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Silyl modification of biologically active compounds. 11. Synthesis, physico-chemical and biological evaluation of *N*-(trialkoxysilylalkyl)tetrahydro(iso,silaiso) quinoline derivatives

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***N*-(trialkoxysilylalkyl) derivatives of 1,2,3,4-tetrahydroquinoline, 1,2,3,4-tetrahydroisoquinoline and 4,4-dimethyl-4-sila-1,2,3,4-tetrahydroisoquinoline were prepared and characterized by elemental analysis, ^{1}H, ^{13}C and ^{29}Si NMR spectroscopy. *In vivo* psychotropic properties and *in vitro* cytotoxic effects of 3-[*N*-(1,2,3,4-tetrahydroisoquinolyl)]propyltriethoxysilane methiodide and 3-[*N*-(1,2,3,4-tetrahydroisoquinolyl)]propylsilatrane are reported. Comparative study of ^{29}Si shifts in newly synthesized compounds suggested donor–acceptor interaction between nitrogen and silicon atom, which increased electron density at Si nuclei, revealing a stronger increment of N → Si transannular bond in comparison with N → Si α-effect. The molecular structure of 3-[*N*-(1,2,3,4-tetrahydroisoquinolyl)]propylsilatrane features a penta-coordinate silicon atom having $CSiO_3$ pattern and Si. . .N intramolecular interaction. Copyright © 2005 John Wiley & Sons, Ltd.**

KEYWORDS: tetrahydroquinoline; tetrahydroisoquinoline; silicon; psychotropic activity; cytotoxicity; ^{29}Si NMR; X-ray crystal structure

INTRODUCTION

Earlier we reported on the synthesis and physico-chemical and biological investigation of *N*-trialkylsiloxyalkyl[1] and *N*-trialkylsilylalkoxyalkyl[2] derivatives of 1,2,3,4-tetrahydroquinoline, 1,2,3,4-tetrahydroisoquinoline and 4,4-dimethyl-4-sila-1,2,3,4-tetrahydroisoquinoline.

The objective of this account is to highlight a study of physico-chemical and biological aspects of *N*-(trialkoxysilyl)alkyl derivatives of 1,2,3,4-tetrahydroquinoline, 1,2,3,4-tetrahydroisoquinoline and 4,4-dimethyl-4-sila-1,2,3,4-tetrahydroisoquinoline.

In some cases, due to their specific biological properties (lower toxicity and increased penetration through lipophilic barriers, e.g. the blood–brain barrier) organosilicon derivatives could possess improved pharmacological characteristics in comparison with their parent precursors.[1–5]

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The choice of tetrahydro(iso)quinoline derivatives for pharmacological investigation was stipulated by their potential biological properties. Quinoline or hydrogenated quinoline moieties are present as structural fragments in Amsacrine, Bruneomycinum, Vincristine and Vinblastinum, which are widely used in oncology.[6,7] According to the literature data, some quinoline or tetrahydroquinoline ring-containing compounds possess antiproliferative activity by inhibition of topoisomerase II[8,9] or topoisomerase I,[10] or have cytostatic effects.[11,12]

It has been reported that tetrahydro(iso)quinoline based compounds display affinity to serotonin (5-HT_{1A}),[13,14] dopamine[15] and NMDA receptors,[16] and possess sedative properties.[17] Neurotropic properties of tetrahydro(iso, silaiso)quinoline derivatives were confirmed by investigation.[4,18] Novel substances obtained (Scheme 1) have been characterized by ^{1}H, ^{13}C and ^{29}Si data. The molecular structure of 1-{3-[*N*-(1,2,3,4-Tetrahydroisoquinolyl)propyl]}silatrane has been determined.

3-[*N*-(1,2,3,4-tetrahydroisoquinolyl)]propyltrimethoxysilane methiodide and 1-{3-[*N*-(1,2,3,4-Tetrahydroisoquinolyl)propyl]}silatrane have been investigated for

cytotoxicity against different tumour cell lines *in vitro* and psychotropic activity along a number of tests *in vivo*.

EXPERIMENTAL

Chemicals and instrumentation

^{1}H, ^{13}C and ^{29}Si NMR spectra were obtained on Varian Mercury 200 spectrometer at 200, 50 and 40 MHz, respectively, at 303 K with $CDCl_3$ as a solvent and internal standard ($\delta = 7.25$ ppm for $CHCl_3$). Mass spectra under electron impact conditions were recorded on a Hewlett-Packard apparatus (HP-6890, GC with HP5MS, 70 eV). Elemental analyses (C, H, N) were performed on Carlo Erba 1108 elemental analyser. Elemental analysis results agreed with calculated values.

