Sila-haloperidol: A Silicon Analogue of the Dopamine (D_2) Receptor Antagonist Haloperidol§

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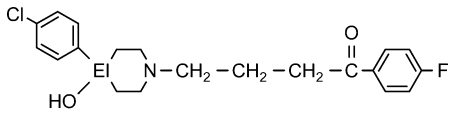
Haloperidol (**1a**), a dopamine (D_2) receptor antagonist, is in clinical use as an antipsychotic agent. Carbon/silicon exchange (sila-substitution) at the 4-position of the piperidine ring of **1a** ($R_3COH \rightarrow R_3SiOH$) leads to sila-haloperidol (**1b**). Sila-haloperidol was synthesized in a multistep synthesis, starting from tetramethoxysilane, and was isolated as the hydrochloride **1b**·HCl. ESI-MS studies of aqueous solutions of the silanol **1b** and the corresponding disiloxane **10** at different pH values revealed a remarkable stability of **1b**. The C/Si analogues **1a**·HCl and **1b**·HCl were structurally characterized by single-crystal X-ray diffraction and solution ([D_6]DMSO) NMR spectroscopy. Analogous chair conformations of the piperidinium (**1a**·HCl) and 4-silapiperidinium (**1b**·HCl) skeleton were observed in the crystal, and two analogous chair conformations of the cations were detected in solution, the molar ratios of these two conformers differing substantially (**1a**·HCl, 13:1; **1b**·HCl, 2:1). In radioligand binding studies, the C/Si analogues **1a** and **1b** displayed similar potencies at recombinant human dopamine hD_1, hD_4, and hD_5 receptors, whereas the silicon compound **1b** was 4.7-fold more potent at hD_2 receptors than its carbon analogue **1a**; i.e., sila-substitution of haloperidol has changed the receptor selectivity profile.

Introduction

Schizophrenia is a neuropsychiatric disorder which affects approximately 1% of the world population.[1,2] Although the exact pathogenesis of the disease is not known, a dopaminergic hyper- or dysfunction in the brain ("dopamine hypothesis") is generally accepted as the main pathway, leading to symptoms such as hallucinations, delusions, and disorganized speech ("positive" symptoms) or affective flattening, anhedonia, and avolition ("negative" symptoms).[1−3] Treatment of schizophrenia today involves a variety of drugs, which are classified as "typical" and "atypical" antipsychotics, depending on the neuroreceptor subtype selectivity and the extent of extrapyramidal side effects they cause.

The antipsychotic haloperidol (**1a**) was developed in the late 1950s and soon introduced into clinical therapy.[4,5] Its antipsychotic potential is based on the potent blockade of dopamine (D_2) receptors in the brain. The initiation of adverse, mainly extrapyramidal side effects defines it as a "typical" antipsychotic. Even though numerous newer "atypical" drugs have been developed, haloperidol has remained a first-line candidate for the treatment of schizophrenia, owing to its efficacy in countering especially the "positive" symptoms of the disease, and has been increasingly used as a benchmark by which other antipsychotics are measured.



El = C: Haloperidol (**1a**)
El = Si: Sila-haloperidol (**1b**)

In context with our research program dealing with the development of silicon-based drugs,[6,7] we sought to examine the biological effects of sila-substitution (C/Si exchange) of the quaternary R_3COH carbon atom of the 4-hydroxy-4-(4-chlorophenyl)piperidin-1-yl group of haloperidol. We report here on the synthesis of sila-haloperidol hydrochloride (**1b**·HCl), the crystal structure analyses and solution ([D_6]DMSO) NMR studies of **1a**·HCl and **1b**·HCl, and the pharmacological characterization of the C/Si analogues **1a** and **1b**. These investigations were complemented by ESI-MS experiments of aqueous solutions of sila-haloperidol at different pH values, to study whether and to what extent this silanol undergoes a condensation reaction (disiloxane

§ Dedicated to Professor Johann Weis on the occasion of his 60th birthday.

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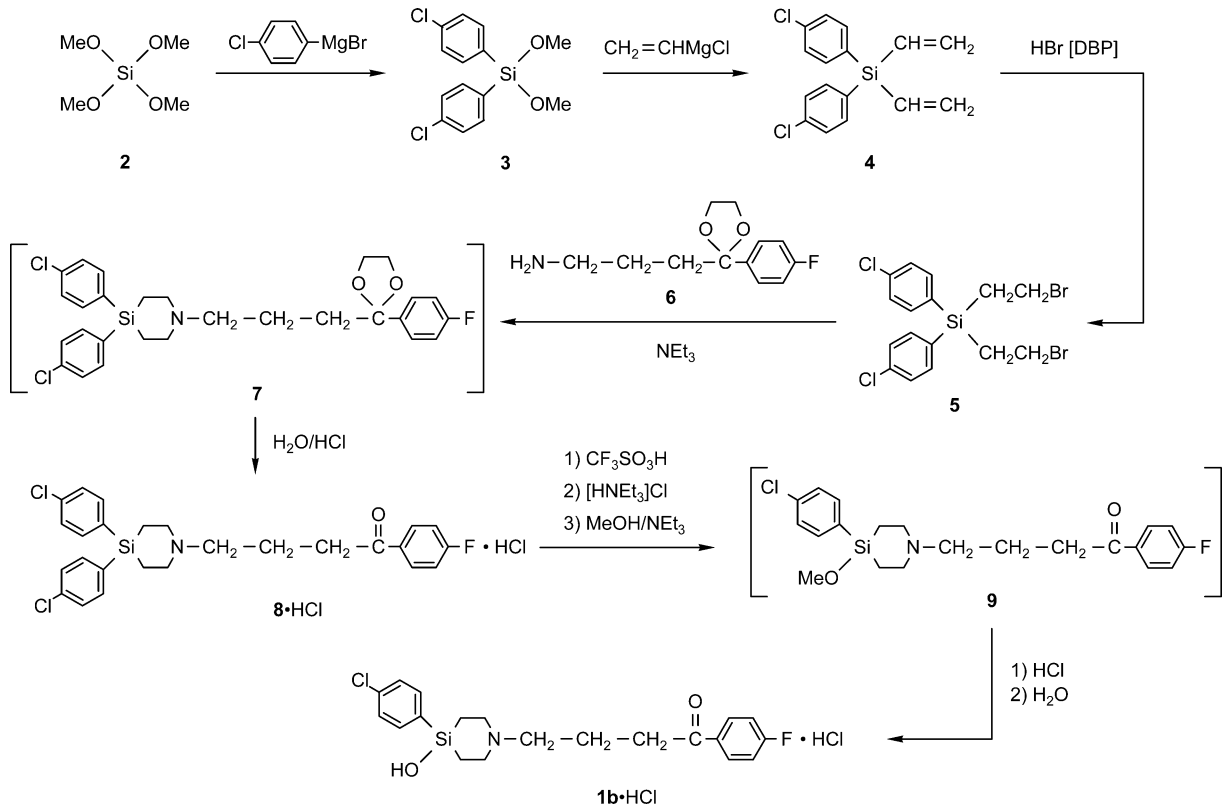
Scheme 1



formation). Preliminary results of the investigations presented here have been reported elsewhere.[8]

Results and Discussion

Syntheses. Sila-haloperidol (**1b**) was synthesized in a multistep synthesis, starting from tetramethoxysilane (**2**), and was isolated as the hydrochloride **1b**·HCl (Scheme 1). Thus, treatment of **2** with (4-chlorophenyl)-magnesium bromide gave bis(4-chlorophenyl)dimethoxysilane (**3**). Reaction of **3** with vinylmagnesium chloride yielded bis(4-chlorophenyl)divinylsilane (**4**), which upon reaction with hydrogen bromide, in the presence of dibenzoyl peroxide, afforded bis(2-bromoethyl)bis(4-chlorophenyl)silane (**5**). Reaction of **5** with 3-[2-(4-fluorophenyl)-1,3-dioxolan-2-yl]propylamine[9] (**6**) gave the cyclization product 4,4-bis(4-chlorophenyl)-1-{3-[2-(4-fluorophenyl)-1,3-dioxolan-2-yl]propyl}-4-silapiperidine (**7**; isolated as a crude product, not purified), which upon hydrolysis with hydrochloric acid yielded 4,4-bis-(4-chlorophenyl)-1-[4-oxo-4-(4-fluorophenyl)butyl]-4-silapiperidine (**8**; isolated as the hydrochloride **8**·HCl). Treatment of **8**·HCl with trifluoromethanesulfonic acid, followed by sequential treatment with triethylammonium chloride and methanol/triethylamine, gave 4-(4-chlorophenyl)-4-methoxy-1-[4-oxo-4-(4-fluorophenyl)butyl]-4-silapiperidine (**9**; isolated as a crude product, not purified). Transformation of **9** into the hydrochloride **9**·HCl and its subsequent hydrolysis finally afforded 4-(4-chlorophenyl)-4-hydroxy-1-[4-oxo-4-(4-fluorophenyl)butyl]-4-silapiperidinium chloride (sila-haloperidol hydrochloride, **1b**·HCl).

Treatment of **8**·HCl with trifluoromethanesulfonic acid, followed by workup with an aqueous sodium hydroxide solution, yielded the corresponding disiloxane **10** as the main product, which was isolated as the bis[(2*E*)-3-carboxyacrylate] **10**·2HOOCCH=CHCOOH (Scheme 2).

