Selective, Centrally Acting Serotonin 5-HT$_2$ Antagonists. 1. 2- and 6-Substituted 1-Phenyl-3-(4-piperidinyl)-1*H*-indoles

Jens Perregaard,* Kim Andersen, John Hyttel, and Connie Sánchez

Research & Development, H. Lundbeck A/S, Ottiliavej 9, DK-2500 Copenhagen-Valby, Denmark

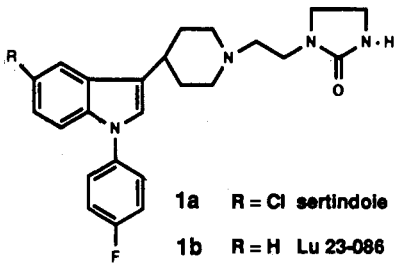
Received July 14, 1992

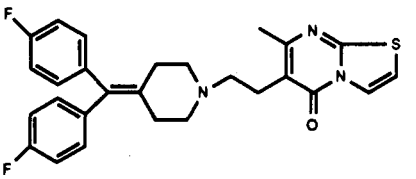
A series of 1-[2-[4-(1*H*-indol-3-yl)-1-piperidinyl]ethyl]-2-imidazolidinones has been synthesized. The 1-position of the indole is substituted with phenyl groups and in the 2- or 6-positions are additional substituents. An analogous series with the imidazolidinone ring opened to corresponding urea derivatives was also prepared. High potency and selectivity for 5-HT$_2$ receptors (as compared with D$_2$ and α_1 receptor affinities) were obtained with medium-large substituents such as 6-chloro, 6-methyl, and 6-trifluoromethyl or a 2-methyl substituent. Larger 6-substituents such as isopropyl considerably reduced activity, while the smaller 6-fluoro substituent afforded unselective compounds. Selective 5-HT$_2$ antagonists were found by combining 6-substitution with both unsubstituted 1-phenyl and substituted 1-phenyl groups (2-F, 4-F, 4-Cl). However, 3-substitution of the phenyl group markedly reduced 5-HT$_2$ receptor affinity, especially with a 3-trifluoromethyl substituent. Introduction of a 3-(2-propyl) substituent in the imidazolidinone ring reduced binding to α_1 adrenoceptors with a factor of 3–8. Practically no influence on 5-HT$_2$ and D$_2$ receptor affinities were found by the presence of this substituent compared to the 3-unsubstituted derivatives. 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 they had a long duration of action (>24 h). Especially urea derivatives were found to be considerably more potent at 24 h than at 2 h after subcutaneous administration. Some of the compounds potently inhibited isolation-induced aggression in mice, an effect which, however, did not correlate to 5-HT$_2$ receptor-mediated activities. On the basis of these structure–activity studies 1-[2-[4-[6-chloro-1-(4-fluorophenyl)-1*H*-indol-3-yl]-1-piperidinyl]ethyl]-3-(2-propyl)-2-imidazolidinone (Lu 26-042, compound 4c) was selected for further pharmacological and toxicological investigations.

Introduction

Recently, we have reported the development of a new series of 5-substituted 1-(4-fluorophenyl)indoles as potent, centrally acting dopamine D$_2$ and serotonin 5-HT$_2$ antagonists.[1] Sertindole, 1-[2-[4-[5-chloro-1-(4-fluorophenyl)-1*H*-indol-3-yl]-1-piperidinyl]ethyl]-2-imidazolidinone (Figure 1, **1a**), which is a member of this series of compounds, is presently under clinical evaluation as an antipsychotic agent. Sertindole is an atypical neuroleptic since it selectively blocks dopaminergic activity in limbic brain areas in rats after chronic treatment.[2,3] Despite having strong binding affinities for both adrenergic α_1, dopamine D$_2$, and serotonin 5-HT$_2$ receptors, sertindole only shows potent antiserotonergic 5-HT$_2$ activity in acute in vivo pharmacological testing.[4]

During recent years the development of selective ligands for subtypes of serotonin receptors[5] has implicated an important role of these receptors in psychiatric disorders such as anxiety and depression.[6–8] For many years benzodiazepines have been the predominant therapy in the treatment of anxiety. However, it has now been realized that serious side effects, such as sedation and drowsiness, abuse and dependence, and withdrawal symptoms (e.g. rebound anxiety), are associated with this medication.[9] An alternative group of drugs, which has





2 ritanserin

Figure 1. Structures of reference compounds.

(1) Perregaard, J.; Arnt, J.; Bøgesø, K. P.; Hyttel, J.; Sánchez, C. Noncataleptogenic, Centrally Acting Dopamine D-2 and Serotonin 5-HT$_2$ Antagonists within a Series of 3-Substituted 1-(4-Fluorophenyl)-1*H*-indoles. *J. Med. Chem.* **1992**, *35*, 1092–1101.

(2) Skarsfeldt, T.; Perregaard, J. Sertindole, a New Neuroleptic with Extreme Selectivity in A10 Versus A9 Dopamine Neurones in the Rat. *Eur. J. Pharmacol.* **1990**, *182*, 613–614.

(3) Domeney, A. M.; Arnt, J.; Costall, B.; Naylor, R. J.; Sánchez, C.; Smith, A. G. The Effect of Sertindole on Raised Mesolimbic Dopaminergic Activity in the Rat. *Br. J. Pharmacol.*, in press.

(4) Sánchez, C.; Arnt, J.; Dragsted, N.; Hyttel, J.; Lembøl, H. L.; Meier, E.; Perregaard, J.; Skarsfeldt, T. Neurochemical and In Vivo Pharmacological Profile of Sertindole, a Limbic-Selective Neuroleptic Compound. *Drug Dev. Res.* **1991**, *22*, 239–250.

(5) Peroutka, S. J. 5-Hydroxytryptamine Receptor Subtypes. *Pharmacol. Toxicol.* **1990**, *67*, 373–383.

(6) Broekkamp, C. L. E.; Berendsen, H. H. G.; Jenck, F.; VanDelft, A. M. L. Animal Models for Anxiety and Response to Serotonergic Drugs. *Psychopathology* **1989**, *22* (*Suppl.*) 2–12.

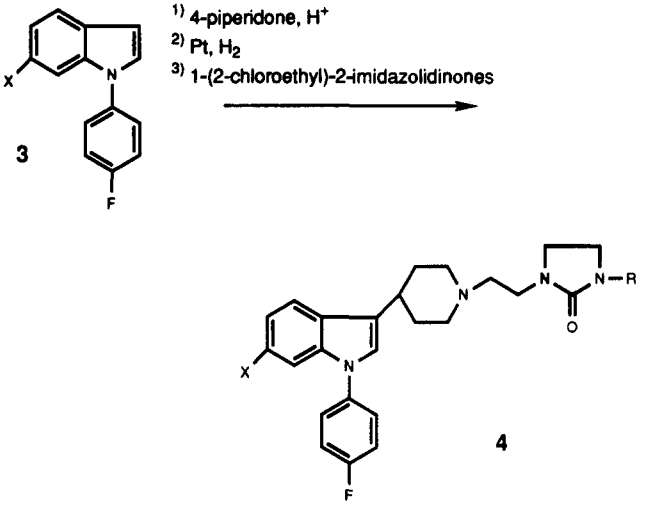
(7) Zemlan, F. R.; Garver, D. L. Depression and Antidepressant Therapy: Receptor Dynamics. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* **1990**, *14*, 503–523.

(8) Healy, D. The Marketing of 5-Hydroxytryptamine: Depression or Anxiety. *Br. J. Psychiatry* **1991**, *158*, 737–742.

0022-2623/92/1835-4813$03.00/0

demonstrated anxiolytic as well as antidepressant properties, is the 5-HT_{1A} agonists or partial agonists such as the marketed anxiolytic buspirone and related 2-pyrimidylpiperazines.[10] Also selective 5-HT_3 antagonists[11] and 5-HT_2 antagonists[12] have shown potential anxiolytic activity in a series of animal models. Clinical studies with 5-HT_2 antagonists, such as the prototype compound ritanserin (Figure 1, **2**), have furthermore suggested improvements in dysthymic disorders[13] as well as improvement of negative symptoms of schizophrenia[14] and of quality of sleep.[15] Many 5-HT_2 antagonists such as ritanserin are not selective with respect to 5-HT_{1C} receptor binding.[16] We have earlier found that sertindole and related 5-substituted 3-(4-piperidinyl)-1*H*-indoles are active in animal models predictive of anxiolytic activity like in isolation-induced aggression in mice and in the light/dark exploration paradigm in mice and rats.[17] Combined with the interesting clinical prospects indicated above for selective 5-HT_2 antagonists, these findings prompted us to investigate possibilities of refining the serotonergic component by introducing proper substituents in these indole derivatives. Since substituted 1-[2-[4-[1-(4-fluorophenyl)-1*H*-indol-3-yl]-1-piperidinyl]ethyl]-2-imidazolidinones were found to be the most potent antiserotonergic derivatives in the nonselective 5-substituted indole series compared to corresponding piperazinyl and tetrahydropyridinyl derivatives,[1] we decided further to investigate the subgroup of 3-(4-piperidinyl)-1*H*-indoles. We have already reported that the 5-unsubstituted sertindole analogue, Lu 23-086 (Figure 1, **1b**) had strong affinity for D_2 receptors ([^{3}H]spiperone, IC_{50} = 18 nM)[1] and also for α_1 adrenoceptors ([^{3}H]prazosin, IC_{50} = 3.0 nM, unpublished result). We have reported that *trans*-(1*R*,3*S*)-1-[2-[4-[3-(4-fluorophenyl)-1-indanyl]-1-piperazinyl]ethyl]-2-imidazolidinone (irindalone) is a potent 5-HT_2 antagonist with no affinity for dopamine D_2 receptors and with rather weak effects in the central nervous system[18,19] which is in contrast to the binding and central activities of the corresponding indole, Lu 23-086. In this report we present further structure/activity investigations within the group of 3-(4-piperidinyl)-1*H*-indoles with the purpose of developing new selective 5-HT_2 antagonists with prominent effects in the central nervous system.