GLC analysis was conducted on a Chrom-5 chromatograph with a flame-ionization detector and glass column (1.2 m × 3 mm) with 5% OV-17 on Chromosorb W-AW (60–80 mesh). Melting points were determined on a Boetius melting point apparatus and were taken uncorrected.

Solvents and reagents used in this study were purchased from Fluka, Acros and Aldrich. The syntheses involving air-sensitive compounds were carried out under dry argon. All solvents used were freshly dried using standard techniques and all glassware was oven-dried. Dimethyl[(2-bromomethyl)phenyl]chloromethylsilane was synthesized according to the literature procedure[19].

*[N-(1,2,3,4-tetrahydroisoquinolyl)] methyltriethoxysilane (**1**)*

The stirred solution of tetrahydroisoquinoline (6.65 g, 0.05 mol), (chloromethyl)triethoxysilane (10.64 g, 0.05 mol) and triethylamine(10.10 g, 0.10 mol) in 25 ml of xylene was heated at 80 °C under argon for 5 h. The precipitate of ammonium salt formed was filtered off and the solvent was evaporated under reduced pressure. Product **1** was isolated by vacuum distillation as light yellow liquid; b.p. 162–163 °C/5 mmHg; yield 63%. ^{1}H NMR ($CDCl_3$), δ (ppm): 1.27 (9H, t, $J = 7.0$ Hz, C-CH_3), 2.20 (2H, s, NCH_2Si), 2.84 (2H, t, $J = 5.4$, Hz, 4-CH_2), 2.93 (2H, t, $J = 5.4$ Hz, 3-CH_2), 3.67 (2H, s, $ArCH_2N$), 3.89 (6H, q, $J = 7.0$ Hz, OCH_2), 6.93–7.22 (4H, m, Ar). ^{13}C NMR ($CDCl_3$), δ (ppm): 18.04 (C-2′), 29.22 (N–C–Si), 43.81 (C-4), 53.89 (C-3), 58.36 (C–O), 59.44 (C-1), 125.15 (C-5), 125.62 (C-7), 126.06 (C-8), 128.20 (C-6), 133.83 (C-9), 135.20 (C-10). Anal. found: C, 61.92; H, 8.75; N, 4.55. Calcd for $C_{16}H_{27}NO_3Si$: C, 62.10; H, 8.79; N, 4.53%.

*3-[N-(1,2,3,4-Tetrahydroisoquinolyl)] propyltrimethoxysilane (**2**)*

The stirred solution of tetrahydroisoquinoline (6.65 g, 0.05 mol), (3-chloropropyl)trimethoxysilane (9.94 g, 0.05 mol) and triethylamine(10.10 g, 0.10 mol) in 25 ml xylene was heated at 80 °C under argon for 8 h. The precipitate of ammonium salt formed was filtered off and the solvent was evaporated under reduced pressure. The product **2** was isolated by vacuum distillation as yellow liquid; yield 6.49 g, 44%; b.p. 197 °C/4 mmHg. ^{1}H NMR ($CDCl_3$), δ (ppm): 0.69 (2H, t, $J = 4$ Hz, $SiCH_2$), 1.73 (2H, quin, $J = 4$ Hz, β-CH_2), 2.40–3.00 (6H, m, 4-CH_2 + α-CH_2N + 3-CH_2), 3.58 (9H, s, OCH_3), 3.67 (2H, s, $ArCH_2N$), 6.85–7.10 (4H, m, Ar). Anal. found: C, 61.11; H, 8.51; N, 4.74. Calcd for $C_{15}H_{25}NO_3Si$: C, 61.02; H, 8.47; N, 4.76%. MS: $[M]^+$: $m/z = 295$ (2%); $[M\text{-}OMe]^+$: $m/z = 264$ (1%); 172 (1%); $[M\text{-}CH_2Si(OMe)_3]^+$: $m/z = 160$ (2%); $[M\text{-}CH_2CH_2Si(OMe)_3]^+$: $m/z = 146$ (100%); $[M\text{-}CH_2CH_2CH_2Si(OMe)_3]^+$: $m/z = 132$ (28%).

*[N-(1,2,3,4-Tetrahydroisoquinolyl)] methyltriethoxysilane methiodide (**3**)*

The mixture of compound **1** (0.31 g, 1.0 mmol) and methyl iodide (0.71 g, 5.0 mmol) in 1 ml of diethyl ether was stirred at room temperature under argon for 1 h. The liquid was decantated from the lightly yellow precipitate of product **3**. The product was dried under vacuum for 1 h; yield 0.40 g, 89%; m.p. 74–76 °C.

