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QSAR Study on Competition Binding of Rodenticides (PATs) to H_1 Receptor in Rat and Guinea Pig Brain

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Abstract—A quantitative structure–activity relationship (QSAR) study on binding activity for a series of rodenticides (PAT analogues) to the [^{3}H]-mepyramine-labeled H_1 receptor in rat and guinea pig brain is attempted topologically. From the pool of molecular descriptors we, observed that the most significant descriptor is the molecular redundancy index (MRI). Multiple regression analysis gave excellent results with MRI upon introduction of some dummy parameters (indicator parameters). Predictive ability of the proposed models is discussed using cross-validation parameters. © 2002 Published by Elsevier Science Ltd.

Introduction

The competition binding activity of rodenticides namely phenylaminotetralines (PAT analogues) to the [^{3}H]-mepyramine-labeled H_1 receptor in rat and guinea pig brain are well known.[1,2] Recently Bucholtz et al.[3] reported the synthesis and biological evaluation of additional PATs analogues in order to identify binding site. They observed that structurally diverse H_1 ligands do not show significant differences in the affinity at [^{3}H] (−) *trans* H_2-PAT sites versus [^{3}H]-mepyramine-labeled H_1 receptors. Their results indicate similar distribution of [^{3}H] (+) *trans* H_2-PAT sites versus [^{3}H]-mepyramine-labeled H_1 receptor, suggest that both radioligands label the same histamine H_1 receptors in rodent brain.

Also, Bucholtz et al.[3] have investigated the effect of substituents on the binding site and reported competitional binding activity ($pK_{0.5}$) for a series of 1-phenyl-3-amino-1,2,3,4-tetrahydronaphthalenes as ligands for histamine H_1 receptors and used SYBYL molecular modelling software for structure generation and CoMFA. However, till-date no attempt is made for topological modeling of the competitional binding activities ($pK_{0.5}$) of these ligands. Consequently, we have undertaken the present investigation. An earlier study[4] made by us has indicated that such a study involving topological indices should first start with a large pool of topological indices and then to select out most useful topological indices. Our study has also indicated that a pool of molecular descriptors: negentropy (N),[5,6] molecular redundancy index (MRI),[6] first-order valence connectivity index ($^1\chi^V$),[7–9] Wiener (W),[10] and Szeged (Sz)[11,12] indices are more useful for modeling binding activity.

We have, therefore, calculated these indices for the set of compounds used in the present investigation (Fig. 1, Table 1).

The quantitative structure–activity relationships (QSARs) based on topological indices are increasingly being used in several areas of chemistry, biochemistry, pharmacology, and environmental research.[13–15] An

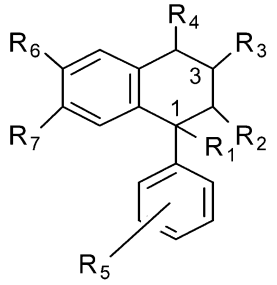

Figure 1. 1-Phenyl-3-amino-1,2,3,4-tetrahydronaphthalenes used in the present study.

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interesting achievement of these studies was the effort for numerically encode molecules according to their structural features. The conversion of the structural formula into a numerical value, often called topological or graph theoretical index can be achieved in many ways.[13–15] The rules were even set to search for topological indices of biochemical interests.[16]

It appears that among many topological indices that have been proposed since the Wiener index[10] in 1947, the connectivity index[7] is the most often used index in QSAR.

