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MODIFICATION OF N^1-(2,6-DIMETHYLPHENYL)-N^2,N^2-DIETHYLGLYCINAMIDE AND 4-AMINO-*N*-[2-(DIETHYLAMINO)ETHYL]BENZAMIDE IN ORDER TO INCREASE THEIR ANTIARRHYTHMIC EFFECT

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A structure–antiarrhythmic activity relationship has been investigated using a chloroform model of arrhythmia in rats. A mathematical model capable of predicting and recognizing antiarrhythmic activity with 84% reliability is formulated. Optimization of the molecular design of lidocaine and procainamide, which have weak antiarrhythmic activity, has resulted in modeling and predicting 51 much more effective antiarrhythmic compounds that can be synthesized for further testing.

Key words: antiarrhythmic activity, *N*-phenylacetamide derivatives, chemical structure optimization.

Antiarrhythmic drugs differ in potency, mechanism of action, and degree of manifestation of side effects [1 – 3]. Several of the currently employed drugs either are insufficiently effective or exhibit proarrhythmic activity with prolonged used [4, 5]. Effective antiarrhythmic therapy (AAT) is in some cases impossible to apply in patients with ventricular arrhythmia because of fatal disruptions of the heart rhythm. Thus, the search for new biologically active compounds with potent antiarrhythmic activity (AAA) is a critical task.

Lidocaine [N^1-(2,6-dimethylphenyl)-N^2,N^2-diethylglycinamide] exhibits local anesthetic and antiarrhythmic (Class 1b) properties [1, 2]. However, the low effectiveness (ED_{50} = 0.495 mmol/kg) and, when used in high doses, the pronounced side effects with respect to the cardiovascular system such as bradycardia, delayed conductance, and arterial hypotension up to the point of developing collapse [1 – 3] make it impossible to apply it generally as an antiarrhythmic agent.

Procainamide {4-amino-*N*-[2-(diethylamino)ethyl]-benzamide} is an Class IA antiarrhythmic membrane-stabilizing agent that reduces excitability and conductance of myocardium and suppresses pulse formation in automatic ectopic foci. The chemical structure and pharmacological properties of procainamide are similar to those of novocaine. Procainamide also acts as a local anesthetic. However, the most important pharmacological feature of procainamide is its ability to reduce excitability and conductance of myocardium and to suppress pulse formation in automatic ectopic foci. In addition, it exhibits weak antiarrhythmic ac-

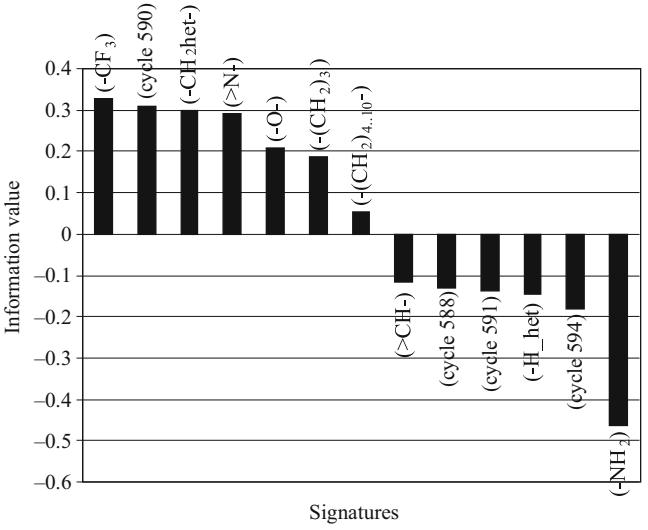

Fig. 1. Effect of functional groups and cyclic fragments (Table 4) on effectiveness of antiarrhythmic activity.