^{1}H NMR ($CDCl_3$), δ (ppm): 1.31 (9H, t, $J = 7$ Hz, C-CH_3), 3.22–3.49 (4H, m, 4-CH_2 + N^+CH_2Si), 3.67 (3H, s, N^+-CH_3), 4.02 (6H, m, OCH_2), 4.11 (2H, m, 3-CH_2), 4.98 (2H, bs, $ArCH_2N$+), 7.11–7.56 (4H, m, Ar). Anal. found: C, 45.01; H, 6.67; N, 3.11. Calcd for $C_{17}H_{30}INO_3Si$: C, 45.23; H, 6.70; N, 3.10%.

*3-[N-(1,2,3,4-Tetrahydroisoquinolyl)] propyltrimethoxysilane methiodide (**4**)*

The light yellow product **4** was formed as for **3**; yield 0.34 g, 76%; m.p. 84–84 °C. ^{1}H NMR ($CDCl_3$), δ (ppm): 0.71 (2H, t, $J = 4$ Hz, $SiCH_2$), 1.96 (2H, m, β-CH_2), 3.24 (2H, t, $J = 5$ Hz, 4-CH_2), 3.49 (3H, s, NCH_3), 3.56 (9H, s, OCH_3), 3.78 (2H, m, α-CH_2N^+), 4.07 (2H, m, 3-N^+CH_2), 4.89 (2H, bs, $ArCH_2N^+$), 7.09–7.42 (4H, m, Ar). ^{13}C NMR ($CDCl_3$), δ (ppm): 5.19 (C—Si), 16.06 (β–C–N), 23.59 (C-4), 48.45 (C–N), 50.54 (C-O), 57.69 (α–C–N), 62.35 (C-3), 63.78 (C-1), 125.61 (C-5), 127.21 (C-7), 127.51 (C-8), 128.54 (C-6), 128.63 (C-9), 128.73 (C-10). Anal. found: C, 43.85; H, 6.43; N, 3.21. Calcd for $C_{16}H_{28}INO_3Si$: C, 43.94; H, 6.45; N, 3.20%.

*1-[N-(1,2,3,4-tetrahydroisoquinolyl)methyl]silatrane (**5**)*

The mixture of compound **1** (1.55 g, 5.0 mmol) and triethanolamine (0.73 g, 5.0 mmol) in hexane (5 ml) was heated at 60 °C under argon for 1 h. The precipitate formed was filtered off and washed with hexane to give amorphous product **5**; yield 1.43 g, 89%; m.p. 145–147 °C. ^{1}H NMR ($CDCl_3$), δ (ppm): 1.99 (2H, s, NCH_2Si), 2.72–2.94 (4H, m, 3-CH_2 + 4-CH_2), 2.82 (6H, t, $J = 6$ Hz, 2′-CH_2N), 3.66 (2H, s, $ArCH_2N$), 3.80 (6H, t, $J = 6$ Hz, 1′-CH_2O), 7.04 (4H, m, Ar). ^{13}C NMR ($CDCl_3$), δ (ppm): 29.23 (N–C–Si), 49.71 (C-4), 51.07 (2′C–N), 54.22 (C-3), 57.64 (C-O), 59.88 (C-1), 124.95 (C-5), 125.33 (C-7), 126.40 (C-8), 128.25 (C-6), 134.65 (C-9), 136.43 (C-10). Anal. found: C, 59.75; H, 7.51; N, 8.77. Calcd for $C_{16}H_{24}N_2O_3Si$: C, 59.97; H, 7.55; N, 8.74%.

