In vitro study of the electrophysiological properties of several cardioactive drugs in mammalian hearts

PhD Thesis

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1. Introduction

Cardiovascular diseases, and in particular, cardiac arrhythmias, such as ventricular fibrillation have a leading role in mortality in developed countries. The most serious ventricular arrhythmia – ventricular fibrillation – causes the death of more than 3.000.000 people all over the world and 300.000 – 350.000 people in the USA and Europe annually, which statistically means that one person dies every minute on each continent. In Hungary exact data are not available, but according to calculations there are 25.000 – 26.000 sudden cardiac death cases annually, or 50 – 60 deaths per day. In the majority of the cases sudden cardiac death occurs when victims are not in hospital, consequently, survival probability is very low. Most frequently (50 %) the background of the on-the-spot diagnosed circulation collapse is ventricular tachycardia /fibrillation/. Sudden cardiac death is often the very first sign of the symptom-free cardiovascular disease. Sudden cardiac death is a complex national health problem affecting families and having significant social and economic consequences, since usually it is the head of the family, a seemingly healthy man, who dies tragically. Survivors of the crisis can live a life of full volume in good conditions provided that they get the most appropriate treatment. Accordingly, cardiac arrhythmias represent a major area of cardiovascular research. One of the main goals of pharmacological research is to develop a safe ventricular antiarrhythmic drug that can be applied either in acute cases or for treating postinfarction patients.

According to the classification of Vaughan Williams (1970), based on electrophysiological actions, the antiarrhythmic drugs can be defined by four classes. Class I consist of antiarrhythmic agents that block sodium channels, reducing the maximum increase rate of depolarization (V_{max}). Class II agents are the β-blockers, the Class III drugs act through delaying repolarization of cardiac myocytes and thus cause a lengthening of APD (potassium-channel blockers), while Class IV antiarrhythmics block calcium currents in cardiac tissue.

Concepts regarding the treatment of cardiac arrhythmias changed significantly in the past decade, owing to the revolutionary development of electrophysiological methods (patch-clamp, molecular biology). The Cardiac Arrhythmia Suppression Trial (CAST) showed that flecainide and encainide, two Class I/C sodium channel blocker antiarrhythmic drugs, increased mortality rates approximately threefold compared with placebo due to

proarrhythmic effects. Consequently, the interest of drug development for treatment of ventricular tachycardia (VT) and atrial fibrillation (AF) has been shifted toward those agents that prevent and terminate re-entrant arrhythmias by prolonging the action potential duration (APD) and effective refractory period (ERP), resulting in an increase in arrhythmia wavelength and a block development within the re-entrant circuit.

Class III antiarrhythmic action, *i.e.* lengthening of cardiac action potential duration (APD) and prolongation of the repolarization, is usually caused by blockade of one or more potassium channels. Sodium channels are not affected, thus conduction velocity remains unchanged. A great number of non-cardiac drugs cause lengthening of repolarization in both ventricular muscle cells and Purkinje fibres by using a similar mode of action.

One arrhythmogen factor that can result in ventricular arrhythmias occurring in myocardial ischaemia or poisoning with digitalis is delayed afterdepolarization (DAD), which arises in heart muscle cells following Ca^{2+} overload. Reducing the incidence of these trigger mechanism (DAD) or their pharmacological blockade would be extremely desirable from a clinical point of view.

Maintenance of the Ca^{2+} homeostasis in the myocardium is mainly regulated by the sodium-calcium exchanger (NCX). Mammalian Na^{+}/Ca^{2+} exchangers are members of three branches of a much larger family of transport proteins [the CaCA (Ca^{2+}/cation antiporter) superfamily] whose main role is to provide control of Ca^{2+} flux across the plasma membranes or intracellular compartments. Since cytosolic levels of Ca^{2+} are much lower than those found extracellularly or in sequestered stores, the major function of NCX is to extrude Ca^{2+} from the cytoplasm. The exchangers are, however, fully reversible and thus, under special conditions of subcellular localization and compartmentalized ion gradients, NCX may allow Ca^{2+} entry and may play more specialized roles in Ca^{2+} movement between compartments. The NCX branch of Na^{+}/Ca^{2+} exchangers comprises three members: NCX1 has been most extensively studied, and is broadly expressed with particular abundance in heart, brain and kidney, NCX2 is expressed in brain, and NCX3 is expressed in brain and skeletal muscle.