Scheme I. Synthesis of 6-Substituted 1-[2-[4-[1-(4-Fluorophenyl)-1*H*-indol-3-yl]-1-piperidinyl]ethyl]-2-imidazolidinones **4** (detailed reaction conditions have recently been published[1])



Chemistry

Previously, we have developed convenient methods for the synthesis of 5-substituted 1-(4-fluorophenyl)-1*H*-indoles.[1,20] These methods have been adapted to the synthesis of corresponding 6-substituted 1-(4-fluorophenyl)-1*H*-indoles (**3**), which are the starting materials for the synthesis of 6-substituted 1-[2-[4-[1-(4-fluorophenyl)-1*H*-indol-3-yl]-1-piperidinyl]ethyl]-2-imidazolidinones (**4**) (Scheme I). The most versatile method is considered to be the preparation via 3-acetoxy-1-(4-fluorophenyl)-1*H*-indoles (the reported method D).[1] Reaction conditions for the addition of 4-piperidones and subsequent water elimination were also discussed in detail in these papers. Catalytic hydrogenation of the intermediate 3-(1,2,3,6-tetrahydro-4-pyridinyl)indoles followed by alkylation with 1-(2-chloroethyl)-2-imidazolidinones afforded the desired 6-substituted indoles 4. Substituents X and R are shown in Table I. Properly substituted imidazolidinones were available according to literature procedures.[1,21,22] Since the optimal 6-substituents regarding central 5-HT_2 antagonistic potency and selectivity (see below) within this series of compounds were found to be 6-methyl and 6-chloro we decided to investigate the influence of substituents Y of the 1-phenyl group with these subseries (Scheme II). The 1-unsubstituted 6-chloro- and 6-methyl-3-(4-piperidinyl)-1*H*-indoles (**5**) (Scheme II) were available from the corresponding 6-substituted indoles by base-catalyzed addition of 4-piperidone under subsequent elimination of water followed by alkylation with 1-(2-chloroethyl)-3-(2-propyl)-2-imidazolidinone and finally catalytic hydrogenation of the tetrahydropyridinyl double bond. Reduction of the double bond required several days at low pressure (2–3 atm). This reaction sequence has

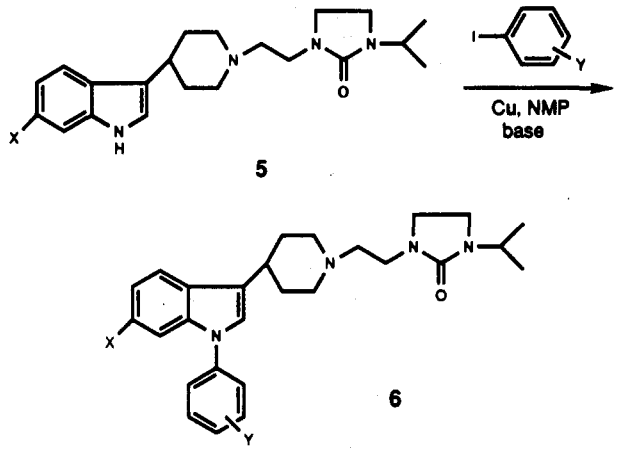
(9) Montgomery, S. A. Benzodiazepines. In *Anxiety and Depression*; Wrightson Biomedical Publishing Ltd.: Petersfield, 1990; pp 75–84.
(10) Glitz, D. A.; Pohl, R. 5-HT_{1A} Partial Agonists: WHat is Their Future. *Drugs* **1991**, *41*, 11–18.
(11) Jones, B. 5-HT_3 Receptor Antagonists in Anxiety and Schizophrenia. *Drug News Perspect.* **1990**, *3*, 106–111.
(12) Colpaert, F. C.; Meert, T. F.; Niemegeers, C. J. E.; Janssen, P. A. J. Behavioural and 5-HT Antagonist Effects of Ritanserin: A Pure and Selective Antagonist of LSD Discrimination in Rat. *Psychopharmacology* **1985**, *86*, 45–54.
(13) Bersani, G.; Pozzi, F.; Marini, S.; Grispini, A.; Pasini, A.; Ciani, N. 5-HT_2 Receptor Antagonism in Dysthymic Disorder: a Double-Blind Placebo-Controlled Study with Ritanserin. *Acta Psychiatr. Scand.* **1991**, *83*, 244–248.
(14) Niemegeers, C. J. E.; Awouters, F.; Heylen, S. L. E.; Gelders, Y. G. 5-HT_2 Receptor Antagonists in Schizophrenia: Preclinical and Clinical Considerations. In *Biological Psychiatry*; G. Racagni et al., Eds.; Elsevier Science Publishers B. V, 1991; Vol. 1, pp 535–537.
(15) Sharply, A. L.; Solomon, R. A.; Fernando, A. I.; daRoza Davis, J. M.; Cowen, P. J. Dose-Related Effects of Selective 5-HT_2 Receptor Antagonists on Slow Wave Sleep in Humans. *Psychopharmacology* **1990**, *101*, 568–569.
(16) Hoyer, D. Molecular Pharmacology and Biology of 5-HT_{1C} Receptors. *Trends Pharmacol. Sci.* **1988**, *9*, 89–94.
(17) Perregaard, J.; Costall, B. International Patent Publication No. WO 92/00070, 1992; *Chem. Abstr.* **1992**, *116*, 194150f.
(18) Bøgesø, K. P.; Arnt, J.; Boeck, V.; Christensen, A. V.; Hyttel, J.; Jensen, K. G. Antihypertensive Activity in a Series of 1-Piperazino-3-phenylindans with Potent 5-HT_2 Antagonistic Activity. *J. Med. Chem.* **1988**, *31*, 2247–2256.
(19) Arnt, J.; Bøgesø, K. B.; Boeck, V.; Christensen, A. V.; Dragsted, N.; Hyttel, J.; Skarsfeldt, T. In Vivo Pharmacology of Irindalone, a 5-HT_2 Receptor Antagonist With Predominant Peripheral Effects. *Drug Dev. Res.* **1989**, *16*, 59–70.
(20) Perregaard, J. U.S. Patent No. 4,710,500, 1987; *Chem. Abstr.* **1987**, *106*, 67110m.
(21) Johnston, T. P.; McCaleb, G. S.; Montgomery, J. A. The Synthesis of Antineoplastic Agents. XXXII. N-Nitrosureas. *J. Med. Chem.* **1963**, *6*, 669–681.
(22) Costeli, J.; Zûst, A. *Ger. Offen.* 2035370, 1971; *Chem. Abstr.* **1971**, *74*, 87985z.

Table I. Substituents and Binding Affinities of 6-Substituted 1-[2-[4-(1*H*-indol-3-yl)-1-piperidinyl]ethyl]-2-imidazolidinones with 1-(4-Fluorophenyl) (4) or with Other 1-Phenyl Substituents (6)

	substituents[a]			receptor binding affinities[b]		
compd	X	Y	R	serotonin 5-HT₂ [³H]ketanserin	dopamine D₂ [³H]spiperone	α₁-adrenergic [³H]prazosin
4a	CH_3		$CH(CH_3)_2$	1.6	190	85
4b	CH_3		H	0.82	270	24
4c	Cl		$CH(CH_3)_2$	1.5	130	70
4d	Cl		H	1.4	56	9.6
4e	CF_3		$CH(CH_3)_2$	2.9	280	91
4f	CF_3		H	1.7	260	33
4g	F		$CH(CH_3)_2$	1.3	28	13
4h	F		H	0.73	36	2.2
4i	$CH(CH_3)_2$		$CH(CH_3)_2$	16	2000	730
4j	$CH(CH_3)_2$		H	18	2600	250
6a	CH_3	4-Cl		6.0	620	450
6b	CH_3	H		2.0	500	120
6c	CH_3	2-F		2.5	730	370
6d	CH_3	3-F		11	3200	670
6e	CH_3	3-CF_3		150	3200	NT[c]
6f	Cl	H		4.5	290	39
6g	Cl	2-F		3.7	300	120
sertindole				0.39	4.1	3.4
Lu 23-086				0.72	18	3.0
ritanserin				0.40	12	47

[a] Refers to substituents of structures 4 in Scheme I and of structures 6 in Scheme II. [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; α_1 2.20; 5-HT_2 2.05. [c] NT: not tested.

Scheme II. Ullmann Arylations of 6-Substituted 1-[2-[4-(1*H*-indol-3-yl)-1-piperidinyl]ethyl]-3-(2-propyl)-2-imidazolidinones



5

6

earlier been reported for a 5-chloro analogue of compounds **5**.[1] 1-Arylation with properly substituted iodobenzenes under Ullmann conditions conveniently provided the 1-phenyl-substituted indoles **6** according to Scheme II. Various substituents X and Y are indicated in Table I.

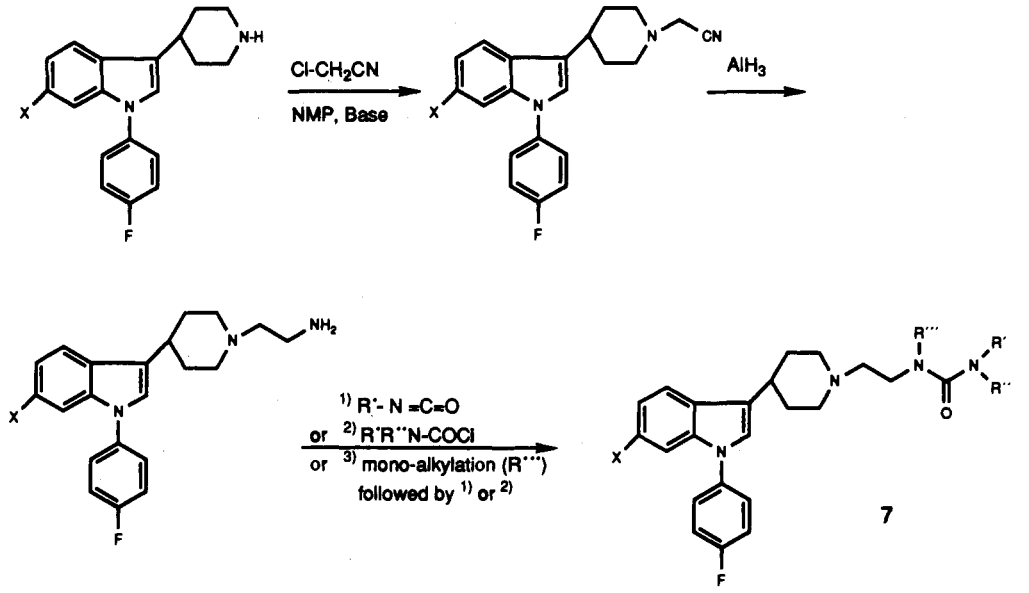
In order to investigate the significance of the imidazolidinone ring structure on antiserotonergic activity a series of corresponding open chain urea derivatives **7** (Scheme III) was prepared while retaining the optimal 6-chloro or 6-methyl substituents and the 1-(4-fluorophenyl) group. As starting materials, were used 6-chloro- or 6-methyl-substituted 1-(4-fluorophenyl)-3-(4-piperidinyl)-1*H*-indoles prepared by catalytic hydrogenation of tetrahydropyridinylindoles as discussed above. Alkylation with chloroacetonitrile was most conveniently performed in *N*-methyl-2-pyrrolidinone (NMP) to avoid precipitation of hydrochlorides of the starting piperidines. These hydrochlorides are virtually insoluble in most common solvents like acetone, methyl isobutyl ketone, and ethanol. The cyano group was reduced with AlH_3 (formed in situ from 3 equiv of $LiAlH_4$ by addition of $AlCl_3$). The primary ethylenamines were converted into the desired ureas **7**, as indicated in Scheme III, via proper alkylation/acylation procedures. These procedures are elaborated in more details in the Experimental Section. Substituents of the ureas **7** are shown in Table II.

