Arch Biol Sci. 2017;69(3):463-468 https://doi.org/10.2298/ABS160912121B

Estimation of plasma protein binding of selected antipsychotics using computed molecular properties

Jelena D. Berić[1], Ratomir M. Jelić[1], Dejan M. Nešić[2,*], Jasna B. Trbojević-Stanković[3] and Jadranka V. Odović[3]

[1] *Faculty of Medicinal Science, University of Kragujevac*, Kragujevac, Serbia

[2] *School of Medicine Institute of Medical Physiology, University of Belgrade*, Belgrade, Serbia

[3] *Department of Dialysis, Clinical Hospital Center "Dr Dragiša Mišović", School of Medicine, University of Belgrade*, Belgrade, Serbia

[4] *Faculty of Pharmacy, Department of Analytical Chemistry, University of Belgrade*, Belgrade, Serbia

***Corresponding author**: dejance@med.bg.ac.rs

Received: September 12, 2016; **Revised**: October 11, 2016; **Accepted**: October 12, 2016; **Published online**: November 4, 2016

Abstract: The plasma protein binding (PPB) data of twelve antipsychotics (aripiprazole, clozapine, olanzapine, quetiapine, risperidone, sertindole, ziprasidone, chlorpromazine, flupentixol, fluphenazine, haloperidol, zuclopenthixol) were estimated using computed molecular descriptors, which included the electronic descriptor – polar surface area (PSA), the constitutional parameter – molecular weight (Mw), the geometric descriptor – volume value (Vol), the lipophilicity descriptor (log*P*) and aqueous solubility data (log*S*), and the acidity descriptor (pK_a). The relationships between computed molecular properties of the selected antipsychotics and their PPB data were investigated by simple linear regression analysis. Low correlations were obtained between the PPB data of the antipsychotics and PSA, Mw, Vol, pKa, log*S* (R <0.30) values, while relatively higher correlations ($0.35<R^2<0.70$) were obtained for the majority of logP values. Multiple linear regression (MLR) analysis was applied to access reliable correlations of the PPB data of the antipsychotics and the computed molecular descriptors. Relationships with acceptable probability values ($P<0.05$) were established for five lipophilicity descriptors (logP values) with application of the acidity descriptor (pKa) as independent variables: AlogP (R^2=0.705), XlogP3 (R^2=0.679), ClogP (R^2=0.590), XlogP2 (R^2=0.567), as well as for the experimental lipophilicity parameter, logPexp (R^2=0.635). The best correlations obtained in MLR using AlogP and pKa as independent variables were checked using three additional antipsychotics: loxapine, sulpiride and amisulpride, with the PPB values of 97%, "less than" 40% and 17%, respectively. Their predicted PPB values were relatively close to the literature data. The proposed technique confirmed that lipophilicity, together with acidity significantly influences the PPB of antipsychotics. The described procedure can be regarded as an additional *in vitro* approach to the modeling of the investigated group of drugs.

Key words: antipsychotics; molecular descriptors; molecular properties; plasma protein binding

INTRODUCTION

Psychotic illnesses can be categorized into several mental disorders such as psychoses, neuroses and mood disorders. Antipsychotic drugs, which are historically known as antischizophrenic or neuroleptic drugs, are traditionally used in schizophrenia treatment [1-5]. Today, there are many antipsychotic drugs and new medical entities are continuously introduced into clinical practice. They can be classified into two main groups: the first group contains originally developed drugs. These are antipsychotics of the first generation. This group is known as typical antipsychotics [1-5]. The other group represents newly developed antipsychotics, which are are known as atypical or antipsychotics of the second generation [1-5].

Considering their mechanism of action, antipsychotic drugs are mostly dopamine receptor antagonists. However, they can affect other targets, including cholinergic, α adrenergic, histamine or serotonin receptors, which can increase their medical efficacy. With the aim of improving the quality of life of millions of patients, changes in the modes of application as well as the introduction of newly synthesized antipsychotic drugs has significantly increased in recent years [1-5].

