Kowalska Magdalena, Fijałkowski Łukasz, Nowaczyk Alicja. The biological activity assessment of potential drugs acting on cardiovascular system using Lipinski and Veber Rules. Journal of Education, Health and Sport. 2018;8(12):184-191. eISNN 2391-8306. DOI http://dx.doi.org/10.5281/zenodo.2066519
http://ojs.ukw.edu.pl/index.php/johs/article/view/6360

The journal has had 7 points in Ministry of Science and Higher Education parametric evaluation. Part B item 1223 (26/01/2017).
1223 Journal of Education, Health and Sport eISSN 2391-8306 7

The authors declare that there is no conflict of interests regarding the publication of this paper.

Received: 25.11.2018. Revised: 30.11.2018. Accepted: 08.12.2018.

The biological activity assessment of potential drugs acting on cardiovascular system using Lipinski and Veber Rules

Magdalena Kowalska, Łukasz Fijałkowski, Alicja Nowaczyk

Department of Organic Chemistry, Faculty of Pharmacy, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University, Dr. A. Jurasza 2, 85-094 Bydgoszcz

Abstract

Advanced computational methods (*in silico*) play major role in the early stages of developing new pharmaceuticals. Precise knowledge on molecular structure gives the possibility of forecasting the drug candidates basic properties. Despite many drugs registered in the arrhythmia treatment, this disease currently is still a big therapeutic problem. Therefore, intensive search for new drugs acting on the cardiovascular system are performed.

In the presented work, 77 pyrrolidin-2-one derivatives were analyzed for antiarrhythmic activity. Values of the key parameters proposed by Lipinski and Veber were obtained using computational chemistry methods. It's worth pointing out that the studied group of derivatives shows similar physicochemical properties to the anti-arrhythmic drugs used.

Key words: Lipinski's rule, Veber rule, pyrrolidin-2-one derivatives

Introduction

The most common cause of death in Europe is cardiovascular disease **[**Nichols i in. 2014]. According to the World Health Organization, this is the reason for the death of 4.3 million people a year. Frequent cardiovascular disorders are: hypertension, ischemic heart disease, heart failure and arrhythmias. Currently, these diseases are referred to as civilization diseases. Their treatment is

extremely expensive - each year, the European Union dedicates approximately 192 billion EUR to the treatment of heart disease [Allender et al. 2008].

One of the most common heart disorder is arrhythmia. The mechanism of arrhythmia formation may be associated with the occurrence of various factors. Incorrect ion exchange in cells, causing disorders in cell depolarization and repolarization is the most common factor leading to arrhythmias. Moreover, may be the cause of a circular course of stimulation, the so-called ,,reentry". The reentry wave arises as a result of the propagation of the excitation from the damaged site. [Żuchowski, Guzik 2012]

Based on electrophysiological properties, currently used anti-arrhythmic drugs have been divided into several classes. Proposed by V. Williams in 1970. the classification remains valid until today with minor changes (Figure 1).

Calculation methods

The introduction of new medicine on the market is long and extremely expensive process. According to analyzes, the costs of developing a new drug have been growing exponentially since the 1950s. The duration of the research of new drug recently is ranging from 15 to 20 years, while the costs of their conduction reach even 300-900 million dollars. Increasing standards of research and the needs to reduce costs have become an impulse for the development of a new type of methods. These are tests based on *in silico* methods, involving computer simulations of reality using computational models and generation of data libraries. Information technologies are used at every stage of research on a new medicines. They play a key role in the design of compounds in preclinical trials. The implementation of computational methods to the drug design process allowed to significantly reduce the number of lab experiments on animals. Moreover computational methods are used in the evaluation of pharmacokinetic and pharmacodynamic parameters of the drug.

