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QSAR models of Celecoxib analogues and derivatives as COX-2 inhibitor to predict their anti-inflammatory effect

Chen Chen, Hongzong Si*

Abstract: Celecoxib is a new generation of non-steroidal anti-inflammatory drugs. It can inhibit the production of prostaglandins (PG) by selectively inhibiting cyclooxygenase-2 (COX-2), so as to achieve the effect of anti-inflammatory and analgesic. In this study, we used quantitative structure-activity relationship (QSAR) model to predict the IC50 values of those compounds and indicate their anti-inflammatory effect. The CODESSA program was utilized to calculate all the 63 compounds which came from four literatures, and established linear models as well. In the linear QSAR model, R^2、R^2cv、S^2 were selected for model evaluation, and their values in each group were calculated, respectively. Moreover, we divided all these compounds into training set and test set randomly, and established nonlinear model by the gene expression programming (GEP) method, R^2 and MSE were calculated respectively. As a result, in the training set, R^2 and MSE were 0.93,0.04 in Group 1, 0.91, 0.002 in Group 2, 0.73, 0.03 in Group 3, 0.85,0.004 in Group 4.In the test set, R^2 and MSE were 0.74, 1.12 in Group 1, 0.85, 0.14 in Group 2, 0.64, 0.02 in Group 3, 0.727, 0.01 in Group 4. Ultimately, we found that the consequence of nonlinear model is better than that of linear model in each group. Hence, nonlinear model was supposed the development of these compounds as COX-2 inhibitor.

Keywords: Celecoxib analogues and derivatives; Quantitative structure-activity relationship; Heuristic method; Gene expression programming

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1. Introduction

Inflammation is a multifarious occurrence concerning humoral and cellular reactions through innumerable inflammatory mediators[1]. This process is exaggerated and induced by several stimuli as microbial infection or tissue injuries[2], which can occur in various parts of the body and often accompanied by systemic reactions such as pyrexia and leukocytosis.

Non-steroidal anti-inflammatory drugs (NSAIDs), constitute one of the most widely prescribed drugs for treatment of inflammation, pain and pyrexia. The exert action through non selective inhibition of both constitutive COX-1 and inducible COX-2 enzymes that catalyze the first two steps of prostaglandin biosynthesis from arachidonic acid[3]. Daily, over 30 million people with inflammatory symptoms are estimated for NSAIDs [4]. Celecoxib is a highly selective COX-2 inhibitor, which is rapidly absorbed by oral administration and the bioavailability is about 99%. After absorption, it is widely distributed in all tissues of the body, and is oxidized and metabolized in the liver. The methyl group in the benzene ring is hydroxylated and carboxylated, which is finally combined with glucuronic acid and excreted in urine[5]. The facts have proved that it provides excellent efficacy as an analgesic and anti-inflammatory drug. However, a five-year analysis indicates that celecoxib is associated with an elevated risk for cardiovascular and thrombotic adverse events, particularly in patients with preexisting atherosclerotic heart disease[6]. Therefore, it's necessary to develop some new drugs.

Obviously, it's a large workload to develop a new drug. Therefore, we can analyze the structure of compounds to provide help for the development of new drugs. Quantitative structure–activity relationship (QSAR) model is a mathematical method that can be used to evaluate the property of a compound from its physiochemical properties of molecular structures, and it can be used for drugs by screening and mechanistic understanding of drug action. This technique has many advantages, such as lower-cost and higher speed, even can be used to evaluate drug candidates that have not been synthesized[7, 8]. The steps of establishing a model include collecting data, selecting descriptors and establishing a model. In this study, we first established a linear model by the HM, and then established a nonlinear model by the GEP, after that we combined the two models together to evaluate the application value of new drugs.

2. Experiment

2.1. Data collection

The first step of QSAR research is to collect data. 63 compounds and the IC50 values were obtained from the four literatures [5, 9-11] and listed in Table 1. We further took logarithm of these values (Table 1). Moreover, according to an approximate proportion of 1:2, we randomly separated all these data set into raining set and test set, respectively. The training set was used to build,

