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REVIEW ARTICLE

Azaadamantanes, a New Promising Scaffold for Medical Chemistry[1]

E. V. Suslov[a], K. Yu. Ponomarev[a], K. P. Volcho[a, 2], and N. F. Salakhutdinov[a]

[a] *Novosibirsk Institute of Organic Chemistry, Siberian Branch, Russian Academy of Sciences, Novosibirsk, 630090 Russia*

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Abstract—Azaadamantanes are nitrogen-containing analogs of adamantane, which contain one or more nitrogen atoms instead of carbon atoms. This substitution leads to several specific chemical and physical properties. The azaadamantane derivatives have less lipophilicity compared to their adamantane analogs, which affects both their interaction with biological targets and bioavailability. The significant increase in the number of publications during the last decade (2009–2020) concerning the study of reactivity and biological activity of azaadamantanes and their derivatives indicates a great theoretical and practical interest in these compounds. Compounds with pronounced biological activity have been already discovered among azaadamantane derivatives. The review is devoted to the biological activity of azaadamantanes and their derivatives. It presents the main methods for the synthesis of di- and triazaadamantanes and summarizes the accumulated data on studying the biological activity of these compounds. The prospects for the use of azaadamantanes in medical chemistry and pharmacology are discussed.

Keywords: diazaadamantanes, triazaadamantanes, rigit compounds, medicinal chemistry, pharmacology, biological activity, antiviral activity, antimicrobial activity, antitumor activity

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INTRODUCTION

Azaadamantanes are nitrogenous analogs of adamantine, which contain one or more nitrogen atoms instead of carbon atoms (Fig. 1). These compounds have been known since the 50s of the last century [1, 2]. However, systematic study of the biological activity of azaadamantanes and their derivatives began more recently, and the main successes have been achieved in the last 20 years. The partial substitution of the nitrogen atoms for carbon significantly changes both chemical and physical properties, thus leading, in particular, to higher solubility in water of azaadamantanes compared to adamantanes. The various biological activity of azaadamantanes [3–10] in combination with moderate toxicity and different ways of their synthesis from available reagents makes them attractive for use as a basic block in the design of new biologically active compounds.

Some diazaadamantane derivatives have been found in nature, e.g., the alkaloids acosmine, acosmine acetate, and panacosmine isolated from the *Acosmium panamense* seed extract and dasycarpumine isolated from the *Acosmium dasycarpum* extract [9]. Acosmin and its derivative bowdichine, the ester of 3,4,5-trimethoxybenzoic acid, were obtained from the bark of the stem of *Bowdichia virgilioides* [9]. It should be noted that the biological role of these compounds is not yet clear, and their biological activity has not been studied.

The first section of this review provides brief information on the main methods for the synthesis of di- and triazaadamantanes with the nodal arrangement of the nitrogen atoms. For the first time, we systemized the accumulated literature data on the biological activity of these types of azaadamantanes. The review is structured according to the type of biological activity of azaadamantanes.

METHODS OF THE SYNTHESIS OF AZAADAMANTANES

The methods of the synthesis of azaadamantanes are considered in detail in the works [3, 4, 11, 12]. In this review, for the reader's convenience, we present the most widely used approaches to the synthesis of 1,3-diazaadamantanes and 1,3,5-triazaadamantanes, the skeletons of which are most often found in the biologically active azaadamantane derivatives. Usually, the methods for the synthesis of azaadamantanes are

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Abbreviations: MTD maximum tolerated dose; MIC, minimum inhibitory concentration; TGI, tumor growth inhibition; CC_{50}, concentration causing 50% death of cells; ED_{50}, median effective dose required to achieve 50% of the desired response in 50% of experimental units; IC_{50}, half maximal inhibitory concentration; LD_{50}, median dose causing 50% death of experimental units; LD_{100}, median dose causing 100% death of experimental units; SI, selectivity index.

[2] Corresponding author: phone: +7 (383) 330-88-70; e-mail: volcho@nioch.nsc.ru.

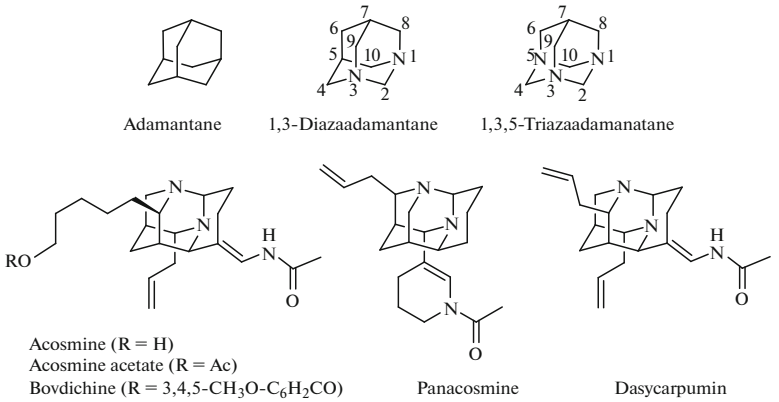
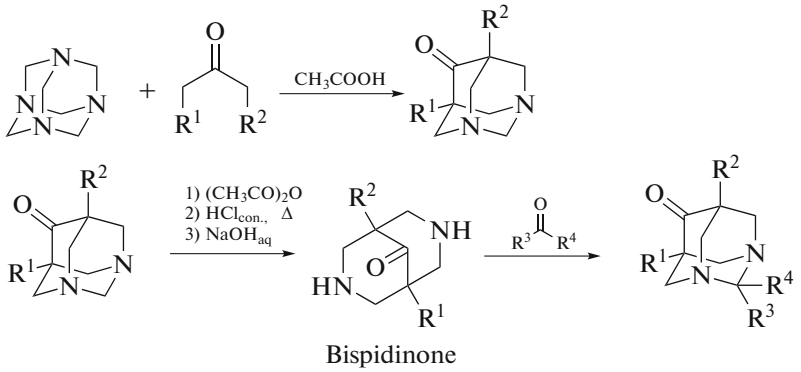


Fig. 1. Examples of azaadamantanes structure. Some natural diazaadamantane derivatives [9].

based on the condensation of acyclic or monocyclic compounds, followed by the closure of three cycles of the heteroadamantane structure in one stage.

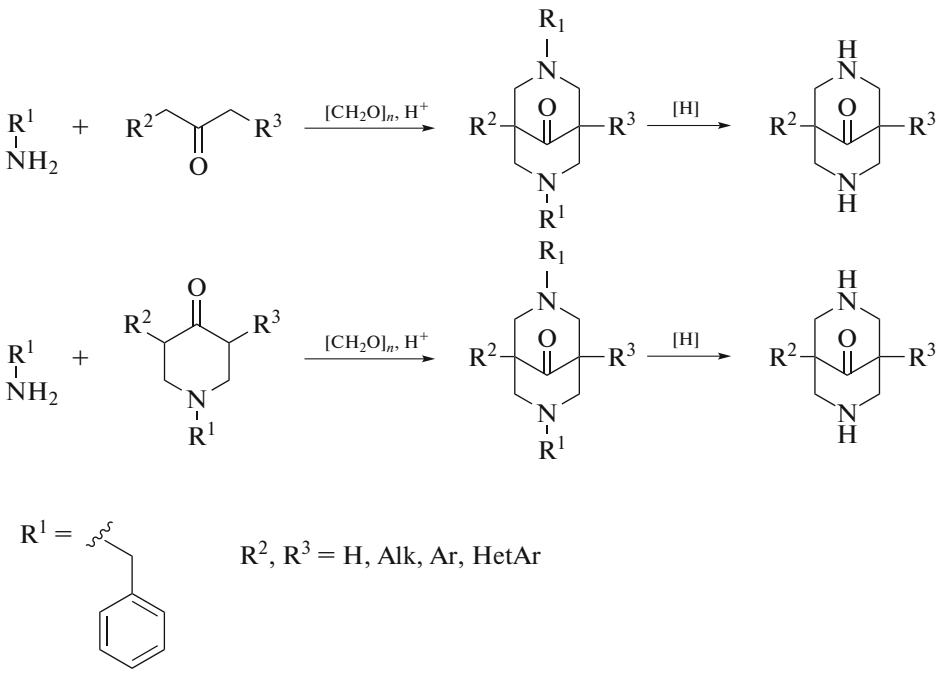
Synthesis of 1,3-diazaadamantane and its derivatives. A frequently used method, which makes it possible to obtain azaadamantanes that contain two nitrogen atoms in nodal positions in good yields, is the condensation of various ketones with urotropine (hexamethylenetetramine) involving several successive Mannich reactions (Scheme 1) [11]. Both aromatic and aliphatic ketones can be used as a carbonyl component. This approach allows for the synthesis of diazaadamantanes that contain both symmetric and asymmetric substituents in positions 5 and 7 of the heteroadamantane structure.



Scheme 1. Synthesis of 1,3-diazaadamantanes by condensation of ketones with urotropine and preparation of their 2-substituted derivatives [11].

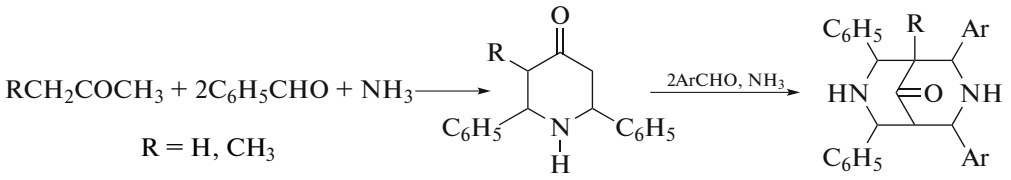
The keto group in position 6 of the diazaadamantane backbone can be reduced to the hydroxyl group [13] or methylene group [14] or converted into another functional group [15] using classical methods of organic synthesis for the modification of ketones. The aminal methylene group in position 2 of diazaadamantane can be relatively easily replaced by another fragment of the diazaadamantane cycle under the action of various reagents [16, 17], usually acetic anhydride. Resulting bispidine can be converted back to diazaadamantane under the action of various condensing agents, such as ketones, aldehydes, dihalides, etc.

One of the most common methods for the synthesis of bispidines, in addition to the disclosure of the diazaadamantane backbone (Scheme 1), is the interaction of amines and ketones with formaldehyde under acidic conditions by the Mannich reaction (Scheme 2) [18, 19]. However, it should be taken into account that the nitrogen-containing component should contain a well-leaving protective group (e.g., benzyl) to obtain *N*,*N*-unsubstituted bispidine.



