2-Methylimidazol-1-yl-Substituted Analogs of Hexahydro-difenidol (HHD) and Hexahydro-sila-difenidol (HHSiD) as M_3 Receptor-Preferring Muscarinic Antagonists: A Study on C/Si Bioisosterism

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The hexahydro-sila-difenidol (HHSiD, **1b**) and *p*-fluoro-hexahydro-sila-difenidol (*p*-F-HHSiD, **2b**) derivatives cyclohexyl[3-(2-methylimidazol-1-yl)propyl]phenylsilanol (**4b**) and cyclohexyl(4-fluorophenyl)[3-(2-methylimidazol-1-yl)propyl]silanol (**5b**) were synthesized in three-step syntheses, starting from (3-chloropropyl)cyclohexyldimethoxysilane. In addition, the corresponding carbon analogs **4a** and **5a** (→ Si/C replacement) were prepared in two-step syntheses, starting from 2-(3-chloropropyl)-2-phenyl-1,3-dioxolane and 2-(3-chloropropyl)-2-(4-fluorophenyl)-1,3-dioxolane, respectively. The C/Si pairs **4a**/**4b** and **5a**/**5b** were studied for their affinities at recombinant human muscarinic M_1, M_2, M_3, M_4, and M_5 receptors stably expressed in CHO-K1 cells by evaluating their ability to inhibit the binding of the muscarinic antagonist [^{3}H]*N*-methylscopolamine. These studies revealed that compounds **4a**, **4b**, **5a**, and **5b** behave as simple competitive antagonists at M_1−M_5 receptors. The exchange of the piperidin-1-yl group of the parent compounds HHD (**1a**), HHSiD (**1b**), *p*-F-HHD (**2a**), and *p*-F-HHSiD (**2b**) by a 2-methylimidazol-1-yl moiety resulted in a novel, potent, and M_3-preferring antimuscarinic agent, compound **4b**. The affinities of compounds **4a**, **5a**, and **5b** for muscarinic M_1 (pK_i = 7.74−7.93), M_2 (pK_i = 7.03−7.14), M_3 (pK_i = 8.04−8.11), M_4 (pK_i = 7.63−7.94), and M_5 receptors (pK_i = 7.29−7.52) were very similar at the individual receptor subtypes and in turn very similar to those of the parent compounds **1a**, **2a**, and **2b**. In contrast, replacement of the piperidin-1-yl substituent of **1b** by a 2-methylimidazol-1-yl group (→ **4b**) increased the affinity for M_1−M_5 receptors up to 8.3-fold. The muscarinic receptor affinity profile of **4b** was found to be M_3 (pK_i = 8.69) > M_1 (pK_i = 8.39) ≥ M_4 (pK_i = 8.32) > M_5 (pK_i = 8.02) > M_2 (pK_i = 7.43). Thus, compound **4b** displayed a M_3 versus M_2 receptor selectivity (18.2-fold). The receptor subtype affinities of the carbon compound **5a** were very similar to those of the corresponding silicon analog **5b**, whereas sila-substitution of **4a** (→ **4b**) increased the affinities for M_1−M_5 receptors, this increase being greatest at M_3 and M_5 receptors (4-fold).

Introduction

Some years ago, we reported on the syntheses of the M_3 subtype-preferring muscarinic antagonists hexahydro-sila-difenidol[1] (HHSiD, **1b**) and *p*-fluoro-hexahydro-sila-difenidol[2] (*p*-F-HHSiD, **2b**). As shown by pharmacological and binding studies,[3−6] the silicon compounds**1b** and **2b** as well as their corresponding carbon analog, hexahydro-difenidol (HHD, **1a**) and *p*-fluoro-hexahydro-difenidol (*p*-F-HHD, **2a**), display a pronounced selectivity for native M_3 versus M_2 muscarinic receptors. As a result, the commercially available silanols **1b** and **2b** are two of the most commonly used muscarinic antagonists to pharmacologically identify and characterize the M_3 receptors in isolated cells or intact tissues.[7−12] We have now attempted to further increase the antimuscarinic potency and selectivity of

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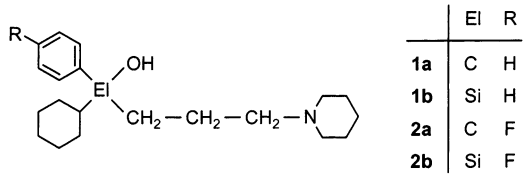
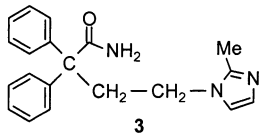
these two silanols by replacing their piperidin-1-yl group by a 2-methylimidazol-1-yl moiety. These studies were inspired by the observation that incorporation of the 2-methylimidazol-1-yl ring as a surrogate for an aliphatic amino group in a series of related muscarinic antagonists generated M_3 selectivity and enhanced antimuscarinic potency.[13−15] The selective compound KRP-197 (**3**) (affinity profile: M_1, $M_3 > M_2$) has been identified as a candidate drug for the treatment of urinary bladder dysfunction.[15]



	El	R
1a	C	H
1b	Si	H
2a	C	F
2b	Si	F



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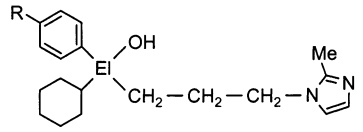
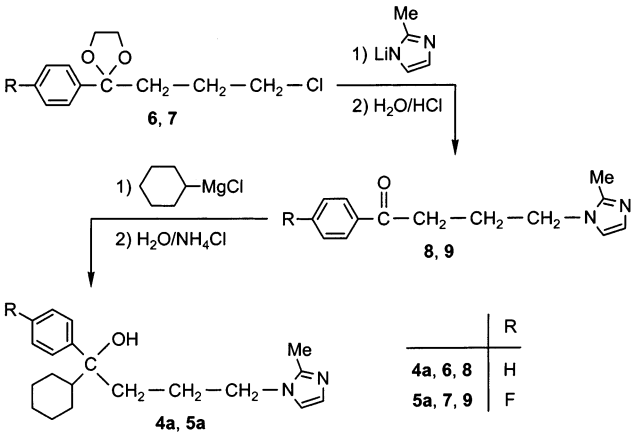


