N-(Silylmethyl)amines, -amides, and -amino acids: biological activity and prospects in drug synthesis

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The data on biological activity of the compounds with the geminal fragment N—C—Si are systematized. The examples of using *N*-(silylmethyl)amines and related compounds in syntheses of biologically active substances, including natural compounds, are considered.

Key words: *N*-(silylmethyl)amines, *N*-(silylmethyl)amides, *N*-(silylmethyl)amino acids, biological activity.

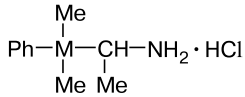
Silicon is the nearest analog of carbon, its content exceeds 27% of the weight of the Earth crust. The carbon chemistry is associated with the chemistry of life on the Earth, while the main silicon compounds in the nature are silica and silicates, inorganic compounds with the bond Si—O. Silicon compounds have been considered for a long time to be biologically inert. Only the recent four decades were marked by a series of fundamental achievements in the area of bioorganosilicon chemistry (see Refs 1—11 and the literature cited therein). The solution of a series of natural scientific problems of prebiotic chemistry and philosophic questions of the life origin on the Earth are related to the study of biosilicification processes[12—16] and the role of silicon compounds in prebiotic catalysis.[17—19] Amines and amino groups of amino acids and peptides are involved in biosilicification.[20—23] In principle, the formation *in situ* and participation in these transformations of compounds with the geminal fragment N—C—Si cannot be excluded. Biological activity of *N*-(silylmethyl)amino compounds has partially been discussed earlier.[1,2—6,8—11,24] The purposes of the present review are as follows: first, to systematize literature data on the biological activity of compounds with the geminal fragment N—C—Si (amines, amides, and amino acids) and, second, to provide readers with information about both the application of these compounds as pharmaceutical preparations or their potent suitability for use in medicine and their use in the synthesis of biologically active substances, including natural compounds.

Biological activity of compounds with the geminal fragment N—C—Si

Screening and molecular design are the two different approaches to search for biologically active compounds, including silicon derivatives.[5,7—9] The first approach is based on random choice, but it allows chemists to reveal the biological properties of the synthesized compounds. Molecular design assumes the target modification of an organic compound with the known biological activity by both the introduction of the silyl group into any position of the molecule and the bioisosteric replacement of one of the carbon atoms of the skeleton by silicon. Bioisosteric replacement is one of the most fortunate approaches of molecular design, which is successfully used in medicinal chemistry,[25—28] and carbon and silicon atoms represent a classical example of bioisosteres (see, *e.g.*, Ref. 26). Differences in electronegativity and covalent radii of silicon and carbon atoms result in a change in the stereoelectronic properties of the molecule, providing a change in the chemical behavior and physiological activity of the compound.[5,9] The introduction of the silicon atom in the molecule enhances lipophilicity of the molecule, which increases its bioaccessibility.

N-(Silylmethyl)amines and their salts

The first representatives of amines containing the silyl group in the geminal position were synthesized in 1951.[29,30] In spite of the opinion popular in the middle of the last century that silicon compounds are biologically inert, (1-aminoethyl)dimethylphenylsilane hydrochloride **1**, isostructural analog of sympathomimetic amine **2**, was synthesized[31] as early as in 1964. This work supported by the US National Institute of Health became one of the first studies devoted to investigation of bioisosterism of silicon. Amines **1** and **2** differed in acidity (pK_a 10.26



1, **2**

M = Si (**1**), C (**2**)

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Table 1. Insectorepellent activity of compounds **3—11** of the general formula $Bu_2NCH_2SiMe_{3-n}(OR')_n$

Compound	R′	*n*	Coefficient of repellent action (%) at consumption/g m^{-2}			Duration of action, days at consumption/g m^{-2}	
			5	20	40	20	40
3	$Bu_2NCH_2CH_2$	1	96	93	93	12	22
4	MeC(O)	1	90	91	95	12	22
5	Et	1	98	98	100	13	20
6	Et	2	90	96	98	5	10
7	Et	3	90	94	75	28	85
8	Me	3	65	77	75	28	28
9	Pr	3	53	55	82	0	13
10	Bu	3	34	75	76	0	1
11	Me_3Si	1	90	97	96	5	10

and 9.73, respectively); however, their biological activity and toxicity did not substantially differ (LD_{50} 102—107 and 105—113 mg kg^{-1}, respectively).

A considerable number of *N*-(silylmethyl)amines, their hydrochlorides, and iodomethylates were synthesized and studied during several decades. It turned out that these compounds exhibit surprisingly diverse biological activity.

Insectorepellent activity

A broad variety of (organylaminomethyl)alkoxysilanes $R_2NCH_2SiMe_{3-n}(OR')_n$ with a wide range of substituents at the nitrogen and silicon atoms was synthesized and their biological activity was studied.[1,32—36] *N*-(Organylaminomethyl)triethoxysilanes $R_2NCH_2Si(OEt)_3$ manifest insectorepellent activity with respect to the insectary culture of fleas *X. Cheopis*, which depends on the nature of radicals at the nitrogen atom and decreases in the following order for the fragments R_2N—: Bu_2N— > Me_2N— > $(C_5H_{11})_2N$— > AllNH— > BuNH— > 2-furfurylamino > > PhNH— > $(i\text{-}C_5H_{11})_2N$— > perhydroazepino > $Bu^i{}_2N$— > > Pr_2N— > $(CH_2)_5N$— > $O(CH_2CH_2)_2N$— > > Et_2N—.[1,32,33] The highest coefficient and duration of repellent action were observed for (*N*,*N*-dibutylaminomethyl)triethoxysilane. The substituents at the silicon atom also exert an effect on the insectorepellent activity. For example, compound **5** exhibits the highest activity in the series of compounds **3—11** of the general formula $Bu_2NCH_2SiMe_{3-n}(OR')_n$ (Table 1).

Triethyl(piperidinomethyl)silane hydrochloride $(CH_2)_5NCH_2SiEt_3 \cdot HCl$ exhibits the insecticide effect: its use in a concentration of 0.06% decreases fertility of cereal moth *Silotroga cerealella* Oliv. by 84% due to the chemosterilizing effect.[1]

Fungistatic, antimicrobial, herbicidal, and biostimulating activity

N-(Silylmethyl)amines **12—14** and ammonium salts **15—17** containing various substituents at the nitrogen and

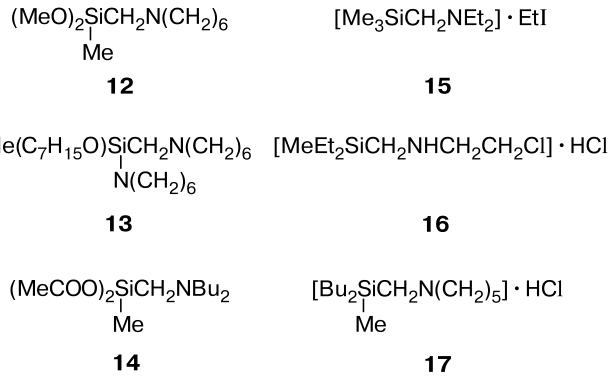


Table 2. Minimum concentration (μg mL^{-1}) of *N*-(silylmethyl)amines **12—17** at which the growth of various microorganisms is suppressed

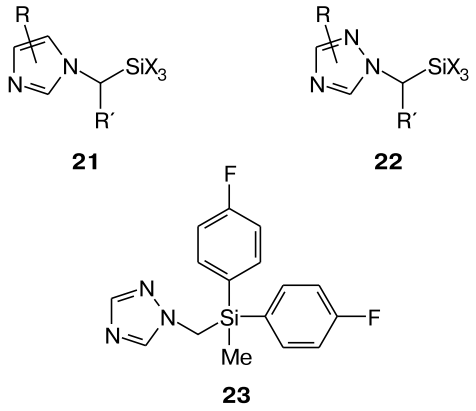
Compound	*Candida aibicans*	*Epidermophyton* Kaufman Wolf	*Trichophyton Gypseum*	*Staphylococcus aureus haemoliticus*	*Bac. Mycoides*	*Escherichia coli*	*Proteus vulgaris i*	*Ps. Aeruginosa*
12	>83.3	>83.3	>83.3	166	333	>250	>250	166
13	>83.3	>83.3	>83.3	333	666	>250	>250	250
14	>83.3	>83.3	>83.3	41	83	250	>250	166
15	>83.3	55.6	55.6	—	—	—	—	—
16	>83.3	>83.3	>83.3	—	—	—	—	—
17	>400	>400	200	266.6	266.6	—	—	—

silicon atoms possess fungistatic and antimicrobial activity[34,35] (Table 2).

