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Silyl modification of biologically active compounds. 12. Silyl group as true incentive to antitumour and antibacterial action of choline and colamine analogues

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A series of triorganylsilyl(β-dialkylaminoethoxy)silanes was prepared and characterized by elemental analysis, ^{1}H, ^{13}C, ^{29}Si NMR and mass spectroscopy. Comparative study of ^{29}Si resonance of newly synthesized compounds showed correlation between its value and substituent nature at the silicon atom, and is shifted upfield for β-triorganyl(*N*,*N*-dialkylaminoethoxy)silanes in comparison with corresponding methiodides, revealing weak N···Si interaction for proper silanes. *In vitro* antitumour and antimicrobial properties were investigated. The biological activity data exhibited a marked enhancement of inhibitory activity on trialkylsilylation against tumour cell lines and all the test bacterial/fungal strains. Copyright © 2006 John Wiley & Sons, Ltd.

KEYWORDS: organosilicon compounds; alkanolamines; drug research; antitumour activity; antimicrobial activity

INTRODUCTION

One of the research directions of our team deals with silyl modification of biologically active compounds to improve their biological properties, such as to increase lipophilicity and the therapeutic index, to achieve prolonged action, to lower toxicity and therapeutic dose, and some others, in comparison with unmodified precursors.[1–8]

The mode of action of this class of compounds has been proposed to be connected with their penetration through lipophilic barriers inside the body, which can also facilitate their transport to the site of action.[5,6,9]

Previously we have reported on the positive influence of O- and N-silylation,[10–15] silylalkylation,[13,16] siloxyalkylation[17] and sila-substitution[18] of some biologically active compounds on their psychotropic activity, antitumour properties and toxicity display. For medicines having hydrophilic functions the easiest way to increase their potency is silylation by replacing the active hydrogen of hydrophilic hydroxy, amino, amido or mercapto function with the triorganylsilyl group.

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The increasing number of resistant bacterial strains, especially the highly resistant β-lactamase producing *Staphylococcus aureus* and Gram-negative strains, necessitates the development of new effective chemotherapeutic agents of low toxicity.[19]

Reviewing the families of natural and synthetic antimicrobial drugs, we established that almost all of them contain =N–C–C–O– sequence.[20] Indeed this moiety is present in groups of penicilline, cephalosporine, tetracycline, streptomycine and levomycetine antibiotics, in antibiotics of the aminoglycoside, macrolide and polyenene groups, but also in 8-hydroxyquinoline, nitrofuran and quinoxaline containing antimicrobial remedies.[20] Several natural alkaloids (vincristine, vinblastine) and hormonal drugs (tamoxifen) having this sequence are used in medical practice as antitumour drugs.[20]

Therefore the aim of this investigation is to study the structure and antitumour and antimicrobial activity relationship by the wide variation of trialkylsilyl substituents at the oxygen atom of different β-ethanolamine derivatives, which can lead to finer selection of prospective compounds for the investigations *in vivo*. Our interest in this research is based on the expectation that such modification or structural restrictions, caused by the presence of positively charged *O*-organosilicon substituent and positively charged quaternized nitrogen

atom, may influence on the co-ordination behaviour of these compounds in their possible reaction with biological nucleophiles and complex molecules, but also on their adsorptive activities on the cell surface, on permeability of the latter and, as a consequence, on antitumour and antimicrobial properties of β-alkanolamines.[21] In addition it was proved that the antimicrobial activity of some tetraalkylammonium salts is under the control of their molecular hydrophobicy, adsorbability, surface activity and electron density of the ammonium nitrogen atom.[22] In addition, the ^{29}Si NMR examination of the synthesized compounds from the electronic point of view, as regards the electron density on the silicon atom, is presented.

EXPERIMENTAL

Chemicals and instrumentation

^{1}H, ^{13}C and ^{29}Si NMR spectra were obtained on a 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 a Carlo Erba 1108 elemental analyser. Elemental analysis results agreed with calculated values. GLC analysis was conducted on a Chrom-5 chromatograph with flame-ionization detector and glass column (1.2 m × 3 mm) with 5% OV-17 on a 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.

Synthesis

An outline is given in Scheme 1.

General procedure

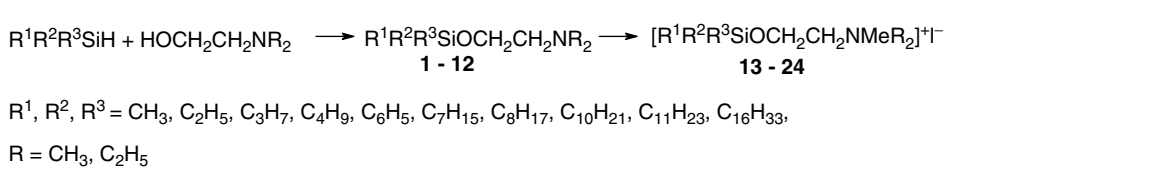
The equimolar amount of hydrosilane was added to the solution of *N*,*N*-disubstituted β-dialkylaminoethanol (10 mmol) in 5 ml hexane. The reaction mixture was refluxed under stirring for 4–10 h in presence of trace amount of metallic sodium. The course of the reaction was followed by GLC data. After the dehydrocondensation reaction was finished, hexane was removed *in vacuo*, and the residue was distilled at normal or reduced pressure to give the desired product, which was further converted to the corresponding methiodide according to the procedure described in Zablotskaya *et al*.[17]

Propyldimethyl(β-dimethylaminoethoxy)silane (**1**) was obtained as clear colourless liquid. Yield 73%, b.p. 77–79 °C. ^{1}H NMR, δ (ppm): 0.07 (6H, s, $SiCH_3$), 0.59 (2H, t, $J = 7$ Hz, $SiCH_2$), 0.95 (3H, t, $J = 7$ Hz, CH_3), 1.36 (2H, m, CH_2), 2.25 (6H, s, NCH_3), 2.43 (2H, t, $J = 6.6$ Hz, NCH_2), 3.67 (2H, t, $J = 6.6$ Hz, OCH_2). ^{13}C NMR ($CDCl_3$), δ (ppm): −2.11 (CH_3Si), 16.69 (CH_3–C), 18.06 and 18.87 (CH_2Si and CH_2–C), 46.02 (CH_3N), 60.90 (CH_2N), 61.56 (CH_2O). MS: $m/z = 189$ ($[M]^+$, 1%); 174 (5%); 146 (9%); 72 ($[M - OSiMe_2Pr]^+$, 10%); 58 (100%).

