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PredMS: a random forest model for predicting metabolic stability of drug candidates in human liver microsomes

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Abstract

Motivation: Poor metabolic stability leads to drug development failure. Therefore, it is essential to evaluate the metabolic stability of small compounds for successful drug discovery and development. However, evaluating metabolic stability *in vitro* and *in vivo* is expensive, time-consuming and laborious. In addition, only a few free software programs are available for metabolic stability data and prediction. Therefore, in this study, we aimed to develop a prediction model that predicts the metabolic stability of small compounds.

Results: We developed a computational model, PredMS, which predicts the metabolic stability of small compounds as stable or unstable in human liver microsomes. PredMS is based on a random forest model using an in-house database of metabolic stability data of 1917 compounds. To validate the prediction performance of PredMS, we generated external test data of 61 compounds. PredMS achieved an accuracy of 0.74, Matthew's correlation coefficient of 0.48, sensitivity of 0.70, specificity of 0.86, positive predictive value of 0.94 and negative predictive value of 0.46 on the external test dataset. PredMS will be a useful tool to predict the metabolic stability of small compounds in the early stages of drug discovery and development.

Availability and implementation: The source code for PredMS is available at https://bitbucket.org/krictai/predms, and the PredMS web server is available at https://predms.netlify.app.

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Supplementary information: Supplementary data are available at *Bioinformatics* online.

1 Introduction

Drug metabolism, which refers to enzyme-catalyzed reactions that chemically transform drugs and other xenobiotics into metabolites readily excreted from the body, must be considered during the drug development process. Most drug metabolic processes occur in the liver and can be categorized into two phases. Phase I reactions include oxidation, reduction and hydrolysis and may involve cytochrome P450 enzymes, NADPH and oxygen. Phase II reactions involve conjugation with endogenous substances such as glucuronic acid, sulfate and glycine. Since drug metabolism affects the pharmacokinetics, therapeutics and toxicity of drugs, elucidating the metabolic profiles of new chemical entities is crucial for successful drug discovery and development (Kola and Landis, 2004; Korfmacher, 2009; Pelkonen *et al.*, 2005).

Drug metabolism is typically evaluated by *in vitro* cellular and *in vivo* animal models (Sloczynska *et al.*, 2019). While studies on *in vivo* models have provided valuable data, these are often expensive and low-throughput screening systems. Thus, *in vitro* cellular models are recommended as a preliminary screening system for large numbers of compounds. The assays are carried out by incubating a compound with microsomes, cytosol or hepatocytes (Jia and Liu, 2007; Poulin *et al.*, 2012). In general, the percentage of drugs remaining at 30 min (% remaining at 30 min), half-life ($t_{1/2}$) and intrinsic clearance (Cl_{int}) are used to express metabolic stability. The percentage remaining at 30 min is that of the parent compound removed after 30 min, $t_{1/2}$ is the time taken for 50% of the parent compound to disappear, and Cl_{int} is the maximum activity of the liver toward a compound unaffected by physiological determinants (Perryman *et al.*, 2016). In general, the metabolic stability of compounds in the presence of human liver microsomes is classified as stable if $\geq$50% of the parent compound remains after 30 min. Otherwise, the compounds are deemed unstable (Liu *et al.*, 2015; Shah *et al.*, 2020; Sloczynska *et al.*, 2019). Although *in vitro* cellular

models are inexpensive and more high-throughput than *in vivo* models, they are still expensive and laborious for screening large numbers of compounds.

Machine learning (ML)-based approaches have recently been used to evaluate molecular properties such as absorption, distribution, metabolism, excretion and toxicity for large-scale screening processes. For example, various ML models that predict molecular properties such as blood–brain barrier permeability (Shaker *et al.*, 2021), cytochrome P450 inhibition (Li *et al.*, 2018), drug interactions (Ryu *et al.*, 2018) and cardiotoxicity (Lee *et al.*, 2019; Ryu *et al.*, 2020) have been developed to accelerate the drug discovery and development process. These ML models use large-scale training data on thousands of compounds from the scientific literature and/or public databases (Gaulton *et al.*, 2012; Gilson *et al.*, 2016). However, publicly available data and software for the metabolic stability of small compounds are limited.

