N^+/Si Replacement as a Tool for Probing the Pharmacophore of Allosteric Modulators of Muscarinic M_2 Receptors: Synthesis, Allosteric Potency, and Positive Cooperativity of Silicon-Based W84 Derivatives

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W84 (**1**) is an allosteric agent for the "common allosteric site" of muscarinic M_2 receptors, its allosteric action being characterized by an inhibition of [^{3}H]*N*-methylscopolamine ([^{3}H]-NMS) dissociation. A series of silicon-based derivatives of **1** (compounds **2**−**7**) were synthesized and studied for their allosteric interaction with porcine heart muscarinic M_2 receptors. Compound **2** (2-fold isosteric N^+/Si exchange in the molecular framework of **1**) and compounds **3**−**7** (single isosteric N^+/Si exchange, varying $(CH_2)_n$ chain length (n = 4−8) between the N and Si atom) were prepared by two-step (**2**) or four-step (**3**−**7**) syntheses, starting from $ClSiMe_2H$ (synthesis of **2**) or $ClSiMe_2(CH_2)_3Cl$ (syntheses of **3**−**7**). The identities of **2**−**7** were established by elemental analyses (C, H, N), NMR studies (^{1}H, ^{13}C, ^{15}N, ^{29}Si), and MS experiments. In addition, the solvate **3**·MeC(O)Me was structurally characterized by single-crystal X-ray diffraction. The electrostatically neutral compound **2** did not interfere with the muscarinic M_2 receptors, whereas the dicationic agent W84 (**1**) and the monocationic derivatives **3**−**7** inhibited [^{3}H]NMS dissociation. W84 (**1**) decreased [^{3}H]NMS equilibrium binding (negative cooperativity), whereas the silicon compound **5** enhanced [^{3}H]NMS equilibrium binding (positive cooperativity); i.e., exchange of one positively charged nitrogen atom in **1** by a silicon atom switched the allosteric action from negative to positive cooperativity. The silicon compounds **3**, **4**, and **6** enhanced [^{3}H]NMS equilibrium binding as well, whereas **7** behaved similarly to W84 (**1**).

Introduction

All five muscarinic receptor subtypes have allosteric binding sites in addition to the orthosteric conventional ligand binding site.[1−4] The cardiac M_2 receptor appears to be especially sensitive to allosteric modulation;[2,5,6] its allosteric site is well-defined,[7,8] and affinity data for a number of structurally different compounds have been reported for receptors occupied by [^{3}H]*N*-methylscopolamine ([^{3}H]NMS).[9] Orthosteric and allosteric ligands and the receptor interact with each other, as described by the ternary complex model of allosteric interactions.[10] The allosteric effect on ligand equilibrium binding can be quantified by the factor of cooperativity α: α > 1 indicates negative cooperativity, i.e., a decrease of equilibrium binding; α = 1 characterizes neutral cooperativity, i.e., no change of equilibrium binding upon formation of the ternary complex; α < 1 denotes positive cooperativity, i.e., an increase of equilibrium binding. In the case of muscarinic receptors, the formation of a ternary complex results in an inhibition of dissociation of the orthosteric ligand, such as [^{3}H]NMS. Thus, an inhibition of [^{3}H]NMS dissociation is indicative of an allosteric interaction. The concentration of an allosteric agent for a half-maximum effect on orthosteric ligand dissociation ($EC_{50,diss}$) corresponds to a 50% occupancy of the ligand-occupied receptors by the respective allosteric test compound.[8] According to the allosteric model, $EC_{50,diss}$ should be equal to αK_A, K_A being the equilibrium dissociation constant of the allosteric test compound binding to ligand-free receptors. α,ω-Bis(ammonio)alkanes of the W84 type belong to the archetypal

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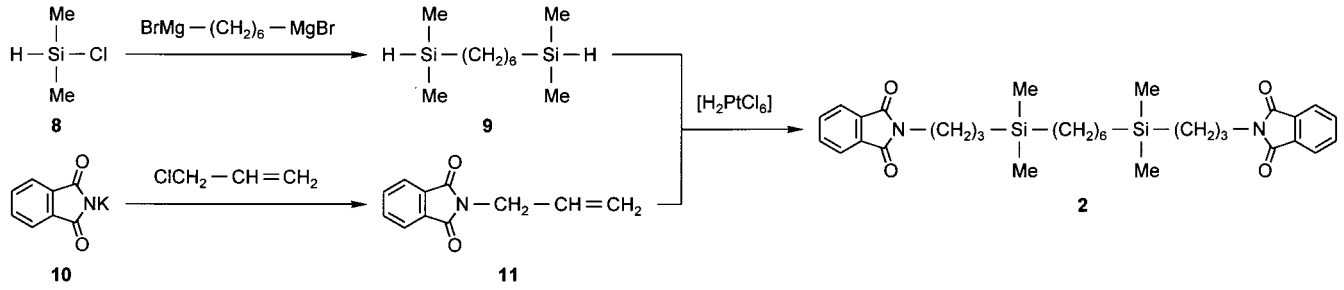
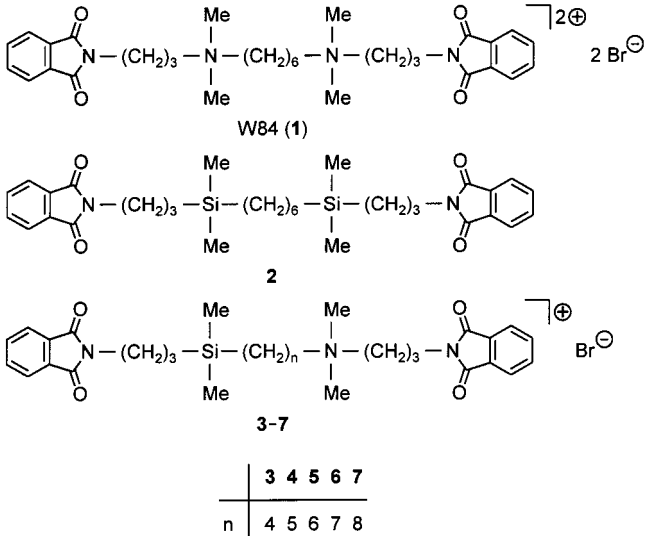
Scheme 1



allosteric agents. By appropriate structural modification of compounds of this particular formula type, agents with greatly enhanced affinity for the [^{3}H]NMS-occupied M_2 receptor have been developed; however, as with the parent compound W84 (**1**) (Chart 1), its more potent derivatives decreased the equilibrium binding of [^{3}H]-NMS.[8,11] In contrast, other allosteric modulators such as the rigid compound alcuronium enhance M_2 [^{3}H]NMS equilibrium binding.[12] Here we report on the switch of the allosteric action of W84-type allosteric modulators from negative to positive cooperativity by an N^+/Si exchange leading to novel promising lead structures for the development of enhancers of ligand binding to muscarinic M_2 receptors.

The presence of two cationic ammonium centers has been generally accepted to be an essential structural element of the W84-type allosteric modulators, although no systematic crosscheck has been performed for the requirement of both positively charged ammonium centers.[13,14] To probe the pharmacophore of these allosteric modulators more systematically, electrostatically neutral and monocationic derivatives obtained by an N^+/Si exchange in a homologous series of W84-type α,ω-bis(ammonio)alkanes were studied. We report here on (i) the synthesis of the silicon compounds **2** (2-fold N^+/Si exchange; electrostatically neutral derivative) and **3**−**7** (single N^+/Si exchange; derivatives with one quaternary ammonium group), (ii) the crystal structure analysis of **3**·MeC(O)Me, and (iii) the pharmacological characterization of compounds **1**−**7** at porcine heart muscarinic M_2 receptors. The studies presented here were carried out as part of our research program dealing with the development of silicon-based drugs.[15,16] Preliminary results of these investigations have already been published elsewhere.[17,18]

Chart 1



Results and Discussion

Syntheses. 1,6-Bis[dimethyl(3-phthalimidopropyl)-silyl]hexane (**2**) was synthesized by a two-step synthesis, starting from chlorodimethylsilane (**8**) (Scheme 1). Treatment of **8** with 1,6-bis(bromomagnesio)hexane in diethyl ether gave 1,6-bis(dimethylsilyl)hexane (**9**; 75% yield), which upon a platinum-catalyzed (H_2PtCl_6) hydrosilylation reaction with *N*-allylphthalimide (**11**; obtained by treatment of potassium phthalimide (**10**) with allyl chloride) in toluene afforded **2** in 54% yield.

