[Article]

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多种类杂环化合物的药理和毒理活性系数构效关系

朱志臣¹ 王 强^{2,*} 贾青竹³ 夏淑倩⁴ 马沛生⁴¹天津城建大学理学院, 天津 300384; ²天津科技大学材料科学与化学工程学院, 天津 300457;³天津科技大学海洋科学与工程学院, 天津 300457; ⁴天津大学化工学院, 天津 300072)

摘要: 杂环类化合物在卫生保健和药物分子设计领域发挥关键作用, 在西药中占有重要地位. 本工作针对扩展距离矩阵提出了一组范数指数, 基于扩展距离矩阵的范数指数构建了一个新的构效关系模型, 并对杂环类化合物二苯并呋喃的芳烃受体亲和性(pEC₅₀)以及芳香和杂环芳香胺的诱导有机体变异力(lnR)进行了计算预测. 结果表明, 基于扩展距离矩阵范数指数建立的构效关系模型可以很好地预测 pEC₅₀和lnR. 其中, pEC₅₀预测结果的平均绝对误差(AAD)为0.403, 相关性系数 $r^2=0.876$, lnR预测结果的AAD为0.702, $r^2=0.779$. 与其他预测方法的对比结果表明, 本工作不仅能够利用一个完全相同的数学表达模型同时对 pEC₅₀和lnR进行预测, 而且预测结果在准确性和稳定性上都有显著改善.

关键词: 二苯并呋喃; 芳香和杂环芳香胺; 芳烃受体亲和性; 诱导有机体变异力; 构效关系; 范数指数; 预测

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Structure–Property Relationship for the Pharmacological and Toxicological Activity of Heterocyclic Compounds

ZHU Zhi-Chen¹ WANG Qiang^{2,*} JIA Qing-Zhu³ XIA Shu-Qian⁴ MA Pei-Sheng⁴¹School of Science, Tianjin University of Urban Construction, Tianjin 300384, P. R. China;²School of Material Science and Chemical Engineering, Tianjin University of Science and Technology, Tianjin 300457, P. R. China;³School of Marine Science and Engineering, Tianjin University of Science and Technology, Tianjin 300457, P. R. China;⁴School of Chemical Engineering and Technology, Tianjin University, Tianjin 300072, P. R. China)

Abstract: Heterocyclic molecules play a crucial role in health care and in pharmaceutical drug design. A large number of drugs used in Western medical practice are heterocyclic molecules. In this study, a set of norm indexes of the extended distance matrix are proposed. From these a stable and accurate structure–property relationship model was developed for the prediction of the aryl hydrocarbon receptor binding affinity (pEC₅₀) of dibenzofurans and the mutagenic potency (lnR) of aromatic and heteroaromatic amines. Our results indicate that the new model, based on these norm indexes, provides very satisfactory results, and that the average absolute differences for pEC₅₀ prediction and lnR prediction were 0.403 and 0.702 with r^2 (square correlation coefficient) values of 0.876 and 0.779, respectively. A comparison of these results with other methods demonstrates that our method, based only on the same mathematical model, performed better in terms of both accuracy and stability.

Key Words: Dibenzofuran; Aromatic and heteroaromatic amine; Aryl hydrocarbon receptor affinity; Mutagenic potency; Structure–property relationship; Norm index; Prediction

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*Corresponding author. Email: wang_q@tust.edu.cn; Tel: +86-22-58088631, +86-13652089933.

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1 Introduction

Heterocyclic compounds are important as drugs. According to Hammond,¹ the most important objective of synthesis is not production of new compounds, but production of properties. And for the drug discovery process, the aim is at bringing to market new drugs with desirable pharmaco-dynamicity, and favorable ADMET (Absorption, Distribution, Metabolism, Elimination, and Toxicity) properties.²⁻⁵ Therefore, drug designers and toxicologists pay much attention to the beneficial and deleterious effects of heterocyclic moieties in molecules.

In view of the fact that most potential therapeutic agents and the majority of known drugs do not have experimental data available for their evaluation, theoretical calculations are very useful in the initial screening of compound libraries. Previous studies have demonstrated that quantitative structure–activity/property relationships (QSAR/QSPR) approach is successful in predicting activities, properties, and toxicities including mutagenicity (described as $\ln R$) of aromatic and hetero-aromatic amines.⁶⁻¹² For example, the aryl hydrocarbon receptor binding affinity (described as pEC_{50}) is well documented in the field of toxicology for organics.¹³⁻¹⁵ Basak *et al.*¹⁶ proposed a hierarchical quantitative structure–activity relationship (HiQSAR) approach for the pEC_{50} prediction. According to their investigation, the topostructural (TS) and topochemical (TC) descriptors could provide a good model for the pEC_{50} prediction with a r^2 value of 0.852. And with Basak *et al.*'s method, the r^2 value is of 0.748 for $\ln R$ prediction.¹⁷ In order to explore the binding mode and interaction mechanism between hydroxylated polychlorinated biphenyls and aryl hydrocarbon receptor, Cao *et al.*¹⁸ proposed some comparative molecular similarity index analysis models by using molecular dynamics simulations. And their optimum 3D-QSAR model could show good predictive ability ($r^2=0.913$) and good mechanism interpretability.

