Original article

Simple graph-theoretical model for flavonoid binding to P-glycoprotein

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Three sets of flavonoid derivatives (N=32, 40, and 74) and logarithms of their dissociation constants ($\log K_d$) that describe flavonoid affinity toward P-glycoprotein were modelled using six connectivity indices. The best results were obtained with the zero-order valence molecular connectivity index (${}^{0}\chi^{v}$) for all three sets. Standard errors of the calibration models were around 0.3, and of the constants from the test sets even a little lower, 0.22 and 0.24. Despite using only one descriptor, our model proved better in internal (cross-validation) and especially in external (test set) statistics than much more demanding methods used in previous 3D QSAR modelling.

KEY WORDS: connectivity indices; dissociation constant; flavonoids; molecular modelling; P-glycoprotein

There is a rising interest in the research of bioflavonoids, secondary phenolic plant metabolites that have been evidenced as strong antioxidants (1-5) and therefore regarded as potential anti-cancer agents (6, 7). No less important are the research efforts to elucidate their metabolism and mode of action. Noteworthy are the measurements of their affinity to a variety of proteins such as human serum albumin (8), bovine serum albumin (9) or blood plasma (10), and milk proteins (11). Among them P-glycoprotein (P-gp), a 170 kDa transmembrane protein (12), has received particular attention because it expels hydrophobic compounds from the cell, which leads to resistance to cytostatic agents through a mechanism termed multidrug resistance (MDR) (13-15). The search for effective and safe P-gp inhibitors is in progress, and flavonoids seem very promising as MDR modulators. Investigations of flavonoid binding to P-glycoprotein using pharmacophore modelling (DISCOtech, CoMFA, CoIMFA, MIF) (16-18) have yielded a fair agreement with experimental findings and showed the dominance of steric and hydrophobic interactions (fields) in flavonoid binding to P-glycoprotein (17).

The aim of our study was, however, to develop a simpler but as reliable method with the same purpose, that is, to predict the dissociation constant, K_{d} , of P-glycoprotein/ flavonoid complexes. The dissociation constant K_{d} could be modelled with only one molecular descriptor from the class of valence connectivity indices, just as the third-order valence connectivity index (${}^{3}\chi^{v}$) was successfully applied to predict the stability of coordination compounds (19), especially of copper(II) chelates with peptides (20-22). Moreover, ${}^{3}\chi^{\nu}$ and other related graph-theoretical indices have been applied in quantitative structure activity relationship (QSAR) analysis (23-25), and particularly in the QSAR of 15 flavonoids isolated from Jerusalem thorn (*Paliurus spina-christi* Mill.) used in Croatian traditional herbal medicine (26). The authors have shown that the first-order valence connectivity index linearly correlated (*r*=0.993) with the hydrophobicity of flavonoids, *i.e.* with their octanol/water partition coefficient (log *P*) and Van der Waals volumes (*r*=0.999).

For this purpose, we used three sets of flavonoid derivatives and their dissociation constants (pK_d), which describe flavonoid affinity toward P-glycoprotein (16-18). The best fitting models and the best internal and external (cross-validation and test set) predictions for all sets were obtained with zero-order connectivity index (${}^{0}\chi^{\nu}$).

METHODS

Calculation of topological indices

We calculated topological indices using the E-DRAGON program developed by R. Todeschini and co-workers, capable of yielding 119 topological indices in a single run along with many other molecular descriptors (27, 28). Connectivity matrices were constructed with the aid of the online SMILES Translator and Structure File Generator (29).

The zero-order valence molecular connectivity index, ${}^{0}\chi^{\nu}$, was defined as (23, 30-32):

$${}^{0}\chi^{\nu} = \sum_{\text{vertex}} [\delta(i)]^{-0.5}$$
^[1]

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where $\delta(i)$ denotes weight (valence values) of vertex (atom) *i* in a vertex-weighted molecular graph. The valence value, $\delta(i)$, of a vertex *i* is defined by:

$$\delta(i) = [Z^{\nu}(i) - H(i)]/[Z(i) - Z^{\nu}(i) - 1]$$
[2]

where $Z^{i}(i)$ is the number of valence electrons belonging to the atom corresponding to vertex *i*, Z(i) is its atomic number, and H(i) is the number of hydrogen atoms attached to it.

