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Synthesis, crystal structure analysis, and pharmacological characterization of desmethoxy-sila-venlafaxine, a derivative of the serotonin/noradrenaline reuptake inhibitor sila-venlafaxine

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Dedicated to Professor Siegfried Hünig on the occasion of his 85th birthday.

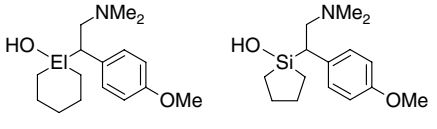
Abstract

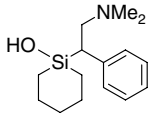
rac-Desmethoxy-sila-venlafaxine (*rac*-**3**) is a derivative of the noradrenaline-selective serotonin/noradrenaline reuptake inhibitor *rac*-sila-venlafaxine (*rac*-**1b**), a silicon analogue of the serotonin-selective serotonin/noradrenaline reuptake inhibitor *rac*-venlafaxine (*rac*-**1a**) (*rac*-**1a**, *rac*-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexan-1-ol; *rac*-**1b**, *rac*-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]-1-silacyclohexan-1-ol). The synthesis and crystal structure analyses of *rac*-**3** and *rac*-**3** · HCl are reported, and the pharmacological properties of *rac*-**1a**, *rac*-**1b**, *rac*-**2** (a sila-venlafaxine derivative with a silacyclopentanol skeleton instead of a silacyclohexanol framework), and *rac*-**3** are compared (comparison of the pharmacological selectivity profiles with respect to serotonin, noradrenaline, and dopamine reuptake inhibition).

Keywords: Sila-venlafaxine; Silicon; Silicon-based drugs; Serotonin/noradrenaline reuptake inhibitor; Structure–activity relationships; Venlafaxine

1. Introduction

In a series of recent publications, we have reported on the synthesis and pharmacological characterization of *rac*-sila-venlafaxine (*rac*-**1b**) [1–3], a sila-analogue of the serotonin/noradrenaline reuptake inhibitor *rac*-venlafaxine (*rac*-**1a**) [4,5]. In context with structure–activity relationship (SAR) studies, the enantiomers (*R*)-**1b** and (*S*)-**1b** and the derivative *rac*-**2** have also been investigated [3]. In continuation of these SAR studies, we have now succeeded in synthesizing and characterizing the sila-venlafaxine derivative *rac*-desmethoxy-sila-venlafaxine (*rac*-**3**). We report here on the syntheses and crystal structure analyses of *rac*-**3** and its hydrochloride *rac*-**3** · HCl, and we compare the pharmacological properties of *rac*-**1a**, *rac*-**1b**, *rac*-**2**, and *rac*-**3**. Preliminary results of these studies have been reported elsewhere [6]. For a recent review on silicon-based drugs, see Ref. [7].





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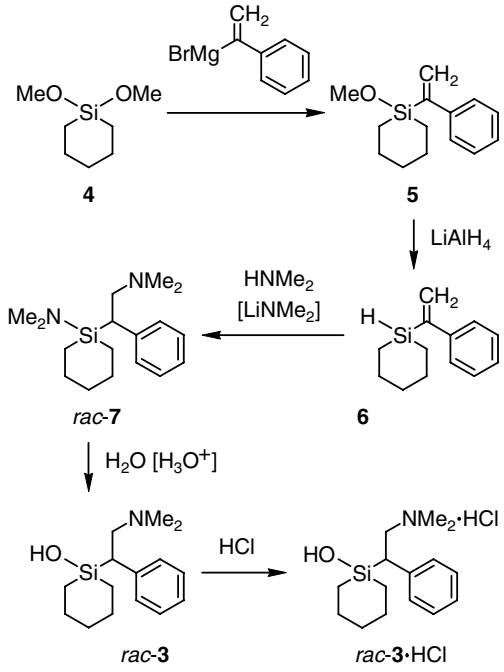
Racemic venlafaxine hydrochloride (Effexor™, Wyeth-Ayerst; Efexor™, Wyeth, Wyeth-Lederle; Trevilor™, Wyeth) is in clinical use as an antidepressant [8]. Venlafaxine is a monoamine reuptake inhibitor, with an activity profile different from traditional tricyclic antidepressants. It potently inhibits serotonin and noradrenaline synaptic transport, but exhibits weak potency at dopamine transporters as well as a range of other receptors (e.g. histaminic, muscarinic, adrenergic) responsible for the adverse effects of traditional antidepressants [9]. Venlafaxine is rapidly absorbed but undergoes extensive metabolism to active metabolites [10].

In context with our systematic studies on sila-substituted drugs [7], we were interested in the pharmacological properties of racemic sila-venlafaxine (*rac*-**1b**) and its derivatives *rac*-**2** and *rac*-**3**. Sila-substitution of *rac*-**1a** (→*rac*-**1b**) was expected to affect the chemical and physicochemical properties and the structure of venlafaxine and therefore to alter its biological properties, potentially resulting in improvements on the venlafaxine safety profile. Structural variations of *rac*-**1b** (→*rac*-**2**, *rac*-**3**) could lead to further alterations of the biological properties.