Recently, a universal positional distributive contribution theory for the prediction of various properties of organic compounds was developed.¹⁹⁻²¹ In this theory, the specific position of a group in the molecule was considered as the position factor. Here, the position factor was used to take into account longer distance interactions, which could distinguish the overall isomer including *cis*- and *trans*- or *Z*- and *E*-structures of organic compounds for their thermodynamics properties. Moreover, our previous works suggest that it is possible to use a totally same universal framework to predict the critical properties and the thermodynamics properties of organic compounds containing various functionalities.

Very recently, a topological index was proposed based on atom characters (e.g., atom radius and atom electronegativity etc.) by our research group, which has been successfully used for predicting the critical micelle concentration (CMC) of various surfactants,²² the decomposition temperature,²³ toxicity of ionic liquids,²⁴ and the aquatic toxicity for various narcotic pollutants.²⁵ And, it is logical to see if this topological index could be used for prediction of pharmacological and toxicological ac-

tivities of drugs.

In this work, based on this topological index and through data mining, a universal model has been developed for prediction of the two different properties. The major objectives of this study are: (i) to propose a set of norm indexes, (ii) to establish a more general QSPR model for prediction of pharmacological and toxicological activities of heterocyclic compounds, and (iii) to compare the performance of our model with other methods.

2 Methodology

2.1 Pharmacological and toxicological activity data

2.1.1 Aryl hydrocarbon (AH) receptor data

In this work, a set of 32 dibenzofurans compounds (structure shown as in Fig.1) with AH receptor binding potency values obtained from the literature²⁶ were used for QSAR model development, and the experimental data are listed in Table S1 (shown as Supporting Information).

2.1.2 Mutagenicity of aromatic and heteroaromatic amines

The set of 95 aromatic and heteroaromatic amines used to study mutagenic potency (described as $\ln R$) was obtained from Debnath *et al.*,²⁷ and their experimental mutation rates are listed in Table S2 (shown as Supporting Information).

2.2 Proposed method

In our previous work,²² the extended adjacency matrix M_A , the extended interval matrix M_B , the extended interval jump matrix M_C , and extended distance matrix M_D are defined, respectively.

$$M_A = \begin{bmatrix} M_a \\ M_c \end{bmatrix}; \quad M_B = \begin{bmatrix} M_b \\ M_c \end{bmatrix}; \quad M_C = \begin{bmatrix} M_c \\ M_e \end{bmatrix}; \quad M_D = \begin{bmatrix} M_d \\ M_e \end{bmatrix}$$

The constituents of the distance matrix M_d and the extended matrix, M_e , are described as follows.

$$M_a = (a_{ij}), \quad a_{ij} = \begin{cases} 1 & (\text{if } i \text{ and } j \text{ are adjacent}) \\ 0 & (\text{otherwise}) \end{cases}$$

$$M_b = (a_{ij}), \quad a_{ij} = \begin{cases} 2 & (\text{if the path length between } i \text{ and } j \text{ is } 2) \\ 0 & (\text{otherwise}) \end{cases}$$

$$M_c = (a_{ij}), \quad a_{ij} = \begin{cases} 3 & (\text{if the path length between } i \text{ and } j \text{ is } 3) \\ 0 & (\text{otherwise}) \end{cases}$$

$$M_d = (a_{ij}), \quad \text{distance matrix } a_{ij} = n \\ (\text{if the path length between the atoms } i \text{ and } j \text{ is } n)$$

Fig.1 Structure for the dibenzofuran data set provided in Table S1

$$M_c = \begin{bmatrix} \text{electronegativity fraction} \\ \text{van der Waals radius} \\ \text{the minimum bond length with adjacent} \\ \text{atom except hydrogen} \\ \text{the number of adjacent atom except hydrogen} \\ \text{the number of adjacent hydrogen atom} \end{bmatrix}$$

Here, as for M_A , M_B , M_C , and M_D , a set of norm indexes have been proposed as follows.

$$M'_A = a_{a1} \text{norm}(M_A, 1) + a_{a2} \text{norm}(M_A, 2) + a_{a3} \text{norm}(M_A, \text{fro}) + a_{a4} \text{norm}(M_A, \text{inf})$$

$$M'_B = a_{b1} \text{norm}(M_B, 1) + a_{b2} \text{norm}(M_B, 2) + a_{b3} \text{norm}(M_B, \text{fro})$$

$$M'_C = a_{c1} \text{norm}(M_C, 1) + a_{c2} \text{norm}(M_C, 2) + a_{c3} \text{norm}(M_C, \text{fro})$$

$$M'_D = a_{d1} \text{norm}(M_D, 1) + a_{d2} \text{norm}(M_D, 2) + a_{d3} \text{norm}(M_D, \text{fro}) + a_{d4} \text{norm}(M_D, \text{inf})$$

where $\text{norm}(M_A, 1)$ means the largest column sum of matrix M_A , $\text{norm}(M_A, 2)$ means the largest singular value of matrix M_A , $\text{norm}(M_A, \text{fro})$ is the frobenius-norm of matrix M_A , and $\text{norm}(M_A, \text{inf})$ is the infinite-norm of matrix M_A .

