Synthesis and Pharmacological Properties of Silicon-Containing 1,4-Dihydropyridine Derivatives: Calcium Channel Antagonists and α_1 Adrenoceptor Antagonists of the Sila-niguldipine Type

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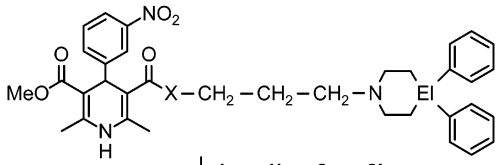
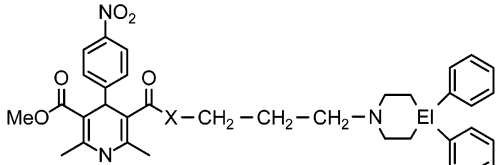
Racemic 3-(4,4-diphenyl-4-silapiperidin-1-yl)propyl methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (*rac*-sila-niguldipine, *rac*-**1b**), a sila analogue of the calcium antagonist *rac*-niguldipine (*rac*-**1a**), and the sila-niguldipine derivatives *rac*-**2b**−*rac*-**4b** were synthesized in multistep syntheses, starting from dichlorodiphenylsilane. The silicon compounds *rac*-**1b**−*rac*-**4b** contain a 4,4-diphenyl-4-silapiperidin-1-yl group instead of the 4,4-diphenylpiperidin-1-yl moiety in the parent carbon compound *rac*-**1a**. *rac*-Sila-niguldipine and the precursor 3-(4,4-diphenyl-4-silapiperidin-1-yl)propanol (**11**) were structurally characterized by single-crystal X-ray diffraction. The pharmacological profiles of *rac*-**1b**−*rac*-**4b** were compared with that of *rac*-**1a** across a range of receptor binding assays (radioligand binding studies at α_{1A} and α_2 adrenoceptors, the L-type Ca^{2+} channel, and the serotonin 5-HT receptor). The silicon compounds *rac*-**2b**−*rac*-**4b** exhibit a profile similar to that of SNAP 5089 and therefore may be of potential benefit in the treatment of diseases such as benign prostatic hyperplasia (BPH).

Introduction

Calcium channel blockers are widely used in the treatment of cardiovascular diseases, such as angina pectoris, certain types of cardiac arrhythmia, hypertension, and others.[1,2] Within this class of drugs, substituted 4-aryl-1,4-dihydropyridines represent the most extensively studied type of compound. Niguldipine (**1a**) is an example of this class of calcium antagonists, which binds with high affinity to Ca^{2+} channels and to α_1 adrenoceptors.[3,4] Certain niguldipine derivatives with a 4-nitrophenyl substituent instead of the 3-nitrophenyl group and/or an amide linkage instead of an ester group, compounds **2a**−**4a** (**4a**: SNAP 5089), were shown to maintain high α_1-adrenoceptor affinity while binding to Ca^{2+} channels is reduced.[4] This receptor selectivity pattern makes those compounds promising candidates for many therapeutic indications such as benign prostatic hyperplasia (BPH).[5] In context with our research program dealing with the development of silicon-based drugs,[6,7] we examined the biological effects of sila-substitution (C/Si exchange) of the quaternary carbon atom of the 4,4-diphenylpiperidin-1-yl group of **1a**−**4a**. We report here on the synthesis and pharmacological characterization of racemic sila-niguldipine (*rac*-**1b**) and its derivatives *rac*-**2b**−*rac*-**4b**.



	1a	1b	2a	2b
El	C	Si	C	Si
X	O	O	NH	NH



	3a	3b	4a	4b
El	C	Si	C	Si
X	O	O	NH	NH

Results and Discussion

Syntheses. Racemic sila-niguldipine (*rac*-**1b**) and its 4-nitrophenyl derivative *rac*-**3b** were synthesized in multistep syntheses, starting from the dichlorosilane **5** (Scheme 1). Thus, treatment of **5** with vinylmagnesium chloride gave the divinylsilane **6**,[8] which upon addition of hydrogen bromide afforded the bis(2-bromoethyl)-silane **7**.[9] Reaction of **7** with 3-((trimethylsilyl)oxy)-propylamine[10] (**9**) (prepared by silylation of 3-amino-propanol (**8**) with hexamethyldisilazane) gave the

