was 0.079, and the standard deviation of fit was 8.9. The coordinates reported in the supplementary material are for this refinement. The CRYM system of computer programs was used.[51]

Data for (*R*)-5: $C_{16}H_{23}N_3O \cdot HBr \cdot H_2O$ M_r = 291.391 × 80.92 × 18.01; triclinic; space group $P\bar{1}$; unit cell a = 7.284 (4) Å, b = 8.417 (2) Å, c = 14.519 (4) Å; α = 81.12 (3)°, β = 102.68 (4)°, γ = 102.53 (3)°; V = 842.39 Å^3; Z = 2; D_c = 1.46 g cm^{-3}; λ(Cu Kα) = 1.5418 Å; μ = 3.2 mm^{-1}; T = 123(2) K.

Dopamine and Serotonin Binding Assays. Receptor binding studies for the D2 dopamine receptor were carried out using [^{3}H]raclopride (specific activity 80 Ci/mmol, NEN) using homogenates of rat striata prepared with a Polytron and diluted 1:300.[29] Incubation was for 1 h at room temperature, at which time samples were filtered over SS #24 filters (pretreated with 0.05% PEI) and rinsed three times with 0.5 mL of 50 mM TRIS pH 7.4 buffer. Filters were counted using standard liquid scintillation techniques. Nonspecific binding was determined using haloperidol (1 μM). IC_{50} values were obtained using at least four concentrations of the drug, in triplicate, and calculated using log-probit analysis. K_i values were calculated from IC_{50} values using standard methods; standard error was <5%.

Receptor binding studies for the $5HT_{1A}$ receptor were carried out using [^{3}H]DPAT (specific activity 85 Ci/mmol, NEN) using homogenates of bovine hippocampus prepared with a Polytron and diluted 1:400.[30] Incubation was for 1 h at room temperature, at which time samples were filtered over SS #24 filters (pretreated with 0.05% PEI) and rinsed three times with 0.5 mL of 50 mM TRIS pH 7.4 buffer. Nonspecific binding was determined using serotonin (1 μM).

Amine Synthesis. Brain levels of DOPA and 5-HTP in the rat were determined as described previously.[10] Briefly, Upjohn CF-1 rats were injected sc with test drug or vehicle at time zero. Fifteen minutes later the rats received an aromatic decarboxylase inhibitor (*m*-hydroxybenzylhydrazine at 100 mg/kg ip). The rats were sacrificed 30 min later, and the tissues in the ventral limbic brain area were removed and frozen for later analysis. Tissues were weighed and extracted in 0.1 N perchloric acid containing an internal standard of dihydroxybenzylamine (2 μg/mL). The extract was then analyzed by HPLC using a Bioanalytical Systems ODS column. DOPA and 5-HTP were detected electrochemically and quantified by peak integration using Waters Maxima software. Biochemical differences were compared between a control (n = 6) and a test group (n = 6) by unpaired t test.

Recordings from Dopaminergic and Serotonergic Neurons. Charles River male Sprague-Dawley rats (280–330 g) were anesthetized with chloral hydrate (400 mg/kg ip). Supplemental doses were administered as needed to maintain anesthesia. The femoral artery and vein were cannulated for blood pressure and drug administration. The animal's head was held in a stereotaxic device and a small burr hole drilled at the appropriate location. Extracellular action potentials were recorded with a glass microelectrode (tip size < 1 μm) filled with pontamine sky blue dye in 2 M sodium chloride. Dopaminergic neurones were identified by their long duration action potential (>2.5 ms), shape, and firing pattern (>12 spikes/s) as previously described.[56] The recording electrode was hydraulically lowered into the substantia nigra pars compacta area (P 5.0–6.0 mm, L 2.0–2.2 mm, V 7.0–8.0 mm) according to the coordinates of Paxinos and Watson.[57] Serotonergic neurones were identified by their large, biphasic positive–negative action potentials with slow and regular firing rates (approximately 0.8–2.5 spikes/s) as previously described.[58] The recording electrode was hydraulically advanced to reach the dorsal raphe nucleus (A 0.5–1.7 mm, L 0 mm, V 3.5–4.2 mm) according to the coordinates of Paxinos and Watson.[57] At the termination of each recording session, the location of the cell was identified by passing a 10-μA cathodic current for 10–20 mins. The brain was then removed, sectioned, and stained, and the pontamine sky blue deposit verified in each animal. Only those cells found to be in the appropriate area were included in the study. All drug solutions were made in distilled water. Each drug injection contained no more than 0.15 mL of a given concentration, followed by 0.2–0.4 mL of physiological saline to clean the catheter of any residual drug. Drug effects were measured as changes in firing rates as indicated by an integrated ratemeter output throughout the experiment. The dose required to depress neuronal firing by 50% was taken as the ED_{50}, measured by interpolation of the dose–response curve for each individual cell.

Supplementary Material Available: Tables of atomic coordinates, isotropic thermal parameters, bond lengths and angles, torsion angles, anisotropic thermal parameters, hydrogen bonds, and close intermolecular contacts (6 pages). Ordering information is given on any current masthead page. The atomic coordinates are deposited at the Cambridge Crystallographic Data Centre.

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Noncataleptogenic, Centrally Acting Dopamine D-2 and Serotonin 5-HT$_2$ Antagonists within a Series of 3-Substituted 1-(4-Fluorophenyl)-1*H*-indoles

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A series of 1-(4-fluorophenyl)-1*H*-indoles substituted at the 3-position with 1-piperazinyl, 1,2,3,6-tetrahydro-4-pyridinyl, and 4-piperidinyl was synthesized. Within all three subseries potent dopamine D-2 and serotonin 5-HT$_2$ receptor affinity was found in ligand binding studies. Quipazine-induced head twitches in rats were inhibited by most derivatives as a measure of central 5-HT$_2$ receptor antagonism. Piperazinyl and tetrahydropyridyl indoles were cataleptogenic, while piperidyl substituted indoles surprisingly were found to be noncataleptogenic or only weakly cataleptogenic. Noncataleptogenic piperidyl derivatives also failed to block dopaminergic-mediated stereotypies, that is methyl phenidate-induced gnawing behavior in mice. These profiles resemble that of the atypical neuroleptic clozapine. 1-Ethyl-2-imidazolidinone was found to be the optimal substituent of the basic nitrogen atom in order to avoid catalepsy. The atypical neuroleptic 1-[2-[4-[5-chloro-1-(4-fluorophenyl)-1*H*-indol-3-yl]-1-piperidinyl]ethyl]-2-imidazolidinone (sertindole, compound **14c**) was selected for further development as a result of these structure/activity studies.

Introduction

Treatment of psychoses such as schizophrenia, mania, paranoia, and the like with neuroleptic drugs has been well established since the introduction of chlorpromazine about 40 years ago. For most schizophrenic patients, positive symptoms like hallucinations and delusions are alleviated by this medication while negative symptoms like blunted affect, emotional withdrawal, apathy, and motor retardation are poorly treated. Severe side effects are frequently experienced during antipsychotic drug treatment. In-

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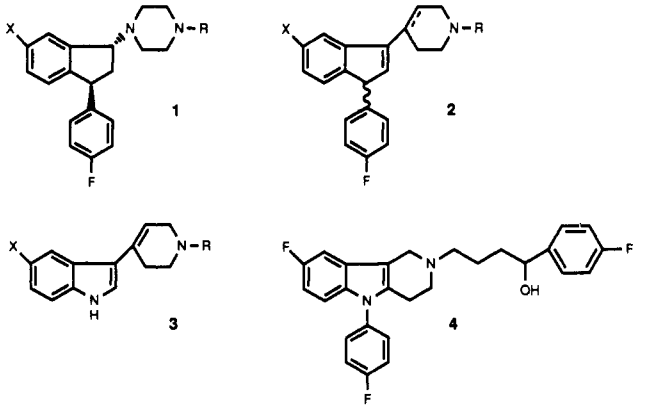
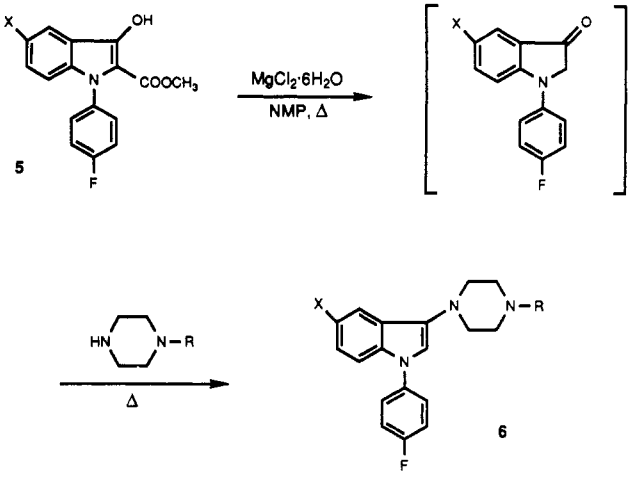