Heptyldimethyl(β-dimethylaminoethoxy)silane[10] (**2**) was obtained as clear colourless liquid. Yield 84%, b.p. 141–143 °C/22 Torr. ^{1}H NMR, δ (ppm): 0.14 (6H, s, $SiCH_3$), 0.62 (2H, t, $J = 7$ Hz, $SiCH_2$), 0.91 (3H, t, $J = 6$ Hz, CH_3), 1.30 (10H, bs, CH_2), 2.31 (6H, s, NCH_3), 2.46 (2H, t, $J = 7$ Hz, NCH_2), 3.71 (2H, t, $J = 7$ Hz, OCH_2). ^{13}C NMR ($CDCl_3$), δ (ppm): −2.16 (CH_3Si), 14.08 (CH_3–C), 16.24 (CH_2Si), 22.65, 23.16, 29.35, 31.81 and 33.41 (C–CH_2–C), 46.01 (CH_3N), 60.86 (CH_2N), 61.55 (CH_2O). Anal. found: C, 63.58; H, 12.68; N, 5.67. Calcd for $C_{13}H_{31}NOSi$: C, 63.67; H, 12.65; N 5.71. MS: $m/z = 245$ ($[M]^+$, 4%); 230 ($[M - Me]^+$, 36%); 146 ($[M - C_7H_{15}]^+$, 100%); 130 (8%); 102 (13%); 88 (18%).

Octyldimethyl(β-dimethylaminoethoxy)silane (**3**) was obtained as a clear colourless liquid. Yield 83%, b.p. 136 °C/5 Torr. ^{1}H NMR, δ (ppm): 0.12 (6H, s, $SiCH_3$), 0.61 (2H, t, $J = 7.7$ Hz, $SiCH_2$), 0.91 (3H, t, $J = 6.5$ Hz, CH_3), 1.29 (12H, bs, CH_2), 2.29 (6H, s, NCH_3), 2.47 (2H, t, $J = 6.6$ Hz, NCH_2), 3.70 (2H, t, $J = 6.6$ Hz, OCH_2). ^{13}C NMR ($CDCl_3$), δ (ppm): −2.17 (CH_3Si), 14.06 (CH_3–C), 16.25 (CH_2Si), 22.65, 23.18, 29.21, 29.28, 31.90 and 33.41 (C–CH_2–C), 46.04 (CH_3N), 61.15 (CH_2N), 61.59 (CH_2O). MS: $m/z = 259$ ($[M]^+$, 1%); 244 ($[M - Me]^+$, 5%); 146 (9%); 72 ($[M - OSiMe_2C_8H_{17}]^+$, 9%); 58 (100%).

Decyldimethyl(β-dimethylaminoethoxy)silane[10] (**4**) was obtained as a clear light-yellow liquid. Yield 81%, b.p. 154–155 °C/3 Torr. ^{1}H NMR, δ (ppm): 0.16 (6H, s, $SiCH_3$), 0.64 (2H, t, $J = 8$ Hz, $SiCH_2$), 0.92 (3H, t, $J = 7$ Hz, CH_3), 1.33 (16H, bs, CH_2), 2.36 (6H, s, NCH_3), 2.54 (2H, t, $J = 6.5$ Hz, NCH_2), 3.77 (2H, t, $J = 6.5$ Hz, OCH_2). ^{13}C NMR ($CDCl_3$), δ (ppm): −2.18 (CH_3Si), 14.07 (CH_3–C), 16.23 (CH_2Si), 22.61, 23.13, 29.31, 29.54, 31.88 and 33.42 (C–CH_2–C), 45.99 (CH_3N), 60.83 (CH_2N), 61.52 (CH_2O). MS: $m/z = 287$ ($[M]^+$, 1%); 146 (9%); 72 ($[M - OSiMe_2Dc]^+$, 11%); 58 (100%).



Scheme 1. Synthesis of compounds **1–24**.

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Undecyldimethyl(β-dimethylaminoethoxy)silane (**5**) was obtained as a clear colourless liquid. Yield 80%, b.p. 149–150 °C/5 Torr. ^{1}H NMR, δ (ppm): 0.08 (6H, s, $SiCH_3$), 0.57 (2H, t, $J = 8$ Hz, $SiCH_2$), 0.86 (3H, t, $J = 6.2$ Hz, CH_3), 1.24 (12H, bs, CH_2), 2.24 (6H, s, NCH_3), 2.42 (2H, t, $J = 6.6$ Hz, NCH_2), 3.67 (2H, t, $J = 6.6$ Hz, OCH_2). ^{13}C NMR ($CDCl_3$), δ (ppm): −2.21 (CH_3Si), 14.02 (CH_3–C), 16,22 (CH_2Si), 22.62, 23.11, 29.29, 29.52, 29.65, 31.85 and 33.38 (C–CH_2–C), 45.99 (CH_3N), 60.86 (CH_2N), 61.54 (CH_2O). MS: $m/z = 300$ ($[M - H]^+$, 1%); 286 ($[M - Me]^+$, 3%); 146 (11%); 72 ($[M - OSiMe_2C_{11}H_{23}]^+$, 9%); 58 (100%).

Hexadecyldimethyl(β-dimethylaminoethoxy)silane (**6**) was obtained as a clear light-yellow liquid. Yield 24%, b.p. 165–167 °C/5 Torr. ^{1}H NMR, δ (ppm): 0.08 (6H, s, $SiCH_3$), 0.57 (2H, t, $J = 8$ Hz, $SiCH_2$), 0.86 (3H, t, $J = 6.2$ Hz, CH_3), 1.24 (12H, bs, CH_2), 2.24 (6H, s, NCH_3), 2.42 (2H, t, $J = 6.6$ Hz, NCH_2), 3.67 (2H, t, $J = 6.6$ Hz, OCH_2). ^{13}C NMR ($CDCl_3$), δ (ppm): −2.16 (CH_3Si), 14.09 (CH_3–C), 16.25 (CH_2Si), 22.67, 23.16, 23.22, 29.35, 29.68, 31.91 and 33.44 (C–CH_2–C), 45.99 (CH_3N), 60.80 (CH_2N), 61.50 (CH_2O). MS: $m/z = 356$ ($[M - Me]^+$, 1%); 146 (12%); 72 ($[M - OSiMe_2C_{16}H_{33}]^+$, 8%); 58 (100%).

