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Cyclohexyl(4-fluorophenyl)(3-piperidinopropyl)silanol (*p*-fluoro-hexahydro-sila-difenidol, *p*-F-HHSiD) and derivatives: synthesis and antimuscarinic properties

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Abstract

Four different syntheses of the potent and selective muscarinic antagonist cyclohexyl(4-fluorophenyl)(3-piperidinopropyl)silanol (*p*-fluoro-hexahydro-sila-difenidol, *p*-F-HHSiD (**2b**); isolated as hydrochloride **2b**·HCl) are described (starting materials: $(CH_3O)_3SiCH_2CH_2CH_2Cl$ and $Si(OCH_3)_4$). In addition, the synthesis of the corresponding carbon analogue *p*-fluoro-hexahydro-difenidol (*p*-F-HHD (**2a**); isolated as **2a**·HCl) and the syntheses of three *p*-F-HHSiD derivatives (**3**–**5**), with a modified cyclic amino group, are reported (**3**: piperidino/pyrrolidino exchange, isolated as **3**·HCl; **4**: piperidino/hexamethylenimino exchange, isolated as **4**·HCl; **5**: quaternization of **2b** with methyl iodide). The chiral compounds **2a**, **2b**, **3**, **4** and **5** were prepared as racemates. In functional pharmacological studies, **3**–**5** behaved as simple competitive antagonists at muscarinic M1 receptors in rabbit vas deferens, M2 receptors in guinea-pig atria, and M3 receptors in guinea-pig ileal smooth muscle. The pyrrolidino (**3**) and hexamethylenimino (**4**) analogues of the parent drug *p*-F-HHSiD (**2b**) displayed the highest affinity for M1 and M3 receptors (pA_2 values: 7.0–7.4) but exhibited lower affinity for cardiac M2 receptors (pA_2: 5.9 and 6.0). Their affinity profile (M1 ~ M3 > M2) is different from that of *p*-F-HHSiD (**2b**) (M3 > M1 > M2), but qualitatively very similar to that of *p*-F-HHD (**2a**). The methiodide **5** exhibited the highest affinity for M1 receptors (pA_2: 8.5) but lower affinity for M2 and M3 receptors by factors of 5.6 and 3.6, respectively.

Introduction

Some years ago, we reported the synthesis of the potent and selective muscarinic antagonist hexahydro-sila-difenidol (HHSiD (**1b**); Scheme 1) [1]. This silicon compound is now a commercially available drug that is used in experimental pharmacology and physiology for the classification of muscarinic receptor subtypes [2–6]. In functional experiments and radioligand binding studies, HHSiD shows approximately the same high affinity for muscarinic M1, M3 and M4 receptors, whereas its

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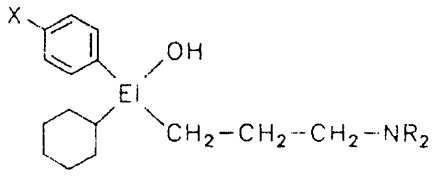
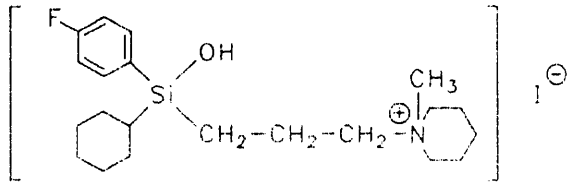




5

	NR_2	X	El
1a		H	C
1b		H	Si
2a		F	C
2b		F	Si
3		F	Si
4		F	Si

Scheme 1

affinity for M2 receptors is lower by more than one order of magnitude. The carbon analogue hexahydro-difenidol (HHD (**1a**); Scheme 1) exhibits a similar affinity profile, but is somewhat less selective in functional studies than the silicon compound **1b** [5]. The selectivity patterns of **1a** and **1b** have recently been confirmed in binding studies involving cloned muscarinic m1–m5 receptors expressed in Chinese hamster ovary cells [7].

In the course of structure–activity relationship studies we synthesized the *p*-fluoro derivatives of HHD and HHSiD, *p*-fluoro-hexahydro-difenidol (*p*-F-HHD (**2a**)) and *p*-fluoro-hexahydro-sila-difenidol (*p*-F-HHSiD (**2b**)) (Scheme 1), and studied the pharmacological properties of these C/Si analogues. These investigations were carried out as a part of our systematic studies of C/Si bioisosterism (for a recent review on this subject, see ref. 8). Like the parent drugs **1a** and **1b**, the derivatives **2a** and **2b** were found to be selective muscarinic antagonists [3,6], the silicon compound **2b** displaying a greater selectivity in functional assays than its carbon analogue **2a** [3]. *p*-Fluoro-hexahydro-sila-difenidol (**2b**) is now a commercially available drug that is used as a selective tool in muscarinic receptor research. Various biological data for this muscarinic antagonist, determined in our and other laboratories, have been published elsewhere [3,6,9–20]. Preliminary results of studies on the metabolism of the C/Si pair **2a**/**2b** in the rat have been described recently [21].

We report here the synthesis of the racemic C/Si analogues **2a** and **2b**. In addition, the synthesis and some antimuscarinic properties of the racemic *p*-F-HHSiD derivatives **3**–**5** (Scheme 1) are described. The muscarinic receptors studied were M1 receptors in rabbit vas deferens, cardiac M2 receptors in guinea-pig atria, and M3 receptors in guinea-pig ileal smooth muscle. The syntheses [22] and some antimuscarinic properties [6,23] of the pure enantiomers of **2a** have been reported elsewhere.

Results and discussion

(a) Syntheses

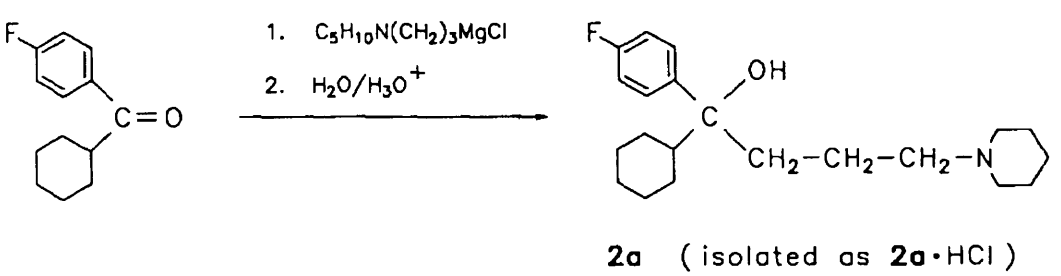
The carbon compound *p*-fluoro-hexahydro-difenidol (**2a**) (isolated as **2a** · HCl) was prepared as shown in Scheme 2 by reaction of cyclohexyl 4-fluorophenyl ketone with (3-piperidinopropyl)magnesium chloride, followed by aqueous workup (overall yield 76%).

The silicon analogue *p*-fluoro-hexahydro-sila-difenidol (**2b**) (isolated as **2b** · HCl) was synthesized by four different procedures, starting from the commercially available (3-chloropropyl)trimethoxysilane (Scheme 3) or tetramethoxysilane (Scheme 4).

As shown in Scheme 3, **2b** was obtained from (3-chloropropyl)trimethoxysilane by two similar four-step routes (overall yields of **2b** · HCl were 39 and 38%, respectively) which differ only in the sequence of introduction of the piperidino and 4-fluorophenyl group. In the first step of both syntheses, the (3-chloropropyl)trimethoxysilane was transformed into the corresponding cyclohexylsilane **6** by reaction with cyclohexylmagnesium chloride by a procedure described in ref. 1. Conversion of **6** with (4-fluorophenyl)lithium into the (4-fluorophenyl)silane **7** and its subsequent reaction with piperidine yielded the (3-piperidinopropyl)silane **8**. Alternatively, **8** was obtained by conversion of the (3-chloropropyl)silane **6** with piperidine into the (3-piperidinopropyl)silane **11**, followed by reaction of the latter with (4-fluorophenyl)lithium. Finally, the silanol **2b** was prepared by acid-catalyzed hydrolysis of the methoxysilane **8** and then isolated as the hydrochloride **2b** · HCl.

