Bulgarian Chemical Communications, Volume 51, Issue 1, (pp. 60 – 65) 2019

In silico investigation of the relation between calcium channel blockers' molecular descriptors and oral bioavailability data

J. V. Odović*

Department of Analytical Chemistry, Faculty of Pharmacy, University of Belgrade, Vojvode Stepe 450, Belgrade, Serbia

Received November 2, 2017; Accepted November 11, 2018

Calcium channel blockers are commonly prescribed antihypertensive drugs. In this study, nine calcium channel blockers (amlodipine, felodipine, isradipine, nicardipine, nifedipine, nimodipine, nisoldipine, verapamil and diltiazem) were investigated to evaluate the relationship between their molecular properties and oral bioavailability data collected from relevant literature. Several molecular descriptors of calcium channel blockers: lipophilicity descriptors, different log*P* values (Alog*Ps*, AClog*P*, AB/log*P*, milog*P*, Alog*P*, Mlog*P*, KOWWINlog*P*, XLOG*P*2, XLOG*P*3), aqueous solubility data (log*S*), electronic descriptor - polar surface area (PSA), constitutional parameter - molecular weight (Mw), geometric descriptor - volume value (Vol), acidity descriptor (pKa) were calculated using different software packages. The relationships between computed molecular descriptors and literature-obtained oral bioavailability data were firstly investigated using simple linear regression analysis showing relatively poor correlations with $R^2 < 0.6$. In continuation, multiple linear regression was applied to achieve higher correlation between calcium channel blockers' oral bioavailability and their molecular properties, on the first place lipophilicity and one additional, molecular descriptor. The best correlations were established between calcium channel blockers' oral bioavailability and their lipophilicity data (milog*P* or KOWWINlog*P*) with application of acidity descriptor as additional independent variable (R^2 = 0.783 and R^2 = 0.826). Application of computed molecular descriptors in evaluating drugs bioavailability was checked on three additional, fourth generation CCBs, cilnidipine, lacidipine, lercandipine.

Keywords: Calcium channel blockers, oral bioavailability, lipophilicity, acidity.

INTRODUCTION

High blood pressure, hypertension, is a world widespread disease. Typically, hypertension has no symptoms but it may have deadly consequences if not treated. Calcium channel blockers (CCBs) are among the most widely applied drugs in cardiovascular medicine. They can be applied not only in hypertension but also in angina pectoris, post-myocardial infarction, supraventricular dysrhythmias, hypertrophic cardiomyopathy [1-3].

According to their structural and functional distinctions CCBs can be subdivided in: dihydropyridine derivatives: amlodipine, felodipine, isradipine, lacidipine, lercanidipine, nicardipine, nifedipine, nisoldipine; phenylalkylamine: verapamil and benzothiazepine derivatives: diltiazem [1].

Drugs' clinical success mostly depends on their absorption, distribution, metabolism or route of elimination (ADME) [4]. A number of molecular physicochemical properties such as lipophilicity, acidity (pKa), molecular weight (Mw), molecular volume (Vol), polar surface area (PSA) or solubility data (logS), play important role in drugs absorption, penetration into tissues, degree of distribution, degree of plasma protein binding, activity and route of elimination [5-10].

Lipophilicity is one of the most significant physicochemical properties of biologically active molecules. Its importance in drug research is a consequence of hydrophobic interactions of the drugs with their biological targets, penetration across biological membranes during drug transport, as well as toxic aspects of drug action [4]. The lipophilicity influences drugs' absorption, distribution, binding to plasma proteins and elimination [7]. It can be characterized by the *n*-octanol/water partition coefficient (log$P_{O/W}$). The traditional technique for determination of selected molecule's lipophilicity, its log*P* value, is the so-called *shake flask* method [7]. Besides, different chromatographic techniques, high-performance liquid chromatography or thin-layer chromatography, are well known as methods that can yield significant amounts of retention data which can be correlated with physicochemical and biological properties, on the first place lipophilicity, for large sets of structurally different compounds. However, today, *in silico* obtained hydrophobicity parameters, calculated log*P* values, are generally accepted as a measure of drug's lipophilicity. Also numbers of other calculated molecular descriptors are applied in evaluation of different drugs' ADME properties [6 -10].

* To whom all correspondence should be sent:
E-mail: jodovic@pharmacy.bg.ac.rs

According to the available literature, a number of authors investigated antihypertensive drugs including those belonging to CCBs group, their design and synthesis [11,12] as well as pharmacokinetics, pharmacodynamics and efficacy [13-16].

