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Synthesis and preliminary studies of biological activity of amino derivatives of 4-azatricyclo-[5.2.1.0^{2,6}]dec-8-ene-3,5-dione with silicon in the structure

Abstract: A series of 38 new derivatives of cyclic imides containing silicon in the structure was synthesized and characterized by ^{1}H NMR, ESI-MS, and elemental analysis. Selected compounds (**1l,m**, **1g**, **1o,p**, **2l,m**, and **2o,p**) were tested for their cytotoxic properties in human chronic myelogenous leukemia (K562), human cervical cancer (HeLa), and normal endothelial cells (HUVEC). Seven compounds showed significant cytotoxicity. In addition, two compounds (**1l** and **2l**) were tested toward affinity for 5-HT$_{1A}$, 5-HT$_6$, and 5-HT$_7$ serotonin receptors, and all aryl/heteroarylopiperazino derivatives were tested for antimicrobial activity. The compounds tested toward affinity for selected serotonin receptors showed high and moderate affinity for 5-HT$_{1A}$ and 5-HT$_7$, while the antimicrobial activity of tested compounds was not significant.

Keywords: cytotoxic activity; HeLa; 5-HT$_{1A}$ ligands; 5-HT$_7$ ligands; K562; organosilicon compounds.

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Introduction

The synthesis and preliminary biological studies of cyclic imides containing an alkylpiperazine or aminoalkyl fragment and silicon in their structure are described. It is well known that N-substituted imides are an important group of compounds having pharmacological activity. Among them, compounds can be found that display antiviral, antibacterial, anticancer, or antifungal activity [1–9]. In addition, many cyclic imides containing an alkylpiperazine moiety are selective ligands for 5-HT family receptors, including 5-HT$_{1A}$, 5-HT$_{2A}$, and 5-HT$_7$ [10–13].

It is also known that silicon is a basic and necessary constituent for growth and development of living organisms. Organosilicon chemistry was initiated in 1846 by Ebelman, and since that time, silicon compounds have attracted attention of the scientific community. In recent years, silicon-containing bioactive compounds have been reported [14–21]. The incorporation of silicon into organic compounds can improve biological properties such as selectivity, potency, penetration, pharmacokinetics, and pharmacodynamics. Furthermore, replacement of a carbon atom by a silicon atom in existing drugs is an attractive approach to finding new drug candidates [14–19]. Some of organosilicon agents have advanced to clinical studies [20, 21]. The literature describes also new small organosilicon molecules. These molecules can affect the central nervous system. Some of them show anticancer [22] and anti-inflammatory activity [23]. This work describes the synthesis and preliminary biological evaluation of 38 new compounds containing silicon in their structure.

Results and discussion

Chemistry

The synthesis was carried out by a three-step procedure for aryl/heteroarylpiperazine derivatives and by a two-step procedure for aminoalkyl derivatives (Scheme 1).

In the first step, the starting imides **1** and **2** were obtained in a Diels-Alder reaction. These compounds **1**

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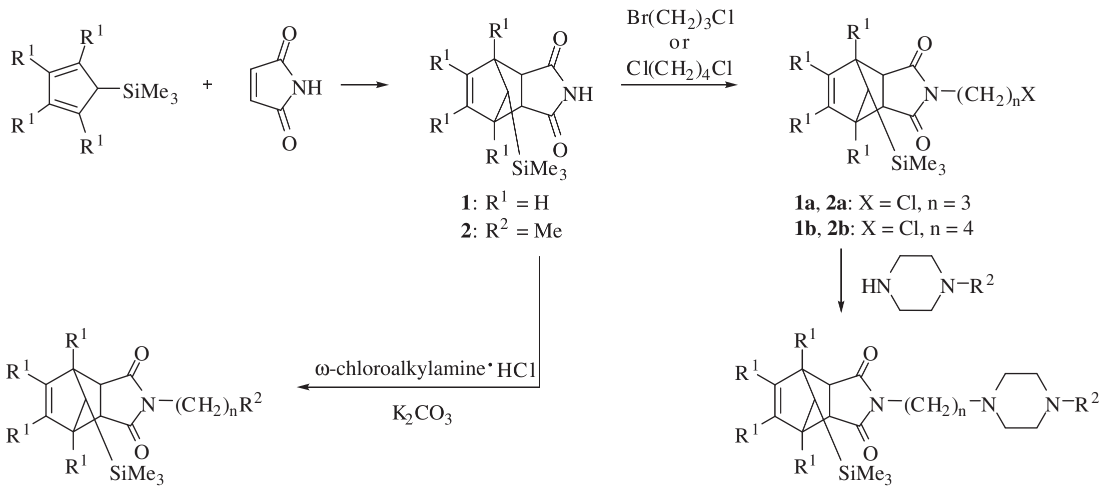

