Classification of Cytochrome P450 1A2 Inhibitors and Noninhibitors by Machine Learning Techniques

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ABSTRACT:

The cytochrome P450 (P450) superfamily plays an important role in the metabolism of drug compounds, and it is therefore highly desirable to have models that can predict whether a compound interacts with a specific isoform of the P450s. In this work, we provide in silico models for classification of CYP1A2 inhibitors and noninhibitors. Training and test sets consisted of approximately 400 and 7000 compounds, respectively. Various machine learning techniques, such as binary quantitative structure activity relationship, support vector machine (SVM), random forest, kappa nearest neighbor (kNN), and decision tree methods were used to develop in silico models, based on Volsurf and Molecular Operating Environment descriptors. The best models were obtained using the SVM, random forest, and kNN methods in combination with the BestFirst variable selection method, resulting in models with 73 to 76% of accuracy on the test set prediction (Matthews correlation coefficients of 0.51 and 0.52). Finally, a decision tree model based on Lipinski’s Rule-of-Five descriptors was also developed. This model predicts 67% of the compounds correctly and gives a simple and interesting insight into the issue of classification. All of the models developed in this work are fast and precise enough to be applicable for virtual screening of CYP1A2 inhibitors or noninhibitors or can be used as simple filters in the drug discovery process.

Cytochromes P450 (P450s) are heme-containing enzymes found in both prokaryotes and eukaryotes, and they are involved in a wide range of cellular biotransformation functions. From a pharmaceutical perspective, the most important function is the degradation of drugs (Nebert and Russell, 2002). In general, hydrophobic compounds are converted into more hydrophilic species to facilitate excretion.

The most important P450 isoforms involved in metabolism of drugs in humans are CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4. CYP1A2 constitutes 12% of the total P450 content in the liver and plays an important role in the metabolic clearance of ~5% of currently marketed drugs. The substrates for the CYP1A2 subfamily are generally characterized as neutral, flat, aromatic, and lipophilic (two to four aromatic rings) with at least one putative hydrogen bond donor (Smith et al., 1997), in agreement with the observed contacts in the recent crystal structure of CYP1A2 (Sansen et al., 2007). Examples of drugs that are CYP1A2 substrates are acetaminophen, caffeine, clozapine, haloperidol, olanzapine, propranolol, tacrine, theophylline, and zolmitriptan (drug interactions: cytochrome P450 drug interaction table, Indiana University School of Medicine, http://medicine.iupui.edu/flockhart/table.htm).

In silico approaches are attractive because they can be used in an early stage of the drug discovery process and thereby reduce the number of experimental studies and improve the success rates. For this purpose, various traditional in silico modeling methods and more recently developed nonlinear machine learning methods have been used (Chohan et al., 2005; de Graaf et al., 2005; Kriegl et al., 2005a; Yap and Chen, 2005; Fox and Kriegl, 2006; Yap et al., 2006; Eitrich et al., 2007; Terfloth et al., 2007; Zhou et al., 2007). Machine learning methods are particularly useful for data mining of large databases to discover patterns or rules to derive models for problems for which the underlying mechanism is not clear. For example, support vector machine (SVM) methods have been applied to classify inhibitors of the CYP3A4 enzyme with a success rate of approximately 70% for the test set (807/538 compounds in training/test sets) (Kriegl et al., 2005b; Terfloth et al., 2007; Zhou et al., 2007). Thus, in silico methods seem promising for making reliable models for sets of a large number of compounds. In this study, we used approximately 400 compounds to construct models for CYP1A2 inhibition and to explore the accuracy of various machine learning...
assay was equal to its luciferase detection reagent. The luciferin 6-methyl ether concentration in the luciferin formation is monitored by luminescence after the addition of a 6-methyl ether to luciferin was measured. The inconclusive compounds were not considered in this study to avoid uncertainty in model building. In addition to the PubChem data set, we also collected from the PubChem BioAssay database (http://www.ncbi.nlm.nih.gov). In this work, we used the scores from the PCA obtained by the SIMCA-P program (version 11.0; Umetrics, Umeå, Sweden) [correlation coefficient (R^2) = 0.81; cross-validated correlation coefficient (Q^2) = 0.66; 25 principal components (PCs)]. The layers were determined according to the Hotelling’s T2 parameter, which measures the distance between the projection of a compound and the center of the model. The compounds were then allocated into the individual layers according to their Hotelling’s T2 values for the corresponding model. The software package MODDE (version 7.0; Umetrics) was used to perform the DOOD-based training set selection.

