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The correlation of plasma protein binding and molecular properties of selected antifungal drugs

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Abstract: Antifungal agents are the group of drugs commonly prescribed in the treatment of fungal infections, which are widely spread among the global population. Their properties, such as absorption, distribution, metabolism, route of elimination or plasma protein binding (*PPB*), considerably influence their therapeutic success, while a number of the molecular physicochemical properties of the drug notably influence all these processes. Lipophilicity (log *P*), molecular weight (*Mw*), volume (*Vol*), polar surface area (*PSA*) and solubility (log *S*) play important roles in drug absorption, penetration into tissues, distribution and route of elimination or the degree of plasma protein binding. In this study, the relationships between these five molecular properties of eight antifungal drugs and their plasma protein binding data obtained from relevant literature were investigated. The Selected physicochemical molecular descriptors of the drug were calculated using software packages. The established relationships between *PPB* and *PSA*; *Mw*; *Vol* and log *S* were showed relatively poor correlation ($r < 0.35$). The best correlation was obtained for the relationship between *PPB* data and the lipophilicity descriptor *X* log *P*3 (correlation coefficient $r = 0.55$). In further investigation, multiple linear regression analysis was applied. The best correlation was obtained with application of lipophilicity with polar surface area ($r = 0.918$) and volume ($r = 0.916$) or molecular weight ($r = 0.896$) as independent variables.

Keywords: Antimycotics; therapeutic success; lipophilicity; polar surface area; molecular weight; volume; solubility.

INTRODUCTION

Many drugs bind with human plasma proteins. Plasma protein binding (*PPB*) is the reversible interaction of drugs with the proteins, which has great influence on the pharmacokinetic properties and pharmacodynamics properties of a drug. The efficiency of a drug may be affected by the degree to which it binds since only a fraction of unbound drug is able to cross cell membranes and exhibit pharmacological effects. Excessive plasma protein binding decreases the concen-

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tration of free and thus active drug form, requiring higher doses to achieve therapeutic concentration. Furthermore, administrating two drugs simultaneously can sometimes affect the unbound fraction of both. Thus, estimation of the binding of plasma protein is an important part of the characterization of drugs.

Fungal infections are widespread among the global population, with a tendency to increase and to develop resistance to appropriate and applicable drugs. It has been estimated that there are more than 5 million fungal species worldwide and approximately 300 fungal species have been recorded to cause disease in humans.[1] Most fungi are resistant to conventional antimicrobial drugs. In comparison to the number of drugs available to treat bacterial infections, the number of drugs available to treat fungal infections is comparatively small.[2]

Antifungal drugs, also called antimycotic drugs, are used to treat fungal infection (superficial and systemic infection). The first antifungal drug, amphotericin B deoxycholate, was introduced in 1958. This drug shows potent, broad–spectrum antifungal activity but is associated with significant renal toxicity and infusion reactions. The first generation of azole drugs became available in the 1990s and were frequently used as therapeutic alternatives to amphotericin B.[2] The second-generation of azole drugs, including voriconazole, posaconazole, and isavuconazole, entered market at the beginning of the 2000s. The major advantage of these agents is their extended spectrum of activity.[3]

Based on their site of action, antifungals can be grouped into three classes: azoles, which inhibit the synthesis of ergosterol (the main fungal sterol); polyenes, which interact physicochemically with fungal membrane sterols; and 5-fluorocytosine, which inhibits macromolecular synthesis.[4] Beside the antimycotic spectrum, the clinical efficacy of an antifungal drug is related to the plasma protein binding.[5] The activity of a drug can be the result of limited penetration of the protein-bound drug to the site of infection as well as limited ability of the protein-bound drug to bind at the site of activity.