The zero-order connectivity index is the first member of the family of valence connectivity indices. The valence connectivity indices of higher orders $({}^{1}\chi^{\nu}, {}^{2}\chi^{\nu}, {}^{3}\chi^{\nu}$, etc.) are taking into account paths, more precisely, neighbouring vertices (atoms) making up those paths. For example, ${}^{3}\chi^{\nu}$ is taking into account all paths of the length 3, that is, three consecutive chemical bonds in a vertex-weighted molecular graph.

$${}^{3}\chi^{\nu} = \sum_{\text{path}} [\delta(i) \ \delta(j) \ \delta(k) \ \delta(l)]^{-0.5}$$
[3]

Regression calculations

Regression calculations, including the leave-one-out procedure (LOO) of cross validation, were done using the CROMRsel program (33). The standard error of the cross-validation estimate was defined as:

$$S.E._{cv} = \sqrt{\sum_{i} \frac{\Delta X_i^2}{N-1}}$$
[4]

where ΔX and N denote cv residuals and the number of reference points, respectively.

RESULTS

The first set consisted of 32 flavonoids (marked *a* in Table 1). It was further divided into the training (N=25) and test set (N=7) (16). Regressions on the full (N=32) and the training set (N=25) yielded similar statistics (Table 2, Figure 1), with the standard errors very close to those of the test set (SE_{test}=0.22).

The second set included 42 flavones (marked *b* in Table 1). Two compounds were excluded from the set: **34** because of the very different structure and **42** because it was the same as **23**. The new set (N=40) was also divided into the training (N=31) and test set (N=9) (17). Regressions on the full (N=40) and the training set (N=31) of flavones yielded similar statistics (Table 2, Figure 2), and the standard error of prediction of the test set (SE_{test}=0.24) was even lower.

The third set (marked c in Table 1) consisted of 78 flavonoids, including calcone (compounds 1-22), flavone (compounds 23-64), and aurone derivatives (compounds 65-78) (18). We excluded the derivatives of dehydrosylibin and xanthone (18) and compounds 14, 34, and 67 because

of their unrelated structure and flavone **42** because of the same structure as flavone **23**.

Regression on the new set of 74 flavonoid derivatives yielded R^2 =0.790 and SE=0.37 (Table 2, Figure 3). The regressions on separate groups of compounds gave similar standard errors (N=21, R^2 =0.861, SE=0.26 for calcones and N=40, R^2 =0.900, SE=0.30 for flavones). The results for aurones however were much worse: N=13, R^2 =0.073, SE=0.59, but they lie around the same regression line as calcones and flavones.

DISCUSSION

The first set was previously investigated by Li et al. (16) using pharmacophore modelling and comparative molecular field analysis (CoMFA). They built three models for the training set (*N*=25) with steric, electrostatic, and both steric and electrostatic descriptors (standard CoMFA).

The steric model yielded worse results (R^2 =0.951, R^2_{cv} =0.764, SE=0.200) than the electrostatic model (R^2 =0.987, R^2_{cv} =0.789, SE=0.105). The standard model was in between (R^2 =0.980, R^2_{cv} =0.716, SE=0.131), but it also gave the best predictions for the test set (N=7). The SE_{test} was 0.35, 0.30, and 0.24, for the steric, electrostatic, and standard CoMFA model, respectively.

Our model yielded worse fit statistics (R^2 =0.918, SE=0.24) but better cross-validated statistics (R^2_{cv} =0.905, SE_{cv}=0.26), and the best predictions for the test set of all CoMFA models (SE_{test}=0.22).

The second set (41 flavonoids without compound **35**) was previously investigated by Kothandan et al. (17) using ligand-based and receptor-guided alignment molecular docking and 3D-QSAR. On the training set (*N*=32) the best CoMFA and CoMSIA models for ligand-based alignment yielded R^2 =0.951, R^2_{cv} =0.747, SE=0.21 and R^2 =0.936, R^2_{cv} =0.810, SE=0.25, respectively. For receptor-guided alignment the models yielded R^2 =0.976, R^2_{cv} =0.712, SE=0.16 and R^2 =0.987, R^2_{cv} =0.805, SE=0.12, for CoMFA and CoMSIA respectively. But these models gave the SE of predictions of the constants from the test set (*N*=9) in the range from 0.42 to 0.54.

