ARTICLE IN PRESS

Journal of Saudi Chemical Society (2013) xxx, xxx–xxx

King Saud University

Journal of Saudi Chemical Society

www.ksu.edu.sa
www.sciencedirect.com

ORIGINAL ARTICLE

Quantitative structure–activity relationship based modeling of substituted indole Schiff bases as inhibitor of COX-2

Amrita Dwivedi, Ajeet Singh *, A.K. Srivastava *

QSAR Research Laboratory, Department of Chemistry, University of Allahabad, Allahabad–211002, India

Received 27 November 2012; accepted 30 January 2013

KEYWORDS
COX-2 inhibitors;
Physicochemical parameters;
QSAR

Abstract We have performed the quantitative structure activity relationship (QSAR) study for N-1 and C-3 substituted indole shiff bases to understand the structural features that influence the inhibitory activity toward the cyclooxygenase-2 (COX-2) enzyme. The calculated QSAR results revealed that the drug activity could be modeled by using molecular connectivity indices ($^0\chi$, $^1\chi$, $^2\chi$), wiener index (W) and mean wiener index (WA) parameters. The predictive ability of models was cross validated by evaluating the low residual activity, appreciable cross validated r^2 values (R^2_{cv}) and leave one out (LOO) technique.

1. Introduction

The non-steroidal anti-inflammatory drugs (NSAIDs) like aspirin are among the most common medications in the world (Vane, 1971). The mechanism of action of these drugs is the inhibition of the cyclooxygenase (COX) enzyme, which catalyzes the first step of the biosynthesis of PGG2 from arachidonic acid to generate prostaglandin H2 (Hamberg and Samuelsson, 1973). The next hierarchical step in enzyme catalysis is to convert prostaglandin H2 to other prostaglandins and thromboxanes and finally bind to G-protein-coupled receptors and effect diverse biological responses (Funk, 2001).

On the basis of crystal structures, the two isoforms (COX-1 and COX-2) have been identified. Cyclooxygenase-1 (COX-1) which is mainly associated with prostaglandin production in gastric mucosa and thromboxane production in platelets (Smith et al., 2000) and COX-2 whose expression is upregulated in response to inflammatory stimuli and elevates prostaglandin levels as part of the inflammatory response. Identification of this alternate role of COX-2 has led to development of the COX-2 selective NSAIDs such as rofecoxib, celecoxib, and valdecoxib. These drugs have good anti-inflammatory activity, but with reduced ulcerogenicity compared to nonselective NSAIDs. Despite their commercial success, current COX-2 selective inhibitors may still exhibit undesirable side effects, including the increased risk of adverse thromboembolytic events in susceptible individuals (Solomon et al., 2002; FitzGerald, 2004). Enzyme specificity is also an issue, as the sulfonamide containing inhibitors celecoxib and valdecoxib can also inhibit carbonic anhydrase II (Klebe et al., 2004).

* Corresponding authors. Tel.: +91 5322461236.
E-mail addresses: ajeetmoleucle@gmail.com (A. Singh), draksrivastava1@rediffmail.com (A.K. Srivastava).

Peer review under responsibility of King Saud University.

ELSEVIER Production and hosting by Elsevier

1319-6103 © 2013 Production and hosting by Elsevier B.V. on behalf of King Saud University.
http://dx.doi.org/10.1016/j.jscs.2013.01.007