Monika Schafer Korting *et al.* published that the influence of protein binding on azole (itraconazole and ketoconazole) antifungal activity is probably less reduced by albumin than is to be expected from *in vitro* binding studies.[6] On the other hand, despite a free fraction of 1 % in plasma, terbinafine (an allylamine derivative), rapidly penetrates into brain tissue, but inhibition of *Aspergillus* is lower in the presence of serum proteins.[7] Reduced bioavailability resulting from binding by serum may at least partly account for the low efficacy of terbinafine in experimental models of systemic infection, in contrast to its high efficacy in infections of the skin, nails and hair.[8]

The relevance of antifungal protein binding has been shown for most drugs[9] (Table I.). As can be seen, the range of serum protein binding ranges from 11 % (fluconazole) to 99 % (itraconazole and terbinafine)[10]. The extent of binding is dependent on the structure and physicochemical properties of the drug molecule.

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TABLE I. Plasma protein binding of antifungal drugs

No.	Antifungal	Plasma protein binding, %
1	Amphotericin B	>90
2	Fluconazole	11±1
3	Itraconazole	99.8
4	Ketoconazole	99
5	Posaconazole	98
6	Terbinafine	99
7	Voriconazole	58
8	Caspofungin	96.5

The aim of this study was to establish the correlation between protein binding and the physicochemical properties of selected antifungal drugs, *i.e.*, amphotericine B (polyene antifungals, systemic infections); terbinafine (allylamines, superficial infections); ketoconazole (imidazole derivative, systemic); fluconazole, itraconazole, posaconazole, voriconasole (triazole derivatives, systemic) and caspofungin.

Amphotericin B is the drug of choice for many systemic life–threatening fungal infections. It consists of two distinct regions, a hydrophobic and a hydrophilic one, and cannot cross the blood–brain barrier. Amphotericine B is insoluble in water thus several formulations have been invented to improve its intravenous bioavailability.

Terbinafine belongs to a newer allylamine class of antifungals. It is highly lipophilic and is used topically for superficial skin infections as a cream or powder. Terbinafine hydrochloride tablets are used to treat fungal nail and skin infections. In plasma, terbinafine is >99 % bound to plasma proteins and there are no specific binding sites.

Azoles (imidazoles and triazoles) are the largest class of antimycotics. Ketoconazole was the first orally active antifungal. It is slightly soluble in water (p*K*a 6.5) and more hydrophilic than other derivatives of imidazole (clotrimazole, miconazole). Fluconazole has two triazole rings and a hydroxy group that makes it water-soluble (log P = 0.31). As a free base, fluconazole is suitable for both oral and *i.v.* administration. Itraconazole, structurally related to ketoconazole and posaconazole, is a novel itraconazole analogue designed after its active ω–1 hydroxy metabolite. Voriconazole is a fluconazole analogue with an additional methyl group and one triazole ring replaced by fluorinated pyrimidine.

Caspofungin is a lipopeptide antifungal drug that belongs to a new class of antifungal agents with a broad spectrum of activity against all Candida species.

EXPERIMENTAL

The following antifungal agents were included in this investigation:

1. amphotericin B, (1*R*,3*S*,5*R*,6*R*,9*R*,11*R*,15*S*,16*R*,17*R*,18*S*,19*E*,21*E*,23*E*,25*E*,27*E*,29*E*,31*E*,33*R*,35*S*,36*R*,37*S*)-33-[(3-amino-3,6-dideoxy-β-D-mannopyranosyl)oxy]-1,3,5,6,9,

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11,17,37-octahydroxy-15,16,18-trimethy-13-oxo-14,39-dioxabicyclo[33.3.1]nonatriaconta--19,21,23,25,27,29,31–heptaene–36–carboxylic acid;

2. fluconazole, 2-(2,4-difluorophenyl)-1,3-bis(1*H*-1,2,4-triazol-1-yl)propan-2-ol;

3. itraconazole, (±)-1-[(*RS*)-2-butyl]-4-[*p*-[4-[*p*-[[(2*R*,4*S*)-rel-2-(2,4-dichlorophenyl)-2--(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-Δ2--1,2,4-triazolin-5-one;

4. ketoconazole, 1-[4-[4-[[2-(2,4-dichlorophenyl)-2-(imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazin-1-yl]ethanone;

