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Short communication

Rationalization of physicochemical characters of 1,5-diarylpyrazole analogs as dual (COX-2/LOX-5) inhibitors: A QSAR approach

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Abstract

Arachidonic acid metabolizing enzymes cyclooxygenases and lipoxygenases lead to the formation of various eicosanoids involved in variety of human diseases, like inflammation, fever, pain, rheumatic and osteoarthritis, etc. Non-steroidal anti-inflammatory drugs are useful tools in the treatment of prostaglandin mediated complications. The development of dual inhibitors may prevent a drift of arachidonic acid metabolism towards the other pathway, leading to potential side effects. Hence emphasis was focused on quantification of structure–activity relationship, with a view to delineating the influence of key COX-2/LOX-5 activity, to explore structural insights to aid the designing of safer dual inhibitors. The quantification of the structural features of 1,5-diarylpyrazole analogs with various biological activities gave some important structural insights, i.e. Hy (hydrophilic factor) and Mor17v (3D molecular representation of structure based on electron diffraction code). These two physicochemical properties may be helpful in development of more selective dual COX-2/LOX-5 inhibitors.

Keywords: COX-2; LOX-5; QSAR

1. Introduction

Arachidonic acid metabolizing enzymes cyclooxygenases (COXs) and lipoxygenases (LOXs) lead to the formation of various eicosanoids involved in variety of human diseases, like inflammation, fever, pain, rheumatic and osteoarthritis, etc. [1]. Non-steroidal anti-inflammatory drugs (NSAIDs) are useful tools in the treatment of prostaglandin mediated inflammation, pain, rheumatic and osteoarthritis. Vane [2] proposed that the mechanism of action of NSAIDs through their inhibition of prostaglandin biosynthesis. At the beginning of 1990 two COX isoforms were discovered: [3] one (COX-1) constitutively present in many tissues such as stomach, kidney and platelets and the other (COX-2) cytokine inducible and expressed mainly in a wide range of anti-inflammatory cells. Moreover, dynamically evolving research shows the different roles of LOXs and their metabolites product in inflammation and allergic reaction. The development of dual inhibitors may prevent a drift of arachidonic acid metabolism towards the other pathway, leading to the potential side effects. The QSAR analysis of selective COX-2 inhibitors is the current highly interested area of research in this therapeutic area [4,5]. The emphasis will be focused on quantification of structure function relationship with a view to delineating the influence of key COX-2/LOX-5 activity to explore structure insights to aid the designing of safer dual inhibitors. The quantification of responsible physicochemical properties was done with the help of regression techniques.

2. Experimental

The cyclooxygenase-1, cyclooxygenase-2 and lipoxygenase-5 inhibitory activity data of 1,5-diarylpyrazole derivatives was taken from the reported work of Pommery et al. [6] (Table 1).

Abbreviations: COX-2, cyclooxygenases-2; LOX-5, lipoxygenases-5; QSAR, quantitative structure–activity relationship

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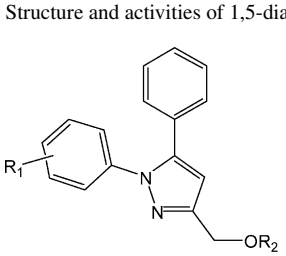
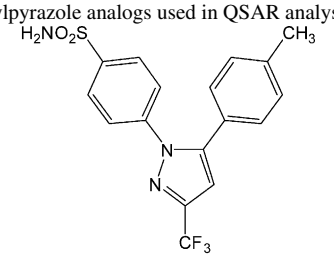
Table 1
Structure and activities of 1,5-diarylpyrazole analogs used in QSAR analysis



Comp. No. 1-19



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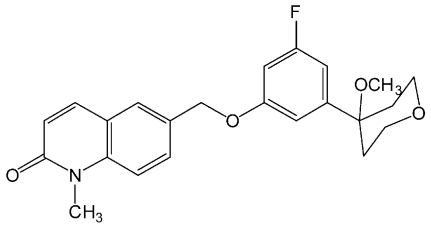


