Acta Pharmaceutica Sciencia
53: 117 – 126 (2011)

Hansch analysis of anti-inflammatory and analgesic activities of substituted 1-alkyl/aryl-3-ethoxy carbonyl-5-hydroxy-2-methyl indoles

Balasubramanian Narasimhan[1]*, Ruma Saharan[2] and Pradeep Kumar[1]

[1]Faculty of Pharmaceutical Sciences, Maharshi Dayanand University, Rohtak - 124 001, India.
[2]Advanced Centre for Biotechnology, Maharshi Dayanand University, Rohtak - 124 001, India.

Abstract

The anti-inflammatory and analgesic activities of substituted 1-alkyl/aryl-3-ethoxy carbonyl-5-hydroxy-2-methyl indoles were correlated with their physicochemical parameters using Hansch analysis. The multiple linear regression (MLR) model developed for anti-inflammatory activity indicated the importance of lipophilic parameter, log octanol/water partition coefficient (log P) and electronic parameter, energy of lowest unoccupied molecular orbital (LUMO) in describing the anti-inflammatory activity. The QSAR model developed for the analgesic activity demonstrated the importance of topological parameter, Kier's alpha shape index of first order ($\kappa\alpha_1$) in describing the analgesic activity. The developed QSAR models were cross-validated by leave-one-out technique.

Keywords: substituted indole derivatives, Hansch analysis, LUMO, $\kappa\alpha_1$, log P

Introduction

The majority of currently known non-steroidal anti-inflammatory and analgesic drugs (NSAIDs), mainly act peripherally by blocking the production of prostaglandins through inhibition of cyclooxygenase (COX) enzymes, COX-1 and COX-2, to varying extents. These drugs tend to produce side effects such as gastrointestinal ulceration and suppression of renal function due to inhibition of the constitutive COX-l, which is responsible for the production of prostaglandins, responsible for gastroprotection and vascular homeostasis. Therefore, the main trend nowadays in pain therapy focuses on improved nonsteroidal analgesics which are effective as an analgesic but devoid of the side effects which are inherent to traditional NSAIDs (Sukuroglu et al. 2005).

Indoles have been widely identified as a privileged structure with representation in over 3000 natural isolates and are known to possess broad spectrum of biological and pharmaceutical activity. Indomethacin and tenidap are indole derivatives, which were found to possess anti-inflammatory activity with analgesic and antipyretic properties. They inhibit production of eicosanoids like prostacyclin, thromoxanes and prostaglandins by inhibition of COX and thereby reduce oedema (Sujatha et al. 2009). Badiger et al. reported a series of N-substituted indole analogues with anti-inflammatory and analgesic potential (Badiger et al. 2009).

***Corresponding author:** naru2000us@yahoo.com

Quantitative structure–activity relationships (QSARs) are mathematical models approximating the often complex relationships between chemical properties and biological activities of compounds. Common objectives of such models are a) to allow prediction of biological activity of untested and sometimes yet unavailable compounds and b) to extract clues of which chemical properties of compounds are likely determinants for their biological activities. QSARs are increasingly used by authorities, industries, and other institutions due to the fact that completing even the most basic biological testing of compounds of concern would take decades. Therefore, predictive models (PMs) such as QSARs are necessary for aiding in chemicals management because they may considerably reduce costs, avoid animal testing and speed up managerial decisions (Eriksson et al. 2003).

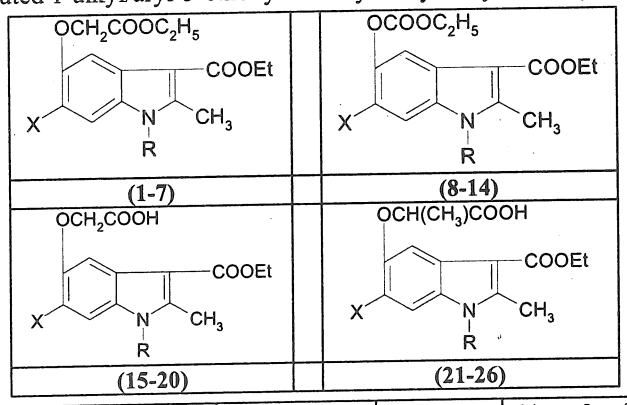
Based on these facts and in continuation of research work to create QSAR models (Narasimhan et al. 2007, Kumar et al. 2009 and 2010, Sharma et al. 2009) that show substantial predictive promise, in the present study we report the QSAR study on analgesic and anti-inflammatory potential of substituted 1-alkyl/aryl-3-ethoxy carbonyl-5-hydroxy-2-methyl indoles reported by Badiger et al. (2009).

