

1 **Combining Multi-Dimensional Molecular Fingerprints to Predict hERG**

2 **Cardiotoxicity of Compounds**

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21 **Abstract**

22 At present, drug toxicity has become a critical problem with heavy medical and
23 economic burdens. acLQTS (acquired Long QT Syndrome) is acquired cardiac ion
24 channel disease caused by drugs blocking the hERG channel. Therefore, it is
25 necessary to avoid cardiotoxicity in the drug design and computer models have been
26 widely used to fix this plight. In this study, we present a molecular fingerprint based
27 on the molecular dynamic simulation and uses it combined with other molecular
28 fingerprints (multi-dimensional molecular fingerprints) to predict hERG
29 cardiotoxicity of compounds. 203 compounds with hERG inhibitory activity (pIC50)
30 were retrieved from a previous study and predicting models were established using
31 four machine learning algorithms based on the single and multi-dimensional
32 molecular fingerprints. Results showed that MDFP has the potential to be an
33 alternative to traditional molecular fingerprints and the combination of MDFP and
34 traditional molecular fingerprints can achieve higher prediction accuracy. Meanwhile,
35 the accuracy of the best model, which was generated by consensus of four algorithms
36 with multi-dimensional molecular fingerprints, was 0.694 (RMSE) in the test dataset.
37 Besides, the number of hydrogen bonds from MDFP has been determined as a critical
38 factor in the predicting models, followed by rgyr and sasa. Our findings provide a new
39 sight of MDFP and multi-dimensional molecular fingerprints in building models of
40 hERG cardiotoxicity prediction.

41 **Keywords:** Molecular dynamic simulation; Molecular fingerprint; Machine learning;
42 hERG;

43 **1. Introduction**

44 Drug-induced toxicity has become a critical reason for the failure of drug
45 discovery and development in recent years (Wallace, 2015). A previous study showed
46 that there were more than half of drugs failed (54%) in clinical development among
47 640 novel therapeutics, while 17% of them failed because of drug-induced toxicity
48 (Hwang et al., 2016). Besides, it has also been reported that the mean costs required to
49 bring a new drug to market increased from \$374.1 million to \$1335.9 million after
50 counting for costs of failed trials (Wouters et al., 2016). Thus, it has become an urgent
51 task to find ways to identify the toxicity of compounds on a large scale in drug
52 development.

53 Acquired Long QT syndrome (acLQTS), one of the most important diseases
54 caused by drug-induced toxicity, is a potentially life-threatening cardiac arrhythmia
55 disease that increases the risk for syncope, sudden cardiac death (SCD), and seizures
56 (Tester & Ackerman, 2014). The hERG protein is a tetrameric potassium ion channel
57 and mainly relates to cardiotoxicity and acLQTS (Liu et al., 2020). It has been
58 reported that the potassium ion channel (hERG channel) may be blocked caused by
59 antiarrhythmic drug binding, which leads to prolonged repolarization time and
60 acLQTS (Witchel, 2007). At present, multiple drug candidates have failed due to the
61 cardiotoxicity of hERG, such as cisapride, terfenadine, sertindole, pimozone, and
62 astemizole, which have become a significant limiting factor in drug discovery and
63 development (Bergström & Lindmark, 2019; Villoutreix & Taboureau, 2019).

64 Computer-aided drug design (CADD) has been thought of as an alternate choice

65 to reduce the amount of time and money in the development of drug design,
66 especially in predicting drug toxicity (Maia et al., 2020). Molecular fingerprints are a
67 way of CADD and are used to encoding the structure of molecules (O'Boyle et al.,
68 2011). It has been deployed as descriptors for predicting biological activities and
69 compound properties (Muegge & Mukherjee, 2014). Frequently used molecular
70 fingerprints are structure-based and property-based (Kelley, 2018; Rogers & Hahn,
71 2010; Riniker & Landrum, 2013; Riniker, 2017). A previous study of hERG
72 cardiotoxicity prediction showed that the accuracy of the best model developed by
73 molecular descriptors reached 0.54 (R^2), while RMSE was 0.63 (Johnson et al., 2007).
74 Another study of the hERG channel also showed that the accuracy of the regression
75 model by descriptors was 0.60 (Q^2) and 0.55 (RMSE) for pIC50 (Radchenko et al.,
76 2017). These results showed the practicalities and effectiveness based on commonly
77 used molecular fingerprints. However, there are still no fingerprints that considered
78 the time factor applied on the cardiotoxicity prediction of hERG.

79 Molecular dynamics fingerprints (MDFP) are the fingerprints based on
80 calculating the trajectory of molecular dynamic simulation and have rapidly become a
81 hotspot. After adding the dimension of time, MDFP can be seen as a choice of the
82 traditional molecular fingerprint. The study of p-glycoprotein substrates prediction
83 showed that gradient tree boosting (GTB) methods in combination with MDFP was
84 the only model which achieved a good accuracy on the in-house dataset (Esposito et
85 al., 2020). Meanwhile, the research of free-energy prediction showed good
86 performance with a heterogeneous fusion model by MDFP (Riniker, 2017). Besides,

87 studies of self-solvation free energies and application of MDFP in SAMPL6
88 octanol–water log P blind challenge also revealed a high prediction rate (Gebhardt et
89 al., 2020; Wang & Riniker, 2019). As a consequence, MDFP can be an alternative
90 choice of traditional molecular fingerprints and has great application potential on the
91 cardiotoxicity prediction of hERG.