To evaluate the effect of 2-substitution on 5-HT_2 receptor affinity a 2-methyl substituent was introduced. Addition of 1-methyl-4-piperidone to 1-unsubstituted 5-methoxy-2-methyl-1*H*-indole has previously been shown to give the corresponding 3-(4-tetrahydropyridinyl)indole under acidic reaction conditions;[23] but attempts to arylate either 2-methyl-1*H*-indole or 2-methyl-3-(1,2,3,6-tetrahydro-4-pyridinyl)-1*H*-indole using our modified Ullmann reaction conditions were unsuccessful. However, Unangst et al.[24] were able to arylate 2-carboxy-5-methoxy-1*H*-indole with bromobenzene using cupric oxide as catalyst in refluxing DMF. We adapted this method and thus prepared 2-carboxy-1-(4-fluorophenyl)-1*H*-indole (**8**, Scheme IV). Reduction of the carboxylic acid group was accomplished in a two-step sequence via the hydroxymethyl derivative **9**. Acid-catalyzed (trifluoroacetic acid) addition of 4-piperidone afforded the tetrahydropyridinyl compound **11** which was N-alkylated with 1-(2-chloroethyl)-2-imidazolidinone to **12**. The double bond of **12** was quite resistant to catalytic hydrogenation, possibly due to steric hindrance from the 2-methyl group. The reduction of **12** to the piperidino compound **13** was not complete until after 39 h of continuous hydrogenation.

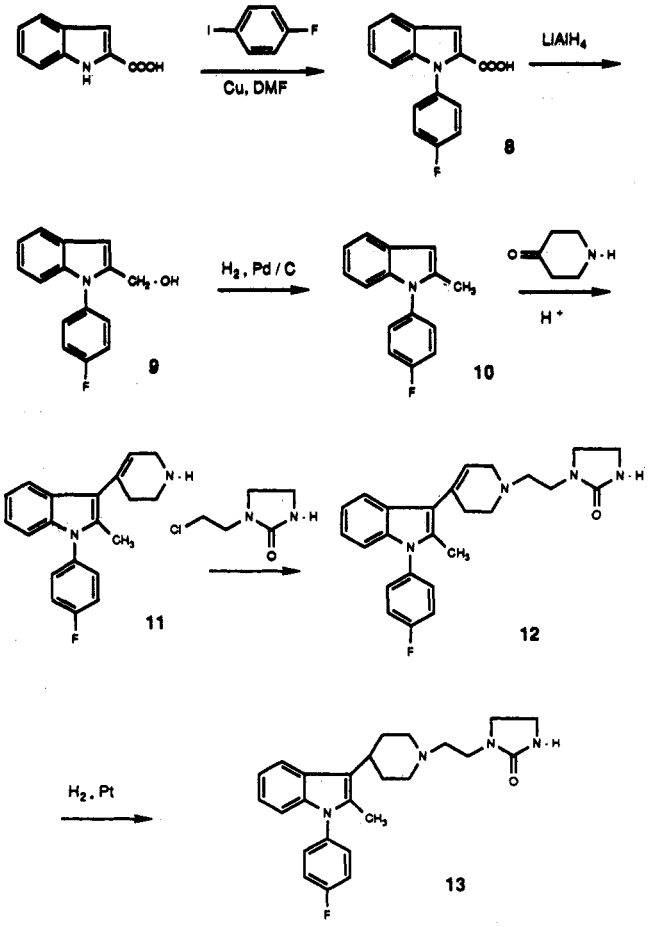
(23) Guillaume, J.; Dumont, C.; Laurent, J.; Nédeléc, L. 3-(1,2,3,6-Tetrahydro-γ-pyridinyl)-1*H*-indoles: Synthesis, Serotonergic and Antidopaminergic Properties. *Eur. J. Med. Chem.* **1987**, *22*, 33–43.

(24) Unangst, P. C.; Connor, D. T.; Stabler, S. R.; Weikert, R. J. Synthesis of Novel 1-Phenyl-1H-indole-2-carboxylic Acids. I. Utilization of Ullmann and Dieckmann Reactions for the Preparation of 3-Hydroxy, 3-Alkoxy, and 3-Alkyl Derivatives. *J. Heterocycl. Chem.* **1987**, *24*, 811–815.

Scheme III. Synthesis of Urea Derivatives 7



Scheme IV. Synthesis of 1-[2-[4-[1-(4-Fluorophenyl)-2-methyl-1*H*-indol-3-yl]-1,2,3,6-tetrahydropyridin-1-yl]-ethyl]-2-imidazolidinone (12) and 1-[2-[4-[1-(4-fluorophenyl)-2-methyl-1*H*-indol-3-yl]-1-piperidinyl]ethyl]-2-imidazolidinone (13)



Results and Discussion

The pharmacological test models are described in detail in the Experimental Section. Receptor binding affinities (dopamine D_2, adrenergic α_1, serotonin 5-HT_2) are reported in Tables I and II and compared to relevant reference compounds (structures Figure 1). From Table I, structures 4, it appears that by simply moving the 5-substituent to the 6-position in the indole ring high 5-HT_2 receptor affinity is retained, while affinities for D_2 receptors are generally weakened by a factor of 10–20. Binding data for 5-substituted indoles were recently published.[1] Exceptions are the 6-fluoro derivatives (**4g,h**) which have considerable binding to D_2 receptors. The 6-(2-propyl)-substituted derivatives (**4i,j**) are selective, but 5-HT_2 receptor affinities are rather weak. Compared to the reference compounds, sertindole and Lu 23-086, a decrease in α_1 adrenoceptor affinity also derives from introduction of 6-substituents. However, the 6-fluoro compounds have retained high α_1 adrenoceptor affinity. Introduction of 3-(2-propyl) substituents of the imidazolidinone ring seems to reduce the α_1 adrenoceptor component by a factor of 3–8, while 5-HT_2 and D_2 receptor affinities are not influenced. Binding data of compounds **6** (Table I) show that the 4-fluoro substituent of the phenyl group is not essential for high 5-HT_2 receptor affinity as previously assumed[1] based upon structure/activity studies within phenylindans.[18] Both the unsubstituted (**6b,f**), 2-fluoro (**6c,g**), and 4-chloro (**6a**) phenylindoles bind with high affinities, while 3-substitution (**6d,e**) seems to weaken the binding somewhat, especially for the 3-trifluoromethyl substitution (**6e**). The starting materials, **5a** and **5b**, for the synthesis of indoles **6** were also tested in the three receptor binding assays (Table II). These 1-unsubstituted indoles have considerably weaker 5-HT_2 receptor affinity. They are generally 50 times less potent than the 1-(4-fluorophenyl) analogues, however, with adrenergic α_1 affinities preserved. This confirms the earlier reported importance of the 1-(4-fluorophenyl) substituent in sertindole, or at least that 1-phenyl substituents must be present to obtain potent 5-HT_2 receptor binding. The 1-unsubstituted sertindole analogue was also found to be virtually inactive as a 5-HT_2 antagonist.[1]

Ureas **7** (Table II), which were synthesized as open-chain analogues of imidazolidinone derivatives, were potent 5-HT_2 antagonists. Generally, they appear to have the same 5-HT_2 receptor selectivity as the imidazolidinones **4a–d**.

It has previously been indicated that 2-methyl substitution in simple 1-unsubstituted 3-(4-tetrahydropyridin-

Table II. Substituents and Binding Affinities of Urea Derivatives **7**, 1-Unsubstituted Indoles **5**, and 2-Methyl-Substituted Compounds **12** and **13**

compd[c]	substituents[a] X	R′	R″	R‴	receptor binding affinities[b] serotonin 5-HT$_2$ [^{3}H]ketanserin	dopamine D$_2$ [^{3}H]spiperone	α_1-adrenergic [^{3}H]prazosin
7a	Cl	CH_3	H	CH_3	1.6	82	16
7b	Cl	$CH(CH_3)_2$	H	CH_3	2.2	74	26
7c	Cl	CH_3	CH_3	H	1.3	27	29
7d	CH_3	CH_3	CH_3	H	2.6	38	22
7e	CH_3	$CH(CH_3)_2$	H	H	1.8	300	76
5a	CH_3				60	590	27
5b	Cl				66	200	34
12					1.1	160	23
13					0.59	380	76

[a] Refers to substituents in structures **7** in Scheme III and structures **5** (only X) in Scheme II. [b] See footnote to Table I. [c] Reference compounds are shown in Table I.

yl)indoles results in a loss of potency at 5-HT$_2$ receptor sites of 1 order of magnitude.[25] It was anticipated that the 2-methyl substituent would force the six-membered basic ring out of coplanarity with the indole ring. Our binding data for the 2-methyl-substituted indoles **12** and **13** (Table II) clearly showed that no 5-HT$_2$ binding affinity has been lost in comparison to the 2-unsubstituted analogue, Lu 23-086 (Table I). However, a considerable decrease in D$_2$ and α_1 affinities was found resulting in high selectivity of these two compounds. In fact, compound **13** was found to be the most potent and selective of the compounds in Tables I and II with regard to receptor binding. Taylor et al. also reported potent 5-HT$_{1A}$ receptor affinity for some of the 1-unsubstituted 3-(4-tetrahydropyridinyl)indoles.[25] We have tested compounds **4a** and **4c** for 5-HT$_{1A}$ receptor affinity ([^{3}H]-8-OHDPAT binding). No significant binding was found in concentrations below 1000 nM (unpublished results). Unfortunately, we have not yet had the opportunity to evaluate our compounds for 5-HT$_{1C}$ receptor affinity. Since it is known from literature[16] that many 5-HT$_2$ antagonists equipotently bind to this structurally closely related receptor it would be interesting to measure such affinities.