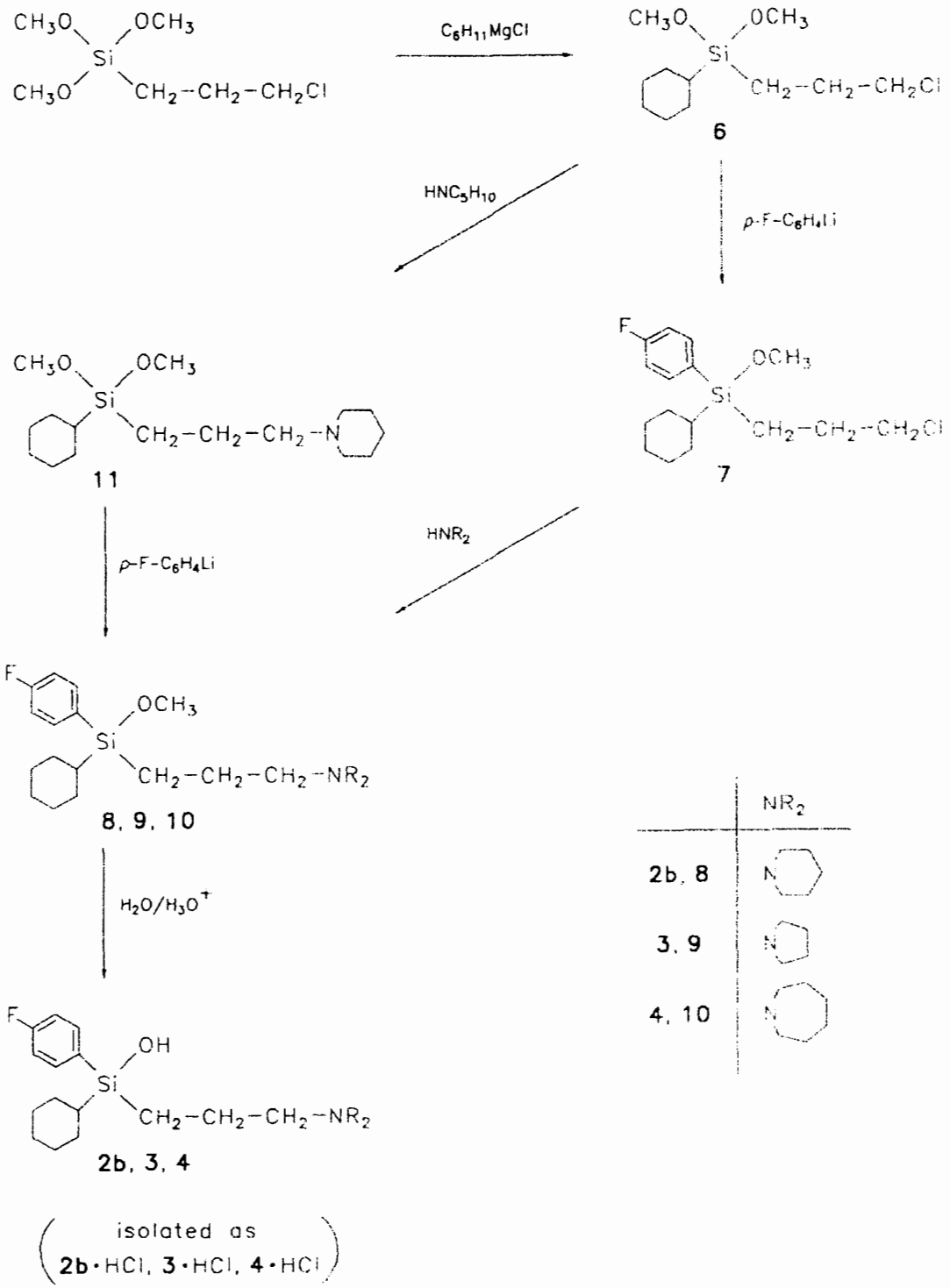
As shown in Scheme 4, **2b** was obtained from tetramethoxysilane by a four-step or a five-step route that differ only in the method used for the formation of the SiOH function (total yield 23 and 12%, respectively; related to **2b** · HCl). In the first step tetramethoxysilane was converted into the corresponding (4-fluorophenyl)silane **12** by reaction with (4-fluorophenyl)lithium. Conversion of **12** by cyclohexylmagnesium chloride into the corresponding cyclohexylsilane **13** and reaction of the latter with (3-piperidinopropyl)magnesium chloride yielded the (3-piperidinopropyl)silane **8**, which upon acid-catalyzed hydrolysis gave the silanol **2b**. Alternatively, **2b** was synthesized by a base-catalyzed hydrolysis of the hydridosilane **14**, which was obtained from the corresponding methoxysilane **8** by reaction with lithium aluminium hydride.

The *p*-fluoro-hexahydro-sila-difenidol derivatives **3** and **4** were prepared by a route analogous to one of those used in the synthesis of **2b** (sequence **7** → **8** → **2b**), as outlined in Scheme 3. In the first step, the (3-pyrrolidinopropyl)silane **9** and the (3-hexamethyleniminopropyl)silane **10** were synthesized by reaction of the (3-chlo-



2a (isolated as **2a**·HCl)

