Articles

Sila-Analogues of High-Affinity, Selective σ Ligands of the Spiro[indane-1,4′-piperidine] Type: Syntheses, Structures, and Pharmacological Properties

Reinhold Tacke,*,† Vera I. Handmann,† Rüdiger Bertermann,† Christian Burschka,† Martin Penka,† and Christoph Seyfried‡

Institute of Inorganic Chemistry, University of Würzburg, Am Hubland, D-97074 Würzburg, Germany, and Merck KGaA, Department of CNS Research, Biomedical Research, Frankfurter Strasse 250, D-64293 Darmstadt, Germany

Received May 3, 2002

The 1′-organylspiro[indane-1,4′-piperidine] derivatives **1a**−**4a** (organyl = benzyl (**1a**), 4-methoxybenzyl (**2a**), 2-phenylethyl (**3a**), 3-methylbut-2-enyl (**4a**)) are high-affinity, selective σ ligands. The corresponding sila-analogues **1b**−**4b** (→ replacement of the carbon spirocenter by a silicon atom) were synthesized in three-step syntheses, starting from dichlorodivinylsilane, and were isolated as the hydrochlorides **1b**·HCl−**4b**·HCl. To get information about the structure of the title compounds and their respective carbon analogues in the solid state and in solution, crystal structure analyses (**1a**·HCl, **2a**, **2b**·HCl) and temperature-dependent solution ^{1}H NMR studies (**2a**·HCl, **2b**·HCl) were performed. These structural investigations were complemented by computational studies of related model species. The C/Si pairs **1a**/**1b**−**4a**/**4b** were studied for their affinities for various central nervous system receptors (σ, 5-HT$_{1A}$, 5-HT$_{2A}$, α$_1$, α$_2$, M, D$_2$) using radioligand binding assays. The σ affinities of the sila-analogues **2b**−**4b** were found to be similar to those of the parent carbon compounds **2a**−**4a**, whereas sila-substitution of **1a** (→ **1b**) resulted in a decrease of affinity of about 1 order of magnitude. On the other hand, a significant increase of affinity for the dopamine D$_2$ and the serotonin 2A (5-HT$_{2A}$) receptors was observed for the sila-analogues **1b**−**4b**, the sila-substitution effect being especially pronounced for **4a**/**4b** (6-fold affinity increase for the D$_2$ receptor) and **3a**/**3b** (37-fold affinity increase for the 5-HT$_{2A}$ receptor).

Introduction

A few years ago, a series of high-affinity, selective σ ligands of the spiro[indane-1,4′-piperidine] type were reported, such as compounds **1a**−**4a**.[1,2] These ligands were prepared to investigate the functional role of the central σ recognition site. As the identity of σ receptors is still discussed controversially,[3] it appeared worthwhile to contribute to this subject and to study the pharmacological effects of the replacement of the carbon spirocenters of **1a**−**4a** by silicon atoms. Sila-substitution (C/Si exchange) has been demonstrated to be a useful approach for SAR studies and to be a challenging method for the improvement of the biological properties of organic drugs.[4,5] Since the covalent radii of carbon (0.77 Å) and silicon (1.17 Å) differ significantly, replacement of the carbon spirocenters in the conformationally restricted frameworks of **1a**−**4a** by silicon atoms should result in structural changes and hence possibly also in changes of the pharmacological properties. We report here on the syntheses of the silicon compounds **1b**−**4b** (isolated as hydrochlorides) and the pharmacological characterization of the C/Si pairs **1a**/**1b**−**4a**/**4b** (studies for their affinities for various central nervous receptor systems using radioligand binding assays). These in-

* To whom correspondence should be addressed. Tel: +49-931-888-5250. Fax: +49-931-888-4609. E-mail: r.tacke@mail.uni-wuerzburg.de.
† University of Würzburg.
‡ Merck KGaA.

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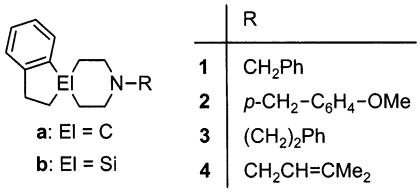
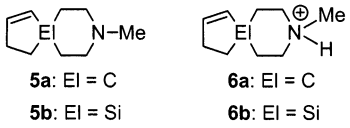
10.1021/om020354u CCC: $25.00
Publication on Web 01/28/2003

vestigations were complemented by solution NMR studies of **1b**·HCl−**4b**·HCl (^{1}H, ^{13}C, ^{29}Si), VT ^{1}H NMR experiments with **2a**·HCl and **2b**·HCl, and crystal structure analyses of **1a**·HCl, **2a**, and **2b**·HCl. In addition, the structures of the carbon/silicon pairs **5a**/**5b** and **6a**/**6b** were investigated by computational methods. The studies presented here were carried out as part of our systematic investigations on C/Si bioisosterism (for recent papers on this subject, see ref 5).

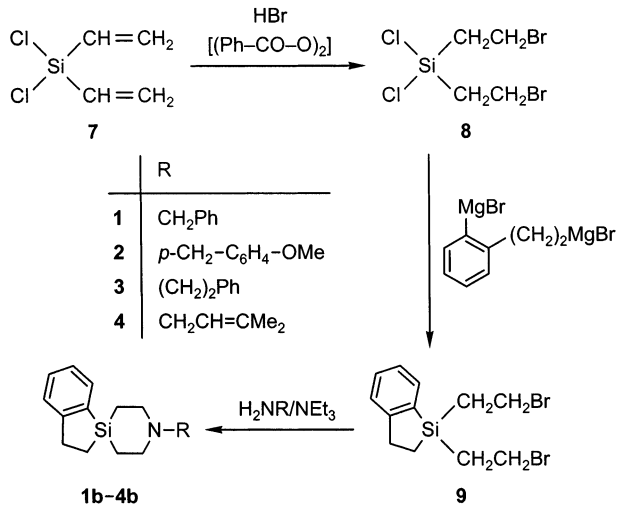




Results and Discussion

Syntheses. The 1,4′-silaspiro[indane-1,4′-piperidine] derivatives **1b**−**4b** (isolated as hydrochlorides) were prepared according to Scheme 1 by three-step syntheses,

Scheme 1



starting from dichlorodivinylsilane (**7**). The dibenzoyl peroxide-catalyzed hydrobromination of **7** in *n*-pentane led to bis(2-bromoethyl)dichlorosilane (**8**) (82% yield). Reaction of **8** with 1-bromomagnesio-2-(2-bromomagnesioethyl)benzene in tetrahydrofuran gave 1,1-bis(2-bromoethyl)-1-silaindane (**9**) (64% yield), which on treatment with benzylamine, (4-methoxybenzyl)amine, (2-phenylethyl)amine, or (3-methylbut-2-enyl)amine in trichloromethane, in the presence of triethylamine, afforded the respective spirocyclic compounds **1b**−**4b** (46−61% yield). Subsequent reaction with hydrogen chloride in diethyl ether gave the corresponding hydrochlorides **1b**·HCl−**4b**·HCl (56−72% yield).

The identities of compounds **1b**·HCl−**4b**·HCl, **8**, and **9** were established by elemental analyses (C, H, N), solution NMR studies (^{1}H, ^{13}C, ^{29}Si), and mass-spectrometric investigations (**1b**·HCl−**4b**·HCl). In addition,

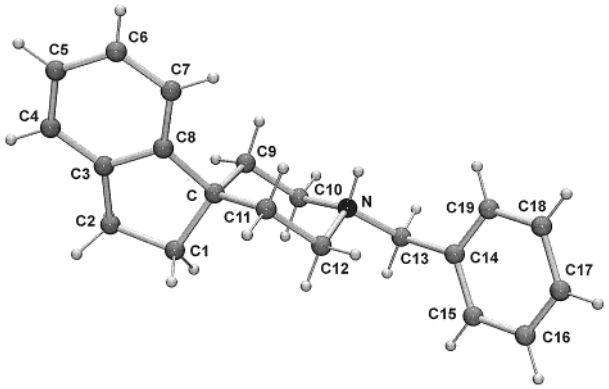


Figure 1. Structure of the cation in the crystal of **1a**·HCl, showing the atomic numbering scheme. The cation and the chloride anion form an N−H···Cl hydrogen bond (N−H, 0.882(18) Å; H···Cl, 2.227(18) Å; N···Cl, 3.1043(12) Å; N−H···Cl, 172.4(15)°).[9]

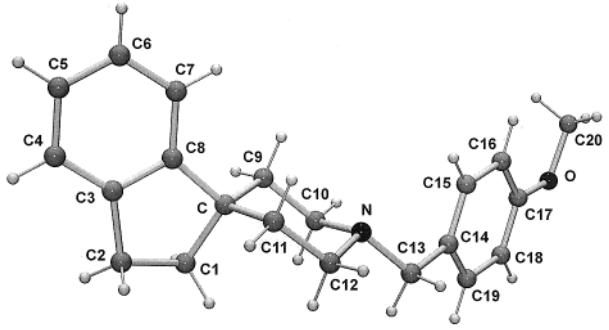


Figure 2. Structure of **2a** in the crystal, showing the atomic numbering scheme.

compound **2b**·HCl was characterized by a crystal structure analysis.

