Syntheses and Pharmacological Properties of the Histaminic H_1 Antagonists Sila-terfenadine-A, Sila-terfenadine-B, Disila-terfenadine, and Sila-fexofenadine: A Study on C/Si Bioisosterism

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Received June 8, 2004

Sila-substitution (C/Si exchange) of one or both of the two quaternary carbon atoms of the histaminic H_1 antagonist terfenadine (**1a**) leads to sila-terfenadine-A (**1b**; $R_3COH \rightarrow R_3SiOH$), sila-terfenadine-B (**1c**; $R_4C \rightarrow R_4Si$), or disila-terfenadine (**1d**; $R_3COH \rightarrow R_3SiOH$, $R_4C \rightarrow R_4Si$). Sila-substitution of the quaternary carbon atom of the histaminic H_1 antagonist fexofenadine (**2a**) affords sila-fexofenadine (**2b**; $R_3COH \rightarrow R_3SiOH$). The silicon compounds *rac*-**1b**, *rac*-**1c**, *rac*-**1d**, and *rac*-**2b** were synthesized in multistep syntheses, and the identities of these compounds and their precursors were established by elemental analyses and multinuclear NMR studies. Some of the precursors were additionally characterized by single-crystal X-ray diffraction. The pharmacological profiles of *rac*-**1a**, *rac*-**1b**, *rac*-**1c**, *rac*-**1d**, *rac*-**2a**, and *rac*-**2b** were assessed across a range of histaminic receptor binding assays (radioligand binding studies at histamine central H_1, peripheral H_1, H_2, and H_3 receptors). The silicon compounds, within experimental error, exhibited an affinity and selectivity profile similar to their corresponding carbon analogues.

Introduction

Histaminic H_1 antagonists were utilized for the first time in the 1940s for the treatment of allergic disorders. Clinically, these antihistamines were used to alleviate the symptoms of various allergic conditions. These relatively nonselective agents also possessed significant anticholinergic activity, which enabled their utility in treating motion sickness and as adjunct therapy for the amelioration of Parkinsonism. Unfortunately, the sedative side-effects of the classic histaminic H_1 antagonists were immense, and the search for sedation-free H_1 receptor antagonists finally led to the clinical introduction of terfenadine (**1a**),[1] which became the world's leading nonsedating antihistamine in 1994. However, soon it turned out that terfenadine can cause severe cardiovascular side effects.[2] As opposed to this, the actual pharmacologically active compound, the carboxylic acid metabolite of terfenadine, fexofenadine (**2a**),[3] does not show such side effects. Therefore, the nonsedating histaminic H_1 antagonist fexofenadine itself was introduced to the market as a clinical replacement for terfenadine with an improved safety profile. The cardiovascular side effects of terfenadine were subsequently attributed to its affinity for the hERG ion channel, which fexofenadine was shown not to affect.

In connection with our systematic studies on C/Si bioisosterism,[4] we investigated the pharmacological effects of sila-substitution (C/Si exchange) of one or both of the two quaternary carbon atoms in the terfenadine molecule ($C_3COH \rightarrow C_3SiOH$; $C_4C \rightarrow C_4Si$). In addition,

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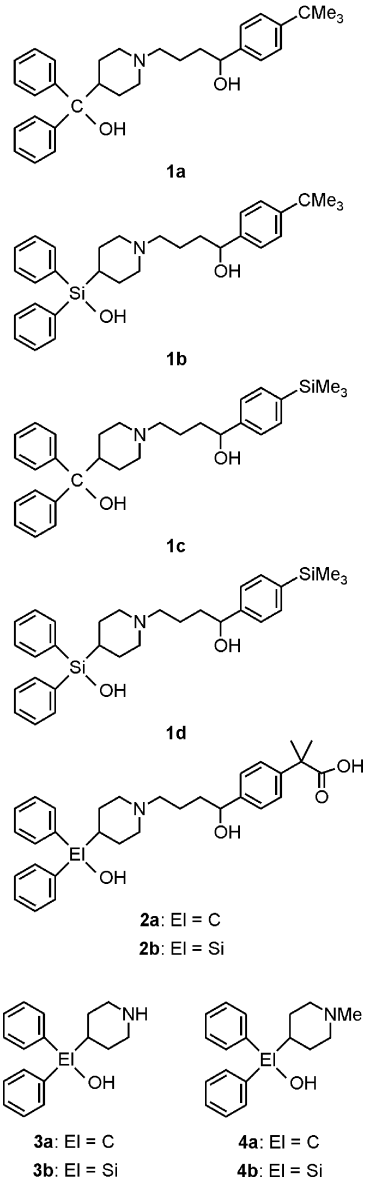
10.1021/om040084a CCC: $27.50
Publication on Web 09/02/2004

the replacement of the quaternary carbon atom of fexofenadine by a silicon atom was studied ($C_3COH \rightarrow C_3SiOH$). We report here on the syntheses of the racemic silicon compounds sila-terfenadine-A (*rac*-**1b**), sila-terfenadine-B (*rac*-**1c**), disila-terfenadine (*rac*-**1d**), and sila-fexofenadine (*rac*-**2b**) and their pharmacological characterization (in this context, see also ref 5). In addition, we report on the syntheses of the related silanols sila-azacyclonol (**3b**) and *N*-methyl-sila-azacyclonol (**4b**). These compounds represent sila-analogues of the neuroleptic azacyclonol (**3a**) and its *N*-methyl derivative **4a**.



Results and Discussion

Syntheses. *rac*-Sila-terfenadine-A (*rac*-**1b**) was prepared in a multistep synthesis, starting from difluorodiphenylsilane[6] (**5**) (Scheme 1). In the first step, fluoro(1-methylpiperidin-4-yl)diphenylsilane (**6**) was synthesized by reaction of **5** with (1-methylpiperidin-4-yl)-magnesium chloride in tetrahydrofuran (yield 65%). Treatment of **6** with 1-chloroethyl chloroformate in dichloromethane, followed by reaction with methanol, gave 4-(fluorodiphenylsilyl)piperidinium chloride (**7**) (yield 58%), which upon treatment with sodium methanolate in methanol afforded methoxydiphenyl(piperidin-4-yl)silane (**8**) (yield 82%). Successive treatment of 4-(4-*tert*-butylphenyl)-4-oxobutanoic acid[7] (**9**) with triethylamine, ethyl chloroformate, and **8** in tetrahydrofuran gave the amide **10** (isolated as crude product; not purified), which upon reduction with lithium aluminum hydride in tetrahydrofuran, followed by hydrolysis, finally afforded *rac*-**1b** (yield 62%).

rac-Sila-terfenadine-B (*rac*-**1c**) was synthesized according to Scheme 2, starting from 4-(4-(trimethylsilyl)-phenyl)-4-oxobutanoic acid (**11**). Thus, successive treatment of **11** with triethylamine, ethyl chloroformate, and diphenyl(piperidin-4-yl)methanol[8] (**3a**) in tetrahydrofuran gave the amide **12** (isolated as crude product; not purified), which upon reduction with lithium aluminum hydride in tetrahydrofuran, followed by hydrolysis, finally afforded *rac*-**1c** (yield 67%). The carboxylic acid **11** was obtained by reaction of (4-bromophenyl)trimethylsilane[9] (**13**) with magnesium in diethyl ether, followed by treatment with butanedioic anhydride in diethyl ether and subsequent hydrolysis with hydrochloric acid (yield 48%).

rac-Disila-terfenadine (*rac*-**1d**) was prepared according to Scheme 3, again starting from **11** and following the method used for the preparation of *rac*-**1b** (yield 32%; the amide **14** was isolated as crude product and not purified).

rac-Sila-fexofenadine (*rac*-**2b**) was synthesized according to Scheme 4, starting from 4-(4-(1-(4,4-dimethyl-4,5-dihydro-1,3-oxazol-2-yl)-1-methylethyl)phenyl)-4-oxobutanoic acid (**15**). Thus, successive treatment of **15** with triethylamine, ethyl chloroformate, and **8** in tetrahydrofuran gave the amide **16** (isolated as crude product; not purified), which upon reduction with lithium aluminum hydride in tetrahydrofuran, followed by hydrolysis, afforded the intermediate *rac*-**17** (isolated as crude product; not purified). Successive treatment of *rac*-**17** with hydrochloric acid and a solution of sodium hydroxide in methanol/water finally gave *rac*-**2b** (yield 42%). The carboxylic acid **15** was obtained by reaction of 2-(1-(4-bromophenyl)-1-methylethyl)-4,4-dimethyl-4,5-dihydro-1,3-oxazole[10] (**18**) with magnesium in diethyl ether, followed by treatment with butanedioic acid anhydride in diethyl ether and subsequent hydrolysis with hydrochloric acid (yield 43%).

