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Modelling of absorption, distribution and physicochemical properties of AT$_1$ receptor antagonists
Modelovanie absorpcie, distribúcie a fyzikálnochemických vlastnosti antagonistov AT$_1$ receptorov

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Abstract The theoretical chemistry methods were used to elucidate absorption, distribution and physicochemical properties of AT$_1$ receptor antagonists and dual angiotensin II and endothelin A receptor antagonist (PS-433540). Computed partition coefficients (ALOGPS method) studied for drugs varied between 2.98 and 6.66. Neutral compounds are described as lipophilic drugs. Telmisartan is a drug with the highest lipophilicity. The neutral forms of the studied AT$_1$ receptor antagonists are practically insoluble in water, and their computed solubilities is in interval between 2.04 and 22.65 mg/l (ALOGpS method). The calculated pK$_a$ values for tetrazolyle moiety are in the range 3.92–5.00 and for carboxylic moiety 3.12–5.50. Telmisartan (polar surface area = 72.95 Å) and irbesartan (polar surface area = 87.14 Å) belong to the AT$_1$ receptor antagonists with increased absorption.

Slovak abstract Pre objasnenie absorpcie, distribúcie a fyzikálnochemických vlastností antagonistov AT$_1$ receptorov a duálneho antagonistu angiotenzínu II a endotelínového receptora A (PS - 433540) boli použité metódy teoretickej chémie. Vypočítané hodnoty rozdeľovacieho koeficientu (ALOGPS metódou) študovaných liečiv sú v rozmedzí medzi 2,98 a 6,66. Neutrálne zlúčeniny sú definované ako lipofilné liečivá. Telmisartan je liečivo s najvyššou lipofilitou. Neutrálne formy študovaných antagonistov AT$_1$ receptorov sú prakticky nerozpustné vo vode, ich vypočítané rozpustnosti sú v rozmedzí medzi 2,04 a 22,65 mg/l (metóda ALOGpS). Vypočítané hodnoty pK$_a$ tetrazolylových skupín, sú v rozmedzí 3,92 - 5,00 a pre karboxylovú skupinu 3,12 - 5,50. Telmisartan (polárny povrch = 72,95 Å) a irbesartan (polárny povrch = 87,14 Å) zaraďujeme k antagonistom AT$_1$ receptorov so zvýšenou absorpciou.

1. INTRODUCTION

Losartan was the first nonpeptide AT$_1$ receptor antagonist approved by the Food and Drug Administration (1995). After losartan, a large number of AT$_1$ receptor antagonists was introduced into the market: valsartan, irbesartan, eprosartan, candesartan, telmisartan, olmesartan, azilsartan and fimasartan (Je et al., 2012; Lee et al., 2012; Woo et al., 2012) (Fig. 1). All AT$_1$ receptor antagonists are primarily used for the treatment of hypertension. However, losartan (COZAAR® label information) and irbesartan (AVAPRO® label information) are used for the treatment of diabetic nephropathy. Telmisartan is indicated for the reduction of the risk of myocardial infarction,

stroke or death caused by cardiovascular disorders in patients who are unable to take angiotensin-converting-enzyme (ACE) inhibitors (MICARDIS® label information). Valsartan (DIOVAN® label information) and candesartan (ATACAND® label information) are used for the treatment of heart failure (NYHA class II-IV).

AT$_1$ receptor antagonists possess some additional properties. The valsartan reduces levels of ß-amyloid protein in brain and improves the evidence of spatial learning in model of Alzheimer's disease (Wang et al. 2007). Losartan reduces uric acid serum levels, whose reduction may be useful in