ChEMBL is a representative database providing large-scale data on metabolic stability of compounds assayed in liver microsomes and plasma of humans (5234 compounds), rats (2829 compounds) and mice (1136 compounds) (Gaulton *et al.*, 2012). Podlewska and Kafel developed a freely available online tool, MetStabOn, which predicts cellular metabolic stability using the ChEMBL database (Podlewska and Kafel, 2018). MetStabOn consists of six ML models constructed for three species (i.e. human, rat and mouse) and assays performed on liver microsomes and plasma. Specifically, a regression model of MetStabOn was developed using sequential minimal optimization (SMO), which is a modification of the support-vector machine (SVM), and five classification models were developed using a decision tree (DT), k-nearest neighbor (kNN), naïve Bayes (NB), random forest (RF) and SMO. MetStabOn predicts metabolic stability of given compounds and categorizes them as having low ($t_{1/2} \leq 0.6$), medium ($0.6 < t_{1/2} \leq 2.32$) or high ($t_{1/2} > 2.32$) stability. Three classification models (i.e. kNN, RF and SMO) have shown reasonably good prediction performance, with an overall accuracy of over 0.7 in terms of predicting the metabolic stability of small compounds in liver microsomes of humans, rats and mice. However, the prediction performance of MetStabOn has limited generalizability, as the prediction performance was evaluated only using 10-fold cross-validation, and the prediction results have not been experimentally validated.

In this study, we developed a computational model called PredMS, which predicts the metabolic stability for a given compound in the human microsome and classifies the compound as stable (≥50% remaining at 30 min) or unstable (<50% remaining at 30 min) (Fig. 1). To develop PredMS, we first generated in-house data on metabolic stability of a diverse set of 1917 compounds (1049 stable and 868 unstable compounds in human liver microsomes). Then, we tested six ML algorithms, including artificial neural network (ANN), kNN, logistic regression (LR), NB, RF and SVM, to develop the best model with the highest prediction performance. When evaluated using 5-fold cross-validation, the RF-based model showed the highest area under the receiver operating characteristic (AUROC) of 0.73. Hence, we used the RF model in PredMS to predict metabolic stability in human liver microsomes. We also generated external test data on 61 compounds for rigorous validation of prediction performance.

2 Materials and methods

2.1 Chemicals

Test compounds were obtained from the Korea Research Institute of Chemical Technology (Daejeon, Korea). β-Nicotinamide adenine dinucleotide phosphate (β-$NADP^+$) was purchased from Sigma-Aldrich (St. Louis, MO, USA). Pooled human liver microsomes were purchased from BD Gentest (Woburn, MA, USA). Solvents were HPLC grade (Fisher Scientific, Pittsburgh, PA, USA), and other chemicals were of the highest grade available.

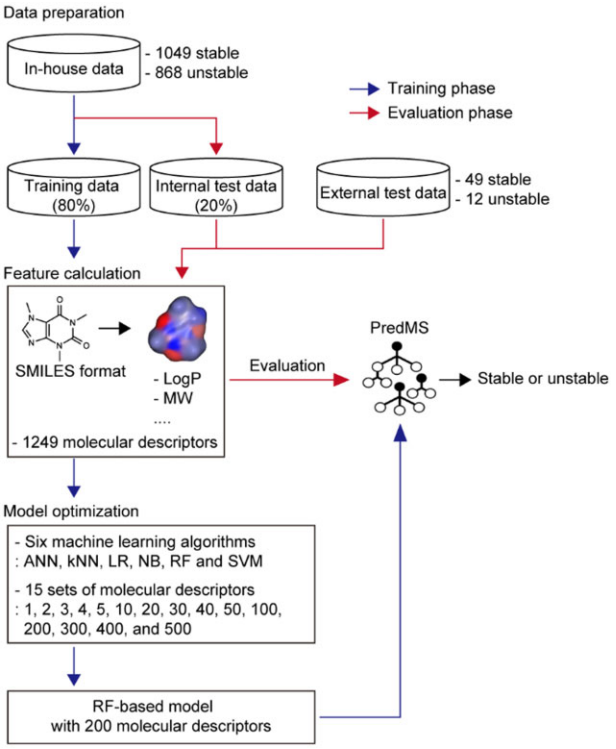

Fig. 1. Schematic workflow of PredMS development. PredMS predicts the metabolic stability of a compound given in the SMILES format and classifies it as stable or unstable in human liver microsomes. PredMS is based on a RF algorithm trained with the in-house training data, comprising a chemically diverse set of chemical compounds. PredMS performance was evaluated by using the internal and external test data