92 Multi-dimensional molecular fingerprints are indicated as multiple molecular
93 fingerprints combining together in order to predict more accurately. Previous studies
94 showed that multi-dimensional molecular fingerprints were better than the single
95 molecular fingerprint in drug development (Kyaw et al., 2020). Thus, in this study, we
96 studied MDFP and multi-dimensional molecular fingerprints (MDFP with other
97 molecular fingerprints) in predicting hERG cardiotoxicity of compounds. The
98 extensive open dataset of hERG compounds with IC50 values has been collected from
99 previous studies. Then, molecular dynamic simulation was conducted to generate
100 MDFP and traditional molecular fingerprints have also been generated by Baseline2D,
101 ECFP4, and PropertyFP. Finally, the regression models were built by machine
102 learning with four algorithms. Our study provides new sights on the combination of
103 multi-dimensional molecular fingerprints and the research of predicting the hERG
104 cardiotoxicity of compounds.

105 **2. Methods**

106 **2.1. Toxicity Datasets**

107 A high-quality hERG inhibitor dataset has been collected from the previous
108 study (Munawar et al., 2019). The IC50 value is the biochemical half-maximal

109 inhibitory concentration and has been used to represent the inhibiting abilities of
110 compounds on hERG in this dataset (Kalliokoski et al., 2013). The data of toxicity
111 have been eliminated if the name and IC50 values were repeated. The repeated
112 molecules have also been averaged if the difference IC50 values were less than one
113 order of magnitude (Feng et al., 2021). Finally, 203 compounds have been collected
114 with specific IC50 values of the hERG. The distribution of training and testing sets
115 followed by 80% and 20%, respectively. The training sets were used for 5-fold
116 cross-validation and the testing sets were used to check the prediction performance of
117 the established model for new compounds. Besides, pIC50 is the negative log unit of
118 the IC50 values and has been used to represent inhibiting abilities better than IC50
119 (Cortés-Ciriano et al., 2020). Therefore, IC50 of compounds was converted to pIC50.

120 **2.2. MD Simulations**

121 Molecular dynamics (MD) simulation was performed by GROMACS (2020.4).
122 For compounds in the dataset, mol2 files were obtained from Zinc15
123 (<http://zinc15.docking.org/>) by using SMILES files. The topology of compounds was
124 generated with AMBER14SB force field by ACPYPE (<https://www.bio2byte.be/>)
125 (Sousa da Silva et al., 2012). Afterward, the compounds were placed in a
126 dodecahedron box with a size of 1.0 nm centrally and solvated with the TIP3P water
127 model. Then, the descent energy minimization with 100ps was applied to the system.
128 An additional equilibration of 1ns under NVT and NPT conditions was carried out,
129 while the constant temperature was 300 K and the constant pressure was 1 bar,
130 respectively (Sun et al., 2020). Finally, the system was performed with running 5 ns

131 MD simulation and coordinates were written every 10ps, energies every 1ps.

132 **2.3. 2D Molecular Fingerprints**

133 Three types of molecular fingerprints have been used in this study. Baseline2D
134 was obtained using RDKit and its elements mainly consisted of 10 counts: number of
135 heavy atoms, number of rotatable bonds, number of N, O, F, P, S, Cl, Br, and I atoms
136 (Riniker, 2017; Wang & Riniker, 2019). The PropertyFP fingerprint was also obtained
137 using the Descriptastorus package from RDKit (Kelley, 2018). It contained nearly 200
138 atoms features and properties. Besides, ECFP4 was generated using the RDKit
139 implementation of the Morgan algorithm with a vector length of 2048 and a radius of
140 2 (Rogers & Hahn, 2010).

141 **2.4. MD Fingerprints**

142 The MD trajectories were analyzed by the GROMACS toolkit (Ogunwa, 2019).
143 Following features has been generated: radius of gyration (rgyr), solvent-accessible
144 surface area (sasa), root mean squared error (rmsd), total energy (tenergy), hydrogen
145 bonds (hbond), kinetic energy (kinetic), Lennard-Jones short-range energies (LJ-SR)
146 and Lennard-Jones 1-4 energies (LJ-14). The average (avr), median (mid), and
147 standard deviation (std) of features were calculated using the R version 3.6.1 (Team,
148 2013). [Fig. 1](#) showed the MDFP with all properties.

149 **2.5. Feature Selection**

150 Feature selection is critically important for predictive models, especially in
151 machine learning (Johnson et al., 2018). It provides an effective way to reduce the
152 dimensionality of data sets, identify informative features, and remove irrelevant

153 features, improving the learning accuracy of machine learning models (Holder et al.,
154 2017). In this study, zero variation and near-zero variation features were deleted
155 firstly using the nearZeroVar function in the R package caret (version 6.0–84) (Kuhn,
156 2008). Then, recursive feature elimination (RFE) was performed to select the optimal
157 feature subset using the rfe function in the caret package in a 10 times 5-fold
158 cross-validation setting (Darst et al., 2018). In the RFE process, all features are first
159 ranked according to the feature importance values obtained by the random forest (RF)
160 algorithm, and then RF models are trained iteratively on the features that are gradually
161 reduced according to the ranking to evaluate the performance of the feature subsets
162 (Tang et al., 2020).

