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QSAR of Cyclooxygenase–2 (COX–2) Inhibition by 2,3–Diarylcyclopentenones Based on MEDV–13

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QSAR of Cyclooxygenase–2 (COX–2) Inhibition by 2,3–Diarylcyclopentenones Based on MEDV–13[#]

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Abstract

A molecular electronegativity distance vector based on 13 atomic types (MEDV–13) is employed to describe the chemical structures of a series of selective cyclooxygenase–2 (COX–2) inhibitors, 2,3–diarylcyclopentenones (DAPs) including rofecoxib (MK–0966) and celecoxib (SC–58635), and develop the quantitative structure–activity relationships (QSAR) between the MEDV–13 descriptors and the biological activities (pIC₅₀) of the inhibitory molecules. Using multiple linear regression (MLR), a 4–variable linear model for the training set of 18 DAPs is developed, with the correlation coefficient and the root mean square error 0.9798 and 0.137 in calibration and 0.9539 and 0.209 in leave–one–out prediction, respectively.

Keywords. Molecular electronegativity distance vector (MEDV–13); selective cyclooxygenase–2 (COX–2) inhibitor; 2,3–diarylcyclopentenones; QSAR.

1 INTRODUCTION

It is known that there are two isoforms of cyclooxygenase (COX), each with a distinct physiological role [1–2]. One isoform, COX–1, is constitutively produced in a variety of tissues and appears to be important in the maintenance of normal physiological functions including gastric cytoprotection. The second isoform, COX–2, is induced by a wide variety of inflammatory stimuli and appears to be largely responsible for the high–level production of prostaglandins that results in inflammation [3]. A nonsteroidal anti–inflammatory drug (NSAID) that inhibits COX–2 while sparing COX–1 has the potential to be anti–inflammatory yet nontoxic to the gastrointestinal tract.

[#] Dedicated to Professor Milan Randić on the occasion of the 70th birthday.

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In the last several years, extensive libraries of selective COX-2 inhibitors have been developed by different laboratories. However, quantitative structure-activity relationship (QSAR) studies related to the selective COX-2 inhibitors only appeared in a few literatures [4-12]. Recently, several molecular descriptors based on the two-dimensional topological structure of molecules have been defined and tested in QSAR models [13-20]. In our previous paper [12], a molecular electronegativity distance vector based on 13 atomic types (MEDV-13) was employed to derive a QSAR model between inhibiting COX-2 activity and structural characteristics of indomethacin and its amides and esters (ImAE). The MEDV-13 descriptors [21-22] were combined with principal component regression (PCR). In this paper, the MEDV-13 is used for QSAR study of a set of 2,3-diarylcyclopentenones (DAPs), a series of selective COX-2 inhibitors. It is well known that a QSAR model developed by PCR technique is in general a latent model. So, in order to build a more explicit QSAR model than PCR model, a combinatory MEDV-GA-MLR method proposed in our previous paper [23] will be used in the present study. A genetic algorithm (GA) program is employed to select an optimal subset from the original MEDV-13 descriptor set. In the second step, general multiple linear regression (MLR) is used to develop a QSAR model.

2 MATERIALS AND METHODS

2.1 Data Set

A data set containing 24 compounds with inhibitory activity against the COX-2 inducible isoform was collected for this QSAR study. All values are expressed in terms of pIC_{50} or $\log 1/\text{IC}_{50}$ where IC_{50} represents the drug concentration that inhibits 50% of activity. All the IC_{50} values in unit of μM refer to the time-dependant COX-2 inhibition and are average values from duplicate experiments. These compounds include MK-0966, SC-58635 and twenty-two 2,3-diarylcyclopentenones (DAPs) whose chemical structures are presented in Figure 1 and Table 3. To examine the predictive ability of the QSAR model, six inhibitors of (from **19** to **24**) are selected from 24 DAP compounds to construct a testing set or predictive set and the remaining 18 inhibitors acting as a training set (M1) are employed to calibrate the QSAR model.

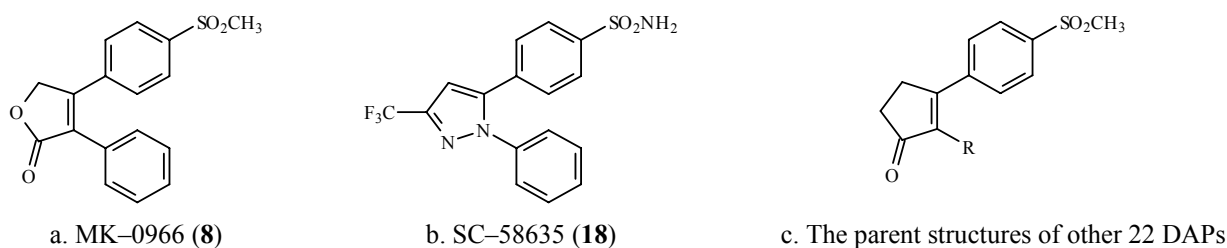


Figure 1. The skeleton structures of the 24 DAP derivatives.