1o-s, **2o-s**

1c-n, **2c-n**

1o: R^1 = H; R^2 = $N(Me)_2$; n = 2
1p: R^1 = H; R^2 = $N(Et)_2$; n = 2
1q: R^1 = H; R^2 = morpholino; n = 2
1r: R^1 = H; R^2 = piperidino; n = 2
1s: R^1 = H; R^2 = $N(Me)_2$; n = 3
2o: R^1 = Me; R^2 = $N(Me)_2$; n = 2
2p: R^1 = Me; R^2 = $N(Et)_2$; n = 2
2q: R^1 = Me; R^2 = morpholino; n = 2
2r: R^1 = Me; R^2 = piperidino; n = 2
2s: R^1 = Me; R^2 = $N(Me)_2$; n = 3

1c: R^1 = H; R^2 = 2-pyridyl; n = 3
1d: R^1 = H; R^2 = 2-pyrimidinyl; n = 3
1e: R^1 = H; R^2 = Ph; n = 3
1f: R^1 = H; R^2 = 2-OMe-Ph; n = 3
1g: R^1 = H; R^2 = 2-F-Ph; n = 3
1h: R^1 = H; R^2 = 2-Cl-Ph; n = 3
1i: R^1 = H; R^2 = 2-pyridyl; n = 4
1j: R^1 = H; R^2 = 2-pyrimidinyl; n = 4
1k: R^1 = H; R^2 = Ph; n = 4
1l: R^1 = H; R^2 = 2-OMe-Ph; n = 4
1m: R^1 = H; R^2 = 2-F-Ph; n = 4
1n: R^1 = H; R^2 = 2-Cl-Ph; n = 4

2c: R^1 = Me; R^2 = 2-pyridyl; n = 3
2d: R^1 = Me; R^2 = 2-pyrimidinyl; n = 3
2e: R^1 = Me; R^2 = Ph; n = 3
2f: R^1 = Me; R^2 = 2-OMe-Ph; n = 3
2g: R^1 = Me; R^2 = 2-F-Ph; n = 3
2h: R^1 = Me; R^2 = 2-Cl-Ph; n = 3
2i: R^1 = Me; R^2 = 2-pyridyl; n = 4
2j: R^1 = Me; R^2 = 2-pyrimidinyl; n = 4
2k: R^1 = Me; R^2 = Ph; n = 4
2l: R^1 = Me; R^2 = 2-OMe-Ph; n = 4
2m: R^1 = Me; R^2 = 2-F-Ph; n = 4
2n: R^1 = Me; R^2 = 2-Cl-Ph; n = 4

Scheme 1 Synthesis of the investigated compounds **1**, **1a–1s**, **2**, and **2a–2s**.

and **2** were N-alkylated by treatment with 1,4-dichlorobutane or 1-bromo-3-chloropropane. The resultant N-(ω-haloalkyl)imides **1a,b** and **2a,b** were condensed with aryl/heteroarylopiperazines to yield the desired products **1c–n** and **2c–n**. The aminoalkyl derivatives **1o–s** and **2o–s**) were obtained by the reaction of starting imides **1** and **2** with an appropriate ω-haloalkylamine. The structures of all compounds were supported by ^{1}H NMR, MS, and elemental analysis. For the purpose of biological evaluations, the obtained compounds were converted into their hydrochlorides. Synthesis and characterization of selected compounds are given in Experimental, and the synthesis and characterization of all compounds can be found in the Supplementary Material.

Anticancer activity

Nine selected derivatives **1l,m**, **1g**, **1o,p**, **2l,m**, and **2o,p** were screened for cytotoxic properties in human cervix carcinoma (HeLa), human chronic myelogenous leukemia (K562), and normal endothelial (HUVEC) cells, using MTT assay. The experimental conditions can be found in the Supplementary Material.