2.2 Liver microsomal metabolic stability

We determined the NADPH-dependent metabolic stability of test compounds in human liver microsomes. The reaction mixture consisted of human liver microsomes (BD Gentest) in 100 mM potassium phosphate buffer (pH 7.4) and a final concentration of 1 μM of the tested compound. After preincubation at 37°C for 5 min, the reaction was initiated by adding NADPH regenerating solution (BD Biosciences, Bedford, MA, USA). Samples (30 μl) were collected after 30 min. The reaction was terminated by adding 120 μl of ice-cold acetonitrile with imipramine (100 ng/ml, internal standard). The mixture was vortexed and centrifuged at 4°C for 5 min at 4000 rpm. The clear supernatant was collected, transferred to liquid chromatography (LC) vials and analyzed by LC-MS/MS to quantify test compounds.

2.3 Data preparation

The metabolic stability of a small compound in human liver microsomes was assessed as the percentage of compound remaining after 30 min (% remaining at 30 min). For the generation of in-house data, the metabolic stabilities of 1917 compounds were measured and used for model development. We defined compounds with <50% remaining at 30 min as unstable and the other compounds as stable in human liver microsomes. The in-house data were divided into a training dataset (80%) and an internal test dataset (20%). The training dataset was used for hyper-parameter optimization, and the internal test dataset was used for model evaluation (Fig. 1). The metabolic stabilities of 61 compounds were additionally measured and used as external test data for model evaluation.

2.4 Preparation of molecular features

The chemical structures of the compounds were presented in the simplified molecular-input line-entry system (SMILES) format (Weininger, 1988). To use chemical structures as model inputs, the

molecular descriptors for each compound were calculated. The molecular descriptors were calculated using the Python package, *Mordred* (Moriwaki *et al.*, 2018). Only the molecular descriptors that could be calculated for all compounds were considered. In total, 1249 molecular descriptors (i.e. features) were used for model development.

To reduce the number of molecular features, feature selection was conducted using an RF-based feature selection method that calculates each molecular feature's importance in predicting metabolic stability. Feature importance was calculated using the Python package, *scikit-learn* (Pedregosa *et al.*, 2011). After calculating the functional importance, we selected the top n features (i.e. molecular descriptors) with high feature importance for model development. In this study, we tested 15 sets of molecular descriptors: 1, 2, 3, 4, 5, 10, 20, 30, 40, 50, 100, 200, 300, 400 and 500.

2.5 Optimization of ML algorithms

Six ML algorithms, including ANN, kNN, LR, NB, RF and SVM, were tested to find the optimal method for predicting metabolic stability, an ML algorithm inspired by the biological neuronal network of the human brain. An ANN structure consists of artificial neurons organized into layers (Angermueller *et al.*, 2016). In general, the ANN structure consists of an input layer, hidden layer(s) and an output layer. The ANN learns non-linear relationships from the data. kNN is a non-parametric algorithm used for classification and regression tasks (Laaksonen and Oja, 1996). During the training phase, the kNN algorithm stores the data points. In the prediction phase, kNN classifies a new data point by considering the similarity of the training phase data points. LR is a regression algorithm used when the dependent variable is dichotomous, and it can be used for binary classification (Carey *et al.*, 1993). NB is a probabilistic classifier based on the Bayesian theorem, which calculates the probability of the classes for a given dataset (Yousef *et al.*, 2006). The NB model assumes that all features are independent. RF is an ensemble learning algorithm that constructs multiple DTs (Vincenzi *et al.*, 2013). The final decision is made based on the majority of the DTs. RF can be used for both classification and regression tasks.

We optimized the hyper-parameters for each ML algorithm and selected the optimal hyper-parameter showing the highest AUROC using the grid search cross-validation method. The ANN algorithm was implemented using the package *Keras* (version 2.2.5) with a TensorFlow backend (version 2.0.0) (Abadi *et al.*, 2016). The kNN, LR, NB, RF and SVM algorithms were implemented using the *scikit-learn* Python package (Suykens and Vandewalle, 1999). The performance of the model was evaluated using seven performance metrics: accuracy (ACC), AUROC, Matthew's correlation coefficient (MCC), sensitivity (SEN), specificity (SPE), positive predictive value (PPV) and negative predictive value (NPV).