2.2 Molecular Descriptors and Primary Variable Selection

The structures of all 24 inhibitors (DAPs) against the COX-2 are described by the molecular electronegativity distance vector based on 13 atomic types, MEDV-13, developed in our previous papers [21–22]. From the literature [21], the relative electronegativity, q , of a non-hydrogen atom was calculated using the atomic types, atomic attributes and intrinsic state (I) of the atom defined in the literature. The values of 13 atomic types, 43 atomic attributes and 43 intrinsic state (I) for various non-hydrogen atoms located in different molecular chemical environments (substructures) are summarized in Table 1. The relative electronegativity for the i th non-hydrogen atom, q_i , is obtained with the formula:

$$q_i = I_i + \sum_{\substack{\text{all } j \\ j \neq i}} (I_i - I_j) / d_{ij}^2 \quad (1)$$

where d_{ij} is the shortest graph distance between two atoms i and j . Then, the molecular electronegativity distance vector descriptors based on 13 atomic types (MEDV-13), x_{kl} , are calculated with the equation:

$$x_v = x_{kl} = \sum_{i \in k, j \in l} \frac{q_i q_j}{d_{ij}^2} \quad (k, l = 1, 2, 3, \dots, 13; l \geq k; v = 1, 2, 3, \dots, 91) \quad (2)$$

where k or l is the atomic type of the atom i or j in the molecule. From Eq (2), the MEDV-13 have at best 91 elements (x_v , $v = 1, 2, 3, \dots, 91$) but due to the absence of some atomic types in all molecules used in a QSAR model some x variables have a constant value of zero and, obviously, are not considered in developing the QSAR equation. For the 24 compounds in this paper, there are only 55 nonzero MEDV descriptors (nos. 1, 2, 3, 4, 6, 9, 10, 12, 13, 14, 15, 16, 17, 18, 19, 21, 22, 24, 25, 26, 27, 28, 29, 30, 32, 33, 35, 36, 38, 39, 40, 42, 45, 46, 48, 49, 51, 54, 55, 57, 59, 60, 62, 63, 66, 69, 70, 77, 78, 80, 81, 84, 85, 90 and 91). The descriptors with too many zero values were eliminated from the QSAR analysis.

Table 1. The Atomic Types, Atomic Attributes and Intrinsic State I for Various Non-Hydrogen Atoms^a

atom	type	attribute	I	atom	type	attribute	I	atom	type	attribute	I
-CH ₃	1	1	2.0000	~C≈	3	16	1.8333	≥N=	7	30	2.2361
-CH ₂ -	2	2	1.5000	-OH	9	17	2.4495	-SH	9	31	1.7691
-CH<	3	3	1.3333	-O-	10	18	1.8371	-S-	10	32	1.1567
>C<	4	4	1.2500	=O	9	19	3.6742	=S	9	33	2.3134
=CH ₂	1	5	3.0000	~O	9	20	3.0619	>S=	11	34	1.1340
=CH-	2	6	2.0000	-NH ₂	5	21	2.2361	≥S≤	12	35	1.1227
=C<	3	7	1.6667	-NH-	6	22	1.6771	-F	13	36	2.6458
=C=	2	8	2.5000	>N-	7	23	1.0882	-Cl	13	37	1.9108
≡CH	1	9	4.0000	=NH	5	24	3.3541	-Br	13	38	1.6536
≡C-	2	10	2.5000	=N-	6	25	2.2361	-I	13	39	1.5345
~CH ₂	1	11	2.5000	≡N	5	26	4.4721	-PH ₂	5	40	1.6149
~CH-	2	12	1.7500	~NH	5	27	2.7951	-PH-	6	41	1.0559
~C<	3	13	1.5000	~N-	6	28	1.9566	>P-	7	42	0.8696
~CH~	2	14	2.0000	~N~	6	29	2.2361	≥P<	8	43	0.9006
-C≈	3	15	1.6667								

^a The symbols “~” and “≈” represent one and two conjugated double bonds, respectively

