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REVIEW ARTICLE

Structure and biological action of analogs and derivatives of biogenic polyamines

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Abstract

Objectives. *Biogenic polyamines are widely present in nature. They are characteristic of both protozoan cells and multicellular organisms. These compounds have a wide range of biological functions and are necessary for normal growth and development of cells. Violation of polyamine homeostasis can cause significant abnormalities in cell functioning, provoking various pathological processes, including oncological and neuropsychiatric diseases. The impact on the "polyamine pathway" is an attractive basis for the creation of many pharmacological agents with a diverse spectrum of action. The purpose of this review is to summarize the results of the studies devoted to understanding the biological activity of compounds of the polyamine series, comparing their biological action with action on certain molecular targets. Due to the structural diversity of this group of substances, it is impossible to fully reflect the currently available data in one review. Therefore, in this work, the main attention is paid to the derivatives, acyclic saturated polyamines.*

Results. *The following aspects are considered: biological functionality, biosynthesis and catabolism, cell transport, and localization of biogenic polyamines in the living systems. Structural analogs and derivatives of biogenic polyamines with antitumor, neuroprotective, antiarrhythmic, antiparasitic, antibacterial, and other biological activities are represented; the relationship between biological activity and the target of exposure is reflected. It was found that the nature of the substituent, the number of cationic centers, and the length of the polyamine chain have a great influence on the nature of the effect.*

Conclusions. *At present, the use of polyamine structures is restrained by cytotoxicity and nonspecific toxic effects on the central nervous system. Further research in the field of biochemistry, cell transport, and a deeper understanding of receptor interaction mechanisms will help making polyamines as the basis for potential drug formulation.*

Keywords: *polyamines, biogenic amines, putrescine, polyamine derivatives, spermine, spermidine, polyamine biosynthesis, polyamine catabolism, polyamine transport, antiarrhythmic activity, antibacterial activity, antitumor activity, polyamine analogs, neurodegenerative diseases*

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ОБЗОРНАЯ СТАТЬЯ

Структура и биологическое действие аналогов и производных биогенных полиаминов

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Аннотация

Цели. *Биогенные полиамины широко представлены в живой природе. Они характерны как для клеток простейших, так и для многоклеточных организмов. Данные соединения обладают широким спектром биологической активности и необходимы для нормального роста и развития клеток. Нарушение гомеостаза полиаминов может вызывать существенные отклонения в функционировании клетки, провоцируя протекание патологических процессов различного рода, включая онкологические и психоневрологические заболевания. Воздействие на «полиаминовый путь» является привлекательным базисом для создания ряда фармакологически активных веществ с различным спектром действия. Целью данного обзора является обобщение результатов исследований, посвященных изучению биологической активности соединений полиаминового ряда; сопоставление биологического действия с воздействием на определенные молекулярные мишени. В виду структурного многообразия данной группы веществ невозможно в полной мере отразить имеющиеся на сегодняшний момент данные в одном обзоре. Поэтому в настоящей работе основное внимание уделено производным насыщенных полиаминов ациклического строения.*

Результаты. *В общем виде рассмотрены следующие аспекты: биологическая активность, биосинтез и катаболизм, клеточный транспорт и локализация биогенных полиаминов в живых системах. Представлены структурные аналоги и производные биогенных полиаминов, обладающие противоопухолевой, нейропротекторной, антиаритмической, противопаразитарной, антибактериальной и некоторыми другими видами биологической активности; отражена взаимосвязь между биологической активностью и мишенями воздействия. Установлено, что на характер воздействия большое влияние оказывает природа заместителя, количество катионных центров, а также длина полиаминовой цепи.*

Выводы. *В настоящее время применение структур полиаминового ряда сдерживается наличием цитотоксичности, а также неспецифического токсического воздействия на ЦНС. Дальнейшие исследования в области биохимии, клеточного транспорта, а также более глубокое понимание механизмов рецепторного взаимодействия позволят использовать полиамины в качестве основы для создания потенциальных лекарственных препаратов.*

Ключевые слова: *полиамины, биогенные амины, путресцин, производные полиаминов, спермин, спермидин, биосинтез полиаминов, катаболизм полиаминов, транспорт полиаминов, антиаритмическая активность, антибактериальная активность, противоопухолевая активность, аналоги полиаминов, нейродегенеративные заболевания*

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INTRODUCTION

Polyamines (polymethylene polyamines) represent a large group of compounds that are widespread among biological entities. Structurally, polyamines are quite diverse, but the majority of their compounds are based on three biogenic polyamines: putrescine **1**, spermidine **4**, and spermine **7**. Cadaverine **2**, norspermidine **3**, homospermidine **5**, norspermine **6**, and homospermine **8** are similar to the three basic polyamines, but with different molecular chain length (Fig. 1).

Structural fragments of polyamines exist in several alkaloids and toxins [1, 2]. To date, many conjugates of polyamines with other biomolecules, such as amino acids, oligonucleotides, steroids, etc., have been isolated and characterized [3, 4].

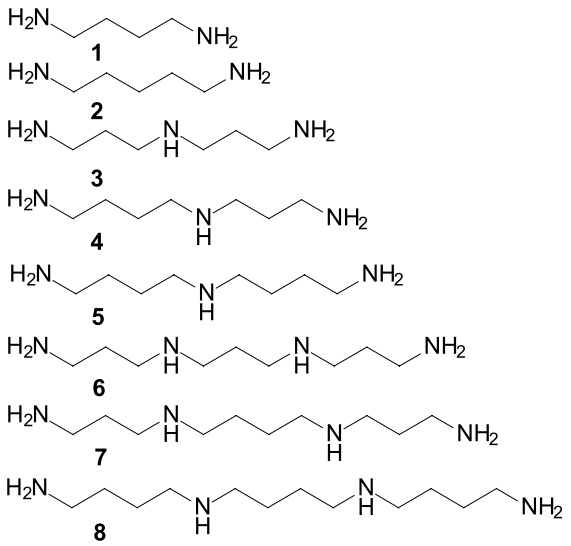

Fig. 1. Basic polyamines.

In living systems, at physiological pH values, these compounds exist in ionized form, representing organic polycations. The presence of a positive charge reflects a wide range of biological functionalities. Polyamines are involved in a variety of biological processes, such as cell growth, proliferation, and cell differentiation [5]. They are essential components of normal cell growth and development.

Polyamines can interact with negatively charged protein fragments, nucleic acids, and phospholipids [6]. The formation of conjugates, as well as "bridging" structures with high-molecular compounds such as RNA and DNA, has a stabilizing effect on their conformations, protecting them against denaturation, occurring under the influence of heat, chemical reagents, or radiation [7, 8]. Under oxidative stress, polyamines act as antioxidants, neutralizing reactive oxygen species [9].

The first mentions of polyamines are also associated with the name of the Dutch naturalist Leeuwenhoek, who isolated crystals of spermine phosphate in 1678. However, the correct structure of spermine was established only in 1926 by Rosenheim [10]. In 1898, Poehl proposed the use of spermine for the treatment of various diseases. In 1938, Zeller, in his works, described the enzyme—diamine oxidase (DAO), an impetus for the development of the polyamine biochemistry [11].

BIOSYNTHESIS AND CATABOLISM OF POLYAMINES

In all living systems, polyamines are formed from precursor amino acids, which are mainly L-arginine (Arg), L-ornithine (Orn), L-lysine (Lys), and L-methionine (Met). However, among bacteria and eukaryotes,

there are differences in the qualitative composition of polyamines, and in their biosynthesis and catabolism pathways [12]. Figure 2 shows the general scheme of biosynthesis of basic polyamines in living cells.