The basis for the design of the discussed compounds was the result of our previous study reported in a patent application [24]. This previous work indicated that aminoalkyl derivatives show the best activity. Accordingly, imide derivatives containing aliphatic amines **1o,p** and **2o,p** were included in this study in an attempt to determine the influence of the imide structure on the biological activity. The remaining compounds **1l,m** and **2l,m** are methoxyphenyl and fluorophenyl derivatives.

In the initial screening, human cancer cell viability after 48 h of incubation with the given compound at the concentration of 100 μM was measured. Next, for compounds that reduced cancer cell survival by more than 50%, the IC_{50} values (concentration of compound that reduces cancer cell survival by 50%) were determined. To do that, cell viability was measured in the presence of different concentrations of the tested compound (1, 1×10^{-2}, 1×10^{-4}, and 1×10^{-6} mM), and subsequently, based on dose-viability curves, the IC_{50} values were calculated. Cells exposed to 1% DMSO (a vehicle) served as the control with 100% survival. Cells treated with 1 μM staurosporine served as the internal control of the cytotoxicity experiments [25, 26].

In the initial screening, seven compounds, **2o,p**, **2l,m**, **1l,m**, and **1g** (Table 1), that, at concentration of 100 μM, reduced viability of either K562 or HeLa cells (or both) by more than 50%, as compared with control cells, were identified. Interestingly, compound **1g** and all compounds of **2** series show substantial toxicity toward both K562 and HeLa cell lines. Meanwhile, compounds **1l,m** are selectively toxic to human leukemia cells (K562) and less toxic for human cervical carcinoma (HeLa) cells. Results presented in Table 1 indicate that compounds **2o,p**, **2l,m**, **1l,m**, and **1g** are also toxic against human normal endothelial cells. Therefore, these compounds do not show any selectivity between cancer and normal cells.

Next, for the seven compounds identified in the initial screening, IC_{50} values were calculated (Table 2). As can be seen, these compounds show rather similar toxicity toward K562 and HeLa cancer cells, with IC_{50} values in the range of 40–80 μM.

Based on cytotoxicity results, we would like to point out some structural features of the tested compounds that may influence their toxicity. First, among derivatives of 10-(trimethyl)silyl-4-azatrcicyclo[5.2.1.02,6]-dec-8-ene-3.5-dione, only aryl/heteroarylpiperazine derivatives (compounds **1g** and **1l,m**) are toxic for the tested cell lines, while aminoalkyl derivatives (**1o** and **1p**) demonstrate no substantial toxicity. Interestingly, derivatives of **1** show rather enhanced selectivity toward leukemia cells (K562), except for compound **1g**, which is toxic for both K562 and HeLa cells. Meanwhile, introduction of methyl groups into the imide system results in cytotoxic activity of both piperazine and aminoalkyl derivatives of **2** (compounds **2l,m** and **2o,p**, Table 1). These compounds are not selectively toxic toward K562 or HeLa cells (Table 1), which is also evidenced by similar IC_{50} values (Table 2).

Microbiology

The selected derivatives (**1a–n** and **2a–n**) were tested for their antimicrobial activity against a selection of Gram-positive cocci, Gram-negative rods, and yeasts. None of the tested compounds showed significant antimicrobial activity.

Table 1 Cell viability after 48-h incubation with a given compound at the concentration of 100 μM.

Compound	HeLa viability (%)	K562 viability (%) survival	HUVEC (%)
1o	98.3±3.8	87.2±5.4	Nd
1p	87±7.5	80.5±6.4	Nd
2o	20±2.3	1.6±0.1	0
2p	4.2±1.2	0.06±0.01	0
2l	0	0	0
1l	65.3±7.6	3.2±0.3	8.3
2m	1.2±0.2	0.05±0.01	15.1
1m	84.2±9.4	16.6±4.8	0
1g	5.7±1.0	0.7±0.2	11.5

Nd, not determined.

Table 2 IC_{50} values for tested compounds after 48-h incubation with K562 or HeLa cells.

Compound	HeLa IC_{50} 48 h (μM)	K562 IC_{50} survival
2o	80±4.6	70±3.7
2p	50±1.6	70±5.8
2l	40±3.9	80±2.1
1l	Nd	70±6.6
2m	60±4.9	50±3.3
1m	Nd	60±3.4
1g	60±2.8	50±8.9

Nd, not determined.

