Unsaturated derivatives of the muscarinic antagonists hexahydro-sila-difenidol (HHSiD) and p-fluoro-hexahydro-sila-difenidol (p-F-HHSiD) with an (E)-Si–CH=CH–CH₂–N moiety: syntheses and binding affinities at muscarinic receptor subtypes ☆

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Abstract

The unsaturated HHSiD (1) and p-F-HHSiD (2) derivatives (E)-cyclohexyl(phenyl)(3-piperidino-1-propen-1-yl)silanol (5, isolated as 5 · HCl) and (E)-cyclohexyl(4-fluorophenyl)(3-piperidino-1-propen-1-yl)silanol (6, isolated as 6 · HCl) were synthesized in four steps, starting from $(CH_3O)_3SiH$. Reaction of 5 and 6 with CH_3Cl gave the corresponding methochlorides 7 and 8, respectively. All compounds were obtained as racemic mixtures. The binding affinities at muscarinic receptor subtypes (M1–M4) of the silanols 5–8 were determined and compared with those of the selective muscarinic antagonists 1 and 2 and their methiodides 3 and 4. These studies demonstrated that the ammonium compounds 3, 4, 7 and 8 display similar binding affinities at M1–M4 receptors and comparable receptor subtype selectivities. On the other hand, the conformationally restricted amines 5 and 6 ((E)-Si–CH=CH–CH₂–N moiety) exhibit higher affinities but lower receptor subtype selectivities than the more flexible parent compounds 1 and 2 (Si–CH₂–CH₂–CH₂–N moiety).

1. Introduction

Some years ago, we reported the syntheses of the receptor-selective muscarinic antagonists hexahydro-sila-difenidol (HHSiD, 1) [1] and p-fluoro-hexahydro-sila-difenidol (p-F-HHSiD, 2) [2] (Scheme 1). Because of their unique selectivity profiles at muscarinic receptor subtypes [3–5], both silanols are used world-wide as tools in experimental pharmacology and physiology for the classification of muscarinic receptor subtypes. In the last few years, numerous biological data for these two

drugs have been reported in about 300 publications (see, for example, Refs. [3–11] (HHSiD) and Refs. [3], [5], [8] and [12–22] (p-F-HHSiD)). Recently, HHSiD (1) and p-F-HHSiD (2) were recommended by an international nomenclature commission as M3-selective antagonists for the identification of muscarinic receptor subtypes [23]. Both silanols have been commercially available drugs for about 4 years.

In the course of structure–activity relationship studies, we synthesized a variety of HHSiD (1) and p-F-HHSiD (2) derivatives and studied their antimuscarinic properties. The goal of these studies was (i) to investigate the structural requirements for antimuscarinic potency and selectivity of these drugs and (ii) to improve further their pharmacological properties by derivatization. We report here the syntheses and pharmacological

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☆ Dedicated to Professor Dr. Peter Paetzold on the occasion of his 60th birthday.
* Corresponding author.
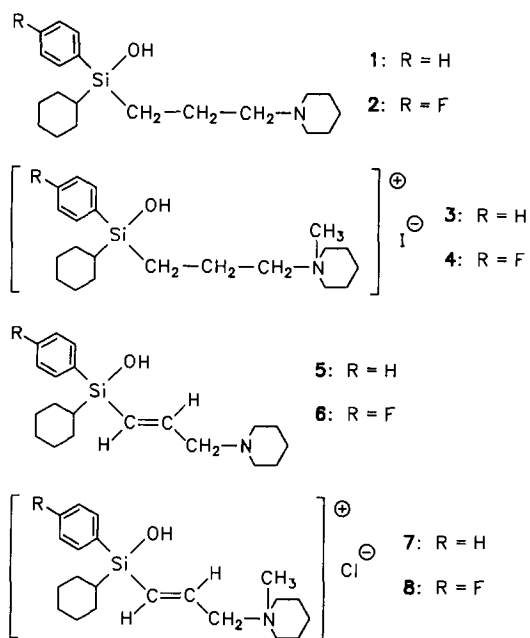
Scheme 1.

characterization of the unsaturated derivatives **5** and **6** (Scheme 1). These silanols contain a conformationally restricted (E)-Si–CH=CH–CH$_2$–N moiety instead of the more flexible saturated Si–CH$_2$–CH$_2$–CH$_2$–N group. The corresponding methochlorides **7** and **8** (Scheme 1) were included in these investigations. All compounds were synthesized as racemic mixtures. The antimuscarinic properties of **5–8** were characterized by radioligand binding studies (M1, M2, M3 and M4 receptors) and compared with the binding affinities of the parent compounds **1** and **2** and their methiodides **3** and

4 (Scheme 1). The studies presented here were carried out as part of our systematic investigations on biologically active organosilicon compounds (for a recent review on this subject, see Ref. [24]).