5. posaconazole, 4-[4-[4-[4-[[(3*R*,5*R*)-5-(2,4-difluorophenyl)tetrahydro-5-(1*H*-1,2,4--triazol-1-ylmethyl)-3-furanyl]methoxy]phenyl]-1-piperazinyl]phenyl]-2-[(1*S*,2*S*)-1-ethyl-2--hydroxypropyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one;

6. terbinafine, [(2*E*)-6,6-dimethylhept-2-en-4-yn-1-yl](methyl)(naphthalen-1-ylmethyl)amine;

7. voriconazole, (2*R*,3*S*)-2-(2,4-difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1*H*--1,2,4-triazol-1-yl)butan-2-ol;

8. caspofungin, (10*R*,12*S*)-*N*-{(2*R*,6*S*,9*S*,11*R*,12*S*,14a*S*,15*S*,20*S*,23*S*,25a*S*)-12-[(2-aminoethyl)amino]-20-[(1*R*)-3-amino-1-hydroxypropyl]-23-[(1*S*,2*S*)-1,2-dihydroxy-2-(4-hydroxyphenyl)ethyl]-2,11,15-trihydroxy-6-[(1*R*)-1-hydroxyethyl]-5,8,14,19,22,25-hexaoxotetracosahydro-1*H*-dipyrrolo[2,1-*c*:2',1'-l][1,4,7,10,13,16]hexaazacyclohenicosin-9-yl}-10,12--dimethyltetradecanamide.

The physicochemical properties of the selected antifungal drugs were described with 5 selected molecular descriptors: log *P* (lipophilicity); log *S* (solubility); *PSA* (polar surface area, electronic descriptor); *Mw* (molecular weight, constitutional parameter) and *Vol* (volume value, geometric descriptor). The log *P* coefficient is well–known as one of the principal parameters for an estimation of the lipophilicity of drugs and determines their pharmacokinetic properties.[11] For the selected antifungal compounds, seven different lipophilicity parameters: *A* log *P*s, *AC* log *P*, *mi* log *P*, *A* log *P*, *M* log *P*, *X* log *P*2 and *X* log *P*3 were calculated. The most suitable log *P* value was chosen based on its best matching with the values of binding degree of plasma protein data, which were obtained from relevant literature.[12-14] The values of log *P* and log *S* were calculated using the software package Virtual Computational Chemistry Laboratory. The *PSA*, *Mw* and *Vol* were calculated using the Molinspiration software package.[15,16]

The calculation of the lipophilicity descriptors, different log *P* values (*A* log *Ps*, *AC* log *P*, *mi* log *P*, *A* log *P*, *M* log *P*, *X* log *P2*, *X* log *P*3) were performed using the Virtual Computational Chemistry Laboratory software package.[16] The first letters of molecular descriptor mark are related to the method of calculation of lipophilicity. The methods applied can be divided into substructure-based (atom-based and fragmental methods) and property-based methods. The atom-based methods provide several lipophilicity descriptors (*A* log *P*, *AC* log *P*, *X* log *P*2, *X* log *P3,*) in which molecules are reduced to the single atoms and commonly do not apply corrections, while the fragmental methods reduce molecules into fragments with corrections application and summing contributions of all fragment to provide final log *P* value (*mi* log *P*). The property–based methods use the description of the entire molecules and include: empirical methods based on the 3D structure of the molecule or methods based on topological descriptors (*M* log *P, A* log *Ps*).[17-19] The abbreviations used for descriptors are: *A* log*Ps*, neural networks are used to predict the log *P*; *AC* log *P*, atom-additive method; *mi* log *P*, calculation include charge interactions and organometallic compounds; *A* log *P*, classical atomic contribution approach; *M* log *P*, Moriguchi octanol–water partition

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coefficient; *X* log *P2*, additive atom/group model and *X* log *P3*, based on additive atom/group model that starts from the known log *P* value of a similar reference compound.[20]

Statistical analysis was performed using Microsoft Excel 2003 and Origin 7.0 Pro (Origin Lab Corporation, USA).

