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REVIEW

Comparative study of the biological activity of organosilicon and organogermanium compounds

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The literature data and the results of our own investigations on the comparative study of the biological activity of isostructural organogermanium and organosilicon compounds have been summarized. It has been shown that the series of organogermanium and organosilicon compounds is more active than the carbon analogues, the majority of organogermanium compounds are less toxic than the sila analogues, the biological activity of the compounds under study appears to be similar but can dramatically differ in the degree of activity, and, moreover, in some particular cases sila and germa analogues exhibit the opposite biological effects.

Keywords: Organosilicon, Organogermanium, Biological activity

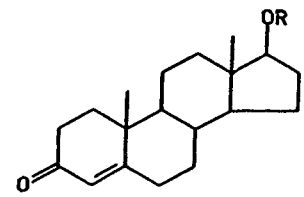
1 PATHWAYS IN THE SEARCH FOR NEW BIOLOGICALLY ACTIVE ORGANOSILICON AND ORGANOGERMANIUM COMPOUNDS

Nowadays three main approaches aiming at the development of biologically active derivatives of organosilicon[1-5] and organogermanium[6,7] compounds have been elaborated.

(1) modification of biologically active organic compounds by introducing silicon- or germanium-containing substituents;
(2) preparation of silicon and germanium analogues of known pharmaceuticals by substitution of one or some carbon atoms for silicon or germanium atoms;
(3) synthesis and study of biological activity of structurally-specific organosilicon and organogermanium compounds lacking organic analogues.

In the first case modification can occur either at a heteroatom (oxygen, sulphur, nitrogen) or at carbon atoms, i.e.

Usually such a modification does not evoke any changes in the mode of action of the drug but influences both the effect and duration of its action, and sometimes even enhances it. Thus, for example, *O*-trimethylsilyltestosterone (**Ib**) appears to be more active and possesses a more prolonged action than the testosterone itself.[8,9] This can be explained by the more rapid transport of the silylated compound **Ib** across the lipid barrier, followed by hydrolysis affording testosterone (**Ia**). As a result, the anabolic agent Silabolin has been developed and registered in the USSR.[10]



Ia R = H
Ib R = Me_3Si

Instead of the readily hydrolysable trimethylsiloxy group, one can use other hydrolytically more stable triorganylsilyl groups; the hydrolysis rate diminishing in the order:[11,12]

$Me_3Si > Me_2EtSi > Et_3Si > t\text{-}BuMe_2Si > t\text{-}BuPh_2Si$

Introduction of these groups into the molecular framework of the silylated compounds can generate some biological properties not inherent in the initial drug. Thus, for example, the introduction of dimethyl(tert-butyl)silyl groups into the molecule of the antitumour drug methotrexate (**IIa**)

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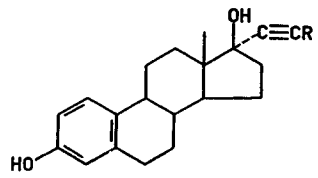
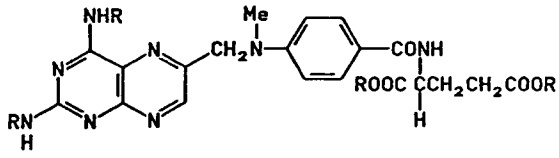
Table 1 Hormonal activity of ethynyloestradiol derivatives after peroral administration to rats



Compound	R	Antifertility	Oestrogenic potency	A/O[a]
IVa	H	100	100	
IVb	Me	1	0.07	14
IVc	Et_3Si	600	37	16
IVd	Me_2(t-Bu)Si	600	20	20

[a]Ratio of antifertility activity to oestrogenic potency.

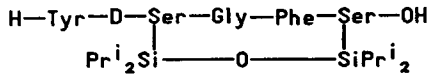
yields compound **IIb** which exhibits activity against experimental allergic encephalomyelitis and, in contrast to methotrexate, prevents serious paralysis and mortality in animals.[13]



IIa R = H
IIb R = Me_2(t-Bu)Si

It can be assumed that the activity of the silylated methotrexate **IIb** is posited by the increase of lipophilicity and ability to pass across the blood–brain barrier.

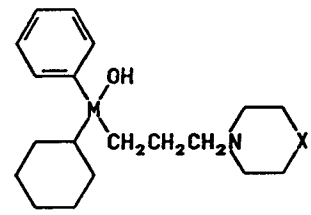
The introduction of the disiloxanyl group (instead of the triorganylsilyl one) into the enkephalin molecule noticeably enhances the activity (by 67-fold) due to the stabilization of the active conformation **III**.[14]



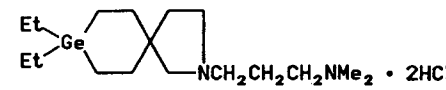
III

C-silylation of drugs is also used to design new bioactive agents. For example, 17-(triethylsilyl)ethynyloestradiol (**IVc**) and the 17-(dimethyl-t-butylsilyl) derivative (**IVd**) possess extremely high antifertility properties and, at the same time, reduced oestrogenic activity (Table 1).[15]

Sila analogues of the antimuscarinic drugs (**V**) are used in experimental pharmacology to classify subtypes of muscarinic receptors,[4,16–18] whereas the germa analogue (**VI**), 2-(3-dimethylaminopropyl) - 8, 8 - diethyl - 2 - azaspiroi[4, 5]decane (spirogermanium) was the first organogermanium compound tested clinically as an antitumour agent.[7,20–24]