	El	R
4a	C	H
4b	Si	H
5a	C	F
5b	Si	F

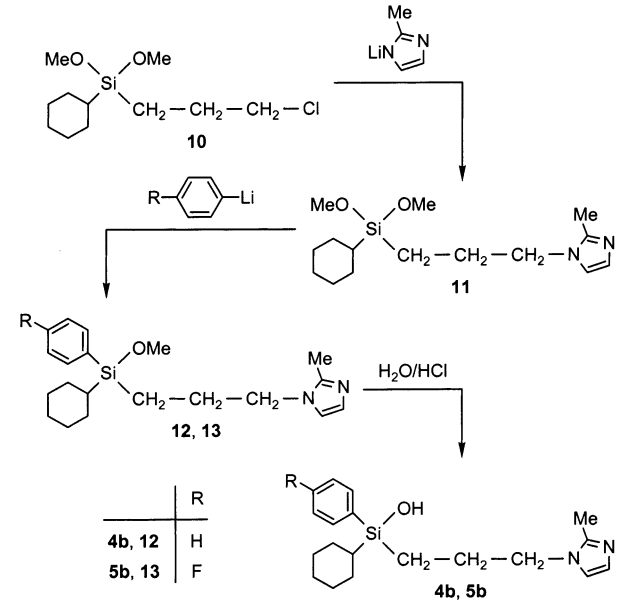
We report here on the syntheses and pharmacological characterization of the HHSiD and *p*-F-HHSiD derivatives **4b** and **5b** and their respective carbon analogs **4a** and **5a** (all compounds synthesized as racemates). Compounds **4a**, **4b**, **5a**, and **5b** were tested for their affinities at recombinant human muscarinic M_1, M_2, M_3, M_4, and M_5 receptors. For reasons of comparison, HHSiD (**1b**) was included in the pharmacological experiments. The studies presented here were carried out as part of our systematic studies on C/Si bioisosterism (for recent publications, see refs 16−20).

Scheme 1



	R
4a, 6, 8	H
5a, 7, 9	F

Scheme 2



	R
4b, 12	H
5b, 13	F

Results and Discussion

Syntheses. The carbon compound 1-cyclohexyl-4-(2-methylimidazol-1-yl)-1-phenylbutan-1-ol (**4a**) was prepared by a two-step synthesis, starting from 2-(3-chloropropyl)-2-phenyl-1,3-dioxolane (**6**). Treatment of **6** with (2-methylimidazol-1-yl)lithium in tetrahydrofuran/*n*-hexane and subsequent hydrolysis with hydrochloric acid gave 4-(2-methylimidazol-1-yl)-1-phenylbutan-1-one (**8**) (49% yield), which on reaction with cyclohexylmagnesium chloride in diethyl ether, followed by hydrolysis, afforded compound **4a** (88% yield). The corresponding *p*-fluoro derivative **5a** was prepared analogously, starting from **7** (**7** → **9** (44% yield) → **5a** (91% yield)) (Scheme 1).

The silicon compound cyclohexyl[3-(2-methylimidazol-1-yl)propyl]phenylsilanol (**4b**) was prepared by a three-step synthesis, starting from (3-chloropropyl)cyclohexyldimethoxysilane (**10**) (Scheme 2). Treatment of **10** with (2-methylimidazol-1-yl)lithium in dimethylformamide/tetrahydrofuran/*n*-hexane gave cyclohexyldimethoxy[3-(2-methylimidazol-1-yl)propyl]silane (**11**) (75% yield), which on reaction with phenyllithium in diethyl ether afforded cyclohexyl(methoxy)[3-(2-methylimidazol-1-yl)propyl]phenylsilane (**12**) (78% yield). Subsequent hy-

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Table 1. Affinities (pK_i Values) for Compounds 1b, 4a, 4b, 5a, and 5b Obtained in Radioligand Binding Studies at Human Muscarinic M_1, M_2, M_3, M_4, and M_5 Receptors Stably Expressed in CHO-K1 Cells[a]

	pK_i values				
compd	M_1	M_2	M_3	M_4	M_5
1b	7.85 ± 0.07	6.97 ± 0.06	7.77 ± 0.07	7.52 ± 0.07	7.12 ± 0.05
4a	7.93 ± 0.11	7.14 ± 0.05	8.11 ± 0.14	7.94 ± 0.05	7.44 ± 0.07
4b	8.39 ± 0.16	7.43 ± 0.04	8.69 ± 0.13	8.32 ± 0.07	8.02 ± 0.11
5a	7.90 ± 0.09	7.03 ± 0.03	8.04 ± 0.02	7.71 ± 0.01	7.29 ± 0.03
5b	7.74 ± 0.06	7.07 ± 0.09	8.09 ± 0.04	7.63 ± 0.06	7.52 ± 0.08

[a] Data are presented as means ± SD of at least three experiments in duplicate.

Table 2. Pharmacological Selectivity Ratios for Compounds 1b, 4a, 4b, 5a, and 5b

	selectivity ratios[a]			
compd	M_3/M_1	M_3/M_2	M_3/M_4	M_3/M_5
1b	0.8	6.3	1.8	4.5
4a	1.5	9.3	1.5	4.7
4b	2.0	18.2	2.3	4.7
5a	1.4	10.2	2.1	5.6
5b	2.2	10.5	2.9	3.7

[a] K_i ratios (pK_i = −log K_i) are given as a measure of receptor selectivity; these values were calculated from the antilogs of the differences between the respective pK_i values.

drolysis of the methoxysilane **12** in hydrochloric acid/2-propanol gave the silanol **4b** (83% yield). The corresponding *p*-fluoro derivative **5b** was prepared analogously, starting from **10** (**10** → **11** (75% yield) → **13** (74% yield) → **5b** (81% yield)) (Scheme 2).

To improve the solubility in water, compounds **4a**, **4b**, **5a**, and **5b** were transformed into their corresponding hydrochlorides (see Experimental Section). Compounds **4a**, **4a**·HCl, **4b**, **4b**·HCl, **5a**, **5a**·HCl, **5b**, **5b**·HCl, **12**, and **13** were isolated as crystalline solids (racemic mixtures), whereas **8**, **9**, and **11** were obtained as liquids. The identities of all compounds were established by elemental analyses (C, H, N) and NMR spectroscopic studies (^{1}H, ^{13}C, ^{29}Si).

Pharmacological Studies. Compounds **1b**, **4a**, **4b**, **5a**, and **5b** were studied for their affinities (pK_i values) at recombinant human muscarinic M_1, M_2, M_3, M_4, and M_5 receptors stably expressed in CHO-K1 cells (binding studies with [^{3}H]*N*-methylscopolamine ([^{3}H]NMS) as the radioligand). The results of these investigations are summarized in Tables 1 and 2 and illustrated in Figure 1.

The Hill coefficients (0.83 ± 0.11 to 1.15 ± 0.05) of all saturation and competition curves were not significantly different from unity, indicating the presence of a single recombinant muscarinic receptor subtype (M_1, M_2, M_3, M_4, or M_5) in the five CHO-K1 cell lines and a competitive antagonism by compounds **1b**, **4a**, **4b**, **5a**, and **5b** at M_1−M_5 receptors.

Although the muscarinic receptor affinity profiles of the C/Si pairs **4a**/**4b** and **5a**/**5b** are similar (Tables 1 and 2, Figure 1), some differences are noted that are indicative of structure−activity relationships. In particular, the antimuscarinic properties of **4b** were distinct in several ways.