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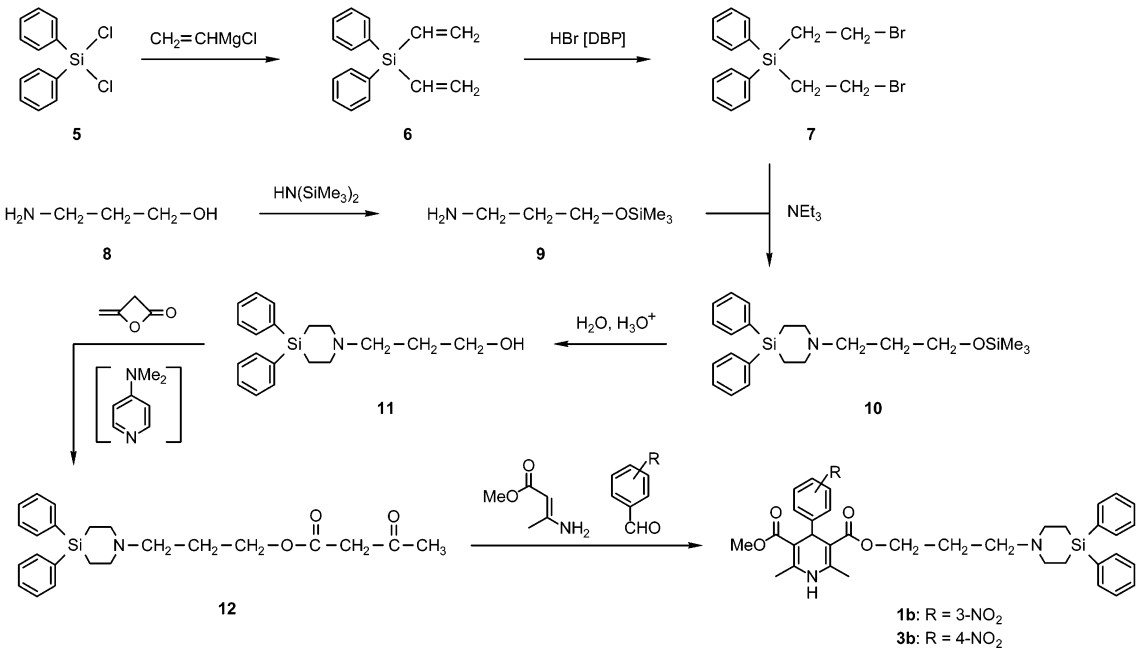
Scheme 1



4-silapiperidine derivative **10** (isolated as the crude product, not purified), which upon hydrolysis yielded the 4-silapiperidine derivative **11**. Treatment of **11** with diketene, in the presence of 4-(dimethylamino)pyridine, gave the 3-oxobutanoate **12** (isolated as the crude product, not purified), which upon reaction with 3-nitrobenzaldehyde and methyl 3-aminocrotonate finally afforded *rac*-sila-niguldipine (*rac*-**1b**). The derivative *rac*-**3b** was obtained analogously by using 4-nitrobenzaldehyde instead of 3-nitrobenzaldehyde.

The sila-niguldipine derivatives *rac*-**2b** and *rac*-**4b** were prepared in three-step syntheses, starting from **7** (Scheme 2). Thus, treatment of **7** with propane-1,3-diamine gave the 4-silapiperidine derivative **13**, which upon reaction with diketene gave the 3-oxobutanamide **14** (isolated as the crude product, not purified). Reaction of **14** with 3-nitrobenzaldehyde and methyl 3-aminocrotonate finally afforded *rac*-**2b**. The derivative *rac*-**4b** was obtained analogously by using 4-nitrobenzaldehyde instead of 3-nitrobenzaldehyde.

Crystal Structure Analyses. The compounds *rac*-**1b** and **11** were structurally characterized by single-crystal X-ray diffraction. Their molecular structures are depicted in Figures 1 and 2.

As in other 1,4-dihydropyridines (DHPs),[11−13] the 1,4-DHP ring of *rac*-**1b** adopts a flat boat conformation, the 3-nitrophenyl substituent occupying a pseudoaxial position and the nitro group being orientated synperiplanar with respect to the C4-*H* hydrogen atom. To the best of our knowledge, compounds *rac*-**1b** and **11** represent the first 1-silapiperidine derivatives that have been structurally characterized by single-crystal X-ray diffraction. In both compounds, the 1-silapiperidine skeleton adopts a chair conformation, with the exocyclic *N*-organyl group in an axial (*rac*-**1b**) or equatorial position (**11**). As can be seen from Figures 1 and 2, the structures of the two 1-silapiperidine skeletons are very similar.

Pharmacological Studies. The pharmacological profiles of *rac*-sila-niguldipine (*rac*-**1b**) and its derivatives *rac*-**2b**−*rac*-**4b** were compared with that of *rac*-niguldipine (*rac*-**1a**) across a range of receptor binding assays. The data obtained in these studies are shown in Table 1. *rac*-Sila-niguldipine (*rac*-**1b**) exhibits essentially the same affinity and selectivity profile as the carbon analogue *rac*-niguldipine (*rac*-**1a**), indicating that sila-substitution of the quaternary carbon atom of the 4,4-diphenylpiperidin-1-yl group has not affected the in vitro pharmacological profile. A comparison of the data for the O/NH analogues *rac*-**1b** and *rac*-**2b** shows, as expected by comparison with literature data for SNAP 5089 (*rac*-**4a**),[4] that for the amide derivative *rac*-**2b** affinity at the α_{1A} adrenoceptor is retained while binding to the L-type Ca^{2+} channel is reduced by up to 2 orders of magnitude. A similar loss of potency for the L-type Ca^{2+} channel but not α_{1A} adrenoceptor was