The medical success or failure of drugs, their therapeutic effect, as well as side effects, are influenced by their pharmacokinetic properties, the absorption, distribution, metabolism, route of elimination (ADME criteria). Furthermore, a drug's *in vivo* efficiency is significantly influenced by its plasma protein binding (PPB). Once we understand these pharmacokinetic processes and include the obtained knowledge in the design and synthesis of new drugs, we will be able to significantly increase the drugs' therapeutic success and reduce their unwanted effects [6,7].

The physicochemical properties of molecules exert a considerable influence on the ADME properties of drugs. The molecular weight and volume, lipophilicity as well as solubility, followed by polar surface area (PSA) and acidity, significantly affect the drugs' absorption, distribution and penetration into tissues, PPB and route of elimination [8-11]. If more lipophilic molecules are to be compared with less lipophilic ones with similar properties, they will mostly show higher degrees of absorption and PPB, as well as better penetration into tissues and distribution. On the other hand, less lipophilic drugs are mostly eliminated in the urine, while highly lipophilic ones usually exhibit high degrees of fecal elimination. The lipophilicity effects agree with Lipinski's "rule of 5" [12]. This rule predicts that low absorption or permeation of a drug is more likely when the calculated lipophilicity descriptor is found to be greater than 5, and when the molecular weight is greater than 500, as well as when there are more than 5 hydrogen-bond donors and 10 hydrogen-bond acceptors in a drug molecule [12].

Many authors have studied this group of drugs. From the early years of their discovery and development to the present day, the design and synthesis, pharmacokinetics, pharmacodynamics and efficacy of antipsychotics have been examined [4,5,13-15].

In our previous research, we studied the relationships between PPB data (also including absorption and elimination) of selected antihypertensive drugs and their computed molecular descriptors, and established suitable models [16-21]. The aim of the present study was to evaluate the relationships between the PPB data of twelve selected antipsychotics and their computed molecular properties. By application of MLR, molecular descriptors which are most appropriate for estimating the antipsychotics' PPB were identified, and in the final stage of study, the best established model was checked on three additional drugs, loxapine, sulpiride and amisulpride.

MATERIALS AND METHODS

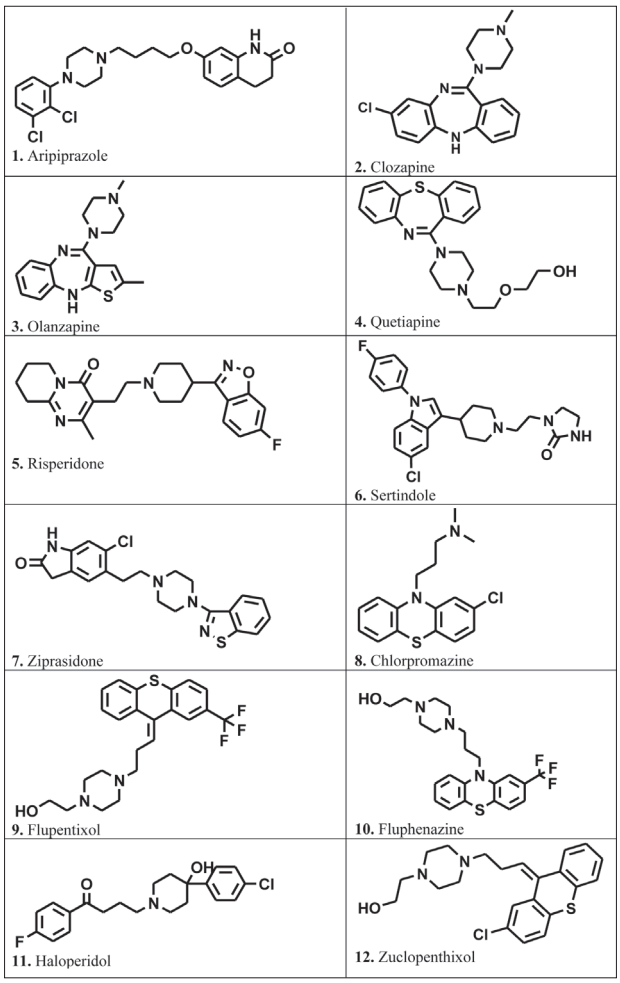
Calculation of the molecular descriptors and statistical analysis