Comp. No. 21

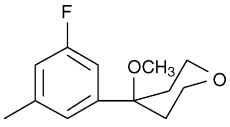
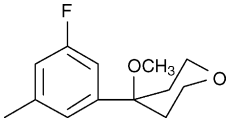
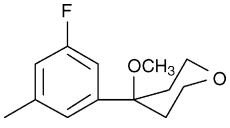
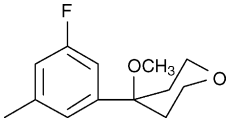
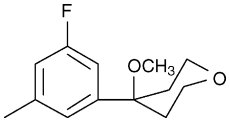
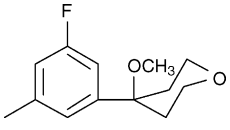
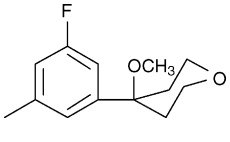
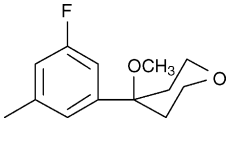
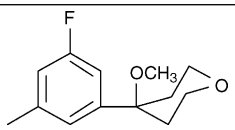
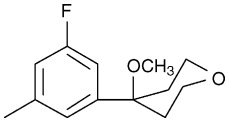
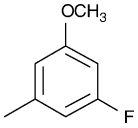
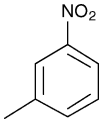
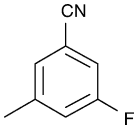
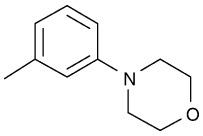
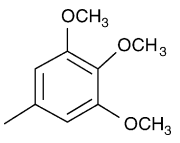
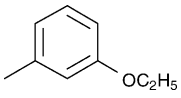
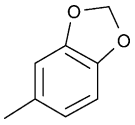
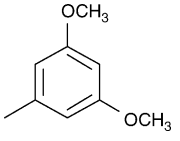
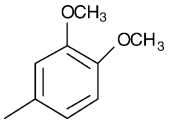
Compound no.	R_1	R_2	IC_{50} (μM)			Selectivity (COX-1/COX-2)
			LOX-5	COX-1	COX-2	
1	4-CH_3SO_2		0.30	26.08	0.045	579
2	4-H		0.57	7.14	0.61	12
3	4-F		0.48	1.13	0.96	1
4	4-Cl		0.83	1.81	0.93	2
5	4-CH_3		0.72	1.56	0.93	1
6	4-OCH_3		0.77	0.036	0.30	0.12
7	4-OCF_3		0.85	ND	0.82	–
8	4-NH_2SO_2		0.74	25.7	0.10	257

Table 1 (*Continued*)

Compound no.	R_1	R_2	IC_{50} (μM)			Selectivity (COX-1/COX-2)
			LOX-5	COX-1	COX-2	
9	4,5-di CH_3		0.76	ND	0.41	–
10	4,5-di Cl		0.80	ND	0.70	–
11	4-CH_3SO_2		>10	44.33	0.31	142
12	4-CH_3SO_2		>10	>100	0.74	>134
13	4-CH_3SO_2		>10	99.56	0.57	176
14	4-CH_3SO_2		>10	38.08	0.92	41
15	4-CH_3SO_2		>10	17.59	0.22	78
16	4-CH_3SO_2		>10	>100	0.90	>112
17	4-CH_3SO_2		>10	15.81	0.45	35
18	4-CH_3SO_2		>10	25.05	0.87	29
19	4-CH_3SO_2		>10	>100	0.70	>142
20	Celecoxib	–	>10	13.5	0.036	375
21	ZD-2138	–	0.083	>100	>100	–

The biological activity data (IC_{50} in μM) was converted to negative logarithmic dose in mole (pIC_{50}) for quantitative structure–activity relationship (QSAR) analysis.