*1-{3-[N-(1,2,3,4-tetrahydroisoquinolyl)propyl]} silatrane (**6**)*

The reagent mixture of compound **2** (1.00 g, 3.39 mmol) and triethanolamine (0.505 g, 3.39 mmol) in hexane (5 ml) was heated at 60 °C under argon for 1 h. The precipitate formed was filtered off, washed with hexane and recrystallized from a mixture of $CHCl_3$ and hexane (1 : 1) to give colourless crystals of product **6**; yield 1.10 g, 93%; m.p. 134–135 °C. ^{1}H NMR ($CDCl_3$), δ (ppm): 0.47 (2H, m, CH_2Si), 1.73 (2H, m, β-CH_2), 2.56 (2H, m, 4-CH_2), 2.82 (8H, t, α-CH_2N + 2′-CH_2N), 2.87 (2H, t, $J = 5$ Hz, 3-CH_2), 3.67 (2H, bs, $ArCH_2N$, 3.80 (6H, t, $J = 6$ Hz, 1′-CH_2O), 7.09 (4H, m, Ar). ^{13}C NMR ($CDCl_3$), δ (ppm): 13.87 (C–Si), 22.38 (β–C–N), 29.20 (C-4), 50.87 (α–C–N), 51.03 (2′–C–N), 56.07 (C-3), 57.72 (C-O), 62.43 (C-1), 125.21 (C-5), 125.66 (C-7), 126.46 (C-8), 128.43 (C-6), 134.53 (C-9), 135.40 (C-10). Anal. found: C, 62.10; H, 8.11; N, 8.06. Calcd for $C_{18}H_{28}N_2O_3Si$: C, 62.03; H, 8.10; N, 8.04%.

*3-[N-(1,2,3,4-tetrahydroquinolyl)] propyltrimethoxysilane (**7**)*

The stirred solution of tetrahydroquinoline (6.65 g, 0.05 mol), (3-chloropropyl)trimethoxysilane (9.94 g, 0.05 mol) and triethylamine (10.10 g, 0.10 mol) in 20 ml of dimethylformamide was heated at 80 °C under argon for 11 h. The precipitate of ammonium salt was filtered off and product **7** was isolated by vacuum distillation as dark yellow liquid; yield 2.1 g, 14%; b.p. 162 °C/8 mmHg. ^{1}H NMR ($CDCl_3$), δ (ppm): 0.61 (2H, t, $J = 4$ Hz, $SiCH_2$), 1.67 (2H, m, β-CH_2), 1.90 (2H, m, 3-CH_2), 2.69 (2H, t, $J = 5$ Hz, 4-CH_2), 3.20 (4H, m, 2-CH_2 + NCH_2), 3.55 (9H, s, OCH_3), 6.51–7.07 (4H, m, Ar). ^{13}C NMR ($CDCl_3$), δ (ppm): 6.05 (C–Si), 18.83 (β–C–N), 21.62 (C-3), 27.69 (C-4), 48.99 (C-2), 50.22 (α–C–N), 54.06 (C–O), 110.93 (C-5), 115.70 (C-7), 122.23 (C-6), 126.74 (C -8), 128.84 (C-10), 144.44 (C -9). Anal. found: C, 61.08; H, 8.43; N, 4.78. Calcd for $C_{15}H_{25}NO_3Si$: C, 61.02; H, 8.47; N, 4.76%. MS: $[M]^+$: $m/z = 295$ (10%); [M - OMe]$^+$: $m/z = 264$ (1%); [M-$CH_2CH_2Si(OMe)_3$]$^+$: $m/z = 146$ (100%).

*3-[N-(4,4-dimethyl-4-sila-1,2,3,4-tetrahydroisoquinolyl]propyltriethoxysilane (**8**)*

Dimethyl(2-bromomethylphenyl)chloromethyl silane (13.88 g, 0.05 mol) was dropped into the stirred mixture of (3-aminopropyl)triethoxysilane (11.7 g, 0.05 mol) and triethylamine (10.10 g, 0.10 mol); the mixture was heated at 80 °C under argon for 11 h. The precipitate of ammonium salt was filtered off and product **8** was isolated by vacuum distillation as yellow liquid; yield 4.44 g, 23%; b.p. 193–195 °C/8 mmHg. ^{1}H NMR ($CDCl_3$), δ (ppm): 0.26 (6H, s, $SiMe_3$), 0.64 (2H, t, $J = 4$ Hz, cycl.$SiCH_2$), 1.21 (9H, t, $J = 7$ Hz, C-CH_3), 2.14 (2H, s, $SiCH_2N$), 2.51 (2H, t, α-CH_2N), 3.59 (2H, s $ArCH_2N$), 3.78 (6H, m, OCH_2), 7.00–7.54 (4H, m, Ar). ^{13}C NMR ($CDCl_3$), δ (ppm): −2.14 (C–Si-4), 7.62 (C–Si–O), 18.15 (C-2′), 20.14 (β–C–N), 43.78 (C-3), 58.13 (C–O), 61.30 (α–C–N), 65.03 (C-1), 125.80 (C-5), 126.55 (C-7), 128.66 (C-8), 133.43 (C-6),133.48 (C-9), 145.73 (C-10). Anal. found: C, 59.89; H, 9.23; N, 3.66. Calcd for $C_{19}H_{35}NO_3Si_2$: C, 59.84; H, 9.19; N, 3.64%. MS: $[M]^+$: $m/z = 381$ (1%); [M-Me]$^+$: $m/z = 366$ (3%); [M-3Me]$^+$: $m/z = 336$ (3%); [M-$CH_2CH_2Si(OEt)_3$]$^+$: $m/z = 190$ (100%); [M-$CH_2CH_2CH_2Si(OEt)_3$]$^+$: $m/z = 176$ (36%).