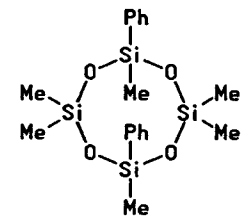


M = C, Si
X = CH_2, $\overset{+}{N}Me_2\bar{S}O_3Me$ V



VI

Three substances belonging to the third type of compounds (two organosilicon and one organogermanium) have been tested clinically. 2,6-*cis*-Diphenylhexamethylcyclotetrasiloxane (Cisobitan), **VII**, has been shown to suppress prostatitis carcinoma;[25] complexes of sodium and potassium methylsiliconate with various hydroxycarboxylic acids such as citric, salicylic and ascorbic acids have found application in the treatment of cardiovascular diseases;[2,26–28] and 2-carboxyethylgermsesquioxane (**IX**) (Ge-132, proxygermanium) has been revealed to possess antitumour,[7,29,30] interferon-inducing[31,32] and immuno-modulating[7,33,34] properties.



VII

$MeSi(OH)_2OKnRCOOHmH_2O$ **VIII**
$(HOOCCH_2CH_2GeO_{1.5})_n$ **IX**

Table 2 Properties of carbon, silicon and germanium

Element	Electronic configuration	Electro-negativity	Covalent radius (Å)
C	$1s^2 2s^2 2p^2$	2.5–2.6	0.77
Si	$1s^2 2s^2 2p^2 3s^2 3p^2$	1.8–1.9	1.17
Ge	$1s^2 2s^2 2p^2 3s^2 3p^6 3d^{10} 4s^2 4p^2$	2.02	1.22

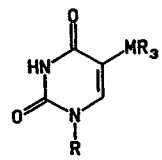
Table 3 Average bond length M–X (Å)

	X		
M	H	C	O
C	1.09	1.54	1.43
Si	1.47	1.88	1.63
Ge	1.53	1.96	1.65

Table 4 Energies of M–X Bonds (kcal mol^{-1})

	X	
M	H	C
C	99	85
Si	77	72
Ge	69	58

Table 5 Cytotoxicity of uracil derivatives (EC_{50}, μg kg^{-1}) to melanoma B_{16} cells



		M	
Compound	R	Si	Ge
XI	H	32	32
XII		32	32

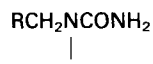
2 ORGANOSILICON AND ORGANOGERMANIUM COMPOUNDS WITH SIMILAR ACTIVITY (Si ≈ Ge)

Analysing the properties of organosilicon and organogermanium compounds only, the groups of substances can be considered as sila–germa-analogues. Being in the same group with carbon in the Periodic system of elements, they differ from the latter in their physicochemical properties. It can be expected that these physicochemical effects may, in principle, result in differing biological effects.

Silicon and germanium have considerably larger covalent radii (1.17 and 1.22 Å) than carbon (0.77 Å), less electronegativity (1.9, 2.0 and 2.5), different electronic energies in their outer layers (Table 2), greater bond lengths with hydrogen, carbon and oxygen (Table 3), lower bond energies[35] with hydrogen and carbon and higher bond energies with oxygen (Table 4). Moreover, at the attachment of aryl, vinyl and ethynyl groups or atoms with lone electron pairs, silicon and germanium, in contrast to carbon, are capable of forming (*p–d*) π-bonds involving 3*d* (4*d* for Ge) orbitals, whereas carbon tends to form (*p–p*) π multiple bonds with carbon, oxygen and nitrogen. Besides, silicon and germanium can yield penta- and hexa-coordinated derivatives; this is possible for carbon only in some special cases.

By their physicochemical properties silicon and germanium are considerably closer to each other than to carbon; that is why one can expect similarity in their biological activity. But, on the other hand, the difference in rates of M–C (M = Si, Ge)

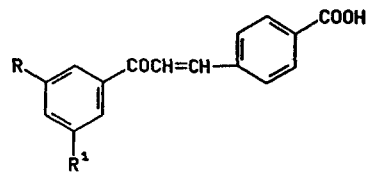
Table 6 Effect of the concentration of *N*-substituted *N*-nitrosourea on the cytotoxicity to leukaemia L1210 cells



			T/C[a]		
Compound	R	Lipophilicity, log *K'*	1	2	3
XVa	H	0.116	0.68	0.08	0.009
XVb	Me_3C	0.667	1	—	1
XVc	Me_3Si	0.717	0.80	0.08	0.010
XVd	Me_3Ge	0.733	0.68	0.07	0.016
XVe	Me_2PhSi	1.073	0.087	0.002	—
XVf	Me_2PhGe	1.094	0.093	0.002	—

[a]T/C denotes the ratio of surviving cells in the test dish to control (~10^6 cell cm^{-3}) after a 24-h incubation.

Table 7 Differentiation-inducing activity of retinoids to HL-60



Compound	R	R^1	EC_{50} (mol dm^{-3})	Relative activity[a]
XVIa	Me_3C	Me_3C	2.1×10^{-10}	640
XVIb	Me_3Si	Me_3Si	1.4×10^{-10}	860
XVIc	Me_3Ge	Me_3Ge	2.1×10^{-10}	1000
XVIIa	Me_3C	H	1.6×10^{-7}	0.81
XVIIb	Me_3Si	H	4.4×10^{-8}	1.8

[a]Ratio of the retinoic acid EC_{50} to the EC_{50} of the compound under study, defined under identical conditions, and multiplied by 100.