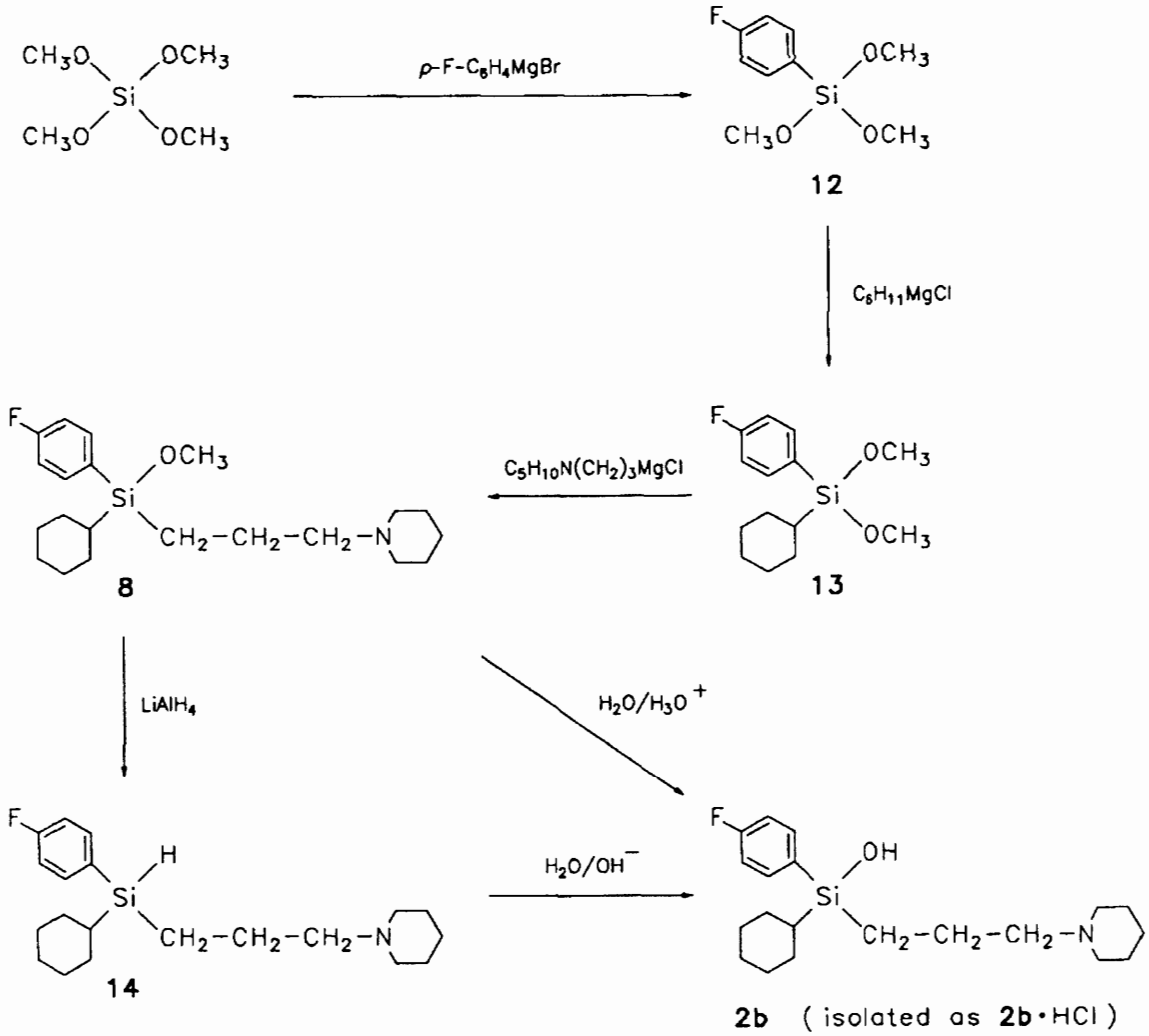
Scheme 2



Scheme 3

ropropyl)silane **7** with pyrrolidine and hexamethylenimine, respectively. Acid-catalyzed hydrolysis of the methoxysilanes **9** and **10** then yielded the corresponding silanols **3** and **4**, which were isolated as the hydrochlorides **3** · HCl and **4** · HCl (total yield 31 and 29%, respectively, based on the (3-chloropropyl)trimethoxysilane initially used).

The methiodide **5** was obtained by quaternization of **2b** with methyl iodide as outlined in Scheme 5 (yield 89%).

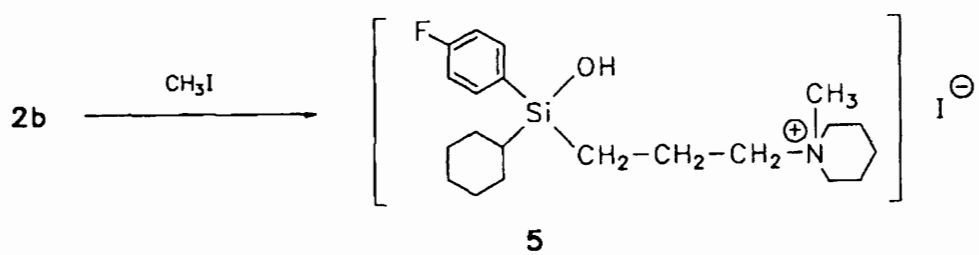


Scheme 4

The silanols **2a** · HCl, **2b** · HCl, **3** · HCl, **4** · HCl and **5** were isolated as pure crystalline compounds, whereas the silanes **6–14** were obtained as pure colourless liquids. The identities of all the new compounds described in this paper were confirmed by elemental analysis and by NMR spectroscopic (^{1}H, ^{13}C, ^{29}Si) and mass spectrometric studies (EI MS, FAB MS).

(b) Pharmacological studies

Neurogenic twitch contractions of rabbit vas deferens were inhibited by the M1 receptor agonist 4-Cl-McN-A-343 [2] (EC_{50} = 25 n*M*). This effect was concentra-



Scheme 5

Table 1

Affinities (pA_2 values) and slopes of Arunlakshana-Schild plots (in parentheses) for *p*-fluoro-hexahydro-difenidol (**2a**), *p*-fluoro-hexahydro-sila-difenidol (**2b**) and compounds **3**–**5** at muscarinic M1 receptors in rabbit vas deferens, M2 receptors in guinea-pig atria and M3 receptors in guinea-pig ileum. The parameters given represent the mean ± s.e.mean. K_D ratios ($pA_2 = -\log K_D$) are given as a measure of receptor selectivity. These values were calculated from the antilog of the differences between the respective pA_2 values

Compound	pA_2 values			Selectivity ratios		
	Vas deferens (M1)	Atria (M2)	Ileum (M3)	M1/M2	M3/M1	M3/M2
2a [a]	7.56 ± 0.07	6.58 ± 0.03	7.93 ± 0.03	9.5	2.3	22
2b [b]	6.68 ± 0.03	6.01 ± 0.06	7.84 ± 0.03	4.7	14	68
3	7.38 ± 0.03	5.94 ± 0.05 [c]	7.12 ± 0.04	28	0.5	15
	(1.10 ± 0.05)		(0.98 ± 0.08)			
4	7.03 ± 0.04	6.04 ± 0.04 [c]	7.17 ± 0.03	9.8	1.4	13
	(1.19 ± 0.05)		(0.96 ± 0.06)			
5	8.47 ± 0.04	7.72 ± 0.03	7.91 ± 0.03	5.6	0.3	1.6
	(0.97 ± 0.07)	(1.02 ± 0.05)	(1.07 ± 0.06)			

[a] Data taken from ref. 3. [b] Data taken from ref. 9. [c] Only two concentrations (1 and 3 μmol/l) of the antagonists were investigated due to the negative inotropic effects of the antagonists themselves at higher concentrations. The pA_2 values were therefore determined from the individual dose ratios according to ref. 26.

tion-dependently antagonized by the *p*-F-HHSiD (**2b**) derivatives **3**–**5**. Similarly, compounds **3**–**5** antagonized the negative inotropic responses in guinea-pig atria (M2 receptors; $EC_{50} = 6$ nM) and ileal contractions (M3 receptors; $EC_{50} = 20$ nM) induced by the potent muscarinic agonist arecaidine propargyl ester [24]. Increasing concentrations of **3**–**5** produced parallel shifts of the agonist concentration-response curves progressively to the right without appreciable 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 (Table 1) were not significantly different from unity. Thus, **3**–**5** were apparently simple competitive muscarinic antagonists at M1, M2 and M3 receptors. These results are summarized in Table 1 (which includes published data for *p*-F-HHD (**2a**) and *p*-F-HHSiD (**2b**) [3,9]), and illustrated in Fig. 1.

Compounds **2a**, **2b** and **3**–**5** showed quite wide variations in their affinities for muscarinic receptors in vas deferens, atria, and ileum, their pA_2 values (Table 1, Fig. 1) differing by more than two orders of magnitude. The influence of the ring size of the cyclic amino group on affinity and receptor selectivity can be seen by comparison of the data for silanols **2b**, **3** and **4**. As with the parent compound, *p*-F-HHSiD (**2b**), the pyrrolidino (**3**) and hexamethylenimino (**4**) analogue exhibited the same affinity at M2 receptors. In contrast, reduction in ring size of **2b** (→ **3**) and ring extension (→ **4**) resulted in an increase and decrease in affinity for M1 and M3 receptors, respectively. Thus, the silanols **3** and **4** show a selectivity pattern (M1 ≈ M3 > M2) similar to that of the carbinol *p*-F-HHD (**2a**) but different from that of its sila-analogue *p*-F-HHSiD (**2b**) (M3 > M1 > M2).

N-Methylation of **2b** (→ **5**) increased the affinity for M1 and M2 receptors by factors of 63 and 50, respectively. In contrast, the affinity for M3 receptors was unaffected. Thus, the methiodide **5** exhibits high affinity, with preference for M1 over M2 and M3 receptors.

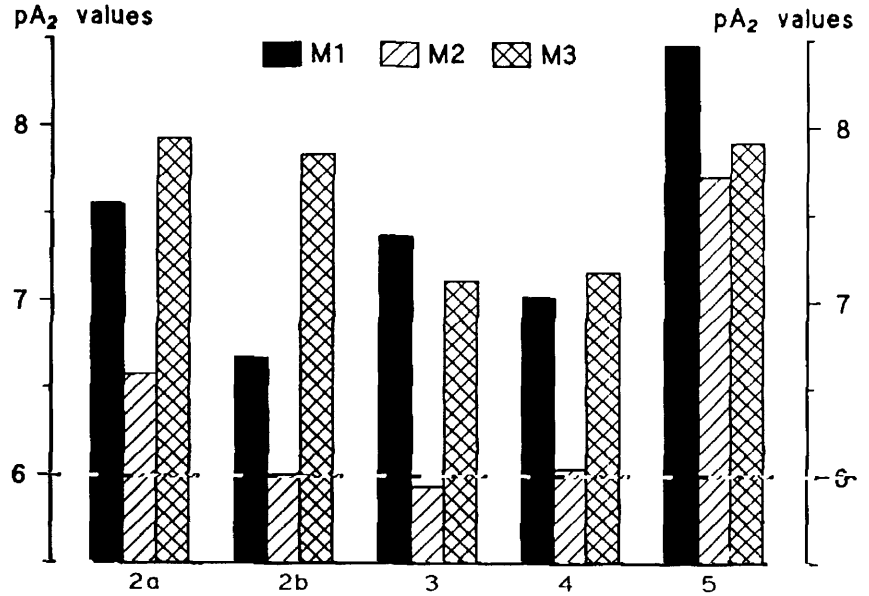


Fig. 1. Affinity profiles of *p*-fluoro-hexahydro-difenidol (**2a**), *p*-fluoro-hexahydro-sila-difenidol (**2b**) and compounds **3**–**5** at muscarinic M1 receptors in rabbit vas deferens, M2 receptors in guinea-pig atria and M3 receptors in guinea-pig ileum.

