ELSEVIER

Journal of Organometallic Chemistry 501 (1995) 145–154

Journal of Organometallic Chemistry

Fluorine-containing derivatives of the muscarinic antagonists sila-pridinol and sila-difenidol: syntheses and antimuscarinic properties ☆

Reinhold Tacke [a,*], Daiyo Terunuma [a], Andrea Tafel [a], Mathias Mühleisen [a], Bernhard Forth [a], Magali Waelbroeck [b], Jan Gross [c], Ernst Mutschler [c], Thomas Friebe [c], Günter Lambrecht [c]

[a] *Institut für Anorganische Chemie, Universität Karlsruhe, Engesserstraße, Geb. 30.45, D-76128 Karlsruhe, Germany*

[b] *Laboratoire de Chimie Biologique et de la Nutrition, Faculté de Médecine et de Pharmacie, Université Libre de Bruxelles, Route de Lennik 808, B-1070 Bruxelles, Belgium*

[c] *Pharmakologisches Institut für Naturwissenschaftler, Biozentrum Niederursel, Universität Frankfurt, Marie-Curie-Straße 9, Geb. N 260, D-60439 Frankfurt, Germany*

Received 10 April 1995

Abstract

The fluorine-containing sila-pridinol and sila-difenidol derivatives *p*-fluoro-sila-pridinol (**5a**), *p,p'*-difluoro-sila-pridinol (**6a**), *p*-fluoro-sila-difenidol (**7a**), *p,p'*-difluoro-sila-difenidol (**8a**), *p*-fluoro-sila-difenidol methiodide (**9a**) and *p,p'*-difluoro-sila-difenidol methiodide (**10a**) were synthesized, starting from the silanes $Cl_3SiCH{=}CH_2$ (**5a** and **6a**) and $(CH_3O)_3Si(CH_2)_3Cl$ (**7a–10a**) respectively. The chiral compounds **5a**, **7a** and **9a** were obtained as racemic mixtures. The muscarinic pharmacology of the silanols **5a–10a** was studied and compared with that of their carbon analogues, the carbinols **5b–10b** (studies on silicon–carbon bioisosterism). The affinities and receptor selectivities (M1–M4 receptors) of the Si–C pairs **5a/5b–10a/10b** were found to depend on the following structural parameters: length of the carbon chain El–$(CH_2)_n$–N (El = Si or C; n = 2, 3), *N*-methylation, fluorine substitution of the phenyl rings and the nature of the central atom (silicon or carbon). Most interestingly, replacement of the central carbinol carbon atom in *p*-fluoro-difenidol methiodide (**9b**) by a silicon atom (→ **9a**) leads to an increase in affinity for muscarinic receptor subtypes by factors of 32–81. Such a high increase in biological activity by sila-substitution (C–Si exchange) has not yet been reported.

Keywords: Sila-pridinol; Sila-difenidol; Si/C bioisosterism; Muscarinic receptor subtypes

1. Introduction

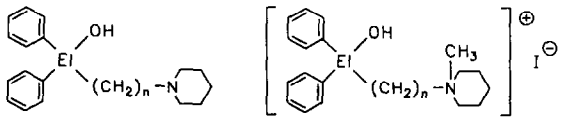
In previous papers, we reported the syntheses and some pharmacological properties of the muscarinic antagonists sila-pridinol (**1a**) [1–5], sila-difenidol (**2a**) [3–7], sila-pridinol methiodide (**3a**) [5] and sila-difenidol methiodide (**4a**) [5,6] (Scheme 1). All these silanols were found to exhibit a significantly higher antimuscarinic potency than their corresponding carbon analogues pridinol (**1b**), difenidol (**2b**), pridinol methiodide (**3b**) and difenidol methiodide (**4b**) (Scheme 1). Differences in potency up to one order of magnitude were observed.

We report here the syntheses of the fluorine-containing silanols **5a–10a** (**5a**, **7a** and **9a** obtained as racemic mixtures) and the antimuscarinic properties of the Si–C pairs **5a/5b–10a/10b** (Scheme 2). The carbon analogues **5b–10b** (**5b**, **7b** and **9b** obtained as racemic mixtures) were prepared according to standard procedures (no experimental data given) [8]. The affinities of compounds **5a/5b–10a/10b** for muscarinic receptors were studied by the use of functional pharmacological experiments (M1, M2 and M3 receptors) and radioligand binding studies (M1, M2, M3 and M4 receptors). The studies presented here were carried out as a part of

☆ Dedicated to Professor Herbert Schumann on the occasion of his 60th birthday.

* Corresponding author.

SSDI 0022-328X(95)05622-X



	El	n
1a	Si	2
1b	C	2
2a	Si	3
2b	C	3

	El	n
3a	Si	2
3b	C	2
4a	Si	3
4b	C	3

Scheme 1.

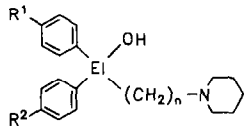
our systematic investigations on silicon–carbon bioisosterism (for a recent review on this subject, see [9]).

2. Results and discussion

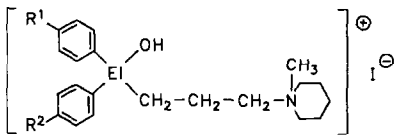
2.1. Syntheses

p-Fluoro-sila-pridinol (**5a**) was prepared by a five-step synthesis, starting from commercially available trichloro(vinyl)silane (**11**) (Scheme 3). In the first step, **11** was transformed into tripiperidino(2-piperidinoethyl)silane (**12**) with a mixture of piperidine and its lithium amide. This conversion involves an amide-catalysed addition of piperidine to the vinyl group and a substitution of the three chlorine atoms of **11** by piperidino moieties. Subsequent methanolysis of the triaminosilane **12** (isolated as crude product) gave the corresponding trimethoxysilane **13** (yield, 83%, related to **11**), which upon reaction with (4-fluorophenyl)magnesium bromide yielded the (4-fluorophenyl)silane **14** (yield, 68%). Conversion of **14** with phenylmagnesium bromide into the corresponding phenylsilane **15** (yield, 52%) and subsequent hydrolysis of its Si–OCH_3 group gave the silanol **5a** (yield, 58%). The overall yield of *p*-fluoro-sila-pridinol (**5a**) was 17% (related to **11**).

p,p'-Difluoro-sila-pridinol (**6a**) was prepared analogously, starting from the above-mentioned trimethoxy-



	El	R^1	R^2	n
5a	Si	F	H	2
5b	C	F	H	2
6a	Si	F	F	2
6b	C	F	F	2
7a	Si	F	H	3
7b	C	F	H	3
8a	Si	F	F	3
8b	C	F	F	3

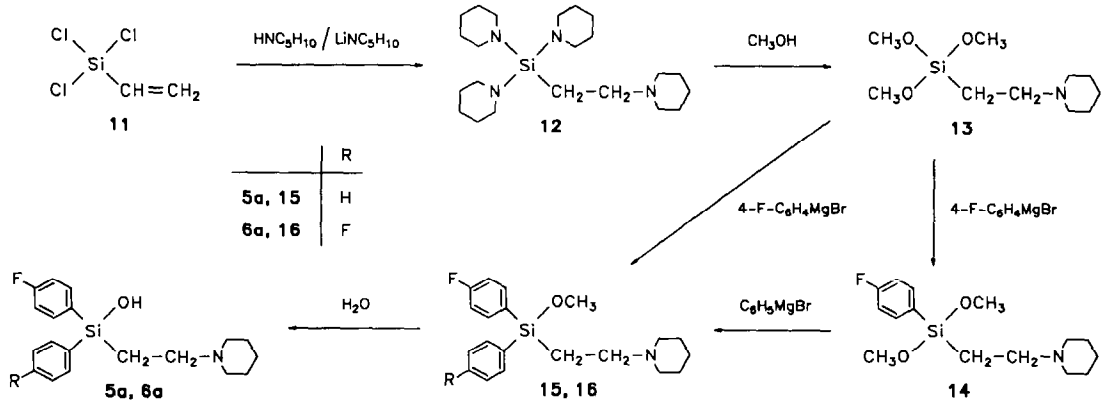


	El	R^1	R^2
9a	Si	F	H
9b	C	F	H
10a	Si	F	F
10b	C	F	F

Scheme 2.