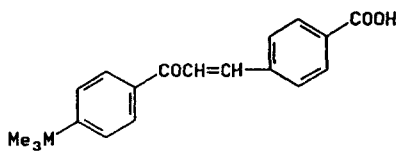
bond cleavage, the lower capacity of germanium to form (p–d) π-bonds and the somewhat greater lipophilicity of triorganylgermyl derivatives can cause some quantitative differences in potency.

Really, there exist two groups of compounds. The first embraces analogous derivatives of silicon and germanium with close biological activity (bioisosters); the second incorporates germanium and silicon structural analogues exhibiting different biological properties.

5-Trimethylsilyluracil (**XI**), its germanium counterpart and their 1-(2-tetrahydrofuryl) derivatives (**XII**) display similar cytotoxicity to melanoma B_{16} cells (Table 5)).[37]

5-Trimethylsilyl[38] and trimethylgermyl derivatives[39] of 2′-deoxyuridine are close in their

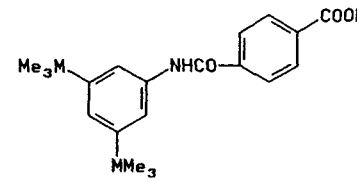
Table 8 Differentiation-inducing activity of retinoids to HL-60



Compound	M	EC_{50} (mol dm^{-3})	Relative activity*
XVIIIa	C	2.8×10^{-8}	3.9
XVIIIb	Si	Inactive at 10^{-6}	—
XVIIIc	Ge	Inactive at 10^{-6}	—

* As for Table 7

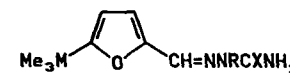
Table 9 Differentiation-inducing activity of retinoids **XXII** to HL-60



M	EC_{50} (mol dm^{-3})	Relative activity*
C	3.6×10^{-8}	15
Si	3.0×10^{-8}	13
Ge	4.2×10^{-8}	15

* As for Table 7

Table 10 Inhibition of the growth of melanoma B_{16} in mice by derivatives of furfural (%)*

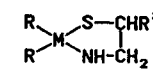


Compound	X	R	M	
			Si	Ge
XXIII	O	H	40	43
XXIV	S	H	40	48
XXV	O	CH_2COOH	52	48

* Compared to a control not containing a furfural derivative

antimetabolic properties: β-anomers (**XIVa,b**) possess weak biological action, α-anomers inhibit the replication of herpes simplex virus HSV-1,[38–40] reveal cytotoxic properties in *in vitro* experiments

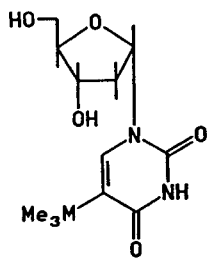
Table 11 Radioprotective potency (dose reducing factor)* of thiazolidines **XXVI**



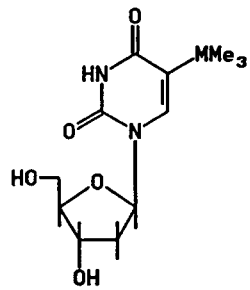
R	R^1	M		
		C	Si	Ge
C_6H_5	H	1.20	1.60	1.60
p-$MeOC_6H_4$	H	1.30	1.40	1.45
p-FC_6H_4	CH_3	—	1.20	1.20
p-ClC_6H_4	CH_3	—	1.20	1.25

* Compared to no thiazolidine derivative being present

on cell culture of human ovary carcinoma CaOv and fail to display antitumour action *in vivo* to leukaemia P388 in mice. The α-anomer of the 5-trimethylgermyl derivative (**XIIIb**) suppresses the incorporation of 2′-deoxyuridine and thymidine into the DNA of hepatoma 22A cells *in vitro* very effectively (by 88 and 27%) than the β-anomer (50 and 0%, respectively). It is worthy of note that the therapeutic effect of the silyl derivative (**XIIIa**) on the culture of chicken fibroplasts infected with HSV-1 is somewhat higher than that of the germanium analogue (**XIIIb**).



XIIIa M = Si
XIIIb M = Ge



XIVa M = Si
XIVb M = Ge

Silicon (**XVc**) and germanium (**XVd**) analogues of *N*-neopentyl-*N*-nitrosourea (**XVb**) exhibit considerably higher cytotoxicity to leukaemia L1210 cells than the carbon analogue (**XVb**).[41] One can suppose that this is determined by their greater lipophilicity (Table 6). However, a practically similar potency of silicon and germanium derivatives (**XVc,d**) within the concentration interval from 1 to 3 nmol dm^{-3}, close to the activity of *N*-methyl-*N*-nitrosourea, indicates the possibility of splitting Si–C and Ge–C bonds under experimental conditions with the formation of the same biomethylating agent; this has been confirmed by the investigations. Dimethylphenyl derivatives (**XVe,f**) are significantly more cytotoxic due to either their increased lipophilicity or to the splitting of the phenyl group.

Table 12 Radioprotective potency (DRF)* of silatranyl and germatranyl derivatives of cysteamine

$N(CH_2CH_2X)_3MSCH_2CH_2NH_2 \cdot HCl$

		M	
Compound	X	Si	Ge
XXVII	O	1.3	1.4
XXVIII	S	1.4	1.35

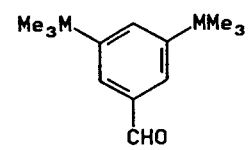
* See Table 11

Some trimethylsilyl and trimethylgermyl derivatives of retinobenzoic acids show high retinoidal activity in human promyelocytic leukaemia cells HL-60.[42]

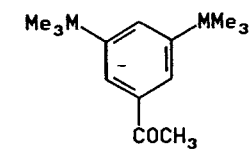
Thus, (*E*)-4-{3-[3,5-bis(trimethylsilyl)phenyl]-3-oxo-1-propenyl}benzoic acid, **XVIb**, and its germanium analogue **XVIc** are one order of magnitude more potent than retinoic acid. Both compounds show activity similar to that of the carbon analogue (Table 7).