Using the molecular modeling software MacMimic (Instar Software, Lund, Sweden), we analyzed low energy conformations of compounds **13** and Lu 23-086. For simplicity, calculations were performed with the piperidinyl *N*-methyl derivatives. The piperidine ring in Lu 23-086 was rotated, and the piperidine ring and the 2-methyl group in **13** were simultaneously rotated. Both rotations were performed with the piperidine ring in a chair conformation. The 4-fluorophenyl group was fixed in a low energy conformation which corresponds to the crystal structure determined for two polymorphic crystal forms of sertindole[1] (personal communication S. Larsen et al., Dept. of Chemistry, University of Copenhagen, 1992). Two low energy conformations of the piperidine ring, which were not related by symmetry, were found for both compounds (Figure 2). Conformations with the *N*-piperidine lone pair in the plane, defined by the indole ring, are designated structures A, while structures B are defined by the *N*-piperidine lone pair pointing away from the plane defined by the indole ring. We find conformation A of **13** to be the energetically most stable conformer, with an energy difference of 2.2 kcal/mol to conformation B of **13**

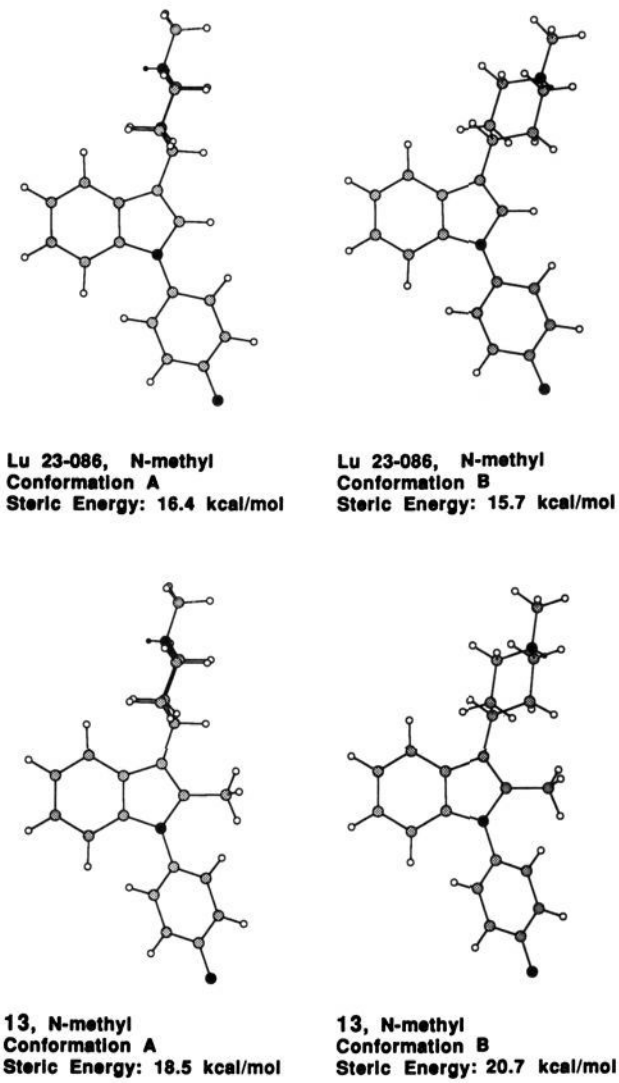


Figure 2. Low-energy conformations of the *N*-methylpiperidinyl analogues of Lu 23-086 (structure **1b**, Figure 1) and compound **13**.

(Figure 2). On the contrary, for Lu 23-086, conformation B is the global energy minimum with an energy difference to conformation A of 0.7 kcal/mol. Certainly, comparison of the 5-HT$_2$ binding data of both **13** and Lu 23-086 does not reflect these differences in global and local energy minima. However, further conformational analysis of **13** by rotation of the 4-fluorophenyl group revealed a local energy minimum with the piperidine ring in a planar

(25) Taylor, E. W.; Nikam, S. S.; Lambert, G.; Martin, A. R.; Nelson, D. L. Molecular Determinants for Recognition of RU 24969 Analogs at Central 5-Hydroxytryptamine Recognition Sites: Use of a Bilinear Function and Substituent Volumes to Describe Steric Fit. *Mol. Pharmacol.* **1988**, *34*, 42–53.

Table III. Pharmacological Activity of 2- and 6-Substituted 3-(4-Piperidinyl)-1H-Indoles

compd	inhibition of quipazine-induced head twitches[a] 2 h (sc)	24 h (sc)	24 h (po)	inhibition of pergolide-induced rotations[a] 2 h (sc)	inhibition of isolation-induced aggression[a] threshold: 90 s	threshold: 180 s
4a	0.042 (0.018–0.096)	0.036 (0.010–0.12)	0.11 (0.056–0.22)	>18	13 (2.9–59)	7.3 (2.6–20)
4c	0.11 (0.064–0.18)	0.052 (0.017–0.16)	0.055 (0.026–0.12)	>17	2.3 (1.6–3.2)[b]	2.0 (1.4–2.8)[b]
4h	0.034 (0.012–0.095)	NT[c]	0.038 (0.0091–0.16)	25 (12–50)	NT	NT
4i	>0.54	>4.3	NT	NT	NT	NT
5a	>0.84	NT	NT	NT	NT	NT
6b	0.014 (0.0027–0.073)	0.032 (0.0089–0.12)	0.056 (0.017–0.18)	>22	>11	>11
7a	0.049 (0.010–0.24)	0.0092 (0.0027–0.031)	0.022 (0.010–0.048)	>23	>23	>23
7b	0.18 (0.11–0.29)	0.016 (0.0042–0.061)	0.032 (0.014–0.074)	>21	>21	>21
13	0.18 (0.072–0.45)	0.11 (0.039–0.31)	0.078 (0.031–0.20)	29 (9.7–87)	NT	NT
sertindole	0.035 (0.022–0.056)	0.030 (0.014–0.066)	0.039 (0.020–0.078)	3.7 (1.5–8.9)	5.9 (3.7–9.4)	7.5 (4.4–13)
Lu 23-086	0.036 (0.011–0.12)	0.082 (0.014–0.48)	0.26 (0.12–0.57)	5.1 (1.8–14.4)	1.9 (1.3–2.9)	1.7 (1.1–2.6)
ritanserin	0.10 (0.056–0.18)	0.98 (0.35–2.7)	NT	>21	>10	>10
eltoprazine	NT	NT	NT	NT	8.0 (3.5–18.4)	5.4 (2.3–12.4)

[a] Results are expressed as ED_{50} values in μmol/kg. 95% Confidence limits in brackets. [b] Test results for the free base. [c] NT: not tested.

conformation B (Figure 2) and less than 1 kcal/mol above the global minimum A in steric energy. Provided that these indoles interact with the 5-HT_2 receptor in the same molecular shape, the equipotency in binding seems reasonable. We believe that the planar conformations (structures B) with the basic nitrogen lone pair pointing away from the plane defined by the indole ring are the active conformations, which are supported by planarity in condensed indole ring systems as in the potent and selective 5-HT_2 antagonist sergolexole from the ergot series.[26]

In Table III are reported some important in vivo pharmacological activities of selected compounds. Quipazine is a 5-HT_2 agonist which induces the characteristic head twitch syndrome in rats.[19] 6-Substituted indoles **4** and **6** potently inhibited these head twitches. Even 24 h after administration of the substances the syndrome was effectively prevented both after subcutaneous and oral administration. The urea derivatives **7a** and **7b** were even 10 times more efficient 24 h after administration compared to 2 h after the administration. In fact, compound **7a** was the most potent 5-HT_2 antagonist in vivo within the present series of indoles. These potencies and very long duration of action are quite outstanding compared to the corresponding test results of ritanserin (Table III). Only the 6-(2-propyl)-substituted indole **4i** and the 1-unsubstituted indole **5a** were without significant central antiserotonergic activity, which is in agreement with the weak binding of these compounds. To confirm the absence of 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.[27] This test model is very sensitive to classical dopamine D_2 antagonists. Neuroleptics, like haloperidol and fluphenazine, are active in the 0.01–0.05 μmol/kg range.[4] Sertindole and Lu 23-086 are very weak antagonists in this test model (Table III). Except for the less selective 6-fluoro derivative **4h** none of the 6-substituted derivatives were able to block the pergolide-induced circling behavior (Table III). The very selective 2-methyl derivative **13** had an inexplicable marginal activity.

Some of the indoles were tested for antiaggressive effects in isolation-induced aggressive mice (Table III). Sertindole and Lu 23-086 were active and quite potent in the test model. For comparison the serenic compound eltoprazine[28] was also tested (Table III). Eltoprazine is presently being evaluated for its potential as an antiaggressant agent in clinical trials. Compounds **4a** and in particular **4c** potently prevented aggressive behavior in the test model, while other selective 5-HT_2 antagonists like **6b**, **7a**, and **7b**, as well as ritanserin were totally inactive. So it seems that this antiaggressive potential of some of the 1-phenylindoles cannot be related to their 5-HT_2 antagonistic activity.

Compound **4c**, with the compound code Lu 26-042, has been selected for further pharmacological and toxicological studies. This particular compound has shown high 5-HT_2 receptor selectivity (relative to D_2 and α_1 receptors) compared to the reference compound ritanserin, efficient CNS penetration both after subcutaneous and oral administration, and a long duration of action. Furthermore, the antiaggressive potential is pronounced in comparison with clinically studied serenics such as eltoprazine.

Experimental Section

Melting points were determined on a Büchi SMP-20 apparatus and are uncorrected. ^1H 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. 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, dt = double triplet, dq = double quartet, tt = triplet of triplets, 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. Standard workup procedures refer to extraction with ethyl acetate from proper aqueous solutions, drying of combined organic extracts (anhydrous $MgSO_4$), filtering, and finally evaporation of the solvent in vacuo.

1-(2-Chloroethyl)-2-imidazolidinone was prepared according to literature.[1,21] The preparation of **1-(2-chloroethyl)-3-(2-propyl)-2-imidazolidinone** followed the method reported by Costeli and Zūst.[22]

6-Substituted 1-(4-fluorophenyl)-1H-indoles (**3**) were prepared according to methods previously described.[1] Method C from

(26) Cohen, M. L.; Fuller, R. W.; Kurz, K. D.; Parli, C. J.; Mason, N. R.; Meyers, D. B.; Smallwood, J. K.; Toomey, R. E. *J. Pharmacol. Exp. Ther.* **1988**, *244*, 106–112.

(27) 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.

(28) Wasielewski, S. Serenics: New Drugs with Specific Antiagressive Effect. *Med. Monatsschr. Pharm.* **1991**, *14*, 290–291.

this reference was used for the synthesis of the 6-fluoro (**3a**), 6-(2-propyl) (**3d**), and 6-trifluoromethyl (**3e**) indoles while the 6-chloro (**3b**) and 6-methyl (**3c**) derivatives were obtained by the earlier described method D. The following compounds were synthesized:

6-Fluoro-1-(4-fluorophenyl)-1*H*-indole (3a) was obtained as an oil: ^{1}H NMR ($CDCl_3$) δ 6.65 (d, 1 H), 6.90–7.00 (m, 1 H), 7.10–7.30 (m, 4 H), 7.40–7.50 (m, 2 H), 7.55–7.65 (m, 1 H).

6-Chloro-1-(4-fluorophenyl)-1*H*-indole (3b) was obtained as an oil: ^{1}H NMR ($CDCl_3$) δ 6.65 (d, 1 H), 7.10 (dd, 1 H), 7.15–7.25 (m, 3 H), 7.35–7.45 (m, 3 H), 7.55 (d, 1 H).

1-(4-Fluorophenyl)-6-methyl-1*H*-indole (3c): mp 42–43 °C (*n*-heptane); ^{1}H NMR ($CDCl_3$) δ 2.55 (s, 3 H), 6.70 (d, 1 H), 7.05 (d, 1 H), 7.20–7.35 (m, 4 H), 7.45–7.55 (m, 2 H), 7.65 (d, 1 H). Anal. ($C_{15}H_{12}FN$) C, H, N.