2. Results and discussion

2.1. Syntheses

The unsaturated HHSiD derivative (E)-cyclohexyl(phenyl)(3-piperidino-1-propen-1-yl)silanol (**5**, isolated as **5** · HCl) was prepared by a four-step synthesis, starting from commercially available trimethoxysilane (**9**) (Scheme 2). In the first step, a platinum-catalyzed (H$_2$PtCl$_6$) hydrosilylation of 3-piperidino-1-propyne with the hydridosilane **9** was carried out to give a mixture of (E)-trimethoxy(3-piperidino-1-propen-1-yl)silane (**10**) and the isomeric by-product trimethoxy-(3-piperidino-1-propen-2-yl)silane (**10′**). The isomers **10** and **10′** were separated by fractional distillation (spinning band column) and isolated in 54 and 29% yields, respectively. Conversion of **10** with cyclohexylmagnesium chloride into the cyclohexylsilane **11** (yield 77%) and subsequent reaction of the latter with phenylmagnesium bromide gave the corresponding phenylsilane **12** (yield 73%). Acid-catalyzed hydrolysis of the Si–OCH$_3$ group of **12** yielded the silanol **5**, which on reaction with hydrogen chloride was isolated as the hydrochloride **5** · HCl (yield 81%). The overall yield of **5** · HCl was 25% (based on **9**).

The unsaturated *p*-F-HHSiD derivative (E)-cyclohexyl(4-fluorophenyl)(3-piperidino-1-propen-1-yl)silanol

	R
5, 7, 12	H
6, 8, 13	F
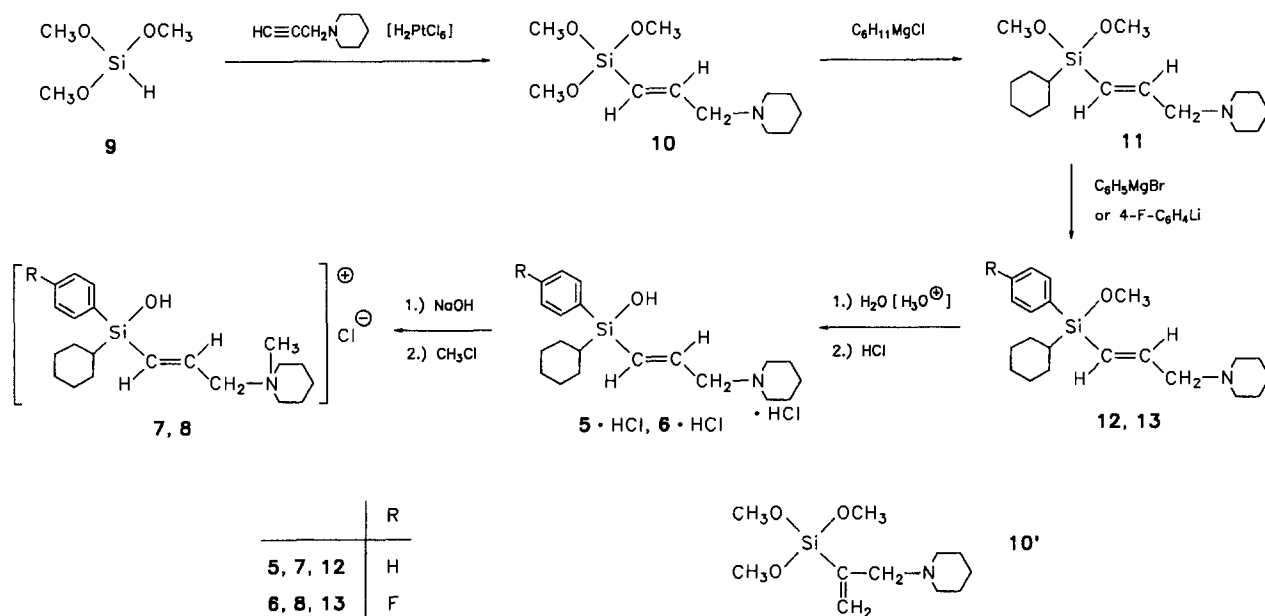
Scheme 2.

Table 1
Affinities (pK_i values) and receptor selectivities (M4 over M2) for compounds 1–8 obtained in binding studies on homogenates of human NB-OK 1 cells (M1 receptors), rat heart (M2 receptors), rat pancreas (M3 receptors) and rat striatum (M4 receptors)

Compound	pK_i [a]				Selectivity ratio (M4/M2) [b]
	Human NB-OK 1 M1	Rat heart M2	Rat pancreas M3	Rat striatum M4	
1 [c]	7.8	6.7	7.8	7.9	16
2 [c]	7.8	6.5	7.8	7.8	20
3 [c]	8.8	8.0	8.2	8.6	4.0
4 [c]	8.3	7.6	—	8.3	5.0
5	8.6	7.6	8.3	8.7	13
6	7.9	7.3	7.9	8.1	6.3
7	8.9	8.2	8.5	9.1	7.9
8	8.2	7.7	8.1	8.2	3.2

[a] All experiments were repeated three times in duplicate. The standard deviations of the pK_i values were generally close to 0.10 and always lower than 0.15.
[b] K_i ratios are given as a measure of receptor selectivity; these values were calculated from the antilogs of the differences between the respective pK_i values.
[c] Data taken from Ref. [8].