Compounds **3** and **4** were isolated as colorless liquids, whereas compounds **1b**·HCl, **5**, **8**·HCl, and **10**·2HOOC-CH=CHCOOH were obtained as colorless solids. The identities of all compounds were established by elemental analyses (C, H, N) and solution NMR studies (^{1}H, ^{13}C, ^{19}F, ^{29}Si). In addition, the crystal structures of **1b**·HCl and **8**·HCl were determined.

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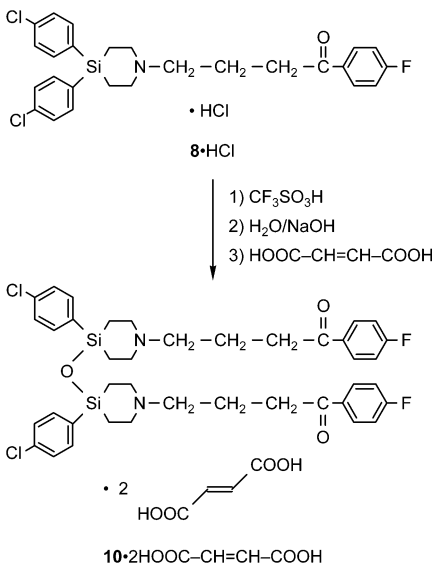
Table 1. Crystal Data and Experimental Parameters for the Crystal Structure Analyses of 1a·HCl, 1b·HCl, and 8·HCl

	1a·HCl	**1b**·HCl	**8**·HCl
empirical formula	$C_{21}H_{24}Cl_2FNO_2$	$C_{20}H_{24}Cl_2FNO_2Si$	$C_{26}H_{27}Cl_3FNOSi$
formula mass, g mol^{-1}	412.31	428.39	522.93
collection T, K	173(2)	173(2)	173(2)
λ(Mo Kα), Å	0.710 73	0.710 73	0.710 73
cryst syst	monoclinic	triclinic	monoclinic
space group (No.)	$P2_1/c$ (14)	$P\bar{1}$ (2)	$P2_1/c$ (14)
a, Å	16.0457(18)	7.0438(13)	11.2032(12)
b, Å	9.8850(6)	8.3250(14)	9.5983(8)
c, Å	13.4783(16)	18.390(3)	23.208(3)
α, deg	90	91.54(2)	90
β, deg	112.015(13)	91.39(2)	90.999(14)
γ, deg	90	90.50(2)	90
V, Å^3	1981.9(3)	1077.6(3)	2495.2(5)
Z	4	2	4
D(calcd), g cm^{-3}	1.382	1.320	1.392
μ, mm^{-1}	0.353	0.380	0.443
F(000)	864	448	1088
cryst dimens, mm	0.5 × 0.5 × 0.3	0.3 × 0.2 × 0.2	0.5 × 0.4 × 0.4
2θ range, deg	4.94−54.00	4.90−52.84	3.64−49.82
index ranges	$-20 \le h \le 17$	$-8 \le h \le 8$	$-13 \le h \le 13$
	$-12 \le k \le 10$	$-10 \le k \le 10$	$-11 \le k \le 11$
	$-17 \le l \le 17$	$-22 \le l \le 22$	$-27 \le l \le 23$
no. of collected rflns	13 299	12 231	12 724
no. of indep rflns	4281	4125	4321
R_{int}	0.0303	0.0327	0.0263
no. of rflns used	4281	4125	4321
no. of params	250	250	301
S[a]	1.056	0.977	1.042
weight params a/b[b]	0.0513/0.7378	0.0614/0.0000	0.0408/0.7956
$R1$[c] ($I > 2\sigma(I)$)	0.0356	0.0364	0.0275
$wR2$[d] (all data)	0.0975	0.0956	0.0744
max/min residual electron density, e Å^{-3}	+0.542/−0.549	+0.307/−0.299	+0.260/−0.190

[a] $S = \{\sum[w(F_o^2 - F_c^2)^2]/(n - p)\}^{0.5}$; 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] $R1 = \sum||F_o| - |F_c||/\sum|F_o|$. [d] $wR2 = \{\sum[w(F_o^2 - F_c^2)^2]/\sum[w(F_o^2)^2]\}^{0.5}$.

Scheme 2



Crystal Structure Analyses. Compounds **1a**·HCl, **1b**·HCl, and **8**·HCl were structurally characterized by single-crystal X-ray diffraction.[10] The crystal data and the experimental parameters used for the crystal structure analyses are summarized in Table 1. Selected bond lengths and angles are given in Table 2. The structures of the cations of **1a**·HCl, **1b**·HCl, and **8**·HCl are depicted in Figures 1−3.

(10) Crystal structure of the corresponding amine **1a**: Reed, L. L.; Schaefer, J. P. *Acta Crystallogr., Sect. B* **1973**, *29*, 1886−1890.

As can be seen from Figures 1−3, the piperidinium ring of **1a**·HCl and the 4-silapiperidinium ring of **1b**·HCl adopt a chair conformation, with the exocyclic N-organyl group in an equatorial (**1a**·HCl, **1b**·HCl) or axial (**8**·HCl) position. The OH groups of the C/Si analogues **1a**·HCl and **1b**·HCl occupy axial positions. The bond lengths and angles of all three compounds are in the expected range and do not need further discussion.

Superposition of the structures of the cations of the C/Si analogues **1a**·HCl and **1b**·HCl (Figure 4) reveals significant differences. Due to the longer covalent radius of the silicon atom, the 4-silapiperidinium skeleton of **1b**·HCl is more "flattened" than the piperidinium skeleton of **1a**·HCl. As a consequence, the C/Si analogues differ in their relative orientation of the N-organyl side chain toward the hydroxy and 4-chlorophenyl groups.

NMR Studies. The ^{1}H, ^{13}C, and ^{29}Si NMR spectra of **1b**·HCl revealed the existence of two conformers (molar ratio ca. 2:1) of the cation in solution (solvent [D$_6$]-DMSO). This ratio differs significantly from that found for the carbon analogue **1a**·HCl (ca. 13:1) (Figure 5), indicating considerable differences in the energies of the respective two conformers of the piperidinium and 4-silapiperidinium skeletons. The existence of these conformers was confirmed by 2D ^{1}H,^{1}H EXSY NMR experiments (for details, see the Experimental Section). In the case of the silicon compound **1b**·HCl, the structures of the two conformers (**1b**α and **1b**β) could be revealed with the help of ^{13}C NMR spectroscopy and ^{1}H,^{1}H COSY and ^{1}H,^{1}H NOESY experiments (Figure 6).

Table 2. Selected Bond Lengths (Å) and Angles (deg) for the Piperidinium Skeleton of 1a·HCl and the 4-Silapiperidinium Skeletons of 1b·HCl and 8·HCl

1a·HCl		**1b**·HCl		**8**·HCl	
C−O1	1.4317(16)	Si−O1	1.6205(13)	Si−C1	1.8817(15)
C−C7	1.5231(19)	Si−C7	1.851(2)	Si−C7	1.8694(15)
C−C13	1.5322(19)	Si−C13	1.859(2)	Si−C13	1.8694(16)
C−C16	1.5295(19)	Si−C16	1.8671(18)	Si−C16	1.8736(16)
N−C14	1.4983(18)	N−C14	1.501(2)	N−C14	1.504(2)
N−C15	1.4996(18)	N−C15	1.502(2)	N−C15	1.507(2)
N−C17	1.4991(17)	N−C17	1.498(2)	N−C17	1.4996(19)
C13−C14	1.5207(19)	C13−C14	1.516(2)	C13−C14	1.528(2)
C15−C16	1.5146(19)	C15−C16	1.517(2)	C15−C16	1.530(2)
O1−C−C7	109.58(11)	O1−Si−C7	107.34(8)	C1−Si−C7	112.54(7)
O1−C−C13	110.70(11)	O1−Si−C13	113.82(9)	C1−Si−C13	108.36(7)
O1−C−C16	105.37(11)	O1−Si−C16	112.86(8)	C1−Si−C16	107.96(7)
C7−C−C13	110.81(11)	C7−Si−C13	111.02(9)	C7−Si−C13	111.20(7)
C7−C−C16	113.30(11)	C7−Si−C16	111.20(9)	C7−Si−C16	113.23(7)
C13−C−C16	106.94(11)	C13−Si−C16	100.61(8)	C13−Si−C16	103.02(7)
C14−N−C15	111.89(11)	C14−N−C15	113.28(12)	C14−N−C15	113.38(12)
C14−N−C17	112.61(11)	C14−N−C17	110.42(13)	C14−N−C17	114.22(12)
C15−N−C17	109.51(11)	C15−N−C17	109.89(12)	C15−N−C17	112.02(12)
C−C13−C14	111.28(11)	Si−C13−C14	113.53(12)	Si−C13−C14	110.29(11)
C−C16−C15	110.85(11)	Si−C16−C15	112.74(12)	Si−C16−C15	110.96(10)
N−C14−C13	111.32(11)	N−C14−C13	113.23(13)	N−C14−C13	113.36(12)
N−C15−C16	111.22(11)	N−C15−C16	113.03(13)	N−C15−C16	114.25(12)

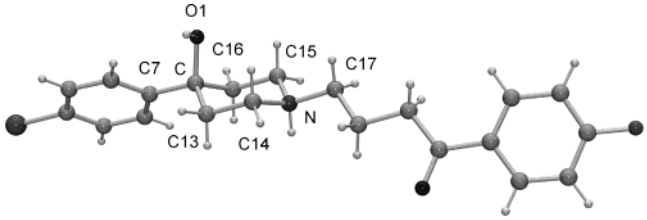


Figure 1. Structure of the cation in the crystal of **1a**·HCl.