1-(4-Fluorophenyl)-6-(2-propyl)-1*H*-indole (3d) was obtained as an oil: ^{1}H NMR ($CDCl_3$) δ 1.30 (d, 6 H), 3.00 (h, 1 H), 6.65 (d, 1 H), 7.10 (dd, 1 H), 7.10–7.55 (m, 6 H), 7.60 (d, 1 H).

1-(4-Fluorophenyl)-6-(trifluoromethyl)-1*H*-indole (3e) was obtained as an oil: ^{1}H NMR ($CDCl_3$) δ 6.70 (d, 1 H), 7.15–7.60 (m, 6 H), 7.70 (broad s, 1 H), 7.75 (d, 1 H).

General Procedure for the Synthesis of 1-(4-fluorophenyl)-3-(4-piperidinyl)-1*H*-indoles (4) (Table I). These methods have been described in detail for the synthesis of corresponding 5-substituted indole derivatives.[1]

1-[2-[4-[1-(4-Fluorophenyl)-6-methyl-1*H*-indol-3-yl]-1-piperidinyl]ethyl]-3-(2-propyl)-2-imidazolidinone (4a). To a gently refluxing solution of 4-piperidone hydrochloride hydrate (280 g, 1.8 mol) in a mixture of trifluoroacetic acid (1 L) and acetic acid (0.5 L) was added dropwise a solution of 1-(4-fluorophenyl)-6-methyl-1*H*-indole (**3c**) (120 g, 0.53 mol) in acetic acid (0.5 L) during 2.5 h under N_2. After final addition the mixture was refluxed for another 0.5 h. After cooling to room temperature the mixture was poured onto crushed ice (5 kg). By addition of diluted aqueous NH_4OH, the pH was adjusted to >9. The 3-(1,2,3,6-tetrahydro-4-pyridinyl)-1*H*-indole derivative was isolated according to the standard procedure above leaving 138 g (85%) of crude 1-(4-fluorophenyl)-6-methyl-3-(1,2,3,6-tetrahydro-4-pyridinyl)-1*H*-indole as a viscous oil. To a solution of the thus obtained crude tetrahydropyridinyl derivative (46 g, 0.15 mol) in a mixture of acetic acid (50 mL) and ethanol (200 mL) was added PtO_2 (1.2 g). The mixture was hydrogenated in a Parr apparatus for 20 h at 2–3 atm. The catalyst was filtered off and the solvents evaporated in vacuo. The remaining viscous oil was dissolved in H_2O (2 L), and pH was adjusted to 10 by addition of diluted aqueous NH_4OH. Standard workup procedures as above afforded 30 g (65%) of crude 1-(4-fluorophenyl)-6-methyl-3-(4-piperidinyl)-1*H*-indole which was used without further purification. To a solution of the thus obtained crude piperidinylindole (30 g, 0.097 mol) in methyl isobutyl ketone (MIBK) (300 mL) were added 1-(2-chloroethyl)-3-(2-propyl)-2-imidazolidinone (24 g, 0.13 mol), finely powdered anhydrous K_2CO_3 (24 g, 0.17 mol), and KI (2 g). This mixture was refluxed for 8 h. Inorganic salts were filtered off and MIBK evaporated in vacuo. The remaining oil was subjected to column chromatography on SiO_2. The title compound **4a** was eluted with ethyl acetate containing 4% v/v of triethylamine. The pure product crystallized from acetone: yield 24.6 g (60%); mp 124–125 °C; ^{1}H NMR ($CDCl_3$) δ 1.15 (d, 6H), 1.80 (dq, 2H), 2.10 (broad d, 2H), 2.25 (t, 2H), 2.40 (s, 3H), 2.55 (t, 2H), 2.85 (tt, 1H), 3.10 (broad d, 2H), 3.30 (m, 2H), 3.35–3.45 (m, 4H), 4.20 (h, 1H), 6.90 (s, 1H), 6.95 (d, 1H), 7.15–7.30 (m, 3H), 7.40–7.45 (m, 2H), 7.55 (d, 1H). Anal. ($C_{28}H_{35}FN_4O$) C, H, N.

1-[2-[4-[1-(4-Fluorophenyl)-6-methyl-1*H*-indol-3-yl]-1-piperidinyl]ethyl]-2-imidazolidinone (4b): mp 186–188 °C (methyl isobutyl ketone); ^{1}H NMR ($CDCl_3$) δ 1.90 (dq, 2H), 2.15 (broad d, 2H), 2.25 (t, 2H), 2.50 (s, 3H), 2.65 (t, 2H), 2.90 (tt, 1H), 3.15 (broad d, 2H), 3.40–3.50 (m, 4 H), 3.55–3.65 (m, 2H), 4.65 (s, 1H), 7.00 (s, 1H), 7.05 (dd, 1H), 7.20–7.30 (m, 3H), 7.40–7.50 (m, 2H), 7.65 (d, 1H). Anal. ($C_{25}H_{26}FN_4O$) C, H, N.

1-[2-[4-[6-Chloro-1-(4-fluorophenyl)-1*H*-indol-3-yl]-1-piperidinyl]ethyl]-3-(2-propyl)-2-imidazolidinone oxalate hemihydrate (4c): mp 117–119 °C (acetone); ^{1}H NMR (DMSO-d_6) δ 1.05 (d, 6H), 2.00–2.15 (m, 4H), 2.95–3.35 (m, 9H), 3.45 (t, 2H), 3.60 (broad d, 2H), 3.90 (h, 1H), 7.15 (dd, 1H), 7.30–7.40 (m, 3H), 7.50 (s, 1H), 7.55–7.65 (m, 2H), 7.80 (d, 1H), 8.30 (broad s, 3H). Anal. ($C_{27}H_{32}ClFN_4O$·oxalate·hemihydrate) C, H, N. The free base was also isolated and recrystallized from ethanol: mp 134 °C. Anal. ($C_{27}H_{32}ClFN_4O$) C, H, N.

1-[2-[4-[6-Chloro-1-(4-fluorophenyl)-1*H*-indol-3-yl]-1-piperidinyl]ethyl]-2-imidazolidinone (4d): mp 180–182 °C (acetone); ^{1}H NMR ($CDCl_3$) δ 1.85 (dq, 2H), 2.10 (broad d, 2H), 2.25 (dt, 2H), 2.65 (t, 2H), 2.85 (tt, 1H), 3.15 (broad d, 2H), 3.35–3.50 (m, 4H), 3.55–3.65 (m, 2H), 4.70 (s, 1H), 7.05 (s, 1H), 7.15 (dd, 1H), 7.20–7.30 (m, 2H), 7.40–7.50 (m, 3H), 7.65 (d, 1H). Anal. ($C_{24}H_{26}ClFN_4O$) C, H, N.

1-[2-[4-[1-(4-Fluorophenyl)-6-(trifluoromethyl)-1*H*-indol-3-yl]-1-piperidinyl]ethyl]-3-(2-propyl)-2-imidazolidinone dioxalate (4e): mp 139–141 °C (acetone); ^{1}H NMR (DMSO-d_6) δ 1.05 (d, 6H), 2.00–2.20 (m, 4H), 3.05–3.35 (m, 9H), 3.45 (t, 2H), 3.60 (broad d, 2H), 3.95 (h, 1H), 7.40–7.50 (m, 3H), 7.60–7.70 (m, 2H), 7.70 (s, 1H), 7.75 (s, 1H), 8.00 (d, 1H), 9.60 (broad s, 4H). Anal. ($C_{28}H_{32}F_4N_4O$·dioxalate) C, H, N.

1-[2-[4-[1-(4-Fluorophenyl)-6-(trifluoromethyl)-1*H*-indol-3-yl]-1-piperidinyl]ethyl]-2-imidazolidinone (4f): mp 187–188 °C (acetone); ^{1}H NMR ($CDCl_3$) δ 1.80 (dq, 2H), 2.05 (broad d, 2H), 2.25 (t, 2H), 2.05 (t, 2H), 2.85 (tt, 1H), 3.10 (broad d, 2H), 3.35–3.45 (m, 4H), 3.50–3.60 (m, 2H), 4.60 (s, 1H), 7.20 (s, 1H), 7.20–7.30 (m, 2H), 7.35–7.45 (m, 3H), 7.65 (s, 1H), 7.75 (d, 1H). Anal. ($C_{25}H_{26}F_4N_4O$) C, H, N.

1-[2-[4-[6-Fluoro-1-(4-fluorophenyl)-1*H*-indol-3-yl]-1-piperidinyl]ethyl]-3-(2-propyl)-2-imidazolidinone (4g): mp 140–141 °C (di-2-propyl ether); ^{1}H NMR ($CDCl_3$) δ 1.15 (d, 6H), 1.85 (dq, 2H), 2.10 (broad d, 2H), 2.25 (dt, 2H), 2.60 (t, 2H), 2.90 (tt, 1H), 3.15 (broad d, 2H), 3.25–3.35 (m, 2H), 3.40–3.50 (m, 4H), 4.20 (h, 1H), 6.95 (dt, 1H), 7.05 (s, 1H), 7.15 (dd, 1H), 7.20–7.30 (m, 2H), 7.40–7.50 (m, 2H), 7.65 (dd, 1H). Anal. ($C_{27}H_{32}F_2N_4O$) C, H, N.

1-[2-[4-[6-Fluoro-1-(4-fluorophenyl)-1*H*-indol-3-yl]-1-piperidinyl]ethyl]-2-imidazolidinone (4h): mp 160–162 °C (diethyl ether); ^{1}H NMR ($CDCl_3$) δ 1.80 (dq, 2H), 2.10 (broad d, 2H), 2.20 (t, 2H), 2.55 (t, 2H), 2.85 (tt, 1H), 3.10 (broad d, 2H), 3.30–3.45 (m, 4H), 3.50–3.60 (m, 2H), 4.60 (s, 1H), 6.90 (dt, 1H), 7.05 (s, 1H), 7.10 (dd, 1H), 7.15–7.25 (m, 2H), 7.35–7.45 (m, 2H), 7.60 (dd, 1H). Anal. ($C_{24}H_{26}F_2N_4O$) C, H, N.

1-[2-[4-[1-(4-Fluorophenyl)-6-(2-propyl)-1*H*-indol-3-yl]-1-piperidinyl]ethyl]-3-(2-propyl)-2-imidazolidinone oxalate (4i): mp 179–180 °C (acetone); ^{1}H NMR (DMSO-d_6) δ 1.05 (d, 6H), 1.25 (d, 6H), 1.95–2.20 (m, 4H), 3.00 (h, 1H), 3.05 (broad t, 2H), 3.10–3.40 (m, 7H), 3.45 (t, 2H), 3.55 (broad d, 2H), 3.95 (h, 1H), 7.05 (d, 1H), 7.30 (s, 1H), 7.35–7.45 (m, 3H), 7.55–7.60 (m, 2H), 7.65 (d, 1H). Anal. ($C_{30}H_{39}FN_4O$·oxalate) C, H, N.