The selected methods are based on different concepts and are representative of the common approaches considered for classification. The machine learning methods applied in this work are presented in brief below.

**SVM.** SVM is a nonlinear model, developed by Vapnik (2000). The SVM method constructs a hyperplane, which discriminates between data points of distinct classes (binary SVM) such that the margin between both classes is maximized. This margin models the linear decision hyperplane. The final position and orientation of the hyperplane are defined by a subset of training vectors, the so-called support vectors. The SVM approaches were used in association with a radial bias function as the kernel function. The kernel exponent was set to 1.0 [SVM^2 (default)] and the polynomial kernel to 2.0 [SVM^3] for linear and nonlinear SVM classifiers, respectively.

**kNN algorithm.** This method was developed by Zheng and Tropsha (2000). The k-nearest neighbor models are based on the assumption that similar compounds have similar physicochemical and biological activity profiles and can define a class membership of its nearest neighbors. Compounds are represented by their position vectors defined in the physicochemical space and then biological activity is assigned by a majority vote of its neighbors. The neighbors are taken from a set of compounds for which the correct classification is known. Finally, properties or activities of new compounds are assigned on the basis of the majority vote of neighbors defined previously. For the k-NN nearest neighbor algorithm, we used Euclidian distances and five k-NN nearest neighbors to avoid tied votes.

**Random forest method.** With the random forest method (Witten and Frank, 2005), multiple classification trees are constructed from an input vector. The input vector is then placed down of the classification trees in the forest, and each tree gives a classification, or votes, for that class. Finally, the random forest chooses the classification having the most votes. The forest error rate depends on two factors: 1) the correlation between any two trees in the forest and 2) the strength of each individual tree in the forest. A tree with a low error rate is a strong classifier. The main advantage of this approach is the possibility of handling thousands of input variables without overfitting in a very fast way. The random forest method was used with 10 trees and 1 seed.

**Decision tree (C4.5/J48).** This method is a divide-and-conquer approach to the problem of learning from a set of independent instances that naturally leads to a style of representation. First, an attribute is selected to place at the root node and make one branch for each possible value. This splits up the data set into subsets, one for every value of the attribute. This process can be repeated recursively for each branch, using only those instances that actually reach the branch (Witten and Frank, 2005).

**Binary Q SAR.** This method is based on the Bayesian inference technique, which is used to classify whether a compound is active or inactive on the basis of its associated molecular descriptors. A probabilistic distribution of active and inactive compounds in a training set is determined using a partial least-squares method. The binary Q SAR model derived can subsequently be used to predict the probability of new compounds to be active against given targets. The binary Q SAR methodology has been described in detail in the literature (Gao et al., 1999; Labute, 1999; Gao, 2001).

The influence of various factors on the accuracy of the predictions was investigated. A smoothing factor was used to minimize the sensitivity of the derived model to the selection of binary boundaries. We analyzed different smoothing factors (Gao et al., 1999; Labute, 1999; Gao, 2001) ranging from 0.08 to 0.25 with different numbers of principal components ranging from 1 to maximum (data not shown). For descriptor selection, different variable combinations were evaluated. Finally, we selected 110 (MOE/VolSurf) descriptors.
for model development. The descriptors include MOE 2D descriptors such as subdivided surface area descriptors (SlogP descriptors), number of aromatic atoms, number of hydrogen atoms, atomic valence connectivity index, carbon valence connectivity index, molecular weight, and Balaban’s connectivity topological index and Volsurf descriptors using the DRY and N1 probes.

**Software.** Weka data mining software (version 3.2; Waikato Environment for Knowledge Analysis, University of Waikato, Hamilton, NZ, http://www.cs.waikato.ac.nz/ml/weka/) (Witten and Frank, 2005) was used for the inhibitor/noninhibitor classification. The software provides a set of classification and regression methods, variable selection methods, and clustering methods (SVM3, SVM4, kNN, random forest, and decision tree). The binary QSAR was performed using the MOE program.

**Attribute Selection.** For attribute selection we used the automatic variable selection procedure (CfsSubsetEval) in Weka software. CfsSubsetEval was combined with either the BestFirst or a genetic algorithm (Witten and Frank, 2005).