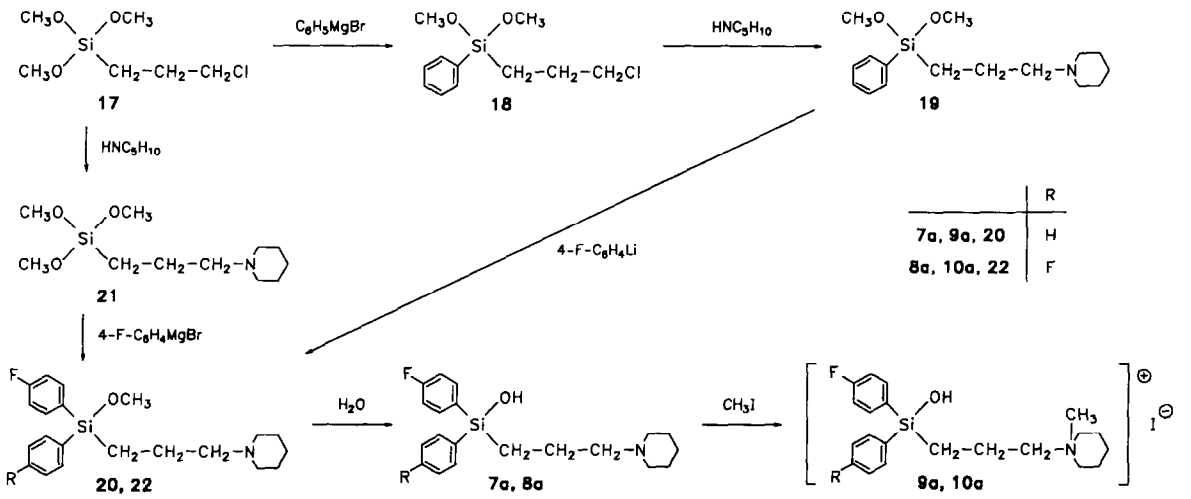
(2-piperidinoethyl)silane (**13**) (Scheme 3). Thus conversion of **13** with two equivalents of (4-fluorophenyl)magnesium bromide into the corresponding di(4-fluorophenyl)silane **16** (yield, 60%) and subsequent hydrolysis of its Si–OCH_3 group gave the silanol **6a** (yield, 64%). The overall yield of *p,p'*-difluoro-sila-pridinol (**6a**) was 32% (related to **11**).

p-Fluoro-sila-difenidol (**7a**) was prepared by a four-step synthesis, starting from commercially available (3-chloropropyl)trimethoxysilane (**17**) (Scheme 4). In the first step, **17** was transformed into the phenylsilane **18** by reaction with phenylmagnesium bromide (yield,



	R
5a, 15	H
6a, 16	F

Scheme 3.



Scheme 4.

73%). Conversion of the (3-chloropropyl)silane (**18**) with piperidine into the corresponding (3-piperidinopropyl)silane (**19**) (yield, 85%) and reaction of the latter with (4-fluorophenyl)lithium gave the (4-fluorophenyl)silane (**20**) (yield, 88%), which upon hydrolysis of its $Si-OCH_3$ group yielded the silanol **7a** (yield, 85%). The overall yield of *p*-fluoro-sila-difenidol (**7a**) was 46% (related to **17**).

p,p'-Difluoro-sila-difenidol (**8a**) was synthesized by a three-step synthesis, starting from (3-chloropropyl)trimethoxysilane (**17**) (Scheme 4). Conversion of **17** with piperidine into the corresponding (3-piperidinopropyl)-

Table 1
Affinities (pA_2 values) and slopes of Arunlakshana–Schild plots (in parentheses) as well as receptor selectivities for **7a**, **7b**, **9a** and **9b** at muscarinic M1 receptors in rabbit vas deferens (RVD), M2 receptors in guinea-pig atria (GPA) and M3 receptors in guinea-pig ileum (GPI)

Compound	pA_2 values [a]			Selectivity ratios [b]		
	RVD (M1)	GPA (M2)	GPI (M3)	M1/M2	M1/M3	M3/M2
7a	7.45 ± 0.09 (1.16 ± 0.09)	6.46 ± 0.05 (0.89 ± 0.09)	7.44 ± 0.05 (1.22 ± 0.07)	9.8	1.0	9.6
7b	6.13 ± 0.03 (1.01 ± 0.13)	5.71 ± 0.03 (0.99 ± 0.04)	6.19 ± 0.03 (0.96 ± 0.08)	2.6	0.9	3.0
9a	8.41 ± 0.03 (1.10 ± 0.05)	8.14 ± 0.03 (1.07 ± 0.07)	7.90 ± 0.04 (0.92 ± 0.05)	1.9	3.2	0.6
9b	6.67 ± 0.07 (0.98 ± 0.05)	6.23 ± 0.03 (0.90 ± 0.05)	6.01 ± 0.05 (0.84 ± 0.08)	2.8	4.6	0.6

[a] The parameters given represent the mean ± standard error of the mean ($n = 3–4$).
[b] K_D ratios are given as a measure of receptor selectivity (M1 over M2; M1 over M3; M3 over M2); these values were calculated from the antilogarithms of the differences between the respective pA_2 values.

Table 2
Affinities (pK_i values) and receptor selectivities (M1 over M2) for **5a/5b–10a/10b** obtained in binding studies on homogenates of human NB-OK 1 cells (NB-OK 1) (M1 receptors), rat heart (RH) (M2 receptors), rat pancreas (RP) (M3 receptors) and rat striatum (RS) (M4 receptors)

Compound	pK_i values [a]				Selectivity ratio (M1/M2) [b]
	NB-OK 1(M1)	RH (M2)	RP (M3)	RS (M4)	
5a/5b	8.3/8.1	7.1/6.8	7.4/7.1	7.9/7.7	16/20
6a/6b	8.1/8.0	6.8/6.5	7.4/–	7.5/7.4	20/32
7a/7b	7.5/6.5	6.4/5.7	7.3/6.4	7.6/6.4	13/6.3
8a/8b	7.2/6.8	6.1/5.9	7.1/6.6	7.2/6.7	13/7.9
9a/9b	8.2/6.6	7.8/6.1	7.7/6.2	8.1/6.5	2.5/3.2
10a/10b	7.6/6.8	7.1/6.0	7.1/6.1	7.2/6.4	3.2/6.3

[a] All experiments were repeated three times in duplicate. The standard deviations of the pK_i values were generally close to ±0.10, always lower than ±0.15.
[b] K_i ratios are given as a measure of receptor selectivity (M1 over M2); these values were calculated from the antilogarithms of the differences between the respective pK_i values.

Table 3
Affinity ratios between the silanols **5a–10a** and the corresponding carbinols **5b–10b** 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

Compound	Si–C affinity ratios [a]			
	Human NB-OK 1(M1)	Rat heart (M2)	Rat pancreas (M3)	Rat striatum (M4)
5a/5b	1.6	2.0	2.0	1.6
6a/6b	1.3	2.0	–	1.3
7a/7b	10	5.0	7.9	16
8a/8b	2.5	1.6	3.2	3.2
9a/9b	40	50	32	40
10a/10b	6.3	13	10	6.3

[a] These values are the antilogarithms of the differences between the respective pK_i values (see Table 2).

silane **21** (yield, 78%) and reaction of the latter with two equivalents of (4-fluorophenyl)magnesium bromide gave the di(4-fluorophenyl)silane (**22**) (yield, 66%), which upon hydrolysis of its Si–OCH_3 moiety yielded the silanol **8a** (yield, 81%). The overall yield of *p,p'*-difluoro-sila-difenidol (**8a**) was 42% (related to **17**).

p-Fluoro-sila-difenidol methiodide (**9a**) and *p,p'*-difluoro-sila-difenidol methiodide (**10a**) were synthesized by *N*-quaternization of **7a** and **8a** respectively with methyl iodide (yields, 66% and 78% respectively) (Scheme 4).