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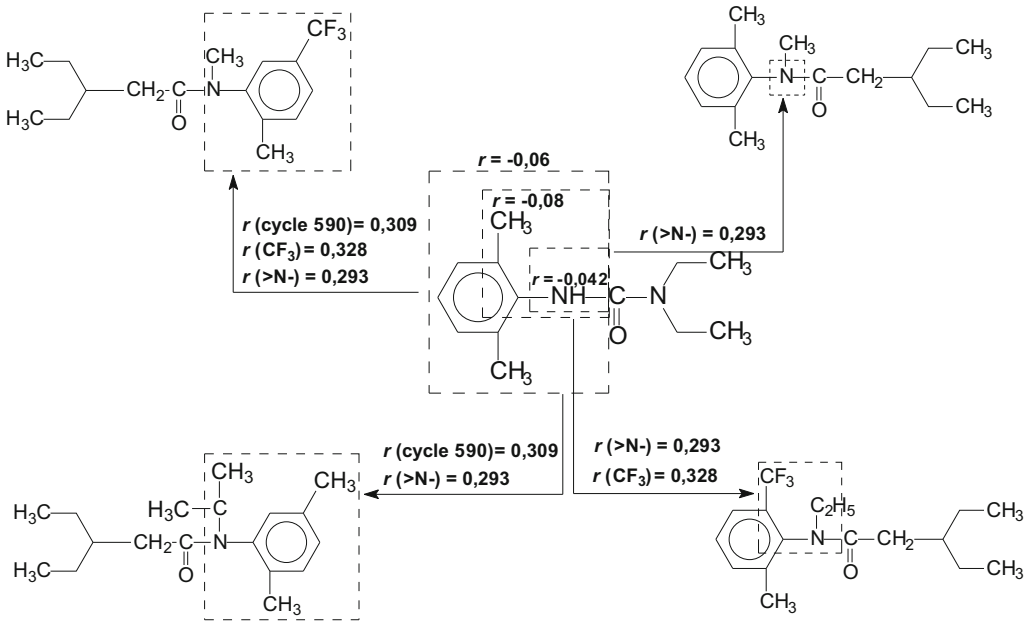


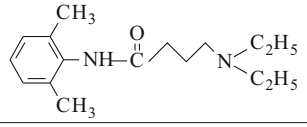
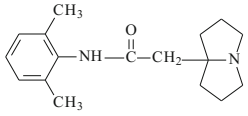
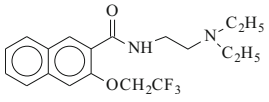
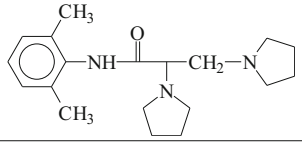
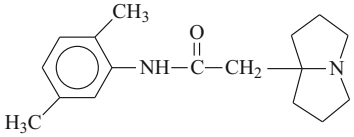
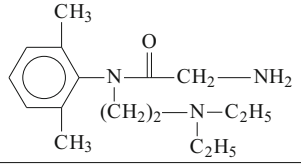
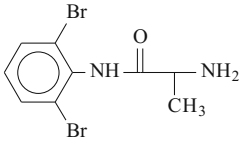
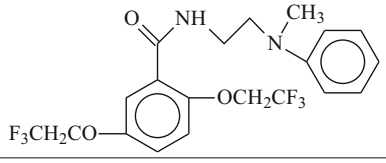
Fig. 2. Scheme of N^1-(2,6-dimethylphenyl)-N^2, N^2-diethylglycinamide structural modification.

tivity with ED_{50} = 1.03 mmol/kg [4, 5]. Another drawback of procainamide is the fact that it can cause systemic lupus erythematosus to develop and produce other side effects [3]. These characteristics of lidocaine and procainamide indicate that their antiarrhythmic activities are not high enough. Moreover, they are approved, synthesized industrially, and employed currently as drugs, i.e., have passed all phases of pharmacological testing. All aforementioned data allow them to be selected for modification in order to increase their antiarrhythmic properties.

EXPERIMENTAL PART

A structure–AAA relationship was studied using the main procedures of the SARD-21 (Structure Activity Relationship & Design) computer system [6 – 9]. The training set was formulated based on literature data for the structure and

TABLE 1. Typical Structures of Training Set Compounds

Structure	ED_{50}, mmol/kg	Structure	ED_{50}, mmol/kg
Class of high-effective compounds			
	0.14		0.08
	0.15		0.05
Class of low-effective compounds			
	0.23		0.70
	0.47		> 0.50

Note: ED_{50}, mmol/kg is the effective dose of a studied compound that exhibits under the given conditions an effect in 50% of the experimental units (rats) expressed in mmol of compound per kg of mass.