2.3 Optimal Variable Selection Based on the Genetic Algorithm

After the primary selection of variables, the original variable set entering into the optimal variable selection includes 24 MEDV descriptors. Apparently, it is impossible to directly use multiple linear regression (MLR) to construct an effective QSAR model due to the number of independent variables ($m = 24$) being more than the number of compounds in the training set (M1). So, it is essential to select an optimal subset of descriptors from the original descriptor set consisting of 24 MEDV descriptors. A genetic algorithm (GA) program developed in our previous paper [23] is used to search the optimal subset of descriptors. Because many GA methods can only find some optimal subsets while miss the best subset in some cases, the GA procedure must be run in many initial populations. On the other hand, a predictive ability of a model for the external molecules is usually more important than the estimation ability for the internal molecules, so the fitness values in our GA procedure uses the correlation coefficient of predictions (q) obtained in a leave-one-out (LOO) cross-validation (CV) step rather than the correlation coefficient of estimations in the modeling step as a fitness function.

In our GA procedure, the length of the binary bit sub-string (bm) for an anonymous variable (x) is calculated with the formula:

$$bm = \text{int}(\log(1 + (m - 1) \cdot 10^{bt}) / \log(2)) \quad (3)$$

where m refers to the variable number entering into GA analysis and here $m = 24$, and bt is the effective bit number for the integer m (we have used $bt = 2$). The operator *int* makes the value in the bracket an integer. For the sample of 24 DAPs, $bm = 11$. Let the variable number in an optimal subset be Vn , and the length of total binary string for a chromosome equals $Vn \times bm$.

The decoding of a binary sub-string as a variable (x) is performed with the following equation:

$$x = 1 + \text{decimal}(010100100101)_{\text{binary}} \cdot \frac{m - 1}{2^{bm} - 1} \quad (4)$$

To eliminate the correlations between the independent variables, we set the fitness value of an individual to be zero if the absolute value of the correlation coefficient between arbitrary two variables in an individual is more than 0.75.

3 RESULTS AND DISCUSSION

3.1 Best Subset

To examine the correlation between the fitness values and various subsets in the different number of the variables (Vn), it is essential to run the GA procedure many times with the values $Vn = 2, 3, 4, 5, 6, 7$, and 8. Here, the initial operating parameters, the number of the individuals in a population, the crossover and mutation probability in the GA program are set to be 120, 0.75, and

0.01, respectively. For various optimal subsets of Vn equal to 2, 3, 4, 5, 6, 7, and 8, the combination of the variables together with several important statistic parameters such as the root mean square error of estimations (*RMSEE*) and the root mean square error of predictions obtained using leave-one-out (LOO) cross validation procedure (*RMSEP*) are listed in Table 2. In order to identify the best subset from the seven subsets in Table 2, the *RMSEE* and *RMSEP* are plotted versus the number of the variables (Vn) as shown in Figure 2.

Table 2. The Statistic Results of Various Combination of the MEDV Descriptors for the Training Set

Vn	q^2	<i>RMSEP</i>	r^2	<i>RMSEE</i>	F	r_T	<i>RMST</i>	MEDV-13 descriptors
2	0.7387	0.502	0.9240	0.188	91.192	0.9350	0.228	9 62
3	0.7992	0.412	0.9441	0.162	78.819	0.9253	0.241	9 59 62
4	0.9099	0.209	0.9600	0.137	77.938	0.9086	0.261	2 9 21 62
5	0.9364	0.176	0.9617	0.134	60.187	0.9113	0.261	9 21 35 62 77
6	0.9321	0.181	0.9617	0.134	45.996	0.9118	0.260	9 21 25 35 62 77
7	0.9346	0.176	0.9639	0.130	38.148	0.9268	0.234	9 13 21 25 26 62 77
8	0.9341	0.177	0.9690	0.120	35.113	0.9429	0.211	9 13 14 32 35 36 62 81

The results in Table 2 and Figure 2 show that the correlation coefficient in the calibration step (r) monotonically increases for increasing Vn and the correlation coefficient in LOO prediction step (q) gradually increases until a maximum value (approximate 0.934). From the root mean square errors (*RMS*), some similar results can be acquired. With the increase of Vn , *RMSEE* is monotonically decreasing and *RMSEP* gradually decreases until a minimum value (approximate 0.176). The best subset is the combination of 4 descriptors ($Vn = 4$) of nos. x_2 , x_9 , x_{21} , and x_{62} (see Table 3 for their numerical values) due to the almost constant *RMSEE* and *RMSEP* with further increase of Vn .