The chiral compounds **5a**, **7a**, **9a**, **15** and **20** were prepared as racemic mixtures. The silanes **13–16** and **18–22** were isolated as pure (^1H and ^{13}C NMR) colourless liquids, whereas the silanols **5a–10a** were obtained as pure (^1H and ^{13}C NMR) crystalline solids. The identity of all new compounds described in this paper was confirmed by elemental analyses and by NMR spectroscopy and mass spectrometry (MS) studies.

2.2. Pharmacological studies

The Si–C pairs **5a/5b–10a/10b** were studied for their affinities for muscarinic M1, M2, M3 and M4 receptors by radioligand binding experiments. In addition, the binding affinities of **7a**, **7b**, **9a** and **9b** were compared with their functional antimuscarinic properties at M1–M3 receptors. The results of these investigations are summarized in Tables 1–3 and illustrated in Fig. 1.

All compounds investigated in functional studies (**7a**, **7b**, **9a** and **9b**) antagonized in a concentration-dependent manner the 4-F-PyMcN$^+$-induced inhibition of the neurogenic twitch contraction in rabbit vas deferens (M1 receptors). Furthermore, they inhibited the negative inotropic responses in guinea-pig atria and ileal contractions (M2 and M3 receptors respectively) induced by arecaidine propargyl ester. Compounds **7a**, **7b**, **9a** and **9b** produced parallel shifts of the agonist concentration–response curves without changes in basal tension or maximum agonist responses. Arunlakshana–Schild plots were linear over the antagonist concentration range examined, and the slopes of the regression lines were not significantly different from unity. In addition, all the competition curves obtained in binding studies were compatible with the existence of a single receptor subtype; the Hill coefficients were not different from unity. Thus all compounds studied exhibited an apparently competitive antagonism at M1–M3 receptors in functional and at M1–M4 receptors in binding experiments.

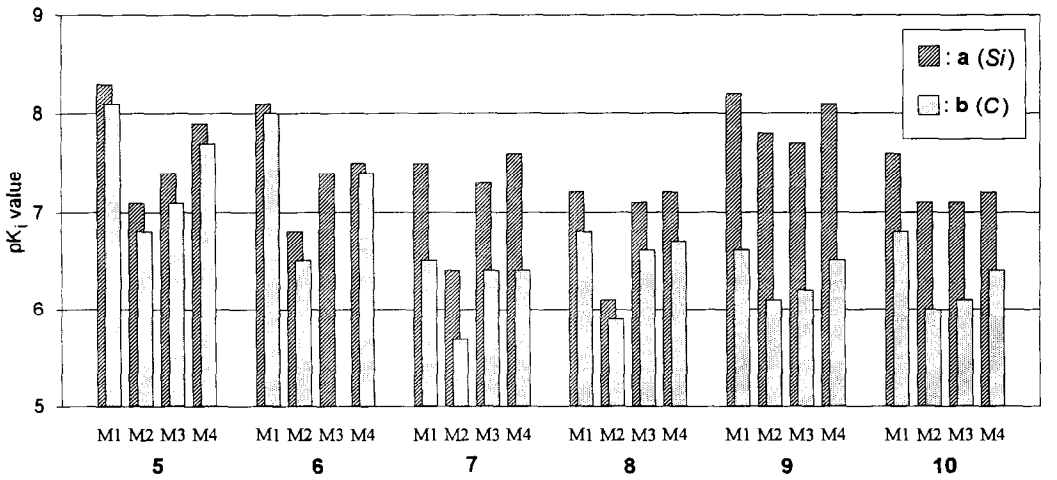


Fig. 1. Affinity profiles (pK_i values) of **5a/5b–10a/10b** at muscarinic M1 receptors in human NB-OK 1 cells, M2 receptors in rat heart, M3 receptors in rat pancreas and M4 receptors in rat striatum.

The pK_i values obtained in binding studies for **7a**, **7b**, **9a** and **9b** at M1–M3 receptors were very similar to their antimuscarinic potencies (pA_2 values) determined in functional experiments at M1, M2 and M3 receptors.

The selectivity pattern of all compounds investigated corresponded to the following rank order: M1 ⩾ M4 ⩾ M3 ⩾ M2. Only **7a**, **7b**, **8a** and **8b** had a clear preference for M1, M3 and M4 over M2 receptors. In this series, the greatest selectivity was found for the silanol **6a** (M1 > M2 = 32-fold).

In general, all silanols (**5a–10a**) displayed higher affinities for the four muscarinic receptor subtypes than their corresponding carbon analogues (**5b–10b**). This increase in affinity by C–Si exchange was rather low (up to 3.2-fold) for the Si–C pairs with an El–CH_2–CH_2–N chain (El = Si or C) (**5b** → **5a**; **6b** → **6a**) and also for the Si–C pair **8a**/**8b**, but high for all the other Si–C pairs with an El–CH_2–CH_2–CH_2–N moiety (El = Si or C) (**7b** → **7a**; **9b** → **9a**; **10b** → **10a**). The greatest difference in affinity between the Si–C analogues studied was observed for **9a** and **9b** (up to 81-fold; functional studies).

Introduction of a second fluorine atom in the *para* position of the unsubstituted phenyl group did not affect the affinity of the carbinols (**5b** → **6b**; **7b** → **8b**; **9b** → **10b**) in a special way but consistently decreased receptor affinity of the silanols (**5a** → **6a**; **7a** → **8a**; **9a** → **10a**) up to eightfold (M4: **9a** → **10a**).

Compounds with an ethylene group between the El (El = Si or C) and the N atom (**5a**, **5b**, **6a** and **6b**) always displayed higher receptor affinities than the corresponding compounds with a propylene moiety (**7a**, **7b**, **8a** and **8b**).

Furthermore, *N*-methylation did not influence the affinity of the carbinols (**7b** → **9b**; **8b** → **10b**) to a greater extent but increased the affinity of the silanols (**7a** → **9a**; **8a** → **10a**) at all muscarinic receptor subtypes (except for **10a** at M3 and M4 receptors), the increase being highest at M2 receptors. Thus *N*-methylation reduced the receptor selectivity of **7a** and **8a**.

In conclusion, the high increase in receptor affinity by sila-substitution (up to about two orders of magnitude) is the most interesting result obtained in these structure–activity relationship studies. Such a high increase in biological activity by sila-substitution (C–Si exchange) has not yet been described in the literature. These results again demonstrate that sila-substitution is a very useful method for drug design.

3. Experimental details

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. ^1H and ^{13}C NMR spectra were recorded on a Bruker WM-400 (^1H, 400.1 MHz; ^{13}C, 100.6 MHz) and a Bruker AC-250 spectrometer (^1H, 250.1 MHz; ^{13}C, 62.9 MHz) respectively. Chemical shifts were determined relative to internal $CHCl_3$ (^1H, $\delta = 7.25$ ppm) and $CDCl_3$ (^{13}C, $\delta = 77.05$ ppm) 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 (electron impact (EI) MS, 70 eV; field desorption (FD) MS, methanol, 11 kV) and a Finnigan MAT 8430 mass spectrometer (fast atom bombardment (FAB) MS, glycerol (liquid matrix), xenon (FAB source)) respectively. The selected *m/z* values given refer to the isotopes ^1H, ^{12}C, ^{14}N, ^{16}O, ^{19}F, ^{28}Si and ^{35}Cl.

