A Novel Silicon-Based Uncharged Allosteric Modulator for Ligand Binding to Muscarinic M_2 Receptors: Synthesis and Pharmacological Characterization[§]

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N,*N*,*N*′,*N*′-Tetramethyl-*N*,*N*′-bis(3-phthalimidopropyl)hexane-1,6-diaminium bromide (W84, **1**) is an allosteric agent for the "common allosteric site" of muscarinic M_2 receptors that slows the dissociation of the orthosteric ligand [^{3}H]*N*-methylscopolamine ([^{3}H]NMS) and submaximally diminishes [^{3}H]NMS binding. The silicon-containing W84 derivatives (6-(dimethyl(3-(1,8-naphthalimido)propyl)silyl)hexyl)dimethyl(3-(1,8-naphthalimido)propyl)ammonium bromide (**5**) and (6-(dimethyl(3-(1,8-naphthalimido)propyl)silyl)hexyl)methyl(3-(1,8-naphthalimido)propyl)amine (**6**; isolated as **6**·HCl) were synthesized in four-step syntheses, starting from $ClMe_2SiH$. In contrast to W84 (**1**) (a 2-fold positively charged agent) and compound **5** (a singly positively charged agent), compound **6** is an uncharged allosteric modulator for ligand binding to muscarinic M_2 receptors. Similar to **5**, the action of **6** is characterized by an enhancement of [^{3}H]NMS binding.

Introduction

In context with our systematic studies on silicon-based drugs,[1,2] we have recently reported on an N^+/Si exchange in the allosteric agent W84 (**1**) to give the silicon compound **2**.[2d] W84 is an archetypal ligand of the "common allosteric site" of muscarinic M_2 receptors,[3,4] its allosteric action being characterized by an inhibition of the dissociation of the orthosteric ligand [^{3}H]*N*-methylscopolamine ([^{3}H]NMS). Interestingly, the parent drug W84 (a 2-fold positively charged agent) decreases [^{3}H]NMS equilibrium binding (negative cooperativity), whereas the silicon compound **2** (a singly positively charged agent) has been found to enhance [^{3}H]NMS equilibrium binding (positive cooperativity); that is, replacement of one of the two ammonium nitrogen atoms in **1** by a silicon atom switches the allosteric action from negative to positive cooperativity.[2d] Positive cooperativity has also been found for the related silicon compounds **3**[2d] and **4**[2g] (in this context, see also ref 5). The effect of **4** on [^{3}H]NMS binding at cloned human M_1−M_5 receptors has been demonstrated to be M_2-selective: [^{3}H]NMS binding was increased only at M_2 receptors, whereas it was hardly changed at the other four receptor subtypes.[2g]

As the allosteric agents **1**−**4** contain one (**2**−**4**) or two (**1**) positively charged ammonium groups, they are expected to lack the ability to cross the blood−brain barrier. To overcome this problem, which considerably restricts the potential therapeutic perspectives of allosteric modulators of these formula types, we have synthesized the neutral compound **6**, which might be able to cross the blood−brain barrier and hopefully would still behave as an allosteric enhancer of [^{3}H]NMS binding at muscarinic M_2 receptors. For reasons of comparison (structure−activity relationships), a singly positively charged ammonium derivative of **6**, compound

[§] Dedicated to Professor Wolfdieter Schenk on the occasion of his 60th birthday.

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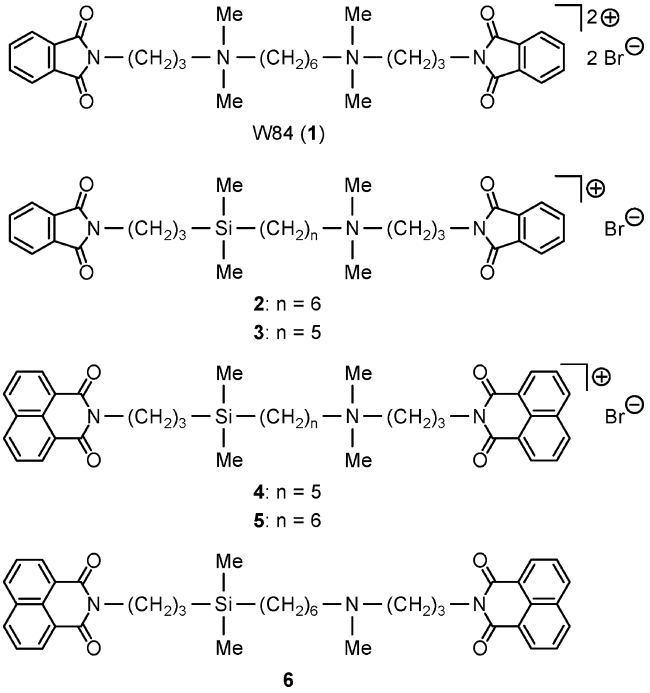


5, was also synthesized. This compound can also be regarded as a derivative of **4**, with a $(CH_2)_6$ chain instead of the $(CH_2)_5$ moiety. We report here on the synthesis of (6-(dimethyl(3-(1,8-naphthalimido)propyl)-silyl)hexyl)dimethyl(3-(1,8-naphthalimido)propyl)ammonium bromide (**5**) and (6-(dimethyl(3-(1,8-naphthalimido)-propyl)silyl)hexyl)methyl(3-(1,8-naphthalimido)propyl)amine (**6**; isolated as the hydrochloride **6**·HCl) and their pharmacological characterization.