Experimental

(a) Syntheses

All synthetic procedures were performed under nitrogen and in dry solvents unless stated otherwise. Melting points were determined with a Büchi apparatus (type 510) and are uncorrected. Kugelrohr distillations were performed with a Büchi GKR-50 apparatus. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-400 spectrometer (operating at 400.1 and 100.6 MHz, respectively) and on a Bruker WP-300 spectrometer (operating at 300.1 and 75.5 MHz, respectively). ^{29}Si NMR spectra were recorded on a Bruker WP-300 spectrometer operating at 59.6 MHz. Chemical shifts (ppm) were determined with respect to those of $(CH_3)_4Si$ (^{1}H, δ 0) and $CDCl_3$ (^{13}C, δ 77.05) as internal references and to that of $(CH_3)_4Si$ (^{29}Si, δ 0) as external reference (in the case of **2a** · HCl, CD_3OD was used as internal reference; ^{13}C, δ 49.0). Assignment of the ^{13}C NMR data was supported by DEPT experiments. Mass spectra were obtained with a Varian-MAT-711 and a Finnigan-MAT-8430 mass spectrometer (EI MS: 70 eV; FAB MS: glycerol (liquid matrix), xenon (FAB source)). The *m/z* values given refer to the isotopes ^{1}H, ^{12}C, ^{14}N, ^{16}O, ^{19}F, ^{28}Si, ^{35}Cl and ^{127}I.

*1-Cyclohexyl-1-(4-fluorophenyl)-4-piperidino-1-butanol hydrochloride (*p*-fluoro-hexahydro-difenidol hydrochloride) (**2a** · HCl)*

A Grignard reagent was prepared as described in ref. 1 from 1-chloro-3-piperidinopropane (0.74 g, 4.58 mmol) and magnesium turnings (0.15 g, 6.17 mmol) in THF (5 ml), and was then added dropwise at 0 °C during 5 min to a stirred solution of cyclohexyl 4-fluorophenyl ketone (0.72 g, 3.49 mmol) in diethyl ether (20 ml). After 4 h stirring at room temperature and subsequent heating under reflux for 4 h, saturated aqueous NH_4Cl solution (10 ml) was added at room temperature. The organic phase was separated and the aqueous layer extracted three times with

diethyl ether (3 × 20 ml). After drying of the combined organic layers with anhydrous Na_2SO_4 and removal of the solvent under reduced pressure, the residue was dissolved in diethyl ether (20 ml) and an 0.5 *M* ethereal HCl solution (7.0 ml, 3.5 mmol HCl) was added. The mixture was stirred at room temperature for 10 min and the resulting precipitate was filtered off, washed with diethyl ether (20 ml), and recrystallized from 2-propanol to give 0.98 g (yield 76%) of colourless crystals; m.p. 240 °C. ^{1}H NMR (CD_3OD): δ 0.9–1.3, 1.3–1.6 and 1.6–2.1 (m, 21H; $CCHC_2$, CCH_2C), 2.7–2.9, 2.9–3.1 and 3.3–3.5 (m, 6H; NCH_2C), 7.0–7.1 and 7.35–7.45 (m, 4H; CC_6H_4F), NH and OH not localized. ^{13}C NMR (CD_3OD): δ 20.0, 22.7, 24.2 (2C), 27.6, 27.7, 27.8, 27.9 and 28.5 (CCH_2C), 37.0 ($OCCH_2C$), 50.3 (C-1, CC_6H_{11}), 54.1 (2C) (NCH_2C, NC_5H_{10}), 58.6 ($CCH_2CH_2CH_2N$), 79.3 (COH), 115.3 (d, ^2J(CF) 21.3 Hz; C-3/C-5, CC_6H_4F), 129.1 (d, ^3J(CF) 7.7 Hz; C-2/C-6, CC_6H_4F), 142.0 (d, ^4J(CF) 3.1 Hz; C-1, CC_6H_4F), 162.9 (d, ^1J(CF) 243.4 Hz; C-4, CC_6H_4F). FAB MS: *m/z* 334 (100%, cation of the salt). Anal. Found: C, 68.1; H, 9.1; N, 3.7. $C_{21}H_{33}ClFNO$ (369.9) calc: C, 68.18; H, 8.99; N, 3.79%.

*Cyclohexyl(4-fluorophenyl)(3-piperidinopropyl)silanol hydrochloride (p-fluoro-hexahydro-sila-difenidol hydrochloride) (**2b** · HCl)*

Method a. Hydrochloric acid (0.5 *M*, 430 ml) was added to a stirred solution of **8** (5.50 g, 15.1 mmol) in 2-propanol (160 ml). The clear mixture was stirred at room temperature for 16 h and pH was then adjusted to 8 with 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 was dissolved in diethyl ether (100 ml) and 0.5 *M* ethereal HCl (30.0 ml, 15.0 mmol HCl) was added at room temperature. After 15 min stirring at room temperature, the crude product was filtered off and recrystallized from 2-propanol to give 5.00 g (yield 86%) of colourless crystals; m.p. 187 °C. For analytical data, see below.

Method b. A mixture of **14** (0.60 g, 1.79 mmol) and KOH (11 mg, 0.2 mmol) in ethanol/water (96/4, v/v) (25 ml) was stirred for 24 h at room temperature. After removal of the solvent under reduced pressure, water (10 ml) and 2-propanol (5 ml) were added and the resulting mixture was extracted three times with diethyl ether (3 × 10 ml). The combined extracts were dried over anhydrous Na_2SO_4, the solvent removed under reduced pressure, and the residue dissolved in diethyl ether (10 ml). After addition of 1.3 *M* ethereal HCl (1.5 ml, 2.0 mmol HCl), the mixture was stirred at room temperature for 15 min, and the crude product then filtered off, washed with diethyl ether, and recrystallized from 2-propanol to give 0.38 g (yield 55%) of colourless crystals; m.p. 187 °C.

^{1}H NMR ($CDCl_3$): δ 0.7–2.2 (m, 21H; $SiCH_2C$, $SiCHC_2$, CCH_2C), 2.5–2.7, 2.8–3.0 and 3.3–3.4 (m, 6H; NCH_2C), 5.2 ('s', broad, 1H; SiOH), 6.9–7.0 and 7.5–7.6 (m, 4H; SiC_6H_4F), 10.9 ('s', broad, 1H; NH). ^{13}C NMR ($CDCl_3$): δ 9.8 ($SiCH_2C$), 17.6, 21.8 and 22.5 (2C) (CCH_2C), 26.2 (C-1, SiC_6H_{11}), 26.4, 26.6 (2C), 27.5 and 27.6 (CCH_2C), 52.6 and 52.9 (NCH_2C, NC_5H_{10}), 59.1 ($SiCH_2CH_2CH_2N$), 114.7 (d, ^2J(CF) 19.5 Hz; C-3/C-5, SiC_6H_4F), 132.0 (d, ^4J(CF) 3.7 Hz; C-1, SiC_6H_4F), 135.7 (d, ^3J(CF) 7.4 Hz; C-2/C-6, SiC_6H_4F), 163.6 (d, ^1J(CF) 248.0 Hz; C-4, SiC_6H_4F). ^{29}Si NMR ($CDCl_3$): δ 1.3. FAB MS: *m/z* 350 (100%, cation of the salt). Anal. Found: C, 62.6; H, 8.9; N, 3.6. $C_{20}H_{33}ClFNOSi$ (386.0) calc: C, 62.23; H, 8.62; N, 3.63%.