163 **2.6. Model Construction**

164 In this study, RF, SVM, gradient boosting machine (GBM), and partial least
165 square regression (PLS) was used for machine learning model construction. All
166 models were executed beyond R (version 3.6.1) with using the randomForest (version
167 4.6–12) (Liaw & Wiener, 2002), the kernlab (version 0.9-25) (Karatzoglou et al.,
168 2004), the gbm (version 2.1.5) (Brandon et al., 2019), and the pls (version 2.7-1)
169 packages (Bjørn-Helge et al., 2019), respectively.

170 *2.6.1 Random forest*

171 RF is the machine learning ensemble classifier and has been applied in many
172 fields (Breiman, 2001). By constructing multiple decision trees, the RF classifier has
173 been considered as better performance than the single decision tree (Gandhi et al.,
174 2018). In the current study, the randomforest function has been used to build RF

175 classifiers. The number of classification trees and variables randomly selected for
176 each node split have been set as $n_{tree} = 500$, while m_{try} was optimized from one-third
177 of the number of features minus 10 to plus 15. The relative importance of molecular
178 fingerprints has also been calculated by the `importance` function of the package.

179 *2.6.2 Support vector machine*

180 SVM is a generalized linear classifier based on the principle of structural risk
181 reduction for pattern recognition (Huang et al., 2018). It is well known as a supervised
182 learning algorithm that analyzes data and recognizes patterns (Nedaie et al., 2018). In
183 this study, the radial basis function (RBF) kernel was used for building the SVM
184 classifier. Meanwhile, the random search method (Bergstra & Bengio, 2012) was also
185 applied to optimize specific SVM parameters with the regularization parameter C and
186 σ parameter by using the `caret` package, while C was from e^{-2} to e^6 , σ was from e^{-7}
187 to e with the step of $e^{0.5}$.

188 *2.6.3 Gradient boosting machine*

189 GBM is also a tree-based machine learning model. It has been considered as a
190 step-wise, additive type model which sequentially fits new-tree-based models (Golden
191 et al., 2019). Meanwhile, it also has many advantages, especially worked well in
192 practice (Cho et al., 2019). In this study, the total number of trees (`n.trees`) and the
193 maximum depth of each tree (`interaction.depth`) have been optimized by using the
194 `caret` package and have been set from 1 to 3000 and 1 to 10, respectively. Besides,
195 `shrinkage` and `n.minobsinnode` were set as 0.005 and 10.

196 *2.6.4 Partial least square regression*

197 PLS calculates a group of latent variables in connection with the output
198 maximally and determines the relationship between the input and output data (Foodeh
199 et al., 2020). It is a stretch of the multiple linear regression models and is widely used
200 in many domains (Wu et al., 2020). Unlike multiple linear regression (MLR), it can
201 handle the data with noisy, strongly collinear, and X-variables (Dong et al., 2018). In
202 this study, n_components for PLS were optimized from 1 to the greatest features or
203 sample sizes.

204 **2.7. Model Evaluation**

205 In order to test the predictive performance of the models, 5-fold cross-validation
206 with 10 repeats has been used to evaluate the models. After randomly divided the
207 original dataset into five equal subsets, four of them were used for training and the
208 other was used for testing. Then the 5-fold cross-validation was repeated ten times to
209 reduce the randomness. This cross-validation progress was performed 10 times with
210 different random seeds of 2, 4, 8, 16, 32, 64, 128, 256, 512, and 1024. Then, average
211 values were calculated to evaluate the prediction performance of the models.

212 Root-mean-squared error (RMSE), mean unsigned error (MUE), and R^2 has been
213 used to evaluate the predictive performance of the models. These indicators were
214 calculated by the following formulas:

$$RMSE = \sqrt{\frac{1}{n} \sum_{i=1}^n (P - E)^2}$$
$$MUE = \frac{1}{n} \sum_{i=1}^n |P - E|$$

$$R^2 = 1 - \frac{\sum_i (P - E)^2}{\sum_i (\bar{E} - E)^2}$$

215 Where P , \bar{E} , E , n represent predictive value, the average of experimental value,
216 experimental value, and compound numbers, respectively.

217 **3. Results and discussion**

218 **3.1. Feature selection**

219 In this study, 203 compounds were collected from the previous study and divided
220 into training and testing datasets with 80% to 20%, respectively. In order to build
221 models to predict hERG cardiotoxicity, MDFP, Baseline2D, ECFP4, and PropertyFP
222 have been calculated for the compounds in the dataset. [Table 1](#) illustrated the number
223 of features calculated from each type of molecular fingerprint and the detailed
224 description of these features is shown in the supplementary files ([Table S1](#) and [Table](#)
225 [S2](#)). After the feature selection by RF-RFE, 11 and 6 features have been selected from
226 MDFP and Baseline2D, respectively. Meanwhile, there were also 99 features selected
227 from ECFP4 and 71 from PropertyFP. Percentage increase in MSE (%IncMSE)
228 obtained by RF was used to evaluate the importance of features. [Fig. 2](#) showed the top
229 ten features (Baseline2D for six) which important to the prediction models. The
230 results of MDFP showed that the number of hydrogen bonds between compounds and
231 water has a significant effect on predicting hERG cardiotoxicity, followed by kinetic
232 energy and surface area. Besides, the results of 2D molecular fingerprints indicated
233 that the number of heavy atoms, number of O atoms (oxygenes), and number of F
234 atoms (fluorines) were the most important features in Baseline2D, while MolLog P in
235 PropertyFP and 3218693969 in ECFP4. Above all, after calculating features in all

