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Studies on the IC_{50} of Metabolically Stable Dibenzo[b、e]oxepin-11（6H）-ones as Highly Selective p38 MAP Kinase Inhibitors

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Abstract: **In this study, the QSAR (quantitative structure-activity relationship) model led to the discussion of a highly potent and selective ligand for the p38α MAP kinase inhibitors between the physical and chemical structure information of inhibition rate of cancer. All 62 ligands for the p38α MAP kinase inhibitors were divided randomly into training set with 48, and test set with 14. After molecular mechanics optimization with MM+ and AM1 by Hyperchem software, numerous descriptors were calculated by CODESSA software, including constitution, topolopy, geomrtry, electron, quantum chemistry descriptors. HM was used for the selection of optimal descriptor combination, which was as a group descriptors to build linear QSAR models by HM and GEP, respectively. As a significant result, HM has a precision of 0.82 and 0.76 in the training and test set, and the GEP accuracy of the training and test sets is 0.82 and 0.82. The results show that the both two quantitative constitutive relationship model has good prediction ability and two points, and further optimize the p38α MAP kinase inhibitor. The method is an effective application of carcinogenic compounds. The study can confirm some pivotal factors that influence the value of IC_{50} and draw some new drugs. It will save lots of energy and resources.**

Keywords: P38α MAP kinase; P38α MAP kinase inhibitors; Quantitative structure-activity; Gene expression programming; Heuristic method; Cancer

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1. Introduction

p38α MAP kinase is a member's proliferation activity (MAP) kinase family, acting as the integration point for multiple biochemical signals, and participating in various cell processes such as proliferation, differentiation, transcription regulation and development. It plays a central role in the biosynthesis of the proinflammatory cytokines interleukin-1β (IL-1β) and tumor necrosis factor-R (TNF-R) at the translational and transcriptional levels[1-3]. As a result, the inhibitor of this kinase will probably become a promising new drug for treating rheumatoid arthritis, cancer and inflammatory diseases. However, the clinical development of the first-generation p38 inhibitor was hampered by its severe liver toxicity and the interference of the liver cell pigment P450 enzyme. Therefore, it is necessary to discover the more powerful inhibitors of p38α MAP kinases with different structures[4].

p38 signaling pathway can influence the occurrence of cancer by regulating the cell cycle and monitoring points. Under UV irradiation and the action of spindle damage, the p38 pathway is activated. Through the phosphorylation of downstream substrates to control the cell cycle and maintain the integrity of the genome. The p38 signaling pathway is also involved in the inhibition of fibroblast contact and inhibits the occurrence of tumor. In addition, p38 can regulate the activity of C by A, B, etc, control the tumor growth by activating cell senescence. Therefore, the p38 signaling pathway has a certain anti cancer function, which provides a new idea for clinical research.

Using 2-(2-amino) amino-substituted dibenzosuberone as starting compound, it can improve the biological activity in p38α MAP kinase detection and human whole blood TNF-α release test by introducing hydrophilic residues[5]. The SARs of Skepinone-L15[6] are transferred to the class of dibenzo[b,e]oxepin-11(6H)-ones: structural optimization of compound 7 by the introduction of hydrophilic residues at positions 7, 8, 9, and 10 should increase the biological activity in a human whole blood TNF-α release assay[7].

Therefore, it is a very important to assess the security risk of compounds. However, it is a huge project a large number of compounds are measured by experimental means[8]. So, it is necessary to develop a simple, fast, and available method to measure the security risk of the compound. Quantitative structure activity relationship (QSAR) method not only can quickly establish a reliable prediction model, can also

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reveal interact with the body of the poison damage mechanism, a real green compounds for safer, more environmental protection, and will provide reference for the design and synthesis of information[9].

Based on the structure of kinase and inhibitors, this dissertation uses QSAR and to study the interaction mode between the targeted protein and their inhibitors and to investigate the selectivity mechanism of some inhibitors. This study aims at gaining insights into the key structural features affecting activity, and the interaction mechanism for inhibitor-protein binding and selectivity, guiding the design, structural modification and activity prediction of PKI (protein kinase inhibitor) and to aid the design and synthesize of highly effective inhibitors targeted PK.

Gene expression programming introduced by Ferreira[10] is a method of automatic programming, it overcomes some limitations of the genetic algorithms and genetic programming, which workes with the two elements, chromosome and the expression tree[11]. The advantages of GEP in decision tree design make it a successful method to solve classification problems[12,13].