Using these norm indexes, two QSPR models for pEC_{50} and $\ln R$ prediction are expressed as Eq.(1) and Eq.(2). The modeling work is performed with ordinary least squares regression.

$$\text{pEC}_{50} = M'_A + M'_B + M'_C + M'_D + b_1 \exp(1/N) + b_2 \exp(1/M_w) + M_0 \quad (1)$$

$$\ln R = M'_A + M'_B + M'_C + M'_D + b_1 \exp(1/N) + b_2 \exp(1/M_w) + M_0 \quad (2)$$

Here, N for total number of atoms, M_w is molecular weight, M_0 is the constant added. As for parameters a , b_1 , b_2 , and M_0 , the regression results for prediction of pEC_{50} and $\ln R$ are summarized in Table 1.

Some statistical metrics for our predictive models are as follows. PRESS stands for the predicted sum of squared error, AD stands for the absolute difference, RD means relative deviation, and AAD is the average absolute difference.

Table 1 Parameters for prediction of pEC_{50} and $\ln R$

Parameters		pEC_{50}	$\ln R$
M_A	a_{a1}	-22.7744	-0.3525
	a_{a2}	-48.5409	29.6775
	a_{a3}	-462.3183	-13.7446
	a_{a4}	-5.9163	0.4876
M_B	a_{b1}	-0.1887	-0.0163
	a_{b2}	156.6532	-19.0118
	a_{b3}	428.6100	10.4300
M_C	a_{c1}	0.2801	-0.0005
	a_{c2}	-55.6900	-10.7641
	a_{c3}	16.3321	4.3405
M_D	a_{d1}	0.2730	0.2099
	a_{d2}	-18.5465	-1.1891
	a_{d3}	14.0124	0.6848
	a_{d4}	-0.1447	-0.0874
	b_1	3544.4709	53.2849
	b_2	10679.1349	-274.4253
	M_0	-14604.7935	205.8309

$$\text{PRESS} = \sum_{i=1}^n (\text{pEC}_{50,i,\text{expt}} - \text{pEC}_{50,i,\text{pred}})^2 \quad (3)$$

$$\text{SS}_{\text{Total}} = \sum_{i=1}^n (\text{pEC}_{50,i,\text{expt}} - \sum (\text{pEC}_{50,i,\text{expt}}/N))^2 \quad (4)$$

$$r^2 = 1 - \frac{\text{PRESS}}{\text{SS}_{\text{Total}}} \quad (5)$$

$$\text{AD} = |\text{pEC}_{50,i,\text{expt}} - \text{pEC}_{50,i,\text{pred}}| \quad (6)$$

$$\text{RD} = \left| \frac{\text{pEC}_{50,i,\text{expt}} - \text{pEC}_{50,i,\text{pred}}}{\text{pEC}_{50,i,\text{expt}}} \right| \times 100\% \quad (7)$$

$$\text{AAD} = \frac{1}{N} \sum_{i=1}^N \left| \frac{\text{pEC}_{50,i,\text{expt}} - \text{pEC}_{50,i,\text{pred}}}{\text{pEC}_{50,i,\text{expt}}} \right| \times 100\% \quad (8)$$

3 Results and discussions

3.1 pEC_{50} prediction results

The pEC_{50} prediction results are provided in Table S1 (shown as Supporting Information), along with the differences between the experimental and predicted values. The calculated by model Eq.(1) vs experimental pEC_{50} scatter plot for this regression is presented in Fig.2(a). And statistical metrics for the predictive model are listed in Table 2. The results in Fig.2(a) indicate that the predicted pEC_{50} agree well with the “experimental results”. The AAD for pEC_{50} prediction of 32 dibenzofurans compounds is 0.403. Also, our high-quality prediction model is evidenced by a r^2 value of 0.876 and a PRESS value of 7.734.

3.2 $\ln R$ prediction results

The $\ln R$ prediction results are provided in Table S2, Table 2, and Fig.2(b). Results indicate that our new model Eq.(2) for predicting $\ln R$ has good overall accuracy. The AAD for $\ln R$ prediction of 95 aromatic and heteroaromatic amines is 0.702, the r^2 value is 0.779, and the PRESS value is 80.3.