1-[2-[4-[1-(4-Fluorophenyl)-6-(2-propyl)-1*H*-indol-3-yl]-1-piperidinyl]ethyl]-2-imidazolidinone (4j): mp 175–177 °C (di-2-propyl ether); ^{1}H NMR ($CDCl_3$) δ 1.35 (d, 6H), 1.85 (dq, 2H), 2.15 (broad d, 2H), 2.30 (t, 2H), 2.65 (t, 2H), 2.95 (tt, 1H), 3.05 (h, 1H), 3.10 (broad d, 2H), 3.45–3.55 (m, 4H), 3.60–3.70 (m, 2H), 4.45 (s, 1H), 7.05 (s, 1H), 7.15 (d, 1H), 7.20–7.35 (m, 3H), 7.45–7.55 (m, 2H), 7.65 (d, 1H). Anal. ($C_{27}H_{33}FN_4O$) C, H, N.

Indoles (**6**) (Table I) with 1-phenyl substituents different from 1-(4-fluorophenyl) were prepared according to Scheme II as outlined below:

1-[2-[4-(6-Methyl-1*H*-indol-3-yl)-1-piperidinyl]ethyl]-3-(2-propyl)-2-imidazolidinone (5a). To an ice-cooled solution of potassium hydroxide (16 g, 0.29 mol) in methanol (200 mL) were added 6-methyl-1*H*-indole (10 g, 0.076 mol) and 4-piperidone hydrochloride hydrate (30 g, 0.20 mol). The mixture was refluxed for 16 h. After cooling to room temperature, inorganic salts were filtered off, and the solvent was evaporated in vacuo. The remaining oil was extracted with ethyl acetate (2 × 100 mL) from brine (500 mL). Workup according to the standard procedure afforded 16 g (99%) of 6-methyl-3-(1,2,3,6-tetrahydro-4-pyridinyl)-1*H*-indole as a viscous oil: ^{1}H NMR (DMSO-d_6) δ 2.40 (s, 3H), 2.90 (t 2H), 3.15–3.25 (m, 2H), 3.40 (broad s, 2H), 6.15 (broad s, 1H), 6.85 (d, 1H), 7.15 (s, 1H), 7.30 (s, 1H), 7.65 (d, 1H), 10.95 (s, 1H). All of this oil was dissolved in MIBK (0.5 L) and finely powdered anhydrous K_2CO_3 (32 g, 0.23 mol), KI (6 g), and 1-(2-chloroethyl)-3-(2-propyl)-2-imidazolidinone (32 g, 0.17 mol) were added. The mixture was refluxed for 19 h, and inorganic salts were filtered off while still hot. MIBK was evaporated in vacuo. Finally the alkylated product was worked up according to the standard procedure above. Crystallization from ether yielded

15.5 g (56%) of pure1-[2-[4-(6-methyl-1*H*-indol-3-yl)-1-(1,2,3,6-tetrahydropyridinyl)]ethyl]-3-(2-propyl)-2-imidazolidinone: mp 170–174 °C; ^{1}H NMR ($CDCl_3$) δ 2.45(s, 3H), 2.55 (broad s, 2H), 2.65 (t, 2H), 2.80 (t, 2H), 3.20–3.35 (m, 4H), 3.35–3.50 (m, 4H), 4.15 (h, 1H), 6.15 (broad s, 1H), 6.95 (d, 1H), 7.05 (d, 1H), 7.15 (s, 1H), 7.75 (d, 1H), 8.70 (s, 1H). To all of the thus obtained tetrahydropyridinylindole dissolved in acetic acid (400 mL) was added PtO_2 (0.8 g), and the mixture was hydrogenated in a Parr apparatus at 2–3 atm for 68 h. The catalyst was filtered off and the acetic acid evaporated in vacuo. The remaining oil was dissolved in H_2O and pH was adjusted to 9–10 by addition of diluted aqueous NaOH solution. The title compound **5a** was extracted with dichloromethane (2 × 100 mL) and worked up as above, yield 13.8 g (90%). A recrystallized sample from ethyl acetate had mp 185 °C; ^{1}H NMR ($CDCl_3$) δ 1.15 (d, 6H), 1.75 (dq, 2H), 2.05 (broad d, 2H), 2.20 (dt, 2H), 2.40 (s, 3H), 2.55 (t, 2H), 2.80 (tt, 1H), 3.05 (broad d, 2H), 3.20–3.30 (m, 2H), 3.30–3.40 (m, 4H), 4.15 (h, 1H), 6.85 (d, 1H), 6.90 (d, 1H), 7.15 (s, 1H), 7.50 (d, 1H), 8.25 (s, 1H). Anal. ($C_{22}H_{32}N_4O$) C, H, N.

In a similar way was prepared **1-[2-[4-(6-chloro-1*H*-indol-3-yl)-1-piperidinyl]ethyl]-3-(2-propyl)-2-imidazolidinone (5b)**: mp 212–213 °C (methyl isobutyl ketone); ^{1}H NMR (DMSO-d_6) δ 1.05 (d, 6H), 1.65 (dq, 2H), 1.90 (broad d, 2H), 2.05 (t, 2H), 2.45 (t, 2H), 2.70 (tt, 1H), 2.95 (broad d, 2H), 3.10–3.20 (m, 4H), 3.25–3.35 (m, 2H), 3.90 (h, 1H), 6.95 (dd, 1H), 7.10 (s, 1H), 7.35 (d, 1H), 7.55 (d, 1H), 10.90 (s, 1H). Anal. ($C_{21}H_{29}ClN_4O$) C, H, N.

General Procedure for the Arylation of Indoles 5. This is a modified Ullmann procedure as previously described for the arylation of 3-unsubstituted indoles.[1]

1-[2-[4-[1-(4-Chlorophenyl)-6-methyl-1*H*-indol-3-yl]-1-piperidinyl]ethyl]-3-(2-propyl)-2-imidazolidinone Oxalate (6a). To a solution of 1-[2-[4-(6-methyl-1*H*-indol-3-yl)-1-piperidinyl]ethyl]-3-(2-propyl)-2-imidazolidinone (**5a**) (3.4 g, 0.01 mol) in *N*-methyl-2-pyrrolidone (NMP) (30 mL) were added 4-chloroiodobenzene (5 g, 0.025 mol), K_2CO_3 (3.5 g, 0.025 mol), CuI (0.5 g), and ZnO (0.16 g). The mixture was heated at 160 °C under N_2 for 5 h under vigorous stirring. After cooling to room temperature, ethyl acetate (200 mL) was added and precipitated salts were filtered off. Diluted aqueous NH_4OH (400 mL) was added and the organic phase was separated and subsequently washed with brine (2 × 50 mL) and H_2O (50 mL). The organic phase was worked up as described above affording the crude title compound **6a** as an oil. Purification was performed by column chromatography on SiO_2 (eluted with ethyl acetate/triethylamine 100:4), yield 3.8 g (94%). An oxalate salt crystallized from acetone: mp 178 °C; ^{1}H NMR (DMSO-d_6) δ 1.05 (d, 6H), 1.95–2.20 (m, 4H), 2.40 (s, 3H), 3.10 (m, 3H), 3.15–3.40 (m, 6H), 3.45 (t, 2H), 3.60 (broad d, 2H), 3.90 (h, 1H), 6.95 (d, 1H), 7.35 (d, 2H), 7.55–7.65 (m, 5H), ~7.3 (broad s, 2H). Anal. ($C_{29}H_{35}ClN_4O$·oxalate) C, H, N.

In a corresponding way other 1-phenyl-substituted derivatives **6** in Table I were prepared:

1-[2-[4-(6-Methyl-1-phenyl-1*H*-indol-3-yl)-1-piperidinyl]ethyl]-3-(2-propyl)-2-imidazolidinone (6b): mp 93 °C (di-2-propyl ether); ^{1}H NMR ($CDCl_3$) δ 1.10 (d, 6H), 1.80 (dq, 2H), 2.10 (broad d, 2H), 2.20 (dt, 2H), 2.45 (s, 3H), 2.55 (t, 2H), 2.85 (tt, 1H), 3.10 (broad d, 2H), 3.20–3.25 (m, 2H), 3.30–3.40 (m, 4H), 4.15 (h, 1H), 7.00 (dd, 1H), 7.05 (s, 1H), 7.25–7.35 (m, 1H), 7.35 (s, 1H), 7.45–7.50 (m, 4H), 7.55 (d, 1H). Anal. ($C_{28}H_{36}N_4O$) C, H, N.

1-[2-[4-[1-(2-Fluorophenyl)-6-methyl-1*H*-indol-3-yl]-1-piperidinyl]ethyl]-3-(2-propyl)-2-imidazolidinone oxalate hemihydrate (6c): mp 150–152 °C (acetone); ^{1}H NMR (DMSO-d_6) δ 1.05 (d, 6H), 1.95–2.20 (m, 4H), 2.35 (s, 3H), 3.00–3.35 (m, 9H), 3.45 (t, 2H), 3.55 (broad d, 2H), 3.90 (h, 1H), 6.95–7.00 (m, 2H), 7.30 (s, 1H), 7.35–7.65 (m, 5H). Anal. ($C_{28}H_{35}FN_4O$·oxalate·hemihydrate) C, H, N.

1-[2-[4-[1-(3-Fluorophenyl)-6-methyl-1*H*-indol-3-yl]-1-piperidinyl]ethyl]-3-(2-propyl)-2-imidazolidinone oxalate hemihydrate (6d): mp 133–135 °C (acetone); ^{1}H NMR (DMSO-d_6) δ 1.05 (d, 6H), 1.95–2.20 (m, 4H), 2.40 (s, 3H), 3.00–3.35 (m, 9H), 3.45 (t, 2H), 3.55 (broad d, 2H), 3.90 (h, 1H), 7.00 (d, 1H), 7.20 (dt, 1H), 7.40–7.50 (m, 4H), 7.55–7.65 (m, 2H). Anal. ($C_{25}H_{35}FN_4O$·oxalate·hemihydrate) C, H, N.

1-[2-[4-[6-Methyl-1-[3-(trifluoromethyl)phenyl]-1*H*-indol-3-yl]-1-piperidinyl]ethyl]-3-(2-propyl)-2-imidazolidinone oxalate hemihydrate (6e): mp 97 °C (acetone); ^{1}H NMR (DMSO-d_6) δ 1.05 (d, 6H), 2.05 (dq, 2H), 2.20 (broad d, 2H), 2.40 (s, 3H), 3.00–3.10 (m, 3H), 3.10–3.35 (m, 6H), 3.45 (t, 2H), 3.55 (broad d, 2H), 3.95 (h, 1H), 7.00 (d, 1H), 7.35 (s, 1H), 7.50 (s, 1H), 7.65 (d, 1H), 7.70 (broad d, 1H), 7.80 (t, 1H), 7.85 (broad s, 1H), 7.90 (broad d, 1H). Anal. ($C_{29}H_{35}F_3N_4O$·oxalate·hemihydrate) C, H, N.

