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Original article

Synthesis, structure–activity relationship of some new anti-arrhythmic 5-arylidene imidazolidine-2,4-dione derivatives

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Abstract

The synthesis of unsubstituted and halogen substituted 5-arylidene basic amide derivatives of imidazolidine-2,4-dione is described. Structural elucidation based on X-ray analysis was performed for four representative compounds. The effect of the studied compounds on the electrocardiogram was examined in vitro in the non-working heart perfusion test and that of an anti-arrhythmic activity in the rat coronary artery ligation-reperfusion model. The most active compound: (5*Z*)-(3-chloro)benzylidene-3-{2-[4-(hydroxyethyl)piperazin-1-yl]-2-oxoethyl}imidazolidine-2,4-dione has shown properties of the compounds belonging to class Ia, according to the Vaughan Williams classification. Chosen compounds evaluated in vivo were devoid of anticonvulsant and neurotoxical activity.

Keywords: Anti-arrhythmic activity; 5-Arylidene imidazolidine-2,4-dione derivatives; X-ray structure determination; Anticonvulsant properties

1. Introduction

Sodium channels found in neurons have pharmacological and physiological properties different from those in skeletal muscle or cardiac cells. It was found that anticonvulsant diphenylhydantoin (**DPH**) at therapeutically relevant concentrations inhibits allosterically the binding of [^{3}H]BTX-B to neuronal voltage sodium channel (NVSC) [1–7]. This indicated the NVSC as potential anticonvulsant receptor site. Other agents, like local anesthetics and anti-arrhythmics, also interact with NVSC and are able to inhibit [^{3}H]BTX-B binding [8–10]. These three classes of therapeutic agents often possess overlapping pharmacological activity, which could be illustrated by anti-arrhythmic properties of the anticonvulsant **DPH** and the local anesthetic lidocaine. There is a controversy concerning whether anticonvulsants, local anesthetics and anti-arrhythmics act at either the same or at different sites of NVSC (one-site [11] and two-site [12] models). The results of some investigations have also suggested that log*P* [13] and 5-phenyl ring orientation [14,15] are important for the efficient binding of hydantoin derivatives to NVSC. Assuming that the peripheral actions of anti-arrhythmics may be connected with appropriate lipophilic properties, we have designed the synthesis of **DPH** derivatives with altered log*P* values. A series of basic amide derivatives of diphenyl hydantoin acetic acid was obtained. It was found that introduction of the chain containing a tertiary amine nitrogen atom to **DPH** moiety allowed to obtain the compounds showing anti-arrhythmic properties [16,18]. The introduced modifications make possible the lipophilicity alteration, provide the basic chemical character of the obtained derivatives and diminish the major disadvantages of **DPH** connected with its marked central effects caused by the facilitated brain penetration [16–19]. The earlier discussion of the structure–activity relationships of **DPH** derivatives provided us with a model indicating areas essential for the anti-arrhythmic activity of its derivatives [16]. This model is presented in Fig. 1 for one of the most active compounds of this type—5,5-diphenyl-3-[2-[4-(2-hydroxyethyl)piperazin-1-yl]-2-oxoethyl]imidazoline-2,4-dione (**RH$_7$**). It was summarized that the activity of the studied compounds depended on the presence of protonated

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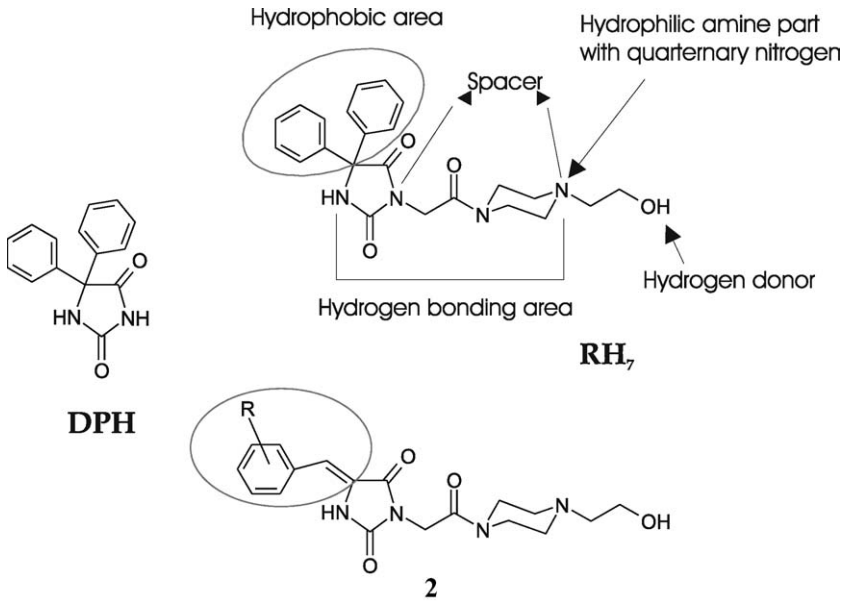

Fig. 1. The areas essential for anti-arrhythmic activity shown for **RH$_7$** [16] to be compared with the structure of the starting compound (**DPH**) and derivatives (**2a**–**g**) described in this paper.

tertiary nitrogen atom and at least one phenyl ring, and sufficient flexibility of the molecule which enabled the spacer to adopt a desired length for interaction with the receptor binding sites. It was stressed that the presence of a hydrogen donating terminal hydroxyl group and carbonyl accepting group within the spacer seems to be important for the anti-arrhythmic activity.

To explore the required properties of the hydrophobic area of the anti-arrhythmic pharmacophore model (Fig. 1) the above results were considered in our present work on designing the new compounds. Hence the compounds of the series **2** possess unchanged basic amide substituent at the position 3 and arylidene group (unsubstituted or halogen substituted) at position 5 of the imidazolidine-2,4-dione (Fig. 2). The arylidene group, in which phenyl ring is connected to the imidazolidine-2,4-dione moiety through a double bond in configuration (*Z*), was chosen since it allowed to examine the limitation of the hydrophobic area of the pharmacophore. The phenyl ring was either unsubstituted or substituted with halogen atoms (Cl, Br) at different positions (*para*, *ortho* or *meta*; Table 1). The compounds (**2a**–**2g**) were evaluated in vitro for their anti-arrhythmic properties. In order to estimate their electrophysiological profile of action they were tested on the isolated rat heart. Selected compounds were examined in vivo for anticonvulsant activity and neurotoxicity. Their physicochemical properties such as log*P*, log*D* and pK_a were estimated using PALLAS program [20]. Four representative compounds were chosen for the evaluation of their spatial properties by X-ray structure analysis: unsubstituted (**2a**), substituted with chlorine atom in *para* position (**2g**) and substituted with bromine atom either in *meta* (**2c**) or in *para* (**2d**) positions of the arylidene ring.

2. Chemistry

Fig. 2 illustrates the synthetic approach chosen for the preparation of amides **2a**–**2g**. The acids **1a**–**1g**, upon reaction with 2-hydroxyethylpiperazine (HEP) in the presence of benzotriazol-1-yloxy-tris(dimethylamino)-phosphonium hexafluorophosphate (BOP—coupling agent) gave amides **2a**–**2g**. The obtained basic amides were converted into hydrochlorides, which are better soluble in water. The purity of the obtained compounds was checked by TLC technique. The structures of **2a**–**2g** were confirmed by the examination of their IR, ^{1}H NMR and MS spectra as well as by elemental analyses.

