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Silyl modification of biologically active compounds. 13.† Synthesis, cytotoxicity and antibacterial action of *N*-methyl-*N*-(2-triorganylsiloxyethyl)-1,2,3,4-tetrahydro(iso) quinolinium iodides

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A series of *N*-methyl-*N*-(2-triorganylsiloxyethyl)-1,2,3,4-tetrahydro(iso)quinolinium iodides has been synthesized via dehydrocondensation reaction of *N*-(2-hydroxyethyl)-1,2,3,4-tetrahydroisoquinoline, *N*-(2-hydroxyethyl)-1,2,3,4-tetrahydroquinoline and 4,4-dimethyl-*N*-(2-hydroxyethyl)-4-sila-1,2,3,4-tetrahydroisoquinoline with trialkyl(aryl)hydrosilanes and subsequent alkylation, and characterized by ^{1}H, ^{13}C and ^{29}Si NMR and mass spectroscopy. The biological activity data exhibited a marked enhancement of inhibitory activity against tumour cell lines and almost all the test bacterial/fungal strains in comparison with their 2-hydroxyethyl precursors. Cytotoxicity in the microgram range against HT-1080 (human fibrosarcoma) and MG-22A (mouse hepatoma) cancer cell lines was observed for most of compounds. Copyright © 2012 John Wiley & Sons, Ltd.

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Keywords: silicon; silylation; choline; drug research; tetrahydro(iso)quinoline; antitumour activity; antimicrobial activity

Introduction

Functional groups containing silicon might provide lipophilicity to a drug, allowing it to pass the cell membrane by passive diffusion. This strategy has been successfully applied in the antitumour drug analogues silatecans (silicon-containing camptothecins)[1,2] and silaplatins (cisplatin analogues),[3] the HIV-1 reverse transcriptase inhibitor TSAO-T[4] and the effective anabolic 'silabolin'.[5] Some silicon-containing drugs have entered phase I or II human clinical trials.[6–10] Silylation of biologically active compounds, possessing hydrophilic functional groups, is one of the most effective methods for increasing lipophilicity, ensuring drug permeability through lipophilic barriers inside living organisms; silylation therefore can positively influence biological activity appearance or enhancement.[11,12] Trialkylsilyl derivatives of polyene macrolide antibiotic nystatin had a high level of antifungal activity against a wide set of test strains and their acute toxicity (LD_{50}) was two to three times lower than that of the initial antibiotic.[13] A 2′-*O*-*tert*-butyldimethylsilyl group was found to be necessary for optimal antiproliferative activity of N^6,5′-bis-ureidoadenosine nucleosides.[14] Its 2′,3′-bis-O-*tert*-butyldimethylsilyl derivative exhibited broad-spectrum antiproliferative activity and was accepted as a new member of the N^6,5′-bis-ureidoadenosine class of anticancer nucleosides.[15] Cytotoxicity study of (2*R*,3*S*)-disubstituted tetrahydropyranes bearing a *tert*-butyldimethylsilyl group at position 3 of the ring considerably induced cytotoxicity against HL60 human leukaemia cells and MCF7 breast cancer cells *in vitro* and pointed to the relevant role of the *tert*-butyldimethylsilyl group in the enhancement of cytotoxic action.[16] 5′-Triphenylsilyl modification of deoxyuridine acyclic analogues resulted in obtaining more potent inhibitors of *Plasmodium falciparum* deoxyuridine 5′-triphosphate nucleotidohydrolase, a target for the development of antimalarial drugs, in comparison with their 5′-trityloxy derivatives.[17] Within our research activity, directed at the targeted modification of biologically active compounds aimed at the improvement of their biological properties, including increased drug accumulation and prolongation of drug retention inside cells, we have found that 5′-O-*tert*-butyldimethylsilyluridine, unlike uridine, exhibits antitumour activity, suppressing the development of human lung fibrosarcoma cells,[18] and *N*-(4-phenyl-2-thiazolyl)-2-(4-trimethylsiloxypiperidino)acetamide revealed the higher cytotoxic effect on MG-22A cells in comparison with its unsilylated analogue.[19]

We have reported recently that silylation represents a plausible strategy to modulate cytotoxic and antibacterial properties in choline and colamine analogues. A first series of silylated choline analogues was synthesized.[20] It was demonstrated that some

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silyl-modified aliphatic ethanolamines are low toxic compounds and reveal biological activity, inhibiting tumour growth and possessing antimicrobial properties, in comparison with their unsilylated precursors. Rather small structural modifications (for instance, silyl group nature) can significantly influence their activity. Inspired by the results, and to make more general conclusions, we have synthesized a new series of silylated derivatives of *N*-(2-hydroxyethyl)-1,2,3,4-tetrahydroisoquinoline, which could be considered heterocyclic choline analogues, possessing an ambivalent nature, namely, lipophilic and hydrophilic fragment combination in one molecule, and investigated their biological properties against tumour HT-1080 and MG-22A and normal NIH 3 T3 cell lines, and also against some Gram-positive – *Bacillus cereus* MSCL 330 (BC) and *Staphylococcus aureus* MSCL 334 (SA) – and Gram-negative microbial strains – *Proteus mirabilis* MSCL 590 (PM), *Escherichia coli* MSCL 332 (EC) and *Pseudomonas aeruginosa* MSCL 331 (PA) – and fungi – *Candida albicans* MSCL 378 (CA) – in comparison with their 2-hydroxyethyl precursors. Choline is recognized as a metabolic marker of active tumour tissue due to its ability to accumulate in cancer cells.[21] There are some structural requirements of choline derivatives for 'conversion' of pneumococcal amidase, and this amino alcohol has been identified as an allosteric ligand necessary for recognition and degradation of cell wall by the enzyme.[22]

On the other hand, quinoline derivatives, including tetrahydro(iso)quinoline ones, are biologically active compounds possessing a wide spectrum of biological activity. Structural fragments of quinoline and its derivatives are included in the molecules of antitumour drugs, for instance in amsacrine, bruneomicine and vinblastine.[5,23,24] The tetrahydroisoquinoline ring system is an important structural motif[25] that is commonly encountered in naturally occurring alkaloids, with interesting biological activities. Typical examples include saframycin-B,[26] narciclasine[27] and ecteinascidin-743.[28] In this regard, tetrahydroisoquinoline has become widely identified as a 'privileged' structure, with representation in several medicinal agents of diverse therapeutic action, and are potential drug candidates.[29,30] Tetrahydroisoquinoline derivatives possess antitumour properties.[31–33]

Experimental

Chemicals and Instrumentation

^{1}H, ^{13}C and ^{29}Si NMR spectra were obtained on Varian Mercury 200 and Varian Mercury 400 spectrometers with $CDCl_3$ or DMSO-d_6 as solvent and $CDCl_3$ ($\delta = 7.25$ ppm for $CHCl_3$) as internal standard for compounds containing a silicon atom in the molecule, and with hexamethyldisiloxane ($\delta = 0.055$ ppm) as internal standard for the other compounds. Heteronuclear single-quantum correlation and heteronuclear multiple-bond correlation NMR 2-D correlation spectra were taken for compounds **1–4**, **8**, **9d**, **12d**, **12 g** and **12 h** for an unambiguous assignment of ^{1}H and ^{13}C signals. Mass spectra under electron impact conditions were recorded on an Agilent Technologies 5975C mass spectrometer (GC 7890A, 70 eV) and on Waters 3100 mass spectrometer (LC Alliance Waters 2695). Elemental analyses (C, H, N) were performed on a Carlo Erba 1108 elemental analyser. Elemental analysis results agreed with calculated values. Melting points were determined on a Boetius melting point apparatus and were taken uncorrected. Analytical thin-layer chromatography (TLC) was performed on 60 F_{254} (Merck) silica gel plates and Machery-Nagel silica gel plastic plates, with visualization under UV (254 nm). Column chromatography was performed using Merck silica gel (0.040–0.063 nm). Solvents and reagents used in this study were purchased from Fluka, Acros and Aldrich. 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.

Synthesis

N-(2-Hydroxyethyl)-1,2,3,4-tetrahydroisoquinoline **(1)**,[34] *N*-(2-hydroxyethyl)-1,2,3,4-tetrahydroquinoline **(2)**,[34], *N*-(2-hydroxyethyl)-*N*-methyl-1,2,3,4-tetrahydroisoquinolinium iodide **(3)**,[34] *N*-(2-hydroxyethyl)-*N*-methyl-1,2,3,4-tetrahydroquinolinium iodide **(4)**,[34] bromomethyldimethyl(2-methylphenyl)silane **(5)**,[34] (2-bromomethylphenyl)bromomethyl-dimethylsilane **(6)**,[34] 4,4-dimethyl-*N*-(2-hydroxyethyl)-4-sila-1,2,3,4-tetrahydroisoquinoline **(7)**[34] and 4,4-dimethyl-*N*-(2-hydroxyethyl)-*N*-methyl-4-sila-1,2,3,4-tetrahydroisoquinolinium iodide **(8)**[34] were characterized by comparing their ^{1}H NMR spectra with those reported in the literature.

An outline is given in Scheme 1.

N-(2-Diethylmethylsiloxyethyl)-1,2,3,4-tetrahydroisoquinoline (**9a**)

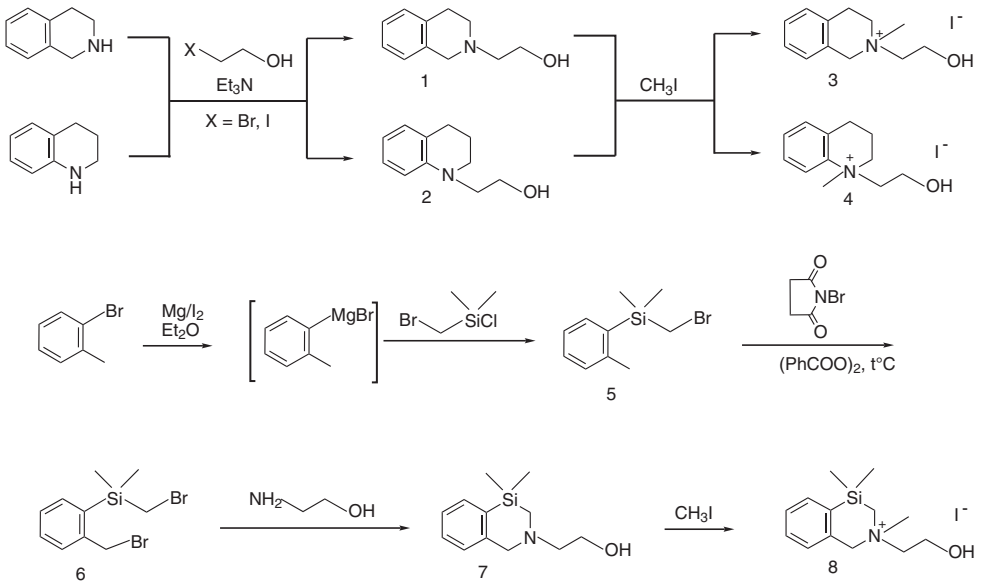
Diethylmethylsilane (0.59 g, 5.77 mmol) was added to *N*-(2-hydroxyethyl)-1,2,3,4-tetrahydroisoquinoline (0.88 g, 4,97 mmol) and the reaction mixture was heated at 70 °C under stirring for 4 h in the presence of a trace amount of metallic sodium. The course of the reaction was followed using data provided by gas chromatography–mass spectrometry (GC-MS). If necessary (presence of unreacted alcohol detected by TLC), more hydrosilane was added. Once the dehydrocondensation reaction had reached completion, the reaction mixture was cooled to room temperature and the solid traces were filtered off. The resulting crude residue was purified by column chromatography on silica gel eluted with chloroform–methanol (4:1) to give the desired diethylmethylsilyl ether as a clear light-yellow liquid.

