σ Ligands with Subnanomolar Affinity and Preference for the σ_2 Binding Site. 1. 3-(ω-Aminoalkyl)-1*H*-indoles

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A series of 4-(1*H*-indol-3-yl)-1-butyl-substituted 4-phenylpiperidines, 4-phenyl-1,2,3,6-tetrahydropyridines, and 4-phenylpiperazines was synthesized. The phenyl group was optionally substituted with 4-fluoro or 2-methoxy substituents. High affinity for both σ_1 and σ_2 binding sites was achieved with these compounds. Additionally, these compounds had relatively high affinity for serotonin 5-HT_{1A} and 5-HT_{2A}, dopamine D_2, and adrenergic α_1 receptors. Introduction of a 4-fluorophenyl substituent at the indole nitrogen atom rendered very selective σ_2 ligands with subnanomolar affinity for the σ_2 binding site. The prototype of such a compound was 1-(4-fluorophenyl)-3-[4-[4-(4-fluorophenyl)-1-piperidinyl]-1-butyl]-1*H*-indole, **11a** (code no. Lu 29-253). This compound had the following binding affinities: IC_{50} (σ_1) = 16 nM, IC_{50} (σ_2) = 0.27 nM, IC_{50} (5-HT_{1A}) = 22 000 nM, IC_{50} (5-HT_{2A}) = 270 nM, IC_{50} (D_2) = 4200 nM, IC_{50} (α_1) = 220 nM. Spiro-joining of the phenyl and the piperidine rings into a spiro[isobenzofuran-1(3*H*),4′-piperidine] ring system resulted in even more selective compounds. Variations of the 1-substituent at the indole and of the chain length of the alkylene spacer group were studied. The optimal compound was the spiro analogue of compound **11a**. This compound is 1′-[4-[1-(4-fluorophenyl)-1*H*-indol-3-yl]-1-butyl]spiro[isobenzofuran-1(3*H*),4′-piperidine], **14f** (code no. Lu 28-179), with the binding affinities: IC_{50} (σ_1) = 17 nM, IC_{50} (σ_2) = 0.12 nM, IC_{50} (5-HT_{1A}) = 21 000 nM, IC_{50} (5-HT_{2A}) = 2000 nM, IC_{50} (D_2) = 800 nM, IC_{50} (α_1) = 330 nM. However, the most selective σ_2 versus σ_1 ligand was the tropane derivative 1-(4-fluorophenyl)-3-[4-[3-(4-fluorophenyl)-8-azabicyclo[3.2.1]oct-2-en-8-yl]-1-butyl]-1*H*-indole, **15a**. This compound had the following binding affinitites: IC_{50} (σ_1) = 1200 nM, IC_{50} (σ_2) = 2.5 nM. Potent anxiolytic activity in the black/white box exploration test in rats was found with the two most prominent σ_2 ligands Lu 29-253 and Lu 28-179. Good penetration into the CNS was documented both after subcutaneous and peroral administration of Lu 28-179 by ex vivo binding studies. Long duration of action was demonstrated both in ex vivo binding ($T_{1/2} \sim 20$ h) and in the black/white box exploration test.

Introduction

Focus on development of very potent and selective σ ligands has been intensified during recent years. Recognition of σ binding sites was originally based on the finding that benzomorphans, such as SK&F 10,047 and pentazocine, had additional binding to non-opiate receptors[1,2] and on the clinical observation of psychomimetic side effects of these compounds.[3] The existence of at least two distinct σ binding sites denoted σ_1 and σ_2 has recently become evident.[4,5] The (+)-enantiomers of opiate ligands, such as (+)-pentazocine (**1**), specifically label the σ_1 binding site, while, until now, no highly selective σ_2 ligand has been available. (−)-Pentazocine is a mixed σ_1/σ_2 ligand of moderate affinity. Efforts have mainly been addressed to the design and synthesis of selective σ_1 ligands, although some attempts to elucidate the structural elements that determine σ_2 preference were reported.[6,7] Quite recently, some (+)-isomers of certain 5-phenylmorphane derivatives were reported to exhibit high affinity and selectivity for the σ_2 binding site. However, these compounds also seem to exhibit high affinity for opiate μ receptors.[8] It must be emphasized that interpretation of σ_1/σ_2 selectivity from results dated more than 2−3 years back is often quite confusing. Binding assays at that time were generally nonselective, both regarding radioligands and the biological tissue applied. As the characterization of the subtypes of binding sites generally only involves ligand binding with no indication of functionality, it has been suggested that the term receptors should be avoided.[4] The role of the different σ binding sites in psychiatric conditions still remains speculative. At a very early stage rimcazole (**2**), which is a weak but rather selective σ ligand,[9] was tested in the clinic in schizophrenic patients. Though some limited but promising results from these early phase II studies have been published,[10,11] the clinical development was discontinued by Burroughs-Wellcome. (+)-Pentazocine was reported to have anxiogenic properties while the opposite enantiomer induced relaxation in humans.[12] In rats both (+)-pentazocine and 1,3-di(2-tolyl)guanidine (DTG) were anxiogenic.[13] Newer and more potent, but also unselective, σ ligands, such as BMY 14802 (**3**)[14] and DuP 734 (**4**),[15,16] were predicted to have antipsychotic potential from animal experiments. Both of these compounds have proceeded to clinical trials.

Some years ago, during the development of low-efficacy serotonin 5-HT_{1A} agonists,[17,18] we found that within a series of 1-[4-(1*H*-indol-3-yl)-1-butyl]-4-arylpiperazines and corresponding indoline derivatives **7** some of the indole derivatives were quite potent σ ligands as well. We became interested in exploring the possibilities of developing selective high-affinity σ ligands based on this series of compounds. The antipsychotic butyrophenone derivative haloperidol (**5**) is a potent σ ligand

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Table 1. Structures and σ Binding Affinities of 4-Phenylpiperidines and 1-Phenylpiperazines[a]

compd	X	Y	σ binding affinities[b] (IC_{50} values, nM) [^{3}H]-(+)-pentazocine (σ_1)	[^{3}H]DTG (σ_2)	σ_1/σ_2
9a	N	2-OCH_3	14.	21.	0.67
9b	CH	2-OCH_3	4.5	3.3	1.4
9c	N	4-F	5.6	1.3	4.3
9d	CH	H	1.5	0.48	3.1
9e	CH	4-F	1.4	4.0	0.35
9f	C=	4-F	7.5	2.3	3.3
11a	CH	4-F	16.	0.27	59.
11b	N	4-F	440.	7.5	59.
11c	CH	H	44.	0.44	100.
11d	N	H	27.	0.69	39.
15a[c]			1200.	2.5	480.
DTG			36.	52.	0.69
1 (+)-pentazocine			3.0	2100.	0.0014
(−)-pentazocine			8.9	29.	0.31
2 rimcazole			690.	180.	3.8
3 BMY 14802			60.	230.	0.26
4 DuP 734			2.6	23.	0.11
5 haloperidol			0.65	17.	0.038
6 L-687,384			0.26	12.	0.021

[a] Structures **9** and **11** refer to Scheme 1. Structures of reference compounds are shown in Figure 1. [b] Results are expressed as IC_{50} values (nM) and are the logarithmic mean of at least two, or, in the case of the σ_2 binding, three determinations. Two full (in the case of σ_2, three 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 n drugs. In cases of ratios greater than 2 × sd (95% confidence interval), extra determinations were performed and outliers were discarded. The following sd ratios were obtained: σ_1 1.8 (n = 74); σ_2 2.3 (n = 100). [c] See Chart 1 for structure.

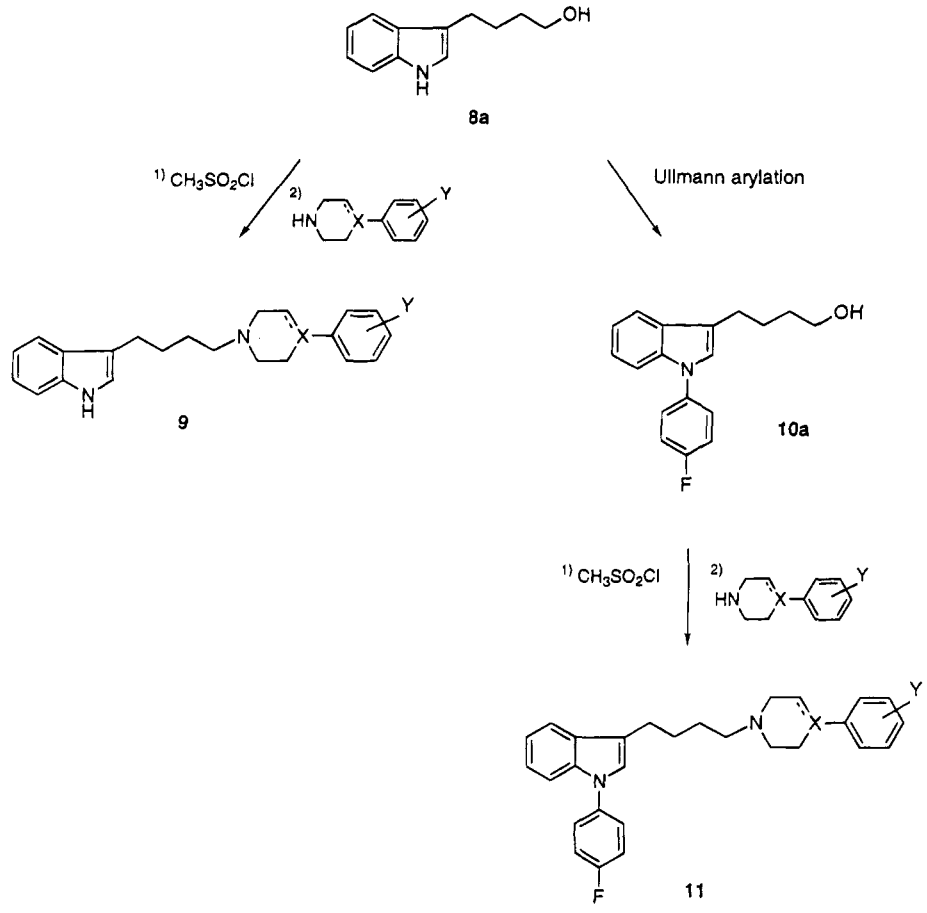
with preference for σ_1 binding sites. However, **5** also blocks classical receptors, especially dopamine D_2 receptors. Many attempts have been made recently to extract the σ pharmacophore of **5** in close analogues, and thus retain σ binding and eliminate interaction with dopamine receptors.[19-22] Compound **3** is actually an example of a haloperidol derivative that has lost affinity for D_2 receptors. Also in our original series of 4-(1*H*-indol-3-yl)-1-butylpiperazines[17,18] with 5-HT_{1A} serotonergic activity, some structural features, such as C-4, chain length, and terminal aryl groups, are common to **5**. As the 1-(2-methoxyphenyl)piperazine moiety is a well-established 5-HT_{1A} pharmacophore, it would be interesting to remove the 2-alkoxy substituent and to replace the piperazine ring with a piperidine ring as in **5**. In this report and in the succeeding part 2, we present further structural investigations. In this paper substituents at the indole nitrogen atom, spiro-joining of the piperidine and the phenyl rings to a spiro-[isobenzofuran-1(3*H*),4'-piperidine] ring system, and variation of length of the interspacing alkylene chain are studied. In part 2 the spiropiperidine system as well as substituents in the benzene part of these sytems are varied, and replacement of the indoloalkyl side chain with more simple alkyl or phenylalkyl side chains is studied. The purpose of this project was to develop selective σ ligands, especially aiming at σ_2 selectivity.