3.1.2. (4-Fluorophenyl)phenyl(2-piperidinoethyl)silanol (p-fluoro-sila-pridinol) (5a)

A solution of **15** (2.80 g, 8.15 mmol) in a mixture of ethanol (16.2 ml) and water (3.7 ml) was stirred at room temperature for 20 h. The precipitate formed was isolated by filtration and recrystallized from diethyl ether to give 1.57 g (yield, 58%) of colourless crystals (melting point (m.p.), 129 °C). ^1H NMR ($CDCl_3$): δ 1.2–1.3 (m, 2H, $SiCH_2C$); 1.4–1.5 and 1.5–1.7 (m, 6H, CCH_2C); 2.3–2.6 and 2.6–2.7 (m, 6H, NCH_2C); 7.0–7.1, 7.3–7.5 and 7.5–7.7 (m, 9H, SiC_6H_5, SiC_6H_4F) ppm; SiOH not localized. ^{13}C NMR ($CDCl_3$): δ 11.4 ($SiCH_2C$); 24.3 (C-4, NC_5H_{10}); 26.0 (C-3/C-5, NC_5H_{10}); 54.3 (C-2/C-6, NC_5H_{10}); 54.6 ($SiCCH_2N$); 115.0 (d, $^2J(CF) = 19.7$ Hz, C-3/C-5, SiC_6H_4F); 127.9 (C-3/C-5, SiC_6H_5); 129.8 (C-4, SiC_6H_5); 132.8 (d, $^4J(CF) = 3.7$ Hz, C-1, SiC_6H_4F); 134.0 (C-2/C-6, SiC_6H_5); 136.1 (d, $^3J(CF) = 7.5$ Hz, C-2/C-6, SiC_6H_4F); 137.0 (C-1, SiC_6H_5); 164.1 (d, $^1J(CF) = 248.5$ Hz, C-4, SiC_6H_4F) ppm. EI MS: *m/z* 329 (9%, M^+), 98 (100%, $CH_2{=}NC_5H_{10}^+$). Anal. Found: C, 69.2; H, 7.3; N, 4.3. $C_{19}H_{24}FNOSi$ (329.5) calc.: C, 69.26; H, 7.34; N, 4.25%.

3.1.3. Di(4-fluorophenyl)(2-piperidinoethyl)silanol (p,p'-difluoro-sila-pridinol) (6a)

A solution of **16** (1.70 g, 4.70 mmol) in a mixture of ethanol (9.0 ml) and water (2.2 ml) was stirred at room temperature for 20 h. The precipitate formed was isolated by filtration and recrystallized from diethyl ether to give 1.04 g (yield, 64%) of colourless crystals (m.p., 121–122 °C), ^1H NMR ($CDCl_3$): δ 1.2–1.3 (m, 2H, $SiCH_2C$); 1.4–1.6 and 1.6–1.7 (m, 6H, CCH_2C); 2.3–2.7 (m, 6H, NCH_2C); 7.0–7.1 and 7.5–7.7 (m, 8H, SiC_6H_4F) ppm; SiOH not localized. ^{13}C NMR ($CDCl_3$): δ 11.4 ($SiCH_2C$); 24.2 (C-4, NC_5H_{10}); 26.0 (C-3/C-5, NC_5H_{10}); 54.3 (C-2/C-6, NC_5H_{10}); 54.6 ($SiCCH_2N$); 115.1 (d, $^2J(CF) = 19.8$ Hz, C-3/C-5, SiC_6H_4F); 132.6

(d, ^4J(CF) = 3.8 Hz, C-1, SiC_6H_4F); 136.1 (d, ^3J(CF) = 7.6 Hz, C-2/C-6, SiC_6H_4F); 164.2 (d, ^1J(CF) = 248.9 Hz, C-4, SiC_6H_4F) ppm. EI MS: *m/z* 347 (5%, M^+), 98 (100%, $CH_2{=}NC_5H_{10}^+$). Anal. Found: C, 65.8; H, 6.8; N, 4.0. $C_{19}H_{23}F_2NOSi$ (347.5) calc.: C, 65.68; H, 6.67; N, 4.03%.

3.1.4. *(4-Fluorophenyl)phenyl(3-piperidinopropyl)-silanol (p-fluoro-sila-difenidol) (**7a**)*

Hydrochloric acid (0.5 M, 270 ml) was added to a stirred solution of **20** (3.30 g, 9.23 mmol) in 2-propanol (100 ml). The resulting mixture was stirred at room temperature for 16 h and the pH was then adjusted to 8 with 1 M aqueous NaOH solution. The mixture was extracted three times with diethyl ether (3 × 100 ml), and the extracts were combined, washed with water (20 ml) and dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the oily residue crystallized within about 10 days at room temperature. Recrystallization from diethyl ether : 2-propanol (3 : 1, v/v) gave 2.70 g (yield, 85%) of colourless crystals (m.p. 64 °C). ^{1}H NMR ($CDCl_3$): δ 1.1–1.2 (m, 2H, $SiCH_2C$); 1.5–1.6 and 1.7–1.9 (m, 8H, CCH_2C); 2.8–3.1 (m, 6H, NCH_2C); 7.1–7.2, 7.3–7.4 and 7.5–7.7 (m, 9H, SiC_6H_5, SiC_6H_4F); 9.1 (broad "s", 1H, SiOH) ppm. ^{13}C NMR ($CDCl_3$): δ 12.4 ($SiCH_2C$); 18.0 ($SiCCH_2CN$); 22.2 (C-4, NC_5H_{10}); 22.7 (C-3/C-5, NC_5H_{10}); 53.1 (C-2/C-6, NC_5H_{10}); 59.1 ($SiCCCH_2N$); 115.0 (d, ^2J(CF) = 19.7 Hz, C-3/C-5, SiC_6H_4F); 127.9 (C-3/C-5, SiC_6H_5); 129.8 (C-4, SiC_6H_5); 132.0 (d, ^4J(CF) = 3.6 Hz, C-1, SiC_6H_4F); 134.1 (C-2/C-6, SiC_6H_5); 136.1 (C-1, SiC_6H_5); 136.3 (d, ^3J(CF) = 7.6 Hz, C-2/C-6, SiC_6H_4F); 164.1 (d, ^1J(CF) = 249.0 Hz, C-4, SiC_6H_4F) ppm. EI MS: *m/z* 343 (2%, M^+), 98 (100%, $CH_2{=}NC_5H_{10}^+$). Anal. Found: C, 70.5; H, 7.6; N, 4.0. $C_{20}H_{26}FNOSi$ (343.5) calc.: C, 69.93; H, 7.63; N, 4.08%.

3.1.5. *Di(4-fluorophenyl)(3-piperidinopropyl)silanol (p,p'-difluoro-sila-difenidol) (**8a**)*

A solution of **22** (5.26 g, 14.0 mmol) in a mixture of ethanol (22.4 ml) and water (5.6 ml) was stirred at room temperature for 17 h. After removal of the solvents under reduced pressure, the oily residue was diluted with diethyl ether (100 ml) and the resulting solution dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the residue crystallized from *n*-pentane to give 4.11 g (yield, 81%) of colourless crystals (m.p., 69 °C) ^{1}H NMR ($CDCl_3$): δ 1.1–1.2 (m, 2H, $SiCH_2C$); 1.4–1.6 and 1.6–1.8 (m, 8H, CCH_2C); 2.3–2.4 (m, 6H, NCH_2C); 7.0–7.1 and 7.5–7.6 (m, 8H, SiC_6H_4F); 9.4 (broad "s", 1H, SiOH) ppm. ^{13}C NMR ($CDCl_3$): δ 15.7 ($SiCH_2C$); 19.8 ($SiCCH_2CN$); 24.1 (C-4, NC_5H_{10}); 25.0 (C-3/C-5, NC_5H_{10}); 54.6 (C-2/C-6, NC_5H_{10}); 61.3 ($SiCCCH_2N$); 114.9 (d, ^2J(CF) = 19.6 Hz, C-3/C-5, SiC_6H_4F); 133.2 (d, ^4J(CF) = 3.8 Hz, C-1, SiC_6H_4F); 136.0 (d, ^3J(CF) = 7.5 Hz, C-2/C-6, SiC_6H_4F); 164.0 (d, ^1J(CF) = 248.3 Hz, C-4, SiC_6H_4F) ppm. EI MS: *m/z* 361 (8%, M^+), 98 (100%, $CH_2{=}NC_5H_{10}^+$). Anal. Found: C, 66.5; H, 7.0; N, 3.9. $C_{20}H_{25}F_2NOSi$ (361.5) calc.: C, 66.45; H, 6.97; N, 3.87%.