Yield 0.77 g (56%). LC-MS (*m/z*, %): 278 (M^++1, 100), 277 (M^+, 58), 262 ($M^+ - CH_3$, 9), 248 ($M^+ - C_2H_5$, 12), 174 (32), 161 ($M^+ - OSi(C_2H_5)_2CH_3 + 1$, 52), 144 (26). GC-MS (*m/z*, %): 277 (M^+, 2), 262 ($M^+ - CH_3$, 3), 248 ($M^+ - C_2H_5$, 5), 146 ($M^+ - CH_2CH_2OSi(C_2H_5)_2CH_3$, 100), 132 (26). ^{1}H NMR ($CDCl_3$, δ, ppm): 012 (3H, s, $SiCH_3$), 0.66 (4H, m, $SiCH_2$), 1.00 (6H, m, C&bond;CH_3), 2.76 (2H, m, α-CH_2N), 2.86 and 2.97 (total 4H, m and m, 3- and 4-CH_2N), 3.75 (2H, m, 1-CH_2N), 3.88 (2H, t, $J = 6.6$ Hz, OCH_2), 7.0–7.2 (4H, m, 5-, 6-, 7- and 8-H). ^{13}C NMR ($CDCl_3$, δ, ppm): −5.01 ($SiCH_3$), 6.16 ($SiCH_2$), 6.70 ($SiCCH_3$), 28.99 (4-CH_2), 50.66 (3-CH_2N), 55.74 (1-CH_2N), 58.07 (OCH_2), 59.17 (α-CH_2N), 125.63 (7-C), 125.99 (8-C), 126.46 (6-C), 128.60 (5-C), 134.12 (9-C), 134.40 (10-C). ^{29}Si NMR ($CDCl_3$, δ, ppm): +19.90. Anal. calcd for $C_{16}H_{27}NOSi$: C, 69.26; H, 9.81; N, 5.05; found: 68.97; H, 9.73; N, 5.11.

N-(2-Triethylsiloxyethyl)-1,2,3,4-tetrahydroisoquinoline (**9b**)

Compound **9b** was obtained following the procedure described for **9a**, from 1.80 g (10.16 mmol) *N*-(2-hydroxyethyl)-1,2,3,4-tetrahydroisoquinoline (**1**) and 1.20 g (10.32 mmol) triethylsilane, as a clear light-yellow liquid.

Yield 2.25 g (77%). LC-MS (*m/z*, %): 292 (M^++1, 51), 291 (M^+, 49); 290 ($M^+ - 1$, 100), 262 ($M^+ - C_2H_5$, 32), 176 ($M^+ - Si(C_2H_5)_3$, 5), 158 (88), 131 (50). GC-MS (*m/z*, %): 291 (M^+, 1), 262 ($M^+ - C_2H_5$, 3), 146 ($M^+ - CH_2OSi(C_2H_5)_3$, 100), 132 ($M^+ - CH_2CH_2OSi(C_2H_5)_3 - 1$, 16). ^{1}H NMR ($CDCl_3$, δ, ppm): 0.63 (6H, m, $SiCH_2$), 0.97 (9H, m, $SiCCH_3$), 2.71 (2H, t, $J = 6.5$ Hz, α-CH_2N), 2.81 and 2.89 (total 4H, m and m, 3- and 4-CH_2N), 3.69 and 3.71 (total 2H, d and d,



Scheme 1. Synthesis of compounds **1–8**.

$J = 5.2$ Hz, 1-CH_2N), 3.84 (2H, t, $J = 6.5$ Hz, OCH_2), 6.9–7.2 (4H, m, 5-, 6-, 7- and 8-H). ^{13}C NMR ($CDCl_3$, δ, ppm): 4.41 ($SiCH_2$), 6.75 ($SiCCH_3$), 29.00 (4-CH_2), 51.60 (3-CH_2N), 56.65 (1-CH_2N), 60.23 (OCH_2), 61.22 (α-CH_2N), 125.51 (7-C), 126.03 (8-C), 126.51 (6-C), 128.61 (5-C), 134.16 (9-C), 134.82 (10-C). ^{29}Si NMR ($CDCl_3$, δ, ppm): +19.62. Anal. calcd for: $C_{17}H_{29}NOSi$: C, 70.07; H, 10.03; N, 4.80; found: C, 69.78; H, 10.04; N, 4.72.

N-(2-Di-*n*-butylethylsiloxyethyl)-1,2,3,4-tetrahidroisoquinoline (**9c**)

Compound **9c** was obtained following the procedure described for **9a**, from 0.89 g (5.00 mmol) *N*-(2-hydroxyethyl)-1,2,3,4-tetrahydroisoquinoline (**1**) and 1.21 g (7.02 mmol) dibutylethylsilane, as a clear light-yellow liquid.

Yield 1.31 g (75%). LC-MS (*m/z*, %): 348 (M^++1, 26), 347 (M^+, 100), 160 ($M^+ - OSi(C_4H_9)_2C_2H_5$, 25). GC-MS (*m/z*, %): 347 (M^+, 2), 318 ($M^+ - C_2H_5$, 3), 290 ($M^+ - C_4H_9$, 5), 146 ($M^+ - CH_2OSi(C_4H_9)_2C_2H_5$, 100), 132 ($M^+ - CH_2CH_2OSi(C_4H_9)_2C_2H_5 - 1$, 27). ^1H NMR ($CDCl_3$, δ, ppm): 0.52–0.71 (6H, m, $SiCH_2$), 0.93–1.10 (15H, m, $SiCCH_3$, $SiCCH_2CC$ and $SiCCCCH_3$), 1.79 (4H, m, $SiCCCH_2C$), 2.71 (2H, t, $J = 5.6$ Hz, α-CH_2N), 2.80 and 2.91 (total 4H, m and m, 3- and 4-CH_2), 3.69 (2H, s, 1-CH_2N), 3.70 (2H, t, $J = 5.6$ Hz, OCH_2), 7.0–7.2 (4H, m, 5-, 6-, 7- and 8-H). ^{13}C NMR ($CDCl_3$, δ, ppm): 4.09 ($SiCH_2$) and 8.36 ($SiCCH_3$), 22.13, 25.33, 25.97, 26.42 (CCH_2 CH_2 CH_3), 29.06 (4-CH_2), 50.72 (3-CH_2N), 55.79 (1-CH_2N), 58.12 (OCH_2), 59.27 (α-CH_2N), 125.53 (7-C), 126.05 (8-C), 126.53 (6-C), 128.63 (5-C), 134.16 (9-C), 134.42 (10-C). ^{29}Si NMR($CDCl_3$, δ, ppm): +16.74. Anal. calcd for: $C_{21}H_{37}NOSi$: C, 72.56; H, 10.73; N, 4.03; found: C, 72.80; H, 10.65; N, 4.10.

N-(2-Di-*n*-heptylmethylsiloxyethyl)-1,2,3,4-tetrahydroisoquinoline (**9d**)

Compound **9d** was obtained following the procedure described for **9a**, from 0.89 g (5.00 mmol) *N*-(2-hydroxyethyl)-1,2,3,4-tetrahydroisoquinoline (**1**) and 1.46 g (6.02 mmol) diheptylmethylsilane, as clear yellow liquid.

Yield 1.19 g (57%). LC-MS (*m/z*, %): 417 (M^+, 71), 416 ($M^+ - 1$, 100), 318 ($M^+ - C_7H_{15}$, 15), 161 ($M^+ - OSi(C_7H_{15})_2CH_3 + 1$, 98), 160 ($M^+ - OSi(C_7H_{15})_2CH_3$, 57). GC-MS (*m/z*, %): 318 ($M^+ - C_7H_{15}$, 9), 158 ($M^+ - OSi(C_7H_{15})_2CH_3 - 2$, 2), 146 ($M^+ - CH_2OSi(C_7H_{15})_2CH_3$, 100), 132 ($M^+ - CH_2CH_2OSi(C_7H_{15})_2CH_3 - 1$, 27). ^1H NMR ($CDCl_3$, δ, ppm): 0.08 (3H, s, $SiCH_3$), 0.55 (4H, m, $SiCH_2$), 0.88 (6H, t, $J = 6.8$ Hz, $2CH_3$), 1.26 (20H, m, $10CH_2$), 2.70 (2H, t, $J = 6.4$ Hz, α-CH_2N), 2.80 and 2.88 (total 4H, m and m, 3- and 4-CH_2), 3.71 (4H, m, 1-CH_2N and OCH_2), 7.1–7.20 (4H, m, 5-, 6-, 7- and 8-H). ^{13}C NMR ($CDCl_3$, δ, ppm): −4.10 ($SiCH_3$), 14.12 (CH_3), 15.02 ($SiCH_2$), 22.70, 23.19, 29.03, 29.05, 31.82 and 33.52 (CH_2, 4-CH_2), 50.68 (3-CH_2N), 55.78 (1-CH_2N), 58.08 (OCH_2), 59.16 (α-CH_2N), 125.52 (7-C), 126.05 (8-C), 126.54 (6-C), 128.61 (5-C), 134.18 (9-C), 134.46 (10-C). ^{29}Si NMR ($CDCl_3$, δ, ppm): +18.20. Anal. calcd for: $C_{26}H_{47}NOSi$: C, 74.75; H, 11.34; N, 3.35; found: C, 75.04; H, 11.40; N, 3.29.

N-(2-*n*-Dimethyloctylsiloxyethyl)-1,2,3,4-tetrahydroisoquinoline (**9e**)

Compound **9e** was obtained following the procedure described for **9a**, from 0.88 g (4.95 mmol) *N*-(2-hydroxyethyl)-1,2,3,4-tetrahydroisoquinoline (**1**) and 1.28 g (7.43 mmol) dimethyloctylsilane, as a clear yellow oil.