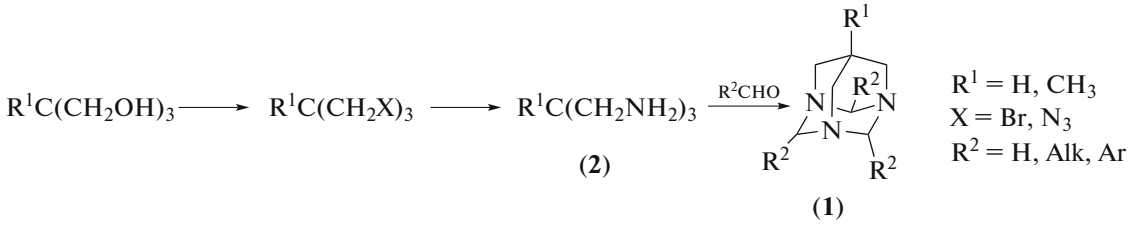
Scheme 2. Synthesis of bispidines by the interaction of amines and ketones with formaldehyde [18, 19].

Another modification of the Mannich reaction for the synthesis of bispidines is the use of ammonia or ammonium acetate as a nitrogen-containing component and aromatic aldehydes instead of formaldehyde (Scheme 3) [20–25]. In this case, various substituted piperidones are formed as intermediates, which can be converted into corresponding diazaadamantanes (Scheme 1).



Scheme 3. Synthesis of bispidines by the interaction of ammonia with ketones and aromatic aldehydes [20–25].

Synthesis of 1,3,5-triazaadamantane and its derivatives. The most common method for the synthesis of 1,3,5-triazaadamantane derivatives (**1**) is based on the preparation of triamines (**2**) from tris(oxymethyl)methane and its homologs through the synthesis and reduction of the corresponding triazides, followed by the interaction of the resulting triamine with various compounds that contain the carbonyl group (Scheme 4) [26].



Scheme 4. Synthesis of 1,3,5-triazaadamantanes from tris(oxymethyl)methane and its homologs [26].

The synthesis of the derivatives of 1,3,5-triazaadamantane that contain different functional groups in position 7 of the heteroadamantane structure can be based on 7-nitro-1,3,5-triazaadamantane (**3**), which, in turn, is synthesized by condensation of nitromethane with hexamethylenetetramine in the presence of

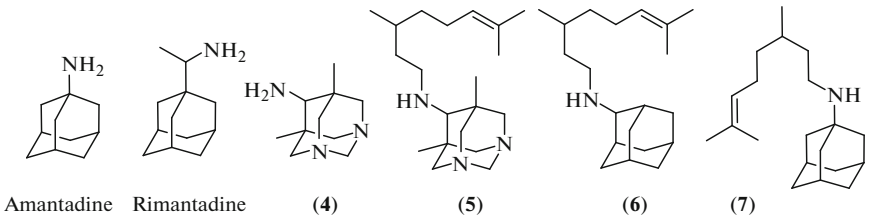


Fig. 2. Aminoadamanatanes and aminodiadamantanes with antiviral activity [30–32].

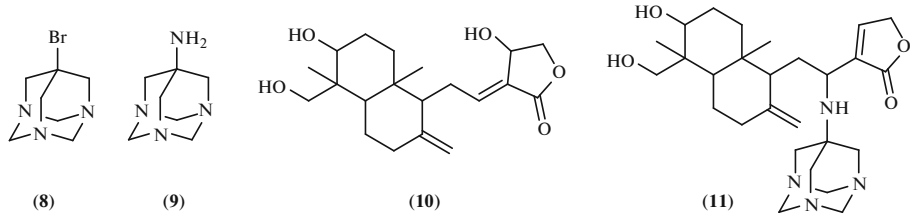
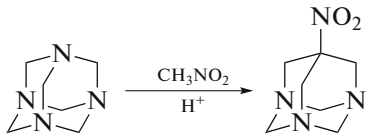


Fig. 3. 7-Substituted 1,3,5-triazaadamantanes with antiviral activity.

acetic acid [27] (Scheme 5). The subsequent modification of the nitro group can be performed using classical methods of organic chemistry.



Scheme 5. Synthesis of 7-nitro-1,3,5-triazaadamantane [27].

The existing methods for the synthesis of di- and triazaadamantane derivatives, especially those based on the condensation of hexamethylenetetramine with carbonyl and nitro compounds, make these azaadamantanes available for study and use in the synthesis of other azaadamantane derivatives.

BIOLOGICAL ACTIVITY OF AZAADAMANTANES

Antiviral activity. Some of the first antiviral drugs against the influenza virus were amantadine and rimantadine (Fig. 2). Their antiviral effect is due to blocking the ion M2 channels of the virus, thus preventing its penetration into the cell [28]. However, at present, almost all epidemically important strains of the influenza virus have developed resistance to these drugs [29]. The introduction of two nitrogen atoms and two methyl groups in compound (**4**) (Fig. 2) made it possible to partially overcome the resistance of the A/California/07/09 (H1N1)pdm09 influenza virus strain to rimantadine and increased the selectivity index SI to 13, compared with SI = 5 for rimantadine (SI = CC_{50}/IC_{50}, where CC_{50} is the concentration causing the death of 50% of cells and IC_{50} is the half-maximal inhibitory concentration) [30]. The addition of citronellal, the fragment of the monoterpenoid, to aminodiazaadamantane (**4**), followed by subsequent reduction led to the formation of amine (**5**), which demonstrated the high SI value of 30 at the IC_{50} value of 8 μM [31]. The introduction of the citronellal residue into 1- or 2-aminoadamantanes that do not contain nodal nitrogen atoms (compounds (**6**) and (**7**)) also led to an increase, although less significant, in the activity against the influenza virus (SI = 22) [32]. The results of computer modeling [30] suggest that diazaadamantane (**5**) can bind to the M2 protein channel, although its effect on other molecular targets cannot be excluded.

Among the triazaadamantane derivatives, the pronounced antiviral activity was shown for 7-nitro-1,3,5-triazaadamantane (**3**) (Scheme 5) against the Frunze strain of influenza A virus at a concentration of 1 μM, its hydrochloric acid salt against the 1C and 9C herpes viruses at a concentration of 100 μM, and 7-bromo- and 7-amino-1,3,5-triazaadamantanes (**8**) and (**9**) (Fig. 3) against the virus Newcastle disease at a concentration of 0.125 μM [16].

The authors of the works [33, 34] have synthesized and studied the biological activity of new derivatives of native diterpenoid andrographolide (**10**) (Fig. 3), which exhibit a wide range of biological activity. It was shown that compound (**11**), which combines the 7-amino-1,3,5-triazaadamantane and andrographolide fragments, inhibits the replication of various viruses including SARS coronavirus (strain Urbani), enterovirus-71 (strain Tainan/4643/98), and Rift Valley fever virus (strain MP-12) [35] at a concentration of 1 μg/mL. Compound (**11**) at a higher concentration (50 μg/mL) was effective against viruses of influenza (A H1N1/09), hepatitis A (pHM175), hepatitis B (02094), hepatitis C (CON1), herpes simplex (type 2), human papillomavirus (type 8), HIV-1 (group M), Dengue fever (type 2, New Guinea C), Japanese

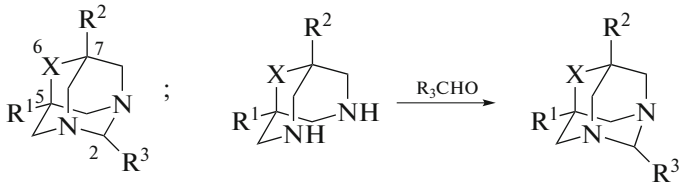
encephalitis (SA14/V1), and equine encephalitis of Venezuelan origin (TC-83).

Thus, one can conclude that although di- and triazaadamantanes exhibit only moderate inhibitory activity against some viruses, their attachment to other biologically active compounds can significantly enhance the potential of the resulting products.

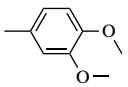
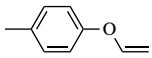
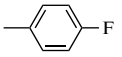
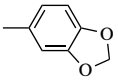
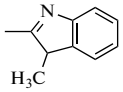
Antimicrobial activity. Much attention was paid to the study of the antimicrobial activity of azaadamantane derivatives, and the most significant contribution was made by researchers from Armenia. In 1986, they published data on the synthesis of 2-substituted 5,7-dimethyl-1,3-diazaadamantanes that contained aliphatic, aromatic, heteroaromatic, heterocyclic, and spirocyclic substituents. They also synthesized monosaccharides based on 1,5-dimethyl-3,7-diazabicyclo[3.3.1] nonan-9-one (**12**) and various aldehydes and ketones [36]. The antibacterial activity of the compounds (**13**–**19**) was studied on a model of generalized staphylococcal infection in white mice caused by *Staphylococcus aureus* (*S. aureus* strain 4-O) (Fig. 4).

The most active compounds contained fragments of pyridine (**15**) and 2,2-dimethyltetrahydropyran (**16**), which prolonged the life of infected animals by 20–30% when administered once at doses of 800 and 1500 mg/kg, respectively. The other studied diazaadamantane derivatives did not increase the life expectancy of infected animals compared to the control. It has been shown that these diazaadamantane derivatives are low-toxic and are well tolerated by animals with a single administration at doses of 1500–2000 mg/kg.

In 2008, Arutyunyan et al. presented the results of studying the antibacterial activity of a large set of 2-substituted diazaadamantanes, i.e., derivatives that contained the methyl, ethyl, or isopropyl substituents at positions 5 and 7 and the methylene, carbonyl, or alcohol groups at position 6 of the diazaadamantane molecule. Various aromatic and heteroaromatic fragments were used as substituents at position 2 (Scheme 6) [37]. The activity of the previously described 6-amino-5,7-dimethyl-1,3-diazaadamantane (**4**) was also studied.



(**4**), (**20**–**27**) (**28**–**38**)

	R^1	R^2	R^3	X
(20)	CH_3	H	H	CH_2
(21)	CH_3	CH_3	H	CO
(22)	CH_3	*i*-C_3H_7	H	CO
(23)	CH_3	C_6H_5	H	CO
(24)	CH_3	CH_3	H	CHOH
(25)	CH_3	*i*-C_3H_7	H	CHOH
(26)	C_2H_5	C_2H_5	H	CHOH
(27)	*i*-C_3H_7	*i*-C_3H_7	H	CHOH
(4)	CH_3	CH_3	H	NH_2
(28)	CH_3	CH_3		CO
(29)	CH_3	CH_3		CH_2
(30)	CH_3	CH_3		CH_2
(31)	CH_3	CH_3		CH_2
(32)	CH_3	CH_3		CH_2
(33)	CH_3	CH_3		CH_2
(34)	CH_3	CH_3		CHOH
(35)	C_2H_5	C_2H_5		CHOH
(36)	C_2H_5	C_2H_5		CHOH
(37)	C_2H_5	C_2H_5		CHOH
(38)	C_2H_5	C_2H_5		CHOH

Scheme 6. 5,7-Dialkyldiazaadamantanes and the synthesis of their 2-aryl-substituted derivatives [37].

