SYNTHESIS AND LOCAL ANESTHETIC ACTIVITY OF 1,2-DISUBSTITUTED IMIDAZO[1,2-a]BENZIMIDAZOLES

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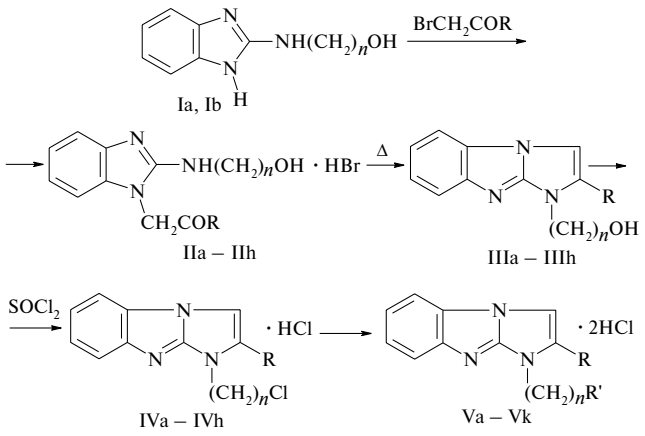
As is known [1], imidazo[1,2-a]benzimidazole derivatives exhibit analgesic [2], antiinflammatory [3], hypotensive [3, 4], antiarrhythmogenic [5], antiaggregant and hypoglycemic [6], and other types of biological activity. However, these data mostly refer to 2,9-disubstituted imidazo-[1,2-a]benzimidazoles, while the 1,2-disubstituted imidazo-[1,2-a]benzimidazoles (in particular, those containing dialkylaminoalkyl pharmacophores) have been studied to a much smaller extent. It was demonstrated that such compounds are capable of producing a local anesthetic effect [7].

In continuation of the previous investigations of compounds in the series of 1H-imidazo[1,2-a]benzimidazole, we used a scheme proposed previously [8] to synthesize a series of new dihydrochlorides of 2-substituted 1-dialkylaminoalkylimidazo[1,2-a]benzimidazoles (Va – Vk) and studied their local anesthetic properties.

In the first stage of synthesis, reactions of amino alcohols I with the corresponding bromomethyl ketones in 2-propanol yielded acylmethyl derivatives II. It was found that the thermal cyclization of compounds II to 1-hydroxyalkyl-substituted compounds III can be most readily conducted in monoethanolamine. With this solvent, all reactions proceed smoothly irrespective of the structure of radical R. The subsequent substitution of chlorine for the OH group and the replacement of chlorine by amino group leads to 1-dialkylaminoalkyl derivatives, which converted into water-soluble dihydrochlorides under the action of HCl (Table 1).

The proposed structures of the synthesized compounds were confirmed by the results of spectroscopic measurements. The IR spectra of alcohols III display no characteristic absorption bands related to the stretching vibrations of C=O (1700 – 1710 cm^{-1}) and C=N (1670 – 1687 cm^{-1}) groups, which were present in the spectra of compounds II. Instead, absorption bands at 1490 – 1505, 1590 – 1605, 1600 – 1610 (C=C), and 1625 – 1635 cm^{-1} (C=N) characteristic of the imidazo[1,2-a]benzimidazole ring appear. The same bands are present in the IR spectra of compounds V. The optical absorption related to the OH and NH groups in compounds II is manifested by two overlapping bands in the range from 3050 to 3300 cm^{-1}; a broad band due to the OH group in alcohols III appears in approximately the same range (3100 – 3200 cm^{-1}). Parameters of the corresponding ^{1}H NMR spectra are listed in Table 2.



II – IV: n = 2 (a – d), 3 (e – h); R = $C(CH_3)_3$ (a, e), C_6H_5 (b, f); C_6H_4-Cl-4 (c, h), α-$C_{10}H_7$ (d), C_6H_4Br-4 (g);
V: n = 2 (a – e), 3 (f – k); R = $C(CH_3)_3$ (a, f, g), C_6H_5 (b, c, h, i); C_6H_4-Cl-4 (d, j), α-$C_{10}H_7$ (e), C_6H_4Br-4 (k); R′ = $NHC(CH_3)_3$ (a), $NHCH(CH_3)_2$ (b), $N(C_2H_5)_2$ (c, f, h, j, k), $N(CH_2CH_2)_2O$ (d), $N(CH_2)_5$ (e), $NHCH(CH_2)_5$ (g), $N(CH_2)_4$ (i).