Sila-azacyclonol (**3b**) and *N*-methyl-sila-azacyclonol (**4b**) were prepared according to Scheme 5. The silanol **3b** was obtained by hydrolysis of the methoxysilane **8** in acetone (yield 91%). Compound **4b** was prepared by a two-step synthesis, starting from dimethoxydiphenyl-

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(6) Synthesis of **5**: Lickiss, P. D.; Lucas, R. *J. Organomet. Chem.* **1996**, *510*, 167−172.

(7) Synthesis of **9**: Jackson, R. A.; Rhodes, C. J. *J. Chem. Soc., Perkin Trans. 2* **1993**, 53−57.

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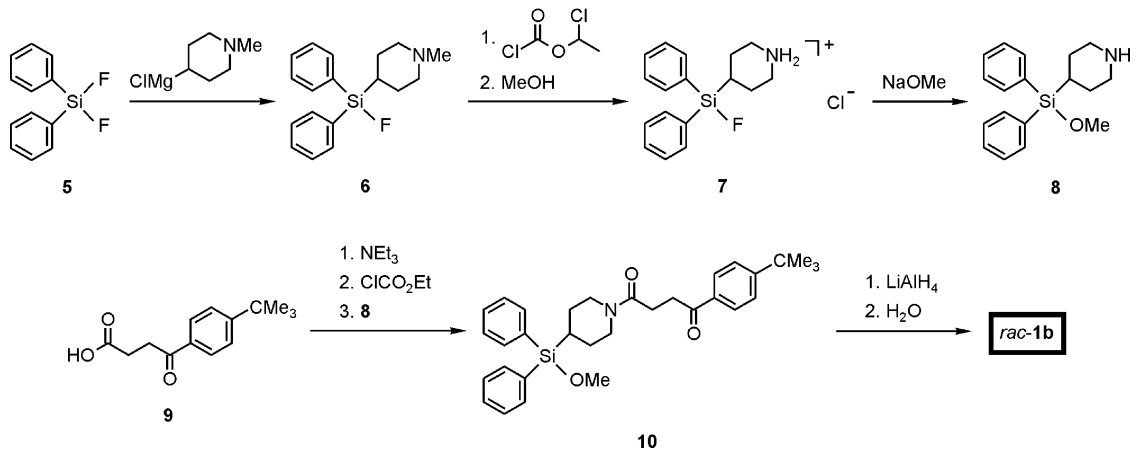
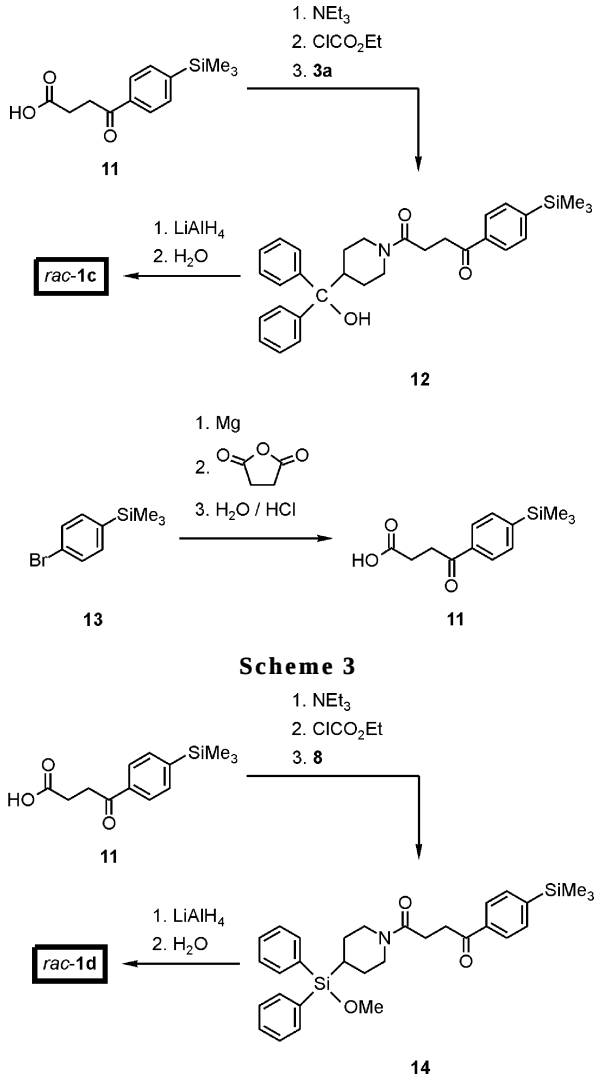
Scheme 1

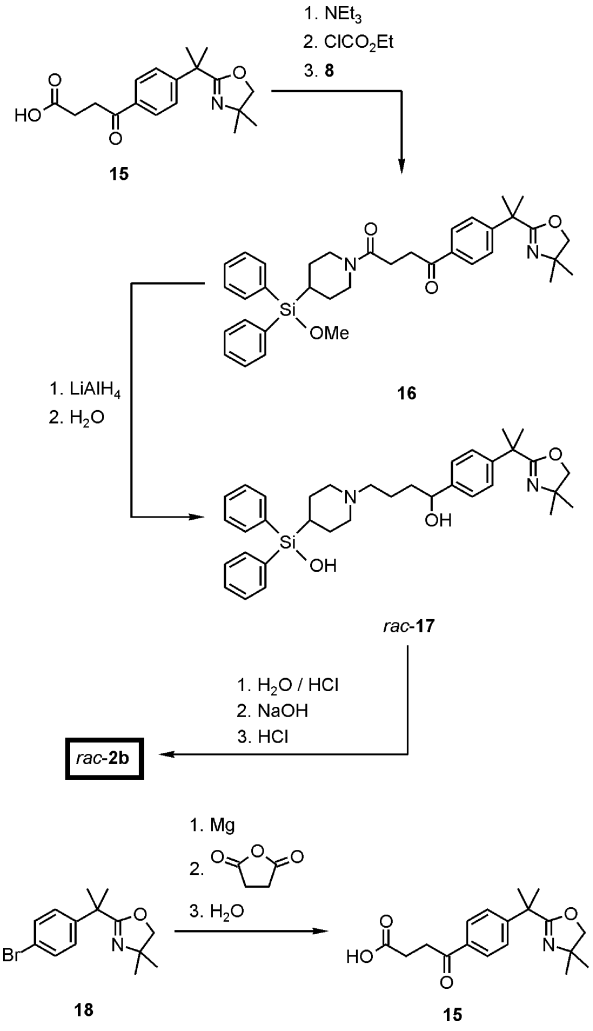


Scheme 2



Scheme 3

Scheme 4



silane (**19**). Thus, treatment of **19** with (1-methylpiperidin-4-yl)magnesium chloride in tetrahydrofuran gave methoxy(1-methylpiperidin-4-yl)diphenylsilane (**20**) (yield 69%), which upon hydrolysis in acetone gave **4b** (yield 85%).

Compounds **6** and **20** were isolated as liquids, whereas *rac*-**1b**, *rac*-**1c**, *rac*-**1d**, *rac*-**2b**, **3b**, **4b**, **7**, **8**, **11**, and **15** were obtained as solids. The identities of all compounds were established by elemental analyses (C, H, N) and NMR studies (^{1}H, ^{13}C, ^{19}F, ^{29}Si). In addition, the crystal structures of **4b**·CH_2Cl_2, **7**, and **8** were determined.

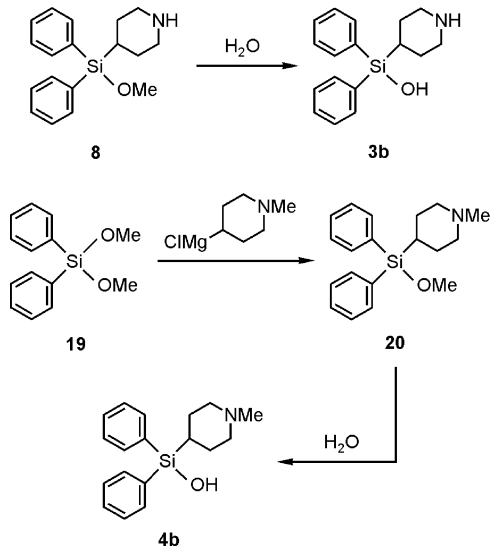
Crystal Structure Analyses. To get some structural information about the C/Si-analogous (1-organylpiperidin-4-yl)diphenylmethanol and -silanol skeletons of the title compounds, the C/Si analogues **4a** and **4b** (studied as the solvate **4b**·CH_2Cl_2) were structurally characterized by single-crystal X-ray diffraction. In addition, crystal structure analyses of the precursors **7** and **8** were

Table 1. Crystal Data and Experimental Parameters for the Crystal Structure Analyses of 4a, 4b·CH_2Cl_2, 7, and 8