2.1. Partition coefficient determination

The values of log*P*, log*D*, and pK_a of basic and acidic groups of **2a**–**2g**, **RH$_7$** and **DPH** were calculated with PALLAS program (version 1.2), using prediction modules: prolog P 5.1, prolog D 2.0 and pKalc 3.1. The obtained results are given in Table 1. As expected, investigated compounds and **RH$_7$** possess hydrophilic properties (negative values of log*P*), while DPH is hydrophobic.

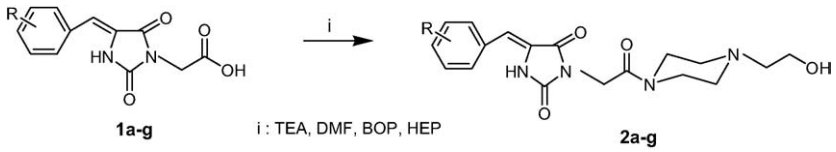

Fig. 2. Synthesis of the new anti-arrhythmic hydantoin derivatives (**2a**–**2g**).

Table 1
Structures and physicochemical data of compounds **2a**–**2g**, **RH$_7$** and phenytoin (**DPH**)

Compounds	R[1]	pK_a [a]		Log$P$ [a]	Log$D$ [a]	
		Acidic groups [b]	Basic groups [c]		pH 7.0	pH 7.4
2a	H	15.11	7.08–4.10	–1.74	–2.08	–1.91
2b	2-Br	15.11	7.08–4.10	–0.87	–1.21	–1.04
2c	3-Br	15.11	7.08–4.10	–0.80	–1.14	–0.98
2d	4-Br	15.11	7.08–4.10	–0.86	–1.20	–1.03
2e	2-Cl	15.11	7.08–4.10	–1.03	–1.37	–1.20
2f	3-Cl	15.11	7.08–4.10	–0.96	–1.30	–1.13
2g	4-Cl	15.11	7.08–4.10	–1.02	–1.36	–1.19
RH$_7$	–	15.11	7.08–4.10	–1.09	–1.43	–1.26
DPH	–	8.06, 8.31 [d]	None	1.65	1.62	1.57

[a] Calculated by PALLAS program for free bases.
[b] Acidic groups: RCH_2OH, N-imide for DPH.
[c] Basic groups: $RRRNH^+$, RCH_2OH.
[d] Literature data [32].

3. Pharmacological activity

3.1. In vitro tests

Compounds **2d** and **2e** were excluded from the pharmacological in vitro examination since these compounds possessed too low water solubility (in basic concentration 10^{-5} M were not soluble).

3.1.1. Non-working heart perfusion

The novel imidazolidine-2,4-dione derivatives (**2a**, **2b**, **2c**, **2f**, **2g**), used at concentration 10^{-9}–10^{-5} M, decreased the number of cardiac beats per minute (10–46%), causing sinus bradycardia (Fig. 3), prolonged P–Q (by ca. 2–112%), Q–T (by 2–57%) intervals and QRS complex (by 4.5–87%; Fig. 4). The strongest cardiodepressive activity was shown by compound **2b**, which in dose of 10^{-6} M prolonged P–Q by 112%, QRS by 30% and Q–T by ca. 56%, and reduced the coronary flow by 30% (Fig. 4). Given in dose of 10^{-5} M **2b** produced arrhythmia. Other compounds of this series decreased the coronary flow by ca. 2–40%. The results obtained for **RH$_7$**, Epanutin and quinidine were also included in Figs. 3 and 4.

3.1.2. Ventricular arrhythmias associated with coronary artery occlusion and reperfusion in the non-working isolated perfused rat heart

During the 30 min period of coronary artery reperfusion, all hearts in the control developed ventricular premature beats (VBs). The incidence of ventricular tachycardia (VT) and ventricular fibrillation (VF) was 75% and 50%, respectively (Table 2). Perfusion with compound **2f** at concentration of 10^{-5} M, decreased the number of VBs from 100%, in untreated hearts, to 50%. The incidence of VT was reduced from 75% to 50%, while the incidence of VF was reduced from 50% to 25%. Although the remaining compounds, used in concen-

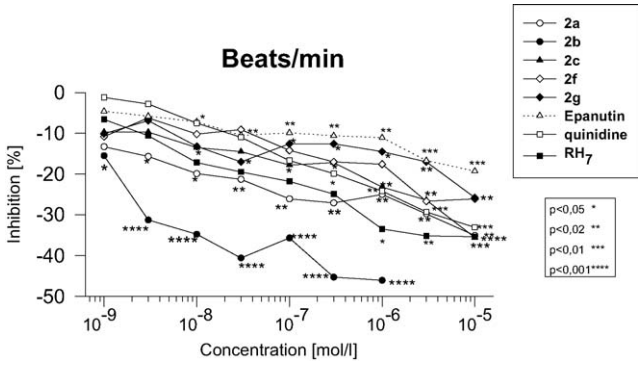

Fig. 3. Effect of the increasing concentration of the tested compounds on heart rate.

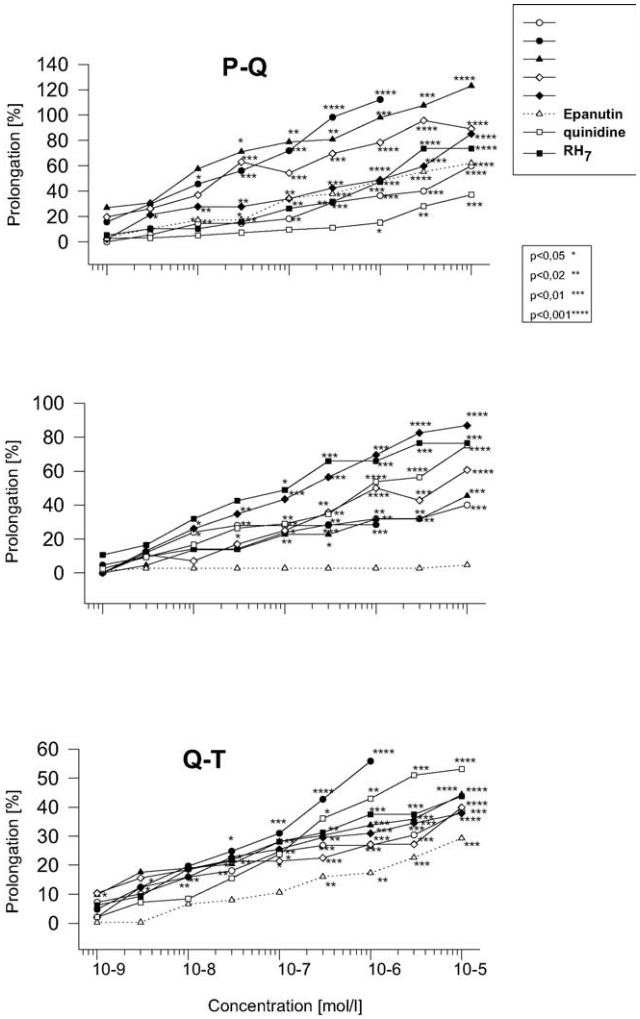

Fig. 4. Effect of the tested compounds on ECG parameters.