The {ω-[dimethyl(3-phthalimidopropyl)silyl]alkyl}-dimethyl(3-phthalimidopropyl)ammonium bromides **3**−**7** (n = 4−8) were synthesized by four-step syntheses, starting from chloro(3-chloropropyl)dimethylsilane (**12**) (Scheme 2), which upon treatment with lithium aluminum hydride in diethyl ether afforded (3-chloropropyl)-dimethylsilane (**13**) in 86% yield. Reaction of **13** with potassium phthalimide in dimethylformamide, in the presence of methyltrioctylammonium chloride (Aliquat-336), yielded dimethyl(3-phthalimidopropyl)silane (**14**; 51% yield). The platinum-catalyzed (H_2PtCl_6) hydrosilylation of the ω-bromo-1-alkenes $Br(CH_2)_{n-2}CH{=}CH_2$ (n = 4−8) in toluene afforded the respective (ω-bromoalkyl)dimethyl(3-phthalimidopropyl)silanes **15**−**19** (59−67% yield), which upon treatment with dimethyl-(3-phthalimidopropyl)amine (**20**) finally gave compounds **3**−**7** in 41−70% yield.

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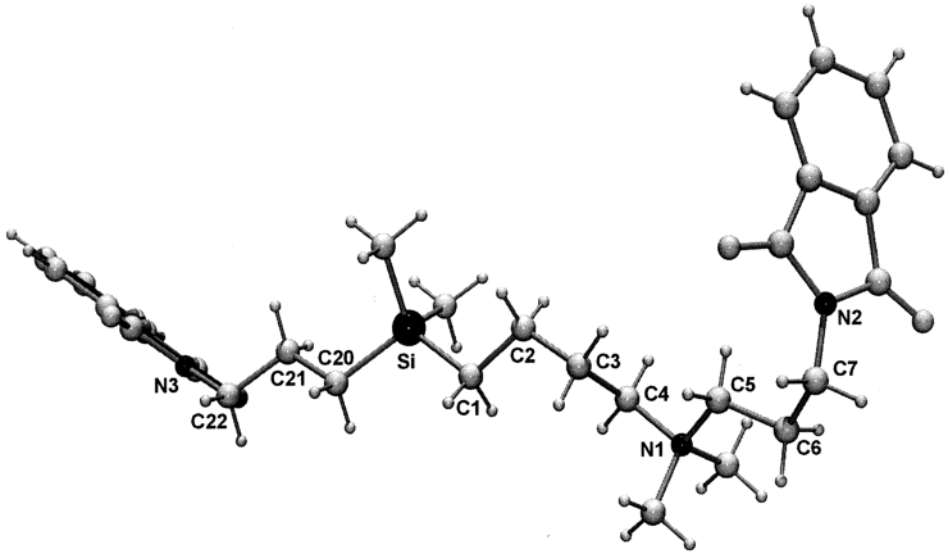

Figure 1. Structure of the cation in the crystal of **3**·MeC(O)Me, showing the atomic numbering scheme of the chain connecting the nitrogen atoms N2 and N3.

Scheme 2

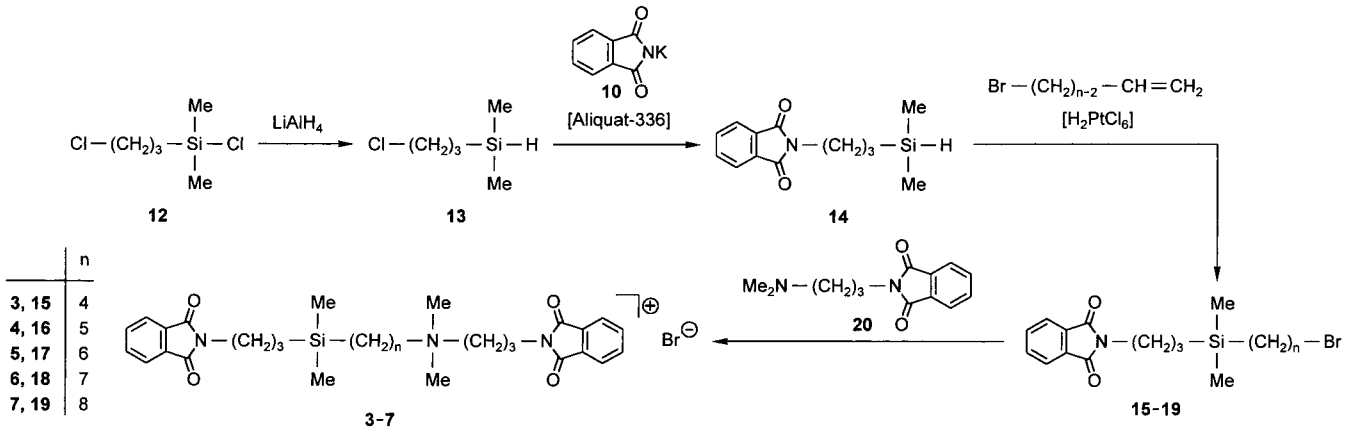

Table 1. Torsion Angles (deg) along the Chain Connecting the Nitrogen Atoms N2 and N3

N2−C7−C6−C5	−60.6(3)	C3−C2−C1−Si	−178.6(2)
C7−C6−C5−N1	−174.25(18)	C2−C1−Si−C20	−162.0(2)
C6−C5−N1−C4	−165.90(19)	C1−Si−C20−C21	−174.49(17)
C5−N1−C4−C3	−54.1(2)	Si−C20−C21−C22	−176.75(16)
N1−C4−C3−C2	−174.78(19)	C20−C21−C22−N3	−178.08(19)
C4−C3−C2−C1	78.7(3)		

The identities of the NMR-spectroscopically pure compounds **2**−**7**, **9**, and **13**−**19** were established by elemental analyses (C, H, N), solution ^{1}H, ^{13}C, ^{15}N, and ^{29}Si NMR studies, and mass-spectrometric investigations. In addition, a crystal structure analysis of **3**·MeC(O)Me was performed.

Crystal Structure Analysis. The compound **3**·MeC(O)Me was structurally characterized by single-crystal X-ray diffraction. The structure of the cation in the crystal is depicted in Figure 1. The torsion angles along the chain connecting the nitrogen atoms N2 and N3 are listed in Table 1.

As can be seen from Figure 1 and Table 1, the chain connecting the nitrogen atoms N2 and N3 does not adopt an all-trans conformation. This finding demonstrates that the cation of **3**·MeC(O)Me (and the cations of the derivatives **4**−**7** as well) can easily match external steric and/or electronic requirements (such as the crystal packing) by adopting a suitable conformation. This conformational flexibility may also be of importance for the receptor binding (in this context, see also ref 19).

Pharmacological Studies. The allosteric action of compounds **1**−**7** on [^{3}H]NMS dissociation and [^{3}H]NMS equilibrium binding was studied at porcine heart muscarinic M_2 receptors. The half-life of compounds **3**−**7** under the pharmacological assay conditions (pH 7.3, 37 °C) was >9 h, as shown by UV spectroscopy. Compound **2**, characterized by a 2-fold N^+/Si exchange in the molecular framework of W84, did not interfere with the M_2 receptors at all, whereas the parent drug W84 (**1**) and the silicon compounds **3**−**7** (single N^+/Si exchange, varying $(CH_2)_n$ chain length) displayed an allosteric action. The effect of compound **5** on the time course of [^{3}H]NMS dissociation from porcine heart muscarinic M_2 receptors is displayed in Figure 2. The time course of [^{3}H]NMS dissociation was monophasic under all conditions, and the apparent rate constant k_{-1} of [^{3}H]NMS dissociation was reduced concentration-dependently. To generate a concentration-effect curve, the apparent rate constant k_{-1} of dissociation was expressed as a percent-

(19) Studies dealing with the structures and muscle-relaxing properties of compounds of the formula type $[Me_3N(CH_2)_2Me_2Si(CH_2)_n$-$SiMe_2(CH_2)_2NMe_3]I_2$ (n = 1−5): Tacke, R.; Linoh, H.; Attar-Bashi, M. T.; Sheldrick, W. S.; Ernst, L.; Niedner, R.; Frohnecke, J. *Z. Naturforsch.* **1982**, *37b*, 1461−1471.