COX-1 selective inhibitors also have therapeutic value, as it was shown recently that COX-1 is over expressed in some ovarian cancer cells, where it stimulates angiogenesis (Gupta et al., 2003). Thus, a more detailed understanding of COX isoform differences could aid in the design of more selective, and potent, inhibitors of both COX isoforms. Both COX-1 and COX-2 are isomorphs however, the selectivity of COX-2 over COX-1 is due to the central channel of COX-2 which is larger (~17%) than that of COX-1. This difference in size is due to the change of some amino acid residues that increase the size and change the chemical environment of the binding pocket of NSAIDs. The most critical structural feature conferring sensitivity to inhibition by COX-2 is the exchange of valine in COX-2 at positions 434 and 523 in place of isoleucine in COX-1. (It is important to note that the residues in COX-2 are given the same number as their equivalent amino acids in COX-1 for convenience; however, the exact amino acid residue number in COX-2 should be calculated by subtracting 14 from the COX-1 number) (Luong et al., 1996; Iyashiro and Penning et al., 1996; Copeland et al., 1994). Also in COX-2, 17th amino acids are absent from the N terminus and 18th amino acids are inserted at the C terminus in comparison to COX-1. (Otto and Smith, 1995; Herschman, 1996).

The COX-2 enzyme is the inducible isoform that is produced by various cell types

upon exposure to cytokines, mitogens, and endotoxins released during injury and therefore molecules that inhibit its enzymatic activity would be of therapeutic value (Smith and Dewitt, 1996) The gastrointestinal side effects associated with NSAIDs are due to the inhibition of gastroprotective PGs synthesized through the COX-1 pathway. Thus, selective inhibition of COX-2 over COX-1 is considered to be highly useful for the treatment of inflammation and inflammation associated disorders with reduced gastrointestinal toxicities when compared with NSAIDs (Meade et al., 1993).

The present work aims to develop the understanding toward the inhibition of COX-2 with the help of QSAR. For this purpose we have taken the activity data (IC_{50}) that were reported by Kaur et al. (2012). The physicochemical properties of a drug play a major role in the development of formulation and bioavailability and thus we have taken some physicochemical parameters like molecular connectivity indices ($^0\chi$, $^1\chi$, $^2\chi$) with wiener index (W) as, mean wiener index (W_A), and molecular weight (MW) for the present article.

2. Experimental section

2.1. Methodology

Inhibitory activity as reported by Kaur et al. (2012) as IC_{50} were converted into their log units (log IC_{50}) and used in the present investigation. An attempt has been made to correlate the activity of these compounds with various physicochemical parameters such as surface tension (st) (Hansch and Fujita, 1964), wiener index (W), mean wiener index (W_A), molecular weight (MW) (Hansch and Fujita, 1964) and molecular connectivity ($^0\chi$, $^1\chi$, $^2\chi$) and have been used to study the relationship between parameters and properties. St and mw were calculated by ACD Lab Chem. Sketch Software version 12 (ACD/ChemSketch 10 (2006); www.acdlabs.com) whereas W, W_A, $^0\chi$, $^1\chi$, $^2\chi$ were evaluated by E-Dragon Software (www.vcclab.org/). The multiple regressions used to derive the correlation were executed with the SPSS 7.5 version program.

2.2. Parameters used

2.2.1. Molecular connectivity index

The first order connectivity index $\chi^{(G)}$ of a graph G is defined by Randic (1975) as follows:

$$\chi = \chi^{(G)} = \sum_{jk}[\delta_j\delta_k]^{-0.5}$$

where δ_j and δ_k are the valences of vertices j and k that are equal to the number of bonds connected to the atoms j and k, in G. In the case of hetero-systems the connectivity is given in terms of valence delta values δ_j and δ_k of atoms j and k and is denoted by χ^r. This version of the connectivity index is called the valence connectivity index and is defined as follows:

$$X^r = \chi^{r(G)} = \sum_{jk}[\delta_j^r\delta_k^r]^{-0.5}$$

where, the sum of all bonds j and k of the molecule is taken. Valence delta values are given by the following expression:

$$\Delta_j^v = \frac{Z_j^v - H_j}{Z_j - Z_k - 1}$$

where Z_j is the atomic number of atom j, Z_j^v is the number of valence electrons of the atom j and H_j is the number of hydrogen atoms attached to atom j. The Δ_j^v values are available in the book written by Kier and Hall (1976).

