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Antiarrhythmic activity of 4,6-di(het)aryl-5-nitro-3,4-dihydropyrimidin-(1*H*)-2-ones and its effects on arterial pressure in rats

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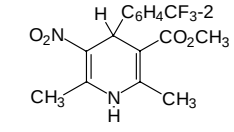
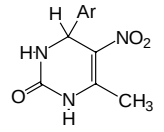
Abstract—The antiarrhythmic activity of 4,6-di(het)aryl-5-nitro-3,4-dihydropyrimidin-(1*H*)-2-ones toward two types of experimental rat arrhythmia has been studied. With $CaCl_2$ induced arrhythmia model, several agents have demonstrated high antiarrhythmic activity and the lack of influence on arterial pressure of rats.

The dialkyl 4-aryl-1,4-dihydropyridine-3,5-dicarboxylates (**I**) are calcium channel antagonists of dihydropyridine type (DHP) used worldwide as the therapeutics for the treatment of cardiovascular diseases such as hypertension, cardiac arrhythmias, and angina pectoris.[1–3] The esters of 4-aryl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acids (**II**) (DHPM), structurally related to the DPH compounds, have been known for a long time. However, these compounds have received significant attention only in the past two decades after their hypotensive and spasmolytic properties were demonstrated.[4,5] Overall, DHPM compounds were found to have pharmacological profile similar to that of classical DHP calcium channel blocking.[6,7] Several lead derivatives of DHPM compounds have been shown to be superior in potency and duration of antihypertension activity as compared to classical DHP drugs.

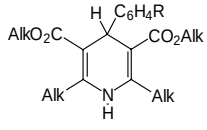
Most of discussed dihydropyridines **I** and dihydropyrimidinones **II** contain an ester group in the position 5 of the heterocycle.[6,7] They can also bear other carbonyl functions without loss of basic biological activity. However, substitution of NO_2 for COOAlk in the dihydropyridines alters their biological action. In particular, it has led to Ca agonist Bay K 8644 (**III**) featuring higher acute toxicity.[8] At the same time, it was shown that nitro derivatives of dihydropyrimidinones (**IV**) are Ca antagonists or agonists depending upon character and position of a substituent in the Ar group having low acute toxicity.[9,10]



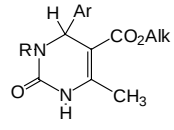
III



IV



I



II

Previously, we have synthesized a number of low general toxic 4-aryl-5-nitro-6-phenyl-3,4-dihydro-(1*H*)pyrimidin-2-ones (**Va**–**Vd**) in 57 – 64% yields.[11] The overall synthetic strategy for the preparation of compounds **Va**–**Vf** is based on the modification of classical three-component Biginelli condensation.[7] The process involves (includes) the one-pot cyclocondensation of an α-nitro-acetophenone (1.0 equiv) with an aryl (heteroaryl) aldehyde (1.5 equiv) and urea (5 equiv) in isopropanol in the presence of concd HCl. That is outlined in Scheme 1.

Keywords: Antiarrhythmic activity; 4,6-Di(het)aryl-5-nitro-3,4-dihydropyrimidin-(1*H*)-2-ones; Arrhythmia.
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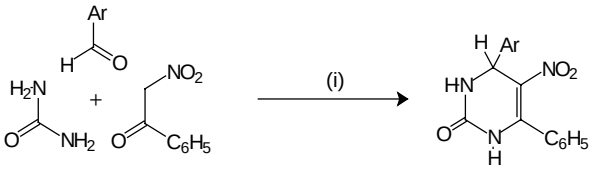

V a-f

Scheme 1. Reagents and conditions: (i) *i*-PrOH, concd HCl, reflux, 12–15 h. Ar=C_6H_5 (**a**), 4-HOC_6H_4 (**b**), 3-FC_6H_4 (**c**), 3-$O_2NC_6H_4$ (**d**), 3-Py (**e**), 2-Th (**f**).