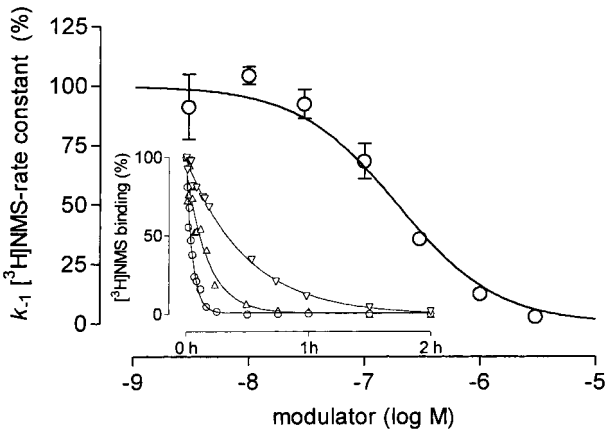

Figure 2. Effect of compound **5** on the dissociation kinetics of [^{3}H]NMS (0.2 nM): (ordinate) apparent rate constant of dissociation k_{-1} as a percentage of the value under control conditions; (abscissa) concentration of test compound (log M). Indicated are mean values ± SEM of two to four independent experiments derived from complete dissociation curves as shown in the inset; sigmoidal curve fitting. Inset: effect of compound **5** (▽, 1 μM; △, 0.3 μM) on the time course of [^{3}H]NMS dissociation (○, control curve): (ordinate) [^{3}H]NMS-specific binding as percentage of the starting level; (abscissa) hours after addition of atropine to measure [^{3}H]NMS dissociation (test compounds were applied together with atropine). Representative set of experiments; monoexponential curve fitting.

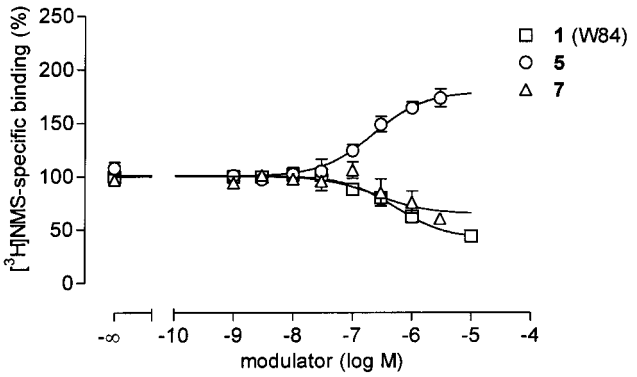

Figure 3. Effect of compounds W84 (**1**), **5**, and **7** on [^{3}H]-NMS (0.2 nM) equilibrium binding: (ordinate) data expressed as percent of specific [^{3}H]NMS binding in the absence of the test compound; (abscissa) concentration of the test compound. Analysis of the binding data was according to the ternary complex model of allosteric interactions.[10] Indicated are mean values ± SEM of two to four independent experiments carried out as triplicate determinations.

age of the value under control conditions. The concentration-effect curve approached the zero level of k_{-1} at high concentrations of the test compound. Thus, in the ternary complex with compound **5**, [^{3}H]NMS dissociation is completely prevented. The Hill coefficient n_H characterizing the slope of the concentration-effect curve was not significantly different from unity ($P > 0.05$). The inflection point of the curve ($EC_{50,diss}$) is a measure of the allosteric potency of the test compound (Table 2). $EC_{50,diss}$ corresponds to a 50% occupancy of the [^{3}H]-NMS-occupied receptor by the test compound and denotes the dissociation constant of allosteric agent binding to a ligand-occupied receptor.[8] As with compound **5**, W84 (**1**) was investigated using a number of different concentrations, and the silicon compounds **3**−**7** were each applied in two concentrations (0.03 and 0.3 μM) that allowed an estimate of the concentration-effect relationship (Table 2). For these compounds the concentration-effect curves were generated by sigmoidal curve fitting fixing the top and bottom values at 100% and 0%, respectively. The Hill slope was fixed at $n_H = -1$, as found for compounds **1** and **5**. The $pEC_{50,diss}$ values (Table 2) obtained in this screening-like approach were later verified by the equilibrium binding assay (difference $pEC_{50,diss} - p(\alpha K_A)$ close to zero, see below).

Equilibrium binding experiments as shown in Figure 3 provide the factor of cooperativity (α) between the respective modulator and [^{3}H]NMS and the binding constant pK_A for allosteric modulator binding to ligand-free receptors. The allosteric modulator W84 (**1**) reduced [^{3}H]NMS equilibrium binding, indicating a negative cooperativity ($\alpha = 3.36$). This result is in agreement with data published previously.[5] In contrast, compound **5** increased [^{3}H]NMS binding, which reflects positive cooperativity ($\alpha = 0.36$). The other silicon compounds also increased [^{3}H]NMS binding, except for compound **7**, which decreased [^{3}H]NMS equilibrium binding ($\alpha = 1.43$) (Figure 3). The extent by which compound **7** reduced [^{3}H]NMS equilibrium binding was rather small, and the curve-fitting procedure failed to yield the two parameters α and K_A simultaneously from the data. In case of the other test compounds, we found that $EC_{50,diss}$ and αK_A, which both reflect allosteric modulator binding affinity for [^{3}H]NMS-occupied receptors, were in excellent agreement (Table 2). Therefore, in the case of compound **7** we assumed that the difference ($pEC_{50,diss} - p(\alpha K_A)$) is equal to zero and replaced the term K_A of

Table 2. Compilation of the Parameters To Characterize the Interaction of the Allosteric Test Compounds W84 (1) and 3−7 with the [^{3}H]NMS-Occupied and the Unoccupied Muscarinic M_2 Receptors[a]

compd	$pEC_{50,diss}$	α	pK_A	$p(\alpha K_A)$	$pEC_{50,diss} - p(\alpha K_A)$
1	6.00 ± 0.06	3.36 ± 0.68	6.41 ± 0.18	5.88	0.12
3	6.81 ± 0.07*	0.33 ± 0.07*	6.11 ± 0.30[n.s.]	6.60	0.21
4	7.09 ± 0.10*	0.18 ± 0.04*	6.10 ± 0.17[n.s.]	6.85	0.24
5	6.72 ± 0.08*	0.36 ± 0.03*	6.46 ± 0.14[n.s.]	6.90	−0.18
6	6.68 ± 0.07*	0.37 ± 0.07*	6.35 ± 0.31[n.s.]	6.79	−0.11
7	6.41 ± 0.06*	1.43 ± 0.13*	6.56[b,n.s.]	6.41	0[b]

[a] $pEC_{50,diss}$ denotes the −log concentration of the test compound at which radioligand dissociation is reduced to 50% of the control value; $EC_{50,diss}$ corresponds to a 50% occupancy of ligand-occupied receptors by the test compound. α is the factor of cooperativity between the allosteric agent and [^{3}H]NMS. pK_A denotes the −log equilibrium dissociation constant of the allosteric test compound binding to ligand-free receptors. $p(\alpha K_A)$ reflects the −log dissociation constant for the binding of the allosteric test compound to [^{3}H]NMS-occupied receptors. The difference between $pEC_{50,diss}$ and $p(\alpha K_A)$ compares the two descriptors derived from kinetic and equilibrium binding experiments, respectively. Mean values ± SEM, $n = 2-4$ experiments. For each modulator, the values for $pEC_{50,diss}$, α, and pK_A were compared with those obtained with W84 (**1**) by an unpaired *t* test. Asterisks indicate a significant difference, $P < 0.01$. n.s. = not significant. [b] Curve fitting for compound **7** required to set $K_A = EC_{50,diss}/\alpha$ (for details, see text).

the Ehlert equation (see Experimental Section) by $EC_{50,diss}/\alpha$ and thus obtained a reasonable estimate of α. The parameters characterizing the effects of the tested allosteric modulators **1** and **3**−**7** are compiled in Table 2.

The prominent finding of these binding studies is that the exchange of one positively charged nitrogen atom in the allosteric agent W84 (**1**) by a silicon atom (→ compound **5**) switches the allosteric action from an inhibition to an augmentation of [^{3}H]NMS equilibrium binding. An allosteric elevation of muscarinic ligand binding is obtained, if the allosteric agent has a higher affinity for the ligand-occupied receptor compared with the free receptor. In the case of W84 (**1**), however, the affinity for free M_2 receptors ($pK_A = 6.41 \pm 0.18$, Table 2) is 3.36-fold higher ($\alpha = 3.36$) than the affinity for the [^{3}H]NMS-occupied receptor ($p(\alpha K_A) = 5.88$). The equilibrium dissociation constants pK_A of the allosteric modulator binding of compounds **3**−**7** to free receptors were not significantly different from the pK_A value of W84 ($P > 0.05$). In contrast, the affinity for the [^{3}H]-NMS-occupied receptor was significantly increased by the N^+/Si exchange ($P < 0.01$), thereby leading to the switch in cooperativity. The only exception was compound **7**, which showed an augmented affinity for the [^{3}H]NMS-occupied receptor compared with W84 (**1**), but this augmentation was not sufficient for a switch in cooperativity ($\alpha > 1$).