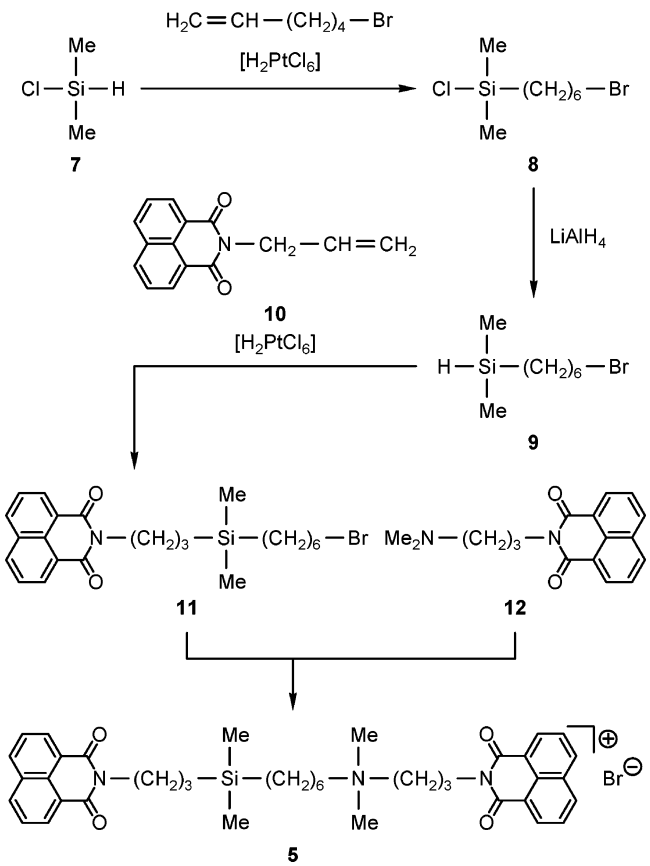
Results and Discussion

Syntheses. Compound **5** was synthesized in a four-step synthesis, starting from chlorodimethylsilane (**7**) (Scheme 1). Thus, platinum-catalyzed (H_2PtCl_6) hydrosilylation of 6-bromo-1-hexene with **7** afforded (6-bromohexyl)chlorodimethylsilane (**8**) (yield 83%), which upon reaction with lithium aluminum hydride gave (6-bromohexyl)dimethylsilane (**9**) (yield 91%). Subsequent platinum-catalyzed (H_2PtCl_6) hydrosilylation of *N*-allyl-1,8-naphthalimide (**10**) with **9** gave (6-bromohexyl)-dimethyl(3-(1,8-naphthalimido)propyl)silane (**11**) (yield 86%), which was reacted with dimethyl(3-(1,8-naphthalimido)propyl)amine (**12**) to afford **5** (yield 73%, with respect to **11**).

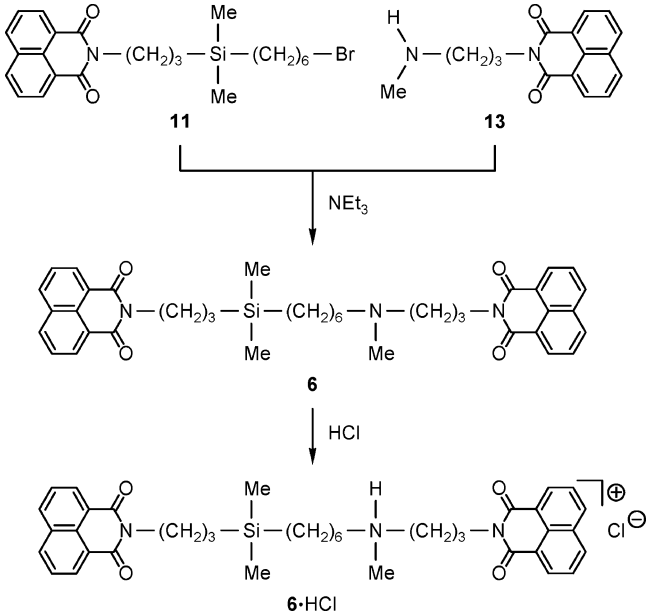
Compound **6** was prepared analogously to the synthesis of **5** in a four-step synthesis and was isolated as the hydrochloride **6**·HCl (Scheme 2). Thus, in the last step compound **11** was reacted with methyl(3-(1,8-naphthalimido)propyl)amine (**13**) in the presence of excess triethylamine to afford **6**.[6] Treatment of **6** with an ethereal hydrogen chloride solution gave the corresponding hydrochloride **6**·HCl (yield 56%, with respect to **11**).

Compound **13** was synthesized by reaction of 1,8-naphthalic acid anhydride (**14**) with *N*-methyl-1,3-propanediamine (**15**) in refluxing glacial acetic acid (yield 70%) (Scheme 3).

Scheme 1



Scheme 2



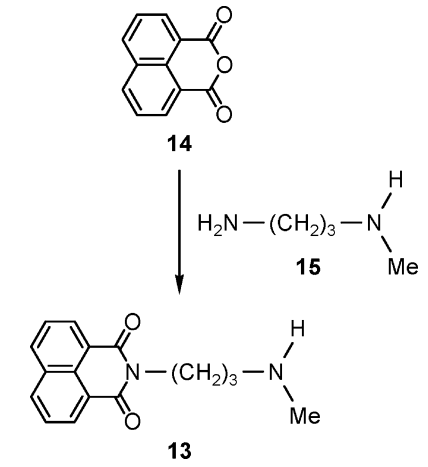
Compounds **5**, **6**·HCl, and **13** were isolated as solids, whereas **8**, **9**, and **11** were obtained as liquids. The identities of all compounds were established by NMR studies and elemental analyses (except for **6**).[7]

Pharmacological Studies. Compounds **1** (W84), **5**, and **6** were studied for their allosteric effects on ligand

(6) After chromatographic purification, compound **6** was isolated in ca. 60% yield as a highly viscous, yellowish oil, which contained some residual ethyl acetate (ca. 5 wt %) that could not be removed in vacuo.

(7) Stockton, J. M.; Birdsall, N. J. M.; Burgen, A. S. V.; Hulme, E. C. *Mol. Pharmacol.* **1983**, *23*, 551−557.