It is known that NCX, at the forward mode, extrudes Ca^{2+} from the cell to the extracellular space during diastole, at relatively low free cytoplasmic Ca^{2+} concentration and negative transmembrane potential. Since the extrusion of one Ca^{2+} is coupled with 3 Na^{+} entering the cell, during the forward mode of the NCX net inward current is carried, which can cause substantial depolarization leading to early (EAD) and delayed (DAD) after-depolarizations, especially when intracellular Ca^{2+} is elevated. EAD and DAD is generally thought to play an important role in arrhythmogenesis, especially in conditions where

potassium conductance is decreased, such as heart failure. Therefore one may speculate that specific blockers of NCX could be potential antiarrhythmics in dysrhythmias related to Ca^{2+} overload. This hypothesis could not be directly tested since the available NCX inhibitors, at least in higher concentrations, also decreased the L-type calcium current (I_{Ca}) which in turn decreased intracellular Ca^{2+} load, thereby indirectly changing the magnitude of NCX. In 1996 it was found that KB-R7943 (2-[2-[4-94-nitrobenzyloxy)phenyl]ethyl]isothiourea), an effective inhibitor of NCX in the reverse mode but not in the forward mode, reduced the incidence of ischaemia and reperfusion arrhythmia induced by calcium overload. However, KB-R7943 also inhibits the L-type calcium current which makes the interpretation of its antiarrhythmic effect rather uncertain.

In 2001, Matsuda et al. reported SEA-0400 (2-[4-[(2,5-difluorophenyl)methoxy]phenoxy]-5-ethoxy-aniline), a newly developed, more potent, and selective NCX inhibitor. It is completely coincidental that SEA-0400 and KB-R7943 have a common benzyloxyphenyl structure, suggesting that this portion is important for inhibitory action against NCX.
SEA-0400 is highly specific for NCX because it hardly inhibits other receptors, channels and transporters. In 2002, SN-6 was found by screening newly synthesized benzyloxyphenyl derivatives for NCX1 inhibition. This compound showed inhibitory potency for NCX1 similar to KB-R7943, but was more specific for NCX1 than KB-R7943.

One of the goals of my PhD project was to investigate the effect of SEA-0400 on the NCX and I_{Ca} currents of dog ventricular myocytes, and also on the formation of EAD and DAD in the dog ventricular muscle and Purkinje fibres, using the conventional microelectrode and patch-clamp techniques.

In the case of antiarrhythmic drugs the delicate balance between drug efficacy and unexpected adverse side effects is narrower than in any other class of therapeutic agents. Sotalol, amiodarone, ibutilide and dofetilide are moderately effective in patients with chronic atrial fibrillation. However, amiodarone appears to be most efficacious. Moreover, amiodarone and dofetilide is efficacious in patients who have had a myocardial infarction and those with heart failure. The safety of commercially available d,l-sotalol in these patients is poorly understood. *Torsades de pointes* is the most serious adverse effect of sotalol and dofetilide. Amiodarone has minimal proarrhythmic risk, but has numerous noncardiac toxicities that require frequent monitoring. Dronedarone, a noniodinated benzofuran derivative, has been shown to be more effective in vivo than amiodarone in several arrhythmia models, particularly in preventing ischemia- and reperfusion-induced ventricular fibrillation and in reducing mortality. However, further experimental studies and long-term

clinical trials are required to provide additional evidence of efficacy and safety of this drug. Azimilide statistically reduced the incidence of new atrial fibrillation in recent survivors of myocardial infarction at high risk for sudden cardiac death. In addition, class III antiarrhythmic agents are increasingly being used as adjunct therapy to decrease the frequency of ICD discharges in patients with ventricular arrhythmias and implantable cardioverter defibrillators (ICDs). The antiarrhythmic efficacy of most pure class III drugs is compromised by their inherent property to induce excessive lengthening of the action potential (reverse frequency dependence) and their inability to prolong the action potential when most needed, namely during tachycardia. Overall, an ideal antiarrhythmic agent does not exist, and drug selection should be highly individualized.

Based on these results in antiarrhythmic field we synthesized a series of molecules that combine several modes of actions to find a drug that has powerful antiarrhythmic potential with lack of proarrhythmic side effects. One possible direction of development was to test the combination of the hydroxy-benzopyran ring of vitamin E with the methylsulfonyl-aminophenyl moiety of class III antiarrhythmic drugs. Specifically, the new compounds combine pharmacophores identified for the most active Class III antiarrhythmics. Thus, they contain two aromatic rings, one methylsulfonyl amino group, and at least one tertiary amine, such as a 1,4-piperazine or methylamine moiety.