The molecular modeling study was performed using CS ChemOffice [7] version 8.0, and Dragon [8] program while the regression analysis was carried out on VALSTAT [9]. Structures of all the compounds were sketched using builder module of the program. The sketched structures were subjected to energy minimization using molecular mechanics (MM2) until the RMS gradient value became smaller than 0.1 kcal/mol Å. The energy minimized molecules were subjected to re-optimization via Austin model-1 (AM1) method until the RMS gradient attained a value smaller than 0.0001 kcal/mol Å using MOPAC. The geometry optimization of the lowest energy structure was carried out using EF routine. The descriptor values for all the molecules were calculated using "compute properties" module of program. The minimized molecule was saved as MOL file format. Pursuly, the MOL file was used for calculation of various physicochemical properties using Dragon program.

The data was transferred to the statistical program in order to establish a correlation between physicochemical parameters as independent variables and pIC_{50} as dependent variable employing sequential multiple linear regression analysis method. In sequential multiple regression, the program searches all the permutations and combinations sequentially for the data set. The ± data within the parentheses is the standard deviation, associated with the coefficient of descriptors in regression equations. The best model was selected from the various statistically significant equations on the basis of the observed squared correlation coefficient (r^2), the standard error of estimate (SEE), the sequential Fischer test (F), the bootstrapping squared correlation coefficient (r^2_{bs}), the bootstrapping standard deviation (S_{bs}), the cross validated squared correlation coefficient using leave-one-out procedure (q^2), Chance statistics (evaluated as the ratio of the equivalent regression equations to the total number of randomized sets; a chance value of 0.001 corresponds to 0.1% chance of fortuitous correlation) and outliers (on the basis of Z-score value).

3. Results and discussion

Rationalization of physicochemical characters for COX-2 inhibitory activity was performed with the help of 20 compounds of 1,5-diarylpyrazole analogs using regression analysis technique. From several significant expressions Eq. (1) was considered as model on the basis of statistics (Table 2)

$$\begin{aligned} pIC_{50(COX\text{-}2)} &= 1.230 \pm 0.224\,\text{Mor14v} - 1.258 \\ &\quad \pm 0.397\,\text{Mor22m} + 9.971 \\ &\quad \pm 1.508\,\text{Hy} + 13.597, \\ n = 20,\ r = 0.870,\ r^2 &= 0.756,\ \text{SEE} = 0.233,\ F = 16.591 \end{aligned} \quad (1)$$

Model has a better correlation coefficient ($r = 0.870$), which accounted for more than 75.6% of the variance in the activity. The equation shows that in the multi-variant model, the dependent variable can be predicted from a linear combination of the independent variables. The P value less than 0.001 for each physicochemical parameter involved in model generation suggests the statistical significant relationship between the descriptors and activity. The data showed overall internal statistical significance level better than 99.9% as it exceeded the tabulated $F_{(3,16,\alpha=0.001)} = 10.3$. The model was further tested for outlier by Z-score method and no compound was found to be an outlier, which suggested that the model is able to explain the structurally diverse analogs. The cross-validated squared correlation coefficient ($q^2 = 0.400$), predictive residual sum of square ($S_{PRESS} = 0.365$) and standard error of prediction ($S_{DEP} = 0.327$) suggested a good internal consistency as well as predictive ability of the biological activity with low S_{DEP} (Table 3). The r^2_{bs} is at par with the conventional squared correlation coefficient (r^2). Randomized biological activity test (Chance < 0.001) revealed that the results were not based on chance correlation. The inter correlation among the parameters is less than 0.460. In general the model fulfills the statistical validation criteria to the significant extent however; it is a useful theoretical base for proposing more active compounds. In model Mor14v [10–13] and Hy [13] contributed positively while Mor22m contributed negatively to the activity.

