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# Synthesis and cytotoxic activity of new 2-[(3-aminopropyl)dimethylsilyl]-5-triethylsilylfurans

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**Highly cytotoxic 3-aminopropyl derivatives of 5-triethylsilyl-2-dimethylsilylfuran ($LC_{50}$ 1–3 μg $ml^{-1}$) have been prepared by hydrosilylation of heterocyclic *N*-allylamines with corresponding hydrosilane in the presence of Speier's catalyst. The influence of the amine structure on the cytotoxicity has been investigated.** 

**Keywords:** 2-[(3-aminopropyl)dimethylsilyl]-5-triethylsilylfurans; 5-triethylsilyl-2-dimethylsilylfuran; hydrosilylation; synthesis; $^{1}H$; $^{13}C$; $^{29}Si$ NMR; cytotoxic activity

## Introduction

Heterocycles are important building blocks for the construction of anticancer drugs.[1] The fragment analysis[2] of clinically used antineoplastic agents shows that in many cases a heterocyclic amino group has been introduced to increase the solubility and bioavailability of the active substance, e.g. piperidine in *Arzoxifene*[3–6], *Flavopiridol*[7] and *Perifosine*,[8–10] morpholine in *Canertinib*,[11,12] *Gefinitib*[13–15] and *Mofarotene*,[16] thiomorpholine in *Prinomastat*,[17] piperazine in *Dasatinib*[18] and *Imatinib*,[19,20] and pyrrolidine in *Idoxifene*[21,22]. These heterocyclic amines are also used for formation of libraries of cytotoxic agents[23]. In some cases the benzene ring has been substituted for thiophene or furan to enhance the activity and increase the therapeutic index. Examples are thiophene-containing folate analogue *Raltitrexed*[24] and antimetastatic agent *Batimastat*[25,26] and furan-containing anticancer agent *Lapatinib*.[27]

Our previous investigations have demonstrated that heterylaminoalkyl(siloxy)-silanes, which contain an alkyl(or siloxy) group attached to the silicon atom, have anticancer, neurotropic and bacteriostatic activity.[28,29]

Taking into consideration the information gained from the fragment analysis of known anticancer drugs and the fact that silylation increases the lypophilicity of the compounds and can change their metabolism,[30–32] we decided to combine in one molecule the fragments of silylated furan and heterocyclic amine and to test their cytotoxicity.

## Experimental

### Materials and Methods

The $^{1}H$, $^{13}C$ and $^{29}Si$ NMR spectra were recorded on a Varian 200 Mercury instrument at 200, 50 and 40 MHz, respectively, in $CDCl_3$ as a solvent, $(Me_3Si)_2O$ as a standard for $^{1}H$, TMS (external) as the standard for $^{29}Si$, and the signal on the residual proton of the solvent ($\delta$ 77.05 ppm) for $^{13}C$. The mass spectra under electron impact conditions were recordered on a GC-MS Agilent Technologies 7890 GC system with 5975C EI/CI MSD (70 eV) on capilary column HP-5. IR spectra (KBr) were registered on a Shimadzu Prestige-21 spectrometer. All solvents were dried on $CaH_2$, and distilled prior to use. Thin-layer chromatography (TLC) was performed on a Merck silica gel 60 $F_{254}$ with various eluents. Column chromatography was performed on Silica gel (0.060–0.200 mm, pore diameter 6 nm, 'Acros'). 2-Triethylsilylfuran was prepared by the known method.[33]