Evaluation of the antiarrhythmic and antioxidant activity of the new compounds was carried out on isolated rat heart preparations using the non-recirculating Langendorff mode. The new analogues were present, at 10 μM concentration, during ischaemia and reperfusion. Selected compounds were further studied by a conventional microelectrode method in order to get insight into their cellular mode of action.

Another possible area for development of new antiarrhythmics are amiodarone-like drugs, that combine Class IB+III antiarrhythmic effects. Our chemical collaboration partner designed and developed a new agent, SZV-123, that based on some preliminary screening proved to have strong antiarrhythmic potential, therefore it was selected for a more intensive electrophysiological screening project. We have analysed the effects of SZV-123 on the action potential parameters and main repolarizing transmembrane ionic currents by applying the conventional and whole-cell patch-clamp techniques.

Ventricular repolarization is governed by a fine balance between inward currents, such as the fast sodium (I_{Na}) and the L-type calcium (I_{Ca}) currents, and outward currents, such as the transient outward (I_{to}), rapid delayed rectifier (I_{Kr}), slow delayed rectifier (I_{Ks}) and inward rectifier (I_{K1}) potassium current. Under normal conditions impairment or block of one type of

outward potassium currents can not be expected to cause excessive and potentially dangerous APD lengthening, since other potassium currents may provide sufficient repolarizing capacity, which can be considered as a “repolarization reserve”. However, in situations where the density of one or more types of potassium channels is decreased by inheritance or remodelling, inhibition of other potassium channels may lead to unexpectedly augmented APD prolongation, resulting in proarrhythmic reactions. Genetic channelophathies of certain potassium channels, which normally contribute to repolarization, can attenuate the capability of the heart to repolarize.

The rapid component of the delayed rectifier potassium current (I_{Kr}) has been identified in several mammalian species, including human. Pharmacological agents that selectively block I_{Kr} (e.g., E-4031, sotalol and dofetilide) markedly increase APD, QT duration and ventricular refractoriness, and high doses of these drugs are associated with the induction of *Torsades de Pointes*. Mutations in ion channel genes, including HERG and KCNE2, that suppress I_{Kr} result in a specific form of the inherited long QT syndrome, the LQT2, which is also associated with rhythm disorders and an increased incidence of sudden cardiac death. As such, I_{Kr} plays a major role in action potential repolarization in health and in specific cases of arrhythmogenesis.

The role of the slow delayed rectifier potassium current (I_{Ks}) in human ventricular muscle action potential repolarization, on the other hand, has been often debated. As with I_{Kr}, I_{Ks} has been identified in several mammalian species, including humans and mutations in KCNQ1 and KCNE1, the alpha and beta-subunits of the I_{Ks} potassium channel, are associated with another specific form of the inherited long QT syndrome, LQT1. We previously reported that complete pharmacological block of I_{Ks}, by either chromanol 293B or L-735,821, has little effect on APD in isolated dog and rabbit ventricular muscle over a wide range of physiologic pacing frequencies. These findings led us to speculate that I_{Ks} normally plays little role in ventricular muscle action potential repolarization. However, when APD is abnormally long, I_{Ks} likely provides an important safety mechanism that when removed increases arrhythmic risk. Our previously reported findings have now been confirmed by other investigators and supported by computer simulations suggesting that I_{Ks} does not play a role in adaptations of APD to changes in heart rate. However, the role of I_{Ks} in human ventricular muscle remains controversial; although, our preliminary characterization of I_{Kr} and I_{Ks} in isolated human ventricular myocytes suggests that these currents behave much the same as they do in isolated dog and rabbit ventricular myocytes. The purpose of the present study, therefore, was to confirm our initial findings while further elucidating the role of I_{Ks} in normal human

ventricular muscle action potential repolarization and in preparations where repolarization reserve was attenuated and sympathetic activation was increased by exogenous dofetilide and adrenaline.

In addition, we investigated and compared the role and relative contribution of two particularly important repolarizing potassium currents I_{Kr} and I_{K1} to the repolarization in human, dog and rabbit hearts at the cellular levels.