Figure 1. Structures of neuroleptic compounds: (1*R*,3*S*)-*trans*-3-(4-fluorophenyl)indans (**1**), 3-(4-fluorophenyl)-1-indenes (**2**), 3-(1,2,3,6-tetrahydro-4-pyridyl)-1*H*-indoles (**3**), and 8-fluoro-5-(4-fluorophenyl)-2-[4-hydroxy-4-(4-fluorophenyl)butyl]-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole (flutroline **4**).

voluntary movement disorders or extrapyramidal side effects (EPS) such as a parkinsonian syndrome, akathisia, dystonia, and tardive dyskinesia occur in a high percentage of patients treated with classical neuroleptics like chlorpromazine, fluphenazine, and haloperidol. A common feature of this class of compounds is the ability to induce catalepsy in rodents. Catalepsy has been suggested to correlate to the propensity of a drug to induce EPS or specifically drug-induced Parkinsonism in patients.[1] In the mid-1960s clinical studies of clozapine proved this compound to be an efficacious drug in the treatment of psychoses without producing EPS.[2] Unfortunately, severe incidences (some fatal) of clozapine-induced agranulocytosis have put very strict limitations to the clinical use of this otherwise beneficial neuroleptic drug.[3] Clozapine is the prototype of the atypical antipsychotic drugs.[4,5] Compared to classical neuroleptics these compounds are not or only weakly cataleptogenic in rodents. Attempts to correlate these properties to receptor affinity profiles seem to indicate the importance of high affinity for central 5-HT$_2$ receptors.[6,7] It has also been suggested that properly balanced D-1/D-2 receptor interactions in combination with 5-HT$_2$ receptor blockade favor an atypical neuroleptic profile.[7] Clozapine is also a potent antimuscarinic compound. A hypothesis of imbalance in DA/acetylcholine systems has been suggested for drug-induced EPS.[8] The low propensity of certain anticholinergic

Scheme I. Syntheses of 1-[1-(4-Fluorophenyl)-1*H*-indol-3-yl]piperazines (**6**)



neuroleptics including clozapine to induce EPS has consequently been attributed to a restoration of this imbalance. Central α_1 adrenoceptor antagonism has also been implicated to account for low incidences of EPS after treatment with atypical neuroleptics. Repeated coadministration of the α_1 antagonist prazosin and haloperidol was found to reduce the effect of haloperidol in nigrostriatal areas, which are believed to be the origin of motor dysfunctions.[9] 5-HT$_2$ receptor blockade has additionally been suggested to correlate with clinical improvement of the negative symptoms of schizophrenia.[10]

Our previous studies within a series of *trans*-3-phenyl-1-piperazinoindans (**1**) (Figure 1) of (1*R*,3*S*) configuration revealed marked neuroleptic activity in certain of these compounds with concomitantly potent 5-HT$_2$ receptor blocking activity.[11,12] One of these indan derivatives, tefludazine (**1**, X = CF_3, R = CH_2CH_2OH, racemic mixture),[13] was selected as a candidate for clinical trials, but the development was discontinued due to toxicological findings in preclinical animal studies. Like classical neuroleptics tefludazine potently induced catalepsy in rats. We have previously shown that the rather complex situation of isomerism of phenylindans (trans/cis isomers each with a pair of stereoisomers) could be reduced to only stereoisomerism by introducing a double bond in the indan ring and substituting the piperazine ring by a 1,2,3,6-tetrahydropyridine or a piperidine ring. This series of 3-phenyl-1-(1,2,3,6-tetrahydro-4-pyridyl)- and 3-phenyl-

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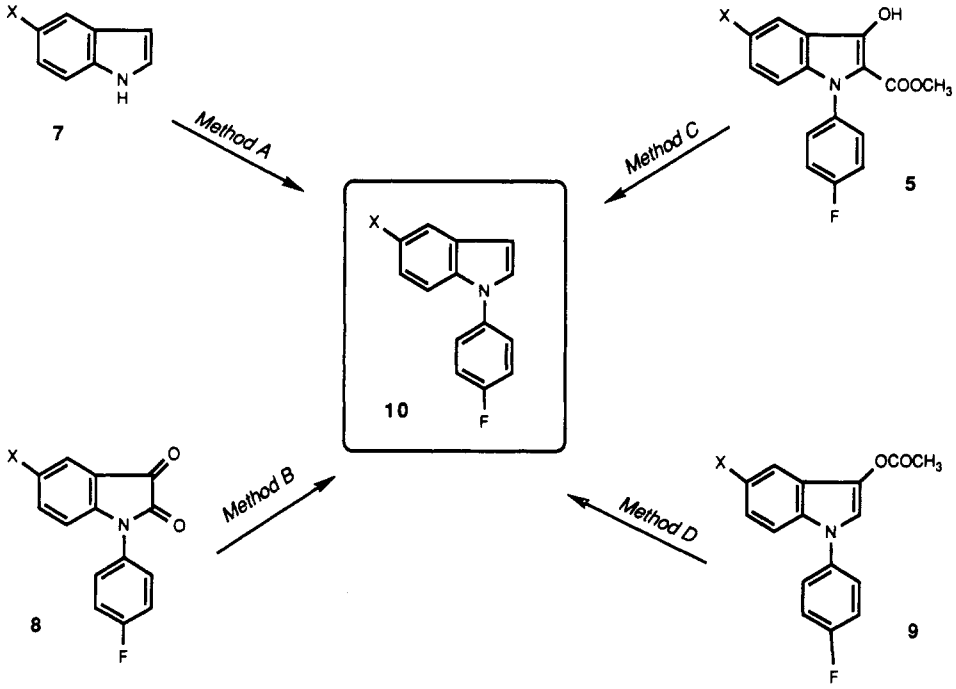
Scheme II. Syntheses of 1-(4-Fluorophenyl)-1*H*-indoles (10)



1-(4-piperidyl)indenes (2) (Figure 1) also retained potent neuroleptic activity.[14] Encouraged by the reported weak neuroleptic activity of 1-unsubstituted 3-(1,2,3,6-tetrahydro-4-pyridyl)-1*H*-indoles (3)[15] and strong neuroleptic potency of certain 5-(4-fluorophenyl)tetrahydro-γ-carbolines (flutroline 4, Figure 1),[16] we felt prompted to investigate the potential neuroleptic activity of 1-phenyl-substituted indole analogues of structures 1 and 2. By introducing the indole structure, problems with the geometric and optical isomerism associated with indans (1) and indenes (2), respectively, were eliminated. This paper will discuss the chemical development and the structure/activity relationships of these new indole neuroleptics, which have led to the discovery of the new atypical neuroleptic, sertindole (recommended INN name) (compound **14c**).[17,18]

Chemistry

The present study has been restricted to 1-(4-fluorophenyl)-substituted indoles since studies of the previously mentioned indans (1) and indenes (2) have indicated this particular aryl substituent as optimal both for neuroleptic activity as assessed by antistereotypic effects (methyl phenidate and amphetamine antagonism)[12] and 5-HT_2 receptor affinity.[11]

3-Piperazino-1*H*-indoles 6. 5-Substituted 1-(4-fluorophenyl)-3-hydroxy-1*H*-indole-2-carboxylic acid methyl esters (5) (Scheme I) were used as readily available substrates for the syntheses of the 3-piperazino derivatives. The methods of Unangst et al.[19,20] were adapted for the preparation of esters 5. Hydrolysis, decarboxylation, and subsequent addition of the appropriately N-substituted piperazines to the intermediate 3-indolinones were performed as a one-pot reaction sequence under an inert nitrogen atmosphere (Scheme I). This special reaction

Table I. 1-[1-(4-Fluorophenyl)-1*H*-indol-3-yl]piperazines (6)

compd	X	R	mp, °C	formula[a]
6a	CF_3	CH_2CH_2OH	167	$C_{21}H_{21}F_4N_2O$
6b	Cl	CH_3	136–137	$C_{19}H_{19}ClFN_3$
6c	Cl	IMID[b]	173	$C_{23}H_{25}ClFN_5O$

[a] Microanalyses (C, H, N) were within ±0.4 of the theoretical values. [b] IMID = 

Table II. 1-(4-Fluorophenyl)-1*H*-indoles (10)

compd	X	method[a]	mp, °C	formula[b]
10a	H	A	40	$C_{14}H_{10}FN$
10b	NO_2	A	144–145	$C_{14}H_9FN_2O_2$
10c	CN	A	110–112	$C_{15}H_9FN_2$
10d	F	A or B	oil[c]	
10e	CH_3	B	oil[c]	
10f	CF_3	C	53	$C_{15}H_{19}F_4N$
10g	CH_3SO_2	C	126	$C_{15}H_{12}FNO_2S$
10h	Cl	C or D	86–87	$C_{14}H_9ClFN$
10i	OCH_3	D	96	$C_{15}H_{12}FNO$
10j	Br	D	101	$C_{14}H_9BrFN$

[a] See Scheme II and Experimental Section for reaction conditions. [b] Microanalyses (C, H, N) were within ±0.4% of the theoretical values. [c] ^1H NMR spectra are reported in the Experimental Section for compounds which were obtained as an oil.

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sequence was elaborated to avoid isolation of the intermediate 3-indolinones which, upon exposure to air, are very susceptible to undergo oxidative dimerizations to indigo type of products.[21] Synthesized 1-[1-(4-fluorophenyl)-1*H*-indol-3-yl]piperazines (**6**) are shown in Table I.

