SYNTHESIS AND CHOLESTEROL LEVEL LOWERING ACTIVITY OF MACROCYCLIC SILICON CONTAINING BENZIMIDAZOLE SULFIDES

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ABSTRACT

New silicon containing macrocyclic benzimidazole sulfides were synthesized using organometallic and phase transfer catalytic methods. These compounds were tested for cholesterol level lowering activity. It has been found that macrocycle **4** produced a high antiatherosclerotic activity – protected increasing LDL cholesterol level. This compound has excellent atherosclerotic coefficient (0.074 ± 0.026).

Key Words: Macrocyclic benzimidazole sulfides; Silicon derivatives; Phase transfer catalysis; Cholesterol level lowering activity; Toxicity.

INTRODUCTION

Thiazolobenzimidazole and similar tricyclic benzimidazole sulfides have received considerable attention owing to their biological activity.[1] These heterocycles exhibit wide spectrum of activity on the heart and blood circulatory system. Thiazolobenzimidazole and related compounds exhibited vasodilating,[2] antihypertensive [3-5] and cardiotonic [6] activity and protected against cerebral infarction [7]. Imidazo[2,1-b]thiazoles exhibit cardiovascular properties [8] and were ligands for metabotropic glutamate receptors (these compounds were used in prevention or treatment of cerebral infarction) [9]. Triazolo[3,4-b]thiadiazoles showed antihypertensive activity [10,11].

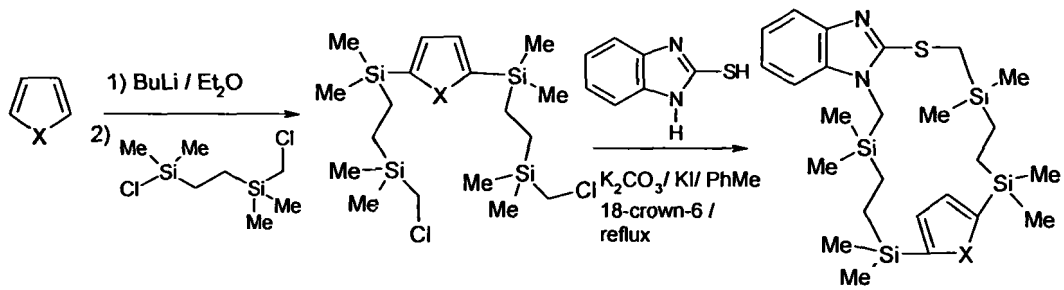
Besides, this aryl substituted silanes exhibit high cholesterol level lowering [12-14] and were used for the treatment of type II diabetes [15]. High lowering level of serum cholesterol with aromatic silicon containing sulfides was described in patents [16,17]. We have found that silicon and germanium containing aliphatic derivatives [18] and silacyclic derivatives of heteroaromatic sulfides [19] selectively lowered the low density lipoprotein (LDL) level in mice with the high cholesterol diet in nutrition. Recently, we published our investigations on 3-(hetarylthio)-1-propynyl(dimethylalkyl)silanes [20], silicon containing indole sulphides [21] and bis(phenylthiomethyl)dimethylsilane [22] as cholesterol lowering agents.

Synthesis of thiazolobenzimidazole derivatives was described in the review.[1] Among main methods for the synthesis of thiazolo[3,2-*a*]benzimidazole ring systems are based on the reaction of 2-mercaptobezimidazoles with α-halocarbonyl compounds[23] or α-haloacetals[24]. These type compounds can be obtained also from 1-(β-hydroxyethyl)-2-mercaptobenzimidazoles[25], 2-acyl- or 2-cyanomethylthiobenzimidazoles [26, 27] or by reaction of p-benzoquinone with 2-aminothiazoles[28]. However, in general the synthesis of thiazolo[3,2-*a*]benzimidazole, thiazino[3,2-*a*]benzimidazole, thiazepino[3,2-*a*]benzimidazole and similar macrocyclic derivatives was based on interaction of 2-mercaptobenzimidazole (or 2,3-dihydrobenzimidazole-2-thione) with α,ω-dihaloalkanes in the $NaHCO_3$ / KI / *i*-PrOH [29], EtOH / DMF then aq. $NaHCO_3$[30], Na / cellosolve [31] and NaOH / H_2O / PhH / cetyltributylammonium bromide [32] systems.

Taking into account the above mentioned data we synthesized new macrocyclic silicon containing benzimidazole sulfides and investigated their cholesterol level lowering activity.

RESULTS AND DISCUSSION

2,5-Bis-{[2-(chloromethyldimethylsilanyl)ethyl]-dimethyl-silanyl}furan (**1**) and 2,5-bis-{[2-(chloromethyldimethylsilanyl)ethyl]-dimethyl-silanyl}thiophene (**2**) were prepared by the reaction of 2.5-dililthium-furan or thiophene with 1-(chloro-dimethyl-silanyl)-2-(chloromethyl-dimethylsilanyl)ethane. Products **1** and **2** were isolated by column chromatography in 70 or 86% yields.