The affinities and selectivity ratios of compounds **4a**, **5a**, and **5b** were found to be very similar at the individual muscarinic receptor subtypes and, in turn,

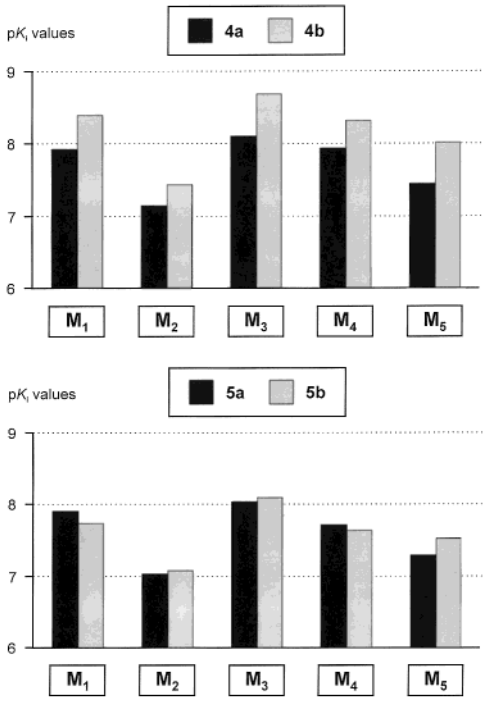

Figure 1. Affinity profiles (pK_i values) of the C/Si analogs **4a**/**4b** and **5a**/**5b** at human muscarinic M_1, M_2, M_3, M_4, and M_5 receptors.

similar to those of the parent compounds **1a**, **1b**, **2a**, and **2b**.[5,6,21,22] In contrast, replacement of the piperidin-1-yl group of HHSiD (**1b**) by a 2-methylimidazol-1-yl moiety (→ **4b**) increased the affinities for M_1 (3.5-fold), M_2 (2.9-fold), M_3 (8.3-fold), M_4 (6.3-fold), and M_5 receptors (7.9-fold). As a result, compound **4b** was found to have the highest binding affinities at M_1−M_5 receptors and the greatest M_3 versus M_2 receptor selectivity (18.2-fold).

Comparison of the binding affinities of the C/Si pairs **4a**/**4b** and **5a**/**5b** outlined the effect of sila-substitution (C/Si exchange) on the antimuscarinic properties. It is obvious from the data in Table 1 that the replacement of the central carbon atom of **5a** by a silicon atom (→ **5b**) has little influence on the affinities for M_1−M_5 receptors. This also holds true for the sila-substitution of compounds **1a** (→ **1b**) and **2a** (→ **2b**) (Table 1; refs 5, 6, 21, and 22), indicating a strongly pronounced C/Si bioisosterism. However, replacement of the central carbon atom of **4a** by a silicon atom (→ **4b**) increased the affinity for M_1−M_5 receptor subtypes, this increase being greatest at M_3 and M_5 receptors (4-fold).

Comparison of the phenyl/*p*-fluorophenyl pairs **4a**/**5a** and **4b**/**5b** defines the effect of a *p*-fluoro substituent in the phenyl ring on affinity for M_1−M_5 receptors. The influence of a fluoro substituent in para position of **4a** (→ **5a**) on affinity was very moderate. In contrast, fluoro substitution of **4b** (→ **5b**) reduced the binding affinity for all muscarinic receptor subtypes up to 4.9-fold, this decrease in affinity being smallest at M_2 receptors (2.3-fold). These results support the view that the drug position in the muscarinic receptor binding sites is adapted depending on the actual drug structure and is

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not necessarily indentical when comparing carbon/silicon bioisosters.[3,5]

It is noteworthy that compounds **4a**, **4b**, **5a**, and **5b** possess a center of chirality (central carbon or silicon atom) and therefore exist as (*R*)- and (*S*)-enantiomers, but we investigated the binding affinities of the racemic mixtures. The pK_i values listed in Table 1 may therefore be lower by at most 0.3 log units than the pK_i values of the respective high-affinity enantiomers (eutomers).[5] This is due to the presence of 50% of the corresponding low-affinity enantiomers (distomers) in the binding assays. However, we have demonstrated that enantiopure silanols (R_3SiOH) racemize in aqueous solution.[23]

Taken together, we have indentified a novel, highly potent, and M_3 receptor-preferring muscarinic antagonist. The silanol **4b** may provide a pharmacological tool for the investigation of muscarinic receptor subpopulations in vivo and may have potential utility in controlling M_3 receptor-mediated contraction of visceral smooth muscle, e.g., instability of the urinary bladder detrusor muscle.[12] The results obtained in this study again demonstrate the high potential of the sila-substitution concept in the development of new drugs with improved pharmacological properties.

Experimental Section

Chemistry. General Procedures. All syntheses were carried out under dry nitrogen. The solvents used were dried and purified according to standard procedures and stored under dry nitrogen. Melting points (uncorrected) were determined with a Büchi Melting Point B-540 apparatus. The ^{1}H, ^{13}C, 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; ^{29}Si, 59.6 MHz). Chemical shifts (ppm) were determined relative to internal $CHCl_3$ (^{1}H, δ 7.24; solvent $CDCl_3$), $CDCl_3$ (^{13}C, δ 77.0; solvent $CDCl_3$), DMSO-d_5 (^{1}H, δ 2.49; solvent DMSO-d_6), and DMSO-d_6 (^{13}C, δ 39.5; solvent DMSO-d_6), and external TMS (^{29}Si, δ 0; solvent $CDCl_3$). Assignment of the ^{1}H NMR data for **4a**·HCl, **5a**, **5a**·HCl, **12**, and **13** was supported by ^{1}H,^{1}H COSY experiments. Assignment of the ^{13}C NMR data for all compounds was supported by DEPT 135 experiments, and for **4a**·HCl, **5a**, **5a**·HCl, **12**, and **13** by additional ^{13}C,^{1}H HMQC and ^{13}C,^{1}H HMBC experiments.

