σ Ligands with Subnanomolar Affinity and Preference for the σ_2 Binding Site. 2. Spiro-Joined Benzofuran, Isobenzofuran, and Benzopyran Piperidines

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Spiro[isobenzofuran-1(3*H*),4′-piperidines] and the corresponding benzofuran and benzopyran derivatives have been synthesized and evaluated as σ ligands. The compounds are related to Lu 28-179 (1′-[4-[1-(4-fluorophenyl)-1*H*-indol-3-yl]-1-butyl]spiro[isobenzofuran-1(3*H*),4′-piperidine]) that has been demonstrated to be a selective σ_2 ligand with affinity in the subnanomolar range. The object of the study was to determine the structural factors governing σ_1/σ_2 affinity and selectivity within this class of compounds. The N-substituent in spiro[isobenzofuran-1(3*H*),4′-piperidines] is highly important, both for affinity and selectivity. Spiropiperidines with no or small N-substituents (H, Me, Et) exert very low affinity for both σ_1 and σ_2 binding sites ($IC_{50}(\sigma_1,\sigma_2) > 100$ nM), whereas medium-sized substituents (e.g., Pr, Bu, $Ph(CH_2)_2$) result in potent, but unselective compounds ($IC_{50}(\sigma_1,\sigma_2) = 2-5$ nM). Increasing the chain length and the lipophilicity of the N-substituent result in compounds in which high affinity for σ_2 binding sites is retained and with selectivity for σ_2 vs σ_1 binding sites (e.g., 4-cyclohexyl-1-butyl: $IC_{50}(\sigma_1) = 1.5$ nM, $IC_{50}(\sigma_2) = 0.07$ nM). Introduction of substituents in the benzene ring of the spiro[isobenzofuran-1(3*H*),4′-piperidine] ring system of Lu 28-179 mainly affects affinity for σ_1 binding sites. Compounds with substituents (F, CF_3) in the 4- or 7-position of the isobenzofuran display high affinity for σ_2 binding sites ($IC_{50}(\sigma_2) = 0.5-2$ nM) and very low affinity for σ_1 binding sites ($IC_{50}(\sigma_1) > 100$ nM). Compounds with substituents (F, CF_3, Me) in the 5- or 6-position of the isobenzofuran exert increased affinity for σ_1 binding sites ($IC_{50}(\sigma_1) = 5-30$ nM, $IC_{50}(\sigma_2) = 0.3-7$ nM), thus rendering unselective compounds. Exchanging the isobenzofuran moiety of Lu 28-179 with thioisobenzofuran, benzofuran, or benzopyran also has a pronounced effect on both affinity and selectivity for σ binding sites. The position of the oxygen atom and the position of the spiroconnection with the 4-position of the piperidine ring were varied, and only compounds in which both the benzene ring and the heteroatom are attached directly to the piperidine ring retain high affinity and selectivity for σ_2 binding sites (e.g., 3,4-dihydro-1′-[4-[1-(4-fluorophenyl)-1*H*-indol-3-yl]-1-butyl]spiro[1*H*-2-benzopyran-1,4′-piperidine]: $IC_{50}(\sigma_1) = 53$ nM, $IC_{50}(\sigma_2) = 0.9$ nM). All other variations result either in unselective compounds or in compounds with low affinity for σ binding sites. In conclusion, the data presented provide detailed information concerning structural requirements for binding to σ_1 and σ_2 binding sites, respectively, and together with Lu 28-179, some of the compounds presented in this work belong to the most potent and selective σ_2 ligands described so far.

Introduction

Although σ binding sites have attracted much attention in recent years, several major issues concerning structure and function of these sites still remain to be unraveled. The initial wealth of information that was gathered (reviewed by Walker et al.[1]) gave rise to numerous ideas and theories. However, more recent evidence has prompted early data to be re-evaluated leaving surprisingly many questions about some of the very fundamental properties of σ binding sites.[2]

It is now generally accepted that two subtypes of σ binding sites exist,[3] σ_1 and σ_2. Recent reports suggest the existence of a σ_3 subtype.[4-6] The σ_1 binding site is labeled selectively by (+)-pentazocine (Figure 1) and corresponds to the original σ binding site described by Su.[7] It has been characterized centrally in rodents[8-10] and primates,[11] as well as in peripheral tissue.[1] The σ_2 site was originally characterized in PC12 cells[12] and has since then been characterized centrally in rodents[13,14] and humans.[15] The two subtypes are distinct and do not appear to be located on a common macromolecule, and they do not represent two different affinity states of the same receptor.[16] In rat brain a greater density of σ_2 binding sites compared to σ_1 binding sites has been found,[13] whereas the opposite is true in guinea pig brain.[17] In both rat brain and guinea pig brain a marked regional variation in the ratio of σ_1 to σ_2 binding sites was observed.[14,17] From a therapeutic point of view, it is interesting that σ binding sites of the σ_2 type are abundant in human cerebral cortex.[15] An interesting finding concerns the subcellular location of both σ_1 and σ_2 binding sites. Recent studies have confirmed that localization of either type of binding site to synaptic regions of plasma membranes is unlikely and that they most probably are intracellular binding sites.[16]

Despite major efforts, the quest for relationships between in vitro and in vivo activities, and binding affinities of σ ligands, respectively, has been surprisingly unsuccessful. Although a large amount of data on in vitro functional effects has been published,[1] the major part of these studies apply unselective ligands, thus rendering the conclusions regarding σ effects very uncertain.[2] The main part of these in vitro activities is associated with σ_1 activity, whereas data on in vitro σ_2

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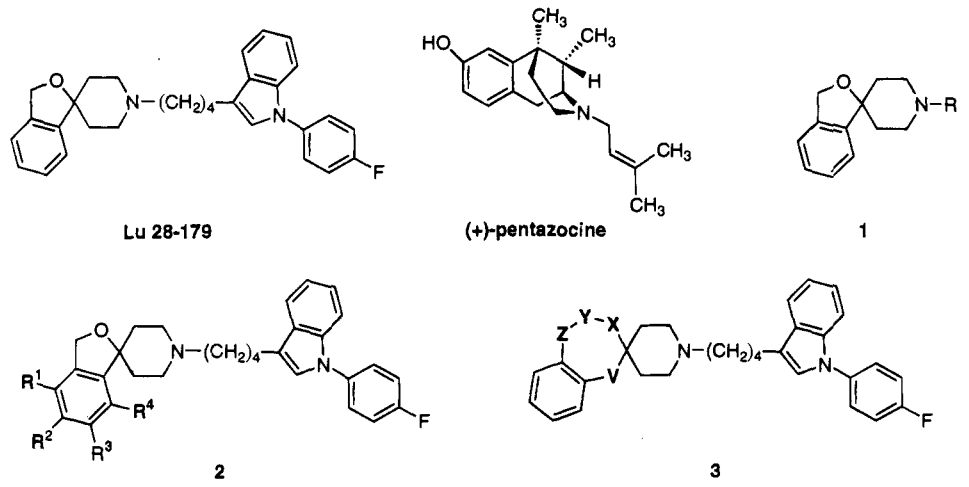


Figure 1. Reference compounds and target compounds.

activities are virtually nonexistent. The same is true for in vivo effects. Only the involvement of σ binding sites in motor function seems to be based on more solid evidence.[18] A consequence of these incomplete results is the lack of a reliable assay for determination of efficacy of σ ligands, and this lack is a serious problem in the characterization of new σ ligands.