In recently published papers acidity, lipophilicity, solubility or absorption were evaluated for a large group of antihypertensive drugs [17], as well as for selected ACE imhibitors [18] based on their molecular structure with application of computer programs. Also, in our previous papers the correlation between ACE inhibitors' lipophilicity, investigated using ultra-high performance liquid chromatography–tandem mass spectrometry and reversed-phase thin-layer chromatography, and oral absorption [19] as well as the effect of calcium channel blockers' molecular properties on their route of elimination [20] were studied. In continuation to these researches, the aim of this study was to investigate the correlation between oral bioavailability data of nine calcium channel blockers and their different molecular properties calculated using three different software packages [21-23]. The most suitable molecular descriptor should be established.

THEORETICAL

Investigated drugs

In this study nine most often prescribed calcium channel blockers were investigated:

1. Amlodipine - (3-ethyl 5-methyl2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydro-3,5-pyridinedicarboxylate);
2. Felodipine - (ethyl methyl 4-(2,3-dichlorophenyl)-2,6-dimethyl-1,4-dihydro-3,5-pyridinedicarboxylate);
3. Isradipine - (isopropyl methyl 4-(2,1,3-benzoxadiazol-4-yl)-2,6-dimethyl-1,4-dihydro-3,5-pyridinedicarboxylate);
4. Nicardipine - (2-[benzyl(methyl)amino] ethylmethyl2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydro-3,5-pyridinedicarboxylate);
5. Nifedipine = (dimethyl 2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydro-3,5-pyridinedicarboxylate);
6. Nimodipine - (isopropyl 2-methoxyethyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydro-3,5-pyridinedicarboxylate);
7. Nisoldipine - (isobutyl methyl 2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydro-3,5-pyridinedicarboxylate);
8. Verapamil - (2-(3,4-dimethoxyphenyl)-5-{[2-(3,4-dimethoxyphenyl)ethyl](methyl)amino}-2-isopropylpentanenitrile) and
9. Diltiazem - ((2S,3S)-5-[2-(dimethylamino) ethyl]-2-(4-methoxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl acetate).

Additionally, three CCBs of fourth generation: cilnidipine, lacidipine, lercandipine, were selected for testing the applicability of the correlation established in the first part of the study.

Calculations

The CCBs lipophilicity descriptors, nine different log*P* values (Alog*Ps*, AClog*P*, AB/log*P*, milog*P*, Alog*P*, Mlog*P*, KOWWINlog*P*, XLOG*P*2, XLOG*P*3), as well as their aqueous solubility data (log*S*) were calculated using the software package, Virtual Computational Chemistry Laboratory [21]. The software package Molinspiration Depiction Software (Molinspiration Cheminfirmatics) [22] was used for the calculation of several molecular descriptors, electronic descriptor - polar surface area (PSA); constitutional parameter - molecular weight (Mw) and geometric descriptor - volume value (Vol) while software package DrugBank [23] was used for the calculation of CCBs acidity descriptors pK_a values. The values of CCBs molecular descriptors, Mw, Vol and PSA were presented in our previous paper where the effect of calcium channel blockers' molecular properties on their route of elimination [20] was investigated, while selected lipophilicity descriptors (milog*P* and KOWWINlog*P*), as well as acidity descriptors, pKa values are presented in Table 1. The oral bioavailability data of the investigated CCBs (Table 2) were obtained from the relevant literature [1]. The statistical analysis of the regressions was performed using Microsoft Excel 2003 and Origin 7.0 PRO (Origin Lab Corporation, USA).

RESULTS AND DISCUSSION

The bioavailability is one of the most important pharmacologic properties in drug design and development. It is a subcategory of absorption and represents the fraction of drugs' administered dose that reaches the systemic circulation. High bioavailability reduces the amount of the administered drug necessary to achieve a desired pharmacological effect and consequently can reduce the risk of side-effects and toxicity. On the contrary, poor oral bioavailability can result in low efficacy and lead to unpredictable response to a drug.

Bioavailability for intravenously administered drugs is 100%. However, for orally administered drugs, bioavailability usually decreases due to incomplete absorption and first-pass metabolism, as well as due to high degree of plasma protein binding. Furthermore, drugs administration with or

without food also affects absorption. Concurrent intake of other drugs may alter absorption and first-pass metabolism, while intestinal motility alters the dissolution and may affect the degree of chemical degradation of the drug by intestinal microflora.