2.2.2. Indicator parameters

Indicator variables or parameters, sometimes called dummy variables or de novo constants (Recantint et al., 1986) are used in linear multiple regression analysis to account for certain features which cannot be described by continuous variables. In QSAR equations, they normally describe a certain structural element, be it a substituent or another molecular fragment. Thus, Free Wilson analysis may be interpreted as a regression analysis approach using only indicator variables.

2.2.3. Molecular weight (MW)

Molecular weight descriptor has been used as the descriptor in systems such as transport studies where diffusion is the mode of operation. It is an important variable in QSAR studies pertaining to cross-resistance of various drugs in multi-drug resistant cell lines

2.2.4. Wiener index (W)

Wiener index (W) is a widely and oldest used topological index. It is based on the vertex-distances of the respective molecular graph. The Wiener index (W) was proposed in 1947 by Wiener and it is defined as the sum of overall bonds of the product of the number of vertices on each side of the bond. Let us denote a molecular graph G and $v_1, v_2, v_3, \ldots, v_n$ its vertices. Let $d(v_j; v_k/G)$ stand for the distance between the vertices v_{ij} and v_k. Then the Wiener (1947) index is defined as:

$$W = W(G) = 1/2\sum_j^n\sum_k^n d(v_j, v_k|G)$$

3. Results and discussion

The 2D structures of the molecules were drawn using Chem Sketch software. Several physicochemical parameters were calculated for the present series (Kaur et al., 2012) such as wiener index (W), mean wiener index (WA), molecular connectivity $(^0\chi)^5$, $(^1\chi)^5$, $(^2\chi)^5$ and molecular weight (MW), which have been found to be useful in QSAR based drug modeling (Srivastava et al., 2008a, b, c; Agarwal et al., 2003, 2005, 2006; Khadikar et al., 2002, 2003a, b, 2005a, b). Except molecular weight (MW) all physicochemical parameters were calculated with E-Dragon software, molecular weight was calculated by ACD Lab Chem Sketch software. The indicator parameter has also been used which accounts for the Fluorine (F) group at R_2 position. Regression analysis was performed by using SPSS 7.5 version. It is important to note that the indicator parameter should not be orthogonal in the matrix correlation (Table 2) and its value must be less than 0.50.

All the compounds of the series along with, calculated physicochemical parameters are given in Table 1. In multiple regression analysis, the independent variables must be orthogonal and consequently the autocorrelation among the descriptors was checked and is given in the correlation matrix in Table 2. Statistically significant models were obtained when one of the parameters (W), (W_A), ($^0\chi$), ($^1\chi$), ($^2\chi$), (MW), is combined with the indicator parameter. The models obtained are reported as:

$$\mathbf{pIC_{50}} = 0.876(\pm 0.608)\mathrm{I} + 0.374(\pm 0.161)^2\chi + 1.173 \quad (1)$$

$n = 10$, $R = 0.910$, $R^2 = 0.829$, $R_A^2 = 0.780$, S.E. $= 0.359$, $F_{(2,7)} = 16.935$, $Q = 2.535$

$$\mathbf{pIC_{50}} = 0.833(\pm 0.616)\mathrm{I} + 0.001(\pm 0.001)W + 3.431 \quad (2)$$

$n = 10$, $R = 0.906$, $R^2 = 0.821$, $R_A^2 = 0.770$, S.E. $= 0.366$, $F_{(2,7)} = 16.089$, $Q = 2.475$

$$\mathbf{pIC_{50}} = 0.870(\pm 0.623)\mathrm{I} + 1.181(\pm 0.526)\mathrm{W_A} - 1.074 \quad (3)$$

$n = 10$, $R = 0.906$, $R^2 = 0.820$, $R_A^2 = 0.769$, S.E. $= 0.367$, $F_{(2,7)} = 15.960$, $Q = 2.469$

$$\mathbf{pIC_{50}} = 0.822(\pm 0.669)\mathrm{I} + 0.239(\pm 0.118)0\chi + 1.169 \quad (4)$$