The results obtained with compound **7** show that the N^+/Si replacement does not necessarily lead to positive cooperativity. Further studies will have to elucidate why the N^+/Si exchange enhances allosteric modulator affinity for NMS-occupied receptors but not for free receptors. In any case, our findings reveal that the two positively charged nitrogen atoms in the various tested W84-type α,ω-bis(ammonio)alkanes are not a prerequisite for an allosteric interaction with the muscarinic M_2 receptor.[4,13,14] This result is important with respect to therapeutic perspectives of muscarinic allosteric modulators, since uncharged agents have a higher propensity to penetrate the blood/brain barrier. Therefore, one of the next steps will be to replace the remaining quaternary ammonium moiety in the silicon compounds **3**−**7** by a tertiary amino group. Furthermore, it will be interesting to find out whether the silicon-containing agents could also enhance the binding of the orthosteric endogenous ligand acetylcholine.

Experimental Section

Chemistry. All syntheses were carried out under dry nitrogen. The organic solvents used were dried and purified according to standard procedures and stored under dry nitrogen. A Büchi GKR 50 apparatus was used for the bulb-to-bulb distillations. Melting points were determined with a Büchi B540 apparatus in open glass capillaries and are uncorrected. The reported R_f values refer to TLC experiments using silica gel TLC plates (silica gel 60 F_{254}, layer thickness 0.2 mm; Merck 105554). The ^{1}H, ^{13}C, ^{15}N, and ^{29}Si solution NMR spectra were recorded on a Bruker DRX-300 NMR spectrometer (^{1}H, 300.1 MHz; ^{13}C, 75.5 MHz; ^{15}N, 30.4 MHz; ^{29}Si, 59.6 MHz). $CDCl_3$ and DMSO-d_6 were used as solvents. Spectra were recorded at 22 °C ($CDCl_3$) or at 30 °C (DMSO-d_6). Chemical shifts were determined relative to internal $CHCl_3$ (^{1}H, δ 7.24), internal $CDCl_3$ (^{13}C, δ 77.0), internal DMSO-d_5 (^{1}H, δ 2.49), internal DMSO-d_6 (^{13}C, δ 39.5), external TMS (^{29}Si, δ 0), or external formamide (^{15}N, δ −268). Assignment of the ^{1}H NMR data was supported by ^{1}H,^{1}H and ^{13}C,^{1}H correlation experiments, assignment of the ^{13}C NMR data was supported by DEPT 135 and ^{13}C,^{1}H correlation experiments, and ^{15}N shifts were obtained from ^{15}N,^{1}H correlation experiments, which concomitantly facilitated the signal assignment. Mass spectra (EI MS, 70 eV; CI MS, reactant gas methane) were recorded with a ThermoQuest Trio 1000 mass spectrometer. The selected *m*/*z* values given refer to the isotopes ^{1}H, ^{12}C, ^{14}N, ^{16}O, ^{28}Si, ^{35}Cl, and ^{79}Br. IR spectra were obtained with a Bruker Equinox 55 IR spectrometer. UV spectra were recorded with a Beckman DU 640 spectrophotometer.

1,6-Bis[dimethyl(3-phthalimidopropyl)silyl]hexane (2).[20] A solution of hexachloroplatinic acid hexahydrate (1.00 mg, 1.93 μmol) in 2-propanol (250 μL) was added to a mixture of **9** (1.05 g, 5.19 mmol) and **11** (2.00 g, 10.7 mmol; incompletely dissolved at room temperature) in toluene (10 mL). The mixture was heated under reflux for 36 h until the characteristic Si−H IR absorption band at 2111 cm^{-1} (film of the reaction mixture in toluene) had disappeared completely. The solvent was removed under reduced pressure and the residue purified by column (diameter 3.5 cm) chromatography on 120 g of silica gel (0.063−0.200 mm; Fluka, 60741) using dichloromethane as eluent to yield 1.99 g of a white solid; $R_f = 0.76$ (TLC). This product was redissolved in dichloromethane (5 mL) and the solution diluted with *n*-hexane (15 mL). Upon partial evaporation of the solvent by passing a dry nitrogen gas stream over the surface of the solution, a white solid precipitated. Precipitation was completed at −25 °C for 1 month to give NMR-spectroscopically pure **2** in 54% yield as a white amorphous solid (1.61 g, 2.79 mmol); mp 67−68 °C. ^{1}H NMR ($CDCl_3$): δ −0.08 (s, 12 H, SiCH_3), 0.40−0.52 (m, 8 H, SiCH_2C), 1.17−1.23 (m, 8 H, C(CH_2)$_4$C), 1.56−1.68 (m, 4 H, NCH$_2$CH_2C), 3.62 (t, $^3J_{HH} = 7.4$ Hz, 4 H, NCH_2C), 7.68 (dd, $^3J_{HH} = 5.5$ Hz, $^4J_{HH} = 3.0$ Hz, 4 H, *H*-4/*H*-5, C(O)C$_6$H$_4$C(O)), 7.81 (dd, $^3J_{HH} = 5.5$ Hz, $^4J_{HH} = 3.0$ Hz, 4 H, *H*-3/*H*-6, C(O)C$_6$H$_4$C(O)). ^{13}C NMR ($CDCl_3$): δ −3.5 (SiCH_3), 12.4 (N(CH$_2$)$_2$$CH_2$Si), 15.1 (Si$CH_2$-(CH$_2$)$_4$$CH_2$Si), 23.2 (NCH$_2$$CH_2$C), 23.7 (SiCH$_2$$CH_2$(CH$_2$)$_2$$CH_2$-CH$_2$Si), 33.3 (Si(CH$_2$)$_2$($CH_2$)$_2$(CH$_2$)$_2$Si), 41.1 (N$CH_2$C), 123.1 (*C*-3/*C*-6, C(O)C$_6$H$_4$C(O)), 132.2 (*C*-1/*C*-2, C(O)C$_6$H$_4$C(O)), 133.8 (*C*-4/*C*-5, C(O)C$_6$H$_4$C(O)), 168.5 (*C*═O). ^{15}N NMR ($CDCl_3$): δ −217. ^{29}Si NMR ($CDCl_3$): δ 2.9. CI MS: *m*/*z* (%) 577 (16) ((M + H)$^+$), 246 (100) (M$^+$ − R(CH$_2$)$_3$Si(CH$_3$)$_2$(CH$_2$)$_6$; R = phthalimido moiety). Anal. Calcd for $C_{32}H_{44}N_2O_4Si_2$: C, 66.63; H, 7.69; N, 4.86. Found: C, 66.30; H, 7.78; N, 4.81.

{4-[Dimethyl(3-phthalimidopropyl)silyl]butyl}dimethyl-(3-phthalimidopropyl)ammonium Bromide (3). A solution of **15** (1.18 g, 3.09 mmol) and **20** (923 mg, 3.97 mmol) in ethanol (12 mL) was heated under reflux for 24 h. After the mixture was cooled to room temperature, the solvent was removed at 30 mbar, and ethyl acetate (50 mL) was added. The solution was concentrated in vacuo to a volume of 10 mL by lowering the pressure slowly from 200 mbar to 30 mbar.[21] The addition of ethyl acetate and subsequent evaporation of the solvent were repeated until the product precipitated almost quantitatively as a white amorphous solid. This product was isolated by centrifugation (1100 × g, 5 min) and washed with *n*-pentane (2 × 20 mL). The resulting solid was dissolved in ethanol (20 mL), and the whole purification procedure was repeated twice following the protocol described above. After drying in vacuo (2 days, 1 × 10^{-4} mbar, 60 °C), compound **3** was obtained in 84% yield as a white amorphous solid (1.59 g, 2.59 mmol). For purification purposes, a boiling saturated solution of **3** in acetone was concentrated by distillation at atmospheric pressure until the solution started to turn opaque.[22] The precipitation was completed by storing the suspension for

(20) Systematic nomenclature: phthalimido ≡ 1,3-dioxo-1,3-dihydroisoindol-2-yl.