On a similar training set (N=31; we excluded compounds **34** and **42** but kept **35**) our model gave worse fit statistics ($R^2=0.885$, SE=0.32), but again better cross-validated statistics ($R^2_{cv}=0.870$, SE_{cv}=0.34) and far better test set (N=9; the same as in reference 17) predictions (SE_{test}=0.24).

The third set originally consisted of 89 flavonoids, but Boccard et al. (18) obtained an acceptable model for 83 compounds (after omitting compounds **13**, **14**, **68**, **71**, **72**, and **78** in reference 3). Using the 3D-QSAR and statistical tools [principal component analysis (PCA) and partial leastsquares (PLS) regression], their model yielded R^2 =0.76 and R^2_{ev} =0.71.

Our model was built on a smaller set (N=74) and yielded both better fit (R^2 =0.790, SE=0.37) and cross-validated

| No.* | SMILES formula | Set(s) | $\mathbf{p}K_{d}$ | ⁰ χ ^ν |
|-----------------|--|-----------------------|-------------------|-----------------------------|
| 1 | O=C(/C=C/C1=CC=CC=C1)C2=C(0)C=C(0)C=C20 | с | 5.34 | 2.555 |
| 2 | O=C(/C=C/C1=CC=C(O)C=C1)C2=C(O)C=C(O)C=C2O | с | 5.32 | 2.648 |
| 3 | O=C(/C=C/C1=CC=C(OC)C=C1)C2=C(O)C=C(O)C=C2O | с | 5.64 | 2.871 |
| 4 | O=C(/C=C/C1=CC=C(F)C=C1)C2=C(O)C=C(O)C=C2O | с | 5.44 | 2.625 |
| 5 | O=C(/C=C/C1=CC=C(C1)C=C1)C2=C(O)C=C(O)C=C2O | с | 5.89 | 2.877 |
| 6 | O=C(/C=C/C1=CC=C(Br)C=C1)C2=C(O)C=C(O)C=C2O | с | 6.24 | 3.154 |
| 7 | O=C(/C=C/C1=CC=C(I)C=C1)C2=C(O)C=C(O)C=C2O | с | 6.60 | 3.344 |
| 8 | O=C(/C=C/C1=CC=C(CC)C=C1)C2=C(O)C=C(O)C=C2O | с | 5.68 | 3.143 |
| 9 | O=C(/C=C/C1=CC=C(CCC)C=C1)C2=C(O)C=C(O)C=C2O | с | 6.00 | 3.273 |
| 10 | O=C(/C=C/C1=CC=C(CCCCCC)C=C1)C2=C(0)C=C(0)C=C20 | с | 6.57 | 4.054 |
| 11 | O=C(/C=C/C1=CC=C(C2CCCC2)C=C1)C3=C(O)C=C(O)C=C3O | с | 6.28 | 4.768 |