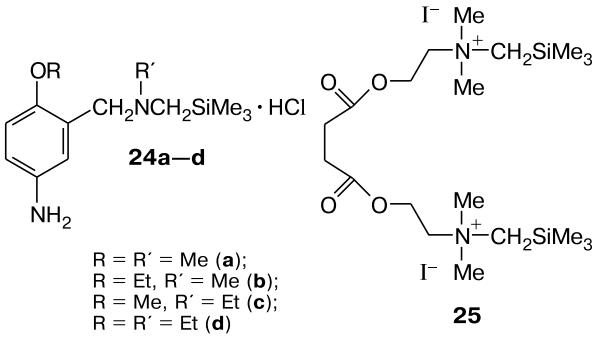
Hetarylaminomethylsiloxane iodomethylates **18—20** also exhibit antimicrobial and fungistatic activity[36] (Table 3). It was marked[36] in an analysis of the dependence of the antimicrobial activity on the structure of the studied compounds that the character of the nitrogen-containing heterocycle exerts the main effect. The growth of gram-positive bacteria on the strains *Staphylococcus aureus* 209 is retarded in the following order of heterocycles: pyrrolidine < hexamethyleneimine < *N*-methylpiperazine. Unfortunately, the authors of this work present no comparative (own or literature) data on the antimicrobial activity of the nitrogen-containing heterocycles. Antimicrobial activity is studied in aqueous media, but the Si—C bond in geminal amines $RR'NCH_2SiX_3$ and their salts is readily cleaved by hydroxyl-containing agents to form the corresponding derivative of methylamine RR´NMe.[37,38] It is not excluded that the results obtained are incorrect and show the antimicrobial activity of the heterocyclic amines formed upon hydrolysis. For example, it is known that piperazine fragment is present in molecules of antibacterial drugs such as urosept and ciprofloxacin.

N-(Silylmethyl)imidazoles **21** (see Refs 39—42) and -1,2,4-triazoles **22** (see Refs 42—54) containing various substituents both in the organic fragment and at the silicon atom exhibit bactericidal and fungicidal activity. They are fungicides of a wide range of effect and in concentrations of 10—200 mg L^{-1} efficiently suppress the growth of *Puccinia recondita*, *Sphaerotheca fuliginea*, *Erisyphe graminis*, *Podosphaera leucotricha*, *Venturia inaequalis*, *Puricularia orizae*, *Cercosporidium personatum*, *Bipolaris ryzae*, *Cercospora beticola*, *Monalinia fructicola*, and *Rhizoctonia solani*. Among these compounds, [bis(4-fluorophenyl)]-methyl[(1*H*-1,2,4-triazol-1-yl)methyl]silane (flusilazole) **23** [44,50—52] inhibition ergosterol biosynthesis[55,56] is most known. This compound is used in agriculture for the protection of cereals and oil-bearing crops, wines, fruit trees, bananas, sugar-beet, and corn from pathogenic fungi *Spaerotheca fuliginea*, *Venturia inaequalis*, *Cercospora canescens*, *Septoria nodorum*, *Pyrenophora teres*, *Cochliobolus sativus*, *Pseudocercosporella herpotrichoides*, *Puccinia recondita*, and *Erisiphe graminus*.

N-Alkyl-*N*-trimethylsilylmethyl-5-amino-2-alkoxybenzylamine hydrochlorides **24a—d** have herbicidal activity.[57] Diammonium derivative **25** manifests stimulating activity in a concentration of 10^{-4}—10^{-7} mol with respect to biosynthesis of lysine, nucleic acids, protein, and adenylate kinase enzyme (on lysine producent *Brevibacterium* 22l).[58]



R = H, Alk, Ar, CH_2Ar, $CH{=}CH_2$; R´ = H, Alk; SiX_3 = $SiAlk_nAr_{3-n}$



Antioxidant and hypocholesterol activity

N-Silylmethylated aromatic amines **26a—e** *in vitro* are powerful inhibitors of the copper-induced trans-oxidation of human cholesterol LDL.[59,60] The degree of trans-oxidation of lipids was measured and compounds **26a,b** were determined to be most efficient as antioxidants (Table 4). Their inhibition effect is comparable to the action of the well known antioxidants, vitamin E and probucol. Organosilicon amine **26a** is more than ten times efficient than its carbon analog (see Table 4, compound **26f**). Dis-

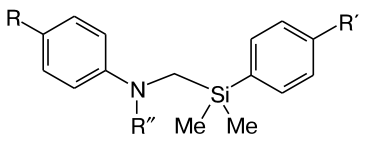
Table 3. Minimum concentration (μg mL^{-1}) of hetarylaminomethylsiloxanes **18—20** at which the growth of various microorganisms is suppressed[36]

Compound	*Staphylococcus aureus haemoliticus*	*Escherichia coli*	*Ps. Aeruginosa*
$[(Me_3SiO)_3SiCH_2N^+Me(CH_2)_4]\cdot I^-$ (**18**)	250	>500	>500
$[(Me_3SiO)_3SiCH_2N^+Me(CH_2)_6]\cdot I^-$ (**19**)	15.6	>500	500
$[(Me_3SiO)_3SiCH_2N^+Me(CH_2CH_2)_2NMe]\cdot I^-$ (**20**)	1.96	250	250

Table 4. Comparative antioxidant activity of compounds **26a—f**

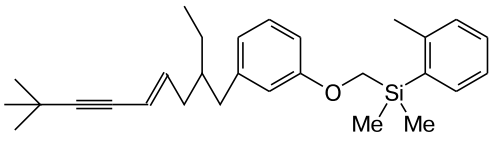
Compound	R	R′	R″	IC_{50} /μmol L^{-1}
26a	H	H	H	7.8
26b	OMe	H	H	3.0
26c	H	H	Et	15
26d	CF_3	H	Et	~100
26e	H	CF_3	Et	20
$PhNHCH_2CMe_2Ph$ (**26f**)	—	—	—	100
Vitamin E	—	—	—	10
Probucol	—	—	—	5.3

tinctive properties of *N*-(silylmethyl)amines are the enhanced basicity and a low ionization potential of the nitrogen atom.[61—64] This provides their antioxidant properties: compounds **26a—e** are oxidized much more rapidly than lipids. The efficiency of amine **26b** as an antioxidant is considerably higher than that of amine **26d**, because the replacement of the electron-donating methoxy group by the electron-withdrawing trifluoromethyl group in the aniline aromatic ring results in an increase in the ionization potential of amine and a lower stability of the amine radical cation that formed upon oxidation.



26a—e

Compound **27** is an efficient inhibitor of squalene epoxidase, which is the key enzyme in cholesterol biosynthesis.[65] The replacement of the oxygen atom in this molecule by the nitrogen atom resulted in the formation of a powerful oral inhibitor of squalene epoxidase **28** with the antioxidant properties,[60] which is potentially suitable for the treatment of atherosclerosis.



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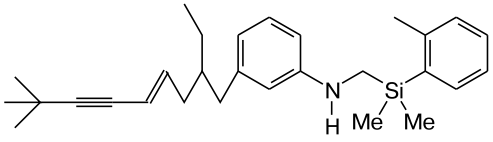
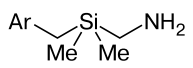


28

Inhibitors of monoaminooxidase

The oxidative deamination of endogenic monoamine neuromediators, such as dopamine, serotonine, adrenaline, or noradrenaline, and trace amines, for example, phenylethylamine, as well as a series of amine xenobiotics, proceeds under the action of flavin-containing enzyme of monoaminooxidase (MAO), which exists in two forms: MAO-A and MAO-B.[66—68] These forms differ in tissue distribution, structure, and substrate specificity. The form MAO-A has a higher affinity to serotonine, octopamine, adrenaline, and noradrenaline, while the form MAO-B has a higher affinity to phenylethylamine and tyramine; dopamine is deaminated by the both forms.[69,70] The enzyme MAO-B is widely distributed in the organism, including brain.[71] The activity of MAO significantly increases in the brain with aging, especially for patients with Alzheimer´s and Parkinson´s diseases. Inhibitors of monoaminooxidases are used for the treatment of a series of neuropsychical diseases.[70,72]

The ability of *N*-(silylmethyl)amines to inactivate the enzyme MAO has first been discovered for substituted (benzylsilyl)-methylamines **29**.[73—76] The test to MAO of the rat brain showed the powerful, irreversible, and selective to MAO-B (selectivity MAO-B/MAO-A ≈ 10^4)[74] inhibition activity of these compounds.