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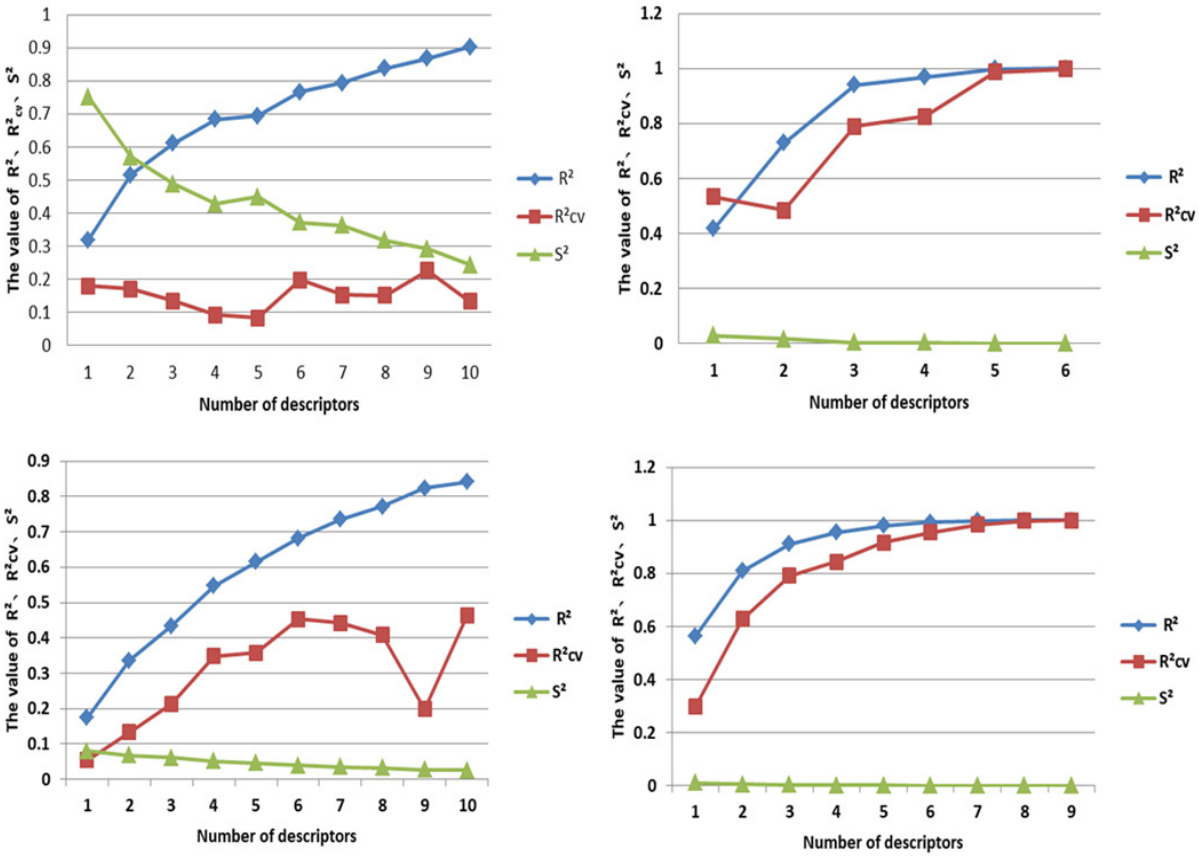

Figure 1. Influence of the number of descriptors on the R²、R²cv and S² in groups 1-4

train and optimize the model, while the test set was used to evaluate the predictive ability of the model.

*The compounds of test set

2.2. Calculation of the descriptors

Descriptors are the mathematical representation of a molecule, which can be contained different sources of chemical information transformed and coded to deal with chemical, biological and pharmacological problems[12]. In this study, we drew all the 63 chemical structures in the Chemdraw software, and then these molecular structures were imported into the Hyperchem software for optimization. In order to achieve the lowest energy steady state of each compound, semi-empirical AM1 or PM3 methods were used for precise optimization. After that, we got the .ARC, .END and .MNO files of each structure by employing MOPAC6.0 program. Ultimately, the exported files were submitted to the software CODESSA so as to set up an equation which was helpful to do the subsequent prediction

2.3. The linear model building by heuristic method

In order to enable descriptors to better reflect the relationship between chemical structure and biological activity, it is necessary to select descriptors to reduce the unrepresentative descriptors to increase the accuracy of the results. The HM implemented in CODESSA soft ware is used to calculate molecular descriptors and build linear models. The criteria for model evaluation are regression coefficient (R^2), cross-validation regression coefficients (R^2cv), standard deviation (S^2) and the F-test value, the t-test value. Due to different research methods of each literature, we selected the descriptors of these compounds which from different literatures respectively.