The initial stage in the polyamine biosynthesis is the decarboxylation of amino acid precursors. In plants and bacteria, putrescine can be formed in two ways: 1) directly from ornithine with the help of the enzyme ornithine decarboxylase (ODC); 2) indirectly, through the formation of agmatine from arginine with the help of arginine decarboxylase (ADC), followed by the conversion of agmatine to putrescine by the enzyme agmatinase [13].

In animal cells, putrescine is produced exclusively by the first pathway, i.e. from L-ornithine [14]. Putrescine formation is a limiting step in the polyamine biosynthesis [15].

Under the action of the enzyme S-adenosylmethionine synthase, also known as methionine adenosine transferase (MAT), and the ATP molecule, L-methionine is converted to S-adenosylmethionine (SAM), which is transformed by pyruvate-dependent S-adenosylmethionine decarboxylase (S-adenosylmethionine decarboxylase), deforming into S-AdoMet nosylmethioninamine (dsSAM). Spermidine and spermine are formed by transfer of an aminopropyl group from dsSAM via spermidine synthase (SpdSy) and spermine synthase (SpmSy), respectively [16].

Cadaverine is formed from L-lysine with the participation of the enzyme lysine decarboxylase (LDC) [17].

Notably, putrescine and cadaverine are more common among bacteria than other polyamines [18]. In mammals, putrescine is a source for the formation of higher polyamines, such as spermine and spermidine [19].

Initially, it was assumed that two main enzymes are responsible for the catabolism of polyamines in mammals: spermine/spermidine-N^1-acetyltransferase (SSAT) and acetylpolyamine oxidase (APAO) [20]. A recent study [21] has identified another enzyme responsible for the degradation of polyamines: spermine oxidase (SMO). It is a cytosolic enzyme that catalyzes the direct transformation of spermine to spermidine. The key difference between this enzyme and APAO is that the former does not require

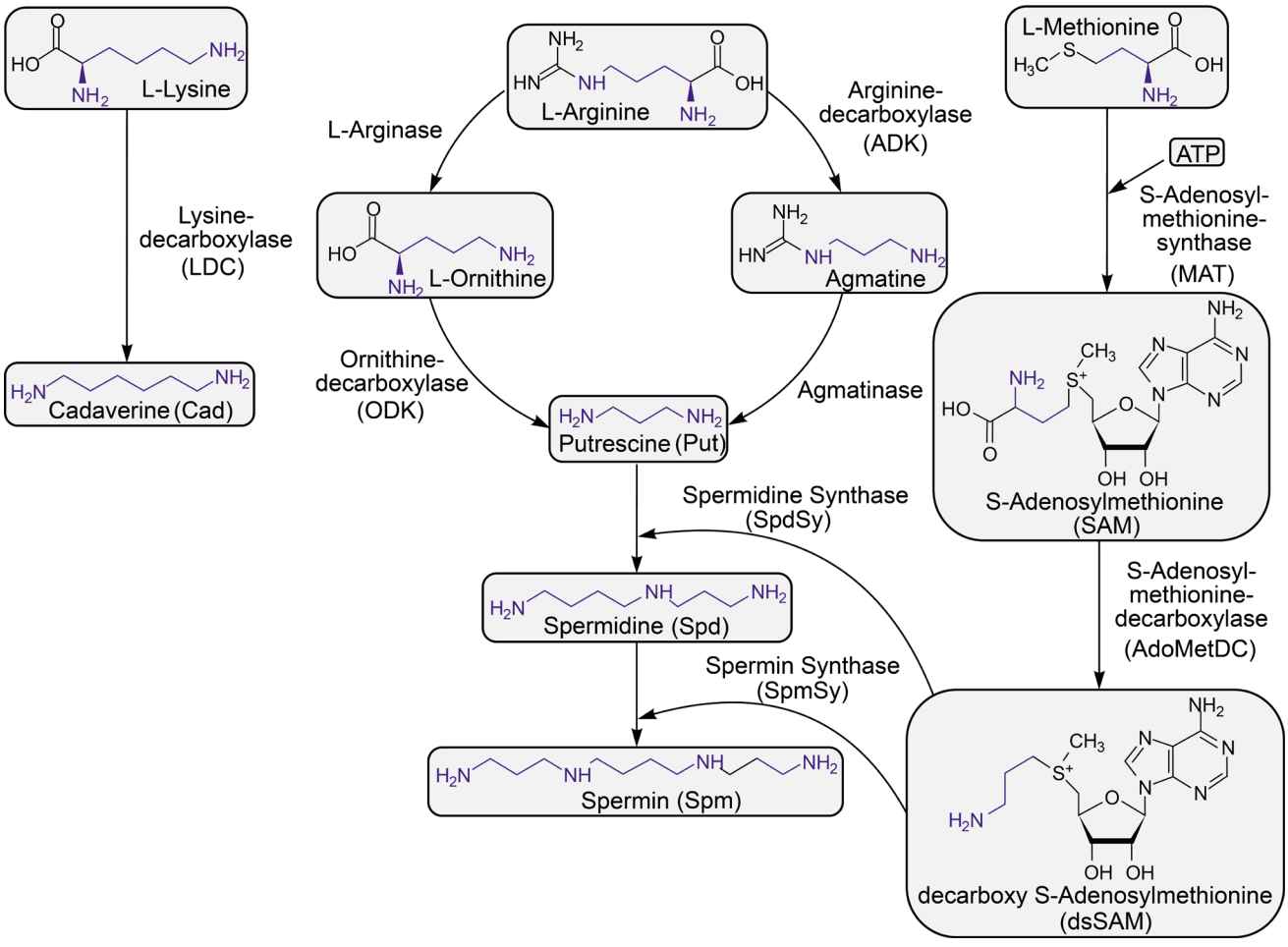

Fig. 2. General scheme of biosynthesis of basic polyamines.

preliminary acetylation of the substrate [22].

In general, the catabolism of polyamines in mammals is shown in Fig. 3.

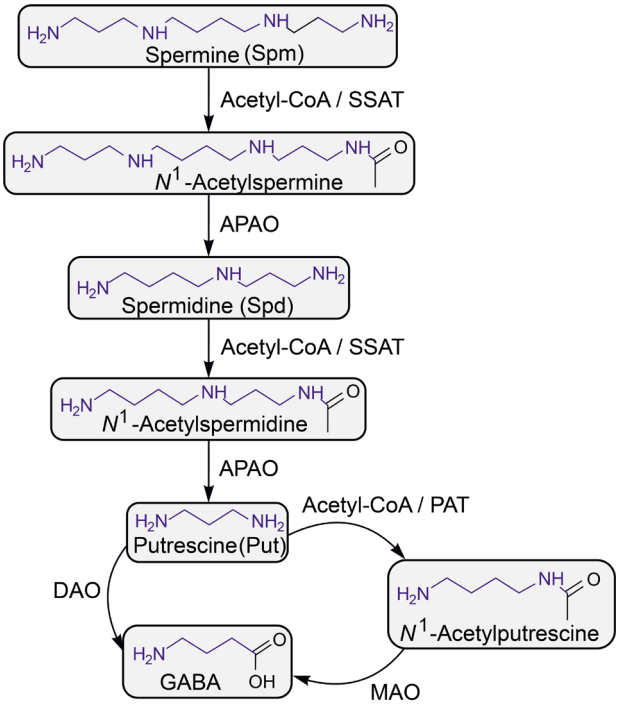

Fig. 3. General scheme of catabolic transformations of polyamines.

