Journal of Molecular Graphics and Modelling 28 (2009) 245–252

Contents lists available at ScienceDirect

Journal of Molecular Graphics and Modelling

journal homepage: www.elsevier.com/locate/JMGM

Prediction of hepatic microsomal intrinsic clearance and human clearance values for drugs

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ARTICLE INFO

Article history:
Received 19 May 2009
Received in revised form 20 July 2009
Accepted 3 August 2009
Available online 8 August 2009

Keywords:
QSAR
Hepatic clearance
Human clearance
Drug metabolism
Cytochrome P450 enzyme

ABSTRACT

Twenty-nine drugs of different structures were used in theoretical QSAR analysis of human hepatic microsomal intrinsic clearance (*in vitro* $T_{1/2}$ and *in vitro* CL'_{int}) and whole body clearance (CL_{blood}). The examined compounds demonstrated a wide range of scaled intrinsic clearance values. Constitutional, geometrical, physico-chemical and electronic descriptors were computed for the examined structures by use of the Marvin Sketch 5.1.3_2, the Chem3D Ultra 7.0.0 and the Dragon 5.4 program. Partial least squares regression (PLSR), has been applied for selection of the most relevant molecular descriptors and development of quantitative structure–activity relatioship (QSAR) model for human hepatic microsomal intrinsic clearance (*in vitro* $T_{1/2}$).

Optimal QSAR models with nine and ten variables, $R^2 > 0.808$ and cross-validation parameter $q^2_{pre} > 0.623$, were selected and compared. Since the microsomal *in vitro* $T_{1/2}$ data can be used for calculation of *in vitro* CL'_{int} and *in vivo* CL_{blood}, the developed QSAR model will enable one to analyze the kinetics of cytochrome P450-mediated reactions in term of intrinsic clearance and whole body clearance.

A comparison is made between predictions produced from the QSAR analysis and experimental data, and there appears to be generally satisfactory correlations with the literature values for intrinsic clearance data.

1. Introduction

The cytochromes P450 (CYP) represent a superfamily of heme-thiolate proteins of which over 5000 members are currently known [1,2]. These enzymes are generally associated with the Phase 1 oxidative metabolism of foreign compounds [1,2].

The use of *in vitro* drug metabolism data in the understanding of *in vivo* pharmacokinetic data has recently become an area of scientific interest [3,4].

Several investigators have recently reported correlation between *in vivo* clearance values and clearance values calculated from human liver microsomal metabolism intrinsic clearance data, such as *in vitro* $T_{1/2}$ and *in vitro* CL'_{int} [3–6].

Intrinsic clearance values can be obtained by determination of the maximal velocity of the enzyme-catalyzed reaction (V_{max}) and *Michaelis* constant for the enzyme–substrate complex (K_m), leading to the derivation of CL_{int} from the ratio of these two quantities. This approach is very useful for drugs where the compound is metabolized by one major route [5,7].

The other method for calculation of intrinsic clearance (CL'_{int}), called "*in vitro* $T_{1/2}$ method", is based on measurement of the first-order rate constant for consumption of the substrate at low concentration [7]. In the determination of the *in vitro* $T_{1/2}$, the $Analyte/Internal_{standard}$ peak height ratios were converted to remaining percentage drug. The slope of the linear regression was used in the conversion to *in vitro* $T_{1/2}$ [7]. From the *in vitro* $T_{1/2}$ data can be calculated for the *in vitro* clearance (CL'_{int}) and the *in vivo* drug clearance CL_{blood} values [7]. Therefore, the development of QSAR model for prediction of the human hepatic microsomal intrinsic clearance *in vitro* $T_{1/2}$ value would enable evaluation of the other two important pharmacokinetic parameters, viz. the *in vitro* drug clearance (CL'_{int}) and the *in vivo* drug clearance CL_{blood}.

The human hepatic microsomal metabolism data were obtained for 29 drugs, using the *in vitro* $T_{1/2}$ approach [3]. The drugs used in this experiment spanned a broad range of structural types and expressed a wide range of intrinsic clearance values (CL'_{int}: 0.5–189 mL/(min kg)). Main objective of the theoretical study described herein is to calculate molecular descriptors for the selected compounds and then to develop QSAR model for prediction of the both, *in vitro* and *in vivo* drug clearance parameters ($T_{1/2}$, CL'_{int}, and CL_{blood}). Furthermore, the molecular descriptors that were used for QSAR model formation could

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doi:10.1016/j.jmgm.2009.08.002

indicate on molecular properties that play an important role in pharmacokinetics of drugs.

2. Experimental

The human *in vitro* $T_{1/2}$ clearance data for 29 drugs were collected from the literature [3], as they were tested using the same experimental procedure. The compounds were selected with an intention of covering a wide range of *in vitro* $T_{1/2}$ values. The *in vitro* clearance (CL'_{int}) and the *in vivo* drug clearance CL_{blood} values were calculated (Eqs. (1) and (2)) [7].