(21) Rapid decrease in pressure resulted in the formation of an oily product.

Table 3. ^{1}H, ^{15}N, and ^{29}Si NMR Data for Compounds 3−7 (δ, DMSO-d_6)[a]

	3 ($n = 4$)	**4** ($n = 5$)	**5** ($n = 6$)	**6** ($n = 7$)	**7** ($n = 8$)
$NCH_2CH_2CH_2Si$	3.51 (t, $^3J_{HH} = 7.2$ Hz, 2 H)	3.49 (t, $^3J_{HH} = 7.3$ Hz, 2 H)	3.52 (t, $^3J_{HH} = 7.3$ Hz, 2 H)	3.50 (t, $^3J_{HH} = 7.3$ Hz, 2 H)	3.51 (t, $^3J_{HH} = 7.3$ Hz, 2 H)
$NCH_2CH_2CH_2Si$/ $Si(CH_2)_{n-2}CH_2CH_2N^+$	1.47−1.69 (m, 4 H)	1.46−1.68 (m, 4 H)	1.49−1.65 (m, 4 H)	1.48−1.65 (m, 4 H)	1.48−1.65 (m, 4 H)
H_2CSiCH_2	0.38−0.55 (m, 4 H)	0.36−0.52 (m, 4 H)	0.39−0.52 (m, 4 H)	0.36−0.50 (m, 4 H)	0.38−0.49 (m, 4 H)
$SiCH_3$	−0.08 (s, 6 H)	−0.09 (s, 6 H)	−0.07 (s, 6 H)	−0.09 (s, 6 H)	−0.08 (s, 6 H)
$SiCH_2(CH_2)_{n-3}(CH_2)_2N^+$	1.15−1.30 (m, 2 H)	1.15−1.32 (m, 4 H)	1.13−1.33 (m, 6 H)	1.10−1.28 (m, 8 H)	1.12−1.28 (m, 10 H)
$Si(CH_2)_{n-1}CH_2N^+$	3.19−3.30 (m, 2 H)	3.19−3.31 (m, 2 H)	3.16−3.26 (m, 2 H)	3.19−3.30 (m, 2 H)	3.19−3.29 (m, 2 H)
N^+CH_3	2.99 (br s, 6 H)	3.01 (br s, 6 H)	2.97 (br s, 6 H)	3.00 (br s, 6 H)	2.99 (br s, 6 H)
$N^+CH_2CH_2CH_2N$	3.30−3.41 (m, 2 H)	3.31−3.42 (m, 2 H)	3.27−3.38 (m, 2 H)	3.30−3.41 (m, 2 H)	3.29−3.40 (m, 2 H)
$N^+CH_2CH_2CH_2N$	1.95−2.12 (m, 2 H)	1.95−2.11 (m, 2 H)	1.95−2.10 (m, 2 H)	1.96−2.10 (m, 2 H)	1.96−2.10 (m, 2 H)
$N^+CH_2CH_2CH_2N$	3.64 (t, $^3J_{HH} = 6.0$ Hz, 2 H)	3.63 (t, $^3J_{HH} = 6.2$ Hz, 2 H)	3.64 (t, $^3J_{HH} = 6.2$ Hz, 2 H)	3.64 (t, $^3J_{HH} = 6.2$ Hz, 2 H)	3.64 (t, $^3J_{HH} = 6.3$ Hz, 2 H)
$C(O)C_6H_4C(O)$	7.78−7.89 (m, 8 H)	7.79−7.87 (m, 8 H)	7.79−7.90 (m, 8 H)	7.80−7.87 (m, 8 H)	7.79−7.89 (m, 8 H)
$N(CH_2)_3Si$	−218	−218	−218	−218	−218
N^+	−327	−327	−328	−326	−326
$N^+(CH_2)_3N$	−222	−221	−221	−221	−221
Si	3.1	3.0	2.9	2.9	2.9

[a] For experimental details, see Experimental Section.

Table 4. ^{13}C NMR Data for Compounds 3−7 (δ, DMSO-d_6)[a]

	3 ($n = 4$)	**4** ($n = 5$)	**5** ($n = 6$)	**6** ($n = 7$)	**7** ($n = 8$)
$NCH_2CH_2CH_2Si$	40.4	40.4	40.4	40.4	40.4
$NCH_2CH_2CH_2Si$	22.5	22.5	22.5	22.5	22.5
$NCH_2CH_2CH_2Si$	11.6	11.6	11.7	11.7	11.7
$SiCH_3$	−3.6	−3.5	−3.5	−3.5	−3.5
$SiCH_2(CH_2)_{n-1}N^+$	14.1	14.3	14.4	14.4	14.4
$SiCH_2CH_2(CH_2)_{n-2}N^+$	20.3	22.9	23.1	23.1	23.2
$Si(CH_2)_2CH_2(CH_2)_{n-3}N^+$	25.3	29.5	32.4	32.6	32.8
$Si(CH_2)_3CH_2(CH_2)_{n-4}N^+$	62.8	21.4	25.4	28.1	28.39 or 28.44
$Si(CH_2)_4CH_2(CH_2)_{n-5}N^+$		63.0	21.58 or 21.59	25.6	28.39 or 28.44
$Si(CH_2)_5CH_2(CH_2)_{n-6}N^+$			63.1	21.6 or 21.7	25.7
$Si(CH_2)_6CH_2(CH_2)_{n-7}N^+$				63.0	21.6 or 21.7
$Si(CH_2)_7CH_2N^+$					63.0
$N^+CH_2CH_2CH_2N$	60.7	60.5	60.6	60.6	60.6
$N^+CH_2CH_2CH_2N$	21.6	21.6	21.58 or 21.59	21.6 or 21.7	21.6 or 21.7
$N^+CH_2CH_2CH_2N$	34.6	34.6	34.6	34.6	34.6
N^+CH_3	49.9	49.9	49.9	49.9	49.9
C-1/*C*-2, $C(O)C_6H_4C(O)$	131.5, 131.7	131.4, 131.6	131.5, 131.7	131.5, 131.7	131.5, 131.7
C-3/*C*-6, $C(O)C_6H_4C(O)$	122.9, 123.0	122.9, 123.0	122.98, 123.04	122.9, 123.0	122.9, 123.0
C-4/*C*-5, $C(O)C_6H_4C(O)$	134.4 (4 C)	134.4 (4 C)	134.39, 134.41	134.4 (4 C)	134.37, 134.38
C═O	167.89, 167.93	167.86, 167.90	167.9, 168.0	167.89, 167.93	167.90, 167.95

[a] For experimental details, see Experimental Section.

1 day at room temperature and for 3 days at −25 °C. After it was dried in vacuo (2 days, 1×10^{-4} mbar, 60 °C), compound **3** was obtained in 70% yield as an amorphous white solid (1.33 g, 2.16 mmol). For NMR data, see Tables 3 and 4. CI MS: *m*/*z* (%) 520 (13) ($(M_{cation} - CH_2)^+$), 519 (1) ($(M_{cation} - CH_3)^+$), 95 (100) ($BrCH_4^+$). Anal. Calcd for $C_{30}H_{40}BrN_3O_4Si$: C, 58.62; H, 6.56; N, 6.84. Found: C, 58.24; H, 6.54; N, 6.76.

{5-[Dimethyl(3-phthalimidopropyl)silyl]pentyl}-dimethyl(3-phthalimidopropyl)ammonium Bromide (4). Preparation from **16** (1.31 g, 3.30 mmol) and **20** (996 mg, 4.29 mmol) was analogous to the synthesis of **3**: 91% yield (3-fold precipitation from ethanol/ethyl acetate); 41% yield (subsequent 3-fold precipitation from acetone); mp 175 °C. For NMR data, see Tables 3 and 4. CI MS: *m*/*z* (%) 534 (25) ($(M_{cation} - CH_2)^+$), 533 (3) ($(M_{cation} - CH_3)^+$), 95 (100) ($BrCH_4^+$). Anal. Calcd for $C_{31}H_{42}BrN_3O_4Si$: C, 59.23; H, 6.73; N, 6.68. Found: C, 58.71; H, 6.73; N, 6.63.