The spirocyclic skeleton of compounds **1b**−**4b** (**1b**·HCl−**4b**·HCl) represents a new type of spirosilaheterocycle (for reviews on silaheterocycles, see refs 6−8).

Crystal Structure Analyses. Compounds **1a**·HCl, **2a**, and **2b**·HCl were structurally characterized by single-crystal X-ray diffraction. The structures of **1a**·HCl (cation), **2a**, and **2b**·HCl (cation) are depicted in Figures 1−3. The crystal data and the experimental parameters used for the crystal structure analyses are summarized in Table 1. Selected interatomic distances and angles are listed in Table 2.

The structural features of the spiro[indane-1,4′-piperidinium] skeleton of **1a**·HCl and the spiro[indane-1,4′-piperidine] skeleton of **2a** are very similar, the piperidinium (piperidine) ring adopting a chair conformation and the respective carbon atoms C1 (axial), C8 (equatorial), and C13 (equatorial) occupying identical positions of this ring. The conformations of the indane skeletons of **1a**·HCl and **2a** are also very similar. For both compounds, the mean deviations from the calculated best planes generated by the carbon atoms C and C3 to C8 are very small (**1a**·HCl, 0.02 Å; **2a**, 0.004 Å), the

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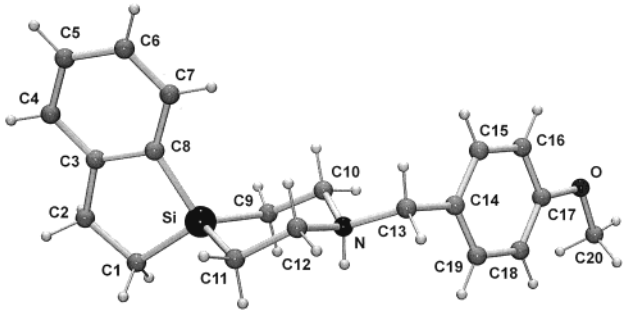

Figure 3. Structure of the cation in the crystal of **2b**·HCl, showing the atomic numbering scheme. The cation and the chloride anion form an N−H···Cl hydrogen bond (N−H, 0.87(4) Å; H···Cl, 2.25(4) Å; N···Cl, 3.119(5) Å; N−H···Cl, 173(4)°).[9]

Table 1. Crystal Data and Experimental Parameters for the Crystal Structure Analyses of 1a·HCl, 2a, and 2b·HCl

	1a·HCl	**2a**	**2b**·HCl
empirical formula	$C_{20}H_{24}ClN$	$C_{21}H_{25}NO$	$C_{20}H_{26}ClNOSi$
formula mass, g mol^{-1}	313.85	307.42	359.96
collection *T*, K	173(2)	173(2)	173(2)
λ(Mo Kα), Å	0.71073	0.71073	0.71073
cryst syst	monoclinic	monoclinic	orthorhombic
space group (no.)	$P2_1/n$ (14)	$P2_1/c$ (14)	*Pbca* (61)
a, Å	5.9448(7)	14.3714(19)	12.6552(15)
b, Å	25.491(2)	6.0997(6)	11.9374(16)
c, Å	11.4305(14)	19.511(3)	25.50(3)
β, deg	102.627(14)	93.613(18)	90
V, Å^3	1690.3(3)	1707.0(4)	3853(5)
Z	4	4	8
D(calcd), g cm^{-3}	1.233	1.196	1.241
μ, mm^{-1}	0.223	0.072	0.267
F(000)	672	664	1536
cryst dimens, mm	0.5 × 0.5 × 0.1	0.5 × 0.5 × 0.4	0.3 × 0.1 × 0.1
2θ range, deg	3.98−49.76	4.18−53.94	4.54−46.68
index ranges	$-7 \le h \le 7$	$-18 \le h \le 18$	$-14 \le h \le 10$
	$-30 \le k \le 27$	$-7 \le k \le 7$	$-13 \le k \le 12$
	$-13 \le l \le 13$	$-24 \le l \le 24$	$-28 \le l \le 19$
no. of collected reflns	8085	15215	6736
no. of ind reflns	2880	3560	2641
R_{int}	0.0327	0.0299	0.0636
no. of reflns used	2880	3560	2641
no. of params	202	209	221
S^a	1.041	1.050	0.991
weight params *a*/*b*^{b}	0.0534/0.1880	0.0600/0.2271	0.0743/0.0000
$R1^c$ [$I > 2\sigma(I)$]	0.0323	0.0381	0.0604
$wR2^d$ (all data)	0.0869	0.1054	0.1471
max./min. residual electron density, e Å^{-3}	+0.227/−0.147	+0.256/−0.137	+0.607/−0.245

^{a} $S = \{\Sigma[w(F_o^2 - F_c^2)^2]/(n - p)\}^{0.5}$; n = no. of reflections; p = no. of parameters. ^{b} $w^{-1} = \sigma^2(F_o^2) + (aP)^2 + bP$, with $P = [\max(F_o^2, 0) + 2F_c^2]/3$. ^{c} $R1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$. ^{d} $wR2 = \{\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{0.5}$.

deviations of the respective carbon atoms C1 (**1a**·HCl, 0.36 Å; **2a**, 0.40 Å) and C2 (**1a**·HCl, −0.02 Å; **2a**, −0.04 Å) from this plane also being very similar. The five-membered ring generated by the carbon atoms C, C1, C2, C3, and C8 can be described as an envelope conformation with a dihedral angle between the above-mentioned plane (C, C3 to C8) and the plane generated by the carbon atoms C, C1, and C2 (**1a**·HCl, 24.9°; **2a**, 26.9°).

Table 2. Selected Interatomic Distances (Å) and Angles (deg) for 1a·HCl, 2a, and 2b·HCl

	1a·HCl (El = C)	**2a** (El = C)	**2b**·HCl (El = Si)
El−C1	1.5572(18)	1.5529(14)	1.852(5)
El−C8	1.519(2)	1.5199(15)	1.880(5)
El−C9	1.540(2)	1.5326(13)	1.864(5)
El−C11	1.5320(19)	1.5403(14)	1.882(5)
N−C10	1.4977(18)	1.4631(13)	1.497(6)
N−C12	1.5023(18)	1.4658(13)	1.501(5)
C1−C2	1.535(2)	1.5380(14)	1.526(7)
C2−C3	1.512(2)	1.5073(16)	1.521(6)
C3−C8	1.391(2)	1.3941(14)	1.397(6)
C9−C10	1.509(2)	1.5191(15)	1.511(6)
C11−C12	1.523(2)	1.5173(15)	1.518(7)
C1−El−C8	101.62(11)	101.82(8)	94.5(2)
C1−El−C9	112.49(11)	112.74(8)	116.8(2)
C1−El−C11	113.20(11)	111.63(9)	114.5(3)
C8−El−C9	107.69(11)	112.98(9)	116.6(2)
C8−El−C11	113.40(11)	110.32(8)	113.8(2)
C9−El−C11	108.29(12)	107.38(8)	101.5(2)
C10−N−C12	109.58(11)	109.88(8)	114.7(3)
C10−N−C13	109.22(10)	110.44(8)	113.5(3)
C12−N−C13	113.68(11)	109.00(9)	108.6(3)
El−C1−C2	105.86(11)	106.05(8)	106.8(3)
C1−C2−C3	103.38(12)	103.00(9)	112.1(4)
C2−C3−C8	110.20(13)	110.44(9)	116.7(4)
El−C8−C3	111.38(12)	111.16(9)	108.7(3)
El−C9−C10	113.75(12)	111.80(9)	113.6(3)
N−C10−C9	110.59(11)	111.06(8)	113.9(4)
El−C11−C12	113.38(11)	112.76(8)	111.8(3)
N−C12−C11	109.27(11)	112.03(9)	114.2(3)

The structural features of the 1,4′-silaspiro[indane-1,4′-piperidinium] skeleton of the silicon compound **2b**·HCl differ significantly from those of the spirocyclic skeletons of the carbon compounds **1a**·HCl and **2a**. The 4-silapiperidinium ring of **2b**·HCl is also characterized by a chair conformation, but the relative orientation of the carbon atoms C1 (equatorial), C8 (axial), and C13 (equatorial) differs significantly from that observed for **1a**·HCl and **2a**. Furthermore, the conformation of the silaindane skeleton of **2b**·HCl differs from the conformations of the indane systems of **1a**·HCl and **2a**. The mean deviation from the calculated best plane generated by the silicon atom and the carbon atoms C3 to C8 is again very small (0.02 Å); however, the carbon atoms C1 and C2 deviate much less from this plane (C1, −0.14 Å; C2, 0.09 Å), as in the case of **1a**·HCl and **2a**; that is, the five-membered ring built up by the silicon atom and the carbon atoms C1, C2, C3, and C8 is best described as an almost planar (or slightly twisted) conformation rather than an envelope conformation.