EXPERIMENTAL CHEMICAL PART

The ^{1}H NMR spectra were recorded on a Varian XL-300 spectrometer at a working frequency of 300 MHz. The IR absorption spectra were measured on a Specord 75-IR spectrophotometer (Germany) using samples prepared as nujol mulls. The course of reactions was monitored and the

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purity of reaction products was checked by TLC on Al_2O_3 plates eluted in chloroform and developed by exposure to iodine vapor in a wet chamber. The synthesis of compounds II – III, IVb, IVd, IVf, and Ve was described previously [8]. The yields and physicochemical characteristics of the synthesized amines V and intermediate products II – IV (except for those indicated above) are presented in Table 1. The data of elemental analyses (C, H, N, Hal) agree with the results of analytical calculations.

1-Acylmethyl-2-hydroxyalkylaminobenzimidazole hydrobromides (IIa – IIh). A mixture of equimolar amounts of 2-hydroxyalkylaminobenzimidazole (I) and the corresponding bromomethyl ketone in 2-propanol was boiled for 3.5 – 5 h and cooled. Then the precipitate of salt II was separated by filtration and thoroughly washed with ethanol and acetone.

1-Hydroxyalkyl-2-R-imidazo[1,2-a]benzimidazoles (IIIa – IIIh). A mixture of 10 mmole of hydrobromide IIc with 4 – 8 ml of monoethanolamine was heated on a bath at 155 – 165°C for 4 – 6 h and cooled. Then the reaction mass was thoroughly triturated with 25 – 35 ml of cold water until all oily clots disappeared. The precipitate was separated by filtration, washed with water, dried, and recrystallized.

1-(ω-Chloroalkyl)-2-R-imidazo[1,2-a]benzimidazole hydrochlorides (IVa – IVh). 1-Hydroxyalkyl derivatives III were chlorinated with thionyl chloride as described in [8] with TLC monitoring: for alcohol III, $R_f \sim 0.1$; for chlorine-substituted compound IV, $R_f = 0.7 – 0.8$.

1-Alkylaminoalkyl-2-R-imidazo[1,2-a]benzimidazole dihydrochlorides (Va – Vk).

Method A. Reactions with high-boiling amines. A mixture of 5 mmole of hydrochloride IV and 20 – 30 mmole of the corresponding amine (morpholine, piperidine, pyrrolidine, cyclohexylamine) was boiled for 4 – 6 h, cooled, diluted with 40 – 50 ml of water, and extracted with chloroform or benzene. The extract was washed with water to remove excess amine, dried over anhydrous Na_2SO_4, and passed through an Al_2O_3 layer (h = 3 cm, d = 3.5 cm) by elution with the same solvents. Then the solvent was evaporated and the residue of base V in the form of yellowish crystals or oil was dried in a vacuum desiccator over KOH. The target dihydrochlorides were obtained by treating the base in anhy-

TABLE 1. Yields and Physicochemical Characteristics of 1-(Dialkylaminoalkyl)imidazo[1,2-a]benzimidazoles V and Some Intermediate Products of Their Synthesis