| 12 | O=C(/C=C/C1=CC=C(CCCCCCCC)C=C1)C2=C(O)C=C(O)C=C2O | С | 7.70 | 4.554 |
| 13 | O=C(/C=C/C1=CC=C(CCCCCCCCC)C=C1)C2=C(O)C=C(O)C=C2O | С | 7.22 | 5.054 |
| 14 | 0=C(/C=C/C1=CC=C(CCCCCCCCCCCCCCCCCCCCCCCC | С | 4.85 | 6.054 |
| 15 | O=C(/C=C/C1=CC=C(C/C=C(C)/C)C=C1)C2=C(O)C=C(O)C=C2O | С | 6.28 | 3.481 |
| 16 | $O=C(/C=C/C1=CC(0)=C(0)C=C1)C2=C(0)C=C(0)C(C/C=C(C)\setminus C)=C2O$ | С | 6.36 | 3.749 |
| 17 | 0 = C(/C = C/C1 = CC = C1)C2 = C(0)C = CC = C2 | С | 5.05 | 2.396 |
| 18 | 0 = C(/C = C/C1 = CC = CC = C1)C2 = C(0)C = CC(C(C)(C = C)C) = C2 | С | 6.36 | 3.743 |
| 19 | 0 = C(/C = C/C1 = C(=C(0)) C = C1) C2 = C(0) C = C2 | C | 4.96 | 2.49 |
| 20 | 0 = C(/C = C/C) = C(0)(C = C(0)(C = C))(C = C)(0)(C = C)(C = C)(| C | 6.28 | 3.294 |
| 21 | 0 - C(/C - C/C) - C(0)(-C)(2 - C)(0)(-C) - C(0)(-C) - C(0)(-C) - C(0)(-C)(-C) - C(0)(-C)(-C)(-C)(-C)(-C)(-C)(-C)(-C)(-C)(-C | C | 5.74 | 2.712 |
| 22 | 0 - C(/C - C(C)/C) - C(U)/C | c ot bt o | 5.00 | 2.031 |
| $\frac{23}{24}$ | 0 = C1C2 = C(-C2 - C2 - C2 - C2 - C2 - C2 - C2 - C | a, 0, 0 | 5.00 | 2.01 |
| 24 | $0 = C1C_2 = C(C_1(C_1(C_1)(C_1)) = C_2(C_1(C_2) = C_2(C_2(C_2)) = C_1(C_2) = C_1(C_2) = C_1(C_2) = C_2(C_2(C_2)) = C_2(C_2)) = C_2(C_2(C_2)) = C_2(C_2(C_2)) = C_2(C_2)) = C_2(C_2(C_2)) = C_2(C_2(C_2)) = C_2(C_2)) = C_2(C_2(C_2)) = C_2(C_2)) = C_2(C_2(C_2)) = C_2(C_2)) = C_2(C$ | a, b, c | 6.35 | 4 292 |
| 25 | $0 = C1C^2 = C(0)C(C/C=C(0)/C) = C(0)C=C^2OC(C^3=CC=C^3) = C10$ | a, b, c | 6.68 | 3 966 |
| 20 | O = C1C2 = C(0)C = C(0)C(C/C = C(C)/C) = C2OC(C3 = CC = C3) = C1O | a, b, c | 6.66 | 3 952 |
| 28 | O=C1C2=C(O)C=C(O)C=C2OC(C3=CC=C(O)C=C3)=C1O | a, b, c | 5.17 | 3.065 |
| 29 | O=C1C2=C(O)C=C(O)C=C2OC(C3=CC=C(OC)C=C3)=C1O | a, b, c | 5.35 | 3.288 |