	4a	**4b**·CH_2Cl_2	**7**	**8**
empirical formula	$C_{19}H_{23}NO$	$C_{19}H_{25}Cl_2NOSi$	$C_{17}H_{21}ClFNSi$	$C_{18}H_{23}NOSi$
formula mass, g mol^{-1}	281.38	382.39	321.89	297.46
collection T, K	173(2)	173(2)	173(2)	173(2)
λ(Mo Kα), Å	0.71073	0.71073	0.71073	0.71073
cryst syst	monoclinic	monoclinic	monoclinic	triclinic
space group (no.)	$P2_1/n$ (14)	$P2_1/c$ (14)	$C2$ (5)	$P\bar{1}$ (2)
a, Å	9.1459(18)	19.236(4)	21.771(4)	9.2055(15)
b, Å	16.091(3)	11.537(2)	5.9011(12)	9.3204(15)
c, Å	11.469(2)	20.081(4)	14.810(3)	11.599(2)
α, deg	90	90	90	79.20(2)
β, deg	105.63(3)	111.39(3)	117.84(3)	68.567(19)
γ, deg	90	90	90	62.134(17)
V, Å^3	1625.4(6)	4149.6(14)	1682.4(6)	818.8(2)
Z	4	8	4	2
D(calcd), g cm^{-3}	1.150	1.224	1.271	1.207
μ, mm^{-1}	0.070	0.376	0.301	0.143
F(000)	608	1616	680	320
cryst dimens, mm	0.5 × 0.4 × 0.4	0.4 × 0.3 × 0.3	0.4 × 0.3 × 0.3	0.4 × 0.3 × 0.2
2θ range, deg	4.48−46.56	4.12−44.00	6.22−52.74	5.28−56.00
index ranges	$-10 \le h \le 10$, $-17 \le k \le 17$, $-12 \le l \le 12$	$-20 \le h \le 20$, $-8 \le k \le 12$, $-21 \le l \le 21$	$-26 \le h \le 26$, $-7 \le k \le 7$, $-18 \le l \le 18$	$-12 \le h \le 12$, $-11 \le k \le 11$, $-15 \le l \le 15$
no. of collected reflns	14 649	12 174	10 877	10 717
no. of indep reflns	2326	4877	3408	3636
R_{int}	0.0910	0.0640	0.0806	0.0446
no. of reflns used	2326	4877	3408	3636
no. of restraints	0	0	1	0
no. of params	188	435	196	200
S[a]	0.852	0.828	0.953	1.067
weight params a/b[b]	0.0396/0.0000	0.0323/0.0000	0.0352/0.0000	0.0493/0.1399
$R1$[c] [$I > 2\sigma(I)$]	0.0372	0.0408	0.0305	0.0351
$wR2$[d] (all data)	0.0844	0.0831	0.0732	0.0972
max/min residual electron density, e Å^{-3}	+0.122/−0.124	+0.505/−0.381	+0.194/−0.264	+0.268/−0.275

[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 5



performed. The crystal data and the experimental parameters used for the crystal structure analyses are summarized in Table 1. The molecular structures of **4a**, **4b**, **7**, and **8** are depicted in Figures 1−4. Selected interatomic distances and angles are listed in the respective figure captions. In the crystal of **4b**·CH_2Cl_2, there are two silanol molecules (molecules I and II) in the asymmetric unit that differ only slightly from each other, whereas the structure of the carbon analogue **4a** is quite different. As is obvious from Figures 1 and 2, these different molecular structures of the C/Si analogues are due to quite different hydrogen-bonding systems in the crystals of **4a** and **4b**·CH_2Cl_2.[11] The bond distances and angles of **4a**, **4b**·CH_2Cl_2, **7**, and **8** are within the normal range and do not need further comments.

Pharmacological Studies. The pharmacological profiles of *rac*-**1a**, *rac*-**1b**, *rac*-**1c**, *rac*-**1d**, *rac*-**2a**, and *rac*-**2b** were assessed across a range of histamine receptor binding assays (radioligand binding studies at histamine central H_1, peripheral H_1, H_2, and H_3 receptors). The data are summarized in Table 2. As an example, receptor binding of the four analogues *rac*-**1a**, *rac*-**1b**, *rac*-**1c**, and *rac*-**1d** at histamine central H_1 receptors is shown in Figure 5.

When comparing *rac*-**1b**, *rac*-**1c**, and *rac*-**1d** with *rac*-**1a**, and *rac*-**2b** with *rac*-**2a**, the silicon compounds, within experimental variation, exhibit an affinity and selectivity profile similar to their corresponding carbon analogues. These data suggest that sila-substitution of the quaternary carbon atoms of terfenadine (R_3COH, R_4C) and fexofenadine (R_3COH) has not significantly affected the in vitro pharmacological profile; that is, there are strongly pronounced bioisosteric relationships between the respective C/Si analogues. Future studies

(11) The hydrogen-bonding system of **4a** was analyzed by using the program *PLATON*: Spek, A. L. *PLATON*; University of Utrecht: Utrecht, The Netherlands, 1998. The hydrogen-bonding system of **4b**·CH_2Cl_2 was analyzed by using the program *SHELXL-97*; see ref 12. In this context, see also: Jeffrey, G. A.; Saenger, W. *Hydrogen Bonding in Biological Structures*; Springer-Verlag: Berlin, Germany, 1991; pp 15−24.

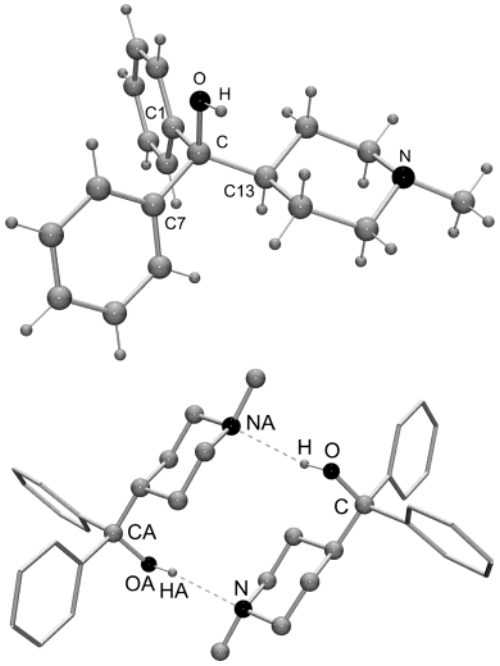


Figure 1. Molecular structure of **4a** in the crystal (top). Selected interatomic distances (Å) and angles (deg): C−C1 1.536(3), C−C7 1.536(2), C−C13 1.552(3), C−O 1.430(2), C1−C−C7 108.43(14), C1−C−C13 109.27(15), C1−C−O 106.15(16), C7−C−C13 113.21(16), C7−C−O 109.61(14), C13−C−O 109.92(15). The molecules form intermolecular O−H···N hydrogen bonds (O−H 0.87(3), H···N 2.15(3), O···N 2.883(2), O−H···N 141(2)), resulting in the formation of centrosymmetric dimers (bottom).

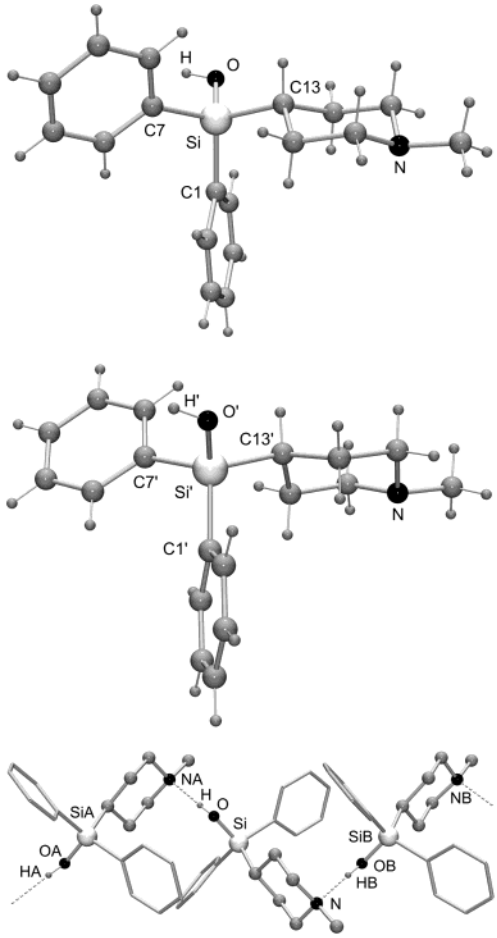


Figure 2. Structures of molecules I (top) and II (middle) in the crystal of **4b**·CH_2Cl_2. Selected interatomic distances (Å) and angles (deg), molecule I: Si−C1 1.866(4), Si−C7 1.884(3), Si−C13 1.866(4), Si−O 1.636(3), C1−Si−C7 109.73(16), C1−Si−C13 109.54(18), C1−Si−O 109.68(15), C7−Si−C13 109.53(16), C7−Si−O 111.72(16), C13−Si−O 106.58(14); molecule II: Si′-C1′ 1.883(4), Si′−C7′ 1.871(4), Si′−C13′ 1.876(3), Si′−O′ 1.631(3), C1′−Si′−C7′ 109.85(16), C1′−Si′−C13′ 109.77(17), C1′−Si′−O′ 109.08(15), C7′−Si′−C13′ 110.69(15), C7′−Si′−O′ 110.83(16), C13′−Si′−O′ 106.55(15). Molecules I and II each form intermolecular O−H···N hydrogen bonds (O−H 0.844, H···N 1.895, O···N 2.738, O−H···N 177.72; O′−H′ 0.807, H′···N′ 1.922, O′···N′ 2.729, O′−H′···N′ 178.50), resulting in the formation of infinite chains along [0 1 0] (bottom, hydrogen-bonding system of molecule I).

will evaluate the effects of the carbon/silicon switch in vivo as well as assess any impact on hERG channel affinity in vitro, and these data will be reported elsewhere.