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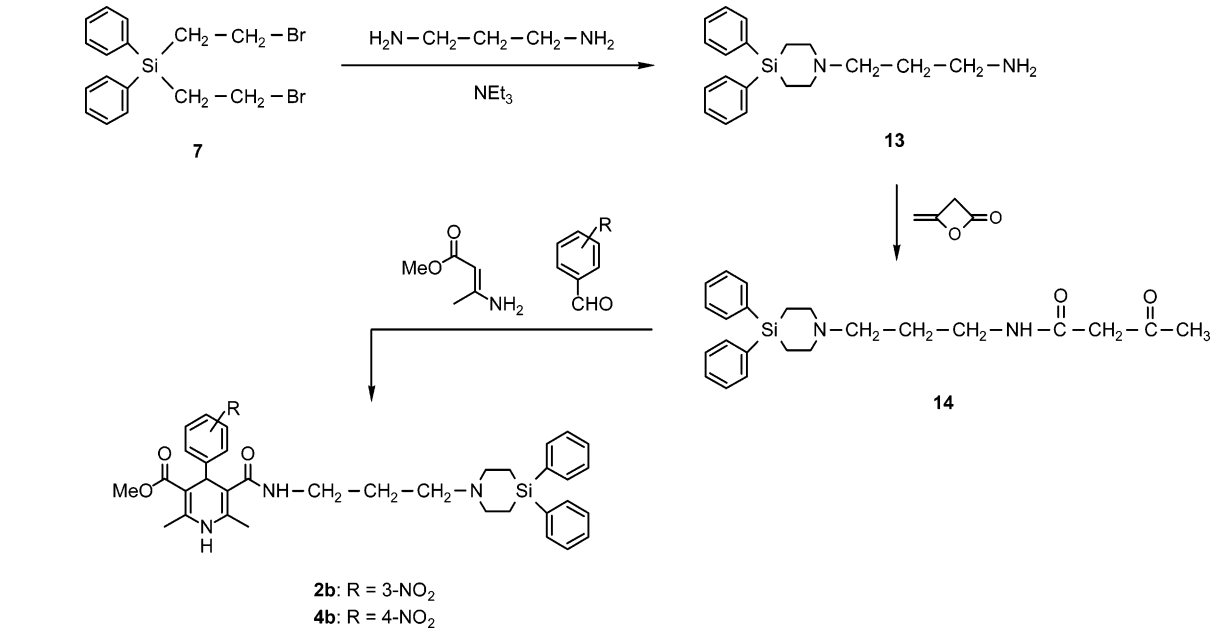
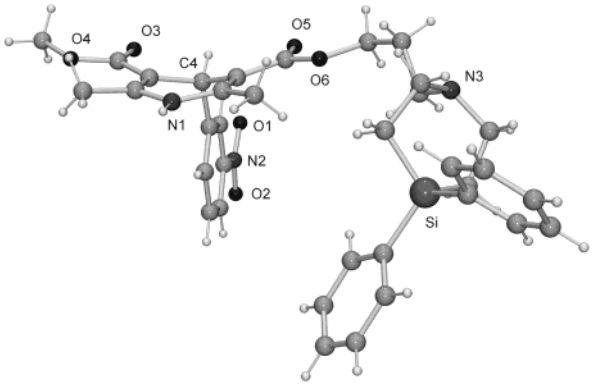
Scheme 2



2b: R = 3-NO_2
4b: R = 4-NO_2



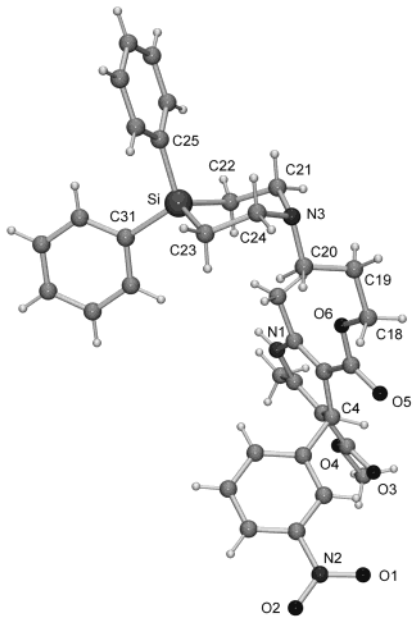


Figure 1. Two perspectives of the structure of one of the two enantiomers in the crystal of *rac*-**1b**.

observed with the 4-nitrophenyl derivative *rac*-**3b**. These data demonstrate that an ester rather than an amide linkage and a 4-(3-nitrophenyl) rather than 4-(4-nitrophenyl) substituent are preferred in order to maintain potency at the L-type Ca^{2+} channel. When both the amide linkage and the 4-(4-nitrophenyl) moiety are incorporated (→*rac*-**4b**), no additional loss of potency for the α_{1A} adrenoceptor or L-type Ca^{2+} channel was observed in comparison with *rac*-**2b** or *rac*-**3b**.