Chemistry

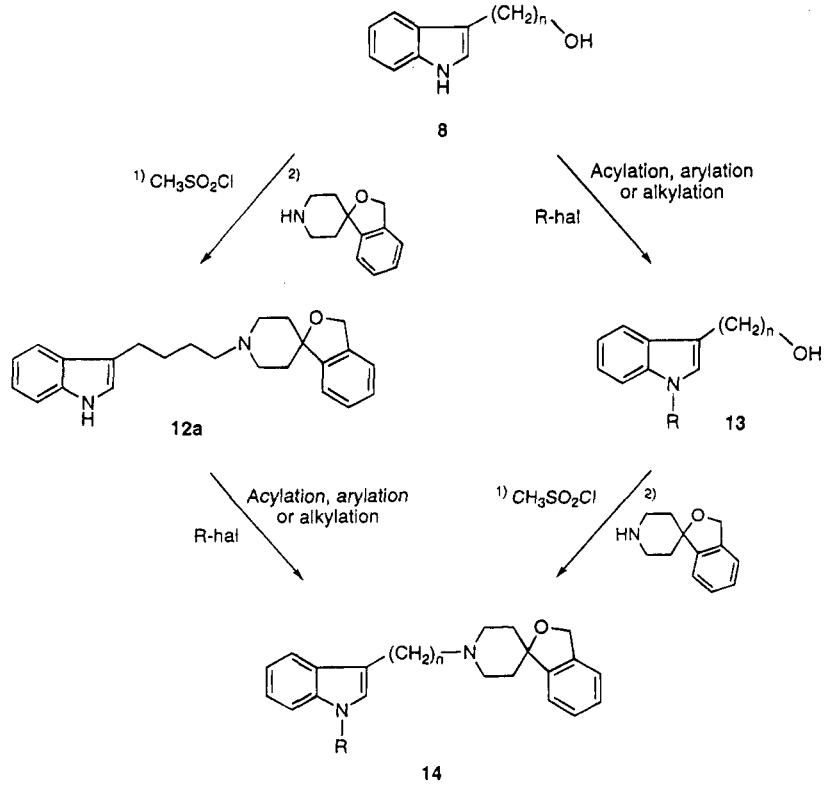
The synthesis of 3-[4-(4-phenyl-1-piperidinyl)-1-butyl]-1*H*-indole, **9d**, and 3-[4-[4-(4-fluorophenyl)-1-(1,2,3,6-tetrahydro)pyridinyl]-1-butyl]-1*H*-indole, **9f** (Table 1), has been reported by Böttcher et al. in a study of dopaminergic activity of 3-(1,2,3,6-tetrahydropyridylalkyl)indoles.[23] Commercially available 4-(1*H*-indol-3-yl)butanoic acid was coupled with N-unsubstituted 4-phenylpiperidines or 4-phenyl-1,2,3,6-tetrahydropyridines to the corresponding carboxamides by use of *N,N'*-carbonyldiimidazole as coupling agent. The amides were subsequently reduced with dihydrobis(methoxyethanato-*O,O'*)aluminate sodium. We have chosen a slightly different approach for the synthesis in order to minimize the number of synthetic steps after a suitable common intermediate. The methanesulfonate ester of 4-(1*H*-indol-3-yl)-1-butanol (Scheme 1) was prepared in large quantities and high yields by using a modified literature procedure of the synthesis of 4-(1*H*-indol-3-yl)-1-butanol, **8a**.[24] Properly substituted phenylpiperidines, phenyl-1,2,3,6-tetrahydropyridines, and phenylpiperazines were easily alkylated with the methanesulfonate ester to 1-unsubstituted indoles, **9**. The 1-(4-fluorophenyl)-substituted indoles, **11**, were prepared via Ullmann arylation of 4-(1*H*-indol-3-yl)-1-butanol, **8a**, with 4-fluoroiodobenzene to give 4-[1-(4-fluorophenyl)-1*H*-indol-3-yl]-1-butanol, **10a**. N-Alkylation of piperidines and piperazines was performed using as previously the methanesulfonate ester as a leaving group (Scheme 1). Alternatively, it is also possible to arylate indoles of structure **9** using the Ullmann procedure. A similar sequence is shown in Scheme 2 for the synthesis of spiro derivatives, **14a−14m**. Substituents Y in the phenyl ring and the constituents X of the basic 6-membered ring are indicated in Table 1.

In an early paper by Manallack et al.,[25] a planar σ pharmacophore was constructed with the basic nitrogen atom almost in the plane of a benzene ring with its center 5.06 Å away and with the nitrogen electron lone pair almost perpendicular to this plane. At the other end of the receptor, lipophilic substituents at the basic nitrogen atom implicated the presence of a lipophilic pocket as a secondary binding site. A contemporary 5-HT_{1A} receptor model[26,27] had a very similar arrangement of a benzene ring and a basic nitrogen atom 5.2−5.6 Å away from the center of the benzene ring and with the electron lone-pair pointing away from the plane of the benzene ring. These very similar models are a good rationale for the associated σ affinity of our series **7** of 5-HT_{1A} agonists. We wanted to challenge this model and force the benzene and the piperidine rings out of coplanarity in order to position the nitrogen electron

Scheme 1. Synthesis of 1-Unsubstituted (**9**) and 1-(4-Fluorophenyl)-Substituted (**11**) 3-[4-(4-Phenylpiperidin-1-yl)-1-butyl]-1*H*-indoles and Corresponding 1,2,3,6-Tetrahydropyridinyl and Piperazinyl Derivatives



Scheme 2. Synthesis of Spiro[isobenzofuran-1(3*H*),4'-piperidines] with 1-Unsubstituted (**12a**) and 1-Substituted ω-Alkyl-3-indole (**14**) Substituents at the Piperidine Nitrogen Atom



lone pair in the plane of the benzene ring. One way of introducing such conformational restrictions on the benzene and the piperidine rings would be via a spiro-joined system such as the spiro[isobenzofuran-1(3*H*),4'-piperidine] in which the two rings are perpendicular to each other. The unsubstituted spiro-joined piperidine

Table 2. Structures and σ Binding Affinities of Spiro[isobenzofuran-1(3*H*),4′-piperidines] **12a** and **14**[a]

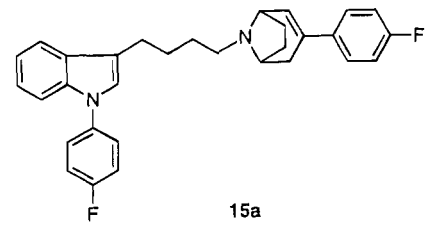
compd	n	R	σ binding affinities[b] (IC_{50} values, nM) [^{3}H]-(+)-pentazocine (σ_1)	[^{3}H]DTG (σ_2)	σ_1/σ_2
12a	4	H	2.5	0.41	6.1
14a	4	CH_3	2.1	0.30	7.0
14b	4	CH_3CO	5.7	0.21	27.
14c	4	CH_3SO_2	1.3	0.05	26.
14d	4	$CH_3C_6H_4SO_2$	10.	0.17	59.
14e	4	$C_6H_5CH_2$	5.2	0.48	11.
14f	4	4-F-C_6H_4	17.	0.12	140.
14g	3	4-F-C_6H_4	10.	2.8	3.6
14h	2	4-F-C_6H_4	15.	3.0	5.0
14i	1	4-F-C_6H_4	3.0	4.7	0.64
14j	4	2-thienyl	7.7	0.24	32.
14k	4	3-thienyl	7.0	0.25	28.
14l	4	2-thiazolyl	14.	0.19	74.
14m	4	4-pyridyl	14.	0.41	34.

[a] Structures refer to Scheme 2. [b] See footnote to Table 1.

had previously been synthesized by Marxer et al.[28] Alkylation of this spiropiperidine with the methanesulfonate ester of properly substituted 1*H*-indol-3-yl-ω-alkanols **8** or **13** is shown in Scheme 2. In the butyl series the effect of various substituents R at the indole nitrogen atom was studied. The majority of these substituents were most conveniently introduced on the common intermediate **12a** by acylation or Ullmann arylation procedures. Acylations were performed in the presence of tetrabutylammonium hydrogen sulphate as a phase-transfer catalyst. Heteroaryl substituents in compounds **14j−14m** were all introduced by arylating the 1-unsubstituted indole **12a** with the proper bromo heteroaromatic compound. As above, the butanol derivative **10a** was conveniently used to introduce the 4-[1-(4-fluorophenyl)-1*H*-indol-3-yl]-1-butyl substituent in compound **14f**. The 1-alkyl groups (methyl and benzyl) of the indoles **14a** and **14e** were introduced at an early stage in the syntheses by alkylation of potassium salts of 4-(1*H*-indol-3-yl)butanoic acid and 4-(1*H*-indol-3-yl)-1-butanol, respectively. Potassium *tert*-butoxide in DMF was used as base to generate the indole potassium salts. Variation of chain length of the alkylene spacer group from C-1 to C-4 was also studied. The 1-(4-fluorophenyl)-substituted derivatives were chosen for this study. The C-2 and C-3 (n = 2 and 3 in Scheme 2) derivatives **14h** and **14g** were prepared from 2-(1*H*-indol-3-yl)-1-ethanol and 3-(1*H*-indol-3-yl)-1-propanol, respectively. These procedures were analogous to the synthesis of the C-4 derivative **14f**. The preparation of the starting 3-indolo-ω-alcohols has previously been described.[24,29] We were not able to synthesize the methanesulfonate ester of 1-(4-fluorophenyl)-1*H*-indol-3-ylmethanol in order to obtain the C-1 derivative. As an alternative method indole-3-carboxaldehyde was arylated to give 1-(4-fluorophenyl)-1*H*-indole-3-carboxaldehyde. Reductive alkylation of spiro[isobenzofuran-1(3*H*),4′-piperidine] with this aldehyde in the presence of sodium cyanoborohydride and molecular sieves afforded the C-1 derivative **14i** in 28% yield. The substituents R at the indole nitrogen atom and the chain length n of the alkylene spacer group of the spiropiperidines are indicated in Table 2.