The agar-diffusion method was used to study the antibacterial activity of the compounds against gram-positive staphylococci (*S. aureus* 209p, *S. aureus* 1, *S. aureus* Makarov, *S. aureus* 34, and *S. aureus* 118) and gram-negative bacteria (*Shigella dysenteriae Flexneri* (*Sh. dysent. Flexneri*), *Salmonella enterica* serovar *Typhimurium* (*E. typhi*), *Escherichia coli* (*E. coli*), and *Proteus* (*Prot.*). The activity of the tested compounds

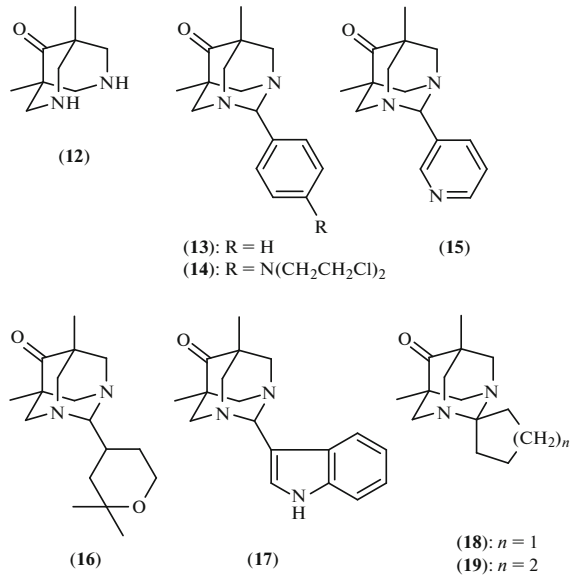


Fig. 4. 1,5-Dimethylbispidin-9-one and its derivatives, 2-substituted 5,7-dimethyl-1,3-diazaadamantan-6-ons with antibacterial activity [36].

was evaluated by the diameter (mm) of the zone of no microorganism growth at the site of application at a dose of 4 mg after the cultivation with microorganisms for 24 h. The activity was considered high or intermediate if the growth suppression zone was >20 mm or 15–20 mm, respectively (Table 1).

The most effective compounds against both gram-positive and gram-negative microorganisms were 5,7-dimethyl-1,3-diazadamantantane (**20**) and its 2-pyridyl-substituted analog (**29**). These compounds were found to be more effective than sulfadimesine but less effective than norsulfazol, which were used as the reference drugs. Introduction of the carbonyl, hydroxyl, or amino groups to position 6 (compounds (**4**), (**20–27**)) and the pyridyl-3- (**32**), (**35**) or furyl groups (**37**) to position 2 led to a decrease in the antibacterial activity of the compounds. Introduction of the aromatic (compounds (**30**), (**31**), (**33**), (**36**)), thienyl (**34**), or indole (**38**) groups to position 2 led to the disappearance of antibacterial properties.

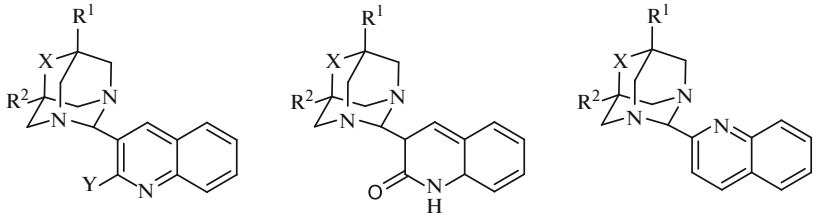
Later, the authors of [38] described the study of the activity of various quinolines (**39–53**) (Fig. 5) against gram-positive (*S. aureus* 209p) and gram-negative (*Sh. dysent. Flexneri* 6858, *E. coli* 0-55) bacteria. These compounds contained the diazaadamantane fragment with the methyl, ethyl, or propyl substituents at positions 5 and 7 and carbonyl, alcohol, or methylene groups at position 6. The antibacterial activity was evaluated by the method described in the work of Arutyunyan et al. [37] using 5-nitro-8-hydroxyquinoline as a positive control. Compounds (**40, 41, 43, 44, 49–53**) showed weak antibacterial activity (d = 10–13 mm) against all studied bacterial species, which was significantly lower compared to that of nitroquinoline (d = 20–28 mm). The other compounds demonstrated no antibacterial properties.

The antibacterial activity of azomethines (**54–66**) (Scheme 7) in the form of dihydrochlorides was studied [39] against gram-positive (*S. aureus* 209p, *S. aureus* 1) and gram-negative (*Sh. dysent. Flexneri* 6858, *E. coli* 0-55) bacteria using the diffusion in agar and serial dilutions methods. The tested compounds (5 mg) were placed on Petri dishes and incubated with microorganisms. The diameter of the zones of no microorganism growth after incubation for 20–24 h

Table 1. Antibacterial activity of compounds (**4**), (**20–27**), (**29**), (**32**), (**35**), and (**37**) [37]

Compound	Diameter of no growth zone, mm[a]					
	Gram-positive bacteria		Gram-negative bacteria			
	S. aureus 209p	*S. aureus* 1	*Sh. dysent. Flexneri* 6858	*E. typhi* 79	*E. coli* 0-55	*Prot.*
(**4**)	9	7	7	7	–	–
(**20**)	22	13	13	15	18	14
(**21**)	5	5	5	6	–	–
(**22**)	5	5	13	15	7	10
(**23**)	0	0	7	7	–	–
(**24**)	5	6	5	6	–	–
(**25**)	6	0	0	6	–	–
(**26**)	10	10	10	15	15	11
(**27**)	7	7	7	10	–	–
(**29**)	22	20	18	22	15	13
(**32**)	10	10	13	14	10	5
(**35**)	9	13	6	8	–	–
(**37**)	9	7	9	10	–	–
Norsulfazol	30	30	20	30	–	–
Sulfadimesine	14	14	0	0	–	–

[a] A dash (–) means no activity. Compounds (**28**), (**30**), (**31**), (**33**), (**34**), (**36**), and (**38**) were not active against studied bacteria.



(**39–47**) (**48–50**) (**51–53**)

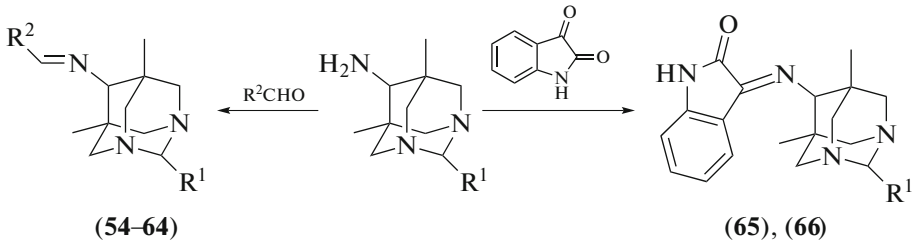
(**39**) $R^1 = R^2 = CH_3$, X = CO, Y = Cl
(**40**) $R^1 = R^2 = CH_3$, X = CHOH, Y = Cl
(**41**) $R^1 = R^2 = CH_3$, $X = CH_2$, Y = Cl
(**42**) $R^1 = R^2 = CH_3$, X = CO, Y = I
(**43**) $R^1 = R^2 = CH_3$, X = CHOH, Y = I
(**44**) $R^1 = R^2 = CH_3$, $X = CH_2$, Y = I
(**45**) $R^1 = R^2 = C_2H_5$, X = CO, Y = Cl
(**46**) $R^1 = R^2 = C_3H_7$, X = CO, Y = Cl
(**47**) $R^1 = CH_3$, $R^2 = C_3H_7$, X = CO, Y = Cl

(**48**) $R^1 = R^2 = CH_3$, X = CO
(**49**) $R^1 = R^2 = CH_3$, X = CHOH
(**50**) $R^1 = R^2 = CH_3$, $X = CH_2$

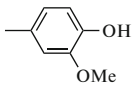
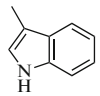
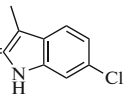
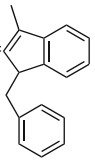
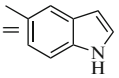
(**51**) $R^1 = R^2 = CH_3$, X = CO
(**52**) $R^1 = R^2 = CH_3$, X = CHOH
(**53**) $R^1 = R^2 = C_2H_5$, X = CO

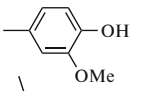
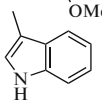
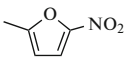
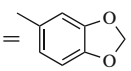
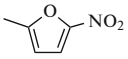
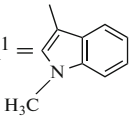
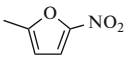
Fig. 5. 2-Quinoline-substituted 1,3-diazaadamantanes with antibacterial activity [37].

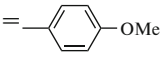
was measured as described in works [37, 38]. For the most active compounds, their minimum suppressive concentration (MIC) against *S. aureus* 209p and *Sh. dysent. Flexneri* 6858 was evaluated in tests with serial dilutions. Furazolidone was used as a positive control.



(**54–64**) (**65**), (**66**)

(**54**) R^1 = H R^2 = 
(**55**) R^1 = H R^2 = 
(**56**) R^1 = H R^2 = 
(**57**) R^1 = H R^2 = 
(**58**) R^1 = H R^2 = 

(**59**) R^1 =  R^2 = 
(**60**) R^1 =  R^2 = 
(**61**) R^1 =  R^2 = 
(**62**) R^1 =  R^2 = 
(**63**) R^1 =  R^2 = 
(**64**) R^1 =  R^2 = 

(**65**) R^1 = H
(**66**) R^1 = 

Scheme 7. 6-Aminodiazaadamantanes and the synthesis of their azomethine derivatives [39].

Table 2. Antibacterial activity of compounds (**54**), (**56**–**60**), and (**62**–**66**) [39]

Compound	Diameter of no growth zone, mm (MIC, mg/mL)[a]			
	Gram-positive bacteria		Gram-negative bacteria	
	S. aureus 209p	*S. aureus* 1	*Sh. dysent. Flexneri* 6858	*E. coli* 0-55
(**54**)	14	14	15	13
(**56**)	13	13	15	13
(**57**)	18	19	30 (125)	28
(**58**)	14	14	15	15
(**59**)	0	0	15	15
(**60**)	18	18	32 (125)	28
(**62**)	30 (125)	27	25 (250)	23
(**63**)	32 (125)	28	27 (250)	24
(**64**)	29 (125)	25	23 (250)	23
(**65**)	14	14	14	12
(**66**)	15	14	15	15
Furazolidone	25 (31)	24	24 (31)	23

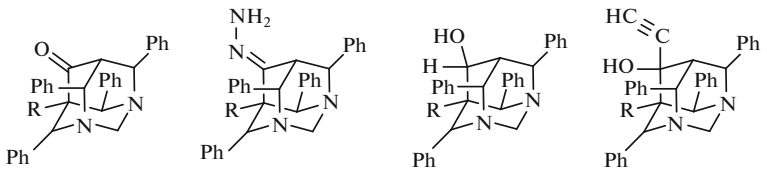
[a] Compounds (**55**) and (**61**) were not active against studied bacteria.