**Matthews Correlation Coefficient.** Matthews correlation coefficient (MCC) is a measure of the quality of a binary classification. It takes into account true positives and negatives and is generally regarded as a balanced measure that can also be used if the classes are of very different sizes. It returns a value between −1 and +1. A coefficient of +1 represents a perfect prediction, 0 an average random prediction, and −1 the worst possible prediction. In general, MCC values greater than 0.4 are considered to be predictive in machine learning methods (Chohan et al., 2005).

$$\text{MCC} = \frac{TP \times TN - FP \times FN}{\sqrt{(TP + FP)(TP + FN)(TN + FP)(TN + FN)}}$$

where TP are true positives, TN are true negatives, FP are false positives, and FN are false negatives.

**Cross-Validation.** All models developed were cross-validated with K-fold cross-validation. In K-fold cross-validation, the original sample is divided into K subsamples. Of the K subsamples, a single subsample is retained as the validation data for testing the model, and the remaining K−1 subsamples are used as training data. The cross-validation process is then repeated K times, with each of the K subsamples used exactly once as the validation data. Here, we performed 5-fold cross-validation. All cross-validations were carried out with the procedures in Weka software, and 5-fold cross-validation was chosen.

**Results and Discussion**

**Description of Training and Test Sets.** The 7469 compounds extracted from PubChem and considered in this work constitute the largest set of compounds used for constructing in silico models of CYP1A2. Visual inspection of randomly selected compounds revealed compounds resembling drug compounds as well as compounds being clearly nondrug-like. Although Lipinski’s Rule-of-Five (Lipinski et al., 2001) is not a direct measure of drug-likeness, we calculated the violations of each of the four rules for the CYP1A2 data set: 544 compounds had molecular weight greater than 500; 132 compounds had more than 10 hydrogen bond acceptors; 293 compounds had more than 5 hydrogen bond donors, and 551 compounds had a partition coefficient, logP value, greater than 5. In total, only approximately 15% of the compounds in the data set violated one or several of the Lipinski’s rules.

From DOOD, a training set consisting of 411 compounds (192 inhibitors and 219 noninhibitors) was constructed, and the remaining 7058 compounds were used as a test set. DOOD was used because it has previously been successfully applied for the selection of suitable training sets (Gavaghan et al., 2007). The score plot from the PCA shows that the diversity of the whole data set is satisfactorily reflected in the training set (Figure 1). Only a minority of the compounds are outside the 95% confidence interval, and, of those, most form a cluster located in the lower right part of the score plot, corresponding to the compounds violating Lipinski’s Rule-of-Five. Inspection of these structures revealed that there is no structural similarity within this group, but that 95% of these compounds were noninhibitors.

**Construction of Binary QSAR Models.** Binary QSAR models for classification of active (inhibitors) and inactive (noninhibitors) compounds were developed using the 214 calculated MOE and 110 Volsurf descriptors. We selected these descriptors because previously they have been applied successfully for classification or IC50 predictions for P450 ligands (Eriksson et al., 2004; Kriegl et al., 2005b). Most of these descriptors cover properties such as lipophilicity [e.g., LogP-derived descriptors or Volsurf descriptors based on the hydrophobic interactions (DRY probe)], the hydrophilicity [e.g., polar surface area-derived descriptors or Volsurf descriptors based on the hydrophilic interactions (N1 probe)], or the number of various types of atoms (e.g., number of aromatic atoms or hydrogen atoms).

The influence of various factors such as the number of descriptors, the number of principle components (PCA), and smoothing factors on the accuracy of the predictions was investigated (see Materials and Methods). Finally, we selected 110 (MOE and Volsurf) descriptors for model development, including those describing the lipophilicity, hydrophilicity, various atom counts, and connectivity. Use of default settings in MOE for smoothing factors and number of PCs gave a binary QSAR model with a significant difference in predictive power between the training and test set, in particular for the CYP1A2 inhibitors, for which 96% are correctly predicted in the training set, but only 55% in the test set. Therefore, a model that is based on only three principal components was considered. This leads to a correctly predicted number of compounds on 70 and 66% for the training and test sets, respectively, but at the same time it yields a more balanced model with respect to the predictivity of inhibitors and noninhibitors (Table 1).

**Construction of Models by Other Machine Learning Methods.** We developed models with other methods to investigate whether the quality of the models could be improved. For that purpose, classification models of active and inactive compounds were generated using the SVM, kNN, random forest, and decision tree methods.