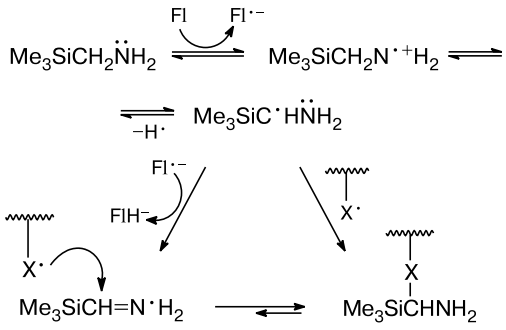


29

Ar = Ph, 4-ClC_6H_4, 4-FC_6H_4, 2,4-$F_2C_6H_3$

(Alkylsilylmethyl)amines, including the simplest of them, $NH_2CH_2SiMe_3$, are also efficient inhibitors of MAO.[77,78] The study of the mechanism of MAO inactivation by *N*-(silylmethyl)amines[77—81] showed that the key stage of this process is the reaction of one-electron transfer between the amine and flavin-containing fragment of the enzyme, which is provided by the low ionization potential of the nitrogen atom of amine. Based on the results obtained, the authors suggested that the deprotonation of the *N*-(silylmethyl)amine radical cation is more preferential and proposed[78] a possible mechanism of its further transformation into the product of C-alkylation of MAO with *N*-(silylmethyl)amine (Scheme 1).

Scheme 1



Fl is flavin-containing fragment of enzyme, X is residue of MAO

Cholinolytic and neurotropic activity

Cholinoblockers (cholinolytics) are widely used in medical practice. They are drugs that block central and peripheral cholinoreceptors. Nicotine- and muscarine-sensitive cholinoreceptors (n- and m-cholinoreceptors, respectively) are distinguished and, correspondingly, n- and m-cholinoblockers. n-Cholinoblockers are subdivided into ganglioblockers (block n-cholinoreceptors of vegetative ganglia) and curare-like remedies (block n-cholinoreceptors of skeletal muscles). The following types are distinguished among m-cholinoreceptors: m_1-cholinoreceptors in the central nervous system (CNS) and in vegetative ganglia; m_2-cholinoreceptors in the heart; m_3-cholinoreceptors in smooth muscles and in the most part of endocrine glands; m_4-cholinoreceptors in the heart, wall of lung alveoli, and CNS; and m_5-cholinoreceptors in the CNS, salivary glands, iris, and mononuclear blood cells.[82] Search for selective cholinoblockers is an important task of experimental pharmaceutical chemistry and, hence, it is not surprising that a series of synthesized *N*-(silylmethyl)amines was tested to cholinolytic activity.

Ammonium salts of siloxanes **30a—f** are[83,84] analogs of ammonium salts of organic diamines, which are widely used in medicine for muscular system weakening. The curare-like effect was detected for the isolated nerve-muscle preparation: compound **30b** in a concentration of 10^{-4} g mL^{-1} suppresses the amplitude of muscle traction by 80%. The elongation of the siloxane chain enhances this effect.[84] These compounds are highly toxic, which is characteristic of curare-like compounds (LD_{50} is 2—35.8 mg kg^{-1} for intraperitoneal injection to white mice), and it increases with an increase in the number of siloxane units.[84]

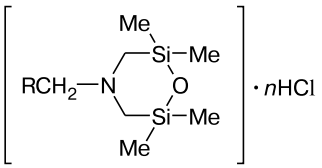
$[R_3N^+CH_2(SiMe_2O)_nSiMe_2CH_2N^+R_3] \cdot 2X^-$

30a—i

30	R	X	*n*	30	R	X	*n*
a	Et	Cl	1	**f**	Me	Cl	1
b	Et	I	1	**g**	Me	Cl	2
c	Et	I	3	**h**	Me	Cl	3
d	Me	I	1	**i**	Me	Cl	4
e	Et	I	2				

4-Organyl-4-aza-1-oxa-2,6-disilacyclohexanes and their salts **31** are muscle relaxants.[85—87]

N-(Silylmethyl)diamine iodomethylates **32a—d** also manifest curare-like activity similar to that of their carbon analogs.[88,89] In authors´ opinion, this is related to their spatial structure. The calculated distances between the nitrogen atoms in the both series of compounds are close: for example, for compounds **32a—c** $d_{N...N}$ are 12.3, 13.5, and 14.8 Å, respectively; while for their carbon analogs $d_{N...N}$ are 12.5, 13.8, and 15.0 Å.[89]



31a—n

31	R	*n*	31	R	*n*
a	4-ClC_6H_4	0	**h**	4-$Me_2NCH_2C_6H_4$	1
b	4-FC_6H_4	1	**i**	3-ClC_6H_4	1
c	4-MeC_6H_4	1	**j**	3-MeC_6H_4	1
d	4-$MeOC_6H_4$	1	**k**	2-ClC_6H_4	1
e	3,4-$Cl_2C_6H_3$	0	**l**	2-Pyridyl	0
f	3-$CF_3C_6H_4$	1	**m**	$O(CH_2CH_2)_2NCH_2$	0
g	4-$Me_2NC_6H_4$	0	**n**	2-Thienyl	0

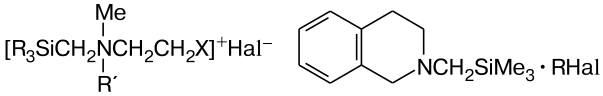
$[MeR_2N^+CH_2Si(CH_2)_nSiCH_2N^+R_2Me] \cdot 2I^-$

32a—d

R_2N = Me_2N, *n* = 4 (**a**), 5 (**b**), 6 (**c**);
R_2N = $(CH_2)_5N$, *n* = 5 (**d**)

Compounds **30f—i** also have ganglioblocking activity and they are reversible inhibitors of cholinesterase.[84] These compounds differ from their carbon analogs by a higher selectivity of cholinesterase activity to butyrylcholinesterase.

N-Silylmethylated choline derivatives **33** manifest n-cholinolytic activity.[90] Ammonium salts of *N*-trimethylsilyltetrahydroisoquinoline **34b** and *N*-organyl-1-dimethylsilatetrahydroisoquinolines **35** and **36** possess very weak curare-like, ganglioblocking activity and hypotensive effect (Table 5).[91]



33a—f **34a,b**

33	R_3Si	R´	X	Hal
a	Me_3Si	Me	OH	I
b	Et_3Si	Me	OH	I
c	Me_3Si	H	Cl	Cl
d	Me_3Si	Me	Cl	I
e	$MeEt_2Si$	Me	Cl	I
f	Me_3Si	Me	O(O)Me	I

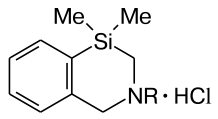
34: RHal = HCl (**a**), MeI (**b**)

1-Cyclohexyl-2-(*N*-methylpiperazin-1-yl)-1-phenylethanol sulfomethylate (**37**) (Hexocyclium) is an efficient m-cholinoblocker.[92,93] The first silicon-containing analogs of this compound, (*N*-methylpiperazinomethyl)-arylcyclohexylsilanol sulfomethylates **38a**,**b**, were synthesized in the late 1980s.[94—96] The pharmacological studies showed that the bioisosteric replacement C/Si gave no

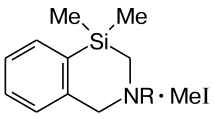
Table 5. Curare-like ganglioblocking activity and the hypotensive effect of compounds **34b**, **35c,d**, and **36a**,**b**,**d**—**g**

Compound	Curare-like activity	Ganglioblocking activity	Hypotensive effect
	ED_{50}/mg kg^{-1}		ED_{30}/mg kg^{-1}
34b	>2.0	—	1.8
35c	>1.0	—	1.5
35d	>1.0	—	0.45
36a	>1.2	0.38	0.2
36b	>2.0	0.45	0.4
36d	≥1.0	—	1.0
36e	>4.0	—	~2.5
36f	≥1.8	—	0.2*
36g	>1.2	~1.2	1.5

* ED_{20}.