Drugs physical properties such as hydrophobicity, acidity, solubility, molecular mass, volume and polar surface area, as well as drugs formulation, age and gender of the patients or dosing scheme also exert important influence on drugs' BA. Drug's oral absorption and bioavailability, as well as duration of action or efficiency of its elimination is highly affected by its lipophilicity, acidity, solubility, molecular size and other molecular properties. The molecules with high lipophilicity show higher degree of oral absorption and bioavailability, better penetration into tissues and distribution compared to less lipophilic ones with similar properties [1-3,24,25].

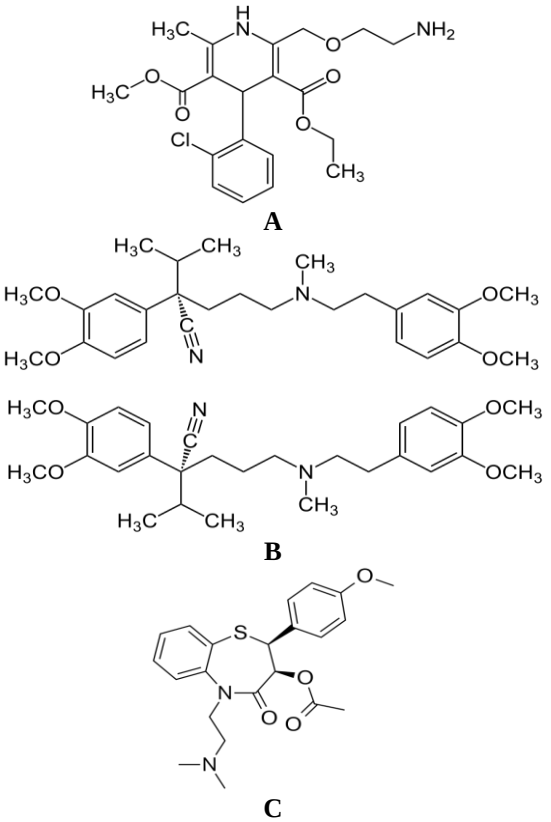

Figure 1. The structures of the CCBs representatives: **A)** Amlodipine; **B)** Verapamil; **C)** Diltiazem

According to the available literature, CCBs pharmacokinetics, pharmacodynamics and efficacy were investigated by a number of authors [13-16]. Still, most of these methods have certain limitations and a new approach for fast, reliable and cost-effective evaluation of CCBs oral bioavailability should be developed. Since drugs oral bioavailability importantly affects drugs activity, the application of computed molecular descriptors in prediction of drugs oral bioavailability is of great importance, especially for the newly synthesized drugs.

In this research nine CCBs (amlodipine, felodipine, isradipine, nicardipine, nifedipine, nimodipine, nisoldipine, verapamil and diltiazem) were studied in order to evaluate the correlation between their oral bioavailability data obtained from relevant literature and calculated molecular descriptors. The structures of the CCBs representatives: A) Amlodipine, dihydropyridine derivative; B) Verapamil, phenylalkylamine; and C) Diltiazem, benzothiazepine derivative are presented in Fig. 1.The main goal was to establish a high-throughput approach using simple or multiple linear regression analysis capable of predicting oral bioavailability data of selected CCBs. Several CCBs molecular descriptors (electronic descriptor – PSA, constitutional parameter – Mw, geometric descriptor – Vol, values, aqueous solubility data – logS and acidity descriptor – pKa), as well as a number of lipophilicity descriptors (Alog*Ps*, AClog*P*, AB/log*P*, milog*P*, Alog*P*, Mlog*P*, KOWWINlog*P*, XLOG*P*2, XLOG*P*3) were calculated using different software packages.

According to the data available from the literature, most of CCBs, with exception of amlodipine and nifedipine, have relatively low oral bioavailability because of extensive first-pass metabolism. Their oral bioavailability varies from 5% for nisoldipine, through 58% (45% to 70%) for nifedipine, to around 80% for amlodipine [1-3]. The CCBs selected molecular descriptors are presented in Table 1.

Table 1. Calculated molecular descriptors of investigated CCBs.