Scheme 3



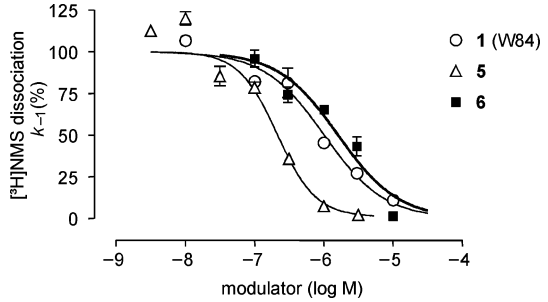


Figure 1. Concentration−effect curves of the test compounds **1** (W84), **5**, and **6** for the allosteric delay of [^{3}H]-NMS dissociation from porcine heart M_2 receptors. *Ordinate*: apparent rate constant of dissociation (k_{-1}) as a percentage of the value under control conditions. *Abscissa*: log concentration of the test compounds. Indicated are mean values ± SEM of 2−4 independent dissociation experiments; sigmoidal curve fitting. Except for compound **5**, the slope factors n_H of all curves were not significantly different from unity (F test, $p < 0.05$).

binding to porcine heart muscarinic M_2 acetylcholine receptors. The uncharged compound **6** (which probably interacts with the receptor as the protonated species) revealed an allosteric inhibition of the dissociation of the conventional orthosteric ligand [^{3}H]NMS from the muscarinic M_2 receptors. The concentration−effect curve (Figure 1) reflects the formation of ternary complexes between **6** and [^{3}H]NMS-occupied M_2 receptors. Compound **6** did not fully reach the affinity of the quaternary ammonium derivative **5** (Figure 1), but had an affinity equal to that of the archetypal allosteric agent W84 (**1**). Whereas W84 reduced the equilibrium binding of [^{3}H]-NMS, compound **6** clearly enhanced binding of this orthosteric ligand (Figure 2). The ammonium compound **5** revealed a more pronounced positive cooperativity with [^{3}H]NMS (Figure 2), although the difference between the −log cooperativity factors, pα, of both agents did not reach the level of significance (Table 1). The pharmacological characteristics of compound **5** were similar to those of the $(CH_2)_5$ chain-containing compound **4**.[2g] The curves shown in Figure 2 additionally yield the affinities, pK_A, of the compounds for free M_2 receptors that are not occupied with [^{3}H]NMS (Table 1). Compounds **5** and **6** shared equal affinities, whereas the affinity of W84 was considerably higher. The rather low affinities of **5** and **6** for free receptors relative to

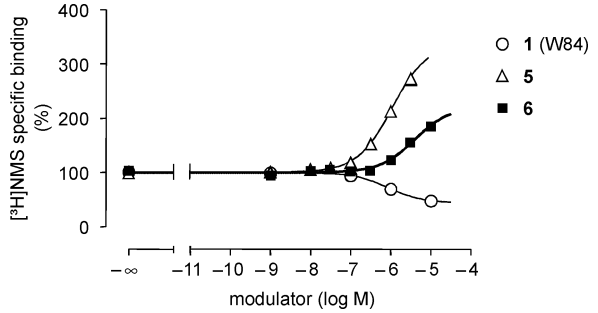


Figure 2. Concentration−effect curves for the influence of the test compounds on [^{3}H]NMS (0.2 nM) equilibrium binding. *Ordinate*: specific [^{3}H]NMS binding expressed as a percentage of binding in the absence of the test compound. *Abscissa*: log concentration of the test compound. Indicated are mean values ± SEM of 3 independent experiments carried out as triplicate determinations. Curve fitting is based on the ternary complex model of allosteric interactions.[7]

Table 1. Affinity Values and Cooperativity Factors to Characterize the Allosteric Interaction of the Test Compounds 1 (W84), 5, and 6 with [^{3}H]NMS-Occupied and Free Muscarinic M_2 Receptors[a]

compound	p$EC_{50,diss}$	pα	pK_A
1	5.99 ± 0.07	−0.46 ± 0.01	6.17 ± 0.02
5	6.66 ± 0.06[b]	+1.85 ± 0.38[b]	4.64 ± 0.41
6	5.79 ± 0.07[c]	+0.93 ± 0.02	4.82 ± 0.10

[a] p$EC_{50,diss}$ indicates the −log concentration of the test compound at which orthosteric radioligand dissociation was reduced to 50% compared with control conditions and reflects the affinity of the modulator to NMS-occupied M_2 receptors. pα is the −log factor of cooperativity between [^{3}H]NMS and the test compound; a positive sign indicates an enhancement of [^{3}H]NMS equilibrium binding by the modulator (positive cooperativity), whereas a negative sign denotes a reduction of [^{3}H]NMS equilibrium binding (negative cooperativity). pK_A is the −log value of the equilibrium dissociation constant of the test compound and reflects its affinity for free receptors. Mean values ± SEM, n = 2−4 independent experiments. [b] This value is significantly different from the respective parameter value of compound **1** (calculated with an unpaired t test, Welch-corrected if necessary). [c] This value is significantly different from the respective parameter value of compound **5** (calculated with an unpaired t test, Welch-corrected if necessary).

[^{3}H]NMS-occupied receptors explain why these agents elevate [^{3}H]NMS equilibrium binding.

In conclusion, the uncharged silicon compound **6** has been demonstrated to enhance orthosteric ligand binding at muscarinic M_2 receptors, analogously to the singly positively charged agents **2**−**5**. It will be interesting to find out whether **6** has a subtype selectivity for M_2 receptors as previously seen with compound **4**.[2g] Although **6** probably interacts with the receptors as the protonated species, this neutral silicon compound is a promising new allosteric enhancer at M_2 receptors that might be able to cross the blood−brain barrier and thus to reach the central nervous system. Both the neutral agent **6** and its hydrochloride **6**·HCl are soluble in dichloromethane, indicating a high degree of lipophilicity. Currently, we are trying to prove this concept by developing an ^{18}F-labeled derivative of **6** that can be used for PET (positron emission tomography) studies.

Experimental Section

Chemistry. General Procedures. 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 melting point B-540 apparatus using samples in open glass capillaries. The ^{1}H, ^{13}C, ^{15}N, 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; ^{15}N, 30.4 MHz; ^{29}Si, 59.6 MHz). CD_2Cl_2, $CDCl_3$, or [D$_6$]DMSO was used as the solvent. Chemical shifts (ppm) were determined relative to internal $CHDCl_2$ (^{1}H, δ 5.32; CD_2Cl_2), internal CD_2Cl_2 (^{13}C, δ 53.8; CD_2Cl_2), internal $CHCl_3$ (^{1}H, δ 7.24; $CDCl_3$), internal $CDCl_3$ (^{13}C, δ 77.0; $CDCl_3$), internal [D$_5$]DMSO (^{1}H, δ 2.49; [D$_6$]DMSO), internal [D$_6$]DMSO (^{13}C, δ 39.5; [D$_6$]DMSO), external formamide (^{15}N, δ −268; CD_2Cl_2), or external TMS (^{29}Si, δ 0; CD_2Cl_2, $CDCl_3$, [D$_6$]DMSO). Assignment of the ^{1}H NMR data was supported by $^{1}H,^{1}H$, $^{13}C,^{1}H$, and $^{29}Si,^{1}H$ 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.