The degradation of higher polyamines is the SSAT-catalyzed acetylation of the substrate (Spd and Spm) acetyl-CoA. Acetylation is necessary because APAO exhibits extremely low activity with respect to nonacetylated polyamines [23]. Acetylpolyamine oxidase (APAO) catalyzes the degradation of N^1-acetylspermine and N^1-acetylspermidine to spermidine and putrescine, respectively. In this case, the formation of toxic products, hydrogen peroxide and unstable 3-acetamidopropanal, occurs.

Compared to spermidine and spermine, putrescine has a shorter biological half-life [24]. It is known that the catabolism of putrescine is not the same for all tissues of the mammalian body. The main enzyme catalyzing the decomposition of putrescine is diamine oxidase (DAO); however, in the mammalian brain, DAO activity is low [25]. It was shown in [26] that putrescine degradation in the mammalian brain, is catalyzed by monoamine oxidase (MAO) with the substrate, monoacetylputrescine, formed under the action of acetyl CoA and putrescine N^1-transferase [27]. Subsequently, it is oxidized to *N*-acetyl-4-aminobutyrate, which is converted to γ-aminobutyric acid (GABA) [28].

Another pathway of putrescine catabolism is associated with the copper-containing enzyme DAO, which catalyzes the degradation of 3–6 long-chain diamines, and histamine, by oxidative deamination. DAO is able to degrade putrescine to form γ-aminobutanal, which is then converted to GABA [29].

DAO is a rate-limiting enzyme in the terminal catabolism of polyamines since the oxidation products of putrescine are not involved in the polyamine interconversion cycle [30].

As reported [31], diamine oxidase (DAO) is largely responsible for the metabolism of cadaverine.

TRANSPORT AND LOCALIZATION OF POLYAMINES

While the presence of polyamines is typical for all living organisms, the level, ratio, and qualitative composition of these compounds are different for plants, animals, and bacteria. So, in the body of animals, the content of polyamines is heterogeneous. Not surprisingly, the highest concentration of polyamines is present in the tissues with active cell proliferation (hair follicles, mucosal epithelium, spinal cord, etc.) as they are necessary for cell division.

The level of extracellular polyamines is low. Thus, the content of spermidine in cerebrospinal fluid samples (0.12 ± 0.4 nmol/mL) is almost two orders of magnitude lower than in the white matter of the spinal cord (15.9 ± 1.25 nmol/mg), the content of spermine is 12 times lower (0.14 ± 0.01 nmol/mL and 1.69 ± 0.10 nmol/mg), and the content of putrescine is 4 times lower (0.23 ± 0.05 nmol/mL and 0.96 ± 0.19 nmol/mg) [32].

The homeostasis of polyamines is maintained via the regulation of their biosynthesis, catabolism, and transport in the body [33–34].

While the mammalian body synthesizes polyamines on its own, food products and intestinal microbiota act as additional sources [35]. A previous report investigated and confirmed the absorption of polyamines by cells [36]. Research showed that inhibition of polyamine biosynthesis by α-difluoromethylornithine (DFMO) stimulates the absorption of these compounds from the external environment.

Currently, the transport pathways of polyamines are well studied for unicellular organisms, such as *E. coli* [37]. However, for multicellular organisms, including mammals, the functioning of the polyamine transport system has not been fully understood. A comprehensive review [38] established three models describing the transport of polyamines in mammalian cells. In general, the transport of polyamines depends

on the carrier, temperature, pH-medium, time, concentrations of Na^+, Mn^{2+}, Ca^{2+}, Mg^{2+} ions, and is also dependent on potential.

The first model [39] includes two stages: transport of the substrate into the cytosol via a voltage-dependent membrane transporter, and vesicular sequestration requiring an H^+ gradient.

The second model describes glypican-mediated endocytosis. It is assumed that spermidine, binding to heparan sulfate fragments of glypican, enters the cell, where it is separated from glypican by oxidation of NO, which leads to the accumulation of polyamine in special vesicles [40].

According to the third model [41], endocytosis of polyamines is caveolin-mediated: by means of a certain "polyamine receptor" whose structure has not been established. As in the previous model, the secretion of polyamines into vesicles is mediated by NO.

Understanding the role of polyamines in the functioning of living systems, opens new ways of influencing physiological and pathological cellular processes. Creation of synthetic analogs and derivatives of biogenic polyamines will expand the arsenal of drugs.

ANTITUMOR ACTIVITY

As noted earlier, the concentration of polyamines is the highest in rapidly renewing tissues since these compounds are involved in the processes of cell differentiation and proliferation. The rate of synthesis and absorption of extracellular polyamines is noticeably higher in actively proliferating cells, including tumor cells [42]. Due to this fact, polyamines can be promising structures for the design of novel anticancer drugs. The first successful step in this direction was the study [43] devoted to the synthesis of mono- and dicyano-derivatives of biogenic polyamines—spermine and spermidine—with different chain lengths. Among several compounds, five exhibited antitumor activities, confirmed *in vivo* [44].

To date, many different biogenic polyamine derivatives have been developed, exhibiting an antitumor effect, including symmetric and asymmetric alkylated, heterofunctional, heterochain, sterically hindered, and even metal complex analogs [45, 46].

In general, targeting the enzymes of biosynthesis and catabolism, causes disruption of polyamine homeostasis in the tumor cell, leading to a cytostatic and/or apoptotic effect [47].

Alkylated analogs

Porter [48, 49] was one of the first to study the antitumor activity of *N*-alkyl and *N*-acyl derivatives of spermidine (Fig. 4). These compounds are able to compete with unmodified spermidine for cellular uptake, replacing it, and leading to inhibition of cell growth.

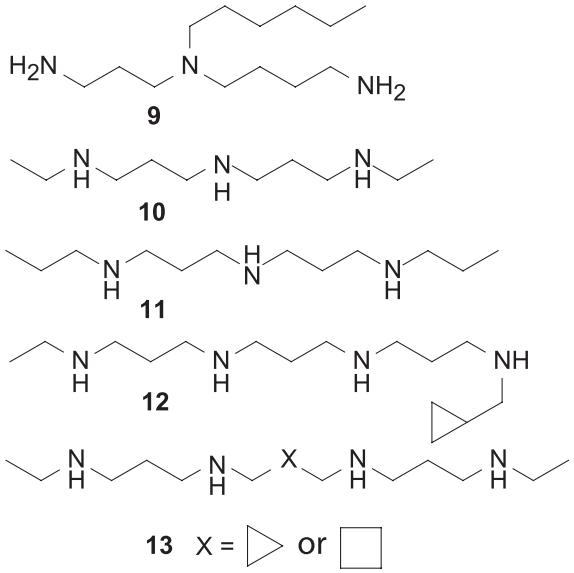

Fig. 4. *N*-alkyl and *N*-acyl derivatives of spermidine.

The best antiproliferative activity is exhibited by N^4- and N^1, N^8-alkyl substituted derivatives of spermidine, namely N^4-hexyl-, N^1, N^8-bis (ethyl) and N^1, N^8-bis (propyl) spermidines **9**–**11**.