*Cyclohexyl(4-fluorophenyl)(3-pyrrolidinopropyl)silanol hydrochloride (**3** · HCl)*

Prepared as described for the synthesis of **2b** · HCl (method a), by hydrolysis of **9** (7.00 g, 20.0 mmol) in a mixture of 0.5 *M* hydrochloric acid (570 ml) and 2-propanol (210 ml) and subsequent transformation of the crude amine **3** into its hydrochloride by reaction with 0.5 *M* ethereal HCl (40.0 ml, 20.0 mmol HCl). Yield 5.22 g (70%) of colourless crystals; m.p. 150 °C (2-propanol). ^{1}H NMR ($CDCl_3$): δ 0.8–1.2 and 1.6–2.1 (m, 19H; $SiCH_2C$, $SiCHC_2$, CCH_2C), 2.7–3.1 and 3.6–3.7 (m, 6H; NCH_2C), 5.1 ('s', broad, 1H; SiOH), 6.9–7.0 and 7.5–7.6 (m, 4H; SiC_6H_4F), 11.2 ('s', broad, 1H; NH). ^{13}C NMR ($CDCl_3$): δ 9.9 ($SiCH_2C$), 19.7 and 23.1 (2C) (CCH_2C), 26.2 (C-1, SiC_6H_{11}), 26.5, 26.6 (2C), 27.57 and 27.62 (CCH_2C), 53.2 and 53.5 (NCH_2C, NC_4H_8), 57.3 ($SiCH_2CH_2CH_2N$), 114.8 (d, ^2J(CF) 19.5 Hz; C-3/C-5, SiC_6H_4F), 131.8 (d, ^4J(CF) 3.6 Hz; C-1, SiC_6H_4F), 135.8 (d, ^3J(CF) 7.2 Hz; C-2/C-6, SiC_6H_4F), 163.7 (d, ^1J(CF) 248.2 Hz; C-4, SiC_6H_4F). ^{29}Si NMR ($CDCl_3$): δ 1.6. FAB MS: *m/z* 707 (2%, 2 × cation of the salt + Cl^-), 336 (100%, cation of the salt). Anal. Found: C, 61.6; H, 8.6; N, 3.8. $C_{19}H_{31}ClFNOSi$ (372.0) calc: C, 61.35; H, 8.40; N, 3.77%.

*Cyclohexyl(4-fluorophenyl)(3-hexamethyleniminopropyl)silanol hydrochloride (**4** · HCl)*

Prepared as described for the synthesis of **2b** · HCl (method a), by hydrolysis of **10** (7.00 g, 18.5 mmol) in a mixture of 0.5 *M* hydrochloric acid (530 ml) and 2-propanol (195 ml) and subsequent transformation of the crude amine **4** into its hydrochloride by reaction with 0.5 *M* ethereal HCl solution (37.0 ml, 18.5 mmol HCl). Yield 4.64 g (63%) of colourless crystals; m.p. 185° (2-propanol). ^{1}H NMR ($CDCl_3$): δ 0.7–2.1 (m, 23H; $SiCH_2C$, $SiCHC_2$, CCH_2C), 2.8–3.0 and 3.3–3.5 (m, 6H; NCH_2C), 5.2 ('s', broad, 1H; SiOH), 6.9–7.0 and 7.5–7.6 (m, 4H; SiC_6H_4F), 10.9 ('s', broad, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 9.8 ($SiCH_2C$), 18.0 and 23.1 (2C) (CCH_2C), 26.2 (C-1, SiC_6H_{11}), 26.4, 26.5, 27.5 and 27.6 (in total 7C) (CCH_2C), 53.8 and 54.2 (NCH_2C, NC_6H_{12}), 59.3 ($SiCH_2CH_2CH_2N$), 114.6 (d, ^2J(CF) 19.5 Hz; C-3/C-5, SiC_6H_4F), 132.0 (d, ^4J(CF) 3.5 Hz; C-1, SiC_6H_4F), 135.7 (d, ^3J(CF) 7.3 Hz; C-2/C-6, SiC_6H_4F), 163.6 (d, ^1J(CF) 248.1 Hz; C-4, SiC_6H_4F). ^{29}Si NMR ($CDCl_3$): δ 1.6. FAB MS: *m/z* 763 (2%, 2 × cation of the salt + Cl^-), 364 (100%, cation of the salt). Anal. Found: C, 63.5; H, 8.9; N, 3.5. $C_{21}H_{35}ClFNOSi$ (400.1) calc: C, 63.05; H, 8.82; N, 3.50%.

*Cyclohexyl(4-fluorophenyl)(3-piperidinopropyl)silanol methiodide (**5**)*

Methyl iodide (2.60 g, 18.3 mmol) was added to a solution of **2b** (2.80 g, 8.01 mmol) in ethanol (**2b** was obtained from **2b** · HCl by reaction with NaOH and subsequent aqueous workup). The mixture was stirred at 30 °C for 3 h, pentane (75 ml) was added dropwise, and the mixture stirred for a further 90 min. The precipitate was filtered off, washed with pentane (25 ml), dried *in vacuo*, and recrystallized from acetone/pentane to give 3.50 g (yield 89%) of colourless crystals; m.p. 98 °C. ^{1}H NMR ($CDCl_3$): δ 0.8–1.2 and 1.6–2.1 (m, 21H; $SiCH_2C$, $SiCHC_2$, CCH_2C), 3.07 (s, 3H; NCH_3), 3.5–3.6 (m, 6H; NCH_2C), 4.4 ('s', broad, 1H; SiOH), 7.0–7.1 and 7.6–7.7 (m, 4H; SiC_6H_4F). ^{13}C NMR ($CDCl_3$): δ 9.3 ($SiCH_2C$), 18.3, 20.0 (2C), 20.5, 26.5, 26.6 (2C), 27.3 and 27.6 (CCH_2C), 28.2 (C-1, SiC_6H_{11}), 48.3 (NCH_3), 61.0, 61.1 and 65.7 (NCH_2C), 114.8 (d, ^2J(CF) 19.6 Hz; C-3/C-5, SiC_6H_4F), 131.5 (d, ^{4}8iJ(CF) 3.8 Hz; C-1, SiC_6H_4F), 136.0 (d, ^3J(CF) 7.4 Hz;

C-2/C-6, SiC_6H_4F), 163.7 (d, ^1J(CF) 248.2 Hz; C-4, SiC_6H_4F). FAB MS: *m/z* 364 (100%, cation of the salt). Anal. Found: C, 51.7; H, 7.1; N, 3.0. $C_{21}H_{35}FINOSi$ (491.5) calc: C, 51.32; H, 7.18; N, 2.85%.

(3-Chloropropyl)cyclohexyldimethoxysilane (6)

Synthesis as described in ref. 1 (yield 71%).