Conversion to *in vitro* intrinsic CL'_{int} (in units of mL/(min kg)) was done using the following formula [7]:

$$CL'_{int} = \frac{0.693}{\text{in vitro } T_{1/2}} \cdot \frac{\text{ml, incubation}}{\text{mg, microsomes}} \cdot \frac{45\,\text{mg, microsomes}}{\text{gm, liver}} \cdot \frac{20\,\text{gm, liver}}{\text{kg, body-weight}} \quad (1)$$

Prediction of *in vivo* human clearance values (CL_{blood}) was obtained using the following formula [3]:

$$CL_{blood} = Q\left(1 - e^{(-CL_{int}/Q)}\right) \quad (2)$$

The QSAR study was started with the pK_a calculation and selection of dominant molecules/cations at physiological pH for all examined compounds (**1**–**29**, Fig. 1), using the Marvin Sketch 5.1.3_2 program [8]. The Marvin 5.1.3_2 computational algorithms are based on the fundamental chemical structure theory to estimate a variety of chemical reactivity parameters.

Minimum energy conformations of all analyzed compounds (**1**–**29**, Fig. 1) were obtained by the Molecular Orbital PACkage/Parametric Method Vs.3 (MOPAC/PM_3) method [9,10]. Since steric and conformational effects may also operate in the intrinsic clearance, the minimum energy of conformers was compared to the multiple isoforms and the conformers with lowest energy were selected for the study. Molecular properties of the examined models were determined by use of the Marvin Sketch 5.1.3_2 [8], ChemSAR for Excel in Chem3D Ultra 7.0.0 [11] and Dragon 5.4 programs [12]. The Marvin 5.1.3_2 and Chem3D Ultra 7.0.0 programs were applied for computation of 26 molecular descriptors, while the Dragon 5.4 program was used for calculation of more than 1600 molecular descriptors that are divided into 20 logical blocks.

Partial least square regression (PLSR), recently developed generalization of multiple linear regression (MLR) [13], has been used for calculation of variable importance in the projection (VIP) and QSAR model development. For the regression analysis was employed Soft Independent Modeling of Class Analogy SIMCA P+ 12.0 program [14].

In multilinear modeling, a summary of the importance of every variable (x_k) for both Y and X matrices is given by VIP_k parameter. The x-variables with VIP value larger than 1 are the most relevant for explaining the regression model, the x-variables with $1.0 > VIP > 0.5$ are moderately influental, while x-variables with VIP value smaller than 0.5 are not relevant for the model [13].

The quality of the regression fits was estimated using parameters such as square of correlation coefficient (R^2Y), F ratio, P values, root mean square error of estimation (RMSEE), and $Q^2(Y)$ [15].

Validation of the PLSR models was done by use of the Leave-n-out cross-validation method and Permutation test. Predictive power of the model is determined by $Q^2(Y)$, which is cross-validated version of R^2 and root mean square error of prediction (RMSEP). In the performed cross-validation the data set was split into seven groups. A model is fitted to the data leaving one of the groups out all the time, compute VIP and select the best variables. The formed PLS model then predicts the left-out group. This procedure is repeated until all groups have been left-out, which results in number of parallel models. The difference between observed and the predicted values in the left-out group are calculated for each model and used for calculation of the prediction error (RMSEP). In this setting were defined PRESS (predicted sum of squares), RMSEP and $Q^2(Y)$ as

$$\text{PRESS} = \sum_{i=1}^{n} e_{(i)}^2 \quad (3)$$

$$\text{RMSEP} = \sqrt{\frac{\text{PRESS}}{n}} \quad (4)$$

$$Q^2(Y) = 1 - \frac{\text{PRESS}}{\text{SSTo}} \quad (5)$$

Variation, sum of squares (total): SSTo.

PLSR models with $Q^2(Y) \geq 0.5$ can be considered to have good predictive capability [16].

The response permutation test (Y scrambling) is applied in order to investigate the statistical significance of the $R^2(Y)$ and $Q^2(Y)$ and to test the model for overfitting due to the chance correlation [13]. In this test the Y-matrix is randomly re-ordered (100 times in this project) while the X-matrix is kept intact. A model is fitted to the new Y-data and the new $R^2(Y)$, $Q^2(Y)$ and VIP parameters are calculated. Lines are fitted through the $R^2(Y)$-values and through the $Q^2(Y)$-values, yielding two separate intercepts. For a valid model, the $R^2(Y)$-intercept should not exceed the 0.4 while the $Q^2(Y)$-intercept <0.05 [13].

3. Results and discussion

The prediction of human pharmacokinetic parameters for new compounds has become an important approach in the drug discovery process. New chemical entities require extensive clinical studies before administration to humans, and therefore it is essential to create methods to exclude compounds from this process that would be expected to exhibit unsatisfactory human pharmacokinetic properties. Recently, it developed the simplest method to predict human clearance from human hepatic microsomal lability data, termed the *in vitro* $T_{1/2}$ approach [7]. In this method, the test compound is incubated with human liver microsomes in the presence of appropriate cofactors (nicotinamide adenine dinucleotide phosphate hydride (NADPH) for CYP catalyzed reactions) and measured the first-order rate of consumption of the test compound ($-k$) and the *in vitro* $T_{1/2} = -0.693/k$ [3]. The obtained *in vitro* $T_{1/2}$ values are then converted (Eqs. (1) and (2)) to intrinsic clearance values (*in vitro* CL'_{int}) and scaled-up to whole body clearance values (CL_{blood}) [7].

Since the *in vitro* $T_{1/2}$ values of drugs can be used to predict the *in vitro* CL'_{int} and the *in vivo* CL_{blood} clearance of drugs [7], was decided to perform QSAR study on human hepatic microsomal intrinsic clearance *in vitro* $T_{1/2}$ data for twenty-nine drugs of different structures [3]. A preliminary data analysis showed a good spread and distribution of the *in vitro* $T_{1/2}$ values [3] (Table 1), which spanned about a 120 min range (*in vitro* $T_{1/2}$: 3.90–120.0 min). This was a good precondition for the derivation of meaningful models.