The literature has explored compounds containing hydrophlic substituents resulted in a highly improved biological activity in the human whole blood TNF-α release assay. In our study, we calculated 62 molecular structures of CODESSA software in the literature. Then, the heuristic method (HM) is used to select six descriptors to establish a linear model. To get a better prediction model, we developed another QSAR model by GEP to predict the IC50 of compounds containing hydrophlic substituents resulted in a highly improved biological activity in the human whole blood TNF-α release assay.

2. Materials and method

2.1. Data Set

Sixty-two compounds were collected from the literature[14]. Table 1 shows the structure of p38 MAP kinase inhibitor and the IC_{50} value. In a random digital table, several sets are divided into two groups: a training set of 48 compounds and a testing set of 14 compounds. This model is developed by training set and evaluates the prediction ability of the model through the test set.

2.2. Calculation of the Descriptors

In QSAR models, compounds are usually represented by digital molecular descriptors. A mathematical formula is established for the molecular descriptors of chemical information, indicating the relationship between the structure and the activity of the compound.In this study, all 62 molecules were inhaled in HyperChem4.0[15]. Then, the molecular structure is not only optimized by using the MM + molecular mechanical force field, but also in the MOPAC 6.0 program, the more accurate optimization is obtained through the semi-empirical AM1 method[16]. Finally, the MOPAC file is exported and used as a feed for the CODESSA program[17] to calculate the molecular descriptors. The molecular descriptors are divided into six groups: constitutional, topological, geometrical, electrostatic, quantum-chemical and thermodynamic[18].

2.3. Linear Model by Heuristic Method

When the molecular description was generated, the study preselected the descriptor in CODESSA and established a linear model. HM has no software limitations. In the case of high speed, it is easy to select several descriptors that are closely related to each other and make a good estimate of the logarithm set. The details of selecting descriptors can be referenced in the literature, coefficient regression (R^2), cross-validation coefficient regression (R^2_{CV}), f-test (F), standard deviation (S^2) to test the quality of correlation. In the word, six descriptors are selected from the 354 descriptors and the linear model is produced by the HM.

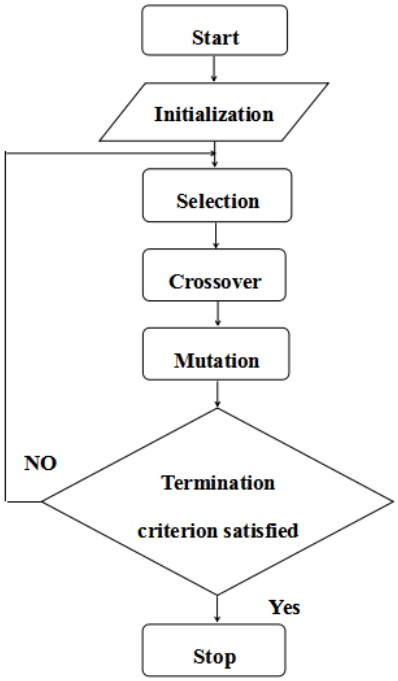

Figure 1: The flow chart of GEP.

2.4. Nonlinear Model by the GEP Algorithm

GEP is a non-parameterized method, which was proposed by ferrera in 1999[19], and the gene expression program is a new algorithm based on biological gene structure and function[20]. It uses all the advantages of genetic algorithms (GA) and genetic programming (GP) to eliminate some of their own limitations. GEP uses fixed-length, non-linear or linear chromosome sequences to solve complex problems, forming different shapes and sizes of expression trees, when evaluating its fineness[21]. The separation of GEP's search space and solution space can be extended to the unconstrained search of the genomic space, realizing the purpose of solving classification problems

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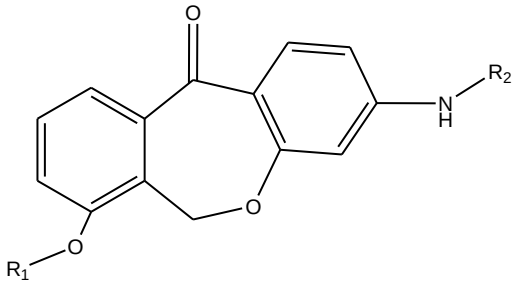
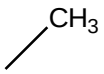
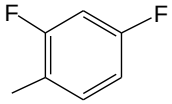
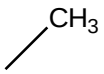
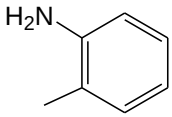
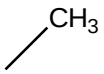
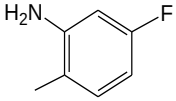
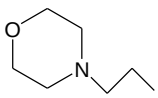
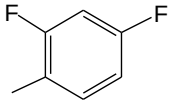
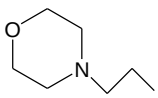
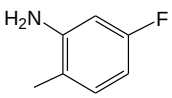
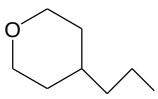
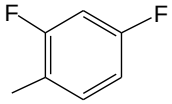
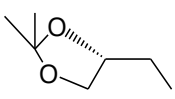
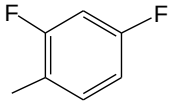
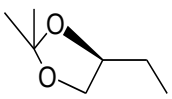
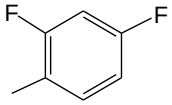
with simple coding[22].

