*H*-indol-1-yl]-1-piperidinyl]ethyl]-2-imidazolidinone (10e): mp 186–188 °C (ethanol); ^{1}H 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)-1*H*-indol-1-yl]-1-piperidinyl]ethyl]-2-imidazolidinone (10f): mp 182–184 °C (diethyl ether); ^{1}H 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-1*H*-indol-1-yl]-1-piperidinyl]ethyl]-2-imidazolidinone (10g): mp 163–165 °C (diethyl ether); ^{1}H 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. ($C_{25}H_{28}FN_4O$) C, H, N.

1-[2-[4-[3-(4-Fluorophenyl)-5-methyl-1*H*-indol-1-yl]-1-piperidinyl]ethyl]-3-(2-propyl)-2-imidazolidinone oxalate (10j): mp 175–177 °C (acetone); ^{1}H 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. ($C_{28}H_{35}FN_4O \cdot C_2H_2O_4$) C, H, N.

1-[2-[4-[2,5-Dimethyl-3-(4-fluorophenyl)-1*H*-indol-1-yl]-1-piperidinyl]ethyl]-2-imidazolidinone (10i). To a refluxing mixture of 1-[2-[4-[2,5-dimethyl-3-(4-fluorophenyl)-1*H*-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; ^{1}H 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-1*H*-indol-1-yl]-1-piperidinyl]ethyl]-2-imidazolidinone (10h)**: mp 141–144 °C (diethyl ether); ^{1}H 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)-1*H*-indole fumarate (10k): mp 170–172 °C (ethanol); ^{1}H 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)-1*H*-indole (10l): mp 110–112 °C (*n*-heptane); ^{1}H 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. ($C_{22}H_{25}FN_2$) C, H, N.

The following urea derivatives were prepared as described previously[1] 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-1*H*-indole (10m)**: mp 126–128 °C (diethyl ether); ^{1}H 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. ($C_{25}H_{31}FN_4O$) C, H, N.

1-[1-[2-(1,3-Dimethyl-1-ureido)ethyl]-4-piperidinyl]-3-(4-fluorophenyl)-5-methyl-1*H*-indole hydrochloride (10n): mp 204–205 °C (acetone); ^{1}H 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. ($C_{25}H_{31}FN_4O \cdot HCl \cdot 0.65H_2O$) C, H, N.

Synthesis of 3-(4-Fluorophenyl)-5-methyl-1-(1-methyl-4-piperazinyl)-1*H*-indole (14). 1-Amino-3-(4-fluorophenyl)-5-methyl-1*H*-indole (13). Potassium *tert*-butoxide (7.5 g, 0.067 mol) was added to a solution of 3-(4-fluorophenyl)-5-methyl-1*H*-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; ^{1}H 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)-1*H*-indole (14). To a mixture of 1-amino-3-(4-fluorophenyl)-5-methyl-1*H*-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; ^{1}H NMR ($CDCl_3$) 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. ($C_{20}H_{22}FN_3O$) 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. ED_{50} values were calculated by log-probit analyses. IC_{50} 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 D$_2$ Receptors. Affinity of test compounds to dopamine D_2 receptors was estimated by their ability to displace [^{3}H]spiperone from rat striatal membranes as described by Hyttel.[28]

5-HT$_2$ Receptors. 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.[28]

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.[29]

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