Preparation of 1-Cyclohexyl-4-(2-methylimidazol-1-yl)-1-phenylbutan-1-ol (4a). An emulsion of **8** (2.00 g, 8.76 mmol) in diethyl ether (6 mL) was added dropwise at room temperature (rt) over a period of 10 min to a stirred Grignard reagent prepared from cyclohexyl chloride (1.25 g, 10.5 mmol) and magnesium turnings (270 mg, 11.1 mmol) in diethyl ether (15 mL). The resulting mixture was stirred for 1 h at rt, heated under reflux for 1 h, and then stirred for 1 day at rt. The supernatant was removed by decantation and the solid residue washed with diethyl ether (30 mL). A suspension of this solid in diethyl ether (50 mL) was added at 0 °C to a saturated aqueous NH_4Cl solution (25 mL). The organic phase was separated and the aqueous layer extracted with diethyl ether (3 × 70 mL), and the combined organic extracts were dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the solid crude product recrystallized from diethyl ether at −20 °C to give **4a** as a colorless crystalline solid (2.41 g, 88%), mp 152−154 °C. ^{1}H NMR ($CDCl_3$): δ 0.77−1.41, 1.51−1.91, and 1.92−2.11 (m, 16 H, CCH_2C, C_3CH, COH), 2.21 (s, 3 H, CCH_3), 3.62−3.78 (m, 2 H, NCH_2C), 6.66 (s, 1 H, N−CH=CH−N=C), 6.82 (s, 1 H, N−CH=CH−N=C), 7.15−7.34 (m, 5 H, CC_6H_5). ^{13}C NMR ($CDCl_3$): δ 12.9 (CCH_3), 25.1 (NCH_2CH_2C), 26.3 (CCH_2C), 26.51 (CCH_2C), 26.54 (CCH_2C), 26.6 (CCH_2C), 27.2 (CCH_2C), 36.1 (OCCH_2C), 46.2 (NCH_2C), 48.5 (C_3CH), 78.8 (C_3CO), 118.9 (*C*-4, imidazole), 125.5 (*C*-2/*C*-6, CC_6H_5), 126.4 (*C*-4, CC_6H_5), 126.9 (*C*-5, imidazole), 128.0 (*C*-3/*C*-5, CC_6H_5), 144.3 (*C*-2, imidazole), 144.8 (*C*-1, CC_6H_5). Anal. Calcd for $C_{20}H_{28}N_2O$: C, 76.88; H, 9.03; N, 8.97. Found: C, 76.5; H, 9.0; N, 8.9.

Preparation of the Hydrochloride 4a·HCl. A 1 M ethereal HCl solution (710 μL, 710 μmol HCl) was added at 0 °C over a period of 5 min to a stirred solution of **4a** (221 mg, 707 μmol) in tetrahydrofuran (60 mL) (slow formation of a precipitate) and the mixture then kept undisturbed at 0 °C for 20 min and at rt for a further 15 min. The solid product was separated by centrifugation, washed with tetrahydrofuran (3 × 15 mL), and then recrystallized from acetone/dichloromethane (3:1 (v/v)) to give **4a**·HCl as a colorless crystalline solid (201 mg, 81%), mp 211−214 °C. ^{1}H NMR (DMSO-d_6): δ 0.74−1.36 and 1.41−1.90 (m, 15 H, CCH_2C, C_3CH), 2.48 (s, 3 H, CCH_3), 3.99 (t, ^3J(HH) = 7.1 Hz, 2 H, NCH_2C), 4.6 (s, 1 H, COH), 7.12−7.21 and 7.23−7.35 (m, 5 H, CC_6H_5), 7.51 (δ_A) and 7.54 (δ_X) (^3J(AX) = 2.1 Hz, 2 H, N−CH_X=CH_A−N=C), 14.6 (br s, 1 H, NH). ^{13}C NMR (DMSO-d_6): δ 10.1 (CCH_3), 24.0 (NCH_2CH_2C), 26.12 (CCH_2C), 26.15 (CCH_2C), 26.20 (CCH_2C), 26.3 (CCH_2C), 27.0 (CCH_2C), 34.7 (OCCH_2C), 47.0 (NCH_2C), 48.2 (C_3CH), 77.1 (C_3CO), 117.7 (*C*-4, imidazole), 121.8 (*C*-5, imidazole), 125.7 (*C*-4, CC_6H_5), 125.9 (*C*-2/*C*-6, CC_6H_5), 127.4 (*C*-3/*C*-5, CC_6H_5), 143.7 (*C*-2, imidazole), 145.7 (*C*-1, CC_6H_5). Anal. Calcd for $C_{20}H_{29}ClN_2O$: C, 68.85; H, 8.38; N, 8.03. Found: C, 69.0; H, 8.3; N, 7.9.

Preparation of Cyclohexyl[3-(2-methylimidazol-1-yl)-propyl]phenylsilanol (4b). Hydrochloric acid (0.5 M, 80 mL) was added at rt to a stirred solution of **12** (1.00 g, 2.92 mmol) in 2-propanol (30 mL) and the mixture stirred at rt for 16 h, followed by extraction with diethyl ether (2 × 30 mL). The pH of the aqueous layer was adjusted to 8 by addition of 1 M aqueous NaOH solution and the resulting mixture extracted with diethyl ether (3 × 100 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, the solvent was removed under reduced pressure, and the solid crude product was recrystallized from diethyl ether at −20 °C to give **4b** as a colorless crystalline solid (796 mg, 83%), mp 89 °C. ^{1}H NMR ($CDCl_3$): δ 0.62−0.98 (m, 3 H, SiCH_2C, SiCHCH_2), 1.02−1.32 and 1.50−1.86 (m, 12 H, CCH_2C), 2.05 (s, 3 H, CCH_3), 3.68 (t, ^3J(HH) = 7.4 Hz, 2 H, NCH_2C), 5.9 (br s, 1 H, SiOH), 6.64 (δ_A) and 6.69 (δ_X) (^3J(AX) = 1.1 Hz, 2 H, N−CH_X=CH_A−N=C), 7.27−7.38 and 7.50−7.58 (m, 5 H, SiC_6H_5). ^{13}C NMR ($CDCl_3$): δ 10.3 (SiCH_2C), 12.3 (CCH_3), 24.7 (SiCH$_2$CH_2C), 26.3 (SiCHCH_2), 26.73 (CCH_2C), 26.75 (CCH_2C), 26.81 (CCH_2C), 27.79 (CCH_2C), 27.83 (CCH_2C), 48.9 (NCH_2C), 119.0 (*C*-4, imidazole), 125.9 (*C*-5, imidazole), 127.6 (*C*-3/*C*-5, SiC_6H_5), 129.2 (*C*-4, SiC_6H_5), 133.8 (*C*-2/*C*-6, SiC_6H_5), 137.1 (*C*-1, SiC_6H_5), 144.0 (*C*-2, imidazole). ^{29}Si NMR ($CDCl_3$): δ 0.7. Anal. Calcd for $C_{19}H_{28}N_2OSi$: C, 69.46; H, 8.59; N, 8.53. Found: C, 69.7; H, 8.5; N, 8.3.

