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IN SILICO EVALUATION OF ANGIOTENSIN II RECEPTOR ANTAGONIST'S PLASMA PROTEIN BINDING USING COMPUTED MOLECULAR DESCRIPTORS

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The discovery of new pharmacologically active substances and drugs modeling led to necessity of predicting drugs properties and its ADME data. Angiotensin II receptor antagonists are a group of pharmaceuticals which modulate the renin-angiotensin-aldosterone system and today represent the most commonly prescribed anti-hypertensive drugs. The aim of this study was to compare different molecular properties of seven angiotensin II receptor antagonists / blockers (ARBs), (eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan) and their plasma protein binding (PPB) data. Several ARBs molecular descriptors were calculated using software package Molinspiration Depiction Software as well as Virtual Computational Chemistry Laboratory (electronic descriptor – PSA, constitutional parameter – Mw, geometric descriptor – Vol, lipophilicity descriptors - logP values, aqueous solubility data – logS). The correlations between all collected descriptors and plasma protein binding data obtained from relevant literature were established. In the simple linear regression poor correlations were obtained in relationships between PPB data and all calculated molecular descriptors. In the next stage of the study multiple linear regression (MLR) was used for correlation of PPB data with two different descriptors as independent variables. The best correlation (R^2=0.70 with $P<0.05$) was established between PPB data and molecular weight with addition of volume values as independent variables. The possible application of computed molecular descriptors in drugs protein binding evaluation can be of great importance in drug research. *Acta Medica Medianae 2014;53(1):19-24.*

Key words: *molecular descriptor, angiotensin II receptor antagonists, plasma protein binding*

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Introduction

Fast and reliable evaluation of drug's properties, absorption, distribution, metabolism and elimination (ADME) has been recognized as critical in accelerating of drug discovery process and clinical success of drug candidates (1).

The number of molecular physicochemical properties may significantly influence drugs ADME properties. Lipophilicity, solubility, molecular weight, volume of drug's molecule, polar surface area, play important role in drugs absorption, penetration into tissues and degree of distribution as well as degree of plasma protein binding (PPB) (2-5).

The drug's plasma protein binding (PPB) degree significantly influences its in vivo efficiency. Drug molecules in vivo are either bound to proteins and lipids in plasma (termed plasma protein binding (PPB)), to proteins and lipids in tissues, or are free (unbound) and diffuse among the aqueous environment of the blood and tissues. Depending on a specific affinity for plasma protein, a portion of the bound and unbound drug may differ. In most cases, only free drug molecules interact with the therapeutic target, a receptor, to produce efficacy. Also, free drug's fraction is the one that can be metabolized and excreted. One of the advantages of drug's modeling is the finding of an optimum drug's PPB range (6,7).

Angiotensin II receptor antagonists, also known as angiotensin receptor blockers (ARBs), AT1-receptor antagonists or sartans, are a group of pharmaceuticals which modulate the renin-angiotensin-aldosterone system. They were introduced in clinical practice three decades ago and today represent the most commonly prescribed antihypertensive drugs (6,8,9). Their main uses are in the treatment of hypertension, diabetic nephropathy and congestive heart failure. They have been shown to reduce proteinuria in

diabetic nephropathy and hospitalization and mortality rate in heart failure patients (6,8,9). ARBs may be used instead of an angiotensin-converting enzyme (ACE) inhibitors in patients not able to tolerate certain side effects of an ACE inhibitor, such as persistent cough. ARBs are well tolerated by most individuals. The most common side effects are cough, hyperkalemia, hypotension, dizziness, headache, drowsiness, diarrhea, abnormal taste sensation and rash. Compared to ACE inhibitors, cough occurs less often with ARBs. Contra-indications for their use are pregnancy and bilateral renal artery stenosis (6,8-10).

Various ARBs are similar in actions and side effects. Candesartan Cilexetil, Olmesartan Medoxomil and Losartan differ from the other compounds in several respects. They are only compounds with active metabolites, and they have the highest renal elimination (around 35%) of all the agents. The ARBs plasma protein binding values are relatively similar and range from 95 to 100%.

According to the available literature, a number of authors investigated pharmacological properties of drugs from ARBs group as well as their similarities and differences (11-13). Also, the number antihypertensive drug's acidity, lipophilicity, solubility or absorption were theoretically considered by the use of computer programs based on their molecular structure (3-5).

In our previous studies, the lipophilicity of several ACE inhibitors examined under different chromatographic conditions (14-16) was correlated with ACE inhibitors in silico lipophilicity data. Also, in recently published papers, ACE inhibitors lipophilicity data were correlated in MLR analysis (with addition of different molecular descriptors as independent variables) with their absorption (17) as well as PPB data (18). Continuing these researches, the aim of the present study was to compare different molecular descriptors of seven ARBs (eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan) and their plasma protein binding (PPB) data.