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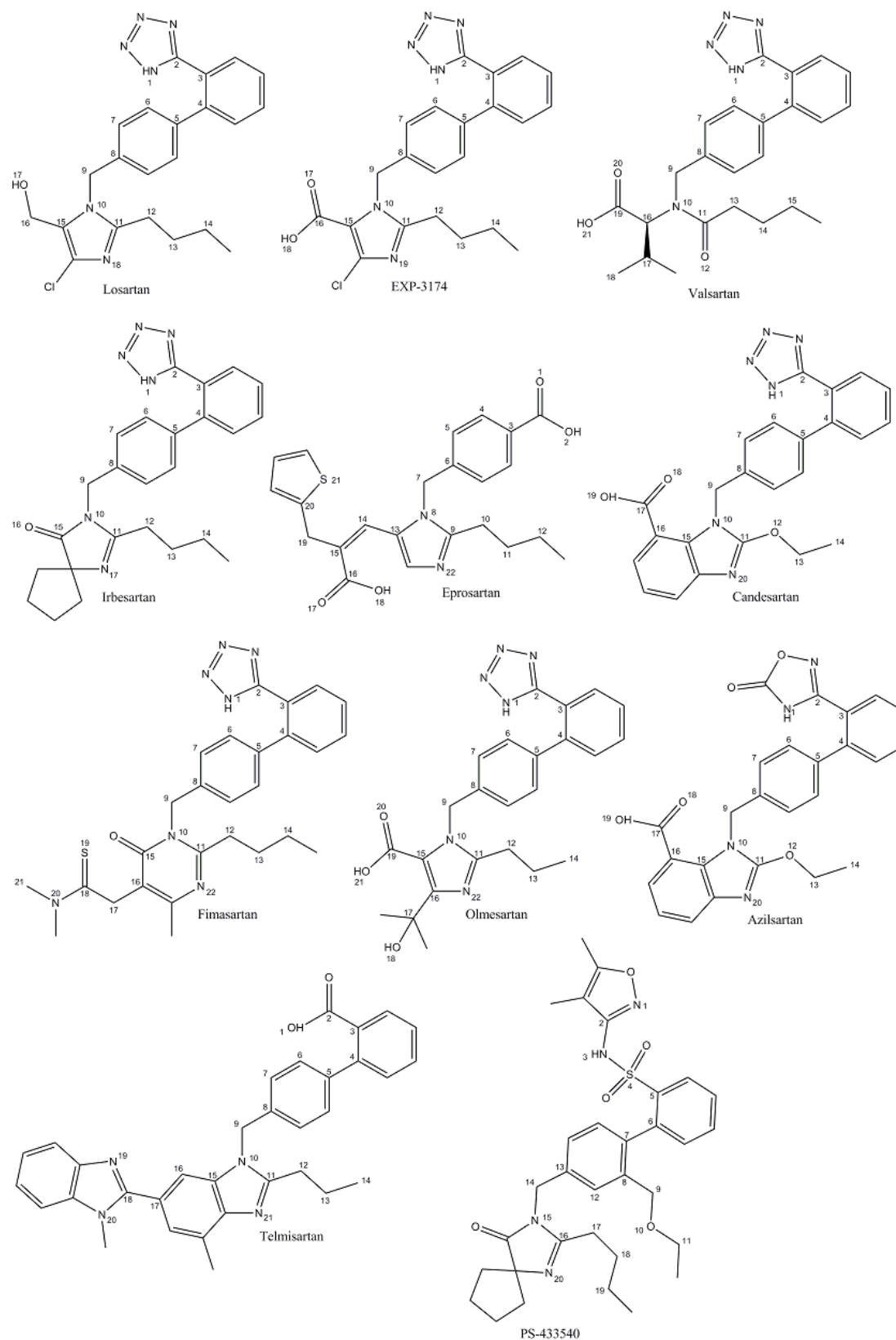
Figure 1. Structure and atom labeling in the studied AT$_1$ receptor antagonists.

the management of cardiovascular risk (Alderman & Aiyer, 2002; Hoieggen et al. 2004; Sica & Schoolwerth, 2002). Irbesartan, losartan and EXP-3174 can interfere with platelet activation and vasoconstriction induced by a thromboxane receptor agonist (Fukuhara et al., 2001; Jimenez et al., 2001; Li et al., 2000; Nunez et al., 2000; Sato et al., 2007). Telmisartan inhibits proliferation of vascular smooth muscle cells and has antiproliferative effects in cardiac fibroblasts (Benson et al., 2008). After telmisartan therapy, a significant decrease in plasmatic markers of prothrombotic state and fibrinogen level was found (Remková et al., 2008). Some of the AT_1 receptor antagonists have the ability to activate peroxisome proliferator-activated receptor gamma (PPAR-γ), an intracellular receptor involved in the regulation of glucose and lipid metabolism (Benson et al., 2004; Schupp et al., 2004). These observations, together with the known metabolic benefits of PPAR-γ activation, raise the possibility that AT_1 receptor antagonists such as telmisartan that stimulates PPAR-γ as well as blocks the AT_1 receptor might be more effective in protecting against coronary heart disease than AT_1 receptor antagonists that block the AT_1 receptor alone. After oral administration of very low doses of azilsartan in a mouse model of type II diabetes, a significant increase in PPAR-γ gene expression in adipose tissue was found (Iwai et al., 2007). In this paper, the results of theoretical calculations were used for the study of the lipophilicity, solubility, pK_a, polar surface area (PSA) and selected absorption, distribution, metabolism and excretion (ADME) properties of both clinically useful and experimental AT_1 receptor antagonists (Murugesan et al., 2005). The results of theoretical studies of these drugs were compared with the available experimental data and discussed in the relation to the present theories of these agents' activity.

2. EXPERIMENTAL

2.1 Material and methods

The program Jaguar (version 7.9, Schrödinger, LLC, New York, NY, 2012) was selected for the calculations of the macroscopic pK_a of AT_1 receptor antagonists.

Initial conformations of AT_1 receptor antagonists used for the theoretical calculation were prepared in the graphical interface of the program Maestro (version 9.3, Schrödinger, LLC, New York, NY, 2012). The 2D structure of all ligands was converted to 3D model of ligands in LigPrep, while specified chiralities were retained. The energy of all ligands was minimised in 50 steps by Steepest Descent algorithm with Convergence Gradient in the program MacroModel (version 9.9, Schrödinger, LLC, New York, NY, 2012). Program ConfGen (version 2.3, Schrödinger, LLC, New York, NY, 2012) was used to find the most stable conformation for each ligand. Conformers were generated using torsional search method followed by minimisation of each generated structure using OPLS-2005 force field, with constant dielectric electrostatic treatment (GB/SA solvation model). Five most stable

conformers were generated per structure using a preprocess minimisation of 50 steps and postprocess minimisation of 1 step. The minimised conformers were filtered through a relative energy window of 100 kJ/mol and root-mean-square deviation of 1.00 Å. For the pK_a calculations in Jaguar, the most stable conformations of the studied AT_1 receptor antagonists optimised by CPCM method (Barone & Cossi 1998; Cossi et al., 2003) at B3LYP/6-31G(d) level of theory using the program Gaussian 09 were used.