Preparation of the Hydrochloride 4b·HCl. A 1 M ethereal HCl solution (650 μL, 650 μmol HCl) was added at 0 °C over a period of 5 min to a stirred solution of **4b** (212 mg, 645 μmol) in tetrahydrofuran (30 mL). After 5 min, diethyl ether (40 mL) was added and the mixture then kept undisturbed at 0 °C for 20 min and at rt for a further 15 min. The solid product was separated by centrifugation, washed with tetrahydrofuran (3 × 20 mL), and then recrystallized from *n*-hexane/dichloromethane (2.5:1 (v/v)) to give **4b**·HCl as a colorless crystalline solid (226 mg, 96%), mp 150 °C. ^{1}H NMR ($CDCl_3$): δ 0.66−0.96 (m, 3 H, SiCH_2C, SiCHCH_2), 0.99−1.31, 1.48−1.78, and 1.79−2.07 (m, 12 H, CCH_2C), 2.62 (s, 3 H, CCH_3), 3.5 (br s, 1 H, SiOH), 3.97 (t, ^3J(HH) = 7.2 Hz, 2 H, NCH_2C), 7.05−7.13 (m, 2 H, N−CH=CH−N=C), 7.27−7.36 and 7.47−7.57 (m, 5 H, SiC_6H_5), 15.4 (s, 1 H, NH). ^{13}C NMR ($CDCl_3$): δ 9.7 (SiCH_2C), 10.6 (CCH_3), 24.1 (SiCH$_2$CH_2C), 26.2

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(Si*C*HC$_2$), 26.65 (C*C*H$_2$C), 26.66 (C*C*H$_2$C), 26.74 (C*C*H$_2$C), 27.67 (C*C*H$_2$C), 27.71 (C*C*H$_2$C), 49.8 (N*C*H$_2$C), 117.9 (*C*-4, imidazole), 120.7 (*C*-5, imidazole), 127.8 (*C*-3/*C*-5, Si*C*$_6$H$_5$), 129.5 (*C*-4, Si*C*$_6$H$_5$), 133.7 (*C*-2/*C*-6, Si*C*$_6$H$_5$), 136.1 (*C*-1, Si*C*$_6$H$_5$), 143.6 (*C*-2, imidazole). ^{29}Si NMR (CDCl$_3$): δ 2.1. Anal. Calcd for $C_{19}H_{29}ClN_2OSi$: C, 62.52; H, 8.01; N, 7.68. Found: C, 62.2; H, 7.7; N, 7.6.

Preparation of 1-Cyclohexyl-1-(4-fluorophenyl)-4-(2-methylimidazol-1-yl)butan-1-ol (5a). This compound was prepared analogously to the synthesis of **4a** by addition of a Grignard reagent, prepared from cyclohexyl chloride (1.17 g, 9.86 mmol) and magnesium turnings (250 mg, 10.3 mmol) in diethyl ether (15 mL), to an emulsion of **9** (2.00 g, 8.12 mmol) in diethyl ether (6 mL). The solid crude product was recrystallized from diethyl ether at −20 °C to give **5a** as a colorless crystalline solid (2.44 g, 91%), mp 146−147 °C. ^{1}H NMR (CDCl$_3$): δ 0.76−1.43 and 1.48−1.90 (m, 16 H, CC*H*$_2$C, C$_3$C*H*, CO*H*), 2.25 (s, 3 H, CC*H*$_3$), 3.64−3.81 (m, 2 H, NC*H*$_2$C), 6.69 (s, 1 H, N−CH=C*H*−N=C), 6.85 (s, 1 H, N−C*H*=CH−N=C), 6.93−7.02 and 7.16−7.25 (m, 4 H, CC$_6$*H*$_4$F). ^{13}C NMR (CDCl$_3$): δ 12.8 (C*C*H$_3$), 25.0 (NCH$_2$*C*H$_2$C), 26.3 (C*C*H$_2$C), 26.4 (C*C*H$_2$C), 26.5 (C*C*H$_2$C), 26.6 (C*C*H$_2$C), 27.2 (C*C*H$_2$C), 36.1 (OC*C*H$_2$C), 46.2 (N*C*H$_2$C), 48.6 (C$_3$*C*H), 78.5 (C$_3$*C*O), 114.7 (d, ^2J(CF) = 21.1 Hz, *C*-3/*C*-5, CC$_6$H$_4$F), 119.1 (*C*-4, imidazole), 126.3 (*C*-5, imidazole), 127.2 (d, ^3J(CF) = 7.6 Hz, *C*-2/*C*-6, CC$_6$H$_4$F), 132.8 (d, ^4J(CF) = 3.2 Hz, *C*-1, CC$_6$H$_4$F), 144.5 (*C*-2, imidazole), 161.4 (d, ^1J(CF) = 244.9 Hz, *C*-4, CC$_6$H$_4$F). Anal. Calcd for $C_{20}H_{27}FN_2O$: C, 72.70; H, 8.24; N, 8.48. Found: C, 72.2; H, 8.2; N, 8.3.

Preparation of the Hydrochloride 5a·HCl. This compound was prepared analogously to the synthesis of **4a**·HCl by addition of a 1 M ethereal HCl solution (670 μL, 670 μmol HCl) to a solution of **5a** (220 mg, 666 μmol) in tetrahydrofuran (60 mL) and was isolated as a colorless crystalline solid (213 mg, 87%), mp 217 °C. ^{1}H NMR (DMSO-d_6): δ 0.71−1.38 and 1.40−1.94 (m, 15 H, CC*H*$_2$C, C$_3$C*H*), 2.50 (s, 3 H, CC*H*$_3$), 4.00 (t, ^3J(HH) = 6.9 Hz, 2 H, NC*H*$_2$C), 4.7 (s, 1 H, CO*H*), 7.02−7.18 and 7.26−7.41 (m, 4 H, CC$_6$*H*$_4$F), 7.52 (δ_A) and 7.54 (δ_X) (^3J(AX) = 2.1 Hz, 2 H, N−C*H*$_X$=C*H*$_A$−N=C), 14.5 (br s, 1 H, N*H*). ^{13}C NMR (DMSO-d_6): δ 10.2 (C*C*H$_3$), 24.0 (NCH$_2$*C*H$_2$C), 26.1 (2 C) (C*C*H$_2$C), 26.2 (C*C*H$_2$C), 26.3 (C*C*H$_2$C), 26.9 (C*C*H$_2$C), 34.8 (OC*C*H$_2$C), 47.0 (N*C*H$_2$C), 48.2 (C$_3$*C*H), 76.9 (C$_3$*C*O), 114.1 (d, ^2J(CF) = 20.8 Hz, *C*-3/*C*-5, CC$_6$H$_4$F), 117.8 (*C*-4, imidazole), 121.8 (*C*-5, imidazole), 127.9 (d, ^3J(CF) = 7.8 Hz, *C*-2/*C*-6, CC$_6$H$_4$F), 141.8 (d, ^4J(CF) = 2.9 Hz, *C*-1, CC$_6$H$_4$F), 143.7 (*C*-2, imidazole), 160.6 (d, ^1J(CF) = 241.5 Hz, *C*-4, CC$_6$H$_4$F). Anal. Calcd for $C_{20}H_{28}ClFN_2O$: C, 65.47; H, 7.69; N, 7.64. Found: C, 65.0; H, 7.7; N, 7.6.