2.4. The nonlinear model building by gene expression programming

Gene expression programming (GEP) is a method to develop computer programs and mathematical equations based on evolutionary algorithms. GEP encodes complicated expressions as linear strings of fixed length, which are called genomes or chromosomes, and can be converted to nonlinear solutions expressed as Expression Trees (ETs) with different sizes and shapes[13]. In the meantime, regression coefficient (R^2) and mean-square error (MSE) were used as a criterion for evaluating models. After plenty of operations, the algorithm can

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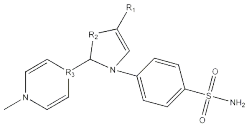
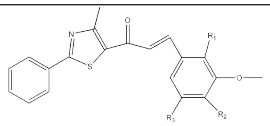
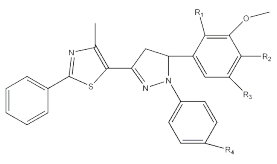
Table 1 The log(IC50) values of compounds

Group	Compound						log(IC50)
	infrastructure	No.	R1	R2	R3	R4	
1		1a*	$-CH_3$	N	C		0.987
		1b	$-CH_3$	N	N		-1.213
		1c	$-CH_3$	O	C		-1.239
		1d*	$-CH_3$	O	N		-1.304
		1e	$-CH_3$	S	C		-0.185
		1f*	$-CH_3$	S	N		-1.216
		1g	$-CF_3$	N	C		-0.257
		1h	$-CF_3$	N	N		1.310
		1i*	$-CF_3$	O	C		1.276
		1j	$-CF_3$	O	N		-0.104
		1k	$-CF_3$	S	C		-0.907
		1l*	$-CF_3$	S	N		1.101
		1m	$-CCl_3$	N	C		-1.082
		1n	$-CCl_3$	N	N		-1.164
		1o	$-CCl_3$	O	C		-1.136
		1p*	$-CCl_3$	O	N		1.004
		1q	$-CCl_3$	S	C		-1.103
		1r	$-CCl_3$	S	N		-1.063
2		2a	OCH_3	H	H		-0.276
		2b*	H	OCH_3	H		0.131
		2c	H	OCH_3	OCH_3		-0.164
		3a	O	H	H	SO_2CH_3	-0.090
		3b*	H	OCH_3	H	SO_2CH_3	-0.462
		3c	H	OCH_3	OCH_3	SO_2CH_3	-0.297
		3d	OCH_3	H	H	SO_2NH_2	-0.507
		3e*	H	OCH_3	H	SO_2NH_2	-0.375
		3f	H	OCH_3	OCH_3	SO_2NH_2	-0.057

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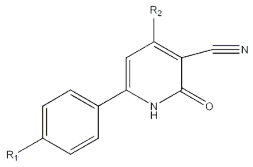
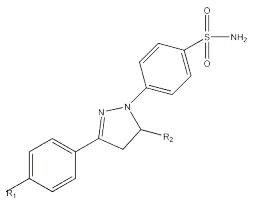
3		4a*	NO_2	C_6H_5		-0.580
		4b	NO_2	$4\text{-}CH_3\text{-}C_6H_4$		-0.462
		4c	NO_2	$4\text{-}Cl\text{-}C_6H_4$		-0.863
		4d	NO_2	$4\text{-}F\text{-}C_6H_4$		-0.663
		4e*	NO_2	$2\text{-}C_4H_3O$		-0.079
		4f	NO_2	$2\text{-}C_4H_3S$		0.060
		4g	$CH_2CH(CH_3)_2$	C_6H_5		-0.531
		4h*	$CH_2CH(CH_3)_2$	$4\text{-}CH_3\text{-}C_6H_4$		-0.431
		4i	$CH_2CH(CH_3)_2$	$4\text{-}Cl\text{-}C_6H_4$		-0.708
		4j	$CH_2CH(CH_3)_2$	$4\text{-}F\text{-}C_6H_4$		0.032
		4k	$CH_2CH(CH_3)_2$	$2\text{-}C_4H_3O$		-0.045
		4l*	$CH_2CH(CH_3)_2$	$2\text{-}C_4H_3S$		-0.568
		4m	$NHSO_2CH_3$	C_6H_5		-0.204
		4n	$NHSO_2CH_3$	$4\text{-}CH_3\text{-}C_6H_4$		-0.114
		4o	$NHSO_2CH_3$	$4\text{-}Cl\text{-}C_6H_4$		-0.531
		4p*	$NHSO_2CH_3$	$4\text{-}F\text{-}C_6H_4$		-0.398
		4q	$NHSO_2CH_3$	$2\text{-}C_4H_3O$		-0.462
		4r	$NHSO_2CH_3$	$2\text{-}C_4H_3S$		-1.009
		6a	$NHSO_2CH_3$	C_6H_5		-0.114
		6b*	$NHSO_2CH_3$	$4\text{-}CH_3\text{-}C_6H_4$		-0.875
		6c	$NHSO_2CH_3$	$4\text{-}Cl\text{-}C_6H_4$		-0.380
		6d*	$NHSO_2CH_3$	$4\text{-}F\text{-}C_6H_4$		-0.591
		6e	$NHSO_2CH_3$			-0.544
		6f	$NHSO_2CH_3$			-0.892