3 Results and discussion

3.1 Chemical diversity of the compounds in the ChEMBL database

As the predictive performance of the ML algorithm depends on the training data diversity, we first checked the chemical diversity of compounds in the ChEMBL database (Gaulton *et al.*, 2012). Then, we analyzed the chemical diversity of 2126 compounds with information on metabolic stability in humans found in the ChEMBL database. For examining the diversity of molecular properties, we used t-distributed stochastic neighbor embedding (t-SNE), a dimensional reduction method, to project high-dimensional data onto low-dimensional space (Chakravarti, 2018; Popova *et al.*, 2018). For 2126 compounds, molecular descriptors representing molecular properties were calculated and used as input for t-SNE. As shown in Figure 2A, compounds in the ChEMBL database appear clustered (i.e. form groups with low chemical diversity), indicating that several compounds have similar molecular properties. The use of data with low chemical diversity for model training could cause problems with overfitting and model generalization (Buda *et al.*, 2018). In addition, metabolic stability data in the ChEMBL database were collected

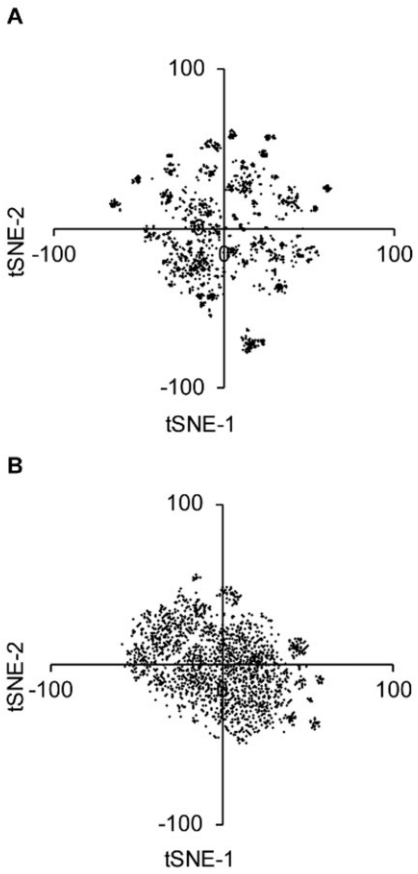

Fig. 2. Visualization results of chemical diversity using t-distributed stochastic neighbor embedding (t-SNE). (**A**) Chemical diversity of 2126 compounds with information on metabolic stability in the ChEMBL database. (**B**) Chemical diversity of 1917 compounds in the in-house data

from a variety of data sources, including research articles, patents and public databases such as PubChem BioAssay (Wang *et al.*, 2012) and BindingDB (Gilson *et al.*, 2016). Therefore, the metabolic stability data in the ChEMBL database may differ from the data obtained under similar experimental conditions.

3.2 Generation of in-house metabolic stability data in humans

To address overfitting and model generalization problems, we generated in-house metabolic stability data of structurally diverse compounds from Korea Chemical Bank by estimating stability under the same experimental condition. In total, 1917 compounds were selected for experiments, and their metabolic stability, expressed as % remaining at 30 min, was measured (Section 2). In contrast to the compounds in the ChEMBL database, these 1917 compounds showed greater chemical diversity and did not form clusters (Fig. 2B). To prepare the training data for classification tasks, we divided the 1917 compounds into two groups (i.e. stable and unstable in human liver microsomes): compounds with $\geq$50% remaining at 30 min were classified as stable, and those with $<$50% remaining at 30 min as unstable. According to this classification, we identified 1049 (54.7%) stable and 868 (45.3%) unstable compounds in human liver microsomes. These data were used as a training dataset to develop ML models predicting metabolic stability.

3.3 Development of ML models

To prepare inputs for ML algorithms, we used 1249 molecular descriptors as a feature vector for each compound. To obtain the optimal number of features, we tested 15 sets of molecular descriptors

as features using a feature selection method (see Section 2). The number indicates the size of subsets out of 1249 molecular descriptors that contain the n most important molecular descriptors for classifying metabolic stability. Through this analysis, we found that the most important molecular descriptor for predicting metabolic stability was the logarithm of octanol and the water partition coefficient (SLogP).