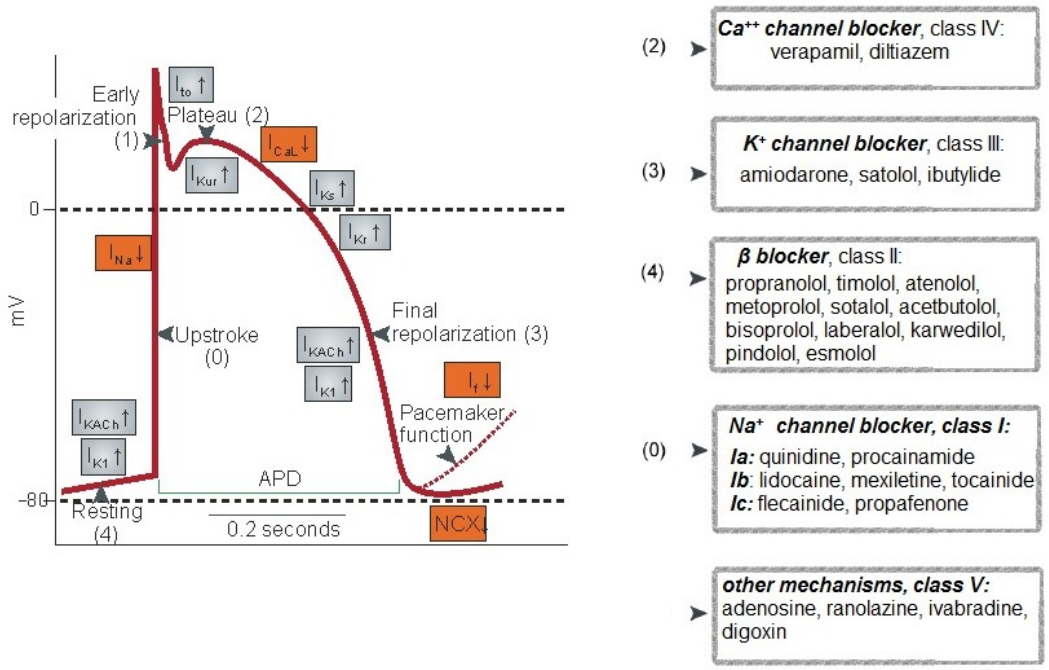

Figure 1. Distribution of antiarrhythmic drugs according to Vughan Williams. A-diagram of the action potential in cardiac cells, B-points of the drug grip, C-classes and examples of drugs, D-clinical use of antiarrhythmics

In clinical trials *in silico* methods are used to rate the safeness of drug administration. Moreover these methods are also used to determine medicines formulation. Pharmacoeconomic assessment is possible thanks to computational models comparing different drugs and treatment regimens used in a given disease. [Polak, Wiśniowska 2008]

The analysis of the compound physicochemical properties plays a key role in its utility as a pharmacological agent . *In silico* methods allow to predict, with high probability, what compounds could be active in a human organism. [Haznar et al. 2011] The scientists compared physicochemical and biological parameters of known compounds and selected collections of physicochemical parameters that have a decisive influence on the solubility and permeability of a chemical substance through the biological membrane.

Materials and methods

In the search for new compounds with potential effects on the cardiovascular system, a group of researchers in the Department of Physical Chemistry of Drug Analysis at the Chair of Pharmaceutical Chemistry, Pharmaceutical Faculty of the Jagiellonian University, in a team led by prof. dr. Barbara Malawska has synthesized a number of 77 N- (arylpiperazinylpropyl) pyrrolidin-2-one derivatives. The subject of the synthesis were pyrrolidin-2-one derivatives having antiarrhythmic, hypotensive, α-adrenolytic and antidepressive activity. Diagrams of structures of synthesized derivatives are collected in Table 1 [Kulig at al. 2010]