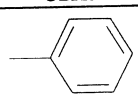
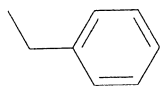
Materials and Methods

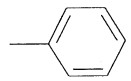
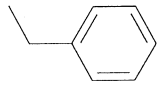
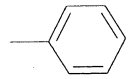
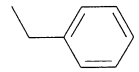
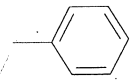
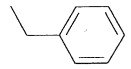
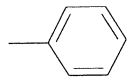
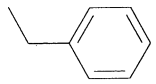
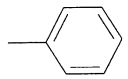
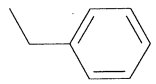
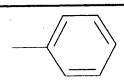
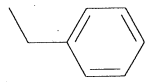
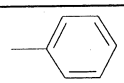
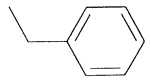
Data set

A set of 26 compounds of substituted 1-alkyl/aryl-3-ethoxy carbonyl-5-hydroxy-2-methyl indoles has been selected form reported work of Badiger et al. (2009) and is given in Table 1. The biological activity reported in % inhibition (anti-inflammatory) and % analgesia were converted to logarithmic value (log BAai and log BA respectively) for eliminating much clustering, rendering it more suitable for QSAR study.

Table 1. Chemical structure and analgesic and anti-inflammatory potential of substituted 1-alkyl/aryl-3-ethoxy carbonyl-5-hydroxy-2-methyl indoles



Comp. No.	R	X	% Inhibition after 2h	Log BAai	% analgesia after 1 h	Log BA
1	H	H	9.2	0.96	-	-
2	C2H5	H	7.2	0.86	-	-
3		H	72.7	1.86	65.95	1.82
4		H	12.7	1.10	-	-

Comp. No.	R	X	% Inhibition after 2h	Log BAai	% analgesia after 1 h	Log BA
5	H	CH_3	32.7	1.36	5.85	0.77
6		CH_3	67.3	1.83	68.62	1.84
7		CH_3	45.4	1.66	-	-
8	H	H	18.2	1.26	-	-
9	C2H5	H	40	1.60	5.85	0.77
10		H	45.4	1.66	-	-
11		H	10.9	1.04	-	-
12	H	CH_3	19.98	1.30	-	
13		CH_3	40.0	1.60	49.99	1.73
14		CH_3	27.3	1.44	-	-
15	C2H5	H	8.4	0.92	-	-
16		H	63.6	1.80	5.85	0.77
17		H	16.4	1.21	-	-
18	H	CH_3	30.9	1.49	-	-
19		CH_3	45.4	1.66	-	-
20		CH_3	47.3	1.67	51.50	1.71
21	C2H5	H	16.4	1.21	-	-
22		H	60.0	1.78	63.63	1.80
23		H	18.5	1.27	-	-
24	H	CH_3	21.8	1.34	-	-
25		CH_3	63.6	1.80	65.95	1.82
26		CH_3	52.7	1.72	-	-

Descriptor generation

The next step in developing a model is generation of the numerical description of the molecular structures. The structures of substituted 1-alkyl/aryl-3-ethoxy carbonyl-5-hydroxy-2-methyl indoles were sketched using DS viewer pro 6.0 and energy minimized. The energy minimized structures were used to calculate the molecular descriptors like hydrophobic, geometric, electronic and topological characters (Table 2) using the software TSAR 3.3 for windows. The values of descriptors selected for MLR model are presented in Table 3.