236 molecular fingerprints, the following features have been selected as the most critical
237 with heavyatoms, oxygens, fluorines, the median of hydrogen bonds, and 3218693969.
238 These features may be played important roles in predicting the hERG cardiotoxicity
239 and should be paid extra attention in the development of drug candidates.

240 **3.2. Prediction performance of the models**

241 After performing feature selection, the GBM, PLS, RF, and SVM algorithms
242 were used for generating ML models based on the resulting fingerprints. The
243 performance of these machine learning models was evaluated by 10 times 5-fold
244 cross-validation and their performances were presented in [Table 2](#). The results showed
245 that the RMSE of each machine learning model based on PropertyFP is the lowest,
246 with a range of 0.860-0.960, followed by MDFP, with a range of 0.967-1.039, while
247 ECFP4 and Baseline2D are poor quality. R^2 and MUE also showed the same pattern.
248 [Table 3](#) illustrated the performance of these models which were used to predict the
249 pIC50 of the molecules in the testing set. In general, the models show better RMSE
250 values in the test set than in the 5-fold cross-validation, indicating that the model has
251 not been overfitted. Meanwhile, compared with the models based on different
252 molecular fingerprints, the performance in the testing set was similar, while
253 Baseline2D was slightly better (RMSE=0.721 to 0.795) and MDFP also obtained a
254 good performance (RMSE=0.755 to 0.819). These results indicated that MDFP can
255 effectively predict the activity of hERG inhibitors, and the predictive performance of
256 the MDFP was similar to the traditional molecular fingerprints.

257 The predictive performance of the MDFP model combined with other molecular

258 fingerprints was also investigated in this study. [Table 4](#) and [Table 5](#) showed the
259 performance of models in the 5-fold cross-validation sets and testing sets while
260 MDFP combined with other molecular fingerprints, respectively. The results showed
261 that the combination of MDFP and other molecular fingerprints can obtain a model
262 with better prediction performance. For example, the model established by the single
263 molecular fingerprint (MDFP or PropertyFP) in the 5-fold cross-validation had the
264 best performance as PropertyFP-SVM (RMSE=0.860). However, the model
265 established by multi-dimensional molecular fingerprints (MDFP and PropertyFP) was
266 MDFP+PropertyFP-SVM (RMSE=0.837), which showed a better performance than
267 using the single molecular fingerprints. Besides, models combining MDFP with other
268 molecular fingerprints also showed better predictive performance in the testing set
269 ([Table 5](#)), while the best model was the SVM model trained on MDFP++ (MDFP with
270 all other fingerprints) (RMSE=0.696±0.015). These results illustrated that the
271 performance of multi-dimensional molecular fingerprints was better than the single
272 molecular fingerprints and MDFP may provide additional effective predictors for the
273 prediction of hERG inhibitor activity.

274 In order to improve the prediction performance of the model, we further
275 averaged the prediction results of the four machine learning models to obtain a
276 consensus value. The prediction performance was shown in [Table 3](#) and [Table 5](#). [Fig.](#)
277 [3](#) and [Fig. 4](#) showed the predicted values vs experimental values for MDFP and
278 MDFP++, respectively. The values of other molecular fingerprints have been
279 demonstrated in the supplementary files ([Fig. S1 to S6](#)). It was found that the

280 performance of consensus models was significantly better than the other models
281 (except PropertyFP). Among the models established by a single molecular fingerprint,
282 the consensus model based on Baseline2D had the highest accuracy (RMSE=0.713),
283 while the consensus model based on MDFP also obtained a better RMSE of
284 0.745. Meanwhile, in the model based on the multi-dimensional molecular
285 fingerprints, MDFP+ECFP4 and MDFP++ obtained high accuracy with RMSE of
286 0.694 and 0.695, respectively. These results indicated that the integrated model can
287 obtain a better method for predicting the activity of hERG inhibitors.

288 In summary, these results illustrated that the MDFP was effective compared with
289 traditional molecular fingerprints and can truly be an alternative to the other
290 molecular fingerprints. Meanwhile, the prediction accuracies of all ML models on
291 multi-dimensional molecular fingerprints were better than the single molecular
292 fingerprints in predicting the hERG cardiotoxicity. Besides, the integrated models
293 showed the best prediction than the single models among most of the molecular
294 fingerprints. Thus, the models obtained by multiple machine learning methods could
295 be more accurate in predicting the hERG cardiotoxicity of compounds.