RESULTS AND DISCUSSION

The lipophilicity considerably influences the ADME properties, namely, absorption, distribution, metabolism and elimination, of a drug[17,18] and it is generally known that molecules with high lipophilicity show higher values of plasma protein binding as well as better oral absorption. Consequently, such molecules show better bioavailability, distribution and penetration into tissues, in comparison to the ones with similar properties but less lipophilic characteristics.

Considering these, seven lipophilicity parameters, log *P* values, for all selected antifungal agents were calculated using the Virtual Computational Chemistry Laboratory software package.

These methods, depending on the manner of calculation (property-based and substructure-based methods) and differences in-between provide dissimilarities among the absolute log *P* values.[19,20]

All the collected log *P* and log *S* values of the investigated antifungal agents are given in Table II.

TABLE II. The lipophilicity and solubility values of the investigated antifungal agents

No.	Antifungal	*A* log *P*s	*AC* log *P*	*mi* log *P*	*A* log *P*	*M* log *P*	*X* log *P*2	*X* log *P*3	*A* log *S*	*AC* log *S*	Ave log *S*
1	Amphotericin B	–0.66	2.38	–2.49	–0.16	–1.01	0.80	0.00	–4.05	–5.08	–4.56
2	Fluconazole	0.58	–0.21	–0.12	0.75	3.49	0.38	0.35	–2.34	–2.17	–2.26
3	Itraconazole	5.48	4.95	5.32	6.47	5.13	6.47	5.66	–4.86	–7.30	–6.08
4	Ketoconazole	4.30	2.88	3.77	3.61	3.00	3.96	4.34	–4.76	–2.99	–3.88
5	Posaconazole	4.71	3.88	4.33	5.13	4.90	5.48	4.59	–4.77	–7.42	–6.09
6	Terbinafine	5.51	5.55	5.72	5.34	4.98	5.89	5.59	–5.60	–6.14	–5.87
7	Voriconazole	1.65	1.11	1.49	2.07	3.68	0.97	1.51	–3.55	–3.23	–3.39
8	Caspofungin	0.17	–2.75	–4.59	NA	NA	–1.32	0.34	–3.47	–3.54	–3.51

Terbinafine and the group of azoles, *i.e.*, itraconazole, posaconazole and ketoconazole, have the highest lipophilicity. The difference in the chemical structures of the azoles contribute to different values of log *P*s. Thus, itraconazole is the aryl-triazolone derivative of ketokonazole with a *N*-1-branched alkyl group that contribute to lipophilicity; posaconazole is the hydroxylated analogue of itraconazole. Amphotericin B, fluconazole and caspofungin show the lowest lipophilicity.

Intercorrelations of different log *P* values were calculated for the seven investigated molecules (caspofungin was not included in the intercorrelation since its *A* log *P* and *M* log *P* values were not available). The obtained results

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show good agreements, with correlation coefficients, mostly higher than 0.7 (Table III). The best results were observed for the *X* log *P*3 data.

TABLE III. Intercorrelations between different log *P* values of investigated antifungal agents (with the exception of caspofungin)

	A log *P*s	*AC* log *P*	*mi* log *P*	*A* log *P*	*M* log *P*	*X* log *P*2	*X* log *P*3
A log *P*s	1						
AC log *P*	0.8117	1					
mi log *P*	0.9910	0.7597	1				
A log *P*	0.9771	0.8298	0.9680	1			
M log *P*	0.7989	0.4065	0.8590	0.8096	1		
X log *P*2	0.9555	0.9196	0.9170	0.9671	0.6670	1	
X log *P*3	0.9932	0.8680	0.9720	0.9752	0.7321	0.9760	1

Solubility is a molecular property with important influences on the absorption and transport of a drug to the blood, as well as on the degree of plasma protein binding. Molecules with very low solubility usually exhibit high lipophilicity and these properties can lead to poor oral absorption. The average calculated solubility values (Ave log *S*) of antifungal agents range from (–6.08) for itraconazole and (–6.09) for posaconazole to (–2.26) for fluconazole and (–3.39) for voriconazole (Table II).