Later, a wide variety of alkyl derivatives of biogenic polyamines were obtained and studied; among them, were asymmetric **12**, and conformationally hindered **13** derivatives of norspermine [50, 51].

Bis-alkylated, at the terminal amino groups, analogs of polyamines cause enhanced induction of the catabolytic enzyme SSAT, thereby depleting intracellular reserves of polyamines [52]. Moreover, methylated derivatives have a cytostatic effect, while ethyl and propyl analogs are characterized by a cytotoxic effect [53].

Also, in the context of structural analogy, it is worth mentioning the antidiarrheal activity of alkylated spermine analogs [54].

The greatest progress has been made for N^1N^{14}-diethylhomospermine (DENSpm); studies advanced to phase II clinical trials as an antineoplastic drug for patients with inoperable liver cancer, but clinical trials were stopped due to low efficacy and toxic effects on the central nervous system [55].

Heterochain analogs

Heterochain analogs of biogenic polyamines are structurally interesting since, in addition to methylene units and amino groups, atoms of oxygen, sulfur, silicon, etc. are included in the structure of the molecule (Fig. 5).

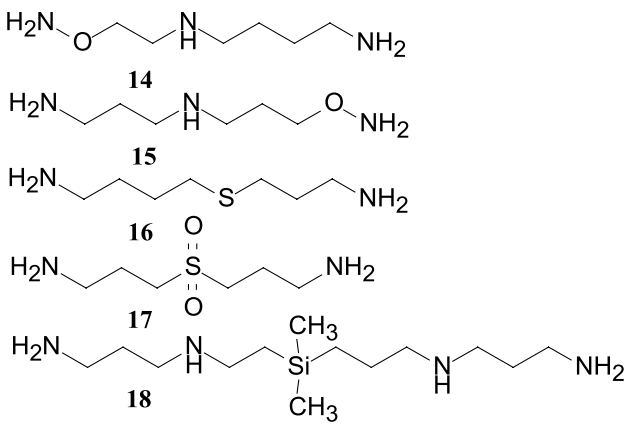

Fig. 5. Heterochain analogs of biogenic polyamines.

Khomutov and co-authors were among the first to demonstrate the inhibitory ability of the amino-hydroxy analogue of putrescine against ornithine decarboxylase (ODC), an enzyme of polyamine biosynthesis [56]. In their further studies, a series of amino-oxyanalogues of spermine and spermidine was synthesized, and it was found that analogs 1-Ao-Spd **14** and 8-Ao-Spd **15** compete with natural (unmodified) substrates to enter the cell. The study of the effect of **14** and **15** on the growth of the L1210 cell culture showed the absence of cytotoxicity and the presence of cytostatic effects IC_{50} = 70 and 100 μM for 1-Ao-Spd and 8-Ao-Spd, respectively. For the spermine analog (mono-Ao-Spm), the IC_{50} value was 500 μM [57–59].

Later [60], heterochain analogs containing sulfur **16**, oxygen, and sulfuryl group **17** were obtained. However, structures of this type were not widely used.

Organosilicon derivatives were obtained and investigated for antitumor activity on L1210 cancer lines and on transplanted Lewis lung carcinoma (DBA/2). The best results were achieved with the use of (6-amino-3-azagexyl), (7-amino-4-azageptyl)-dimethylsilane (AzhexAzhepSi) **18**, the introduction of two daily doses of 25 mmol/kg had a significant cytostatic effect. AzhexAzhepSi and difluoromethylornithine (DFMO) have a cumulative effect on tumor reduction. DFMO blocks putrescine synthesis from ornithine, while dimethylsilyl analogs inhibit the polyamine oxidase catabolic enzyme, thereby depleting the polyamine pool and accumulating "mimetics" in the cell [61].

ANTIBACTERIAL AND FUNGICIDAL ACTIVITY

Resistance development in bacterial pathogens to general antibiotics, is a big problem in modern medicine and pharmacology. To address the problem, immense research is aimed at formulating new antibacterial agents [62].

Potential antibacterial agents have been found in the metabolites of the sea sponge *Suberea ianthelliformis*, as reported by Xu in a study [63]. Structurally, these alkaloids are derivatives of polyamines—spermine and spermidine. According to [64], *Ianthelliformisamine A* **19** and *Ianthelliformisamine C* **20** (Fig. 6) demonstrate antibacterial activity against the gram-negative bacterium *P. aeruginosa*, the EC_{50} values are 7 μM and 9 μM, respectively.

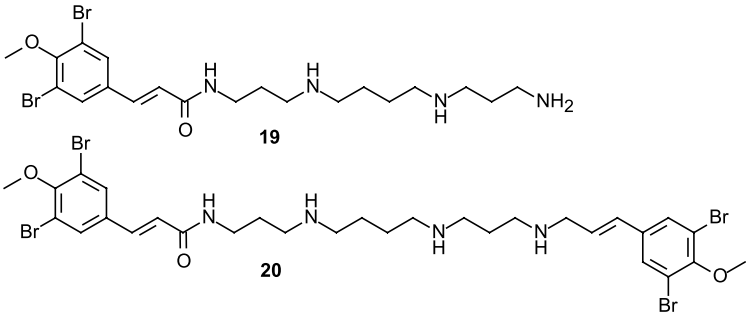

Fig. 6. *Ianthelliformisamine A* **19** and *Ianthelliformisamine C* **20**.

Khan [65] was the first to synthesize and study the antibacterial activity of several structural analogs of *Ianthelliformisamine A–C* (Fig. 7). The best results were demonstrated by samples **21** and **22**: the minimum inhibitory concentrations of MIC for *E. coli* are 1.2 and 0.15 μM, respectively; for *S. aureus* MIC = 0.12 and 0.15 μM, respectively.

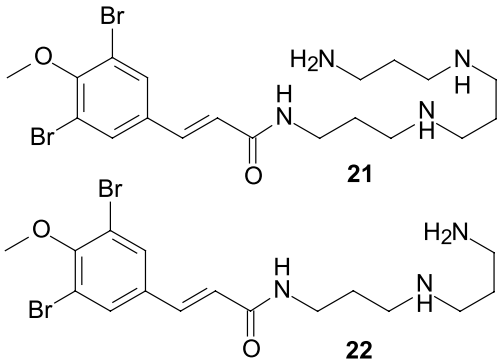

Fig. 7. Structural analogs of *Ianthelliformisamine A–C* (**21**, **22**).

Compounds **23**, **24** are similar analogs of the alkaloids of the sea sponge *Suberea ianthelliformis* (Fig. 8). They have good antibacterial activity against the gram-positive bacteria *S. intermedius* and *S. aureus*, the MIC values are 3.125 and 6.25 μM,

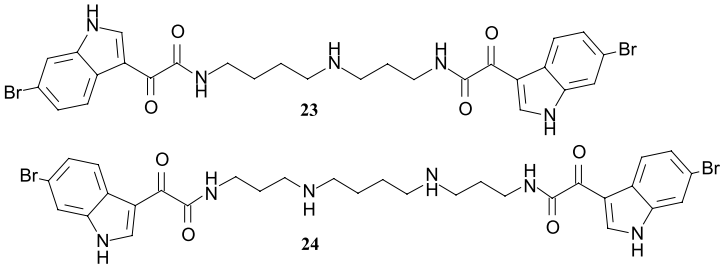

Fig. 8. Analogues **23**, **24** of the alkaloids of the sea sponge *Suberea ianthelliformis*.

respectively. Compound **23** has a strong fungicidal effect against *C. albicans* (MIC = 17.2 μM) and *C. neoformans* (MIC = 1.1 μM) [66].