Comparison of the three experimentally established structures with the calculated conformations of the model species **5a**, **6a**, and **6b** revealed the following correlation: **1a**·HCl, **6a**α; **2a**, **5a**α; **2b**·HCl, **6b**γ (see Computational Studies).

NMR Studies. ^{1}H, ^{13}C, and ^{29}Si NMR studies of the silicon compounds **1b**·HCl−**4b**·HCl showed the existence of two conformers of the respective ammonium cations (molar ratio ca. 1:1) in solution (solvent $CDCl_3$). To get more structural information about these species and their corresponding carbon analogues, the carbon/silicon pair **2a**·HCl/**2b**·HCl was studied exemplarily by VT ^{1}H NMR experiments in the temperature range 295−393 K using [D_6]DMSO as the solvent. Below 373 K (363 K), two conformers of the ammonium cation of **2a**·HCl (molar ratio 1:14.3) (**2b**·HCl (molar ratio 1:1.2)) were observed. These conformations are configurationally stable on the NMR time scale under the experi-

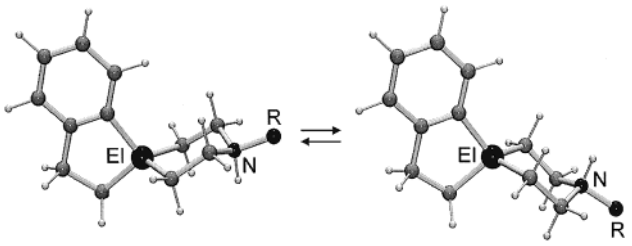

Figure 4. Interconversion of the two different chair conformations of the cations of **2a**·HCl (El = C) and **2b**·HCl (El = Si) in solution (R = *p*-CH_2−C_6H_4−OMe). To convert these conformations into each other, the following steps are necessary: (a) nitrogen deprotonation, (b) nitrogen inversion, (c) nitrogen reprotonation, and (d) inversion of the six-membered ring system (the sequence of the last two steps is interchangeable).

mental conditions used. Upon heating, broadening of the resonance signals and finally coalescence was observed (**2a**·HCl, T_C = 373 K; **2b**·HCl, T_C = 363 K), the temperature dependence of the ^{1}H NMR spectra being completely reversible on subsequent cooling. This dynamic behavior can be interpreted in terms of a conversion of the two conformers into each other, the activation free enthalpy for this process amounting to $\Delta G^{\ddagger}$ = 76.7(1.1) kJ mol^{-1} (**2a**·HCl) and $\Delta G^{\ddagger}$ = 77.1(1.1) kJ mol^{-1} (**2b**·HCl). It is likely to assume that the two conformers of the cations of **2a**·HCl and **2b**·HCl correspond to the calculated conformers **α** and ***γ*** of the model species **6a** and **6b** (**6aα** ⇌ **6a*γ***; **6bα** ⇌ **6b*γ***) (Figure 4; see also Computational Studies). The energy differences between these two conformers were deduced from their molar ratios (determined by integration of the respective resonance signals in the ^{1}H NMR spectra) and found to be very small (**2a**·HCl; $\Delta G°$ = 6.5 kJ mol^{-1}; **2b**·HCl, $\Delta G°$ = 0.4 kJ mol^{-1}). This is again in good accordance with the results obtained in the computational studies of the model species **6a** and **6b**.

Computational Studies. To get more information about the stereochemistry of the title compounds and their carbon analogues, the related model species **5a**, **5b**, **6a**, and **6b** were investigated by quantum-chemical methods. For this purpose, HF studies (geometry optimizations) of the respective **α**, ***β***, ***γ***, and ***δ*** conformers (Figure 5) were performed at the TZP[10] (triple-ζ plus polarization) level, using the *TURBOMOLE*[11] program system.[12] The local minima of the two different chair conformations of **5a** with the *N*-methyl group in the equatorial position, conformers **5aα** and **5a*γ***, differ only slightly in their energy (energy difference 0.9 kJ mol^{-1}). Carbon/silicon exchange leads to similar results, the energies of the local minima of the conformers **5bα** and **5b*γ*** differing by only 0.2 kJ mol^{-1}. Protonation of the nitrogen atoms of **5aα**, **5a*γ***, **5bα**, and **5b*γ*** leads to comparable energy differences (**6aα**/**6a*γ***, 0.1 kJ mol^{-1}; **6bα**/**6b*γ***, −0.5 kJ mol^{-1}). A much stronger effect is observed when changing the equatorial position of the *N*-methyl group into the axial site, the **α** and ***γ*** conformers being energetically significantly more stable than the corresponding ***β*** and ***δ*** conformers (**5aα**/**5a*β***, 14.5 kJ mol^{-1}; **5a*γ***/**5a*δ***, 14.4 kJ mol^{-1}; **5bα**/**5b*β***, 7.4 kJ mol^{-1}; **5b*γ***/**5b*δ***, 7.7 kJ mol^{-1}; **6aα**/**6a*β***, 10.0 kJ mol^{-1}; **6a*γ***/**6a*δ***, 10.0 kJ mol^{-1}; **6bα**/**6b*β***, 6.5 kJ mol^{-1}; **6b*γ***/**6b*δ***, 6.8 kJ mol^{-1}).

Table 3. Calculated Interatomic Distances (Å) and Angles (deg) for 5aα, 6aα, 6bα, and 6b*γ*

	5aα (El = C)	**6aα** (El = C)	**6bα** (El = Si)	**6b*γ*** (El = Si)
El−C1	1.556	1.556	1.897	1.890
El−C8	1.515	1.515	1.852	1.859
El−C9	1.541	1.542	1.911	1.911
El−C11	1.535	1.536	1.911	1.911
N−C10	1.450	1.502	1.511	1.511
N−C12	1.450	1.502	1.511	1.511
C1−C2	1.543	1.543	1.555	1.553
C2−C3	1.507	1.505	1.511	1.511
C3−C8	1.315	1.314	1.328	1.328
C9−C10	1.525	1.522	1.525	1.525
C11−C12	1.523	1.521	1.525	1.525
C1−El−C8	101.5	102.0	95.1	95.0
C1−El−C9	112.6	112.6	114.9	116.4
C1−El−C11	113.1	113.1	115.0	116.5
C8−El−C9	110.0	109.8	116.7	115.3
C8−El−C11	111.8	111.4	116.4	115.1
C9−El−C11	107.7	107.9	99.9	99.7
C10−N−C12	111.5	111.0	113.8	114.0
C10−N−C13	111.9	112.1	110.8	110.8
C12−N−C13	112.1	112.2	110.8	110.8
El−C1−C2	106.4	106.1	104.3	104.6
C1−C2−C3	102.9	103.0	111.0	111.0
C2−C3−C8	112.0	112.5	120.8	120.8
El−C8−C3	113.4	112.9	108.7	108.6
El−C9−C10	113.1	113.6	113.5	113.1
N−C10−C9	111.5	111.1	112.8	112.8
El−C11−C12	112.6	113.1	113.5	113.0
N−C12−C11	111.0	110.5	112.8	112.8