Table 2
Effects of tested compounds on reperfusion-induced arrhythmia. Arrhythmia severity index was calculated according to Bernauer and Ernenputsch [21]

Compound	Concentration (M)	VBs incidence (%)	VT incidence (%)	VF incidence (%)	Arrhythmia severity index
Control		100	75	50	5.25 ± 0.9
2a	10^{-5}	75	50	25	3.75 ± 0.8
2b	10^{-6}	50	50	50	4.25 ± 0.6
2c	10^{-5}	60	60	20	3.6 ± 2.4
2f	10^{-5}	50	50	25	3.25 ± 0.8*
2g	10^{-5}	75	25	50	4.0 ± 1.0
Control		100	80	40	5.6 ± 0.6
RH_7	10^{-5}	50	50	25	3.25 ± 1.7*
Control		100	80	50	5.2 ± 1.5
quinidine	10^{-5}	100	50	0	2.5 ± 2.2**
Control		100	75	50	5.8 ± 0.7
lidocaine	10^{-5}	100	37.5	12.5	3.25 ± 0.7***
Control		100	62.5	37.5	5.2 ± 1.0
Epanutin	10^{-5}	100	25	0	2.6 ± 0.4**

Each value was obtained from six to eight hearts. Significantly different to control: * $P < 0.05$, ** $P < 0.02$, *** $P < 0.01$. VBs – ventricular premature beats, VT – ventricular tachycardia, VF – ventricular fibrillation.

trations of 10^{-6}–10^{-5} M, did not show significant anti-arrhythmic activity in this test, their activity was differentiated. The differences in their activity can be described by the values of the arrhythmia severity index [21], which are presented in Table 2.

The *Langendorff-non-working rat heart* has been used to study the effects of tested compounds on the electrocardiogram (ECG; Table 3).

Our results indicate that the tested compounds reduced the heart rate and induced a dose-dependent prolongation of the P–Q and Q–T intervals, and caused a widening of the QRS. The electrocardiographic changes, observed after administration of the compounds, were identical to those observed for quinidine, whereas Epanutin prolonged P–Q and Q–T interval, but did not change the QRS complex (Table 3). These results confirmed that the tested compounds could be included into the class IA of anti-arrhythmic drugs.

The numerous and varied methods could be used in screening of new antiarryhythmic agent [22]. Curtis et al. [23] noted in their review of rat ischemia–reperfusion models that the model of re-entry induced by ischemia plus reperfusion (rat coronary ligation-reperfusion) in vitro and in vivo can be recommended as a screen for new anti-arrhythmic drugs. Furthermore Brooks et al. [24] suggest that the rat coronary artery ligation-reperfusion model can be used to identify a new anti-arrhythmic agents of any Vaughan Williams class.

Following this suggestion the anti-arrhythmic activity of tested compounds was examined in reperfusion-induced arrhythmia rat models in vitro.

Compared with control hearts, only compound **2f** statistically diminished reperfusion-induced arrhythmias in the isolated rat heart (Langendorff-type preparation). The effect of compound **2f** on reperfusion-induced arrhythmias was comparable to that reported for lidocaine in the same experimental procedure and only slightly weaker than that of Epanutin, but was lower than that of quinidine.

In summary, the pharmacological results obtained by us clearly indicate that **2f** showed a notable anti-arrhythmic activity in the reperfusion-induced arrhythmia in vitro. On the basis of these results, compound **2f** was selected for further pharmacological evaluation.

3.2. In vivo tests

3.2.1. Anticonvulsant properties

Anticonvulsant assays were performed for compounds **2a**, **2c**, **2f** and **2g**. In doses up to 300 mg kg^{-1} these derivatives have shown no neurotoxicity and were devoid of anticonvulsant activity in the used tests. The obtained results indicate that examined compounds, similarly as the other investigated in our group basic derivatives of hydantoin [16,19] are lacking of CNS activity characteristic for the starting DPH.

4. Crystal structure analysis

The molecular structures of **2a**, **2c**, **2d** and **2g** in the crystalline state, found using X-ray diffraction experiments, are shown in Fig. 5. 5-Benzylidene-imidazolidine moiety is characterized by a relatively small angle between the mean planes of its rings, five-membered one and the aromatic fragment. The angles are ranging from 11.8(1) to 6.6(1)° for chlorine and bromine derivatives. So, the moiety is almost planar for all of the derivatives except of **2a** (without halogen substituent), for which the angle of 23.5(1)° is observed. The molecules differ significantly in conformation of the side-chain defined by a set of the chosen torsion angles presented in Table 4. **2d** and **2g** contain two symmetrically independent molecules (I and II) in the asymmetric part of the unit cell. Because of space group symmetry $P\bar{1}$, each of the molecules has an equivalent molecule related by the crystallographic center of symmetry. As can be seen from Fig. 6, the relation between molecules of type I and II could be described in general as pseudo-translation (in Fig. 5 this is shown for **2d**) and pseudo-center of symmetry (in Fig. 5 this is shown for **2g**). Fig. 6 presents the differences between molecules I and II

