Novel *σ* Receptor Ligands. Part 2. SAR of Spiro[[2]benzopyran-1,4′-piperidines] and Spiro[[2]benzofuran-1,4′-piperidines] with Carbon Substituents in Position 3

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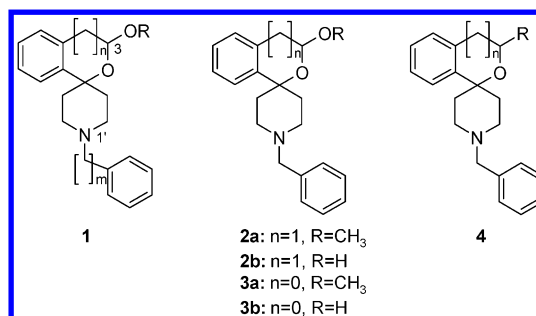
Several spiro[[2]benzopyran-1,4′-piperidines] and spiro[[2]benzofuran-1,4′-piperidines] were synthesized and evaluated for their binding properties for σ_1 and σ_2 receptors. The key step for the introduction of a one carbon residue is the reaction of the cyclic methyl acetals **2a** and **3a** with trimethylsilyl cyanide to yield the nitriles **5** and **20**. The reaction of the lactols **2b** and **3b** with stabilized phosphoranes affords spiropiperidines with a two carbon residue in position 3. In agreement with previously reported σ_1 and σ_2 receptor binding data, the investigated spiro compounds display higher affinity for σ_1 vs σ_2 receptors. Compounds with a cyano group in position 3 of the spirocycle show high σ_1 receptor affinity and selectivity. The spirobenzopyran nitrile **5** and the homologous spirobenzofuran nitriles **20** and **23** show almost identical σ_1 affinities, whereas the spirobenzopyran nitrile **13** with a methylene spacer is 10-fold less potent. Among the reported compounds, 1′-benzyl-3,4-dihydrospiro[[2]benzopyran-1,4′-piperidine]-3-carbonitrile **5** represents the most potent σ_1 receptor ligand with a K_i value of 1.54 nM and a σ_1/σ_2 selectivity ratio of 1030.

Introduction

σ Receptors were originally classified as subtypes of the opioid class of receptors.[1] Because most of the *σ* receptor-mediated effects are not sensitive to the opioid antagonist naloxone, this classification was discarded.[2] Later, it became clear that *σ* receptors are a new family of receptors consisting of σ_1 and σ_2 subtypes.[3] Recently, the σ_1 receptor has been cloned.[4−6] The amino acid sequence displays no homology to any other known mammalian protein but shows 30% identity to the yeast enzyme sterol C_8−C_7 isomerase.[7] The cloned receptor is likely to possess one transmembrane domain. The σ_2 receptor has not been cloned yet. At present, neurosteroids such as progesterone are thought to be the endogenous ligands for σ_1 receptors.[8] The biochemical and physiological role of *σ* receptors and the mechanism of signal transduction are not completely understood so far.[9] Yet, they seem to be involved in pathophysiological processes such as psychosis, depression, and uncontrolled cell proliferation. Therefore, potential applications of *σ* receptor ligands are, for example, in the treatment of psychosis, depression, acute and chronic neurodegeneration, and cancer.[10] Some compounds are already in clinical trials for the treatment of psychosis (e.g., BMY-14802)[11] and depression (e.g., E-5842).[12] The well-known highly potent antipsychotic haloperidol turned out to be a highly potent *σ* receptor ligand (compare Table 1).

In Part 1,[13] we described the synthesis of novel spiro-[[2]benzopyran-1,4′-piperidines] **1** (*n* = 1) and spiro[[2]-benzofuran-1,4′-piperidines] **1** (*n* = 0) with different oxygen substituents connected to position 3 and various residues in position 1′ (e.g., *m* = 0−4, compare Chart 1). We also discussed structure−affinity relationships
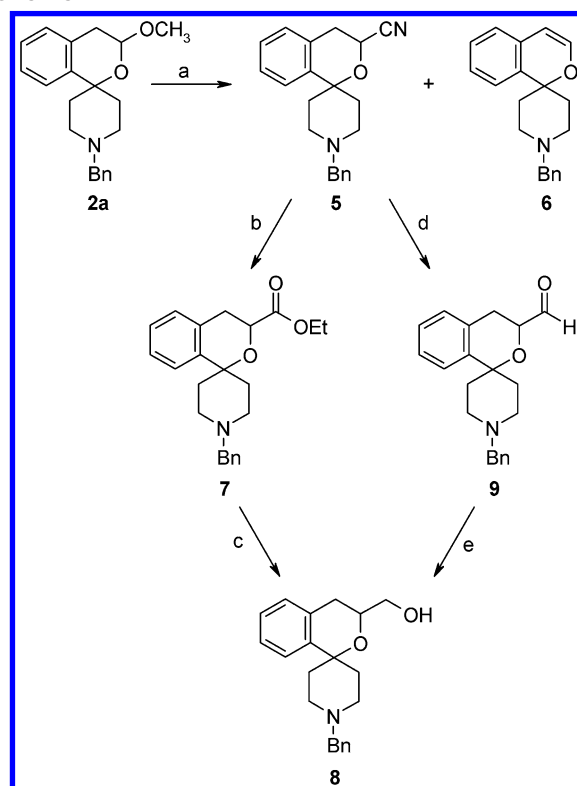
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Chart 1

2a: n=1, R=CH₃
2b: n=1, R=H
3a: n=0, R=CH₃
3b: n=0, R=H

of the prepared spiropiperidines **1** regarding σ_1 and σ_2 receptors. Compounds with the benzyl residue in position 1′ of the spiropiperidine ring system revealed the highest σ_1 receptor affinity. Some compounds with appropriate substituents in position 3, especially **2a** and **3a** with the methoxy group, displayed high σ_1/σ_2 selectivities (compare Tables 1 and 2).[13] As a continued effort to further characterize the structure−affinity relationships within this class of compounds, we modified the substituents in position 3 of the spiro compounds **1**. Herein, we report on the preparation and in vitro evaluation of novel spiropiperidines **4** (*n* = 0, 1) with carbon−carbon connected residues in position 3 and the benzyl group in position 1′.

Chemistry

Recently, we described the synthesis of the spiro[[2]-benzopyran-1,4′-piperidines] **2a,b**.[13] Proceeding from both compounds, we synthesized a second series of compounds containing one or two carbon residues in position 3 of the spirocyclic ring system. The introduction of a one carbon residue succeeded by the reaction of **2a** with trimethylsilyl cyanide in the presence of the Lewis acid boron trifluoride diethyl ether complex ($BF_3 \cdot Et_2O$)[14] at −25 °C to afford the nitrile **5** in 23% yield and the

Scheme 1[a]

[a] Reagents and conditions: (a) Trimethylsilyl cyanide, BF₃·Et₂O, CH₂Cl₂, −25 °C (**5**, 23%) or trimethylsilyl cyanide, tetracyanoethylene, CH₃CN, reflux (**5**, 30%). (b) EtOH, H₂SO₄, reflux (60%). (c) LiAlH₄, Et₂O, −15 °C (31%). (d) DIBAL, toluene, −78 °C and then NH₄Cl (14%). (e) LiAlH₄, Et₂O, −15 °C (33%).

alkene **6**[13] in 44% yield (Scheme 1). To prevent the elimination of methanol that leads to the formation of the benzopyran **6** and to improve the yield of **5**, we looked for alternative methods. Instead of BF₃·Et₂O, the neutral catalyst tetracyanoethylene was used.[15] In this case, heating of the reaction mixture for a prolonged time was necessary for completion of the transformation. The yield of **5** could be improved from 23 to 30%.

The nitrile **5** was transformed into the ester **7** in 60% yield by refluxing in a mixture of concentrated H₂SO₄ and ethanol. The synthesis of the methanol derivative **8** succeeded in two ways. Reduction of the ester **7** with LiAlH₄ afforded **8** in 31% yield. It was also possible to reduce **5** with diisobutylaluminum hydride (DIBAL)[16] in toluene to give the unstable aldehyde **9**, which was subsequently reduced with LiAlH₄, leading to **8** (33% yield).

The introduction of a two carbon residue in position 3 of the spirocyclic system was possible starting from the lactol **2b** (Scheme 2). Thus, **2b** was refluxed with ethoxycarbonylmethylene triphenylphosphorane (**10**)[17] in acetonitrile. Under these conditions, two products were isolated, the α,β-unsaturated ester **11** and the cyclized ester **12**. Sodium *tert*-butoxide catalyzed the intramolecular Michael reaction of **11** to yield the spiro compound **12**. If the reaction of **2b** with the Wittig reagent **10** was conducted in toluene at reflux temperature, the only product obtained was **12** in 67% yield. This tandem reaction comprises the three steps ring opening of the lactol to afford the hydroxyaldehyde, Wittig reaction, and intramolecular Michael addition. The ethanenitrile **13** was prepared by the Horner−

Scheme 2[a]
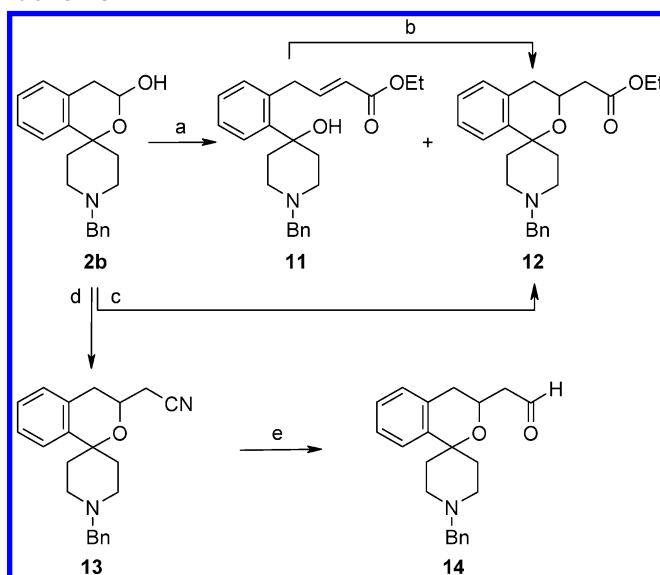
[a] Reagents and conditions: (a) Ph₃P=CHCO₂Et (**10**), CH₃CN, reflux. (b) NaOtBu, CH₂Cl₂, room temperature (50%). (c) Ph₃P=CHCO₂Et (**10**), toluene, reflux (67%). (d) (EtO)₂P(O)CH₂CN, Cs₂CO₃, THF, reflux (77%). (e) DIBAL, toluene, −78 °C; NH₄Cl (42%).