The therapeutic potential of σ ligands for several possible indications has been hypothesized, but the main focus has been on psychosis.[19] The presumed antipsychotic activity of σ ligands has been associated mainly with σ_1 binding sites and is based on several lines of evidence, while the basis for application of σ ligands in other indications is more speculative.[19]

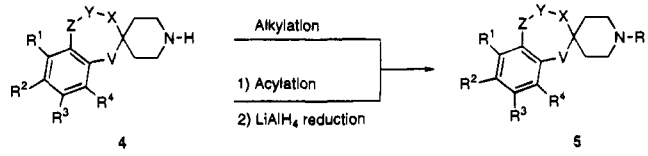
One of the major problems in elucidating the physiological function of σ binding sites has been the lack of subtype-selective ligands. As mentioned above, it seems at present that (+)-pentazocine is a selective σ_1 ligand. Recently, several types of compounds have been claimed to be selective σ_1 ligands, including a series of diamines structurally related to U50488,[20,21] 5-substituted 1-propyl-1,2,3,6-tetrahydropyridines,[22,23] and derivatives of 4-phenylpiperidines and -piperazines.[24] Selective ligands for the σ_2 binding site have until now been very elusive, and only some recently described 5-phenylmorphane derivatives have shown selectivity for σ_2 vs σ_1 binding sites with affinity in the nanomolar range.[25] However, these derivatives also have affinity for opioid receptors.[26]

We have previously described the spiropiperidine derivative Lu 28-179 (Figure 1) as a σ ligand with high affinity for σ_2 binding sites and with potent anxiolytic activity in rats.[27,28] In the preceding article[29] we demonstrated the selectivity of Lu 28-179 and related compounds for the σ_2 binding site. In order to further elucidate the structural requirements for this unique selectivity within this class of spiropiperidines, various structural modifications (Figure 1) were performed. These include variations of the N-substituent (**1**), introduction of substituents in the spiropiperidine ring system (**2**), and variation of the spiro ring system (**3**).

Chemistry

The compounds were prepared by two methods. Alkylation of various spiropiperidines **4** (Scheme 1) by use of either commercially available alkyl halides or methanesulfonates, which were prepared from the corresponding alcohols, generally gave the target compounds in good yields. In several cases it was more convenient to prepare the alkylated piperidine derivatives **5** in two steps: Acylation of the spiropiperidine followed by reduction of the resulting amide with lithium aluminum hydride. The isopropyl derivative **1e** was prepared by reductive alkylation using acetone as alkylating reagent and H_2/Pd–C as the reducing agent.

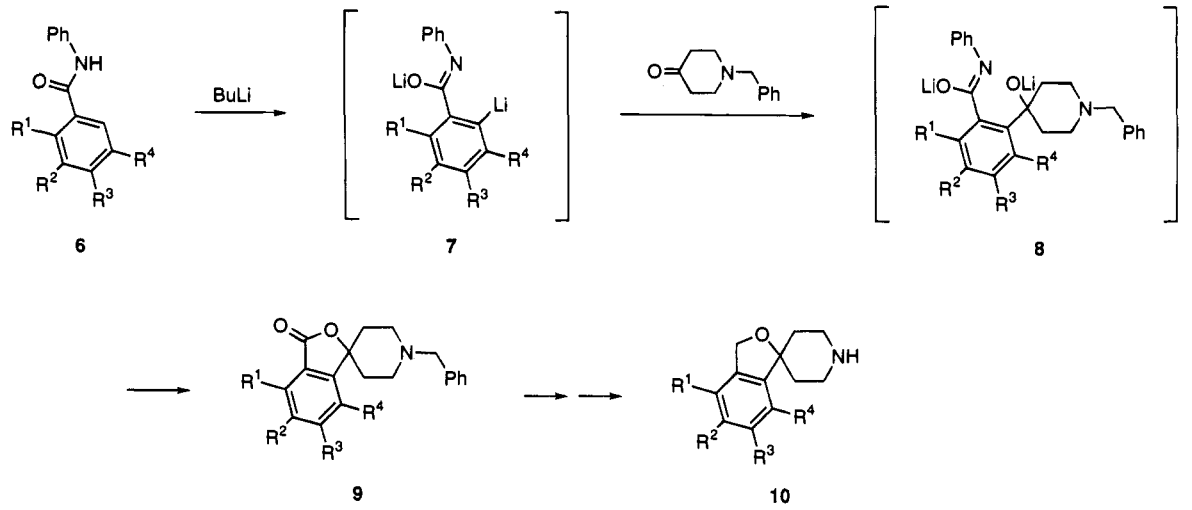
Scheme 1. General Method for Preparation of Target Compounds



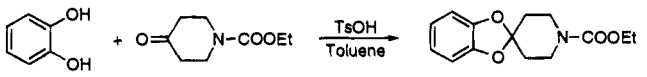
The parent spiropiperidine **1a** could be prepared in excellent yield by the method described by Marxer et al.[30] As shown in Scheme 2, this synthesis consists of dilithiation of benzanilides **6**. The ortho lithiation of the benzene ring is facilitated by the anion-stabilizing effect of the lithioamide group (**7**). Addition of 1-benzyl-4-piperidone followed by acidic workup directly gave the lactone **9**, which was converted to the corresponding isobenzofuran by reduction to the diol, followed by dehydration with phosphoric acid, as recently described.[31] Introduction of substituents in the benzene ring has a pronounced effect on the outcome of this reaction. Ortho-substituted benzanilides can, of course, only give one type of product, **2a** and **2e**. The same is true for para-substituted benzanilides, **2c**, **2f**, and **2h**. Meta substitution can principally give two products, depending on which ortho carbon is being lithiated. However, introduction of fluorine in the meta position of the benzanilide only gave one product, in which the ring closure occurred ortho to fluorine, **2d**. Contrary, the corresponding methyl derivative solely gave ring closure para to the methyl group (**2g**). These results clearly indicate that the strongly electronegative fluorine atom stabilizes an ortho carbanion, whereas the electron-donating methyl group exerts the least destabilizing effect in the position para to the methyl group.

The various spiropiperidines used in the syntheses of **3a–j**, except **3d**, were generally prepared according to literature methods (see the Experimental Section for references). In some instances, these procedures result in either *N*-methyl or *N*-benzyl derivatives. *N*-Methyl derivatives were converted to the corresponding second-

Scheme 2. General Method for Preparation of Spiro[isobenzofuran-1(3*H*),4′-piperidines]



Scheme 3. Preparation of the Spiro[1,3-benzodioxole-2,4′-piperidine] Nucleus



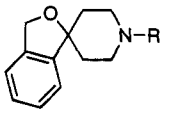
ary amines by treatment with ethyl chloroformate to give the corresponding carbamate, followed by acidic or alkaline hydrolysis of the carbamate group. *N*-Benzyl derivatives were debenzylated by catalytic hydrogenation. The spiro[1,3-benzodioxole-2,4′-piperidine] ring system in **3d** has not been described previously. It was easily prepared in good yields by ketalization of 1-benzyl-4-piperidone with pyrochatecol, as depicted in Scheme 3.

Results and Discussion

Affinity of new compounds for σ_1 and σ_2 binding sites is shown in Tables 1–3, and affinity of reference compounds is shown in Table 4. [^{3}H]-(+)-Pentazocine was used for labeling of σ_1 binding sites, whereas [^{3}H]-DTG was used for labeling of σ_2 binding sites. Further details are given in the Experimental Section. Although DTG has equal affinity for σ_1 and σ_2 binding sites, the [^{3}H]DTG binding assay using whole rat brain homogenates, except cerebellum, is specific for σ_2 binding sites due to the greater density of σ_2 binding sites compared to σ_1 binding sites in rat brain. The σ_2 specificity of our [^{3}H]DTG binding assay was confirmed by testing a series of compounds with and without the presence of 200 nM of (+)-pentazocine. In all cases, addition of (+)-pentazocine reduced the specific binding with less than 10% (results not shown). Furthermore, as seen in Table 4, (+)-pentazocine exerts very low affinity in the [^{3}H]-DTG assay.

It is evident from the data in Table 1 that the N-substituent is of major importance for affinity of spiropiperidines for both σ_1 and σ_2 binding sites. The parent compound **1a** and derivatives with small substituents, **1b** and **1c**, are virtually inactive. Increasing the chain length of the N-substituent results in compounds (**1f–h**) with increasing affinity for both σ_1 and σ_2 binding sites. Subnanomolar affinity is retained by further lengthening of the N-substituent, as demonstrated by the series **1i–n**. The isopropyl derivative **1e** displays higher affinity than the ethyl derivative **1c**.