The Marvin 5.1.3_2, the Chem3D Ultra 7.0.0, and the Dragon 5.4 programs were applied for computation of 1628 molecular descriptors of the optimized molecular models.

Partial least square regression (PLSR) (Ericson, 2001) together with the Leave-n-out (LnO) validation, have been used for calculation of Variable Importance in the Projection (VIP) and QSAR model development (SIMCA P+ 12.0, Umetrics AB, 2008). The

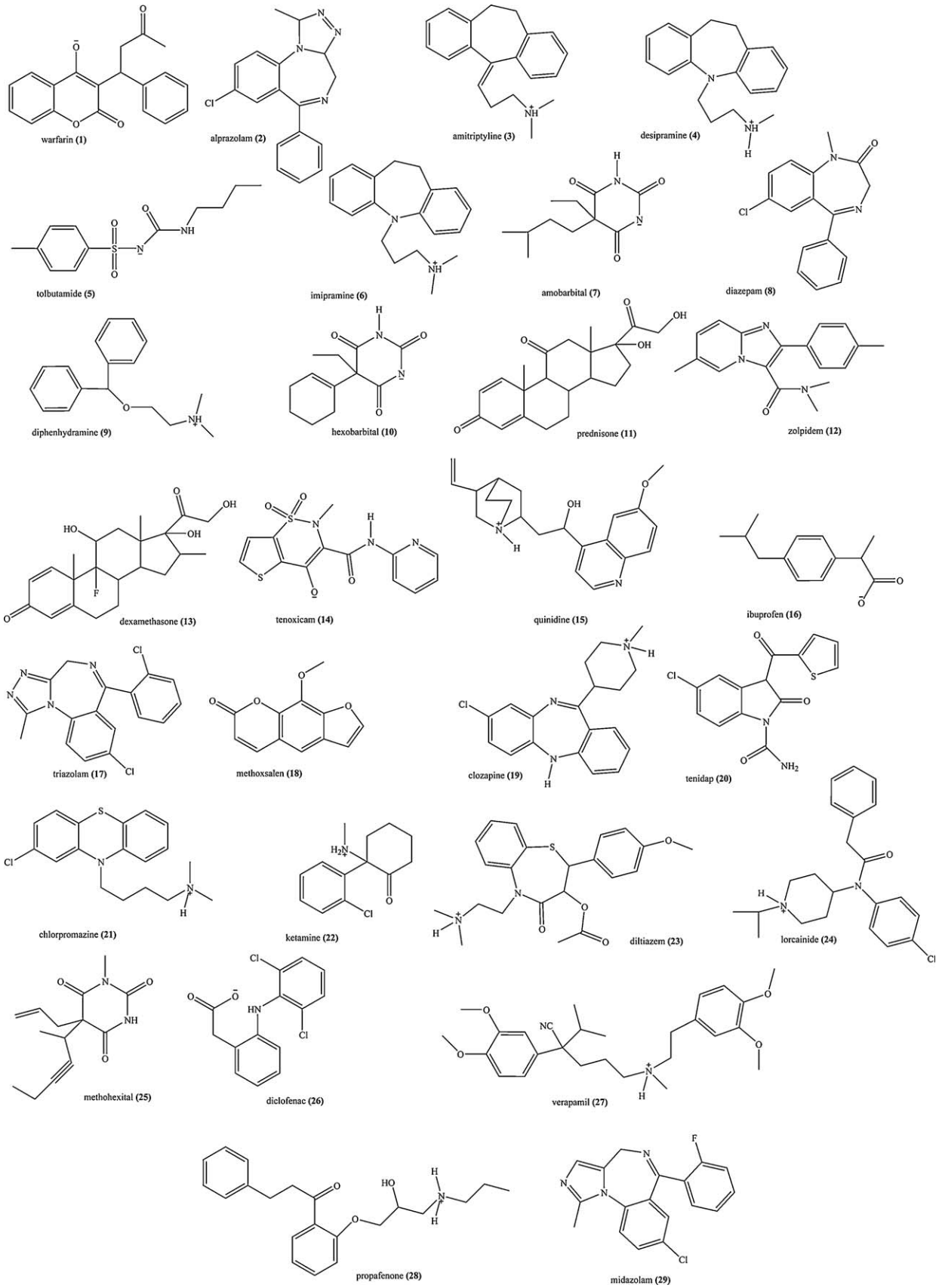

Fig. 1. Structural formulas of the drugs used for the QSAR study. The depicted structures are the most dominant forms of the compounds at pH 7.5 (ChemAxon Marvin 5.1.3_2 program).

Table 1
PLS regression analysis relating the ten variables of the examined drugs with experimentally measured *in vitro* $T_{1/2}$ values. Intrinsic clearance values CL'_{int} were calculated from *in vitro* $T_{1/2}$ data as described in Section 2. RMSEE: root mean square error of estimation; RMSEP: root mean square error of prediction.