Table 2. QSAR descriptors used in the study

S.No.	QSAR descriptor	Type
1	log P	Lipophilic
2	Zero order molecular connectivity indices ($^0\chi$)	Topological
3	First order molecular connectivity indices ($^1\chi$)	Topological
4	Second order molecular connectivity indices ($^2\chi$)	Topological
5	Valence zero order molecular connectivity indices ($^0\chi^v$)	Topological
6	Valence first order molecular connectivity indices ($^1\chi^v$)	Topological
7	Valence second order molecular connectivity indices ($^2\chi^v$)	Topological
8	Kier's alpha first order shape indice ($\kappa\alpha_1$)	Topological
9	Kier's alpha second order shape indice ($\kappa\alpha_2$)	Topological
10	Kier's first order shape indice (κ_1)	Topological
11	Randic topological index	Topological
12	Balaban topological index	Topological
13	Wiener's topological index	Topological
14	Kier's second order shape indice (κ_2)	Topological
15	Ionization potential	Electronic
16	Dipole moment (μ)	Electronic
17	Energy of highest occupied molecular orbital (HOMO)	Electronic
18	Energy of lowest unoccupied molecular orbital (LUMO)	Electronic
19	Total energy (Te)	Electronic
20	Molar refractivity (MR)	Steric

Table 3. Values of selected parameters used in regression analysis.

Comp.	log p	MR	$^0\chi$	$^0\chi^v$	κ_1	κ_2	$\kappa\alpha_1$	$\kappa\alpha_2$	LUMO	HOMO	μ
1	1.57	80.63	16.11	12.89	18.34	8.74	16.51	7.42	-0.25	-8.74	4.09
2	2.16	90.28	17.69	14.55	20.31	9.63	18.48	8.30	-0.30	-8.62	3.72
3	3.73	104.05	20.10	16.23	22.68	10.86	20.10	9.03	-0.54	-8.69	6.43
4	3.59	110.14	20.80	16.94	23.66	11.57	21.08	9.71	-0.21	-8.64	4.38
5	2.04	85.68	16.98	13.82	19.33	8.91	17.49	7.61	-0.30	-8.61	4.91
6	4.20	109.09	20.97	17.15	23.66	11.04	21.08	9.24	-0.51	-8.58	5.64
7	4.06	115.19	21.67	17.86	24.64	11.74	22.05	9.91	-0.26	-8.55	4.33
8	2.37	76.07	15.41	12.19	17.36	8.02	15.53	6.73	-0.37	-8.83	2.18
9	2.96	85.72	16.98	13.84	19.33	8.91	17.49	7.61	-0.31	-8.72	2.74
10	4.53	99.49	19.39	15.52	21.70	10.16	19.13	8.37	-0.52	-8.67	4.43
11	4.40	105.58	20.10	16.23	22.68	10.86	20.10	9.03	-0.31	-8.72	2.64
12	2.84	81.11	16.28	13.11	18.34	8.20	16.51	6.93	-0.31	-8.69	2.65
13	5.00	104.53	20.26	16.44	22.68	10.35	20.10	8.58	-0.51	-8.64	2.95
14	4.86	110.62	20.97	17.15	23.66	11.04	21.08	9.24	-0.30	-8.63	2.84
15	1.79	80.76	16.28	12.88	18.34	8.20	16.51	6.93	-0.32	-8.75	4.46
16	3.36	94.53	18.68	14.56	20.73	9.47	18.16	7.72	-0.48	-8.65	4.85
17	3.22	100.63	19.39	15.27	21.70	10.16	19.13	8.37	-0.33	-8.62	4.46
18	1.66	76.16	15.57	12.15	17.36	7.51	15.53	6.28	-0.31	-8.63	5.13
19	3.82	99.57	19.55	15.48	21.70	9.67	19.13	7.94	-0.54	-8.66	3.16
20	3.69	105.67	20.26	16.19	22.68	10.35	20.10	8.58	-0.29	-8.60	6.39
21	2.32	85.25	17.15	13.75	19.33	8.39	17.49	7.14	-0.29	-8.68	4.60
22	3.89	99.03	19.55	15.43	21.70	9.67	19.13	7.94	-0.53	-8.65	4.59
23	3.76	105.12	20.26	16.14	22.68	10.35	20.10	8.58	-0.29	-8.69	4.45
24	2.20	80.65	16.44	13.02	18.34	7.71	16.51	6.50	-0.30	-8.62	3.97
25	4.36	104.07	20.42	16.35	22.68	9.87	20.10	8.16	-0.47	-8.57	4.02
26	4.22	110.16	21.13	17.06	23.66	10.54	21.08	8.80	-0.27	-8.57	1.77

Pearson correlation analysis

Since there was large number of descriptors for each compound, we used Pearson's correlation matrix as a qualitative model (Table 4), in order to select the suitable descriptors for MLR analysis. This technique was adopted for choosing a suitable set of generated descriptors for developing a multiple linear regression model. The best generated MLR model was used to prepare a calibration model, which predicts the anti-inflammatory activity of substituted indole derivatives.