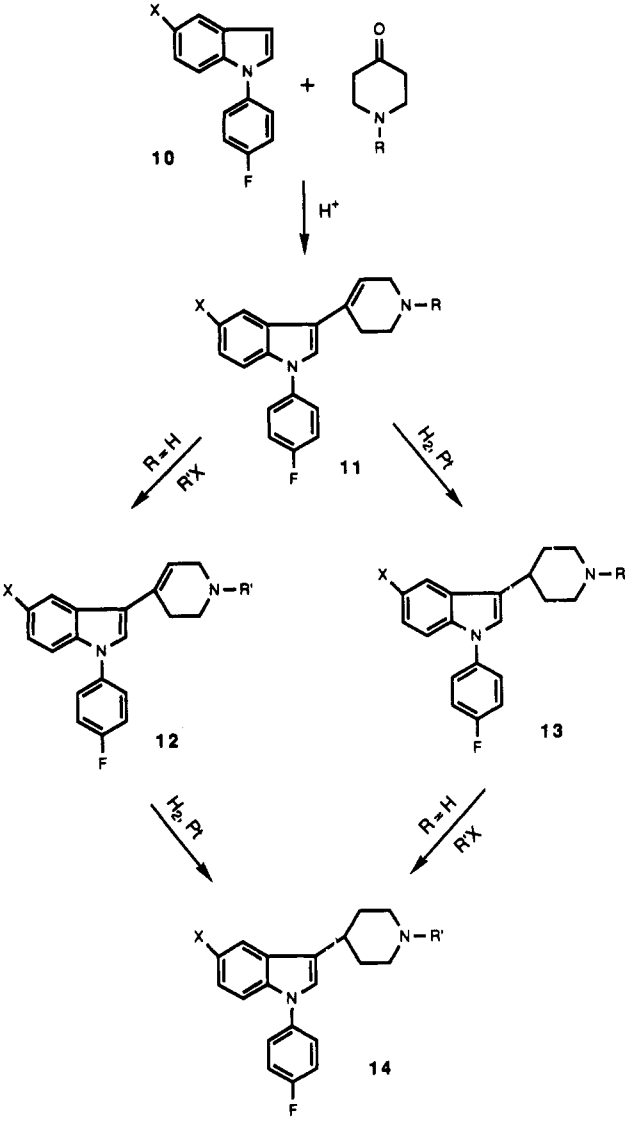
3-(1,2,3,6-Tetrahydro-4-pyridyl)-1*H*-indoles (11 and 12) and 3-(4-Piperidyl)-1*H*-indoles (13 and 14). Key intermediates for the preparation of 3-(1,2,3,6-tetrahydro-4-pyridyl) and 3-(4-piperidyl) derivatives were the 1-(4-fluorophenyl)-substituted indoles (**10**) (Scheme II, Table II). Literature procedures, albeit very rare, for the preparation of 1-phenylindoles either involve copper-catalyzed Ullmann arylation[22] with aryl halides or nucleophilic aromatic substitution[23] of corresponding fluorobenzenes by 1-unsubstituted indoles. The Ullmann arylation procedure (method A, Scheme II) was preferred when 1-unsubstituted indoles (**7**) were either commercially available at reasonable costs and quantities or if they could be conveniently prepared according to known methods. The 5-unsubstituted (**10a**), 5-NO_2 (**10b**), 5-CN (**10c**), and 5-F (**10d**) 1-(4-fluorophenyl)-1*H*-indoles were prepared accordingly (Table II).

Method B involves 1-(4-fluorophenyl)-substituted isatins, which were obtained by treatment of corresponding diphenylamines with oxalyl chloride followed by ring-closure reaction under Friedel–Craft ($AlCl_3$) conditions. Ring closure was preferentially directed to the benzene ring with the most electron-donating substituents, which of course put limitations to the versatility of the method. Using this method we have prepared the 5-fluoro- and 5-methylisatins unambiguously. Diborane reduction of 1-unsubstituted or 1-methylisatins to indoles were reported by Sirowej et al.[24] We found that their method was also useful for the reduction of 1-(4-fluorophenyl)isatins (**8**) to the corresponding 1-(4-fluorophenyl)-1*H*-indoles (**10**) (method B, Scheme II). Taking proper safety precautions (exclusion of air and strict control of reaction temperatures) we managed to control the B_2H_6 reductions on a laboratory scale which provided a few hundred grams of the desired indoles [5-F (**10d**) and 5-CH_3 (**10e**), Table II].

Certain indoles (**10**) are inaccessible or at least inconveniently prepared by methods A or B in large-scale quantities. As shown above, 3-hydroxyindole-2-carboxylic acid esters (**5**) were suitable precursors for indolin-3-ones (Scheme I). Under appropriate reaction conditions these air-sensitive indolin-3-ones were reduced with $NaBH_4$ without prior isolation. The 3-hydroxyindolines thus formed subsequently underwent acid-catalyzed water elimination to the desired indoles (**10**) (method C, Scheme II). The 5-CF_3 (**10f**), 5-methylsulfonyl (**10g**), and 5-chloro (**10h**) compounds were synthesized by method C (Table II).

Since indolin-3-ones were the key intermediates in procedure C we anticipated 3-acetoxyindoles **9** to be more easily available precursors. These acetyl-protected indolin-3-ones were prepared simply in a one-step reaction from properly substituted *N*-(*o*-carboxyphenyl)-*N*-phenylglycines according to similar literature procedures.[25-27]

Scheme III. Syntheses of 3-(1,2,3,6-Tetrahydro-4-pyridyl)-1*H*-indoles (**11** and **12**) and 3-(4-Piperidyl)-1*H*-indoles (**13** and **14**)



Deprotection was expected under suitable transesterification reaction conditions. Actually, we found, that alcoholysis of the 3-acetoxy esters took place in methanol in the presence of $NaBH_4$ with further reduction of the in situ formed indolin-3-one. The resulting 3-hydroxyindolines eliminated water under acidic conditions, as above, to afford the desired indoles (**10**) (Scheme II, method D). The 5-chloro (**10h**), 5-methoxy (**10i**), and 5-bromo (**10j**) indoles were prepared accordingly (Table II). Method D appears to be the most versatile of the four methods in Scheme II.

Addition of 4-piperidones to 1-(4-fluorophenyl)-1*H*-indoles (**10**) under acidic conditions afforded 1-(4-fluorophenyl)-3-(1,2,3,6-tetrahydro-4-pyridyl)-1*H*-indoles (**11**) (Scheme III). It has previously been reported that also

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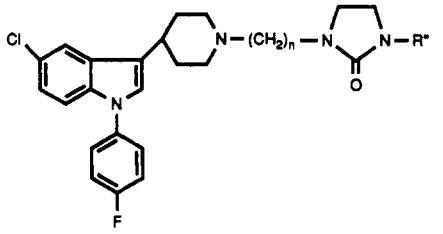
Table III. 3-(1,2,3,6-Tetrahydro-4-pyridyl)-1*H*-indoles (11, R Substituent, and 12, R′ Substituent) and 3-(4-Piperidyl)-1*H*-indoles (13, R Substituent, and 14, R′ Substituent)

compd	X	R/R′	mp, °C	formula[a]
11a	Cl	H	138–140	$C_{19}H_{16}ClFN_2$
11b	CF_3	H	128–130	$C_{20}H_{16}F_4N_2$
11c	H	CH_3	268–270	$C_{20}H_{19}FN_2 \cdot HCl \cdot {}^1/_4H_2O$
11d	Cl	CH_3	>285	$C_{20}H_{18}ClFN_2 \cdot HBr$
11e	F	CH_3	256	$C_{20}H_{18}F_2N_2 \cdot HCl$
11f	NO_2	CH_3	176	$C_{20}H_{18}FN_3O_2$
12a	Cl	IMID[b]	146	$C_{24}H_{24}ClFN_4O$
12b	CF_3	IMID	164–165	$C_{25}H_{24}F_4N_4O$
12c	CN	IMID	207	$C_{25}H_{24}FN_5O$
13a	Cl	H	196–201	$C_{19}H_{18}ClFN_2 \cdot$fumarate
13b	Cl	CH_2CH_2OH	266–269	$C_{21}H_{22}ClFN_2O \cdot HCl$
14a	H	IMID	174–175	$C_{24}H_{27}FN_4O$
14b	F	IMID	181	$C_{24}H_{26}F_2N_4O$
14c	Cl	IMID	154–155	$C_{24}H_{26}ClFN_4O$
14d	Br	IMID	171–172	$C_{24}H_{26}BrFN_4O \cdot {}^1/_2H_2O$
14e	CH_3	IMID	187–189	$C_{25}H_{29}FN_4O$
14f	CF_3	IMID	169–171	$C_{25}H_{26}F_4N_4O$
14g	CN	IMID	209	$C_{25}H_{26}FN_5O$
14h	CH_3SO_2	IMID	188–192	$C_{25}H_{29}FN_4O_2S \cdot$fumarate
14i	CH_3O	IMID	167	$C_{25}H_{29}FN_4O_2$

[a] Microanalyses (C, H, N) were within ±0.4% of the theoretical values. [b] R′ = IMID (see Table I, footnote *b*).