All the studied azomethine hydrochlorides, except for compounds (**55**) and (**61**), had antibacterial activity (Table 2). Dihydrochlorides (**62**–**64**) that contained the nitrofuryl groups showed the greatest bacteriostatic activity. They had a comparable effect on gram-positive and gram-negative bacteria and were, as a rule, more active than furazolidone. Dihydrochloride (**57**) and (**60**) with the indole groups were effective against gram-negative bacteria. The MIC values for hydrochlorides (**57**), (**60**), and (**62**–**64**) were 125–250 μg/mL, which were significantly higher than this value for the reference drug furazolidone (MIC = 31 μg/mL).

Antimicrobial activity of several 4,8,9,10-tetraphenyl-1,3-diazaadamantanes (**67**–**72**) against gram-positive and gram-negative bacteria, spore-forming bacteria, yeast-like fungi, and dermatophyte fungi (*Bacillus mycoides, Bacillus subtilis* (*B. subtilis*), *Bacillus anthracis, S. aureus, Bacteria carativorum, Corynebacterium, E. coli; Saccharomyces cerevisiae, Sarcina lutea, Epidermophyton rubrum, Trichophyton gypseum, Fusarium aolani,* and *Candida albicans*) was studied by Baisalbayeva et al. on a nutrient medium using the method of serial dilutions (Fig. 6) [40]. The activity of the compounds was evaluated by the minimum bacteriostatic or mycostatic concentration (μg/mL).

Among the studied compounds, diazaadamantanes (**67**) and (**71**) showed significant activity against gram-positive bacteria *Corynebacterium* (MIC = 7.4 and 0.27 μg/mL, respectively) and compound (**68**) against *Sarcina lutea* (MIC = 0.5 μg/mL). The other compounds were less active (MIC = 14–67 μg/mL). Data on the use of the reference drug are not provided in the article.

The antibacterial activity of 4,8,9,10-tetraaryl-1,3-diazaadamantanes (**73**–**95**) that contained various substituents in the aromatic ring and the previously mentioned compounds (**67**), (**68**), and (**71**) that contained unsubstituted phenyl groups was studied against the *B. subtilis, S. aureus*, and *E. coli* bacteria by Balaji et al. [41] (Fig. 7, Table 3). The authors evaluated the MIC values by the diffusion in agar method



(**67**), (**69**), (**71**), (**72**): R = H
(**68**), (**70**): R = CH_3

Fig. 6. 4,8,9,10-Tetraphenyl-1,3-diazaadamantanes with antibacterial activity [40].

(**73–83**) (**84–95**)

	R^1	R^2		R^1	R^2
(**73**), (**85**)	H	4-F–C_6H_4	(**79**), (**91**)	H	4-CH_3O–C_6H_4
(**74**), (**86**)	H	2-Cl–C_6H_4	(**80**), (**92**)	H	4-C_2H_5O–C_6H_4
(**75**), (**87**)	H	4-Cl–C_6H_4	(**81**), (**93**)	H	2,5-CH_3O–C_6H_3
(**76**), (**88**)	H	4-Br–C_6H_4	(**82**), (**94**)	H	3,4-CH_3O–C_6H_3
(**77**), (**89**)	H	4-CH_3–C_6H_4	(**83**), (**95**)	H	3,4,5-CH_3O–C_6H_2
(**78**), (**90**)	H	2-CH_3O–C_6H_4	(**84**)	CH_3	C_6H_5

Fig. 7. 4,8,9,10-Tetraaryl-1,3-diazaadamantanes with antibacterial activity [41].

using a microbial inoculum (106 cells/mL) (Table 3). Streptomycin was chosen as a control.

Diazaadamantanes (**80**), (**85**), (**87**), (**88**), and (**93**) showed high activity against *B. subtilis* bacteria (MIC = 6.25–12.5 μg/mL), compounds (**68**), (**71**), (**81**), (**83**), (**85**), and (**8**8) were active against *S. aureus* (MIC = 6.25–12.5 μg/mL), and compounds (**82**) and (**95**) were active against *E. coli* (MIC = 12.5 and 6.25 μg/mL, respectively). The other compounds inhibited the growth of bacteria at concentrations of 25–100 μg/mL or had no inhibitory activity at all. The reference drug, streptomycin, suppressed the growth of the *B. subtilis* and *S. aureus* bacteria at a concentration of 12.5 μg/mL and *E. coli bacteria,* at 6.25 μg/mL. In general, fluoro-, chloro-, bromo-, or alkoxy-substituted aryldiazaadamantanes were more active in comparison with compounds unsubstituted at the aromatic fragment [41].

Much less attention was paid to the study of the bacteriostatic and fungistatic action of 7-substituted 1,3,5-triazaadamantanes. The first data were obtained in the 70s of the last century by Hodge et al. [42] for 7-nitro- (**3**), 7-amino- (**9**), and 7-hydroxylamino- (**96**) 1,3,5-triazaadamantanes (Fig. 8). Using the stroke method, the fungistatic effect of compounds (**3**) and (**9**) against fungi of the *Fusarium oxysporum* species was shown only at high concentrations (500–1000 μg/mL). Triazaadamantanamine (**9**) at the same concentrations was also active against *Aspergillus fumigatus*. Compound (**96**) was found to be active against *S. aureus* and *Pasteurella pseudotuberculosis* (MPC = 250–500 μg/mL), *Streptococcus fecalis* (MPC = 500–

Table 3. Antibacterial activity of compounds (**67**), (**68**), (**71**), (**80–83**), (**85**), (**87**), (**88**), (**93**), and (**95**) [41]

Compound	MIC, mg/mL[a]		
	B. subtilis	*S. aureus*	*E. coli*
(**67**)	50	–	25
(**68**)	–	12.5	–
(**71**)	12.5	12.5	100
(**80**)	12.5	–	100
(**81**)	50	12.5	50
(**82**)	50	50	12.5
(**83**)	50	12.5	50
(**85**)	6.25	6.25	100
(**87**)	6.25	50	50
(**88**)	6.25	6.25	–
(**93**)	6.25	–	50
(**95**)	50	–	6.25
Streptomycin	12.5	12.5	6.25

[a] A dash (–) means no activity. Compounds (**72–79**), (**84**), (**86**), (**89–92**), and (**94**) had low antibacterial activity (MIC > 50 mg/mL) or were not active against studied bacteria.

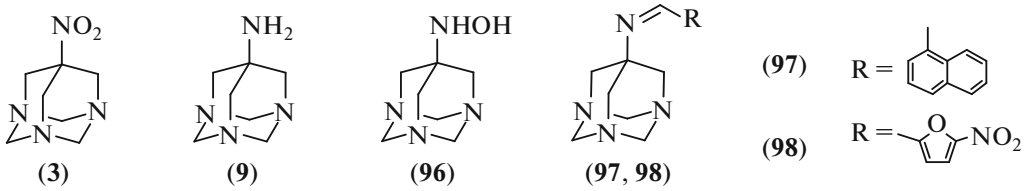


Fig. 8. 7-Substituted 1,3,5-triazaadamantanes and some of their derivatives with antibacterial activity [42].

750 μg/mL), and *Streptococcus hemolyticus* and *Sh. dysent.* (MPC = 500–1000 μg/mL). Data on the reference preparation are not provided in the work.

The antibacterial activity of the 7-amino-triazaadamantane derivatives (**97**) and (**98**) in the form of hydrochloric acid salts that contained the naphthyl and 5-nitrofuryl substituents, respectively, was studied by Arutyunyan et al. (Table 4) [39]. Nitrofuryl-containing compound (**98**) showed moderate bacteriostatic activity against gram-positive and gram-negative bacteria. The method of serial dilutions showed that the MIC value for compound (**98**) was 125 μg/mL, which is significantly higher than that for the reference drug furazolidone.

The presence of antiprotozoal activity of quaternary salts of 5,7-dimethyl-1,3-diazaadamantanone was suggested after virtual screening using the trypanothione reductase (TryR) model and studied by Perez-Pineiro et al. [43]. Inhibition of this enzyme led to the accumulation of toxic oxygen products in trypanosomes, thus causing the oxidation of thiols in the cell membrane and the death of parasites. It has been shown that some bromobenzyl-containing diazaadamantanes (Fig. 9) can bind to trypanothione reductase. However, even for the most active *N*-(3-brombenzyl) derivative of diazaadamantane (**99**), the IC_{50} value was more than 100 μM, which significantly exceeded the effective concentration of known drugs, e.g., nifurtimox [44].

Summarizing the literature data, it can be noted that diazaadamantane derivatives, which contain the methyl substituents at positions 5 and 7, the heteroaromatic substituent at position 2, and the alcohol or nitrofuran group at position 6 attached through the azomethine fragment, have the greatest antibacterial activity. In addition, antibacterial properties were found for 4,8,9,10-tetraaryl-1,3-diazaadamantanes that contain various substituents in the aromatic ring. Despite the small amount of data on the activity of the triazaadamantane derivatives, it should be noted that they have a lower inhibitory effect on microorganisms compared to diazaadamantanes.

Antitumor activity. The study of the antitumor activity of azaadamantanes was started by Chachoyan et al. in 1991 [45]. They obtained and studied diazaadamantanes (**17**), (**100–110**) (Fig. 10) that contained fragments of substituted indoles and showed their high antitumor activity [46].

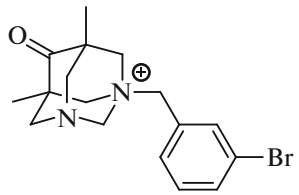
The antitumor activity of the compounds was studied in rats with transplantable tumors, i.e., sarcoma 45, Pliss lymphosarcoma, and Shvets leukemia. The most active compounds were also studied in mice with sarcomas 180 and 37. The therapeutic effect of the compounds was evaluated by the percentage of tumor growth inhibition (TGI, %) and compared with the effectiveness of the previously studied 5-(dimethylaminosulfonyl)-indole-3-carboxylic acid (**111**) [46] and 5,7-dimethyl-6-oxo-1,3-diazaadamantane hydrochloric acid (**21**). A single therapeutic dose for each compound was assessed as ~1/20 of LD_{100}.