Very recently a new molecular graph distance-based topological index was introduced by Gutman,[11] which Gutman and one of the present authors (PVK) named Szeged index and abbreviated as Sz.[12,17] Compared to W and χ-index very little is known on the role of Sz in QSAR. Same is the case with negentropy and molecular redundancy index introduced by Kier.[6]

Preliminary investigation using the aforementioned indices for modeling binding activity of the compounds used (Table 1) indicated that only MRI index is the most suitable index for this purpose. This was found to be the case in our earlier studies[18–25] also in that from a largest pool of topological indices only MRI was found to be most suitable for QSAR analysis. Also, as discussed below, excellent results are obtained in multiple regression analysis[26–29] upon introduction of indictor parameters. Hence, this study deals only with the use of MRI index in modeling binding activity ($pK_{0.5}$) of the compounds under present study (Fig. 1, Table 1). The binding activities needed for the present investigation were adopted from the earlier work.[3]

Results and Discussion

Table 1 contains structural details of rodenticides (PATs analogues) used. The competition binding activities ($pK_{0.5}$) for the set of PATs used in the present investigation are shown in Table 1. The estimated values of MRI are also given in Table 2. Table 2 also contains the assumed values of indicator parameters (Ip_1, Ip_2, Ip_3, Ip_4). This forms a pool of molecular descriptors to be used in the present study and is used for obtaining statistically significant QSAR models. The results, as discussed below, indicated that MRI index in combination with indicator parameters gives statistically significant results.

The correlation matrix indicated inter-correlations of MRI and indicator parameters used (Table 3). Table 3 also suggests that some combinations of MRI and indicator parameters will be more useful for modeling $pK_{0.5}$.

The regression analyses indicated that no mono-parametric model could be obtained for modeling $pK_{0.5}$.

Out of the several bi-parametric models attempted by us, only the regression equation containing MRI and Ip_1 was found to be the best for modeling $pK_{0.5}$. This model is found as under:

$$pK_{0.5} = -20.5562\ (\pm 2.6662)\mathrm{MRI} + 1.8364\ (\pm 0.1917)\mathrm{Ip}_1 + 12.2214 \quad (1)$$

$$n = 26,\ \ \mathrm{Se} = 0.4621,\ \ \ R_A^2 = 0.8192,$$
$$R = 0.9130,\ \ F = 56.621$$

Table 1. Structural details of the compounds used in the present study

Compd	Config.	R_1	R_2	R_3	R_5	R_6	R_7	R_4
1	(±)-*trans*	H	H	$N(CH_3)_2$	H	Cl	OH	CH_2
2	(±)-*trans*	H	H	$N(CH_3)_3$	H	H	H	CH_2
3	(±)-*trans*	H	H	$NH(CH_3)$	H	H	H	CH_2
4	(±)-*trans*	H	H	$NCH_3(C_3H_5)$	H	H	H	CH_2
5	(±)-*trans*	H	H	$N(C_3H_5)_2$	H	H	H	CH_2
6	(±)-*cis*	H	$N(CH_3)_2$	H	H	H	H	CH_2
7	(±)-*trans*	H	$N(CH_3)_2$	H	H	H	H	CH_2
8	(±)-*cis*	H	H	$N(CH_3)_2$	H	H	H	C_2H_4
9	(±)-*trans*	H	H	$N(CH_3)_2$	H	H	H	C_2H_4
10	(±)-*cis*	H	H	$N(CH_3)_2$	H	OH	OH	CH_2
11	(±)-*trans*	CH_3	H	$N(CH_3)_2$	H	H	H	CH_2
12	(±)-*cis*	CH_3	H	$N(CH_3)_2$	H	H	H	CH_2
13	(±)-*trans*	H	H	$N\ CH_3\ (CH_2)_2C_6H_5$	H	H	H	CH_2
14	(±)-*trans*	H	H	$N\ CH_3\ (CH_2)_3C_6H_5$	H	H	H	CH_2
15	(±)-*trans*	H	H	$N\ CH_3\ (CH_2)_4C_6H_5$	H	H	H	CH_2
16	(±)-*trans*	H	H	$N(CH_3)_2$	*o*-CH_3	H	H	CH_2
17	(±)-*trans*	H	H	$N(CH_3)_2$	*p*-Cl	H	H	CH_2
18	(±)-*trans*	H	H	$N(CH_3)_2$	*p*-CH_3	H	H	CH_2
19	(±)-*cis*	H	H	$N(CH_3)_2$	*p*-F	H	H	CH_2
20	(±)-*cis*	H	H	$N(CH_3)_3$	H	H	H	CH_2
21	(±)-*trans*	H	H	$NH(CH_3)$	H	Cl	OH	CH_2
22	(±)-*trans*	H	H	$NH(C_3H_5)$	H	H	H	CH_2
23	(±)-*trans*	H	H	$NH(CH_2)_3C_6H_5$	H	H	H	CH_2
24	(±)-*trans*	H	H	$NH(CH_2)_3C_6H_5$	H	H	H	CH_2
25	(±)-*trans*	H	H	$NH(CH_2)_4C_6H_5$	H	H	H	CH_2
26	(±)-*trans*	H	H	NH_2	H	H	H	CH_2