Scheme 3[a]
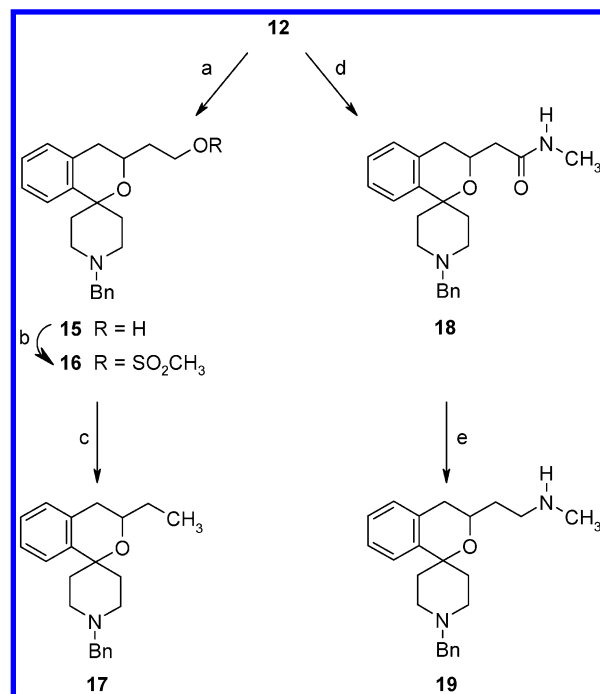
[a] Reagents and conditions: (a) LiAlH₄, Et₂O, −15 °C (96%). (b) CH₃SO₂Cl, Et₃N, CH₂Cl₂, −10 °C. (c) LiAlH₄, THF, reflux (40%, 2 steps). (d) CH₃NH₂, EtOH, room temperature (99%). (e) LiAlH₄, Et₂O, CH₂Cl₂, −35 °C (40%).

Emmons variation of the Wittig reaction using diethyl cyanomethylphosphonate in tetrahydrofuran (THF) and cesium carbonate as base.[18] The nitrile **13** was transformed into the aldehyde **14** by reduction with DIBAL in 42% yield.

The ester **12** was converted into the alcohol **15** by reduction with LiAlH₄ in diethyl ether (Scheme 3). The hydroxy group of **15** was removed in two steps.[19] Activation of **15** with methanesulfonyl chloride afforded the mesylate **16**, and subsequent nucleophilic substitu-

Scheme 4[a]
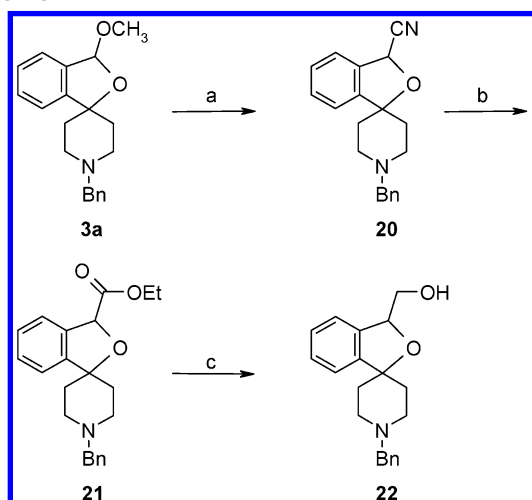
[a] Reagents and conditions: (a) Trimethylsilyl cyanide, tetracyanoethylene, CH_3CN, reflux (68%). (b) EtOH, H_2SO_4, reflux (39%). (c) $LiAlH_4$, Et_2O, −15 °C (75%).

tion with $LiAlH_4$ led to the ethyl derivative **17**. An amino group was introduced by aminolysis of the ester **12** to yield the amide **18**, which was reduced with $LiAlH_4$ to give the secondary amine **19**.

The introduction of carbon residues in position 3 of the spiro[[2]benzofuran-1,4′-piperidines] was performed in a similar way to the spirobenzopyrans (Scheme 4). Treatment of the cyclic methyl acetal **3a** with trimethylsilyl cyanide and tetracyanoethylene in acetonitrile provided the nitrile **20**. Tetracyanoethylene was used because the yield of the nitrile **5** in the spirobenzopyran series was higher using tetracyanoethylene than with $BF_3 \cdot Et_2O$. In contrast to the spirobenzopyran analogue **2a**, elimination of methanol is not possible so that no side product can arise; therefore, the yield was more than doubled (68% for **20** vs 30% for **5**). The nitrile **20** was transformed into the ester **21** by refluxing with $EtOH/H_2SO_4$. The ester **21** was subsequently reduced with $LiAlH_4$ to yield the methanol derivative **22**.

Proceeding from the lactol **3b**, reaction with the Wittig reagent cyanomethylene triphenylphosphorane directly yielded the ethanenitrile **23**. An α,β-unsaturated nitrile analogous to **11** was not detected, as the base cesium carbonate was added (Scheme 5). To obtain the ester **24**, the lactol **3b** was reacted with the Wittig reagent **10**. The ester **24** was reduced with $LiAlH_4$ to afford the alcohol **25**.

Receptor Binding Studies

The σ receptor affinities of the spiropiperidines were determined in radioligand binding experiments. In the $σ_1$ assay, homogenates of guinea pig brains were used as receptor material. The $σ_1$ selective compound [³H]-(+)-pentazocine was employed as radioligand, and the nonspecific binding was determined in the presence of a large excess of haloperidol.[13] A rat liver membrane preparation served as a source for $σ_2$ receptors in the $σ_2$ assay. Because a $σ_2$ selective radioligand is not available, the nonselective radioligand [³H]ditolylguanidine was employed in the presence of nonradiolabeled (+)-pentazocine (100 nM) for selective masking of $σ_1$ receptors. Performing the $σ_2$ assay in the presence of

Scheme 5[a]
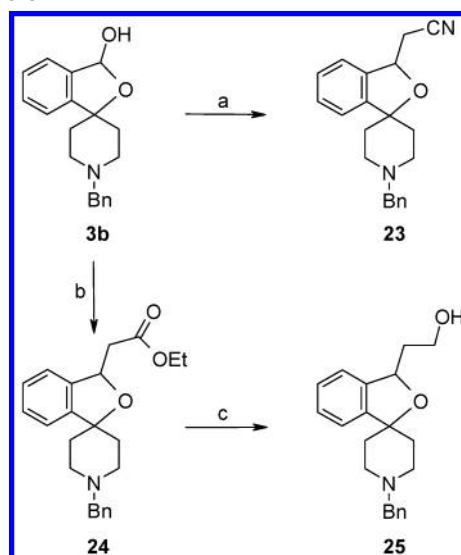
[a] Reagents and conditions: (a) $Ph_3P{=}CHCN$, Cs_2CO_3, toluene, reflux (76%). (b) $Ph_3P{=}CHCO_2Et$ (**10**), Cs_2CO_3, toluene, reflux (88%). (c) $LiAlH_4$, Et_2O, −15 °C (75%).

an excess of nontritiated 1,3-di(o-tolyl)guanidine resulted in the nonspecific binding of the radioligand.[13]

Results and Discussion

The σ receptor affinities of the spiro[[2]benzopyran-1,4′-piperidines] with various substituents R in position 3 are shown in Table 1. For comparison, the K_i values of two compounds (**2a,b**) described in Part 1[13] are included in Table 1. Additionally, the K_i values of the three reference compounds haloperidol, ditolylguanidine, and BMY-14802 are given.

Table 1. σ Receptor Affinities of Spiro[[2]benzopyran-1,4′-piperidines] with Various Substituents R in Position 3

compd	R	$K_i \pm$ SEM (nM)[a]		$σ_1/σ_2$ selectivity
		$σ_1$	$σ_2$	
2a	OCH_3	1.29 ± 0.18[b]	3500 ± 352[b]	2710
2b	OH	2.17 ± 0.40[b]	513 ± 71.6[b]	236
5	CN	1.54 ± 0.31	1590 ± 388	1030
13	CH_2CN	15.9 ± 4.04	4700 ± 129	295
7	CO_2Et	9.33 ± 2.08	$10\,540 \pm 2190$	1130
12	CH_2CO_2Et	183 ± 25.9	$22\,700 \pm 1730$	124
8	CH_2OH	7.16 ± 0.66	2089 ± 606	292
15	CH_2CH_2OH	12.7 ± 2.60	8460 ± 280	668
17	CH_2CH_3	11.7 ± 2.55	3900 ± 1270	333
18	$CH_2CONHCH_3$	170 ± 17.2	$34\,000 \pm 7480$	200
19	$CH_2CH_2NHCH_3$	148 ± 0.33	4360 ± 1100	29
14	CH_2CHO	55.1 ± 12.8	9910 ± 3260	180
	haloperidol	2.20 ± 0.31	34.2 ± 2.3	16
	ditolylguanidine	164 ± 47	63.9 ± 10.8	0.4
	BMY-14802	265 ± 32	391 ± 62	1.5

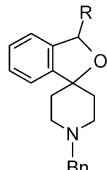[a] K_i values ± SEM from three independent experiments. Radioligands and tissues used for receptor binding studies were as follows: $σ_1$, [³H]-(+)-pentazocine (guinea pig brain); $σ_2$, [³H]-ditolylguanidine in the presence of 100 nM (+)-pentazocine (rat liver). [b] Ref 13.

Generally, the $σ_2$ receptor affinities of all of the investigated spiropiperidines are lower than their $σ_1$

receptor affinities. Among the test compounds with a one carbon residue in position 3, the nitrile **5** displays the highest affinity to σ_1 ($K_i = 1.54$ nM) and σ_2 ($K_i = 1590$ nM) receptors. The σ_1 affinity is somewhat lower as compared to the methoxy derivative **2a**, but the σ_1/σ_2 selectivity is still very high (1030-fold). In comparison with **5**, the homologous ethanenitrile **13** is about 10-fold less potent at σ_1 receptors ($K_i = 15.9$ nM). Transformation of the homologous nitriles **5** and **13** into their ethyl esters **7** and **12** led to a reduced σ_1 and σ_2 receptor affinity, respectively. However, the σ_1/σ_2 selectivity of the ester **7** is still very high (1130-fold). Reduction of the ester moieties of **7** and **12** afforded the smaller alcohols **8** ($K_i = 7.16$ nM) and **15** ($K_i = 12.7$ nM), respectively, with increased σ_1 receptor affinities. The lactol **2b** without a methylene spacer moiety shows an even smaller K_i value (2.17 nM). Apparently, the σ_1 receptor affinity is diminished by an increase of the substituent's volume in position 3. The ethyl derivative **17** (R = CH_2CH_3, $K_i = 11.7$ nM) displays an almost 10-fold lower affinity for σ_1 receptors than the bioisosteric methoxy derivative **2a** (R = OCH_3, $K_i = 1.29$ nM). The methanol derivative **8** (R = CH_2OH) with the hydroxymethyl group in position 3 binds σ_1 receptors less effectively than the methoxy counterpart **2a**. These observations indicate that the presence and the position of the oxygen atom in the C-3 substituent are important for high σ_1 receptor affinity. On the other hand, the σ_2 receptor affinities of **2a**, **8**, and **17** are quite similar.