$n = 10$, $R = 0.888$, $R^2 = 0.789$, $R_A^2 = 0.728$, S.E. $= 0.398$, $F_{(2,7)} = 13.064$, $Q = 2.231$

$$\mathbf{pIC_{50}} = 0.829(\pm 0.678)\mathrm{I} + 0.012(\pm 0.006)\mathrm{MW} + 1.249 \quad (5)$$

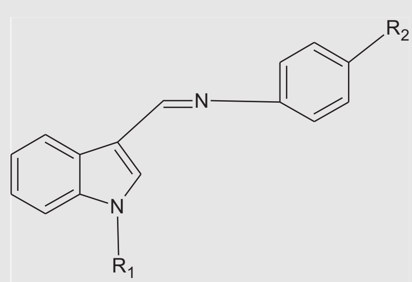
$n = 10$, $R = 0.885$, $R^2 = 0.784$, $R_A^2 = 0.722$, S.E. $= 0.402$, $F_{(2,7)} = 12.706$, $Q = 2.201$

$$\mathbf{pIC_{50}} = 0.730(\pm 0.773)\mathrm{I} + 0.327(\pm 0.201)1\chi + 1.342 \quad (6)$$

$n = 10$, $R = 0.843$, $R^2 = 0.711$, $R_A^2 = 0.628$, S.E. $= 0.466$, $F_{(2,7)} = 8.609$, $Q = 1.809$In the calculated model Eqs (1)–(6), we have used as the symbol n for the number of compounds in the data set, R for the correlation coefficient, R^2 for the coefficient of determination, R_A^2 for the adjusted R^2, SE for the standard error of estimate, F for the variance ratio (Diudea, 2000; Bikash et al., 2003) and Q for the quality of fit (Pogliani, 1994; Pogliani, 1996). The positive sign of coefficients of indicator parameter shows that the F group has a positive influence on activity and should be retained at R_2 position in the future drug designing. The above equations show that the coefficient of different orders of molecular connectivity parameters ($^0\chi$· $^1\chi$· $^2\chi$), mw, W_A and W are positive and this indicates that bulkier substituents with more branching should be preferred for future modeling. The high values of R, R^2 and low values of S.E. indicate the statistical significance of the proposed mentioned models.

On the basis of calculated statistical parameter it is evident that model 1 is the best among all bi-parametric models discussed above. The quality factor Q is the ratio of correlation coefficient to its standard error of estimation i.e. $Q = R/\mathrm{S.E.}$ thus higher the value of R, the lower the S.E., the greater will

Table 1 Biological activity and physicochemical data of substituted indole Schiff bases.



Sl. no.	R_1	R_2	W	W_A	$^0\chi$	$^1\chi$	$^2\chi$	MW	I	pIC_{50}
1	H	F	664	4.34	12.372	8.826	7.749	238.260	1	4.764
2	H	CH_3	664	4.34	12.372	8.826	7.749	234.296	0	4.517
3	H	CF_3	1045	4.976	14.872	10.038	9.707	288.267	0	4.936
4	CH_2Ph	F	1613	5.377	17.062	12.293	10.811	328.382	1	6.149
5	CH_2Ph	CH_3	1613	5.377	17.062	12.293	10.811	324.418	0	4.757
6	CH_2Ph	CF_3	2270	6.005	19.562	13.504	12.769	378.390	0	6.076
7	COPh	F	1744	5.366	17.933	12.720	11.232	342.366	1	6.367
8	COPh	CH_3	1744	5.366	17.933	12.720	11.232	338.402	0	4.906
9	COPh	CF_3	2437	6.002	20.433	13.932	13.190	392.373	0	6.495
10	COPh	Cl	1744	5.366	17.933	12.720	11.232	358.820	0	5.185