Here and hereafter, n represents the number of compounds, Se stands for standard error of estimation, R^2_A and R are adjusted R-squared and multiple correlation coefficients, respectively, and F is the Fisher's ratio.

The above model 1 [eq (1)] shows that use of MRI and Ip_1 accounts for 83.4% of variance in $pK_{0.5}$. Also that, the presence of $-N(CH_3)_2$ at R_3 plays a dominant role in the exhibition of $pK_{0.5}$. The negative coefficient associated with MRI indicates that decrease in the magnitude of MRI favours the exhibition of $pK_{0.5}$.

Addition of one more molecular descriptor, namely Ip_2 to the above model [eq (1)] resulted into tri-parametric model with improved quality. This improved tri-parametric model is found as below:

$$\begin{aligned} pK_{0.5} = &-20.7518\ (\pm 2.7753)\mathrm{MRI} \\ &+ 1.9821\ (\pm 0.2185)Ip_1 - 0.3822\ (\pm 0.2890)Ip_2 \\ &+ 12.5220 \end{aligned} \qquad (2)$$

$$n = 26,\ \ \mathrm{Se} = 0.4547,\ \ \ R^2_A = 0.8249,\ \ R = 0.9197,\ \ F = 40.247$$

Table 2. Competitional binding affinity ($pK_{0.5}$), calculated MRI and indicator parameters

Compd	$pK_{0.5}$	MRI	Ip_1	Ip_2	Ip_3	Ip_4	$pK_{0.5}$ estimated from			
							Model 2		Model 4	
							Est.	Res	Est.	Res
1	9.46	0.2240	1	0	1	1	9.63	−0.17	9.39	0.07
2	7.76	0.3176	1	0	0	1	7.60	0.16	7.31	0.45
3	7.25	0.2133	0	0	0	1	7.07	0.18	7.04	0.21
4	8.77	0.2506	0	0	0	1	7.88	0.89	7.87	0.90
5	8.26	0.2212	0	0	0	1	7.71	0.55	7.70	0.50
6	6.22	0.2856	0	0	0	0	6.31	−0.09	6.64	−0.42
7	6.33	0.2856	0	0	0	1	6.31	0.02	6.26	0.07
8	7.26	0.3059	1	0	0	0	7.85	−0.59	7.95	−0.69
9	7.98	0.2431	1	0	0	1	8.58	−0.60	8.31	−0.33
10	8.32	0.2771	1	0	1	0	8.48	−0.16	8.59	−0.27
11	8.04	0.2810	1	0	0	1	8.39	−0.35	8.12	−0.08
12	9.02	0.2809	1	0	0	0	8.39	0.63	8.51	0.51
13	7.15	0.2484	0	0	0	1	7.12	0.03	7.09	0.06
14	6.78	0.2382	0	0	0	1	7.34	−0.56	7.32	−0.54
15	6.97	0.2527	0	0	0	1	7.17	0.20	7.15	−0.18
16	8.29	0.2502	1	1	0	1	8.68	−0.39	8.81	−0.52
17	8.35	0.2527	1	1	0	1	8.62	0.27	8.76	−0.41
18	8.85	0.2502	1	1	0	1	8.68	0.17	8.81	0.04
19	9.12	0.2527	1	1	0	0	8.62	0.50	8.76	0.36
20	7.23	0.3500	1	0	0	0	6.89	0.34	6.97	0.26
21	9.60	0.2593	1	0	1	1	8.86	0.74	8.99	0.61
22	8.38	0.1843	0	0	1	1	8.51	−0.13	8.52	−0.14
23	7.35	0.2206	0	0	0	1	7.72	−0.37	7.71	−0.36
24	5.90	0.3040	0	0	0	1	5.91	−0.01	5.86	0.04
25	6.12	0.3081	0	0	0	1	5.82	0.30	5.76	0.36
26	6.20	0.2631	0	0	0	1	6.80	−0.60	6.76	−0.56