(6, isolated as 6 · HCl) was prepared analogously, starting from the above-mentioned silane 11 (Scheme 2). Thus, conversion of 11 with (4-fluorophenyl)lithium into the corresponding (4-fluorophenyl)silane 13 (yield 74%) and subsequent hydrolysis of its Si–OCH$_3$ group gave the silanol 6, which on reaction with hydrogen chloride was isolated as the hydrochloride 6 · HCl (yield 75%). The overall yield of 6 · HCl was 23% (based on 9).

The quaternary ammonium derivatives 7 and 8 were obtained by reaction of 5 and 6, respectively, with methyl chloride (yields 76 and 69%, respectively) (Scheme 2).

The chiral compounds 5 · HCl, 6 · HCl, 7, 8, 12 and 13 were synthesized as racemic mixtures. The silanes 10–13 and 10′ were obtained as pure (^{1}H and ^{13}C NMR) colourless liquids, whereas the silanols 5 · HCl, 6 · HCl, 7 and 8 were isolated as pure (^{1}H and ^{13}C

NMR) crystalline solids. The identity of all new compounds described in this paper was confirmed by elemental analyses and by NMR-spectroscopic and mass-spectrometric studies.

2.2. Pharmacological studies

Compounds 5–8 were studied with respect to their affinities for muscarinic M1, M2, M3 and M4 receptors by radioligand binding experiments. The results of these investigations are summarized in Table 1 (which includes published data of the parent drugs HHSiD and p-F-HHSiD and their methiodides) and Fig. 1.

All compounds investigated exhibited an apparently competitive antagonism at M1–M4 receptors, since all competition curves (not shown) were compatible with the existence of a single receptor subtype, and the Hill coefficients were not significantly different from unity.
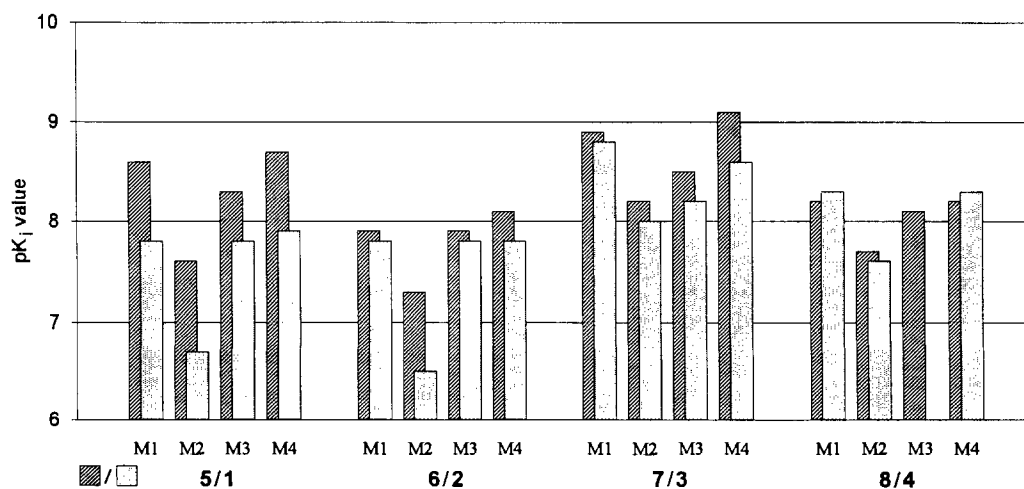

Fig. 1. Affinity profiles (pK_i values) of compounds 1–8 at muscarinic M1 receptors in human NB-OK 1 cells, M2 receptors in rat heart, M3 receptors in rat pancreas and M4 receptors in rat striatum. Data were taken from Table 1.

The olefinic compounds **5–8** displayed a similar selectivity profile: the binding affinities were generally high at M1 and M4, high (**6**, **8**) or intermediate (**5**, **7**) at M3 and low at M2 receptors. The highest receptor selectivity was found for **5** (13-fold M4 over M2 receptors).

Substitution in the *para* position of the phenyl ring (**5** → **6**; **7** → **8**) reduced the affinity at all muscarinic receptors up to 7.9-fold (**7** → **8**; M4) and also reduced the receptor selectivity. This contrasts with the results obtained with **1** and **2**, which exhibited very similar binding affinities and receptor selectivities.

On the other hand, *N*-methylation (**5** → **7**; **6** → **8**) increased the affinity at the four muscarinic receptors, this increase being greatest at M2 receptors (up to four-fold). Thus, the quaternary ammonium compounds **7** and **8** displayed lower selectivities (M4/M2) than the corresponding amines **5** and **6**, respectively. The same enhancement of affinity by *N*-methylation was obtained for compounds **1** (→ **3**) and **2** (→ **4**), but in this series the increase of M2 receptor affinity (up to 40-fold) was much higher, resulting in a greater loss of receptor selectivity.