{6-[Dimethyl(3-phthalimidopropyl)silyl]hexyl}-dimethyl(3-phthalimidopropyl)ammonium Bromide (5). Preparation from **17** (1.25 g, 3.05 mmol) and **20** (868 mg, 3.74 mmol) was analogous to the synthesis of **3**: 87% yield (3-fold precipitation from ethanol/ethyl acetate); 56% yield (subsequent 3-fold precipitation from acetone); mp 174−175 °C. For NMR data, see Tables 3 and 4. CI MS: *m*/*z* (%) 548 (24) ($(M_{cation} - CH_2)^+$), 547 (3) ($(M_{cation} - CH_3)^+$), 95 (100) ($BrCH_4^+$). Anal. Calcd for $C_{32}H_{44}BrN_3O_4Si$: C, 59.80; H, 6.90; N, 6.54. Found: C, 59.53; H, 6.90; N, 6.53.

{7-[Dimethyl(3-phthalimidopropyl)silyl]heptyl}-dimethyl(3-phthalimidopropyl)ammonium Bromide (6). Preparation from **18** (1.26 g, 2.97 mmol) and **20** (972 mg, 4.18 mmol) was analogous to the synthesis of **3**: 81% yield (3-fold precipitation from ethanol/ethyl acetate); 58% yield (subsequent 3-fold precipitation from acetone); mp 146−147 °C. For NMR data, see Tables 3 and 4. CI MS: *m*/*z* (%) 562 (19) ($(M_{cation} - CH_2)^+$), 561 (2) ($(M_{cation} - CH_3)^+$), 95 (100) ($BrCH_4^+$). Anal. Calcd for $C_{33}H_{46}BrN_3O_4Si$: C, 60.35; H, 7.06; N, 6.40. Found: C, 60.16; H, 7.09; N, 6.38.

{8-[Dimethyl(3-phthalimidopropyl)silyl]octyl}dimethyl-(3-phthalimidopropyl)ammonium Bromide (7). Preparation from **19** (1.13 g, 2.58 mmol) and **20** (837 mg, 3.60 mmol) was analogous to the synthesis of **3**: 78% yield (3-fold precipitation from ethanol/ethyl acetate); 55% yield (subsequent 3-fold precipitation from acetone); mp 177−178 °C. For NMR data, see Tables 3 and 4. CI MS: *m*/*z* (%) 576 (16) ($(M_{cation} - CH_2)^+$), 575 (2) ($(M_{cation} - CH_3)^+$), 95 (100) ($BrCH_4^+$). Anal. Calcd for $C_{34}H_{48}BrN_3O_4Si$: C, 60.88; H, 7.21; N, 6.26. Found: C, 60.89; H, 7.24; N, 6.22.

(22) Cooling of a saturated boiling solution of **3** in acetone to room temperature yielded crystals, which were suitable for a single-crystal X-ray diffraction analysis. Since **3** crystallizes with one acetone molecule in the asymmetric unit (see Crystal Structure Analysis), a solvent-free sample (mp 138−139 °C) was prepared by precipitation from ethanol/ethyl acetate. In the case of compounds **4**, **5**, and **7**, no precipitate was obtained at all upon cooling unless the solution was concentrated until precipitation occurred from the hot solution. The solubilities of **3**−**7** in boiling acetone varied within approximately 1 order of magnitude (**6**, best solubility; **7**, poorest solubility).

Chlorodimethylsilane (8). This compound was commercially available (Acros Organics, 16284).

1,6-Bis(dimethylsilyl)hexane (9). 1,6-Bis(bromomagnesio)hexane was prepared from magnesium turnings (4.32 g, 178 mmol) and 1,6-dibromohexane (18.1 g, 74.2 mmol) in diethyl ether (50 mL). The Grignard reagent was added dropwise over a period of ca. 1 h to a stirred solution of **8** (14.7 g, 155 mmol) in diethyl ether (100 mL) in such a way that the solvent permanently refluxed (formation of a precipitate). The mixture was heated under reflux for another 1 h, cooled to room temperature, and then poured into vigorously stirred 0.1 M hydrochloric acid (150 mL) at room temperature. The aqueous layer was separated and extracted with dichloromethane (5 × 50 mL), and the combined organic phases were dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue distilled in vacuo to give **9** in 75% yield (related to 1,6-dibromohexane) as a colorless liquid (11.3 g, 55.8 mmol); bp 64−66 °C/2 mbar. IR (film): $\tilde{\nu}$ 2111 cm^{-1} (SiH). ^{1}H NMR ($CDCl_3$): δ 0.04 (d, $^3J_{HH}$ = 3.5 Hz, 12 H, SiC*H*$_3$), 0.51−0.61 (m, 4 H, SiC*H*$_2$C), 1.27−1.37 (m, 8 H, CC*H*$_2$C), 3.83 ("nonet", $^3J_{HH}$ = 3.5 Hz, 2 H, Si*H*). ^{13}C NMR ($CDCl_3$): δ −4.4 (Si*C*H$_3$), 14.2 (Si*C*H$_2$C), 24.3 (SiCH$_2$*C*H$_2$C), 32.9 (SiCH$_2$CH$_2$*C*H$_2$C). ^{29}Si NMR ($CDCl_3$): δ −12.9. EI MS: *m*/*z* 202 (<1) (M^+), 59 (100) ($M^+ - (CH_2)_6Si(CH_3)_2H$). Anal. Calcd for $C_{10}H_{26}Si_2$: C, 59.32; H, 12.94. Found: C, 59.13; H, 12.30.

Potassium Phthalimide (10). This compound was commercially available (Acros Organics, 17086).

***N*-Allylphthalimide (11).** Compound **11** was prepared from **10** (29.7 g, 160 mmol) and allyl chloride (14.1 g, 184 mmol) analogously to the procedure published in ref 23: 62% yield (18.7 g, 99.9 mmol) of a colorless crystalline product; mp 68−69 °C. ^{1}H NMR ($CDCl_3$): δ 4.27 (δ_M), 5.17 (δ_A), 5.23 (δ_B), and 5.87 (δ_G) ($^2J_{AB}$ = 1.5 Hz, $^3J_{AG,cis}$ = 10.2 Hz, $^4J_{AM}$ = 1.5 Hz, $^3J_{BG,trans}$ = 17.2 Hz, $^4J_{BM}$ = 1.5 Hz, $^3J_{GM}$ = 5.7 Hz, 5 H, NC(H$_M$)$_2$CH$_G$=CH$_A$H$_B$), 7.70 (dd, $^3J_{HH}$ = 5.3 Hz, $^4J_{HH}$ = 3.2 Hz, 2 H, *H*-4/*H*-5, C(O)C$_6$H$_4$C(O)), 7.84 (dd, $^3J_{HH}$ = 5.3 Hz, $^4J_{HH}$ = 3.2 Hz, 2 H, *H*-3/*H*-6, C(O)C$_6$H$_4$C(O)). ^{13}C NMR ($CDCl_3$): δ 40.0 (N*C*H$_2$C), 117.7 (NCH$_2$CH=*C*H$_2$), 123.3 (*C*-3/*C*-6, C(O)C$_6$H$_4$C(O)), 131.5 (NCH$_2$*C*H=CH$_2$), 132.1 (*C*-1/*C*-2, C(O)C$_6$H$_4$C(O)), 134.0 (*C*-4/*C*-5, C(O)C$_6$H$_4$C(O)), 167.9 (*C*=O). Anal. Calcd for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.32; H, 5.00; N, 7.48.

Chloro(3-chloropropyl)dimethylsilane (12). This compound was commercially available (Fluka, 26230).

(3-Chloropropyl)dimethylsilane (13). Compound **12** (39.5 g, 231 mmol) was added dropwise to a stirred suspension of lithium aluminum hydride (6.08 g, 160 mmol) in diethyl ether (100 mL) at a rate that kept the solvent under weak reflux. The mixture was stirred under reflux for 30 min, cooled to room temperature, and then added to an ice-cooled mixture of 4 M hydrochloric acid (300 mL) and diethyl ether (200 mL). The organic phase was separated and the aqueous layer extracted with dichloromethane (4 × 50 mL), and the combined organic extracts were dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue distilled in vacuo to give **13** in 86% yield as a colorless liquid (27.2 g, 199 mmol), bp 70 °C/100 mbar. ^{1}H NMR ($CDCl_3$): δ 0.07 (d, $^3J_{HH}$ = 3.7 Hz, 6 H, SiC*H*$_3$), 0.64−0.72 (m, 2 H, SiC*H*$_2$C), 1.73−1.85 (m, 2 H, CC*H*$_2$C), 3.49 (t, $^3J_{HH}$ = 7.0 Hz, 2 H, CC*H*$_2$Cl), 3.86 ("nonet", $^3J_{HH}$ = 3.7 Hz, Si*H*). ^{13}C NMR ($CDCl_3$): δ −4.6 (Si*C*H$_3$), 11.8 (Si*C*H$_2$C), 28.0 (C*C*H$_2$C), 47.6 (C*C*H$_2$Cl). ^{29}Si NMR ($CDCl_3$): δ −12.6. Anal. Calcd for $C_5H_{13}ClSi$: C, 43.93; H, 9.59; Cl, 25.94. Found: C, 44.04; H, 9.20; Cl, 25.96. For a brief description of an analogous preparation of compound **13**, see ref 24.