3.1.6. *1-{1-[(4-Fluorophenyl)hydroxy(phenyl)silyl]propan-3-yl}-1-methylpiperidinium iodide (p-fluoro-sila-difenidol methiodide) (**9a**)*

Methyl iodide (5.60 g, 39.5 mmol) was added at room temperature to a solution of **7a** (2.70 g, 7.86 mmol) in acetonitrile (42 ml). The mixture was stirred under reflux for 2 h and then cooled to room temperature; the precipitate was isolated by filtration. Recrystallization from diethyl ether : 2-propanol (1 : 3, v/v) gave 2.50 g (yield, 66%) of pale-yellow crystals (m.p., 164 °C). ^{1}H NMR ($CDCl_3$): δ 1.1–1.2 (m, 2H, $SiCH_2C$); 1.5–1.9 (m, 8H, CCH_2C); 3.03 (s, 3H, NCH_3); 3.3–3.5 (m, 6H, NCH_2C); 7.0–7.1, 7.2–7.4 and 7.6–7.7 (m, 9H, SiC_6H_5, SiC_6H_4F) ppm; SiOH not localized. ^{13}C NMR ($CDCl_3$): δ 12.5 ($SiCH_2C$); 17.9 ($SiCCH_2CN$); 22.4 (C-4, NC_5H_{10}); 22.9 (C-3/C-5, NC_5H_{10}); 53.1 (NCH_3); 63.1 ($SiCCCH_2N$); 65.3 (C-2/C-6, NC_5H_{10}); 115.1 (d, ^2J(CF) = 19.7 Hz, C-3/C-5, SiC_6H_4F); 129.0 (C-3/C-5, SiC_6H_5); 130.8 (C-4, SiC_6H_5); 133.0 (d, ^4J(CF) = 3.6 Hz, C-1, SiC_6H_4F); 133.2 (C-2/C-6, SiC_6H_5); 136.3 (C-1, SiC_6H_5); 137.7 (d, ^3J(CF) = 7.6 Hz, C-2/C-6, SiC_6H_4F); 164.2 (d, ^1J(CF) = 249.0 Hz, C-4, SiC_6H_4F) ppm. FAB MS (positive): *m/z* 358 (80%, cation of the salt), 98 (100%, $CH_2{=}NC_5H_{10}^+$). Anal. Found: C, 51.8; H, 6.1; N, 2.9. $C_{21}H_{29}FINOSi$ (485.4) calc.: C, 51.96; H, 6.02; N, 2.89%.

3.1.7. *1-{1-[Di(4-fluorophenyl)hydroxysilyl]propan-3-yl}-1-methylpiperidinium iodide (p,p'-difluoro-sila-difenidol methiodide) (**10a**)*

Methyl iodide (1.00 g, 7.05 mmol) was added at room temperature to a solution of **8a** (500 mg, 1.38 mmol) in a mixture of acetone (5 ml) and *n*-pentane (5 ml). After stirring at room temperature for 2 h, the precipitate was isolated by filtration and recrystallized from acetone : *n*-pentane (1 : 1, v/v) to give 540 mg (yield, 78%) of colourless crystals (m.p., 142 °C). ^{1}H NMR ($CDCl_3$): δ 1.0–1.3 (m, 2H, $SiCH_2C$); 1.6–2.2 (m, 8H, CCH_2C); 3.09 (s, 3H, NCH_3); 3.4–3.5 and 3.5–3.6 (m, 6H, NCH_2C); 5.0 (broad "s", 1H, SiOH); 7.0–7.1 and 7.5–7.7 (m, 8H, SiC_6H_4F) ppm. ^{13}C NMR ($CDCl_3$): δ 11.8 ($SiCH_2C$); 16.6 ($SiCCH_2CN$); 20.0 (C-3/C-5, NC_5H_{10}); 20.6 (C-4, NC_5H_{10}); 48.5 (NCH_3); 61.2 (C-2/C-6, NC_5H_{10}); 65.8 ($SiCCCH_2N$); 115.1 (d, ^2J(CF) = 21.7 Hz, C-3/C-5, SiC_6H_4F); 131.4 (d, ^4J(CF) = 3.9 Hz, C-1, SiC_6H_4F); 136.4 (d, ^3J(CF) = 7.5 Hz, C-2/C-6, SiC_6H_4F); 164.0 (d, ^1J(CF) = 249.4 Hz, C-4, SiC_6H_4F) ppm. FD MS: *m/z* 376 (100%, cation of the salt). Anal. Found: C, 50.1; H, 5.6;

N, 2.7. $C_{21}H_{28}F_2INOSi$ (503.4) calc.: C, 50.10; H, 5.61; N, 2.78%.

3.1.8. Trichloro(vinyl)silane (11)

Trichloro(vinyl)silane was commercially available (Aldrich).

3.1.9. Trimethoxy(2-piperidinoethyl)silane (13)

A 1.6 M solution of *n*-butyllithium in *n*-hexane (656 ml, 1.05 mol *n*-BuLi) was added at 0 °C within 2.5 h to a stirred solution of piperidine (119 g, 1.40 mol) in tetrahydrofuran (THF) (100 ml). The reaction mixture was then allowed to warm up to room temperature during 45 min and stirred for a further 30 min. Then a solution of **11** (50.0 g, 310 mmol) in THF (150 ml) was added dropwise at 0 °C during 45 min, and the resulting mixture was stirred at room temperature for 72 h. After addition of a solution triethylamine (21.8 g, 220 mmol) in THF (80 ml) and a solution of chlorotrimethylsilane (20.6 g, 190 mmol) in THF (80 ml), the reaction mixture was stirred at room temperature for 5 h, the precipitate filtered off and the solvent removed completely in vacuo. Then *n*-pentane (450 ml) was added to the residue, the resulting precipitate filtered off and the solvent removed completely under reduced pressure. After addition of methanol (300 ml) to the residue (crude tripiperidino(2-piperidinoethyl)silane (**12**); identity proved by ^1H NMR, ^{13}C NMR and EI MS studies), the mixture was stirred at room temperature for 16 h. Then the solvent was removed in vacuo, *n*-pentane (200 ml) was added to the residue, the resulting precipitate filtered off, and the solvent removed under reduced pressure. The oily residue was distilled in vacuo (Vigreux column) to yield 60.0 g (83%) of a colourless liquid (boiling point (b.p.), 77 °C (1 Torr)). ^1H NMR ($CDCl_3$): δ 0.8–0.9 (m, 2H, $SiCH_2C$); 1.3–1.6 (m, 6H, CCH_2C); 2.3–2.4 (m, 6H, NCH_2C); 3.51 (s, 9H, OCH_3) ppm. ^{13}C NMR ($CDCl_3$): δ 7.5 ($SiCH_2C$); 24.5 (C-4, NC_5H_{10}); 27.0 (C-3/C-5, NC_5H_{10}); 50.4 (OCH_3); 52.9 ($SiCCH_2N$); 53.8 (C-2/C-6, NC_5H_{10}) ppm. EI MS: *m/z* 233 (7%, M^+), 98 (100%, $CH_2{=}NC_5H_{10}^+$). Anal. Found: C, 51.6; H, 9.9; N, 6.1. $C_{10}H_{23}NO_3Si$ (233.4) calc.: C, 51.46; H, 9.93; N, 6.00%.