296 **3.3. MDFP features associated with cardiotoxicity**

297 To further reveal the contributions of fingerprint features associated with
298 cardiotoxicity, the correlation coefficient has been used to determine the feature
299 between MDFP and pIC50. Correlation is a measure of a monotonic association
300 between 2 variables and Pearson's correlation coefficient has become one of the most
301 frequently used statistics (Armstrong, 2019). In this study, Pearson, Kendall, and

302 Spearman correlations were used to evaluate the important features of MDFP with
303 pIC50. [Table 6](#) showed the correlation coefficient between the feature of MDFP and
304 pIC50. The median of rgyr has been determined as the most relevant feature with
305 pIC50 (Kendall = 0.35, Pearson = 0.51, and Spearman = 0.49), followed by the
306 median of sasa and kinetic with the high correlation coefficient. These results showed
307 the features which extracted from MDFP had strong correlations with pIC50 and can
308 be used to predict cardiotoxicity in the future study.

309 **3.4. Compared with other models**

310 Recently, a couple of computational models have been developed for toxicity
311 prediction. Among them, cardiotoxicity prediction has become a hotspot with multiple
312 studies. [Table 7](#) showed the comparisons between our model and other models for
313 cardiotoxicity prediction. Compared with other models, the consensus model with
314 MDFP and ECFP4 showed the lowest RMSE and MUE, with higher R^2 . Meanwhile,
315 the molecular fingerprints of previous studies were used by only one dimension,
316 which may prove that multi-dimensional fingerprints performed well in predicting the
317 cardiotoxicity of hERG. Besides, although it was lower than QSAR-SVM, the
318 consensus with MDFP still better than the other models as 0.745 ± 0.005 (RMSE),
319 which illustrated the advantages of MDFP. These findings showed that MDFP and
320 multi-dimensional molecular fingerprints with machine learning methods can be an
321 outstanding model in predicting cardiotoxicity.

322 **4. Conclusion**

323 In this study, MDFP and multi-dimensional molecular fingerprints were used for

324 building machine learning models to predict the hERG cardiotoxicity of compounds.
325 203 compounds were firstly identified to establish the 5-fold cross-validation and
326 testing datasets. Then molecular dynamic simulation has been used to generate
327 molecular dynamic molecular fingerprints. Baseline2D, ECFP4, and PropertyFP were
328 used to generate traditional molecular fingerprints. After that, critical features have
329 been selected by RF-RFE and 4 machine learning algorithms, namely RF, SVM,
330 GBM, and PLS were used for building predicting models based on the single
331 fingerprints and multi-dimensional molecular fingerprints. Besides, the correlation
332 between MDFP and pIC50 has also been surveyed. Results showed that MDFP has
333 the potential to be an alternative choice of molecular fingerprints and
334 multi-dimensional molecular fingerprints are better than single fingerprints in
335 predicting cardiotoxicity. It also illustrated that the consensus model with MDFP and
336 ECFP4 has the optimum prediction effect and hydrogen bonds are critically important
337 in the models with MDFP. Our finding provides a new sight into the application of
338 MDFP and multi-dimensional molecular fingerprints in predicting the hERG
339 cardiotoxicity of compounds. Cell and animal experiments will be carried out to
340 validate further.

341 **Conflict of interests**

342 The authors declare that they have no conflict of interests.

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349 **Data Availability Statement**

350 All data and models generated or used during the study appear in the submitted
351 article.

352 **Author contributions**

353 WZD, LZ, and HSL conceived the project, developed the prediction method, designed,
354 and implemented the experiments, analyzed the result, and wrote the paper. YN, JSW,
355 and XXX implemented the experiments, analyzed the result, and wrote the paper.
356 SYH and SYL analyzed the result. All authors read and approved the final manuscript.

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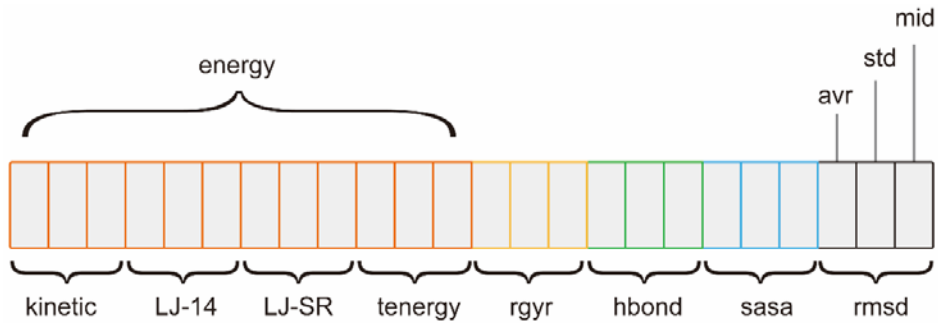


Fig.1. Schematic representation of the MDFP variant with all properties: kinetic, LJ-14, LJ-SR, tenergy, rgyr, hbond, sasa, rmsd. Each property is represented by the avr (average), std (standard deviation), and mid (median).