(3-Chloropropyl)cyclohexyl(4-fluorophenyl)methoxysilane (7)

A 1.6 *M* solution of n-butyllithium (0.20 mol) in n-hexane (125 ml) was added dropwise at −45 °C during 30 min to a stirred solution of 1-bromo-4-fluorobenzene (35.0 g, 0.20 mol) in diethyl ether (250 ml). The mixture was stirred at −30 °C for 1 h then added dropwise at −10 °C during 1 h to a stirred solution of **6** (50.2 g, 0.20 mol) in diethyl ether (200 ml). The mixture was stirred at room temperature for 16 h, then saturated aqueous NH_4Cl solution (400 ml) was added at 0 °C and the organic layer separated. The aqueous phase was extracted three times with diethyl ether (3 × 50 ml) and the combined organic extracts were dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the residue was distilled *in vacuo* (Vigreux column) to give 48.0 g (yield 76%) of a colourless liquid; b.p. 120 °C/0.1 Torr. ^{1}H NMR ($CDCl_3$): δ 0.9–1.3 and 1.6–1.9 (m, 15H; $SiCH_2C$, $SiCHC_2$, CCH_2C), 3.53 (s, 3H; OCH_3), 3.53 (t, 2H; CCH_2Cl), 7.0–7.1 and 7.4–7.5 (m, 4H; SiC_6H_4F). ^{13}C NMR ($CDCl_3$): δ 9.2 ($SiCH_2C$), 25.2 (C-1, SiC_6H_{11}), 26.7, 26.8, 26.9 (2C), 27.8 and 27.9 (CCH_2C), 47.9 (CCH_2Cl), 51.4 (OCH_3), 115.1 (d, ^2J(CF) 19.5 Hz; C-3/C-5, SiC_6H_4F), 130.1 (d, ^4J(CF) 3.9 Hz; C-1, SiC_6H_4F), 136.1 (d, ^3J(CF) 7.5 Hz; C-2/C-6, SiC_6H_4F), 164.1 (d, ^1J(CF) 248.8 Hz; C-4, SiC_6H_4F). ^{29}Si NMR ($CDCl_3$): δ 5.4. EI MS: *m/z* 237 (9%, $M^+ - C_3H_6Cl$), 231 (45%, $M^+ - C_6H_{11}$), 189 (100%, $C_7H_7ClFOSi^+$). Anal. Found: C, 61.2; H, 7.7. $C_{16}H_{24}ClFOSi$ (314.9) calc: C, 61.03; H, 7.68%.

Cyclohexyl(4-fluorophenyl)methoxy(3-piperidinopropyl)silane (8)

Method a. A solution of **7** (15.0 g, 47.6 mmol) and piperidine (12.2 g, 143 mmol) in methanol (25 ml) was heated under reflux for 16 h. After removal of the solvent under reduced pressure, n-pentane (100 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 residue distilled *in vacuo* (Vigreux column) to give 14.7 g (yield 85%) of an oily liquid; b.p. 151 °C/0.001 Torr. For analytical data, see below.

Method b. A 1.6 *M* solution of n-butyllithium (0.10 mol) in n-hexane (63.0 ml) was added dropwise at −35 °C during 30 min to a stirred solution of 1-bromo-4-fluorobenzene (17.5 g, 0.10 mol) in diethyl ether (100 ml). The mixture was stirred at −35 °C for 2 h then added dropwise at 0 °C during 30 min to a stirred solution of **11** (25.9 g, 86.5 mmol) in diethyl ether (200 ml). The mixture was stirred at room temperature for 16 h, then saturated aqueous NH_4Cl solution (100 ml) was added. The organic phase was separated and the aqueous layer extracted three times with diethyl ether (3 × 300 ml). The combined organic extracts were washed with water (20 ml) and 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 21.9 g (yield 70%) of a colourless liquid; b.p. 151 °C/0.001 Torr. For analytical data, see below.

Method c. A Grignard reagent was prepared according to ref. 1 from 1-chloro-3-piperidinopropane (7.44 g, 46.0 mmol) and magnesium turnings (1.46 g, 60.1 mmol) in THF (25 ml) and was then added dropwise at 0 °C during 1 h to a stirred solution of **13** (9.50 g, 35.4 mmol) in diethyl ether (150 ml). After stirring at room temperature for 15 h and heating under reflux for 8 h, saturated aqueous NH_4Cl solution (80 ml) was added at room temperature. The organic phase was separated and the aqueous layer extracted three times with diethyl ether (3 × 40 ml). After drying of the combined organic extracts over anhydrous Na_2SO_4 and removal of the solvent under reduced pressure, the oily residue was distilled *in vacuo* (Vigreux column) to give 10.1 g (yield 78%) of an oily liquid; b.p. 151 °C/0.001 Torr.

^{1}H NMR ($CDCl_3$): δ 0.8–1.3 and 1.4–1.8 (m, 21H; $SiCH_2C$, $SiCHC_2$, CCH_2C), 2.3–2.4 (m, 6H; NCH_2C), 3.49 (s, 3H; OCH_3), 7.0–7.1 and 7.4–7.5 (m, 4H; SiC_6H_4F). ^{13}C NMR ($CDCl_3$); δ 9.3 ($SiCH_2C$), 20.4 and 24.5 (CCH_2C), 25.2 (C-1, SiC_6H_{11}), 25.9 (2C), 26.8, 26.9 (2C), 27.8 and 27.9 (CCH_2C), 51.4 (OCH_3), 54.6 (2C) (NCH_2C, NC_5H_{10}), 63.1 ($SiCH_2CH_2CH_2N$), 114.9 (d, ^2J(CF) 19.5 Hz; C-3/C-5, SiC_6H_4F), 130.6 (d, ^4J(CF) 3.7 Hz; C-1, SiC_6H_4F), 136.2 (d, ^3J(CF) 7.3 Hz; C-2/C-6, SiC_6H_4F), 164.0 (d, ^1J(CF) 248.4 Hz; C-4, SiC_6H_4F). ^{29}Si NMR ($CDCl_3$): δ 5.9. EI MS: *m/z* 363 (3%, M^+), 98 (100%, $CH_2{=}NC_5H_{10}^+$). Anal. Found: C, 69.5; H, 9.4; N, 3.8. $C_{21}H_{34}FNOSi$ (363.6) calc: C, 69.37; H, 9.43; N, 3.85%.

Cyclohexyl(4-fluorophenyl)methoxy(3-pyrrolidinopropyl)silane (9)

Prepared as described for the synthesis of **8** (method a) by reaction of **7** (15.0 g, 47.6 mmol) with pyrrolidine (10.2 g, 143 mmol) in methanol (25 ml). Yield 13.8 g (83%) of an oily liquid; b.p. 153 °C/0.001 Torr. ^{1}H NMR ($CDCl_3$): δ 0.8–1.0, 1.1–1.2 and 1.5–1.8 (m, 19H; $SiCH_2C$, $SiCHC_2$, CCH_2C), 2.4–2.5 (m, 6H; NCH_2C), 3.49 (s, 3H; OCH_3), 7.0–7.1 and 7.4–7.5 (m, 4H; SiC_6H_4F). ^{13}C NMR ($CDCl_3$): δ 9.5 ($SiCH_2C$), 22.7 and 23.4 (2C) (CCH_2C), 25.2 (C-1, SiC_6H_{11}), 26.8, 26.9 (2C), 27.8 and 27.9 (CCH_2C), 51.4 (OCH_3), 54.2 (2C) (NCH_2C, NC_4H_8), 60.1 ($SiCH_2CH_2CH_2N$), 114.9 (d, ^2J(CF) 19.4 Hz; C-3/C-5, SiC_6H_4F), 130.6 (d, ^4J(CF) 3.7 Hz; C-1, SiC_6H_4F), 136.1 (d, ^3J(CF) 7.2 Hz; C-2/C-6, SiC_6H_4F), 163.9 (d, ^1J(CF) 248.3 Hz; C-4, SiC_6H_4F). ^{29}Si NMR ($CDCl_3$): δ 5.9. EI MS: *m/z* 349 (2%, M^+), 84 (100%, $CH_2{=}NC_4H_8^+$). Anal. Found: C, 68.8; H, 9.3; N, 4.1. $C_{20}H_{32}FNOSi$ (349.6) calc: C, 68.72; H, 9.23; N, 4.01%.