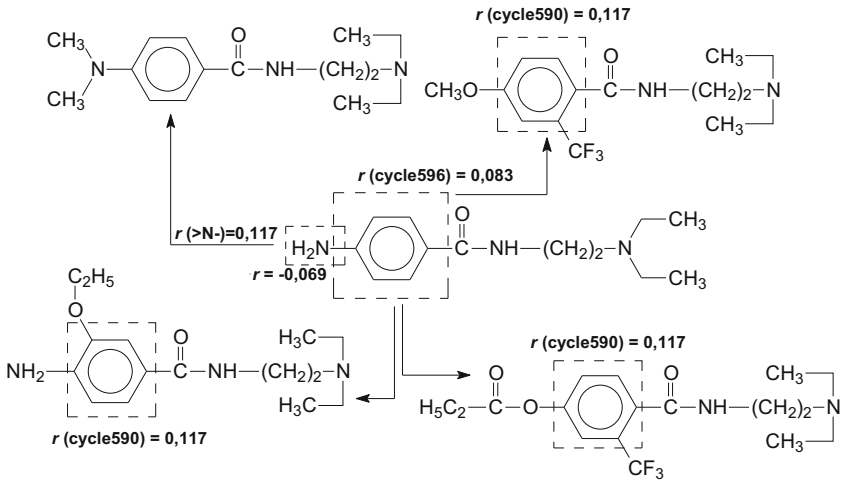


Fig. 3. Scheme of 4-amino-*N*-[2-(diethylamino)ethyl]benzamide structural modification.

TABLE 2. Deciding Set of Signatures Formulated in Terms of the Given Model

No.	Signature	Information value
1	{(-CH_2het-)-(-CF_3)} # {(-NH-)-(1,2,4-trisubstituted benzene)} # {(CH_2het-(N-)}	0.606
2	{(C=O)-(1,2,4-trisubstituted benzene)} # {(-CHarom-(N-)} # {(-$(CH_2)_2$-)-(N-)}	0.591
3	{(-CHarom-(C=O)} # {(-NH-)-(1,2,4-trisubstituted benzene)} # {(-CH_2het-)-(N-)}	0.584
4	{(-CH_2het-)-(-O-) # {(-NH-)-(1,2,4-trisubstituted benzene)} # {(-CH_2het-)-(N-)}	0.549
5	{(-CHarom-(-O-)} # {(-O-)-(1,2,4,5-tetrasubstituted benzene)} # {(-CH_2het-)-(N-)}	0.549
6	{(-O-)-(1,2,4-trisubstituted benzene)} # {(-CHarom-(N-)} # {(-$(CH_2)_2$-)-(N-)}	0.532
7	{(-NH-)-(1,2,4-trisubstituted benzene)} # {(-CHarom-(-O-)} # {(-CH_2het)-(N-)}	0.523
8	{(-CHarom<)-(-NH-)} ! {(-CH_2het-)-(>N-)} ! {(-CHarom<)-(>N-)}	– 0.575
9	(-NH_2) # (2,3-disubstituted naphthalene) # (7a-substituted hexahydro-1*H*-pyrrolizine)	– 0.571
10	(1,2,4-trisubstituted benzene) # (N-) # (-CHarom-)	– 0.550
11	{(>CH-)-(>C=O)} # {(-CH_2het-)-(>C=O)} # {(-CH_2het-)-(>N-)}	– 0.546
12	{(CH-)-(-NH_2)} # {(-NH-)-(1,2,4-trisubstituted benzene)} # {(-CH_2het-)-(-NH_2)}	– 0.530
13	{(-CH_3)-(-CHarom} # {(-NH-)-(1,2-disubstituted benzene)} # {(-CH_2het-)-(N-)}	– 0.523
14	(-CF_3) # (>N-) # (CHarom<)	– 0.514

Note: & = conjunction sign (logical "and"); ! = disjunction sign (logical "or and"); # = strong disjunction sign (logical "or not").