Lipophilicity and water solubility calculations were carried out using web-based VCCLAB (http://www.vcclab.org/lab/alogps/) (Tetko 2005; Tetko et al., 2005, 2006). Calculations of molecular polar surface areas (the fragment-based method of Ertl and coworkers (Ertl et al,. 2000, 2003) were performed using the Molinspiration Cheminformatics software (http://www.molinspiration.com). The program QikProp (version 3.5, Schrödinger, LLC, New York, NY, 2012) was used for the calculation of ADME properties. All the molecular modelling procedures were performed on a HPC-LISA (SUN BLADE X6270, 16 x Intel Xeon 2.53 Ghz, 96 GB RAM, Rocks 6.0.2) at Department of Pharmaceutical Chemistry in the Laboratory of Chemical and Biological Information Systems and Technologies (Toxicological and Anti-doping Center).

3. RESULTS AND DISCUSSION

3.1 Lipophilicity and solubility

The computed and experimental log P values (P is the partition coefficient of the molecule in the 1-octanol/water system) are shown in Table 1. The ALOGPs method is a part of the ALOGPS 2.1 program (Tetko & Tanchuk, 2002) used to predict lipophilicity (Tetko et al., 2001a) and aqueous solubility (Balakin et al., 2006; Tetko et al., 2001b) of ligands. The lipophilicity calculations within this program are based on the associative neural network approach and the efficient partition algorithm. The KowWin program (Meylan & Howard, 1995) estimates the log 1-octanol/water partition coefficient (log P) of organic chemicals and drugs using an atom/fragment contribution method developed by Syracuse Research Corporation (http://www.syrres.com). The XLOGP2 is atom-additive method applied for corrections (Wang et al., 1997, 2000). All available experimental log P values of some AT_1 receptor antagonists were extracted from the literature (Tosco et al., 2008; Inglot et al., 2008). Neutral compounds are characterised as lipophilic drugs.

Telmisartan is a drug with the highest lipophilicity of studied compounds. The high lipophilicity of telmisartan is in good agreement with the low PSA value of telmisartan (72.95 Å²) and is associated with the long half-life of telmisartan and with the activation of PPAR-γ within the cell nucleus (Erbe et al., 2006; Wienen et al., 2000). Olmesartan is a drug with the lowest lipophilicity. This result is in agreement with the highest PSA value of olmesartan (129.82Å²). The experimental log P values of AT_1 receptor antagonists are preferably

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Table 1. Calculated partition coefficients of the AT$_1$ receptor antagonists.

No.	Drug	Experimental data			Theoretical calculations (of lipophilicity)		
		log P[a]	log P[b,c]	log P[b,d]	ALOGPs	KowWin	XLOGP2
1	Losartan		2.01[e] 2.75[f]	6.08[e] 5.02[f]	3.81	4.01	4.83
2	EXP-3174				3.92	4.81	5.26
3	Valsartan	3.78[g]	2.41[e] 3.26[f]	5.22[e] 5.71[f]	3.11	3.65	4.60
4	Irbesartan		1.88[e] 3.41[f]	5.85[e] 6.13[f]	4.11	5.31	4.75
5	Eprosartan		0.44[e] 1.86[f]	3.64[e] 4.61[f]	3.57	6.37	3.85
6	Candesartan		4.91[e] 5.93[f]	7.79[e] 6.73[f]	3.44	4.79	4.86
7	Candesartan cilexetil				5.12	6.83	7.81
8	Telmisartan		4.24[e] 4.47[f]	5.92[e] 6.48[f]	6.66	8.42	7.72
9	Olmesartan		2.01[e] 3.07[f]	6.05[e] 5.15[f]	2.98	3.63	3.89
10	Olmesartan medoxomil				4.15	3.29	5.95
11	Azilsartan				3.15	6.44	5.31
12	Azilsartan medoxomil				3.95	6.10	6.12
13	Fimasartan				3.49	3.95	4.02
14	PS-433540				5.56	7.34	5.86

[a] *(Tosco et al., 2008).*
[b] *(Inglot et al., 2008).*
[c] *Liquid chromatography.*
[d] *Thin-layer chromatography.*
[e] *Mobile phase – acetonitrile in phosphate buffer (pH = 5,0).*
[f] *Mobile phase – methanol in phosphate buffer (pH = 5,0).*
[g] *Experimentally obtained by potentiometry.*

reproduced by the ALOGPs, so this method was used for further calculations.

Log S, an intrinsic solubility in the neutral state, is an indication of compounds' solubility (S). The log S values were calculated using ALOGPS predictor. This method uses E-state indices as the descriptors and a neural network (Tetko et al., 2001b) as the modelling 'engine'. The computed solubilities of studied drugs were compared with the available experimental data (European Pharmacopoeia, Council of Europe, Strasbourg, 2014) and are shown in Table 2. Drug solubility is one of the important factors that affect the drug movement from a point of administration into the blood site. It is very significant to know the drug solubility and that the insufficient solubility of drugs can lead to poor absorption (Zhao et al., 2002). The investigation of the rate-limited steps of human oral absorption of 238 drugs (including warfarin) showed (Zhao et al., 2002) that the absorption of a drug is usually very low if the calculated solubility is <0.0001 mg/l.

