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Assessment of the relationship between the molecular properties of calcium channel blockers and plasma protein binding data

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Abstract: In this study we investigated the relationship between the calcium channel blockers (CCBs), amlodipine, felodipine, isradipine, nicardipine, nifedipine, nimodipine, nisoldipine, verapamil and diltiazem, and their calculated molecular descriptors: polar surface area (PSA), molecular weight (Mw), volume value (Vol), aqueous solubility data (logS), lipophilicity (logP), acidity (pKa values) and plasma protein binding (PPB) data, obtained from relevant literature. The relationships between the computed molecular properties of selected CCBs and their PPB data were investigated by simple linear regression analysis that revealed very low correlations ($R2<0.35$). When multiple linear regression (MLR) analysis was applied to investigate reliable correlations between the CCBs' calculated molecular descriptors and PPB data, the best correlations were found for the relationships between CCBs, and PPB data and lipophilicity, and with application of the molecular descriptor (Mw, Vol, or pKa) data as additional independent variables ($R2=0.623$; $R2=0.741$; $R2=0.657$, respectively), with an acceptable probability value ($P<0.05$), confirming that lipophilicity, together with other molecular properties, are essential for the drugs' PPB. We conclude that this could be considered as an additional *in vitro* approach for modeling CCBs.

Key words: calcium channel blockers; hydrophobicity; molecular properties; lipophilicity; plasma protein binding

INTRODUCTION

High blood pressure or hypertension is a global health problem. Calcium channel blockers (CCBs) are widely used drugs in cardiovascular medicine for the treatment of hypertension, angina pectoris, supraventricular dysrhythmias, hypertrophic cardiomyopathy or after myocardial infarction [1-5]. According to available literature data, CCBs have variable oral bioavailability (from 5% for nisoldipine, through 58% for nifedipine, to about 80% for amlodipine) due to an extensive first-pass metabolism of most of these drugs. Their half-life is relatively short, mostly less than 12 h, with the exception of amlodipine. The plasma protein binding values (PPB) of CCBs are relatively similar and they are ranged from 75% for diltiazem to 99% for felodipine and nisoldipine. They have dual routes of elimination, renal and fecal [1-5].

CCBs can be combined with other antihypertensive drugs, such as angiotensin receptor blockers or drugs which block the rennin-angiotensin system [1-5]. The drugs' properties such as absorption, distribution, plasma protein binding, metabolism and routes of elimination noticeably influence their clinical success [6]. On the other hand, the number of the drugs' physical and chemical properties significantly influence these properties and consequently the clinical success of drugs.

Lipophilicity, molecular weight, molecular volume, polar surface area, acidity and solubility play important roles in drugs absorption, penetration into tissues, distribution, plasma protein binding and the route of elimination [7-10]. The molecules with high lipophilicity show a higher degree of absorption, higher plasma protein binding, better penetration into tis-

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sues and distribution compared to the less lipophilic ones. Also, weakly lipophilic drugs are mostly eliminated in the urine, while highly lipophilic drugs usually exhibit a high degree of fecal elimination, according to the well-known Lipinski "rule of 5". However, this rule also predicts that low absorption or permeation of drugs is more likely when there are more than 5 hydrogen-bond donors, 10 hydrogen-bond acceptors, if the molecular weight is greater than 500 and the calculated logP is greater than 5 [11].

A number authors have studied various antihypertensive drugs, including CCBs, their design and synthesis [12,13], pharmacokinetics, pharmacodynamics and efficacy [14-17]. We have examined the correlations between the calculated molecular descriptors, mainly the lipophilicity of selected antihypertensive drugs, their PPB data, absorption and elimination in established and appropriate models [18-22]. The aim of the present study was to estimate the relationship between plasma protein binding data of nine CCBs (amlodipine, felodipine, isradipine, nicardipine, nifedipine, nimodipine, nisoldipine, verapamil and diltiazem) and their *in silico* molecular properties.