Table 3
Influence of tested compounds on heart and ECG parameters

Compounds	Parameters	Concentration (mol l^{-1})									
		0	10^{-9}	3×10^{-9}	10^{-8}	3×10^{-8}	10^{-7}	3×10^{-7}	10^{-6}	3×10^{-6}	10^{-5}
2a	Beats per minute	188±17	163 ± 6	158 ± 10*	158 ± 13*	148 ± 13**	139 ± 11**	137 ± 11**	141 ± 11**	132 ± 12**	122 ± 11***
	P–Q (ms)	55 ± 4	55 ± 4	58 ± 3	63 ± 4**	63 ± 4**	65 ± 4**	72 ± 6***	75 ± 6***	77 ± 7***	83 ± 8****
	QRS (ms)	25 ± 2	25 ± 2	28 ± 1	31 ± 2*	32 ± 3**	32 ± 3**	32 ± 3**	33 ± 2**	33 ± 2**	35 ± 2***
	Q–T (ms)	138 ± 5	148 ± 6*	152 ± 4*	160 ± 6**	163 ± 6**	172 ± 7**	177 ± 7***	175 ± 7***	180 ± 7***	183 ± 6***
2b	Beats per minute	258 ± 13	218 ± 6*	177 ± 11****	168 ± 10****	153 ± 20****	167 ± 8****	141 ± 13****	139 ± 9****		
	P–Q (ms)	57 ± 0.3	66 ± 6	74 ± 13	83 ± 8*	89 ± 5***	98 ± 6***	113 ± 6****	121 ± 0.8****		
	QRS (ms)	21 ± 1	22 ± 1	23 ± 1	24 ± 2	24 ± 1	26 ± 2**	27 ± 2***	27 ± 2***		
	Q–T (ms)	145 ± 2	152 ± 6	163 ± 12	170 ± 5	181 ± 11*	190 ± 15***	207 ± 13****	226 ± 8****		
2c	Beats per minute	185 ± 17	167 ± 12	167 ± 9	160 ± 11	158 ± 17	152 ± 9*	153 ± 13*	142 ± 8**	136 ± 11**	119 ± 9****
	P–Q (ms)	52 ± 6	66 ± 8	68 ± 12	82 ± 11	89 ± 7*	93 ± 12**	94 ± 8**	103 ± 9***	108 ± 11***	116 ± 9****
	QRS (ms)	22 ± 1	22 ± 1	23 ± 2	25 ± 1	25 ± 1	27 ± 1*	27 ± 1*	29 ± 2**	29 ± 2**	32 ± 3***
	Q–T (ms)	142 ± 8	156 ± 5	167 ± 11	169 ± 19	171 ± 1*	182 ± 11**	185 ± 11**	190 ± 8***	193 ± 13***	205 ± 9****
2f	Beats per minute	176 ± 19	157 ± 13	165 ± 16	158 ± 14	160 ± 19	150 ± 23	146 ± 15	145 ± 16	129 ± 21	130 ± 24
	P–Q (ms)	46 ± 3	55 ± 2	58 ± 3	63 ± 3	75 ± 6***	71 ± 4***	78 ± 8***	82 ± 8****	90 ± 12****	87 ± 12****
	QRS (ms)	28 ± 1	28 ± 1	31 ± 3	30 ± 2	33 ± 3	35 ± 2	38 ± 2**	42 ± 2****	40 ± 3***	45 ± 2****
	Q–T (ms)	173 ± 8	191 ± 11	200 ± 11	205 ± 10	210 ± 12*	210 ± 11*	212 ± 13**	220 ± 21***	220 ± 14***	242 ± 16****
2g	Beats per minute	159 ± 15	143 ± 13	148 ± 13	138 ± 16*	132 ± 16*	139 ± 16*	139 ± 16*	136 ± 14*	132 ± 13**	118 ± 7**
	P–Q (ms)	47 ± 3	48 ± 3	57 ± 2*	60 ± 2**	60 ± 2**	63 ± 2**	67 ± 3***	70 ± 3***	75 ± 3****	87 ± 2****
	QRS (ms)	23 ± 2	23 ± 2	26 ± 2	29 ± 1*	31 ± 1**	33 ± 1***	36 ± 1***	39 ± 1***	42 ± 2****	43 ± 2****
	Q–T (ms)	145 ± 6	148 ± 6	163 ± 7*	168 ± 8*	178 ± **	182 ± 10**	188 ± 12**	190 ± 11***	195 ± 10***	200 ± 11****
RH_7	Beats per minute	177 ± 12	165 ± 13	158 ± 15	146 ± 16	142 ± 16	138 ± 16	133 ± 19	117 ± 18*	114 ± 13**	114 ± 20**
	P–Q (ms)	47 ± 5	50 ± 6	52 ± 5	55 ± 5	60 ± 4	62 ± 6	67 ± 5**	70 ± 4***	82 ± 6****	82 ± 6****
	QRS (ms)	24 ± 2	26 ± 2	27 ± 3	31 ± 3	34 ± 4	35 ± 3*	39 ± 4***	39 ± 4***	42 ± 5***	42 ± 5***
	Q–T (ms)	160 ± 8	170 ± 6	175 ± 10	190 ± 13	195 ± 13	205 ± 13*	210 ± 13**	220 ± 16***	220 ± 17***	230 ± 21***
Epanutin	Beats per minute	188 ± 9	178 ± 9	177 ± 8	174 ± 9*	168 ± 9**	169 ± 9**	167 ± 9**	167 ± 7**	152 ± 9***	151 ± 9***
	P–Q (ms)	48 ± 3	50 ± 3	53 ± 2	57 ± 2*	57 ± 2*	65 ± 2**	67 ± 2***	72 ± 3****	75 ± 3****	78 ± 3****
	QRS (ms)	21 ± 2	21 ± 2	22 ± 2	22 ± 2	22 ± 2	22 ± 2	22 ± 2	22 ± 2	22 ± 2	22 ± 2
	Q–T (ms)	125 ± 3	125 ± 3	125 ± 3	133 ± 4	135 ± 6	138 ± 6*	145 ± 8**	147 ± 7**	153 ± 6***	162 ± 3***
quinidine	Beats per minute	159 ± 11	157 ± 10	154 ± 7	147 ± 8	141 ± 9	132 ± 10	130 ± 11*	120 ± 10**	112 ± 13***	106 ± 13***
	P–Q (ms)	53 ± 3	54 ± 4	54 ± 4	55 ± 2	56 ± 4	58 ± 3	58 ± 5	61 ± 2*	68 ± 3**	72 ± 2***
	QRS (ms)	23 ± 2	24 ± 2	26 ± 2	27 ± 1	30 ± 2*	31 ± 2**	31 ± 2**	36 ± 3****	37 ± 2****	40 ± 3****
	Q–T (ms)	157 ± 12	157 ± 12	160 ± 13	169 ± 11	170 ± 12	181 ± 8*	194 ± 9*	213 ± 16**	224 ± 16***	237 ± 17****

The data are the means of six experiments ± S.E.M. Statistical analyses were performed using a one-way ANOVA test. * $P < 0.05$, ** $P < 0.02$, *** $P < 0.01$, **** $P < 0.001$.

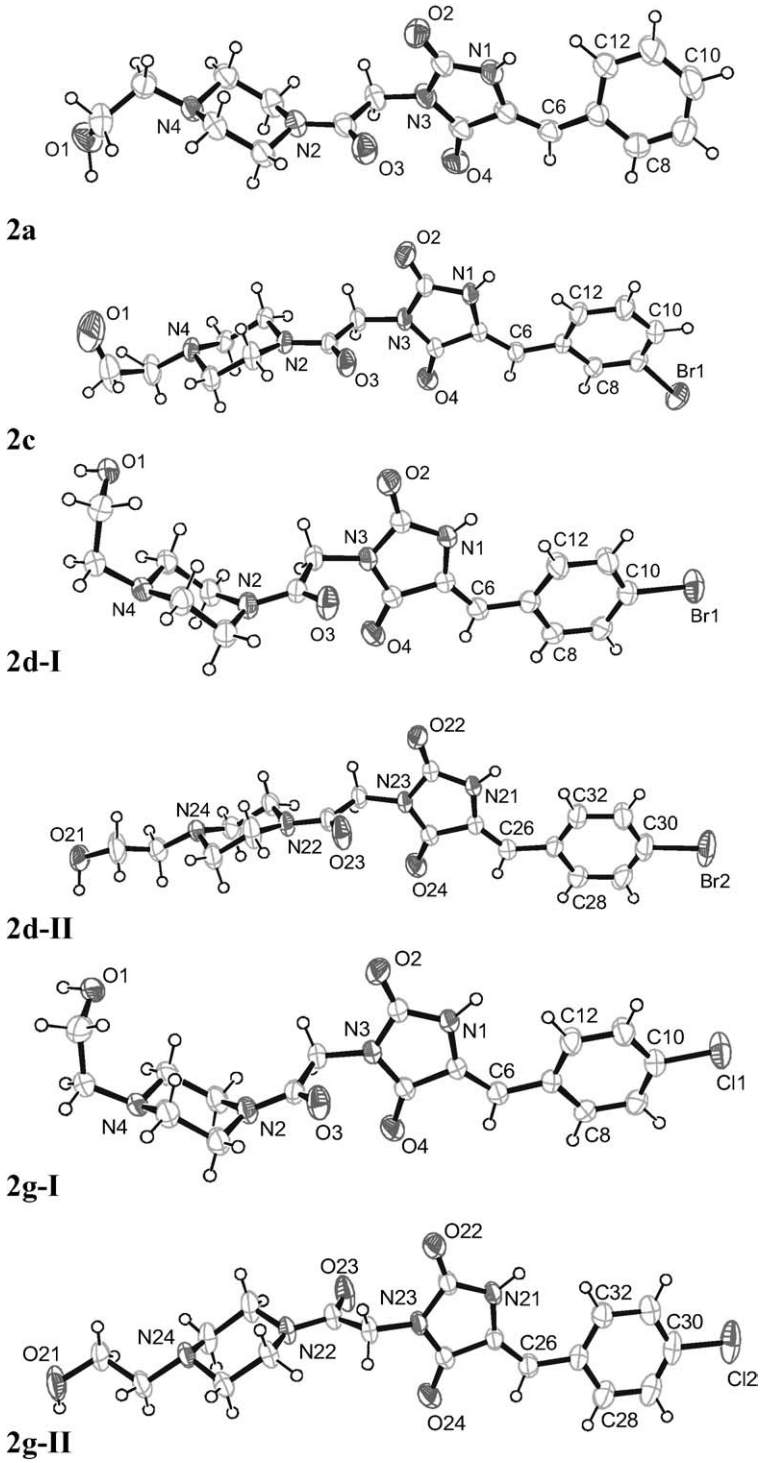

Fig. 5. Comparison of the molecular geometry of the studied compounds in the crystalline state. ORTEP3 [31] drawings show the molecular conformation and atom numbering schemes. Displacement ellipsoids are shown with 50% probability level: **2a**, **2c**, **2d–I**, **2d–II**, the second of two symmetrically independent molecules is related to **2d–I** by a pseudo-translation; **2g–I** presents the geometry similar to **2d–I**, **2g–II**, the second of two symmetrically independent molecules is related to **2g–I** by a pseudo-center of symmetry.