The σ_1 receptor affinities of ester **12** ($K_i = 183$ nM) and amide **18** ($K_i = 170$ nM) are almost identical. The secondary amine **19** displays a somewhat higher σ_1 affinity ($K_i = 148$ nM) as compared to the ester **12** and the amide **18**. The acetaldehyde derivative **14** ($K_i = 55.1$ nM) exhibits a 4-fold lower affinity for σ_1 receptors than the ethanol derivative **15**.

Table 2. σ Receptor Affinities of Spiro[[2]benzofuran-1,4′-piperidines] with Various Substituents R in Position 3

compd	R	$K_i \pm$ SEM (nM)[a]		σ_1/σ_2 selectivity
		σ_1	σ_2	
3a	OCH_3	$1.14 \pm 0.22^{b,c}$	1280 ± 137^c	1130
3b	OH	7.33 ± 0.60^c	761 ± 13.0^c	104
20	CN	2.18 ± 0.45^b	766 ± 149	352
23	CH_2CN	2.16 ± 0.50	1660 ± 424	768
21	CO_2Et	8.95 ± 1.57	7130 ± 1390	796
24	CH_2CO_2Et	15.1 ± 3.45	6770 ± 2000	449
22	CH_2OH	5.66 ± 1.13	1980 ± 857	349
25	CH_2CH_2OH	7.27 ± 0.43	2530 ± 427	348

[a] K_i values $\pm$ SEM from three independent experiments, except when specified. Radioligands and tissues used for receptor binding studies were as follows: σ_1, [^{3}H]-(+)-pentazocine (guinea pig brain); σ_2, [^{3}H]-ditolylguanidine in the presence of 100 nM (+)-pentazocine (rat liver). [b] Four independent experiments. [c] Ref 13.

The σ receptor affinities of the five-membered 2-benzofuran derivatives are shown in Table 2. For comparison, the K_i values of two compounds (**3a,b**) described in Part 1[13] are additionally listed in Table 2. The homologous nitriles **20** and **23** reveal the highest σ_1 receptor affinity of the spirobenzofurans ($K_i = 2.18$ and 2.16 nM, respectively). Surprisingly, the additional methylene spacer group of **23** does not influence considerably the interaction with σ_1 receptors. In this case, the cyano group is decisive for high σ_1 receptor affinity. The σ_1 receptor affinities of the nitriles **20** and **23** are somewhat decreased in comparison with the methoxy derivative **3a** ($K_i = 1.14$ nM).

The difference in receptor affinity of the homologous esters **21** ($K_i = 8.95$ nM) and **24** ($K_i = 15.1$ nM) is much lower than in the 2-benzopyran series. The acetic acid ester **24** is 12-fold more potent than the corresponding derivative **12** of the spirobenzopyran series. In the 2-benzofuran series as well as in the 2-benzopyran series, the nitriles show good σ_1 receptor affinities, which are decreased in the corresponding esters. The σ_1 affinity is improved again when the esters are reduced to the respective alcohols. The homologous alcohols **3b** ($K_i = 7.33$ nM), **22** ($K_i = 5.66$ nM), and **25** ($K_i = 7.27$ nM) display very similar σ_1 affinities, whereas in the 2-benzopyran series a significant decrease in σ_1 receptor binding is observed with insertion of methylene spacer groups between the spiropiperidine and the hydroxy group (compounds **2b**, **8**, and **15**, Table 1). The σ_2 receptor affinities of the 2-benzofurans are generally lower than their σ_1 receptor affinities, but they tend to be higher as compared to the corresponding 2-benzopyran derivatives.

Conclusion

In this paper, we have presented novel spiropiperidines with carbon substituents in position 3. Some of these compounds display high affinity and selectivity for σ_1 receptors. In particular, the compounds **5**, **20**, and **23** bearing a cyano group bind with high affinity to σ_1 receptors. The carbonitrile **5** reveals the highest σ_1 affinity and additionally very high σ_1 selectivity. A distance of one or two carbon atoms between the cyano group and the phenyl moiety of the spirocyclic 2-benzopyrans or 2-benzofurans seems to be the optimum for σ_1 receptor binding. The σ receptor binding profiles of the nitriles **5** and **20** are similar to those of the corresponding methoxy derivatives **2a** and **3a**,[13] respectively. These results demonstrate the remarkable similarity of the methoxy and the cyano moiety within this class of σ receptor ligands. In contrast to the acetalic methoxy derivatives **2a** and **3a**, the nitriles **5** and **20** represent stable compounds, which are not hydrolyzed or isomerized in acidic solvents.

Experimental Section

General. Moisture sensitive reactions were conducted under dry nitrogen. THF, Et_2O, and toluene were distilled from sodium/benzophenone ketyl, CH_2Cl_2 from CaH_2, and CH_3CN from P_2O_5 prior to use. Thin-layer chromatography (TLC) was conducted with Merck silica gel 60 F_{254} plates. Flash chromatography[20] was conducted with Merck silica gel 60, 0.040−0.063 mm, and the terms in parentheses for flash chromatography include the following: diameter of the column (cm), eluent, fraction size (mL), R_f. Melting points were determined with an SMP 2 (Stuart Scientific) and are uncorrected. Elemental analyses were conducted with an VarioEL (Elementaranalysesysteme GmbH). The mass spectrometer used was model 5989A (Hewlett-Packard) and models MAT 312, MAT 8200, MAT 44, and TSQ 7000 (Finnigan). The ionization method used was electron impact (EI) at 70 eV. IR spectra

were obtained from a Perkin-Elmer 1605 FT-IR spectrophotometer, and wavenumbers are given in cm^{-1}. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Varian Unity 300 NMR spectrometer operating at 27 °C. Chemical shifts (δ) are reported in ppm downfield from tetramethylsilane. Coupling constants (J) are given with 0.5 Hz resolution. The assignments of ^{1}H NMR and ^{13}C NMR signals were supported by two-dimensional (2D) NMR techniques (correlation spectroscopy, COSY).

1′-Benzyl-3,4-dihydrospiro[[2]benzopyran-1,4′-piperidine]-3-carbonitrile (5) and 1′-Benzylspiro[[2]benzopyran-1,4′-piperidine] (6).[13] Tetracyanoethylene (13 mg, 0.1 mmol) was dissolved in CH$_3$CN (1 mL) under nitrogen. Then, a solution of **2a** (108 mg, 0.33 mmol) in CH$_3$CN (1 mL) was added and the mixture was stirred at room temperature for 5 min. Trimethylsilyl cyanide (0.1 mL) was then added, and the reaction mixture was refluxed. Six further portions of trimethylsilyl cyanide (0.1 mL each) were added over a period of 15 h. When the reaction was completed, the solvent was removed under reduced pressure, and the residue was dissolved in CH$_2$Cl$_2$. Then, some silica gel was added and the suspension was concentrated under reduced pressure. The residue was purified by flash chromatography (2 cm, petroleum ether:EtOAc = 3:1, 10 mL).

Fraction 1 (R_f = 0.16) contained **6**[13] (42 mg, 42%) as a colorless oil, which solidified on standing; fraction 2 contained the nitrile **5** (R_f = 0.05) as a colorless oil, yield 32 mg (30%). IR (film): $\tilde{\nu}$ (cm^{-1}) = 2938, 2817 (C–H); 2214 (C≡N); 1097, 1044 (C–O); 732, 700 (C–H). ^{1}H NMR (CDCl$_3$): δ (ppm) 1.85–2.01 (m, 3 H, N(CH$_2$CH_2)$_2$), 2.20 (td, J = 12.8, 4.3 Hz, 1 H, N(CH$_2$CH_2)$_2$), 2.43 (td, J = 11.0, 2.7 Hz, 1 H, N(CH_2CH$_2$)$_2$), 2.54 (td, J = 12.5, 2.3 Hz, 1 H, N(CH_2CH$_2$)$_2$), 2.71–2.84 (m, 2 H, N(CH_2CH$_2$)$_2$), 3.03 (dd, J = 15.9, 3.4 Hz, 1 H, ArCH_2CH), 3.27 (dd, J = 15.9, 9.8 Hz, 1 H, ArCH_2CH), 3.56 (d, J = 13.1 Hz, 1 H, NCH_2Ph), 3.61 (d, J = 13.1 Hz, 1 H, NCH_2Ph), 4.71 (dd, J = 9.8, 3.4 Hz, 1 H, ArCH$_2$CH), 7.11 (d, J = 7.0 Hz, 1 H, arom), 7.14–7.42 (m, 8 H, arom). ^{13}C NMR (CDCl$_3$): δ (ppm) 33.4 (1 C, ArCH$_2$CH), 36.1 (1 C, N(CH$_2$$CH_2$)$_2$), 38.3 (1 C, N(CH$_2$$CH_2$)$_2$), 48.9 (1 C, N($CH_2CH_2$)$_2$), 49.0 (1 C, N($CH_2CH_2$)$_2$), 58.3 (1 C, ArCH$_2$$C$H), 63.2 (1 C, N$CH_2$Ph), 76.1 (1 C, Ar$C$O), 118.6 (1 C, CN), 125.5 (1 C, arom CH), 126.9 (1 C, arom CH), 127.0 (1 C, arom CH), 127.4 (1 C, arom CH), 128.2 (2 C, arom CH), 128.6 (1 C, arom CH), 129.2 (2 C, arom CH), 129.8 (1 C, arom C), 138.5 (1 C, arom C), 140.2 (1 C, arom C). MS (EI): m/z 318 [M$^+$], 227 [M$^+$ – CH$_2$Ph], 91 [CH$_2$Ph$^+$]. HRMS: calcd for C$_{21}$H$_{22}$N$_2$O, 318.1732; found, 318.1733.