Calculation of antipsychotics' molecular descriptors based on their molecular structures was performed using several software packages. The descriptors PSA, Mw and Vol were calculated with Molinspiration Depiction Software (www.molinspiration.com). The lipophilicity descriptors, seven different log*P* values (Alog*Ps,* AClog*P,* milog*P*, Alog*P,* Mlog*P,* XLOG*P*2, XLOG*P*3), and their aqueous solubility data (log*S*), were calculated using the software package Virtual Computational Chemistry Laboratory (www.vcclab.org). The calculation of another lipophilicity parameter, Clog*P* values, was performed with the ChemDraw ultra 12.0 software package. DrugBank (www.drugbank.ca) was used for calculation of the acidity descriptors (pK_a values). The PPB data, as well as values of the experimental lipophilicity parameters (logPexp) of the investigated drugs, were obtained using the DrugBank (www.drugbank.ca). Microsoft Excel 2003 was used for statistical analysis.

RESULTS AND DISCUSSION

For all investigated antipsychotics (Tables 1 and 2), different molecular descriptors (Table 3) were obtained. According to the available data, the selected drugs mostly have high and relatively similar values of PPB, ranging from 77% for risperidone to 99% for sertindole, ziprasidone, fluphenazine, zuclopenthixol, 100% for aripiprazole (Table 4) and 97%, <40% and 17%, for loxapine, sulpiride and amisulpride, respectively. In the preliminary investigation, the relationships between the drug PPB and all calculated molecular descriptors were investigated using simple linear regression. Low correlations with R^2<0.30 were obtained between the PPB values and the values of PSA, Mw, Vol, pKa and log*S,* while relatively higher correlations (0.35<R^2<0.70) were obtained for the majority of logP values.

Table 1. The structures of the investigated antipsychotics.



*ChemDraw ultra 12.0 software package

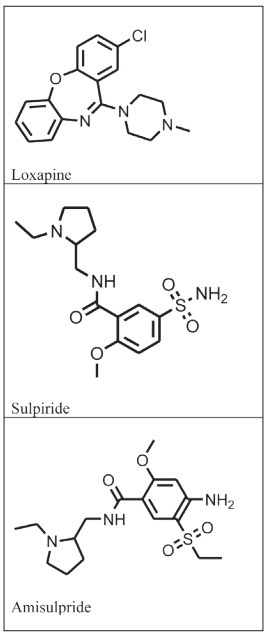
In the next stage of the study, relationships between the PPB and two different molecular descriptors were investigated by MLR. When the experimental lipophilicity parameters and additional molecular descriptors, Mw, Vol and pKa as independent variables, were used for PPB estimation, a relationship with an acceptable probability value of $P<0.05$ and $R^2=0.635$ was established only for logPexp values with the acidity descriptors (pKa) as the second variable (Eq. 1).

Eq.1:

$PPB_{pred}(\%)=6.158(\pm1.804)\ \log P\text{exp}-6.064(\pm2.581)\ pKa+118.263(\pm18.097)$,

with n=10; $R^2=0.635$; S.D.=5.041; F=6.103.

Table 2. The structures of loxapine, sulpiride and amisulpride.



*Chemdraw ultra 12.0 software package

Relationships with acceptable probability values ($P<0.05$) were established for the calculated lipophilicity descriptors, AlogP, XlogP3, ClogP and XlogP2, with application of pKa as follows: $R^2=0.705$; $R^2=0.679$; $R^2=0.590$ and $R^2=0.567$, respectively. The obtained correlations are presented by the following equations: Eq. 2; Eq. 3; Eq. 4; Eq. 5.

Eq.2:

$PPB_{pred}(\%)=9.904(\pm2.138)\ A\log P\text{-}4.165(1.936)\ pKa+83.358(\pm14.425)$,

where n=12; $R^2=0.705$; S.D.=4.212; F=10.766;

Eq.3:

$PPB_{pred}(\%)=7.178(\pm1.649)\ X\log P3\text{-}\ 5.108(\pm2.128)\ pKa+108.207(\pm15.002)$,

where n=12; $R^2=0.677$; S.D.=4.398; F=9.502;

Eq.4:

$PPB_{pred}(\%)=7.330(\pm2,040)\ C\log P\text{-}4.598(\pm2.275)\ pKa+100.816(\pm16.753)$,

where n=12; $R^2=0.590$; S.D.=4.966; F=6.484.