The neutral forms of the studied AT$_1$ receptor antagonists are practically insoluble in water; their computed solubilities are in interval between 2.04 and 22.65 mg/l (ALOGpS). Increased solubility of valsartan (22.65 mg/l) can be caused by error of computational algorithm. The anion forms of the studied AT$_1$ receptor antagonists are practically insoluble in water; their computed solubilities are in interval between 3.22 and 89.41 mg/l (ALOGpS). In the clinical praxis, the AT$_1$ receptor antagonists are used as the salts forms, such as eprosartan mesylate, losartan potassium and fimasartan as potassium trihydrate. Losartan potassium is freely soluble in water. Fimasartan as potassium trihydrate is very slightly soluble in water.

3.2 Dissociation constants

The AT$_1$ receptor antagonists contain acidic carboxyl, tetrazolyl, 4,5-dihydro-1,2,4-oxadiazol-5-one (azilsartan)

Table 2. Calculated solubilities of AT$_1$ receptor antagonists.

No.	Drug	Experimental.[a]	ALOGpS
1	Losartan	Freely soluble in water[b]	−4.97 (4.56 mg/l)
	Losartan N-terminal anion		−3.91 (54.33 mg/l)
2	EXP-3174		−5.05 (3.90 mg/l)
	EXP-3174 N-terminal anion		−4.21(28.13 mg/l)
	EXP-3174 C-terminal anion		−4.96 (5.03 mg/l)
	EXP-3174 dianion		−4.14 (34.33 mg/l)
3	Valsartan	practically insoluble in water	−4.28 (22.65 mg/l)
	Valsartan N-terminal anion		−4.44 (16.41 mg/l)
	Valsartan C-terminal anion		−4.24 (25.98 mg/l)
	Valsartan dianion		−4.38 (19.57 mg/l)
4	Irbesartan		−4.70 (8.46 mg/l)
	Irbesartan N-terminal anion		−4.58 (11.63 mg/l)
5	Eprosartan		−4.69 (8.66 mg/l)
	Eprosartan C3-terminal anion		−4.59 (11.28 mg/l)
	Eprosartan C16-terminal anion		−4.58 (11.67 mg/l)
	Eprosartan dianion		−4.45 (16.15 mg/l)
6	Candesartan		−4.77 (7.45 mg/l)
	Candesartan N-terminal anion		−3.92 (55.43 mg/l)
	Candesartan C-terminal anion		−4.75 (8.21 mg/l)
	Candesartan dianion		−3.89 (61.47 mg/l)
7	Candesartan cilexetil	Practically insoluble in water	−5.48 (2.04 mg/l)
8	Telmisartan	Practically insoluble in water	−5.17 (3.50 mg/l)
	Telmisartan C-terminal anion		−5.22 (3.22 mg/l)
9	Olmesartan		−4.63 (10.51 mg/l)
	Olmesartan N-terminal anion		−3.83 (68.43 mg/l)
	Olmesartan C-terminal anion		−4.54 (13.25 mg/l)
	Olmesartan dianion		−3.73 (89.41 mg/l)
10	Olmesartan cilexetil	Practically insoluble in water	−4.77 (9.50 mg/l)
11	Azilsartan		−4.57 (12.30 mg/l
	Azilsartan N-terminal anion		−4.37 (20.28 mg/l)
	Azilsartan C-terminal anion		−4.59 (12.18 mg/l)
	Azilsartan dianion		−4.30 (17.47 mg/l)
12	Azilsartan medoxomil		−4.78 (9.49 mg/l)
13	Fimasartan	Very slightly soluble in water[c]	−5.03 (4.69 mg/l)
	Fimasartan N-terminal anion		−4.94 (5.97 mg/l)
14	PS-433540		−4.69 (12.24 mg/l)
	PS-433540 N-terminal anion		−4.62 (14.57 mg/l)

[a] *Powdered substance is mixed with appropriate solvent in tube (European Pharmacopoeia, Council of Europe, Strasbourg, 2014).*
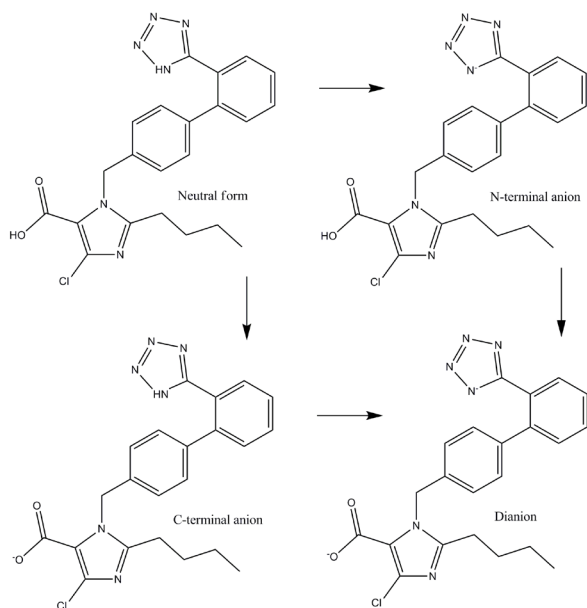[b] *Potassium salt.*
[c] *Potassium trihydrate salt.*