Table IV. 5-Chloro-3-(4-piperidyl)-1*H*-indoles (14)



compd	*n*	R″	mp, °C	formula[a]
14c	2	H	154–155	$C_{24}H_{26}ClFN_4O$
14j	3	H	203–205	$C_{25}H_{28}ClFN_4O \cdot$fumarate
14k	4	H	178–179	$C_{26}H_{30}ClFN_4O \cdot$oxalate
14l	5	H	145–147	$C_{27}H_{32}ClFN_4O \cdot$oxalate
14m	6	H	156–158	$C_{28}H_{34}ClFN_4O \cdot {}^3/_4$oxalate
14n	2	CH_3	198–199	$C_{25}H_{28}FClN_4O \cdot$fumarate
14o	2	isopropyl	92–96	$C_{27}H_{32}ClFN_4O \cdot$oxalate$\cdot {}^1/_2H_2O$
14p	2	cyclopentyl	102–105	$C_{29}H_{34}ClFN_4O \cdot$oxalate$\cdot {}^3/_4H_2O$
14q	2	C_6H_5	171–172	$C_{30}H_{30}FClN_4O$

[a] Microanalyses (C, H, N) were within ±0.4% of the theoretical values.

alkaline reaction conditions catalyzed the addition of 4-piperidones to 1-unsubstituted indoles.[28] We found that only acids and most conveniently a mixture of trifluoroacetic acid and acetic acid under very restricted reaction procedures provided high yields of the products (11). Minor changes of reaction conditions were found to result in high proportions of "bis" products deriving from addition of another mole of 1-(4-fluorophenyl)-1*H*-indole to the assumed intermediate 4-(3-indolyl)piperidyl carbonium ion. With appropriate acid catalysts and excess of the indole 10 4,4-bis(3-indolyl)piperidines were formed as the main products. The preparation of compound **15a** is an example of optimal conditions for this unwanted side reaction (see Experimental Section). Using 4-piperidone hydrochloride, hydrate N-unsubstituted derivatives (R = H) (11) were prepared. Alkylation of such unsubstituted derivatives with 1-(2-chloroethyl)-2-imidazolidinone yielded imidazolidinone derivatives (12) (Scheme III, Table III). The piperidyl compounds **13a** and **13b** (Table III) were prepared by catalytic hydrogenation of the corresponding tetrahydropyridyl derivatives 11 (Scheme III). Platinum was found to be the best choice of catalyst in order to minimize catalytic dehalogenation of the 5-chloro-substituted indoles. The preferred way of synthesizing compounds **14a–q** was via alkylation of the N-unsubstituted 3-(4-piperidyl) derivatives **13** with appropriately substituted 1-(ω-chloroalkyl)-2-imidazolidinones (Scheme III). However, an alternative route was catalytic hydrogenation of compounds **12** (Scheme III). To investigate the influence of the alkyl chain length on pharmacological activity a series of alkylimidazolidinone derivatives (n = 2 to n = 6, structures **14c** and **14j–m** in Table IV) were synthesized. Substitution of the 3-position of the imidazolidinone ring was also studied (structures **14n–q** in Table IV). The 1-(ω-chloroalkyl)-substituted 2-imidazolidinones[29,30] and the 3-substituted 1-(2-chloroethyl)-2-imidazolidinones[31] used as alkylating agents in these syntheses were obtained according to procedures described in the literature. To investigate the significance of the 1-(4-fluorophenyl) substituent for neuroleptic activity we prepared the 1-unsubstituted indole analogue (**16**) of our key compound **14c**. Compound **16** is structurally related to the earlier reported compounds **3** (Figure 1).[15,28]

Results and Discussion

The pharmacological test models are described in detail in the Experimental Section. Pharmacological and biochemical activity of the compounds are reported in Table V and compared to relevant reference compounds (risperidone, clozapine, haloperidol, and tefludazine). Risperidone is a new 3-(4-piperidyl)benzisoxazole neuroleptic with a potent, central antiserotonergic effect currently in clinical trials.[32,33] Clozapine and haloperidol are examples of an atypical and of a classical neuroleptic, respectively, both of which are clinically effective. Tefludazine is a racemic *trans*-3-(4-fluorophenyl)indan derivative (see Introduction and Figure 1) structurally related to our 1-(4-fluorophenyl)-1*H*-indole series. Antagonism of methyl phenidate-induced gnawing behavior and induction of catalepsy are in vivo test models for central D-2 antagonism in which classical neuroleptics show potent activity. In the [^{3}H]spiperone binding assay the affinity for central dopamine D-2 receptors is measured. Quipazine is a 5-HT_2 agonist which induces the well-known "head twitch syndrome" in rats.[34] Centrally active 5-HT_2 antagonists are known to inhibit this syndrome. [^{3}H]Ketanserin binding is used to measure the affinity for cortical 5-HT_2 receptors.

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Table V. Biochemical and Pharmacological Activity of 3-Substituted 1-(4-Fluorophenyl)-1*H*-indoles

	dopamine D-2 receptors			serotonin 5-HT$_2$ receptors	
compd	methyl phenidate antg. (mice)[a]	catalepsy max effect (rats)[a]	[^{3}H]spiperone binding[b]	quipazine inhibition (rats)[a]	[^{3}H]ketanserin binding[b]
6a	0.079 (0.029–0.22)	0.060 (0.029–0.13)	2.6	0.023 (0.0096–0.055)	1.4
6b	0.12 (0.041–0.35)	0.23 (0.079–0.67)	1.0	0.041 (0.011–0.16)	0.30[c]
6c	7.8 (3.3–18)	4.5 (2.6–7.7)	21	0.015 (0.0033–0.068)	4.4
11a	17.0 (6.3–45)	>61	NT[d]	1.5 (0.65–3.5)	NT
11b	2.1 (0.64–6.9)	>14	NT	>0.86	NT
11c	1.3 (0.62–2.7)	3.6 (1.6–8.3)	1.6	0.15 (0.047–0.48)	NT
11d	0.085 (0.037–0.20)	0.085 (0.034–0.21)	1.1	0.058 (0.017–0.20)	0.53[c]
11e	0.44 (0.21–0.92)	0.64 (0.32–1.3)	0.74	0.15 (0.075–0.30)	3.0[c]
11f	0.022 (0.015–0.033)	0.025 (0.013–0.048)	0.76	0.0091 (0.0036–0.023)	1.9[c]
12a	2.0 (0.74–5.4)	2.2 (1.1–4.4)	2.3	0.22 (0.12–0.42)	NT
12b	0.37 (0.15–0.89)	0.49 (0.16–1.5)	NT	0.14 (0.067–0.29)	NT
12c	NT	0.37 (0.13–1.1)	2.1	NT	3.2
13a	>90	NT	23	1.5 (0.18–12)	3.8
13b	1.5 (0.44–5.1)	3.8 (0.73–20)	4.5	0.034 (0.0085–0.14)	2.7
14a	>98	>98	18	0.036 (0.011–0.12)	0.72
14b	>78	>78	4.7	0.052 (0.027–0.099)	0.48
14c	>180	>91	4.1	0.035 (0.022–0.056)	0.39
14d	>82	>41	3.8	0.032 (0.094–0.11)	1.3
14e	98.0 (47–210)	>91	3.7	0.0083 (0.0030–0.023)	0.30
14f	22.0 (9.2–53)	45.0 (17–120)	1.9	0.11 (0.048–0.25)	1.0
14g	NT	34.0 (9.2–130)	2.2	NT	1.3
14h	>67	>17	5.8	54% inhibition at 0.13 μmol/kg	8.0
14i	>76	>46	24	0.77 (0.29–2.1)	1.0
14j	57.0 (41–80)	11.0 (6.9–18)	3.4	1.8 (0.51–6.3)	1.0
14k	>72	NT	78	>2.2	59
14l	14.0 (6.7–29)	NT	4.2	1.5 (0.58–3.4)	1.5
14m	2.7 (1.6–4.6)	20.0 (14–28)	2.2	>2.2	2.5
14n	2.6 (1.1–6.0)	31.0 (21–47)	6.5	0.021 (0.0091–0.048)	0.24
14o	>69	>69	12	0.046 (0.018–0.12)	2.1
14p	>67[e]	NT	NT	>2.1	NT
14q	>77[e]	NT	92	>0.15	4.4
15a	NT	NT	760	NT	120
16	NT	47.0 (31–71)	810	>14	25
risperidone	0.95 (0.40–2.3)	>6.1	4.0	0.050 (0.016–0.15)	0.76
clozapine	98.0 (70–137)	>120	410	1.5 (0.68–3.3)	7.8
haloperidol	0.30 (0.19–0.48)	0.36 (0.43–0.30)	7.5	0.63 (0.33–1.2)	18
tefludazine	0.20 (0.095–0.42)	0.12 (0.071–0.20)	10	0.029 (0.016–0.052)	2.8

[a] Results are expressed as ED_{50} values in μmol/kg (sc administration). 95% confidence limits in parentheses. [b] 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; 5-HT$_2$, 2.05. [c] [^{3}H]Spiperone binding. [d] NT = not tested. [e] PO administration.