3.1.10. (4-Fluorophenyl)dimethoxy(2-piperidinoethyl)-silane (14)

A Grignard reagent was prepared from 1-bromo-4-fluorobenzene (5.25 g, 30.0 mmol) and magnesium turnings (870 mg, 35.8 mmol) in diethyl ether (30 ml) and then added dropwise at 0 °C within 1 h to a stirred solution of **13** (7.74 g, 33.2 mmol) in diethyl ether (50 ml). After stirring the reaction mixture at room temperature for 16 h, the solvent was removed under reduced pressure and *n*-pentane (70 ml) added to the residue. The resulting mixture was kept at −20 °C for 12 h, the precipitate formed was filtered off, the solvent removed under reduced pressure, and the oily residue distilled in vacuo (Vigreux column) to give 6.70 g (yield, 68%) of a colourless liquid (b.p., 98–101 °C (0.01 Torr)). ^1H NMR ($CDCl_3$): δ 1.0–1.2 (m, 2H, $SiCH_2C$); 1.3–1.5 and 1.5–1.6 (m, 6H, CCH_2C); 2.2–2.4 (m, 6H, NCH_2C); 3.52 (s, 6H, OCH_3); 7.0–7.1 and 7.5–7.6 (m, 4H, SiC_6H_4F) ppm. ^{13}C NMR ($CDCl_3$): δ 10.5 ($SiCH_2C$); 24.5 (C-4, NC_5H_{10}); 25.9 (C-3/C-5, NC_5H_{10}); 50.6 (OCH_3); 53.0 ($SiCCH_2N$); 53.9 (C-2/C-6, NC_5H_{10}); 115.1 (d, $^2J(CF) = 19.7$ Hz, C-3/C-5, SiC_6H_4F); 128.5 (d, $^4J(CF) = 3.6$ Hz, C-1, SiC_6H_4F); 136.4 (d, $^3J(CF) = 7.6$ Hz, C-2/C-6, SiC_6H_4F); 164.4 (d, $^1J(CF) = 249.3$ Hz, C-4, SiC_6H_4F) ppm. EI MS: *m/z* 297 (6%, M^+), 98 (100%, $CH_2{=}NC_5H_{10}^+$). Anal. Found: C, 60.7; H, 8.2; N, 4.7. $C_{15}H_{24}FNO_2Si$ (297.4) calc.: C, 60.57; H, 8.13; N, 4.71%.

3.1.11. (4-Fluorophenyl)methoxy(phenyl)(2-piperidinoethyl)silane (15)

A Grignard reagent was prepared from bromobenzene (2.90 g, 18.5 mmol) and magnesium turnings (490 mg, 20.2 mmol) in diethyl ether (40 ml) and then added dropwise at room temperature within 45 min to a stirred solution of **14** (5.00 g, 16.8 mmol) in diethyl ether (20 ml). After stirring the reaction mixture at room temperature for 16 h, the solvent was removed under reduced pressure and *n*-pentane (100 ml) was added to the residue. The resulting mixture was kept at −20 °C for 12 h, the precipitate formed was filtered off, the solvent removed under reduced pressure, and the oily residue distilled in vacuo (Vigreux column) to give 3.00 g (yield, 52%) of a colourless liquid (b.p., 128–130 °C (0.01 Torr)). ^1H NMR ($CDCl_3$): δ 1.4–1.5 and 1.5–1.6 (m, 8H, $SiCH_2C$, CCH_2C); 2.3–2.5 (m, 6H, NCH_2C); 3.52 (s, 3H, OCH_3); 7.0–7.1, 7.2–7.4 and 7.5–7.6 (m, 9H, SiC_6H_5, SiC_6H_4F) ppm. ^{13}C NMR ($CDCl_3$): δ 11.7 ($SiCH_2C$); 24.5 (C-4, NC_5H_{10}); 26.0 (C-3/C-5, NC_5H_{10}); 51.4 (OCH_3); 53.4 ($SiCCH_2N$); 54.0 (C-2/C-6, NC_5H_{10}); 115.2 (d, $^2J(CF) = 19.6$ Hz, C-3/C-5, SiC_6H_4F); 128.0 (C-3/C-5, SiC_6H_5); 130.1 (C-4, SiC_6H_5); 130.2 (d, $^4J(CF) = 3.9$ Hz, C-1, SiC_6H_4F); 134.3 (C-1, SiC_6H_5); 134.6 (C-2/C-6, SiC_6H_5); 136.7 (d, $^3J(CF) = 7.7$ Hz, C-2/C-6, SiC_6H_4F); 164.3 (d, $^1J(CF) = 249.4$ Hz, C-4, SiC_6H_4F) ppm. EI MS: *m/z* 343 (8%, M^+), 98 (100%, $CH_2{=}NC_5H_{10}^+$). Anal. Found: C, 69.8; H, 7.6; N, 4.2. $C_{20}H_{26}FNOSi$ (343.5) calc.: C, 69.93; H, 7.63; N, 4.08%.

3.1.12. Di(4-fluorophenyl)methoxy(2-piperidinoethyl)-silane (16)

A Grignard reagent was prepared from 1-bromo-4-fluorobenzene (13.7 g, 78.3 mmol) and magnesium turnings (2.19 g, 90.1 mmol) in diethyl ether (60 ml) and then added dropwise at room temperature within 1.5 h to a solution of **13** (7.74 g, 33.2 mmol) in diethyl

ether (20 ml). After stirring under reflux for 5 h, the solvent was removed under reduced pressure and *n*-pentane (70 ml) added to the residue. The resulting mixture was kept at −20 °C for 12 h, the precipitate formed was filtered off, the solvent removed under reduced pressure, and the oily residue distilled in vacuo (Vigreux column) to give 7.20 g (yield, 60%) of a colourless liquid (b.p., 135 °C (0.01 Torr)). ^{1}H NMR ($CDCl_3$): δ 1.3–1.6 (m, 8H, $SiCH_2C$, CCH_2C); 2.3–2.5 (m, 6H, NCH_2C); 3.49 (s, 3H, OCH_3); 7.1–7.2 and 7.5–7.6 (m, 8H, SiC_6H_4F) ppm. ^{13}C NMR ($CDCl_3$): δ 11.7 ($SiCH_2C$); 24.5 (C-4, NC_5H_{10}); 25.9 (C-3/C-5, NC_5H_{10}); 51.3 (OCH_3); 53.3 ($SiCCH_2N$); 54.0 (C-2/C-6, NC_5H_{10}); 115.1 (d, ^2J(CF) = 19.8 Hz, C-3/C-5, SiC_6H_4F); 129.8 (d, ^4J(CF) = 3.7 Hz, C-1, SiC_6H_4F); 136.6 (d, ^3J(CF) = 7.8 Hz, C-2/C-6, SiC_6H_4F); 163.3 (d, ^1J(CF) = 249.6 Hz, C-4, SiC_6H_4F) ppm. EI MS: *m/z* 361 (14%, M^+), 98 (100%, $CH_2{=}NC_5H_{10}^+$). Anal. Found: C, 66.5; H, 7.0; N, 3.9. $C_{20}H_{25}F_2NOSi$ (361.5) calc.: C, 66.45; H, 6.97; N, 3.87%.

3.1.13. (3-Chloropropyl)trimethoxysilane (17)

(3-Chloropropyl)trimethoxysilane was commercially available (Aldrich).