As for the binary QSAR model described in the last section, care was taken with respect to what descriptors were included in the model building to avoid overfitting and to reduce the noise. Therefore, we generated models using all MOE and Volsurf variables, as well as a variable selection by the so-called BestFirst and a genetic algorithm (Tables 2 and 3; Fig. 2). In general, the quality of the models improved when the BestFirst variable selection was used, whereas variables selected by the genetic algorithm did not improve the model.
compared with use of all variables. For example, the total number of correctly predicted compounds in the test set is largest using the BestFirst method (SVMD: 73%; SVM^E: 75%; random forest: 76%; kNN: 74%; and decision tree: 71%) (Fig. 2), and its ability to predict both active and inactive compounds is more balanced compared with the models generated with all descriptors and descriptors selected by the genetic algorithm (Table 3). Thus, in the remaining text we will only comment on the models generated by the BestFirst method for variable selection.

Overall, the different methods yield models of similar quality. Of the 7058 compounds in the test set, 4984 to 5375 (71–76%) are correctly predicted. Thus, the different methods are quite similar in performance, with SVM^E and the random forest methods being the best methods and the decision tree method being a reasonable method. This finding is also reflected in the MCC values that are 0.51 to 0.52 for the SVM^E and the random forest methods and 0.41 for the decision tree method. However, it should be noted that the smallest discrep-

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**TABLE 1**

<table>
<thead>
<tr>
<th>Set</th>
<th>Predicted Compounds</th>
<th>Correctly Predicted</th>
<th>MCC</th>
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<td>TP</td>
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<tr>
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<td>45</td>
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TP, number of true positives; FP, number of false positives; TN, number of true negatives; FN, number of false negatives.

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**TABLE 2**

<table>
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<th>Method</th>
<th>Predicted Compounds</th>
<th>Correctly Predicted</th>
<th>MCC</th>
<th>5-Fold CV</th>
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<td>71</td>
<td>29</td>
<td>72</td>
<td>28</td>
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TP, number of true positives; FP, number of false positives; TN, number of true negatives; FN, number of false negatives; CV, cross-validation; SVM^D, support vector machine, linear model; SVM^E, support vector machine, nonlinear model; RF, random forest method; kNN, kappa nearest neighbors method; C4.5/J48, decision tree method.

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**TABLE 3**

<table>
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<th>Set</th>
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<th>MCC</th>
<th>5-Fold CV</th>
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<td>29</td>
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TP, number of true positives; FP, number of false positives; TN, number of true negatives; FN, number of false negatives; MCC, Matthews correlation coefficient; CV, cross-validation; SVM^D, support vector machine, linear model; SVM^E, support vector machine, nonlinear model; RF, random forest method; kNN, kappa nearest neighbors method; C4.5/J48, decision tree method.
with a probability given for each compound with the random forest method. Compounds is also reflected in the MCC values of 0.31 and 0.36 (Table 1). The model is clearly worse than the other methods, and, again, this result is balanced and not overfitted model. As seen in Fig. 2, the binary QSAR of 89 drugs (39 active and 50 inactive), Of these compounds, 24 violated Lipinski’s Rule-of-five, primarily because of lipophilicity. Figure 4 shows that this small external set of compounds span the same chemical space as the large PubChem dataset; thus, it should be possible to predict their 1A2 activity with the developed models. The best method was again the SVM method, which classifies 60 of the 89 compounds correctly (Table 4). It is interesting to note that the performance seems to be slightly poorer for this set of compounds compared with the PubChem data set, which might be attributed to the smaller size of the set of compounds. Another explanation may arise from the fact that a different experimental assay was used to determine the inhibitory constants of the external test set compared with the PubChem data set. This may lead to different experimental classifications for which the models were not trained.

**External Test Set of Drug Compounds.** In the following, we have focused on the best machine learning methods (SVM, random forest, kNN, and decision tree) to classify a small external set of 89 drug molecules (39 active and 50 inactive). Of these compounds, 24 violated Lipinski’s Rule-of-five, primarily because of lipophilicity. Figure 4 shows that this small external set of compounds span the same chemical space as the large PubChem dataset; thus, it should be possible to predict their 1A2 activity with the developed models. The best method was again the SVM method, which classifies 60 of the 89 compounds correctly (Table 4). It is interesting to note that the performance seems to be slightly poorer for this set of compounds compared with the PubChem data set, which might be attributed to the smaller size of the set of compounds. Another explanation may arise from the fact that a different experimental assay was used to determine the inhibitory constants of the external test set compared with the PubChem data set. This may lead to different experimental classifications for which the models were not trained.