Triethyl(β-dimethylaminoethoxy)silane[10] (**7**) was obtained as a clear light-yellow liquid. Yield 76%, b.p. 103–105 °C/22 Torr. ^{1}H NMR, δ (ppm): 0.58 (6H, m, $SiCH_2$), 0.93 (9H, m, CH_3), 2.22 (6H, s, NCH_3), 2.43 (2H, t, $J = 7$ Hz, NCH_2), 3.68 (2H, t, $J = 7$ Hz, OCH_2). Anal. found: C, 59.09; H, 12.35; N, 6.84. Calcd for $C_{10}H_{25}NOSi$: C, 59.11; H, 12.32; N 6.86. MS: $m/z = 203$ ($[M]^+$, 1%); 174 ($[M - Et]^+$, 8%); 72 ($[M - OSiEt_3]^+$, 10%); 58 (100%).

Triethyl(β-diethylaminoethoxy)silane[10] (**8**) was obtained as a clear light-yellow liquid. Yield 76%, b.p. 131–133 °C/34 Torr. ^{1}H NMR, δ (ppm): 0.59 (6H, m, $SiCH_2$), 0.99 (15H, m, $SiCH_2$–CH_3 and NCH_2–CH_3), 2.54 (6H, m, NCH_2), 3.67 (2H, t, $J = 7$ Hz, OCH_2). MS: $m/z = 231$ ($[M]^+$, 1%); 202 ($[M - Et]^+$, 6%); 100 (4%); 86 (100%); 59 (10%).

Ethyldibuthyl(β-dimethylaminoethoxy)silane (**9**) was obtained as a clear colourless liquid. Yield 60%, b.p. 123 °C/22 Torr. ^{1}H NMR, δ (ppm): 0.58 (3H, s, Si–CH_2–CH_3), 0,62 (3H, s, Si–CH_2–CH_2), 0.94 (13H, m, CH_3 and C–CH_2–C), 1.61 (4H, m, C–CH_2–C), 2.25 (6H, s, NCH_3), 2.44 (2H, t, $J = 6.7$ Hz, NCH_2), 3.67 (2H, t, $J = 6.7$ Hz, OCH_2). ^{13}C NMR ($CDCl_3$), δ (ppm): 6.95 and 6.47 (CH_2Si), 24.19 and 26.35 (CH_3–C and C–CH_2–C), 46.15 (CH_3N), 61.15 (CH_2N), 61.58 (CH_2O). MS: $m/z = 259$ ($[M]^+$, 1%); 244 ($[M - Me]^+$, 5%); 230 ($[M - Et]^+$, 8%); 202 ($[M - C_4H_9]^+$, 10%); 72 ($[M - OSiEtBu_2]^+$, 10%); 58 (100%).

Diheptylmethyl(β-dimethylaminoethoxy)silane (**10**) was obtained as a light-yellow liquid. Yield 44%, b.p. 142–143 °C/2 Torr. ^{1}H NMR, δ (ppm): 0.06 (3H, s, $SiCH_3$), 0.57 (4H, t, $J = 6.5$ Hz, $SiCH_2$), 0.87 (6H, t, $J = 6.2$ Hz, CH_3), 1.26 (20H, m, CH_2), 2.25 (6H, s, NCH_3), 2.43 (2H, t, $J = 6.5$ Hz, NCH_2), 3.67 (2H, t, $J = 6.5$ Hz, OCH_2). ^{13}C NMR ($CDCl_3$), δ (ppm): −3.94 (CH_3Si), 14.09(CH_3–C), 14.98 (CH_2Si), 22.71, 23.18, 29.05, 31.83 and 33.52 (C–CH_2–C), 46.09 (CH_3N), 61.08 (CH_2N), 61.63 (CH_2O). MS: $m/z = 314$ ($[M - Me]^+$, 1%); 230 ($[M - Et]^+$, 5%); 72 ($[M - OSiMeHp_2]^+$, 8%); 58 (100%).

Didecylmethyl(β-dimethylaminoethoxy)silane[10] (**11**) was obtained as a clear light-yellow liquid. Yield 71%, b.p. 193–194 °C/2 Torr. ^{1}H NMR, δ (ppm): 0.09 (3H, s, $SiCH_3$), 0.56 (4H, m, $SiCH_2$), 0.91 (6H, m, CH_3), 1.30 (32H, m, CH_2), 2.26 (6H, s, NCH_3), 2.44 (2H, t, $J = 7$ Hz, NCH_2), 3.67 (2H, t, $J = 7$ Hz, OCH_2). ^{13}C NMR ($CDCl_3$), δ (ppm): −3.97 (CH_3Si), 14.06 (CH_3–C), 14.97 (CH_2Si), 22.66, 29.33, 29.58, 29.65, 31.90 and 33.53 (C–CH_2–C), 46.06 (CH_3N), 61.04 (CH_2N), 61.60 (CH_2O). Anal. found: C, 72.66; H, 13.32; N, 3.41. Calcd for $C_{25}H_{55}NOSi$: C, 72.62; H, 13.31; N 3.42. MS: $m/z = 413$ ($[M]^+$, 73%); 398 ($[M - Me]^+$, 100%); 384 (5%); 370 (5%); 356 (6%); 342 (4%); 328 (3%); 300 (15%).