1-[2-[4-(6-Chloro-1-phenyl-1*H*-indol-3-yl)-1-piperidinyl]ethyl]-3-(2-propyl)-2-imidazolidinone (6f): mp 100 °C (di-2-propyl ether/diethyl ether, 1:1); ^{1}H NMR ($CDCl_3$) δ 1.15 (d, 6H), 1.85 (dq, 2H), 2.10 (broad d, 2H), 2.20 (dt, 2H), 2.60 (t, 2H), 2.85 (tt, 1H), 3.10 (broad d, 2H), 3.20–3.30 (m, 2H), 3.35–3.45 (m, 4H), 4.15 (h, 1H), 7.05–7.10 (m, 2H), 7.30–7.40 (m, 1H), 7.40–7.55 (m, 5H), 7.60 (d, 1H). Anal. ($C_{27}H_{33}ClN_4O$) C, H, N.

1-[2-[4-[6-Chloro-1-(2-fluorophenyl)-1*H*-indol-3-yl]-1-piperidinyl]ethyl]-3-(2-propyl)-2-imidazolidinone oxalate (6g): mp 106–109 °C (acetone); ^{1}H NMR (DMSO-d_6) δ 1.05 (d, 6H), 2.00–2.30 (m, 4H), 3.10–3.40 (m, 9H), 3.55 (t, 2H), 3.65 (broad d, 2H), 3.90 (h, 1H), 7.15–7.20 (m, 2H), 7.35–7.55 (m, 4H), 7.55 (t, 1H), 7.85 (d, 1H), 10.90 (broad s, 3H). Anal. ($C_{27}H_{32}ClFN_4O$·1.5 oxalate) C, H, N.

General Procedure for the Synthesis of Urea Derivatives 7 (Table II). Intermediate 6-substituted 1-(4-fluorophenyl)-3-(4-piperidinyl)-1*H*-indoles were prepared as shown above for the preparation of compounds **4**.

6-Chloro-1-(4-fluorophenyl)-3-[1-[2-(1,3-dimethyl-1-ureido)ethyl]-4-piperidinyl]-1*H*-indole (7a). Intermediate 6-chloro-1-(4-fluorophenyl)-3-(4-piperidinyl)-1*H*-indole was prepared according to the method above and purified as the hemifumarate salt: mp 221 °C; ^{1}H NMR (DMSO-d_6) δ 1.85 (dq, 2H), 2.05 (broad d, 2H), 2.85 (dt, 2H), 3.05 (tt, 1H), 3.25 (broad d, 2H), 6.45 (s, 1H), ~6.80 (broad s, 2H), 7.15 (dd, 1H), 7.35–7.45 (m, 4H), 7.55–7.60 (m, 2H), 7.70 (d, 1H). To a solution of the free base (75 g, 0.23 mol) (liberated from an aqueous solution of the fumarate salt by addition of diluted NaOH solution and extracted and isolated according to the standard procedure above) in NMP (500 mL) was added triethylamine (30 mL). Chloroacetonitrile (17 g, 0.23 mol) was added dropwise during 15 min. The mixture was heated at 60–70 °C for 2 h and was subsequently poured onto ice (2 kg). The precipitated 1-[4-[6-chloro-1-(4-fluorophenyl)-1*H*-indol-3-yl]-1-piperidinyl]acetonitrile was filtered off and dried, yield 84 g (100%). An analytical sample was recrystallized from 2-propyl ether: mp 163–164 °C; ^{1}H NMR ($CDCl_3$) δ 1.85 (dq, 2H), 2.15 (broad d, 2H), 2.55 (dt, 2H), 2.85 (tt, 1H), 2.90 (broad d, 2H), 3.60 (s, 2H), 7.05 (s, 1H), 7.10 (dd, 1H), 7.10–7.20 (m, 2H), 7.35–7.45 (m, 3H), 7.55 (d, 1H). To a suspension of lithium aluminum hydride (12.5 g, 0.33 mol) in dry ether (250 mL) cooled to 0 °C was added dropwise a solution of $AlCl_3$ (12.5 g, 0.094 mol) in dry ether (250 mL). To the resulting solution of AlH_3 was added dropwise a solution of the above prepared acetonitrile (35 g, 0.095 mol) in dry tetrahydrofuran (THF) at 10–15 °C during 40 min. The mixture was refluxed for 1.5 h. After cooling to 10 °C, concentrated NaOH was cautiously added to hydrolyze excess AlH_3 and organoaluminum intermediates. Inorganic salts were filtered off and the filtercake thoroughly extracted with dichloromethane. The combined solutions were dried (anhydrous $MgSO_4$) and finally worked up as above leaving 27 g (76%) of the crude 2-[4-[6-chloro-1-(4-fluorophenyl)-1*H*-indol-3-yl]-1-piperidinyl]ethylamine as an oil: ^{1}H NMR ($CDCl_3$) δ 1.45 (broad s, 2H), 1.85 (dq, 2H), 2.05 (broad d, 2H), 2.20 (t, 2H), 2.45 (t, 2H), 2.75–2.90 (m, 3H), 3.00 (broad d, 2H), 7.05 (s, 1H), 7.15 (dd, 2H), 7.15–7.25 (m, 2H), 7.35–7.45 (m, 3H), 7.55 (d, 1H). To the thus isolated crude primary amine (27 g, 0.073 mol) in dichloromethane (200 mL) was added triethylamine (15 mL). The solution was cooled to 5 °C and a solution of ethyl chloroformate (9 mL) in dichloromethane (15 mL) was added dropwise below 10 °C. The mixture was finally stirred for another 1 h at room temperature. Water (500 mL) was added, and the organic phase was separated and worked up according to the standard procedure above leaving the crude ethyl *N*-[2-[4-[6-chloro-1-(4-fluorophenyl)-1*H*-indol-3-yl]-1-piperidinyl]ethyl]carbamate as an oil (30.5 g, 95%): ^{1}H NMR ($CDCl_3$) δ 1.30 (t, 3H), 1.80 (dq, 2H), 2.05 (broad d, 2H), 2.15 (dt, 2H), 2.55 (t, 2H), 2.85 (tt, 1H), 3.05 (broad d, 2H), 3.25–3.35 (m, 2H), 4.15 (q, 2H), 5.20

(broad s, 1H), 7.05 (s, 1H), 7.10 (dd, 1H), 7.15–7.25 (m, 2H), 7.35–7.45 (m, 3H), 7.55 (d, 1H). All of the thus isolated oil was dissolved in dry THF (200 mL) and added dropwise to a suspension of lithium aluminum hydride (15 g) in dry THF (500 mL). The mixture was refluxed for 1.5 h and ice-cooled, and excess lithium aluminum hydride was destroyed by cautiously adding 4 M NaOH solution (15 mL). Inorganic salts were filtered off, and the filtercake was extracted with dichloromethane. The combined organic extracts were evaporated leaving crude 6-chloro-1-(4-fluorophenyl)-3-[1-[2-(*N*-methylamino)ethyl]-4-piperidinyl]-1*H*-indole as an oil (25.5 g, 96%): ^{1}H NMR ($CDCl_3$) δ 1.85 (dq, 2H), 2.05 (broad d, 2H), 2.15 (t, 2H), 2.50 (s, 3H), 2.60 (t, 2H), 2.80 (t, 2H), 2.85 (tt, 1H), 3.05 (broad d, 2H), 3.40 (s, 1H), 7.05 (s, 1H), 7.10 (dd, 1H), 7.15–7.25 (m, 2H), 7.35–7.45 (m, 3H), 7.55 (d, 1H). A solution of the crude methylamine derivative (3.3 g, 0.0085 mol) in dichloromethane was cooled to 5 °C, and 2 mL of methyl isocyanate was added. The mixture was stirred at room temperature for 2 h. After evaporation of volatile compounds, the crude title compound **7a** was purified by HPLC. Elution with a mixture of ethyl acetate/ethanol/triethylamine 80:20:4 afforded 1.2 g (32%) of pure **7a**. An analytical sample was crystallized from a 1:1 mixture of diethyl ether and di-2-propyl ether: mp 106 °C; ^{1}H NMR ($CDCl_3$) δ 1.75 (dq, 2H), 2.10 (broad d, 2H), 2.30 (dt, 2H), 2.55 (t, 2H), 2.75 (d, 3H), 2.85 (tt, 1H), 2.90 (s, 3H), 3.05 (broad d, 2H), 3.35 (t, 2H), 6.75 (broad s, 1H), 7.00 (s, 1H), 7.15 (dd, 1H), 7.15–7.25 (m, 2H), 7.35–7.45 (m, 3H), 7.60 (d, 1H). Anal. ($C_{24}H_{28}ClFN_4O$) C, H, N.

We have furthermore in a corresponding way prepared the following urea derivatives **7**:

6-Chloro-1-(4-fluorophenyl)-3-[1-[2-[1-methyl-3-(2-propyl)-1-ureido]ethyl]-4-piperidinyl]-1*H*-indole (7b): mp 127 °C (di-2-propyl ether); ^{1}H NMR ($CDCl_3$) δ 1.15 (d, 6H), 1.80 (dq, 2H), 2.10 (broad d, 2H), 2.25 (dt, 2H), 2.55 (t, 2H), 2.85 (tt, 1H), 2.90 (s, 3H), 3.10 (broad d, 2H), 3.30 (t, 2H), 3.90 (h, 1H), 6.05 (broad d, 1H), 7.00 (s, 1H), 7.10 (dd, 1H), 7.15–7.25 (m, 2H), 7.35–7.40 (m, 3H), 7.55 (d, 1H). Anal. ($C_{29}H_{32}ClFN_4O$) C, H, N.

6-Chloro-1-(4-fluorophenyl)-3-[1-[2-(3,3-dimethyl-1-ureido)ethyl]-4-piperidinyl]-1*H*-indole hydrochloride hemihydrate (7c): mp 115–116 °C (acetone); ^{1}H NMR (DMSO-d_6) δ 2.10–2.35 (m, 4H), 2.85 (s, 6H), 3.05–3.50 (m, 7H), 3.65 (broad d, 2H), 6.90 (broad s, 1H), 7.20 (dd, 1H), 7.35–7.45 (m, 3H), 7.50 (s, 1H), 7.55–7.65 (m, 2H), 7.90 (d, 1H). Anal. ($C_{24}H_{28}ClFN_4O$·HCl·hemihydrate) C, H, N.