The interatomic distances and angles of the local minima **5aα**, **6aα**, and **6b*γ*** are listed in Table 3. These conformers correspond to those observed in the experimentally established structures of **2a**, **1a**·HCl, and **2b**·HCl (see Crystal Structure Analyses). As can be seen from the superpositions depicted in Figure 6, a good agreement between the calculated and experimentally established conformations of the respective spiro[indane-1,4′-piperidine] (**5aα**, **2a**), spiro[indane-1,4′-piperidinium] (**6aα**, **1a**·HCl), and 1,4′-silaspiro[indane-1,4′-piperidinium] (**6b*γ***, **2b**·HCl) skeletons was observed. As in the experimentally established structures, the six-membered rings of **5aα**, **6aα**, and **6b*γ*** adopt a chair conformation, whereas the five-membered rings adopt an envelope conformation (C3−C8−C−C1 dihedral angle: **5aα**, −12.1°; **6aα**, −11.9°) or an almost flat ring system in the case of **6b*γ*** with an C3−C8−Si−C1 dihedral angle of 1.3°.[13]

A comparison of the calculated interatomic distances and angles of the C/Si-analogous conformers **6aα** and **6bα** reveals the structural consequences of sila-substitution of the spiro[indane-1,4′-piperidinium] skeleton (Table 3). Due to the larger covalent radius of the silicon atom, significant deviations of all six C−Si−C angles from the ideal tetrahedral angle were observed for **6bα**.

(10) Schäfer, A.; Horn, H.; Ahlrichs, R. *J. Chem. Phys.* **1992**, *97*, 2571−2577.

(11) Program system *TURBOMOLE*: Ahlrichs, R.; Bär, M.; Häser, M.; Horn, H.; Kömel, C. *Chem. Phys. Lett.* **1989**, *162*, 165−169.

(12) Calculated energies (HF + single-point MP2 + *E*(vib0) energies (Hartree)): **5aα**, −444.7044685; **5a*β***, −444.6989606; **5a*γ***, −444.7041332; **5a*δ***, −444.6986531; **5bα**, −695.8453077; **5b*β***, −695.8424759; **5b*γ***, −695.8452185; **5b*δ***, −695.8422881; **6aα**, −445.0744994; **6a*β***, −445.0706983; **6a*γ***, −445.0744555; **6a*δ***, −445.0706597; **6bα**, −696.2179931; **6b*β***, −696.2155261; **6b*γ***, −696.2181892; **6b*δ***, −696.2155943.

(13) A conformer of **6b** with fixed C_s symmetry could not be found as a local minimum.

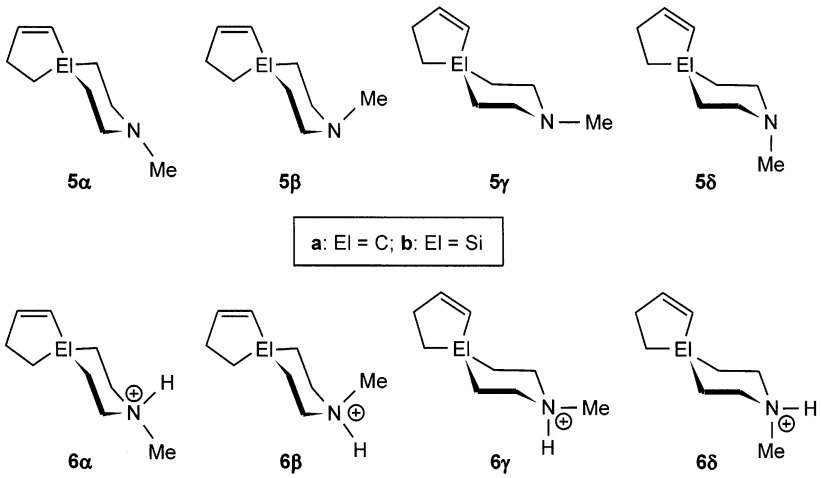

Figure 5. Structures of the local minima of the conformers **5aα**−**5aδ**, **5bα**−**5bδ**, **6aα**−**6aδ**, and **6bα**−**6bδ**.

Table 4. Affinities (IC_{50} Values in nM) of the C/Si Pairs 1a/1b−4a/4b for Various Central Nervous System Receptors[a]

receptor	1a	1b	2a	2b	3a	3b	4a	4b
σ	1.6 ± 0.4	27 ± 5.5	12.8 ± 3.6	23 ± 10.7	4.2 ± 1.8	8.3 ± 1.1	3.5 ± 1.0	3.0 ± 1.1
5-HT_{1A}	>10 000	>10 000	>10 000	>10 000	9600 ± 2700	3300 ± 440	>10 000	>10 000
5-HT_{2A}	6500 ± 300	3700 ± 400	>10 000	4200 ± 1400	3100 ± 1500	83 ± 20	>10 000	5500 ± 1300
α_1	>10 000	∼10 000	>10 000	∼10 000	7300 ± 2300	10 000	>10 000	10 000
α_2	>10 000	>10 000	∼10 000	>10 000	∼10 000	>10 000	>10 000	>10 000
ACh (M)	8500 ± 3500	∼10 000	>10 000	>10 000	>10 000	>10 000	>10 000	6500 ± 2400
D_2	2900 ± 910	860 ± 60	1600 ± 60	360 ± 27	8900 ± 710	4700 ± 850	2200 ± 600	350 ± 5

[a] The data given represent IC_{50} values in nM, means ± SEM of three independent determinations, except for **1b** (σ receptor) and **3a** (α_1 receptor), with only two IC_{50} values (for further details, see Experimental Section).

These differences are distinctly larger than those calculated for respective C−C−C angles at the spirocenter of the carbon analogue **6aα**. As shown by the superposition of the structures of the C/Si pair **6aα**/**6bα** in Figure 7, sila-substitution of the spiro[indane-1,4′-piperidinium] skeleton results in significant changes of the overall structure.

Pharmacological Studies. The C/Si pairs **1a**/**1b**−**4a**/**4b** were studied for their affinities (IC_{50} values) for various central nervous system receptors using radioligand binding assays with membrane preparations from the following sources: σ, guinea pig whole brain; 5-HT_{1A}, rat hippocampus; 5-HT_{2A}, human recombinant receptor stably expressed in a CHO-K1 cell line; α_1, rat cortex; α_2, rat cortex; ACh (M), rat cerebrum; D_2, human recombinant receptor stably expressed in A9L4 cells. The data obtained in these studies are summarized in Table 4.

As shown in Table 4, the IC_{50} values of the parent carbon compounds **1a**−**4a** for the σ receptor obtained in the present study are well in line with results described in the literature.[1] Interestingly, our values are somewhat higher than those reported in ref 1, whereas the rank order of affinity remains the same (1.6−3.5−4.2−12.8 nM (this study) versus 0.72−1.2−2.8−3.5 nM (ref 1) for **1a**−**4a**−**3a**−**2a**). These small differences can be explained by minor changes in methodology. Also, Chambers et al.[1] used guinea pig cerebellar membranes, whereas we used whole guinea pig brain. Good agreement of data was also found for the dopamine D_2 receptors (IC_{50} values in the 1−9 μM range), although receptors from different species (native rat striatum and human recombinant receptors) and different ligands were used. Thus, the high σ/D_2 selectivity could be confirmed in this study for compounds **1a**−**4a**. As to the other receptors listed in Table 4, even less than the D_2 affinity (≥10 μM) was found in most cases.

The σ affinities of the sila-analogues **2b**−**4b** were found to be similar to those of the parent carbon compounds **2a**−**4a**, whereas sila-substitution of **1a** (→ **1b**) resulted in a decrease of affinity of about 1 order of magnitude (Table 4, Figure 8). It remains to be seen whether this change can be explained, as soon as more is known about the three-dimensional structure of the σ receptor in its native membrane-incorporated configuration. Conversely, the known stereochemical sila-substitution effects might contribute to elucidate the biologically active site of the σ receptor.

On the other hand, a significant increase of affinity for the dopamine D_2 and the serotonin 2A (5-HT_{2A}) receptors was observed for the sila-analogues **1b**−**4b** (Table 4, Figures 9 and 10). This holds true for all four C/Si pairs studied and is especially pronounced for **4a**/**4b** (6-fold affinity increase for the D_2 receptor) and **3a**/**3b** (37-fold affinity increase for the 5-HT_{2A} receptor).