Preparation of Cyclohexyl(4-fluorophenyl)[3-(2-methylimidazol-1-yl)propyl]silanol (5b). This compound was prepared analogously to the synthesis of **4b** by hydrolysis of **13** (1.07 g, 2.97 mmol) in a mixture of 0.5 M hydrochloric acid (80 mL) and 2-propanol (30 mL). The solid crude product was recrystallized from diethyl ether at −20 °C to give **5b** as a colorless crystalline solid (833 mg, 81%), mp 87−88 °C. ^{1}H NMR (CDCl$_3$): δ 0.61−0.93 (m, 3 H, SiC*H*$_2$C, SiC*H*C$_2$), 1.00−1.29 and 1.51−1.80 (m, 12 H, CC*H*$_2$C), 2.04 (s, 3 H, CC*H*$_3$), 3.70 (t, ^3J(HH) = 7.4 Hz, 2 H, NC*H*$_2$C), 3.9 (br s, 1 H, SiO*H*), 6.56−6.81 (m, 2 H, N−C*H*=C*H*−N=C), 6.97−7.10 and 7.46−7.58 (m, 4 H, SiC$_6$*H*$_4$F). ^{13}C NMR (CDCl$_3$): δ 10.4 (SiCH$_2$C), 12.4 (C*C*H$_3$), 24.7 (SiCH$_2$*C*H$_2$C), 26.3 (SiC*H*C$_2$), 26.70 (C*C*H$_2$C), 26.73 (C*C*H$_2$C), 26.80 (C*C*H$_2$C), 27.76 (C*C*H$_2$C), 27.80 (C*C*H$_2$C), 48.9 (N*C*H$_2$C), 114.9 (d, ^2J(CF) = 16.6 Hz, *C*-3/*C*-5, SiC$_6$H$_4$F), 119.1 (*C*-4, imidazole), 126.0 (*C*-5, imidazole), 132.4 (d, ^4J(CF) = 3.6 Hz, *C*-1, SiC$_6$H$_4$F), 135.8 (d, ^3J(CF) = 7.3 Hz, *C*-2/*C*-6, SiC$_6$H$_4$F), 144.2 (*C*-2, imidazole), 163.9 (d, ^1J(CF) = 248.2 Hz, *C*-4, SiC$_6$H$_4$F). ^{29}Si NMR (CDCl$_3$): δ 1.1. Anal. Calcd for $C_{19}H_{27}FN_2OSi$: C, 65.86; H, 7.85; N, 8.08. Found: C, 65.4; H, 7.9; N, 8.0.

Preparation of the Hydrochloride 5b·HCl. A 1 M ethereal HCl solution (500 μL, 500 μmol HCl) was added at 0 °C over a period of 5 min to a stirred solution of **5b** (174 mg, 502 μmol) in diethyl ether (25 mL) (slow formation of a precipitate) and the mixture then kept undisturbed at 0 °C for 20 min and at rt for a further 15 min. The solid product was separated by centrifugation, washed with tetrahydrofuran (3 × 20 mL), and then recrystallized from *n*-hexane/trichloromethane (1:2.5 (v/v)) to give **5b**·HCl as a colorless crystalline solid (183 mg, 95%), mp 92−94 °C. ^{1}H NMR (CDCl$_3$): 0.59−0.97 (m, 3 H, SiC*H*$_2$C, SiC*H*C$_2$), 0.99−1.32, 1.47−1.77, and 1.78−2.11 (m, 12 H, CC*H*$_2$C), 2.67 (s, 3 H, CC*H*$_3$), 3.7 (br s, 1 H, SiO*H*), 3.89−4.21 (m, 2 H, NC*H*$_2$C), 6.89−7.28 and 7.42−7.59 (m, 6 H, N−C*H*=C*H*−N=C, SiC$_6$*H*$_4$F), 15.2 (s, 1 H, N*H*). ^{13}C NMR (CDCl$_3$): 9.8 (SiC*H*$_2$C), 10.9 (C*C*H$_3$), 24.1 (SiCH$_2$*C*H$_2$C), 26.3 (SiC*H*C$_2$), 26.62 (C*C*H$_2$C), 26.65 (C*C*H$_2$C), 26.73 (C*C*H$_2$C), 27.65 (C*C*H$_2$C), 27.69 (C*C*H$_2$C), 49.9 (N*C*H$_2$C), 115.0 (d, ^2J(CF) = 19.6 Hz, *C*-3/*C*-5, SiC$_6$H$_4$F), 118.0 (*C*-4, imidazole), 121.0 (*C*-5, imidazole), 131.8 (d, ^4J(CF) = 3.6 Hz, *C*-1, SiC$_6$H$_4$F), 135.8 (d, ^3J(CF) = 7.3 Hz, *C*-2/*C*-6, SiC$_6$H$_4$F), 143.6 (*C*-2, imidazole), 163.9 (d, ^1J(CF) = 248.6 Hz, *C*-4, SiC$_6$H$_4$F). ^{29}Si NMR (CDCl$_3$): δ 1.8. Anal. Calcd for $C_{19}H_{28}ClFN_2OSi$: C, 59.59; H, 7.37; N, 7.31. Found: C, 59.5; H, 7.5; N, 7.1.

Preparation of 2-(3-Chloropropyl)-2-phenyl-1,3-dioxolane (6). Synthesis is as described in ref 24.

Preparation of 2-(3-Chloropropyl)-2-(4-fluorophenyl)-1,3-dioxolane (7). Synthesis is as described in ref 25.

Preparation of 4-(2-Methylimidazol-1-yl)-1-phenylbutan-1-one (8). A 1.6 M solution of *n*-butyllithium in *n*-hexane (55.1 mL, 88.2 mmol of *n*-BuLi) was added dropwise at −40 °C over a period of 1 h to a stirred solution of 2-methylimidazole (7.24 g, 88.2 mmol) in tetrahydrofuran (90 mL). The resulting suspension was stirred at −40 °C for 15 min, and a solution of **6** (20.0 g, 88.2 mmol) in tetrahydrofuran (50 mL) was added dropwise at −40 °C over a period of 1 h. After the mixture was allowed to warm to rt, potassium iodide (6.00 g, 36.1 mmol) was added and the resulting mixture heated under reflux for 5 days and then cooled to rt, followed by addition of saturated aqueous NaHCO$_3$ solution (50 mL). The mixture was stirred at rt for 15 min, and the solvents were removed under reduced pressure. The resulting residue was partitioned between dichloromethane (400 mL) and 1 M aqueous NaHCO$_3$ solution (200 mL). The organic layer was separated and extracted with 1 M aqueous NaHCO$_3$ solution (2 × 100 mL) and then with 1 M aqueous NaCl solution (100 mL). The organic phase was dried over anhydrous Na$_2$SO$_4$ and the solvent removed under reduced pressure. Methanol (160 mL) and 2 M hydrochloric acid (160 mL) were added to the residue, and the mixture was heated under reflux for 9 h. The methanol was removed under reduced pressure and the residue extracted with diethyl ether (50 mL). The pH of the aqueous solution was then adjusted to 9.5 by addition of Na$_2$CO$_3$, and the resulting solution was concentrated under reduced pressure (→ ca. 80 mL), purified by filtration, and then extracted with dichloromethane (3 × 200 mL). The combined organic extracts were washed with saturated aqueous NaCl solution (2 × 50 mL), the organic phase was dried over anhydrous Na$_2$SO$_4$, and the solvent was removed under reduced pressure. The oily residue was distilled in a Kugelrohr apparatus (oven temperature 190 °C, 0.01 mbar) to give **8** as a yellowish liquid (9.87 g, 49%). ^{1}H NMR (CDCl$_3$): δ 2.14 (tt, ^3J(HH) = 6.8 Hz, ^3J(HH) = 7.2 Hz, 2 H, CC*H*$_2$C), 2.94 (t, ^3J(HH) = 6.8 Hz, 2 H, C(O)C*H*$_2$C), 2.34 (s, 3 H, CC*H*$_3$), 3.93 (t, ^3J(HH) = 7.2 Hz, 2 H, NC*H*$_2$C), 6.79 (δ_A) and 6.88 (δ_X) (^3J(AX) = 0.9 Hz, 2 H, N−C*H*$_X$=C*H*$_A$−N=C), 7.38−7.48 and 7.49−7.59 (m, 5 H, CC$_6$*H*$_5$). ^{13}C NMR (CDCl$_3$): δ 13.3 (C*C*H$_3$), 25.1 (C*C*H$_2$C), 34.8 (C(O)*C*H$_2$C), 45.4 (N*C*H$_2$C), 119.0 (*C*-4, imidazole), 127.2