There are five major elements in GEP, including the function set (+, -, *, /, Q, etc.), terminal set (a, b, c, d, etc.), fitness function, control parameters, and termination conditions. Firstly, the randomly generated chromosomes are the initial population. Then the chromosomes were expressed as ETs and the fitness of each individual was assessed. Thirdly, according to their fitness, choose the best individual to undertake the transformation. Finally, a certain number of new generations repeat the process and repeat the process until a solution is found. More detailed information and practical application of GEP algorithms can be found in this work. The steps for GEP are shown in Figure 1.

Table 1 Experimental and calculated pIC_{50} of the trisubstututed thiazoles as p38α MAPK kinase (HM and GEP)



Compound			Exp. pIC_{50}	Calculate			
Number	R^1	R^2		HM		GEP	
				Pred.[a]	Residue[b]	Pred.	Residue
1			1.20	1.0511	-0.1489	1.2333	0.0333
2			1.03	0.6991	-0.3309	1.0155	0.0145
3			1.06	1.1357	0.0757	1.2844	0.2244
4*			1.47	1.0835	-0.3865	1.3192	0.1508
5			1.14	0.8299	-0.3101	0.9405	0.1995
6*			0.24	0.6912	0.4512	0.1095	0.1304
7			0.25	0.4461	0.1961	0.1418	0.1082
8*			0.32	0.4461	0.1261	0.1418	0.1782

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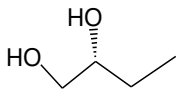
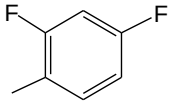
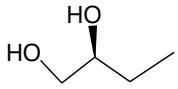
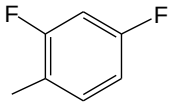
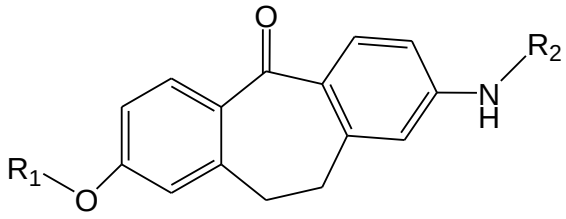
9*			1.60	1.5478	-0.0522	1.6444	0.0444
10			1.38	1.5478	0.1678	1.6444	0.2644



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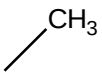
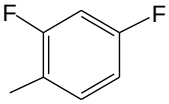
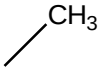
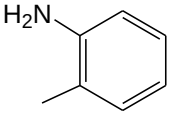
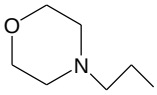
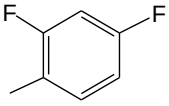
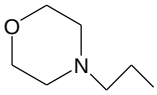
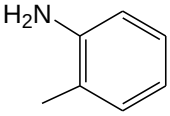
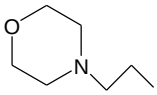
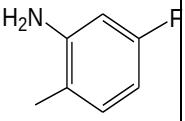
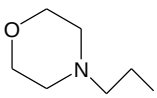
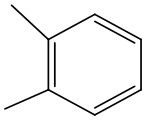
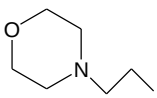
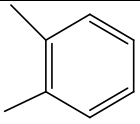
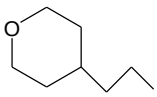
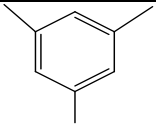
				Pred.[a]	Residue[b]	Pred.	Residue
11			0.66	1.0382	0.3782	0.8400	0.1800
12			0.88	0.6856	-0.1944	0.7967	0.0833
13			1.48	1.2053	-0.2747	1.2394	0.2406
14			0.83	0.8768	0.0468	1.1550	0.3250
15			1.39	1.3398	-0.0502	1.2291	0.1609
16			1.07	0.4254	-0.6446	0.6098	0.4602
17			0.80	0.6481	-0.1519	0.7657	0.0343
18			0.25	0.8549	0.6049	0.7400	0.4900