Equally interesting antibacterial agents are analogs of motuporamine A (an alkaloid of the sea sponge *Xestosponga exigua*) containing a polyamine fragment (Fig. 9). Structures **25**, **26** have a strong antibacterial effect against staphylococci (*S. aureus* and *S. intermedius*), gram-positive enterococcus (*E. faecalis*), Escherichia coli (*E. coli*), and against gram-negative Pseudomonas aeruginosa (*P. aeruginosa*); MIC values are in the range from 1.56 to 12.5 μM [67].

It is also worth mentioning that bis-acetylated polyamines **29** have less pronounced antibacterial properties than previously described compounds. The authors note the possibility of using these structures as sensitizers of some bacterial pathogens, but their use is constrained by nonspecific toxicity [68].

Presumably, the mechanism of action of polyamine antibiotics is based on depolarization and/or disruption of the cell membrane integrity. The development of such structures might solve the problem of bacterial resistance [69].

ANTIPARASITIC ACTIVITY

A considerable danger, especially for the population of tropical and subtropical regions, is represented by vector-borne diseases, such as malaria and leishmaniosis, caused by the simplest parasitic organisms, including *P. falciparum*, *L. tropica*, *L. donovani*, *T. cruzi*, etc. Emergence of bacterial resistance to several conventional as well as modern drugs, such as solusurmin, chloroquine, primaquine, mefloquine, etc., has become a significant problem in medicine [70].

A new approach in the chemotherapy of such diseases may be the "polyamine pathway." Thus, unicellular parasites have an increased need for polyamines due to their tendency to proliferate. Interference with the metabolism of polyamines is likely to have a depressing effect on the vital activity of these microorganisms [71].

This was confirmed in [72]. Several bis(benzyl) polyamine analogs **30** with different chain lengths have been studied (Fig. 10), and the inhibitory effect (*in vivo*) on the growth of chloroquine-resistant *P. falciparum*.

According to the test results, the structure MDL 27695 (n = 7) has the best inhibitory effect against both chloroquine-resistant and chloroquine-sensitive *P. falciparum* strains. Later, the effectiveness of this compound against *L. donovani*, the causative agent of leishmaniasis, was confirmed [73]. A study [74] noted the possibility of using such analogs to combat African sleeping sickness caused by *T. cruzi* (Chagas disease).

In addition, the authors of a study [75] reported a similar antiparasitic activity of *N*, *N*-substituted analogs of biogenic diamines—putrescine and cadaverine.

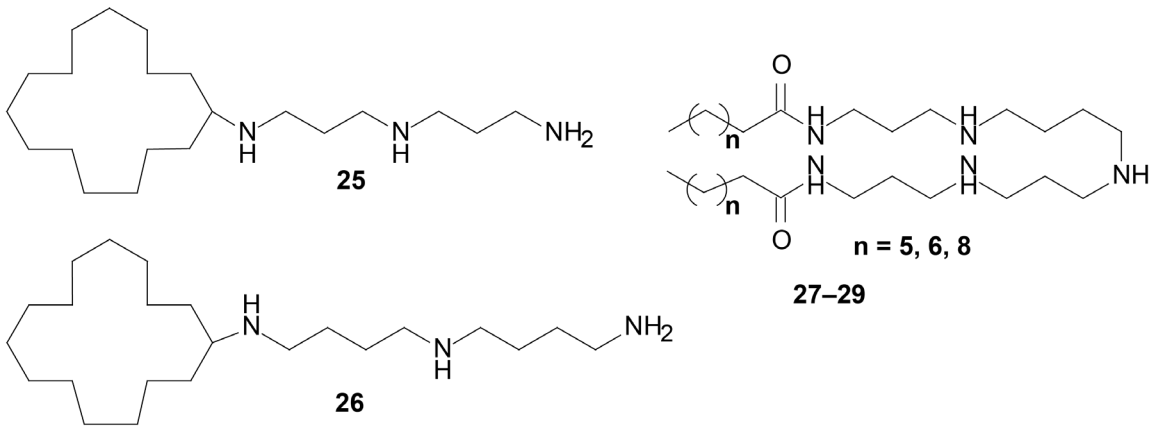

Fig. 9. Analogs of motuporamine A **25**, **26** and bis-acetylated polyamines **27**–**29**.

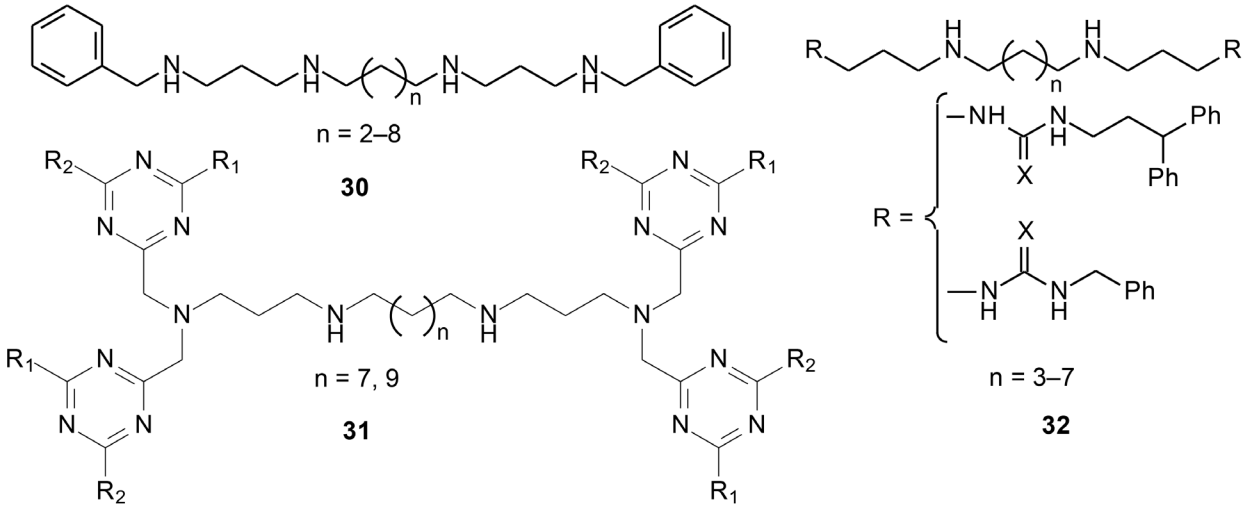

Fig. 10. Bis(benzyl)polyamine analogs **30**, 1,3,5-triazine-substituted polyamines **31**, bis(thiourea)derivatives of biogenic polyamines **32**.

1,3,5-triazine-substituted polyamines **31** exhibited antiplasmid activity against *P. falciparum*, as reported by Klenke [76]. Long-chain methylated structures (n = 9, R_1, R_2 = $NHCH_3$, $N(CH_3)_2$) showed the greatest antimalarial activity against *P. falciparum*; EC_{50} values are 0.0477 to 0.0698 for the NF54 line (wild type) and 0.0519 to 0.0622 for K1 (primaquine, chloroquine resistant), respectively. These structures also showed good activity against *T. cruzi* [77]. However, it is worth noting that the outstanding antiplasmid activity is weighed down by the presence of acute toxicity.