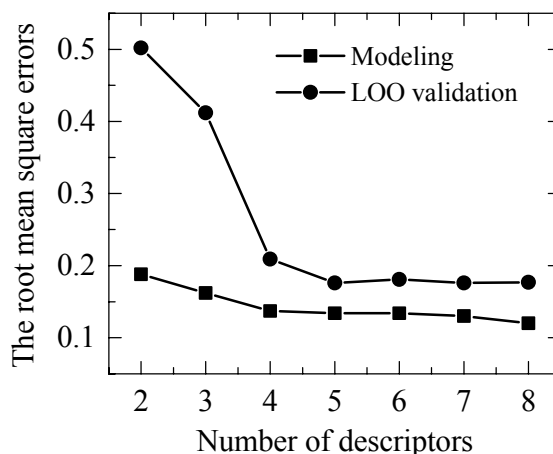


Figure 2. Plot of *RMSEE* and *RMSEP* versus the number of variables.

From the literatures [21–22], the four descriptors in the best subset are closely correlated with five atomic types (k) of various non-hydrogen atoms. The atomic type defined in the literature [21] characterizes the local chemical environment of the atom located in its molecule. For our COX-2 inhibitors under study, the five atomic types (k), $k = 1, 2, 6, 9$ and 12 , reflect the importance of

several substructures, -CH₃ (no. 1), =CH- (no. 2), =N- (no. 6), =O (no. 9), and >S< (no. 12) in the molecules, which are considered to be the main factors affecting the COX-2 inhibitory activity of these molecule.

3.2 Best QSAR Model

The multiple linear regression (MLR) is employed to develop the best QSAR model for the COX-2 inhibitors. The dependent variable in the QSAR model is the pIC₅₀ of 18 inhibitors in the training set (M1) and the independent variables are the optimal MEDV descriptors in the best subset. The model with $r^2 = 0.9600$ and $RMSEE = 0.137$ is shown in the following QSAR equation:

$$\begin{aligned} \text{pIC}_{50} = & (9.1909 \pm 0.5571) - (0.03607 \pm 0.01263) x_2 - (0.3577 \pm 0.0299) x_9 + \\ & + (0.08946 \pm 0.03773) x_{21} + (4.5060 \pm 0.3787) x_{62} \end{aligned} \quad (5)$$

$n = 18, m = 4, r^2 = 0.9600, r = 0.9798, RMSEE = 0.137, F = 77.938$

The r and $RMSEE$ between the pIC₅₀ observed experimentally and the values calculated with Eq (5) are 0.9798 and 0.137, respectively. The calculated pIC₅₀ values are presented in Table 3 together with the observed pIC₅₀ and the optimal descriptors (x_2, x_9, x_{21}, x_{62}) for the 24 COX-2 inhibitors.

Table 3. The Best Descriptors and the Observed and Calculated pIC₅₀ for 24 COX-2 Inhibitors

No	Substituted group (R)	x_2	x_9	x_{21}	x_{62}	Obs. pIC ₅₀	Calc. pIC ₅₀
1	4-bromo-2-pyridyl	2.1652	7.7235	16.0876	-0.2783	6.201	6.535
2	4-methyl-3-pyridyl	5.2994	8.6203	15.8147	-0.2012	6.357	6.424
3	4-chloro-2-pyridyl	2.1549	7.7138	15.9728	-0.2772	6.721	6.534
4	3-pyridyl	2.1889	7.6866	16.7021	-0.1977	6.770	6.966
5	2-pyridyl	2.1736	7.6841	16.3043	-0.2723	6.815	6.595
6	tert-butylacetylenyl	16.7655	9.7537	19.1431	0	6.824	6.810
7	5-chloro-3-pyridyl	2.1701	7.7163	16.3733	-0.2055	7.060	6.891
8	MK-0966	2.2064	7.6715	16.4469	0	7.699	7.838
9	3,5-difluorophenoxy	2.1720	7.7388	15.9607	0	7.770	7.772
10	3,5-difluorophenyl	2.1639	7.7025	16.4254	0	7.824	7.827
11	3-fluoro-4-chlorophenyl	2.1916	7.7246	16.8155	0	7.824	7.853
12	2-benzothiophenyl	2.3060	7.8103	17.7170	0	7.854	7.899
13	3-fluorophenyl	2.2128	7.6999	17.1056	0	7.854	7.887
14	3,5-dichlorophenyl	2.2209	7.7567	17.0775	0	7.854	7.864
15	phenoxy	2.2546	7.7349	17.0015	0	7.959	7.864
16	3-chloro-4-fluorophenyl	2.1947	7.7289	16.8493	0	8.046	7.854
17	phenylacetylenyl	2.3851	7.6359	20.8440	0	8.222	8.238
18	SC-58635	0	0	12.0802	-0.3482	8.699	8.703
19	5-bromo-3-pyridyl	2.1802	7.7260	16.4866	-0.2072	6.523	6.890*
20	4-methoxy-3-pyridyl	3.7938	8.3709	15.8905	-0.2028	6.824	6.567*
21	4-fluorophenyl	2.2239	7.6992	17.3255	0	7.721	7.906*
22	3,4-difluorophenyl	2.1680	7.7017	16.5439	0	7.854	7.838*
23	phenyl	2.2613	7.6973	17.7730	0	7.959	7.946*
24	3,4,5-trichlorophenyl	2.1801	7.7816	16.5006	0	8.222	7.805*