Yield 1.32 g (77%). LC-MS (*m/z*, %): 348 (M^++1, 100), 347 (M^+, 62), 332 ($M^+ - CH_3$, 10). GC-MS (*m/z*, %): 332 ($M^+ - CH_3$, 5), 234 ($M^+ - C_8H_{17}$, 12), 146 ($M^+ - CH_2OSi(CH_3)_2C_8H_{17}$, 100). ^1H NMR ($CDCl_3$, δ, ppm): 0.10 (6H, s, $SiCH_3$), 0.60 (2H, m, $SiCH_2$), 0.87 (3H, t, $J = 6.8$ Hz, CH_3), 1.25 (12H, bs, &bond;CH_2&bond;), 2.70 (2H, t, $J = 6.6$ Hz, α-CH_2N), 2.80 and 2.89 (2H and 2H, t and t, $J = 5.9$ Hz, 3- and 4-CH_2), 3.69 (2H, s, 1-CH_2N), 3.81 (2H, t, $J = 6.6$ Hz, OCH_2), 6.9–7.0 (1H, m, 8-H), 7.0–7.2 (3H, m, 5-, 6- and 7-H). ^{13}C NMR ($CDCl_3$, δ, ppm): −2.13 ($SiCH_3$), 14.07 (CH_3), 16.31 ($SiCH_2$), 22.72, 23.24, 23.33, 29.25, 29.32, 29.39, 32.0, 33.43 (CH_2), 29.02 (4-CH_2), 51.48 (3-CH_2N), 56.61 (1-CH_2N), 60.06 (OCH_2), 60.92 (α-CH_2N), 125.51 (7-C), 126.05 (8-C), 126.54 (6-C), 128.57 (5-C), 134.22 (9-C), 134.83 (10-C). ^{29}Si NMR ($CDCl_3$, δ, ppm): +18.32. Anal. calcd for $C_{21}H_{37}NOSi$: C, 72.56; H, 10.73; N, 4.03; found: C, 72.28 ; H, 10.63; N, 4.10.

N-(2-*n*-Decyldimethylsiloxyethyl)-1,2,3,4-tetrahidroisoquinoline (**9f**)

Compound **9f** was obtained as clear yellow oil following the procedure described for **9a**, from 5.05 g (28.5 mmol) *N*-(2-hydroxyethyl)-1,2,3,4-tetrahydroisoquinoline (**1**) and 6.28 g (31.2 mmol) decyldimethylsilane, by heating the reagents at 80 °C under stirring for 15 h.

Yield 8.04 g (75%). LC-MS (*m/z*, %): 376 (M^++1, 100), 375 (M^+, 52), 160 ($M^+ - OSi(CH_3)_2C_{10}H_{21}$, 10). GC-MS (*m/z*, %): 375 (M^+, 2), 360 ($M^+ - CH_3$, 4), 234 ($M^+ - CH_3$&bond;$C_{10}H_{21}$, 9), 146 ($M^+ - CH_2OSi(CH_3)_2C_{10}H_{21}$, 100). ^{1}H NMR ($CDCl_3$, δ, ppm): 0.10 (6H, s, $SiCH_3$), 0.59 (2H, m, $SiCH_2$), 0.83 (3H, t, J = 6.8 Hz, CH_3), 1.2–1.4 (16H, m, CH_2), 2.71 (2H, t, J = 5.4 Hz, α-CH_2N), 2.81 and 2.90 (2H and 2H, t, J = 5.8 Hz, 3- and 4-CH_2), 3.70 (2H, s,1-CH_2N), 3.71 (2H, t, J = 5.4 Hz, OCH_2), 7.0–7.05 (1H, m, 8-H), 7.05–7.2 (3H, m, 5-, 6- and 7-H). ^{13}C NMR ($CDCl_3$, δ, ppm): −2.10 ($SiCH_3$), 14.09 (CH_3), 16.31 ($SiCH_2$), 22.66 23.16, 29.07, 29.34, 29.57, 29.64, 31.89 and 33.43 (CH_2), 28.98 (4-CH_2), 50.73 (3-CH_2N), 55.71 (1-CH_2N), 58.09 (OCH_2), 59.32 (α-CH_2N), 125.66 (7-C), 126.23 (8-C), 126.49 (6-C), 128.65 (5-C), 134.15 (9-C), 134.46 (10-C). ^{29}Si NMR ($CDCl_3$, δ, ppm): +18.36. Anal. calcd for $C_{23}H_{41}NOSi$: C, 73.54; H, 11.00; N, 3.73; found: C, 73.28; H, 10.54; N, 3.78.

N-(2-*n*-Dimethylundecylsiloxyethyl)-1,2,3,4-tetrahidroisoquinoline (**9 g**)

Compound **9 g** was obtained as a clear yellow oil following the procedure described for **9a**, from 0.76 g (3.54 mmol) *N*-(2-hydroxyethyl)-1,2,3,4-tetrahydroisoquinoline (**1**) and 0.91 g (4.25 mmol) dimethylundecylsilane, by heating the reagents at 90 °C under stirring for 15 h.

Yield 0.68 g (49%). LC-MS (*m/z*, %): 390 (M^++1, 100). GC-MS (*m/z*, %): 390 (M^++1, 1), 147 ($M^+ - CH_2OSi(CH_3)_2C_{11}H_{23} + 1$, 100). ^{1}H NMR ($CDCl_3$, δ, ppm): 0.07 (6H, s, $SiCH_3$), 0.53 (2H, m, $SiCH_2$), 0.88 (3H, t, J = 6.8 Hz, CH_3), 1.25 (18H, m, CH_2), 2.71 (2H, t, J = 5.8 Hz, α-CH_2N), 2.79 and 2.88 (2H and 2H, t and t, J = 5.9 Hz, 3- and 4-CH_2), 3.70 (4H, m, 1-CH_2N + OCH_2), 7.0–7.2 (4H, m, 5-, 6-, 7- and 8-H). ^{13}C NMR ($CDCl_3$, δ, ppm): −2.21 ($SiCH_3$), 14.03 (CH_3), 17.72 ($SiCH_2$), 22.63, 23.11, 29.28, 29.62, 29.74, 31.82 and 33.43 (CH_2), 28.92 (4-CH_2), 50.71 (3-CH_2N), 55.70 (1-CH_2N), 58.12 (OCH_2), 59.34 (α-CH_2N), 125.62 (7-C), 126.2 1(8-C), 126.39 (6-C), 128.63 (5-C), 134.02 (9-C), 134.31 (10-C). ^{29}Si NMR ($CDCl_3$, δ, ppm): +18,23. Anal. calcd for $C_{24}H_{43}NOSi$: C, 73.97; H, 11.12; N, 3.59; found: C, 74.21; H, 11.19; N, 3.52.

N-(2-*n*-Hexadecyldimethylsiloxyethyl)-1,2,3,4-tetrahidroisoquinoline (**9h**)

Compound **9 h** was obtained as a clear yellow oil following the procedure described for **9a**, from 0.80 g (4.50 mmol) *N*-(2-hydroxyethyl)-1,2,3,4-tetrahydroisoquinoline (**1**) and 2.56 g (9.0 mmol) hexadecyldimethylsilane, by heating the reagents at 85 °C under stirring for 15 h.

Yield 0.78 g (38%). LC-MS (*m/z*, %): 460 (M^++1, 100), 459 (M^+, 5), 160 ($M^+ - OSi(CH_3)_2C_{16}H_{33}$, 96). GC-MS (*m/z*, %): 459 (M^+, 2), 444 ($M^+ - CH_3$, 3), 234 ($M^+ - C_{16}H_{33}$, 9), 146 ($M^+ - CH_2OSi(CH_3)_2C_{16}H_{33}$, 100). ^{1}H NMR ($CDCl_3$, δ, ppm): 0.10 (6H, s, $SiCH_3$), 0.60 (2H, m, $SiCH_2$), 0.87 (3H, t, J = 6.8 Hz, CH_3), 1.24 (28H, m, CH_2), 2.71 (2H, t, J = 6.0 Hz, α-CH_2N), 2.80 and 2.87 (2H and 2H, m and m, 3- and 4-CH_2), 3.71 (2H, s, 1-CH_2N), 3.81 (2H, t, J = 6.0 Hz, OCH_2), 7.00 (1H, m, 8-H), 7.10 (3H, m, 5-, 6- and 7-H). ^{13}C NMR ($CDCl_3$, δ, ppm): −4.42 ($SiCH_3$), 14.13 (CH_3), 16.41 $SiCH_2$), 23.25, 24.42, 29.38, 29.61, 29.73, 31.94, 33.21 and 33.52 (CH_2), 29.02 (4-CH_2), 51.62 (3-CH_2N), 56.81 (1-CH_2N), 60.23 (OCH_2), 60.92 (α-CH_2N), 125.51 (7-C), 126.13 (8-C), 126.52 (6-C), 128.69 (5-C), 134.2 2 (9-C), 134.83 (10-C). ^{29}Si NMR ($CDCl_3$, δ, ppm): +18.33. Anal. calcd for $C_{29}H_{53}NOSi$: C, 75.75; H, 11.62; N, 3.05; found: C, 75.98; H, 11.69; N, 3.01.

N-(2-Methyldiphenylsiloxyethyl)-1,2,3,4-tetrahydroisoquinoline (**9i**)

Compound **9i** was obtained as a clear yellow oil following the procedure described for **9a**, from 0.63 g (3.8 mmol) *N*-(2-hydroxyethyl)-1,2,3,4-tetrahydroisoquinoline (**1**) and 1.0 g (5.0 mmol) methyldiphenylsilane.

Yield 1.22 g (91%). LC-MS (*m/z*, %): 374 (M^++1, 100), 296 ($M^+ - C_6H_5$, 98). GC-MS (*m/z*, %): 372 ($M^+ - 1$, 2), 295 ($M^+ - C_6H_5$ 1, 9), 146 ($M^+ - CH_2OSi(C_6H_5)_2CH_3$, 100). ^{1}H NMR ($CDCl_3$, δ, ppm): 0.55 (3H, s, $SiCH_3$), 2.64 (4H, m, 3- and 4-CH_2), 2.74 (2H, t, J = 6.0 Hz, α-CH_2N), 3.52 (2H, s, 1-CH_2N), 3.81 (2H, t, J = 6.0 Hz, OCH_2), 6.84 (1H, m, 8-H), 6.98 (3H, m, 5-,6- and 7-H), 7.2–7.5 (10H, m, C_6H_5-H). ^{13}C NMR ($CDCl_3$, δ, ppm): −2.98 ($SiCH_3$), 29.04 (4-CH_2), 51.49 (3-CH_2N), 56.41 (1-CH_2N), 60.02 (OCH_2), 61.68 (α-CH_2N), 125.42 (7-C), 126.03 (8-C), 126.51 (6-C), 128.66 (5-C), 134.12 (9-C), 134.71 (10-C), 127.81, 129.77, 134.32, 137.51 (C_6H_5-C). ^{29}Si NMR ($CDCl_3$, δ, ppm): −2.39. Anal. calcd for $C_{24}H_{27}NOSi$: C, 77.16; H, 7.28; N, 3.75; found: C, 76.85; H, 7.20; N, 3.81.