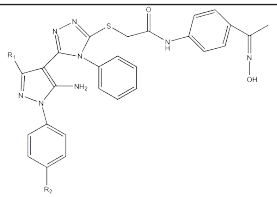
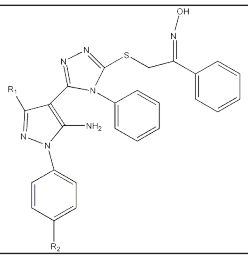
4		16a	H	H		-0.274
		16b	H	SO_2NH_2		0.260
		16c*	H	SO_2CH_3		0.032
		16d	CH_3	H		-0.045
		16e	CH_3	SO_2NH_2		0.215
		16f*	CH_3	SO_2CH_3		0.009
		19a	H	H		0.056
		19b	H	SO_2NH_2		0.041
		19c*	H	SO_2CH_3		0.237
		19d	CH_3	H		0.092
		19e	CH_3	SO_2NH_2		0.051
		19f*	CH_3	SO_2CH_3		0.208

Table2. Selected descriptors and statistical parameters of group 1-4

	Descriptors	Physical-Chemical meaning	Coefficient	DX	t-test
Group1	Constant	Intercept	-9.3301e+00	2.0520e+00	-4.5468
	WNSA-3(x1)	WNSA-3 Weighted PNSA (PNSA3*TMSA/1000) [Quantum-Chemical PC]	-1.2832e-01	3.2101e-02	-3.9973
	MBOCA(x2)	Min bond order of a C atom	3.8962e+00	1.2975e+00	3.0029
	MEROA(x3)	Max electroph. react. index for a O atom	2.7498e+03	1.4742e+03	1.8654
Group2	Constant	Intercept	-2.9913e-01	6.3502e-02	-4.7106
	MNROA(x1)	Min nucleoph. react. index for a O atom	2.2097e+03	9.8633e+02	2.2403
Group3	Constant	Intercept	-2.4639e+01	6.6693e+00	-3.6944
	HDCA(x1)	HDCA H-donors charged surface area [Quantum-Chemical PC]	7.7194e-02	1.7643e-02	4.3753
	MCICNB(x2)	Min coulombic interaction for a C-N bond	-1.2754e-01	4.8080e-02	-2.6527
	MBCMO(x3)	Max bonding contribution of a MO	6.9899e+00	2.0191e+00	3.4618
	MEECHB(x4)	Max exchange energy for a C-H bond	1.7964e+00	6.1205e-01	2.9350
	RNCS(x5)	RNCS Relative negative charged SA (SAMNEG*RNCG) [Zefirov's PC]	3.4245e-02	1.6444e-02	2.0825
Group4	Constant	Intercept	3.5850e+01	6.7157e+00	5.3382
	MRECSB(x1)	Min resonance energy for a C-S bond	-3.6695e+00	6.8033e-01	-5.3937
	HAHDCA(x2)	HA dependent HDCA-2/ SQRT(TMSA) [Quantum-Chemical PC]	6.1327e+00	1.2275e+00	4.9960

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Table 3. The correlation coefficients R^2、R^2cv、S^2

	R^2	R^2cv	S^2
Group 1	0.6115	0.1349	0.4889
Group 2	0.4176	0.5325	0.0285
Group 3	0.6152	0.3577	0.0456
Group 4	0.8087	0.6268	0.0051

find an optimal solution.

3. Results

3.1 Results of HM

By calculating, more than 500 descriptors in total of these compounds were obtained in the project CODESSA. In order to find the best linear model, we need choose the appropriate number of descriptors to describe the activity of log(IC50) value of these compounds.HM was used to process these structural parameters, and constructed linear model with several descriptors respectively. The R^2、R^2cv、$S^2$of these models are shown in Figure 1.