Ethyldiphenyl(β-dimethylaminoethoxy)silane[10] (**12**) was obtained as a clear light-yellow liquid. Yield 52%, b.p. 170–173 °C/4 Torr. ^{1}H NMR, δ (ppm): 0.87–1.31 (5H, m, $SiCH_2CH_3$), 2.22 (6H, s, NCH_3), 2.50 (2H, m, NCH_2), 3.81 (2H, m, OCH_2), 7.24–7.71 (10H, m, SiAr). ^{13}C NMR ($CDCl_3$), δ (ppm): 6.59 (CH_2Si), 6.97 (CH_3–CSi), 44.98 (CH_3N), 58.58 (CH_2N), 61.17 (CH_2O), 127.75 (C_m), 129.59 (C_p), 134.22 (C_o), 136.67 (C_i). Anal. found: C, 72.19; H, 8.49; N, 4.73. Calcd for $C_{18}H_{25}NOSi$: C, 72.21; H, 8.47; N 4.72. MS: $m/z = 413$ ($[M]^+$, 73%); 398 ($[M - Me]^+$, 100%); 384 (5%); 370 (5%); 356 (6%); 342 (4%); 328 (3%); 300 (15%).

Propyldimethyl(β-dimethylaminoethoxy)silane methiodide (**13**) was obtained as white powder. Yield 85%, m.p. 153 °C. ^{1}H NMR, δ (ppm): 0.13 (6H, s, $SiCH_3$), 0.61 (2H, m, $SiCH_2$), 0.96 (3H, t, $J = 7.2$ Hz, CH_3), 1.40 (2H, m, CH_2), 3.49 (9H, s, N^+CH_3), 3.88 (2H, t, $J = 4.8$ Hz, OCH_2), 4.06 (2H, m, N^+CH_2). ^{13}C NMR ($CDCl_3$), δ (ppm): −2.37 (CH_3Si), 16.48 (CH_3–C), 17.89 and 18.28 (CH_2Si and C–CH_2–C), 54.85 (CH_3N^+), 57.21 (CH_2N^+), 67.53 (CH_2O). Anal. found: C, 36.21; H, 7.89; N, 4.23. Calcd for $C_{10}H_{26}INOSi$: C, 36.25; H, 7.91; N 4.22.

Heptyldimethyl(β-dimethylaminoethoxy)silane methiodide[10] (**14**) was obtained as a light-yellow powder. Yield 82%, m.p. 191–193 °C. ^{1}H NMR, δ (ppm): 0.15 (6H, s, $SiCH_3$), 0.44 (2H, m, $SiCH_2$), 0.96 (3H, t, $J = 6$ Hz, CH_3), 1.41 (10H, m, CH_2), 3.56 (9H, s, N^+CH_3), 3.86 (2H, t, $J = 4.6$, OCH_2), 4.07 (2H, m, N^+CH_2). ^{13}C NMR ($CDCl_3$), δ (ppm): −2.45 (CH_3Si), 13.96 (CH_3–C), 15.74 (CH_2Si), 22.51, 22.89, 28.80, 31.61 and 33.13 (C–CH_2–C), 54.82 (CH_3N^+), 57.20 (CH_2N^+), 67.56 (CH_2O). Anal. found: C, 43.47; H, 8.82; N, 3.63. Calcd for $C_{14}H_{34}INOSi$: C, 43.41; H, 8.80; N 3.62.

Octyldimethyl(β-dimethylaminoethoxy)silane methiodide (**15**) was obtained as white crystals. Yield 91%, m.p. 181 °C. ^{1}H NMR, δ (ppm): 0.12 (6H, s, $SiCH_3$), 0.58 (2H, t, $J = 8$ Hz, $SiCH_2$), 0.86 (3H, t, $J = 6$ Hz, CH_3), 1.25 (12H, bs, CH_2), 3.61 (9H, s, N^+CH_3), 3.87 (2H, m, OCH_2), 4.04 (2H, m, N^+CH_2). ^{13}C NMR ($CDCl_3$), δ (ppm): −2.52 (CH_3Si), 13.90 (CH_3–C), 15.65 (CH_2Si), 22.43, 22.81, 29.00, 31.65 and 33.11 (C–CH_2–C), 54.73 (CH_3N^+), 57.13 (CH_2N^+), 67.44 (CH_2O).

Decyldimethyl(β-dimethylaminoethoxy)silane methiodide[10] (**16**) was obtained as whight powder. Yield 84%, m.p. 196–197 °C. ^{1}H NMR, δ (ppm): 0.15 (6H, s, $SiCH_3$), 0.44

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(2H, m, $SiCH_2$), 0.98 (3H, t, $J = 6$ Hz, CH_3), 1.36 (16H, m, CH_2), 3.51 (9H, s, N^+CH_3), 3.85 (2H, t, $J = 4.6$, OCH_2), 4.05 (2H, m, N^+CH_2). ^{13}C NMR ($CDCl_3$), δ (ppm): −2.43 (CH_3Si), 13.98 (CH_3–C), 15.76 (CH_2Si), 22.55, 22.93, 29.46, 29.49, 31.78 and 33.21 (C–CH_2–C), 54.83 (CH_3–N^+), 57.22 (CH_2–N^+), 67.57 and (CH_2O). Anal. found: C, 47.51; H, 9.33; N, 3.25. Calcd for $C_{17}H_{40}INOSi$: C, 47.55; H, 9.32; N 3.26.

Undecyldimethyl(β-dimethylaminoethoxy)silane methiodide (**17**) was obtained as white powder. Yield 96%, m.p. 187 °C. ^1H NMR, δ (ppm): 0.13 (6H, s, $SiCH_3$), 0.59 (2H, t, $J = 8$ Hz, $SiCH_2$), 0.87 (3H, t, $J = 6$ Hz, CH_3), 1.25 (18H, s, CH_2), 3.52 (9H, s, N^+CH_3), 3.87 (2H, t, $J = 4$ Hz, OCH_2), 4.07 (2H, m, N^+CH_2). ^{13}C NMR ($CDCl_3$), δ (ppm): −2.43 (CH_3Si), 14.00 (CH_3–C), 15.78 (CH_2Si), 22.57, 22.94, 29.19, 29.46, 29.50, 29.57, 31.78 and 33.24 (C–CH_2–C), 54.84 (CH_3N^+), 57.24 (CH_2N^+) and 67.58 (CH_2O). Anal. found: C, 48.78; H, 9.56; N, 3.17. Calcd for $C_{18}H_{42}INOSi$: C, 48.75; H, 9.54; N 3.16.