Using the in-house data and each subset of molecular descriptors, we tested six ML algorithms (i.e. ANN, kNN, LR, NB, RF and SVM) to obtain the best ML model with the highest AUROC (Fig. 3 and Section 2), which is a widely used performance metric for model evaluation. The in-house data were divided into training data (80%) and internal test data (20%). The training dataset was used to search optimal hyper-parameters for each ML algorithm using the grid search cross-validation method. The internal test dataset was used to evaluate the model performance of the best ML model. Using this procedure, we found that the RF-based model with 200 molecular descriptors exhibited the highest AUROC of 0.73 (Fig. 3; see Supplementary Table S1 for the list of 200 molecular descriptors). In addition, the RF-based model showed robust prediction performance regardless of the number of molecular descriptors. In this study, four hyper-parameters (i.e. number of trees in the forest, maximum number of levels in each DT, minimum number of data points placed in a node before the node is split, and minimum number of data points allowed in a leaf node) were optimized (Supplementary Table S2). Therefore, we employed the RF model for developing PredMS. As a result of the evaluation using the internal test data, PredMS exhibited an ACC of 0.68, MCC of 0.34, SEN of 0.76, SPE of 0.57, PPV of 0.70 and NPV of 0.64 (Table 1).

3.4 Evaluation of PredMS performance using test data

Comparing the prediction performance of the ML models with existing models is an essential step for model validation, but no web servers and/or software were publicly available (as of March 2021) for this purpose. For example, MetStabOn, a web-based prediction tool for predicting metabolic stability, was temporarily unavailable (Podlewska and Kafel, 2018). Thus, we generated external test data to validate PredMS instead of comparing model performance with other tools. To achieve this, we selected 61 compounds that are available and open to the public and measured their metabolic stabilities using the same protocols as the training data. The information of metabolic stability data of 61 compounds is available in Supplementary Table S3. We identified 49 (80.3%) stable and 12 (19.7%) unstable compounds in the external test data. Moreover, these 61 compounds were structurally different from the training data compounds; the maximum structural similarity was a Tanimoto coefficient of 0.53 (Fig. 4). Thus, the external test data serve as a benchmark dataset for the metabolic stability model. When evaluated using the external test data, PredMS achieved an ACC of 0.74, MCC of 0.48, SEN of 0.70, SPE of 0.86, PPV of 0.94 and NPV of 0.46 (Table 1).

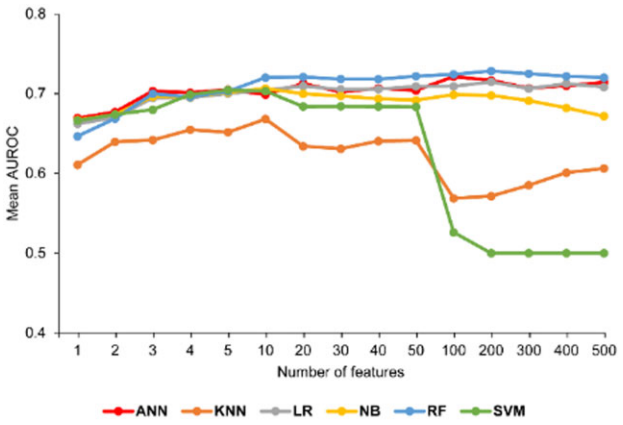

Fig. 3. Model performance with respect to feature number. Mean AUROC value calculated by 5-fold cross-validation was used to compare model performance of each ML algorithm with respect to the number of features. ANN, artificial neural network; kNN, k-nearest neighbor; LR, logistic regression; NB, naïve Bayes; RF, random forest; SVM, support vector machine

Table 1. Prediction performance of PredMS on the internal and external test data

Data	ACC	MCC	SEN	SPE	PPV	NPV
Internal test data	0.68	0.34	0.76	0.57	0.70	0.64
External test data	0.74	0.48	0.70	0.86	0.94	0.46

ACC, accuracy; MCC, Matthew's correlation coefficient; SEN, sensitivity; SPE, specificity; PPV, positive predictive value; NPV, negative predictive value