Crystal structure determination

The crystal structure of compound **6** was established by X-ray structure analysis. A single crystal diffractometer 'Syntex $P2_1$' (MoK_α-radiation, $\lambda = 0.71073$ Å) was used for data collection. Colourless crystals of **6**, $C_{18}H_{28}N_2O_3Si$, $M = 348.52$, were monoclinic, space group $P2_1/c$ with $a = 12.375(7)$, $b = 9.173(5)$, $c = 17.244(8)$ Å, $\beta = 108.08(4)°$; $V = 1860.8(17)$ Å^3, $Z = 4$, $F(000) = 752$, $\mu = 0.144$ mm^{-1}, $D_{calc} = 1.244$ g/cm^3, $2\theta_{max} = 48.0°$. A total of 1768 reflection intensities were collected at room temperature using $\theta/2\theta$ scan technique; one standard reflection showed no significant decay. The structure was solved using the maximum-determinant method.[20] For structure refinement, 1299 independent reflections with $|F| > 4\sigma(F)$ were used. The structure refinement was carried out with the AREN complex of programs.[21] The C4, C6 and C11 atoms were found to be disordered over two sites with 50% site occupancy factors; these atoms were refined isotropically. The final R-factor is 0.088. CCDC deposition no. −269 459.

In vivo psychotropic activity

Compounds **4** and **6** were studied for neurotropic activity on BALB/c mice of both sexes weighing 18–23 g in autumn according to the procedure described in Zablotskaya *et al*.[12]

In vitro cytotoxicity

Monolayer tumour cell lines MG-22A (mouse hepatoma), HT-1080 (human fibrosarcoma) and normal mouse fibroblasts (NIH 3T3) were cultivated for 72 h in DMEM (Dulbecco's modified Eagle's medium) standard medium (Sigma) without an indicator and antibiotics.[22] Tumour cell lines were taken from the European Collection of Cell Culture (ECACC).

After the ampoule was thawed, not more than four passages were performed. The control cells and cells with tested substances in the range $2–5 \times 10^4$ cells/ml concentration (depending on line nature) were placed on a separate 96-well plates. The volume of each plate was 200 µl. Solutions containing test compounds were diluted and added to wells to give final concentrations of 50, 25, 12.5 and 6.25 µg/ml. Control cells were treated in the same manner but in the absence of test compounds. The plates were incubated for 72 h, 37 °C, 5% CO_2. The number of surviving cells was determined using tri(4-dimethylaminophenyl)methyl chloride (crystal violet, CV) or 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) coloration, which was assayed by multiscan spectrophotometer. The number of living cells on the control plate was taken in calculations as 100%.[22,23] The TD_{50} was calculated using Graph Pad Prism® 3.0 program, $r < 0.05$.

RESULTS AND DISCUSSION

Chemistry

[*N*-(1,2,3,4-Tetrahydroisoquinolyl)]methyltriethoxysilane (**1**), 3-[*N*-(1,2,3,4-tetrahydroisoquinolyl)]propyltrimethoxysilane (**2**) and 3-[*N*-(1,2,3,4-tetrahydroquinolyl)]propyltrimethoxysilane (**7**) were synthesized by alkylation of 1,2,3,4-tetrahydroisoquinoline or 1,2,3,4-tetrahydroquinoline with the corresponding chloroalkyltrialkoxysilanes in the presence of triethylamine. 3-[*N*-(4,4-dimethyl-4-sila-1,2,3,4-tetrahydroisoquinolyl]propyltriethoxysilane (**8**) was obtained by the cyclization of dimethyl[(2-bromomethyl)phenyl]chloromethylsilane[19] with (3-aminopropyl)triethoxysilane. All the syntheses were carried out under dry argon. Thus the obtained [*N*-(1,2,3,4-tetrahydroisoquinolyl)]methyltriethoxysilane (**1**) and 3-[*N*-(1,2,3,4-tetrahydroisoquinolyl)]propyltrimethoxysilane (**2**) were transformed further into corresponding salts **3** and **4** by interaction with methyl iodide, and into silatranes **5** and **6** by interaction with triethanolamine (Scheme 1).