Table 1. In Vitro Affinities for σ Binding Sites:[a] Variation of Side Chain

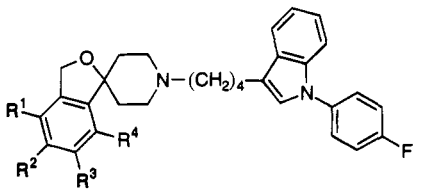


compd	R	[^{3}H]-(+)-pentazocine (σ_1)	[^{3}H]DTG (σ_2)	σ_1/σ_2
1a	H	630	11000	0.06
1b	Me	160	1300	0.12
1c	Et	140	270	0.52
1d	*n*-Pr	4.7	23	0.20
1e	*i*-Pr	31	49	0.63
1f	*n*-Bu	2.5	7.3	0.34
1g	$(CH_2)_2Ph$	2.2	2.9	0.76
1h	$(CH_2)_3Ph$	0.56	1.1	0.51
1i	$(CH_2)_4Ph$	0.27	0.25	1.1
1j	$(CH_2)_5Ph$	0.82	0.20	4.1
1k	$(CH_2)_6Ph$	0.53	0.20	2.7
1l	$(CH_2)_4C_6H_{11}$	1.5	0.07	21
1m	$(CH_2)_3OC_6H_{11}$	0.40	0.07	5.7
1n	$(CH_2)_3SC_6H_{11}$	0.96	0.26	3.7
1o	$(CH_2)_3SO_2CH_3$	6.3	430	0.015

[a] 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 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).

This indicates that steric hindrance around the basic nitrogen atom is tolerated by σ binding sites. The finding that affinity for σ binding sites depends on the nature of the N-substituent has been demonstrated in several other series of σ ligands.[32–35] However, the σ_1/σ_2 ratio also seems to depend on the structure of the N-substituent (Table 1). Derivatives with small substituents have preference for σ_1 vs σ_2 binding sites. By increasing the chain length of the N-substituent, a shift toward σ_2 selectivity is seen, and **1l**, which has a very lipophilic N-substituent, is outstanding, having both a very high affinity for σ_2 binding sites and a selectivity factor of 21 vs σ_1. Introducing the 1-(4-fluorophenyl)-

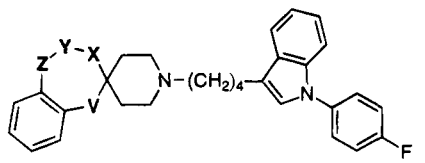
Table 2. In Vitro Affinities for σ Binding Sites:[a] Substituent Effects



compd	R^1	R^2	R^3	R^4	[^{3}H]-(+)-pentazocine (σ_1)	[^{3}H]DTG (σ_2)	σ_1/σ_2
2a	F	H	H	H	290	1.8	160
2b	H	H	F	H	5.5	0.31	18
2c	H	H	H	F	150	0.58	260
2d	CF_3	H	H	H	180	2.6	69
2e	H	H	CF_3	H	30	7.0	4.3
2f	H	Me	H	H	9.5	2.3	4.1
2g	H	H	*i*-Pr	H	65	70	0.93

[a] Results are expressed as IC_{50} values (nM). See footnote in Table 1.

Table 3. In Vitro Affinities for σ Binding Sites:[a] Ring Variations



compd	X	Y	Z	V	[^{3}H]-(+)-pentazocine (σ_1)	[^{3}H]DTG (σ_2)	σ_1/σ_2
3a	S	CH_2	–	–	35	0.14	250
3b	CH_2	O	–	–	3.8	12	0.32
3c	CH_2	–	–	O	360	340	1.1
3d	O	–	–	O	430	270	1.6
3e	O	CH_2	–	CH_2	23	1.1	21
3f	CH_2	O	–	CH_2	200	250	0.8
3g	CH_2	CH_2	–	O	81	23	3.5
3h	O	CH_2	CH_2	–	53	0.90	59
3i	CH_2	O	CH_2	–	3.4	0.34	10
3j	CH_2	CH_2	O	–	7.0	3.0	2.3

[a] Results are expressed as IC_{50} values (nM). See footnote in Table 1.

Table 4. In Vitro Affinities for σ Binding Sites:[a] Reference Compounds

compd	[^{3}H]-(+)-pentazocine (σ_1)	[^{3}H]DTG (σ_2)	σ_1/σ_2
Lu 28-179	17	0.12	140
DTG	36	52	0.70
(+)-pentazocine	3.0	2100	0.001
(−)-pentazocine	8.9	29	0.31
rimcazole	690	180	3.8
BMY 14802	60	230	0.26
DuP 734	2.6	23	0.11
haloperidol	0.65	17	0.04
L-687,384	0.26	12	0.02

[a] Results are expressed as IC_{50} values (nM). See footnote in Table 1.

indole group results in Lu 28-179[29] (Table 4) that is one of the most potent and σ_2-selective compounds described until now.

If this dependence of the σ_1/σ_2 ratio on lipophilicity of the N-substituent holds true, it should be possible to obtain σ_1-selective compounds by introducing hydrophilic N-substituents. Indeed, the methylsulfonyl derivative **1o** exerts potent and selective affinity for σ_1 binding sites. Of course, lipophilicity of the N-substituent is not the only factor governing the σ_1/σ_2 ratio (vide infra). However, the present data provides evidence that the nature of this substituent is one of the key factors governing σ_1/σ_2 selectivity.

In order to study the effects of substituents in the spiropiperidine ring system on affinity and selectivity for σ_1/σ_2 binding sites, Lu 28-179 was chosen as model structure (Table 2). Fluorine or trifluoromethyl substituents in either the 4- or 7-position of the isobenzofuran moiety (**2a**, **2c**, and **2d**) generally reduce affinity for both σ_1 and σ_2 binding sites by a factor 5−20, while the high σ_2 selectivity of Lu 28-179 is retained in these derivatives. This slight reduction in affinity for σ binding sites by introduction of substituents in the spiropiperidine ring system has been described previously in a corresponding spirotetralin series.[36] However, introduction of substituents in the 5- or 6-positions significantly reduces σ_1/σ_2 selectivity. The 5-methyl derivative **2f** is almost equipotent at σ_1 and σ_2 binding sites with somewhat reduced σ_2 affinity compared to Lu 28-179. The 6-trifluoromethyl derivative **2e** exerts a similar trend, whereas the corresponding 6-fluoro derivative **2b** has retained the high affinity for σ_2 binding sites and displays a higher degree of σ_2 selectivity than **2e** and **2f**. The more bulky and lipophilic 6-isopropyl derivative **2g** is unselective with greatly reduced σ_2 affinity compared to Lu 28-179. The significant impact of substituents in the 5- or 6-position of the isobenzofuran on both σ_1 and σ_2 affinity might indicate that this benzene ring is involved in binding to a primary σ_1/σ_2 binding site.

The structure of the spiropiperidine ring system to a very large extent determines the affinity for both σ_1 and σ_2 binding sites (Table 3). The sulfur analogue, **3a**, of Lu 28-179 exerts the same pharmacological profile as Lu 28-179, both with respect to selectivity and potency. The corresponding indan derivatives with various N-substituents have also been described as very potent σ ligands,[36] although the σ_1/σ_2 selectivity of these derivatives is unknown. Interestingly, interchanging the oxygen atom and the neighboring methylene group in Lu 28-179 to give **3b** causes a complete shift in profile. The σ_2 affinity of **3b** is reduced by a factor 100 compared to Lu 28-179, whereas the σ_1 affinity is enhanced by a factor 5. Obviously, this shift in profile cannot be due to conformational differences but must be due to a change in electrostatic interactions of **3b** with the binding site. Compound **3b** is the ring-closed analogue of the corresponding (2-methoxyphenyl)piperidine and piperazine derivatives described in the preceding article,[29] and they are also equipotent at σ_1 and σ_2 binding sites. Oxygen atoms in this particular position of the phenyl ring thus have detrimental effects on both σ_2 selectivity and potency.