2. Results and discussion

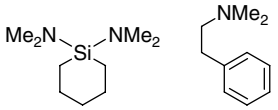
2.1. Syntheses

The title compound *rac*-**3** and its hydrochloride *rac*-**3** · HCl were prepared in multistep syntheses, starting from 1,1-dimethoxy-1-silacyclohexane (**4**) (Scheme 1). Thus, reaction of **4** with (1-phenylvinyl)magnesium bromide gave 1-methoxy-1-(1-phenylvinyl)-1-silacyclohexane (**5**) (59% yield), which upon treatment with lithium aluminum hydride afforded 1-(1-phenylvinyl)-1-silacyclohexane (**6**) (83% yield). Compound **6** was then reacted with dimethylamine, in the presence of lithium dimethylamide, to give *rac*-1-(dimethylamino)-1-(2-(dimethylamino)-1-phenylethyl)-1-silacyclohexane (*rac*-**7**) (40% yield). Hydrolysis of *rac*-**7** yielded *rac*-**3** (91% yield), which upon treatment with an ethereal hydrogen chloride solution gave the corresponding hydrochloride *rac*-**3** · HCl (93% yield).



Scheme 1.

In the course of the synthesis of *rac*-**7**, the formation of 1,1-bis(dimethylamino)-1-silacyclohexane (**8**) and dimethyl-(2-phenylethyl)amine (**9**) was observed (comparison with authentic samples, GC–MS analysis of the reaction mixture), resulting from an Si–C bond cleavage induced by a nucleophilic attack of $LiNMe_2$ at the silicon atom. This cleavage reaction is mainly responsible for the poor yield of *rac*-**7**.



8 **9**

Compounds *rac*-**3** and *rac*-**3** · HCl were isolated as colorless crystalline solids, whereas **5**, **6**, *rac*-**7**, and **8** were obtained as colorless liquids. The identities of all these compounds were established by elemental analyses (C, H, N) and NMR studies (^{1}H, ^{13}C, ^{29}Si), and *rac*-**3** and *rac*-**3** · HCl were additionally characterized by crystal structure analyses.

2.2. Crystal structure analyses

Compounds *rac*-**3** and *rac*-**3** · HCl were structurally characterized by single-crystal X-ray diffraction. The crystal data and experimental parameters used for these studies are given in Table 1. The molecular structure of *rac*-**3** and the structure of the cation of *rac*-**3** · HCl are depicted in Figs. 1 and 2; selected bond distances and angles are given in the respective figure legends.

Compounds *rac*-**3** and *rac*-**3** · HCl crystallize in the space group $P2_1/n$. The asymmetric unit of *rac*-**3** contains two molecules (A and B), with very similar structures. The crystal structures of *rac*-**3** and *rac*-**3** · HCl are governed by hydrogen bonds [11]. Compound *rac*-**3** forms intermolecular O–H···N hydrogen bonds that lead to infinite chains of the molecules along [1 0 0]. These chains are built up by molecules A and B in an alternating manner (···A···B···A···B···), the absolute configurations of A and B in a given chain being opposite. Compound *rac*-**3** · HCl forms O–H···Cl and N–H···Cl hydrogen bonds, leading to the formation of infinite chains along [1 0 0]. These chains are built up by the ammonium cations and chloride anions, the absolute configurations of all the cations in a given chain being identical.

Table 1
Crystal data and experimental parameters for the crystal structure analyses of *rac*-**3** and *rac*-**3** · HCl

	rac-**3**	*rac*-**3** · HCl
Empirical formula	$C_{15}H_{25}NOSi$	$C_{15}H_{26}ClNOSi$
Formula mass (g mol^{-1})	263.45	299.91
Collection T (K)	173(2)	173(2)
λ (Mo Kα) (Å)	0.71073	0.71073
Crystal system	Monoclinic	Monoclinic
Space group (no.)	$P2_1/n$ (14)	$P2_1/n$ (14)
a (Å)	11.9830(10)	6.0012(5)
b (Å)	11.1445(10)	26.724(3)
c (Å)	23.160(2)	10.7674(9)
β (°)	99.162(11)	103.940(9)
V (Å^3)	3053.5(5)	1676.0(3)
Z	8	4
D_{calc} (g cm^{-3})	1.146	1.189
μ (mm^{-1})	0.144	0.293
$F(000)$	1152	648
Crystal dimensions (mm)	$0.5 \times 0.5 \times 0.3$	$0.5 \times 0.4 \times 0.2$
2θ Range (°)	5.02–54.16	4.94–53.92
Index ranges	$-15 \leqslant h \leqslant 15$, $-14 \leqslant k \leqslant 14$, $-29 \leqslant l \leqslant 19$	$-7 \leqslant h \leqslant 7$, $-34 \leqslant k \leqslant 34$, $-13 \leqslant l \leqslant 13$
Number of collected reflections	17801	14764
Number of independent reflections	6592	3483
R_{int}	0.0441	0.0515
Number of reflections used	6592	3483
Number of parameters	331	178
S[a]	1.016	1.040
Weight parameters a/b[b]	0.0572/0.4079	0.0551/0.4269
R_1[c] $[I > 2\sigma(I)]$	0.0391	0.0355
wR_2[d] (all data)	0.1063	0.0972
Maximum/minimum residual electron density (e Å^{-3})	+0.272/−0.315	+0.307/−0.361

[a] $S = \{\sum[w(F_o^2 - F_c^2)^2]/(n-p)\}^{0.5}$; n is the number of reflections; p is the number of parameters.
[b] $w^{-1} = \sigma^2(F_o^2) + (aP)^2 + bP$, with $P = [\max(F_o^2, 0) + 2F_c^2]/3$.
[c] $R_1 = \sum||F_o| - |F_c||/\sum|F_o|$.
[d] $wR_2 = \{\sum[w(F_o^2 - F_c^2)^2]/\sum[w(F_o^2)^2]\}^{0.5}$.