Compound	*In vitro* $T_{1/2}$[a], [min]	Molecular polarizability [Å^3]	BIC2	JGI6	RDF045m	Mor24e	G3u	G3m	G3e	nNR$_2$-Ph	C-017
Warfarin (1)	>120	33.08	0.706	0.015	7.128	−0.446	0.187	0.167	0.214	0	1
Alprazolam (2)	105 ± 66	33.21	0.732	0.022	10.214	0.056	0.175	0.175	0.189	1	0
Amitriptyline (3)	92 ± 13	35.17	0.657	0.014	8.914	−0.773	0.186	0.165	0.176	0	1
Desipramine (4)	74 ± 24	32.75	0.699	0.012	5.918	−0.889	0.190	0.162	0.168	1	0
Tolbutamide (5)	71 ± 12	27.53	0.786	0.013	4.260	−0.061	0.191	0.162	0.162	0	0
Amobarbital (7)	66 ± 5	22.81	0.671	0.009	5.507	−0.622	0.236	0.180	0.203	0	0
Imipramine (6)	66 ± 5	34.59	0.682	0.014	6.147	−0.803	0.179	0.174	0.164	1	0
Diazepam (8)	54 ± 19	30.46	0.720	0.021	6.038	−0.478	0.197	0.197	0.182	0	0
Diphenhydramine (9)	49 ± 24	31.33	0.609	0.016	8.819	−0.681	0.176	0.170	0.170	0	0
Hexobarbital (10)	48 ± 6	23.68	0.740	0.028	4.935	−0.688	0.231	0.250	0.222	0	1
Prednisone (11)	47 ± 1	37.50	0.805	0.032	7.743	−1.219	0.163	0.159	0.185	0	1
Zolpidem (12)	44 ± 5	34.32	0.695	0.019	8.907	−0.267	0.220	0.194	0.187	0	0
Dexamethasone (13)	42 ± 3	39.62	0.798	0.031	16.031	−0.589	0.229	0.166	0.178	0	1
Tenoxicam (14)	38 ± 11	31.13	0.834	0.024	5.868	−0.102	0.217	0.184	0.200	0	0
Quinidine (15)	37 ± 5	40.14	0.835	0.017	9.606	−1.014	0.176	0.159	0.159	0	0
Ibuprofen (16)	36 ± 4	23.54	0.674	0.040	5.388	−0.449	0.200	0.200	0.184	0	0
Triazolam (17)	33 ± 2	35.49	0.744	0.024	20.505	−0.526	0.179	0.193	0.179	0	0
Methoxsalen (18)	31 ± 3	22.62	0.837	0.023	4.302	0.045	0.240	0.192	0.204	0	0
Clozapine (19)	27 ± 5	36.66	0.757	0.017	10.526	−0.855	0.211	0.199	0.177	0	0
Tenidap (20)	26 ± 2	29.73	0.834	0.021	13.169	0.120	0.224	0.197	0.188	0	0
Chlorpromazine (21)	25 ± 6	37.81	0.730	0.018	14.931	−0.638	0.188	0.199	0.177	1	0
Ketamine (22)	23 ± 3	25.95	0.763	0.028	11.204	−0.800	0.197	0.165	0.190	0	0
Diltiazem (23)	21 ± 3	44.77	0.781	0.020	16.197	−1.207	0.192	0.159	0.156	0	0
Lorcainide (24)	13 ± 2	42.20	0.719	0.020	19.327	−1.243	0.174	0.165	0.165	0	0
Methohexital (25)	13 ± 2	36.97	0.819	0.022	5.257	−0.915	0.217	0.189	0.161	0	0
Diclofenac (26)	11 ± 3	29.08	0.718	0.014	18.595	−0.279	0.250	0.171	0.171	0	0
Verapamil (27)	10 ± 0.2	51.53	0.691	0.024	9.352	−1.194	0.169	0.175	0.169	0	0
Propafenone (28)	8 ± 0.4	39.33	0.747	0.015	4.321	−1.207	0.241	0.241	0.183	0	0
Midazolam (29)	3.9 ± 0.1	34.07	0.782	0.024	17.289	−0.500	0.184	0.177	0.162	0	0
R^2	0.844										
RMSEE	11.333										
$Q^2(Y)$	0.623										
RMSEP	11.969										
F-ratio	9.227										
P-value	1.20E−04										

[a] Each *in vitro* $T_{1/2}$ value represents mean ± S.D. for triplicate determinations [3].

most important variables with the highest VIP values were selected for QSAR model development (Ericson, 2001).

Among 1628 molecular properties that were considered in generating the QSAR model, ten descriptors, viz. molecular polarizability; bond information content (neighborhood symmetry of 2nd-order) (BIC2); mean topological charge index of order 6 (JGI6); radial distribution function-4.5/weighted by atomic masses of the ligands (RDF045m); 3D-MoRSe-signal 24/weighted by atomic Sanderson electronegativities (Mor24e); 3rd component symmetry directional weighted holistic invariant molecular (WHIM) index/unweighted (G3u); 3rd component symmetry directional WHIM index/weighted by atomic masses (G3m); 3rd component symmetry directional WHIM index/weighted by atomic Sanderson electronegativities (G3E); number of tertiary aromatic amines (nNR$_2$-Ph) and =CR$_2$ atom center fragments (C-017), resulted in a statistically significant model. The molecular polarizability descriptor is calculated by use of the Marvin 5.1.3_2 computational algorithms, while the other selected descriptors for the QSAR model-1 (2) were obtained by use of the Dragon 5.4 program.

The selected molecular descriptors were used for development of QSAR model-1 (with all ten descriptors) and QSAR model-2 (with nine descriptors, without the nNR$_2$-Ph descriptor (as descriptor with the lowest VIP value)).

The molecular polarizability property provides information about the distribution of electrons based on the presence of an applied electric field. In general, molecules with more delocalized electrons have higher values for this property.