Compound **6a** is the 3-[1-(2-hydroxyethyl)-4-piperazinyl]-substituted indole analogue of tefludazine. The pharmacological profiles are almost identical for the two compounds except for a slightly higher potency of compound **6a**. Both compounds are more potent 5-HT$_2$ antagonists than haloperidol, but are, nevertheless, cataleptogenic at low doses like classical neuroleptics. Also other 3-(4-piperazinyl)indoles (**6b** and **6c**) are cataleptogenic. However, ethyl-2-imidazolidinone substitution (**6c**) seems to reduce antidopaminergic effects considerably (Table V), while a potent 5-HT$_2$-blocking activity is still retained or even slightly more prominent in vivo. The secondary amines **11a** and **11b** (tetrahydropyridylindoles) and **13a** (piperidylindole) have no or only weak effects in vivo, although compound **13a** retains considerable receptor affinities. Secondary amines of structure **3** are reported to be 5-HT agonists[28] as these compounds induce 5-HT syndromes. No such activating effects have been observed with the secondary amine derivatives in our series. In fact, both compounds **11a** and **13a** exert 5-HT$_2$-antagonistic effects, although very weak, as shown by inhibition of quipazine-induced head twitches (Table V).

The *N*-methyl tetrahydropyridyl derivatives **11c–f** are similar in profiles to the corresponding piperazinylindoles **6**. Generally, they appear to be at least 50–100 times more potent than corresponding 1-unsubstituted indoles (**3**) as D-2 antagonists when measured by the ability to antagonize methyl phenidate-induced stereotypies.[15,28] Guillaume et al.[28] reported antagonism of apomorphine-induced stereotypies for the 5-unsubstituted (ED_{50} = 50 μmol/kg) and the 5-chloro (ED_{50} = 21 μmol/kg) 1-unsubstituted indole analogues of **11c** and **11d**, respectively. 5-HT$_2$ receptor affinities were reported by Taylor et al. for a series of 1-unsubstituted 3-(1,2,3,6-tetrahydro-4-pyridyl)-1*H*-indoles.[35] Generally, they have found higher or equal affinity for the 5-HT$_{1A}$ receptor than for the 5-HT$_2$ receptor. The indoles from our 1-(4-fluorophenyl) series have insignificant binding to 5-HT$_{1A}$ receptors (unpublished data). To our knowledge no in vivo 5-HT$_2$-antagonistic effects have been reported in the literature for 1-unsubstituted indoles. Apparently, the 5-substituent of the indole ring does not influence receptor binding significantly (compounds **11c** to **11f**, Table V). The in vivo potency is also seen to be very little influenced by the variation of 5-substitution. It seems, however, that the 5-unsubstituted indole (**11c**) and the 5-fluoroindole (**11e**)

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Table VI. Inhibition of Quipazine-Induced Head Twitches 24 h after Subcutaneous Administration of Test Compounds

compd	quipazine inhibition: ED_{50}, μmol/kg,[a] 24 h[b]
11d	>0.19
12a	1.2 (0.38–3.8)
12b	>0.66
14a	0.082 (0.014–0.48)
14b	0.0097 (0.0022–0.043)
14c	0.030 (0.014–0.066)
risperidone	>3.0
clozapine	>31

[a] 95% confidence limits in parentheses. [b] For 2 h values see Table V.

are somewhat weaker than the 5-chloro- and the 5-nitroindoles (**11d** and **11f**, respectively), especially in the antidopaminergic tests (methyl phenidate antagonism and catalepsy, Table V). This is actually contrary to previously reported structure/activity relationships in the indan series (**1**)[12] in which only 6-trifluoromethyl substitution was found to produce potent antistereotypic effects and catalepsy. Within a series of 1-[1-(2-hydroxyethyl)-4-piperazinyl]-substituted indans the 6-trifluoromethyl derivative (tefludazine) was reported to antagonize methyl phenidate-induced gnawing with an ED_{50} = 0.07 μmol/kg (ip), while the corresponding 6-F and 6-Cl derivatives were very weak. The 6-unsubstituted indan was virtually inactive. We have recently presented results of QSAR studies of an extended series of 5-substituted indoles which further confirm this negligible influence of the 5-substituent.[36] Replacement of simple *N*-alkyl substituents by an ethyl-2-imidazolidinone side chain (compounds **12a–c**) seems to decrease in vivo antidopaminergic activities to the same extent as observed within the piperazinyl series (**6**), however with high dopamine receptor affinity preserved (compounds **11d** and **12a** for direct comparison).

The piperidyl derivatives **14c**, **14f**, and **14g** are the corresponding analogues to compounds **12a**, **12b**, and **12c**, respectively, where the double bond of the tetrahydropyridyl ring has been saturated. Important pharmacological properties are induced by this minor structural change. The propensity of inducing catalepsy almost vanishes like the antistereotypic activity, although strong D-2 receptor affinities are preserved (Table V). These piperidyl derivatives very effectively bind to 5-HT_2 receptors, and high potency in the quipazine inhibition test indicates good CNS penetration. This profile is found in the whole series **14a–i** where the 5-substituent of the indole is systematically varied (structures in Table III, results in Table V). Furthermore, the compounds **14** are found to be long-acting in the quipazine inhibition test (Table VI). Equipotency is measured 2 and 24 h after administration of test substances. Risperidone, clozapine, and the close, unsaturated analogues **11** and **12** are either inactive or considerably weaker 24 h after administration.

By using molecular modeling software (MacMimic Programme, Instar Software) the three-dimensional structures of the three series of indoles were build by energy minimization and low-energy conformations were found by independently rotating the 6-membered basic rings and the 4-fluorophenyl substituent. Piperazinyl (**6**), tetrahydropyridyl (**11** and **12**) and piperidyl (**13** and **14**) derivatives exist as extended, planar structures in their low-energy states. These planar structures almost perfectly superimpose each other. Equipotency within the three series of compounds in D-2 and 5-HT_2 receptor affinities (Table V) are in agreement with these close structural relationships. Thus, no spatial requirements for receptor interaction seem to explain the lack of cataleptogenic and antistereotypic effects of the piperidyl derivatives. However, one might consider whether the localized electron density, imposed by the piperazine nitrogen and the double bond of the tetrahydropyridyl ring connected to the 3-position of the indole ring, somehow induces the cataleptogenic potential of compounds **6** and **11**, **12**. Synthesis is in progress to pursue this hypothesis. Such differences in electronic environments would be important for interaction with electron-rich or electron-deficient receptor binding sites. Recently, new dopamine receptor subtypes have been identified by cloning techniques. Atypical neuroleptics such as clozapine were found to bind either equipotently or with preference to the dopamine D-3[37] or D-4[38] receptor subtypes in comparison with their dopamine D-2 receptor affinities. Classical neuroleptics had relatively higher affinity for D-2 receptors. Whether our piperidyl derivatives have similar affinity profiles as atypical neuroleptics for these recently recognized dopamine receptor subtypes has not yet been studied. The recently developed neuroleptic risperidone is a benzisoxazole substituted in the 3-position with a 4-piperidino ring. It shows strong but short acting central 5-HT_2 antagonistic activity[32,33] and it is not cataleptogenic, at least in doses up to about 6 μmol/kg (Table V).[33] Thus, to some extent, the pharmacological profile of risperidone resembles that of our piperidino derivatives.

By stepwise increments of the chain length of compound **14c** from C_3 to C_6 carbon atoms (compounds **14j–m**, Table V) antistereotypic effect increases and weak catalepsy is reintroduced while quipazine inhibition decreases. Except for the C_4 chain compound, **14k**, which has insignificant receptor affinity, chain-length variation seems not to influence receptor affinities in vitro. We have also found inactivity resulting from *N*-butyl-2-imidazolidinone side chains within other series of neuroleptics (unpublished results). Small 3-substituents such as methyl (**14n**) or isopropyl (**14p**) on the imidazolidinone ring are tolerated, while larger substituents such as cyclopentyl (**14p**) or phenyl (**14q**) significantly decrease activities. Both the "bis" derivative **15a** and the 1-unsubstituted indole **16** are virtually inactive. The distinctly different profiles of compound **16** and **14c** (Table V) emphasize the importance of the 1-(4-fluorophenyl) substituent of the indole ring for potent antidopaminergic and antiserotonergic activity within this series of neuroleptic indoles.

Compound **14c**, which has one of the most interesting pharmacological profiles, was selected for extended pharmacological investigations. These studies have revealed a highly potent and selective antidopaminergic activity within limbic areas in rat brain.[18,39] This interesting atypical neuroleptic profile suggests rewarding clinical effects in the treatment of psychoses with an ex-

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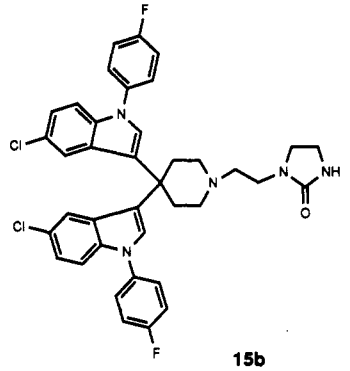
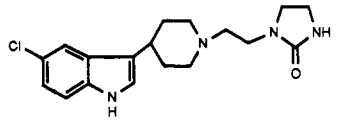
(39) Skarsfeldt, T. Electrophysiological Profile of the New Atypical Neuroleptic, Sertindole, on Midbrain Dopamine Neurones in Rats: Acute and Repeated Treatment. *Synapse*, in press.