If only one R_3M group exists in the *meta*-position, silicon (**XVIIb**) and germanium (**XVIIc**) derivatives are more active than the carbon analogue (**XVIIa**) but inferior to retinoic acid in activity (Table 7), whereas, in the case of *para*-substituted chalcones (**XVIII**) (the only case when the *para*-isomer is active) the substitution of a t-butyl group (2.8×10^{-8}) for a trimethylsilyl or trimethylgermyl group leads to complete loss of activity (Table 8).[42]

It is interesting to note the absolute loss of another activity caused by the same change in the compound structure. Substitution of t-butyl groups by trimethylsilyl or trimethylgermyl in 3,5-di(t-butyl)-benzaldehyde (**XIX**) and -acetophenone (**XX**) both having a musk scent, results in the complete loss of scent, whilst in the case of the corresponding trinitrobenzene derivatives (**XXI**) this type of substitution increases the musk scent in the silicon derivative and its conservation in the germanium analogue.[43] The question whether these changes of biological properties are caused by the changes in molecular volumes or lipophilicity of the compounds or by the existence of (*p–d*) π-interaction with the benzene ring in silicon and germanium derivatives needs further study.

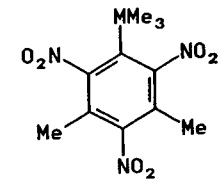


XIX



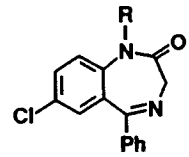
XX

M = C, Si, Ge



XXI

Table 13 Pharmacological properties of benzodiazepine derivatives



Compound	R	LD_{50} (mg kg^{-1})	Rotating rod test ED_{50} (mg kg^{-1})	Potentiation* of pentobarbital anaesthesia
XXIXa	Me	750	5.4	80
XXIXb	Me_3Si	1000	2.5	—
XXIXc	Me_3Ge	1000	2.0	120

* Defined as: to control in what 3 mg/kg of pentobarbital was administered p/o without benzodiazepine derivatives.

Me_3M-substituted retinobenzoic acid, **XXII** (M = C, Si, Ge), with an amide group between the aromatic rings, possesses similar retinoidal activity (Table 9).[42]

Silicon[44] and germanium[45] derivatives of the semicarbazone (**XXIII**, **XXV**) and thiosemicarbazone (**XXIV**) of furfural exhibit similar antitumour activity to melanoma B_{16} in mice (Table 10)).

Some of the cyclic silicon and germanium derivatives of cysteamine (**XXVI**) possess similar or close radioprotective potency (Table 11). Sometimes their activity exceeds that of the carbon analogue.[46]

Similar radioprotective potency has been found for derivatives of cysteamine, with its sulphur atom being bound with silatrane or germatrane groups (**XXVII**),[47] as well as for their trithia analogues (**XXVIII**) (Table 12).[48]

The introduction of trimethylsilyl (**XXIXb**) or trimethylgermyl (**XXIXc**) groups to the nitrogen atom of diazepam does not affect its main biological properties (sedative, anticonvulsant, myorelaxant activities).[49] The germanium derivative **XXIXc** possesses higher locomotor activity than the carbon analogue and, to a greater extent, enhances hexenal anaesthesia if compared with the *N*-methyl derivative (**XXIXa**). At the same time silicon and germanium derivatives have been shown to possess practically similar toxicity and to differ little from each other in the rotating rod test

Table 14 Toxicity of silatranes and germatranes **XXX** (LD_{50}, mg kg^{-1})

$\overset{\downarrow}{R}M(OCH_2CH_2)_3N$

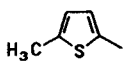
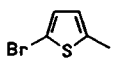
R	M: Si	M: Ge
	0.3	16.5
C_6H_5	0.33	48
	0.42	20.5
	0.42	21
	1.8	89
	125	2050
	14.5	1630
$NCCH_2CH_2$	1340	4300
$CH_2=CH$	1750	5600
$ClCH_2$	2800	2960

Table 15 Toxicity (LD_{50}, mg kg^{-1}) of $RCH_2\overset{\downarrow}{M}(OCH_2CH_2)_3N$ and $R\overset{\downarrow}{O}Ge(OCH_2CH_2)_3N$

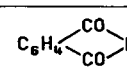
Compound	R	M: Si	M: Ge
XXXI		4470	4100
XXXII	Me_3M	3500	~3500

Table 16 Toxicity (LD_{50}, mg kg^{-1}) and radioprotective potency (DRF)† of aminoalkylthio-silatranes and -germatranes RSCHR'CH_2NHR''.HCl (**XXXIII**)

		R					
				$N(CH_2CH_2O)_3M$			
		H		Si		Ge	
R'	R''	LD_{50}	DRF	LD_{50}	DRF	LD_{50}	DRF
H	H	450	1.55	600	1.3	700	1.4
CH_3	H	500	1.5	1200[a]	1.05	1500	1.5
H	$(CH_2)_3NH_2$.HCl	400	1.5	—	—	900	1.45

[a] Base administered p.o., the others i.p.
† See Table 11.

