**SUPPLEMENTARY DATA**

**S1: Data description**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Model | Total compounds | Training set | | | Test set | | |
| **Total** | **actives** | **inactives** | **Total** | **actives** | **inactives** |
| |  | | --- | | **CYP3A4** | | 10373 | 9335 | 2168 | 7167 | 1038 | 241 | 797 |
| CYP2D6 | 7805 | 7024 | 1137 | 5887 | 781 | 126 | 655 |
| CYP2C9 | 8072 | 7264 | 850 | 6414 | 808 | 94 | 714 |
| CYP1A2 | 7558 | 6802 | 1208 | 5594 | 756 | 134 | 622 |
| CYP2C19 | 8155 | 7339 | 1366 | 7339 | 816 | 152 | 664 |

**S2: Comparison with other models reported in literature**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Models | Accuracy | | | Sensitivity | | | Specificity | | | AUC (ROC) | | |
|  | **SuperCypPred** | **admetSAR**(1) | **vNN**(2) | **SuperCypPred** | **admetSAR** | **vNN** | **SuperCypPred** | **admetSAR** | **vNN** | **SuperCypPred** | **admetSAR** | **vNN** |
| CYP3A4 | **0.97** | 0.64 | 0.88 | **0.98** | 0.86 | 0.76 | **0.96** | 0.52 | 0.92 | **0.99** | 0.84 | - |
| CYP2D6 | 0.86 | 0.85 | **0.89** | **0.92** | 0.44 | 0.61 | 0.87 | **0.96** | 0.94 | **0.93** | 0.84 | - |
| CYP2C9 | **0.97** | 0.80 | 0.91 | **0.97** | 0.63 | 0.55 | **0.96** | 0.88 | **0.96** | **0.98** | 0.85 | - |
| CYP1A2 | **0.95** | 0.81 | 0.90 | **0.98** | 0.79 | 0.70 | **0.98** | 0.83 | 0.95 | **0.99** | 0.88 | - |
| CYP2C19 | **0.93** | 0.80 | 0.87 | **1.00** | 0.74 | 0.64 | **0.99** | 0.84 | 0.93 | **1.00** | 0.87 | - |
| Overall Best performance (average values) | **0.93** | 0.78 | 0.89 | **0.97** | 0.68 | 0.65 | **0.95** | 0.80 | 0.94 | **0.97** | 0.85 | - |

**S3: Prediction comparison for a set of drugs (KNOWN CYP inhibitors) from the Indiana University School of Medicine** (3)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **CYPS** | **Inhibitor strength** | **Drug name** | **SuperCypPred** | **admetSAR** |
| 1A2 | **Strong** | Fluvoxamine | 0.837 | 0.91 |
|  | **Strong** | Ciprofloxacin | **Inactive (0.92)** | **inactive** |
|  | **weak** | Cimetidine | **Inactive (0.89)** | **inactive** |
| 2C9 | **Strong** | fluconazole | 0.59 | **Inactive (0.54)** |
|  | **Moderate** | Amiodarone | 0.70 | 0.80 |
| 2D6 | **Strong** | Bupropion | **Inactive (0.63)** | 0.89 |
|  | **Strong** | Cinacalcet | 0.95 | 0.81 |
|  | **Strong** | fluoxetine | 0.96 | 0.89 |
|  | **Strong** | paroxetine | 0.85 | **Inactive (0.92)** |
|  | **Strong** | quinidine | 0.98 | 0.89 |
|  | **Moderate** | duloxetine | 0.86 | 0.69 |
|  | **Moderate** | sertraline | 0.70 | Inactive (0.64) |
|  | **Moderate** | terbinafine | 0.88 | 0.67 |
|  | **weak** | amiodarone | 0.78 | 0.89 |
|  | **weak** | cimetidine | 0.60 | **Inactive (0.92)** |
| 3A4 | **Strong** | Indinavir | 0.73 | 0.65 |
|  | **Strong** | nelfinavir | **Inactive (0.51)** | 0.54 |
|  | **Strong** | ritonavir | 0.69 | 0.58 |
|  | **Strong** | clarithromycin | **Inactive (0.89)** | **Inactive (0.55)** |
|  | **Strong** | itraconazole | 0.78 | 0.52 |
|  | **Strong** | ketoconazole | 1.00 | 0.79 |
|  | **Strong** | nefazodone | **Inactive (0.52)** | **Inactive (0.87)** |
|  | **Strong** | saquinavir | 0.825 | 0.52 |
|  | **Strong** | telithromycin | 0.61 | **Inactive (0.84)** |
|  | **Moderate** | aprepitant | 0.509 | **Inactive** (0.52) |
|  | **Moderate** | erythromycin | **Inactive (0.55)** | **Inactive (0.57)** |
|  | **Moderate** | fluconazole | 0.57 | Inactive (0.81) |
|  | **Moderate** | verapamil | 0.86 | 0.79 |
|  | **Moderate** | diltiazem | 0.55 | 0.79 |
|  | **weak** | cimetidine | **Inactive (0.79)** | **Inactive (0.83)** |

**SuperCypPred: Predicted correctly 22 out of 30 drugs: 73% prediction accuracy**

**AdmetSAR**(1)**: Predicted correctly 19 out of 30 drugs: 63% prediction accuracy**

**False prediction**

**References:**

1. Yang,H., Lou,C., Sun,L., Li,J., Cai,Y., Li,W., Liu,G. and Tang,Y. (2018) admetSAR 2 . 0 : web-service for prediction and optimization of chemical ADMET properties. 10.1093/bioinformatics/bty707/5085368.

2. Schyman,P., Liu,R., Desai,V. and Wallqvist,A. (2017) vNN web server for ADMET predictions. *Frontiers in Pharmacology*, **8**, 1–14.

3. Table,D.I., Interactions,D. and Table,D.I. (2007) Cytochrome P450 Drug Interaction Table “ Flockhart Table ” Cytochrome P450-Based Drug Interactions.