35a—f

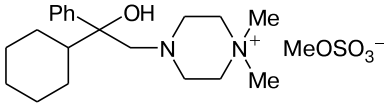


36a—g

35	R
a	Pr
b	$(CH_2)_2OH$
c	$(CH_2)_2Cl$
d	$(CH_2)_2OC(O)Ph$
e	$(CH_2)_2OC(O)Me$
f	$(CH_2)_2NMe_2$

36	R
a	Pr
b	$(CH_2)_2OH$
c	$(CH_2)_2OC(O)Ph$
d	$(CH_2)_2OC(O)Me$
e	$(CH_2)_3SiMe_3$
f	$(CH_2)_2NMe_2$
g	$C_{16}H_{33}$

substantial change in the properties. Compounds **38** exhibit a high inhibition activity toward various muscarinic receptors.[94,97—106]



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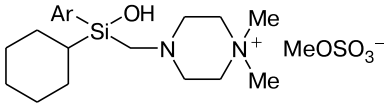


38a—d

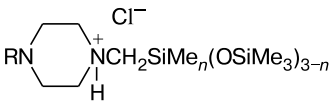
38: Ar = Ph (**a**), 2-$MeOC_6H_4$ (**b**), 4-ClC_6H_4 (**c**), 4-FC_6H_4 (**d**)

Compounds **34**—**36** exert a neurotropic effect: they increase the lifetime of mice under the hypoxia conditions and enhance the effect of hexanal narcosis[91] (Table 6). Hydrochlorides **39a**—**c** and iodomethylates **18**—**20** of hetarylaminomethylsiloxanes[36] also exhibit analogous properties (see Table 6).

Table 6. Neurotropic activity of compounds **18**—**20**, **34a**, **35a**—**f**, **36e**, and **39a**—**c**

Compound	Toxicity*, LD_{50}/mg kg^{-1}	M ± m** (% to reference)	
		Hypoxia	Hexenal narcosis
18	58	318.4	117.3
19	22.4	146.2	87.7
20	—	133.6	124.3
34a	163	—	116.9
35a	70.8	232.9	104.2
35b	72	192.6	175.4
35c	163	194.5	154.8
35d	365	116.3	95.8
35e	103	171.7	83.1
35f	141	139.4	154.9
36e	70	—	152.7
39a	224	125.0	168.4
39b	224	173.3	186.6
39c	2240	161.4	180.0

* On mice of the line BALB/c.
** M and m are the arithmetical values of the parameter and the standard error, respectively.



39a—c

R = Me, n = 1 (**a**); R = Me, n = 0 (**b**); R = Ph, n = 0 (**c**)

Antitumor activity

A complex of 1,3-diamino-2,2-dimethylpropane with $PtCl_2$ ($Me_2C(CH_2NH_2)_2 \cdot PtCl_2$, cisplatin) suppresses tumor growth. *N*-(Silylmethyl)amines form analogous complexes **40**—**43** with the Pt^{II} and Pt^{IV} salts,[107—109] including the full analog of cisplatin: compound **41a** (silaplatinum).

The pharmacological studies showed that these compounds have a wide range of antitumor activity and efficiently inhibit both the growth *in vitro* of leukemia cells (CCRF-CEM, HL-60(TB), K-562, MOLT-4, RPMI-8226), lung carcinomas (DMS-114, DMS 273), large intestine carcinomas (COLO 205, HCC-2998, DLD-1, HCT-15, HCT-116, HT29, KM12, KM20L2, SW-620), and melanoma (LOX IMVI, MALME-3M, M14, M19-MEL, SK-MEL-2, SK-MEL-5, SK-MEL-28, UACC-62, UACC-257) and *in vivo* of leukemia cells L1210 (mice) (Tables 7 and 8).[107,108]

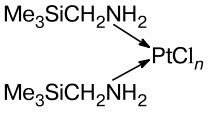
1-[(1-Tetrahydroquinolyl)methyl]silatrane (**44**) in doses of 10—45 mg kg^{-1} elongates the mice lifetime by 50—140%, suppressing leukemia L5178.[110]

Hydrochlorides **39a**—**c** and iodomethylates **18**—**20** of hetarylaminomethylsiloxanes have no antitumor activity to lympholeucosis P388 Lewis lung carcinoma.[36]

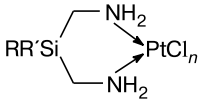
Table 7. Activity of complexes **40a,b**, **41a—f**, and **43a—d** *in vitro*[107]

Compound	$-\log GL_{50}$	$-\log TGI$	$-\log LC_{50}$	Compound	$-\log GL_{50}$	$-\log TGI$	$-\log LC_{50}$
40a	5.35	4.72	4.07	**41f**	5.52	4.33	4.02
40b	5.23	4.64	4.06	**43a**	4.50	4.05	4.00
41a	4.69	4.08	4.01	**43b**	5.35	4.31	4.00
41b	5.32	4.38	4.02	**43c**	4.93	4.17	4.01
41c	5.49	4.50	4.03	**43d**	5.38	4.30	4.01
41d	5.21	4.40	4.02	Cisplatin	5.35	4.45	3.35
41e	4.71	4.09	4.01				

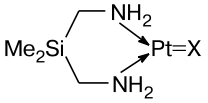
Note. $\log GL_{50}$ is logarithm of the concentration at which tumor growth is inhibited by 50%; logTGI is logarithm of the concentration at which tumor growth is inhibited by 100%; $\log LC_{50}$ is logarithm of the concentration killing 50% of cancer cells.



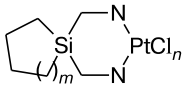
40a,b



41a—f



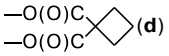
42a—d



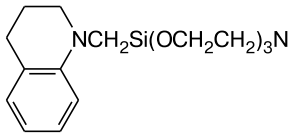
43a—d

40: n = 2 (**a**), 4 (**b**)

41	R	R´	n	**41**	R	R´	n
a	Me	Me	2	**d**	Me	Et	4
b	Me	Me	4	**e**	Et	Et	2
c	Me	Et	2	**f**	Et	Et	4

42: X = I_2 (**a**), SO_4^{2-} (**b**), OC(O)C(O)O (**c**),  (**d**)

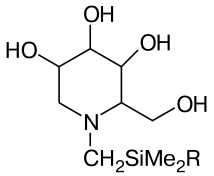
43: m = 1, n = 2 (**a**); m = 1, n = 4 (**b**); $m = n$ = 2 (**c**); m = 2, n = 4 (**d**)



44

Other types of biological activity

1,5-Dideoxy-1,5-imino-D-sorbitol hydrochloride inhibits digestion enzyme α-amylase, which is responsible for starch cleavage to oligosaccharides. The replacement of the carbon atom by the silicon atom enhances lipophilicity of the molecule. Therefore, *N*-silylmethyl-substituted derivatives of 1,5-dideoxy-1,5-imino-D-sorbitol **45a—c** were synthesized.[111] It turned out that these compounds selectively and with high rate deactivate the



45a—c

R = Me (**a**), Pr (**b**), Ph (**c**)

Table 8. Antitumor activity of compounds **41a,b** and **42b,c,d** against leukemia L1210 *in vivo*[108]

Compound-	Dose/mg kg^{-1}											
	5			10			15			20		
	T/G	S/T	MST	T/G	S/T	MST	T/G	S/T	MST	T/G	S/T	MST
41a	>273	1/4	21.5	>330	2/4	22.5	>302	2/4	16.3	>327	2/4	16.8
41b	—	—	—	—	—	18.5	—	—	21	—	—	—
42b	>271	1/4	—	>297	2/4	—	165	0/4	—	106	0/4	—
42c	152	0/4	—	197	0/4	—	144	0/4	—	—	—	—
42d	—	—	—	—	—	11.0	—	—	—	—	—	12.0
Cisplatin	242	0/4	—	—	—	17.3	—	—	—	—	—	15.0
Reference	—	—	8.6	—	—	—	—	—	—	—	—	—

Note. T/G (%) = (T/G)·100% is an increase in the lifetime in the tested group (T) with respect to the reference group (G); S/T is the ratio of the number of survived mice after 30 days (S) to the total number of tested mice (T); MST/days is the average lifetime.

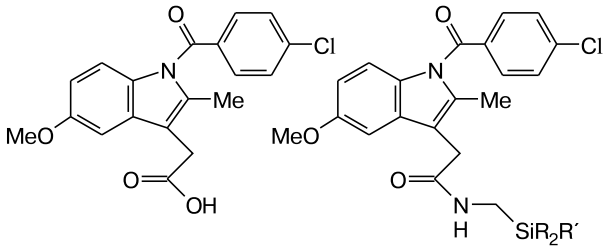
digestion enzyme and are potentially suitable as oral drugs against diabetes.