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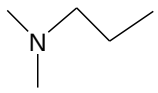
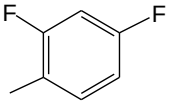
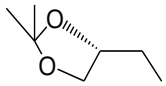
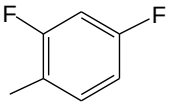
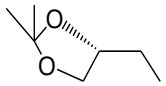
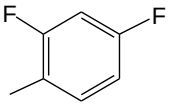
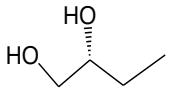
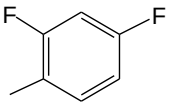
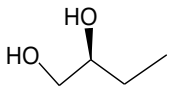
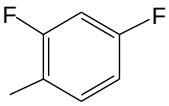
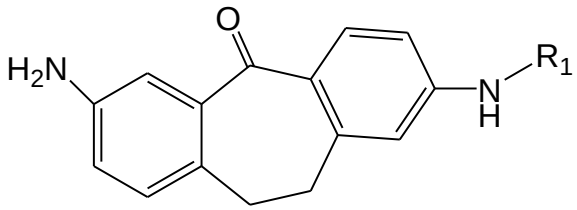
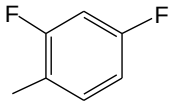
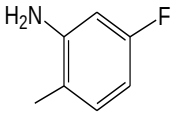
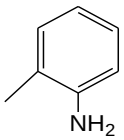
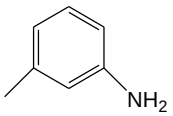
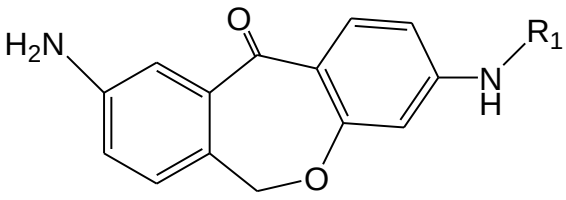
19*			1.28	1.2097	-0.0703	1.1787	0.1013
20			0.18	0.5233	0.3433	0.0544	0.1256
21			0.29	0.6130	0.3230	0.5928	0.3028
22			1.57	1.4526	-0.1174	1.5136	0.0564
23			1.68	1.9589	0.2789	1.7853	0.1053



Compound		Exp. pIC_{50}	Calculate			
			HM		GEP	
Number	R^1		Pred.[a]	Residue[b]	Pred.	Residue
24*		1.37	1.4111	0.0411	1.4751	0.1051
25*		0.82	1.3193	0.4993	1.4330	0.6130
26*		0.69	0.7325	0.0425	1.0258	0.3358
27*		0.19	0.9069	0.7169	0.8631	0.6731



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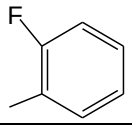
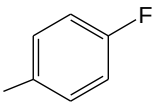
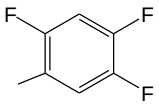
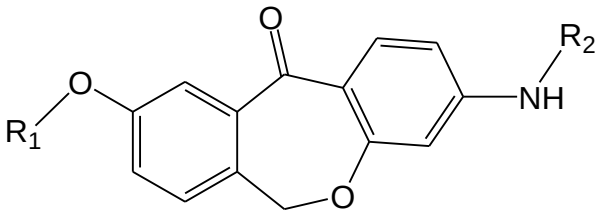
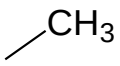
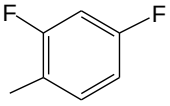
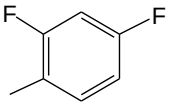
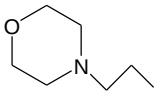
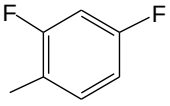
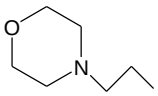
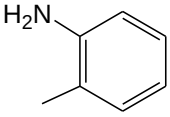
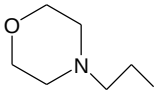
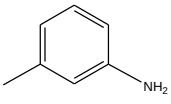
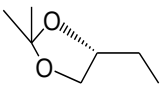
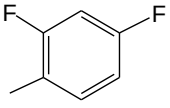
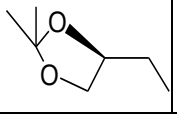
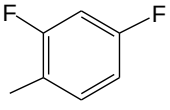
Compound		Exp.	Calculate			
Number	R^1	pIC_{50}	HM		GEP	
			Pred.[a]	Residue[b]	Pred.	Residue
28*		0.95	1.2842	0.3342	1.2430	0.2930
29		0.99	1.0613	0.0713	1.0169	0.0269
30		1.13	1.4423	0.3123	1.4638	0.3338