AAA of *N*-phenylacetamide derivatives and amides of aromatic carboxylic acids that were obtained from a chloroform model of arrhythmia in rats [10 – 18]. It contained 41 structures of compounds with pronounced AAA (Class A) and 63 structures of compounds exhibiting this property to a much weaker extent (Class B). Table 1 presents typical structures of compounds included in the training set and the corresponding ED_{50} values.

Representation of the chemical structures in fragment descriptor (FD) language. We examined three types of FD: 1) initial fragments including elements of cyclic systems and the cyclic systems themselves; 2) substructural descriptors of several chemically bound initial fragments; 3) logical combinations (conjunctions, disjunctions, strong disjunctions) generated based on the first and second types of descriptors.

Estimation of the information value of all signatures. The nature of the influence of FD on AAA was estimated from the information value coefficient *r* (correlation of quality signatures) ($-1 < r < 1$), according to which the greater the positive value of the information value was, the greater was the probability that this signature affected the manifestation of

TABLE 3. Recognition of Training and Examination Sets using the Deciding Set of Signatures (DSS)

Recognition result	Training set			Examination set
	Series A	Series B	Whole set	
Geometric approach	80.49	82.54	81.51	85.00
Voting	85.37	82.54	83.95	85.000

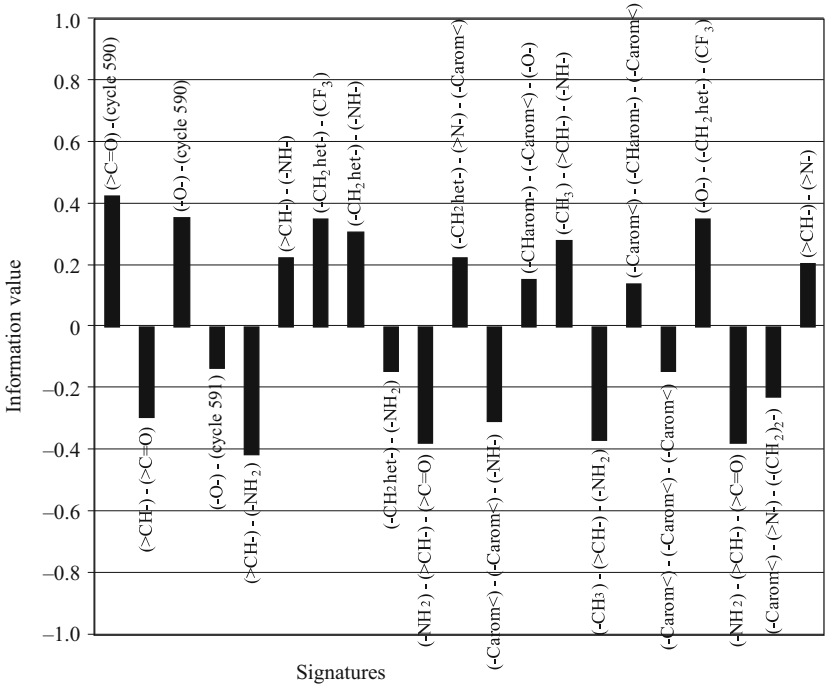


Fig. 4. Effect of substructural signatures on effectiveness of antiarrhythmic activity.

TABLE 4. Fragment of Examination Set with Structure Recognition Results by the Two Methods