The compounds **Va**–**Vd** have revealed significant antiarrhythmic activity toward two types of rat arrhythmia.[11] The model arrhythmias were induced by calcium chloride and epinephrine hydrochloride. The doses effective in 50% of the test animals (ED_{50}) were determined with rats upon single intraperitoneal administration. The ED_{50} values were calculated using the experimental data for five doses of each compound (ranging from 3 to 10 mg kg^{-1}) and reference drugs Lidocaine and Quinidine (3–12 mg kg^{-1}). A criterion of positive action was complete lack of arrhythmia signs. The results of tests showed that the average antiarrhythmic activity of compounds **Va**–**Vc** upon intraperitoneal administration is greater than those of Lidocaine and Quinidine by a factor of 31 and 15, respectively, with the calcium chloride arrhythmia model, and by a factor of 21 and 8, respectively, with the epinephrine hydrochloride arrhythmia model.[11]

In the present work, the antiarrhythmic activities of compounds **Va**–**Vf** were studied with rats upon intravenous injection. The synthesis of **Va**–**Vd** was described earlier,[11] compounds **Ve** (Ar = pyrid-3-yl) and **Vf** (Ar = thien-2-yl) were prepared by the same method.[12]

The pharmacological studies have been carried out on several groups of mature male rats in accordance with The Guideline for the Care and Use of Laboratory Animals. Each experimental group of rats contained 10 animals. The mature male rats, 190–220 g weight, were obtained from the Institute of Cytology and Genetics, Siberian Branch of the Russian Academy of Sciences, Novosibirsk. Model arrhythmias were induced by one-step intravenous injection of 10% $CaCl_2$ solution in a dose of 250 mg kg^{-1}, or of epinephrine hydrochloride in a dose of 0.3 mg kg^{-1}, to rats narcotized with thiopental sodium (30 mg kg^{-1}, ip). The doses of arrhythmogenes are absolutely lethal (LD_{100}) for rates. The test agents were mixed with Twin 66, the mixtures diluted with physiologic salt solution, and the resulted forms were injected in the same famous vein of an animal. This administration way allows blocking the acute arrhythmia directly. We have used two experimental models, with injection of agent 1 min before, or 1 min after, the injection of an arrhythmogene. The reference antiarrhythmic drugs were Allapininum and Verapamil introduced intravenously in doses of 0.3 and 1.1 mg kg^{-1}, respectively.

Electrocardiograms were recoded in second standard lead using LabLincV electrophysiological complex (Coulbourn, USA), during 10 min. A duration of RR, PQ, QRS, QT, and P wave intervals was estimated, together with amplitudes of P, T, and R waves. Statistical data processing was performed using the STATISTICA software. As a deviation of median, a standard error was used. In acute experiments, pressure measurements were performed by cannulation of carotid artery. An arterial pressure was registered using LabLincV. Average values of systolic arterial pressure were exposed to statistical processing.

We have found that a priori administration of test agents **V**–**Ve** to rats completely prevented the arrhythmia progression. However, the individual effective doses depended strongly on the chemical nature of a substituent in the Ar group of the dihydropyrimidinone.

The highest arrhythmia protection was displayed by **Vc** and **Vd** agents, characterized by minimal doses of 3.5×10^{-4} and 4.5×10^{-5} mg kg^{-1}, respectively (Table 1). The **Va**, **Vb**, **Ve** agents showed lower activity (3.5×10^{-2} mg kg^{-1}), whilst thienyl derivative **Vf** revealed the lowest antiarrhythmic activity in the series (3.5 mg kg^{-1}). It should be noted that Nifedipine injected in the dose of 3.5 mg kg^{-1} either before or after administration of $CaCl_2$ prevented the arrhythmia progression, whereas Verapamil in the dose of 1.1 mg kg^{-1} and Allapininum[13] in the dose of 0.3 mg kg^{-1} gave the 50% effect only.

Roughly, the antiarrhythmic activity of dihydropyrimidinones **V** diminishes with an increase of electron donor ability of (het)aryl substituents, as follows: 3-$O_2NC_6H_4$ > 3FC_6H_4 > 3-Py, C_6H_5, 4-HOC_6H_4 > 2-Th.