It was found that the indolyl-1,3-diazaadamantane derivatives, regardless of the position and nature of substituents in the indole ring, and compound (**111**) are usually nontoxic substances ($LD_{100} \geq 5000$ mg/kg) (Table 5). Compounds (**100**), (**101**), and (**105**) ($LD_{100} = 3500–4000$ mg/kg) have slightly higher toxicity, while diazaadamantane (**21**) is significantly more toxic ($LD_{100} = 1100$ mg/kg). The introduction of the indole fragments into the structure of diazaadamantane reduces its toxicity.

Unsubstituted indole-1,3-diazaadamantane (**17**), like compound (**111**), exhibits antitumor activity

Table 4. Antibacterial activity of compounds (**97**) and (**98**) [39]

Compound	Diameter of no growth zone, mm (MIC, mg/mL)[a]			
	Gram-positive bacteria		Gram-positive bacteria	
	S. aureus 209p	*S. aureus* 1	*Sh. dysent. Flexneri* 6858	*E. coli* 0-55
(**97**)	16	14	17	15
(**98**)	28 (125)	26	30 (125)	28
Furazolidone	25 (31)	24	24 (31)	23



(**99**)

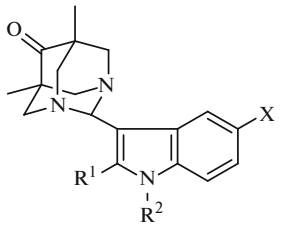
Fig. 9. Quaternary ammonium derivative of 5,7-dimethyl-1,3-diazaadamantan-6-one with antiprotozoal activity [43].

against sarcoma 45 (TGI = 71%), which exceeds the effect of compound (**21**) on this cell line [45]. In the models of sarcoma 180 and Ehrlich ascites carcinoma, compounds (**21**), (**102**), and (**112**) did not have a significant antitumor effect. The introduction of the alkylaminosulfonyl group into position 5 of the indole ring in indolyl-1,3-diazaadamantane (compounds (**105**–**109**) leads to a decrease of antitumor activity (TGI = 29.0–62.0%; this effect is unreliable ($p > 0.05$) for compounds (**107**) and (**108**)). In the case of the introduction of the dimethylsulfonyl group (compound (**105**)), antitumor activity against sarcoma 45 is completely lost, while maintaining therapeutic efficacy against Shvets leukemia (TGI = 21.7–42.0%) and sarcoma 180 (TRO = 45.854.0%).

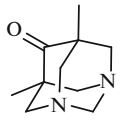
In contrast to compounds (**103**) and (**105**), compounds (**104**) and (**106**) that contained the methyl groups at position 1 or positions 1 and 2 of the indole ring showed noticeable antitumor activity against sarcoma 37 (TGI = 65.7 and 58.0%, respectively). At the same time, a similar change in the structure of compound (**107**) when converting to compound (**108**) did not significantly influence its antitumor effect. The initial 5-(dimethylaminosulfonyl)-indole-3-carboxylic acid (**111**) showed moderate activity against Pliss lymphosarcoma (TGI = 45.0%). The compounds (**105**–**110**) showed a less pronounced antiproliferative effect (TGI = 27.5–44.0%). Compounds (**17**), (**103**), and (**104**) had a stimulating effect on the growth of sarcoma 180, Shvets leukemia, and Pliss lymphosarcoma, respectively.

The physicochemical properties and the membranotropic and antioxidant activity of the most active compounds (**104**) and (**106**) were studied [45]. It was found that at the tested concentrations (0.01, 0.1, 1, and 10 mg/mL), they do not affect the resistance of erythrocyte membranes to the action of 0.1 n HCl and a mixture of plant saponins [45]. However, due to the high affinity to biological membranes, compounds (**104**) and (**106**) reduce the resistance of erythrocyte membranes by their sensitizing, thus leading to a hemolytic effect at concentrations up to 10 mg/mL. Compound (**104**) has the greatest hemolytic effect. It was also found that compounds (**104**) and (**106**) have significant antioxidant activity and inhibit the processes of Fe-induced liposome peroxidation. The antioxidant activity of these compounds is comparable to that of the well-known antioxidant ionol (2,6-ditretbutyl-4-methylphenol) at a concentration of 0.1 mg/mL.

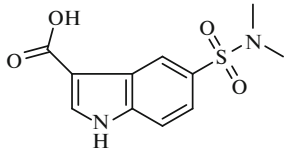
A few years later, the same team of authors presented the results of studying the biological activity of several series of heterocyclic and spirocyclic diazaadamantane (Fig. 11, 12) [7, 47, 48]. The antitumor activity of these compounds was studied on the transplanted tumor cell lines, i.e., sarcoma 180, 37, and 45, Shvets leukemia, Walker's carcinosarcoma, and ascitic and solid forms of Ehrlich's carcinoma. The therapeutic effect of the compounds was evaluated by the TGI value (%) and an increase in the life expectancy of experimental mice with ascites in comparison with the control. The dose for each substance was found as 1/20 LD_{100} for rats and 1/10 LD_{100} for mice.



(**17**), (**100**–**110**)



(**21**)



(**111**)

(**17**) $R^1 = H$ $R^2 = H$ $X = H$
(**100**) $R^1 = H$ $R^2 = CH_3$ $X = H$
(**101**) $R^1 = CH_3$ $R^2 = H$ $X = H$
(**102**) $R^1 = CH_3$ $R^2 = CH_3$ $X = H$
(**103**) $R^1 = H$ $R^2 = H$ $X = OCH_3$
(**104**) $R^1 = CH_3$ $R^2 = CH_3$ $X = OCH_3$
(**105**) $R^1 = H$ $R^2 = H$ $X = SO_2N(CH_3)$
(**106**) $R^1 = H$ $R^2 = CH_3$ $X = SO_2N(CH_3)_2$
(**107**) $R^1 = H$ $R^2 = H$ $X = SO_2N(C_2H_5)_2$
(**108**) $R^1 = H$ $R^2 = CH_3$ $X = SO_2N(C_2H_5)_2$
(**109**) $R^1 = H$ $R^2 = H$ $X = SO_2$-morpholino
(**110**) $R^1 = H$ $R^2 = H$ $X = SO_2N(CH_2CH_2Cl)_2$

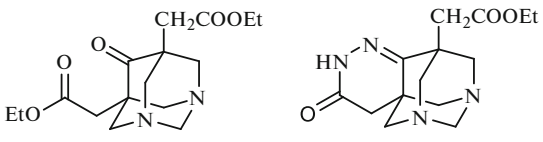
Fig. 10. 5-(Dimethylaminosulfonyl)-indole-3-carboxylic acid, 5,7-dimethyl-1,3-diazaadamantane-6-one and its 2-indole-substituted derivatives with antitumor activity [45].

Table 5. Toxicity and antitumor activity of compounds (**17**), (**21**), and (**100**–**111**) [45, 46]

Compound	LD_{100}, mg/kg (mice)	TGI, %[a]				TGI, %[a]		
		Dose, mg/kg	Sarcoma 45	Pliss lympho-sarcoma	Shvets leukemia	Dose, mg/kg	Sarcoma 180	Sarcoma 37
(**17**)	>5000	250	71.0	–	0	500	Stim.	–
(**100**)	4000	200	36.0	–	43.0	–	–	–
(**101**)	4000	200	47.0	0	0	500	–	–
(**102**)	>5000	250	19.0	0	0	500	–	55.5
(**103**)	>5000	250	37.0	0	Stim.	–	–	–
(**104**)	5000	250	45.0	Stim.	45.5	500	55.0	65.7
(**105**)	3500	160	0	29.0	21.7	350	45.8	–
(**106**)	5000	250	62.0	27.5	42.0	500	54.0	58
(**107**)	5000	250	34.0	28.0	34.8	–	–	–
(**108**)	5000	250	29.0	32.0	0	500	–	–
(**109**)	5000	250	56.5	36.0	39.0	–	–	–
(**110**)	5000	250	0	44.0	24.0	500	41.6	–
(**111**)	5000	250	65.0	45.0	–	–	–	–
(**21**)	1100	50	52.0	0	0	–	–	–

[a] A dash (–) means no activity. Compound (**21**) was studied in the form of the hydrochloride salt. Stim. means stimulating effect on the tumor growth.

Diazaadamantane (**112**) and pyridazinone (**113**) synthesized from (**112**) (Fig. 11) turned out to be low-toxic substances (LD_{100} = 2500 and >5000 mg/kg, respectively). It was shown that diazaadamantane (**112**) showed moderate activity against sarcoma 45 (TGI = 50%) at a dose of 120 mg/kg, had no reliable antitumor effect on Shvets leukemia, and stimulated the growth of sarcoma 180 at a dose of 250 mg/kg. The administration of compound (**112**) had no therapeutic effect on mice with sarcoma 37, Walker's carcinosarcoma, ascetic carcinoma, and solid Ehrlich carcinoma. Pyridazinone (**113**) at a dose of 500 mg/kg was effective against sarcomas 37 (TGI = 62%) and 180 (TGI = 46%) and extended the life of experimental mice with Ehrlich ascites carcinoma by 28% with no visible toxic effects on the body of experimental animals. At the same time, compound (**113**) did not affect Walker's carcinosarcoma, sarcoma 45, Shvets's leukemia, and the solid form of Ehrlich's carcinoma



(**112**) (**113**)

Fig. 11. 5,7-Di(ethoxycarbonylmethyl)-1,3-diazaadamantane-6-one and its pyridazinone derivative with antitumor activity [47].

[47]. Data on the use of the reference drug are not provided in the article.

Results of the study of spirocyclic (**16**), (**18**), (**19**) (Fig. 4), (**114**–**116**), 2-phosphoryl- (**117**), (**118**), 2-alkyl- (**119**–**121**), 2-phospho- (**122**), (**123**) derivatives, and unsubstituted 5,7-dimethyl-1,3-diazaadamantane-6-one (**21**) (Fig. 12) are presented in Table 6 [7, 48].

Toxicity and antitumor activity of compounds (**16**), (**18**), (**19**), and (**114**–**123**) was compared with that of unsubstituted 5,7-dimethyl-6-oxo-1,3-diazaadamantane (**21**) in the form of hydrochloride. In general, spirocyclic compounds were moderately toxic (LD_{100} = 300–800 mg/kg for compounds (**16**), (**19**), (**115**), and (**116**)) or low-toxic (LD_{100} = 1400 and >2500 mg/kg for compounds (**18**) and (**114**)) [7]. Relatively low toxicity (LD_{100} = 1000–2500 mg/kg) was shown for compounds (**120**), (**122**), and (**123**). Diazaadamantanes (**117**) and (**118**), which were obtained by introducing a substituted phosphoryl group into compound (**21**), and 2-(4'-hydroxyphenyl)diazaadamantane (**119**) were found to be nontoxic (LD_{100} = 4000–5000 mg/kg) [48].