$pK_{0.5}$, log of competition binding activity ($K_{0.5}$); MRI, molecular redundancy index; Ip_1, Ip_2, Ip_3, Ip_4, indicator parameters (see text for details); Res, Residue (difference between observed and estimated $pK_{0.5}$).

Comparison of the above models 1 and 2, expressed by eqs (1) and (2), indicated that the tri-parametric model [eq (2)] resulted with decrease in Se and increase in the magnitude of both R^2_A and R, which shows that it is a better model than the earlier bi-parametric model. Also, addition of Ip_2 is statistically significant and has its fair share in modeling $pK_{0.5}$. It is worth mentioning that in the aforementioned tri-parametric model [eq (2)], MRI and Ip_1 also play similar role as that in the bi-parametric model 1 [eq (1)]. The quality of tri-parametric model 2 [eq (2)] is thus improved because of the further addition of Ip_2 in that the effect due to substitution at R_5 is involved. The negative coefficient of Ip_2 indicates that replacement of H by substituent R_5 play a negative role in the exhibition of $pK_{0.5}$.

In addition to the above, another tri-parametric model consisting of the combination of MRI, Ip_1 and Ip_3 also resulted into significant statistical model. However, its quality is slightly poorer than the model 2 [eq (2)]. This tri-parametric model takes the following form:

$$\begin{aligned} pK_{0.5} = &-19.2614\ (\pm 2.9358)\mathrm{MRI} \\ &+ 1.7606\ (\pm 0.2045)Ip_1 + 0.2958\ (\pm 0.2831)Ip_3 \\ &+ 11.8731 \end{aligned} \qquad (3)$$

$$n = 26,\ \ \mathrm{Se} = 0.4612,\ \ \ R^2_A = 0.8199,\ \ R = 0.9173,\ \ F = 38.928$$

Comparison of this model 3 [eq (3)] with the model 1 expressed by eq (1) indicates that they gave almost similar value of R^2_A. This means that added Ip_3 has no significant contribution to the model expressed by eq (1) though there is slight decrease in Se (0.4612) and slight increase in R (0.9173).

The above models 1–3 [eqs (1)–(3)] prompted us to try one more tri-parametric model by adding Ip_4 to the model 1 [eq (1)]. Such an attempt had resulted in the most significant tri-parametric model containing MRI, Ip_1 and Ip_4 as mentioned below.

Table 3. Correlation matrics for the inter-correlation of molecular descriptors and correlation with the activity

	$pK_{0.5}$	MRI	Ip_1	Ip_2	Ip_3	Ip_4
$pK_{0.5}$	1.0000					
MRI	−0.4124	1.0000				
Ip_1	0.6353	0.3265	1.0000			
Ip_2	0.3695	−0.1393	−0.4264	1.0000		
Ip_3	0.4846	−0.3205	0.2132	−0.1818	1.0000	
Ip_4	−0.1092	−0.4560	−0.3652	0.2336	−0.2725	1.0000

$pK_{0.5}$, log of competition binding activity ($K_{0.5}$), MRI; molecular redundancy index; Ip_1, Ip_2, Ip_3, Ip_4, indicator parameters (see text for details).

$$\begin{aligned} \mathrm{p}K_{0.5} = & -22.2297\ (\pm 2.7997)\mathrm{MRI} \\ & + 1.7591\ (\pm 0.1925)\mathrm{Ip}_1 - 0.3789\ (\pm 0.2426)\mathrm{Ip}_4 \\ & + 12.9920 \end{aligned} \quad (4)$$

$$n = 26,\ \ \mathrm{Se} = 0.4482,\ \ \ R_{\mathrm{A}}^2 = 0.8298,$$
$$R = 0.9221,\ \ F = 41.632$$

Hence, regression parameters and quality of the model 4 [eq (4)] establish that this model is the most appropriate model for modeling $\mathrm{p}K_{0.5}$.