Hexadecyldimethyl(β-dimethylaminoethoxy)silane methiodide (**18**) was obtained as white powder. Yield 57%, m.p. 204–205 °C. ^1H NMR, δ (ppm): 0.13 (6H, s, $SiCH_3$), 0.59 (2H, t, $J = 7$ Hz, $SiCH_2$), 0.87 (3H, t, $J = 6$ Hz, CH_3), 1.25 (28H, s, CH_2), 3.51 (9H, s, N^+CH_3), 3.88 (2H, t, $J = 5$ Hz, OCH_2), 4.06 (2H, m, N^+CH_2). ^{13}C NMR ($CDCl_3$), δ (ppm): −2.44 (CH_3Si), 13.65 (CH_3–C), 15.77 (CH_2Si), 22.06, 22.95, 29.22, 29.49, 29,55, 29.60, 31.82 and 33.28 (C–CH_2–C), 54.83 (CH_3N^+), 57.22 (CH_2N^+) and 67.37 (CH_2O). Anal. found: C, 53.81; H, 10.21; N, 2.73. Calcd for $C_{23}H_{52}INOSi$: C, 53.78; H, 10.20; N 2.73.

Triethyl(β-dimethylaminoethoxy)silane methiodide[10] (**19**) was obtained as white powder. Yield 92%, m.p. 215–217 °C. ^1H NMR, δ (ppm): 0.62 (6H, m, $SiCH_2$), 0.96 (9H, m, CH_3), 3.51 (9H, s, N^+CH_3), 3.86 (2H, m, OCH_2), 4.10 (2H, m, N^+CH_2). ^{13}C NMR ($CDCl_3$), δ (ppm): 3.91 (CH_2Si), 6.56 (CH_3–CSi), 54.78 (CH_3N^+), 57.47 (CH_2N^+), 67.65 (CH_2O). Anal. found: C, 38.19; H, 8.14; N, 4.05. Calcd for $C_{11}H_{28}INOSi$: C, 38.26; H, 8.12; N 4.06.

Triethyl(β-diethylaminoethoxy)silane methiodide[10] (**20**) was obtained as a white powder. Yield 56%, m.p. 155–156 °C. ^1H NMR, δ (ppm): 0.61 (6H, m, $SiCH_2$), 0.96 (9H, m, SiC–CH_3), 1.45 (6H, t, $J = 7$ Hz, N^+CH_2–CH_3), 3.27 (3H, s, N^+CH_3), 3.44–3.89 (6H, m, N^+–CH_2–CH_3 + OCH_2), 4.04 (2H, m, N^+–CH_2–CH_2). ^{13}C NMR (DMSO), δ (ppm): 7.74 (CH_3–CSi and CH_2Si), 54.65 (CH_3N^+), 56.48 (CH_2N^+), 61.22 (CH_2O). Anal. found: C, 41.80; H, 8.59; N, 3.72. Calcd for $C_{13}H_{32}INOSi$: C, 41.82; H, 8.58; N 3.75.

Ethyldibutyl(β-dimethylaminoethoxy)silane methiodide (**21**) was obtained as a white powder. Yield 65%, m.p. 145 °C. ^1H NMR, δ (ppm): 0.61 (6H, m, $SiCH_2$), 0.91 (13H, m, CH_3 and CH_2), 1.74 (4H, m, CH_2), 3.53 (9H, s, N^+CH_3), 3.87 (2H, m, OCH_2), 4.07 (2H, m, N^+CH_2). ^{13}C NMR ($CDCl_3$), δ (ppm): 6.04 and 6.84 (CH_2Si), 23.68, 24.01, 26.16 (CH_3–C and C–CH_2–C), 54.76 (CH_3N^+), 57.32 (CH_2N^+), 67.80 (CH_2O). Anal. found: C, 44.86; H, 9.03; N, 3.48. Calcd for $C_{15}H_{36}INOSi$: C, 44.88; H, 9.04; N 3.49.

Diheptylmethyl(β-dimethylaminoethoxy)silane methiodide (**22**) was obtained as a white oily solid. Yield 62%, m.p. 67 °C. ^1H NMR, δ (ppm): 0.10 (3H, s, $SiCH_3$), 0.59 (4H, t, $J = 6$ Hz, $SiCH_2$), 0.88 (6H, t, $J = 5$ Hz CH_3), 1.26 (20H, bs, CH_2), 3.52 (9H, s, N^+CH_3), 3.86 (2H, m, OCH_2), 4.05 (2H, m, N^+CH_2). ^{13}C NMR ($CDCl_3$), δ (ppm): −4.21 (CH_3Si), 13.97 (CH_3–C), 14.40 (CH_2Si), 22.52, 22.94, 28.79, 31.63 and 33.25 (C–CH_2–C), 54.80 (CH_3N^+), 57.30 (CH_2N^+) and 67.65 (CH_2O). Anal. found: C, 51.01; H, 9.85; N, 2.96. Calcd for $C_{20}H_{46}INOSi$: C, 50.94; H, 9.83; N 2.97.

Didecylmethyl(β-dimethylaminoethoxy)silane methi odide[10] (**23**) was obtained as a white oily solid. Yield 63%, m.p. 104 °C. ^1H NMR, δ (ppm): 0.09 (3H, s, $SiCH_3$), 0.61 (4H, m, $SiCH_2$), 0.90 (6H, m, CH_3), 1.45 (32H, m, CH_2), 3.51 (9H, s, N^+CH_3), 3.82 (2H, m, OCH_2), 4.10 (2H, m, N^+CH_2). ^{13}C NMR ($CDCl_3$), δ (ppm): −4.16 (CH_3Si), 14.03 (CH_3–C), 14.47 (CH_2Si), 22.59, 23.01, 29.20, 29.25, 29.50, 29.55, 31.82 and 33.36 (C–CH_2–C), 54.87 (CH_3N^+), 57.35 (CH_2N^+), 67.72 (CH_2O). Anal. found: C, 56.19; H, 10.43; N, 2.53. Calcd for $C_{26}H_{58}INOSi$: C, 56.22; H, 10.45; N 2.52.