Another group of compounds for the suppression of vital activity of *P. falciparum*, includes bis(urea) and bis(thiourea) derivatives of biogenic polyamines **32**, the synthesis and biological tests of which are described in the work of Verlinden [78]. The best results were demonstrated by structures with a longer carbon chain (n = 6, 7), the EC_{50} value varied from 100 to 650 nM. In addition, the antimalarial effect was slightly higher in samples with diphenylpropylcarbamate fragments.

Niemand presented anthracene conjugates of biogenic polyamines (Fig. 11); investigated *in vitro* inhibitory effect on the growth of *P. falciparum* and some cancer cell lines. The best effect was demonstrated by N^1-[(anthracene-9-yl)methyl] butane-1,4-diamine **33**; the EC_{50} value for malaria plasmodium was 0.64 ± 0.04 mM [79].

The inhibitory effect on the development of *P. falciparum* is also exerted by 1,14-diphenylacetamide derivatives of spermine **34**, as reported previously [80].

What is also worth noting are the indoleglyoxamide analogs **35**, which have an aniplasmid effect, especially against *T. brucei*; EC_{50} values range from 0.18 to 0.27 mM [81].

In general, the antiparasitic effect of polyamine analogs is chemotherapeutic in nature. Disruption of metabolic processes caused by inhibition of enzymes of biosynthesis/catabolism of polyamines, as well as interaction with DNA/RNA, causes the death of pathogenic organisms [82].

ANTIARHYTHMIC ACTIVITY

In substances, structurally similar to biogenic polyamines, biological activities in relation to the cardiovascular system, can be explained based on the principle of structural similarity [83].

Thus, biogenic polyamines, localized in the cytoplasm, can modulate the activity of voltage-dependent sodium channels (Na_V), as reported by Huang and Moczydlowski in a study [84]. In the later work, the same authors compared the sensitivity of various isoforms of sodium channels (Na_V) in mammals and concluded that the cardiac canal (Na_V 1.5) is more sensitive to the blocking action of polyamines than other isoforms [85].

In addition to sodium channels, polyamines—spermine, spermidine along with Mg^{2+} cations, regulate the conductance of inward rectification potassium channels (Kir), eg. Kir 2.1 [86]. Modulation of these type of channels affects the heart rate, and the action potential of cardiomyocytes [87].

The hypothesis was confirmed in a study [88] wherein the antiarrhythmic activity of polyamine

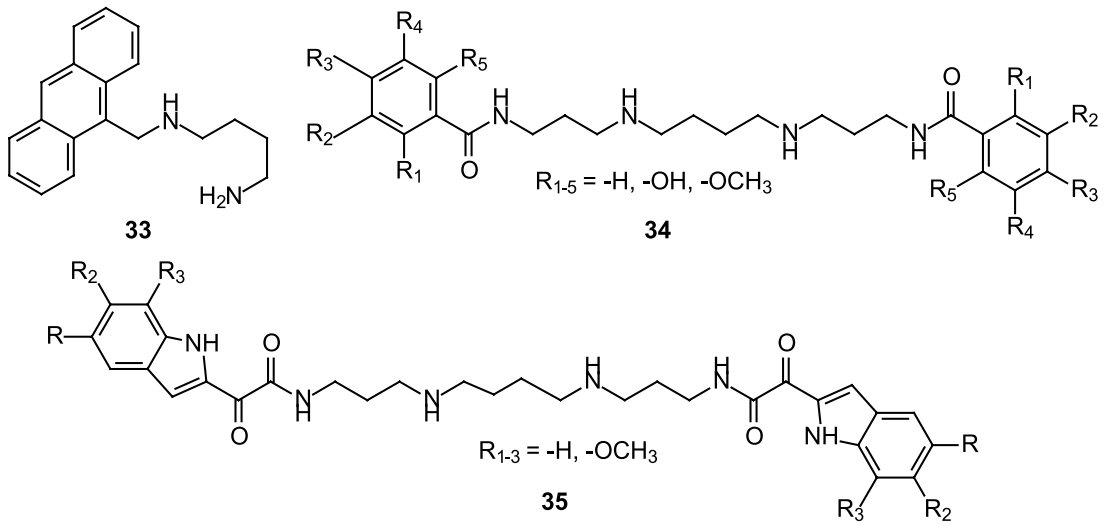

Fig. 11. N^1-[(anthracene-9-yl)methyl]butane-1,4-diamine **33**, 1,14-diphenylacetamide derivatives of spermine **34**, indoleglyoxamide analogs **35**.

analogs was studied in Wistar rats; ventricular fibrillation was provoked with isoprenaline. The highest antiarrhythmic activity was demonstrated by the structures PYR 3.3.3 and PYR 3.4.3 **36** (Fig. 12); when rats were administered a dose of 59 mmol/kg, the survival rate of the animals was 60%.

Another example of the antiarrhythmic effect of biogenic polyamine analogs is described in a study [89], in which the activity of linear methoxyphenyltriazaalkanes **37** was investigated.

Half-lethal doses (LD_{50}) for the intraperitoneal route of administration for the compounds ranged from 35.1 to 163.3 mg/kg. As per the aconite model of arrhythmia, structures containing two methylene units between amino groups (n = x = 2) were active, while for the calcium chloride model, molecules with three methylene units between nitrogen atoms (n = x = 3) were active, indicating different targets of impact. An exception is N^1-(2,3,4-trimethoxybenzyl)-N^2-{2-[(2,3,4-trimethoxybenzyl)amino]ethyl}-1,2-ethanediamine, which is active in all the studied models of arrhythmia. In addition, some compounds exhibited a statistically significant anti-ischemic effect, as confirmed in the isoprenaline model of ischemia.

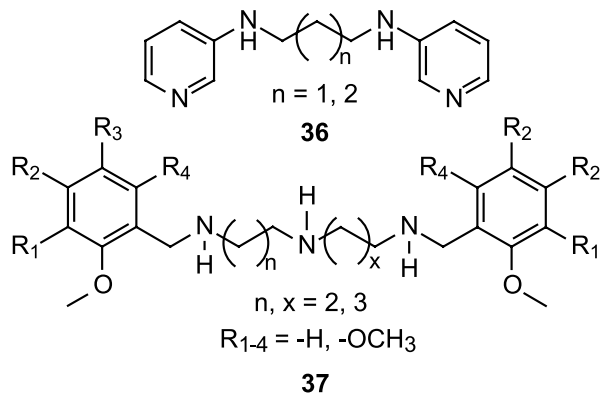

Fig. 12. PYR 3.3.3 and PYR 4.4.4 **36**, linear methoxyphenyltriazaalkanes **37**.

Several years of scientific research and a colossal amount of work have resulted in the development of a novel class of N-substituted aminoamides, potential new generation antiarrhythmic drugs.

These compounds **38** can be considered as derivatives of putrescine (n = 2), cadaverine (n = 3), or their analogs (n > 3) (Fig. 13) based on their structures.

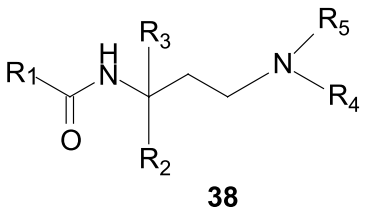

Fig. 13. Compounds **38**—derivatives of putrescine, cadaverine and their analogs.