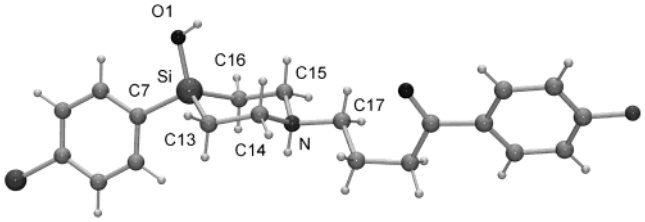


Figure 2. Structure of the cation in the crystal of **1b**·HCl.

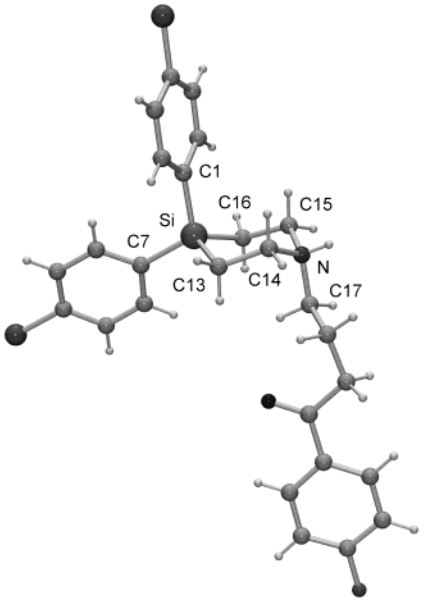


Figure 3. Structure of the cation in the crystal of **8**·HCl.

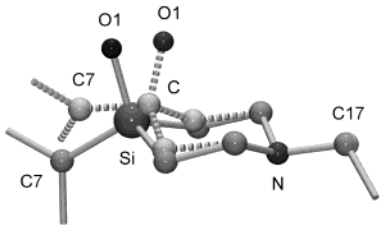


Figure 4. Superposition of the piperidinium skeleton of **1a**·HCl (dashed bonds) and the 4-silapiperidinium skeleton of **1b**·HCl (solid bonds). The hydrogen atoms are omitted for clarity.

In both conformers, the 4-chlorophenyl substituent is orientated equatorially, and the [4-oxo-4-(4-fluorophenyl)butyl] group occupies an equatorial position in the dominating species **1b**α (this structure was also found in the crystal of **1b**·HCl; see above) and an axial position in the minor conformer **1b**β. The two conformers can be interconverted into each other by a process involving nitrogen deprotonation/reprotonation, nitrogen inversion, and ring inversion.

In the case of the carbon compound **1a**·HCl, the analogous conformation **1a**α was attributed to the dominating species using the same NMR experiments (^{1}H,^{1}H COSY and ^{1}H,^{1}H NOESY); the molar ratio **1a**α:**1a**β was found to be considerably higher (ca. 13:1) than the molar ratio **1b**α:**1b**β.

ESI-MS Studies. The silanol−disiloxane equilibrium, 2**1b** ⇌ **10** + H_2O, was investigated at 20 °C by ESI-MS experiments. For this purpose, 10 μM buffered aqueous solutions of **1b**·HCl and **10**·2HOOCCH=CHCOOH at different pH values (pH 5.0, 7.4, and 10.0) were analyzed. Some results of these studies are depicted in Figures 7 and 8. The mass spectra of the aqueous solutions of **1b**·HCl show the characteristic peak for protonated sila-haloperidol (ammonium cation; *m*/*z* 392) at any pH value measured. This holds true for both freshly prepared samples and solutions which were kept at 20 °C for 24 h (Figure 7). When samples of **10**·2HOOCCH=CHCOOH were analyzed, the monoprotonated disiloxane (monoammonium cation; *m*/*z* 765) was detected only in the case of a freshly prepared solution

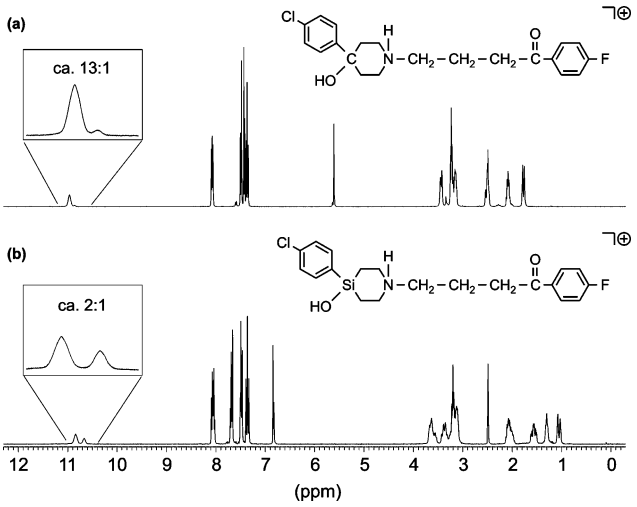


Figure 5. ^{1}H NMR spectra of the C/Si analogues (a) **1a**·HCl and (b) **1b**·HCl**,** showing the respective pairs of NH protons, which correspond to the two conformers present in solution ([D_6]DMSO, 300.1 MHz, 22 °C).

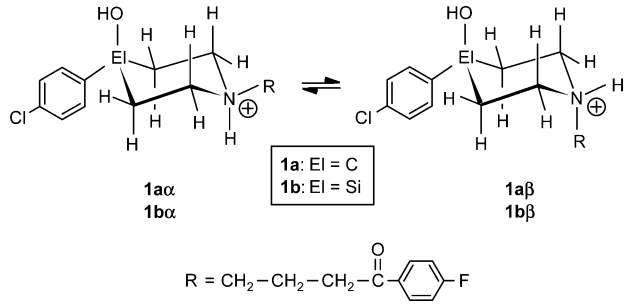


Figure 6. Conformers α and *β* of the cations of the C/Si analogues **1a**·HCl and **1b**·HCl in solution.

at pH 5.0 to a significant extent, along with the dominant 2-fold protonated disiloxane (diammonium cation; *m*/*z* 383) and protonated sila-haloperidol. After an equilibration period of 24 h at 20 °C, protonated sila-haloperidol was found almost exclusively (Figure 8). Under physiological (pH 7.4) and alkaline conditions (pH 10.0), the disiloxane molecule is cleaved rapidly to release the corresponding silanol, which was the only detectable species in freshly prepared and aged samples. The stability of the silanol in water could also be confirmed for solutions of **1b**·HCl at higher concentrations (2.5 mM, pH 1.0 and pH 5.0; 1 mM, pH 7.4 and pH 10.0). In none of these samples were measurable amounts of the disiloxane observed. In conclusion, the silanol−disiloxane equilibrium ($2R_3SiOH \rightleftharpoons R_3SiOSiR_3 + H_2O$) in aqueous solution lies far to the left, the sila-haloperidol molecule being the only detectable species.

Pharmacological Studies. Dopamine receptors are members of the superfamily of membrane-bound G-protein coupled receptors (GPCRs) and the main pharmacological targets of haloperidol. They can be divided into the G_s coupled D_1-like subtype (D_1, D_5; stimulation of adenylate cyclase) and the G_i coupled D_2-like subtype (D_2, D_3, D_4; inhibition of adenylate cyclase).[11] Haloperidol (**1a**) and sila-haloperidol (**1b**) were evaluated at available recombinant human dopamine receptors hD_1, hD_2, hD_4, and hD_5, using the radioligands [^{3}H]SCH23390 and [^{3}H]spiperone, respectively. The C/Si analogues displayed similar potencies at hD_1, hD_4, and hD_5 receptors in radioligand binding experiments (Figure 9, Table 3). However, at hD_2 receptors, the silicon compound **1b** was 4.7-fold more potent than its carbon analogue **1a** in displacing the radioligand [^{3}H]spiperone (Figure 9, Table 3). All radioligand binding K_i values of **1a** in this study (Table 3) were in the range of literature data.[12] All Hill slopes in radioligand binding were not signifi-

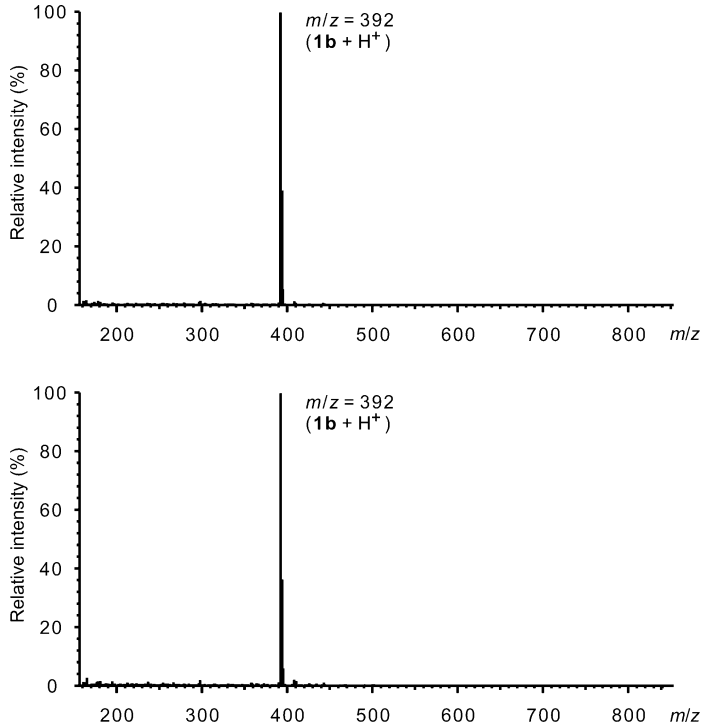


Figure 7. ESI-MS spectra of 10 *μ*M buffered aqueous solutions (pH 5.0) of **1b**·HCl, showing the signal of the ammonium cation (*m*/*z* 392). The spectra were measured 30 min (above) and 24 h (below) after sample preparation at 20 °C (for details, see Experimental Section).