Compound			Exp.	Calculate			
Number	R^1	R^2	pIC_{50}	HM		GEP	
				Pred.[a]	Residue[b]	Pred.	Residue
31			0.94	1.0211	0.0811	1.0701	0.1301
32			0.91	1.3870	0.4770	1.3323	0.4222
33			1.68	1.4912	-0.1888	1.4935	0.1865
34			0.97	1.0133	0.0433	1.1242	0.1542
35			0.84	1.0698	0.2298	1.1260	0.2860
36			0.68	0.8170	0.1370	0.8662	0.1862
37			1.32	0.8170	-0.5030	0.8662	0.4538

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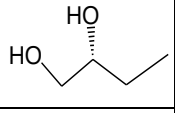
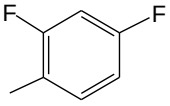
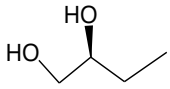
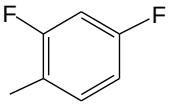
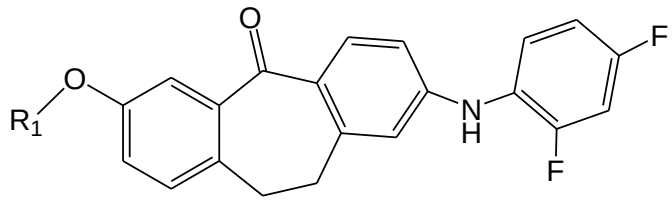
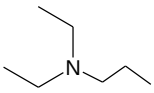
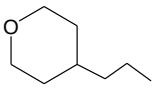
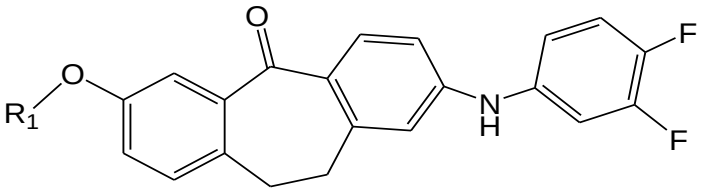
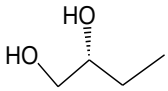
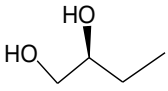
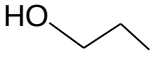
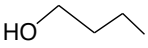
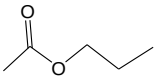
38*			1.21	1.6185	0.4085	1.6318	0.4218
39*			1.85	1.6185	-0.2315	1.6318	0.2182



Compound		Exp. pIC_{50}	Calculate			
Number	R^1		HM		GEP	
			Pred.[a]	Residue[b]	Pred.	Residue
40		1.00	1.0442	0.0442	1.0902	0.0902
41		1.10	0.8869	-0.2131	1.0741	0.0259



Compound		Exp. pIC_{50}	Calculate			
Number	R^1		HM		GEP	
			Pred.[a]	Residue[b]	Pred.	Residue
42		1.21	1.3673	0.1573	1.5817	0.3717
43		1.85	1.3673	-0.4827	1.5817	0.2683
44		1.70	1.5866	-0.1134	1.6971	0.0029
45		2.10	1.5058	-0.5942	1.5781	0.5219
46		1.66	1.8285	0.1685	1.4807	0.1793

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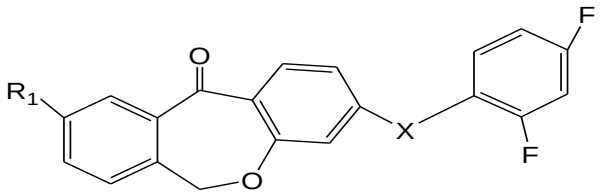
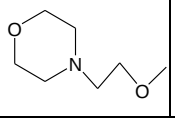
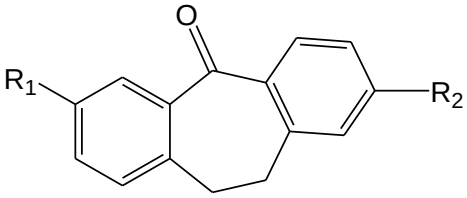
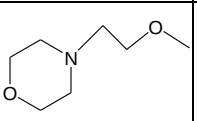
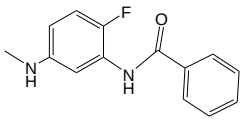
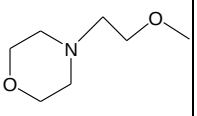
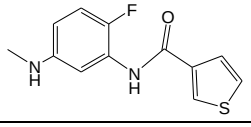
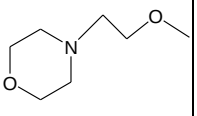
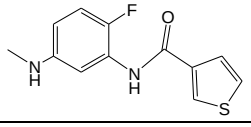
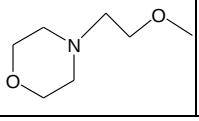
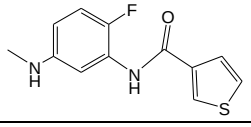
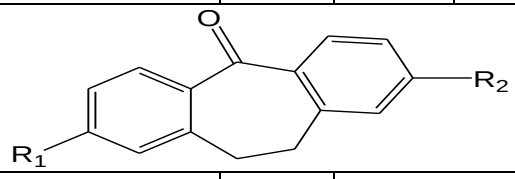