Ethyl 1′-Benzyl-3,4-dihydrospiro[[2]benzopyran-1,4′-piperidine]-3-carboxylate (7). A solution of **5** (84 mg, 0.26 mmol) in EtOH (3 g), H$_2$O (65 mg), and concentrated H$_2$SO$_4$ (1 g) was refluxed for 11.5 h. Then, an aqueous solution of NaOH (3 M) was added to give pH 10 and the mixture was extracted with CH$_2$Cl$_2$. The organic layer was dried (Na$_2$SO$_4$), and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (1 cm, petroleum ether:EtOAc = 3:1, 10 mL, R_f = 0.06) to afford a colorless oil, yield 58 mg (60%). IR (film): $\tilde{\nu}$ (cm^{-1}) = 2939, 2816 (C–H); 1743 (C=O); 1112, 1045 (C–O); 741, 699 (C–H). ^{1}H NMR (CDCl$_3$): δ (ppm) 1.33 (t, J = 7.3 Hz, 3 H, OCH$_2$CH_3), 1.81 (dd, J = 13.7, 2.8 Hz, 1 H, N(CH$_2$CH_2)$_2$), 1.94 (dd, J = 12.2, 4.3 Hz, 1 H, N(CH$_2$CH_2)$_2$), 2.02 (dd, J = 14.3, 2.8 Hz, 1 H, N(CH$_2$CH_2)$_2$), 2.21 (td, J = 12.5, 4.9 Hz, 1 H, N(CH$_2$CH_2)$_2$), 2.44 (td, J = 11.9, 3.1 Hz, 1 H, N(CH_2CH$_2$)$_2$), 2.60 (td, J = 11.3, 2.4 Hz, 1 H, N(CH_2CH$_2$)$_2$), 2.66–2.81 (m, 2 H, N(CH_2CH$_2$)$_2$), 2.94 (dd, J = 15.9, 3.4 Hz, 1 H, ArCH_2CH), 3.08 (dd, J = 15.9, 11.3 Hz, 1 H, ArCH_2CH), 3.55 (d, J = 12.8 Hz, 2 H, NCH_2Ph), 3.60 (d, J = 12.8 Hz, 2 H, NCH_2Ph), 4.24–4.31 (m, 2 H, OCH_2CH$_3$), 4.35 (dd, J = 11.3, 3.4 Hz, 1 H, ArCH$_2$CH), 7.10 (d, J = 7.0 Hz, 1 H, arom), 7.12–7.40 (m, 8 H, arom). MS (EI): m/z 365 [M$^+$], 274 [M$^+$ – CH$_2$Ph], 91 [CH$_2$Ph$^+$]. HRMS: calcd for C$_{23}$H$_{27}$NO$_3$, 365.1991; found, 365.1993. Anal. (C$_{23}$H$_{27}$NO$_3$) N; C: calcd, 75.6; found, 75.1; H: calcd, 7.45; found, H 8.15.

(1′-Benzyl-3,4-dihydrospiro[[2]benzopyran-1,4′-piperidin]-3-yl)methanol (8). Procedure 1. Compound **7** (69 mg,

0.19 mmol) was dissolved in Et$_2$O (5 mL) under nitrogen. This solution was cooled to −15 °C, and a solution of LiAlH$_4$ (1 M in THF, 0.29 mL, 0.29 mmol) was slowly added. After 1 h, the mixture was hydrolyzed by addition of H$_2$O. The salts were filtered off and washed with EtOAc. The organic layer was dried (Na$_2$SO$_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography (1 cm, petroleum ether:EtOAc 1:1, 5 mL, R_f = 0.03) to afford a colorless oil, yield 19 mg (31%).

Procedure 2. Compound **5** (94 mg, 0.28 mmol) was dissolved in anhydrous toluene (5 mL) under nitrogen. This solution was cooled to −78 °C, and a solution of DIBAL (1 M in cyclohexane, 0.45 mL, 0.45 mmol) was slowly added. After 1.5 h at −78 °C, a saturated aqueous solution of NH$_4$Cl (3 mL) was added. This mixture was stirred for 1 h at room temperature. Then, an aqueous solution of NaOH (2 M) was added to give pH 10 and the mixture was extracted with EtOAc. The organic layer was dried (Na$_2$SO$_4$) and concentrated under reduced pressure at 30 °C. The crude product was purified by flash chromatography (1 cm, petroleum ether:EtOAc = 3:2, 5 mL, R_f = 0.06) to afford a colorless oil, yield 13 mg (14%). The aldehyde **9** was immediately reduced to yield the alcohol **8**.

1′-Benzyl-3,4-dihydrospiro[[2]benzopyran-1,4′-piperidine]-3-carbaldehyde (9). IR (film): $\tilde{\nu}$ (cm^{-1}) 2923, 2814 (C–H); 1738 (C=O); 1107, 1074, 1046 (C–O); 756, 734, 699 (C–H). ^{1}H NMR (CDCl$_3$): δ (ppm) 1.77 (dd, J = 13.7, 2.4 Hz, 1 H, N(CH$_2$CH_2)$_2$), 1.87–2.05 (m, 2 H, N(CH$_2$CH_2)$_2$), 2.25 (td, J = 13.1, 4.9 Hz, 1 H, N(CH$_2$CH_2)$_2$), 2.42 (td, J = 11.0, 3.7 Hz, 1 H, N(CH_2CH$_2$)$_2$), 2.59 (td, J = 12.2, 2.1 Hz, 1 H, N(CH_2CH$_2$)$_2$), 2.70–2.83 (m, 2 H, N(CH_2CH$_2$)$_2$), 2.84–2.90 (m, 2 H, ArCH_2-CH), 3.59 (s, 2 H, NCH_2Ph), 4.17 (dd, J = 8.5, 6.4 Hz, 1 H, ArCH$_2$CH), 7.07–7.40 (m, 9 H, arom), 9.84 (s, 1 H, CHO).

Compound **9** (6 mg, 0.019 mmol) was dissolved in Et$_2$O (4 mL) under nitrogen. This solution was cooled to −15 °C, and a solution of LiAlH$_4$ (1 M in THF, 0.03 mL, 0.03 mmol) was slowly added. After 1 h, the mixture was hydrolyzed by addition of 2 drops of H$_2$O. The salts were filtered off and washed with Et$_2$O. The organic layer was removed under reduced pressure. The crude product was purified by flash chromatography (0.8 cm, petroleum ether:EtOAc = 1:1, 5 mL, R_f = 0.03) to afford a colorless oil, yield 2 mg (33%).

Compound 8. IR (film): $\tilde{\nu}$ (cm^{-1}) 3430 (O–H); 2924, 2812 (C–H); 1104, 1047 (C–O); 757, 699 (C–H). ^{1}H NMR (CDCl$_3$): δ (ppm) 1.72 (dd, J = 13.4, 2.7 Hz, 1 H, N(CH$_2$CH_2)$_2$, 1.91 (td, J = 12.6, 4.3 Hz, 1 H, N(CH$_2$CH_2)$_2$), 2.08 (dd, J = 14.3, 2.7 Hz, 1 H, N(CH$_2$CH_2)$_2$), 2.25 (td, J = 12.5, 4.6 Hz, 1 H, N(CH$_2$CH_2)$_2$), 2.36 (td, J = 12.5, 2.7 Hz, 1 H, N(CH_2CH$_2$)$_2$), 2.47 (dd, J = 11.6, 2.7 Hz, 1 H, N(CH_2CH$_2$)$_2$), 2.57 (dd, J = 15.9, 2.7 Hz, 1 H, ArCH_2CH), 2.72–2.83 (m, 2 H, N(CH_2CH$_2$)$_2$), 2.80 (dd, J = 15.9, 11.3 Hz, 1 H, ArCH_2CH), 3.59 (s, 2 H, NCH_2Ph), 3.69 (dd, J = 11.3, 7.0 Hz, 1 H, CHCH_2OH), 3.81 (dd, J = 11.3, 3.1 Hz, 1 H, CHCH_2OH), 3.88–3.98 (m, 1 H, ArCH$_2$CHCH$_2$OH), 7.09 (d, J = 7.3 Hz, 1 H, arom), 7.12–7.41 (m, 8 H, arom). MS (EI): m/z 323 [M$^+$], 232 [M$^+$ – CH$_2$Ph], 91 [CH$_2$Ph$^+$]. HRMS: calcd for C$_{21}$H$_{25}$NO$_2$, 323.1885; found, 323.1876.

Ethyl (*E*)-4-[2-(1-Benzyl-4-hydroxypiperidin-4-yl)phenyl]but-2-enoate (11) and Ethyl 2-(1′-Benzyl-3,4-dihydrospiro[[2]benzopyran-1,4′-piperidin]-3-yl)acetate (12). Procedure 1. A solution of the lactol **2b** (93 mg, 0.30 mmol) and Ph$_3$P=CHCO$_2$Et (**10**) (157 mg, 0.45 mmol) in CH$_3$CN (3 mL) was refluxed for 40 h. The solvent was removed under reduced pressure. The residue was purified by flash chromatography (2 cm, petroleum ether:EtOAc = 1:2, 10 mL). Fraction 1 (R_f = 0.26) contained compound **12** as colorless oil (6 mg, 5%), fraction 3 (R_f = 0.05) contained the α,β-unsaturated ester **11** as colorless oil (36 mg, 31%), and fraction 2 contained a mixture of **11** and **12** (53 mg, 46%).

Procedure 2. A mixture of **11** (36 mg, 0.09 mmol) and NaO^{t}Bu (3 mg) in CH$_2$Cl$_2$ (2 mL) was stirred for 24 h at room temperature. A saturated aqueous solution of NaCl (2 mL) was added, and the mixture was extracted with CH$_2$Cl$_2$. The organic layer was dried (Na$_2$SO$_4$) and concentrated under reduced pressure. Flash chromatography (1 cm, petroleum

ether:EtOAc = 1:1, 5 mL, R_f = 0.10) afforded **12** as colorless oil, yield 17 mg (50%).

Procedure 3. A solution of the lactol **2b** (217 mg, 0.70 mmol) and Ph$_3$P=CHCO$_2$Et (**10**) (489 mg, 1.4 mmol) in anhydrous toluene (10 mL) was refluxed for 32 h. The solvent was removed under reduced pressure. The residue was purified by flash chromatography (2 cm, petroleum ether:EtOAc = 2:1, 10 mL, R_f = 0.07) to afford **12** as colorless oil, yield 179 mg (67%).

Compound 11. IR (film): $\tilde{\nu}$ (cm^{-1}) 3430 (O–H); 2934, 2829 (C–H); 1727 (C=O); 1158, 1037 (C–O); 749, 700 (C–H). ^{1}H NMR (CDCl$_3$): δ (ppm) 1.27 (t, J = 7.0 Hz, 3 H, OCH$_2$CH_3), 1.97 (dd, J = 14.3, 2.5 Hz, 2 H, N(CH$_2$CH_2)$_2$), 2.19 (td, J = 12.5, 4.3 Hz, 2 H, N(CH$_2$CH_2)$_2$), 2.54 (td, J = 11.6, 2.4 Hz, 2 H, N(CH_2CH$_2$)$_2$), 2.77 (br d, J = 11.3 Hz, 2 H, N(CH_2CH$_2$)$_2$), 3.25 (dd, J = 7.0, 1.5 Hz, 2 H, ArCH_2CH=CH), 3.58 (s, 2 H, NCH_2Ph), 4.16 (q, J = 7.3 Hz, 2 H, OCH_2CH$_3$), 5.98 (dt, J = 15.6, 7.2 Hz, 1 H, (*E*)-ArCH$_2$CH=CH), 7.18–7.44 (m, 9 H, arom), 7.48 (br d, J = 15.9 Hz, 1 H, (*E*)-ArCH$_2$CH=CH).