The aforementioned model 4 [eq (4)] indicates that MRI along with substitution of $-\mathrm{N}(\mathrm{CH}_3)_2$ and *trans*-conformation is the most favourable condition for the exhibition of $\mathrm{p}K_{0.5}$.

It is interesting to record that while deciding the quality of model one has to consider both Se and R simultaneously. We have a parameter in the literature which accounts for such variation of Se and R simultaneously. This parameter is called quality factor and is symbolized as Q.[30,31] It is defined as the ratio of R to Se ($Q = R/\mathrm{Se}$). Hence, the highest R-value and smallest Se will result into highest quality factor Q yielding the most significant model.

The Q-values obtained for the above mentioned models (1–4) are found as: 1.976, 2.023, 1.989, and 2.057, respectively. Thus, we observed that model 4 is the most significant model while second best model for modeling $\mathrm{p}K_{0.5}$ is model 2.

It is interesting to record that all the four proposed models invariably contain a MRI term whose coefficient is negative and centered around (≈20). Similarly, all these models also contain Ip_1 term having (+)ve coefficient around 1.8.

In models 2 and 4 the added variable (Ip_2, Ip_4) have (−)ve coefficient of the order of 0.38 indicating their (−)ve contribution in developing the proposed model. On the other hand, model 3 shows that the coefficient of Ip_3 like Ip_1 is (+)ve suggesting its (+)ve role in exhibiting competition binding energy ($\mathrm{p}K_{0.5}$).

The aforementioned results also help us in proposing mechanism of physiological functions. Since in all the four proposed models the slope as well as the intercepts

Table 4. Cross-validation parameters for the models proposed in the discussion

Model no.	Parameter involved	PRESS	SSY	$\frac{\mathrm{PRESS}}{\mathrm{SSY}}$	r_{cv}^2	S_{PRESS}	PSE
1	MRI, Ip_1 (2)	4.9106	24.6046	0.1996	0.8004	0.4621	0.4188
2	MRI, Ip_1, Ip_2 (3)	4.5491	24.9661	0.1822	0.8178	0.4547	0.4030
3	MRI, Ip_1, Ip_3 (3)	4.6787	24.8365	0.1876	0.8124	0.4612	0.4088
4	MRI, Ip_1, Ip_4 (3)	4.4204	25.0948	0.1762	0.8239	0.4483	0.3973

PRESS, predicted residuals sum of squares; SSY, sum of the squares of regression value; r_{cv}^2, cross-validation correlation coefficient; S_{PRESS}, uncertainty of prediction; PSE, predictive square error.