The silacyclohexane skeletons of *rac*-**3** and *rac*-**3** · HCl adopt a chair conformation, with the OH groups in an equatorial position. In the crystal structures of the closely related compounds *rac*-**1b** · HCl, (*R*)-**1b** · HBr, and *rac*-**2**, the OH groups occupy axial sites. The structures of *rac*-**3** and *rac*-**3** · HCl are characterized by relatively long Si1–C6 (*rac*-**3**, molecule A), Si21–C26 (*rac*-**3**, molecule B), and Si–C6 (*rac*-**3** · HCl) distances (1.8931(15)–1.9041(14) Å), the reason for this elongation being unclear. Similar Si–C bond elongations were also observed for *rac*-**1b** · HCl, (*R*)-**1b** · HBr, and *rac*-**2** [2]. All the other bond distances and angles of *rac*-**3** and *rac*-**3** · HCl are in the expected range and do not need further discussion.

2.3. Pharmacological studies

Compounds *rac*-**1a**, *rac*-**1b**, *rac*-**2**, and *rac*-**3** were tested as their hydrochlorides for their efficacy in serotonin, noradrenaline, and dopamine reuptake inhibition assays (Table 2). The data are shown in Table 3 and Fig. 3.

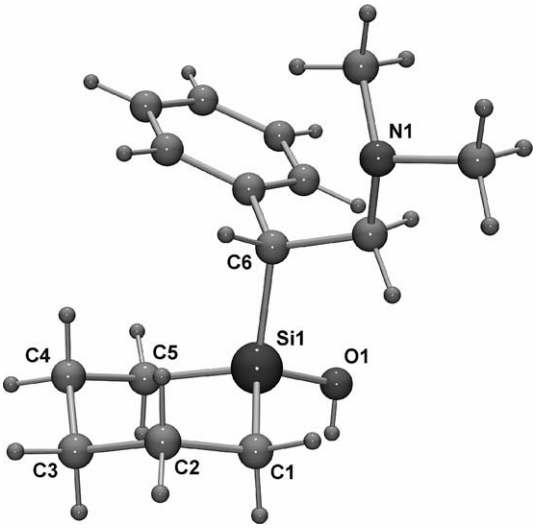


Fig. 1. Structure of *rac*-**3** in the crystal. The unit cell contains two molecules (A and B), with very similar structures (only one enantiomer of molecule A depicted). Selected bond distances (Å) and angles (°) for molecule A: Si1–O1 1.6200(11), Si1–C1 1.8655(17), Si1–C5 1.8608(16), Si1–C6 1.8931(15), C1–C2 1.529(2), C2–C3 1.524(2), C3–C4 1.519(2), C4–C5 1.533(2), O1–Si1–C1 113.78(7), O1–Si1–C5 115.47(7), O1–Si1–C6 105.45(6), C1–Si1–C5 103.76(7), C1–Si1–C6 109.26(7), C5–Si1–C6 109.03(7), Si1–C1–C2 110.99(11), C1–C2–C3 113.03(15), C2–C3–C4 114.65(15), C3–C4–C5 113.42(15), C4–C5–Si1 110.50(11). Data for molecule B (the atoms are labelled by adding "20" to the label number of the corresponding atoms in molecule A): Si21–O21 1.6259(12), Si21–C21 1.8609(16), Si21–C25 1.8560(18), Si21–C26 1.8988(15), C21–C22 1.528(2), C22–C23 1.518(3), C23–C24 1.515(3), C24–C25 1.536(3), O21–Si21–C21 111.95(7), O21–Si21–C25 113.66(8), O21–Si21–C26 108.25(7), C21–Si21–C25 103.91(8), C21–Si21–C26 109.09(7), C25–Si21–C26 109.87(7), Si21–C21–C22 112.40(12), C21–C22–C23 113.44(15), C22–C23–C24 114.22(16), C23–C24–C25 112.50(15), C24–C25–Si21 111.13(13).

The silicon compound *rac*-sila-venlafaxine (*rac*-**1b**) exhibits a substantially altered monoamine reuptake inhibition profile when compared with its carbon analogue *rac*-venlafaxine (*rac*-**1a**). Activity at the noradrenaline and dopamine transporters is essentially unaffected by sila-substitution (within experimental biological variation), whereas the potency at serotonin transporters is reduced by two orders of magnitude. In contrast, whilst the potency of the sila-venlafaxine derivative *rac*-**2** (a compound with a silacyclopentanol skeleton instead of a silacyclohexanol framework) at serotonin receptors has also been reduced by two orders of magnitude when compared to the parent drug *rac*-venlafaxine (*rac*-**1a**), the dopamine transporter selectivity is increased, leading to a compound essentially equipotent at all three monoamine transporters. The title compound *rac*-desmethoxy-sila-venlafaxine (*rac*-**3**) exhibits a significant reduction in activity at both serotonin and noradrenaline reuptake transporters, resulting in a non-selective compound with a weak monoamine reuptake inhibitor activity profile.