Experimental Section

General Procedures. Except for the preparations of **3b** and **4b**, all syntheses were carried out under dry nitrogen. Tetrahydrofuran (THF), diethyl ether, *n*-pentane, methanol, and dichloromethane were dried and purified according to standard procedures and stored under nitrogen. Melting points were determined with a Büchi melting point B-540 apparatus in open glass capillaries and are uncorrected. ^{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 $CDCl_3$, CD_2Cl_2, CD_3OD, 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 $CHDCl_2$ (^{1}H, δ 5.32; CD_2Cl_2), internal CHD_2OD (^{1}H, δ 3.30; CD_3OD), internal [D_5]DMSO (^{1}H, δ 2.49; [D_6]DMSO), internal $CDCl_3$ (^{13}C, δ 77.0; $CDCl_3$), internal CD_2Cl_2 (^{13}C, δ 53.8; CD_2Cl_2), internal CD_3OD (^{13}C, δ 49.0; CD_3OD), internal [D_6]DMSO (^{13}C, δ 39.5; [D_6]DMSO), external $CFCl_3$ (^{19}F, δ 0), or external TMS (^{29}Si, δ 0). Assignment of the ^{1}H NMR data was supported by ^{1}H,^{1}H COSY experiments, and assignment of the ^{13}C NMR data was supported by DEPT 135 and ^{13}C,^{1}H COSY experiments.

Preparation of *rac*-(1-(4-(4-*tert*-Butylphenyl)-4-hydroxybutyl)piperidin-4-yl)diphenylsilanol (*rac*-Sila-terfenadine-A, *rac*-1b). Triethylamine (1.37 g, 13.5 mmol) was added dropwise at −40 °C within 5 min to a stirred solution of **9** (1.08 g, 4.61 mmol) in THF (20 mL). Subsequently, ethyl chloroformate (500 mg, 4.61 mmol) was added dropwise at the same temperature within 1 min, and the resulting mixture was then warmed within 10 min to −20 °C and stirred for 30 min. Subsequently, a solution of **8** (1.37 g, 4.61 mmol) in THF (5 mL) was added dropwise at −20 °C within 1 min, and the resulting mixture was then warmed to 20 °C and stirred for 16 h. Diethyl ether (70 mL) and water (16 mL) were added, and the two-phase mixture was stirred at 20 °C for 30 min. The aqueous phase was separated and discarded, and the organic layer was washed successively with hydrochloric acid (5%, 16 mL) and saturated brine (16 mL) and was then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue (consisting of **10**; crude product, not further purified) was dissolved in THF (30 mL). This solution was added dropwise at 0 °C within 1 h to a stirred suspension of lithium aluminum hydride (LAH) (740 mg, 19.5 mmol) in THF (10 mL). After the mixture was stirred at 20 °C for 1 h, a solution of potassium sodium tartrate (3.15 g, 15.0 mmol) in water (30 mL) was added dropwise at 0 °C within 30 min, and the mixture was then stirred at 20 °C for

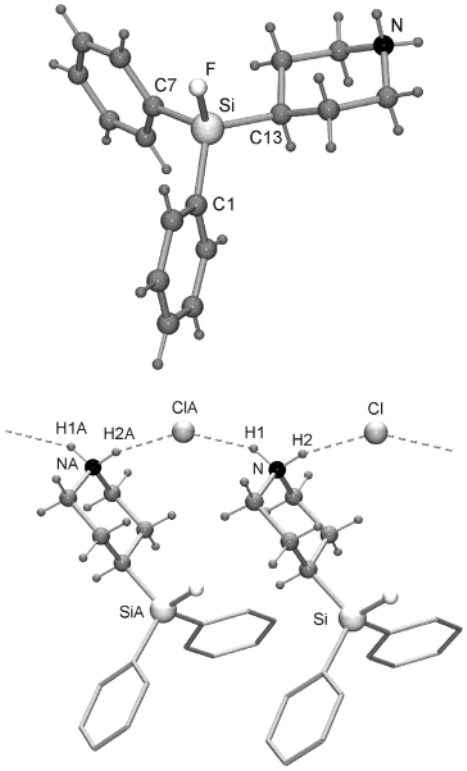


Figure 3. Structure of the cation in the crystal of **7** (top). Selected interatomic distances (Å) and angles (deg): Si−C1 1.862(2), Si−C7 1.860(2), Si−C13 1.872(2), Si−F 1.6084(13), C1−Si−C7 111.51(9), C1−Si−C13 110.74(9), C1−Si−F 106.29(8), C7−Si−C13 113.43(9), C7−Si−F 106.78(8), C13−Si−F 107.68(8). The cations and anions form intermolecular N−H···Cl hydrogen bonds (N−H1 0.94(3), H1···ClA 2.26(3), N···ClA 3.121(2), N−H1···ClA 153(3); N−H2 0.91(3), H2···Cl 2.26(3), N···Cl 3.147(2), N−H2···Cl 166(3)), resulting in the formation of infinite chains along [0 1 0] (bottom).

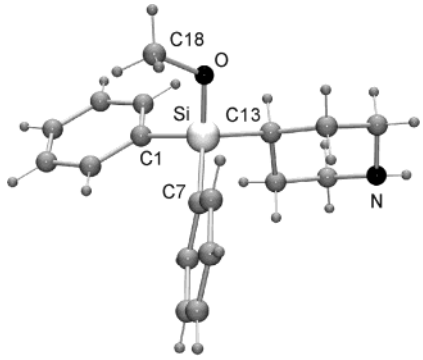


Figure 4. Molecular structure of **8** in the crystal. Selected interatomic distances (Å) and angles (deg): Si−C1 1.8737(14), Si−C7 1.8709(14), Si−C13 1.8726(12), Si−O 1.6478(10), C18−O 1.4256(16), C1−Si−C7 109.47(6), C1−Si−C13 110.31(6), C1−Si−O 110.95(5), C7−Si−C13 112.55(6), C7−Si−O 109.25(6), C13−Si−O 104.22(5), Si−O−C18 123.46(8).