Eq.5:

PPB_{pred}(%)=8.434(±2.460) Xlog*P*2-5.267(±2.553) pKa+104.196(±17.285)

where n=12; R^2=0.567; S.D.=5.102; F=5.905.

The presented correlations can be considered as good [22]. The values of the antipsychotics' PPB predicted using the presented equations are shown in Table 4.

The ADME properties [23] and their PPB influence the *in vivo* efficacy of drugs. The main plasma-binding proteins are albumin, α_1-acid glycoprotein and lipoproteins. Drug molecules *in vivo* may be bound to proteins and lipids in the plasma, to proteins and lipids in tissues, or they can be free and diffuse in the aqueous environment of the blood and tissues [24-26]. The degree of drug affinity for plasma proteins considerably influences their distribution in target tissue, effectiveness, duration of action, elimination, and their therapeutic and side effects. Therefore, the estimation of drug PPB is of great importance for comprehending their pharmacokinetics and pharmacodynamics [24-26]. The collected descriptors play important roles in drug absorption, distribution, metabolism, elimination and PPB, with lipophilicity as one of the most important molecular properties that is responsible for a drug's increased absorption, penetration into tissues, higher degree of distribution and higher degree of PPB [9-12]. Several lipophilicity descriptors (Alog*Ps,* AClog*P,* milog*P*, Alog*P,* Mlog*P,* XLOG*P*2*,* XLOG*P*3, ClogP and logPexp) were obtained for the investigated group of drugs using several software packages that include different calculation methods. The differences between these methods resulted in distinctions between absolute logP values [27].

Table 3. Molecular descriptors of antipsychotics.

No	pKa	Mw	Vol	logPexp*	ClogP	Alog*P*	XLOG*P*2	XLOG*P*3
1.	7.46	448	395	4.50	4.63	5.00	4.49	4.64
2.	7.50	327	292	3.23	4.10	3.95	3.74	3.08
3.	7.24	312	286	2.00	3.40	3.21	2.32	2.86
4.	7.06	384	352	2.80	3.37	3.18	2.83	2.14
5.	8.76	410	374	2.50	2.71	3.32	3.07	2.72
6.	8.59	441	390	NA**	5.07	4.68	4.10	4.07
7.	7.09	413	352	3.80	3.58	4.26	3.77	4.02
8.	9.20	319	285	5.41	5.80	4.74	4.92	5.19
9.	8.51	435	379	4.51	4.34	4.82	4.42	4.51
10.	8.21	438	381	4.36	4.62	4.44	4.16	4.36
11.	8.05	376	337	4.30	3.85	3.89	3.98	3.23
12.	8.43	401	361	NA	4.13	4.54	4.12	4.31

Numbers denote the investigated antipsychotics as indicated in Table 1.
*Drug Bank: www.drugbank.ca.
**NA – not available.

Table 4. Drug PPB data (*) collected using the software package Drug Bank and values predicted using (1) logPexp and pKa; (2) AlogP and pKa; (3) XlogP3 and pKa; (4) ClogP and pKa; (5) XlogP2 and pKa.

	PPB (*)	PPB (1)	PPB (2)	PPB (3)	PPB (4)	PPB (5)
1.	100	101	105	103	100	103
2.	97	93	94	92	96	96
3.	93	87	88	92	92	86
4.	83	93	88	88	93	91
5.	77	81	83	83	80	84
6.	100	NA**	97	94	98	94
7.	99	99	99	101	94	99
8.	95	96	95	98	101	97
9.	95	94	99	97	93	97
10.	99	95	96	98	97	96
11.	95	96	91	90	92	95
12.	99	NA	96	96	92	95

The numbers denote the investigated drugs as indicated in Table 1.
**NA (logPexp was not available).

Regarding the importance of physicochemical properties, the relationships between the PPB and all calculated molecular descriptors were investigated by simple linear regression. Low correlations (R^2<0.30) were obtained between the PPB data and PSA, Mw, Vol, pKa and log*S* data*,* while relatively higher correlations were obtained for the logP values. The best correlations were obtained for the following parameters: AlogPs (R^2=0.69), AlogP (R^2=0.55), milogP (R^2=0.49), XlogP3 (R^2=0.47) and ClogP (R^2=0.42). For XlogP2 and logPexp values, the coefficients R^2 were 0.36 and 0.35, respectively, while AClogP and MlogP provided correlations with R^2<0.20.