### Chemistry

*5-Triethylsilyl-2-dimethylsilylfuran (**1**)*

A solution of 3.8 g (20 mmol) of 2-triethylsilylfuran in 40 ml of dry ether was placed in a three-necked flask fitted with a reflux condenser, a thermometer, a magnetic stirrer and a rubber stopper in a stream of argon. The flask with the solution was cooled to −30 °C, and 8.3 ml (20 mmol) of a 2.5N solution of *n*-BuLi in hexane was added dropwise so slowly to maintain the temperature below −25 °C. When all the *n*-BuLi had been added the mixture was stirred for 1 h at −10 °C, and for 2 h at 10 °C. Then 1.98 g (20 mmol) of dimethylchlorosilane was added dropwise at −25 °C. After the addition of chlorosilane the mixture was stirred for 10 min at −25 °C, the temperature was slowly raised to room temperature, and the mixture was stirred for 12 h. The precipitate was filtered off through $Al_2O_3$, solvents evaporated and the residue was distilled under reduced pressure at 66–67 °C (4.5 mmHg), to give 3.4 g (70.8%) of the compound **1**. $^{1}H$ NMR: $\delta$ ppm 0.37 (s, 6H, Si–$CH_3$), 0.77–1.05 (m, 15H, Si–$C_2H_5$), 4.45 (m, 1H, SiH), 6.67 (m, 1H, $H^3$ furan), 6.72 (d, $J$ = 3.6 Hz, 1H, $H^4$ furan), $^{29}Si$ NMR: $\delta$ ppm −3.62 ($SiEt_3$), −28.40 (Si–H), GC-MS (*m/z*, %): 240 ($M^+$, 9), 211 ($M^+ - C_2H_5$, 61), 183 (12), 161 (46), 133 (100), 117 (9), 105 (63), 83 (21), 71 (17), 59 (84). IR spectrum $\nu$, $m^{-1}$ (Si–H) 2129.5.

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**Table 1.** The spectral characteristics of 2-[(3-aminopropyl)dimethylsilyl]-5-triethylsilylfurans (**2–11**)

| Compound | $\delta^{13}C$ δ (ppm) C(4) | C(3) | C(5) | C(2) | $(C_2H_5)_3Si-$, $Si(CH_3)_2CH_2CH_2CH_2$ R | $\delta^{29}Si$ (ppm) |
|---|---|---|---|---|---|---|
| **2** | 120.06 | 119.37 | 163.77 | 162.70 | 56.48, 47.89, 21.27, 13.11, 7.34, −3.34 | −3.80, −9.67 |
| **3** | 120.05 | 119.33 | 163.88 | 162.70 | 57.74, 53.95, 41.69, 29.34, 21.30, 20.81, 14.12, 13.04, 7.36, 3.45, −3.31 | −3.84, −9.63 |
| **4** | 120.04 | 119.36 | 163.71 | 162.68 | 59.91, 54.14, 23.32, 13.32, 7.34, 3.42, −3.45 | −3.81, −9.63 |
| **5** | 120.02 | 119.35 | 163.72 | 162.71 | 62.95, 54.58, 25.97, 24.49, 21.11, 13.16, 7.33, 3.40, −3.37 | −3.85, −9.56 |
| **6** | 120.09 | 119.40 | 163.70 | 162.45 | 57.72, 55.80, 52.32, 34.79, 26.31, 24.19, 19.54, 13,24, 7.39, 3.46, −3.34 | −3.87, −9.71 |
| **7** | 120.04 | 119.36 | 163.74 | 162.71 | 61.67, 55.45, 27.71, 27.01, 21.45, 13.01, 7.34, 3.41, −3.41 | −3.85, −9.67 |
| **8** | 120.06 | 119.44 | 163.53 | 162.75 | 66.97, 62.32, 53.70, 20.81, 12.96, 7.33, 3.40, −3.40 | −3.83, −9.62 |
| **9** | 120.05 | 119.43 | 163.56 | 162.77 | 62.67, 54.97, 27.99, 20.74, 12.98, 7.34, 3.40, −3.35 | −3.80, −9.63 |
| **10** | 120.02 | 119.38 | 163.58 | 162.71 | 61.98, 55.14, 53.18, 21.16, 13.03, 7.32, 3.38, −3.43 | −3.83, −9.68 |
| **11** | 120.09 | 119.47 | 163.65 | 162.79 | 151.39, 129.8, 119.61, 62.00, 53.14, 49.14, 21.17, 13.08, 7.38, 3.44, −3.37 | −3.77, −9.57 |