Compound**	Yield, %	M.p.(decomp.), °C	Solvent for crystallization	Empirical formula
IIa	90.7	212 – 213	ethanol	$C_{15}H_{21}N_3O_2 \cdot HBr$
IIc	90.2	258 – 259	60 % ethanol	$C_{17}H_{16}ClN_3O_2 \cdot HBr$
IIe	89.7	220 – 221	2-propanol	$C_{16}H_{23}N_3O_2 \cdot HBr$
IIg	92.0	214 – 215	ethanol	$C_{18}H_{18}BrN_3O_2 \cdot HBr$
IIh	92.4	200 – 201	ethanol	$C_{18}H_{18}ClN_3O_2 \cdot HBr$
IIIa	93.7	157 – 158*	ethyl acetate	$C_{15}H_{19}N_3O$
IIIc	97.6	194*	acetonitrile	$C_{17}H_{14}ClN_3O$
IIIe	83.7	128 – 129*	acetonitrile	$C_{16}H_{21}N_3O$
IIIg	95.4	199 – 200*	ethanol	$C_{18}H_6BrN_3O$
IIIh	93.5	187 – 188*	ethanol	$C_{18}H_{16}ClN_3O$
IVa	100	200 – 201	acetone – ether	$C_{15}H_{18}ClN_3 \cdot HCl$
IVc	89.4	213 – 214	acetonitrile	$C_{17}H_{13}Cl_2N_3 \cdot HCl$
IVe	98.0	191 – 192	acetonitrile	$C_{16}H_{20}ClN_3 \cdot HCl \cdot H_2O$
IVg	93.7	210	ethanol	$C_{18}H_{15}BrClN_3 \cdot HCl$
IVh	90.4	207 – 208	ethanol	$C_{18}H_{15}Cl_2N_3 \cdot HCl$
Va	82.0	265 – 266	acetonitrile	$C_{19}H_{28}N_4 \cdot 2HCl$
Vb	79.0	250 – 251	acetonitrile	$C_{20}H_{22}N_4 \cdot 2HCl$
Vc	83.5	225 – 226	acetonitrile	$C_{21}H_{24}N_4 \cdot 2HBr$
Vd	87.8	177	ethanol	$C_{21}H_{21}ClN_4O \cdot 2HCl$
Vf	85.2	220 – 221	ethanol	$C_{20}H_{30}N_4 \cdot 2HCl \cdot 2H_2O$
Vg	75.0	245 – 246	acetonitrile	$C_{22}H_{32}N_4 \cdot 2HCl$
Vh	81.0	241 – 242	2-propanol	$C_{22}H_{26}N_4 \cdot 2HCl$
Vi	87.0	256 – 257	nitromethane	$C_{22}H_{24}N_4 \cdot 2HCl$
Vj	88.5	219 – 220	ethanol	$C_{22}H_{25}BrN_4 \cdot 2HCl$
Vk	82.7	228 – 229	ethanol	$C_{22}H_{25}ClN_4 \cdot 2HCl \cdot H_2O$

* Melts without decomposition.
** The characteristics of compounds IIb, IId, IIf, IIIb, IIId, IIIf, and Ve are given in [8].