Using MLR, all collected lipophilicity descriptors were tested as the first independent variable. Mw, Vol and pKa were chosen as the second independent variable values, while the values of PSA and log*S* could not be used since their relationships with log*P* provided correlations with R^2>0.30. It was observed that two lipophilicity parameters, MlogP and AClogP, were exceptions since they could not be used with pKa as the second independent variable since their correlation with R^2 was about 0.50. Moreover, these two lipophilicity descriptors with additional molecular descriptors, Mw and Vol, provided low correlations with R^2<0.40.

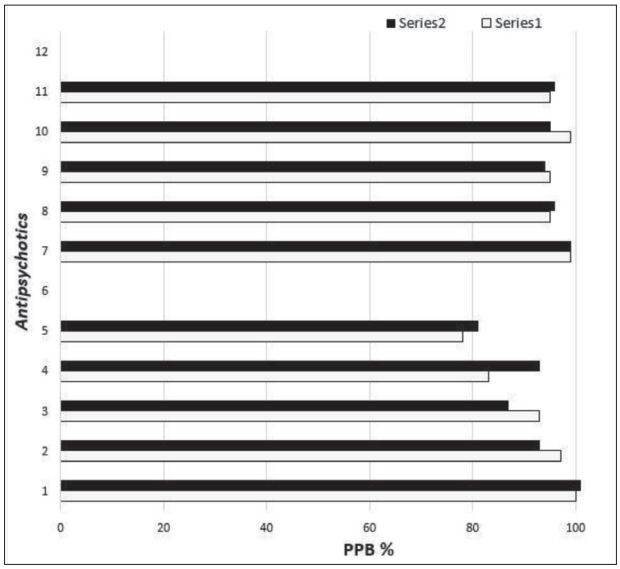


Fig. 1. Relationships between PPB data of antipsychotics collected using the software package Drug Bank (Series 1) and values predicted using logPexp and pKa (Series 1). The numbers denote the investigated antipsychotics, as indicated in Table 1.

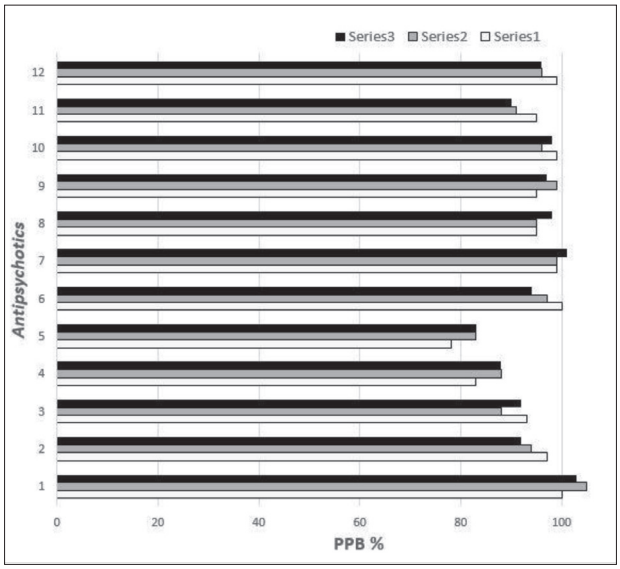


Fig. 2. Relationships between the PPB data data of antipsychotics collected using the software package Drug Bank (Series 1) and values predicted using AlogP and pKa (Series 2), and XlogP3 and pKa (Series 3). The numbers denote the investigated antipsychotics, as indicated in Table 1.

Application of other seven lipophilicity descriptors (logPexp and 6 calculated descriptors, Alog*Ps,* milog*P*, Alog*P,* XLOG*P*2*,* XLOG*P*3 and ClogP), with the additional molecular descriptors (molecular weight, volume or acidity as independent variables) in MLR provided correlations with R^2>0.55. However, using MLR, the relationships with acceptable probability values (P<0.05) were established for the experimental lipophilicity parameter, logPexp (R^2=0.635), as well as for four calculated lipophilicity descriptors (logP values) with the application of the acidity descriptor, pKa, as the second independent variable; AlogP (R^2=0.705), XlogP3 (R^2=0.679), ClogP (R^2=0.590), XlogP2 (R^2=0.567) was noted. All obtained correlations can be considered as good, with acceptable P values [22].