These data suggest that the sila-niguldipine derivatives *rac*-**2b**, *rac*-**3b**, and *rac*-**4b**, exhibiting a profile of activity similar to that for SNAP 5089, may therefore be of potential benefit in the treatment of diseases such as benign prostatic hyperplasia (BPH).

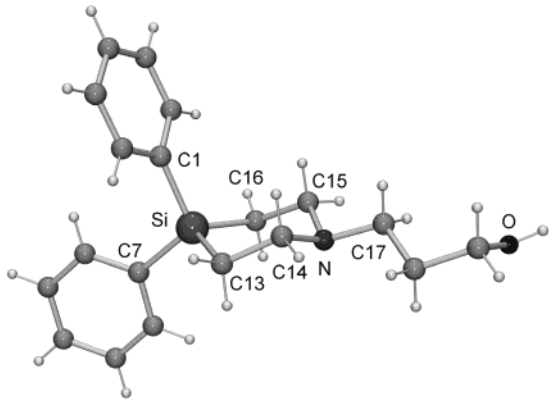


Figure 2. Structure of **11** in the crystal.

Table 1. Binding Profiles of Compounds *rac*-1a and *rac*-1b−*rac*-4b at α_{1A} and α_2 Adrenoceptors, the L-Type Ca^{2+} Channel, and the Serotonin 5-HT Receptor[a]

compd	α_{1A}	α_2 nonspecific	Ca^{2+} channel L-type	5-HT nonspecific
rac-**1a**	0.68	68% at 10 μM	0.45	13% at 1 μM
rac-**1b**	0.46	59% at 10 μM	0.49	9% at 1 μM
rac-**2b**	0.82	nd	44.6	IA at 1 μM
rac-**3b**	0.56	nd	32.9	IA at 1 μM
rac-**4b**	0.39	nd	68.0	9% at 1 μM

[a] Data expressed as K_i values (nM) or percent inhibition of binding. Data represent the mean of two determinations. IA = inactive; n.d. = not determined.

Experimental Section

General Procedures. All syntheses were carried out under dry nitrogen. Acetone, acetonitrile, dichloromethane, diethyl ether, ethanol, ethyl acetate, methanol, *n*-pentane, 2-propanol, tetrahydrofuran (THF), and toluene were dried and purified according to standard procedures and stored under nitrogen. Melting points were determined with a Büchi B-540 melting point apparatus in open glass capillaries and are uncorrected. ^{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) using CD_2Cl_2 or $CDCl_3$ as the solvent. Chemical shifts (ppm) were determined relative to internal $CDHCl_2$ (^{1}H, δ 5.32; CD_2Cl_2), $CHCl_3$ (^{1}H, δ 7.24; $CDCl_3$), CD_2Cl_2 (^{13}C, δ 53.8; CD_2Cl_2), $CDCl_3$ (^{13}C, δ 77.0; $CDCl_3$), or external TMS (^{29}Si, δ 0; CD_2Cl_2, $CDCl_3$). Analysis and assignment of the ^{1}H NMR data were supported by ^{1}H,^{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 and ^{13}C,^{1}H COSY experiments. Analysis and assignment of the ^{1}H NMR and ^{13}C NMR data was further supported by comparison with the data for related DHP systems reported in ref 14.