4-Organyl-4-aza-1-oxa-2,6-disilacyclohexanes and their salts **31** also exert a contraceptive effect suppressing spermatogenesis in animal males.[112]

N-(Silylmethyl)carboxamides

Inhibitors of enzymes

Cyclooxygenase (COX) is the heme-containing membrane-bound enzyme that transforms arachidonic acid into prostaglandins. Two forms of this enzyme exist in the human organism: COX-1 and COX-2. The pharmacological inhibition of cyclooxygenase weakens inflammation and pain symptoms. Widely known drugs aspirin, iburpofen, and indometacin **46** manifest the high inhibition activity toward COX. The latter is an indolylacetic acid derivative and one of the most active non-steroid anti-inflammatory drugs used in medicine. Synthesized *N*-(silylmethyl)amides of indometacin **47a,b** inhibit COX more weakly that indometacin (Table 9).[10,113—115] However, the selectivity of compound **47b** to COX-2 is considerably higher than that of indometacin.



46 **47a,b**

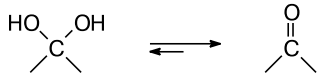
47: R = R′ = Me (**a**); R = Me, R′ = Ph (**b**)

Proteolytic enzymes (proteases) cleave the peptide bond between amino acids of proteins. The synthesis of drugs inhibiting proteases is the most important task of the modern medicinal chemistry.[116] Inhibitors of proteases contain amide bonds, and the inhibition process proceeds through the protonation of the carbonyl carbon atom to form an intermediate containing two hydroxyl groups at one carbon atom. It is well known that 1,1-diols are unstable and are usually rapidly dehydrated to form the carbonyl carbon atom (Scheme 2).

Table 9. Inhibition of COX by compounds **46** and **47a,b**

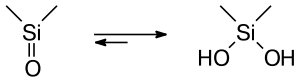
Compound	IC_{50}/mol L^{-1}	
	COX-1	COX-2
46	$4.7 \cdot 10^{-8}$	$5.9 \cdot 10^{-7}$
47a	$2.7 \cdot 10^{-6}$	$3.9 \cdot 10^{-7}$
47b	$1 \cdot 10^{-5}$	$3.1 \cdot 10^{-7}$

Scheme 2



The chemistry of silicon differs sharply from the chemistry of carbon; silanones are very unstable compounds, and the equilibrium is shifted to the formation of silanediols (Scheme 3),[117] which can form strong hydrogen bonds.

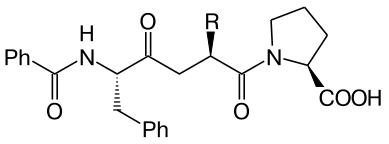
Scheme 3



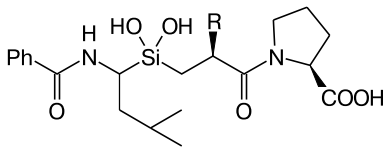
The bioisosteric replacement of the carbonyl carbon atom in the polypeptide chain of the inhibitor by the group $Si(OH)_2$ resulted in the preparation of new inhibitors of proteases.[118—125] The first representatives of such silanediols were synthesized as a mixture of diastereomers as analogs of model ketones **48a**,**b**, which suppress the angiotensin-converting enzyme (ACE).[118,119] The ACE is the enzyme circulating in the exocellular space (exopeptidase), which catalyzes the cleavage of angiotensin decapeptide I to angiotensin octapeptide II. Angiotensins I and II control the arterial blood pressure in the organisms. The inhibition activity of compounds **49** by ~14 times lower than that of model ketone **48**. It is assumed that this is reasoned by both the replacement of the benzyl group by isopropyl and the fact that the test was carried out with a mixture of diastereomers **49**. Further studies showed that the inhibition activity with respect to ACE of three stereoisomers of ketone **48** is somewhat higher (IC_{50} = = 1—46 nmol) than that of the corresponding stereoisomers of its silicon analog **50** (IC_{50} = 3.8—207 nmol). However, stereoisomer (2*R*,5*S*)-**50** exhibits considerably higher inhibition activity than its carbon analog (IC_{50} 72 and 3200 nmol, respectively).[120—122]

One of the most studied enzymes is thermolysine[126] produced by bacteria *Bacillus thermoproteolytics* and widely used for protein structure determination. Thermolysine is classified as a thermostable metalloproteinase and contains zinc and calcium ions. Compound **51a** (derivative of phosphoric acid amide) is an efficient inhibitor of thermolysine. Its activity is 1000 times higher than that of the corresponding ester **51b**.[122]

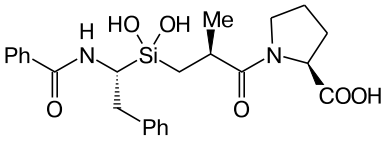
One of the reason of such a drastic distinction is a possibility of hydrogen bonding by the group —NH—P(O). Silanediol **52** (silicon analog of compound **51a**) capable of hydrogen bonding has inhibition activity close to that of



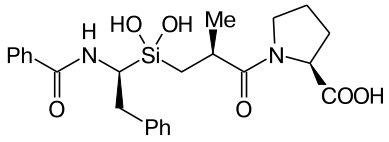
48a,b



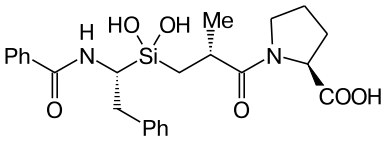
49a,b



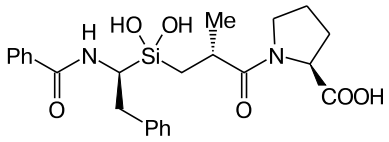
(2*S*,5*R*)-**50**



(2*S*,5*S*)-**50**

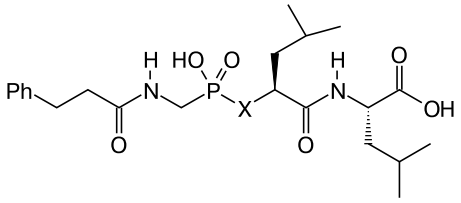


(2*R*,5*R*)-**50**

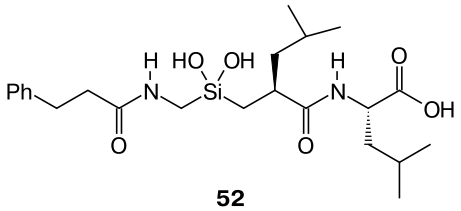


(2*R*,5*S*)-**50**

48, **49:** R = H (**a**), Me (**b**)



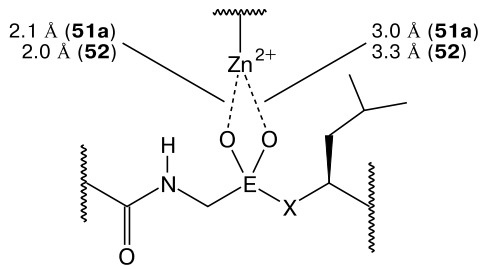
51a,b



52

X = NH (**a**), O (**b**)

compound **51a**.[122–125] The X-ray diffraction study of the structures of complexes of compounds **51a** and **52** with thermolysine showed that, in both cases, complexation proceeds between the zinc-containing region of the enzyme and the silicon- or phosphorus-containing group. The both complexes have similar structures and, interestingly, the distances between the oxygen and zinc atoms in both structures are almost identical.[121,125]

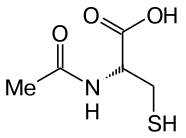


β-Lactamases (group of bacterial enzyms) are aimed at struggling with β-lactame antibiotics and induce the formation of bacterial strains resistant to these antibiotics. One of the methods of struggling against this process is the use of inhibitors of β-lactamases in medical practice. Search for these inhibitors is an important task of the modern medical chemistry. Phenylacetic acid *N*-(trihydroxysilylmethyl)-amide ($PhCH_2C(O)NHCH_2Si(OH)_3$) exhibits a weak inhibition activity with respect to β-lactamase *Enterobacter cloacae* P99.[127]

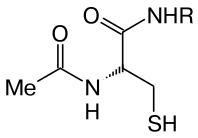
Other types of biological activity

N-(Silylmethyl)amides of indometacin **47a,b** *in vitro* possess a powerful antiproliferative effect. They suppress cell growth of human pancreatic carcinoma *MiaPaCa-2* at considerably lower concentrations than indometacin (IC_{50} < 6.0 μmol and IC_{50} > 100 μmol, respectively).[113,115,128]