16 h, followed by extraction with ethyl acetate (40 mL). The organic phase was dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure, and the solid residue was recrystallized from diethyl ether at −20 °C to give *rac*-**1b** in 62% yield as a colorless crystalline solid (1.40 g, 2.87 mmol); mp 88 °C. ^{1}H NMR ([D$_6$]DMSO): δ 1.00−1.13 (m, 1 H, SiC*H*), 1.24 (s, 9 H, CC*H*$_3$), 1.26−1.58 (m, 8 H, NCH$_2$C*H*$_2$CH, NCH$_2$C*H*$_2$C*H*$_2$CH), 1.65−1.74 and 2.72−2.81 (m, 4 H, NC*H*$_2$-CH$_2$CH), 2.12−2.17 (m, 2 H, NC*H*$_2$CH$_2$CH$_2$CH), 4.38−4.44 (m, 1 H, C*H*OH), 5.3 (br s, 1 H, CO*H*), 6.53 (s, 1 H, SiO*H*), 7.16−7.29 (m, 4 H, C$_6$*H*$_4$), 7.30−7.38 and 7.53−7.59 (m, 10 H, SiC$_6$*H*$_5$). ^{13}C NMR (CDCl$_3$): δ 23.0 (Si*C*H), 23.8 (NCH$_2$*C*H$_2$-CH$_2$CH), 25.5 (NCH$_2$*C*H$_2$CH), 25.6 (NCH$_2$*C*H$_2$CH), 31.4 (*C*CH$_3$), 34.3 (*C*CH$_3$), 39.8 (NCH$_2$CH$_2$*C*H$_2$CH), 54.5 (N*C*H$_2$CH$_2$CH), 55.9 (N*C*H$_2$CH$_2$CH), 59.2 (N*C*H$_2$CH$_2$CH$_2$CH), 73.2 (NCH$_2$CH$_2$-CH$_2$*C*H), 124.9 (*C*-2/*C*-6 or *C*-3/*C*-5, C$_6$H$_4$), 125.3 (*C*-2/*C*-6 or *C*-3/*C*-5, C$_6$H$_4$), 127.66 (*C*-3/*C*-5, SiC$_6$H$_5$), 127.68 (*C*-3/*C*-5, SiC$_6$H$_5$), 129.40 (*C*-4, SiC$_6$H$_5$), 129.42 (*C*-4, SiC$_6$H$_5$), 134.2 (*C*-2/*C*-6, SiC$_6$H$_5$), 134.3 (*C*-2/*C*-6, SiC$_6$H$_5$), 135.7 (*C*-1, SiC$_6$H$_5$), 135.8 (*C*-1, SiC$_6$H$_5$), 142.5 (*C*-1 or *C*-4, C$_6$H$_4$), 149.3 (*C*-1 or *C*-4, C$_6$H$_4$). ^{29}Si NMR (CDCl$_3$): δ −8.3. Anal. Calcd for C$_{31}$H$_{41}$-NO$_2$Si: C, 76.34; H, 8.47; N, 2.87. Found: C, 76.1; H, 8.3; N, 3.0.

Table 2. Binding Profiles of Compounds *rac*-1a, *rac*-1b, *rac*-1c, *rac*-1d, *rac*-2a, and *rac*-2b at Histamine Central H_1 and Peripheral H_1, H_2, and H_3 Receptors[a]

compd	$H_{1\ central}$	$H_{1\ peripheral}$	H_2	H_3
rac-**1a**	1.5	0.5	11.0	4% at 100 μM
rac-**1b**	0.3	1.9	1.8	60% at 100μM
rac-**1c**	0.6	0.4	7.9	5% at 100 μM
rac-**1d**	0.4	0.6	5.1	13% at 100 μM
rac-**2a**	0.9	3.4	0% at 1 μM	14% at 1 μM
rac-**2b**	0.3	1.3	4% at 1 μM	6% at 1 μM

[a] Data expressed as K_i values (μM) or percent inhibition of binding. Data represent the mean of at least two determinations.

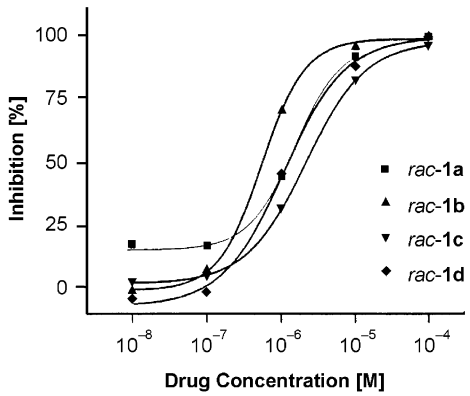


Figure 5. Representative examples of binding curves obtained for compounds *rac*-**1a**, *rac*-**1b**, *rac*-**1c**, and *rac*-**1d** at histamine central H_1 receptors (tissue, guinea pig cerebellum; radioligand, [^{3}H]pyrilamine; for further details, see Experimental Section).

Preparation of *rac*-(1-(4-Hydroxy-4-(4-(trimethylsilyl)-phenyl)butyl)piperidin-4-yl)diphenylmethanol (*rac*-Silaterfenadine-B, *rac*-1c). This compound was prepared analogously to the synthesis of *rac*-**1b** by addition of triethylamine (1.67 g, 16.5 mmol) and ethyl chloroformate (600 mg, 5.53 mmol) to a solution of **11** (1.38 g, 5.51 mmol) in THF (20 mL), followed by treatment with a solution of **3a** (1.47 g, 5.50 mmol) in THF (10 mL). The resulting amide **12** (crude product, not further purified) was dissolved in THF (20 mL), and the solution was then added to a suspension of LAH (380 mg, 10.0 mmol) in THF (10 mL), followed by treatment with a solution of potassium sodium tartrate (2.23 g, 10.6 mmol) in water (30 mL). The resulting solid crude product was recrystallized from diethyl ether at −20 °C to give *rac*-**1c** in 67% yield as a colorless crystalline solid (1.81 g, 3.71 mmol); mp 164 °C. ^{1}H NMR ([D$_6$]DMSO): δ 0.21 (s, 9 H, SiC*H*$_3$), 1.15−1.58 (m, 8 H, NCH$_2$C*H*$_2$CH, NCH$_2$C*H*$_2$C*H*$_2$CH), 1.75−1.86 and 2.71−2.83 (m, 4 H, NC*H*$_2$CH$_2$CH), 2.14−2.21 (m, 2 H, NC*H*$_2$CH$_2$CH$_2$CH), 2.38−2.48 (m, 1 H, C$_6$H$_5$CC*H*), 4.41−4.50 (m, 1 H, C*H*OH), 5.22 (s, 1 H, C$_6$H$_5$CHO*H*), 5.4 (br s, 1 H, CO*H*), 7.09−7.13 (m,

4 H, C_6H_4), 7.22−7.32 and 7.41−7.51 (m, 10 H, C_6H_5). ^{13}C NMR ($CDCl_3$): δ −1.1 (SiCH_3), 23.8 ($NCH_2CH_2CH_2CH$), 25.7 (NCH_2CH_2CH), 25.8 (NCH_2CH_2CH), 39.5 ($NCH_2CH_2CH_2CH$), 44.1 (C_6H_5CCH), 53.3 (NCH_2CH_2CH), 54.5 (NCH_2CH_2CH), 58.7 ($NCH_2CH_2CH_2CH$), 73.5 ($NCH_2CH_2CH_2CH$), 79.2 (C_6H_5C), 125.1 (*C*-2/*C*-6 or *C*-3/*C*-5, C_6H_4), 125.6 (*C*-3/*C*-5, C_6H_5), 125.7 (*C*-3/*C*-5, C_6H_5), 126.42 (*C*-4, C_6H_5), 126.44 (*C*-4, C_6H_5), 128.1 (*C*-2/*C*-6, C_6H_5), 128.2 (*C*-2/*C*-6, C_6H_5), 133.2 (*C*-2/*C*-6 or *C*-3/*C*-5, C_6H_4), 138.4 (*C*-1 or *C*-4, C_6H_4), 145.95 (*C*-1, C_6H_5), 146.04 (*C*-1, C_6H_5), 146.4 (*C*-1 or *C*-4, C_6H_4). ^{29}Si NMR ($CDCl_3$): δ −4.4. Anal. Calcd for $C_{31}H_{41}NO_2Si$: C, 76.34; H, 8.47; N, 2.87. Found: C, 76.0; H, 8.2; N, 2.9.

Preparation of *rac*-(1-(4-Hydroxy-4-(4-(trimethylsilyl)-phenyl)butyl)piperidin-4-yl)diphenylsilanol (*rac*-Disila-terfenadine, *rac*-1d). This compound was prepared analogously to the synthesis of *rac*-**1b** by addition of triethylamine (1.59 g, 15.7 mmol) and ethyl chloroformate (570 mg, 5.25 mmol) to a solution of **11** (1.31 g, 5.23 mmol) in THF (20 mL), followed by treatment with a solution of **8** (1.56 g, 5.24 mmol) in THF (5 mL). The resulting amide **14** (crude product, not further purified) was dissolved in THF (20 mL), and the solution was then added to a suspension of LAH (400 mg, 10.5 mmol) in THF (10 mL), followed by treatment with a solution of potassium sodium tartrate (2.35 g, 11.2 mmol) in water (30 mL). The resulting solid crude product was recrystallized from diethyl ether at −20 °C to give *rac*-**1d** in 32% yield as a colorless crystalline solid (840 mg, 1.67 mmol); mp 80 °C. ^{1}H NMR ([D_6]DMSO): δ 0.21 (s, 9 H, SiCH_3), 1.01−1.12 (m, 1 H, Si*CH*), 1.28−1.57 (m, 8 H, NCH_2CH_2CH, $NCH_2CH_2CH_2CH$), 1.67−1.77 and 2.73−2.83 (m, 4 H, NCH_2CH_2CH), 2.12−2.19 (m, 2 H, $NCH_2CH_2CH_2CH$) 4.42−4.48 (m, 1 H, C*H*OH), 5.4 (br s, 1 H, CO*H*), 6.53 (s, 1 H, SiO*H*), 7.24−7.28 (m, 4 H, C_6H_4), 7.32−7.43 and 7.54−7.59 (m, 10 H, SiC_6H_5). ^{13}C NMR ($CDCl_3$): δ −1.2 (SiCH_3), 23.0 (Si*C*H), 23.8 ($NCH_2CH_2CH_2CH$), 25.5 (NCH_2CH_2CH), 25.6 (NCH_2CH_2CH), 39.9 ($NCH_2CH_2CH_2CH$), 54.6 (NCH_2CH_2CH), 55.9 (NCH_2CH_2CH), 59.3 ($NCH_2CH_2CH_2CH$), 73.4 ($NCH_2CH_2CH_2CH$), 125.1 (*C*-2/*C*-6 or *C*-3/*C*-5, C_6H_4), 127.71 (*C*-3/*C*-5, SiC_6H_5), 127.73 (*C*-3/*C*-5, SiC_6H_5), 129.46 (*C*-4, SiC_6H_5), 129.48 (*C*-4, SiC_6H_5), 133.1 (*C*-2/*C*-6 or *C*-3/*C*-5, C_6H_4), 134.30 (*C*-2/*C*-6, SiC_6H_5), 134.32 (*C*-2/*C*-6, SiC_6H_5), 135.8 (*C*-1, SiC_6H_5), 135.9 (*C*-1, SiC_6H_5), 138.3 (*C*-1 or *C*-4, C_6H_4), 146.3 (*C*-1 or *C*-4, C_6H_4). ^{29}Si NMR ($CDCl_3$): δ −4.2 (*Si*CH_3), −8.3 (*Si*O). Anal. Calcd for $C_{30}H_{41}NO_2Si_2$: C, 71.52; H, 8.20; N, 2.78. Found: C, 71.0; H, 8.0; N, 2.9.