In conclusion, comparison of the antimuscarinic properties of the conformationally restricted olefinic compounds **5–8** with those of the more flexible derivatives **1–4** shows that the quaternary ammonium compounds **3**, **4**, **7** and **8** display similar affinities and selectivities, whereas the amines **5** and **6** exhibit higher affinities but lower receptor selectivities than the parent compounds **1** and **2**.

3. Experimental section

3.1. Syntheses

3.1.1. General aspects

All syntheses were performed under dry nitrogen. The organic solvents used were dried according to standard procedures. Melting points were determined with a Leitz Laborlux S microscope equipped with a heater (Leitz, Model M 350) and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-400 (^{1}H, 400.1 MHz; ^{13}C, 100.6 MHz) and a Bruker AC-250 spectrometer (^{1}H, 250.1 MHz; ^{13}C, 62.9 MHz), respectively. Chemical shifts (ppm) were determined relative to internal CHCl$_3$ (^{1}H, δ 7.25) and CDCl$_3$ (^{13}C, δ 77.05), respectively. Assignment of the ^{13}C data was supported by DEPT experiments; the results of these experiments are included in the assignments. Mass spectra were obtained with a Varian MAT 711 mass spectrometer (EI MS, 70 eV; FD MS, methanol, 11 kV) and a Finnigan MAT 8430 mass spectrometer (FAB MS, glycerol (liquid matrix), xenon (FAB source)), respectively. The selected m/z values given refer to the isotopes ^{1}H, ^{12}C, ^{14}N, ^{16}O, ^{19}F, ^{28}Si and ^{35}Cl.

3.1.2. (E)-1-{1-[Cyclohexylhydroxy(phenyl)silyl]-1-propen-3-yl}piperidinium chloride (5 · HCl)

A solution of **12** (2.44 g, 7.10 mmol) in a mixture of 0.5 M hydrochloric acid (200 ml) and 2-propanol (75 ml) was stirred at room temperature for 16 h and adjusted to pH 8 with 1 M NaOH solution. The mixture was extracted three times with diethyl ether (3 × 50 ml) and the combined organic extracts washed with water (10 ml) and then dried over anhydrous Na$_2$SO$_4$. After removal of the solvent under reduced pressure, the oily residue was dissolved in diethyl ether (50 ml) and 1.32 M ethereal HCl (5.40 ml, 7.13 mmol HCl) was added dropwise at room temperature over 3 min. After stirring for 15 min at room temperature, the precipitate formed was isolated by filtration, washed with diethyl ether (10 ml) and recrystallized from 2-propanol/diethyl ether (2:1, v/v) to give 2.10 g (yield 81%) of colourless crystals; m.p. 214°C. ^{1}H NMR (CDCl$_3$): δ 0.9–1.1, 1.1–1.4, 1.6–1.8 and 2.1–2.2 (m, 17H, SiCHC$_2$, CCH$_2$C); 2.6–2.7, 3.4–3.5 and 3.6–3.7 (m, 6H, NCH$_2$C); 4.5 (broad 's', 1H, SiOH); 6.28 (d, ^3J(HH) 18.6 Hz, 1H, SiCH=C); 6.57 (dt, ^3J(HH) 18.6 Hz, ^3J(HH) 6.7 Hz, 1H, SiC=CHC); 7.3–7.4 and 7.5–7.6 (m, 5H, SiC$_6$H$_5$); 11.4 (broad 's', 1H, NH). ^{13}C NMR (CDCl$_3$): δ 21.9 and 22.7 (2C) (CCH$_2$C); 25.8 (C-1, SiC$_6$H$_{11}$); 26.59, 26.69, 26.73 and 27.7 (2C) (CCH$_2$C); 52.6 and 52.7 (C-2/C-6, NC$_5$H$_{10}$); 61.8 (C=CCH$_2$N); 127.8 (C-3/C-5, SiC$_6$H$_5$); 129.7 (C-4, SiC$_6$H$_5$); 134.1 (C-2/C-6, SiC$_6$H$_5$); 135.5 (C-1, SiC$_6$H$_5$); 136.0 and 138.7 (SiCH=CHC). FAB MS: m/z 330 (100%, cation of the salt). Anal. Found: C, 65.7; H, 8.9; N, 3.8. C$_{20}$H$_{32}$ClNOSi (366.0) Calc: C, 65.63; H, 8.81; N, 3.83%.