Figure 2a. The dissociation pathway of the losartan. (Figure shows only selected drugs, other drugs make analogous deprotonation reactions).
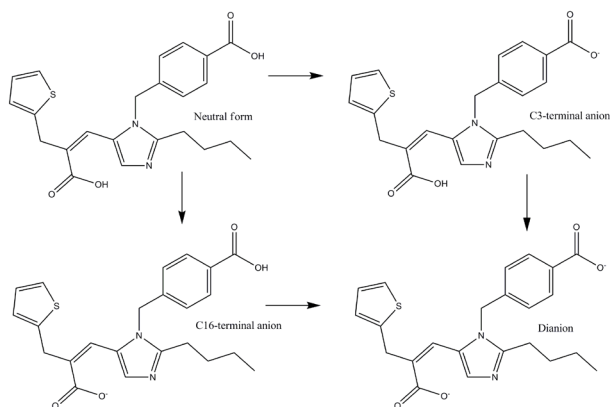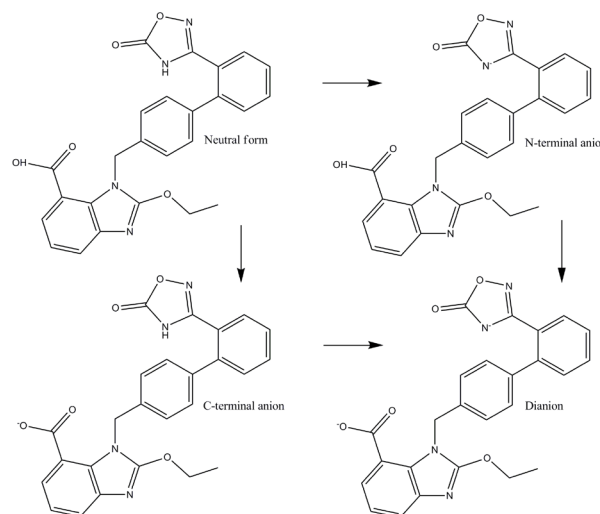

Figure 2c. The dissociation pathways of the azilsartan. (Figure shows only selected drugs, other drugs make analogous deprotonation reactions).
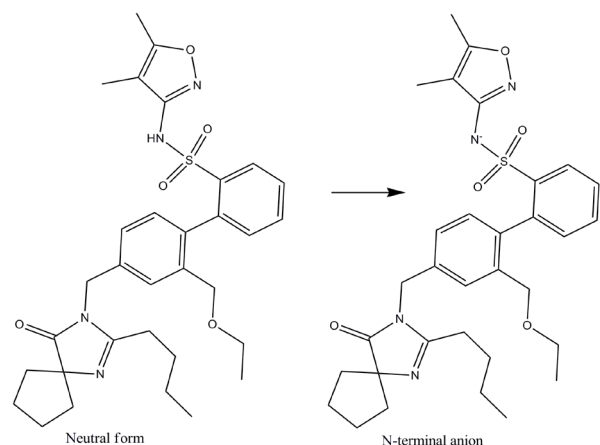

Figure 2b. The dissociation pathways of the eprosartan. (Figure shows only selected drugs, other drugs make analogous deprotonation reactions).

Figure 2d. The dissociation pathways of the PS-433540. (Figure shows only selected drugs, other drugs make analogous deprotonation reactions).

and sulphonamide (PS-433540) group, and thus they may undergo deprotonation reactions (Fig. 2).

However, dissociation constant in solution, that is, the pK$_a$, is a measure of the strength of an acid or a base. Therefore, this parameter is very useful for understanding the behaviour of drug molecules at the site of action. Dissociation plays an important role in both partition and receptor binding processes of the drug action. Accordingly, it is important to know whether the drug molecules exist predominantly in the neutral or ionised forms. The Jaguar program was used for the prediction of the AT$_1$ receptor antagonists' pK$_a$ value in condensed phase (water).

The calculated pK$_a$ values are presented in Table 3. Theoretical computed values of the pK$_a$ were compared with available experimental data (Cagigal et al., 2001; Tosco et al., 2008).

The presence of two acidic groups in some AT$_1$ receptor antagonists reduces gastrointestinal absorption and bioavailability. Two acidic groups are present in the structure of valsartan, eprosartan, candesartan, olmesartan and azilsartan. In the drug form, they are used as prodrugs, non-effective precursors that have favourable pharmacokinetic properties. This was achieved by esterification of the carboxylic acid by alcohols. The ester bond is easily hydrolysed into the active form after the absorption of the drug into the body. In clinical practice, candesartan (candesartan cilexetil), olmesartan (olmesartan medoxomil) and azilsartan (azilsartan

Table 3. *Experimental and calculated pK$_a$ values of the AT$_1$ receptor antagonists investigated, (pH = 7.4).*

No.	Drug	Experimental data				Calculated values			
						Jaguar[c]			
		pK$_a$		Dissociated form (%)		pK$_a$		Dissociated form (%)	
		Tetrazole	Carboxyl	Tetrazole	Carboxyl	Tetrazole	Carboxyl	Tetrazole	Carboxyl
1	Losartan	4.25[a] 3.15[b]		99.93[a] 99.99[b]		5.00		99.60	
2	EXP-3174					4.52	3.62	99.87	99.98
3	Valsartan	4.70[a] 4.90[b]	3.60[a]	99.80[a] 99.68[b]	99.98[a]	4.30	5.50	99.92	98.76
4	Irbesartan	4.42[a] 4.70[b]		99.90[a] 99.80[b]		4.60		99.84	
5	Eprosartan						4.32[d] 3.12[e]		99.92 99.99
6	Candesartan	4.66[a] 3.90[b]	3.67[a]	99.82[a] 99.97[b]	99.98[a]	3.92	3.82	99.97	99.97
7	Telmisartan		4.45[b]		99.89[b]		4.92		99.67
8	Olmesartan					4.82	3.72	99.74	99.98
9	Azilsartan						5.22		99.34
10	Fimasartan					4.72		99.79	