Material and methods

Materials

This study included seven most often prescribed ARBs: 1. candesartan, 2. eprosartan, 3. irbesartan, 4. losartan, 5. olmesartan, 6. telmisartan and 7. valsartan (Figure 1).

Methods

The PPB data of examined ARBs were obtained from the relevant literature (6). The software package Molinspiration Depiction Software (Molinspiration Cheminfirmatics) (19) was used for the calculation of electronic descriptor-polar surface area (PSA); constitutional parameter - molecular weight (Mw); geometric descriptor - volume value (Vol). Another software package, Virtual Computational Chemistry Laboratory (20) was used to calculate ARBs lipophilicity descriptors, different logP values (AlogPs, AClogP, AB/logP, MilogP, AlogP, MlogP, KOWWIN logP, XLOGP2, XLOGP3), as well as their aqueous solubility data (logS).

The Microsoft Excel 2003 and Origin 7.0 PRO (Origin Lab Corporation, USA) were used to perform the statistical analysis of the regression.

Results

In this research seven ARBs - candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan and valsartan (Figure 1) were studied in order to evaluate the correlation between their PPB data collected from relevant literature and calculated molecular descriptors.

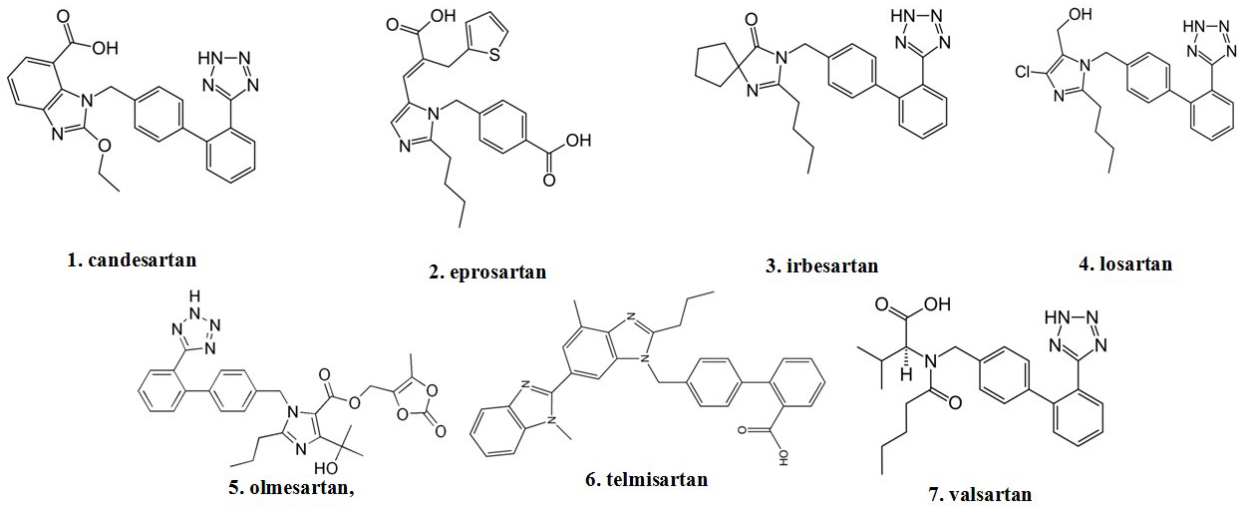

Figure 1. The chemical structures of the investigated ARBs

The ARBs molecular descriptors (logP, logS, PSA, Vol, Mw) were calculated using the software package Molinspiration Depiction Software and Virtual Computational Chemistry Laboratory. All calculated descriptors, electronic descriptor – PSA, constitutional parameter – Mw, geometric descriptor – Vol, lipophilicity descriptors - logP values, as well as aqueous solubility data – logS, play important role in drugs PPB and may significantly influence ARBs properties.

The nine different logP values (AlogPs, AClogP, AB/logP, MilogP, AlogP, MlogP, KOWWIN logP, XLOGP2, XLOGP3) as lipophilicity descriptors of seven investigated ARBs were calculated using different software packages (19,20). According to Mannhold et al., the methods applied for logP calculation can be classified as: substructure-based and property-based methods (21). Additionally, substructure-based methods can be divided into: fragmental and atom-based methods.