2. Major specific experimental goals

a.) To study the effect of SEA0400, a newly developed NCX inhibitor devoid of I_{Ca} blocking property, on the NCX and I_{Ca} currents of dog ventricular myocytes, and also on the formation of EAD and DAD in the dog ventricular muscle and Purkinje fibres.

b.) To investigate the *in vitro* electrophysiological effects of a series of molecules that combine the hydroxy-benzopyran ring of vitamin E with the methylsulfonyl-aminophenyl moiety of Class III antiarrhythmic drugs, that can represent novel cardioprotective compounds with improved efficacy in the treatment of life-threatening arrhythmias in rabbit cardiac preparations.

c.) To investigate the *in vitro* electrophysiological effects of SZV-123, a new amiodarone-like (combined Class IB+III) antiarrhythmic, that can be a novel cardioprotective compound with improved efficacy in the treatment of life-threatening arrhythmias, in dog and rabbit cardiac preparations.

d.) To elucidate the role of I_{Ks} current in normal human ventricular muscle, and in preparations where repolarization reserve was attenuated and sympathetic activation was increased by exogenous dofetilide and adrenaline.

e.) To study and compare the role and relative contribution of rapid delayed rectifier I_{Kr} and inward rectifier potassium currents (I_{K1}) in the repolarization of human, dog and rabbit ventricular muscle.

3. Methods

3.1. Species and cardiac preparations

Experiments were carried out in ventricular preparations isolated from dog, rabbit hearts and from undiseased human cardiac ventricular preparations. The protocols used on rabbit and dog cardiac preparations were conducted in compliance with the *Guide for the Care and Use of Laboratory Animals* (USA NIH publication No 85-23, revised 1985), and were approved by the review board of Committee on Animal Research (CAR) of the Albert Szent-Györgyi Medical University (54/1999 OEj).

Human hearts were obtained from organ donors whose hearts were explanted to obtain pulmonary and aortic valves for transplant surgery. Before cardiac explantation, organ donor patients did not receive medication, except dobutamine, furosemide, and plasma expanders. The investigations conform to the principles outlined in the Declaration of Helsinki and all experimental protocols were approved by the Albert Szent-Györgyi Medical University Ethical Review Board (No. 51-57/1997). Proper consent was obtained for use of each individual's tissue for experimentation.

3.2. Conventional microelectrode technique

Cardiac preparations (trabeculae, papillary muscle and Purkinje fibres) from untreated New-Zealand white rabbits and adult mongrel dogs of either sex and from undiseased human ventricles were used. The preparations were immediately rinsed in oxygenated Locke's solution containing (in mM): NaCl 123, KCl 4.7, $NaHCO_3$ 20, $CaCl_2$ 1.8, $MgCl_2$ 1.0 and D-glucose 10. The pH of this solution was 7.35 ± 0.05 when gassed with 95% O_2 and 5% CO_2 at 37 °C. The tip of the papillary/trabeculae muscles obtained from the right ventricle were individually mounted in a tissue chamber (volume 50 ml). Each ventricular preparation was initially stimulated (HSE (Hugo Sachs Elektronik) stimulator type 215/II, March-Hugstetten, Germany) at a basic cycle length (BCL) of 1000 ms (frequency=1 Hz), using 2 ms rectangular constant voltage pulses isolated from ground and delivered across bipolar platinum electrodes in contact with the preparation. Each preparation was allowed to equilibrate for least 1, while they were continuously superfused with Tyrode's solution. Temperature of the superfusate was kept constant at 37 °C. Transmembrane potentials were recorded using conventional

microelectrode techniques. Microelectrodes filled with 3M KCl and having tip resistances of 15-20 Mohm were connected to the input of a high impedance electrometer (HSE microelectrode amplifier type 309), which was connected to ground. The first derivative of transmembrane potentials was electronically obtained by an HSE differentiator (type 309). The voltage outputs from all amplifiers were displayed on a dual beam memory oscilloscope (Tektronix 2230 100 MHz digital storage oscilloscope, Beaverton, OR, USA).

The maximum diastolic potential, action potential amplitude and action potential duration (APD) measured at 50 and 90% repolarization ($APD_{50\text{-}90}$) were obtained using a software developed in our department (HSE-APES) on an IBM 386 microprocessor based personal computer connected to the digital output of the oscilloscope. After control measurements the preparations were superfused for 60 min with Tyrode's solution containing the compound under study, and then the electrophysiological measurements were resumed.