Bond information content (BIC2) is molecular descriptor calculated as information content of molecules, based on the calculation of equivalence classes from the molecular graph. Among them, the indices of neighborhood symmetry take into account also neighbor degree and edge multiplicity.

Mean topological charge index of order 6 (JGI6) was proposed to evaluate the charge transfer between pairs of atoms and therefore, the global charge transfer in the molecule [17,18].

Radial distribution function-4.5/weighted by atomic masses of the ligands (RDF045m) is descriptor based on the distance distribution in the molecule. The radial distribution function of an ensemble of n-atoms can be interpreted as the probability distribution of finding an atom in a spherical volume of radius R.

3D-MoRSe-signal 24/weighted by atomic Sanderson electronegativities (Mor24e) is 3D-MoRSE descriptor (3D Molecule Representation of Structures based on Electron diffraction) derived from electron diffraction is in use for simulation of the infrared spectra [19].

3rd Component symmetry directional WHIM indices (G3u (unweighted), G3m (weighted by atomic mass), and G3e (weighted by atomic Sanderson electronegativities)) are based on the statistical indices calculated on the projections of atoms along principal axes [20,21]. They are built in such a way as to capture relevant molecular 3D information regarding the molecular size, shape, symmetry, and atom distribution with respect to invariant reference frames.

Number of tertiary aromatic amines (nNR$_2$-Ph) is functional group counts descriptor.

Atom centered $=CR_2$ fragments descriptor (C-017), is defined by looking at the first neighbors of carbon atoms [22]. The neighbors of a carbon atom can be hydrogens (represented as H), carbons (represented as R) and heteroatoms (represented as X) in various combinations.

The selected variables were organized in groups of descriptors with dominant electronic effect (molecular polarizability, JGI6, Mor24e, G3e), descriptors with dominant steric/symmetry effects (BIC2, RDF045m, G3u, G3m), and descriptors related to the specific functional groups (nNR_2-Ph and C-017).

The most rigorous way for predictive validation is to use an external validation set. In this project however, the number of examined drugs is limited. This makes it difficult to split the data into training set for model building and test set for external validation. In this case Leave-n-out cross-validation (LnO with $n \cong N/7$, N-observables) [15], together with CV-ANOVA (analysis of variance testing of cross-validated predictive residuals, *F*-test) [23] and response permutation test [13] are optimal validation procedure during formation of the PLSR models [13].

During the cross-validation a model is fitted to the data leaving one of the groups out all the time, the VIP for all variables are computed and the best variables were selected. The formed PLSR model than predicts the left-out group.

The *F*-test, based on the ratio of two sample variances MS (Regression)/MS (Residual), then formally assesses the significance of the model. The *P*-value indicates the probability level where a model with this *F*-value may be the result of just chance. The common practice is to interpret a *P*-value lower than 0.05 as pointing to a significant model.

The response permutation test (*Y* scrambling) was used in order to investigate the statistical significance of the $R^2(Y)$ and $Q^2(Y)$ and to test the model for overfitting due to the chance correlation [13]. For a valid model, the $R^2(Y)$-intercept should not exceed the 0.4 while the $Q^2(Y)$-intercept < 0.05 [13].

The QSAR model-1, with the ten descriptors and two significant components ($A = 2$), was developed with the corresponding PLS regression parameters R^2 (0.844) and RMSEE (11.333). Predictive ability of the generated QSAR model-1 was examined by means of cross-validation ($Q^2(Y)$: 0.623 and RMSEP: 11.969) together with CV-ANOVA testing (*F*-ratio: 9.227 and *P*-value: 0.00012). The PLS regression model has succeeded the performed cross-validation and CV-ANOVA test (Table 1), so it was concluded that the QSAR model-1 has good predictive potential.