3.3 Comparison with the HiQSAR approach

The pEC_{50} prediction results with the HiQSAR approach proposed by Basak *et al.*¹⁶ had been used for comparison, and the comparison results are also provided in Table S1 and Table 2. According to Basak *et al.*,¹⁶ the topostructural (TS) and topochemical (TC) descriptors could provide a good model for the pEC_{50} prediction with a r^2 value of 0.852. Using their method, the AAD for pEC_{50} prediction is 0.452, and the PRESS value is 9.270. In addition, with the method of Basak *et al.*,¹⁷ the AAD for $\ln R$ prediction is 0.747, the r^2 value is of 0.748, and the PRESS value is 87.6. Comparison results therefore indicate that obvious improvement could be obtained with our method.

In Basak *et al.*'s research, prediction for pEC_{50} and $\ln R$ of organic compounds was based on about 72 or even more optimal descriptors which had been selected from 300 descriptors. Moreover, in their work, the number of descriptors is large with respect to the number of chemical compounds in the data set, so the ordinary least-square regression is inappropriate.

While, in our work, based on the extended distance matrix, a set of norm indexes have been proposed. By using these norm indexes, the structure and the composition of molecules could be determined stably, accurately, and completely, and also, the isomers could be distinguished well. Moreover, it should be

Fig.2 Scatter plot showing the correlation between predicted by our models and experimental pEC_{50} (a) and $\ln R$ (b)

Table 2 Regression results for prediction of pEC_{50} and $\ln R$ based on our models and Basak *et al.*'s method

	pEC_{50}		$\ln R$	
	Basak <i>et al.</i> 's method ¹⁶	our model	Basak <i>et al.</i> 's method ¹⁷	our model
r^2	0.852	0.876	0.748	0.779
PRESS	9.270	7.734	87.6	80.3
AAD	0.452	0.403	0.747	0.702

strongly stated that firstly, only 17 indices are considered for property prediction of chemical compounds, among which 14 indices are deduced from these norm indexes. Secondly and more importantly, a totally same mathematical model is developed for predicting pEC_{50} and $\ln R$ of organic compounds containing various functionalities with better prediction performance.

Therefore, it could be demonstrated that our method with these norm indexes could result in significant improvement both in accuracy and generality for predicting pEC_{50} and $\ln R$. Also, owing to the much less variables considered, this algorithm could perform well in the ductility, which is very important and particularly valuable for a prediction method.

3.4 Leave-one-out cross-validation

In this work, the leave-one-out algorithm was used for the validation of the prediction of our QSPR models, and results are also shown in Table 3. Results show that the r^2 and PRESS are acceptable and they are as good as the results calculated by Eq.(1) and Eq.(2). The calculated values by leave-one-out cross-validation demonstrate that our QSPR models Eq.(1) and Eq.(2) based on these norm indexes have good predictive stability and reliability for predicting the pEC_{50} and $\ln R$.

Table 3 Regression results for prediction of pEC_{50} and $\ln R$ based on our model and predicting ability test by leave-one-out cross-validation

	Method	Sample number	PRESS	r^2
pEC_{50}	model Eq.(1) in this work	32	7.734	0.876
	leave-one-out cross-validation	32	7.932	0.865
	this work for training set	27		0.899
$\ln R$	model Eq.(2) in this work	95	80.306	0.779
	leave-one-out cross-validation	95	82.670	0.763
	this work for training set	74		0.814

4 Conclusions

In this work, a set of norm indexes for predicting the AH receptor prediction (pEC_{50}) of 32 dibenzofurans and the mutagenic potency $\ln R$ of 95 aromatic and heteroaromatic amines was proposed. Based on these norm index, a totally same mathematical model was developed for predicting pEC_{50} and $\ln R$ of organic compounds containing various functionalities. Results indicated that pEC_{50} and $\ln R$ were successfully predicted with a significant degree of confidence. With our method, the AAD values for pEC_{50} prediction and $\ln R$ prediction are 0.403 and 0.702, r^2 values are of 0.876 and 0.779, respectively. Also, this research provides better prediction results as compared to the HiQSAR method of Basak *et al.*, despite the fact that lesser descriptors were considered and used in this research as compared to other models. Moreover, our results demonstrated that it is possible to use a totally same mathematical model for predicting pEC_{50} and $\ln R$ of organic compounds containing various functionalities with better prediction performance.

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Supporting Information: Experimental and predicted the aryl hydrocarbon (AH) receptor binding affinity (pEC_{50}) of dibenzofurans and the mutagenic potency $\ln R$ of aromatic and heteroaromatic amines based on this model and Basak *et al.*'s method, and a detailed procedure for the pEC_{50} estimation have been included. This information is available free of charge via

the internet at <http://www.whxb.pku.edu.cn>.