N-(2-*n*-Decyldimethylsiloxyethyl)-1,2,3,4-tetrahydroquinoline (**10**)

Compound **10** was obtained as clear yellow oil following the procedure described for **9a**, from 3.24 g (18.3 mmol) *N*-(2-hydroxyethyl)-1,2,3,4-tetrahydroquinoline (**2**) and 4.02 g (20.1 mmol) decyldimethylsilane, by heating the reagents at 80 °C under stirring for 26 h.

Yield 1.66 g (24%). LC-MS (*m/z*, %): 376 (M^++1, 50), 375 (M^+, 100). GC-MS (*m/z* %): 375 (M^+, 11), 234 ($M^+ - C_{10}H_{21}$, 3), 146 ($M^+ - CH_2O$-$SiMe_2C_{10}H_{21}$, 100). ^{1}H NMR ($CDCl_3$, δ, ppm): 0.07 (6H, s, $SiCH_3$), 0.57 (2H, m, $SiCH_2$), 0.87 (3H, t, J = 6.8 Hz, CH_3), 1.25–1.30 (16H, m, CH_2), 1.94 (2H, m, 3-CH_2N), 2.77 (2H, m, 4-CH_2), 3.32 (2H, m, 2-CH_2N), 3.39 (2H, t, J = 6.8 Hz, α-CH_2N), 3.73 (2H, t, J = 6.8 Hz, OCH_2),. 6.58, 6.67, 6.93 and 7.02 (total 4H, m, dd, m and m, 5-, 6-,7- and 8-H). ^{13}C NMR ($CDCl_3$, δ, ppm): −2.14 ($SiCH_3$), 14.11 (CH_3), 16.30 ($SiCH_2$), 22.24 (3-CH_2), 22.69, 23.18, 29.34, 29.35, 29.60, 29.67, 31.93 and 33.22 (CH_2), 28.18 (4-CH_2), 50.42 (2-CH_2N), 53.63 (α-CH_2N), 59.13 (OCH_2), 110.40, 115.49, 127.06, 129.16 (5-, 6-, 7-, 8-C), 122.06 (9-C) and 145.24 (10-C). ^{29}Si (δ, ppm): +18.62 Anal. calcd for $C_{23}H_{41}NOSi$: C, 73.54; H, 11.00; N, 3.73; found: C, 73.28; H, 11.04; N, 3.68.

N-(2-*n*-Decyldimethylsiloxyethyl)-4,4-dimethyl-4-sila-1,2,3,4-tetrahidroisoquinoline (**11**)

Compound **11** was obtained as a clear yellow oil following the procedure described for **9a**, from 0.4 g (1.4 mmol) *N*-(2-hydroxyethyl)-4,4-dimethyl-4-sila-1,2,3,4-tetrahydroisoquinoline (**7**) and 0.31 g (1.54 mmol) of decyldimethylsilane.

Yield 0.13 g (22%). LC-MS (*m/z*, %): 420 (M^++1, 100). GC-MS (*m/z*, %): 389 ($M^+ - 2CH_3$, 33), 388 ($M^+ - 2CH_3 - 1$, 100). ^{1}H NMR ($CDCl_3$, δ, ppm): 0.09 (6H, s, $SiCH_3$-acycl.), 0.27 (6H, s, $SiCH_3$-cycl.), 0.57 (2H, m, $SiCH_2$), 0.87 (3H, t, J = 6.8 Hz, CH_3), 1.25 (16H, m, CH_2), 2.21 (2H, s, $SiCH_2N$), 2.72 (2H, t, J = 5.2 Hz, α-CH_2N), 3.65 (2H, m, OCH_2), 3.67 (2H, s, 1-CH_2N), 7.0–7.5 (4H, m, 5-, 6-, 7- and 8-H). ^{13}C NMR ($CDCl_3$, δ, ppm): −2.12 ($SiCH_3$), −2.01 ($SiCH_3$-cycl.), 14.1 (CH_3), 16.32 ($SiCH_2$), 22.66, 23.18, 29.34, 29.37, 29.59, 29.66, 31.91 and 33.20 (CH_2), 44.15 ($SiCH_2N$), 58.1 (1-CH_2N), 61.2 (OCH_2), 63.5 (α-CH_2N), 125.14, 126.61, 128.94, 133.61 (5-, 6-, 7- and 8-C), 134.35, 145.42 (9,10-C). ^{29}Si NMR ($CDCl_3$, δ, ppm): −13.50, +18.06. Anal. calcd for $C_{24}H_{45}NOSi_2$: C, 68.67; H, 10.80; N, 3.33; found: C, 68.91; H, 10.73; N, 3.25.

N-(2-Diethylmethylsiloxyethyl)-*N*-methyl-1,2,3,4-tetrahydroisoquinolinium iodide (**12a**)

A solution of diethylmethylsilyl ether **9a** (0.84 g, 3.03 mmol) in hexane (5 ml) was heated at 60 °C for 5 h with methyl iodide (2.22 g, 15.60 mmol). After cooling to room temperature the reaction mixture was filtered, and the solid was washed with hexane

and dried for 6 h *in vacuo* to give the desired methiodide as a yellow powder.

Yield 0.41 g (33%), m.p. 138–139 °C. LC-MS (*m/z* %): 293 ($M^+ - I + 1$, 19), 292 ($M^+ - I$, 100), 197 (2), 188 (9), 183 (5). ^{1}H NMR ($CDCl_3$, δ, ppm): 0.08 (3H, s, $SiCH_3$), 0.59 (4H, q, $J = 7.9$ Hz, $SiCH_2$), 0.91 (6H, t, $J = 7.9$ Hz, SiC-CH_3), 3.24 (2H, bt, $J = 6.1$ Hz, 4-CH_2, 3.54 (3H, s, N^+CH_3), 3.9–4.3 (6H, m, α-CH_2N^+, 3-CH_2N^+ and OCH_2), 4.74 and 5.07 (total 2H, d and d, $J = 15.1$ Hz, 1-CH_2N^+), 7.1–7.4 (4H, m, 5-, 6-, 7- and 8-H). ^{13}C NMR ($CDCl_3$, δ, ppm): −5.12 ($SiCH_3$), 5.77 ($SiCH_2$), 6.65 (SiC&–CH_3), 23.86 (4-C), 49.06 (N^+CH_3), 57.23 (OCH_2), 59.80 (3-CH_2N^+), 62.87 (1-CH_2N^+), 63.63 (α-CH_2N^+), 125.96, 127.34, 127.81, 128.54, 128.90 and 129.06 (5-,6-,7-,8-,9- and 10-C). ^{29}Si NMR ($CDCl_3$, δ, ppm): +24.23 ($^2J_{SiCH} = 6.0$ Hz). Anal. calcd for $C_{17}H_{30}INOSi$: C, 48.68; H, 7.21; N, 3.34; found: C, 48.42; H, 7.15; N 3.41.

N-Methyl-*N*-(2-triethylsiloxyethyl)-1,2,3,4-tetrahydroisoquinolinium iodide (**12b**)

A solution of triethylsilyl ether **9b** (1.44 g, 8.13 mmol) and of methyl iodide (5.75 g, 4.05 mmol) in ethyl ether (23 ml) was heated at 40 °C for 3 h, the precipitate was filtered off, washed with 50 ml hexane and dried for 6 h *in vacuo* to give the desired product as a light yellow powder.

Yield 1.86 g (67%), m.p. 93–95 °C. LC-MS (*m/z*, %): 307 ($M^+ - I + 1$, 25), 306 ($M^+ - I$, 100), 203 ($M^+ - CH_3I - 3C_2H_5 - 1$, 79), 179 (22), 147 (39). ^{1}H NMR ($CDCl_3$, δ, ppm): 0.64 (6H, q, $J = 7.8$ Hz, $SiCH_2$), 0.94 (9H, t, $J = 7.8$ Hz, SiC&bond;CH_3), 3.27 (2H, bt, $J = 5.8$ Hz, 4-CH_2), 3.58 (3H, s, N^+CH_3), 3.9–4.3 (6H, m, α-CH_2N^+, 3-CH_2 and OCH_2), 4.79 and 5.11 (total 2H, d and d, $J = 15.8$ Hz, 1-CH_2N^+), 7.15 (1H, m, 8-H), 7.2–7.4 (3H, m, 5-, 6- and 7-H). ^{13}C NMR ($CDCl_3$, δ, ppm): 3.95 ($SiCH_2$), 6.62 (SiC-CH_3), 23.80 (4-C), 49.07 (N^+CH_3), 57.3 (OCH_2), 59.62 (3-C), 62.66 (1-CH_2N^+), 63.45 (α-CH_2N^+), 125.98, 127.22, 127.62, 128.56, 128.79 and 128.87 (5-,6-,7-,8-,9- and 10-C). ^{29}Si NMR ($CDCl_3$, δ, ppm): +23.84. Anal. calcd for $C_{18}H_{32}INOSi$: C, 49.88; H, 7.44; N, 3.23; found: C, 49.59; H, 7.37; N 3.29.

N-(2-Di-*n*-butylethylsiloxyethyl)-*N*-methyl-1,2,3,4-tetrahydroisoquinolinium iodide (**12c**)

Compound **12c** was obtained following the procedure described for **12b**, from 0.90 g (2.58 mmol) dibutylethylsilyl ether **9c**, as a light-yellow oily powder.

Yield 0.52 g (41%), m.p. 124–126 °C. LC-MS (*m/z*, %): 363 ($M^+ - I$, 72), 362 ($M^+ - I - 1$, 100). ^{1}H NMR ($CDCl_3$, δ, ppm): 0.63 (6H, m, $SiCH_2$), 0.92 (13H, m, SiC&bond;CH_3, $SiCCH_2CC$ and $SiCCCCH_3$), 1.74 (4H, m, $SiCCCH_2C$), 3.26 (2H, bt, $J = 6.2$Hz, 4-CH_2), 3.55 (3H, s, N^+CH_3), 4.00–4.15 (6H, m, α-CH_2N^+, 3-CH_2N^+, OCH_2), 4.79 and 5.06 (total 2H, d and d, $J = 15.1$ Hz, 1-CH_2N^+), 7.1–7.3 (4H, m, 5-, 6-, 7- and 8-H). ^{13}C NMR ($CDCl_3$, δ, ppm): 6.04 ($SiCH_2$) and 6.89 ($SiCCH_3$), 23.65, 24.04 and 26.21 (CCH_2 CH_2 CH_3 and 4-C), 48.94 (N^+CH_3), 57.14 (OCH_2), 59.62 (3-C), 62.72 (1-CH_2N^+), 63.63 (α-CH_2N^+), 125.92, 127.21, 127.65, 128.52, 128.81 and 128.91 (5-,6-,7-,8-,9- and 10-C). ^{29}Si NMR ($CDCl_3$, δ, ppm): +21.49. Anal. calcd for $C_{22}H_{40}INOSi$: C, 53.98; H, 8.24; N, 2.86; found: C, 53.70; H, 8.16; N 2.93.