Fluconazole, a bis triazole derivative, has the highest solubility (–2.26), which is in accordance with its chemical structure. Its analogue, voriconazole, has a fluorine substituted pyrimidine ring instead of one of the triazoles that makes it less soluble in comparison with Fluconazole, but still more soluble than the other investigated compounds. Ketoconazole has similar solubility to that of voriconazole (–3.88 and –3.39 respectively) that can be attributed to four oxygen atoms in its structure, even without two triazole rings. Amfotericin B has a long carbohydrate chain indicating its low solubility, but the large number of hydroxy groups, as well as a free carboxylic group, makes it more water soluble (–4.56). The naphthalene ring in the terbinafine structure and the longer carbohydrate chain indicates the lower water solubility/higher lipophilicity of this compound. Itraconazole and Posaconazole are the most lipophilic of all the examined structures, which is obvious from their structure. They have the highest molecular weight and many carbon atoms, and three benzene rings indicating their low water solubility (–6.08 for ketoconazole and –6.09 for posaconazole). It is necessary to emphasize that the water solubility assessment of all the above compounds is not simple. Solubility largely depends on the 3D structure, and not only on the basic structural elements.

Additional molecular properties such as molecular weight, molecular volume and polar surface area (Table IV) play important roles in the pharmacokinetics of drugs.

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TABLE IV. The calculated molecular descriptors, molecular weight (*Mw*), volume value (*Vol*) and polar surface area (*PSA*) for the antifungal agents

No.	Antifungal	*Mw* / Da	*Vol* / Å^3	*PSA* / Å^2
1	Amphotericin B	924	865	320
2	Fluconazole	306	249	82
3	Itraconazole	706	608	105
4	Ketoconazole	531	452	69
5	Posaconazole	701	623	116
6	Terbinafine	291	307	3
7	Voriconazole	349	285	77
8	Caspofungin	1093	1026	412

Among all investigated antifungal drugs, terbinafine (with a *PSA* value of 3 Å^2) exhibits the lowest value of *PSA*, while amphotericin B and caspofungin show much higher values of PSA (320 and 412 Å^2, respectively). However, the other five investigated antifungal drugs showed *PSA* values in the range 69–116 Å^2. Similarly to the ordering of the *PSA* values, the molecular weights of investigated drugs are in the range 291 Da for terbinafine to 924 Da for amphotericin B and 1093 Da for caspofungin, while the volume value is the lowest for fluconazole (249 Da) and the highest for amphotericin B (865 Da) and caspofungin (1026 Da).

From the obtained results, it could be concluded that the lowest values of *PSA* (3 Å^2) and *Mw* (291 Da) are associated with terbinafine, while the highest values of all three parameters were obtained for amphotericin B and caspofungin, *i.e.*, *Mw* (924 and 1093 Da, respectively), *PSA* (320 and 412 Å^2, respectively) and *Vol* (865 and 1026 Å^3, respectively). Terbinafine was already shown to have a very high value of lipophilicity and low water solubility, while amphotericin B and caspofungin could be indicated as antifungal agents with relatively low lipophilicity and high water solubility.

Plasma protein binding

According to the data obtained from the relevant literature, the investigated antifungal agents (amphotericin B, fluconazole, itraconazole, ketoconazole, posaconazole, terbinafine, voriconazole and caspofungin) have high and relatively similar values of plasma protein binding (Table I). The degree of plasma protein binding degree (*PPB*) ranges from 90 (amphotericin B) to 99.8 % (itraconazole). Ketoconazole, posaconazole, terbinafine and caspofungin also have high and very similar values of *PPB*: 99, 98, 99 and 97 %, respectively. However, fluconazole and voriconazole represent exceptions and they have significantly lower values of plasma protein binding (12 and 58 %, respectively).[12–14]

Statistical analysis was performed in order to determine whether there are relationships between *PPB* and the molecular descriptors. The correlations between *PPB* % and the calculated molecular descriptors of the antifungal agents

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were investigated using simple linear regression. The relationships between *PPB* and *PSA*, *Mw*, *Vol* and log *S* were established showing relatively poor correlation ($r < 0.35$). The best correlation was obtained for the relationship between *PPB* data and the lipophilicity descriptor *X* log *P*3 (correlation coefficient $r = 0.55$). Therefore, the lipophilicity descriptor *X* log *P*3 was chosen for further study.