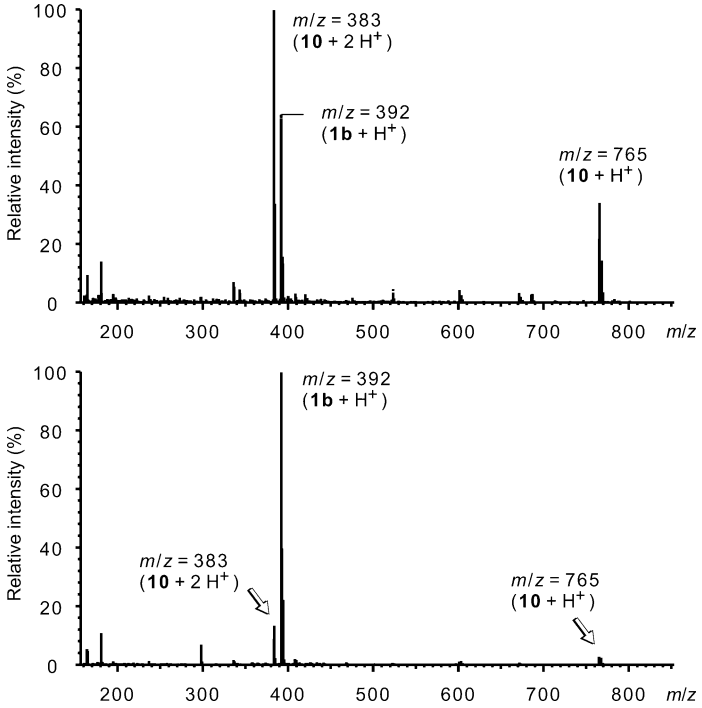


Figure 8. ESI-MS spectra of 10 μM buffered aqueous solutions (pH 5.0) of **10**·2HOOCCH═CHCOOH showing the signals of the monoammonium cation (*m*/*z* 765) and the diammonium cation (*m*/*z* 383). The signal of protonated **1b** (*m*/*z* 392) is also present, indicating hydrolytic cleavage of the disiloxane. The spectra were measured 30 min (above) and 24 h (below) after sample preparation at 20 °C (for details, see Experimental Section).

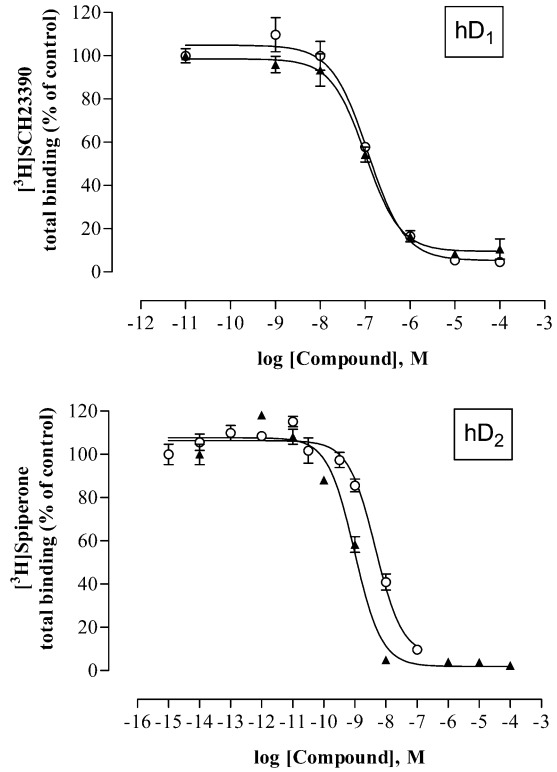


Figure 9. Receptor binding of **1a** (○) and **1b** (▲): inhibition of [^{3}H]SCH23390 binding by increasing concentrations of the test compounds at hD_1 receptors (above) and inhibition of [^{3}H]spiperone binding by increasing concentrations of the test compounds at hD_2 receptors (below). Data are means ±SEM from one experiment with three replicates. Hill slopes were not significantly different from unity.

cantly different from unity (except for **1b** at hD_5 receptors, which was close to unity; 95% confidence interval −0.480 to −0.901), indicating a competitive behavior of **1a** and **1b** at the dopamine receptors examined.

Table 3. Inhibition Constants K_i (Mean ± SD, nM, $n = 3$) and Corresponding Hill Slopes (n_H) for 1a and 1b at Human Dopamine Receptors Obtained by Radioligand Binding Studies

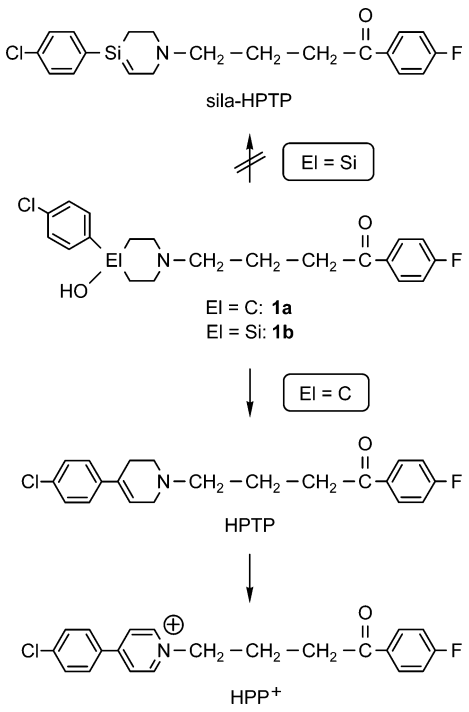
	1a		**1b**	
receptor	K_i	n_H	K_i	n_H
hD_1	100 ± 21.5	−1.029	94.5 ± 18.0	−1.130
hD_2	4.0 ± 1.1	−0.814	0.85 ± 0.21	−0.779
hD_4	6.0 ± 1.0	−1.111	10.0 ± 1.5	−1.006
hD_5	36.7 ± 5.4	−0.935	21.0 ± 5.7	−0.691

It is quite remarkable that sila-substitution of **1a** (→**1b**) leads to an increase of affinity for hD_2 receptors by a factor of 4.7, although the C/Si exchange was performed in a region of the haloperidol molecule, where various substitutions are allowed without changing the affinity for dopamine receptors significantly (in this context, see other butyrophenones such as pipamperone or benperidol).[13,14] As a consequence of the silicon-induced increase of potency at hD_2 receptors, the C/Si analogues differ in their pharmacological selectivity profile.

Conclusions

Sila-haloperidol (**1b**), a silicon analogue of the dopamine (D_2) receptor antagonist haloperidol (**1a**), was synthesized in a multistep synthesis, starting from tetramethoxysilane, and was isolated as the hydrochloride **1b**·HCl. ESI-MS studies of aqueous solutions of the silanol **1b** and the corresponding disiloxane **10** at different pH values revealed a remarkable stability of the silanol; i.e., the silanol-disiloxane equilibrium, 2**1b** ⇌ **10** + H_2O, lies far to the left. As shown by crystal

Scheme 3



structure analyses, the piperidinium ring of **1a**·HCl and the 4-silapiperidinium ring of **1b**·HCl adopt a chair conformation in the crystal, with the exocyclic N-organyl group and the 4-chlorophenyl group in equatorial positions, the 4-silapiperidinium skeleton being more "flattened" than the piperidinium framework. NMR studies demonstrated the existence of two analogous conformers of the cations of **1a**·HCl and **1b**·HCl in solution ([D$_6$]-DMSO), with molar ratios of 13:1 and 2:1, respectively. These different molar ratios indicate considerable differences in the energies of the respective two conformers of the piperidinium and 4-silapiperidinium skeletons. Biological sila-substitution effects were observed as well. In radioligand binding studies, the C/Si analogues **1a** and **1b** displayed similar potencies at recombinant human dopamine hD$_1$, hD$_4$, and hD$_5$ receptors, whereas the silicon compound **1b** was 4.7-fold more potent at hD$_2$ receptors than its carbon analogue **1a**; i.e., sila-substitution of **1a** has changed the receptor selectivity profile.