Among the studied compounds, diazaadamantanes with the fragments of cyclopentane (**18**) and cyclohexane (**19**) showed moderate therapeutic activity against sarcoma 45 and 180 (TGI = 50 and 40%, respectively) [7]. Phosphor-containing diazaadamantanes (**122**) and (**123**) exhibited comparable activity against both types of tumors. Phenoxy-containing

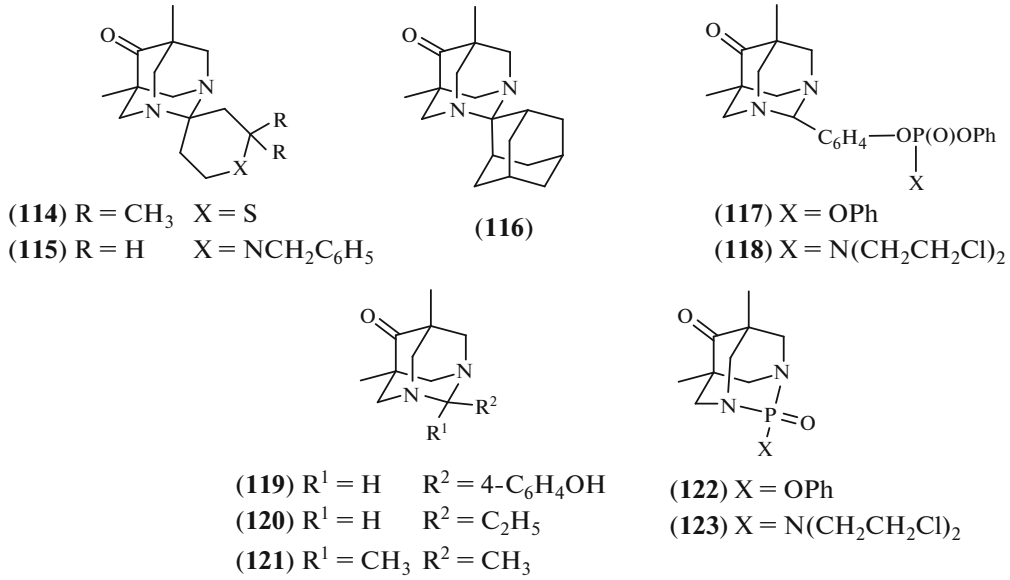


Fig. 12. 2-Spiro-, 2-I phosphoryl-, 2-alkyl-, 2-phospho-5,7-dimethyl-1,3-diazoadamantane-6-ones with antitumor activity [7, 48].

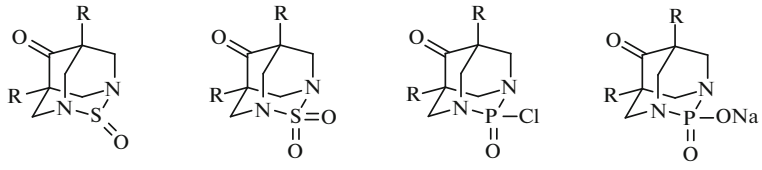
compound (**122**) suppressed the growth of sarcoma 45 and sarcoma 180 by 52.5% by 42.0%, respectively. Compound (**123**) that contained the bis(2-chloroethyl)amine group inhibited the growth of sarcoma 45 and sarcoma 180 by 35.0% and 33.6%, respectively, under the same conditions. The TGI values for unsubstituted 1,3-diazaadamantane (**21**) when using against sarcoma 45 and 180 were 52.0% and 33.0%, respectively.

Significant antitumor activity was found for compound (**115**) that contained the benzylpiperidine ring. The growth of sarcoma 180 and Shvets leukemia was inhibited by 76.0% and 69.0%, respectively, without a toxic effect on experimental animals. Among the stud-

Table 6. Acute toxicity and antitumor activity of compounds 1,3-diazaadamantanes (**16**), (**18**), (**19**), (**21**), and (**114**–**123**) [7, 48]

Compound	LD_{100}, mg/kg (mice)	MTD mg/kg (mice)	Dose (mg/kg) × the number of injections	Sarcoma 45 (rats)	Dose (mg/kg) × the number of injections	Sarcoma 180 (mice)
				TGI, %[a]		TGI, %[a]
(**16**)	500	400	25 × 8	38.7	50 × 6	–
(**18**)	1400	1200	70 × 8	50.0	125 × 6	–
(**19**)	800	500	40 × 8	0	50 × 6	40.0
(**114**)	>2500	NA	150 × 8	0	250 × 6	–
(**115**)	300	200	15 × 8	40.3	30 × 6	76.0
(**116**)	550	400	25 × 8	18.0	50 × 6	31.0
(**117**)	4000	3000	150	30.5	300 × 1	–
(**118**)	5000	NA	250	–	500 × 1	–
(**119**)	5000	NA	250	–	500 × 1	–
(**120**)	1250	1000	60	–	125 × 1	–
(**121**)	1100	900	50	–	100 × 1	–
(**122**)	2500	2000	120	52.5	250 × 1	42.0
(**123**)	1000	850	50	35.0	100 × 1	33.6
(**21**)	1100	800	50 × 8	52.0	100 × 6	33.0

[a] A dash (–) means no activity. Compound (**21**) was studied in the form of the hydrochloride salt. NA means not available data for compounds (**114**), (**118**), and (**119**).



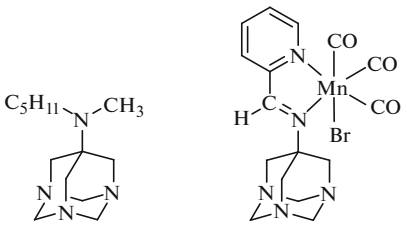
(**124**) (**125**) (**126**) (**127**)

R = 4-CF_3–C_6H_4–CH_2

Fig. 13. 2-Thio- and 2-phospho-5,7-dimethyl-1,3-diazoadamantane-6-ones with antitumor activity [49].

ied diazaadamantane derivatives, only compounds (**115**) and (**116**) led to a significant increase (by 26–39%) in life expectancy in mice with Ehrlich ascites carcinoma [7]. All other synthesized compounds showed no antitumor effect against Walker carcinosarcoma, Shvets leukemia, and Ehrlich ascites carcinoma.

The synthesis and study of the antitumor activity of several series of 2-thio- and 2-phospho-containing 1,3-diazaadamantanes (Fig. 13) against mouse melanoma cells B16-F10 were carried out by Sharabi-Ronen et al. [49]. According to the authors, 2-thio-containing 1,3-diazaadamantanes (**124**) and (**125**) showed low activity against tumor cells (IC_{50} > 200 μM). More promising results were obtained for phosphorus-containing analogs (**126**) and (**127**), which showed significant antitumor activity (IC_{50} = 10–60 μM) [49]. In addition to the cytotoxicity of the resulting compounds, the authors studied the influence of the most active 5,7-di(4-(trifluoromethyl)benzyl-1,3-diaza-2-phosphoadamantanes (**126**) and (**127**) on the cell cycle and the activation of apoptosis. Researchers assessed the changes in the mitochondrial membrane potential using the JC-1 reagent, studied the activation of caspases 3 and 7, used staining with annexin V-FITC/PI, and identified morphological changes. They showed that compounds (**126**) and (**127**) caused the cell cycle arrest in the G2/M phase, thus leading to apoptosis of mouse melanoma cells B16-F10.



(**128**) (**129**)

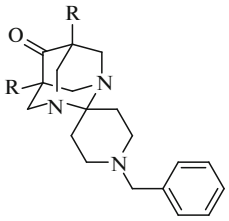
Fig. 14. *N*,*N*-Dialkyl-substituted 1,3,5-triazaadamantane with antiproliferative activity and metal-organic complex of 1,3,5-triazaadamantane with presumed antitumor activity [35, 50].

The antitumor activity of triazaadamantanes remains less studied. Among the derivatives of 7-amino-1,3,5-triazaadamantane including substituted oxyindoline-, epoxyisoindole-, pyrrolidine-, acetamide-, and 6,6-disubstituted triazaadamantanes that contain aromatic groups, antiproliferative activity was found in compound (**128**) (Fig. 14) against the HT29 cell lines (rectal cancer, IC_{50} = 1 μg/kg), MCF7 (breast cancer, IC_{50} = 2.3 μg/kg), Panc-1 (pancreatic cancer, IC_{50} = 3.4 μg/kg), and NCI-H460 (lung cancer, IC_{50} = 3.4 μg/kg) [35]. In addition, compound (**128**) at a dose of 70 mg/kg suppressed the growth of sarcoma 180 by 54% in mice [35].

Organometallic triazaadamantane complexes with CO molecules coordinated to manganese ions have been proposed as potential antitumor agents [50]. It is assumed that these compounds when introduced into the body will emit CO during irradiation. It is known that at the low concentrations (<200 ppm), CO exhibits anti-inflammatory and antiapoptotic properties in healthy cells [51], while exposure to CO during chemotherapy causes apoptosis of the prostate cancer cells [52]. The authors consider compound (**129**) to be the most promising (Fig. 14), which has moderate pH-dependent solubility in water, thus providing an additional advantage in the selectivity of action. At physiological pH, the triazaadamantane fragment is not charged and can diffuse through lipid membranes. However, protonation and capture of the triazaadamantane fragment can occur in cancer cells at a relatively low pH level. The protonated fragment of triazaadamantane can also lead to DNA damage. In addition, aqueous solutions of complex (**129**) are stable in the dark and insensitive to reducing agents, such as sodium dithionite and glutathione. They quickly release three CO molecules when exposed to low-power visible light. Studies on the delivery of CO to cancer cells using compound (**129**) were planned [50] but their results have not yet been published.

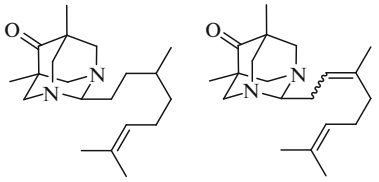
INTERACTION OF AZAADAMANTANES WITH DNA, ENZYMES, AND RECEPTORS

The ability to bind to the nitrogenous bases of the DNA molecule, thus increasing the rate of strand exchange in short nucleotides was found for 1'-benzyl-



(**130**) R = C_3H_7
(**131**) R = C_4H_9

Fig. 15. 5,7-Dialkyl-substituted 1,3-diazaadamantanes capable of binding to nitrogenous bases of DNA [53].