MATERIALS AND METHODS

Nine frequently used CCBs, amlodipine, felodipine, isradipine, nicardipine, nifedipine, nimodipine, nisoldipine, verapamil, diltiazem, were investigated (Table 1). The software package Molinspiration Depiction Software (www.molinspiration.com) was used for the calculation of electronic descriptors, polar surface area (PSA), the constitutional parameter, molecular weight (Mw) and the geometric descriptor, volume value (Vol). The CCBs aqueous solubility data (log*S*) as well as the CCBs lipophilicity descriptors, nine different log*P* values (Alog*Ps,* AClog*P,* AB/log*P,* milog*P*, Alog*P,* Mlog*P,* KOWWINlog*P,* XLOG*P*2, XLOG*P*3) were calculated using the software package Virtual Computational Chemistry Laboratory (www.vcclab.org) Chemdraw ultra 12.0 was used for calculating another lipophilicity parameter – Clog*P* values. The software package DrugBank (www.drugbank.ca) was used for the calculation the acidity descriptor, pK_a. The relationships between CCB PPB data and different molecular descriptors were investigated using multiple linear regression analysis (MLR). The calculated molecular descriptors are presented in Table 2. Microsoft Excel 2003 and Origin 7.0 PRO (Origin Lab Corporation, USA) were used for statistical analysis. The data for the PPB were obtained from the relevant literature [2] and are presented in Table 2.

Table 1. The investigated CCBs.

1. Amlodipine	3-ethyl-5-methyl2-[(2-aminoethoxy) methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate;
2. Felodipine	3-ethyl-5-methyl4-(2,3-dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate;
3. Isradipine	3-methyl-5-propan-2-yl-4-(2,1,3-benzoxadiazol-4-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate;
4. Nicardipine	3-{2-[benzyl(methyl)amino]ethyl} 5-methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate;
5. Nifedipine	3,5-dimethyl-2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate;
6. Nimodipine	3-(2-methoxyethyl)-5-propan-2-yl-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate;
7. Nisoldipine	3-methyl 5-(2-methylpropyl) 2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate**;**
8. Verapamil	2-(3,4-dimethoxyphenyl)-5-{[2-(3,4-dimethoxyphenyl)ethyl](methyl)amino}-2-(propan-2-yl)pentanenitrile;
9. diltiazem	(2S,3S)-5-[2-(dimethylamino)ethyl]-2-(4-methoxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl acetate.

RESULTS AND DISCUSSION

According to literature data, CCBs have relatively similar and high values of PPB that range from 75% for diltiazem, to 99% for felodipine and nisoldipine (Table 2) [2]. The molecular descriptors were calculated using four different software packages (Table 2). To assess PPB of CCBs using *in silico* molecular descriptors, correlations between CCBs plasma and PPB data obtained from relevant literature and all six calculated molecular descriptors (PSA, Mw, Vol, log*P*, pKa, log*S*) were initially investigated using simple linear

Table 2. The CCBs calculated molecular descriptors as well as plasma protein binding degree data collected from relevant literature (1) and predicted using ClogP and Mw (2); ClogP and Vol values (3); ClogP and pKa values (4).

	1. Amlodipine	2. Felodipine	3. Isradipine	4. Nicardipine	5. Nifedipine	6. Nimodipine	7. Nisoldipine	8. Verapamil	9. Diltiazem
ClogP	3.43	2.24	3.92	5.23	3.13	4.00	4.58	4.47	1.19
pKa	9.46	5.39	5.33	8.18	5.33	5.41	5.32	9.68	8.18
logS	-4.02	-4.64	-3.15	-4.63	-3.76	-4.19	-4.40	-4.79	-3.90
Mw	408.9	384.3	371.4	479.5	346.3	418.4	388.4	454.6	414.5
Vol	363.9	323.3	330.1	437.4	302.8	378.8	353.0	454.3	377.7
PSA	100	65	104	114	110	120	110	64	59
PPB (1)	93	99	95	96	96	96	99	90	75
PPB (2)	92	89	99	94	97	94	100	93	81
PPB (3)	93	91	99	95	98	95	100	89	79
PPB (4)	87	92	98	97	95	98	100	91	82

regression, which in most cases provided very poor correlations, with coefficients R^2<0.10. The only correlation between CCB data regarding PPB and their calculated values of PSA, pKa and ClogP provided slightly higher correlations, with R^2~0.35. Examination of the relationships between CCB PPB data and different molecular descriptors Mw, Vol and pKa data as additional independent variables by MLR provided significantly higher correlations (R^2=0.623; R^2=0.741; R^2=0.657 respectively) with acceptable probability values (P<0.05). The obtained correlations are presented by the following equations as follows:

Eq.1:

$PPB._{pred}(\%) = 4.945(\pm1.632)\text{Clog}P - 0.103(\pm0.049)\,Mw + 117.607(\pm18.612)$,

with n=9; R^2=0.623; S.D.=5.229; F=4.962;

Eq.2:

$PPB_{pred}(\%) = 5.420(\pm1.383)\text{Clog}P - 0.103(\pm0.034)\,Vol + 111.770(\pm11.342)$,

with n=9; R^2=0.741; S.D.=4.339; F=8.569;

Eq.3:

$PPB_{pred}(\%) = 3.692(\pm1.411)\text{Clog}P - 2.129(\pm0.92)\,pKa + 94.745(\pm8.063)$,

with n=9; R^2=0.657; S.D.=4.987; F=5.756.