Preparation of (6-(Dimethyl(3-(1,8-naphthalimido)-propyl)silyl)hexyl)dimethyl(3-(1,8-naphthalimido)propyl)-ammonium Bromide (5). A solution of **11** (1.11 g, 2.41 mmol) and **12** (710 mg, 2.51 mmol) in ethanol (12 mL) was heated under reflux for 48 h. After the mixture was cooled to 20 °C, the solvent was removed at 30 mbar, and ethyl acetate (50 mL) was added. The solution was concentrated in vacuo to a volume of ca. 10 mL by lowering the pressure slowly from 200 mbar to 30 mbar. The addition of ethyl acetate and subsequent removal of the solvent were repeated until the product precipitated almost quantitatively as a white amorphous solid, which was isolated by centrifugation (1100*g*, 5 min), washed with *n*-pentane (2 × 20 mL), and dried in vacuo (2 h, 0.001 mbar, 20 °C). To further purify the product, a boiling saturated solution of the solid in acetone was concentrated by distillation at atmospheric pressure until the product precipitated significantly. The precipitation was completed by storing the suspension at 20 °C for 1 day, and the product was isolated by centrifugation and washed with *n*-pentane (2 × 20 mL). The purification procedure was repeated twice, and the resulting product was finally dried in vacuo (8 h, 0.001 mbar, 60 °C) to give **5** in 73% yield as an amorphous white solid (1.31 g, 1.76 mmol); mp 189 °C (dec). ^{1}H NMR ([D$_6$]DMSO): δ −0.07 (s, 6 H, SiCH_3), 0.37−0.47 (m, 2 H, SiCH_2(CH$_2$)$_5$N$^+$), 0.47−0.58 (m, 2 H, N(CH$_2$)$_2$CH_2Si), 1.13−1.30 (m, 6 H, SiCH$_2$(CH_2)$_3$(CH$_2$)$_2$N$^+$), 1.48−1.68 (m, 4 H, NCH$_2$CH_2CH$_2$Si and Si(CH$_2$)$_4$CH_2CH$_2$N$^+$), 2.01−2.18 (m, 2 H, N$^+$CH$_2$CH_2CH$_2$N), 2.99 (s, 6 H, N$^+$CH_3), 3.15−3.29 (m, 2 H, Si(CH$_2$)$_5$CH_2N$^+$), 3.35−3.46 (m, 2 H, N$^+$CH_2(CH$_2$)$_2$N), 3.88−3.99 (m, 2 H, NCH_2(CH$_2$)$_2$Si), 4.08 (t, $^{3}J_{HH}$ = 6.3 Hz, 2 H, N$^+$(CH$_2$)$_2$CH_2N), 7.76−7.85 (m, 4 H, *H*-3/*H*-6, 1,8-naphthalimido moiety (≡ naphth)), 8.35−8.45 (m, 8 H, *H*-2/*H*-7 and *H*-4/*H*-5, naphth). ^{13}C NMR ([D$_6$]-DMSO): δ −3.4 (SiCH_3), 12.0 (N(CH$_2$)$_2$$CH_2$Si), 14.4 (Si$CH_2$-(CH$_2$)$_5N^+$), 21.2 (N$^+CH_2CH_2CH_2$N), 21.6 (Si(CH$_2$)$_4$$CH_2CH_2N^+$), 22.0 (NCH$_2$$CH_2CH_2$Si), 23.0 (SiCH$_2$$CH_2$(CH$_2$)$_4N^+$), 25.4 (Si-(CH$_2$)$_3$$CH_2$(CH$_2$)$_2N^+$), 32.3 (Si(CH$_2$)$_2$$CH_2$(CH$_2$)$_3N^+$), 36.9 (N$^+$-(CH$_2$)$_2$$CH_2$N), 42.5 (N$CH_2$(CH$_2$)$_2$Si), 50.0 (N$^+$$CH_3$), 60.8 (N$^+$$CH_2$-(CH$_2$)$_2$N), 63.0 (Si(CH$_2$)$_5$$CH_2N^+$), 121.9 (*C*-1/*C*-8, naphth), 122.0 (*C*-1/*C*-8, naphth), 127.1 (5 C, *C*-8a and *C*-3/*C*-6, naphth), 127.3 (*C*-8a, naphth), 130.59 (*C*-2/*C*-7, naphth), 130.63 (*C*-2/*C*-7, naphth), 131.1 (*C*-4a, naphth), 131.2 (*C*-4a, naphth), 134.2 (*C*-4/*C*-5, naphth), 134.3 (*C*-4/*C*-5, naphth), 163.2 ((O=C)$_2$N(CH$_2$)$_3$-Si), 163.6 (N$^+$(CH$_2$)$_3$N(C=O)$_2$). ^{29}Si NMR ([D$_6$]DMSO): δ 2.9. Anal. Calcd for $C_{40}H_{48}BrN_3O_4Si$: C, 64.68; H, 6.51; N, 5.66. Found: C, 64.6; H, 6.6; N, 5.6.