N-(2-Di-*n*-heptylmethylsiloxyethyl)-*N*-methyl-1,2,3,4-tetrahydroisoquinolinium iodide (**12d**)

Compound **12d** was obtained following the procedure described for **12b**, from 0.65 g (1.56 mmol) diheptylmethylsilyl ether **9d**, as a yellow oily product.

Yield 0.52 g (44%), m.p. 104–106 °C. LC-MS (*m/z*, %): 433 ($M^+ - I + 1$, 40), 432 ($M^+ - I$, 100). GC-MS (*m/z*, %): 417 ($M^+ - CH_3I$, 2), 402 ($M^+ - CH_3I - CH_3$, 2), 318 ($M^+ - CH_3I - C_7H_{15}$, 5); 146 ($M^+ - CH_3I - CH_2OSiCH_3(C_7H_{15})_2$, 100), 132 ($M^+ - CH_3I - CH_2CH_2OSiCH_3(C_7H_{15})_2$, 26). ^{1}H NMR ($CDCl_3$, δ, ppm): 0.08 (3H, s, $SiCH_3$), 0.60 (4H, m, $SiCH_2$), 0.86 (6H, t, $J = 6.8$Hz, $2CH_3$), 1.24 (20H, m, $10CH_2$), 3.25 (2H, m, 4-CH_2), 3.56 (3H, s, N^+CH_3), 3.99–4.2 (6H, m, α-CH_2N^+, 3-CH_2N^+, OCH_2), 4.76 and 5.10 (total 2H, d and d, $J = 15.0$ Hz, 1-CH_2N^+); 7.1–7.4 (4H, m, 5-, 6-, 7- and 8-H). ^{13}C NMR ($CDCl_3$, δ, ppm): −4.08 ($SiCH_3$), 14.12 (CH_3), 15.03 ($SiCH_2$), 23.12, 28.89, 31.73 and 33.42 (CH_2), 23.92 (4-CH_2), 49.21 (N^+CH_3), 57.24 (OCH_2), 59.78 (3-CH_2N^+), 62.73 (1-CH_2N), 63.41 (α-CH_2N^+), 126,11, 127.32, 127.70, 128.6, 129.02 and 129.91 (5-, 6-, 7-, 8-, 9- and 10-C). ^{29}Si NMR ($CDCl_3$, δ, ppm): +22.35. Anal. calcd for $C_{27}H_{50}INOSi$: C, 57.94; H, 9.00; N, 2.50; .found: C, 57.68; H, 8.86; N 2.58.

N-(2-*n*-Dimethyloctylsiloxyethyl)-*N*-methyl-1,2,3,4-tetrahydroisoquinolinium iodide (**12e**)

Compound **12e** was obtained following the procedure described for **12b**, from 0.96 g (2.76 mmol) of dimethyloctylsilyl ether **9e**, as a yellow powder.

Yield 0.36 g (27%), m.p. 144–145 °C. LC-MS (*m/z*, %): 363 ($M^+ - I + 1$, 100); 346 ($M^+ - CH_3I - 1$, 5). GC-MS (*m/z*, %): 332 ($M^+ - CH_3I - CH_3$, 5), 146 ($M^+ - CH_3I - CH_2OSi(CH_3)_2C_8H_{17}$, 100). ^{1}H NMR ($CDCl_3$, δ, ppm): 0.11 (6H, s, $SiCH_3$), 0.58 (2H, m, $SiCH_2$), 0.87 (3H, t, $J = 7.0$ Hz, CH_3), 1.2–1.3 (12H, m, CH_2), 3.2 (2H, m, 4-CH_2), 3.56 (3H, s, N^+CH_3), 3.9–4.2 (6H, m, α-CH_2N^+, 3-CH_2N^+, OCH_2), 4.77 and 5.07 (total 2H, d and d, $J = 14.9$ Hz, 1-CH_2N^+), 7.11 (1H, d, 8-H), 7.2–7.4 (3H, m, 5-, 6- and 7-H). ^{13}C NMR ($CDCl_3$, δ, ppm): −2.57 ($SiCH_3$), 13.93 (CH_3), 15.78 ($SiCH_2$), 22.52, 22.96, 29.02, 29.16, 31.78 and 33.27 (CH_2), 23.84 (4-CH_2), 49.13 (N^+CH_3), 56.91 (OCH_2), 59.59 (3-CH_2N^+), 62.54 (1-CH_2N^+), 63.42 (α-CH_2N^+), 126,03, 127.24, 127.58, 128.62, 128.77 and 128.85 (5-, 6-, 7-, 8-, 9- and 10-C). ^{29}Si NMR ($CDCl_3$, δ, ppm): +22.37. Anal. calcd for $C_{22}H_{40}INOSi$: C, 53.98; H, 8.24; N, 2.8; found: C, 53.79; H, 8.15; N 2.93.

N-(2-*n*-Decyldimethylsiloxyethyl)-*N*-methyl-1,2,3,4-tetrahydroisoquinolinium iodide (**12f**)

Compound **12f** was obtained following the procedure described for **12b**, from 0.23 g (0.80 mmol) decyldimethylsilyl ether **9f**, as a yellow oily precipitate.

Yield 0.28 g (68%), m.p. 142 °C. LC-MS (*m/z*, %): 391 ($M^+ - I + 1$, 15), 390 ($M^+ - I$, 55), 389 ($M^+ - I - 1$, 95), 376 ($M^+ - CH_3I + 1$, 100). GC-MS (*m/z*, %): 391 ($M^+ - I + 1$, 1), 234 ($M^+ - CH_3I - C_{10}H_{21}$, 4), 146 ($M^+ - CH_3I - CH_2OSi(CH_3)_2C_{10}H_{21}$, 100). ^{1}H NMR ($CDCl_3$, δ, ppm): 0.11 (6H, s, $SiCH_3$), 0.58 (2H, m, $SiCH_2$), 0.85 (3H, t, $J = 6.8$ Hz, CH_3), 1.24 (16H, m, CH_2), 3.26 (2H, m, 4-CH_2), 3.54 (3H, s, N^+CH_3), 4.0–4.2 (6H, m, α-CH_2N^+ 3-CH_2N^+, OCH_2), 4.76 and 5.08 (total 2H, d and d, $J = 15.3$ Hz, 1-CH_2N^+), 7.11 (1H, d, 8-H), 7.1–7.4 (3H, m, 5-, 6- and 7-H). ^{13}C NMR ($CDCl_3$, δ, ppm): −2.43 ($SiCH_3$), 14.01 (CH_3), 15.78 ($SiCH_2$), 22.61, 23.02, 29.24, 29.38, 29.49, 31.85 and 33.22 (CH_2), 23.82, (4-C), 49.21 (N^+CH_3), 57.03 (OCH_2), 59.67 (3-C), 62.71 (1-CH_2N^+), 63.52 (α-CH_2N^+), 126.02 (9-C), 127.31 (8-C), 127.68 (5-C), 128.57 (6-C), 128.92 (7-C), 129.03 (10-C). ^{29}Si NMR ($CDCl_3$, δ, ppm): +22.50. Anal. calcd for $C_{24}H_{44}INOSi$: C, 55.69; H, 8.57; N, 2.71; found: C, 55.84; H, 8.66; N 2.55.

N-(2-*n*-Dimethylundecylsiloxyethyl)-*N*-methyl-1,2,3,4-tetrahydroisoquinolinium iodide (**12g**)

Compound **12 g** was obtained following the procedure described for **12b**, from 0.11 g (0.28 mmol) dimethylundecylsilyl ether **9 g**, as a yellow oily precipitate.

Yield 0.06 g (40%), m.p. 92–94 °C. LC-MS (*m/z*, %): 405 ($M^+ - I + 1$, 11), 404 ($M^+ - I$, 58), 390 ($M^+ - CH_3I + 1$, 100), 346 (2), 181 (2), 160

(42). GC-MS (*m/z*, %): 530 ($M^+ - 1$, 3), 374 ($M^+ - CH_3I - CH_3$, 2), 146 ($M^+ - CH_3I - CH_2OSi(CH_3)_2C_{11}H_{23}$, 100). ^{1}H NMR ($CDCl_3$, δ, ppm): 0.10 (6H, s, $SiCH_3$), 0.57 (2H, m, $SiCH_2$), 0.85 (3H, t, $J = 6.8$Hz, CH_3), 1.23 (18H, m, CH_2), 3.24 (2H, m, 4-CH_2), 3.54 (3H, s, N^+CH_3), 4.0–4.2 (6H, m, α-CH_2N^+, 3-CH_2N^+, OCH_2), 4.76 and 5.08 (total 2H, d and d, $J = 14.3$ Hz, 1-CH_2N^+), 7.1–7.4 (4H, m, 5-, 6-, 7- and 8-H). ^{13}C NMR ($CDCl_3$, δ, ppm): −2.40 ($SiCH_3$), 14.03 (CH_3), 15.82 ($SiCH_2$), 22.61, 23.1, 29.32, 29.48, 29.62, 31.81 and 33.34 (CH_2), 23.82 (4-CH_2), 49.12 (N^+CH_3), 57.03 (OCH_2), 59.76 (3-CH_2N^+), 62.79 (1-CH_2N^+), 63.65 (α-CH_2N^+), 126.01 (9-C), 127.28 (8-C), 127.82 (5-C), 128.63 (6-C), 128.87 (7-C) and 129.02 (10-C). ^{29}Si NMR ($CDCl_3$, δ, ppm): +22.67 ($^2J_{SiCH} = 6.8$ Hz). Anal. calcd for $C_{25}H_{46}INOSi$: C, 56.48; H, 8.72; N, 2.64; found: C, 56.72; H, 8.83; N 2.57.

N-(2-*n*-Hexadecyldimethylsiloxyethyl)-*N*-methyl-1,2,3,4-tetrahydroisoquinolinium iodide (**12 h**)

Compound **12 h** was obtained following the procedure described for **12b**, from 0.67 g (1.5 mmol) hexadecyldimethylsilyl ether **9 h**, as a yellow powder.