In contrast to the σ receptor, whose role is unclear, and with robust functional tests lacking, all the other receptors tested are G-protein coupled receptors with known signal transduction and readily available functional tests. The silicon compounds **3b** and **4b** are interesting in several aspects: the extent of their respective affinities (IC_{50} values: **3b**, ca. 80 nM for 5-HT_{2A}; **4b**, ca. 350 nM for D_2) makes them eligible for in vivo testing in models for antipsychotic activity since these two receptors are prime mechanistic targets in the development of antipsychotics. Furthermore, these compounds might be interesting in vitro tools to study signal transduction mechanisms.

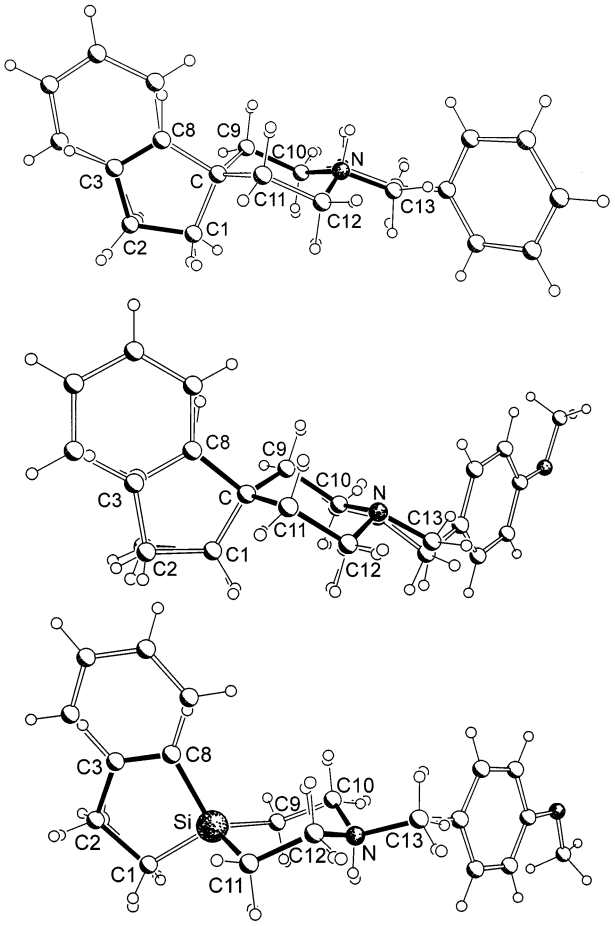

Figure 6. Superpositions of the calculated (filled bonds) and experimentally established structures (unfilled bonds) of **6aα** and the cation of **1a**·HCl (above), **5aα**, and **2a** (middle), as well as **6bγ** and the cation of **2b**·HCl (below).

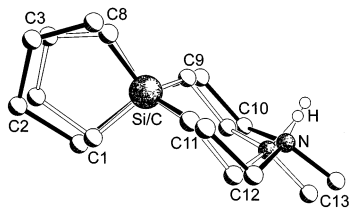

Figure 7. Superposition (atoms: Si/C, C1, C8, C9, and C11) of the calculated structures of the conformers **6aα** (unfilled bonds) and **6bα** (filled bonds). Hydrogen atoms (except for NH) are omitted for clarity.

In conclusion, the results obtained in this study again demonstrate the high potential of the sila-substitution concept in the development of new drugs with improved pharmacological properties. The different changes of receptor affinity for various receptor systems and thus the change of selectivity profiles (in this context, see also ref 5d and literature cited therein) is certainly one of the most promising aspects of the sila-substitution approach.

Experimental Section

Chemistry. General Procedures. All syntheses were carried out under dry nitrogen. The organic solvents used were dried and purified according to standard procedures and stored under dry nitrogen. Melting points were determined with a Büchi B-540 apparatus in open glass capillaries. The ^{1}H, ^{13}C, and ^{29}Si solution NMR spectra were recorded at 22 °C on a Bruker DRX-300 NMR spectrometer (^{1}H, 300.1 MHz; ^{13}C, 75.5 MHz; ^{29}Si, 59.6 MHz). $CDCl_3$ and [D_6]DMSO were used as solvents. Chemical shifts (ppm) were determined relative to internal $CHCl_3$ (^{1}H, δ 7.24), internal [D_5]DMSO (^{1}H, δ 2.49), internal $CDCl_3$ (^{13}C, δ 77.0), or external TMS (^{29}Si, δ 0). Assignment of the ^{1}H NMR data was supported by ^{1}H,^{1}H and ^{13}C,^{1}H correlation experiments, and assignment of the ^{13}C NMR data was supported by DEPT 135 and ^{13}C,^{1}H correlation experiments. Mass spectra (CI MS (positive), reactant gas methane) were recorded with a ThermoQuest Trio 1000 mass spectrometer. The selected *m*/*z* values given refer to the isotopes ^{1}H, ^{12}C, ^{14}N, ^{16}O, and ^{28}Si.

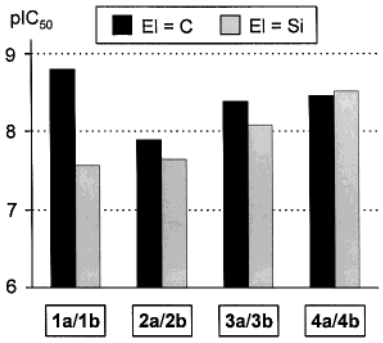

Figure 8. Affinities (pIC_{50} values) of the C/Si pairs **1a**/**1b**−**4a**/**4b** for the σ receptor.

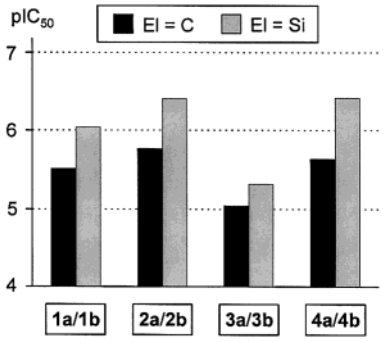

Figure 9. Affinities (pIC_{50} values) of the C/Si pairs **1a**/**1b**−**4a**/**4b** for the D_2 receptor.

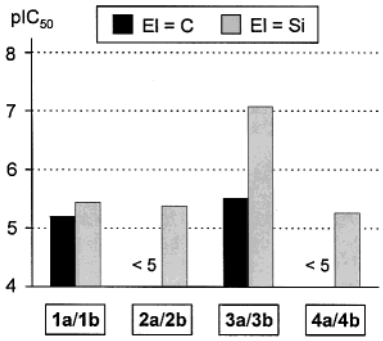

Figure 10. Affinities (pIC_{50} values) of the C/Si pairs **1a**/**1b**−**4a**/**4b** for the 2A (5-HT_{2A}) receptor.

Preparation of 1′-Benzylspiro[indane-1,4′-piperidinium] Chloride (1a·HCl). This compound was synthesized according to ref 1.

Preparation of 1′-Benzyl-1,4′-silaspiro[indane-1,4′-piperidinium] Chloride (1b·HCl). (a) A solution of **9** (2.00 g, 5.74 mmol), benzylamine (8.62 g, 80.4 mmol), and triethylamine (1.69 g, 16.7 mmol) in trichloromethane (30 mL) was heated under reflux for 1 day. After the mixture was stirred for a further 2 days at room temperature, water (25 mL) was added. The organic phase was separated and the aqueous layer