TABLE 2. Parameters of the ^{1}H NMR Spectra of the Synthesized Compounds

Compound	Solvent	Proton chemical shift δ, ppm
IIa*	$CDCl_3$	0.87 (1H, bs, OH), 1.16 (9H, s, $C(CH_3)_3$), 1.2 (1H, s, NH), 3.48 (2H, t, CH_2), 3.74 (2H, t, CH_2), 4.6 (2H, s, CH_2CO), 6.66 – 6.75 (1H, m), 6.93 – 7.02 (2H, m), 7.2 – 7.38 (1H, m, H_{arom})
IIc	DMCO-d_6	3.55 (2H, t, CH_2), 3.68 (2H, t, CH_2), 6.07 (2H, s, CH_2CO), 7.10 – 8.10 (8H, m, H_{arom}), 9.10 (1H, t, NH)
IIe*	$CDCl_3$	1.33 (9H, s, $C(CH_3)_3$), 1.80 (2H, q, CH_2), 3.0 – 3.6 (2H, bs, NH, OH), 3.70 (4H, k, NCH_2, CH_2O), 4.80 (2H, s, CH_2O), 6.90 (1H, d), 7.0 – 7.14 (2H, dt), 7.43 (1H, d, H_{arom})
IIh	DMCO-d_6	1.85 (2H, q, CH_2), 3.6 (4H, k, NCH_2, CH_2O), 6.15 (2H, s, CH_2CO), 7.1 – 8.2 (8H, m, H_{arom}), 9.12 (1H, t, NH)
IIIa	$CDCl_3$	1.36 (9H, s, $C(CH_3)_3$), 4.10 (2H, t, CH_2), 4.25 (2H, t, CH_2), 6.23 (1H, bs, OH), 6.82 (1H, s, 3-H), 6.96 – 7.56 (4H, m, H_{arom})
IIIc	$CDCl_3$	4.08 (4H, s, $2CH_2$), 5.2 – 6.4 (1H, bs, OH), 7.08 – 7.64 (9H, m, H_{arom})
IIIe	$CDCl_3$	1.43 (9H, s, $C(CH_3)_3$), 2.04 (2H, q, CH_2), 3.57 (2H, t, CH_2O), 4.42 (2H, t, NCH_2), 6.27 (1H, bs, OH), 6.96 (1H, s, 3-H), 7.06 – 7.28 (2H, m, 6,7-H), 7.48 – 7.64 (2H, dd, 5,8-H)
IIIh	$CDCl_3$	1.94 (2H, q, CH_2), 3.60 (2H, t, CH_2), 4.26 (2H, t, CH_2), 7.1 – 7.75 (9H, m, H_{arom})
IVd*	$CDCl_3$	1.33 (9H, s, $C(CH_3)_3$), 2.47 (2H, q, CH_2), 3.68 (2H, t, CH_2), 4.23 (2H, t, CH_2), 6.75 (1H, s, 3-H), 6.9 – 7.5 (4H, m, H_{arom})
IVh	DMCO-d_6 – CCl_4	2.1 (2H, q, CH_2), 3.63 (2H, t, CH_2), 4.50 (2H, t, CH_2), 7.37 – 8.26 (9H, m, H_{arom}), 14.9 – 16.0 (1H, bs, $=N^+H–$)
Va	DMCO-d_6	1.33 (9H, s, $C(CH_3)_3$), 1.46 (9H, s, $C(CH_3)_3$), 3.6 (2H, t, CH_2), 4.8 (2H, t, CH_2), 7.4 – 8.05 (5H, m, H_{arom}), 9.7 (2H, bs, 2 $N^+H–$)
Vb	DMCO-d_6 – CCl_4	1.35 (6H, d, $2CH_3$), 3.25 (2H, m, CH_2), 3.35 (1H, m, CH), 4.78 (2H, t, CH_2), 7.40 – 7.52 (2H, dt), 7.60 – 7.68 (5H, m), 7.71 – 7.75 (1H, d), 8.02 – 8.08 (1H, d, H_{arom}), 8.35 (1H, s, 3-H), 7.09 (2H, bs, NH, $=N^+H–$)
Vc	DMCO-d_6 – CCl_4	1.17 (6H, t, $2CH_3$), 3.14 (4H, k, $2CH_2$), 3.40 (2H, t, CH_2), 4.90 (2H, t, N – CH_2), 7.35 – 8.35 (10H, m, H_{arom}), 10.00 – 12.50 (1H, broad signal, $=N^+H–$)
Ve	DMCO-d_6 – CCl_4	3.15 (4H, t, $O(CH_2)_2$), 3.55 (2H, t, NCH_2), 3.84 (4H, t, $N(CH_2)_2$), 4.68 (2H, t, NCH_2), 7.37 – 7.66 (7H, m, H_{arom}), 8.0 (1H, d, 5-H), 8.38 (1H, s, 3-H)
Ve	DMCO-d_6 – CCl_4	1.25 (6H, t, $2CH_3$), 1.46 (9H, s, $C(CH_3)_3$), 2.30 (2H, q, CH_2), 3.10 (6H, m, $CH_2N(CH_2)_2$), 4.45 (2H, t, NCH_2), 7.40 – 8.00 (5H, m, H_{arom}), 10.40 (2H, bs, 2 N^+H)
Vg	DMCO-d_6 – CCl_4	1.21 – 1.70 (6H, m, $(CH_2)_3$), 1.43 (9H, s, $C(CH_3)_3$), 1.80 (2H, m, CH_2), 2.0 (2H, m, CH_2), 2.25 (2H, m, CH_2), 2.92 (1H, m, CH), 3.2 (2H, m, CH_2), 4.6 (2H, t, CH_2), 7.4 – 8.0 (5H, m, H_{arom}), 9.1 (2H, bs, 2 N^+H)
Vh	DMCO-d_6 – CCl_4	1.23 (6H, m, $2CH_3$), 2.27 (2H, q, CH_2), 3.13 (6H, m, $CH_2N(CH_2)_2$), 4.40 (2H, t, NCH_2), 7.40 – 8.35 (10H, m, H_{arom}), 11.15 (1H, bs, $=N^+H–$), 13.50 – 17.00 (1H, bs, $=N^+H–$)
Vi	DMCO-d_6 – CCl_4	1.98 (4H, m, $(CH_2)_2$), 2.30 (2H, m, CH_2), 3.22 (6H, m, $N(CH_2)_3$), 4.38 (2H, t, NCH_2), 7.40 – 8.08 (9H, m, H_{arom}), 8.34 (1H, s, 3-H), 11.50 (2H, bs, 2 N^+H)
Vj	DMCO-d_6 – CCl_4	1.12 (6H, t, $2CH_3$), 2.19 (2H, q, CH_2), 3.08 (6H, m, $CH_2N(CH_2)_2$), 4.30 (2H, t, NCH_2), 7.40 – 7.80 (7H, m, H_{arom}), 8.05 (1H, d, 5-H), 8.40 (1H, s, 3-H), 9.50 – 10.5 (2H, bs, 2 N^+H)
Vk	DMCO-d_6 – CCl_4	1.11 (6H, t, $2CH_3$), 2.19 (2H, q, CH_2), 3.0 (6H, m, $CH_2N(CH_2)_2$), 4.15 (2H, t, NCH_2), 7.08 – 7.70 (7H, m, H_{arom}), 7.80 (1H, d, 5-H), 8.02 (1H, s, 3-H), 10.20 (1H, bs, $=N^+H$)