CCBs	milog*P*	KOWWINlog*P*	pKa
1.	2.58	2.07	8.79
2.	4.80	4.46	16.04
3.	3.81	3.49	16.14
4.	5.00	3.90	7.99
5.	3.07	2.50	15.92
6.	4.10	3.13	15.85
7.	4.19	3.90	15.93
8.	4.55	4.80	9.60
9.	3.34	2.79	8.37

The numbers denote CCBs.

The correlations between CCBs oral bioavailability data obtained from relevant literature and the calculated descriptors (PSA, Mw, Vol, pKa, log*P*, log*S*) were firstly investigated using simple linear regression. The relationships between CCBs oral bioavailability and the majority of their molecular descriptors, PSA, Mw, Vol, pKa,

log*P*, log*S*, provided correlations with coefficient R^2 lower than 0.40. Only for lipophilicity descriptors milog*P* and KOWWINlog*P* correlations with R^2=0.570 and R^2=0.542, respectively, were established.

Following, in the next stage of the study, the relationships between CCBs oral bioavailability data and two different CCBs molecular descriptors were investigated using multiple linear regression (MLR). The lipophilicity descriptors milog*P* or KOWWINlog*P* values were chosen as the first independent variable since they showed best correlations with CCBs oral bioavailability, while values of Mw, Vol, pKa and PSA were chosen as possible second independent variable. Values of aqueous solubility data, log*S* values, were not applicable as the second independent variable, since their relationships with milog*P* and KOWWINlog*P* values provide correlations with R^2 = 0.413 and R^2 = 0.385, respectively.

The MLR analyses with application of lipophilicity descriptor, KOWWINlog*P* and one additional calculated molecular descriptor, Mw, Vol or PSA, as independent variable provided correlations with coefficients (R^2) from 0.607 to 0.660 (R^2 = 0.607; R^2 = 0.618; R^2 = 0.660, respectively). Similar correlation with slightly lower coefficient, R^2 = 0.590 was obtained in MLR with application of milog*P* and PSA as independent variables while better correlations were achieved with application of milog*P* and Mw or Vol values as independent variables (R^2 = 0.725 and R^2 = 0.671, respectively).

However, the best correlations between CCBs bioavailability and calculated molecular descriptors, with acceptable correlation coefficients (R^2), as well as probability value ($P < 0.05$) were established using MLR analysis with application of lipophilicity descriptors, milog*P* or KOWWINlog*P* values and acidity descriptor, pKa as independent variables ((Eq. 1.) and (Eq. 2.)):

$$BA_{pred}(\%) = -20.972(\pm5.065)\text{milog}P - 3.112(\pm1,067)pK_a + 155.575(\pm23.544) \quad \text{Eq. 1.}$$

with n = 9; R^2 = 0.822; S.D. = 11.629; F = 13.881

$$BA_{pred}(\%) = -18.068(\pm5.051)\text{KOWWINlog}P - 3.036(\pm1.186)pK_a + 134.319(\pm22.292) \quad \text{Eq. 2.}$$

with n = 9; R^2 = 0.781; S.D. = 12.904; F = 10.711

The CCBs bioavailability data collected from relevant literature, as well as those predicted using MLR with application of computed lipophilicity descriptor, milog*P* or KOWWINlog*P* and acidity descriptor, pKa as independent variables are presented in Table 2 and in Figure 2.

The interrelationships between obtained BA data of calcium channel blockers investigated, those collected from relevant literature, predicted from milog*P* and pKa values and those predicted from KOWWINlog*P* and pKa values were studied. Obtained coefficients are presented in Table 3 and it can be seen that very good agreements were obtained between all three BA values.

Table 2. CCBs BA data collected from relevant literature (1); predicted from milog*P* and pKa values (2) and KOWWINlog*P* and pKa values (3).

CCBs	BA (1)	BA (2)	BA (3)
1.	77	74	70
2.	15	5	5
3.	20	25	22
4.	35	26	40
5.	58	42	41
6.	13	20	30
7.	5	18	15
8.	27	30	18
9.	50	60	58

(1) BA (%) data obtained from literature [1]. The numbers denote CCBs.