The fragmental methods cut molecules into different fragments with application of correction factors. The final logP value (KOWWINlogP, ClogP, MilogP, etc) is the result of all fragment contributions summing. The atom-based method cut molecules down to the single atoms and commonly does not apply corrections. Several logP values (AlogP, XlogP2, XlogP3, etc) can be calculated using the atom-based method (21).

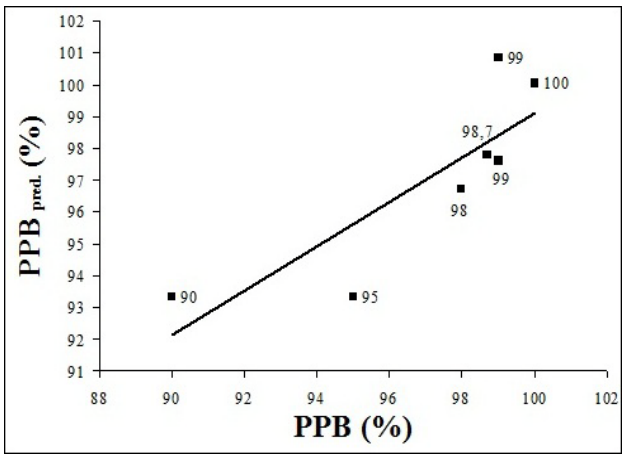

Figure 2. The relationship between ARBs literature available PPB data (6) and predicted PPB_{pred} data (using molecular weight, Mw and volume values, Vol) (R^2 =0.7039)

The second, property-based methods employ the description of the entire molecules and include: methods based on topological descriptors, empirical or methods based on molecule's 3D-structure (AlogPs) (21).

The differences between all presented calculation methods result in distinctions in absolute obtained logP values.

The PPB data of examined ARBs and their calculated molecular descriptors (logS, PSA, Vol, Mw) as well as selected logP data calculated using different methods are presented in Table 1.

The relationships between all collected descriptors and plasma protein binding data obtained from relevant literature were examined. The poor correlations obtained using simple linear regression indicated the necessity of MLR with application of two different descriptors as independent variables. The best correlation was established between PPB data and molecular weight with addition of volume values as independent variables. From regression parameters obtained in this correlation, predicted PPB data were calculated. The correlation between predicted and literature available PPB data for ARBs is presented in Figure 2.

Discussion

The main topic of this study was to establish a high throughput approach using simple or multiple linear regression (MLR) analysis capable for PPB prediction of selected ARBs as well as the new synthesized drugs.

In the first stage of study, the correlations between all collected descriptors and plasma protein binding data obtained from relevant literature were investigated by the use of simple linear regression. Since applied software packages (19,20) could calculate nine different lipophilicity descriptors, logP values, relationships between all calculated logP values and PPB data were examined. Very poor correlations (R^2<0.20) were obtained in all relationships. For relationship between Mw and PPB data, the correlation with R^2 value of 0.172 was observed, while for PPB data and calculated logP values even lower correlations were obtained (R^2<0.10). In addition, relationships between PPB data and logS values, Vol or PSA provide correlations with R^2<0.03.

Table 1. PPB data and calculated molecular descriptors of investigated ARBs

Compound	1	2	3	4	5	6	7
PPB %[a]	99.0	98.0	90.0	98.7	99.0	100.0	95.0
KOWWIN	4.79	6.37	5.31	4.01	3.63	8.42	3.65
AlogP	4.60	4.78	4.93	4.89	4.18	7.77	4.62
Alog*Ps*	4.02	3.57	4.51	4.50	3.35	6.66	3.68
log*S*	-5.30	-3.60	-5.28	-4.63	-4.68	-5.72	-4.86
Mw	440.46	424.52	428.54	422.92	446.51	514.63	435.53
Volume	382.14	380.77	400.20	374.12	403.61	475.76	408.69
T PSA	118.83	92.42	87.14	92.52	129.82	72.95	112.08

[a] literature data (6)

The poor correlations obtained in simple linear regression between all five calculated descriptor and PPB data indicated the necessity for MLR, applying two different descriptors as independent variable, probably due to the influence of several molecule properties on ARBs PPB.

In the final stage of this study, MLR was used for the correlation of PPB data with two different descriptors as independent variables. All possible correlations were examined. In all examined relations, established correlation coefficients, probability values (P) and F values were considered. The majority of relationships provide poor correlation coefficients (R^2 lower than 0.40) with P values much higher than 0.05 and with unacceptable F values.