Numerous works have aimed at developing and studying the biological action of a number of structures containing various substituents at the amine (NR_4R_5 = $N(CH_3)_2$, $N(C_2H_5)_2$, piperidyl, morpholino, $N(C_3H_7)_2$, $N(C_4H_9)_2$), amide (R_1 = CH_3, H, C_6H_5, $CH_2C_6H_5$, 1-adamantyl, cyclohexyl, etc.) groups and in the main chain of the molecule (R_2 = alkyl, C_6H_5, RC_6H_4; R_3 = H, alkyl) [90].

In the test results, it was found that these compounds are less toxic, highly active antiarrhythmic agents, as demonstrated in the aconite model of rat arrhythmia (the antiarrhythmic index values are an order of magnitude higher in comparison with novocainamide); half-lethal dose (LD_{50}) values for most compounds ranged from 110 to 940 mg/kg with the intraperitoneal administration [91].

NEUROPROTECTIVE ACTIVITY

Observing the effect of polyamines on ion channels, one cannot fail to note the ability of polyamines to modulate the *N*-methyl-D-aspartate receptor (NMDA receptor), one of the subtypes of ionotropic glutamate receptors (iGlu) [92], which plays an important role in neuronal communication, the mechanism of synaptic plasticity, and therefore, in the process of thinking and memory [93]. Disruption of the receptor function can lead to several pathological conditions, such as schizophrenia, neurodegenerative diseases, depressive disorders, etc. [94–96]. Since the discovery of the relationship between these disorders and iGlu receptors, several attempts have been made to develop pharmacological agents for the treatment and correction of such conditions.

Several studies [97–100] report the neuroprotective action of biogenic polyamines, such as putrescine, spermidine, and spermine, against various damages, including mechanical, neurotoxic, and ischemia. Thus, an ischemic stroke initiates excessive activation of excitatory synapses, accompanied with a steady influx of Ca^{2+} through glutamate receptors; an increase in the intracellular Ca^{2+} triggers neuronal death [101].

Polyamine analogs that can competitively bind to the NDMA receptor in comparison with glutamate are its antagonists and thus, may have a neuroprotective effect against some damages.

Sulfanyl derivatives of spermine (Fig. 14), N^1-dansylspermine (N^1-DnsSpm) **39** and N^1-(*n*-octosulfonyl) spermine (N^1-OsSpm) **40**, are able to inhibit NDMA NR1 and NR2A receptors several times stronger than spermine; this circumstance allows considering these compounds as potential neuroprotective agents [102, 103]. In addition, Kirby [104] reports that high doses of N^1-dansylspermine (N^1-DnsSpm) have an antiepileptic effect.

It is also worth mentioning anthracene **41** and anthraquinone **42** derivatives of spermine and homospermine, also potent antagonists, as demonstrated in [105] using recombinant NMDA receptors (NRs).

In addition to sulfanyl, anthracene, and anthraquinone derivatives, the literature also describes indane **43** [106], adamantane **44** [107], benzyl [108], and quinoline structures [109], based on fragments of biogenic polyamines.

Natural derivatives of polyamines—polyamine toxins—present in the venom of some insects and spiders deserve special attention (Fig. 15). Polyamine toxins **45** were first isolated from the venom of the spider *Argiope lobata* and characterized in a study [110]. Later, the ability of these compounds to act on the central nervous system of mammals was discovered. Polyamine toxins are generally non-selective (iGlu) receptor antagonists and the blocking effect is carried out by a non-competitive mechanism [111]. A similar mechanism is at the heart of the drug (Ebixa®) used for moderate to severe Alzheimer's dementia [112].

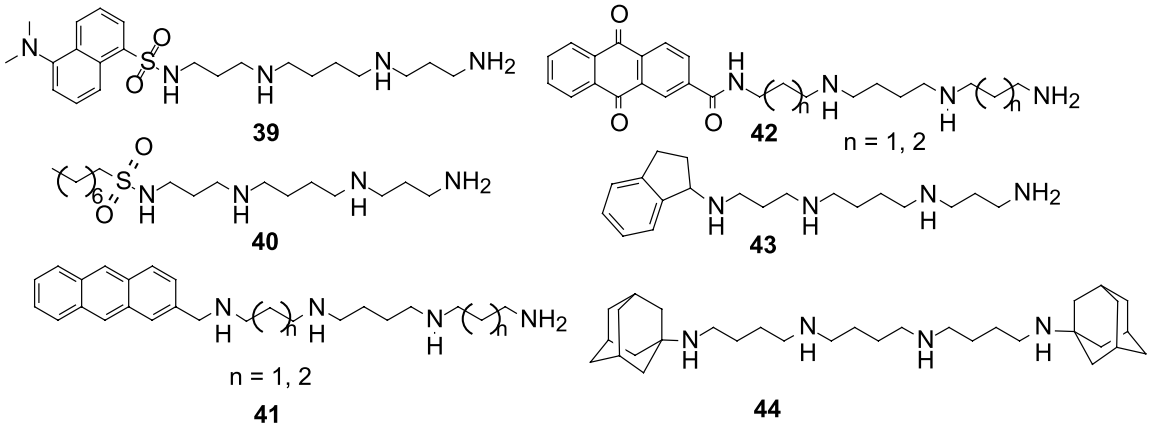

Fig. 14. Sulfanyl derivatives of spermine **39**, **40**, anthracene **41** and anthraquinone **42** derivatives of spermine and homospermine, indane **43**, adamantane **44** structures.

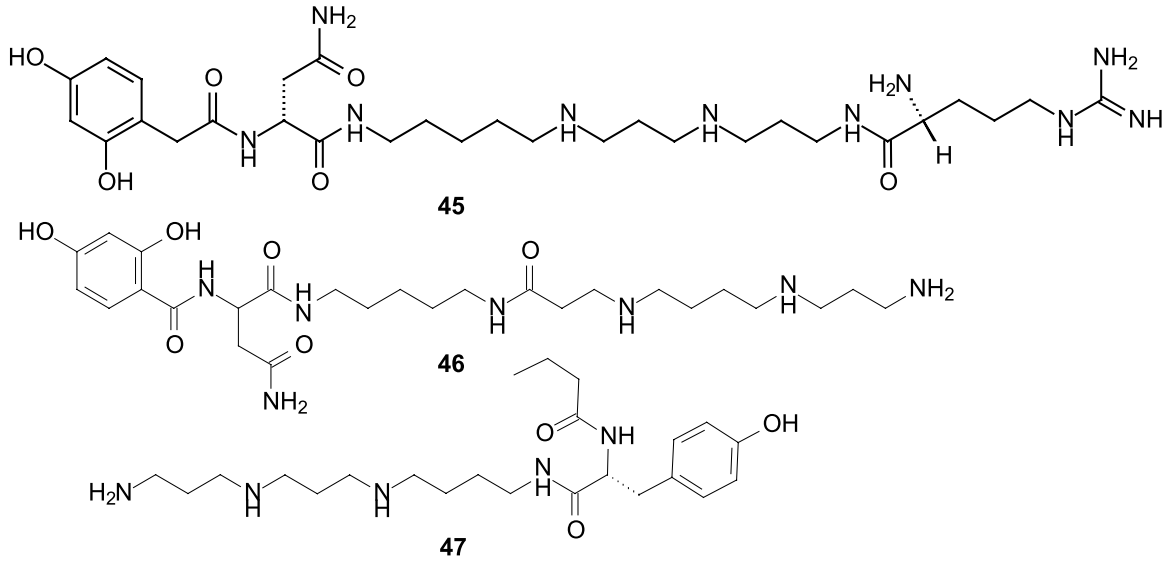

Fig. 15. Polyamine toxins found in spider **45**, **46** and wasp **47** venom.