The greatly reduced affinity for both σ binding sites of compounds **3c** and **3d** are not particularly surprising, considering the completely different geometry of the benzene ring relative to the piperidine ring when compared to Lu 28-179. The same trend is observed in the six-membered ring analogues **3f** and **3g**. However, it is interesting to note that compound **3e**, in which the oxygen atom has the same position relative to the piperidine ring as in Lu 28-179, has high affinity for σ_2 binding sites and does exert σ_2 selectivity. Furthermore, the carbocyclic spiropiperidine analogues of **3e,f** with either a keto or a hydroxy group in the 1-position have

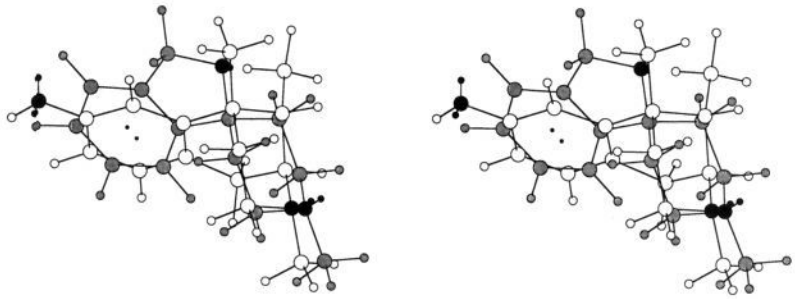


Figure 2. Stereoview of superimposition of the *N*-methyl analogue of (+)-pentazocine and **1b**. The *N*-methyl derivatives were chosen for simplicity. Structure with open circles is (+)-pentazocine, and structure with light shaded circles is **1b**. Black circles represent hetero atoms and their respective lone pairs. The fit is made by superimposing three points: Centers of the benzene rings, 4-positions of the piperidine rings, and the nitrogen atoms. RMS of the fit is 0.353 Å.

been described as potent σ ligands.[37] Thus, the relative position of the benzene ring is not the only factor governing affinity and selectivity for σ binding sites. The heteroatom is also of importance.

In the six-membered ring compounds **3h–j** the benzene ring is attached directly to the piperidine ring as in Lu 28-179. Not surprisingly, when considering the position of the oxygen atom, compound **3h** resembles Lu 28-179 very much in binding profile, although **3h** is somewhat less selective toward σ_1. By moving the oxygen atom to the 2- or 3-position (compounds **3i,j**), a significant increase in σ_1 affinity is observed. This shift in profile is similar to the shift mentioned above for Lu 28-179 and compound **3b**. The carbocyclic *N*-benzyl analogue L-687,384[36] (Table 4) is very selective for σ_1 binding sites. However, whether this selectivity is due to the absence of oxygen atoms in the spiropiperidine ring system and/or to the *N*-benzyl substituent still needs to be clarified.

Finally, it shall be mentioned that selected compounds (**1i, 1m, 2d, 3e, 3h,** and **3j**) have been tested for affinity for 5-HT_{1A}, 5-HT_{2A}, and D_2 receptors and for α_1 adrenoceptors (results not shown). None of the compounds exert any appreciable affinity for these receptors (IC_{50} > 250 nM), and thus they are selective σ ligands.

In recent years, several pharmacophore models of the σ binding site have been presented (for brief review, see ref 38). Most of the models suggest that σ ligands have three points of interaction with the σ binding site: A basic nitrogen atom, a lipophilic group that in most cases consists of a benzene ring in proximity of the basic nitrogen atom, and a larger lipophilic group attached to the basic nitrogen atom. However, due to the lack of σ_2 selective ligands, none of these models explain the differences in binding to σ_1 and σ_2 subtypes. The results obtained in this study and in the preceding article[29] give rise to several considerations that might help to understand the structural requirements for binding to σ_1 and σ_2 binding sites, respectively.

As shown in Figure 2, there is an excellent fit between (+)-pentazocine and the conformation of **1b**, in which the benzene ring is placed in an axial position of the piperidine ring (the *N*-methyl derivatives were chosen for simplicity; see the Experimental Section for calculational details). An equally excellent fit between (−)-pentazocine and **1b** can be obtained (not shown). The only difference from the fit with (+)-pentazocine is the spatial position of the β-methyl group relative to the basic nitrogen in pentazocine. Therefore, it is obvious to assume that the axial conformation is the biologically active conformation both for binding to σ_1 and σ_2 binding sites, although this assumption must be taken with some caution since the axial conformation lies 2.6 kcal/mol higher in energy than the equatorial conformation. Similar results have been reported for calculations on the corresponding spiro[tetralin-1,4′-piperidines].[39] Assuming the axial conformation is active, the close fit between **1b** and both enantiomers of pentazocine might indicate that the core structure is not the determinant for σ_2 selectivity because of the high σ_1 selectivity of (+)-pentazocine. From this point of view, it is more likely that either the N-substituent, an optional substituent in the benzene ring, or both govern σ_2 selectivity. Interestingly, (−)-pentazocine is almost equipotent at σ_1 and σ_2 binding sites (Table 4). Although this might be explained by different spatial localizations of the β-methyl group relative to the basic nitrogen of the two enantiomers of pentazocine, respectively, it can also be explained by differences in the spatial localizations of the hydroxy groups of the enantiomers. This assumption would be in agreement with the sensitivity of the σ_1/σ_2 ratio toward substituent pattern in the phenyl ring found in the series **2a–g**. It shall be mentioned that an earlier study has shown that the phenolic group of pentazocine is not critical for binding to σ sites.[40] Furthermore, Glennon et al.[41] have claimed that the primary σ pharmacophore of pentazocine and other benzomorphans consists of amine-substituted 2-phenylaminoethanes, and in these derivatives substituents in the phenyl ring are of minor importance for σ affinity. However, the results in this study indicate that substituents in the benzene ring might very well be important for σ_1/σ_2 selectivity.

As mentioned above, most σ models include a lipophilic pocket, and the results in this study emphasize the importance of this binding site. However, the dependence of σ_1/σ_2 selectivity on lipophilicity of the N-substituent clearly indicates that this site might be more than merely a lipophilic binding site. The high σ_1 selectivity of **1o** indicates the presence of a further hydrophilic binding site.

Conclusion

This work presents a series of spiropiperidines to which some of the most potent and σ_2 selective ligands described so far belong. The structural determinants governing σ_1/σ_2 selectivity have been investigated, and at least two factors were found to be critical. Small, less lipophilic and larger hydrophilic N-substituents

favor σ_1 selectivity, whereas large lipophilic N-substituents result in highly potent σ_2 selective compounds. Substituents in the benzene ring of the spiropiperidine ring system also have pronounced effect on σ_1/σ_2 selectivity, although further work is needed to fully clarify this aspect. The results presented in this and the preceding studies provide valuable information for understanding the structural requirements for binding to σ_1 and σ_2 binding sites. Furthermore, the lead compound in this series, Lu 28-179, exerts potent anxiolytic activity in rats, thus indicating that σ_2 ligands of this class might constitute a completely new class of anxiolytics.

Experimental Section

Melting points were determined on a Büchi SMP-20 apparatus and are uncorrected. ^{1}H NMR spectra were recorded at 250 MHz on a Bruker AC 250 spectrometer. Deuterated chloroform (99.8% D), benzene (99.5% D), or dimethyl sulfoxide (99.9% D) were used as solvents. TMS was used as internal reference standard. Chemical shifts 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, sx = sextet, h = heptet, dd = double doublet, dt = double triplet, m = multiplet. NMR signals corresponding to acidic protons are omitted. Microanalyses were performed by Lundbeck Analytical Department, and results obtained were within ±0.4% of the theoretical values, except where otherwise stated. Standard workup procedure refers to extraction with an organic solvent from a proper aqueous solution, drying of the organic extracts over anhydrous magnesium sulfate, filtration, and removal of solvent in vacuo. In all chromatographic purifications, silica gel of type Kiselgel 60, 230–400 mesh ASTM, was used.

Starting Materials. The parent spiro[isobenzofuran-1(3*H*),4′-piperidine], **1a**, was prepared according to Marxer et al.[30] The corresponding secondary spiropiperidines with substitutents in the benzene ring, **10**, were all prepared by similar procedures and characterized as follows:

4-Fluorospiro[isobenzofuran-1(3*H*),4′-piperidine]: colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.70–1.95 (m, 4H), 2.95–3.15 (m, 4H), 5.10 (s, 2H), 6.95 (t, 2H), 7.20–7.30 (m, 1H).

6-Fluorospiro[isobenzofuran-1(3*H*),4′-piperidine] hydrochloride: mp 221–24 °C (ethanol/acetone); ^{1}H NMR (DMSO-d_6) δ 1.80 (d, 2H), 2.20 (dt, 2H), 3.05 (dt, 2H), 3.30 (d, 2H), 5.00 (s, 2H), 7.00 (dd, 1H), 7.15 (dt, 1H), 7.35 (dd, 1H).