Yield 0.80 g (89%), m.p. 59 °C. LC-MS (*m/z*, %): 475 ($M^+ - I + 1$, 100), 474 ($M^+ - I$, 67), 460 ($M^+ - CH_3I + 1$, 49). GC-MS (*m/z*, %): 460 ($M^+ - CH_3I + 1$, 3), 445 ($M^+ - CH_3I - CH_3 + 1$, 4), 234 ($M^+ - CH_3I$ $C_{16}H_{33}$, 11), 146 ($M^+ - CH_3I - CH_2OSi(CH_3)_2C_{16}H_{33}$, 100). ^{1}H NMR ($CDCl_3$, δ, ppm): 0.11 (6H, s, $SiCH_3$), 0.58 (2H, m, $SiCH_2$), 0.86 (3H, t, $J = 7.0$ Hz, CH_3), 1.24 (28H, bs, CH_2), 3.25 (2H, m, 4-CH_2), 3.56 (3H, s, N^+CH_3), 3.9–4.2 (6H, m, α-CH_2N^+, 3-CH_2N^+, OCH_2), 4.78 and 5.07 (total 2H, d and d, $J = 15.4$ Hz, 1-CH_2N^+), 7.11 (1H, d, 8-H), 7.1–7.4 (3H, m, 5-, 6- and 7-H). ^{13}C NMR ($CDCl_3$, δ, ppm): −2.4 ($SiCH_3$), 14.01, 15.79, 22.57, 22.98, 23.83, 29.24, 29.48, 29.54, 29.6, 31.81, 33.26 (4-C, CH_2, CH_3, $SiCH_2$), 49.10 (N^+CH_3), 57.00 (OCH_2), 59.68 (3-C), 62.65 (1-CH_2N^+), 63.49 (α-CH_2N^+), 126.01 (9-C), 127.29 (8-C), 127.68 (5-C), 128.58 (6-C), 128.83 (7-C), 128.94 (10-C). ^{29}Si NMR ($CDCl_3$, δ, ppm): +22.49. Anal. calcd for $C_{30}H_{56}INOSi$: C, 59.88; H, 9.38; N, 2.33; found: C, 59.63; H, 9.32; N, 2.40.

N-Methyl-*N*-(2-methyldiphenylsiloxyethyl)-1,2,3,4-tetrahydroisoquinolinium iodide (**12i**)

Compound **12i** was obtained following the procedure described for **12b**, from 1.22 g (3.3 mmol) methyldiphenylsilyl ether **9i**, as a white powder.

Yield 0.41 g (24%), m.p. 96 °C. LC-MS (*m/z*, %): 388 ($M^+ - I$, 100). GC-MS (*m/z*, %): 516 (M^++1, 1), 373 ($M^+ - CH_3I$, 4), 295 ($M^+ - CH_3I$ $C_6H_5 - 1$, 12), 146 ($M^+ - CH_3I - CH_2OSiCH_3(C_6H_5)_2$, 100). ^{1}H NMR ($CDCl_3$, δ, ppm): 0.67 (3H, s, $SiCH_3$), 3.17 (2H, m, 4-CH_2), 3.50 (3H, s, N^+CH_3), 4.0–4.2 (6H, m, α-CH_2, 3-CH_2, OCH_2), 4.73 and 5.02 (total 2H, d and d, $J = 14.9$ Hz, 1-CH_2N^+), 6.9–7.2 (4H, m, 5-, 6-, 7- and 8-H), 7.3–7.5 (10H, m, C_6H_5-H). ^{13}C NMR ($CDCl_3$, δ, ppm): −3.60 ($SiCH_3$), 23.65 (4-CH_2), 49.12 (N^+CH_3), 57.41 OCH_2), 59.49 (3-CH_2N^+), 62.22 (1-CH_2N^+), 63.13 (α-CH_2N^+), 125.81, 127.09, 127.41, 128.42, 128.63 and 128.68 (5-, 6-, 7-, 8-, 9- and 10-C), 128.14, 130.42, 133.61, 133.65, 134.04 (C_6H_5&bond;C). ^{29}Si NMR ($CDCl_3$, δ, ppm): −0.36. Anal. calcd for $C_{25}H_{30}INOSi$: C, 58.25; H, 5.87; N, 2.72; found: C, 58.52; H, 5.78; N 2.64.

N-(2-*n*-Decyldimethylsiloxyethyl)-*N*-methyl-1,2,3,4-tetrahydroquinolinium iodide (**13**)

Compound **13** was obtained following the procedure described for **12b**, from 1.574 g (4.20 mmol) decyldimethylsilyl ether **10**, as an oil.

Yield 0.772 g (35%). LC-MS (*m/z*, %): 391 ($M^+ - I + 1$, 17), 390 ($M^+ - I$, 54), 389 ($M^+ - I$, 100). ^{1}H NMR ($CDCl_3$, δ, ppm): 0.11 (6H, s, $SiCH_3$), 0.58 (2H, m, $SiCH_2$), 0.87 (3H, t, $J = 6.8$ Hz, CH_3), 1.24 (16H, m, CH_2), 2.25 and 2.39 (total 2H, m and m, 3-CH_2N), 3.00 and 3.06 (total 2H, m and m, 4-CH_2), 3.84 (3H, s, N^+CH_3), 3.92 and 4.59 (total 2H, m and m, 2-CH_2N^+), 3.92 and 4.13 (total 2H, m and m, α-CH_2N^+), 4.33 and 4.42 (total 2H, m and m, OCH_2), 7.3–7.5 (3H, m, 5-, 6- and 7-H), 7.91 (1H, d, $J = 8.3$, 8-H). ^{13}C NMR ($CDCl_3$, δ, ppm): −2.42 ($SiCH_3$), 14.10 (CH_3), 15.82 ($SiCH_2$), 17.63 (3-CH_2), 22.67, 23.65, 28.69 , 29.28, 29.65, 31.85 and 33.30 (CH_2), 25.82 (4-C), 56.28 (α-CH_2N^+), 57.25 (N^+CH_3), 62.35 (2-C), 65.87 (OCH_2), 121.98, 128.65, 129.31, 131.39 (5-, 6-, 7-, 8-C), 130.80 (9-C) and 141.69 (10-C). ^{29}Si NMR ($CDCl_3$, δ, ppm): +22.63. Anal. calcd for $C_{24}H_{44}INOSi$: C, 55.69; H, 8.57; N, 2.71; found: C, 55.52; H, 8.51; N 2.75.

N-(2-*n*-Decyldimethylsiloxyethyl)-4,4-dimethyl-*N*-methyl-4-sila-1,2,3,4-tetrahidroisoquinolinium iodide (**14**)

Compound **14** was obtained following the procedure described for **12b**, from 0.13 g (0.31 mmol) decyldimethylsilyl ether **11**, as a dark-yellow powder.

Yield 0.04 g (24%), m.p. 46 °C. LC-MS (*m/z*, %): 434 ($M^+ - I$, 100). ^{1}H NMR ($CDCl_3$, δ, ppm): 0.10 (6H, s, $SiCH_3$-acycl.), 0.47 (6H, m, $SiCH_3$-cycl.), 0.57 (2H, m, $SiCH_2$), 0.86 (3H, t, $J = 6.8$ Hz, CH_3), 1.24 (16H, m, CH_2), 3.42 (3H, s, N^+CH_3), 3.52 and 3.68 (1H and 1H, d and d, $J = 14.8$ Hz, $SiCH_2N^+$), 3.88 (2H, t, $J = 4.7$ Hz, α-CH_2N^+), 4.18 (2H, m, OCH_2), 4.86 and 4.96 (1H and 1H, d and d, $J = 14.5$ Hz, 1-CH_2N^+), 7.4–7.8 (4H, bm, 5-, 6-, 7- and 8-H). ^{13}C NMR ($CDCl_3$, δ, ppm): −2.42 ($SiCH_3$), −1.25 ($SiCH_3$-cycl.), 14.00 (CH_3), 15.82 ($SiCH_2$), 22.55, 22.96, 23.82, 29.20, 29.45, 29.52, 31.78, and 33.23 (CH_2), 53.22 (N^+CH_3), 55.45 ($SiCH_2N^+$), 55.72 (OCH_2), 67.41 ($ArCH_2N^+$), 67.95 (α-CH_2N^+), 129.33, 129.77, 131.23, 131.28, 133.96, 135.17 (5-, 6-, 7-, 8-, 9- and 10-C). ^{29}Si NMR ($CDCl_3$, δ, ppm): −13.46, +22.23. Anal. calcd for $C_{25}H_{48}INOSi_2$: C, 53.45; H, 8.61; N, 2.49; found: C, 53.20; H, 8.50; N 2.57.

Biological Tests

Cytotoxicity

Monolayer tumour cell lines HT-1080 (human fibrosarcoma), MG-22A (mouse hepatoma) and normal mouse fibroblasts (NIH 3 T3) were cultivated for 72 h in Dulbecco's modified Eagle's medium (DMEM) standard medium (Sigma) without an indicator and antibiotics.[35]

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 of $2–5 \times 10^4$ cells ml^{-1} concentration (depending on line nature) were placed on 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^{-1}. Control cells were treated in the same manner but in the absence of test compounds. The plates were incubated for 72 h at 37 °C and 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-2*H*-tetrazolium bromide (MTT) coloration, which was assayed by multiscan spectrophotometer. The quantity of live cells on the control plate was taken in calculations for 100%.[35,36] The LC_{50} was calculated using the Graph Pad Prism® 3.0 program, $r < 0.05$. Concentration of NO was determined according to the procedure described in Fast *et al.*[36]

Antimicrobial activity

For the determination of antimicrobial activity, several reference microbial strains, received from the Microbial Strain Collection

of Latvia (MSCL), Riga, Latvia, were used: *Staphylococcus aureus* MSCL 334 (SA), *Bacillus cereus* MSCL 330 (BC), *Proteus mirabilis* MSCL 590 (PM), *Escherichia coli* MSCL 332 (EC), *Pseudomonas aeruginosa* MSCL 331 (PA) and *Candida albicans* MSCL 378 (CA). All bacteria were cultivated on Plate Count Agar (Sanofi Diagnostics Pasteur, France) at 37 °C for 24 h. *Candida albicans* was cultivated on Difco™ Malt Extract Agar (Becton, Dickinson and Co., UK) at 37 °C for 48 h. Antimicrobial activity was determined by agar well diffusion method.[37] The agar diffusion test was performed on Mueller–Hinton (Carl Roth GmbH + Co. KG, Germany) agar for bacteria and Malt Extract Agar for yeast. Suspensions of 18–24 h microbial cultures of turbidity $A_{540} = 0.16 \pm 0.20$ were used and uniformly spread on Petri plates. Aliquots of 70 μl of each test sample solution, corresponding solvent and reference antimicrobial drugs solutions were added to 6.0 μm diameter agar wells. Gentamicin (KRKA, Slovenia) and fluconazole (Diflucan, Pfizer Ltd, UK), 10 mg ml^{-1} and 5 mg ml^{-1}, were used as reference antibiotics. The antimicrobial activity was evaluated based on the diameter of zone of inhibition. After incubation at 37 °C for 24 h for bacteria and 48 h for yeast under aerobic conditions, the diameter of the clear zone (no growth) around the well in the bacterial lawn was measured. The inhibition zone diameter was measured in millimetres (mm). The tests were performed in duplicate. The results were expressed as the arithmetic average. The observed zones of growth inhibition are presented in Table 4.

Results and Discussion

Chemistry

The synthesis of the compounds used in this study is outlined in Schemes 1 and 2.