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多类型杂环化合物的药理和毒理活性系数构效关系

朱志臣¹ 王 强^{2,*} 贾青竹³ 夏淑倩⁴ 马沛生⁴

(¹天津城建大学理学院, 天津 300384; ²天津科技大学材料科学与化学工程学院, 天津 300457;

³天津科技大学海洋科学与工程学院, 天津 300457; ⁴天津大学化工学院, 天津 300072)

Structure-Property Relationship for the Pharmacological and Toxicological Activity of Heterocyclic Compounds

ZHUZhi-Chen¹ WANG Qiang^{2,*} JIA Qing-Zhu³ XIA Shu-Qian⁴

MA Pei-Sheng⁴

(¹*School of Science, Tianjin University of Urban Construction, Tianjin 300384, P. R. China;*

²*School of Material Science and Chemical Engineering, Tianjin University of Science and Technology, Tianjin*

300457, P. R. China; ³*School of Marine Science and Engineering, Tianjin University of Science and Technology,*

Tianjin 300457, P. R. China; ⁴*School of Chemical Engineering and Technology, Tianjin University, Tianjin*

300072, P. R. China)

*Corresponding author. Email: wang_q@tust.edu.cn; Tel: +86-22-58088631, +86-13652089933.

Table S1 Experimental and predicted AH receptor binding affinity pEC₅₀ based on our model eq. (1) and Basak et al.' method, for the set of 32 dibenzofurans compounds

Chemical	exp. pEC ₅₀ ²⁶	Basak <i>et al.</i> ' Method ¹⁶		This work	
		pred. pEC ₅₀	AD ^a	pred. pEC ₅₀	AD
2-Cl	3.553	3.169	0.384	3.665	0.112
3-Cl	4.377	4.199	0.178	4.506	0.129
4-Cl	3.000	3.692	-0.692	3.270	0.270
2,3-diCl	5.326	4.964	0.362	5.346	0.020
2,6-diCl	3.609	4.279	-0.67	4.958	1.349
2,8-diCl ^b	3.590	4.251	-0.661	4.128	0.538
1,2,7-trCl	6.347	5.646	0.701	6.436	0.089
1,3,6-trCl	5.357	4.705	0.652	5.265	0.093
1,3,8-trCl ^b	4.071	5.330	-1.259	4.806	0.735
2,3,8-trCl	6.000	6.394	-0.394	6.471	0.471
1,2,3,6-teCl	6.456	6.480	-0.024	6.922	0.466
1,2,3,7-teCl	6.959	7.066	-0.107	7.769	0.810
1,2,4,8-teCl	5.000	4.715	0.285	5.381	0.381
2,3,4,6-teCl ^b	6.456	7.321	-0.865	6.991	0.535
2,3,4,7-teCl	7.602	7.496	0.106	7.917	0.315
2,3,4,8-teCl	6.699	6.976	-0.277	7.266	0.567
2,3,6,8-teCl	6.658	6.008	0.650	6.224	0.434
2,3,7,8-teCl	7.387	7.139	0.248	7.774	0.387
1,2,3,4,8-peCl ^b	6.921	6.293	0.628	6.822	0.099
1,2,3,7,8-peCl	7.128	7.213	-0.085	7.598	0.470
1,2,3,7,9-peCl	6.398	5.724	0.674	6.723	0.325
1,2,4,6,7-peCl	7.169	6.135	1.035	7.015	0.154
1,2,4,7,8-peCl	5.886	6.607	-0.720	6.136	0.250
1,2,4,7,9-peCl	4.699	4.937	-0.238	5.454	0.755
1,3,4,7,8-peCl	6.699	6.513	0.186	6.607	0.092

2,3,4,7,8-peCl	7.824	7.479	0.345	8.194	0.370
2,3,4,7,9-peCl	6.699	6.509	0.190	6.919	0.220
1,2,3,4,7,8-heCl	6.638	6.802	-0.164	7.029	0.391
1,2,3,6,7,8-heCl ^b	6.569	7.124	-0.555	7.469	0.900
1,2,4,6,7,8-heCl	5.081	5.672	-0.591	5.648	0.567
2,3,4,6,7,8-heCl	7.328	7.019	0.309	7.513	0.185
Dibenzofuran	3.000	2.765	0.235	3.422	0.422

^a AD: the absolute difference

^b Compounds for the testing set members

Table S2 Experimental and predicted mutagenic activity lnR based on our model eq. (2) and Basak et al.' method for the set of 95 aromatic and heteroaromatic amines

Chemicals	exp. lnR ²⁷	Basak SC et al. Method ¹⁷		This work	
		pred. lnR	AD ^a	pred. lnR	AD
2-Bromo-7-aminofluorene	2.62	1.99	0.63	2.58	0.04
2-Methoxy-5-methylaniline(<i>p</i> -cresidine)	-2.05	-2.82	0.77	-2.74	0.69
5-Aminoquinoline ^b	-2.00	-1.85	0.15	-1.87	0.13
4-Ethoxyaniline(<i>p</i> -phenetidine)	-2.30	-3.26	0.96	-2.27	0.03
1-Aminonaphthalene ^b	-0.60	-0.61	0.01	-2.01	1.41
4-Aminofluorene	1.13	1.14	0.01	0.25	0.88
2-Aminoanthracene ^b	2.62	1.34	1.28	1.20	1.42
7-Aminofluoranthene	2.88	3.10	0.22	2.44	0.44
8-Aminoquinoline	-1.14	-1.76	0.62	-1.21	0.07
1,7-Diaminophenazine	0.75	0.88	0.13	1.07	0.32
2-Aminonaphthalene	-0.67	-0.32	0.35	-1.42	0.75
4-Aminopyrene	3.16	2.57	0.59	2.91	0.25
3-Amino-3'-nitrobiphenyl ^b	-0.55	0.07	0.62	-0.50	0.05
2,4,5-Trimethylaniline	-1.32	-1.18	0.14	-1.52	0.20