Compound 12. IR (film): $\tilde{\nu}$ (cm^{-1}) 2928, 2819 (C–H); 1735 (C=O); 1219, 1044 (C–O); 742, 699 (C–H). ^{1}H NMR (CDCl$_3$): δ (ppm) 1.33 (t, J = 7.0 Hz, 3 H, OCH$_2$CH_3), 1.69 (dd, J = 13.4, 2.44 Hz, 1 H, N(CH$_2$CH_2)$_2$), 1.88 (td, J = 12.5, 4.4 Hz, 1 H, N(CH$_2$CH_2)$_2$), 2.09 (dd, J = 14.0, 2.4 Hz, 1 H, N(CH$_2$CH_2)$_2$), 2.19 (td, J = 12.8, 4.3 Hz, 1 H, N(CH$_2$CH_2)$_2$), 2.33 (td, J = 12.2, 1.5 Hz, 1 H, N(CH_2CH$_2$)$_2$), 2.45 (td, J = 12.5, 2.1 Hz, 1 H, N(CH_2CH$_2$)$_2$), 2.55–2.83 (m, 6 H, CHCH_2COO (2 H), N(CH_2-CH$_2$)$_2$ (2 H), ArCH_2CH (2 H)), 3.54 (s, 2 H, NCH_2Ph), 4.11–4.31 (m, 3 H, ArCH$_2$CH (1 H), OCH_2CH$_3$ (2 H)), 7.06 (d, J = 7.3 Hz, 1 H, arom), 7.11–7.41 (m, 8 H, arom). MS (EI): m/z 379 [M$^+$], 302 [M$^+$ – Ph], 288 [M$^+$ – CH$_2$Ph], 91 [CH$_2$Ph$^+$]. Anal. (C$_{24}$H$_{29}$NO$_3$) C, H, N.

2-(1′-Benzyl-3,4-dihydrospiro[[2]benzopyran-1,4′-pi-peridin]-3-yl)ethanenitrile (13). A mixture of the lactol **2b** (55 mg, 0.18 mmol), (EtO)$_2$P(O)CH$_2$CN (48 mg, 0.27 mmol), and Cs$_2$CO$_3$ (59 mg, 0.18 mmol) in THF (10 mL) was refluxed for 22 h. Then, H$_2$O (5 mL) was added and the mixture was extracted with CH$_2$Cl$_2$. The organic layer was dried (Na$_2$SO$_4$), and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (2 cm, petroleum ether:EtOAc = 1:2, 10 mL, R_f = 0.26) to afford a colorless oil, which solidified on standing, mp 84 °C, yield 46 mg (77%).

IR (film): $\tilde{\nu}$ (cm^{-1}) 2931, 2818 (C–H); 2252 (C≡N), 1103, 1073 (C–O); 741, 700 (C–H). ^{1}H NMR (CDCl$_3$): δ (ppm) 1.72 (dd, J = 13.4, 2.7 Hz, 1 H, N(CH$_2$CH_2)$_2$), 1.88–2.09 (m, 2 H, N(CH$_2$CH_2)$_2$), 2.23 (td, J = 12.8, 4.6 Hz, 1 H, N(CH$_2$CH_2)$_2$), 2.48–2.61 (m, 2 H, N(CH_2CH$_2$)$_2$), 2.67–2.89 (m, 6 H, CHCH_2-CN (2 H), N(CH_2CH$_2$)$_2$ (2 H), ArCH_2CH (2 H)), 3.60 (s, 2 H, NCH_2Ph), 4.04–4.14 (m, 1 H, ArCH$_2$CH), 7.08 (d, J = 7.0 Hz, 1 H, arom), 7.15–7.43 (m, 8 H, arom). MS (EI): m/z 332 [M$^+$], 241 [M$^+$ – CH$_2$Ph], 91 [CH$_2$Ph$^+$]. HRMS: calcd for C$_{22}$H$_{24}$N$_2$O, 332.1889; found, 332.1890.

2-(1′-Benzyl-3,4-dihydrospiro[[2]benzopyran-1,4′-pi-peridin]-3-yl)acetaldehyde (14). Compound **13** (25 mg, 0.075 mmol) was dissolved in anhydrous toluene (3 mL) under nitrogen. This solution was cooled to −78 °C, and a solution of DIBAL (1 M in cyclohexane, 0.15 mL, 0.15 mmol) was slowly added. After 2.5 h at −78 °C, a saturated aqueous solution of NH$_4$Cl (3 mL) was added. This mixture was stirred for 30 min at room temperature. An aqueous solution of NaOH (2 M) was added to give pH 10, and the mixture was extracted with CH$_2$Cl$_2$. The organic layer was dried (Na$_2$SO$_4$), and the solvent was removed under reduced pressure at 30 °C. The crude product was purified by flash chromatography (1 cm, petroleum ether:EtOAc = 1:1, 5 mL, R_f = 0.08) to afford a colorless oil, yield 11 mg (42%).

IR (film): $\tilde{\nu}$ (cm^{-1}) 2927, 2816 (C–H); 1725 (HC=O); 1110, 1052 (C–O); 742, 701 (C–H). ^{1}H NMR (CDCl$_3$): δ (ppm) 1.69 (dd, J = 13.4, 2.4 Hz, 1 H, N(CH$_2$CH_2)$_2$), 1.93 (td, J = 14.3, 4.5 Hz, 1 H, N(CH$_2$CH_2)$_2$), 2.08 (dd, J = 14.6, 2.7 Hz, 1 H, N(CH$_2$CH_2)$_2$), 2.22 (td, J = 12.2, 4.6 Hz, 1 H, N(CH$_2$CH_2)$_2$), 2.33 (td, J = 12.2, 2.7 Hz, 1 H, N(CH_2CH$_2$)$_2$), 2.45 (td, J = 11.3, 2.4 Hz, 1 H, N(CH_2CH$_2$)$_2$), 2.65 (ddd, J = 16.2, 4.0, 1.8 Hz, 1 H, CHCH_2CHO), 2.71–2.88 (m, 5 H, N(CH_2CH$_2$)$_2$ (2 H),

ArCH_2CH (2 H), CHCH_2CHO (1 H)), 3.57 (s, 2 H, NCH_2Ph), 4.27–4.37 (m, 1 H, CHCH$_2$CHO), 7.07 (d, J = 6.7 Hz, 1 H, arom), 7.12–7.41 (m, 8 H, arom), 9.93 (t, J = 2.2 Hz, 1 H, CHCH$_2$CHO). MS (EI): m/z 335 [M$^+$], 244 [M$^+$ – CH$_2$Ph], 91 [CH$_2$Ph$^+$]. HRMS: calcd for C$_{22}$H$_{25}$NO$_2$, 335.1885; found, 335.1883.

2-(1′-Benzyl-3,4-dihydrospiro[[2]benzopyran-1,4′-pi-peridin]-3-yl)ethanol (15). Compound **12** (200 mg, 0.53 mmol) was dissolved in Et$_2$O (5 mL) under nitrogen. This solution was cooled to −15 °C, and a solution of LiAlH$_4$ (1 M in THF, 1.3 mL, 1.3 mmol) was slowly added. After 2 h, the mixture was hydrolyzed by addition of H$_2$O and subsequently extracted with EtOAc. The organic layer was dried (Na$_2$SO$_4$) and concentrated under reduced pressure. The crude product (207 mg) was purified by flash chromatography (2 cm, petroleum ether:EtOAc = 1:1, 16 mL, R_f = 0.03) to afford a colorless oil, yield 170 mg (96%). Compound **15** was converted into the hydrochloride in the usual manner to obtain **15·**HCl as colorless needles, mp 221 °C (Et$_2$O/CH$_3$OH).

IR (base, film): $\tilde{\nu}$ (cm^{-1}) 3394 (O–H); 2939, 2821 (C–H); 1094, 1049 (C–O); 741, 700 (C–H). ^{1}H NMR (base, CDCl$_3$): δ (ppm) 1.71 (dd, J = 13.4, 2.7 Hz, 1 H, N(CH$_2$CH_2)$_2$), 1.84–2.01 (m, 3 H, N(CH$_2$CH_2)$_2$ (1 H), CH_2CH$_2$OH (2 H)), 2.08 (dd, J = 14.2, 4.5 Hz, 1 H, N(CH$_2$CH_2)$_2$), 2.22 (td, J = 13.1, 4.4 Hz, 1 H, N(CH_2CH$_2$)$_2$), 2.30–2.44 (m, 2 H, N(CH_2CH$_2$)$_2$), 2.61 (dd, J = 15.9, 2.7 Hz, 1 H, ArCH_2CH), 2.72–2.83 (m, 2 H, N(CH_2CH$_2$)$_2$,), 2.83 (dd, J = 15.9, 11.3 Hz, 1 H, ArCH_2CH), 3.57 (s, 2 H, NCH_2Ph), 3.89 (t, J = 5.5 Hz, 2 H, CH$_2$CH_2OH), 3.96–4.05 (m, 1 H, ArCH$_2$CH), 7.04 (d, J = 7.0 Hz, 1 H, arom), 7.10–7.40 (m, 8 H, arom). MS (base, EI): m/z 337 [M$^+$], 246 [M$^+$ – CH$_2$Ph], 91 [CH$_2$Ph$^+$]. Anal. (C$_{22}$H$_{27}$ClNO$_2$) C, H, N.

1′-Benzyl-3-ethyl-3,4-dihydrospiro[[2]benzopyran-1,4′-piperidine] (17). A solution of **15** (55 mg, 0.16 mmol) and Et$_3$N (25 mg, 0.25 mmol) in CH$_2$Cl$_2$ (5 mL) was cooled to −10 °C, and CH$_3$SO$_2$Cl (22 mg, 0.20 mmol) was added. After 2 h at −10 °C, an aqueous solution of NaOH (0.5 M) was added to the mixture to give pH 10. Then, it was extracted with CH$_2$Cl$_2$. The organic layer was dried (Na$_2$SO$_4$) and concentrated under reduced pressure. The crude product contained the mesylate **16**, which was immediately reduced.