(**132**) (**133**)

Fig. 16. Derivatives of 5,7-dimethyl-1,3-diazaadamantane with inhibitory activity against Tdp1 enzyme [56].

5,7-dialkyl-1,3-diazaspyro[adamantane-2,4'-piperidine]-6-ones (**130**) and (**131**) (Fig. 15) [53]. The authors used the calf thymus DNA and oligonucleotides

d(CAATCGGATCGAATTCGATCCGATTG) (ds26),

Cy3d(CAATCGGATCGAATTCGATCCGATTG) (Cy3ds26), and

Cy5 (CAATCGGATCGAATTCGATCCGATTG) (Cy5ds26).

The interaction of 1,3-diazaadamantanes with DNA was recorded using fluorescence-controlled displacement of the thiazole orange dye (TO) from its complex with DNA by diazaadamantanes. To register the displacement, TO was added to DNA (0.25 μM) at the concentration (C_{TO} = 1 μM), which provided almost full filling of the binding sites with DNA. After the formation of the complex with DNA, the fluorescence of the dye increases significantly. Titration of the complex by 1,3-diazaadamantane caused fluorescence quenching associated with the displacement of TO from the complex.

It turned out that *n*-butyl-containing diazaadamantane (**131**) and propyl-containing diazaadamantane (**130**) bind to DNA at pH 7.8 with K_a = 180 and 15 M^{-1}, respectively. The affinity of both 1,3-diazaadamantanes to DNA increases at pH 6.5, the association constants of 5,7-dialkyl-substituted diazaadamantanes with DNA become close to each other (1400 and 500 M^{-1}, respectively). Thus, diazaadamantanes (**130**) and (**131**) demonstrated pH-dependent affinity to DNA [54, 55].

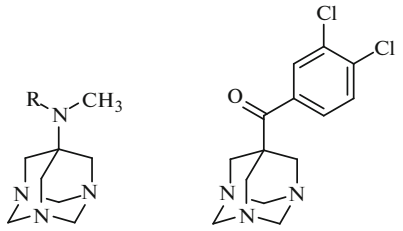
The inhibitory activity of the 5,7-dimethyl-1,3-diazaadamantane derivatives against some enzymes is reported in the work of Zakharenko et al. [56].

1,3-Diazaadamantanes (**132**) and (**133**) (Fig. 16) that contained the acyclic monoterpene fragments of citronellal and citral, respectively, showed inhibitory activity against DNA repair enzyme Tdp1 (tyrosyl-DNA phosphodiesterase 1), which is a promising target for complex antitumor therapy [57–59]. The effect of some antitumor drugs, e.g., camptothecin and its clinically important derivatives topotecan and irinotecan [60], is mediated by inhibition of the cleavage of topoisomerase 1B (Top1) from the 3' end of DNA [61, 62]. Tdp1 can cleave the phosphodiester bond between tyrosine in Top1 and the 3' phosphate of DNA when this reaction does not occur for natural reasons. Thus, compounds capable of inhibiting Tdp1 can increase the therapeutic efficacy of Top1 inhibitors [63–66].

Zakharenko et al. [56] have used the method of fluorescent detection of Tdp1 activity [67], which is based on the ability of Tdp1 to remove bulk substituents from the 3' end of DNA. Fluorescence donor FAM (5(6)-carboxyfluorescein) and fluorescence quencher BHQ1 (Black Hole Quencher-1) were attached to the 5' and 3' ends, respectively, of a 16-meric oligonucleotide. The fluorescence of the fluorophore is quenched because BHQ1 is located within the Forster radius. Incubation of the biosensor oligonucleotide with Tdp1 leads to the removal of BHQ1 from the 3' end of the oligonucleotide, thus promoting an increase in fluorescence. The IC_{50} values for compounds (**132**) and (**133**) are 14.8 and 16.7 μM, which correspond to moderate activity. To date, there are known compounds that inhibit Tdp1 in the submicromolar range [68–70].

Golubovskaya et al. [71] studied the ability of small triazaadamantane-containing molecules to bind to the focal adhesive kinase (FAK or protein tyrosine kinase 2, PTK2), thus preventing its binding to the p53 protein. FAK (PTK2) is a nonreceptor tyrosine kinase, which controls cellular processes, such as proliferation, adhesion, distribution, mobility, and survival [72]. The p53 protein inhibits the formation of malignant tumors [73]. Activation of p53 reduces the viability and clonogenicity of cancer cells and inhibits tumor growth in vivo. A reliable decrease in the viability of the HCT116 p53 cancer cell line was shown for butyl- and hexyl-containing *N*-alkyl-*N*-methyl-1,3,5-triazaadamantanes (**134**) and (**135**), respectively, which were selected as a result of molecular docking (Fig. 17). However, their affinity to FAK was insufficient to prevent its binding to p53.

Eisenbarth et al. [74] studied the ability of *N*-butyl-*N*-methyl triazaadamantane (**134**) (Fig. 17) to suppress the autoimmune response that causes type 1 diabetes. The authors studied the response of cloned T lymphocytes limited by DQ8 to the amino acids 9–



(**134**) R = C_4H_9 (**136**)
(**135**) R = C_6H_{13}

Fig. 17. 1,3,5-Triazaadamantane derivatives capable of binding to various proteins, i.e., FAK (**134**), (**135**) [71]), HLA-DQ8 (**134**) [74]), and CCR1 (**136**) [76].

23 of the insulin B chain. They also studied the T cell response to the inhibition of the interaction of these proteins with the molecules of the main histocompatibility complex of class II encoded by the *DQ8* gene. Compound (**134**) was used at concentrations of <0.1 μM and >100 μM (IC_{50}) in the first and second cases, respectively. The demonstrated activity is not high enough to consider compound (**134**) as a preparation to prevent and treat type 1 diabetes.

It is known that the binding to the CB1 receptor prevents its interaction with chemokines, which are involved in the development and maintenance of numerous inflammatory and immunological states and other disorders [75]. Affinity to the CCR1 receptor (IC_{50} = 2 μM) was demonstrated for compound (**136**) (Fig. 17) [76]. It should be noted that this activity can be considered moderate because there are compounds, which bind to the CCR1 receptor at a subnanomolar concentration [77].

EFFECT OF AZAADAMANTANS ON THE NERVOUS SYSTEM

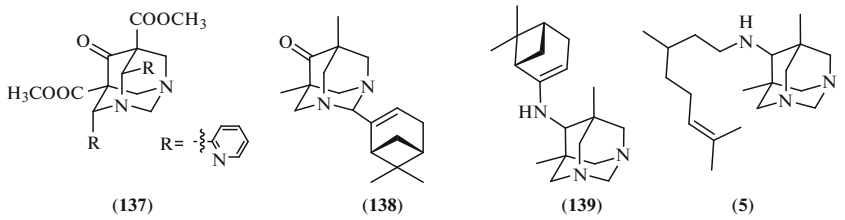
Some diazaadamantane derivatives were found to have significant analgesic activity. Among 8,9-substituted dimethyl 5,7-carboxyl-1,3-diazaadamantanes that contained the aromatic and heteroaromatic substituents, 2-pyridine-containing compound (**137**) (Fig. 18) was shown to reduce pain in the Randall–Selitto test (paw compression) by 80% when administered orally at a dose of 1 mg/kg. [78]

The pronounced analgesic activity was found in 2-substituted 5,7-dimethyl-1,3-diazaadamantan-6-one (**138**) that contained the (–)-myrtenal fragment (Fig. 18) [79]. Experiments were performed on mice using the acetic acid-induced writhing test and hot plate test. The results showed that diazaadamantane (**138**) when administered orally at a dose of 20 mg/kg significantly reduced pain manifestations by 61% and 82%, respectively, which was not inferior to the reference drug, diclofenac sodium. Compound (**138**) showed moderate acute toxicity in mice; its LD_{50} value exceeds 1000 mg/kg, while LD_{50} of diclofenac sodium is 370 mg/kg [80].

The ulcerogenic activity (related to the formation of defects in the gastrointestinal mucosa) of compound (**138**) in comparison with the nonsteroidal anti-inflammatory drug indomethacin was studied on Wistar rats [81]. Compound (**138**) or indomethacin were injected in the animals at a dose of 30 and 20 mg/kg, respectively, for three days. In the group of animals treated with compound (**138**), all animals survived by the end of the experiment, and no ulcers were detected. Half of the animals treated with indomethacin died to the end of the experiment, and erosions and ulcers were found in the remaining animals [79].

An important problem that inevitably arises during the search for effective analgesics is the study of the possible mechanism of their action. (–)-Myrtenol has the same monoterpene fragment as compound (**138**) and exhibits an anti-inflammatory effect [82]. Nevertheless, compound (**138**) at a dose of 60 mg/kg does not show anti-inflammatory activity in mice after the administration of 3% formalin as a phlogogen (from Latin *phlogosis*, inflammation; a pathogenic irritant, which can cause an inflammatory reaction) [79].

It was shown that compound (**138**) affected the behavior of mice in the open field test by reducing the speed and distance of movement but did not significantly influence the research activity of animals [79]. This inhibitory effect on the motor activity of animals is characteristic of opioid analgesics [83, 84] and analgesics, which affect the cannabinoid system, such as Δ^9-tetrahydrocannabinol [85]. To identify a possible mode of action, researchers studied the effect of the nonselective opioid receptor antagonist naloxone [86] and the selective cannabinoid CB1 receptor antagonist rimonabant [87] on the analgesic activity of com-



(**137**) (**138**) (**139**) (**5**)

Fig. 18. Derivatives of 1,3-diazaadamantane with analgesic (**137**–**139**) and hyperalgesic (**5**) activity [78, 79].

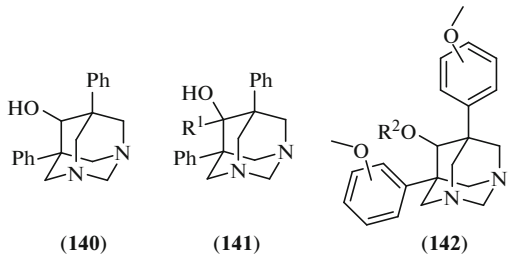
pound (**138**) in the acetic acid-induced writhing test. The analgesic activity of compound (**138**) was maintained against the background of naloxone administration, while the administration of rimonabant led to the leveling of the analgesic effect of compound (**138**) [79]. The results suggest that the analgesic effect of compound (**138**) is at least partially mediated by the cannabinoid system with the involvement of CB1 receptors.

An analgesic activity comparable to diazaadamantane (**138**) was found in the secondary amine (**139**), which also contains the (–)-myrtenal fragment. However, this fragment in (**139**) is attached to the heteroadamantane backbone through the amino group. Compound (**139**) at a dose of 20 mg/kg reduced the pain of the animals in the acetic acid-induced writhing test and hot plate test by 46 and 89%, respectively [15].