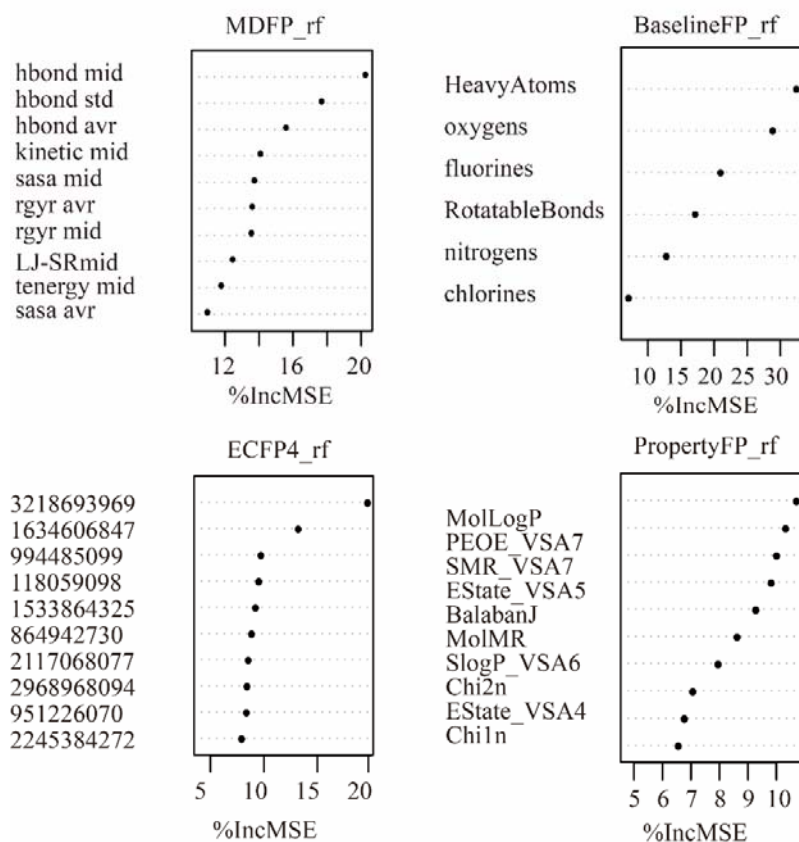


Fig. 2. The most important features selected by RF-RFE from MDFP, Baseline2D, ECFP4, and PropertyFP fingerprints.

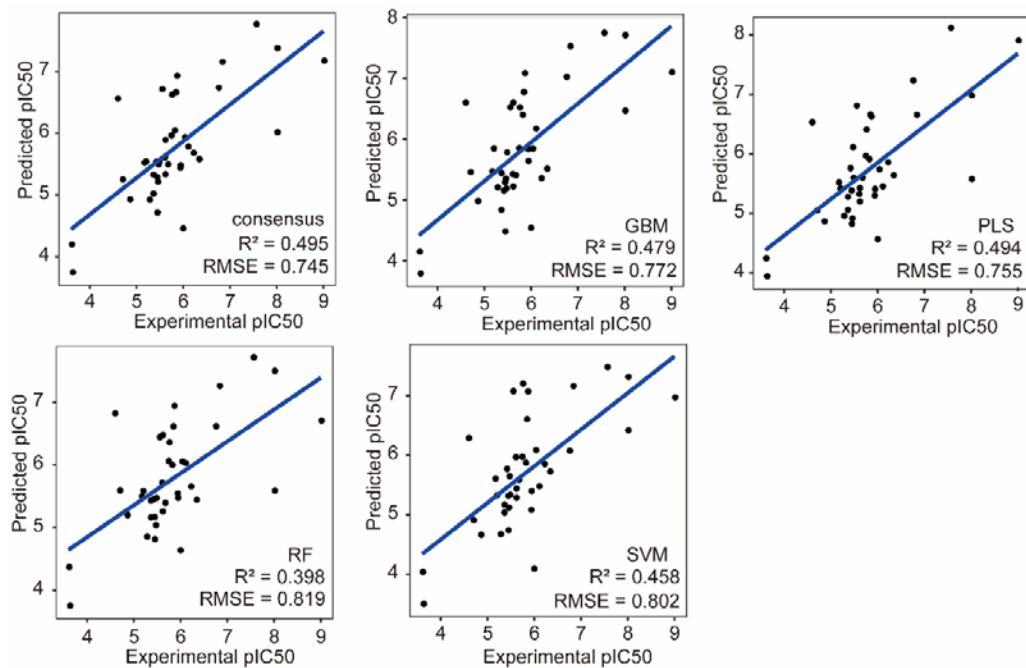


Fig. 3. pIC50: The experimental values of the 10th operation for the data set. Predictions were generated using consensus, GBM, PLS, RF, SVM trained on MDFP. The linear regression lines are shown in blue.

