

S3: Scoring matrix

A scoring matrix was devised to facilitate the identification of drug candidates that are most promising for further screening and validation in the present study. The scoring matrix was constructed to assign each FDA-approved drug a numerical score ranging from 0 to 1, with the highest score corresponding to the most favorable candidates. In this study, the pIC50 values and AutoDock Vina affinity values of FDA-approved drugs were standardized using to facilitate comparison among these values. Hence, the following steps were followed to construct this matrix:

$$y_{std} = \frac{y - y_{min}}{y_{max} - y_{min}} \quad (1)$$

- i. The estimated pIC50 values of FDA-approved drugs were standardized using formula (1); where y is the pIC50 value of a drug, y_{min} is the lowest pIC50 value among all pIC50 values predicted, and y_{max} is the highest pIC50 value among all pIC50 values predicted. This way, all pIC50 values were transformed to be distributed between 0 and 1.
- ii. The determined *AutoDock Vina* affinity values of all FDA-approved drugs were also standardized using formula (1); where y is the AutoDock Vina affinity value (Kcal/mol), y_{min} is the lowest affinity value among all AutoDock Vina affinity values calculated, and y_{max} is the highest affinity value among all AutoDock Vina affinity values calculated. This way, all AutoDock Vina affinity values were transformed to be distributed between 0 and 1.

$$Score = (0.3 \times y_{std, pIC50}) + (0.7 \times y_{std, affinity}) \quad (2)$$

- iii. In preparation for the subsequent molecular dynamics analysis, candidate drugs were scored based on the computational evidence in regard to their binding pose to MDM2. The scoring was performed using formula (2), which assigns a weight of 70% to the AutoDock Vina affinity value and 30% to the pIC50 value predicted by the machine learning model. The resulting scores, ranging from 0 to 1 (with 1 being the most preferred candidate and 0 being the least preferred), were used to select the drugs for analysis by molecular dynamics method in a sequential manner.