7-Fluorospiro[isobenzofuran-1(3*H*),4′-piperidine]: colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.75 (d, 3H), 2.15 (m, 1H), 2.95–3.10 (m, 4H), 5.10 (s, 2H), 6.85–7.00 (m, 2H), 7.15–7.30 (m, 1H).

4-(Trifluoromethyl)spiro[isobenzofuran-1(3*H*),4′-piperidine] hydrochloride: mp 268–75 °C (ethanol/acetone); ^{1}H NMR (DMSO-d_6) δ 1.80 (d, 2H), 2.25 (dt, 2H), 3.10 (dt, 2H), 3.30 (d, 2H), 5.20 (s, 2H), 7.50 (d, 1H), 7.60 (t, 1H), 7.70 (d, 1H).

6-(Trifluoromethyl)spiro[isobenzofuran-1(3*H*),4′-piperidine] hydrochloride: mp 255–63 °C (ether/acetone/ethanol); ^{1}H NMR (DMSO-d_6) δ 1.70 (d, 2H), 2.30 (dt, 2H), 3.05 (dt, 2H), 3.30 (d, 2H), 5.00 (s, 2H), 7.50 (s, 1H), 7.60 (d, 1H), 7.70 (d, 1H).

5-Methylspiro[isobenzofuran-1(3*H*),4′-piperidine]: colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.60–2.00 (m, 4H), 2.35 (s, 3H), 2.95–3.10 (m, 4H), 5.00 (s, 2H), 6.95–7.10 (m, 3H).

6-(2-Propyl)spiro[isobenzofuran-1(3*H*),4′-piperidine] hydrochloride: mp 201–11 °C (ethanol/acetone); ^{1}H NMR (DMSO-d_6) δ 1.20 (d, 6H), 1.75 (d, 2H), 2.25 (dt, 2H), 2.90 (h, 1H), 3.05 (dt, 2H), 3.25 (d, 2H), 5.00 (s, 2H), 7.00 (s, 1H), 7.20 (s, 2H).

The various spiropiperidine ring systems used in the syntheses of **3a–c** and **3e–j** were prepared according to literature methods: spiro[benzo[c]thiophene-1(3*H*),4′-piperidine][42] (synthesis of **3a**), spiro[benzofuran-3(2*H*),4′-piperidine][43] (synthesis of **3b**), spiro[benzofuran-2(3*H*),4′-piperidine][44] (synthesis of **3c**), 1,4-dihydrospiro[3*H*-2-benzopyran-3,4′-piperidine][31] (synthesis of **3e**), spiro[2*H*-1-benzopyran-3(4*H*),4′-piperidine][45] (synthesis of **3f**), 3,4-dihydrospiro[2*H*-1-benzopyran-2,4′-piperidine][46] (synthesis of **3g**), 3,4-dihydrospiro[1*H*-2-benzopyran-1,4′-piperidine][46] (synthesis of **3h**), spiro-[1*H*-2-benzopyran-4(3*H*),4′-piperidine][47] (synthesis of **3i**), and 2,3-dihydrospiro[4*H*-1-benzopyran-4,4′-piperidine] (synthesis of **3j**); this last compound was obtained as a colorless oil (^{1}H NMR ($CDCl_3$) δ 1.60 (dd, 2H), 1.95–2.05 (m, 2H), 2.05 (t, 2H), 2.75–3.05 (m, 4H), 4.10 (t, 2H), 6.80 (d, 1H), 6.90 (dt, 1H), 7.10 (dt, 1H), 7.40 (d, 1H)) by a method analogous to the preparation of the corresponding carbocyclic compound 3,4-dihydrospiro[naphthalene-1(2*H*),4′-piperidine].[48]

1′-Methylspiro[isobenzofuran-1(3*H*),4′-piperidine] Maleate (1b). A solution of **1a** (2.0 g, 10 mmol) in 99% formic acid (4 mL) and 30% aqueous formaldehyde (4 mL) was heated to 100 °C for 1 h. Concentration in vacuo and addition of ammonia followed by standard workup with ether gave the free base of **1b** as an oil. Crystalline maleate, **1b**, was obtained from acetone by addition of maleic acid: yield 0.8 g, 24%; mp 168–70 °C; ^{1}H NMR (DMSO-d_6) δ 1.85 (d, 2H), 2.15 (dt, 2H), 2.90 (s, 3H), 3.25 (dt, 2H), 3.45 (d, 2H), 5.05 (s, 2H), 6.00 (s, 2H), 7.15–7.25 (m, 1H), 7.30–7.40 (m, 3H). Anal. ($C_{13}H_{17}NO\cdot C_4H_4O_4$) C, H, N.

1′-Ethylspiro[isobenzofuran-1(3*H*),4′-piperidine] Maleate (1c). Acetic acid anhydride (2.0 mL, 20 mmol) was added dropwise to a solution of **1a** (2.0 g, 10 mmol) in methylene chloride (50 mL). After stirring for 30 min at room temperature, the reaction mixture was concentrated in vacuo leaving crude 1′-acetylspiro[isobenzofuran-1(3*H*),4′-piperidine] as an oil. Tetrahydrofuran (100 mL) was added, and the resulting solution was treated with lithium aluminum hydride (1.0 g, 25 mmol), followed by reflux for 2 h. Quench with aqueous sodium hydroxide followed by standard workup with ethyl acetate gave the free base of **1c** as an oil. Crystalline maleate, **1c**, was obtained from an acetone/ether solution by addition of maleic acid: yield 1.5 g, 43%; mp 128–29 °C; ^{1}H NMR (DMSO-d_6) δ 1.25 (t, 3H), 1.85 (d, 2H), 2.15 (dt, 2H), 3.00–3.40 (m, 4H), 3.50 (d, 2H), 5.00 (s, 2H), 6.05 (s, 2H), 7.10–7.20 (m, 1H), 7.25–7.40 (m, 3H). Anal. ($C_{14}H_{19}NO\cdot C_4H_4O_4$) C, H, N.

1′-(1-Propyl)spiro[isobenzofuran-1(3*H*),4′-piperidine] Maleate (1d). A mixture of **1a** (2.0 g, 10 mmol), propionyl chloride (3 g, 32 mmol), potassium carbonate (5.0 g, 36 mmol), water (100 mL), and toluene (100 mL) was stirred at room temperature for 3 h. The phases were separated, and the organic phase was washed with water. Removal of toluene in vacuo gave crude 1′-propionylspiro[isobenzofuran-1(3*H*),4′-piperidine] as an oil. Tetrahydrofuran (100 mL) was added, and the resulting solution was treated with lithium aluminum hydride (1.0 g, 25 mmol). After reflux for 3 h, the reaction was quenched with aqueous sodium hydroxide followed by standard workup. The resulting oil was dissolved in ethyl acetate, and addition of maleic acid gave crystalline **1d**: yield 0.7 g, 19%; mp 107–09 °C; ^{1}H NMR (DMSO-d_6) δ 0.95 (t, 3H), 1.70 (sx, 2H), 1.85 (d, 2H), 2.15 (dt, 2H), 2.80–3.65 (m, 6H), 5.00 (s, 2H), 6.05 (s, 2H), 7.10–7.25 (m, 1H), 7.25–7.40 (m, 3H). Anal. ($C_{15}H_{21}NO\cdot C_4H_4O_4$) C, H, N.

In a similar manner the following spiro[isobenzofuran-1(3*H*),4′-piperidine] derivatives were prepared.

1′-Phenethylspiro[isobenzofuran-1(3*H*),4′-piperidine] maleate (1g): mp 161–63 °C (acetone/ether); ^{1}H NMR (DMSO-d_6) δ 1.85 (d, 2H), 2.20 (dt, 2H), 3.00–3.10 (m, 2H), 3.10–3.50 (m, 4H), 3.60 (d, 2H), 5.05 (s, 2H), 6.05 (s, 2H), 7.15–7.45 (m, 9H). Anal. ($C_{20}H_{23}NO\cdot C_4H_4O_4$) C, H, N.

1′-(3-Phenyl-1-propyl)spiro[isobenzofuran-1(3*H*),4′-piperidine] maleate (1h): mp 142–44 °C (acetone/ether); ^{1}H NMR (DMSO-d_6) δ 1.85 (d, 2H), 2.00 (qui, 2H), 2.15 (dt, 2H), 2.65 (t, 2H), 3.00–3.30 (m, 4H), 3.55 (d, 2H), 5.05 (s, 2H), 6.05 (s, 2H), 7.05–7.40 (m, 9H). Anal. ($C_{21}H_{25}NO\cdot C_4H_4O_4$) C, H, N.