*2-[(3-Diethylaminopropyl)dimethylsilyl]-5-triethylsilylfuran (**2**)*

A solution of 0.25 g (1.1 mmol) of silane **1**, and 0.12 g (1.1 mmol) *N*,*N*-diethylallylamine and one drop of $H_2PtCl_6 \cdot 6H_2O$ (0.1% in *i*-PrOH) were placed in a flask with a reflux condenser, a thermometer and a magnetic stirrer. The mixture was heated at 90 °C for 1 h, cooled and analyzed by GC-MS. Separation by column chromatography ($CH_2Cl_2$:$CH_3OH$ = 20 : 1) gave 0.25 g (66.7%) of compound **2.** $^1H$ NMR δ ppm: 0.23 (s, 6H, Si–$CH_3$), 0.66–0.77 (m, 8H, Si–$CH_2$, $CH_3$), 0.95–1.00 (m, 15H, $SiC_2H_5$), 1.45–1.53 (m, 2H, $CH_2$), 2.36–2.40 (m, 2H, $CH_2N$), 2.46–2.51 (m, 4H, $CH_2N$), 6.59 (s, 2H, $H^3H^4$). GC-MS, *m/z* (%): 353 ($M^+$, 4), 181 (18), 153 (32), 140 (24), 125(15), 86 (100), 59 (40).

The compounds **3**–**11** were prepared and isolated in the same manner as described for compound **2**. The $^{13}C$ and $^{29}Si$ NMR data for compounds **2–11** are given in Table 1.

*2-[(3-Di-n-butylaminopropyl)dimethylsilyl]-5-triethylsilylfuran (**3**)*

Compound **3** was prepared from **1** and *N*,*N*-di-*n*-butylallylamine. Yield 75.8%. $^1H$ NMR δ (ppm): 0.24 (s, 6H, Si–$CH_3$), 0.66–1.00 (m, 25H, Si–$CH_2$, Si–$C_2H_5$, $CH_3$), 1.20–1.51 (m, 14H, $CH_2$), 2.34–2.38 (m, 6H, $CH_2N$), 6.60 (s, 2H, $H^3H^4$). GC-MS, *m/z* (%): 409 ($M^+$, 7), 394 ($M^+$ − Me, 3), 195 (34), 170 (9), 142 (100), 125(5), 100 (14), 59 (10).

*2-[(3-Pyrrolidinopropyl)dimethylsilyl]-5-triethylsilylfuran (**4**)*

Compound **4** was prepared from **1** and *N*-allylpyrrolidine. Yield 62.2%. $^1H$ NMR δ (ppm): 0.24 (s, 6H, Si–$CH_3$), 0.70–1.00 (m, 17H, Si–$CH_2$, Si–$C_2H_5$), 1.55–1.68 (m, 2H, $CH_2$), 1.78–1.86 (m, 4H, $CH_2N$), 2.42–2.55 (m, 6H, $CH_2N$, $CH_2$), 6.59 (s, 2H, $H^3H^4$). GC-MS, *m/z* (%): 353 ($M^+$, 4), 181 (18), 153 (32), 140 (24), 125(15), 86 (100), 59 (40).

*2-[(3-Piperidinopropyl)dimethylsilyl]-5-triethylsilylfuran (**5**)*

Compound **5** was prepared from **1** and *N*-allylpiperidine. Yield 70.8%. $^1H$ NMR δ (ppm): 0.23 (s, 6H, Si–$CH_3$), 0.66–0.99 (m, 17H, Si–$CH_2$, Si–$C_2H_5$), 1.40–1.42 (m, 2H, $CH_2$), 1.50–1.60 (m, 6H, $CH_2$), 2.24–2.40 (m, 6H, $CH_2N$), 6.59 (s, 2H, $H^3H^4$). GC-MS, *m/z* (%): 365 ($M^+$, 5), 336 ($M^+$ − Me, 5), 182 (12), 153 (18), 124 (11), 96 (100), 82 (10), 59 (18).