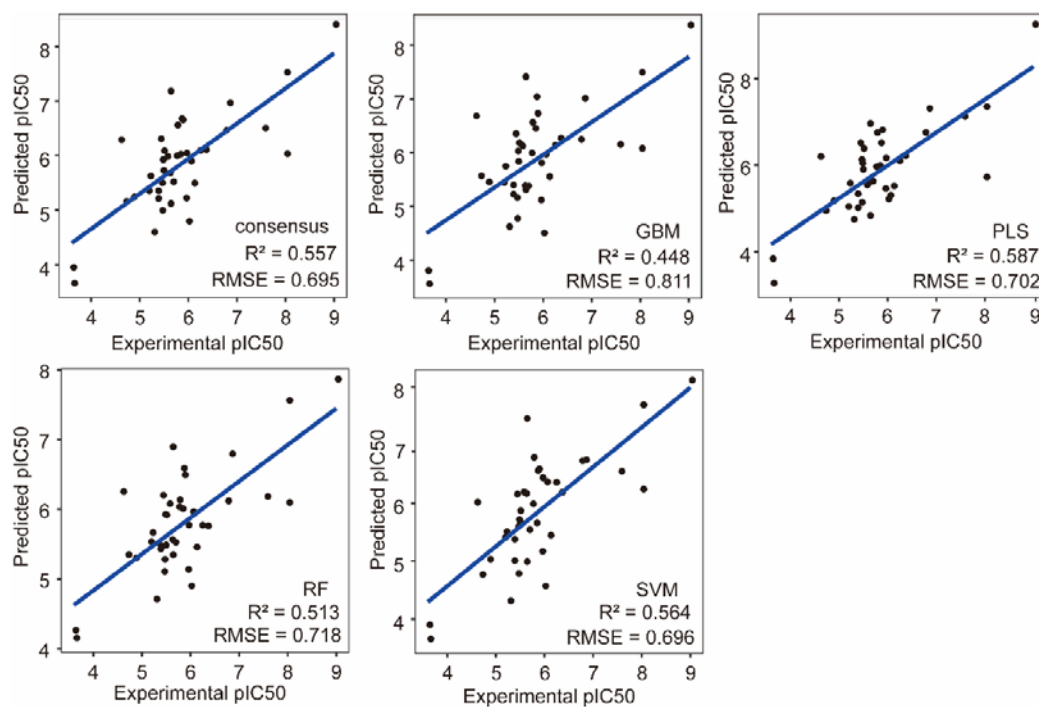


Fig. 4. pIC50: The experimental values of the 10th operation for the data set. Predictions were generated using consensus, GBM, PLS, RF, SVM trained on MDFP++. The linear regression lines are shown in blue. MDFP++ including MDFP, Baseline2D, ECFP4, and PropertyFP.

Table 1 The number of features for the different molecular fingerprints.

fingerprints	number of features	number of selected feature
MDFP	24	11
Baseline2D	10	6
ECFP4	2298	99
PropertyFP	200	71

Table 2 Cross-validation performance for models trained using different ML algorithms on the molecular fingerprints (MDFP, Baseline2D, ECFP4, PropertyFP). Performance metrics are represented as average and standard deviation of 10 times 5-fold cross-validation runs of different random seeds.

fingerprint	ML models	RMSE	R ²	MUE
MDFP	GBM	0.985±0.005	0.523±0.004	0.774±0.005
	PLS	1.039±0.005	0.482±0.006	0.797±0.003
	RF	0.977±0.005	0.534±0.006	0.768±0.004
	SVM	0.967±0.007	0.541±0.006	0.745±0.007
Baseline2D	GBM	1.112±0.009	0.394±0.009	0.884±0.006
	PLS	1.189±0.004	0.321±0.007	0.956±0.003
	RF	1.036±0.011	0.465±0.011	0.813±0.008
	SVM	1.014±0.006	0.492±0.006	0.791±0.006
ECFP4	GBM	1.072±0.006	0.433±0.007	0.837±0.007
	PLS	1.084±0.004	0.433±0.004	0.850±0.006
	RF	1.043±0.004	0.464±0.004	0.827±0.004
	SVM	1.009±0.004	0.497±0.004	0.800±0.004
PropertyFP	GBM	0.941±0.008	0.562±0.006	0.747±0.007
	PLS	0.959±0.008	0.551±0.006	0.776±0.008
	RF	0.960±0.004	0.559±0.004	0.763±0.005
	SVM	0.860±0.006	0.634±0.006	0.676±0.009

Table 3 Cross-validation performance for models tested using different ML algorithms on the molecular fingerprints (MDFP, Baseline2D, ECFP4, PropertyFP). Performance metrics are represented as average and standard deviation of 10 times 5-fold cross-validation runs of different random seeds.

fingerprint	ML models	RMSE	R ²	MUE
MDFP	GBM	0.772±0.008	0.479±0.008	0.582±0.009
	PLS	0.755±0	0.494±0	0.564±0
	RF	0.819±0.011	0.398±0.012	0.570±0.006
	SVM	0.802±0.010	0.458±0.007	0.586±0.005
	consensus	0.745±0.005	0.495±0.005	0.524±0.003
Baseline2D	GBM	0.794±0.005	0.472±0.004	0.568±0.004
	PLS	0.772±0.000	0.441±0.000	0.548±0.000
	RF	0.795±0.015	0.423±0.015	0.545±0.011
	SVM	0.721±0.005	0.525±0.005	0.520±0.011
	consensus	0.713±0.003	0.520±0.004	0.507±0.002
ECFP4	GBM	0.858±0.008	0.348±0.010	0.664±0.009
	PLS	0.752±0.001	0.495±0.010	0.578±0.006
	RF	0.865±0.009	0.315±0.011	0.635±0.011
	SVM	0.737±0	0.491±0	0.553±0
	consensus	0.761±0.001	0.457±0.003	0.571±0.003
PropertyFP	GBM	0.813±0.005	0.432±0.006	0.632±0.008
	PLS	0.764±0.002	0.492±0.003	0.596±0.001
	RF	0.709±0.006	0.529±0.009	0.540±0.006
	SVM	0.761±0.035	0.488±0.040	0.605±0.033
	consensus	0.730±0.008	0.508±0.010	0.560±0.008