These data demonstrate the importance of the *p*-methoxy moiety in maintaining serotonin and noradrenaline reuptake inhibition, whereas sila-substitution effects

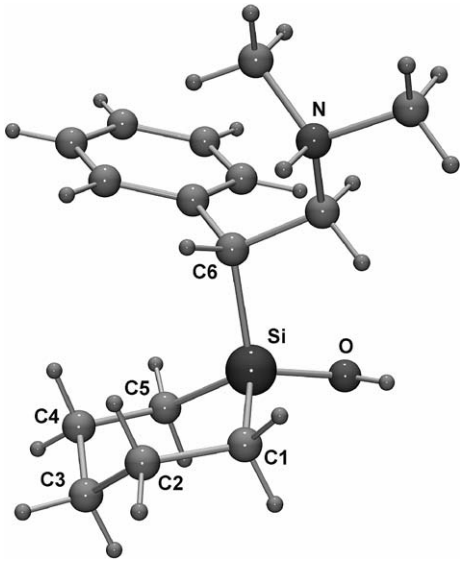


Fig. 2. Structure of the cation of *rac*-**3** · HCl in the crystal (only one enantiomer depicted). Selected bond distances (Å) and angles (°): Si–O 1.6348(12), Si–C1 1.8602(15), Si–C5 1.8481(15), Si–C6 1.9041(14), C1–C2 1.537(2), C2–C3 1.524(2), C3–C4 1.531(2), C4–C5 1.526(2), O–Si–C1 113.03(7), O–Si–C5 110.04(7), O–Si–C6 108.25(6), C1–Si–C5 105.73(7), C1–Si–C6 108.34(7), C5–Si–C6 111.47(7), Si–C1–C2 111.57(10), C1–C2–C3 113.39(15), C2–C3–C4 114.23(13), C3–C4–C5 113.42(15), C4–C5–Si 110.93(11).

changes in serotonin and dopamine reuptake activities therefore identifying *rac*-sila-venlafaxine (*rac*-**1b**) as a drug with a refined selectivity profile consistent with selective noradrenaline reuptake inhibition. Compounds with this pharmacological profile may provide therapeutic benefit in the treatment of various CNS disorders.

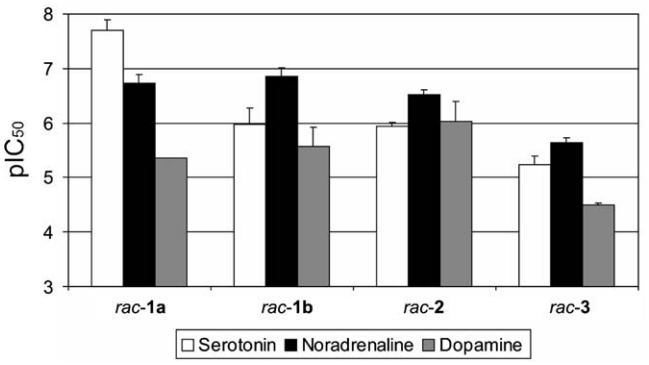


Fig. 3. In vitro efficacy of compounds *rac*-**1a**, *rac*-**1b**, *rac*-**2**, and *rac*-**3** regarding serotonin, noradrenaline, and dopamine reuptake inhibition. pIC_{50} denotes the negative decadic logarithm of the half-maximum effect concentration (M). The monoamine reuptake inhibition profiles of *rac*-**1a**, *rac*-**1b**, *rac*-**2**, and *rac*-**3** were generated via radioligand transporter assays using recombinant human monoamine transporter proteins. The data represent the mean of at least 2 determinations.

3. Experimental

3.1. Syntheses

3.1.1. General procedures

Except for the hydrolysis *rac*-**7** → *rac*-**3**, all syntheses were carried out under dry nitrogen. The organic solvents used were dried and purified according to standard procedures and stored under dry nitrogen. A Büchi GKR 50 apparatus was used for the bulb-to-bulb distillations. Melting points were determined with a Büchi Melting Point B-540 apparatus using open glass capillaries. The ^{1}H, ^{13}C,

Table 2
Experimental conditions for pharmacological assays

Assay[a]	SERT	NET	DAT
Cell line	Human HEK-293	Human MDCK	Human CHO-K1
Radioligand	^{3}H-serotonin	^{3}H-noradrenaline	^{3}H-dopamine
Incubation time (min)	10	10	10
Incubation temperature (°C)	25	25	25
Incubation buffer[b]	5 mM Tris–HCl, 7.5 mM HEPES, 120 mM NaCl, 5.4 mM KCl, 1.2 mM $CaCl_2$, 1.2 mM $MgSO_4$, 5 mM glucose, 1 mM ascorbic acid, pH 7.1		
References	[18]	[19]	[20,21]

[a] SERT, serotonin reuptake transporter; NET, noradrenaline (norephinephrine) reuptake transporter; DAT, dopamine reuptake transporter.
[b] The incubation buffer was identical for all three assays.