3.3. Whole cell patch-clamp measurements

Isolation of rabbit, dog and human ventricular myocytes

Single ventricular myocytes were obtained by enzymatic dissociation. The cells were stored at room temperature in HEPES buffered Tyrode solution. containing (mM): NaCl 144, NaH_2PO_4 0.33, KCl 4.0, $CaCl_2$ 1.8, $MgCl_2$ 0.53, Glucose 5.5, and HEPES 5.0 at pH of 7.4 (adjusted with NaOH).

Experimental protocols for potassium current measurements

Membrane currents (potassium and calcium currents) were recorded with Axopatch-1D and 200B patch-clamp amplifiers (Axon Instruments, Union City, CA, USA.) using the whole-cell configuration of the patch-clamp technique. After establishing a high (1-10 Gohm) resistance seal by gentle suction, the cell membrane beneath the tip of the electrode was disrupted by suction or by application of 1.5 V electrical pulses for 1-5 ms. The series resistance was typically 4-8 Mohm before compensation (50-80%, depending on the voltage protocols). Experiments where the series resistance was high, or substantially increased during measurement, were discarded. Membrane currents were digitized using a 333 kHz analogue-to-digital converter (Digidata 1200 and 1322A, Axon Instruments) under software control (pClamp 7.0 and 8.0 Axon Instruments). Analyses were performed using Axon (pClamp 8.0) software after low-pass filtering at 1 kHz. All patch-clamp data were collected at 37 ˚C.

3.4. Drugs

SEA-0400 was obtained from Orion Pharma (Espoo, Finland) and was dissolved in 100 % DMSO to make 30 mM stock solution.

Series of new drugs that combine the hydroxy-benzopyran ring of vitamin E with the methylsulfonyl-aminophenyl moiety of class III antiarrhythmic drugs were synthesised and tested. Effects of two families of compounds that were active in ischaemia and reperfusion studies were further analysed. One class contained the piperazine analogues, while the other contained the methylamino analogues. The compounds were dissolved in 100 % DMSO to make 10 mM stock solution.

I_{Kr} blockers D-sotalol (Bristol-Myers Squibb Co., Wallingford, CT, USA), E-4031 (Institute for Drug Research Ltd., Budapest, Hungary) and dofetilide (synthetised by chemical partner) were prepared daily from aqueous or DMSO stock. I_{Ks} blockers chromanol 293B (Aventis Pharma, Frankfurt, Germany), HMR-1556 (Aventis Pharma) and L-735,821 (Merck-Sharpe & Dohme Co, West Point, PA, USA) were similarly diluted from stock solutions containing 100 % DMSO.

3.5. Statistical analysis

Results were compared using Student's t-tests for paired and unpaired data. Differences were considered significant when $P< 0.05$. Data are expressed as mean ± standard error of the mean (SEM)

4. Results and conclusions

The main findings and the conclusions of the present thesis are as follows:

1. The effect of SEA-0400, a newly developed NCX inhibitor devoid of I_{Ca} blocking property, on the formation of EAD and DAD in the dog ventricular muscle and Purkinje fibers was investigated. Evidence has been obtained for the NCX inhibitory activity of SEA-0400 and its potency to suppress elementary arrhythmogenic phenomena, such as EAD and DAD. Considering the pros and contras, further research is needed with both *in vitro* and *in vivo* methods to elucidate the potential therapeutic targets and, in a wider sense, the possible beneficial effect of specific NCX inhibition [**I**].

2. We synthesized and studied a series of compounds combining the hydroxy-benzopyran ring of vitamin E with the methylsulfonyl-aminophenyl moiety of class III antiarrhythmic drugs. These drugs were the piperazine analogues (5a-5e) and methylamino analogues (19a and 19b). Among piperazine derivatives, compounds 5c and 5e suppressed reperfusion tachycardia, while compound 5e reduced premature beats and MDA content, combining antiarrhythmic and antioxidant properties. Methylamino derivative 19a exhibited antioxidant activity and reduced premature beats, and induce a fast recovery of the heart during reperfusion. Compounds 5c, 19a and 19b facilitated the recovery of QRS and QT intervals during reperfusion, to the normal values. The cardioprotective compounds 5c-5e and 19a-19b do not induce excessive lengthening of the action potential, exhibiting moderate class III antiarrhythmic actions [**III**].