1-(4-Fluorophenyl)-3-[1-[2-(3,3-dimethyl-1-ureido)ethyl]-4-piperidinyl]-6-methyl-1*H*-indole 1.5-oxalate hemihydrate (7d): mp 161 °C (acetone); ^{1}H NMR (DMSO-d_6) δ 1.95–2.30 (m, 4H), 2.40 (s, 3H), 2.80 (s, 6H), 3.05–3.25 (m, 5H), 3.40–3.50 (m, 2H), 3.55–3.65 (m, 2H), 6.70 (broad t, 1H), 6.95 (d, 1H), 7.30 (s, 1H), 7.35–7.45 (m, 3H), 7.55–7.65 (m, 3H). Anal. ($C_{25}H_{30}FN_4O$·1.5-oxalate·hemihydrate) C, H, N.

1-(4-Fluorophenyl)-6-methyl-3-[1-[2-[3-(2-propyl)-1-ureido]ethyl]-4-piperidinyl]-1*H*-indole (7e): mp 173–174 °C (diethyl ether); ^{1}H NMR ($CDCl_3$) δ 1.15 (d, 6 H), 1.85 (dq, 2H), 2.10–2.30 (m, 4H), 2.40 (s, 3H), 2.55 (t, 2H), 2.85 (tt, 1H), 3.05 (broad d, 2H), 3.25 (q, 2H), 3.85 (h, 1H), 4.70 (broad d, 1H), 4.90 (broad t, 1H), 6.95 (s, 1H), 7.00 (dd, 1H), 7.15–7.30 (m, 3H), 7.40–7.50 (m, 2H), 7.55 (d, 1H). Anal. ($C_{26}H_{33}FN_4O$) C, H, N.

1-[2-[4-[1-(4-Fluorophenyl)-2-methyl-1*H*-indol-3-yl]-1,2,3,6-tetrahydropyridin-1-yl]ethyl]-2-imidazolidinone (12). A solution of indole-2-carboxylic acid (50 g, 0.31 mol), 4-fluoroiodobenzene (90 g, 0.41 mol), potassium hydroxide (40 g, 0.71 mol), and CuO (12 g, 0.15 mol) in dimethylformamide (DMF) (600 mL) was heated at reflux. Water/DMF were distilled off until the temperature had reached 148 °C. Reflux was continued for another 6 h. After cooling to room temperature diethyl ether (500 mL) was added and the precipitated salts were filtered off and subsequently dissolved in water (1 L). By addition of diluted HCL, pH was adjusted to 2. 1-(4-Fluorophenyl)-1*H*-indole-2-carboxylic acid (**8**) was worked up by extraction with ethyl acetate according to the standard procedure above: yield 41 g (52%); mp 213 °C; ^{1}H NMR (DMSO-d_6) δ 6.95 (d, 1H), 7.20 (t, 1H), 7.30 (t, 1H), 7.30–7.50 (m, 5H), 7.75 (d, 1H), 13.00 (broad s, 1H). To a suspension of lithium aluminum hydride (7.5 g, 0.20 mol) in dry THF (150 mL) was added dropwise a solution of the carboxylic acid **8** (38 g, 0.15 mol) in dry THF (200 mL) at gentle reflux. Refluxing was continued for another 1.5 h. The mixture was ice-cooled and excess lithium aluminum hydride was destroyed by carefully adding aqueous 4 M NaOH solution. Inorganic salts were filtered off, the filtercake was thoroughly extracted with dichloromethane, and the combined organic phases were evaporated in vacuo. The thus isolated 1-(4-fluorophenyl)-2-(hydroxymethyl)-1*H*-indole (**9**) was recrystallized from a mixture of di-2-propyl ether and heptane 1:1, yielding 32 g (87%) of pure **9**: mp 65–66 °C; ^{1}H NMR ($CDCl_3$) δ 1.90 (broad s, 1H), 4.50 (s, 2H), 6.55 (s, 1H), 7.05–7.20 (m, 5H), 7.30–7.40 (m, 2H), 7.60 (d, 1H). To a solution of **9** (32 g, 0.13 mol) in ethanol (600 mL) was added 5% palladium on carbon (50% H_2O) (15 g). Catalytic hydrogenation at 2–3 atm was continued for 20 h in a Parr apparatus. The catalyst was finally filtered off and ethanol evaporated in vacuo. The remaining oil was purified by filtering through SiO_2 (eluted with dichloromethane/heptane 1:1). After evaporation of the solvents, 18 g (62%) of 1-(4-fluorophenyl)-2-methyl-1*H*-indole (**10**) was obtained. A crystalline sample precipitated from heptane: mp 43 °C; ^{1}H NMR ($CDCl_3$) δ 2.25 (s, 3H), 6.40 (s, 1H), 7.00–7.30 (m, 7H), 7.55 (dd, 1H). To a solution of 4-piperidone hydrochloride hydrate (30 g, 0.20 mol) in a mixture of trifluoroacetic acid (150 mL) and acetic acid (75 mL) under N_2 and at gentle reflux was added dropwise a solution of the 2-methylindole (**10**) (9 g, 0.040 mol) in acetic acid (75 mL) during 40 min. The mixture was refluxed for another 50 min. Excess volatile acids were evaporated in vacuo. Water (500 mL) was added and pH adjusted to >9 by addition of diluted aqueous NH_4OH. 1-(4-Fluorophenyl)-2-methyl-3-(1,2,3,6-tetrahydro-4-pyridinyl)-1*H*-indole (**11**) was extracted with ethyl acetate and worked up according to the standard procedure above. The yield of crude **11** was 12 g (98%), which was used without further purification. To a solution of **11** (6 g, 0.020 mol) in MIBK (80 mL) were added 1-(2-chloroethyl)-2-imidazolidinone (5 g, 0.034 mol), finely powdered anhydrous K_2CO_3 (3.5 g, 0.025 mol), and KI (0.4 g). The mixture was refluxed for 16 h. Inorganic salts were filtered off, and MIBK was evaporated in vacuo. The title compound **12** was purified by column chromatography on SiO_2 (eluted with ethyl acetate/ethanol/triethylamine 80:20:4): yield 4.1 g (49$); mp 172–177 °C; ^{1}H NMR ($CDCl_3$) δ 2.25 (s, 3H), 2.60–2.65 (m, 2H), 2.70 (t, 2H), 2.80 (t, 2H), 3.30 (q, 2H), 3.40–3.50 (m, 4H), 3.55–3.60 (m, 2H), 4.55 (s, 1H), 5.75 (broad s, 1H), 6.95–7.15 (m, 3H), 7.20–7.40 (m, 4H), 7.55–7.60 (m, 1H). Anal. ($C_{25}H_{27}FN_4O$) C, H, N.

1-[2-[4-[1-(4-Fluorophenyl)-2-methyl-1*H*-indol-3-yl]-1-piperidinyl]ethyl]-2-imidazolidinone (13). To a solution of compound **12** (2.3 g, 0.0055 mol) in acetic acid (120 mL) was added PtO_2 (0.2 g). The mixture was hydrogenated in a Parr apparatus at 3 atm for 39 h. The catalyst was filtered off, and most of the acetic acid was evaporated in vacuo. To the remaining oil was added water (200 mL), and pH was adjusted to >9 by addition of diluted aqueous NH_4OH. The title compound **13** was worked up according to the standard procedure above. A crystalline product was obtained from diethyl ether: yield 1.8 g (78%); mp 182 °C; ^{1}H NMR ($CDCl_3$) δ 1.71 (broad d, 2H), 2.15–2.40 (m, 4H), 2.20 (s, 3H), 2.55 (t, 2H), 2.80 (tt, 1H), 3.10 (broad d, 2H), 3.35–3.45 (m, 4H), 3.50–3.60 (m, 2H), 4.75 (s, 1H), 6.95–7.10 (m, 3H), 7.10–7.30 (m, 4H), 7.75–7.80 (m, 1H). Anal. ($C_{25}H_{29}FN_4O$) C, H, N.

Pharmacological Test Methods. Animals. Male Wistar rats (Mol:Wist, SPF, 170–270 g) and male mice (NMRI/BOM,-SPF 16–18 g) were used. We have recently described the handling procedures in details.[4]

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.[19] 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 heat 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.[27] 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).

Inhibition of Isolation-Induced Aggression in Mice. The test method is a modified version of the method described by McMillen et al.[29] Mice were kept isolated for 3 weeks in macrolon type II cages. After the isolation period the mice were trained to attack a nonaggressive intruder mouse of the same strain. The nonaggressive mice were housed in groups of 20 in plastic cages. An attack was defined as biting or as an attempt to bite the intruder mouse. Only mice with attack latencies of less than 25 s were included in the pharmacological studies. The animals were pretested immediately before drug treatment and 2 h after sc administration of test substance. The maximum observation time was 180 s. At least eight aggressive mice were tested per dose. Results were stated as fractions of mice with attack latencies greater than or equal to threshold values of 180 s or 90 s.

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.[30]

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.[30]

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.[31]

Molecular Mechanics Calculations. Conformational energies and energy-minimized geometries were calculated using the molecular mechanics program MM2(91) developed by Allinger and coworkers.[32] In addition to standard force field parameters the following constants were selected by analogy: the V2 term of the torsional force constant for the N_{sp2}–C_{sp2}–C_{sp2}–C_{sp3} (type 40-2-2-1) and the C_{sp2}–N_{sp2}–C_{sp2}–C_{sp3} (type 2-40-2-1) were set to 15.0 and the V1 and V3 terms to 0.0. In the case of the N_{sp2}–C_{sp2}–C_{sp3}–H (type 40-2-1-5), V3 was set to −0.24 and the V1 and V2 terms to 0.0. K_b and θ for the N_{sp2}–C_{sp2}–C_{sp3} (type 40-2-1) angle were set to 0.55 and 121.4, respectively. The energy calculations were done on the unprotonated amine including the lone pair on the basic nitrogen atom.

Acknowledgment. We are very grateful to Dr. Klaus Gundertofte, who provided force field parameters for the MM2 calculations. We acknowledge the very skillful technical assistance of E. Beicker Olsen and J. W. Stenberg for the syntheses of compounds. The preparation of this manuscript by Mrs. S. Henriksen is highly appreciated. Finally, we thank all from the staff of the Lundbeck Research Departments, who have contributed to the fulfilment of the present study.

(29) McMillen, B. A.; DaVanzo, E. A.; Scott, S. M.; Song, A. H. N-Alkyl Substituted Aryl-Piperazine Drugs: Relationship Between Affinity for Serotonin Receptors and Inhibition of Aggression. *Drug Dev. Res.* 1988, *12*, 53–62.

(30) Hyttel, J. Age-Related Decrease in the Density of Dopamine D_1 and D_2 Receptors in Corpus Striatum of Rats. *J. Pharmacol. Toxicol.* 1987, *61*, 126–129.

(31) Skarsfeldt, T.; Hyttel, J. The St 587-Induced Flexor Reflex in Pithed Rats: A Model to Evaluate Central α_1-receptor Blocking Properties. *Eur. J. Pharmacol.* 1986, *125*, 333–340.

(32) Burkert, U.; Allinger, N. L. *Molecular Mechanics*; American Chemical Society: Washington, DC, 1982.