Table 4 Cross-validation performance for models trained using different ML algorithms on the molecular fingerprints (MDFP + Baseline2D, MDFP + ECFP4, MDFP + PropertyFP, MDFP++). Performance metrics are represented as average and standard deviation of 10 times 5-fold cross-validation runs of different random seeds.

fingerprint	ML models	RMSE	R ²	MUE
MDFP + Baseline2D	GBM	0.991±0.005	0.516±0.005	0.767±0.005
	PLS	1.068±0.007	0.458±0.004	0.820±0.004
	RF	0.950±0.006	0.560±0.006	0.738±0.005
	SVM	0.938±0.008	0.568±0.007	0.717±0.008
MDFP + ECFP4	GBM	0.975±0.005	0.529±0.006	0.745±0.006
	PLS	1.021±0.010	0.509±0.005	0.797±0.009
	RF	0.945±0.005	0.566±0.004	0.740±0.005
	SVM	0.935±0.005	0.569±0.004	0.740±0.005
MDFP + PropertyFP	GBM	0.915±0.008	0.585±0.006	0.722±0.009
	PLS	0.948±0.011	0.568±0.009	0.754±0.011
	RF	0.944±0.005	0.578±0.004	0.742±0.004
	SVM	0.837±0.006	0.654±0.006	0.659±0.007
MDFP++	GBM	0.920±0.008	0.580±0.006	0.723±0.008
	PLS	0.958±0.007	0.556±0.005	0.754±0.007
	RF	0.940±0.005	0.578±0.004	0.742±0.005
	SVM	0.873±0.007	0.623±0.005	0.686±0.007

Table 5 Predictions were generated using different ML models trained on MDFP combined with multi-dimensional molecular fingerprints (MDFP + Baseline2D, MDFP + ECFP4, MDFP + PropertyFP, MDFP++) in test. MDFP++ including MDFP, Baseline2D, ECFP4, and PropertyFP.

fingerprint	ML models	RMSE	R ²	MUE
MDFP + Baseline2D	GBM	0.728±0.008	0.525±0.008	0.544±0.008
	PLS	0.751±0.007	0.502±0.011	0.559±0.006
	RF	0.789±0.009	0.427±0.011	0.560±0.008
	SVM	0.781±0.003	0.494±0.002	0.551±0.001
	consensus	0.721±0.003	0.524±0.003	0.518±0.003
MDFP + ECFP4	GBM	0.758±0.007	0.491±0.007	0.569±0.004
	PLS	0.702±0	0.555±0	0.535±0
	RF	0.750±0.012	0.472±0.016	0.553±0.007
	SVM	0.698±0.003	0.550±0.004	0.522±0.008
	consensus	0.694±0.002	0.548±0.003	0.515±0.004
MDFP + PropertyFP	GBM	0.799±0.009	0.456±0.010	0.615±0.008
	PLS	0.794±0.000	0.481±0.004	0.610±0.003
	RF	0.709±0.008	0.527±0.011	0.549±0.009
	SVM	0.723±0.011	0.518±0.012	0.578±0.012
	consensus	0.719±0.003	0.523±0.003	0.554±0.003
MDFP++	GBM	0.811±0.008	0.448±0.009	0.619±0.009
	PLS	0.702±0	0.587±0	0.526±0
	RF	0.718±0.010	0.513±0.014	0.554±0.006
	SVM	0.696±0.015	0.564±0.011	0.516±0.017
	consensus	0.695±0.004	0.557±0.004	0.518±0.003

Table 6 Correlation coefficient between the features of MDFP and pIC50.

feature	kendall	pearson	spearman
rgyr mid	0.35	0.51	0.49
sasa mid	0.30	0.41	0.43
kinetic mid	0.28	0.32	0.42
LJ-SR mid	0.28	0.25	0.41
rgyr avr	0.23	0.20	0.33
sasa avr	0.20	0.16	0.29
sasa std	0.17	0.01	0.25
hbond avr	-0.08	-0.14	-0.12
hbond std	-0.09	-0.09	-0.13
hbond mid	-0.12	-0.19	-0.17
tenergy mid	-0.28	-0.42	-0.41

Table. 7 Performance indicators of several cardiotoxicity prediction models reported in the literature.

models	RMSE	R ²	MUE	Reference
QSAR-SVM	0.79 ± 0.05	0.58 ± 0.05	-	(Simeon & Jongkon, 2019)
QSAR-DNN	0.90 ± 0.06	0.49 ± 0.04	-	
MLR-Canvas	1.186	0.191	0.941	(Subramanian et al., 2016)
DNN-DeepChem	1.03	0.351	0.763	
PLS-FFD	1.07	0.48	-	(Munawar et al., 2019)
consensus-MDFP	0.745±0.045	0.495±0.005	0.524±0.003	
consensus-MDFP+ECFP4	0.694±0.002	0.548±0.003	0.515±0.004	