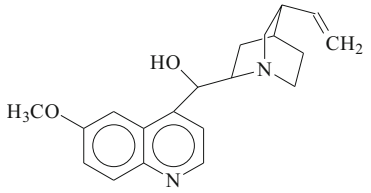
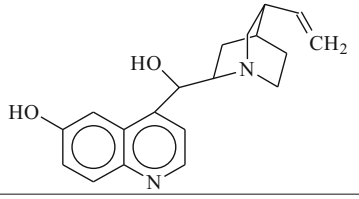
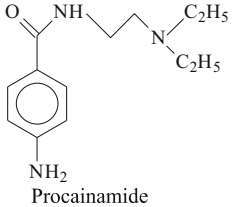
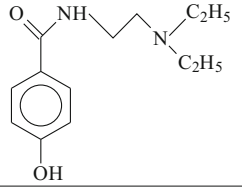
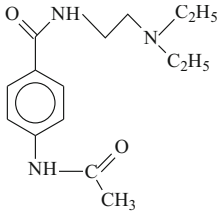
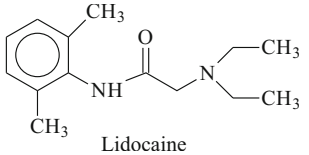
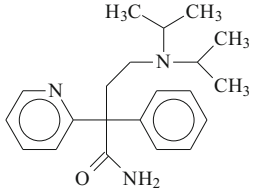
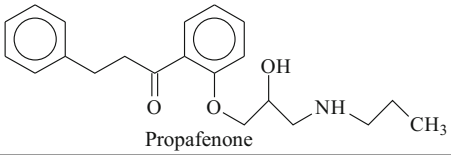
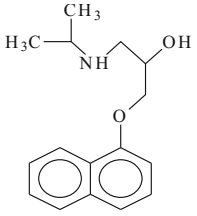
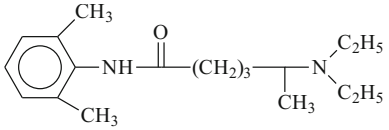
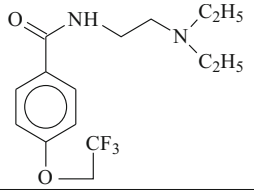
No.	Structural formula	Recognition by		Literature data	
		geometric approach	voting	ED_{50}, mmol/kg	series
1	 Quinidine	B	B	0.22	B
2		A	A	0.08	A
3	 Procainamide	B	B	1.30	B
4		B	B	0.58	B

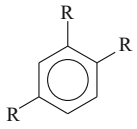
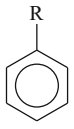
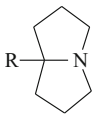
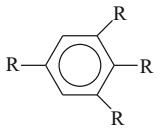
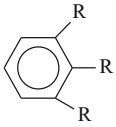
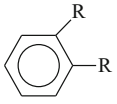
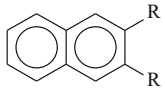
TABLE 4. (Continued)

No.	Structural formula	Recognition by		Literature data	
		geometric approach	voting	ED_{50}, mmol/kg	series
5		B	B	0.35	B
6	 Lidocaine	A	A	0.50	B
7	 Disopyramide	A	A	0.06	A
8	 Propafenone	A	A	0.07	A
9	 Propranolol	A	A	0.10	A
10		B	B	0.10	A
11		B	B	0.54	B

the target property (positive and negative sign "+" and "–", respectively) [6].

Formulation of the mathematical recognition and prediction model and its validation for compounds with known antiarrhythmic activity. A complete description of the descriptors for the studied groups of compounds is excessive. Therefore, we contracted its size to the optimal level and determined the most significant factors, i.e., the deciding set of signatures (DSS). The criteria for including signatures in the DSS were the maximum information value, minimum interdependence, and optimum recognition of recognized objects. Recognition and prediction models for the studied type of activity were formulated by combining the deciding set of structural parameters and the classification rules as logical equations of the type $C = F(S)$, where C is the property (AAA); F, the recognition rules (algorithm of sample recog-

TABLE 5. Cyclic Fragments and Their Corresponding Codes

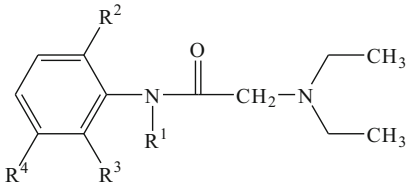
 590	 594	 586	 588
 587	 585	 591	

nition by which the studied compounds were classified, the geometric or voting method); *S*, the DSS.