[a] *Potentiometric method [47].*

[b] *Spectrofluorimetric method [55].*

[c] *Calculation in program Jaguar, (root-mean-square deviation for carboxyl group = 0.4; root-mean-square deviation for tetrazole group = 0.7).*

[d] *C16-carboxyl group.*

[e] *C3-carboxyl group.*

medoxomil) are used as prodrugs. Then the active form binds to the active site of the AT$_1$ receptor.

AT$_1$ receptor antagonists also contain a basic nitrogen group in their structure, namely, imidazole (losartan, EXP-3174, eprosartan, olmesartan), benzimidazole (candesartan, telmisartan, azilsartan), pyrimidine (fimasartan), diaza-spiro[4.4]non-1-ene (irbesartan, PS-433540), isoxazole (PS-433540) or tertiary amino group (valsartan, fimasartan). Basic nitrogen atom is not significantly ionised at physiological pH of 7.4 in these functional groups (Table 4).

The computed pK$_a$ values for tetrazolyl acidic group of the AT$_1$ receptor antagonists are in the range 3.92–5.00 (for calculated value, the root-mean-square deviation is 0.7). The calculated pK$_a$ values for the carboxylic acid are in the range 3.12–5.50 (for calculated value, the root-mean-square deviation is 0.4). At physiological pH of 7.4, these two acidic groups are ionised at a high rate (98.76–99.99; Table 3) and drugs will exist as dianions. These values are in relatively good agreement with experimental data (Table 3) (Tosco et al., 2008; Inglot et al., 2008). PS-433540 contains a sulphonamide acid group with pK$_a$ of 6.22 (for calculated value, the root-mean-square deviation is 0.6). At pH = 7.4, the sulphonamide is largely ionised (93.80%). For the calculation of the azilsartan

4,5-dihydro-1,2,4-oxadiazol-5-one group, SPARC program was used (Hilal et al., 1995). The pK$_a$ value of this group is pK$_a$ = 6.80. The Jaguar program does not include parameterisation for 4,5-dihydro-1,2,4-oxadiazol-5-one group.

Theoretical pK$_a$ values of olmesartan computed by Jaguar indicate that C-terminal carboxyl group is more acidic (pK$_a$ = 3.72) than N-terminal tetrazolyl group (pK$_a$ = 4.82). This order of acidity explains why in prodrug of olmesartan, C-terminal carboxyl group is shielded with medoxomil group.

Theoretical pK$_a$ values of candesartan computed by Jaguar indicate that C-terminal carboxyl group is more acidic (pK$_a$ = 3.82) than N-terminal tetrazolyl group (pK$_a$ = 3.92). This result is in a good agreement with experimental pK$_a$ values of candesartan (Table 3). This order of acidity explains why in prodrug of candesartan C-terminal carboxyl group, there is shielded with cilexetil group.

3.3 Polar surface area and "rules of five properties"

The high oral bioavailability is an important factor for the development of bioactive molecules as therapeutic agents. Passive intestinal absorption, reduced molecular flexibility (measured by the number of rotatable bonds), low PSA or

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Table 4. Calculated pKa values for the base center of the AT$_1$ receptor antagonists investigated (pH = 7.4).

		Jaguar[a]	
No.	Drug	pK$_a$	Dissociated form (%)
1	Losartan	N$_{18}$ = 2.90	0.0
2	EXP-3174	N$_{19}$ = 0.38	0.0
3	Valsartan	-	
4	Irbesartan	N$_{17}$ = 1.10	0.0
5	Eprosartan	N$_{22}$ = 4.18	0.06
6	Candesartan	N$_{20}$ = 1.98	0.0
7	Telmisartan	N$_{19}$ = 5.88	2.93
		N$_{20}$ = −7.3	0.0
		N$_{21}$ = 4.88	0.30
8	Olmesartan	N$_{22}$ = 2.08	0.0
9	Azilsartan	N$_{20}$ = 2.08	0.0
10	Fimasartan	N$_{20}$ = 0.08	0.0
		N$_{22}$ = 4.28	0.08
11	PS-433540	N$_1$ = -2.62	0.0
		N$_{20}$ = 0.78	0.0

[a] *Calculation in program Jaguar.*

total hydrogen bond count (sum of donors and acceptors) are important predictors of good oral bioavailability (Refsgaard et al., 2005; Veber et al., 2002). Properties of molecules such as bioavailability or membrane permeability were often grouped into simple molecular descriptors such as log P (partition coefficient), molecular weight (MW) or counts of hydrogen bond acceptors and donors in molecule (Muegge, 2003). Lipinski (Lipinski et al., 1997) used these molecular properties in formulating his 'Rule of Five'. The rule states that most molecules with good membrane permeability have log P <5, molecular weight <500, a number of hydrogen bond acceptors <10 and a number of hydrogen bond donors <5. This rule is widely used as a filter for drug-like properties. Table 5 contains calculated percentage of absorption (%ABS), molecular PSA (polar surface area) and Lipinski parameters of the AT$_1$ receptor antagonists investigated. Magnitude of absorption is expressed by the percentage of absorption. Absorption percentage was calculated (Zhao et al., 2002) using the expression: %ABS = 109 − 0.345 PSA. PSA was determined by the fragment-based method of Ertl and coworkers (Ertl et al,. 2000, 2003).