Preparation of Racemic 3-(4,4-Diphenyl-4-silapiperidin-1-yl)propyl Methyl 2,6-Dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (*rac*-Sila-nigulpine, *rac*-1b). 4-(Dimethylamino)pyridine (10 mg, 82 μmol) was added in one portion to a stirred solution of **11** (1.80 g, 5.78 mmol) and diketene (550 mg, 6.54 mmol) in THF (20 mL) at 0 °C, and the resulting solution was then warmed to 20 °C and stirred at this temperature for 48 h. The solvent was removed in vacuo to give 2.10 g of 3-(4,4-diphenyl-4-silapiperidin-1-yl)propyl 3-oxobutanoate (**12**; oily crude product, not further purified). A solution of this product, 3-nitrobenzaldehyde (840 mg, 5.56 mmol), and methyl 3-aminocrotonate (640 mg, 5.56 mmol) in 2-propanol (20 mL) was heated under reflux for 72 h. The mixture was then cooled to 20 °C, the solvent was removed under reduced pressure, and the resulting highly viscous crude product was purified by preparative column chromatography (column length, 350 mm; i.d., 35 mm; silica gel 60, 0.015−0.040 mm, Merck 15111) using ethyl acetate as the eluent. The pure product fractions were combined, the solvent was removed in vacuo, and the residue was crystallized from acetone/diethyl ether (1/2 (v/v)) at −20 °C to give *rac*-**1b** in 43% yield as a yellowish crystalline solid (1.55 g, 2.48 mmol); mp 168−169 °C. ^{1}H NMR (CD_2Cl_2): δ 1.25−1.41 (m, 4 H, SiCH_2CH$_2$N), 1.68−1.82 (m, 2 H, NCH$_2$CH_2CH$_2$O), 2.33 (s, 3 H, CCH_3), 2.36 (s, 3 H, CCH_3), 2.28−2.43 (m, 2 H, NCH_2CH$_2$-CH$_2$O), 2.65−2.80 (m, 4 H, SiCH$_2$CH_2N), 3.61 (s, 3 H, OCH_3), 4.00−4.18 (m, 2 H, NCH$_2$CH$_2$CH_2O), 5.11 (s, 1 H, C$_3$CH), 6.1 (br s, 1 H, NH), 7.32−7.44 and 7.50−7.60 (m, 11 H, SiC$_6H_5$, *H*-5 of C$_6$H$_4$NO$_2$), 7.67 (ddd, $^3J_{H-4/H-5}$ = 7.7 Hz, $^4J_{H-4/H-6}$ = 1.1 Hz, $^4J_{H-2/H-4}$ = 1.7 Hz, 1 H, *H*-4, C$_6$H$_4$NO$_2$), 7.97 (ddd, $^3J_{H-5/H-6}$ = 8.2 Hz, $^4J_{H-4/H-6}$ = 1.1 Hz, $^4J_{H-2/H-6}$ = 2.3 Hz, 1 H, *H*-6, C$_6$H$_4$NO$_2$), 8.12 (dd, $^4J_{H-2/H-4}$ = 1.7 Hz, $^4J_{H-2/H-6}$ = 2.3 Hz, 1 H, *H*-2, C$_6$H$_4$NO$_2$). ^{13}C NMR (CD_2Cl_2): δ 11.4 (SiCH$_2$-CH$_2$N), 19.59 (CCH$_3$), 19.60 (CCH$_3$), 27.0 (NCH$_2$CH$_2$CH$_2$O), 40.2 (C$_3$CH), 51.2 (OCH$_3$), 52.5 (SiCH$_2$CH$_2$N), 54.7 (NCH$_2$CH$_2$-CH$_2$O), 62.9 (NCH$_2$CH$_2$CH$_2$O), 103.15 (C$_2$C=C), 103.23 (C$_2$C=C), 121.5 (*C*-4, C$_6$H$_4$NO$_2$), 123.1 (*C*-2, C$_6$H$_4$NO$_2$), 128.3 (*C*-3/*C*-5, SiC$_6H_5$), 129.1 (*C*-5, C$_6$H$_4$NO$_2$), 129.7 (*C*-4, SiC$_6H_5$), 134.7 (*C*-6, C$_6$H$_4$NO$_2$), 135.0 (*C*-2/*C*-6, SiC$_6H_5$), 136.3 (*C*-1, SiC$_6H_5$), 145.46 (NCC=C), 145.50 (NCC=C), 148.6 (*C*-1, C$_6$H$_4$NO$_2$), 150.3 (*C*-3, C$_6$H$_4$NO$_2$), 167.3 (*C*=O), 167.8 (*C*=O). ^{29}Si NMR (CD_2Cl_2): δ −15.3. Anal. Calcd for $C_{35}H_{39}N_3O_6Si$: C, 67.18; H, 6.28; N, 6.71. Found: C, 67.0; H, 6.5; N, 6.5.