In order to investigate the influence of steric hindrance around the basic piperidine nitrogen atom, we synthesized the tropane analogue **15a** (Chart 1) of the

Chart 1. Structure of the Tropane Derivative **15a**



15a

4-(4-fluorophenyl)piperidine derivative **11a**. The 3-(4-fluorophenyl)-8-azabicyclo[3.2.1]oct-2-ene was prepared from 8-methyl-8-azabicyclo[3.2.1]octan-3-one by addition of (4-fluorophenyl)lithium, elimination of water, and removal of the 8-methyl group via carbamate formation. The corresponding procedure is described in detail in the Experimental Section for the synthesis of 4-(4-fluorophenyl)-1,2,3,6-tetrahydropyridine. Alkylation of 3-(4-fluorophenyl)-8-azabicyclo[3.2.1]oct-2-ene with the methanesulfonate ester of 4-[1-(4-fluorophenyl)-1*H*-indol-3-yl]-1-butanol proceeded smoothly to compound **15a**.

Results and Discussion

The pharmacological test models are described in detail in the Experimental Section. Binding affinities for the σ_1 and the σ_2 binding sites are reported in Tables 1 and 2 and compared to relevant reference compounds (structures, see Figure 1). [^{3}H]-(+)-Pentazocine was used as ligand for labeling σ_1 binding sites. [^{3}H]DTG labeling of whole rat brain homogenates, except cerebellum, was used to determine σ_2 binding affinities. It has been concluded that this assay is specific for determination of σ_2 binding affinities.[4,30] (+)-Pentazocine had only insignificant affinity (Table 1) and for a series of compounds identical binding data were obtained both with and without the presence of an excess of (+)-pentazocine in our [^{3}H]DTG binding assay. These data strongly support the σ_2 selectivity of our assay. Table 3 shows binding data for selected compounds to 5-HT_{1A} receptors and other receptors (D_2, 5-HT_{2A}, α_1) to which the reference compounds and our original series of arylpiperazines **7** with partial 5-HT_{1A} agonist properties were known to bind. The 1-(2-methoxyphenyl)piperazine derivative **9a** is a prototype of a compound from this original series. It is a rather weak ligand with equipotent affinity at both σ sites (Table 1), but it has high affinity for 5-HT_{1A} receptors, as previously reported.[18] Generally, **9a** possesses quite high affinity for all receptors measured (Table 3), especially noradrenergic α_1 adrenoceptors. Replacement of the piperazine ring with a piperidine ring (compound **9b**, Table 1) improved affinity to both σ sites. However, affinities for other receptors were only slightly weakened (Table 3). Removing the 2-methoxy substituent (compound **9d**) or replacing it with a 4-fluorine atom, as in the derivatives **9c**, **9e**, or **9f**, all resulted in potent σ ligands with almost equal affinity for both σ sites. The unsubstituted 4-phenylpiperidine **9d** was the most potent derivative with subnanomolar affinities. However, these compounds without substituents at the indole nitrogen atom also retained considerable affinity for the classical receptors, as indicated in Table 3. Compared to the reference compounds (Table 1), these derivatives were very potent and the σ_2 component was generally more predominant. All the reference compounds show preference for the σ_1 binding site except DTG, (−)-pent-

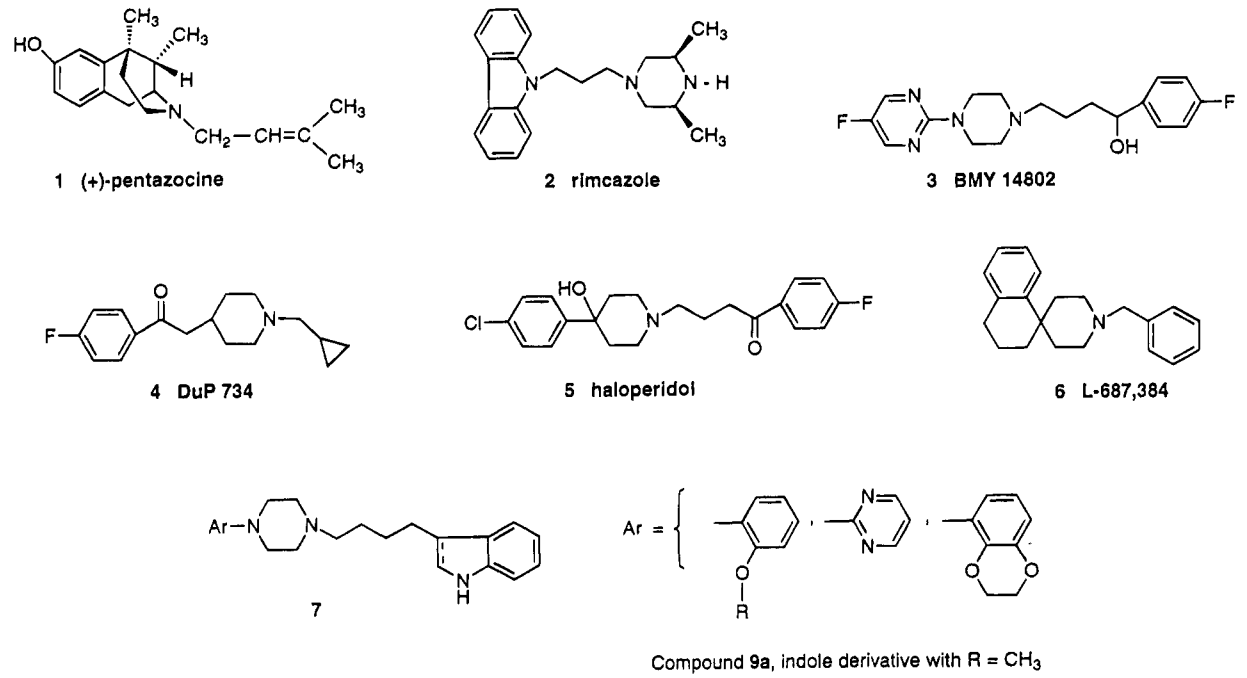


Figure 1. Reference and lead compounds.

Table 3. Selectivity of Selected σ Ligands and Reference Compounds

	binding affinities (IC_{50} values, nM)[a]			
compd	[^{3}H]-8-OHDPAT 5-HT_{1A}	[^{3}H]ketanserin 5-HT_{2A}	[^{3}H]spiroperidol D_2	[^{3}H]prazosine α_1
9a	17.	150.	15.	2.7
9b	56.	83.	20.	11.
9c	37.	14.	180.	12.
9d	110.	25.	45	14.
9e	27.	34.	160.	20.
9f	71.	27.	51.	24.
11a	22000.	270.	4200.	220.
11b	>10000	250.	3000.	420
12a	130.	360.	1300.	30.
14f	21000.	2000.	800.	330.
15a	>10000.	3700.	8000.	350.
3 BMY 14802	320.	830.	8400.	1500.
4 DuP 734	44000.	66.	640.	21.
5 haloperidol	3200.	55.	7.5	18.
6 L-687,384	>100000.	7100.	3700.	1000.

[a] Method for determination of IC_{50} values is described in footnote to Table 1. The following sd ratios were obtained: 5-HT_{1A} 1.4 (n = 100); D_2 1.7 (n = 38); α_1 1.4 (n = 44); 5-HT_{2A} 1.5 (n = 30).

azocine, and **2** that have equipotent but moderate to low affinities for both subtypes of σ sites (Table 1). The 4-phenacylpiperidine derivative **4** has additional binding to 5-HT_{2A} and α_1 receptors (Table 3). It has been reported that replacing the fluorine atom of **4** with a cyano group results in a more selective σ ligand.[15] The spirotetralin derivative from Merck, L-687,384 (**6**),[31] is a very potent and selective σ_1 ligand. Compound **3** is weak, and interaction with 5-HT_{1A} receptors (Table 3) cannot be ruled out as being responsible for its pharmacological properties.[32]

The next step was the introduction of a 4-fluorophenyl substituent at the indole nitrogen atom (compounds **11a–d**) that resulted in total elimination of the serotonin 5-HT_{1A} component (Table 3). Affinities for 5-HT_{2A}, D_2, and α_1 receptors were also considerably reduced, although less dramatically than 5-HT_{1A} receptor binding. Compounds **11a**, **11c**, and **11d** were very potent σ_2 ligands, while the piperazine derivative **11b** was less potent. Interestingly, all 1-(4-fluorophenyl)-substituted derivatives displayed pronounced preference for the σ_2 binding site with selectivity ratios of 40–100. The best ratios reported previously were below 10 and for compounds with much lower affinity for the receptor.[7]

All the spiropiperidines with a C-4 spacer chain had subnanomolar σ_2 binding affinities (Table 2), while shorter chain lengths (compounds **14g–i**) seem to reduce potency by a factor of about 10. Furthermore, all the spiropiperidines, except the C-1 derivative **14i**, show selectivity for σ_2 versus σ_1 binding sites. The 4-[1-(4-fluorophenyl)-1*H*-indol-3-yl]-1-butyl-substituted derivative **14f** was again the most selective σ_2 compound with a selectivity ratio of 140. As seen for the nonspiro derivatives, the 1-unsubstituted indole **12a** had considerable binding to the classical receptors (Table 3). These binding affinities were efficiently reduced by introduction of 1-substituents in the indole (compd **14f**, Table 3). Spirotetralin and spiroindan derivatives with high σ binding affinity have been synthesized by Chambers et al.[31] However, no indication of σ_1 or σ_2 preference were given for these series of compounds. [^{3}H]DTG labeling of guinea pig cerebellum was used for radioligand binding. Probably this assay measures both σ_1 and σ_2. As the compound 1′-benzyl-3,4-dihydrospiro-

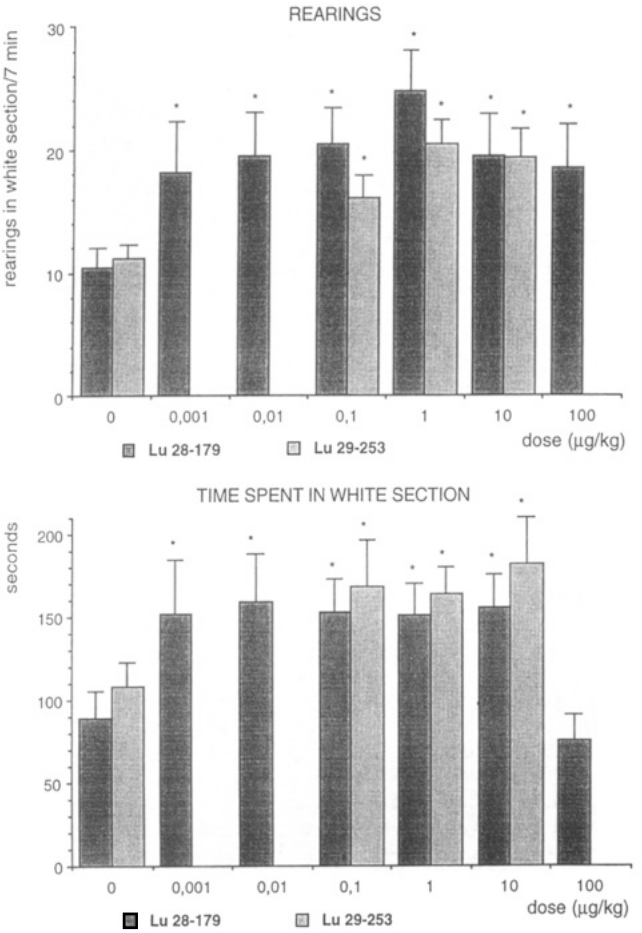


Figure 2. Effects of compounds **11a** and **14f** in the black/white exploration test in rats. Rearings in the white section is counted during a 7 min period, and the total time spent in the white section is measured. *p < 0.05 (one-way ANOVA, Dunnetts test) compared to control.