However, a very good correlation (R^2=0.70 with P<0.05) was established by MLR between PPB data and Mw with addition of Vol as independent variables (Figure 2). The values of predicted PPB were calculated according to presented equations:

PPB_{pred} (%) = 0.2807 (±0.0927) Mw + 0.2310 (±0.0862) Vol + 65.5290 (±13.9569) ...(1)

with n=7, R^2=0.7039, S.D.=2.3377, F=4.7537

The correlation presented can be considered as good, as it was proposed (R^2 from 0.49 to 0.79) in literature (22), with acceptable P values as well as F values.

In our recently published paper (18) for group of angiotensin-converting enzyme (ACE) inhibitors, the good correlation (R^2=0.7520) was established between protein binding values and their KOWWIN logP data. The good correla-tion which was found between ARBs plasma protein binding values and in silico molecular descriptors - constitutional parameter, Mw and geometric descriptor, Vol confirmed that all physicochemical molecular properties have significant influence on drugs PPB and could play important role in clinical success of drugs candidates. Lipinski et al. also noted the rise in complexity and size of the average drug molecule, resulting in non-deliverable agents (23). The increased size, high log P values or low water solubility led to higher protein binding, and higher probability of being rapidly cleared metabolically or via biliary excretion (24).

Since high protein binding degree may cause decrease of drugs action and activity, the application of computed molecular descriptors in drugs protein binding prediction can be of great importance especially at new synthesized drugs investigations, aiming at patient's benefits. The calculation of drugs molecular descriptors could be considered as high-throughput screening technique for evaluation of selected compounds protein binding degree - one quarter of respondents (25,8%) believe that people with epilepsy see themselves as less valuable compared to others, and one-fifth of respondents think that patients with epilepsy are stigmatized in our community.

Conclusion

The discovery of new pharmacologically active substances and drugs modeling led to necessity of predicting drugs properties and its ADME data. This study included the seven most often prescribed ARBs. Five different ARBs molecular descriptors were determined using software packages. The correlations between ARBs calculated molecular descriptors and their plasma protein binding data obtained from relevant literature were examined. In simple linear regression, very poor correlations were obtained in relationships between PPB data and all calculated molecular descriptors logP values, log*S* values, Vol, Mw and PSA indicated the necessity for MLR applying two different descriptors as independent variable. The best correlation was established between PPB data and molecular weight with addition of volume values as independent variables. The possible application of computed molecular descriptors in drugs protein binding evaluation can be of great importance in drug research.