Preparation of Racemic Methyl 5-(((3-(4,4-Diphenyl-4-silapiperidin-1-yl)propyl)amino)carbonyl)-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylate (*rac*-2b). Diketene (700 mg, 8.33 mmol) was added dropwise within 1 min to a stirred solution of **13** (2.00 g, 6.44 mmol) in toluene (20 mL) at 20 °C, and the mixture was then stirred at this temperature for 24 h. The solvent was removed in vacuo to give 2.35 g of *N*-(3-(4,4-diphenyl-4-silapiperidin-1-yl)propyl)-3-oxobutanamide (**14**; oily crude product, not further purified). A solution of this product, 4-nitrobenzaldehyde (1.00 g, 6.62 mmol), and methyl 3-aminocrotonate (760 mg, 6.60 mmol) in 2-propanol (20 mL) was heated under reflux for 72 h. The mixture was then cooled to 20 °C, the solvent was removed under reduced pressure, and the resulting highly viscous crude product was purified by preparative column chromatography (column length, 350 mm; i.d., 35 mm; silica gel 60, 0.015−0.040 mm, Merck 15111) using successively ethyl acetate, ethyl acetate/methanol (9/1 (v/v)), and ethyl acetate/methanol (7/3 (v/v)) as the eluent. The pure product fractions were combined, the solvent was removed in vacuo, and the residue was crystallized from ethanol to give *rac*-**2b** in 21% yield as a yellowish crystalline solid (830 mg, 1.33 mmol); mp 98−100 °C. ^{1}H NMR (CD_2Cl_2): δ 1.12−1.32 (m, 4 H, SiCH_2CH$_2$N), 1.49−1.67 (m, 2 H, NCH$_2$CH_2CH$_2$NH), 2.08 (s, 3 H, CCH_3), 2.30 (s, 3 H, CCH_3), 2.33−2.55 (m, 2 H, NCH_2CH$_2$CH$_2$NH), 2.63−2.82 (m, 4 H, SiCH$_2$CH_2N), 3.12−3.26 and 3.35−3.45 (m, 2 H, NCH$_2$CH$_2$CH_2NH), 3.49 (s, 3 H, OCH_3), 5.00 (s, 1 H, C$_3$CH), 5.8 (br s, 1 H, NH), 7.06 (t, $^3J_{HH}$ = 4.9 Hz, 1 H, C(O)-NH), 7.33−7.43 and 7.47−7.54 (m, 11 H, SiC$_6H_5$, *H*-5 of C$_6$H$_4$-NO$_2$), 7.60 (ddd, $^3J_{H-4/H-5}$ = 8.0 Hz, $^4J_{H-4/H-6}$ = 1.1 Hz, $^4J_{H-2/H-4}$ = 2.3 Hz, 1 H, *H*-4, C$_6$H$_4$NO$_2$), 7.95−8.01 (m, 1 H, *H*-6, C$_6$H$_4$-NO$_2$), 8.04−8.08 (m, 1 H, *H*-2, C$_6$H$_4$NO$_2$). ^{13}C NMR (CD_2Cl_2): δ 10.5 (SiCH$_2$CH$_2$N), 18.1 (CCH$_3$), 19.9 (CCH$_3$), 25.8 (NCH$_2$CH$_2$-CH$_2$NH), 39.8 (NCH$_2$CH$_2$CH$_2$NH), 41.6 (C$_3$CH), 51.0 (OCH$_3$), 52.3 (SiCH$_2$CH$_2$N), 56.2 (NCH$_2$CH$_2$CH$_2$NH), 99.8 (CC(O)NH), 109.2 (CC(O)O), 121.6 (*C*-4, C$_6$H$_4$NO$_2$), 122.5 (*C*-2, C$_6$H$_4$NO$_2$), 128.4 (*C*-3/*C*-5, SiC$_6H_5$), 129.5 (*C*-5, C$_6$H$_4$NO$_2$), 129.9 (*C*-4, SiC$_6H_5$), 134.1 (*C*-6, C$_6$H$_4$NO$_2$), 134.8 (*C*-2/*C*-6, SiC$_6H_5$), 135.4 (NCC=CC(O)NH), 135.8 (*C*-1, SiC$_6H_5$), 147.0 (NCC=CC(O)O), 148.8 (*C*-1, C$_6$H$_4$NO$_2$), 149.5 (*C*-3, C$_6$H$_4$NO$_2$), 167.9 (*C*(O)O), 168.2 (*C*(O)NH). ^{29}Si NMR (CD_2Cl_2): δ −16.2. Anal. Calcd for $C_{35}H_{40}N_4O_5Si$: C, 67.28; H, 6.45; N, 8.97. Found: C, 66.7; H, 6.5; N, 8.7.

Preparation of Racemic 3-(4,4-Diphenyl-4-silapiperidin-1-yl)propyl Methyl 2,6-Dimethyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (*rac*-3b). This compound was synthesized analogously to the synthesis of *rac*-**1b** using 4-nitrobenzaldehyde instead of 3-nitrobenzaldehyde. The product *rac*-**3b** was isolated, after crystallization from methanol, in 35% yield as a yellowish crystalline solid (1.28 g, 2.05 mmol); mp 159−160 °C. ^{1}H NMR (CD_2Cl_2): δ 1.25−1.35 (m, 4 H, SiCH_2CH$_2$N), 1.67−1.80 (m, 2 H, NCH$_2$CH_2CH$_2$O), 2.32 (s, 3 H, CCH_3), 2.34 (s, 3 H, CCH_3), 2.32−2.44 (m, 2 H, NCH_2-CH$_2$CH$_2$O), 2.68−2.80 (m, 4 H, SiCH$_2$CH_2N), 3.61 (s, 3 H, OCH_3), 4.00−4.15 (m, 2 H, NCH$_2$CH$_2$CH_2O), 5.09 (s, 1 H, C$_3$CH), 5.9 (br s, 1 H, NH), 7.32−7.41, 7.42−7.49, 7.50−7.57, and 8.04−8.10 (m, 14 H, aryl-*H*). ^{13}C NMR (CD_2Cl_2): δ 11.4 (SiCH$_2$CH$_2$N), 19.65 (CCH$_3$), 19.67 (CCH$_3$), 27.0 (NCH$_2$CH$_2$-CH$_2$O), 40.4 (C$_3$CH), 51.2 (OCH$_3$), 52.5 (SiCH$_2$CH$_2$N), 54.7 (NCH$_2$CH$_2$CH$_2$O), 62.9 (NCH$_2$CH$_2$CH$_2$O), 103.0 (C$_2$C=C), 103.1 (C$_2$C=C), 123.6 (*C*-3/*C*-5, C$_6$H$_4$NO$_2$), 128.3 (*C*-3/*C*-5, SiC$_6H_5$), 129.1 (*C*-2/*C*-6, C$_6$H$_4$NO$_2$), 129.7 (*C*-4, SiC$_6H_5$), 134.9 (*C*-2/*C*-6, SiC$_6H_5$), 136.3 (*C*-1, SiC$_6H_5$), 145.4 (2 C) (NCC=C), 146.7 (*C*-4, C$_6$H$_4$NO$_2$), 155.5 (*C*-1, C$_6$H$_4$NO$_2$), 167.2 (*C*=O), 167.7 (*C*=O). ^{29}Si NMR (CD_2Cl_2): δ −15.4. Anal. Calcd for $C_{35}H_{39}N_3O_6Si$: C, 67.18; H, 6.28; N, 6.71. Found: C, 66.9; H, 6.4; N, 6.4.