The synthesized compounds **1–8** were characterized by the data from elemental analysis, ^{1}H, ^{13}C and ^{29}Si NMR, and chromatomass-spectroscopy. The ^{29}Si NMR spectral data of compounds are presented in Table 1.

Comparative study of ^{29}Si shifts in newly synthesized compounds (Table 1) suggested donor–acceptor interaction between nitrogen and silicon atom in compounds **1, 5** and **6**, that increased electron density at Si nuclei, revealing a stronger increment of the N → Si transannular bond (compounds **6**) in comparison with N → Si α-effect (compound **1**).

Molecular structure of 3-[*N*-(1,2,3,4-tetrahydroisoquinolyl)]propylsilatrane (6)

The molecular structure of $C_9H_{10}N(CH_2)_3Si(OCH_2CH_2)_3N$, 6, is shown in Fig. 1 and selected geometric parameters

Table 1. ^{29}Si NMR data of compounds **1** and **4–8**

Compound	$\delta^{29}Si$, ppm
1	−51.98
4	−44.80
5	−72.71
6	−64.80
7	−42.13
8	−13.23; −44.90

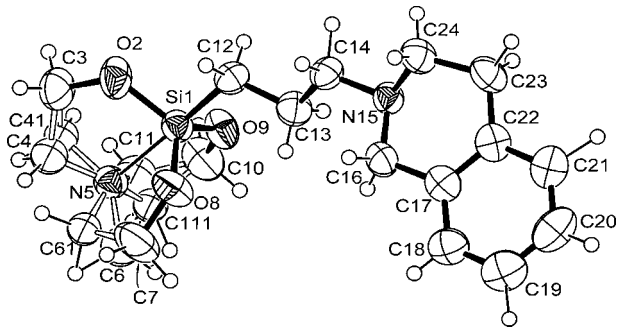
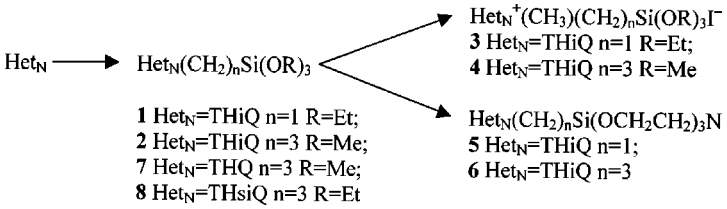


Figure 1. Molecular structure of compound **6**.

Table 2. Selected bond lengths (Å) and angles (°) of compound **6**

N5 → Si1	2.207(7)
Si1–O2	1.644(6)
Si1–O8	1.645(6)
Si1–O9	1.653(6)
Si1–C12	1.868(8)
C12–C13	1.519(11)
N15–C14	1.460(9)
N15–C16	1.453(9)
N15–C24	1.451(9)
O2–Si1–O8	117.4(3)
O2–Si1–O9	117.6(3)
O8–Si1–O9	119.0(3)
O2–Si1–C12	97.3(3)
O8–Si1–C12	97.9(3)
O9–Si1–C12	99.3(3)
O2–Si1 ← N5	81.8(3)
O8–Si1 ← N5	81.7(3)
O9–Si1 ← N5	82.0(3)
N5 → Si1–C12	178.7(3)
C14–N15–C16	111.8(6)
C14–N15–C24	111.0(6)
C16–N15–C24	108.2(6)

are collected in Table 2. The structure features a pentacoordinate geometry for the silicon atom, defined by one C, one N and three O atoms, and shows a distorted trigonal bipyramidal configuration stabilized by the transannular N → Si interaction. The Si…N transannular bond length is equal to 2.207(7) Å, and this is close to that observed in



Scheme 1. Synthesis of compounds **1–8**. Het$_N$ = 1,2,3,4-tetrahydroquinoline (THQ), 1,2,3,4-tetrahydroisoquinoline (THiQ) and 4,4-dimethyl-4-sila-1,2,3,4-tetrahydroisoquinoline (THsiQ).