imposed to fit the imidazolidine ring of **2d** and **2g**, respectively. A detail inspection of Table 4 reveals that the differences between molecules I and II should be considered separately for three fragments of the side-chain at imidazolidine N3 atom. The conformational changes of the piperazine ring itself do not follow the rules observed in the first fragment. So, for pseudo-translational molecule II the conformation of piperazine ring is pseudo-centrosymmetric when compared to I, whereas for pseudo-centrosymmetric molecule II it is related by the pseudo-translation to I. The observation may be explained by the effect of piperazine ring inversion, which in solution is a dynamic process, as confirmed by ^{1}H NMR

Table 4
Selected torsion angles in the side-chain substituted at imidazolidine N3 atom

Compounds	RH_7 [16]	2a	2c	2d		2g	
				I	II [a]	I	II [b]
Fragment of side-chain between imidazolidine and piperazine rings							
N1–C5–C6–C7		–4.0(2)	2.0(5)	3.2(6)	1.4(6)	3.0(4)	–1.1(4)
C5–C6–C7–C8		–21.9(4)	11.4(4)	8.2(5)	4.8(5)	9.9(3)	–5.6(4)
O4–C4–N3–C1	5.8(3)	–4.0(4)	–4.8(4)	–2.0(5)	–7.5(5)	–1.3(3)	7.6(3)
C4–N3–C1–C3	81.1(2)	92.8(3)	98.5(3)	77.1(4)	90.9(3)	76.1(2)	–90.0(2)
N3–C1–C3–O3	–2.3(3)	–10.5(3)	–4.0(3)	21.2(4)	15.4(4)	19.8(3)	–15.1(3)
N3–C1–C3–N2	177.2(2)	170.7(2)	175.3(2)	–160.6(3)	–167.0(3)	–161.8(2)	167.2(2)
C1–C3–N2–C13	–9.1(3)	8.3(2)	–3.7(2)	–0.02(4)	–5.9(4)	0.8(3)	5.3(3)
Piperazine ring							
C3–N2–C13–C14	133.5(2)	–141.0(2)	–146.2(2)	–116.2(3)	156.5(3)	–118.4(2)	–155.5(2)
N2–C13–C14–N4	56.9(3)	54.4(3)	–54.9(3)	–56.1(3)	55.2(3)	–55.7(2)	–54.9(2)
C16–N2–C13–C14	–53.2(3)	–50.2(3)	49.3(3)	56.5(3)	–48.1(4)	55.4(2)	47.7(3)
C15–C16–N2–C13	53.1(3)	52.0(3)	–49.3(3)	–57.3(3)	48.7(4)	–56.1(2)	–48.4(3)
N4–C15–C16–N2	–56.1(3)	–57.3(3)	55.5(2)	58.5(3)	–55.9(4)	57.8(2)	56.0(3)
C14–N4–C15–C16	60.6(3)	61.5(2)	–61.6(3)	–60.2(3)	63.1(4)	–59.7(2)	–63.2(2)
C13–C14–N4–C15	–61.0(3)	–60.4(2)	60.8(3)	58.4(3)	–63.1(3)	58.3(2)	63.0(2)
C13–C14–N4–C17	175.0(7)	176.5(2)	–178.6(2)	–174.9(2)	–175.9(2)	–174.3(2)	176.4(2)
Terminal fragment of side-chain							
C14–N4–C17–C18	–84.8(5)	–81.8(3)	69.6(4)	–59.3(4)	68.3(4)	–60.0(3)	–67.9(3)
N4–C17–C18–O1	177.2(7)	–78.0(3)	70.7(5)	74.3(4)	167.1(3)	72.9(3)	–168.7(2)

[a] Related to I by pseudo-translation.
[b] Related to I by pseudo-center of symmetry.

spectra, but in the crystalline state the different conformations are stabilized by the mutual spatial arrangements of the molecules and a specific hydrogen bond system. Different types of intermolecular hydrogen bonds formed by the hydroxyl group are also responsible for conformational changes of the terminal fragment of the side-chain.

NH and OH groups, the potential hydrogen donors, are involved in intermolecular hydrogen bonds. The lone electron pair of N4 amine atom and the carbonyl oxygen atom O3 serve as acceptors in the hydrogen bonds formed by the hydroxyl group or water molecules if they are present in the crystal structure (e.g. **2c**, **2d**, **2g**).

To compare the conformation of the studied molecules to that of 5,5-diphenyl-3-{2-oxo-2-[4-(2-hydroxyethyl)-1-piperazinyl]ethyl}hydantoin [16], $\mathbf{RH_7}$ (the most active antiarrhythmic derivative of DPH with the same substituent at N3 as the studied compounds), five descriptors defining the mutual spatial arrangement of the areas essential for the antiarrhythmic activity were chosen and their values for studied compounds are shown in Table 5. Only one benzene ring of $\mathbf{RH_7}$ was taken into account (this one which is at longer distance to N4 and previously was considered to interact with a receptor-pocket [16]). Distances Ph...N4 and Ph...O3 and N4...O3 characterize the position of the hydrophobic area (Ph) against the hydrophilic amine part (N4) and against the carbonyl group (O3) which both can be involved in additional hydrogen bonds. N3...N4 distance defines the length of the spacer between the hydrophobic and hydrophilic parts of the molecule, and N4...O1 describes the position of hydroxyl group (hydrogen donor) against the amine part. Although the distances of Ph to N4 and O3 are much elongated when compared to $\mathbf{RH_7}$, the flexibility of the molecules assure the fit-

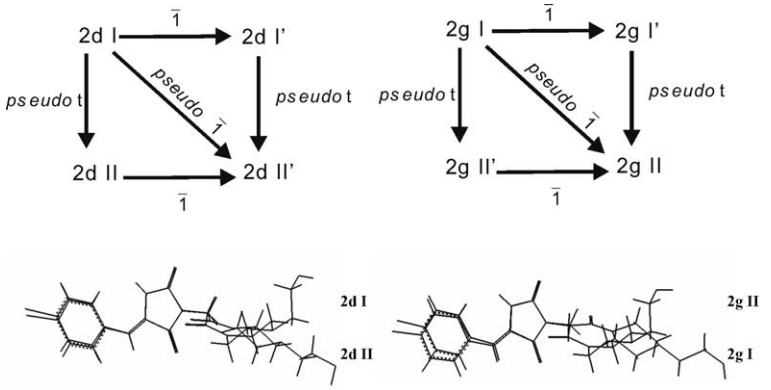

Fig. 6. Relationships between molecules in the crystal structures of **2d** and **2g**: beside of the crystallographic center of symmetry a pseudo-translation and a pseudo-center of symmetry were detected. The conformational differences of symmetry independent molecules of **I** and **II** are shown in projection onto imidazolidine ring.