3-Aminofluorene	0.89	1.25	0.36	0.80	0.09
3,3_-Dichlorobenzidine ^b	0.81	-0.17	0.98	1.12	0.31
2,4-Dimethylaniline(2,4-xylydine)	-2.22	-2.17	0.05	-2.13	0.09
2,7-Diaminofluorene	0.48	1.11	0.63	1.91	1.43
3-Aminofluoranthene	3.31	2.65	0.66	2.86	0.45
2-Aminofluorene	1.93	1.03	0.90	1.07	0.86
2-Amino-4_-nitrobiphenyl ^b	-0.62	-0.27	0.35	-0.27	0.35
4-Aminobiphenyl	-0.14	-0.34	0.20	-0.81	0.67
3-Methoxy-4-methylaniline(<i>o</i> -cresidine)	-1.96	-2.84	0.88	-2.66	0.70
2-Aminocarbazole	0.60	0.69	0.09	1.19	0.59
2-Amino-5-nitrophenol	-2.52	-2.86	0.34	-1.63	0.89
2,2_-Diaminobiphenyl ^b	-1.52	-0.15	1.37	-1.08	0.44
2-Hydroxy-7-aminofluorene	0.41	1.13	0.72	2.09	1.68
1-Aminophenanthrene	2.38	1.19	1.19	0.93	1.45
2,5-Dimethylaniline	-2.40	-1.98	0.42	-3.06	0.66
4-Amino-2_-nitrobiphenyl ^b	-0.92	-0.05	0.87	0.11	1.03
2-Amino-4-methylphenol	-2.10	-4.05	1.95	-2.12	0.02
2-Aminophenazine ^b	0.55	1.54	0.99	1.17	0.62
4, 4_-Diaminophenyl	0.31	-0.62	0.93	0.27	0.04
2,4-Dinitroaniline	-2.00	-2.07	0.07	-1.78	0.22
2,4-Diaminoisopropylbenzene	-3.00	-2.56	0.45	-3.21	0.21
2,4-Difluoroaniline ^b	-2.70	-2.43	0.27	-2.19	0.51
4,4_-Methylenedianiline	-1.60	-0.96	0.64	-0.44	1.16
3,3_-Dimethylbenzidine ^b	0.01	0.28	0.27	0.72	0.71
2-Aminofluoranthene	3.23	3.27	0.04	2.83	0.40
2-Amino-3-nitrobiphenyl	-0.89	-0.64	0.25	-0.44	0.45
1-Aminofluoranthene	3.35	3.00	0.35	2.36	0.99
4,4_-Ethylenebis(aniline)	-2.15	-1.10	1.05	-1.87	0.28
4-Chloroaniline ^b	-2.52	-2.60	0.08	-2.74	0.22

2-Aminophenanthrene	2.46	1.45	1.01	1.55	0.91
4-Fluoroaniline	-3.32	-3.26	0.06	-3.00	0.32
9-Aminophenanthrene ^b	2.98	1.36	1.62	0.63	2.35
3,3'-Diaminobiphenyl	-1.30	-1.14	0.16	-0.40	0.90
2-Aminopyrene	3.50	2.69	0.81	2.92	0.58
2,6-Dichloro-1,4-phenylenediamine	-0.69	-1.02	0.33	-1.54	0.85
2-Amino-7-acetamidofluorene	1.18	0.37	0.81	1.20	0.02
2,8-Diaminophenazine ^b	1.12	0.77	0.35	1.57	0.45
6-Aminoquinoline	-2.67	-1.52	1.15	-0.66	2.01
4-Methoxy-2-methylaniline(m-cresidine)	-3.00	-2.65	0.35	-2.37	0.63
3-Amino-2'-nitrobiphenyl	-1.30	-0.38	0.92	-0.55	0.75
2,4'-Diamino-biphenyl ^b	-0.92	-0.72	0.20	-0.18	0.74
1,6-Diaminophenazine	0.20	-0.34	0.54	0.15	0.05
4-Aminophenyldisulfide	-1.03	0.91	1.94	-1.29	0.26
2-Bromo-4,6-dinitroaniline	-0.54	-1.06	0.52	-0.58	0.04
2,4-Diamino- <i>n</i> -butylbenzene	-2.70	-2.36	0.34	-2.08	0.62
4-Aminophenyl ether ^b	-1.14	-0.45	0.69	-0.11	1.03
2-Aminobiphenyl	-1.49	-0.27	1.22	-1.30	0.19
1,9-Diaminophenazine	0.04	0.00	0.04	0.62	0.58
1-Aminofluorene	0.43	1.25	0.82	0.42	0.01
8-Aminofluoranthene	3.80	3.05	0.75	3.47	0.33
2-Chloroaniline	-3.00	-2.43	0.57	-3.14	0.14
2-Amino- <i>aaa</i> -trifluorotoluene	-0.80	-1.88	1.08	-1.96	1.16
2-Amino-1-nitronaphthalene	-1.17	-0.25	0.92	-1.09	0.08
3-Amino-4'-nitrobiphenyl	0.69	0.43	0.26	-0.59	1.28
4-Bromoaniline ^b	-2.70	-1.48	1.22	-2.19	0.51
2-Amino-4-chlorophenol	-3.00	-1.57	1.43	-2.43	0.57
3,3'-Dimethoxybenzidine	0.15	1.11	0.96	-0.04	0.19
4-Cyclohexylaniline	-1.24	-1.75	0.51	-0.99	0.25