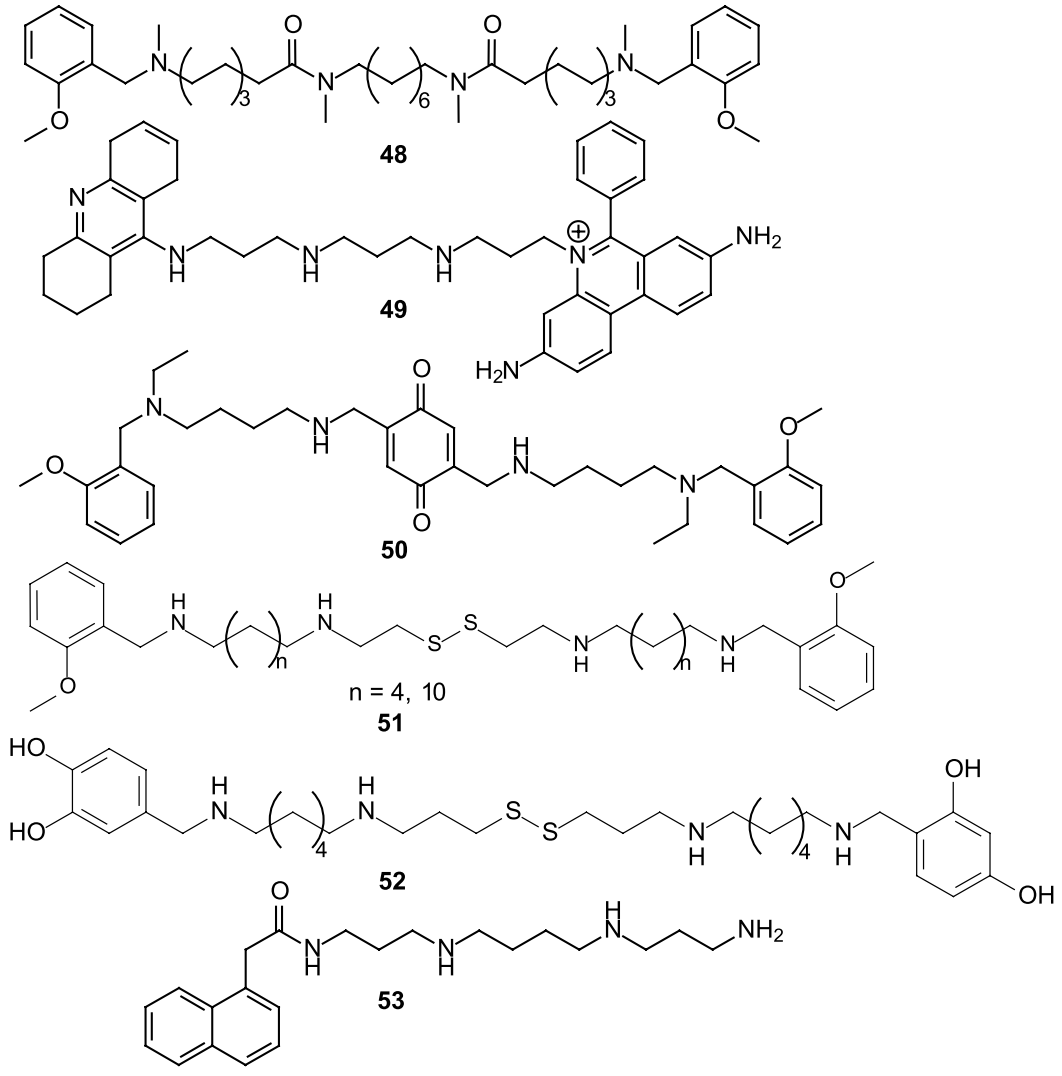

Fig. 16. Engineered structures to fight Alzheimer's disease.

Another example of a polyamine spider toxin is JSTX-3 **46**, isolated from the venom of *Nephila clavata*; JSTX-3 is able to noncompetitively block the AMPA glutamate receptor, providing neuroprotective effects [113]. In addition, the antiepileptic effect of this toxin was noted, as demonstrated *in vitro* on neurons of the human CA1 hippocampus [114].

The toxin PhTX-433 **47**, present in the venom of wasps of the species *Philanthus triangulum*, is a potent antagonist of AMPA and the kainate receptor [115]. Its strong blocking effect on nicotinic acetylcholine receptors (nACh) was also noted [116]. Their activity against iGlu receptors made it possible to use PhTX-433 to determine their subunit composition [117].

Interest in the structures and the associated biological action in the mammalian CNS were not limited to the natural polyamine toxins only. Attempts have been made to establish the structure-activity relationship [118], which led to the creation of several synthetic analogs—antagonists of glutamate [119, 120] and nicotinic acetylcholine [121, 122] receptors.

Moreover, it is necessary to consider compounds with potential therapeutic benefits in treating neurodegenerative diseases. A common feature for the diseases of this group is irreversible, progressive death of nerve cells with the onset of symptoms of impaired memory and motor functions. Currently, there are no drugs that can cure (prevent the pathological process) the patients suffering from diseases of this group. Moreover, the mechanisms underlying these disorders have not yet been established.

The pharmacology of neurodegenerative diseases is reduced to maintenance therapy. The main targets of exposure are ionotropic channels and conjugated enzymes of neurotransmitter degradation.

Below are the structures of the polyamine series that are of potential interest in the fight against these pathologies.

Based on the concept of multi-target-directed-ligands explained by Bolognesi [123], several structures **48**–**50** were designed to control the Alzheimer's disease (Fig. 16). All of them exhibited an inhibitory effect on acetylcholinesterase (AChE), slowing down the degradation of the main neurotransmitter, acetylcholine, with IC_{50} values ranging from 1.5 nM to 0.17 μM. In addition, the inhibitory effect of compounds **49**, **50**, and **53** was recorded [124] on the aggregation of amyloid protein (Aβ40), which has a destructive effect on the nervous tissue. The deposition of amyloid aggregates is among the main hypotheses regarding the mechanisms of Alzheimer's disease [125, 126].

Disulfide analogs of benextramine **51**, **52** (a known blocker of α-adrenergic receptors), have another target of action, different from the structures described above. Di Paolo demonstrated the ability of these compounds to inhibit human monoamine oxidase isoforms (MAO A and MAO B), one of the main enzymes of monoamine catabolism [127]. Biogenic monoamines—dopamine, serotonin, catecholamines—are the most important neurotransmitters, in the degradation of which MAO is involved.

Blocking the action of monoamine oxidase is an attractive target to fight neurodegenerative diseases, such as Parkinson's and Alzheimer's disease, as well as some neuropsychiatric disorders, including depression [128–130].

CONCLUSIONS

Research in the polyamine biochemistry will provide an in-depth understanding of the role of these compounds in the functioning of living systems—from primitive bacteria to humans. The study of the cellular transport of polyamines, their interactions with receptors, membranes, macromolecules of nucleic acids, and proteins, will significantly expand the arsenal of pharmacological agents to combat pathologies, such as oncological, cardiovascular and neuropsychiatric diseases.

Authors' contribution

The authors equally contributed to the research work, the arrangement of the materials and the technical design of the article were made by O.S. Egorov.

The authors declare no conflicts of interest.

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