Dimethyl(3-phthalimidopropyl)silane (14). A mixture of **13** (10.0 g, 73.2 mmol), **10** (15.0 g, 81.0 mmol), and methyltrioctylammonium chloride (Aliquat-336; 7.65 g, 18.9 mmol) in DMF (50 mL) was heated at exactly 60 °C for 14 h. After it was cooled to room temperature, the suspension was added slowly to a stirred mixture of concentrated hydrochloric acid (20 mL), water (50 mL), and ice (100 g). The crude product was extracted with dichloromethane (5 × 50 mL), the aqueous layer still containing some ice. The combined organic extracts were dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure and the residue purified by column (diameter 5.5 cm) chromatography on 570 g of silica gel (0.040−0.063 mm; Macherey & Nagel, 815381) using diethyl ether/*n*-hexane (2:3 (v/v)) as eluent; R_f = 0.58 (TLC). After the solvent was removed under reduced pressure, the product (10.3 g) was isolated as a colorless oil, which became solid at −25 °C. Subsequent sublimation in vacuo (100−120 °C/1 × 10^{-2} mbar) afforded **14** in 51% yield as an amorphous solid (9.17 g, 37.1 mmol); mp 33 °C. IR (KBr): $\tilde{\nu}$ 2113 cm^{-1} (SiH). ^{1}H NMR ($CDCl_3$): δ 0.03 (d, $^3J_{HH}$ = 3.6 Hz, 6 H, SiC*H*$_3$), 0.53−0.64 (m, 2 H, SiC*H*$_2$C), 1.61−1.75 (m, 2 H, CC*H*$_2$C), 3.64 (t, $^3J_{HH}$ = 7.5 Hz, 2 H, NC*H*$_2$C), 3.86 ("nonet", $^3J_{HH}$ = 3.6 Hz, 1 H, Si*H*), 7.67 (dd, $^3J_{HH}$ = 5.5 Hz, $^4J_{HH}$ = 3.0 Hz, 2 H, *H*-4/*H*-5, C(O)C$_6$H$_4$C(O)), 7.81 (dd, $^3J_{HH}$ = 5.5 Hz, $^4J_{HH}$ = 3.0 Hz, 2 H, *H*-3/*H*-6, C(O)C$_6$H$_4$C(O)). ^{13}C NMR ($CDCl_3$): δ −4.6 (Si*C*H$_3$), 11.3 (Si*C*H$_2$C), 23.6 (C*C*H$_2$C), 40.7 (N*C*H$_2$C), 123.1 (*C*-3/*C*-6, C(O)C$_6$H$_4$C(O)), 132.1 (*C*-1/*C*-2, C(O)C$_6$H$_4$C(O)), 133.8 (*C*-4/*C*-5, C(O)C$_6$H$_4$C(O)), 168.4 (*C*=O). ^{15}N NMR ($CDCl_3$): δ −217. ^{29}Si NMR ($CDCl_3$): δ −12.5. EI MS: *m*/*z* (%) 247 (8) (M^+), 59 (100) ($M^+ - (CH_2)_3R$; R = phthalimido moiety). Anal. Calcd for $C_{13}H_{17}NO_2Si$: C, 63.12; H, 6.93; N, 5.66. Found: C, 62.81; H, 6.99; N, 5.60.

(4-Bromobutyl)dimethyl(3-phthalimidopropyl)silane (15). A solution of hexachloroplatinic acid hexahydrate (10.0 mg, 19.3 μmol) in 2-propanol (50 μL) was added to a solution of **14** (1.33 g, 5.38 mmol) and 4-bromo-1-butene (798 mg, 5.91 mmol) in toluene (12 mL). An exothermic reaction occurred immediately, the solution turned orange, and the solvent started to boil. As soon as the reaction started to become less vigorous, the mixture was immediately heated under reflux with a preheated oil bath (140 °C; no drop in temperature below reflux temperature at any time) for 1 h (reaction control by IR analysis; film of the reaction mixture, absence of the Si−H absorption band at 2113 cm^{-1}). The mixture was filtered over 30 g of silica gel (0.040−0.063 mm; Macherey & Nagel), which was subsequently eluted with ethyl acetate (300 mL). After the solvent was removed under reduced pressure, the residue was purified by column (diameter 4.5 cm) chromatography on 300 g of silica gel (0.015−0.040 mm; Merck, 115111) using diethyl ether/*n*-hexane (1:1 (v/v)) as eluent; R_f = 0.70 (TLC). After the solvent was removed in vacuo, a colorless oily product (1.42 g) was isolated that contained minor amounts of the byproduct *N*-propylphthalimide,[25] which was separated by bulb-to-bulb distillation (100−160 °C/1 × 10^{-3} mbar, byproduct; 200 °C/1 × 10^{-3} mbar, product **15**) to give **15** in 67% yield as an analytically pure (GC and NMR) colorless liquid (1.38 g, 3.61 mmol). For NMR data, see the Supporting Information. EI MS: *m*/*z* (%) 366 (1) ($M^+ - CH_3$), 246 (100) ($M^+ - (CH_2)_4Br$). Anal. Calcd for $C_{17}H_{24}BrNO_2Si$: C, 53.40; H, 6.33; N, 3.66. Found: C, 53.20; H, 6.27; N, 3.74.

(5-Bromopentyl)dimethyl(3-phthalimidopropyl)silane (16). Preparation from **14** (1.39 g, 5.62 mmol) and 5-bromo-1-pentene (881 mg, 5.91 mmol) was analogous to the synthesis of **15**: 67% yield (distillation, 205 °C/1 × 10^{-3} mbar). For NMR data, see the Supporting Information. EI MS: *m*/*z* (%) 395 (<1) (M^+), 380 (1) ($M^+ - CH_3$), 246 (100) ($M^+ - (CH_2)_5$-

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(25) *N*-Propylphthalimide was also isolated during the workup of compounds **15**−**19**, the yields of this byproduct ranging from 1 to 9% (related to **14**).

Br). Anal. Calcd for $C_{18}H_{26}BrNO_2Si$: C, 54.54; H, 6.61; N, 3.53. Found: C, 54.36; H, 6.55; N, 3.51.

(6-Bromohexyl)dimethyl(3-phthalimidopropyl)silane (17). Preparation from **14** (1.50 g, 6.06 mmol) and 6-bromo-1-hexene (1.00 g, 6.13 mmol) was analogous to the synthesis of **15**: 60% yield (distillation, 210 °C/1 × 10^{-3} mbar). ^{1}H NMR ($CDCl_3$): δ −0.08 (s, 6 H, SiCH_3), 0.40−0.54 (m, 4 H, H_2CSiCH_2), 1.17−1.31 (m, 4 H, $SiCH_2(CH_2)_2(CH_2)_3Br$), 1.31−1.43 (m, 2 H, $CCH_2(CH_2)_2Br$), 1.55−1.68 (m, 2 H, NCH_2CH_2-CH_2Si), 1.80 ("quint", $^3J_{HH}$ = 7.1 Hz, 2 H, $CCH_2CH_2CH_2Br$), 3.36 (t, $^3J_{HH}$ = 7.1 Hz, 2 H, $CCH_2CH_2CH_2Br$), 3.62 (t, $^3J_{HH}$ = 7.4 Hz, 2 H, $NCH_2CH_2CH_2Si$), 7.68 (dd, $^3J_{HH}$ = 5.5 Hz, $^4J_{HH}$ = 3.0 Hz, 2 H, *H*-4/*H*-5, $C(O)C_6H_4C(O)$), 7.81 (dd, $^3J_{HH}$ = 5.5 Hz, $^4J_{HH}$ = 3.0 Hz, 2 H, *H*-3/*H*-6, $C(O)C_6H_4C(O)$). ^{13}C NMR ($CDCl_3$): δ −3.5 ($SiCH_3$), 12.3 ($NCH_2CH_2CH_2Si$), 14.9 ($SiCH_2$-$(CH_2)_5Br$), 23.2 ($NCH_2CH_2CH_2Si$), 23.6 ($SiCH_2CH_2(CH_2)_4Br$), 27.8 ($Si(CH_2)_3CH_2(CH_2)_2Br$), 32.6 ($Si(CH_2)_2CH_2(CH_2)_3Br$), 32.7 ($Si(CH_2)_4CH_2CH_2Br$), 34.0 ($Si(CH_2)_5CH_2Br$), 41.0 (NCH_2CH_2-CH_2Si), 123.1 (*C*-3/*C*-6, $C(O)C_6H_4C(O)$), 132.1 (*C*-1/*C*-2, $C(O)$-$C_6H_4C(O)$), 133.8 (*C*-4/*C*-5, $C(O)C_6H_4C(O)$), 168.4 (*C*=O). ^{15}N NMR ($CDCl_3$): δ −218. ^{29}Si NMR ($CDCl_3$): δ 2.9. EI MS: *m*/*z* (%) 409 (<1) (M^+), 394 (1) ($M^+ - CH_3$), 246 (100) ($M^+ - (CH_2)_6$-Br). Anal. Calcd for $C_{19}H_{28}BrNO_2Si$: C, 55.60; H, 6.88; N, 3.41. Found: C, 55.69; H, 6.95; N, 3.42.