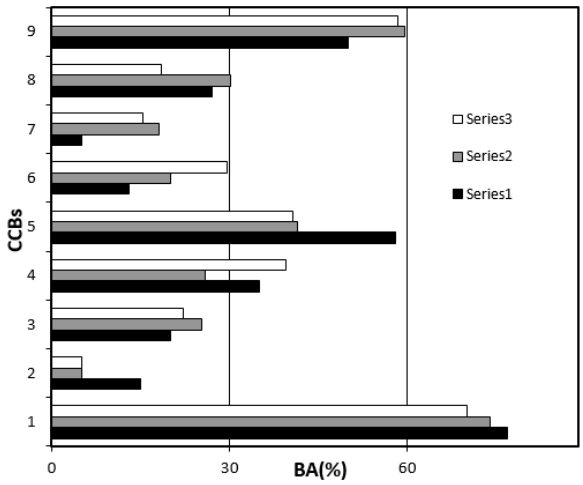

Figure 2. Relationship between CCBs bioavailability data collected from relevant literature and [1] *(Series 1)*; predicted using MLR with application of milog*P* and pKa values *(Series 2)* and KOWWINlog*P* and pKa values *(Series 3)*. The numbers denote CCBs.

Table 3. Interrelations between different BA data of calcium channel blockers investigated: those collected from relevant literature (1); predicted from milog*P* and pKa values (2) and KOWWINlog*P* and pKa values (3).

	BA (1)	BA (2)	BA (3)
BA (1)	1		
BA (2)	0.908	1	
BA (3)	0.884	0.935	1

Following, in the final stage of the study, the best established correlation obtained in MLR with application of milogP and pKa as independent

variables, was used to calculate the values of oral bioavailability for additional CCBs – nitrendipine, as well as three fourth-generation drugs: cilnidipine, lacidipine and lercandipine.

There are limited data available in the literature for these CCBs, showing relatively low values of their oral BA: for nitrendipine 10-23% and for lacidipine and lercandipine: 18.5% (range 4 to 52) and around 10%, respectively. The calculated pKa values for nitrendipine, cilnidipine, lacidipine and lercandipine were 15.88, 15.61; 16.12 and 8.64, respectively [23]. The values of their lipophilicity parameters, milogP, which provided best correlation, Eq.1, were 3.94, 5.72, 5.46 and 7.87, respectively [22] indicating large differences between nitrendipine (with milogP 3.94) and the very lipophilic CCBs of fourth generation.

Considering computed molecular descriptors and using MLR (Eq. 1) for nitrendipine as additional checking CCB, a value of 23% for oral BA was obtained, showing very good agreement between literature available and predicted oral BA data.

However, for selected CCBs of fourth generation, BA values around zero were calculated, indicating their low oral BA, but also their incompatibility with the established model (Eq 1). These results could be explained with their molecular properties. Namely, lercandipine is one of the CCBs with highest molecular weight (Mw = 612), volume value (575), lipophilicity (milogP = 7.87) and the lowest solubility (logS = -6.00). Cilnidipine and lacidipine also have very high lipophilicity (with milog P 5.72 and 5.46) and very low solubility, log*S* values (-4.99 and -4.67 respectively). Considering these values it can be seen that these three drugs, CCBs of fourth generation, are not in accordance with "Lipinski's rule of five" and they should not be considered in relationship between CCBs lipophilicity and oral BA data established for CCBs which belong to drugs of first to third generation.

The acceptable correlations that were found using MLR analyses between oral bioavailability of drugs belonging to first to third generation of CCBs data with application of their *in silico* obtained molecular descriptors – lipophilicity parameter (milog*P* and KOWWINlog*P*) and in the first place acidity descriptor (pK_a) and in addition constitutional descriptor - molecular weight (Mw) and geometric descriptor - volume value (Vol) confirmed descriptors calculations as a useful screening technique which is, however, not always capable of exact evaluation of oral bioavailability of compounds with some deviation in structure.

CONCLUSION

This study included nine often prescribed calcium channel blockers. The correlation between calcium channel blockers oral bioavailability data and different molecular descriptors was investigated. Relatively poor correlation was obtained between oral bioavailability data and calculated molecular descriptors using simple linear regression analysis ($R^2 < 0.4$). However, the application of two molecular descriptors milogP or KOWWINlog*P* values and Mw, Vol or pKa as independent variables in MLR analysis provided better correlations. The best correlations were established using MLR analysis with application of lipophilicity (milog*P* or KOWWINlog*P*) and acidity descriptor (pKa) as independent variable ($R^2 = 0.783$ and $R^2 = 0.826$, respectively). As a result, applicability of calculated molecular descriptors especially lipophilicity descriptors, milog*P* and KOWWINlog*P* and acidity descriptor, pKa, in CCBs oral bioavailability evaluation was established.