Please cite this article in press as: Dwivedi, A. et al., Quantitative structure–activity relationship based modeling of substituted indole Schiff bases as inhibitor of COX-2. Journal of Saudi Chemical Society (2013), http://dx.doi.org/10.1016/j.jscs.2013.01.007

Table 2 Correlation matrix demonstrating physicochemical parameters with indicator parameters.

	pIC_{50}	W	W_A	$^0\chi$	$^1\chi$	$^2\chi$	MW	I
pIC_{50}	1.000							
W	0.749	1.000						
WA	0.735	0.985	1.000					
$^0\chi$	0.731	0.992	0.983	1.000				
$^1\chi$	0.711	0.980	0.963	0.990	1.000			
$^2\chi$	0.738	0.992	0.994	0.995	0.974	1.000		
MW	0.725	0.985	0.977	0.995	0.983	0.990	1.000	
I	0.311	−0.245	−0.270	−0.243	−0.188	−0.272	−0.249	1.000

Table 3 Comparison between observed and predicted activities and their residual values for equation 3.

	pIC_{50}	Predicted	Residual
1.	4.764	4.94471	−.18071
2.	4.517	4.06908	.44792
3.	4.936	4.80079	.13521
4.	6.149	6.08898	.06002
5.	4.757	5.21335	−.45635
6.	6.076	5.94505	.13095
7.	6.367	6.24631	.12069
8.	4.906	5.37068	−.46468
9.	6.495	6.10238	.39262
10.	5.185	5.37068	−.18568

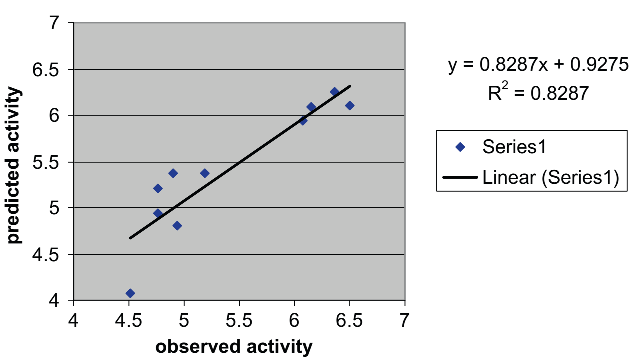


Figure 1 A plot showing comparison between observed and predicted activity values using equation (1).

be the Q. The predictive power as determined by the Pogliani Q parameter for the model expressed by Eq. (1) [Q = 2.535] confirms that this model has excellent statistics as well as excellent predictive power. It is to note that the activity and indicator parameters show best correlation with $^2\chi$, followed by W and W_A descriptors (Table 2). The remaining descriptors are not correlated up to the mark with activity and indicator parameters that reflect in the model equations (Eqs. (4)–(6)).

Predicted and residual activity values for model no. 1 are given in Table 3. Predicted values are the calculated activities obtained from model no. 1 and the residual values are the difference between the observed biological activities and calculated activities. The plot of observed pIC_{50} verses predicted pIC_{50} for Eq. (1) is shown in graph (Fig. 1) and the predicted R^2 was found to be fairly large.

4. Cross validation

The cross validation analysis was performed using leave one out (LOO) method (Cramer et al., 1988) in which one compound is removed from the data set and the activity is correlated using the rest of the data set. The cross-validated R^2 was found to be very close to the value of R^2 for the entire data set and hence these models can be termed as statistically significant.

Cross validation provides the values of PRESS, SSY and R^2_{cv} and PSE from which we can test the predictive power of the proposed model. The meanings of these cross- validated parameters are given as a footnote to the Table 4. It is argued that PRESS, is a good estimate of the real predictive error of the model and if it is smaller than SSY the model predicts better than chance and can be considered statistically significant. Furthermore, the ratio of PRESS/SSY can be used to calculate approximate confidence intervals of prediction of a new compound. To be a reasonable QSAR model PRESS/SSY should be smaller than 0.4 and for our best models the value of this ratio is 0.207. The calculated result revealed that this model is excellent. Also, if PRESS value is transformed into a dimensionless term by relating it to the initial sum of squares, we obtain R^2_{cv} i.e. the complement to the traces of unexplained

Table 4 Predictive error of coefficient of correlation (PE) and cross-validation parameters for the proposed models.