1′-(5-Phenyl-1-pentyl)spiro[isobenzofuran-1(3*H*),4′-piperidine] oxalate (1j): mp 115–17 °C (acetone/ether); ^{1}H NMR (DMSO-d_6) δ 1.30 (qui, 2H), 1.60 (qui, 2H), 1.65–1.90 (m, 4H), 2.30 (dt, 2H), 2.60 (t, 2H), 2.95–3.20 (m, 4H), 3.45

(d, 2H), 5.00 (s, 2H), 7.10–7.40 (m, 9H). Anal. ($C_{23}H_{29}NO{\cdot}C_2H_2O_4$) C, H, N.

1′-(6-Phenyl-1-hexyl)spiro[isobenzofuran-1(3*H*),4′-piperidine] oxalate (1k): mp 156–57 °C (ethanol/ether); ^{1}H NMR (DMSO-d_6) δ 1.20–1.40 (m, 4H), 1.50–1.75 (m, 4H), 1.80 (d, 2H), 2.30 (dt, 2H), 2.60 (t, 2H), 2.95–3.20 (m, 4H), 3.40 (d, 2H), 5.00 (s, 2H), 7.05–7.40 (m, 9H). Anal. ($C_{24}H_{31}NO{\cdot}C_2H_2O_4$) C, H, N.

1′-(2-Propyl)spiro[isobenzofuran-1(3*H*),4′-piperidine] Maleate (1e). A mixture of **1a** (2.0 g, 10 mmol), 5% Pd/C (2.5 g), acetone (2.0 g, 35 mmol), and ethanol (100 mL) was hydrogenated in a Parr apparatus at 3.5 atm of hydrogen pressure for 16 h. Filtration and removal of solvent in vacuo gave an oil that was dissolved in ethyl acetate. Addition of maleic acid gave **1e** that was recrystallized from acetone/ether: yield 2.0 g, 82%; mp 145–47 °C; ^{1}H NMR (DMSO-d_6) δ 1.30 (d, 6H), 1.85 (d, 2H), 2.25 (dt, 2H), 3.15 (dt, 2H), 3.40 (d, 2H), 3.55 (h, 1H), 5.00 (s, 2H), 6.05 (s, 2H), 7.10–7.20 (m, 1H), 7.25–7.40 (m, 3H). Anal. ($C_{15}H_{21}NO{\cdot}C_4H_4O_4$) C, H, N.

1′-(1-Butyl)spiro[isobenzofuran-1(3*H*),4′-piperidine] Oxalate (1f). A mixture of **1a** (2.0 g, 10 mmol), *n*-butyl bromide (4.0 g, 30 mmol), potassium carbonate (5.0 g, 35 mmol), and catalytic amounts of potassium iodide in methyl isobutyl ketone (MIBK) (100 mL) was refluxed for 16 h. The reaction mixture was washed with water followed by extraction with 1 M methanesulfonic acid. The acidic phase was separated and made alkaline with conc ammonia. Extraction with ether, drying over magnesium sulfate, and removal of solvent in vacuo gave the crude free base of **1f**. The oxalate salt, **1f**, was obtained from acetone by addition of oxalic acid. The salt was recrystallized from ethanol/ether: yield 1.2 g, 35%; mp 171–73 °C; ^{1}H NMR (DMSO-d_6) δ 0.95 (t, 3H), 1.30 (sx, 2H), 1.65 (qui, 2H), 1.80 (d, 2H), 2.35 (dt, 2H), 3.00–3.20 (m, 4H), 3.50 (d, 2H), 5.05 (s, 2H), 7.20–7.40 (m, 4H). Anal. ($C_{16}H_{23}NO{\cdot}C_2H_2O_4$) C, H, N.

1′-(4-Phenyl-1-butyl)spiro[isobenzofuran-1(3*H*),4′-piperidine] Fumarate (1i). A solution of 4-phenyl-1-butanol (20 g, 0.13 mol) and triethylamine (15 g, 0.15 mol) in methylene chloride (200 mL) was cooled to 5 °C. A solution of methanesulfonyl chloride (12 mL, 0.15 mol) in methylene chloride (50 mL) was added dropwise at 5 °C. After stirring for 1 h at 10 °C, the reaction mixture was washed with water, dried over magnesium sulfate, and concentrated in vacuo, giving 4-phenyl-1-butyl methanesulfonate as an oil (27 g, 91%). A portion of the oil (6.0 g, 25 mmol) was dissolved in MIBK (75 mL) together with **1a** (2.0 g, 10 mmol). Potassium carbonate (14 g, 0.1 mol) and catalytic amounts of potassium iodide were added followed by reflux for 20 h. Filtration and removal of solvent in vacuo gave an oil that was purified by flash chromatography (eluent: ether/methanol/triethylamine, 93:5:2). The free base of **1i** was obtained as an oil. The fumarate salt, **1i**, crystallized from acetone/ethanol by addition of fumaric acid: yield 0.6 g, 14%; mp 197–99 °C; ^{1}H NMR (DMSO-d_6) δ 1.50–1.65 (m, 4H), 1.70 (d, 2H), 2.10 (dt, 2H), 2.50–2.80 (m, 4H), 3.10 (d, 2H), 5.00 (s, 2H), 6.55 (s, 2H), 7.10–7.35 (m, 9H). Anal. ($C_{22}H_{27}NO{\cdot}C_4H_4O_4$) C, H, N.

In a similar manner the following spiro[isobenzofuran-1(3*H*),4′-piperidine] derivatives were prepared.

1′-(4-Cyclohexyl-1-butyl)spiro[isobenzofuran-1(3*H*),4′-piperidine] oxalate (1l): mp 139–42 °C (acetone/ether); ^{1}H NMR (DMSO-d_6) δ 0.90 (qui, 2H), 1.00–1.40 (m, 8H), 1.50–1.75 (m, 7H), 1.80 (d, 2H), 2.30 (dt, 2H), 2.90–3.20 (m, 4H), 3.40 (d, 2H), 5.00 (s, 2H), 7.15–7.40 (m, 4H). Anal. ($C_{22}H_{33}NO{\cdot}C_2H_2O_4$) C, H, N.

1′-(3-Cyclohexyloxy-1-propyl)spiro[isobenzofuran-1(3*H*),4′-piperidine] fumarate (1m): mp 154–55 °C (acetone/methanol); ^{1}H NMR (DMSO-d_6) δ 1.05–1.30 (m, 4H), 1.35–1.55 (m, 1H), 1.55–1.90 (m, 9H), 2.10 (dt, 2H), 2.55–2.85 (m, 4H), 3.10 (d, 2H), 3.20 (p, 1H), 3.45 (t, 2H), 5.00 (s, 2H), 6.55 (s, 2H), 7.15–7.35 (m, 4H). Anal. ($C_{21}H_{31}NO_2{\cdot}C_4H_4O_4$) C, H, N.

1′-[3-(Cyclohexylthio)-1-propyl]spiro[isobenzofuran-1(3*H*),4′-piperidine] oxalate (1n): mp 170–74 °C (acetone/ether); ^{1}H NMR (DMSO-d_6) δ 1.10–1.40 (m, 5H), 1.45–2.05 (m, 9H), 2.30 (dt, 2H), 2.55 (t, 2H), 2.70 (qui, 1H), 3.00–3.25 (m, 4H), 3.45 (d, 2H), 5.00 (s, 2H), 7.10–7.40 (m, 4H). Anal. ($C_{21}H_{31}NOS{\cdot}C_2H_2O_4$) C, H, N.

1′-[3-(Methylsulfonyl)-1-propyl]spiro[isobenzofuran-1(3*H*),4′-piperidine] oxalate (1o): mp 163–64 °C (acetone); ^{1}H NMR (DMSO-d_6) δ 1.80 (d, 2H), 2.15 (qui, 2H), 2.30 (dt, 2H), 3.00 (s, 3H), 3.00–3.35 (m, 9H), 3.45 (d, 2H), 5.05 (s, 2H), 7.15–7.40 (m, 4H). Anal. ($C_{16}H_{23}NO_3S{\cdot}C_2H_2O_4$) C, H, N.