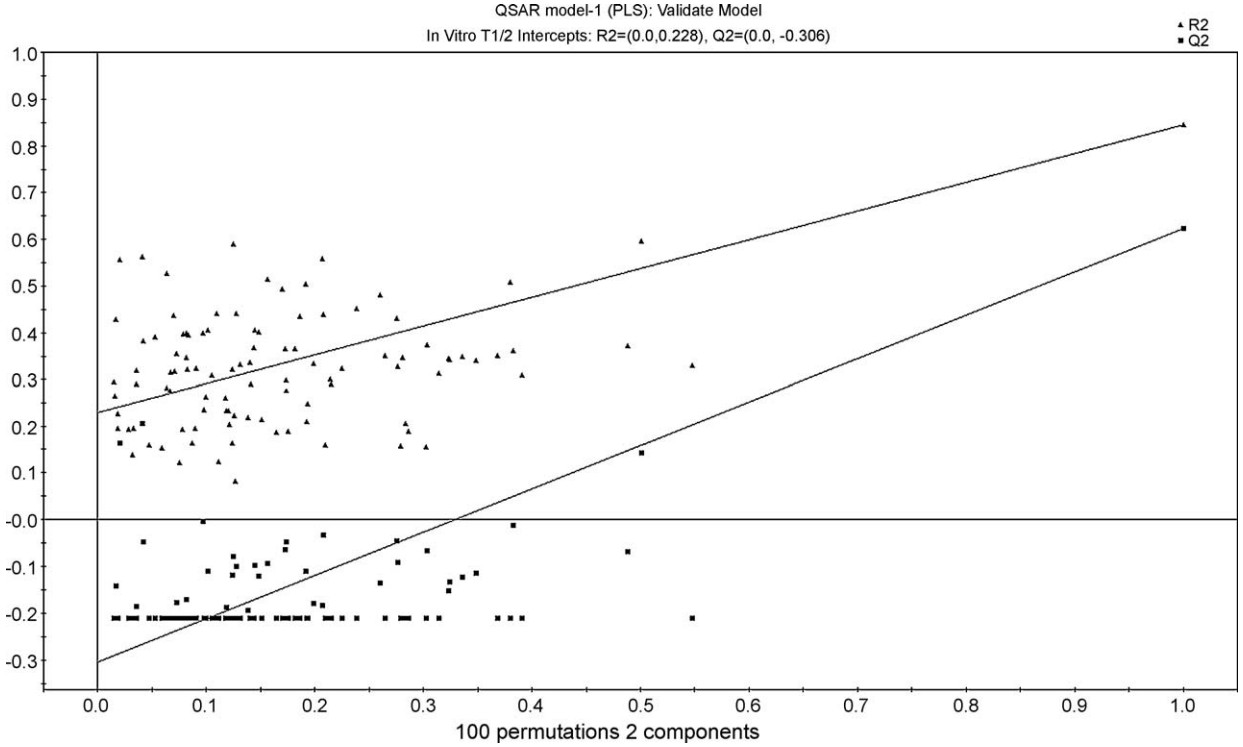

Fig. 2. Validation plot from the response permutation test showing valid QSAR model-1.

Table 2
Correlation matrix between the selected descriptors.

	In vitro $T_{1/2}$	Molecular polarizability	BIC2	JGI6	RDF045m	Mor24e	G3u	G3m	G3e	nNR_2-Ph	C-017
In vitro $T_{1/2}$	1.000	0.075	0.120	0.084	0.153	0.088	0.063	0.065	0.121	0.121	0.187
Molecular polarizability		1.000	0.002	0.003	0.149	0.398	0.205	0.065	0.322	0.003	0.000
BIC2			1.000	0.079	0.005	0.029	0.049	0.000	0.000	0.049	0.000
JGI6				1.000	0.007	0.000	0.005	0.028	0.038	0.060	0.054
RDF045m					1.000	0.007	0.028	0.073	0.134	0.002	0.007
Mor24e						1.000	0.119	0.009	0.156	0.004	0.017
G3u							1.000	0.272	0.173	0.084	0.001
G3m								1.000	0.226	0.008	0.000
G3e									1.000	0.019	0.171
nNR_2-Ph										1.000	0.033
C-017											1.000

The QSAR model-2, with the nine descriptors (without the nNR_2-Ph descriptor, as descriptor with the lowest VIP value) and two significant components ($A = 2$), was created with the PLS regression and validation parameters, such as R^2: 0.808, RMSEE: 12.592, $Q^2(Y)$: 0.629 and RMSEP: 13.299, *F*-ratio: 9.746 and *P*-value: 7.8969e−05. The significantly higher RMSEE and RMSEP for QSAR model-2 than for QSAR model-1 indicated on better prognostic potential of the QSAR model-1.

Therefore, the QSAR model-1 was selected as optimal PLS regression model for prediction of the *in vitro* $T_{1/2}$ values of drugs (Table 1). Further testing of the QSAR model-1 was performed by use of the response permutation test [13] and principal component analysis (PCA).

The response permutation test (*Y* scrambling) is used to investigate the statistical significance of the $R^2(Y)$ and $Q^2(Y)$ and to test the model for overfitting due to the chance correlation [13]. In