Table 3
Monoamine reuptake transporter inhibition profiles[a,b]

Compound	SERT	NET	DAT
rac-**1a**	0.020 ± 0.007	0.184 ± 0.056	4.425 ± 0.005
rac-**1b**	1.063 ± 0.538	0.138 ± 0.041	2.739 ± 1.531
rac-**2**	1.155 ± 0.166	0.305 ± 0.057	0.941 ± 0.537
rac-**3**	5.698 ± 1.701	2.310 ± 0.452	31.44 ± 1.83

[a] SERT, serotonin reuptake transporter; NET, noradrenaline (norephinephrine) reuptake transporter; DAT, dopamine reuptake transporter.
[b] Data expressed as IC_{50} values (μM, mean ± SD) and represent the mean of at least 2 determinations.

and ^{29}Si NMR spectra were recorded on a Bruker DRX-300 NMR spectrometer (^{1}H, 300.1 MHz; ^{13}C, 75.5 MHz; ^{29}Si, 59.6 MHz). CD_2Cl_2, [D_6]DMSO, or [D_8]THF were used as the solvent. All spectra were recorded at 22 °C. Chemical shifts were determined relative to internal $CHDCl_2$ (^{1}H, δ 5.32; CD_2Cl_2), CD_2Cl_2 (^{13}C, δ 53.8; CD_2Cl_2), [D_5]DMSO (^{1}H, δ 2.49; [D_6]DMSO), [D_6]DMSO (^{13}C, δ 39.5; [D_6]DMSO), [D_7]THF (^{1}H, δ 1.73; [D_8]THF), [D_8]THF (^{13}C, δ 25.3; [D_8]THF), or external TMS (^{29}Si, δ 0; CD_2Cl_2, [D_6]DMSO, [D_8]THF). Analysis and assignment of the ^{1}H NMR data was supported by ^{1}H,^{1}H and ^{13}C,^{1}H correlation experiments and partially by simulations using the WIN-DAISY software package (version 4.05, Bruker) [12]. Assignment of the ^{13}C NMR data was supported by DEPT 135 and ^{13}C,^{1}H correlation experiments. The $^{2}J_{HH}$ coupling constants reported for the C=CH_2 groups represent absolute values.

3.1.2. rac-1-(2-(Dimethylamino)-1-phenylethyl)-1-silacyclohexan-1-ol (rac-desmethoxy-sila-venlafaxine, rac-3)

A solution of *rac*-**7** (7.88 g, 27.1 mmol) in diethyl ether (50 ml) was added in one single portion at 0 °C to a stirred two-phase mixture of diethyl ether (50 ml) and 2 M potassium acetate/acetic acid buffer (pH 4.5, 150 ml). The pH of the aqueous phase changed to pH ca. 7 within 10 min and was readjusted to pH 5.0 by addition of small portions of glacial acetic acid. The mixture was stirred at 0 °C for a further 1 h, with the pH of the aqueous phase remaining constantly at pH 5.0 during this time. The aqueous layer was separated, the organic phase was extracted with 1 M potassium acetate/acetic acid buffer (pH 5.0) (3 × 100 ml), and the aqueous solutions were combined. Diethyl ether (50 ml) was added, and the pH of the aqueous phase was adjusted to pH 10.5 by addition of small portions of a saturated aqueous potassium carbonate solution. The organic layer was separated, the aqueous phase was extracted with diethyl ether (5 × 100 ml), and the organic extracts were combined, followed by addition of *n*-hexane (200 ml). The solvent was removed under reduced pressure in a water bath (5–15 °C) until a residual volume of 150 ml was obtained, whereupon residual water separated from the organic phase (formation of a two-phase system). The organic layer was separated, the aqueous phase was extracted with *n*-hexane (2 × 100 ml), and the organic solutions were combined. The solvent was removed completely under reduced pressure in a water bath (5–15 °C) to give a colorless oil. Crystallization of this oil from *n*-pentane (120 ml) at 4 °C over a period of 1 day and then at −20 °C for a further 6 days afforded *rac*-**3** in 91% yield as a colorless crystalline solid (6.50 g, 24.7 mmol) (isolated by quick decantation of the cold solvent, followed by drying in vacuo (0.001 mbar, 20 °C, 6 h)); m.p. 63 °C. ^{1}H NMR (CD_2Cl_2): δ 0.45–0.78 and 1.00–1.69 (m, 10H, Si(CH_2)$_5$), 2.30 (s, 6H, NCH_3), 2.54 (δ_C), 2.58 (δ_A), and 3.16 (δ_B) (3H, $^{2}J_{AB} = -12.0$ Hz, $^{3}J_{AC} = 5.3$ Hz, $^{3}J_{BC} = 12.1$ Hz, SiCH_CC$H_A H_B$N), 5.1 (br s, 1H, SiO*H*), 7.03–7.09 (m, 2H, *H*-2/*H*-6, Aryl), 7.09–7.14 (m, 1H, *H*-4, Aryl), 7.20–7.29 (m, 2H, *H*-3/*H*-5, Aryl). ^{13}C NMR (CD_2Cl_2): δ 12.5 (Si*C*H_2C), 14.5 (Si*C*H_2C), 24.5 (SiCH_2*C*H_2C), 24.6 (SiCH_2*C*H_2C), 29.9 (Si(CH_2)$_2$*C*H_2C), 34.3 (Si*C*HC$_2$), 45.5 (N*C*H_3), 61.6 (N*C*H_2C), 125.2 (*C*-4, Aryl), 127.9 (*C*-2/*C*-6, Aryl), 128.6 (*C*-3/*C*-5, Aryl), 141.9 (*C*-1, Aryl). ^{29}Si NMR (CD_2Cl_2): δ 9.5. Anal. Calc. for $C_{15}H_{25}NOSi$: C, 68.39; H, 9.56; N, 5.32. Found: C, 68.0; H, 9.7; N, 5.5%.