1,2 **3, 4**

1, 3; X = O
2, 4; X = S

Scheme 1

Macrocylic compounds **3** and **4** were synthesized in the phase transfer catalytic system chlorosilanes **1** or **2** / solid K_2CO_3 / solid KI / 18-crown-6 /toluene at reflux in high dilution (Scheme 1). Desired products were isolated in 48 or 49 % yields by column chromatography (see Materials and Methods). Macrocycles **3** and **4** were identified by ^1H, ^{13}C and Si^{29} NMR spectra, LC-MS, and elemental analysis.

The Table 1 data shows the serum lipid level at the end of the experiment. The high cholesterol in nutrition - Cholesterol group showed the marked increase in the total and LDL cholesterol in comparison to the intact control group. The HDL level in Cholesterol group did not differ from the Intact control group.

It has been found that 4,4,7,7,12,12,15,15-octamethyl-11-methylsulfanyl-2-thia-17,24-diaza-4,7,12,15-tetra-sila-tricyclo[15.7.0.0*18,23*]-tetracosa-1(24),8,10,18 (23),19,21-hexaene (**4**) produced a high antiatherosclerotic activity – protected against increase LDL cholesterol level. This compound has excellent atherosclerotic coefficient (0.074 ± 0.026). The preliminary analysis of the structure-activity relationship indicates that substitution of furan ring to thiophene ring in macrocyclic compounds increase cholesterol level lowering activity. Besides, this compound **4** has a low acute toxicity (> 2000 mg/kg).

EXPERIMENTAL

^1H, ^{13}C and Si^{29} NMR spectra were recorded on a Mercury 200 (Varian) instrument at 200, 50.3 and 39.74 MHz using $CDCl_3$ as a solvent and tetramethylsilane (TMS) as internal standard. Mass spectra were registered on a GC-MS HP 6890 (70 eV). 1-(Chloro-dimethyl-silanyl)-2-(chloromethyl-dimethylsilanyl)ethane was prepared as described in literature [33].

2,5-Bis-{[2-(chloromethyldimethylsilanyl)ethyl]-dimethyl-silanyl}-furan (1).

To a solution of 1.22g (0.018 mol) furan in 50 ml of ether was added dropwise 20 ml (0.04 mol) of 2 N *n*-BuLi at room temperature. After 30 min 9.17 g (0.04 mol) 1-(chloro-dimethyl-silanyl)-2-(chloromethyl-dimethylsilanyl)ethane was added. The reaction mixture was refluxed for 1h, hydrolyzed with a saturated solution of ammonium chloride, extracted with ether, dried over Na_2SO_4 and evaporated. The residue was dried by flash chromatography using petroleum ether as eluent to give 12.7 g (70% yield) of pure compound **1** as a colorless liquid. MS, *m/z* (I, %): 424 (M^+-2Me, <1); 193 (62); 167 (44); 145 (68); 73 (95); 59 (100). ^1H NMR δ ppm: 0.08, 0.24 (24H, all s, $SiMe_2$); 0.3-0.9 (8H, m, CH_2CH_2); 2.77 (4H, s, CH_2); 6.37 and 7.64 (2H, both m, furan protons). ^{13}C NMR δ ppm : –5.15; -3.96; 5.71; 7.10 (all $SiCH_3$ and $SiCH_2$); 29.94 (CH_2Cl); 109.27 and 146.63 (furan C).

2,5-Bis-{[2-(chloromethyldimethylsilanyl)ethyl]-dimethyl-silanyl}-thiophene (2).

To a solution of 1.47g (0.018 mol) thiophene in 50 ml of ether was added dropwise 20 ml (0.04 mol) of 2N *n*-BuLi at room temperature. After 30 min 9.17 g (0.04 mol) 1-(chloro-dimethyl-silanyl)-2-(chloromethyl-dimethylsilanyl)ethane was added. The reaction mixture was refluxed for 1h, hydrolyzed with a saturated solution of ammonium chloride, extracted with ether, dried over Na_2SO_4 and evaporated. The residue was dried by flash chromatography using petroleum ether as eluent to give 16.1 g (86% yield) of pure compound **2** as a colorless liquid. MS, *m/z* (I, %): 469 (M^+, <1); 233 (68); 211 (41); 197 (51); 183 (28); 164 (35); 107 (21); 93 (29); 73 (100); 59 (67). ^1H NMR δ ppm: 0.08, 0.30 (24H, all s, $SiMe_2$); 0.6-0.7 (8H, m, CH_2CH_2); 2.78 (4H, s, CH_2); 7.18 and 7.60 (2H, both m, thiophene protons).

10-Ethylidene-4,4,7,7,11,11,14,14-octamethyl-8-methylene-9-oxa-2-thia-16,23-diaza-4,7,11,14-tetrasila-tricyclo[14.7.0.0*17,22*]-tricosa-1(23),17(22),18,20-tetraene (3).