4-Phenoxyaniline	0.38	-0.72	1.10	0.01	0.37
4,4_-Methylenebis(<i>o</i> -ethylaniline) ^b	-0.99	-0.78	0.21	-0.67	0.32
2-Amino-7-nitrofluorene	3.00	1.87	1.13	1.98	1.02
Benzidine	-0.39	0.20	0.59	-0.21	0.18
1-Amino-4-nitronaphthalene	-1.77	-0.23	1.54	-1.10	0.67
4-Amino-3_-nitrobiphenyl	1.02	0.45	0.57	-0.23	1.25
4-Amino-4_-nitrobiphenyl ^b	1.04	-0.80	1.84	0.19	0.85
1-Aminophenazine	-0.01	1.32	1.33	0.46	0.47
4,4_-Methylenebis(<i>o</i> -fluoroaniline)	0.23	0.28	0.05	-0.64	0.87
4-Chloro-2-nitroaniline	-2.22	-2.12	0.10	-1.76	0.46
3-Aminoquinoline	-3.14	-1.26	1.88	-0.66	2.48
3-Aminocarbazole	-0.48	-0.55	0.07	0.83	1.31
4-Chloro-1,2-phenylenediamine ^b	-0.49	-2.21	1.72	-2.58	2.09
3-Aminophenanthrene	3.77	1.36	2.41	1.55	2.22
3,4_-Diaminobiphenyl	0.20	-0.46	0.66	-0.15	0.35
1-Aminoanthracene	1.18	1.42	0.24	0.48	0.70
1-Aminocarbazole	-1.04	-0.54	0.50	0.49	1.53
9-Aminoanthracene	0.87	1.08	0.21	0.64	0.23
4-Aminocarbazole	-1.42	-0.32	1.10	0.44	1.86
6-Aminochrysene ^b	1.83	3.35	1.52	3.29	1.46
1-Aminopyrene	1.43	3.72	2.29	2.79	1.36
4-4_-Methylenebis(<i>o</i> -isopropylaniline)	-1.77	-0.34	1.43	-1.45	0.32
2,7-Diaminophenazine	3.97	0.87	3.10	1.64	2.33

^a AD: the absolute difference

^b Compounds for the testing set members

Example:

Prediction of the aryl hydrocarbon (AH) receptor binding affinity (described as pEC₅₀) of 2-Cl-dibenzofuran is exemplified as follows. For this compound, the total number of

group N is 21, and molecular weight M is 202.56.

Firstly, the structure for the 2-Cl-dibenzofuran is drawn and optimized by Gaussian software.

Secondly, the distant matrix M_d , and the extended matrix M_e is described as below.

$$M_d = \begin{bmatrix} 0 & 1 & 2 & 3 & 2 & 1 & 2 & 3 & 4 & 5 & 4 & 3 & 3 & 2 \\ 1 & 0 & 1 & 2 & 3 & 2 & 3 & 4 & 5 & 6 & 5 & 4 & 4 & 1 \\ 2 & 1 & 0 & 1 & 2 & 3 & 4 & 4 & 5 & 6 & 6 & 5 & 3 & 2 \\ 3 & 2 & 1 & 0 & 1 & 2 & 3 & 3 & 4 & 5 & 5 & 4 & 2 & 3 \\ 2 & 3 & 2 & 1 & 0 & 1 & 2 & 2 & 3 & 4 & 4 & 3 & 1 & 4 \\ 1 & 2 & 3 & 2 & 1 & 0 & 1 & 2 & 3 & 4 & 3 & 2 & 2 & 3 \\ 2 & 3 & 4 & 3 & 2 & 1 & 0 & 1 & 2 & 3 & 2 & 1 & 2 & 4 \\ 3 & 4 & 4 & 3 & 2 & 2 & 1 & 0 & 1 & 2 & 3 & 2 & 1 & 5 \\ 4 & 5 & 5 & 4 & 3 & 3 & 2 & 1 & 0 & 1 & 2 & 3 & 2 & 6 \\ 5 & 6 & 6 & 5 & 4 & 4 & 3 & 2 & 1 & 0 & 1 & 2 & 3 & 7 \\ 4 & 5 & 6 & 5 & 4 & 3 & 2 & 3 & 2 & 1 & 0 & 1 & 4 & 6 \\ 3 & 4 & 5 & 4 & 3 & 2 & 1 & 2 & 3 & 2 & 1 & 0 & 3 & 5 \\ 3 & 4 & 3 & 2 & 1 & 2 & 2 & 1 & 2 & 3 & 4 & 3 & 0 & 5 \\ 2 & 1 & 2 & 3 & 4 & 3 & 4 & 5 & 6 & 7 & 6 & 5 & 5 & 0 \end{bmatrix}$$