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(*C*-5, imidazole), 127.9 (*C*-2/*C*-6 or *C*-3/*C*-5, CC_6H_5), 128.7 (*C*-2/*C*-6 or *C*-3/*C*-5, CC_6H_5), 133.4 (*C*-4, CC_6H_5), 136.4 (*C*-1, CC_6H_5), 142.5 (*C*-2, imidazole), 198.6 (*C*═O). Anal. Calcd for $C_{14}H_{16}N_2O$: C, 73.66; H, 7.06; N, 12.27. Found: C, 73.5; H, 7.2; N, 12.1.

Preparation of 1-(4-Fluorophenyl)-4-(2-methylimidazol-1-yl)butan-1-one (9). This compound was prepared analogously to the synthesis of **8**, starting from **7** (30.0 g, 123 mmol), and was purified by distillation in a Kugelrohr apparatus (oven temperature 175 °C, 0.01 mbar) to give a yellowish liquid (13.3 g, 44%). ^{1}H NMR ($CDCl_3$): δ 2.13 ("quint", ^3J(HH) = 6.8 Hz, ^3J(HH) = 6.8 Hz, 2 H, CCH_2C), 2.35 (s, 3 H, CCH_3), 2.90 (t, ^3J(HH) = 6.8 Hz, 2 H, C(O)CH_2C), 3.93 (t, ^3J(HH) = 6.8 Hz, 2 H, NCH_2C), 6.79 (δ_A) and 6.88 (δ_X) (^3J(AX) = 1.1 Hz, 2 H, N−CH_X═CH_A−N═C), 7.04−7.14 and 7.86−8.00 (m, 4 H, CC_6H_4F). ^{13}C NMR ($CDCl_3$): δ 12.7 (CCH_3), 24.6 (CCH_2C), 34.2 (C(O)CH_2C), 44.9 (NCH_2C), 115.8 (d, ^2J(CF) = 21.8 Hz, *C*-3/*C*-5, CC_6H_4F), 119.0 (*C*-4, imidazole), 126.7 (*C*-5, imidazole), 130.5 (d, ^3J(CF) = 9.4 Hz, *C*-2/*C*-6, CC_6H_4F), 132.8 (d, ^4J(CF) = 2.9 Hz, *C*-1, CC_6H_4F), 144.5 (*C*-2, imidazole), 165.8 (d, ^1J(CF) = 255.4 Hz, *C*-4, CC_6H_4F), 196.9 (*C*═O). Anal. Calcd for $C_{14}H_{15}FN_2O$: C, 68.28; H, 6.14; N, 11.37. Found: C, 68.1; H, 6.3; N, 11.3.

Preparation of (3-Chloropropyl)cyclohexyldimethoxysilane (10). Synthesis is as described in ref 1.

Preparation of Cyclohexyldimethoxy[3-(2-methylimidazol-1-yl)propyl]silane (11). A 1.6 M solution of *n*-butyllithium in *n*-hexane (54.8 mL, 87.7 mmol of *n*-BuLi) was added dropwise at −30 °C over a period of 1 h to a stirred solution of 2-methylimidazole (7.20 g, 87.7 mmol) in tetrahydrofuran (60 mL). The mixture was allowed to warm to rt within 6 h and then stirred for 11 h. The resulting suspension was added in portions at rt over a period of 45 min to a stirred solution of **10** (20.0 g, 79.7 mmol) in dimethylformamide (100 mL) and the mixture heated under reflux for 17 h. After the solvent was removed under reduced pressure, diethyl ether (200 mL) was added and the mixture kept at rt for 16 h. The precipitate was removed by filtration, the filtrate concentrated under reduced pressure, and the residue distilled in vacuo (Vigreux column) to give **11** as a colorless liquid (17.8 g, 75%), bp 145 °C/0.001 mbar. ^{1}H NMR ($CDCl_3$): δ 0.47−0.54 (m, 2 H, SiCH_2C), 0.70−0.87 (m, 1 H, SiCHC$_2$), 1.03−1.28 and 1.58−1.88 (m, 12 H, CCH_2C), 2.35 (s, 3 H, CCH_3), 3.50 (s, 6 H, OCH_3), 3.78 (t, ^3J(HH) = 7.3 Hz, 2 H, NCH_2C), 6.79 (δ_A) and 6.87 (δ_X) (^3J(AX) = 1.3 Hz, 2 H, N−CH_X═CH_A−N═C). ^{13}C NMR ($CDCl_3$): δ 7.4 (SiCH_2C), 12.9 (CCH_3), 24.2 (SiCHC_2), 24.4 (SiCH_2CH_2C), 26.7 (3 C) (CCH_2C), 27.6 (CCH_2C), 48.5 (NCH_2C), 50.6 (OCH_3), 119.0 (*C*-4, imidazole), 126.8 (*C*-5, imidazole), 144.3 (*C*-2, imidazole). ^{29}Si NMR ($CDCl_3$): δ −7.7. Anal. Calcd for $C_{15}H_{28}N_2O_2Si$: C, 60.77; H, 9.52; N, 9.45. Found: C, 60.7; H, 9.6; N, 9.4.