Preparation of Racemic Methyl 5-(((3-(4,4-Diphenyl-4-silapiperidin-1-yl)propyl)amino)carbonyl)-2,6-dimethyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3-carboxylate (*rac*-4b). This compound was synthesized analogously to the synthesis of *rac*-**2b** using 4-nitrobenzaldehyde instead of 3-nitrobenzaldehyde. Instead of a chromatographic purification, the product was purified by crystallization. For this

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Table 2. Experimental Data for Pharmacological Assays of Compounds *rac*-1a and *rac*-1b−*rac*-4b

assay	α_{1A} adrenergic	α_2 adrenergic nonspecific	Ca^{2+} channel L-type	5-HT nonspecific
tissue source	Wistar rat submaxillary gland	Wistar rat cerebral cortex	Wistar rat cerebral cortex	Sprague Dawley rat cerebral cortex
radioligand	0.25 nM [^{3}H]prazosin	0.7 nM [^{3}H]rauwolscine	0.1 nM [^{3}H]nitrendipine	2 nM [^{3}H]serotonin
nonspecific ligand	10 μM phentolamine	1 μM yohimbine	1 μM nifedipine	10 μM serotonin
incubation time, min	60	30	90	15
incubation temp, °C	25	25	25	37
incubation buffer	50 mM Tris-HCl, 0.5 mM EDTA, pH 7.4	20 mM Hepes, 2.5 mM Tris-HCl, pH 7.4	50 mM Tris-HCl, pH 7.7	50 mM Tris-HCl, 4 mM $CaCl_2$, 10 μM pargyline, 0.1% ascorbate, pH 7.7
ref	20	21, 22	23, 24	25

purpose, the crude product was dissolved in acetone (4 mL), followed by addition of diethyl ether (16 mL), and the resulting solution was then kept undisturbed at −20 °C for 72 h. The precipitate was isolated by filtration and recrystallized from acetone/diethyl ether (15 mL, 1/2 (v/v)) to give *rac*-**4b** in 29% yield as a yellowish crystalline solid (1.18 g, 1.89 mmol); mp 209−210 °C. ^{1}H NMR (CD_2Cl_2): δ 1.10−1.26 (m, 4 H, $SiCH_2$-CH_2N), 1.47−1.60 (m, 2 H, $NCH_2CH_2CH_2NH$), 2.06 (s, 3 H, CCH_3), 2.29 (s, 3 H, CCH_3), 2.32−2.52 (m, 2 H, $NCH_2CH_2CH_2$-NH), 2.60−2.76 (m, 4 H, $SiCH_2CH_2N$), 3.12−3.25 and 3.33−3.50 (m, 2 H, $NCH_2CH_2CH_2NH$), 3.49 (s, 3 H, OCH_3), 4.99 (s, 1 H, C_3CH), 5.7 (br s, 1 H, NH), 7.1 (br s, 1 H, C(O)NH), 7.33−7.44, 7.46−7.57, and 8.01−8.09 (m, 14 H, aryl H).^{13}C NMR (CD_2Cl_2): δ 10.8 ($SiCH_2CH_2N$), 18.0 (CCH_3), 19.9 (CCH_3), 25.9 ($NCH_2CH_2CH_2NH$), 40.2 ($NCH_2CH_2CH_2NH$), 41.9 (C_3CH), 51.0 (OCH_3), 52.4 ($SiCH_2CH_2N$), 56.7 ($NCH_2CH_2CH_2NH$), 99.6 (*C*C(O)NH), 109.4 (*C*C(O)O), 123.9 (*C*-3/*C*-5, $C_6H_4NO_2$), 128.3 (*C*-3/*C*-5, SiC_6H_5), 128.5 (*C*-2/*C*-6, $C_6H_4NO_2$), 129.8 (*C*-4, SiC_6H_5), 134.8 (*C*-2/*C*-6, SiC_6H_5), 134.9 (NC*C*=CC(O)NH), 136.0 (*C*-1, SiC_6H_5), 146.8 (*C*-4, $C_6H_4NO_2$), 147.1 (NC*C*=CC(O)O), 154.6 (*C*-1, $C_6H_4NO_2$), 167.8 (*C*(O)O), 168.2 (*C*(O)NH). ^{29}Si NMR (CD_2Cl_2): δ −16.1. Anal. Calcd for $C_{35}H_{40}N_4O_5Si$: C, 67.28; H, 6.45; N, 8.97. Found: C, 66.8; H, 6.4; N, 8.8.