Table 5
Distances (Å) between potential pharmacophore centers in of the studied molecules as found from the crystal structures. The data are compared to those observed for **DPH** derivative **RH$_7$** [16]

Compounds	N4...Ph	O3...Ph	N4...O3	Spacer N4...N3	N4...O1
RH$_7$ [16]	10.48 [a]	6.78 [b]	4.90	6.34	
2a	12.309(5)	7.697(4)	4.927(3)	6.404(3)	3.073(2)
2c	12.531(3)	8.003(3)	4.949(2)	6.458(2)	3.033(4)
2d	12.243(4)	7.850(4)	4.766(3)	6.276(3)	3.184(3)
	12.409(4)	8.168(4)	4.931(3)	6.459(4)	3.716(3)
2g	12.251(3)	7.815(3)	4.782(2)	6.290(2)	3.172(2)
	12.402(3)	8.064(2)	4.925(2)	6.457(2)	3.714(2)

[a] N4...Ph′ = 9.82.
[b] O3...Ph′ = 3.15.

ting to the suitable receptor sites the remaining significant groups: N4 amine, O3 carbonyl and O1 hydroxyl groups. In general the overall shape and the molecular volume of the studied molecules significantly differ from those of **RH$_7$** (V mol^{-1} = 440 for **2a**, 476 for **2c**, 477 for **2d** and 469 Å^3 for **2g** against 544 Å^3 for **RH$_7$**), but the set of torsion angles in the side-chain observed for the studied compounds is essentially the same as that for **RH$_7$** (Table 4).

5. Discussion

The new compounds **2a**–**2g** reported in Fig. 2 and Table 1 were evaluated in vitro for anti-arrhythmic properties and influence on ECG parameters of isolated heart of rat. **2d** and **2e** were excluded from these tests because of not sufficient solubility. It was stated that the investigated compounds have shown anti-arrhythmic properties expressed with the following decreasing activity **2f** ≈ **RH$_7$** > **2c** > **2a** > **2g** > **2b**. As a measure of this classification arrhythmia severity index according to Bernauer and Ernenputsch [21] was used (Table 2). The activity of **2f** was comparable to **RH$_7$**, previously obtained most active structure [18]. The comparison of the influence of the investigated structures on ECG parameters with that expressed by quinidine and Epanutin used as a reference allowed include them into the class Ia of anti-arrhythmic drugs. The activity of the most active **2f** was comparable to that reported for lidocaine and slightly weaker than that of Epanutin. It is worth to notice that the second active compound **2c** possessed similarly to **2f** substituent in *meta* position. Contrary to Epanutin representative compounds **2a**, **2c** and **2g**, **2f** were devoid of anticonvulsant activity. They were deprived of neurotoxicity either.

In order to discuss presented above results physicochemical and spatial properties of the investigated compounds were examined. The investigated compounds and **RH$_7$** are the structures with basic character contrary to starting acidic DPH (Table 1). Their structures differ only with the place and character of halogen group introduced into the arylidene substituent. Lipophilicity calculated with log*P* and log*D* values comprises in (–1.74 ÷ –0.80) and (–2.08 ÷ –1.14 pH 7.0; –1.91 ÷ –0.98 pH 7.4), respectively. So the ionization influences their lipophilic properties similarly as it was found for **RH$_7$**, but in much lower degree than for DPH. These properties and greatly lower lipophilic character of the investigated compounds (significantly lower than log*P* = 2 believed as necessary for compound to act at CNS) may explain the lack of the anticonvulsant properties and neurotoxicity. The introduction of halogens causes increase of lipophilic properties stronger marked for bromine than for chlorine. However the position of the substituent has almost no influence on lipophilicity according to the calculations [20]. Lipophilicity is also not the only reason for the differentiated solubility of the investigated compounds since **2d** with log*P* = (–0.86) and **2e** log*P* = (–1.03) were not sufficiently soluble, whereas **2c** log*P* = (–0.80) and **2b** log*P* = (–0.87), showing comparable lipophilic character, were soluble enough to enable the pharmacological tests in vitro. Since the compounds have shown differentiated anti-arrhythmic properties it was interesting to correlate the observed results with the spatial distribution of their functional groups and to compare to **RH$_7$**. X-ray structure analysis revealed high flexibility of the molecules defined in Table 4 by chosen torsional angles. The flexibility assures both the close packing of the molecules in the crystalline state and an relatively easy access of their functional groups to the specific receptor sites. Having equally distributed hydrogen donors and acceptors the studied molecules show significant ability to be involved in a complex hydrogen bond system. The geometrical parameters of pharmacologically important descriptors (Table 5), selected according to the receptor-pocket model, confirm the earlier suggestion [16] that only one phenyl substituent at C5 of imidazolidine-2,4-dione moiety is necessary for the interaction with the hydrophobic pocket of the receptor. In the crystalline state the overall shape and volume of the studied compounds significantly differ from that of **RH$_7$** with only slight influence of the position and character of the halogen substituent. On the other hand a geometrical similarity of the studied compounds (measured by the torsional angles) does not explain the observed differences in the pharmacological activity. Presumably not only spatial properties of the molecules but also the electronic properties modified by the influence of halogen substituent at the arylidene part are responsible for the observed differences in the activity.

6. Conclusions

The investigated series of compounds led to a new structures with the anti-arrhythmic properties which could be related to the presence and spatial distribution of the specific pharmacophore elements necessary to interact with biological structures. Contrary to the starting compound, which was phenytoin (class Ib), the obtained basic arylidene derivatives of imidazolidine-2,4-dione possess anti-arrhythmic properties of class Ia. Their activity depends on the position and electrophilic character of the substituent in the arylidene moiety: the privileged substituent position is *meta*; 3-Cl derivative (**2f**) has lower arrhythmia severity index than 3-Br derivative (**2c**). So, the obtained structures allowed to specify additional properties of the pharmacophore essential for anti-arrhythmic activity, however, this problem needs further investigations.

It is worth to emphasize that the examined compounds are devoid of anticonvulsant and neurotoxic properties.

7. Experimental

7.1. Chemistry

The m.p.s measured with Mel-Temp II melting point apparatus, are uncorrected. The IR spectra were recorded on Perkin–Elmer 297 spectrophotometer; ^{1}H NMR spectra were recorded on Bruker 300 or 500 MHz NMR instruments using tetramethylsilane (TMS) as internal standard (chemical shifts in δ, ppm); MS spectra were performed on Finningan MAT-CH7A (70 eV) apparatus. Thin layer chromatography was performed on silica gel plates Merck (GF_{254}) using following eluent: *n*-butanol/formic acid/water (7:2:2). Elemental analyses were performed in the Department of Pharmaceutical Chemistry, Medical College, Jagiellonian University on Elemental Vario-EL III apparatus for C, H, N and were within ±0.4% of theoretical values.

The synthesis of [(4*Z*)-4-arylidene-2,5-dioxoimidazolidin-1-yl]acetic acids (**1a**–**1g**) was described elsewhere (submitted for publication).

*7.2. General procedure for the synthesis of amides **2a**–**2g***

A mixture of an acid **1a**–**1g** (10 mmol), HEP (1.3 g, 10 mmol) and TEA (1.0 g, 10 mmol) in 30 ml dry DMF was stirred with BOP (4.4 g, 10 mmol) for 3 h at room temperature. The whole mixture was poured into water. The solid formed was filtered, washed with water and stirred with 10% $NaHCO_3$. The residue (compounds **2a**–**2g**) was recrystallized from ethanol.