The physiological relevance of this changed receptor binding profile has to be investigated in future studies. In any case, haloperidol and sila-haloperidol are expected to differ substantially in vivo: metabolic studies have revealed that the carbon compound **1a** is converted to a pyridinium-type metabolite, which has been speculated to be responsible for the long-term, irreversible Parkinsonism-like side effects of haloperidol.[15] As shown in Scheme 3, this metabolism involves water elimination and formation of a carbon−carbon double bond (→HPTP) and subsequent oxidation (→HPP$^+$). As a matter of principle, an analogous metabolism of the silicon compound **1b** is not possible, because the silicon−carbon double bond is not stable under physiological conditions and, hence, **1b** cannot undergo water elimination to form sila-HPTP. Thus, the C/Si analogues **1a** and **1b** must differ in their ADMET profile and, consequently, in their in vivo activity. This, together with its higher potency at hD$_2$ receptors, makes sila-haloperidol a highly interesting research object for further biological studies.

Experimental Section

Syntheses. General Procedures. All syntheses were carried out under dry nitrogen. Acetone, acetonitrile, dichloromethane, diethyl ether, methanol, *n*-pentane, 2-propanol, tetrahydrofuran (THF), toluene, and triethylamine were dried and purified according to standard procedures and stored under nitrogen. Melting points were determined with a Büchi melting point B-540 apparatus using samples in open glass capillaries. ^{1}H, ^{13}C, ^{19}F, and ^{29}Si NMR spectra were recorded at 22 °C on a Bruker DRX-300 NMR spectrometer (^{1}H, 300.1 MHz; ^{13}C, 75.5 MHz; ^{19}F, 282.4 MHz; ^{29}Si, 59.6 MHz) using $CDCl_3$ or [D$_6$]DMSO as the solvent. Chemical shifts (ppm) were determined relative to internal $CHCl_3$ (^{1}H, δ 7.24; $CDCl_3$), internal [D$_5$]DMSO (^{1}H, δ 2.49; [D$_6$]DMSO), internal $CDCl_3$ (^{13}C, δ 77.0; $CDCl_3$), internal [D$_6$]DMSO (^{13}C, δ 39.5; [D$_6$]-DMSO), external $CFCl_3$ (^{19}F, δ 0), and external TMS (^{29}Si, δ 0). Analysis and assignment of the ^{1}H NMR data were supported by ^{1}H,^{1}H COSY and ^{29}Si,^{1}H COSY experiments and partially by simulations using the WIN-DAISY software package (version 4.05, Bruker). Assignment of the ^{13}C NMR data was supported by DEPT 135, ^{13}C,^{1}H HMQC, and ^{13}C,^{1}H HMBC experiments.

Haloperidol Hydrochloride (1a·HCl). This compound was commercially available (Biotrend, Köln, Germany). ^{1}H NMR ([D$_6$]DMSO; data for two conformers): δ 1.70−1.83 (m, 2 H, OCC*H*$_A$H$_B$CH$_2$N), 1.97−2.17 (m, 2 H, NCH$_2$C*H*$_2$CH$_2$C), 2.20−2.37 and 2.41−2.58 (m, 2 H, OCCH$_A$*H*$_B$CH$_2$N; partially overlapped by the [D$_5$]DMSO signal), 3.08−3.50 (m, 8 H, OCCH$_2$C*H*$_2$N, NC*H*$_2$CH$_2$C*H*$_2$C), 5.60 and 5.63 (s, 1 H, OH), 7.31−7.61 (m, 6 H, *H*-3/*H*-5, CC_6H_4F, and *H*-2/*H*-3/*H*-5/*H*-6, CC_6H_4Cl), 8.02−8.14 (m, 2 H, *H*-2/*H*-6, CC_6H_4F), 10.9 and 11.0 (br s, 1 H, NH). ^{13}C NMR ([D$_6$]DMSO; data for the dominating conformer): δ 17.9 (NCH$_2$*C*H$_2$CH$_2$C), 34.8 (OC*C*H$_2$CH$_2$N), 35.3 (NCH$_2$CH$_2$*C*H$_2$C), 48.2 (OCCH$_2$*C*H$_2$N), 55.3 (N*C*H$_2$CH$_2$CH$_2$C), 68.0 (O*C*CH$_2$CH$_2$N), 115.7 (d, $^2J_{CF}$ = 22.2 Hz, *C*-3/*C*-5, CC_6H_4F), 126.6 (*C*-2/*C*-6, CC_6H_4Cl), 128.0 (*C*-3/*C*-5, CC_6H_4Cl), 130.9 (d, $^3J_{CF}$ = 9.8 Hz, *C*-2/*C*-6, CC_6H_4F), 131.4 (*C*-4, CC_6H_4Cl), 133.2 (d, $^4J_{CF}$ = 2.9 Hz, *C*-1, CC_6H_4F), 147.0 (*C*-1, CC_6H_4Cl), 165.0 (d, $^1J_{CF}$ = 251.8 Hz, *C*-4, CC_6H_4F), 197.3 (*C*O). ^{19}F NMR ([D$_6$]-DMSO; data for the dominating conformer): δ −106.5.

Preparation of 4-(4-Chlorophenyl)-4-hydroxy-1-[4-oxo-4-(4-fluorophenyl)butyl]-4-silapiperidinium Chloride (Sila-haloperidol Hydrochloride, 1b·HCl). Trifluoromethanesulfonic acid (2.60 g, 17.3 mmol) was added dropwise at 0 °C within 1 min to a stirred suspension of **8**·HCl (3.00 g, 5.74 mmol) in dichloromethane (25 mL), and the resulting mixture was then stirred at 0 °C for 30 min and at 20 °C for a further 24 h. After the solution was cooled to 0 °C, triethylammonium chloride (2.60 g, 18.9 mmol) was added in one portion, and the mixture was stirred at 0 °C for 30 min. The dichloromethane was removed from the solution by distillation under reduced pressure, toluene (30 mL) was added to the residue at 20 °C with stirring, and the mixture was then kept at −20 °C for 16 h. The upper layer of the resulting two-phase system was separated from the lower layer (triethylammonium trifluoromethanesulfonate) by means of a syringe and cooled to 0 °C. To this stirred solution was added dropwise a mixture of methanol (900 mg, 28.1 mmol) and triethylamine (5.00 g, 49.4

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mmol) at 0 °C, and the resulting mixture was then kept at −20 °C for 16 h. The precipitate was filtered off and discarded, and the solvent, the excess methanol, the triethylamine, and the chlorobenzene (formed in the Si−C cleavage reaction) were removed from the filtrate under reduced pressure to yield 4-(4-chlorophenyl)-4-methoxy-1-[4-oxo-4-(4-fluorophenyl)butyl]-4-silapiperidine (**9**) as an oily crude product (1.80 g). This product was redissolved in THF (20 mL), and the solution was then cooled to 0 °C. A 2.0 M ethereal hydrogen chloride solution (3.0 mL, 6.00 mmol of HCl) was added dropwise at 0 °C, immediately followed by the addition of water (200 mg, 11.1 mmol). The mixture was stirred at 0 °C for 30 min and then kept at −20 °C for 16 h, and the resulting precipitate was isolated by filtration and recrystallized from 2-propanol/water (1.5:1 (v/v)) (5 mL) by slow evaporation of the solvent at 20 °C to give **1b**·HCl in 30% yield as a colorless crystalline solid (740 mg, 1.73 mmol); mp 165 °C. ^{1}H NMR ([D$_6$]DMSO; data for two conformers): δ 0.98−1.13, 1.22−1.38, and 1.44−1.65 (m, 4 H, SiCH_2CH$_2$N), 1.92−2.17 (m, 2 H, NCH$_2$CH_2CH$_2$C), 3.05−3.47 and 3.50−3.73 (m, 8 H, SiCH$_2$CH_2N, NCH_2CH$_2$CH_2C), 6.83 and 6.84 (s, 1 H, OH), 7.25−7.40 (m, 2 H, *H*-3/*H*-5, CC$_6$H$_4$F), 7.44−7.53 (m, 2 H, *H*-3/*H*-5, SiC$_6$H$_4$Cl), 7.62−7.84 (m, 2 H, *H*-2/*H*-6, SiC$_6$H$_4$Cl), 8.02−8.14 (m, 2 H, *H*-2/*H*-6, CC$_6$H$_4$F), 10.7 and 10.8 (br s, 1 H, NH). ^{13}C NMR ([D$_6$]DMSO; data for two conformers, the dominating conformer being marked with an asterisk (*)): δ 9.5 and 11.7* (SiCH$_2$CH$_2$N), 17.9* and 18.2 (NCH$_2$$CH_2CH_2$C), 35.1 and 35.3* (NCH$_2CH_2$$CH_2$C), 50.5 and 51.6* (SiCH$_2$$CH_2$N), 51.9 and 55.6* (N$CH_2CH_2CH_2$C), 115.7 (d, $^2J_{CF}$ = 21.8 Hz, *C*-3/*C*-5, CC$_6$H$_4$F), 127.97* and 128.02 (*C*-3/*C*-5, SiC$_6$H$_4$Cl), 130.9 (d, $^3J_{CF}$ = 9.8 Hz, *C*-2/*C*-6, CC$_6$H$_4$F), 133.2 (d, $^4J_{CF}$ = 2.9 Hz, *C*-1, CC$_6$H$_4$F), 134.1* and 134.4 (*C*-1, SiC$_6$H$_4$Cl), 135.3* and 135.4 (*C*-4, SiC$_6$H$_4$Cl), 135.5* and 135.6 (*C*-2/*C*-6, SiC$_6$H$_4$Cl), 165.0 (d, $^1J_{CF}$ = 251.8 Hz, *C*-4, CC$_6$H$_4$F), 197.3 (*C*O). ^{19}F NMR ([D$_6$]DMSO; data for two conformers): δ −106.4. ^{29}Si NMR ([D$_6$]DMSO; data for two conformers, the dominating conformer being marked with an asterisk (*)): δ −10.4 and −10.6*. Anal. Calcd for C$_{20}$H$_{24}$Cl$_2$FNO$_2$Si (428.41): C, 56.07; H, 5.60; N, 3.27. Found: C, 56.0; H, 5.8; N, 3.3.