Mor14v, 3D molecular representation of structure based on electron diffraction code (MoRSE Code) was calculated by summing atom weights viewed by a different angular scattering function. The values of these code functions were calculated at 32 evenly distributed values of scattering angle(s) in the range 0–31 $Å^{-1}$ from the three-dimensional atomic co-ordinates of a molecule. The 3D-MoRSE code was calculated using following expression:

$$I(s) = \sum_{i=2}^{N} \sum_{j=1}^{i-1} A_i A_j \frac{\sin \text{sr}_{ij}}{\text{sr}_{ij}}$$

Table 2
QSAR statistics of significant equations

Equation	r^2	SEE	F	ICAP[a]	r^2_{bs}	S_{bs}	Chance	q^2	S_{PRESS}	S_{DEP}	Outlier
(1)	0.756	0.233	16.591	0.460	0.713	0.225	<0.001	0.400	0.365	0.327	Nil
(3)	0.797	0.438	21.552	0.300	0.780	0.149	<0.001	0.626	0.549	0.527	Nil
(4)	0.830	0.401	26.792	–	0.818	0.157	<0.001	0.715	0.519	0.460	Nil
(6)	0.776	0.579	19.048	0.420	0.795	0.089	<0.002	0.648	0.723	0.643	Nil
(8)	0.885	0.114	30.890	0.144	0.591	0.237	<0.001	0.729	0.176	0.150	Nil

[a] The maximum limit of inter-correlation among the descriptors used in generation of equations.

Table 3
Observed, calculated and calculated (loo) pIC_{50} values with *Z*-score and residual of 1,5-diarylpyrazole analogs used in QSAR analysis for COX-2 inhibitory activity by Eq. (1)

Compound no.	Observed	Calculated	Cal_{res}	*Z*-score	Cal(loo)	$Cal(loo)_{res}$
1	7.347	7.248	0.099	0.461	7.103	0.244
2	6.215	6.031	0.183	0.857	5.991	0.224
3	6.018	6.242	−0.224	−1.049	6.262	−0.245
4	6.032	6.270	−0.238	−1.114	6.292	−0.261
5	6.032	6.183	−0.151	−0.708	6.231	−0.200
6	6.523	6.356	0.167	0.783	6.332	0.191
7	6.086	6.588	−0.501	−2.347	6.654	−0.568
8	7.000	6.938	0.062	0.290	6.925	0.075
9	6.387	6.026	0.362	1.693	5.938	0.449
10	6.155	6.344	−0.189	−0.883	6.360	−0.205
11	6.509	6.353	0.156	0.729	6.341	0.168
12	6.131	6.432	−0.301	−1.408	6.483	−0.352
13	6.244	6.223	0.022	0.101	6.220	0.024
14	6.036	5.882	0.154	0.720	5.842	0.194
15	6.658	6.610	0.048	0.224	6.594	0.063
16	6.046	6.151	−0.105	−0.492	6.163	−0.118
17	6.347	6.257	0.090	0.420	6.242	0.105
18	6.060	5.940	0.120	0.562	5.907	0.154
19	6.155	6.171	−0.016	−0.075	6.174	−0.019
20	7.444	7.180	0.264	1.236	6.440	1.004

where *s* is the scattering angle, r_{ij} the interatomic distance of *i*th and *j*th atom and A_i and A_j are atomic properties of *i*th and *j*th atom, respectively, including atomic number, atomic mass, partial atomic charges, residual electro-negativities, and atom polarizability.

Hy is hydrophilic factor contributed positively to the model. It is an empirical index obtained as a function of count the hydrophilic groups.

The simple regression analysis study revealed that Hy contributed positively and linearly to the activity (Eq. (2)) with correlation coefficient value 0.521 and statistical significance level better than 98% as it exceeded the Student's *t*-value 2.587 against tabulated $t_{0.02(2),18} = 2.552$

$$pIC_{50(COX\text{-}2)} = 5.340 \pm 2.064\,Hy + 10.435,$$
$$n = 20,\ r = 0.521,\ r^2 = 0.271,\ SEE = 0.380,\ F = 6.694 \quad (2)$$