3.1.3. rac-[2-(1-Hydroxy-1-sila-1-cyclohexyl)-2-phenylethyl]dimethylammonium chloride (rac-desmethoxy-sila-venlafaxine hydrochloride, rac-3 · HCl)

A 2 M ethereal hydrogen chloride solution (10.5 ml, 21.0 mmol of HCl) was added in one single portion at 20 °C to a stirred solution of *rac*-**3** (5.27 g, 20.0 mmol) in dichloromethane (50 ml). The resulting solid was dissolved in dichloromethane (150 ml) at reflux temperature, and the solution was then kept undisturbed at 4 °C for 1 day and at −20 °C for a further 3 days. The precipitate was isolated by filtration at −20 °C, washed with diethyl ether (20 ml), and dried in vacuo (0.001 mbar, 20 °C, 6 h) to give *rac*-**3** · HCl in 93% yield (including workup of the mother liquor) as a colorless crystalline solid (5.60 g, 18.7 mmol); m.p. 186–187 °C (dec.). ^{1}H NMR ([D_6]DMSO) [13]: δ 0.24–0.41, 0.51–0.71, and 1.12–1.59 (m, 10H, Si(CH_2)$_5$), 2.56 (δ_M), 2.61 (δ_N), 2.83 (δ_C), 3.42 (δ_A), 3.81 (δ_B), and 9.8 (br, δ_G) (10H, $^{2}J_{AB} = -13.1$ Hz, $^{3}J_{AC} = 2.5$ Hz, $^{3}J_{BC} = 12.5$ Hz, $^{3}J_{GM}$ and $^{3}J_{GN}$ not resolved, SiCH_CC$H_A H_B$NH_G(C(H_M)$_3$)(C(H_N)$_3$)), 6.06 (s, 1H, SiO*H*), 7.11–7.19 (m, 1H, *H*-4, Aryl), 7.23–7.34 (m, 4H, *H*-2/*H*-6, *H*-3/*H*-5, Aryl). ^{13}C NMR ([D_6]DMSO): δ 12.3 (Si*C*H_2C), 13.2 (Si*C*H_2C), 23.6 (SiCH_2*C*H_2C), 23.7 (SiCH_2*C*H_2C), 29.1 (Si(CH_2)$_2$*C*H_2C), 32.1 (Si*C*HC$_2$), 41.6 (N*C*H_3), 42.9 (N*C*H_3), 57.3 (C*C*H_2N), 125.4 (*C*-4, Aryl), 127.7 (*C*-2/*C*-6, Aryl), 128.5 (*C*-3/*C*-5, Aryl), 139.1 (*C*-1, Aryl). ^{29}Si NMR ([D_6]DMSO): δ 2.8. Anal. Calc. for $C_{15}H_{26}ClNOSi$: C, 60.07; H, 8.74; N, 4.67. Found: C, 60.0; H, 8.9; N, 4.8%.

3.1.4. 1,1-Dimethoxy-1-silacyclohexane (4)

This compound was synthesized according to Ref. [3].

3.1.5. 1-Methoxy-1-(1-phenylvinyl)-1-silacyclohexane (5)

A solution of 1-bromo-1-phenylethene (28.0 g, 153 mmol) in diethyl ether (140 ml) was added dropwise within 15 min to a suspension of magnesium turnings (4.10 g, 169 mmol) in diethyl ether (10 ml), followed by heating under reflux for an additional 1 h. (The Grignard reaction proceeded smoothly, but required gentle heating to get started.) The resulting dark brown Grignard reagent [14] was cooled to 20 °C, separated from the excess magnesium turnings by decantation, and then added dropwise at 20 °C within 10 min to a stirred solution of **4** (24.6 g, 153 mmol) in diethyl ether (50 ml). The resulting mixture was heated under reflux for 3 days (precipitation of magnesium salts) and was then cooled to 20 °C, followed by filtration. The filter cake was washed with *n*-hexane (300 ml), the filtrate

and the wash solution were combined, and the solution was concentrated under reduced pressure at 5–15 °C to a volume of 200 ml and then kept undisturbed at 20 °C for 1 day (postprecipitation of magnesium salts). The precipitate was separated by filtration, the filter cake was washed with *n*-hexane (50 ml), the filtrate and the wash solution were combined, the solvent was removed completely under reduced pressure at 5–15 °C, and the residue was distilled in vacuo to give **5** in 59% yield as a colorless liquid (21.2 g, 91.2 mmol), b.p. 80–81 °C/0.001 mbar. ^{1}H NMR (CD_2Cl_2): δ 0.71–0.98 (m, 4H, SiCH_2C), 1.31–1.57 (m, 2H, Si(CH$_2$)$_2$CH_2C), 1.60–1.81 (m, 4H, SiCH$_2$CH_2C), 3.45 (s, 3H, OCH_3), 5.73 (δ_A) and 6.05 (δ_B) (2H, $^2J_{AB} = 2.8$ Hz, C=C$H_A H_B$), 7.21–7.28 (m, 1H, *H*-4, Aryl), 7.28–7.34 (m, 4H, *H*-2/*H*-6, *H*-3/*H*-5, Aryl). ^{13}C NMR (CD_2Cl_2): δ 12.5 (Si*C*H$_2$C), 24.6 (SiCH$_2$*C*H$_2$C), 30.2 (Si(CH$_2$)$_2$*C*H$_2$C), 50.6 (O*C*H$_3$), 126.99 (*C*-2/*C*-6, Aryl), 127.00 (*C*-4, Aryl), 128.6 (*C*-3/*C*-5, Aryl), 129.5 (C=*C*H$_2$), 143.7 (*C*-1, Aryl), 148.9 (*C*=CH$_2$). ^{29}Si NMR (CD_2Cl_2): δ 3.4. Anal. Calc. for $C_{14}H_{20}OSi$: C, 72.36; H, 8.67. Found: C, 72.4; H, 8.8%.