Sl. no.	Model	n	R	$1-R^2$	PE	6PE	PRESS	SSY	PRESS/SSY	R^2_{cv}	PSE
1.	1.	10	0.910	0.171	0.036	0.216	.900	4.353	0.207	0.793	0.300
2.	2.	10	0.906	0.179	0.038	0.222	.939	4.314	0.218	0.782	0.148
3.	3.	10	0.906	0.180	0.038	0.228	.945	4.308	0.219	0.781	0.307
4.	4.	10	0.888	0.211	0.044	0.264	1.110	4.143	0.268	0.732	0.333
5.	5.	10	0.885	0.216	0.046	0.276	1.135	4.118	0.276	0.724	0.337
6.	6.	10	0.843	0.289	0.061	0.366	1.518	3.735	0.406	0.594	0.390

PRESS = $\sum(X_{obs} - X_{cal})^2$; SSY = $\sum(X_{obs} - X_{mean})^2$; PSE = $\surd$PRESS/n.

Please cite this article in press as: Dwivedi, A. et al., Quantitative structure–activity relationship based modeling of substituted indole Schiff bases as inhibitor of COX-2. Journal of Saudi Chemical Society (2013), http://dx.doi.org/10.1016/j.jscs.2013.01.007

variance over the total variance. The PRESS and R^2_{cv} have good properties. However, for practical purposes of end users the use of square root of PRESS/n, which is called predictive square error (PSE), is more directly related to the uncertainty of the predictions. The PSE values also support our results. The calculated cross-validated parameters confirm the validity of the models (Diudea, 2000; Bikash et al., 2003).

5. Predictive error of coefficient of correlation (PE)

The predictive error of coefficient of correlation (PE) (Chatterjee et al., 2000) is yet another parameter used to decide the predictive power of the proposed models. This parameter is calculated by using the following expression:

$$PE = \frac{2}{3}\frac{1 - R^2}{3\sqrt{n}}$$

where R^2 is the coefficient of determination and N is the number of compounds used in the proposed model. We have calculated the PE value of all the proposed models and they are reported in Table 4. It is argued that if

(i) $R <$ PE, then correlation is not significant;
(ii) $R >$ PE, several times (at least three times), then correlation seems to be good; and if
(iii) $R >$ 6PE, then the correlation is definitely good.
(iv) For all the models developed the condition $R >$ 6PE and hence they can be said to have good predictive power.

6. Conclusion

In this work, we have reported the QSAR calculated values that are based on regression analysis using experimental PIC_{50} values. Calculated result revealed that, for future drug designing in this series, the more bulkier substituents having more branching should be preferred. The positive sign of coefficient of indicator parameter (I) clearly indicates that fluorine at R_2 position should be retained as it is beneficial toward the activity.

Acknowledgments

The author A.K. Srivastava gratefully acknowledges the Department of Science and Technology, (DST) New Delhi, India for the grant, Grant No. DST/40-70/2011 (SR). Author A. Singh wishes to acknowledge the UGC, New Delhi, India, for the Dr. D. S. Kothari's postdoctoral fellowship.

References

Agarwal, V.K., Bano, S., Khadikar, P.V., 2003. Topological approach to quantifying molecular lipophilicity of heterogenous set of organic compounds. Bioorg. Med. Chem. 11 (18), 4039–4047.

Agarwal, V.K., Gupta, M., Singh, J., Khadikar, P.V., 2005. A novel method of estimation of lipophilicity using distance based topological indices: dominating role of equalized electronegativity. Bioorg. Med. Chem. 13 (6), 2109–2120.