3-thiocyanatopropylsilatrane, 2.209(4) Å.[24] For other propylsilatrane derivatives the transannular bonds are shorter. These values are 2.181(7) Å in (3-chloropropyl)silatrane,[25] 2.164(4) Å in (3-cyanopropyl)silatrane,[26] 2.165(2) Å in [*N*-(2-aminoethyl)aminopropyl]silatrane,[27] 2.173(2) Å in (3-hydroxypropyl)silatrane[28] and 2.177(4) Å in (3-mercaptopropyl)silatrane.[29] There are two forms of the molecule **6** in the crystal structure: right and left zigzag conformation of the atrane cage with 50% occupancy each for the disordered pairs of C4, C41, C6, C61, C11 and C111 atoms (see the Experimental section). Both molecules exist in the same crystallographic position and the disorder is not removed by a fall in symmetry of the crystal lattice. The six-membered ring, N15, C16, C17, C22, C23 and C24, is near to the envelope conformation. The deviation of pyramidal nitrogen atom N15 from the plane of C16, C17, C22, C23, C24 is 0.656(6) Å. The intermolecular contacts in the crystal structure correspond to sums of van der Waals radii.

Biological evaluation

Neurotropic properties and cytotoxicity of 3-[*N*-(1,2,3,4-tetrahydroisoquinolyl)]propyltrimethoxysilane methiodide (**4**) and 1-{3-[*N*-(1,2,3,4-tetrahydroisoquinolyl)propyl]} silatrane (**6**) were investigated.

The compounds were tested for psychotropic activity *in vivo* on mice under intraperitoneal administration in doses of 5 mg kg^{-1}. The action on the CNS was evaluated on indicators of hexenal- and ethanol-induced narcosis, phenamine hyperthermia, phenamine hyperactivity, corazol-induced convulsions, electroshock, conditional reflex of passive avoidance, retrograde amnesia, training and Porsolt. The results of biological investigation are presented in Table 3.

The investigated compounds possessed strongly marked sedative action. The result of their interaction with ethanol and hexenal in the test of ethanol- and hexenal-induced anaesthesia was the opposite. With respect to hexenal-induced narcosis, 3-[*N*-(1,2,3,4-tetrahydroisoquinolyl)]propyltrimethoxysilane methiodide (**4**) was the more active compound, prolonging the hexenal anaesthesia by 23%. In contrast, 1-{3-[*N*-(1,2,3,4-tetrahydroisoquinolyl)propyl]}silatrane (**6**) exhibited the antagonistic action to ethanol, prolongating the ethanol action by 25% in the test of ethanol-induced narcosis.

Both compounds were phenamine antagonists. 3-[*N*-(1,2,3,4-tetrahydroisoquinolyl)]propyltrimethoxysilane methiodide (**4**) almost fully depressed the phenamine action (by 87%). Contrary to the test for maximal electroshock, where no protective properties were found, compounds **4** and **6** demonstrated an anticonvulsive activity in the test for corazol-induced convulsions, increasing the threshold of corazol convulsions in tonic phase to 58%.

The cytotoxicity of compounds **4** and **6** was tested *in vitro* on two monolayer tumour cell lines: MG-22A (mouse hepatoma), HT-1080 (human fibrosarcoma), and normal 3T3 cell lines. The experimental evaluation of cytotoxicity properties is presented in Table 4.

The compounds tested had no toxic effect on HT-1080 and 3T3 cell lines, revealing low cytotoxic effect on MG-22A cell lines, and were non-toxic.

Table 3. Neurotropic activity of compounds **4** and **6** *in vivo* (on mice)

Test	**4**	**6**
Phenamine hyperthermia (°C, 60 min)	−3.1	−2.0
Phenamine-induced hyperactivity, 60 min (%)[a]	13[b]	59[b]
Hexenal-induced narcosis (%)[a]	123[b]	100
Ethanol-induced narcosis (%)[a]	110	125[b]
Corazol-induced convulsions (clonic/tonic) (%)[a]	108/158[b]	99/142[b]
Electroshock (mg kg^{-1})	>50	>50
Retrograde amnesia (%)[a]	63.3	63.3

[a] With respect to control (100%).
[b] Differences in relation to control are statistically significant at $p < 0.5$.