*7.2.1. (5Z)-benzylidene-3-{2-[4-(hydroxyethyl)piperazin-1-yl]-2-oxoethyl}imidazolidine-2,4-dione (**2a**)*

Yield 72%, m.p. 234–236 °C, R_f –0.46; IR [cm^{-1}]: 3420 (OH), 3230 (NH), 1771, 1720, 1657 (CO), 1595 (Ar-CH=); ^{1}H NMR [DMSO-d_6] δ: 2.40-2.49 (m, 6H $(H_2C)_2NCH_2$), 3.32–3.52 (m, 6H, $CON(CH_2)_2$, CH_2OH), 4.40 (s, 3H, N_3CH_2, OH), 6.57 (s, 1H, Ar-CH=), 7.33–7.45 (m, 3H, Ph-3-H, Ph-4-H, Ph-5-H), 7.71 (d, J = 8.0 Hz, 2H, Ph-2-H, Ph-6-H), 10.85 (s, 1H, N_1H). MS [%]: 358 ([M$^+$], 2), 327(100), 298(20, 272(3), 201(8), 163(8), 164(2), 99(21), 56(11), 28(4). Anal. $C_{18}H_{22}N_4O_4$ (C, H, N).

*7.2.2. (5Z)-(2-bromo)benzylidene-3-{2-[4-(hydroxyethyl)-piperazin-1-yl]-2-oxoethyl} imidazolidine-2,4-dione (**2b**)*

Yield 52%, m.p. 215–217 °C, R_f –0.44; IR [cm^{-1}]: 3440 (OH, NH), 1764, 1720, 1648 (CO), 1610 (Ar-CH=); ^{1}H NMR [DMSO-d_6] δ: 2.04–2.14 (m, 6H $(H_2C)_2NCH_2$), 3.67–3.76 (m, 6H, $CON(CH_2)_2$, CH_2OH), 4.35 (s, 1H, OH), 4.50 (s, 2H, N_3CH_2), 6.44 (s, 1H, Ar-CH=), 7.24–7.33 (t, J = 15.0 Hz, 1H, Ph-4-H), 7.45 (t, J = 15.0 Hz, 1H, Ph-3-H), 7.46–7.74 (m, 2H, Ph-3-H, Ph-6-H), 11.10 (s, 1H, N_1H). Anal. $C_{18}H_{21}N_4O_4Br$ (C, H, N).

*7.2.3. (5Z)-(3-bromo)benzylidene-3-{2-[4-(hydroxyethyl)-piperazin-1-yl]-2-oxoethyl} imidazolidine-2,4-dione (**2c**)*

Yield 68%, m.p. 234–236 °C, R_f –0.52; IR [cm^{-1}]: 3440 (OH), 3300 (NH), 1758, 1710, 1652 (CO), 1602 (Ar-CH=); ^{1}H NMR [DMSO-d_6] δ: 2.39-2.49 (m, 6H $(H_2C)_2NCH_2$), 3.37–3.52 (m, 6H, $CON(CH_2)_2$, CH_2OH), 4.40 (s, 2H, N_3CH_2), 4.38 (t, J = 9.0 Hz, 1H, OH), 6.58 (s, 1H, Ar-CH=), 7.36 (t, J = 8.0 Hz, 1H, Ph-5-H), 7.53 (d, J = 7.7 Hz, 1H, Ph-4-H), 7.64 (d, J = 7.7 Hz, 1H, Ph-6-H), 7.95 (s, 1H, Ph-2-H), 11.10 (s, 1H, N_1H). Anal. $C_{18}H_{21}N_4O_4Br$ (C, H, N).

*7.2.4. (5Z)-(4-bromo)benzylidene-3-{2-[4-(hydroxyethyl)piperazin-1-yl]-2-oxoethyl} imidazolidine-2,4-dione (**2d**)*

Yield 70%, m.p. 250–252 °C, R_f –0.47; IR [cm^{-1}]: 3429 (OH, NH), 1771, 1712, 1660 (CO), 1587 (Ar-CH=); ^{1}H NMR [DMSO-d_6] δ: 2.40–2.53 (m, 6H $(H_2C)_2NCH_2$), 3.37–3.52 (m, 6H, $CON(CH_2)_2$, CH_2OH), 4.43 (s, 2H, N_3CH_2), 4.50 (t, J = 8.0 Hz, 1H, OH), 6.57 (s, 1H, Ar-CH=), 7.63 (s, 4H, H-arom.), 10.98 (s, 1H, N_1H). Anal. $C_{18}H_{21}N_4O_4Br{\cdot}0.5H_2O$ C, H, N).

*7.2.5. (5Z)-(2-chloro)benzylidene-3-{2-[4-(hydroxyethyl)piperazin-1-yl]-2-oxoethyl} imidazolidine-2,4-dione (**2e**)*

Yield 52%, m.p. 198–200 °C, R_f –0.43; IR [cm^{-1}]: 3400 (OH, NH), 1768, 1720, 1650 (CO), 1600 (Ar-CH=); ^{1}H NMR [DMSO-d_6] δ: 2.40–2.53 (m, 6H $(H_2C)_2NCH_2$), 3.37–3.52 (m, 6H, $CON(CH_2)_2$, CH_2OH), 4.43 (s, 2H, N_3CH_2), 4.40 (t, J = 9.0 Hz, 1H, OH), 6.57 (s, 1H, Ar-CH=), 7.63 (s, 4H, H-arom.), 10.98 (s, 1H, N_1H). Anal. $C_{18}H_{21}N_4O_4Cl$ (C, H, N).

*7.2.6. (5Z)-(3-chloro)benzylidene-3-{2-[4-(hydroxyethyl)-piperazin-1-yl]-2-oxoethyl} imidazolidine-2,4-dione (**2f**)*

Yield 65%, m.p. 214–216 °C, R_f –0.47; IR [cm^{-1}]: 3421 (OH, NH), 1765, 1717, 1658 (CO), 1592 (Ar-CH=); ^{1}H NMR [DMSO-d_6] δ: 2.40–2.53 (m, 6H $(H_2C)_2NCH_2$), 3.37–3.52 (m, 6H, $CON(CH_2)_2$, CH_2OH), 4.43 (s, 2H, N_3CH_2), 4.40 (t,

J = 9.0 Hz, 1H, OH), 6.57 (s, 1H, Ar-CH=), 7.63 (s,4H, H-arom.), 10.98 (s, 1H, N_1H). Anal. $C_{18}H_{21}N_4O_4Cl$ (C, H, N).

*7.2.7. (5Z)-(4-chloro)benzylidene-3-{2-[4-(hydroxyethyl)-piperazin-1-yl]-2-oxoethyl} imidazolidine-2,4-dione (**2g**)*

Yield 78%, m.p. 242–244 °C, R_f –0.49; IR [cm^{-1}]: 3420 (OH, NH), 1771, 1721, 1660 (CO), 1590 (Ar-CH=); ^{1}H NMR [DMSO-d_6] δ: 2.41–2.53 (m, 6H ($H_2C)_2NCH_2$), 3.39–3.53 (m, 6H, CON($CH_2)_2$, CH_2OH), 4.43 (s, 2H, N_3CH_2), 4.50 (s, 1H, OH), 6.59 (s, 1H, Ar-CH=), 7.50 (d, J = 8.0 Hz, 2H, Ph-3-H, Ph-5-H), 7.71 (d, J = 8.0 Hz, 2H, Ph-2-H, Ph-6-H), 10.98 (s, 1H, N_1H). MS [%]: 392 ([M^+], (3), 375(4), 361(100), 331(30), 305(3), 256(2), 235(7), 205(50), 180(9), 150(4), 109(8). Anal. $C_{18}H_{21}N_4O_4Cl{\cdot}0.5H_2O$ (C, H, N).

7.3. Pharmacological tests

7.3.1. Materials and methods

7.3.1.1. Compounds. DPH sodium salt (Epanutin, Parke-Davis), lidocaine (Lignocainum hydrochloricum, Polfa), quinidine sulfate (Polfa), sodium heparin (Heparinum, Polfa), thiopental sodium (Thiopental, Biochemie GmbH).