Preparation of *rac*-(1-(4-(4-(1-Carboxy-1-methylethyl)-phenyl)-4-hydroxybutyl)piperidin-4-yl)diphenylsilanol (*rac*-Sila-fexofenadine, *rac*-2b). Triethylamine (4.26 g, 42.1 mmol) was added dropwise at −20 °C within 5 min to a stirred solution of **6** (4.16 g, 13.1 mmol) in THF (55 mL). Subsequently, ethyl chloroformate (1.42 g, 13.1 mmol) was added dropwise at the same temperature within 1 min, and the resulting mixture was then stirred at −20 °C for 30 min. A solution of **4** (3.90 g, 13.1 mmol) in THF (15 mL) was added dropwise at −20 °C within 1 min, and the resulting mixture was then warmed to 20 °C and stirred for 16 h. The precipitate was separated by centrifugation and discarded, and the solvent of the supernatant was removed under reduced pressure. The solid residue (consisting of **8**; crude product, not further purified) was dissolved in THF (100 mL), and the resulting solution was added dropwise at 0 °C within 1 h to a stirred suspension of LAH (2.23 g, 58.8 mmol) in THF (25 mL). After the mixture was stirred at 0 °C for 1 h, a solution of potassium sodium tartrate (6.97 g, 33.2 mmol) in water (65 mL) was added dropwise at 0 °C within 30 min, and the mixture was stirred at 20 °C for 16 h, followed by addition of ethyl acetate (100 mL). The organic phase was separated and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. Water (30 mL) was added to the solid residue (consisting of *rac*-**9**; crude product, not further purified), followed by addition of 4 M hydrochloric acid (30 mL; after the addition of the first few drops, the solid dissolved), and the mixture was then kept undisturbed at 20 °C for 3 h. The resulting oily precipitate was separated by decantation, dried in vacuo, and dissolved in methanol (55 mL), followed by addition of a solution of sodium hydroxide (21.2 g, 530 mmol) in water (55 mL). The mixture was heated under reflux for 4 days, the solvents were removed under reduced pressure, and the remaining solid was dissolved in water (60 mL), followed by addition of 12 M hydrochloric acid (ca. 45 mL) until a pH of 8 was achieved. The precipitate was isolated by centrifugation, washed with water, and dried in vacuo. The remaining product was redissolved in methanol (10 mL), and the solution was then kept at −20 °C for 2 days to give *rac*-**7** in 42% yield as a colorless solid (2.86 g, 5.52 mmol). ^{1}H NMR ([D_6]DMSO/(DCl in D_2O (37%)) (50:1 (v/v))): δ 1.25−1.49 (m, 7 H, Si*CH*, CCH_3), 1.50−1.90 (m, 8 H, NCH_2CH_2CH, $NCH_2CH_2CH_2CH$), 2.70−2.85 and 3.32−3.40 (m, 4 H, NCH_2CH_2CH), 2.89−2.98 (m, 2 H, $NCH_2CH_2CH_2CH$), 4.45−4.53 (m, 1 H, C*H*OH), 7.25−7.42 and 7.54−7.62 (m, 14 H, C_6H_4, SiC_6H_5). ^{13}C NMR ([D_6]DMSO/(DCl in D_2O (37%)) (50:1 (v/v))): δ 19.8 ($NCH_2CH_2CH_2CH$), 20.8 (Si*C*H), 23.6 (NCH_2CH_2CH), 26.5 (CCH_3), 36.0 ($NCH_2CH_2CH_2CH$), 45.5 (CCH_3), 52.7 (NCH_2CH_2CH), 56.4 ($NCH_2CH_2CH_2CH$), 71.2 ($NCH_2CH_2CH_2CH$), 125.3 (*C*-2/*C*-6 or *C*-3/*C*-5, C_6H_4), 125.7 (*C*-2/*C*-6 or *C*-3/*C*-5, C_6H_4), 127.9 (*C*-3/*C*-5, SiC_6H_5), 129.7 (*C*-4, SiC_6H_5), 134.2 (*C*-2/*C*-6, SiC_6H_5), 135.6 (*C*-1, SiC_6H_5), 143.5 (*C*-1 or *C*-4, C_6H_4), 144.0 (*C*-1 or *C*-4, C_6H_4), 177.6 (*C*═O). ^{29}Si NMR ([D_6]DMSO/(DCl in D_2O (37%)) (50:1 (v/v))): δ −11.0. Anal. Calcd for $C_{31}H_{39}NO_4Si$: C, 71.92; H, 7.59; N, 2.71. Found: C, 71.2; H, 7.6; N, 2.8.

Preparation of Diphenyl(piperidin-4-yl)methanol (Aza-cyclonol, 3a). This compound was synthesized according to ref 8.

Preparation of Diphenyl(piperidin-4-yl)silanol (Sila-azacyclonol, 3b). A solution of **8** (450 mg, 1.51 mmol) in acetone/water (5:1 (v/v)) (12 mL) was kept undisturbed at 20 °C for 5 days. The resulting precipitate was isolated by filtration, washed with acetone (5 mL), and then dried in vacuo to give **3b** in 91% yield as a colorless crystalline solid (390 mg, 1.38 mmol); mp 213 °C (dec). ^{1}H NMR ([D_6]DMSO/(DCl in D_2O (37%)) (50:1 (v/v))): δ 1.35−1.48 (m, 1 H, Si*CH*), 1.49−1.72 (m, 4 H, NCH_2CH_2CH), 2.69−2.82 and 3.10−3.18 (m, 4 H, NCH_2CH_2CH), 7.29−7.41 and 7.50−7.57 (m, 10 H, SiC_6H_5). ^{13}C NMR ([D_6]DMSO/(DCl in D_2O (37%)) (50:1 (v/v))): δ 21.1 (Si*C*H), 23.2 (NCH_2CH_2CH), 44.7 (NCH_2CH_2CH), 128.4 (*C*-3/*C*-5, SiC_6H_5), 130.2 (*C*-4, SiC_6H_5), 134.5 (*C*-2/*C*-6, SiC_6H_5), 136.0 (*C*-1, SiC_6H_5). ^{29}Si NMR ([D_6]DMSO/(DCl in D_2O (37%)) (50:1 (v/v))): δ −10.8. Anal. Calcd for $C_{17}H_{21}NOSi$: C, 72.04; H, 7.47; N, 4.94. Found: C, 71.8; H, 7.5; N, 4.9.

Preparation of (1-Methylpiperidin-4-yl)diphenylmethanol (*N*-Methyl-azacyclonol, 4a). This compound was synthesized according to ref 8.