6-Fluoro-1′-[4-[1-(4-fluorophenyl)-1*H*-indol-3-yl]-1-butyl]spiro[isobenzofuran-1(3*H*),4′-piperidine] Hydrochloride (2b). A mixture of 4-[1-(4-fluorophenyl)-1*H*-indol-3-yl]-1-butyl methanesulfonate[29] (2.0 g, 6 mmol) and 6-fluorospiro[isobenzofuran-1(3*H*),4′-piperidine] hydrochloride (1.4 g, 6 mmol) was dissolved in MIBK (100 mL). Potassium carbonate (4 g, 30 mmol) and catalytic amounts of potassium iodide were added followed by reflux for 25 h. Filtration and removal of solvent in vacuo gave an oil that was applied to flash chromatography (eluent: ethyl acetate/heptane/triethylamine, 7:5:1) giving the free base of **2b** as an oil. Crystalline **2b** was obtained from ether/acetone by addition of HCl/ether: yield 1.2 g, 40%; mp 227–31 °C; ^{1}H NMR (DMSO-d_6) δ 1.65–2.00 (m, 6H), 2.50 (dt, 2H), 2.80 (t, 2H), 3.00–3.25 (m, 4H), 3.50 (d, 2H), 5.00 (s, 2H), 6.90 (dd, 1H), 7.15 (qui, 3H), 7.25–7.50 (m, 4H), 7.50 (s, 1H), 7.55–7.70 (m, 3H). Anal. ($C_{30}H_{30}F_2N_2O{\cdot}HCl$) C, H, N.

In a similar manner the following spiropiperidine derivatives were prepared.

4-Fluoro-1′-[4-[1-(4-fluorophenyl)-1*H*-indol-3-yl]-1-butyl]spiro[isobenzofuran-1(3*H*),4′-piperidine] oxalate (2a): mp 160–63 °C (acetone); ^{1}H NMR (DMSO-d_6) δ 1.60–2.00 (m, 6H), 2.35 (dt, 2H), 2.80 (t, 2H), 3.00–3.25 (m, 4H), 3.45 (d, 2H), 5.10 (s, 2H), 7.00–7.25 (m, 4H), 7.30–7.50 (m, 5H), 7.50–7.70 (m, 3H). Anal. ($C_{30}H_{30}F_2N_2O{\cdot}C_2H_2O_4$) C, H, N.

7-Fluoro-1′-[4-[1-(4-fluorophenyl)-1*H*-indol-3-yl]-1-butyl]spiro[isobenzofuran-1(3*H*),4′-piperidine] oxalate (2c): mp 186–89 °C (acetone); ^{1}H NMR (DMSO-d_6) δ 1.60–2.00 (m, 6H), 2.35 (dt, 2H), 2.75 (t, 2H), 3.00–3.20 (m, 4H), 3.45 (d, 2H), 5.05 (s, 2H), 7.00–7.25 (m, 4H), 7.25–7.50 (m, 5H), 7.50–7.70 (m, 3H). Anal. ($C_{30}H_{30}F_2N_2O{\cdot}C_2H_2O_4$) C, H, N.

1′-[4-[1-(4-Fluorophenyl)-1*H*-indol-3-yl]-1-butyl]-4-(trifluoromethyl)spiro[isobenzofuran-1(3*H*),4′-piperidine] hemifumarate (2d): mp 192–95 °C (acetone/ethanol); ^{1}H NMR (DMSO-d_6) δ 1.55–1.75 (m, 4H), 1.80 (t, 1H), 2.00 (dt, 1H), 2.45 (dt, 2H), 2.50–2.60 (m, 4H), 2.75–2.95 (m, 4H), 5.10 (s, 2H), 6.60 (s, 1H), 7.15 (qui, 1H), 7.35 (t, 3H), 7.40–7.65 (m, 8H). Anal. ($C_{31}H_{30}F_4N_2O{\cdot}0.5C_4H_4O_4$) C, H, N.

1′-[4-[1-(4-Fluorophenyl)-1*H*-indol-3-yl]-1-butyl]-6-(trifluoromethyl)spiro[isobenzofuran-1(3*H*),4′-piperidine] sesquifumarate (2e): mp 100–5 °C (acetone/ethanol). ^{1}H NMR (DMSO-d_6) δ 1.60–1.90 (m, 6H), 2.30 (dt, 2H), 2.70–3.00 (m, 6H), 3.25 (d, 2H), 5.10 (s, 2H), 6.60 (s, 3H), 7.15 (qui, 1H), 7.30–7.75 (m, 11H). Anal. ($C_{31}H_{30}F_4N_2O{\cdot}1.5C_4H_4O_4$) C, H, N.

1′-[4-[1-(4-Fluorophenyl)-1*H*-indol-3-yl]-1-butyl]-5-methylspiro[isobenzofuran-1(3*H*),4′-piperidine] oxalate (2f): mp 154–56 °C (acetone); ^{1}H NMR (DMSO-d_6) δ 1.60–1.90 (m, 6H), 2.25 (dt, 2H), 2.30 (s, 3H), 2.80 (t, 2H), 3.00–3.20 (m, 4H), 3.45 (d, 2H), 5.00 (s, 2H), 7.00–7.25 (m, 5H), 7.30–7.55 (m, 4H), 7.55–7.70 (m, 3H). Anal. ($C_{31}H_{33}FN_2O{\cdot}C_2H_2O_4$) C, H, N.

1′-[4-[1-(4-Fluorophenyl)-1*H*-indol-3-yl]-1-butyl]-6-(2-propyl)spiro[isobenzofuran-1(3*H*),4′-piperidine] oxalate (2g): mp 139–44 °C (ethanol); ^{1}H NMR (DMSO-d_6) δ 1.20 (d, 6H), 1.65–195 (m, 6H), 2.30 (dt, 2H), 2.80 (t, 2H), 2.90 (h, 1H), 3.05–3.25 (m, 4H), 3.45 (d, 2H), 5.00 (s, 2H), 7.00–7.25 (m, 5H), 7.30–7.55 (m, 4H), 7.55–7.70 (m, 3H). Anal. ($C_{33}H_{37}FN_2O{\cdot}C_2H_2O_4$) C, H, N.

1′-[4-[1-(4-Fluorophenyl)-1*H*-indol-3-yl]-1-butyl]spiro[benzo[*c*]thiophene-1(3*H*),4′-piperidine] maleate (3a): mp 179–80 °C (acetone/methanol); ^{1}H NMR (DMSO-d_6) δ 1.65–1.90 (m, 4H), 2.00 (d, 2H), 2.40 (dt, 2H), 2.80 (t, 2H), 3.00 (t, 2H), 3.10–3.35 (m, 4H), 3.60 (d, 2H), 4.25 (s, 2H), 6.05 (s, 2H), 7.05–7.25 (m, 3H), 7.25–7.55 (m, 7H), 7.55–7.70 (m, 3H). Anal. ($C_{30}H_{31}FN_2S{\cdot}C_4H_4O_4$) C, H, N.

1'-[4-[1-(4-Fluorophenyl)-1*H*-indol-3-yl]-1-butyl]spiro-[benzofuran-3(2*H*),4'-piperidine] maleate (3b): mp 175–78 °C (acetone); ^{1}H NMR (DMSO-d_6) δ 1.65–1.80 (m, 4H), 1.90 (d, 2H), 2.05 (dt, 2H), 2.80 (t, 2H), 2.95–3.25 (m, 4H), 3.50 (d, 2H), 4.45 (s, 2H), 6.05 (s, 2H), 6.80 (d, 1H), 6.90 (t, 1H), 7.05–7.25 (m, 4H), 7.30–7.55 (m, 4H), 7.55–7.70 (m, 3H). Anal. ($C_{30}H_{31}FN_2O\cdot C_4H_4O_4$) C, H, N.

1'-[4-[1-(4-Fluorophenyl)-1*H*-indol-3-yl]-1-butyl]spiro-[benzofuran-2(3*H*),4'-piperidine] fumarate (3c): mp 148–50 °C (ethyl acetate); ^{1}H NMR (DMSO-d_6) δ 1.55–1.80 (m, 4H), 1.80–2.00 (m, 4H), 2.60–2.90 (m, 8H), 3.00 (s, 2H), 6.60 (s, 2H), 6.75 (d, 1H), 6.80 (t, 1H), 7.00–7.25 (m, 4H), 7.30–7.45 (m, 3H), 7.50 (d, 1H), 7.55–7.70 (m, 3H). Anal. ($C_{30}H_{31}FN_2O\cdot C_4H_4O_4$) H, N; C: calcd, 71.55; found, 71.01.