Symbol	**SMILES**
MG-1	OC(CN1CCN(CC1)c2ccccc2)CN3CCCC3=O
MG-2	OC(CN1CCN(CC1)c2cccc(Cl)c2)CN3CCCC3=O
EP-9	OC(CN1CCN(CC1)c2ccccc2OC)CN3CCCC3=O
EP-13	OC(CN1CCN(CC1)c2ccc(Cl)cc2)CN3CCCC3=O
EP-16	O=C3CCCN3CC(OC(C)=O)CN1CCN(CC1)c2ccccc2Cl
EP-17	OC(CN1CCN(CC1)c2ccccc2Cl)CN3CCCC3=O
EP-18	O=C3CCCN3CC(OC(C)=O)CN1CCN(CC1)c2ccccc2OC
EP-22	O=C3CCCN3CC(OC(=O)NCC)CN1CCN(CC1)c2ccccc2
EP-23	O=C3CCCN3CC(OC(=O)NCCC)CN1CCN(CC1)c2ccccc2
EP-24	CC(C)NC(=O)OC(CN1CCN(CC1)c2ccccc2)CN3CCCC3=O
EP-25	O=C3CCCN3CC(OC(=O)NCCCC)CN1CCN(CC1)c2ccccc2
EP-26	O=C3CCCN3CC(OC(=O)NCC)CN1CCN(CC1)c2ccccc2OC
EP-27	O=C3CCCN3CC(OC(=O)NCCC)CN1CCN(CC1)c2ccccc2OC
EP-28	CC(C)NC(=O)OC(CN1CCN(CC1)c2ccccc2OC)CN3CCCC3=O
EP-29	O=C3CCCN3CC(OC(=O)NCCCC)CN1CCN(CC1)c2ccccc2OC
EP-32	CC(C)NC(=O)OC(CN1CCN(CC1)c2ccccc2Cl)CN3CCCC3=O
EP-34	O=C3CCCN3CC(OC)CN1CCN(CC1)c2ccccc2
EP-35	OC(CN1CCN(CC1)c2ccccc2F)CN3CCCC3=O
EP-36	OC(CN1CCN(CC1)c2cccc(OC)c2)CN3CCCC3=O
EP-37	OC(CN1CCN(CC1)c2ccccc2OCC)CN3CCCC3=O
EP-38	OC(CN1CCN(CC1)c2ccccc2C)CN3CCCC3=O
EP-40	OC(CN1CCN(CC1)c2ccccc2O)CN3CCCC3=O
EP-41	O=C3CCCN3CCCN1CCN(CC1)c2ccccc2
EP-42	COc3ccccc3N2CCN(CCCN1CCCC1=O)CC2
EP-43	OC(CN1CCN(CC1)c2ccccc2OC(C)C)CN3CCCC3=O
EP-44	Clc3ccccc3N2CCN(CCCN1CCCC1=O)CC2