N-Acetyl-L-cysteine **53** has a wide range of biological action on the organism and is used in medical practice as a mucolytic, antibiotical, and detoxication drug. In addition, compound **53** is a strong antioxidant. The study showed that *N*-(silylmethyl)amides of *N*-acetyl-L-cysteine **54** are stronger antioxidants than compound **53** due to an increase in lipophilicity of the molecules and, as a consequence, their bioaccessibility.[129,130]



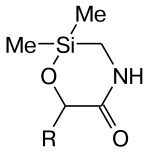
53



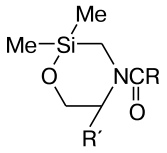
54a,b

54: R = CH_2SiMe_3 (**a**), CH_2SiMe_2Ph (**b**)

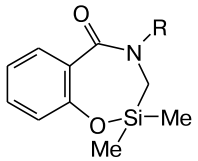
Six- and seven-membered 4-aza-1-oxa-2-silacyclanes **55—57** can find use in medicine as correctors of adaptation mechanisms.[131—133] These compounds are lowly toxic (LD_{50} = 400—500 mg kg^{-1}). The influence on the resistance of mice to the action of sharp hyperbaric hypoxia and acute immersion cooling was studied at doses of (0.025—0.1)LD_{50}. The nature of substituent R in compounds **55** substantially affects the biological effect. For instance, compound **55a** in a dose of 0.05LD_{50} exerts a pronounced antihypoxic effect; however, its action is inefficient under the conditions of acute immersion cooling. The replacement of the methyl group by phenyl gave opposite results: compound **55b** considerably enhances the survival of mice upon cooling, but its action is inefficient for hypoxia. The study of metabolism showed that these compounds affect the biochemical composition of the blood (Table 10).



55a—c



56a—d

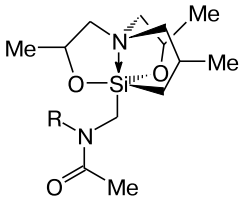


57a,b

55: R = Me (**a**), Ph (**b**), $CMe_2CH_2OSiMe_3$ (**c**)
56: R = Me, R′ = H (**a**); R = Me, R′ = Et (**b**); R = 4-pyridyl, R′ = H (**c**); R = $Me_3SiO(CH_2)_3$, R′ = H (**d**)
57: R = Me (**a**), $(CH_2)_2OSiMe_3$ (**b**)

It is assumed that the hypoalbunemic effect changing the blood viscosity can be a reason for an increase in mice survival for both hypoxia and hyperthermia. An increase in the glucose level upon the injection of compound **55b** is considerably higher than that upon the injection of compound **55a**. The level of triglycerides somewhat decreases upon the injection of compound **55a**, the injection of compound **55b** increases the triglyceride level. Such a change in energy metabolism explains the opposite effect of compounds **55a**,**b** under the conditions of hypoxia and hyperthermia. It is mentioned[133] that compound **55a** is close to ethomersol (antihypoxant with the stress-protector effect, 2-mercaptobenzimidazole derivative) in pharmacological characteristics, while compound **55b** is close to phenazepam (tranquilizer of the benzodiazepine series).

N-(Silatran-1-ylmethyl)acetamides **58a**,**b**, compounds with the hypervalent silicon atom, have recently[134] been synthesized and the data on their biological activity were obtained. These compounds are almost non-toxic (for oral injection LD_{50} > 3000 mg kg^{-1}, and for intraperitoneal injection the values of LD_{50} were 2000 and 3000 mg kg^{-1} for **58a**,**b**, respectively). The injection of these drugs induces diarrhea and death because of bleeding. The preliminary intradermal injection of atropine prevents diarrhea and death of laboratory animals. These compounds exhibit a weak antimuscarinic activity compared to acetylcholin. The values of IC_{50} for compounds **58a**,**b** are close, being ~$7.7 \cdot 10^{-4}$ (for acetylcholin $IC_{50} = 3.3 \cdot 10^{-4}$).



58a,b

R = Me (**a**), $(CH_2)_2OH$ (**b**)

Polyesters with the terminal *N*-(silylmethyl)carbamate or -carbamide group are used in stomatology.[135—137]

Amino acids containing the geminal fragment N—C—Si

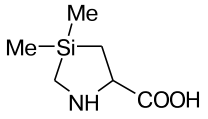
Amino acids are in the composition of proteins and enzymes and play the key role in biochemical processes that occur in living organisms. They are used in pharmaceutical, food, and agrochemical industry. O,N-Silylated amino acids are known from the middle of the XX century, and the use of silyl protective groups is widely applied in the chemistry of amino acids. However, the chemistry of amino acids containing the silicon groups bound to the carbon atom is being developed actively during the recent decade.[138] These compounds are rather promising for the preparation of pharmaceuticals of the new generation. A series of publications is devoted to the methods of synthesis and chemical properties of amino acids containing

Table 10. Influence of compounds **55a,b** on the biochemical composition of blood

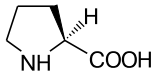
Compound	Total protein	Albumins	Globulins	Glucose	Uric acid	Creatinine	Triglycerides
	g L^{-1}			mg dL^{-1}			
55a	105	66	175	118	121	67	93
55b	93	78	123	144	97	35	112

the group Si—$(C)_n$—N. The problems of bioisosteric replacement C/Si for amino acids with the fragment Si—$(C)_2$—N were also considered.

Biological activity of amino acids containing the geminal fragment Si—C—N is rather poorly studied. Among them, derivatives of silaproline (Sip) **59**, analog of proline **60**, are most studied. Their first representatives were synthesized in 2000.[139]

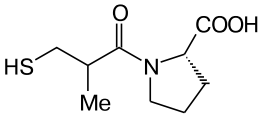


59

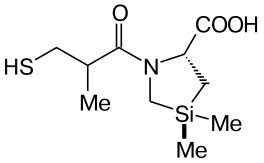


60

Captopril **61** is an inhibitor of ACE and is widely used in modern therapy for the treatment of arterial hypertension. Synthesized silicon-containing analog of silacaptopril **62** is also capable of complete inhibiting ACE.[140] The concentration dependences of the inhibition activity for compounds **61** and **62** are similar. The value of IC_{50} for silacaptopril is lower than that for captopril (43 and 6.3 nmol, respectively).



61



(*R*/*S*,*R*)-**62**

Neurotensin is a neuropeptide possessing a hormonal action and providing a hypotensive effect.[141] Peptide H-Lys-Lys-Pro-Tyr-Ile-Leu-OH (**63**), neurotensin analog, is active only in the presence of the protease inhibitor, whereas the silicon analog H-Lys-Lys-Sip-Tyr-Ile-Leu-OH (**64**) has intrinsic activity.[142] The replacement of proline in the peptide chain by silaproline diminishes the affinity to peptide binding with neurotensin receptors hNTR1 and hNTR2 (Table 11). For example, the activity of compound **64** toward hNTR1 decreases by 100 times, while toward hNTR2 it decreases by 5 times compared to neurotensin. Peptide H-Lys-Lys-Pro-Tyr-TMS-Ala-Leu-OH (**65**), analog of peptide **63** in which isoleucine is replaced by 3-trimethylsilylalanine, manifests very low activity toward neurotensin receptors. In this case, the second bioisosteric replacement of silaproline in compound **65** results in almost inactive compound **66**.