According to this figure, we can see that with the increasing of the number of descriptors, $R^2$and R^2cv will increase, while S^2will decrease. Obviously, if a new descriptor was added, there was no obvious change in the statistical results, which indicated that the appropriate number of descriptors was reached. Compounds from these four groups, we selected 3, 1, 5 and 2 descriptors by screening as the best linear model (Figure 2). The details of these descriptors are listed in Table 2. And the correlation coefficients R^2、R^2cv、S^2 in the heuristic method are list in Table 3.

From Table 2, we can get the four mathematical formulas which are able to demonstrate the linear model built by these descriptors. They are follows:

Group 1: Log (IC50)=-9.330-0.128WNSA+3.896MBOCA+2749.8MEROA

Group 2: Log (IC50)=-0.299+2209.7MNROA

Group 3: Log (IC50)=-24.639+0.077HDCA-0.128MCICNB+6.99MBCMO+1.796MEECHB+0.034RNCS

Group 4: Log (IC50)=35.85-3.67MRECSB+6.133HAHDCA

As can be seen from Table 3, the consequence of group 4 is relatively more ideal where R2=0.8087, R^2cv=0.6268 and S^2=0.0051. For the rest, the correlation coefficients calculated by HM method are not satisfactory for all these compounds of different origins.

Table 4.The number of compounds in each training set and test set and the value of R2, MSE and the mathematical formula of log(IC50)

	training set			test set			mathematical formula
	Number	R2	MSE	Number	R2	MSE	
Group 1	12	0.932	0.038	6	0.735	1.119	Log(IC50)=sqrt(x2)+cos(x1+(cos(x1-x2)/cos1))+(cos(1/x3))*x2)+x3+cos（(cos(sqrt(x2))+x2*x1+sqrt(cos(x2))）
Group 2	6	0.914	0.002	3	0.851	0.140	Log(IC50)=lg(cos(cos((cos(cos1)/x1))))+lg(cos(cos(lg2x1+lg(cos(cos((2lgx1)/x1)))+2x1*lgx1-3x1
Group 3	17	0.729	0.034	7	0.642	0.023	Log(IC50)=(sin((((x5+x2)/sin(x3))+x5))/x4)+(sin((x2*((x4*x3)/log(x5))))/x2)+2x1-2x1/x3+(sin(sin(sin(x4)))-x1)
Group 4	8	0.849	0.004	4	0.727	0.007	Log(IC50)=x2+2lg(exp(lg(x2)))+(lg(lg(x1)))*(x2-x1)*x1+x2+exp(x2*x1)*(x2*x1)/((x1*x1)-2x1)

3.2. Results of GEP

In order to receive a more accurate model, we put all the datasets into the program automatic problem solver (APS) with the selected descriptors to establish a nonlinear model. Table 4 displayed the number of compounds in each training set and test set and the mathematical formula of log(IC50) of the model. Moreover, Table 8 showed the parameters for the simple symbolic regression problem.

x1-x5:The descriptors in the Table 2.From Table 4, it can be seen that $R^2$is relatively high and MSE is relatively low in both the training set and the test set.

4. Discussion

By establishing the QSAR model, we can carry out in-depth analysis. In the linear models, R^2, R^2cv and S2 were used as criterion to evaluate the model. In

Table 5.The parameter setting for GEP

Parameter names	Values			
	Group 1	Group 2	Group 3	Group 4
Number of chromosomes	50	50	100	50
Function set	"+","-","*","/", "Sqrt","Inv","Cos"	"+","-","*","/", "Pow10","Log","Cos"	"+", "-","*","/", "Ln", "Sin"	"+","-","*","/", "Exp","Log"
Number of genes	5	5	5	5
Gene head size	8	8	8	8
Linking function	"+"	"+"	"+"	"+"
Mutation rate	0.044	0.044	0.044	0.044
1-Point recombination rate	0.3	0.3	0.3	0.3
2-Point recombination rate	0.3	0.3	0.3	0.3
Gene recombination rate	0.1	0.1	0.1	0.1
IS transposition rate	0.1	0.1	0.1	0.1
RIS transposition rate	0.1	0.1	0.1	0.1
Gene transposition rate	0.1	0.1	0.1	0.1
Selection range	100	100	100	100
Precision	0.01	0.01	0.01	0.01

general, the larger R^2 and R^2cv is, the smaller S2 is, and the better the fitting degree of the model is [14]. Obviously, the consequence of the linear models is not satisfactory. Therefore, linear models are not enough to find their correlation and a nonlinear model is needed. In the nonlinear model, we selected $R^2$and MSE as the evaluation criteria of the model. Consequently, the result calculated by GEP method is clearly better, which means the fitting ability of the GEP method is more prominent.