Radioligand binding

Compounds **1l** and **2l** were evaluated for *in vitro* affinity for $5\text{-}HT_{1A}$, $5\text{-}HT_6$, and $5\text{-}HT_7$ receptors by means of radioligand binding assays [27–29] and the results are showed in Table 3. The experimental conditions can be found in the Supplementary Material.

The selected compounds belong to the long-chain arylpiperazine group, and they contain the necessary structural elements that determine affinity for $5\ HT_{1A}$ receptors: 1-(2-methoxyphenyl)piperazine moiety, butyl chain, and amide/imide fragment. The influence of the piperazine fragment and alkyl chain on affinity is well

Table 3 $5\text{-}HT_{1A}$, $5\text{-}HT_7$, and $5\text{-}HT_6$ receptor binding data for compounds **1l** and **2l**.

Compound	K_i (nM)		
	$5\text{-}HT_{1A}$	$5\text{-}HT_7$	$5\text{-}HT_6$
1l	1±0.2	44±3	16380±950
2l	76±9	53±4	2650±120
NAN 190[a]	0.6±0.1[b]	87±2[c]	–
Clozapine[a]	143±11[d]	18±2[d]	4±0.3[d]

[a]Standard compound added as a reference. [b]Data from references [30, 31]. [c]Data from reference [11]. [d]Data from reference [31, 32].

known, but the importance of imide fragment has not been determined in detail. However, we can find literature reports that indicate that terminal imide plays an important role in the process of ligand recognition by serotonin reports. In addition, among derivatives that are 5-HT$_{1A}$ receptor ligands, many demonstrate high affinity for 5-HT$_7$ receptors [10–13]. The aim of the study was to determine the impact of the imide structure on the affinity. Comparison of the results for these two derivatives allows for the formulation of the initial conclusions as follows. The K_i values show that compound **1l** displays high affinity for 5-HT$_{1A}$ receptors (K_i=1 nM) and moderate affinity for 5-HT$_7$ receptors (K_i=44 nM) and compound **2l** has lower but still significant affinity for 5-HT$_{1A}$ and 5-HT$_7$ receptors (K_i=76 and 53 nM, respectively) in comparison with reference compounds. Moreover, both compounds display low affinity for 5-HT$_6$ receptors. Generally, these results are consistent with literature reports.

Conclusions

Compounds containing silicon are toxic against cancer cells. However, these compounds also show toxicity for normal cells, which means that their selectivity must be improved.

Two compounds were tested for affinity for the serotonin receptor, and both show significant affinity for 5-HT$_{1A}$ as well as 5-HT$_7$ receptors. Selected compounds were also tested for microbial action, but they did not show any activity. This lack of activity may be related to the relatively large size of evaluated compounds, which may hinder the penetration through the bacterial cell membrane.

Experimental

Chemistry

All chemicals and solvents were purchased from Aldrich. Melting points were determined in a capillary in Electrothermal 9100 apparatus and are uncorrected. The ^{1}H NMR spectra were recorded in $CDCl_3$ on a Varian UNITY-plus 300 spectrometer operating at 300 MHz. Mass spectral (MS ESI) measurements were carried out on a Mariner PE Biosystems instrument with time of flight (TOF) detector. The spectra were obtained in the positive ion mode with a declustering potential of 140–300 V. Elemental analyses were recorded on a CHN model 2400 Perkin-Elmer instrument. Chromatographic columns were filled with Merck Kieselgel 0.05–0.2 mm (70–325 mesh ASTM) silica gel. Reactions were monitored, and the purity of the compounds was checked by thin layer chromatography using Merck silica gel GF254 aluminum sheets and eluting with chloroform-methanol (95:5, v/v). Spots were detected by their absorption under UV light.

General procedure of the preparation of imides 1 and 2

A mixture of 2,4-cyclopentadien-1-yl(trimethyl)silane (for imide **1**, 0.02 mol) or 2,3,4,5-tetramethyl-2,4-cyclopentadien-1-yl)-trimethylsilane (for imide **2**, 0.02 mol) and 1*H*-pyrrole-2,5-dione (0.022 mol) in benzene (15 mL) was heated under reflux for 8 h. When the reaction was completed, the mixture was cooled and the resultant precipitate was crystallized from benzene.