The proposed methodology and correlations that were found in the presented study confirmed that molecular properties, especially lipophilicity and acidity but also molecular weight and volume are essential for drugs oral bioavailability. Obtained correlations could be regarded as a new, additional, *in vitro* approach appropriate for evaluating oral bioavailability of the investigated group of calcium channel blockers. The application of computed molecular descriptors can be highly useful in drug research.

Acknowledgment: *This work was partly supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia as a part of Project TR34031.*

REFERENCES

1. T. L. Lemke, D.A. Williams (eds.), The Foye's Principles of Medicinal Chemistry, 7th edn., Lippincott Williams & Wilkins, Philadelphia, 2013.
2. H. P. Rang, J. M. Ritter, R. J. Flower, G. Henderson, Rang and Dale's Farmacology, 8th edn., Elsevier, Churchill Livingstone, 2012.
3. A. C. Moffat, M. D. Osselton, B. Widdop (eds.), Clarke's Analysis of Drugs and Poisons 4th edn., Pharmaceutical Press, London, 2011.
4. L. Di, E. H. Kernsy, *Curr. Opin. Chem. Biol.*, **7,** 402 (2003).
5. M. Remko, A. Remková, R. Broer, *Molecules*, **21** (185), 1 (2016).
6. Z. Mandić, **(**ed.) Physico-Chemical Methods in Drug Discovery and Development, IAPC Publishing, Zagreb, Croatia, 2012.

7. T. Hartmann, J. Schmitt, *Drug Discov. Today Techn*. **1**(4) 431 (2004)
8. A. T. Florence, D. Attwood, Physicochemical Principles of Pharmacy, 6th ed., Pharmaceutical Press, London, 2016.
9. Y. H. Zhao, J. Le, M. H. Abraham, A. Hersey, P. J. Eddershaw, C. N. Luscombe, D. Boutina, G. Beck, B. Sherbone, I. Cooper, J. A. Platts, *J. Pharm. Sci.*, **90**, 749 (2001).
10. Y. H. Zhao, M. H. Abraham, J. Le, A. Hersey, C. N. Luscombe, G. Beck, B. Sherborne, I. Cooper, *Pharmac. Res.*, **19,** 1446 (2002).
11. J. A. M. Christiaans, A. D. Windhorst, P. M. Groenenberg, H. Van der Goot, H. Timmerman, *Eur. J. Med. Chem.*, **28**, 859 (1993).
12. P. K. Kalavagunta, P. K. Bagul, A. Jallapally, S. Kantevari, S. K. Banerjee, N. Ravirala, *Eur. J. Med. Chem.*, **83,** 344 (2014).
13. E. D. Pozo, J.M. Baeyens, *Eur. J. Pharmacol*. **128**(1–2), 49 (1986).
14. L. Sepehr-Ara, S. A. Seyed Ahmad Mohajeri, M. Mahmoudian, *Pathophysiology*, **18(**3),175 (2011).
15. I. Whyte, N. Buckley, A. Dawson, *Medicine*, **40**, 112 (2012).
16. C. Mayama, *Eur. J. Pharmacol.* **739,** 96 (2014).
17. M. Remko, M. Swart, M. F. Bickelhaupt, *Bioorg. Med. Chem.* **14,** 1715 (2006).
18. M. Remko, *Chem. Papers*, **61**(2), 133 (2007).
19. J. V. Odovic, B. D. Markovic, R. D. Injac, S. M. Vladimirov, K. D. Karljikovic-Rajic, *J. Chromatogr. A.*, **1258**, 94 (2012).
20. J. Trbojević-Stanković, J. Odović, R. Jelić, D. Nešić, B.Stojimirović, *Arch. Biol. Sci.*, **67**(3), 801 (2015).
21. Tetko IV. Virtual Computational Chemistry Laboratory. Available from URL: http://vcclab.org (accessed on September 2017).
22. Molinspiration software or free molecular property calculation services. Available from URL: http://molinspiration.com (accessed on September 2017).
23. Program available online: http://drugbank.ca (accessed on September 2017).
24. C. A. Lipinski, *J. Pharmacol. Toxicol. Met.*, **44**, 235 (2000).
25. A. K. Ghose, V. N. Viswanadhan, J. J Wendoloski, *J. Combin. Chem.*, **1**, 55 (1999).
26. A. G. Asuero, A. Sayago, A. G. Gonzalez, *Crit. Rev. Anal. Chem.*, **36,** 41 (2006).