7.3.1.2. Animals. The experiments were carried out on male Wistar rats (180–250 g). Animals were in cages in room at 20 ± 2 °C with natural light–dark cycles. The animals had free access to standard pellet diet and water, and were used after a minimum of 3 days acclimation to the housing conditions. Control and experimental groups consisted of 8–10 animals each.

7.3.1.3. Reference compound. DPH sodium salt (DPH-Na, i.e. Epanutin), lidocaine and quinidine were used as a reference compounds.

7.3.1.4. Statistical analysis. The data are expressed as mean ± S.E.M. The results were statistically analyzed by the one-way ANOVA or Student's t-test. Differences were considered significant when $P < 0.05$.

7.3.2. Non-working heart perfusion

Hearts from thiopental-anaesthetized (45–60 mg kg^{-1}, i.p.) rats were perfused according to the Langendorff technique [25] at constant pressure of 70 cmH_2O (6.87 kPa) with Chenoweth–Koelle solution continuously gassed with 95% O_2 plus 5% CO_2 of the following composition (mmol l^{-1}): NaCl (120.0), KCl (5.6), $MgCl_2$ (2.2), $NaHCO_3$ (19.0), $CaCl_2$ (2.4), and glucose (10.0).

The effect of tested compounds, in concentration of 10^{-8}–10^{-4} M, on coronary flow (cardiac effluent), ECG (obtained by two stainless steel electrodes, one inserted into the muscle of the ventricular wall and another attached to the metal aortic cannula) were assessed after 15–20 min of initial stabilization.

7.3.3. Ventricular arrhythmias associated with coronary artery occlusion and reperfusion in the Krebs non-working isolated perfused rat heart [26]

Non-working isolated hearts were mounted as described above for recording coronary flow and ECG. After a 15 min stabilization period, acute regional myocardial ischemia was produced for 15 min by installing a clip on the left coronary artery close to its origin (ischaemic period). The clip was then reopened, and changes during reperfusion were monitored for 30 min (reperfusion period). Occlusion and reperfusion was verified by measuring coronary flow before occlusion, after occlusion and after reperfusion.

Ligation of the coronary artery resulted in 25–35% reduction in coronary flow. Reperfusion was followed by a return of the coronary flow. Reperfusion-induced arrhythmias, manifested by VBs, VT and VF.

ECGs were analyzed according to the guidelines of the Lambeth Conventions [27] for VBs, bigeminy, salvos (less than four successive VBs), VT (four or more successive VBs) and VF.

In order to obtain a measure for the intensity of the arrhythmias, an arrhythmia severity index was calculated for each heart according to Bernauer and Ernenputsch [21]: the occurrence of up to 10 ventricular extrasystoles during the first 30 min of reperfusion was attributed the value 1, more than 10 the value 2, VT or ventricular flutter the value 3, and VF the value 4. Bigeminy and salvos were not quantified separately but included with VBs.

Agents were added to the perfusion medium 15 min before coronary artery ligation and the concentration was maintained for the rest of the perfusion period.

7.3.4. Anticonvulsant assays

Antiepileptic activity and neurological toxicity assays were carried out by the Antiepileptic Drug Development Program, Epilepsy Branch, National Institute of Neurological and Communicative Disorders and Stroke, National Institute of Health in Bethesda, USA. Compounds were injected intraperitoneally into mice as suspensions in 0.5% methylcellulose at three dosage levels (30, 100 and 300 mg kg^{-1}). Phase I of the evaluation was a qualitative assay which used small groups of animals (1–8) and included three tests: maximal electroshock seizure (MES), subcutaneous pentylenetetrazol (ScMet), and rotorod test for neurological toxicity (Tox) with anticonvulsant activity and neurotoxicity noted 30 min and 4 h after administration. The details of these procedures have been published [28,29].

7.4. X-ray crystallography

The crystals of **2a** and **2c** were recrystallized from ethanol solution at room temperature, while those of **2d** and **2g** were obtained from the mixture of ethanol and izopropanol in 1:1 ratio.

Crystal data for **2a**: $C_{18}H_{22}N_4O_4$, MW = 358.40, triclinic, $P\bar{1}$, a = 7.177(2), b = 10.144(3), c = 12.471(3) Å, α

= 103.60(3), β = 93.07(2), γ = 91.79(2), V = 880.31(4) Å^3, Z = 2, D = 1.352 mg m^{-3}, λ(CuKα) = 1.54178 Å, μ = 0.80 mm^{-1}, F(000) = 380, T = 295 K; for **2c**: $C_{18}H_{21}N_4O_4Br{\cdot}H_2O$, MW = 455.31, triclinic, P$\bar{1}$, a = 8.7410(1), b = 10.5510(2), c = 10.7900(2) Å, α = 81.7950(9), β = 82.0720(9), γ = 88.3300(13), V = 975.48(3) Å^3, Z = 2, D = 1.550 mg m^{-3}, λ(MoKα) = 0.71073 Å, μ = 2.15 mm^{-1}, F(000) = 468, T = 293 K; for **2d**: $C_{18}H_{21}N_4O_4Br{\cdot}0.5H_2O$, MW = 446.31, triclinic, P$\bar{1}$, a = 10.6371(6), b = 13.6917(9), c = 13.6939(8) Å, α = 79.230(10), β = 86.390(10), γ = 87.040(10), V = 1953.7(2) Å^3, Z = 4, D = 1.517 mg m^{-3}, λ(CuKα) = 1.54178 Å, μ = 3.172 mm^{-1}, F(000) = 916, T = 295 K; for **2g**: $C_{18}H_{21}N_4O_4Cl{\cdot}0.5H_2O$, MW = 401.85, triclinic, P$\bar{1}$, a = 10.5930(8), b = 13.5175(10), c = 13.6729(11) Å, α = 79.660(10), β = 88.290(10), γ = 87.290(10), V = 1923.3(3) Å^3, Z = 4, D = 1.388 mg m^{-3}, λ(CuKα) = 1.54178 Å, μ = 2.066 mm^{-1}, F(000) = 844, T = 295 K.

Intensities were collected at room temperature using diffractometers KM-4 (**2a**, **2d**, **2g**) and Nonius KappaCCD (**2c**). The structures were solved by direct methods. All non-hydrogen atoms were located in the initial E-map, some of the H atoms were found in successive difference Fourier maps and for some H atoms the positions were calculated from geometrical constrains. All non-hydrogen atoms were refined, against F^2, by full-matrix least-squares with anisotropic displacement parameters while H atoms were refined in isotropic approximation. The final residuals were for **2a** [2988 reflections with $I > 2\sigma(I)$]: R1 = 0.0597, wR2 = 0.1606, goodness-of-fit parameter S = 1.054; for **2c** [4632 reflections with $I > 2\sigma(I)$]: R1 = 0.0527, wR2 = 0.1438, goodness-of-fit parameter S = 1.021; for **2d** [7161 reflections with $I > 2\sigma(I)$]: R1 = 0.0566, wR2 = 0.1541, goodness-of-fit parameter S = 1.031; for **2g** [7044 reflections with $I > 2\sigma(I)$]: R1 = 0.0542, wR2 = 0.1514, goodness-of-fit parameter S = 1.056. The program to solve and refine the structures were SHELXS and SHELXL included in the SHELX97 programs package [30]; the program used to generate graphics was ORTEP3 [31].

The finale fractional atomic coordinates with their thermal displacement parameters for all crystal structures together with the other numerical data are deposited as supplementary material.

7.5. Supplementary material

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publications number: **2a** CCDC 233893, **2c** CCDC 233894, **2d** CCDC 233895, **2g** 233896. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336-033, deposit@ccdc.cam.ac.uk).

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