General procedure for preparation of alkyl derivatives 1a,b and 2a,b

The mixture of imide **1** or **2** (0.01 mol), anhydrous K_2CO_3 (0.01 mol), and 1-bromo-3-chloropropane (0.02 mol) or 1,4-dichlorobutane (0.02 mol) in acetonitrile (30 mL) was heated under reflux for 24–38 h. When the reaction was completed, the mixture was filtered and the solution concentrated. The residue was purified by column chromatography eluting with chloroform/methanol, 9:0.2, v/v.

General procedure for preparation of 4-arylpiperazino derivatives of *N*-substituted imides 1c–n and 2c–n

To the mixture of *N*-halogenoalkyl imide derivative (0.01 mol), a powdered anhydrous K_2CO_3 (0.01 mol) and a catalytic amount of KI in acetonitryle (30 mL), an appropriate amine was added, and the mixture was heated under reflux for 48–60 h. Then, an inorganic residue was filtered off and the solvent was evaporated. The residue was purified by column chromatography eluting with chloroform or chloroform/methanol, 90:0.5, v/v. Some compounds were converted into their hydrochlorides to improve their solubility for biological evaluations.

General procedure for preparation of *N*-alkylamino derivatives of imides 1o–s and 2o–s

A mixture of imide **1** or **2,** powdered anhydrous K_2CO_3 (0.01 mol), a catalytic amount of 98% 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and an appropriate chloroalkylamine hydrochloride(0.01 mol) in acetone (30 mL) was heated for 8–14 h. After the reaction was completed, the inorganic residue was filtered off and the solvent was evaporated. The obtained compound was purified by column chromatography eluting with chloroform or chloroform/methanol, 50:0.2, v/v. All new derivatives were converted to into their hydrochlorides.

Characterization of selected products

4-{3-[4-(2-Pyridyl)piperazino]-propyl}-10-(trimethyl)silyl-4-azatricyclo[5.2.1.0^{2,6}]-dec-8-ene-3.5-dione (1c): This compound was obtained in 64% yield as a white powder; mp 175–177°C; ^{1}H NMR: δ 8.18 (m, 1H, Ar), 7.46 (m, 1H, Ar), 6.16 (m, 2H, Ar), 6.02 (m, 2H, C8-H, C9-H), 3.52 (t, 4H, -CH_2-piperazine, J = 5 Hz), 3.39 (m, 4H, C2-H, C6-H, -CH_2-alkyl), 3.27 (m, 2H, C1-H, C7-H), 2.51 (m, 4H, -CH_2-piperazine), 2.34 (t, 2H, -CH_2-alkyl, J = 7 Hz), 1.66 (m, 2H, -CH_2-alkyl), 1.22 (s, 1H, C10-H), 0.05 (s, 9H, -CH_3); ESI-MS: m/z 439.4 [M+H^+]. Anal. Calcd for $C_{24}H_{34}N_4O_2Si$: C, 65.72; H, 7.81; N, 12.77. Found: C, 65.70; H, 7.74; N, 12.87.

4-{3-[4-(Pyrimidin-2-yl)piperazino]-propyl}-10-(trimethyl)silyl-4-azatricyclo[5.2.1.0^{2,6}]-dec-8-ene-3.5-dione (1d): This compound was obtained in 74% yield as a white powder; mp 130–135°C; ^{1}H NMR: δ 8.30 (d, 2H, Ar, J = 4.8Hz), 6.46 (t, 1H, Har, J = 4.8Hz), 6.02 (m, 2H, C8-H, C9-H), 3.80 (t, 4H, -CH_2-piperazine, J = 7 Hz), 3.39 (m, 4H, C2-H, C6-H, -CH_2-alkyl), 3.27 (m, 2H, C1-H, C7-H), 2.51 (t, 4H, -CH_2-piperazine, J = 5 Hz), 2.33 (t, 2H, -CH_2-alkyl, J = 7 Hz), 1.66 (m, 2H, -CH_2-alkyl), 1.22 (s, 1H, C10-H), 0.05 (s, 9H, -CH_3); ESI-MS: m/z 440.4 [M+H^+]. Anal. Calcd for $C_{23}H_{33}N_5O_2Si$: C, 62.84; H, 7.57; N, 15.93. Found: C, 62.71; H, 7.54; N, 15.95.