Tetramethoxysilane (2). This compound was commercially available (Sigma-Aldrich, Taufkirchen, Germany).

Preparation of Bis(4-chlorophenyl)dimethoxysilane (3). A 0.87 M solution of (4-chlorophenyl)magnesium bromide in diethyl ether (300 mL, 261 mmol of 4-ClC$_6$H$_4$MgBr) was added dropwise at 20 °C within 90 min to a stirred solution of **2** (18.5 g, 122 mmol) in diethyl ether (200 mL). The mixture was stirred at 20 °C for 16 h and then heated under reflux for 4 h. The resulting precipitate was filtered off and washed with diethyl ether (3 × 150 mL), and the filtrate and wash solutions were combined. The solvent was removed by distillation under atmospheric pressure, and *n*-pentane (250 mL) was added to the residue. The resulting precipitate was filtered off and discarded, the solvent of the filtrate was removed under reduced pressure, and the residue was distilled in vacuo (Vigreux column) to give **3** in 72% yield as a colorless liquid (27.5 g, 87.8 mmol); bp 115 °C/0.05 mbar. ^{1}H NMR (CDCl$_3$): δ 3.60 (s, 6 H, OCH$_3$), 7.36 (AA′ part of an AA′BB′ system, $^4J_{AA'}$ = 1.6 Hz, $^3J_{AB}$ = $^3J_{A'B'}$ = 7.9 Hz, $^5J_{AB'}$ = $^5J_{A'B}$ = 0.5 Hz, $^4J_{BB'}$ = 2.2 Hz, 4 H, *H*-3/*H*-5, SiC$_6$H$_4$Cl), 7.55 (BB′ part of an AA′BB′ system, 4 H, *H*-2/*H*-6, SiC$_6$H$_4$Cl). ^{13}C NMR (CDCl$_3$): δ 50.9 (OCH$_3$), 128.4 (*C*-3/*C*-5, SiC$_6$H$_4$Cl), 130.1 (*C*-1, SiC$_6$H$_4$Cl), 136.2 (*C*-2/*C*-6, SiC$_6$H$_4$Cl), 137.0 (*C*-4, SiC$_6$H$_4$Cl). ^{29}Si NMR (CDCl$_3$): δ −29.8. Anal. Calcd for C$_{14}$H$_{14}$Cl$_2$O$_2$Si (313.25): C, 53.68; H, 4.50. Found: C, 53.5; H, 4.5.

Preparation of Bis(4-chlorophenyl)divinylsilane (4). A 1.7 M solution of vinylmagnesium chloride in THF (80 mL, 136 mmol of CH$_2$=CHMgCl) was added dropwise at 20 °C within 90 min to a stirred solution of **3** (19.5 g, 62.2 mmol) in diethyl ether (200 mL). After the mixture was stirred at 20 °C for 16 h and heated under reflux for 6 h, a saturated aqueous ammonium chloride solution (500 mL) was added at 0 °C. The organic phase was separated, the aqueous layer was extracted with diethyl ether (3 × 350 mL), and the combined organic extracts were dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was distilled in vacuo (Vigreux column) to give **4** in 77% yield as a colorless liquid (14.6 g, 47.8 mmol); bp 126 °C/0.02 mbar. ^{1}H NMR (CDCl$_3$): 5.82 (δ_C), 6.30 (δ_B), and 6.46 (δ_A) (ABC system, J_{AB} = 14.6 Hz, J_{AC} = 20.3 Hz, J_{BC} = 3.4 Hz, 6 H, SiCH$_A$=CH$_B$H$_C$), 7.37 (AA′ part of an AA′BB′ system, $^4J_{AA'}$ = 1.6 Hz, $^3J_{AB}$ = $^3J_{A'B'}$ = 7.9 Hz, $^5J_{AB'}$ = $^5J_{A'B}$ = 0.5 Hz, $^4J_{BB'}$ = 2.2 Hz, 4 H, *H*-3/*H*-5, SiC$_6$H$_4$Cl), 7.45 (BB′ part of an AA′BB′ system, 4 H, *H*-2/*H*-6, SiC$_6$H$_4$Cl). ^{13}C NMR (CDCl$_3$): δ 128.3 (*C*-3/*C*-5, SiC$_6$H$_4$Cl), 132.1 (*C*-1, SiC$_6$H$_4$Cl), 132.9 (SiCH=CH$_2$), 136.2 (*C*-4, SiC$_6$H$_4$Cl), 136.8 (*C*-2/*C*-6, SiC$_6$H$_4$Cl), 137.3 (SiCH=CH$_2$). ^{29}Si NMR (CDCl$_3$): δ −20.1. Anal. Calcd for C$_{16}$H$_{14}$Cl$_2$Si (305.28): C 62.95, H 4.62. Found: C 62.7, H 4.7.

Preparation of Bis(2-bromoethyl)bis(4-chlorophenyl)silane (5). A gas stream of hydrogen bromide was passed for 4 h at 20 °C through a stirred solution of **4** (12.0 g, 39.3 mmol) in *n*-pentane (100 mL) in the presence of dibenzoyl peroxide (200 mg, 83 μmol) (reaction control by GC). Water (100 mL) was added to the mixture at 0 °C, the organic phase was separated, and the aqueous layer was extracted with diethyl ether (2 × 100 mL). The combined organic extracts were dried over anhydrous sodium sulfate, and the solvent was removed by distillation under atmospheric pressure. The yellowish oily residue was dissolved in diethyl ether (50 mL), and the solution was kept at −20 °C for 48 h to afford **5** (isolated by filtration) in 73% yield as a colorless crystalline solid (13.4 g, 28.7 mmol); mp 48−49 °C. ^{1}H NMR (CDCl$_3$): δ 1.90 (AA′ part of an AA′XX′ system, $^2J_{AA'}$ = 14.3 Hz, $^3J_{AX}$ = $^3J_{A'X'}$ = 12.6 Hz, $^3J_{AX'}$ = $^3J_{A'X}$ = 5.2 Hz, $^2J_{XX'}$ = 9.9 Hz, 4 H, SiCH_2CH$_2$Br), 3.43 (XX′ part of an AA′XX′ system, 4 H, SiCH$_2$CH_2Br). 7.4 (br s, 8 H, SiC$_6$H$_4$Cl). ^{13}C NMR (CDCl$_3$): δ 19.7 (SiCH$_2$CH$_2$Br), 29.0 (SiCH$_2$$CH_2$Br), 128.9 (*C*-3/*C*-5, SiC$_6$H$_4$Cl), 130.2 (*C*-1, SiC$_6$H$_4$Cl), 136.0 (*C*-2/*C*-6, SiC$_6$H$_4$Cl), 137.1 (*C*-4, SiC$_6$H$_4$Cl). ^{29}Si NMR (CDCl$_3$): δ −8.6. Anal. Calcd for C$_{16}$H$_{16}$Br$_2$Cl$_2$Si (467.10): C, 41.14; H, 3.45. Found: C, 41.1; H, 3.5.

Preparation of 3-[2-(4-Fluorophenyl)-1,3-dioxolan-2-yl]propylamine (6). This compound was synthesized according to ref 9.

Preparation of 4,4-Bis(4-chlorophenyl)-1-[4-oxo-4-(4-fluorophenyl)butyl]-4-silapiperidinium Chloride (8·HCl). A mixture of **5** (5.00 g, 10.7 mmol), **6** (2.50 g, 11.1 mmol), triethylamine (3.00 g, 29.6 mmol), acetonitrile (30 mL), and toluene (30 mL) was heated for 16 h at 90 °C in a 250 mL autoclave. After the mixture was cooled to 20 °C, the precipitate was filtered off and discarded. Water (60 mL) was added to the filtrate, the organic phase was separated, and the aqueous layer was extracted with toluene (2 × 50 mL). The combined organic extracts were dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure to give 4,4-bis(4-chlorophenyl)-1-{3-[2-(4-fluorophenyl)-1,3-dioxolan-2-yl]propyl}-4-silapiperidine (**7**) as a highly viscous crude product. This product was dissolved in acetone (40 mL), 6 M hydrochloric acid (2 mL) was added, and the mixture was then heated at 60 °C for 2 h. After the mixture was cooled to 20 °C, a 6 M aqueous sodium hydroxide solution (6 mL) and toluene (40 mL) were added. The organic phase was separated, the aqueous layer was extracted with toluene (2 × 50 mL), and the combined organic extracts were dried over anhydrous sodium sulfate. After the solution was concentrated by distillation under atmospheric pressure (removal of acetone), a 3.0 M ethereal hydrogen chloride solution (5.0 mL, 15.0 mmol of HCl) was added dropwise at 20 °C, and the mixture was then cooled to −20 °C. The resulting precipitate was isolated by filtration and then recrystallized from 2-propanol to give **8**·HCl in 63% yield as a colorless crystalline solid (3.50 g, 6.69 mmol); mp 181 °C. ^{1}H NMR (CDCl$_3$): δ 1.40−1.58 (m, 2 H, SiCH_AH$_B$CH$_2$N), 2.15−2.37 (m, 4 H, SiCH$_A$$H_BCH_2N, NCH_2CH_2$-CH$_2$C), 2.90−3.13 (m, 4 H, SiCH$_2$CH_AH$_B$N, NCH_2CH$_2$CH$_2$C), 3.17 (t, $^3J_{HH}$ = 6.4 Hz, 2 H, NCH$_2$CH$_2$CH_2C), 3.70−3.86 (m, 2