Table 17 Toxicity and radioprotective potency* of (aminoalkylthio)thiagermatranes and -germocanes

Compound		LD_{50} (mg kg^{-1})	DRF
XXXIV	$N(CH_2CH_2S)_3GeSCH_2CH_2NH_2HCl$	500	1.35
	$N(CH_2CH_2SH)_3HCl$	150	1.25
XXXV	$HN(CH_2CH_2S)_2Ge(SCH_2CH_2NH_2HCl)_2$	200	1.25
	$HN(CH_2CH_2SH)_2HCl$	50	1

* See Table 11

Table 18 Toxicity (LD_{50}, mg kg^{-1}) of hydroxamic acids **XXXVI**

$Me_3MCH_2CH(R)CONHOH$

		R	
Compound	M	H	Me
XXXVIa	Si	815	410
XXXVIb	Ge	2000	815
XXXVIc	Sn	20.5	178

Table 19 Acute toxicity of adamantane derivatives

Compound		LD_{50} (mg kg^{-1})
XXXVII	$AdCH_2CH_2SiMe_3$	26
XXXVIII	$AdCH_2CH_2GeMe_3$	1480
XXXIX	$AdCH_2CH_2CH_2GeMe_3$	>5000
XL	$AdGe(OCH_2CH_2)_3N$	>5000

(Table 13). This may be caused by the hydrolytic splitting of the M–N bond yielding a single unsubstituted compound.

3 COMPOUNDS WITH HIGHER ACTIVITY FOR SILA ANALOGUES (Si > Ge)

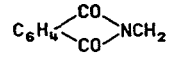
3.1 Toxicity

Low toxicity is characteristic of many organogermanium compounds.[7] Thus, the mean lethal doses of 2-carboxyethylgermsesquioxane and its

Table 20 Acute toxicity of titanocene derivatives (LD_{50}, mg kg^{-1})

		M	
Compound		Si	Ge
XLII	$(Me_3MC_5H_4)_2TiCl_2$	360	400
XLIII	$Me_2M(C_5H_4)TiCl_2$	220	280

Table 21 Influence of organogermanium and organosilicon compounds on locomotor activity of mice

Compound	EC_{50} (mg kg^{-1})			
	Rotating rod test		Hypothermia	
	Si	Ge	Si	Ge
$AdCH_2CH_2MMe_3$	6.9	>1000	12	>1000
$RM(OCH_2CH_2)_3N$				
R = 	103	>1000	103	815
R = 	14.5	41	14.5	45
R = 	1.5	71	1.5	51
R = 	0.0016	1	0.008	2.7
R = 	0.0016	1.2	0.005	1.2

derivatives using various administration routes to mice and rats varies from 10 000 to 3000 mg kg^{-1},[7,50-53] for cyclogermoxanes they vary from 4000 to 1300 mg kg^{-1},[54] for tetraorganylgermanes administered i.p. to mice (according to the substituent nature at the germanium atom) from 8300 to 2000 mg kg^{-1},[55,56] for adamantylgermanes from 5150 to 1480 mg kg^{-1},[57] for various trialkyl- and triaryl-germanes administered subcutaneously to mice from 5000 to 1250 mg kg^{-1},[58] and for a majority of alkyl-, hetaryl- and carbofunctional germatranes administered i.p. to mice from 10 000 to 2000 mg kg^{-1}.[50,57,59,60]

However, certain representatives of every series of compounds can appear to be considerably toxic. Thus, for example, whilst the mean lethal dose of the majority of trialkylacetoxygermanes administered i.p. to rats is more than 900 mg kg^{-1}, the LD_{50} of the triethyl derivative does not exceed 20 mg kg^{-1}.[61] Ethyl derivatives belonging to the hexa-alkyldigermoxane and cyclogermoxane series are also more toxic than butyl derivatives (200- and 44-fold, respectively).[61] Thienylgermatrane appears to be the most toxic among the germatranes studied.[60]

Table 22 Antitumour activity (prolongation of life span) of organosilicon and organogermanium compounds

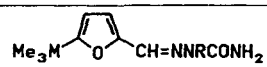
Compound		Tumour	M	
			Si	Ge
XXIII				
	R = H	LLC	52	43
XXV	R = CH_2COOH	LLC	62	48
XLIV	$Me_3MOGe(OCH_2CH_2)_3N$	Ehrlich's ascite tumour	58	44
		Sarcoma 37	75	60

Table 23 Toxicity (LD_{50}, mg kg^{-1}) of organosilicon and organogermanium derivatives of cysteamine

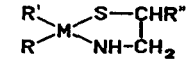
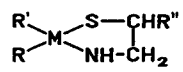
Compound				M		
				C	Si	Ge
XXVI						
	R	R′	R″			
	Et	Et	H	800	1000	600
	Me	Ph	H	1000	800	600
	Me	*p*-$MeOC_6H_4$	H	1500	1500	600
	Me	*p*-FC_6H_4	H	1000	800	600
	Me	Ph	Me	—	750	500
	Me	*p*-$MeOC_6H_4$	Me	—	1000	600
	Me	*p*-FC_6H_4	Me	—	1000	500
	Me	*p*-ClC_6H_4	Me	—	1000	700
XXVIII	$N(CH_2CH_2S)_3MSCH_2CH_2X$					
	X = NH_2HCl			—	800	500
	X = $NH(CH_2)_3NH_2HCl$			—	300	150
XLV	$Me_2M(SCH_2CH_2NH_2)_2$			300	800	300