extracted with diethyl ether (3 × 50 mL), and the combined organic extracts were dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the oily residue distilled in a Kugelrohr apparatus (oven temperature 170 °C, 0.001 mbar) to give **1b** in 61% yield as a yellowish liquid (1.03 g, 3.51 mmol). (b) A 1 M ethereal HCl solution (1.6 mL, 1.60 mmol HCl) was added at 0 °C within 10 min to a solution of **1b** (466 mg, 1.59 mmol) in diethyl ether (20 mL) (slow formation of a precipitate), and the mixture was then kept undisturbed at 0 °C for 30 min and at room temperature for a further 1 h. The precipitate was isolated by centrifugation, washed with diethyl ether (3 × 10 mL), and recrystallized from acetone/diethyl ether (10:1 (v/v)). The product was finally dried in vacuo (0.001 mbar, 20 °C, 7 h) to give **1b**·HCl in 70% yield (related to **1b**) as a colorless crystalline solid (368 mg, 1.12 mmol); mp 204 °C. ^{1}H NMR ($CDCl_3$; data for two conformers): δ 0.63−1.33 (m, 4 H, SiC*H*HCH$_2$N, SiC*H*$_2$CH$_2$C), 1.74−2.25 (m, 2 H, SiCH*H*CH$_2$N), 2.67−3.35 (m, 4 H, SiCH$_2$C*H*HN, SiCH$_2$C*H*$_2$C), 3.53−3.94 (m, 2 H, SiCH$_2$CH*H*N), 4.12−4.53 (m, 2 H, NC*H*$_2$C), 6.89−7.91 (m, 9 H, CC$_6$*H*$_5$, SiC$_6$*H*$_4$C), 12.2 (br s, 1 H, N*H*). ^{13}C NMR ($CDCl_3$; data for two conformers): δ 7.5 and 8.0 (Si*C*H$_2$CH$_2$C), 9.50 and 9.54 (Si*C*H$_2$-CH$_2$N), 31.0 and 31.1 (SiCH$_2$*C*H$_2$C), 52.5 and 52.9 (SiCH$_2$*C*H$_2$N), 60.4 and 60.7 (N*C*H$_2$C), 125.6, 125.8, 126.0, and 126.2 (*C*-5 and *C*-6, silaindane), 128.5 (*C*-4, CC$_6$H$_5$), 129.2 (*C*-3/*C*-5, CC$_6$H$_5$), 130.4 and 130.5 (*C*-4, silaindane), 131.35 and 131.39 (*C*-2/*C*-6, CC$_6$H$_5$), 133.2 (*C*-1, CC$_6$H$_5$), 133.3 and 133.4 (*C*-7, silaindane), 135.3 and 135.4 (*C*-7a, silaindane), 153.7 and 153.9 (*C*-3a, silaindane). ^{29}Si NMR ($CDCl_3$; data for two conformers): δ 5.4 and 6.1. CI MS: *m*/*z* (%) 294 (100) (M(cation)); fragments. Anal. Calcd for $C_{19}H_{24}ClNSi$: C, 69.17; H, 7.33; N, 4.25. Found: C, 68.8; H, 7.2; N, 4.3.

Preparation of 1′-(4-Methoxybenzyl)spiro[indane-1,4′-piperidinium] Chloride (2a·HCl). This compound was synthesized according to ref 1.

Preparation of 1′-(4-Methoxybenzyl)-1,4′-silaspiro[indane-1,4′-piperidinium] Chloride (2b·HCl). (a) A solution of **9** (2.00 g, 5.74 mmol), (4-methoxybenzyl)amine (7.88 g, 57.4 mmol), and triethylamine (1.45 g, 14.3 mmol) in trichloromethane (30 mL) was heated under reflux for 1 day, and the mixture was then stirred for a further 2 days at room temperature. Workup analogously to the synthesis of **1b** and subsequent distillation in a Kugelrohr apparatus (oven temperature 225 °C, 0.001 mbar) gave **2b** in 61% yield as a yellowish liquid (1.13 g, 3.49 mmol). (b) A 1 M ethereal HCl solution (2.4 mL, 2.40 mmol HCl) was added at 0 °C within 10 min to a solution of **2b** (748 mg, 2.31 mmol) in diethyl ether (30 mL) (slow formation of a precipitate), and the mixture was then kept undisturbed at 0 °C for 15 min and at room temperature for a further 1 day. The precipitate was isolated by centrifugation, washed with diethyl ether (3 × 25 mL) and acetone (3 × 10 mL), and recrystallized from acetone. The product was finally dried in vacuo (0.001 mbar, 20 °C, 6 h) to give **2b**·HCl in 72% yield (related to **2b**) as a colorless crystalline solid (597 mg, 1.66 mmol); mp 234 °C. ^{1}H NMR ($CDCl_3$; data for two conformers): δ 0.97−1.20 (m, 4 H, SiC*H*HCH$_2$N, SiC*H*$_2$CH$_2$C), 1.82−2.17 (m, 2 H, SiCH*H*CH$_2$N), 2.88−3.25 (m, 4 H, SiCH$_2$C*H*HN, SiCH$_2$C*H*$_2$C), 3.67−3.85 (m, 2 H, SiCH$_2$CH*H*N), 3.79 and 3.80 (s, 3 H, OC*H*$_3$), 4.14−4.19 (m, 2 H, NC*H*$_2$C), 6.86−7.00 (m, 2 H, *H*-3/*H*-5, OC$_6$H$_4$C), 7.12−7.37 (m, 3 H, *H*-4, *H*-5, and *H*-6, silaindane), 7.42−7.50 and 7.71−7.81 (m, 1 H, *H*-7, silaindane), 7.51−7.64 (m, 2 H, *H*-2/*H*-6, OC$_6$H$_4$C), 12.0 (br s, 1 H, N*H*). ^{13}C NMR ($CDCl_3$; data for two conformers): δ 7.6 and 7.9 (Si*C*H$_2$CH$_2$C), 9.6 (Si*C*H$_2$-CH$_2$N), 31.0 and 31.2 (SiCH$_2$*C*H$_2$C), 52.2 and 52.5 (SiCH$_2$*C*H$_2$N), 55.31 and 55.32 (OC*H*$_3$), 60.1 and 60.3 (NCH$_2$C), 114.5 and 114.6 (*C*-3/*C*-5, OC$_6$H$_4$C), 120.32 and 120.33 (*C*-1, OC$_6$H$_4$C), 125.6, 126.0, 126.31, and 126.32 (*C*-5 and *C*-6, silaindane), 130.5 and 130.6 (*C*-4, silaindane), 132.8 (*C*-2/*C*-6, OC$_6$H$_4$C), 132.0 and 133.4 (*C*-7, silaindane), 135.4 (*C*-7a, silaindane), 153.5 and 154.0 (*C*-3a, silaindane), 160.7 and 160.8 (*C*-4, OC$_6$H$_4$C). ^{29}Si NMR ($CDCl_3$; data for two conformers): δ 5.2 and 6.2. CI MS: *m*/*z* (%) 324 (100) (M(cation)); fragments. Anal. Calcd for $C_{20}H_{26}ClNOSi$: C, 66.73; H, 7.28; N, 3.89. Found: C, 66.6; H, 7.0; N, 4.0.

Preparation of 1′-(2-Phenylethyl)spiro[indane-1,4′-piperidinium] Chloride (3a·HCl). This compound was synthesized according to ref 1.

Preparation of 1′-(2-Phenylethyl)-1,4′-silaspiro[indane-1,4′-piperidinium] Chloride (3b·HCl). (a) A solution of **9** (2.00 g, 5.74 mmol), (2-phenylethyl)amine (6.96 g, 57.4 mmol), and triethylamine (1.45 g, 14.3 mmol) in trichloromethane (30 mL) was heated under reflux for 1 day and the mixture then stirred for a further 2 days at room temperature. Workup analogously to the synthesis of **1b** and subsequent distillation in a Kugelrohr apparatus (oven temperature 210 °C, 0.001 mbar) gave **3b** in 46% yield as a yellowish liquid (816 mg, 2.65 mmol). (b) A 1 M ethereal HCl solution (2.2 mL, 2.20 mmol HCl) was added at 0 °C within 10 min to a solution of **3b** (667 mg, 2.17 mmol) in diethyl ether (30 mL) (slow formation of a precipitate) and the mixture then kept undisturbed at 0 °C for 15 min and at room temperature for a further 1 day. The precipitate was isolated by centrifugation, washed with diethyl ether (3 × 25 mL) and acetone (3 × 10 mL), and recrystallized from acetone/diethyl ether (20:1 (v/v)). The product was finally dried in vacuo (0.001 mbar, 20 °C, 6 h) to give **3b**·HCl in 56% yield (related to **3b**) as a colorless crystalline solid (420 mg, 1.22 mmol); mp 255 °C. ^{1}H NMR ($CDCl_3$; data for two conformers): δ 1.01−1.30 (m, 4 H, SiC*H*HCH$_2$N, SiC*H*$_2$CH$_2$C), 1.75−2.12 (m, 2 H, SiCH*H*CH$_2$N), 2.99−3.45 (m, 8 H, SiCH$_2$C*H*HN, SiCH$_2$C*H*$_2$C, NC*H*$_2$C*H*$_2$C), 3.72−3.94 (m, 2 H, SiCH$_2$CH*H*N), 7.14−7.41, 7.50−7.59, and 7.73−7.83 (m, 9 H, SiC$_6$*H*$_4$C, CC$_6$*H*$_5$), 12.6 (br s, 1 H, N*H*). ^{13}C NMR ($CDCl_3$; data for two conformers): δ 7.7 and 7.9 (Si*C*H$_2$CH$_2$C), 9.2 (Si*C*H$_2$-CH$_2$N), 30.43 and 30.46 (NCH$_2$*C*H$_2$C), 31.1 and 31.2 (SiCH$_2$-*C*H$_2$C), 52.9 and 53.2 (SiCH$_2$*C*H$_2$N), 57.3 and 57.5 (NCH$_2$-CH$_2$C), 125.8, 126.1, and 126.4 (*C*-5 and *C*-6, silaindane), 127.3 and 127.4 (*C*-4, CC$_6$H$_5$), 128.71 and 128.72 (*C*-2/*C*-6 or *C*-3/*C*-5, CC$_6$H$_5$), 129.0 and 129.3 (*C*-2/*C*-6 or *C*-3/*C*-5, CC$_6$H$_5$), 130.6 and 130.7 (*C*-4, silaindane), 132.0 and 133.3 (*C*-7, silaindane), 133.4 and 135.1 (*C*-7a, silaindane), 136.1 (*C*-1, CC$_6$H$_5$), 153.5 and 154.1 (*C*-3a, silaindane). ^{29}Si NMR ($CDCl_3$; data for two conformers): δ 5.7 and 6.2. CI MS: *m*/*z* (%) 308 (100) (M(cation)); fragments. Anal. Calcd for $C_{20}H_{26}ClNSi$: C, 69.84; H, 7.62; N, 4.07. Found: C, 69.6; H, 7.4; N, 4.1.

