3-(Hetarylthio)-1-Propynyl(Dimethylalkyl)Silanes as Selective Cholesterol Level Lowering Agents

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ABSTRACT

3-(Hetarylthio)-1-propynyl(dimethylalkyl)silanes selectively lowered the low-density lipoprotein (LDL) level in mice with a high cholesterol diet in nutrition. The quinoline derivatives were found to be the most active.

Keywords: alkynes, silanes, selective cholesterol level lowering agents

INTRODUCTION

Heteroaromatic sulfides exhibit a wide spectrum of activity on the heart and blood circulatory system /1, 2/. Cholesterol lowering properties of alkynyl derivatives of benzo[b/thiophenyl and benzo[d/isothizolyl alkylamines were recently described /3/. Acylbenzenesulfonamide derivatives derivatives have been investigated as hypoglycemics /4/. Among these compounds 4-(3-trifluoromethyl)phenylethynyl-N-(2-(5-ketohexanoylamino)sulfonylphenyl)benzamide, at 30 mg/kg twice a day for 1 week, gave 66.7% decrease of blood sugar in diabetic mice. Alkynyl derivatives of 5-methyl-2-phenyloxazole /5/, 3-phenyl-3-alkoxypropanoic acids /6/ and alkynylphenyl N-thiazolepropionamides exhibit high antidiabetic activity. Propargyl derivatives of 4-phenyl-pyrrolidin-2-ones showed high 17-β-hydroxysteroid dehydrogenase-II inhibitory activity /8/. These compounds were used as remedies for hypercholesterolemia and diabetes mellitus. Among heterocyclic compounds high activity of quinoline sulfides on the heart and blood circulatory system was described /9-12/. Sulfur-containing alkynyl derivatives of tetrahydroquinolone were studied as inhibitors of platelet activating factor /13/.

Aromatic silanes exhibit high cholesterol level lowering /14-16/ and were used for the treatment of type II diabetes /17/. High lowering level of serum cholesterol of aromatic silicon containing sulfides was described in patents /18-19/. Recently we have found that silicon-and-germanium-containing aliphatic derivatives of heteroaromatic sulfides /1/ and silacyclic derivatives of heteroaromatic sulfides /2/ selectively lower the low-density lipoprotein (LDL) level in mice with a high cholesterol diet in nutrition.

In continuation our investigations in the field of cholesterol lowering agents the 3-(hetarylthio)-1-propynyl(dimethylalkyl)silanes have been synthesized in order to increase selectivity of action on the high-and-low-density lipoproteins.

MATERIALS AND METHODS

Chemistry

^{1}H NMR spectra were recorded on a Varian 200 Mercury instrument (200MHz) using $CDCl_3$ as solvent and hexamethyldisiloxane (HMDSO) as internal standard. Mass spectra were registered on a GC-MS HP 6890 (70 eV). GC analysis was performed on a Chrom-5 instrument equipped with flame-ionization detector, using a glass column packed with 5 % OV-101 / Chromosorb W-HP (80-100 mesh) (1.2 m x 3 mm). 3-(Hetarylarylthio)-1-propynyl(dimethylalkyl)silanes **1-7** were obtained by metallation of propargylated thiols with n-BuLi followed by addition of trimethylchlorosilane /20/. Spectroscopic characteristics of alkynes **1-6** were described in article /20/.

3-[2-Quinolyl)thio/-1-propynyl(chloromethyldimethylsilylethyl)(dimethyl)silane) (7). ^{1}H NMR, δ, ppm: 0.03 and 0.09 (both s, 12H, $SiMe_2$), 0.50 (m, 4H, $SiCH_2$), 1.23 (s, 2H, CH_2Cl), 4.18 (s, 2H, SCH_2), 7.4-7.9 (m, 6H, quinoline ring protons).

Pharmacology

Cholesterol level lowering activity and acute toxicity of synthesized compounds were determined as described in Ref. 1. All animal experiments were performed in accordance with the regulations of the Animal Ethical Committee of BaltLASA, Riga, Latvia.