3.1.6. 1-(1-Phenylvinyl)-1-silacyclohexane (*6*)

A solution of **5** (20.8 g, 89.5 mmol) in diethyl ether (40 ml) was added at 20 °C within 10 min to a stirred suspension of lithium aluminum hydride (1.70 g, 44.8 mmol) in diethyl ether (145 ml). The mixture was heated under reflux for 6.5 h and then added carefully at 0 °C to a stirred mixture of 4 M hydrochloric acid (165 ml) and diethyl ether (80 ml). The organic phase was separated, the aqueous layer was extracted with diethyl ether (3 × 100 ml), and the organic solutions were combined and dried over anhydrous magnesium sulfate in an ice bath, followed by an additional thorough dynamic drying using a chromatographic column densely packed with anhydrous magnesium sulfate (column diameter, 3.5 cm; column length, 15 cm). The magnesium sulfate was finally washed with diethyl ether (2 × 200 ml), the organic solutions were combined, the solvent was removed under reduced pressure, and the residue was distilled in vacuo (Vigreux column, 15 cm) to give **6** in 83% yield as a colorless liquid (15.1 g, 74.6 mmol); b.p. 60–61 °C/0.001 mbar. ^{1}H NMR (CD_2Cl_2): δ 0.69–0.85, 0.92–1.05, 1.25–1.41, 1.51–1.70, and 1.79–1.94 (m, 10H, Si(CH_2)$_5$), 4.26–4.33 (δ_X), 5.69 (δ_A), and 6.03 (δ_B) (3H, $^2J_{AB} = 2.6$ Hz, $^4J_{BX} = 0.4$ Hz, H_XSiC=C$H_A H_B$), 7.21–7.28 (m, 1H, *H*-4, Aryl), 7.28–7.36 (m, 4H, *H*-2/*H*-6, *H*-3/*H*-5, Aryl). ^{13}C NMR (CD_2Cl_2): δ 10.8 (Si*C*H$_2$C), 25.2 (SiCH$_2$*C*H$_2$C), 30.1 (Si(CH$_2$)$_2$*C*H$_2$C), 126.8 (*C*-2/*C*-6, Aryl), 127.1 (*C*-4, Aryl), 128.5 (C=*C*H$_2$), 128.7 (*C*-3/*C*-5, Aryl), 144.0 (*C*-1, Aryl), 148.7 (*C*=CH$_2$). ^{29}Si NMR (CD_2Cl_2): δ −19.8. Anal. Calc. for $C_{13}H_{18}Si$: C, 77.16; H, 8.97. Found: C, 77.0; H, 9.2%.

3.1.7. rac-1-(Dimethylamino)-1-(2-(dimethylamino)-1-phenylethyl)-1-silacyclohexane (*rac*-*7*)