Preparation of 1′-(3-Methylbut-2-enyl)spiro[indane-1,4′-piperidinium] Chloride (4a·HCl). This compound was synthesized according to ref 1.

Preparation of 1′-(3-Methylbut-2-enyl)-1,4′-silaspiro-[indane-1,4′-piperidinium] Chloride (4b·HCl). (a) A solution of **9** (2.00 g, 5.74 mmol), (3-methylbut-2-enyl)amine (6.85 g, 80.4 mmol), and triethylamine (1.69 g, 16.7 mmol) in trichloromethane (30 mL) was heated under reflux for 1 day and the mixture then stirred for a further 2 days at room temperature. Workup analogously to the synthesis of **1b** and subsequent distillation in a Kugelrohr apparatus (oven temperature 180 °C, 0.001 mbar) gave **4b** in 46% yield as a yellowish liquid (718 mg, 2.64 mmol). (b) A 1 M ethereal HCl solution (1.1 mL, 1.10 mmol HCl) was added at 0 °C within 10 min to a solution of **4b** (292 mg, 1.08 mmol) in diethyl ether (20 mL) (slow formation of a precipitate), and the mixture was then kept undisturbed at 0 °C for 30 min and at room temperature for a further 1 h. The precipitate was isolated by centrifugation, washed with diethyl ether (3 × 10 mL), and recrystallized from acetone/diethyl ether (10:1 (v/v)). The product was finally dried in vacuo (0.001 mbar, 20 °C, 7 h) to give **4b**·HCl in 63% yield (related to **4b**) as a colorless crystalline solid (210 mg, 682 μmol); mp 211−212 °C. ^{1}H NMR ($CDCl_3$; data for two conformers): δ 0.97−1.25 (m, 4 H, SiC*H*HCH$_2$N, SiC*H*$_2$CH$_2$C), 1.75−2.30 (m, 2 H, SiCH*H*CH$_2$N), 1.70, 1.73, 1.80, and 1.83 (s, 6 H, CC*H*$_3$), 2.87−3.33 (m, 4 H, SiCH$_2$C*H*HN, SiCH$_2$C*H*$_2$C), 3.48−3.88 (m, 4 H, SiCH$_2$CH*H*N,

NCH_2CH), 5.46−5.65 (m, 1 H, NCH_2CH), 7.12−7.38 (m, 3 H, *H*-4, *H*-5, and *H*-6, silaindane), 7.51−7.64 and 7.70−7.81 (m, 1 H, *H*-7, silaindane), 12.0 (br s, 1 H, N*H*). ^{13}C NMR ($CDCl_3$; data for two conformers): δ 7.6 and 8.0 ($SiCH_2CH_2C$), 9.70 and 9.71 ($SiCH_2CH_2N$), 18.4 18.5, and 26.0 (CCH_3), 31.0 and 31.2 ($SiCH_2CH_2C$), 52.1 and 52.5 ($SiCH_2CH_2N$), 54.7 and 55.0 (NCH_2CH), 112.5 and 112.6 (NCH_2CH), 125.6, 126.0, 126.26, and 126.32 (*C*-5 and *C*-6, silaindane), 130.5 and 130.6 (*C*-4, silaindane), 132.0 and 133.4 (*C*-7, silaindane), 135.5 (*C*-7a, silaindane), 143.8 and 143.9 (CCH_3), 153.5 and 153.9 (*C*-3a, silaindane). ^{29}Si NMR ($CDCl_3$; data for two conformers): δ 5.9 and 6.7. CI MS: *m*/*z* (%) 272 (100) (M(cation)); fragments. Anal. Calcd for $C_{17}H_{26}ClNSi$: C, 66.31; H, 8.51; N, 4.55. Found: C, 66.1; H, 8.4; N, 4.9.

Preparation of Dichlorodivinylsilane (7). This compound was synthesized according to ref 14.

Preparation of Bis(2-bromoethyl)dichlorosilane (8). A gas stream of dry hydrogen bromide was passed for 5 h at room temperature through a stirred solution of **7** (40.0 g, 261 mmol) in *n*-pentane (200 mL) in the presence of dibenzoyl peroxide (500 mg, 2.06 mmol), and the resulting mixture was then stirred for a further 16 h at room temperature (course of the reaction monitored by GC). The solvent was removed under reduced pressure and the residue distilled in vacuo to give **8** in 82% yield as a colorless liquid (67.5 g, 214 mmol); bp 74 °C/0.001 mbar. ^{1}H NMR ($CDCl_3$): δ 1.89−2.00 (m, 4 H, $SiCH_2C$), 3.48−3.64 (m, 4 H, $SiCH_2CH_2Br$). ^{13}C NMR ($CDCl_3$): δ 25.5 ($SiCH_2CH_2Br$), 26.2 ($SiCH_2C$). ^{29}Si NMR ($CDCl_3$): δ 25.2. Anal. Calcd for $C_4H_8Br_2Cl_2Si$: C, 15.26; H, 2.56. Found: C, 15.4; H, 2.6.

Preparation of 1,1-Bis(2-bromoethyl)-1-silaindane (9). 1-Bromomagnesio-2-(2-bromomagnesioethyl)benzene was prepared from magnesium turnings (2.57 g, 106 mmol) and 1-bromo-2-(2-bromoethyl)benzene (5.42 g, 20.5 mmol) in tetrahydrofuran (65 mL), and the Grignard reagent was then added dropwise over a period of 30 min at room temperature to a stirred solution of **8** (5.00 g, 15.9 mmol) in tetrahydrofuran (45 mL). The mixture was heated under reflux for 1 h and then allowed to cool to room temperature, followed by addition of water (50 mL) and diethyl ether (100 mL). The organic phase was separated and the aqueous layer extracted with diethyl ether (3 × 100 mL), and the combined organic extracts were dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue purified by column (diameter 3 cm) chromatography on silica gel (0.015−0.040 mm, Merck 15111; 200 g) using petroleum ether (40−60 °C) as the eluent to give **9** in 64% yield as a yellowish liquid (3.54 g, 10.2 mmol). ^{1}H NMR ($CDCl_3$): δ 1.01−1.18 (m, 2 H, $SiCH_2CH_2C$), 1.60−1.68 (m, 4 H, $SiCH_2CH_2Br$), 3.02−3.21 (m, 2 H, $SiCH_2CH_2C$), 3.39−3.50 (m, 4 H, $SiCH_2CH_2Br$), 6.91−7.62 (m, 4 H, SiC_6H_4C). ^{13}C NMR ($CDCl_3$): δ 8.2 ($SiCH_2CH_2C$), 20.6 ($SiCH_2CH_2Br$), 30.1 ($SiCH_2CH_2Br$), 31.8 ($SiCH_2CH_2C$), 126.05 (*C*-5 or *C*-6, silaindane), 126.12 (*C*-5 or *C*-6, silaindane), 130.3 (*C*-4, silaindane), 132.6 (*C*-7, silaindane), 133.8 (*C*-7a, silaindane), 153.8 (*C*-3a, silaindane). ^{29}Si NMR ($CDCl_3$): δ 15.5. Anal. Calcd for $C_{12}H_{16}Br_2Si$: C, 41.40; H, 4.63. Found: C, 41.6; H, 4.6.