Multiple linear regression

We have applied multiple linear regression technique to develop the QSAR models to predict the analgesic and anti-inflammatory potential of substituted 1-alkyl/aryl-3-ethoxy carbonyl-5-hydroxy-2-methyl indoles selected for the present study. MLR is the classical approach to regression problems in QSARs. MLR assumes the predictor variables, normally called X, to be mathematically independent (orthogonal). Mathematical independence means that the rank of X is K (the number of X-variables). A limitation of MLR is the sensitivity to correlated descriptors. One practical workaround is to use long and lean data matrices where the number of compounds substantially exceeds the number of chemical descriptors-where interrelatedness among variables usually drops. It has been recommended that the ratio of compounds to variables should be at least 5.

MLR is satisfactorily applied in QSAR studies if the main problem of the selection of variables is faced and solved. MLR is usually used to fit the regression model (Eq. 1), which models a response variable, y, as a linear combination of the X-variables, with the coefficients b. The deviations between the data (y) and the model (Xb) are called residuals, and are denoted by e:

$$y = Xb + e \qquad \text{Eq. 1}$$

For many response variables (columns in the response matrix Y), regression normally forms one model for each of the M y-variables, that is, M separate models (Eriksson et al. 2003).

Cross validation

The models were cross-validated by the 'leave one out' scheme where a model is built with N- 1 compounds and the Nth compound is predicted. Each compound is left out of the model derivation and predicted in turn. An indication of the performance of the model is obtained from the cross-validated (or predictive q^2) method, which is defined as (Eq. 2);

$$q^2 = (SD - PRESS / SD) \qquad \text{Eq. 2}$$

Where, SD is the sum of squares deviation for each activity from the mean. PRESS (predictive sum-of-squares) is the sum of the squared difference between the actual and that of the predicted values when the compound is omitted from the fitting process. The model with high q^2 value is said to have high predictability (Kumar et al. 2009).

Results and Discussion

In the present study, a data set of 26 substituted 1-alkyl/aryl-3-ethoxy carbonyl-5-hydroxy-2-methyl indoles derivatives was subjected to linear free energy regression analysis for model generation. Preliminary analysis was carried out in terms of correlation analysis. A correlation matrix constructed for anti-inflammatory and analgesic activity of indole derivatives is presented in Table 4.

In general, high colinearity ($r > 0.8$) was observed between different parameters. The high interrelationship was observed between ${}^0\chi^v$ and $\kappa\alpha_1$ ($r= 0.998$) and low interrelationship was observed between ${}^2\chi^v$ and LUMO ($r= -0.502$). The correlation matrix indicated the predominance of electronic parameter LUMO and topological parameter $\kappa\alpha_1$ in describing the anti-inflammatory and analgesic activity of indole derivatives, respectively.

Table 4. Correlation matrix for analgesic and anti-inflammatory potential of substituted 1-alkyl/aryl-3-ethoxy carbonyl-5-hydroxy-2-methyl indoles

	log BA	log P	MR	$^0\chi$	$^0\chi^v$	$^2\chi$	$^2\chi^v$	$\kappa\alpha_1$	LUMO	Log BAai
log BA	1.000									
log P	0.779	1.000								0.569
MR	0.906	0.829	1.000							0.430
$^0\chi$	0.912	0.852	0.995	1.000						0.476
$^0\chi^v$	0.919	0.839	0.986	0.979	1.000					0.440
$^2\chi$	0.872	0.821	0.966	0.981	0.925	1.000				0.519
$^2\chi^v$	0.894	0.796	0.970	0.979	0.942	0.988	1.000			0.484
$\kappa\alpha_1$	0.919	0.804	0.984	0.973	0.998	0.915	0.937	1.000		0.402
LUMO	-0.549	-0.665	-0.563	-0.612	-0.562	-0.596	-0.502	-0.528	1.000	-0.651

The anti-inflammatory of synthesized indole derivatives is explained by the electronic parameter, energy of lowest unoccupied molecular orbital (LUMO) (Eq. 2).