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References

1. Di L, Kernsy EH. Profiling drug - like properties in discovery research. Curr Opin Chem Biol 2003; 7:402-8. [CrossRef] [PubMed]
2. Hartmann T, Schmitt J. Lipophilicity – beyond octanol/water: a short comparison of modern technologies. Drug Discov Today Technol 2004; 1(4):431-9. [CrossRef]
3. Remko M. Acidity, lipophilicity, solubility, absorption, and polar surface area of some ACE inhibitors. Chem Pap 2007; 61(2):133-41. [CrossRef]
4. Remko M, Swart M, Bickelhaupt FM. Theoretical study of structure, pKa, lipophilicity, solubility, absorption and polar surface area of some centrally acting antihypertensives. Bioorg Med Chem 2006; 14:1715-28. [CrossRef] [PubMed]
5. Zhao YH, Le J, Abraham MH, Hersey A, Eddershaw PJ, Luscombe CN, et al. 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. [CrossRef] [PubMed]
6. Lemke TL, Williams DA, eds. The Foye's Principles of Medicinal Chemistry, 6th ed. Philadelphia: Wolters Kluwer, Lippincott Williams & Wilkins; 2008.
7. Stella VJ, Borchardt RT, Hageman MJ, Oliyai R, Maag H, Tilley JW. Biotechnology: Pharmaceutical Aspects, Prodrugs: Challenges and Rewards, 18th Springer Science, Business Media. New York; 2007.
8. Sweetman SC, ed. Martindale: The Complete Drug Reference. 36th ed. London: Pharmaceutical; 2009.
9. Beale JM, Block JH, eds. Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry. 12th ed. Philadelphia: Wolters Kluwer, Lippincott Williams and Wolters; 2011.
10. Moffat AC, Osselton MD, Widdop B, eds. Clarke's Analysis of Drugs and Poisons. 4th ed. London: Pharmaceutical Press; 2011.
11. Cheung BMY. Sartans for hypertension – implica tions of the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial. Hong Kong Med J 2004; 10(5): 359. [PubMed]
12. Zwieten van PA. Angiotensin II receptor antagonists (AT1 blockers, ARBs, sartans): similarities and diffe rences. Neth Heart J 2006; 14(11): 381-7. [PubMed]
13. Husain A, Md Mitra SAM, Bhasin PS. A review of pharmacological and pharmaceutical profile of irbesartan. Pharmacophore 2011; 2(6): 276-86.
14. Odovic J, Stojimirovic B, Aleksic M, Milojkovic-Opsenica D, Tesic Z. Reversed-phase thin-layer chromatography of some angiotensin converting enzyme (ACE) inhibitors and their active metabo lites. J Serb Chem Soc 2006; 71(6):621-8. [CrossRef]
15. Odovic J, Aleksic M, Stojimirovic B, Milojkovic-Opsenica D, Tesic Z. Normal-phase thin-layer chromatography of some ACE inhibitors and their metabolites. J Serb Chem Soc 2009; 74(6):677-88. [CrossRef]
16. Odovic JV, Stojimirovic BB, Aleksic MB, Milojković-Opsenica DM, Tešic ŽLj. Examination of the hydrophobicity of ACE inhibitors and their active metabolites by salting-out thin-layer chromato graphy. J Planar Chromatogr 2005;18:98-103. [CrossRef]
17. Odovic JV, Markovic BD, Injac RD, Vladimirov SM, Karljikovic-Rajic KD. Correlation between ultra-high performance liquid chromatography–tandem mass spectrometry and reversed-phase thin-layer chroma tography hydrophobicity data for evaluation of angiotensin-converting enzyme inhibitors absorp tion. J Chromatogr A 2012; 1258:94-100. [CrossRef] [PubMed]
18. Odovic J, Trbojevic-Stankovic J. Correlation between Angiotensin-converting enzyme inhibitors lipo philicity and protein binding data. Acta Med Medianae 2012; 51(4): 13-18.
19. Molinspiration software or free molecular property calculation services. [Internet] [cited 2013 Apr]. Available from: www.molinspiration.com
20. Tetko IV. Virtual Computational Chemistry Labora tory. [Internet] [cited 2013 Apr]. Available from: www.vcclab.org
21. Mannhold R, Poda GI, Tetko IV. Calculation of molecular lipophilicity: state-of-the-art and comparison of logP methods on more than 96,000 compounds. J Pharm Sci 2009; 98:861-93. [CrossRef] [PubMed]
22. Asuero AG, Sayago A, Gonzalez AG. The correlation coefficient: An overview. Crit Rev Anal Chem 2006; 36:41-59. [CrossRef]
23. Lipinski CA. Drug-like properties and the causes of poor solubility and poor permeability. J Pharmacol Toxicol Met 2000; 44:235–49. [CrossRef] [PubMed]
24. Ghose AK, Viswanadhan VN, Wendoloski JJ. A Knowledge-Based Approach in Designing Combina torial or Medicinal Chemistry Libraries for Drug Discovery. J Comb Chem 1999; 1: 55–68. [CrossRef] [PubMed]

IN SILICO PROCENA VEZIVANJA ZA PROTEINE PLAZME ANTAGONISTA RECEPTORA ANGIOTENZINA II PRIMENOM IZRAČUNATIH MOLEKULSKIH DESKRIPTORA

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Ispitivanje novih farmakološki aktivnih supstanci i modeliranje lekova dovelo je do neophodnosti predviđanja osobina leka. Cilj istraživanja bio je da se uporede izračunati molekulski deskriptori sedam antagonista receptora angiotenzina II (ARBs), (eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan) sa dostupnim podacima njihovog vezivanja za proteine plazme (PPB). Molekulski deskriptori ispitivanih ARBs izračunati su korišćenjem softverskih paketa Molinspiration Depiction Software i Virtual Computational Chemistry Laboratory. Ispitane su korelacije između izračunatih deskriptora i vrednosti vezivanja za proteine plazme odabranih lekova. Niske vrednosti korelacije (R^2<0,20) dobijene su poređenjem vrednosti PPB i izračunatih molekulskih deskriptora (logP vrednosti, logS vrednosti, vrednosti Vol, molekulske mase Mr i vrednosti polarne površine molekula PSA). U sledećoj fazi istraživanja, primenom višestruke regresione analize (MLR), ispitana je zavisnost PPB podataka od dva različita molekulska deskriptora kao nezavisnih promenljivih. Najbolja korelacija (R^2=0,70 i P<0,05) uspostavljena je između PPB podataka i molekulske mase, uz dodatak vrednosti Vol kao nezavisnih promenljivih. Mogućnost primene izračunatih molekulskih deskriptora u proceni vrednosti vezivanja ispitivanih lekova za proteine plazme od velikog je značaja za razvoj i ispitivanje novih lekova. *Acta Medica Medianae 2014;53(1):19-24.*

Ključne reči: *molekulski deskriptori, ARBs, vezivanje za proteine plazme*