* Compound studied in the base form.

TABLE 3. Local Anesthetic Activity (Renier Index) of Compounds Va, Vc, Vh, Vi, and Vk Tested on Rabbit Cornea

Compound	Solution concentration, %				
	0.0625	0.125	0.25	0.5	1
Va	–	120.5 ± 18.6	368.7 ± 34.8	534.0 ± 35.0	689.8 ± 44.3
Vc	–	–	236.2 ± 56.6	367.5 ± 67.2	565.2 ± 70.7
Vh	539.0 ± 29.3	630.0 ± 30.9	749.3 ± 19.2	1139.8 ± 28.7	1280.5 ± 13.9
Vi	742.5 ± 17.6	852.3 ± 17.7	1250.0 ± 44.3	1300.0 ± 0.0	
Vk	–	–	–	205.0 ± 25.6	452.0 ± 51.4
Dicaine	174.4 ± 22.9	346.4 ± 19.5	821.0 ± 40.5	1038.0 ± 47.9	1149.5 ± 27.3 (+)

Notes: (+) hyperemia of the palpebral conjunctiva.

drous acetone with HCl solution in ether or 2-propanol. After recrystallization, the product was dried to constant weight at 105 – 110°C.

Method B. Reactions with low-boiling amines. A mixture of 5 mmole of hydrochloride IV and 30 mmole of the corresponding amine (diethylamine, isopropylamine, *tert*-butylamine) in a sealed ampule was heated on a bath at 145 – 150°C for 5 – 6 h, cooled, poured into 50 ml of water, and then treated as described for method A above.

EXPERIMENTAL PHARMACOLOGICAL PART

The surface anesthetic activity (Table 3) was studied on rabbit cornea by the Renier – Valet method [9], the infiltration anesthetic action was determined on guinea pig skin [10], the conduction anesthetic activity was determined on the sciatic nerve of rabbit [9], and the local irritant effect was estimated by the test on rabbit eye [11]. The reference drugs were lidocaine, marcaine, and dicaine.

The synthesized compounds were also characterized with respect to the acute toxicity (LD_{50}), which was determined by subcutaneous injections in mice followed by observation for 48 h (Table 4).

The local anesthetic properties of the synthesized compounds were studied in a broad range of concentrations, which allowed each substance to be characterized by the average effective concentration (EC_{50}) [12, 13]. The comparative analysis of the properties of compounds V with respect to the surface and infiltration anesthetic activity was based on the ratio of EC_{50} values for the reference drugs and the samples studied. The therapeutic breadth was characterized by the LD_{50}/EC_{50} ratio [14].

RESULTS AND DISCUSSION

It was found that a surface anesthetic effect is produced by compounds Va, Vc, and Vh – Vk (Table 3), the most active of which (Vh and Vi, in a concentration of 0.0626 and 0.125%, respectively) exceed dicaine in this respect. Note that 100% anesthesia (Renier index, 1300.0) was produced only by compound Vi at a concentration of 0.5%. For comparison, the EC_{50} of compounds Vh, Vi, and dicaine are 2.6, 1.2, and 6.3 mM.

TABLE 4. Infiltration Anesthetic Activity of Compounds Va – Vc and Vf – Vk Studied on Guinea Pig Skin