Since there is more than one descriptor that influences *PPB*, multiple linear regression analysis (MLR) was applied. Multiple regression models have the possibility to describe how a single response variable (*PPB*) depends linearly on the *X* log *P*3 values and one additional molecular descriptor: *Mw*, or *Vol*, or *PSA*, or log *S*.

The obtained correlation coefficients (r) were in the range from 0.896 to 0.918. The lowest correlation coefficient (0.563) was obtained for aqueous solubility data (log *S*). The best r value were established for the electronic descriptor *PSA* (0.918) and the geometric descriptor *Vol* (0.916).

According Asuero *et al.*,[21] all relationships with obtained correlation coefficients higher than 0.80 could be considered as very good, especially in the case of the limited number of compounds (eight investigated antifungal drugs). The best-established correlations using MLR analysis are presented with Eqs. (1)–(3):

$$\text{Predicted } PPB, \% = 14.835\ (\pm 2.948)\ X \log P3 + 0.217\ (\pm 0.052)\ PSA + 8.049\ (\pm 15.372) \quad (1)$$

with $n = 8$; $r = 0.918$; $SD = 14.755$; $F = 13.379$;

$$\text{Predicted } PPB, \% = 9.872\ (\pm 2.390)\ X \log P3 + 0.085\ (\pm 0.020)\ Vol + 6.651\ (\pm 15.897) \quad (2)$$

with $n = 8$; $r = 0.916$; $SD = 14.941$; $F = 12.986$.

$$\text{Predicted } PPB, \% = 9.740\ (\pm 2.635)\ X \log P3 + 0.079(\pm 0.022)\ \text{Mw} + 5.862\ (\pm 18.177) \quad (3)$$

with $n = 8$; $r = 0.896$; $SD = 16.494$; $F = 10.206$

All results obtained using MLR analysis (applying two different descriptors as independent variables) are presented in Table V and Fig. 1.

TABLE V. The antifungal agents *PPB* data (%) collected from the literature (*) and predicted using: A) *X* log *P*3 and *PSA*; B) *X* log *P*3 and *Vol* data; C) X log *P*3 and *Mw*; D) *X* log *P*3; log *S*

No.	Antifungal	*	A	B	C
1	Amphotericin B	90	77	81	79
2	Fluconazole	12	31	31	33
3	Itraconazole	100	115	115	117
4	Ketoconazole	99	87	88	90
5	Posaconazole	98	101	105	106
6	Terbinafine	99	92	88	83
7	Voriconazole	58	47	46	48
8	Caspofungin	97	102	98	96

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Intercorrelations between all the obtained *PPB* data for the investigated antifungal agents: those collected from relevant literature[12–14] and predicted using *X* log *P*3 and PSA; *X* log *P*3 and *Vol* data; *X* log *P*3 and Mw and *X* log *P*3 and log *S*, are presented in Table VI.

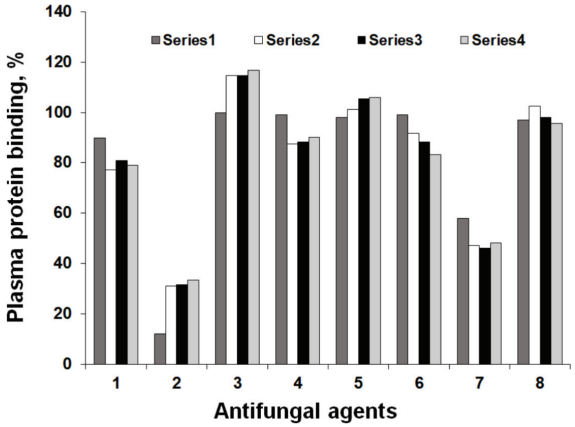

Fig. 1. The relationship between the *PPB* of the antifungal agents collected from literature (series 1) and those predicted using *X* log *P*3 and *PSA* (series 2); *X* log *P*3 and *Vol* (series 3); *X* log *P*3 and *Mw* (series 4).