Preparation of (6-(Dimethyl(3-(1,8-naphthalimido)-propyl)silyl)hexyl)methyl(3-(1,8-naphthalimido)propyl)ammonium Chloride (6·HCl). A mixture of **11** (1.60 g, 3.47 mmol), **13** (930 mg, 3.47 mmol), triethylamine (3.52 g, 34.8 mmol), and acetonitrile (25 mL) was heated under reflux for 3 days and was then cooled to 20 °C, diluted with ethyl acetate (50 mL), and washed with a 1 M aqueous potassium carbonate solution (50 mL). The organic layer was separated, and the aqueous phase was extracted with ethyl acetate (2 × 50 mL). All organic solutions were combined and dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure, and the oily residue was purified by column chromatography on silica gel (column dimensions, 81 × 3 cm; silica gel (32−63 μm, ICN 02826), 250 g; eluent, ethyl acetate/triethylamine, 99:1 (v/v)). The relevant fractions (TLC control) were combined, and the solvent was removed in vacuo (0.001 mbar, 20 °C, 2 days) to give 1.4 g of a highly viscous, yellowish oil (compound **6**).[6] This product was dissolved in dichloromethane (66 mL), and 1.06 mL of a 2 M ethereal hydrogen chloride solution (2.12 mmol of HCl) was added at 20 °C. The resulting hydrochloride was crystallized by vapor diffusion of diethyl ether into this solution at 20 °C over a period of ca. 2 weeks, and the product was isolated by decantation, redissolved in dichloromethane (61 mL), recrystallized and isolated as described above, and finally dried in vacuo (0.001 mbar, 20 °C, 4 h) to give **6**·HCl in 56% yield (with respect to **11**) as a colorless crystalline solid (1.34 g, 1.96 mmol); mp 222−223 °C. ^{1}H NMR (CD_2Cl_2 [8]): δ −0.04 (s, 6 H, SiCH_3), 0.43−0.54 (m, 2 H, SiCH_2(CH$_2$)$_5$N$^+$), 0.54−0.64 (m, 2 H, N(CH$_2$)$_2$CH_2Si), 1.21−1.41 (m, 6 H, SiCH$_2$(CH_2)$_3$(CH$_2$)$_2$N$^+$), 1.58−1.72 (m, 2 H, NCH$_2$CH_2CH$_2$Si), 1.72−1.92 (m, 2 H, Si(CH$_2$)$_4$CH_2CH$_2$N$^+$), 2.18−2.45 (m, 2 H, N$^+$CH$_2$CH_2CH$_2$N), 2.74 (d, $^{3}J_{HH}$ = 4.2 Hz, 3 H, N$^+$CH_3), 2.85−3.31 (m, 4 H, Si(CH$_2$)$_5$CH_2N$^+$ and N$^+$CH_2-(CH$_2$)$_2$N), 3.98−4.08 (m, 2 H, NCH_2(CH$_2$)$_2$Si), 4.25 (t, $^{3}J_{HH}$ = 6.8 Hz, 2 H, N$^+$(CH$_2$)$_2$CH_2N), 7.65−7.76 (m, 4 H, *H*-3/*H*-6, naphth), 8.13−8.22 (m, 4 H, *H*-4/*H*-5, naphth), 8.46−8.53 (m, 4 H, *H*-2/*H*-7, naphth), 12.4 (br s, 1 H, N*H*). ^{13}C NMR (CD_2Cl_2): δ −3.4 (SiCH_3), 12.8 (N(CH$_2$)$_2$$CH_2$Si), 15.1 (Si$CH_2$-(CH$_2$)$_5N^+$), 22.8 (NCH$_2CH_2CH_2$Si), 23.3 (N$^+CH_2$$CH_2CH_2$N), 23.6 (Si(CH$_2$)$_4$$CH_2CH_2N^+$), 23.9 (SiCH$_2$$CH_2$(CH$_2$)$_4N^+$), 26.7 (Si-(CH$_2$)$_3$$CH_2$(CH$_2$)$_2N^+$), 33.1 (Si(CH$_2$)$_2$$CH_2$(CH$_2$)$_3N^+$), 37.9 (N$^+$-(CH$_2$)$_2$$CH_2$N), 39.8 (N$^+$$CH_3$), 43.5 (N$CH_2$(CH$_2$)$_2$Si), 53.7 (N$^+$$CH_2$-(CH$_2$)$_2$N), 56.0 (Si(CH$_2$)$_5$$CH_2N^+$), 122.5 (*C*-1/*C*-8, naphth), 123.0 (*C*-1/*C*-8, naphth), 127.19 (*C*-3/*C*-6, naphth), 127.22 (*C*-3/*C*-6, naphth), 128.27 (*C*-8a, naphth), 128.28 (*C*-8a, naphth), 131.1 (*C*-2/*C*-7, naphth), 131.4 (*C*-2/*C*-7, naphth), 131.83 (*C*-4a, naphth), 131.86 (*C*-4a, naphth), 134.1 (*C*-4/*C*-5, naphth), 134.5 (*C*-4/*C*-5, naphth), 164.2 ((O=C)$_2$N(CH$_2$)$_3$Si), 164.4 (N$^+$(CH$_2$)$_3$N-(C=O)$_2$). ^{15}N NMR (CD_2Cl_2): δ −331 (*N*$^+$), −204 (*N*(CH$_2$)$_3$Si or N$^+$(CH$_2$)$_3$*N*), −206 (*N*(CH$_2$)$_3$Si or N$^+$(CH$_2$)$_3$*N*). ^{29}Si NMR (CD_2Cl_2): δ 2.9. Anal. Calcd for $C_{39}H_{46}ClN_3O_4Si$: C, 68.45; H, 6.78; N, 6.14; Cl, 5.18. Found: C, 68.3; H, 6.8; N, 6.2; Cl, 5.1.