*2-{[3-(2-Methylpiperidino)propyl]dimethylsilyl}-5-triethylsilylfuran (**6**)*

Compound **6** was prepared from **1** and *N*-allyl–2-methylpiperidine. Yield: 60.4%. $^1H$ NMR δ (ppm): 0.23 (s, 6H, Si–$CH_3$), 0.60–1.03 (m, 20H, Si–$CH_2$, Si–$C_2H_5$, C–$CH_3$), 1.24–1.28 (m, 3H, $CH_2$, CH), 1.44–1.70 (m, 6H, $CH_2$), 2.08–2.46 (m, 2H, $CH_2$), 2.58–2.84 (m, 2H, $CH_2$), 6.60 (s, 2H, $H^3H^4$). GC-MS, *m/z* (%): 379 ($M^+$, 13), 364 ($M^+$ − Me, 33), 350 (11), 239 (5), 207 (6), 182 (20), 169 (13), 153 (40), 133 (25), 141 (25), 113 (100), 98 (25), 87(27), 69 (18), 55 (55).

*2-[(3-Hexamethyleneiminopropyl)dimethylsilyl]-5-triethylsilylfuran (**7**)*

Compound **7** was prepared from **1** and *N*-allylhexamethyleneimine. Yield: 57.1%. $^1H$ NMR δ(ppm): 0.23 (s, 6H, Si–$CH_3$), 0.74–1.00 (m, 17H, Si–$C_2H_5$, Si–$CH_2$), 1.51–1.62 (m, 10H, $CH_2$), 2.40–2.50 (m, 2H, $CH_2$), 2.62 (bs, 4H, $CH_2N$), 6.60 (s, 2H, $H^3H^4$). GC-MS, *m/z* (%): 379 ($M^+$, 5), 207 (5), 153 (9), 112 (100), 59 (5).

*2-[(3-Morpholinopropyl)dimethylsilyl]-5-triethylsilylfuran (**8**)*

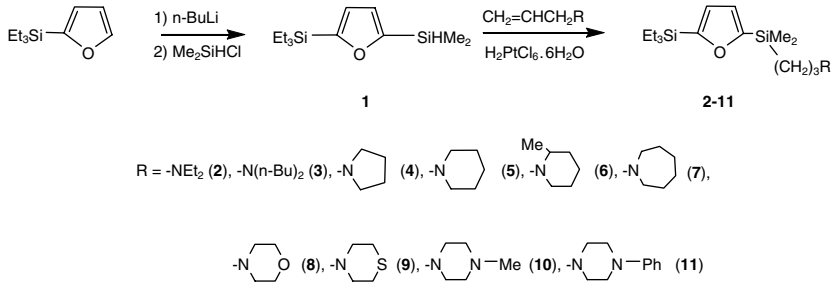
Compound **8** was prepared from **1** and *N*-allylmorpholine. Yield: 60%. $^1H$ NMR δ (ppm): 0.24 (s, 6H, Si–$CH_3$), 0.73–1.00 (m, 17H, Si–$C_2H_5$, Si–$CH_2$), 1.53–1.60 (m, 2H, $CH_2$), 2.27–2.50 (m, 6H, $CH_2$), 3.68–3.78 (m, 4H, $CH_2N$), 6.60 (s, 2H, $H^3H^4$). GC-MS, *m/z* (%): 367 ($M^+$, 14), 352 ($M^+$ − Me, 27), 280 (5), 252 (15), 208(5), 181 (30), 153 (85), 142(67), 127 (54), 100 (100), 87(55), 70 (30), 59 (100).

*2-[(3-Thiomorpholinopropyl)dimethylsilyl]-5-triethylsilylfuran (**9**)*

Compound **9** was prepared from **1** and N-allylthiomorpholine. Yield: 49.7%. $^1H$ NMR δ (ppm): 0.24 (s, 6H, Si–$CH_3$), 0.66–1.00 (m, 17H, Si–$CH_2$, Si–$C_2H_5$), 1.49–1.60 (m, 2H, $CH_2$), 2.30–2.34 (m, 2H, $CH_2N$), 2.66 (s, 8H, $CH_2$), 6.60 (s, 2H, $H^3H^4$). GC-MS, *m/z* (%): 368 ($M^+$ − Me, 5), 200 (8), 181 (12), 173 (24), 158 (42), 142 (16), 128 (43), 116 (100), 105 (25), 88 (49), 73 (10), 59 (69).