To find any major differences in the properties of the molecules showing COX-2 inhibitory activity over COX-1, we have searched physicochemical properties which are responsible for the COX-1 inhibitory activity using fourteen compounds. Several di-variant significant equations were obtained. Eq. (3) with correlation coefficient ($r = 0.893$) was considered as model, which accounts for more than 79.7% of the variance in the activity

$$pIC_{50(COX\text{-}1)} = -0.307 \pm 0.116\,Mor04u - 5.084 \pm 0.779\,Mor17v + 2.938,$$
$$n = 14,\ r = 0.893,\ r^2 = 0.797,\ SEE = 0.438,\ F = 21.552 \quad (3)$$

The data showed overall better statistical significance level with $F_{(2,11)} = 21.552$ against the tabulated value for sequential Fischer test at 99.9% significance ($F_{(2,11,\alpha=0.001)}$=16.4). The inter-correlations of the descriptor (ICAP < 0.300) in the model are insignificant indicating that all the descriptors in the model were contributing independently to the biological activity. The model was subjected to cross validation, the value of cross-validated squared correlation coefficient ($q^2 = 0.626$), predictive residual sum of square ($S_{PRESS} = 0.594$) and standard error of predictivity ($S_{DEP} = 0.527$) suggested good predictive ability of the biological activity of diversified structure (Table 4). Bootstrapping technique suggested the robustness of the model and indicating that contribution of molecular descriptor values of each molecule to the correlation is nearly same (Table 2). The chance of fortuitous correlation was checked with the help of scrambled biological activity data set, the value of chance statistics (Chance < 0.001) revealed that the results were not based on chance correlation. The model showed that no compound was found to be outlier on the basis of *Z*-score technique which depicted that the model is able to explain the structurally diversified analogs. The model showed that the Mor04v (3D-MoRSE Code) and Mor17v (3D-MoRSE Code) contributed negatively. The non-linear (parabolic) correlation also searched for the COX-1 inhibitory activity. In parabolic correlation somewhat more significant model (Eq. (4)) was obtained as compared to linear one

$$pIC_{50(COX\text{-}1)} = 14.737 \pm 4.551(Mor17v)^2 + 9.461 \pm 4.358\,Mor17v + 5.936,$$
$$n = 14,\ r = 0.911,\ r^2 = 0.830,\ SEE = 0.401,\ F = 26.792 \quad (4)$$

Table 4
Observed, calculated and calculated (loo) pIC_{50} values with Z-score and residual of 1,5-diarylpyrazole analogs used in QSAR analysis for linear (Eq. (3)), non-linear (Eq. (4)) analysis of COX-1 and linear (Eq. (6)) analysis of COX-1/COX-2 selectivity