Agarwal, V.K., Singh, J., Louis, B., Khadikar, P.V., 2006. The topology of molecule and its lipophilicity. Curr. Comput. -Aided Des. 2, 369–403.

ACD/ChemSketch 10, 2006. Advanced Chemistry Development, Inc., Toronto, ON, Canada, www.acdlabs.com/acdlabs-rss-feed.xml.

Bikash, D., Shovanlal, G., Subrata, B., Soma, S., Jha, T., 2003. QSAR study on some pyridoacridine ascididiamine analogues as antitumor agents. Bioorg. Med. Chem. 11 (24), 5493–5499.

Copeland, R.A., Williams, J.M., Giannaras, J., Nurnberg, S., Covington, M., Pinto, D., Pick, S., Trzaskos, J.M., 1994. Mechanism of selective inhibition of the inducible isoform of prostaglandin G/H synthase. Proc. Natl. Acad. Sci. USA 91, 11202–11206.

Cramer III, R.D., Bunce, J.D., Patterson, D.E., 1988. Cross validation, bootstrapping, and partial least squares compared with multiple regression in conventional QSAR studies. Quant. Struct. Act. Relat. 7, 18–25.

Chatterjee, S., Hadi, A.S., Price, B., 2000. Regression Analysis by Example, 3rd ed. Willey VCH, New York.

Diudea, M.V., 2000. QSPR/QSAR Studies for Molecular Descriptors. Ed Nova Science, Huntingdon, New York.

E-Dragon Software for calculation of topological indices: www.vcclab.org/.

Funk, C.D., 2001. Prostaglandins and leukotrienes. Advances in eicosonoid biology. Science 294, 1871–1875.

FitzGerald, G.A., 2004. Coxibs and cardiovascular disease. N. Engl. J. Med. 351, 1709–1711.

Gupta, R.A., Tejada, L.V., Tong, B.J., Das, S.K., Morrow, J.D., Dey, S.K., DuBois, R.N., 2003. Cyclooxygenase-1 is overexpressed and promotes angiogenic growth factor production in ovarian cancer. Cancer Res. 63, 906–911.

Hamberg, M., Samuelsson, B., 1973. Detection and isolation of an endoperoxide intermediate in prostaglandin biosynthesis. Proc. Natl. Acad. Sci. USA 70, 899–903.

Herschman, H.R., 1996. Prostaglandin synthase 2. Biochim. Biophys. Acta 1299, 125–140.

Klebe, G., Weber, A., Casini, A., Heine, A., Kuhn, D., Supuran, C.T., Scozzafava, A., 2004. Unexpected nanomolar inhibition of carbonic anhydrase by COX-2-selective celecoxib: new pharmacological opportunities due to related binding site recognition. J. Med. Chem. 47, 550–557.

Kaur, J., Bhardwaj, A., Huang, Z., Knaus, E.E., 2012. N-1 and C-3 substituted indole schiff bases as selective COX-2 inhibitors: synthesis and biological evaluation. Bioorg. Med. Chem. Lett. 22, 2154–2159.

Kier, L.B., Hall, L.H., 1976. Molecular Connectivity in Chemistry and Drug Research. Academic, New York.

Khadikar, P.V., Singh, S., Srivastava, A., 2002. Novel estimation of lipophilic behavioural polychlorinated biphenys. Bioorg. Med. Chem. Lett. 12, 1125–1128.

Khadikar, P.V., Singh, S., Mandoloi, D., Joshi, S., Bajaj, A.V., 2003a. QSAR study on bioconcentration factor (BCF) of polyhaloginated biphenlys using the PI index. Bioorg. Med. Chem. 11, 5045–5050.

Khadikar, P.V., Mandoloi, D., Bajaj, A.V., Joshi, S., 2003b. QSAR study on solubility of alkanes in water and their partition coefficient in different solvent system using PI index. Bioorg. Med. Chem. Lett. 13, 419–422.