N-Methyl-*N*-(2-triorganylsiloxyethyl)-1,2,3,4-tetrahydroisoquinolinium iodides (**12a–i**) were envisioned as being prepared from the common precursor alcohol **1**[34] in moderate to good overall yields (24–89%). *N*-(2-Decyldimethylsiloxyethyl)-*N*-methyl-1,2,3,4-tetrahydroquinolinium iodide (**13**) was prepared analogously from **2**. *N*-(2-Decyldimethylsiloxyethyl)-4,4-dimethyl-*N*-methyl-4-sila-1,2,3,4-tetrahydroisoquinolinium iodide (**14**) was synthesized by a series of sequenced reactions starting from 2-bromotoluene (Schemes 1 and 2). The reaction of dehydrocondensation,[38] a special feature of hydrosilanes in their ability to undergo alcoholysis leading to alkoxysilanes and gaseous hydrogen, was used in coupling the silyl group to the organic substrates **1**, **2** and **7**.

The interaction of *N*-(2-hydroxyethyl)-1,2,3,4-tetrahydroisoquinoline (**1**) with triorganylhydrosilanes $R^1R^2R^3SiH$ resulted in 38–91% yield. It was revealed using GC-MS monitoring that under the same reaction conditions the yield of the reaction products depends on both the nature of hydrosilane and the nature of the heterocycle.

The influence of nature of the heterocyclic base on the reaction result was more evident, provided the same triorganylsilane was used and the same reaction conditions: *N*-(2-decyldimethysiloxyethyl)-1,2,3,4-tetrahydroisoquinoline (**9f**) was obtained with a yield of 75% and the yield of *N*-(2-decyldimethysiloxyethyl)-1,2,3,4-tetrahydroquinoline (**10**), in its turn, was significantly lower: 24%. In the latter case the reaction proceeded more slowly and it took a longer time in comparison with the *N*-(2-hydroxyethyl)-1,2,3,4-tetrahydroisoquinoline: 26 and 15 h, correspondingly, to obtain the product with the highest yield. During dehydrocondensation of **1** with different trialkylhidrosilanes, the tendency of the reaction yield decrease has been observed with carbon chain elongation of the alkyl substituent at the Si atom. The yield of compounds **9a–f**, possessing C_2–C_{10} alkyl chain length, ranged within 56–77%; for compounds **9 g** (C_{11}) and **9 h** (C_{16}) it was lower – 49% and 38%, respectively – and the reaction time for **9f** and **9 h** was longer.

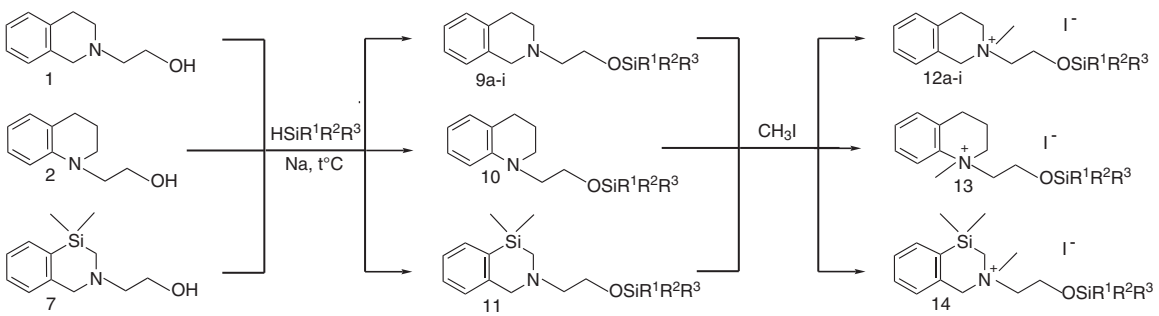
The compounds synthesized were characterized by multinuclear NMR data. The values of ^{29}Si NMR chemical shifts are presented in Tables 1 and 2. ^{29}Si NMR resonance depends upon the substituent at the silicon atom, and qualitatively similar changes for ^{29}Si chemical shifts of tetrahydroisoquinoline derivatives **9a–h** and their methiodides **12a–h** during transition along the sequence should be noted:

$$EtBu_2 < Hp_2Me < OctMe_2 \leq DcMe_2 \leq (C_{11}H_{23})Me_2 \leq (C_{16}H_{33})Me_2 < Et_3 < Et_2Me$$

The low field shifting of ^{29}Si NMR resonance from 16.74–19.90 to 21.49–24.23 ppm and the narrowing of its interval from 3.16 to 2.74 ppm have been noted for compounds containing positively charged nitrogen (**12a–h**) in comparison with proper *N*-(2-triorganylsiloxyethyl)-1,2,3,4-tetrahydroisoquinolines (**9a–h**). The highest changes in δ (^{29}Si) values (4.75 ppm) under nitrogen quaternization were observed for compound **12c** with ethyldibutyl substituent, revealing stronger N. . .Si interaction in the appropriate silane.

Biological evaluation

In vitro antitumour and antimicrobial properties of the compounds synthesized were investigated. A comparison of **8**, **12a–i** and **13** with **3** and **4** provided evidence that the latter compounds



$R^1R^2R^3$: Et_2Me (9a, 12a); Et_3 (9b, 12b); $EtBu_2$ (9c, 12c); $MeHp_2$ (9d, 12d); Me_2Oct (9e, 12e); Me_2Dc (9f, 10, 11, 12f, 13, 14); $Me_2(C_{11}H_{23})$ (9g, 12g); $Me_2(C_{16}H_{33})$ (9h, 12h); $MePh_2$ (9i, 12i)

Scheme 2. Synthesis of compounds **9–14**.

Table 1. ^{29}Si NMR resonance of, *N*-(2-triorganosiloxyethyl)-1,2,3,4-tetrahydroisoquinolines (**9a–i**), *N*-(2-decyldimethylsiloxyethyl)-1,2,3,4-tetrahydroquinoline (**10**) and *N*-(2-decyldimethylsiloxyethyl)-4,4-dimethyl-4-sila-1,2,3,4-tetrahydroisoquinoline (**11**) $R^1R^2R^3SiOCH_2CH_2$–Het_N

Compound	R^1	R^2	R^3	δ ^{29}Si (ppm)
9a	CH_3	C_2H_5	C_2H_5	+19.90
9b	C_2H_5	C_2H_5	C_2H_5	+19.62
9c	C_2H_5	C_4H_9	C_4H_9	+16.74
9d	CH_3	C_7H_{15}	C_7H_{15}	+18.20
9e	CH_3	CH_3	C_8H_{17}	+18.32
9f	CH_3	CH_3	$C_{10}H_{21}$	+18.36
9 g	CH_3	CH_3	$C_{11}H_{23}$	+18.24
9 h	CH_3	CH_3	$C_{16}H_{33}$	+18.33
9i	CH_3	C_6H_5	C_6H_5	−2.39
10	CH_3	CH_3	$C_{10}H_{21}$	+18.62
11	CH_3	CH_3	$C_{10}H_{21}$	−13.5, +18.06

Table 2. ^{29}Si NMR resonance of, *N*-methyl-*N*-(2-triorganosiloxyethyl)-1,2,3,4-tetrahydroisoquinolinium (**12a–i**), *N*-(2-decyldimethylsiloxyethyl)-*N*-methyl-1,2,3,4-tetrahydroquinolinium (**13**) and *N*-(2-decyldimethylsiloxyethyl)-4,4-dimethyl-*N*-methyl-4-sila-1,2,3,4-tetrahydroisoquinolinium iodides (**14**) $[R^1R^2R^3SiOCH_2CH_2$–$Het_NMe]^+I^-$

Compound	R^1	R^2	R^3	δ ^{29}Si (ppm)
12a	CH_3	C_2H_5	C_2H_5	+24.23
12b	C_2H_5	C_2H_5	C_2H_5	+23.84
12c	C_2H_5	C_4H_9	C_4H_9	+21.49
12d	CH_3	C_7H_{15}	C_7H_{15}	+22.35
12e	CH_3	CH_3	C_8H_{17}	+22.37
12f	CH_3	CH_3	$C_{10}H_{21}$	+22.50
12 g	CH_3	CH_3	$C_{11}H_{23}$	+22.67
12 h	CH_3	CH_3	$C_{16}H_{33}$	+22.49
12i	CH_3	C_6H_5	C_6H_5	–0.36
13	CH_3	CH_3	$C_{10}H_{21}$	+22.63
14	CH_3	CH_3	$C_{10}H_{21}$	–13.46, +22.23

possessed lower biological activity, practically did not reveal cytotoxic properties and in general were less active concerning the microbial strains examined. The experimental evaluation of cytotoxic properties is presented in Table 3.

In this study, two monolayer tumour cell lines – HT-1080 (human fibrosarcoma) and MG-22A (mouse hepatoma) – and normal mouse fibroblasts (NIH 3 T3) have been employed to evaluate the antiproliferative activity of the synthesized tetrahydro(iso)quinoline compounds in culture. *N*-(2-Hydroxyethyl)-*N*-methyl-1,2,3,4-tetrahydroisoquinolinium iodide (**3**) and 4,4-dimethyl-*N*-(2-hydroxyethyl)-*N*-methyl-4-sila-1,2,3,4-tetrahydroisoquinolinium iodides (**8**) did not exhibit cytotoxic action at all. Thus this study clearly demonstrates that human fibrosarcoma and mouse hepatoma cells are highly responsive to some *N*-methyl-*N*-(2-triorganylsiloxyethyl)-1,2,3,4-tetrahydroisoquinolinium iodides. The following sequence of organosilicon substituents in the cytotoxicity display concerning HT-1080 tumour cell lines has been revealed:

$$Me_2(C_{11}H_{23}) < MePh_2 < Me_2(C_{16}H_{33}) < Et_3 < MeHp_2 < EtBu_2$$

Almost the same sequence has been determined concerning MG-22A tumour cell lines:

$$Me_2Dc < Et_2Me < MePh_2 \leq Me_2(C_{16}H_{33}) < Et_3 < MeHp_2 < Me_2(C_{11}H_{23}) < EtBu_2$$

The present investigation shows that compounds **12c** and **12d** induced growth inhibition of HT-1080 and MG-22A cells, and compound **12 g** exhibits selective cytotoxic action against MG-22A cells at a significant level. In general, *N*-methyl-*N*-(2-triorganylsiloxyethyl)-1,2,3,4-tetrahydroisoquinolinium iodides screened had high NO generation activity, being most active for **12d** in both the HT-1080 and MG-22A tests: 300% and 250% respectively (Table 3). All the compounds synthesized possess low toxicity or are non-toxic compounds (LD_{50} = 450–3200 mg kg^{-1}).

The antibacterial and antifungal activity of compounds **12a–i**, **13** and **14** have been investigated in dimethyl sulfoxide against two Gram-positive – *Bacillus cereus* MSCL 330 (BC) and *Staphylococcus aureus* MSCL 334 (SA) – and three Gram-negative microbial strains – *Proteus mirabilis* MSCL 590 (PM), *E. coli* MSCL 332 (EC) and *Pseudomonas aeruginosa* MSCL 331 (PA) – and fungi – *Candida albicans* MSCL 378 (CA) – in comparison with 2-hydroxyethyl precursors **3**, **4** and **8**, using the agar ditch diffusion method.[37] The results of the study are presented in Table 4.