LR-QSAR model for anti-inflammatory activity

$$\log BAai = -1.872\ LUMO + 0.761 \qquad \text{Eq. 3}$$

$n = 26$; $r = 0.651$; $r^2 = 0.423$; $q^2 = 0.344$; $F = 17.62$; $s=0.237$; $p<0.0002$

Here and thereafter, n: number of data points, r: correlation coefficient, q^2: cross validated r^2: obtained by leave one out method, s: standard error of the estimate and F: Fischer statistics.

The electronic parameter LUMO which denote the energy of the lowest unoccupied molecular orbital, directly relates to the electron affinity and characterizes the susceptibility of the molecule towards an attack by nucleophiles (Ohlan et al. 2007). According to the FMO concept, the HOMO and LUMO of a molecule play important roles in intermolecular interactions. Extending the concept to binding in drug-receptor systems, the major contribution to binding involves the interaction between the HOMO of the drug with the LUMO of the receptor and that between LUMO of the drug with the HOMO of the receptor. The extents of these stabilizing interactions are inversely related to the energy gap between the interacting orbitals (Jesudason et al. 2009).

The addition of lipophilic parameter, log P as a second parameter to the electronic parameter LUMO appreciable improved the r value from 0.651 to 0.723 (Eq. 4)

MLR-QSAR model for anti-inflammatory activity

$$\log BAai = 0.104 \log P - 1.429\ LUMO + 1.438 \qquad \text{Eq. 4}$$

$n = 26$; $r = 0.723$; $r^2 = 0.523$; $q^2 = 0.387$; $F = 12.62$; $s=0.220$; $p < 0.002$

The cross-validation of Eq. 4 was subsequently checked by employing ''leave one out'' (LOO) method. The $q^2 > 0.5$ qualifies a QSAR model to be a valid one (Wold et al. 1995). In equation 4 q^2 is less than 0.5, which shows that the developed model is an invalid one. But one should not forget the recommendations of Golbraikh and Tropsha (2002) who have recently reported that the only way to estimate the true predictive power of a model is to test their ability to predict accurately the biological activities of compounds. As the observed and predicted values are close

to each other, the QSAR model for anti-inflammatory activity is a valid one (Table 5, Fig. 1) (Golbraikh and Trophsa 2002).

Table 5. Table showing observed, predicted and residual analgesic and anti-inflammatory potential of substituted 1-alkyl/aryl-3-ethoxy carbonyl-5-hydroxy-2-methyl indoles

	Log BA (Anti-inflammatory)			Log BA Analgesic		
	obs	pre	resi	obs	Pre*	resi
1	0.96	1.10	-0.14	-	**0.44**	-
2	0.86	1.23	-0.37	-	**1.14**	-
3	1.86	1.74	0.12	1.82	1.73	0.09
4	1.10	1.25	-0.15	-	**2.07**	-
5	1.36	1.21	0.15	0.77	0.79	-0.02
6	1.83	1.74	0.09	1.84	2.08	-0.24
7	1.66	1.37	0.29	-	**2.42**	-
8	1.26	1.35	-0.09	-	**0.09**	-
9	1.60	1.33	0.27	0.77	0.79	-0.02
10	1.66	1.79	-0.13	-	**1.38**	-
11	1.04	1.47	-0.43	-	**1.73**	-
12	1.30	1.32	-0.02	-	**0.44**	-
13	1.60	1.83	-0.23	1.70	1.73	-0.03
14	1.44	1.51	-0.07	-	**2.07**	-
15	0.92	1.21	-0.29	-	**0.44**	-
16	1.80	1.62	0.18	0.77	1.03	-0.26
17	1.21	1.37	-0.16	-	**1.38**	-
18	1.49	1.19	0.30	-	**0.09**	-
19	1.66	1.74	-0.08	-	**1.38**	-
20	1.67	1.37	0.30	1.71	1.73	-0.02
21	1.21	1.23	-0.02	-	**0.79**	-
22	1.78	1.73	0.05	1.80	1.38	0.42
23	1.27	1.38	-0.11	-	**1.73**	-
24	1.34	1.23	0.11	-	**0.44**	-
25	1.80	1.69	0.11	1.82	1.73	0.09
26	1.72	1.40	0.32	-	**2.07**	-

* Bold values indicate the analgesic activity predicted by developed QSAR equation 5.