[naphthalene-1(2*H*),4′-piperidine] (**6**, L-687,384)[33] has been studied in some detail, we prepared and tested this spiro derivative. Surprisingly, **6** is a very potent and specific σ_1 ligand contrary to the indole derivatives within the present series. Given this result, one might speculate whether a benzylic type of substituents favor σ_1 affinity. Within our series we observed that the corresponding C-1 derivative **14i** was the most potent σ_1 ligand among homologous spiropiperidines (**14f–i**) and, contrary to all the other spiro derivatives, was equipotent for the two σ binding sites. The σ_1/σ_2 affinities and selectivities related to phenylalkyl chain lengths will be further discussed in part 2 of this series of articles.

Compounds **11a** (Lu 29-253) and **14f** (Lu 28-179) have been investigated further in various animal models predictive for anxiolytic activity. Exploratory behavior of rodents in a black and white, two-compartment test box is reduced in the brightly lit, white compartment and the animals spend more time exploring the dark compartment. Facilitation of the explorative behavior in the white compartment is suggested to reflect anxiolytic activity.[39] In the black/white box exploration test both compounds were active over a large dose range (Figure 2). The total time spent in the white compartment and the number of rearings in this compartment were both significantly increased.[34,35] The lowest effective dose tested for Lu 28-179 was 0.001 µg/kg, while Lu 29-253 was effective in doses at least from 0.1 µg/kg. Ex vivo ^{3}H-DTG binding in rats showed that Lu 28-179 has excellent CNS penetration with optimal effect about 3–6 h both after subcutaneous (3.0 µmol/kg) and peroral (3.0 µmol/kg) administration. A half-life of about 20 h in the CNS was also demonstrated by ex vivo binding measurements. The long half-life of this compound was also reflected in the black/white box exploration test, in which potent activity was still present 24 h after the administration.[36] Papers presenting the anxiolytic potential of Lu 28-179 in other test models are in preparation.[36] Compared to certain benzodiazepines, such as diazepam, the anxiolytic effect was more pronounced and no sedation was observed.

In conclusion, the present study has provided very potent σ ligands with a preference for the σ_2 binding site. IC_{50} values well below 1 nM were achieved for a majority of the compounds. Compound **15a** was the most selective σ_2 ligand, compared to its σ_1 affinity, with a ratio of about 500. However, compounds **11a** and **14f** were also very selective with selectivity ratios of 60 and 140, respectively. Compared to reference compounds these selectivities are quite outstanding. Selectivity with respect to a large number of receptors and transporter systems was also measured for these two compounds. No affinity of any significance (IC_{50} values > 100 nM) was found. Determination of intrinsic activity, i.e., the agonist/antagonist profile of the present series of compounds, still awaits proper biological methods. Whether the relaxation reported with (−)-pentazocine in humans is related to its σ_2 component can only be clarified by testing a more specific σ_2 ligand for anxiety in the clinic.

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 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, qui = quintet, h = heptet, dd = double doublet, dt = double triplet, dq = double quartet, tt = triplet of triplets, m = multiplet. NMR signals corresponding to acidic protons are generally omitted. 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 the indicated organic solvent from proper aqueous solutions, drying of combined organic extracts (anhydrous $MgSO_4$ or Na_2SO_4), filtering, and evaporation of the solvent in vacuo. For column chromatography, silica gel of type Kieselgel 60, 230–400 mesh ASTM, was used.

3-Indole-ω-alkanols (8). 4-(1*H*-Indol-3-yl)-1-butanol (**8a**) was prepared following a modification of a literature procedure.[24] Gaseous HCl was bubbled through a solution of 4-(1*H*-indol-3-yl)butanoic acid (100 g, 0.49 mol) in methanol (1 L) until saturation was achieved. The mixture was stirred at room temperature for 1.5 h. Methanol was evaporated in vacuo. The remaining oil was dissolved in diethyl ether (500 mL), washed with brine (2 × 100 mL), and dried (anhydrous $MgSO_4$). The solvent was evaporated leaving the indole-substituted butanoic acid methyl ester as a semisolid material: yield 103 g (96%). An analytical sample was recrystallized from *n*-heptane: mp 59–60 °C; ^{1}H NMR ($CDCl_3$) δ 2.10 (qui, 2H), 2.40 (t, 2H), 2.85 (t, 2H), 3.70 (s, 3H), 7.00 (d, 1H), 7.10–7.25 (m, 2H), 7.35 (d, 1H), 7.65 (d, 1H), 8.00 (broad s, 1H). A solution of the methyl ester (100 g, 0.46 mol) in dry tetrahydrofuran (THF) (1 L) was added dropwise to a suspension of $LiAlH_4$ (25 g, 0.66 mol) in dry THF (1 L) at such a rate that the temperature was maintained at about 40 °C. After

the mixture was stirred for an additional 40 min, water (25 mL) was added cautiously to the cooled solution (below 10 °C). Under vigorous stirring of the solution, concentrated aqueous NaOH solution (25 mL) was added dropwise. Inorganic salts were filtered off, and the solvents were evaporated in vacuo. The remaining oil was dissolved in dichloromethane (500 mL) and dried (anhydrous $MgSO_4$). The crude alcohol that was left after evaporation of dichloromethane was used without further purification: yield 88 g (100%); ^{1}H NMR ($CDCl_3$) δ 1.60–1.85 (m, 4H), 2.80 (t, 2H), 3.70 (t, 2H), 6.95 (d, 1H), 7.10–7.25 (m, 2H), 7.35 (d, 1H), 7.65 (d, 1H), 8.05 (broad s, 1H).

In a corresponding way **3-(1*H*-indol-3-yl)-1-propanol (8b)**[24] and **2-(1*H*-indol-3-yl)ethanol (8c)** were prepared.[29]

N-Phenylpiperazine, *N*-(4-fluorophenyl)piperazine, *N*-(2-methoxyphenyl)piperazine, and 4-phenylpiperidine were all commercially available. **4-(4-Fluorophenyl)piperidine** was prepared as follows. A mixture of 4-fluorobenzaldehyde (230 g, 1.85 mol) and ethyl acetoacetate (480 g, 3.69 mol) was cooled to 0 °C, and piperidine (25 mL) was added dropwise during 0.5 h. The mixture was left at room temperature for 3 days. The resulting solid product was dissolved in ethanol (1.0 L) and refluxed. After cooling to room temperature the crystalline product was filtered off and dried in vacuo: yield 463 g (69%); mp 160 °C. This product (450 g, 1.23 mol) was added portionwise to a solution of KOH (350 g) in water (300 mL) kept at 85–90 °C. The mixture was finally stirred for another 2 h at 80–85 °C. Ice (2 kg) and ethyl acetate (500 mL) were added. The aqueous phase was separated, and pH was adjusted to 1 by cautious addition of concentrated aqueous HCl (CO_2 evolves). The precipitated 3-(4-fluorophenyl)-glutaric acid was filtered off, washed with water, and dried: yield 207 g (75%); mp 141–143 °C. A mixture of the glutaric acid derivative (110 g, 0.49 mol) and urea (34 g, 0.57 mol) was heated at 160–180 °C for 2 h. After cooling below 80 °C ethanol (250 mL) was added and the mixture was refluxed for 10 min. The precipitated 4-(4-fluorophenyl)-2,6-piperidinedione was collected after cooling to 0 °C: yield 86 g (86%); mp 199 °C. To a suspension of $LiAlH_4$ (50 g, 1.32 mol) in dry THF (1 L) was added all of the piperidinedione (0.42 mol) in small portions at 40–60 °C. The resulting mixture was finally refluxed for 1.5 h. Water (20 mL), concentrated aqueous NaOH (20 mL), and water (200 mL) were sequentially added with caution. Inorganic salts were filtered off and the solvents evaporated in vacuo. The remaining oil was dissolved in dichloromethane (500 mL) and dried (anhydrous Na_2SO_4), and the solvent was evaporated, leaving 72 g (95%) of the 4-(4-fluorophenyl)piperidine; ^{1}H NMR ($CDCl_3$) δ 1.60 (dq, 2H), 1.80 (broad d, 2H), 2.35 (s, 1H), 2.60 (tt, 1H), 2.70 (dt, 2H), 3.20 (broad d, 2H), 7.00 (t, 2H), 7.10–7.20 (m, 2H).