EP-45	Fc3ccccc3N2CCN(CCCN1CCCC1=O)CC2
EP-46	CCOc3ccccc3N2CCN(CCCN1CCCC1=O)CC2
EP-47	Cc3ccccc3N2CCN(CCCN1CCCC1=O)CC2
EP-48	COc1cccc(c1)N3CCN(CCCN2CCCC2=O)CC3
EP-49	Clc1cccc(c1)N3CCN(CCCN2CCCC2=O)CC3
EP-50	Clc1ccc(cc1)N3CCN(CCCN2CCCC2=O)CC3
EP-52	OC(CN1CCN(CC1)c2ccccc2C(F)(F)F)CN3CCCC3=O
EP-53	Oc3ccccc3N2CCN(CCCN1CCCC1=O)CC2
EP-54	OC(CN1CCN(CC1)c2ccc(O)cc2)CN3CCCC3=O
EP-55	OC(CN1CCN(CC1)c2ccc(OC)cc2)CN3CCCC3=O
EP-56	OC(CN1CCN(CC1)c2ccc(OC)cc2)CN3CCCC3=O
EP-57	OC(CN1CCN(CC1)c2ccc(F)cc2F)CN3CCCC3=O
EP-58	OC(CN1CCN(CC1)c2c(OC)cccc2Cl)CN3CCCC3=O
EP-59	OC(CN1CCN(CC1)c2cccc(O)c2)CN3CCCC3=O
EP-61	FC(F)(F)c3ccccc3N2CCN(CCCN1CCCC1=O)CC2
EP-62	COc1ccc(cc1)N3CCN(CCCN2CCCC2=O)CC3
EP-63	Oc1ccc(cc1)N3CCN(CCCN2CCCC2=O)CC3
EP-64	Fc3ccc(N2CCN(CCCN1CCCC1=O)CC2)c(F)c3
EP-65	COc3cccc(Cl)c3N2CCN(CCCN1CCCC1=O)CC2
EP-66	Oc1cccc(c1)N3CCN(CCCN2CCCC2=O)CC3
EP-2	O=C2CCCN2CC(O)CNCc1ccc(Cl)cc1
EP-8	O=C2CCCN2CC(O)CNCc1ccccc1Cl
EP-10	O=C2CCCN2CC(O)CNCc1ccc(OC)cc1
EP-11	O=C2CCCN2CC(O)CNCc1ccc(OC)c(OC)c1
EP-15	O=C2CCCN2CC(O)CNCc1ccccc1
BM-47	O=C2CCCN2CC(O)CNCCc1ccccc1
EP-5	O=C3CCCN3CC(O)CNC(c1ccccc1)c2ccccc2
EP-39	O=C2CCCN2CC(O)CNCCNc1ccccc1
EP-6	OC(CN1CCN(CC1)c2ccccc2)CN3CCCC3
EP-19	OC(CN1CCN(CC1)c2ccccc2OC)CN3CCCC3
EP-12	OC(CN1CCN(CC1)c2ncccn2)CN3CCCC3=O
EP-14	O=C4CCCN4CC(O)CN1CCN(CC1)C(c2ccccc2)c3ccccc3
EH-60	O=C1(N(CCC1C2(=CC=CC=C2))CC(O)CN4(CCN(C3(=CC=CC=C3))CC4))
EH-61	O=C1(N(CCC1(C2(=CC=CC=C2))C)CC(O)CN4(CCN(C3(=CC=CC=C3))CC4))
EH-62	O=C1(N(CCC1(C2(=CC=CC=C2))CC)CC(O)CN4(CCN(C3(=CC=CC=C3))CC4))
EH-63	O=C1(N(CCC1(C2(=CC=CC=C2))CCC)CC(O)CN4(CCN(C3(=CC=CC=C3))CC4))
EH-64	O=C1(N(CCC1(C2(=CC=CC=C2))C(C)C)CC(O)CN4(CCN(C3(=CC=CC=C3))CC4))
EP-67	O=C1(N(CCC1(C2(=CC=CC=C2))C3(=CC=CC=C3))CC(O)CN5(CCN(C4(=C(OC)C=CC=C4))CC5))
EP-68	FC(F)(F)C5(=C(N4(CCN(CC(O)CN3(C(=O)C(C1(=CC=CC=C1))(C2(=CC=CC=C2))CC3))CC4))C=CC=C5)
EP-69	O=C1(N(CCC1(C2(=CC=CC=C2))C3(=CC=CC=C3))CC(O)CN5(CCN(C4(=C(C=CC=C4)C))CC5))
EP-70	O=C1(N(CCC1(C2(=CC=CC=C2))C3(=CC=CC=C3))CC(O)CN5(CCN(C4(=C(OCC)C=CC=C4))CC5))
EP-71	O=C1(N(CCC1(C2(=CC=CC=C2))C3(=CC=CC=C3))CC(O)CN5(CCN(C4(=CC=CC=C4)CC5))
EP-72	FC5(=CC=C(N4(CCN(CC(O)CN3(C(=O)C(C1(=CC=CC=C1))

	(C2(=CC=CC=C2))CC3))CC4))C=C5)
EP-73	O=C1(N(CCC1(C2(=CC=CC=C2))C3(=CC=CC=C3))CC(O)CN5(CCN(C4(=CC=C(OC)C=C4))CC5))
EH-65	O=C1(N(CCC1C2(=CC=CC=C2))CC(O)CN4(CCC(C3(=CC=CC=C3))CC4))
EH-66	O=C1(N(CCC1(C2(=CC=CC=C2))C)CC(O)CN4(CCC(C3(=CC=CC=C3))CC4))
EH-67	O=C1(N(CCC1(C2(=CC=CC=C2))CC)CC(O)CN4(CCC(C3(=CC=CC=C3))CC4))
EH-68	O=C1(N(CCC1(C2(=CC=CC=C2))CCC)CC(O)CN4(CCC(C3(=CC=CC=C3))CC4))
EH-69	O=C1(N(CCC1(C2(=CC=CC=C2))C(C)C)CC(O)CN4(CCC(C3(=CC=CC=C3))CC4))
EP- 74	O=C1(N(CCC1)CC(O)CN3(CCC(C2(=CC=CC=C2))CC3))
EP- 75	O=C1(N(CCC1)CCCN3(CCC(C2(=CC=CC=C2))CC3))

Table 1. Chemical formula and symbols of pyrrolidin-2-one derivatives as SMILES codes.