Preparation of Diphenyldivinylsilane (6). This compound was synthesized from commercially available dichlorodiphenylsilane (**5**) according to ref 8.

Preparation of Bis(2-bromoethyl)diphenylsilane (7). This compound was synthesized from **6** according to ref 9, except for the use of *n*-pentane instead of *n*-heptane as the solvent.

Preparation of 3-((Trimethylsilyl)oxy)propylamine (9). This compound was synthesized from commercially available 3-aminopropanol (**8**) according to ref 10.

Preparation of 3-(4,4-Diphenyl-4-silapiperidin-1-yl)-propanol (11). A mixture of **7** (6.00 g, 15.1 mmol), **9** (2.50 g, 17.0 mmol), triethylamine (3.00 g, 29.6 mmol), acetonitrile (30 mL), and toluene (30 mL) was heated in a 250 mL autoclave at 80 °C for 16 h. After the reaction mixture was cooled to 20 °C, the precipitate was removed by filtration, water (50 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 4.80 g of crude 4,4-diphenyl-1-(3-((trimethylsilyl)oxy)propyl)-4-silapiperidine (**10**; oily crude product, not further purified). This product was dissolved in acetone (40 mL), 2 M hydrochloric acid (2 mL) was added, and the resulting mixture was stirred at 20 °C for 2 h, followed by successive addition of 6 M aqueous sodium hydroxide solution (6 mL) and dichloromethane (50 mL). The organic phase was separated, the aqueous layer was extracted with dichloromethane (2 × 50 mL), and the combined organic extracts were dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was crystallized from acetone to give **11** in 77% yield as a colorless crystalline product (3.60 g, 11.6 mmol); mp 78 °C. Anal. Calcd for $C_{19}H_{25}NOSi$: C, 73.26; H, 8.09; N, 4.50. Found: C, 73.2; H, 8.2; N, 4.5.

Preparation of 4,4-Diphenyl-1-(3-aminopropyl)-4-silapiperidine (13). A mixture of **7** (5.00 g, 12.6 mmol), propane-1,3-diamine (5.60 g, 75.5 mmol), triethylamine (3.00 g, 29.6 mmol), acetonitrile (40 mL), and toluene (40 mL) was heated in a 250 mL autoclave at 70 °C for 18 h. After the reaction mixture was cooled to 20 °C, the precipitate was isolated by filtration and discarded, and the solvent of the filtrate was removed under reduced pressure. Water (40 mL) and dichloromethane (100 mL) were added successively to the residue, the organic phase was separated, and the aqueous layer was extracted with dichloromethane (2 × 50 mL). The combined organic extracts were dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure, and the residue was purified by Kugelrohr distillation (185 °C/0.05 mbar) to give **13** in 69% yield as a colorless liquid (2.70 g, 8.70 mmol). Anal. Calcd for $C_{19}H_{26}N_2Si$: C, 73.49; H, 8.44; N, 9.02. Found: C, 73.5; H, 8.6; N, 9.0.

Crystal Structure Analyses. Suitable single crystals of *rac*-**1b** and **11** were obtained by crystallization from solutions in acetone at 20 °C. 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 (*rac*-**1b**, Bruker SMART-APEX CCD; **11**, Stoe IPDS; graphite-monochromated Mo Kα radiation (λ = 0.710 73 Å)). The structures were solved by direct methods.[15,16] All non-hydrogen atoms were refined anisotropically.[17] A riding model was employed in the refinement of the hydrogen atoms.

Pharmacological Assays. Receptor binding affinities of *rac*-**1a** and *rac*-**1b**−*rac*-**4b** for α_{1A} and α_2 adrenoceptors, the L-type Ca^{2+} channel, and the serotonin 5-HT receptor were determined using radioligand binding assays via contract research services.[18,19] Radioactivity levels were detected by scintillation counting. The experimental conditions for each assay are shown in Table 2. K_i values were calculated from IC_{50} determinations using the equation of Cheng and Prusoff.[26]

Supporting Information Available: Text giving ^{1}H, ^{13}C, and ^{29}Si NMR data for **11** and **13**, figures showing concentration-effect curves for *rac*-**1a** and *rac*-**1b** and affinity profiles

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for *rac*-**1a** and *rac*-**1b**−*rac*-**4b**, and tables of crystal data and structure solution and refinement details, atomic coordinates, bond lengths and angles, and anisotropic thermal parameters for *rac*-**1b** and **11**. 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-216001 (*rac*-**1b**) and CCDC-216002 (**11**). 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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