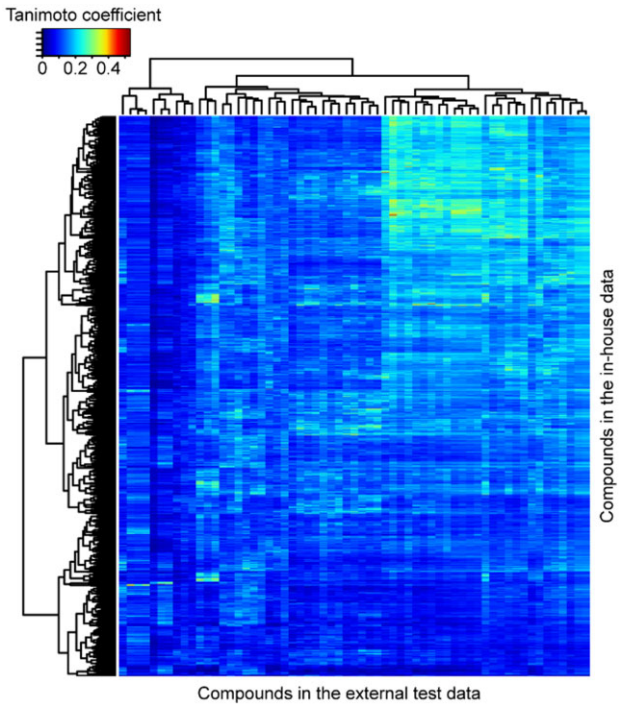

Fig. 4. Heat map of pairwise structural similarities between compounds in the in-house data and the external test data. Structural similarity between two compounds was calculated using Tanimoto coefficient and extended connectivity fingerprints with a maximum diameter parameter of 4

Thus, PredMS appears to exhibit reasonable prediction performance for practical applications. For example, PredMS had a PPV of 0.94, indicating that 94% of compounds predicted to be stable were actually stable in human liver microsomes. However, at this time, we cannot conclude that the PredMS prediction performance is sufficiently accurate. This is because, first, there were no tools to compare the PredMS prediction performance, and second, there was no benchmark dataset to compare with the prediction performance. To address these issues, we provided not only the prediction model, PredMS, as a baseline but also an external test dataset that can serve as a benchmark for model comparison in the future.

Moreover, to further improve the prediction performance of metabolic stability, securing high-quality training data is critical. As shown in Figure 2, learning with high-quality training data (e.g. compounds with structural diversity) will contribute to building an accurate metabolic stability prediction model. In addition, securing high-quality benchmark datasets is also important to ensure the rigorous evaluation of model performance.

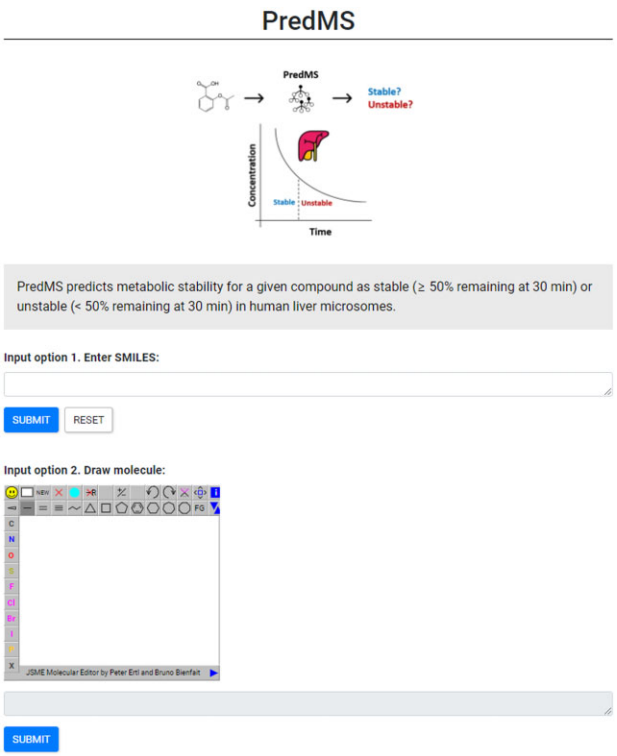

Fig. 5. User interface of PredMS web server

4 Conclusion

In this study, we developed a computational model, RF-based PredMS, which predicts the metabolic stability of given compounds and classifies these compounds as stable (≥50% remaining at 30 min) or unstable (<50% remaining at 30 min) in human liver microsomes. To build a reliable prediction model, we generated in-house metabolic stability data on a chemically diverse set of 1917 compounds for model training and optimization. In addition, we generated an external test dataset consisting of 61 compounds for model evaluation. PredMS exhibited an ACC of 0.74, MCC of 0.48, SEN of 0.70, SPE of 0.86, PPV of 0.94 and NPV of 0.46 on the external test data. Our external test data could serve as a benchmark dataset for model validation. In addition, the PredMS web server is available at https://predms.netlify.app/(Fig. 5). For the implementation of PredMS, users can input the molecular structure as a SMILES string or draw the molecular structure using the JSME Molecular Editor (Bienfait and Ertl, 2013). The PredMS will be a useful tool to predict the metabolic stability of small compounds in the early stages of drug discovery and development.

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Conflict of Interest: none declared.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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