3.1.14. (3-Chloropropyl)dimethoxy(phenyl)silane (18)

A Grignard reagent was prepared from bromobenzene (78.5 g, 500 mmol) and magnesium turnings (12.1 g, 498 mmol) in diethyl ether (350 ml) and then added dropwise at room temperature during 1.5 h to a stirred solution of **17** (99.4 g, 500 mmol) in diethyl ether (500 ml). After stirring at room temperature for 16 h and heating under reflux for 4 h, the precipitate was filtered off and the filtrate concentrated under reduced pressure. Then *n*-pentane (400 ml) was added and the resulting precipitate filtered off. The filtrate was concentrated under reduced pressure and the residue distilled in vacuo (Vigreux column) to give 89.4 g (yield, 73%) of a colourless liquid (b.p., 106 °C (0.1 Torr)). ^{1}H NMR ($CDCl_3$): δ 1.1–1.3 (m, 2H, $SiCH_2C$); 1.6–2.0 (m, 2H, CCH_2C); 3.42 (centre of an m, 8H, CCH_2Cl, OCH_3); 7.2–7.6 (m, 5H, SiC_6H_5) ppm. ^{13}C NMR ($CDCl_3$): δ 11.1 ($SiCH_2C$); 26.5 (CCH_2C); 47.7 (CCH_2Cl); 51.3 (OCH_3); 127.9 (C-3/C-5, SiC_6H_5); 130.0 (C-4, SiC_6H_5); 134.0 (C-1, SiC_6H_5); 134.5 (C-2/C-6, SiC_6H_5) ppm. EI MS: *m/z* 244 (1%, M^+), 167 (100%, $M^+ - CH_2CH_2CH_2Cl$). Anal. Found: C, 54.2; H, 7.2. $C_{11}H_{17}ClO_2Si$ (244.8) calc.: C, 53.97; H, 7.00%.

3.1.15. Dimethoxy(phenyl)(3-piperidinopropyl)silane (19)

A solution of **18** (29.4 g, 120 mmol) and piperidine (51.9 g, 610 mmol) in methanol (125 ml) was heated under reflux for 16 h. After removal of the solvent under reduced pressure, *n*-pentane (150 ml) was added and the mixture kept at room temperature for 2 h. The precipitate was filtered off, the filtrate concentrated under reduced pressure, and the oily residue distilled in vacuo (Vigreux column) to give 29.8 g (yield, 85%) of a colourless liquid (b.p., 120 °C (0.01 Torr)). ^{1}H NMR ($CDCl_3$): δ 0.7–0.8 (m, 2H, $SiCH_2C$); 1.3–1.4 and 1.5–1.6 (m, 8H, CCH_2C); 2.2–2.3 (m, 6H, NCH_2C); 3.53 (s, 6H, OCH_3); 7.2–7.4 and 7.5–7.6 (m, 5H, SiC_6H_5) ppm. ^{13}C NMR ($CDCl_3$): δ 9.9 ($SiCH_2C$); 19.9 ($SiCCH_2CN$); 24.4 (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}); 62.5 ($SiCCCH_2N$); 127.0 (C-3/C-5, SiC_6H_5); 127.8 (C-4, SiC_6H_5); 132.8 (C-1, SiC_6H_5); 134.2 (C-2/C-6, SiC_6H_5) ppm. EI MS: *m/z* 293 (5%, M^+), 98 (100%, $CH_2{=}NC_5H_{10}^+$). Anal. Found: C, 65.3; H, 9.2; N, 4.7. $C_{16}H_{27}NO_2Si$ (293.5) calc.: C, 65.48; H, 9.27; N, 4.77%

3.1.16. (4-Fluorophenyl)methoxy(phenyl)(3-piperidinopropyl)silane (20)

A 1.6 M solution of *n*-butyllithium in *n*-hexane (54.7 ml, 87.5 mmol *n*-BuLi) was added dropwise at −35°C during 40 min to a stirred solution of 1-bromo-4-fluorobenzene (15.7 g, 89.7 mmol) in diethyl ether (100 ml). The mixture was stirred at −35 °C for 30 min and then added dropwise at −20°C during 60 min to a stirred solution of **19** (25.0 g, 85.2 mmol) in diethyl ether (200 ml). The mixture was stirred at room temperature for 16 h; then saturated aqueous NH_4Cl solution (30 ml) and water (30 ml) were added. The organic phase was separated, the aqueous layer extracted four times with diethyl ether (4 × 50 ml), and the combined organic extracts were dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the oily residue was distilled in vacuo (Vigreux column) to give 26.9 g (88%) of a colourless liquid (b.p., 148 °C (0.2 Torr)). ^{1}H NMR ($CDCl_3$): δ 1.1–1.2 (m, 2H, $SiCH_2C$); 1.4–1.7 (m, 8H, CCH_2C); 2.2–2.4 (m, 6H, NCH_2C); 3.51 (s, 3H, OCH_3); 7.0–7.1, 7.3–7.5 and 7.5–7.6 (m, 9H, SiC_6H_5, SiC_6H_4F) ppm. ^{13}C NMR ($CDCl_3$): δ 11.3 ($SiCH_2C$); 20.3 ($SiCCH_2CN$); 24.5 (C-4, NC_5H_{10}); 26.0 (C-3/C-5, NC_5H_{10}); 51.4 (OCH_3); 54.6 (C-2/C-6, NC_5H_{10}); 62.8 ($SiCCCH_2N$); 115.1 (d, ^2J(CF) = 19.7 Hz, C-3/C-5, SiC_6H_4F); 127.9 (C-3/C-5, SiC_6H_5); 130.0 (C-4, SiC_6H_5); 130.4 (d, ^4J(CF) = 3.6 Hz, C-1, SiC_6H_4F); 134.4 (C-1, SiC_6H_5); 134.6 (C-2/C-6, SiC_6H_5); 136.3 (d, ^3J(CF) = 7.6 Hz, C-2/C-6, SiC_6H_4F); 164.1 (d, ^1J(CF) = 249.0 Hz, C-4, SiC_6H_4F) ppm. EI MS: *m/z* 357 (1%, M^+), 98 (100%, $CH_2{=}NC_5H_{10}^+$). Anal. Found: C, 70.5; H, 8.1; N, 4.0. $C_{21}H_{28}FNOSi$ (357.5) calc.: C, 70.55; H, 7.89; N, 3.92%.

3.1.17. Trimethoxy(3-piperidinopropyl)silane (21)

A solution of **17** (10.0 g, 50.3 mmol) and piperidine (10.7 g, 126 mmol) in methanol (75 ml) was heated

under reflux for 24 h. After removal of the solvent under reduced pressure, *n*-pentane (300 ml) was added and the mixture kept at room temperature for 2 h. The precipitate was filtered off, the filtrate concentrated under reduced pressure, and the oily residue distilled in vacuo (Vigreux column) to give 9.70 g (yield, 78%) of a colourless liquid (b.p., 98 °C (3 Torr)). ^{1}H NMR ($CDCl_3$): δ 0.5–0.6 (m, 2H, $SiCH_2C$); 1.3–1.4 and 1.5–1.6 (m, 8H, CCH_2C); 2.2–2.3 (m, 6H, NCH_2C); 3.50 (s, 9H, OCH_3) ppm. ^{13}C NMR ($CDCl_3$): δ 6.8 ($SiCH_2C$); 19.8 ($SiCCH_2CN$); 24.4 (C-4, NC_5H_{10}); 25.9 (C-3/C-5, NC_5H_{10}); 50.4 (OCH_3); 54.5 (C-2/C-6, NC_5H_{10}); 62.4 ($SiCCCH_2N$) ppm. EI MS: *m/z* 247 (4%, M^+), 98 (100%, $CH_2{=}NC_5H_{10}^+$). Anal. Found: C, 53.5; H, 10.3; N, 5.8. $C_{11}H_{25}NO_3Si$ (247.4) calc.: C, 53.40; H, 10.18; N, 5.66%.