The half maximal inhibitory concentration (IC50) is a measure of the efficacy of a substance in inhibiting a specific biological or biochemical process. For a drug, IC50 represents the concentration of a drug that is required for 50% inhibition of activity of its targeted enzyme in vitro[15]. Therefore, a lower IC50 value means a higher activity of the derivatives and analogues. Of all the descriptors, the coefficients of WNSA-3, MCICNB and MRECSB are negative, while the other coefficients are positive, which implies that the three descriptors have a positive effect on the activity of the compound, while the others have a negative effect.

In order to better understand the factors that affect log（IC50）, we discussed descriptors more deeply. Based on the absolute values of the coefficients in each equation, these descriptors can be ranked high to low within each group, the result is MEROA> MBOCA>WNSA-3, MNROA, MBCMO> MEECHB> MCICNB> HDCA> RNCS, HAHDCA>MRECSB. And next is a discussion about the effects of these descriptors on the activities of all compounds.

In Group 1, WNSA-3 is responsible for the representation of polar interactions between molecules which are generally calculated from the contribution related to the atomic partial charge and the molecular-accessible surface area[16]. MBOCA indicated the bond length of C atom would decrease the activity of compounds. MEROA is Max electroph. react. index for a O atom. Maximum electrophilic reactivity index for an O atom measures the stabilization energy when the molecule gains an additional electronic charge. A positive sign of the regression coefficient would imply a stronger electrophile exhibiting higher inhibitory effect[17].

In Group 2, MNROA is Min nucleoph. react. index for a O atom, which belongs to the charge distribution–related descriptors of the quantum chemical descriptors group, estimates the relative reactivity of the O atoms in the molecule for a given series of compounds, and

is related to activation of the corresponding chemical reaction[18], while the positive coefficient for this descriptor indicates that may increase the inhibitory activity of the compounds.

In Group 3, HDCA is H-donor charged surface area which is indicative for hydrogen bonding interactions between fragment and residues[19]. Because the coefficient of HDCA is positively correlated with IC50, this interaction will increase the value of IC50. MCICNB indicated that reducing coulombic interaction for a C-N bond would decrease the activity of compounds in the experiment. MBCMO is Max bonding contribution of a MO. B. Due to the positive correlation of MBCMO to IC50, higher value of this descriptor and a better IC50 value can be obtained. MEECHB is Max exchange energy for a C-H bond. When a suitable stimulus is applied, a compound could perform a bond exchange reaction (BER), when an active unit replaces a unit in an existing bond to form a new bond[20]. Obviously max exchange energy for a C-H bond will increase the value of IC50 of these compounds. RNCS is Relative negative charged SA. It is an electrostatic descriptor and it deals with the features responsible for polar interactions between molecules, which is sensitive to both the size and the charge of the molecule[21] . Thus, this descriptor will also affect the activity of compounds.

In Group4, MRECSB is Min resonance energy for a C-S bond related to the energy of quantum mechanics[22]. Because MRECSB and IC50 are negatively correlated, as MRECSB increases, IC50 decreases. HAHDCA is the ratio of the sum of solvent-accessible surface area of H-bonding acceptor atoms to the total solvent-accessible molecular surface area, which is connected to the hydrogen bonding-acceptor ability of the molecule[23]. Therefore, HAHDCA has an impact on the activity of compounds.

All of the descriptors indicated that the physical properties of drugs are the key factors for the construction of QSAR models and their prediction.

5. Conclusion

In summary, two different QSAR models were established for 63 celecoxib analogues and derivatives to predict their biological activities as COX-2 inhibitors. Through the comparison between HM linear analysis and GEP nonlinear analysis, it can be seen that the nonlinear result is obviously better than the linear result, so GEP may have higher efficiency and development potential in data processing capability. In addition, by analyzing all the descriptors, it can be known that higher WNSA-3 and lower MBOCA, MEROA in Group 1, lower MNROA in Group 2, higher MCICNB and lower HDCA, MBCMO, MEECHB, RNCS in Group 3, higher MRECSB and lower HAHDCA in Group 4 are beneficial to the improvement of drug activity. It is hoped that the above model can provide guidance for the future drug design and modification of related new drugs.

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