Ethyldiphenyl(β-dimethylaminoethoxy)silane methiodide[10] (**24**) was obtained as a light yellow powder. Yield 86%, m.p. 109–110 °C. ^1H NMR, δ (ppm): 0.92 (2H, m, $SiCH_2$), 1.29 (3H, m, CH_3), 3.50 (9H, s, N^+CH_3), 3.84 (2H, m, OCH_2), 4.09 (2H, m, N^+CH_2), 7.29–7.73 (10H, m, Ar). ^{13}C NMR ($CDCl_3$), δ (ppm): 6.64 (CH_2Si), 6.85 (CH_3–CSi), 54.81 (CH_3N^+), 57.81 (CH_2N^+), 67.57 (CH_2O), 127.87 (C_m), 129.81 (C_p), 134.21 (C_o), 136.13 (C_i). Anal. found: C, 51.69; H, 6.32; N, 3.22. Calcd for $C_{19}H_{28}INOSi$: C, 51.71; H, 6.31; N 3.22.

Biological tests

Cytotoxicity

Monolayer tumour cell lines HT-1080 (human fibrosarcoma), MG-22A (mouse hepatoma) 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.[23] 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 × 10^4 cells/ml concentration (depending on line nature) were placed on a separate 96 wells plates. The volume of each plate was 200 µl. Solutions containing test compounds were diluted and added in wells to give the final concentrations of 50, 25, 12.5 and 6.25 µg/ml. Control cells were treated in the same manner only in the absence of test compounds. The plates were incubated for 72 h, 37 °C, 5% CO_2. The number of survived 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) colouration which was assayed by multiscan spectrophotometer. The quantity of alive cells on the control plate was taken in calculations for 100%.[23,24] The LC_{50} was calculated using Graph Pad Prism® 3.0 program, $r < 0.05$. The concentration of NO was determined according to the procedure described in Fast *et al*.[24]

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Antimicrobial activity

The microbial strains were obtained from the National Chemical Laboratory (NCL), Pune, India. The standard microbial strains studied were *Staphylococcus aureus* ATCC 25923, *Bacillus cereus* ATCC 11778, *Proteus mirabilis* NCIM 2241, *Escherichia coli* ATTC 25922, *Candida tropicalis* ATCC 4563 and *Candida albicans* ATCC 2091.

A loop of the strain was inoculated in 30 ml of nutrient broth and was incubated at 37 °C for 24 h to activate the strain. The plates were prepared by dissolving 38 g of Mueller Hinton Agar no. 2 in 1000 ml distilled water. In order to proceed with the Agar ditch diffusion method,[25,26] 30 ml of the autoclaved Mueller Agar no. 2 media was added into a 100 mm diameter Petri dish. 0.2 ml of the activated strain was inoculated into the media when it reached a temperature of 40–42 °C. Care was taken to ensure proper homogenization. The experiment was performed under strict aseptic conditions. After solidification of the media, a ditch was made in the plate with the help of a cup-borer (0.85 cm). A recommended concentration (100 µl) of the test sample (1 mg/0.1 ml and 0.5 mg/0.1 ml in DMSO) was introduced in the respective well. Inoculating into the well 0.1 ml of the pure solvent the controls were maintained for each bacterial strain. Other wells were supplemented with reference antimicrobial drugs: gentamicin, piperacillin, nystatin and fluconazole (1 mg/0.1 ml and 0.5 mg/0.1 ml in DMSO). The plates were incubated immediately overnight at 37 °C.

Activity was determined by measuring the diameter (in millimetres) of zones showing complete inhibition. The mean value obtained for three individual replicates was used to calculate the zone of growth inhibition of each sample. The observed zones of growth inhibition are presented in Tables 3 and 4.

RESULTS AND DISCUSSION

β-Triorganyl-(*N*,*N*-dialkylaminoethoxy)silanes (**1–12**) and their methiodides (**13–24**), being considered as derivatives of choline, and colamine possessing increased lipophilicity were synthesized by the dehydrocondensation reaction between β-(*N*,*N*-dialkylamino)ethanol and triorganylsilanes in the presence of a trace amount of metallic sodium and subsequent reaction with methyl iodide (Scheme 1). The compounds synthesized were characterized by multinuclear NMR data. The values of ^{29}Si chemical shifts are given in Tables 1 and 2.

It was found that ^{29}Si NMR resonance of β-triorganyl(*N*,*N*-dialkylaminoethoxy)silanes (**1–12**) ($\delta = 16.47–18.50$ ppm) is shifted upfield in comparison with their *N*-methylammonium salts (**13–24**) ($\delta = 21.25–23.68$ ppm), revealing week N···Si interaction for proper silanes. The value of the ^{29}Si chemical shift depends upon the substituent at the silicon atom. It becomes more positive with decreased shielding of the silicon atom along the sequences for silanes:

$$PrMe_2 < EtBu_2 < Hp_2Me < Dc_2Me < OctMe_2 < DcMe_2 < (C_{11}H_{23})Me_2 < (C_{16}H_{33})Me_2$$

Table 1. ^{29}Si NMR resonance of β-triorganyl(*N*,*N*-dimethylaminoethoxy)silanes

$R^1R^2R^3SiOCH_2CH_2N(CH_3)_2$

Compound	R^1	R^2	R^3	δ^{29}Si
1	CH_3	CH_3	C_3H_7	16.47
3	CH_3	CH_3	C_8H_{17}	18.18
4	CH_3	CH_3	$C_{10}H_{21}$	18.26
5	CH_3	CH_3	$C_{11}H_{23}$	18.35
6	CH_3	CH_3	$C_{16}H_{33}$	18.50
9	C_2H_5	C_4H_9	C_4H_9	16.52
10	CH_3	C_7H_{15}	C_7H_{15}	17.91
11	CH_3	$C_{10}H_{21}$	$C_{10}H_{21}$	17.96

Table 2. ^{29}Si NMR resonance of β-triorganyl(*N*,*N*-dimethylaminoethoxy)silane methiodides

$[R^1R^2R^3SiOCH_2CH_2NMe_3]^+I^-$

Compound	R^1	R^2	R^3	δ^{29}Si
13	CH_3	CH_3	C_3H_7	22.18
14	CH_3	CH_3	C_7H_{15}	22.42
15	CH_3	CH_3	C_8H_{17}	22.37
16	CH_3	CH_3	$C_{10}H_{21}$	22.46
17	CH_3	CH_3	$C_{11}H_{23}$	22.31
18	CH_3	CH_3	$C_{16}H_{33}$	22.49
19	C_2H_5	C_2H_5	C_2H_5	23.68
21	C_2H_5	C_4H_9	C_4H_9	21.25
22	CH_3	C_7H_{15}	C_7H_{15}	22.22
23	CH_3	$C_{10}H_{21}$	$C_{10}H_{21}$	22.28