A 2.5 M solution of *n*-butyllithium in *n*-hexane (32.4 ml, 81.0 mmol of *n*-BuLi) was added dropwise at −50 °C within 15 min to a stirred solution of dimethylamine (17.3 g, 384 mmol) in tetrahydrofuran (100 ml). The resulting mixture was warmed to −12 °C within 2 h and then cooled to −40 °C, followed by dropwise addition of a solution of **6** (14.9 g, 73.6 mmol) in tetrahydrofuran (20 ml) within a period of 20 min (evolution of hydrogen; rise in temperature from −40 °C to −33 °C; change of color from colorless to scarlet red). The resulting solution was stirred at −30 °C for 3 h and then kept undisturbed at 4 °C for 16 h. Subsequently, the solution was placed in an ice bath and stirred again, followed by addition of chlorotrimethylsilane (16.0 g, 147 mmol) in one single portion (change of color from scarlet red to colorless). The mixture was stirred at 0 °C for 5 min, warmed to 20 °C within 30 min, and then stirred at 20 °C for a further 30 min. The solvent was removed completely under reduced pressure at 5–15 °C, followed by addition of *n*-hexane (70 ml). The mixture was stirred at 20 °C for 15 min, the resulting precipitate was separated by filtration, and the filter cake was washed with *n*-hexane (20 ml). The filtrate and the wash solution were combined, the solvent was removed completely under reduced pressure at 5–15 °C, and the residue was distilled in vacuo in a Kugelrohr apparatus (first fraction, ⩽90 °C/0.002 mbar, 8.3 g (mainly consisting of **8** and **9** [15]); second fraction, 90–125 °C/0.0005 mbar, 12.5 g (crude product)). The crude product was redistilled in vacuo (Vigreux column, 5 cm) to give *rac*-**7** in 40% yield as a colorless oily liquid (8.63 g, 29.7 mmol); b.p. 112–114 °C/0.02 mbar. ^{1}H NMR ([D_8]THF): δ 0.36–0.71, 0.85–0.98, 1.12–1.30, and 1.35–1.79 (m, 10H, Si(CH_2)$_5$), 2.12 (s, 6H, CNCH_3), 2.36–2.46 (m, 1H, SiCHC$_2$), 2.42 (s, 6H, SiNCH_3), 2.59–2.76 (m, 2H, CCH_2N), 6.96–7.05 (m, 3H, *H*-2/*H*-6, *H*-4, Aryl), 7.11–7.20 (m, 2H, *H*-3/*H*-5, Aryl). ^{13}C NMR ([D_8]THF): δ 11.9 (Si*C*H$_2$C), 12.7 (Si*C*H$_2$C), 24.90 (SiCH$_2$*C*H$_2$C), 24.93 (SiCH$_2$*C*H$_2$C), 31.1 (Si(CH$_2$)$_2$*C*H$_2$C), 37.4 (Si*C*HC$_2$), 38.6 (SiN*C*H$_3$), 45.7 (CN*C*H$_3$), 61.2 (C*C*H$_2$N), 124.9 (*C*-4, Aryl), 128.5 (*C*-3/*C*-5, Aryl) 128.7 (*C*-2/*C*-6, Aryl), 143.9 (*C*-1, Aryl). ^{29}Si NMR ([D_8]THF): δ 0.8. Anal. Calc. for $C_{17}H_{30}N_2Si$: C, 70.28; H, 10.41; N, 9.64. Found: C, 70.0; H, 10.3; N, 9.5%.

3.1.8. 1,1-Bis(dimethylamino)-1-silacyclohexane (*8*)

A 2.5 M solution of *n*-butyllithium in *n*-hexane (18.0 ml, 45.0 mmol of *n*-BuLi) was added dropwise at −50 °C within 15 min to a stirred solution of dimethylamine (7.12 g, 158 mmol) in tetrahydrofuran (70 ml). The resulting mixture was warmed to −15 °C within 2 h, followed by dropwise addition of 1,1-dichloro-1-silacyclohexane (3.73 g, 22.1 mmol; synthesized according to Ref. [3]) at −15 °C within a period of 25 min. The resulting solution was warmed to 20 °C within 4 h and then stirred at 20 °C for a further 12 h. The solvent was removed completely under reduced pressure at 5–15 °C, followed by addition of *n*-hexane (100 ml) (formation of a precipitate). The mixture was stirred at 20 °C for 1 day, the resulting precipitate was separated by filtration, and the filter cake was washed with *n*-hexane (20 ml). The filtrate and the wash solution

were combined, the solvent was removed completely under reduced pressure at 5–15 °C, and the residue was distilled in vacuo (Vigreux column, 5 cm) to give **8** in 75% yield as a colorless liquid (3.07 g, 16.5 mmol); b.p. 69–70 °C/3 mbar. ^{1}H NMR (CD_2Cl_2): δ 0.61–0.70 (m, 4H, SiCH_2C), 1.33–1.44 (m, 2H, Si(CH_2)$_2$CH_2C), 1.57–1.67 (m, 4H, SiCH$_2$CH_2C), 2.46 (s, 12H, NCH_3). ^{13}C NMR (CD_2Cl_2): δ 11.7 (SiCH_2C), 25.1 (SiCH$_2$$CH_2$C), 30.7 (Si($CH_2$)$_2$$CH_2$C), 37.8 (N$CH_3$). ^{29}Si NMR ($CD_2Cl_2$): δ −6.0. Anal. Calc. for $C_9H_{22}N_2Si$: C, 58.00; H, 11.90; N, 15.03. Found: C, 57.9; H, 12.0; N, 15.1%.

3.1.9. Dimethyl(2-phenylethyl)amine (*9*)

This compound was commercially available.

3.2. Crystal structure analyses

Suitable single crystals of *rac*-**3** and *rac*-**3** · HCl were obtained directly from the preparation of these compounds. The crystals were mounted in inert oil (perfluoroalkyl ether, ABCR) on a glass fiber and then transferred to the cold nitrogen gas stream of the diffractometer (Stoe IPDS; graphite-monochromated Mo Kα radiation ($\lambda = 0.71073$ Å)). The structures were solved by direct methods [16]. All non-hydrogen atoms were refined anisotropically [17]. The N*H* hydrogen atoms were localized in difference Fourier syntheses and refined freely. A riding model was employed in the refinement of the C*H* and O*H* hydrogen atoms.

3.3. Pharmacological studies

Receptor binding activities were determined using radioligand cellular uptake inhibition assays via contract research services (MDS Pharma Services, Taipei, Taiwan). Radioactivity levels were detected by scintillation counting. The experimental conditions for each assay are given in Table 2.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jorganchem.2006.04.015.

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[14] Surprisingly, this Grignard reagent did not react with 1,1-dichloro-1-silacyclohexane in refluxing diethyl ether (analogous reaction conditions, GC control).

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