H, $SiCH_2CH_AH_BN$), 7.08 (AA′ part of an AA′XX′Z system, $^4J_{AA'}$ = 2.5 Hz, $^3J_{AX} = {}^3J_{A'X'}$ = 8.6 Hz, $^5J_{AX'} = {}^5J_{A'X}$ = 0.4 Hz, $^3J_{AZ} = {}^3J_{A'Z}$ = 8.3 Hz, $^4J_{XX'}$ = 2.3 Hz, $^4J_{XZ} = {}^4J_{X'Z}$ = 5.4 Hz, 2 H, *H*-3/*H*-5, CC_6H_4F), 7.28 (AA′ part of an AA′BB′ system, $^4J_{AA'}$ = 1.6 Hz, $^3J_{AB} = {}^3J_{A'B'}$ = 8.0 Hz, $^5J_{AB'} = {}^5J_{A'B}$ = 0.5 Hz, $^4J_{BB'}$ = 2.2 Hz, 2 H, *H*-3/*H*-5, SiC_6H_4Cl), 7.44 (BB′ part of an AA′BB′ system, 2 H, *H*-2/*H*-6, SiC_6H_4Cl), 7.44 (AA′ part of an AA′BB′ system, $^4J_{AA'}$ = 1.6 Hz, $^3J_{AB} = {}^3J_{A'B'}$ = 8.0 Hz, $^5J_{AB'} = {}^5J_{A'B}$ = 0.5 Hz, $^4J_{BB'}$ = 2.2 Hz, 2 H, *H*-3′/*H*-5′, SiC_6H_4Cl), 7.49 (BB′ part of an AA′BB′ system, 2 H, *H*-2′/*H*-6′, SiC_6H_4Cl), 7.93 (XX′ part of an AA′XX′Z system, 2 H, *H*-2/*H*-6, CC_6H_4F), 12.3 (br s, 1 H, NH). ^{13}C NMR ($CDCl_3$): δ 8.6 ($SiCH_2CH_2N$), 18.0 ($NCH_2CH_2CH_2C$), 35.2 ($NCH_2CH_2CH_2C$), 52.5 ($SiCH_2CH_2N$), 56.2 ($NCH_2CH_2CH_2C$), 115.8 (d, $^2J_{CF}$ = 22.2 Hz, *C*-3/*C*-5, CC_6H_4F), 128.59 (*C*-3/*C*-5, SiC_6H_4Cl), 128.64 (*C*-1, SiC_6H_4Cl), 129.2 (*C*-3′/*C*-5′, SiC_6H_4Cl), 129.8 (*C*-1′, SiC_6H_4Cl), 130.6 (d, $^3J_{CF}$ = 9.5 Hz, *C*-2/*C*-6, CC_6H_4F), 132.5 (d, $^4J_{CF}$ = 2.9 Hz, *C*-1, CC_6H_4F), 135.8 (*C*-2/*C*-6, SiC_6H_4Cl), 136.2 (*C*-2′/*C*-6′, SiC_6H_4Cl), 137.1 (*C*-4, SiC_6H_4Cl), 137.4 (*C*-4′, SiC_6H_4Cl), 165.9 (d, $^1J_{CF}$ = 255.4 Hz, *C*-4, CC_6H_4F), 196.6 (*C*O). ^{19}F NMR ($CDCl_3$): δ −104.4 (Z part of an AA′XX′Z system).^{29}Si NMR ($CDCl_3$): δ −16.7. Anal. Calcd for $C_{26}H_{27}Cl_3FNOSi$ (522.95): C, 59.72; H, 5.20; N, 2.68. Found: C, 59.5; H, 5.1; N, 2.7.

Preparation of 4,4′-Oxybis{4-(4-chlorophenyl)-1-[4-oxo-4-(4-fluorophenyl)butyl]-4-silapiperidinium} Bis[(2*E*)-3-carboxyacrylate] (10·2HOOCCH═CHCOOH). Trifluoromethanesulfonic acid (1.00 g, 6.66 mmol) was added dropwise at 0 °C within 1 min to a stirred suspension of **8**·HCl (1.20 g, 2.29 mmol) in dichloromethane (15 mL), and the resulting mixture was then stirred at 0 °C for 30 min and at 20 °C for a further 24 h. A 2.0 M aqueous sodium hydroxide solution (5 mL, 10 mmol of NaOH) was added, and the mixture was stirred at 20 °C for a further 30 min. The organic phase was separated, the aqueous layer was extracted with dichloromethane (2 × 15 mL), and the combined organic extracts were washed with water (2 × 15 mL) and then dried over anhydrous sodium sulfate. The solvent and the chlorobenzene (formed in the Si−C cleavage reaction) were removed under reduced pressure, and the oily residue was dissolved in 2-propanol (8 mL). The resulting solution was stirred at 20 °C for 16 h and then warmed to 50 °C, followed by the addition of a hot (50 °C) solution of fumaric acid (270 mg, 2.33 mmol) in 2-propanol (10 mL) in one portion. After the resulting mixture was stirred at 50 °C for 60 min, the solvent was removed by distillation under reduced pressure, the residue was dissolved in methanol (4 mL), and this solution was kept at −20 °C for 48 h to afford **10**·2HOOCCH═CHCOOH in 36% yield as a colorless solid (415 mg, 416 μmol); mp 201−202 °C dec. ^{1}H NMR ([D$_6$]DMSO): δ 0.65−1.30 (m, 8 H, $SiCH_2CH_2N$), 1.75−1.98 (m, 4 H, $NCH_2CH_2CH_2C$), 2.55−3.25 (m, 16 H, $SiCH_2CH_2N$, $NCH_2CH_2CH_2C$), 6.54 (s, 4 H, CC*H*═C*H*C), 7.22−7.66 and 7.96−8.10 (m, 16 H, SiC_6H_4Cl and CC_6H_4F), 11.0−14.0 (br s, ca. 2 H, OH). ^{13}C NMR ([D$_6$]DMSO): δ 12.6 ($SiCH_2CH_2N$), 20.6 ($NCH_2CH_2CH_2C$), 35.4 ($NCH_2CH_2CH_2C$), 51.1 ($SiCH_2CH_2N$), 55.4 ($NCH_2CH_2CH_2C$), 115.6 (d, $^2J_{CF}$ = 21.4 Hz, *C*-3/*C*-5, CC_6H_4F), 128.1 (*C*-3/*C*-5, SiC_6H_4Cl), 130.8 (d, $^3J_{CF}$ = 9.5 Hz, *C*-2/*C*-6, CC_6H_4F), 133.6 (d, $^4J_{CF}$ = 2.4 Hz, *C*-1, CC_6H_4F), 134.3 (*C*-1, SiC_6H_4Cl), 134.5 (C*C*H═*C*HC), 135.2 (*C*-2/*C*-6, SiC_6H_4Cl), 135.4 (*C*-4, SiC_6H_4Cl), 164.9 (d, $^1J_{CF}$ = 251.8 Hz, *C*-4, CC_6H_4F), 166.9 (*C*O, anion), 198.0 (*C*O, cation). ^{19}F NMR ([D$_6$]DMSO): δ −106.9. ^{29}Si NMR ([D$_6$]DMSO): δ −8.8. Anal. Calcd for $C_{48}H_{52}Cl_2F_2N_2O_{11}Si_2$ (998.02): C, 57.77; H, 5.25; N, 2.81. Found: C, 57.3; H, 5.4; N, 2.9.

Crystal Structure Analyses. Suitable single crystals of **1a**·HCl, **1b**·HCl, and **8**·HCl were obtained by crystallization from 2-propanol/water (**1a**·HCl, **1b**·HCl) or 2-propanol (**8**·HCl) at 20 °C. The crystals were mounted in inert oil (perfluoroalkyl ether; ABCR, Karlsruhe, Germany) on a glass fiber and then transferred to the cold nitrogen gas stream of the diffractometer (Stoe IPDS; graphite-monochromated Mo Kα radiation (λ = 0.710 73 Å)). The structures were solved by direct methods.[16,17] All non-hydrogen atoms were refined anisotropically.[18] A riding model was employed in the refinement of the C*H* hydrogen atoms.

NMR Studies. ^{1}H, ^{13}C, and ^{29}Si NMR studies of the C/Si analogues **1a**·HCl and **1b**·HCl demonstrated the existence of two conformers of the respective ammonium cations (**1a**·HCl, molar ratio ca. 13:1; **1b**·HCl, molar ratio ca. 2:1) in solution (solvent [D$_6$]DMSO). These conformers are configurationally stable on the NMR time scale under the experimental conditions used. To prove the existence of the two conformers, 2D ^{1}H,^{1}H EXSY experiments were carried out at 22 °C (solvent [D$_6$]DMSO). In the case of **1a**·HCl, the site exchange for the C(OH)CH_2CH_2N protons of the piperidinium skeleton and the *H*-2/*H*-6 protons of the 4-chlorophenyl substituent was accomplished by this study, showing strong cross-peaks between the respective signals of the two conformers. In the case of **1b**·HCl, the $SiCH_2CH_2N$ and $SiCH_2CH_2N$ protons of the 4-silapiperidinium skeleton were monitored. 2D ^{1}H,^{1}H NOESY NMR experiments were carried out to establish the structures of the respective conformers. The mixing time was on the order of the spin−lattice relaxation time T_1, calculated by a standard 1D T_1-inversion recovery experiment.