In a similar way **4-(2-methoxyphenyl)piperidine** was prepared: mp 204–210 °C (diisopropyl ether); ^{1}H NMR ($CDCl_3$) δ 1.65 (dq, 2H), 1.85 (broad d, 2H), 2.80 (tt, 1H), 3.10–3.30 (m, 4H), 3.85 (s, 3H), 6.90 (d, 1H), 7.00 (t, 1H), 7.15–7.25 (m, 2H). **Spiro[isobenzofuran-1(3*H*),4′-piperidine]** was prepared as described by Marxer et al.[28] The synthesis of **4-(4-fluorophenyl)-1,2,3,6-tetrahydropyridine** was a modification of a literature method[37] as follows. To a solution of 1.6 M *n*-butyllithium in *n*-hexane (250 mL) in dry diethyl ether (300 mL) kept at −50 to −40 °C was added dropwise a solution of 4-bromofluorobenzene (73 g, 0.42 mol) in dry diethyl ether (150 mL). After the mixture was stirred for another 40 min at −50 °C, a solution of 1-benzyl-4-piperidone (57 g, 0.30 mol) in dry diethyl ether (200 mL) was added dropwise. The mixture was further stirred until the temperature reached −10 °C. Diluted hydrochloric acid was added. The organic phase was discarded. To the partly precipitated hydrochloric salt remaining in the aqueous phase was added diethyl ether followed by aqueous NH_4OH until pH > 9. The organic phase was separated and worked up leaving 1-benzyl-4-(4-fluorophenyl)-4-piperidinol as an oil: yield 82 g (97%) ^{1}H NMR ($CDCl_3$) δ 1.70 (dq, 2H), 1.80 (broad s, 1H), 2.15 (dt, 2H), 2.50 (dt, 2H), 2.80 (broad d, 2H), 3.60 (s, 2H), 7.05 (t, 2H), 7.25–7.40 (m, 5H), 7.50 (dd, 2H). The 4-piperidinol (82 g, 0.29 mol) was refluxed in trifluoroacetic acid (500 mL) for 1.5 h. Most of the trifluoroacetic acid was evaporated in vacuo. To the remaining oil was added diethyl ether, water, and aqueous NH_4OH until pH > 9. The organic phase was worked up as above: yield 76 g (96%) of 1-benzyl-4-(4-fluorophenyl)-1,2,3,6-tetrahydropyridine; ^{1}H NMR ($CDCl_3$) δ 2.50–2.60 (m, 2H), 2.75 (t, 2H), 3.15 (q, 2H), 3.65 (s, 2H), 6.00 (h, 1H), 7.00 (t, 2H), 7.30–7.50 (m, 7H), 7.50 (dd, 2H). To a solution of all the thus isolated oil (0.28 mol) in 1,1,1-trichloroethane (760 mL) kept at reflux was added dropwise 2,2,2-trichloroethyl chloroformate (45 mL) during 40 min. The mixture was refluxed for 3 h. The solvent was removed by evaporation, and the carbamate was purified by filtering through silica gel using dichloromethane/heptane 1:3 as eluent: yield 90 g (93%); ^{1}H NMR ($CDCl_3$) δ 2.50–2.60 (m, 2H), 3.70–3.80 (m, 2H), 4.20 (broad d, 2H), 4.80 (s, 2H), 6.00 (broad s, 1H), 7.05 (t, 2H), 7.45 (dd, 2H). The carbamate group was removed by addition of Zn-powder (100 g, 1.53 mol) to a solution of the carbamate derivative (50 g, 0.14 mol) in a mixture of acetic acid (450 mL) and water (50 mL) kept at 45 °C. Small lots of Zn were added during 1.5 h. Inorganic salts were filtered off, and the solvents were evaporated in vacuo. The 4-(4-fluorophenyl)-1,2,3,6-tetrahydropyridine was isolated as an oil by extraction from an alkaline aqueous phase with ethyl acetate, according to the general workup procedure: yield 23 g (93%); ^{1}H NMR ($CDCl_3$) δ 1.75 (s, 1H), 2.35–2.45 (m, 2H), 3.10 (t, 2H), 3.50 (q, 2H), 6.00–6.10 (m, 1H), 6.95 (t, 2H), 7.30–7.40 (m, 2H).

3-(4-Fluorophenyl)-8-azabicyclo[3.2.1]-oct-2-ene was prepared analogously: To a solution of 1.6 M *n*-butyllithium in *n*-hexane (500 mL) in dry diethyl ether (600 mL) kept at −45 °C was added dropwise a solution of 4-bromofluorobenzene (145 g, 0.84 mol) in dry diethyl ether (350 mL). After stirring for another 20 min at −50 °C, a solution of 8-methyl-8-azabicyclo[3.2.1]octan-3-one (85 g, 0.64 mol) in dry diethyl ether (200 mL) was added dropwise. The mixture was further stirred until the temperature reached −20 °C. Diluted hydrochloric acid was added. The organic phase was discarded. To the partly precipitated hydrochloric salt remaining in the aqueous phase was added diethyl ether followed by aqueous NH_4OH until pH > 9. The organic phase was separated and worked up leaving 3-(4-fluorophenyl)-8-methyl-8-azabicyclo-[3.2.1]octan-3-ol that crystallized from diethyl ether: yield 96 g (64%); mp 169 °C. All of the 4-piperidinol (96 g, 0.41 mol) was refluxed in trifluoroacetic acid (500 mL) for 1 h. Most of the trifluoroacetic acid was evaporated in vacuo. To the remaining oil was added diethyl ether, water, and aqueous NH_4OH until pH > 9. The organic phase was worked up as above: yield 87 g (98%) of 3-(4-fluorophenyl)-8-methyl-8-azabicyclo[3.2.1]oct-2-ene; mp 62–63 °C (from 2-propyl ether/*n*-heptane, 1:1). To a solution of the thus isolated azabicyclo-[3.2.1]oct-2-ene (54 g, 0.25 mol) in 1,1,1-trichloroethane (550 mL) kept at 70 °C was added dropwise 2,2,2-trichloroethyl chloroformate (38 mL) during 2 h. The mixture was refluxed for 3 h. The solvent was removed by evaporation, and the carbamate was purified by filtering through silica gel using dichloromethane as eluent: yield 59 g (64%); ^{1}H NMR ($CDCl_3$) δ 1.70–1.85 (m, 1H), 1.95–2.40 (m, 4H), 3.10 (broad d, 1H), 4.55–4.80 (m, 4H), 6.35 (s, 1H), 7.00 (t, 2H), 7.35 (dd, 2H). The carbamate group was removed by addition of Zn powder (40 g, 0.61 mol) to a solution of the carbamate derivative (17 g, 0.045 mol) in a mixture of acetic acid (170 mL) and water (20 mL) kept at 45 °C. Small lots of Zn were added during 1.5 h. Inorganic salts were filtered off, and the solvents were evaporated in vacuo. The 3-(4-fluorophenyl)-8-azabicyclo-[3.2.1]oct-2-ene was isolated as an oil by extraction from an alkaline aqueous phase with ethyl acetate according to the general workup procedure: yield 7 g as an oil (76%); ^{1}H NMR ($CDCl_3$) δ 1.60–1.70 (m, 1H), 1.80–2.20 (m, 5H), 2.45 (d, 1H), 2.85 (dd, 1H), 3.80–3.90 (m, 2H), 6.45 (d, 1H), 6.95 (t, 2H), 7.25–7.35 (m, 2H). The oxalate salt crystallized from acetone: mp 154–155 °C.

General Procedure for the Synthesis of 1-Unsubstituted 3-[4-(4-Phenyl-1-piperidinyl)-1-butyl]-1*H*-indoles and Corresponding 1,2,3,6-Tetrahydropyridiny, and Piperazinyl Derivatives, 9 (Table 1). 3-[4-[4-(2-Methoxyphenyl)-1-piperazinyl]-1-butyl]-1*H*-indole (9a). A solution of 4-(1*H*-indol-3-yl)-1-butanol, **8a** (316 g, 1.67 mol), and triethylamine (340 mL) in dichloromethane (3.2 L) was cooled to 0 °C, and methanesulfonyl chloride (170 mL, 2.20 mol) dissolved in dichloromethane (300 mL) was added dropwise while keeping the temperature below 5 °C. After the mixture

was stirred for an additional 45 min at 15 °C, water (2.0 L) was added. The organic phase was separated and worked up according to the standard procedure leaving the methanesulfonate ester that was used without further purification. For storage the ester was kept in a refrigerator. Yield 450 g (100%) as an oil. A mixture of the methanesulfonate ester (8 g, 0.030 mol), *N*-(2-methoxyphenyl)piperazine (5.5 g, 0.029 mol), and potassium carbonate (6.0 g, 0.043 mol) in acetone (100 mL) was refluxed for 24 h. The acetone was evaporated, and the residue was dissolved in water (200 mL) and diethyl ether (200 mL). The aqueous phase was made acidic by addition of acetic acid, and the organic phase was separated and discarded. Aqueous NH_4OH was added to adjust the pH to >10. Extraction with diethyl ether and workup as above afforded 10 g of crude **9a**. Pure title compound crystallized from diethyl ether: yield 7.8 g (74%); mp 113–115 °C; ^1H NMR ($CDCl_3$) δ 1.60–1.85 (m, 4H), 2.40 (t, 2H), 2.65 (broad s, 4H), 2.85 (t, 2H), 3.10 (broad s, 4H), 3.85 (s, 3H), 6.90 (t, 1H), 6.90–7.05 (m, 4H), 7.10–7.20 (m, 2H), 7.35 (d, 1H), 7.60 (d, 1H), 8.00 (broad s, 1H). Anal. ($C_{23}H_{28}N_3O$) C, H, N.

In a corresponding way the following indoles **9** were prepared.

3-[4-[4-(2-Methoxyphenyl)-1-piperidinyl]-1-butyl]-1*H*-indole hemioxalate (9b): mp 183–188 °C (acetone); ^1H NMR (DMSO-d_6) δ 1.60–1.80 (m, 8H), 2.50–2.60 (m, 2H), 2.65–2.75 (m, 4H), 2.95–3.05 (m, 1H), 3.25 (d, 2H), 3.75 (s, 3H), 6.85–7.20 (m, 7H), 7.35 (d, 1H), 7.50 (d, 1H), 10.80 (s, 1H). Anal. ($C_{24}H_{30}N_2O$·hemioxalate) C, H, N.

3-[4-[4-(4-Fluorophenyl)-1-piperazinyl]-1-butyl]-1*H*-indole (9c): mp 124–126 °C (diisopropyl ether); ^1H NMR ($CDCl_3$) δ 1.55–1.85 (m, 4H), 2.45 (t, 2H), 2.60 (t, 4H), 2.80 (t, 2H), 3.15 (t, 4H), 6.80–7.00 (m, 4H), 6.95 (s, 1H), 7.05–7.20 (m, 2H), 7.35 (d, 1H), 7.60 (d, 1H), 8.00 (broad s, 1H). Anal. ($C_{22}H_{26}FN_3$) C, H, N.

3-[4-(4-Phenyl-1-piperidinyl)-1-butyl]-1*H*-indole (9d): mp 131–132 °C (diisopropyl ether); ^1H NMR ($CDCl_3$) δ 1.60–1.85 (m, 8H), 2.05 (dt, 2H), 2.40–2.55 (m, 3H), 2.80 (t, 2H), 3.05 (broad d, 2H), 6.95 (s, 1H), 7.05–7.40 (m, 8H), 7.60 (d, 1H), 7.95 (broad s, 1H). Anal. ($C_{23}H_{28}N_2$) C, H, N.