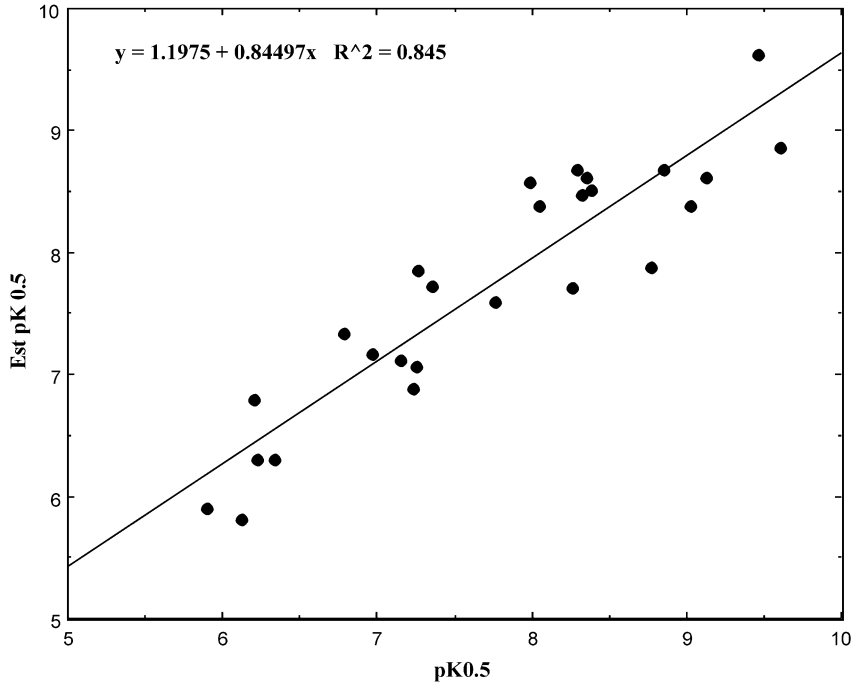

Figure 2. Correlation of observed and estimated $\mathrm{p}K_{0.5}$ values (using model 2) for the rodenticides used in the present study.

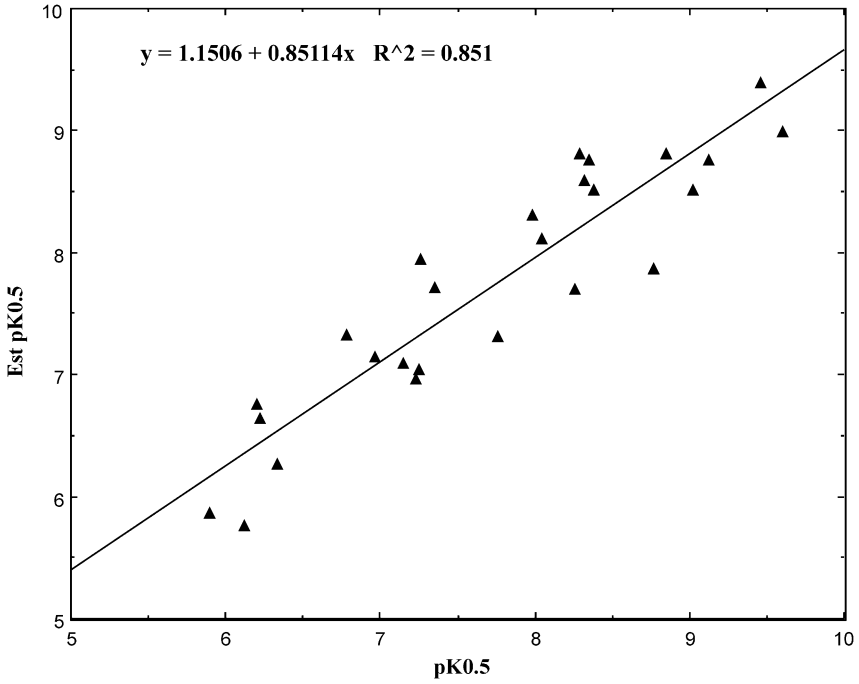

Figure 3. Correlation of observed and estimated $pK_{0.5}$ values (using model 4) for the rodenticides used in the present study.

are similar, the involved mechanism of action likewise will be the same. Thus, there exists a positive result and indication of QSAR in mechanism of physiological function.

We now proceed to investigate predictive potential of the proposed model employing cross-validation method.[26–29] The calculated cross-validation parameters are presented in Table 4.

The ratio of PRESS to SSY for the proposed models 1–4 indicate that their predictive potential is excellent.[26–29]

It is interesting to record that the values of Se and S_{PRESS} are similar. Both these parameters, therefore, are not useful in deciding predictive potentiality of the models. We have, therefore, used predictive squared error (PSE) for finally judging the predictive potentials of the models. These values as recorded in Table 4 are more directly related to uncertainty of the prediction than Se and S_{PRESS}. The lowest value of PSE (0.3973) for model 4 indicated to be the best model.