NMR Data for 6. ^{1}H NMR (CD_2Cl_2): δ −0.03 (s, 6 H, SiCH_3), 0.45−0.56 (m, 2 H, SiCH_2(CH$_2$)$_5$N), 0.56−0.66 (m, 2 H, N(CH$_2$)$_2$CH_2Si), 1.18−1.33 (m, 6 H, SiCH$_2$(CH_2)$_3$(CH$_2$)$_2$N), 1.33−1.45 (m, 2 H, Si(CH$_2$)$_4$CH_2CH$_2$N), 1.62−1.76 (m, 2 H, NCH$_2$CH_2CH$_2$Si), 1.79−1.91 (m, 2 H, N(CH$_3$)CH$_2$CH_2CH$_2$N), 2.18 (s, 3 H, NCH_3), 2.24−2.33 (m, 2 H, Si(CH$_2$)$_5$CH_2N), 2.44 (t, $^{3}J_{HH}$ = 7.1 Hz, 2 H, N(CH$_3$)CH_2(CH$_2$)$_2$N), 4.03−4.20 (m, 4 H, NCH_2(CH$_2$)$_2$Si and N(CH$_3$)(CH$_2$)$_2$CH_2N), 7.69−7.77 (m, 4 H, *H*-3/*H*-6, naphth), 8.17−8.23 (m, 4 H, *H*-4/*H*-5, naphth), 8.50−8.56 (m, 4 H, *H*-2/*H*-7, naphth). ^{13}C NMR (CD_2Cl_2): δ −3.4 (SiCH_3), 12.8 (N(CH$_2$)$_2$$CH_2$Si), 15.4 (Si$CH_2$(CH$_2$)$_5$N), 22.9 (NCH$_2CH_2CH_2$Si), 24.2 (SiCH$_2$$CH_2$(CH$_2$)$_4$N), 26.1 (N(CH$_3$)-CH$_2$$CH_2CH_2$N), 27.5 (Si(CH$_2$)$_3$$CH_2$(CH$_2$)$_2$N or Si(CH$_2$)$_4$$CH_2$-CH$_2$N), 27.7 (Si(CH$_2$)$_3$$CH_2$(CH$_2$)$_2$N or Si(CH$_2$)$_4$$CH_2CH_2$N), 34.0 (Si(CH$_2$)$_2$$CH_2$(CH$_2$)$_3$N), 39.2 (N(CH$_3$)(CH$_2$)$_2$$CH_2$N), 42.1 (N$CH_3$), 43.6 (N$CH_2$(CH$_2$)$_2$Si), 55.8 (N(CH$_3$)$CH_2$(CH$_2$)$_2$N), 58.3 (Si-(CH$_2$)$_5$$CH_2$N), 123.19 (*C*-1/*C*-8, naphth), 123.20 (*C*-1/*C*-8, naphth), 127.2 (4 C, *C*-3/*C*-6, naphth), 128.4 (2 C, *C*-8a, naphth), 131.13 (*C*-2/*C*-7, naphth), 131.14 (*C*-2/*C*-7, naphth),

(8) Absence of dichloromethane as the solvent of crystallization was verified by recording a ^{1}H NMR spectrum of **6**·HCl in [D$_6$]DMSO. However, due to the poor solubility of **6**·HCl in [D$_6$]DMSO, this solvent was not suitable for recording ^{13}C, ^{15}N, and ^{29}Si NMR spectra of this compound.

131.9 (2 C, *C*-4a, naphth), 134.1 (4 C, *C*-4/*C*-5, naphth), 164.26 (N(*C*=O)$_2$), 164.31 (N(*C*=O)$_2$). ^{29}Si NMR (CD_2Cl_2): δ 2.9.

Chlorodimethylsilane (7). This compound was commercially available (Acros, 16284).

Preparation of (6-Bromohexyl)chlorodimethylsilane (8). Hexachloroplatinic acid hexahydrate (5 mg, 9.7 μmol) was added at 20 °C to a solution of **7** (19.1 g, 202 mmol) and 6-bromo-1-hexene (27.4 g, 168 mmol) in toluene (200 mL), and the mixture was heated immediately in a preheated oil bath (140 °C). After the reaction had started, the oil bath was removed. As soon as the reaction started to become less vigorous, the mixture was heated under reflux (no drop in temperature below reflux temperature at any time), and further portions of $H_2PtCl_6\cdot 6H_2O$ and **7** were added sequentially: first portion (after 30 min), addition of $H_2PtCl_6\cdot 6H_2O$ (5 mg, 9.7 μmol; dissolved in 2-propanol (50 μL)), followed by addition of **7** (5.00 g, 52.8 mmol); second to fifth portion (after 40, 50, 60, and 70 min), $H_2PtCl_6\cdot 6H_2O$ (5 mg, 9.7 μmol; dissolved in 2-propanol (50 μL)) and **7** (1.00 g, 10.6 mmol). After addition of the last portion, the mixture was heated under reflux for a further 50 min. The solvent was removed by distillation under normal pressure, and the residue was distilled in vacuo to give **8** in 83% yield (with respect to 6-bromo-1-hexene) as a colorless liquid (35.8 g, 139 mmol); bp 100−101 °C/3 mbar. ^{1}H NMR ($CDCl_3$): δ 0.38 (s, 6 H, SiC*H*$_3$), 0.74−0.84 (m, 2 H, SiC*H*$_2$(CH$_2$)$_5$Br), 1.28−1.49 (m, 6 H, SiCH$_2$(C*H*$_2$)$_3$(CH$_2$)$_2$Br), 1.77−1.89 (m, 2 H, Si(CH$_2$)$_4$C*H*$_2$CH$_2$Br), 3.38 (t, $^3J_{HH}$ = 6.8 Hz, 2 H, Si(CH$_2$)$_5$C*H*$_2$Br). ^{13}C NMR ($CDCl_3$): δ 1.6 (Si*C*H$_3$), 18.8 (Si*C*H$_2$(CH$_2$)$_5$Br), 22.8 (SiCH$_2$*C*H$_2$(CH$_2$)$_4$Br), 27.7 (Si(CH$_2$)$_3$*C*H$_2$(CH$_2$)$_2$Br), 32.0 (Si(CH$_2$)$_2$*C*H$_2$(CH$_2$)$_3$Br), 32.6 (Si(CH$_2$)$_4$*C*H$_2$CH$_2$Br), 33.9 (Si(CH$_2$)$_5$*C*H$_2$Br). ^{29}Si NMR ($CDCl_3$): δ 32.1. Anal. Calcd for $C_8H_{18}BrClSi$: C, 37.29; H, 7.04. Found: C, 37.5; H, 7.1.