3.1.3. (E)-1-{1-[Cyclohexyl(4-fluorophenyl)hydroxysilyl]-1-propen-3-yl}piperidinium chloride (6 · HCl)

This was prepared analogously to the synthesis of **5** · HCl: hydrolysis of **13** (5.00 g, 13.8 mmol) in a mixture of 0.5 M hydrochloric acid (400 ml) and 2-propanol (150 ml); separation of the crude amine **6** and its transformation into **6** · HCl by reaction with 1.32 M ethereal HCl (10.5 ml, 13.9 mmol HCl); yield 3.97 g (75%) of colourless crystals; m.p. 204°C. ^{1}H NMR (CDCl$_3$): δ 0.8–1.0, 1.0–1.4, 1.6–1.8 and 2.1–2.2 (m, 17H, SiCHC$_2$, CCH$_2$C); 2.6–2.7 and 3.4–3.7 (m, 6H, NCH$_2$C); 4.8 (s, 1H, SiOH); 6.25 (d, ^3J(HH) 18.6 Hz, 1H, SiCH=C); 6.58 (dt, ^3J(HH) 18.6 Hz, ^3J(HH) 6.6 Hz, 1H, SiC=CHC); 7.0–7.1 and 7.5–7.6 (m, 4H, SiC$_6$H$_4$F); 11.7 (broad 's', 1H, NH). ^{13}C NMR (CDCl$_3$): δ 22.0 and 22.7 (2C) (CCH$_2$C); 25.9 (C-1, SiC$_6$H$_{11}$); 26.57, 26.66, 26.71, 27.65 and 27.68 (CCH$_2$C); 52.8 (C-2/C-6, NC$_5$H$_{10}$); 61.9 (C=CCH$_2$N); 115.0 (d, ^2J(CF) 19.6 Hz, C-3/C-5, SiC$_6$H$_4$F); 131.1 (d, ^4J(CF) 3.7 Hz, C-1, SiC$_6$H$_4$F); 136.1 (d, ^3J(CF) 7.4 Hz, C-2/C-6, SiC$_6$H$_4$F); 136.4 and 138.2 (SiCH=CHC); 164.1 (d, ^1J(CF) 248.9 Hz,

C-4, SiC_6H_4F). FAB MS: m/z 348 (100%, cation of the salt). Anal. Found: C, 62.4; H, 8.0; N, 3.7. $C_{20}H_{31}CIFNOSi$ (384.0) Calc: C, 62.56; H, 8.14; N, 3.65%.

3.1.4. (E)-1-{1-[Cyclohexylhydroxy(phenyl)silyl]-1-propen-3-yl}-1-methylpiperidinium chloride (7)

A solution of 5 (obtained from 5 · HCl (120 mg, 0.33 mmol) by reaction with aqueous NaOH and isolation by extraction with diethyl ether) in acetone (20 ml) was added to methyl chloride (5.00 g, 99.0 mmol) at −35°C and the mixture was stirred for 3 h at −35°C and 16 h at room temperature. The solvent and the excess methyl chloride were removed under reduced pressure, and the remaining solid was washed with diethyl ether (5 ml) and then recrystallized from 2-propanol/diethyl ether (4:1, v/v) to give 95 mg (yield 76%) of colourless crystals; m.p. 195–196°C. ^1H NMR ($CDCl_3$): δ 0.9–1.0, 1.0–1.2 and 1.6–1.8 (m, 17H, $SiCHC_2$, CCH_2C); 3.22 (s, 3H, NCH_3); 3.4–3.5 (m, 4H, NCH_2C); 4.08 (δ_A) and 4.24 (δ_B) (m, AB part of the ABX system $SiCH=CH_XCH_AH_BN$, $J(AB) = 13.3$ Hz, $J(AX) = 7.0$ Hz, $J(BX) = 6.4$ Hz, 2H); 6.2 (broad s, 1H, SiOH); 6.42 (d, $^3J(HH) = 18.4$ Hz, 1H, SiCH=C); 6.74 (m, $SiCH=CHCH_2N$, 1H); 7.3–7.4 and 7.5–7.6 (m, 5H, SiC_6H_5). ^{13}C NMR ($CDCl_3$): δ 20.1 (2C) and 20.8 (CCH_2C); 26.2 (C-1, SiC_6H_{11}); 26.7, 26.8 (2C) and 27.8 (2C) (CCH_2C); 48.4 (NCH_3); 60.6 and 60.8 (C-2/C-6, NC_5H_{10}); 67.8 (C=CCH_2N); 127.7 (C-3/C-5, SiC_6H_5); 129.4 (C-4, SiC_6H_5); 134.18 (C-2/C-6, SiC_6H_5); 134.24 (SiCH=C); 136.4 (C-1, SiC_6H_5); 142.3 (SiC=CHC). FD MS: m/z 344 (100%, cation of the salt). Anal. Found: C, 66.1; H, 9.0; N, 3.6. $C_{21}H_{34}CINOSi$ (380.0) Calc: C, 66.37; H, 9.02; N, 3.69%.