In order to confirm our results, we have finally estimated $pK_{0.5}$ using models 2 and 4 and compared these values with the observed $pK_{0.5}$. Such a comparison is shown in Table 2 and demonstrated in Figures 2 and 3, respectively. The predictive correlation coefficients 0.845 and 0.851, respectively, for models 2 and 4 (Figs 2 and 3, respectively) confirm our finding that the model 4 is most appropriate for modeling $pK_{0.5}$.

Conclusion

The results and discussions made so far lead us to the following conclusions:

i. Though W and χ indices are widely used in QSAR study they are not found good in the present case for modeling competition binding activity ($pK_{0.5}$) of the rodenticides (PATs analogues) used in the present study. Same is found to be the case with Sz and N. Instead MRI is found to be most appropriate index for the present study;
ii. Introduction of dummy (indicator) parameters resulted into statistically significant models in that all the four indicator parameters (Ip_1, Ip_2, Ip_3, Ip_4) were useful and that use of Ip_1 and Ip_4 along with MRI gave the best results;
iii. Se and S_{PRESS} are not good parameters for indicating the quality of models for the set of compounds used. It is PSE which is found to be the best in deciding predictive potential of the models;
vi. MRI is basically an information theoretic index. Hence, information content, *trans*-conformation, are the basic factors for the execution of competition binding activity ($pK_{0.5}$) of the rodenticides used in the present study.
v. The results also show that the presence of $-N(CH_3)_2$ group (Ip_1) in the rodenticides (PATs) and also *trans*-conformation (Ip_4) accounts for the binding activity.

Experimental

Methodology of modeling activity

Topological indices. We have stated earlier that out of the pool of topological indices only MRI is useful, therefore, we are giving here brief description of the calculation of MRI, as the details of calculations are already available in the literature.[22–29]

Molecular redundancy index (MRI). The MRI[6] is derived from information theory and molecular graph theory and is defined as:

$$\mathrm{MRI} = \frac{\Sigma\ n_i \log n_i}{N \log N}$$

where n_i is the number of atoms of the same kind in the ith atom set, i is the number of different atoms in the molecule.

Indicator parameters (Ip_1, Ip_2, Ip_3, Ip_4). Indicator variables (parameters), sometimes called dummy variables or de novo constants,[19] 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[19] analysis may be interpreted as a regression analysis approach using only indicator variables.

The indicator parameters (variables) take on only two values, usually zero and one. In the present case the indicator parameter Ip_1 was taken as unity when $-N(CH_3)_2$ group is present at R_3. Similarly, Ip_2 is used as unity when R_5 is other than H. When R_6 and R_7 are other than H the indicator parameter taken is Ip_3 and its value is taken as unity. Ip_4 is taken as one when the compound is trans.

Competition binding activity. As stated earlier the binding activities are adopted from the earlier work.[3] Furthermore, these binding constant, $K_{0.5}$ (nm) as reported by Bucholtz et al.[3] were then converted into their log units so as to yield $pK_{0.5}$ and finally used in the present investigation. Non-linear regression analysis of inhibition data was used by Bucholtz et al.[3] to determine IC_{50} values using prism 2.0 (Graph Pat San Francisco, CA, USA). IC_{50} values which in turn were converted into $K_{0.5}$ (nm) using the Cheng–Prussof equation,[18] where $K_{0.5} = IC_{50}/(1 + L^*/KD)$. The experiments were repeated by the at least three times to determine mean ($K_{0.5} \pm SEM$), which was subsequently changed to log $K_{0.5}$ ($= pK_{0.5}$).

Regression analysis

QSAR models were proposed using multiple regression analysis and predictive potential of the models was determined by cross-validation methods.[19–21] Multiple regression analyses were carried out using Regress-1 software as supplied by Professor I. Lukovits, Hungarian Academy of Sciences, Budapest, Hungary. Similarly, W and Sz were calculated employing his Wiener-1 program.

Computation

All the computations were carried out in Power Macintosh 9600/233.

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