Table 24 Radioprotective (DRF) properties of thiazolidines **XXVI**



R	R′	R″	M		
			C	Si	Ge
CH_3	*p*-FC_6H_4	H	1.15	1.05	1.25
C_6H_5	C_6H_5	H	—	1.10	1.40
CH_3	C_6H_5	CH_3	—	1.50	1.75
CH_3	*p*-$MeOC_6H_4$	CH_3	—	1.10	1.45

Table 25 Radioprotective properties of cysteamine derivatives **XLV**

$RR'M(SCHR''CH_2NH_2)_2$

R	R′	R″	M		
			C	Si	Ge
CH_3	CH_3	H	1.15	1.1	1.3
iC_5H_{11}	iC_5H_{11}	CH_3	1	—	>1.6
CH_3	C_6H_5	CH_3	1	—	>1.5

Table 26 Influence of hydroxamic acids $Me_3MCH_2CHRCONHOH$ (**XXXVI**) on the life span (%) of mice under hypoxic hypoxia, and their anticonvulsive potency

Compound	M	R		Corazole spasms* (%)
		H	CH_3	
XXXVIa	Si	174.8	167.9	103.9
XXXVIb	Ge	206.6	174.0	156.8
XXXVIc	Sn	144.1	198.6	214.2

* Increase of the lethal dose of corazole compared with when no hydroxamic acid being present.

In most cases organogermanium compounds are less toxic than the corresponding organosilicon compounds and, sometimes, than the carbon analogues as well. Silatranes and germatranes **XXX** containing pentacoordinated silicon and germanium appear to be obvious illustrations of this statement. Compounds containing phenyl[1,2] and 2-thienyl[62] groups at the silicon atom have been shown to be the most toxic silatranes ($LD_{50} \sim 0.3\ mg\ kg^{-1}$). Thienyl derivatives are the most toxic (16–21 $mg\ kg^{-1}$) in the germatrane series, whilst they are less toxic (by 50-fold) than the corresponding silatranes.[60]

Introduction of methyl and bromo substituents in the 5-position of the thiophene ring slightly affects the toxicity, whereas 3-thienylsilatrane is 6 times less toxic than the 2-isomer.[60]

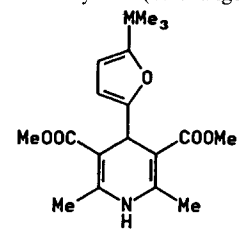
All furylgermatranes exhibit less toxicity than the corresponding silatranes.[60,62] In the case of the thiophene series, 2-derivatives display the highest toxicity, whilst in the furan series, on the contrary, 2-derivatives are less toxic than the 3-isomers.

In the group of highly toxic compounds germanium derivatives reveal a toxicity 50-fold less compared with the silicon analogues. In the group of compounds of medium toxicity the toxicity is 10–16 times lower, and in the group of low toxicity it is 3 times lower (Table 14).

Phthalimidomethyl derivatives (**XXXI**) of silatrane and germatrane have been found to be of low toxicity (Table 15).[59] Organylsiloxy and organylgermoxy derivatives of germatrane (**XXXII**)[63] differ insignificantly in their toxic potency.

The high toxicity of thienyl derivatives can be caused neither by the atrane skeleton in the molecule (alkyl derivatives of the same structure possess extremely low toxicity—4–5 $g\ kg^{-1}$), nor by the existence of the π-system (vinylgermatrane has extremely low toxicity—5600 $mg\ kg^{-1}$), nor by the hydrolysis of M–O or M–C_{ar} bonds, as the products of the complete hydrolysis are also low-

Table 27 The influence of 1,4-dihydropyridine derivatives on the cardiovascular system (% change)

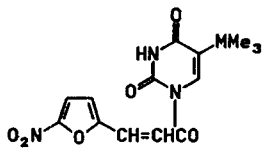


XLIa M = Si
XLIb M = Ge

Activity[a]	M	
	Si	Ge
Arterial pressure (0.1 $mg\ kg^{-1}$)	3	12
Vasodilation (0.1 $mg\ kg^{-1}$)	0	11
Blood flow increase (0.05 $mg\ kg^{-1}$)		
– common carotid	0	31
– femoral artery	25	25

[a] The i.v. dose is shown in parentheses.

Table 28 Cytotoxicity (EC_{50}, $\mu g\ cm^{-3}$) of organogermanium and organosilicon compounds to melanoma B_{16} cells

Compound		M	
		Si	Ge
XLVI		32	10
XXXII	$Ph_3MOGe(OCH_2CH_2)_3N$	10	3.2

toxicity substances; for example, the LD_{50} of 1-hydroxygermatrane is 8400 mg kg^{-1}.[50] Perhaps, the whole complex of factors (atrane skeleton with aryl group attached, ease of $M-C_{ar}$ bond splitting followed by the subsequent bioarylation) is responsible for the exhibition of so high a toxicity.

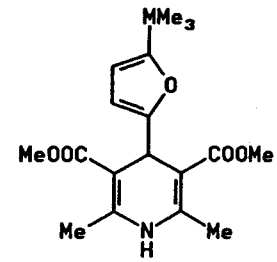
Introduction of the germatranyl group into aminothiol molecules considerably (to a greater extent even, than the introduction of the silatranyl group) decreases the toxicity of the compound (Table 16); radioprotective properties remain at the same level.[47]

The same can be observed in the case of the ring closure of trithiagermatrane (**XXXIV**) and dithiagermocane (**XXXV**) (Table 17).