Modification of lidocaine and procainamide, which have weak antiarrhythmic activity according to the literature. The obtained data were used to determine the direction of modification. The order of substitution was established. The optimal structural groups and their combinations that had a positive effect on the AAA effectiveness were also identified. A total of 289 compounds, the effectiveness of which was estimated according to the previously formulated model, was proposed as a result of the modification.

Effective structures identified as a result of the prediction were analyzed using the PASS program [7].

TABLE 6. Results of N^1-(2,6-Dimethylphenyl)-$N^{2,}$ N^2-diethylglycinamide Modification



Compound	R^1	R^2	R^3	R^4
1	CH_3	CH_3	CH_3	–
2	C_2H_5	CH_3	CH_3	–
3	$CH(CH_3)_2$	CH_3	CH_3	–
4	$CH(CH_3)C_2H_5$	CH_3	CH_3	–
5	CH_3	CF_3	CH_3	–
6	C_2H_5	CF_3	CH_3	–
7	$CH(CH_3)_2$	CF_3	CH_3	–
8	$CH(CH_3)C_2H_5$	CF_3	CH_3	–
9	CH_3	CH_3	–	CF_3
10	CH_3	CH_3	–	CH_3
11	C_2H_5	CH_3	–	CF_3
12	C_2H_5	CH_3	–	CH_3
13	$CH(CH_3)_2$	CH_3	–	CF_3
14	$CH(CH_3)_2$	CH_3	–	CH_3
15	$CH(CH_3)C_2H_5$	CH_3	–	CF_3

RESULTS AND DISCUSSION

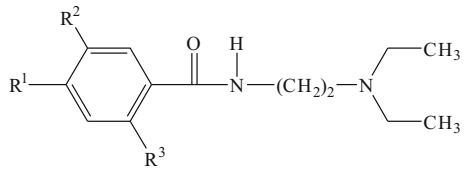
The DSS and mathematical prediction and recognition model of AAA in the series of *N*-phenylacetamide derivatives and amides of aromatic carboxylic acids were formulated as a result of the work (Table 2). Fragment signatures and their logical combinations that were potentially responsible for manifestation of AAA were entered into the DSS during automatic selection by the program algorithm. The reliability of the established dependences was checked by testing the DSS on compounds of the training set and an examination set containing 20 structures of compounds with known effective antiarrhythmic activity that did not appear in the training set. This included employed antiarrhythmic drugs (high- and low-effective). The maximum reliability level of the target-property prediction was 85% for compounds of the training set and for structures of the examination series according to the voting and geometric methods, respectively (Table 3). Table 4 presents a fragment of the examination set with structure recognition results according to the two methods (voting and geometric).

An analysis of signature space of the formulated model examined the influence on the activity of both separate groups and their various combinations. It was shown that the trifluoromethyl group and a tertiary N atom were most significant for high-effective antiarrhythmic agents. The 1,2,4-trisubstituted benzene was significant among the cyclic signatures (Fig. 1, Table 5). A primary amine in addition to *meta*-, *ortho*-, and 1,2,3-trisubstituted benzene were encountered primarily in the class of low-effective compounds (Figs. 2 and 3, Table 5).

It was established that the level and nature of the signature effect on the manifestation of antiarrhythmic activity depended on both the type and the mode of bonding with neighboring signatures. Thus, sequential bonding of a secondary amine and carbonyl group with a 1,2,4-trisubstituted benzene fragment was characteristic of active compounds. However, combination of a carbamide fragment with 1,2,4-trisubstituted benzene had a negative effect on the manifestation of the target property (Fig. 4).

