

## 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 Cheminformatics) (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, ClogP, 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.

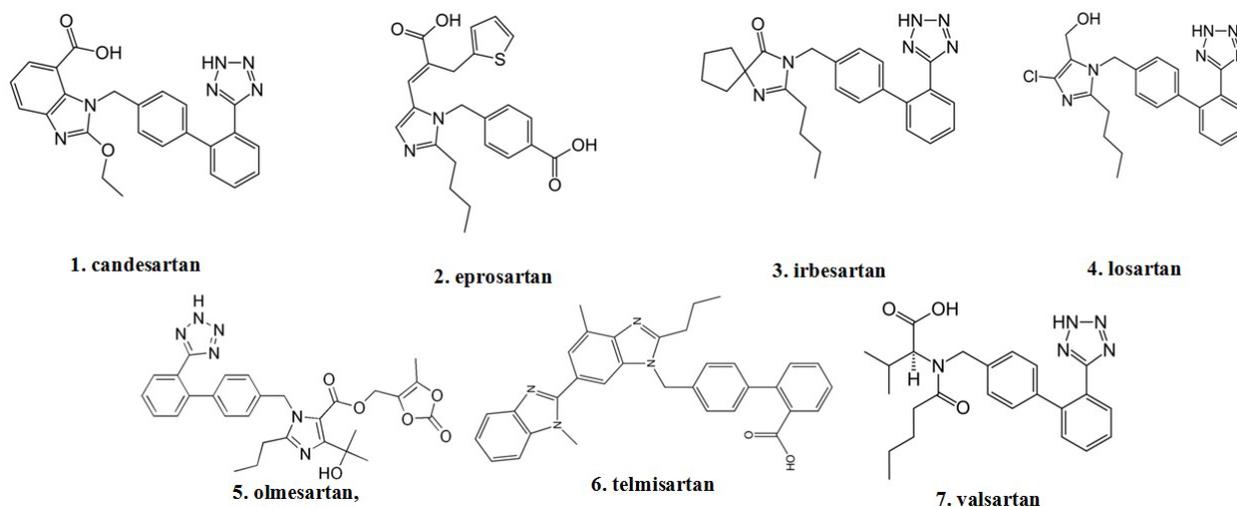


Figure 1. The chemical structures of the investigated ARBs

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, ACllogP, 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).

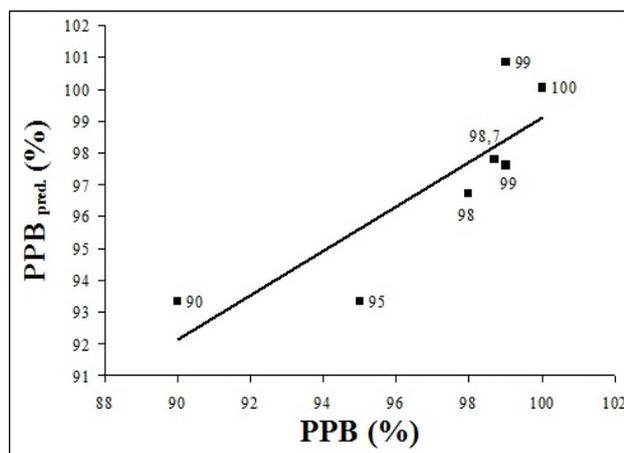


Figure 2. The relationship between ARBs literature available PPB data (6) and predicted PPB<sub>pred</sub> data (using molecular weight, Mw and volume values, Vol) ( $R^2=0.7039$ )

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 % <sup>a</sup>	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
AlogPs	4.02	3.57	4.51	4.50	3.35	6.66	3.68
logS	-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

<sup>a</sup> 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:

$$PPB_{pred} (\%) = 0.2807 (\pm 0.0927) Mw + 0.2310 (\pm 0.0862) Vol + 65.5290 (\pm 13.9569) \quad \dots(1)$$

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 correlation 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 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, logS 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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## 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 molekularni deskriptori sedam antagonista receptora angiotenzina II (ARBs), (eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan) sa dostupnim podacima njihovog vezivanja za proteine plazme (PPB). Molekularni 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 molekularnih 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 molekularna 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 molekularnih 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:** molekularni deskriptori, ARBs, vezivanje za proteine plazme