1,4-Dihydro-1'-[4-[1-(4-fluorophenyl)-1*H*-indol-3-yl]-1-butyl]spiro[3*H*-2-benzopyran-3,4'-piperidine] oxalate (3e): mp 142–43 °C (ethanol/acetone); ^{1}H NMR (DMSO-d_6) δ 1.60–2.00 (m, 8H), 2.70 (s, 2H), 2.75 (t, 2H), 2.90–3.20 (m, 4H), 3.25 (d, 2H), 4.70 (s, 2H), 7.00–7.20 (m, 6H), 7.30–7.50 (m, 4H), 7.50–7.70 (m, 3H). Anal. ($C_{31}H_{33}FN_2O\cdot C_2H_2O_4$) C, H, N.

1'-[4-[1-(4-Fluorophenyl)-1*H*-indol-3-yl]-1-butyl]spiro-[2*H*-1-benzopyran-3(4*H*),4'-piperidine] fumarate (3f): mp 148–51 °C (ethanol); ^{1}H NMR (DMSO-d_6) δ 1.40–1.60 (m, 4H), 1.60–1.80 (m, 4H), 2.65 (s, 2H), 2.70–3.95 (m, 8H), 3.90 (s, 2H), 6.75 (d, 1H), 6.80 (t, 1H), 7.05 (d, 2H), 7.10–7.25 (m, 2H), 7.30–7.45 (m, 3H), 7.50 (d, 1H), 7.55–7.70 (m, 3H). Anal. ($C_{31}H_{33}FN_2O\cdot C_4H_4O_4$) C, H, N.

3,4-Dihydro-1'-[4-[1-(4-fluorophenyl)-1*H*-indol-3-yl]-1-butyl]spiro[2*H*-1-benzopyran-2,4'-piperidine] oxalate (3g): mp 142–43 °C (acetone/ether); ^{1}H NMR (DMSO-d_6) δ 1.55–2.10 (m, 10H), 2.55–2.90 (m, 4H), 2.90–3.20 (m, 4H), 3.30 (d, 2H), 6.80 (t, 2H), 7.00–7.25 (m, 4H), 7.30–7.50 (m, 4H), 7.50–7.70 (m, 3H). Anal. ($C_{31}H_{33}FN_2O\cdot C_2H_2O_4$) C, H, N.

3,4-Dihydro-1'-[4-[1-(4-fluorophenyl)-1*H*-indol-3-yl]-1-butyl]spiro[1*H*-2-benzopyran-1,4'-piperidine] oxalate (3h): mp 110–12 °C (acetone); ^{1}H NMR (DMSO-d_6) δ 1.60–1.90 (m, 4H), 1.95 (d, 2H), 2.30 (dt, 2H), 2.65–2.85 (m, 4H), 2.95–3.20 (m, 4H), 3.35 (d, 2H), 3.85 (t, 2H), 7.00–7.25 (m, 6H), 7.30–7.50 (m, 4H), 7.50–7.70 (m, 3H). Anal. ($C_{31}H_{33}FN_2O\cdot C_2H_2O_4$) C, H, N.

1'-[4-[1-(4-Fluorophenyl)-1*H*-indol-3-yl]-1-butyl]spiro-[1*H*-2-benzopyran-4(3*H*),4'-piperidine] maleate (3i): mp 189–90 °C (acetone); ^{1}H NMR (DMSO-d_6) δ 1.65–1.95 (m, 6H), 2.15 (dt, 2H), 2.85 (t, 2H), 2.95–3.25 (m, 4H), 3.45 (d, 2H), 3.95 (s, 2H), 4.70 (s, 2H), 6.05 (s, 2H), 7.00 (d, 1H), 7.10–7.50 (m, 9H), 7.50–7.70 (m, 3H). Anal. ($C_{31}H_{33}FN_2O\cdot C_4H_4O_4$) C, H, N.

2,3-Dihydro-1'-[4-[1-(4-fluorophenyl)-1*H*-indol-3-yl]-1-butyl]spiro[4*H*-1-benzopyran-4,4'-piperidine] fumarate (3j): mp 214–16 °C (acetone); ^{1}H NMR (DMSO-d_6) δ 1.50–1.85 (m, 6H), 2.00 (t, 2H), 2.20 (dt, 2H), 2.65 (t, 2H), 2.70–2.90 (m, 4H), 3.10 (d, 2H), 4.05 (t, 2H), 6.60 (s, 2H), 6.70 (d, 1H), 6.85 (t, 1H), 7.00–7.25 (m, 3H), 7.25–7.50 (m, 5H), 7.50–7.70 (m, 3H). Anal. ($C_{31}H_{33}FN_2O\cdot C_4H_4O_4$) C, H, N.

1'-[4-[1-(4-Fluorophenyl)-1*H*-indol-3-yl]-1-butyl]spiro-[1,3-benzodioxole-2,4'-piperidine] Hydrochloride (3d). A mixture of 1-(ethoxycarbonyl)-4-piperidone (17 g, 0.1 mol), pyrochatecol (13 g, 0.12 mol), and catalytic amounts of 4-toluenesulfonic acid in dry toluene (250 mL) was refluxed with a water separator for 3 h. After cooling, the reaction mixture was washed with 2 N sodium hydroxide solution and concentrated in vacuo. The remaining oil was purified by flash chromatography (eluent: ethyl acetate/heptane, 1:1) giving 1'-(ethoxycarbonyl)spiro[1,3-benzodioxole-2,4'-piperidine] as an oil (22 g, 84%): ^{1}H NMR ($CDCl_3$) δ 1.25 (t, 2H), 2.00 (t, 4H), 3.70 (t, 4H), 4.20 (q, 2H), 6.70–6.85 (m, 4H). The oil was dissolved in ethanol (250 mL) and water (20 mL). Solid sodium hydroxide (10 g) was added followed by reflux for 20 h. Concentration in vacuo followed by standard workup with methylene chloride gave an oil that was applied to flash chromatography (eluent: ethyl acetate/methanol/triethylamine, 4:5:1). Spiro[1,3-benzodioxole-2,4'-piperidine] was obtained as an oil, which crystallized on standing (10 g, 62%): mp 108–10 °C; ^{1}H NMR ($CDCl_3$) δ 2.00 (t, 4H), 3.10 (t, 4H), 6.60–6.85 (m, 4H). A portion of the spiro[1,3-benzodioxole-2,4'-piperidine] was alkylated with 4-[1-(4-fluorophenyl)-1*H*-indol-3-yl]-1-butyl methanesulfonate as described in the synthesis of **2c** giving the title compound in 47% yield: mp 203–7 °C (acetone); ^{1}H NMR (DMSO-d_6) δ 1.65–1.95 (m, 4H), 2.15–2.55 (m, 4H), 2.80 (t, 2H), 3.00–3.30 (m, 4H), 3.45–3.70 (m, 2H), 6.75–7.00 (m, 4H), 7.20 (qui, 2H), 7.40 (t, 2H), 7.45–7.55 (m, 2H), 7.55–7.70 (m, 3H). Anal. ($C_{29}H_{29}FN_2O_2\cdot HCl$) C, H, N.

Pharmacological Test Methods. Animals. Male Wistar rats (Mol:Wist, SPF, 170–270 g) were used. We have recently described the handling procedures in detail.[49]

Calculations. 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.

Binding to σ Binding Sites. Affinity of test compounds for 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.[8] Affinity of test compounds for σ_2 binding sites was estimated by their ability to displace [^{3}H]-1,3-di(o-tolyl)guanidine (DTG) from rat brain homogenates minus cerebellum, as described by Sonesson et al.[50]

Molecular Modeling Methods. Conformational energies and energy-minimized geometries were calculated using the molecular mechanics program MM2(91) developed by Allinger and co-workers.[51] The energy calculations were done on the unprotonated amine including the lone pair on the basic nitrogen atom. The obtained structures were studied using the MacMimic program (Instar Software, Lund, Sweden).

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