**Structural Characteristics of Inhibitors, Noninhibitors, and Misclassified Compounds.** It is important to understand why compounds are classified as they are. In general, it turned out that differences in the hydrophobic and hydrophilic natures of the CYP1A2 compounds are important for discriminating inhibitors from noninhibitors. In Volsurf, the hydrophobic and hydrophilic properties of a compound may be visualized with the so-called DRY (hydrophobic properties) and N1 (hydrogen donor properties) probes, as shown in Fig. 5. Compound A, an inhibitor of CYP1A2, has a large hydrophobic region and a small polar region, which is common for most of the inhibitors. Noninhibitors, such as compound B, are characterized by slightly smaller hydrophobic regions and much larger polar regions. These characteristics fit well with the general idea of CYP1A2 ligands being hydrophobic with one hydrogen bond acceptor (Smith et al., 1997; Sansen et al., 2007). A compound with characteristics such as those of compound C is likely to be predicted as a noninhibitor, because it has a large polar region and therefore fails in the prediction. Likewise, compound D, which is a noninhibitor, is mainly hydrophobic, and this is probably why this prediction also fails.

**Lipinski-Decision Tree Model.** Although the models derived by the machine learning methods perform satisfactorily, it would be useful to develop a simple “back-of-the-envelope calculation” such as Lipinski’s Rule-of-Five. Such a method would be extremely fast and useful to develop a simple “back-of-the-envelope calculation” such as Lipinski’s Rule-of-Five. Such a method would be extremely fast and therefore potentially useful for high-throughput screening and at the same time allow easy interpretation. Thus, a decision tree model was subsequently developed on the basis of the four Lipinski parameters: molecular weight, numbers of hydrogen bond acceptors and donors, and lipophilicity. The so-called Lipinski-decision tree model performed surprisingly well (Table 5): 71 and 67% of the compounds in the training and test sets, respectively, were correctly predicted, even

![Fig. 3. True predictions for probabilities of belonging to a certain class (data shown for random forest predictions of compounds in the test set). In Weka software, compounds with a probability smaller or larger than 50% are classified as inactive or active, respectively. White/black, true predictions for inactive/active compounds.](image1)

![Fig. 4. The 89 drug molecules in the external test set projected on the score plot from principal component analysis of the PubChem data set.](image2)
though the balance between TP and TN is relatively far off. As illustrated in Fig. 6, compounds classified as inhibitors are characterized as having either 1) more than two hydrogen bond donors, logP $\leq 3.7$ and less than six hydrogen bond donors or 2) 2 hydrogen bond donors and a molecular weight between 198 and 516. Compounds that fall outside these ranges are considered to be noninhibitors. This decision model is in good agreement with the conclusion derived from inspection of the molecular interaction fields (Fig. 4) discussed in the previous section. Finally, we tested the Lipinski-decision tree model on a set of known 1A2 substrates and inhibitors (Table 6) (drug interactions: cytochrome P450 drug interaction table, Indiana University School of Medicine, http://medicine.iupui.edu/flockhart/table. htm). Of these, 34 compounds corresponding to 79% were correctly predicted as 1A2 ligands.

### Conclusion

In this article, we have reported the application of different machine learning classification methods such as support vector machine (linear and nonlinear), random forest, kNN, decision tree, and binary QSAR for the classification of cytochrome P450 1A2 ligands. Models that are based on the support vector machine method are superior to binary QSAR models. Use of the SVM, random forest, and kNN methods and the BestFirst variable selection method resulted in models with 73 to 76% of the test set correctly predicted. Finally, a decision tree model based on Lipinski’s Rule-of-Five descriptors was developed, classifying 67% of the compounds in the test set correctly. This model is easy to interpret and offers structural insight into the classification of new CYP1A2 inhibitors.

Inspection of the molecular interaction fields illustrates the importance of hydrophobicity and hydrogen bond donors and acceptors. These features are in agreement with the Lipinski-decision tree model and agree with previously reported pharmacophore models and X-ray structure of the cytochrome P450 1A2 isoenzyme.

The models developed in this work are fast and precise enough to be applicable for virtual screening of large databases for identification of 1A2 inhibitors or noninhibitors. Moreover, they can be used as filters to quickly assess the likelihood that a newly designed compound shows an interaction with CYP1A2. As such, the models can play an important role in preventing the risk of, e.g., drug-drug interactions through metabolism at an early stage of the drug development process.
Acknowledgments. We thank Professor Gabriele Cruciani (University of Perugia, Perugia, Italy) for providing the Volsurf software.

References


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