3.1.5. (E)-1-{1-[Cyclohexyl(4-fluorophenyl)hydroxysilyl]-1-propen-3-yl}-1-methylpiperidinium chloride (8)

This was prepared from 6 · HCl (250 mg, 0.65 mmol) analogously to the synthesis of 7; recrystallization from acetone/n-pentane (4:1, v/v) at −20°C; yield 180 mg (69%) of colourless crystals; m.p. 189°C. ^1H NMR ($CDCl_3$): δ 0.9–1.0, 1.0–1.3 and 1.6–1.8 (m, 17H, $SiCHC_2$, CCH_2C); 3.27 (s, 3H, NCH_3); 3.5–3.6 (m, 4H, NCH_2C); 4.14 (δ_A) and 4.25 (δ_B) (m, AB part of the ABX system $SiCH=CH_XCH_AH_BN$, $J(AB) = 13.2$ Hz, $J(AX) = 7.3$ Hz, $J(BX) = 6.4$ Hz, 2H); 6.40 (d, $^3J(HH)$ 18.4 Hz, 1H, SiCH=C); 6.74 (m, $SiCH=CHCH_2N$, 1H); 7.0–7.1 and 7.5–7.6 (m, 4H, SiC_6H_4F); SiOH not localized. ^{13}C NMR ($CDCl_3$): δ 20.1 (2C) and 20.8 (CCH_2C); 26.2 (C-1, SiC_6H_{11}); 26.7, 26.8 (2C) and 27.7 (2C) (CCH_2C); 48.4 (NCH_3); 60.7 and 60.8 (C-2/C-6, NC_5H_{10}); 67.7 (C=CCH_2N); 114.9 (d, $^2J(CF)$ 19.5 Hz, C-3/C-5, SiC_6H_4F); 131.9 (d, $^4J(CF)$ 3.8 Hz, C-1, SiC_6H_4F); 134.4 (SiCH=C); 136.2 (d, $^3J(CF)$ 7.4 Hz, C-2/C-6, SiC_6H_4F); 142.2 (SiC=CHC); 163.9 (d, $^1J(CF)$ 248.4 Hz, C-4,

SiC_6H_4F). FD MS: m/z 362 (100%, cation of the salt). Anal. Found: C, 62.2; H, 8.3; N, 3.6. $C_{21}H_{33}CIFNOSi$ (398.0) Calc: C, 63.37; H, 8.36; N, 3.52%.

3.1.6. (E)-Trimethoxy(3-piperidino-1-propen-1-yl)silane (10)

Hexachloroplatinic acid hexahydrate (10 mg, 0.02 mmol) was added to a mixture of 9 (65.5 g, 536 mmol) and 3-piperidino-1-propyne (66.0 g, 536 mmol) and the resulting mixture was stirred at 85°C for 10 h. After cooling to room temperature, n-pentane (100 ml) was added and the solution purified by filtration. Then the filtrate was concentrated under reduced pressure and the residue distilled in vacuo (spinning band column) to give 70.8 g (yield 54%) of a colourless liquid; b.p. 75°C/0.5 Torr (In this distillation, 38.3 g of the isomer 10' (yield 29%) were isolated as the first fraction (for the characterization of 10', see below).) ^1H NMR ($CDCl_3$): δ 1.3–1.4 and 1.4–1.6 (m, 6H, CCH_2C); 2.3–2.4 (m, 4H, NCH_2C); 2.99 (dd, $^3J(HH)$ 5.9 Hz, $^4J(HH)$ 1.6 Hz, 2H, C=CCH_2N); 3.50 (s, 9H, OCH_3); 5.50 (dt, $^3J(HH)$ 18.9 Hz, $^4J(HH)$ 1.6 Hz, 1H, SiCH=C); 6.41 (dt, $^3J(HH)$ 18.9 Hz, $^3J(HH)$ 5.9 Hz, 1H, SiC=CHC). ^{13}C NMR ($CDCl_3$): δ 24.2 (C-4, NC_5H_{10}); 25.9 (C-3/C-5, NC_5H_{10}); 50.5 (OCH_3); 54.6 (C-2/C-6, NC_5H_{10}); 64.7 (C=CCH_2N); 120.2 (SiCH=C); 150.9 (SiC=CHC). EI MS: m/z. 245 (15%, M^+), 98 (100%, $CH_2=NC_5H_{10}^+$). Anal. Found: C, 53.9; H, 9.5; N, 5.7. $C_{11}H_{23}NO_3Si$ (245.4) Calc: C, 53.84; H, 9.45; N, 5.71%.

3.1.7. Trimethoxy(3-piperidino-1-propen-2-yl)silane (10')

This was isolated as a by-product in the synthesis of 10 (see above); colourless liquid; b.p. 69°C/0.9 Torr. ^1H NMR ($CDCl_3$): δ 1.4–1.6 (m, 6H, CCH_2C); 2.3–2.4 (m, 4H, NCH_2C); 2.95–3.0 (m, 2H, $SiCCH_2N$); 3.57 (s, 9H, OCH_3); 5.65–5.7 and 5.8–5.85 (m, 2H; C=CH_2). ^{13}C NMR ($CDCl_3$): δ 24.6 (C-4, NC_5H_{10}); 26.0 (C-3/C-5, NC_5H_{10}); 50.7 (OCH_3); 54.7 (C-2/C-6, NC_5H_{10}); 64.8 (SiCCH_2N); 131.0 (C=CH_2); 140.6 (C=CH_2). EI MS: m/z 245 (20%, M^+), 98 (100%, $CH_2=NC_5H_{10}^+$). Anal. Found: C, 54.0; H, 9.4; N, 5.7. $C_{11}H_{23}NO_3Si$ (245.4) Calc: C, 53.84; H, 9.45; N, 5.71%.