The best established correlations were obtained with Eq.1; Eq.2 and Eq.3 by MLR analysis with logPexp, AlogP or XlogP3 and pKa as independent variables, and are presented in Figs. 1 and 2. The relationships between the degree of PPB obtained with the software package Drug Bank and those predicted using logPexp and pKa are presented in Fig. 1. Since for sertindole and zuclopenthixol the values of logPexp were not available [24], their PPB values could not be predicted using Eq.1 and consequently they are not presented on Fig 1.

The relationships between PPB obtained with the software package [24] and those predicted using AlogP or XlogP3 and pKa as independent variables are presented in Fig 2. The best established correlation (Eq.2) obtained using AlogP and pKa as independent variables was checked using three additional antipsychotics: the typical antipsychotic loxapine and two atypical antipsychotics, sulpiride and amisulpride. Their PPB values in the literature are 97%, <40% and 17%, respectively. These values were out of the 77%-100% range where the values for PPB modelling belong. Their pKa values were 7.18, 9.12 and 9.37, respectively [24]. The values of their lipophilicity parameter AlogP, which provided the best model (Eq.2), were 3.96; 0.83 and 1.13, respectively [23]. The correlation presented can be considered as suitable for PPB prediction of antipsychotics since the predicted PPB values were relatively close to the literature data for loxapine (93%), sulpiride (26%) and amisulpride (27%).

The correlations between antipsychotics' PPBD and their molecular descriptors, lipophilicity parameters (logPexp, Alog*P,* XLOG*P*2*,* XLOG*P*3 and ClogP) and the acidity descriptor (pKa) as independent variables determined by MLR, confirmed that the proposed *in silico* technique can be considered a high-throughput screening approach for estimating PPB.

The important role of lipophilicity and acidity may be a consequence of drug interactions during transport to their biological targets and their interactions with their receptors. The proposed methodology, which established lipophilicity and acidity as essential for the PPB of antipsychotic drugs, can be considered as an innovative approach for investigating the degree of PPB of antipsychotic drugs.

Acknowledgments: This work was partly supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia as part of Project 172016.

Authors' contribution: Jelena Berić, Jadranka Odović and Ratomir Jelić were responsible for the study conception and design and the drafting of the manuscript. Jelena Berić and Dejan Nešić collected the literature. Jadranka Odović and Jelena Berić provided statistical expertise. Jadranka Odović and Ratomir Jelić made critical revisions to the paper.