2-(1′-Benzyl-3,4-dihydrospiro[[2]benzopyran-1,4′-pi-peridin]-3-yl)ethyl Methanesulfonate (16). IR (film): $\tilde{\nu}$ (cm^{-1}) 2923 (C–H); 1356, 1174 (ROSO$_2$CH$_3$); 1114, 1046 (C–O); 741, 701 (C–H). ^{1}H NMR (CDCl$_3$): δ (ppm) 1.68 (dd, J = 13.4, 2.4 Hz, 1 H, N(CH$_2$CH_2)$_2$), 1.84–2.28 (m, 5 H, N(CH$_2$CH_2)$_2$ (3 H), CH_2CH$_2$OSO$_2$CH$_3$ (2 H)), 2.35 (br t, J = 11.9 Hz, 1 H, N(CH_2CH$_2$)$_2$), 2.47 (br t, J = 11.9 Hz, 1 H, N(CH_2-CH$_2$)$_2$), 2.63 (dd, J = 15.9, 3.4 Hz, 1 H, ArCH_2CH), 2.68–2.82 (m, 2 H, N(CH_2CH$_2$)$_2$), 2.74 (dd, J = 15.9, 10.4 Hz, 1 H, ArCH_2-CH), 3.01 (s, 3 H, ROSO$_2$CH_3), 3.59 (s, 2 H, NCH_2Ph), 3.91 (tt, J = 10.1, 3.1 Hz, 1 H, ArCH$_2$CH), 4.42–4.57 (m, 2 H, CH$_2$CH_2OSO$_2$CH$_3$), 7.05 (d, J = 7.3 Hz, 1 H, arom), 7.10–7.43 (m, 8 H, arom).

The crude product **16** (58 mg) was dissolved in THF (4 mL). Then, a solution of LiAlH$_4$ (1 M in THF, 1 mL, 1 mmol) was added and the mixture was refluxed for 2 d. Then, H$_2$O was added and the salts were filtered off and washed with CH$_2$Cl$_2$. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (0.8 cm, petroleum ether:EtOAc = 1:1, 5 mL, R_f = 0.2) to afford a colorless oil, yield 18 mg (40%).

Compound 17. IR (film): $\tilde{\nu}$ (cm^{-1}) 2924, 2813 (C–H); 1067, 1046 (C–O); 755, 734, 698 (C–H). ^{1}H NMR (CDCl$_3$): δ (ppm) 1.07 (t, J = 7.5 Hz, 3 H, CH$_2$CH_3), 1.59–1.75 (m, 3 H, N(CH$_2$CH_2)$_2$ (1 H), CH_2CH$_3$ (2 H)), 1.88 (td, J = 14.0, 4.4 Hz, 1 H, N(CH$_2$CH_2)$_2$), 2.05 (dd, J = 14.0, 2.7 Hz, 1 H, N(CH$_2$CH_2)$_2$), 2.23 (td, J = 13.1, 4.6 Hz, 1 H, N(CH$_2$CH_2)$_2$), 2.44 (td, J = 11.0, 2.7 Hz, 1 H, N(CH_2CH$_2$)$_2$), 2.56 (td, J = 11.3, 2.7 Hz, 1 H, N(CH_2CH$_2$)$_2$), 2.63–2.80 (m, 4 H, N(CH_2CH$_2$)$_2$ (2 H), ArCH_2-CH (2 H)), 3.59 (s, 2 H, NCH_2Ph), 3.57–3.68 (m, 1 H, CHCH$_2$-CH$_3$), 7.06 (d, J = 7.0 Hz, 1 H, arom), 7.13 (td, J = 6.7, 2.1 Hz, 1 H, arom), 7.17–7.41 (m, 7 H, arom). MS (EI): m/z 321 [M$^+$], 230 [M$^+$ – CH$_2$Ph], 91 [CH$_2$Ph$^+$]. HRMS: calcd for C$_{22}$H$_{27}$NO, 321.2093; found, 321.2092.

2-(1′-Benzyl-3,4-dihydrospiro[[2]benzopyran-1,4′-piperidin]-3-yl)-*N*-methylacetamide (18). Compound **12** (97 mg, 0.25 mmol) was stirred for 11 d in a solution of CH$_3$NH$_2$ in EtOH (3 M, 3 mL) at room temperature. The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography (2 cm, EtOAc:acetone = 9:1, 10 mL, R_f = 0.03) to afford a colorless oil, yield 90 mg (99%). Compound **18** was converted into the hydrochloride in the usual manner to obtain **18·HCl** as colorless crystals, mp 88−90 °C (Et$_2$O/CH$_3$OH).

IR (base, film): $\tilde{\nu}$ (cm^{-1}) 3298 (N−H); 2937, 2820 (C−H); 1648 (amide I); 1561 (amide II); 1097, 1049 (C−O); 740, 700 (C−H). ^{1}H NMR (base, CDCl$_3$): δ (ppm) 1.70 (dd, J = 13.4, 2.5 Hz, 1 H, N(CH$_2$C*H*$_2$)$_2$), 1.89 (td, J = 12.8, 4.5 Hz, 1 H, N(CH$_2$C*H*$_2$)$_2$), 2.03−2.12 (m, 1 H, N(CH$_2$C*H*$_2$)$_2$), 2.20−2.33 (m, 2 H, N(CH$_2$C*H*$_2$)$_2$ (1 H), N(C*H*$_2$CH$_2$)$_2$ (1 H)), 2.39 (dd, J = 11.0, 2.1 Hz, 1 H, N(C*H*$_2$CH$_2$)$_2$), 2.46 (dd, J = 14.3, 8.2 Hz, 1 H, ArC*H*$_2$CH), 2.57 (dd, J = 14.3, 3.5 Hz, 1 H, ArC*H*$_2$CH), 2.64−2.85 (m, 4 H, N(C*H*$_2$CH$_2$)$_2$ (2 H), C*H*$_2$CONH (2 H)), 2.87 (d, J = 4.9 Hz, 3 H, CONHC*H*$_3$), 3.56 (s, 2 H, NC*H*$_2$Ph), 4.12−4.23 (m, 1 H, ArCH$_2$C*H*), 6.18 (br s, 1 H, CON*H*CH$_3$), 7.06 (d, J = 7.0 Hz, 1 H, arom), 7.11−7.40 (m, 8 H, arom). MS (EI): m/z 364 [M$^+$], 273 [M$^+$ − CH$_2$Ph], 91 [CH$_2$Ph$^+$]. HRMS: calcd for C$_{23}$H$_{28}$N$_2$O$_2$, 364.2151; found, 364.2152.

2-(1′-Benzyl-3,4-dihydrospiro[[2]benzopyran-1,4′-piperidin]-3-yl)-*N*-methylethanamine (19). The amide **18** (35 mg, 0.096 mmol) was dissolved in anhydrous Et$_2$O (4 mL) and some drops of CH$_2$Cl$_2$. The solution was cooled to −35 °C, and a solution of LiAlH$_4$ (1 M in THF, 0.15 mL, 0.15 mmol) was slowly added. The mixture was stirred for 5 h at room temperature. Then, H$_2$O was added and the precipitate was sucked off and washed with EtOAc. The organic layer was dried (Na$_2$SO$_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography (1 cm, CH$_3$OH:ammonia = 98:2, 5 mL, R_f = 0.05) to afford a colorless oil, yield 13 mg (40%).

IR (film): $\tilde{\nu}$ (cm^{-1}) 3424 (N−H); 2939, 2812 (C−H); 1095, 1046 (C−O); 751, 701 (C−H). ^{1}H NMR (CDCl$_3$): δ (ppm) 1.68 (dd, J = 13.4, 2.7 Hz, 2 H, N(CH$_2$C*H*$_2$), (1 H), N*H* (1 H)), 1.82 (q, J = 6.7 Hz, 2 H, CHC*H*$_2$CH$_2$NH), 1.90 (dd, J = 12.5, 4.6 Hz, 1 H, N(CH$_2$C*H*$_2$)$_2$), 2.03 (dd, J = 13.7, 2.1 Hz, 1 H, N(CH$_2$C*H*$_2$)$_2$), 2.23 (td, J = 12.8, 4.3 Hz, 1 H, N(CH$_2$C*H*$_2$)$_2$), 2.34 (td, J = 12.5, 2.7 Hz, 1 H, N(C*H*$_2$CH$_2$)$_2$), 2.49 (s, 3 H, NHC*H*$_3$), 2.49 (td, J = 14.0, 2.7 Hz, 1 H, N(C*H*$_2$CH$_2$)$_2$), 2.61 (dd, 15.9, 3.1 Hz, 1 H, ArC*H*$_2$CH), 2.68−2.88 (m, 5 H, N(C*H*$_2$CH$_2$)$_2$ (2 H), CHCH$_2$C*H*$_2$NH (2 H), ArC*H*$_2$CH (1 H)), 3.59 (s, 2 H, NC*H*$_2$Ph), 3.77−3.88 (m, 1 H, ArCH$_2$C*H*), 7.05 (d, J = 7.0 Hz, 1 H, arom), 7.10−7.42 (m, 8 H, arom). MS (EI): m/z 350 [M$^+$], 259 [M$^+$ − CH$_2$Ph], 91 [CH$_2$Ph$^+$]. HRMS: calcd for C$_{23}$H$_{30}$N$_2$O, 350.2358; found, 350.2364.

1′-Benzyl-3*H*-spiro[[2]benzofuran-1,4′-piperidine]-3-carbonitrile (20). Tetracyanoethylene (33 mg, 0.26 mmol) was dissolved in CH$_3$CN (2 mL) under nitrogen. Then, a solution of **3a** (403 mg, 1.3 mmol) in CH$_3$CN (2 mL) was added and the mixture was stirred for 5 min. Trimethylsilyl cyanide (0.4 mL) was added, and the mixture was refluxed. Two additional portions of trimethylsilyl cyanide (0.3 mL each) were added within a period of 4 h. When the reaction was completed, the solvent was removed under reduced pressure and the residue was dissolved in CH$_2$Cl$_2$. Then, some silica gel was added and the suspension was concentrated under reduced pressure. The residue was purified by flash chromatography (3 cm, petroleum ether:EtOAc = 4:1, 20 mL, R_f = 0.05) to afford a colorless oil, which solidified on standing, mp 114−115 °C, yield 268 mg (68%).