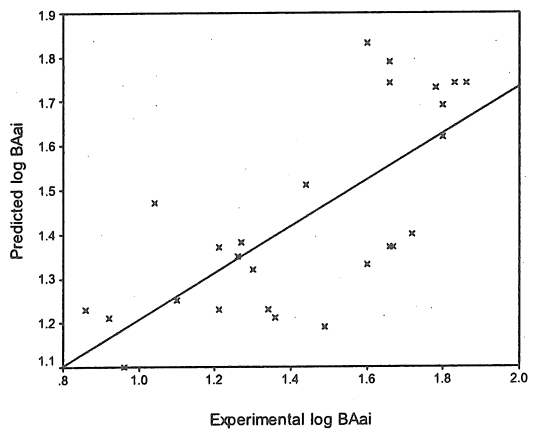


Figure 1. Plot of predicted log BAai against the experimental log BAai for the linear regression model developed by Eq. 4

To determine the existence of the systemic error in the model development we have plotted logBAai observed against logBAai residual values (Fig. 2). The propagation of residuals on both

sides of zero indicated that there is no systemic error in the development of QSAR model (Sharma et al. 2009).

Eq. 5 developed to predict the analgesic activity of substituted 1-alkyl/aryl-3-ethoxy carbonyl-5-hydroxy-2-methyl indoles derivatives demonstrated the importance of topological parameter, Kiers first order alpha shape index ($\kappa\alpha_1$) in explaining analgesic activity.

LR-QSAR model for analgesic activity

$$\log BA = 0.358\ \kappa\alpha_1 - 5.471 \qquad \text{Eq. 5}$$

$n = 9$; $r = 0.919$; $r^2 = 0.845$; $q^2 = 0.761$; $F = 38.09$; $s = 0.214$; $p < 0.0002$

In case of Eq. 5, the high q^2 values ($q^2 > 0.5$) supported the validity of developed QSAR model. Further the comparison of observed and predicted analgesic activities also in favor of the developed QSAR model i.e. they lie close to each other as evidenced by low residual values (Table 5).

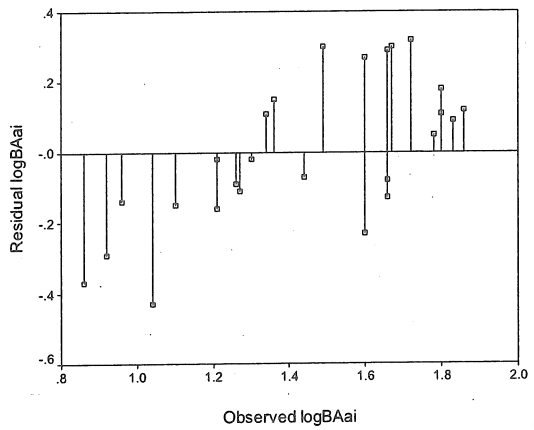


Figure 2. Plot of residual logBAai against the observed log BAai for the linear regression model developed by Eq. 2

It is important to note that when the predictability of analgesic equation is extended to the calculation of analgesic activity of remaining 17 compounds used in anti-inflammatory activity revealed that compounds **4, 7, 14, 26** having analgesic activity more than the standard drug diclofenac (logBA=1.84) which may be studied further clinically in order to develop new chemical entity (NCE) for the treatment of pain.

It is important to note that Eq. 3 - Eq. 5 were derived using the entire data set as there were no outliers in the data set. Even though the sample size and the 'Rule of Thumb' allowed us to go for development of penta-parametric model in multiple linear regression analysis, the high colinearity among the parameters restricted us to go for bi-parametric model only. The 'rule of thumb' gives information about the number of parameters to be selected for regression analysis in QSAR based on the number of compounds. According to this rule for QSAR model development one should select one parameter for a five-compound data set (Narasimhan et al. 2007).

Generally for QSAR studies, the biological activities of compounds should span 2-3 orders of magnitude. But in the present study the range of anti-inflammatory and analgesic activities of the indole derivatives are within one order of magnitude. But it is important to note that the predictability of the QSAR models developed in the present study is high evidenced by their low residual values. This is in accordance with results suggested by the Bajaj et al. (2005), who stated that the reliability of the QSAR model lies in its predictive ability even though the activity data are in the narrow range.