The heteroatom affects dramatically the toxicity of β-trimethylsilyl-, β-trimethylgermyl- and β-trimethyltin-propiohydroxamic acids.[64] The acute toxicity of the tin-substituted acid (**XXXVIc**) administered i.p. to albino mice ($LD_{50} = 20.5$ mg kg^{-1}) is 100 times higher than that of the acid containing germanium (**XXXVIb**) (2000 mg kg^{-1}), and 40 times higher if compared with the acid containing silicon (815 mg kg^{-1}) (Table 18). The organogermanium derivative appears to be the least toxic in the series of the corresponding isobutyrohydroxamic acids.[64]

Adamantyl derivatives of germanium (**XXXVIII**) are considerably less toxic than the corresponding derivatives of silicon (**XXXVII**) (Table 19).[57] Increase of the distance between the adamantane ring and germanium atom decreases toxicity further (**XXXIX**). Adamantylgermatrane (**XL**) (LD_{50} 5 g kg^{-1}) exhibits low toxicity as well.

The trimethylgermyl derivative of 4-(2-furyl)-2,6-dimethyl-3,5-dimethoxycarbonyl-1,4-dihydropyridine (**XLI**) is 3 times less toxic than its sila analogue (**XLIa**).



XLIa M = Si

XLIb M = Ge

Germyl derivatives of dichlorotitanocene (**XLII**) and (**XLIII**) are also somewhat less toxic than their silicon counterparts (Table 20).[65]

3.2 Psychotropic and antitumour activities

Due to the biological inertness of many organogermanium compounds one can expect that organosilicon compounds exhibit greater potency. In practice, organosilicon compounds in therapeutic doses reveal a more pronounced psychotropic effect on the CNS (Table 21). For example, adamantylethylsilane, phthalimidomethyl-, 2- and 3-furyl- and 2- and 3-thienyl-silatranes are more active in rotating rod tests and also in their analgesic and hypothermic action.[57,59,60,62]

In some cases organosilicon compounds show higher antitumour potency compared with the analogous derivatives of germanium. Thus, trimethylsilyl derivatives of furfural semicarbazone exhibit curative activity against Lewis lung carcinoma[44,45] and trimethylsiloxygermatrane **XLIV**, has been found to prolong the life of animals with Ehrlich ascite tumour and sarcoma 37.[50] In the last case both germanium (60%) and silicon (75%) derivatives appear to be more active than 1-hydroxygermatrane (44%), unsubstituted in the hydroxyl group (Table 22).[50]

4 COMPOUNDS WITH HIGHER ACTIVITY OF GERMA ANALOGUES (Ge > Si)

Until now, a higher toxicity in organogermanium compounds (compared with organosilicon compounds) has been shown only for linear (**XLV**) and cyclic (**XXVI**, **XXVIII**) derivatives of cysteamine (Table 23).[46,48,66]

There exists considerable information on organogermanium compounds which have a greater biological potential than their silicon analogues.

Table 29 Antitumour activity of organogermanium and organosilicon compounds

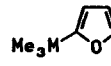
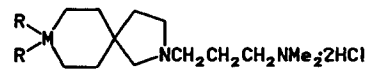
Compound		Tumour	M	
			Si	Ge
XXIV		LLC	33	48
XLIV	$Me_3MOGe(OCH_2CH_2)_3N$	Adenocarcinoma 755	28	46

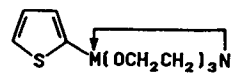
Table 30 Cytotoxic and immunomodulating properties of azaspiranes



Activity	R	M		
		C	Si	Ge
Antiarthritic	Me	0.12	0	—
	Et	0.57	0.92	1
	Pr	1.35	—	—
Induction of suppressors	Me	0	0	
	Et	88	63	100
	Pr	172		
IC_{50} (μmol dm^{-3}) colony-forming assay (HT-29)	Me	170	80	—
	Et	19	—	12

Table 31 Toxicity of Et_3MCl to bacteria and algae

Compound	M	LD_{50} (μmol dm^{-3})		Total surface area (Å)
		E. coli	*S. capricornutum*	
XLVIIa	Si	8.07	>5.76	202.61
XLVIIb	Ge	6.71	1.77	213.36
XLVIIc	Sn	2.40	1.60	212.80
XLVIId	Pb	0.51	1.11	228.53

Table 32 Influence of  on the duration of anaesthesia (min, $P>0.05$)

Drug	M		
	Si	Ge	Control
Thiopental (30 mg kg^{-1}, i.v.)	19.8	2	3.4
Barbital (150 mg kg^{-1}, i.p.)	69.5	35.5	53.8
Chloral hydrate (300 mg kg^{-1}, i.p.)	30	25	28

In some cases germyl modification of aminothiols increases their radioprotective properties in comparison not only with carbon analogues but also with the analogous derivatives of silicon. Cyclic derivatives of cysteamine **XXVI** containing one or two aryl groups at the germanium atom show such activity (Table 24).