Compound	Local anesthesia	Toxicity in mice (0.5% solution, s.c.)		LD_{50}/EC_{50}
	EC_{50}, mmole/liter	LD_{50}, mg/kg	LD_{50}, mmole/kg	
Va	0.67	106.2 (97.6 – 114.8)	0.28	4084.6
Vb	0.97	72.0 (64.4 – 80.0)	0.18	1894.7
Vc	0.55	84.8 (81.9 – 87.9)	0.17	3140.7
Vf	1.03	232.6 (222.4 – 243.4)	0.58	5673.2
Vg	0.66	78.3 (75.4 – 81.3)	0.18	2796.4
Vh	0.81	41.8 (37.5 – 46.1)	0.10	1229.4
Vi	0.31	46.0 (42.4 – 49.0)	0.11	3538.5
Vj	2.57	108.4 (99.1 – 117.7)	0.22	846.9
Vk	2.56	94.8 (83.5 – 106.1)	0.21	817.2
Lidocaine	3.81	283.0 (271.5 – 295.1)	1.05	2747.6
Marcaine	1.09	62.0 (54.7 – 70.2)	0.20	1823.5

The anesthesia onset time upon the instillation of 0.5% solutions into the conjunctival sac of rabbit was 1.5 – 2 min for compounds Va, Vc, and Vh – Vk, against 0.5 – 1 min for dicaine. The duration of the anesthetic effect for compounds Vh and Vi was 50 – 60 and 60 – 70 min, respectively (against 45 – 55 min for dicaine).

Compounds Vh and Vi produced no irritant effect on tissues of the anterior part of the eye in the entire concentration range studied, while a 1% solution of dicaine induced hyperemia of the palpebral conjunctiva.

Under the infiltration anesthesia conditions, compounds Va – Vc and Vf – Vk produced a significant analgesic action (Table 4). The most active compound was Vi, the effect of

TABLE 5. Conduction Anesthetic Activity of Compounds Va – Vc and Vf – Vj (0.5% Solution) Studied on Sciatic Nerve of Rabbit

Compound	Anesthesia onset time, min	Anesthesia depth[1], %	Complete anesthesia duration, min	Total action time, min
Va	9.4 ± 0.8 (7.0 – 11.8)	100.0	297.0 ± 5.4 (282.1 – 311.9)	362.0 ± 11.8° (329.2 – 394.8)
Vb	12.8 ± 0.9 (10.4 – 15.2)	100.0	264.0 ± 12.9 (228.2 – 299.8)	330.0 ± 12.4° (295.4 – 364.6)
Vc	10.5 ± 0.9 (8.1 ± 12.9)	100.0	326.0 ± 5.2* (303.6 – 351.4)	418.0 ± 12.3*° (383.3 – 452.7)
Vf	10.8 ± 0.8 (8.7 – 13.0)	100.0	38.8 ± 1.7* (34.0 – 42.6)	160.0 ± 2.6*° (153.4 – 166.6)
Vg	9.2 ± 0.4 (7.4 – 11.0)	100.0	312.0 ± 9.6 (285.0 – 339.0)	425.0 ± 12.6*° (389.5 – 460.5)
Vh	12.0 ± 1.2 (8.6 – 15.4)	100.0	311.0 ± 1.9* (305.0 – 316.0)	489.0 ± 1.9*° (483.3 – 494.4)
Vi	6.2 ± 0.4*° (5.0 – 7.4)	100.0	355.0 ± 5.4* (330.0 – 380.0)	438.0 ± 9.4*° (382.0 – 482.0)
Vj	9.2 ± 0.8 (7.0 – 11.3)	100.0	45.0 ± 2.2* (39.3 – 50.7)	139.2 ± 2.4* (133.0 – 145.8)
Lidocaine	15.0 ± 1.6 (10.6 – 19.4)	68.0 ± 4.9 (54.4 – 81.6)	–	141.0 ± 4.3 (129.0 – 153.0)
Marcaine	11.0 ± 0.6 (9.2 – 12.8)	100.0	285.0 ± 4.3 (265.0 – 305.0)	346.0 ± 7.5 (311.0 – 381.0)

Note: reliable differences from * marcaine and ° lidocaine; [1] estimated 30 min after application to nerve.

which significantly exceeded those of both marcaine and lidocaine. In addition, compounds Va, Vf, and Vi were superior to lidocaine and marcaine with respect to the therapeutic breadth.

In the test for conduction anesthesia, an analgesic effect was observed for compounds Va – Vc, and Vf – Vk (Table 5), which were comparable to marcaine and lidocaine in the anesthesia onset time. The only exception was for compound Vi, which acted even faster. As for the depth of anesthesia, all compounds possessing this property were comparable in this respect to marcaine and superior to lidocaine.

Thus, we have found highly active local anesthetics in the series of 1,2-disubstituted imidazo[1,2-a]benzimidazoles, which can be of interest for further detailed preclinical investigation.

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