IR (film): $\tilde{\nu}$ (cm^{-1}) 2944, 2813(C−H); 1044 (C−O); 741, 699 (C−H); (no C≡N-valence vibration). ^{1}H NMR (CDCl$_3$): δ (ppm) 1.72 (ddd, J = 13.4, 5.2, 2.5 Hz, 1 H, N(CH$_2$C*H*$_2$)$_2$), 1.92−2.18 (m, 3 H, N(CH$_2$C*H*$_2$)$_2$), 2.45 (td, J = 11.3, 2.7 Hz, 1 H, N(C*H*$_2$CH$_2$)$_2$), 2.53 (td, J = 11.9, 3.1 Hz, 1 H, N(C*H*$_2$CH$_2$)$_2$), 2.83−2.94 (m, 2 H, N(C*H*$_2$CH$_2$)$_2$), 3.63 (s, 2 H, NC*H*$_2$Ph), 5.86 (s, 1 H, ArC*H*), 7.18−7.22 (m, 1 H, arom), 7.24−7.47 (m, 8 H, arom). ^{13}C NMR (CDCl$_3$): δ (ppm) 36.9 (1 C, N(CH$_2$*C*H$_2$)$_2$), 37.2 (1 C, N(CH$_2$*C*H$_2$)$_2$), 49.6 (1 C, N(*C*H$_2$CH$_2$)$_2$), 49.9 (1 C, N(*C*H$_2$CH$_2$)$_2$),

63.3 (1 C, N*C*H$_2$Ph), 68.8 (1 C, Ar*C*HCN), 88.1 (1 C, Ar*C*O), 118.4 (1 C, *C*N), 121.4 (1 C, arom CH), 122.0 (1 C, arom CH), 127.1 (1 C, arom CH), 128.2 (2 C, arom CH), 128.8 (1 C, arom CH), 129.2 (2 C, arom CH), 129.8 (1 C, arom C), 133.8 (1 C, arom C), 138.3 (1 C, arom C), 145.5 (1 C, arom C). MS (EI): m/z 304 [M$^+$], 227 [M$^+$ − Ph], 213 [M$^+$ − CH$_2$Ph], 91 [CH$_2$Ph$^+$]. HRMS: calcd for C$_{20}$H$_{20}$N$_2$O, 304.1576; found, 304.1573. Anal. (C$_{20}$H$_{20}$N$_2$O) C, H, N; C: calcd, 78.9; found, 78.4.

Ethyl 1′-Benzyl-3*H*-spiro[[2]benzofuran-1,4′-piperidine]-3-carboxylate (21). A solution of **20** (101 mg, 0.33 mmol) in EtOH (3 g), H$_2$O (68 mg), and concentrated H$_2$SO$_4$ (1.1 g) was refluxed for 7.5 h. Then, an aqueous solution of NaOH (3 M) was added to give pH 10 and the mixture was extracted with CH$_2$Cl$_2$. The organic layer was dried (Na$_2$SO$_4$), and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (2 cm, petroleum ether: EtOAc = 2:1, 10 mL, R_f = 0.06) to afford a colorless oil, yield 46 mg (39%).

IR (film): $\tilde{\nu}$ (cm^{-1}) 2943, 2811 (C−H); 1755 (C=O); 1196, 1075 (C−O); 755, 700 (C−H). ^{1}H NMR (CDCl$_3$): δ (ppm) 1.29 (t, J = 7.0 Hz, 3 H, OCH$_2$C*H*$_3$), 1.75 (dd, J = 13.7, 2.4 Hz, 1 H, N(CH$_2$C*H*$_2$)$_2$), 1.98−2.11 (m, 2 H, N(CH$_2$C*H*$_2$)$_2$), 2.19 (td, J = 13.4, 4.3 Hz, 1 H, N(CH$_2$C*H*$_2$)$_2$), 2.60 (td, J = 11.9, 3.1 Hz, 1 H, N(C*H*$_2$CH$_2$)$_2$), 2.71 (td, J = 11.6, 4.3 Hz, 1 H, N(C*H*$_2$CH$_2$)$_2$), 2.98 (br d, J = 11.3 Hz, 2 H, N(C*H*$_2$CH$_2$)$_2$), 3.71 (s, 2 H, NC*H*$_2$-Ph), 4.22 (q, J = 7.0 Hz, 2 H, OC*H*$_2$CH$_3$), 5.66 (s, 1 H, ArC*H*CO), 7.18 (dd, J = 6.1, 1.5 Hz, 1 H, arom), 7.27−7.42 (m, 8 H, arom). MS (EI): m/z 351 [M$^+$], 260 [M$^+$ − CH$_2$Ph], 91 [CH$_2$Ph$^+$]. HRMS: calcd for C$_{22}$H$_{25}$NO$_3$, 351.1834; found, 351.1833.

(1′-Benzyl-3*H*-spiro[[2]benzofuran-1,4′-piperidin]-3-yl)-methanol (22). Compound **21** (35 mg, 0.1 mmol) was dissolved in Et$_2$O (5 mL) under nitrogen. This solution was cooled to −15 °C, and a solution of LiAlH$_4$ (1 M in THF, 0.2 mL, 0.2 mmol) was slowly added. After 30 min, the mixture was hydrolyzed by addition of some H$_2$O. The salts were filtered off and washed with EtOAc. The organic layer was concentrated under reduced pressure. The crude product was purified by flash chromatography (1 cm, petroleum ether:EtOAc = 1:1, 5 mL, R_f = 0.04) to afford a colorless oil, yield 23 mg (75%).

IR (film): $\tilde{\nu}$ (cm^{-1}) 3386 (O−H); 2917, 2812 (C−H); 1050 (C−O); 745, 699 (C−H). ^{1}H NMR (CDCl$_3$): δ (ppm) 1.71 (br d, J = 13.7 Hz, 2 H, N(CH$_2$C*H*$_2$)$_2$), 1.95 (td, J = 13.4, 4.3 Hz, 1 H, N(CH$_2$C*H*$_2$)$_2$), 2.15 (td, J = 13.1, 4.3 Hz, 1 H, N(CH$_2$C*H*$_2$)$_2$), 2.49 (br t, J = 11.3 Hz, 2 H, N(C*H*$_2$CH$_2$)$_2$), 2.80−2.91 (m, 2 H, N(C*H*$_2$CH$_2$)$_2$), 3.61 (s, 2 H, NC*H*$_2$Ph), 3.76 (dd, J = 11.6, 5.8 Hz, 1 H, CHC*H*$_2$OH), 3.95 (dd, J = 11.6, 3.4 Hz, 1 H, CHC*H*$_2$-OH), 5.27−5.32 (m, 1 H, ArC*H*CH$_2$OH), 7.15−7.21 (m, 2 H, arom), 7.25−7.41 (m, 7 H, arom). MS (EI): m/z 309 [M$^+$], 218 [M$^+$ − CH$_2$Ph], 91 [CH$_2$Ph$^+$]. HRMS: calcd for C$_{20}$H$_{23}$NO$_2$, 309.1729; found, 309.1729. Anal. (C$_{20}$H$_{23}$NO$_2$) C, N; H: calcd, 7.49; found, 8.16.

2-(1′-Benzyl-3*H*-spiro[[2]benzofuran-1,4′-piperidin]-3-yl)ethanenitrile (23). A mixture of **3b** (78 mg, 0.26 mmol), Ph$_3$P=CHCN (159 mg, 0.53 mmol), and Cs$_2$CO$_3$ (20 mg) in anhydrous toluene (10 mL) was refluxed for 40 h. The solvent was removed under reduced pressure. The residue was purified by flash chromatography (2 cm, petroleum ether:EtOAc = 2:1, 10 mL, R_f = 0.08) to afford a colorless oil, which solidified on standing, mp 113 °C, yield 64 mg (76%).

IR (film): $\tilde{\nu}$ (cm^{-1}) 2942, 2811 (C−H); 2252 (C≡N); 1050 (C−O); 741, 698 (C−H). ^{1}H NMR (CDCl$_3$): δ (ppm) 1.69 (dd, J = 13.7, 2.7 Hz, 1 H, N(CH$_2$C*H*$_2$)$_2$), 1.85 (dd, J = 13.7, 2.7 Hz, 1 H, N(CH$_2$C*H*$_2$)$_2$), 1.97 (td, J = 13.0, 4.6 Hz, 1 H, N(CH$_2$C*H*$_2$)$_2$), 2.16 (td, J = 13.4, 4.4 Hz, 1 H, N(CH$_2$C*H*$_2$)$_2$), 2.40−2.57 (m, 2 H, N(C*H*$_2$CH$_2$)$_2$), 2.81−2.92 (m, 4 H, N(C*H*$_2$CH$_2$)$_2$ (2 H), ArCHC*H*$_2$CN (2 H)), 3.62 (s, 2 H, NC*H*$_2$Ph), 5.43 (t, J = 5.5 Hz, 1 H, ArC*H*CH$_2$CN), 7.19 (dd, J = 5.5, 2.8 Hz, 1 H, arom), 7.25−7.41 (m, 8 H, arom). ^{13}C NMR (CDCl$_3$): δ (ppm) 26.1 (1 C, *C*H$_2$CN), 37.4 (1 C, N(CH$_2$*C*H$_2$)$_2$), 38.2 (1 C, N(CH$_2$*C*H$_2$)$_2$), 49.7 (1 C, N(*C*H$_2$CH$_2$)$_2$), 49.9 (1 C, N(*C*H$_2$CH$_2$)$_2$), 63.3 (1 C, N*C*H$_2$Ph), 76.8 (1 C, Ar*C*HCH$_2$CN), 85.5 (1 C, Ar*C*O), 116.9 (1 C, *C*N), 121.2 (2 C, arom CH), 127.0 (1 C, arom CH), 128.2 (3

C, arom CH), 128.8 (1 C, arom CH), 129.3 (2 C, arom CH), 138.2 (1 C, arom C), 138.3 (1 C, arom C), 146.0 (1 C, arom C). MS (EI): m/z 318 [M$^+$], 227 [M$^+$ − CH$_2$Ph], 91 [CH$_2$Ph$^+$]. HRMS: calcd for C$_{21}$H$_{22}$N$_2$O, 318.1732; found, 318.1733.

Ethyl 2-(1′-Benzyl-3H-spiro[[2]benzofuran-1,4′-piperidin]-3-yl)acetate (24). A mixture of **3b** (266 mg, 0.90 mmol), Ph$_3$P=CHCO$_2$Et (**10**) (627 mg, 1.8 mmol), and Cs$_2$CO$_3$ (50 mg) in anhydrous toluene (20 mL) was refluxed for 15 h. The solvent was removed under reduced pressure. The residue was purified by flash chromatography (3 cm, petroleum ether: EtOAc = 3:1, 20 mL, R_f = 0.05) to afford a colorless oil, yield 289 mg (88%).