ESI-MS Studies. (a) Chemicals. Water (HPLC gradient grade) was purchased from Acros (Geel, Belgium). Acetic acid (98%, analytical reagent grade), ammonium hydroxide solution (25%, analytical reagent grade), and ammonium acetate (analytical reagent grade) were purchased from Fluka (Taufkirchen, Germany).

(b) Sample Preparation. A 10 mM aqueous ammonium acetate buffer was prepared from a 1.0 M stock solution by diluting with water and adjusting the pH with 98% acetic acid (pH 5), 0.25% ammonium hydroxide solution (pH 7.4), or 2.5% ammonium hydroxide solution (pH 10). For measurements at pH 1, 0.1 M hydrochloric acid was used as the solvent.

Sample solutions of **1b**·HCl and **10**·2HOOCCH═CHCOOH with a concentration of 10 μM were prepared from 0.4 mM aqueous stock solutions by dilution with the respective buffer (pH 5, pH 7.4, pH 10) or 0.1 M hydrochloric acid (pH 1) and were analyzed by ESI-MS (i) 30 min and (ii) 24 h after preparation.

Sample solutions with concentrations of 2.5 mM (pH 1, pH 5) and 1 mM (pH 7.4, pH 10) of **1b**·HCl were prepared by dissolving the appropriate amount of **1b**·HCl in 0.1 M hydrochloric acid (pH 1) or in the respective buffer solution (pH 5, pH 7.4, pH 10). At pH 10, acetonitrile was used as a cosolvent (buffer/acetonitrile 1:1 (v/v), 4 mL) for reasons of solubility. These samples were allowed to stand for 24 h after preparation, were then diluted to a concentration of 0.1 mM by addition of water, and were analyzed instantaneously by ESI-MS.

(c) ESI-MS Analysis. Analysis was performed with a Finnigan MAT triple-stage quadrupole TSQ 7000 mass spectrometer with an ESI interface. Data acquisition and evaluation were conducted on a Digital Equipment Personal DECstation 5000/33 using Finnigan MAT ICIS 8.1 software. Nitrogen served both as sheath and auxiliary gas. The electrospray ionization parameters were as follows: temperature of the heated capillary, 200 °C; electrospray capillary voltage, 3.5 kV; sheath gas, 70 psi (1 psi = 6894.74 Pa); auxiliary gas, 10 units. For measurement, the sample solutions were continuously delivered at a flow rate of 20 μL min^{-1} by means of a syringe pump system (Harvard apparatus, No. 22). Positive ions were detected by scanning from 200 to 800 u with a total scan duration of 1.0 s; 60 scans were collected within 1 min. The multiplier voltage was set to 1.3 kV.

Pharmacological Studies. (a) Materials. cDNA for hD_1 and hD_5 dopamine receptors was kindly provided by Dr. D.

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Grandy (Portland, OR). The pcDNA vector containing the coding sequence of the hD_{2L} (long form) dopamine receptor was a gift from Dr. W. Sadée (San Francisco, CA). Compounds **1a** and **1b** were studied as hydrochlorides. All the other compounds and materials were obtained from Sigma Chemicals (Taufkirchen, Germany) unless otherwise stated.

(b) Cell Culture. Stable cell lines of human embryonic kidney (HEK293) cells (ATCC, Rockville, MD) were generated as previously described.[19,20] Briefly, pcDNA3 vectors containing a fragment coding for the entire human hD_1, hD_2, and hD_5 dopamine receptors were transfected into HEK293 cells by lipofection with Roti-Fect transfection reagent (Roth, Karlsruhe, Germany). Clonal selection was performed by adding 400 μg/mL G-418 to the culture medium. Stable HEK293 clonal cell lines were grown in Dulbecco's modified Eagle Medium Nutrient Mixture F-12 Ham (DMEM/F12 1:1 Mixture) containing 10% fetal bovine serum, 100 μg/mL of streptomycine, 100 U/mL of penicillin G, and 1 mM L-glutamine. A stable clonal Chinese hamster ovary (CHO) cell line transfected with the human dopamine receptor $D_{4.4}$ was kindly provided by Dr. H. van Tol (Toronto, Canada). Stably transfected CHO cells were preserved in Ham F12 medium supplemented with 10% fetal bovine serum, 100 μg/mL of streptomycine, 100 U/mL of penicillin G, and 1 mM L-glutamine. HEK293 and CHO cells were incubated at 37 °C under 5% CO_2.

(c) Cell Membrane Preparations. HEK293 or CHO cells were grown in 145 mm tissue culture dishes (Cellstar TC-Dishes; Greiner Bio-One, Frickenhausen, Germany) to reach a confluence of ca. 80%. Then, the growth medium was removed and replaced with fresh culture medium enriched with 5 mM sodium butyrate. Cells were grown for an additional period of 16 h and then harvested by scraping, resuspended in ice-cold Krebs-HEPES buffer (118 mM NaCl, 4.7 mM KCl, 1.2 mM $MgSO_4$, 1.2 mM KH_2PO_4, 4.2 mM $NaHCO_3$, 11.7 mM D-Glucose, 1.3 mM $CaCl_2$, 10 mM HEPES, pH 7.4), and disrupted using a Polytron homogenizer on ice (PT 10-35; Kinematica AG, Basel, Switzerland). After centrifugation at 40 000 × g at 2 °C, the supernatant was discarded, and the pellet was washed twice with ice-cold Krebs-HEPES buffer (2 × 15 mL). Eventually, the pellet was resuspended in Krebs-HEPES buffer (15 mL) and stored at −80 °C until use for radioligand binding.

(d) Radioligand Binding Assays. The equilibrium dissociation constants K_d of the radioligands used ([^{3}H]SCH23390 for hD_1 and hD_5; [^{3}H]spiperone for hD_2 and hD_4) and receptor densities of the respective dopamine receptor cell membrane preparations (B_{max} values) were determined according to the method of Lazareno and Birdsall, as described previously.[21,22] Total protein was estimated with the Bradford assay:[23] hD_1, K_d = 2.41 nM, B_{max} = 8184 fmol/mg of protein; hD_2, K_d = 0.69 nM, B_{max} = 2022 fmol/mg of protein; hD_4, K_d = 0.14 nM, B_{max} = 19 500 fmol/mg of protein; hD_5, K_d = 1.07 nM, B_{max} = 656 fmol/mg of protein. Binding experiments with **1a** and **1b** were carried out in a total volume of 1.1 mL according to the method described previously.[21] Cell membranes were resuspended in Krebs-HEPES buffer containing 0.5% bovine serum albumin and added to pretreated microcentrifuge tubes (sigmacote; protein content, ca. 90 μg/tube) containing **1a** and **1b** in increasing concentrations. After the addition of 110 μL of radioligand, incubations were carried out at 26 °C for 2 h and terminated by rapid filtration of 1 mL through pretreated glass fiber filters (Schleicher und Schuell, Dassel, Germany; pretreated with 0.2% polyethylene imine for at least 12 h), followed by washing with ice-cold water (2 × 5 mL). Filters were transferred to scintillation vials, and 5 mL of readyprotein (Beckman, Krefeld, Germany) were added. After an incubation period of at least 30 min, radioactivity retained on the filters was determined by liquid scintillation spectroscopy using a Beckman scintillation counter. For binding studies at hD_1 and hD_5 receptors, [^{3}H]SCH23390 (66.0 Ci/mmol; Nycomed Amersham, Buckinghamshire, U.K.) was used, with a final concentration of 0.2 nM. At hD_2 and hD_4 receptors, [^{3}H]-spiperone (118 Ci/mmol; Nycomed Amersham, Buckinghamshire, U.K.) was used, with a final concentration of 0.1 nM.

(e) Data Analysis of Binding Assays. Concentration−response curves were constructed using a nonlinear regression curve fit (sigmoidal dose−response equation with variable Hill slope) by means of Prism software 3.0 from GraphPad (GraphPad Software; San Diego, CA). Inhibition constants K_i from radioligand binding were calculated according to the Cheng-Prusoff equation:[24]

$$K_i = IC_{50}/(1 + L/K_d)$$

where IC_{50} is the molar concentration of the test compound at half-maximum displacement of the radioligand, L is the molar concentration of the radioligand, and K_d is the equilibrium dissociation constant of the radioligand.

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Supporting Information Available: Tables of crystal data, structure solution and refinement, atomic coordinates, bond lengths and angles, and anisotropic displacement parameters for **1a**·HCl, **1b**·HCl, and **8**·HCl. This material is available free of charge via the Internet at http://www.pubs.acs.org. In addition, 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-236881 (**1a**·HCl), CCDC-236882 (**1b**·HCl), and CCDC-236883 (**8**·HCl). Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. (fax, (+44) 1223/336033; e-mail, deposit@ccdc.cam.ac.uk).

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