The aim of this work is to analyze the relationship between molecular structure and anti-arrhythmic activity of pyrrolidin-2-one derivatives group using computational chemistry methods. The first stage of the calculation procedure was formulation of libraries of the analyzed chemical structures using the OSIRIS DataWarrior software [Sander et al. 2015]. One of the libraries' consist of the analyzed compounds, while the other anti-arrhythmic drugs. Then, for each of the analyzed structures, selected physicochemical and biological parameters of the tested compounds were determined using software: OSIRIS DataWarrior, admetSAR and Mollinspiration. Having the necessary data, a comparative analysis of the structures and applied anti-arrhythmic drugs towards potential therapeutic properties was made.

Historically, the first set of the most important parameters used to predict the utility of a given compound as a pharmacological agent, has been proposed by Lipinski. These principle is known as Rule of Five. According to this rule, the drug candidates should have a value equal to or a multiple of 5. Optimal properties and corresponding values are: number of active hydrogen atoms (HBD> 5), number of binding sites for hydrogen atoms (HBA> 10), logarithm of octanol / water partition coefficient (LogP <5)), molecular weight (MW <500DA). It is believed that molecules that do not meet two or more conditions of Lipinski's rule are "worse" drug candidates.

The second set of relevant parameters used to determine the "similarity" of drug structures was proposed by Veber. [Kerns, Di 2008]. He classifies the compound as similar to the drug by analyzing: molecular weight (MW), having a value less than 770 DA, sum of binding sites and active hydrogen atoms (HAD <12), number of rotatable bonds (RTB <10) and polar surface of the molecule (PSA <140 A).

In this study, the physicochemical parameters of N- (arylpiperazinylpropyl) -pyrrolidin-2-one derivatives and applied anti-arrhythmic drugs were determined using *in silico* calculation methods. Then a comparative analysis of the obtained parameters was performed. The results of the analysis are presented in Figure 2.

Results

The results of this study indicate that most of the tested compounds meet all the criteria Rule of Five. 34% of the 77 substances show deviations from the Lipinski's Rule. One group is characterized by a deviation from molar mass, the other one is deviation from the number of proton acceptors.

The first of the analyzed parameters is MW. The high molecular weight limits the administration of the substance in the form of an oral drug. Most oral medications have a MW <500 Da. In drug design practice, high molecular weight substances are considered as drugs for use on the

surface of the skin or in the form of injections. [Lipiński 2000]. The result of this investigation shows that only one of the compounds, i.e. EP-68, exceeds slightly the value of 500 Da. In the whole group of compounds, the molecular weight is in the range 248-524 Da.

The next analyzed parameter is LogP. The result in the research group shows that the range of changes in the LogP value ranges from -0.4 to 4.5. These results indicate high lipophilicity and probably high permeability of the test compounds through biological membranes. Analysis of all tested derivatives showed that the highest numerical value of LogP = 4.5 has structure EP-74. It can be predicted with a high probability that this derivative will best penetrate biological barriers.

The greatest deviation from the rule of five concerns the parameter determining the number of hydrogen bonds with acceptor character. From this data, we can see that the largest group of compounds (39%) are molecules with 5 proton acceptors. A high number of HBA usually determines possibility of attaching more molecules of water, which determines the hydrophilic nature of the molecule. However, too many hydrogen bond acceptor groups inhibit the permeability of the compound through biological membranes. A similar correlation occurs with the number of hydrogen bond donors. An excessive number of HBD limits the permeability of substances through the cell bilayer [Grabowski 2000]. It is worth emphasizing that the maximum number of HBDs was not exceeded among the tested compounds. It allows to predict that the majority of compounds (about 68%) will show high permeability through membranes.