2,5-Dimethyl-2-phenylgermathiazolidine revealed the highest protective property (its radiation reducing factor, 1.75, exceeding that of cysteamine, 1.5) for the irradiation of mice with ^{60}Co.[46]

Bis(2-aminoethylthio)germanes **XLV**, particularly with aryl or longer (isoamyl) alkyl groups at the germanium atom, exhibit a higher radioprotective activity exceeding that of the analogous compounds of carbon and silicon (Table 25).[66]

Trimethylgermylpropiohydroxamic acid (**XXXVI**) prolongs the life of mice under hypoxic hypoxia by 206% and is more active than the analogous derivatives of silicon, (**XXXVIa**) (175%), and tin, (**XXXVIc**) (144%).[64] Introduction of one methyl group into the alkyl chain of the acid increases the activity of the tin derivative (**XXXVIc**) (R = Me) and decreases, to some extent, the activity of the derivatives of other elements. Germanium derivative (**XXXVIb**) (R = Me) still remains more potent than its sila analogue (Table 26).[64]

Germanium derivatives of isobutyrohydroxamic acid (**XXXVIb**) (R = Me) exceed the silicon analogue **XXXVIa** (R = Me) in their protective potency in the case of Corazole convulsions (Table 26).[64]

4-(5-Trimethylgermyl-2-furyl)-substituted 1,4-dihydropyridine, **XLIb**, administered i.v. in a 0.05 mg kg^{-1} dose increases the blood flow in the common carotid of cats by 31%, and in a 0.1 mg kg^{-1} dose it dilates the coronary vessels by 11% and decreases the arterial pressure by 12%,

while the sila analogue is practically inactive in these tests (Table 27).

Some organogermanium compounds possess higher cytotoxicity than their silicon analogues. Thus, 1-(5-nitrofurylacroyl)-5-trimethylgermyluracil, **XLVI**,[37] and triphenylgermoxygermatrane, (**XXXII**)[63] suppress the growth of melanoma B_{16} cells three times more effectively than their silicon analogues (Table 28).

The germanium derivative of furfural thiosemicarbazone (**XXIV**) (in contrast to the semicarbazone derivatives) inhibits the growth of Lewis lung carcinoma,[44,45] and trimethylgermoxygermatrane, (**XLIV**), impedes the growth of adenocarcinoma 755[50] more effectively than the corresponding sila derivatives (Table 29).

The dihydrochloride of 2-(3-dimethylaminopropyl)-8,8-diethyl-2-aza-8-germaspiro[4,5]-decane **VI** (spirogermanium) inhibits the formation of the cell colonies of human colon carcinoma HT-29 more effectively than the carbon analogue, while the dimethylsila derivative appears to be twice as effective compared with the carbon derivative.[67] Data on compounds with similar substituents at germanium and silicon are absent, whereas the data on the carbon analogues demonstrate that substitution of the methyl groups for ethyl noticeably increases biological potency.

In the experiments on rats spirogermanium exceeds both silicon and carbon analogues in its activity towards adjuvant arthritis.[68] It is a more active inducer of the suppressor cells.[68–72] It has been shown that the ethyl derivative is considerably more effective than the methyl one, whereas the propyl derivative of the carbon analogue is 1.7 times more active than spirogermanium (Table 30). However, in this case as well, there is no comparative analysis of the activity of dipropyl derivatives of silicon and germanium.

Trialkylchlorogermanes **XLVIIb** are stronger inhibitors of the growth of *Escherichia coli* bacteria and *Selenastrum capricornutum* algae than the analogous chlorosilanes (**XLVIIa**), but their activity is inferior to the tin derivatives (**XLVIIc**).[73] An attempt has been made to correlate the toxicity of these compounds towards micro-organisms with the total surface area of their molecules (Table 31). Good correlation has been observed in the series of tin derivatives, whilst all the elements of Group IVB (except triethyl derivatives) do not obey a common correlation. As the experiments have been carried out in aqueous/methanol medium, various chemical conversions have occurred.

This is why quantitative correlation failed to be found but the greater activity of germanium compounds compared with the analogous silanes has been confirmed experimentally.

5 CONCLUSION

In most cases organogermanium and organosilicon compounds reveal similar activity, differing only quantitatively. Cases when silicon and germanium compounds are analogous in their structure but display opposite biological effects present interest for investigation.

The comparison of the neurotropic activity of phthalimidomethylgermatrane, (**XXXIb**), and its sila analogue demonstrates that at practically equal toxicity silicon compound (**XXXIa**) shows depressant properties 10 times more elevated than the corresponding germanium derivative (**XXXIb**). On the contrary, the germanium compound decreases the narcotic action of hexenal by 40%. Thus, the silicon compound (**XXXIa**) exhibits predominantly depressing activity, while activating action is typical for the germanium analogue (**XXXIb**).[59]

Analogous comparison of 1-(2-thienyl)-germatrane, **XLVIIIb**, and -silatrane, (**XLVIIIa**), shows that both compounds act as stimulants in rotating rod tests but the acting dose of silatrane is three orders of magnitude less than that of the germanium analogue (**XLVIIIb**). The latter decreases, to some extent, the narcotic action of thiopental sodium, barbital sodium and chloral hydratst, while 2-thienyl-silatrane, on the contrary, considerably increases the duration of anaesthesia induced by thiopental sodium (Table 32).[62]

Analysis of the data accumulated up to the present demonstrates that:

(1) organosilicon and organogermanium compounds that are more active than their carbon counterparts have been obtained;
(2) the majority of organogermanium compounds are less toxic than the analogous organosilicon compounds;
(3) the biological action of organic compounds of silicon and germanium is similar but can dramatically differ in the degree of action;
(4) in some cases opposite biological effects can be observed.

A search for new biologically active compounds in the organogermanium and organosilicon compound series can lead to the development of novel pharmaceuticals. As organosilicon compounds are more available and less expensive, one can expect that mainly in this series of compounds the search will be most productive. However, as their organogermanium counterparts are not inferior in activity (and sometimes are even superior) and very often are less toxic, it appears obvious, after finding a highly active organosilicon compound, to synthesize and study the biological properties of its germanium analogue.

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