Compound			Exp. pIC_{50}	Calculate			
Number	R^1	X		HM		GEP	
				Pred.[a]	Residue[b]	Pred.	Residue
47		NH	1.37	1.2653	-0.1047	1.3362	0.0338
48*		O	0.12	-0.1663	-0.2863	0.4880	0.4325
49*		NH	0.09	0.0267	-0.0633	0.4619	0.3719



Compound			Exp. pIC_{50}	Calculate			
	R^1	R_2		HM		GEP	
				Pred.[a]	Residue[b]	Pred.	Residue
50			3.00	2.7073	-0.2927	2.5675	0.4325
51			2.77	2.4847	-0.2853	2.7061	0.0639
52			2.74	2.3886	-0.3514	2.5464	0.1936
53			2.80	2.7233	-0.0767	2.7140	0.0860



Compound	Exp.	Calculate

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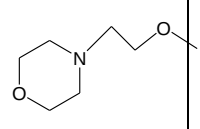
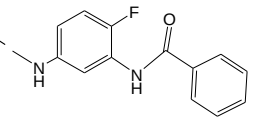
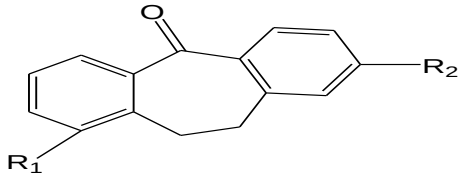
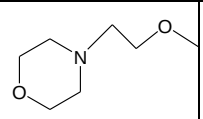
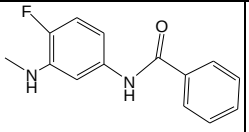
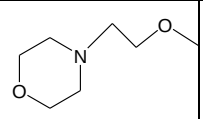
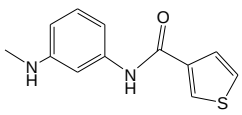
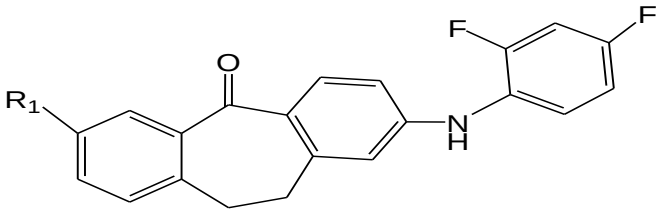
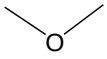
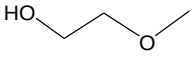
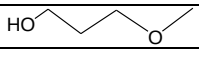
	R^1	R_2	pIC_{50}	HM		GEP	
				Pred.[a]	Residue[b]	Pred.	Residue
54			1.77	2.3496	0.5796	2.4710	0.7010



Compound			Exp. pIC_{50}	Calculate			
	R^1	R_2		HM		GEP	
				Pred.[a]	Residue[b]	Pred.	Residue
55			2.00	1.7427	-0.2573	1.9256	0.0744
56			1.60	1.9796	0.3796	1.8369	0.2369



Compound		Exp. pIC_{50}	Calculate			
Number	R^1		HM		GEP	
			Pred.[a]	Residue[b]	Pred.	Residue
57		0.94	0.9117	-0.0283	0.9714	0.0314
58		1.31	1.2520	-0.0580	1.4324	0.1224
59		1.36	1.1093	-0.2507	1.0183	0.3416
60		1.72	1.1934	-0.5266	1.1259	0.5941
61		1.89	1.8581	-0.0319	1.6509	0.2391

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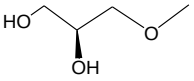
62		1.77	1.7266	-0.0434	1.7266	0.0434

*The compounds of the testing set.