Compounds obtained as a result of the modification were tested using the formulated model. A total of 15 derivatives of lidocaine and 36 of procainamide exhibited (with 82%

TABLE 7. Results of 4-Amino-*N*-[2-(diethylamino)ethyl]benzamide Modification



Compound	R^1	R^2	R^3
1	NH_2	CF_3	–
2	NH_2	OCF_3	–
3	NH_2	$N(CH_3)_2$	–
4	NH_2	$N(CH_3)CH(CH_3)_2$	–
5	OCH_3	–	–
6	OCH_2CF_3	–	–
7	$N(CH_3)CH(CH_3)C_2H_5$	–	–
8	OCH_3	OCH_3	–
9	$N(CH_3)CH(CH_3)_2$	$C(O)NHCH_3$	–
10	$C(O)NHCH_3$	$C(O)NHCH_3$	–
11	$N(CH_3)CH(CH_3)C_2H_5$	–	OCH_3
12	OCH_3	–	CF_3
13	$OC(O)C_2H_5$	–	CF_3
14	CF_3	–	OCH_2CF_3
15	$C(O)NHCH_3$	–	OCH_2CF_3
16	$C(O)NHCH_3$	CF_3	–
17	$N(CH_3)CH(CH_3)_2$	OCH_2CF_3	–
18	CF_3	–	–
19	NH_2	$N(CH_3)CH(CH_3)C_2H_5$	–
20	$N(CH_3)CH(CH_3)_2$	–	–
21	NH_2	–	CH_3
22	$C(O)NHCH_3$	–	–
23	NH_2	OC_2H_5	–
24	OCH_2CF_3	–	OCH_2CF_3
25	OCH_2CF_3	OCH_3	–
26	CF_3	–	$N(CH_3)_2$
27	CF_3	OC_2H_5	–
28	$N(CH_3)CH(CH_3)_2$	OC_2H_5	–
29	CF_3	–	CF_3
30	OCH_3	–	OCH_3
31	$OC(O)C_2H_5$	$N(CH_3)CH(CH_3)C_2H_5$	–
32	OC_2H_5	–	–
33	$N(CH_3)_2$	–	–
34	CF_3	OCH_3	–
35	$OC(O)C_2H_5$	–	–
36	$N(CH_3)_2$	$N(CH_3)CH(CH_3)C_2H_5$	–

probability) highly effective antiarrhythmic activity (Tables 6 and 7). Our results were confirmed by results of AAA prediction using resources of the PASS information system (Table 8). Furthermore, many of the proposed compounds also exhibited a broad spectrum of biological activity (e.g., SO_2 inhibition, sodium-channel blockage, antiseborrhea effect,

TABLE 8. Results of Theoretical Prediction of Antiarrhythmic Activity

Compound	SARD-21		PASS	
	Voting	Geometry	Pa	Pi
N^1-(2,6-Dimethylphenyl)-N^2, N^2-diethylgycinamide modification				
1	A	A	0.692	0.005
2	A	A	0.690	0.007
3	A	A	0.577	0.012
4	A	A	0.553	0.014
5	A	A	0.585	0.011
6	A	A	0.647	0.008
7	A	A	0.559	0.014
8	A	A	0.539	0.016
9	A	A	0.512	0.014
10	A	A	0.569	0.010
11	A	A	0.572	0.010
12	A	A	0.627	0.007
13	A	A	0.900*	0.007*
14	A	A	0.521	0.013
15	A	A	0.867*	0.010*
4-Amino-*N*-[2-(diethylamino)ethyl]benzamide modification				
1	A	A	0.652	0.005
2	A	A	0.663	0.005
3	A	A	0.624	0.007
4	A	A	0.568	0.010
5	A	A	0.744	0.005
6	A	A	0.740	0.005
7	A	A	0.646	0.005
8	A	A	0.751	0.005
9	A	A	0.635	0.006
10	A	A	0.786	0.004
11	A	A	0.626	0.007
12	A	A	0.689	0.005
13	A	A	0.583	0.009
14	A	A	0.723	0.005
15	A	A	0.717	0.005
16	A	A	0.710	0.005
17	A	A	0.553*	0.008*
18	A	A	0.745	0.005
19	A	A	0.541	0.012
20	A	A	0.677	0.005
21	A	A	0.698	0.005
22	A	A	0.784	0.004
23	A	A	0.671	0.005
24	A	A	0.740	0.005
25	A	A	0.703	0.005
26	A	A	0.661	0.005
27	A	A	0.751	0.005
28	A	A	0.640	0.006
29	A	A	0.758	0.005
30	A	A	0.743	0.005
31	A	A	0.508	0.014
32	A	A	0.759	0.005
33	A	A	0.766	0.004
34	A	A	0.736	0.005
35	A	A	0.605	0.008
36	A	A	0.595	0.008

Note: Pa, probability to be active (the given compound exhibits antiarrhythmic activity); Pi, probability to be inactive (the given compound does not exhibit antiarrhythmic activity); *, probable sodium-channel blockage.

treatment of urological disorders, etc.). The study of them will be continued.