Few ligands violate Rule of Five. PS-433540 has higher molecular mass (592.76 g/mol) and higher value of lipophilicity (clog P = 5.56). The telmisartan and irbesartan belong to the AT$_1$ receptor antagonists with increased absorption (telmisartan PSA = 72.95 Å; irbesartan PSA = 87.14Å). Although telmisartan violates Rule of Five (too high log P and molecular weight), the low number of rotatable

bonds (7) and lower PSA (72.95 Å) can compensate these violations.

The relatively high value of PSA of candesartan, olmesartan and azilsartan (values between 118.83 Å and 129.83Å) results in lower absorption in comparison with telmisartan (Table 5). Candesartan, olmesartan and azilsartan contain two ionisable acidic functional groups (tetrazolyl ring or 4,5-dihydro-1,2,4-oxadiazol-5-one and carboxyl group), and in physiological conditions, they are present in the form of charged species. Ionisation of acidic groups and high PSA of these drugs is not compatible with their oral application. Therefore, their prodrug forms were prepared: candesartan cilexetil, olmesartan medoxomil and azilsartan medoxomil. Although the forms of these prodrugs violate the Rule of Five (molecular mass 558.60–610.67 g/mol), they are metabolised to active forms in vivo, which are biologically active. Valsartan also contains two ionisable acidic groups, but lower value of the PSA compensates this deficiency, in comparison to candesartan, olmesartan and azilsartan. The calculated percentage of absorption does not correlate with the available experimental percentage of absolute absorption (Table 5) [MICROMEDEX® 2.0. (http://www.thomsonhc.com/micromedex2/librarian/); Lexicomp® (http://www.lexi.com)].

3.4 ADME properties

The pharmacokinetic ADME parameters of the AT$_1$ receptor antagonists were calculated using the QikProp program. All descriptors and pharmaceutically relevant properties were analysed, and significant descriptors are discussed in the following. These properties were

1. Predicted apparent Caco-2 cell permeability in nanometre per second (*QPPCaco*).
2. Predicted human oral absorption on 0 to 100% scale (*P.H.O.A.*).
3. Predicted apparent MDCK cell permeability in nanometre per second (*QPPMDCK*).
4. Predicted brain–blood partition coefficient (*QPlogBB*).
5. Predicted central nervous system activity (*CNS*).
6. Prediction of binding to human serum albumin (*QPlogKhsa*).

Blood–brain barrier (BBB) permeability is a crucial factor that needs careful examination in the process of drug discovery. Drugs targeted in the CNS must cross BBB to exhibit therapeutic effect, whereas for non-CNS drugs, passage through the BBB may lead to unwanted side effects. The degree of BBB penetration is defined as the ratio of the steady-state concentrations of the drug in the brain and in the blood: BB = C$_{brain}$/C$_{blood}$. C is the concentration of the compound. BB of the most prescribed CNS drugs is >0.3 (log BB > −0.5), drugs with BB <0.1 (log BB < −1) penetrate poorly into the brain (Abraham et al., 1997). Log BB was calculated using the Clark equation: log BB = −0.0148 PSA + 0.152 clogP

Table 5. Calculated absorption (%ABS), polar surface area (PSA) and Lipinski parameters of the AT_1 receptor antagonists studied.

No.	Drug	%ABS	Exp, Absolute absorption [%]	Volume	PSA	NROTB	n ON acceptors	n OHNH donors	Log P, calcd,[c]	Formula weight
1	Losartan	77.08	25–35[a]	374.12	92.52	8	7	2	3.81	422.92
2	EXP-3174	71.19		376.30	109.59	8	8	2	3.92	436.90
3	Valsartan	70.33	10–35[a]	408.69	112.08	10	8	2	3.11	435.53
4	Irbesartan	78.94	60–80[a]	400.20	87.14	7	7	1	4.11	428.54
5	Eprosartan	77.11	6–29[a]	380.77	92.42	10	6	2	3.57	424.52
6	Candesartan	68.01		382.14	118.83	7	9	2	3.44	440.46
7	Candesartan cilexetil	59.54	15[a]	543.44	143.37	13	12 (violation)	1	5.12	610.67 (violation)
8	Telmisartan	83.83	42–58[a]	475.76	72.95	7	6	1	6.66 (violation)	514.63 (violation)
9	Olmesartan	64.21		403.61	129.82	8	9	3	2.98	446.51
10	Olmesartan medoxomil	53.05	26[a]	491.47	162.18	11	12 (violation)	2	4.15	558.60 (violation)
11	Azilsartan	66.48	60[b]	391.00	123.25	7	9	2	3.15	456.46
12	Azilsartan medoxomil	55.31	–	478.86	155.61	10	12 (violation)	1	3.95	568.54 (violation)
13	Fimasartan	77.05		461.88	92.60	10	8	1	3.49	501.66
14	PS-433540	69.63		541.20	114.11	12	9	1	5.56 (violation)	592.76 (violation)

[a] *MICROMEDEX® (http://www.thomsonhc.com/micromedex2/librarian/).*

[b] *Lexicomp® (http://www.lexi.com)].*

[c] *ALOGPs.*

+ 0.139 (Clark, 1999). ALOGPs values were selected for clogP (calculated logP).