| 30 | O=C1C2=C(C=C(C(C)(C)C=C)=C2OC(C3=CC=C(C=C3)OC)=C1O)O)O | a, b, c | 6.70 | 4.608 |
| 31 | O=C1C2=C(0)C=C(0)C=C2OC(C3=CC=C(F)C=C3)=C10 | a, b, c | 5.17 | 3.042 |
| 32 | O=C1C2=C(0)C=C(0)C=C2OC(C3=C(C1)C=C(C1)C=C3)=C1O | a, b, c | 5.40 | 3.659 |
| 33 | O=C1C2=C(0)C=C(0)C=C2OC(C3=CC=C(I)C=C3)=C1O | a, b ^t , c | 5.96 | 3.761 |
| 34 | O=C1C2=C(O)C=C(O)C=C2OC(C(C3=CC=CC3)C4=CC=CC=C4)=C1O | b, c | 5.70 | 4.49 |
| 35 | O=C1C2=C(0)C=C(0)C=C2OC(C3=CC=C(CCCCCCCC)C=C3)=C1O | a ^t , b, c | 7.22 | 4.97 |
| 36 | O=C1C2=C(C=C(C=C2OC(C3=CC=C3)=C1OC)O)O | a, b, c | 5.05 | 3.158 |
| 37 | O=C1C2=C(C=C(C(C(C)(C)C=C)=C2OC(C3=CC=C3)=C1OC)OC)O | a, b, c | 6.82 | 4.683 |
| 38 | O=C1C2=C(0)C=C(0)C=C2OC(C3=CC(0)=C(0)C=C3)=C1O | a, b, c | 5.15 | 3.173 |
| 39 | 0=C1C2=C(C=C(C=C2OC=C1C3=CC=C(C=C3)0)0)0 | b, c | 4.58 | 3.02 |
| 40 | 0=C1C2=CC=CC=C2OC(C3=CC=CC=C3)=C1 | b ^t , c | 4.47 | 2.693 |
| 41 | 0=C1C2=CC=C(0)C=C2OC(C3=CC=C3)=C1 | a, b, c | 4.46 | 2.771 |
| 42 | 0=C1C2=CC=CC=C2OC(C3=CC=C3)=C10 | b, c | 5.00 | 2.81 |
| 43 | 0=C1C2=C(0)C=C(0)C=C2OC(C3=CC=C3)=C1 | a, b ^t , c | 5.05 | 2.853 |
| 44 | O=C1C2=C(O)C(C)=C(O)C=C2OC(C3=CC=C3)=C1 | a^{t} , b, c | 5.51 | 3.277 |
| 45 | 0=C1C2=C(0)C=C(0C)C=C20C(C3=CC=C3)=C1 | a ^r , b, c | 5.20 | 3.077 |
| 46 | 0=C1C2=C(0)C(0)=C(0C)C=C20C(C3=CC=CC3)=C1 | a, b, c | 5.89 | 3.477 |
| 4/ | $ = \bigcup_{i \in I} (\bigcup_{i \in$ | a, b ⁱ , c | 5.00 | 2.946 |
| 48 | 0 = 0 + 0 + 0 = 0 + 0 + 0 + 0 + 0 + 0 + | a', b, c | 5.2 | 2.999 |
| 49 | $\frac{(-1)^{2}-(-1)^{2}$ | a, o, c | 5.00 | 3.045 |
| 51 | $(-1)^2 - (-1)^2 -$ | a, u, c | 6.69 | 3.213 |
| 52 | 0 = 0 + 0 = 0 + 0 = 0 + 0 = 0 + 0 = 0 = | 0, C | 6.55 | 3.040 |
| 53 | $0 = C_1 C_2 = C_1 C_1 C_1 C_2 = C_2 C_2 C_2 C_2 C_2 C_2 C_2 C_2 C_2 C_2$ | b ^t c | 7 48 | 4 74 |
| | | 0,0 | 1.10 | ··/ T |