The established correlations can be considered as good [23]. All values of CCBs' PPB data predicted using the above equations are presented in Table 2 and Fig. 1.

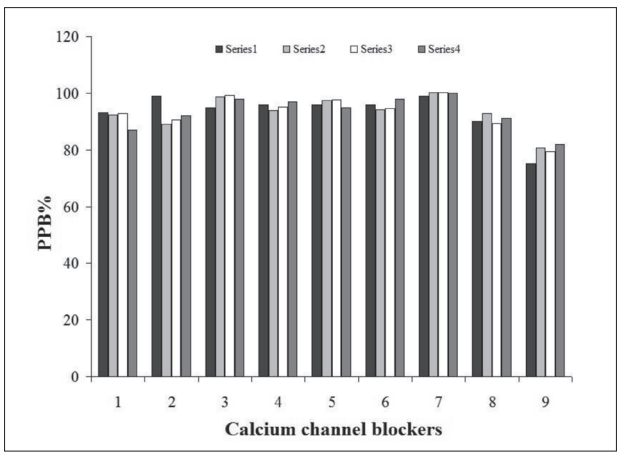

Fig. 1. Relationships between the PPB data of the investigated CCBs. The data were obtained from [2] (S1) and predicted using ClogP and Mw (S2), ClogP and Vol (S3), and ClogP and pKa values (S4). The numbers refer to the CCBs as presented in Table 1.

All calculated descriptors play important roles in the drugs' absorption, distribution, metabolism, elimination as well as plasma protein binding [24,25]. In the first step of the investigation, the correlations between CCBs and PPB data obtained from relevant literature and all calculated descriptors were investigated using simple linear regression. The PPB data and their calculated molecular descriptors showed very low correlations, with R2 lower than 0.10. Only for correlations between PPB data and the molecular descriptors PSA, pKa, and ClogP were better. Following this preliminary investigation, in the next stage of the study, the relationships between PPB and two different CCB molecular descriptors were investigated using MLR. ClogP as a lipophilicity descriptor was initially chosen as the first independent variable, since from all lipophilicity descriptors it showed the best

correlations with the CCB PPB data, the values of Mw, Vol, pKa and logS were chosen as possible, second independent variables; the values of the electronic descriptor PSA could not be used since the correlation of R2 with ClogP values was 0.39.

Lipophilicity is one of the most important physicochemical properties of a drug. Lipophilic molecules have higher absorption, penetration into tissues and a wider distribution. Molecules with higher lipophilicity [26,27] show higher values of PPB in comparison to the less lipophilic compounds with similar properties. Lipophilicity can be characterized by the partition coefficient ($\log P_{O/W}$) in *n*-octanol/water. The so-called shake flask method is a traditional technique for experimental determination of a molecule's log*P* values, as a measure of its lipophilicity. Thin-layer chromatography as well as high-performance liquid chromatography are established methods for evaluating a molecule's lipophilicity. For structurally different compounds, these methods can yield a significant amount of retention data, which can be well correlated with their lipophilicity [26,27]. The calculated log*P* values and *in silico*-obtained hydrophobicity parameters, are generally accepted measures of a drug's lipophilicity [26,27].

The numbers of lipophilicity descriptors (ClogP, AlogP, MlogP, KOWWINlogP, AlogPs, AClogP, AB/logP, milogP, XLOGP2, XLOGP3) were calculated for the investigated group of CCBs using several different software packages. Different log*P* can be calculated by substructure-based and property-based methods [26,27], with two groups of substructure-based methods: fragmental and atom-based. The fragmental-based methods cut molecules into different fragments, and after application of correction factors and summing all fragment contributions, log*P* (Clog*P*, KOWWINlog*P*, Milog*P*) is obtained. The atom-based methods (Alog*P*, Xlog*P*2, Xlog*P*3) cut molecules to single atoms and usually do not apply corrections [26,27]. The property-based methods use the description of the entire molecules, including methods based on topological descriptors, methods based on molecules' 3D-structure or empirical methods (Alog*P*s) [26,27]; the distinctions between absolute logP values of selected CCBs are caused by the differences between the calculation methods [26,27].

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