The AT_1 receptor antagonists can be considered as moderately well absorbed drugs (Caco-2 cell permeability is 5.26–633.07 nm/s, predicted human oral absorption is 55.42–100.00%). These values of AT_1 receptor antagonists are different because of the special structure of each drug. After analysis of the computed log BB values of the studied drugs showed that telmisartan penetrates through BBB easily and irbesartan penetrates through BBB with difficulty. All the other drugs with log BB close to −1 penetrates poorly into the brain (Table 6). Valsartan would probably not cross BB, which is inconsistent with the experimental data (Wang et al. 2007). This inconsistency can be caused by an active transport mechanism through BBB (Pardridge, 2012). The QikProp brain–blood partition coefficient (*QPlogBB*) is in the range −2.36 to −1.16 and the predicted MDCK cell permeability for AT_1 receptor antagonists are in the range 4.55–411.97 nm/s. Prediction of binding of AT_1 receptor antagonists to human serum albumin is in the acceptable range from −0.09 to 1.70. Table 7 shows a set of the ADME descriptors calculated by QikProp. Parameters of BBB permeability *(QPPMDCK, QPlogBB, CNS, Log BB Clark)* were defined only for active forms of AT_1 receptor antagonists.

CONCLUSIONS

This theoretical study was set out to determine lipophilicity, solubility, gas-phase acidity, pK_a and ADME properties of 10 antagonists of angiotensin AT_1 receptor and PS-433540 (dual angiotensin II and endothelin A receptor antagonist). Using the theoretical methods, the following conclusions can be drawn.

I. The experimental log P values of AT_1 receptor antagonists are preferably reproduced by the ALOGPs method. Computed partition coefficients of the AT_1 receptor antagonists are in interval 2.98 and 6.66 mg/l (ALOGPs method). Thus these compounds can be described as lipophilic drugs. Telmisartan is a drug with the highest lipophilicity, which is in correlation with PPAR-γ agonist effect.

II. The neutral forms of the studied AT_1 receptor antagonists are practically insoluble in water, their computed solubilities are in interval between 2.04 and 22.65 mg/l (ALOGpS). The anion forms of the studied AT_1 receptor antagonists are practically insoluble in water, their computed solubilities in interval between 3.22 and 89.41 mg/l (ALOGpS).

III. The computed pK_a values for tetrazolyl acid group of the AT_1 receptor antagonists are in the range 3.92–5.00. The calculated pK_a values for the carboxylic acid are in

Table 6. ADME properties of AT$_1$ receptor antagonists.

No.	Drug	QPPCaco	P.H.O.A.	QPPMDCK	QPlogBB	CNS	Log BB Clark	QPlogKhsa
1	Losartan	186.35	90.61	190.35	−1.62	−2	−0.65	0.50
2	EXP-3174	41.95	81.81	46.56	−1.69	−2	−0.89	0.36
3	Valsartan	28.49	73.37	21.42	−1.98	−2	−1.05	−0.09
4	Irbesartan	633.07	100.00	301.82	−1.26	−2	−0.53	0.52
5	Eprosartan	5.26	56.76	4.55	−2.36	−2	−0.69	0.30
6	Candesartan	39.77	80.90	19.28	−1.77	−2	−1.10	0.43
7	Candesartan cilexetil	232.80	69.71	-	-	-	-	1.55
8	Telmisartan	202.65	88.09	112.06	−1.16	−2	0.07	1.70
9	Olmesartan	25.94	75.80	12.15	−2.19	−2	−1.33	0.33
10	Olmesartan medoxomil	57.27	55.42	-	-	-	-	0.58
11	Azilsartan	44.83	80.64	21.95	−1.68	−2	−1.21	0.32
12	Azilsartan medoxomil	78.03	58.43	-	-	-	-	0.52
13	Fimasartan	482.45	90.64	411.97	−1.36	−2	−0.70	0.69
14	PS-433540	619.70	92.42	297.67	−1.58	−2	−0.70	0.53

the range 3.20–5.50. At physiological pH of 7.4, these two acidic groups ionised at a high rate (98.76–99.99) and drugs exist as dianions. The pK$_a$ value of the 4,5-dihydro-1,2,4-oxadiazol-5-one moiety of azilsartan is 6.80 which is ionised at physiological pH partially (78,79). PS-433540 contains a sulphonamide acid group with pK$_a$ = 6.22, that is, at pH = 7.4 largely ionised (93.80%).

IV. PS-433540 has higher molecular weight (592.76) and higher log P (5.56). The telmisartan violation of the Rule of Five (too high log P and molecular weight) is compensated by the low number of rotatable bonds (7) and lower PSA (72.95 Å). Lower absorption of candesartan, olmesartan and azilsartan (PSA = 118.83–129.82 Å) was improved by preparing their prodrug forms with improved oral bioavailability. The absorption and distribution parameters of the AT$_1$ receptor antagonists were calculated by QikProp. The AT$_1$ receptor antagonists can be considered as moderately well absorbed drugs.

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