15b



16

pected low risk of causing EPS. Further studies are needed to unravel the especially favorable neuroleptic profiles arising from 3-(4-piperidyl) substitution in comparison with piperazinylindoles and tetrahydropyridylindoles.

Experimental Section

Melting points were determined on a Büchi SMP-20 apparatus and are uncorrected. ^{1}H NMR spectra were recorded of all novel compounds at 80 MHz on a Bruker WP 80 DS spectrometer or at 250 MHz on a Bruker AC 250 spectrometer. TMS was used as internal reference standard. Chemical shift values are expressed in parts per million values. Content of water in crystalline compounds was determined by Karl Fischer titration. Microanalysis were performed by Lundbeck Analytical Department and results obtained were within ±0.4% of the theoretical values.

2-Imidazolidinone Side Chains. 1-(2-Chloroethyl)-, 1-(3-chloropropyl)-, 1-(4-chlorobutyl)-, 1-(5-chloropentyl)-, and 1-(6-chlorohexyl)-2-imidazolidinones were prepared from the corresponding 1-hydroxyalkyl-2-imidazolidinones by refluxing with thionyl chloride according to published procedures.[29,30]

3-Methyl-, 3-(2-propyl)-, 3-cyclopentyl-, and 3-phenyl-1-(2-chloroethyl)-2-imidazolidinones were obtained by reacting diethanolamine with the appropriately N-substituted isocyanates followed by treatment of the resulting urea derivatives with thionyl chloride and subsequent ring closure of the N-substituted *N'*,*N'*-bis(2-chloroethyl)ureas at 120–150 °C. The reaction procedures have previously been described.[31]

General Procedure for the Synthesis of 3-(1-Piperazinyl)-1*H*-indoles (6) (Table I). 5-Substituted 1-(4-fluorophenyl)-3-hydroxy-1*H*-indole-2-carboxylic acid methyl esters (5) were prepared according to synthetic procedures reported in the literature.[19,20,40]

4-[1-(4-Fluorophenyl)-5-(trifluoromethyl)-1*H*-indol-3-yl]-1-piperazineethanol (6a). To 1-(4-fluorophenyl)-3-hydroxy-5-(trifluoromethyl)-1*H*-indole-2-carboxylic acid methyl ester (100 g, 0.28 mol) in *N*-methyl-2-pyrrolidone (NMP) (500 mL) was added $MgCl_2 \cdot 6H_2O$ (120 g, 0.59 mol). The mixture was heated under stirring at 150 °C for 1 h under a N_2 atmosphere. The temperature was raised to 180 °C and excess H_2O was flushed away by a gentle stream of N_2. 1-(2-Hydroxyethyl)piperazine (160 g, 1.2 mol) in NMP (200 mL) was added. The temperature was kept at 190 °C for 1.5 h. The mixture was cooled and poured into a solution of NH_4Cl (400 g) in H_2O (5 L). A mixture of diethyl ether (2 L) and ethyl acetate (2 L) was added. After the mixture was stirred for 10 min the organic phase was separated, washed with brine (2 × 1 L), dried ($MgSO_4$), filtered, and finally evaporated in vacuo. The remaining solid material was stirred with diethyl ether (400 mL) and the crystalline title compound **6a** was filtered off: yield 76.3 g (68%); mp 167 °C; ^{1}H NMR ($CDCl_3$) δ 2.55 (broad s, 1 H), 2.65 (t, 2 H), 2.80 (t, 4 H), 3.15 (t, 4 H), 3.70 (t, 2 H), 6.90 (s, 1 H), 7.20 (t, 2 H), 7.40–7.45 (m, 4 H), 7.95 (s, 1 H). Anal. ($C_{21}H_{21}F_4N_2O$) C, H, N.

Compounds **6b** and **6c** were prepared similarly from the appropriately 1-substituted piperazines. 1-[2-(1-Piperazinyl)-ethyl]-2-imidazolidinone for the preparation of compound **6c** was synthesized according to an earlier published procedure.[11]

General Procedures for the Syntheses of 1-(4-Fluorophenyl)-1*H*-indoles (10) (Table II). Method A. The 1-unsubstituted indoles (7) were either commercially available or prepared according to literature methods.

1-(4-Fluorophenyl)-5-nitro-1*H*-indole (10b). A mixture of 5-nitro-1*H*-indole (50 g, 0.31 mol), 1-fluoro-4-iodobenzene (100 g, 0.45 mol), finely powdered anhydrous K_2CO_3 (60 g, 0.43 mol), CuBr (40 g, 0.18 mol), and Cu bronze (1 g) in NMP (300 mL) was heated at 180 °C under N_2 for 4 h. After cooling (below 100 °C) the mixture was poured into dilute hydrochloric acid (1.8 L). Diisopropyl ether (200 mL) was added. After the mixture was stirred, the precipitated material was filtered off, washed with water, and subsequently dried in vacuo. Purification was performed by dissolving in dichloromethane, treating the solution with activated carbon, and finally filtering through silica gel (eluted with heptane/dichloromethane). Dichloromethane was evaporated, and the remaining crystalline material was recrystallized from 2-propanol. **10b**: yield 55.3 g (52%); mp 144–145 °C; ^{1}H NMR ($CDCl_3$) δ 6.85 (d, 1 H), 7.25 (t, 2 H), 7.40–7.50 (m, 3 H), 8.10 (dd, 1 H), 8.65 (d, 1 H). Anal. ($C_{14}H_9FN_2O_2$) C, H, N.

The 5-unsubstituted (**10a**), 5-cyano (**10c**), and 5-fluoro (**10d**) indoles were prepared accordingly.

Method B. The 5-substituted 1-(4-fluorophenyl)isatins (8) were prepared from the corresponding diphenylamines by reaction with oxalyl chloride and subsequent cyclization under Friedel–Craft catalysis ($AlCl_3$) as described by Sarges et al.[41] The method of reduction with diborane in THF was adapted from the known reduction of 1-methylated or 1-unsubstituted isatins.[24]

1-(4-Fluorophenyl)-5-methyl-1*H*-indole (10e). A solution of 1-(4-fluorophenyl)-5-methylisatin (80 g, 0.31 mol) in dry THF was cooled to −50 °C and kept under N_2. Gaseous B_2H_6 (~0.5 mol), liberated from $NaBH_4$ (45 g) and BF_3 etherate (80 g) in anhydrous diglyme, was dissolved in the mixture by carrying it with a stream of N_2, which was bubbled through the THF solution. The temperature was gradually (>2 h) raised to 10 °C and kept there until the reaction had succeeded according to TLC analysis. The mixture was poured into ice-cooled H_2O (2 L). $KHSO_4$ (80 g, 0.59 mol) and diethyl ether (800 mL) were added. The organic phase was separated and worked up as in method A. Evaporation of the solvents afforded the title compound **10e** as an oil: yield 52 g (75%); ^{1}H NMR ($CDCl_3$) δ 2.45 (s, 3 H), 6.55 (d, 1 H), 7.05 (double d, 1 H), 7.15 (t, 2 H), 7.20 (s, 1 H), 7.35 (d, 1 H), 7.40–7.50 (m, 3 H).

5-Fluoro-1-(4-fluorophenyl)-1*H*-indole (10d) was similarly prepared as an oil: ^{1}H NMR ($CDCl_3$) δ 6.65 (d, 1 H), 6.95 (double t, 1 H), 7.20 (t, 2 H), 7.30–7.45 (m, 5 H).

Method C. 1-(4-Fluorophenyl)-5-(trifluoromethyl)-1*H*-indole (10f). To a solution of 1-(4-fluorophenyl)-3-hydroxy-5-(trifluoromethyl)-1*H*-indole-2-carboxylic acid methyl ester (280 g, 0.79 mol) in NMP (1.8 L) was added $MgCl_2 \cdot 6H_2O$ (480 g, 2.4 mol). The mixture was heated under N_2 at 120–150 °C for 2 h. The temperature was then gradually (0.5 h) raised to 160 °C while H_2O was flushed off by a gentle stream of N_2. After the mixture was cooled to 60 °C ethanol (1.8 L) was added and $NaBH_4$ (42 g, 1.1 mol) was added at a suitable rate to keep the temperature at 45–55 °C. After stirring for another 0.5 h the mixture was poured into a saturated aqueous NH_4Cl solution (3 L) and diethyl ether (2 L). The organic phase was separated, dried ($MgSO_4$), and filtered and the solvent evaporated. The crude 3-hydroxyindoline was dissolved in dichloromethane (1.2 L) and trifluoroacetic acid (100 mL) and refluxed for 1 h. The mixture was subsequently poured into ice-cooled dilute aqueous NH_4OH solution (3 L). The organic phase was separated and worked up as in method A, leaving the title compound **10f** as an oil: yield 205 g (93%); crystallization from heptane afforded the pure indole;

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mp 53 °C; ^{1}H NMR ($CDCl_3$) δ 6.80 (d, 1 H), 7.25 (t, 2 H), 7.35–7.50 (m, 5 H), 8.05 (broad s, 1 H). Anal. ($C_{15}H_{19}F_4N$) C, H, N.