Preparation of (6-Bromohexyl)dimethylsilane (9). Compound **8** (34.9 g, 135 mmol) was added at 20 °C within a period of 5 min to a stirred suspension of lithium aluminum hydride (3.74 g, 98.5 mmol) in diethyl ether (250 mL), causing the mixture to boil under reflux during the addition. The resulting mixture was heated under reflux for 30 min, cooled to 20 °C, and then added dropwise to a stirred mixture of concentrated hydrochloric acid (100 mL), diethyl ether (200 mL), and ice (200 g) (to avoid ignition, this step was also performed under a nitrogen atmosphere). The organic layer was separated, the aqueous phase was extracted with diethyl ether (3 × 100 mL), and the combined organic extracts were dried over anhydrous magnesium sulfate in an ice bath, followed by an additional thorough dynamic drying over anhydrous magnesium sulfate using a standard chromatographic column densely packed with anhydrous magnesium sulfate (column dimensions, 15 × 3.5 cm). The magnesium sulfate was finally washed with diethyl ether (300 mL), the organic solutions were combined, the solvent was removed under reduced pressure, and the residue was distilled in vacuo to give **9** in 91% yield as a colorless liquid (27.6 g, 124 mmol); bp 80 °C/3 mbar. ^{1}H NMR ($CDCl_3$): δ 0.04 (d, $^3J_{HH}$ = 3.7 Hz, 6 H, SiC*H*$_3$), 0.50−0.62 (m, 2 H, SiC*H*$_2$(CH$_2$)$_5$Br), 1.25−1.48 (m, 6 H, SiCH$_2$(C*H*$_2$)$_3$(CH$_2$)$_2$Br), 1.83 ("quint", $^3J_{HH}$ = 7.0 Hz, 2 H, Si(CH$_2$)$_4$C*H*$_2$CH$_2$Br), 3.38 (t, $^3J_{HH}$ = 7.0 Hz, 2 H, Si(CH$_2$)$_5$C*H*$_2$Br), 3.82 ("nonett", $^3J_{HH}$ = 3.7 Hz, 1 H, Si*H*). ^{13}C NMR ($CDCl_3$): δ −4.5 (Si*C*H$_3$), 14.0 (Si*C*H$_2$(CH$_2$)$_5$Br), 24.2 (SiCH$_2$*C*H$_2$(CH$_2$)$_4$Br), 27.9 (Si(CH$_2$)$_3$*C*H$_2$(CH$_2$)$_2$Br), 32.2 (Si(CH$_2$)$_2$*C*H$_2$(CH$_2$)$_3$Br), 32.7 (Si(CH$_2$)$_4$*C*H$_2$CH$_2$Br), 34.0 (Si(CH$_2$)$_5$*C*H$_2$Br). ^{29}Si NMR ($CDCl_3$): δ −12.9. Anal. Calcd for $C_8H_{19}BrSi$: C, 43.04; H, 8.58. Found: C, 43.0; H, 8.5.

Preparation of *N*-Allyl-1,8-naphthalimide (10). This compound was synthesized according to ref 2g.

Preparation of (6-Bromohexyl)dimethyl(3-(1,8-naphthalimido)propyl)silane (11). Hexachloroplatinic acid hexahydrate (5 mg, 9.7 μmol) was added at 20 °C to a solution of **9** (4.07 g, 18.2 mmol) and **10** (4.12 g, 17.4 mmol) in toluene (60 mL), and the mixture was heated immediately under reflux in a preheated oil bath for 30 min, followed by addition of another portion of $H_2PtCl_6\cdot 6H_2O$ (5 mg, 9.7 μmol; dissolved in 2-propanol (50 μL)) and heating under reflux for a further 1 h. The reaction mixture was filtered over silica gel (30 g, 0.063−0.200 mm (Fluka, 60741)) packed in a chromatographic column (column dimensions, 10 × 3.5 cm), the product was then eluted with ethyl acetate (500 mL), and the organic solutions were combined. The solvent was removed under reduced pressure, and the residue was purified by bulb-to-bulb distillation in vacuo (Kugelrohr apparatus, 240−250 °C/0.001 mbar) to give **11** in 86% yield (with respect to **10**) as a slightly yellowish viscous liquid (6.84 g, 14.9 mmol). ^{1}H NMR ($CDCl_3$): δ −0.06 (s, 6 H, SiC*H*$_3$), 0.42−0.52 (m, 2 H, SiC*H*$_2$(CH$_2$)$_5$Br), 0.54−0.64 (m, 2 H, N(CH$_2$)$_2$C*H*$_2$Si), 1.20−1.31 (m, 4 H, SiCH$_2$(C*H*$_2$)$_2$(CH$_2$)$_3$Br), 1.31−1.43 (m, 2 H, Si(CH$_2$)$_3$C*H*$_2$(CH$_2$)$_2$Br), 1.62−1.75 (m, 2 H, NCH$_2$C*H*$_2$CH$_2$Si), 1.80 ("quint", $^3J_{HH}$ = 7.0 Hz, 2 H, Si(CH$_2$)$_4$C*H*$_2$CH$_2$Br), 3.36 (t, $^3J_{HH}$ = 7.0 Hz, 2 H, Si(CH$_2$)$_5$C*H*$_2$Br), 4.07−4.16 (m, 2 H, NC*H*$_2$(CH$_2$)$_2$Si), 7.71 (dd, $^3J_{HH}$ = 7.2 Hz, $^3J_{HH}$ = 8.3 Hz, 2 H, *H*-3/*H*-6, naphth), 8.16 (dd, $^3J_{HH}$ = 8.3 Hz, $^4J_{HH}$ = 1.1 Hz, 2 H, *H*-4/*H*-5, naphth), 8.55 (dd, $^3J_{HH}$ = 7.2 Hz, $^4J_{HH}$ = 1.1 Hz, 2 H, *H*-2/*H*-7, naphth). ^{13}C NMR ($CDCl_3$): δ −3.5 (Si*C*H$_3$), 12.5 (N(CH$_2$)$_2$-*C*H$_2$Si), 15.0 (Si*C*H$_2$(CH$_2$)$_5$Br), 22.6 (NCH$_2$*C*H$_2$CH$_2$Si), 23.6 (SiCH$_2$*C*H$_2$(CH$_2$)$_4$Br), 27.8 (Si(CH$_2$)$_3$*C*H$_2$(CH$_2$)$_2$Br), 32.65 (Si(CH$_2$)$_2$*C*H$_2$(CH$_2$)$_3$Br or Si(CH$_2$)$_4$*C*H$_2$CH$_2$Br), 32.73 (Si-(CH$_2$)$_2$*C*H$_2$(CH$_2$)$_3$Br or Si(CH$_2$)$_4$*C*H$_2$CH$_2$Br), 34.1 (Si(CH$_2$)$_5$-*C*H$_2$Br), 43.3 (N*C*H$_2$(CH$_2$)$_2$Si), 122.7 (*C*-1/*C*-8, naphth), 126.8 (*C*-3/*C*-6, naphth), 128.1 (*C*-8a, naphth), 131.1 (*C*-2/*C*-7, naphth), 131.5 (*C*-4a, naphth), 133.8 (*C*-4/*C*-5, naphth), 164.1 (*C*=O). ^{29}Si NMR ($CDCl_3$): δ 2.9. Anal. Calcd for $C_{23}H_{30}BrNO_2Si$: C, 59.99; H, 6.57; N, 3.04. Found: C, 60.1; H, 6.5; N, 3.1.