3. We studied the cellular electrophysiological effects of SZV-123 a new amiodarone-like antiarrhythmic compound that combine Class IB+III actions, in isolated dog and rabbit cardiac muscle. SZV-123 lengthened repolarization in a frequency independent manner, and decreased V_{max} only at faster rates than physiological. This property of the SZV-123 can be related to the Class I/B type sodium channel blocking effect. The frequency dependent Class I sodium channel blocking of the SZV-123 can be associated with a mexiletine-like fast restoration kinetics therefore it can be expected to decrease the conduction velocity only at frequencies higher than physiological. It can be concluded that SZV-123 indeed possesses an

amiodarone-like multichannel blocking (Class I/B + III) antiarrhythmic effects, therefore this molecule is promising for treatment of ventricular arrhythmias.

4. The role of I_{Kr} and I_{Ks} were examined in human cardiac preparations from the hearts of individuals without heart disease. I_{Ks} current in the absence of sympathetic stimulation plays no obvious role in altering action potential repolarization and QT duration at normal heart rates in human ventricular myocytes isolated. However, when human ventricular muscle repolarization reserve is attenuated and sympathetic stimulation is elevated, I_{Ks} plays an increasingly important role in limiting action potential prolongation. These findings should not be misconstrued as meaning that I_{Ks} does not play an important role in the normal heart where sympathetic stimulation is allways present and fluctuating continuously. We also believe, that I_{Ks} is vitally important in the normal heart where it prevents excessive action potential prolongation in the setting of an elevated sympathetic tone following a single long diastolic interval after the compensatory pause that follows a premature ventricular depolarization, or during bradycardia or when APD is prolonged by other means (eg, by unintentional I_{Kr} block, hypothyroidism, or serum hypokalaemia) [**II**].

5. The current density of I_{K1} is considerably less in human than in the dog and rabbit ventricle, while I_{Kr} density is about the same in the three preparations. Pharmacological inhibition of I_{K1} elicits minor changes in the human ventricle, but prolongs ventricular repolarization in the dog and rabbit. Inhibition of I_{Kr} evokes modest prolongation of repolarization in the dog ventricle, but largely or markedly lengthens it in the rabbit and human, respectively, suggesting an important role of I_{K1} as part of the repolarization in both species but I_{K1} contributes more to normal repolarization in the dog and rabbit than in humans. In other words based on experiments in the dog with drugs potentially blocking I_{Kr}/HERG channels one can underestimate the expected degree of repolarization lengthening in human. Therefore using dog in certain types of safety pharmacology studies predicting the possible QTc lengthening side effects of various non cardiac drugs has no particular advantage over other animal models like the commonly used rabbit models even if one considers the more similarity the behaviours of the individual channels the better correlation of heart rate between human and large than small mammals [**IV**].

5. List of publications related to the subject of the PhD Thesis

Full length papers

I. Zsolt A. Nagy, László Virág, András Tóth, Péter Biliczki, Károly Acsai, Tamás Bányász, Péter Nánási, Julius Gy. Papp, András Varró. Selective inhibition of sodium-calcium exchanger by SEA-0400 decreases early and delayed afterdepolarization in canine heart.
British Journal of Pharmacology 2004; 143, 827−831
IF(2004)= 3.825 Nr. citations: 6

II. Norbert Jost, László Virág, Miklós Bitay, János Takács, Csaba Lengyel, Péter Biliczki, **Zsolt A. Nagy**, Gábor Bogáts, David A. Lathrop, Julius G. Papp, András Varró. Restricting excessive cardiac action potential and QT prolongation.
Circulation 2005; 112: 1392-1399
IF(2005): 10.94 Nr. citations: 39

III. Maria Koufaki, Christina Kiziridi, Panagiota Papazafiri, Athanasios Vassilopoulos, András Varró, **Zsolt A. Nagy**, Attila Farkas and Alexandros Makriyannis. Synthesis and biological evaluation of benzopyran analogues bearing class III antiarrhythmic pharmacophores.
Bioorganic & Medicinal Chemistry 14, 6666-6678, 2006.
IF(2006) = 2.624 Nr. citations: 3

Quotable abstracts

IV. Norbert Jost, László Virág, Viktória Szűts, Csaba Lengyel, Péter Biliczki, **Zsolt A. Nagy**, György Seprényi, Péter P. Kovács, János Szabad, Julius Gy. Papp, András Varró. Comparison of the contributing effect of the inward rectifier potassium current to repolarization in human, dog and rabbit hearts
Cardiologia Hungarica, 36, SupplA, A21, 2006.

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