REFERENCES

1. Lemke TL, Williams DA.The Foye's Principles of Medicinal Chemistry, 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2013. 1377 p.
2. Moffat AC, Osselton MD, Widdop B. Clarke's Analysis of Drugs and Poisons. 4th ed. London: Pharmaceutical Press; 2011. 1500 p.
3. Rang HP, Ritter JM, Flower RJ, Henderson G. Rang and Dale's Farmacology. 8th ed. Churchill Livingstone: Elsevier; 2012. 625 p.
4. Jašović Gašić M, Vuković O, Pantović M, Cvetić T, Marić Bojović N. Antipsychotics – History of development and field of indication, new wine – old glasses. Psychiatr Danub. 2012;24(Suppl. 3):342-4.
5. Seeman P, Lee T. Antipsychotic drugs: direct correlation between clinical potency and presynaptic action on dopamine neurons. Science. 1975;188(4194):1217-9.
6. Di L, Kernsy EH. Profiling drug – like properties in discovery research. Curr Opin Chem Biol. 2003;7:402-8.
7. Brunton LL, Chabner BA, Knollmann BC. Goodman and Gilman's: The Pharmacological Basis of Therapeutics. 12th ed. New York: The McGraw-Hill Companies, Inc.; 2011. 2084 p.
8. Hartmann T, Schmitt J. Lipophilicity – beyond octanol/water: a short comparison of modern technologies. Drug Discov Today Techn. 2004;1(4):431-9.
9. Remko M, Swart M, Bickelhaupt MF. Theoretical study of structure, pKa, lipophilicity, solubility, absorption and polar surface area of some centrally acting antihypertensives. Bioorg Med Chem. 2006;14:1715-28.
10. Remko M. Acidity, lipophilicity, solubility, absorption, and polar surface area of some ACE inhibitors. Chem. Pap. 2007;61(2):133-41.
11. Zhao YH, Le J, Abraham MH, Hersey A, Eddershaw PJ, Luscombe CN, Boutina D, Beck G, Sherbone B, Cooper I, Platts JA. Evaluation of human intestinal absorption data and subsequent derivation of a quantitative structure-activity relationship (QSAR) with the Abraham descriptors. J Pharm Sci. 2001;90:749-84.
12. Lipinski CA. Drug-like properties and the causes of poor solubility and poor permeability. J Pharmacol Toxicol Met. 2000;44:235-49.
13. Reddy VP, Kozielska M, Suleiman AA, Johnson M, Vermeulen A, Liu J, Greef R, Groothuis GMM, Danhof M, Proost JH. Pharmacokinetic-pharmacodynamic modelling of antipsychotic drugs in patients with schizophrenia: Part II: The use of subscales of the PANSS score. Schizophr Res. 2013;144:153-61.
14. Mauri MC, Volonteri LS, Colasanti A, Fiorentini A, De Gaspari IF, Bereggi SR. Clinical pharmacokinetics of atypical antipsychotics: a critical review of the relationship between plasma concentrations and clinical response. Clin Pharmacokinet. 2007;46(5):359-88.
15. Mauri MC, Paletta S, Maffini M, Colasanti A, Dragogna F, Di Pace C, Altamura AC. Clinical pharmacology of atypical antipsychotics: an update. EXCLI Journal. 2014;13:1163-91.
16. Odovic J, Trbojevic-Stankovic J. Correlation between Angiotensin-converting enzyme inhibitors lipophilicity and protein binding data. Acta Medica Medianae. 2012;51(4):13-8.
17. Trbojević J, Jelić M, Trbojević-Stanković J, Nešić D, Odović J. The estimation of relationship between calcium channel blockers' molecular properties and plasma protein binding data. Arch Biol Sci. 2016;DOI:10.2298/ABS160609094O.
18. Odović J, Trbojević-Stanković J. In silico evaluation of angiotensin II receptor antagonist's plasma protein binding using computed molecular descriptors. Acta Medica Medianae. 2014;53(1):19-24.
19. Odovic J, Markovic B, Vladimirov S, Karljikovic-Rajic K. In Vitro modeling of angiotensin-converting enzyme inhibitor's absorption with chromatographic retention data and selected molecular descriptors. J Chromatogr B. 2014;953:102-7.
20. Trbojević J, Odović J, Trbojević-Stanković J, Nešić D, Jelić R. The relationship between angiotensin II receptor antagonists' bioavailability and molecular properties. Arch Biol Sci. 2016;68(2):273-8.
21. Trbojević - Stanković J, Odović J, Jelić R, Nešić D, Stojimirović B. The influence of certain molecular descriptors of fecal elimination of angiotensin II receptor antagonists. Arch Biol Sci. 2015;67(1):103-9.
22. Asuero AG, Sayago A, Gonzalez AG. The correlation coefficient: An overview. Crit Rev Anal Chem. 2006;36:41-59.
23. Kaitin KI. Obstacles and opportunities in new drug development. Clin Pharmacol Ther. 2008;83:210-2.
24. Mahanthappa M, Gowda BG, Gowda JI, Rengaswamy R. Spectroscopic, voltammetry and molecular docking study of binding interaction of antipsychotic drug with bovine serum albumin. J Electrochem Sci Eng. 2016;6(2):155-64.
25. Mannens G, Meuldermans W, Snoeck E, Heykants J. Plasma protein binding of risperidone and its distribution in blood. Psychopharmacology. 1994;114(4):566-72.
26. Stojanović S, Janković S, Matović Z, Jakovljević I, Jelić R. Interaction between tigecycline and human serum albumin in aqueous solution. Monatsh Chem. 2015;146:399-409.
27. Mannhold R, Poda GI, Tetko I. Calculation of molecular lipophilicity: state-of-the-art and comparison of log *P* methods on more than 96,000 compounds. J Pharm Sci. 2009;98:861-93.