Khadikar, P.V., Jaiswal, M., Gupta, M., Mandolai, D., Sisodia, R.S., 2005a. QSAR studies on 1,2-dithiol-3-thiones:modeling of lipophilicity, quinone reductase specific activity and production of growth hormone. Bioorg. Med. Chem. Lett. 15, 1249–1255.

Khadikar, P.V., Sharma, V., Verma, R.G., 2005b. Novel estimation of lipophilicity using ^{13}C NMR chemical shifts as molecular descriptor. Bioorg. Med. Chem. Lett. 15, 421–425.

Luong, C., Miller, A., Barnett, J., Chow, J., Ramesha, C., Browner, M.F., 1996. Flexibility of the NSAID binding site in the structure of human cyclooxygenase-2. Nat. Struct. Biol. 3, 927–933.

Please cite this article in press as: Dwivedi, A. et al., Quantitative structure–activity relationship based modeling of substituted indole Schiff bases as inhibitor of COX-2. Journal of Saudi Chemical Society (2013), http://dx.doi.org/10.1016/j.jscs.2013.01.007

Meade, E.A., Smith, W.L., DeWitt, D.L., 1993. Differential inhibition of prostaglandin endoperoxide synthase (cyclooxygenase) isozymes by aspirin and other non-steroidal anti-inflammatory drugs. J. Biol. Chem. 268, 6610–6614.

Otto, J.C., Smith, W.L., 1995. Prostaglandin endoperoxide synthases-1 and -2. J. Lipid Mediat. Cell Signal 12, 139–156.

Pogliani, L., 1994. Structural property relationships of amine acids and some peptides. Amino acids 6, 141–156.

Pogliani, L., 1996. Modeling with special descriptors derived from a medium size set of connectivity indices. J. Phys. Chem. 100, 18065–18077.

Randic, M., 1975. Characterization of molecular branching. J. Am. Chem. Soc. 97, 6609–6615.

Recantint, M., Klein, T.K., Yang, Z., McClarin, J., Langridge, R., Hansch, C., 1986. Quantitative structure-activity relationships and molecular graphics in ligand receptor interactions: amidine inhibition of trypsin. Mol. Pharmacol. 29, 436–446.

Smith, W.L., DeWitt, D.L., Garavito, M., 2000. Cyclooxygenases: structural, cellular and molecular biology. Annu. Rev. Biochem. 69, 145–182.

Solomon, D.H., Glynn, R.J., Levin, R., Avorn, J., 2002. Nonsteroidal antiinflammatory drug use and acute myocardial infarction. Arch. Intern. Med. 162, 1099–1104.

Smith, W.L., DeWitt, D.L., 1996. Prostaglandin endoperoxide H synthases-1 and -2. Adv. Immunol. 62, 167–215.

Srivastava, A.K., Archana, S., Jaiswal, M., 2008a. A series of p-arylthio cinnamides as QSAR studies on antagonists of biochemical ICAM-1/LFA-1 interaction in relation to anti-inflammatory activity. Oxid. Commun. 31, 44–51.

Srivastava, A.K., Jaiswal, M., Archana, S., Chaurasia, S., 2008b. QSAR of substituted N-benzyl piperidines in the GBR series. J. Ind. Chem. Soc. 85, 842–848.

Srivastava, A.K., Pathak, V.K., Archana, S., Jaiswal, M., 2008c. QSAR based modeling of a new class of RNA polymerase inhibitors. J. Ind. Chem. Soc. 85, 627–631.

Vane, J.R., 1971. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin like drugs. Nat. New Biol. 231, 232–235.

Wiener, H., 1947. Structural determination of paraffin boiling points''. J. Am. Chem. Soc. 69, 17–20.

Please cite this article in press as: Dwivedi, A. et al., Quantitative structure–activity relationship based modeling of substituted indole Schiff bases as inhibitor of COX-2. Journal of Saudi Chemical Society (2013), http://dx.doi.org/10.1016/j.jscs.2013.01.007