Cyclohexyl(4-fluorophenyl)(3-hexamethyleniminopropyl)methoxysilane (10)

Prepared as described for the synthesis of **8** (method a) by reaction of **7** (15.0 g, 47.6 mmol) with hexamethylenimine (14.2 g, 143 mmol) in methanol (25 ml). Yield 15.3 g (85%) of an oily liquid; b.p. 166 °C/0.001 Torr. ^{1}H NMR ($CDCl_3$): δ 0.8–0.9, 1.0–1.2 and 1.5–1.7 (m, 23H; $SiCH_2C$, $SiCHC_2$, CCH_2C), 2.4–2.6 (m, 6H; NCH_2C), 3.49 (s, 3H; OCH_3), 7.0–7.1 and 7.4–7.5 (m, 4H; SiC_6H_4F). ^{13}C NMR ($CDCl_3$): δ 9.2 ($SiCH_2C$), 21.0 (CCH_2C), 25.2 (C-1, SiC_6H_{11}), 26.8, 26.9 (2C), 27.0 (2C), 27.8, 27.9 and 28.0 (2C) (CCH_2C), 51.4 (OCH_3), 55.6 (2C) (NCH_2C, NC_6H_{12}), 61.8 ($SiCH_2CH_2CH_2N$), 114.9 (d, ^2J(CF) 19.7 Hz; C-3/C-5, SiC_6H_4F), 130.7 (d, ^4J(CF) 3.8 Hz; C-1, SiC_6H_4F), 136.2 (d, ^3J(CF) 7.2 Hz; C-2/C-6, SiC_6H_4F), 163.9 (d, ^1J(CF) 248.6 Hz; C-4, SiC_6H_4F). ^{29}Si NMR ($CDCl_3$): δ 6.1. EI MS: *m/z* 377 (6%, M^+), 112 (100%, $CH_2{=}NC_6H_{12}^+$). Anal. Found: C, 70.1; H, 9.7; N, 3.7. $C_{22}H_{36}FNOSi$ (377.6) calc: C, 69.98; H, 9.61; N, 3.71%.

*Cyclohexyldimethoxy(3-piperidinopropyl)silane (**11**)*

A solution of **6** (50.1 g, 0.20 mol) and piperidine (51.1 g, 0.60 mol) in methanol (100 ml) was heated under reflux for 16 h. The solvent was removed under reduced pressure and diethyl ether (100 ml) and saturated aqueous NH_4Cl solution (100 ml) were added. The organic layer was separated and the aqueous phase extracted three times with diethyl ether (3 × 100 ml). The combined organic extracts were washed with water (15 ml) and dried over anhydrous Na_2SO_4. After removal of the solvent, the oily residue was distilled *in vacuo* (Vigreux column) to give 52.5 g (yield 88%) of a colourless liquid: b.p. 112 °C/0.05 Torr. ^{1}H NMR ($CDCl_3$): δ 0.2–0.3, 0.4–0.6 and 0.9–1.5 (m, 21H; $SiCH_2C$, $SiCHC_2$, CCH_2C), 2.0–2.1 (m, 6H; NCH_2C), 3.20 (s, 6H; OCH_3). ^{13}C NMR ($CDCl_3$): δ 7.8 ($SiCH_2C$), 19.8 (CCH_2C), 24.1 (C-1, SiC_6H_{11}), 24.1, 25.6, 26.3, 26.4 and 27.4 (CCH_2C), 49.9 (OCH_3), 54.2 (NCH_2C, NC_5H_{10}), 62.5 ($SiCH_2CH_2CH_2N$). FAB MS: *m/z* 300 (20%, $(M + H)^+$), 98 (100%, $CH_2{=}NC_5H_{10}^+$). Anal. Found: C, 64.2; H, 11.6; N, 4.7. $C_{17}H_{33}NO_2Si$ (299.5) calc: C, 64.16; H, 11.10; N, 4.68%.

*(4-Fluorophenyl)trimethoxysilane (**12**)*

A Grignard reagent was prepared from 1-bromo-4-fluorobenzene (87.6 g, 0.50 mol) and magnesium turnings (12.5 g, 0.51 mol) in diethyl ether (300 ml) and then added dropwise at 0 °C during 4.5 h to a stirred solution of tetramethoxysilane (75.7 g, 0.50 mol) in diethyl ether (1 l). The mixture was stirred at room temperature for 15 h then heated under reflux for 4 h. The precipitate was filtered off and washed with n-pentane, the filtrate was combined with the washings and the solvent removed under reduced pressure. Then n-pentane (500 ml) was added and the mixture kept for 5 h at −20 °C. The precipitate formed was filtered off, the solvent of the filtrate was evaporated under reduced pressure and the residue distilled *in vacuo* (Vigreux column) to give 44.8 g (yield 42%) of a colourless liquid: b.p. 79 °C/10 Torr. ^{1}H NMR ($CDCl_3$): δ 3.60 (s, 9H; OCH_3), 7.0–7.1 and 7.6–7.7 (m, 4H; SiC_6H_4F). ^{13}C NMR ($CDCl_3$): δ 50.9 (OCH_3), 115.3 (d, ^2J(CF) 19.9 Hz; C-3/C-5, SiC_6H_4F), 125.1 (d, ^4J(CF) 3.9 Hz; C-1, SiC_6H_4F), 137.0 (d, ^3J(CF) 7.8 Hz; C-2/C-6, SiC_6H_4F), 164.7 (d, ^1J(CF) 250.0 Hz; C-4, SiC_6H_4F). ^{29}Si NMR ($CDCl_3$): δ −55.0. EI MS: *m/z* 216 (69%, M^+), 91 (100%, $C_2H_3O_2Si^+$). Anal. Found: C, 50.1; H, 6.1. $C_9H_{13}FO_3Si$ (216.3) calc: C, 49.98; H, 6.06%.

*Cyclohexyl(4-fluorophenyl)dimethoxysilane (**13**)*

A Grignard reagent was prepared from cyclohexyl chloride (23.8 g, 0.20 mol) and magnesium turnings (5.35 g, 0.22 mol) in diethyl ether (75 ml) and then added dropwise at 0 °C during 3 h to a stirred solution of **12** (43.4 g, 0.20 mol) in diethyl ether (500 ml). The mixture was stirred at room temperature for 5 h then heated under reflux for 5 h, and the precipitate then filtered off and washed with n-pentane. The filtrate was combined with the washings, the solvent removed under reduced pressure, and the residue distilled *in vacuo* (Vigreux column) to give 44.7 g (yield 83%) of a colourless liquid: b.p. 99 °C/0.7 Torr. ^{1}H NMR ($CDCl_3$): δ 1.0–1.3 and 1.6–1.8 (m, 11H; SiC_6H_{11}), 3.58 (s, 6H; OCH_3), 7.0–7.1 and 7.5–7.6 (m, 4H; SiC_6H_4F). ^{13}C NMR ($CDCl_3$): δ 24.2 (C-1, SiC_6H_{11}), 26.6 (2C), 26.7 and 27.7 (2C) (CCH_2C), 50.8 (OCH_3), 115.0 (d, ^2J(CF) 19.8 Hz; C-3/C-5, SiC_6H_4F), 127.8 (d, ^4J(CF) 3.8 Hz; C-1, SiC_6H_4F), 136.8 (d, ^3J(CF) 7.6 Hz; C-2/C-6, SiC_6H_4F), 164.3 (d, ^1J(CF) 249.0 Hz; C-4, SiC_6H_4F). ^{29}Si NMR ($CDCl_3$): δ −19.1.

EI MS: m/z 268 (2%, M^+), 185 (100%, $M^+ - C_6H_{11}$). Anal. Found: C, 62.7; H, 7.9. $C_{14}H_{21}FO_2Si$ (268.4) calc: C, 62.65; H, 7.89%.

*Cyclohexyl(4-fluorophenyl)(3-piperidinopropyl)silane (**14**)*

A solution of **8** (2.00 g, 5.50 mmol) in di-n-butyl ether (5 ml) was added dropwise at room temperature during 15 min to a stirred suspension of lithium aluminium hydride (0.42 g, 11.1 mmol) in di-n-butyl ether (15 ml). The mixture was under reflux for 16 h and the insoluble material then filtered off and the solvent removed from the filtrate under reduced pressure. The residue was purified by Kugelrohr distillation (150 °C/0.005 Torr) to give 1.50 g (yield 82%) of a colourless liquid. ^{1}H NMR ($CDCl_3$): δ 0.7–1.0, 1.1–1.2 and 1.4–1.7 (m, 21H; $SiCH_2C$, $SiCHC_2$, CCH_2C), 2.2–2.3 (m, 6H; NCH_2C), 4.1 (m, centre, 1H; SiH), 7.0–7.1 and 7.4–7.5 (m, 4H; SiC_6H_4F). ^{13}C NMR ($CDCl_3$): δ 8.0 ($SiCH_2$1C), 22.0 (CCH_2C), 23.6 (C-1, SiC_6H_{11}), 24.5, 26.0 (2C), 26.7, 27.81, 27.83, 28.2 and 28.3 (CCH_2C), 54.6 (2C) (NCH_2C, NC_5H_{10}), 62.8 ($SiCH_2CH_2CH_2N$), 115.0 (d, ^2J(CF) 19.5 Hz; C-3/C-5, SiC_6H_4F), 130.3 (d, ^4J(CF) 3.9 Hz; C-1, SiC_6H_4F), 136.9 (d, ^3J(CF) 7.2 Hz; C-2/C-6, SiC_6H_4F), 163.8 (d, ^1J(CF) 248.0 Hz; C-4, SiC_6H_4F). ^{29}Si NMR ($CDCl_3$): δ −4.5. EI MS: m/z 333 (< 1%, M^+), 98 (100%, $CH_2{=}NC_5H_{10}^+$). Anal. Found: C, 72.0; H, 9.7; N, 4.2. $C_{20}H_{32}FNSi$ (333.6) calc: C 72.02; H, 9.67; N, 4.20%.