IR (film): $\tilde{\nu}$ (cm^{-1}) 2941, 2811 (C−H); 1735 (C=O); 1162, 1045 (C−O); 744, 699 (C−H). ^{1}H NMR (CDCl$_3$): δ (ppm) 1.28 (t, J = 7.3 Hz, 3 H, OCH$_2$CH_3), 1.64−1.76 (m, 2 H, N(CH$_2$CH_2)$_2$), 1.95 (td, J = 12.8, 4.6 Hz, 1 H, N(CH$_2$CH_2)$_2$), 2.10 (td, J = 13.4, 4.4 Hz, 1 H, N(CH$_2$CH_2)$_2$), 2.48 (br t, J = 11.6 Hz, 2 H, N(CH_2CH$_2$)$_2$), 2.74 (d, J = 6.7 Hz, 2 H, ArCHCH_2CO), 2.79−2.88 (m, 2 H, N(CH_2CH$_2$)$_2$), 3.60 (s, 2 H, NCH_2Ph), 4.21 (q, J = 7.3 Hz, 2 H, OCH_2CH$_3$), 5.61 (t, J = 6.7 Hz, 1 H, ArCHCH$_2$CO), 7.12−7.19 (m, 1 H, arom), 7.23−7.40 (m, 8 H, arom). MS (EI): m/z 365 [M$^+$], 274 [M$^+$ − CH$_2$Ph], 91 [CH$_2$Ph$^+$]. HRMS: calcd for C$_{23}$H$_{27}$NO$_3$, 365.1991; found, 365.1989. Anal. (C$_{23}$H$_{27}$NO$_3$) N; C: calcd, 75.4; found, 74.9; H: calcd, 7.45; found, 8.17.

2-(1′-Benzyl-3H-spiro[[2]benzofuran-1,4′-piperidin]-3-yl)ethanol (25). Compound **24** (130 mg, 0.36 mmol) was dissolved in Et$_2$O (5 mL) under nitrogen. This solution was cooled to −15 °C, and a solution of LiAlH$_4$ (1 M in THF, 0.89 mL, 0.89 mmol) was slowly added. After 30 min, the mixture was allowed to warm to room temperature, and after another 30 min, some H$_2$O was added. The mixture was extracted with EtOAc. The organic layer was dried (Na$_2$SO$_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography (1 cm, petroleum ether:EtOAc = 1:1, 5 mL, R_f = 0.03) to afford a colorless oil, yield 86 mg (75%). Compound **25** was converted into the hydrochloride in the usual manner to obtain **25**·HCl as colorless crystals, mp 216 °C (Et$_2$O/CH$_3$OH).

IR (base, film): $\tilde{\nu}$ (cm^{-1}) 3411 (O−H); 2940, 2819 (C−H); 1050 (C−O); 744, 700 (C−H). ^{1}H NMR (base, CDCl$_3$): δ (ppm) 1.69−1.80 (m, 2 H, N(CH$_2$CH_2)$_2$), 1.85−1.99 (m, 2 H, N(CH$_2$CH_2)$_2$ (1 H), CH_2CH$_2$OH (1 H)), 2.09−2.26 (m, 2 H, N(CH$_2$CH_2)$_2$ (1 H), CH_2CH$_2$OH (1 H)), 2.34−2.50 (m, 2 H, N(CH_2CH$_2$)$_2$), 2.79−2.92 (m, 3 H, N(CH_2CH$_2$)$_2$ (2 H), OH (1 H)), 3.58 (s, 2 H, NCH_2Ph), 3.81−3.98 (m, 2 H, CH$_2$CH_2OH), 5.41 (dd, J = 8.9, 3.1 Hz, 1 H, ArCH), 7.09−7.19 (m, 2 H, arom), 7.25−7.40 (m, 7 H, arom). MS (base, EI): m/z 323 [M$^+$], 232 [M$^+$ − CH$_2$Ph], 91 [CH$_2$Ph$^+$]. Anal. (C$_{21}$H$_{26}$ClNO$_2$) C, H, N.

Pharmacology. σ_1 and σ_2 receptor binding assays were conducted as previously reported.[13] The σ_1 binding assay was performed using a guinea pig brain membrane preparation as receptor material and [^{3}H]-(+)-pentazocine as the radioligand. Nonspecific binding was determined with 10 μM haloperidol.[21] The σ_2 receptor affinity was determined using rat liver membrane preparations with the radioligand [^{3}H]ditolylguanidine in the presence of 100 nM (+)-pentazocine to mask σ_1 binding sites. Nonspecific binding was determined with 10 μM ditolylguanidine.[22,23] K_i values were calculated according to Cheng and Prusoff[24] and represent data from at least three independent experiments, each performed in triplicate. The results are given as mean ± standard error of the mean (SEM).

References

(1) Martin, W. R.; Eades, C. G.; Thompson, J. A.; Huppler, R. E.; Gilbert, P. E. The effects of morphine- and nalorphine-like drugs in the nondependent and morphine-dependent chronic spinal dog. *J. Pharmacol. Exp. Ther.* **1976**, *197*, 517−532.

(2) Tam, S. W. Naloxone-inaccessible sigma receptor in rat central nervous system. *Proc. Natl. Acad. Sci. U.S.A.* **1983**, *80*, 6703−6707.

(3) Quirion, R.; Bowen, W. D.; Itzhak, Y.; Junien, J. L.; Musacchio, J. M.; Rothman, R. B.; Su, T.-P.; Tam, W.; Taylor, D. P. A proposal for the classification of sigma binding sites. *Trends Pharmacol. Sci.* **1992**, *13*, 85−86.

(4) Hanner, M.; Moebius, F. F.; Flandorfer, A.; Knaus, H.-G.; Striessnig, J.; Kempner, E.; Glossmann, H. Purification, molecular cloning, and expression of the mammalian sigma1-binding site. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 8072−8077.

(5) Kekuda, R.; Prasad, P. D.; Fei, Y.-J.; Leibach, F. H.; Ganapathy, V. Cloning and Functional Expression of the Human Type 1 Sigma Receptor (hSigmaR1). *Biochem. Biophys. Res. Commun.* **1996**, *229*, 553−558.

(6) Seth, P.; Fei, Y.-J.; Li, H. W.; Huang, W.; Leibach, F. H.; Ganapathy, V. Cloning and Functional Characterization of a σ Receptor from Rat Brain. *J. Neurochem.* **1998**, *70*, 922−931.

(7) Moebius, F. F.; Striessnig, J.; Glossmann, H. The mysteries of sigma receptors: new family members reveal a role in cholesterol synthesis. *Trends Pharmacol. Sci.* **1997**, *18*, 67−70.

(8) Bastianetto, S.; Monnet, F.; Junien, J.-L.; Quirion, R. Steroidal Modulation of Sigma Receptor Function. In *Contemporary Endocrinology: Neurosteroids: A New Regulatory Function in the Nervous System*; Baulieu, E.-E., Robel, P., Schumacher, M., Eds.; Humana Press: Totowa, 1999; pp 191−205.

(9) Walker, J. M.; Bowen, W. D.; Walker, F. O.; Matsumoto, R. R.; De Costa, B.; Rice, K. C. Sigma Receptors: Biology and Function. *Pharmacol. Rev.* **1990**, *42*, 353−402.

(10) Bowen, W. D. Sigma receptors: recent advances and new clinical potentials. *Pharm. Acta Helv.* **2000**, *74*, 211−218.

(11) (a) Monograph BMY-14802-1. *Drugs Future* **1987**, *12*, 752−753. (b) Monograph BMY-14802. *Drugs Future* **1995**, *20*, 821−822.

(12) Guitart, X.; Ballarin, M.; Codony, X.; Dordal, A.; Farré, A. J.; Frigola, J.; Mercè, R. *Drugs Future* **1999**, *24*, 386−392.

(13) Maier, C. A.; Wünsch, B. Novel Spiropiperidines as Highly Potent and Subtype Selective σ-Receptor Ligands. Part 1. *J. Med. Chem.* **2002**, *45*, 438−448.

(14) Cohen, N.; Schaer, B.; Saucy, G.; Borer, R.; Todaro, L.; Chiu, A.-M. Lewis Acid Mediated Nucleophilic Substitution Reactions of 2-Alkoxy-3,4-dihydro-2H-1-benzopyrans: Regiochemistry and Utility in the Synthesis of 3,4-Dihydro-2H-1-benzopyran-2-carboxylic Acids. *J. Org. Chem.* **1989**, *54*, 3282−3292.

(15) Miura, T.; Masaki, Y. Carbon−carbon bond formation and reduction of aldehydes, ketones and acetals with silylated nucleophiles catalysed by tetracyanoethylene. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2155−2158.

(16) Stevenson, G. I.; Huscroft, I.; MacLeod, A. M.; Swain, C. J.; Cascieri, M. A.; Chicchi, G. G.; Graham, M. I.; Harrison, T.; Kelleher, F. J.; Kurtz, M.; Ladduwahetty, T.; Merchant, K. J.; Metzger, J. M.; MacIntyre, D. E.; Sadowski, S.; Sohal, B.; Owens, A. P. 4,4-Disubstituted Piperidine High-Affinity NK$_1$ Antagonists: Structure−Activity Relationships and in Vivo Activity. *J. Med. Chem.* **1998**, *41*, 4623−4635.

(17) Subrahmanyam, D.; Renuka, B.; Kumar, G. S.; Vandana, V.; Deevi, D. S. 9-Deoxopodophyllotoxin derivatives as anti-cancer agents. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2131−2134.

(18) Bloch, R.; Seck, M. Optically active five-membered oxygen-containing rings, a synthesis of (+)-Eldanolide. *Tetrahedron* **1989**, *45*, 3731−3740.

(19) Rossi, R.; Salvadori, P. A. Synthesis of Both Enantiomers of 6-Methyl-3-octanone, a Component of the Alarm Pheromone of Ants in the Genus Crematogaster. *Synthesis* **1979**, 209−210.

(20) Still, W. C.; Kahn, M.; Mitra, A. Rapid Chromatographic Technique for Preparative Separations with Moderate Resolution. *J. Org. Chem.* **1978**, *43*, 2923−2925.

(21) DeHaven-Hudkins, D. L.; Fleissner, L. C.; Ford-Rice, F. Y. Characterization of the binding of [^{3}H](+)-pentazocine to σ recognition sites in guinea pig brain. *Eur. J. Pharmacol.* **1992**, *227*, 371−378.

(22) Mach, R. H.; Smith, C. R.; Childers, S. R. Ibogaine Possesses a Selective Affinity for σ_2 Receptors. *Life Sci.* **1995**, *57*, PL 57−62.

(23) Hellewell, S. B.; Bruce, A.; Feinstein, G.; Orringer, J.; Williams, W.; Bowen, W. D. Rat liver and kidney contain high densities of σ_1 and σ_2 receptors: characterization by ligand binding and photoaffinity labeling. *Eur. J. Pharmacol. Mol. Pharmacol. Sect.* **1994**, *268*, 9−18.

(24) Cheng, Y.; Prusoff, W. H. Relationship between the inhibition constant (K_i) and the concentration of inhibitor which causes 50% inhibition (IC$_{50}$) of an enzymatic reaction. *Biochem. Pharmacol.* **1973**, *22*, 3099−3108.