Preparation of (1-Methylpiperidin-4-yl)diphenylsilanol (*N*-Methyl-sila-azacyclonol, 4b). A solution of **20** (1.00 g, 3.21 mmol) in acetone/hydrochloric acid (10%) (5:1 (v/v)) (12 mL) was stirred at 20 °C for 1 h. Diethyl ether (20 mL) and a saturated aqueous sodium hydrogencarbonate solution (20 mL) were added, and the organic phase was separated and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the solid residue was recrystallized from dichloromethane at −20 °C (crystallization of **4b**·CH_2Cl_2). To remove the solvent, the solvate was dried in vacuo to give **4b** in 85% yield as a colorless solid (816 mg, 2.74 mmol). ^{1}H NMR (CD_2Cl_2): δ 0.99−1.12 (m, 1 H, Si*CH*), 1.50−1.83 and 2.75−2.85 (m, 8 H, NCH_2CH_2CH), 2.08 (s, 3 H, NCH_3), 6.2 (br s, 1 H, SiO*H*), 7.21−7.32 and 7.46−7.55 (m, 10 H, SiC_6H_5). ^{13}C NMR (CD_2Cl_2): δ 23.0 (Si*C*H), 26.7 (NCH_2CH_2CH), 47.2 (NCH_3), 57.8 (NCH_2CH_2CH), 128.5 (*C*-3/*C*-5, SiC_6H_5), 130.2 (*C*-4, C_6H_5), 135.0 (*C*-2/*C*-6, C_6H_5), 137.3 (*C*-1, C_6H_5). ^{29}Si NMR (CD_2Cl_2): δ −9.7. Anal. Calcd for $C_{18}H_{23}NOSi$: C, 72.68; H, 7.79; N, 4.71. Found: C, 72.5; H, 7.7; N, 4.7.

Difluorodiphenylsilane (5). This compound was synthesized according to ref 6.

Preparation of Fluoro(1-methylpiperidin-4-yl)diphenylsilane (6). A mixture of magnesium turnings (2.84 g, 117 mmol) and iodine (500 mg, 3.94 mmol) was heated at 80 °C for 30 min in a sealed flask and was then cooled to 20 °C, followed by successive addition of THF (4 mL) and 4-chloro-1-methylpiperidine (1.00 g, 7.48 mmol). After the reaction had started (reflux), a solution of 4-chloro-1-methylpiperidine (12.3 g, 92.1 mmol) in THF (40 mL) was added dropwise in such a way that the solvent refluxed permanently. The mixture was stirred under reflux for a further 2 h and was then added dropwise at 20 °C within 1 h to a stirred solution of **5** (22.0 g, 99.9 mmol) in THF (200 mL). After the resulting mixture was stirred at 20 °C for 16 h, *n*-pentane (200 mL) was added, and the precipitate was filtered off and discarded. The solvent of the filtrate was removed under reduced pressure, and the residue was distilled in a Kugelrohr apparatus (oven temperature 195 °C, 0.01 mbar) to give **6** in 65% yield as a colorless oily liquid (19.3 g, 64.4 mmol). ^{1}H NMR ($CDCl_3$): δ 1.15−1.28 (m, 1 H, SiC*H*), 1.55−1.76 (m, 4 H, NCH_2CH_2CH), 1.80−1.92 and 2.78−2.86 (m, 4 H, NCH_2CH_2CH), 2.18 (s, 3 H, NCH_3), 7.29−7.41 and 7.53−7.58 (m, 10 H, SiC_6H_5). ^{13}C NMR ($CDCl_3$): δ 22.1 (d, $^2J_{CF}$ = 14.2 Hz, Si*C*H), 25.7 (NCH_2CH_2-CH), 46.7 (NCH_3), 57.0 (NCH_2CH_2CH), 128.0 (*C*-3/*C*-5, SiC_6H_5), 130.6 (*C*-4, SiC_6H_5), 132.1 (d, $^2J_{CF}$ = 15.3 Hz, *C*-1, SiC_6H_5), 134.4 (d, $^3J_{CF}$ = 2.2 Hz, *C*-2/*C*-6, SiC_6H_5). ^{19}F NMR ($CDCl_3$): δ −177.7. ^{29}Si NMR ($CDCl_3$): δ 4.3 (d, $^1J_{SiF}$ = 288.3 Hz). Anal. Calcd for $C_{18}H_{22}FNSi$: C, 72.20; H, 7.40; N, 4.68. Found: C, 72.5; H, 7.4; N, 4.6.

Preparation of 4-(Fluorodiphenylsilyl)piperidinium Chloride (7). 1-Chloroethyl chloroformate (14.3 g, 100 mmol) was added dropwise at 0 °C within 10 min to a stirred solution of **6** (15.0 g, 50.1 mmol) in dichloromethane (75 mL). The mixture was stirred at 0 °C for 10 min and then at 20 °C for a further 1.5 h. The solvent was removed under reduced pressure, and diethyl ether (50 mL) was added to the residue. The resulting oily precipitate was separated by centrifugation and discarded, and the solvent of the supernatant was removed under reduced pressure, followed by addition of methanol (40 mL). The resulting solution was stirred at 50 °C for 1 h, the solvent was slowly removed under reduced pressure, and the solid residue was recrystallized from methanol at −20 °C to give **7** in 58% yield as a colorless crystalline solid (9.34 g, 29.0 mmol); mp 211 °C (dec). ^{1}H NMR ($CDCl_3$): δ 1.35−1.51 (m, 1 H, SiC*H*), 1.85−2.09 (m, 4 H, NCH_2CH_2CH), 2.72−2.88 and 3.35−3.45 (m, 4 H, NCH_2CH_2CH), 7.32−7.50 and 7.55−7.61 (m, 10 H, SiC_6H_5), 9.3 (br s, 1 H, N*H*), 9.6 (br s, 1 H, N*H*). ^{13}C NMR ($CDCl_3$): δ 21.6 (d, $^2J_{CF}$ = 14.9 Hz, Si*C*H), 22.7 (NCH_2CH_2CH), 44.7 (NCH_2CH_2CH), 128.4 (*C*-3/*C*-5, SiC_6H_5), 130.6 (d, $^2J_{CF}$ = 14.9 Hz, *C*-1, SiC_6H_5), 131.1 (*C*-4, SiC_6H_5), 134.1 (d, $^3J_{CF}$ = 2.2 Hz, *C*-2/*C*-6, SiC_6H_5). ^{19}F NMR ($CDCl_3$): δ −178.2. ^{29}Si NMR ($CDCl_3$): δ 3.2 (d, $^1J_{SiF}$ = 287.7 Hz). Anal. Calcd for $C_{17}H_{21}ClFNSi$: C, 63.43; H, 6.58; N, 4.35. Found: C, 63.3; H, 6.6; N, 4.2.

Preparation of Methoxydiphenyl(piperidin-4-yl)silane (8). A solution of **7** (13.4 g, 41.6 mmol) in methanol (100 mL) was added dropwise at 20 °C within 30 min to a stirred solution of sodium methanolate in methanol (prepared from sodium (1.91 g, 83.1 mmol) and methanol (45 mL)). After the mixture was stirred at 20 °C for 1 h, the solvent was removed under reduced pressure, and diethyl ether (100 mL) was added. The precipitate was filtered off and washed with diethyl ether (2 × 25 mL), and the filtrate and the wash solutions were combined. The solvent was removed under reduced pressure to give a colorless oil, which crystallized at 20 °C over a period of ca. 3 days to give **8** in 82% yield as a colorless crystalline solid (10.2 g, 34.3 mmol); mp 38 °C. ^{1}H NMR ($CDCl_3$): δ 1.32−1.54 and 1.65−1.74 (m, 5 H, SiC*H*, NCH_2CH_2CH), 1.8 (br s, 1 H, N*H*), 2.55−2.65 and 2.97−3.05 (m, 4 H, NCH_2CH_2CH), 3.49 (s, 3 H, OCH_3), 7.31−7.45 and 7.55−7.61 (m, 10 H, SiC_6H_5). ^{13}C NMR ($CDCl_3$): δ 23.2 (Si*C*H), 27.0 (NCH_2CH_2CH), 48.1 (NCH_2CH_2CH), 51.6 (OCH_3) 127.7 (*C*-3/*C*-5, SiC_6H_5), 129.9 (*C*-4, SiC_6H_5), 133.0 (*C*-1, SiC_6H_5), 135.1 (*C*-2/*C*-6, SiC_6H_5). ^{29}Si NMR ($CDCl_3$): δ −4.2. Anal. Calcd for $C_{18}H_{23}NOSi$: C, 72.68; H, 7.79; N, 4.71. Found: C, 72.5; H, 7.8; N, 4.7.

Preparation of 4-(4-*tert*-Butylphenyl)-4-oxobutanoic Acid (9). This compound was synthesized according to ref 7.