Table 4. *In vitro* cell cytotoxicity against various cell lines and intracellular NO generation caused by compounds **4** and **6**

	HT-1080			MG-22A			NIH 3T3	
	ID_{50}, μg/ml			ID_{50}, μg/ml				
Compound	CV	MTT	NO 100%	CV	MTT	NO 100%	ID_{50}, μg/ml	LD_{50}, mg/kg
4	**	**	7	100	>100	20	**	>2000
6	**	**	6	100	88	14	416	1603

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REFERENCES

1. Lukevics E, Segal I, Zablotskaya A, Germane S. *Chem. Heterocycl. Comp.* 1996; **32**: 682.
2. Segal I, Zablotskaya A, Lukevics E. *Chem. Heterocycl. Comp.* 2005; **41**: 713.
3. Lukevics E, Zablotskaya A. *Metalorg. Khim.* 1993; **6**: 263.
4. Lukevics E, Zablotskaya A, Segal I, Germane S, Popelis J. *Chem. Heterocycl. Comp.* 2003; **39**: 813.
5. Zablotskaya A, Segal I, Germane S, Shestakova I, Domracheva I, Nesterova A, Geronikaki A, Lukevics E. *Chem. Heterocycl. Comp.* 2002; **38**: 859.
6. Milne GWA (ed.). *Ashgate Handbook of Antineoplastic Agents*. Gower: Aldershot, 2000.

7. Malonne H, Atassi G. *Anticancer Drugs* 1997; **8**: 811.
8. Lai Y-Y, Huang L-J, Lee K-H, Xiao Z, Bastow KF, Yamori T, Kuo S-C. *Bioorg. Med. Chem.* 2005; **13**: 265.
9. Ferlin MJ, Gatto B, Chiarelotto G, Palumbo M. *Bioorg. Med. Chem.* 2001; **9**: 1843.
10. Cagir A, Eisenhauer BM, Gao R, Thomas SJ, Hecht SM. *Bioorg. Med. Chem.* 2004; **12**: 6287.
11. Deady LW, Desneves J, Kaye AJ, Finlay GJ, Baguley BC, Denny WA. *Bioorg. Med. Chem.* 2001; **9**: 445.
12. Zablotskaya A, Segal I, Germane S, Shestakova I, Lukevics E, Kniess T, Spies H. *Appl. Organomet. Chem.* 2002; **16**: 550.
13. Heier RF, Dolak LA, Duncan JN, Hyslop DK, Lipton MF, Martin IJ, Mauragis MA, Piercey MF, Nichols NF, Schreur PJKD, Smith MW, Moon MW. *J. Med. Chem.* 1997; **40**: 639.
14. Mokrosz MJ, Bojarski AJ, Duszynska B, Tatarczynska E, Klodzinska A, Deren-Wesolek A, Charakchieva-Minol S, Chojnacka-Wojcik E. *Bioorg. Med. Chem.* 1999; **7**: 287.
15. Matecka D, Lewis D, Rothman RB, Dersch CM, Wojnicki FHE, Glowa JR, DeVries AC, Agu Pert, Rice KC. *J. Med. Chem.* 1997; **40**: 705.
16. Sui Xiong Cai, Kher SM, Zhou Zhang-Lin, Ilyin V, Espitia SA, Tran M, Hawkinson JE, Woodward RM, Weber E, Keana JFW. *J. Med. Chem.* 1997; **40**: 730.
17. *Anticonvulsants*. SmithKline Beecham Pharmaceuticals: UK, 2000.
18. Lukevics E, Segal I, Zablotskaya A, Germane S. *Molecules* 1997; **2**: 180.
19. Sato Y, Fukami Y, Shirai H. *J. Organomet. Chem.* 1978; **153**: 193.
20. Mishnev AF, Belyakov SV. *Krystallografiya.* 1988; **33**: 835.
21. Andrianov VI. *Krystallografiya* 1987; **32**: 228.
22. Freshney PJ. In *Culture of Animal Cells (A Manual of Basic Technique)*. Wiley-Liss: New York, 1994; 296.
23. Fast DJ, Lynch RC, Leu RW. *J. Leucocyt. Biol.* 1992; **52**: 255.
24. Dai Jinbi, Zhang Jiping, Wu Yexin, Wu Guanli. *Chin. J. Struct. Chem.* 1983; **2**: 101.
25. Kemme AA, Bleidelis YaYa, D'yakov VM, Voronkov MG. *Izv. Akad. Nauk., Ser. Khim.* 1976; 2400.
26. Wang Shoudao, Hu Ninghai. *Sci. Sin., Ser. B (Engl. Edn)* 1983; **26**: 1233.
27. Hencsei P, Parkanyi L, Kovacs I. *Chem. Heterocycl. Comp.* 1996; **32**: 1376.
28. Hencsei P, Parkanyi L, Fulop V, Baryshok VP, Voronkov MG, Kuznetsova GA. *J. Organomet. Chem.* 1988; **346**: 315.
29. Hencsei P, Kovacs I, Fulop V. *J. Organomet. Chem.* 1989; **377**: 19.