Table 1 pK_d of flavonoid complexes with P-glycoprotein, SMILES formula, and ${}^{\theta}\chi^{v}$ index of flavonoids

| No.* | SMILES formula | Set(s) | $\mathbf{p}K_{d}$ | ⁰ χ ^ν |
|---------|--|-------------------------------------|-------------------|-----------------------------|
| 54 | O=C1C2=C(O)C(CC3=CC=C3)=C(O)C=C2OC(C4=CC=CC=C4)=C1 | a, b, c | 6.47 | 4.357 |
| 55 | O=C1C2=C(C=C(C(CC3=CC=C3)=C2OC(C4=CC=CC=C4)=C1)O)O | a ^t , b ^t , c | 6.00 | 4.343 |
| 56 | 0=C1C2=C(0)C(CC3=CC=CC=C3)=C(0)C(CC4=CC=CC=C4)=C2OC(C5=CC=C5)=C1 | b, c | 7.44 | 5.822 |
| 57 | O=C1C2=C(O)C=C(OCC3=CC=CC3)C=C2OC(C4=CC=CC=C4)=C1 | b, c | 7.17 | 4.075 |
| 58 | O=C1C2=C(O)C(C/C=C(C)/C)=C(O)C=C2OC(C3=CC=CC=C3)=C1 | a, b, c | 6.52 | 3.847 |
| 59 | O=C1C2=C(O)C=C(O)C(C(C=C)(C)C)=C2OC(C3=CC=CC=C3)=C1 | a, b, c | 6.7. | 4.173 |
| 60 | O=C1C2=C(O)C=C(O)C(C/C=C(C)/C)=C2OC(C3=CC=CC=C3)=C1 | a, b, c | 6.55 | 3.833 |
| 61 | O=C1C2=C(O)C(C/C=C(C)\C)=C(O)C(C/C=C(C)/C)=C2OC(C3=CC=C3)=C1 | b, c | 7.82 | 4.803 |
| 62 | O=C1C2=C(O)C(C/C=C(C)/CC/C=C(C)/C)=C(O)C=C2OC(C3=CC=C3)=C1 | a, b, c | 7.35 | 4.879 |
| 63 | O=C1C2=C(O)C=C(O)C(C/C=C(C)/CC/C=C(C)/C)=C2OC(C3=CC=CC=C3)=C1 | a, b, c | 7.60 | 4.865 |
| 64 | O=C1C2=C(O)C=C(O)C(C(C)(C)C=C)=C2OC(C3=CC=C(O)C=C3)=C1 | a, b ^t , c | 6.15 | 4.267 |
| 65 (76) | O=C1C2=C(OC)C=C(OC)C=C2O/C1=C\C3=CC=C(C#N)C=C3 | с | 4.70 | 3.503 |
| 66 (77) | O=C1C2=C(OC)C=C(OC)C=C2O/C1=C\C3=CC=C(N(C)C)C=C3 | с | 5.59 | 3.873 |
| 67 (78) | O=C1C2=C(OC)C=C(OC)C=C2O/C1=C\C3=CC(OC)=C(OC)C=C3OC | с | 4.04 | 4.188 |
| 68 (79) | O=C1C2=C(O)C=C(OC)C=C2O/C1=C\C3=CC=C3 | с | 5.88 | 3.059 |
| 69 (80) | O=C1C2=C(O)C=C(OC)C=C2O/C1=C\C3=CC=C(F)C=C3 | с | 5.57 | 3.129 |
| 70 (81) | O=C1C2=C(O)C=C(OC)C=C2O/C1=C\C3=CC=C(Cl)C=C3 | с | 6.34 | 3.381 |
| 71 (82) | O=C1C2=C(O)C=C(OC)C=C2O/C1=C\C3=CC=C(Br)C=C3 | с | 6.82 | 3.658 |
| 72 (83) | O=C1C2=C(O)C=C(OC)C=C2O/C1=C\C3=CC=C(I)C=C3 | с | 6.59 | 3.848 |
| 73 (84) | O=C1C2=C(O)C=C(OC)C=C2O/C1=C\C3=CC=C(CN)C=C3 | с | 5.54 | 3.475 |
| 74 (85) | O=C1C2=C(OC)C=C(OC)C=C2O/C1=C\C3=CC=CC=C3 | с | 5.15 | 3.263 |
| 75 (86) | O=C1C2=C(OC)C=C(OC)C=C2O/C1=C\C3=CC=C(F)C=C3 | с | 5.54 | 3.334 |
| 76 (87) | O=C1C2=C(OC)C=C(OC)C=C2O/C1=C\C3=CC=C(Cl)C=C3 | с | 6.00 | 3.586 |
| 77 (88) | O=C1C2=C(OC)C=C(OC)C=C2O/C1=C\C3=CC=C(Br)C=C3 | с | 6.09 | 3.862 |
| 78 (89) | O=C1C2=C(OC)C=C(OC)C=C2O/C1=C\C3=CC=C(I)C=C3 | с | 6.27 | 4.053 |

*Numbers in parentheses correspond to notation in Ref 18.







Figure 1 Linear dependence of the pK_d of flavonoid complexes with P-glycoprotein (set a) on the ${}^{\theta}\chi^{\nu}$ index of flavonoids ($R^2=0.918$, SE=0.24, $SE_{\phi}=0.26$, $SE_{test}=0.22$). Triangles denote predicted values of the pK_d of the test set compounds (N=7) from the calibration model made on the training set (circles, N=25)