3-[4-[4-(4-Fluorophenyl)-1-piperidinyl]-1-butyl]-1*H*-indole (9e): mp 92–93 °C (washed with *n*-heptane); ^1H NMR ($CDCl_3$) δ 1.60–1.90 (m, 8H), 2.05 (dt, 2H), 2.40–2.55 (m, 3H), 2.80 (t, 2H), 3.10 (broad d, 2H), 6.95–7.05 (m, 3H), 7.10–7.25 (m, 4H), 7.35 (d, 1H), 7.65 (d, 1H), 8.05 (broad s, 1 H). Anal. ($C_{23}H_{27}FN_2$) C, H, N.

3-[4-[4-(4-Fluorophenyl)-1-(1,2,3,6-tetrahydro)pyridinyl]-1-butyl]-1*H*-indole (9f): mp 124–125 °C (washed with diethyl ether); ^1H NMR ($CDCl_3$) δ 1.60–1.80 (m, 4H), 2.45–2.55 (m, 4H), 2.70 (t, 2H), 2.80 (t, 2H), 3.15 (q, 2 H), 6.00 (broad s, 1H), 6.95–7.05 (m, 3H), 7.05–7.20 (m, 2H), 7.30–7.40 (m, 3H), 7.65 (d, 1H), 8.00 (broad s, 1H). Anal. ($C_{23}H_{25}FN_2$) C, H, N.

General Procedure for the Synthesis of 1-(4-Fluorophenyl)-Substituted 3-[4-(4-Phenyl-1-piperidinyl)-1-butyl]-1*H*-indoles and Corresponding Piperazinyl Derivatives, 11 (Table 1). 4-[1-(4-Fluorophenyl)-1*H*-indol-3-yl]-1-butanol (10a). A mixture of 4-(1*H*-indol-3-yl)-1-butanol, **8a** (120 g, 0.63 mol), potassium carbonate (110 g, 0.80 mol), 4-fluoroiodobenzene (240 g, 1.09 mol), CuI (30 g), and ZnO (7.5 g) in 1-methyl-2-pyrrolidinone (NMP) (1.2 L) was heated at 155 °C for 6 h. After cooling, precipitated inorganic salts were filtered off. Diethyl ether (500 mL) and diluted aqueous NH_4OH (4.0 L) were added. The organic phase was separated, washed with saturated brine, and subsequently worked up as above. The crude butanol derivative was purified by column chromatography on silica gel (eluted with diethyl ether): yield of pure title compound **10a** as an oil 104 g (58%); ^1H NMR ($CDCl_3$) δ 1.65–1.95 (m, 5H), 2.90 (t, 2H), 3.75 (t, 2H), 7.10 (s, 1H), 7.20 (t, 2H), 7.25 (d, 1H), 7.40–7.50 (m, 3H), 7.70 (d, 1H).

1-(4-Fluorophenyl)-3-[4-[4-(4-fluorophenyl)-1-piperidinyl]-1-butyl]-1*H*-indole Hemifumarate (11a). A solution of 4-[1-(4-fluorophenyl)-1*H*-indol-3-yl]-1-butanol, **10a** (104 g, 0.37 mol), and triethylamine (75 mL) in dichloromethane (1.0 L) was cooled to 0 °C and methanesulfonyl chloride (30 mL, 0.39 mol) dissolved in dichloromethane (150 mL) was added dropwise while keeping the temperature below 10 °C. After the mixture was stirred for additional 1.5 h at room temperature, water (1.5 L) was added. The organic phase was finally worked up, according to the standard procedure, leaving 128 g (95%) of the methanesulfonate ester that was used without further purification. To the methanesulfonate ester (128 g, 0.35 mol) in methyl isobutyl ketone (MIBK) (1 L) was added 4-(4-fluorophenyl)piperidine (as the trifluoroacetic acid salt) (87 g, 0.30 mol) and potassium carbonate (90 g, 0.65 mol). The mixture was heated at reflux temperature for 16 h. After cooling, inorganic salts were filtered off and MIBK evaporated in vacuo. Ethyl acetate (500 mL) and water (2.0 L) were added, and the organic phase was separated and worked up as above. The remaining crude product was dissolved in boiling ethanol (400 mL). After the mixture cooled in an ice bath, the precipitated product was filtered off: yield 78 g (58%). The hemifumarate salt **11a** was crystallized from ethanol: mp 157 °C; ^1H NMR (DMSO-d_6) δ 1.55–1.80 (m, 8H), 2.25 (dt, 2H), 2.60 (broad t, 2H), 2.75 (t, 2H), 3.10 (broad d, 2H), 6.55 (s, 1H), 7.05–7.25 (m, 6H), 7.35 (d, 1H), 7.40 (s, 1H), 7.45 (d, 1H), 7.55–7.65 (m, 3H). Anal. ($C_{29}H_{30}F_2N_2$·hemifumarate) C, H, N.

In a corresponding way the following 1-(4-fluorophenyl)-substituted indoles **11** were prepared.

1-(4-Fluorophenyl)-3-[4-[4-(4-fluorophenyl)-1-piperazinyl]-1-butyl]-1*H*-indole (11b): mp 65–66 °C (ethyl acetate); ^1H NMR ($CDCl_3$) δ 1.60–1.90 (m, 4H), 2.50 (t, 2H), 2.60 (t, 4H), 2.85 (t, 2H), 3.10 (t, 4H), 6.85–7.00 (m, 4H), 7.10 (s, 1H), 7.15–7.25 (m, 4H), 7.40–7.50 (m, 3H), 7.65 (d, 1H). Anal. ($C_{28}H_{29}F_2N_3$) C, H, N.

1-(4-Fluorophenyl)-3-[4-(4-phenyl-1-piperidinyl)-1-butyl]-1*H*-indole fumarate (11c): mp 171–173 °C (ethanol); ^1H NMR (DMSO-d_6) δ 1.60–1.85 (m, 8H), 2.35–2.50 (m, 2H), 2.55–2.85 (m, 5H), 3.20 (broad d, 2H), 6.55 (s, 2H), 7.05–7.50 (m, 11H), 7.55–7.70 (m, 3H). Anal. ($C_{29}H_{31}FN$·fumarate) C, H, N.

1-(4-Fluorophenyl)-3-[4-(4-phenyl-1-piperazinyl)-1-butyl]-1*H*-indole difumarate (11d): mp 120–122 °C (ethanol); ^1H NMR (DMSO-d_6) δ 1.50–1.70 (m, 4H), 2.50 (t, 2H), 2.65 (broad t, 4H), 2.80 (t, 2H), 3.15 (broad t, 4H), 6.60 (s, 4H), 6.80 (t, 1H), 6.90 (d, 2H), 7.10–7.25 (m, 4H), 7.40–7.50 (m, 4H), 7.55–7.65 (m, 3H). Anal. ($C_{28}H_{30}FN_3$·difumarate) C, H, N.

1′-[4-(1*H*-Indol-3-yl)-1-butyl]spiro[isobenzofuran-1(3*H*),4′-piperidine] (12a). A suspension of the methanesulfonate ester (20 g, 0.075 mol) of 4-(1*H*-indol-3-yl)-1-butanol, **8a**, spiro[isobenzofuran-1(3*H*),4′-piperidine] (15 g, 0.079 mol), and potassium carbonate (11 g, 0.080 mol) in MIBK (400 mL) was refluxed overnight. After the mixture was cooled to room temperature, inorganic salts were filtered off. The remaining oil was purified by filtering through silica gel (eluted with 4% triethylamine in a 3:2 mixture of ethyl acetate and *n*-heptane): yield 21 g (77%) of crude title compound that was stirred with diethyl ether and filtered off; mp 150–155 °C; ^1H NMR ($CDCl_3$) δ 1.60–1.85 (m, 6H), 2.00 (dt, 2H), 2.40 (dt, 2H), 2.45–2.55 (m, 2H), 2.85 (t, 2H), 2.85–2.95 (m, 2H), 5.05 (s, 2H), 6.95 (d, 1H), 7.00–7.25 (m, 6H), 7.30 (d, 1H), 7.55 (d, 1H), 8.05 (broad s, 1H). Anal. ($C_{24}H_{28}N_2O$) C, H, N.

Procedures for the Syntheses of 1-Substituted 3-(Spiro[isobenzofuran-1(3*H*),4′-piperidine]-1′-yl-1-butyl)-1*H*-indoles, 14 (Table 2). 1′-[4-(1-Methyl-1*H*-indol-3-yl)-1-butyl]-spiro[isobenzofuran-1(3*H*),4′-piperidine] Oxalate (14a). The sequence of the synthetic steps indicated in Scheme 2 was slightly changed in the preparation of compound **14a**. To a solution of 4-(1*H*-indol-3-yl)butanoic acid (24 g, 0.12 mol) in dry *N*,*N*-dimethylformamide (DMF) (200 mL) was slowly added potassium *tert*-butoxide (28 g, 0.26 mol). The mixture was cooled below 10 °C, and methyl iodide (60 mL, 0.96 mol) was added dropwise during 30 min. The mixture was finally stirred overnight at room temperature. It was poured into water (1 L) and diethyl ether (250 mL), and the organic phase was worked up as previously. The crude product was filtered through silica gel using dichloromethane as eluent, affording 18 g (65%) of pure methyl 4-(1-methyl-1*H*-indol-3-yl)butanoic acid ester as an oil: ^1H NMR ($CDCl_3$) δ 2.05 (p, 2H), 2.40 (t, 2H), 2.80 (t, 2H), 3.65 (s, 3H), 3.75 (s, 3H), 6.80 (s, 1H), 7.10 (t, 1H), 7.15–7.30 (m, 2H), 7.55 (d, 1H). A solution of the methyl ester (17 g, 0.073 mol) in dry THF (100 mL) was added dropwise to a suspension of $LiAlH_4$ (4.5 g, 0.12 mol) in dry THF (150 mL) at such a rate that the temperature was

maintained at about 40 °C. After the mixture was stirred for additional 1 h, water (5 mL) was added cautiously to the cooled solution (below 10 °C). Under vigorously stirring of the solution, concentrated aqueous NaOH solution (5 mL) was added dropwise. Inorganic salts were filtered off, and the solvents were evaporated in vacuo. The remaining oil was dissolved in dichloromethane (500 mL) and dried (anhydrous $MgSO_4$). The crude alcohol that was left after evaporation of dichloromethane was used without further purification: yield 14.9 g (100%); ^{1}H NMR ($CDCl_3$) δ 1.60–1.85 (m, 4H), 2.75 (t, 2H), 3.65 (t, 2H), 3.70 (s, 3H), 6.80 (s, 1H), 7.05 (t, 1H), 7.15–7.30 (m, 2H), 7.60 (d, 1H). The butanol was converted to the methanesulfonate ester, according to the procedure described above for the preparation of compound **9a**: yield 16 g (78%); ^{1}H NMR ($CDCl_3$) δ 1.75–1.90 (m, 4H), 2.80 (t, 2H), 2.90 (s, 3H), 3.70 (s, 3H), 4.20 (t, 2H), 6.80 (s, 1H), 7.10 (t, 1H), 7.15–7.30 (m, 2H), 7.55 (d, 1H). A mixture of the methanesulfonate ester (1.9 g, 0.0068 mol), spiro[isobenzofuran-1(3*H*),4′-piperidine] (1.5 g, 0.0079 mol), and potassium carbonate (1.5 g, 0.011 mol) was heated at reflux in MIBK (50 mL) for 16 h. After cooling to room temperature, inorganic salts were filtered off, MIBK was evaporated in vacuo, and the remaining crude title compound was purified by column chromatography on silica gel (eluted with 4% triethylamine in ethyl acetate and heptane, 2:3). The oxalate salt was finally crystallized from acetone: yield of **14a** 2.3 g (73%); mp 101–102 °C; ^{1}H NMR (DMSO-d_6) δ 1.60–1.80 (m, 6H), 2.25 (dt, 2H), 2.75 (t, 2H), 3.10 (broad t, 4H), 3.40 (broad d, 2H), 3.75 (s, 3H), 5.00 (s, 2H), 7.00 (t, 1H), 7.15 (s, 1H), 7.15 (d, 1H), 7.20–7.30 (m, 1H), 7.30–7.40 (m, 4H), 7.55 (d, 1H). Anal. ($C_{25}H_{30}N_2O$·oxalate) C, H, N.