[a]The predicted pIC_{50}

[b]Residue =log(*Pred.*)-log(*Exp.*)

3. Results and discussion

3.1. Calculation Result of HM

For all the compounds, the CODESSA program fully calculated 354 descriptors. HM was used to select the most relevant descriptor for a set of IC_{50}. Then, a linear model is established for descriptors. The quality of the correlation was tested by the R^2, R^2_{CV}, and the S^2. With the growing of number of R^2 and R^2_{CV} improved, S^2 is decreasing yet.

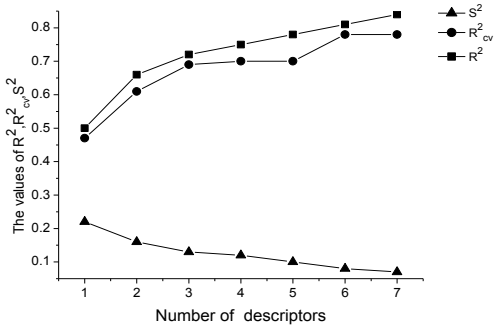


Figure 2: Influence of the number of descriptors on the correlation coefficient, the cross-validation correlation coefficient and the square error.

The details of five descriptors are given in Table 2.

The correlation of descriptors is shown in table 3, which shows that the correlation coefficients of any two descriptors are less than 0.8, indicating that they are independent of each other.

The linear equation model, based on these description parameters, is shown below:

pIC_{50}=0.45261MPCNA+0.013488HDSA-1+0.13231 MAOEP-0.34435MVC-4.1104YZS/YZR

According to the absolute value of the coefficient in the equation, the influence of the descriptors to pIC_{50} of the compound is in the order of YZS/YZR>MPCNA>MVC>MAOEP>HDSA.

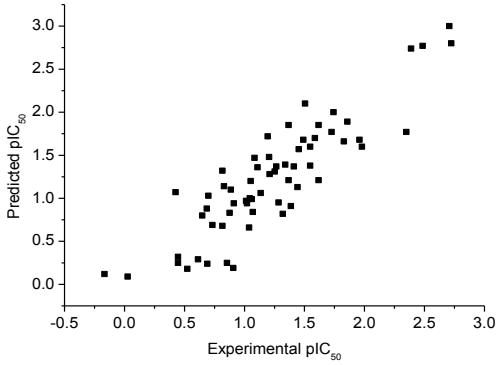


Figure 3: Plot of experimental and calculated pIC50 by HM

MPCNA(Max partial charge for N atom [Zefirov' s PC]) in the construction of ionic surfactant critical micelle concentration model often has a good performance, which provides molecular maximum weighted partial charge, polarity parameters, charge some molecular surface area descriptors. MPCNA has a positive coefficient in model, and it has a negative correlation with IC_{50}. The value of enlargement of polarity parameters lead to decrease of the value of IC_{50}.

Table 2 The physicochemical meaning and statistical parameters

Symbol	Physical-chemical Meaning	Coefficient	T-test
MPCNA	Max partial charge for a N atom [Zefirov's PC]	4.5261e+01	5.6100
HDSA	HA dependent HDSA-1 [Zefirov's PC]	1.3488e-02	6.9299
MAOEP	Max atomic orbital electronic population	1.3231e+01	4.3147
MVC	Min valency of a C atom	-3.4435e+01	-3.8280
YZA/YZR	YZ Shadow / YZ Rectangle	-4.1104e+00	-3.1308

Table 3 Correlation matrix of the descriptors in the model

	MPCNA	HDSA-1	MAOEP	MVC	YZS/YZR
MPCNA	1.000	0.213	0.162	-0.412	-0.612
HDSA-1		1.000	-0.255	-0.058	-0.137

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MAOEP	1.000	0.136	0.092
MVC		1.000	-0.016
YZS/YZR			1.000

HDSA-1 is a quantum chemical descriptor. Hydrogen bond donor and acceptor groups are important for the binding of substrate to the enzyme. HA-dependent HDSA-1 means H-bond acceptor-dependent hydrogen-bonding donor surface area[24]. Increasing the hydrogen-bonding donor surface area leads to increase affinity, so that the value of IC_{50} will decrease. Meanwhile, that decreasing the hydrogen-bonding charged surface area (HDCA) will increase.