Preparation of Dimethyl(3-(1,8-naphthalimido)propyl)amine (12). This compound was synthesized according to ref 2g.

Preparation of Methyl(3-(1,8-naphthalimido)propyl)-amine (13). A mixture of **14** (4.93 g, 24.9 mmol) and **15** (2.23 g, 25.3 mmol) in glacial acetic acid (20 mL) was heated under reflux for 90 min. The solvent was removed under reduced pressure, and the residue was purified by bulb-to-bulb distillation in vacuo[9] (Kugelrohr apparatus, 220 °C/0.05 mbar) to give **13** in 70% yield as a yellow solid (4.65 g, 17.3 mmol); mp 103−106 °C.[10] ^{1}H NMR (CD_2Cl_2): δ 1.89 ("quint", $^3J_{HH}$ = 6.9 Hz, 2 H, NCH$_2$C*H*$_2$CH$_2$N), 2.2 (br s, 1 H, N*H*), 2.40 (s, 3 H, NC*H*$_3$), 2.64 (t, $^3J_{HH}$ = 6.9 Hz, 2 H, N(CH$_2$)$_2$C*H*$_2$NCH$_3$), 4.15−4.23 (m, 2 H, NC*H*$_2$(CH$_2$)$_2$NCH$_3$), 7.74 (dd, $^3J_{HH}$ = 7.3 Hz, $^3J_{HH}$ = 8.3 Hz, 2 H, *H*-3/*H*-6, naphth), 8.21 (dd, $^3J_{HH}$ = 8.3 Hz, $^4J_{HH}$ = 1.1 Hz, 2 H, *H*-4/*H*-5, naphth), 8.53 (dd, $^3J_{HH}$ = 7.3 Hz, $^4J_{HH}$ = 1.1 Hz, 2 H, *H*-2/*H*-7, naphth). ^{13}C NMR (CD_2Cl_2): δ 28.4 (NCH$_2$*C*H$_2$CH$_2$N), 36.4 (N*C*H$_3$), 38.6 (N*C*H$_2$(CH$_2$)$_2$NCH$_3$), 49.5 (N(CH$_2$)$_2$*C*H$_2$NCH$_3$), 123.1 (*C*-1/*C*-8, naphth), 127.2 (*C*-3/*C*-6, naphth), 128.4 (*C*-8a, naphth), 131.2 (*C*-2/*C*-7, naphth), 131.9 (*C*-4a, naphth), 134.2 (*C*-4/*C*-5, naphth), 164.4 (*C*=O). Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 70.9; H, 6.2; N, 10.4.

1,8-Naphthalic Acid Anhydride (14). This compound was commercially available (Acros, 12814).

***N*-Methyl-1,3-propanediamine (15).** This compound was commercially available (Acros, 15557).

Pharmacological Studies. Membrane Preparation. Membrane suspensions of porcine heart ventricular tissue were prepared as published previously.[11]

(9) After the solvent was removed under reduced pressure, the salt **13**·$CH_3C(O)OH$ was obtained. During the subsequent bulb-to-bulb distillation, dissociation of this salt occurred, and acetic acid was collected at <150 °C/0.05 mbar as a lower-boiling fraction in a cooled trap.

(10) Attempts to recrystallize the NMR-spectroscopically almost pure product from various organic solvents failed due to the instability of **13** in solution.

(11) Tränkle, C.; Kostenis, E.; Burgmer, U.; Mohr, K. *J. Pharmacol. Exp. Ther.* **1996**, *279*, 926−933.

[^{3}H]NMS Binding Experiments. The allosteric effects of the test compounds W84 (**1**), **5**, and **6** (studied as **6**·HCl) at muscarinic M_2 receptors were measured using porcine heart homogenates (3 mM $MgHPO_4$, 50 mM Tris-HCl, pH 7.3, 37 °C) and [^{3}H]*N*-methylscopolamine ([^{3}H]NMS) as a radioactive orthosteric ligand (specific activity, 83.5 or 81.0 Ci mmol^{-1}; Perkin-Elmer Life Science, Inc., Boston, MA).

To examine the effects of the test compounds on orthosteric radioligand dissociation, membranes were preincubated with 0.2 nM [^{3}H]NMS for 30 min. The dissociation measurement was started by addition of 1 μM atropine, alone (control conditions) or in combination with a concentration of the test compound. Aliquots of 1 mL each were taken from the assay over a period of 120 min. Membranes were separated by vacuum filtration using glass fiber filters (Schleicher & Schüll, Dassel, Germany), and membrane-bound radioactivity was determined by liquid scintillation counting. Under control conditions, the half-life of [^{3}H]NMS dissociation amounted to $t_{1/2,control} = 2.65 \pm 0.09$ min, mean value ± SEM, $n = 13$ experiments.

The influence of the test compounds on [^{3}H]NMS equilibrium binding, under the same buffer conditions, was measured after incubation times ranging from 1.5 to 9 h, depending on the delay of [^{3}H]NMS dissociation by the allosteric agents. Nonspecific [^{3}H]NMS binding was determined in the presence of 1 μM atropine. The equilibrium dissociation constant of [^{3}H]-NMS binding under control conditions in the absence of a test compound amounted to $pK_D = 9.34 \pm 0.03$, mean value ± SEM, $n = 4$ experiments.

The [^{3}H]NMS equilibrium binding data were analyzed according to the ternary complex model of allosteric interactions[7] using eq 1:

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

where B_0 indicates the equilibrium binding at a fixed radioligand ([^{3}H]NMS) concentration in the absence of the allosteric ligand A, K_D represents the equilibrium dissociation constant of the binding of the radioligand L to free receptors, K_A denotes the equilibrium dissociation constant of the allosteric ligand A at free receptors, and α is the factor of cooperativity for the interaction between the test compound and [^{3}H]NMS. Experimental data were analyzed by nonlinear regression analysis using the software Prism 3.0 from GraphPAD software, San Diego, CA.

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