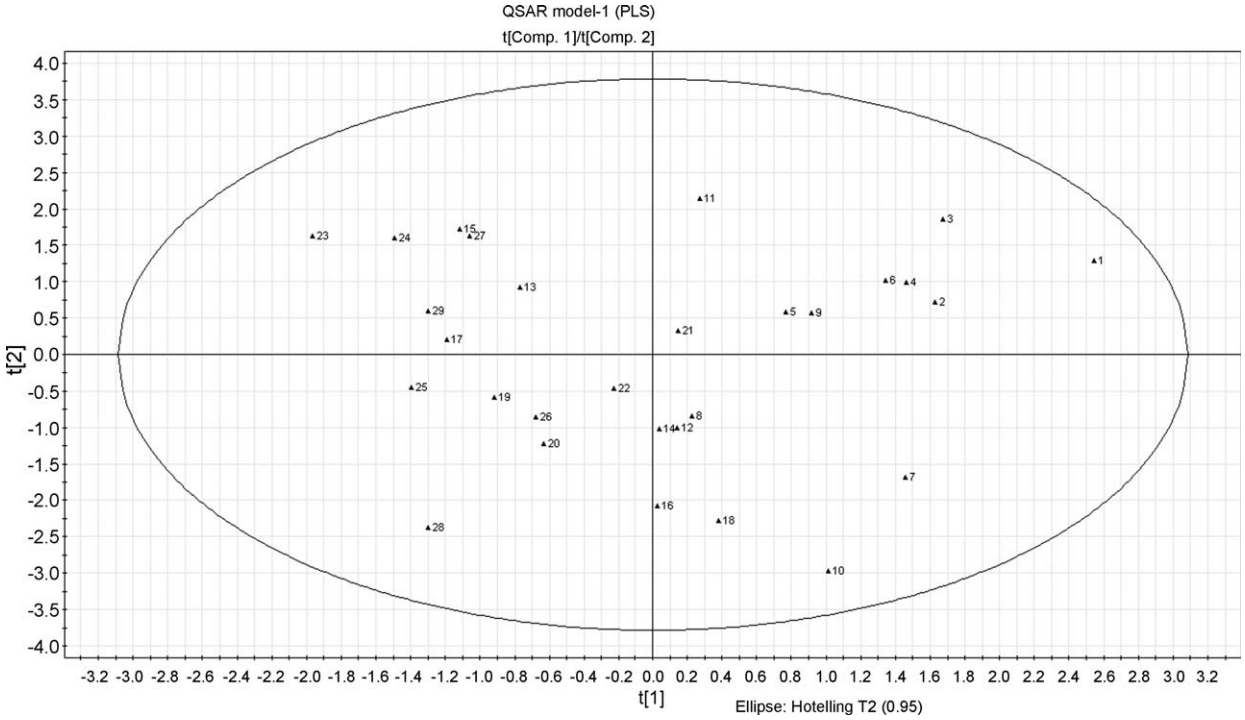

Fig. 3. Score plot *t* (1) *vs.* *t* (2) for the 29 drugs using Dragon 5.4 and Marvin Sketch 5.1.3_2 descriptors.

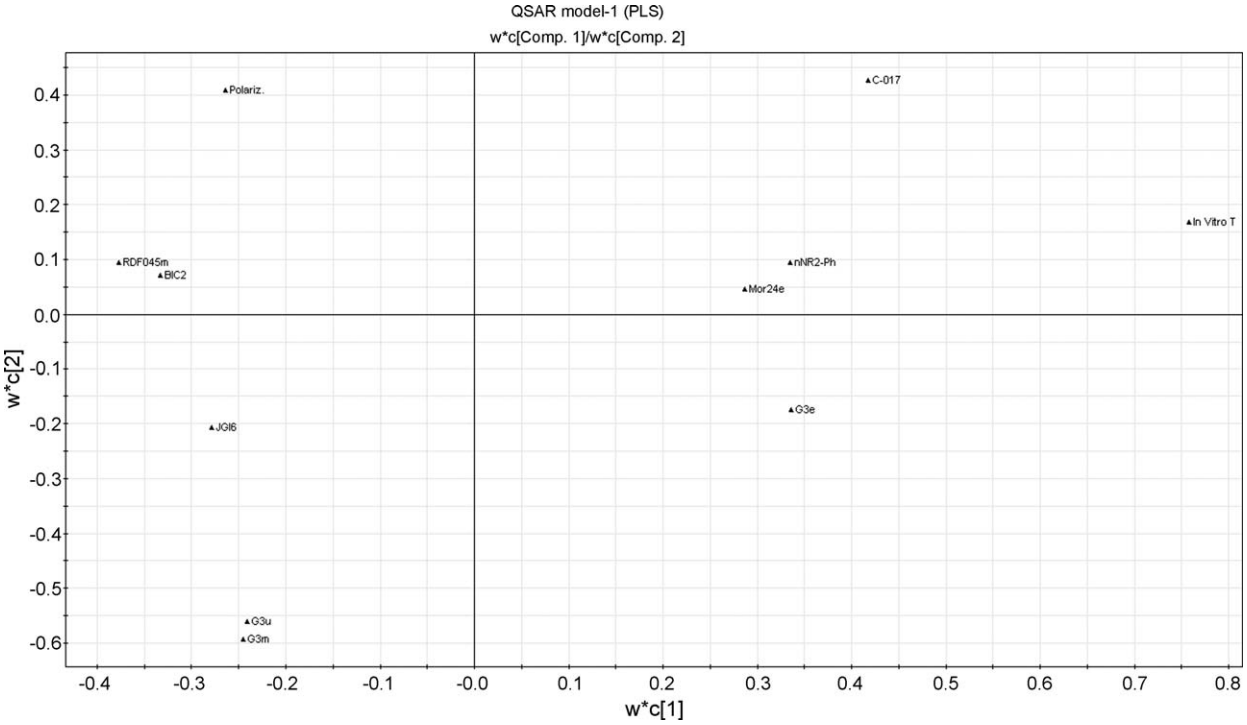

Fig. 4. Weight plot *w*c* (1) *vs.* *w*c* (2) for the 29 drugs using Dragon 5.4 and Marvin Sketch 5.1.3_2 descriptors.