The 5-methylsulfonyl (**10g**) and 5-chloro (**10h**) derivatives were prepared accordingly.

Method D. 3-Acetoxyindoles (**9**) were prepared from *N*-(4-fluorophenyl)-substituted *N*-(*o*-carboxyphenyl)glycines following literature procedures for similar reactions.[25,26,27,40]

1-(4-Fluorophenyl)-5-methoxy-1*H*-indole (10i). To a solution of the potassium salt of 2-bromo-5-methoxybenzoic acid (87 g, 0.31 mol) in NMP (650 mL) were added the potassium salt of *N*-(4-fluorophenyl)glycine (65 g, 0.31 mol) and finely powdered Cu bronze (6 g, 0.09 mol). The mixture was heated at 120–130 °C for 2.5 h under N_2. The mixture was filtered while still hot. The filtrate was poured into H_2O (1.5 L) and diethyl ether (500 mL). By addition of concentrated hydrochloric acid the pH was adjusted to 2. The organic phase was separated, washed with brine (2 × 100 mL), dried ($MgSO_4$), and filtered. Finally, evaporation of the solvent yielded quantitatively crude *N*-(2-carboxy-5-methoxyphenyl)-*N*-(4-fluorophenyl)glycine (103 g, 0.32 mol) as a viscous oil, which was used without further purification. The glycine derivative and sodium acetate (60 g, 0.73 mol) were dissolved in acetic acid anhydride (600 mL). The mixture was refluxed for 1.5 h. Excess acetic acid anhydride was distilled off, and ice-cooled dilute aqueous K_2CO_3 solution (2 L) and diethyl ether (1 L) were added. The mixture was stirred vigorously for 0.5 h. The organic phase was separated, washed with brine (2 × 100 mL), dried ($MgSO_4$), and filtered and the ether evaporated. Stirring with diisopropyl ether (400 mL) initiated crystallization of 3-acetoxy-1-(4-fluorophenyl)-5-methoxy-1*H*-indole. The precipitated crystalline product was filtered off and dried: yield 76 g (82%); mp 95 °C. The thus obtained 3-acetoxyindole derivative (75 g, 0.25 mol) was suspended in ethanol (900 mL) and heated to 50 °C. During 1.5 h $NaBH_4$ (16 g, 0.42 mol) was added while keeping the temperature at 50–55 °C. After the mixture was stirred for another hour most ethanol was evaporated in vacuo. H_2O (500 mL) and diethyl ether (300 mL) were added. The organic phase was separated, and a saturated solution of dry HCl gas in diethyl ether (200 mL) was cautiously added. This mixture was stirred for 10 min and subsequently poured onto crushed ice. The organic phase was separated and worked up as in method A, leaving the title indole as a crystalline product. Recrystallization from cyclohexane yielded 52 g (88%) of **10i**: mp 96 °C; ^{1}H NMR ($CDCl_3$) δ 3.85 (s, 3 H), 6.60 (d, 1 H), 6.85 (dd, 1 H), 7.10–7.25 (m, 4 H), 7.35 (d, 1 H), 7.40–7.50 (m, 2 H). Anal. ($C_{15}H_{12}FNO$) C, H, N.

5-Bromo-1-(4-fluorophenyl)-1*H*-indole (10j) was prepared accordingly.

General Procedure for the Syntheses of 3-(1,2,3,6-Tetrahydro-4-pyridyl)-1*H*-indoles (11 and 12) (Table III). 5-Chloro-1-(4-fluorophenyl)-3-(1,2,3,6-tetrahydro-4-pyridyl)-1*H*-indole (11a). To a solution of 4-piperidone hydrochloride hydrate (65.3 g, 0.43 mol) in a mixture of trifluoroacetic acid (200 mL) and acetic acid (150 mL) kept at 110 °C was added dropwise a solution of 5-chloro-1-(4-fluorophenyl)-1*H*-indole (**10h**) (30 g, 0.12 mol) in acetic acid (150 mL). The mixture was furthermore heated for 0.5 h after completed addition. Upon partially evaporation of the acidic solvents crystallization of the hydrochloric salt of the title compound started. Acetone (400 mL) was added, and after the mixture was stirred for 1 h at room temperature the precipitated salt was filtered off, washed with acetone, and dried: yield 32.4 g (74%); mp 291 °C. The free base (**11a**) was isolated from an aqueous suspension of the hydrochloric salt by addition of dilute aqueous NaOH solution and subsequent extraction with ethyl acetate: mp 138–140 °C; ^{1}H NMR ($CDCl_3$) δ 1.70 (broad s, 1 H), 2.50 (m, 2 H), 3.15 (t, 2 H), 3.65 (m, 2 H), 6.25 (m, 1 H), 7.20–7.50 (m, 7 H), 7.90 (d, 1 H). Anal. ($C_{19}H_{16}ClFN_2$) C, H, N.

By using the above procedure **11b** was prepared accordingly, while 1-methyl-4-piperidone afforded the corresponding N-methylated compounds **11c**, **11d**, **11e**, and **11f**.

1-[2-[4-[5-Chloro-1-(4-fluorophenyl)-1*H*-indol-3-yl]-1,2,3,6-tetrahydro-1-pyridyl]ethyl]-2-imidazolidinone (12a). To a solution of 5-chloro-1-(4-fluorophenyl)-3-(1,2,3,6-tetrahydro-4-pyridyl)-1*H*-indole (**11a**) (4.5 g, 0.014 mol) and 1-(2-chloroethyl)-2-imidazolidinone (2.5 g, 0.017 mol) in methyl isobutyl ketone (MIBK) (70 mL) were added finely powdered anhydrous K_2CO_3 (3 g, 0.022 mol) and KI (0.1 g, catalyst). The mixture was refluxed overnight (16 h). Inorganic salts were filtered off, MIBK was evaporated, and finally the remaining oil was dissolved in boiling 2-propanol. The title compound **12a** precipitated upon cooling: yield 3.8 g (62%); mp 146 °C; ^{1}H NMR ($CDCl_3$) δ 2.60 (broad s, 2 H), 2.65 (t, 2 H), 2.80 (t, 2 H), 3.30 (m, 2 H), 3.40–3.50 (m, 4 H), 3.55–3.60 (m, 2 H), 4.85 (broad s, 1 H), 6.65 (m, 1 H), 7.15–7.45 (m, 7 H), 7.90 (d, 1 H). Anal. ($C_{24}H_{24}ClFN_4O$) C, H, N.

The compounds **12b** and **12c** were prepared analogously.

General Procedure for the Syntheses of 3-(4-Piperidyl)-1*H*-indoles (13 and 14) (Table III). 5-Chloro-1-(4-fluorophenyl)-3-(4-piperidyl)-1*H*-indole (13a). 5-Chloro-1-(4-fluorophenyl)-3-(1,2,3,6-tetrahydro-4-pyridyl)-1*H*-indole (**11a**) (195 g, 0.6 mol) was dissolved in a mixture of ethanol (1.7 L) and acetic acid (300 mL) by gentle heating. PtO_2 (4 g) was added, and the mixture was hydrogenated in a Parr apparatus for 16 h at 2.5–3 atm. The catalyst was filtered off, and the solvents were evaporated in vacuo. The remaining viscous oil was dissolved in H_2O (2 L), and the pH was adjusted to >10 by addition of dilute aqueous NaOH solution. The alkaline aqueous phase was extracted with ethyl acetate (2 × 1 L). The combined organic phases were dried (anhydrous $MgSO_4$) and filtered, and ethyl acetate was evaporated, leaving the 4-piperidyl derivative **13a** as a viscous oil. The fumaric acid salt crystallized from hot ethanol: yield 173 g (65%); mp 217–219 °C; ^{1}H NMR (DMSO-d_6) δ 1.90–2.15 (m, 4 H), 2.95–3.15 (m, 3 H), 3.40 (broad d, 2 H), 6.45 (s, 2 H), 7.20 (dd, 1 H), 7.35–7.45 (m, 3 H), 7.50 (s, 1 H), 7.55–7.65 (m, 2 H), 7.85 (d, 1 H). Anal. ($C_{19}H_{18}ClFN_2 \cdot C_4H_4O_4$) C, H, N.

Compound **13b** was prepared accordingly.