Table 4 Parameters for the simple symbolic regression problem

Parameter Names	Values
Number of Chromosomes	100
Head Size	8
Number of Genes	5
Generations without Change	200
Number of Tries	3
Max. Complexity	5
Selection Range	100
Precision	0.01
0/1 Rounding Threshold	0.1
Mutation	0.044
Inversion	0.1
IS Transposition	0.1
RIS Transposition	0.1
One-Point Recombination	0.3
Two-Point Recombination	0.3
Gene Recombination	0.1
Gene Transposition	0.1
Constants per Gene	10
RNC Mutation	0.01
Dc Mutation	0.044
Dc Inversion	0.1
Dc IS Transposition	0.1

A given atomic species of max atomic orbital electronic population (MAOEP) is another simplified exponent for describing molecular nucleophilicity. MAOEP has positive coefficients on the model and plays a negative role in the value of IC_{50}. The properties of nucleophiles play a key role in the compounds[25]. The good nucleophilicity of the compound promotes the activity of the inhibitor. Substituting base Hydrophlic for protein synthesis of amine reaction is always led to high levels of p38α kinase, so as a result, it has a negative correlation with IC_{50}.

Min valency of C atom has a minus coefficient in model, and it plays positive effects on the value of IC_{50}. Min valency of C atom is a charge type descriptor, which can affect on electron affinity of the molecule. Electron affinity of the molecule of the molecule can contribute to the activity of the inhibitors.

The value of the YZ shadow/YZ rectangle descriptor can be used to estimate size, shape, and orientation of repellent molecules in the space along the principle moments of inertia along the Y and Z-axes[26]. These structural characteristics are important when hydrophobic and steric interactions are available between the repellent and the chemoreceptor[27]. YZ shadow/YZ rectangle descriptor has a minus coefficient in model, and it plays positive effects on the value of IC50.

The APS software presents the model results in the form of the expression tree, and the GEP nonlinear equation model for the expression tree is shown below:

Y=sin{2.1256*cos[Sin(d1+2.1256)+2.1256/d4]}+Sin[Cos(d3/d0+d1*d2)]+d2/[Cosd1/(d2/7.1050)+Sind1*d1]+Sin[(Cosd3-Cos5.8499)*(lnd1/(d3-d2)]+Sin[(d0*d4-d2)/(d4+2.3730)/Sind0]

d0, d1, d2, d3, and d4 represent variables of MPCNA, HDSA, MAOEP, MVC and YZS/YZR, respectively.

HM and GEP algorithm have strong predictive ability. From the analysis and comparison of results, GEP algorithm is better than HM. The QSAR model established by GEP algorithm belongs to the nonlinear function, and it needs to be complex in the linear simple function established by HM. Combining the thought of gene mutation, recombination and inversion with function operation, although the GEP operation is more complex and difficult to operate, the satisfactory results can be obtained after most optimization.

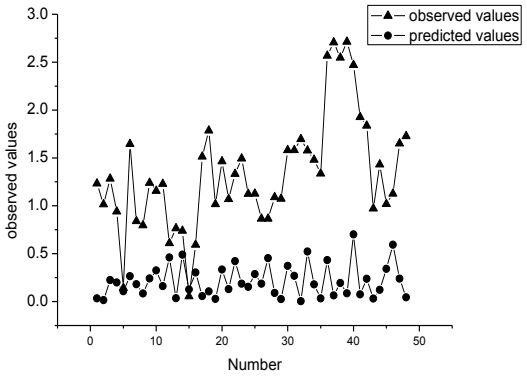

Figure 4: Fitting curve of experimental and calculated IC_{50} in training set by GEP.

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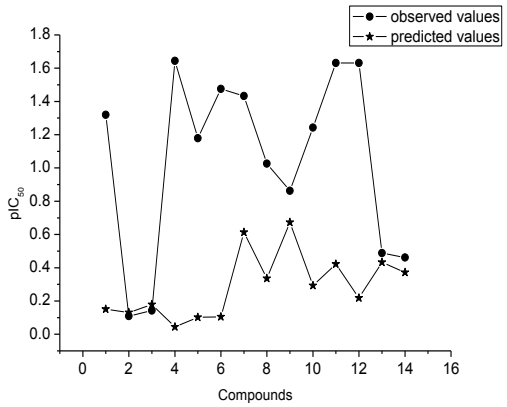

Figure 5: Fitting curve of experimental and calculated IC_{50} in testing set by GEP.

4. Conclusion

The result of this work is excellent. Compared with HM, GEP build a more accurate prediction model. And the study can confirm some pivotal factors that influence the value of IC_{50} and draw some new drugs. For example, compared compound 4 with compound 6, compound 4 increases a nitrogen atom, whose pIC_{50} increases, and compared compound 1 with compound 3, the nucleophilicity of compound 1 is stronger, whose pIC_{50} increases. The inhibitors and selected which have a good value of IC_{50} and have a further observation of them in vivo. It will save lots of energy and resources.

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