Compound no.	Linear model (Eq. (3))						Non-linear model (Eq. (4))					COX-1/COX-2 selectivity (Eq. (6))					
	Observed	Calculated	Cal_{res}	Z-score	Cal(loo)	$Cal(loo)_{res}$	Observed	Calculated	Z-score	Cal(loo)	$Cal(loo)_{res}$	Observed	Calculated	Cal_{res}	Z-score	Cal(loo)	$Cal(loo)_{res}$
1	4.584	5.188	−0.604	−1.500	5.237	−0.653	4.859	−0.275	−0.745	4.907	−0.324	2.763	2.187	0.576	1.081	2.012	0.751
2	5.146	5.883	−0.736	−1.828	6.013	−0.867	5.665	−0.519	−1.408	5.750	−0.604	1.079	0.255	0.824	1.548	0.055	1.024
3	5.947	5.707	0.240	0.597	5.674	0.273	5.391	0.556	1.508	5.304	0.643	0.000	0.362	−0.362	−0.680	0.427	−0.427
4	5.742	5.626	0.117	0.290	5.611	0.132	5.421	0.321	0.870	5.372	0.371	0.301	0.004	0.297	0.559	−0.100	0.402
5	5.807	5.687	0.120	0.299	5.664	0.142	5.762	0.045	0.123	5.754	0.053	0.000	0.071	−0.071	−0.134	0.092	−0.092
6	7.444	6.833	0.611	1.516	6.321	1.123	7.336	0.108	0.293	6.845	0.599	−0.921	0.076	−0.997	−1.873	0.350	−1.271
8	4.590	4.834	−0.244	−0.605	4.989	−0.399	5.184	−0.594	−1.609	5.280	−0.690	2.410	2.248	0.162	0.304	2.222	0.187
11	4.353	4.650	−0.296	−0.736	4.743	−0.390	4.430	−0.077	−0.208	4.445	−0.092	2.152	1.551	0.601	1.129	1.494	0.659
13	4.002	4.177	−0.175	−0.434	4.227	−0.225	4.514	−0.512	−1.390	4.762	−0.760	2.246	2.188	0.058	0.108	2.178	0.068
14	4.419	4.198	0.222	0.550	4.028	0.392	4.565	−0.146	−0.395	4.589	−0.169	1.613	1.260	0.353	0.663	1.232	0.381
15	4.755	4.543	0.212	0.526	4.485	0.270	4.438	0.317	0.859	4.369	0.386	1.892	2.150	−0.258	−0.484	2.186	−0.294
17	4.801	5.033	−0.232	−0.575	5.054	−0.253	4.583	0.218	0.591	4.547	0.254	1.544	1.942	−0.398	−0.747	1.986	−0.442
18	4.601	3.969	0.633	1.570	3.791	0.811	4.484	0.117	0.318	4.441	0.160	1.462	2.306	−0.844	−1.585	2.561	−1.099
20	4.870	4.736	0.134	0.332	4.717	0.153	4.430	0.440	1.192	4.370	0.500	2.574	2.516	0.058	0.109	2.253	0.321

Non-linear regression analysis model having correlation coefficient ($r = 0.911$), accounted for more than 83.0% of the variance in the activity with low standard error of estimation. The value of cross-validated squared correlation coefficient ($q^2 = 0.715$), predictive residual sum of square ($S_{PRESS} = 0.519$) and standard error of predictivity ($S_{DEP} = 0.460$) suggested good predictive ability of the biological activity of diversified structures. The bootstrapping technique, chance statistics and outliers *Z*-score data's supported the robustness and practical applicability of the model (Table 2).

The simple regression study revealed that Hy is the key feature in differentiating the inhibitory activity for COX-2 over COX-1. Hy contributed negatively and linearly to the COX-1 inhibitory activity (Eq. (5)) with correlation coefficient value 0.528 and statistical significance level better than 95.0% as it exceeded the Student's *t*-value 2.156 against tabulated $t_{0.05(2),18} = 2.101$

$$pIC_{50(COX\text{-}1)} = -10.516 \pm 4.877\,Hy - 2.920,$$
$$n = 14,\ r = 0.528,\ r^2 = 0.279,\ SEE = 0.790,\ F = 4.649 \quad (5)$$

In search of the physicochemical properties, responsible for the selectivity of 1,5-diarylpyrazole analogs for COX-2 over COX-1 that is of paramount importance in designing of novel selective COX-2 inhibitors, the correlation was explored between physicochemical properties of the molecule and log of IC_{50} ratio of COX-1 and COX-2. On the basis of correlation coefficient and Fischer sequential test, a di-variant linear expression (Eq. (6)) was considered as model. The selected model having correlation coefficient value equivalent to 0.881, explained 77.6% variance in the selectivity (Table 4)

$$\log Sel_{(COX\text{-}1/COX\text{-}2)} = 5.349 \pm 1.596\,Mor24v + 23.949 \pm 3.924\,Hy + 16.859,$$
$$n = 14,\ r = 0.881,\ r^2 = 0.776,\ SEE = 0.579,\ F = 19.048 \quad (6)$$

The value of cross-validated squared correlation coefficient ($q^2 = 0.648$) suggested the good predictive ability of the model (Fig. 1). The robustness of model was further supported by boot-