Preparation of Cyclohexyl(methoxy)[3-(2-methylimidazol-1-yl)propyl]phenylsilane (12). A 1.6 M solution of *n*-butyllithium in *n*-hexane (24.5 mL, 39.2 mmol of *n*-BuLi) was added dropwise at −35 °C over a period of 30 min to a stirred solution of bromobenzene (6.16 g, 39.2 mmol) in diethyl ether (80 mL). The mixture was stirred at −35 °C for 2 h and then added dropwise at −10 °C over a period of 45 min to a stirred solution of **11** (10.6 g, 35.8 mmol) in diethyl ether (100 mL). The resulting mixture was stirred at −10 °C for 1 h and at rt for a further 15 h, followed by addition of saturated aqueous NH_4Cl solution (30 mL). The organic phase was separated and the aqueous layer extracted with diethyl ether (3 × 60 mL), and the combined organic extracts were dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue distilled in a Kugelrohr apparatus (oven temperature 210 °C, 0.01 mbar). The distillate was dissolved in *n*-pentane (20 mL) and the solution kept undisturbed at −20 °C for 3 days. The resulting solid was isolated by filtration and dried in vacuo (0.001 mbar) for 6 h to give **12** as a colorless crystalline product (9.55 g, 78%), mp 94−95 °C. ^{1}H NMR ($CDCl_3$): δ 0.66−0.89 (m, 2 H, SiCH_2C), 0.90−1.02 (m, 1 H, SiCHC$_2$), 1.03−1.28 and 1.54−1.85 (m, 12 H, CCH_2C), 2.28 (s, 3 H, CCH_3), 3.47 (s, 3 H, OCH_3), 3.75 (t, ^3J(HH) = 7.2 Hz, 2 H, NCH_2C), 6.73 (δ_A) and 6.84 (δ_X) (^3J(AX) = 1.3 Hz, 2 H, N−CH_X═CH_A−N═C), 7.27−7.38 and 7.39−7.47 (m, 5 H, SiC_6H_5). ^{13}C NMR ($CDCl_3$): δ 8.3 (SiCH_2C), 12.9 (CCH_3), 24.5 (SiCH_2CH_2C), 25.0 (SiCHC_2), 26.6 (CCH_2C), 26.75 (CCH_2C), 26.78 (CCH_2C), 27.6 (CCH_2C), 27.7 (CCH_2C), 48.5 (NCH_2C), 51.3 (OCH_3), 118.8 (*C*-4, imidazole), 126.9 (*C*-5, imidazole), 127.8 (*C*-3/*C*-5, SiC_6H_5), 129.5 (*C*-4, SiC_6H_5), 133.9 (*C*-2/*C*-6, SiC_6H_5), 134.1 (*C*-1, SiC_6H_5), 144.2 (*C*-2, imidazole). ^{29}Si NMR ($CDCl_3$): δ 5.2. Anal. Calcd for $C_{20}H_{30}N_2OSi$: C, 70.13; H, 8.83; N, 8.18. Found: C, 69.8; H, 8.6; N, 8.3.

Preparation of Cyclohexyl(4-fluorophenyl)methoxy[3-(2-methylimidazol-1-yl)propyl]silane (13). This compound was prepared analogously to the synthesis of **12**, starting from **11** (10.6 g, 35.8 mmol) and using 1-bromo-4-fluorobenzene (6.86, 39.2 mmol) instead of bromobenzene and was isolated as a colorless crystalline product (9.52 g, 74%), mp 56−57 °C. ^{1}H NMR ($CDCl_3$): δ 0.64−0.88 (m, 3 H, SiCH_2C, SiCHC$_2$), 0.89−1.22 and 1.52−1.82 (m, 12 H, CCH_2C), 2.26 (s, 3 H, CCH_3), 3.43 (s, 3 H, OCH_3), 3.73 (t, ^3J(HH) = 7.1 Hz, 2 H, NCH_2C), 6.70 (δ_A) and 6.82 (δ_X) (^3J(AX) = 1.3 Hz, 2 H, N−CH_X═CH_A−N═C), 6.93−7.05 and 7.32−7.35 (m, 4 H, SiC_6H_4F). ^{13}C NMR ($CDCl_3$): δ 8.3 (SiCH_2C), 12.9 (CCH_3), 24.4 (SiCH_2CH_2C), 24.9 (SiCHC_2), 26.5 (CCH_2C), 26.67 (CCH_2C), 26.68 (CCH_2C), 27.55 (CCH_2C), 27.61 (CCH_2C), 48.4 (NCH_2C), 51.2 (OCH_3), 115.0 (d, ^2J(CF) = 20.0 Hz, *C*-3/*C*-5, SiC_6H_4F), 118.8 (*C*-4, imidazole), 126.9 (*C*-5, imidazole), 129.7 (d, ^4J(CF) = 3.6 Hz, *C*-1, SiC_6H_4F), 135.9 (d, ^3J(CF) = 7.6 Hz, *C*-2/*C*-6, SiC_6H_4F), 144.2 (*C*-2, imidazole), 163.8 (d, ^1J(CF) = 249.3 Hz, *C*-4, SiC_6H_4F). ^{29}Si NMR ($CDCl_3$): δ 5.1. Anal. Calcd for $C_{20}H_{29}FN_2OSi$: C, 66.63; H, 8.11; N, 7.77. Found: C, 66.4; H, 8.1; N, 7.9.

Pharmacological Studies. Radioligand binding studies were performed according to the methods outlined in the literature.[21,22,26] Briefly, [^{3}H]NMS (78−85 Ci mmol^{-1}; Amersham International, Bucks, England) binding to membranes of CHO-K1 cells stably transfected with human M_1−M_5 receptors was measured in a buffer containing 20 mM HEPES (pH 7.4) enriched with 100 mM NaCl and 10 mM $MgCl_2$. Final membrane protein concentrations were (μg ml^{-1}) M_1, 2; M_2, 6; M_3, 2; M_4, 2; and M_5, 5. The incubation of tracer (0.2 nM) and different concentrations of competitors (**1b**, **4a**, **4b**, **5a**, and **5b**; dissolved as hydrochlorides) was 2 h at 25 °C and terminated by filtration over Whatman GF/B filters presoaked in 0.5% polyethylenimine (1−2 h) using a Brandel cell harvester. Nonspecific binding was measured in the presence of 1 μM atropine. Previously estimated [^{3}H]NMS K_D values, obtained in saturation experiments, were 0.19 (M_1), 0.33 (M_2), 0.17 (M_3), 0.10 (M_4), and 0.48 nM (M_5).

Data of the binding experiments were analyzed by a nonlinear, iterative curve-fitting procedure (GraphPAD Software, San Diego, CA). K_i values of compounds **1b**, **4a**, **4b**, **5a**, and **5b** were calculated from IC_{50} values obtained from competition curves using the Cheng-Prusoff equation.[27] All data are presented as arithmetic means ± SD of at least three experiments performed in duplicate. Differences between mean values were tested for statistical significance by Student's *t* test; $P < 0.05$ was accepted as being significant.

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