Cyclic and acyclic signatures characteristic of compounds with pronounced antiarrhythmic activity were identified as a result of the study of the structure–AAA relationship in the series of *N*-phenylacetamide derivative and amides of aromatic carboxylic acids. The formulated DSS allowed the presence of AAA to be predicted in a wide range of compounds (virtual screening) and to rank them according to AAA effectiveness. The mathematical model for predicting AAA had a recognition reliability level greater than 81% according to the two sample recognition theory methods (geometric approach and voting). A total of 51 compounds with the most pronounced AAA was proposed as a result of the structural modification and the analysis of lidocaine and procainamide. New structures were constructed based on selected known drugs for which the modification directions were chosen and substituents characteristic of effective antiarrhythmic agents were incorporated. This all allowed the new structures to be considered as potential drugs and recommended for further synthesis and testing.

REFERENCES

1. N. A. Sysoeva, *Treatment of Heart Rhythm Irregularities* [in Russian], Ovetlei, Moscow (1993).
2. S. P. Golitsin, *Klin. Farmakol. Ter.*, **6**(3), 14 – 16 (1997).
3. R. P. Rakhmanov, *Principles of Antiarrhythmic Therapy* [in Russian], Anko, Moscow (2000).
4. A. V. Nedostup and O. V. Blagova, *Rus. Med. Zh.*, **11**(21), 1168 – 1172 (2003).
5. T. Szabo, L. Geller, B. Merkely, et al., *Life Sci.*, **66**(26), 2527 – 2541 (2000).
6. L. A. Tyurina, O. V. Tyurina, and A. M. Kolbin, *Methods and Results of the Design and Prediction of Biologically Active Compounds* [in Russian], Gilem, Ufa (2007).
7. C. Marot, P. Chavatte, and D. Lesieur, *Quant. Struct.-Act. Relat.*, **19**, 127 – 134 (2000).
8. H.-J. Kim, C. H. Chae, K. Y. Yi, et al., *Bioorg. Med. Chem.*, **12**(7), 1629 – 1641 (2004).
9. V. Poroikov and D. Filimonov, in: *Rational Approaches to Drug Design*, H.-D. Holtje and W. Sippl (eds.), Prous Science, Barcelona (2001), pp. 403 – 407.
10. S. Miyano, K. Sumoto, F. Satoh, et al., *J. Med. Chem.*, **28**, 714 – 717 (1985).
11. E. H. Banitt, J. R. Schmid, and R. Newmark, *J. Med. Chem.*, **29**, 299 – 302 (1986).
12. E. H. Banitt, W. E. Coyne, J. R. Schmid, and A. Mendel, *J. Med. Chem.*, **18**(11), 1130 – 1134 (1975).
13. P. A. Tenthorey, H. J. Adams, G. Kronberg, and B. H. Takman, *J. Med. Chem.*, **24**, 1059 – 1063 (1981).
14. P. A. Tenthorey, A. J. Block, R. A. Ronfeld, et al., *J. Med. Chem.*, **24**, 798 – 806 (1981).
15. R. E. Johnson, E. R. Baizman, C. Becker, et al., *J. Med. Chem.*, **36**, 3361 – 3370 (1993).
16. J. K. Campbell, R. T. Logan, R. J. Marshall, et al., *J. Med. Chem.*, **29**, 244 – 250 (1986).
17. E. W. Byrnes, P. D. McMaster, E. R. Smith, et al., *J. Med. Chem.*, **22**(10), 1171 – 1176 (1979).
18. I. Roufos, S. J. Hays, and D. J. Dooley, et al., *J. Med. Chem.*, **37**, 268 – 274 (1994).