Hydrochloride of 4-[2-(dimethylamino)ethyl]-10-(trimethyl)silyl-4-azatricyclo[5.2.1.0^{2,6}]-dec-8-ene-3.5-dione (1o): This compound was obtained in 67% yield as a white powder; mp 178–180°C; ^{1}H NMR: δ 10.34 (br s, 1H, HCl), 5.98 (t, 2H, C8-H, C9-H, J = 2 Hz), 3.54 (m, 2H, -CH_2-alkyl), 3.41 (m, 2H, C1-H, C7-H), 3.29 (m, 2H, C2-H, C6-H), 3.06 (m, 2H, -CH_2-alkyl), 2.71 (s, 6H, N-CH_3), 1.29 (s, 1H, C10-H), -0.08 (s, 9H, -CH_3); ESI-MS: m/z 307.2 [M+H^+]. Anal. Calcd for $C_{16}H_{26}N_2O_2Si{\cdot}HCl$: C, 56.04; H, 7.94; N, 8.17. Found: C, 56.03; H, 7.93; N, 8.16.

4-{3-[4-(2-Pyridyl)piperazino]-propyl}-10-(trimethyl)silyl-1,7,8,9-tetramethyl-4-azatricyclo[5.2.1.0^{2,6}]-dec-8-ene-3.5-dione (2c): This compound was obtained in 62% yield as a white powder; mp 161–164°C; ^{1}H NMR: δ 8.19 (m, 1H, Ar), 7.47 (m, 1H, Ar), 6.65 (m, 2H, Ar), 3.60 (m, 6H, -CH_2-alkyl, -CH_2-piperazine), 2.94 (s, 2H, C2-H, C6-H), 2.59 (m, 6H, -CH_2-alkyl, -CH_2-piperazine), 1.63 (m, 2H, -CH_2-alkyl), 1.51 (m, 12H, -CH_3), 1.25 (s, 1H, C10-H), -0.04 (s, 9H, -CH_3); ESI-MS: m/z 495.3 [M+H^+]. Anal. Calcd for $C_{28}H_{42}N_4O_2Si$: C, 67.97; H, 8.56; N, 11.32. Found: C, 67.99; H, 8.54; N, 11.31.

4-{3-[4-(Pyrimidin-2-yl)piperazino]-propyl}-10-(trimethyl)silyl-1,7,8,9-tetramethyl-4-azatricyclo[5.2.1.0^{2,6}]-dec-8-ene-3.5-dione (2d): This compound was obtained in 62% yield as a white powder; mp 137–140°C; ^{1}H NMR: δ 8.30 (d, 2H, Ar, J = 4.8 Hz), 6.47 (t, 1H, Ar, J = 4.8 Hz), 3.81 (m, 4H, -CH_2-piperazine), 3.35 (t, 2H, -CH_2-alkyl, J = 7.6 Hz), 2.92 (s, 2H, C2-H, C6-H), 2.45 (m, 4H, -CH_2-piperazine), 2.36 (m, 2H, -CH_2-alkyl) 1.57 (m, 2H, -CH_2-alkyl), 1.51 (d, 12H, -CH_3, J = 2.1 Hz), 1.08 (s, 1H, C10-H), -0.04 (s, 9H, -CH_3); ESI-MS: m/z 496.7 [M+H^+]. Anal. Calcd for $C_{27}H_{41}N_5O_2Si$: C, 65.42; H, 8.34; N, 14.13. Found: C, 65.32; H, 8.44; N, 14.10.

Hydrochloride of 4-[2-(dimethylamino)ethyl]-10-(trimethyl)silyl-1,7,8,9-tetramethyl-4-azatricyclo[5.2.1.0^{2,6}]-dec-8-ene-3.5-dione (2o): This compound was obtained in 65% yield as a white powder; mp 196–197°C; ^{1}H NMR: δ 9.93 (brs, 1H, HCl), 3.52 (t, 2H, -CH_2-alkyl, J = 6.6 Hz), 3.06 (m, 2H, C2-H, C6-H), 3.01 (m, 2H, -CH_2-alkyl), 2.76 (s, 6H, N-CH_3), 1.43 (s, 12H, -CH_3), 1.18 (s, 1H, C10-H), -0.07 (s, 9H, -CH_3); ESI-MS: m/z 363.5 [M+H^+]. Anal. Calcd for $C_{20}H_{34}N_2O_2Si{\cdot}HCl$: C, 60.20; H, 8.84; N, 7.02. Found: C, 60.21; H, 8.74; N, 7.04.

Characterization of all compounds can be found in the online Supplementary Material.

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