1′-[4-(1-Acetyl-1*H*-indol-3-yl)-1-butyl]spiro[isobenzofuran-1(3*H*),4′-piperidine] Oxalate (14b). To a solution of 1′-[4-(1*H*-indol-3-yl)-1-butyl]spiro[isobenzofuran-1(3*H*),4′-piperidine], **12a** (1.8 g, 0.0050 mol), in dichloromethane (40 mL) were added tetrabutylammonium hydrogen sulphate (200 mg) and powdered sodium hydroxide (1 g). A solution of acetyl chloride (0.8 mL, 0.011 mol) in dichloromethane (10 mL) was added dropwise during 10 min below 25 °C. After the mixture was stirred for 1 h at room temperature, water (200 mL) was added. The organic phase was separated and worked up as previously. The crude title compound was subjected to column chromatography on silica gel (eluted with 4% triethylamine in ethyl acetate and heptane 2:3). The oxalate salt crystallized from acetone: yield of **14b** 0.9 g (37%); mp 139–140 °C; ^{1}H NMR (DMSO-d_6) δ 1.65–1.90 (m, 6H), 2.35 (dt, 2H), 2.65 (s, 3H), 3.05–3.20 (m, 4H), 3.45 (broad d, 2H), 5.05 (s, 2H), 7.20–7.30 (m, 6H), 7.60–7.70 (m, 2H), 8.30 (d, 1H). Anal. ($C_{26}H_{30}N_2O_2$·oxalate) C, H, N.

1′-[4-[1-Methylsulfonyl)-1*H*-indol-3-yl]-1-butyl]spiro[isobenzofuran-1(3*H*),4′-piperidine] Oxalate (14c). To a well-stirred suspension of a solution of NaOH (20 g) in water (20 mL), a solution of 4-(1*H*-indol-3-yl)-1-butanol, **8a** (4 g, 0.021 mol), in dichloromethane (60 mL), and tetrabutylammonium hydrogen sulphate (0.8 g) kept at 15 °C was added dropwise a solution of methanesulfonyl chloride (3.0 mL, 0.039 mol) in dichloromethane (25 mL) during 20 min. The temperature was gradually allowed to reach room temperature. Water (100 mL) was added, and the organic phase was separated and worked up as above. Pure methanesulfonate ester of 4-[1-methylsulfonyl]-1*H*-indol-3-yl]-1-butanol was obtained by column chromatography on silica gel (eluted with a 1:1:1 mixture of diethyl ether, dichloromethane, and heptane): yield 1.8 g (27%) as an oil; ^{1}H NMR ($CDCl_3$) δ 1.75–1.90 (m, 4H), 2.80 (t, 2H), 2.95 (s, 3H), 3.10 (s, 3H), 4.25 (t, 2H), 7.20 (s, 1H), 7.20–7.40 (m, 4H), 7.50 (d, 1H), 7.90 (d, 1H). A mixture of the methanesulfonate (1.8 g, 0.0052 mol), spiro[isobenzofuran-1(3*H*),4′-piperidine] (1.3 g, 0.0068 mol), and potassium carbonate (1 g, 0.0072 mol) in MIBK (50 mL) was heated at reflux for 16 h. After cooling, inorganic salts were filtered off, MIBK was evaporated in vacuo, and the remaining oil was subsequently subjected to column chromatography on silica gel (eluted with 4% triethylamine in ethyl acetate and heptane, 2:3). The oxalate salt crystallized from acetone: yield of **14c** 1.2 g (44%); mp 83–85 °C; ^{1}H NMR (DMSO-d_6) δ 1.65–1.85 (m, 6H), 2.35 (dt, 2H), 2.75 (t, 2H), 3.05–3.20 (m, 4H), 3.35 (s, 3H), 3.45 (broad d, 2H), 5.05 (s, 2H), 7.15–7.30 (m, 6H), 7.35 (d, 1H), 7.40 (s, 1H), 7.65 (d, 1H), 7.80 (d, 1H). Anal. ($C_{25}H_{30}N_2O_3S$·oxalate) C, H, N.

1′-[4-[1-(4-Tolylsulfonyl)-1*H*-indol-3-yl]-1-butyl]spiro[isobenzofuran-1(3*H*),4′-piperidine] Fumarate (14d). To a well-stirred mixture of a solution of NaOH (20 g) in water (20 mL), a solution of 1′-[4-(1*H*-indol-3-yl)-1-butyl]spiro[isobenzofuran-1(3*H*),4′-piperidine], **12a** (4.3 g, 0.012 mol) in dichloromethane (60 mL), and tetrabutylammonium hydrogen sulphate (0.8 g), kept at 15 °C, was added dropwise a solution of 4-toluenesulfonyl chloride (3.4 g, 0.018 mol) in dichloromethane (25 mL) during 20 min. The temperature was gradually allowed to reach room temperature. Water (100 mL) was added, and the organic phase was separated and worked up as above. Pure title compound was obtained by column chromatography on silica gel (eluted with 4% triethylamine in ethyl acetate and heptane 2:3). The fumarate salt crystallized from ethanol: yield of **14d** 2.2 g (29%); mp 202–204 °C; ^{1}H NMR (DMSO-d_6) δ 1.55–1.75 (m, 6H), 2.10 (dt, 2H), 2.30 (s, 3H), 2.50–2.75 (m, 6H), 3.00 (broad d, 2H), 5.00 (s, 2H), 6.60 (s, 2H), 7.20–7.40 (m, 8H), 7.60 (d, 2H), 7.80 (d, 2H), 7.90 (d, 1H). Anal. ($C_{31}H_{34}N_2O_3S$·fumarate) C, H, N.

1′-[4-(1-Benzyl-1*H*-indol-3-yl)-1-butyl]spiro[isobenzofuran-1(3*H*),4′-piperidine] Oxalate (14e). A solution of 4-(1*H*-indol-3-yl)-1-butanol, **8a** (5 g, 0.027 mol) in dry DMF (50 mL) was cooled to 10 °C. Potassium *tert*-butoxide (6.1 g, 0.054 mol) was added in small portions during 5 min. A solution of benzyl bromide (9.2 g, 0.054 mol) in dry DMF (10 mL) was added dropwise during 15 min. The temperature was raised to room temperature, and the mixture was stirred for an additional hour. Ethyl acetate (100 mL) and water (300 mL) were added. The organic phase was worked up as previously: yield of crude 4-(1-benzyl-1*H*-indol-3-yl)-1-butanol 10.9 g as an quite impure oil. It was not possible completely to distinguish the NMR signals of the butanol derivative from this mixture. All of the impure butanol derivative was converted into the *O*-methanesulfonate ester using the same procedure as described for the synthesis of compound **11a**: yield 5.7 g (59%) as an oil; ^{1}H NMR ($CDCl_3$) δ 1.65–1.90 (m, 4H), 2.80 (t, 2H), 2.90 (s, 3H), 4.20 (t, 2H), 5.20 (s, 2H), 6.85 (s, 1H), 7.05–7.40 (m, 8H) 7.60 (d, 1H). A mixture of the methanesulfonate ester (5.7 g, 0.016 mol), spiro[isobenzofuran-1(3*H*),4′-piperidine] (2.2 g, 0.012 mol), potassium carbonate (1.7 g, 0.012 mol), and a KI crystal was heated at reflux temperature in MIBK (75 mL) for 16 h. After cooling, inorganic salts were filtered off, and MIBK was evaporated in vacuo. The remaining crude product was purified by column chromatography on silica gel (eluted with 4% triethylamine in ethyl acetate and heptane, 1:1): yield 3.4 g (63%) as an oil. The oxalate salt crystallized from acetone: mp 167 °C; ^{1}H NMR (DMSO-d_6) δ 1.60–1.85 (m, 6H), 2.20 (dt, 2H), 2.70 (t, 2H), 3.00–3.20 (m, 4H), 3.40 (broad d, 2H), 5.00 (s, 2H), 5.35 (s, 2H), 7.00–7.10 (m, 2H), 7.10–7.35 (m, 11H), 7.40 (d, 1H), 7.55 (d, 1H). Anal. ($C_{31}H_{34}N_2O$·oxalate) C, H, N.

1′-[4-[1-(4-Fluorophenyl)-1*H*-indol-3-yl]-1-butyl]spiro[isobenzofuran-1(3*H*),4′-piperidine] Fumarate (14f). A mixture of the methanesulfonate ester (80 g, 0.22 mol) of 4-[1-(4-fluorophenyl)-1*H*-indol-3-yl]-1-butanol, **10a**, prepared as above in the synthesis of compound **11a**, spiro[isobenzofuran-1(3*H*),4′-piperidine] (50 g, 0.26 mol), and potassium carbonate (50 g, 0.36 mol) was heated at reflux temperature in MIBK (900 mL) for 16 h. After cooling, inorganic salts were filtered off, and MIBK was evaporated in vacuo. The crude title compound was purified by column chromatography on silica gel (eluted with 4% triethylamine in ethyl acetate and heptane, 2:3). The fumarate salt crystallized from ethanol: yield of **14f** 97 g (77%); mp 193 °C; ^{1}H NMR (DMSO-d_6) δ 1.65–1.85 (m, 6H), 2.15 (dt, 2H), 2.75 (dt, 2H), 2.80 (broad s, 4H), 3.15 (broad d, 2H), 4.95 (s, 2H), 6.55 (s, 2H), 7.10–7.60 (m, 13H). Anal. ($C_{30}H_{31}FN_2O$·fumarate) C, H, N.