(b) Pharmacological studies

Rabbit isolated vas deferens

Experiments on rabbit isolated vas deferens were carried out as described in ref. 2. Briefly, male New Zealand white rabbits were killed by i. v. injection of pentobarbital sodium (120 mg/kg). Vasa deferentia were isolated and segments of 1.5 cm length were set up in 6 ml organ baths containing modified Krebs buffer (Ca^{++} concentration was 1.0 mM). The bathing fluid was maintained at 31 °C and aerated with 95% O_2/5% CO_2. A basal tension of 750 mg was applied and after a 30 min period of initial equilibration neurogenic isometric twitch contractions were elicited by electrical field stimulation (0.05 Hz, 0.5 ms, 40 V). These effects were concentration-dependently inhibited by the M1 receptor agonist 4-(4-chlorophenylcarbamoyloxy)-2-butynyltrimethylammonium iodide (4-Cl-McN-A-343, synthesized as described in ref. 24) [2].

Guinea-pig isolated left atria and ileal longitudinal muscle

Left atria and strips of ileal longitudinal muscle from adult guinea pigs were set up in 6 ml organ baths, under 500 mg tension, in oxygenated (95% O_2/5% CO_2) Tyrode solution (32 °C). Arecaidine propargyl ester (made as described in ref. 25) was used as an agonist [3]. Left atria were paced electrically (2 Hz, 3 ms, 5 V). Negative inotropic effects to the agonist were measured as changes in isometric tension. Responses of ileal longitudinal muscle strips to arecaidine propargyl ester were measured as isotonic contractions.

Antagonist affinities

Concentration-response curves were constructed by cumulative addition of the agonists. When these responses were constant, concentration-response curves were repeatedly obtained in the presence of antagonists. Two to five different concentra-

tions of each antagonist were used (log concentration interval 0.5; $n = 4$–6 for each conc.). The antagonists were allowed to equilibrate for 30–60 min (vas deferens and ileum) and 1 h (atria), respectively. EC_{50} values of agonists in the absence and presence of antagonists were determined graphically for calculation of dose-ratios. The slopes of the Arunlakshana–Schild plots [26] were determined by least squares linear regression. pA_2 ($= -\log K_D$) values, a measure of the antimuscarinic potencies of the antagonists, were estimated as the intercept on the abscissa scale by fitting to the data the best straight line with a slope of unity [26]. All data (see Table 1) are presented as means ± s.e.means of 8–18 experiments. Differences between mean values were tested for statistical significance by Student's t test; $P < 0.05$ was accepted as being significant.

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References

1 R. Tacke, H. Linoh, H. Zilch, J. Wess, U. Moser, E. Mutschler and G. Lambrecht, Liebigs Ann. Chem., (1985) 2223.
2 M. Eltze, G. Gmelin, J. Wess, C. Strohmann, R. Tacke, E. Mutschler and G. Lambrecht, Eur. J Pharmacol., 158 (1988) 233.
3 G. Lambrecht, R. Feifel, M. Wagner-Röder, C. Strohmann, H. Zilch, R. Tacke, M. Waelbroeck, J. Christophe, H. Boddeke and E. Mutschler, Eur. J. Pharmacol., 168 (1989) 71.
4 M. Waelbroeck, M. Tastenoy, J. Camus, J. Christophe, C. Strohmann, H. Linoh, H Zilch, R. Tacke, E. Mutschler and G. Lambrecht, Br. J. Pharmacol., 98 (1989) 197.
5 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.
6 M. Waelbroeck, J. Camus, M. Tastenoy, E. Mutschler, C. Strohmann, R. Tacke, G. Lambrecht and J. Christophe, Eur. J. Pharmacol. Mol. Pharmacol. Sect., 206 (1991) 95.
7 N.J. Buckley, T.I. Bonner, C.M. Buckley and M.R. Brann, Mol. Pharmacol., 35 (1989) 469.
8 R. Tacke and H. Linoh, in S. Patai and Z. Rappoport (Eds.), The Chemistry of Organic Silicon Compounds, Part 2, John Wiley & Sons Ltd., Chichester, 1989, pp. 1143–1206.
9 G. Lambrecht, R. Feifel, B. Forth, C. Strohmann, R. Tacke and E. Mutschler, Eur. J. Pharmacol., 152 (1988) 193.
10 C. Polidori, M. Massi, G. Lambrecht, E. Mutschler, R. Tacke and C. Melchiorre, Eur. J. Pharmacol., 179 (1990) 159.
11 R.M. Eglen, A.D. Michel, W.W. Montgomery, E.A. Kunysz, C.A. Machado and R.L. Whiting, Br. J. Pharmacol., 99 (1990) 637.
12 R.M. Eglen, C.M. Cornett and R.L. Whiting, Naunyn-Schmiedeberg's Arch. Pharmacol., 342 (1990) 394.
13 R.B. Barlow, D.W. Holdup, G. Harris, M.A. Veale and A. Williams, Br. J. Pharmacol., 99 (1990) 622.
14 S.P. Duckles, Eur. J. Pharmacol., 185 (1990) 227.
15 W. Kromer, E. Baron, M. Beinborn, R. Boer and M. Eltze, Naunyn-Schmiedeberg's Arch. Pharmacol., 341 (1990) 165.
16 L.M. Candell, S.H. Yun, L.L.P. Tran and F.J. Ehlert, Mol. Pharmacol., 38 (1990) 689.
17 R. Feifel, J.F. Rodrigues de Miranda, C. Strohmann, R. Tacke, A.J. Aasen, E. Mutschler and G. Lambrecht, Eur. J. Pharmacol., 195 (1991) 115.

18 F. Dörje, J. Wess, G. Lambrecht, R. Tacke, E. Mutschler and M.R. Brann, J. Pharmacol. Exp. Ther., 256 (1991) 727.
19 C. Polidori, P.L. Pompei, M. Perfumi, C. Melchiorre and M. Massi, Eur. J. Pharmacol., 195 (1991) 139.
20 M. Massi, A. Sajia, C. Polidori, M. Perfumi, G. Costa and C. Melchiorre, Eur. J. Pharmacol., 195 (1991) 245.
21 R. Tacke, S. Brakmann, M. Kropfgans, C. Strohmann, F. Wuttke, G. Lambrecht, E. Mutschler, P. Proksch, H.-M. Schiebel and L. Witte, in A.R. Bassindale and P.P. Gaspar (Eds.), Frontiers of Organosilicon Chemistry, Royal Society of Chemistry, London, 1991, pp. 218–228.
22 C. Strohmann, S. Bauerecker, H.K. Cammenga, P.G. Jones, E. Mutschler, G. Lambrecht and R. Tacke, Liebigs Ann. Chem., (1991) 523.
23 G. Lambrecht, T.P. Friebe, R. Feifel, N. Rettenmayr, M. Wagner-Röder, C. Strohmann, R. Tacke and E. Mutschler, Arch. Pharm. (Weinheim), 323 (1990) 790.
24 W.L. Nelson, D.S. Freeman and F.F. Vinzenzi, J. Med. Chem., 19 (1976) 153.
25 E. Mutschler and K. Hultzsch, Arzneim. Forsch./Drug Res., 23 (1973) 732.
26 R.J. Tallarida, A. Cowan and M.W. Adler, Life Sci., 25 (1979) 637.