* testing set results predicted by the model using the training set

It has been known that a good QSAR model should possess not only high calibration statistics for the internal molecules but also a high predictive ability for the external molecules. A leave-one-out (LOO) cross-validation procedure is used to test the predictive ability of the QSAR

model from Eq (5). In such a cross-validation experiment involving n molecules, a model is built from all but the first molecule, and this model is used to predict the activity of the first molecule. Then all but the second molecule are used to calibrate a QSAR model that predicts the pIC_{50} for the second molecule, and so on. In this way, each molecule is predicted, as though the system had never seen it before, on the basis of all the other molecules. The result shows a good predictive ability of the model with the $q^2 = 0.9099$, $q = 0.9539$, and $RMSEP = 0.209$ between the pIC_{50} predicted by the LOO procedure and the experimental pIC_{50} .

In order to further validate the stability and predictive ability of the model, the QSAR equation is used to predict the pIC_{50} of six compounds in the testing set and the predicted pIC_{50} results are also listed in Table 3. The predicted pIC_{50} values are then compared with the observed ones. The correlation coefficient (R_p) and the root mean square errors (RMS_p) between the observed pIC_{50} values and the predicted ones are $R_p = 0.9086$ and $RMS_p = 0.261$, respectively.

In conclusion, the above results show that the QSAR model developed in this paper has a high calibration ability and good predictive ability. Figure 3, presenting the plot of the pIC_{50} in calibration or prediction versus the experimental pIC_{50} , sustains this conclusion.

3.3 Variable Correlation

The correlation between the independent variables entering into the final QSAR model is an important characteristic of the model and must be validated. In our GA procedure, the controlling method is that the fitness values are considered to be zero if the correlation coefficient between arbitrary pairs of variables is $r^2 \geq 0.75$. All r values between various pairs of variables in the best set are lower than $r = 0.716$. These inter-correlation coefficients are $r(x_2, x_9) = 0.4618$, $r(x_2, x_{21}) = 0.4315$, $r(x_2, x_{62}) = 0.2175$, $r(x_9, x_{21}) = 0.7151$, $r(x_9, x_{62}) = 0.4730$, and $r(x_{21}, x_{62}) = 0.6191$, which shows that there are no significant correlations between the structural descriptors in the best subset.

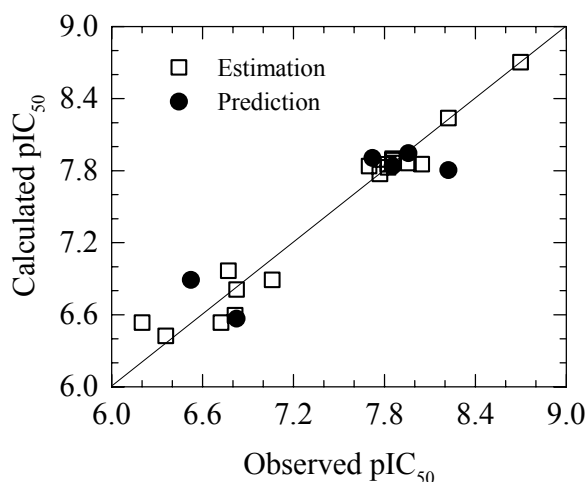


Figure 3. Plot of pIC_{50} Estimated and Predicted versus Observed.

4 CONCLUSIONS

We have described a novel four-variable QSAR model between biological activities expressed by pIC_{50} values and the MEDV-13 for 24 COX-2 inhibitors using the composite QSAR model MEDV-GA-MLR. The results show that model has not only high calibration quality with $r = 0.9798$ and $RMSEE = 0.137$ but also excellent prediction ability with $q = 0.9539$ and $RMSEP = 0.209$ in LOO procedure and $R_p = 0.9086$ and $RMS_p = 0.261$ for the external testing set.

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