It was experimentally shown that the replacement of proline in the peptide chain by silaproline enhances the resitance of the compounds to biodegradation.[142,143] The bioisosteric replacement of the glycine residue by silaproline in peptide H-RPKPQQFFGLM-NH_2 afforded the compound with the high resistance toward the ACE enzyme.[143]

Cell-penetrating peptides makes it possible to deliver physiologically active molecules to the cell and can be used as drug mediators. Therefore, search for peptides with a more powerful penetrating effect is the most important task of the modern medicinal chemistry. The replacement of proline in peptide CF$(VRLPPP)_3$ (**67**) by silaproline (peptide CF-VRLPPSip$(VRLPPP)_2$ (**68**)) does not change the secondary structure of the peptide and does not prevent its aggregation. Such a bioisosteric replacement enhances the amphipathic properties of compound **68** and substantially (by 20 times!) increases the cell permeability of peptide **68** compared to its carbon analog.[144]

Prospects of using *N*-(silylmethyl)amines in the synthesis of drugs

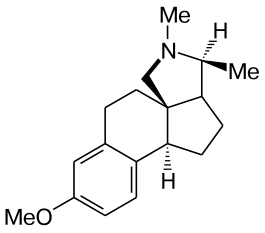
The reactions of 1,3-dipolar intra- and intermolecular cycloaddition of azomethinylides is a promising synthetic direction in the chemistry of pyrrolidine derivatives. The pyrrolidine fragment is in the composition of amino acids (proline and hydroxyproline), some alkaloids, and drugs (for instance, piracetam). The high synthetic potential of intramolecular 1,3-dipolar cycloaddition of azomethinylides makes it possible to construct complicated polycyclic and framework heterocyclic systems including compounds of the natural series.[145—149]

One of the most known and successfully applied methods for azomethinylide generation *in situ* is the desilylation of *N*-(silylmethyl)amines and their derivatives. The enantioselective synthesis of (+)-benzohydrindane **69**, which is a precursor of (+)-conessine **70** (widely known alkaloid ex-

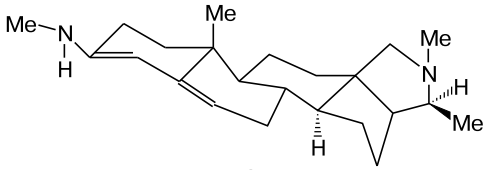
Table 11. Activity of peptides with respect to neurotensin receptors hNTR1 and hNTR2

Peptide	IC_{50}/nmol		IC_{50}(hNTR1)/ /IC_{50}(hNTR2)
	hNTR1	hNTR2	
Neurotensin (NT)	0.16	1.10	0.14
H-Lys-Lys-Pro-Tyr-Ile-Leu-OH (**63**)	0.08	0.47	0.17
H-Lys-Lys-Sip-Tyr-Ile-Leu-OH (**64**)	17.5	5.0	3.50
H-Lys-Lys-Pro-Tyr-TMS-Ala-Leu-OH (**65**)	146.0	133.0	1.10
H-Lys-Lys-Sip-Tyr-TMS-Ala-Leu-OH (**66**)	920.0	238.0	3.87

tracted from the *Holarhena antidysenterica* bark), has earlier[150] been described.



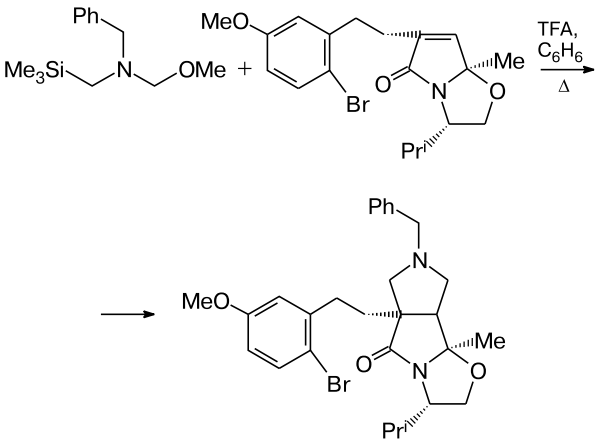
69



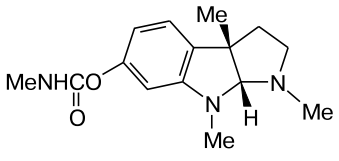
70

The key stage of the synthesis of compound **69** is the diastereoselective intramolecular [3+2] cycloaddition of azomethinylide to the lactame cycle (Scheme 4).

Scheme 4



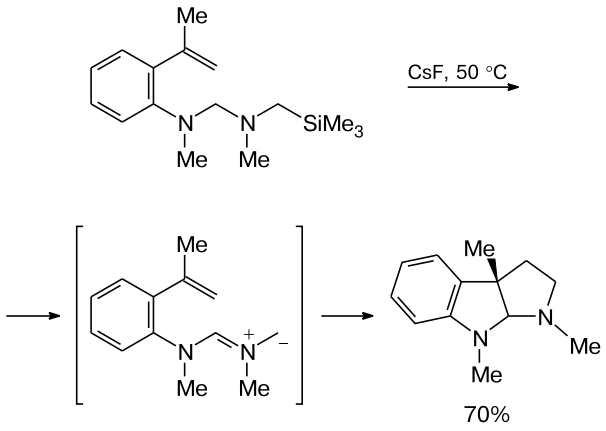
This strategy was used for the synthesis of physostigmine **71**,[151–153] alkaloid from of Calabar bean growing in West Africa. The skeleton of physostigmine is formed in good yield due to the intramolecular cyclization of unstabilized methylide imidate (Scheme 5).



71

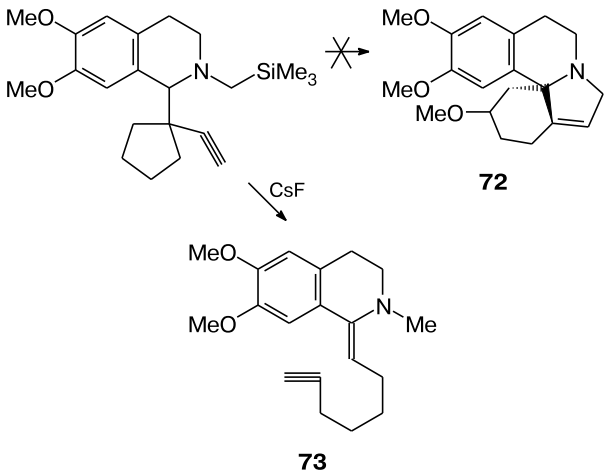
Alkaloid **71** in a low concentration inhibits acetylcholinesterase and eliminates the effect of diazepam overdose. Erythramine **72** is a natural alkaloid extracted from the *Mulungu tree* bark possessing potent curare-like activity. An attempt to form its structural skeleton according to the above methodology failed: as a result,

Scheme 5



enamine with the terminal acetylene group **73** was isolated (Scheme 6).[152]

Scheme 6



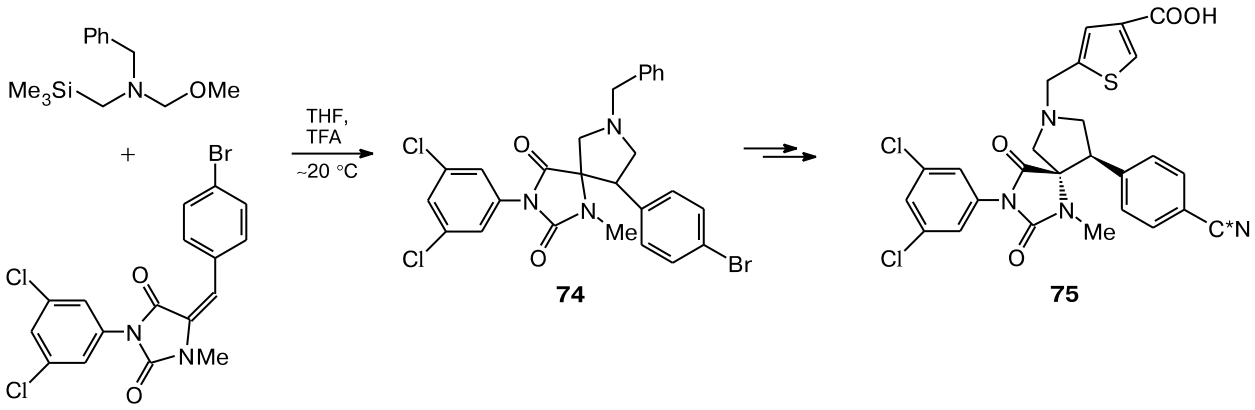
One of the stages of synthesis of the ^{14}C-isotope-labeled antagonist of leukocyte-associated antigen of 5-{[(5*S*,9*R*)-9-(4-[^{14}C]-cyanophenyl)-3-(3,5-dichlorophenyl)-1-methyl-2,4-dioxo-1,3,7-triazaspiro[4.4]nonan-7-yl]methyl}thiophene-3-carboxylic acid (**75**) is the *in situ* generation of azomethinylide from *N*-benzyl-*N*-(methoxymethyl)trimethylsilylmethylamine (Scheme 7).[154]

The blood factor Xa directly converts prothrombin to thrombin. Recently synthesized pyrrolidine derivative **76** is an inhibitor of the factor Xa and can be used as a blood anticoagulant. The strategy of [3+2] cycloaddition was also used when synthesizing **76** (Scheme 8).[155]