(7-Bromoheptyl)dimethyl(3-phthalimidopropyl)silane (18). Preparation from **14** (1.37 g, 5.54 mmol) and 7-bromo-1-heptene (synthesized according to ref 26; 1.04 g, 5.87 mmol) was analogous to the synthesis of **15**: 59% yield (distillation, 215 °C/1 × 10^{-3} mbar). For NMR data, see the Supporting Information. EI MS: *m*/*z* (%) 408 (<1) ($M^+ - CH_3$), 246 (100) ($M^+ - (CH_2)_7Br$). Anal. Calcd for $C_{20}H_{30}BrNO_2Si$: C, 56.60; H, 7.12; N, 3.30. Found: C, 56.42; H, 7.09; N, 3.30.

(8-Bromooctyl)dimethyl(3-phthalimidopropyl)silane (19). Preparation from **14** (1.36 g, 5.50 mmol) and 8-bromo-1-octene (1.14 g, 5.97 mmol) was analogous to the synthesis of **15**: 64% yield (distillation, 220 °C/1 × 10^{-3} mbar). For NMR data, see the Supporting Information. EI MS: *m*/*z* (%) 437 (<1) (M^+), 422 (1) ($M^+ - CH_3$), 246 (100) ($M^+ - (CH_2)_8Br$). Anal. Calcd for $C_{21}H_{32}BrNO_2Si$: C, 57.52; H, 7.36; N, 3.19. Found: C, 57.37; H, 7.46; N, 3.17.

Dimethyl(3-phthalimidopropyl)amine (20). Compound **20** was prepared according to a literature method[27] from phthalic acid anhydride (56.4 g, 381 mmol) and *N*,*N*-dimethylpropane-1,3-diamine (40.9 g, 400 mmol). The crude product was distilled in vacuo (bp 144 °C/1 × 10^{-3} mbar) to give **20** in 91% yield as a slightly yellow liquid (80.1 g, 345 mmol). Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 66.70; H, 6.83; N, 11.88.

Crystal Structure Analysis. A suitable single crystal of **3**·MeC(O)Me was obtained by cooling of a boiling saturated solution of **3** in acetone to room temperature. The crystal was mounted in inert oil on a glass fiber and then transferred to the cold nitrogen gas stream of the diffractometer (Stoe IPDS; graphite-monochromated Mo Kα radiation (λ = 0.710 73 Å)). The structure was solved by direct methods.[28] All non-hydrogen atoms were refined anisotropically.[29] A riding model was employed in the refinement of the hydrogen atoms. The crystal data and experimental parameters used for the crystal structure analysis are summarized in Table 5. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-167551. 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).

Table 5. Crystal Data and Experimental Parameters for the Crystal Structure Analysis of 3·MeC(O)Me

empirical formula	$C_{33}H_{46}BrN_3O_5Si$
formula mass, g mol^{-1}	672.73
collection *T*, K	173(2)
λ(Mo Kα), Å	0.71073
crystal system	monoclinic
space group (No.)	$P2_1/c$ (14)
a, Å	22.710(5)
b, Å	7.6442(15)
c, Å	22.065(4)
β, deg	115.38(3)
V, Å^3	3460.8(12)
Z	4
D(calcd), g cm^{-3}	1.291
μ, mm^{-1}	1.264
F(000)	1416
crystal dimensions, mm	0.5 × 0.3 × 0.3
2θ range, deg	4.30−50.18
index ranges	$-27 \le h \le 27$, $-9 \le k \le 9$, $-26 \le l \le 25$
no. of collected reflections	19 439
no. of independent reflections	6107
absorption correction	analytical
max and min transmission	0.686 and 0.523
R_{int}	0.0428
no. of reflections used	6107
no. of parameters	394
S^a	0.945
weight parameters *a*/*b*^{b}	0.0519/0.0000
$R1^c$ ($I > 2\sigma(I)$)	0.0344
$wR2^d$ (all data)	0.0831
min/max residual electron density, e Å^{-3}	+0.350/−0.345

^{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} $wR2 = \{\sum[w(F_o^2 - F_c^2)^2]/\sum[w(F_o2)^2]\}^{0.5}$.

Determination of the Stability of Compounds 3−7 under Pharmacological Assay Conditions. Three millimolar solutions of **3**−**7** in DMSO were diluted to 100 μM buffer solutions (3.6 mM $MgHPO_4$/50 mM Tris·HCl buffer, pH 7.3), and UV/vis spectra were recorded at 37 °C every 2 h (quartz cell, length 1 cm; buffer solution (see above) as reference). The absorptions recorded at 295, 300, and 305 nm were used for the kinetic analysis, the data being analyzed according to ref 30.

Determination of the Allosteric Effects on [^{3}H]NMS Binding. To determine the allosteric effect of the test compounds on ligand binding to muscarinic M_2 receptors, [^{3}H]*N*-methylscopolamine ([^{3}H]NMS, specific activity 82.0 or 70.0 Ci mmol^{-1}; NEN Life Science Products, NET-636) binding experiments were carried out in porcine heart homogenates (3 mM $MgHPO_4$, 50 mM Tris·HCl, pH 7.3, 37 °C). Homogenates were prepared as described previously.[9] To examine the effect of the test compounds on radioligand dissociation, membranes were preincubated with [^{3}H]NMS (0.2 nM) for 30 min in an assay volume of 24 mL. [^{3}H]NMS dissociation was made visible by addition of 1 μM atropine, alone or in combination with the respective test compound, and aliquots of 1 mL each were removed from the assay over a period of 120 min. Under control conditions, i.e., in the absence of any test compound, the half-life of dissociation amounted to $t_{1/2,control} = 2.36 \pm 0.07$ min, mean ± SEM, n = 14. Membranes were collected by vacuum filtration. Radioactivity was determined by liquid scintillation counting. The effect on [^{3}H]NMS equilibrium binding ($pK_{D,control} = 9.4 \pm 0.04$, mean ± SEM, n = 3) was measured after 2−3.5 h incubation depending on the extent

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by which the test compounds slowed the dissociation kinetics of [^{3}H]NMS.[31] Nonspecific binding of [^{3}H]NMS was determined in the presence of 1 μM atropine. Equilibrium binding data were analyzed according to Ehlert[10] using eq 1

$$B = \frac{B_0([L] + K_D)}{[L] + K_D\left(\frac{K_A + [A]}{K_A + \frac{[A]}{\alpha}}\right)} \quad (1)$$

where B_0 denotes the equilibrium binding at a fixed radioligand concentration in the absence of the allosteric ligand A, K_D is the equilibrium dissociation constant of the binding of the radioligand L to free receptors, K_A is the equilibrium dissociation constant of the allosteric ligand at the free receptors, and α is the cooperativity factor for the interaction between the allosteric modulator and the radioligand. Experimental data were analyzed by nonlinear regression analysis using the software Prism, version 3.0 (GraphPAD software, San Diego, CA).

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Supporting Information Available: Tables giving ^{1}H, ^{13}C, ^{15}N, and ^{29}Si NMR data for compounds **15**−**19** and crystallographic data for **3**·MeC(O)Me. This material is available free of charge via the Internet at http://www.pubs.acs.org.

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