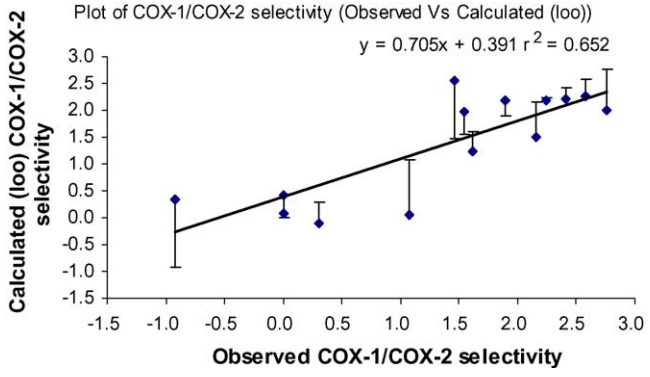


Fig. 1. A graphical representation of observed and calculated (loo) selectivity using Eq. (6) for COX-1/COX-2.

Table 5
Observed, calculated and calculated (loo) pIC_{50} values with *Z*-score and residual of 1,5-diarylpyrazole analogs used in QSAR analysis for LOX-5 inhibitory activity by Eq. (8)

Compound no.	Observed	Calculated	Cal_{res}	*Z-score*	Cal(loo)	$Cal(loo)_{res}$
1	6.523	6.394	0.129	1.261	6.371	0.152
2	6.244	6.267	−0.023	−0.222	6.270	−0.025
3	6.319	6.330	−0.011	−0.106	6.331	−0.012
4	6.081	6.244	−0.163	−1.589	6.261	−0.180
5	6.143	6.222	−0.079	−0.777	6.231	−0.088
6	6.114	5.915	0.198	1.939	5.839	0.274
7	6.071	6.084	−0.014	−0.135	6.087	−0.016
8	6.131	6.231	−0.100	−0.978	6.248	−0.118
9	6.119	6.146	−0.027	−0.266	6.180	−0.061
10	6.097	6.065	0.032	0.310	6.028	0.069
21	7.081	7.023	0.058	0.565	6.788	0.292

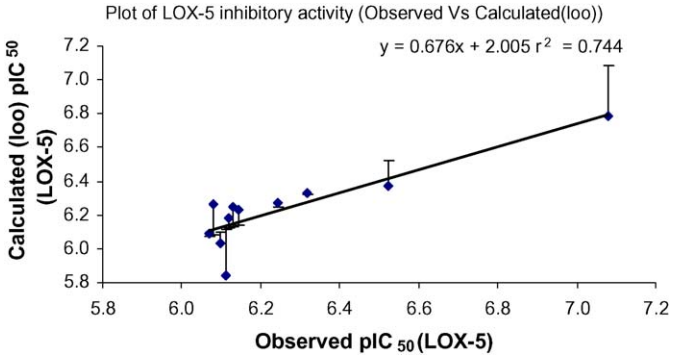


Fig. 2. A graphical representation of observed and calculated (loo) pIC_{50} using model (Eq. (8)) for LOX-5.

strapping technique, chance statistics and outliers *Z*-score data (Table 2). Model showed that Mor24v and Hy contributed positively to the selectivity.

The selectivity ratio of COX-2 over COX-1 showed a positive correlation with Hy (Eq. (7)), explaining about 54.7% variance in the activity. The *t*-value of regression term for descriptor Hy showed statistical level more than 99.5% (Student's *t*-value 3.808 against tabulated $t_{0.001(1),12} = 3.423$) suggesting significance and linear correlation. The contribution of Hy depicted that the interaction of 1,5-diarylpyrazole analogs occurred at hydrophilic pocket of COX-2 receptor

$$\log \mathrm{Sel}_{(\mathrm{COX\text{-}1/COX\text{-}2})} = 18.530 \pm 4.866\,\mathrm{Hy} + 15.454,$$
$$n = 14,\ r = 0.740,\ r^2 = 0.547,\ \mathrm{SEE} = 0.788,\ F = 14.501 \quad (7)$$