An analogous analysis of the parameters set out in the Lipinski Rule was conducted for anti-arrhythmic drugs. There were no significant deviations from the Rule of Five. MW of Digoxin and Amiodarone is above 500 Da. Only one drug, i.e. amiodarone, exceeded the optimal LogP value. The most hydrophilic drug turned out to be Adenosine for which LogP value = -1.74.

The largest deviation, similarly as in the studied derivatives, concerned the number of hydrogen bond acceptors. Among the analyzed drugs, this scope ranged from 1 to 14. The number of hydrogen bond donors is from 0 to 6 and as in the case of the analyzed derivatives is within a fixed range. The drug that has the highest HBD value is digoxin marked in Fig. 2. B in blue.

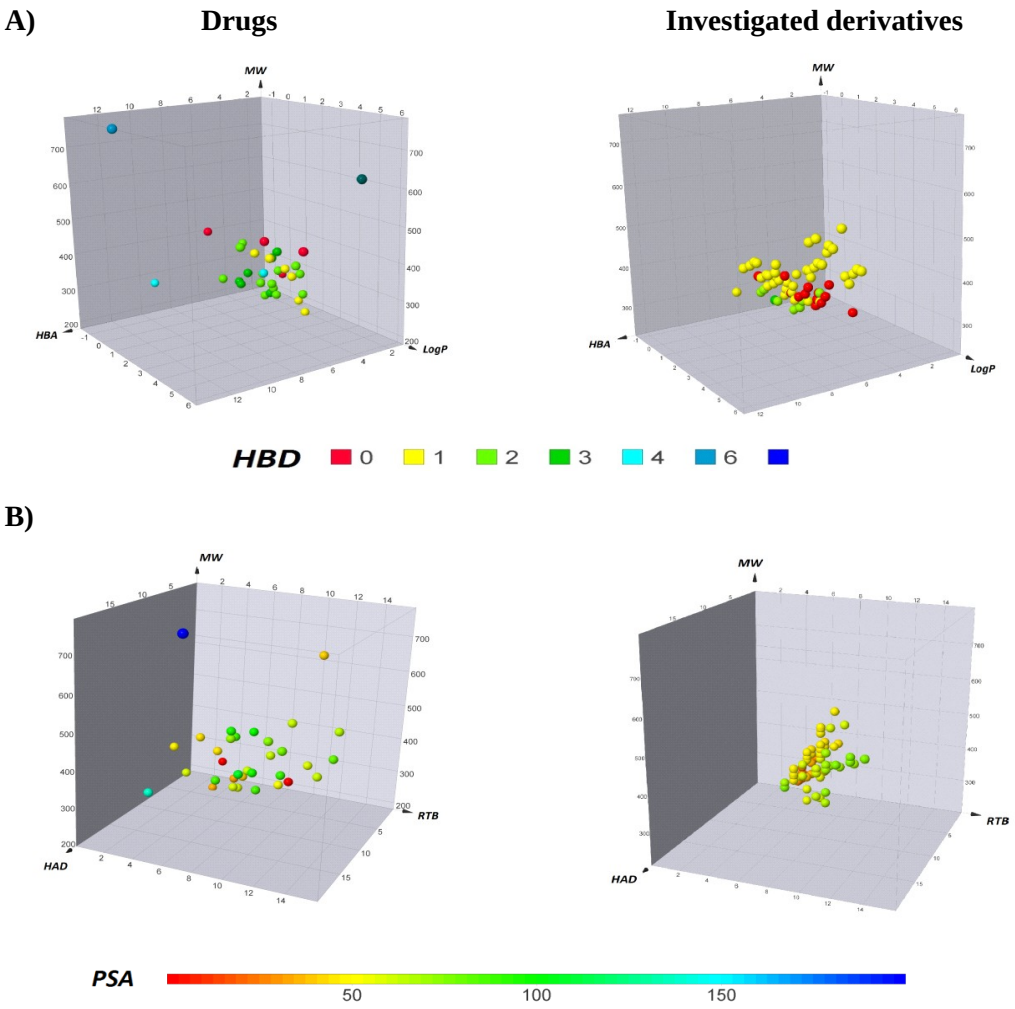

Figure 2. Lipinski (A) and Veber (B) parameters of the analyzed compounds.