An additional promising property of **Vb**–**Vd** agents is their ability to improve myocardium electric conductivity resulting in much distinct ECG waves. The remarkable feature of the agents is the lack of influence on arterial pressure, unlike blockers of calcium canals such as derivatives of 1,4-dihydropyridine.

All **Va**–**Ve** agents did not affect cardiac electric conductivity parameters in epinephrine-induced arrhythmia model. Also, they did not show an antiarrhythmic effect in dosage up to 3.5 mg kg^{-1}, which was affirmed by 100% lethality.

Table 1. Structure–antiarrhythmic activity relationship for nitrodihydropyrimidinones **V** and selected reference compounds

Compound	LD_{50} (mg kg^{-1})	Minimal effective dose (mg kg^{-1})
Va	>5000	3.5×10^{-2}
Vb	>5000	3.5×10^{-2}
Vc	>5000	3.5×10^{-4}
Vd	>1000	4.5×10^{-5}
Ve	>1000	3.5×10^{-2}
Vf	>1000	3.5
Nifedipine	210	3.5
Allapininum[13]		0.3
Verapamil	8.5	1.1 (ED_{50})

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12. Synthesis of **Ve** and **Vf**: at ambient temperature, corresponding (het)aryl aldehyde (0.06 mol) was added to a strired solution of urea (0.2 mol) and concd HCl (6 mL) in isopropanol (75 mL). The reaction mixture was stirred overnight, then α-nitroacetophenone (0.04 mol) was added and the mixture was refluxed for 12–15 h. The precipitate was filtered and subsequently washed with ethanol, aqueous $NaHCO_3$, water, and ethanol. 5-Nitro-6-phenyl-4-(pyrid-3-yl)-3,4-dihydro-(1*H*)pyrimidin-2-one (**Ve**) was recrystallized from DMF, 1.9 g (16%), mp 295–297 °C. ^{1}H NMR (200 MHz, DMSO-d_6): δ/ppm: 5.73 (d, J = 3.5 Hz, 1H), 7.30–7.60 (m, 6H), 7.87 (dt, J = 8.0, 2 Hz, 1H), 8.49 (d, J = 3.5 Hz, 1H), 8.56 (dd, J = 4.5, 1.5 Hz, 1H), 8.66 (d, J = 2 Hz, 1H), 10.25 (s, 1H). MS (EI 70 eV) m/z (%): 296 (7) [M^+], 279 (100), 250 (15), 249 (42), 248 (65), 218 (65), 171 (69). IR (KBr) ν/cm^{-1}: 3199 and 3070 (NH), 1693 (C═O), 1494 and 1322 (NO_2). Anal. Calcd for $C_{15}H_{12}N_4O_3$: C, 60.81; H, 4.08; N, 18.91. Found: C, 60.58; H, 4.08; N, 18.79. 5-Nitro-6-phenyl-4-(thien-2-yl)-3,4-dihydro-(1*H*)pyrimidin-2-one (**Vf**) was recrystallized from ethanol, 7.8 g (65%), mp 235–237 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm: 5.91 (d, J = 3.5 Hz, 1H), 7.05 (dd, J = 5.0, 3.4 Hz, 1H), 7.14 (d, J = 2.6 Hz, 1H), 7.33–7.57 (m, 6H), 8.59 (d, J = 3.5 Hz, 1H), 10.29 (s, 1H). MS (EI 70 eV) m/z (%): 301 (3) [M^+], 284 (76), 255 (36), 254 (43), 253 (100), 202 (46), 171 (94). IR (KBr) ν/cm^{-1}: 3208 and 3095 (NH), 1701 (C═O), 1497 and 1322 (NO_2). Anal. Calcd for $C_{14}H_{11}N_3O_3S$: C, 55.81; H, 3.68; N, 13.95; S, 10.64. Found: C, 55.82; H, 3.69; N, 13.82; S, 11.00.
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