The results were compared with those of standard antibacterial (gentamicin) and antifungal (fluconazole) drugs. *N*-(2-Hydroxyethyl)-*N*-methyl-1,2,3,4-tetrahydroisoquinolinium iodide (**3**) showed low activity against fungi and Gram-negative bacterial strains and was inactive against the Gram-positive bacterial strains tested. Biological activity data exhibited enhancement of inhibitory activity against the tested pathogen microorganisms for *N*-methyl-*N*-(2-triorganylsiloxyethyl)-1,2,3,4-tetrahydro(iso,silaiso)quinolinium iodides **8**, **12** and **14**. In general, Gram-negative bacterial and fungal strains were more resistant to the synthesized compounds than were Gram positive strains. The most effective action of compounds studied has been demonstrated against Gram-positive *Bacillus cereus* MSCL 330 and *Staphylococcus aureus* MSCL 334 and Gram-negative *Pseudomonas aeruginosa* MSCL 331. Compound **12b** was found to be more active against *Bacillus cereus* MSCL 330 and *Staphylococcus aureus* MSCL 334 than gentamicin. The highest antifungal potency was revealed for *N*-(2-hydroxyethyl)-*N*-methyl-1,2,3,4-tetrahydroquinolinium iodide (**4**). Selectivity of antibacterial action was revealed concerning unsilylated **3**, **4** and **8**. Contrary to *N*-(2-hydroxyethyl)-*N*-methyl-1,2,3,4-tetrahydroisoquinolinium iodide (**3**), which is active only against Gram-negative strains, compound **4** is mostly potent against Gram-positive antibacterial strains. Compound **8**, in turn, revealed a wide spectrum of antibacterial activity. Among the heterocyclic choline derivatives **12f**, **13** and **14** bearing the same substituents at the silicon atom (dimethyldecylsilyl group) and their precursors **3**, **4** and **8**, silatetrahydroisoquinoline derivatives **14** and **8** possessed a wide spectrum of biological activity and were the most potent compounds. Contrary to tetrahydroisoquinoline derivatives **12f** and **3**, which exhibited higher activity against Gram-negative antibacterial strains, tetrahydroquinoline derivatives **13** and **4** were mostly potent against Gram-positive strains. The degree of antibacterial activity increased among the number of tetrahydroisoquinoline derivatives with the silyl group nature in the following order concerning Gram-positive strains:

Table 3. *In vitro* cell cytotoxicity and intracellular NO generation caused by N-methyl-N-(2-triorganylsiloxyethyl)-1,2,3,4-tetrahydroisoquinolinium (**12a-i**), N-(2-hydroxyethyl)-N-methyl-1,2,3,4-tetrahydroisoquinolinium (**3**) and 4,4-dimethyl-N-(2-hydroxyethyl)-N-methyl-4-sila-1,2,3,4-tetrahydroisoquinolinium (**8**) iodides

Compound/test	HT-1080			MG-22A			NIH 3 T3	
	LC_{50} (μg ml^{-1})		NO (%)	LC_{50} (μg ml^{-1})		NO (%)	LC_{50} (μg ml^{-1})	LD_{50} (mg kg^{-1})
	CV	MTT	CV	CV	MTT	CV	NR	
3	**	**	2	100	**	4	1000	2202
12a	**	**	5	73	100	9	827	2391
12b	8	16	200	6	10	150	171	1214
12c	<1	<1	150	1	1	150	24	539
12d	3	3	300	3	3	250	14	448
12e	**	**	2	**	**	3	1340	3182
12f	**	**	4	100	100	6	**	>2000
12 g	30	14	200	2	2	150	19	532
12 h	17	16	200	13	16	150	85	1083
12i	19	18	100	13	17	100	41	722
8	**	**	2	**	**	4	452	1671

CV, crystal violet coloration; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2*H*-tetrazolium bromide coloration; NR, neutral red coloration; NO, nitrogen oxide concentration degree, determined according to the procedure.[36]

* LC_{50}, concentration of compound providing 50% cell killing effect.

** No cytotoxic effect.

Table 4. *In vitro* antibacterial and antifungal activity data of *N*-methyl-*N*-(2-triorganylsiloxyethyl)- 1,2,3,4-tetrahydroisoquinolinium (**12a–i**), *N*-(2-*n*-decyldimethylsiloxyethyl)-*N*-methyl-1,2,3,4-tetrahydroquinolinium (**13**) and *N*-(2-*n*-decyldimethylsiloxyethyl)-4,4-dimethyl-*N*-methyl-4-sila-1,2,3,4-tetrahidroisoquinolinium (**14**) iodides given in concentrations of 5 mg ml^{-1} (0.35 mg per disc) and 10 mg ml^{-1} (0.7 mg per disc)

Compound	Diameter of zones showing complete inhibition of growth (mm)											
	SA		BC		EC		PA		PM		CA	
	5	10	5	10	5	10	5	10	5	10	5	10
3	**	**	11	**	**	13	12	16	13	15	11	10
12a	22	26	15	16	9	15	12	20	16	20	11	9
12b	25	30	22	23	11	19	19	19	14	18	11	11
12c	19	20	19	19	11	14	18	20	15	16	16	12
12d	9	8	10	9	9	13	17	18	14	17	13	11
12e	16	18	15	15	12	14	14	20	11	18	11	**
12f	11	11	11	10	9	13	11	18	14	20	11	10
12 g	**	12	13	**	11	13	11	20	10	15	11	9
12 h	**	**	10	**	9	13	10	18	10	19	13	9
12i	13	15	13	14	8	12	17	21	14	18	12	11
4	8	11	8	10	8	9	**	8	**	**	13	18
13	12	13	12	13	8	10	**	**	**	**	11	11
8	18	14	17	15	10	10	10	14	9	**	13	13
14	19	21	17	19	11	12	10	12	**	**	13	14
Gentamicin	25	27	19	22	21	23	40	42	20	21	n	n
Fluconazole (2/0.2 mg ml^{-1})	n/n		n/n		n/n		n/n		n/n		10/**	

n, non-determined.

** No inhibiting effect.

$$Me_2(C_{16}H_{33}) < MeHp_2 < Me_2Dc < Me_2(C_{11}H_{23}) < MePh_2 < Me_2Oct \leq HO(Si_{cycl}Me_2) < Me_2Dc(Si_{cycl}Me_2) < EtBu_2 < Et_2Me < Et_3$$

and in the following order concerning Gram-negative strains:

$$MePh_2 < HO(Si_{cycl}Me_2) < Me_2Dc(Si_{cycl}Me_2) < Me_2(C_{16}H_{33}) \leq Me_2Dc \leq MeHp_2 < Me_2(C_{11}H_{23}) < EtBu_2 < Me_2Oct < Et_2Me < Et_3$$

(*E. coli* MSCL 332)

Table 5. *In vitro* minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of compounds **13** and **14**

Compound	MIC ($\mu g\,ml^{-1}$)					MBC ($\mu g\,ml^{-1}$)
	SA	BC	EC	PA	CA	SA
13	256	>256	>256	>256	>256	—
14	8	32	>256	>256	32	32

$Me_2Dc(Si_{cycl}Me_2) < HO(Si_{cycl}Me_2) < Me_2(C_{16}H_{33}) \leq Me_2Dc < MeHp_2 < Et_3 < Me_2(C_{11}H_{23}) < Et_2Me < Me_2Oct < EtBu_2 < MePh_2$ (*Pseudomonas aeruginosa* MSCL 331) and

$Me_2Dc(Si_{cycl}Me_2) \leq HO(Si_{cycl}Me_2)Me_2 < (C_{11}H_{23}) < EtBu_2 < MeHp_2 < Me_2Oct < MePh_2 \leq Et_3 < Me_2(C_{16}H_{33}) < Me_2Dc < Et_2Me$ (*Proteus mirabilis* MSCL 590)

Compounds **8** and **14** in general were more active concerning the Gram-positive strains and less active against the Gram-negative strains.

In vitro minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) were determined for compounds **13** and **14**. The data obtained (Table 5) show that compound **14** possessed not only bacteriostatic ($8\,\mu g\,ml^{-1}$) but also marked bactericidal action ($32\,\mu g\,ml^{-1}$) against the *Staphylococcus aureus* strain.

Conclusions

A series of *N*-methyl-*N*-(2-triorganosiloxyethyl)-1,2,3,4-tetrahydroisoquinolinium, *N*-(2-decyldimethylsiloxyethyl)-*N*-methyl-1,2,3,4-tetrahydroquinolinium and *N*-(2-decyldimethylsiloxyethyl)-4,4-dimethyl-*N*-methyl-4-silatetrahydroisoquinolinium iodides has been synthesized as potential pharmacological agents. ^{29}Si NMR resonance of *N*-(2-triorganosiloxyethyl)tetrahydro(iso,silaiso)quinolines and *N*-methyl-*N*-(2-triorganosiloxyethyl)-1,2,3,4-tetrahydro(iso,silaiso)quinolinium iodides depended upon the substituent at the silicon atom.

At the basis of LC_{50} data, the structure–antitumour activity relationship was discussed in terms of the nature of the heterocycle and silyl group, which was present in the amphiphilic molecule of heterocyclic choline analogues. It has been revealed that all the synthesized compounds possessed selective cytotoxic action in relation to the studied tumour cells. *N*-(2-Di-*n*-butylethylsiloxyethyl)-*N*-methyl-1,2,3,4-tetrahydroisoquinolinium and *N*-(2-di-*n*-heptylmethylsiloxyethyl)-*N*-methyl-1,2,3,4-tetrahydroisoquinolinium iodides were the most effective in this respect. A specificity of the cytotoxic effect towards MG-22A line was displayed by *N*-(2-*n*-dimethylundecylsiloxyethyl)-*N*-methyl-1,2,3,4-tetrahydroisoquinolinium iodide. All the compounds synthesized had high NO generation activity, exhibited low toxicity or were non-toxic compounds.

The biological activity data exhibited enhancement of inhibitory activity against the tested pathogen microorganisms for *N*-methyl-*N*-(2-triorganylsiloxyethyl)-1,2,3,4-tetrahydroisoquinolinium iodides in comparison with their 2-hydroxyethyl precursors. The degree of antibacterial activity of tetrahydroisoquinoline derivatives depends on the silyl group nature.

The results obtained are in agreement with our previously published data for aliphatic choline analogues and allow one to assume that blocking of the hydroxyl group of *N*-methyl-*N*-(2-hydroxyethyl)-1,2,3,4-tetrahydroisoquinolinium iodides with triorganylsilyl group is essential for improvement of their biological properties.

Supporting information

Supporting information may be found in the online version of this article.

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