Preparation of 4-(4-(Trimethylsilyl)phenyl)-4-oxobutanoic Acid (11). A Grignard reagent was prepared from **13** (10.0 g, 43.6 mmol) and magnesium turnings (1.20 g, 49.4 mmol) in diethyl ether (20 mL) and was then diluted with further diethyl ether (80 mL). The resulting reagent was added dropwise at −78 °C within 90 min to a stirred solution of butanedioic anhydride (4.36 g, 43.6 mmol) in THF (300 mL). After the mixture was warmed to 20 °C within 4 h and stirred at this temperature for a further 12 h, water (100 mL) and hydrochloric acid (2 M, 15 mL) were added. The organic phase was separated and dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure, and the solid residue was recrystallized from diethyl ether at −20 °C to give **11** in 48% yield as a colorless crystalline solid (5.23 g, 20.9 mmol); mp 99 °C. ^{1}H NMR ($CDCl_3$): δ 0.14 (s, 9 H, $SiCH_3$), 2.61 (t, $^3J_{HH}$ = 6.7 Hz, 2 H, CCH_2C), 3.17 (t, $^3J_{HH}$ = 6.7 Hz, 2 H, CCH_2C), 7.46−7.51 and 7.76−7.81 (m, 4 H, C_6H_4), CO*H* not detected. ^{13}C NMR ($CDCl_3$): δ −1.8 (Si*C*H$_3$), 27.8 (C*C*H$_2$C), 33.2 (C*C*H$_2$C), 126.7 (*C*-2/*C*-6 or *C*-3/*C*-5, C_6H_4), 133.3 (*C*-2/*C*-6 or *C*-3/*C*-5, C_6H_4), 136.3 (*C*-1 or *C*-4, C_6H_4), 147.4 (*C*-1 or *C*-4, C_6H_4), 174.9 (C*C*(O)O), 199.1 (C*C*(O)C). ^{29}Si NMR ($CDCl_3$): δ −3.1. Anal. Calcd for $C_{13}H_{18}O_3Si$: C, 62.36; H, 7.25. Found: C, 62.4; H, 7.2.

Preparation of (4-Bromophenyl)trimethylsilane (13). This compound was prepared according to ref 9.

Preparation of 4-(4-(1-(4,4-Dimethyl-4,5-dihydro-1,3-oxazol-2-yl)-1-methylethyl)phenyl)-4-oxobutanoic Acid (15). A Grignard reagent was prepared from **18** (20.0 g, 67.5 mmol) and magnesium turnings (2.13 g, 87.6 mmol) in THF (60 mL) and was then added dropwise at −78 °C within 90 min to a stirred solution of butanedioic anhydride (6.75 g, 67.5 mmol) in THF (270 mL). After the mixture was warmed to 20 °C within 4 h and stirred at this temperature for a further 12 h, the solvent was removed under reduced pressure, and water (100 mL) and dichloromethane (150 mL) were added. The organic phase was separated and dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure, and the residue was crystallized from diethyl ether at −20 °C to give **15** in 59% yield as a colorless crystalline solid (12.7 g, 40.0 mmol); mp 87 °C. ^{1}H NMR ($CDCl_3$): δ 1.27 (s, 6 H, CCH_3), 1.60 (s, 6 H, CCH_3), 2.72 (t, $^3J_{HH}$ = 6.5 Hz, 2 H, CCH_2C), 3.24 (t, $^3J_{HH}$ = 6.5 Hz, 2 H, CCH_2C), 3.84 (s, 2 H, CCH_2O), 7.37−7.45 and 7.87−7.95 (m, 4 H, C_6H_4), 9.9 (br s, 1 H, CO*H*). ^{13}C NMR ($CDCl_3$): δ 26.9 (C*C*H$_3$), 27.9 (C*C*H$_3$), 28.1 (C*C*H$_2$C), 33.2 (C*C*H$_2$C), 41.0 (C_3CN), 66.8 (C_4C), 79.5 (C*C*H$_2$O), 125.8 (*C*-2/*C*-6 or *C*-3/*C*-5, C_6H_4), 128.3 (*C*-2/*C*-6 or *C*-3/*C*-5, C_6H_4), 134.9 (*C*-1 or *C*-4, C_6H_4), 150.7 (*C*-1 or *C*-4, C_6H_4), 170.6 (*C*═N), 177.2 (*C*═O), 197.5 (*C*═O). Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 67.8; H, 7.2; N, 4.2.

Preparation of 2-(1-(4-Bromophenyl)-1-methylethyl)-4,4-dimethyl-4,5-dihydro-1,3-oxazole (18). This compound was prepared according to ref 10.

Dimethoxydiphenylsilane (19). This compound was commercially available (Aldrich).

Preparation of Methoxy(1-methylpiperidin-4-yl)diphenylsilane (20). A Grignard reagent was prepared from 4-chloro-1-methylpiperidine (13.4 g, 100 mmol) and magnesium turnings (3.00 g, 123 mmol) in THF (45 mL) (see preparation of **6**) and was then added dropwise at 20 °C within 1 h to a stirred solution of **19** (15.6 g, 63.8 mmol) in THF (100 mL). After the mixture was stirred under reflux for 2 h and at 20 °C for a further 16 h, *n*-pentane (150 mL) was added. The precipitate was filtered off and discarded, the solvent of the filtrate was removed under reduced pressure, and the

Table 3. Experimental Data of Pharmacological Assays of Compounds *rac*-1a, *rac*-1b, *rac*-1c, *rac*-1d, *rac*-2a, and *rac*-2b at Histamine Receptors

assay	$H_{1\ central}$	$H_{1\ peripheral}$	H_2	H_3
tissue source	guinea pig cerebellum	guinea pig lung	guinea pig striatum	rat cerebral cortex
radioligand	0.5 nM [^{3}H]pyrilamine	1 nM [^{3}H]pyrilamine	0.1 nM [^{125}I]APT	1 nM [^{3}H](*R*)-α-methylhistamine
nonspecific ligand	100 μM triprolidine	100 μM triprolidine	100 μM tiotidine	5 μM (*R*)-α-methylhistamine
incubation time, min	10	15	150	120
incubation temp, °C	22	22	25	22
incubation buffer	50 mM Na_2HPO_4/ KH_2PO_4, pH 7.5	50 mM Na_2HPO_4/ KH_2PO_4, pH 7.5	50 mM Na_2HPO_4/KH_2PO_4, pH 7.5 + 0.1% gelatin	50 mM Na_2HPO_4/KH_2PO_4, pH 7.5
ref	16	16	17	18

residue was distilled in a Kugelrohr apparatus (oven temperature 240 °C, 0.01 mbar) to give **20** in 69% yield as a colorless oily liquid (13.7 g, 44.0 mmol). ^{1}H NMR ($CDCl_3$): δ 1.17−1.31 (m, 1 H, SiC*H*), 1.48−1.53 and 1.74−1.80 (m, 4 H, NCH_2CH_2-CH), 1.80−1.92 and 2.82−2.89 (m, 4 H, NCH_2CH_2CH), 2.20 (s, 3 H, NCH_3), 3.50 (s, 3 H, OCH_3) 7.29−7.43 and 7.55−7.62 (m, 10 H, SiC_6H_5). ^{13}C NMR ($CDCl_3$): δ 21.8 (Si*C*H), 26.1 (NCH_2CH_2CH), 46.7 (NCH_3), 51.6 (OCH_3), 57.2 (NCH_2CH_2CH), 127.9 (*C*-3/*C*-5, SiC_6H_5), 129.9 (*C*-4, SiC_6H_5), 132.9 (*C*-1, SiC_6H_5), 135.1 (*C*-2/*C*-6, SiC_6H_5). ^{29}Si NMR ($CDCl_3$): δ −3.3. Anal. Calcd for $C_{19}H_{25}NOSi$: C, 73.26; H, 8.09; N, 4.50. Found: C, 72.7; H, 7.8; N, 4.4.

Crystal Structure Analyses. Suitable single crystals of **4a** and **4b**·CH_2Cl_2 were obtained by crystallization from dichloromethane at −20 °C, and single crystals of **7** were obtained by crystallization from methanol at −20 °C. Single crystals of **8** were isolated directly from the solidified reaction product. 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.[12] All non-hydrogen atoms were refined anisotropically.[13] A riding model was employed in the refinement of the C*H* hydrogen atoms. The O*H* 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-237714 (**4a**), CCDC-237715 (**4b**·CH_2Cl_2), CCDC-237716 (**7**), and CCDC-237717 (**8**). 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).

Pharmacological Studies. Receptor binding affinities of *rac*-**1a**, *rac*-**1b**, *rac*-**1c**, *rac*-**1d**, *rac*-**2a**, and *rac*-**2b** for histamine central H_1 and peripheral H_1, H_2, and H_3 receptors were determined using radioligand binding assays via contract research services.[14] Radioactivity levels were detected by scintillation counting. The experimental conditions for each assay are shown in Table 3. K_i values were calculated from IC_{50} determinations using the equation of Cheng and Prusoff.[15]

Supporting Information Available: Tables of crystal data, structure solution and refinement, atomic coordinates, bond lengths and angles, and anisotropic thermal parameters for **4a**, **4b**·CH_2Cl_2, **7**, and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

OM040084A

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