Crystal Structure Analyses. Suitable single crystals of **1a**·HCl, **2a**, and **2b**·HCl were obtained by crystallization from trichloromethane (**1a**·HCl), diethyl ether (**2a**), or water (**2b**·HCl) by slow evaporation of the solvent at room temperature. The crystals were mounted in inert oil (perfluoroalkyl ether, ABCR) on a glass fiber and then transferred to the cold nitrogen gas stream of the diffractometer (Stoe IPDS; graphite-monochromated Mo Kα radiation (λ = 0.71073 Å)). The structures were solved by direct methods.[15] All non-hydrogen atoms were refined anisotropically.[16] A riding model was employed in the refinement of the CH hydrogen atoms, whereas the NH hydrogen atoms were localized in difference Fourier syntheses and refined freely.

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-201009 (**1a**·HCl), CCDC-201010 (**2a**), and CCDC-201011 (**2b**·HCl). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44)1223/336033; e-mail: deposit@ccdc.cam.ac.uk).

VT ^{1}H NMR Studies. VT ^{1}H NMR experiments with **2a**·HCl and **2b**·HCl were carried out analogously to the standard ^{1}H NMR measurements using a Bruker DRX-300 NMR spectrometer. [D_6]DMSO served as the solvent. The thermocouple used with the probe was calibrated for high temperatures according to ref 17 using a 80% solution of ethane-1,2-diol in [D_6]DMSO. Spectra were recorded in the temperature range 295−393 K. The time required for temperature equilibration was 15 min. From the spectra the coalescence temperature T_C and the exchange rate k_C at the coalescence point were extracted, and the value for the activation free enthalpy $\Delta G^{\ddagger}$ for the exchange process was calculated by using the Eyring equation:[18]

$$k_C = \pi(\nu_A - \nu_B)/\sqrt{2}$$

$$\Delta G^{\ddagger} = 19.14 T_C[10.32 + \log(T_C/k_C)][\mathrm{J\ mol^{-1}}]$$

A 2D ^{1}H,^{1}H EXSY NMR experiment was carried out to prove the existence of two conformers of the cation of **2a**·HCl. The site exchange for the $NCH_2C_6H_4OMe$ protons was accomplished by this study at room temperature in [D_6]DMSO, showing strong cross-peaks between the respective signals of the two conformers. The mixing time was in the order of the spin−lattice relaxation time T_1, calculated by a standard 1D T_1-inversion recovery experiment.

Computational Studies. HF geometry optimizations at the TZP[10] level (triple-ζ plus polarization) for the conformers **5a**α−**5a**δ, **5b**α−**5b**δ, **6a**α−**6a**δ, and **6b**α−**6b**δ were performed using the *TURBOMOLE* program system.[11] All critical points of the respective potential energy surface were characterized as local minima by calculation of the vibrational frequencies. The calculated energies[12] of **5a**α−**5a**δ, **5b**α−**5b**δ, **6a**α−**6a**δ, and **6b**α−**6b**δ include the single-point MP2 energy (TZP basis set) and the zero-point vibrational energy.

Pharmacological Studies. General Procedures. The test compounds **1a**/**1b**−**4a**/**4b** (used as hydrochlorides) were dissolved in water and the resulting solutions immediately used for testing. IC_{50} values given are the means ± SEM of three independent experiments and three or four concentrations of the drugs run in triplicate, except for compounds **1b** (σ receptor) and **3a** (α_1 receptor), where the means ± SEM of two IC_{50} values are given.

[^{3}H]Di(2-tolyl)guanidine (DTG) Binding (σ Receptor). The assay was adapted from refs 19 and 20. Guinea pig brain was homogenized (glass Teflon homogenizer, 10 strokes, 800 rpm) in 50 mM Tris-HCl buffer (20 mL), pH 7.7. The homogenate was centrifuged at 20 000 rpm in a Sorvall SS-34 rotor for 15 min at 2 °C and the supernatant decanted. The pellet was resuspended in Tris-HCl buffer (20 mL), homogenized, and

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centrifuged again (see above). This step was repeated three times. The pellet was resuspended in Tris-HCl buffer, giving a concentration of 10 mg of orginal tissue/mL and then frozen in aliquots at −28 °C. For use in the assay, the suspension was thawed in a water bath at room temperature and washed twice in 50 mM Tris-HCl buffer with centrifugation at 22000*g* for 10 min. The binding assay was performed in a total volume of 500 μL containing [^{3}H]DTG (0.5 nM) and 4 mg of orginal tissue/mL. Incubations were carried out at 25 °C for 40 min and terminated by rapid filtration (glass fiber filter). Nonspecific binding was determined in the presence of 0.1 μM haloperidol. [^{3}H]DTG, specific radioactivity 1.1 TBq mmol^{-1}, was from NEN.

[^{3}H]8-OH-DPAT Binding (5-HT$_{1A}$ Receptor). The method was adapted from ref 21. Rat hippocampus membranes (0.2 mg protein/tube) were incubated with 0.5 nM [^{3}H]8-OH-DPAT in a total volume of 500 μL at 25 °C for 30 min. Nonspecific binding was determined in the presence of 1 μM serotonin. [^{3}H]8-OH-DPAT, specific radioactivity 5.0 TBq mmol^{-1}, was from NEN.

[^{3}H]Ketanserin Binding (5-HT$_{2A}$ Receptor). The assay was performed according to ref 22. For the human recombinant 5-HT$_{2A}$ receptor, a stable CHO-K1 cell line expressing this receptor (Euroscreen ES-313-M) was utilized, using about 15 μg of membrane protein per assay. The assay contained (final volume 1 mL): 0.5 nM [^{3}H]ketanserin, 50 mM Tris-HCl buffer, pH 7.4, and 10 μM methysergide for nonspecific binding. Incubations were carried out at 37 °C for 15 min. [^{3}H]-Ketanserin, specific radioactivity 2.3 TBq mmol^{-1}, was from NEN.

[^{3}H]Prazosin Binding (α_1 Receptor). The assay was performed as described in ref 22, using rat cortical membranes (0.7 mg protein/mL) and 0.4 nM [^{3}H]prazosin in a total volume of 500 μL. The incubation was carried out at 25 °C for 1 h. Nonspecific binding was determined with 1 μM phentolamine. [^{3}H]Prazosin, specific radioactivity 0.7 TBq mmol^{-1}, was from NEN.

[^{3}H]Idazoxan Binding (α_2 Receptor). The assay was performed as described for the [^{3}H]prazosin inhibition assay with the modification that 1 mg protein/mL of rat cortical membranes was incubated with 0.4 nM [^{3}H]idazoxan. [^{3}H]-Idazoxan, specific radioactivity 2.2 TBq mmol^{-1}, was from Amersham.

[^{3}H]Quinuclidinyl Benzilate (QNB) Binding (Muscarinic Receptors). The assay was performed according to ref 23. Rat cerebrum was homogenized in 10 volumes of 0.32 M sucrose and centrifuged at 1000*g* for 10 min at 2 °C, and 100 μL of supernatant was incubated with 0.4 nM [^{3}H]QNB in a total volume of 500 μL (50 mM phosphate buffer, pH 7.4) at 25 °C for 1 h. Nonspecific binding was determined with 1 μM QNB. [^{3}H]QNB, specific radioactivity 1.5 TBq mmol^{-1}, was from NEN.

[^{3}H]Spiperone Binding (D_2 Receptor). The assay was performed as described in ref 22 for D_2 in rat striatal membranes with the following modification: human D_2 receptors expressed in A9L4 cells (Biotrend) were used, and the inhibition assay was performed in a total volume of 1 mL containing 0.15 nM [^{3}H]spiperone and membrane suspension containing 40−60 μg of protein. [^{3}H]Spiperone, specific radioactivity 3.7 TBq mmol^{-1}, was from Amersham.

Acknowledgment. We thank the Fonds der Chemischen Industrie for financial support.

Supporting Information Available: Tables of atomic coordinates and equivalent isotropic displacement parameters, anisotropic displacement parameters, experimental details of the X-ray diffraction studies, and bond lengths and angles for **1a**·HCl, **2a**, and **2b**·HCl. This material is available free of charge via the Internet at http://pubs.acs.org.

OM020354U

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