In case of LOX-5 inhibitory activity di-variant model (Eq. (8)) showed correlation coefficient value equivalent to 0.941, which explained 88.5% variance in the activity (Table 5 and Fig. 2). The fitness and robustness of the model was further supported by advanced statistical validation parameters (Table 2)

$$\mathrm{pIC}_{50(\mathrm{LOX\text{-}5})} = 1.670 \pm 0.278\,\mathrm{Mor17v} - 0.314 \pm 0.076\,\mathrm{Mor11m} + 7.572,$$
$$n = 11,\ r = 0.941,\ r^2 = 0.885,\ \mathrm{SEE} = 0.114,\ F = 30.890 \quad (8)$$

Simple regression analysis study suggested that Mor17v contributed positively to the LOX-5 inhibitory activity (Eq. (9))

$$\mathrm{pIC}_{50(\mathrm{LOX\text{-}5})} = 1.835 \pm 0.459\,\mathrm{Mor17v} + 7.344,$$
$$n = 11,\ r = 0.800,\ r^2 = 0.640,\ \mathrm{SEE} = 0.191,\ F = 15.989 \quad (9)$$

The 1:1 correlation indicated that Mor17v is the dominant structure feature, which is crucial in explaining the LOX-5 inhibitory activity. The Mor17v also played key role in explaining the COX-1 inhibitory activity of the 1,5-diarylpyrazole analogs, but it contributed negatively to the activity.

The quantification of the structure features of 1,5-diarylpyrazole analogs with various biological activities furnished some important structural insights i.e. hydrophilic factor (Hy) contributed positively to the COX-2 activity as well as COX-1/COX-2 selectivity ratio. Mor17v (3D molecular representation of structure based on electron diffraction code) is the dominant structure feature, which is decisive in explaining the LOX-5 inhibitory activity and also played key role in explaining the COX-1 inhibitory activity, but contributed negatively to it. These structure features may be helpful in development of more selective and potent dual COX-2/LOX-5 inhibitors.

References

[1] C. Charlier, C. Michaux, Eur. J. Med. Chem. 38 (2003) 645–669.
[2] J.R. Vane, Nature 231 (1971) 232–235.
[3] W. Xie, J.G. Chipman, D.L. Robertson, R.L. Erikson, D.L. Simmons, Proc. Natl. Acad. Sci. U.S.A. 88 (1991) 2692–2696.
[4] S.V. Deshpande, M.A. Babu, A.K. Gupta, S.G. Kaskhedikar, A.K. Saxena, Med. Chem. Res. 13 (2004) 337–347.
[5] T. Narsinghani, S.C. Chaturvedi, Bioorg. Med. Chem. Lett. 16 (2006) 461–468.
[6] N. Pommery, T. Taverne, A. Telliez, L. Goossens, C. Charlier, J. Pommery, J. Goossens, R. Houssin, F. Durant, J. Henichart, J. Med. Chem. 47 (2004) 6195–6206.
[7] CS Chem Office, Version 8.0, Cambridge Soft Corporation, Software Publishers Association, 1730 M Street, Suite 700, Washington, DC 20036, USA, Tel.: +1 202 452 1600.
[8] R. Todeschini, V. Consonni, DRAGON-Software for the Calculation of Molecular Descriptors, rel. 1.12 for Windows, 2001.
[9] A.K. Gupta, B.M. Arockia, S.G. Kaskhedikar, Indian J. Pharm. Sci. 66 (2004) 396–402.
[10] J. Gasteiger, J. Sadowski, J. Schuur, P. Selzer, L. Steinhauer, V. Steinhauer, J. Chem. Inf. Comput. Sci. 36 (1996) 1030–1037.
[11] J.H. Schuur, P. Selzer, J. Gasteiger, J. Chem. Inf. Comput. Sci. 36 (1996) 334–344.
[12] J. Schuur, J. Gasteiger, J. Anal. Chem. 69 (1997) 2398–2405.
[13] R. Todeschini, V. Consonni, Handbook of Molecular Descriptors, Wiley/VCH, Weinheim, 2000.