*2-{[3-(4-Methylpiperazino)propyl]dimethylsilyl}-5-triethylsilylfuran (**10**)*

Compound **10** was prepared from **1** and *N*-allyl-4-methylpiperazine. Yield: 59.8%. $^1H$ NMR δ(ppm): 0.22 (s, 6H, Si–$CH_3$), 0.67–0.99 (m, 17H, Si–$C_2H_5$, Si–$CH_2$), 1.49–1.57 (m, 2H, $CH_2$), 2.26–2.52 (m, 13H, $CH_2$, $CH_2N$, $CH_3$), 6.60 (s, 2H, $H^3H^4$). GC-MS, *m/z* (%): 380 ($M^+$, 26), 200 (8), 181 (5), 153 (17), 140 (11), 133 (14), 128(12), 113 (100), 91 (11), 83 (11), 70 (81), 59 (23).




**Scheme 1.** Hydrosilylation reaction of heterocyclic allylamines.

*2-{[3-(4-Phenylpiperazino)propyl]dimethylsilyl}-5-triethylsilylfuran (**11**)*

Compound **11** was prepared from **1** and *N*-allyl-4-phenylpiperazine. Yield: 68.3%. $^1$H NMR $\delta$(ppm): 0.25 (s, 6H, Si–$CH_3$), 0.71–1.00 (m, 17H, $SiCH_2$, Si–$C_2H_5$), 1.54–1.62 (m, 2H, $CH_2$), 2.34–2.38 (m, 2H, $CH_2N$), 2.54–2.57 (m, 4H, $CH_2$), 3.16–3.19 (m, 4H, $CH_2$), 6.61 (s, 2H, $H^3H^4$), 6.81–6.92 (m, 3H, $C_6H_4$), 7.22–7.24 (m, 2H, $C_6H_4$). GC-MS, *m/z* (%): 442 ($M^+$, 12), 207(5), 175(100), 132 (10), 105(8), 70 (12).

### Cytotoxicity *in Vitro*

Monolayer tumor cell lines MG-22A (mouse hepatoma), HT-1080 (human fibrosarcoma) and NIH 3T3 (normal mouse fibroblasts) were cultivated for 72 h in standard Dulbecco's modified Eagle's medium (Sigma) without indicator and antibiotics.[34] 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 $\times$ $10^4$ cell $ml^{-1}$ concentration (depending on line nature) were placed on separate 96-well plates. Solutions containing test compounds were diluted and added into wells to give the final concentrations of 50, 25, 12.5 and 6.25 $\mu g\ ml^{-1}$. The control cells were treated in the same manner only in the absence of test compounds. Plates were cultivated for 72 h. A quantity of survived cells was determined using Crystal Violet (CV), Neutral Red (NR) or 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) coloration, which was assayed by multiscan spectrophotometer Tetretek Multiscan MCC/340. The quantity of living cells on control plate was taken in calculations for 100%.[34,35] Concentration of NO was determined according to Fast *et al*.[35] Mean lethal dose ($LD_{50}$) has been determined on 3T3 cells (alternative to $LD_{50}$ *in vivo* test) according to the protocols of Interagency Coordinating Committee on the Validation of Alternative Methods and National Toxicology Program of Interagency Center for the Evaluation of Alternative Toxicological Methods.[36]

## Results and Discussion

The starting 5-triethylsilyl-2-dimethylsilylfuran (**1**) has been prepared from the furan by two consecutive organolithium syntheses. It has been used for the hydrosilylation of heterocyclic allylamines in the presence of Speier's catalyst (Scheme 1). Hydrosilylation of all studied allyamines by hydrosilane **1** occurred smoothly during 1 h heating of the mixture of compounds with a drop of catalyst. The reaction afforded a series of silylamines **2–11** containing two different heterocycles in good or moderate yield. The $^{13}$C and $^{29}$Si NMR spectra are given in Table 1.