1-[2-[4-[5-Chloro-1-(4-fluorophenyl)-1*H*-indol-3-yl]-1-piperidinyl]ethyl]-2-imidazolidinone (14c). To a suspension of 5-chloro-1-(4-fluorophenyl)-3-(4-piperidyl)-1*H*-indole fumarate (**13a**) (172 g, 0.39 mol) in MIBK (3 L) were added 1-(2-chloroethyl)-2-imidazolidinone (130 g, 0.88 mol), finely powdered anhydrous K_2CO_3 (350 g, 2.5 mol), and KI (2 g, catalyst). The mixture was refluxed for 16 h. The inorganic salts were filtered off. After evaporation of MIBK the title compound **14c** was recrystallized from acetone: yield 152 g (87%); mp 154–155 °C; ^{1}H NMR ($CDCl_3$) δ 1.80 (dt, 2 H), 2.05 (broad d, 2 H), 2.25 (dt, 2 H), 2.60 (t, 2 H), 2.85 (tt, 1 H), 3.10 (broad d, 2 H), 3.35–3.50 (m, 4 H), 3.55–3.60 (m, 2 H), 4.35 (broad s, 1 H), 7.05 (s, 1 H), 7.15–7.25 (m, 3 H), 7.35–7.45 (m, 3 H), 7.65 (d, 1 H). Anal. ($C_{24}H_{26}ClFN_4O$) C, H, N. Another crystal modification was obtained by crystallization from a 1:1 mixture of 2-propanol and ethyl acetate, mp 166 °C.

Other 4-(1-piperidinyl)alkyl-2-imidazolidinone derivatives (**14a–q**) (see Tables III and IV) were prepared either similarly or by catalytic hydrogenation of the corresponding 3-(1,2,3,6-tetrahydro-4-pyridyl)-1*H*-indoles (**12**).

1-[2-[4,4-Bis[5-chloro-1-(4-fluorophenyl)-1*H*-indol-3-yl]-1-piperidinyl]ethyl]-2-imidazolidinone (15b). To a solution of 5-chloro-1-(4-fluorophenyl)-1*H*-indole (**10h**) (10.4 g, 0.04 mol) and 4-piperidone hydrochloride hydrate (3.6 g, 0.02 mol) in acetic acid (180 mL) was added methanesulfonic acid (20 mL). The mixture was gently refluxed under N_2 for 15 min. After cooling ice-cooled dilute aqueous NH_4OH solution (1 L) and diethyl ether (100 mL) were added. After the mixture was stirred for 0.5 h the precipitated 4,4-bis[5-chloro-1-(4-fluorophenyl)-1*H*-indol-3-yl]-piperidine (**15a**) was filtered off: yield 6.7 g (53%); mp 219–222 °C. Anal. ($C_{33}H_{25}Cl_2F_2N_3$), C, H, N. N-Alkylation with 1-(2-chloroethyl)-2-imidazolidinone was performed according to the procedure for the preparation of compound **12a**. The title compound **15b** was isolated in 76% yield after recrystallization from ethanol: mp 284–290 °C; ^{1}H NMR ($CDCl_3$) δ 2.55 (t, 2 H), 2.65 (m, 8 H), 3.35 (t, 2 H), 3.40–3.45 (m, 2 H), 3.50–3.60 (m, 2 H), 4.25 (s, 1 H), 7.05 (dd, 2 H), 7.20–7.30 (m, 10 H), 7.45–7.50 (m, 4 H), 7.50 (d, 2 H). Anal. ($C_{38}H_{33}Cl_2F_2N_5O$) C, H, N.

1-[2-[4-(5-Chloro-1*H*-indol-3-yl)-1-piperidinyl]ethyl]-2-imidazolidinone (16). N-Alkylation of 5-chloro-3-(1,2,3,6-tetrahydro-4-pyridinyl)-1*H*-indole (22 g, 0.1 mol) (preparation published[28]) with 1-(2-chloroethyl)-2-imidazolidinone according to the procedure for the preparation of compound **12a** afforded 1-[2-[4-(5-chloro-1*H*-indol-3-yl)-1,2,3,6-tetrahydro-1-pyridinyl]-ethyl]-2-imidazolidinone in 65% yield as a crystalline product, mp 218–220 °C. The thus obtained 1,2,3,6-tetrahydropyridyl

derivative (20 g, 0.06 mol) was dissolved in acetic acid (150 mL) and H_2O (150 mL) and PtO_2 (0.5 g) was added. The mixture was hydrogenated for 18 h at 3 atm in a Parr apparatus. The catalyst was filtered off and the main proportion of the solvents evaporated in vacuo. By addition of dilute aqueous NH_4OH solution the title compound **16** precipitated and was subsequently filtered off. Recrystallization from ethanol yielded 12.6 g (61%) of pure **16**: mp 222–225 °C; ^{1}H NMR (DMSO-d_6) δ 1.60 (dq, 2 H), 1.85 (broad d, 2 H), 2.05 (t, 2 H), 2.40 (t, 2 H), 2.65 (tt, 1 H), 2.95 (broad d, 2 H), 3.20–3.30 (m, 4 H), 3.40 (t, 2 H), 6.20 (s, 1 H), 7.05 (dd, 1 H), 7.20 (d, 1 H), 7.35 (d, 1 H), 7.55 (d, 1 H), 11.00 (broad d, 1 H). Anal. ($C_{18}H_{23}ClN_4O$) C, H, N.

Pharmacological Test Methods. Animals. Male mice (NMRI/BOM, SPF 18-25 g) and male Wistar rats (Mol:Wist, SPF, 170–270 g) were used. We have recently described the handling procedures in detail.[17]

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 Methyl Phenidate-Induced Gnawing Behavior. The experimental details have been published by Pedersen and Christensen.[42] Test compounds were administered (sc or ip injection—see Tables IV and V) to mice 2 h before methyl phenidate (222 μmol/kg, sc). Immediately after injection of methyl phenidate the mice were placed in pairs in bottomless observation cages (12 × 25 cm) placed on corrugated cardboard. At least five pairs of animals were used per dose. After 1 h the ability to inhibit methyl phenidate-induced gnawing was estimated by inspection of the corrugated cardboard for biting holes.

Catalepsy was estimated according to published procedures.[17] Test compounds were administered by sc injection to rats. The number of cataleptic rats in each dose group was determined each hour during an observation period of 6 h. Maximal effects during this observation period is reported in Table V.

Antagonism of Quipazine-Induced Head Twitches. The experimental details are given by Arnt et al.[43] Test compounds were injected sc 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.

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.[44]

5-HT$_2$ Receptors. Affinity of test compounds to serotonin 5-HT$_2$ receptors was estimated by their ability to displace either [^{3}H]ketanserin or [^{3}H]spiperone from rat cortical membranes as described by Hyttel[44] and Hyttel et al.,[45] respectively.

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Registry No. **5a**, 138900-11-5; **5b**, 138900-12-6; **5f**, 138900-11-5; **5g**, 138900-13-7; **5h**, 138900-12-6; **6a**, 106516-68-1; **6b**, 138923-82-7; **6c**, 138923-83-8; **7a**, 120-72-9; **7b**, 6146-52-7; **7c**, 15861-24-2; **7d**, 399-52-0; **8d**, 87423-61-8; **8e**, 106516-74-9; **9i**, 138900-14-8; **9j**, 138900-15-9; **10a**, 138900-16-0; **10b**, 138900-17-1; **10c**, 138900-18-2; **10d**, 138900-19-3; **10e**, 106515-88-2; **10f**, 138900-20-6; **10g**, 138900-21-7; **10h**, 138900-22-8; **10i**, 138900-23-9; **10j**, 138900-24-0; **11a**, 106516-07-8; **11b**, 106516-09-0; **11c**·HCl, 106515-99-5; **11c** free base, 106516-04-5; **11d**·HBr, 106516-34-1; **11d** free base, 106516-35-2; **11e**·HCl, 138900-25-1; **11e** free base, 106516-03-4; **11f**, 106515-92-8; **12a**, 106516-54-5; **12b**, 106516-55-6; **12c**, 138900-26-2; **13a**·fumarate, 138900-28-4; **13a** free base, 138900-27-3; **13b**·HCl, 138900-29-5; **13b** free base, 138900-30-8; **14a**, 106516-21-6; **14b**, 138900-31-9; **14c**, 106516-24-9; **14d**, 138900-32-0; **14e**, 138923-84-9; **14f**, 138900-33-1; **14g**, 138900-34-2; **14h**·fumarate, 138900-36-4; **14h** free base, 138900-35-3; **14i**, 138900-37-5; **14j**·fumarate, 138900-39-7; **14j** free base, 138900-38-6; **14k**·oxalate, 138900-41-1; **14k** free base, 138900-40-0; **14l**·oxalate, 138900-43-3; **14l** free base, 138900-42-2; **14m**·oxalate, 138900-45-5; **14m** free base, 138900-44-4; **14n**·fumarate, 138900-47-7; **14n** free base, 138900-46-6; **14o**·oxalate, 138900-49-9; **14o** free base, 138900-48-8; **14p**·oxalate, 138900-51-3; **14p** free base, 138900-50-2; **14q**, 138900-52-4; **15a**, 138923-85-0; **15b**, 138923-86-1; **16**, 138900-53-5; 1-[2-[4-(5-chloro-1*H*-indo-3-yl)-1,2,3,6-tetrahydro-1-pyridinyl]ethyl]-2-imidazolidinone, 138900-54-6; 1-(2-hydroxyethyl)piperazine, 103-76-4; 1-methylpiperazine, 109-01-3; 1-[2-(1-piperazinyl)ethyl]imidazolidin-2-one, 104087-61-8; piperidin-4-one, 41661-47-6; 1-methylpiperidin-4-one, 1445-73-4; 1-(2-chloroethyl)imidazolidin-2-one, 2387-20-4.

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