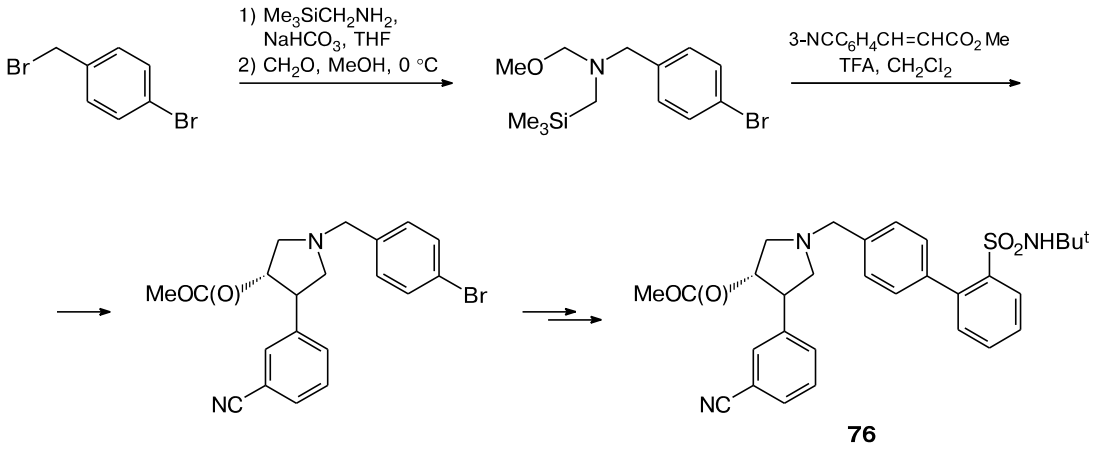
N-(Trimethylsilylmethyl)triflate reacts with trimers of pyrrolidine or tetrahydropyridine in the presence of CsF to form ylides (Scheme 9).[156]

Alkaloids (±)-trachelanthimidine (**77**), (±)-supinidine (**78**), and (±)-isoretronecanol (**79**) were synthesized by

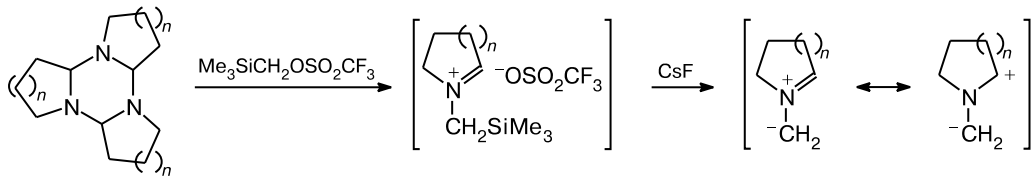
Scheme 7



Scheme 8

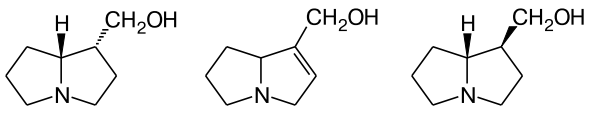


Scheme 9

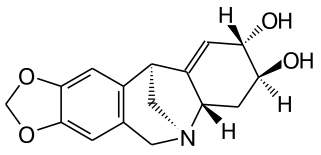


n = 1, 2

the addition of the indicated ylides to double bonds followed by transformations.



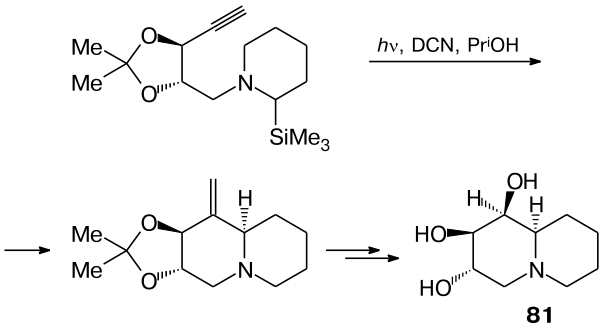
The derivatives of retronicine and indicine alkaloids were synthesized using *N*-(trimethylsilylmethyl)pyrrolidin-2-one for the formation of the ylide structure.[157] The complete synthesis of pancracine (**80**) (5,11-methanomorphanthridine alkaloid, which is present in plants *Pancra-*



tium, *Narcissus*, and *BrunsVigia* and was first isolated in 1955) was described.[158] *N*-(Trimethylsilylmethyl)amino-3-(trimethylsilyl)propan-1-ol was used in its synthesis at one of the first stages.

2-Trimethylsilylpiperidine derivative,[159] which is able to undergo the photoinduced reaction of one-electron transfer followed by cyclization, is involved in the key stage of the formation of the skeleton of polyfunctional alkaloid of the quinolizidine series **81** (Scheme 10). Hydrochloride of compound **81** is a selective powerful inhibitor of glucosidase.

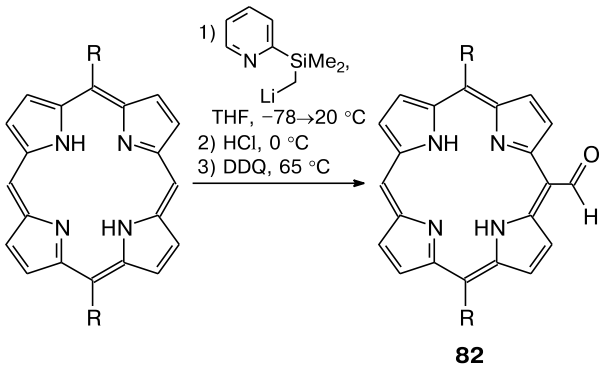
Scheme 10



DCN is 1,4-diacyanonaphthalene

Porphyrins and their analogs attract attention of researchers in the area of chemistry, biology, and medicine due to a unique set of both physical and chemical properties. For instance, dimegine (2,4-bis(1-methoxyethyl)-deuteroporphyrin disodium salt) is a photosensitizer and is used for photodynamic therapy of oncological diseases. The (2-pyridyldimethylsilyl)methyl groups was successfully used as a latent formyl function for the modification of 5,15-substituted porphyrins.[160] *meso*-Formylporphyrins **82** were isolated in 61—91% yields (Scheme 11).

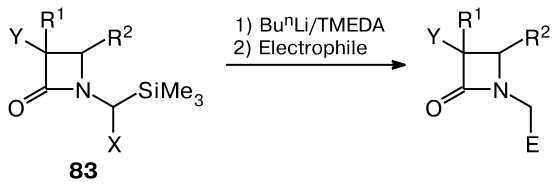
Scheme 11

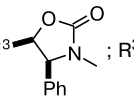


R = Bu^i, Ar

Functionalization of the β-lactame cycle is significant for the chemistry of β-lactame antibiotics. For this purpose, lithiated *N*-(silylmethyl)-β-lactames **83** were successfully used (Scheme 12).[161]

Scheme 12



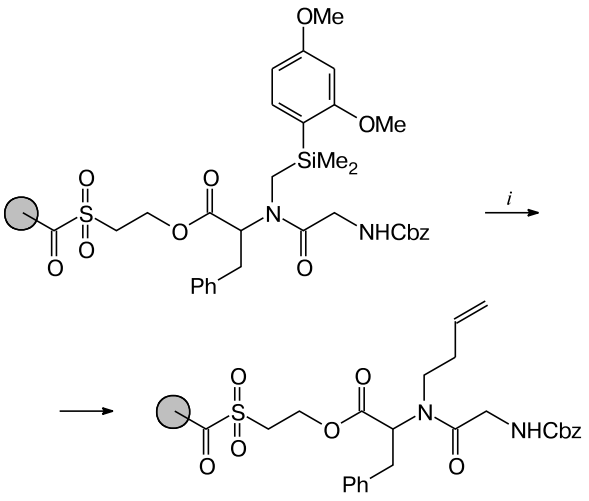
R^1 = Alk; R^2 = H, Alk; X = H, $SiMe_3$; Y = R^3  ; R^3 = H, Ph

Electrophile is MeI, MeOD, BuI, BnBr, CO_2, PhNCO, Me_3SiNCO, $ClCO_2Bn$

E = D, Alk, COOH, COOBn, COONHPh, CN, $CONH_2$

The geminal group N—C—Si is easily subjected to chemical transformations and allows one to introduce new functional groups into such complicated compounds as peptidomimetics (Scheme 13).[162]

Scheme 13



i. 1) $(NH_4)_2[Ce(NO_3)_6]$, $MeOH/CH_2Cl_2$; 2) $AllSiMe_3$.

Cbz is $PhCH_2OC(O)$—; ● is solid support

All examples considered above show that *N*-(silylmethyl)amines are convenient synthones in the synthesis of diverse, including natural, organic compounds and can find wide use in medical chemistry.

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