3.1.18. Di(4-fluorophenyl)methoxy(3-piperidinopropyl)-silane (22)

A Grignard reagent was prepared from 1-bromo-4-fluorobenzene (28.2 g, 161 mmol) and magnesium turnings (4.60 g, 189 mmol) in diethyl ether (100 ml) and then added dropwise at room temperature during 2 h to a stirred solution of **21** (16.8 g, 67.9 mmol) in diethyl ether (40 ml). After heating under reflux for 5 h, the solvent was evaporated under reduced pressure and *n*-pentane (200 ml) was added to the residue. The resulting mixture was kept at −20 °C for 12 h, the precipitate formed was filtered off, the solvent removed under reduced pressure, and the oily residue distilled in vacuo (Vigreux column) to give 16.9 g (yield, 66%) of a colourless liquid (b.p., 143–146 °C (0.01 Torr)). ^{1}H NMR ($CDCl_3$): δ 1.0–1.1 (m, 2H, $SiCH_2C$); 1.3–1.6 (m, 8H, CCH_2C); 2.2–2.3 (m, 6H, NCH_2C); 3.48 (s, 3H, OCH_3); 7.0–7.1 and 7.5–7.6 (m, 8H, SiC_6H_4F) ppm. ^{13}C NMR ($CDCl_3$): δ 10.4 ($SiCH_2C$); 19.5 ($SiCCH_2CN$); 23.7 (C-4, NC_5H_{10}); 24.9 (C-3/C-5, NC_5H_{10}); 50.4 (OCH_3); 53.8 (C-2/C-6, NC_5H_{10}); 61.8 ($SiCCCH_2N$); 114.3 (d, ^2J(CF) = 19.6 Hz, C-3/C-5, SiC_6H_4F); 129.4 (d, ^4J(CF) = 3.9 Hz, C-1, SiC_6H_4F); 135.9 (^3J(CF) = 7.5 Hz, C-2/C-6, SiC_6H_4F); 163.5 (d, ^1J(CF) = 247.8 Hz, C-4, SiC_6H_4F) ppm. EI MS: *m/z* 375 (3%, M^+), 98 (100%, $CH_2{=}NC_5H_{10}^+$). Anal. Found: C, 67.2; H, 7.4, N, 3.7. $C_{21}H_{27}F_2NOSi$ (375.5) calc.: C, 67.17; H, 7.25; N, 3.73%.

3.2. Pharmacological evaluation

3.2.1. Functional pharmacological studies

As a measure of affinity, pA_2 values of **7a**, **7b**, **9a** and **9b** were determined at muscarinic M1 receptors in rabbit vas deferens {1-[4-(4-fluorophenylcarbamoyloxy)-2-butyn-1-yl]-1-methylpyrrolidinium tosylate (4-F–PyMcN$^+$) as agonist}, M2 receptors in guinea-pig atria and M3 receptors in guinea-pig ileum (arecaidine propargyl ester as agonist) according to published procedures [10].

Concentration-response curves of the agonists were constructed in the absence and in the presence of the antagonists. Dose ratios calculated from the respective EC_{50} values of the agonists were used to perform an Arunlakshana–Schild [11] analysis. As the obtained Arunlakshana–Schild plots of all the compounds investigated were linear and the slopes of the regression lines were not significantly different from unity ($P > 0.05$), pA_2 values were estimated as the intercept on the abscissa scale by fitting to the data the best straight line with a slope of unity (constrained plot) [12]. The pA_2 values given in Table 1 correspond to $-\log K_D$ values (K_D is the dissociation constant of the antagonist–receptor complex).

3.2.2. Radioligand binding studies

Radioligand binding studies were carried out with homogenates of human NB-OK 1 neuroblastoma cells (M1 receptors), as well as 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 of the binding experiments were analysed by an iterative curve fitting procedure. Dissociation constants (K_i values) of **5a/5b–10a/10b** were determined from IC_{50} values obtained from competition curves. The pK_i values shown in Table 2 correspond to $-\log K_i$ values. For more details, see [10,13].

3.2.3. Statistics

All pharmacological data are presented as arithmetic means of the indicated number of experiments (see Tables 1 and 2). Linear regression analyses were carried out by the method of least squares. Differences between mean values were tested for statistical significance by Student's *t* test; $P < 0.05$ was accepted as being significant.

Acknowledgements

This work was supported by the Deutsche Forschungsgemeinschaft (G.L. and R.T.), the Fonds der Chemischen Industrie (G.L., E.M. and R.T.), the Fonds de la Recherche Scientifique Médical (M.W.), and the Bayer AG, Germany (R.T). D.T. thanks the Education Ministry of Japan for a research fellowship.

References and notes

[1] R. Tacke, M. Strecker, W.S. Sheldrick, L. Ernst, E. Heeg, B. Berndt, C.-M. Knapstein and R. Niedner, *Chem. Ber., 113* (1980) 1962.

[2] R. Tacke, M. Strecker, G. Lambrecht, U. Moser and E. Mutschler, *Arch. Pharm. (Weinheim), 317* (1984) 207.

[3] G. Lambrecht, R. Feifel, U. Moser, M. Wagner-Röder, L.K. Choo, J. Camus, M. Tastenoy, M. Waelbroeck, C. Strohmann, R. Tacke, J.F. Rodrigues de Miranda, J. Christophe and E. Mutschler, *Trends Pharmacol. Sci. (Suppl.), 10* (1989) 60.

[4] M. Waelbroeck, J. Camus, M. Tastenoy, G. Lambrecht, E. Mutschler, M. Kropfgans, J. Sperlich, F. Wiesenberger, R. Tacke and J. Christophe, *Br. J. Pharmacol., 109* (1993) 360.

[5] R. Tacke, M. Kropfgans, A. Tafel, F. Wiesenberger, W.S. Sheldrick, E. Mutschler, H. Egerer, N. Rettenmayr, J. Gross, M. Waelbroeck and G. Lambrecht, *Z. Naturforsch., 49b* (1994) 898.

[6] L. Steiling, R. Tacke and U. Wannagat, *Liebigs Ann. Chem.*, (1979) 1554.

[7] R. Tacke, M. Strecker, W.S. Sheldrick, E. Heeg, B. Berndt and K.M. Knapstein, *Z. Naturforsch., 34b* (1979) 1279.

[8] (a) For synthesis of (2-aminoethyl)diorganocarbinols see D.W. Adamson, *J. Chem. Soc.*, (1949) S144; D.W. Adamson, P.A. Barrett and S. Wilkinson, *J. Chem. Soc.*, (1951) 52. (b) For synthesis of (3-aminopropyl)diorganocarbinols see K. Miescher and A. Marxer, *U.S. Pat. 2.411.664*, 1946 (*Chem. Abstr., 41* (1947) 6276); P.A. Barrett and S. Wilkinson, *Br. Pat. 683950*, 1952 (*Chem. Abstr., 49* (1955) 909).

[9] R. Tacke and H. Linoh, in S. Patai and Z. Rappoport (eds.), *The Chemistry of Organic Silicon Compounds, Part 2*, Wiley, Chichester, West Sussex, 1989, pp. 1143–1206.

[10] M. Waelbroeck, J. Camus, M. Tastenoy, R. Feifel, E. Mutschler, R. Tacke, C. Strohmann, K. Rafeiner, J.F. Rodrigues de Miranda and G. Lambrecht, *Br. J. Pharmacol., 112* (1994) 505.

[11] O. Arunlakshana and H.O. Schild, *Br. J. Pharmacol., 14* (1959) 48.

[12] R.J. Tallarida and R.B. Murray, *Manual of Pharmacologic Calculations with Computer Programs*, Springer, Berlin, 1986.

[13] M. Waelbroeck, J. Camus, M. Tastenoy, E. Mutschler, C. Strohmann, R. Tacke, L. Schjelderup, A. Aasen, G. Lambrecht and J. Christophe, *Eur. J. Pharmacol. — Mol. Pharmacol. Sect., 227* (1992) 33.