3.1.8. (E)-Cyclohexyldimethoxy(3-piperidino-1-propen-1-yl)silane (11)

A Grignard reagent was prepared from cyclohexyl chloride (15.9 g, 134 mmol) and magnesium turnings (3.40 g, 140 mmol) in diethyl ether (100 ml) and then added dropwise at 0°C over 45 min to a stirred solution of 10 (30.0 g, 122 mmol) in diethyl ether (250 ml). After stirring at room temperature for 18 h and heating under reflux for 4 h, the precipitate was filtered off and the filtrate concentrated under reduced pressure. Then n-pentane (200 ml) was added, the resulting precipitate

removed by filtration, the filtrate concentrated under reduced pressure and the residue distilled in vacuo (Vigreux column) to give 28.1 g (yield 77%) of a colourless liquid; b.p. 90°C/0.005 Torr. ^{1}H NMR (CDCl$_3$): δ 0.7–0.9, 1.1–1.2, 1.3–1.5 and 1.5–1.8 (m, 17H, SiCHC$_2$, CCH$_2$C); 2.3–2.4 (m, 4H, NCH$_2$C); 2.99 (dd, ^{3}J(HH) 6.0 Hz, ^{4}J(HH) 1.5 Hz, 2H, C=CCH$_2$N); 3.46 (s, 6H, OCH$_3$); 5.53 (dt, ^{3}J(HH) 19.0 Hz, ^{4}J(HH) 1.5 Hz, 1H, SiCH=C); 6.30 (dt, ^{3}J(HH) 19.0 Hz, ^{3}J(HH) 6.0 Hz, 1H, SiC=CHC). ^{13}C NMR (CDCl$_3$): δ 24.1 (C-1, SiC$_6$H$_{11}$); 24.2 (C-4, NC$_5$H$_{10}$); 25.9 and 26.5 (CCH$_2$C); 26.8 (C-4, SiC$_6$H$_{11}$); 27.6 (CCH$_2$C); 50.6 (OCH$_3$); 54.5 (C-2/C-6, NC$_5$H$_{10}$); 65.0 (C=CCH$_2$N); 123.5 (SiCH=C); 149.1 (SiC=CHC). EI MS: m/z 297 (9%, M$^+$), 98 (100%, CH$_2$=NC$_5$H$_{10}^+$). Anal. Found: C, 64.7; H, 10.5; N, 4.7. C$_{16}$H$_{31}$NO$_2$Si (297.5) Calc: C, 64.59; H, 10.50; N, 4.71%.

3.1.9. (E)-Cyclohexyl(methoxy)phenyl(3-piperidino-1-propen-1-yl)silane (12)

A 2.21 M solution of phenylmagnesium bromide in diethyl ether (7.60 ml, 16.8 mmol C$_6$H$_5$MgBr) was added dropwise at 0°C over 30 min to a stirred solution of 11 (5.00 g, 16.8 mmol) in diethyl ether (50 ml). The mixture was stirred at room temperature for 16 h and then heated under reflux for 4 h. After cooling to 0°C, saturated aqueous NH$_4$Cl solution (20 ml) was added to the reaction mixture. The organic layer was separated and the aqueous phase extracted with diethyl ether (3 × 20 ml). The combined organic extracts were dried over anhydrous Na$_2$SO$_4$ and the solvent was removed under reduced pressure. Distillation of the oily residue in vacuo (Vigreux column) gave 4.23 g (yield 73%) of a colourless liquid; b.p. 159°C/0.02 Torr. ^{1}H NMR (CDCl$_3$): δ 1.0–1.3 and 1.4–1.8 (m, 17H, SiCHC$_2$, CCH$_2$C); 2.3–2.4 (m, 4H, NCH$_2$C); 3.10 (dd, ^{3}J(HH) 6.0 Hz, ^{4}J(HH) 1.5 Hz, 2H, C=CCH$_2$N); 3.47 (s, 3H, OCH$_3$); 5.92 (dt, ^{3}J(HH) 18.9 Hz, ^{4}J(HH) 1.5 Hz, 1H, SiCH=C); 6.36 (dt, ^{3}J(HH) 18.9 Hz, ^{3}J(HH) 6.0 Hz, 1H, SiC=CHC); 7.3–7.4 and 7.5–7.6 (m, 5H, SiC$_6$H$_5$). ^{13}C NMR (CDCl$_3$): δ 24.3 (C-4, NC$_5$H$_{10}$); 25.3 (C-1, SiC$_6$H$_{11}$); 26.0 (2C), 26.69, 26.73, 26.8 and 27.8 (2C) (CCH$_2$C); 51.4 (OCH$_3$); 54.6 (C-2/C-6, NC$_5$H$_{10}$); 65.4 (C=CCH$_2$N); 125.5 (SiCH=C); 127.7 (C-3/C-5, SiC$_6$H$_5$); 129.5 (C-4, SiC$_6$H$_5$); 134.4 (C-1, SiC$_6$H$_5$); 134.6 (C-2/C-6, SiC$_6$H$_5$); 149.0 (SiC=CHC). EI MS: m/z 343 (21%, M$^+$), 98 (100%, CH$_2$=NC$_5$H$_{10}^+$). Anal. Found: C, 73.4; H, 9.7; N, 4.1. C$_{21}$H$_{33}$NOSi (343.6) Calc: C, 73.41; H, 9.68; N, 4.08%.