2,5-Bis-{[2-(chloromethyldimethylsilanyl)ethyl]-dimethyl-silanyl}-furan (**1**) (0.88 g, 2 mmol) was added to a suspension of 2-mercaptobenzimidazole (0.30 g, 2 mmol), 18-crown-6 (0.052 g, 0.2 mmol), KI (0.64 g, 4 mmol) and powdered K_2CO_3

(1.10 g, 8 mmol) in toluene (240 ml). The reaction mixture was stirred 12 h at reflux. The resulting mixture was filtered, toluene was removed under reduced pressure and the residue was purified by column chromatography (eluent toluene: ethyl acetate 1:1). Yield 0.52 g (49 %) of product **4** as white powder. Anal. Found: C, 56.42; H, 8.67; N, 5.42. Calc. for $C_{25}H_{42}N_2SOSi_4$: C, 56.55; H, 7.97; N, 5.27. ^{1}H NMR δ ppm: 0.00, 0.12, 0.20, 0.22 (24H, all s, $SiMe_2$); 0.6-0.8 (8H, m, CH_2CH_2); 2.65 (2H, s, SCH_2); 3.66 (2H, s, NCH_2); 6.62, 7.25 and 7.65 (6H, all m, aromatic protons). ^{13}C NMR δ ppm: –2.61; 0.00; 5.64; 6.28; 7.60; 7.85; 11.30; 13.70 (all $SiCH_2$ and $SiCH_3$) ; 18.17 (SCH_2); 26.08 (NCH_2); 113.57; 128.87, 129.13; 131.87; 140.01; 147.78; 151.15; 164.00 (all aromatic C).

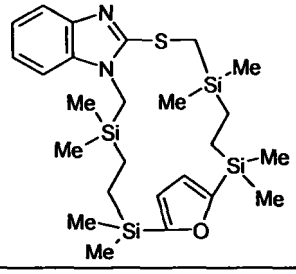
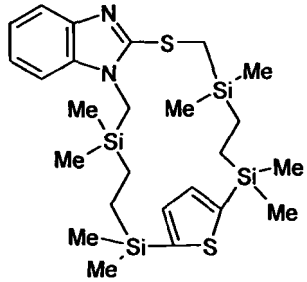
4,4,7,7,12,12,15,15-Octamethyl-11-methylsulfanyl-2-thia-17,24-diaza-4,7,12,15-tetrasila-tricyclo[15.7.0.0*18,23*]-tetracosa-1(24),8,10,18(23),19,21-hexaene (4).

2,5-Bis-{[2-(chloromethyldimethylsilanyl)ethyl]-dimethyl-silanyl}-thiophene (**2**) (1.17 g, 2.5 mmol) was added to a suspension of 2-mercaptobenzimidazole (0.37 g, 2.5 mmol), 18-crown-6 (0.066 g, 0.25 mmol), KI (0.83 g, 5 mmol) and powdered K_2CO_3 (1.38 g, 10 mmol) in toluene (240 ml). The reaction mixture was stirred 12 h at reflux. The resulting mixture was filtered, toluene was removed under reduced pressure and the residue was purified by column chromatography (eluent toluene: ethyl acetate 1:1). Yield 0.66 g (48 %) of product **4** as white powder with m.p. 85-86°C. Anal. Found: C, 54.79; H, 7.79; N, 4.98. Calc. for $C_{25}H_{42}N_2S_2Si_4$: C, 54.88; H, 7.74; N, 5.12. ^{1}H NMR δ ppm: –0.15, 0.12, 0.30, 0.33 (24H, all s, $SiMe_2$); 0.60 (8H, m, CH_2CH_2); 2.63 (2H, s, SCH_2); 3.62 (2H, s, NCH_2); 7.14, 7.32 and 7.70 (6H, all m, aromatic protons). ^{13}C NMR δ ppm: -4.05 (NCH_2Si); -3.85 (SCH_2Si); -2.35 ; -1.74 (both CSi); 6.48; 7.41; 8.87; 8.89 (all CH_2CH_2) ; 15.49 (SCH_2); 34.17 (NCH_2); 108.58; 117.84; 121.07; 121.17; 135.38; 135.53; 136.80; 143.81; 144.15; 154.33 (all aromatic C). ^{29}Si NMR δ ppm: -3.39; -3.16 (both CSi); 4.71; 5.77 (both CH_2Si). ESI-MS, *m/z* = 547 [M+H$^+$].

CHOLESTEROL LEVEL LOWERING ACTIVITY

Cholesterol level lowering activity and acute toxicity of synthesized compounds were determined as described in Ref. 18. All animal experiments were performed in accordance with the regulations of the Animal Ethical Committee of BaltLASA, Riga, Latvia.

Table 1. Cholesterol level lowering activity of compound **3** and **4**

N°	*Compound*	Cholesterol, mg/dl			
		Total	HDL	LDL	K
	Cholesterol	143.2 ± 12.9	99.8	43.4	0.448± 0.155
3		131.2 ± 5.0	116.5	14.7	0.130 ± 0.029
4		134.8 ± 12.8	124.8	10.0	0.074 ± 0.026
	Intact Control	112.9 ± 2.3	111.0	2.0	0.017± 0.00

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