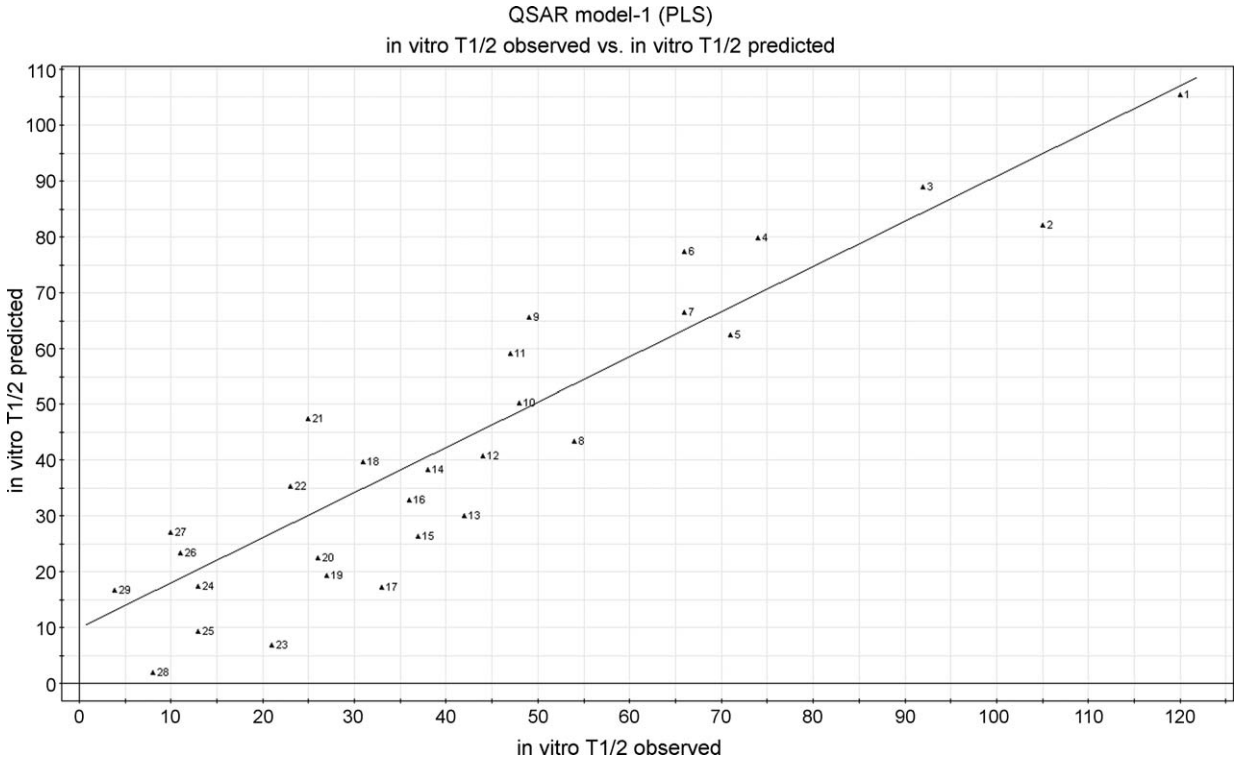

Fig. 5. Plot of observed *vs.* predicted *in vitro* $T_{1/2}$ values of the examined drugs (QSAR model-1).

this test the *Y*-matrix is randomly re-ordered (100 times in this project) while the *X*-matrix is kept intact. A model is fitted to the new *Y*-data and the new $R^2(Y)$ and $Q^2(Y)$ is calculated. Lines are fitted through the $R^2(Y)$-values and through the $Q^2(Y)$-values, yielding two separate intercepts. For a valid model, the $R^2(Y)$-intercept should not exceed the 0.4 while the $Q^2(Y)$-intercept <0.05 [13]. Validation plot for QSAR model-1 (Fig. 2) shows that the model is valid ($R^2(Y)$-intercept (0.0, 0.228) and $Q^2(Y)$-intercept (0.0, −0.306)).

Furthermore, correlation matrix of the selected descriptors illustrates that there is no significant correlations between the descriptors (Table 2).

Principal component analysis of *X*-scores (*t* (1) *vs.* *t* (2), Fig. 3) shows that there is a reasonable homogeneity among the substances without any outliers.

For the interpretation of PLSR models, the standard is to plot weights the *w*c* of one model dimension against another. The weight plot (Fig. 4) shows the first PLS component dominated by atomic Sanderson electronegativities (C-017, nNR_2-Ph, G3e, and Mor24e) on the positive side, and also RDF045m, BIC2, and JGI6 on the negative, and the second component being a mixture of C-017 and molecular polarizability, on the positive, and also G3u, and G3m on the negative side.

From the distribution of the descriptors in Fig. 4 can be concluded that the increased values for molecular polarizability, RDF045m, JGI6, G6m, and G3u, together with decreased values for C-017, nNR_2-Ph, G3e, and Mor24e descriptors will provide lower values for the liver microsomal *in vitro* $T_{1/2}$ parameter.

The fitting power of the QSAR model-1 may be seen on the plot of predicted *vs.* observed *in vitro* $T_{1/2}$ values (Fig. 5).

In summary, these data support that the developed QSAR model-1 is reliable predictive tool for evaluation of the liver microsomal *in vitro* $T_{1/2}$ parameter of the test compounds. Furthermore, the obtained *in vitro* $T_{1/2}$ values can be used to calculate the *in vitro* CL'_{int} (Eq. (1)) and the *in vivo* CL_{blood} (Eq. (2)) clearance for the examined drugs [7,3].

4. Conclusion

In the presented QSAR study it was a developed method for theoretical evaluation of cytochrome P450-mediated pharmacokinetic characteristics for novel pharmacologically active agents. The performed PCA on the developed QSAR model-1 has indicated that the increased values for molecular polarizability, RDF045m, JGI6, G6m, and G3u, together with decreased values for C-017, nNR_2-Ph, G3e, and Mor24e descriptors will provide lower values for the liver microsomal *in vitro* $T_{1/2}$ parameter, and therefore faster clearance (*in vitro* CL'_{int} and *in vivo* CL_{blood}).

The QSAR model-1 evaluation of test compounds pharmacokinetic characteristics will exclude chemical entities that would be expected to exhibit unsatisfactory human pharmacokinetic properties (*in vitro* $T_{1/2}$, *in vitro* CL'_{int} and *in vivo* CL_{blood}). Therefore, the created QSAR model can improve and simplify the drug discovery process.

Acknowledgement

This work was supported by the Ministry of Science and Environmental Protection of the Republic of Serbia, contract #142071B.

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