TABLE VI. Intercorrelations between different *PPB* data (%) of the investigated antifungal agents investigated: those collected from relevant literature (*) and those predicted using: A) *X* log *P*3 and *PSA*; B) *X* log *P*3 and *Vol* data; C) *X* log *P*3 and *Mw*; D) *X* log *P*3 and log *S*

	*	A	B	C	D
*	1				
A	0.918	1			
B	0.916	0.995	1		
C	0.896	0.986	0.996	1	
D	0.563	0.640	0.658	0.690	1

The selection criteria for drug-like properties (namely drugs molecular properties responsible for its medical applicability, safety and efficiency)[22] of the investigated antifungal drugs are reported in Table VII.

TABLE VII. Drug – like properties of the investigated antifungal agents

Molecular weight, Da	291–1093
Lipophilicity descriptor (*X* log *P*3)	0.00–5.66
Average aqueous solubility (Ave log *S*)	(–6.09)–(–2.26)
Volume, Å^3	249–1026
Polar surface area, Å^2	3–412

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CONCLUSIONS

The discovery of new pharmacologically active substances and modelling of drugs with antifungal activity led to the necessity of predicting drugs properties and their ADME data. The relations that were found between the plasma protein binding data of the antifungal drugs and their calculated molecular descriptors confirmed that molecular physicochemical properties of the drugs are essential for drugs plasma protein binding and further for targeting appropriate receptors and drugs activity and medical efficiency. The understanding of molecular physicochemical properties of the investigated drugs is especially important in design and synthesize of new drug candidates with optimal ratio between efficiency and side effects.

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ИЗВОД

КОРЕЛАЦИЈА СТЕПЕНА ВЕЗИВАЊА ЗА ПРОТЕИНЕ ПЛАЗМЕ И ОСОБИНА МОЛЕКУЛА ОДАБРАНИХ АНТИФУНГАЛНИХ ЛЕКОВА

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Антифунгална средства представљају групу лекова који се примењују у лечењу гљивичних инфекција, данас широко распрострањених међу глобалном популацијом. Од њихових особина као што су апсорпција, дистрибуција, метаболизам, пут елиминације или везивање за протеине плазме значајно зависи њихов терапеутски успех, а бројне физичко–хемијске особине молекула лека утичу на све ове процесе. Липофилност ($\log P$), молекулска маса (Mw), запремина (Vol), поларна површина (PSA) и растворљивост ($\log S$) играју важну улогу у апсорпцији лека, продирању у ткива, дистрибуцији, путу елиминације или степену везивања за протеине плазме. У овом раду за осам антифунгалних лекова истражени су односи између особина молекула и степена њиховог везивања за протеине плазме (PPB). Дескриптори физичко–хемијских особина молекула испитиваних антифунгалних лекова израчунати су помоћу одабраних софтверских пакета, док су подаци о њиховом PPB прикупљени из одговарајуће литературе. Односи између PPB и PSA, Mw, Vol и $\log S$ показали су лошу корелацију ($r < 0{,}35$) док је боља корелација добијена је између података о PPB и дескриптора липофилности, $X\log P3$ вредности ($r = 0{,}55$). У даљем испитивању, примењена је вишеструка линеарна регресиона анализа. Најбоље зависности добијене су између PPB вредности и липофилности уз примену поларне површине молекула ($r = 0{,}918$), волумена ($r = 0{,}916$) и молекулске масе ($r = 0{,}896$) као независно променљивих.

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