When comparing the obtained results for arylpiperazine derivatives with data for antiarrhythmic drugs, it can be stated that the values of parameters included in Rule of Five in both groups are similar. These result suggest that the studied group of derivatives shows comparable physicochemical properties to the anti-arrhythmic drugs.

Analyzing the standards set by Veber, it was found that all tested structures have MW values and PSA (Polar Surface Area) below the established limit, which predisposes them to easy passive transport through biological membranes.

In the studied group of derivatives, the sum of acceptors and proton donors in the molecule takes a value lower than 12, which may suggest that the molecules will be able to overcome the biological membranes without any problems.

The parameter determining the number of rotational bonds turns out to be a good descriptor of oral bioavailability of drugs. This indicator is a measure of molecular flexibility. Compounds having a small number of such bonds are less "flexible" and thus usually easier to pass through membrane barriers. The data show that among the tested compounds only one of them has RTB greater than 10, ie **EP-29**.

The studies show that among the drugs used in arrhythmias, digoxin does not meet 3 Veber criteria: MW, PSA and HBD. Drugs such as ibutilide, verapamil, bisoprolol, propafenone, amiodarone, acebutalol, carvedilol, ivabradine do not meet the criterion concerning the number of rotational bonds.

Conclusions

Computational methods are necessary in the process of implementing a new drug on the market. They allow quick assessment of the physicochemical parameters of compounds and the comparison of their properties to already known drugs. Research into new drugs through the use of OSIRIS DataWarrior, admetSAR and Mollinspiration programs provide valuable information in the search for compounds with anti-arrhythmic activity.

Finally, in this study it was proved that the majority of tested derivatives meet the requirements proposed by Lipinski and Veber. These results suggest that the studied group of derivatives show comparable physicochemical properties to the anti-arrhythmic drugs used. Future studies on the current topic are therefore recommended.

References

[1] M. Nichols , N. Townsend, P. Scarborough , M. Rayner . 2014; Cardiovascular disease in Europe 2014: epidemiological update. *EUR HEART J*.;35(42):2950-9.

[2] S. Allender, P. Scarborough, V. Peto, M. Rayner, J. Leal, R. Luengo-Fernandez, i wsp., 2008, European cardiovascular disease statistics..

[3] W. Traczyk, A. Trzebski. Fizjologia człowieka z elementami fizjologii stosowanej i klnicznej. Warszawa: Wydawnictwo Lekarskie PZWL; 2007.

[4] B. Żuchowski, P. Guzik. Podstawy elektrofizjologii serca–nawrotny częstoskurcz węzłowy , 2012, Anestezjologia i Ratownictwo, 6: 212-220

[5] S. Polak, B. Wiśniowska, 2009, Modelowanie komputerowe w badaniach nad lekiem – projektowanie i poszukiwanie cząstki aktywnej, ocena właściwości fizykochemicznych oraz aktywności biologicznej, *Farm Pol*; 65 214 - 223.

[9]Haznar D., Garbacz D., Polak S., Czynniki fizjologiczne wpływające na biodostępność substancji leczniczej, *Farm Pol* 2011; 67 459 - 470.

[7] Kerns E., Di L., Rules for rapid property profiling from structure, Drug - like properties: concepts, structure design and methods: from ADME to toxicity optimization, Wydawnictwo Academic Press; Nowy Jork 2008; 4 37 – 42.

[8] Lipinski C., 2000, Drug-like properties and the causes of poor solubility and poor permeability. *J PHARMACOL TOXICOL*.;44(1):235-49.

[9] Grabowski T., Farmakokinetyka i Biofarmacja. 2000.

[10] Kulig K, Spieces C, Sapa J, Caspers C, Filipek B, Malawska B. Synthesis and pharmacological evaluation of pyrrolidin-2-one derivatives as antiarrhythmic, antihypertensive and α-adrenolytic agents. *PHARMACOL REP*. 2010;62(1):68-85.

[11] Sander T.*, Freyss J., von Korff M., and Rufener C., DataWarrior: An Open-Source Program For Chemistry Aware Data Visualization And Analysis, *J. Chem. Inf. Model.*, 2015, 55 (2): 460–473