RESULTS AND DISCUSSION

Chemistry

S-propargyl derivatives of heterocycles were prepared by the interaction of hetaryl thiols with propargyl bromide in the phase transfer catalytic system solid K_2CO_3 / 18-crown-6 / toluene. Reaction of propargylation of thiols occurred smoothly in good yields (53 - 100%) for all heterocyclic thiols. The silicon derivatives of hetaryl propargyl sulfides **1-7** were obtained by metallation of propargylated thiols with n-BuLi followed by addition of dimethylalkylchlorosilanes. However, the reaction of 2-quinolyl 1-propynyl sulfide with with BuLi and then with $PhMe_2SiCl$, $Ph_2MeSiCl$ or Ph_3SiCl leads to unstable 3-[(2-quinolinyl)thio/-1-propynyl(dimethylphenyl)-, 3-[(2-quinolinyl)thio/-1-propynyl(diphenylmethyl)- and 3-[(2-quinolinyl)thio/-1-propynyl(triphenyl)silanes, correspondingly, which are impossible to use in the biological testing.

Pharmacology

Cholesterol level lowering activity

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

It has been found that 3-[(2-pyridyl)/-1-propynyl(trimethylsilane) (**2**), 3-[2-quinolyl)thio/-1-propynyl(trimethyl)silane) (**6**) and 3-[2-quinolyl)thio/-1-propynyl(chloromethyldimethylsilylethyl) (dimethyl)silane) (**7**) produced a high antiatherosclerotic activity – protection against increased LDL cholesterol level and atherosclerotic coefficient.

Quinoline derivatives **6** and **7** show the highest activity among all investigated compounds. The preliminary analysis of the structure-activity relationship indicates that increasing length of silicon substituent increases cholesterol level lowering activity.

Acute toxicity

Acute toxicity of the studied compounds was described in article /21/. The studied compounds have basically a low acute toxicity (> 1000 mg/kg). Only quinoline derivative **6** exhibits a medium level of toxicity (413 mg/kg).

Table 1

Cholesterol level lowering activity of (hetarylthio)-1-propynyl(dimethylalkyl)silanes

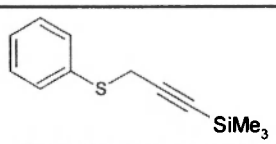
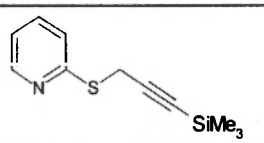
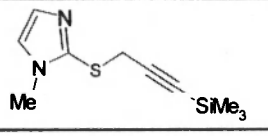
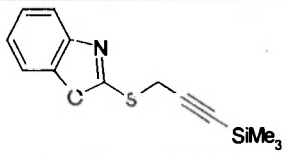
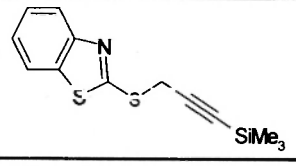
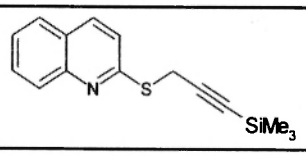
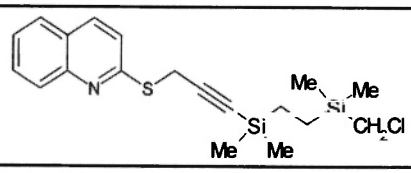
N°	Compound	Cholesterol, mg/dl			
		Total	HDL	LDL	K
	Cholesterol	141.8 ± 10.9 *	88.6± 5.4	53.2 ± 9.4*	0.600± 0.132*
1		129.1 ± 9.3	99.9 ± 7.3	29.2 ± 4.8*	0.290 ± 0.12*
2		141.2 ± 10.5*	128.8 ± 8.75*#	12.4 ± 3.9 #	0.120 ± 0.084#
3		133.8 ± 18.3	57.1 ± 15.6	76.8 ± 5.3*	1.350 ± 0.503*
4		118.1 ± 12.0	104.5 ± 11.6	13.6 ± 3.3*#	0.160 ± 0.10*#

Table 1 (continued)

5		125.5 ± 13.2	111.0 ± 19.7	14.5 ± 14.5	0.150 ± 0.20#
6		123.8 ± 22.9	116.7 ± 15.45	7.0 ± 3.5*	0.070 ± 0.09#
7		122.8 ± 5.8	115.6 ± 6.0	7.2 ± 1.2*	0.064 ± 0.012#
	Intact Control	86.9 ± 4.3#	85.2 ± 2.6	1.7 ± 0.8#	0.019± 0.007#

*P<0.05 vs Intact Control

#P<0.05 vs Cholesterol

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