Figure 2 Linear dependence of the pK_d of flavone complexes with *P*-glycoprotein (set b) on the ${}^{\theta}\chi^{\nu}$ index of flavones (R²=0.885, SE=0.32, SE_{cv}=0.34, SE_{test}=0.24). Triangles denote predicted values of the pK_d of the test set compounds (N=9) from the calibration model made on the training set (circles, N=31)

| Sat | N · | Regression coefficients | | D 2 | SE | SE | |
|---------------|-----|-------------------------|----------|------------|------|------------------|--|
| Set | | a ₁ (SE) | b(SE) | - K- | SE | SL _{ev} | |
| <i>a</i> full | 32 | 0.358(19) | 1.42(24) | 0.921 | 0.23 | 0.25 | |
| a training | 25 | 0.370(23) | 1.26(30) | 0.918 | 0.24 | 0.26 | |
| <i>b</i> full | 40 | 0.360(19) | 1.40(26) | 0.900 | 0.30 | 0.32 | |
| b training | 31 | 0.366(25) | 1.34(33) | 0.885 | 0.32 | 0.34 | |
| <i>c</i> full | 74 | 0.331(20) | 1.82(26) | 0.790 | 0.37 | 0.38 | |

Table 2 Regression models for the estimation of the pK_d of flavonoid complexes with P-glycoprotein

statistics (R_{cv}^2 =0.781, SE_{cv}=0.38). Other valence connectivity indices (${}^1\chi^{\nu}$, ${}^2\chi^{\nu}$, ${}^3\chi^{\nu}$, ${}^4\chi^{\nu}$, and ${}^5\chi^{\nu}$) yielded R^2 in the range 0.542-0.787, and SE 0.37-0.55.

CONCLUSION

Our model for the prediction of dissociation constants of the flavonoid-P-glycoprotein system (K_d) gives results comparable to much more demanding 3D QSAR - CoMFA and CoMSIA models. It may have fared worse in fitting the data but gave better internal (cross-validation) and external predictions (for test sets). In this most important aspect in modelling, our model surpasses CoMFA and CoMSIA.

Our results also show that the model is stable $(SE\approx SE_{ev}\approx SE_{test})$ for the same set), yielding consistent results, regardless of the grouping of flavonoid derivatives (for not too big structural diversity).

The comparison of our model (Set 1, Table 2; N=32) with the CoMFA models gave standard errors of 0.99, 0.96, and 0.99 log K_d units for the electrostatic, steric, and standard model, respectively. These standard errors are much bigger than those obtained by comparison between the CoMFA models: 0.27, 0.15, and 0.21 for the comparison between steric and electrostatic, steric and standard, and electrostatic and standard models, respectively. Therefore, our model gives quite different predictions than the CoMFA models despite similar general agreement with the



Figure 3 Linear dependence of the pK_d of flavonoid complexes with P-glycoprotein (set c) on the ${}^{\theta}\chi^{v}$ index of flavonoids (R²=0.790, SE=0.37, SE_{xy}=0.38)

experiment (SE=0.24 and 0.13, for ${}^{0}\chi^{\nu}$ and the standard CoMFA model, respectively). A much bigger difference in standard error between ${}^{0}\chi^{\nu}$ and each of the CoMFA models, as well as the difference in standard errors between the CoMFA models suggest that the ${}^{0}\chi^{\nu}$ model is not an approximation of the CoMFA models but is the model in its own right.

Our model, as well as models based on topological indices in general, is essentially holistic, which means that it fits all the relevant interactions in a molecule equally well.

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Jednostavan graf-teorijski model vezivanja flavonoida za P-glikoprotein

Upotrebom indeksâ povezanosti modelirani su logaritmi konstanti disocijacije $(\log K_d)$ triju skupova flavonoidnih derivata (*N*=32, 40 i 74); K_d opisuje afinitet flavonoida prema P-glikoproteinu. Najbolji su rezultati postignuti na svim trima skupovima upotrebom valencijskoga molekularnog indeksa povezanosti nultoga reda $({}^{0}\chi^{v})$. Standardne su pogreške modela za kalibraciju oko 0,3, a one za konstante iz seta za provjeru malo su niže - 0,22 i 0,24. Unatoč upotrebi samo jednoga deskriptora, naš se model pokazao boljim u pogledu interne provjere (unakrsna validacija), a posebice u pogledu eksterne provjere (prema skupu za provjeru) od puno zahtjevnijih metoda (3D QSAR) korištenih za modeliranje toga sistema.

KLJUČNE RIJEČI: indeksi povezanosti; konstanta disocijacije; molekularno modeliranje