In a corresponding way the following 1-(4-fluorophenyl)-substituted indoles **13** were prepared:

1′-[3-[1-(4-Fluorophenyl)-1*H*-indol-3-yl]-1-propyl]spiro[isobenzofuran-1(3*H*),4′-piperidine] oxalate (14g): mp 192–193 °C (acetone); ^{1}H NMR (DMSO-d_6) δ 1.80 (broad d, 2H), 2.00–2.35 (m, 4H), 2.80 (t, 2H), 3.05–3.30 (m, 4H), 3.50 (broad d, 2H), 5.05 (s, 2H), 7.10–7.60 (m, 13H). Anal. ($C_{29}H_{29}FN_2O$·oxalate) C, H, N.

1′-[2-[1-(4-Fluorophenyl)-1*H*-indol-3-yl]-1-ethyl]spiro-[isobenzofuran-1(3*H*),4′-piperidine] oxalate (14h): mp 204–205 °C (acetone); ^{1}H NMR (DMSO-d_6) δ 1.85 (broad d, 2H), 2.35 (dt, 2H), 3.10–3.35 (m, 4H), 3.40 (t, 2H) 3.50 (broad d, 2H), 5.05 (s, 2H), 7.10–7.60 (m, 11H), 7.75 (d, 1H). Anal. ($C_{28}H_{27}FN_2O$·oxalate) C, H, N.

1′-[[1-(4-Fluorophenyl)-1*H*-indol-3-yl]methyl]spiro-[isobenzofuran-1(3*H*),4′-piperidine] 1.25Fumarate (14i). A mixture of 1*H*-indole-3-carboxaldehyde (9 g, 0.062 mol), 4-fluoroiodobenzene (27 g, 0.12 mol), potassium carbonate (10 g, 0.072 mol), CuI (4 g), and ZnO (2 g) was heated in NMP (100 mL) at 160 °C for 20 h. After cooling, diluted aqueous NH_4OH (500 mL) and diethyl ether (200 mL) were added. The organic phase was separated and worked up according to the standard procedure: yield of 1-(4-fluorophenyl)-1*H*-indole-3-carboxaldehyde 7.5 g (51%); mp 126–128 °C (diisopropyl ether); ^{1}H NMR ($CDCl_3$) δ 7.25 (t, 2H), 7.30–7.45 (m, 3H), 7.60 (dd, 2H), 7.85 (s, 1H), 8.35–8.45 (m, 1H), 10.10 (s, 1H). To a mixture of the indolecarboxaldehyde (3.0 g, 0.013 mol), spiro-[isobenzofuran-1(3*H*),4′-piperidine] (1.6 g, 0.0084 mol), and sodium cyanoborohydride (4.0 g, 0.064 mol) in dry methanol (16 mL) was added molecular sieve powder (3 Å) (5 g). After the mixture was stirred for 16 h at room temperature, water (200 mL) and ethyl acetate (100 mL) were added. The organic phase was separated and worked up according to the standard procedure. The crude title product was purified by column chromatography on silica gel (eluted with 4% triethylamine in ethyl acetate and heptane, 1:1). The fumarate salt crystallized from ethanol: yield of **14i** 1.3 g (28%); mp 243–244 °C; ^{1}H NMR (DMSO-d_6) δ 1.70 (broad d, 2H), 2.10 (dt, 2H), 2.70 (t, 2H), 3.10 (broad d, 2H), 4.05 (s, 2H), 4.95 (s, 2H), 6.60 (s, 2.5H), 7.15–7.25 (m, 6H), 7.40 (t, 2H), 7.45 (d, 1H), 7.60–7.70 (m, 3H), 7.90 (d, 1H). Anal. ($C_{27}H_{25}FN_2O$·1.25 fumarate) C, H, N.

1′-[4-[1-(3-Thienyl)-1*H*-indol-3-yl]-1-butyl]spiro[iso-benzofuran-1(3*H*),4′-piperidine] Fumarate (14j). A mixture of 1′-[4-(1*H*-indol-3-yl)-1-butyl]spiro[isobenzofuran-1(3*H*),4′-piperidine], **12a** (3.0 g, 0.0083 mol), 3-bromothiophene (3.8 g, 0.023 mol), potassium carbonate (1.6 g, 0.012 mol), CuI (0.5 g), and ZnO (0.2 g) in NMP (40 mL) was heated at 160 °C for 7 h. Inorganic salts were filtered off, and ethyl acetate (200 mL) and diluted aqueous NH_4OH (500 mL) were added. The organic phase was separated and worked up according to the standard procedure. Column chromatography on silica gel (eluted with 4% triethylamine in ethyl acetate and heptane, 1:1) provided the pure title compound. The fumarate salt crystallized from ethanol: yield of **14j** 1.1 g (24%); mp 183 °C; ^{1}H NMR (DMSO-d_6) δ 1.60–1.80 (m, 6H), 2.05 (dt, 2H), 2.55–2.85 (m, 6H), 3.05 (broad d, 2H), 5.00 (s, 2H), 6.60 (s, 2H), 7.10–7.30 (m, 7H), 7.50 (d, 1H), 7.50 (s, 1H), 7.55–7.65 (m, 2H), 7.75–7.80 (m, 1H). Anal. ($C_{28}H_{30}N_2OS$·fumarate) C, H, N.

In a corresponding way the following 1-heteroaryl-substituted indoles **14** were prepared.

1′-[4-[1-(2-Thienyl)-1*H*-indol-3-yl]-1-butyl]spiro[iso-benzofuran-1(3*H*),4′-piperidine] oxalate (14k): mp 198–201 °C (acetone); ^{1}H NMR (DMSO-d_6) δ 1.70–1.90 (m, 6H), 2.20 (dt, 2H), 2.80 (t, 2H), 3.00–3.20 (m, 4H), 3.50 (broad d, 2H), 5.05 (s, 2H), 7.10–7.35 (m, 8H), 7.45 (d, 1H), 7.45 (s, 1H), 7.60 (d, 1H), 7.65 (d, 1H). Anal. ($C_{28}H_{30}N_2OS$·oxalate) C, H, N.

1′-[4-[1-(2-Thiazolyl)-1*H*-indol-3-yl]-1-butyl]spiro[iso-benzofuran-1(3*H*),4′-piperidine] fumarate (14l): mp 165–167 °C (ethanol); ^{1}H NMR (DMSO-d_6) δ 1.55–1.85 (m, 6H), 1.95 (dt, 2H), 2.55–2.65 (m, 4H), 2.75 (t, 2H), 2.95 (broad d, 2H), 4.95 (s, 2H), 6.55 (s, 2H), 7.15–7.30 (m, 5H), 7.40 (t, 1H), 7.45 (d, 1H), 7.60–7.70 (m, 3H), 8.25 (d, 1H). Anal. ($C_{27}H_{29}N_3OS$· fumarate) C, H, N.

1′-[4-[1-(4-Pyridyl)-1*H*-indol-3-yl]-1-butyl]spiro[iso-benzofuran-1(3*H*),4′-piperidine] dioxalate (14m): mp 127–129 °C (acetone); ^{1}H NMR (DMSO-d_6) δ 1.70–1.90 (m, 6H), 2.25 (broad t, 2H), 2.80 (t, 2H), 3.10–3.30 (m, 4H), 3.50 (broad d, 2H), 5.05 (s, 2H), 7.15–7.35 (m, 6H), 7.65–7.75 (m, 4H), 7.85 (d, 1H), 8.65 (d, 2H). Anal. ($C_{29}H_{31}N_3O$·dioxalate) C, H, N.

1-(4-Fluorophenyl)-3-[4-[3-(4-fluorophenyl)-8-azabicyclo-[3.2.1]oct-2-en-8-yl]-1-butyl]-1*H*-indole (15a). A mixture of the methanesulfonate ester (6.0 g, 0.016 mol) of 4-[1-(4-fluorophenyl)-1*H*-indol-3-yl]-1-butanol, **10a**, prepared as described in the synthesis of compound **11a**, 3-(4-fluorophenyl)-8-azabicyclo[3.2.1]oct-2-ene (4.0 g, 0.020 mol), and potassium carbonate (5.0 g, 0.036 mol) was heated at reflux temperature in MIBK (80 mL) for 16 h. After cooling, inorganic salts were filtered off, and MIBK was evaporated in vacuo. The remaining product was purified by column chromatography on silica gel (eluted with 4% triethylamine in ethyl acetate and heptane, 2:3). The pure title compound crystallized from diisopropyl ether: yield of **15a** 1.9 g (25%); mp 74 °C; ^{1}H NMR ($CDCl_3$) δ 0.85–2.20 (m, 9H), 2.55 (t, 2H), 2.75–2.80 (m, 1H), 2.80 (t, 2H), 3.45 (q, 2H), 6.20 (d, 1H), 6.90 (t, 2H), 7.00 (s, 1H), 7.10–7.20 (m, 4H), 7.25–7.35 (m, 2H), 7.35–7.45 (m, 3H), 7.60 (d, 1H). Anal. ($C_{31}H_{30}F_2N_2$) C, H, N.

Pharmacological Test Methods. Animals for Binding. Male Wistar rats (Mol:Wist, SPF, 170–270 g) were used. We have recently described the handling proceduces in detail.[38]

Animals for Behavior. Male Wistar WU rats (Charles River, Germany, 200–250 g) were used.

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.

Black/White Box Exploration Test. This test model is a modified version of the model reported by Colpaert et al.[39] Our modifictions have recently been described in detail.[40] The σ ligands were administered subcutaneously 2 h before the test session or as indicated in this paper.

Binding σ Binding Sites In Vitro. σ_1 Site. Affinity of test compounds to σ_1 binding sites was estimated by their ability to displace [^{3}H]-(+)-pentazocine from rat brain homogenates minus cerebellum, as described by DeHaven-Hudkins et al.[41]

σ_2 Site. Affinity of test compounds to σ_2 binding sites was estimated by their ability to displace [^{3}H]-1,3-di(2-tolyl)-guanidine (DTG) from rat brain homogenates minus cerebellum, as described by Sonesson et al.[30]

Receptor Binding in Vitro. 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.[42]

5-HT_{2A} Receptors. Affinity of test compounds to serotonin 5-HT_{2A} receptors was estimated by their ability to displace [^{3}H]-ketanserin from rat cortical membranes, as described by Hyttel.[42]

5-HT_{1A} Receptors. Affinity of test compounds to serotonin 5-HT_{1A} receptors was estimated by their ability to displace [^{3}H]-8-OH-DPAT from whole rat brain membranes minus cerebellum, as described by Hyttel et al.[43]

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.[44]

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