Conclusion

In conclusion, the QSAR study throws some light for the first time on correlation of anti-inflammatory and analgesic activities of substituted 1-alkyl/aryl-3-ethoxy carbonyl-5-hydroxy-2-methyl indoles with their physicochemical parameters. The QSAR model developed indicated the importance of lipophilic parameter, log of octanol/water partition co-efficient (log P) and electronic parameter, energy of lowest unoccupied molecular orbital (LUMO) in describing the anti-inflammatory activity and the importance of topological parameter, Kier's alpha shape index of first order ($\kappa\alpha_1$) in describing the analgesic activity. Further, the predictive powers of the equation were validated by determination of cross-validated r^2 (q^2) using leave one out (LOO) method. It is important to note that when the predictability of analgesic equation is extended to the calculation of analgesic activity of remaining 17 compounds used in anti-inflammatory activity revealed that four compounds having analgesic activity more than the standard drug diclofenac which may be studied further clinically in order to develop new chemical entity (NCE) for the treatment of pain.

References

Badiger, J., Manjulatha, K., Girish, M., Sharif, A. and Purohit, M.G. (2009). Synthesis and biological evaluation of some N-substituted indoles. *ARKIVOC.* XII: 217-231.

Bajaj, S., Sambi, S.S. and Madan, A.K. (2005). Prediction of anti-Inflammatory activity of *N*-Arylanthranilic acids: computational approach using refined Zagreb Indices. *Croat. Chem. Acta.* 78:165-174.

Eriksson, L., Jaworska, J., Worth, A.P., Cronin, M.T.D., McDowell, R.M. and Gramatica, P. (2003) Methods for reliability, uncertainty assessment, and applicability evaluations of regression based and classification QSARs. *Environ. Health. Perspect.* 111: 1361-1375.

Golbraikh, A. and Tropsha, A. (2002). Beware of q^2!. *J. Mol. Graphics Model.* 20: 269-276.

Jesudason, E.P., Sridhar, S.K., Malar, E.J.P., Shanmugapandiyan, P., Inayathullah, M., Arul, V., Selvaraj, D. and Jayakumar, R. (2009). Synthesis, pharmacological screening, quantum chemical and *in vitro* permeability studies of N-Mannich bases of benzimidazoles through bovine cornea. *Eur. J. Med. Chem.* 44: 2307-2312.

Kumar, D., Judge, V., Narang, R., Sangwan,S., Clerq, E.D., Balzarini, J. and Narasimhan, B. (2010). Benzylidene/2-chlorobenzylidene hydrazides: Synthesis, antimicrobial activity, QSAR studies and antiviral evaluation. *Eur. J. Med. Chem.* 45: 2806-2816.

Kumar, P., Narasimhan, B., Sharma, D., Judge, V. and Narang, R. (2009). Hansch analysis of substituted benzoic acid benzylidene/furan-2-yl-methylene hydrazides as antimicrobial agents. *Eur. J. Med. Chem.* 44: 1853-1863.

Narasimhan, B., Dhake, A.S. and Mourya, V.K. (2007). QSAR studies of 4,5-dihydro-4-oxo-3H-imidazo[4,5-c]pyridines as potent angiotensis II receptor by MLR and NLR analysis. *ARKIVOC.* I: 189-204.

Ohlan, R., Ohlan, S., Judge, V., Narang, R., Ahuja, M. and Narasimhan, B. (2007) 2-(2,4-Difluorophenyl)-1,3-bis(1,2,4-triazol-1-yl)propan-2-ol derivatives: synthesis, antifungal evaluation and QSAR studies by Hansch analysis. *ARKIVOC*. XIV: 172-184.

Sharma, D., Narasimhan, B., Kumar, P., Narang, R., Judge, V., Clerq, E.D. and Balzarini, J. (2009). Synthesis, antimicrobial and antiviral evaluation of substituted imidazole derivatives. *Eur. J. Med. Chem.* 44: 2347-2353.

Sujatha, K., Perumal, P.T., Muraliaharan, D. and Rajenderan, M. (2009). Synthesis, analgesic, and anti-inflammatory activities of bis(indoyl) methanes *Indian J. Chem. B* 48: 267-272.

Sukuroglu, M., Ergun, B.C., Unlu, S., Sahin, M.F., Kupeli, E., Yesilada, E. and Banoglu, E. (2005).Synthesis, analgesic and anti-inflammatory activity of [6-(3,5- Dimethyl-4-chloropyrazole-1-yl)-3(2H)-pyridazinon-2-yl] acetamides. *Arch. Pharm. Res.* 28: 509-517.

Received: 19.05.2010

Accepted: 24.02.2011