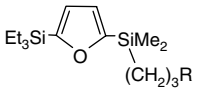
The cytotoxicity of silylamines **2–11** *in vitro* has been investigated on tumor cells HT-1080 (human fibrosarcoma), MG-22A (mouse hepatoma) and normal mouse fibroblasts 3T3 to determine the effect of the amine on the antitumor activity. The experimental evaluation of cytotoxic properties is presented in Table 2. Most of the studied compounds (**2,4–6,10**) exhibited high cytotoxic activity ($LC_{50}$ 1–3 $\mu g\ ml^{-1}$). The amines **4, 6** and **7** showed high cytotoxic activity in cancer cells accompanied by the highest cytotoxic activity on normal cells 3T3 ($LC_{50}$ 0.3–0.8 $\mu g\ ml^{-1}$). It means that the therapeutic index for these compounds is low. In the case of piperidino (**5**) and morpholino (**8**) derivatives some selectivity has been found: amine **5** is cytotoxic against human fibrosarcoma but morpholino derivative **8** is cytotoxic against mouse hepatoma. Morpholino derivative **8** was more active than thiomorpholino derivative **9** for both cancer cells lines and less cytotoxic for normal fibroblasts. The *N*-methylpiperazino derivative **10** showed high cytotoxic activity in both cancer cell lines but substitution of *N*-methyl group for the *N*-phenyl (compound **11**) led to the loss of activity. The toxicity of studied compounds decreases in the series: hexamethyleneimino (**7**) > pyrrolidino (**4**) > piperidino (**5**). Introduction of the sulfur and oxygen atoms leads to a further decrease in toxicity: piperidino (**5**) > thiomorpholino (**9**) > morpholino (**8**).

The diethylamino derivative **2** is the most promising compound in this series of compounds: low toxicity ($LD_{50}$, 646 mg $kg^{-1}$), high cytotoxicity on both cancer cell lines ($LC_{50}$ 2–3 $\mu g\ ml^{-1}$) and lower cytotoxicity on normal fibroblasts ($LC_{50}$ 11 $\mu g\ ml^{-1}$). Its precursor - 2-[(3-diethylaminopropyl)dimethylsilyl]furan containing only one silicon atom at the furan ring is less active ($LC_{50}$ 6–27 $\mu g\ ml^{-1}$) and more toxic ($LD_{50}$ 407 mg $kg^{-1}$). Thus, introduction of the second silyl group at the furan ring improves both the cytotoxicity against cancer cells and the cytoselectivity of the furylsilylamines.

## Conclusion

In summary, we propose an entirely new approach to construction of biologically active compounds – double silylation. It consists of a direct silylation of the furan ring to increase the lipophilicity followed by hydrosilylation for binding with amines. Using this approach we have synthesized a new class of highly active cytotoxic agents ($LC_{50}$ 1–3 $\mu g\ ml^{-1}$ for cancer cell lines HT-1080 and MG-22A) – silylfurylsilylamines containing two silicon atoms in the heterocyclic substituent bound to the heterocyclic amine.

**Table 2.** Cytotoxicity ($LC_{50}$ μg $ml^{-1}$) of




| Cell line | Method | Compounds | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** |
| HT-1080 | CV | 2 | 35 | 2 | 3 | 3 | 3 | 10 | 17 | 3 | 35 |
| | MTT | 3 | 34 | 2 | 3 | 3 | 3 | 7 | 25 | 3 | 32 |
| | $NO^{\bullet}$ | 150 | 71 | 250 | 150 | 133 | 100 | 75 | 150 | 250 | 200 |
| MG-22A | CV | 2 | 19 | 1 | 9.3 | 2 | 2 | 3 | 10 | 2 | 23 |
| | MTT | 2 | 20 | 1 | 6.5 | 2 | 2 | 3 | 19 | 3 | 22 |
| | $NO^{\bullet}$ | 200 | 100 | 250 | 450 | 150 | 100 | 133 | 100 | 150 | 100 |
| NIH 3T3 | NR | 11 | 2 | 0.8 | 5.7 | 0.4 | 0.3 | 14 | 11 | 5 | 30 |
| NIH 3T3 | $LD_{50}$ (mg $kg^{-1}$) | 646 | 168 | 106 | 251 | 76 | 76 | 368 | 345 | 228 | 576 |

$LC_{50}$ (μg $ml^{-1}$) providing 50% cell killing effect [CV, crystal violet coloration, action on cell membranes; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide coloration, influence on the activity of mitochondrial enzymes]; NR, neutral red; $NO^{\bullet}$ concentration.[34]

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