$$M_e = \begin{bmatrix} \frac{1.75}{97.5} & \frac{1.60}{97.5} & \frac{1.75}{97.5} & \frac{1.75}{97.5} & \frac{1.60}{97.5} & \frac{1.60}{97.5} & \frac{1.60}{97.5} & \frac{1.60}{97.5} & \frac{1.60}{97.5} & \frac{1.75}{97.5} & \frac{1.75}{97.5} & \frac{1.75}{97.5} & \frac{1.75}{97.5} & \frac{1.42}{97.5} & \frac{1.16}{97.5} \\ 1.75 & 1.60 & 1.75 & 1.75 & 1.60 & 1.60 & 1.60 & 1.60 & 1.60 & 1.75 & 1.75 & 1.75 & 1.75 & 1.42 & 1.16 \\ 1.3894 & 1.3894 & 1.3814 & 1.3814 & 1.3922 & 1.3924 & 1.3936 & 1.392 & 1.3813 & 1.3813 & 1.3803 & 1.3803 & 1.3933 & 1.7846 \\ 2 & 3 & 2 & 2 & 3 & 3 & 3 & 3 & 2 & 2 & 2 & 2 & 2 & 1 \\ 1 & 0 & 1 & 1 & 0 & 0 & 0 & 0 & 1 & 1 & 1 & 1 & 0 & 0 \end{bmatrix}$$

$$M_e = \begin{bmatrix} \frac{1.75}{97.5} & \frac{1.60}{97.5} & \frac{1.75}{97.5} & \frac{1.75}{97.5} & \frac{1.60}{97.5} & \frac{1.60}{97.5} & \frac{1.60}{97.5} & \frac{1.60}{97.5} & \frac{1.60}{97.5} & \frac{1.75}{97.5} & \frac{1.75}{97.5} & \frac{1.75}{97.5} & \frac{1.75}{97.5} & \frac{1.42}{97.5} & \frac{1.16}{97.5} \\ 1.75 & 1.60 & 1.75 & 1.75 & 1.60 & 1.60 & 1.60 & 1.60 & 1.60 & 1.75 & 1.75 & 1.75 & 1.75 & 1.42 & 1.16 \\ 1.3894 & 1.3894 & 1.3814 & 1.3814 & 1.3922 & 1.3924 & 1.3936 & 1.392 & 1.3813 & 1.3813 & 1.3803 & 1.3803 & 1.3933 & 1.7846 \\ 2 & 3 & 2 & 2 & 3 & 3 & 3 & 3 & 2 & 2 & 2 & 2 & 2 & 1 \\ 1 & 0 & 1 & 1 & 0 & 0 & 0 & 0 & 1 & 1 & 1 & 1 & 0 & 0 \end{bmatrix}$$

Thirdly, in this work, the norm values of the extended matrix are calculated and shown as in Table S3.

Table S3 Norm values of extended matrix for 2-Cl-dibenzofuran

extended matrix	norm(M,1)	norm(M,2)	norm(M,fro)	norm(M,inf)
M _D	57.6696	41.6355	46.7410	53
M _A	9.0621	12.3061	13.5912	32
M _B	11.06215	12.5624	14.0968	
M _C	10.2020	12.4590	13.9542	

Lastly, from parameters in Table 3, the pEC₅₀ of 2-Cl-dibenzofuran is predicted by Eq.

(1):

$$\begin{aligned}
 pEC_{50} &= 0.2730 \times 57.6696 - 18.5465 \times 41.6355 + 14.0124 \times 46.7410 - 0.1447 \times 53 - 22.7744 \times 9.0621 \\
 &\quad - 48.5409 \times 12.3061 - 462.3183 \times 13.5912 - 5.9163 \times 32 - 0.1887 \times 11.0625 \\
 &\quad + 156.6532 \times 12.5624 + 428.6100 \times 14.0970 + 0.2801 \times 10.2020 - 55.6900 \times 12.4590 \\
 &\quad + 16.3321 \times 13.9542 + 3544.4709 \exp\left(\frac{1}{21}\right) + 10679.1349 \exp\left(\frac{1}{202.56}\right) - 14604.7935 \\
 &= 3.665
 \end{aligned}$$

The calculated result is 3.665 while the experimental pEC₅₀ is 3.553.