Along methiodides, even the correlation was not so strong, the same the tendency being maintained:

$$EtBu_2 < PrMe_2 < Hp_2Me < Dc_2Me < (C_{11}H_{23})Me_2 < OctMe_2 < HpMe_2 < DcMe_2 < (C_{16}H_{33})Me_2$$

Biological evaluation

Antitumour and antimicrobial properties of compounds synthesized were investigated. The cytotoxicity was tested *in vitro* on two monolayer tumour cell lines: HT-1080 (human fibrosarcoma), MG-22A (mouse hepatoma), and normal mouse fibroblasts (NIH 3T3). The experimental evaluation of cytotoxic properties is presented in Tables 3 and 4.

A comparison of sily modified compounds with their unsilylated precursors provides evidence that unsilylated compounds, either parent alkanolamine or its methiodide, do not possess cytotoxic properties. Quaternization of nitrogen atom in silyl ethers **4–6, 9** and **11** leads to cytotoxic effect appearance in the corresponding methiodides **16**–**18, 21** and **23**.

Compounds **4, 10** and **12** were the only compounds among silyl ethers **1**–**12** to exhibit low or moderate cytotoxicity. In

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Table 3. *In vitro* cell cytotoxicity and itracellular NO generation caused by β-triorganyl(*N*,*N*-dialkylaminoethoxy)silanes

	HT-1080			MG-22A			NIH 3T3	
Compound/test	LC_{50}, CV[a]	LC_{50}, MTT[b]	NO, CV[c]	LC_{50}, CV[a]	LC_{50}, MTT[b]	NO, CV[c]	LC_{50}, NR[d]	LD_{50}, mg/kg
$HOCH_2CH_2NMe_2$	**	**	5	**	**	5	**	>2000
1	**	**	10	**	**	12	285	954
3	**	**	5	**	**	5	1000	1966
4	**	**	5	>100	100	7	80	774
5	**	**	8	48	45	26	137	902
6	**	**	5	**	**	5	>6	>2000
8	**	**	8	**	**	8	**	>2000
9	**	**	5	**	**	7	**	>2000
10	100	100	14	40	42	37	299	1332
11	**	**	5	**	**	5	100	940
12	32	28	150	21	23	450	32	477

[a] Concentration (μ g/ml) providing 50% cell killing effect (CV: colouration).
[b] Concentration (μ g/ml) providing 50% cell killing effect (MTT: colouration).
[c] NO concentration (CV : coloration), determined according to Fast *et al*.[24]
[d] Concentration (μ g/ml) providing 50% cell killing effect (NR: colouration).
** No cytotoxic effect.

Table 4. *In vitro* cell cytotoxicity and intracellular NO generation caused by β-triorganyl(*N*,*N*-dialkylaminoethoxy)silane methiodides

	HT-1080			MG-22A			NIH 3T3	
Compound/test	IC_{50}[a], CV	IC_{50}[b], MTT	NO[c], CV	IC_{50}[a], CV	IC_{50}[b], MTT	NO[c], CV	IC_{50}[d], NR	LD_{50}, mg/kg
$OHCH_2CH_2NMe_3I$	**	**	10	>100	100	17	**	>2000
13	**	**	10	**	**	16	764	>2000
14	**	**	8	**	**	8	200	1225
15	**	**	7	**	**	10	35	586
16	28	28	67	20	14	120	14	429
17	43	31	200	22	17	250	12	389
18	19	6	600	12	8	325	26	616
19	**	**	7	87	94	14	1050	>2000
20	**	**	4	**	**	5	**	>2000
21	3	3	180	1	6	400	39	614
22	**	**	9	**	**	5	**	>2000
23	0.3	0.4	500	1	0.9	650	7	349
24	31	29	250	27	30	250	53	740

[a] Concentration (μ g/ml) providing 50% cell killing effect (CV: colouration).
[b] Concentration (μ g/ml) providing 50% cell killing effect (MTT: colouration).
[c] NO concentration (CV: colouration), determined according to Fast *et al*.[24]
[d] Concentration (μ g/ml) providing 50% cell killing effect (NR: colouration).
** No cytotoxic effect.

general, about 60% of the tested methiodides showed some cytotoxic effect against tumour cell lines compared with about 30% of the parent silyl ethers.

Between *N*-methyl (**19**) and *N*-ethyl substituted (**20**) triethylsilylethers, **19** was more effective exhibiting moderate cytotoxic effect concerning mouse hepatoma MG-22A in comparison with inactive **20**. In addition, in the group of organosilicon substituted methiodides (**13–24**), the more bulky substituted at silicon atom molecules appeared to exert more marked cytotoxic activity. Among possessing cytotoxic properties methiodides (**16–18, 21, 23** and **24**), the following sequence of the organosilicon substituents in the cytotoxicity display concerning both tumour cell lines has been revealed: $Dc_2Me > EtBu_2 > (C_{16}H_{23})Me_2 > DcMe_2 > (C_{11}H_{23})Me_2 > EtPh_2$.

Didecylmethyl(β-dimethylaminoethoxy)silane methiodide (**23**) and ethyldibuthyl(β-dimethylaminoethoxy)silane methiodide (**21**) possess good cytotoxic activity and NO-induction

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Table 5. *In vitro* antibacterial and anti-fungal activity data of β-triorganyl(*N*,*N*-dialkylaminoethoxy)silane methiodides (**13**–**23**) given at a concentration of 1 mg/disc

Compound	Diameter of zones showing complete inhibition of growth (mm)					
	BC	SA	PM	EC	CT	CA
$[HOCH_2CH_2NMe_3]^+I^-$	8.5	8.5	7.5	9.5	7	7
13	13.5	15.5	10.5	8	7	9.5
14	18	22.5	15.5	13.5	8.5	9.5
15	20.5	20	15.5	14.5	10.5	11
16	16.5	17	12	12.5	11	9.5
17	17	18	10.5	10.5	9	12.5
18	9.5	8.5	7.5	8.5	10.5	7
19	18.5	18.5	13.5	11.5	9	7
20	8.5	8.5	11	8.5	7	7.5
21	27.5	22	28.5	19	16.5	17
22	24.5	21.5	13.5	7	12.5	10.5
23	11	9	10.5	11	7	8.5
Gentamicin	16	16	30	12	—	—
Piperacillin	15	40	22	15	—	—