High analgesic activity was found in the previously mentioned diazaadamantane (**132**) (Fig. 16) that contained the citronellal fragment. This compound at a dose of 20 mg/kg reduced pain in the acetic acid-induced writhing test and hot plate test by 32 and 94%, respectively [79]. Interestingly, citronellal-containing compound (**5**) had no analgesic activity in the acetic acid-induced writhing test and showed hyperalgesic properties (increased the sensitivity of the body to pain stimuli) in the hot plate test. The initial diazaadamantanamine (**4**) did not demonstrate any analgesic activity [79].

Most of the studied diazaadamantane derivatives showed low acute toxicity (hundreds and thousands of mg/kg). However, some of these derivatives, in particular 5,7-diphenyl-substituted diazaadamantanols, exhibit toxic properties at doses of 1 mg/kg. Strychnine-like activity (the ability to cause severe painful tetanic contraction) was detected by Longo et al. [88] for 5,7-diphenyl-1,3-diazaadamantan-6-ol (**140**) (Fig. 19) after intravenous administration (LD_{50} = 1.1 and 2.0 mg/kg for mice and rats, respectively).

To study the structure–toxicity relationship of various 6-substituted 5,7-diphenyldiazaadamantanes, Chiavarelli et al. synthesized several 6-alkyl- and 6-aryl-6-hydroxy derivatives of 5,7-diphenyldiazaadamantane (**141**) [89] and 6-alkyl-6-hydroxydiazaadamantanes that contained the phenyl groups with various substituents at positions 5 and 7 and studied the strychnine-like activity of these compounds [90]. The experiments in mice and rats showed that the introduction of the alkyl substituent (methyl, ethyl, propyl, n-butyl, isobutyl, n-dodecyl, and α-naphthyl) into 5,7-diphenyl-1,3-diazaadamantan-6-ol at position 6 led to a decrease in toxicity (LD_{50} = 12.5–75.0 mg/kg) while maintaining strychnine–like effects on the body of experimental animals (increased excitability with subsequent tonic and tonic–clonic seizures). The introduction of the phenyl group into position 6 also reduced the toxicity of the compound, while the mechanism of convulsions was somewhat different,



(**140**) (**141**) (**142**)

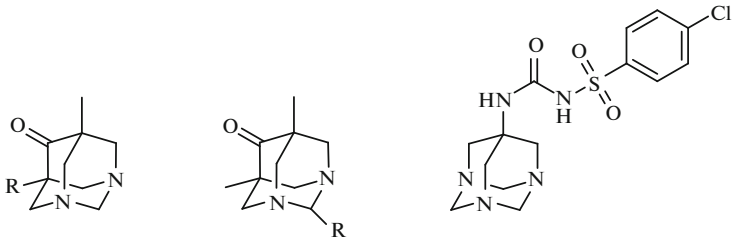
R^1 = CH_3, C_2H_5, C_3H_7, *n*-C_4H_9, *i*-C_4H_9, *n*-$C_{12}H_{25}$, C_6H_5, α-naphthyl
R^2 = H, CH_3, C_2H_5

Fig. 19. 5,7-Diaryl-substituted 1,3-diazaadamantanes with high toxicity and strychnine-like activity [88].

i.e., a small tremor was initially observed followed by clonic convulsions [89].

Among the 6-phenoxy and 6-alkoxy derivatives, the greatest toxicity and strychnine-like effect were observed for 2-methoxy-, 3-methoxy- and 4-methoxyphenyldiazaadamantane–6-ols (**142**) (LD_{50} = 1.5–20 mg/kg) (Fig. 19). 4-Methoxy-containing 5,7-diphenyldiazaadamantanes that contained the 6-alkoxy-substituted group (6-methoxy-and 6-ethoxy-diazaadamantanes) showed significantly lower toxicity (LD_{50} = 100–150 mg/kg) and had only a convulsive (strychnine-like) effect on experimental animals. An increase in the number of the methoxy groups in the phenyl ring with the preservation of the unsubstituted 6-hydroxy group led to a sharp decrease (LD_{50} = 300 mg/kg for the 2,3-dimethoxy derivative) or complete disappearance (for the 2,3,4-trimethoxy derivative) of toxicity [90]. Thus, we can note the key role of the alcohol group at position 6 and phenyl substituents at positions 5 and 7 of diazaadamantane for their strychnine-like action.

Agadzhanyan et al. showed the presence of α-adrenoblocking activity in 5,7-dimethyldiazaadamantane (**115**) (Fig. 12) that contained the benzylpiperidine substituent at the second position of the molecule [91]. The experiments were carried out on the isolated rat vas deferens, and the effect was evaluated by a decrease in contractions caused by transmural electrical irritation or norepinephrine at a concentration of 10 μg/mL. The α-adrenoblockers piperoxan, phentolamine, and sympatholytic octadine were used as reference drugs, which were administered, like the studied compound, at a concentration of 0.05 μM. Compound (**115**) did not significantly affect the contraction of the vas deferens caused by norepinephrine during the first minutes of exposure but its blocking effect developed gradually and led to a 50% decrease in the reaction for 60 minutes. The adrenoprotective effect of the reference drugs piperoxan and phentolamine was manifested much faster and led to a decrease in vas deferens contractions by 30 and 55%, respectively, 10 min after administration of the drugs. By the 60th minute, the effect of piperoxane was



(**143**), (**144**) (**145**), (**28**) (**146**)

(**143**) R = C_6H_5 (**145**) R = CH_3
(**144**) R = $CH_2C_6H_{51}$ (**28**) R = α-C_5H_5N

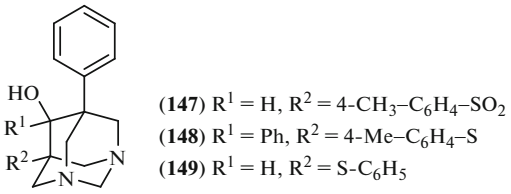
Fig. 20. 5,7-Disubstituted 1,3-diazaadamantanes and 1,3,5-triazaadamantane exhibiting anticonvulsant effect and hypoglycemic activity, respectively [92, 93].

reduced by half, and the effect of phentolamine remained at the initial level. The compound (**115**) did not affect the vas deferens contractions because of transmural electrical irritation and had no sympatholytic activity and inhibitory effect on the transmission of a nerve impulse.

Anticonvulsant and psychotropic properties of some 1,3-diazadamantanes (**28**) (Scheme 6) and (**143**–**145**) (Fig. 20) were studied by Harutyunyan et al. [92] in the test of corazole-induced convulsions and the open field test. The studied 5-methyl-7-phenyl-diazaadamantanone (**143**), 5-methyl-7-benzyl diazaadamantanone (**144**), and 2-methyl, 2-pyridyl-5,7-dimethyldiazaadamantanones (**145**) and (**28**) showed an anticonvulsant effect with ED_{50} = 30–35 mg/kg, while the ED_{50} value for the reference drug diazepam was 0.5 mg/kg. Most of the compounds reduced the motor and research activity due, probably, to their sedative properties.

OTHER TYPES OF AZAADAMANTANE ACTIVITIES

A slight improvement in the hypoglycemic activity (the ability to reduce blood glucose levels) of antidiabetic drugs as a result of the addition of the azaadamantane fragment to biologically active compounds was shown by Agadzhanyan et al. [93]. The substitution of the alkyl group in 4-chloro-*N*-(propylcarbamoyl)benzenesulfonamide (chlorpropamide; a drug used in the treatment of type 2 diabetes mellitus, diabetic microangiopathy (initial forms), and diabetes insipidus) by 1,3,5-triaazaadamantane (Fig. 20) led to the formation of compound (**146**). This compound at doses of 100 and 250 mg/kg reduced the blood glucose level in healthy rats by 13 and 18%, respectively, which barely differed in activity and effectiveness from chlorpropamide. At the same time, compound (**146**) at a dose of 250 mg/kg lowered the glucose level by 31% in rats with alloxan diabetes, while chlorpropamide did it only by 23%.



(**147**) R^1 = H, R^2 = 4-CH_3–C_6H_4–SO_2
(**148**) R^1 = Ph, R^2 = 4-Me–C_6H_4–S
(**149**) R^1 = H, R^2 = S-C_6H_5

Fig. 21. 5,7-Disubstituted 1,3-diazaadamantanes with immunosuppressive activity [94].

The immunosuppressive activity of 5-phenyldiazaadamantanols that contained various substituents at position 7 of the heteroadamantane backbone (Fig. 21) was studied by Yakushev et al. [94]. Compounds (**147**) and (**149**) at doses of 0.5 mg/kg showed immunosuppressive activity against antibodies, which had lysis and agglutinating properties. The increase in the dose to 5 and 50 mg/kg led to the disappearance of the activity of these compounds. At the same time, compound (**148**) at a dose of 5 mg/kg showed immunosuppressive activity against both studied antibodies. At a dose of 50 mg/kg, compound (**148**) was active against antibodies with agglutinating properties.

CONCLUSIONS

Most works concerning the biological activity of diazaadamantanes are devoted to the study of antimicrobial and antitumor activity. Pronounced antibacterial properties were found for tetraphenyl-substituted diazaadamantanes and derivatives that contained the heterocyclic groups at position 2 of the azaadamantane molecule. Various 2-functionalized derivatives and heteroatoms-containing spiro- and condensed derivatives demonstrated antitumor activity, mainly in the in vivo experiments. Among the derivatives of diazaadamantane, compounds with pronounced antiviral, psychotropic, strychnine-like, or analgesic effects were found. Most of the studied compounds showed moderate or low acute toxicity in vivo. How-

ever, several diazaadamantanes with extremely high toxicity (LD_{50} < 10 mg/kg) were also identified.

The triazaadamantane derivatives exhibit antibacterial and antitumor activity, although less pronounced, as a rule, compared to substituted diazaadamantanes. Some derivatives of triazaadamantane have hypoglycemic properties. The presence of three nitrogen atoms in the adamantane backbone leads to an increase in water solubility, which makes it possible to use triazaadamantanes as fragments for the modification of existing drugs and the design of new medicinal compounds.

The accumulated experimental material allows for the association of the structure of substituents in azaadamantanes with their antiviral, antibacterial, and antitumor activity. Di- and triazaadamantanes are promising platforms to search pharmacologically active derivatives due to the possibility of their synthesis in various ways from available reagents and the presence of a variety of biological activity combined with low toxicity.

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COMPLIANCE WITH ETHICAL STANDARDS

This article does not contain any studies with the use of humans or animals as objects of research.

Conflict of Interests

The authors state that there is no conflict of interest.

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