3.1.10. (E)-Cyclohexyl(4-fluorophenyl)methoxy(3-piperidino-1-propen-1-yl)silane (13)

A 1.6 M solution of n-butyllithium in n-hexane (23.2 ml, 37.1 mmol n-BuLi) was added dropwise at −35°C during 20 min to a stirred solution of 1-bromo-4-fluoro-

benzene (6.50 g, 37.1 mmol) in diethyl ether (80 ml). The resulting mixture was kept at −35°C for a further 30 min and then added dropwise at −10°C over 40 min to a stirred solution of 11 (10.0 g, 33.6 mmol) in diethyl ether (100 ml). After stirring for 16 h at room temperature, saturated aqueous NH$_4$Cl solution (50 ml) was added, the organic phase separated and the aqueous layer extracted with diethyl ether (3 × 50 ml). The combined organic extracts were dried over anhydrous Na$_2$SO$_4$ and the solvent was removed under reduced pressure. Distillation of the oily residue in vacuo (Vigreux column) gave 8.95 g (74%) of a colourless liquid; b.p. 148°C/0.003 Torr. ^{1}H NMR (CDCl$_3$): δ 0.9–1.3, 1.4–1.5 and 1.5–1.8 (m, 17H, SiCHC$_2$, CCH$_2$C); 2.3–2.4 (m, 4H, NCH$_2$C); 3.09 (dd, ^{3}J(HH) 5.9 Hz, ^{4}J(HH) 1.5 Hz, 2H, C=CCH$_2$N); 3.45 (s, 3H, OCH$_3$); 5.89 (dt, ^{3}J(HH) 18.9 Hz, ^{4}J(HH) 1.5 Hz, 1H, SiCH=C); 6.33 (dt, ^{3}J(HH) 18.9 Hz, ^{3}J(HH) 6.0 Hz, 1H, SiC=CHC); 7.0–7.1 and 7.5–7.6 (m, 4H, SiC$_6$H$_4$F). ^{13}C NMR (CDCl$_3$): δ 24.3 (C-4, NC$_5$H$_{10}$); 25.3 (C-1, SiC$_6$H$_{11}$); 26.0 (2C), 26.68, 26.73, 26.8 and 27.8 (2C) (CCH$_2$C); 51.4 (OCH$_3$); 54.6 (C-2/C-6, NC$_5$H$_{10}$); 65.3 (C=CCH$_2$N); 114.9 (d, ^{2}J(CF) 19.7 Hz, C-3/C-5, SiC$_6$H$_4$F); 125.3 (SiCH=C); 130.0 (d, ^{4}J(CF) 3.8 Hz, C-1, SiC$_6$H$_4$F); 136.6 (d, ^{3}J(CF) 7.4 Hz, C-2/C-6, SiC$_6$H$_4$F); 149.3 (SiC=CHC); 164.1 (d, ^{1}J(CF) 248.7 Hz, C-4, SiC$_6$H$_4$F). EI MS: m/z 361 (9%, M$^+$), 98 (100%, CH$_2$=NC$_5$H$_{10}^+$). Anal. Found: C, 69.6; H, 9.0; N, 3.9. C$_{21}$H$_{32}$FNOSi (361.6) Calc: C, 69.76; H, 8.92; N, 3.87%.

3.2. Radioligand binding studies

As a measure of affinity, pK_i values of compounds 5–8 were determined in radioligand binding studies with homogenates of human NB-OK 1 neuroblastoma cells (M1 receptors) and homogenates of rat heart (M2 receptors), rat pancreas (M3 receptors) and rat striatum (M4 receptors).

The radioligand was [^{3}H]-N-methylscopolamine (0.24–1.0 nM). Data from the binding experiments were analyzed by an iterative curve-fitting procedure. Dissociation constants (K_i values) of compounds 5–8 were calculated from IC$_{50}$ values obtained from competition curves. The pK_i values, shown in Table 1, correspond to −log K_i values. For more details, see Refs. [4] and [8].

Data are presented as arithmetic means from experiments repeated three times in duplicate.

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