Table 6. *In vitro* antibacterial and anti-fungal activity of β-triorganyl(*N*,*N*-dialkylaminoethoxy)silane methiodides **13**–**23** given at a concentration of 0.5 mg/disc

Compound	Diameter of zones showing complete inhibition of growth (mm)					
	BC	SA	PM	EC	CT	CA
$[HOCH_2CH_2NMe_3]^+I^-$	8	9	7.5	9.5	9	7.5
13	9.5	13	8	8	8	7.5
14	12	10	11	10.5	7.5	7
15	14.5	19.5	17	12	9.5	8
16	16	16.5	13.5	11	10	11.5
17	16	16	11.5	9	8.5	12
18	11.5	10.5	7.5	7.5	8	7.5
19	12	12	9	9.5	7.5	7
20	9.5	9	7.5	7.5	7	8
21	24	30	31	16.5	14	15.5
22	19	15	16	10	9	12.5
23	13	9.5	7.5	8.5	8.5	7
Nystatin	—	—	—	—	7	9
Fluconazole	—	—	—	—	20	16

ability. Didecylmethyl(β-dimethylaminoethoxy)silane methiodide (**23**) is the most active in this respect. It has the highest cytotoxic effect on HT-1080 (human fibrosarcoma) and MG-22A (mouse hepatoma) cell lines and high NO-generation activity, being most active in the test MG-22A (Table 4). All the compounds synthesized are non-toxic or low-toxicity compounds.

The antibacterial and antifungal activity of compounds **13**–**24** in comparison with the unsilylated one has been investigated in dimethyl sulfoxide against two Gram-positive, *Bacillus cereus* ATCC 11778 and *Staphylococcus aureus* ATCC 25923, two Gram-negative, *Proteus mirabilis* NCIM 2241 and *E. coli* ATCC 25922, and two fungi strains, *Candida tropicalis* ATCC 4563 and *Candida albicans* ATCC 2091, using the agar dish diffusion method.[25,26] The results of the study are presented in Tables 5 and 6.

The results were compared with those of the standard antibacterial (gentamicin, piperacillin) and antifungal (nystatin, fluconazole) drugs. The parent unsilylated β-(*N*,*N*-dimethylamino)ethanol methiodide was inactive concerning all the fungi and bacterial strains tested. It was evident that the overall potency of the unsilylated compound was enhanced on the silyl group introduction.

All the organosilicon containing β-ethanolamine methiodides were found to be active against several microbial strains. They exhibited antimicrobial activity against some fungi and bacterial strains either Gram-positive or Gram-negative, even, in general, fungal and Gram-negative strains were more resistant to the synthesized compounds in comparison with Gram-positive ones.

This enhancement of the activity may be rationalized on the basis that their structures possess an Si–O bond, which increases the lipophilicity of the parent alkanolamine. This favours the permeation of the latter more efficiently through the lipoid layer of the micro-organism, thereby destroying them more aggresively.

The most effective action of compounds studied has been demonstrated against Gram-positive *Staphylococcus aureus* ATCC 25923 and *Bacillus cereus* ATCC 11778, and Gram-negative *Proteus mirabilis* NCIM 2241. Compounds **14**–**17, 19, 21** and **22** were found to be more active against *Bacillus cereus* ATCC 11778 than gentamicin and piperacillin. However, the antifungal potency of almost all the compounds synthesized was lower than that of the standard antifungal remedies, excluding compound **21**.

It was revealed that β-dibutylethyl(*N*,*N*-dimethylaminoethoxy)silane methiodide (**21**), having the lowest ^{29}Si value ($\delta = 21.25$ ppm), possessed a wide spectrum of antimicrobial activity, being the most active compound concerning all fungi and bacterial, either Gram-positive or Gram-negative, strains tested.

We established that antibacterial activity shows dependance on the steric environment of the silicon atom, which probably affects the behaviour of silylated compounds in physiological conditions. The degree of antibacterial activity increased with the silyl substituent nature in the following order: $(C_{11}H_{23})Me_2 < Et_3 < OctMe_2 < Hp_2Me < EtBu_2 < HpMe_2$, concerning the Gram-positive SA strain, and $(C_{11}H_{23})Me_2 < HpMe_2 \sim Et_3 < OctMe_2 < Hp_2Me < EtBu_2$, concerning the Gram-negative BC strain.

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The elongation of alkyl chain at the silicon atom till C_{16} in compound **18** was not effective concerning antimicrobial activity. The replacement of dimethylamine substituent into diethylamine led to dramatically decreased antimicrobial activity.

CONCLUSIONS

It has been shown that ^{29}Si NMR resonance of β-triorganyl(*N*,*N*-dialkylaminoethoxy)silanes (**1–12**) (δ = 16.47–18.50 ppm) is shifted upfield in comparison with their methiodides (**13–24**) (δ = 21.25–23.68 ppm) and depends on the substituent at silicon atom. On the basis of the biological activity data obtained concerning tumour cell lines and bacterial/fungal strains, it has been demonstrated that silylation stimulates the overall pharmacological potency appearance or enhancement.

It was found that didecylmethyl(β-dimethylaminoethoxy)-silane methiodide **23** and ethyldibuthyl(β-dimethylamino-ethoxy)silane methiodide **21**, possessing high *in vitro* antitumour activity and NO-induction ability concerning human fibrosarcoma and mouse hepatoma, are the most effective in this respect. It was revealed that ethyldibutyl(*N*,*N*-dimethylaminoethoxy)silane methiodide **21** possesses a wide spectrum of antimicrobial activity, being the most active compound concerning all fungi and bacterial strains tested.

In conclusion, the preliminary data reported in the present study show the feasibility of the synthesis of silylated alkanolamines as potential antitumour and antimicrobial agents. In addition some chemical modifications of the structure moieties should be warranted to reveal the generality of the silyl modification approach.

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